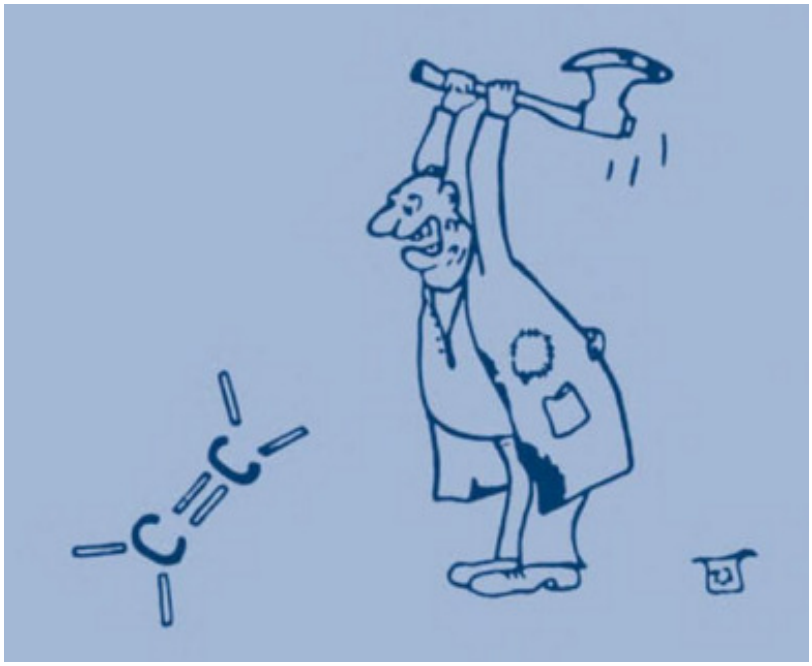
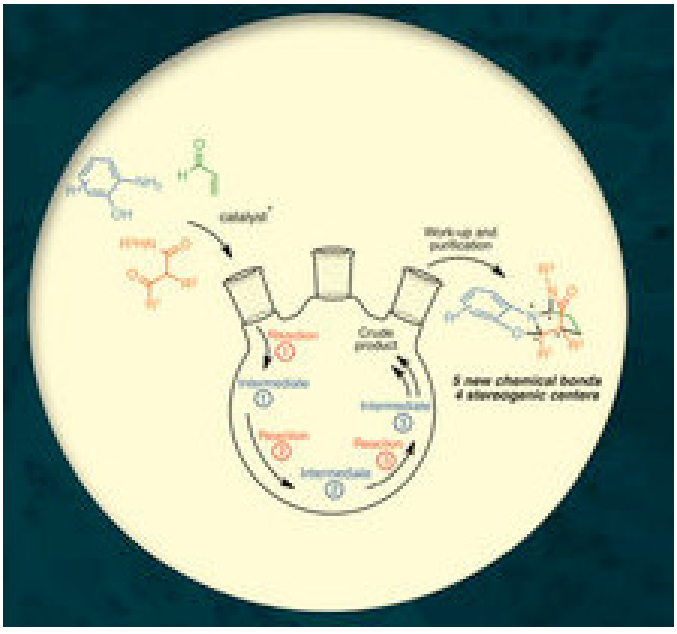
KARNATAKA STATE OPEN UNIVERSITY

Mukthagangotri, Mysore – 570 006

M.Sc. CHEMISTRY

(FOURTH SEMESTER)





Course: MCH T 4.2 Block 1,2,3 and 4

ORGANIC CHEMISTRY-IV

M.Sc. CHEMISTRY

FOURTH SEMESTER

COURSE: MCHT 4.2

ORGANIC CHEMISTRY-IV

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The Registrar
Karnataka State Open University
Mukthagangothri, Mysore - 570 006
Developed by Academic Section, KSOU, Mysore
Karnataka State Open University, 2013

Printed and Published on behalf of Karnataka State Open University. Mysore – 6 by **Registrar (Administration)**

TABLE OF CONTENTS

COURSE INTRODUCTION

. The modern synthetic methodology is concerned with the pathway of organic reactions. In this broad area, various types of significant reactions such as stereoselective, stereospecific, chemoselective, regioselective reactions have been developed. Thus ***block 4.2.2*** *and* ***block 4.2.3*** *are focus to discuss about some important reaction mechanism and novel pathway followed for the modern organic chemistry. An*

expanded discussion of stereochemistry, pericyclic reaction, cyclization reactions were found in ***block 4.2.2*** *and another part like retrosynthetic analysis and its applications were discussed in* ***4.2.3***

The application of these principles in a discussion of modern synthetic methodology (functional group manipulation, carbon–carbon bond formation, retrosynthetic analysis) provides a new organizational framework for understanding many of the most common and most important synthetic reactions

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UNIT-1

Structure

2.0 Objectives of the unit

After studying this unit you are able to

- Explain the different pericyclic reactions
- Write the molecular orbital energy diagram of ethylene molecule
- Write the molecular orbital energy diagram of butadiene molecule
- Write the molecular orbital energy diagram of Hhexatriene molecule
- Explain the electrocyclic reactions
- Explain the stereochemistry of product in thermal electrocyclic reactions
- Explain the stereochemistry of product in photochemical electrocyclic reactions
- Write the Woodward Hoffmann rules of electrocyclic reactions

1.1 Introduction

Most organic reactions occur in several steps. These steps constitute the reaction mechanism and involve either intermediates or polar transition states or free radicals. But, there are some reactions in organic chemistry that give no evidence of involving intermediates when they are subjected to the usual probes for studying mechanisms. Highly polar transition states do not seem to be involved, since the rates of the reactions are not affected with the change in the polarity of the solvent used. The reaction rates are also insensitive to the presence of inhibitor or initiators in free radical reactions. Efforts on to detect free radical intermediates by physical or chemical means are not successful. This lack of evidence for the existence of intermediates leads to the conclusion that, the reactions are single step processes in which bond making and bond breaking both contribute to the structure of transition state. Such processes are called *concerted reactions*. The word concerted specifies that, there is a single transition state and is characterized as a change in the bonding relationship that takes place as a continuous reorganization of the electrons.

1.2 Pericyclic reactions

In organic chemistry, a pericyclic reaction is a type of organic reaction wherein the transition state of the molecule has a cyclic geometry, and the reaction progresses in a concerted fashion. Pericyclic reactions are usually rearrangement reactions. The major classes of pericyclic reactions are

i) Electrocyclic reactions
ii) Sigmatropic reactions
iii) Cycloaddition reactions and
iv) Cheletropic reactions.

In general, these are considered to be equilibrium processes, although it is possible to push the reaction in one direction by designing a reaction by which the product is at a significantly lower

energy level. This is due to a unimolecular interpretation of Le Chatelier's principle. Pericyclic reactions often have related stepwise radical processes associated with them. Some pericyclic reactions, such as the [2+2] cycloaddition, are 'controversial' because their mechanism is not definitively known to be concerted (or may depend on the reactive system). Pericyclic reactions also often have metal-catalyzed analogs, although usually these are also not technically pericyclic, since they proceed via metal-stabilized intermediates, and therefore are not concerted. The present understanding of the mechanism of pericyclic reactions is mainly due to the ingenious work of Woodward and Hoffmann. They recognized that the pathways of such reactions were determined by the symmetry properties of the orbitals that are directly involved and that the symmetry of each participating orbital must be conserved during the concerted process.

Before going to study the different pericyclic reaction, it is necessary to understand molecular orbital symmetry of the alkenes.

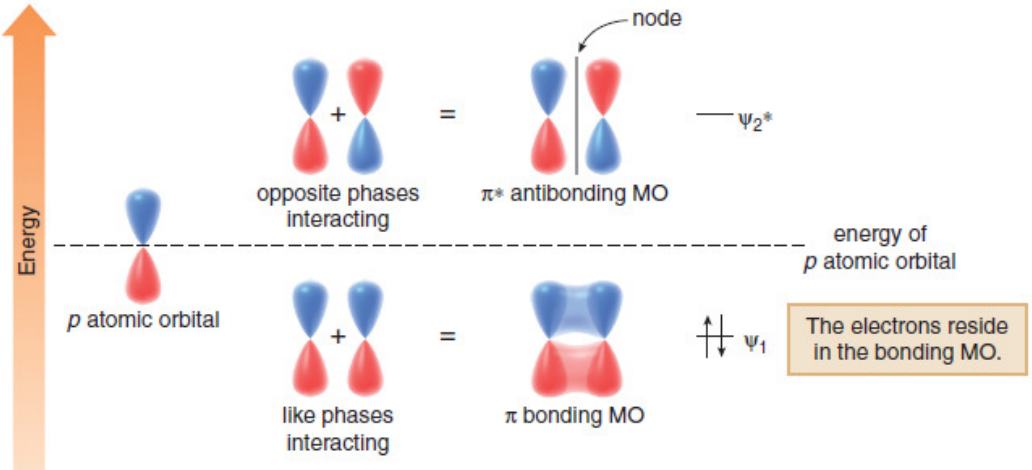
1.3 Background on molecular orbitals

We are familiar about molecular orbital (MO) theory, which describes bonds as the mathematical combination of atomic orbitals that forms a new set of orbitals called molecular orbitals (MOs). The number of atomic orbitals used equals the number of molecular orbitals formed.

Since pericyclic reactions involve π bonds, let's examine the molecular orbitals that result from p orbital overlap in ethylene, 1,3-butadiene, and 1,3,5-hexatriene, molecules that contain one, two, and three π bonds, respectively. It is important to note here that the two lobes of a p orbital are opposite in phase, with a node of electron density at the nucleus.

1.3.1Ethylene molecule

In ethylene (CH_2=CH_2) molecule, the π bond in is formed by side-by-side overlap of two p orbitals on adjacent carbons. These two p orbitals can combine in two different ways as illustrated below.



π-bonding molecular orbital (designated as ψ_1) is formed when two p orbitals of similar phase overlap. The resulting MO has lower in energy compare to individual p-atomic orbitals and called

bonding molecular orbital (BMO). Hence two electrons occupy in this lower-energy bonding molecular orbital. Similarly an antibonding molecular orbital π* (designated as ψ_2^*) is formed when two p orbitals of opposite phases combine each other. Resulting antibounding molecular orbtital has higher energy compare to individual p-atomic orbitals. A destabilizing node occurs when two orbitals of opposite phase combine.

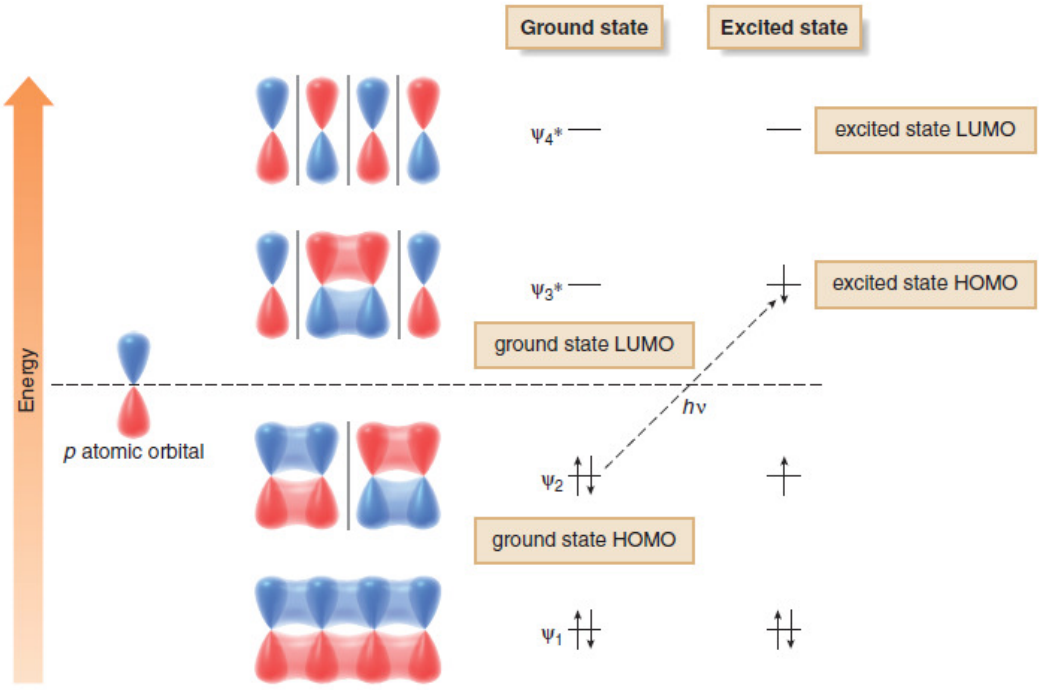
1.3.2 Butadiene molecule

The two π bonds of 1,3-butadiene (CH_2=CH-CH=CH_2) are formed by overlap of four p orbitals on four adjacent carbons. As illustrated below four p orbitals can combine in four different ways to form four molecular orbitals designated as ψ_1 ψ_2 ψ_3 and ψ_4. Among four MO, ψ_1 and ψ_2 are bonding molecular orbitals and ψ_3^* and ψ_4^* are antibonding molecular orbitals.

The two bonding MOs are lower in energy than the p orbitals from which they are formed, whereas the two antibounding MOs are higher in energy than the p orbitals from which they are formed.

In the ground-state electronic arrangement, the four π electrons occupy the two bonding molecular orbitals.

The highest energy orbital that contains electrons is called the highest occupied molecular orbital (HOMO). In the ground state of 1,3-butadiene, ψ_2 is the HOMO. The lowest energy orbital that contains no electrons is called the lowest unoccupied molecular orbital (LUMO). In the ground state of 1,3-butadiene, ψ_3* is the LUMO.



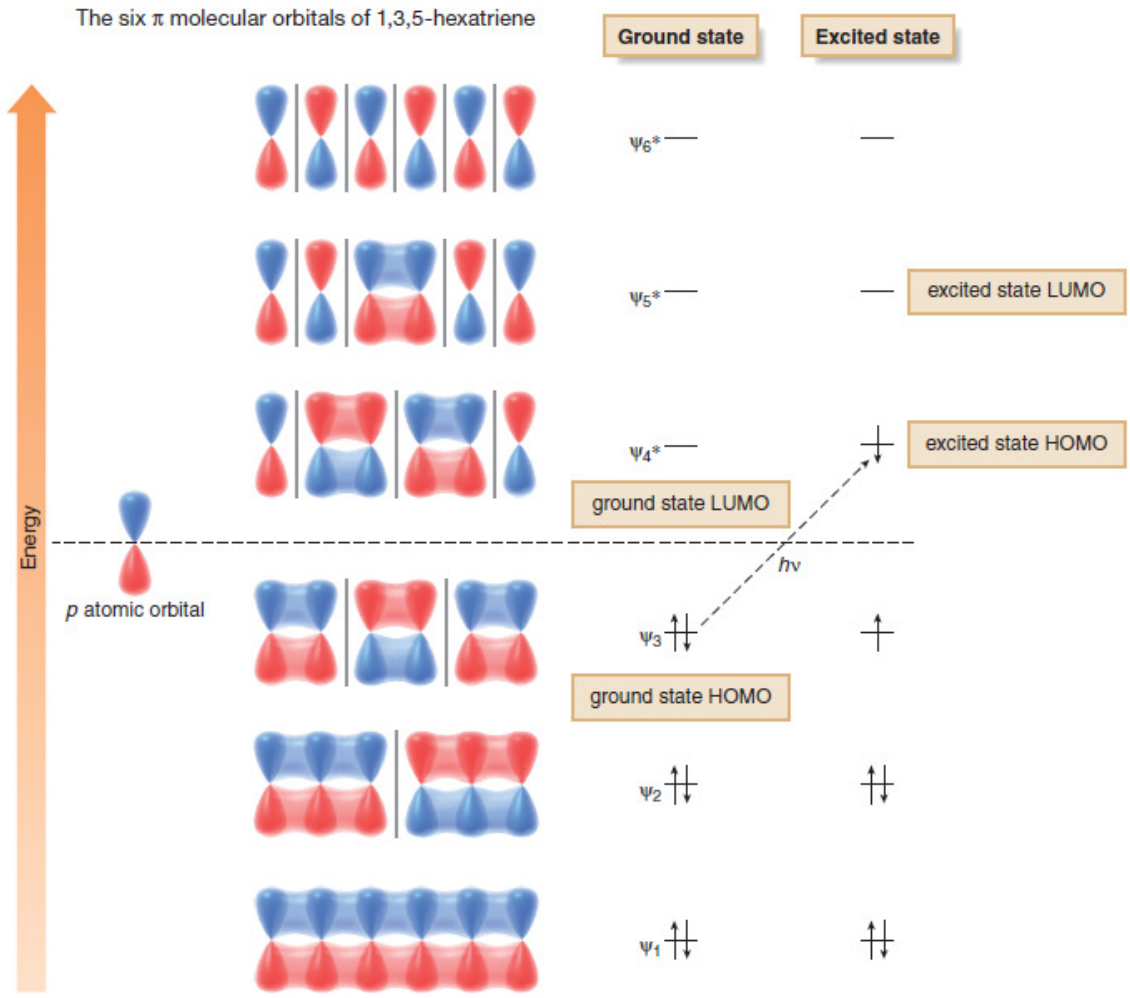
Under the thermal condition reactants utilize their ground state electronic configuration i,e, ψ_2. When 1,3-butadiene absorbs light of appropriate energy, an electron is promoted from ψ_2 (the

HOMO) to ψ_3^* (the LUMO) to form a higher energy electronic configuration, this is called the excited state. In the excited state, the HOMO is now ψ_3^*. Thus in the photochemical reactions, the reactant is in its excited state as a result, the HOMO is ψ_3^* and the LUMO is ψ_4^* for 1,3-butadiene. All conjugated dienes can be described by a set of molecular orbitals that are similar to those illustrated in above figure for 1,3-butadiene.

1.3.3 Hexatriene molecule

The three π bonds of 1,3,5-hexatriene (CH_2=CH–CH=CH–CH=CH_2) are formed by overlap of six p orbitals on six adjacent carbons. As illustrated in below diagram, the six p orbitals can combine in six different ways to form six molecular orbitals designated as ψ_1, ψ_2, ψ_3, ψ_4, ψ_5 and ψ_6. Among them ψ_1, ψ_2 and ψ_3 are bonding molecular orbitals and ψ_4^*, ψ_5^* and ψ_6^* are antibonding molecular orbitals. In the ground state electronic configuration, the six " electrons occupy the three bonding MOs, hence ψ_3 is the HOMO, and ψ_4^* is the LUMO.

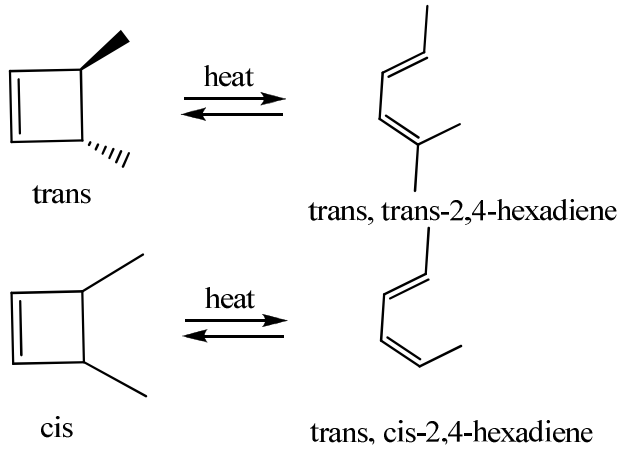
In the excited state, which results from electron promotion from ψ_3^* to ψ_4^*, now ψ_4^* is the HOMO and ψ_5^* is the LUMO.



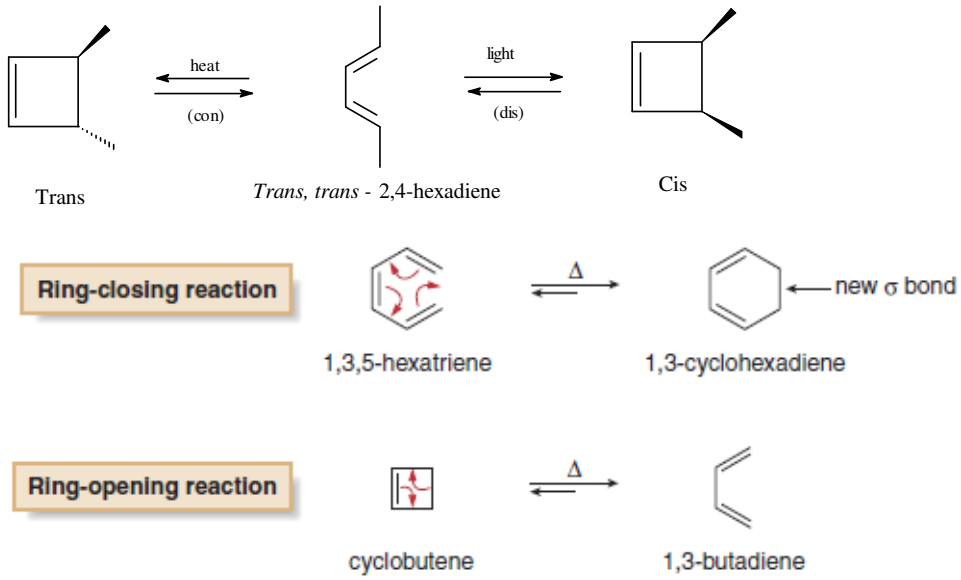
1.4 Electrocyclic reactions

An electrocyclic reaction is a reversible reaction that involves ring closure of a conjugated polyene to a cycloalkene, or ring opening of a cycloalkene to a conjugated polyene.

Under the influence of heat or light, a conjugated polyene can undergo isomerization to form a cyclic compound with the formation of a σ-bond between the ends of a linear polyene. In the process one double bond disappears and the remaining double bonds shift their positions.



The reverse process can also take place i.e., a σ-bond of a cyclic compound is broken to yield a conjugated polyenes. Such interconversions are called electrocyclic reactions, because the closure or the opening involves the movement of electrons and no atoms are gained or lost.



To draw the product in each reaction, use the curved arrows and begin at a π bond. Move the π electrons to an adjacent carbon–carbon bond and continue in a cyclic fashion. In a ring-forming reaction, this process forms a new σ bond that now joins the ends of the conjugated polyene. In a ring-opening reaction, this process breaks a σ bond to form a conjugated polyene with one more π bond.

Whether the reactant or product predominates at equilibrium depends on the ring size of the cyclic compound. Generally, a six-membered ring is favored over an acyclic triene at equilibrium. In contrast, an acyclic diene is favored over a strained four-membered ring. Thus if the π-system of the open chain partner contains kπ electrons, the cyclic partner contains (k-2)π electrons and an additional σ-bond. These reactions are usually categorized by the following criteria

i) Reactions can be either photochemical or thermal

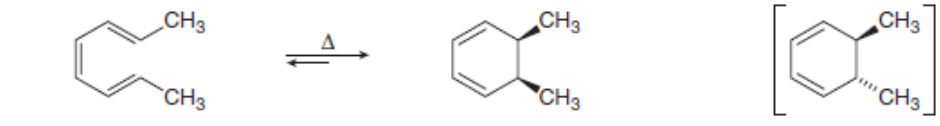
ii) Reactions can be either ring-opening or ring-closing (**electrocyclization**)

iii) Depending on the type of reaction (photochemical or thermal) and the number of pi electrons, the reaction can happen through either a conrotatory (rotation of both bonds in same direction) or disrotatory (rotation of both bonds in opposite direction) mechanism and

iv) The type of rotation determines whether the *cis* or *trans* isomer of the product will be formed.

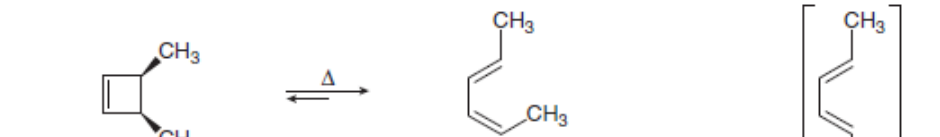
1.5 Stereochemistry and Orbital symmetry

Electrocyclic reactions are completely stereospecific. For example, ring closure of (2*E*,4*Z*,6*E*)-2,4,6-octatriene yields a single product with cis methyl groups on the ring. Also ring opening of cis-3,4-dimethylcyclobutene forms a single conjugated diene with one *Z* alkene and one *E* alkene.



(2*E*,4*Z*,6*E*)-2,4,6-octatriene *cis*-5,6-dimethyl-1,3-cyclohexadiene NOT formed

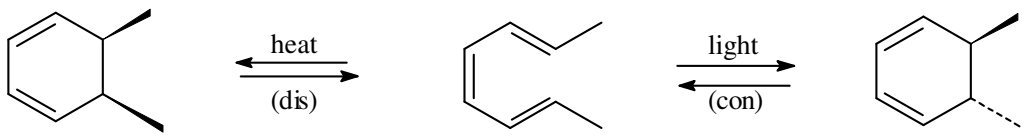
cis product only



cis-3,4-dimethylcyclobutene (2*E*,4*Z*)-2,4-hexadiene NOT formed

(2*E*,4*Z*) diene only

Another classic example is the thermal ring-opening reaction of 3,4-dimethylcyclobutene. The *cis isomer* exclusively yields *cis, trans-2, and 4-hexadiene* whereas the *trans* isomer gives the *trans*, *trans* diene. The main interest of these reactions is completely stereo selective and stereo specific.



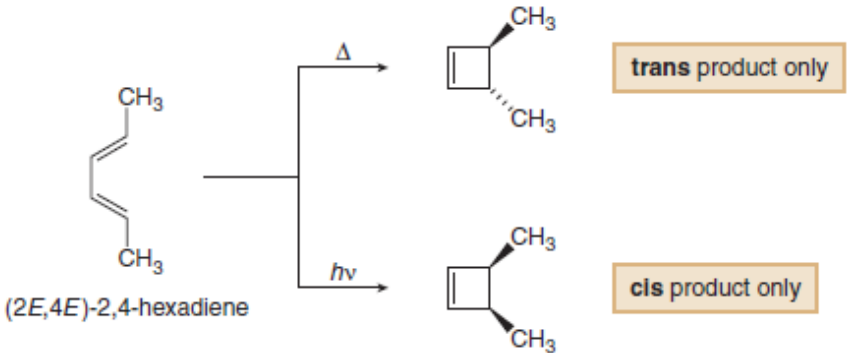
Cis Trans,cis,trans-2,4,6-octatriene Trans

What we notice here is stereochemistry of *trans*-cyclohexadiene is opposite to that of diene-cyclobutadiene system. Stereochemical formation of the product depends upon

i) The number of π electrons and

ii) Whether it is photochemical or thermal.

The stereochemistry of the product of an electrocyclic reaction depends on whether the reaction is carried out under thermal or photochemical reaction conditions. i,e, with heat or light, respectively. Cyclization of (2*E*,4*E*)-2,4-hexadiene with heat forms a cyclobutene with trans methyl groups, whereas cyclization with light forms a cyclobutene with cis methyl groups.

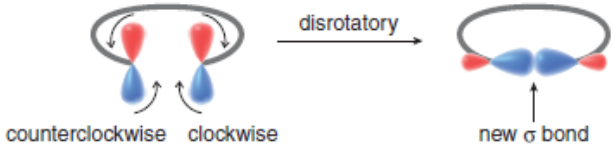


To understand these results, we must focus on the HOMO of the acyclic conjugated polyene that is either the reactant or product in an electrocyclic reaction. In particular, we must examine the p orbitals on the terminal carbons of the HOMO, and determine whether like phases of the orbitals are on the same side or on opposite sides of the molecule.

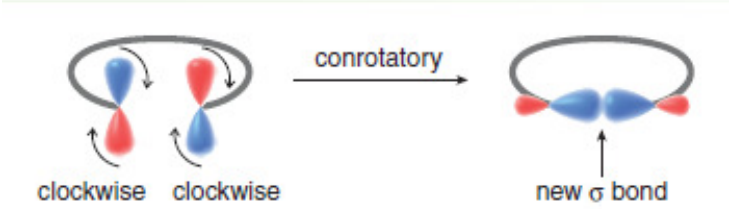
An electrocyclic reaction occurs only when like phases of orbitals can overlap to form a bond. Such a reaction is symmetry allowed. Similarly electrocyclic reaction cannot occur between orbitals of opposite phase. Such a reaction is symmetry forbidden.

To form a bond, the p orbitals on the terminal carbons must rotate so that like phases can interact to form the new σ bond. Two modes of rotation are possible they are described as follows,

When like phases of the p orbitals are on the same side of the molecule, the two orbitals must rotate in opposite directions, one clockwise and one counterclockwise. This type of rotation in opposite directions is said to be disrotatory.



When like phases of the p orbitals are on opposite sides of the molecule, the two orbitals must rotate in the same direction, both clockwise or both counterclockwise. This type of rotation in the same direction is said to be conrotatory.

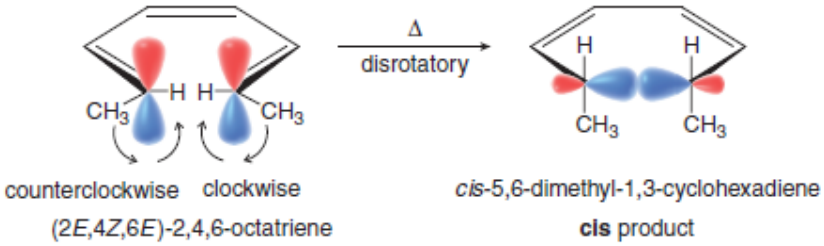


1.6 Thermal electrocyclic reactions or electrochemical reactions under thermal conditions

In order to explain the observed stereochemistry in electrocyclic reactions, first we must examine the symmetry of the molecular orbital that contains the most loosely held π electrons. In a thermal reaction condition, the HOMO of the ground state electronic configuration is considering. As already explain the rotation occurs in a disrotatory or conrotatory fashion so that like phases of the p orbitals on the terminal carbons of this molecular orbital combine. The number of double bonds in the conjugated polyene determines whether rotation is conrotatory or disrotatory.

The following two examples illustrate different outcomes in thermal condition.

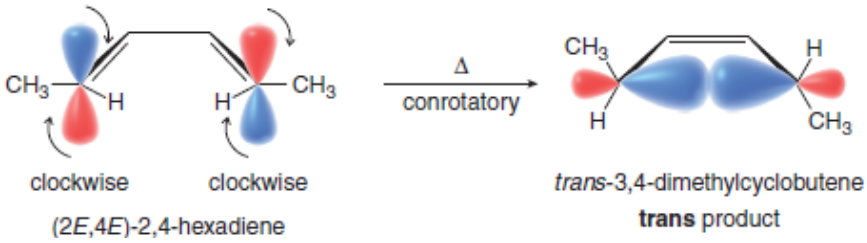
Thermal electrocyclic ring closure of (2*E*,4*Z*,6*E*)-2,4,6-octatriene yields a single product with cis methyl groups on the ring.



Cyclization occurs in a disrotatory fashion because the HOMO of a conjugated triene has like phases of the outermost p orbitals on the same side of the molecule. A disrotatory ring closure is symmetry allowed because like phases of the p orbitals overlap to form the new σ bond of the ring. In the disrotatory ring closure, both methyl groups are pushed down (or up), making them cis in the product.

This is a specific example of the general process observed for conjugated polyenes with an odd number of π bonds. *Thus the HOMO of a conjugated polyene with an odd number of π bonds has like phases of the outermost p orbitals on the same side of the molecule. As a result thermal electrocyclic reactions occur in a disrotatory fashion for a conjugated polyene with an odd number of π bonds.*

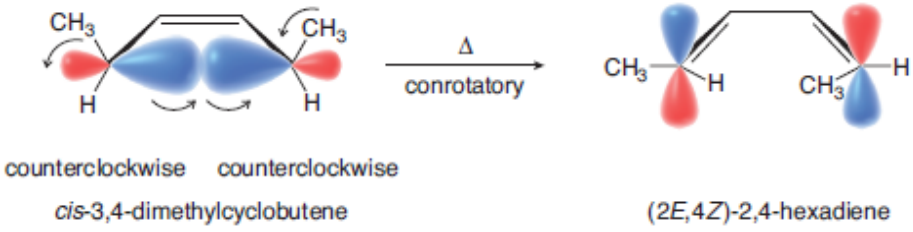
In contrast, thermal electrocyclic ring closure of (2*E*,4*E*)-2,4-hexadiene forms a cyclobutene with trans methyl groups.



Cyclization occurs in a conrotatory fashion because the HOMO of a conjugated diene has like phases of the outermost p orbitals on opposite sides of the molecule. A conrotatory ring closure is symmetry allowed because like phases of the p orbitals overlap to form the new σ bond of the ring. In the conrotatory ring closure, one methyl group is pushed down and one methyl group is pushed up, making them trans in the product.

This is a specific example of the general process observed for conjugated polyenes with an even number of π bonds. *The HOMO of a conjugated polyene with an even number of π bonds has like phases of the outermost p orbitals on opposite sides of the molecule. As a result the thermal electrocyclic reactions occur in a conrotatory fashion for a conjugated polyene with an even number of π bonds.*

Since electrocyclic reactions are reversible, electrocyclic ring-opening reactions follow the same rules as electrocyclic ring closures. Thus, thermal ring opening of cis-3,4-dimethylcyclobutene which ring opens to a diene with an even number of π bonds occurs in a conrotatory fashion to form (2*E*,4*Z*)-2,4-hexadiene as the only product.

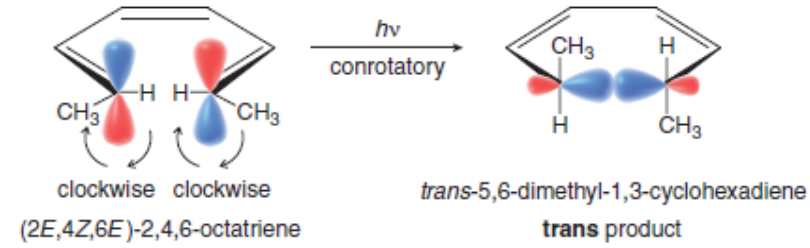


1.7 Photochemical Electrocyclic Reactions or electrochemical reactions under phtochemical conditions

Photochemical electrocyclic reactions follow similar principles as in thermal reactions with one important difference. In photochemical reactions, we must consider the orbitals of the HOMO of the excited state to determine the course of the reaction.

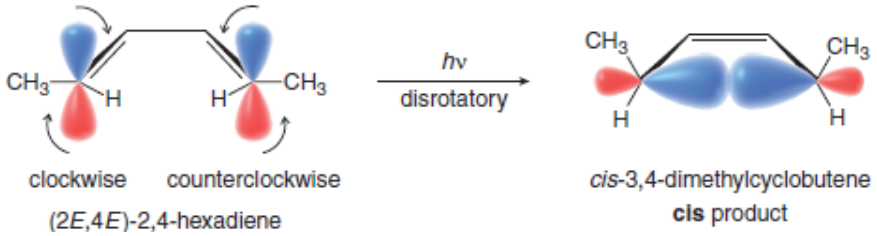
The excited state HOMO has the opposite orientation of the outermost p orbitals compared to the HOMO of the ground state. As a result, the method of ring closure of a photochemical electrocyclic reaction is opposite to that of a thermal electrocyclic reaction for the same number of π bonds.

Photochemical electrocyclic ring closure of (2*E*,4*Z*,6*E*)-2,4,6-octatriene yields a cyclic product with trans methyl groups on the ring.



Cyclization occurs in a conrotatory fashion because the excited state HOMO of a conjugated triene has like phases of the outermost p orbitals on the opposite sides of the molecule. In the conrotatory ring closure, one methyl group is pushed down and one methyl group is pushed up, making them trans in the product. This is a specific example of the general process observed for conjugated polyenes with an odd number of π bonds. *Thus photochemical electrocyclic reactions occur in a conrotatory fashion for a conjugated polyene with an odd number of π bonds*.

Photochemical electrocyclic ring closure of (2*E*,4*E*)-2,4-hexadiene forms a cyclobutene with cis methyl groups.



Cyclization occurs in a disrotatory fashion because the excited state HOMO of a conjugated diene has like phases of the outermost p orbitals on the same side of the molecule. In the disrotatory ring closure, both methyl groups are pushed down (or up), making them cis in the product. This is a specific example of the general process observed for conjugated polyenes with an even number of π bonds. *Thus photochemical electrocyclic reactions occur in a disrotatory fashion for a conjugated polyene with an even number of π bonds.*

The analysis of this class of reactions for conservation of orbital symmetry will be dealt with three levels of sophistication,

a) A Frontier Orbital approach (FMO),

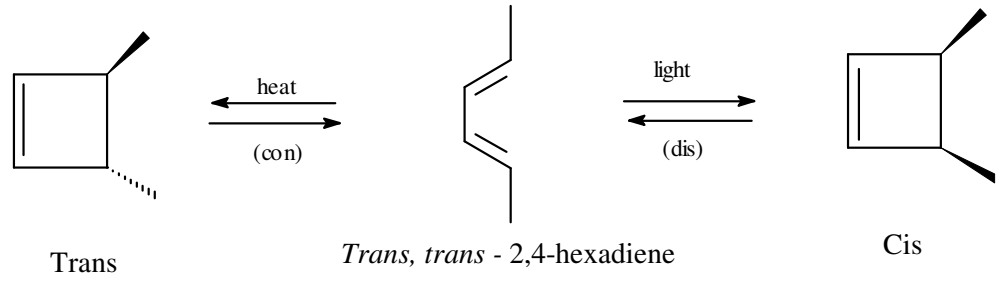
b) Using Orbital Correlation Diagrams and

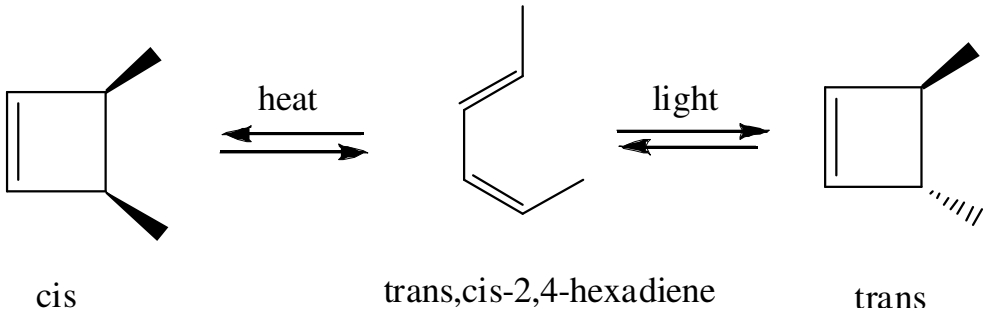
c) Using Mobius method.

1.8 Orbital symmetry analysis of electrocyclization reaction [Frontier Orbital approach (FMO)]

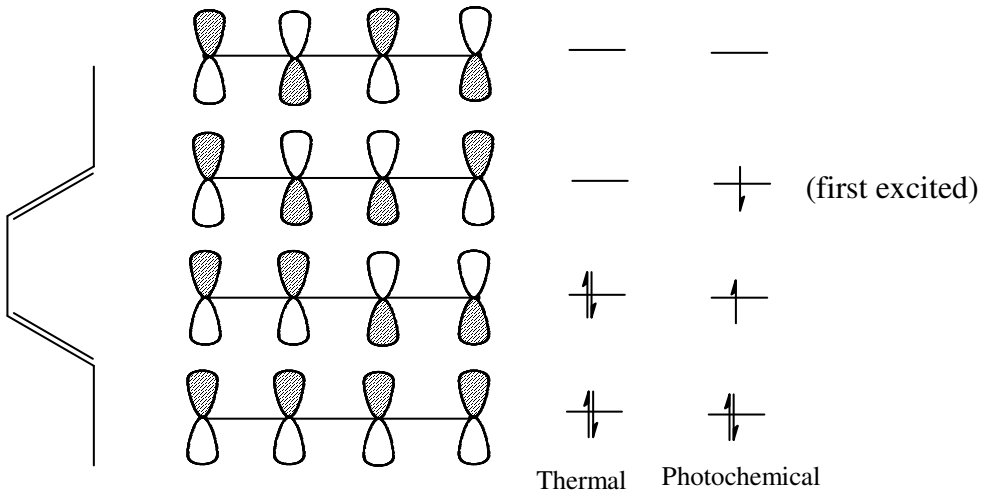
This approach considers only the molecular orbital of highest energy which contains electrons (the Frontier Orbital) and allows the fate of the electrons in this orbital during chemical change cf. simple picture of the reactions of atoms where only the outer shell (valence) electrons of atoms are considered to be involved. In both contexts, these electrons are those of highest energy and therefore are most easily reorganised. Thus for thermal cyclization, HOMO in the ground state is considered and for photochemical cyclization, HOMO of first excited state is considered.

During electrolytic ring-opening as well as elctrocyclic ring closure of a polyene system, there are two possibilities due to symmetry of the system. The one possibility may be disallowed on account of molecular geometry or steric factor operational during transition state. Let us first consider the ring closure of trans, trans-2, 4-hexadiene [4nπ system].





Electronic configuration of phase diagram of butadiene is-

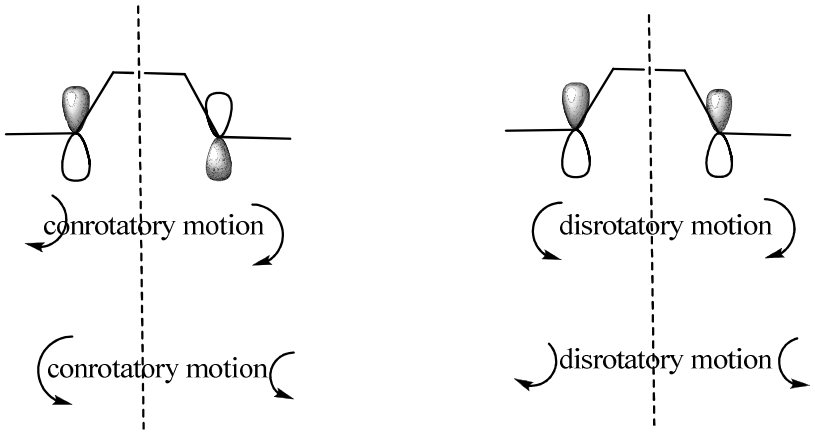


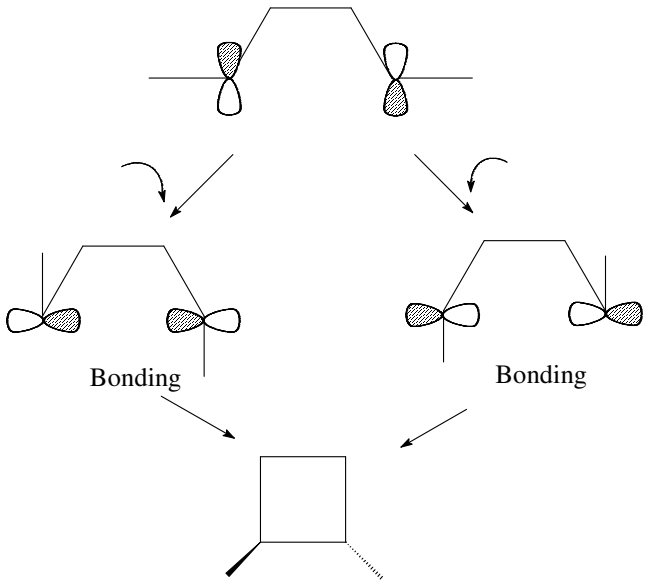
In the thermal isomerisation of butadiene to cyclobutene, a σ-bond is formed between $C_{(1)}$ and $C_{(4)}$ of butadiene. Initially the substituent i.e. hydrogen at $C_{(1)}$ and $C_{(4)}$ of the diene lie in the plane of the carbon atoms where as in the cyclised product, the same substituent lie above and below the plane of the carbon atoms. This transformation is achieved by rotation about $C_{(1)}$, $C_{(2)}$ & $C_{(3)}$, $C_{(4)}$ bonds of the diene.

Moreover, consider the phase diagram of ψ_2 – HOMO ground state. During the cyclization of butadiene to cyclobutene, a σ-bond is formed. The bond could be formed by the overlap of orbitals on $C_{(1)}$ and $C_{(4)}$. This process changes $C_{(1)}$ and $C_{(4)}$ from sp^2 to sp^3 hybrid state. Thus for cyclization, rotation about these bonds is necessary. The rotation could be in two ways

i) Rotation of both bonds in the same direction – **conrotation**

ii) Rotation of both bonds in the opposite direction – **disrotation**

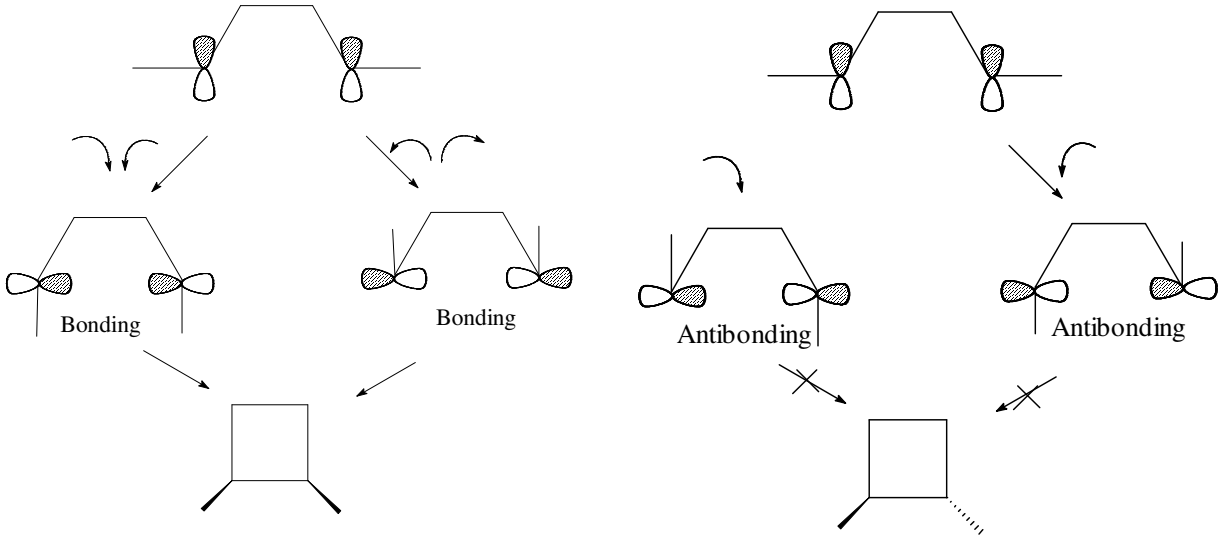




Thus rotation of ψ_2 in butadiene leads to formation of σ-bond in cyclobutene. Thus bonding electrons in butadiene are transformed into two bonding electrons in cyclobutene. Disrotatory

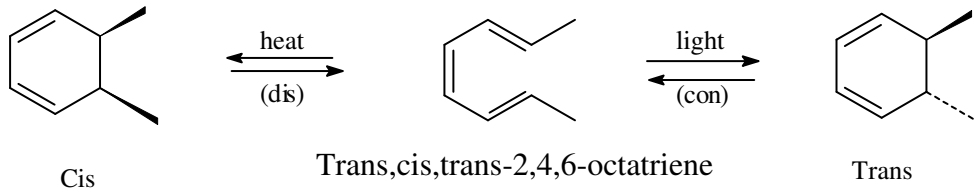
rotation of ψ_2 in butadiene places the bonding electrons into antibonding (σ^*) electrons. In this way for thermal transformation conrotatory process is allowed for butadiene-cyclobutene.

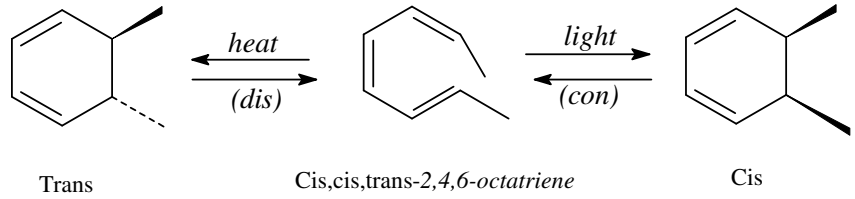
Let us consider the photochemical isomerisation of 1, 3-butadiene to cyclobutene. Here the first excited state is involved and HOMO is the first excited state of butadiene i.e. ψ_3. Now let us analyze whether condolatory process favours the reaction or derogatory.



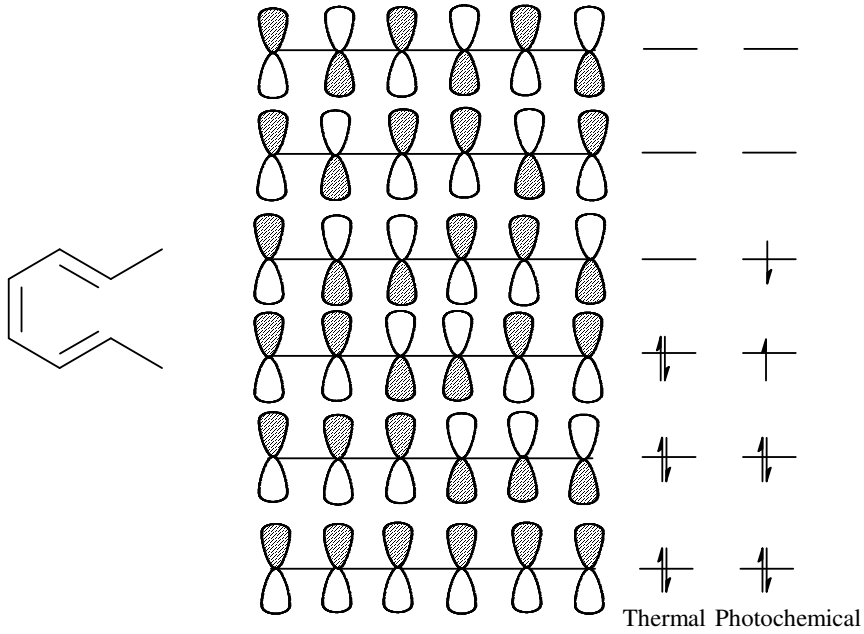
From the above figures it is clear that under photochemical condition, elctrocyclization of butadiene system goes via disrotatory motion while it is conrotatory motion under thermal condition.

Let us first consider the ring closure of trans,trans-2,4,6-octatriene [(4n+2)π system].

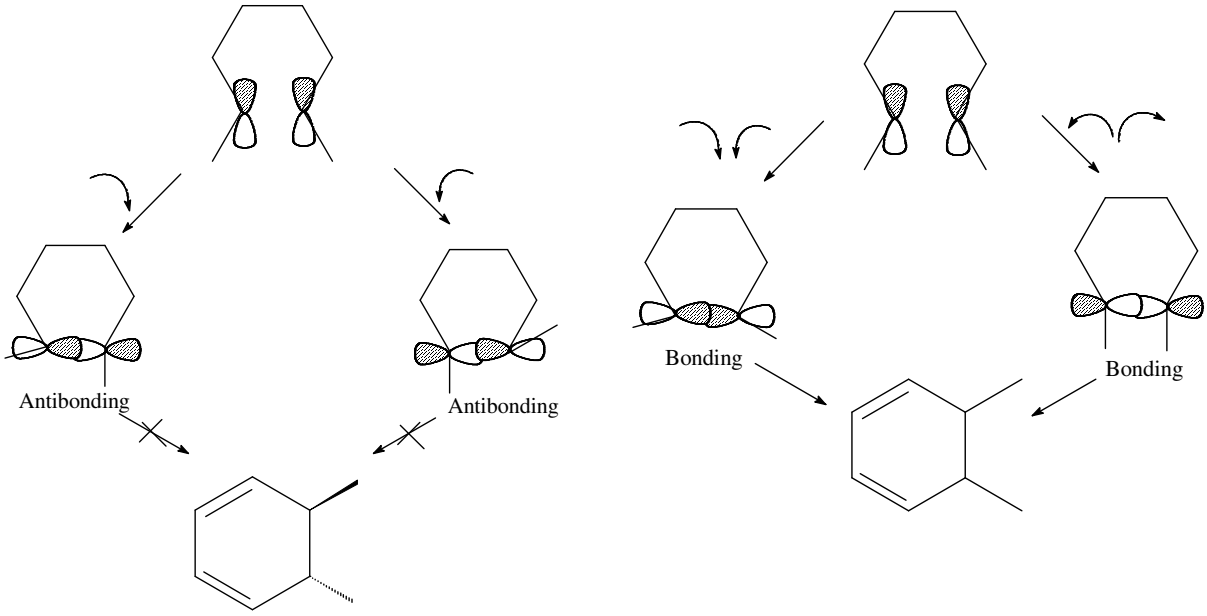




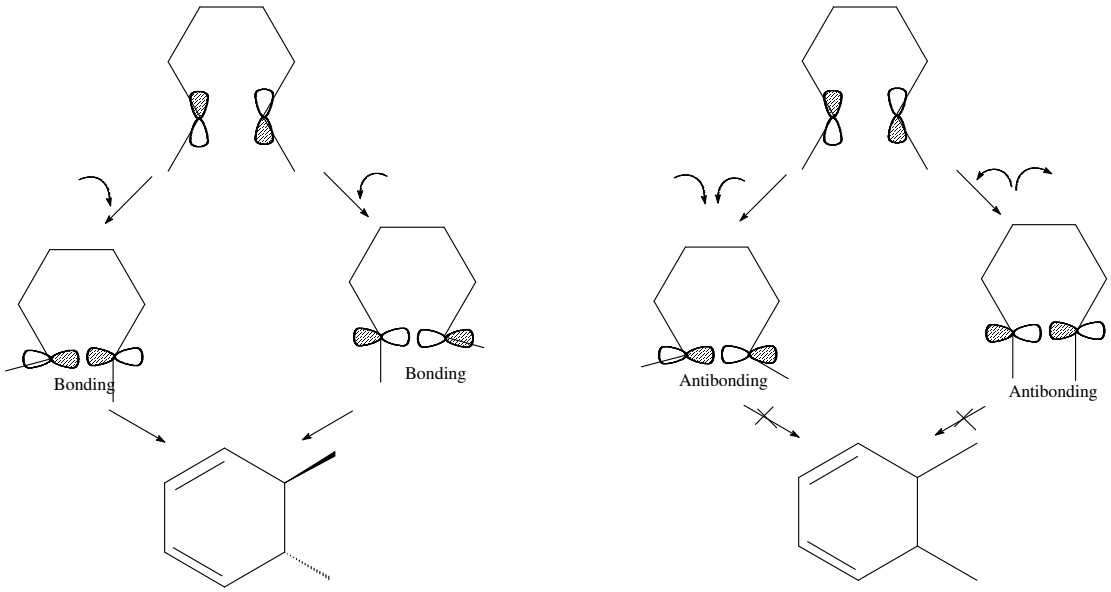
The figure below shows the molecular orbitals of hexatriene.



In case of hexatriene, under thermal condition, ψ_3 will be the HOMO orbital.

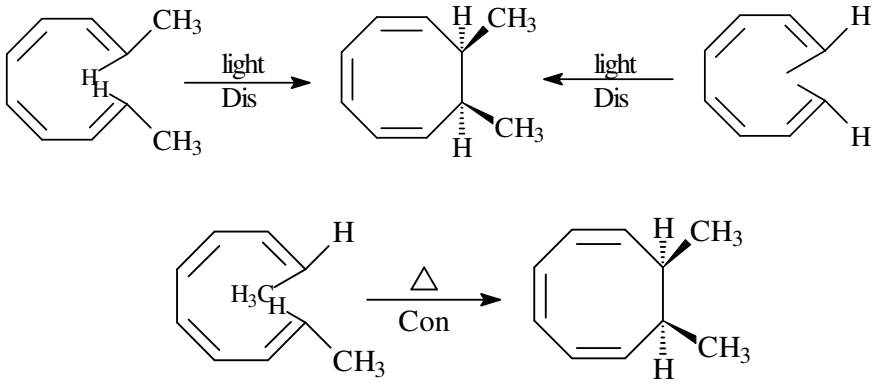


In case of hexatriene, under photochemical condition, ψ_4 will be the HOMO orbital.



From the above figures it is clear that under photochemical condition, elctrocyclization of hexatriene system goes via conrotatory motion while it is disrotatoory motion under thermal condition.

After determining the type of rotation, whether the product will be *cis* or *trans* can be determined by examining the starting molecule. In the example below, the disrotation causes both methyl's to point upwards, causing the product to be **cis**-dimethylcyclohexadiene.



1.9 Woodward Hoffmann rules of electrocyclic reactions

Table below summarizes the rules, often called the Woodward–Hoffmann rules, for electrocyclic reactions under thermal or photochemical reaction conditions. The number of π bonds refers to the acyclic conjugated polyene that is either the reactant or product of an electrocyclic reaction.

π electrons	Thermal	Photochemical
2	Dis	Con
4	Con	Dis
6	Dis	Con

A general form of the selection rules for electorcyclizations are given below

1. Thermal electrocyclic reactions involving 4n electrons proceed in a conrotatory fashion
2. Thermal electrocyclic reactions involving 4n+2 electrons proceed in a disrotatory fashion
3. Photochemical electrocyclic reactions involving 4n electrons proceed in a disrotatory fashion
4. Photochemical electrocyclic reactions involving 4n+2 electrons proceed in a conrotatory fashion

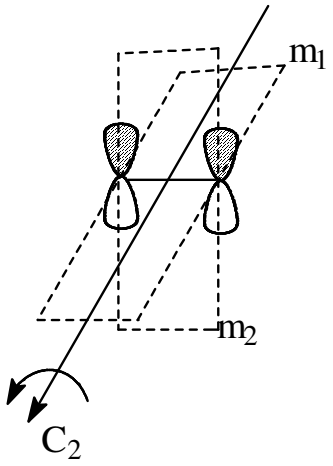
Concerted thermal or photochemical reactions follow the above general rule and are known as Woodward-Hoffmann rules of electrocyclic reactions.

1.10 Correlation diagram method

This is more rigorous method than FMO method but arrives at the same conclusion. In FMO method, only one MO's of the polyene is involved i.e. ground state molecular orbital or first excited state MO depending upon whether the reaction in question is a thermal or a photochemical one. But correlation diagram method considers the MO of the polyene as well as that of the product. Thus it makes it possible to known which orbital of the reactant give rise to which orbital of the product. Such a reaction is known as correlation diagram. This depends upon the consideration of basic chemistry of the product and the reactant orbital. The basic principle therefore is no change in the symmetry of orbitals moving from reactant to product and vice-versa. Therefore it must take place with consideration of orbital symmetry. In order to determine if orbital symmetry is conserved during a reaction we have to examine the symmetry properties of all the molecular orbitals in the reaction with respect to the element of symmetry present in the geometrical change.

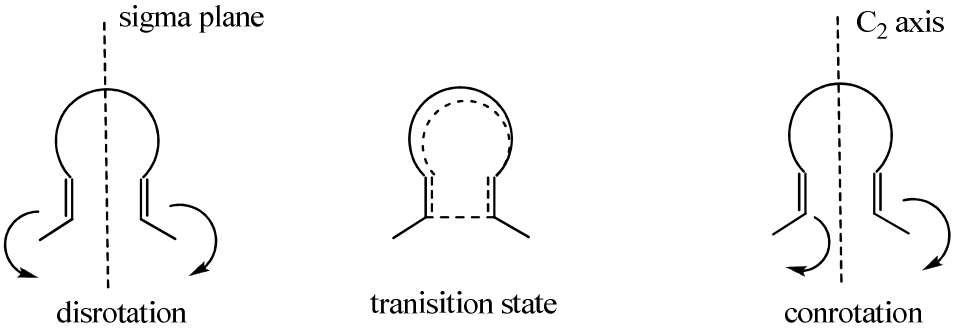
1.11 Symmetry of orbitals

All planar π-systems have a plane symmetry (m_1) bisecting the p-orbitals (the nodal plane) about which are antisymmetric. Another plane, m_2, which is perpendicular to C-C bond and a two fold axis C_2, running through the C-C bond and perpendicular to it.



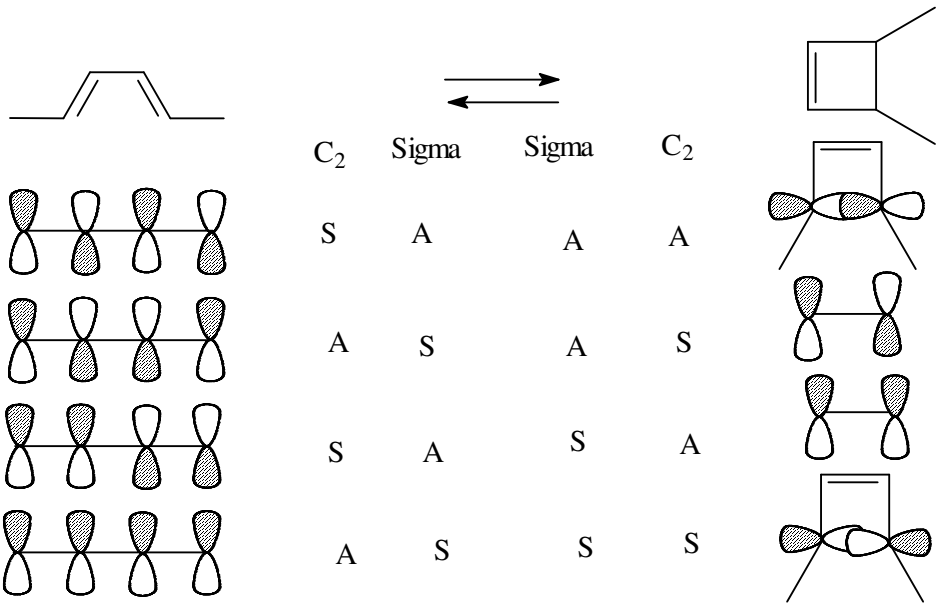
π-Orbital is symmetric (S) with respect to m_2 and π* is antisymmetric (A). On the other hand, if the twofold axis is taken as the element of symmetry, π is antisymmetric and π* is symmetric. Thus the element of symmetry must be specified when orbital are classified as symmetric or antisymmetric.

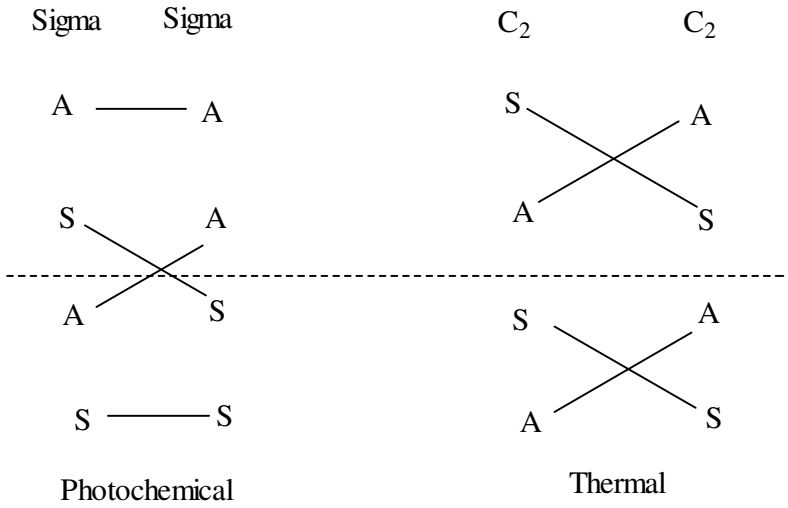
We know that electrocyclic reaction takes place either by disrotatory or by conrotatory process. Now we have to see which symmetry i.e., σ or C_2 is maintained throughout. For this we have to inspect the transition state.



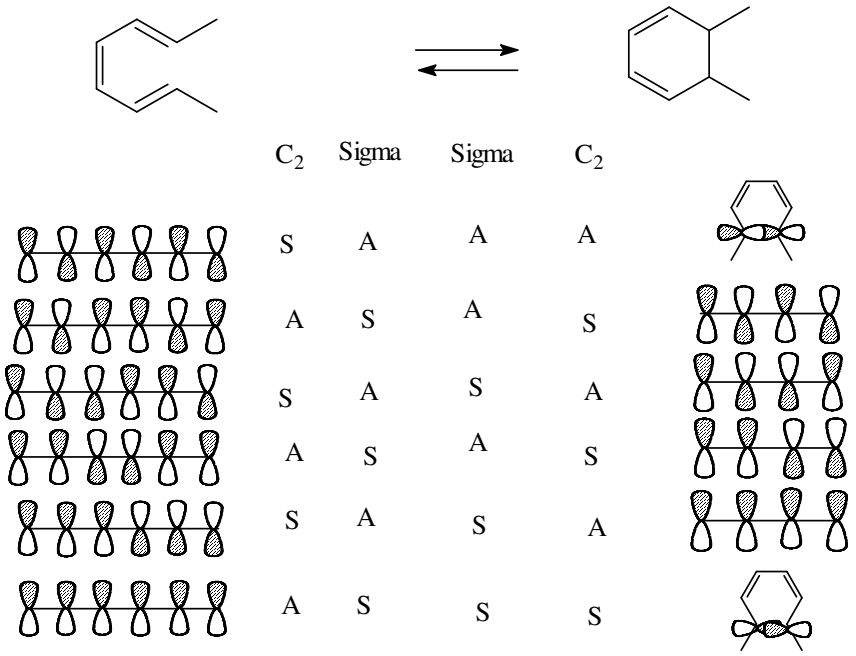
For a disrotatory process, we have to consider σ plane of symmetry is to be considered for correlating and for a conrotatory process C_2 axis of symmetry has to be considered. For a thermal reaction, ground state of reactant should correlate with ground state of product. Similarly for photochemical reaction, first excited state should correlate with first excited state of the product.

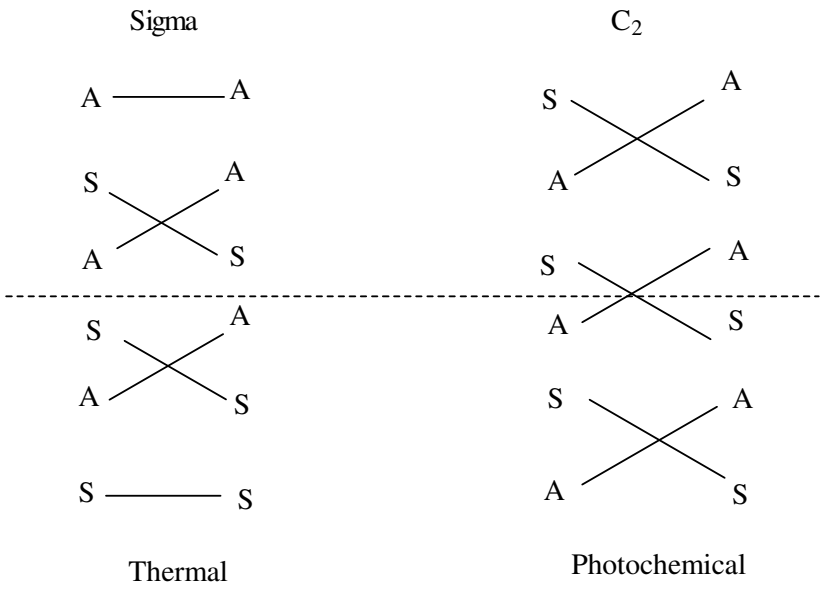
Let us consider the cyclobutane-butadiene system.





Consider the disrotation of cyclobutene to butadiene. A plane of symmetry (σ) is maintained throughout the course of the reaction. In a concerted reaction, it is required that orbital symmetry is conserved throughout. This means that symmetric orbital in the starting material must transform into a symmetry orbital in the product and that an assymmetric orbital must transform into an antisymmetric orbital. Cyclobutene σ, π and π* correlate with the first excited state of butadiene ψ_1, ψ_3 and ψ_2 respectively. The disrotatory process is photochemically allowed (in either direction). Now consider the conrotatory conversion of cyclobutene to butadiene in which C_2 axis symmetry is maintained. The orbitals now correlate in such a way that ground state of cyclobutene σ and π correlates with ground state of butadiene ψ_1 and ψ_2 respectively. The thermal conrotatory is thus allowed in either direction. The first excited state of cyclobutene relates with an upper excited state of butadiene. The photochemical conrotatory opening is thus forbidden. A similar argument shows that the photochemical conrotatory closure of butadiene is also forbidden.





The correlation diagram shows why orbital symmetry controls the sterochemical course of concerted reactions, but they require some little time to construct. We now turn to simple method for making rapid predictions. The approach is based on the postulate that the stereochemistry of an electrocyclization process is determined by the symmetry of the highest occupied molecular orbital (HOMO) of the open chain partner. If the HOMO has the plane of symmetry, the process will be disrotatory. If the HOMO has the C2 axis of symmetry, the process will be conrotatory. The reasons behind this rule can be understand by recalling that overlap of wave function of the same sign is bonding, whereas overlap of wave function of opposite sign is antibonding.

1.12 Summary of the unit

Pericyclic reactions are concerted reactions that proceed via a cyclic transition state. There is no distinct intermediates are isolated or identified in the course of reaction. In pericyclic reactions bond forming and bond breaking steps are simultaneous but not necessarily synchronous. The pericyclic reactions are classified as

1. Electrocyclic ring closing and ring opening reaction
2. Cycloaddition and Cycloreversion reaction
3. Sigmatropic Rearrangements
4. Chelotropic Reaction
5. Group transfer Reaction

Following methods are useful for analyzing pericyclic reaction

1. Orbital symmetry correlation method (Woodward, Hoffmann, Longuet-Higgins and Abrahamson)
2. The frontier orbital method (Woodward, Hoffmann and Fukui)
3. Transition state aromaticity method (Dewar and Zimmerman)

Woodward-Hoffmann rules predicts the allowedness or otherwise of pericyclic reactions under thermal and photo- chemical conditions using the above methods. Therefore a basic understanding of molecular orbitals of conjugated polyene systems and their symmetry properties is essential to apply the above methods.

These steps are followed for constructing MO diagram of polyene systems

1. Although there are C-C and C-H sigma bonds present in the molecule, the π MOs can be constructed independently of them. Although there may be a change in the hybridization of carbon atoms during the course of a pericyclic reaction, the MO levels of the sigma framework are relatively unaffected.

2. For a conjugated polyene system containing n (n = even) π electrons, there will be n/2 π bonding molecular orbitals that are filled MOs and n/2 antibonding MOs that are empty in the ground state electronic configuration of the molecule.

3. The lowest energy MO has zero nodes, the next higher one has one node and the second higher has two nodes and so on. Thus the n^{th} MO will have (n-1) nodes.

4. The nodal points are found at the most symmetric points in a MO. In other words, no MO can be symmetric as well as antisymmetric at the same time with respect to any existing molecular symmetry element. For example the π_2 MO of butadiene has a node at the center of the bond connecting C2 and C3. It is incorrect to assign this node to the center of the bond connecting C1 and C2.

1.13 Key words

Pericyclic reactions; Thermal electrocyclic reactions; Photochemical electrocyclic reactions; Frontier Orbital approach; Woodward Hoffmann rules of electrocyclic reactions; Correlation diagram method; Symmetry of orbitals.

1.14 References for further studies

1) Photochemistry and Pericyclic Reactions; J. Singh; *New Age International*, **2005**.

2) Pericyclic reactions: a textbook: reactions, applications and theory; Sethuraman Sankararaman; *Wiley-VCH*, **2005**.

3) Pericyclic Reactions; G. Gill; *Springer Science & Business Media*, **2012**.

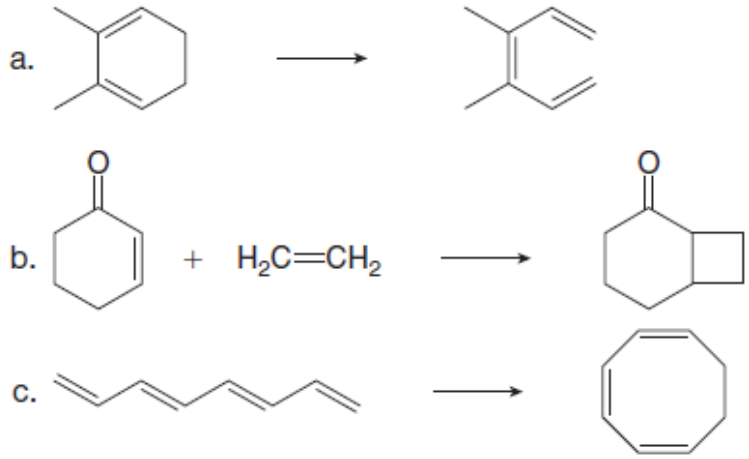
4) Pericyclic Reactions; Ian Fleming; *Oxford University Press*, **2015**.

5) Pericyclic Reactions: A Mechanistic and Problem-Solving Approach; Sunil Kumar, Vinod Kumar, S.P. Singh; *Academic Press*, **2015**.

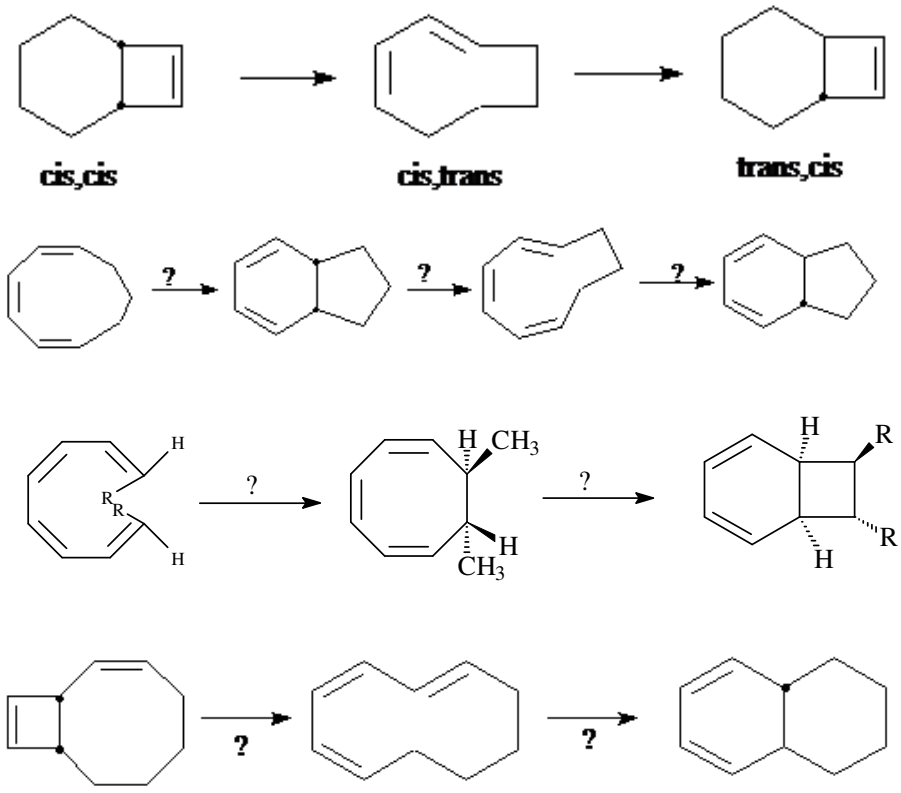
6) Advanced Organic Chemistry: Part A: Structure and Mechanisms; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2007**.

1.15 Questions for self understanding

1) Label the σ bonds that are broken or formed in each reaction



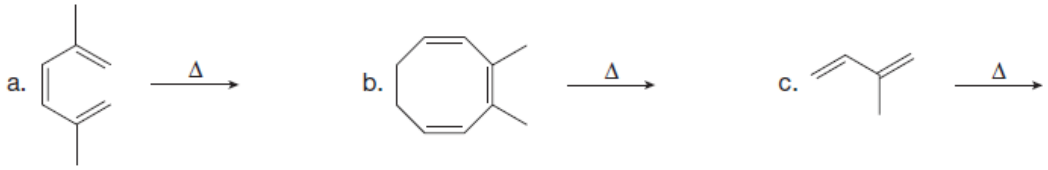
2) Predict which condition (Photochemical or thermo) is favoured in following pericyclic reactions?



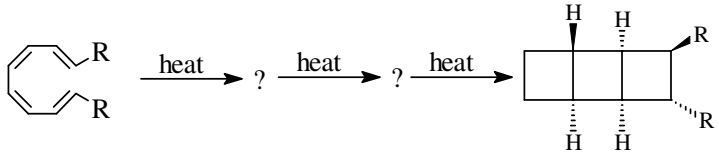
3) Draw the molecular orbitals for 2,4-hexadiene. (a) Label the HOMO and the LUMO in the ground state. (b) Label the HOMO and the LUMO in the excited state.

4) How many " molecular orbitals are present in 1,3,5,7,9-decapentaene (CH_2=CH–CH=CH–CH=CH–CH=CH–CH=CH_2)? (a) How many are bonding MOs and how many are antibonding MOs? (b) How many nodes are present in ψ_1? (c) How many nodes are present in ψ_{10}*?

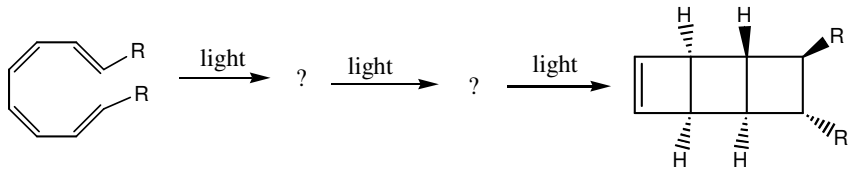
5) Use curved arrows and draw the product of each electrocyclic reaction.



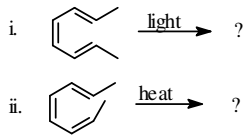
6. What are pericyclic reactions? How they are classified?
7. Show what is happening in each step for the following concerted electrocyclic transformations.



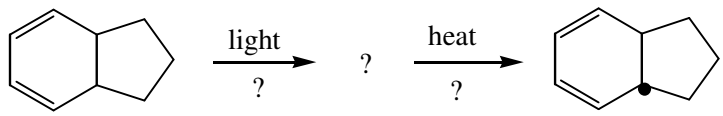
8. Show what is happening in each step for the following concerted electrocyclic transformations.



9. Write all the π-M.O's of 1, 3, 5-hexatriene. Using the FMO method, deduce the stereochemistry of its electrochemical ring closure by thermal and photochemical processes.
10. Predict the product for the following:

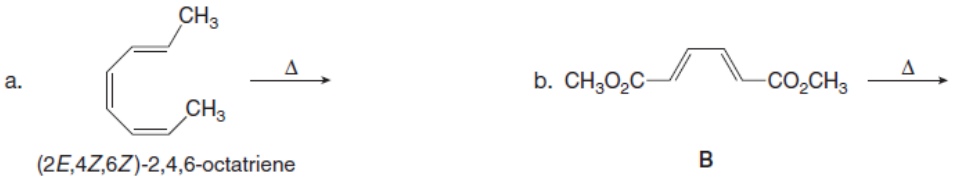


11. During electrocyclic reaction, which orbital symmetry is involved in conrotatory motion? Explain with illustration.
12. Show what is happening in each step for the following concerted electro cyclic transformations.



13. Using correlation diagram, show that electrocyclization of 2,4,6- octatriene is thermally allowed process
14. State Woodward-Hoffmann rule for electrocyclic reactions.

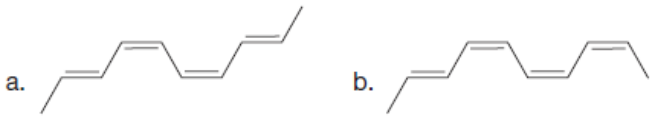
15. Draw the product of each thermal electrocyclic ring closure.



(2*E*,4*Z*,6*Z*)-2,4,6-octatriene B

16. What product is formed when each compound undergoes thermal electrocyclic ring opening or ring closure? Label each process as conrotatory or disrotatory and clearly indicate the stereochemistry around tetrahedral stereogenic centers and double bonds.

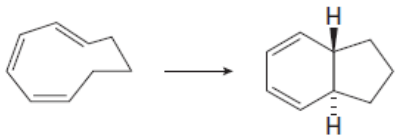
17. What cyclic product is formed when each decatetraene undergoes thermal electrocyclic ring closure?



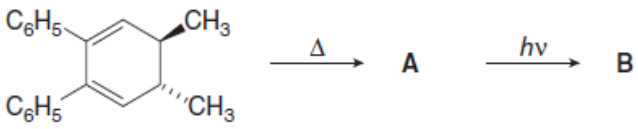
18. Draw the product formed when each triene undergoes electrocyclic reaction under [1] thermal conditions; [2] photochemical conditions.

19. What product would be formed by the disrotatory cyclization of the given triene? Would this reaction occur under photochemical or thermal conditions?

20. Consider the following electrocyclic ring closure. Does the product form by a conrotatory or disrotatory process? Would this reaction occur under photochemical or thermal conditions?



21. Identify A and B in the following reaction sequence. Label each process as conrotatory or disrotatory.



UNIT-2

Structure

2.0 Objectives of the unit

After studying this unit you are able to

- Explain the cycloaddition reactions
- Classify the cycloaddition reaction
- Write the orbital symmetry analysis of cycloaddition reaction
- Explain the Frontier molecular orbital approach under thermal condition
- Explain the Frontier molecular orbital approach under photochemical condition
- Write the correlation diagram
- Explain the Diels-Alder reaction in terms of [4+2] cycloaddition
- Write the Woodward-Hoffmann theory for prediction of the stereochemistry

2.1 introductions

An important body of chemical reactions, differing from ionic or free radical reactions in a number of respects, has been recognized and extensively studied. The three characteristics shared by these reactions, set them apart they are

1. They are relatively unaffected by solvent changes, the presence of radical initiators or scavenging reagents, or (with some exceptions) by electrophilic or nucleophilic catalysts.

2. They proceed by a simultaneous (concerted) series of bond breaking and bond making events in a single kinetic step, often with high stereospecificity.

3. In agreement with 1 & 2, no ionic, free radical or other discernible intermediates lie on the reaction path.

Since reactions of this kind often proceed by nearly simultaneous reorganization of bonding electron pairs by way of cyclic transition states, they have been termed pericyclic reactions. The four principle classes of pericyclic reactions are termed: Cycloaddition, Electrocyclic, Sigmatropic, and Ene Reactions. A general illustration of each class will be displayed by clicking on the following diagram. The cycloaddition and ene reactions are shown in their intermolecular format. Corresponding intramolecular reactions, which create an additional ring, are well known.

2.2 Cycloaddition reactions

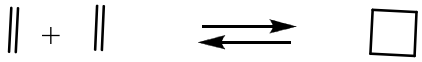
A cycloaddition is a reaction between two compounds with π bonds to form a cyclic product with two new σ bonds. Like electrocyclic reactions, cycloadditions are concerted, stereospecific reactions, and the course of the reaction is determined by the symmetry of the molecular orbitals of the reactants.

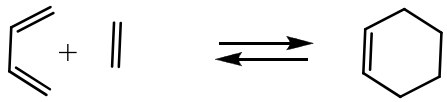
Cycloaddition reactions are very useful reactions in synthetic organic chemistry. Though this is a very old reaction, the mechanism of this reaction is understood only recently after the event of orbital symmetry studies.

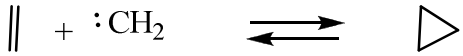
Cycloaddition reaction is a process in which two or more π systems combine to form a stable cyclic molecule, during which sigma bonds are formed between the termini of π systems and no fragment is lost. A concerted mechanism requires a single transition state and no intermediate, which lies on the reaction path between reactants and adduct.

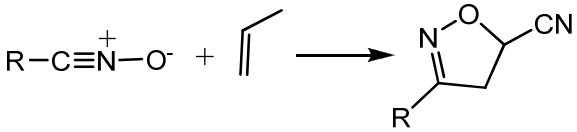
2.3 Classification of cycloaddition reaction

Cycloadditions can be initiated by heat (thermal conditions) or light (photochemical conditions). Cycloadditions are identi! ed by the number of π electrons in the two reactants. Since cycloaddition is such varied process, further classification should be independent of mechanism and system uses only the number of ring atoms provided by each of the component. For instance,

Olefin dimerization  [2+2] cycloaddition

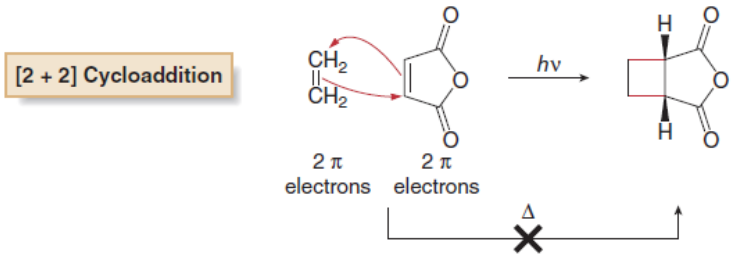
Diel's -Alder cyloaddition  [4+2] cycloaddition

 [2+1] cycloaddition

1,3-dipolar cycloaddition  [3+2] cycloaddition

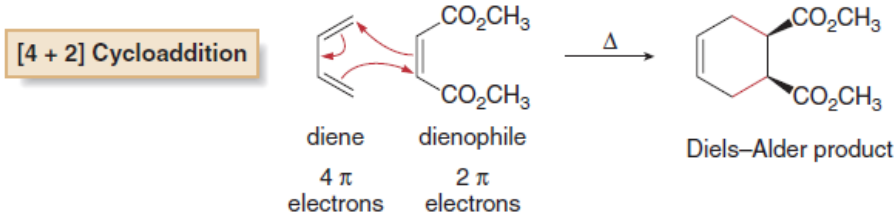
[2 + 2] cycloaddition reaction

A photochemical [2 + 2] cycloaddition occurs between two alkenes, each with two π electrons, to form a cyclobutane. Thermal [2 + 2] cycloadditions do not take place.



[4 + 2] cycloaddition reaction

The Diels–Alder reaction is a thermal [4 + 2] cycloaddition that occurs between a diene with four π electrons and an alkene (dienophile) with two π electrons



Another method of classification of cycloaddition consists of the following facts:

i. The number of electrons of each unit participating in the cycloaddition.

ii. Nature of orbitals undergoing changes (πor σ)

iii. The stereochemical mode of cycloaddition [**Antarafacial (S) and sufrafacial additions (a)**]

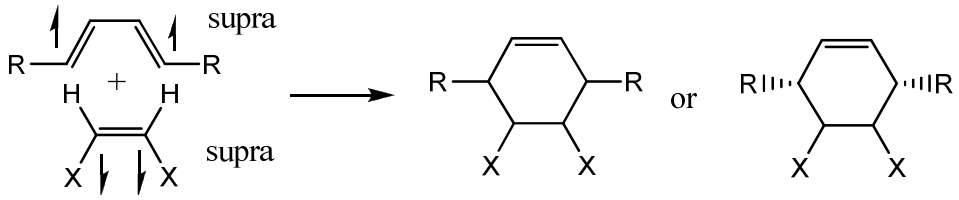
Because during cycloadditions, there is addition of two olefinic systems, therefore, two feasibilities are there:

i. Addition may take place in such a way that lobes of same phases of one component with the lobes of same phases of other component may overlap.

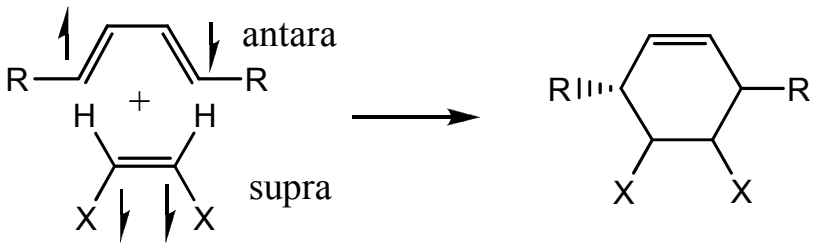
ii. Lobes of same pahse of one component may overlap with lobes of opposite faces of other component.

i) is known as **suprafacial** cycloaddition and ii) as **antarafacial** cycloaddition.

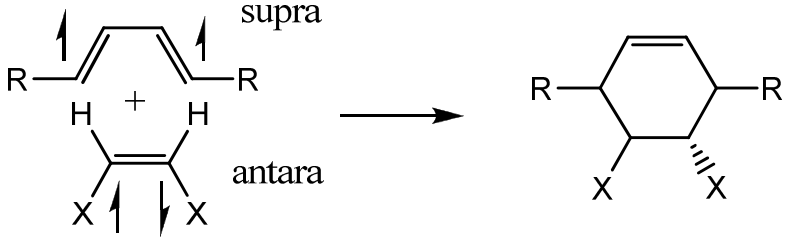
Antarafacial processes are difficult because in them twisting of p-orbitals is required. As both the π-system are involved in the cycloaddition, it is essential to specify the modes with respect to each of them. Specification is made by placing subscript S or a after the number referring π-component. For instance, suprafacial addition with respect to each component of Diles-Alder reaction is specified as π^2**S** +π^4**S** cycloaddition. Another way is simplify writing it as 2S+4S cycloaddition.



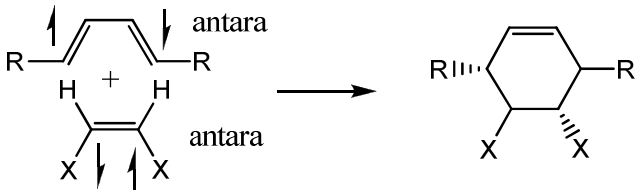
π^2S +π^4S



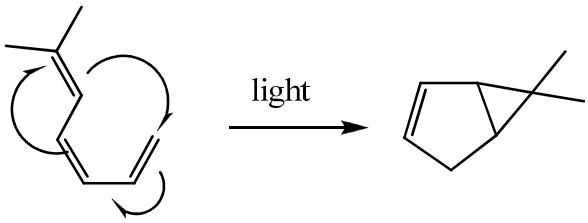
π^2S +π^4A



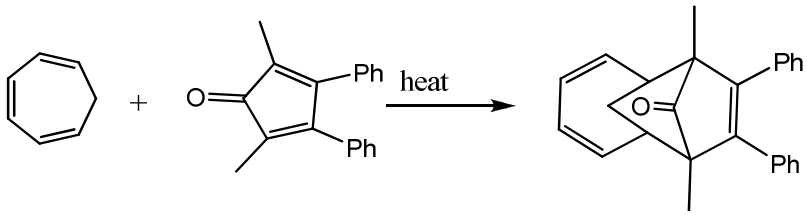
π^2A +π^4S



$\pi^2A + \pi^4A$



$\pi^4S + \pi^2S$

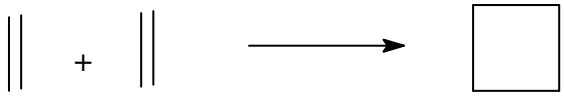


$\pi^6S + \pi^4S$

2.4 Orbital symmetry analysis of cycloaddition reaction

The analysis of cycloaddition reactions for conservation of orbital symmetry will be dealt with three levels of sophistication, a. A Frontier Orbital approach (FMO), b. Using Orbital Correlation Diagrams and c. Using Mobius method.

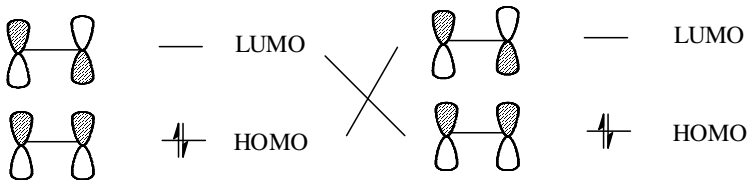
2.4.1 [2+2] – cycloaddition

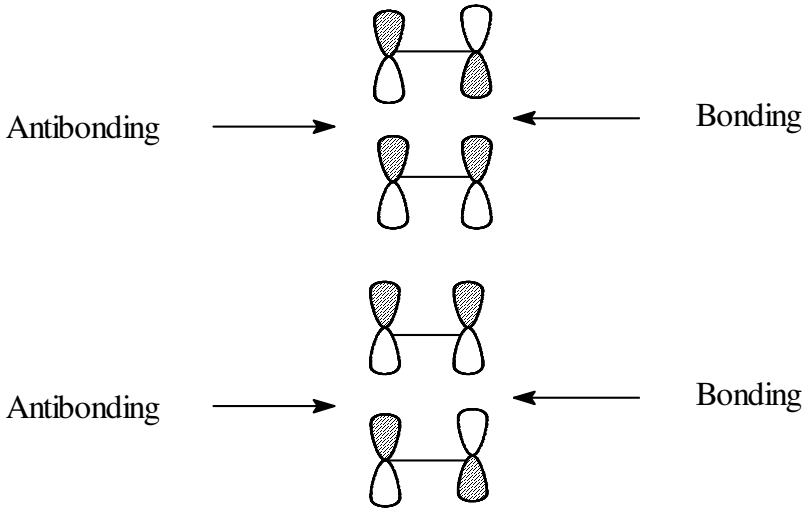


2.4.1Frontier molecular orbital approach

a) Under thermal condition

For thermal reaction we have to consider HOMO of one molecule and LUMO of the other in the ground state.

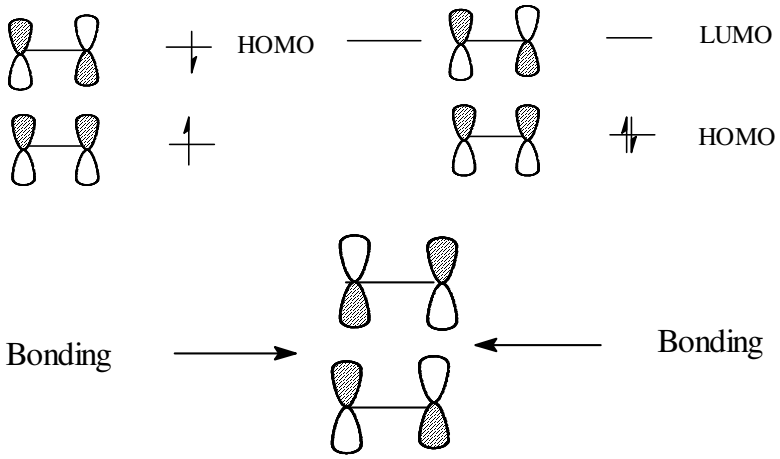




Thus supra-supra is geometrically allowed but symmetry forbidden. Therefore supra-antara is geometrically forbidden but symmetry allowed.

b) Under photochemical condition

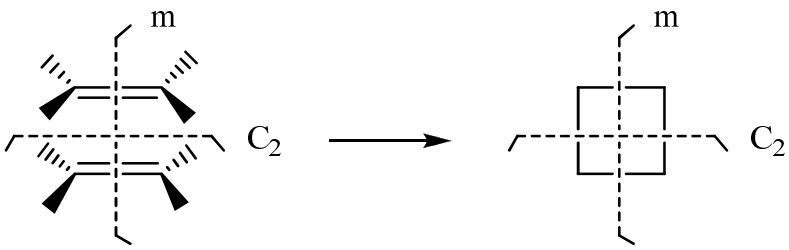
For photochemical reaction, we have to consider HOMO of one excited and LUMO of ground stae molecule.



So far our discussion has assumed that the reaction is suprafacial with respect to both the components. In fact stereochemistry shows that there is true. But orbital symmetry point of view, thermal [2+2] cycloadditions, could if it were supra with respect to one component and antara with respect to other. Almost certainly supra-antara process is impossible in case of ethylene on geometry ground state. But if the ring formed is big enough supra-supra and supra-antara are geometrically possible.

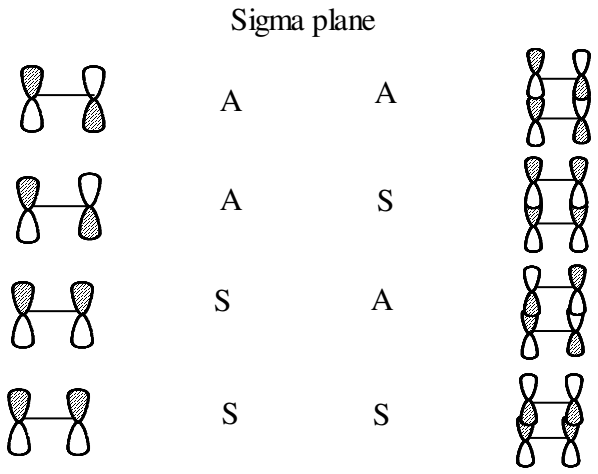
2.5 Correlation diagram method

Control of orbital symmetry on cycloaddition can be expressed by the simple example of suprafacial-suprafacial adition of the two ethylene molecules [2S+2S] to give cyclobutane. During the course of this reaction both minor-plane (m) i.e., vertical symmetry as well as C2-axis of symmetry (C2) i.e., horizontal symmetry are conserved.



Symmetry conservation during cycloaddition

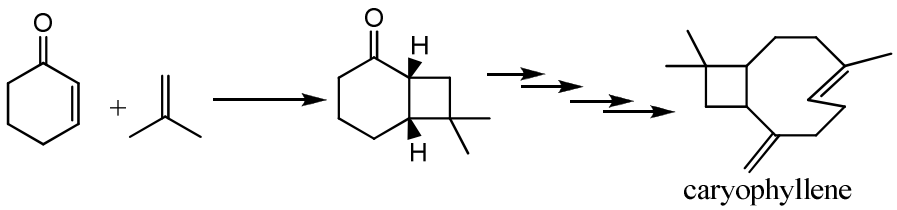
In this transformation four π-orbitals of two ethylene molecules and four σ-orbitals of cyclobutane are involved. As symmetry properties of other orbitals do not undergo change, they are not taken into account. Shape and symmetries of involved orbitals, i.e., π and π* orbitals of both the ethylene molecules and σ and σ* orbitals of cyclobutane are shown in the figure shown below. A correlation diagram may be prepared on the basis of symmetry properties of ethylene molecules and cyclobutane that predicts feasibilities of this cycloaddition.



From the above correlation diagram it is clear that reaction is photochemically feasible because first excited state of ethylene correlates with ground state of cyclobutane making it symmetry allowed. On the other hand this reaction is thermally forbidden on account of the fact that grpound state of one ethylene molecule doesnot give G.S of cyclobutane, therefore, ground state of two ethylene molecule cannot combine to give cyclobutane while conserving symmetry of orbitals.

2.6 Synthetic applications

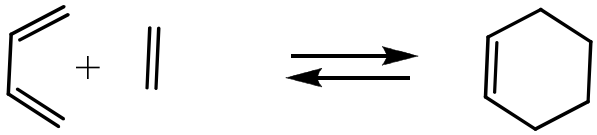
A key step involved in the synthesis of caryophyllene is [2+2] cycloaddition of cyclohexenone with isobutylene.



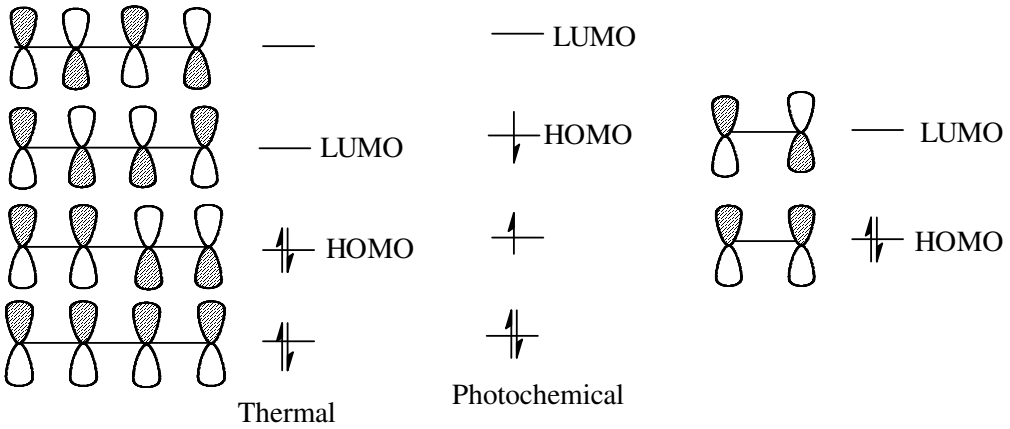
caryophyllene

2.7 Diels-Alder reaction [4+2] – cycloaddition

The **Diels–Alder reaction** is an organic chemical reaction (specifically, a [4+2]cycloaddition) between a conjugated diene and a substituted alkene, commonly termed the dienophile, to form a substituted cyclohexene system. It was first described by Otto Paul Hermann Diels and Kurt Alder in 1928, for which work they were awarded the Nobel Prize in Chemistry in 1950. The Diels–Alder reaction is particularly useful in synthetic organic chemistry as a reliable method for forming 6-membered systems with good control over regio- and stereochemical properties. The underlying concept has also been applied to other π-systems, such as carbonyls and imines, to furnish the corresponding heterocycles, known as the **hetero-Diels–Alder reaction**. Diels–Alder reactions can be reversible under certain conditions; the reverse reaction is known as the **retro-Diels–Alder reaction**



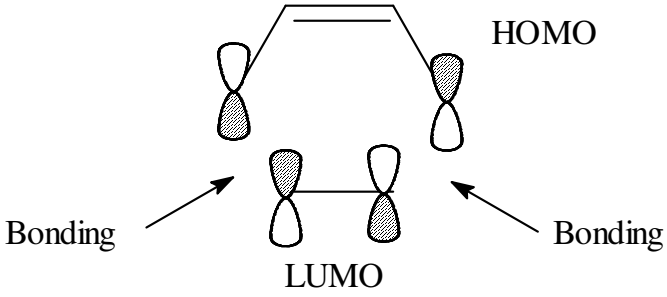
In cycloaddition two new bonds are formed by the use of π-electrons of the reactants. The concerted reaction results from overlap of the other. As in the case of electrocyclic reaction, here also we can concentrate on the HOMO. What we see here is HOMO of each reactant is fully occupied by two electrons. Therefore HOMO-HOMO intereaction is not possible. In order to form bond, each HOMO of diene has to overlap with empty orbital of dienophile.



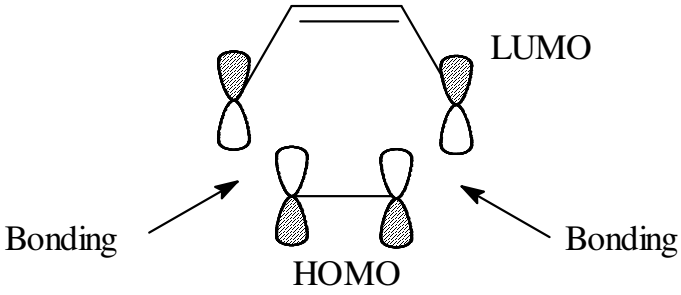
Therefore HOMO picks up the most stable of the empty orbitals i.e. LUMO. In the transition state of the cycloaddition, stabilization chiefly comes from overlap between the HOMO of one reactant and the LUMO of the other in bonding fashion.

2.7.1 Thermal condition

Let us consider the HOMO of diene and LUMO of dienophile

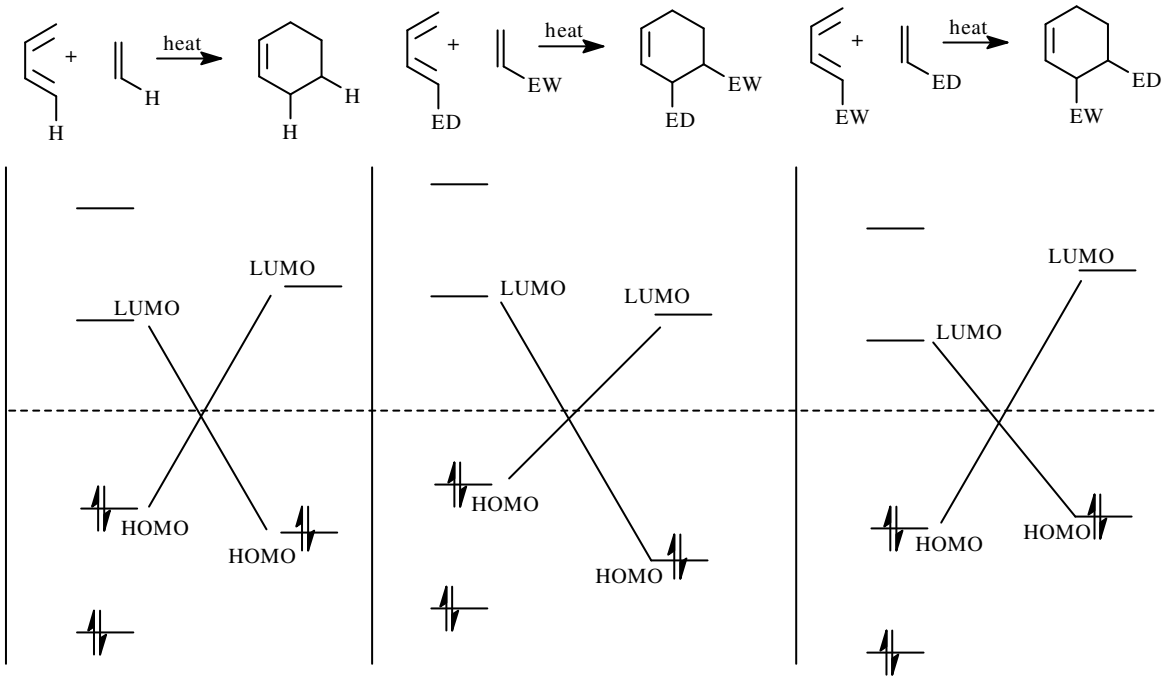


Let us consider the LUMO of diene and HOMO of dienophile



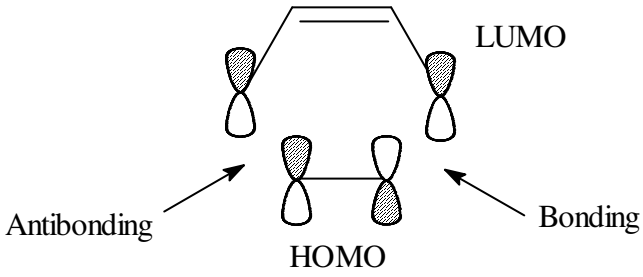
The above phase diagram shows that in both the cases lobes of the same phase overlap. Thus there is flow of electron from HOMO to LUMO and bonding occurs. HOMO-LUMO picture of the DA reaction shows that concerted bond making take place on one face of diene and dienophile. This arrangement is known as SUPRAFACIAL. Since both the diene and dienophiles undergo suprafacial bond making process, the process is designated as supra-supra [4+2] cycloaddition reaction is therefore supra-supra is allowed one.

We note that for a 'normal' electron demand Diels–Alder reaction, the electron-rich diene's, Ψ_2 is the highest occupied molecular orbital (HOMO) while the electron-deficient dienophile's π^* is the lowest unoccupied molecular orbital (LUMO). However, the HOMO-LUMO energy gap is such that the roles can be reversed by switching the substitution pattern: i.e. the diene's $\Psi 3$ might be considered the LUMO if electron withdrawing group (EWG) substituents make it sufficiently electron-deficient and electron donating groups (EDGs) raise the dienophile's filled π orbital's energy sufficiently to make it the HOMO. Such a scenario is termed an inverse electron demand Diels–Alder reaction. Regardless of which situation pertains, the HOMO and LUMO of the components are in phase and a bonding interaction results as can be seen in the diagram below. Since the reactants are in their ground state, the reaction is initiated thermally and does not require activation by light.

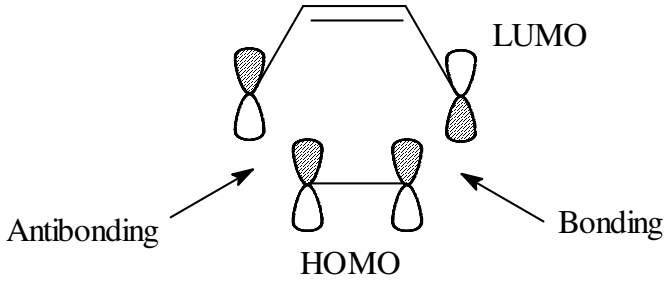


2.7.2 Photochemical condition

Let us consider the HOMO of diene and LUMO of dienophile

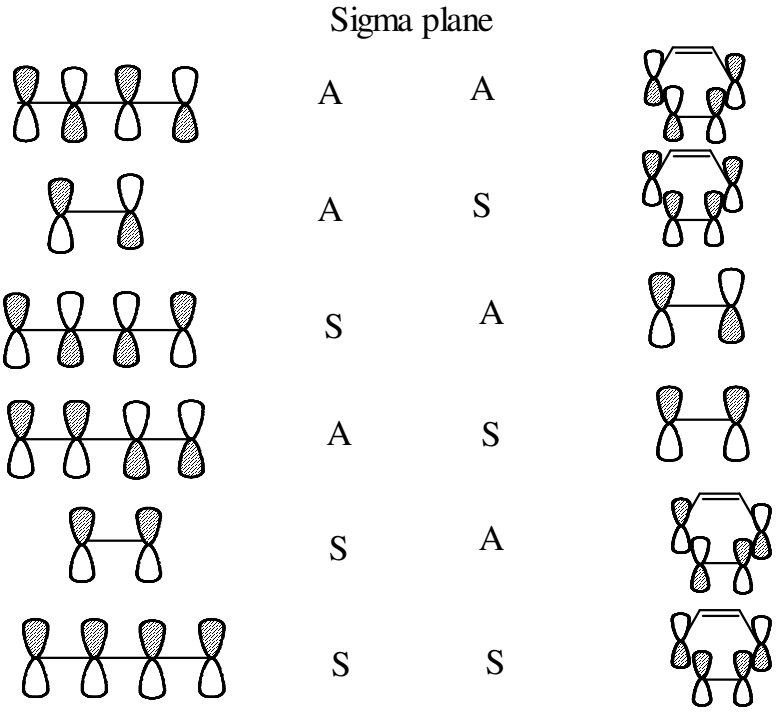


Let us consider the LUMO of diene and HOMO of dienophile



2.8 Correlation diagram

Correlation diagram may also be constructed to predict the feasibility of Diels-Alder reaction which is $\pi 4S + \pi 2S$ cycloaddition. Results have been found in conformity with observed fact that reaction is thermally feasible. In Diels-Alder reaction only m-plane of symmetry is conserved. Symmetry properties and correlation diagram for Diels-Alder reaction is given below.



Diels-Alder reaction involves ψ1, ψ2, ψ3 and ψ4 orbitals of 1, 3-butadiene and π and π* orbitals of ethylene as reactants molecular orbitals and σ1, σ2,π π*, σ1* and σ2* orbitals of cyclohexene which are product molecular orbitals. When these molecular orbitals are arranged in the increasing order of their energies along with their sy6mmetriwes, ground state molecular orbitals of reactants correlate with the ground state molecular orbitals of their product, therefore, reaction is thermally allowed; but photochemically forbidden on account of the fact that first excited state of reactant does not correlates with first excited state of product.

2.9 Woodward Hoffmann rules of cycloaddition reactions

m+n electrons	Thermal	Photochemical
4	forbidden	allowed
6	allowed	forbidden

Concerted thermal or photochemical reactions follow the above general rule and are known as Woodward-Hoffmann rules of cycloaddition reactions.

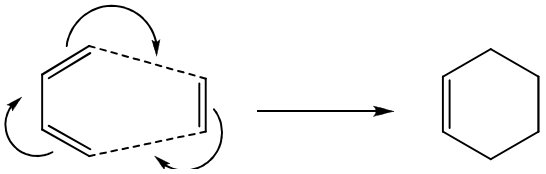
2.9.1 Woodward-Hoffmann theory for prediction of the stereochemistry

In cycloaddition reactions, the situation is slightly different because

a) Two molecules are used and

b) Electron flow takes place from the highest occupied molecular orbital (HOMO) of one molecule to the lowest unoccupied molecular orbital (LUMO) of the other.

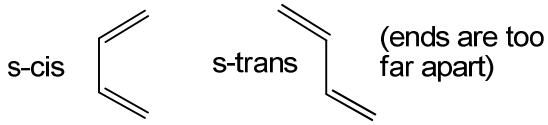
The stereochemistry therefore follows from the wavefunction signs of the orbitals on each molecule. Consider the reaction of a butadiene with an alkene (the Diels-Alder reaction):



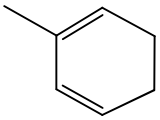
The reaction is *usually* heat-promoted,
but sometimes it is carried out photochemically.

More details of the Diels-Alder reaction

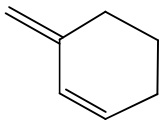
1) Diene must be in the s-cis conformation:



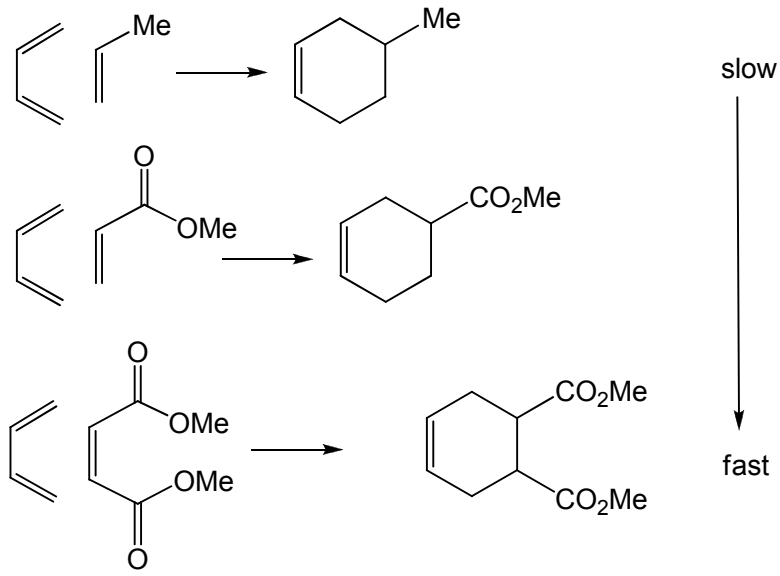
This will react:



But not this:

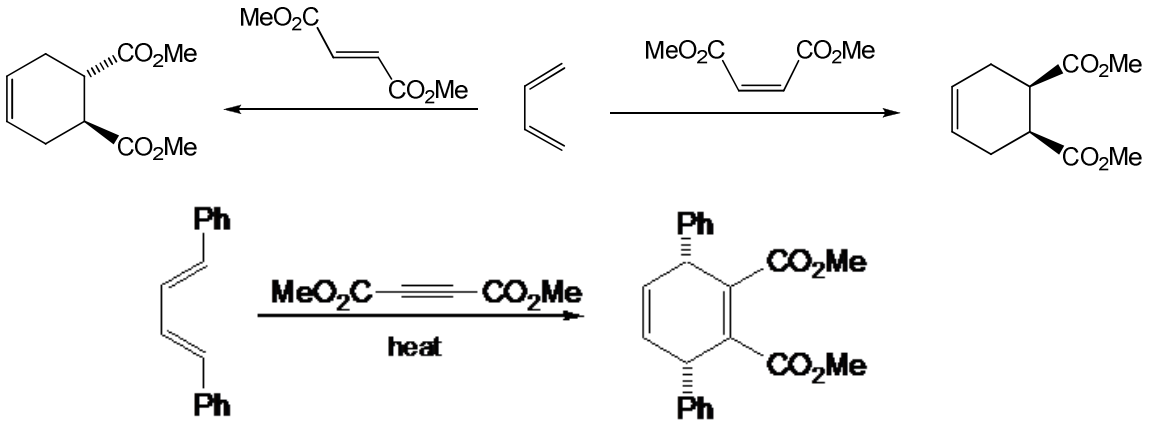


2) Dienophiles with electron-withdrawing groups (EWG) react faster:

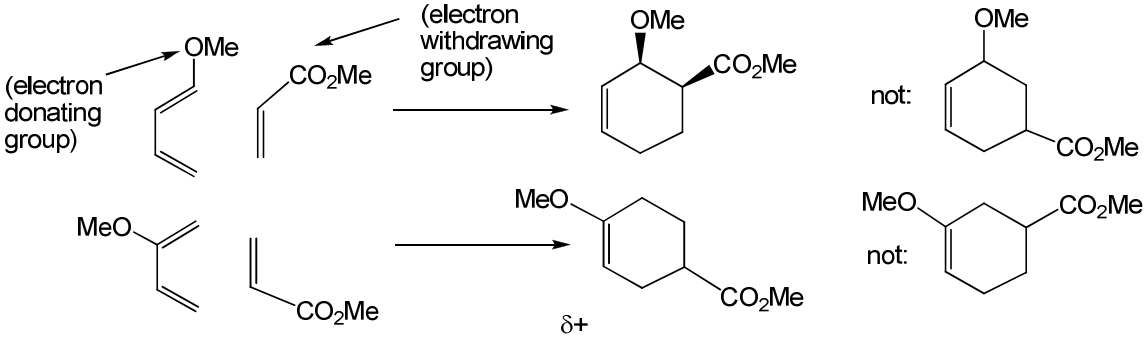


This is because the electron- withdrawing group reduces the LUMO energy and improves the overlap with the orbitals in the diene – more information later in course.

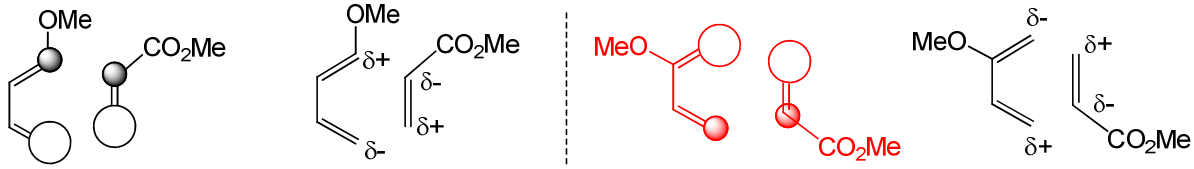
3) The reaction is stereospecfic:



4) With unsymmetrical dienes, the reactions are regioselective:

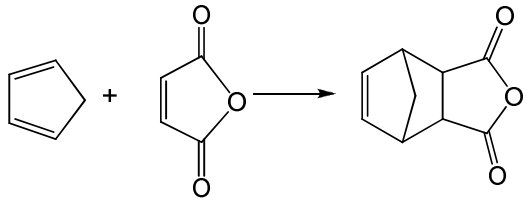


Due to size of MOs, and distribution of partial charges: Please note this correction

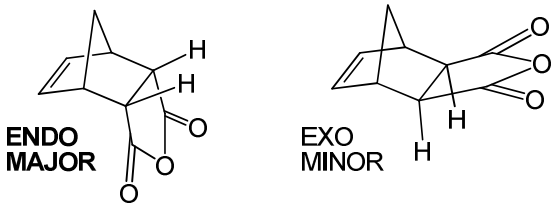


MOs closely matched in size react with each other more efficiently (stepwise analogy).

5) Endo-product often favoured:

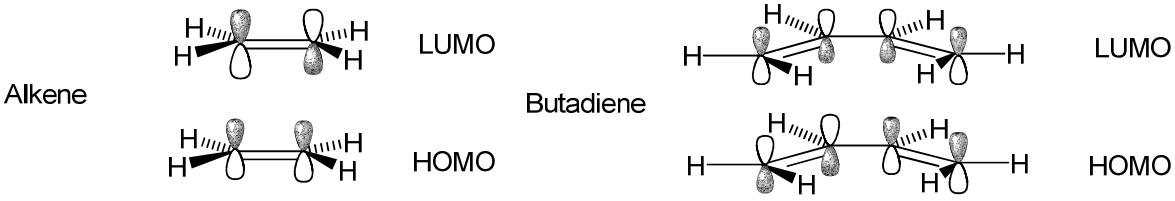


Two isomers can be formed:

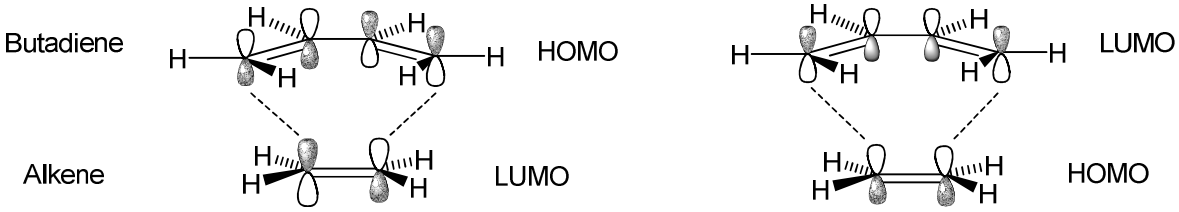


In a kinetically controlled (product is fastest to form, irreversible) the ENDO is favoured but for reversible reactions (thermodynamic control) the EXO may dominate e.g. with furan.

All these observations can be explained by considering the orbitals involved in the reactions. In this Diels-Alder reaction the reagents approach each other in a 'face to face' manner, i.e. so that the p-orbitals of the π-system can combine with each other. The relevant orbitals are shown below



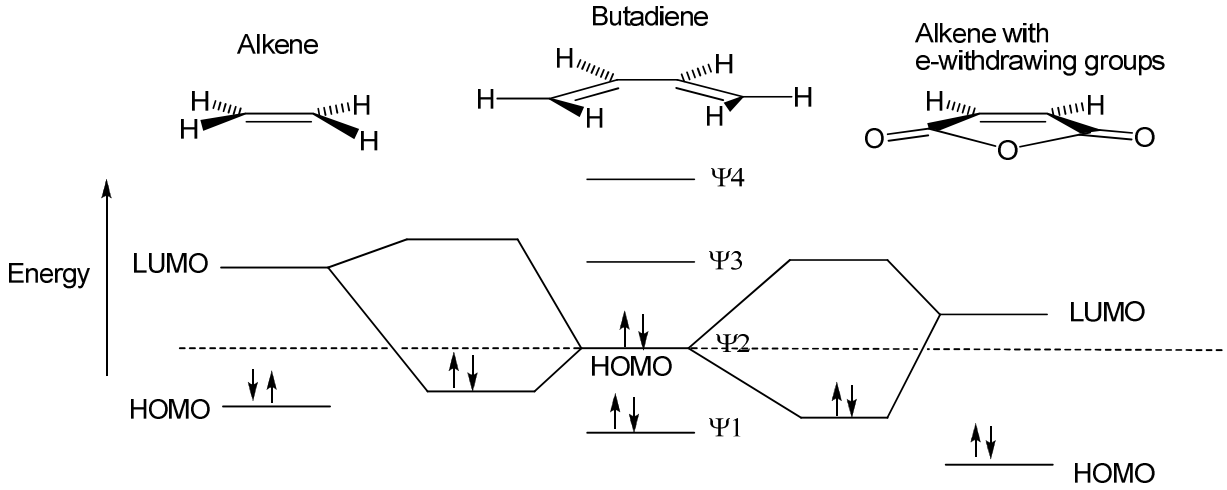
So the following combinations can be employed in the *suprafacial* cycloaddition reaction



In both cases, phases of the wavefunctions on the orbitals are matched so that the reagents can approach each other in a face to face manner and also form bonds easily. In practice, it is usually

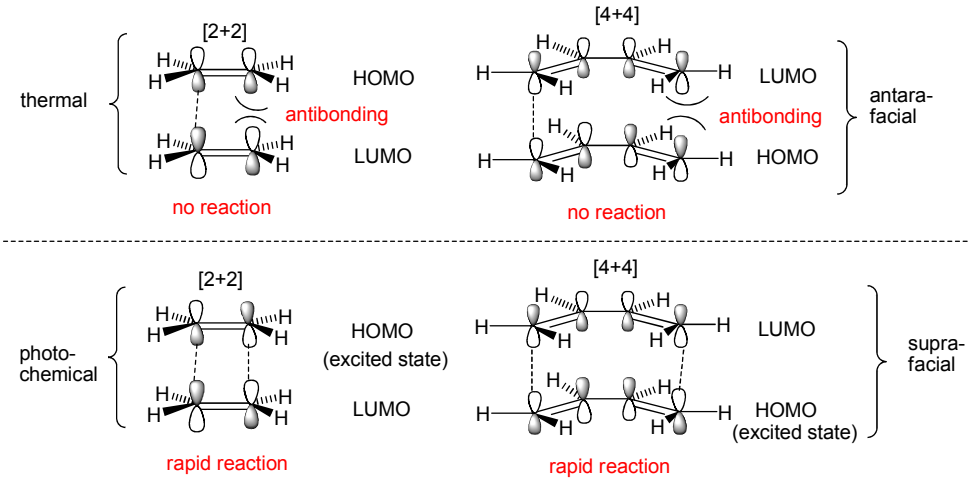
the combination of diene HOMO with alkene LUMO which leads to the product, rather than the diene LUMO and alkene HOMO. Electron-withdrawing groups on the alkene lower its LUMO energy and improve the matching to the diene HOMO. In turn this increases the reaction rate. Hence, electron-withdrawing groups on an alkene generally increase the reaction rate, often very significantly. As might be predicted, electron-donating groups on the diene also improve the rate – by pushing its HOMO energy closer to that of the alkene LUMO.

More closely-matched orbitals give a greater energetic benefit when combined. Hence the closely related butadiene HOMO and alkene LUMO represent the favoured combination. When electron-withdrawing groups are present on the alkene, the benefit is even greater because the HOMO/LUMO levels are even closer. Lewis acids speed it even further.



The Diels-Alder reaction proceeds in a *suprafacial* manner, i.e. the reagents add together in a perfectly-matched face-to-face fashion. **Please note that the terms 'dis- and conrotation do not apply to cycloadditions**.

If we examine [2+2] and [4+4] cycloadditions, we will find that the combination of a HOMO and a LUMO results in an antarafacial component. Often, as a result, the reactions simply fail under thermal conditions, although they might well succeed using photochemical methods.



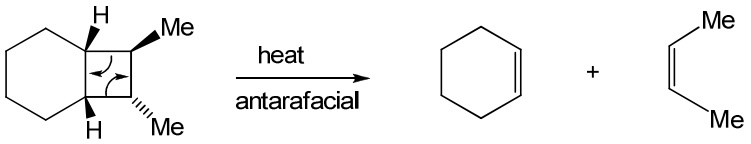
Thus Woodward-Hoffmann rule for prediction of the stereochemistry in cycloaddition reactions is summarized as follows

	Stereochemical Course	
# Electrons	Thermal Mode	Photochemical Mode
4n + 2	[s + s]	[s + a]
4n	[s + a]	[s + s]

or

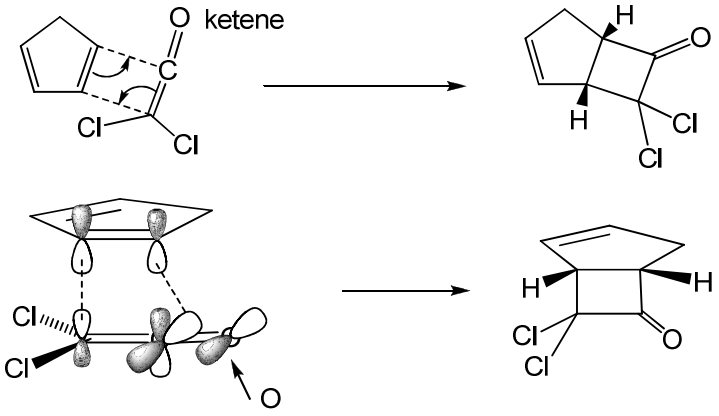
Ring size	No. electrons	Thermal	Photochemical
4,8,12…	4n	Antarafacial	Suprafacial
6,10,14…	4n+2	Suprafacial	Antarafacial

Note that the rules also work in reverse

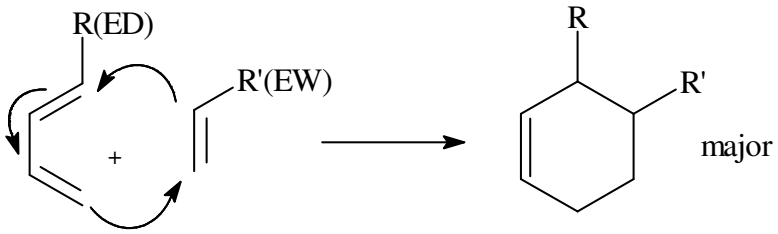


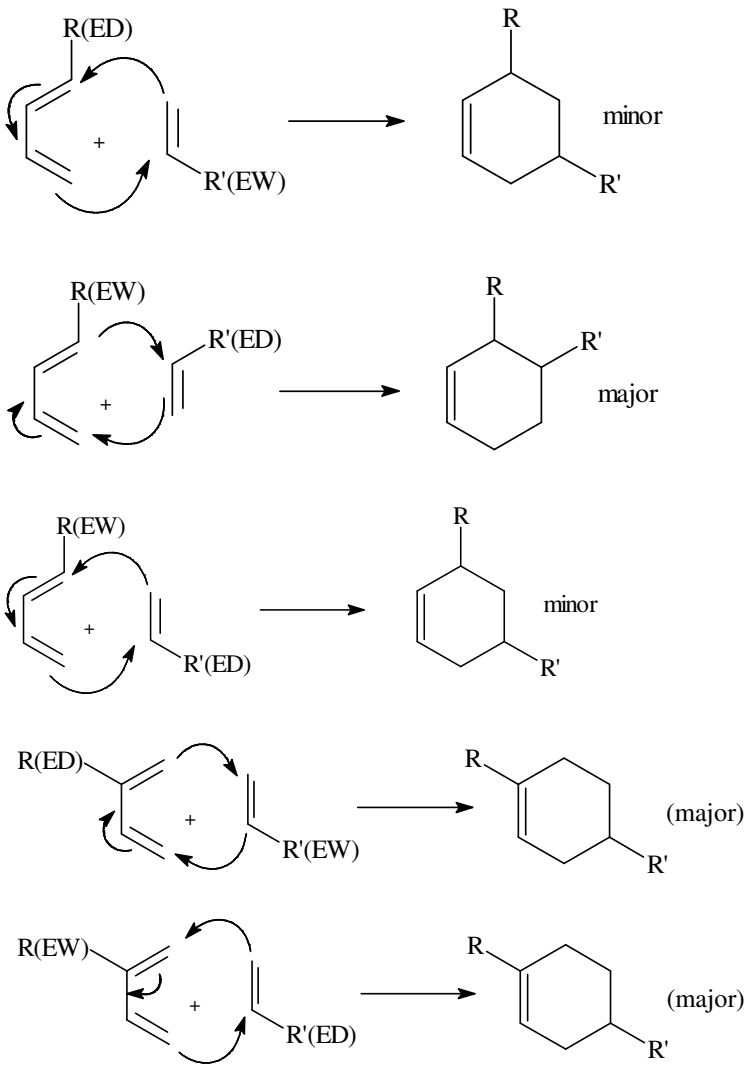
2.9.2 [2+2] cycloadditions involving ketenes [An exception to the Woodward-Hoffmann rules]

This is an important exception to the Woodward-Hoffmann rules which normally insist that [2+2] additions proceed in a (not very favourable) antarafacial manner. The trick here is that the ketene uses both the C=C and C=O p-orbitals in the reaction, through a 'twisted' transition state



2.10 Regioselectivity in Diel's-Alder reaction





2.11 Hetero-Diels–Alder reaction

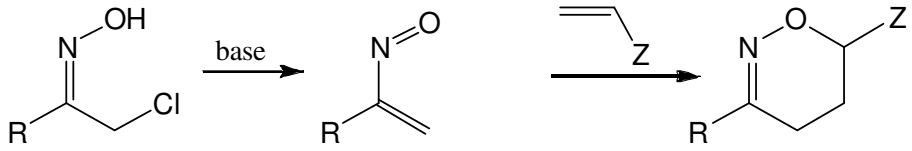
In hetero Diels-Alder reactions, molecular systems in which one or more atoms of the diene or the dienophile are heteroatoms are involved, leading to the formation of heterocyclic systems. In the production of commercially useful organic intermediates and medicines," this technique has become an inevitable tool. In hetero Diels-Alder reactions, carbonyl compounds, nitroso compounds, nitrile group, imino group, alkyl azodicarboxylate etc can function as dienophiles, when they are activated by a strong electronegative group in conjugation with the double or triple bond. Most substrates with diene heteroatoms cyclize according to the same rules of diastereoselectivity as all-carbon dienes. Substrates with dienophile heteroatoms often have different electronic properties than all-carbon dienophiles. This can have large effects on stereoselectivity.

2.11.1 Cycloaddition of nitrosoalkenes

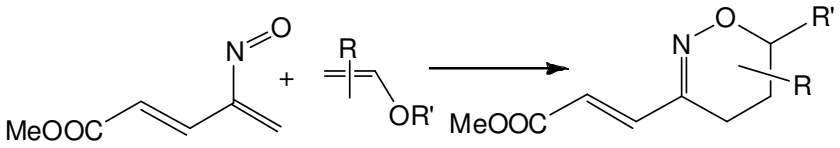
The α-nitrosoalkenes are very useful synthetic intermediates because of double bond in conjugation with nitroso group. These reactive species along with nitrosocarbonyls constitute the two major

sources for the construction of the 1, 2-oxazine structure. Nitrosoalkenes are unstable and highly reactive. Normally they are observed only in solution, their presence sometimes being detectable by blue coloration (they have a λ_{max} close to 700 nm). Nitrosoalkenes have been isolated in only a few cases.

The usual method of generating nitrosoalkenes is by the elimination of hydrogen halide from □-monohaloketooximes in presence of base. The generated nitrosoalkenes are trapped by alkenes to produce 1, 2-oxazine derivatives.

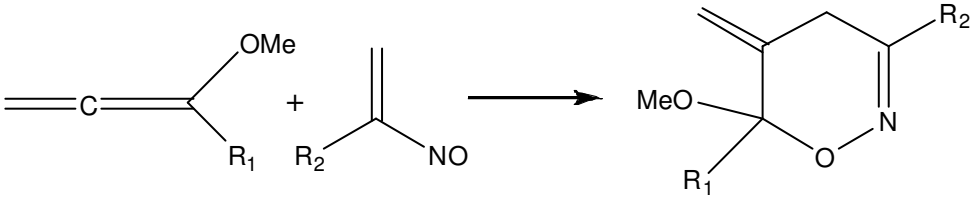


1,2 –Oxazines with an vinylic double bond at position 3 can easily prepared by Hetero-Diel's-Alder reaction of an electron-rich olefin with the nitrosoalkene generated in situ from methyl (E)-5-bromo-4-hydroximino-2-pentenoate and base.



Cyclization or cycloaddition of nitrosoalkene (acting as either a 2π or a 4π component) with dienes, has been extensively covered by Gilchrist and recently by Lyapkalo and Ioffe.

Allenes upon reaction with nitrosoalkenes gave the cycloadduct 1, 2- oxazine**.**

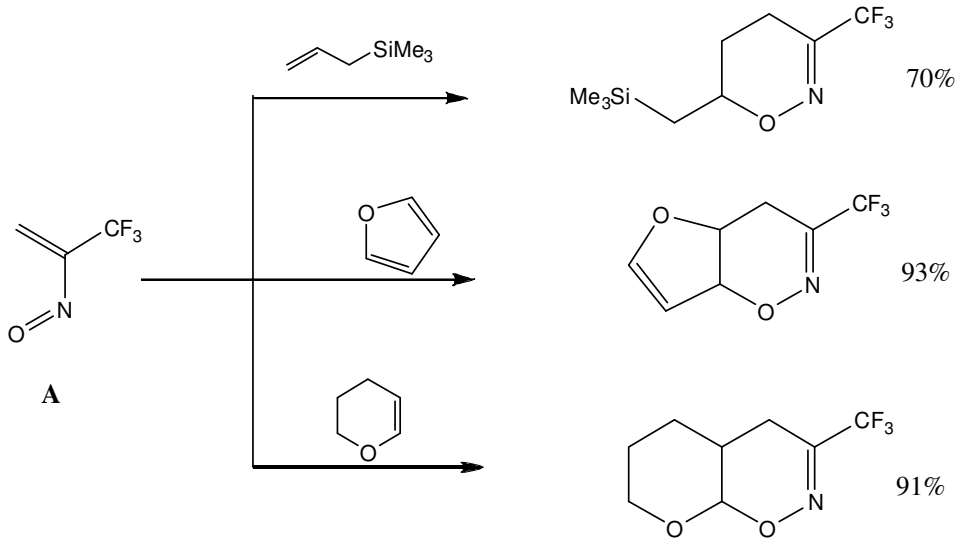


Extending the [4+2] cycloaddition chemistry of nitrosoalkenes that of 1, 1, 1-trifluoro-2-nitrosopropene (**A**) with silyl enol ethers offers a flexible and efficient access to a large variety of 1, 2-oxazines.

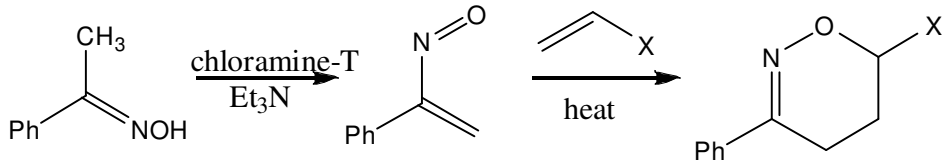
The results demonstrate that **A** is a powerful heterodyne, remarkably more than nitrosostyrene or other alkyl bearing analogues. The reactivity of the species is apparently due to the electronic effects of the CF_3 group. Comparison of HOMO and LUMO energies of **A** with those of nitrosoethylene or nitrosostyrene by MNDO calculations supports the electronic accelerative effect of the group.

Dienophiles **A** bearing substituents larger than ethyl have been found to give no cycloadducts with nitrosostyrene. In contrast **A** has readily been added to those unreactive silyl enol ethers in low to

moderate yields. Other dienophiles have also been used and the corresponding 1, 2-oxazines have been obtained in good to excellent yields.

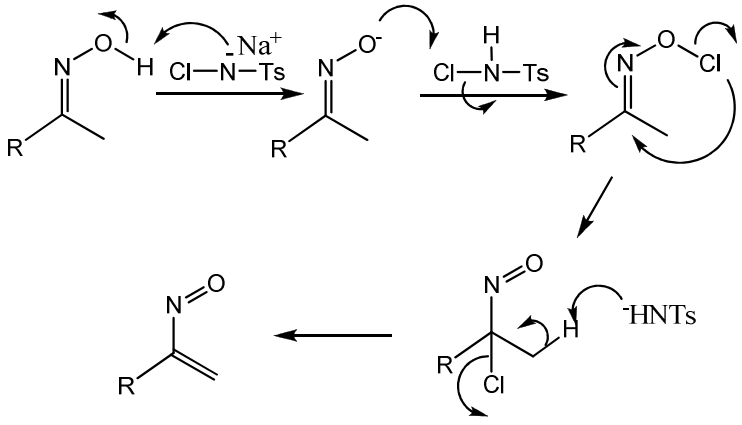


Recently Rai et al utilized chloramine-T for the generation of nitrosoolefin starting from ketooxime. The resultant nitrosoolefins cycloadd with dienophile leads to the formation of oxazine derivative almost in quantitative yield.



2.11.2 Mechanism for the generation of α-nitrosoolefins

When ketooxime containing α-methylene group was treated with chloramine-T produced a blue coloration suggestive of formation of α-chloronitroso compound, which on treatment with triethylamine generates α-nitrosoolefins. The generated α-nitrosoolefin was further treated with alkene to produce 1, 2-oxazine derivatives. This was further confirmed by comparing with the 1, 2-oxazine derivatives synthesized using literature procedure. The formation of α-nitrosoolefin may be rationalized by the probable mechanism proposed below.



Chloramine-T anion pulls a proton from OH of oxime. The generated anion now abstracts positive halogen from neutral chloramine to form neutral molecule with the elimination of sulphonamide anion. The neutral molecule slowly converts to α-chloronitroso compound. The α-chloronitroso compound on treatment with triethylamine generates α-nitrosoolefins with the elimination of HCl. This unstable and highly reactive α-nitrosoolefins undergo cycloaddition with olefinic compounds to produce 1, 2-oxazine derivatives. The mechanism is supported by the similar mechanism proposed by Hassner and Rai for the generation of nitrile oxide from aldoximes using chloramine-T.

2.12 Summary of the unit

A pericyclic reaction in which 2 separate conjugated, overlapping arrays of orbitals combine. Cycloadditions proceed by way of a cyclic transition state, and 2 sigma bonds are formed during the course of the reaction. A suprafacial process ("s" in the table below) is one in which the bonds made or broken lie on the same face of the orbital array undergoing reaction. In an antarafacial process ("a"), the newly formed or broken bonds lie on opposite faces of the reacting orbital array.

The Diels-Alder reaction is a [4+2]-cycloaddition between a conjugated diene and an alkene (dienophile) to form a cyclohexene system. As all pericyclic reactions the Diels-Alder reaction proceeds in a single step. Two new σ-bonds are formed at the same time during a Diels-Alder reaction. Therefore two filled p-orbitals and two empty p-orbitals have to be available. Expressed in FMOs this means the interaction between the HOMO of the diene and the LUMO of the dienophile (or vice versa). It is important to note that in cycloadditions the two molecules approach each other in a co-planar way. Despite the Diels-Alder reaction the thermal reaction between two alkenes does not provide any cyclobutane product. However under photochemical conditions cyclobutane is formed. There are some examples of thermal [2+2] cycloadditions, leading to four-membered rings. However, this reaction can take place under thermal conditions if the carbon taking part in the cycloaddition is also carrying a second double bond. Ketenes are a very prominent group of reagents for these transformations, however, only few are isolable, for example diphenylketene or dichloroketene. The smaller derivatives are so reactive that they spontaneously will undergo a thermal [2+2] cycloaddition with themselves

2.13 Key words

Cycloaddition reactions; Classification of cycloaddition reaction; [2 + 2] cycloaddition reaction; [4 + 2] cycloaddition reaction; Orbital symmetry analysis of cycloaddition reaction; *Frontier molecular orbital approach*; Diels-Alder reaction; Correlation diagram; Woodward Hoffmann rules

of cycloaddition reactions; Regioselectivity in Diel's-Alder reaction; Hetero-Diels–Alder reaction; Cycloaddition of nitrosoalkenes

2.14 References for further studies

1) Photochemistry and Pericyclic Reactions; J. Singh; *New Age International*, **2005**.

2) Pericyclic reactions: a textbook: reactions, applications and theory; Sethuraman Sankararaman; *Wiley-VCH*, **2005**.

3) Pericyclic Reactions; G. Gill; *Springer Science & Business Media*, **2012**.

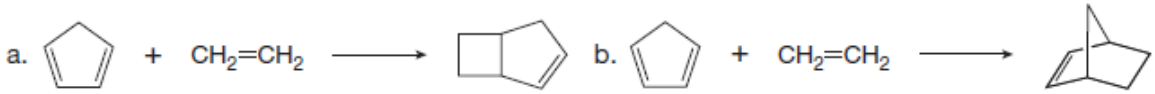
4) Pericyclic Reactions; Ian Fleming; *Oxford University Press*, **2015**.

5) Pericyclic Reactions: A Mechanistic and Problem-Solving Approach; Sunil Kumar, Vinod Kumar, S.P. Singh; *Academic Press*, **2015**.

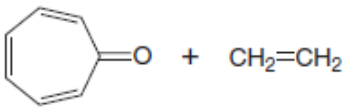
6) Advanced Organic Chemistry: Part A: Structure and Mechanisms; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2007**.

2.15 Questions for self understanding

1) What type of cycloaddition is shown in each equation?



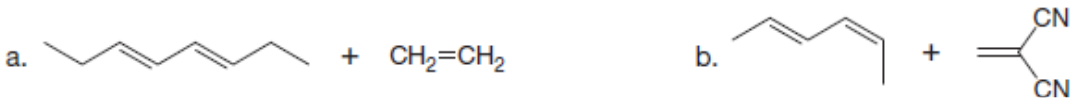
2) Consider cycloheptatrienone and ethylene, and draw a possible product formed from each type of cycloaddition: (a) [2 + 2]; (b) [4 + 2]; (c) [6 + 2].



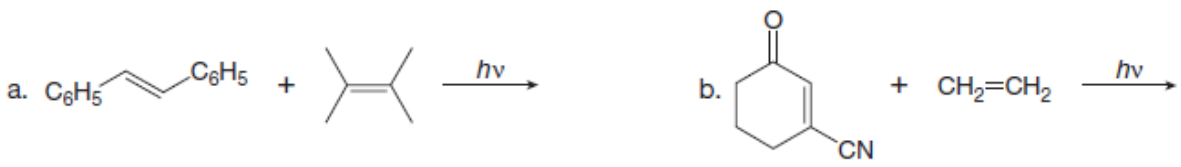
cycloheptatrienone

3) Show that a thermal suprafacial addition is symmetry allowed in a [4 + 2] cycloaddition by using the HOMO of the alkene and the LUMO of the diene.

4) Draw the product (including stereochemistry) formed from each pair of reactants in a thermal [4 + 2] cycloaddition reaction.



5) Draw the product formed in each cycloaddition.



6) Using the Woodward–Hoffmann rules, predict the stereochemistry for each cycloaddition: (a) a [6 + 4] photochemical reaction; (b) an [8 + 2] thermal reaction.

7) Using orbital symmetry, explain why a Diels–Alder reaction does not take place under photochemical reaction conditions.

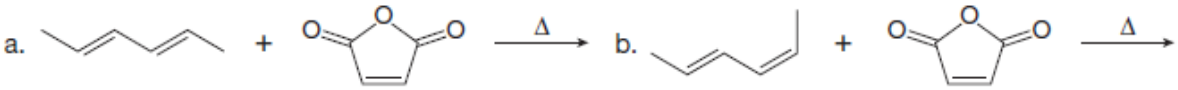
8) Using the Woodward–Hoffmann rules predict the stereochemistry of each reaction.

a). a [6 + 4] thermal cycloaddition

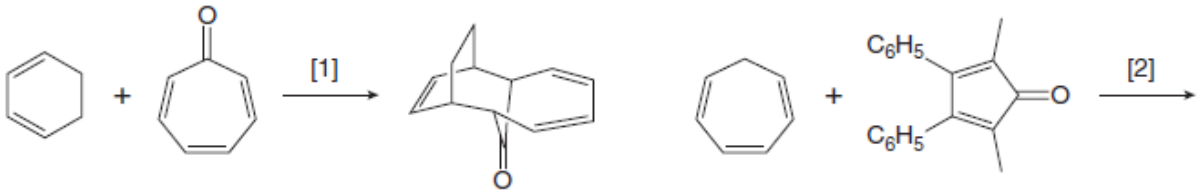
b). a [4 + 4] photochemical cycloaddition

c). photochemical ring opening of 1,3,5-cyclooctatriene

9) Draw the product of each Diels–Alder reaction and indicate the stereochemistry at all stereogenic centers.



11) What type of cycloaddition occurs in Reaction [1]? Draw the product of a similar process in Reaction [2]. Would you predict that these reactions occur under thermal or photochemical conditions?



UNIT-3

Structure

4.0 Objectives of the unit

After studying this unit you are able to

- Write the different reagents used in 1,3-Dipolar cycloaddition reactions
- Write the mechanism of 1, 3-dipolar cycloaddition reaction
- Explain the orbital symmetry analysis of 1, 3-dipolar cycloaddition reaction
- Explain the stereochemistry of 1,3-dipolar cycloaddition reactions:
- Write the different methods of generation of nitrile oxides
- Write the different reactions of nitrile oxides

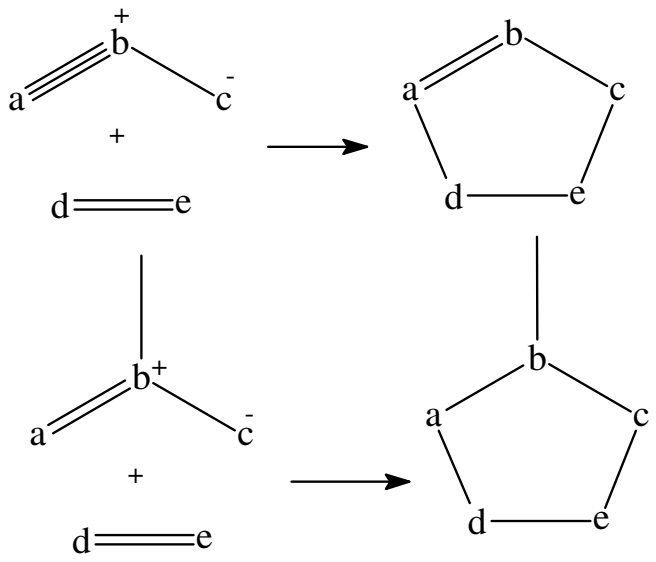
3.1 Introduction

Cyclic frameworks are ubiquitous in many complex and biologically interesting molecules. The construction of cyclic systems has thus been a long endeavor of synthetic organic chemists. Cycloaddition reactions proved to be a powerful tool in this construction. For example, the stereospecific nature of concerted cycloadditions sets the configuration of stereocenters in these molecules. The most familiar of these cycloadditions is the [4π + 2π] Diels-Alder reaction, discovered in 1928 and used extensively in the stereospecific construction of 6-membered ring systems. A 5-membered-ring forming [4π + 2π] analog has also been studied and exploited for many years and are called the 1,3-dipolar cycloaddition reactions.

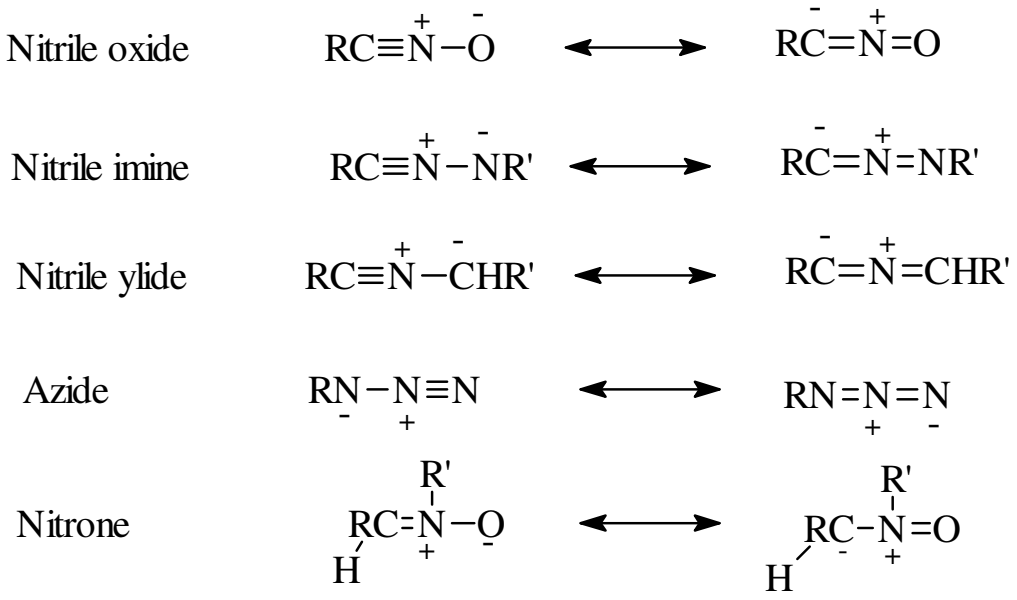
The descriptions of 1,3-dipoles and their cycloadditions go back over 100 years and predate the discovery of the Diels-Alder reaction. Though hotly debated for years, it is now generally accepted that both reactions usually proceed through a concerted reaction mechanism. For the 1,3-dipolar cycloaddition case, this was elegantly demonstrated by Huisgen, based on kinetic measurements, stereochemical results, solvent effects and substituent effects. However, this mechanism was passionately disputed for years between Huisgen and Firestone, who favored the formation of a diradical intermediate. The experimental efforts of several groups involved in this dispute lent support to the concerted mechanism based on the stereospecificity of the reaction. An appreciation of the stereospecificity of these cycloadditions can be illustrated through the use of FMO theory as well as experimental outcomes. Additionally, even though 1,3-dipolar cycloadditions tend to proceed through a concerted mechanism, exceptions have been demonstrated.

3.2 1,3-Dipolar cycloaddition reactions

The general concept of 1, 3-Dipolar cycloaddition reactions was evolved out of the monumental work carried out in the early 1960's by Huisgen and his Coworkers. The reaction can be represented as follows.



In this reaction, a five membered ring is formed by the cycloaddition of a three atom entity, ***a-b-c*** called as 1, 3-dipole molecule and a two atom entity, *d-e* called as dipolarophile. 1, 3-Dipolar molecule is defined as a species that is represented by zwitterionic octet and sextet structures as shown in scheme 1. The three atoms can be a wide variety of combination of C, O and N.



Scheme 1

In all 1, 3-dipoles, there are four electrons in three parallel ψ orbitals. From the resonance structures contributing to the dipole, it is clear that the 1, 3-dipoles can be both nucleophilic and electrophilic in nature. This ambivalence of the 1, 3-dipole is of key importance in understanding its reactivity. The nucleophilic character of the 1, 3-dipole may be stronger than its electrophilic quality. Compounds such as nitrile ylides or diazomethane will cycloadd to electron deficient

dipolarophiles much faster than with electron rich multiple bonds. The opposite is true for ozone, which combines preferably with electron rich dipolarophiles.

The dipolarophile can be virtually any double or triple bonded species. Other multiple bonded functional groups such as imines, azo and nitroso can also act as a dipolarophiles. Because of the wide range of structures that can serve as either a 1, 3-dipole or a dipolarophile, the 1, 3-dipolar cycloaddition is a very useful reaction for the construction of a five membered heterocyclic rings

3.3 Mechanistic consideration of 1, 3-dipolar cycloaddition reaction:

Huygens and co-workers have systematically studied the mechanism of 1, 3-dipolar cycloadditions. In the majority of 1, 3-dipolar cycloadditions, the reaction rate is not markedly influenced by the dielectric constant of the solvent medium in which the reaction is conducted. Firestone has proposed a two stage mechanism involving a biradical intermediate for this reaction. However, there is general agreement that, the reaction is a [3+2] cycloaddition reaction and in terms of orbital symmetry classification, it is classified as a $[\psi^4_s + \psi^2_s]$ cycloaddition reaction analogous to that of Diel's-Alder reaction.

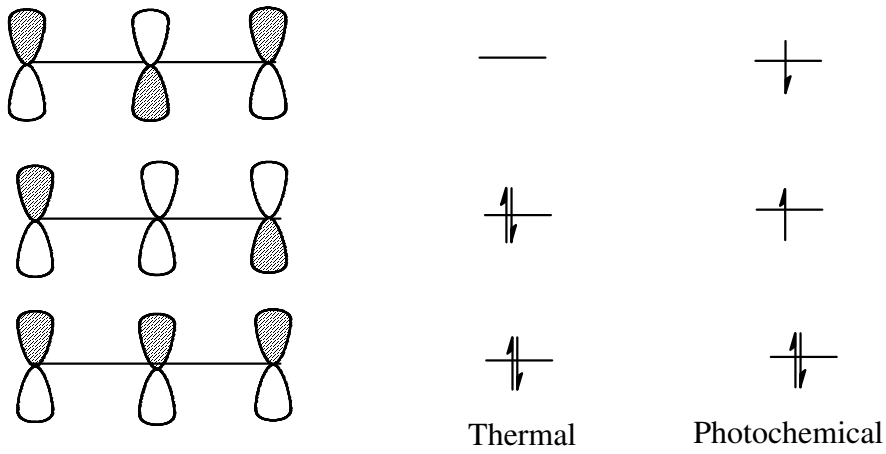
The destruction of charge separation that is implied is more apparent than real, because most 1, 3-dipolar compounds are not largely polar. The polarity implied by any single structure is balanced by the other contributing structures.

3.4 Orbital symmetry analysis of 1, 3-dipolar cycloaddition reaction

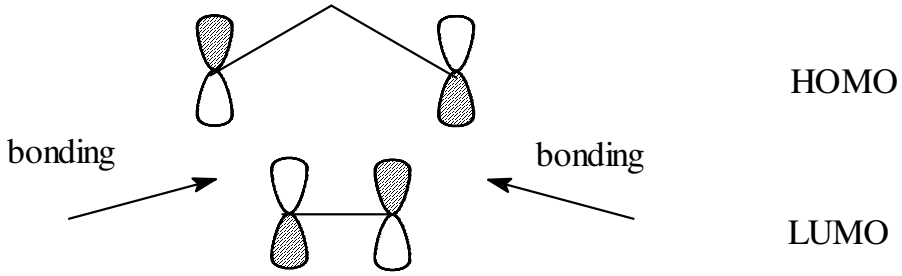
3.4.1 FMO method

In 1, 3-dipolar cycloaddition reaction, two new bonds are formed by the use of Ò electrons of the reactants. The concerted reaction results from the overlap of orbitals of one molecule (dipolar) with the orbitals of the other (dipolarophile). As in the case of electrocyclic reactions, here also one can concentrate on the HOMO. If one does so, what is seen here is HOMO of each reactant is fully occupied by two electrons. Therefore, HOMO-HOMO interaction is not possible. In order to form a bond, each HOMO has to overlap with an empty orbital. Therefore, a HOMO picks up the most stable of the empty orbitals i.e. LUMO.

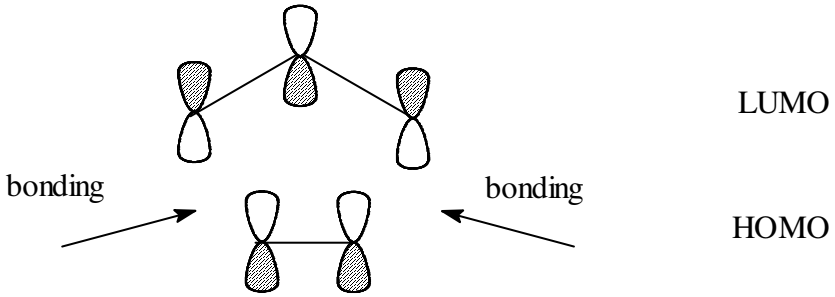
In the transition state of 1, 3-dipolar cycloaddition, stabilization chiefly comes from the overlap between the HOMO of one reactant (dipole or dipolarophile) with the LUMO of the other (dipolarophile or dipole) in bonding fashion.



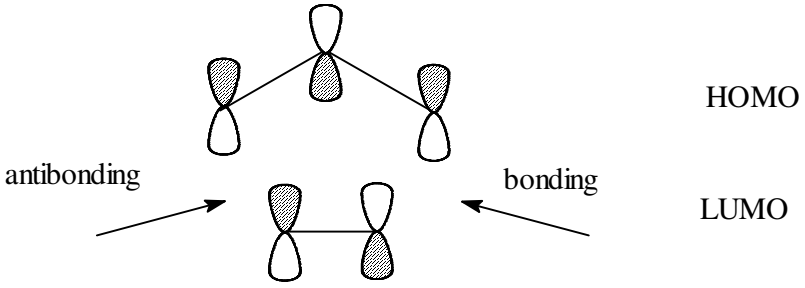
Let us first consider the HOMO of 1,3-dipole and LUMO of dipolarophile.



Let us first consider the LUMO of 1,3-dipole and HOMO of dipolarophile.



Thus 1,3-dipolar cycloaddition is a thermally allowed reaction. For photochemical reaction, HOMO in excited state of one reactant (dipole/dipolarophile) and LUMO in ground state of another (dipolarophile/dipole) has to be considered. HOMO of excited state of 1,3-dipole is ψ_3 and LUMO of ground state of dipolarophile is $\boldsymbol{\pi}^*$



Therefore, $[\pi^4_s + \pi^2_s]$ photochemical reaction is forbidden.

3.5 Stereochemistry of 1,3-dipolar cycloaddition reactions:

The stereochemistry of 1,3-dipolar cycloaddition reaction is a stereospecific *syn* addition with respect to dienophile. With some dipoles, two possible diastereomers can be formed by *syn* addition. These result from two differing orientations of the reactant molecules.

The possibility of two orientations for addition makes this reaction a regioselective as well. The regioselectivity can be interpreted in terms of interaction between the FMO of 1,3-dipole and dienophile. Usually, for dipolarophiles with electron-attracting groups, the dipole-HOMO and dipolarophile-LUMO interaction is dominant. The reverse is true for dipolarophiles with electron-donating groups. However, there are HOMO-LUMO interactions of comparable magnitude.

According to the principle of maximum overlap, the preferred isomers of each interaction can be predicted by union of two sites of the reactants having the largest coefficient value. For example, the addition of methyl cinnamate to diazomethane. Due to the two different possible orientations of methyl cinnamate, the formation of two regioisomers namely pyrazoline-3-carboxylic ester and pyrazoline-4-carboxylic ester is possible. But the pyrazoline-3-carboxylic ester is a preferred one.

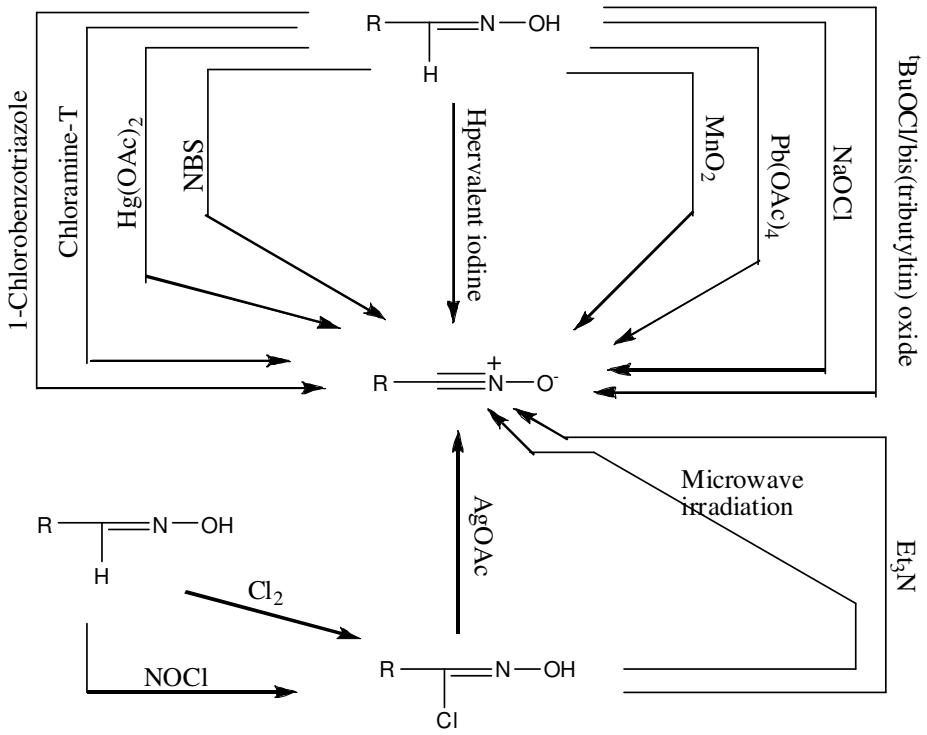
3.6 Generation of nitrile oxides

All known methods for the synthesis of nitrile oxides start with organic system already containing -C-N-O sequence of the nitrile oxide structure. Many methods are reported to generate nitrile oxide. The usual synthetic methods of nitrile oxides involve the oxidative dehydrogenation of aldoximes, the dehydration of primary nitro compounds with aryl isocyanate and the dehydrohalogenation of hydroxyiminoyl halides. Hydroximoyl chlorides are generated from oximes by chlorination with chlorine, N-chlorosuccinimide, nitrosyl chloride, sodium hypochlorite or tert-butyl hypochlorite. Tokunaga et al utilized silver acetate for the generation of nitrile oxide starting from hydroxyimoyl halides. Loupy *et al* developed a new method for the generation of nitrile oxides by microwave irradiation of hydroximoyl chlorides in the presence of dipolarophiles. Nitrile oxides are generated from *O*-trimethylsilylhydroximoyl chlorides by treatment with potassium fluoride in acetonitrile at ~20^{o}C or from hydroximoyl chlorides using molecular sieves (3-5Å) in CH_2Cl_2.

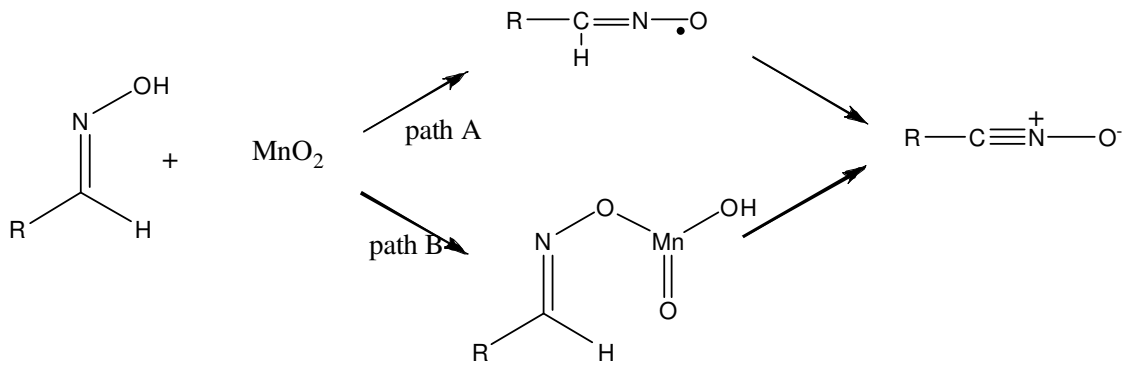
A few oxidative dehydrogenation methods of aldoximes using oxidants such as lead tetraacetate, alkali hypohalite, N-bromosuccinimide in dimethyl formamide followed by base treatment, 1-chlorobenzotriazole, chloramine-T mercuric acetate are reported. *In situ* generation of nitrile oxide from aldoxime by potassium fericycanide require aqueous medium while that of ceric ammonium nitrate can be used only for aromatic aldoximes. Radhakrishna *et al* reported the use of hypervalent iodine compounds as a oxidizing agent for the *in situ* conversion of aldoximes to nitrile oxides. Since the workup require alkaline condition, this method is limited to alkaline resistant compounds. Moreya *et al* reported the *insitu* generation of nitrile oxides by the reaction of aldoximes with

tertiary butyl hypochlorite and bis (tributyltin) oxide. The reaction proceeded efficiently under mild condition in which O-stannylated aldoximes are thought to be the intermediate.

Rai and Hassner's method not only allows *in situ* generation but also allows the isolation of nitrile oxides from aldoximes using chloramine-T as dehydrogenating reagent. This reaction is usually carried out by heating a mixture of aldoxime and an alkene in ethanol in the presence of chloramine-T. By employing this method, we have isolated and characterized the nitrile oxide, of which some are liquids and some are solids. The unstable compound identified by NMR spectrometry slowly dimerizes on standing it alone or in presence of added vinyl sulfone, undergo cycloaddition to yield isoxazoline in good yield.



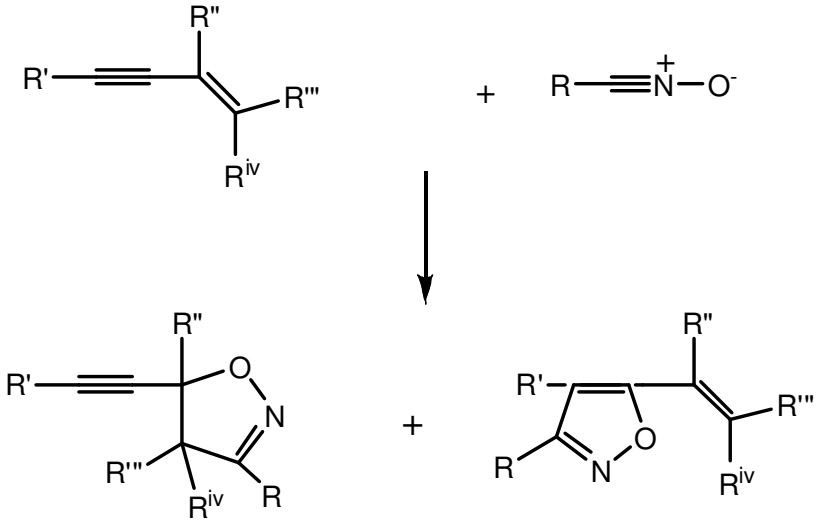
Manganese(IV) oxide (MnO_2) was found effective for the *in situ* generation nitrile oxide from aldoximes. Keigiel *et al* proposed the following mechanism for the oxidation of aldoxime to nitrile oxide (path B), analogous to the oxidation of aldoximes to nitrile oxide by lead tetraacetate.



The exomethylene pyrolidine system undergoes a highly regioselective 1,3-dipolar cycloaddtion reaction with nitrile oxide generated from the corresponding aldoxime afforded spiro isoxazoline protein based aminoacids in good yields and with 1:4 *cis-trans* diastereoselectivity.

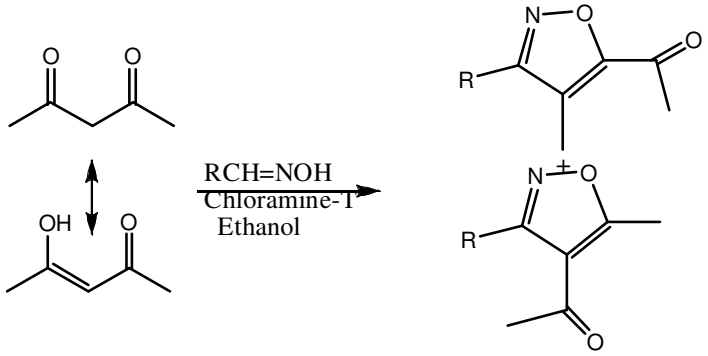
3.7 Reactions of nitrile oxides

Nitrile oxides undergo 1,3-dipolar cycloaddition reactions with various dipolarophiles. Alkenes and alkynes serve as an excellent dipolarophiles. Cycloaddition of nitrile oxides to olefins yield isoxazolines while addition of nitrile oxide to alkyne yield isoxazole directly. If the dipolarophile posses more than one set of unsaturation as in an en-yne, addition to either (or both) site(s) may occur. Indeed with nitrile oxides as dipole and 1,3-en-yne as substrate, the chemoselectivity is very sensitive to the substitution pattern of the en-yne, either product may predominate.

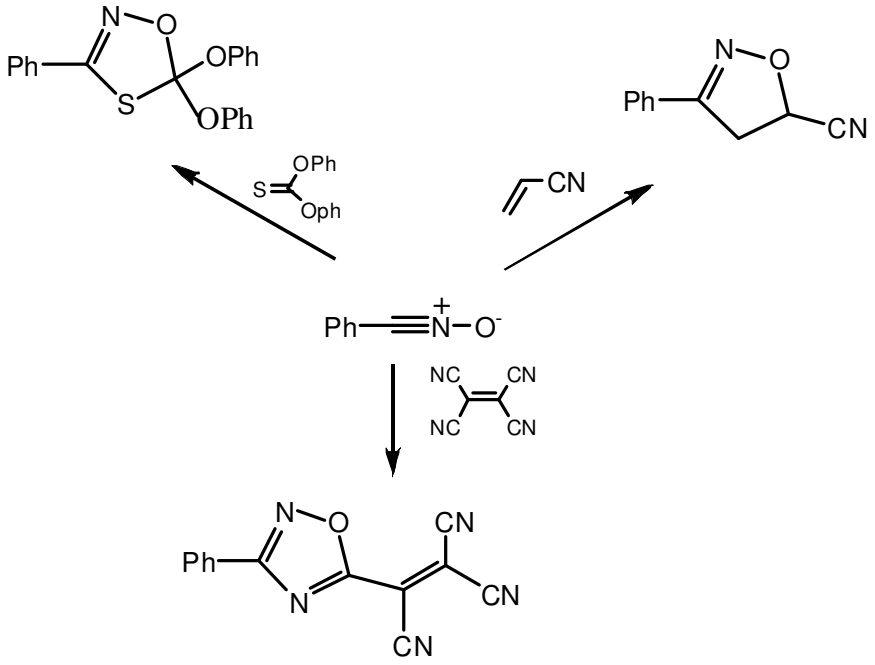


Unlike the frequently unselective reaction of 1,3-en-ynes with 1,3-dipole, nitrile oxides add chemo, regio and stereoselectively to the free double bond of (1,3-en-yne)$Co(CO)_6$ complexes to provide 5-alkenyl-2-oxazoline derivatives in moderate yield. The ability to add nitrile oxides is not restricted to C-C multiple bonds.

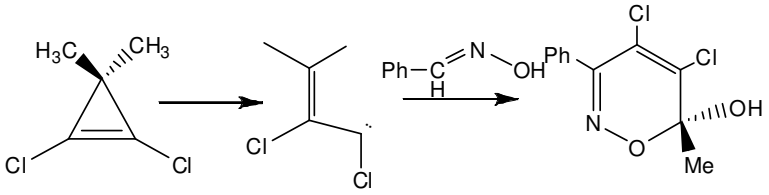
Thus C=O group may act as a dipolarophile and yield 1,3,4-dioxazoles. However C=O is less reactive as a dipolarophile. This is clearly shown by the reaction of nitrile oxide with acetyl acetone. Here acetylacetone prefers to react as an enol (80%) rather than as a ketone.



Though C=S group is not a good dipolarophile in Diel's-Alder reaction, as a dipolarophile C=S group is very reactive. 1,3-Dipoar cycloaddition of nitrile oxides to C=S group yields 1,4,2-oxathiazolines. The C-N group normally does not undergo 1,3-dipolar cycloaddition reaction because it is poorer dipolarophile compared to C=C group. Thus, in the case of acrylonitrile, nitrile oxide reacts with alkene to form cyano substituted 2-isoxazoline. However, if the C=C bond is deactivated by multiple substitution, the C-N group may become a better dipolarophile. Thus, tetracyano ethylene adds nitrile oxide yielding 1,2,4-oxadiazole derivative as one of the product. Apart from this dipolarophile, nitrile oxide adds to other multiple bonds to give corresponding 5-membered heterocycles.



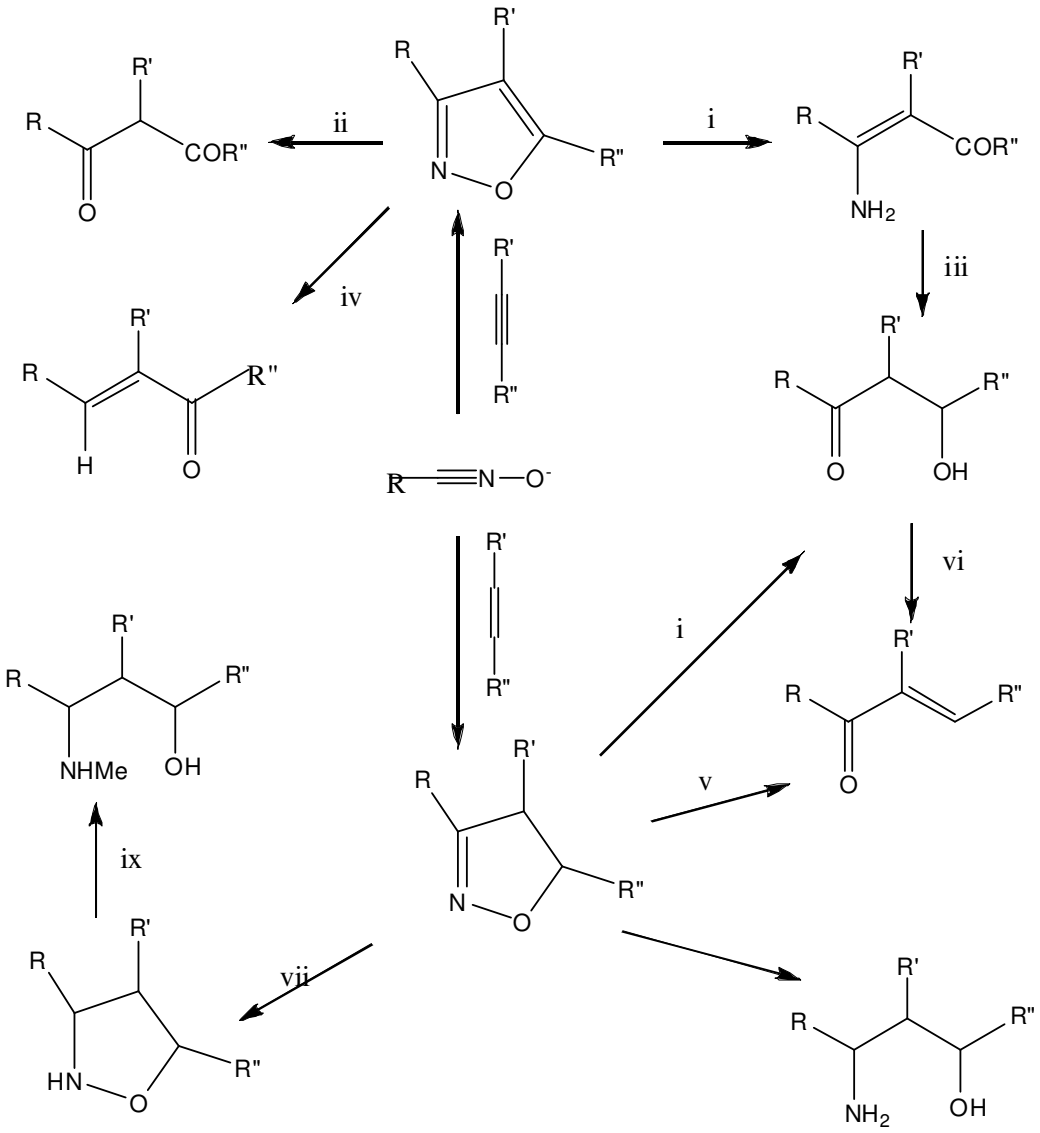
The unusual formal [3+3] cycloaddition of nitrile oxide with vinyl carbene derived by the ring opening of the cyclopropene yield 1,2-oxazines in moderate to good yield but it is not clear whether 1,2-oxazine is directly formed by concerted cycloaddition or by a stepwise process.



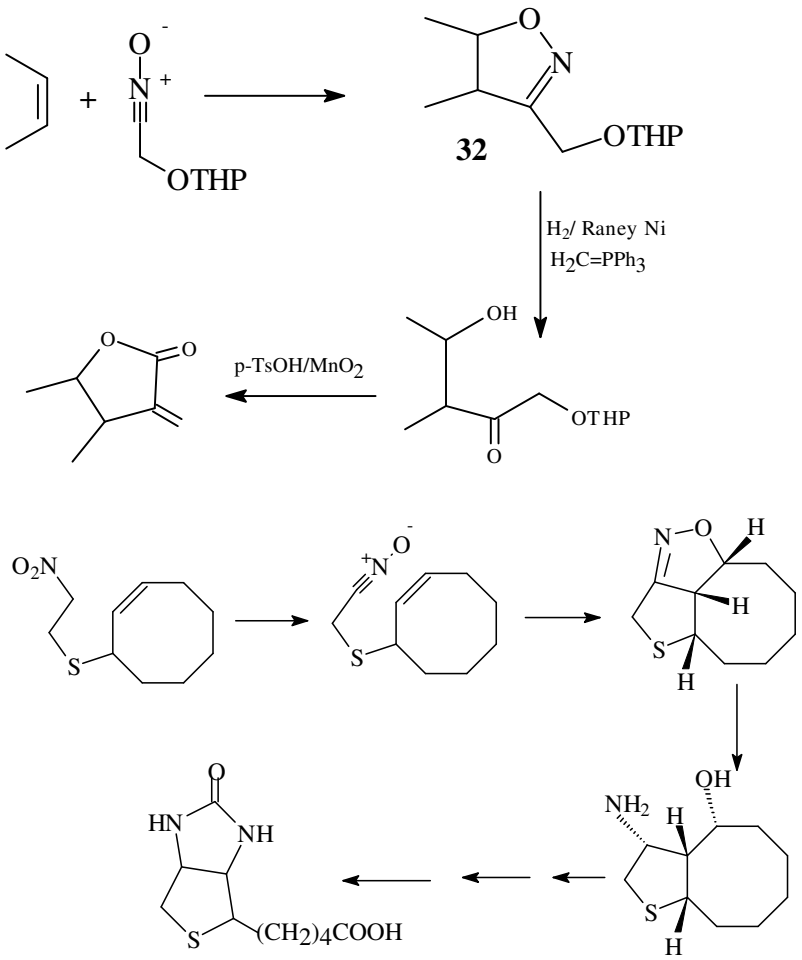
3.8 Application of nitrile oxide cycloaddition reactions

1,3-Dipolar cycloaddition of nitrile oxide to C=C bond of dipolarophile is of considerable importance in organic synthesis, since this reaction yields 2-isoxazolines. Isoxazole and isoxazolines were serve as an important building blocks in the construction of new molecular systems for several reasons. First of all, they can be very efficiently prepared from readily available precursors; secondly, they can be conveniently modified, thus allowing transformation of molecule

with simple structure to functionally complex derivatives; thirdly, a suitable pattern of substituents makes the isoxazoline ring survive under a variety of chemical reaction conditions, thus allowing manipulation in other parts of the molecule; and finally the lability of the nitrogen-oxygen bond to catalytic or chemical reduction under mild conditions unravels a vast array of different functionalities. Baraldi *et al* synthesized β-hydroxy ketones from isoxazolines utilizing molybdenum hexacarbonyl as catalyst for the ring cleavage.



i. H_2, catalyst; or Mo(CO)6 ii. H_3O^+
iii. PhCOCl, Py, $NaBH_4$, AcOH;
iv. Birch reduction, TsOH
v. LDA in THF, $TiCl_3$/HCl
vi. NaOH; vii. $NaBH_4$, MeOH;
viii. LiAlH4; ix. MeI, H_2 catalyst or ZnOH



3.9 Summary of the unit

In addition to making 6-membered rings with Diels-Alder reactions, and 4-membered ring systems by [2+2] cycloadditions, cycloadditions can also furnish 5-membered rings. This reaction is called the 1,3-dipolar cycloaddition. The reagents used for these reactions are called 1,3 dipoles, because of one of the possible resonance structures of these reagents carry a positive and a negative charge in a 1,3 relationship. The 1,3-dipoles react with olefins to make the 5-membered rings, and in analogy to the DA reaction, the olefins are now called dipolarophiles.

1,3-dipoles always have the general structure X-Het-Y (where X and Y are carbons or heteroatoms, Het stands for heteroatom). There are two structurally different classes, linear ones (of the "propargylic anion" type) and bent ones (of the "allyl anion type").

The majority of 1,3-dipolar cycloadditions have been found to proceed through a concerted reaction mechanism. Similar to the Diels-Alder reaction, this results in a stereospecific syn addition of the 1,3-dipole to the dipolarophile.

By making the dipole electron deficient and the dipolarophile electron rich (or vice versa) the bond formation in the concerted reaction will become asynchronous. When this is taken to the extreme,

the bond formation becomes so asynchronous that a zwitterionic intermediate is formed and nonstereospecific 1,3-dipolar cycloadditions occur. Interestingly, similar treatment of Diels-Alder dienes and dienophiles have resulted in similar loss of stereospecificity, showing that these ideas can be applied to other cycloaddition reactions.

Dipolar cycloaddition chemistry has found many useful synthetic applications, particularly with respect to the preparation of compounds with new chiral centers. This approach toward asymmetric syntheses is of major importance in both the pharmaceutical and agricultural industries.

3.10 Key words

1,3-Dipolar cycloaddition reactions; Mechanistic consideration of 1, 3-dipolar cycloaddition reaction: Orbital symmetry analysis of 1, 3-dipolar cycloaddition reaction; FMO method; Stereochemistry of 1,3-dipolar cycloaddition reactions; Generation of nitrile oxides; Reactions of nitrile oxides; Application of nitrile oxide cycloaddition reactions

3.11 References for further studies

1) Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Albert Padwa, William H. Pearson; *John Wiley & Sons*, **2003**.
2) Advanced Organic Chemistry, Part 2; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2000**.
3) Cycloaddition Reactions in Organic Synthesis; Shu Kobayashi, Karl Anker Jørgensen; *John Wiley & Sons*, **2002**.
4) Comprehensive Organic Synthesis; Paul Knochel, Gary A Molander; *Newnes*, **2014**.
5) Cycloaddition Reactions in Organic Synthesis; W. Carruthers; *Elsevier*, **2013**.
6) Methods and Applications of Cycloaddition Reactions in Organic Syntheses; Nagatoshi Nishiwaki; *John Wiley & Sons*, **2013**.

31.2 Questions for self understanding

1) What is 1,3-Dipolar cycloaddition reactions? Explain with example
2) What are dienophiles? Give three examples.
3) Discuss the mechanistic consideration of 1, 3-dipolar cycloaddition reaction:
4) Explain the orbital symmetry analysis of 1, 3-dipolar cycloaddition reaction
5) Explain the 1, 3-dipolar cycloaddition reaction using FMO method
6) Discuss the stereochemistry of 1,3-dipolar cycloaddition reactions
7) Write the different methods of generation of nitrile oxides
8) Discuss the reactions of nitrile oxides
9) Discuss the application of nitrile oxide cycloaddition reactions

UNIT-4

Structure

4.0 Objectives of the unit

After studying this unit you are able to

- Explain the sigmatropic rearrangements
- Write the classification of sigmatropic rearrangements
- Explain the sigmatropic rearrangements based on frontier molecular orbital approach
- Explain the 1,3-sigmatropic rearrangement
- Explain the [1,5]-sigmatropic rearrangement
- Explain the Woodward-Hoffmann Rule for sigmatropic rearrangements
- Explain the 3,3-Sigmatropic rearrangement (Cope rearrangement

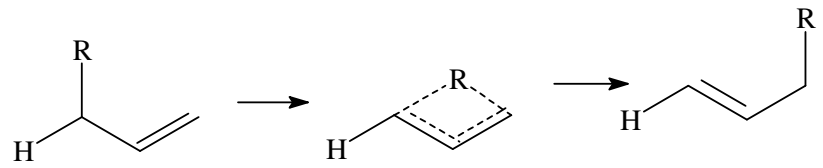
4.1 Introduction

Like electrocyclic reactions, sigmatropic rearrangements are unimolecular processes. Sigmatropic reactions involve the movement of a sigma-bond with the simultaneous rearrangement of the π-system. Sigmatropic rearrangements are the most inherently reversible of all pericyclic reactions, since there is not net change in the number of σ and π bonds. The position of the equilibrium depends on the relative thermodynamic and kinetic stability of the starting material and products. Sigmatropic rearrangements are calssified as [m,n] sigmatropic rearrangements, where m and n are the number of atoms in the fragments in between where the σ bond breaks and forms.

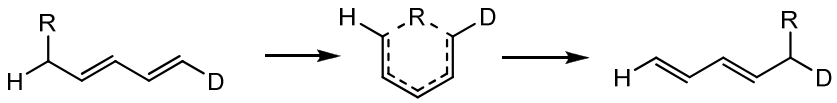
4.2 Sigmatropic rearrangements

Concerted reorganization of electrons during which an atom or a group migrates with its σ-bond from one atom to another along a π frame work (ene or polyene) is called sigmatropic reaction. The reaction is accompanied by simultaneous shift of π-bonds. Characteristic of these reactions are they are concerted, uncatalyzed and involve bond migration through a cyclic transition state.

4.3 Classification

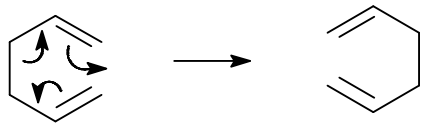


1,3-sigmatropic rearrangement



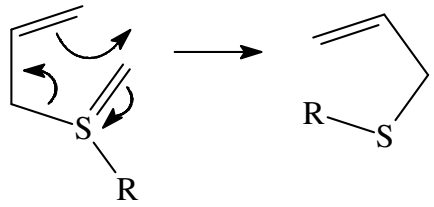
1,5-sigmatropic rearrangement

Here is the designation [1,3] and [1,5] wherein 3 and 5 refers to the carbon atom to which the group R migrating. Here 1 doesnot refer to the migration origin. In otherwords the order [i,j] specifies the number of atoms in the migrating fragement and the number of atoms in the π-system which are directly involved in the bonding changes. In the light of this, Cope rearrangement designated as [3,3] sigmatropic reaction.

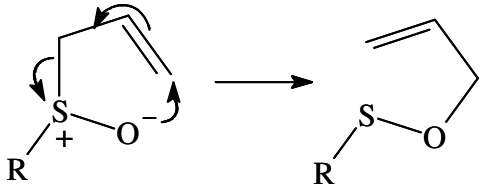


3,3-sigmatropic rearrangement or Cope rearrangeme

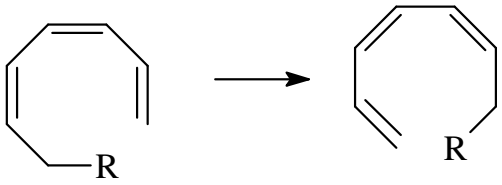
Here first 3 refers to mean that in the product the sigma bond is connected to carbon atom 3 and second 3 refers to mean that the sigma bond is moved to 3rd carbon atoms from the origin.



3,2-sigmatropic rearrangement

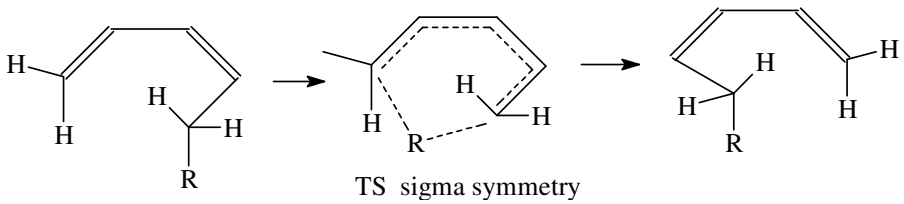


2,3-sigmatropic rearrangement

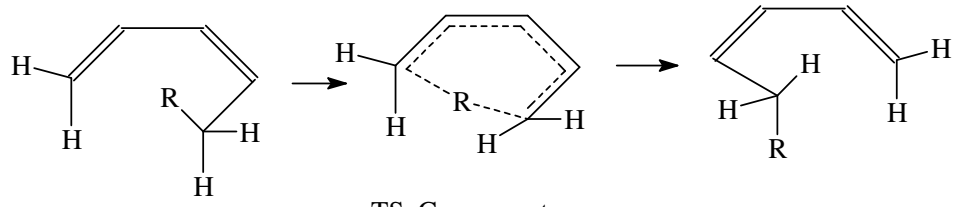


1,7-sigmatropic rearrangement

Thus when a sigma bond moves across two parts polyene system, the number of both termini are indicated. Generally they are represented as [i,j].



TS sigma symmetry



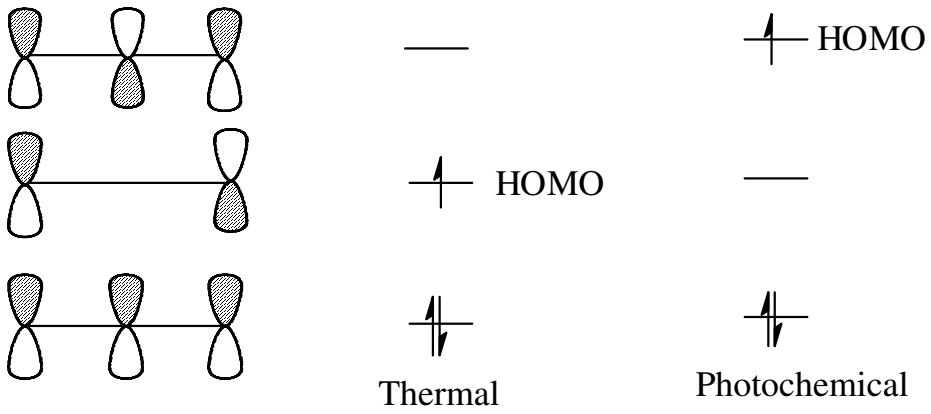
TS C_2 symmetry

4.4 Frontier molecular orbital approach

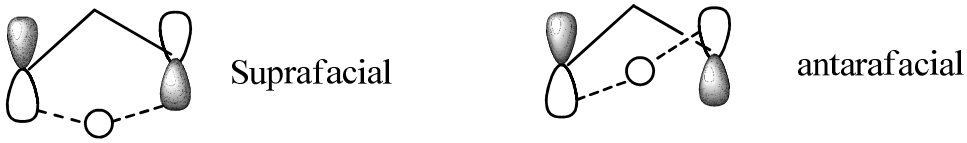
For the analysis of sigmatropic rearrangement it may be assumed that migrating bond undergoes homolytic cleavage to yield a pair of radicals. But bonding character is maintained throughout the rearrangement. Most important bonding interactions are those in which HOMO of two species are produced by cleavage which contain unpaired electrons.

4.4.1 1,3-sigmatropic rearrangement

This method of analysis can be illustrated by the example of antarafacial [1,3] sigmatropic rearrangement of hydrogen in which homolytic cleavage produces H-atom and allyl radical.

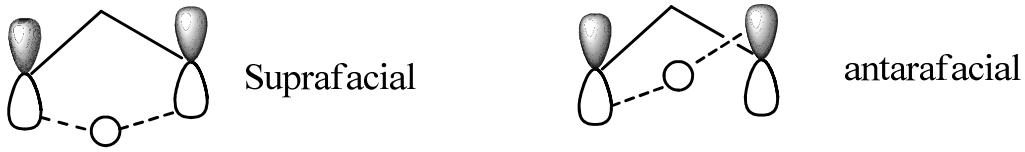


Ground state electronic configuration of allyl radical is ψ_1,ψ_2 and ψ_3. HOMO among these is ψ_2 which has opposite signs on terminal lobes (hence possess C2-axis of symmetry). A bonding interaction can be maintained only in antarafacial mode. Therefore the [1,3]-sigmatropic suprafacial hydrogen shift is considered forbidden. Since the geometry used for the orbital symmetry allowed antarafacial shift.



Thermal

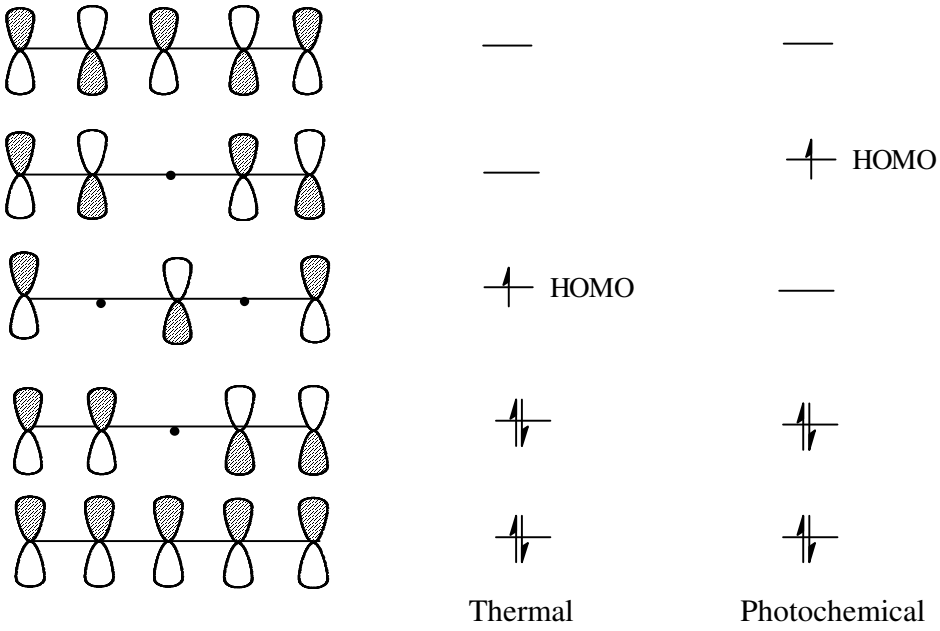
The first excited state of allyl radical has configuration ψ_1 and ψ_3, therefore symmetry properties are reversed. Now HOMO has plane of symmetry. Therefore [1,3]-sigmatropic suprafacial hydrogen shift is allowed process.



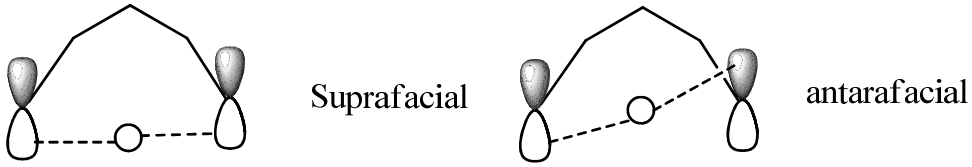
Photochemical

4.4.2 [1,5]-sigmatropic rearrangement

A similar analysis of the 1,5-sigmatropic hydrogen shift leads to the opposite conclusion. Therefore the suprafacial is allowed and the antarafacial mode is forbidden. The frontier orbitals are hydrogen 1S and the pentadienyl ψ3 orbitals respectively.

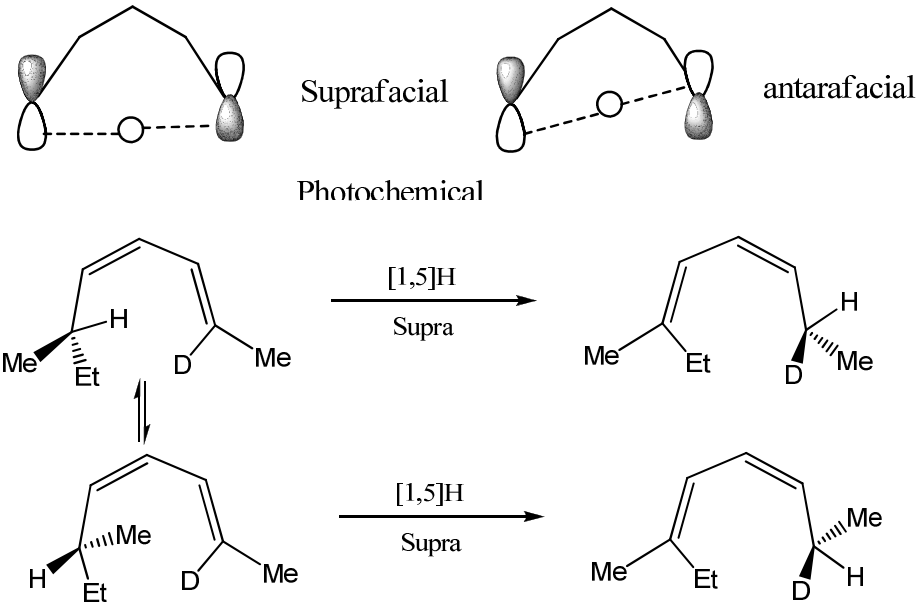


We notice that the interaction between 1S orbital of hydrogen atom and the components of ψ_3 of the pentadienyl at both C1 and C5 is bonding. Here important noteis that hydrogen atom is transfered from top face to the top face of ψ_3. i.e hydrogen remains on the same face of the unsaturated system. This is called supraqfacial process. Therfore [1,5]-sigmatropic shift is allowed.

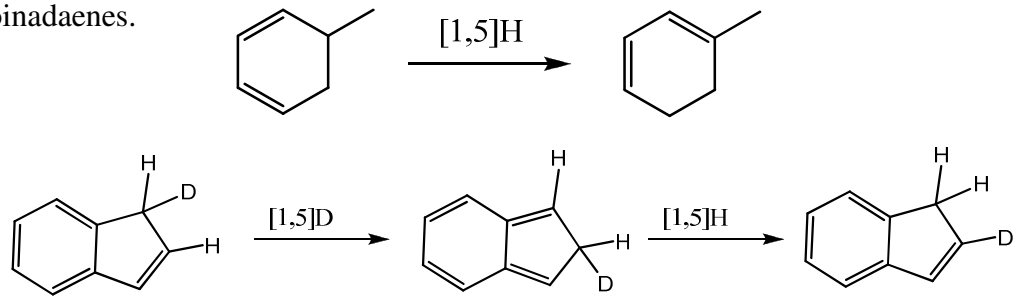


Thermal

The first excited state of pendadienyl radical has configuration ψ_1, ψ_2 and ψ_4, therefore symmetry properties are reversed. Now HOMO has C2-axis of symmetry. Therefore [1,5]-sigmatropic suprafacial hydrogen shift is no longer possible. Therefore photochemical [1,5]-sigmatropic shift proceeds antarafacially.



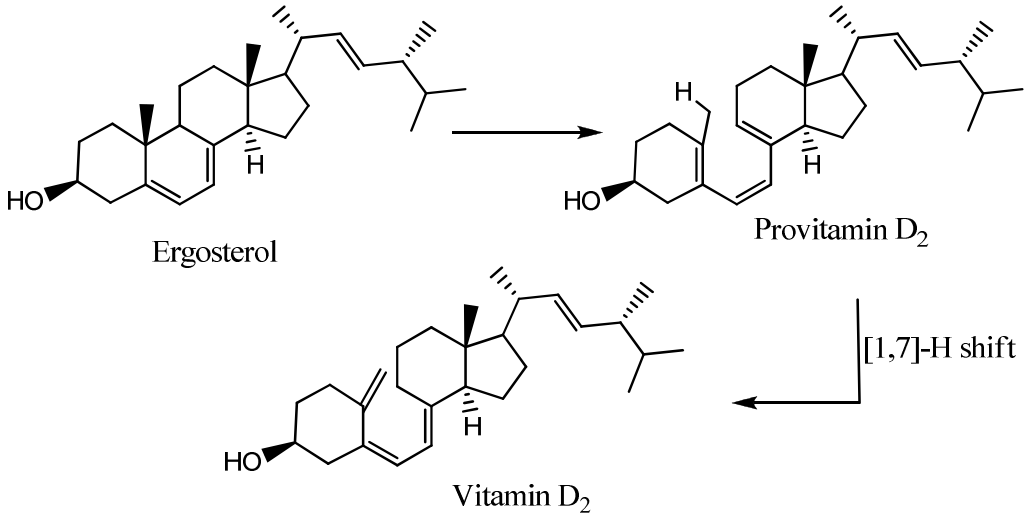
Here energy required for [1,5]-H migration is approximately lower than in open chain system. In this system a [1,5]-H migration simply involves the movement of hydrogen to an adjacent carbon atoms. The preference for over [1,3] shift in such system is demonstrated for 1-deueteroindane. When this was heated, the deuterium becomes scrambled over three non benzenoid carbons. The presence of 2-deuteroindane product mixture indicates that the system prefers to rearrange by successive [1,5] shifts rather than by [1,3] shifts, eventhough [1,5] shifts involve the intermediacy of isoinadaenes.



4.5 Woodward-Hoffmann Rule for sigmatropic rearrangements

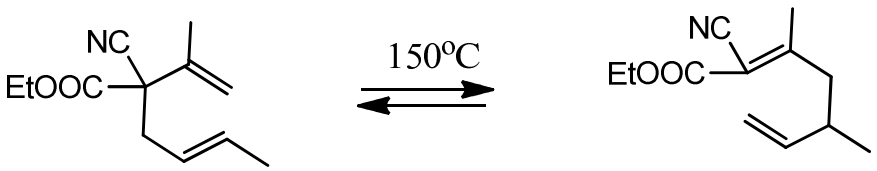
Type	Thermal	Photochemical	Order (i+j)
1,3-	Antara	Supra	4n
1,5-	Supra	Antara	4n+2
3,3-	Supra	Antara	4n+2
1,7-	Antara	Supra	4n

A key step in the human body's synthesis of vitamin D from ergosterol involves 4n+2 elctrocyclization followed by [1,7] sigmatropic reaarangment as shown below.

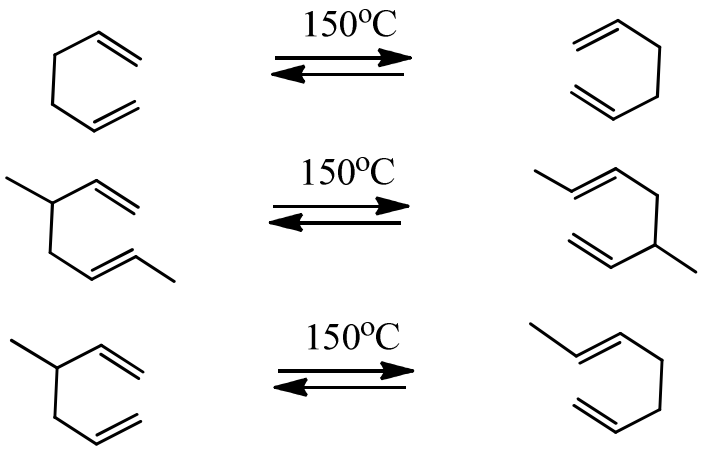


4.6 3,3-Sigmatropic rearrangement (Cope rearrangement)

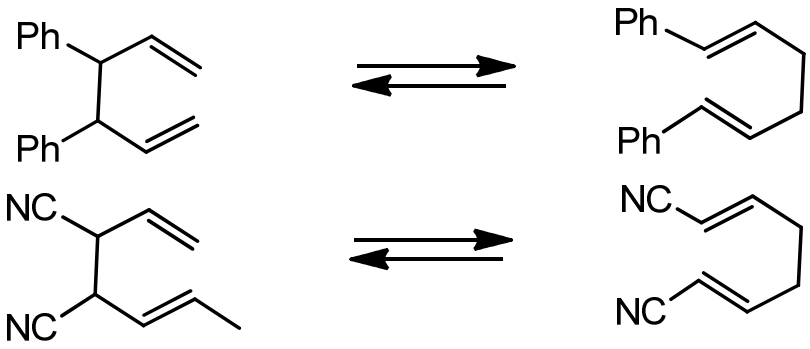
The Cope rearrangement is an organic reaction where a 1,5-diene, under thermal conditions, is converted to another 1,5-diene structural isomer. This reaction belongs to a class of reactions termed "sigma tropic rearrangements" and it is a concerted process. The Cope rearrangement is an equilibrium reaction and the equilibrium position is determined by the overall stability of the starting material and product. It was developed by Arthur C. Cope. In 1940 Cope observed that the unsaturated ester converted into its isomer merely on heating at 150°C. Soon Cope and his collaborators discovered that requirement for such thermal rearrangement is the presence of 1,5-hexadiene system.



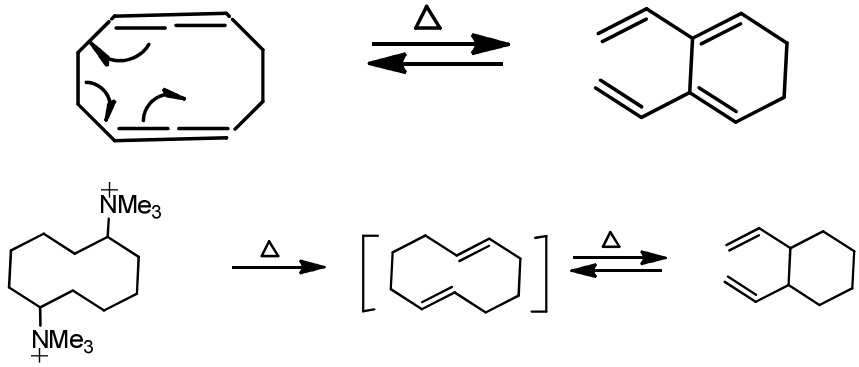
Thus in Cope rearrangement of 1,5-hexadiene derivative a new 1,6-bond is formed at the cost of opening of 3,4-sigma bond with appropriate shift of double bonds. The rearrangement is not detected when the 1,5-hexadiene is symmetrical about 3,4-sigma bond. But if the diene is unsymmetrical, in that case the products formed are different from the starting material and thus the rearrangement id detected.



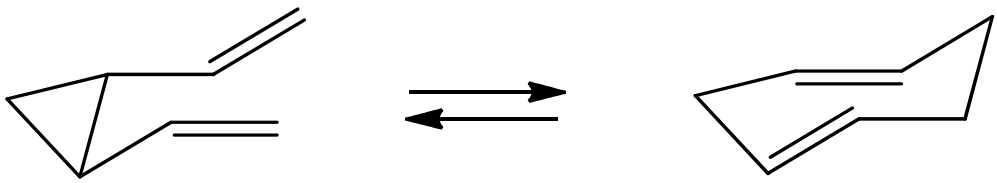
The rearrangement takes place more easily when there is group on 3rd or 4th position with which the double bond can conjugate. Since the product formed is also a 1,5-diene, it is obvious that there is a reversible and always an equilibrium mixture of two isomers is obtained and the mixture is richer in that isomer which is thermodynamically more stable. Even a difference of 4KJ/mole in free energy is enough to tilt the balance in one direction.



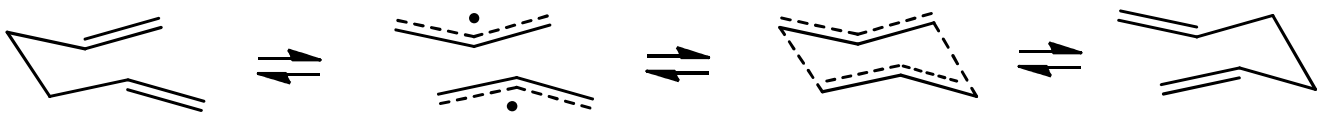
The 1,5-diene system may be inside a ring or part of an alkenic system, but the reaction doesnot take place when one of the double bond is part of an aromatic system. ex. 4-phenyl-1-butene.



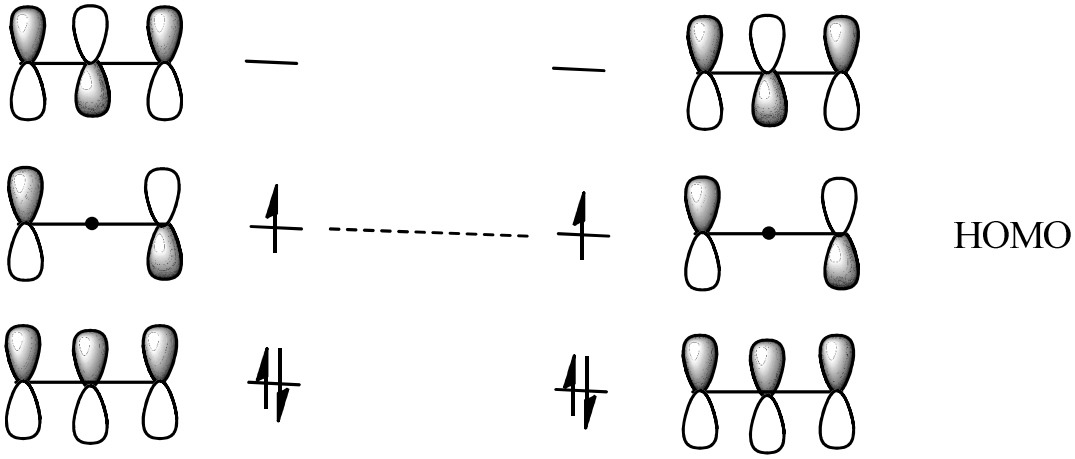
Two vinylic groups attached to a saturated cyclic ring system at vicinal position also undergo Cope rearrangement to produce the ring expanded product.



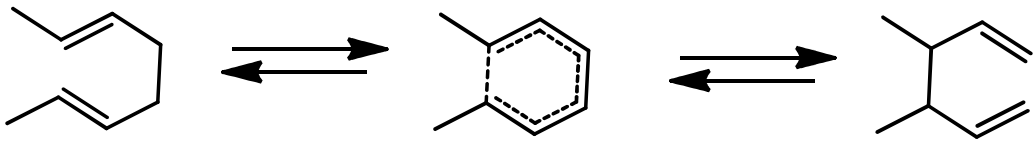
Although the Cope rearrangement is concerted and pericyclic, it can also be considered to go via a transition state that is energetically and structurally equivalent to a diradical. This is an alternative explanation which remains faithful to the uncharged nature of the Cope transition state, while preserving the principles of orbital symmetry. This also explains the high energy requirement to perform a Cope rearrangement. Although illustrated in the chair conformation, the Cope can also occur with cyclohexadienes in the "boat" conformation.



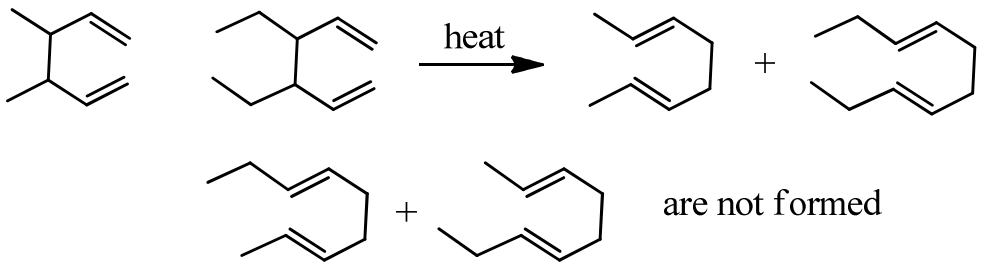
Imagine a fictitious reaction with two allyl radicals coming together in space. The HOMO of an allyl radical on one has the same symmetry as the HOMO of the other. The two unpaired electrons can interact. These radicals could approach each other and form a new bond. But the new bond could form at either end of the pair of radicals.



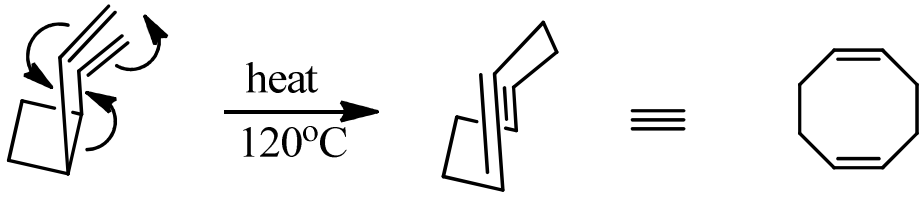
The above description of the transition state is not quite correct. It is currently generally accepted that the Cope rearrangement follows an allowed concerted route through a homoaromatic transition state and not a diradical. Mechanism of the rearrangement involves [3,3]-sigmatropic shift in a manner similar to ortho Cope rearrangement. In Claisen rearrangement it proceed through a six membered transition cyclic state involving one oxygen and five carbon atoms while in Cope rearrangement it proceed through a six membered transition cyclic state involving six carbon atoms.

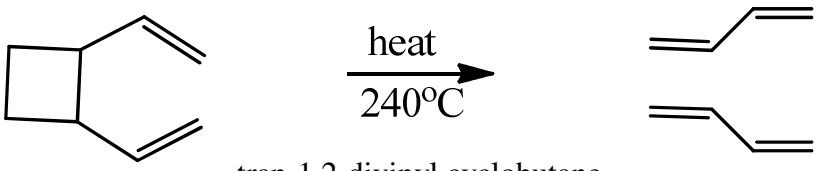


The rearrangement is intramolecular one. This is supported by the following observations: when a mixture of two different 1,5-dienes allowed to undergo Cope rearrangement, cross over products are not formed.



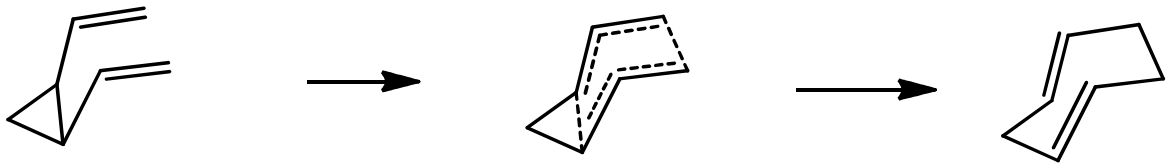
From the consideration of the examples discussed so far, it will be apparent that, in every case, the double bonds of the rearranging hexa-1,5-diene systems are located in closed juxtra position. Therefore this steric relationship is an essential requirement for the rearrangement. This has been proved by the following experiments.



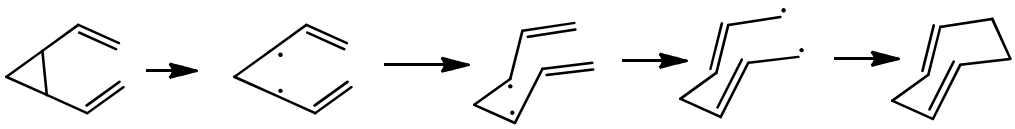


tran-1,2-divinyl cyclobutane

In cis forms, the rearranging diene systems are very close to each other, thus making overlap of the orbitals very easy while in trans, they are far away. It is believed that in case of cyclopropane derivatives, the trans isomer is rearranged to cis form first via a rotation of diradical. This rotation requires less energy, ie why trans isomer undergo rearrangement.



Quasi boat form



The transition state in the C ope rarrangement is a six membered one, question arises as to whether this T. S. is a quassi boat or quassi chair form?.It has been elegantly shown by Doeing and Roth that even in cases of substrates which are free to adopt either the boat or the chair form, the quassi chair form is deifinitley preferred. Eg. when

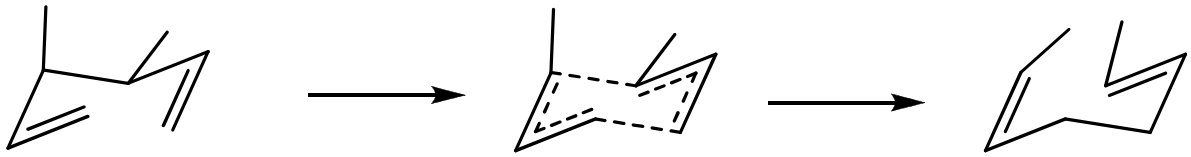
Meso 3,4-dimethyl hexadiene -----→ cis-trans octa2,6-diene (99%)

While the recemic isomer

DLMeso 3,4-dimethyl hexadiene -----→ trans-trans octa2,6-diene (90%)

cis-cis octa2,6-diene (9%)

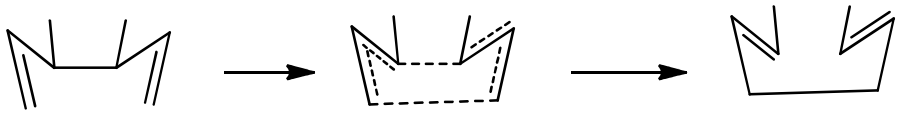
In case of meso form – if the T.S occupies chair conformation there are two ways (actually two are identical): it can do C-3 Me axial r equatorial)



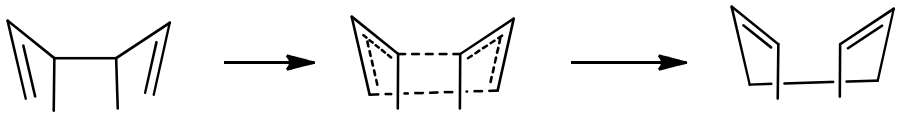
3-Me axial & 4-Me equatorial cis-trans-2,6-octadiene

4-Me axial & 3-Me equatorial trans-cis-2,6-octadiene

We see that in both cases, the product is the same (cis-trans isomer). But if the T.S occupies boat structure, there are two ways to go.



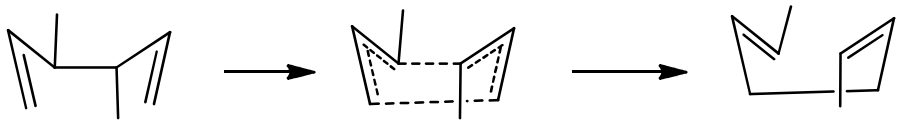
trans-trans-2,6-octadiene



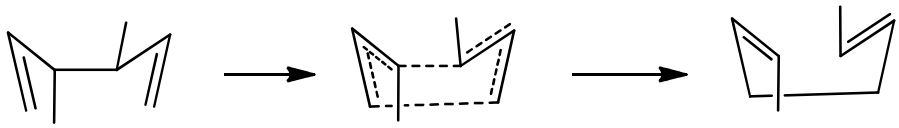
cis-cis-2,6-octadiene

Thus the formation of cis-trans product can be explained only with the chair conformation for one T.S.

In case of DL form, there is only one boat form, the TS can occupy. This TS gives cis-trans olefin and not trans-trans.

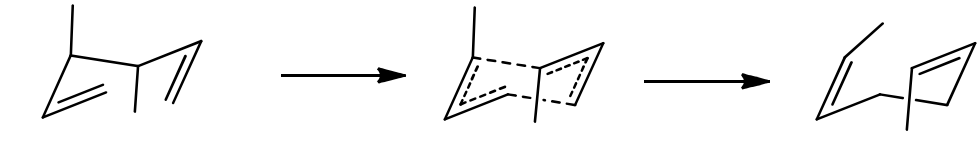


trans-cis-2,6-octadiene

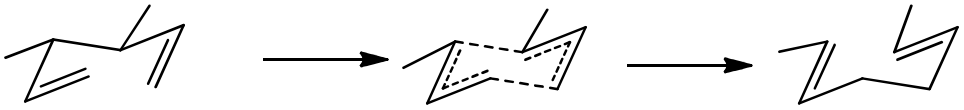


cis-trans-2,6-octadiene

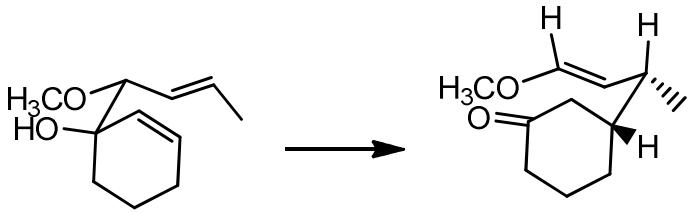
But if the TS of DL(racemic) pair occpuyies chair form, it can occupy two forms. One in which both methyl groups are axial another in which both are equatorial. The diequatorial gives the trans-trans diene (()%), diaxial gives cis-cis diene (9%) being less stable. Thus chair form is preferred in TS.

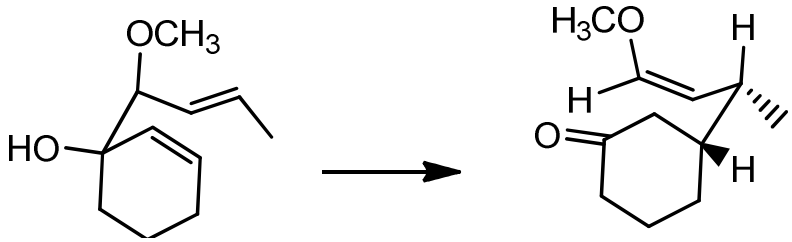


cis-cis-2,6-octadiene

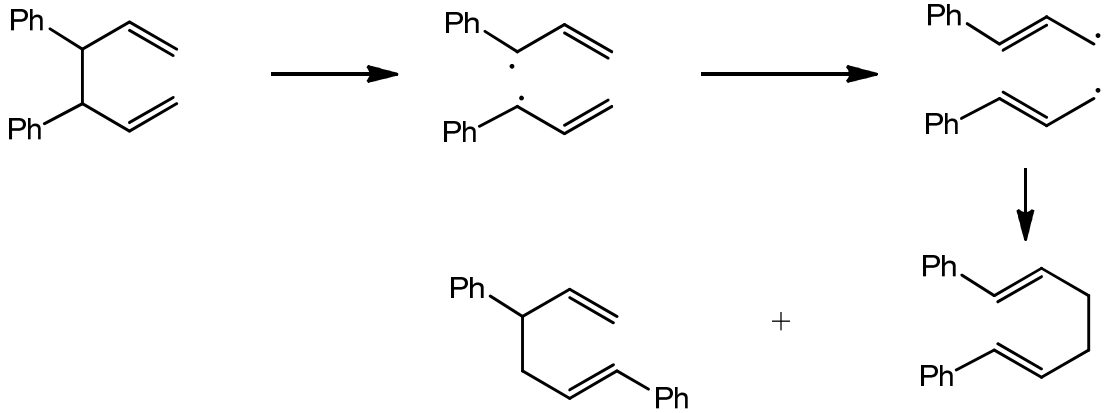


trans-trans-2.6-octadiene

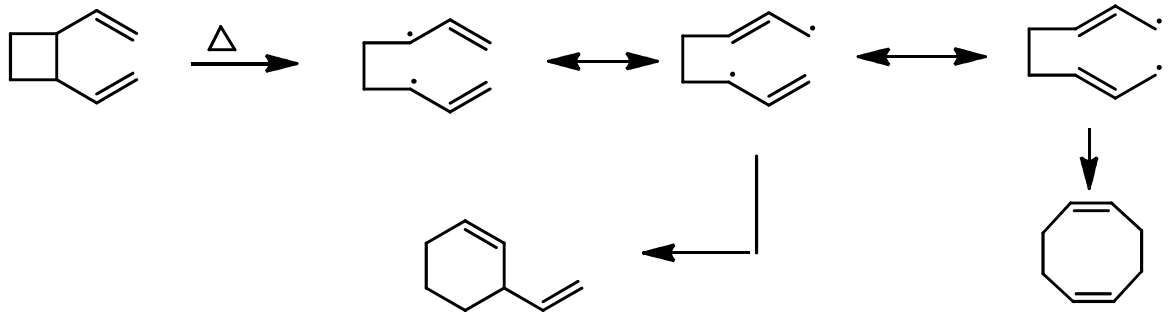




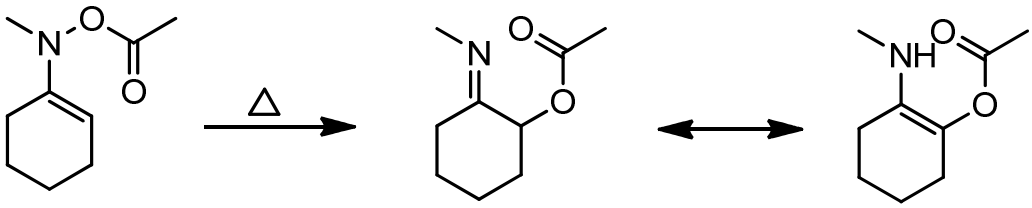
But compounds which can rearrange only through a quassi boat form may undergo reaction via boat form as explained earliar in the cases of trans divinyl cyclopropane. Further reaction is found to be first order. Not all the Cope rearrangements proceed through the six membered T.S mechanism. In certian special cases radical intermediates are observed. For example when 3,4-diphenyl-1,5-hexadene is heated, both 1,6 and 1,4-diphenyl-1,5-hexadienes are formed. This can be explained only through free radical mechanism.



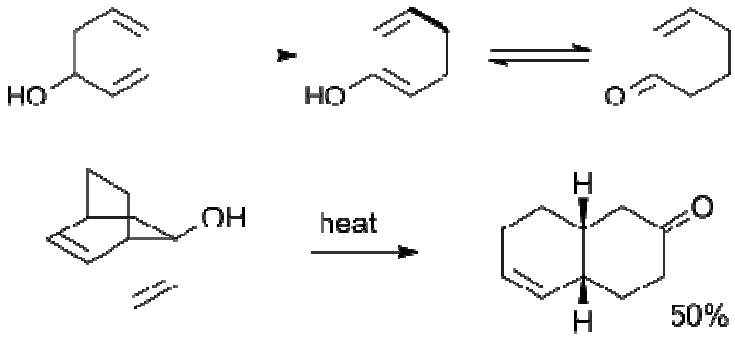
Similarly cis-divinyl cyclobutanes undergoes Cope rearrangement smoothly while trans-divinyl cyclobutanes give 4-vinyl cyclohexene as the main product. These observations can be explained only assuming free readical.



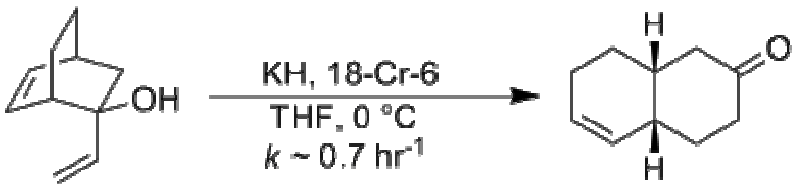
A variant of Cope rearrangement is the α-acetoxylation of ketones.



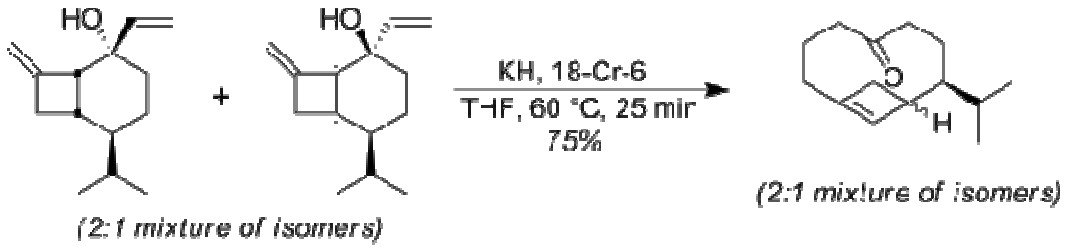
In case of 3-hydroxy-1,5-hexadiene, the reaction is not reversible, because the product formed tautomerixes to ketone or aldehyde. This rearrangement id known as O**xy-Cope rearrangement.** for instance in this reaction:



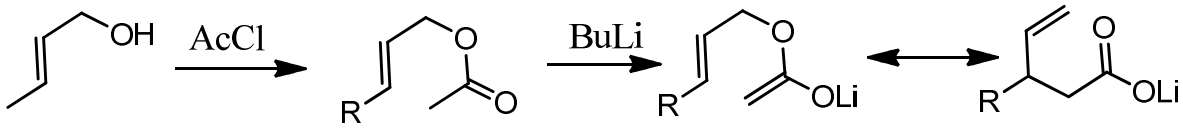
In 1975, Evans and Golob showed that deprotonation of oxy-Cope substrates to form the corresponding alkali metal alkoxides resulted in rate accelerations of 10^{10} to 10^{17} for the oxy-Cope rearrangement. Typically potassium hydride and 18-crown-6 are employed in order to generate a fully dissociated potassium alkoxide.



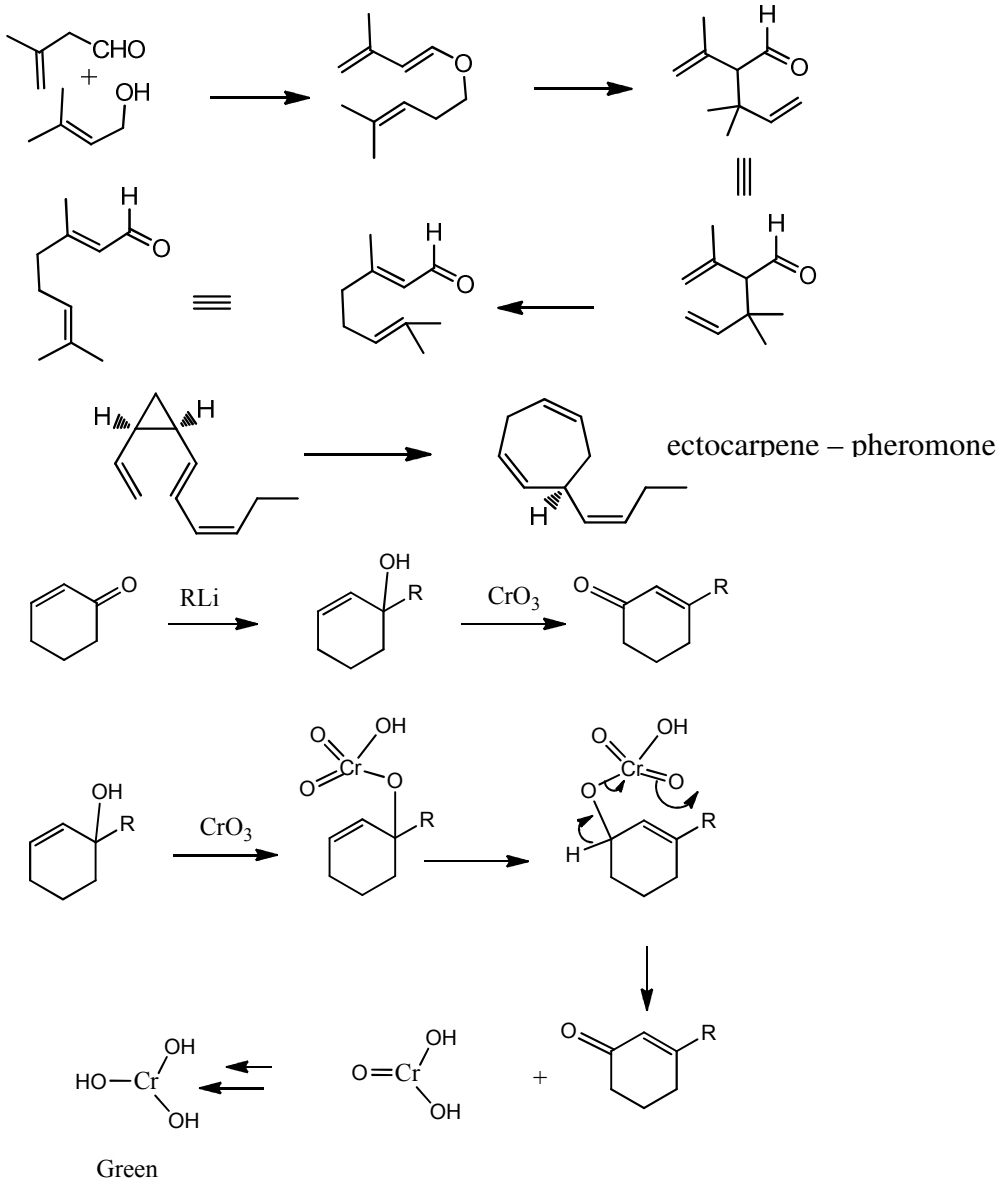
It is noteworthy that the anion-accelerated oxy-Cope reaction can proceed with high efficiency even in systems that do not permit good orbital overlap, as seen in this example from Schreiber's synthesis periplanone B



Key step for the synthesis of 4-pentenoic acid involves the Oxy-Cope rearrangement.



Similar strategy is employed for the industrial synthesis of citral. Heating the enol ether formed by the condensation of dimethyl allyl alcohol with 3-methyl-3-butenal at $0^{o}C$ underwent successive 3,3-sigmatropic rearrangement yielded citral.



4.7 Summary of the unit

A σ -bonded substituent atom or group migrates across a p electron system from one position to another. A σ bond is broken in the reactant, the p bonds move, and a new s bond is formed in the product. Numbers in brackets refer to the two groups connected by the s bond and designate the positions in those groups to which migration occurs. In a [1,5] sigmatropic rearrangement of a diene migration occurs to position 1 of the H group (the only possibility) and to position 5 of the pentadienyl group. In a [3,3] Claisen rearrangement migration occurs to position 3 of the allyl group and also to position 3 of the vinylic ether. Migration of a group across the same face of the π system is a suprafacial rearrangement. Migration of a group from one face of the π system to the other face is called an antarafacial rearrangement. A [1,5] sigmatropic rearrangement involves three electron pairs (two π bonds and one σ bond). Orbital-symmetry rules predict a suprafacial reaction 5-methylcyclopentadiene rapidly rearranges at room temperature. Cope and Claisen Rearrangements are Sigmatropic rearrangement reactions. Both involve reorganization of an odd number of electron pairs (two π bonds and one σ bond). Both react by suprafacial pathways.

4.8 Key words

Sigmatropic rearrangements; Classification; Frontier molecular orbital approach; 1,3-sigmatropic rearrangement; [1,5]-sigmatropic rearrangement; Woodward-Hoffmann Rule for sigmatropic rearrangements; 3,3-Sigmatropic rearrangement (Cope rearrangement)

4.9 References for further studies

1) Organic Chemistry; Joseph M. Hornback; *Cengage Learning*, **2005**.

2) Advanced Organic Chemistry: Part A: Structure and Mechanisms; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2007**.

3) Classics in Stereoselective Synthesis; Erick M. Carreira, Lisbet Kvaerno; *John Wiley & Sons*, **2009**.

4) Molecular Rearrangements in Organic Synthesis; Christian M. Rojas; *John Wiley & Sons*, **2015**.

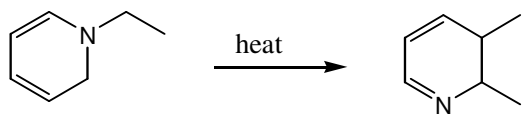
5) Pericyclic Reactions: A Mechanistic and Problem-Solving Approach; Sunil Kumar, Vinod Kumar, S.P. Singh; *Academic Press*, **2015**.

6) Photochemistry And Pericyclic Reactions; J. Singh; *New Age International*, **2005**.

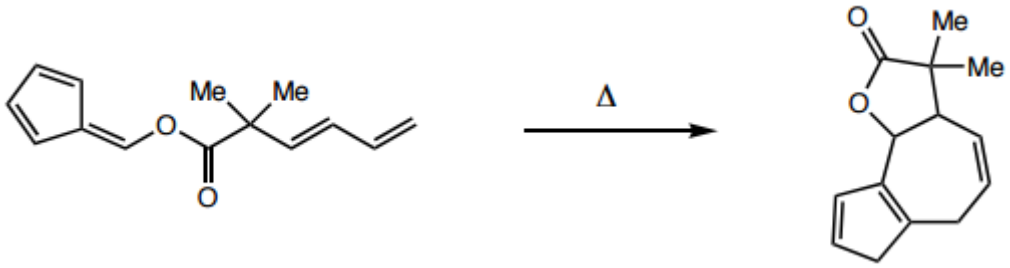
4.10 Questions for self understanding

1. What is meant by sigmatropic rearrangement? Mention the different types of sigmatropic rearrangements.
2. State Woodward-Hoffmann rule for sigmatropic rearrangement.

3. Write all the Frontier orbitals of pentadienyl system and show that [1,5] sigmatropic rearrangement is suprafacial under thermal condition.
4. Using FMO approach prove that 1,3-sigmatropic rearrangement is anatara facial under thermally condition
5. With suitable mechanism, show that under thermal condition α,γ-unstaurated carbonyl compounds readily converted to α,β-unsaturated compound while reverse is true for photochemical condition.
6. Explain the following thermal transformation



7. Provide a mechanism for the following transformation with clear representation of FMO and DewarZimmerman analysis. Be sure to label any pericyclic processes. Also, assign the expected relative stereochemistry in the product.



8. Briefly state the meaning of each of the following terms, giving an example for each.
   a. [3,3] sigmatropic rearrangement
   b. [3,3] sigmatropic rearrangement
   c. [3,3] sigmatropic rearrangement
   d. [3,3] sigmatropic rearrangement;

UNIT-5

Structure

5.0 Objectives of the unit

After studying this unit you are able to

- Explain the Bergman Cyclisation
- Explain the Nazarov cyclization
- Explain the Palladium mediated Cyclizations
- Explain the Intramolecular radical cyclization reactions
- Explain the Simmon-Smith reaction
- Explain the Retro Diels Alder reaction

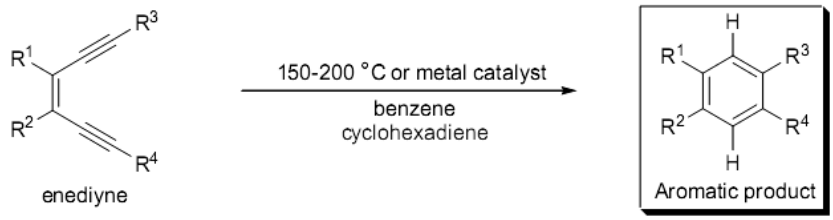
5.1 Introduction

Design and development of highly efficient process for the synthesis of organic compounds is a central scheme in modern organic synthesis. One attractive approach along this line is to apply catalytic process for the transformations of simple starting materials into cyclic scaffolds that can be further elaborated into specific targets. The transition metal-catalyzed carbocyclization and cycloadditions are among the most synthetically useful process for rapidly increasing molecular complexcity. In this unit you are going to study the some common cyclizations reactions frequently utilized in organic synthesis.

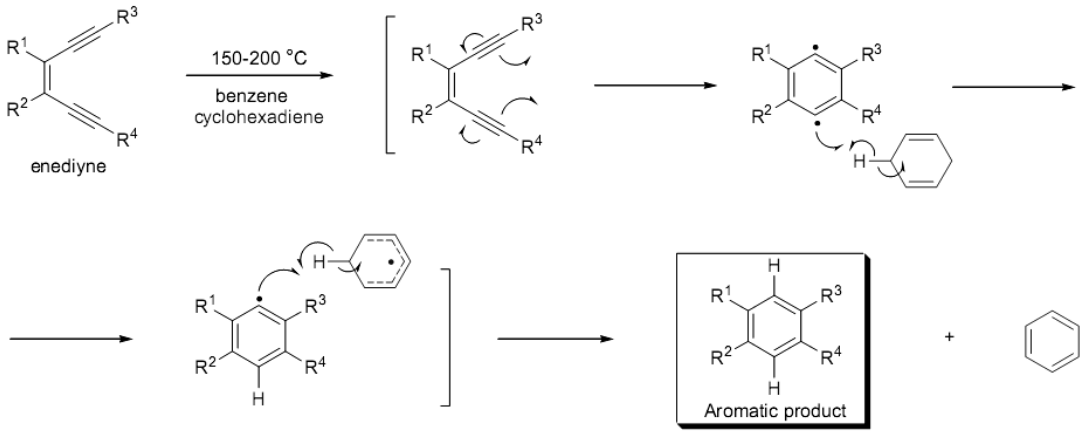
5.2 Bergman Cyclisation

The thermal cycloaromatization of enediynes, which proceeds via the formation of benzenoid diradicals is known as the ***Bergman cycloaromatization*** *reaction.*

It received little attention in the 1970s when it was first reported, but it became the subject of intense research in the 1990s when certain marine natural products containing the enediyne moiety showed remarkable antitumor activity *via* the cleavage of double stranded DNA. *Synthetically the Bergman cyclization was exploited to prepare fused ring systems by tethering alkenes to an enediyne unit and allowing the alkenes to react with the cycloaromatized species to form additional saturated rings*. It is also possible to make fused aromatic ring systems, such as acenaphthenes or perylene derivatives. The Bergman cyclization tolerates a wide range of functional groups, many of which also increase the yield of the cycloaromatization reaction. In this cyclization reaction the distance between the triple bonds is crucial. *As the number of carbon units between the triple bonds increases, higher temperature is required for the cyclization to occur*. In order to observe cyclization at physiological temperatures, the enediyne unit should be part of a 10-membered ring.



Mechanism:

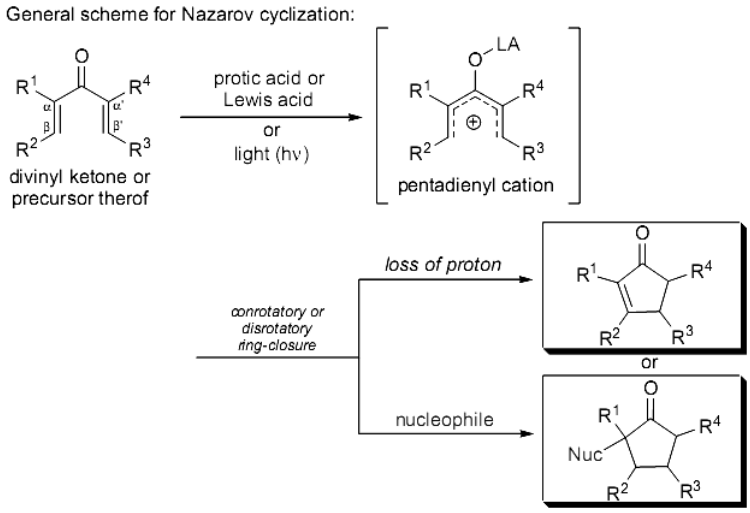


5.3 Nazarov cyclization

The protic or Lewis acid catalyzed ring-closure of divinyl ketones (and their acid-labile precursors) via pentadienylic cations is known as the ***Nazarov cyclization.***

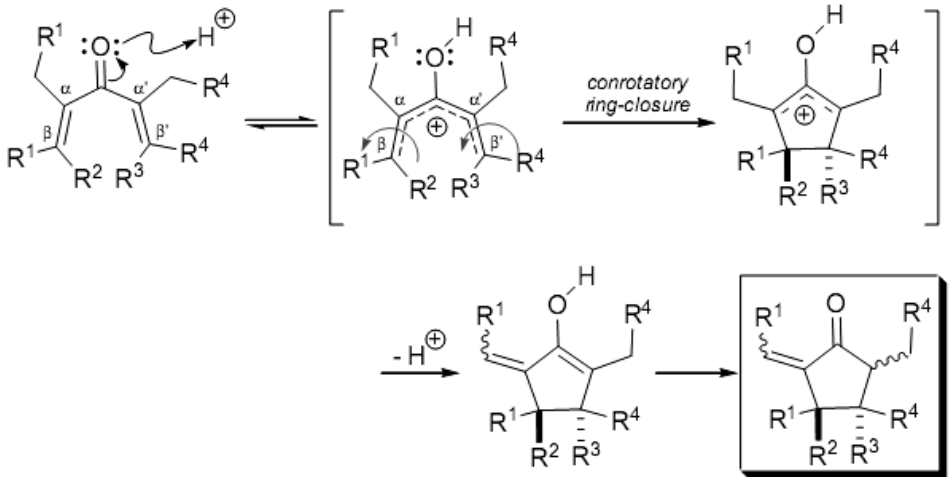
The general features of the reaction are

1) In a broader sense, any compound that affords the key pentadienylic cation or its equivalent is a viable substrate for the transformation.
2) Allyl vinyl ketones are isomerizes in situ to the corresponding divinyl ketones.
3) Electron-donating substituent's in the α and α' positions accelerate the cyclization, whereas rate retardation is observed when they are in the β and β'-positions.
4) Fused cyclic systems are formed when one or both of the groups attached to the ketone are cyclic and
5) The introduction of trialkylsilyl (or trialkylstannyl) groups in the β or β'-position ensures the controlled collapse of the cyclopentenylic cation thus undesired Wagner-Meerwein rearrangements are avoided. The final double bond is formed regioselectively, and the stereocenters at the ring fusion are preserved (silicon-directed Nazarov cyclization).



5.3.1 Mechanism

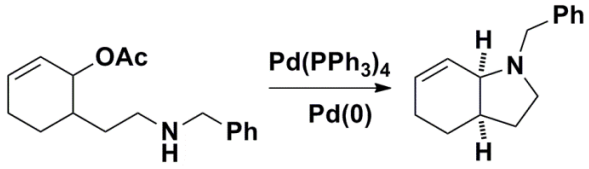
The mechanism of the Nazarov cyclization was not clarified until 1952, when it was realized that the cyclization proceeded via carbocation intermediates. The Nazarov cyclization is a pericyclic reaction that belongs to the class of 4π electrocyclizations. The first step is the coordination of the Lewis acid to the carbonyl group of the substrate and the formation of the pentadienylic cation, which undergoes a conrotatory ring closure to give a cyclic carbocation that may be captured by a nucleophile, may undergo deprotonation, or further rearrangement may take place. The electrocyclization step may precede in a clockwise or counterclockwise fashion (torquoselectivity) generating two diastereomers when the divinyl ketone substrate is chiral. The sense of torquoselection is primarily controlled by steric factors such as the torsional and nonbonding interactions between the substituents in the vicinity of the newly forming bond. Under photochemical conditions the cyclization proceeds in a disrotatory fashion.



5.4 Palladium mediated Cyclizations

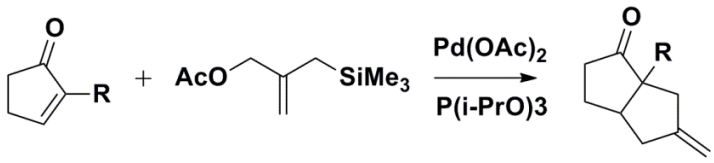
Allylic compounds with good leaving groups, such as bromide and iodide, are excellent allylating agents but they suffer from loss of regiochemistry due to competition between the direct S_N2 and S_N2' reaction. In contrast, π-allyl cation complexes of palladium allow both the stereochemistry and regiochemistry of nucleophilic displacement reactions to be controlled.

The intramolecular reaction works well to give heterocyclic rings. The regioselectivity is usually determined by the length of the chain and how far it can reach. Here a 6/5 fused product is preferred to a bridged product containing two seven-membered rings.



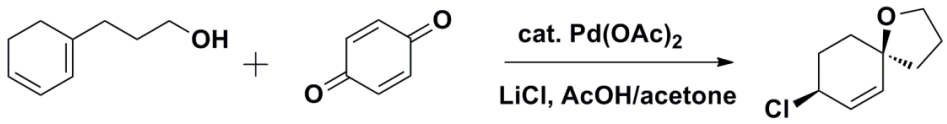
The reaction usually proceeds with retention of configuration at the reacting centre. As in S_N2 reactions going with retention, this can mean only a double inversion. Coordination of Pd to the double bond of the allylic acetate occurs on the less hindered face opposite the leaving group and the nucleophile adds to the face of the π -allyl Pd cation complex opposite the Pd. The net result is displacement of the leaving group by the nucleophile with retention. Thereafter, the nucleophile attacks from the less hindered face of the resulting π-allyl complex (that is, away from the metal) leading to overall retention of configuration.

The normal course of the reaction is to react with an alkene with electron-withdrawing substituents present, which make the substrate prone to Michael-type conjugate addition. The resulting cyclization product has an exo methylene group. Cyclopentenones illustrate this overall 'cycloaddition' nicely. The mechanism is thought to be stepwise with conjugate addition of the carbanion followed by attack of the resulting enolate on the π-allyl palladium unit to form a five-membered ring-not a real cycloaddition at all.

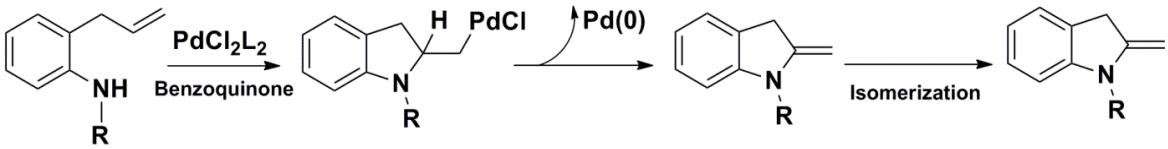


Cyclic ethers and amines can be formed if the nucleophile is an intramolecular alcohol or amine. Stoichiometric palladium can be avoided by using benzoquinone as the stoichiometric oxidant

with a catalytic amount of palladium. In this example intramolecular oxypalladation of a diene is followed by attack of an external nucleophile on a π-allyl complex.

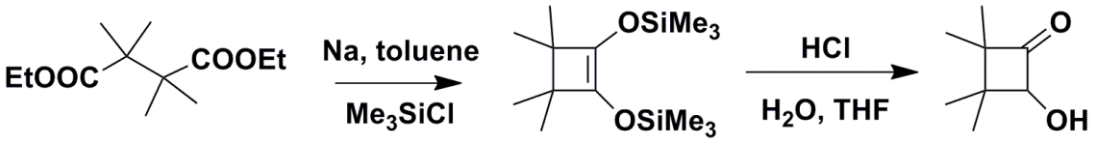


Nitrogen nucleophiles also attack alkenes activated by Pd(II) and benzoquinone can again act as a reoxidant allowing the use of catalytic quantities of palladium. The mechanism follows the same pattern as for oxygen nucleophiles including the final isomerization to produce the most stable regioisomer of product. In this example the product is an aromatic indole so the double bond migrates into the five-membered ring.



5.5 Radical cyclizations

The silyl ethers are rarely desired as final products, and they can easily be hydrolysed to α-hydroxy-ketones with aqueous acid. This improved version makes four-membered rings efficiently.



It ís not by accident that these two examples of the acyloin reaction show the formation of cyclic compounds. It is a particularly powerful method of making carbocyclic rings of from four members upwards. The energy gained by pairing up the two electrons in the radical-radical reaction step is more than the energy due to strain that may be generated in forming the ring. Hence the reaction taking place in forward direction.

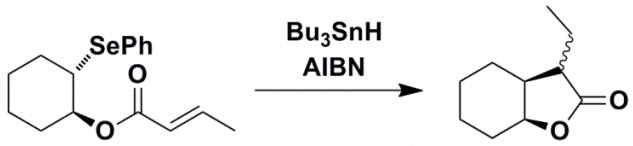
5.5.1 Intramolecular radical cyclization reactions

In general ntramolecular radical reactions are more efficient than intermolecular ones. All of the reactions you have met so far involve radical attack between two molecules. Some of the drawbacks when C-C bonds are made in this way are: the radical trap has to be activated (that is,

electrophilic to capture nucleophilic radicals) and must often be present in excess, and the radical starting material must contain very weak C-X bonds (such as C-Br, C-I, C-Hg). The requirements are much less stringent, however, if the radical reaction is carried out intramolecularly. For example, the below reaction,

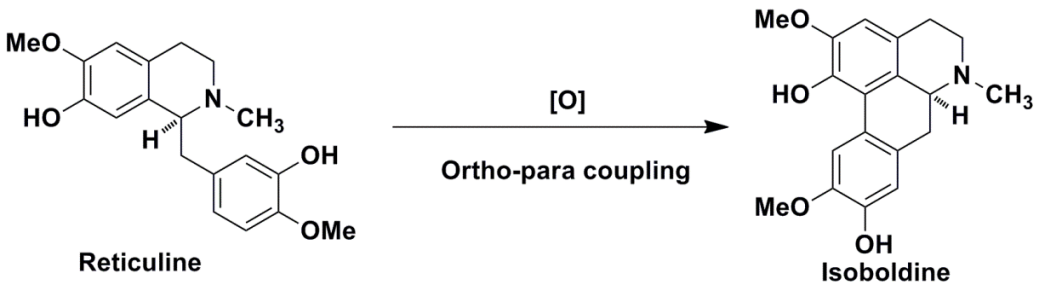
It is important to notice here that, the double bond in this reaction is not activated, in fact, it is nucleophilic, and the reaction still works even though the radical is also substituted with an electron-donating group. The C-S bond that is broken is also relatively strong, yet nonetheless a high yield of product is obtained.

The preference for formation of a smaller ring is a very powerful one. In this below reaction, the five-membered ring forms and not the six-membered one, even though cyclization to give a six-membered ring would also give a stabilized radical.



Radicals are important because they react in ways difficult to achieve with anions and cations and with different selectivity. Though radical reactions are less important than ionic reactions you need to understand their mechanisms because they are widespread in an atmosphere of the oxygen diradical.

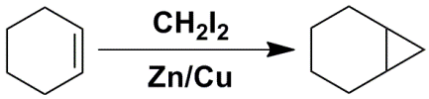
Reticuline is oxidized in the plant to isoboldine by a radical cyclization with the formation of a new C-C bond.



The new bond is between a carbon atom *ortho* to one OH group and a carbon atom *para* to the other. We shall see in all these phenolic couplings that the *ortho* and *para* positions are the only activated ones (*ortho/ortho, ortho/para*, and *para/para* couplings are all possible). Oxidation occurs at the phenolic hydroxyl groups, and the resulting oxygen radicals couple.

5.6 Simmon-Smith reaction

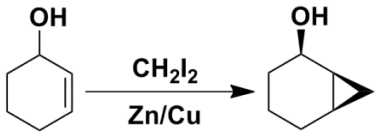
The zinc carbenoid is formed when diiodomethane is reacted with zinc metal. It reacts with alkenes just as a carbene would do in addition to the π-bond and produces a cyclopropane. The reaction is known as the *Simmons-Smith reaction*.



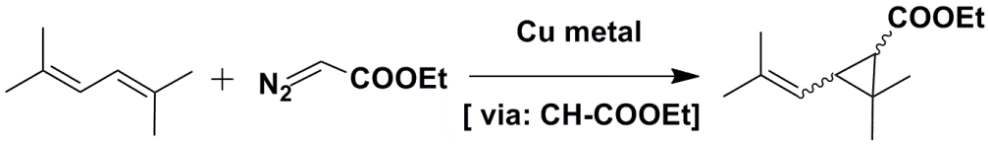
It is the most important way of making cyclopropane compounds, though nowadays a variant that uses more easily handled starting materials is often used. Diethyl zinc replaces the Zn/Cu couple of the traditional Simmons-Smith reaction.

The reaction does not involve a free carbine, the zinc is still associated with the carbon atom at the time of the reaction, and the reacting species is a probably a complex of zinc that we can represent as equilibrium between two zinc carbenoids.

Some of the evidence for this comes from a reaction that not only throws light on to the mechanism of Simmons-Smith cyclopropanations, but makes them of even greater value in synthesis. When an allylic alcohol is cyclopropanated, the new methylene group adds stereoselectively to the same face of the double bond as the alcohol group.

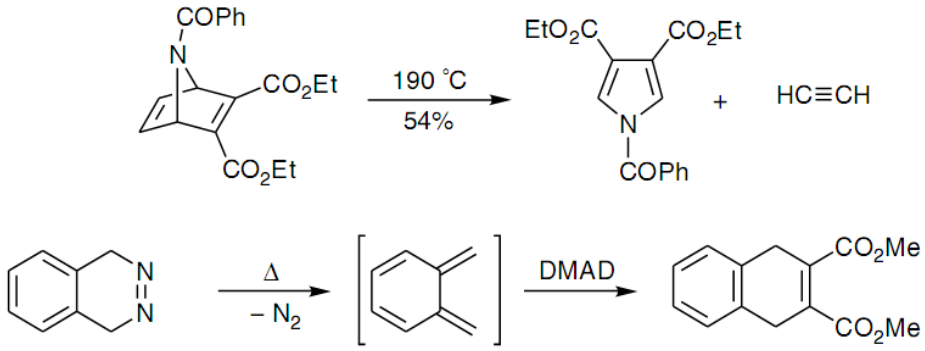


The carbene derived by metal-catalysed decomposition of ethyl diazoacetate attacks alkenes to introduce a two-carbon fragment into a cyclopropaneóan industrial synthesis of ethyl chrysanthemate, a precursor to the pyrethrin insecticides, uses this reaction. The diene in the starting material is more nucleophilic than the single alkene in the product, so the reaction can be stopped after one carbene addition.



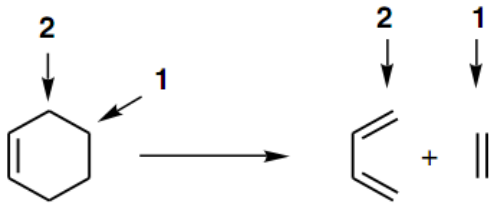
5.7 Retro Diels Alder reaction

The Diels-Alder reaction is reversible and the direction of cycloaddition is favored because two π-bonds are replaced by two σ-bonds. The cycloreversion occurs when the diene and/or dienophile are particularly stable molecules (i.e. formation of an aromatic ring, of nitrogen, of carbon dioxide, of acetylene, of ethylene, of nitriles, etc.) or when one of them can be easily removed or consumed in a subsequent reaction.



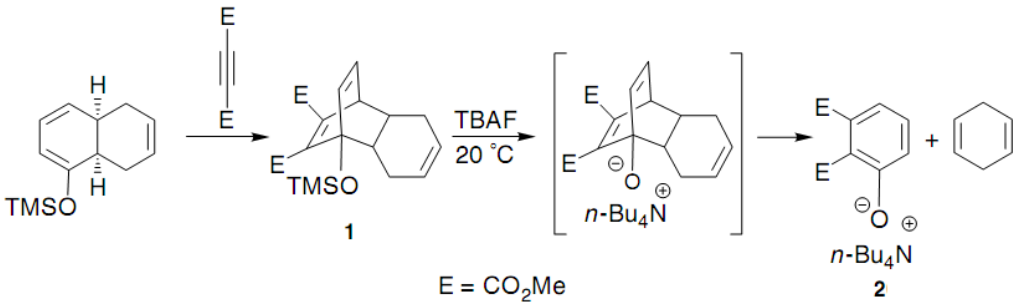
The retro Diels-Alder reaction usually requires high temperature in order to surmount the high activation barrier of the cycloreversion. Moreover, the strategy of retro Diels-Alder reaction is used in organic reactions to mask a diene fragment or to protect a double bond.

The retro Diels-Alder reaction is strongly accelerated when an oxide anion substituent is incorporated at positions 1 and 2 of the six membered ring which has to be cycloreversed, namely at one terminus carbon of the original diene or at one sp^2 carbon of the dienophile.

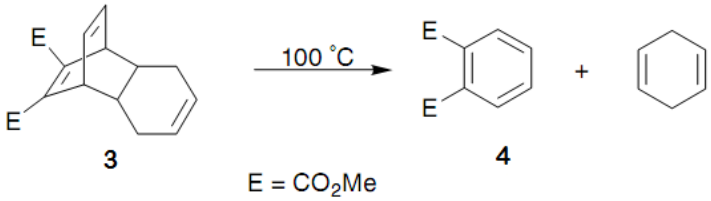


The first example of an oxide –anion accelerated retro Diels-Alder reaction was reported by Papies and Grimme. The adduct **1** treated with tetra-*n*-butylammonium fluoride (TBAF) in THF

at room temperature is immediately converted into **2,** in contrast to the parent **3** which undergo cycloreversion into **4** at 100 °C.

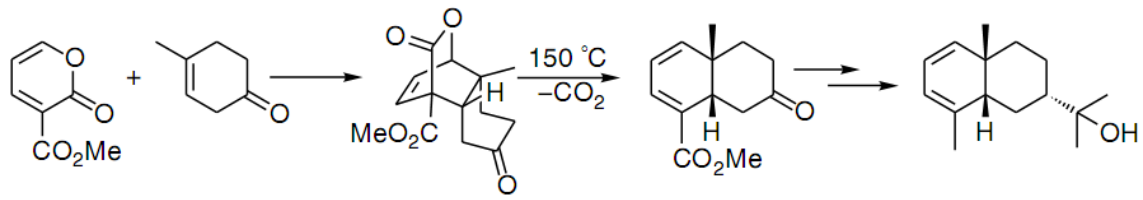


The dramatic oxide-anion acceleration was ascribed by the loss of basicity of about 8pK_b units in transformation of alcoholate ion of precursor **1** into the phenolate ion of the product **2**. This is an example of acceleration of retro Diels-Alder when an oxide substituent is incorporated at the terminus of the 4π component of the Diels-Alder adduct.

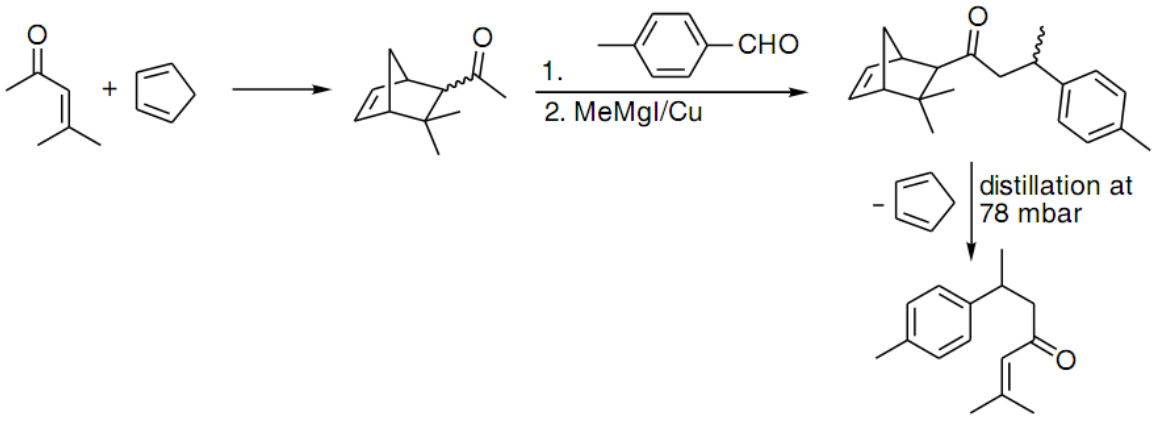


More examples for retro Diels-Alder reaction are given below

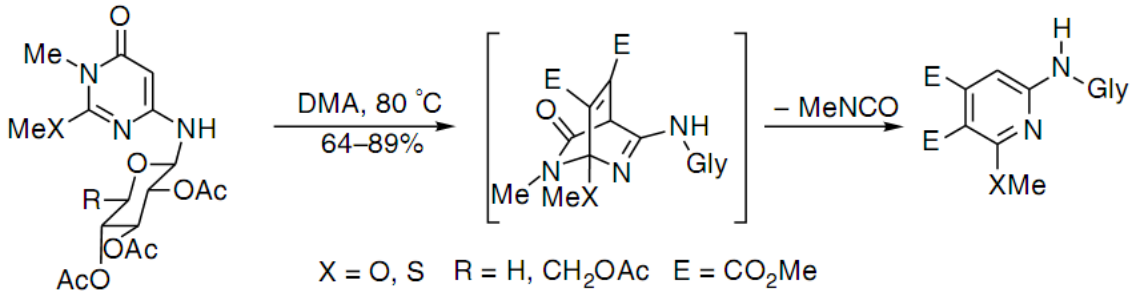
Synthesis of (±)-occidentalol



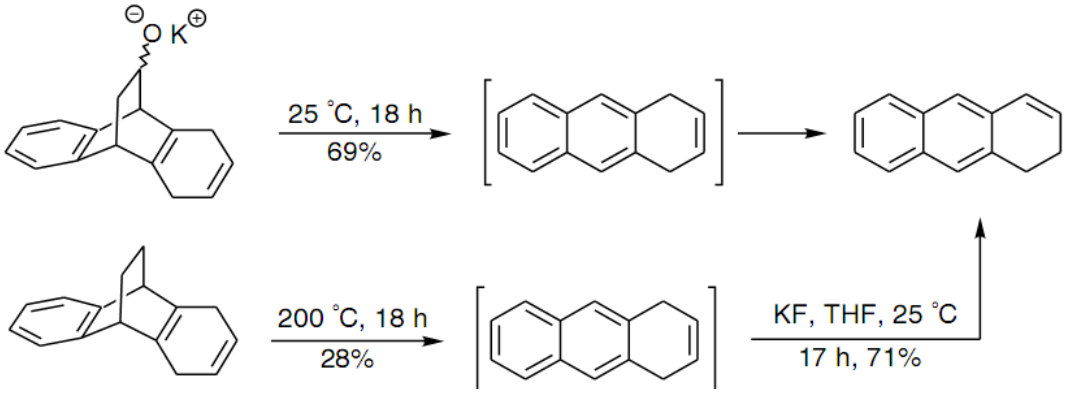
Synthesis of (±)-turmerone



Synthesis of 2-glycosylamino pyridines



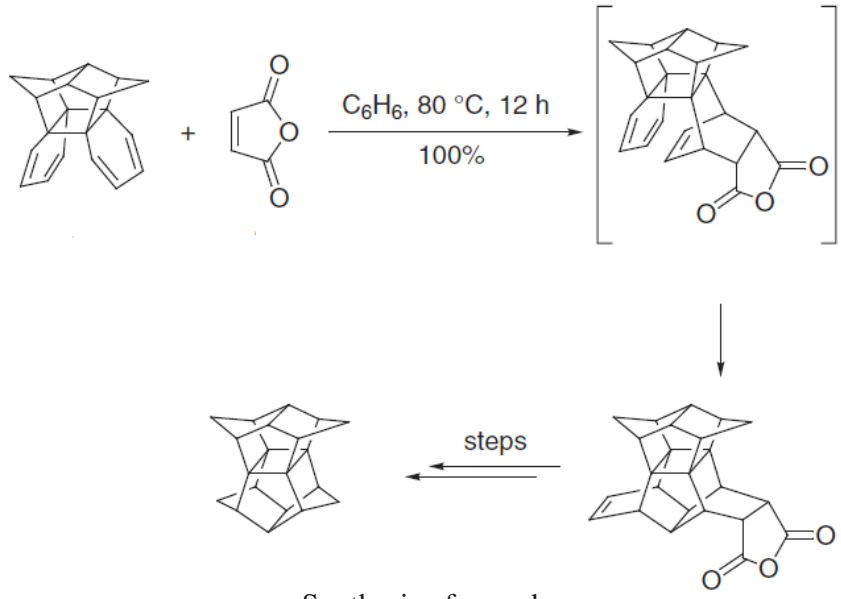
An example of the effect of oxide-anion associated with the 2π component is illustrated in the below equation. The potassium salt of 1,4-dihydro-11-hydroxy-9,10-dihydro-9,10-ethanoanthracene undergo more facile debridging than the 11-deoxygenated parent compound.



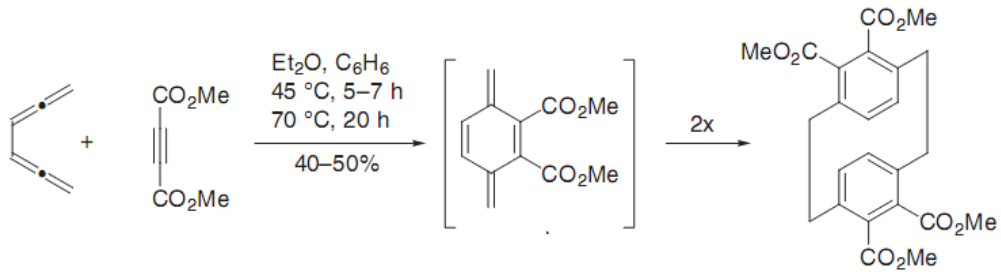
5.8 Pericyclic reactions

The combination of pericyclic transformations as cycloadditions, sigmatropic rearrangements, electrocyclic reactions and ene reactions with each other, and also with non-pericyclic transformations, allows a very rapid increase in the complexity of products. As most of the pericyclic reactions run quite well under neutral or mild Lewis acid acidic conditions, many different set-ups are possible. The majority of the published pericyclic domino reactions deals with two successive cycloadditions, mostly as [4+2]/[4+2] combinations, but there are also [2+2], [2+5], [4+3] (Nazarov), [5+2], and [6+2] cycloadditions. Although there are many examples of the combination of hetero-Diels–Alder reactions with 1,3-dipolar cycloadditions, an impressive combination of two Diels–Alder reactions is also described by Winkler for the synthesis of the taxane skeleton, though two different Lewis acids must be used for the two cycloadditions. Thus, it does not strictly match the definition of a domino reaction. The second largest group of pericyclic domino reactions starts with a sigmatropic rearrangement, which is

most often a Claisen or an oxa- and aza-Cope rearrangement, however, some processes also exist with a 2,3-sigmatropic rearrangement as the second step.



Synthesis of pagodane

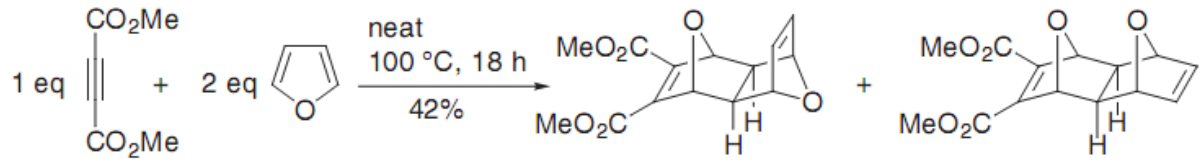


Synthesis of paracyclophanes

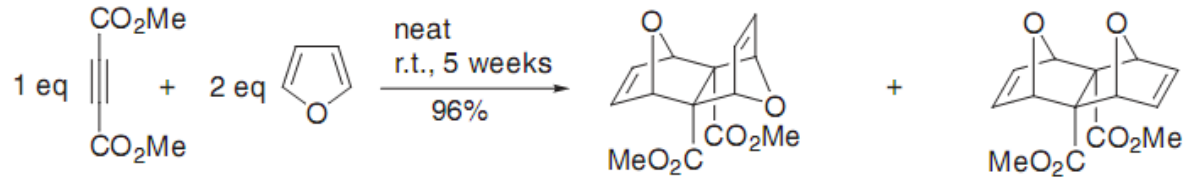
5.8.1 Diels-Alder Reactions

The examples for Diels alder reactions of dimethyl acetylenedicarboxylate and furan are given below,

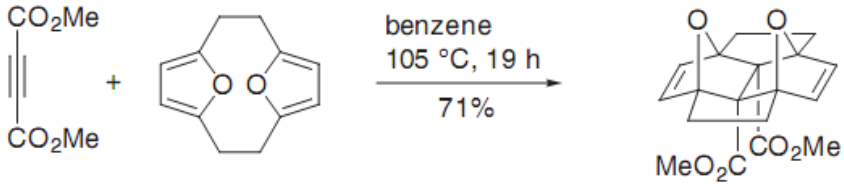
Diels and Alder (1931)



Diels and Olson (1940)

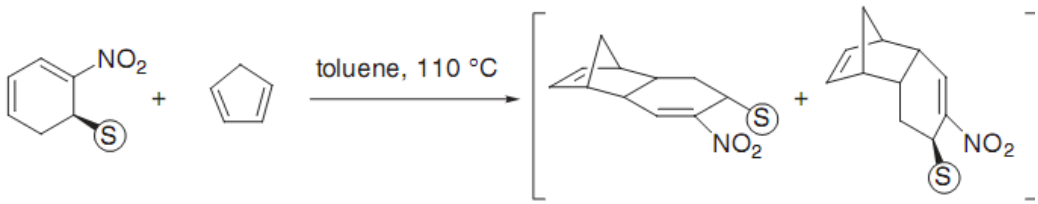


Cram (1961)



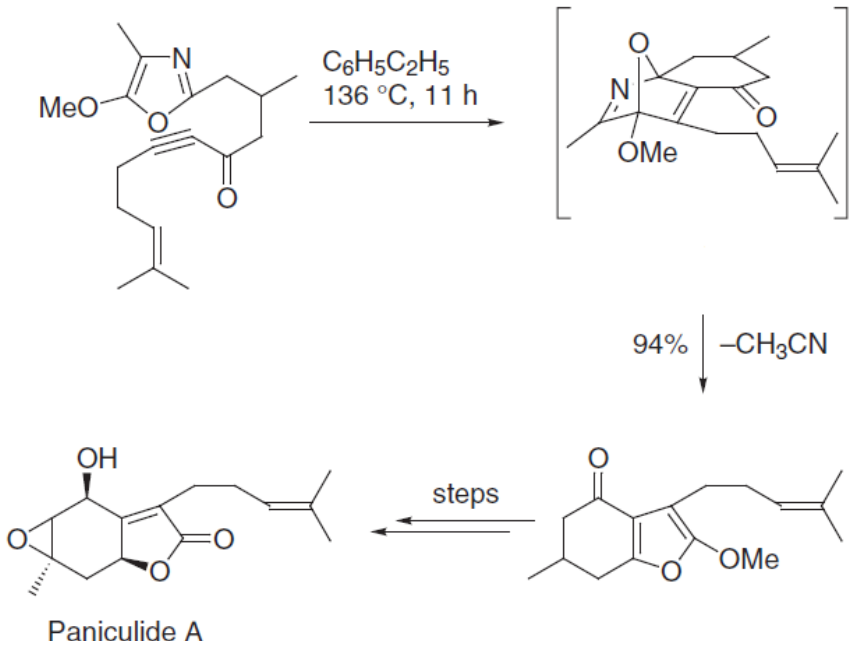
5.8.2 Diels-Alder Reactions/Sigmatropic Rearrangements

In contrast to the lack of examples of the domino Diels–Alder reaction/1,3-dipolar cycloaddition, the combination of a Diels–Alder reaction with a sigmatropic rearrangement has been used intensively.



5.8.3 Diels-Alder/Retro-Diels-Alder Reactions

Diels–Alder reactions can also be coupled with retro-Diels–Alder reactions to form interesting sequences. An illustrative example is the nonisolatable Diels–Alder adduct used by Jacobi and coworkers in a synthesis of paniculide-A. The elimination of acetonitrile from the primary cycloadduct in this sequence is worthy of note.



Paniculide A

5.9 Summary of the unit

Bergman cyclization also known as the Bergman cycloaromatization is a photochemical, thermal or metal-mediated cycloaromatization of enediyens that provide access to substitued arenes. The cyclization initially forms a 1,4-benzenediyl diradical which being highly reactive gives an arene. Bergman proposed that the reaction mechanism of the cyclization under thermal conditions involved the initial generation of a 1,4-benzenediyl diradical species known as para-benzyne. Bergman reports that when the reaction was carried out in a hydrocarbon solvent benzene was formed as the final product. This suggests that the hydrocarbon solvent acts as a hydrogen atom donor to quench the diradical intermediate. This result hints at the radical nature of the mechanism operative in the Bergman cyclization

Metal coordination by ligands attached to enediyne framework has significant effect on the kinetics of BC. It is interesting to note that there is no precedence of metal ion triggering of enediynes in Nature so far and hence this idea is quite novel in the true sense.

An acid-promoted cationic pericyclic reaction that transforms a divinyl ketone into 2-cyclopentenone. This reaction was first reported by Nazarov et al. in 1942, therefore it is generally known as the Nazarov cyclization, or Nazarov reaction. In general, this reaction requires 1 eq. of strong Brønsted acid or Lewis acid and undergoes a 4-π electrocyclic, conrotatory cyclization via a 3-oxy-pentadienylic cation. Although this reaction gives a

thermodynamically favored cyclopentenone with more substituents, the classical reaction protocol generally lacks control over the position of the endocyclic double bond.

Simmons and Smith discovered that the reagent formed by mixing a zinc-copper couple with CH_2I_2 in ether could be used for the stereospecific conversion of alkenes to cyclopropanes. Nowadays, the Simmons-Smith cyclopropanation reaction is one of the most widely used reactions in the organic chemist's arsenal for the conversion of olefins into cyclopropanes. This popularity is mainly due to the stereospecificity of the reaction with respect to the double bond geometry and its compatibility with a wide range of functional groups. The chemoselectivity of the reaction toward some olefins is excellent and very few side reactions are observed with functionalized substrates. The metal carbenoid is electrophilic in nature and electron-rich alkenes usually react much faster than electron-poor alkenes.

5.10 Key words

Bergman Cyclisation; Nazarov cyclization; Palladium mediated Cyclizations; Radical cyclizations; Simmon-Smith reaction; Retro Diels Alder reaction; Pericyclic reactions

5.11 References for further study

1) Modern Methods of Organic Synthesis; W. Carruthers, Iain Coldham; *Cambridge University Press*, **2004**.
2) Synthetic Approaches in Organic Chemistry; Raj K. Bansal; *Jones & Bartlett Learning*, **1996**.
3) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2010**.
4) Modern Organic Synthesis; Michael Nantz; *W. H. Freeman*, **2007**.
5) Organic Synthesis; Michael B Smith; Academic Press, **2011**.
6) Organic Synthesis: The Disconnection Approach; Stuart Warren, Paul Wyatt; *John Wiley & Sons*, **2011**.

5.12 Questions for self understanding

1) With mechanism discuss the Bergman Cyclisation reaction.
2) Explain the Nazarov cyclization reaction with example.
3) Discuss the mechanism of Nazarov cyclization reaction
4) Discus the Palladium mediated cyclizations reactions.
5) Explain the Radical cyclizations reactions.

6) With suitable example explain the intramolecular radical cyclization reactions.

7) Discuss the Simmon-Smith reaction.

8) Discuss the Retro Diels Alder reaction.

9) Discuss the Pericyclic reactions.

UNIT – 6

Structure

6.0 Objectives of the unit

After studying this unit you are able to

- Give the example for stereo selectivity and siastereoselectivity
- Explain the ctereochemical control in Six-membered ring
- Explain the significance of prochirality
- Explain the stereoselectivity reversion by chelation

6.1 Introduction

Addition of non-symmetrical reagent to a non-symmetrical alkene, then two isomeric products that are constitutional isomers can be obtained. For example, the reaction of HCl with propene gives 1-chloropropane and 2-chloropropane. ormally, 2-chloropropane is formed as major product. Since one product is favoured over the other, the reaction is said to be regioselective. Suppose 2-chloropropane was the only product then the reaction is said to be regiospecific.

Similarly when an alkene undergoes addition, two new σ bonds are formed. If we think of an alkene as having two faces, then the two new σ bonds can either both forms on the same face, which we call syn addition, or they can be formed on different faces which we call anti addition

If more than one reaction could occur between a set of reactants under the same conditions giving products that are stereoisomers and if one product forms in greater amounts than the others, the overall reaction is said to be stereoselective. A reaction is also said to be stereoselective, if two different steroisomers of the starting material lead to the same stereochemical outcome in terms of the product. A stereoselective reaction that preferentially gives one of the several conceivable diastereomers as the major product is referred as diastereoselective reaction; diastereomers are stereoisomers that are not mirror images of each other.

6.2 Stereo selectivity and Diastereoselectivity

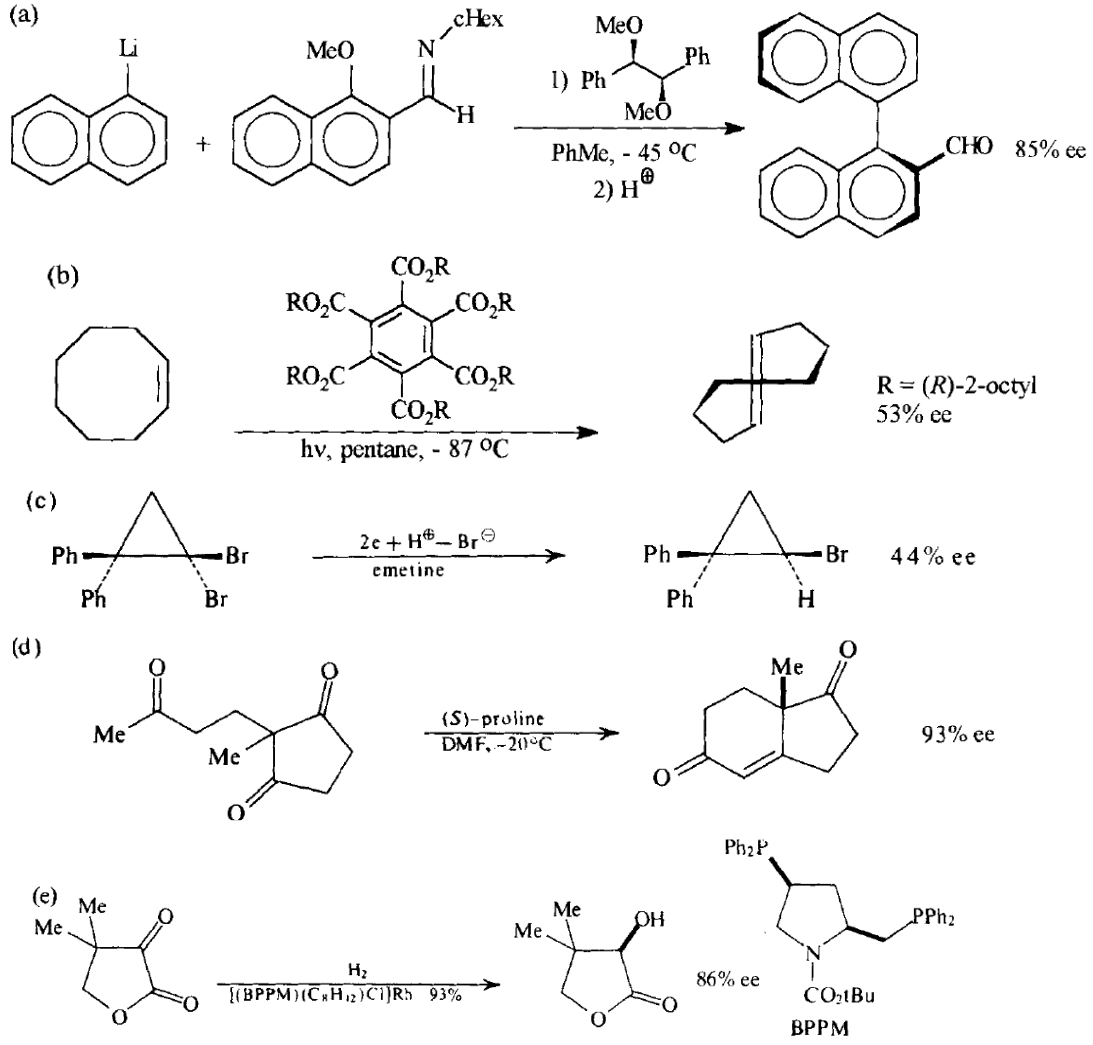
Stereoselective reactions - a reaction where one stereoisomer of a product is formed preferentially over another. The mechanism does not prevent the formation of two or more stereoisomers but one predominates.

Selectivity in the transformation of enantiotopic groups and faces can only be achieved, as explained before, by chiral means. These may be characterized as follows:

(i) Photochemical transformations induced by chiral i.e. circularly polarized light. this is an important method giving only a few percent ee or less.

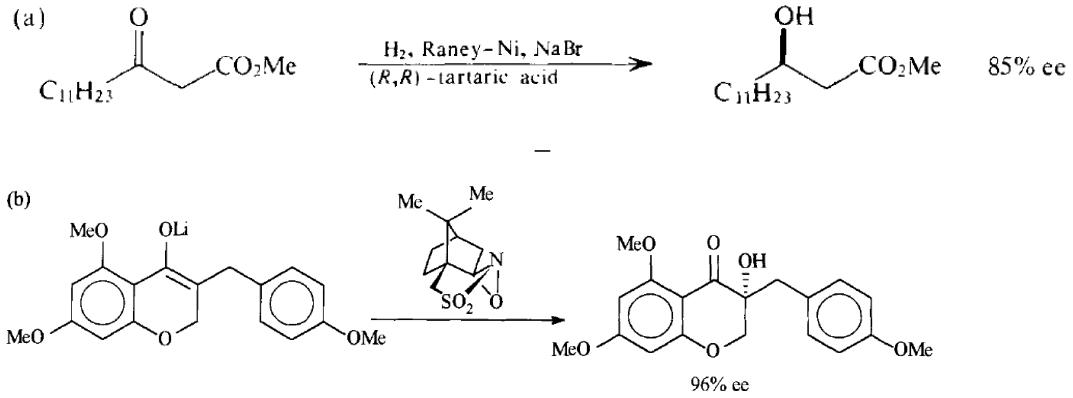
(ii) Reactions conducted in achiral solvent. Chiral solvents are, compared with their generally low efficiency, very expensive and thus do not qualify for practical stereoselective synthesis.

(iii) Reaction carried out in the presence of a chiral additive. Additives in this context are substances which emerge unchanged from a reaction and range from cosolvents through photosensitizers to catalysts. Enantioselective reactions carried out in the presence of chiral additives are illustrated by the photo-isomerization of (Z)- to (E)-cyclooctane in the presence of a chiral sensitizer, the electroreduction of a dibromocyclopropane in the presence of a chiral base, base-catalysed Intramolecular aldol condensation and finally homogenous hydrogenation with a rhodium catalyst prepared from chiral phosphines.



(iv) Reaction of enantiotopic groups or faces with chiral reagents involving the transfer of an achiral species. This approach has been mainly exploited for redox processes. The chiral

complex hydride is just one of the many chiral hydride ion donating reagents developed in the past two decades.

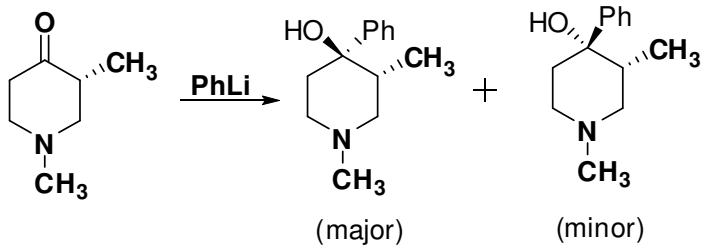


(v) The substrate with enantiotopic groups or faces is linked with a chiral auxillary compound to form a derivative in which the former become diastereotopic. Thus the necessary condition for stereoselectivity with any reagent is met. After the required transformations have been carried out, the chiral auxiliary is removed to give rise to a non-racemic mixture of enantiomers. An ideal chiral auxiliary substance is one which (i) provides high asymmetry in the selectivity determination transition state, (ii) is recoverable and (iii) is readily available in both enentiomeric forms in high optical purity and at low cost.

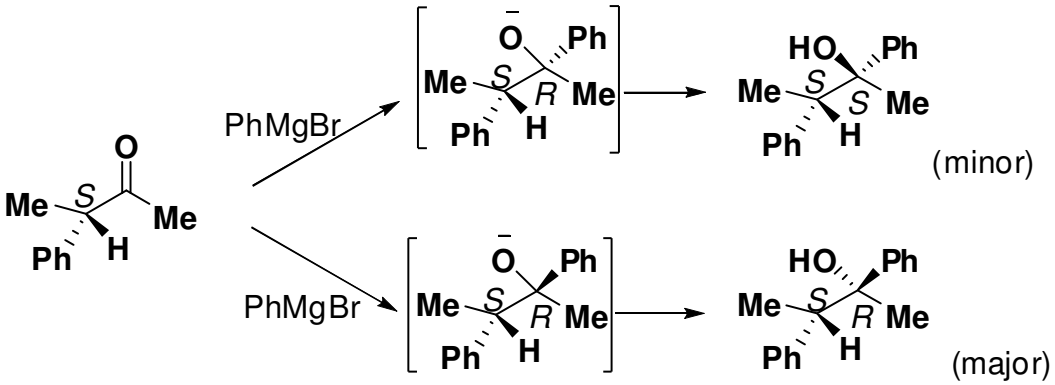
Diastereoselective reactions - a stereogenic centre is introduced into a molecule in such a way that diastereoisomers are produced in unequal amounts.

Diastereoselectivity was first recognized by Emil Fisher, who pointed out that the ratio of diastereomers arising by the formation of a new asymmetric center in a molecule was biased by those already present. No successful attempt was made to predict even qualitatively the direction of this bias until the seminal papers by Prelog and by Cram and Elhafez were published in the early fifties. The rules of Cram and prelog based on these papers and their further developments are closely connected with the addition reactions of carbonyl compounds.

In the reaction below, attack of phenyllithium on trigonal carbonyl carbon occurs preferably from above the plane of the cyclohexane ring, since the nucleophile experiences less steric effect imposed by the methyl substituent. Thus, the reaction that leads to selective formation of one of the two diasteromers is said to be *diastereoselective*. However, the configuration at α-carbon centre remains unchanged throughout the course of the reaction.



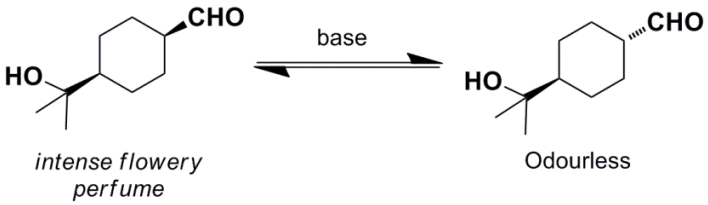
The two diastereomeric products from same reactant already containing a chiral centre are formed from the transition states that are diastereomeric in nature; the latter differ in their free energies. Greater is the difference in the free energies of the transition states, greater is the diastereoselectivity and major diastereomeric product is achieved via transition state of lower energy. In a diastereoselective reaction, a new chiral centre is generated in a molecule that already contains a stereocentre. In general, the diastereoselective reactions are irreversible and kinetically controlled.



In the example given above, addition of Grignard reagent takes place preferably from the *si* face of the α-chiral carbonyl compound giving a major diasteromer and re face attack results in the formation of the minor diasteromer. The transition state for *re* face and *si* face attack are diastereomeric in nature and hence differ in their free energies. Diasteromer that is preferably formed is the one which is obtained via transition state of lower energy.

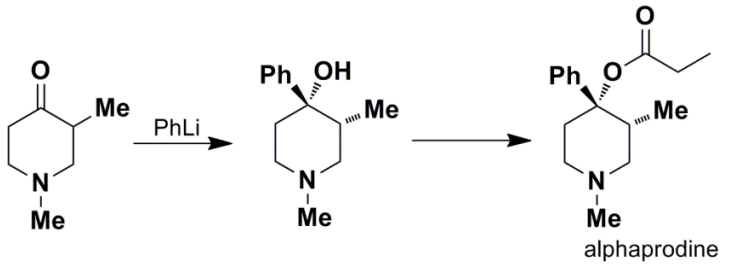
6.3 Stereochemical control in Six-membered ring

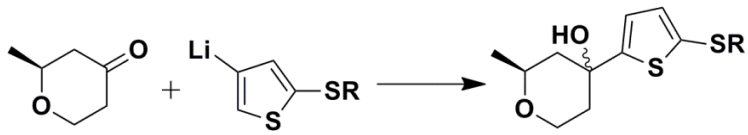
In six membered rings there is an opportunity for more stereogenic centres around the ring. Because of the strong preference for substituents to adopt the equatorial position, diastereoisomers may equilibrate by processes such an enolization. For example, the fine perfumery material is made worthless by enolization. This is because the two substituents are both equatorial in the *trans*-isomer.



Although a disadvantage, in other cases equilibrium to the more stable all-equatorial conformation can be useful source of stereochemical control.

If the nucleophile is not H, (but something larger than OH) then the equatorial attack to dominate both because of ease of approach and because of product stability. A simple example is the addition of PhLi to the heterocyclic ketone below which has one methyl group next to the carbonyl group. This methyl occupies an equatorial position and the incoming phenyl group also prefers the equatorial approach so that good stereoselectivity is observed.

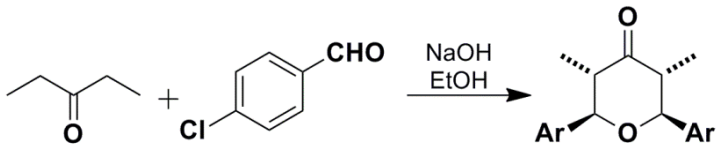




Another example is the manufacture of drug by the addition of lithiated thiophene to another heterocyclic ketone, which initially gave a mixture of diastereoisomers.

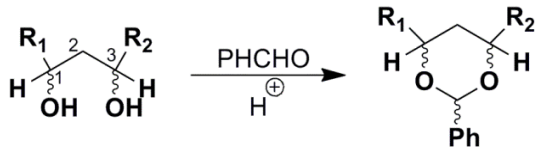
6.4 Conformational control in the formation of six membered rings

In the aldol reaction of pentan-3-one and 4-chlorobenzaldehyde in basic solution, the product turned to be a six membered cyclic keto-ether.

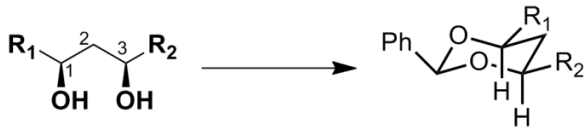


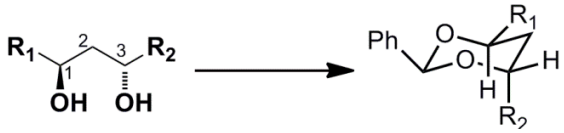
Any reaction that is reversible and that form a six-membered ring can be expected to put as many substituents as possible in the thermodynamically favorable equatorial position. The principle

can be used in structure determination. Free rotation about all the σ-bonds means that the Karplus equation cannot be used as a time-averaged *J* value of about 6-7 Hz will probably be observed for both protons regardless of stereochemistry.



In the reaction of acetal from the1,3-diol with benzaldehyde, the acetal formation is under thermodynamic control, so the most stable possible conformation will result with the large phenyl group equatorial and the two R groups either both equatorial or one equatorial and one axial, deoending on which diastereoisomer started with.

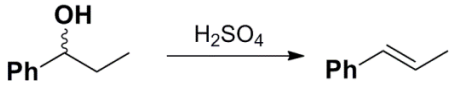




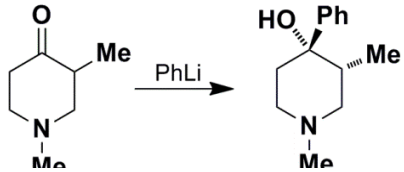
The axial H will show one large *J* value, an equatorial H only small *J* values.

6.5 Making single diastereomers using stereoselective reactions

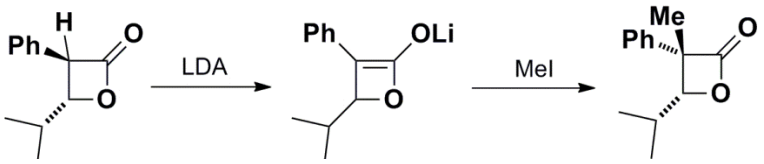
1. E1 reactions are stereoselective: they form predominantly the more stable alkene



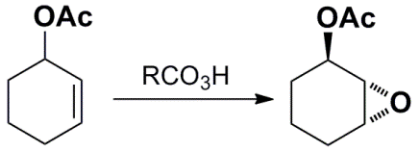
2. Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially.



3. Alkylation of cyclic enolates is stereoselective, with reaction taking place on the less hindered face (four- or five-membered rings) or via axial attack (six-membered rings).

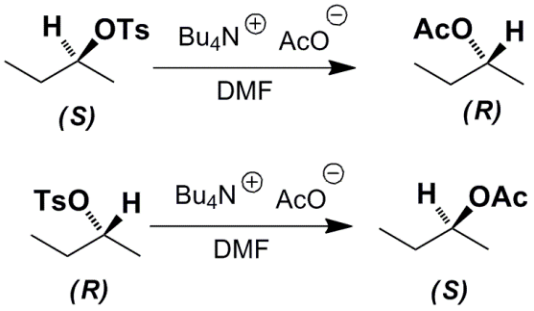


4. Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group.

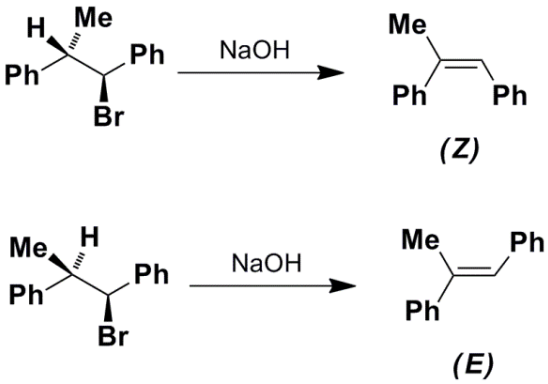


6.6 Making single diastereomers using by stereospecific reactions

1. S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product.

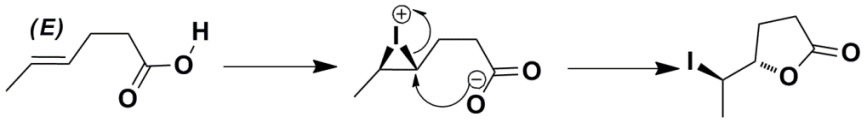


2. E2 reactions are stereospecific: they proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product.

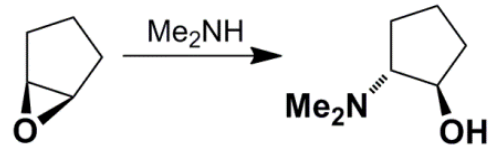


Both of these examples are very interesting because they show how, once we have some stereochemistry in a molecule, we can change the functional groups but keep the stereochemistry-this is the essence of a stereospecific reaction. In the second example, we

change the bromide to a double bond, but we keep the stereochemistry (or 'stereochemical information') because the geometry of the double bond tells us which bromide we started with. Iodolactonization has a similar mechanism; notice how in these two examples the geometry of the double bond in the starting material defines the relative stereochemistry. For a stereospecific alkene transformation, choose the right geometry of the starting material to get the right diastereoisomer of the product.

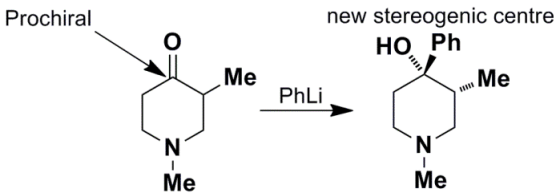


Epoxides are very important because they can be formed stereospecifically from alkenes: cis-alkenes give cis (or syn) -epoxides and trans-alkenes give trans(or anti) -epoxides. Epoxides also react stereospecifically because the ring-opening reaction is an S_N2 reaction. A single diastereoisomer of epoxide gives a single diastereoisomer of product.

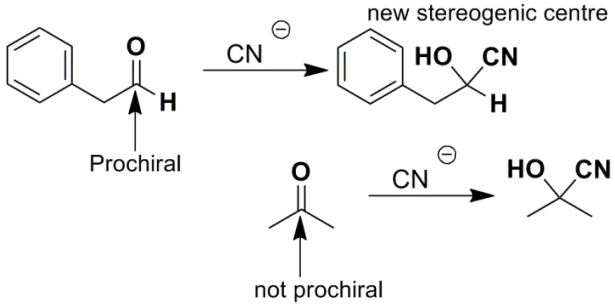


6.7 Prochirality

The creation of a new, tetrahedral stereogenic centre at a carbon that was planar and trigonal. This leads us to our first new definition. Trigonal carbons that aren't stereogenic (or chiral) centres but can be made into them are called *prochiral*.

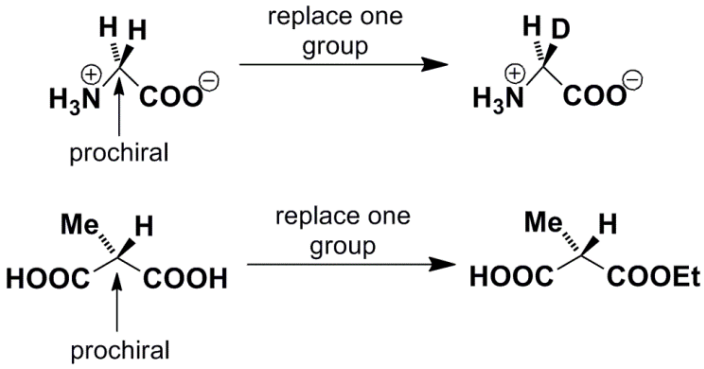


In the below example the first has a prochiral carbonyl group. The second, on the other hand, is not prochiral because no stereogenic centre is created when the compound reacts.



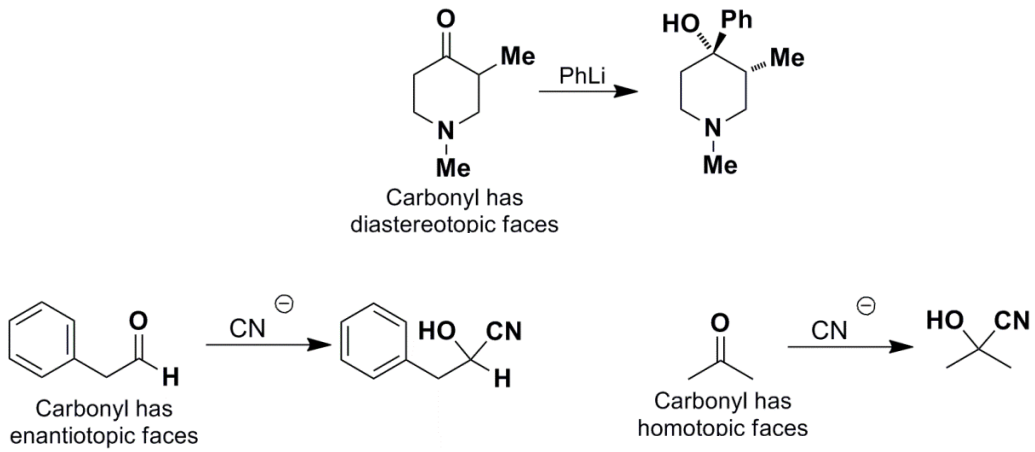
Tetrahedral carbon atoms can be prochiral too-if they carry two identical groups (and so are not a chiral centre) but replacement of one of them leads to a new chiral centre, then the carbon is prochiral.

Glycine is the only α-amino acid without a chiral centre, but replacing one of the two protons on the central carbon with, say, deuterium creates one: the **CH_2** carbon is prochiral. Similarly, converting malonate derivative into its monoester makes a chiral centre where there was none: the central **C** is prochiral.



Replacing one of two enantiotopic groups with another group leads to one of two enantiomers; replacing one of two diastereotopic groups with another group leads to one of two diastereoisomers. Diastereotopic groups are chemically different; enantiotopic groups are chemically identical.

Exactly the same things are true for the faces of a prochiral carbonyl group or double bond. If reaction on one of two faces of the prochiral group generates one of two enantiomers, the faces are enantiotopic; if the reaction generates one of two diastereoisomers, the faces are diastereotopic.



In the above examples, the first example have prochiral C=C or C=O bonds with **diastereotopic** faces: choosing which face of the double bond or carbonyl group to react on amounts to choosing which diastereoisomer to form. In the second example, the faces of the prochiral carbonyl group are **enantiotopic**: choosing which face to attack amounts to choosing which enantiomer to form. In the third example, the two faces of C=O is **homotopic:** an identical product is formed whichever face is attacked.

Almost without exception, every stereoselective reaction there involved a double bond (usually C=C; sometimes C=O) with diastereotopic faces. The diastereotopic faces were distinguished by steric hindrance, or by a nearby hydrogen-bonding group, and so were able to react differently with an incoming reagent.

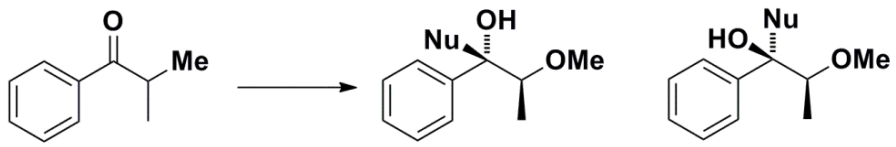
6.8 Stereoselectivity reversion by Chelation

Chelationis the coordination of two heteroatoms carrying lone pairs to the same metal atom, and it changes the conformation of the starting material.

Two things are needed for chelation to occur:

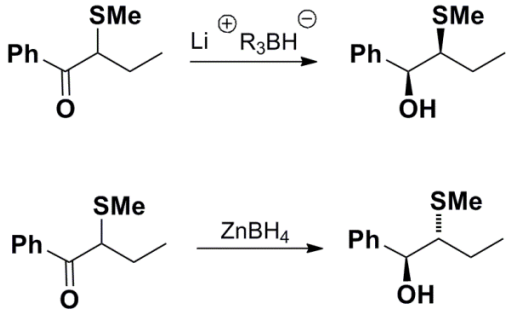
1. a heteroatom with lone pairs available for coordination to a metal
2. a metal ion that prefers to coordinate to more than one heteroatom at once. These are mainly more highly charged ions as shown in the table

Here is example of a reversal in selectivity that can be explained using a nonchelated Felkin-Anh model with Na^+ and a chelated model with Mg^{2+}.



Sulfur is the electronegative atom, so the conformations we need to consider are the two following. Unhindered attack on the second gives the diastereoisomer shown: changing the metal from has reversed the stereoselectivity. The reason is that zinc can chelate sulfur and the carbonyl group. No longer does the most reactive or most populated conformation place the electronegative S atom perpendicular to C=O; instead it prefers S to lie as close to the carbonyl oxygen as possible so that Zn can bridge between S and O.

Not only does chelation control reverse the stereoselectivity, but it gives a much higher degree of stereoselectivity. Stereoselectivities in chelation-controlled additions to C=O groups are typically >95:5. Stereoselectivity is likely to be high if a cyclic transition state is involved.



6.9 Summary of the unit

Stereoselectivity refers to the preferential formation in a chemical reaction of one product stereoisomer (enantiomer or diastereomer) over another, as a result of inherent reaction specificity, or the influence of chiral features in the substrate, reagent, catalyst or environment. The more specific terms enantioselectivity and diastereoselectivity are commonly used in appropriate situations. When this selectivity results in the formation of an excess of one enantiomer over the other from an achiral or racemic substrate it is sometimes called asymmetric induction.

Any reaction which creates a new stereogenic center may proceed in a stereoselective fashion. The reduction of 3-hexyne to trans-3-hexene by sodium in ammonia, or to cis-3-hexene by Lindlar catalytic hydrogenation are examples. Since the substrate, reagents and products are all achiral, this diastereospecificity lies in the nature of the reactions themselves.

A stereoselective reaction in which the possible products are diastereomers is said to be diastereoselective and a stereoselective reaction in which the possible products are enantiomers is said to be enantioselective. Diastereoselective reactions are very common. In contrast, enantioselective reactions are rare becuase they require special chiral reagents or catalysts. Therefore, the term stereoselective is casually used to mean diastereoselective.

6.10 Key words

Stereo selectivity and Diastereoselectivity; Stereochemical control in Six-membered ring; Conformational control in the formation of six membered rings; Prochirality; Stereoselectivity reversion by Chelation

6.12References for further studies

1) Modern Methods of Organic Synthesis; W. Carruthers, Iain Coldham; *Cambridge University Press*, **2004**.
2) Synthetic Approaches in Organic Chemistry; Raj K. Bansal; *Jones & Bartlett Learning*, **1996**.
3) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2010**.
4) Modern Organic Synthesis; Michael Nantz; *W. H. Freeman*, **2007**.
5) Organic Synthesis; Michael B Smith; Academic Press, **2011**.
6) Organic Synthesis: The Disconnection Approach; Stuart Warren, Paul Wyatt; *John Wiley & Sons*, **2011**.

6.12 Questions for self understanding

1) With suitable example explain the terms stereo selectivity and diastereoselectivity.
2) Discuss the stereochemical control in Six-membered ring.
3) Discuss the conformational control in the formation of six membered rings.
4) With example discuss the making of single diastereomers using stereoselective reactions
5) With example discuss the making of single diastereomers using by stereospecific reactions
6) What is prochirality? Explain with suitable example.
7) Discuss the stereoselectivity reversion by chelation.

UNIT-7

Structure

7.0 Objectives of the unit

After studying this unit you are able to

- Explains the Baker yeast assisted reduction in organic synthesis
- Explain the steps followed in Solid-Phase peptide synthesis
- Write the different resins used in SPPS
- Explains the advantages and disadvantages of Boc- SPPS strategy
- Explains the advantages and disadvantages of Fmoc- SPPS strategy
- Explain the advantage of microwave reactions
- Explain the advantage of sonochemistry

7.1 Introduction

Biocatalysis is one of the most important stereoselective preparations of optically active compounds. Baker's yeast (Saccharomyces cerevisiae) mediated enzymatic transformations of organic compounds are well known reactions in organic chemistry. One of the most widely studied and commercially significant whole cell systems employed in biocatalysis is baker's yeast (Saccharomyces cerevisiae), which has been extensively utilised in the asymmetric reduction of a wide variety of ketones. This is largely due to the ready availability, ease of experimental procedures and versatility of this microorganism. Solid phase synthesis has found praise in its ability to separate the resin-attached targets from large amounts of excess reagents and impurities. But this area is still growing with respect to isolating target molecules. Peptide synthesis on solid support is a routine technique widely used in chemistry and biochemistry. The process can be run automatically in a peptide synthesizer to obtain oligopeptides or small proteins. Depending on the amino acid sequence even more than 50 amino acid residues can be introduced. Even larger peptides are prepared from these fragments by native chemical ligation.

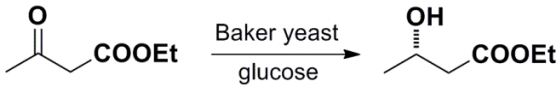
It has long been known that molecules undergo excitation with electromagnetic radiation. This effect is utilized in household microwave ovens to heat up food. However, chemists have only been using microwaves as a reaction methodology for a few years. Some of the first examples gave amazing results, which led to a flood of interest in microwave-accelerated synthesis.

The water molecule is the target for microwave ovens in the home; like any other molecule with a dipole, it absorbs microwave radiation. Microwave radiation is converted into heat with high efficiency, so that "superheating" (external link) becomes possible at ambient pressure. Enormous accelerations in reaction time can be achieved, if superheating is performed in closed

vessels under high pressure; a reaction that takes several hours under conventional conditions can be completed over the course of minutes.

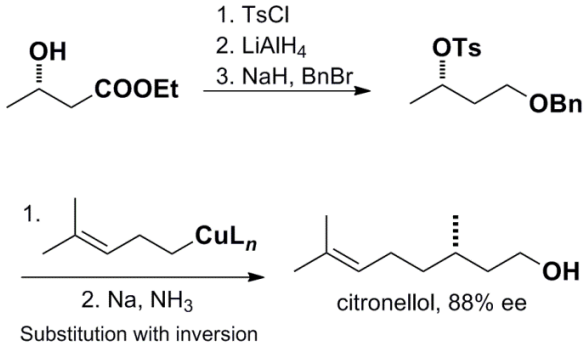
7.2 Baker yeast assisted reduction

Baker Yeast is a good at reducing ketones and the best enantioselectivies are obtained when the ketone carries a β-ester group. The reaction is done by stirring the ketone with an aqueous suspension of live yeast, which must be fed with plenty of sugar.



These reactions are quite messy, and are best done on a large scale. The selectivity of bakerís yeast is the reverse of that of the CBS reagent with respect to the large and small ketone substituents. This is most useful, since (R)-proline is expensive, and an enantiomeric yeast cell would be a rarity indeed.

Note: More effective is the chiral borohydride analogue developed by Corey, Bakshi, and Shibita. It is based upon a stable boron heterocycle made from an amino alcohol derived from proline, and is known as the **CBS** reagent after its developers.



An important application of this bakerís yeast reduction is in the synthesis of citronellol. After reduction and protection of the ester, S_N2 substitution of the secondary tosylate group could be achieved with inversion using a copper nucleophile. The 88% ee obtained here is better than that of many natural samples of citronellol: in common with many other terpenes, citronellol extracted from plants varies greatly in enantiomeric purity.

7.3 Solid-Phase peptide synthesis

The step wise approach to peptide synthesis, when carried out by conventional chemical techniques in which each intermediate is purified before the next step, is of limited value for large peptides because the overall yield is likely to be very low. For example, if 50 synthetic steps were involved, then even if each gave a 90% yield would be only (0.9X100) = 0.5%; for

100 steps, it would be only 0.003%. Since many peptides of medical or biological importance require at least this number of operations.

Bruce Merrifield was first introduced the solid–state synthesis. The growing peptide chain is attached by a chemical bond to a solid support in the form of an insoluble polymer. Instead of purification procedures after each step, impurities and unused reagents are simply removed by washing and filtration. The result is that each step is quantitative, or nearly so, and the overall yield is high. Moreover, the steps can be completed comparatively quickly.

The solid phase method provides an ideal system for cyclization since the dilution is extremely high. In fact, in the ideal situation all molecules are isolated from each other with no means of interaction. Solid Phase Peptide Synthesis (SPPS) can be defined as a process in which a peptide anchored by its C-terminus to an insoluble polymer is assembled by the successive addition of the protected amino acids constituting its sequence. Each amino acid addition is referred to as a cycle consisting of

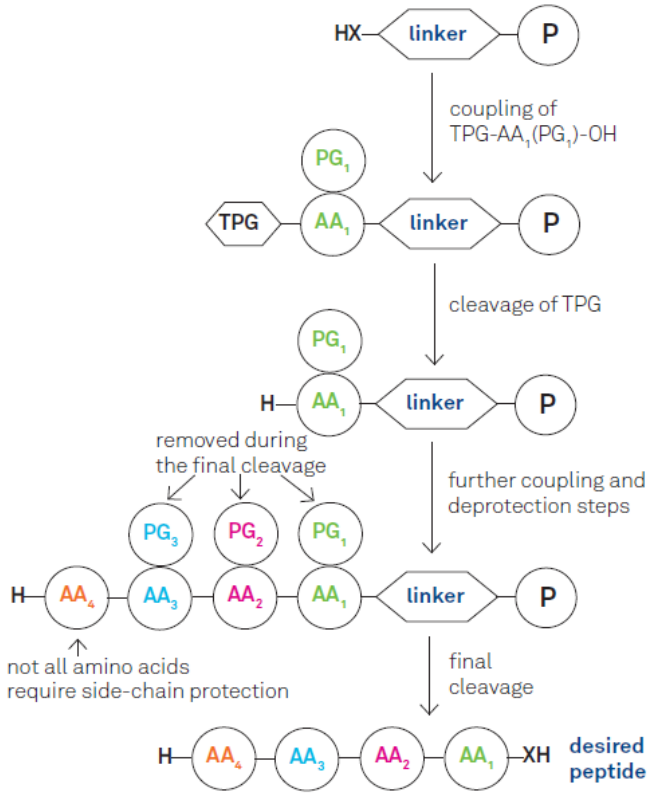


Figure 1: General scheme of SPPS.

X = O, NH; AA = Amino Acid; PG = Protecting Group; P = Polymer Support

TPG = Temporary Protecting Group

a) Cleavage of the N$^{\alpha}$-protecting group

b) Washing steps

c) Coupling of a protected amino acid

d) Washing steps

As the growing chain is bound to an insoluble support the excess of reagents and soluble by-products can be removed by simple filtration. Washing steps with appropriate solvents ensure the complete removal of cleavage agents after the deprotection step as well as the elimination of excesses of reagents and by-products resulting from the coupling step.

The choice of an adequate combination of protecting groups/solid support is the first step on the way to achieve a successful synthesis. For standard SPPS this choice is generally limited to a Boc/benzyl or a Fmoc/tBu based scheme. During the first 15 years of SPPS, the Boc group has been used almost exclusively.

Even if this technique permitted remarkable synthetic achievements the introduction of a new type of protecting group has offered more flexibility for the modification of the peptide chain and/or more specificity in the cleavage of the N^{α}- versus the side-chain protecting groups. The combination Fmoc/tBu has met these requirements and broadened the scope of SPPS. Moreover, the development of new resin derivatives has allowed the cleavage of fully protected sequences which can be further coupled in SPPS or in a classical solution process.

Topic	Fmoc/tBu	Boc/Bzl
Use	Routine synthesis	Requires special equipment
N^{α}/side chain protection	orthogonal[1)]	both acid labile
TFA treatment	final cleavage	repetitive cleavage
HF treatment	none	final cleavage
Automation	yes	yes
Scale	any scale, including final cleavage	HF cleavage: limited scale
Monitoring: N^{α}-deblocking, completion of coupling	UV-absorption, chromophores: Fmoc, dibenzofulvene-piperidine adduct	quantitative ninhydrin test: cumbersome
Synthetic steps	deblock, wash, couple, wash	additional neutralization step
Avoidance of DKP formation	circumvention tedious; synthesis on 2-chlorotrityl resin: suppression of DKP formation	change of coupling protocol: concomitant coupling/neutralization
Final cleavage	in SPPS vessel	special equipment required
Especially recommended for	acid sensitive peptides & derivates, e.g. O-glycosylated or sulfated peptides	base labile peptides; "difficult sequences", aggregation impeded by repetitive TFA treatment

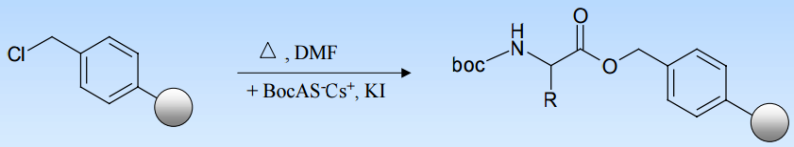
In addition, a variety of selectively cleavable protecting groups offers new perspectives for "on-resin" modification (cyclization, formation of disulfide bridges, derivatization of side chains, etc). The main characteristics of the two general approaches are outlined in above table.

7.3.1Resins for SPPS

Successful SPPS depends upon the choice of the solid support, also called Resin. Choosing the right solid support is often paramount for successful, non-problematic synthesis of the desired peptide. Currently, there are a vast number of commercially available resins, suitable for complex peptide synthesis.

a) Merrifield resin

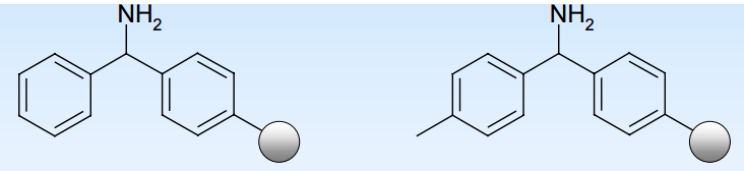
Chloromethylstyrene-divinylbenzene also referred as Merrifield resin was the standard support for the synthesis of peptide acids by Boc SPPS. It is only used in the synthesis of small to medium sized peptides, because the benzylic ester resin linkage is not completely stable towards repetitive treatment with TFA



Attachment of the C-terminal amino acid residue (First amino acid residue) is achieved by heating the resin in DMF with the appropiate amino acid cesium salt in the presence of KI. After the completion of peptide synthesis, the cleavage of the peptide from the resin is done by treatment of resin with HF or TFMSA, or by hydrogenolysis. Alcohols can be released using reducing agents like DIBALH or $LiBH_4$ or methyl esters can be produced by transesterification with NaOMe

b) MBHA resin

Benzhydrylamine / 4-Methylbenzhydrylamine resin also referred as BHA / MBHA resin is used for the synthesis of peptide amides by Boc SPPS. The attachment of the first amino acid can be achieved by standard methods of amide bond formation. After the completion, the cleavage of the peptide from the resin can be done by treatment with HF or TFMSA which yields C- terminal carboxamide derivative. MBHA is more acid sensitive and the peptide amide can be released with HF or TFMSA under less drastic conditions.



7.3.2 Modified resin for SPPS

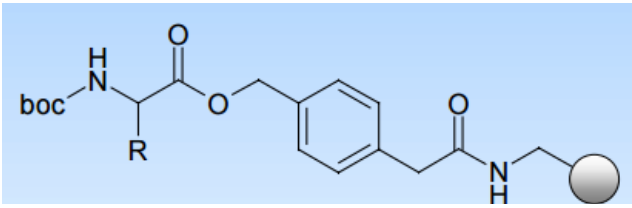
The core resins, by themselves, have limited utility as peptide synthesis resins. Peptides can be cleaved from Merrifield resin and MBHA resin in good yield only with strong acid and are seldom used with Fmoc-amino acids. Peptides attached to aminomethyl resin cannot be removed without destroying or seriously damaging the peptide.

The cleavage properties of the resins can be modified by permanently attaching suitable linkers. By manipulating the structure of the linker, resins ranging from extremely acid labile to base labile can be prepared. Using linkers additionally allows preparation of resins with special applications such as DHP resin utilized as a solid phase support for alcohols or Weinreb resin utilized for preparing aldehydes and ketones.

c) PAM resin

PAM (4-Hydroxymethylphenylacetamidomethyl) resin is the standard support for Boc SPPS. This resign can be synthesized by addition of the PAM-linker on to the aminomethyl resin. Or

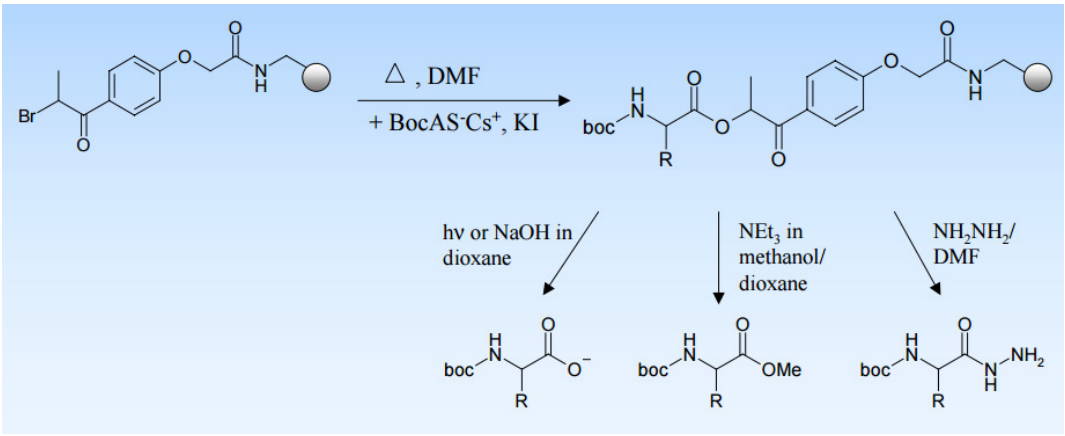
First coupling of the Boc-protected amino acid to the PAM-linker and then reaction with the aminomethyl resin followed by end-capping of unreacted aminomethyl groups can also be followed. Phenylacetamidomethyl function imposes stabilizing effect on the ester linkage (formed by acid group of first amino acid and alcohol group on the resin) thus reduction of losses during repetitive TFA acidolysis is minimized.



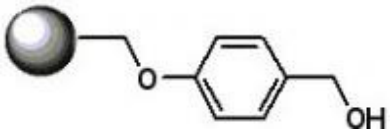
After the completion of synthesis, cleavage of peptide chain for the resin can be done by treatment with HF or TFMSA releases the peptide acid.

d) PPOA resin

Brominated PPOA (Brominated [4-Propionylphenoxy]-acetic acid) resin is a versatile resin for the Boc SPPS of peptide acids, different C-terminal functional moiety like, free carboxylic acid, esters, or hydrazides can be achieved by photolytic or nucleophilic cleavage conditions.

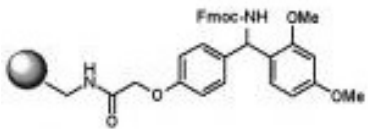


e) Wang Resin

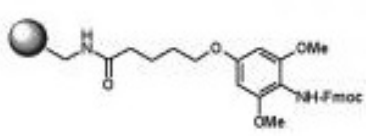


Wang resin is the most widely used solid phase support for acid substrates. The linker attached to the polystyrene core is a 4-hydroxybenzyl alcohol moiety. The linker is bound to the resin through a phenyl ether bond and the substrate is generally attached to the linker by a benzylic ester or ether bond. This linkage has good stability to a variety of reaction conditions, but can be readily cleaved by moderate treatment with an acid, generally trifluoroacetic acid.

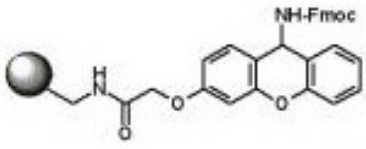
f) Amide/Amine forming Resins



Rink Amide Resin



PAL Resin



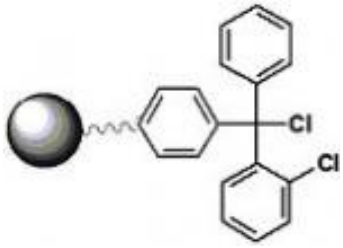
Sieber Amide Resin

The most popular solid phase supports for the formation of amide products include Rink and PAL resins. All of these resins were originally developed for peptide amide synthesis using the Fmoc strategy. These resins are favored due to their higher acid liability. Cleavage can be performed under conditions as mild as 1% TFA. In solid phase organic chemistry, these resins have been used to produce amines by reductive alkylation. To provide stability on storage, each

of these resins is supplied with the amine protected by a Fmoc group, therefore pretreatment with piperidine is required to render the free amine. Acids can be coupled using standard amide forming conditions such as DIC/HOBt, HBTU or BOP.

Rink and PAL resins exhibit similar characteristics with respect to cleavage conditions and the type of products formed. Rink resin, however, has been more widely utilized. PAL is somewhat more acid labile. PAL resin has been found to give cleaner products with long peptide sequences. Sieber Amide Resin is useful for preparing amides and amines and fully protected peptide amide fragments. Products can be cleaved under mild conditions, using 1%TFA in DCM. This resin is less sterically hindered than Rink resin and thus allows for higher loading in sterically demanding applications than Rink resins.

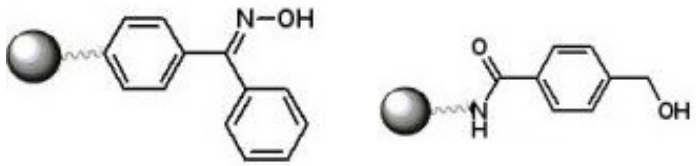
g) Trityl and 2-Chlorotrityl Resins



Trityl resins have been widely used in both solid phase organic and peptide chemistry. These resins are very acid labile and can be cleaved with acetic acid. Protected peptides can be cleaved with 1:4 v/v hexafluoroisopropyl alcohol/dichloromethane with all sidechain protecting groups intact, even trityl groups on sulfhydryl function of homocysteine. These resins are particularly useful when less acid labile protecting groups are required on the substrate following cleavage, or in cases where the substrate can cyclize on the anchoring linkage causing premature cleavage. The bulky triphenylmethyl group prevents such attack through steric hindrance. In addition to being used to immobilize acids and alcohols, trityl resins can also be used to immobilize amines or thiols.

The 2-chlorotrityl resin has better stability during peptide synthesis than the trityl resin. The 2-chlorotrityl resins are available in the chloride form. The chloride form is exceedingly moisture sensitive and must be handled and stored under inert conditions.

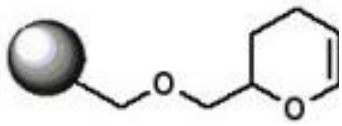
h) Base Labile Resins



Both oxime resin and hydroxymethyl benzoic acid linked resin (HMBA resin) can be cleaved with a variety of nucleophilic agents [ammonia or primary amines (amides), hydrazine (hydrazides), methanol/triethylamine (methyl esters), sodium borohydride (alcohols), sodium hydroxide (acids)] to produce the wide range of products indicated from the same precursor resin. A special application of oxime resin is the formation of cyclic peptides by cyclization cleavage.

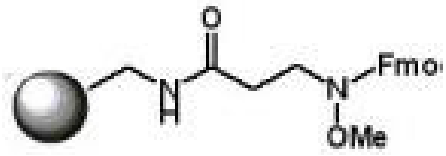
Although oxime resin is compatible with Boc chemistry, the oxime ester linkage is susceptible to TFA. Therefore the Boc group is removed with 25% TFA in DCM during synthesis and end-capping should be performed after each coupling to block any active sites on the resin that may have been exposed. For best results, the peptide should not exceed 10 residues

i) DHP Resin



DHP resin was developed as a solid phase support for alcohols. The DHP linker is less sterically hindered than the trityl linkers are, hence it is preferred for sterically bulky substrates such a s secondary alcohols. Alcohols are attached to the resin under anhydrous catalytic acid conditions, forming an acetal. The bound alcohols can be cleaved from the resin under acidic conditions. DHP resin has been utilized as a sidechain anchor for serine and threonine, as well as hydroxyproline.

j) Weinreb Aminomethyl Resin



This resin was developed by Fehrentz and coworkers to prepare aldehydes by solid phase methodology. An amino acid or carboxylic acid is attached to the resin by standard coupling procedures. Reduction with $LiAlH_4$ releases the product aldehyde. Reacting the resin-substrate with Grignard reagents produces ketones.

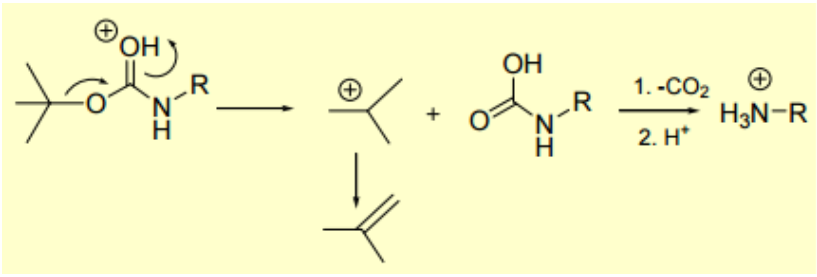
k) Polyethylene Glycol-Polystyrene Grafted Resins

Aggregations resulting from inter and intra chain hydrogen bonding can leave the N-terminal of the growing peptide unavailable for reaction. Grafting polyethylene glycol (PEG) onto the surface of polystyrene beads provides a more polar environment and helps the growing peptide to remain highly solvated. Several brands of PEG-grafted resins are commercially available. These types of resins are often utilized in the synthesis of very long peptides. Since the PEG grafted on the surface of these resins allow greater solvation by water and other protic solvents, these resins are also utilized when protic solvents are required.

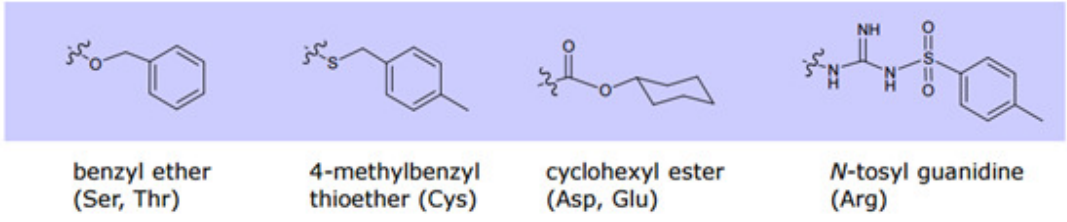
There are two main strategy in SPPS are mainly followed. These strategies are mainly based on the N^{α}-protecting groups of aminoacids. We aware Boc or Fomc are the two main N^{α}-protecting groups weirdly used for aminoacid residues in peptide synthesis. Boc is acid labile hence all the side chain protection groups and resin chosen for SPPS in this method should be acid stable. Similarly Fmoc is base labile hence all the side chain protection groups and resin chosen for SPPS in this method should be base stable stable

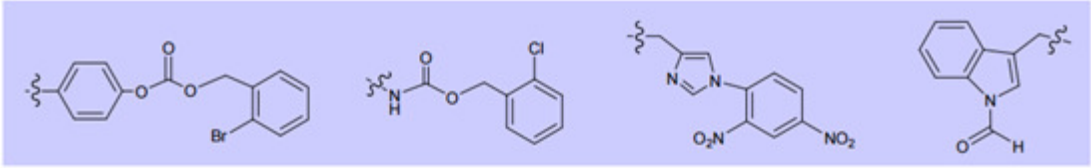
7.3.3 General aspects of Boc strategy

1) Cleavage of the N^{α}-Boc-protection group with TFA (usually 25-50% (v/v) in DCM)

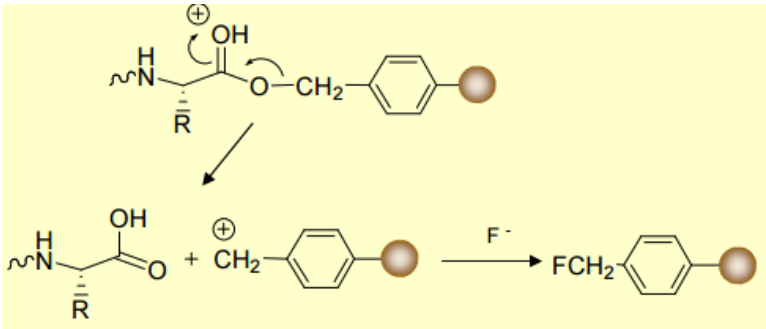


2) Side chain protecting groups must be orthogonal, that means, 1) They are stable against TFA during N-α-Boc deprotection and 2) They are removable at the end of peptide synthesis. The different side chain protecting groups used for side chain function of different aminoacids in Boc SPPS strategy is given below

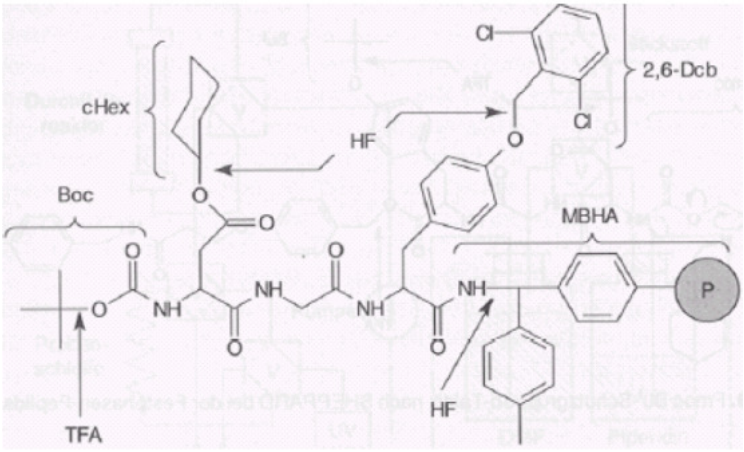




3) Release of the peptide from the resin by treatment with HF



The overall scheme for Boc strategy is out lined in below diagram.



7.3.4 Advantages and disadvantages of Boc- SPPS strategy

Advantages

a) Easy to introduce.

b) Boc-amino acids are stable at room temp. For extended periods (but storage at 4°C is recommended).

c) Deportation with TFA is rapid successful strategy for many peptide synthesis applications.

d) Good coupling results.

Disadvantages

a) Temporary and permanent (side chain) protecting groups are both acid labile.

b) Side chain deprotection during repeated TFA treatment can occur.

c) Repeated TFA-mediated N^{α}-deprotection over the course of a long synthesis may lead to modification and/or degradation of sensitive peptide sequences.

d) Difficulties for fragile peptides that don't survive the relatively harsh final HF cleavage.

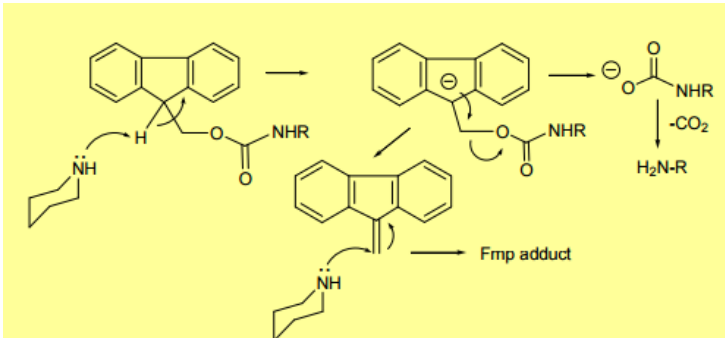
e) Boc-strategy requires the use of "dangerous" HF and expensive laboratory apparatus.

f) Side reactions are possible: t-Bu^{+} reacts with nucleophilic side chains like trp, tyr, met, his.

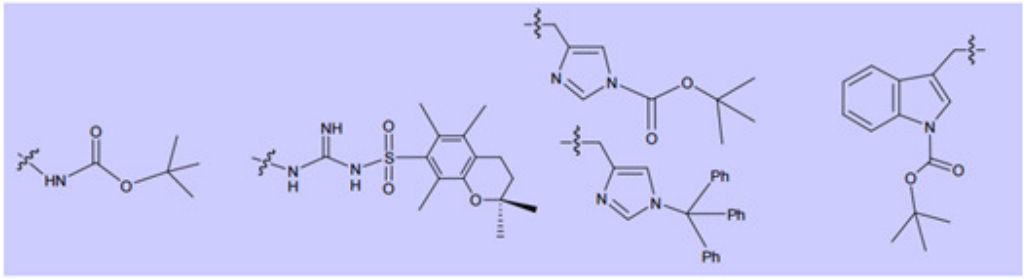
g) Side chain protecting groups/adding of scavengers (1,2-Ethanedithiole) to the deprotection reagent.

7.3.5 General aspects of Boc strategy

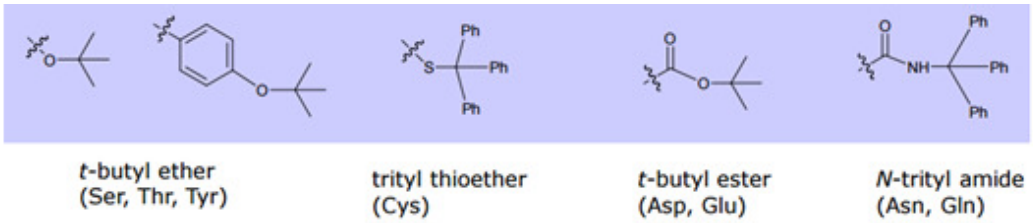
1) Cleavage of the N^{α}-Fmoc-protection group with Pipyridine (usually 20-% (v/v) in DMF)



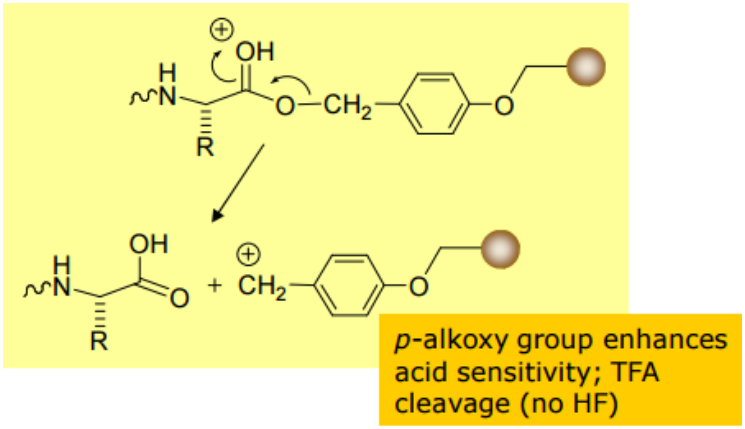
2) Side chain protecting groups must be orthogonal, that means, 1) They are stable against base condition during N-α-Fmoc deprotection and 2) They are removable at the end of peptide synthesis. The different side chain protecting groups used for side chain function of different aminoacids in Boc SPPS strategy is given below



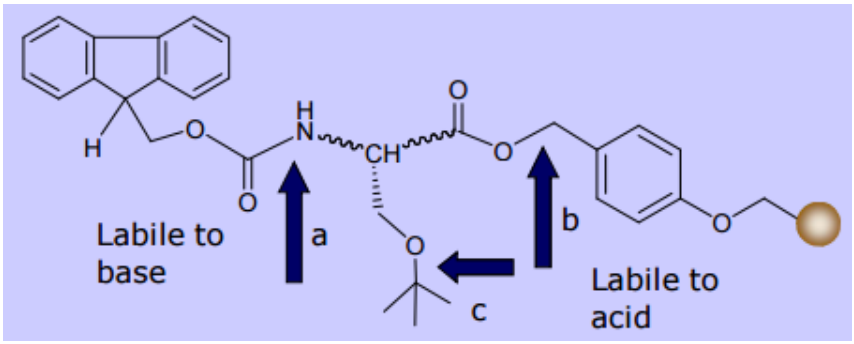
Boc urethane (Lys) | Pmc (tosyl-type) guanidine (Arg) | Boc or trityl imidazole (His) | N^{im}-Boc (Trp)



4) Release of the peptide from the resin by treatment with mild acid treatment



The overall scheme for Fmoc strategy is out lined in below diagram.



7.3.6 Advantages and disadvantages of Fmoc- SPPS strategy

Advantages

a) Orthogonal protection scheme
b) Fmoc-amino acids are easy to prepare in crystalline form in high yield and stable when stored at 4°C
c) Milder reaction conditions: milde base (piperidine) for N^{α}-deprotection, TFA only for the final resin cleavage and deprotection
d) Progress of each deprotection reaction can be followed by real time spectrophotometric monitoring the release of the cleaved Fmoc-group at 300-320 nm

Disadvantages

a) Piperidine vapor is a harmful and toxic
b) Following side reaction is possible while depreotection. 1) aspartimide formation at AspX residues like Asp-Gly, -Ser,-Thr, -Asn, -Gln
c) Linker-bound C-terminal Cys undergoes significant racemisation (ca. 0,5%) with each cycle of Piperidinetreatment

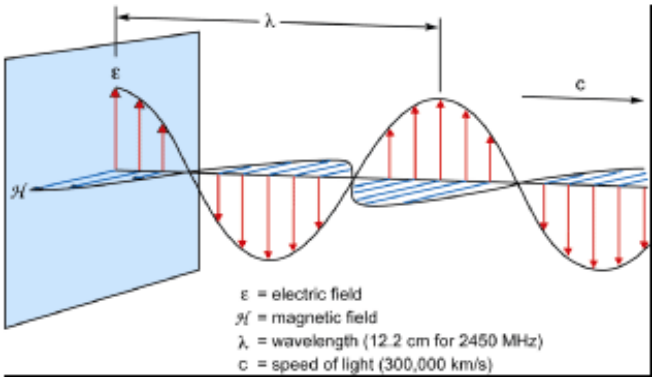
7.4 Microwave reactions and conversions

A microwave travels very rapidly, at the speed of light. However, it varies in length, based on frequency. Commercial microwave uses four frequencies, there are 915 MHz, 2450 MHz, 5800 MHz, and 22,125 MHz. The frequency 2450 MHz has a length of 12.2 cm, which has an appropriate penetration depth (the distance a microwave can travel into a standard sample) for use with small samples.

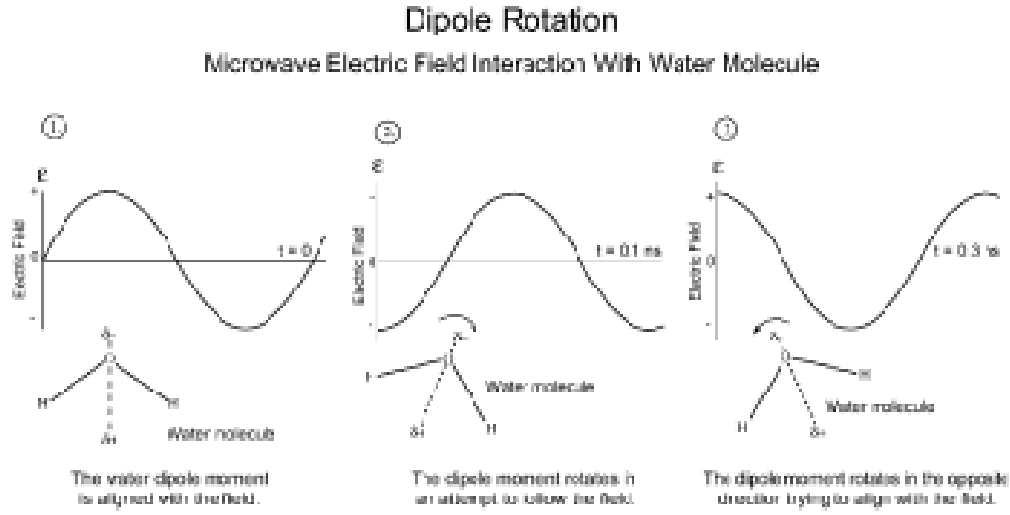
7.4.1 Mechanism of energy gets into the sample in microwave reaction

In organic laboratory the reactions are carried out using heating mantel, hot plate or oil bath to heat the reaction mass**.** Heating mantles transfer thermal energy into a reaction system by following way. The heating mantle first warms the vessel, the vessel then warms the reaction mixture until homogenous temperature. This thermal energy will supply the necessary energy to the reaction mixture to cause the formation of products. The mechanism of energy transfer in a microwave is significantly different from a hotplate or heating mantle. Microwave energy heats the sample through direct activation. Instead of heating the vessel, energy is transferred to the reaction components within the solution, providing two different benefits: 1) more efficient energy transfers to the reaction mixture and 2) reaction components at the center of the reaction are heated at the same rate as reactants near the walls of the vessel.

There are two components in a microwave, they are i) an electric field and ii) a magnetic field



The electric field will interact with any molecule that has a dipole or that is ionic. Because it is a wave, at any given point in time, the electric field is constantly oscillating, from positive to negative and back. These oscillations cause the molecules to rotate such that the appropriate pole will be aligned with the changing field.

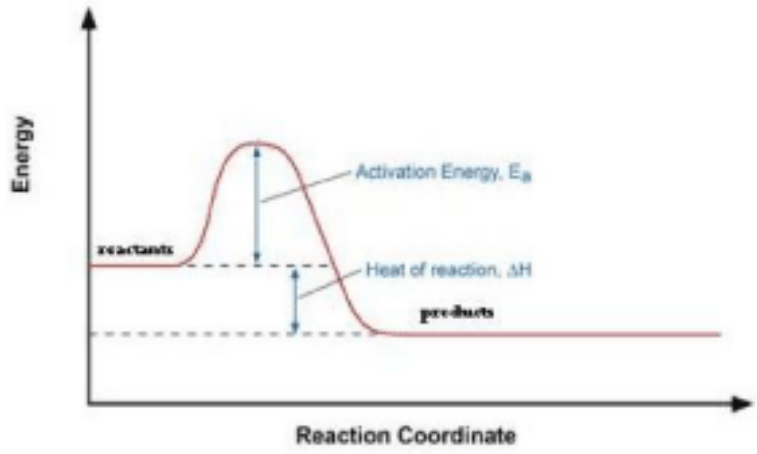


As the molecules move, they generate heat, or thermal energy, as a byproduct, leading to the rapid temperature rise commonly associated with microwave irradiation.

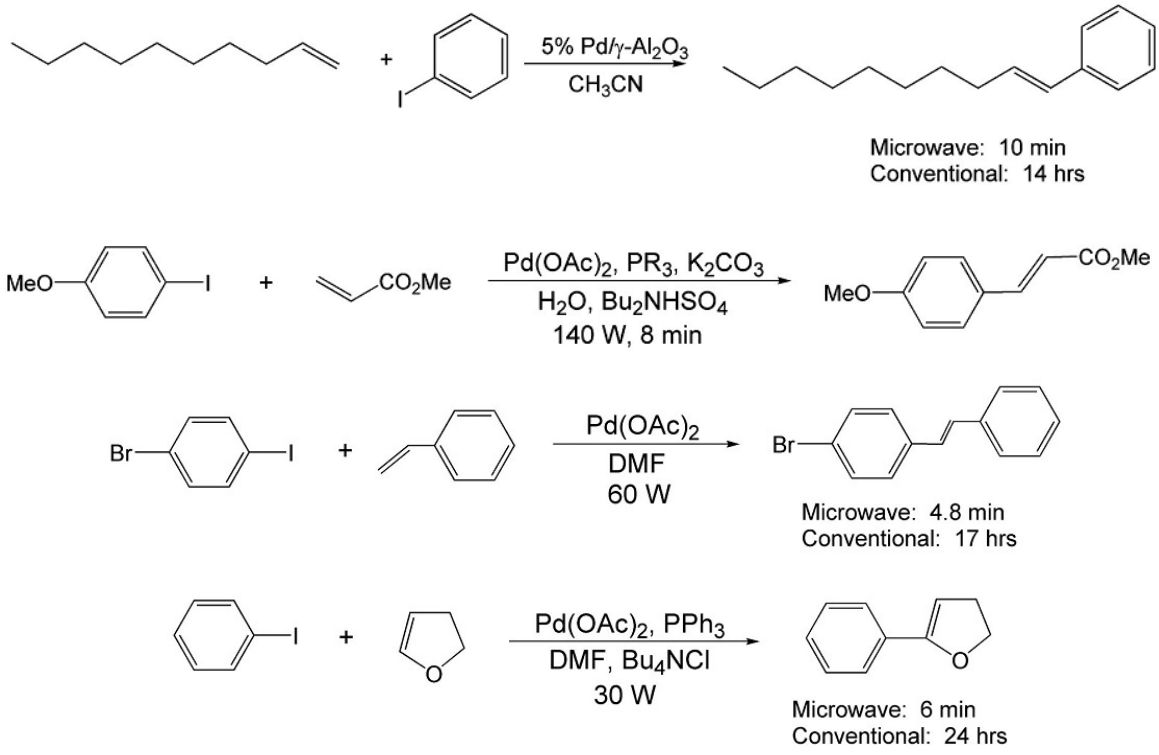
Every solvent and reagent will absorb microwave energy differently. They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field. A solvent that is more polar, for example, will have a stronger dipole to cause more rotational movement in an effort to align with the changing field. A compound that is less polar, however, will not be as disturbed by the changes of the field and, therefore, will not absorb as much microwave energy. Unfortunately, the polarity of the solvent is not the only factor in determining the true absorbance of microwave energy, but it does provide a good frame of reference. Most organic solvents can be broken into three different categories: low, medium, or high absorber. The low absorbers are generally hydrocarbons while the high absorbers are more polar compounds, such as most alcohols.

The energy transfers generated by microwave irradiation occur very rapidly (every nanosecond 10^{-9} seconds). The almost constant energy input is achieved at a rate greater than the molecular relaxation rate, which is on the order to 10^{-5} seconds. Because the energy is added at a rate faster than the molecules are able of fully relaxing, all of the molecules in solution will be in a constant

state of disequilibria. This disequilibria situation will provide more than enough energy to overcome the activation energy barrier (Ea) and drive the reaction to completion.

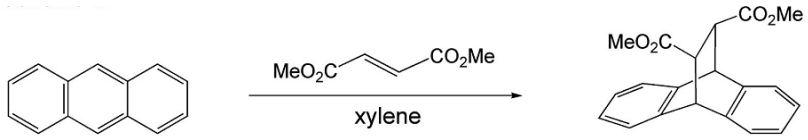


Microwave organic synthesis provides the opportunity to complete the reactions in minutes, offering the option to return to more sequential methods. Types of reaction assisted by microwave given below, Reactions that form carbon-carbon bonds are of supreme importance in synthetic chemistry. Palladium catalyzed cross-coupling reactions have become a significant part of drug discovery. Heck, Suzuki and Stille coupling reactions are easily performed with microwave synthesis instrumentation. Some of the examples given below,



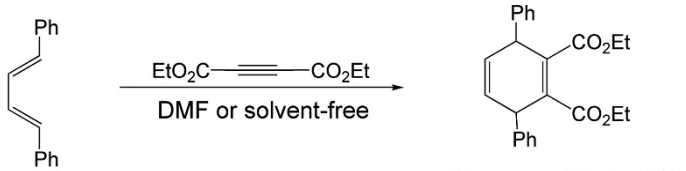
7.4.2 Cycloaddition Reactions

Cycloadditions, which include the Diels-Alder, ene, and Alder-Bong reactions, are important single-step, ring forming reactions in organic synthesis. These transformations usually require high temperature and pressures and long reaction times. For example irradiating anthracene and dimethyl fumarate in a multi-mode instrument at 600 W gave a complete reaction in 10 minutes compared to 72 hours with conventional heating.

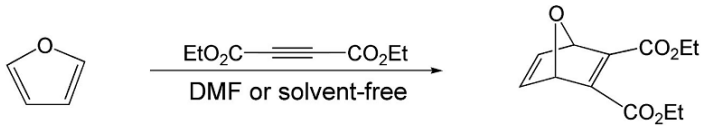


Microwave: 10 min
Conventional: 72 hrs

The below reactions were executed in DMF or solvent free conditions.



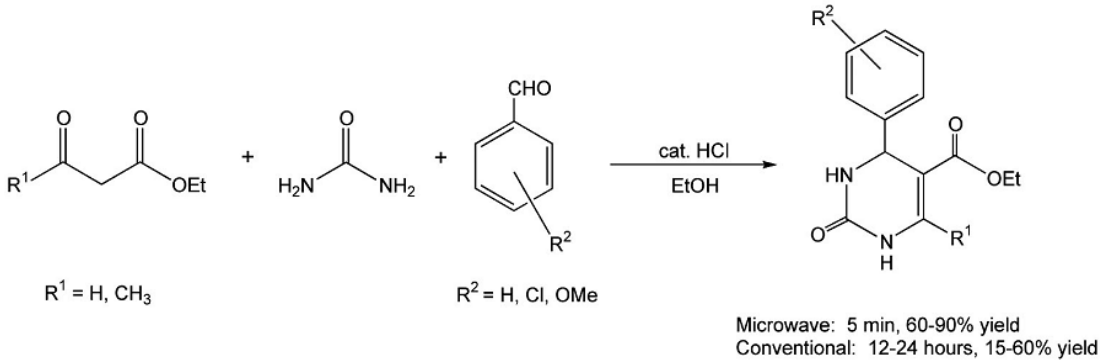
Microwave: 20 min, 58%
Conventional: 6 hrs, 67%



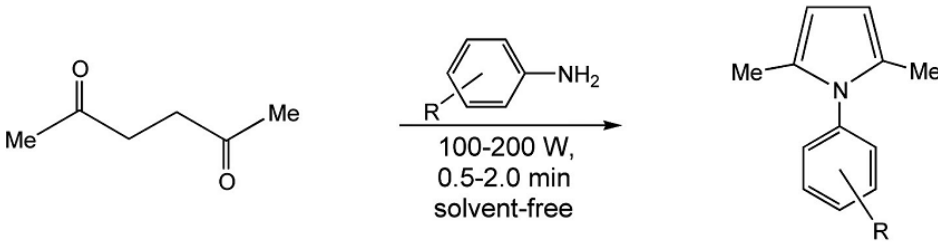
Microwave: 10 min, 86%
Conventional: 15 min, 68%

7.4.3 Heterocyclic reaction

The Biginelli three-component condensation reaction is a one pot synthesis to dihydropyrimidines. These heterocyclic systems contribute to enhanced pharmacological efficiency in a variety of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities. With normal conventional heating, these reactions can take approximately 24 hours for complete transformation with only low to moderate yields. Upon microwave irradiation, the Biginelli reaction was successfully completed in five minutes, with 60-90% yields.



The Pall-Knorr condensation/cyclization reacts 1,4-diketones with primary amines to form N-Substituted pyrroles. This synthsis requires at least twelve hours of prolonged thermal heating and added Lewis acids to activate the diketones. With microwave, transformation occurred in anywhere from 30 seconds to 2 minutes with very high yields (75-90% yields).



7.5 Sonochemistry

The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon called acoustic cavitation. Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size, they can then collide and/or violently collapse.

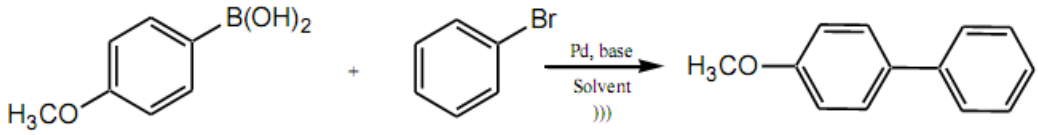
Ultrasound generates cavitation, which is "the formation, growth, and implosive collapse of bubbles in a liquid. Cavitation collapse produces intense local heating (~5000 K), high pressures (~1000 atm), and enormous heating and cooling rates (>109 K/sec)" and liquid jet streams (~400 km/h), which can be used as a source of energy for a wide range of chemical processes. This review will concentrate on theory, reactions and synthetic applications of ultrasound in both homogeneous liquids and in liquid-solid systems. Some recent applications of ultrasound in organic synthesis, such as, Suzuki reaction, Sonogashira reaction, Biginelli reaction, Ullmann

coupling reaction, Knoevenagel condensation, Claisen-Schmidt condensation, Reformatsky reaction, Bouveault reaction, Baylis-Hillman reaction, Michael addition, Curtius rearrangement, Diels-Alder reaction, Friedal-Craft acylation, Heck reaction, Mannich type reaction, Pechmann condensation and effect of ultrasound on phase transfer catalysis, oxidationreduction reactions, ionic liquids and photochemistry are reviewed. Ultrasound found to provide an alternative to traditional techniques by means of enhancing the rate, yield and selectivity to the reactions.

Some of the reactions are explained below with examples.

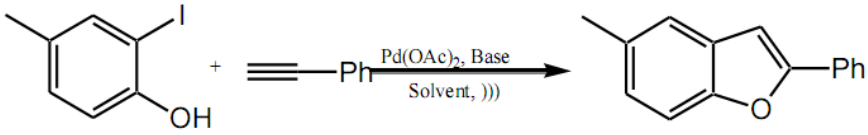
7.5.1 In Suzuki reaction

The Suzuki reaction is one of the most studied carbon-carbon bond forming reaction and useful for the synthesis of several symmetrical/unsymmetrical biaryls. Couple of the methods has been reported for Suzuki reaction under ultrasound and microwave irradiation.



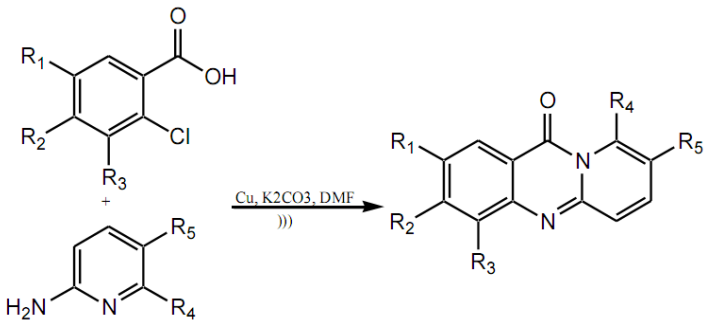
7.5.2 Sonogashira Coupling

A copper-, ligand- and amine-free one-pot synthesis of benzo[b]furans via palladium acetate catalyzed tandem Sonogashira coupling-5-endo-dig-cyclization under ultrasonic irradiation at ambient temperature.



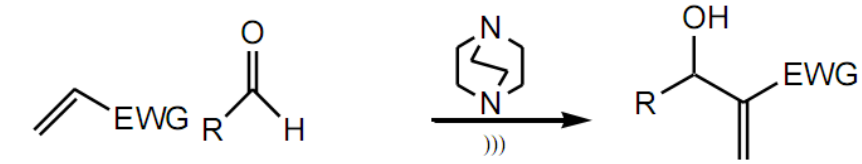
7.5.3 Ullmann Coupling Reaction

The Ullmann condensation between 2-chlorobenzoic acid and 2-aminopyridine derivatives using ultrasound has been described. The reaction was carried out in the presence of anhydrous potassium carbonate and copper powder using DMF as solvent (Scheme 7). In comparison with conventional conditions (stirring for 6 h at reflux temperature), the ultrasound irradiated reaction demonstrated a shorter reaction time (20 min) and greater yields.



7.5.4 Baylis Hillman reaction

The effect on ultrasound radiation was studied on Baylis–Hillman reaction with several aldehydes and different α, β–unsaturated reactants. For all aldehydes tested, the utilization of ultrasound sources augmented the reaction rate and the chemical yields. The use of ultrasound with 1,4-diazabicyclo[2.2.2]octane [DABCO]) is much more effective for catalyzing a Baylis–Hillman.

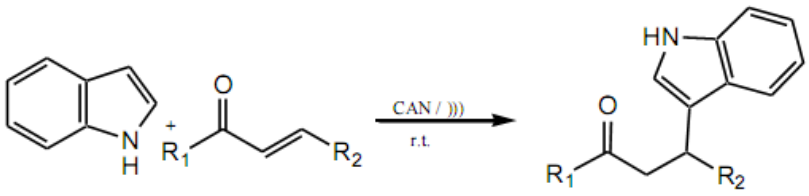


EWG = CO_2R, CN, CHO, $COCH_3$, SO_2Ph

Baylis-Hillman adduct

7.5.5 Michael Addition Reaction

Ceric ammonium nitrate efficiently catalyzes the Michael addition of indole -unsaturated carbonyl ketones by means of alkylation of indole under ultrasonic irradiation to afford the corresponding adduct in excellent yields. Interestingly it was observed that substitution on the indole nucleus occurred exclusively at the 3-position, and N-alkylation products have not been observed.



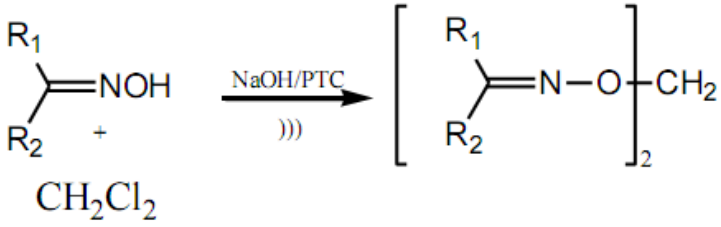
7.5.6 Diels-Alder Reaction

Ultrasound irradiation accelerates hetero Diels-Alder reactions between 1-dimethylamino-1-azadienes and electron-deficient dienophiles. Besides the lower reaction times and increased yields, other advantages of the sonicated reactions are the possibility of isolating previously

unknown adducts due to the milder reaction conditions and, in some cases, the decrease in side reactions.

7.5.7 Effect of ultrasound and phase transfer catalyst

The rate of reacting two immiscible reactants is low because of poor mass transfer. To increase the reaction rate, strong agitation is essential. Phase ransfer catalyst (PTC) is of help in such cases. It transfers the active species from one phse to the other. Ultrasound produces either extremely fine emulsion of immiscible liquids or assists mass transfer and surface activation (in solid/liquidsystem). These factors enhance PTC catalyzed heterogeneous reactions or even replace PTC. A number of such reactions are reported. Ultrasound accelerates the reaction of oxime with dichloromethane in the presence of sodium hydroxide in combination with benzyldimethyltetradecylammonium chloride as a PTC to give methylene dioxime.



7.6 Summary of the unit

Microwave has been used to speed up chemical reactions in the laboratories which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis. In the electromagnetic spectrum the microwave radiation region is located between infrared radiation and radio-waves. Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. In order to avoid interference with these systems, the household and industrial microwave ovens operate at a fixed frequency of 2.45 GHz. The energy of the quantum involved can be calculated by the Planck's law $E = h\nu$ and is found to be 0.3 cal mol^{-1}.

Microwaves couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in the temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity. Only the reaction vessel contents are heated and not the vessel itself; better homogeneity and selective heating of polar molecules might be achieved. The acceleration of chemical reactions by microwave exposure results from the interactions between

the material and electromagnetic field leading to the thermal and specific (non-thermal) effects. For microwave heating, the substance must possess a dipole moment. A dipole is sensitive to external electric field and tries to align itself with the field by rotation. If submitted to an alternating current, the electric field is inversed at each alterance and therefore dipoles tend to move together to follow the inversed electric field. Such a characteristic induces rotation and friction of the molecules, which dissipates as internal homogeneous heating.

The chemical effects of ultrasound do not arise from a direct interaction with molecular species. When liquids that contain solids are irradiated with ultrasound, related phenomena can occur. When cavitation occurs near an extended solid surface, cavity collapse is non-spherical and drives high-speedjets of liquidinto the surface. These jets and associated shock waves can cause substantial surface damage and expose fresh, highly heated surfaces. Ultrasonic irradiation of liquid–powder suspensions produces another effect: high-velocity inter-particle collisions. Cavitation andthe shockwaves it creates in slurry can accelerate solidparticles to high velocities. The resultant collisions are capable of inducing dramatic changes in surface morphology, composition and reactivity.

7.7 Key words

Baker yeast assisted reduction; Solid-Phase peptide synthesis; Resins for SPPS; Modified resin for SPPS; General aspects of Boc strategy; General aspects of Boc strategy; Microwave reactions and conversions; Cycloaddition Reactions; Heterocyclic reaction; Sonochemistry

7.9 References for further studies

1) Modern Methods of Organic Synthesis; W. Carruthers, Iain Coldham; *Cambridge University Press*, **2004**.
2) Synthetic Approaches in Organic Chemistry; Raj K. Bansal; *Jones & Bartlett Learning*, **1996**.
3) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2010**.
4) Modern Organic Synthesis; Michael Nantz; *W. H. Freeman*, **2007**.
5) Organic Synthesis; Michael B Smith; Academic Press, **2011**.
6) Organic Synthesis: The Disconnection Approach; Stuart Warren, Paul Wyatt; *John Wiley & Sons*, **2011**.

7.8 Questions for self understanding

1) With example use of Baker yeast in reduction reaction

2) Discuss the Solid-Phase peptide synthesis

3) Write the structure of different resins used in SPPS.

4) Discuss the general aspects of Boc SPPS strategy

5) Explain the advantages and disadvantages of Boc- SPPS strategy

6) Discuss the general aspects of Fmoc strategy

7) Explain the advantages and disadvantages of Fmoc- SPPS strategy

8) Discuss the use of Microwave for organic reactions

9) Discuss the mechanism of energy gets into the sample in microwave reaction

10) Give one example for following reactions under microwave

a) Cycloaddition Reactions

b) Heterocyclic reaction

11) What is sonochemistry?

12) Discuss the following reaction under sonochemistry

a) In Suzuki reaction

b) Sonogashira Coupling

c) Ullmann Coupling Reaction

d) Baylis Hillman reaction

e) Michael Addition Reaction

f) Diels-Alder Reaction

13) Discuss the effect of ultrasound and phase transfer catalyst

UNIT-8

Structure

8.0 Objectives of the unit

After studying this unit you are able to

- Explain the mechanism of Sharpless Asymmetric Epoxidation
- Explain the mechanism of Robinson Annulation
- Explain the mechanism of Mannich reaction
- Explain the mechanism of Wittig Reaction

8.1 Introduction

There are number of additions reactions of alkenes that occur via concerted mechanisms. Alkene oxidations are among the most synthetically useful reactions because they are able to convert simple hydrocarbon starting materials into oxygen-containing compounds. The resulting heteroatomic functional groups may open up new avenues of synthetic utility or they may reflect aspects of a target natural product.

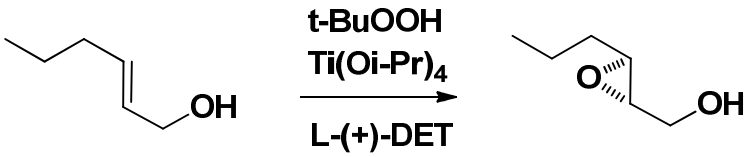
Epoxidation is a method for converting an alkene into an epoxide. The reagent required is always a peroxo species. A peroxo species looks very much like a normal oxygen-containing compound, but with an extra oxygen in it. Historically, the most common such reagent was m-chloroperbenzoic acid (mCPBA).

However, other reagents can also be used, such as hydrogen peroxide (H_2O_2) or potassium hydrogen persulfate ($KHSO_5$), marketed under the trade name Oxone. The latter methods are considered "greener" or more environmentally friendly, because the side poducts (water or sulfate, respectively) are pretty innocuous. These methods are generally slower and are often used with a catalyst. Catalysts used with hydrogen peroxide include Lewis acidic species such as sodium tungstate (Na_2WO_4) needed to activate the peroxide. A similar reaction using titanium (IV) and chiral ligands leads to an enantiomerically pure epoxide; this reaction is called "Sharpless epoxidation". With oxone, ketones are used as oxygen transfer catalysts in a method referred to as "Shi oxidation"

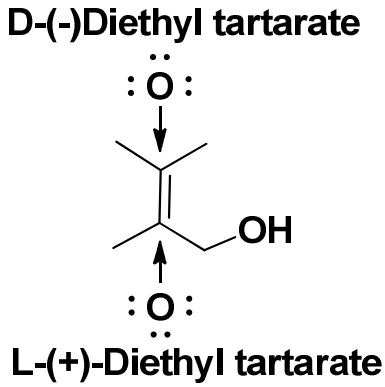
8.2 Sharpless Asymmetric Epoxidation

The epoxidation of alkenes with hydroperoxide gives racemic products in most cases. However, by using chiral ligand, chiral epoxide can be obtained. This epoxidation was discovered by Sharpless and so is known as Sharpless asymmetric epoxidation. Sharpless surmised that, by adding a chiral ligand to the titanium catalyst, he might be able to make the reaction asymmetric.

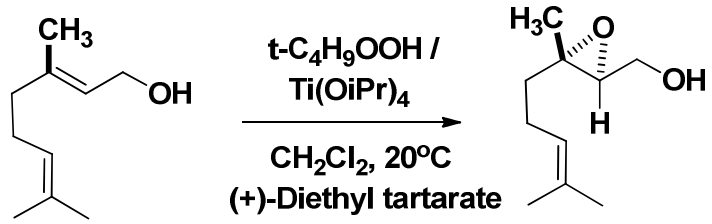
The ligand that works best is diethyl tartrate, and the reaction shown below is just one of many that demonstrate that this is a remarkably good reaction.



The oxidation of allylic alcohols with t-butyl hydroperoxide in presence of either (+) or (-) diethyl tartrate and titanium tetraisopropoxide yields the corresponding asymmetric epoxide in high optical yield. This method is more stereoselective than any other method used for this transformation. In this chiral epoxidation there is uniformly high asymmetric induction and the absolute configuration of the epoxide produced can be predicted. If allylic alcohol is represented as shown below, oxygen is delivered from the top face in the presence of D-(-)diethyl tartarate and from the bottom face in the presence of L-(+)-diethyl tartarate.



A number of examples of highly enantioselective epoxidations of allylic alcohols have been reported. For example,

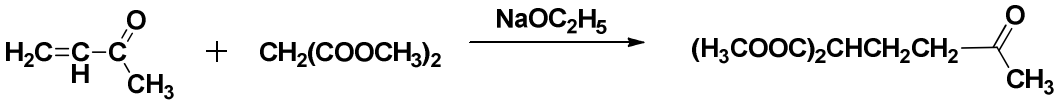


Transition metal-catalysed epoxidations work only on allylic alcohols, so there is one limitation to the method, but otherwise there are few restrictions on what can be epoxidised enantioselectively. When this reaction was discovered in 1981 it was by far the best asymmetric

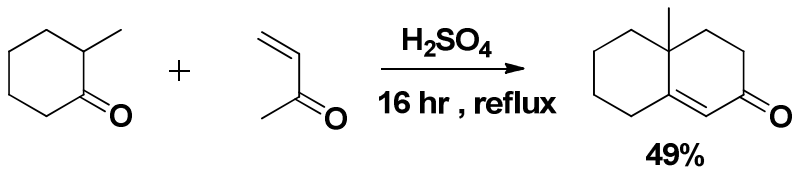
reaction known. The Sharpless oxidation has been used as a key step in the synthesis of terpenes carbohydrates, pheromones, macrocyclic natural products and pharmaceuticals.

8.3 Robinson Annulation

Synthesis of fused cyclohexenones by reaction of cyclanones with vinyl ketones (base or acid catalyzed), a tandem Michael addition-aldol condensation. The Michael addition followed by aldol condensation is an important route for the synthesis of bicyclic ketones and is known as Michael addition is a reaction between an α,β-unsaturated carbonyl compound and a compound with an active methylene group in the presence of a base e.g., sodium ethoxide or a secondary amine. The reaction is illustrated as given below.



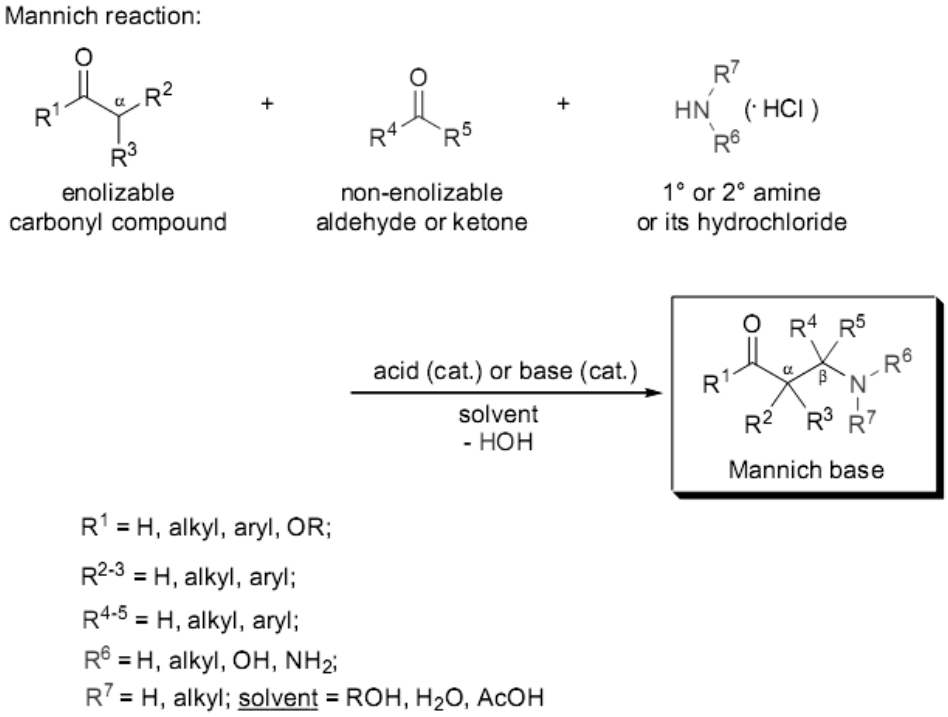
In Robinson annulation , the compounds containing two double bonds conjugated with a carbonyl group react with active methylene compound to give 1,6-addition products.



8.4 Mannich reaction

The condensation of a CH-activated compound (usually an aldehyde or ketone) with a primary or secondary amine (or ammonia) and a non-enolizable aldehyde (or ketone) to afford aminoalkylated derivatives is known as the **Mannich reaction**. More generally, it is the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines. The product of the reaction is a substituted -amino carbonyl compound, which is often referred to as the Mannich base. The general features of the reaction are: 1) the CH-activated component (activated at their α-position) is usually an aliphatic or aromatic aldehyde or ketone, carboxylic acid derivatives, β-dicarbonyl compounds, nitroalkanes, electron-rich aromatic compounds such as phenols (activated at their ortho position) and terminal alkynes; 2) only primary and secondary aliphatic amines or their hydrochloride salts can be used since aromatic amines tend not to react; 3) the non-enolizable carbonyl compound is most often formaldehyde; 4) when the amine component is a primary amine, the initially formed β-amino carbonyl compound can undergo further reaction to eventually yield a N,N-dialkyl derivative (a tertiary amine); however, with secondary amines

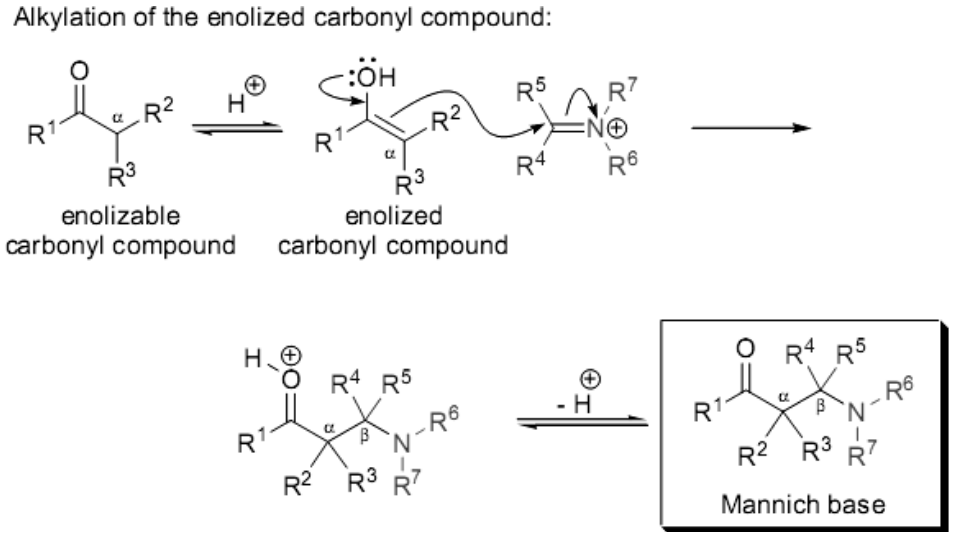
overalkylation is not an issue; 5) the reaction medium is usually a protic solvent such as ethanol, methanol, water, or acetic acid to ensure sufficiently high concentration of the electrophilic iminium ion, which is responsible for the aminoalkylation; 6) unsymmetrical ketones usually give rise to regioisomeric Mannich bases, but the product derived from the aminoalkylation of the more substituted α-position tends to be dominant; and 7) Mannich bases are useful synthetic intermediates, since they can undergo a variety of transformations: β-elimination to afford α,β-unsaturated carbonyl compounds (Michael acceptors), reaction with organolithium, or Grignard reagents to yield β-amino alcohols and substitution of the dialkylamino group with nucleophiles to generate functionalized carbonyl compounds. There have been several improvements to the original three-component Mannich reaction.



8.4.1 Mechanism

The mechanism of the Mannich reaction has been extensively investigated. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion. This iminium ion then reacts with the

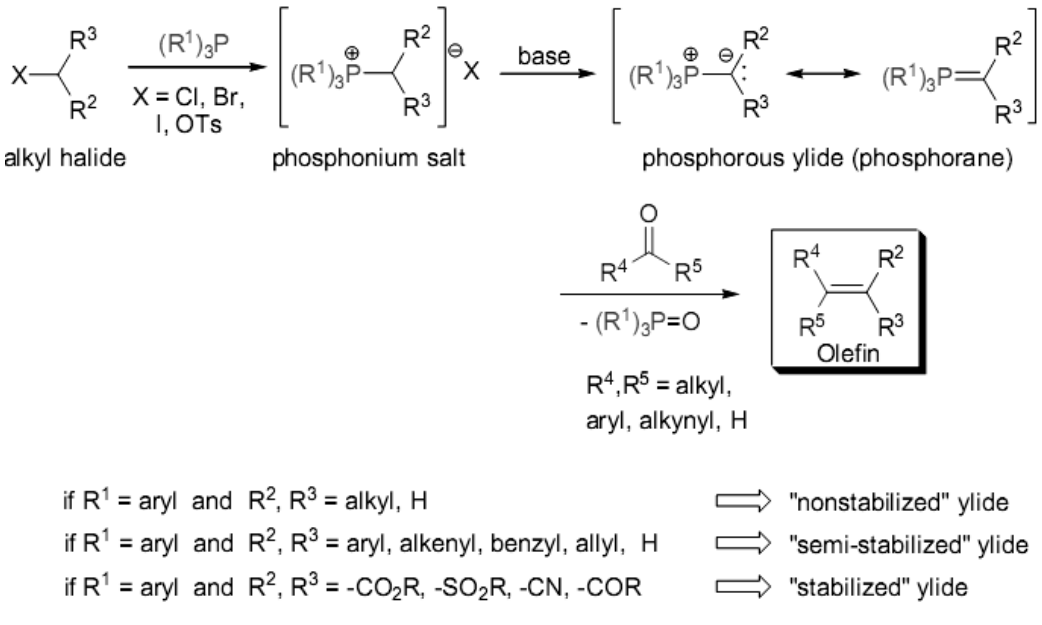
enolized carbonyl compound (nucleophile) at its α-carbon in an aldol-type reaction to give rise to the Mannich base.



8.5 Wittig Reaction

The formation of carbon-carbon double bonds (olefins) from carbonyl compounds and phosphoranes (phosphorous ylides) is known as the **Wittig reaction**.

The Wittig reaction has become one the most important and most effective method for the synthesis of alkenes. The active reagent in this transformation is the phosphorous ylide, which is usually prepared from a triaryl- or trialkylphosphine and an alkyl halide (1° or 2°) followed by deprotonation with a suitable base (e.g., RLi, NaH, NaOR, etc.).



There are three different types of ylides depending on the nature of the R^2 and R^3 substituents: 1) in the stabilized ylides the alkyl halide component has at least one strong electron-withdrawing group (-CO_2R, -SO R, etc.), which stabilizes the formal negative charge on the carbon; 2) semi-stabilized ylides have at least one aryl or alkenyl substituents as the R^2 or R^3 groups, which are less stabilizing; and 3) nonstabilized ylides usually have only alkyl substituents, which do not stabilize the formal negative charge on the carbon.

The general features of the Wittig reaction are

1) The phosphonium salts are usually prepared using triphenylphosphine, and the phosphorous ylides are generated before the reaction or in situ;
2) The ylides are water as well as oxygen-sensitive
3) The phosphorous ylides chemoselectively react with aldehydes (fast) and ketones (slow), other carbonyl groups (e.g., esters, amides) remain intact during the reaction
4) The stereoselectivity, E-or Z-selectivity, is influenced by many factors: type of ylide, type of carbonyl compound, nature of solvent, and the counterion for the ylide formation
5) Non-stabilized ylides under salt-free conditions in a dipolar aprotic solvent with aldehydes afford olefins with high (Z)-selectivity
6) Stabilized ylides give predominantly (E)-olefins with aldehydes under the same salt-free conditions
7) Semi-stabilized ylides usually give alkenes with poorer steroselectivity and
8) Ether solvents such as THF, EtO, DME, MTBE, or toluene are used.

The Wittig reaction has several important variants

1) The Horner-Wittig reaction takes place when the phosphorous ylides contain phosphine oxides in place of triarylphosphines
2) The use of stabilized alkyl phosphonate carbanions is known as the Horner-Wadsworth-Emmons reaction in which (E)-α,β-unsaturated esters are formed
3) In the Schlosser modification, nonstabilized ylides can give pure (E)-alkenes when two equivalents of Li-halide salt is present in the reaction mixture
4) Asymmetric Wittig reaction were also developed and
5) Wittig reaction on solid support allows easy separation of the products from triphenylphosphine oxide.

8.6 Summary of the unit

Sharpless Asymmetric Epoxidation converts primary and secondary allylic alcohols into 2,3 epoxyalcohols. The reaction is enantioselective (only one enantiomer produced). Enantiomer formed depends on stereochemistry of catalyst. The catalyst use is titanium tetra(isopropoxide) with diethyltartrate. The use of + or – tartrate will yield different enantiomers and tertbutylperoxide is used as the oxidizing agent.

The Robinson annulation is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction. The starting materials for a Robinson annulation are an α, β-unsaturated carbonyl compound and an enolate. The Robinson annulation forms a six-membered ring and three new C–C bonds—two σ bonds and one π bond. The product contains an α,β-unsaturated ketone in a cyclohexane ring—that is, a 2-cyclohexenone.

The Mannich reaction consists in the condensation of ammonia or primary or secondary amines, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group.

The "Wittig Reaction" is one of the premier methods for the synthesis of alkenes. It uses a carbonyl compound as an electrophile, which is attacked by a "phosphorus ylide" (the "Wittig reagent".) In the Wittig reaction, however, two smaller carbon units are conjoined to make the alkene double bond. Thus molecules of increasing size and complexity can be quickly assembled. In addition, there is no ambiguity regarding the site of the double bond. (In contrast to elimination reactions, which often give mixtures of "more substituted" and "less substituted" structural isomers.) The Wittig reaction is nicely complementary to the aldol condensation, in which carbonyl compounds are attacked not by a phosphorus ylide but by an enolate.

8.7 Key words

Sharpless Asymmetric Epoxidation; Robinson Annulation; Mannich reaction; Wittig Reaction

8.9 References for further studies

1) Modern Methods of Organic Synthesis; W. Carruthers, Iain Coldham; *Cambridge University Press*, **2004**.
2) Synthetic Approaches in Organic Chemistry; Raj K. Bansal; *Jones & Bartlett Learning*, **1996**.

3) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2010**.
4) Modern Organic Synthesis; Michael Nantz; *W. H. Freeman*, **2007**.
5) Organic Synthesis; Michael B Smith; Academic Press, **2011**.
6) Organic Synthesis: The Disconnection Approach; Stuart Warren, Paul Wyatt; *John Wiley & Sons*, **2011**.

8.9 Questions for self understanding

1) What is Sharpless Asymmetric Epoxidation reaction?
2) What are the different reagents used in SAER?
3) Discuss the mechanism of SAER?
4) Discuss the role of tartaric acid in SAER?
5) What is Robinson Annulation reaction?
6) Discuss the mechanism of Robinson Annulation reaction
7) What is Mannich reaction?
8) Discuss the mechanism of Mannich reaction
9) Briefly discuss Wittig Reaction.

UNIT-9

Structure

9.0 Objectives of the unit

After studying this unit you are able to

- Explain the advantage of linear Synthesis
- Explain the advantage of convergent Synthesis
- Write the Retro synthetic Analysis of given molecule
- List the terminology used in retro synthetic analysis
- Explain the role of Functional Group Interconversion (FIG)
- Explain the two group disconnections approach

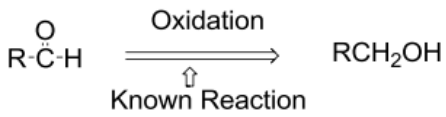
9.1 Introduction

E. J. Corey describe retrosynthesis is "A problem solving technique for transforming the structure of a target molecule (TM) to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercial available starting materials for a chemical synthesis". In this analysis The TM is "broken down" by a series of "bond disconnections" which are referred as "Retrosythetic transforms". Technically it is the reverse of a synthetic reaction. The fragment of a disconection is called a synthon (usually an anion or a cation) and the synthetic equivalent of a synthon is a reagent. The synthon represent what kinds of properties are needed in the individual fragment parts. A retron is a structural subunit in the target molecule (TM) which allows use of a specific transformation. For example, the retron for the Diels-Alder transformation is a six membered ring containing a π-bond. Similarly 3-Hydroxyketones (and α, β-unsaturated ketones) are aldol retrons. Finally the retrosynthesis leads to a connection of bonds-which are actually broken up in the synthesis.

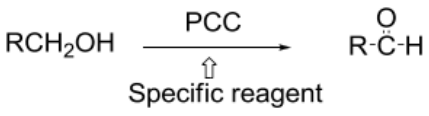
9.2 Synthetic Planning

Synthesis is a construction process that involves converting simple or commercially available molecules into complex molecules using specific reagents associated with known reactions in the retrosynthetic scheme.

Retrosynthetic Scheme



Synthetic Scheme



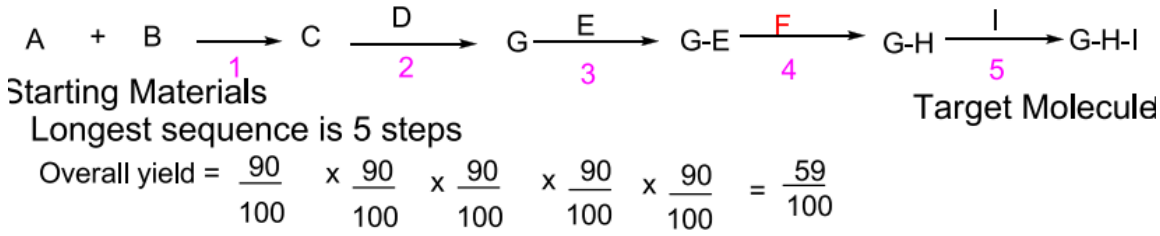
Syntheses can be grouped into two broad categories:

i) Linear syntheses

ii) Convergent syntheses

9.2.1 Linear Synthesis

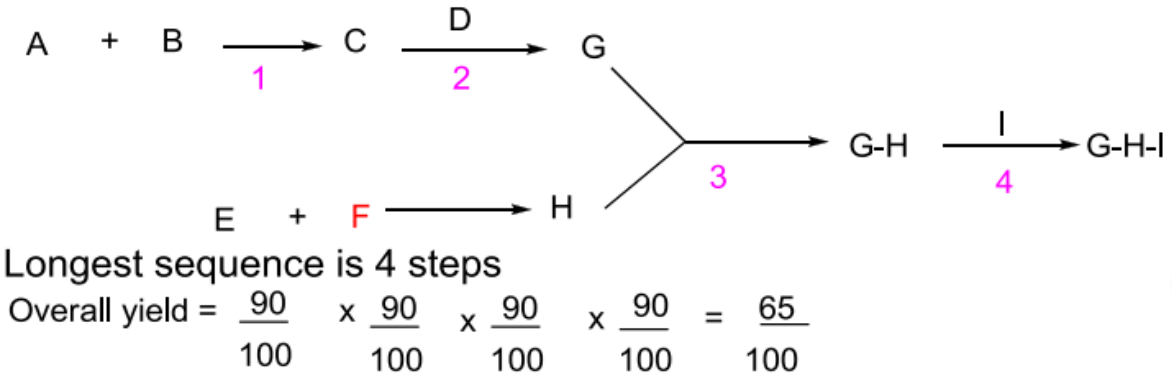
In linear synthesis, the target molecule is synthesized through a series of linear transformations.



Since the overall yield of the synthesis is based on the single longest route to the target molecule, by being long, a linear synthesis suffers a lower overall yield. The linear synthesis is fraught with failure for its lack of flexibility leading to potential large losses in the material already invested in the synthesis at the time of failure.

9.2.2 Convergent Synthesis

In convergent synthesis, key fragments of the target molecule are synthesized separately or independently and then brought together at a later stage in the synthesis to make the target molecule.



A convergent synthesis is shorter and more efficient than a linear synthesis leading to a higher overall yield. It is flexible and easier to execute due to the independent synthesis of the fragments of the target molecule.

9.3 Retro synthetic Analysis

The key idea with retro synthetic analysis and the disconnection approach is: in an imaginary way to sequentially break bonds (i.e. disconnect atoms) within a target structure, to reveal

simpler structures. These imaginary backwards reactions are termed antithetical reactions. The resulting simpler structures then themselves become the new target structures, and are subjected to a further imaginary bond-breaking operation, or disconnection. The idea is that after several iterations of the disconnection the newly revealed target structure will be so simple that it is recognizable either as a commercially available chemical feedstock, or something whose synthesis is straightforward and/or well-established.

9.4 Terminology used in retro synthetic analysis

Target Molecule: The molecule whose synthesis is being planned. Usually written **TM** and identified by the frame number.

Disconnection An analytical operation, which breaks a bond and converts a molecule into a possible starting material. The reverse of a chemical reaction. Symbol ⇒ and a curved line drawn through the bond being broken. Called a dislocation by some people.

FGI Functional Group Interconversion: The operation of writing one functional group for another so that disconnection becomes possible. Again the reverse of a chemical reaction. Symbol ⇒ with FGI written over it.

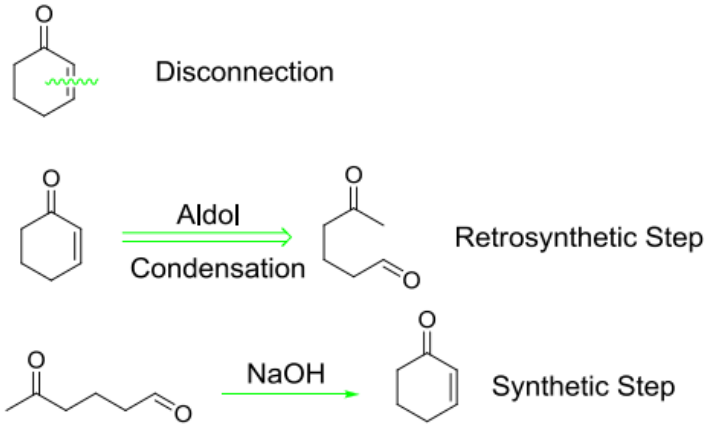
Reagent A compound which reacts to give an intermediate in the planned synthesis or to give the target molecule itself. The synthetic equivalent of a synthon.

Synthetic Equivalent A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.

A disconnection is represented by a wavy (≀) line through the bond being disconnected.

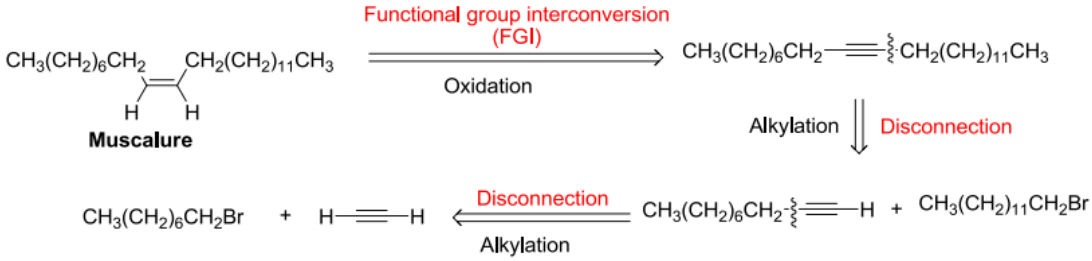
A retrosynthetic arrow (⇒): This open arrow represents going from the target molecule "backwards" to simpler molecules (retrons).

A synthetic arrow (→): This closed arrow represents going in the forward direction. Below figure illustrate these points

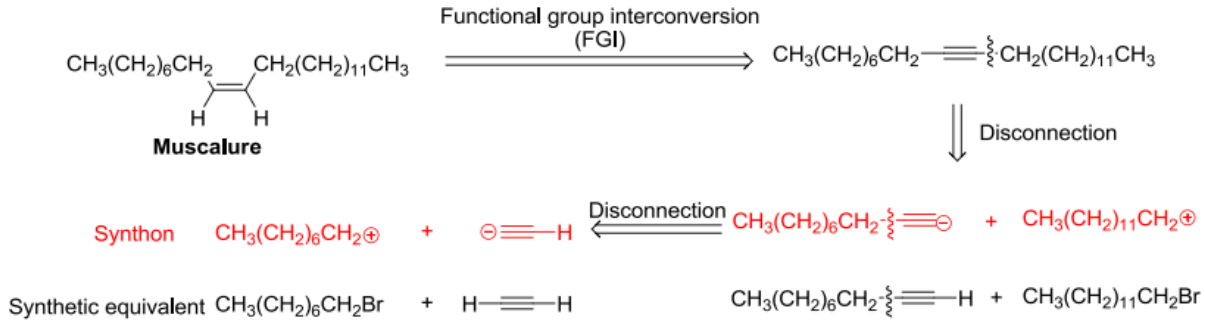


9.5 Functional Group Interconversion (FIG)

Functional group interconversion (FGI) describes a process of converting one functional group to another: e.g. an alcohol to an aldehyde, alkyne to alkene etc. Although FGI doesn't offer much gain to a synthesis, it sets the stage for subsequent disconnection of the intermediate. Revisit the retrosynthetic analysis of Muscalure to identify the disconnections and Functional group interconversions.



The concept of bond polarity within functional groups is of prime importance in disconnections. The disconnection of a bond based on this innate polarity maylead to two pairs of idealized (imaginary) fragments called synthons from which a functional group may be generated.

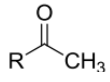


9.6 Synthons and Disconnections

a) Synthon

A synthon is an idealized fragment or species (e.g. CH_3^+ or CH_3^-) generated from a bond disconnection during retrosynthetic analysis. It may not necessarily correspond to a real molecule. A synthetic equivalent is a real molecule or reagent (e.g. CH_3Br or CH_3MgBr) that can be ascribed to a synthon and can be employed in a synthetic step.

Other Synthons and their Synthetic equivalents

Synthon	$R^{\oplus}$	$R^{\ominus}$	
Synthetic equivalent	RI, RBr, ROTs	RMgX, RLi	

Thus synthon is a generalized fragment, usually an ion, produced by a disconnection. (Some people also use synthon for a synthetic equivalent).

b) Disconnections

During retrosynthetic analysis the target molecule is systematically broken down by a combination of disconnection and functional group interconversion (FGI). The term disconnection relates to breaking a carbon-carbon bond of a molecule to generate shorter or simpler fragments. A good disconnection must achieve the greatest simplification of the target molecule. For a complex molecule, this basic disconnection process is repeated until the target is reduced to simple starting materials.

The complete set of disconnections and functional group interconversions for a specified target molecule is what constitutes a retrosynthetic pathway or plan.

c) What to disconnect

To make symmetrical fragments disconnection of target molecule is necessary. The following points are to be taken care while disconnection

i) C–X bonds (C–heteroatom, esters, amides, etc)

ii) either E or Z double bonds

iii) 1–3 bonds away from functional groups

iv) bonds that attach rings to chains (produce the largest fragment)

9.7 Strategies in synthetic planning

1) The main goal of retrosynthetic analysis is to reduce the complexity of the target. This can be achieved as follows

2) 1. The application of powerful transforms by forming key bonds in the molecular skeleton (i.e. C–C bonds) using aldol, Diels-Alder, intramolecular alkylations, C–H activation, cross couplings reactions and forming stereocenters through substrate control (modernly reagent control) cascade reactions.

3) 2. Lateral movement through a non-simplifying transform skeletal rearrangements, transpositions, isomerization reactions, epimerizations etc….

4) 3. Disconnections that actually increase molecular complexity, protecting groups, masking groups, activating/deactivating groups, adding functional groups or bonds.

a) *Strive for success and good cost management*

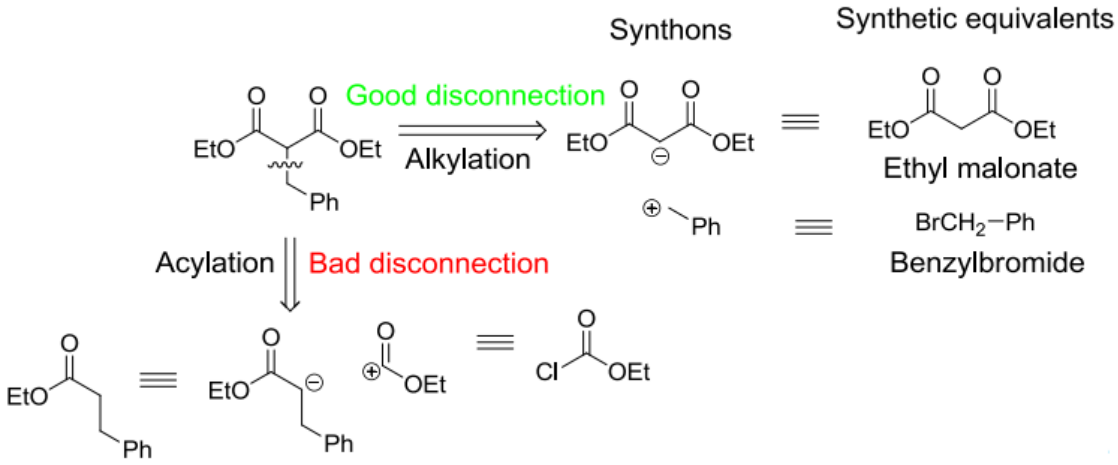
In planning a synthesis generate a large number of retrosynthetic pathways to the target molecule: Examine these retrosynthetic pathways to identify among them an optimal synthetic route for which reagents are readily available and inexpensive.

b) Convergent vs Linear synthesis

When considering a disconnection in the retrosynthetic analysis of a complex target molecule, try (if possible) to divide the molecule into halves at convenient bonds. This will make possible the formulation of a convergent synthesis with several mini-syntheses leading to the target molecule.

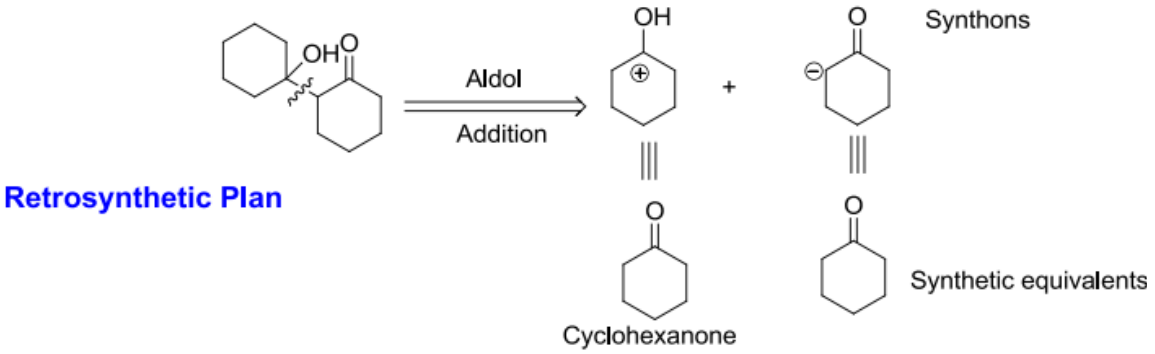
c) Aim for disconnections that lead to the greatest simplification of the target molecule

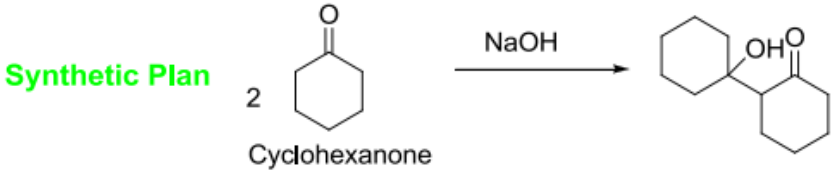
Given a choice of possible disconnections, those located at branch points or on rings are more strategic as they usually give straight chain fragments which are more likely to be commercially available or simply prepared.



d) Identify and exploit any inherent symmetry in a target molecule

Exploiting any symmetry in a TM or its intermediate can dramatically simplify its retrosynthesis. This may also provide an opportunity to identify a convergent pathway in the synthesis.

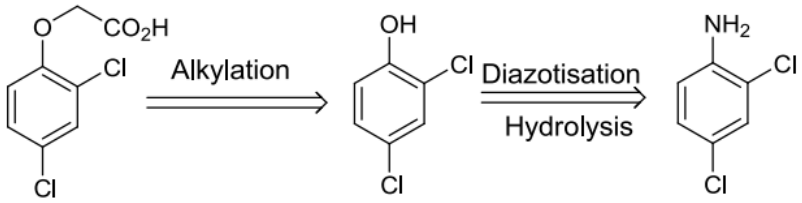




e) Introduce reactive functional groups at a late stage in the synthesis

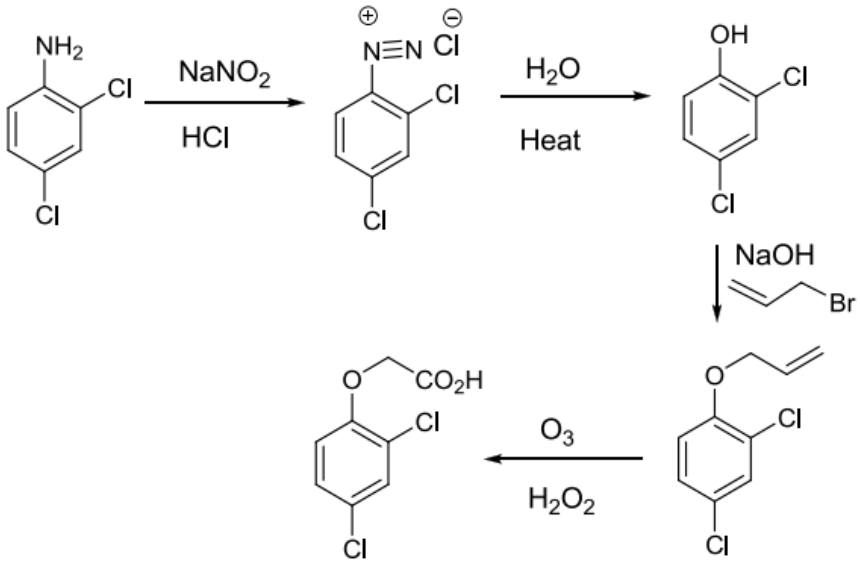
It is often difficult to selectively react at a less reactive functional group when a more reactive functionality is present within the same molecule. Such reactive functional groups are usually among the first to be disconnected during retrosynthetic analysis.

The retrosynthetic analysis of 2,4-dichlorophenoxyacetic acid (2,4-D), a common herbicide for the control of broadleafed weeds, is shown below



2,4-D

Based on the preceding retrosynthetic plan, 2,4-dichlorophenoxyacetic acid (2,4-D) can be synthesized as shown below

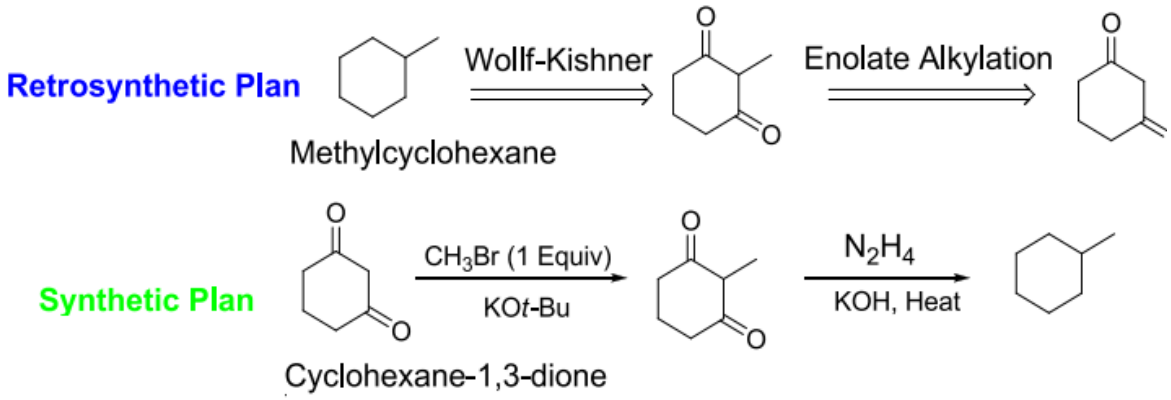


f) During retrosynthetic analysis introduce additional functional groups, if necessary, to facilitate further disconnection

This is called Functional group addition (FGA) strategy. The functional group addition strategy in retrosynthetic analysis involves introducing additional functional groups at strategic locations

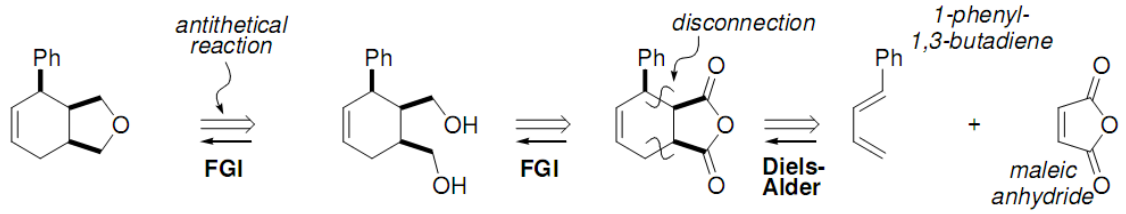
in a retron, if necessary, to guide further disconnections based on known powerful bond making reactions.

Addition of functional groups e.g. double bonds or carbonylgroups can serve to direct reactivity to specific sites of a molecule significantly simplifying a synthesis. For example, one may introduce a carbonyl group in a substituted cyclohexane target molecule which may help guide introduction of a substituent through enolate alkylation.

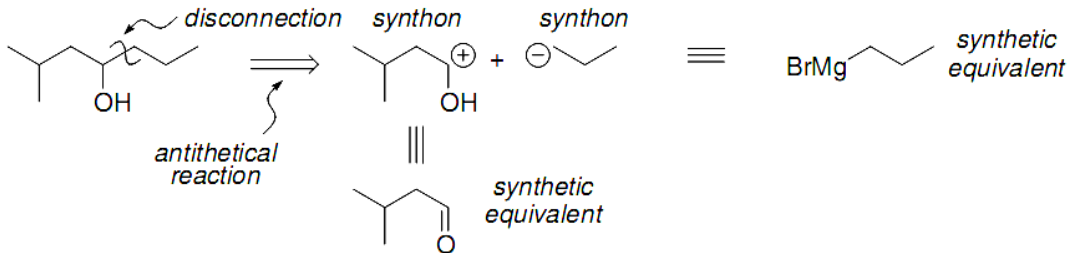


g) Use protecting groups if inevitable

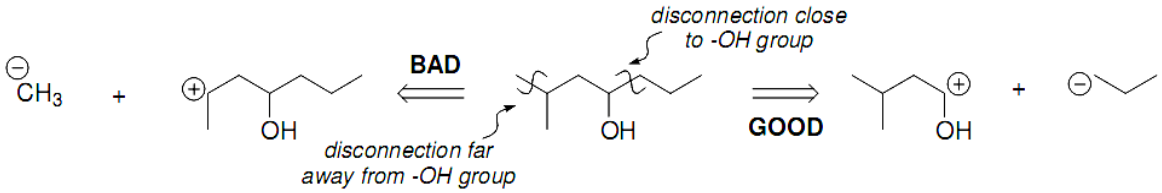
Given that the use of protecting groups adds to the number of steps of a synthesis, use them only when it is absolutely necessary.



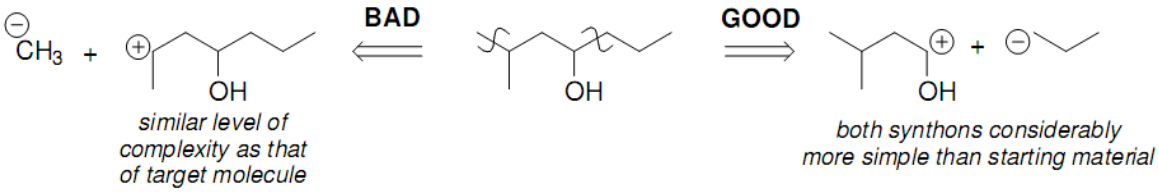
The example shown above has a cycloaddition of a symmetrical dienophile with a 1,3-diene (Diels-Alder reaction) as the strategy-level transformation, and because this is fairly readily recognized (in fact it is a two-group disconnection: more on this later) we didn't really need to think about the polarity of the simpler structures revealed by this disconnection. This is not usually the case; it is much more common for a disconnection to reveal two imaginary fragments, or synthons, which carry a positive or negative charge. Subsequently we need to identify the real (i.e. non-imaginary) chemicals/reactive intermediates which are the synthetic equivalents of the synthons identified.



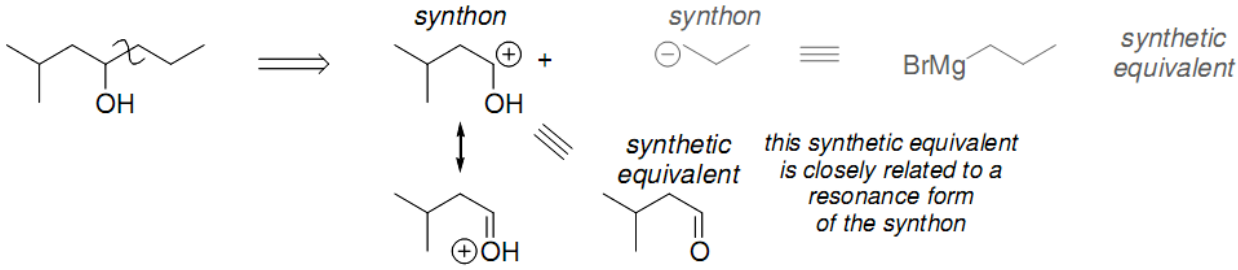
Disconnections very often take place immediately adjacent to, or very close to functional groups in the target molecule (i.e. the one being disconnected). This is pretty much inevitable, given that functionality almost invariably arises from the forward reaction.



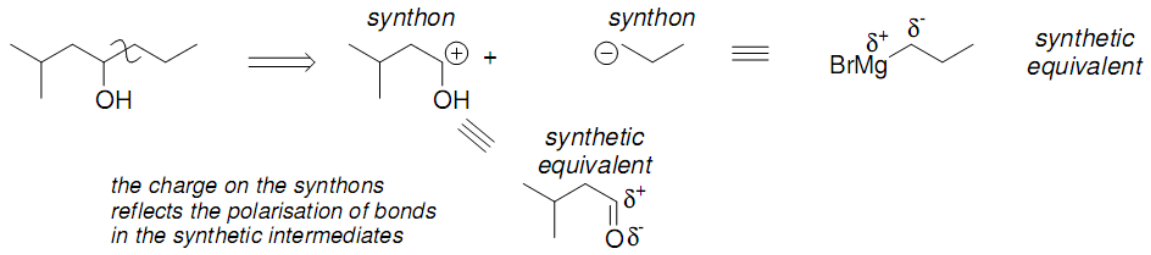
A good disconnection visibly simplifies the target molecule. Otherwise, the synthesis challenge doesn't get any easier



A good trick here is to consider whether you can draw a resonance form of the synthon which looks more like a real reactive intermediate… If it does, you've clearly made a good choice of polarity, and you've most likely gone a long way to identifying the synthetic equivalent!



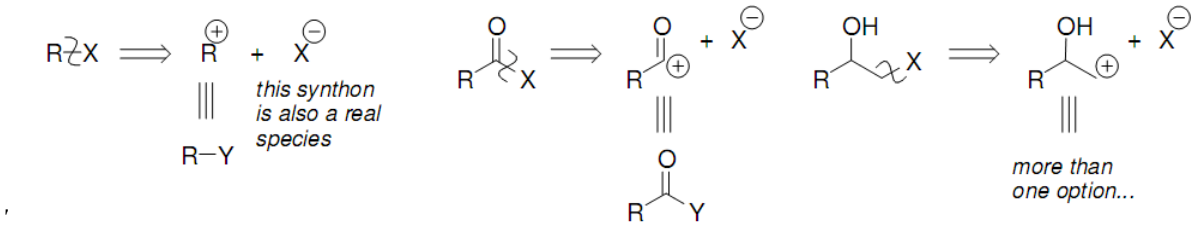
See immediately above, and consider also the inherent polarization of the key reactive bonds within your proposed synthetic equivalent; the synthon is often just an extreme, imaginary version of the real-life situation.



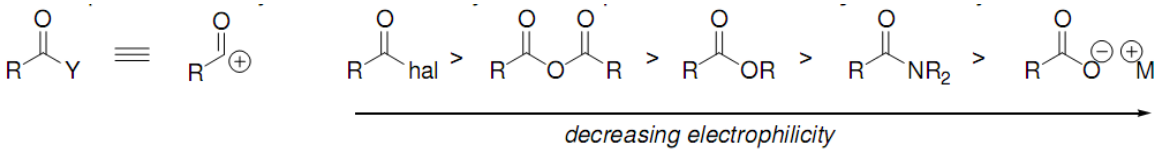
9.8 One Group Disconnections

a) C-X disconnections

If we need to make a C-X bond (where X is a heteroatom), a simple disconnection reveals a - carbocationic synthon, and X. We choose this polarity because X is almost invariably more electronegative than carbon. Clearly the C-X bond could exist in many different chemical environments, which means that there will be a correspondingly wide range of carbocationic synthons and synthetic equivalents.

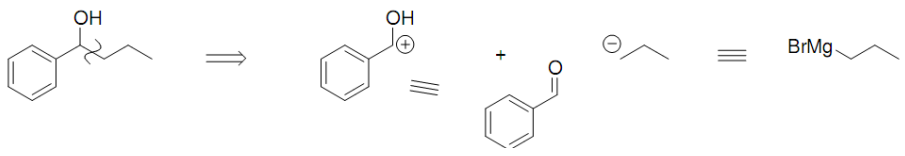


these already on several occasions. We need to be aware of the pecking order of electrophilic reactivity of the various synthetic equivalents of the acyl cation synthon.



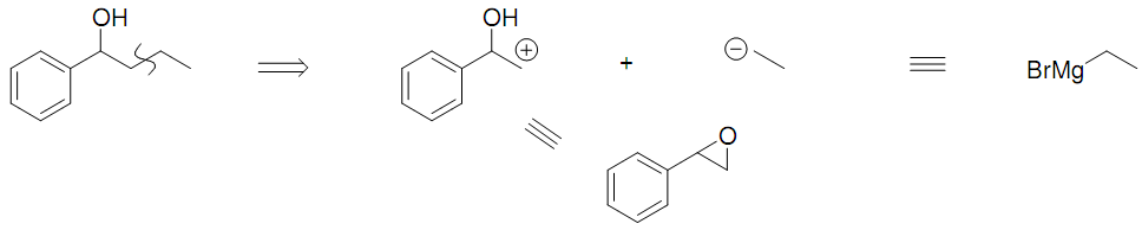
b) C-C disconnections: alcohols

Alcohols are a prime example of the need to disconnect right next to the hydroxyl functional group. This takes us back to a carbanion synthon, and an α-hydroxyalkyl cation synthon. The synthetic equivalent of a carbanion synthon is almost invariably an organometallic compound. Do the resonance form trick and we see that the synthetic equivalent of the hydroxyalkyl cation synthon is a carbonyl compound (aldehyde or ketone).

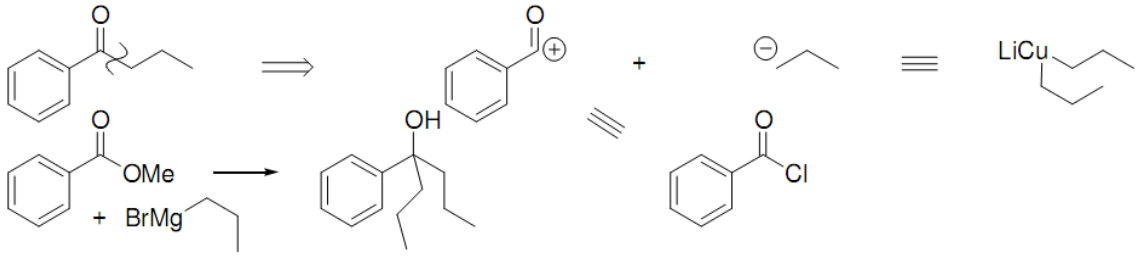


Adding an organometallic compound to a carbonyl compound very often generates a new stereocentre, and it's non-trivial to control which enantiomer of the product is formed. If we disconnect one bond further away from the alcohol in the target, we generate a β- hydroxyalkyl cation synthon, whose synthetic equivalent we've already seen is an epoxide. Epoxides are already chiral, so we have a single enantiomer of the epoxide; we form a single enantiomer of the product alcohol.

c) C-C disconnections: carbonyl compounds

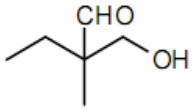


By direct analogy with the disconnection of alcohols, simple carbonyl compounds disconnect back to acyl cation synthons and carbanionic synthons, indicating the need for acylating agents and organometallic compounds. Beware the pitfalls here: as we said last term, the product carbonyl compounds are very often more reactive than the starting acylating agents (of course, this depends on which acylating agent is chosen), so double addition of the organometallic is a real danger: choose wisely



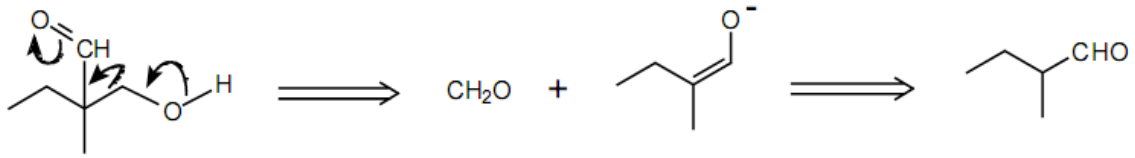
9.9 Two Group Disconnections

When a molecule contains two functional groups, the best disconnection uses the two together.

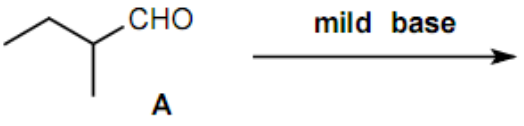


TM 1

Analysis

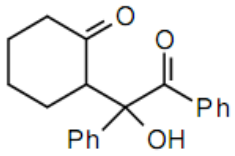


Synthesis



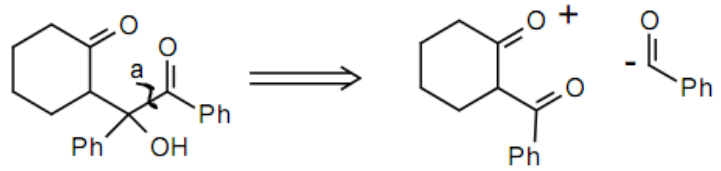
A TM 1

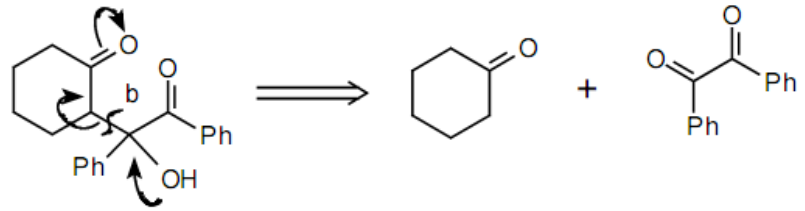
Target Molecule 2



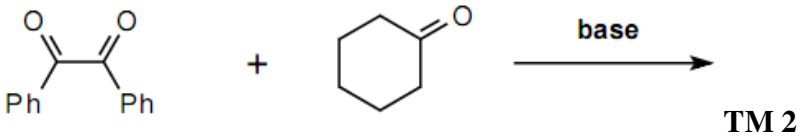
TM2

Analysis





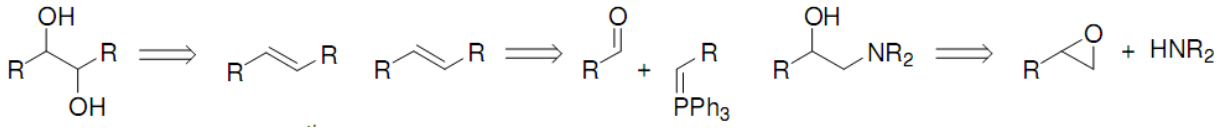
Synthesis



TM 2

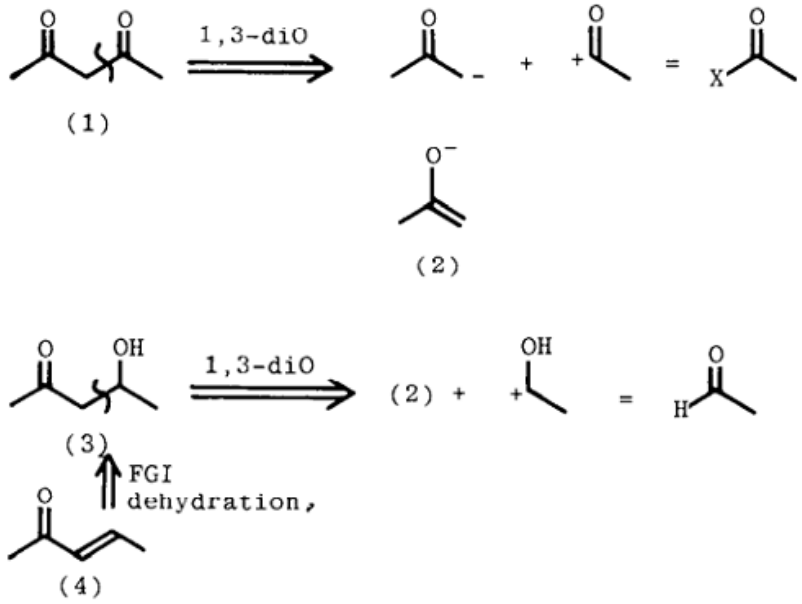
9.10 Synthon approach of 1,2-difunctional compounds

In a way, 1,2-difunctional compounds don't lend themselves brilliantly well to the disconnection approach, in that it's quite often not particularly helpful to identify synthons. As a consequence, there is not really a unified approach to the synthesis of these compounds. Examples are: 1,2-diols, alkenes, 1,2-diaminoalcohols.



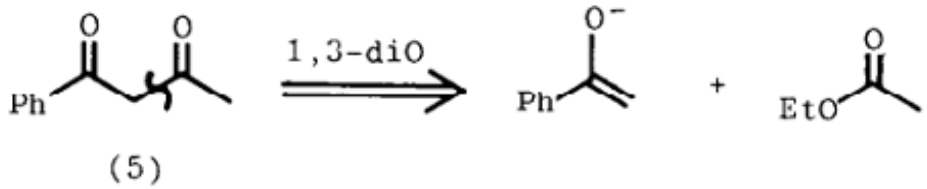
9.11 1,3–dicarbonyl compounds

Direct disconnection of this group of compounds is possible at two oxidation levels, dicarbonyl (1) and β–hydroxyl carbonyl (3). Enones (4) come to this since they are usually made by dehydration of (3).



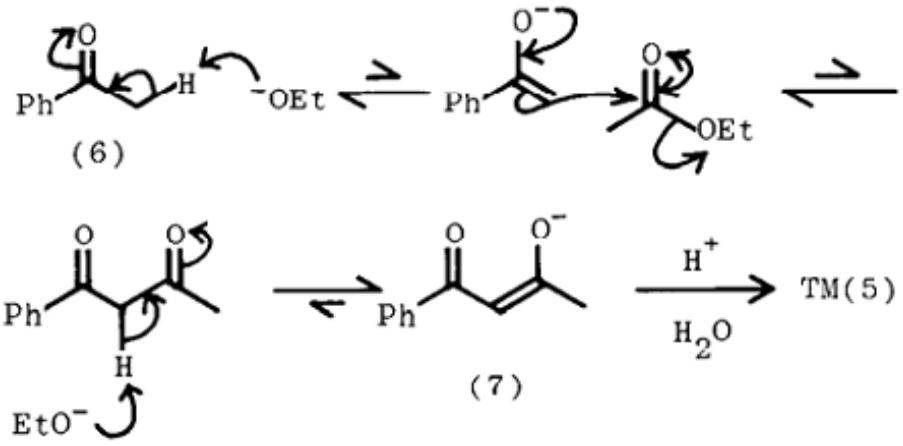
Disconnection (1) means that we are looking for a reaction which is the acylation of an enolate anion (2). This is possible with esters (X=OR) or acid chlorides (X=Cl). The perfumery compounds (5) can be disconnected to the enolate of a ketone and an ester.

Analysis



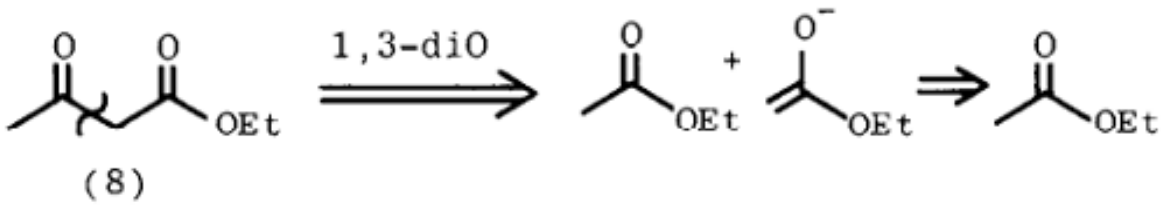
The reaction can be carried out by combination ketone (6) with the ester and strong enough to produce only a small concentration of the enolate, often EtO^-. The reaction is therefore an equilibrium and it is driven by formation of the stable delocalized enolate (7) of the product. Acid work up then releases TM(5).

Synthesis

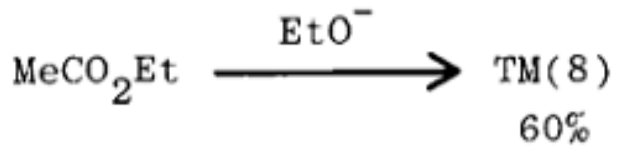


The starting materials are two molecules of same compound. The synthesis is known as the Claisen ester condensation, simply involves treating ethyl acetate with base.

Analysis



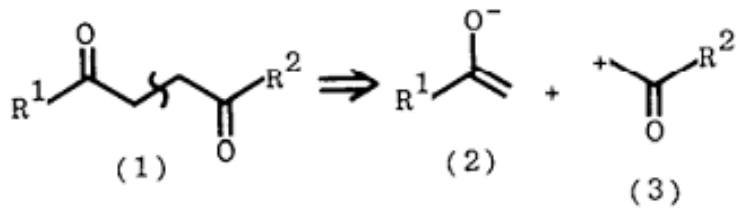
Synthesis



9.12 1,4-dicarbonyl compounds

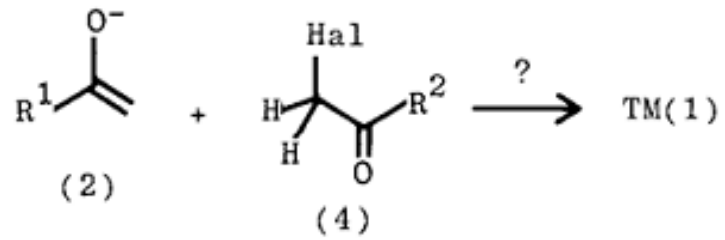
A 1,4–dikeone (1) can be disconnected at its central bond into the neutral enolate (2) but that requires also an unneutral synthon, the α–carbonyl cation (3). We shall need for this synthon as well as for related synthons at different oxidation levels.

Analysis



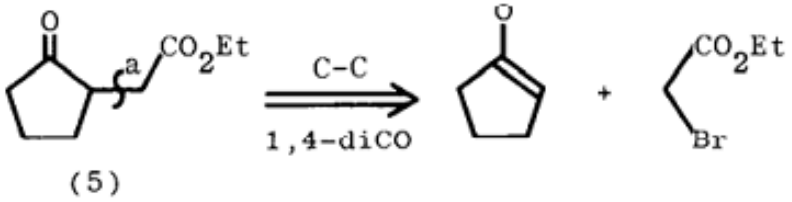
α–Halo carbonyl compounds (4) are useful reagents for synthon (3). In this reaction control is important as the halo substituent in (4) also enhances the acidity of the α–protons (H in 4). The usual method is to use a specific enol equivalent for synthon (2).

Synthesis

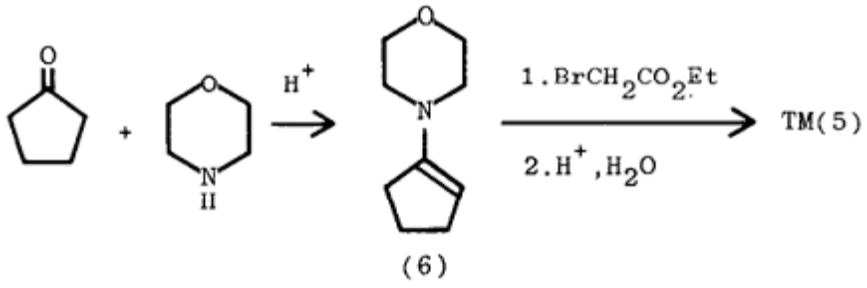


Disconnection of the central bond in (5) is good strategy as it separates the ring from the chain. The most popular specific enol equivalents are enamines (6) and compounds (7) activated with a CO_2Et group: both have ben used in the synthesis of (5).

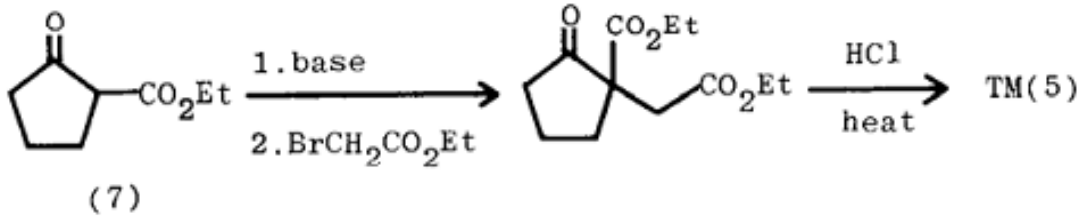
Analysis



Synthesis using enamines

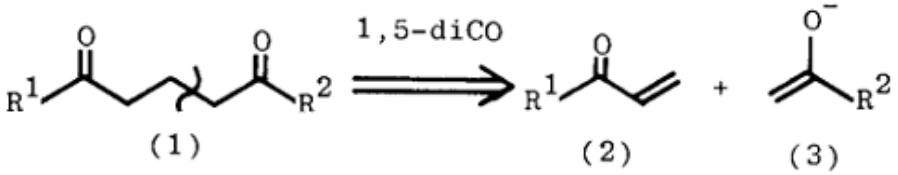


Synthesis with CO_2Et activation group

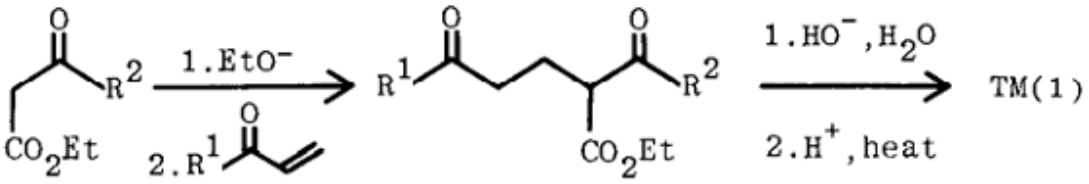


9.13 1,5-Dicarbonyl compounds

1,5–dicarbonyl compounds (1) can be disconnected at either α, β bond in a reverse Michael reaction. All the previous questions of control remain so we should be well advised to have an activating group on enolate (3) to ensure both enolisation at this site and Michael rather than direct addition to (2). The normal CO_2Et group serves very well.

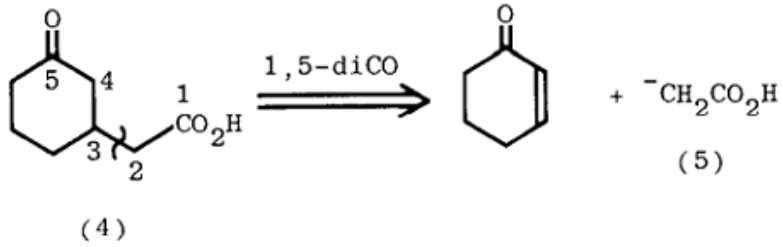


Synthesis

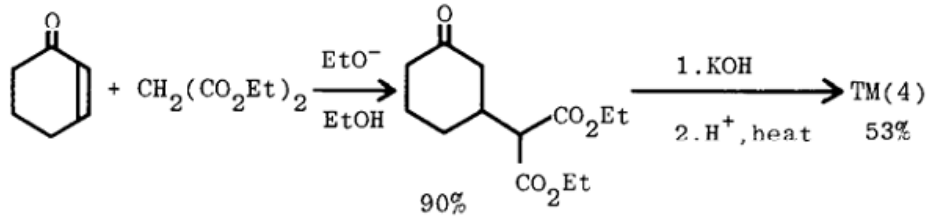


The cyclic ketone (4) is best disconnected where ring and chain meet and synthon (5) is best represented by malonate.

Analysis

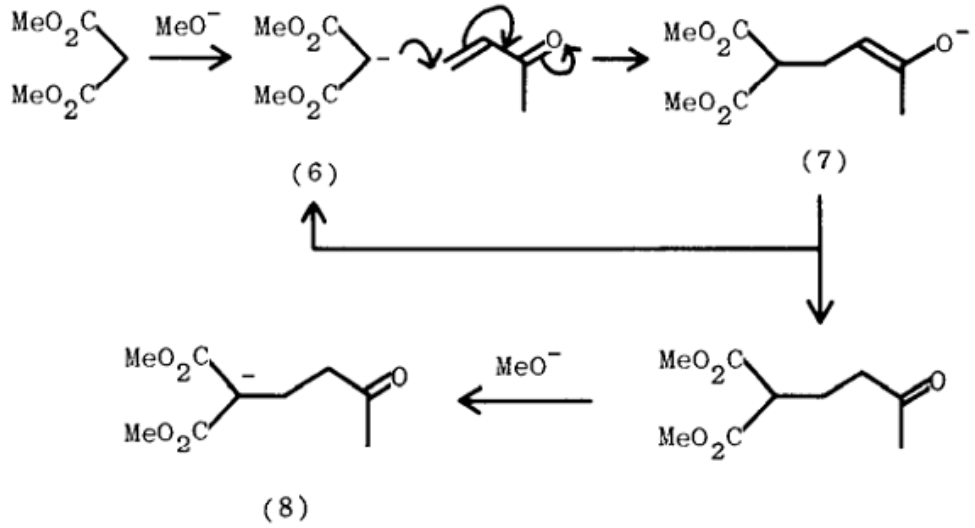


Synthesis



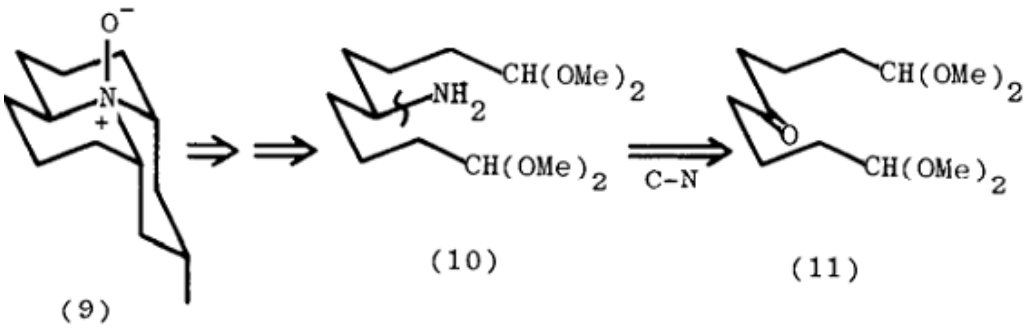
Michael reactions of this kind work best when they follow a catalytic cycle in which the first formed enolate anion of the product (7) is a strong enough base to regenerate the anion (6) of the

starting material. Then only a catalytic amount of base is needed unless a mole is consumed in converting the product into the stable anion (8), as in 1,3–dicarbonyl synthesis.



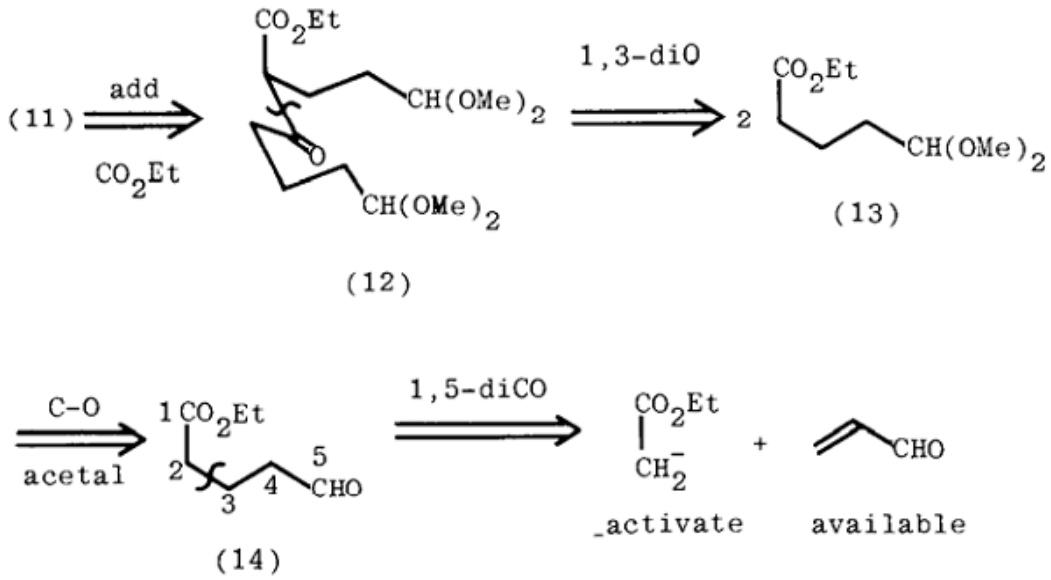
Stevens needed amine (10) in his synthesis of coccinelline (9) – the defence compound ladybirds exude from their knes. The branched primary amine must come from a ketone (11) and it is probably better to leave the acetal protecting groups in place during these manipulations.

Analysis 1



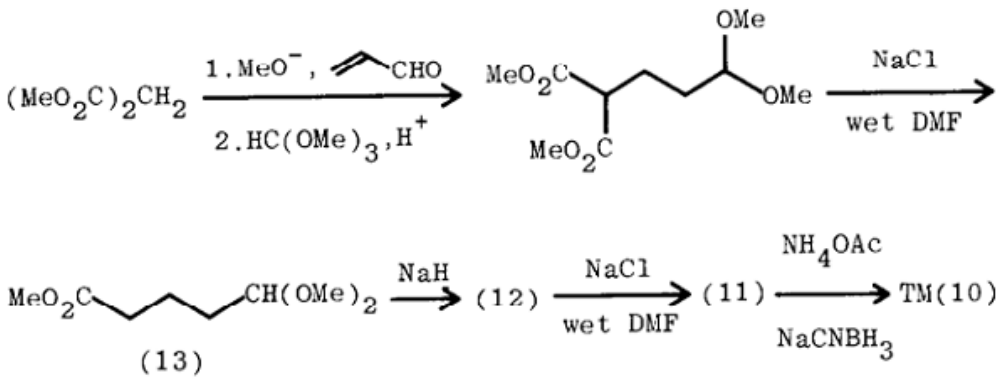
This (11) is a symmetrical ketone so we can use the 1,3–diCO disconnection (12) which follows the addition of a CO_2Et activating group. This strategy is good because it leads back through a self–condensation to a single starting material (13). If we remove the acetal groups, we now have a 1,5–dicarbonyl compound (14) and disconnection by reverse Michael can give malonate as one starting material.

Analysis 2



Stevens chose to protect the aldehyde immediately after the Michael reaction to prevent side reactions on this reactive group, and to put in the amine by reductive amination using sodium cyanoborohydride as the reducing agent. Note the shortcut of decarboxylation with NaCl in wet solvent (DMF or DMSO) when the ester, e.g. (13) is needed.

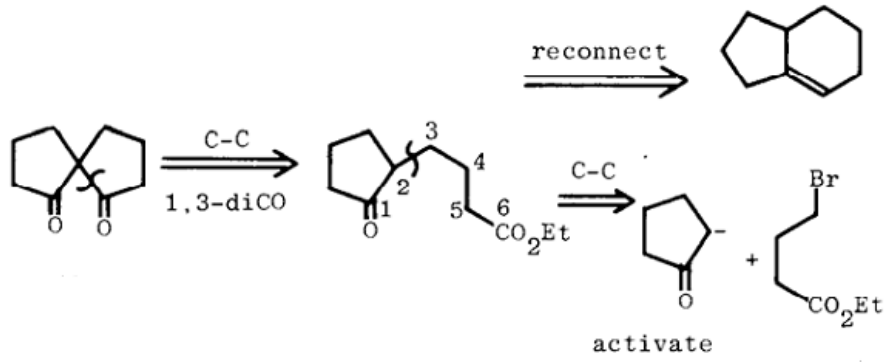
Synthesis



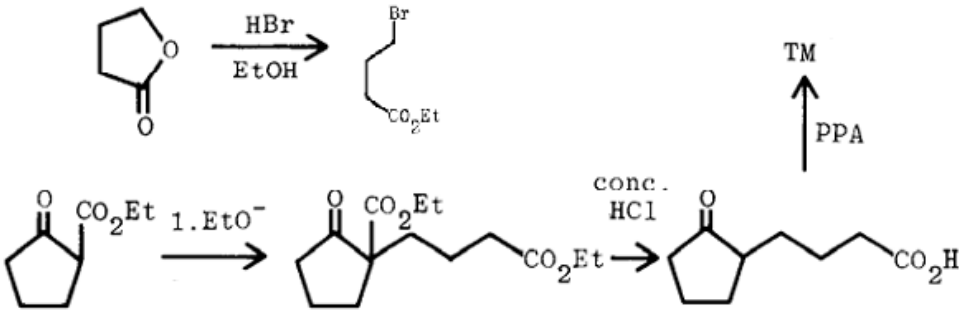
9.14 1,6–Difunctionalized compounds

There is no reason why 1,6–difunctionalized compounds should not be made by conventional methods, essentially ignoring the 1,6–relationship. The symmetrical spiro ketone disconnects to 1,6–dicarbonyl compound which could no doubt be made by cleavage of reconnect molecule. An alternate approach is to disconnect the ring from the chain to give alkyl bromo ester easily made from butyrolactone.

Analysis

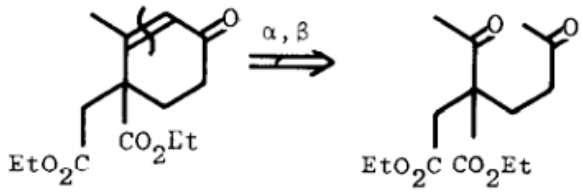


Synthesis



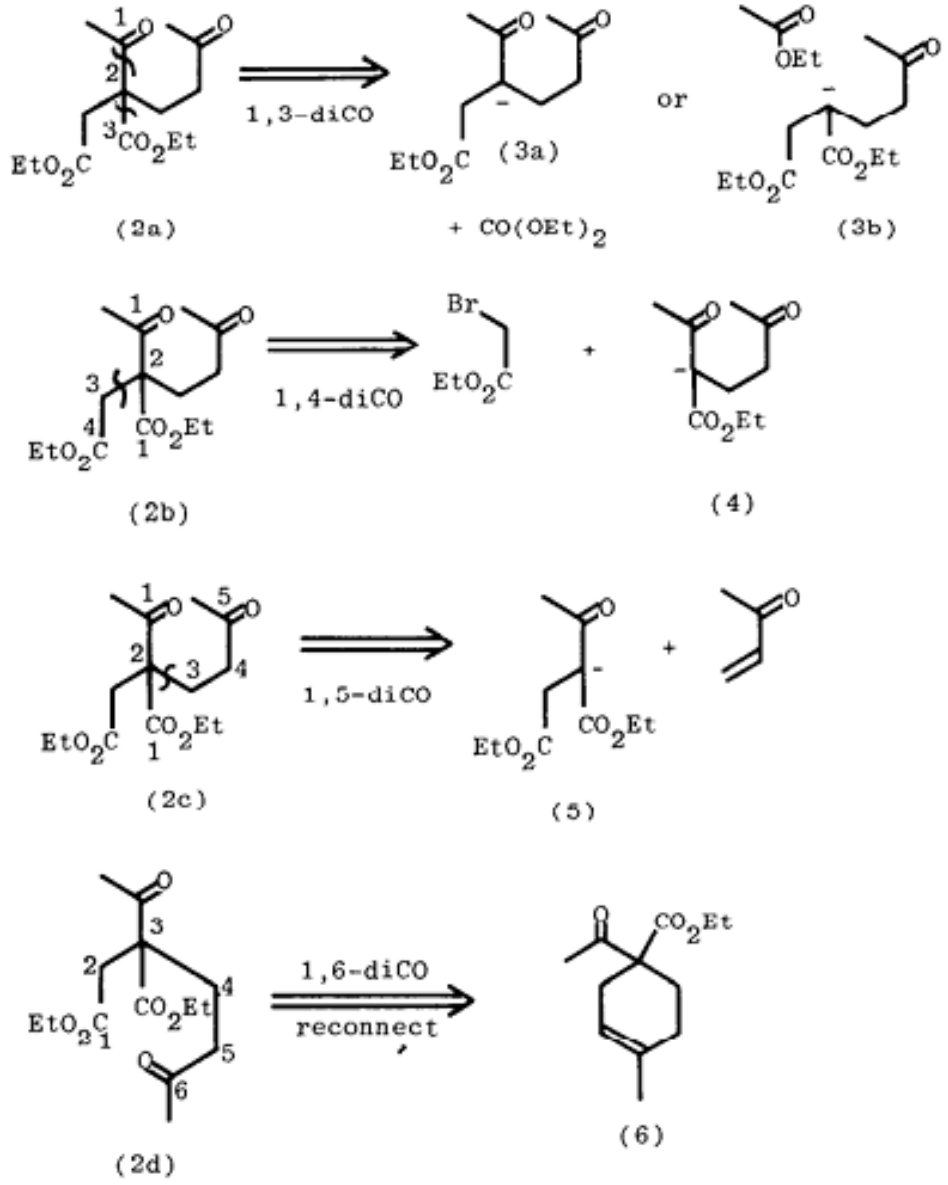
In synthesis of antitumor compound vernolepin, the compound (2) has 1,3, 1,4, 1,5 and 1,6–dicarbonyl relationships (2a–2d). The next stage is to disconnect each of these (reconnect the 1,6) as in analysis 2.

Analysis 1



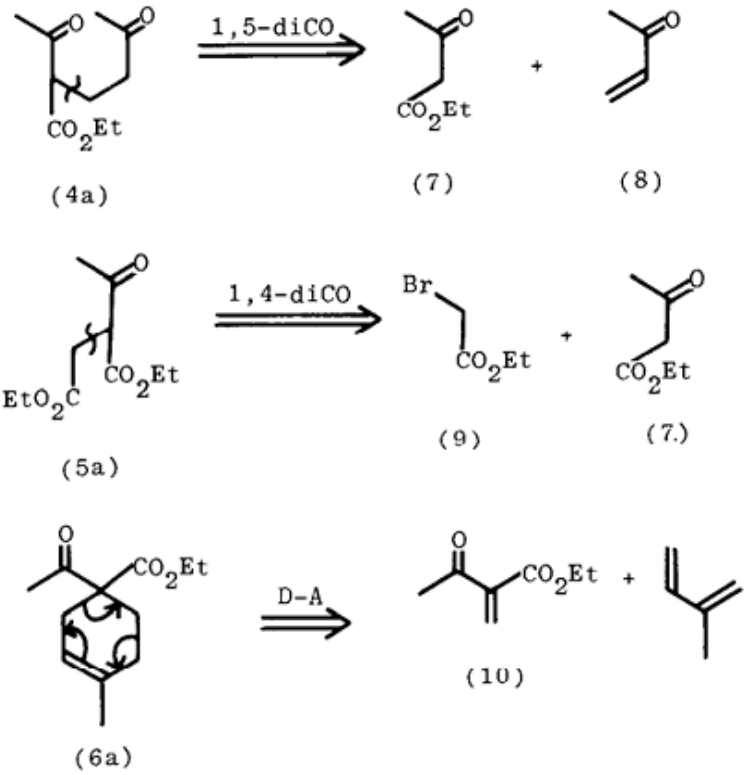
(1) (2)

Analysis 2



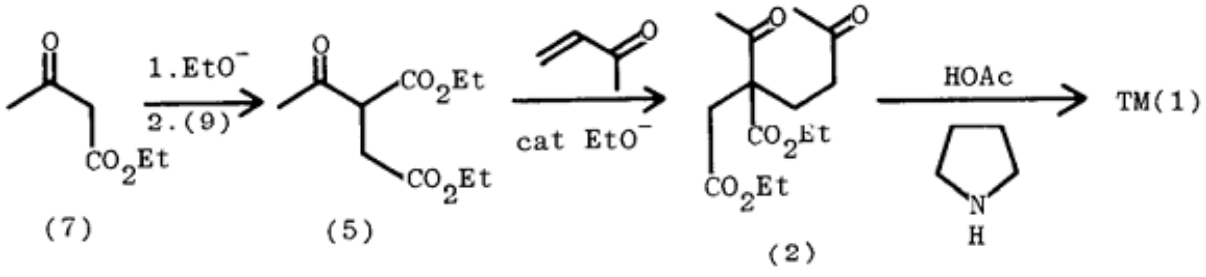
We can forget the 1,3–disconnection as it will be nearly impossible to make specific enolates for (3a) or (3b) – there are at least four roughly equivalebt sites for enolisation in each molecule. The 1,4– and 1,5– disconnections look promising as (4) and (5) are stable enolates and the 1.6 is also promising as (4) and (5) are stable enolates, and the 1,6– is also promising as (6) looks like a Diels–Alder adduct. We can continue the analysis for (4), (5) and (6).

Analysis 3



The starting materials for the 1,4– and the 1,5– approaches are he same (7), (8) and (9) – just the order of events is different. The Diels–Alder strategy is good as the orientation is para and the dienophile can be made by the Mannich method from (7). With three equally good–looking prospects, the best strategy is to try the 1,4 or the 1,5 approaches since the starting material can be used for the other if the one fails. Pratt and Raphael found the 1,5 strategy *via* (5) to be successful– the other may well be so too.

Synthesis



9.15 Summary of the unit

The ultimate goal of Organic Synthesis is to assemble an organic compound (target) from readily available starting materials and reagents in the most efficient way. This process usually begins

with the design of a synthetic plan (Strategy). Retrosynthetic (or antithetic) analysis is a problem solving technique for transforming the structure of a synthetic target molecule (TM) to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis.

The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a TM. Each structure derived antithetically from a target itself becomes a TM for a further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structural as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TM.

The transformation of a molecule into a synthetic precursor is accomplished by application of a transform, the exact reverse of a synthetic reaction, to a target structure. Strategy refers to the general plan to synthesize the TM. Retrosynthetic arrows should provide a clear idea of the strategy. Tactical issues deal with the actual execution of the plan and tactic is closely associated with structure and reactivity.

9.16 Key word

Synthetic Planning; Linear Synthesis; Convergent Synthesis; Retro synthetic Analysis; Terminology used in retro synthetic analysis ; Functional Group Interconversion (FIG); Synthons and Disconnections; Strategies in synthetic planning; Two Group Disconnections; 1,3–dicarbonyl compounds; 1,4-dicarbonyl compounds; 1,5-Dicarbonyl compounds; 1,6–Difunctionalized compounds.

9.17 References for further studies

1) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2010**.

2) Organic Chemistry; Marye Anne Fox, James K. Whitesell; *Jones & Bartlett Learning*, **2004**.

3) Organic Synthesis: Concepts and Methods; Jürgen-Hinrich Fuhrhop, Guangtao Li; *John Wiley & Sons*, **2003**.

4) Organic Synthesis: The Disconnection Approach; Stuart Warren, Paul Wyatt; *John Wiley & Sons*, **2011**.

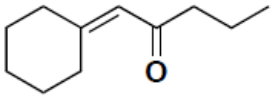
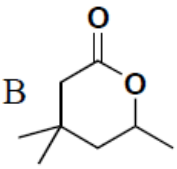
5) The logic of chemical synthesis; E.J. Corey; *John Wiley & Sons*, **2011**.

6) Classics in Total Synthesis III; K. C. Nicolaou, Jason S. Chen; *John Wiley & Sons*, **2011**.

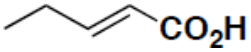
7) Organic Synthetic Methods; James Ralph Hanson; *Royal Society of Chemistry*, **2002**.

9.18 Questions for self understanding

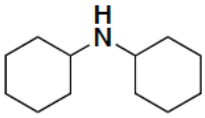
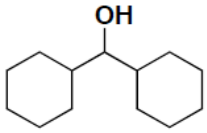
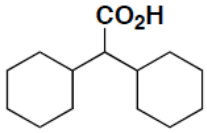
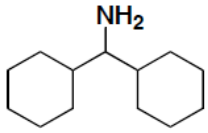
1) Propose a retrosynthetic analysis of the following two compounds. Your answer should include both the synthons, showing your thinking, and the reagents that would be employed in the actual synthesis.

Compound A  Compound B 

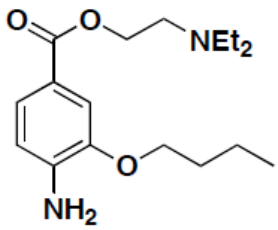
2) Give the retrosynthetic analysis for the following three compounds. Pay special attention to the relationship between the functional groups.

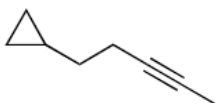
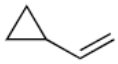
  

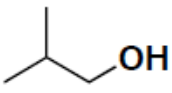
3) How would you make these compounds?

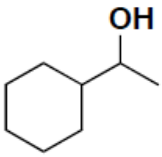
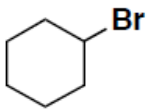
   

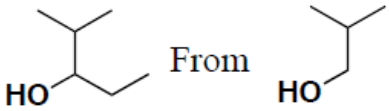
4) Perform the retrosynthetic analysis of the following compound. Remember, your planned synthesis must be synthetically possible and shouldn't suffer from regio- or chemoselectivity issues.

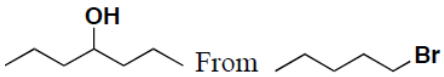


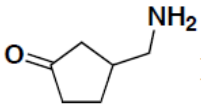
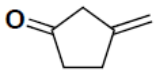
5) How would you synthesise  From 

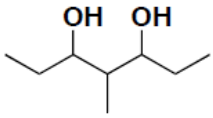
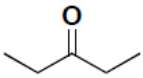
6) How would you synthesise  From 

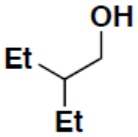
7) How would you synthesise  From 

8) How would you synthesise  From

9) How would you synthesise  From

10) How would you synthesise  From 

11) How would you synthesise  From 

12) How would you synthesise  From 

UNIT-10

Structure

10.0 Objectives of the unit

After studying this unit you are able

- Explain the method of retrosynthesis of small rings
- Explain the different methods for synthesis of three-membered rings
- Explain the different methods for synthesis of four-membered ring
- Explain the different methods for synthesis of five membered rings
- Explain the different methods for synthesis of six membered ring

10.1 Introduction

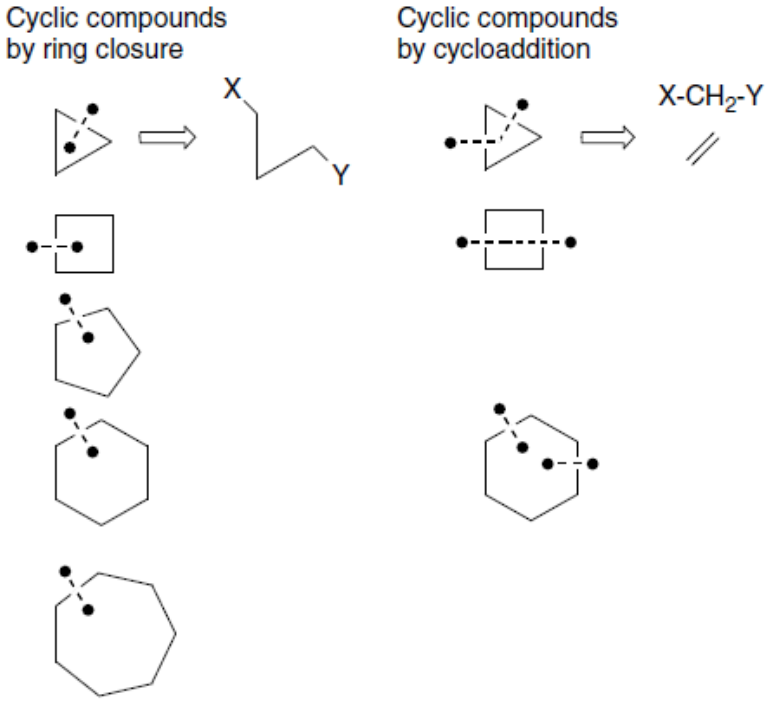
Retrosynthetic analysis will only lead to useful results if it is directed towards some goal. The basic goal is to generate precursors that correspond to available starting materials. However, this goal can be used as a guiding principle only when possible starting materials can be identified from the target structure. In general, obvious starting points cannot be found when it comes to complex target structures (and that is where RA is most useful). The basic goal, then, becomes the generation of precursors that are easier to synthesize than the original target; such precursors are likely to be closer to available compounds than the original target. Stated differently, retrosynthetic analysis is directed towards molecular simplification. Corey has formulated five main types of strategies that lead to the desired simplification. These will be treated briefly, each illustrated by a sample analysis:

A ring in a target structure can be formed by a ring closure reaction from open-chain precursors forming one ring bond. Two ring bonds may be formed in one stroke, when the ring is formed by a cycloaddition reaction. Hence, when addressing the formation of rings in retrosynthesis, both one-bond disconnections and two-bond disconnections have to be evaluated. Regarding cyclopropanes, both alternatives appear to be well precedented. This is also true for cyclobutanes, for which both photo-[2+2]- and ketene- [2+2]-cycloadditions are well established. For the formation of carbocyclic cyclopentanes or cycloheptanes, cycloadditions claim only a minor role, because [3+2]- and [4+3]-cycloaddition reactions are not yet fully developed. Thus, for cyclopentanes and cycloheptanes ring closing reactions, such as intramolecular enolate alkylation and Dieckmann cyclizations, dominate.

10.1 Retrosynthesis of small rings

For one-bond disconnections of a ring (planning ring closure reactions), one selects the cut according to the functional group presence or the presence of substituents (= branches). For two-

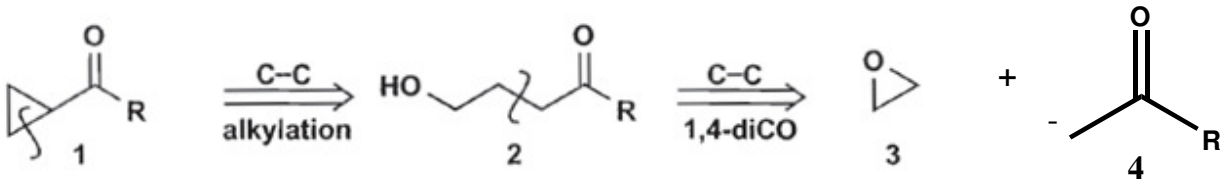
bond disconnections one could envision stepwise formation of these bonds. The available methodology for generating six-membered rings is quite varied and thus provides several options during the planning of a synthesis.



Bond-sets for the construction of cyclic compounds

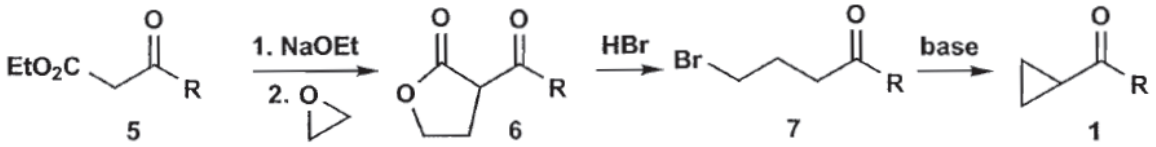
10.2 Three-membered rings

Three-membered rings are kinetically favoured but thermodynamically unstable so that they are often destroyed under the conditions of their formation. Since most carbonyl condensations are revesible, they are generally not good routes to three-membered rings. But the alkylation of enols is usually irreversible so that these can be excellent methods.

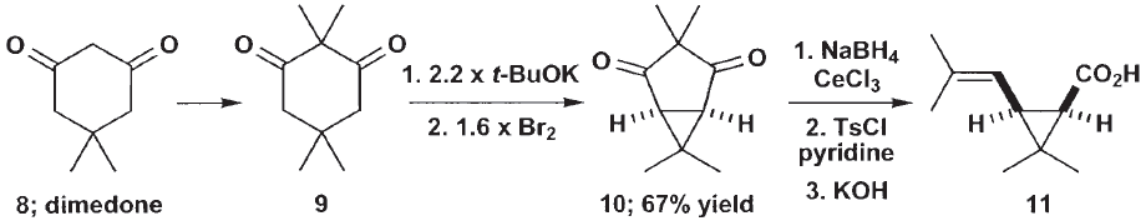


Cyclopropyl ketones can be made by cyclisation of some derivative of the γ-hydroxy ketone. Notice that we proposing to make a three membered carbocuclic ring from an easily made three-membered heterocyclic ring. Addition of ethylene xide to the enolate of the ester compound

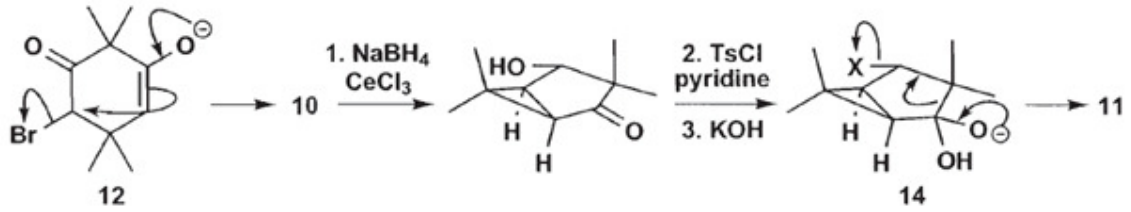
gives the lactone directly and treatment with HBr accomplishes decarboxylation and formation of the bromide in one pot.



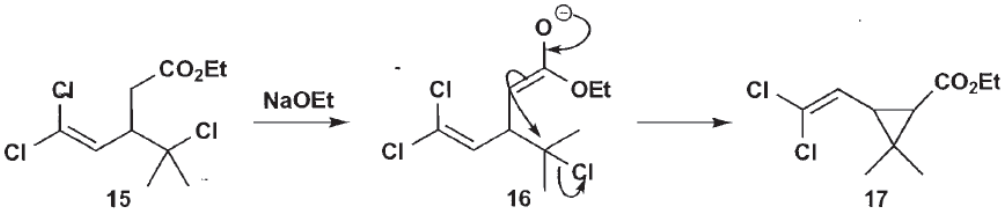
A more dramatic example is the synthesis of cis-chrysanthemic acid **11**, the basis of most modern insecticides, from dimedone **8.** Methylation between the two carbonyl groups gives **9**, with the complete skeleton of **11** – a little reorganisation of the atoms is needed. Treatment with bromine and base gives the inevitably cis fused bicyclicdione **10** and a further three simple steps produce chrysanthemic acid.



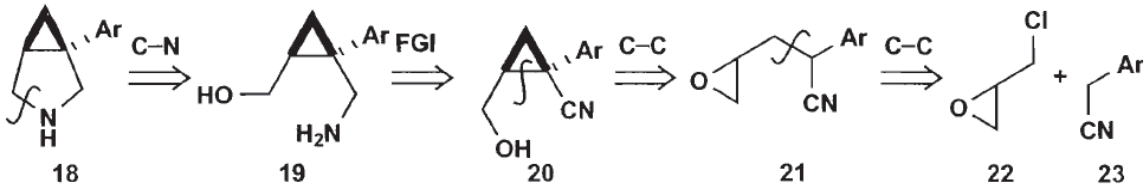
Some explanation is needed. Treatment of **9** with base and bromine must produce the potassium enolate of the bromoketone that cyclises **12** to form the three-membered ring. Reduction presumably gives the exo-alcohol **13** whose tosylate can fragment with hydroxide **14** to give **11.**



A much less promising cyclisation gives the biologically patterned insecticide permethrin **17.** The enolate of the ester in the starting material **15** must cyclise by displacement of chloride at a tertiary centre. Cyclisation to form three-membered rings can be remarkably favourable.

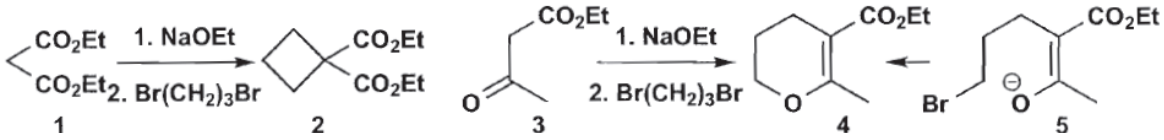


The simple bicyclic amine **18** is drug candidates with Merck for treatment of pain. Disconnection to one of the amino alcohols **19** suggests that the anion of the nitrile **23** might be used to make two C-C bonds in the cyclopropane by alkylation of epichlorhydrin **22** both at the epoxide and at the chloride. If this sequence works, it can be give only the stereochemistry required.



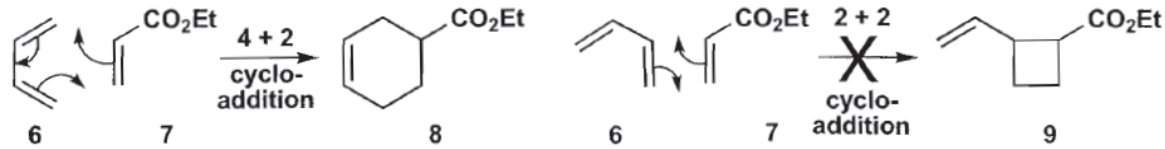
10.3 Four-membered ring

Four-membered rings can occasionally be formed by ordinary cyclisations. The double alkylation of malonate 1 with dibromopropane gives the cyclobutane 2. But Perkin found in his original work on carbocyclic rings that double alkylation of acetoacetate 3 was successful for all ring sizes from three to seven expect four. The enol ether 4 was formed instead of a cyclobutane. It is easy to see how the enolate of the intermiediate 5 is ideally arranged to form 4 but not to form a cyclobutane.

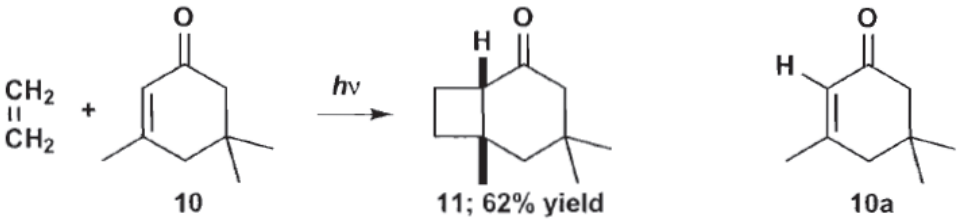


10.3.1Photochemical Cycloadditions

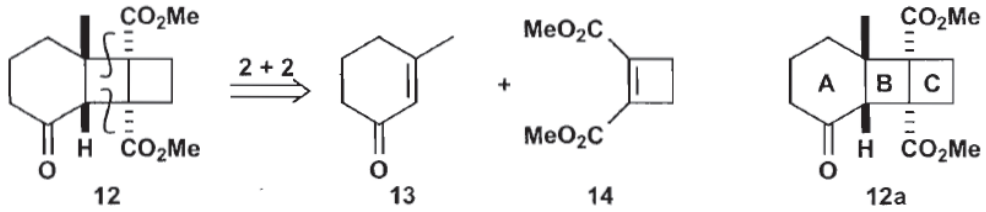
Diels-Alder reactions occur easily when a diene 6 and a dienophile 7 are heated together and six-membered rings 8 are formed. Orbital symmetry allows cycloadditions involving six π-electrons but not those involving four π-electrons.



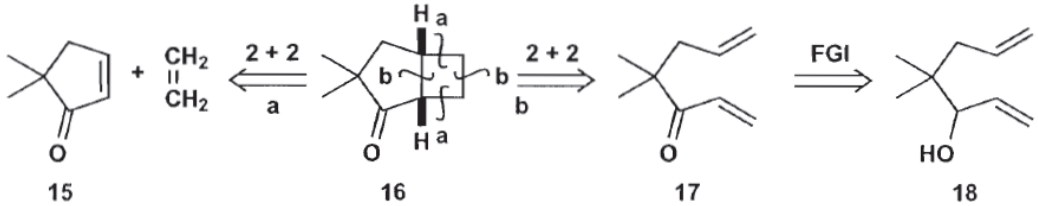
The 2+2 cycloadditions do occur in the excited state so these are photochemical reactions. They work best if one component absorbs the light to form excited state while the other reacts in its ground state. Even ethylene reacts with conjugated enones such as **10** under irradiation to give reasonable yields of the cyclobutane **11.** The stereochemistry of H and Me at the ring junction is determined partly by the fact that they are already cis in the starting material **10a** and partly by the difficult of making trans 4/6 fused system.



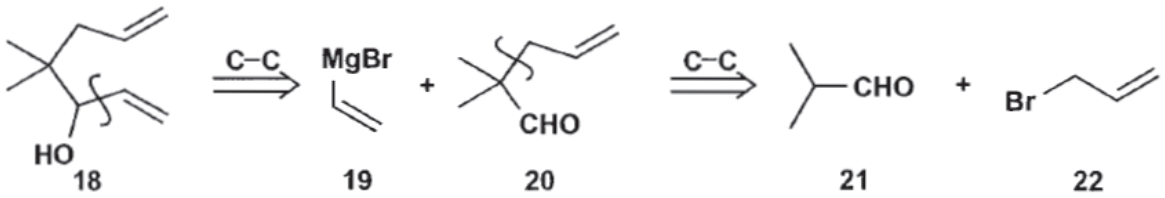
Both components may be functionalised so disconnection of the middle ring of **12** leads to the greatest simplification suggesting two simple starting materials 13 and 14. Irradiation of the mixture does indeed give a good yield of 12. The stereochemistry of the B/C ring junction must be cis 12a, as two four-membered rings must be cis fused, but that of rings A/B follows the guidelines of 11. The relative stereochemistry of the two cis junction, ie, that of rings A and C, is chosen to give least steric hindrance. There is no endo rule. Because both compounds have the alkene conjugated to a carbonyl, the minor product is the dimer of 14.



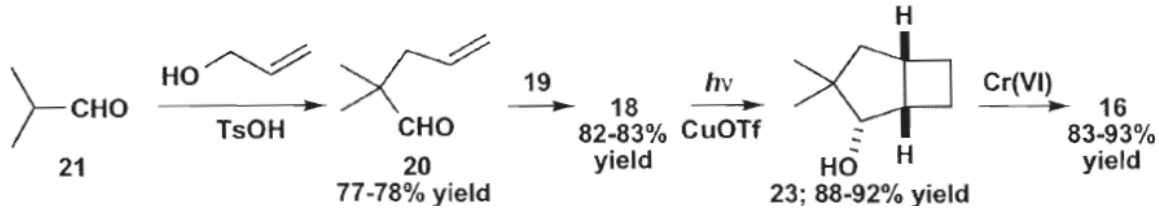
Most cyclobutanes offer a choice between two 2+2 disconnections and the choice can often be made by considering the availability of the starting materials. We already know from **11** that compounds like this can be made by irradiation of ethylene with enones, here 15 , so we shall focus on the alternative 16b. The starting material for an intramolecular photo-cycloaddition would be dienone 17. It was decided to make this by oxidation of 18 because this alcohol was easy to make.



The idea was to add vinyl Grignard 19 to the aldehydes 20 which could be made by allylation of isobutyraldehyde 21. Oxidation to the ketone might be carried out either before or after the cycloaddition.

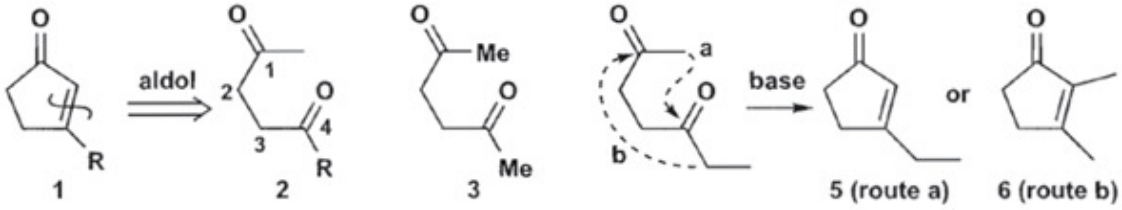


In fact, the allylation was carried out by the Claisen rearrangement and the cycloaddition on the alcohol 18 catalysed by Cu(I). The product was a mixture of the major isomer 23 with some of the exo-alcohol. This is irrelevant as both alcohols oxidise to the ketone 16. The stereochemistry at ethe ring junction can only be cis.

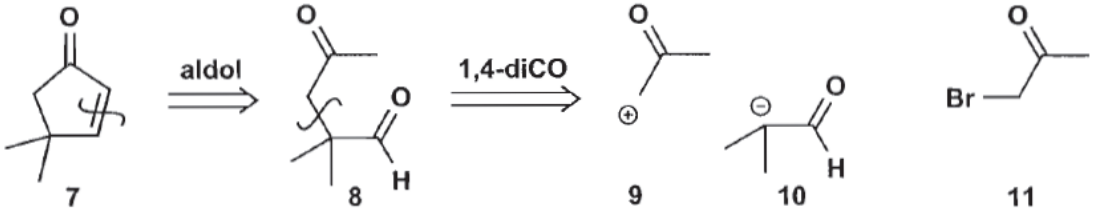


10.4 Five Membered rings

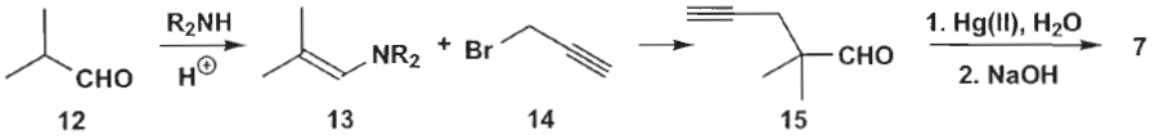
Cyclopentanones 1 disconnect to 1,4-dicarbonyl compounds 2. If R=Me 3, cyclisation can lead only to 1; R=Me but, if R=Et 4, could cyclise to 5 or 6 depending on which ketone forms the enolate. Thermodynamically 6 is favoured as it has a more highly substituted alkene, but it is close.



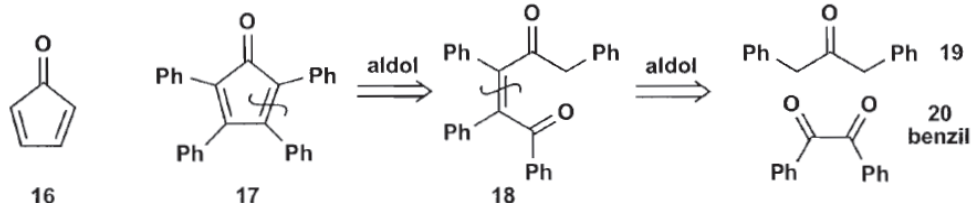
A simple example is the cyclopentanone 7 because the keto-aldehyde 8 can cyclise only one way as the aldehydes cannot enolise. The best 1,4-dicarbonyl disconnection is probably 8 giving some enolate equivalent 10 of isobutyraldehyde and a reagent for the unnatural synthon 9 such as the bromoketone 11.



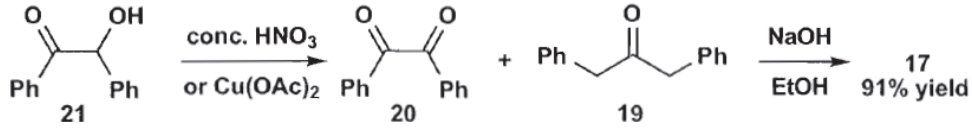
In fact the workers who wanted 7 for photochemical addition to alkenes chose to use propargyl bromide 14 and an enamine 13 of the aldehydes 12. Mercury-catalyst hydration of 15 gave 8 which cyclised to 7 in base.



Some molecules are studied for their theoretical interest: one being cyclopentadienone 16. But it turns out that this dimerises instantly by a Diels Alder reaction and cannot be studied. The simplest cyclopentadienone that can be made is the tetraphenyl compound 17. Aldol disconnection gives 18 but we can now do a second aldol disconnection to reveal the two symmetrical starting materials 19 and 20.

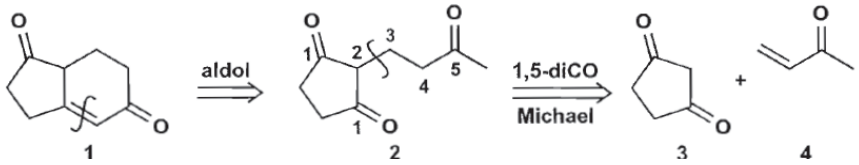


Benzil 20 can be made by the oxidation of benzoin 21 and it combines with 19 in one step under base catalysis without the need to isolate 18. The problem with these compounds is that 16 has only four π-electrons delocalised round the ring and is anti-aromatic. Clearly four phenyl groups help stability but 17 exists as deep purple crystals showing an unusually small gap between the populated and unpopulated orbitals.

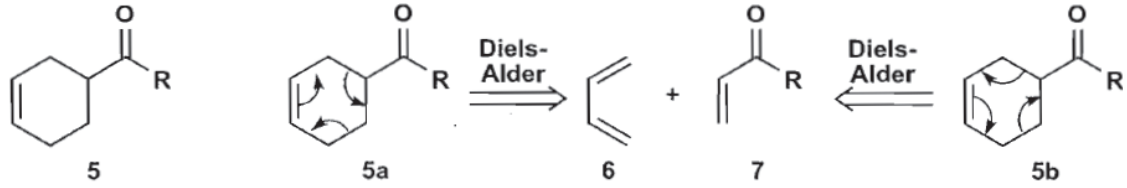


10.5 Six Membered Ring

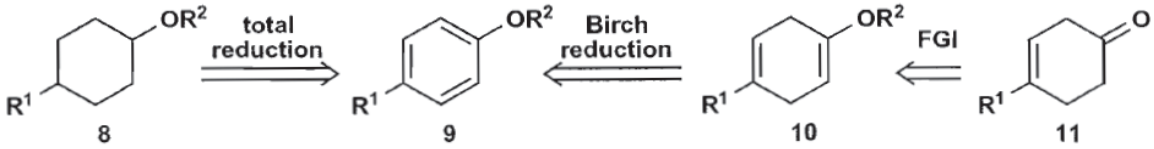
There are three general methods of making carbocyclic six-membered rings and each produces rings with a characteristic substitution pattern. The first uses carbonyl condensations and the best of these is the Robinson annelation. The disconnections are aldol 1 and conjugate addition 2. The target molecule is a conjugated cyclohexane.



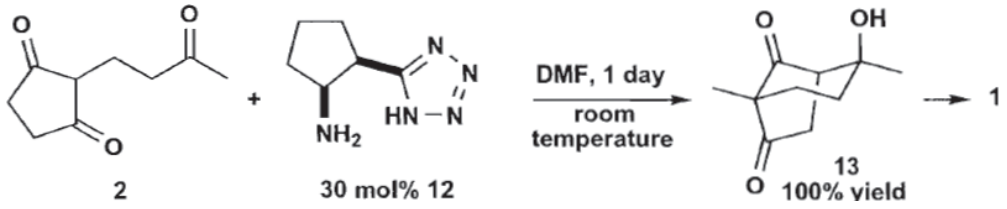
The second method is the Diels- Alder reaction. The target molecule 5 also has a carbonyl group and an alkene but now only the alkene is in the ring, the carbonyl group is outside the ring and remote from the alkene. The simplest way to do disconnection is to draw the mechanism of the imaginary reverse reaction 5a. Start your arrows on the alkene and go whichever way round the ring you prefer 5a or 5b.



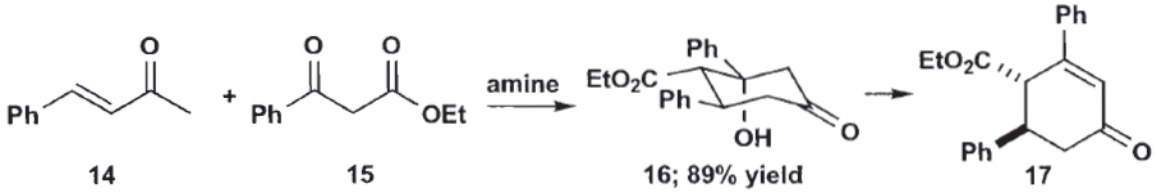
The third is partial or total reduction of an aromatic ring. Any catalogue lists a vast number of available substituted benzene rings. Saturated compound 8 can obviously be made by total reduction of 9 but it may not be obvious that partial reduction allows the enone 11 also to be made from 9. Birch reduction is the only new method here so we shall revise the Robinson and the Diels Alder and concentrate on Birch.



Organic catalysts have been developed, some givin single enantiomers of products and some, such as 12, giving very fast reactions and complete control over the stereochemistry of the aldol intermediate 13.



Neither starting material need be cyclic. Combination of the acyclic enone 14 and β-ketoester 15 with an amine catalyst gives high yields of 16 and good stereoselectively. Both 13 and 16 can easily be dehydrated to the enones 1 or 17.



10.6 Summary of the unit

Rings in a target structure are to be made from acyclic precursors by intramolecular one-bond formation (ring closure reaction) or by two-bond formation in a cycloaddition reaction. Bicyclic and polycyclic target structures are approached in the same way, whereby two-bond disconnections or multi-bond disconnections in reaction cascades are preferred. Multi-bond disconnections may be advantageous, even when a surplus extra bond is generated in the forward synthesis.

10.7 Key words

Retrosynthesis of small rings; Three-membered rings; Four-membered ring; Photochemical; Cycloadditions; Five Membered rings; Six Membered ring

10.8 References for further studies

1) Elements of Synthesis Planning; R. W. Hoffmann; *Springer Science & Business Media*, **2009**.
2) Organic Chemistry; Jonathan Clayden, Nick Greeves, Stuart Warren; *OUP Oxford*, **2012**.
3) Introduction to Strategies for Organic Synthesis; Laurie S. Starkey; *John Wiley & Sons*, **2012**.
4) Organic Synthesis: Concepts and Methods; Jürgen-Hinrich Fuhrhop, Guangtao Li; *John Wiley & Sons*, **2003**.
5) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2007**.

10.9 Questions for self understanding

1) Discuss the retrosynthetic analysis of small rings.
2) With suitable example explain the synthesis of three-membered ring compounds.
3) With suitable example explain the synthesis of four-membered ring compounds.
4) With suitable example explain the synthesis of five Membered ring compounds.
5) With suitable example explain the synthesis of six Membered ring compounds.

UNIT-11

Structure

11.0 Objectives of the unit

After studying this unit you are able to

- Write the retrosynthetic analysis scheme of Camphor
- Write the retrosynthetic analysis scheme of Longofoline
- Write the retrosynthetic analysis scheme of Reserpine
- Write the retrosynthetic analysis scheme of Cortisone

11.1 Introduction

The most desirable bond disconnections in the antithetic manipulation of structure are those in which the following structural features are minimized

i) Appendages

ii) Appendages carrying chiral centers

iii) Rings of medium or large size

iv) Bridged rings

Strategic bonds (to break in the retrosynthetic manipulation) vs. core bonds (not to break!)

Rule 1

A strategic bond must be in a four-, five-, six- or seven-membered "primary" ring (relatively easy to form). A primary ring is one which cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another.

Rule 2

A strategic bond must be directly attached to another ring (exo to another ring, except three membered rings) because a ring disconnection which produces two functionalized appendages leads to a more complex system than a ring disconnection that lead to one or no functionalized appendages.

Rule 3

To achieve maximal simplification of the cyclic system, strategic bonds should be in the ring (or rings) which exhibits the greatest degree of bridging.

The maximum bridging ring is selected from the set of "synthetically significant rings" (all primary rings — Rule 1— plus all secondary rings less than eight membered, ie, those that can be formed from a pair of smaller primary rings) Maximum bridging rings of a molecule are those rings which are bridged at the greatest number of sites.

Rule 4

To avoid the formation of rings having greater than seven members, any bond common to a pair of bridged or fused rings whose envelop is > eight-membered cannot be considered strategic. The bonds that are eliminated from further consideration by this rule are termed core bonds

Exception: when the two fused or bridged rings being examined are directly joined elsewhere by another bond.

Rule 5

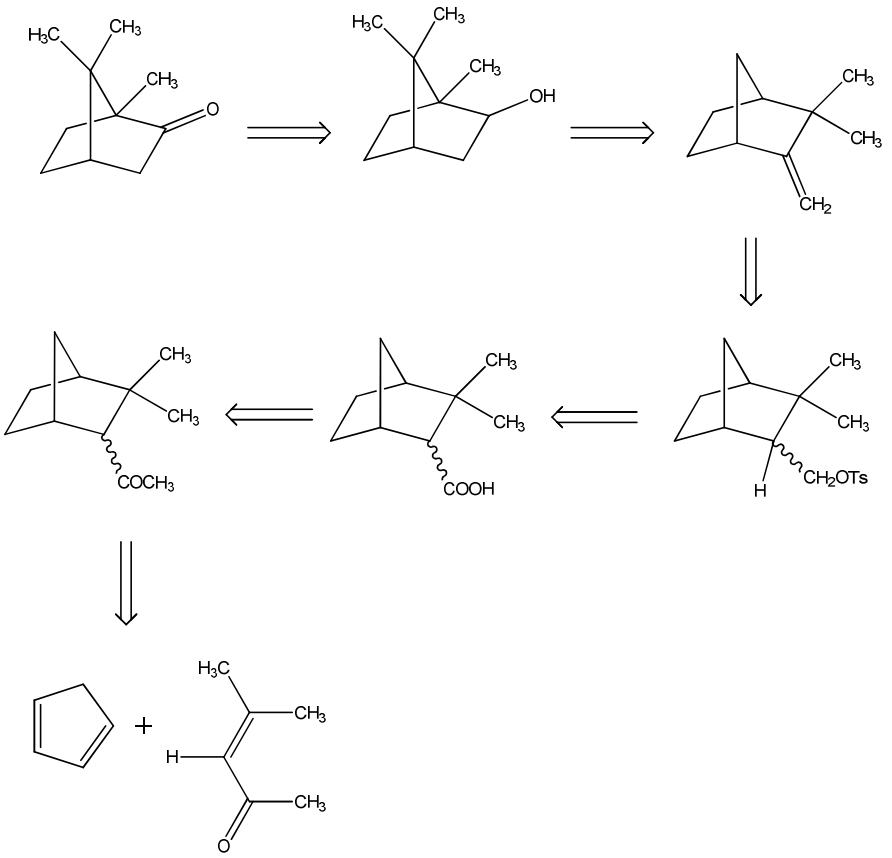
Bonds within aromatic rings are not considered to have potential strategic character.

Rule 6

If a cyclic arc linking a pair of common atoms (fusion atoms, bridgeheads, or spiro ring junction atoms) contains a chiral carbon atom, then none of the bonds in the cyclic arc may be considered strategic. This situation is undesirable because it is difficult to control stereochemistry efficiently at centers on appendages as opposed to centers in rings.

Exception: A bond directly attached to a chiral center can be broken if that center is the only chiral one on the arc linking the two common atoms

11.2. Retrosynthetic Analysis of Camphor

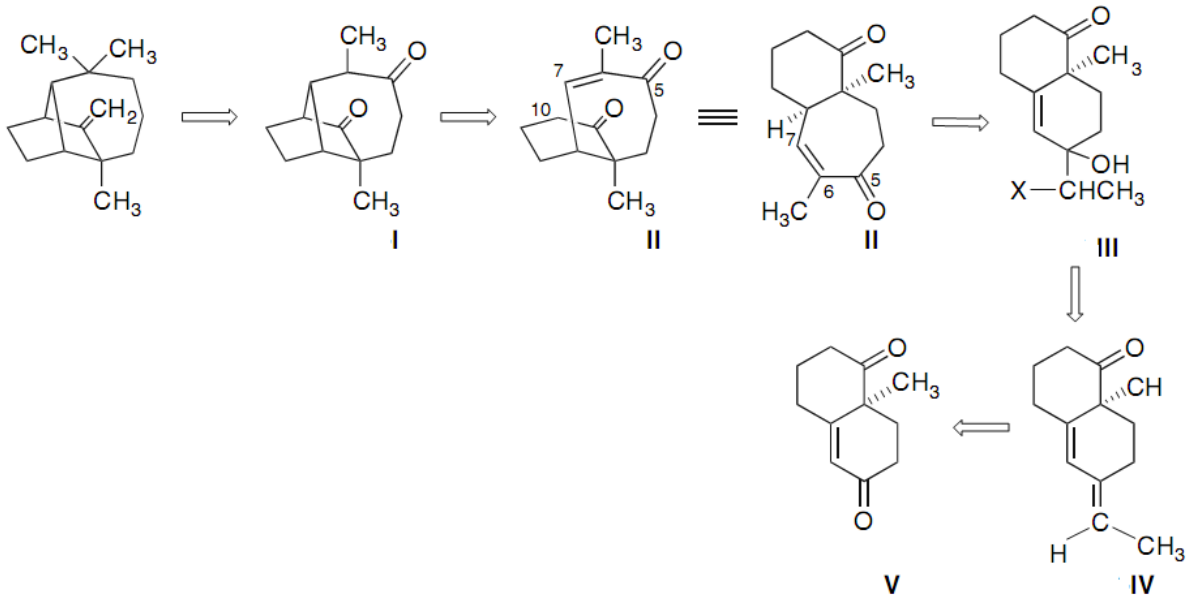


The synthesis of camphor was achieved by oxidation of bomeol which in turn was synthesized by acidolysis of camphene using HCl in acetic acid solvent. The camphene was synthesized by dehydroxylation of tosylated camphenol which was synthesized by reduction of comphenic acid. The camphemic acid as synthesized by oxidation of keto derivative which in turn was synthesized by Deals-Alder reaction of cyclopentadiene with α,β-unsaturated methyl isopropenylketone as shown in below scheme.

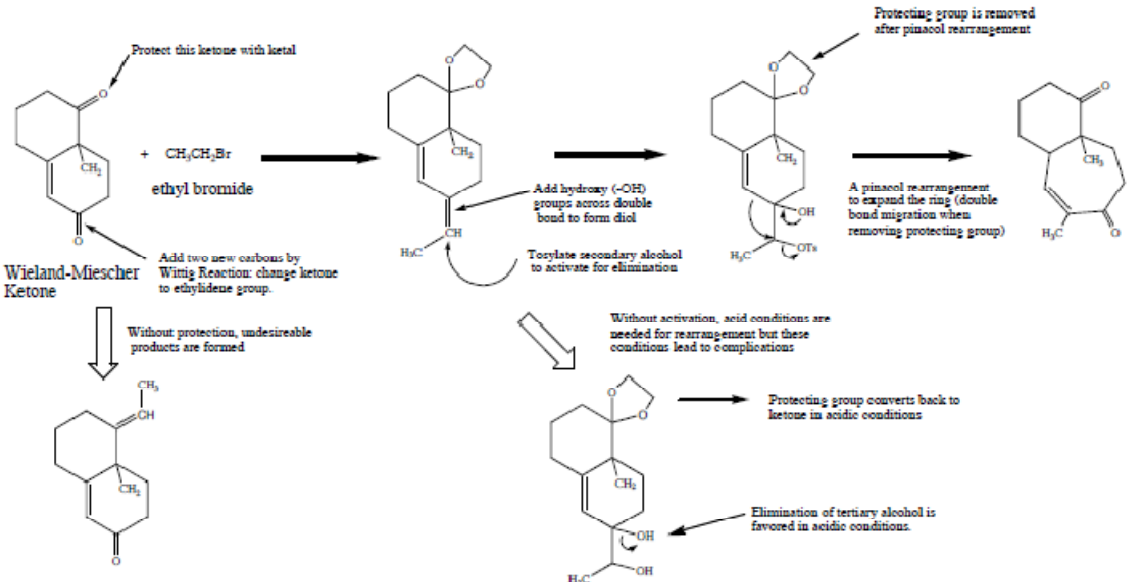
11.3 Retrosynthetic analysis of Longofoline

Longifolene, $C_{15}H_{24}$ (Decahydro-4, 8, 8-trimethyl-9-methylene-1-4-methanoazulene), a tricyclic sesqui-terpene hydrocarbon, is commercially important chemical and is used in perfumery industry owing to the woody odor of its chemically modified forms (The good scent company). It is one of the most abundant sesqui-terpene hydrocarbons naturally occurring in P. longifolia, P. roxburghii SARG and P. sylvestris.

The first successful synthesis of longifolene was described indetail by E.J.Corey and co-workers in 1964. A key disconnection is made ongoing from I to II. This trans-formation simplifies the tricyclic to a bicyclic skeleton. For this disconnection to correspond to a reasonable synthetic step, the functionality in the intermediate to be cyclized must engender rmutual reactivity between C(7) and C(10). This is achieved in diketone II, because an enolate generated by deprotonation at C(10) can undergo an intramolecular Michael addition to C(7). The stereochemistry requires that the ring junction be *cis*.



Retrosynthetic Step II to III is attractive because it suggests a decalin derivative as a key intermediate. Methods for preparing this type of structure are well developed, since they are useful intermediates in the synthesis of other terpenes as well as steroids. Can a chemical reaction be recognized that would permit III to II to proceed in the synthetic sense? The hydroxyl to carbonyl transformation with migration corresponds to the pinacol rearrangement. There trosynthetic transformation II to III corresponds to a workable synthetic step if the group X in III is a leaving group that could promote the rearrangement. The other transformations in the retrosynthetic plan, III to IV to V,are straight forward in concept and lead to identification of V as a potential starting material. Compound V is known as the Wieland-Miescher ketone and can be obtained by Robinson annulations of 2-methylcyclohexane-1,3-dione.



Control steps in the synthesis of longifolene

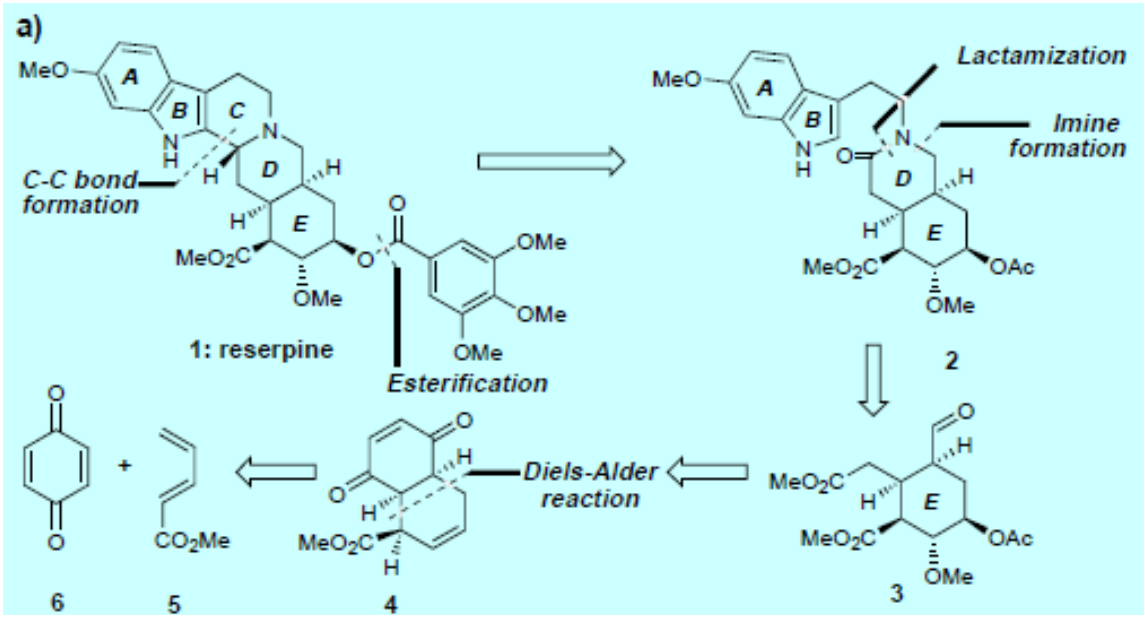
11.4 Retrosynthesis of Reserpine

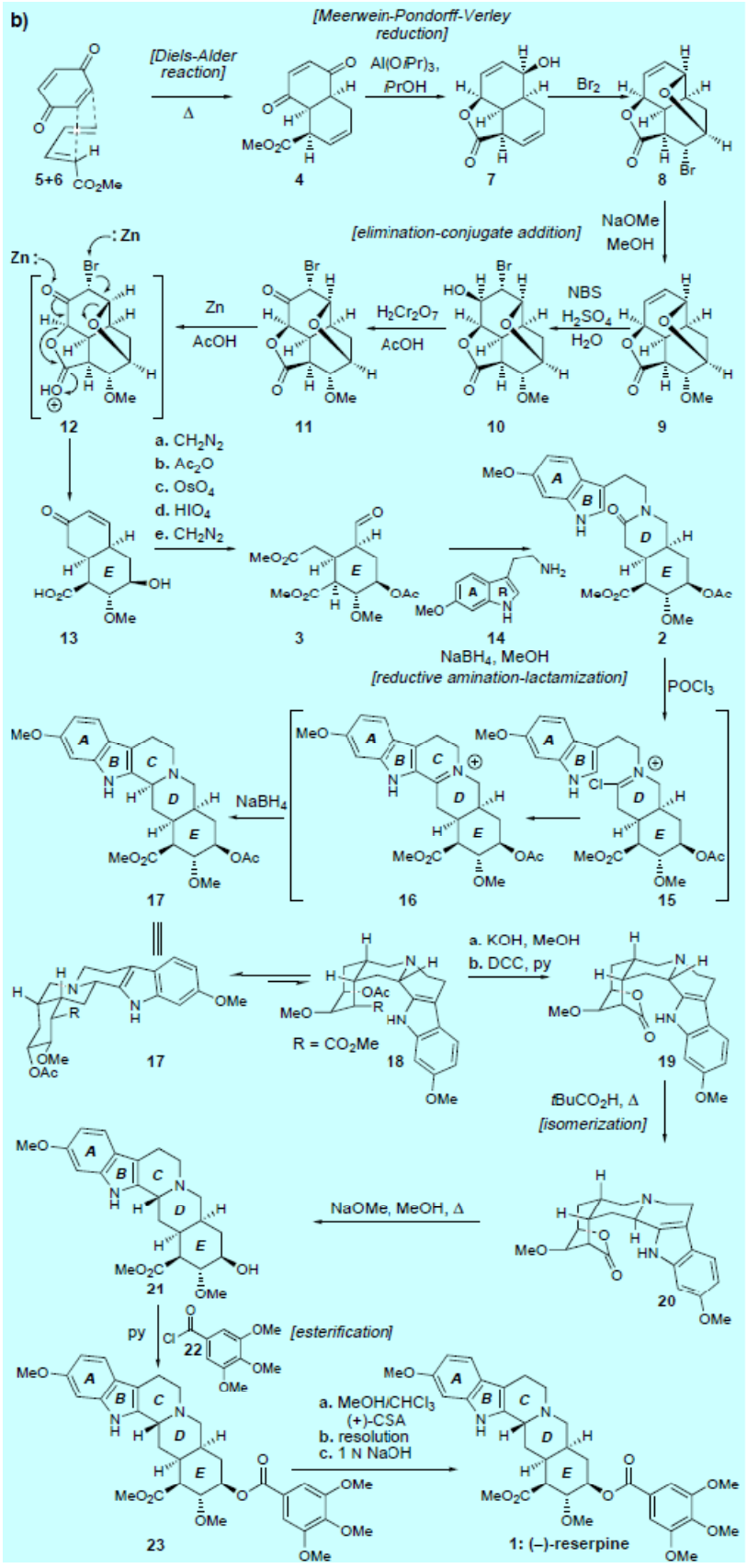
Reserpine a constituent of the Indian snakeroot Rauwolfia serpentina Benth., is an alkaloid substance with curative properties for the treatment of hypertension, as well as nervous and mental disorders.

Reserpine was isolated in 1952 and yielded to structural elucidation in 1955 (Schlittler and co-workers) and to total synthesis in 1958 (Woodward et al.). The first total synthesis of reserpine considered as one of Woodward's greatest contributions to synthesis, inspires admiration and respect by the manner in which it exploits molecular conformation to arrive at certain desired synthetic objectives.

During this synthesis, Woodward demonstrated brilliantly the power of the venerable Diels-Alder reaction to construct a highly functionalized 6-membered ring, to control stereochemistry around the periphery of such a ring, and most importantly, to induce a desired epimerization by constraining the molecule into an unfavorable conformation by intramolecular tethering. All in all, Woodward's total synthesis of reserpine remains as brilliant in strategy as admirable in execution. It was to be followed by several others.

The synthesis of reserpine appropriately represents Woodward's approach to total synthesis. Even though Woodward did not talk about retrosynthetic analysis, he must have practiced it subconsciously. In his mind, reserpine consisted of three parts: the indole (the AB unit), the trimethoxybenzene system, and the highly substituted E-ring cyclohexane. Given the simplicity of the first two fragments and their obvious attachment to fragment 3, Woodward concerned himself primarily with the stereoselective construction of 3 and the stereochemical problem encountered in completing the architecture of the CD ring system. He brilliantly solved the first problem by employing the Diels -Alder reaction to generate a cyclic template onto which he installed the required functionality by taking advantage of the special effects of ring systems on the stereochemical outcomes of reactions. He addressed the second issue, that of the last stereocenter to be set at the junction of rings C and D, by cleverly coaxing his polycycle into an unfavorable conformation (through intramolecular tethering), which forced an isomerization to give the desired stereochemistry.



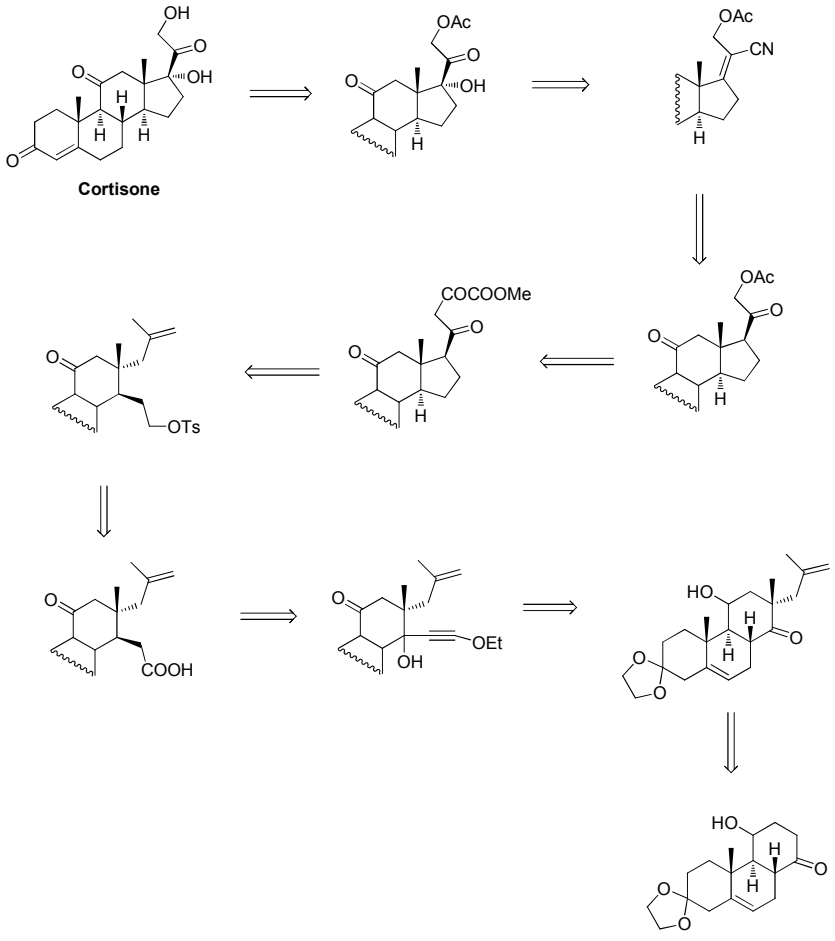

b)
[Meerwein-Pondorff-Verley reduction]
[Diels-Alder reaction]
Δ
Al(OiPr)3, iPrOH
Br2
5+6
4
7
8
NaOMe MeOH
[elimination-conjugate addition]
Zn
AcOH
H2Cr2O7
AcOH
NBS
H2SO4
H2O
12
11
10
9
a. CH2N2
b. Ac2O
c. OsO4
d. HIO4
e. CH2N2
13
3
14
2
NaBH4, MeOH
[reductive amination-lactamization]
POCl3
NaBH4
17
16
15
R = CO2Me
18
a. KOH, MeOH
b. DCC, py
19
tBuCO2H, Δ
[isomerization]
NaOMe, MeOH, Δ
21
20
py
22
[esterification]
a. MeOH/CHCl3
(+)-CSA
b. resolution
c. 1 N NaOH
23
1: (–)-reserpine

These maneuvers clearly constituted unprecedented sophistication and rational thinking in chemical synthesis design. While this rational thinking was to be further advanced and formalized by Corey's concepts on retrosynthetic analysis, the stereocontrol strategies of this era were to dominate synthetic planning for some time before being complemented and, to a large degree, eclipsed by acyclic stereoselection and asymmetric synthesis advances which emerged towards the end of the century.

11.5 Retrosynthesis of Cortisone

Cortisone also known as 17-hydroxy-11-dehydrocorticosterone is a 21-carbon steroid hormone. It is one of the main hormones released by the adrenal gland in response to stress. Structuraly, it is a corticosteroid closely related to cortisol. It is used to treat a variety of ailments and can be administered intravenously, orally, intraarticularly (into a joint), or transcutaneously. Cortisone suppresses the immune system, thus reducing inflammation and attendant pain and swelling at the site of the injury. Risks exist, in particular in the long-term use of cortisone.

The retrosynthetic analysis of Cortisone is given below



11.6 Summary of the unit

Retrosynthesis or retrosynthetic analysis is a strategy for planning an organic synthesis by disconnecting a target molecule into precursor materials. These steps are repeated until available starting materials are reached. The retrosynthetic analysis is not a synthesis form of organic chemistry, but an analytical approach based on the desired product. The target molecule is broken down into smaller and smaller fragments. The actual synthesis can then be designed based on the retrosynthetic analysis.

The method of retrosynthetic analysis is very effective, but it requires a great knowledge of chemical compounds, classes of compounds, chemical reactions, reaction conditions etc.

11.7 Key words

Retrosynthetic Analysis of Camphor; Retrosynthetic analysis of Longofoline; Retrosynthesis of Reserpine; Retrosynthesis of Cortisone

11.8 References for further studies

1) Elements of Synthesis Planning; R. W. Hoffmann; *Springer Science & Business Media*, **2009**.
2) Organic Chemistry; Jonathan Clayden, Nick Greeves, Stuart Warren; *OUP Oxford*, **2012**.
3) Introduction to Strategies for Organic Synthesis; Laurie S. Starkey; *John Wiley & Sons*, **2012**.
4) Organic Synthesis: Concepts and Methods; Jürgen-Hinrich Fuhrhop, Guangtao Li; *John Wiley & Sons*, **2003**.
5) Advanced Organic Chemistry: Part B: Reaction and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer Science & Business Media*, **2007**.

11.9 Questions for self understanding

1) Discuss the retrosynthetic Analysis of Camphor.
2) Discuss the retrosynthetic analysis of Longofoline.
3) Discuss the retrosynthesis of Reserpine.
4) Discuss the retrosynthesis of Cortisone.

UNIT-12

Structure

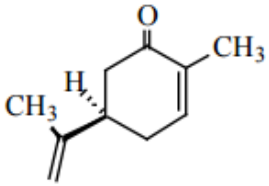
12.0 Objectives of the unit

After studying this unit you are able to

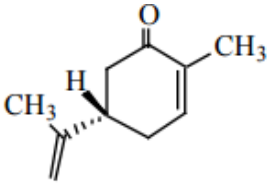
- Explain the method of controlling the geometry of double bonds
- Write the mechanism of Julia Olefination
- Identify the stereospecefic elimination reactions which give single isomer of alkenes
- Write the mechanism for Peterson reaction
- Explain the synthesis *E* and *Z* alkenes by stereosective addition to alkynes
- Explain the conditions for the *E* – selective Wittig reaction
- Explain the conditions for the *Z*–selective Wittig reaction

12.1 Introduction

Many properties of organic compounds are associated with the shape of the molecule. The "two" compounds below are isomers of Carvone, with different orientations of the isopropenyl function. One isomer (the S isomer) has the smell of spearmint whereas the other isomer (the R isomer) has the smell of caraway.



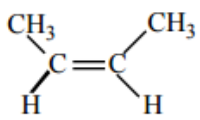
R-Carvone
Spearmint



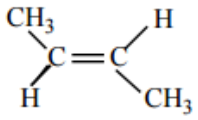
S-Carvone
Caraway

The smells are a result of the way the isomers interact with receptors to send signals to the brain. Many reactions, both chemical and biological, show such effects of molecular shape.

The π-bond in an alkene does not permit rotation, thus all of the atoms attached directly to the alkene lie in a plane. Groups attached to the alkene could be positioned on the same side of the alkene or on opposite sides of the alkene. Such compounds are different in chemical and physical properties as well as in their geometry, and are called geometrical isomers. In 2-butene the methyl groups can be located on the same side or on the opposite side of the double bond, giving rise to two geometrical isomers.



cis- 2-butene



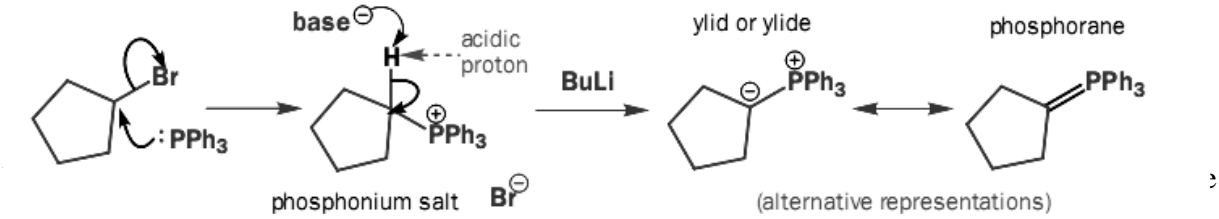
trans- 2-butene

The isomer with the methyl groups on the same side is called the cis isomer, while the isomer with the groups located on opposite sides is called the trans isomer. Trans isomers of compounds are usually more stable than cis isomers.

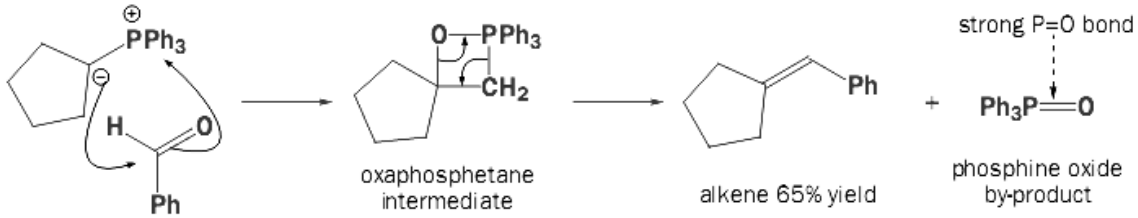
Elimination reactions which follows E1, E2 and E1CB mechanism are the most widely used reactions for synthesis of alkenes. Though the trans isomer is stable at room temperature compare to cis one, the synthesis of predominenly (~98%) either cis or trans alkene is quite difficult through elimination reaction, since the nucleophile can attack the β-hydrogen atom from either side of the living group. Know there are other synthetic methods are available other than elimination reaction from them we can synthesize predominantly one isomer of the alkene. In this unit you will study those reactions.

12.2 Controlling the geometry of double bonds

The important way of making alkenes is **Wittig reaction**. Phosphorus atoms, especially those that are positively charged or that carry electronegative substituents, can increase the acidity of protons adjacent to them on the carbon skeleton. Phosphonium salts (made in a manner analogous to the formation of ammonium salts from amines, in other words, by reaction of an alkyl halide with a phosphine) can therefore be deprotonated by a moderately strong base to give a species known as an ylid, carrying (formally) a positive and a negative charge on adjacent atoms. Ylids can alternatively be represented as doubly bonded species, called **phosphoranes**.

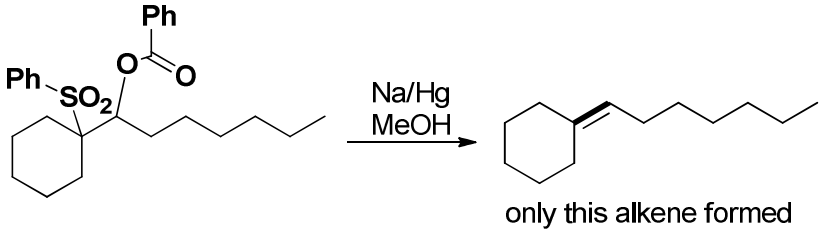


nucleophilic species that will attack the carbonyl groups of aldehydes or ketones, generating the four-membered ring oxaphosphetane intermediates. Oxaphosphetanes are unstable: they undergo elimination to give an alkene (65% yield for this particular example) with a phosphine oxide as a by-product. The phosphorusñoxygen double bond is extremely strong and it is this that drives the whole reaction forward.

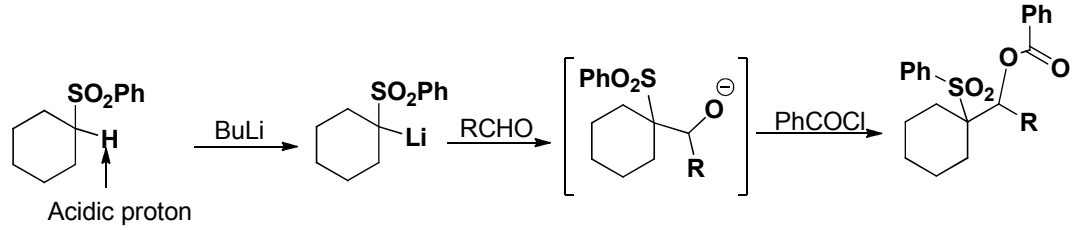


12.3 Julia Olefination

In ths reacrtion the phenylsulfonyl ($PhSO_2$) and benzoate ($PhCO_2$) groups in the starting material are lost to form the double bond but it is completely regioselective. Only the alkene shown is formed, with the double bond joining the two carbons that carried the $PhSO_2$ and $PhCO_2$ groups. This elimination is promoted by a reducing agent, usually sodium amalgam (a solution of sodium metal in mercury) and works for a variety of compounds providing they have a phenylsulfonyl group adjacent to a leaving group. This is called the **Julia olefination**.



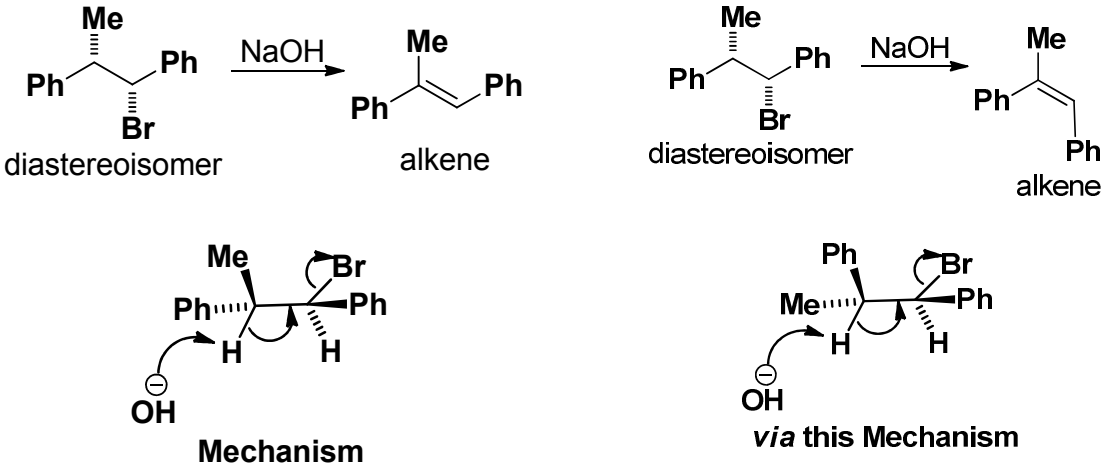
The most common leaving groups are carboxylates such as acetate or benzoate, and the starting materials are very easily made. Sulfones are easily deprotonated next to the sulfur atom by strong bases like butyllithium or Grignard reagents, and the sulfur-stabilized anion will add to aldehydes. A simple esteri?cation step, which can be done in the same reaction vessel as the addition, introduces the acetate or benzoate group. This is how the starting material for the elimination above was made.



The s ene) is known as the Julia olefination. The double bond is formed by joining two separate molecules together (the aldehyde and sulfone).

12.4 Stereospecefic elimination give single isomer of alkenes

The requirement for the H and the Br to be anti-periplanar in the E2 transition state meant that the two diastereoisomers of this alkyl bromide eliminated to alkenes with different double bond geometries.

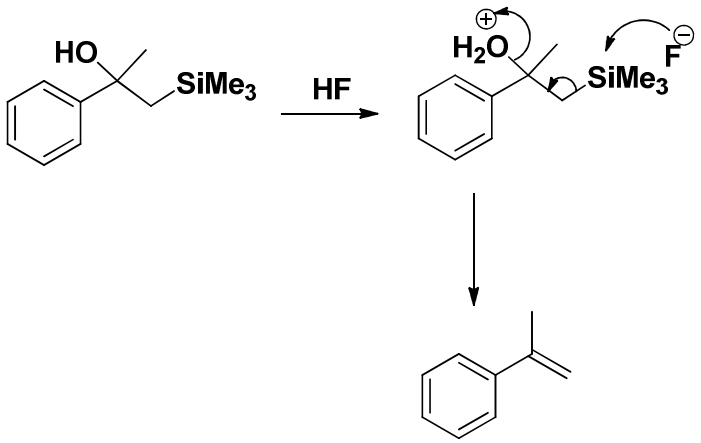


However, reactions like this are of limited use their success relies on the base's lack of choice of protons to attack: provide an alternative H. Therefore, that only trisubstituted double bonds can be made stereospecifically in this way, because the reaction must not have a choice of hydrogen atoms to participate in the elimination.

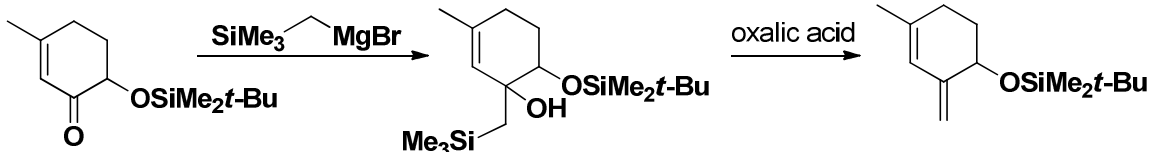
12.5 Peterson reaction

In many organic reaction the Me_3Si react as proton. The acidic proton removed by the bases, silicon is readily removed by hard nucleophiles, particularly F^- or RO^- , and this promote an elimination. This reaction is known as **Peterson reaction.**

An example is shown here.



The eliminations of alcohols under acidic conditions to give alkenes. But, unlike those reactions, it is fully Regioselective, and so is particularly useful for making double bonds where other elimination methods might give the wrong regioisomer or mixtures of regioisomers. In this next example only one product is formed, in high yield, and it has an exocyclic double bond.

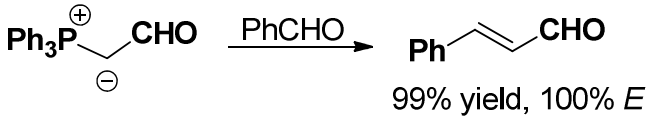


The Peterson reaction is particularly useful for making terminal or exocyclic double bonds connectively because the starting material (the magnesium derivative shown above) is easily made from available Me_3SiCH_2Br. The reaction is also stereospecific, because it is an E2 elimination proceeding *via* an anti-periplanar transition state. In principle, it can therefore be used to make single geometrical isomers of alkenes, the geometry depending on the relative stereochemistry of the starting material. However, this use of the Peterson reaction is limited by difficulties in making diastereoisomerically pure starting materials.

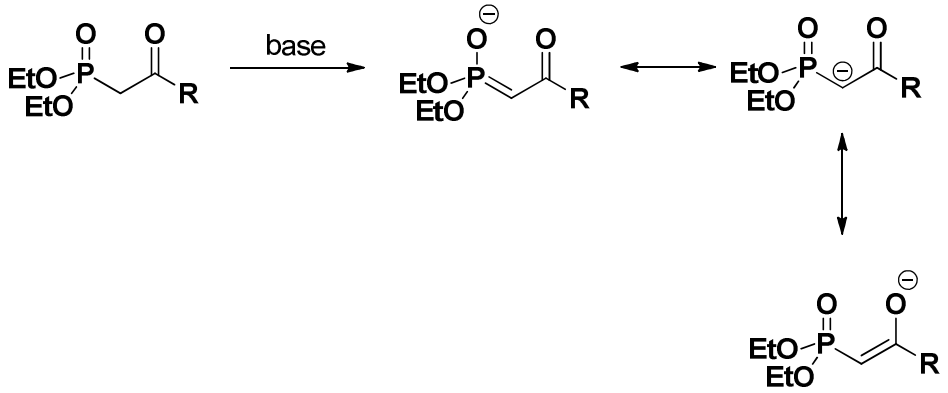
12.6 Synthesis *E* and *Z* alkenes by stereosective addition to alkynes

12.6.1 The *E* – selective Wittig reaction

Stabilized ylids, that is ylids whose anion is stabilized by further conjugation, usually within a carbonyl group, give E-alkenes on reaction with aldehydes.



These stabilized ylids really are stableóthis one, for example, can be recrystallized from water. This stability means though that they are not very reactive, and often it is better not to use the phosphonium salt but a phosphonate instead.



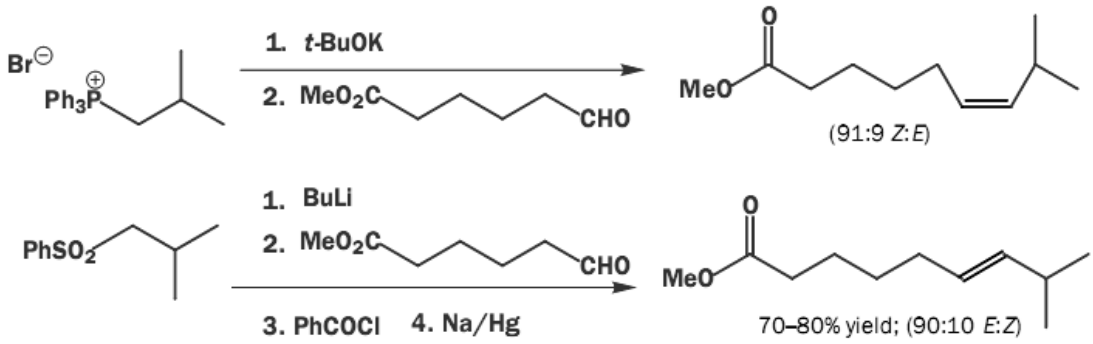
Phosphonate esters can be deprotonated with sodium hydride or alkoxide anions to give enolate-type anions that react well with aldehydes or ketones to give E-alkenes. Alkene-forming reactions with phosphonates are called **Horner–Wadsworth–Emmons** (or Horner–Emmons,

Wadsworth–Emmons, or even Horner–Wittig) reactions. This example is a reaction that was used by some Japanese chemists in the synthesis of polyzonimine, a natural insect repellent produced by millipedes.

Stereoselectivity in this step is therefore no longer kinetically controlled but is thermodynamically controlled: reversal to starting materials provides a mechanism by which the oxaphosphetane diastereoisomers can interconvert. Providing the rate of interconversion is faster than the rate of elimination to alkene, the stereospecific step will no longer reflect the initial kinetic ratio of oxaphosphetane diastereoisomers. It is not unreasonable to suppose that the thermodynamically more stable of the oxaphosphetanes is the trans-diastereoisomer, with the two bulky groups on opposite sides of the ring, and that elimination of this gives E-alkene.

12.6.2 The *Z*–selective Wittig reaction

The *Z* selectivity observed with simple alkyl R groups is nicely complementary to the E selectivity observed in the Julia olefination.



The key intermediates in the synthesis of the *E*- and the *Z*-isomers of capsaicin were the *E* and *Z* unsaturated esters shown below. By using a Wittig reaction with an unstabilized ylid it was possible to make the *Z*-isomer selectively, whilst the Julia olefination gave the *E*-isomer.

The elimination step is the easier one to explain, it is stereospecific, with the oxygen and phosphorus departing in a *syn*-periplanar transition state (as in the base-catalysed Peterson reaction). Addition of the ylide to the aldehyde can, in principle, produce two diastereomers of the intermediate oxaphosphetane. Provided that this step is irreversible, then the stereospecificity of the elimination step means that the ratio of the final alkene geometrical isomers will reflect the stereoselectivity of this addition step. This is almost certainly the case when R is not conjugating or anion-stabilizing; the *syn* diastereoisomer of the oxaphosphetane is formed preferentially, and the predominantly *Z*-alkene that results reflects this. The *Z* selective Wittig reaction therefore consists of a kinetically controlled stereoselective first step followed by a stereospecific elimination from this intermediate.

12.7 Summary of the unit

Julia olifination is also called Julia-Lythgoe olefination is the multistep synthesis, which enables the preparation of (E)-alkenes. The addition of a phenylsulfonyl carbanion to an aldehyde or ketone leads to an intermediate alcohol, which is esterified in situ. The reductive elimination with sodium amalgam to furnish the alkene takes place in a second step. ulia-Kocienski Olefination

Julia-Kocienski olefination is a modified Julia olefination reaction. This modified Julia Olefination enables the preparation of alkenes from benzothiazol-2-yl sulfones and aldehydes in a single step.

The Peterson Reaction allows the preparation of alkenes from α-silylcarbanions. The intermediate β-hydroxy silane may be isolated, and the elimination step i.e, the Peterson Elimination can be performed later. As the outcome of acid or base-induced elimination is different, the Peterson olefination offers the possibility of improving the yield of the desired alkene stereoisomer by careful separation of the two diastereomeric β-hydroxy silanes and subsequently performing two different eliminations.

In the first step of the Peterson olefination, addition of the silylcarbanion to a carbonyl compound and subsequent aqueous work up leads to diastereomeric adducts. Some of these reactions are stereoselective and may be rationalized with simple models: The reaction of benzaldehyde and a silylcarbanion gives the threo-product if the silyl group is small. This implies that in the transition state, the two sterically demanding groups are anti. As the silyl

group becomes more sterically demanding than trimethylsilyl, the selectivity shifts towards the erythro-isomer. Acidic hydrolysis proceeds via an anti-elimination.

In contrast, the base-catalyzed elimination may proceed via a 1,3-shift of the silyl group after deprotonation, or with the formation of a pentacoordinate 1,2-oxasiletanide that subsequently undergoes cycloreversion. The use of α-silyl organomagnesium compounds is helpful for the isolation of the intermediate β-hydroxysilanes, because magnesium strongly binds with oxygen, making the immediate elimination impossible. If excess organolithium or lithium amide base is used to generate the α-silyl carbanion, this base can effect the deprotonation as well, and since the lithium-oxygen bond is not as strong as magnesium-oxygen, the reaction leads directly to the alkene. Some reactions proceed with good diastereoselectivity, so the direct conversion can be an attractive option.

The Wittig Reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. The geometry of the resulting alkene depends on the reactivity of the ylide. If R is Ph, then the ylide is stabilized and is not as reactive as when R = alkyl. Stabilized ylides give (E)-alkenes whereas non-stabilized ylides lead to (Z)-alkenes.

The Schlosser Modification of the Wittig Reaction allows the selective formation of E-alkenes through the use of excess lithium salts during the addition step of the ylide and subsequent deprotonation/protonation steps.

12.8 Key words

Controlling the geometry of double bonds; Julia Olefination; Stereospecefic elimination give single isomer of alkenes; Peterson reaction; Synthesis *E* and *Z* alkenes by stereosective addition to alkynes; The *E* – selective Wittig reaction; The *Z*–selective Wittig reaction

12.9 References for further studies

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12.10 Questions for self under standing

1) Discuss the controlling the geometry of double bonds

2) What is Julia Olefination? Discuss the mechanism of this reaction.

3) With suitable example explain the stereospecefic elimination reaction which gives single 4) isomer of alkenes

4) What is Peterson reaction? Discuss the mechanism of this reaction.

5) Discuss the synthesis *E* and *Z* alkenes by stereosective addition to alkynes

6) Explain the followings

a) The *E* – selective Wittig reaction

b) The *Z*–selective Wittig reaction

UNIT-13

Structure

13.0 Objectives of this unit

After studying this unit you are able to

- Explain the meaning of metathesis
- Explain the olefin -metathesis reaction
- Identify catalysts for olefin-metathesis reaction
- Write the mechanism of Opening Metathesis Polymerization (ROMP)
- Write the mechanism of Ring Closing Metathesis (RCM)
- Write the mechanism of Olefin-Cross Metathesis (CM)
- Write the mechanism of Enyne metathesis (EM)
- Write the mechanism of Diene Metathesis (ADMET)

13.1 Introduction

With the exception of palladium-catalyzed cross-couplings, no other group of reactions has had such a profound impact on the formation of carbon–carbon bonds and the art of total synthesis in the last quarter of a century than the metathesis reactions of olefins, enynes, and alkynes. The Grignard, Diels–Alder, and Wittig reactions are three of the most prominent such processes that played decisive roles in shaping the science of chemical synthesis. During the last quarter of the previous century, two more such reactions emerged as rivals to the aforementioned carbon–carbon bond-forming processes: the palladium-catalyzed cross-coupling reactions and those collectively known as metathesis reactions.

13.2 Metathesis

Metathesis is the formation of a product that has exchanged bonds between starting materials.

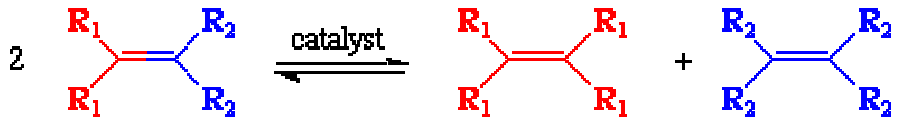
$$A\text{-}B + C\text{-}D \rightarrow A\text{-}D + C\text{-}B$$

It is a double replacement/displacement reaction.

Metathesis in acid-base chemistry and ion exchange is well defined and simple. However, until recently, bond formation in organic reactants is difficult without the presence of catalysts. Metathesis reactions do not occur in nature, but are convenient “short cuts” in organic synthesis.

13.3 Olefin -Metathesis Reaction

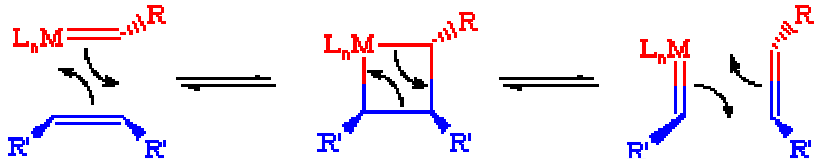
Olefin metathesisis a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds, and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The Olefin-metathesis reaction is the most commonly employed of the metathesis-based carbon–carbon bond forming reactions.



If one of the product alkenes is volatile (such as ethylene) or easily removed, then the reaction shown above can be driven completely to the right. Likewise, using a high pressure of ethylene, internal olefins can be converted to terminal olefins.

13.4 Mechanism

The commonly accepted mechanism for the olefin metathesis reaction was proposed by Chauvin and involves a [2+2] cycloaddition reaction between a transition metal alkylidene complex and the olefin to form an intermediate metallacyclobutane. This metallacycle then breaks up in the opposite fashion to afford a new alkylidene and new olefin. If this process is repeated enough, eventually an equilibrium mixture of olefins will be obtained.



Such cycloaddition reactions between two alkenes to give cyclobutanes is symmetry forbidden and occurs only photochemically. However, the presence of d-orbitals on the metal alkylidene fragment breaks this symmetry and the reaction is quite facile.

13.5 Catalysts for olefin-metathesis reaction

There have been roughly four distinct generations of olefin metathesis catalysts they are

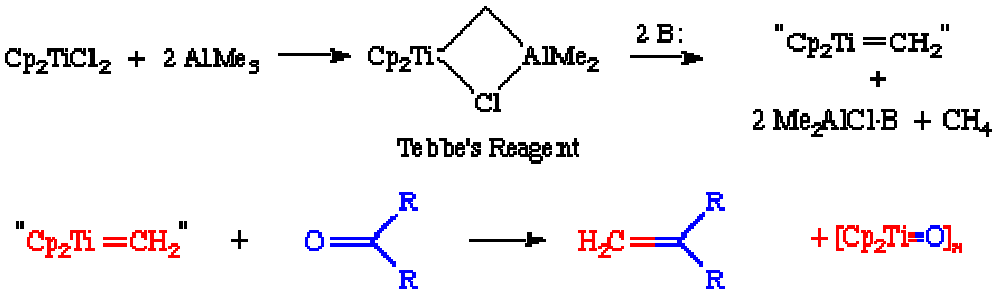
1. "Black Box" heterogeneous catalysts consisting of a high valent transition metal halide, oxide or oxo-halide with an alkylating co-catalyst such as an alkyl zinc or alkyl aluminum. Some of these catalyst systems are placed on an alumina or silica support. Some of which are still used today, include $WCl_6/SnMe_4$ and $Re_2O_7Al_2O_3$.

While these catalysts are exceedingly active, they have an exceedingly low tolerance for functional groups because of their Lewis acidic nature. Likewise, less than one percent of the material is an active catalyst, and nothing is known about the nature of the actual catalytic species in these systems. One commercial application still using these catalysts is the ROMP of dicyclopentadiene to produce tough plastics for use in golf carts, snow mobile hoods etc.

2. *Titanocene-based catalysts*

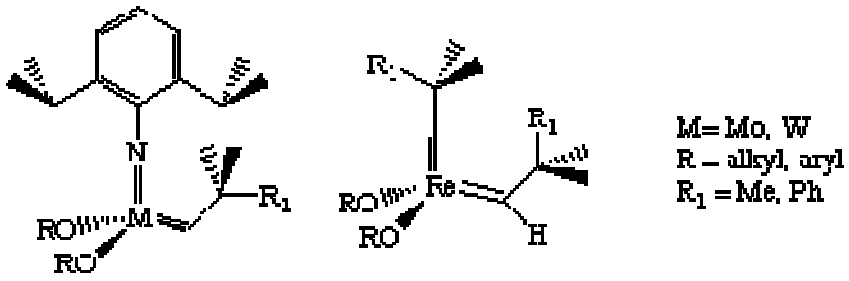
Reaction of Cp_2TiCl_2 with two equivalents of $AlMe_3$ to yield $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$, commonly called Tebbe's Reagent. In the presence of a strong base such as pyridine, the reagent is functionally equivalent to "$Cp_2Ti{=}CH_2$".

These Ti-based catalysts are not nearly as active or tolerant of carbonyl functionalities as the later catalysts, but Grubbs has shown that these Ti complexes undergo stoichiometric Wittig-like reactions with ketones, aldehydes and other carbonyls to form the corresponding methylene derivatives. The mechanism of this reaction is identical to that of the olefin metathesis reaction except that the final step is not reversible.



3. Schrock W, Mo and Re Catalysts

R.R. Schrock has invented a variety of catalysts, but the most important of these are arylimido complexes of Mo with the general formula $(Ar'N)(RO)_2Mo=CHR'$ where Ar' is typically 2,6-diisopropylphenyl, R' can be virtually anything and R is neopentyl or neophyl (CMe_2Ph). These catalysts are exceedingly active, metathesizing over 1,000 equivalents of cis-2-pentene to equilibrium in less than one minute for R = $CMe(CF_3)_2$. The reactivity of these catalysts can be tuned very easily by changing the nature of the alkoxide ligands. For example when R = tert-butyl, the complex reacts only with strained cyclic olefins, making it an ideal ROMP catalyst.

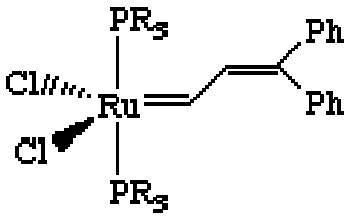


These catalysts have a high tolerance for functionality, although they are air and water-sensitive. Two important features of these catalysts are that they are 100% active and have been fully characterized by NMR and X-ray crystallography. The success of these catalysts stems from their coordinative and electronic unsaturation (making them electrophilic) and their bulky ligands (prevents bimolecular decomposition).

4. Grubbs Ru Catalysts

Bob Grubbs developed a series of Ru catalysts that differ from the previous generations in several distinct ways. First, the metal is not in its highest oxidation state and is supported by

phosphine ligands. Second, these catalysts are so tolerant of functionality that some of them can operate in water on the benchtop. Such functional group tolerance comes at the expense of lower metathesis rates than the Schrock catalysts, but these systems are extremely promising.



13.6 Types of olefin-metathesis reactions

There are four different types of olefin metathesis are presently known. They are

i) Ring closing metathesis (RCM)

ii) Rring opening metathesis polymerization (ROMP)

iii) Olefin cross metathesis (CM) and

iv) Enyne metathesis (EM)

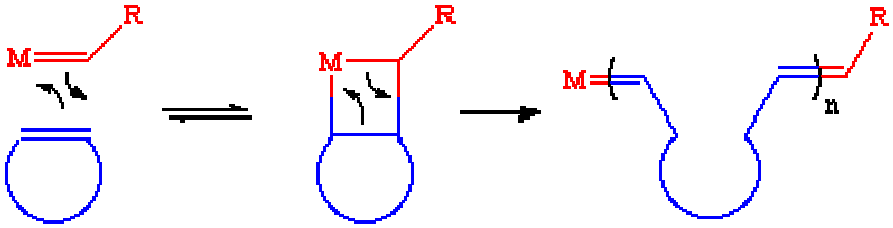
All have become reliable routine methods used widely in both academic and industrial settings.

i) Ring Opening Metathesis Polymerization (ROMP)

A term ring opening metathesis polymerization is coined by Robert Grubbs, is a variant of the olefin metathesis reaction. The reaction uses strained cyclic olefins to produce stereoregular and monodisperse polymers and co-polymers.

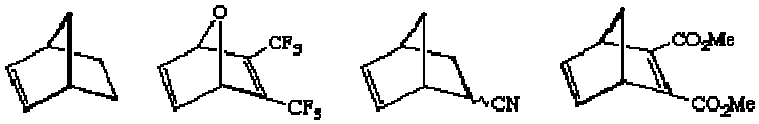
Mechanism

The mechanism of the ROMP reaction involves an alkylidene catalyst and is identical to the mechanism of olefin metathesis with two important modifications. First, as the reaction involves a cyclic olefin, the "new" olefin that is generated remains attached to the catalyst as part of a growing polymer chain as is shown below with a generic strained cyclic olefin



The driving force for the ROMP reaction is the relief of ring strain. Therefore, the second step shown above is essentially irreversible. Olefins such as cyclohexenes or benzene have little or no ring strain and cannot be polymerized. Strained cyclic olefins such as those shown below have sufficient ring strain to make this process possible. Monomers based on norbornene derivatives are especially popular as they can be readily synthesized from Diels-

Alder reactions with cyclopentadiene. Only the unsubstituted bonds are ring-opened and it is very difficult to metathesize or ROMP tri- and tetrasubstituted olefins.



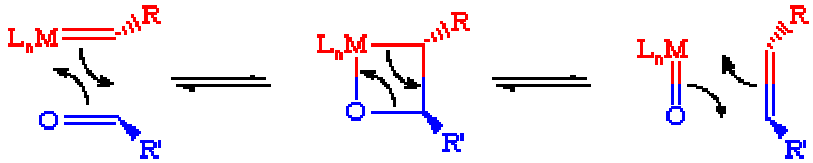
The polymers produced in the ROMP reaction typically have a very narrow range of molecular weights, something that is very difficult to achieve by standard polymerization methods such as free radical polymerization. The polydispersities (the weight average MW divided by the number average MW) are typically in the range of 1.03 to 1.10. These molecular weight distributions are so narrow the polymers are said to be monodisperse.

The catalysts used for ROMP are the same catalysts used for olefin metathesis. However, one has to be a little more careful when selecting a ROMP catalyst. If the catalyst is too active, it can metathesize the unstrained olefinic bonds in the growing polymer chain (a process called "back-biting"), thereby reducing the molecular weight and increasing the molecular weight distribution (polydispersity).

When the reaction is complete, there are two methods for cleaving the polymer from the metal center:

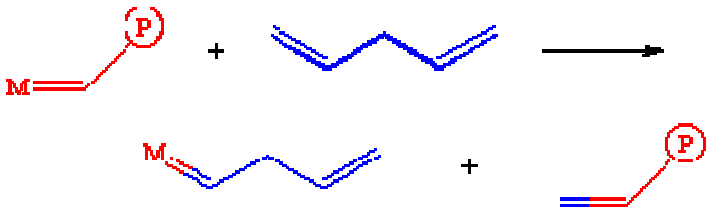
1. *Reaction with aldehyde*

Many metathesis catalysts react with aldehydes in a [2 + 2] fashion just as they do with olefins. The product is a metal oxo and an olefin (or polymer) capped with the former aldehyde functionality. Often a large excess (100 equiv) of aldehyde is used. The cleaved polymer can then be separated from the catalyst by precipitation with methanol



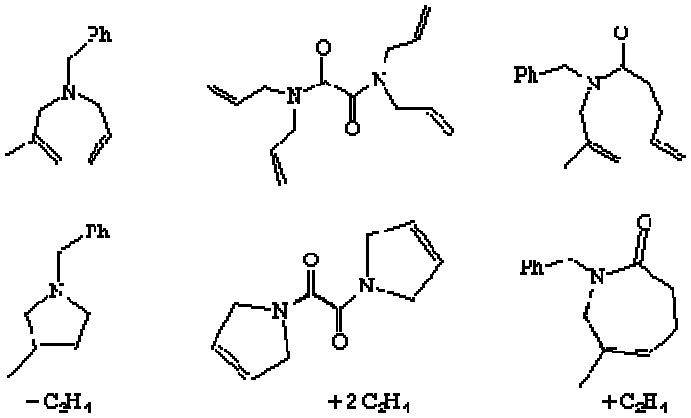
2. *Chain transfer*

Reaction with several equivalents of diene is another way of cleaving the polymer chain. The advantage of this method is that the cleavage does not deactivate the catalyst, permitting additional aliquots of monomer to be polymerized. However, one does have to worry about broadening the MW distribution



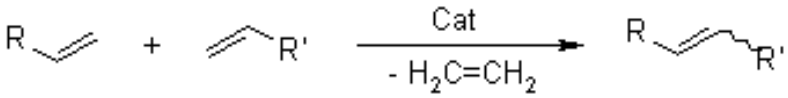
13.7 Ring Closing Metathesis (RCM)

As the name implies, this is the reverse of the ROMP reaction. In order to make it work, the ring being formed cannot have appreciable ring strain. As the RCM and ROMP processes involve equilibria, the RCM reaction sometimes involves running the experiment at low dilution so that most of the reactions are intra- rather than intermolecular. Removal of the volatile byproduct drives the equilibrium to the ring-closed product. In addition, the catalysts are selected to have good reactivity with terminal olefins, but low reactivity with internal ones. The starting materials for each reaction are shown in the top row and the products in the bottom:



13.8 Olefin-Cross Metathesis (CM)

The transalkylidenation of two terminal alkenes under release of ethane is called cross metathesis, and this reaction is also catalyzed by ruthenium carbenoids (Grubbs Catalyst). Statistically, the reaction can lead to three possible pairs of geometric isomers, i.e. E/Z pairs for two homocouplings and the cross-coupling (R-CH=CH-R, R'-CH=CH-R', and R-CH=CH-R'). Thus total of 6 products are formed.

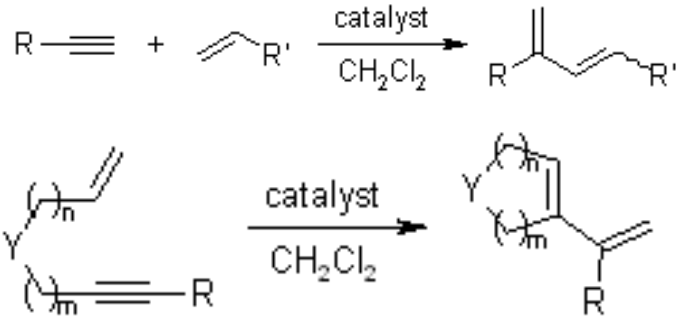


Olefin cross metathesis (CM), represents an understudied area. Low yields and unpredictable reaction make many chemists reluctant to incorporate CM into a complex, target-oriented synthesis plan, especially as a late stage strategy. Indeed, issues such as alkene stereoselectivity and cross product selectivity associated with CM are inevitable challenges dictated by the unique mechanism of olefin metathesis.

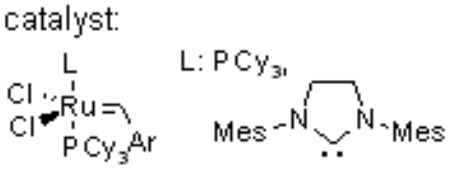
13.9 Enyne metathesis (EM)

Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM), of which both the intramolecular and intermolecular versions are known.

The Enyne Metathesis is a ruthenium-catalyzed bond reorganization reaction between alkynes and alkenes to produce 1,3-dienes. The intermolecular process is called Cross-Enyne Metathesis, whereas intramolecular reactions are referred as Ring-Closing Enyne Metathesis (RCEYM).



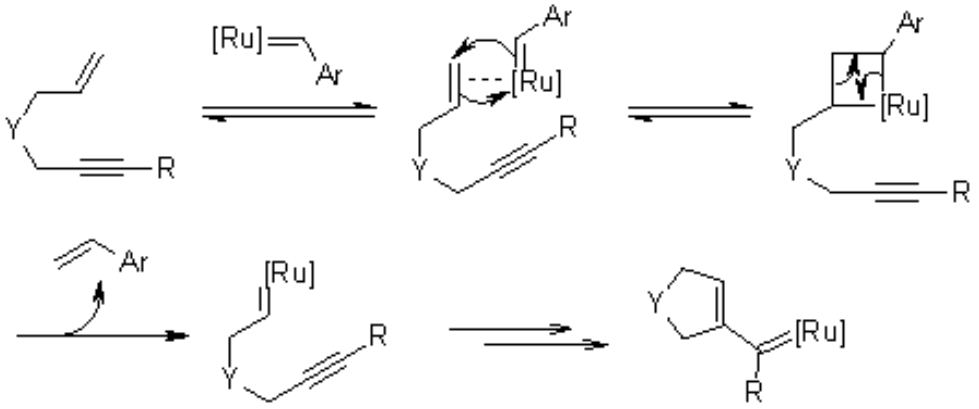
The catalyst used for this reaction is



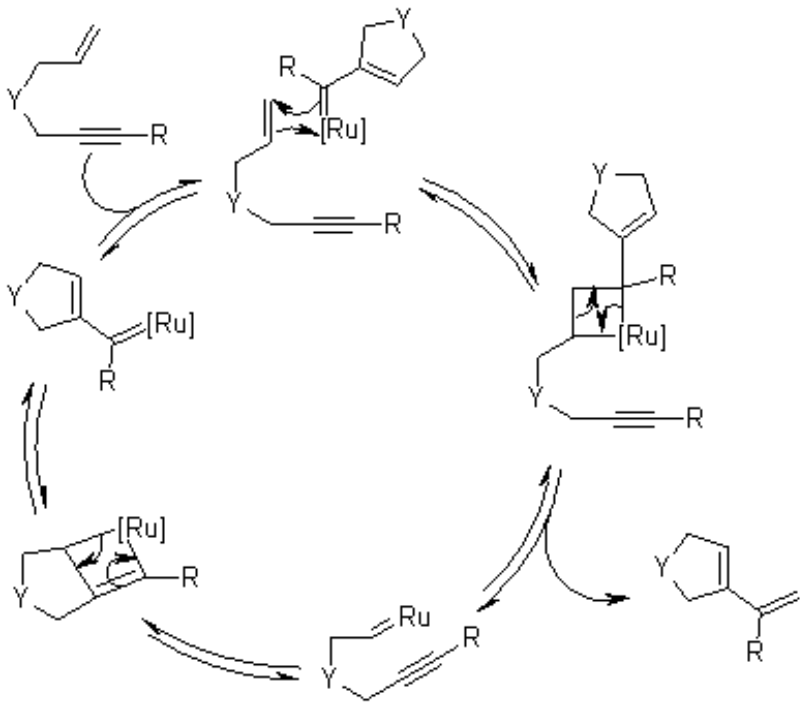
Enyne metathesis also called cycloisomerization reactions were first reported using palladium(II) and platinum(II) salts. These reactions are mechanistically distinct from metal carbene-mediated pathways observed in other metathesis reaction. Nowadays ruthenium carbenes catalyst used for alkene metathesis are also used in enyne bond reorganizations

Mechanism

In the initiation step, the stable catalyst undergoes cycloaddition to the substrate forming a ruthenacylcobutane. Subsequent cycloelimination releases a stable styrene derivative, which generally does not interfere in cross metathesis reactions. The catalyst is then bound to the substrate in form of a metal carbene, which reacts intramolecularly with the triple bond to yield a vinyl carbene.



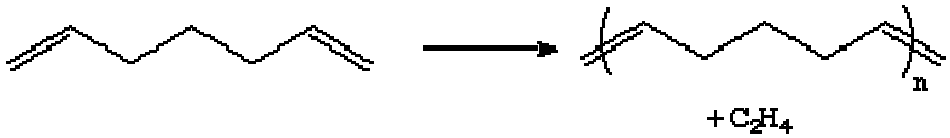
In the catalytic cycle, this vinyl carbene first adds to the double bond of the substrate forming a ruthenacyclobutane. Cycloelimination at this stage gives a ruthenium carbene under release of the product. Subsequent intramolecular cycloaddition with the alkyne gives a vinylcarbene intermediate via a ruthenacyclobutene transition state. The vinyl carbene reacts with another substrate molecule to give the product via methylene transfer, and the catalytic cycle continous. The driving force of the reaction is the formation of a thermodynamically stable, conjugated 1,3-diene.



The other olefin-metathesis reactions which have been seldom use in the organic synthesis are

13.10 Diene Metathesis (ADMET)

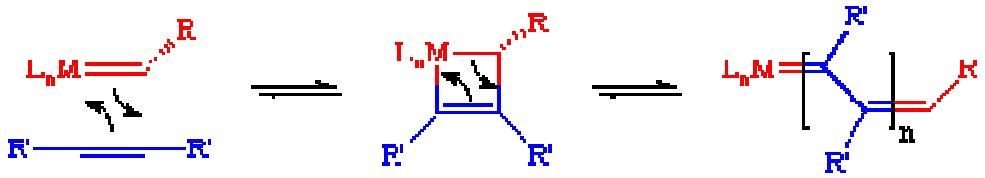
The ADMET method, pioneered by Ken Wagener and Jim Boncella at the U of Florida, uses alpha-omega dienes to produce polymers. The reaction is driven by the removal of ethylene from the system, which can be accomplished with a nitrogen purge



The reverse of this reaction (reacting an unsaturated polymer with excess ethylene in the presence of a metathesis catalyst), has been studied as a possible means of recycling automobile tires.

13.11 Polymerization of Acetylenes

When an acetylene is reacted with an alkylidene, a [2 + 2] cycloaddition occurs as with olefins, a metallacyclobutene is formed instead of a metallacyclobutane. If this metallacycle opens in a productive fashion, the result is a growing polymer chain.



This reaction typically only works well with 2-butyne or terminal acetylenes. Polymerization of terminal acetylenes is complicated by the potential for the R group to insert alpha or beta with respect to the metal. It is extremely challenging to always get a beta insertion and generate a polymer with reproducible properties

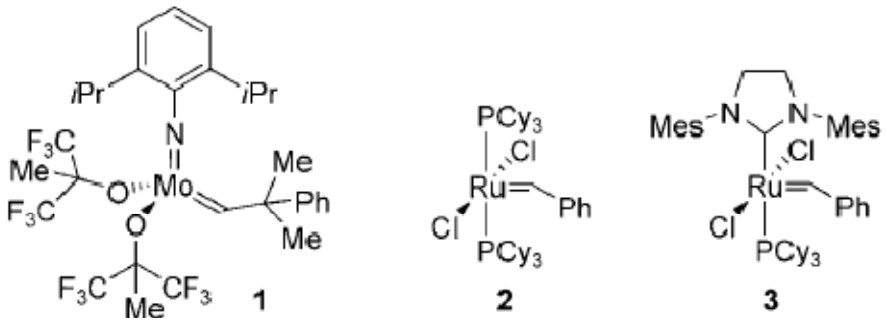
13.12 Grubbs catalysis

Transition metal-chlorides in the presence of co-catalysts were the first to be studied that afforded C-C bond formation, e.g., $CH_3CH_2AlCl_2$ and WCl_6

The Grubbs catalysts are based on a ruthenium atom surrounded by five ligands: two are neutral electron-donating entities (e.g., trialkylphosphines, N-heterocyclic carbenes), two are monoanionic groups (e.g., halides), and one alkylidene moiety (e.g., unsubstituted and substituted methylidenes).

The alkene ring-closing metathesis reaction and the alkene cross-metathesis reaction have found the most widespread and gainful use. The success of the alkene-metathesis reactions is largely due to the advent of today's readily available catalyst systems that display high activity and excellent functional-group tolerance.

The three such catalysts most routinely used by organic chemists (all of which are commercially available) are shown below.



Commonly used alkene metathesis catalysts

The molybdenum-based catalyst 1 was introduced by the Schrock group in 1990 and represented the first real groundbreaking advance in catalyst design since the tungsten carbenes initially used by Katz and co-workers. Catalyst 1 displays superb metathesis activity

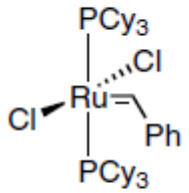
with a wide variety of alkene substrates, and is particularly useful for the formation of sterically crowded systems. The only drawback of catalyst 1 is its pronounced sensitivity to oxygen, moisture, and certain polar or protic functional groups owing to the electrophilicity of the high-oxidation-state transition metal center. Grubbs and co-workers subsequently introduced ruthenium-based carbene complexes, initially optimized to 2, as general and practical metathesis catalysts.

Although less active than the Schrock molybdenum-based systems 1, the Grubbs catalyst 2 exhibits much greater functional-group tolerance and has opened up new vistas in synthetic applications, most notably in the total synthesis of complex products, both natural and designed.

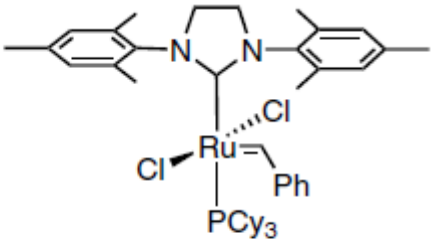
Recent developments in catalyst design have focused largely on the specific tailoring of catalyst reactivity through modifications of the ancillary ligands bound to the ruthenium center. In particular, the replacement of one of the phosphine ligands in 2 with an N-heterocyclic carbene ligand, increases the catalytic activity, thermal stability, and functional-group tolerance of the complex. The catalyst 3 engenders metathesis reactions with particularly high levels of activity, in certain cases approaching that of the Schrock system 1, and with a unique reactivity profile that nicely complements both earlier catalysts 1 and 2.

13.13 First generation and second generation Grubbs catalysts

The Grubbs catalysts are divided into two categories based on the nature of the neutral ligands: $L_2X_2Ru=CHR$ complexes (where L is a phosphine ligand) were discovered first and are referred to as the first-generation Grubbs catalysts, and $(L)(L')X_2Ru=CHR$ complexes (where L is a phosphine ligand and L' a saturated N-heterocyclic carbene or NHC ligand) were subsequently developed and are referred to as the second-generation Grubbs catalysts.



first-generation
Grubbs catalyst



second-generation
Grubbs catalyst

The first-generation Grubbs catalysts have demonstrated attractive functional-group tolerance and handling properties, and have been widely used as highly efficient promoters for ring opening metathesis polymerizations, ring-closing metathesis reactions to make disubstituted

olefins, ethenolysis (i.e., cleavage of the carbon–carbon double bond), cross-metathesis of terminal olefins, and the preparation of 1,3-dienes via enyne metathesis.

These catalysts and their analogues are very useful and are still employed in important processes, including the ethenolysis of feedstocks derived from bio-renewable seed oils and the manufacture of macrocyclic hepatitis C therapeutics.

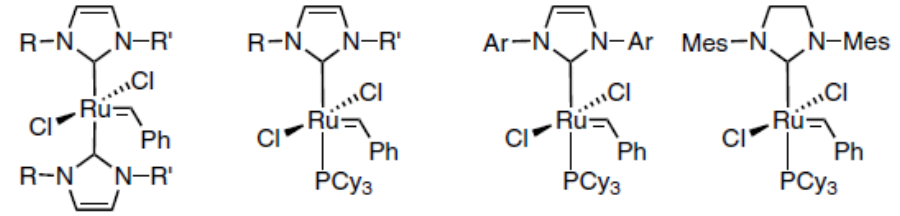
The utility of first-generation catalysts is somewhat limited. Because they suffer from reduced activity compared to the Schrock catalysts.

The ring-closing metathesis to form tri- and tetra substituted cycloalkenes and the crossmetathesis of sterically hindered or electronically deactivated olefins are the some examples of transformations that are poorly or simply not enabled by first generation Grubbs catalysts.

Many of these limitations have been addressed through the development of the second-generation Grubbs catalysts, which possess excellent metathesis activity while retaining the handling characteristics and broad functional-group tolerance of the earlier Grubbs catalysts. The second-generation Grubbs systems have rapidly evolved into a large family of catalysts with varying properties.

13.14 NHC-Based second-generation Grubbs catalysts

The first examples of NHC-containing, olefin metathesis catalysts were disclosed by Herrmann and co-workers. These complexes were bis-NHC ruthenium benzylidene species, 1, where the NHC ligands were unsaturated and contained identical or different, chiral or achiral alkyl substituents on the nitrogen atoms. These catalysts were originally aimed for tuning the properties of the catalysts by changing the nature of the alkyl substituents on the nitrogen atoms and at producing chiral complexes.



1	2	3	4
Herrmann bis-NHC catalyst	Herrmann NHC-phosphine catalyst	Grubbs, Nolan catalyst	second-generation Grubbs catalyst

R and R' are achiral or chiral alkyl groups such as *i*-Pr, Cy, or CHMePh
Ar = aryl; Mes = mesityl

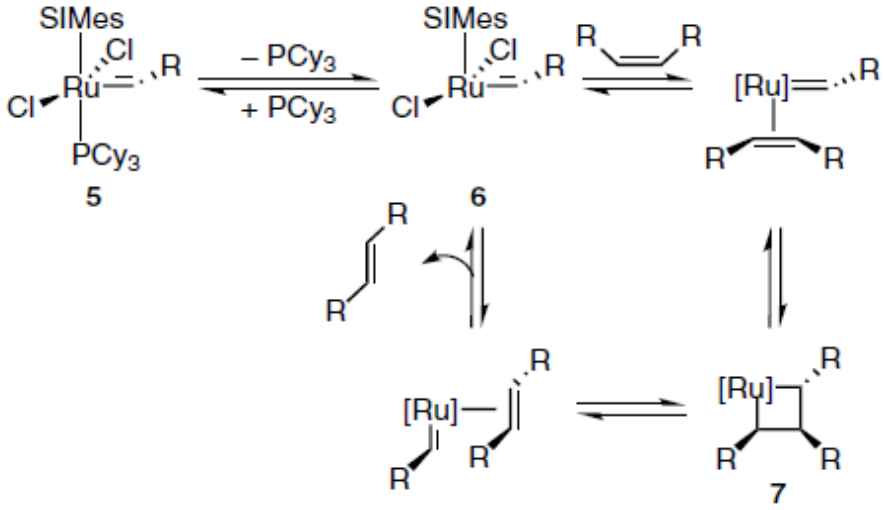
increasing metathesis activity

Herrmann and co-workers had reported mixed NHC–phosphine ruthenium metathesis catalysts. These catalysts contain alkyl-substituted unsaturated NHCs, 2. Grubbs and Nolan

groups independently developed catalysts derived from aryl-substituted unsaturated NHCs, in particular 1,3-dimesitylimidazolin-2- ylidene or IMes, 3. The mixed NHC–phosphine complexes 2 and 3 were found to possess greater metathesis activity and enhanced thermal stability than the first-generation Grubbs catalysts. Later the Grubbs group discovered that replacing one phosphine of the first-generation systems with a saturated mesityl-substituted NHC (or sIMes) ligand afforded a catalyst with even greater activity than the IMes-based compounds. The sIMes catalyst, 4, commonly referred to as the second-generation Grubbs catalyst, quickly superseded the IMes species because it demonstrated superior efficiency in practically all metathesis reactions.

13.15 Mechanistic Considerations and Development of Second-Generation Derivatives

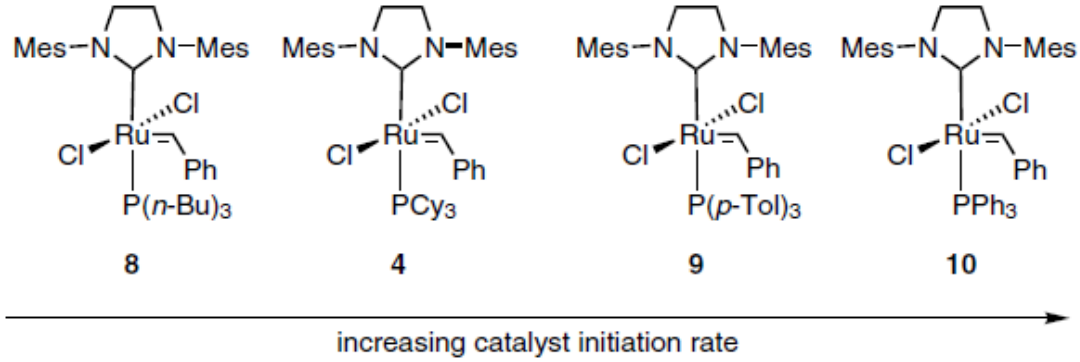
Mechanistic studies of 4 indicated that the catalytic steps involve an initiation event where a 16-electron species 5, undergoes reversible phosphine dissociation to furnish a 14-electron, active catalytic complex, 6. Complex 6 can either rebind a dissociated phosphine or proceed to reversibly coordinate an olefinic substrate to form a ruthenacyclobutane, 7. The breaking apart of the ruthenacyclobutane follows to expel the new olefinic products. In addition, these studies showed that the second-generation catalysts initiate much more slowly than the first-generation ones, and that their enhanced activity is due to the fact that their affinity to coordinate an olefinic substrate in the presence of free phosphine is much greater than that of the first-generation systems.



Mechanism of the Metathesis of a symmetrical cis olefin to its trans isomer

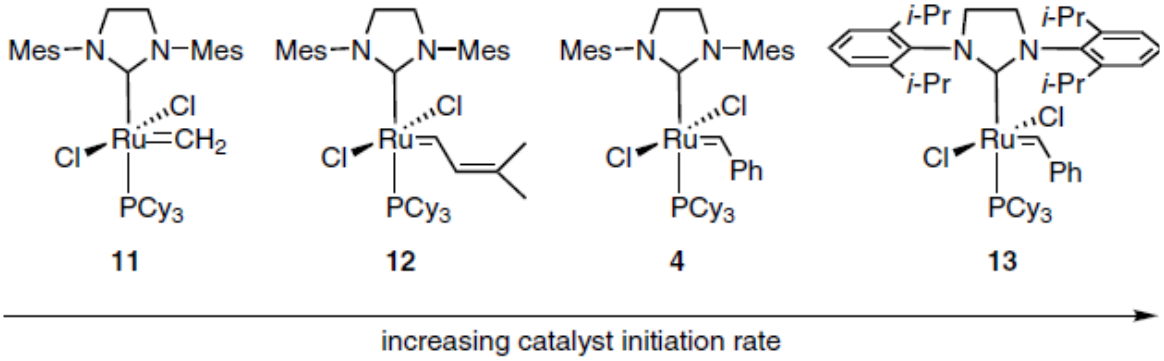
These mechanistic insights guided Grubbs and co-workers to prepare a family of second-generation catalysts with different initiation rates by varying the detachable phosphine ligands. Depending on the application, it is advantageous to employ catalysts that initiate more or less rapidly. For example, when performing ring-opening olefin metathesis

polymerizations (ROMP) of strained cyclic olefinic monomers, slower-initiating catalysts are often desirable because they allow for longer handling of the monomer/catalyst resin before the polymerization starts. Conversely, fast-initiating catalysts, able to promote metathesis at reduced temperatures, are useful in applications where low reaction temperatures are required to prevent catalyst decomposition and formation of undesired byproducts. Thus, analogues of 4, such as complexes 8–10 containing tri(nbutyl) phosphine, tri(p-tolyl)phosphine, and triphenylphosphine, have been synthesized and their phosphine dissociation rates found to vary dramatically with the nature of the phosphine ligand. The phosphine dissociation rate of 10 was about 60 times greater, and that of 8 is about 170 times smaller, than that of 4 measured at 80 °C in toluene.



Effect of the nature of the phosphine ligand on the initiation rate of the second-generation catalyst

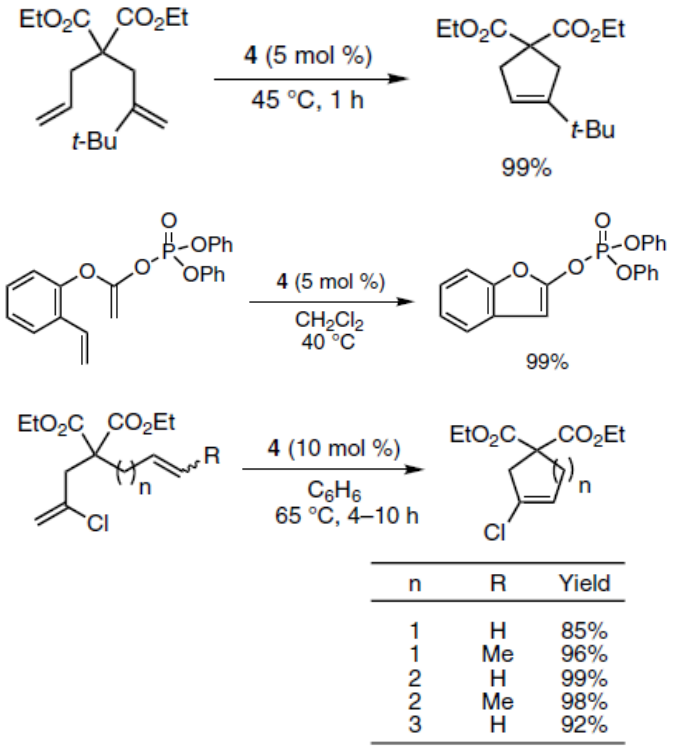
The nature of the halide and alkylidene ligands also has an impact on the catalyst initiation rate. In particular, catalysts containing larger halide ligands initiate more rapidly, while systems with smaller alkylidene moieties (e.g., methylidene) initiate more slowly. Similarly, complex 13, containing a large NHC ligand (i.e., 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-yl or sIDIPP) has proved to be a fast initiator and a highly active catalyst.



Influence of the nature of the alkylidene and NHC ligands on the initiation rate of the second-generation catalyst

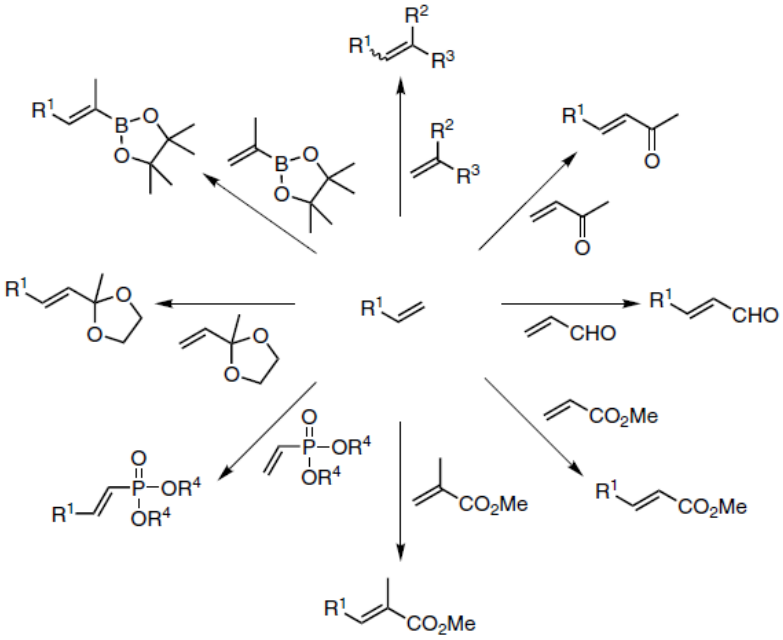
13.16 Applications of second-generation Grubbs catalysts in organic synthesis

By virtue of their greatly enhanced activity compare to their first-generation counterparts, the second-generation catalysts promote the metathesis of sterically demanding or deactivated olefins. In particular, second-generation Grubbs catalysts have shown increased activity in ring-closing metatheses and in macrocyclizations.



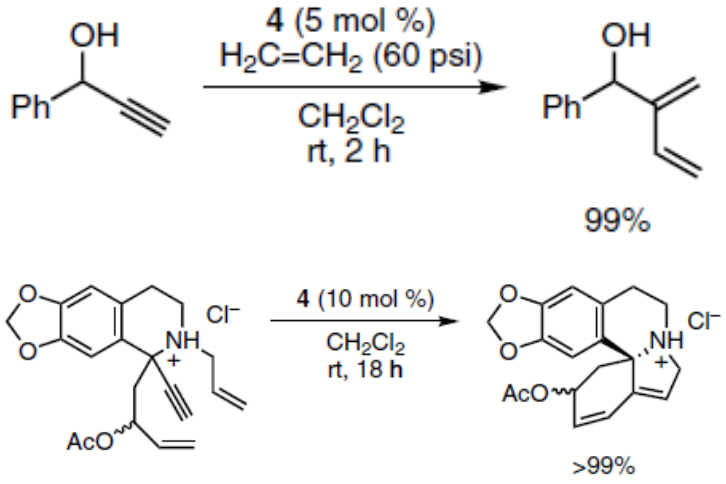
n	R	Yield
1	H	85%
1	Me	96%
2	H	99%
2	Me	98%
3	H	92%

They also catalyze challenging cross-metatheses including the coupling of olefins with α,β-unsaturated carbonyls, vinylphosphonates, and 1,1-disubstituted alkenes



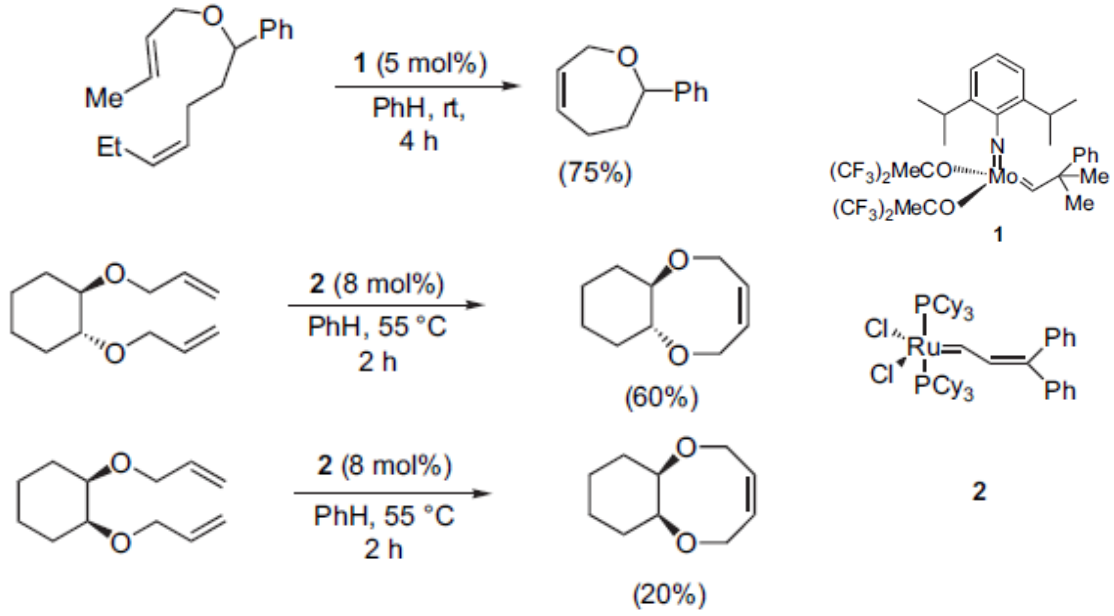
Cross-Metatheses catalyzed by second-generation Grubbs catalysts

The ability of the second-generation catalysts to couple olefins with α,β-unsaturated carbonyls has been utilized to prepare A,B-alternating copolymers by ring-opening insertion metathesis polymerization (ROIMP). Additionally, these catalysts promote the enyne metathesis of alkynes to make interesting 1,3-dienes. Also secondgeneration systems are often the catalysts of choice for the preparation of novel ROMP polymers, including ROMP-based immobilized reagents and scavengers.



13.17 Formation of medium-ring oxygen heterocycles by RCM

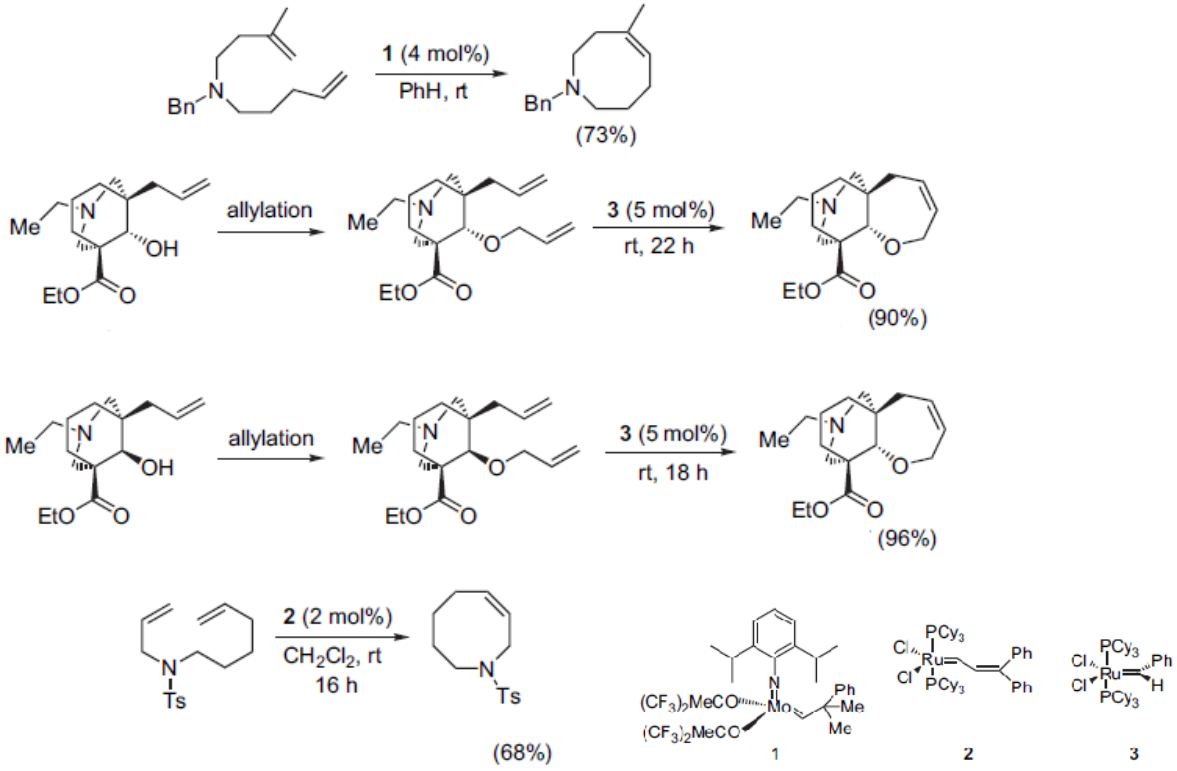
The synthesis of medium-ring oxacycles by RCM methodology tends to work best when some conformational constraints favour ring formation. Some of the structural features that have been helpful include the presence of a ring, a gem-dimethyl group or a large group present within the chain connecting the reacting double bonds. The presence of these beneficial groups, however, does not always guarantee the success of the reaction.



Similarly, there are also reports, which describe successful medium-ring formation by RCM wherein no such conformationally beneficial factors are present.

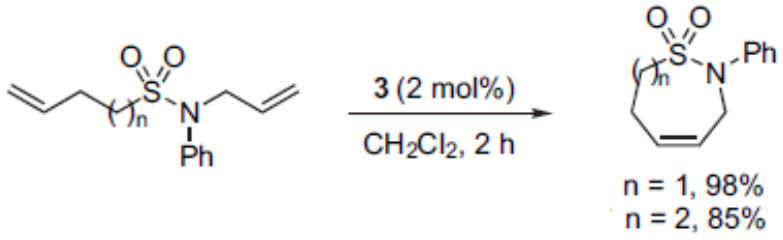
13.18 Formation of medium-ring nitrogen heterocycles by RCM

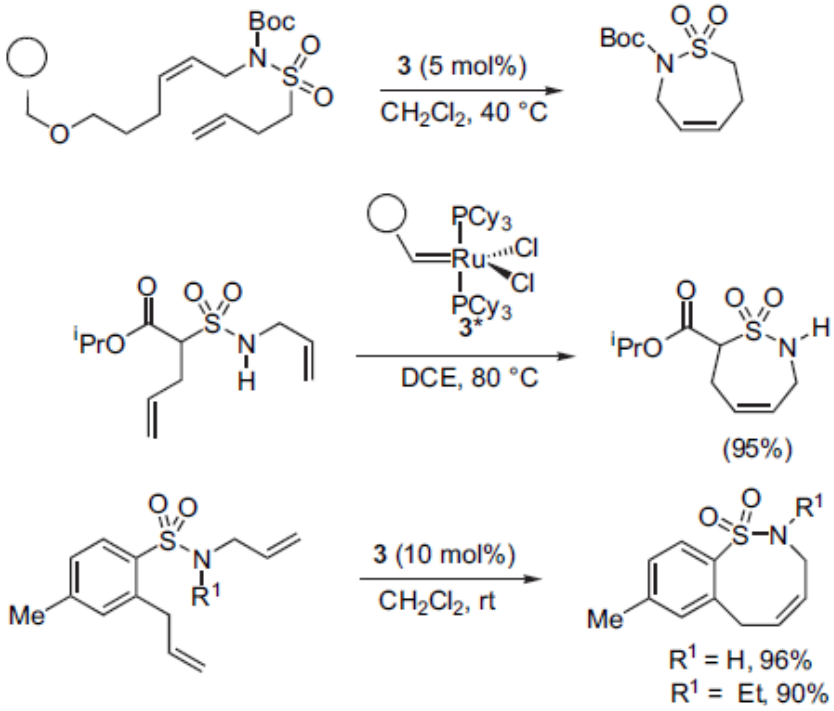
Various nitrogen heterocyclic systems accommodating common to large rings have been conveniently prepared by RCM. These have revealed several general features of RCM of N-tethered dienes of medium-ring azacycle formation.



13.19 Formation of medium-ring sulfur heterocycles by RCM

Although many examples of the synthesis of oxygen and nitrogen containing cyclic molecules by RCM are known, the application of RCM to the synthesis of sulfur-containing medium-ring heterocycles remains very limited. Thus, both the catalysts 2 and 3 were shown to be either unreactive or of low reactivity towards the RCM of α,ψ-dienes containing a sulfide moiety, possibly due to poisoning of the ruthenium catalyst by the sulfide functionality. RCM of substrates containing a sulfonamide group has been well documented





A model for the prediction of the outcome of crossmetathesis reactions has been developed based on the categorization of olefins according to their relative propensity to homodimerize via cross-metathesis and the ability of their homodimers to undergo secondary metathesis. Based on this model, olefinic substrates are divided into four different types. Whether a certain olefin belongs to one type or another depends on the nature of the metathesis catalyst used.

Olefin Type	First-Generation Grubbs Catalysts	Second-Generation Grubbs Catalysts
Type I (facile homodimerization; homodimers are readily consumable)	terminal olefins; allyl silanes; 1° allylic alcohols, ethers, and esters; allyl boronate esters; allyl halides	terminal olefins, 1° allylic alcohols and esters; allyl boronate esters; allyl halides; styrenes (without large ortho substituents); allyl phosphonates; allyl silanes; allyl phosphine oxides; allyl sulfides; protected allylic amines
Type II (more difficult homodimerization; homodimers sparingly consumable)	styrenes; 2° allylic alcohols; vinyl dioxolanes; vinyl boronates	styrenes (with large ortho substituents); acrylates; acrylamides; acrylic acid; acrolein; vinyl ketones; unprotected 3° allylic alcohols; vinyl epoxides; 2° allylic alcohols; perfluorinated alkane olefins
Type III (no homodimerization)	vinyl siloxanes	1,1-disubstituted olefins; non-bulky trisubstituted olefins; vinyl phosphonates; phenyl vinyl sulfone; 4° allylic hydrocarbons; protected 3° allylic alcohols
Type IV (spectator substrates: do not undergo cross-metathesis)	1,1-disubstituted olefins; disubstituted α,β-unsaturated carbonyls; 4° allylic carbon-containing olefins; perfluorinated alkane olefins; protected 3° allylic amines	olefins with vinylic nitro group; protected trisubstituted allylic alcohols

Cross-metatheses between two olefins of Type I yield product mixtures that correspond to statistical distributions. Additionally, reactions between two olefins of the same type
(but not of Type I) give nonselective product mixtures, while reactions between olefins of two different types are selective processes.

13.20 Summary of the unit

The word 'metathesis' describes the interchange of covalent bonds between two molecules. In olefin chemistry, it refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene.

Olefin metathesis has been utilized in four closely related types of reactions, viz.

a) ring-opening metathesis polymerization (ROMP), in which a cyclic olefin is the substrate and a polymer is the product

b) ring-closing metathesis (RCM), in which an acyclic diene is converted into a cyclic olefin;

c) cross-metathesis (CM), in which two different olefins react to form a new product olefin and a by-product as a volatile olefin (usually ethylene) and

d) ring-opening metathesis (ROM), in which a cyclic olefin and an acyclic olefin produce a new acyclic olefin.

Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM), of which both the intramolecular and intermolecular versions are known. Of the above few types, ring-closing metathesis (RCM) has received a great deal of attention from the synthetic organic chemical community and, over the last few years, it has developed as a powerful tool for the synthesis of various carbocyclic and heterocyclic ring systems of different sizes. A large number of catalyst systems have been used to initiate olefin metathesis.

13.21 Key words

Metathesis; Olefin -Metathesis Reaction; Catalysts for olefin-metathesis reaction; Ring Opening Metathesis Polymerization (ROMP) ; Ring Closing Metathesis (RCM); Olefin-Cross Metathesis (CM); Enyne metathesis (EM); Diene Metathesis (ADMET); Polymerization of Acetylenes; Grubbs catalysis; First generation and second generation Grubbs catalysts; NHC-Based second-generation Grubbs catalysts

13.22 References for further studies

1) Olefin Metathesis and Metathesis Polymerization; K. J. Ivin, J. C. Mol; *Academic Press*, **1997**.
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4) Organic Syntheses Based on Name Reactions: a practical guide to 750 transformations; Alfred Hassner, Irishi Namboothiri; *Elsevier*, **2011**.
5) Handbook of Metathesis, Volume 2: Applications in Organic Synthesis; Robert H. Grubbs, Daniel J. O'Leary; *John Wiley & Sons*, **2015**.
6) N-Heterocyclic Carbenes in Transition Metal Catalysis; Frank Glorius; *Springer Science & Business Media*, **2007**.

13.23Questions for self understand

1) What is metathesis?
2) What is Olefin -Metathesis Reaction? Explain with example.
3) Explain the mechanism of olefin-metathesis reaction.
4) Discuss the catalysts used for olefin-metathesis reaction.
5) What are the different types of olefin-metathesis reactions are presently known?
6) What is Ring Opening Metathesis Polymerization (ROMP) reaction? Explain with example.
7) What is Ring Closing Metathesis (RCM)? Explain with example.
8) What is Olefin-Cross Metathesis (CM)? Explain with example.
9) What is Enyne metathesis (EM)? Explain with example.
10) What is Diene Metathesis (ADMET)? Explain with example.
11) What is Polymerization of Acetylenes? Explain with example.
12) Write a note on Grubbs catalysis
13) Discuss the first generation and second generation Grubbs catalysts
14) Discuss the NHC-Based second-generation Grubbs catalysts
15) Explain briefly mechanistic considerations and development of second-generation derivatives
16) Discuss about applications of second-generation Grubbs catalysts in organic synthesis
17) Write a note on followings
    a) Formation of medium-ring oxygen heterocycles by RCM
    b) Formation of medium-ring nitrogen heterocycles by RCM
    c) Formation of medium-ring sulfur heterocycles by RCM

UNIT-14

Structure

14.0 Objectives of the unit

After studying this unit you are able to

- Write the structure of di hydroxylation product
- Write the structure of different ligands used in Sharpless Asymmetric Dihydroxylation reaction
- Explain the the origin of enatnioselectivity in Sharpless asymmetric dihydroxylation reaction
- Draw the empirical rules for predicting the face selectivity in SAD
- Write the structure of product formed in Sharpless Asymmetric Epoxidation reaction
- Explain the application of Sharpless Asymmetric Epoxidation reagent in organic synthesis
- Write the structure of Jacobsen catalyst

14.1 Introduction

The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis. Amongst various syntheses, the enantioselective syntheses of complex natural products containing multiple stereocenters are often the most challenging. The asymmetric catalysis provides a practical, cost effective and efficient synthesis of such molecules. Furthermore, the enantioselective synthesis of natural products by a catalytic process assumes significance since isolation from natural sources can only be accomplished in minute quantities. The use of catalytic methods not only provides an easy access to an enantiomerically pure product but also permitsmaximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogs required for biological activity.

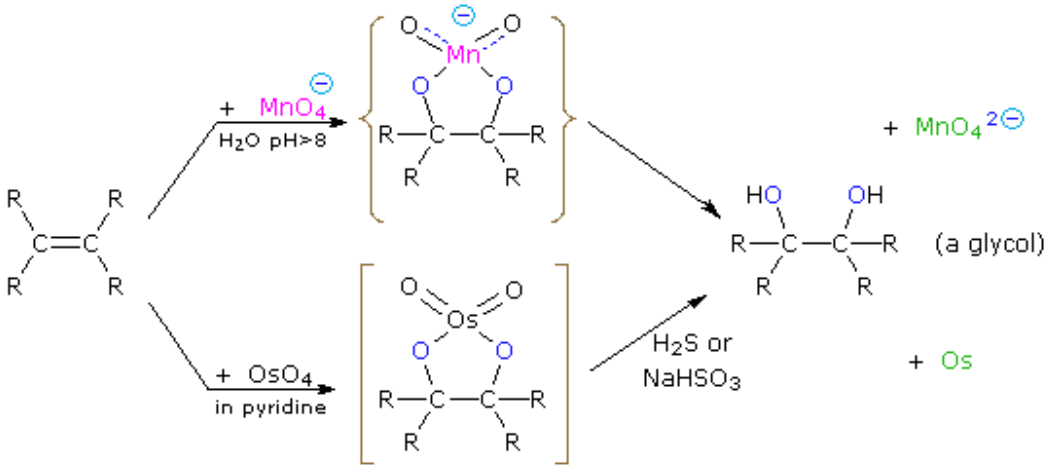
While tremendous advances have been made in asymmetric synthesis, substrate driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. In a kinetic resolution process, one of the enantiomers of the racemic mixture is transformed to the desired product while the other is recovered unchanged.

A verity of functional group transformations for alkenes i,e. the oxidative cyclization, epoxidation, halohydrin formation, dihydroxylation, and aminohydroxylation can be achieved by transition metal-mediated reactions. A common feature in most of these reactions is the phenomenon of ligand acceleration whereas a metal catalyzed process turns over faster in the presence of a coordinating ligand. This causes the reaction to be passed through the ligated pathway with the additional consequence that the ligand may leave its

print on the selectivity determining step. Thus, ligand can influence the chemo-, regio-, and stereoselectivity of the reaction.

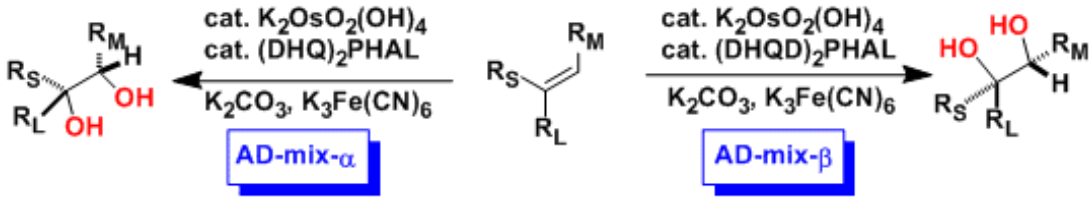
14.2 Di hydroxylation

Dihydroxylation is the process by which an alkene is converted into a vicinal diol. Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism.



Sharpless Asymmetric Dihydroxylation (SAD)

This reaction is a transformation of olefins into syn-diols via an asymmetric cis-dihydroxylation in the presence of a catalytic amount of chiral ligands ($(DHQD)_2PHAL$ or $(DHQ)_2PHAL$) derived from cinchona alkaloids, osmium tetroxide using $K_3Fe(CN)_6$ or NMO as an oxidant and is generally referred to as the Sharpless asymmetric dihydroxylation or Sharpless dihydroxylation.

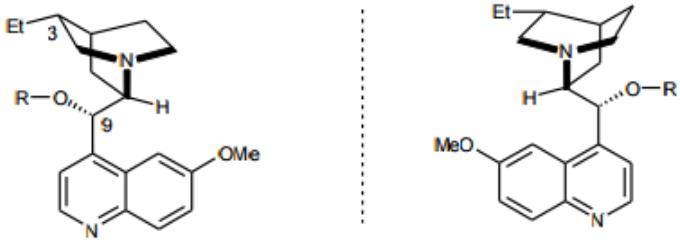


Generally, two reaction systems have been developed for the asymmetric transformation of olefins into syn-diols. The study finds that the reaction is especially suitable for the transformation of electron-rich and sterically less hindered olefins. The Sharpless dihydroxylaton requires an enantiomerically pure molecule to induce the chirality, and many natural chiral molecules (e.g., alkaloids) are suitable for this purpose. Besides the dihydroxylation of olefins, the Sharpless asymmetric dihydroxylation has also been successfully used for the introduction of an α-hydroxyl group adjacent to the carbonyl

functionality, by means of the dihydroxylation of an enol ether. This reaction has a broad application in organic synthesis with respect to the preparation of molecules with syn-diol moieties.

14.3 Ligands used in Sharpless Asymmetric Dihydroxylation

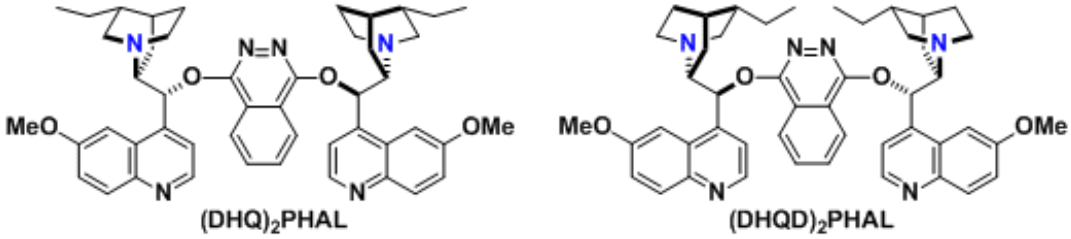
Sharpless and Hentges try to induce enantioselectivity in the osmylation of alkene with chiral pyridine derivatives. But their effort is failed due to the low affinity of the ligand for OsO_4. Later qinuclidine derivatives were used instead of pyridines due to their inherently higher affinity for OsO_4. They found that moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands.



Dihydroquinidine (R = H) DHQD | Dihydroquinine (R = H) DHQ

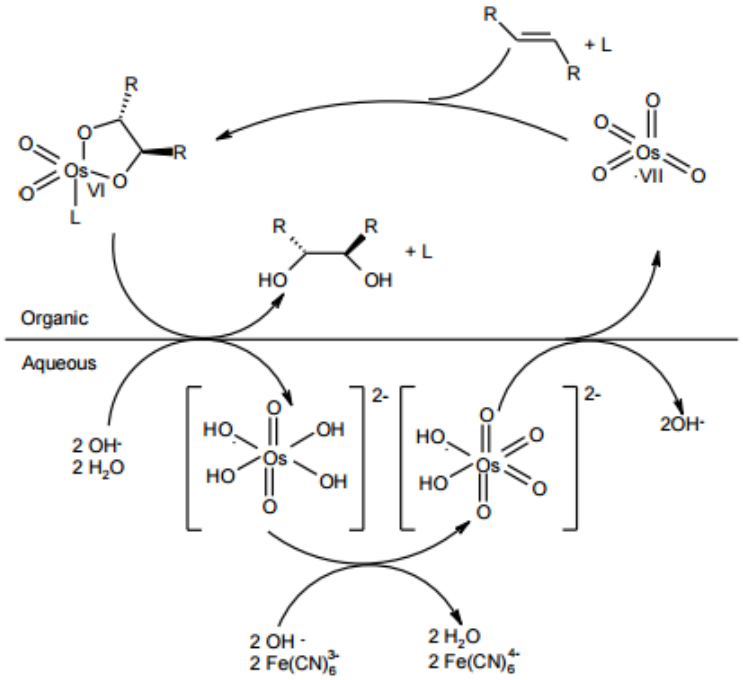
Ligands for AD reaction.

Later they found that PHAL derivatives of DHQ and DHQD are better.



14.4 Mechanism of Sharpless Asymmetric Dihydroxylation

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions. Marko and Sharpless found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was lower than that produced by the stoichiometric reaction. The origin of this discrepancy was due to the presence of a second catalytic cycle which exhibited only low or no enantioselectivity. The participation of second catalytic cycle can be eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer



Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant.

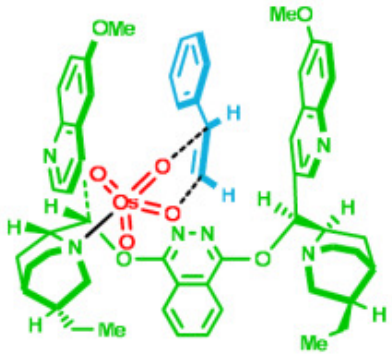
Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented. Sharpless et al. found that the hydrolysis of the osmium (VI) glycolate product might be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial effect on the selectivity. For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

14.5 The origin of enatnioselectivity in Sharpless asymmetric dihydroxylation reaction

The remarkable enatnioselectivity of the Sharpless dihydroxylation is currently best explained by a model which is illustrated for the case of styrene and $(DHQD)_2PHAL$ catalyst by the pretransition state assembly shown in below figure.

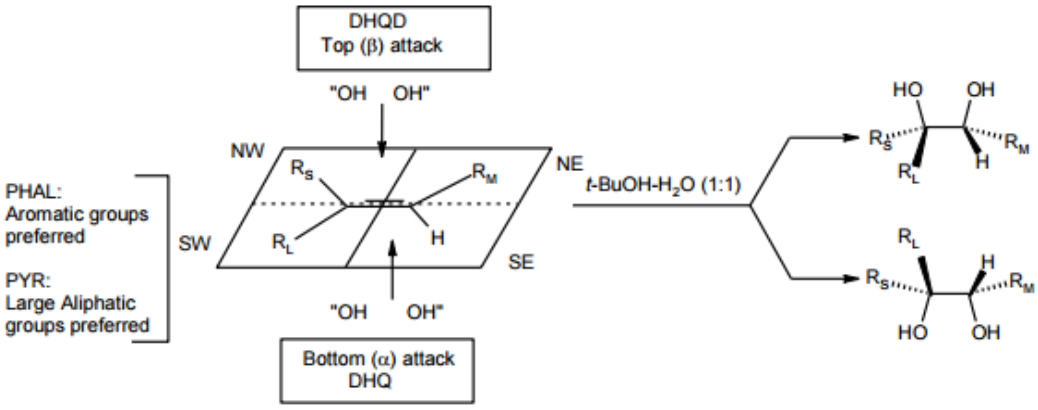
In this model the substrate styrene is held in U-shaped binding region of the catalyst-OsO_4 complex, while one axial and one equatorial oxygen of the OsO_4 subunit attack C=C to form a cyclic osmate ester by [3+2] cycloaddition reaction. The mechanistic model of the

Sharpless dihydroxylation correctly predicts the absolute configuration of the major dihydroxylation product and also provides insights with enantioselectivity.



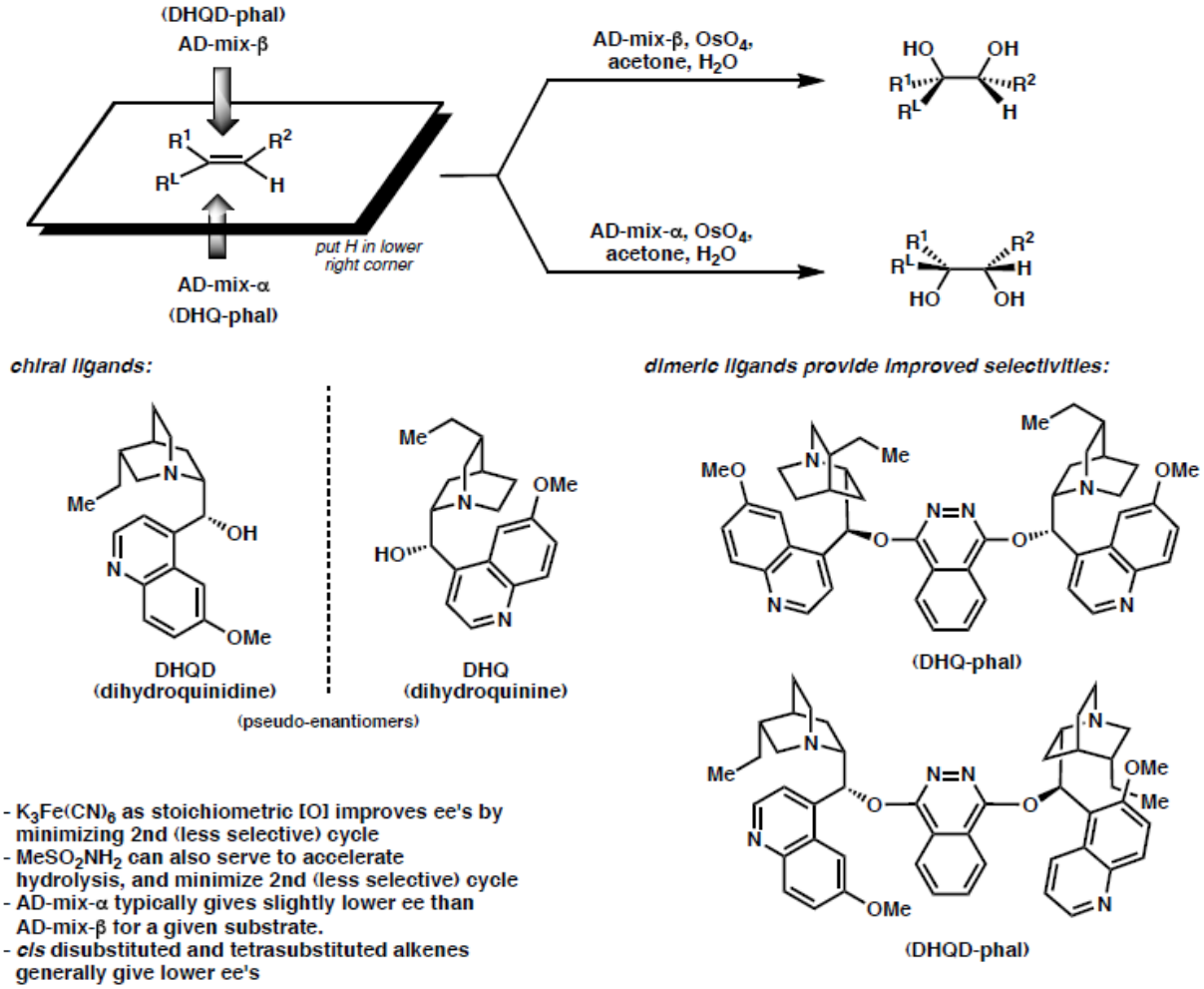
14.6 Empirical rules for predicting the face selectivity in SAD

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device'. The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands. An olefin which is placed into this olefin according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.



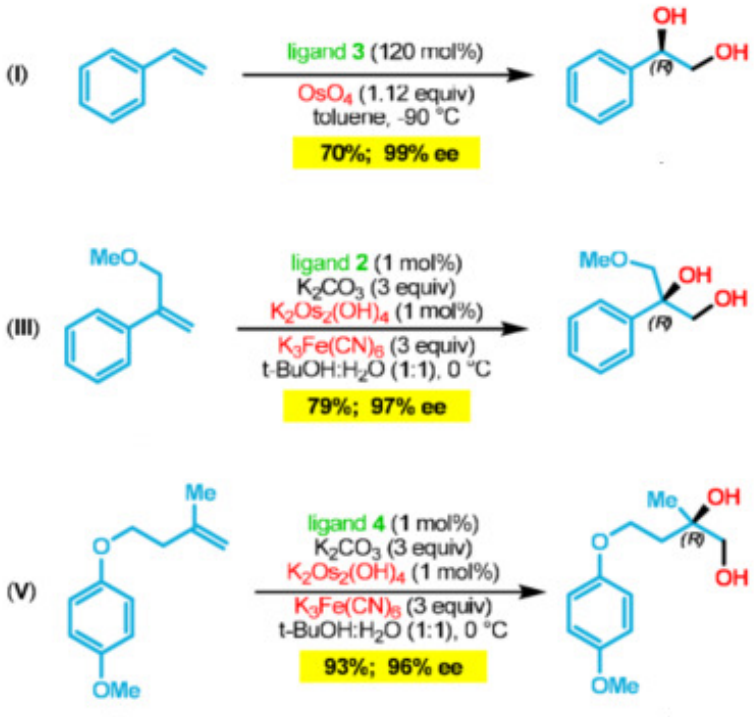
The mnemonic device for predicting the face selectivity.

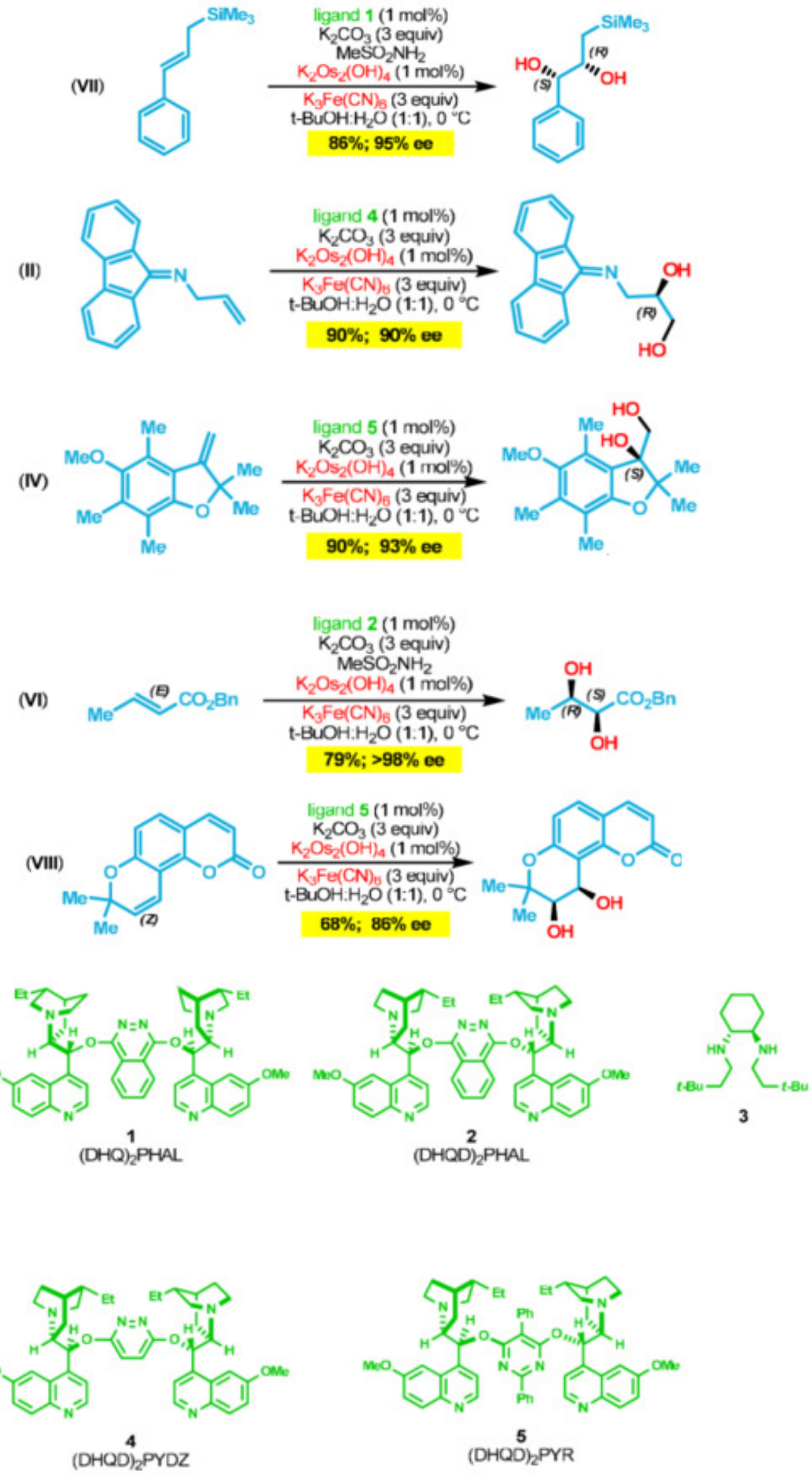
This can also be written as follows



14.7 Application of Sharpless asymmetric di hydroxylation in organic synthesis

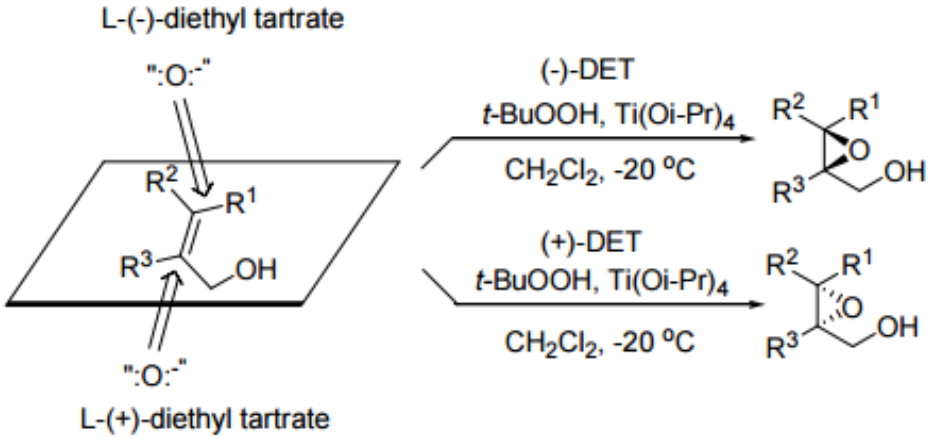
The following reactions demonstrate the potential application of SAD reaction in organic synthesis.




(VII)
SiMe3
ligand 1 (1 mol%)
K2CO3 (3 equiv)
MeSO2NH2
K2Os2(OH)4 (1 mol%)
K3Fe(CN)6 (3 equiv)
t-BuOH:H2O (1:1), 0 °C
86%; 95% ee
HO
OH
(R)
(S)
(II)
ligand 4 (1 mol%)
K2CO3 (3 equiv)
K2Os2(OH)4 (1 mol%)
K3Fe(CN)6 (3 equiv)
t-BuOH:H2O (1:1), 0 °C
90%; 90% ee
N
OH
HO
(IV)
ligand 5 (1 mol%)
K2CO3 (3 equiv)
K2Os2(OH)4 (1 mol%)
K3Fe(CN)6 (3 equiv)
t-BuOH:H2O (1:1), 0 °C
90%; 93% ee
MeO
Me
(VI)
(E)
CO2Bn
ligand 2 (1 mol%)
K2CO3 (3 equiv)
MeSO2NH2
K2Os2(OH)4 (1 mol%)
K3Fe(CN)6 (3 equiv)
t-BuOH:H2O (1:1), 0 °C
79%; >98% ee
(VIII)
(Z)
ligand 5 (1 mol%)
K2CO3 (3 equiv)
K2Os2(OH)4 (1 mol%)
K3Fe(CN)6 (3 equiv)
t-BuOH:H2O (1:1), 0 °C
68%; 86% ee
1
(DHQ)2PHAL
2
(DHQD)2PHAL
3
HN
NH
t-Bu
4
(DHQD)2PYDZ
5
(DHQD)2PYR

14.8 Sharpless Asymmetric Epoxidation

Epoxidation is one of the most useful oxidative transformations of the alkenes. The reagents that have been developed for this process have a high degree of selectivity for the alkenic bond. But epoxidation with high asymmetric induction remains a challenge. Henbest found asymmetric epoxidation using homochiral (enatiomerically pure) percamphoric acid. Asymmetric induction was observed but the enantiomeric excess was a disappointing 8%. Katsuki and Sharpless found that epoxidation of a variety of allylic alcohols in good yield and with an enantiomeric excess (generally greater than 90%) can be done by combination of a titanium (iv) alkoxide, an optically active tartrate ester, and t-Butyl hydroperoxide. In general, the reaction accomplishes the efficient asymmetric synthesis of hydroxymethyl epoxides from allylic alcohols.

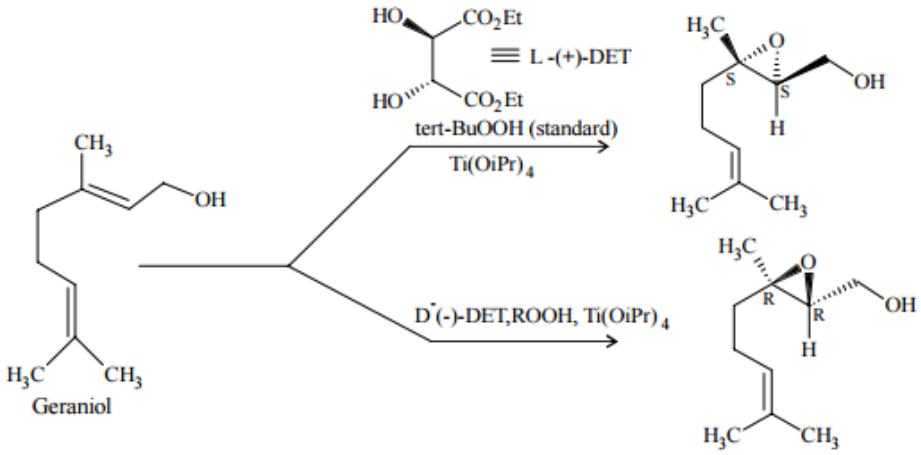


Operationally, the catalyst is prepared by dissolving titanium isopropoxide, diethyl or diisopropyl tartrate (DET or DIPT, respectively), and molecular sieves in DCM at -20 ° C, followed by addition of allylic alcohol or t-BuOOH. After a brief waiting period (presumably to allow the ligand equilibrium to occur on titanium), the final component of the reaction is added.

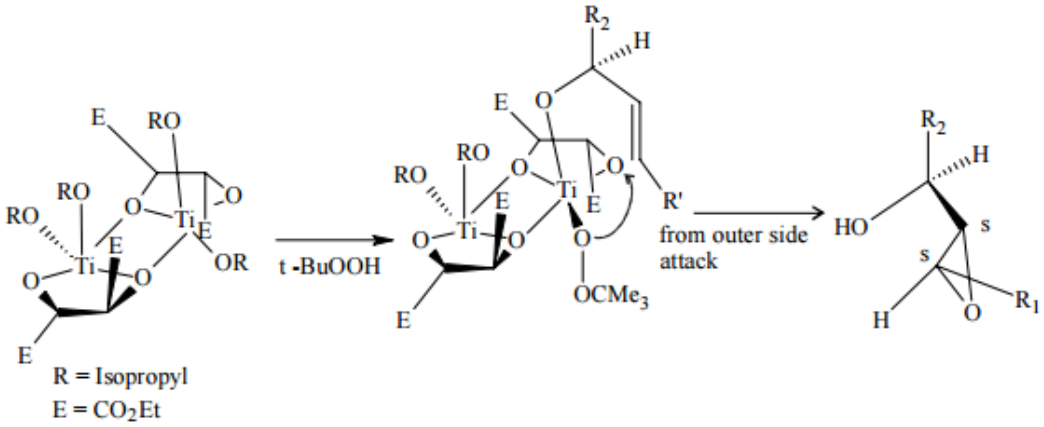
Direction of epoxidation

During enantioselective Sharpless epoxidation of achiral primary allyl alcohols, the direction of the attack of the complexes derived for L-(+) and D- (-) –DET can be remembered with the following mnemonic: L, from lower face; D, doesn't attack from down face.

The oxidation reagent is always a hydroperoxide, which is normally tert- BuOOH and the chiral addition is an enantiomerically pure dialkyl ester of tartaric acid, which is usually the diethyl ester (diethyl tartrate, DET). The reaction is catalyzed by titanium (IV) tetraisopropoxide $Ti(OiPr)_4$. Thus, an achiral primary allylic alcohol geraniol gives either of the enatiomeric epoxides



The mechanism of the reaction is not fully understood but the involvement of the binuclear titanium complex bridged by two tartrate ligands is invoked during this epoxidation reaction. Initially, the tartrate e.g., L(+)DET displaces two isopropoxy groups from the tetraisopropoxide. Further displacement of two more isopropoxy groups by the allylic alcohol e.g. R^1 CH=CHCH$_2$OH and the peroxide sets up the preferred disposition of the alkene and oxidant for the formation of only one of the epoxide enantiomers with a specific DET enantiomer.

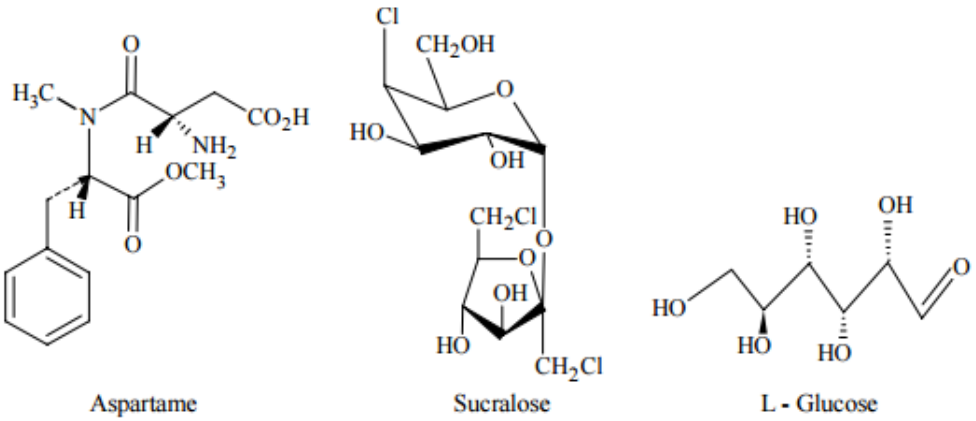


14. 9 Application of the reagent

i) Sweeteners

Sucrose (table sugar) and fructose are the most common natural sweeteners, However, they add to our calorie intake and promote tooth decay. Artificial sweeteners thus became an attractive alternative. One of the widely used artificial sweeteners is aspartame, the methyl ester of a dipeptide formed from phenylalanine and aspartic acid. Aspartame is about 100 times sweeter than sucrose. It however, undergoes slow hydrolysis in solution, decomposes with heat and for these reasons, aspartame cannot be used in soft drinks and for baking. Apart from aspartame, sucralose, the trichloro derivative of sucrose is about 600 times sweeter than sugar and it looks, feels and tastes like sugar. It is stable to heat, for use in baking and it also

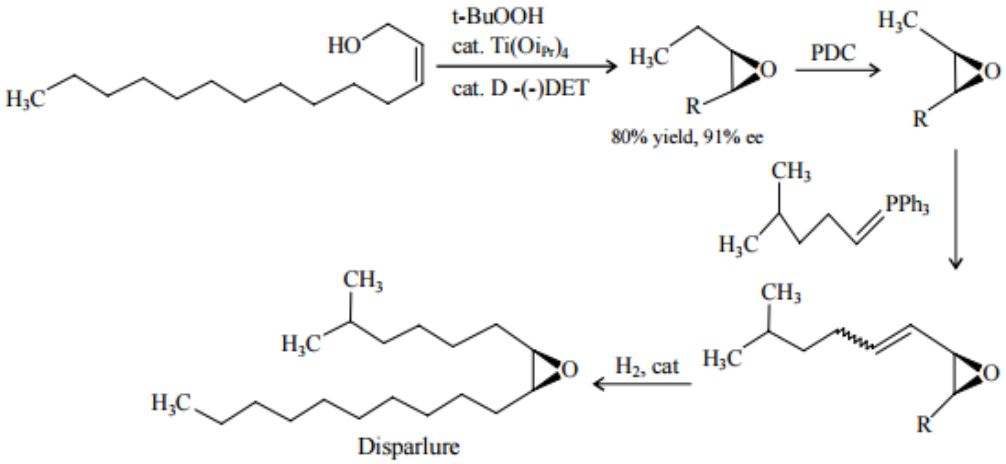
does not cause tooth decay or provide calories. However, much is talked about the prolonged use of these sweeteners as health hazards.



Many other compounds have promise as artificial sweeteners. L-sugars are also sweet and they presumably would provide either zero or very few calories because body enzymes selectively metabolize their enantiomers (the D-sugars). Although sources of L-sugars are rare in nature, all eight L-hexoses have been synthesized by Sharpless et al. by the application of asymmetric epoxidation and other enantioselective synthetic methods. Thus, the proper stereochemistry of an epoxide on reduction can lead to a hydroxyl group with desired stereochemistry in a L-sugar.

ii) Synthesis of other sensitive biologically active compounds

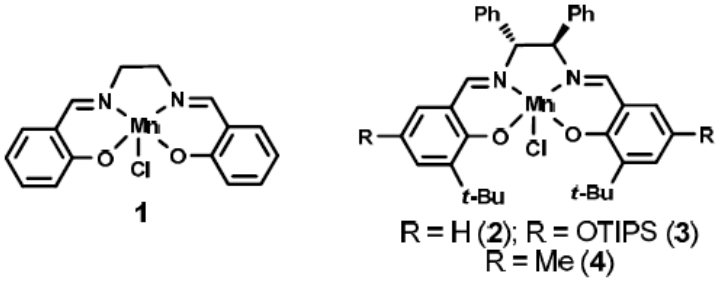
In an industrial process, the American Company, J. T. Baker, employs this process to make synthetic disparlure, which is the pheromone of the gypsy moth.



14.10 Jacobsen catalyst

Kochi's report in 1986 that the (salen)Mn(III) complex 1 catalyzes the efficient epoxidation of olefins by iodosyl benzene (PhIO) led to Jacobsen's finding in 1990 that this reaction is fairly enantioselective (33-93% ee) if the ethylenediamine part of the ligand is replaced by (S,S)- or (R,R)-1,2-diphenyldiaminoethane, and if the positions ortho to the phenolic

hydroxyl carry a bulky group, as in the (R,R)- complex 2. Further improvements included the use of the related catalyst 3, and NaOCl as the terminal oxidant.

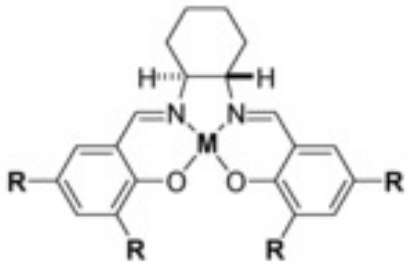


1

R = H (2); R = OTIPS (3)
R = Me (4)

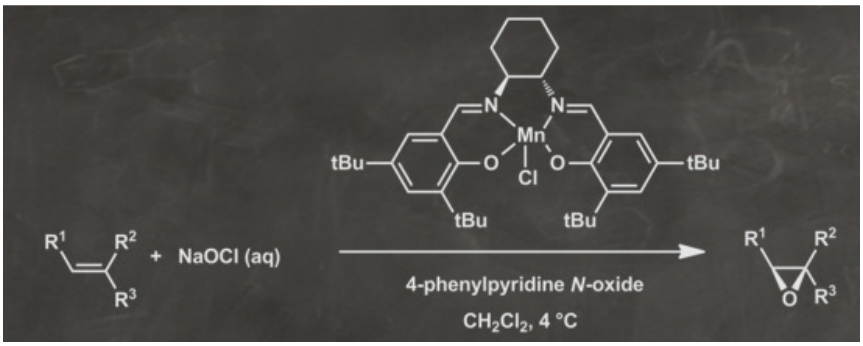
The catalyst 2 is referred as Jacobsen (salen)Mn(III) catalyst.

This catalyst is composed of a large organic ligand complexed to manganease. This type of organic ligand is referred as a "salen". Jacobsen demonstrated that salen metal complex can be used catalytically to achieve high enantiomeric excess in one specific reaction. He has shown that the same ligand set can be used in several completely different transformations. This was accomplished simply by utilizing different transition metals, M, and aryl substituents, R, in the catalyst. The general structural feature of Jacobsen catalyst is given below.



14.11 Enantioselective epoxidation using JacobsenMn(III) catalyst

Jacobsen discovered that manganese complexes of chiral salen ligands catalyze enantioselective epoxidations. Through refinement of the catalyst design and the epoxidation method, we identified the first practical catalysts for the asymmetric epoxidation of simple olefins.



The Jacobsen epoxidation has been applied to the enantioselective epoxidation of mono-, di-, tri- and tetrasubstituted olefins and to unsymmetrical (Z)- disubstituted olefins with good

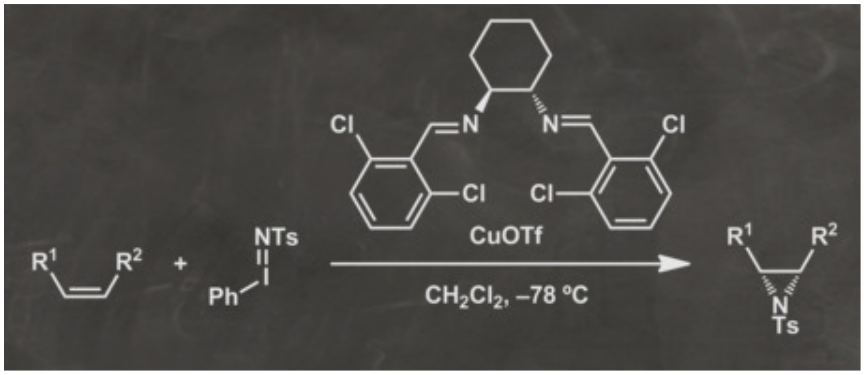
results. However, the epoxidation of (E)-disubstituted alkenes is usually only poorly enantioselective.

The Jacobsen epoxidation takes place with higher yield and enantioselectivity if the olefinic bond is conjugated with a π-system. The rate of the epoxidation, the yield and the enantioselectivity can be affected by the use of various additives, for example pyridine N-oxide, which may imply that a hexacoordinate oxomanganese(V) species is the effective epoxidation reagent, possibly with C2-symmetric, canted, non-planar six-membered chelate rings.

14.12 Catalytic asymmetric aziridination of alkenes

Jacobsen also reported the selective transfer of nitrogen-centered oxidants to organic substrates and he discovered one of the first systems for highly enantioselective catalytic aziridination of alkenes. The most notable feature of the chiral catalysts used for this transformation is their simplicity and accessibility. This work led to useful methods for the synthesis of interesting unnatural amino acid derivatives, and mechanistic studies provided important insights into the fundamental mechanisms of nitrene transfer.

Jacobson demonstrated the catalytic aziridination of olefins with fair to good enantioselectivities with nitrene source such as TsN=IPh, TsN_3 and the chiral catalyst catalyst as shown below

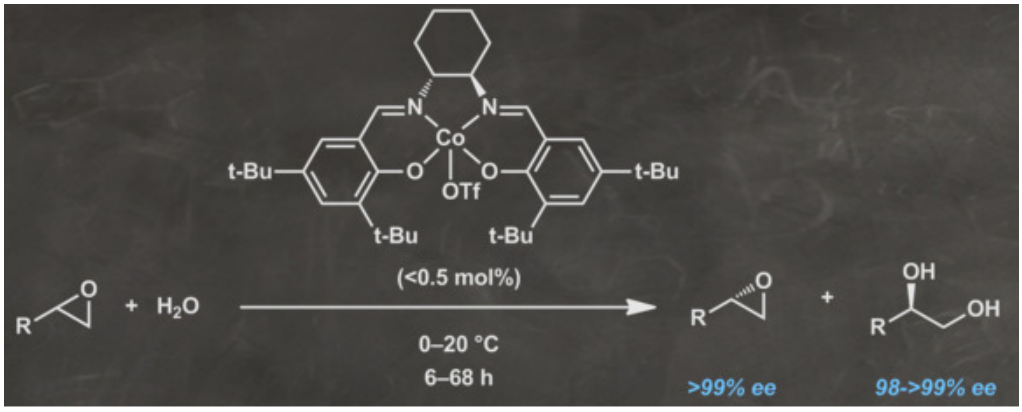


14.13 Desymmetrizations of meso epoxides

Using chromium salen-based catalyst system Jacobsen discovered highly effective desymmetrizations of meso epoxides. the catalysts are completely recyclable and can effect ring-opening reactions cleanly, and in the absence of any solvent. As such, the reactions produce no waste whatsoever.

He then extended the epoxide ring-opening chemistry to the highly efficient hydrolytic kinetic resolution of terminal epoxides. Under the influence of low loadings of chiral (salen)cobalt complexes, racemic epoxides such as propylene oxide, epichlorohydrin, and butadiene monoepoxide can be resolved by ring-opening with nucleophiles such as water with nearly perfect (>250:1) stereoselectivity. This methodology has allowed access to a wide

range of valuable epoxides inexpensively in optically pure form and has accordingly had a major impact on organic synthesis. Within just a few years of its discovery, the hydrolytic kinetic resolution (HKR) was applied to the commercial synthesis of several enantiomerically pure epoxides including propylene oxide and epichlorohydrin on multi-ton scale. Laboratory applications of the HKR to synthesis of a wide range of biologically important targets of varying complexity have also emerged



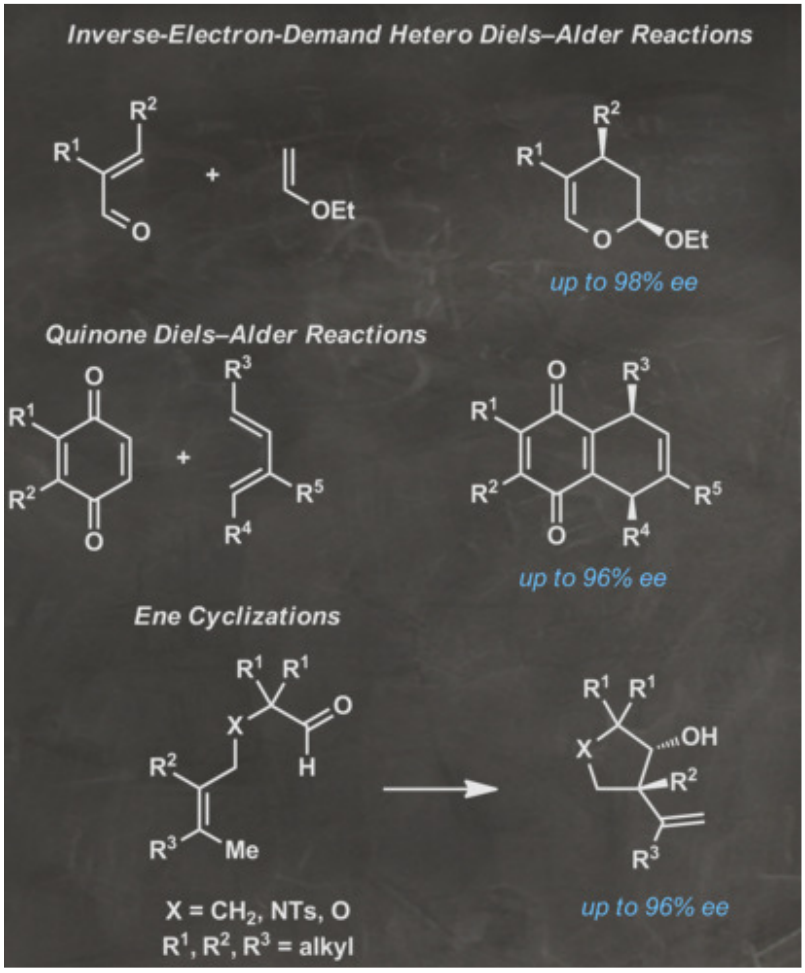
Epoxides are the versatile building blocks extensively used in the synthesis of complex organic compounds. They are used as valuable intermediates, and this has further expanded with the advent of asymmetric catalytic methods for their synthesis. The terminal epoxides are a most important subclass of these compounds, but no general and practical methods were available for their synthesis in enantiomerically pure form. Hydrolytic kinetic resolution (HKR) developed by Jacobsen has emerged in recent times as a powerful tool to synthesize both terminal epoxides and their corresponding diols in highly enantiomerically pure form.2 The process uses water as the only reagent, no added solvent, and low loading of recyclable chiral cobalt-based salen complexes to afford the terminal epoxides and 1,2-diol in high yield and high enantiomeric excess.

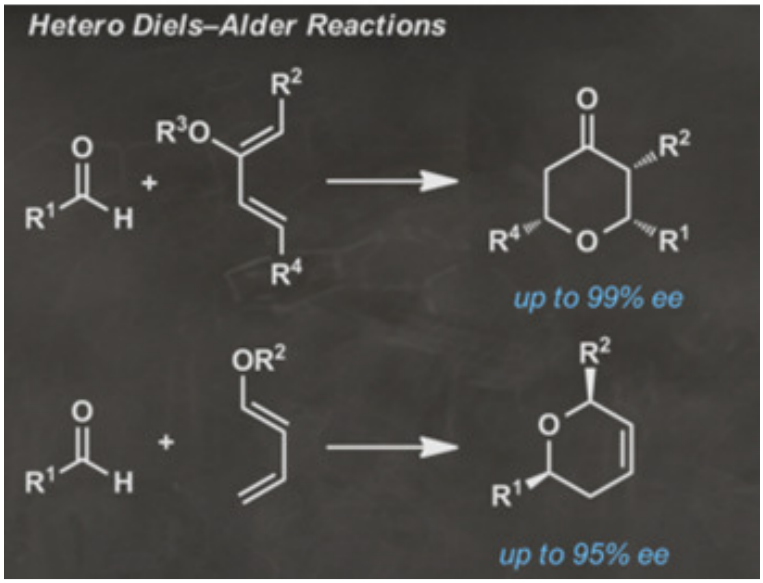
A racemic mixture of an epoxide is treated with water and a catalytic amount of the salen(Co) catalyst 1, one of the epoxide enantiomers reacts much more rapidly than the other . Thus, the product produced is predominantly one enantiomer, and the unreacted epoxide left behind is predominantly one enantiomer.

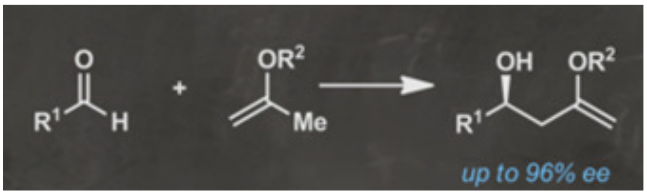
14.14 Enantioselective catalytic cycloaddition

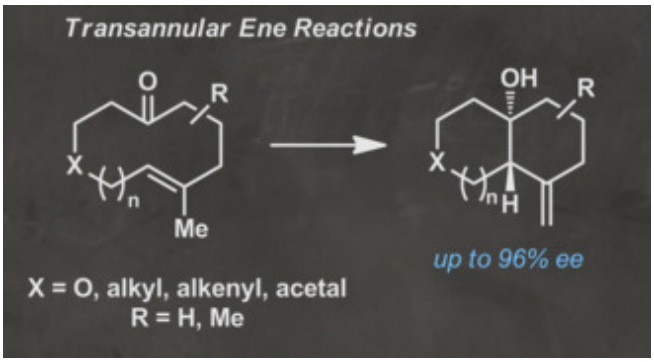
Jacobsen demonstrated the enantioselective catalytic cycloaddition of simple aldehydes or quinone derivatives with moderately nucleophilic dienes and alkenes using novel chromium Schiff base complexes. Hetero-Diels–Alder reactions between aldehydes and dienes bearing a single electron-donating substitutent afford dihydropyranyl products with up to 3 stereogenic centers in nearly perfect diastereoselectivities and high ee's. The same chromium catalysts

promote inverse-electron-demand Diels–Alder reactions with unsaturated aldehydes. Electron-rich alkenes are induced to undergo enantioselective ene reactions with simple aldehydes in intermolecular, intramolecular, and tranannular settings. These reactions have proven broadly useful in natural products synthesis. Perhaps more significant, the chromium catalysts represent a new class of chiral Lewis acids.



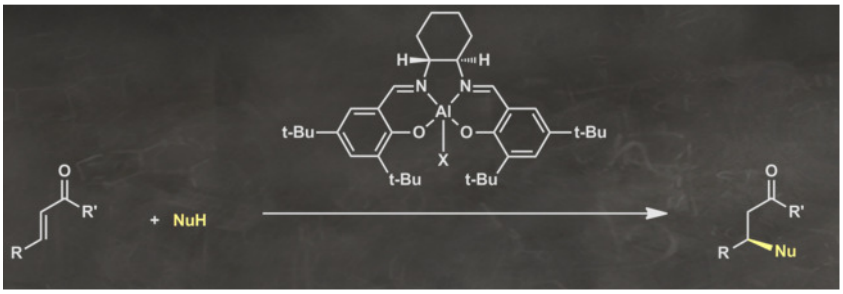


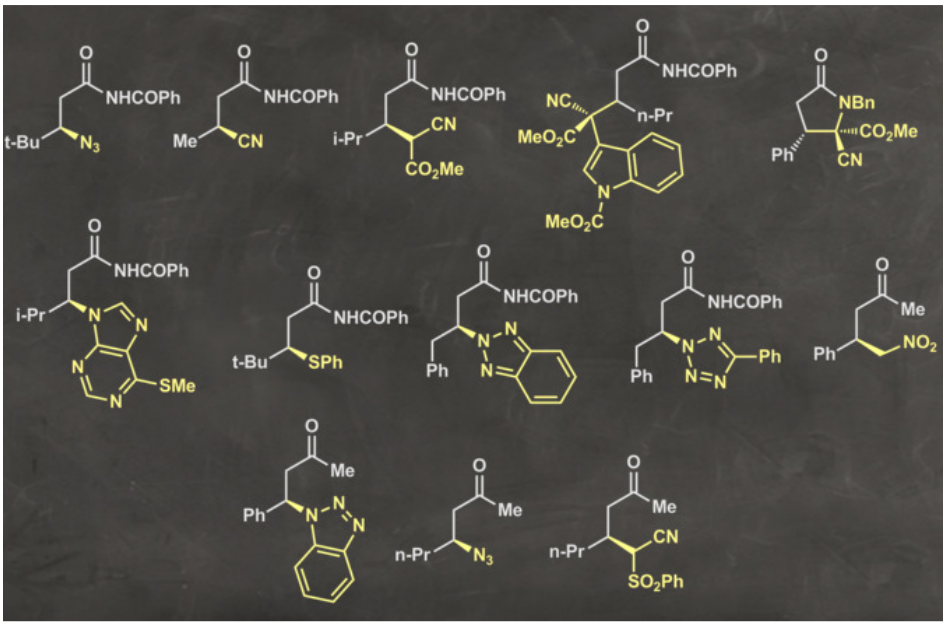




14.16 Conjugate Addition Catalysts

Jacobsen have discovered that (salen)Al(III) complexes catalyze highly enantioselective conjugate additions of mildly basic nucleophiles to α,β-unsaturated imides and ketones. Remarkable generality is displayed in this chemistry with regard to both nucleophile and electrophile partners, and as a result this methodology has broad synthetic utility. Kinetic and mechanistic studies on these transformations have revealed that these reactions represent an important example of bimetallic cooperative activation.





14.17 Summary of the unit

Jacobsen's salen(M) catalyst catalysts are able to promote reactions that produce mostly one enantiomer of a molecule, or alternatively react with only one enantiomer in a racemic mixture. di-t-butyl substituted chiral manganese salen complexes catalyse the efficient asymmetric epoxidation of Z-olefins with good selectivities; the reaction is poor for terminal (low selectivity), E- or trisubstituted olefins (low reactivity).

The success of Mn catalyst in the epoxidation of unfunctionalized olefins led Jacobsen to investigate the use of chiral (salen)metal complexes in other transformations. There are a number of related Jacobsen's salen(Mn) catalyst catalysts in which the cobalt is replaced with another metal, for example, Mn, Al, or Cr.

He first reported the enantioselective aziridination of alkenes using (salen)Cu complexes. This was followed by the discovery that chromium complexes catalyzed the enantioselective opening of meso epoxides with azide. The kinetic and dynamic resolution of certain terminal epoxides was soon added to the repertoire of azide opening reactions. This was significant based on the fact that alkyl terminal epoxides are poor substrates for epoxidation and this resolution protocol furnishes terminal epoxides in high ee.

14.18 Key words

Di hydroxylation

Sharpless Asymmetric Dihydroxylation; Sharpless Asymmetric Epoxidation; Jacobsen catalyst; Enantioselective epoxidation using JacobsenMn(III) catalyst; Catalytic asymmetric aziridination of alkenes; Desymmetrizations of meso epoxides; Enantioselective catalytic cycloaddition; Conjugate Addition Catalysts

14.19 References for further studies

1) Enantioselective Chemical Synthesis: Methods, Logic, and Practice; Elias J. Corey, Laszlo Kurti; *Elsevier*, **2013**.
2) Strategic Applications of Named Reactions in Organic Synthesis; Laszlo Kurti, Barbara Czako; *Elsevier,* **2005**.
3) Catalytic Asymmetric Synthesis; Iwao Ojima; *John Wiley & Sons*, **2004**.
4) Privileged Chiral Ligands and Catalysts; Qi-Lin Zhou; *John Wiley & Sons*, **2011**.
5) Organic Synthesis; Michael B Smith; *Academic Press*, **2011**.

14.20 Questions for self understanding

1) What is di-hydroxylation reaction? What are the different reagents used for alkene dihydroxylation reaction?

2) What are the ligands used in Sharpless Asymmetric Dihydroxylation reaction?

3) Discuss the mechanism of Sharpless Asymmetric Dihydroxylation reaction.

4) Explain briefly the origin of enatnioselectivity in Sharpless asymmetric dihydroxylation reaction.

5) Write a note on empirical rules for predicting the face selectivity in SAD

6) Discuss the application of Sharpless asymmetric di hydroxylation in organic synthesis.

7) What are the reagents and ligads used in Sharpless Asymmetric Epoxidation

8) A Discuss the application of Sharpless Asymmetric Epoxidation reaction in organic synthesis.

9) Write the structure of Jacobsen catalyst.

10) Explain the enantioselective epoxidation of alkenes using JacobsenMn(III) catalyst.

11) Explain the catalytic asymmetric aziridination of alkenes.

12) Explain the desymmetrizations of meso epoxides JacobsenCo(II) catalyst.

13) Explain the enantioselective catalytic cycloaddition using Jacobsen catalyst.

14) Explain the conjugate addition catalysts developed by Jacobsen.

UNIT-15

Structure

15.0 Objectives of the unit

After studying this unit you are able to

- Explain the meaning of organic synthesis
- Write the necessary steps followed in practice of synthesis
- Write the Retrosynthesis scheme of given molecule by making a disconnection
- Write the scheme for synthesis of given molecule by direct Associative Approach
- Write the scheme for synthesis of given molecule by disconnection approach
- Identify the Reagent or synthetic equivalent for different functional group transformations

15.1 Introduction

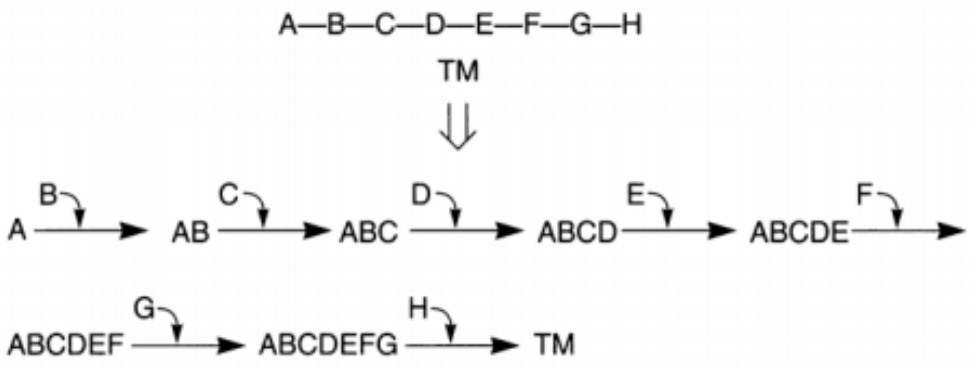
The problem in every organic synthesis actually begins at the end of the synthesis of a target molecule. The major goal of organic synthesis is design a reasonable synthetic path that affords the target molecule as the major product. In the interest of saving both time and money, an ideal synthesis should include readily available starting materials and will be as efficient as possible. The planning of a synthesis involves imagining the possible reactions that could give the desired target molecule. This process is called a retrosynthesis or a retrosynthetic analysis of a target molecule. A special arrow (⇒) is used to denote a retrosynthetic step. The ⇒ arrow leading away from the target molecule represents the "What starting materials could I use to make this product?" and points to an answer to that question. The analysis begins by identifying a functional group (FG) present on the target molecule and recalling the various reactions that are known to give products containing that functional group (or pattern of FGs). The process is continued by analyzing the functional groups in the proposed starting material and doing another retrosynthetic step, continuing to work backwards toward simple, commercially available starting materials. Once the retrosynthetic analysis is complete, then the forward multistep synthesis can be evaluated, beginning with the proposed starting materials and treating them with the necessary reagents to eventually transform them into the desired target molecule.

15.2 Organic synthesis

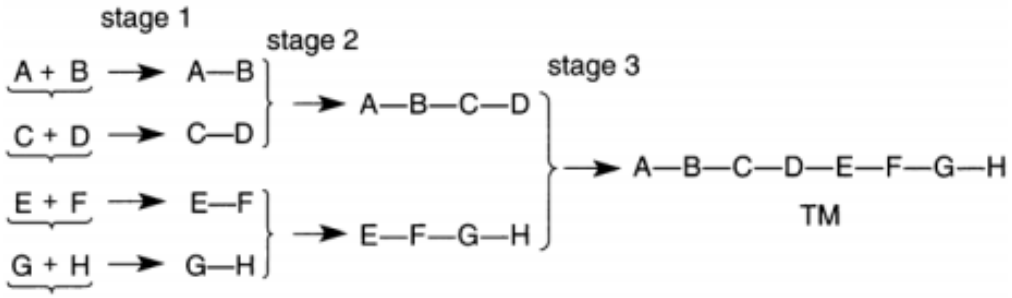
The preparation of a desired organic compound from readily available starting materials can be defined as organic synthesis. The construction of a specific molecule by a single chemical step from constituent fragments is only rarely possible, even for simple structures. Efficient synthesis, therefore, requires multistep construction, using at each stage chemical reactions that (ideally) lead specifically to a single structure.

Linear and Convergent Syntheses

In a linear synthetic scheme, the hypothetical TM is assembled in a stepwise manner. If 80% yield is obtained in each step, 21% (0.87 x 100) overall yield of product can be isolated after 7 steps. If 70%, only 8% overall yield.



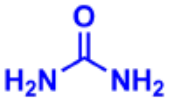
Convergent synthesis should be considered in which two or more fragments of the TM are prepared separately and then joined at the latest-possible stage of the synthesis. Only three stages are involved in the convergent strategy, with overall yield of 51% (0.83 x 100).Another important consideration in choosing a convergent protocol is that failure of a single step in a multistep synthesis does not nulify the chosen synthetic approach as whole, whereas failure of a single step in a linear scheme may require a revision of the whole plan.



15.3 History of organic synthesis

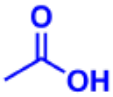
The birth of total synthesis occurred in 19th century. In 1828, the first synthesis reported was by Wohler he synthesize urea from ammonia and carbon monoxide. In 1845, Kolbe coined the word synthesis. The most spectacular synthesis of 19th century was Glucose. Since then there are several outstanding synthesis of organic molecules are reported.

In early days only simple targets were considered for synthesis. These targets were synthesized by often starting with compounds which are closely related to products. These became impractical when the targets became more complex. To tackle this, higher level of intellectual planning, better understanding of reaction mechanisms, working knowledge of reliable reactions, proper understanding of stereochemistry and conformational analysis and skills are required.



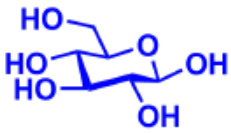
urea

Wohler, 1828



acetic acid

Kolbe, 1845



glucose

Fischer,1890

Also use of new spectroscopic methods makes synthesis simple and faster. The introduction of new technique "Retrosynthetic Analysis" helped a lot in achieving the synthesis of complex target molecules

15.4 Practice of Synthesis

It involves two stages they are

i) Analysis and

ii) Synthesis

Analysis

Analysis of molecules which is considered for synthesis include following steps

- Selecting the target molecule
- Identifying the functional groups/strategic bonds in the molecule
- Disconnection of bonds using known and reliable reactions
- Repeating the disconnection as necessary to reach starting materials and
- Evaluating all the pathways and choose the most attractive and less complicated route

Advantages of analysis lead to chose readily available and inexpensive starting materials and efficient synthetic reactions. It also helps to decide the convenient reaction conditions and flexibility of modification in case of pitfalls. Sometimes analysis provides the advantages of synthesis of analogues of target molecule in quick and elegant route.

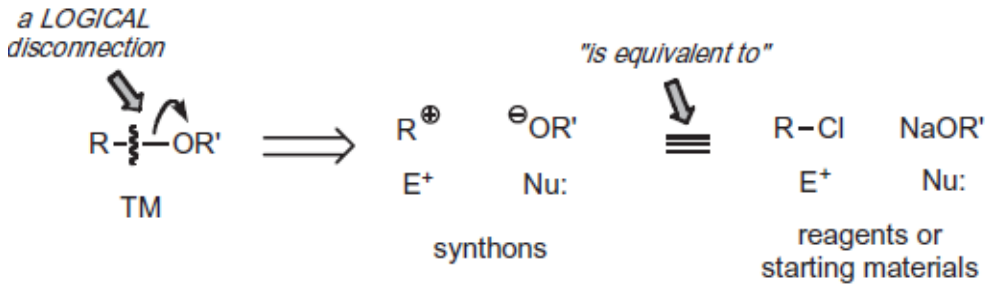
15.5 Design and Execution of Synthesis

Before starting the synthesis of target molecule it is important to write all the possible retrosynthetic pathways and evaluate all the pathways and then go ahead with the most attractive one. Collection of all the relevant literature works, procure of required chemicals is must. Once all these are done then execute the synthesis. If unexpected failure of plan at particular step then modify the plan according to unexpected failures

15.6 Retrosynthesis by making a disconnection

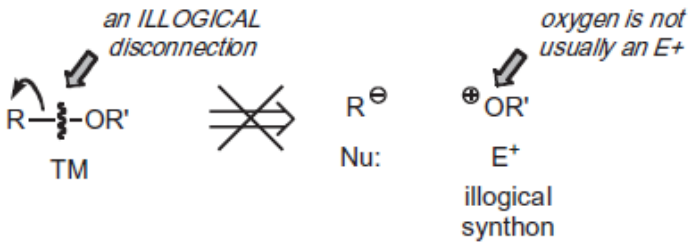
A functional group (or pattern of functional groups) may also be created while doing carbon–carbon sigma bond forming reaction that. In this case, the retrosynthesis involves the disconnection of bond at the position where functional group is present . In a typical carbon–carbon bond-forming reaction, one of the starting material carbons must have been a

nucleophile (Nu^-, electron-rich), and the other must have been an electrophile (E^+, electron-deficient). The pairing of appropriate nucleophiles and electrophiles serves as an important foundation to the logic of organic synthesis, and such strategies will solve a wide variety of synthetic problems. Therefore, the disconnection of the carbon–carbon bond is made heterolytically to give an anion (nucleophile) and a cation (electrophile). These imaginary fragments, called "synthons," are then converted into reasonable starting materials. By familiar with common nucleophiles and electrophiles, one can make logical disconnections. Below example illustrate the logical disconnection of an ether target molecule, affording recognizable alkyl halide E^+ and alkoxide Nu^- starting materials.



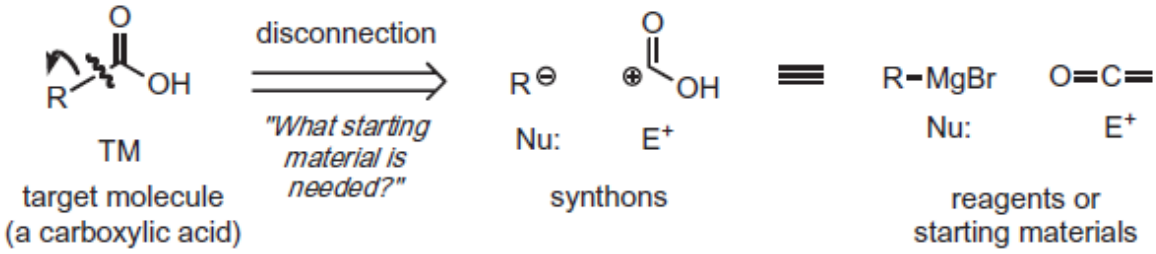
A Logical Disconnection of a Target Molecule

Disconnecting that same carbon–oxygen bond in the other direction (with both electrons going to the carbon) would be an illogical disconnection, since it leads to an electrophilic oxygen synthon for which there is no reasonable equivalent reagent.



An Illogical Disconnection of a Target Molecule

For example, let consider the syntheses of a carboxylic acid target molecule. In the earlier discussion we have seen that a carboxylic acid can be prepared by an FGI if the carbon chain is already in place, but it is also possible to create new carbon–carbon bonds in a carboxylic acid synthesis. Just recall the reaction of a Grignard reagent with carbon dioxide generates a carboxylic acid functional group, so this presents a possible disconnection for the target molecule's retrosynthesis. The logical disconnection is the one that moves the electrons away from the carbonyl, giving reasonable synthons and recognizable starting materials (RMgBr Nu: and CO_2 E^+).



Retrosynthesis via Disconnection of a Target Molecule

The common question which all organic have encountered and try to find answer is that "What Makes a Good Synthesis?"There will be more than one possible synthesis of a desired target molecule hence how can we determine which synthesis is best? This depends on many factors, but there are some general rules that can help to devise a good plan for synthesis they are

1. Start with reasonable starting materials and reagents

A good synthesis begins with commercially available starting materials. Most of these starting materials will have a small number of functional groups (just one or two), although some complex natural products are readily available and inexpensive (e.g., sugars and amino acids). A quick check in any chemical supplier catalog can confirm whether a starting material is ordinary (i.e., available and inexpensive) or exotic (i.e., expensive or not listed).

2. Propose a reaction with a reasonable reaction mechanism

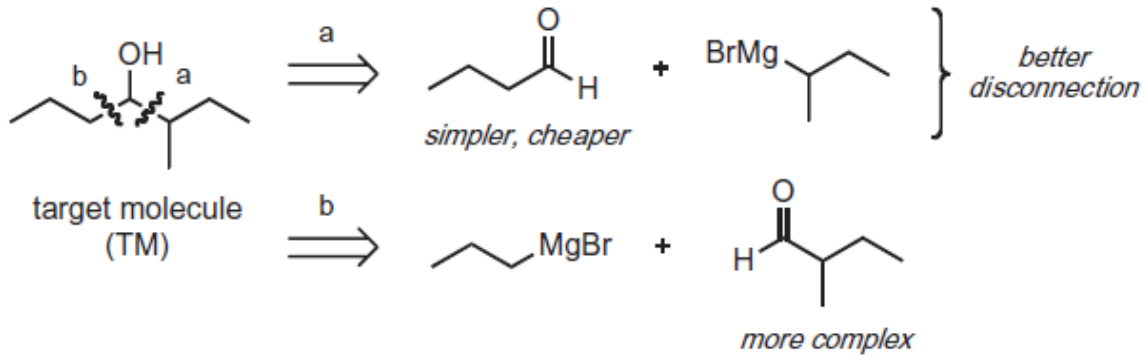
Look for familiar nucleophiles and electrophiles to undergo predictable reactions. A poor choice for a bond disconnection can lead to impossible synthons (and impossible reagents). However, we will learn that certain seemingly impossible synthons are, in fact, possible with the use of synthetic equivalents.

3. Strive for disconnections that lead to the greatest simplification

It is bad practice to put together a 10-carbon target molecule one carbon at a time (an example of a linear synthesis). Remember, the synthetic schemes drawn on paper represent reactions that will be performed in the lab. we should recognize that the more steps in a reaction sequence, the lower the overall yield of product will be. Starting with a nine-carbon starting material, which is nearly as big and possibly as complicated as a 10-carbon target molecule, also would not be a good synthesis.

The most efficient synthesis would be one that links together two five-carbon structures, or perhaps one that combines a four-carbon with a six-carbon compound (described as a convergent synthesis). The more nearly equal the resulting pieces, the better the bond disconnection. One useful strategy is to look for branch points in a target molecule for good places to make a disconnection. In the example below, the starting materials resulting from

disconnection “a” are not only more simple molecules, but also the butanal starting material (butyraldehyde) is one-tenth the price of the aldehyde in disconnection “b” (2-methylbutyraldehyde).



Good Disconnections Lead to Simple, Inexpensive Starting Materials

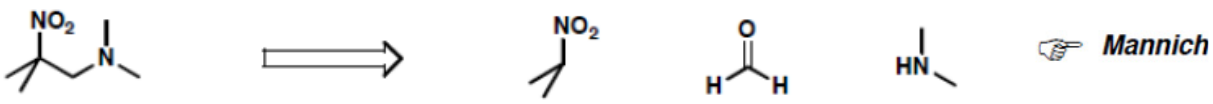
is “one size fits all” approach fails in complex synthetic targets containing a wide variety of functional groups. The molecule as a whole must tolerate the reaction conditions used in the various steps and side reactions with other functional groups should be kept to a minimum.

This fact can be illustrated by following example. Chromic acid oxidation ($Na_2Cr_2O_7$, H_2SO_4) of a 2° alcohol to give a ketone would not be useful if the starting material contains any functional groups that are sensitive to acidic conditions. In such a case, the Swern oxidation might be preferred (DMSO, ClCOCOCl, Et_3N).

New reagents, catalysts, and methods are continuously being developed, with goals of having better selectivity, better tolerance for certain functional groups, being more efficient and/or less expensive, and so on.

15.7 Direct Associative Approach

In the direct associative approach the chemist directly recognizes within the structure of the target molecule a number of readily available structural subunits, which can be properly joined by using standard familiar reactions.



15.8 Disconnection approach

Disconnection means the formal reverse of a bond forming reaction (cleavage of a bond to break the target into two possible starting materials)

There are many thousands of transforms potentially useful in retrosynthetic analysis. They can be classified as follows

i) Functional group interconversion: FGI

ii) Functional group addition: FGA

iii) Functional group removal: FGR

When we disconnect a bond in the target molecule, we are imagining a pair of charged fragments that we could stick together to make the molecule we want. These imaginary charged species are called synthons.

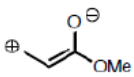
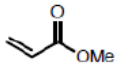
Thus *synthons are idealized (often charged) molecular fragments resulting from a disconnection*. Synthons are of two types they are

i) d_n synthon and

ii) synthon

$d_n$synthon are functionalized nucleophile here d, denotes donor, and n defines the distance between the FG and the reactive centre. Similarly a_n synthon are functionalized electrophile and a, denotes acceptor.

Examples for d_n and a_n synthons are listed below

Synthons "d"				*Synthons "a"*			
Type	*Exemple*	*Reacting materials*	*Functional group*	*Type*	*Exemple*	*Reacting materials*	*Functional group*
d^0	$MeS^{\ominus}$	MeSH		a^0	$^{\oplus}PMe_2$	$ClPMe_2$	
d^1	$^{\ominus}C{\equiv}N$	$KC{\equiv}N$	—C≡N	a^1			—CO—
d^2	$^{\ominus}CH_2CHO$	CH_3CHO	—CHO	a^2			—CO—
d^3	$^{\ominus}C{\equiv}C{-}COOMe$	$HC{\equiv}C{-}COOMe$	$—CO_2Me$	a^3			—COOMe
Alkyl-d	$Me^{\ominus}$	MeLi		Alkyl-a	$Me^{\oplus}$	MeI	

15.9 Reagent or synthetic equivalent

A chemical with polarity that matches the synthon, are called synthetic equivalent of the synthon.Synthetic equivalent is a chemical compound used in practice for a synthon.

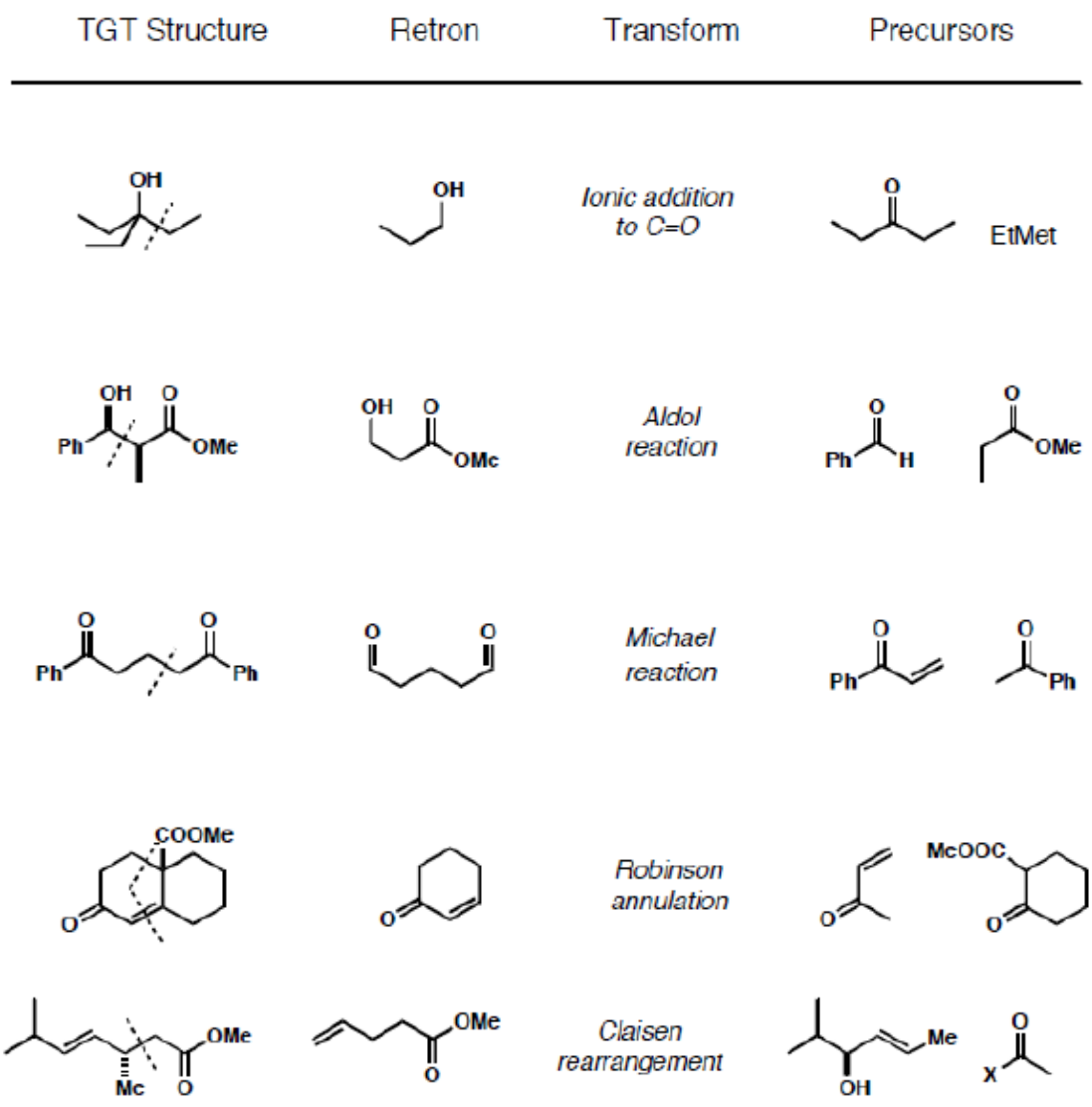
From a retrosynthetic analysis usually a tree of intermediate is produced, having chemical structures as nodes and pathways from bottom to top corresponding to synthetic routes to the target (TGT). Such trees called EXTGT (as they grow out from the target) can be quite complex so strategies for control and guidance in rethrosynthetic analysis are of extremely important so as to avoid explosive branching)

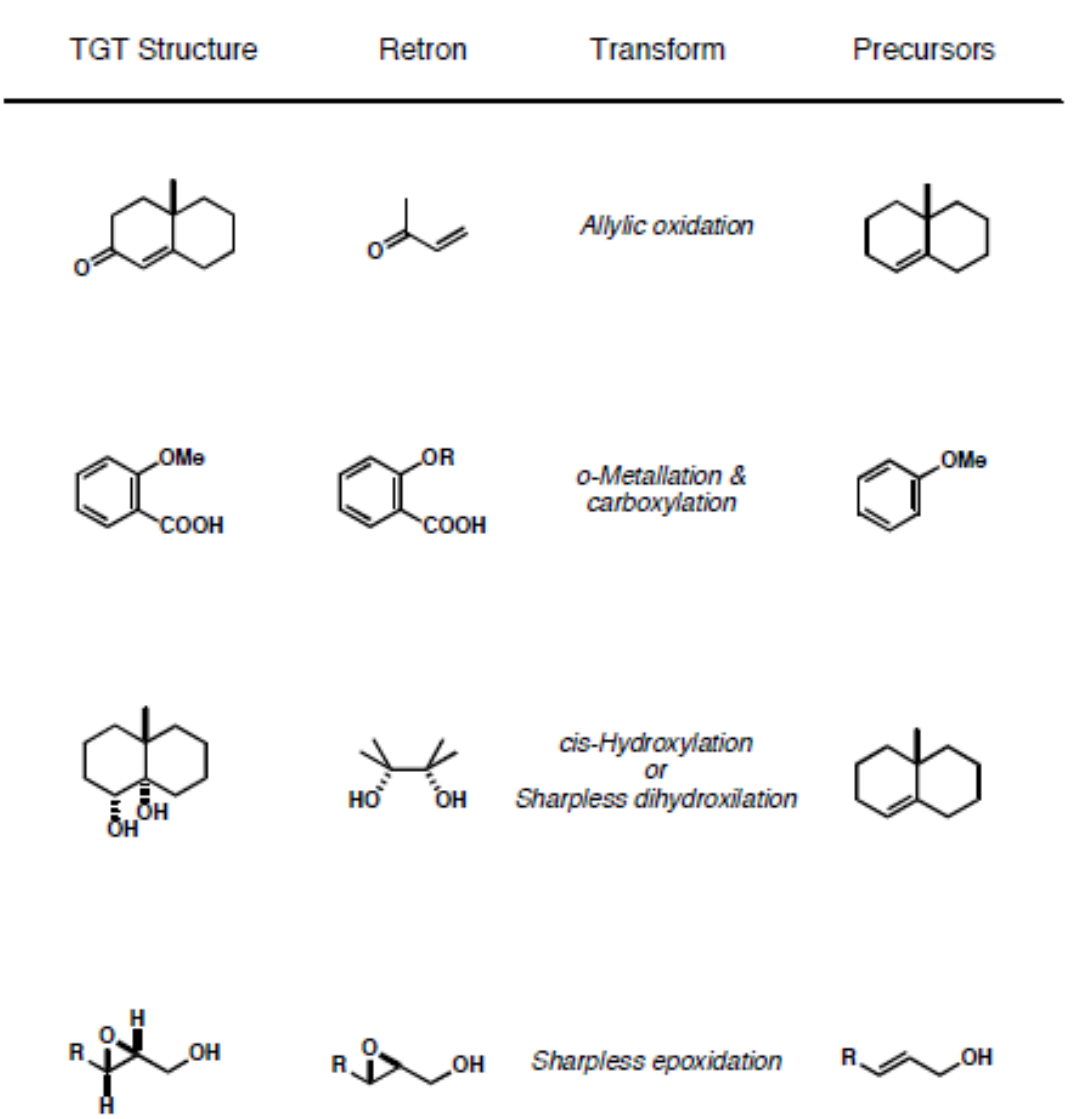
Two types of general strategies are usually followed in retrosynthesis analysis. They are

1) Transform-based strategies and
2) Structure-based strategies

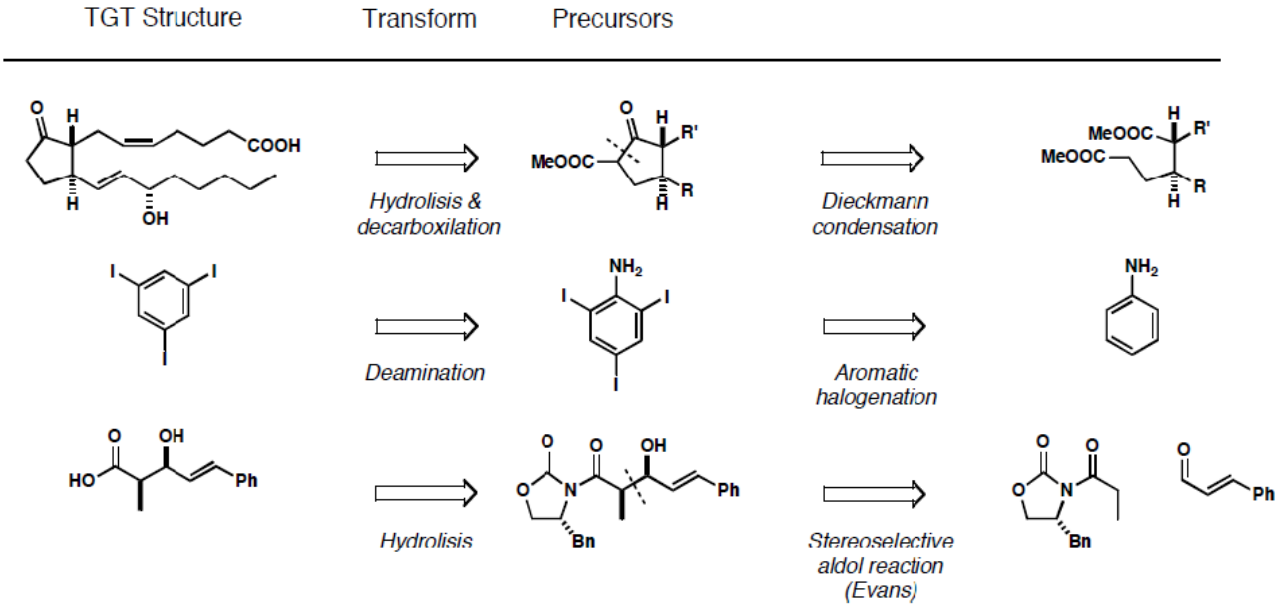
Transform-based strategies rely on the application of powerfully simplifying transforms whereas structure-based strategies rely on the recognition of possible starting materials or key intermediates for a synthesis.

Structurally simplifying transforms effect molecular simplification by disconnecting molecular skeleton, and/or functional groups and/or stereocenters. There are transforms which bring no change in molecular complexity, but which can be useful because they modify a TGT to allow the subsequent application of simplifying transforms. They include rearrangements of molecular skeleton, functional group interchange (FGI), and inversion/transfer of stereocenters.

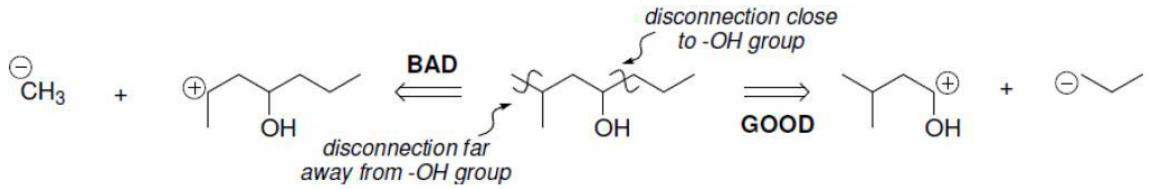




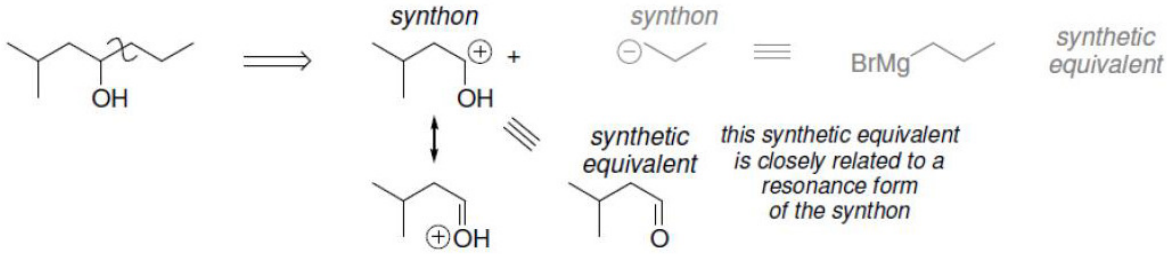
Structurally increasing complexity transforms includes addition of rings or stereocenters and addition functional groups (FGA).



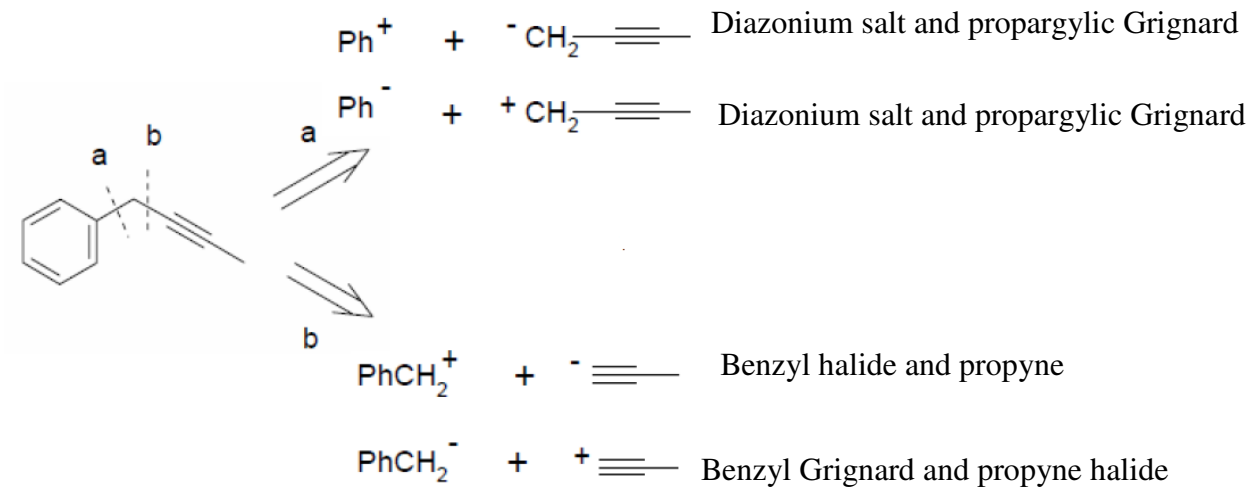
Disconnections very often take place immediately adjacent to, or very close to functional groups in the target molecule (i.e. the one being disconnected). This is pretty much inevitable, given that functionality almost invariably arises from the forward reaction.



A good trick here is to consider whether it is possible to draw a resonance form of the synthon which looks more like a real reactive intermediate. If it yes, then it is the good choice of polarity in identifying the synthetic equivalent.



Use disconnections corresponding to known reliable reactions, choose disconnection corresponding to the highest yielding reaction.



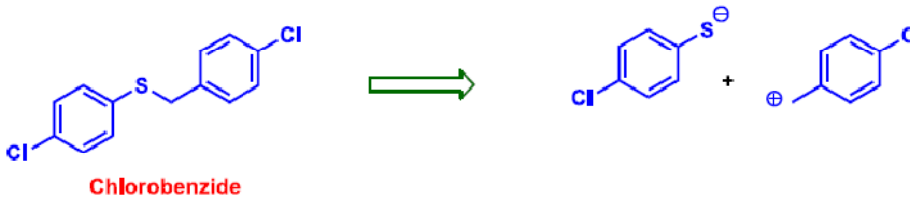
15.10Synthesis practice of some simple organic molecule

Example 1: synthesis of chlorobezoid

The structure of chlorobenzide molecule is

Chlorobenzide

chlorobenzide consists of 2 chlorobenzene nucleus joined by thioether likange. This molecule can be fragmented in to two parts as shown in its retrosynthetic analysis.

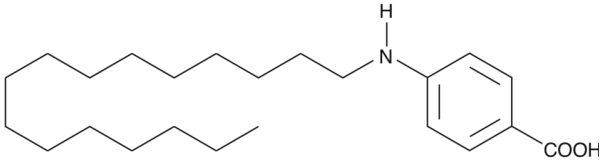


Chlorobenzide

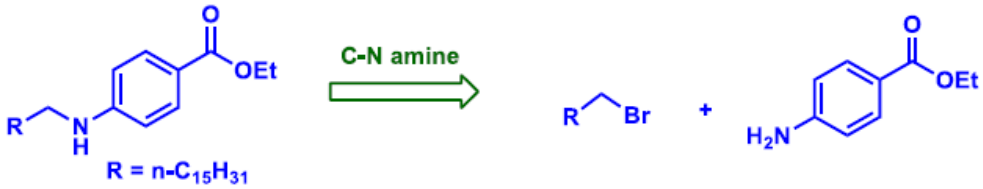
Since sulphur is a good nucleophile and carbon attached to chlorine is a good electrophilic centre the thio ether linkage can easily form by reacting 4-chlorothiobenzene and 4-cholobenzylchloride under suitable S_N2 reaction condition.

Example 2: Synthesis of Cetaben ethyl ester

Cataben is an aromatic aminoacid. It consists of hexadecylamino chain attached to benzoic acid nucleus at para position. Its structure is

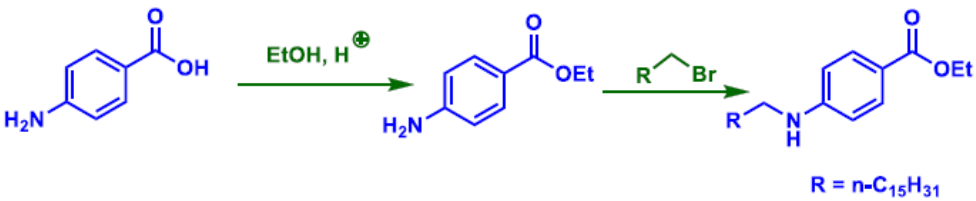


Ethyl ester of cetaben is used in medicine to lower blood lipid levels and the retrosyntesis analysis of this compound is shown below



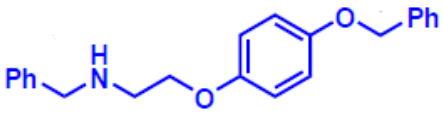
Cetaben ethyl ester

The synthesis starts from commercially available 4-amino benzoic acid as starting material. The esterification of 4-aminobezoic acid with ethyl alcohol in acid media yields 4-amino ethyl benzoate which on alkylation with n-bromo hexadecane yields Cetaben ethylester

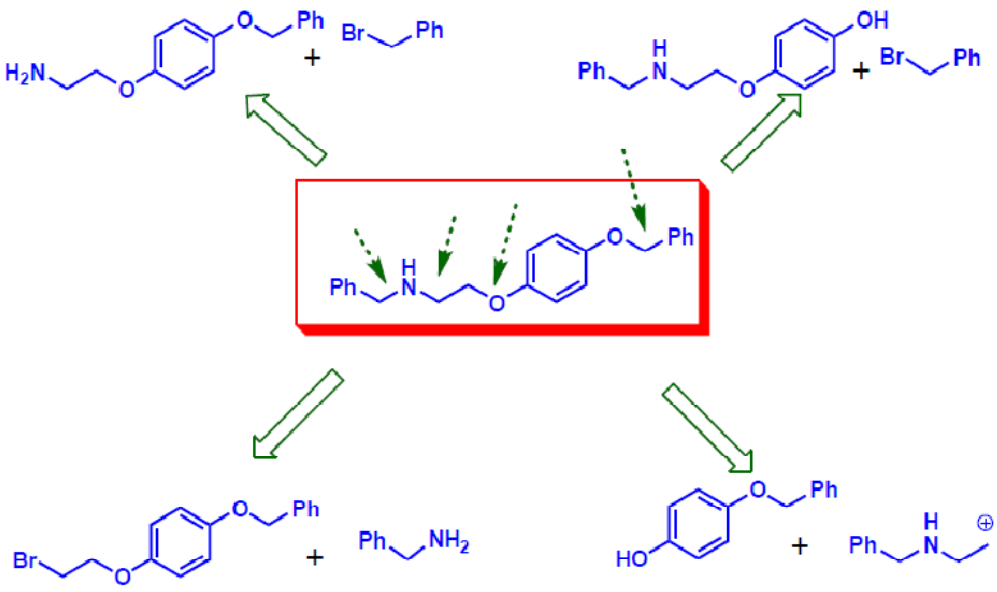


Example 3: Synthesis of ICI-D714

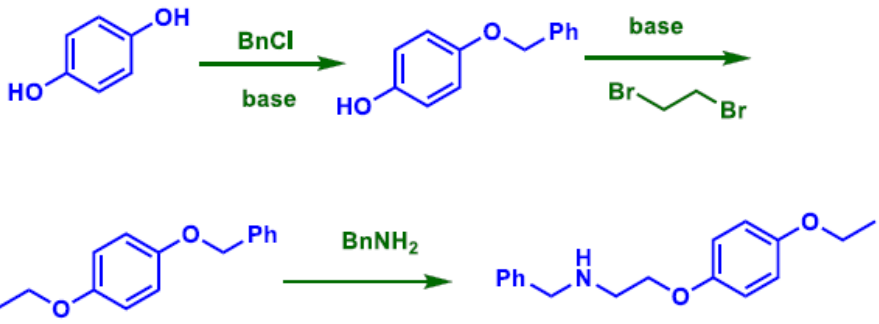
ICI-D714 is a commercial name for the compound shown below it is used as Potential Anti-obesity Drug



More than 3 retrosynthesis analysis schemes can be written for this compound and are shown in below figure.

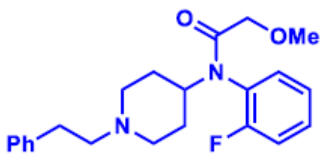


All the retrosynthesis schemes are works equally well and one of the syntheses start from catacol is given below.



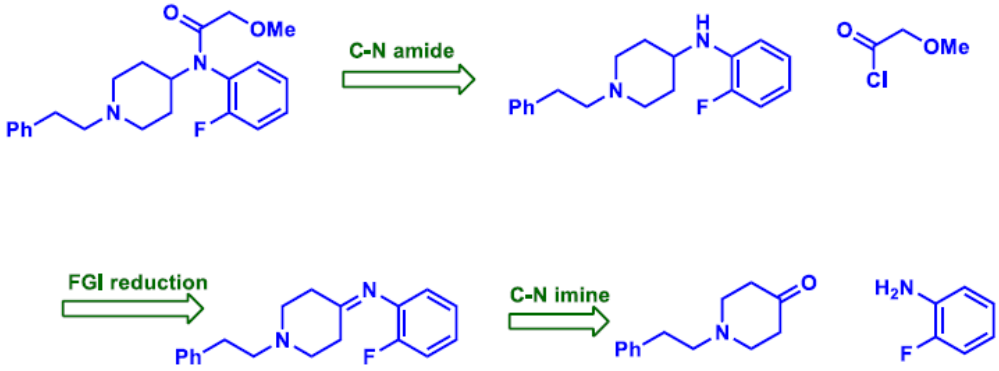
Example 4: Synthesis of Ocfentanil

Ocfentanil is used for opioid painkiller and the structure of ocfentanil is

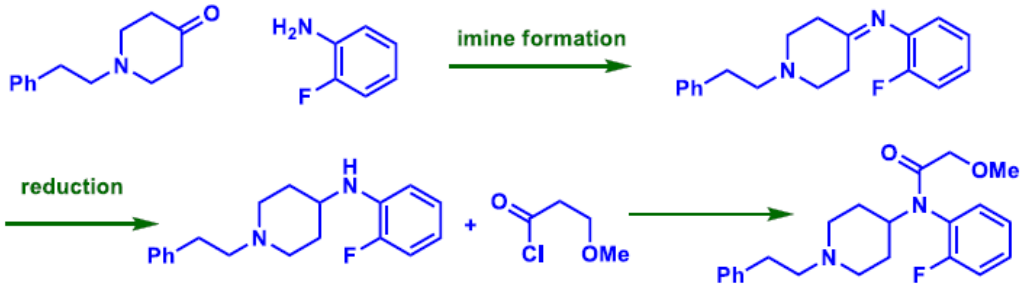


The retrosynthesis analysis and the total synthesis of this molecule based on the retrosynthesis analysis is shown below

Retrosynthesis analysis of Ocfentanil



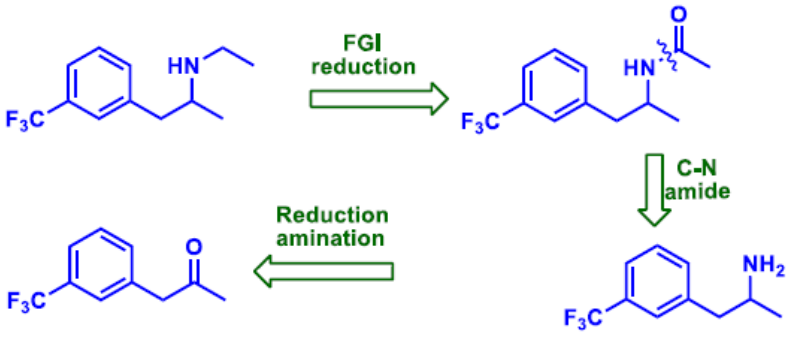
Synthesis of Ocfentanil



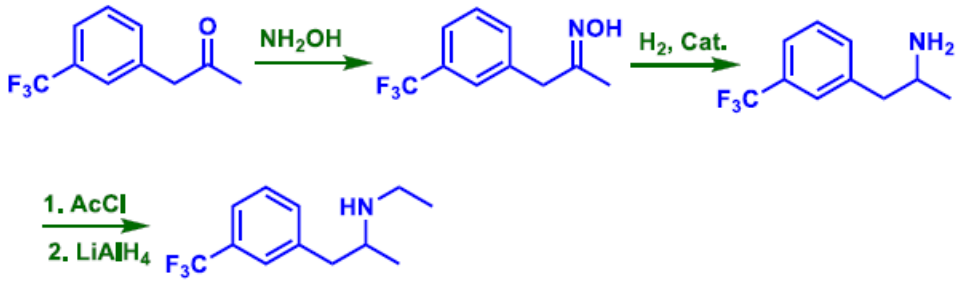
Example 5: Synthesis of Fenfluoramine

Fenfluoramine is a neuroactive drug. The retrosynthesis analysis and the total synthesis of this molecule based on the retrosynthesis analysis is shown below.

Retrosynthesis analysis



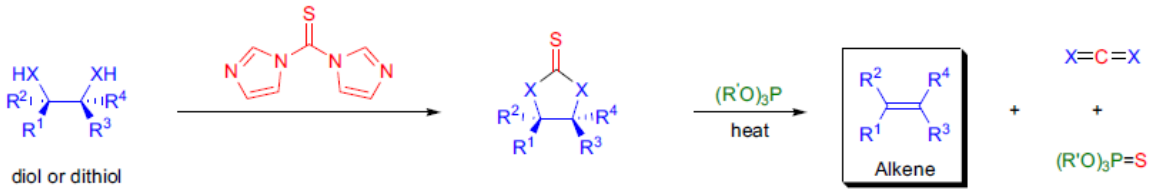
Synthesis



15.11 Strategic Applications of named reactions in organic synthesis

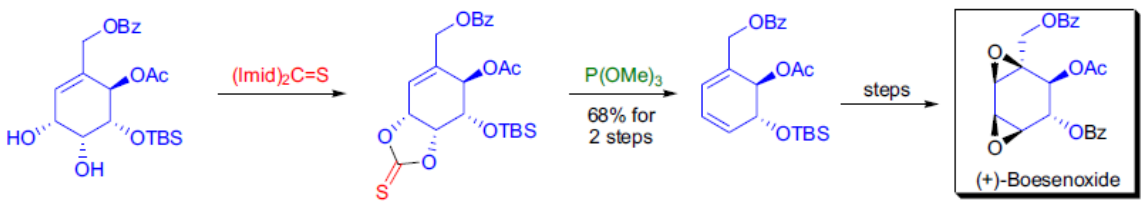
15.11.1 Corey-Winter olefination

In 1963, E.J. Corey and R.A.E. Winter described a new two-step method for the stereospecific synthesis of alkenes from 1,2-diols via cyclic 1,2-thionocarbonates and 1,2-trithiocarbonates. This method of alkene synthesis is called the *Corey-Winter olefination*. In the first step, the 1,2-diol is converted quantitatively to the corresponding cyclic thionocarbonate derivative using thiocarbonyldiimidazole. In the second step, the thionocarbonate is treated with excess trialkylphosphite [$P(OR')_3$, where R'=Me, Et or alkyl] at reflux, and a cis-elimination reaction takes place to yield the alkene and by-products [CO_2 and $(OR)_3P=S$]. The reaction is completely stereospecific and high-yielding. Even highly substituted and strained olefins (e.g., trans-cycloheptene) can be prepared. However, no elimination is observed in those cases in which the cis-elimination would lead to an extremely strained structure (e.g., transcyclohexene). The stereochemistry of the product olefin is only determined by the stereochemistry of the starting 1,2- diol (cis or trans) and usually under the reaction conditions, no isomerization of the product is observed. A cis olefin, may be converted to trans-1,2-diol and subjected to the Corey-Winter procedure to afford the corresponding trans olefin. Similarly, trans olefins can be converted to the corresponding cis olefins.

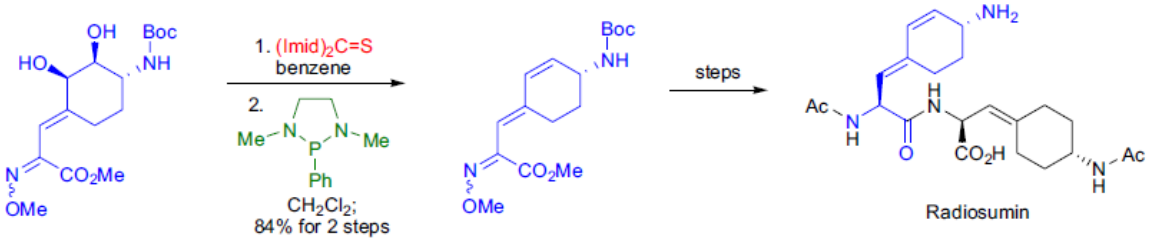


Synthetic Applications

1) The enantiospecific synthesis of naturally occurring cyclohexane epoxides such as (+)-crotepoxide and (+)- boesenoxide was accomplished by T.K.M. Shing et al. The key intermediate 1,3-cyclohexadiene was prepared using the Corey-Winter protocol on a cis-vicinal diol. The resulting diene was then converted to the natural product after several steps.



2. The absolute configuration of radiosumin, a novel potent trypsin inhibitory dipeptide, was determined by T. Shioiri and co-workers by carrying out the first enantioselective total synthesis of the natural product. The s-trans 1,3-diene in one of the key synthetic intermediates was installed by the Corey-Winter olefination using the Corey-Hopkins reagent (1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine).



15.11.2 Corey-fuchs alkyne synthesis

The one-carbon homologation of aldehydes to the corresponding terminal alkynes using carbon tetrabromide and triphenylphosphine is known as the Corey-Fuchs alkyne synthesis. E.J. Corey and P.L. Fuchs examined the synthetic possibility of transforming aldehydes to the corresponding one-carbon chain-extended alkynes. The first step of their procedure involved the conversion of the aldehyde to the corresponding homologated dibromoolefin in two possible ways

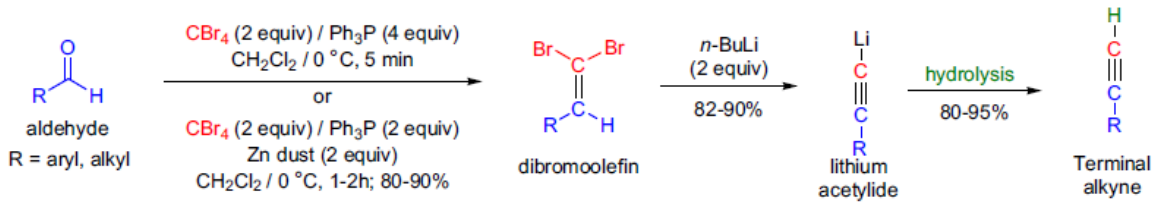
i) Addition of the aldehyde (1 equivalent) to a mixture of triphenylphosphine (4 equivalents) and carbon tetrabromide (2 equivalents) in CH_2Cl_2, at 0 °C or

ii) Addition of the aldehyde to a reagent, which is prepared by mixing zinc dust (2 equivalents) with Ph_3P (2 equivalents) and CBr_4 (2 equivalents) in CH_2Cl_2 at 23 °C for 24-30h (the reaction time to form the alkyne is 1-2h).

Yields are typically 80-90% for this first Wittig-type step. Procedure II, using zinc dust and less Ph_3P, tends to give higher yields of dibromoolefins and simplifies the isolation procedure.

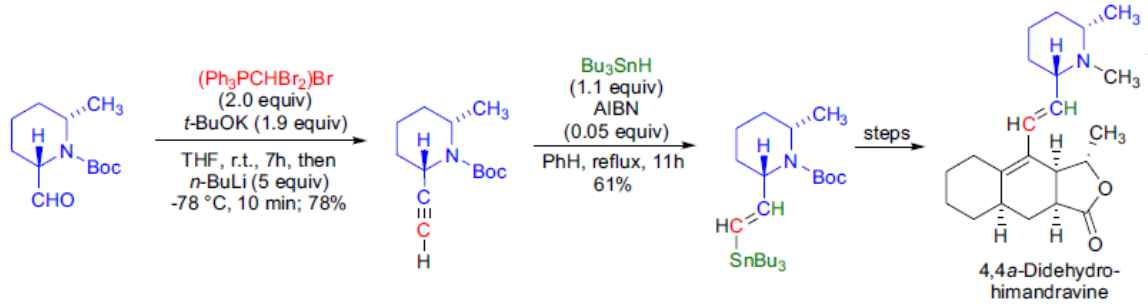
In the second step, the conversion of the prepared dibromoolefins to the corresponding terminal

alkynes is accomplished by treatment with 2 equivalents of n-butyllithium at -78 °C (lithium-halogen exchange and elimination), followed by simple hydrolysis. The intermediate is a lithium acetylide, which can be treated with a number of electrophiles to produce a wide variety of useful derivatives. Recently, a one-pot modified procedure using t-BuOK/(Ph_3PCHBr_2)Br followed by the addition of excess n-BuLi was published.

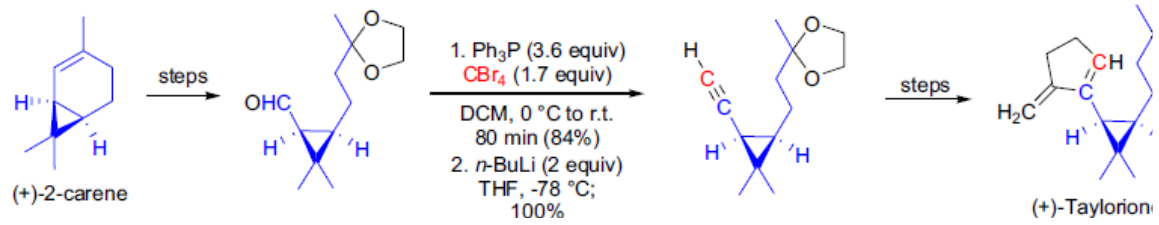


Synthetic applications

1) The total synthesis of Galubulimima alkaloid 4,4*a*-didehydrohimandravine, using an *intramolecular Diels-Alder reaction* and a *Stille coupling* as the key steps, was accomplished in the laboratory of M.S. Sherburn. The required vinylstannane intermediate for the *Stille coupling* was prepared *via* the *one-pot Corey-Fuchs reaction*, followed by *radical hydrostannylation*.



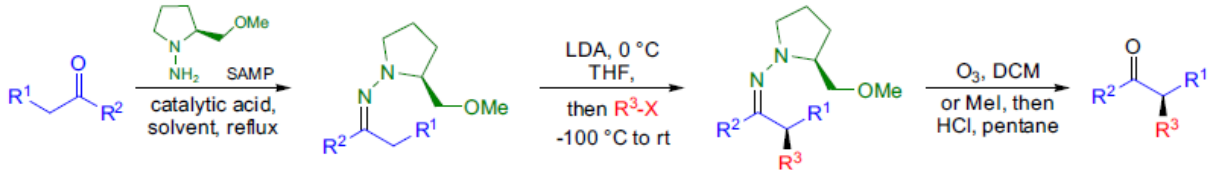
2) W.J. Kerr and co-workers carried out the total synthesis of (+)-taylorione starting from readily available (+)-2-carene and using a modified Pauson-Khand annulation with ethylene gas as the key step. The key terminal alkyne intermediate was prepared by the Corey-Fuchs reaction. Interestingly, the ketal protecting group was sensitive to the excess of CBr_4, so the addition of this reagent had to be monitored carefully to cleanly transform the aldehyde to the desired dibromoolefin.



15.11.3 Enders samp/ramp hydrazone alkylation

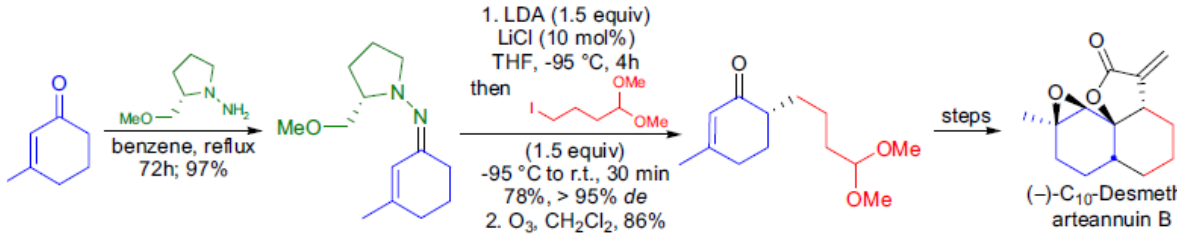
D. Enders reported the asymmetric α-alkylation of ketones via the corresponding (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone derivatives. According to the general procedure, the SAMP hydrazone was deprotonated with lithium diisopropylamide in tetrahydrofuran, and the corresponding lithium derivative was reacted with an alkyl halide. The product was ozonized to provide the α-alkylated ketone with high enantioselectivity.

The opposite enantiomer can be obtained by using (R)-1-amino-2-methoxymethylpyrrolidine (RAMP) as the chiral auxiliary. This transformation can also be carried out on aldehydes. The asymmetric alkylation of ketones and aldehydes via their SAMP/RAMP hydrazone derivatives is referred to as the Enders SAMP/RAMP hydrazone alkylation.

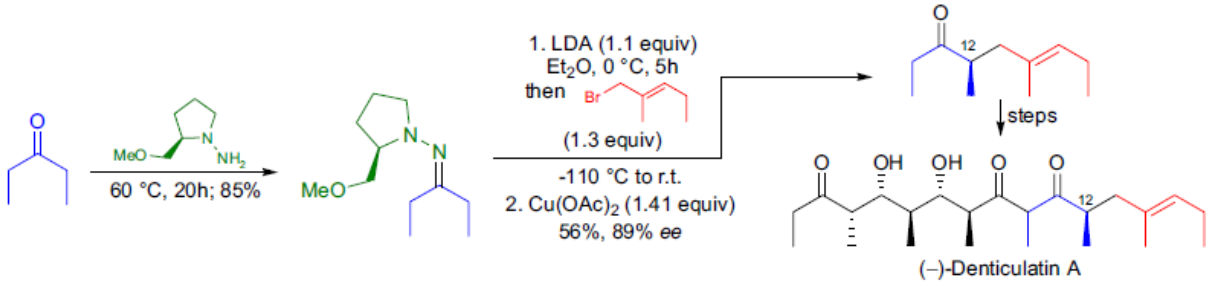


Synthetic applications

1) The synthesis of (−)-C10-desmethyl arteannuin B, a structural analog of the antimalarial artemisinin, was developed by D. Little et al. In their approach, the absolute stereochemistry was introduced early in the synthesis utilizing the Enders SAMP/RAMP hydrazone alkylation method. The sequence begins with the conversion of 3- methylcyclohexenone to the corresponding (S)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone. Deprotonation with lithium diisopropylamide, followed by alkylation in the presence of lithium chloride at -95 °C afforded the product as a single diastereomer. The SAMP chiral auxiliary was removed by ozonolysis.



2) The total synthesis of (−)-denticulatin A, a polypropionate metabolite, was accomplished in the laboratory of F.E. Ziegler. To establish the absolute stereochemistry at C12, they utilized the Enders SAMP/RAMP hydrazone alkylation. To this end, the RAMP hydrazone of 3-pentanone was successfully alkylated with 1-bromo-2-methyl-2(E)- pentene. Hydrolysis of the hydrazone under standard acidic conditions led to loss of the enantiomeric purity. This problem was avoided by using cupric acetate for the cleavage.

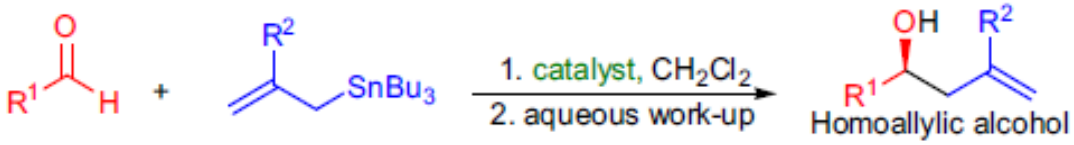


15.11.4 Keck asymmetric allylation

The formation of chiral secondary homoallylic alcohols via the enantioselective addition of allylic nucleophiles to aldehydes is an important tool in organic synthesis. An efficient way to achieve this transformation is to use allylic organometallic reagents in the presence of chiral Lewis acid catalysts. The most widely studied catalysts in the area are the 1,1'-binaphthalene-2,2'-diol (BINOL) complexes of titanium(IV).

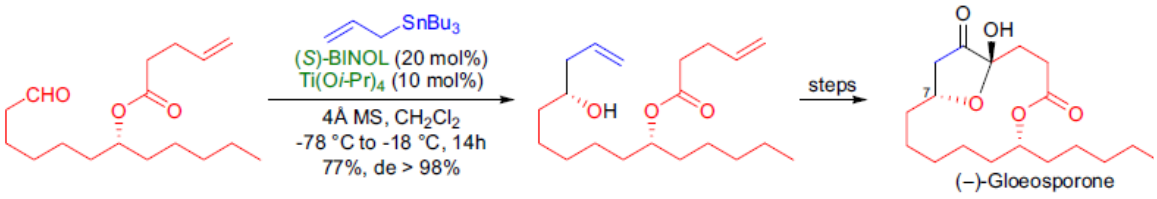
The first application of a Ti(IV)-BINOL complex for enantioselective allylation was reported by K. Mikami. According to this procedure, the catalyst was prepared from $TiCl_2(Oi\text{-}Pr)_2$ and (S)-BINOL in the presence of 4Å molecular sieves in situ. The addition of allylsilanes and allylstannanes to glyoxylate in the presence of 10% of the catalyst provided the products with low enantio- and diastereoselectivity.

The same year, G.E. Keck independently reported the application of the BINOL/Ti(IV) catalyst system for asymmetric allylation. He utilized allyltributylstannane as the nucleophile, and reacted it with aliphatic, aromatic, and unsaturated aldehydes in the presence of 10 mol% catalyst. The catalyst was prepared by combining two equivalents of the (R)- or (S)-BINOL ligand with one equivalent of $Ti(Oi\text{-}Pr)_4$ in dichloromethane, and the mixture was kept at room temperature for five minutes to an hour. The reaction of unbranched aliphatic, aromatic and unsaturated aldehydes with allyltributylstannane in the presence of 10% catalyst provided the homoallylic alcohols with high yields and enantioselectivity; α-branched aldehydes gave the products this reaction is referred to as the Keck asymmetric allylation.

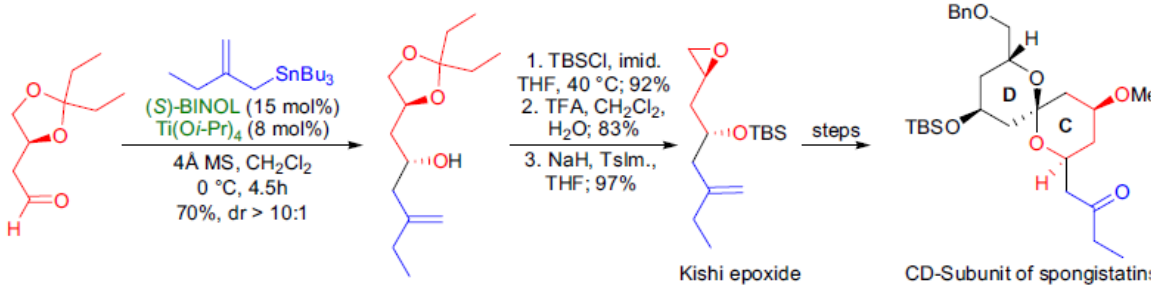


Synthetic Applications

1) A. Fürstner and co-workers devised an efficient synthesis of (–)-gloeosporone, a fungal germination inhibitor. They utilized the Keck asymmetric allylation method to create the 7(R)-homoallylic alcohol subunit. The reaction of the substrate aldehyde in the presence of the in situ generated catalyst provided the product with high yield and as the only diastereomer. It is important to note that it was essential to use freshly distilled $Ti(i\text{-}OPr)_4$ for the preparation of the catalyst in order to get high enantioselectivity and reproducible results.



2) The spongistatins are a family of architecturally complex bisspiroketal macrolides, which display extraordinary cytotoxicity. During the second generation synthesis of the ABCD subunit of spongistatin 1, A.B. Smith and co-workers utilized the Keck allylation to construct the Kishi epoxide. The allylation was carried out under standard conditions, using tributyl-(2-ethylallyl)-stannane as the allylstannane reactant. The desired product was formed in high yield and a diastereomeric ratio greater than 10:1.



15.12 Summary of the unit

Synthesis is a construction process that involves converting simple or commercially available molecules into complex molecules using specific reagents associated with known reactions in the retrosynthetic scheme. Syntheses can be grouped into two broad categories

i) Linear syntheses

ii) Convergent syntheses

In linear synthesis, the target molecule is synthesized through a series of linear transformations. Since the overall yield of the synthesis is based on the single longest route to the target molecule, by being long, a linear synthesis suffers a lower overall yield. The linear synthesis is fraught with failure for its lack of flexibility leading to potential large losses in the material already invested in the synthesis at the time of failure.

In convergent synthesis, key fragments of the target molecule are synthesized separately or independently and then brought together at a later stage in the synthesis to make the target molecule. A convergent synthesis is shorter and more efficient than a linear synthesis leading to a higher overall yield. It is flexible and easier to execute due to the independent synthesis of the fragments of the target molecule. Retrosynthetic analysis and synthetic planning requires training (knowledge of chemistry) and experience (practical application of the

chemistry). A good synthetic plan should consider taking into account the advantage of a convergent synthesis, if possible, over a linear synthesis.

During retrosynthetic analysis the target molecule is systematically broken down by a combination of disconnection and functional group interconversion (FGI). The term disconnection relates to breaking a carbon-carbon bond of a molecule to generate shorter or simpler fragments. A good disconnection must achieve the greatest simplification of the target molecule. For a complex molecule, this basic disconnection process is repeated until the target is reduced to simple starting materials. The complete set of disconnections and functional group interconversions for a specified target molecule is what constitutes a retrosynthetic pathway or plan.

15.13 Key words

Organic synthesis; History of organic synthesis; Practice of Synthesis; Design and Execution of Synthesis; Retrosynthesis by making a disconnection; Direct Associative Approach; Disconnection approach; Reagent or synthetic equivalent; Corey-Winter olefination; Corey-Fuchs alkyne synthesis; Enders samp/ramp hydrazone alkylation; Keck asymmetric allylation.

15.14 References for further studies

1) Elements of Synthesis Planning; R. W. Hoffmann; *Springer Science & Business Media*, **2009**.

2) Organic Synthesis: The Science Behind the Art; William A. Smit, Alekseĭ Feodos′evich Bochkov, Ron Caple; *Royal Society of Chemistry*, **1998**.

3) Strategies and Tactics in Organic Synthesis, Michael Harmata; *Elsevier*, **2014**.

4) Organic Synthesis: Strategy and Control; Paul Wyatt, Stuart Warren; *John Wiley & Sons*, **2013**.

5) Part B: Reactions and Synthesis; Francis A. Carey, Richard J. Sundberg; *Springer*, **2013**.

6) Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design; Florencio Zaragoza Dörwald. *John Wiley & Sons*, **2006**.

15.16 Questions for self understanding

What is organic synthesis?

1) Discuss the design and execution of organic synthesis.

2) What is Retrosynthesis? Give one example.

3) Discuss the synthesis of organic compound by direct associative approach.

4) Discuss the synthesis of organic compound by disconnection approach.

5) Write a note on reagent or synthetic equivalent.

6) What is Corey-Winter olefination reaction? Discuss its application in organic synthesis with suitable example.

7) What is Corey-fuchs alkyne synthesis? Discuss its application in organic synthesis with suitable example.

8) What is Enders samp/ramp hydrazone alkylation? Discuss its application in organic synthesis with suitable example.

9) What is Keck asymmetric allylation? Discuss its application in organic synthesis with suitable example.

UNIT-16

Structure

16.0 Objectives of the unit

After studying this unit you are able to

- Write the scheme for total synthesis of given compound
- Write the scheme for formal total synthesis
- Explain the differences between total synthesis and formal synthesis
- Explain the meaning of cascade reaction
- Identify the different types of cascade reaction used in organic synthesis

16.1 Introduction

The total synthesis is a man-made artificial route to a complex chemical structure starting from a set of simple building block molecules.

Semi-synthesis is a short synthesis plan that begins from natural product starting material whose structure is similar to that of the final target molecule. It is also called Partial synthesis. Thus semi-synthesis is designates as the synthesis of a given molecule from an advanced precursor related to it

One pot synthesis is a term that refers to a chemical process involving more than one reaction step taking place in a single reaction vessel without isolate the intervening intermediates.

Multicomponent reaction is a chemical reaction involving at least three starting molecules that react in a single step. The starting materials may or may not be different in structure and the order of addition of the reactants may or may not matter in obtaining the intended final product.

Formal synthesis is referred as a synthesis plan to a key reaction intermediate on the way to a target molecule that is different from a prior published route. Thus formal total synthesis is the chemical synthesis of an intermediate that has already been transformed into the desired target

Relay approach defines the process in which a key intermediate previously synthetized is obtained by degradation from other product, including the final target molecule

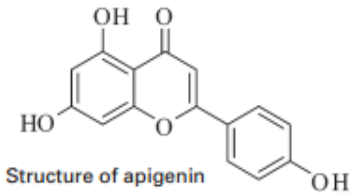
16.2 Total synthesis

As described in previous unit the chemical synthesis is defined as the intentional construction of molecules by means of chemical reactions. *A total Synthesis is defined as the chemical synthesis of complex molecules, usually natural products, from relatively simple, commercially available starting materials.*

16.3 Total synthesis of apigenin

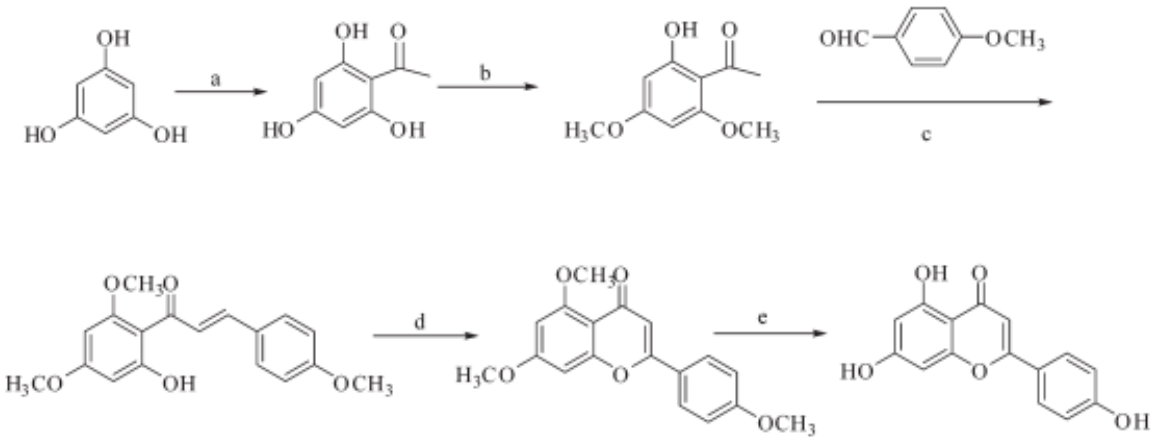
Apigenin is a flavonoid which is used in traditional or alternative medicine for its pharmacological activity. Human exposure to apigenin occurs primarily through the

consumption of chamomile and through its presence as a glycoside in many fruits and vegetables including mint, parsley and celery.



Structure of apigenin

Jian Yang,et.al have been reported the synthesis apigenin from phloroglucinol in five steps. First, phloroglucinol was acylated to 1-(2,4,6-trihydroxy-phenyl)-ethanone by a Fries rearrangement. The efficiency of this transformation was found to depend mainly on the amount of BF_3 . Et_2O that was used. Second, treatment of acylated compound with 2.5 equivalents of methyl p-toluene sulfonate ($TsOCH_3$) instead of dimethylsulfate (Me_2SO_4) in the presence of potassium carbonate in ethanol solution at 80 °C for 3 h afforded O-methylated compound in good yield. Third, condensation of O-methoxy compound with anisaldehyde using ethanolic potassium hydroxide resulted in the chalcone ,which was then treated with iodine in DMSO to afford flavones. Finally, the flavone was treated with pyridine hydrochloride to achieve demethylation to obtain apigenin 1 in good yield

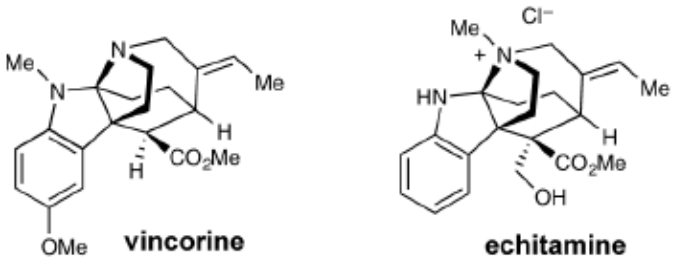


Reagents and conditions: (a) Ac_2O, BF_3 . Et_2O, 50 °C,10h, (b) $TsOCH_3$, K_2CO_3, 80 °C, 3h,(c) KOH, room temperature, 72h, (d) DMSO,I_2, 100 °C,4h, (e) pyridine HCl, 180–190 °C, 6 h.

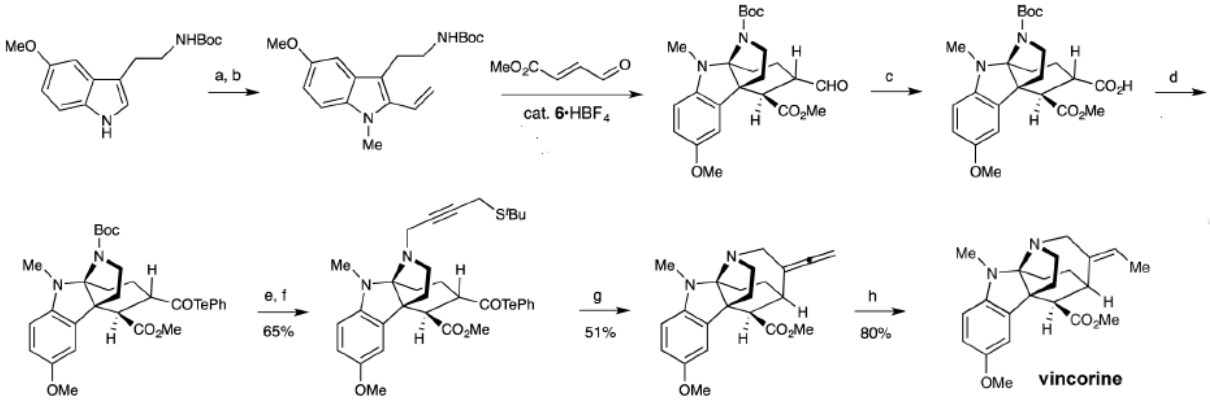
16.3.1 Enantioselective Total Synthesis of (−)-Vincorine

The Vinca alkaloid natural products have historically served as valuable lead candidates in the development of anticancer agents (vinblastine), vasodilators (vincamine), antipsychotics, and anti-hypertensives (reserpine). Members of the biologically active akuammiline family of Vinca alkaloids have emerged as high-profile targets for chemical synthesis and medicinal chemistry studies. Vincorine is the parent compound of an akuammiline alkaloid subclass characterized by a synthetically challenging tetracyclic core that incorporates a strained

seven-membered azepanyl ring and a pyrroloindoline motif. In preliminary assays, the related alkaloids echitamine and corymine were found to exhibit anti-cancer activity and glycine receptor antagonism, respectively.



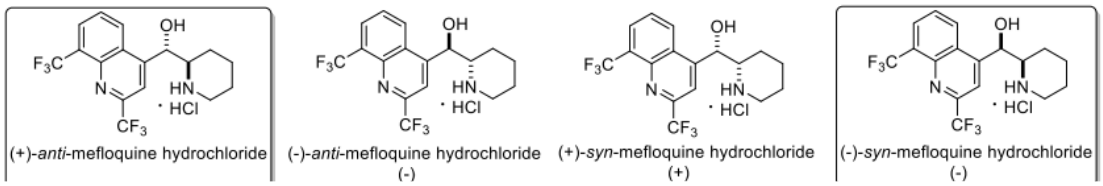
The total synthesis of vincorine was initiated with the preparation of diene in two steps from commercially available 5-methoxy-N′-Boc tryptamine, via methylation and then directed metalation/Negishi coupling. For the key Diels–Alder/cyclization cascade, a survey of chiral secondary amines revealed that the first-generation Diels– Alder imidazolidinone catalyst was both highly efficient and stereoselective. Using optimized reaction conditions (6·HBF_4, MeCN, –20 °C), the tetracyclic vincorine core system was generated. Next rapidly install the final sevenmembered azepanyl ring by way of a 7-exo-dig radical cyclization.



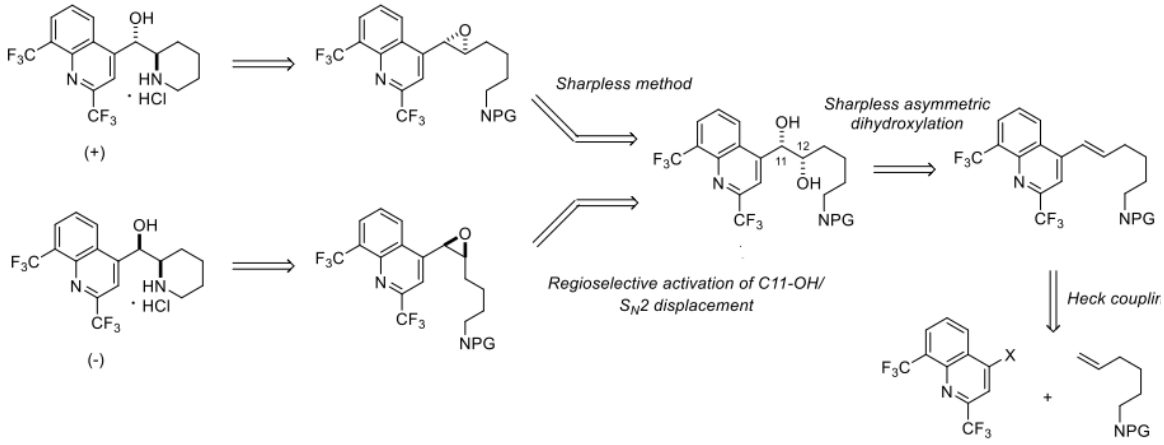
16.3.2 Enantioselective Total Synthesis of (+)-anti- and (-)-syn-Mefloquine Hydrochloride

Anti-Mefloquine hydrochloride (±1) has been used both for treatment of malaria and prophylaxis. The drug is administered in racemic form, and is marketed under the name Lariam. (+)-isomer is at least 1.5 times more active than the (-)-isomer

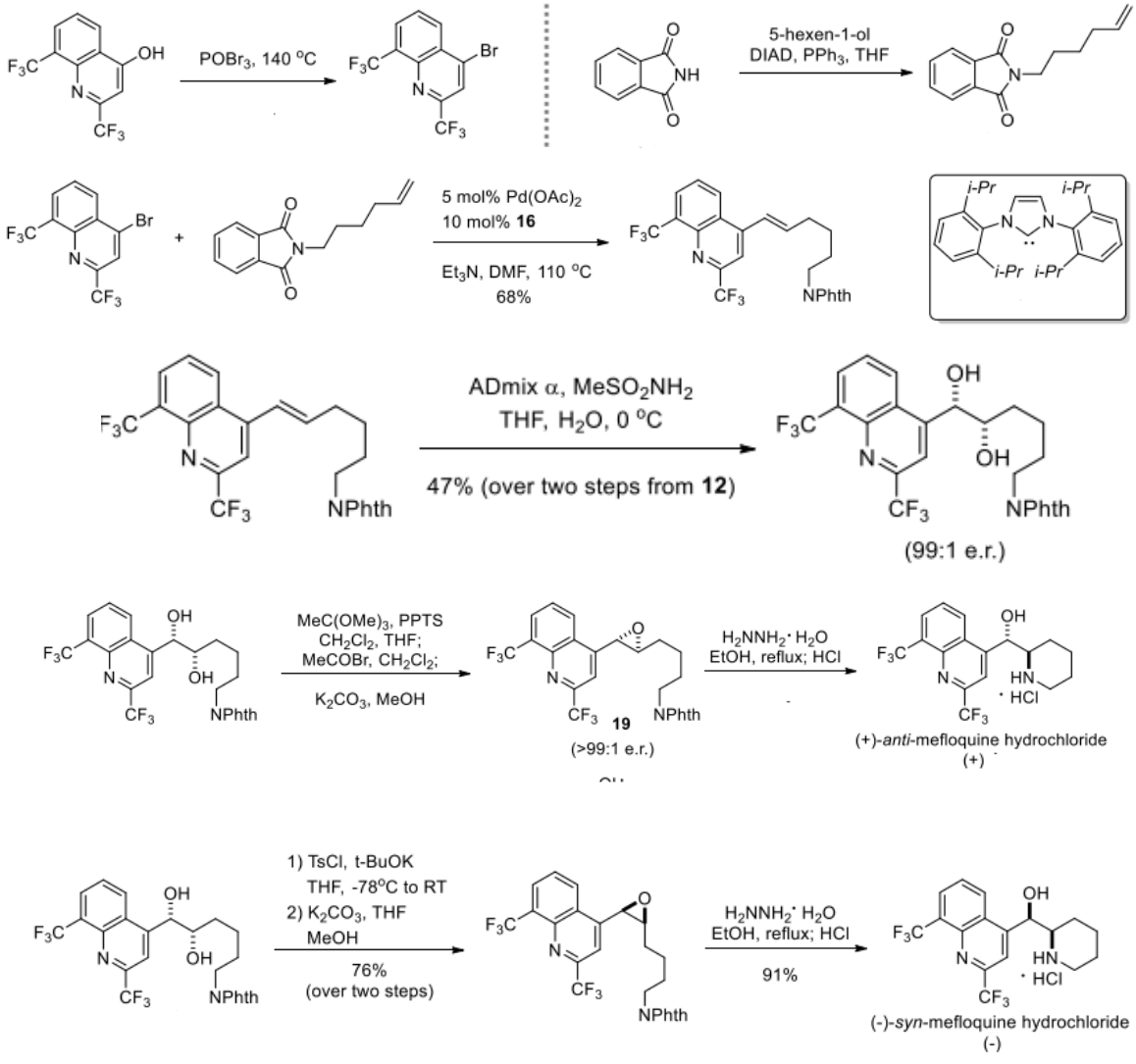
Side effect: psychiatric effects (anxiety, hallucinations, depression, unusual behavior, and suicidal ideations), neurologic effects (dizziness, loss of balance, and tinnitus), and cardiac effects (abnormalities with heart rhythms). Both anti- and syn-mefloquine hydrochloride were previously synthesized by Hall and Leonov groups in 2013.



Retrosynthesis



Forward synthesis



16.4 Formal total synthesis

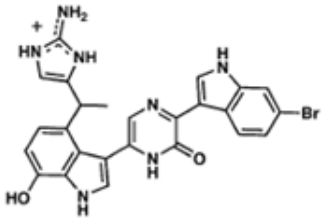
Formal total synthesis is the chemical synthesis of an intermediate that has already been transformed into the desired target.

16.5 Difference between total synthesis and formal synthesis

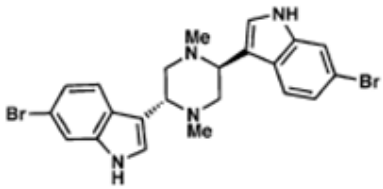
Both processes are used to create a product; the difference between partial and total synthesis is the starting material. For partial synthesis, the process starts with a complex molecules that is usually derived from natural resources - such as plants or cell cultures. Total synthesis is a complete process that starts with simple precursors and does not usually need the assistance of biological processes.

16.6 The formal synthesis of dragmacidin B, trans-dragmacidin C

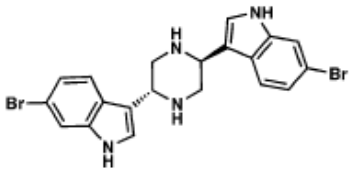
The dragmacidin family of bis(indole) alkaloids represents an emerging class of cytotoxic natural products obtained from deep-water marine sponges. (±) Dragmacidin D, Dragmacidin B and trans- Dragmacidin C shown below are belongs to dragmacidin family



(±)-Dragmacidin D

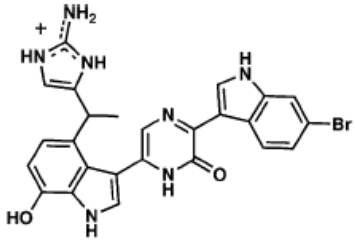


Dragmacidin B

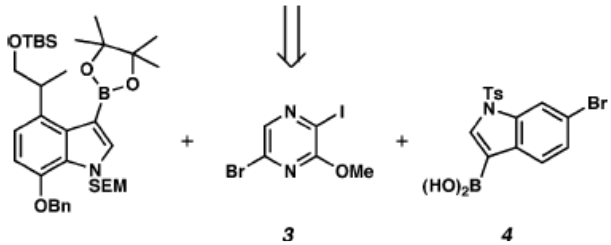


trans-Dragmacidin C

In 2002, Brian M. Stoltz, et.al described the total synthesis of dragmacidin D and their retrosythesis analysis of dragmacidin D is shown below

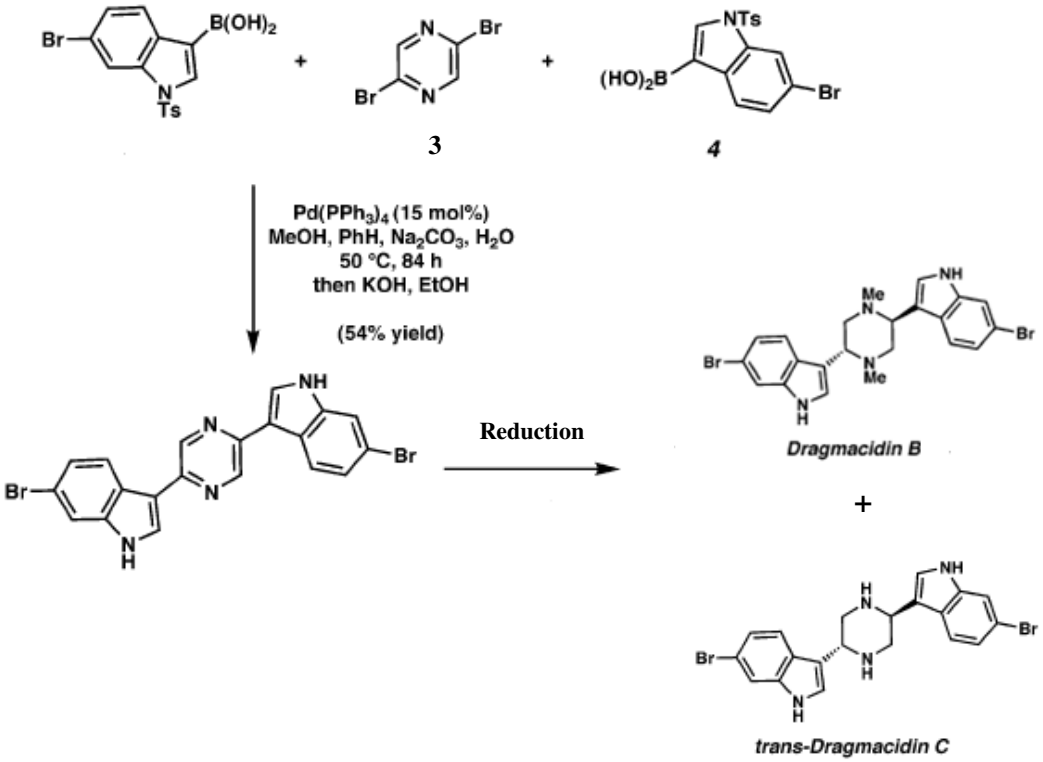


(±)-Dragmacidin D



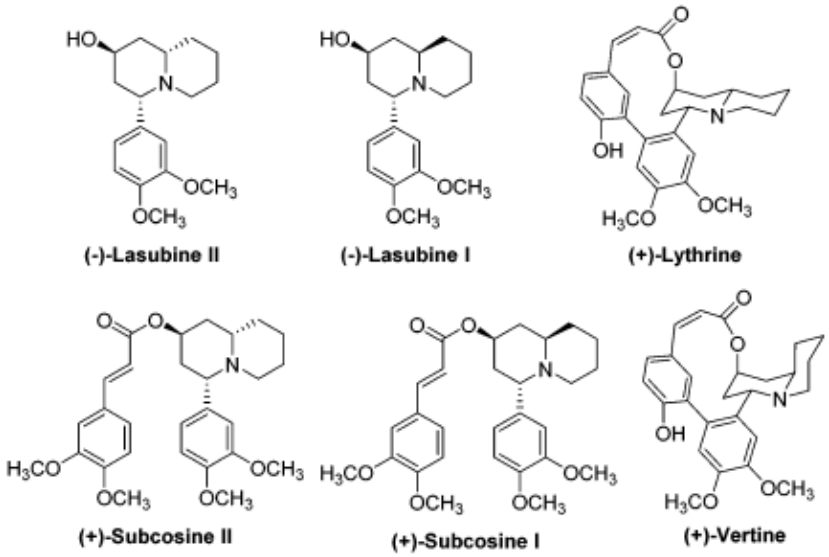
3 4

By utilizing same intermediate 3 and 4 Brian M. Stoltz, et.al reported the formal synthesis of Dragmacidin B and trans- Dragmacidin C in 2005. Their synthesis scheme is shown below



16.7 Formal Synthesis of (+)-Lasubine II and (−)-Subcosine II

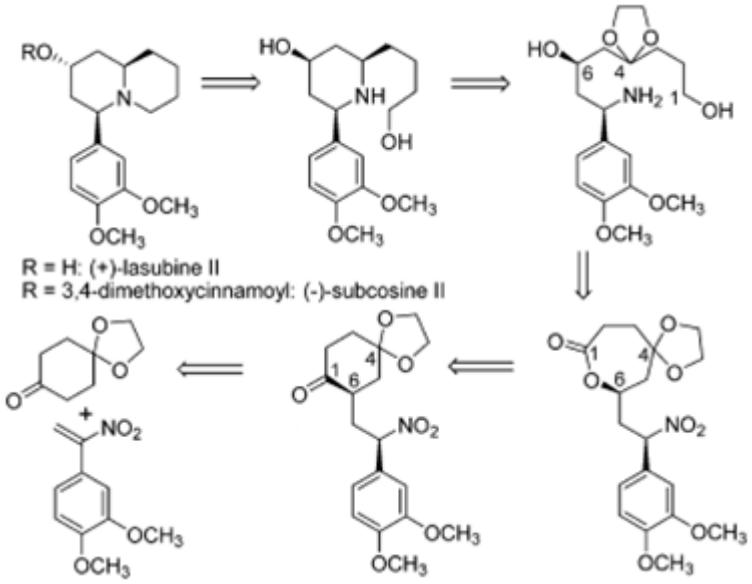
The 4-arylquinolizidine motif is found in several Lythraceae alkaloids of which (−)-lasubine I and (−)-lasubine II are prominent examples.



Selected alkaloids having the 4-arylquinolizidine motif

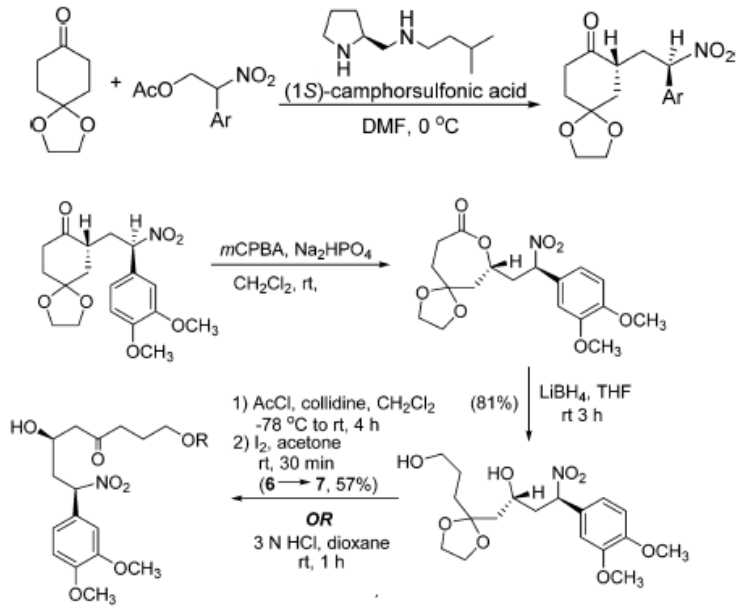
From a structural perspective, the lasubine framework is incorporated in other members of the lythraceous alkaloids such as subcosines I and II and the macrocyclic lactones (+)-lythrine and (+)-vertine. Hence, a synthetic strategy for the lasubines also provides a potential route to the macrocyclic members of the Lythraceae family. Though several enantioselective

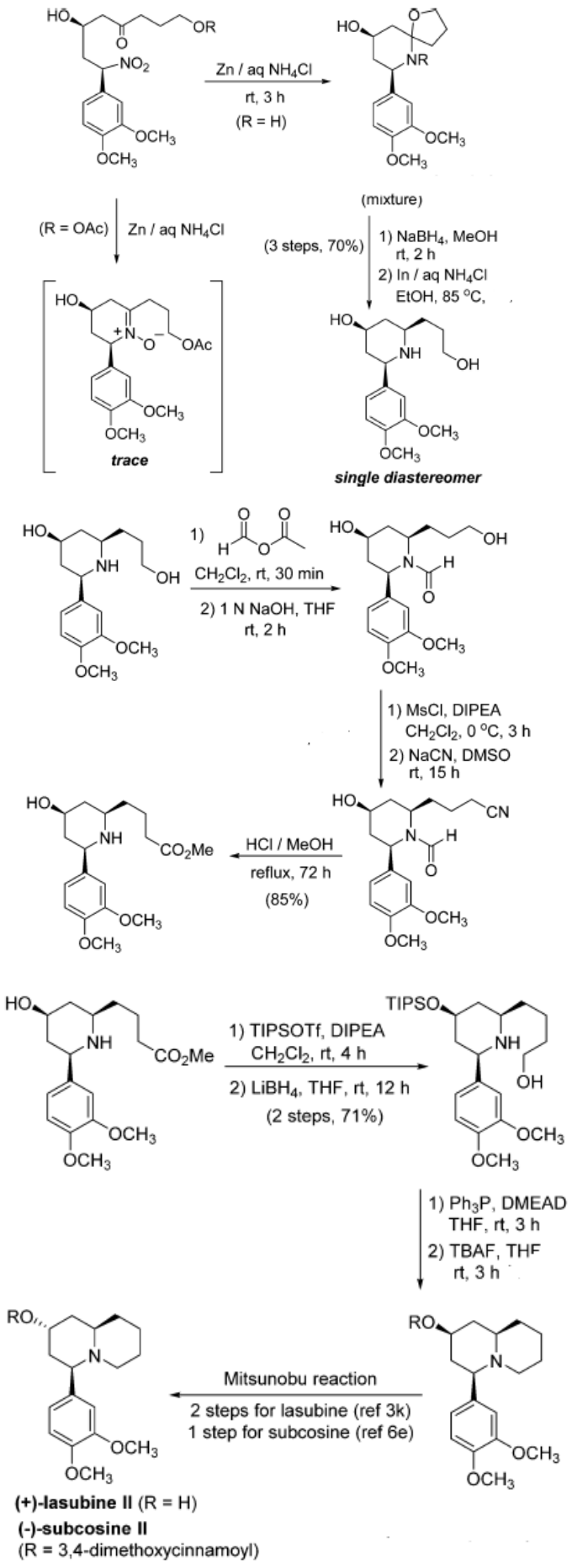
syntheses of lasubine II and subcosine II have been previously reported, in 2015 Sunil V. Pansare, et.al describe the formal syntheses of (+)-lasubine II and (−)-subcosine II. Their strategy employs the previously reported, enantioselective organocatalytic Michael addition of a ketone to an in situ generated α- nitrostyrene as the key step. The retrosynthesis analysis of of (+)-Lasubine II and (−)-Subcosine II by Sunil V. Pansare, et.al is shown below



Retersynthesis strategy for the synthesis of (+)-lasubine II and (−)-subcosine II.

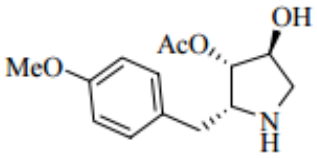
The complete synthesis scheme is shown below




Zn / aq NH4Cl
rt, 3 h
(R = H)
(R = OAc)
Zn / aq NH4Cl
(mixture)
(3 steps, 70%)
1) NaBH4, MeOH
rt, 2 h
2) In / aq NH4Cl
EtOH, 85 °C,
trace
single diastereomer
1)
CH2Cl2, rt, 30 min
2) 1 N NaOH, THF
rt, 2 h
1) MsCl, DIPEA
CH2Cl2, 0 °C, 3 h
2) NaCN, DMSO
rt, 15 h
HCl / MeOH
reflux, 72 h
(85%)
1) TIPSOTf, DIPEA
CH2Cl2, rt, 4 h
2) LiBH4, THF, rt, 12 h
(2 steps, 71%)
1) Ph3P, DMEAD
THF, rt, 3 h
2) TBAF, THF
rt, 3 h
Mitsunobu reaction
2 steps for lasubine (ref 3k)
1 step for subcosine (ref 6e)
(+)-lasubine II (R = H)
(-)-subcosine II
(R = 3,4-dimethoxycinnamoyl)

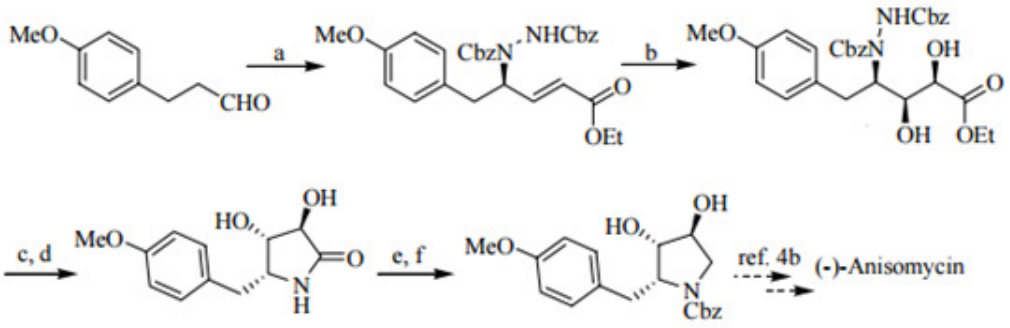
16.8 Formal synthesis of (-) anisomycin

(-) Anisomycin is an antibiotic isolated from the fermentation broth of Streptomyces sp., exhibits a strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to trichomonas vaginitis and of amoebic dysentery



(-)-anisomycin

Arumugam Sudalai et.al have developed and reported a one-pot procedure for the enantioselective synthesis of γ-amino- α,β-unsaturated esters. They have made use of this method for achieving the formal synthesis of (-)-anisomycin (1). Accordingly, L-proline-catalyzed sequential α-amination-Horner-Wadsworth-Emmons olefination of 3-(4-methoxyphenyl)- propanal was carried out to obtain γ-amino-α,β-unsaturated ester.T he Os-catalyzed diastereoselective dihydroxylation of ester furnished the diol. Reductive cyclization of diol was achieved with Raney/Ni (H2, 60 psig) yield with inseparable mixture of diastereomers



Reagents and conditions: (a) DBAD, L-proline, CH_3CN, 0-10 °C, 3 h then triethyl phosphonoacetate, LiCl, DBU, 5 °C, 45 min. (b) OsO4, NMO, acetone-water (c) RaneyNi, MeOH, H_2 (60 psi), 12 h; (d) EtOH, reflux, 4 h. (e) BH_3.THF, THF, reflux, 10 h; (f) aq. Na_2CO_3, Cbz-Cl, CH_2Cl_2, 4 h.

16.9 Cascade reaction [Tandem reaction or Domino reaction]

A cascade reaction or tandem reaction or domino reaction is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates. It allows the organic synthesis of complex multinuclear molecules from a single acyclic precursor. The substrate contains manyfunctional groups that take part in chemical transformations one at the time. Often a functional group is generated in situ from the previous chemical transformation.

The definition includes the prerequisite intramolecular in order to distinguish this reaction type from a multi-component reaction. In this sense it differs from the definition of a biochemical cascade. The main advantages of a cascade reaction in organic synthesis are that the reaction is often fast due to its intramolecular nature, the reaction is also clean, displays high atom economy, does not involve workup and isolation of many intermediates, and adds much complexity in effectively one step.

A domino reaction is a process involving two or more bond transformations (usually involving the C-C bond) which takes place under the same reaction conditions without adding additional reagents and catalyst, and in which subsequent reactions result as a consequence of the functionality formed in the previous step.

A substance with several functionalities which undergo transformations individually in the same pot is not a domine reaction. Clearly the prepliminary formation of an intermediate such as a carbocation or a carbanion is not counted as a reaction step. On the other hand the formation of a diene by a retro-diels- Alder reaction with a subsequent cycloaddition would be considered as a domino reaction.

The classification of domino reactions is based on the intermediate generated in the first step. Thus a clear classification which not only allows a better understanding of the existing domino reaction but also facilitates the investigation of newer domino reactions.

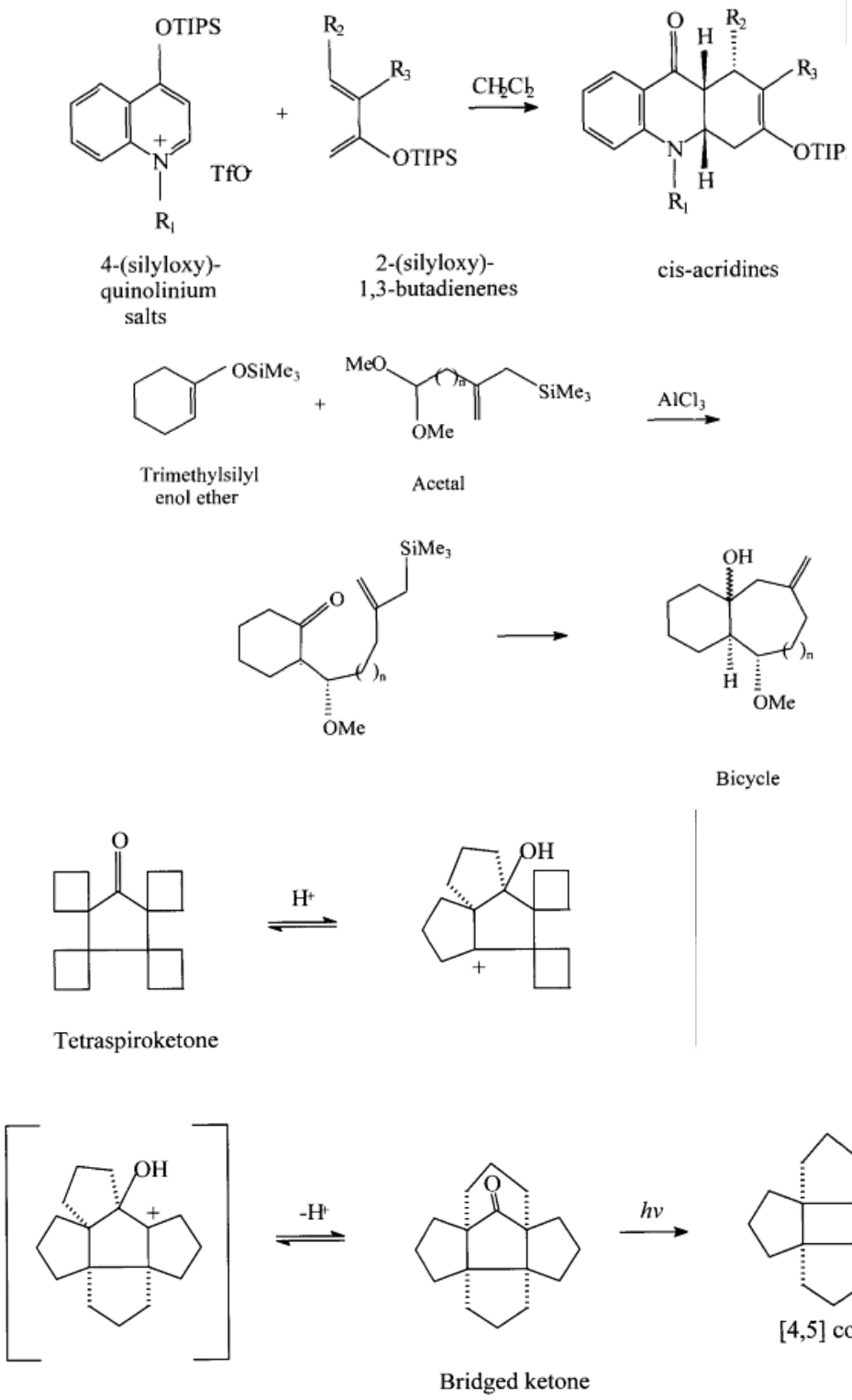
There are altogether four types of domino reactions based on the intermediate generated in the first step.

i) Cationic domino reactions
ii) Anionic domino reactions
iii) Radical domino reactions and
iv) Pericyclic domino reactions

16.9.1 Cationic domino reactions

In these reactions a carbocation is formed, either formally or in reality. This cation can be formed for example elimination of water from alcohols, of alcohols from acetals or by oxidation of a positive particle such as a proton to an alkene or an epoxide. The carbocation then reacts with a nucleophile to form a new carbocation,that undergoes one or more comparable further transformations in a cationic-cationic process, finally being trapped by a nuleophile or stabilized by elimination of a proton.

Some interesting examples of this type of reactions are illustrated below

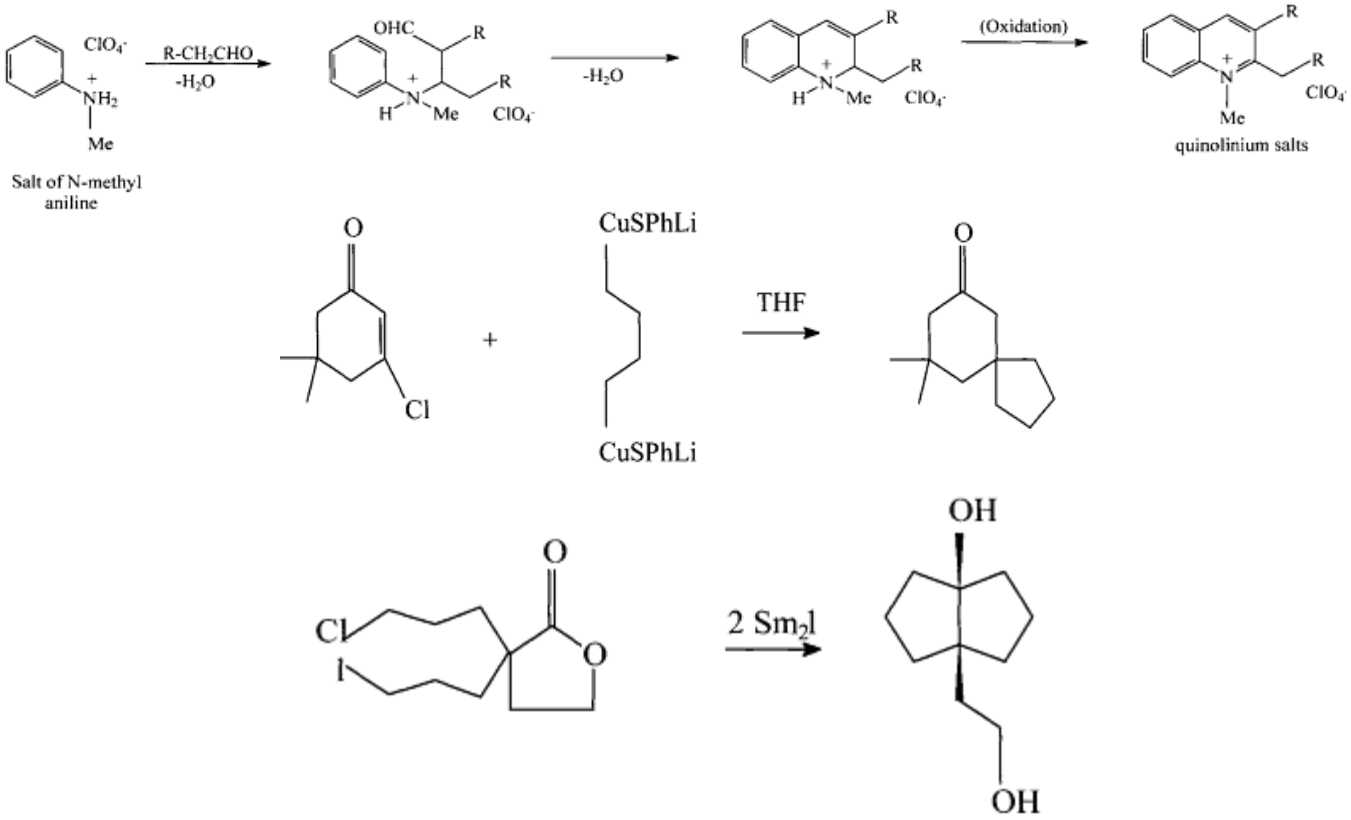


16.9.2 Anionic domino reactions

The anionic domino reactions are the most often encountered domino reactions in literature, especially reactions combining two Michael additions. In this type of reactions the primary step is the formation of an anion or a nucleophile. The majority of cases involve the deprotonation of a C-H group with the formation of a carbanion, which then reacts with an

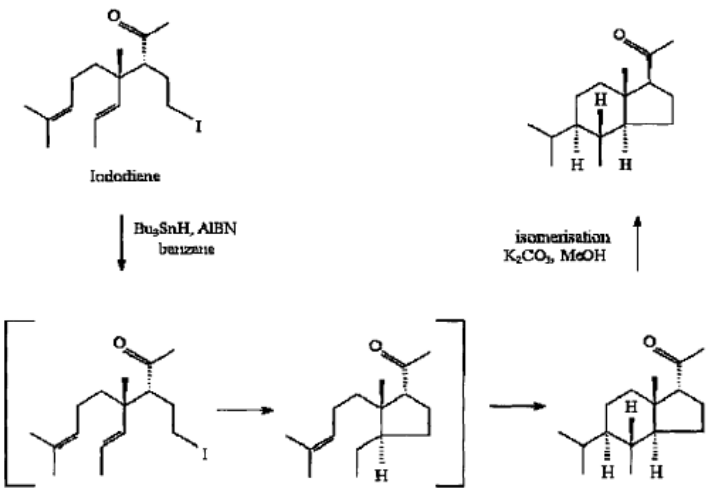
electrophile to form a new anionic functionality. The sequence is complicated by reaction with an electrophile for example a proton or by elimination of an X- group.

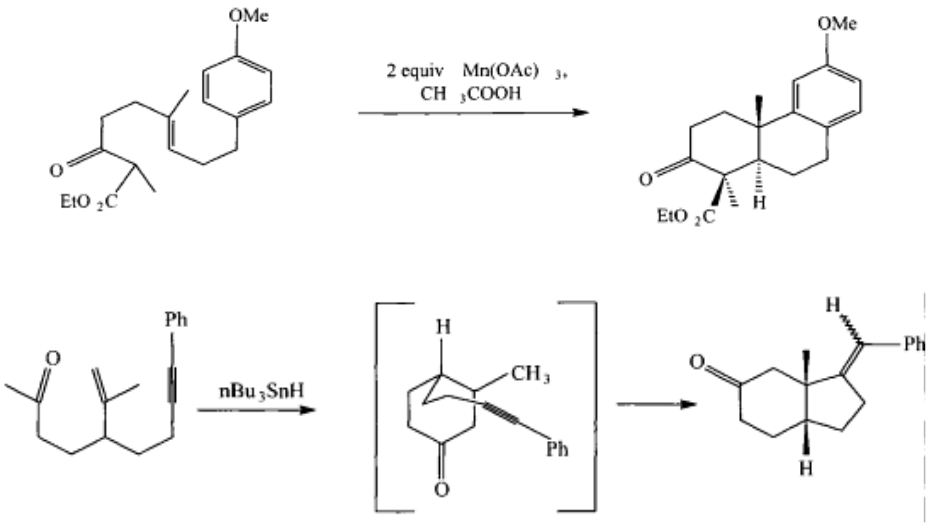
Some of the example of anionic domino type of reactions are illustrated below



16.9.3 Radical domino reactions

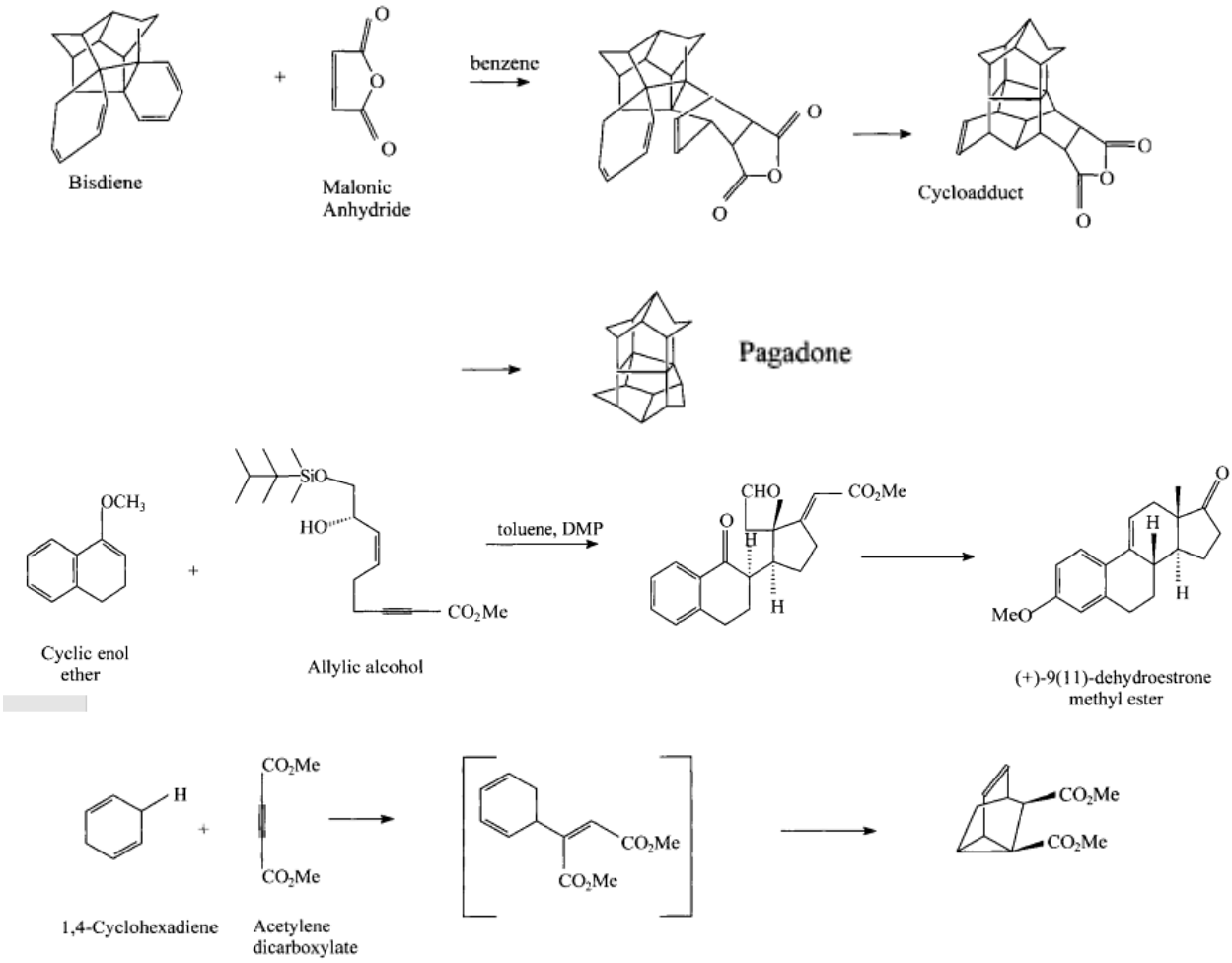
For those reaction sequences that start with a radical primary step, there have been found exclusively examples of homosequence transformations. The formation of radicals can result by the reaction of halogens, phenyl-thio and phenyl selenium compounds. Some examples of radical domino reactions are given below.





16.9.4 Pericyclic domino reactions

Pericyclic reactions can be combined easily with other pericyclic reactions to give sequences. Whether inter or intra molecular, the all-carbon atom or the hetero-atom, normal, neutral or with inverse electron demand this reaction is one of the most efficient methods in the repertoire of the organic chemist. Interesting examples of this type of reactions are illustrate below.



16.9.5 Summary of the unit

Organic Synthesis means the same as synthetic organic chemistry. Total Synthesis is the chemical synthesis of a molecule from a relatively simpler starting materials. Semisynthesis means the synthesis of a given molecule from an advanced precursor related to it. Formal Synthes is the synthesis of a key intermediate that has been already converted into the target molecule and Partial Synthesis is the synthesis of a portion of the naturral product.In synthesis terminology

Tandem means “one after another”

Sequential means “one pot”

Domino means“two or more tranformations forming bonds, taking place under the same reaction conditions”

Cascade “describes how reactions happen-each subsequent change happens under structural change provided by the previous step”

Characteristics of Tandem Reactions

- Occur in succession
- locally, one after another
- Can have independent reaction sites
- Composed of ordinary reactions
- Sometimes *in situ* generation of reactive species

Benefits of Tandem Reactions

- Minimizes steps to build complex molecules
- Cost factor: less waste reduces materials used
- Often reduces natural resources used

16.10 Key words

Total synthesis; Total synthesis of apigenin; Enantioselective Total Synthesis of (−)-Vincorine; Enantioselective Total Synthesis of (+)-anti- and (-)-syn-Mefloquine Hydrochloride; Formal total synthesis; Difference between total synthesis and formal synthesis ; The formal synthesis of dragmacidin B, trans-dragmacidin C; Formal Synthesis of (+)-Lasubine II and (−)-Subcosine II; Formal synthesis of (-) anisomycin; Cascade reaction [Tandem reaction or Domino reaction]; Cationic domino reactions ; Anionic domino reactions; Radical domino reactions; Pericyclic domino reactions.

16.11 References for further studies

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2) Domino Reactions in Organic Synthesis, Lutz F. Tietze, *Chem. Rev*., **1996**, 96 (1), pp 115–136.
3) Studies in Natural Products Chemistry, Volume 35, Atta-ur-Rahman, *Elsevier*, **2008**.
4) Enantioselective Chemical Synthesis: Methods, Logic, and Practice; Elias J. Corey, Laszlo Kurti; *Elsevier*, **2013**.
5) Total Synthesis of Natural Products: At the Frontiers of Organic Chemistry; Jie Jack Li, E.J. Corey; *Springer Science & Business Media*, **2013**.
6) Classics in Total Synthesis: Targets, Strategies, Methods; K. C. Nicolaou, E. J. Sorensen; *Wiley*, **1996**.

16.12 Questions for self understanding

1) What is total synthesis of organic compound?
2) Discuss the total synthesis of apigenin.
3) Explain the enantioselective Total Synthesis of (−)-Vincorine.
4) Explain the enantioselective Total Synthesis of (+)-anti- and (-)-syn-Mefloquine Hydrochloride.
5) What is formal total synthesis of organic compound?
6) Explain the differences between total synthesis and formal synthesis.
7) Explain the formal synthesis of dragmacidin B, trans-dragmacidin C.
8) Explain the formal Synthesis of (+)-Lasubine II and (−)-Subcosine II.
9) Explain the formal synthesis of (-) anisomycin.
10) What is Cascade reaction [Tandem reaction or Domino reaction]?
11) With suitable example explain the cationic domino reactions.
12) With suitable example explain the anionic domino reactions.
13) With suitable example explain the radical domino reactions.
14) With suitable example explain the pericyclic domino reactions.