ORGANIC SYNTHESIS

Kevin Shea
Smith College

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Organic Synthesis

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About the Author

Dr. Kevin Shea is a Professor of Chemistry at Smith College in Northampton, Massachusetts. He earned his BS in chemistry at WPI in Worcester, MA and his PhD in organic chemistry at MIT in Cambridge, MA. His graduate mentor at MIT was Prof. Rick Danheiser. Kevin received Smith's Faculty Teaching Award in 2007 and is a former Director of Smith's Faculty Teaching and Learning Center. He regularly teaches Organic Chemistry I and II (lecture and lab) along with Organic Synthesis (lecture) and Synthesis and Structural Analysis (lab). Kevin's education-based research focuses on innovations in both the lecture and the lab and includes articles in the *Journal of Chemical Education* on using clickers in organic chemistry, incorporating current literature into Organic II, and developing an Organic II CURE (Course-based Undergraduate Research Experience) focused on isolating and derivitizing a natural product with anti-filarial properties. Kevin's research lab is focused on synthetic organic chemistry and includes applications of cobalt-complexed alkynes with results published in *Organic Letters* and the *Journal of Organic Chemistry*.

Introduction and Acknowledgements

Introduction

My goal in writing this text is to help advanced undergraduates and beginning graduate students learn key topics in organic chemistry that often don't come up in your Organic I and II classes. So, you can think about this as an Organic III text. My focus is on key reaction types that enable the construction of complex organic molecules: pericyclic reactions, transition metal catalyzed reactions, rearrangements, fragmentations, radical reactions, and carbene reactions. I hope that this text is a resource that helps you understand the mechanisms of these reactions and enables you to use these reactions in your own syntheses. I have provided a variety of mechanism and synthesis problems to help you practice these skills and make them your own. One of the main goals in my Organic Synthesis class is to engage deeply with current papers from the literature. I hope you will do the same and that this text will help you understand some of the concepts and reactions that often go unspoken in publications.

Acknowledgements

My most important acknowledgement is to my graduate research advisor, Rick Danheiser. Rick is one of the most passionate and dedicated teachers I have ever met. This text is based in large part on Rick's Organic Synthesis graduate class from my first semester at MIT. He was able to clearly convey the complex material encountered in his class and motivated me to learn it deeply. He also helped me see the beauty in organic synthesis and provided an important appreciation for the history of the field. Without the foundation from Rick's class, this text would not exist. Thank you, Rick!

I would also like to thank Kerry Barnett and Leslie Nickerson, who were teaching-research postdocs in my lab between 2017-2021. Kerry and Leslie each taught Organic Synthesis with me once during their time at Smith and both provided key improvements to the class. This text is definitely better thanks to the input of Kerry and Leslie.

Finally, I would like to thank all of the Smith students who have taken Organic Synthesis with me. I have taught this class every other year since 2001, and it is always a joy to teach. I am continually amazed at the enthusiasm and dedication that they all bring to the study of advanced organic chemistry.

CHAPTER OVERVIEW

1: Pericyclic Reactions

1.1: Introduction to Pericyclic Reactions
1.2: Cycloaddition Reactions
1.3: Electrocyclic Reactions
1.4: Sigmatropic Rearrangements

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1.1: Introduction to Pericyclic Reactions

Learning Objectives

After completing this section, you should be able to:

1. identify a reaction as a cycloaddition, electrocyclic reaction, or sigmatropic rearrangement.
2. draw curved arrows to explain the electron movement in a pericyclic reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- pericyclic reaction
- cycloaddition
- electrocyclic reaction
- sigmatropic rearrangement

Study Notes

Pericyclic reactions proceed by a rearrangement of electrons through a cyclic transition state and are distinct from polar and radical reactions that students first learn about in introductory organic chemistry. This brief chapter introduces the topic of pericyclic reactions and provides examples of the three classes of reactions. The following chapters go into depth for cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.

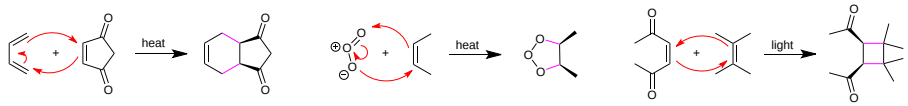
Content

Prior to 1965, pericyclic reactions were known as "no mechanism reactions" since no one could adequately explain why reaction outcomes changed depending on whether reactants were exposed to heat or light. In 1965 Robert Burns Woodward and Roald Hoffmann used Frontier Molecular Orbital Theory, initially proposed by Kenichi Fukui, to develop their Theory of Conservation of Orbital Symmetry where outcomes of pericyclic reactions are explained by examining the Highest Occupied Molecular Orbital (HOMO) or Lowest Unoccupied Molecular Orbital (LUMO) of the reacting system. Their analysis of cycloadditions, electrocyclic reactions, and sigmatropic rearrangements is commonly referred to as the Woodward-Hoffmann Rules. A brief overview of these three reaction types is shown below and a detailed analysis is provided in the subsequent chapters.

All pericyclic reactions are concerted, they occur in one step with no intermediates formed. They are highly stereoselective, thus providing excellent methods for the synthesis of stereocenters. Product formation depends on three things: 1) Structure of the reactant, 2) Number of electrons (orbitals) involved, and 3) Conditions (heat or light). Understanding the outcome of pericyclic reactions is only possible by looking at the molecular orbitals involved, and only in-phase orbitals can overlap to form bonds during pericyclic reactions.

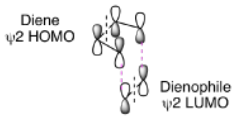
Cycloadditions

Cycloaddition reactions can be inter- or intramolecular and involve two different pi systems combining to form two new sigma bonds. (Cycloadditions are the only pericyclic reactions that can involve intermolecular reactions. The reverse of a cycloaddition is a cycloreversion.) They are the most convergent and synthetically useful pericyclic reactions. Common examples of cycloadditions include the Diels-Alder reaction to form 6-membered rings, dipolar cycloadditions to form 5-membered rings, and photo [2+2] cycloadditions to form 4-membered rings. Examples are shown below with the newly formed sigma bonds in the products highlighted in magenta. It is important to note that the first two examples are possible with heat while the final example only happens with light.



Diels-Alder Reaction Dipolar Cycloaddition Photo [2+2] Cycloaddition

To understand these results, as mentioned above, we must look carefully at the pi system HOMO and LUMO involved in each reaction. An example of this is provided below. In a standard Diels-Alder reaction, an electron rich diene reacts with an electron poor dienophile, meaning the diene reacts from its pi HOMO (psi 2) while the dienophile reacts from its pi LUMO (psi 2). (Note: The dashed black lines in the figure below represent nodes in the pi molecular orbitals of the diene and dienophile.) The two new sigma bonds, shown as dashed magenta lines below, are formed from constructive overlap of the dienophile orbitals with the terminal orbitals of the diene.



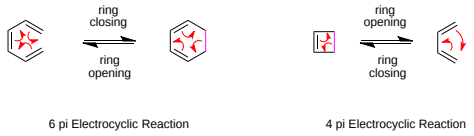
We will explore a more detailed analysis of these orbital interactions in the next chapter. For now, we can summarize the most common outcomes in the table below. We should note that there is one important cycloaddition, the [2+2] thermal reaction of ketenes that does not conform to this generalized analysis.

Generalized Statement of Woodward-Hoffmann Rules for Cycloadditions

Number of Electrons	Thermal	Photochemical
4n + 2	Allowed	Forbidden
4n	Forbidden	Allowed

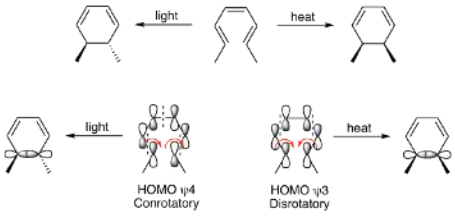
Electrocyclic Reactions

Electrocyclic reactions are intramolecular reactions that are ring closing (form a sigma bond) or ring opening (break a sigma bond). The key sigma bond, either formed or broken, must be at the terminus of a pi system so that either the product or reactant must be a fully conjugated diene, triene, etc. These reactions are often reversible and are classified by the number of pi electrons involved. Thus, 4 pi reactions involve the forming/breaking of 4 membered rings, 6 pi reactions involve the forming/breaking of 6 membered rings, and so on. The 4 pi and 6 pi variants are by far the most common and are illustrated below with the key sigma bond highlighted in magenta.



Electrocyclic reactions happen from the HOMO of the molecule and differ in their outcomes based on orbital rotation for the forming/breaking sigma bond. If the orbitals involved rotate in the same direction (both counterclockwise or both clockwise), the process is called conrotatory. If the orbitals involved rotate in opposite directions (one clockwise and one counterclockwise), the process is called disrotatory. These differences in rotation are critically important when stereocenters are formed or broken.

As illustrated below, treatment of the susbstituted hexatriene shown yields the cis product when heated but the trans product when treated with light. This can be explained by looking at the pi HOMO for each case. For the thermal reaction, the HOMO is psi 3 which rotates in a disrotatory fashion to yield the cis product while the trans product is formed under irradiation due to the conrotatory motion of the HOMO psi 4.



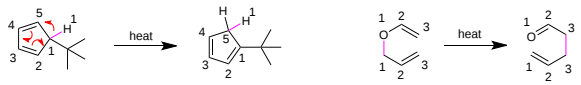
We will delve deeper into this analysis in a subsequent chapter. In general, electrocyclic reactions behave according the generalized rules outlined below.

Generalized Statement of Woodward-Hoffmann Rules for Electrocyclic Reactions

Number of Electrons	Thermal	Photochemical
4n + 2	Disrotatory	Conrotatory
4n	Conrotatory	Disrotatory

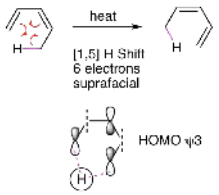
Sigmatropic Rearrangements

Sigmatropic rearrangements involve an intramolecular rearrangement of a pi system where a sigma bond in the reactant is broken and reformed in a different position in the product. The reactant and product have the same number and type of bonds, just different bond locations. The most common examples include hydrogen shifts across a diene system (called a [1,5] H shift) and rearrangements of double allyl-type systems (called [3,3] rearrangements). Sigmatropic rearrangements are labeled based on the position of the sigma bond in the reactant that is broken compared to the position of the sigma bond in the product that is formed. As shown in the examples below, the atoms on the sigma bond in the reactant that is broken (magenta bond) are both labeled "1", and the numbering of atoms on each side of that sigma bond continue until the atoms connected by the new sigma bond in the product (magenta) are reached. Thus, the H shift is [1,5] because the key sigma bond in both the reactant and product is to the H while the H moves from C-1 to C-5. For the [3,3] rearrangement, the broken sigma bond migrates across two allyl-type systems and forms between atoms "3" and "3" in the product. This particular example is a Claisen rearrangement since an allyl vinyl ether is transformed into a 1,4-carbonyl alkene.



[1,5] H Shift [3,3] Rearrangement

Sigmatropic rearrangements can occur on one face of the molecule (think top or bottom, like a syn addition to an alkene) which is called a suprafacial reaction or from one face to the other (think from top to bottom or vice versa, like an anti addition to an alkene) which is called antarafacial. Suprafacial reactions are much more common. For example, a [1,5] H shift like the one shown below illustrates a hydrogen atom (s orbital) moving across a 5 atom pi system in a suprafacial fashion. The bond breaking and the bond forming, magenta dashed lines, are both on the bottom face of the pi system. Since three curved arrows are involved in the mechanism, this is a 6 pi reaction.



We will explore these ideas further in a subsequent chapter. The general rules for sigmatropic rearrangements are shown in the table below.

Generalized Statement of Woodward-Hoffmann Rules for Sigmatropic Rearrangements

Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial	Antarafacial
4n	Antarafacial	Suprafacial

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1.2: Cycloaddition Reactions

Objectives

After completing this section, you should be able to

1. Identify cycloaddition reactions including the Diels-Alder reaction, dipolar cycloaddition, photo [2+2] reaction, thermal ketene [2+2] reaction, and ene reaction.
2. Understand the orbital analysis of cycloaddition reactions
3. Draw curved arrows to illustrate electron flow for cycloaddition reactions
4. Given cycloaddition starting materials, accurately predict the product including stereochemistry
5. Use retrosynthetic analysis to determine starting materials given a cycloaddition target

Key Terms

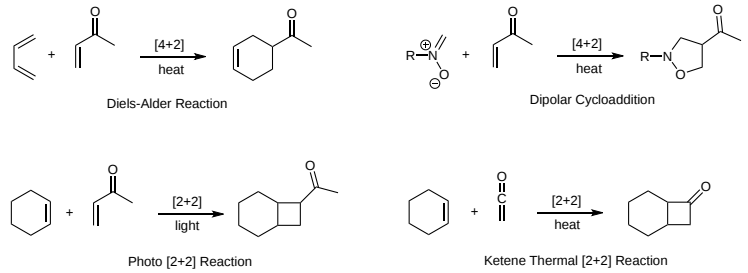
Make certain that you can define, and use in context, the key terms below.

- Diels-Alder reaction
- Diene
- Dienophile
- HOMO
- LUMO
- Dipolar cycloaddition
- Dipole
- Dipolarophile
- Photo [2+2] cycloaddition
- Ketene thermal [2+2] cycloaddition
- Ketene
- Ketenophile
- Ene reaction
- Ene
- Enophile

Study Notes

Cycloadditions are highly synthetically useful reactions that provide access to 4-, 5-, and 6-membered rings with excellent stereocontrol. Your goal is to understand the theoretical basis of these reactions using a molecular orbital analysis and to apply these reactions in synthesis. You should focus on accurately predicting products with a focus on stereochemistry and, given a complicated cyclic product, to accurately predict the starting materials used to generate it.

The previous section provided an overview of cycloaddition reactions. They are one class of pericyclic reactions that involve combination of two different pi systems to yield a cyclic product. They can be inter- or intramolecular and can produce all carbon and heterocyclic ring systems. They are powerful tools that synthetic chemists often employ to generate ring structures central to complex natural products. The following scheme highlights the four major types of cycloaddition reactions that we will study in this chapter: Diels-Alder reaction, dipolar cycloaddition, photo [2+2] reaction, and thermal ketene [2+2] reaction. We will also see an additional cycloaddition reaction, the ene reaction, that is related to the Diels-Alder reaction but doesn't form a ring.

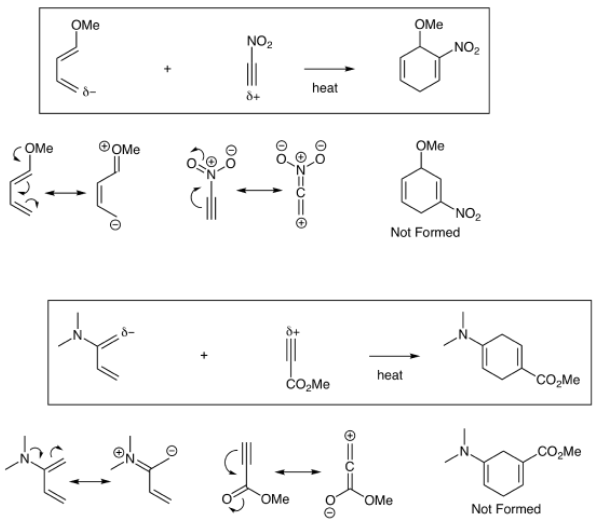


Diels-Alder Reaction

The Diels-Alder reaction is a [4+2] cycloaddition (4 pi electrons from one reactant and 2 pi electrons from the other reactant) that yields a functionalized 6-membered ring product. It is the most useful cycloaddition reaction due to the ubiquity of 6-membered rings and its ability to reliably control stereochemistry in the product. Students generally learn about this reaction in introductory organic chemistry, so this section will start with an overview of key points before addressing more advanced concepts.

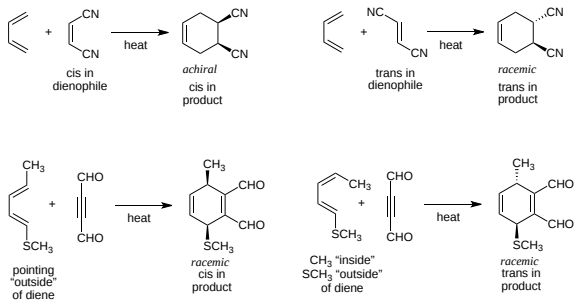
Regiochemistry

In standard Diels-Alder reactions, an electron rich diene (4 pi component) reacts with an electron poor dienophile (2 pi component). To determine how they combine, you must identify the most electron rich terminal atom of the diene and have that atom form a bond with the most electron poor atom of the dienophile. This is sometimes called the Ortho/Para Rule which can lead to confusion since we generally aren't making benzene products. We will avoid this memorization tool and instead focus on drawing resonance structures to find the key electron rich and electron poor atoms as demonstrated below. The examples below also demonstrate that the dieophile can be an alkyne which yields a cyclohexadiene product.



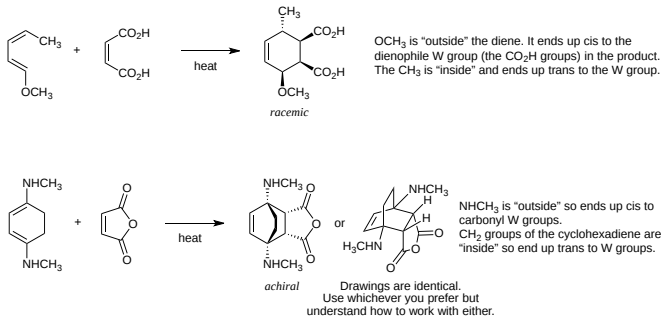
Stereochemistry - Stereospecific for Diene and Dienophile Atoms

Due to the concerted mechanism for cycloaddition reactions, the geometry of atoms on the dienophile or the diene maintain their orientation in the product. This is a critical point for the 4 atoms (both dienophile atoms and the terminal atoms of the diene) that become sp^3 hybridized and thus are potential stereocenters in the product. (As a reminder, when chiral products are formed, we obtain a racemic mixture of enantiomers.) As highlighted below, cis dienophiles yield cis substituents in the product, while trans dienophiles yield trans product substituents. Substituents on the terminal atoms of the diene also can become stereocenters and this analysis is a little less straightforward than for dienophile substituents. The way to think about the diene substituents is whether the are pointing "outside" or "inside" the diene. These orientations are illustrated below. When groups are both pointing "outside" or "inside", we can consider them to be cis and they will end up cis in the product. When one group is pointing "outside" and one "inside", we can consider them as trans and they will be trans in the product. Note: CHO is a common abbreviation for an aldehyde.



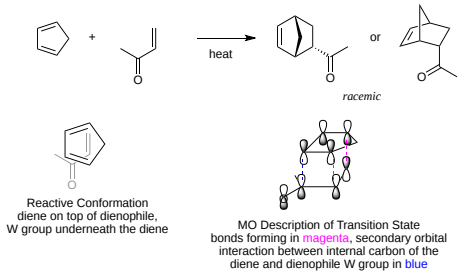
Stereochemistry - Alder Endo Rule

The Alder Endo Rule enables us to predict the product stereochemistry when new stereocenters are created on atoms that originated in both the diene and dienophile. This rule is often described using the terms endo and exo in relation to the structure of bicyclic products. This is often confusing and difficult to apply in many circumstances. Instead we will define it in relation to substituents on the diene and dienophile. (We will explain the orbital origin of this rule shortly.) The Alder Endo Rule states the the electron withdrawing group on the dienophile (W group) ends up cis to groups pointing "outside" the diene in the cyclohexene product. The two reactions below illustrate the Alder Endo Rule and how to apply it. The second reaction highlights what we will see often in this section; cyclic dienes react with cyclic dienophiles to create complicated polycyclic products. We need to pay careful attention to stereochemistry in these cases and can use either option for drawing the result.



Transition State

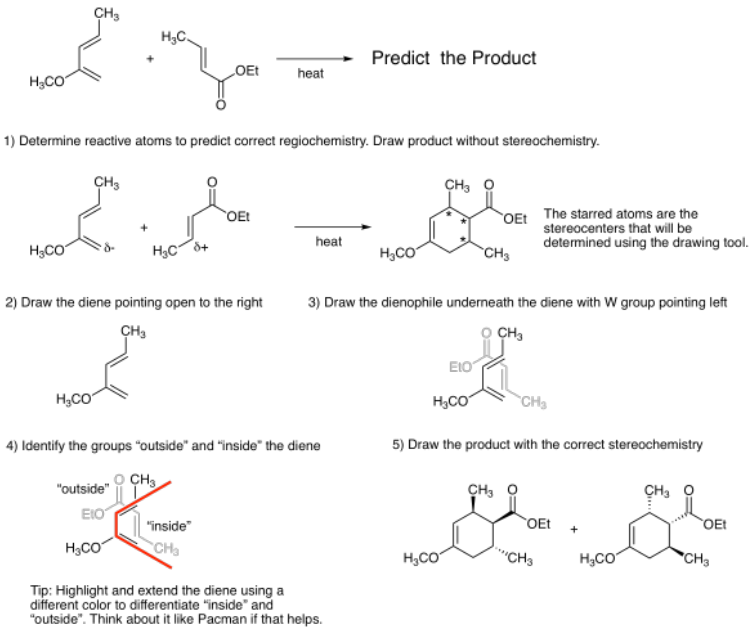
Like all cycloaddition reactions, the Diels-Alder is concerted. Its mechanism has one transition state and no intermediates. The orientation of the reactants in the transition state determines the structure of the product. As previously mentioned, the way we can understand the mechanism is to look at the molecular orbitals involved. This will illustrate that there are primary orbital interactions (shown below in magenta), the orbitals that overlap to form new sigma bonds, and secondary orbital interactions (shown in blue), the orbitals that interact to give rise to the Endo Rule. The reactive conformation and transition state shown below illustrate that the stereochemistry is set when the reactants come together in the transition state with the W group pointing the opposite direction of the CH_2 in the cyclopentadiene ring. Thus, the bridge in the bicyclic product (the CH_2 from the reactant) is trans to the ketone.



Diels-Alder Drawing Tool

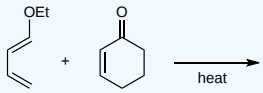
One way to keep track of stereochemistry in the Diels-Alder reaction is to use a drawing tool that mimics the reactive conformation. Note: Follow the rule for determining the regiochemistry and be sure to place the most electron rich terminal atom of

the diene next to the most electron poor atom of the dienophile when using this tool. It is easy to get the incorrect product if you forget this step. First, draw the structure of the cyclohexene product ignoring stereochemistry. (The next steps will enable you to determine the stereoechemistry in the product.) Second, draw the diene with the opening pointing to the right. Third, draw the dienophile underneath the diene with the W group pointing left. Fourth, identify substituents that are positioned "outside" the diene and substituents that are positioned "inside" the diene. All groups "outside" will be cis in the product. All groups "inside" will be cis in the product. "Outside" groups will be trans to "inside" groups in the product. The figure below illustrates how to use the drawing tool. Fifth, redraw the product with all of stereochemistry.

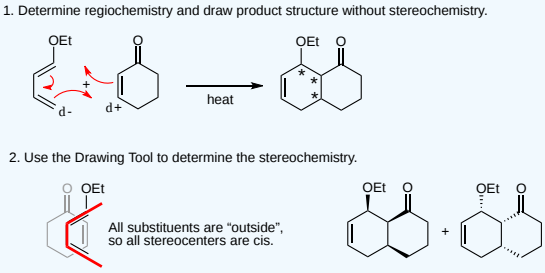


Exercise 1.2.1

Predict the product of this intermolecular Diels-Alder reaction. Clearly show both enantiomers of the product.

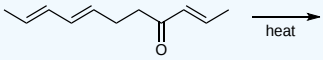


Answer



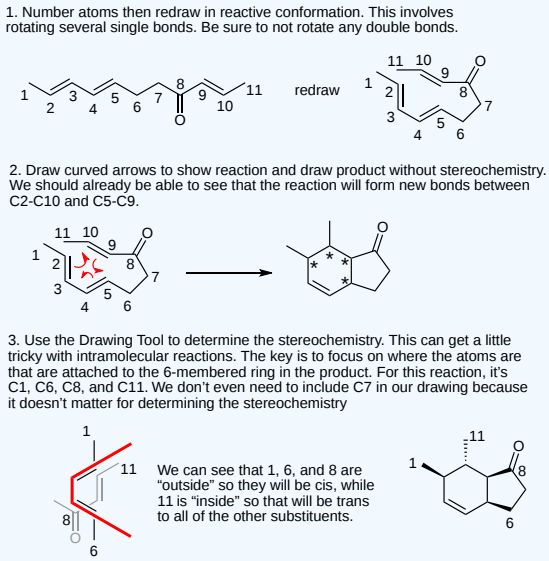
Exercise 1.2.2

Predict the product of this intramolecular Diels-Alder reaction. Clearly show both enantiomers of the product.



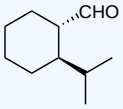
Hints: For intramolecular reactions, regiochemistry considerations are often ignored because one bicyclic structure is much more stable than the other possibility. Be sure to number out the starting material to identify the cyclohexene that will form and the size of the other ring that is produced as a result of the Diels-Alder reaction. Try your best to redraw the molecule in a reactive conformation. The Drawing Tool also works well for intramolecular reactions to help determine the stereochemistry of the product.

Answer



Exercise 1.2.3

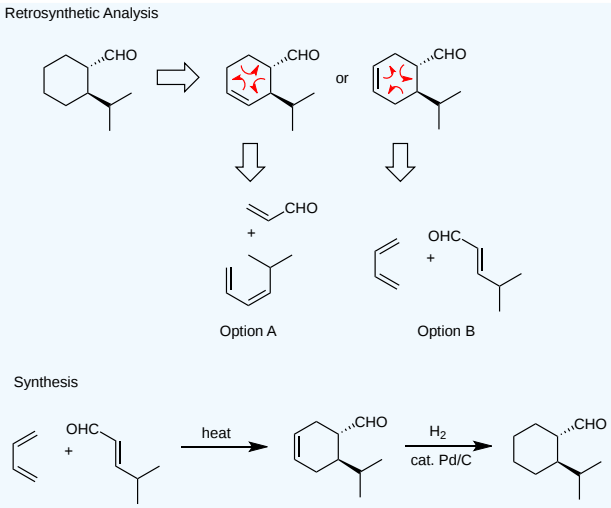
Propose a synthesis of the following substituted cyclohexane.



Hints: This takes more than one step. Try to think retrosynthetically. Focus on forming the stereocenters using the Diels-Alder reaction. Think about the electronic requirements of the Diels-Alder reaction.

Answer

This target is a substituted cyclohexane. The Diels-Alder reaction yields a substituted cyclohexene. So, this product was likely made by alkene hydrogenation of a Diels-Alder product. When thinking backwards, this means we need to determine which position in the six-membered ring contained the double bond. We know that the Diels-Alder reaction is an excellent method for making stereocenters, so we should assume the carbons with the aldehyde and isopropyl groups aren't part of the alkene. We also know that standard Diels-Alder reactions have electron withdrawing groups on the dienophile, so we should place the alkene in a position where the aldehyde starts on the dienophile. This leads to two possibilities for cyclohexene targets.

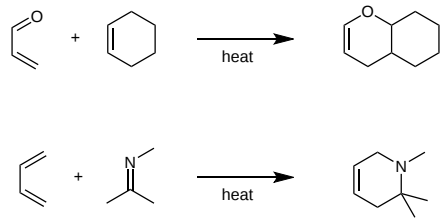


In option A, the atoms that will become stereocenters originate on both the diene and dienophile. This means that the isopropyl group must point "inside" the diene to yield the trans product according to the Endo Rule. This type of diene conformation is sterically very hindered as can be seen just looking at the image, so the diene will prefer to be in an unreactive conformation (rotate the singe bond between the two alkenes) and this reaction will occur slowly. Option B has no drawbacks. We have a simple and reactive diene and a trans dienophile that will yield the desired trans product.

The synthesis follows in two steps from the retrosynthetic analysis.

Forming Heterocycles with the Diels-Alder Reaction

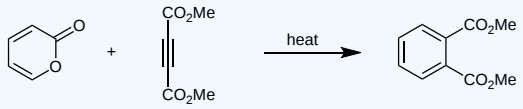
There are many fascinating applications of the Diels-Alder reaction. We have already seen in the problems above that we will encounter intramolecular Diels-Alder reactions to enable us to make complicated polycyclic targets. We will also encounter hetero Diels-Alder reactions where one or more atoms of the diene or dienophile contains atoms other than carbon. Oxygen and nitrogen are most popular and will enable us to make six-membered heterocyclic rings, as shown below. Additionally, it is important to note that Diels-Alder reactions can be promoted not only with heat but also with Lewis acids. These reagents bind to the dienophile electron withdrawing group, making the most reactive carbon more electron poor and, thus, more reactive.



With the right combination of diene, dienophile, and an interesting cascade mechanism, the Diels-Alder reaction can yield benzene products. The reaction shown below is one example. This is a two step process involving a cycloaddition and a cycloreversion. Try to generate a mechanism to explain this interesting reaction. Why is this a favorable process?

? Exercise 1.2.4

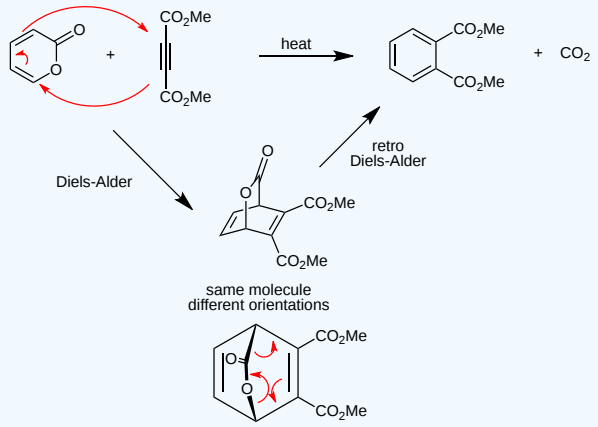
Propose a mechanism and explain why this is a favorable reaction.



Answer

The first step is the Diels-Alder reaction that we would expect to yield the bicyclic intermediate that then breaks down via a retro Diels-Alder reaction (cycloreversion). The intermediate isn't the product because the cycloreversion yields a stable

aromatic product and generates a stable gaseous product that bubbles out of the reaction.



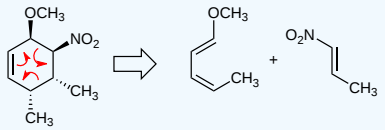
Diels-Alder Reaction and Retrosynthetic Analysis

In one of the problems above, we introduced the idea of thinking backwards using retrosynthetic analysis to help us determine the diene and dienophile that could react to yield a target six-membered ring. This is a skill that we will use often when analyzing complicated targets. The key structural fragment, or retron, that we look for in a molecule that alerts us that we can make it by a Diels-Alder reaction is a six-membered ring. More specifically, it's a six-membered ring containing one pi bond. For a traditional all-carbon Diels-Alder reaction, the retron is a cyclohexene. The following examples highlight how we can use retrosynthetic analysis for standard synthesis problems.

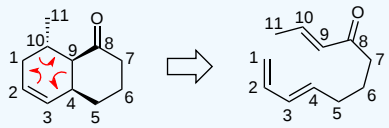
Exercise 1.2.5

Propose a Diels-Alder reaction that will yield each of the target molecules.

Answer



Begin your retrosynthetic analysis by performing a retro Diels-Alder reaction to reveal the diene and dienophile that can combine to make your target. Draw your first curved arrow by starting at the alkene in the six-membered ring. Move the electrons clockwise or counterclockwise then draw the resulting diene and dienophile. The stereochemistry in the product will dictate how the subsitutuents are arranged on the starting materials. In this case, the dienophile contains a nitro electron withdrawing group and a trans methyl. The methoxy substituent on the diene must be pointing out since it ends up cis to the nitro group in the product. The methyl group on the diene must be pointing in because it is trans to the methoxy in the product.

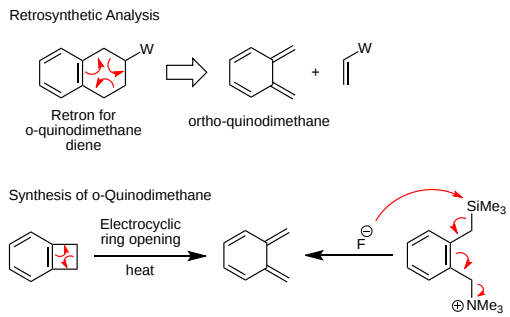


It is often helpful to number all of the atoms in the product before beginning your retrosynthetic analysis. For complicated structures, like this bicyclic target, it is essential to number the atoms. We use the same strategy as the first problem by

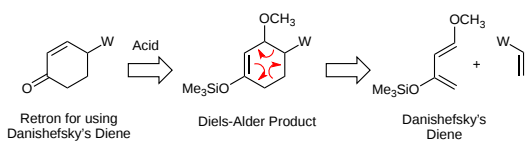
beginning our curved arrows for the retro Diels-Alder at the alkene. This reveals that we are breaking C1-C10 and C4-C9 and that we must perform an intramolecular Diels-Alder to generate the target. Be sure to pay attention to stereochemistry which reveals that the dienophile stereochemistry is trans (since C8 and C11 are trans in the product). Since C5 and the ketone withdrawing group are cis, C5 must be pointing out on the diene.

Synthetically Useful Diels-Alder Dienes

There are several other specific target structures that we need to become familiar with since they will show up in future synthetic applications. The first is a bicyclic 6,6 system with one benzene ring. This is a retron for a Diels-Alder reaction using an ortho-quinodimethane diene. Dienes of this type are highly reactive and are generally made by two different strategies. One is an electrocyclic ring opening, a reaction we will study in more detail in the next chapter, and the other is a fluoride promoted vinylogous elimination reaction.

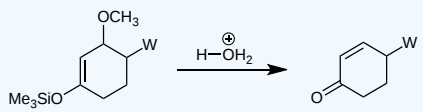


Conjugated cyclohexenones are highly valuable synthetic building blocks. These types of structures are often made using enolate chemistry, specifically the Robinson annulation. They can also be synthesized via the Diels-Alder reaction using a diene developed by Sam Danishefsky which is known as Danishefsky's diene. The Diels-Alder retron for use of this diene is shown below along with the complete retrosynthetic analysis and the structure of Danishefsky's diene. The Diels-Alder product of this reaction yields the target cyclohexenone upon treatment with acid. Propose a mechanism for this process which is a good review of acid promoted carbonyl-type chemistry.

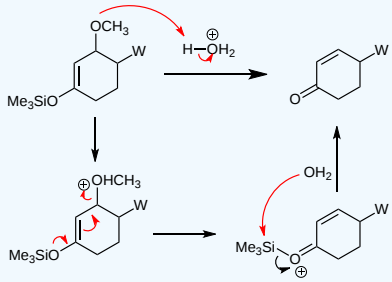


Exercise 1.2.6

Propose a mechanism for the conversion of the Diels-Alder product from use of Danishefsky's diene into the target cyclohexenone product upon treatment with acid.

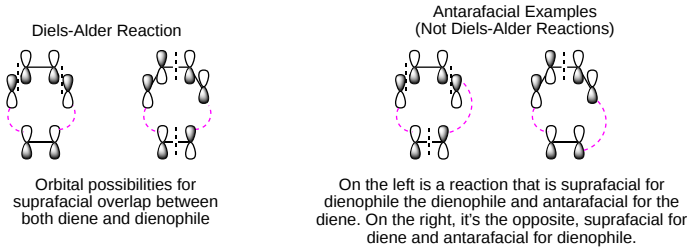


Answer

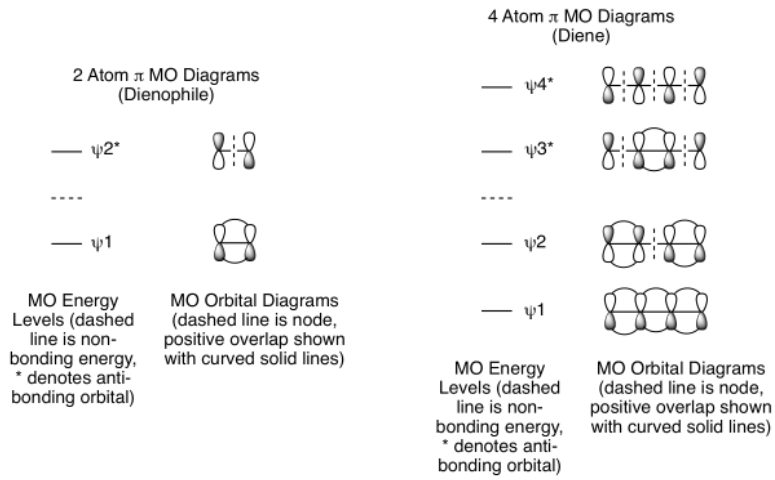


Diels-Alder Reaction Orbital Analysis

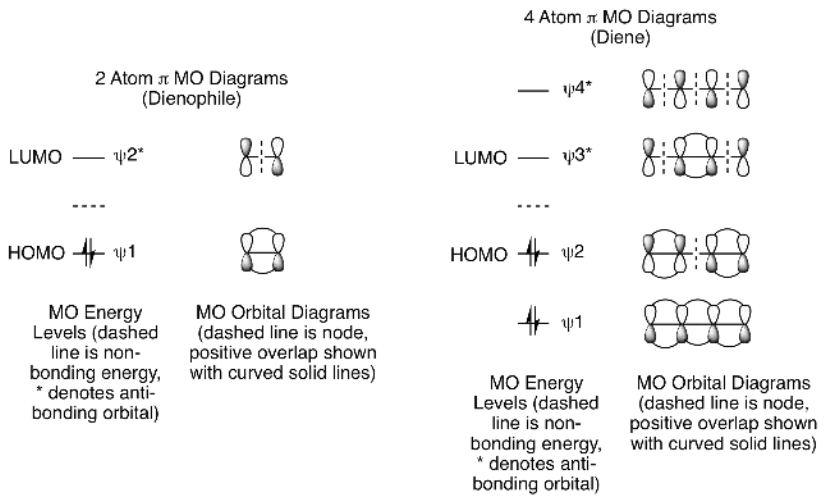
To understand why the Diels-Alder reaction occurs thermally and not photochemically, we must analyze the molecular orbitals involved in the reaction. This type of analysis, often called the Woodward-Hoffmann Rules, was introduced in the previous chapter. We will take a deeper look in this section. As mentioned previously, cycloadditions combine two independent pi systems to form two new sigma bonds. We must have constructive overlap between the Highest Occupied Molecular Orbital (HOMO) of one system (the nucleophile) and the Lowest Unoccupied Molecular Orbital (LUMO) of the other system (the electrophile). There are two possible modes or overlap: suprafacial, where both sigma bonds form on the same side of the pi system, and antarafacial, where the sigma bonds form on opposite sides of the pi system. Examples similar to these modes of overlap are also found in alkene reactions. Suprafacial reactions are similar to alkene syn additions (e.g., H_2, cat. Pd/C) while antarafacial reactions are similar to alkene anti additions (e.g., Br_2). The Diels-Alder reaction is suprafacial with respect to both diene and dienophile, as illustrated below. (The diene is on the top; the dienophile on the bottom. Dashed black lines are nodes; dashed magenta lines are constructive overlap where new sigma bonds can form.) Two examples of antarafacial reactions (that don't actually occur) are shown for comparison. Antarafacial cycloadditions are very unusual, and we will only discuss one example, the ketene thermal [2+2] reaction that will be introduced later in this chapter.



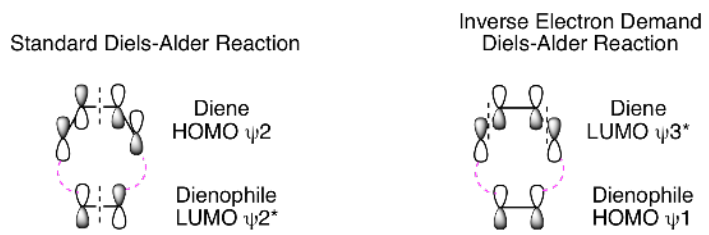
The molecular orbital analysis for cycloadditions involves several steps. First, determine how many atoms from each component are involved in the reaction and draw out their pi molecular orbitals. For the Diels-Alder reaction, there are 4 atoms with p orbitals in the diene and 2 atoms with p orbitals in the dienophile. The reactive orbitals for the Diels-Alder reaction are pi molecular orbitals, so we will focus on the pi MOs for both the diene and dienophile. The dienophile has one pi bond, so we will look at the pi MOs for a 2 atom system. The diene has two pi bonds, so we will look at the pi MOs for a 4 atom system. The details are shown below. We will use these MO Diagrams for all types of pericyclic reactions, they are not specific to the Diels-Alder reaction or cycloadditions.



Second, add electrons to the pi MOs to determine the HOMO and LUMO for each reactant. The dienophile has 1 pi bond, so it has 2 pi electrons. The diene has 2 pi bonds, so it has 4 pi electrons. For the dienophile, the HOMO is psi 1 and the LUMO is psi 2*. For the diene, the HOMO is psi 2 and the LUMO is psi 3*.

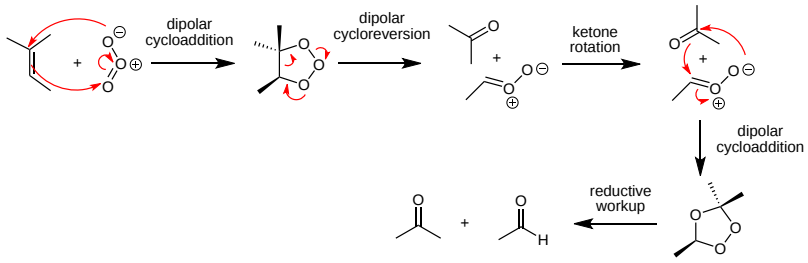


Third, determine if the reaction is possible by combining the HOMO of one component with the LUMO of the other. In a standard Diels-Alder reaction, an electron rich diene reacts with an electron poor dienophile. This means the diene is the nucleophile and reacts from the HOMO, while the dienophile is the electrophile and reacts from the LUMO. The opposite electronic arrangement, diene LUMO plus dienophile HOMO, is also possible. This is known as an Inverse Electron Demand Diels-Alder reaction. Both possibilities are illustrated below. These diagrams clearly demonstrate these reactions are suprafacial with respect to both the diene and dienophile, and, thus, they will happen. (Note: As always, dashed black lines are nodes and dashed magenta lines are positive orbital overlap that results in new sigma bond formation. Solid curved lines showing positive orbital overlap have been omitted for clarity.) To avoid potential confusion, we will delay analysis of photochemical cycloadditions until a little later in the chapter when we get to photo [2+2] reactions. If we did analyze the Diels-Alder under photochemical conditions, it would confirm that this is not possible.



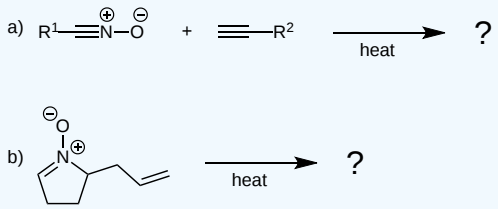
Dipolar Cycloaddition Reactions

Another useful thermal reaction is the dipolar cycloaddition which provides ready access to a variety of 5-membered ring heterocycles. The retron for a dipolar cycloaddition is a five-membered ring heterocycle. The key reaction component is a 3-atom dipole generally consisting of a pi bond adjacent to a negatively charged atom with a lone pair. This provides 4 electrons for the reaction, 2 electrons in the pi bond and 2 electrons from the delocalized lone pair. Thus, this reaction is electronically equivalent to the Diels-Alder reaction with the dipole contributing 4 pi electrons and the dipolarophile contributing 2 pi electrons. Two common 3 atom dipoles that many students encounter in previous organic chemistry classes are diazomethane and ozone. In fact, the ozonolysis mechanism, pictured below, is a wonderful example of dipolar cycloadditions in action. The first step is a dipolar cycloaddition which is followed by a retro dipolar cycloaddition (a cycloreversion). (Note: Retro dipolar cycloadditions are very unusual.) After a molecular rotation of one or the other component, a second dipolar cycloaddition occurs to yield an intermediate that is stable until the reaction is worked up under either oxidative or reductive conditions. This is a very complicated transformation. Problems that we will see using dipolar cycloadditions will generally be much more straightforward. As we will see in the problems that follow, the dipole and dipolarophile can contain triple bonds and, like all cycloadditions, this reaction can occur intramolecularly.

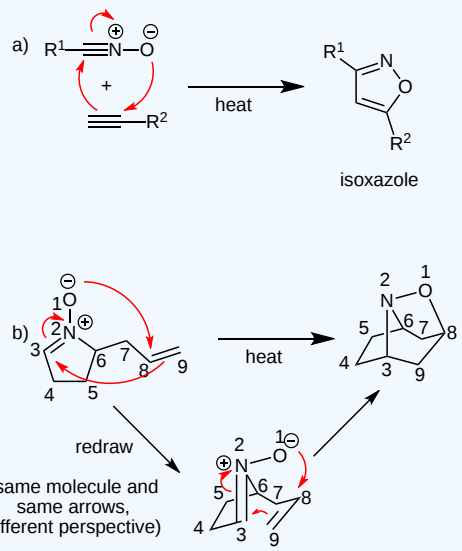


Exercise 1.2.7

What product is generated in each of the following reactions?



Answer



Part a) demonstrates the utility of a dipolar cycloaddition to make an aromatic heterocycle. Think about the regiochemistry of this one based on the electronic analysis we did for the Diels-Alder reaction. In this case, the dipole is the nucleophile with the negatively charged oxygen. Think about why the internal carbon on the alkyne is the most electron poor.

Part b) is complicated because of the challenging tricyclic structure that forms in the reaction. This is an example where numbering the atoms is critical and building a model is a huge help.

The orbital analysis of dipolar cycloadditions is very similar to the Diels-Alder reaction, though it requires us to understand how to generate the pi molecular orbital picture for a 3 atom system (illustrated below). If you have already studied pi molecular orbitals for an allyl system (radical, carbocation, or anion), the dipole in our reactions can be treated as an allyl anion. This is consistent with what we said previously about the dipole being a 3 atom system that has 4 pi electrons. In standard dipolar cycloadditions, the electron rich component is the dipole which reacts from the psi 2 HOMO while the electron poor dipolarophile reacts from the psi 2* LUMO. The orbital picture of the dipolarophile is identical to the Diels-Alder dienophile, both are two atom pi systems. Like the Diels-Alder reaction, the electronics can be reversed so that an electron poor dipole reacts with an electron rich dipolarophile, psi 3* LUMO plus psi 1 HOMO, respectively. Both options are shown below.

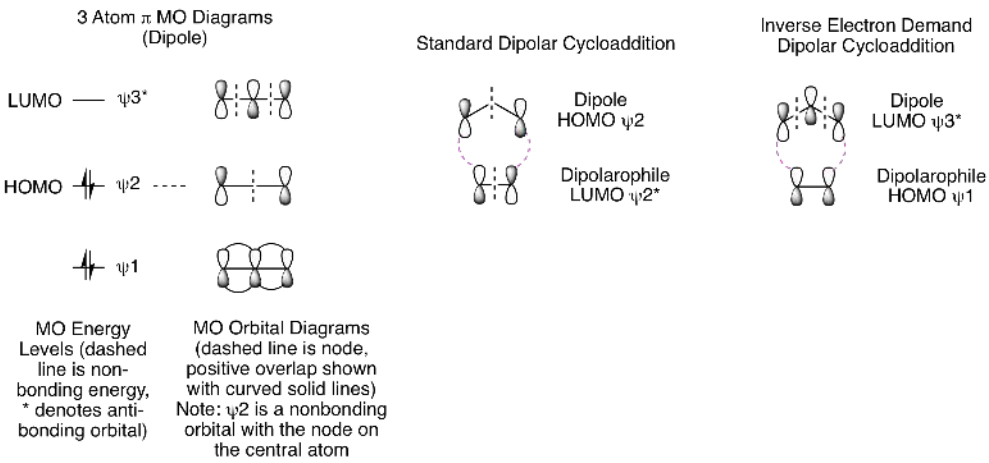
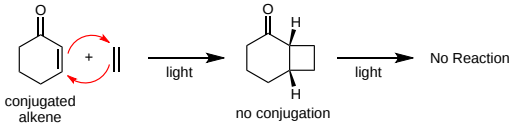
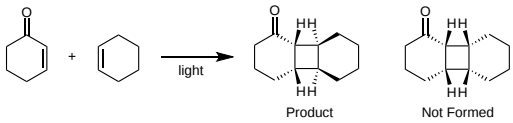


Photo [2+2] Cycloadditions

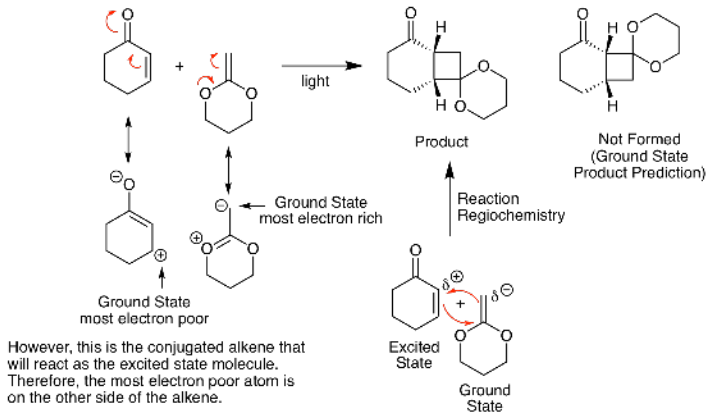
Photochemical [2+2] cycloadditions are excellent reactions for the synthesis of strained products containing 4-membered rings. They produce all carbon and heteroatom rings by both inter- and intramolecular reactions. One of the reaction partners must be conjugated so that it can absorb light and become an excited state molecule. These reactions produce strained 4-membered rings but are not reversible because the products lack conjugation and, thus, can't absorb light to facilitate a cycloreversion.



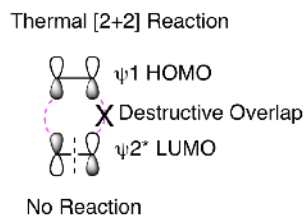
Stereochemistry in photo [2+2] reactions is more straightforward than the Diels-Alder reaction. The steochemistry present in each reactant is maintained in the product, so cis alkenes yield cis product substituents and vice versa. When comparing possible stereochemistry between the two reactants, the least hindered product is favored. For example, in the reaction below, the all cis product is not formed; the trans structure is generated.



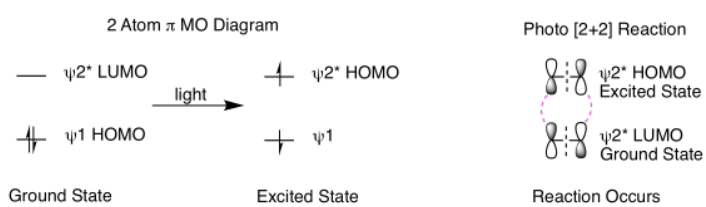
Because this is a photochemical reaction, predicting regiochemistry is the opposite of what we would expect from our standard analysis of thermal reactions like in the Diels-Alder reaction. This result is illustrated below. Instead of combining the most electron rich atom in one reactant with the most electron poor atom of the other reactant, it looks like we are combining the most electron rich atom with the other most electron rich atom (or vice versa). Why does this happen? It is important to remember that, as we will see in more detail shortly, one of the reactants participates in the reaction in its excited state. Molecules in the excited state have the opposite electron configuration than in the ground state. So, the most electron rich atom becomes the most electron poor atom and vice versa. One way to accurately predict the correct regiochemistry is to determine the correct ground state regiochemistry then switch the substituents to get the correct photoreaction regiochemistry.



So, why won't this reaction happen thermally? How does our molecular orbital analysis help us understand the importance of this being a photochemical reaction? First, let's look at the orbital analysis if we tried to do a thermal [2+2] reaction. As shown below, we cannot get suprafacial overlap for both of the 2 pi reactants when trying to combine psi 1 HOMO with psi 2* LUMO. This means that it is not favorable to convert the two reactant pi bonds into two new product pi bonds.

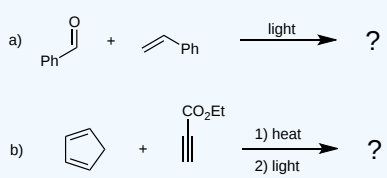


What happens when we shine light on the reaction? Light creates an excited state molecule by promoting an electron in the HOMO to the LUMO, as shown below. This means the excited state HOMO is the ground state LUMO. We need to understand a few key points about photoreactions before doing our molecular orbital analysis. Excited state molecules are very short lived, relaxing back to the ground state very quickly. Therefore, it is practically impossible for two excited state molecules to find each other in a reaction. Instead, reactions occur between one excited state molecule and one ground state molecule. When only one molecule is conjugated, that is the molecule that will form the excited state. If both reactants are conjugated, either can form the excited state. The orbital analysis is shown below. First, we see the orbital picture when a ground state molecule absorbs light to form an excited state. Second, when we analyze the reaction, it is now psi 2* HOMO of the excited state molecule reacting with psi 2* LUMO of the ground state molecule. This gives suprafacial constructive overlap for both orbitals and the 2 reactant pi bonds can be converted into two product sigma bonds. The reaction occurs!



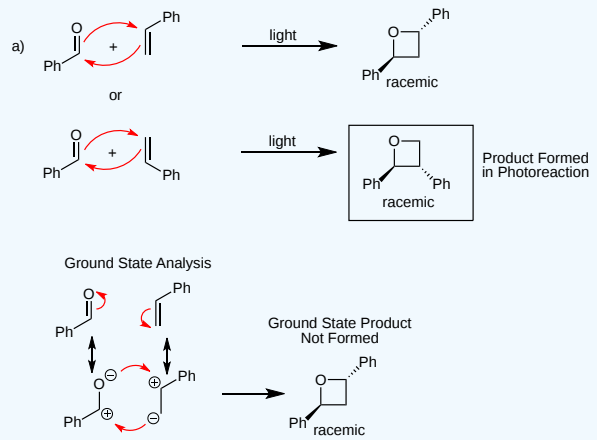
? Exercise 1.2.8

What are the products of the following two reactions? Hints: For a), this is an example of a hetero photo [2+2] cycloaddition. For b), your product is the result of two cycloadditions.

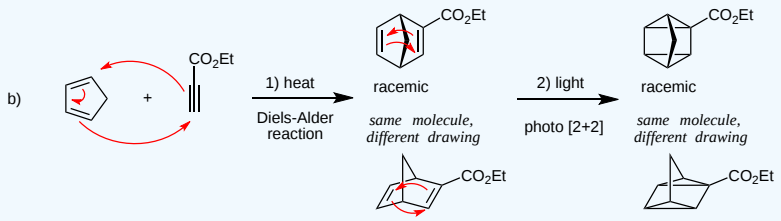


Answer

Part a is known as a Paterno-Bucchi reaction. It's a photo [2+2] reaction that combines a carbonyl with an alkene to form an oxetane. Also, like many organic reactions, it is very unusual for benzenes to participate in cycloadditions. Don't forget to think about stereochemistry and regiochemistry when drawing your product. Since the two benzenes start on each of the reactants, they will end up trans in the product because this is sterically favored. Performing our ground state analysis, it becomes clear that the molecule in the box is the product from the photoreaction.

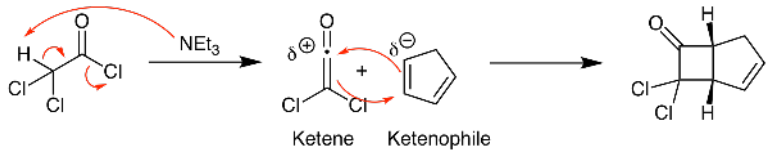


Part b combines a Diels-Alder reaction with a photo [2+2] to make a very interesting and highly strained product. Using photochemistry to generate strain in a target molecule is a very useful synthetic strategy.

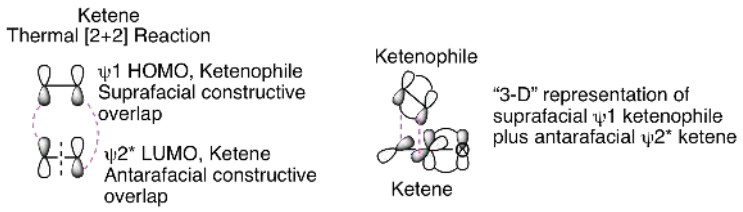


Ketene Thermal [2+2] Cycloaddition

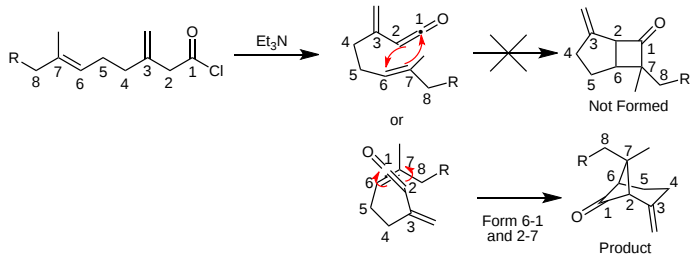
Ketenes are unusual functional groups that react in unexpected ways. (Ketenes contain an sp hybridized carbon connecting a carbonyl directly to an alkene. The all carbon equivalent is an allene. The 2 pi bonds in ketenes and allenes are not conjugated; they are perpendicular.) The most common ketene reaction is a thermal [2+2] cycloaddition. We will explore the orbital explanation for this shortly. First, let's look at a common method for the synthesis of ketenes and an example of a reaction. Ketenes can be reliably synthesized upon reaction of an acid chloride with a non-nucleophilic amine base, in this case triethylamine, via an elimination reaction. Once formed, the ketene undergoes a [2+2] cycloaddition to yield a cyclobutane product. This reaction follows the same stereochemistry rules as photo [2+2] cycloadditions. Since this is a thermal reaction, the regiochemistry is straightforward. Find the most electron rich atom in the ketenophile and react it with the highly electron poor carbonyl carbon of the ketene.



The orbital analysis is exactly the same as our discussion of the photo [2+2] reaction above except that the thermal reaction that doesn't occur in that analysis is now happening. How is that possible? The critical factors are that the ketene carbonyl carbon is both electron poor and unhindered since no other substituents are attached. This means that the ketenophile reacts in a suprafacial orientation from HOMO psi 1 while the ketene reacts in an antarafacial fashion from LUMO psi 2*, as depicted below. This antarafacial reactivity is only possible because of the sp hybridization and resulting lack of steric hinderance for the approaching ketenophile. Thinking about this in three dimensions helps visualize how this is possible (see representation below).

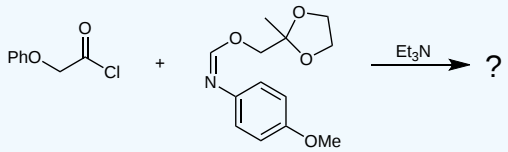


It is normally impossible to see the result of this suprafacial plus anatarafacial reactivity, but the following intramolecular ketene [2+2] reaction clearly illustrates the reaction mechanism. Instead of the standard fused bicycylic product that would result from a suprafacial plus suprafacial reaction, the more complicated bridged bicyclic product is generated. This is only possible because of the suprafacial plus antarafacial reactivity.

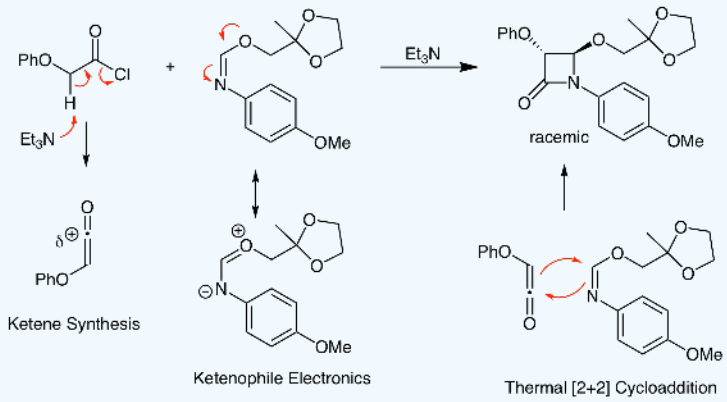


Exercise 1.2.9

Predict the product of the following reaction.



Answer

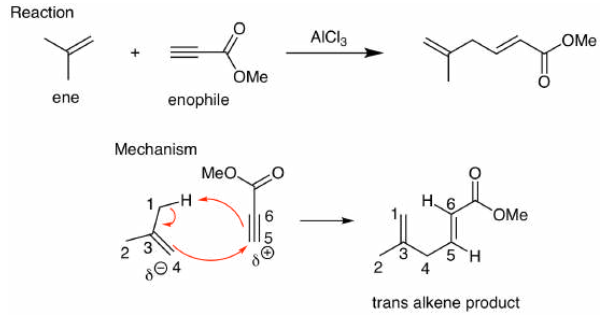


This problem demonstrates to power of the ketene thermal [2+2] reaction to make heterocycles. Combination of a ketene with an imine yields a 4-membered ring amide which is known as a beta lactam. This functional group is present in bioactive molecules like penicillin.

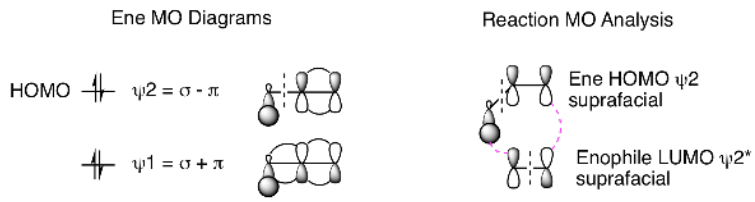
Ene Reaction

Our final cycloaddition reaction is another transformation discovered by Kurt Alder. The Diels-Alder reaction was originally know as the "diene reaction". This transformation involves an alkene, so it was named the "ene reaction". An example with the mechanism is shown below. The alkene is the 4 electron component reacting with its pi bond and an allylic C-H bond. The enophile is the 2 electron component making this another thermal [4+2] reaction. Intermolecular ene reactions happen only with very

electrophilic alkenes or alkynes and often with a Lewis acid catalyst. Intramolecular reactions are much more common and occur with heating or Lewis acid catalysis.

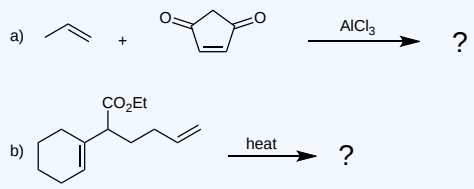


So, is this really a cycloaddition reaction since we aren't using pi bonds in the mechanism? Yes, it is. As we will see in subsequent chapters, sigma bonds, especially C-H bonds, can participate in pericyclic reactions. The orbital picture is shown below where we treat the sigma plus pi bonds of the ene as a 4 atom system. Thus, the reaction occurs between HOMO psi 2 of the ene and LUMO psi 2* of the enophile. With 4 electrons from the ene and 2 electrons from the enophile, this is another 6 electron, thermally allowed cycloaddition, just like the Diels-Alder reaction and dipolar cycloaddition.

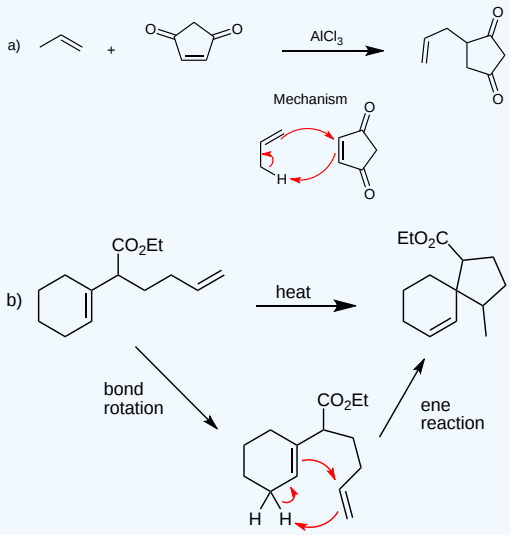


Exercise 1.2.10

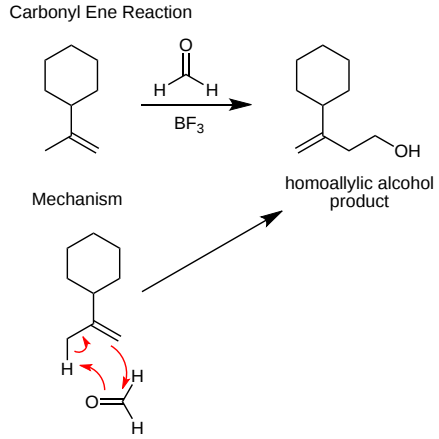
What products are formed in the following reactions? Hint: For b, the product contains a new 5-membered ring.



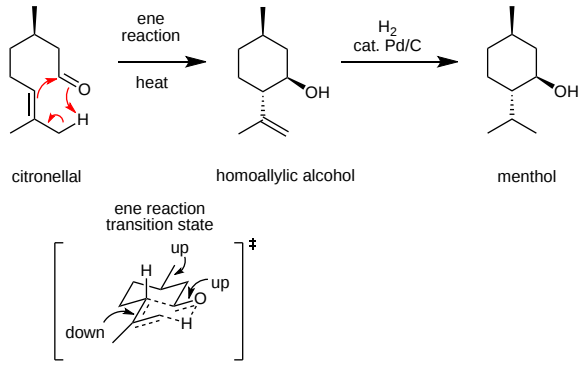
Answer



The most common version of the ene reaction is known as the "carbonyl ene reaction" where the enophile is a carbonyl, usually an aldehyde. This generates a product that is a homoallylic alcohol which is the retron for a carbonyl ene reaction. An example is shown below.



An application of the carbonyl ene reaction is the two-step conversion of citronellal to menthol, as shown below. The first step is an intramolecular carbonyl ene reaction followed by an alkene hydrogenation. An interesting question is how is the stereochemistry controlled in the ene reaction? Like many reactions that we will see in subsequent chapters, the key is a chair-like 6-membered ring transition state. With the stereogenic methyl positioned equatorial, this enables the developing stereocenters, the OH and the propene, to be equatorial in the transition state. Try to remember this strategy when thinking about stereochemistry for intramolecular reactions in the future, not just the ene reaction.

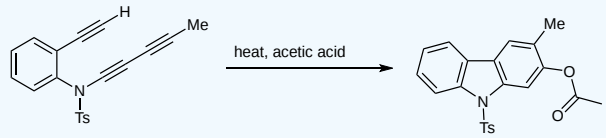


Summary Problems

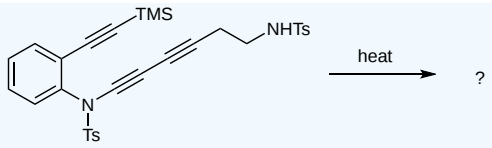
? Exercise 1.2.1

In 2012, Tom Hoye from the University of Minnesota reported a novel Diels-Alder reaction called the Hexadehydro-Diels-Alder reaction with a diyne as the diene and another alkyne as the dienophile. Hint: Benzyne plays a critical role in this reaction mechanism.

a) Here's an example of this novel type of Diels-Alder reaction. Propose a mechanism for this transformation. Hint: The first step is an intramolecular Diels-Alder reaction.



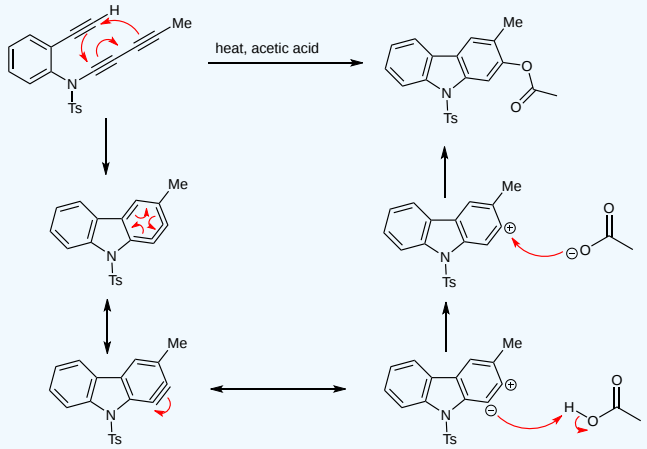
b) Using the mechanism you determined in part a, determine the product of this reaction.



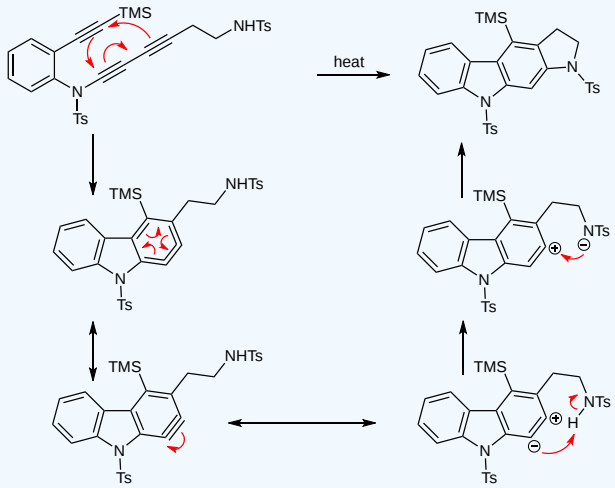
Answer

DOI - 10.1038/nature11518 (*Nature* 2012)

a) The Diels-Alder reaction yields a cyclic allene that is one of the resonance structures for benzyne. So, this is a cycloaddition that yields a benzyne intermediate! Under these reaction conditions, the benzyne reacts as its polar resonance structure to first deprotonate acetic acid and then combine with acetate to yield the final product.

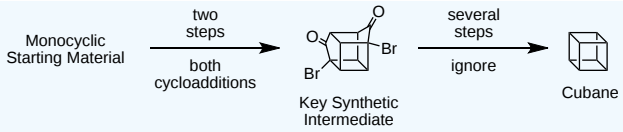


b) In this example, without the addition of acid, the benzyne intermediate deprotonates the sulfonamide proton. The resulting negatively charged nitrogen forms an intramolecular C-N bond resulting in the synthesis of a new 5-membered ring.



Exercise 1.2.2

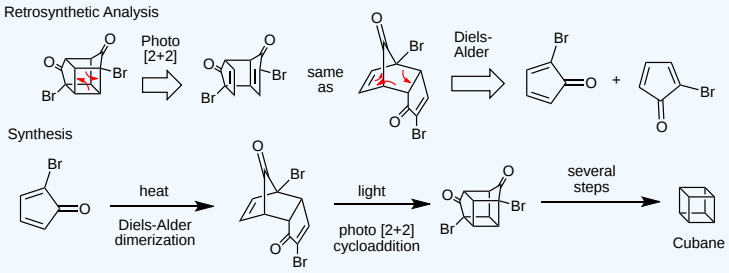
In 1964, Prof. Phil Eaton at the University of Chicago achieved the first synthesis of cubane. A key molecule in his synthesis is shown below. This compound can be prepared in two steps via dimerization (one molecule reacting with itself) of a monocyclic compound followed by an intramolecular reaction. Determine the structure of the starting material and the two reactions needed to prepare the key synthetic intermediate. Hint: Both reactions are cycloadditions. (Don't worry about how to convert the dibromide into cubane.) As a bonus question, how many peaks do you predict will be in the ^{1}H and ^{13}C NMR spectra for cubane?



Answer

DOI - 10.1021/ja01069a041 (*Journal of the American Chemical Society* 1964)

There are several possible photo [2+2] disconnections, but this one reveals a tricyclic compound that can be made by a Diels-Alder reaction between two of the same bromocyclopentadienone molecules. It is a remarkable two-step sequence to generate the highly complex key synthetic intermediate. For the question of cubane's NMR spectra, this molecule is fully symmetrical and yield only one peak in both the ^{1}H and ^{13}C NMR spectra.



1.2: Cycloaddition Reactions is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by Kevin Shea.

1.3: Electrocyclic Reactions

Objectives

After completing this section, you should be able to:

1. Identify electrocyclic reactions including 4 pi, 6 pi, and 8 pi ring opening and closing reactions
2. Understand the orbital analysis of electrocyclic reactions
3. Draw curved arrows to illustrate electron flow for electrocyclic reactions
4. Given electrocylic starting materials, accurately predict the product including stereochemistry
5. Use retrosynthetic analysis to determine starting materials given an electrocyclic target

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Conrotatory
- Disrotatory
- Nazarov reaction

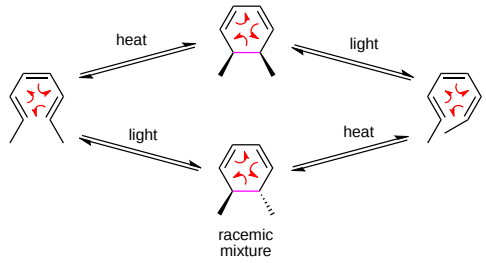
Study Notes

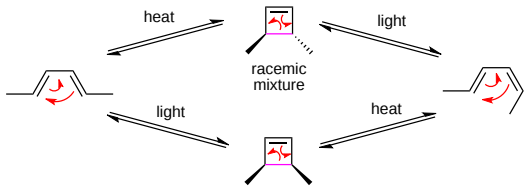
Electrocyclic reactions are often reversible ring opening and closing reactions that cleave and form 4-, 6-, and 8-membered rings with excellent stereocontrol. (The ring opened products must contain a p orbital at every atom.) We will also learn about cationic and anionic electrocyclic reactions that enable formation of 5-membered rings. Your goal is to understand the theoretical basis of these reactions using a molecular orbital analysis and to apply these reactions in synthesis. You should focus on accurately predicting products with a focus on stereochemistry and, given a complicated product, to accurately predict the starting material used to generate it.

Chapter 1.1 provided an overview of pericyclic reactions, including electrocyclic reactions. Electrocyclic reactions are intramolecular reactions involved in the formation of rings starting from a conjugated pi system or the formation of a conjugated pi system by cleaving a ring. In ring forming reactions, a new sigma bond (shown below in magenta) is formed at the terminus of a conjugated pi system, while ring opening reactions break a sigma bond (in magenta below) to generate a fully conjugated pi system. These are important reactions but they are not nearly as synthetically useful as cycloadditions. We will begin by looking at standard ring opening and closing reactions of neutral carbon-containing compounds. We will then explore applications of ionic electrocyclic reactions including the cationic Nazarov reaction for the synthesis of 5-membered rings.

Example Electrocyclic Reactions

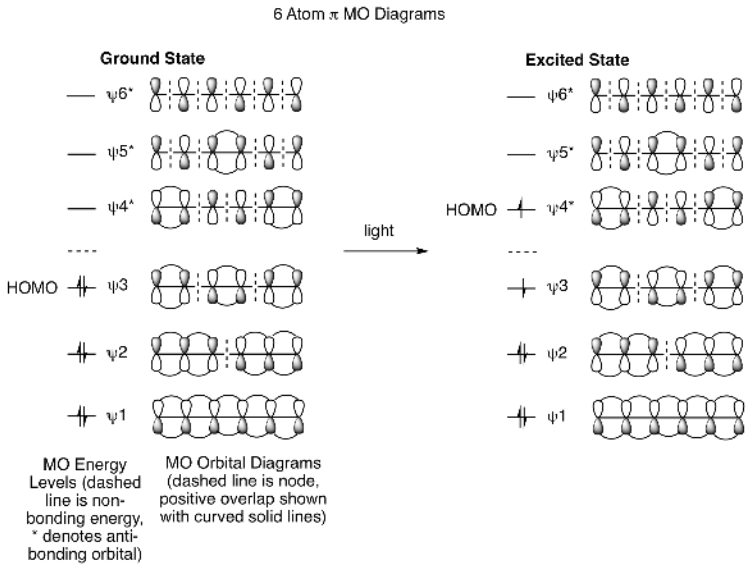
Building on the introduction to electrocyclic reactions presented in Chapter 1.1, we must understand the following results for the formation and cleavage of 6-membered rings. (Note: Electrocyclic reactions are only possible for 1,3-cyclohexadiene derivatives or similar heterocycles and not other 6-membered rings lacking 2 pi bonds in the correct orientation.) We can easily draw curved arrows to illustrate electron flow for these reactions, but without molecular orbital analysis, we are unable to explain the resulting stereochemistry. In the next section, we will perform this molecular orbital analysis. The following scheme also illustrates the results for 4-membered ring systems. We will see an application of electrocyclic reactions in 8-membered ring systems in one of the summary problems at the end of this chapter. (Similar reactions of larger ring systems are possible but are rare for synthetically useful applications.)



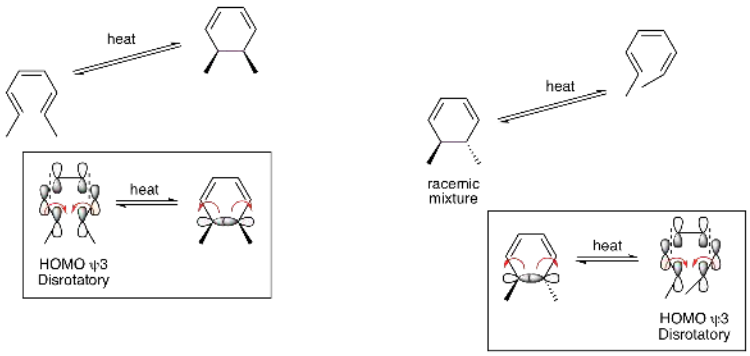


Molecular Orbital Analysis of Electrocyclic Reactions

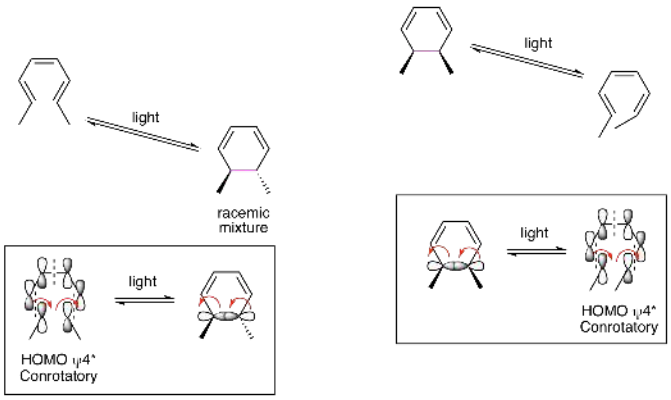
The molecular orbital analysis for electrocyclic reactions is best understood by focusing on the molecule in its acyclic fully conjugated form. (It doesn't matter whether this is the reactant or the product.) For the 6 pi system, we must first generate the pi molecular orbitals, add pi electrons, and identify the Highest Occupied Molecular Orbital (HOMO). This is similar to the strategy we used to understand the molecular orbital basis for cycloadditions in the previous chapter; however, the only reactive orbital for electrocyclic reactions is the HOMO. The ground state and excited state molecular orbital (MO) diagrams are shown below and highlight that the ground state HOMO is psi 3 while the excited state HOMO is psi 4*. Thus, our analysis of the ground state reaction will focus exclusively on psi 3 and the excited state on psi 4*.



We will begin our analysis of the reactions shown above by looking only at the thermal conditions for the 6 pi system. How can the psi 3 MO explain the results? We must draw out the structure with the psi 3 orbital and see how it will rotate to generate positive overlap for the formation of a new sigma bond in the ring at the terminal carbons. The orbitals must rotate in opposite directions, one clockwise and one counterclockwise, to enable positive overlap and bond formation. This process is called disrotatory and provides the insight we need to explain the stereochemical outcome. Also note that the same analysis works when thinking about the ring opening reaction. The question to answer for this process is, "How will the sigma bonding orbitals rotate to yield psi 3 for the acyclic product MO?". Since this is a reversible process, the rotation must be the same for the forward or reverse reaction.

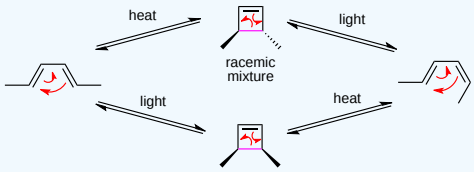


Now lets look at the photochemical reactions. As we've seen in previous chapters, light promotes a ground state electron from the HOMO to the Lowest Unoccupied Molecular Orbital (LUMO). This generates a new HOMO (the previous LUMO) in the excited state molecule. So, when analyzing the 6 pi system, we will look to psi 4* to understand the stereochemical outcomes. Contrary to the thermal reactions, the orbitals now rotate in the same direction, both clockwise or both counterclockwise, to provide positive overlap for the formation of the new sigma bond in the ring forming reaction. This is called conrotatory. For the ring opening reaction, the orbitals forming the sigma bond rotate in the same direction to generate psi 4* in the acyclic molecule. We are now able to explain the stereochemical results. Thermal and photochemical reactions yield different stereochemical results because reactions happen from different HOMOs. These different orbitals rotate by either a disrotatory or conrotatory process. If the thermal reaction is disrotatory, the photoreaction must be conrotatory, and vice versa.



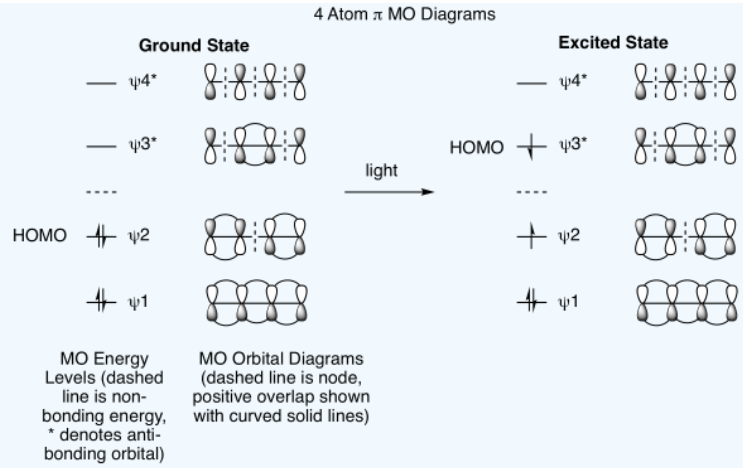
Exercise 1.3.1

Using the same strategy illustrated above, draw out the molecular orbitals for the 4 pi reactions to explain the stereochemistry for both the thermal and photochemical reactions.

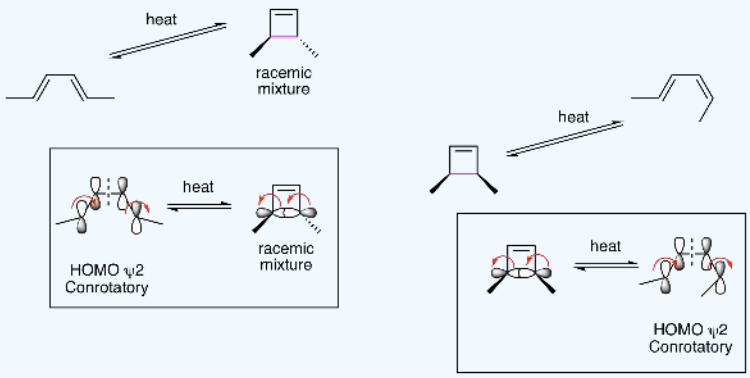


Answer

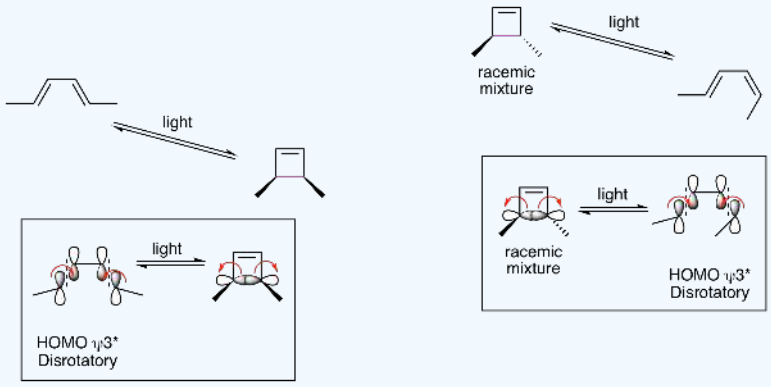
To begin, we must draw out the 4 atom pi MO diagrams to determine the ground state and excited state HOMOs.



This shows that we will be analyzing HOMO psi 2 for the ground state thermal reactions and HOMO psi 3* for the excited state photoreactions. The thermal reactions are shown below and demonstrate that they are proceeding by conrotatory processes to provide the indicated stereochemistry.



This means that the photochemical reactions must be proceeding by disrotatory processes. This is illustrated below and accounts for the indicated stereochemistry.



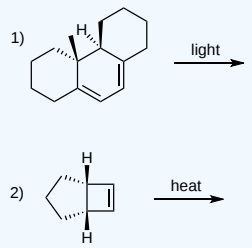
Generalized Statement of Woodward-Hoffmann Rules for Electrocyclic Reactions

The table below provides a useful summary for electrocyclic reactions. Drawing out the key orbitals will always provide you with the correct mode of orbital rotation. However, you can use the number of electrons involved (just count your curved arrows and multiply by two) and the table below to quickly determine whether the reaction is con- or disrotatory.

Number of Electrons	Thermal	Photochemical
4n + 2	Disrotatory	Conrotatory
4n	Conrotatory	Disrotatory

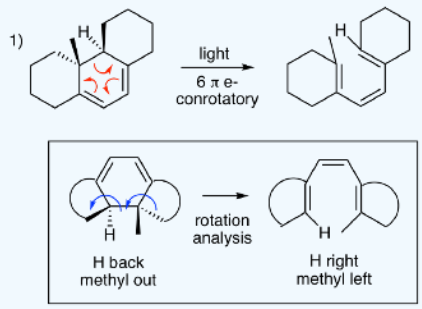
? Exercise 1.3.2

What are the products of the following two reactions? Pay careful attention to stereochemistry.

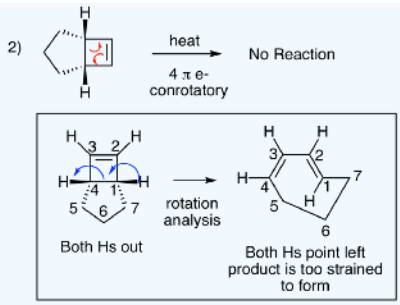


Answer

For the first problem, this is a six pi electrocyclic ring opening. Three curved arrows show that 6 electrons are involved. The central ring is the ring that reacts since it is the only ring that produces a fully conjugated pi system when it opens. The other rings are unreactive. Using the chart above, we can quickly see that this is a conrotatory process (4n+2 = 6, light). So, what is the alkene geometry in the product? We need to do a rotation analysis as illustrated in the box below. (Many students find this easiest if the bond that is breaking/forming is always on the bottom of the structure, so we have rotated the structure of the starting material and the product to make this possible.) The blue rotation arrows are going in the same direction (conrotatory). This puts the H pointing left and the methyl pointing right. When doing this analysis, we can ignore the details of the other rings which are abbreviated by the curved lines. An interesting follow up quesiton is what would happen if the starting material was heated? This would be a 6 pi disrotatory process. What would the product structure look like? This reaction doesn't happen. Why not? (This is a good question to discuss with classmates or your instructor.)

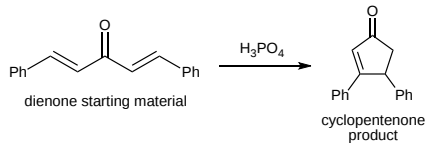


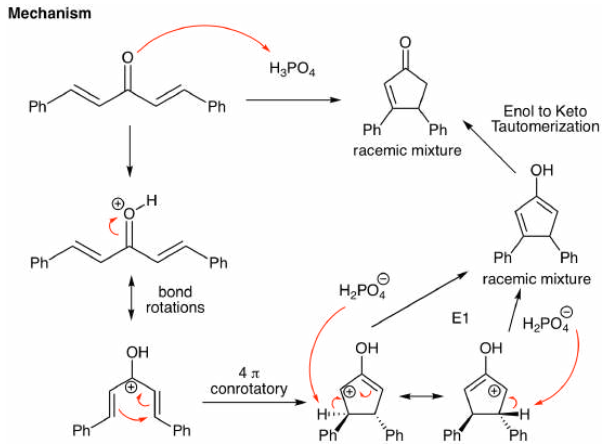
For the second problem, this is a four pi electrocyclic ring opening. Two curved arrows show that 4 electrons are involved. The four membered ring is the ring that reacts since it is the only ring that produces a fully conjugated pi system when it opens. The five membered ring is unreactive. Using the chart above, we see that this is a conrotatory process (4n = 4, heat). What is the alkene geometry in the product? Here's where this problem gets interesting. The result would be one cis alkene and one trans alkene in a 7-membered ring. What happens if you try to build this structure with your model kit? Exactly. You can't do it. There's too much strain, and the molecule doesn't exist. So, this is a trick question. (Sorry.) There is no reaction. What happens if you shine light on this molecule? Another trick question. (Again, sorry.) An isolated alkene doesn't absorb light, so a photoreaction isn't possible.



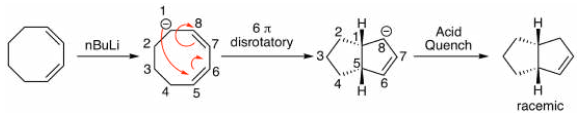
Electrocyclic Reactions of Cations (Nazarov Reaction) and Anions for the Synthesis of 5-Membered Rings

One of the most synthetically useful electrocyclic reactions is the Nazarov reaction. This is a cationic 4 pi thermal reaction (thus, conrotatory) beginning with a conjugated dienone that generates a cyclopentenone product. When thinking retrosynthetically, a cyclopentenone target is the Nazarov retron. An example of the reaction is shown below along with its mechanism. Strong acid is present to protonate the ketone in the first step. This generates a resonance stabilized cation that undergoes the requisite 4 pi ring closing reaction. This generates the cyclopentene ring that contains a resonance stabilized positive charge. The ring closing reaction initially generates two chiral centers, one of which will return to an achiral carbon upon the following E1 reaction. The mechanism ends with an acid catalyzed enol to ketone tautomerization. So, the final product is a racemic cyclopentenone where one new chiral center is present in the product.



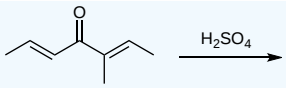


Though much less common, anions can also participate in electrocyclic reactions. For example, deprotonating the most acidic proton in the 8-membered ring shown below with n-butyllithium results in a delocalized carbanion that undergoes a thermal 6 pi (disrotatory) ring closing reaction to form a new 5-membered ring as part of an interesting bicyclic product.



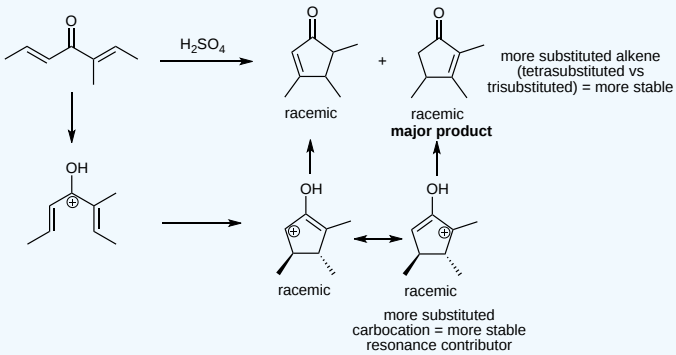
? Exercise 1.3.3

What happens when the starting dienone for the Nazarov reaction is not symmetrical? We explore that in this problem. Draw the two possible Nazarov reaction products and predict which will be the major product.



Answer

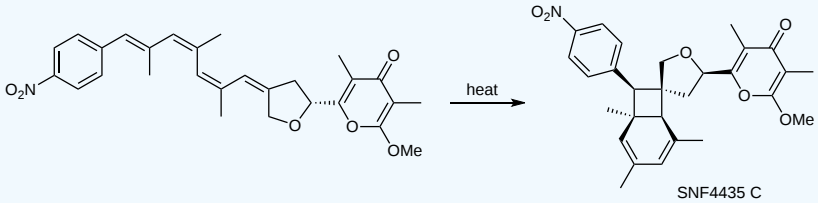
Following the mechanism above, we can identify the two cyclopentenone products. One contains a trisubstituted alkene while the other is a tetrasubstituted alkene. Further, working through the mechanism, the tetrasubstituted alkene product is generated from the more substituted carbocation resonance contributor. So, the major product is the more stable tetrasubstituted alkene that is generated from the more stable resonance contributor of the carbocation.



Summary Problems

? Exercise 1.3.4

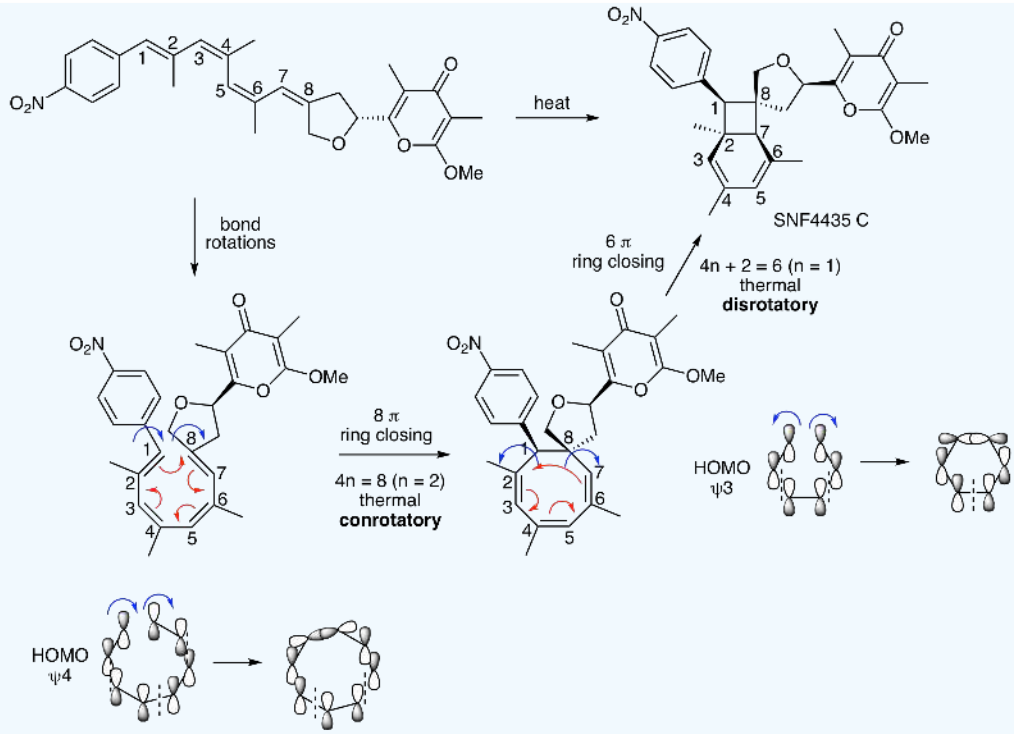
In 2005, Dirk Trauner's lab published an application of electrocyclic reactions for the synthesis of the natural product SNF4435 C. This process involves two consecutive electrocyclic reactions. Propose a mechanism for these two reactions. Clearly state what type of electrocyclic reaction is occuring, draw curved arrows, indicate if it is conrotatory or disrotatory, and draw an MO diagram for each step to explain the observed stereochemistry. The starting material is drawn exactly as depicted in the paper. The first step in your analysis is to redraw this tetraene in a reactive conformation (perform bond rotations being careful not to alter the geometry of an alkenes) so that it is more obvious what electrocyclic reactions are possible.



Answer

DOI - 10.1021/ol051790q (*Organic Letters* 2005)

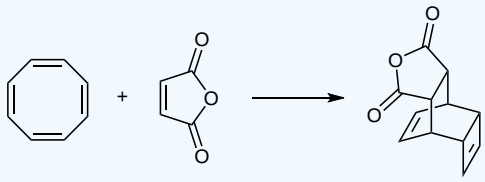
Redrawing the starting material to place carbons 1 and 8 near each other enables you to see that the first step is a conrotatory (thermal) 8 pi electrocyclic ring closing reaction. Drawing the HOMO for this process (psi 4) illustrates that this must be conrotatory. The second reaction is a disrotatory (thermal) 6 pi ring closing reaction that occurs from HOMO psi 3. The stereochemistry agrees with these rotations.



Exercise 1.3.5

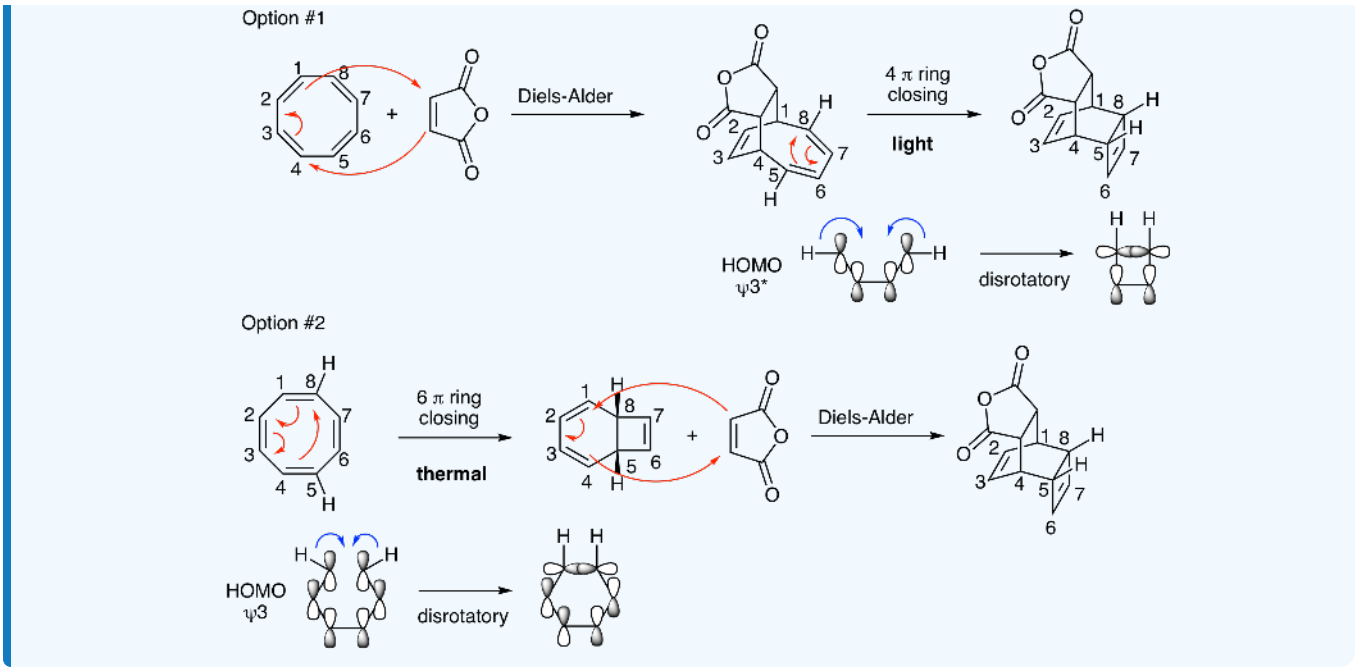
Carolyn Bertozzi is a pioneer of bioortogonal reactions. These are highly selective non-natural reactions that happen spontaneously in biological systems to label biomolecules. An interesting introduction to the work of the Bertozzi lab is described in a 2010 review entitled "Cu-free click cycloaddition reactions in chemical biology" in *Chemical Society Reviews*. A transformation mentioned in that review is pictured below. Propose a mechanism for this reaction. Does it happen thermally or photochemically? Justify your answer with MO diagrams. Hints: This is a two-step reaction. Both are pericyclic reactions; one is a cycloaddition and the other is an electrocyclic reaction.

DOI - 10.1039/B901970G



Answer

This problem can be approached in either the forward or reverse direction. Either way, there are two reasonable possibilities for the mechanism. The cycloaddition must be a Diels-Alder reaction which could happen in the first or second step. If the Diels-Alder happens first, the second step is a 4 pi electrocyclic ring closing reaction (Option #1). If the Diels-Alder happens second, the first step must be a 6 pi electrocyclic ring closing reaction (Option #2). Does it matter? The curved arrows look fine either way. However, as we've seen above, it is critical to analyze the stereochemistry to see what happens with reactions that are con- or disrotatory. The key piece of stereochemical information is that the Hs on carbons 5 and 8 in the product must be syn. This means that the 4 pi ring closing reaction in Option #1 must be disrotatory which requires a photochemical reaction. In Option #2, with the 6 pi ring closing happening first, it would also have to occur in a disrotatory fashion which happens with a thermal reaction. So, Option #1 is a thermal reaction (remember, Diels-Alder reactions must be thermal) followed by a photochemical reaction. Option #2 is two sequential thermal reactions. Both are possible; however, Option #2 is much more reasonable and is what actually happens in the Bertozzi lab.



Contributors

- Prof. Kevin Shea (Smith College)

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1.4: Sigmatropic Rearrangements

Objectives

After completing this section, you should be able to:

1. Identify sigmatropic rearrangements including hyrdride shifts and Cope, Claisen, and Wittig rearrangements
2. Understand the orbital analysis of sigmatropic rearrangements
3. Draw curved arrows to illustrate electron flow for sigmatropic rearrangements
4. Given a sigmatropic rearrangement starting material, accurately predict the product including stereochemistry
5. Use retrosynthetic analysis to determine starting materials given a sigmatropic rearrangement product

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Suprafacial
- Antarafacial
- Hydride shift
- Cope rearrangement
- Claisen rearrangement
- Wittig rearrangement

Study Notes

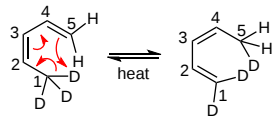
Sigmatropic rearrangements are pericyclic reactions that, no surprise, provide rearranged products. The most common include hydrogen shifts across pi systems and formation of new carbon-carbon bonds across allyl-type structural fragments. The most synthetically useful are the Cope and Claisen rearrangements which are formally classified as [3,3] rearrangements. (See Chapter 1.1: Introduction to Pericyclic Reactions for an explanation of naming sigmatropic rearrangements.) Your goal is to understand the theoretical basis of these reactions using a molecular orbital analysis and to apply these reactions in synthesis. You should focus on accurately predicting products with a focus on stereochemistry and, given a complicated product, to accurately predict the starting material used to generate it.

Chapter 1.1 provided an overview of pericyclic reactions, including sigmatropic rearrangements. Sigmatropic rearrangements are intramolecular reactions involving the migration of a sigma bond across a pi system. Examples include hydrogen atoms migrating across dienes upon heating (some even do this spontaneously at room temperature) and hydrogen atoms migrating across alkenes with light. Double allyl-type systems also commonly react via sigmatropic rearrangements, with 1,5-dienes participating in Cope rearrangements while ally vinyl ethers produce 1,4-enones after Claisen rearrangements. Most of our attention will focus on the applications of Cope and Claisen reactions in synthesis.

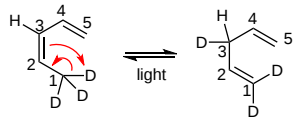
Thermal and Photochemical Hydride Shifts

Building on the introduction to pericyclic reactions presented in Chapter 1.1, we must understand the following results: [1,5] hydrogen shifts occur thermally while [1,3] hydrogen shifts happen photochemically. Labeling substrates with deuterium makes it possible to see the outcomes of these reactions which could otherwise often be invisible. Examples are shown below. As we have seen in previous sections, we need to use molecular orbital diagrams to explain these results.

Thermal [1,5] Sigmatropic Rearrangement



Photochemical [1,3] Sigmatropic Rearrangement



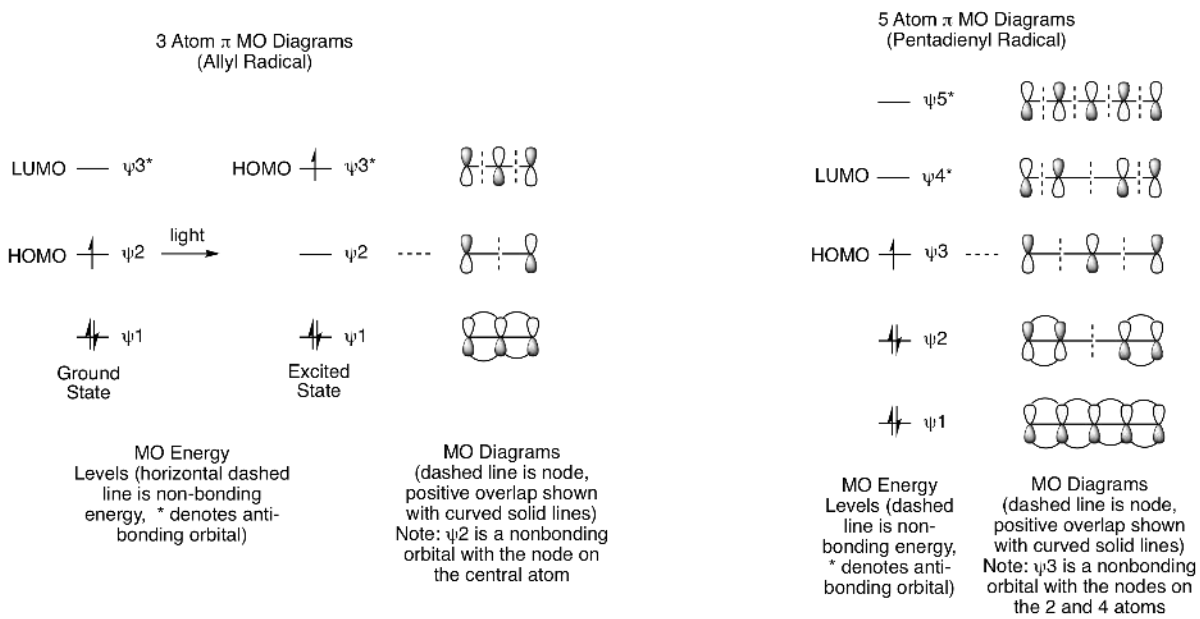
Molecular Orbital Explanation for Sigmatropic Rearrangements

If we think about the transition states for the hydride shift reactions shown above, we can depict the reactions as a hydrogen (or deuterium) atom (a radical) moving across either a pentadienyl radical (heat) or an allyl radical (light).

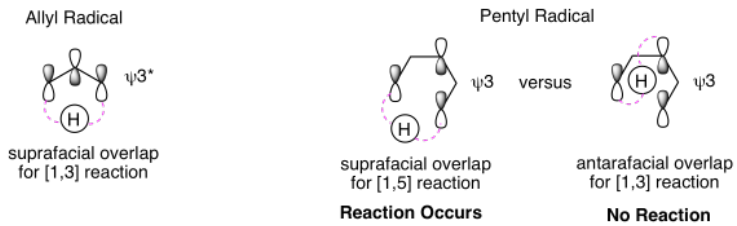
Transition States

[1,5] [1,3]

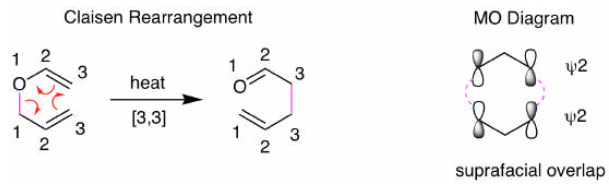
This means that we need to draw a 5-atom and a 3-atom pi molecular orbital diagram so that we can determine the HOMO for each reaction. We can then use those diagrams to explain the experimental results. As shown below, the excited state HOMO for the 3 atom system is psi 3* and the ground state HOMO for the 5 atom system is psi 3.



What does it look like when a hydrogren atom moves across these two orbital systems? As shown below, the H is able to migrate across the same face of the pi system. As mentioned previously, this is called a suprafacial process. If the H moved from the bottom face to the top face (or vice versa), that would be an antarafacial process. Antarafacial hydrogen shifts are possible, but only for rings that are 7-membered or larger. So, the two reactions are explained by the MO diagrams showing that a thermal [1,5] H shift is suprafacial and a photochemical [1,3] H shift is suprafacial. Antarafacial [1,3] or [1,5] H shifts are too high in energy, so they do not occur.



A similar analysis helps explain why thermal [3,3] sigmatropic rearrangements are common. These reactions involve suprafacial overlap between two allyl systems. Looking at the reaction we introduced in Chapter 1.1, the simplest version of the Claisen rearrangement, we can see that the key sigma bond moves across two three-atom systems. For the MO diagram, this means that allyl HOMO psi 2 overlaps in a suprafacial fashion with another allyl HOMO psi 2. We can generalize the orbital analyses of sigmatropic rearrangements as shown in the following section.

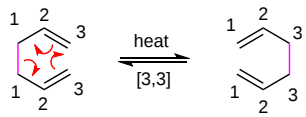


Generalized Statement of Woodward-Hoffmann Rules for Sigmatropic Rearrangements

Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial	Antarafacial
4n	Antarafacial	Suprafacial

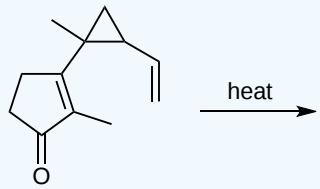
Cope Rearrangement

The Cope rearrangement is a [3,3] sigmatropic rearrangement of a 1,5-diene. It was discovered at Bryn Mawr College by Elizabeth Hardy, a graduate student in Arthur Cope's research lab. As shown below in its simplist form, this is a reversible reaction. Consequently, the Cope retron is also a 1,5-diene. To make the Cope rearrangement synthetically useful, we must introduce a driving force that will favor formation of the product. The two most popular strategies are to provide relief of ring strain and to incorporate a tautomerization as an irreversible final step. The following problems provide examples of these strategies.



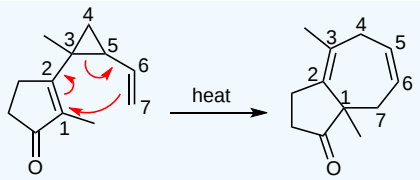
? Exercise 1.4.1

Predict the Cope rearrangement product of this reaction.



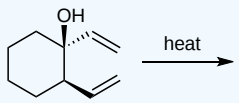
Answer

As mentioned above, this reaction is favorable because it relieves the strain in the cyclopropane ring. This common strategy is a useful way to generate a new 7-membered ring.



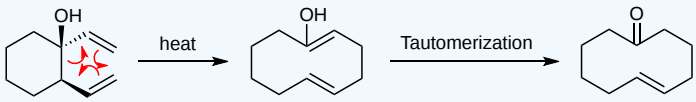
Exercise 1.4.2

Predict the product of this reaction.



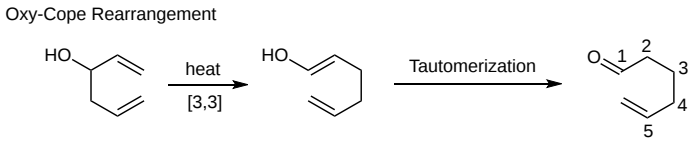
Answer

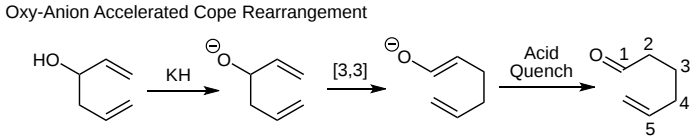
This is an example of an Oxy-Cope rearrangement. In Oxy-Cope reactions, placement of an OH on one of the sp^3 carbons connecting the 1,5-diene results in an enol after the [3,3] sigmatropic rearrangement. An irreversible tautomerization yields the final product.



Oxy-Cope Rearrangement

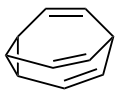
As seen in the previous problem, the Oxy-Cope rearrangement is an important synthetic tool. The product of this reaction is a 1,5-enone. This is the Oxy-Cope retron which will be important when approaching synthesis problems. One way to promote Oxy-Cope reactions is to deprotonate the starting alcohol with a hydride base. These reactions are referred to as oxy-anion accelerated Cope rearrangements.





Cope Rearrangement Application

The most amazing application of the Cope rearrangement is the molecule known as bullvalene. This molecule was designed and synthesized in the lab of William von Eggers Doering and published in 1963. If you play around with the molecule, you see that there are several Cope rearrangements that are initially possible. If you draw those products, you see that even more become apparent. The net result is that this is a fluxional molecule; it does not have a set structure at room temperature. In fact, when heated, its NMR spectra are a singlet at 4.2 in the proton NMR and one peak at 86 in the carbon spectrum. For an excellent article about the bullvalene origin story, check out Addison Ault's paper in the *Journal of Chemical Education*.



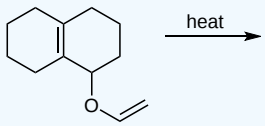
Bullvalene

Claisen Rearrangement

As mentioned above, the Claisen rearrangement is the conversion of an allyl vinyl ether into a 1,4-enone via a [3,3] sigmatropic rearrangement. The simplist Claisen rearrangement is picture below. The forward direction is favored because the product contains a carbonyl, so this is not a reversible reaction. The following two problems provide practice predicting products of Claisen rearrangements.

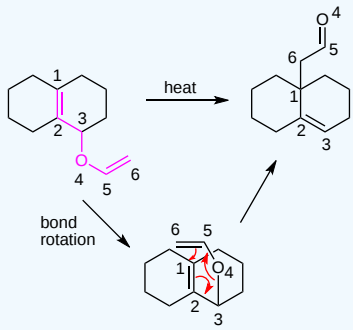
Exercise 1.4.3

Predict the product of the following Claisen rearrangement.



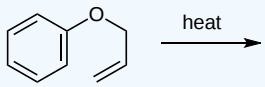
Answer

First, find the allyl vinyl ether. It is highlighted in magenta below. Second, rotate the bonds so that carbons 1 and 6 are near each other. Third, draw the curved arrows. Fourth, draw the product. As with many reactions, numbering your atoms is helpful to ensure you get the correct product.



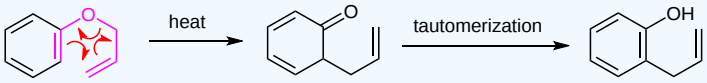
Exercise 1.4.4

Predict the product of the following Claisen rearrangement. Hint: Think carefully about the most stable structure for your product.



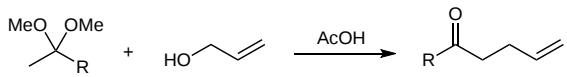
Answer

Draw the curved arrows for the allyl vinyl ether to generate the 1,4-enone. The tricky part of this problem is recognizing that this product is not the lowest energy molecule possible. A keto to enol tautomerization yields the final product. This is another example of the aromatic stability of benzene. We are used to converting enols to ketones. In this case the enol is more stable because of the aromaticity of benzene.



The above reaction is a very common strategy to make a C-C bond at the ortho position of a phenol. Keep this is mind when thinking about synthesis problems. (The starting material above is easily synthesized by treating phenol with sodium hydride and allyl bromide.)

Often the most challenging aspect of the Claisen rearrangement is synthesizing the starting material. Allyl vinyl ethers are difficult to obtain and chemists have developed several useful strategies to make them. How would you do it? The answer to Problem #4 above mentions starting with phenol, a vinyl ether, and reacting it with allyl bromide. However, vinyl ethers are very rare since they readily tautomerize to carbonyls unless they are part of an aromatic ring. One solution is to start with an acetal or ketal in place of the vinyl ether. An example of this strategy is shown below. What is the mechanism for this reaction? This variant of the Claisen rearrangement forms ketones or aldehydes (R=H). We will see below that other common Claisen strategies form esters, carboxylic acids, and amides.

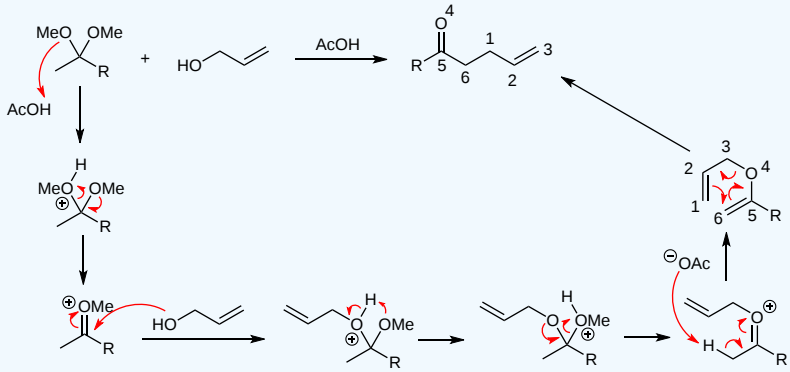


Exercise 1.4.5

Propose a mechanism for the example Claisen reaction shown above. Remember, your mechanism must generate an allyl vinyl ether so that the Claisen rearrangement can occur. Don't forget that AcOH is acetic acid.

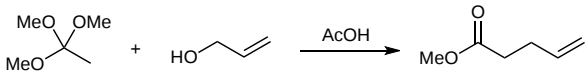
Answer

This is a good review of acid catalyzed ketal mechanistic steps that you learned in intro organic chemistry. The mechanism starts with those standard steps. In the second to last step, the acetate anion (generated in the first step) can deprotonate to form the neutral allyl vinyl ether (this deprotonation looks like the mechanistic step we use to form enamines from secondary amines plus ketones) that undergoes the Claisen rearrangement in the final step.



Johnson-Claisen Rearrangement

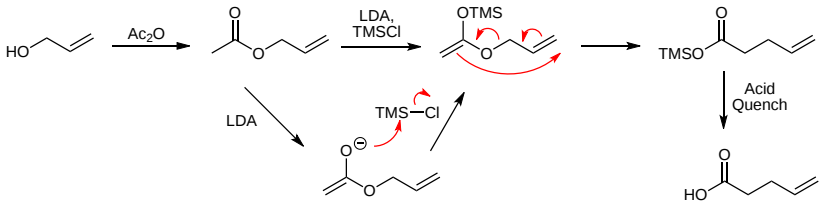
A reaction analogous to the one we just discussed above is the Johnson-Claisen rearrangement that features the unusual orthoester functional group as one of its starting materials and produces ester products. An orthoester is the ester equivalent of a ketal. Using the exact same mechanism as in the answer to Problem #5 above (with R = OMe), we can understand the Johnson-Claisen rearrangement shown below. Thus, the retron for a Johson-Claisen rearrangement is a 1,4-enester.



Ireland-Claisen Rearrangement

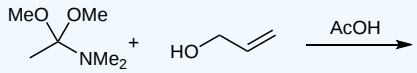
The Ireland-Claisen rearrangement results in the formation of carboxylic acid products and proceeds via a silyl enol ether generated after forming an enolate. The reaction and mechanism are shown below. Continuing our trend of starting with allyl alcohol, we treat it with acetic anhydride to form an allyl ester. Combining that with LDA yields an enolate that reacts with trimethylsilyl chloride (TMSCl) on the oxygen of the enolate (this is standard reactivity for silyl electrophiles with enolates) to yield the key silyl enol

ether. This undergoes the Ireland-Claisen rearrangement to yield a silyl ester that is easily converted to the desired carboxylic acid upon workup with aqueous acid. (This step is analogous to acidic deprotection of silyl ethers to yield alcohols.)



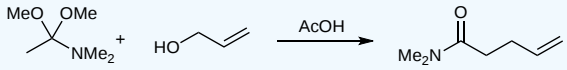
Exercise 1.4.6

What is the product of the following reaction?



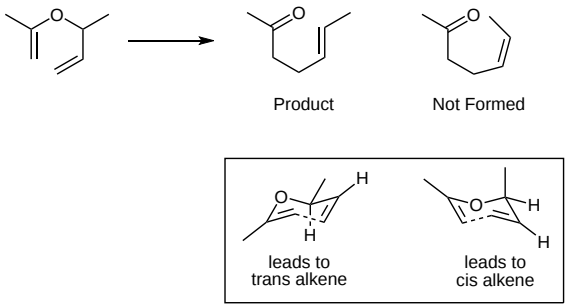
Answer

This is an example of the Eschenmoser-Claisen rearrangement. Using an orthoamide in place of the orthoester in the Johnson-Claisen rearrangement results in the production of an unsaturated amide product by the same mechanism.



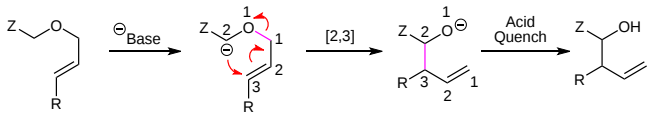
Claisen Rearrangement Alkene Geometry

One final point about the Claisen rearrangement relates to the alkene geometry formed in the reaction. The example below highlights that trans alkenes are formed while cis alkenes are not. Why? This is another example of the importance of chair-like transition states. (We first saw this with the ene reaction in the cycloadditions chapter.) Putting the methyl substituent in the more stable equatorial position leads to the trans product. With the methyl in the less stable axial position, the cis product would form.

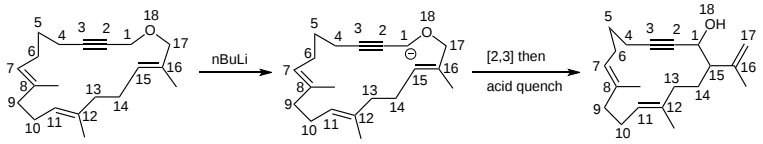


Wittig Rearrangement

All of the sigmatropic rearrangements that we have seen so far are reactions of neutral molecules. That is the case for most sigmatropic rearrangements, but charged molecules also participate in these transformations. The Wittig rearrangement is an anionic [2,3] sigmatropic rearrangement of an allylic ether to yield a homoallylic alcohol. So, the retron for this reaction is the same as the oxo-ene reaction. A generic version of this reaction is shown below. The critical components of the starting material are an allyl ether containing an electron withdrawing "Z" group. Thus, treatment with a strong base results in deprotonation next to the Z group. The resulting anion can participate in a [2,3] sigmatropic rearrangement (numbering from the sigma bond broken to the sigma bond formed) to yield a homoallylic alcohol product, after quenching with acid.

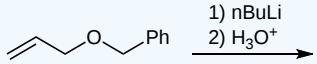


An application of the Wittig reaction is shown below where the electron withdrawing group is a resonance stabilizing alkyne. As this example shows, the Wittig rearrangement can be a powerful ring contraction reaction. In this case, converting an 18-membered ring ether into a 15-membered ring alcohol.



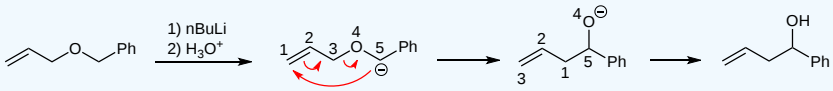
Exercise 1.4.7

What is the product of this Wittig rearrangement?



Answer

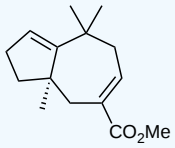
The phenyl is the electron withdrawing group in this molecule. So, draw the anion, then the rearrangement arrows, and finally add the proton to generate the product.



Summary Problems

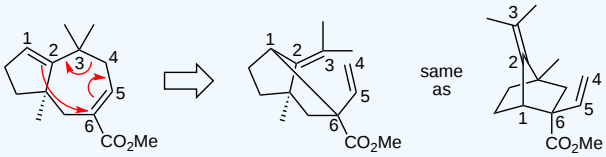
Exercise 1.4.8

Identify the retron in the following molecule then draw the starting material (go back only one step) that would yield the target.



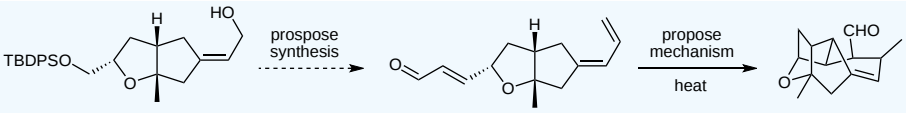
Answer

This molecule contains a 1,5-diene which is the retron for the Cope rearrangement. Drawing the curved arrows for the reaction enables you to determine the starting material used to make the target. Note: There is another 1,5-diene in the molecule; however, the one shown is what was used in the 2010 *Organic Letters* paper to make this molecule.



Exercise 1.4.9

The following transformation appeared in a paper focused on the synthesis of the novel antibiotic platensimycin. Propose a synthetic route for the conversion of the starting allylic alcohol into the triene synthetic intermediate. Then, propose a mechanism for the conversion of this material into the polycyclic product. Hints: One of the steps in your mechanism is a cycloaddition. It might help to think retrosynthetically, going backwards one step from the target for this mechanism.

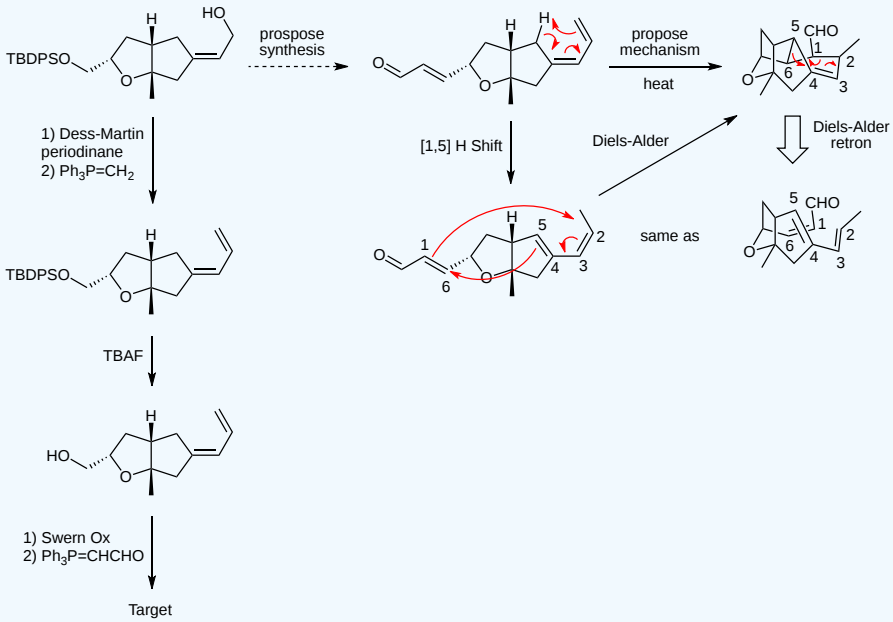


Answer

The synthesis portion of this problem involves three reaction types: oxidation, Wittig, and deprotection. Both oxidations are primary alcohols to aldehydes, so feel free to use PCC, Swern, or Dess-Martin interchangeably. The key Wittig reagents are shown below. After adding the first alkene, then it's time for the deprotection with fluoride (any F minus reagent will work). This reveals the second primary alcohol for the final two steps.

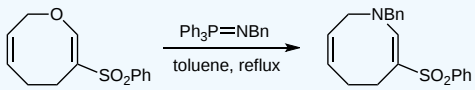
For the mechanism part of the problem, spotting the Diels-Alder retron in the product is the key. This disconnection gets you back to a molecule that is very similar to the starting material. Performing a thermal [1,5] H shift on the starting molecule generates the intramolecular Diels-Alder substrate. This is an excellent example of the importance of hydrogen shifts and the amazing complexity that can be synthesized using intramolecular cycloadditions.

Reference: *Journal of Organic Chemistry* 2009



Exercise 1.4.10

Propose a mechanism for the following reaction. Hints: The mechanism is 4 steps and involves two sigmatropic rearrangements.

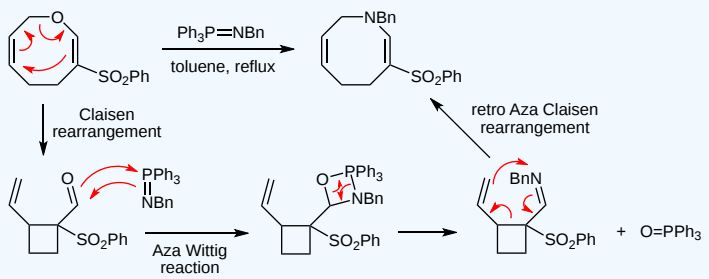


Answer

Looking at the reactants, it's important to recognize that we are starting with an allyl vinyl ether, the starting material for the Claisen rearrangement, and a modified Wittig reagent. This is a nitrogen Wittig reagent which is commonly called an aza Wittig reagent. It reacts just like the Wittig reagents you have seen before but produces an imine instead of an alkene when reacting with a ketone or aldehyde. There is no carbonyl at the start, so our only option is to do the Claisen rearrangement. This yields a molecule with a 4-membered ring and an aldehyde! So, we can now do the aza Wittig reaction. Comparing that imine product with the target 8-membered ring shows that we can do the reverse of our first step, a retro aza (because

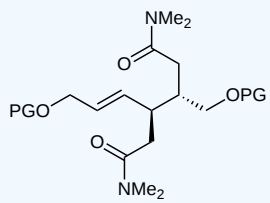
of the nitrogen) Claisen rearrangement, to generate the target. So, in the end it's just substituting NBn for O, but there's a lot going on to make that possible.

Reference: *Organic Letters* 2010



Exercise 1.4.11

Propose a synthesis of the following target starting with any compounds containing six carbons or fewer. Feel free to ignore any carbons that might be in the alcohol protecting groups (PG). Hint: Retrosynthetic analysis should be very helpful.

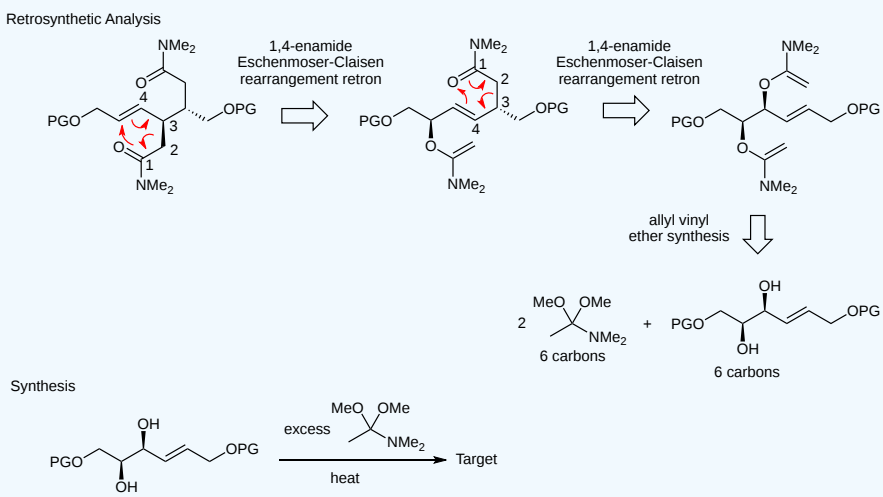


Answer

Let's focus on retrons for this problem. The target contains a 1,4-enamide which is the retron for the Eschenmoser-Claisen rearrangement. Doing that retrosynthetic step reveals a second 1,4-enamide, so we can do another Eschenmoser-Claisen rearrangement. This yields a double amino enol ether that we can disconnect back to a 6-carbon diol and the ortho amide that we have used before for Claisen rearrangements.

For the synthesis part of the problem, all we need to do is heat the diol with excess ortho amide. This yields the allyl vinyl ether we need for the Eschenmoser-Claisen rearrangement, and the entire process can happen again to yield our target. An excellent example of creative synthetic planning!

Reference: Organic Letters 2010



Contributors

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CHAPTER OVERVIEW

2: Transition Metal Catalyzed Carbon-Carbon Bond Forming Reactions

2.1: Introduction to Transition Metals and Mechanistic Steps
2.2: Pd-Catalyzed Cross Coupling Reactions
2.3: Olefin Metathesis
2.4: Co-Mediated Ring Forming Reactions

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2.1: Introduction to Transition Metals and Mechanistic Steps

Objectives

After completing this section, you should be able to:

1. Understand bonding, electron counting, and oxidation states for transition metal complexes
2. Draw and understand common transition metal mechanistic steps

Key Terms

Make certain that you can define, and use in context, the key terms below.

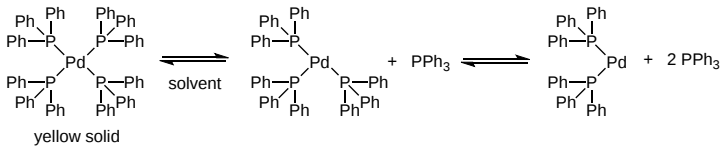
- Transition metal complex
- Ligands
- 18-electron rule
- Metal oxidation state
- Pi donor ligands
- Oxidative addition
- Transmetallation
- Reductive elimination
- Migratory insertion
- Beta hydrogen elimination

Study Notes

Transition metal catalyzed carbon-carbon bond forming reactions provide powerful methods to form key bonds in ways that are often impossible with traditional main group organometallic compounds (e.g., Grignard and organolithium reagents). This chapter provides an introduction to transition metal complexes including their bonding and common reactions. The following chapters will explore the most common transition metal catalyzed reactions including Pd catalyzed cross coupling reactions, olefin metathesis, and Co mediated ring forming reactions.

Content

Before learning about reactions catalyzed by transition metal complexes, we first need to understand a little about their structure and behavior. To begin, we need to update our vocabulary. You've already seen that we refer to molecules containing transition metals as **complexes**. Transition metal complexes contain the metal and other molecules bonded to the metal. These molecules bound to the metal are called **ligands**. Bonds between transition metals and their ligands are weaker than the covalent bonds you are used to from standard organic molecules. This is one reason why transition metals make such excellent catalysts, they are able to make and break bonds to ligands frequently throughout the course of a reaction. For example, tetrakis triphenylphosphine palladium is a yellow solid in which Pd has 4 triphenylphosphine ligands. As shown below, when dissolved in a solvent, this complex exists in equilibrium with complexes containing three and two triphenylphosphine ligands.

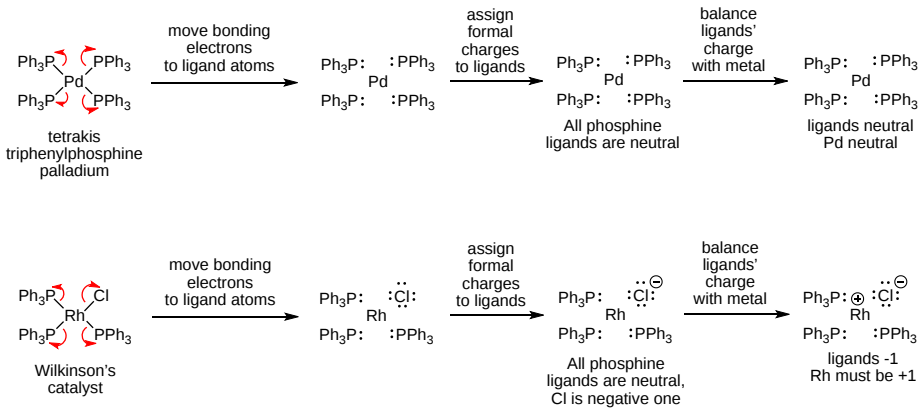


Electron Counting

Much time in introductory organic chemistry is spent discussing the octet rule (based on filling s and p orbitals). Transition metals have ready access to d-orbitals, so the octet rule does not apply. Instead, we add 10 electrons (because of the 5 d orbitals) and come up with the **18-electron rule**. Transition metal complexes containing 18 electrons are generally stable and unreactive. For active catalysts, we must have metals that are surrounded by fewer than 18 electrons. Also, we need to learn how to determine the formal charge on the metal. This is called the metal's **oxidation state**. Metals with high oxidation states are electron poor and are much more reactive than low oxidation state or neutral metal complexes.

We will start by analyzing metal complexes where the ligands are bound to the metal via sigma bonds, like in tetrakis triphenylphosphine palladium above. First, we must determine the oxidation state (formal charge) of the metal. To do this, we will 1) Consider the sigma bond electrons between the metal and the ligand as belonging to the ligand. 2) Assign a formal charge to the ligand atoms bound to the metal using standard organic chemistry formal charge rules. 3) Add up the charges on all of the ligands. 4) The metal oxidation state balances the ligands' summed formal charges so that the overall complex is neutral (or negative if it's an anionic complex/positive if it's a cationic complex).

Let's practice this by looking at a Pd complex ($Pd(PPh_3)_4$) and a Rh complex ($(Ph_3P)_3RhCl$). Phosphine ligands are common in transition metal complexes, and their charge is always neutral. (Just like N, which is in the same column in the periodic table, P is neutral with 3 bonds and a lone pair.) Halogens with eight electrons and no bonds have a negative one formal charge. So, in the Pd complex, the ligands have no formal charge, and Pd has a zero oxidation state: Pd(0). In the Rh complex, the net charge on the ligands is negative one. The metal must balance that charge so that the overall complex is neutral. This means Rh has a +1 oxidation state: Rh(I).



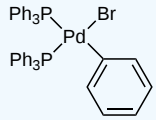
The next step is to detemine the total electron count around the metal to see if it satisfies the 18-electron rule. To do this, we must determine 1) The total electrons donated to the metal from the ligands. 2) The valence electrons from the transition metal based on its oxidation state. 3) Add the ligand electrons plus the metal electrons.

Ligand electron counting is as simple as counting the bonds from the ligands to the metal and multiplying by 2. In both of the complexes above, there are four sigma bonds from the ligands to the metals, so there are 8 electrons from the ligands. To determine the metal's valence electrons, we must look at the periodic table and factor in its oxidation state. In the Pd complex above, we determined it is Pd(0) which means Pd has all of its valence electrons. It is in group 10 in the periodic table, so it has 10 valence electrons. In Wilkinson's catalyst above, we determined it is Rh(I) which means Rh has lost one valence electron. Rh is in group 9, so it has 8 valence electrons as a +1 metal.

Thus, we can complete our analysis of the example complexes above. Tetrakis triphenylphosphine palladium has 8 ligand electrons plus 10 metal electrons for a total of 18 electrons. It satisfies the 18 electron rule and is unreactive until it loses one or two ligands in solution. Wilkinson's catalyst has 8 ligand electrons plus 8 metal electrons for a total of 16 electrons. Thus, it can form one more bond and is reactive.

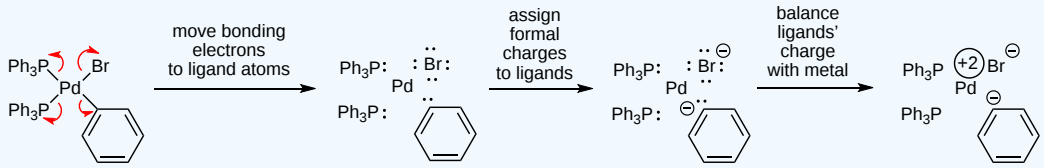
Exercise 2.1.1

The following Pd complex is commonly formed in Pd catalyzed cross coupling reactions. Perform an electron counting analysis on the complex to determine the oxidation state of Pd and the total Pd electron count.

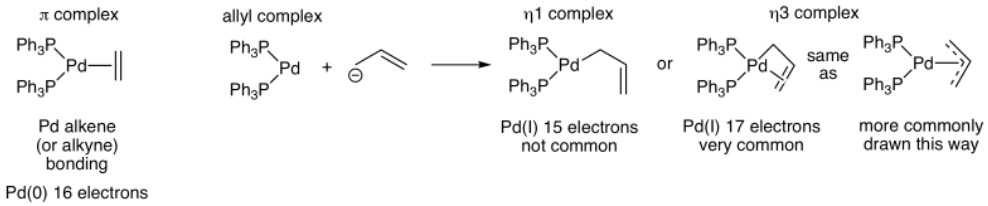


Answer

Following our strategy from above, we can determine that we have two negative one ligands, the Br and the Ph. This means that Pd must balance the net -2 charge by being in its +2 oxidation state: Pd(II). For the total electron count, we again have 8 ligand electrons. Metal ligands are 8 for a +2 Pd (two fewer than the 10 electrons for the neutral Pd). The means our total electron count is 16.

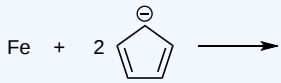


We have one more class of ligands to consider before moving on. These are pi donor ligands. This class of ligands can donate pi electrons via a pi bond. A common example is a pi complex formed when an alkene or alkyne bonds with a metal via its C-C pi bond (see below, left). This results in a neutral, 2 electron ligand. Another example that we will see frequently is an allyl ligand. There are two options for how an allyl anion can bond to a metal (see below, right). It can form a sigma bond which makes it a 2 electron, -1 ligand. However, it can also bond via its alkene pi bond, making it a 4 electron, -1 ligand. This latter option is much more common since it generally helps the metal get closer to an 18-electron complex. Here's another place to expand our transition metal vocabulary. We use the Greek letter eta to describe how many atoms in the ligand are bound to the metal. So, for the first allyl option (2 electrons, -1), we would say it is eta 1 (1 carbon sigma bonded to the metal). For the second allyl option (4 electrons, -1), we would say it is eta 3 (3 carbons bonded to the metal via one sigma and one pi bond).



Exercise 2.1.2

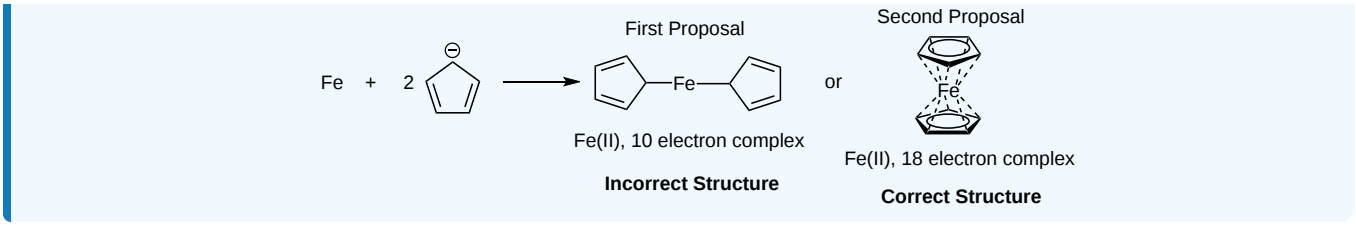
Propose a structure for the iron complex that is formed in the following reaction. Hint: This molecule is very stable.



Answer

This deceptively simple reaction was the start of a new field of chemistry. Originally published as the sigma bond structure in 1951, an alternate "sandwich" complex was published in 1952. An X-ray crystal structure proved the novel sandwich structure and a new subdiscipline of organometallic chemistry was born. For their work in this area, Geoffrey Wilkinson and Ernst Fisher were awarded the Nobel Prize in 1973. This 2001 article in Chemical and Engineering News provides an overview of the discovery. An entertaining examination of this discovery and the subsequent scientific credit appeared in Angewandte Chemie in 2000. This article was co-authored by Roald Hoffmann and examines the role of R.B. Woodward in the ferrocene story. (These are Woodward and Hoffmann from pericyclic reaction fame appearing again!)

The initial proposal is likely the first structure that you drew. This complex has the two cyclopentadienyl ligands (abbreviated Cp) sigma bonded to Fe. This yields a 10 electron Fe(II) complex that would not be very stable. Thinking about the two Cp ligands participating in bonding to the Fe via their pi electrons yields a completely different structure. (Don't forget that the cyclopentadienyl anion is an aromatic anion.) This is the correct structure with each Cp ligand contributing 6 electrons to the complex (still a -1 donor) via eta 5 bonding. This results in a stable 18 electron Fe(II) complex. This fascinating molecule is aromatic, participating like benzene in Friedel-Crafts reactions, and is known as ferrocene. Cp ligands are ubiquitous in organometallic chemistry, so be aware of this unique bonding when reading the literature and you see metal-Cp complexes.



Common Mechanistic Steps

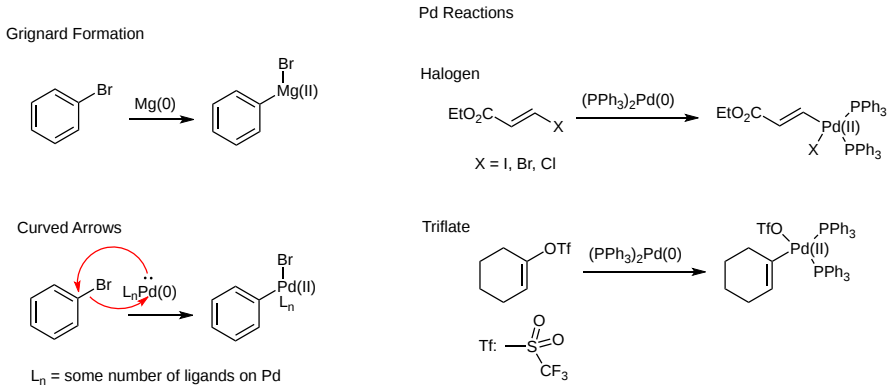
Many transition metal catalyzed reactions share common mechanistic steps that include oxidative addition, reductive elimination, transmetallation, migratory insertion, and beta hydrogen elimination. We will explore each of these individually and then see in the next chapter how that are combined in specific Pd catalyzed cross coupling reactions.

One note about organometallic mechanisms is that chemists often don't use curved arrows to show electron flow. Why? It is often because electron flow isn't always clear. For example, some of these mechanisms might actually be radical reactions. In this chapter, we will shown how electrons could flow if they were polar reactions since this often helps students understand what is happening. However, in keeping with the conventions of transition metal mechanisms, we won't always do this.

Oxidative Addition

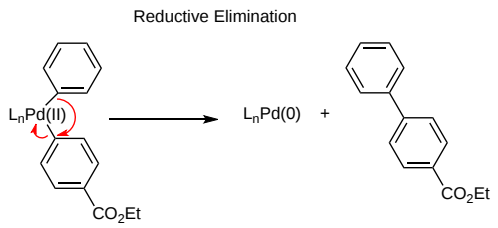
Many transition metal catalyzed reactions begin with a step called oxidative addition where the metal adds to a carbon-halogen bond. You have already seen this reaction type though it may not have been called an oxidative addition. Forming a Grignard reagent from Mg and an organohalogen compound is an oxidative addition. This step is oxidative with respect to the metal because it formally loses electrons when adding carbon and halogen ligands. In the examples below, a neutral metal adds two -1 ligands, meaning the metal becomes +2. We will see many examples of oxidative addition of Pd(0). Two are shown below highlighting the reactivity of halogens and triflates (OTf). (If you haven't met a triflate before, it is a more reactive version of a tosylate that can easily be made from an alcohol or a carbonyl. We will see examples of this in later sections.) A third Pd(0) example is shown to illustrate how you can think about electron flow and curved arrows for oxidative addition. As mentioned above, we generally won't draw curved arrows for this step, and the arrows likely don't depict what is actually happening in the mechanism. The most common and synthetically useful oxidative additions occur between Csp-X/OTf or Csp^2-X/OTf and metals like Pd. So, we will encountered oxidative additions with vinyl, phenyl/aryl, and alkynyl substrates.

Oxidative Addition Examples



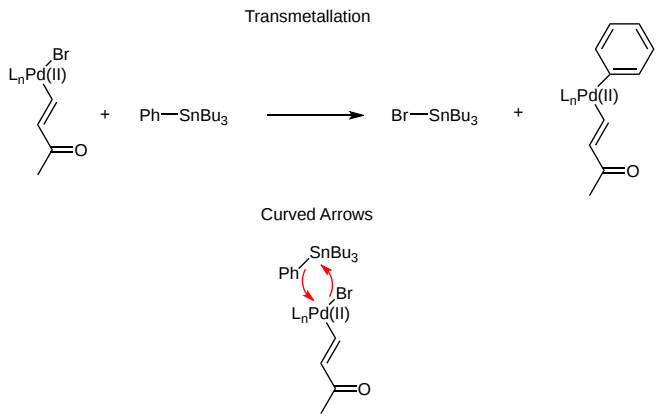
Reductive Elimination

The opposite mechanistic step to oxidative addition is reductive elimination. In this step, two groups bound to the metal, often two carbon ligands, form a new bond while formally giving electrons back to the metal. Thus, this step reduces the metal. It is often the last step in the cycle, regenerating the transition metal catalyst and forming the key carbon-carbon bond in the product. Curved arrows are show below, but this is another step where we will normally resist drawing curved arrows.



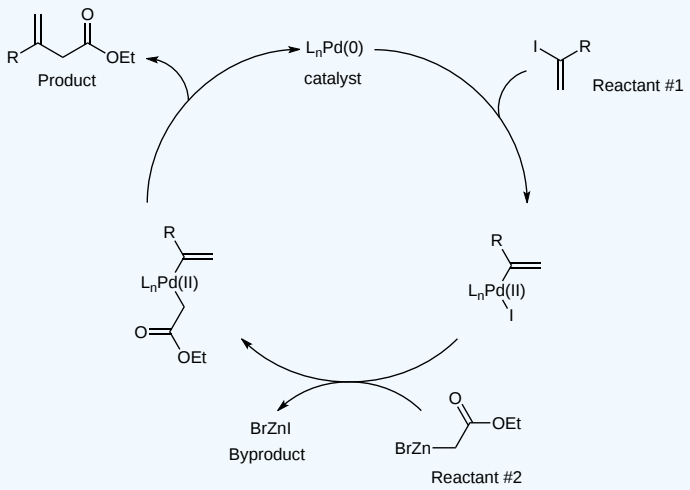
Transmetallation

A common strategy to form a new carbon bond to the transition metal catalyst is to start with a carbon group on a different metal. The stoichiometric metal reagent then transfers the carbon group to the catalytic metal during the catalytic cycle. We will see in the next section that Pd participates in transmetallation with metals like B, Sn, Cu, and Ni. As shown below, the net result is that the halogen group on the catalytic metal (Pd) switches places with the carbon group on the stoichiometric metal (Sn). Also, note that the oxidation state of Pd doesn't change, so this is neither an oxidation nor a reduction.



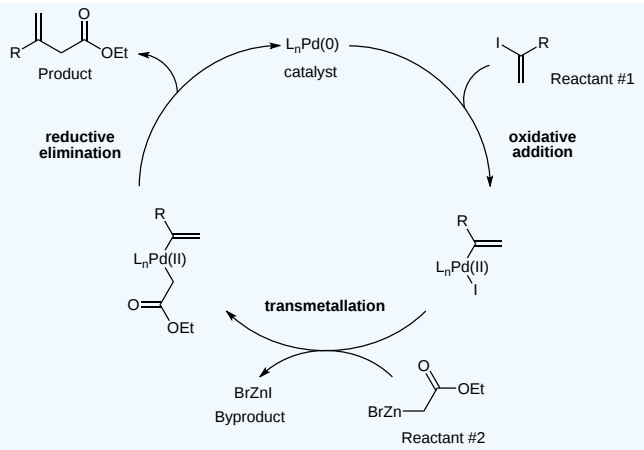
Exercise 2.1.3

Shown below is the catalytic cycle for a Negishi reaction. Label each mechanistic step as oxidative addition, reductive elimination, or transmetallation.



Answer

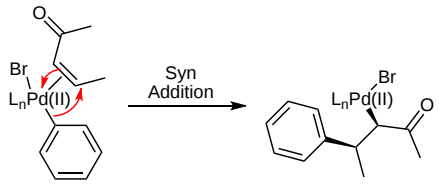
As with many Pd catalyzed reactions, the steps proceed in this order: oxidative addition (making one Pd-C bond), transmetallation (making a second Pd-C bond), and reductive elimination (making the key C-C bond).



Migratory Insertion

Some transition metal catalyzed reactions involve addition of a metal-carbon bond across a pi bond, like an alkene or alkyne, that is also bound to the metal. This is a powerful way to build up complexity in a molecule, especially when it is an intramolecular reaction, and we will see numerous examples of this step when we explore the Heck reaction in the next chapter. As shown below, an alkene (or alkyne) that is complexed to the metal via its pi bond can insert into an adjacent metal-carbon sigma bond. This is a syn addition to the alkene and is similar to the alkene hydrogenation mechanism that you learned in intro organic. The new carbon-carbon bond generally forms at the least hindered/most electron poor carbon of the alkene.

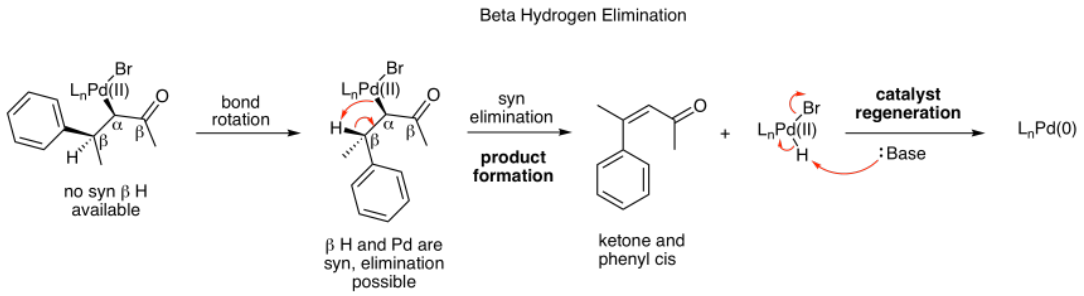
Migratory Insertion



Beta Hydrogen Elimination

For many transition metal complexes bound to an sp^3 hybridized carbon, beta hydrogen elimination is a common mechanistic step. This is a product yielding step and demonstrates the ability of transition metal reactions to form alkene products. Unlike E2 reactions that you learned in intro organic that proceed via an anti elimination, beta hydrogen eliminations are syn eliminations. This has important implications for product alkene geometry and must be carefully considered when proposing this type of mechanistic step. In some complicated substrates, a syn arrangement of the metal and beta hydrogen are not possible. In these cases, the base included in the reaction mixture that usually regenerates the active catalyst instead does a traditional anti E2 reaction to yield an alkene product. We will see examples of this in the following chapter.

Beta hydrogen elimination reactions occur most often after migratory insertion steps. We can explore this mechanism beginning with the product of our migratory insertion step shown above. The migratory insertion product has two beta carbons; however, only the beta carbon on the left has a hydrogen. In the initial conformation, this beta hydrogen is anti to the Pd, so intramolecular elimination is not possible. Thus, our next step is a bond rotation to orient the Pd and beta H syn. Our syn beta hydrogen elimination is now possible, and the reaction occurs. This generates our alkene product with the ketone and phenyl positioned cis, due to their orientation in the reactive conformation. Note that this reaction does not regenerate our Pd(0) catalyst. Instead, we form a Pd(II) complex containing a Pd-H bond. Standard reaction conditions include a base so that deprotonation and loss of bromide regenerates the active catalyst.



Contributors

- Prof. Kevin Shea (Smith College)

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2.2: Pd-Catalyzed Cross Coupling Reactions

Learning Objectives

After completing this section, you should be able to:

1. Identify common Pd-catalyzed carbon-carbon bond forming reactions
2. Draw and understand reaction mechanisms
3. Use reactions in synthesis problems

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Stille reaction
- Suzuki reaction
- Sonogashira reaction
- Heck reaction
- Tsuji-Trost reaction
- Buchwald-Hartwig amination

Study Notes

Palladium catalyzed reactions are the most common transition metal catalyzed cross coupling reactions. Their importance was recognized with the 2010 Nobel Prize for Richard Heck, Ei-ichi Negishi, and Akira Suzuki. These reactions provide straightforward methods for the construction of Csp^2-Csp^2, Csp^2-Csp, and Csp^2-N bonds. We will see many examples of these types of bond formations, and several others, throughout this chapter. While learning this material, don't forget to contrast Pd catalyzed reactions with popular intro orgo carbon-carbon bond forming reactions like Grignard or organolithium reactions with carbonyls and epoxides. At least one component of these reactions was sp^3 hybridized, so it was impossible to generate the types of bonds that are formed most commonly by Pd catalyzed reactions. Adding Pd catalyzed reactions to your organic chemistry toolbox will greatly expand the types of molecules that you are able to synthesize.

Content

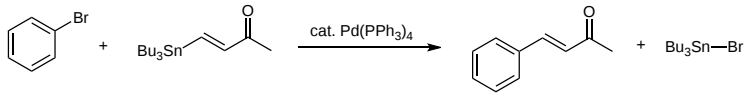
This chapter will focus on learning and applying common Pd catalyzed reactions for the formation of 1) Carbon-Carbon bonds: Stille, Suzuki, Sonogashira, and Heck 2) Carbon-Carbon or Carbon-Oxygen bonds: Tsuji-Trost and 3) Carbon-Nitrogen bonds: Buchwald-Hartwig. If you haven't already, please refer to the previous chapter for a discussion of transition metal structure and bonding along with common mechanistic steps in transition metal catalyzed reactions.

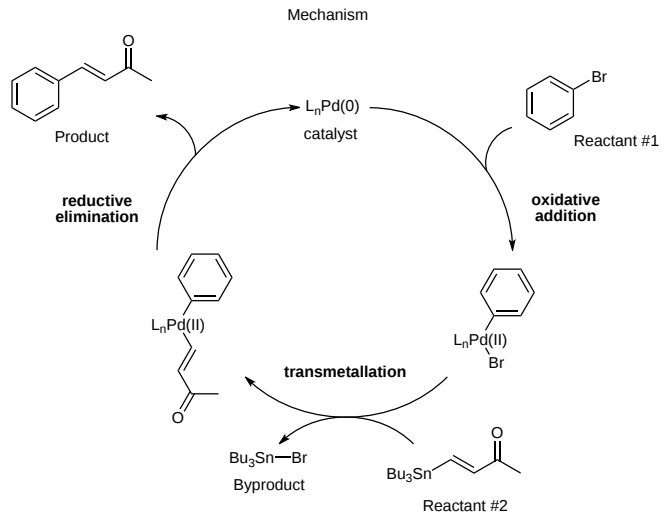
For all of the reactions in this chapter, we will depict the palladium catalyst as $L_nPd(0)$ to acknowledge that some number of ligands are bound to Pd but their actual number and structure are unimportant to the mechanism. Two things happen when a Pd complex dissolves in the reaction solvent. First, bonds to phosphine ligands break to establish an equilibrium with complexes having fewer ligands and open coordination sites for reactions to occur. Second, some reactions will begin with Pd(II) reagents. For example, most Sonogashira reactions are run with $PdCl_2(PPh_3)_2$. These Pd reagents are reduced under the reaction conditions by several possible mechanisms that we won't concern ourselves with here. The net result is that Pd(0) is produced in the flask, and this complex can then catalyze the desired reactions. Even though we will generally ignore the phosphine ligands, the structure of these molecules is critically important to the success of Pd catalyzed reactions. Many of the recent advances in this field were made possible by the development of novel phosphine ligands. The Buchwald-Hartwig reaction is one such example.

Stille Reaction

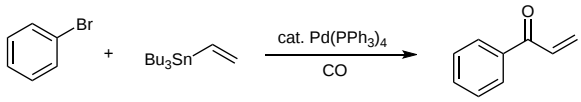
The Stille reaction is the simplest Pd catalyzed cross coupling reaction where an organohalide combines with an organotin in the presence of a Pd(0) catalyst to form a new C-C bond. To avoid side reactions and production of mixtures, both components generally have Csp^2 or Csp atoms bonded to the halogen and the tin. An example reaction and mechanism are shown below. Oxidative addition of bromobenzene with the Pd catalyst yields the first Pd(II) intermediate. Transmetallation transfers the alkene

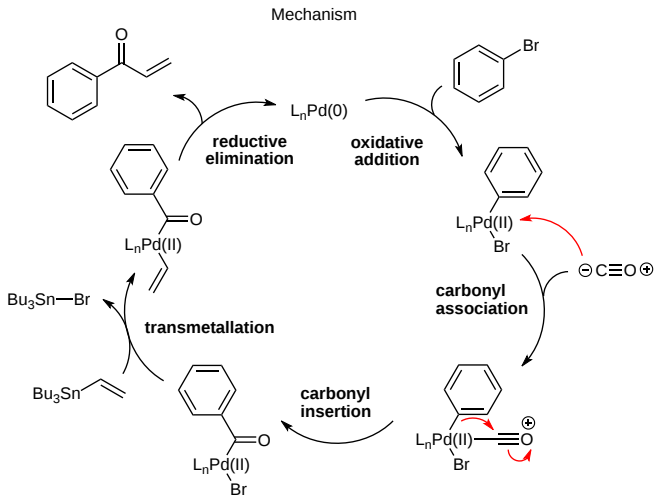
from Sn to Pd, generating the tributyltin bromide byproduct and the desired Pd(II) intermediate with two C-Pd bonds. Finally, reductive elimination generates the desired product and regenerates the Pd(0) catalyst.





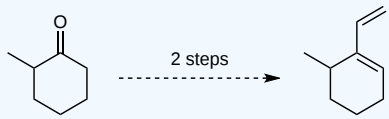
A useful variant of the standard Stille reaction is the carbonylative Stille reaction where a carbonyl can be added between the organohalide and organotin components. This is made possible by running the reaction under an atmosphere of CO gas. An example with the carbonylative mechanism is shown below. After oxidative addition, CO associates with Pd forming a C-Pd bond. Next, the phenyl ligand can perform a carbonyl insertion step (similar to the alkene migratory insertion shown in the previous chapter) to form one new C-C bond. We now return to the regular Stille mechanism with the transmetallation and reductive elimination steps producing the final product and regenerating the catalyst.





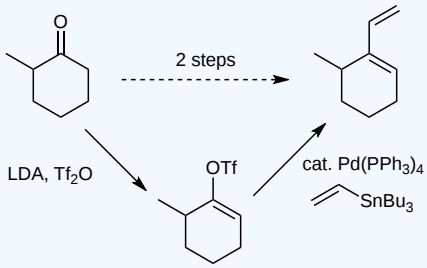
Exercise 2.2.1

Complete the following synthesis in 2 steps, one of which is a Stille reaction.



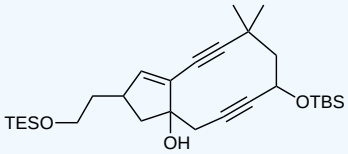
Answer

Thinking retrosynthetically, we must be forming the single bond between the alkenes using a Stille reaction. That means we need to convert the ketone into a vinyl halide or halide equivalent in the first step. This is easily done by forming an enolate and adding triflic anhydride to make a vinyl triflate. As explained in the previous chapter, vinyl triflates participate readily in transition metal catalyzed reactions. So, our two step synthesis is 1) Deprotonation with LDA (to ensure we form the least substituted kinetic enolate) followed by addition of triflic anhydride to yield the vinyl triflate. 2) Stille reaction with vinyl tributyltin to generate the target.



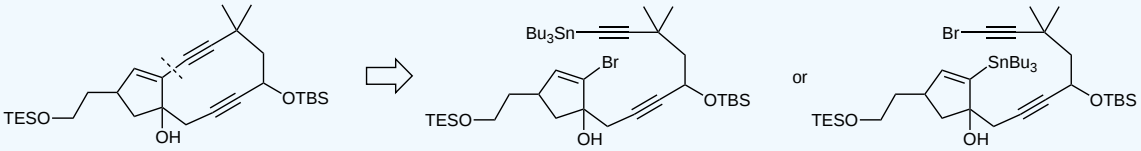
Exercise 2.2.2

Using retrosynthetic analysis, how would you make this target in one step using a Stille reaction?



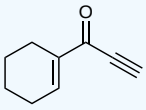
Answer

The key bond is the one between the alkene and the alkyne. This is the bond we will make in the forward direction using the Stille reaction.



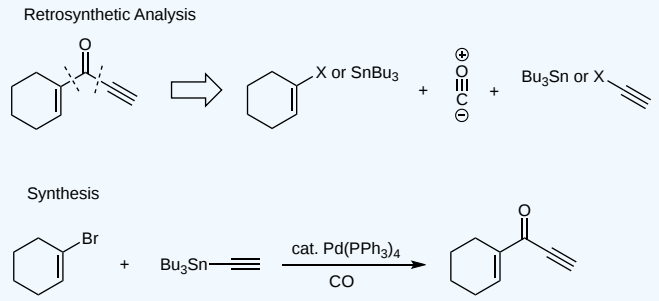
Exercise 2.2.3

Propose a 1 step synthesis of the target using a Stille reaction.



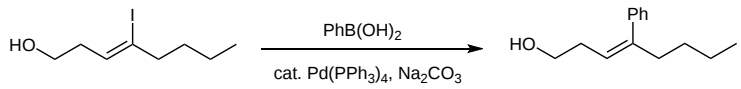
Answer

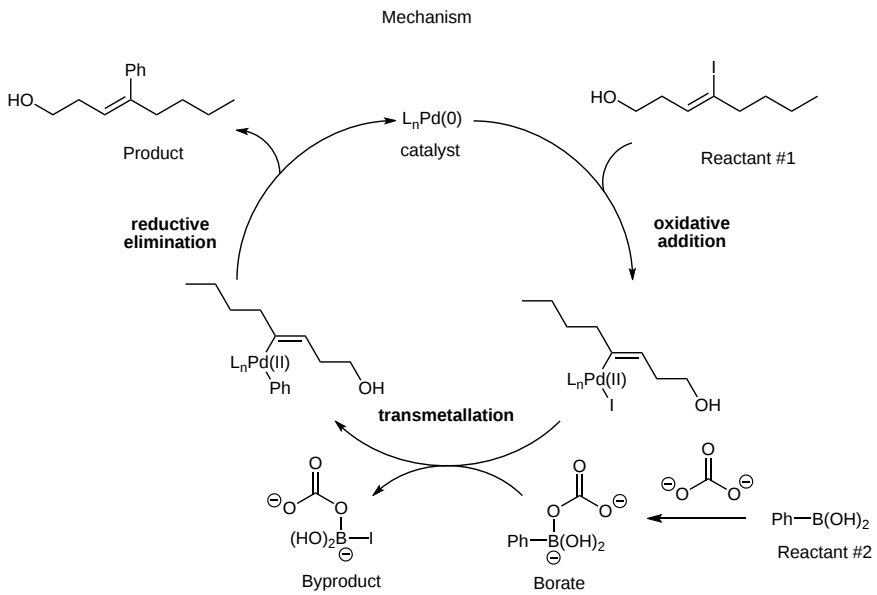
This is the perfect molecule to use the carbonylative Stille reaction. We can start with a vinyl bromide and an alkynyl tin. Combining them with the palladium catalyst under a CO atmosphere yields the target.



Suzuki Reaction

The Suzuki reaction is similar to the Stille reaction but with boron used instead of tin for the transmetallation step. It also differs from the Stille reaction because Suzuki reactions require the presence of a base to activate the boron reagent prior to transmetallation. As shown below, the mechanistic steps are the same for these two popular transformations with the addition of the base promoted boron activation step that forms the reactive borate (negatively charged boron) compound. This borate reagent can be formed by a variety of oxygen bases in addition to carbonate like hydroxide and alkoxides (e.g., ethoxide, t-butoxide).

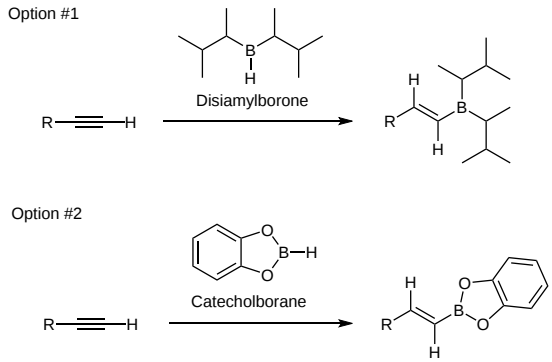




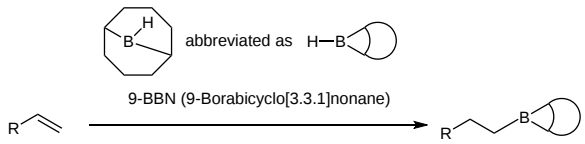
There are several advantages of the Suzuki reaction. First, we are already familiar with forming C-B bonds from intro orgo using a hydroboration reaction. Previously, we always followed this step with an oxidation reaction to form an alcohol. Now we can form the organoboron compound and use it in a Suzuki reaction. We can react alkenes or alkynes in hydroboration reactions to yield organoboron reagents for transmetallation. Several examples are shown below. Hydroboration of terminal alkynes is synthetically useful (internal alkynes yield product mixtures) when using hindered boranes like disiamylborane or catecholborane. Like all hydroborations, the reactions are syn additions with the larger boron adding to the less hindered side of the alkyne resulting in trans alkene products. To generate alkylboron reagents for use in Suzuki reactions, the most common reagent is 9-BBN (pictured below). A second advantage is the Suzuki reaction provides a way to use Pd catalysis to easily make Csp^2-Csp^3 or Csp-Csp^3 bonds which can be challenging to make with other Pd catalyzed reactions. Hydroboration of an alkene provides the requisite B-Csp^3 reagent

(the 9-BBN derivative shown below) that participates in transmetallation then reductive elimination to yield the desired bond. We will see an example of this in one of the problems below.

Hydroboration of alkynes: Synthesis of vinylboron reagents

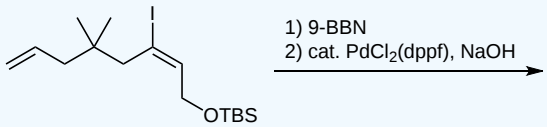


Hydroboration of alkenes: Sythesis of alkylboron reagents



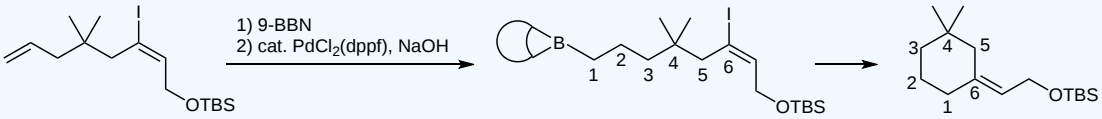
Exercise 2.2.4

What is the product of the follow reaction sequence?



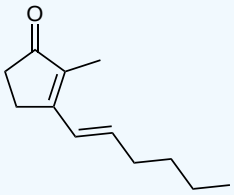
Answer

The first step is a hydroboration reaction with 9-BBN which is selective for the much less hindered terminal alkene. This sets up an example of a very synthetically useful intramolecular Suzuki reaction to form a 6-membered ring.



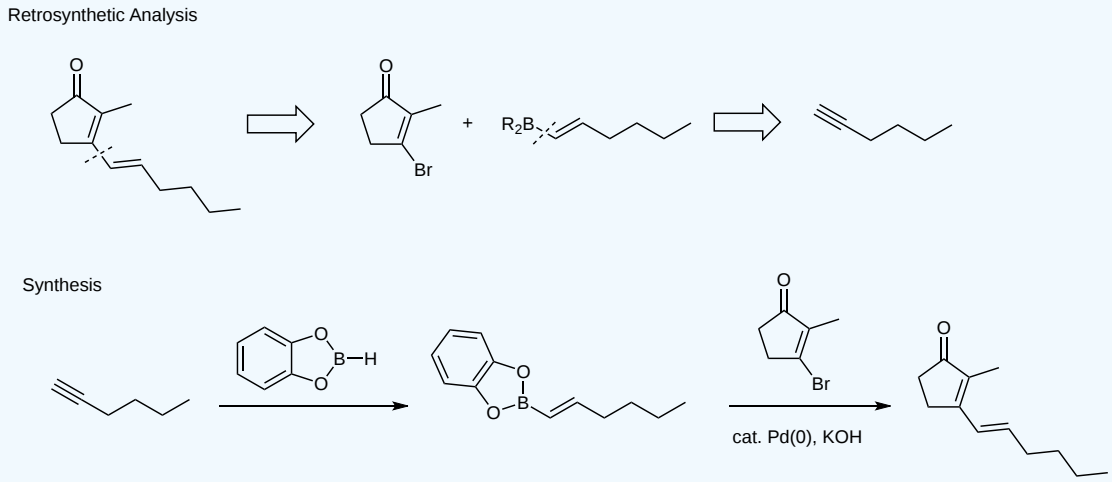
Exercise 2.2.5

Propose a synthesis of the following target starting with compounds containing 6 carbons or fewer. One of your starting materials must be an alkyne.



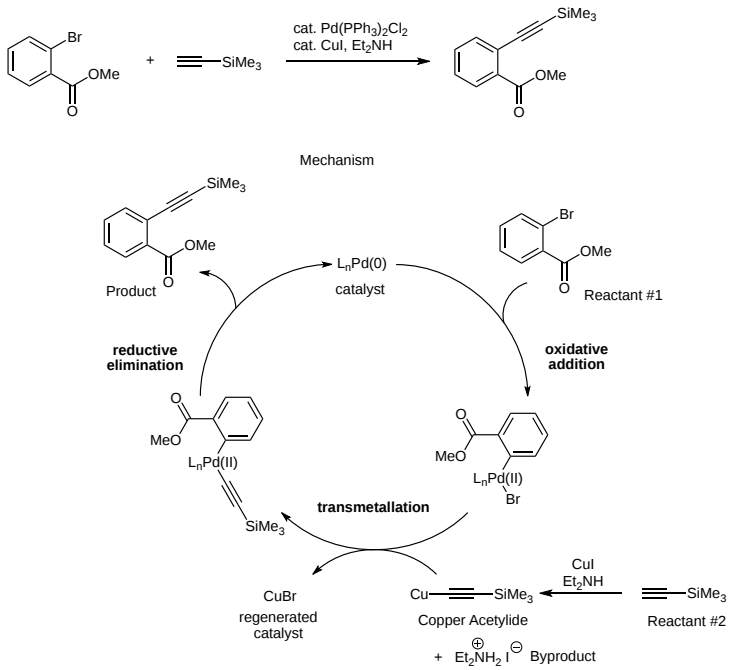
Answer

Thinking retrosynthetically, we can split the molecule between the two alkenes into two 6-carbon fragments that can be combined using a Suzuki reaction. The boron-containing component can then be simplified to the requisite alkyne starting material. In the forward direction, we start with 1-hexyne and hydroborate it with catecholborane (a 6-carbon reagent) to yield the vinylborane that participates in a Suzuki reaction with our 5-membered ring vinyl bromide to yield the target.



Sonogashira Reaction

The Sonogashira reaction enables the combination of an unsaturated carbon-containing halide or triflate with a terminal alkyne to yield a new Csp-Csp or Csp-Csp^2 bond. One interesting aspect of this reaction is that it is catalyzed by a combination of Pd (to form the C-C bond) and Cu (to activate the terminal alkyne for transmetallation). Another key reagent is an amine base that promotes formation of the copper acetylide that participates in the transmetallation step. An example Sonogashira reaction and the mechanism is shown below. This is a very useful reaction and an important addition to our synthesis toolbox.

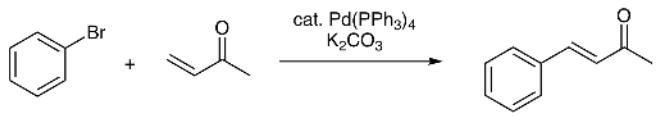


The previous three reactions, Stille, Suzuki, and Sonogashira, share a similar mechanism that includes oxidative addition, transmetallation, and reductive elimination steps. Other reactions with different metals have a similar catalytic cycle with palladium. Although we won't discuss them here, you are well equipped to understand these reactions when you see them in the

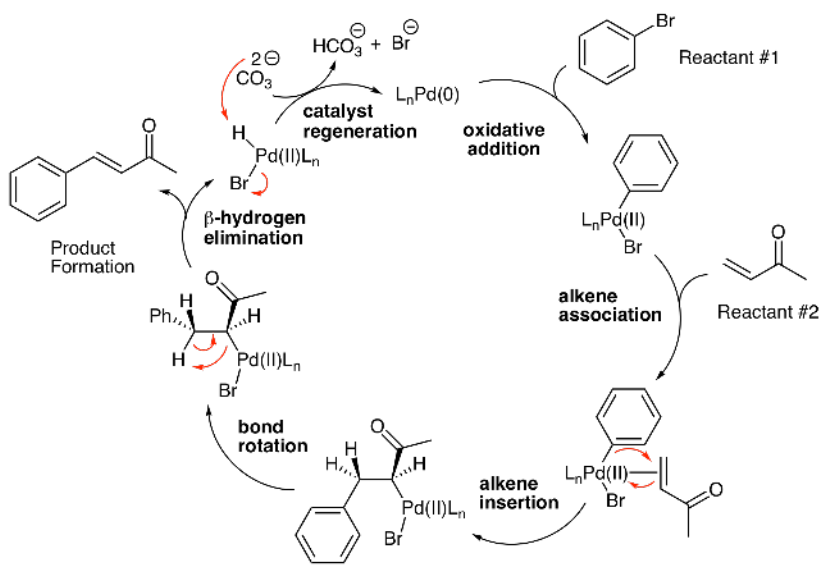
literature. Two of the most common examples are the Negishi reaction (transmetallation with zinc) and the Kumada reaction (transmetallation with magnesium).

Heck Reaction

The Heck reaction proceeds via a different mechanistic pathway than the Stille, Suzuki, or Sonogashira reactions because it does not contain transmetallation or reductive elimination steps. Instead, the Heck reaction relies on an alkene insertion step for carbon-carbon bond formation and beta hydrogen elimination to generate the product. (As a reminder, these steps were described in detail in the previous chapter.) An example of the reaction and its mechanism are shown below. A few key points about the mechanism are worth highlighting. The alkene insertion step usually places the Pd at the more substituted position and the carbon at the least substituted position. This step is a syn addition to the alkene which necessitates a bond rotation in the next step to place a beta hydrogen syn to the Pd. There are two possible Hs that can end up syn but the conformation that places the phenyl and the ketone anti is preferred. (Note that for this mechanism, only one beta carbon has Hs. The other beta carbon is the ketone. In many reactions, there are several alkenes that can form. Heck reactions generally produce the most stable possible alkene product.) This conformation yields the more stable trans alkene product in the beta hydrogen elimination step. The Pd(0) catalyst is regenerated in the final deprotonation step that explains the need for base in the mechanism.



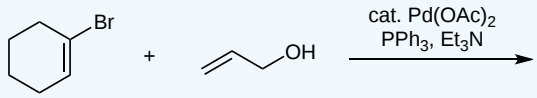
Mechanism



Heck reactions are commonly run intermolecularly, between two different reactants. However, the true power of the Heck reaction for synthesis becomes apparent when studying intramolecular Heck reactions. This is a very useful technique for quickly building molecular complexity. We will see an example of this in one of the problems below.

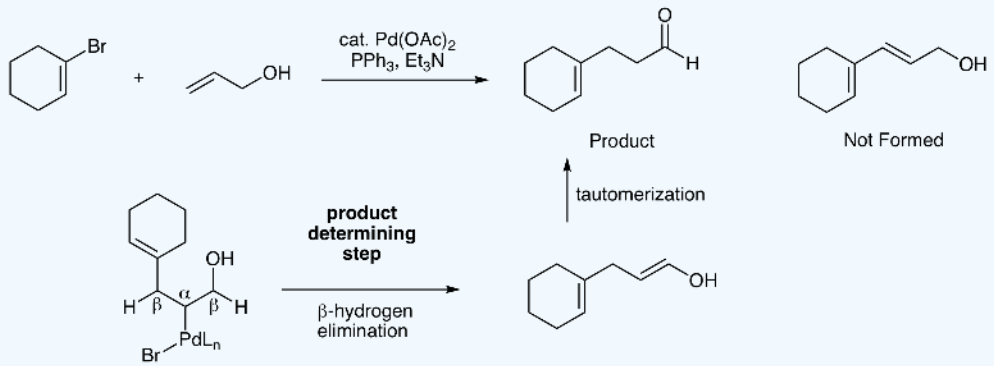
? Exercise 2.2.6

Predict the product of the following intermolecular Heck reaction.



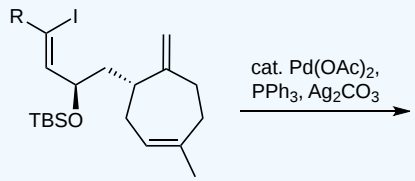
Answer

This is a tricky problem. Most students quickly predict the conjugated diene shown below that doesn't form. This is a good illustration of the importance of evaluating potential products formed from the beta hydrogen elimination step. In this reaction, there are two beta carbons with Hs that can be eliminated with Pd. One option, the beta H on the left, yields the conjugated diene. The other option, the beta H on the right, yields an enol product that tautomerizes to the observed aldehyde product. Carbonyls are more stable than alkenes, so this thermodynamic difference drives the reaction to the aldehyde.



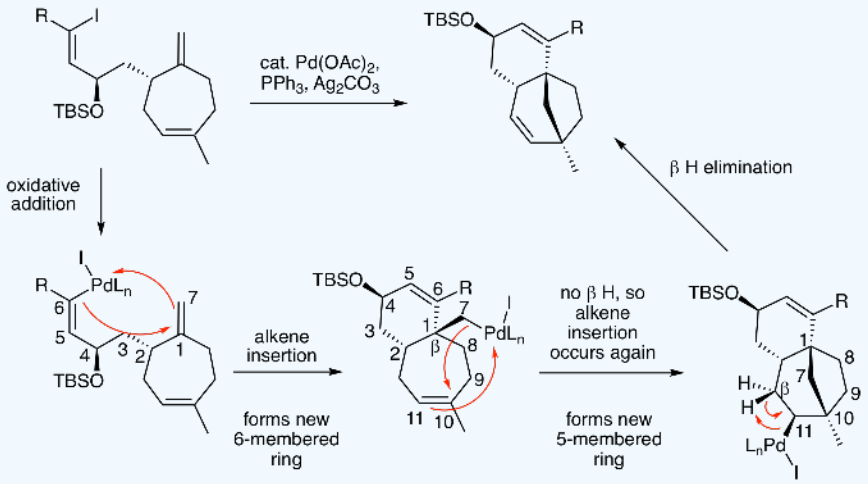
? Exercise 2.2.7

Predict the product of the following intramolecular Heck reaction.



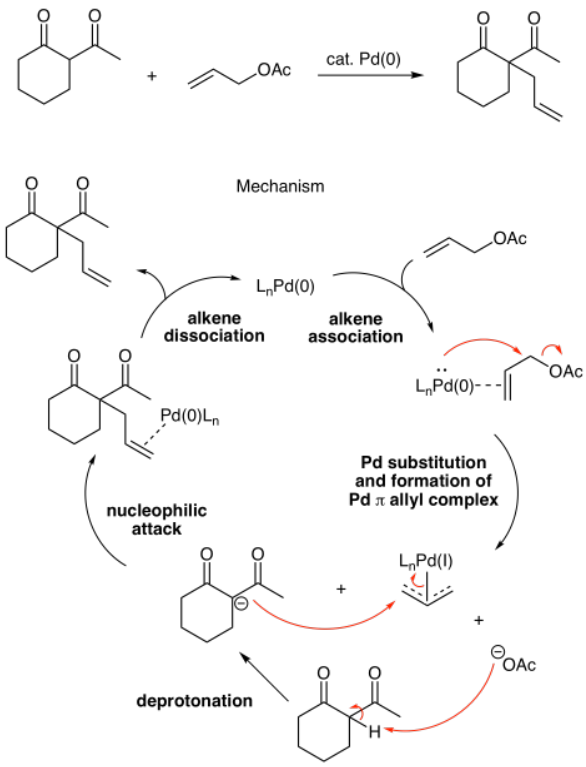
Answer

This is an excellent example of what is known as a Heck zipper reaction where multiple alkene insertions occur to form more than one ring. Working through the mechanism, we can see what is happening. After the initial oxidative addition step, the first alkene insertion occurs to form the new 6-membered ring. Normally, we would next perform a beta hydrogen elimination reaction to generate the product. However, this molecule has a quaternary carbon at the beta position, so beta hydrogen elimination is impossible. When that happens, the molecule undergoes another alkene insertion to form a second new ring. In this case, a new five membered ring. We again look to find a cis beta hydrogen. That is now possible when the Pd is on carbon #11 and the final product is formed.



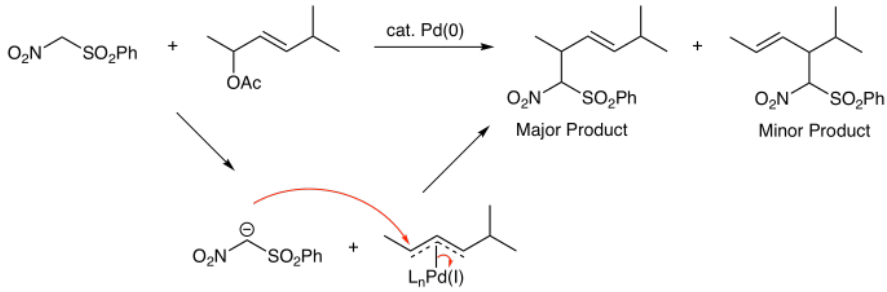
Tsuji-Trost Reaction

The Tsuji-Trost reaction is a highly useful transformation that enables formation of C-O, C-N, and C-C bonds. The key reaction components are an alkene with an allylic leaving group (halide, acetate, or epoxide) and a nucleophile which is an alcohol, an amine, or a carbon with an acidic proton (think 1,3-dicarbonyl). An example with a mechanism is shown below. Reaction of allyl acetate with the 1,3-diketone nucleophile and a palladium catalyst yields the product with a new C-C bond to the allyl group. In the mechanism, which is unlike Pd catalyzed reactions we have already seen, the first step is alkene association. Next, Pd substitutes for the leaving group, generating a pi-allyl Pd complex. The acetate leaving group is now free to act as a base, deprotonating the acidic proton on the nucleophile. The resulting stabilized enolate adds to one of the terminal carbons on the pi-allyl complex, forming the new C-C bond. The final step is alkene dissociation that yields the product and regenerates the catalyst.

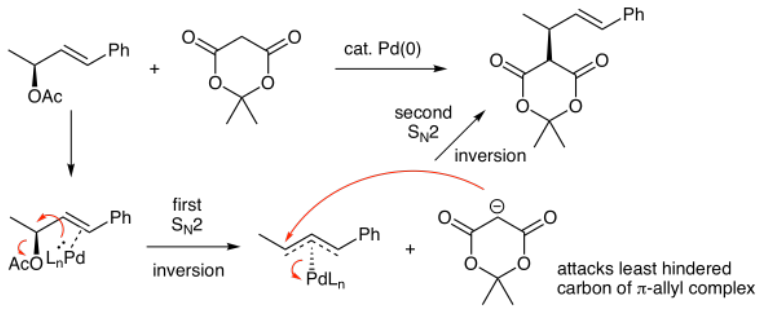


There are several important details to consider for the Tsuji-Trost reaction. First, it can happen inter- or intramolecularly, and we will see examples of each in the problems below. We also must consider regiochemistry and stereochemistry, depending on the structure of the reactants. One example below demonstrates that regioselectivity is governed by sterics, with the nucleophile adding to the less substituted side of the pi-allyl Pd complex. The other example below shows that the reaction is stereospecific, with substitution occurring with retention. As we saw previously in intro orgo, the only way for this to happen is for the mechanism to include two S_N2 reactions. (Remember, S_N1 reactions always yield racemization, equal amounts of retention and inversion.) The two S_N2 reactions are when the Pd displaces the leaving group and when the nucleophile adds to the pi-allyl complex.

Tsuji-Trost Regioselectivity - nucleophile adds to less hindered side of Pd π-allyl complex

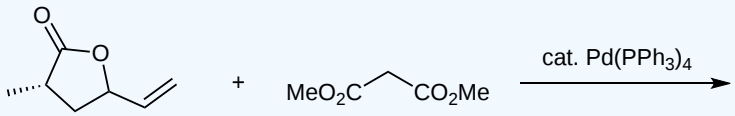


Tsuji-Trost Stereoselectivity - retention resulting from two S_N2 reactions



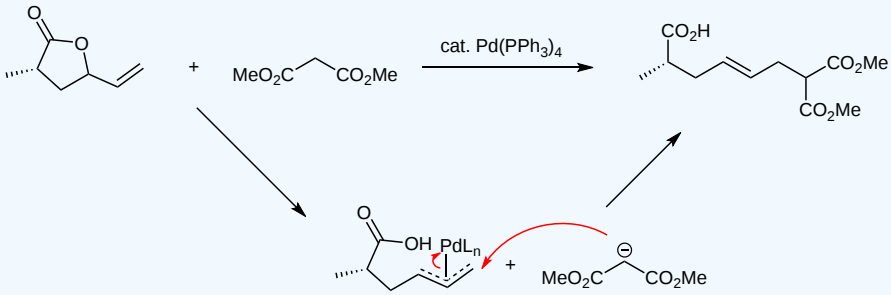
Exercise 2.2.8

Predict the product of this intermolecular Tsuji-Trost reaction.



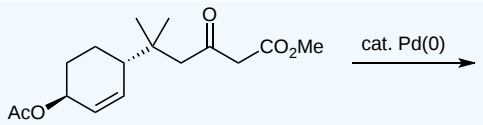
Answer

The pi-allyl Pd complex is formed by breaking open the lactone. Next, the deprotonated diester adds to the least hindered side to yield the product.



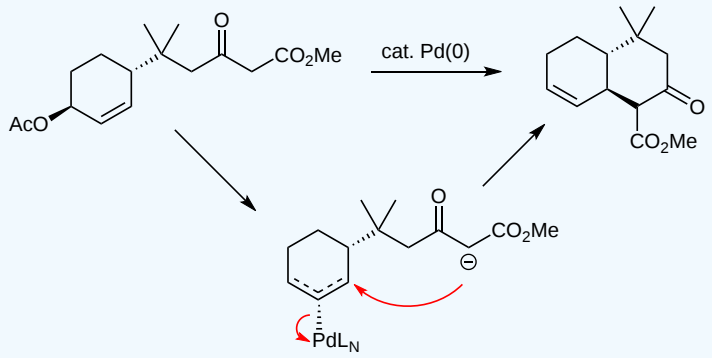
Exercise 2.2.9

Predict the product of this intramolecular Tsuji-Trost reaction.



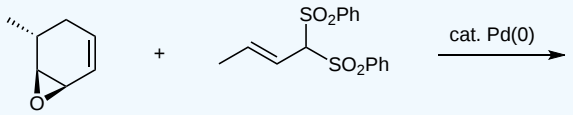
Answer

The Pd adds from the back to yield the pi-allyl complex. The enolate nucleophile adds from the front to form the new 6-membered ring.



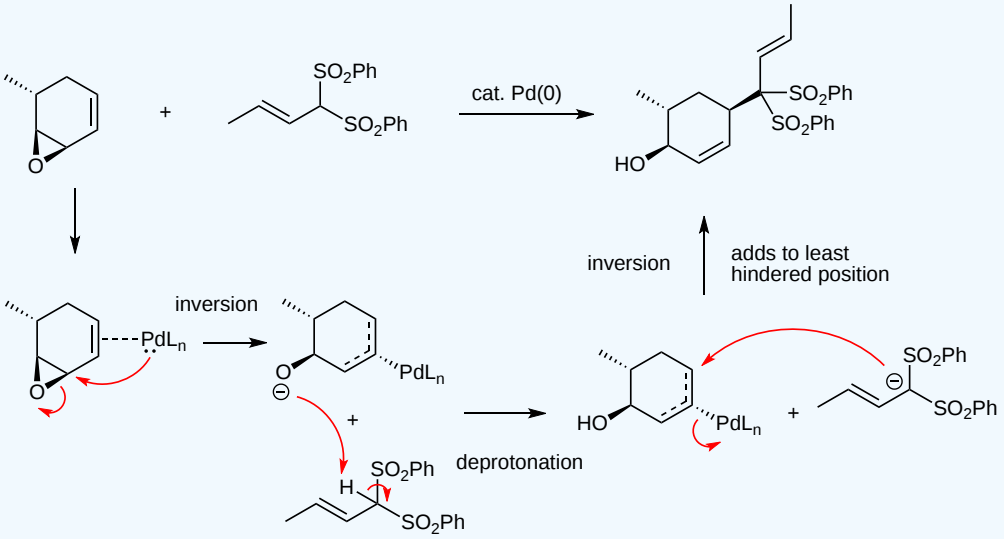
Exercise 2.2.10

Predict the product of this reaction and provide a mechanism to explain its formation.



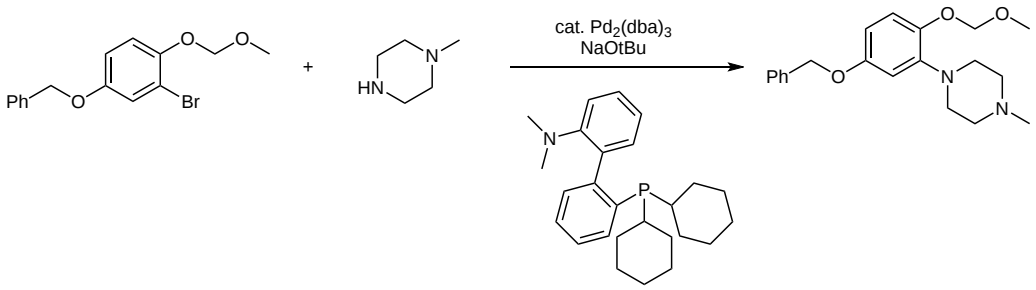
Answer

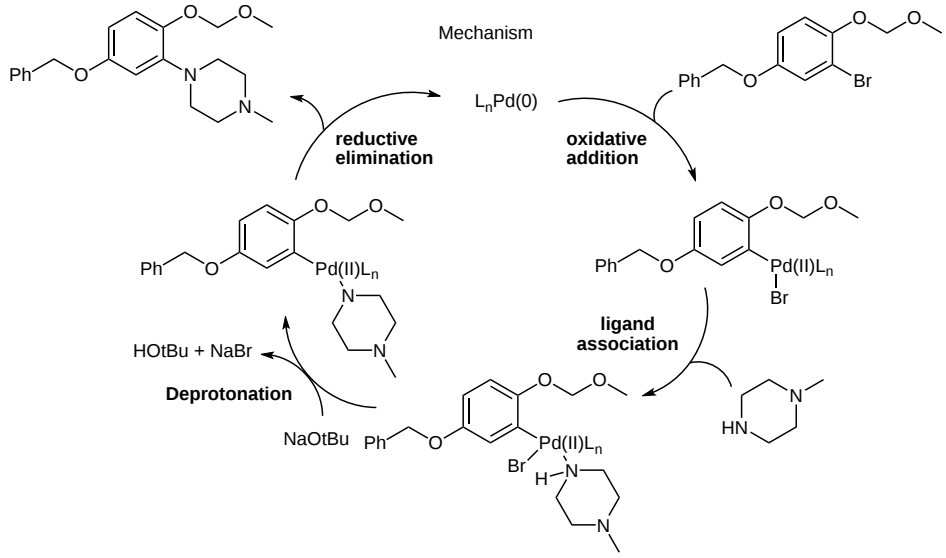
This is an example of an allylic epoxide participating in the Tsuji-Trost reaction. The Pd pi-allyl complex forms by inversion. A deprotonation step generates the carbanion nucleophile that adds with inversion to the least hindered side of the pi-allyl complex.



Buchwald-Hartwig Amination

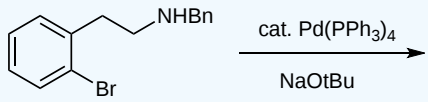
The Buchwald-Hartwig amination was developed by Steve Buchwald (MIT) and John Hartwig (Berkeley) in the late 1990s. It has evolved into one of the most popular methods for the construction of aryl amines which are common functional groups in pharmaceutical compounds and natural products. The reaction combines an aryl halide, a primary or secondary amine, and a base in the presence of a palladium catalyst. As shown in the example below, specialized phosphine ligands pioneered by the Buchwald lab are often critical to the success of these reactions. The mechanism is similar to what we saw for the Stille, Suzuki, and Sonogashira reactions in that it starts with an oxidative addition and ends with a reductive elimination. The middle steps are different and involve the amine associating with Pd before the base deprotonates the amine proton resulting in the loss of halogen from the Pd.





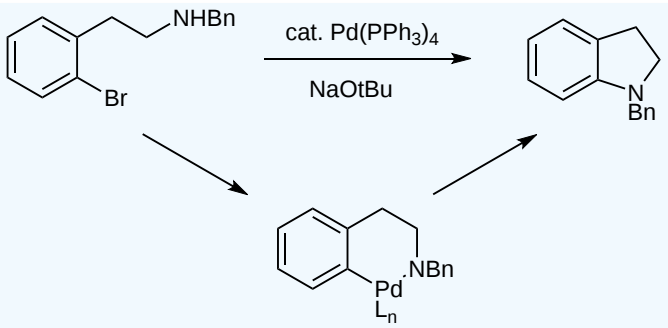
Exercise 2.2.11

Propose a product for this intramolecular Buchwald-Hartwig amination.



Answer

This is an excellent strategy to form a new heterocyclic ring. In this case, it's a five membered ring that is part of the bicyclic dihydroindole system.

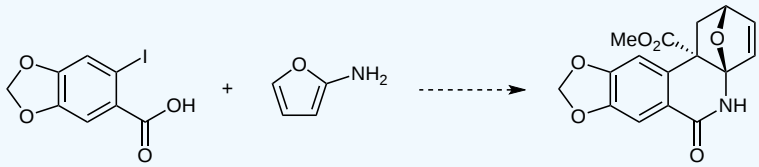


Summary Problems

Use what we have learned about Pd catalyzed reactions to solve these summary problems. You will also need to incorporate reactions from intro orgo and the pericyclic reactions chapter to complete some of the problems.

? Exercise 2.2.12

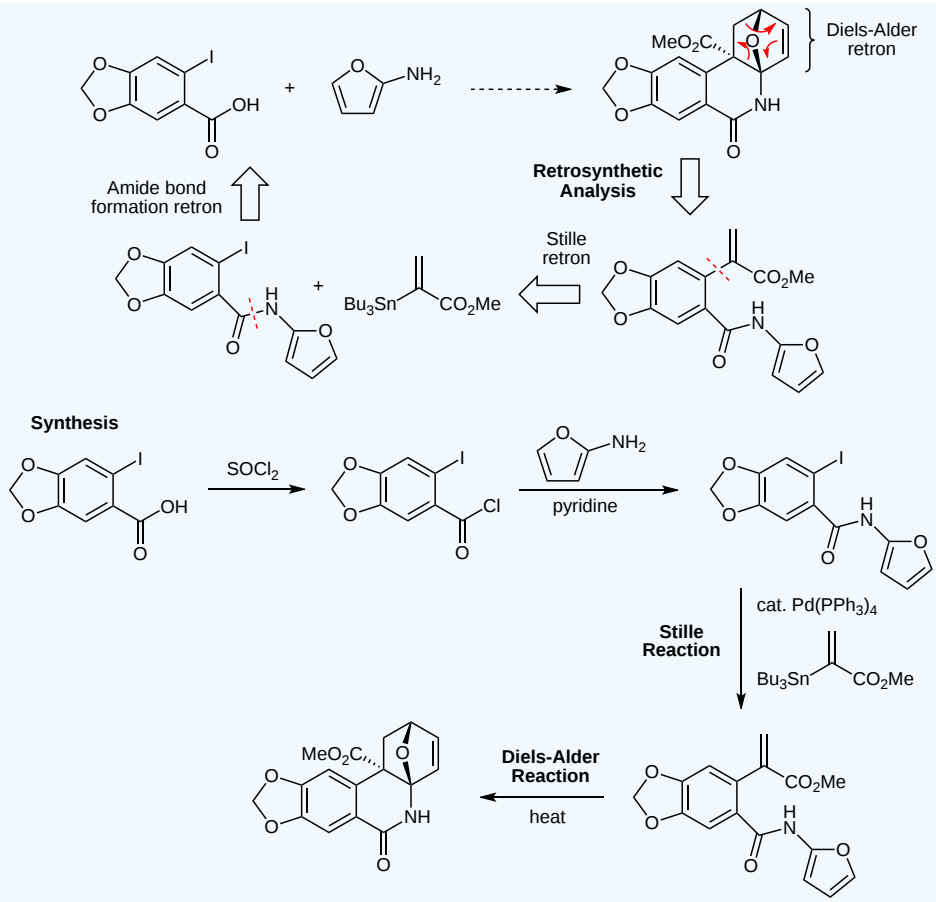
Complete the following synthesis using the indicated starting materials and any other compounds you would like. Hint: Start by finding the retron in the target and going backwards at least one step.



Answer

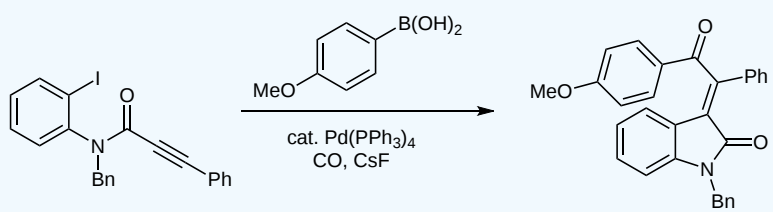
The key is to start by identifying the cyclohexene Diels-Alder retron in the target. This simplifies the molecule and reveals a Stille retron, the single bond between the alkene and benzene ring. The final disconnection is the amide bond formation. In the forward direction, the carboxylic acid is activated as an acid chloride before adding the starting primary amine and pyridine. The next step is a Pd catalyzed Stille reaction between the aryl iodide and vinyl tin compound. The resulting molecule incorporates an electron poor dienophile and a reactive diene (the furan). Heat promotes the Diels-Alder reaction and delivers the target molecule.

Reference - Organic Letters 2006



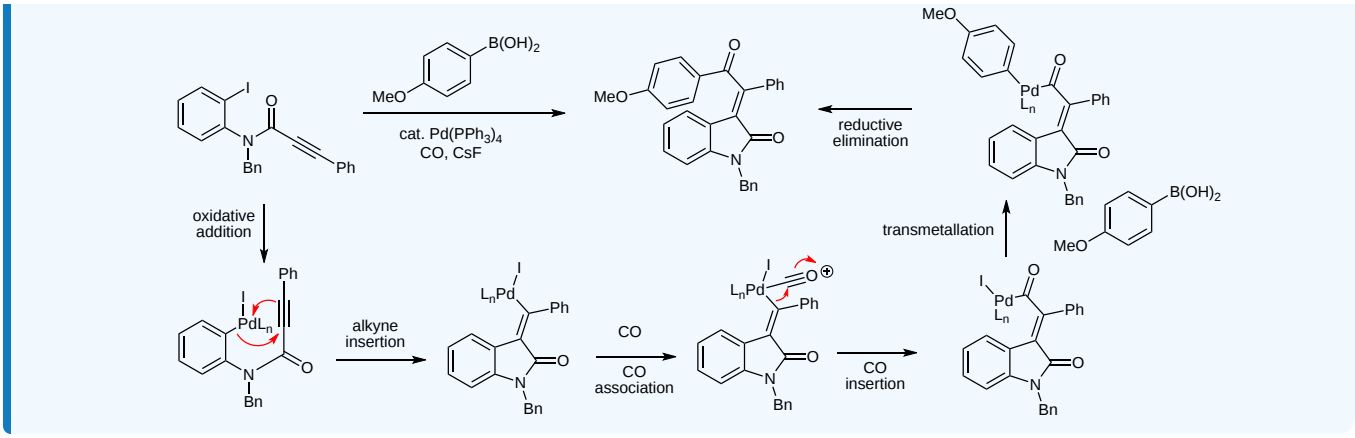
Exercise 2.2.13

Propose a mechanism for the following transformation.



Answer

This mechanism combines steps from the Heck reaction, Suzuki reaction, and a carbonylation. The mechanism begins with an oxidative addition followed by an alkyne insertion (Heck reaction). There is no hydrogen on the beta carbon, so the reaction continues with CO association and insertion steps (carbonylation). At this point, transmetallation between Pd and B occurs followed by reductive elimination (Suzuki reaction) to yield the product. Predicting this as the product of the reaction would be difficult based on what we know. However, given the structure of the product, we do have the skills to propose a mechanism.



Contributors

- Prof. Kevin Shea (Smith College)

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2.3: Olefin Metathesis

Objectives

After completing this section, you should be able to:

1. Identify ring closing and cross metathesis reactions
2. Draw and understand reaction mechanisms
3. Use reactions in synthesis problems

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Schrock catalyst
- Grubbs 1st generation catalyst
- Grubbs 2nd generation catalyst
- Ring closing metathesis
- Olefin (alkene) metathesis
- Alkyne metathesis
- Cross metathesis

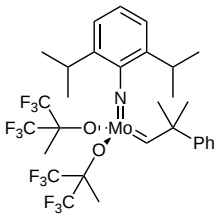
Study Notes

Olefin metathesis reactions enable formation of new carbon-carbon bonds between two starting alkenes while generating ethylene as a byproduct. (This results in the loss of two carbons from the starting material(s) to form ethylene.) Alkyne metathesis, generating acetylene as a byproduct, is also possible but is much less common. The most powerful metathesis reaction is the intramolecular version known as Ring Closing Metathesis (RCM). The intermolecular variation is also useful and is known as Cross Metathesis (CM). Thanks mainly to the work of Robert Grubbs (Caltech) and Richard Schrock (MIT) in the 1990s, these reactions have become popular tools for synthetic organic chemists. For their key research on these reactions, Grubbs and Schrock, along with Yves Chauvin, were awarded the 2005 Nobel Prize in Chemistry. RCM provides you with another highly useful method for the synthesis of rings. This reaction is especially valuable as a method for the synthesis of large rings which are often challenging to synthesize. For the purposes of retrosynthetic analysis using RCM, we look for ring sizes of 5 or larger containing an alkene. So, the cyclohexene Diels-Alder retron is also a ring closing metathesis retron.

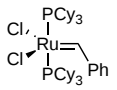
Content

This chapter will focus on learning and applying olefin metathesis reactions for the synthesis of rings. We will meet the most common reaction catalysts, learn the reaction mechanism, and see several examples. We will also see brief examples of alkyne metathesis and cross metathesis.

Olefin metathesis catalysts (shown below) are examples of metal-carbene complexes where the reactive metal (either Ru or Mo) contains a double bond to the carbon ligand that participates in the reaction. Furthermore, these highly reactive catalysts are actually examples of what chemists call precatalysts. The compound introduced into the reaction undergoes one round of the catalytic cycle before forming the molecule that catalyzes all further reactions. The precatalysts are less reactive than the actual catalysts, enabling chemists to handle them more easily outside of the reaction flask. Most of the original research in the Grubbs and Schrock labs was conducted in glove boxes under inert atmosphere conditions since early catalysts were highly sensitive to air and moisture. The popularity of the Grubbs catalysts is their combination of stability outside the glove box, reactivity, and functional group compatibility (only reacting with alkenes and not other functional groups).

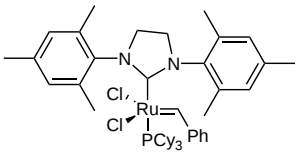


Schrock catalyst



Cy = cyclohexyl

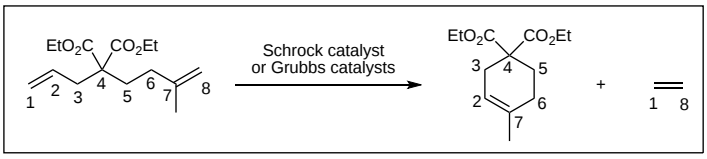
Grubbs 1st generation catalyst



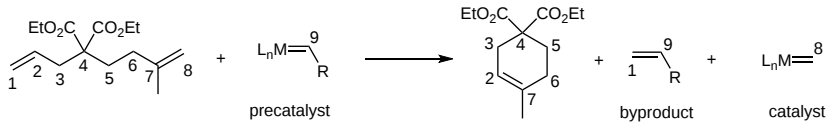
Cy = cyclohexyl

Grubbs 2nd generation catalyst

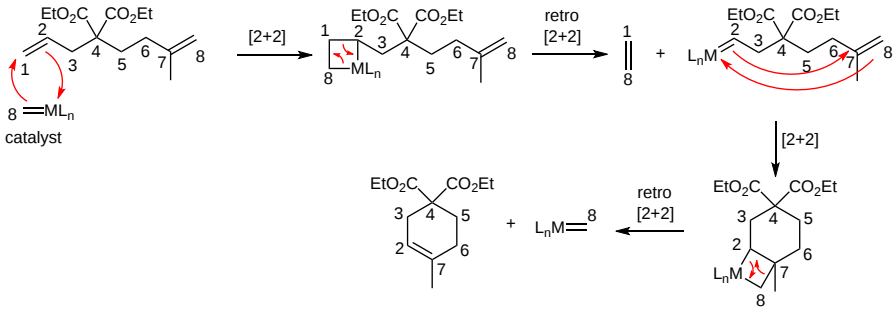
An example ring closing metathesis (RCM) reaction is shown below along with the mechanism. In this case, we are forming a six membered ring. As mentioned above, RCM reactions generate ethylene as a byproduct, meaning that the starting diene has two more carbons than the cyclic product. Don't forget this key point when planning syntheses using RCM. The initial steps of the reaction convert the precatalyst (the molecules shown above) into the actual catalyst for the reaction. Active metathesis catalysts have CH_2 attached to the metal with the structure $L_nM{=}CH_2$. So, initially the alkene byproduct containing the R group present in the precatalyst is formed along with the active catalyst and the desired product. We can now draw out the reaction mechanism with the correct catalyst. (For all future problems, we will ignore the precatalyst reaction and draw mechanisms beginning with what we know is the active catalyst, $L_nM{=}$.) The RCM mechanism is a series of [2+2] and retro [2+2] cycloaddition reactions. Transition metals can react using d orbitals making thermal [2+2] reactions allowed mechanistic steps (unlike what we learned in the cycloadditions chapter about main group [2+2] reactions). A critical point about the first step is the regiochemistry of how the catalyst reacts with the substrate. For the reaction to be productive and lead to ring formation, the metal must react at the more hindered position. This helps explain why there is a strong preference for the catalyst to react with the least hindered alkene first, in this case the monosubstituted C1-C2 alkene. This first step yields a metallocyclobutane that breaks apart by a retro [2+2] cycloaddition to generate the ethylene byproduct and a new metal carbene with the catalyst covalently bonded to our substrate. Ring formation occurs in the next step, our second [2+2] cycloaddition. The final cycloreversion regenerates the catalyst and installs the alkene in our six-membered ring product.



Formation of Active Catalyst - Precatalyst Reaction

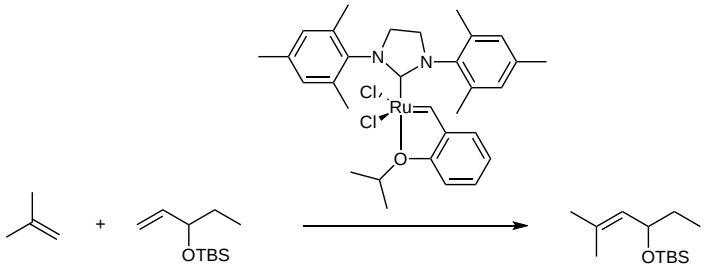


Mechanism

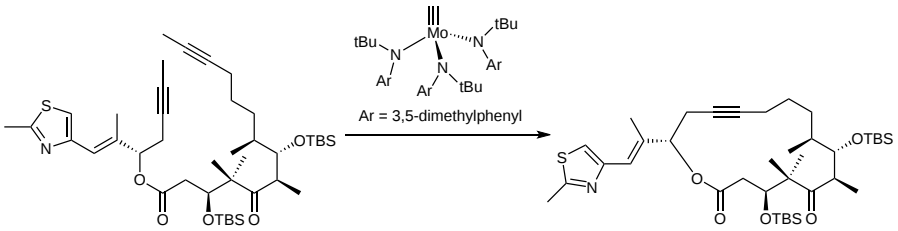


Cross metathesis reactions enable formation of a substituted alkene in an intermolecular reaction with a second alkene. There are significant selectivity challenges to avoid producing large product mixtures, including E/Z product isomers. One example of a relatively straightforward application of cross metathesis is shown below. Producing a new alkene with symmetrical substitution on one side obviates the potential alkene isomer problem. So, starting with isobutylene and a monosubstituted alkene leads to

generation of a trisubstituted alkene product. (As we saw previously with RCM, ethylene is generated as a reaction byproduct.) Note that we have a slightly different catalyst that was developed to promote cross metathesis. This modification of the Grubbs second generation catalyst is know as the Hoveyda-Grubbs catalyst.

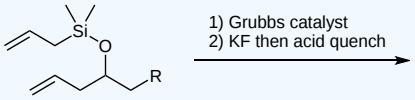


Alkyne metathesis is a useful variant of standard olefin metathesis. Tungsten and molybdenum catalysts have been developed that enable efficient ring closing alkyne metathesis. Not surprisingly, this strategy is only useful for the synthesis of large rings which are able to handle the significant ring strain introduced by a cyclic alkyne. A leader in this field is Alois Fürstner who published the following transformation as part of a total synthesis of epothilone C.



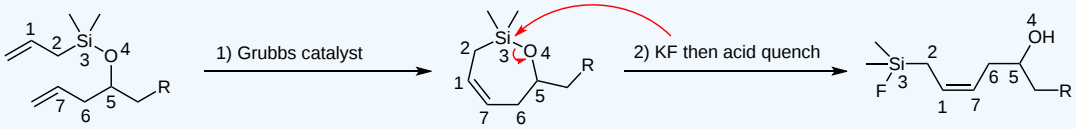
Exercise 2.3.1

Propose a product for the following reaction sequence.



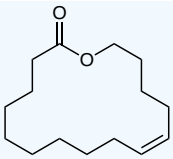
Answer

The first step is a standard ring closing metathesis reaction to form a seven-membered ring. This step highlights that heterocyclic rings can be easily made using olefin metathesis. The second step is less straightforward but should make you think about silyl ether deprotection with fluoride to yield alcohols. In this case, since the silyl group is part of the ring, it opens the ring to yield an acyclic allyl silane. This highlights the possibility of using RCM to selectively synthesize acyclic cis alkenes. You should also note that the allyl silane in the product can be oxidized to an allylic alcohol by treatment with hydrogen peroxide.



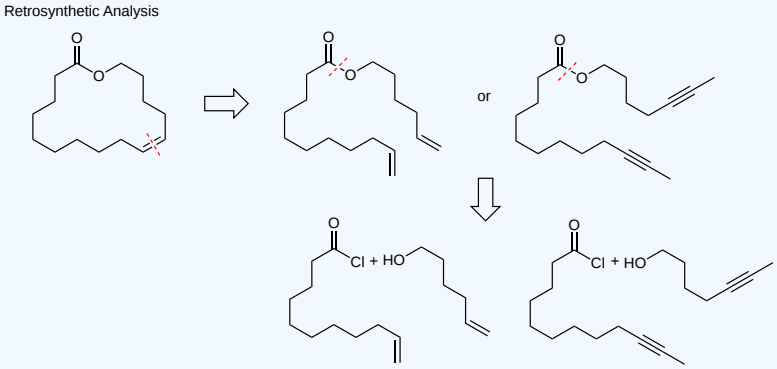
Exercise 2.3.2

Starting with compounds containing 12 carbons or fewer, propose two different syntheses of the target compound. Your answers should both incorporate ring closing metathesis, but you should use two different versions of RCM.



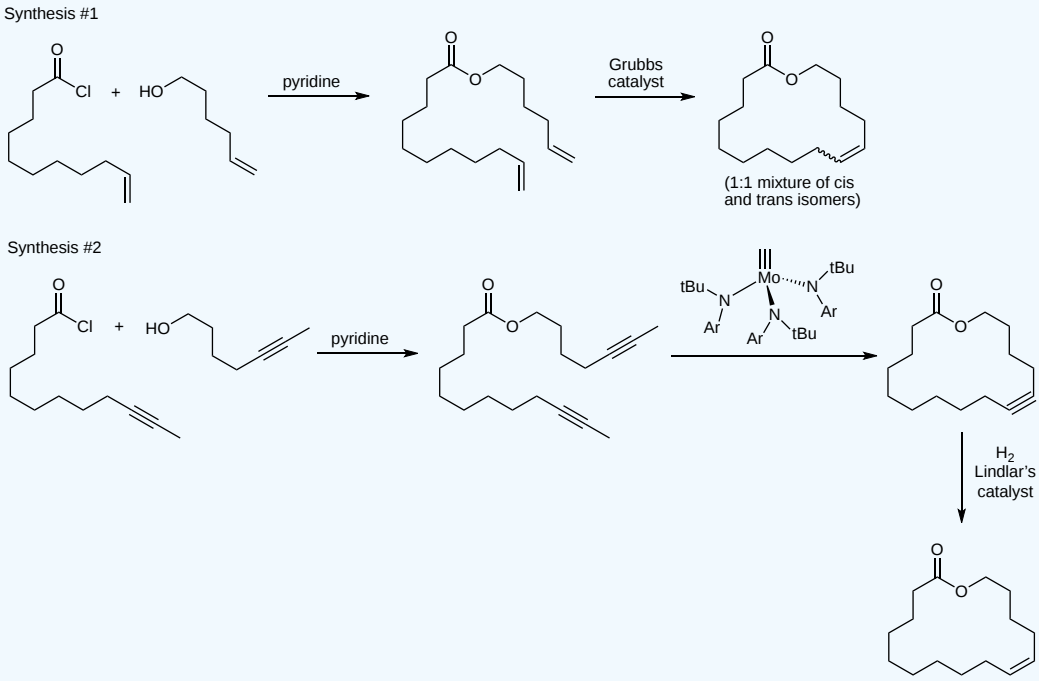
Answer

This problem provides an opportunity to use both alkene and alkyne metathesis. Thinking retrosynthetically, the first disconnection is to break open the ring. Don't forget to add the extra carbons necessary for the alkene and alkyne metathesis reactions. Next, you should break the ester bond to yield an acid chloride and an alcohol that fit the 12 carbons or fewer limitation.



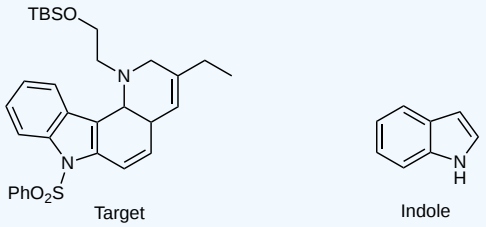
Synthesis #1 is likely the most obvious choice. Form the ester in the first step then use the Grubbs catalyst to form the 16-membered ring. One issue with this synthesis is the unfortunate limitation of alkene RCM for large rings that often generates cis/trans product mixtures. In fact, this reaction yields a 1:1 mixture of the cis and trans isomers.

Synthesis #2 enables you to address this problem while adding an extra step to your synthesis. (This is often preferred over making difficult to separate alkene isomers.) The first step generates the diyne ester that is cyclized using alkyne RCM in the second step. This cyclic alkyne (stable in such a large ring) can be hydrogenated using Lindlar's catalyst to yield exclusively the desired cis alkene.



Exercise 2.3.3

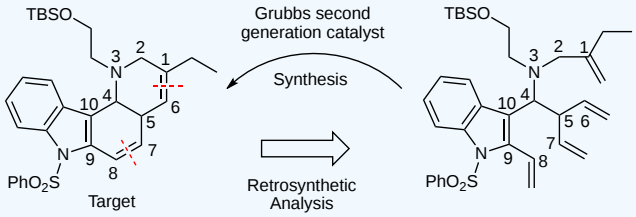
The following target is a key synthetic intermediate in a published synthesis of pseudotabersonine. Propose a one-step synthesis of this tetracycle beginning with a substituted indole as your bicyclic starting material.



Answer

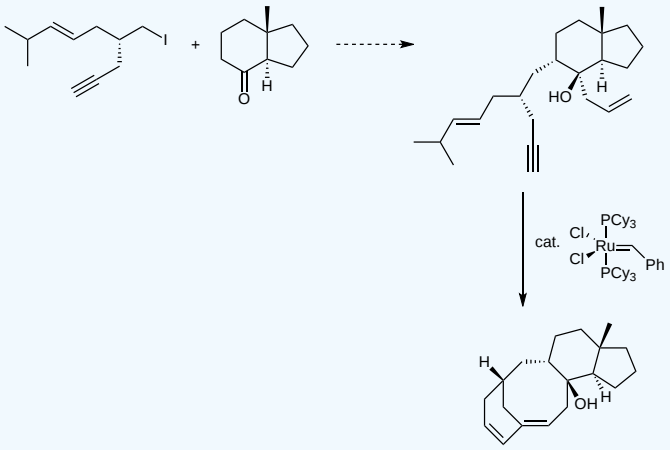
Reference: Organic Letters 2010

Since we are beginning with the two rings in the indole moiety, we must disconnect the other two rings in our retrosynthetic analysis. Both have an alkene making them retrons for alkene ring closing metathesis. As always when using RCM, be sure to add the carbons that will be lost in the forward direction. The resulting tetraene is the starting material that the Martin group reacted with the Grubbs catalyst in their 2010 *Organic Letters* paper.



Exercise 2.3.4

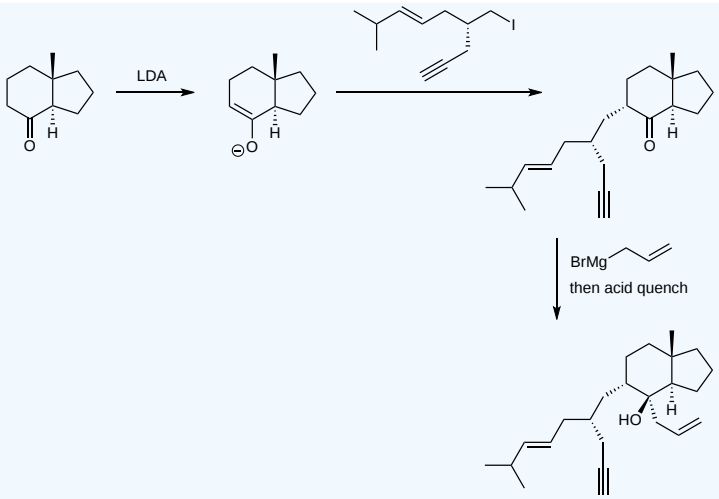
The following synthetic sequence outlines a strategy that can be applied to the synthesis of taxol-like molecules. First, propose a synthesis of the key ring-closing metathesis precursor. Second, propose a mechanism for the ring-closing metathesis reaction.



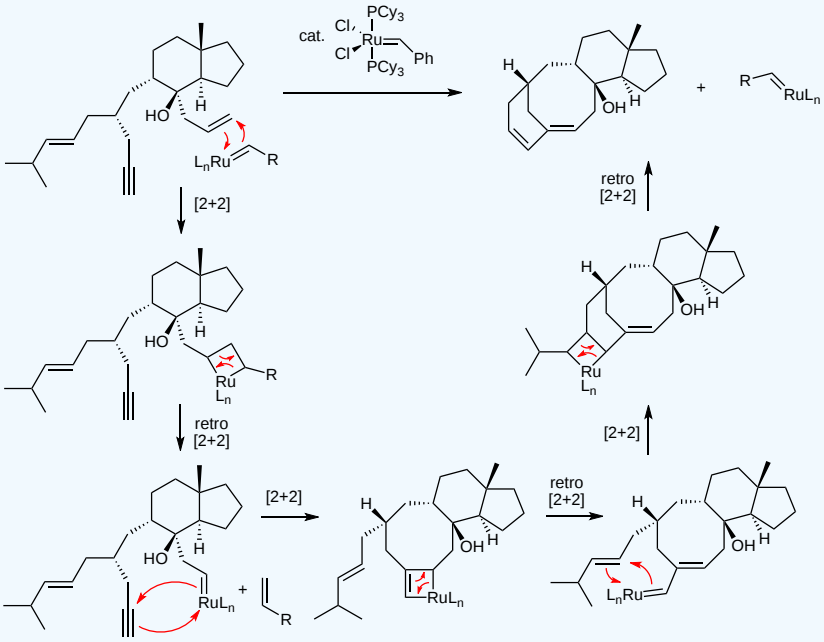
Answer

Reference: Organic Letters 2004

The synthesis part of the question involves reactions from intro orgo. The first step is an enolate alkylation between the two starting materials. The final step is a Grignard addition to the ketone.



This is an interesting substrate for olefin metathesis. It contains two alkenes and an alkyne which all have to react to form the target molecule. The most reactive functional group is the terminal alkene which is where the mechanism begins. We do our standard [2+2] and retro [2+2] reactions to generate the ruthenium intermediate that can react with the alkyne to form the 8-membered ring. This [2+2] reaction yields a metallocyclobutene (not butane) that opens to yield the desired cyclooctene with the ruthenium still in the molecule. This molecule can complete the mechanism with another round of [2+2] and retro [2+2] reactions. Please note this is an example of a RCM reaction that does not use L_nRu= as the catalyst. Because of the structure of alkene in the final [2+2] reaction, the catalyst contains an isopropyl group. This was the result of reaction optimization when synthesizing the target molecule in the Granja lab.



Contributors

- Prof. Kevin Shea (Smith College)

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2.4: Co-Mediated Ring Forming Reactions

Objectives

After completing this section, you should be able to:

1. Identify Pauson-Khand and alkyne cyclotrimerization reactions
2. Draw and understand reaction mechanisms
3. Use these reactions in synthesis problems

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Pauson-Khand reaction
- Alkyne cyclotrimerization reaction

Study Notes

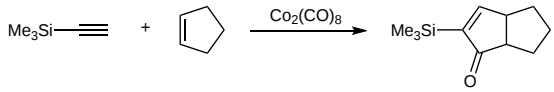
In this chapter, we will learn about two reactions that are commonly promoted by cobalt complexes, the Pauson-Khand reaction for the formation of cyclopentenones and alkyne cyclotrimerization for the synthesis of substituted benzene rings. These transformations are not as common as the Pd-catalyzed bond forming reactions or olefin metathesis reactions that we studied previously. However, they provide novel and powerful strategies for the synthesis of common and important ring structures. When they do appear in organic synthesis applications, they are often intramolecular reactions that quickly build up molecular complexity.

Content

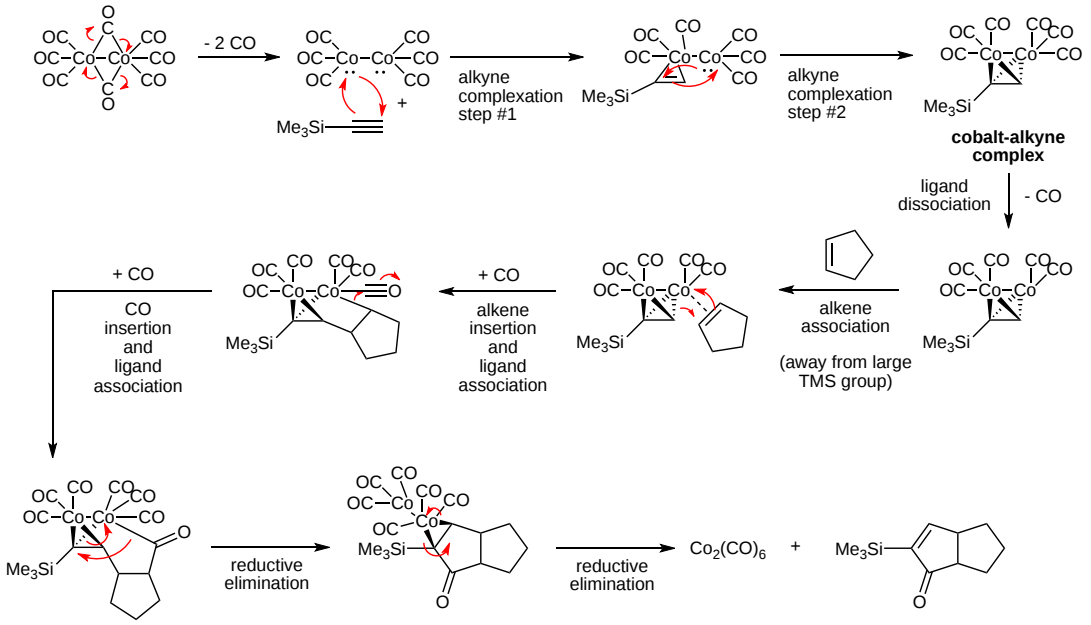
This chapter will focus on ring forming reactions commonly promoted by cobalt. Other metal catalysts or promoters can mediate the Pauson-Khand reaction and alkyne cyclotrimerization reactions. An understanding of the cobalt-mediated reactions will help when you encounter reactions promoted by other metals. Also, unlike the previous transition metal reactions that we have studied, the Pauson-Khand reaction is generally stoichiometric, not catalytic, in cobalt. So, if you end up running this reaction in the lab, pay very careful attention to the equivalents of the cobalt reagent needed to promote the reaction.

Pauson-Khand Reaction

The Pauson-Khand reaction involves combination of an alkene, an alkyne, and carbon monoxide to generate a cyclopentenone. This can happen inter- or intramolecularly, though the intramolecular version is much more popular in synthesis applications. An example of an intermolecular Pauson-Khand reaction is shown below along with its mechanism. In the reaction, trimethylsilylacetylene combines with cyclopentene and carbon monoxide (from dicobalt octacarbonyl) to form a new cyclopentenone ring. The Pauson-Khand retron is a cyclopentenone which is the same retron as the Nazarov reaction (from the electrocyclic reactions section). The first several steps in the mechanism involve reaction of dicobaltoctacarbonyl with the alkyne to form a cobalt-alkyne complex. (The mechanism below is drawn as a 2-electron process. It is also possible to draw this as a radical mechanism. It is unclear which is the actual process.) This is a very unusual structure, with each cobalt bound to both carbons of the initial alkyne. As an aside, cobalt-alkyne complexes can be used as alkyne protecting groups (removed by oxidative decomplexation with a variety of mild oxidants), and they are generally stable. These bright red molecules are stable to TLC and column chromatography. Back to the mechanism, loss of one of the CO ligands leads to alkene association at an open coordination sight with the alkene on the cobalt farthest from the large trimethylsilyl group. The next step is an alkene insertion, like we saw previously in the Pd-catalyzed Heck reaction, to generate new C-C and C-Co bonds. This is accompanied by CO association to keep the Co fully coordinated by ligands. The following step, a CO insertion, is analogous to what we saw previously in Pd-catalyzed carbonylation reactions. One of the CO ligands inserts into the C-Co bond to make another new C-C bond. The mechanism concludes with two reductive eliminations steps to form the final C-C bond in the new 5-membered ring followed by generation of the 5-membered ring alkene. The final reductive elimination step removes cobalt from the molecule thus converting the organometallic complex into the organic product.

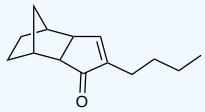


Mechanism



Exercise 2.4.1

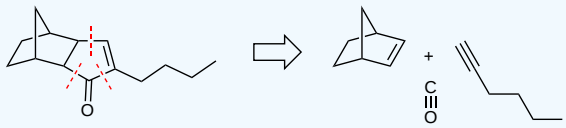
How would you construct the target molecule in one step using a Pauson-Khand reaction?



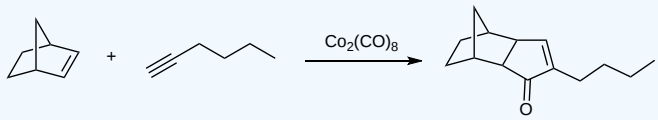
Answer

This molecule contains a cyclopentenone, the Pauson-Khand retron. Thinking retrosynthetically, we can disconnect the molecule as shown below. Both bonds on either side of the carbonyl are disconnected along with the bond on the other side of the alkene. This reveals the starting materails: a bicyclic alkene, a linear alkyne, and carbon monoxide (from dicobalt octacarbonyl). In the forward direction, the alkene and alkyne are combined in the presence of $Co_2(CO)_8$ to yield the target.

Retrosynthetic Analysis

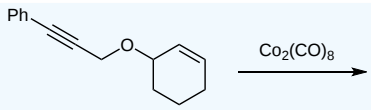


Synthesis



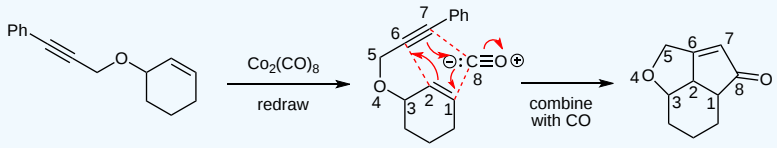
Exercise 2.4.2

Predict the product of the following reaction.



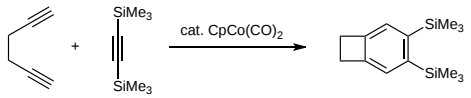
Answer

Since the alkene and alkyne are both in the starting material, this is an intramolecular Pauson-Khand reaction. It's easier to see how the alkene and alkyne will combine if we redraw the molecule with those two functional groups close to each other. It's also possible to draw a shorthand mechanism by including the CO molecule next to the reactant. (To be clear, this is not the mechanism. The actual mechanism for the Pauson-Khand reaction is shown above. This is a shortcut that enables you to illustrate what happens and quickly generate the product structure.) This allows us to number the atoms, draw curved arrows to keep track of electrons (again, not the actual mechanism), and then draw the product. This shows that while forming the key cyclopentenone, we end up with a tricyclic product.

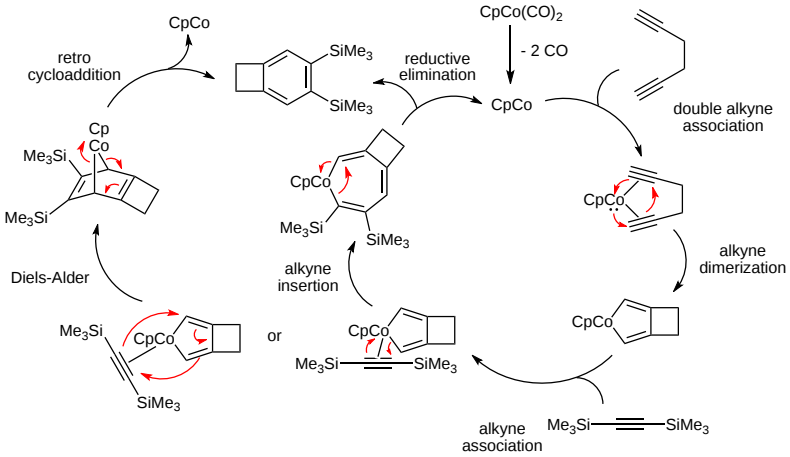


Co-Catalyzed Cyclotrimerization

This fascinating reaction enables the combination of three alkynes in the presence of cobalt to yield a substituted benzene product. The scope of the reaction is limited due to challenges controlling regiochemistry which often necessitates the use of symmetrically disubstituted alkynes. As shown below, the most useful reactions involve the combination of a diyne with a symmetrically disubstituted alkyne like bis(trimethylsilyl)acetylene. An example reaction and the reaction mechanism are shown below. The reaction shows production of a cyclobutane fused benzene which we have seen previously is very useful in a 4 pi electrocyclic ring opening reaction to generate a highly reactive Diels-Alder diene. The mechanism begins with loss of two CO ligands on the cobalt to yield the active catalyst, CpCo. Don't forget that we previously met Cp, the cyclopentadienyl ligand, in the Introduction to Transition Metals chapter. Double alkyne association with the diyne followed by alkyne dimerization yields a cobaltacyclopentadiene intermediate. The next step is alkyne association by bis(trimethylsilyl)acetylene. At this point, there are two mechanistic pathways that can complete the catalytic cycle. One option is alkyne insertion to yield a seven-membered ring intermediate followed by reductive elimination to yield the product. The other option is a Diels-Alder reaction to yield a Co-bridged intermediate that is followed by a retro cycloaddition to regenerate the catalyst and produce the final product. The exact mechanism will depend on the nature of the substrate, but we will not worry about this level of detail.

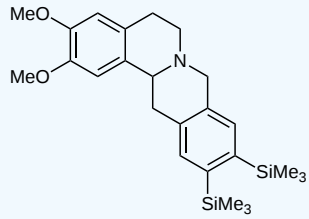


Mechanism



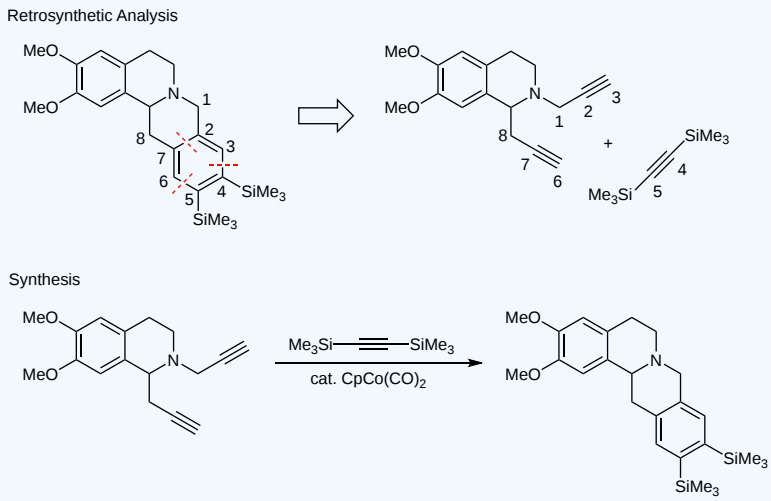
Exercise 2.4.3

Propose a one step synthesis of the target molecule using a cobalt catalyzed cyclotrimerization reaction.



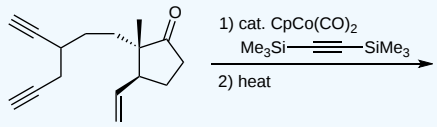
Answer

When doing retrosynthetic analysis, look for the disilyl substituted benzene ring. This shows the two benzene carbons that originated as bis(trimethylsilyl)acetylene. Knowing that, you can disconnect at every other bond to yield the starting alkynes. Similar to our example above, we start with a diyne which combines with the bis(silyl)acetylene and the cobalt catalyst to yield the target.



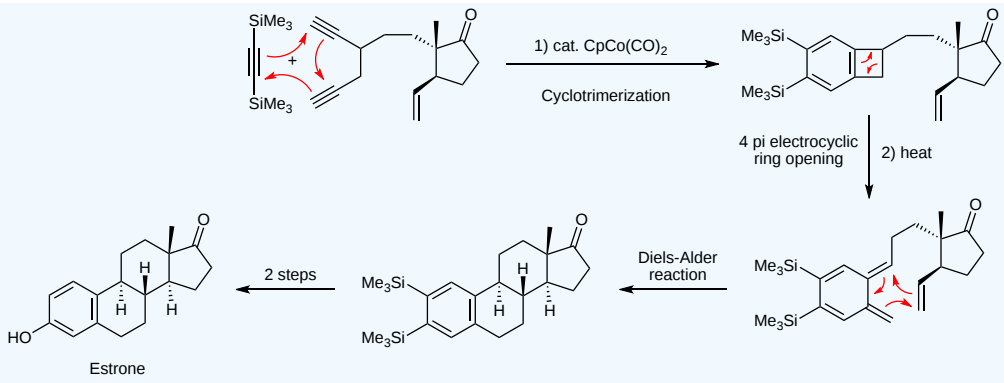
Exercise 2.4.4

Predict the product of the following reaction sequence that was used in a total synthesis of estrone.



Answer

This reaction sequence involves the key steps in Johnson's synthesis of estrone. It begins with a cyclotrimerization to make the cyclobutane-fused benzene. (Note: This is an oversimplified mechanism. The curved arrows do not illustrate the actual mechanism (see above for that). They just help demonstrate the structure of the product.) This undergoes an electrocyclic ring opening reaction to yield a highly reactive diene that participates in a Diels-Alder reaction to yield the complete tetracyclic steroid core. The estrone synthesis was completed in 2 more steps that we won't worry about.



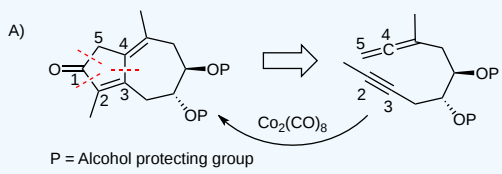
Summary Problems

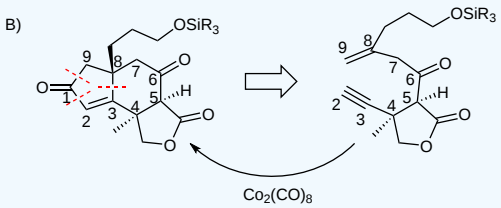
Exercise 2.4.5

Propose one-step syntheses of the following two targets using a cobalt catalyzed or mediated reaction.

Answer

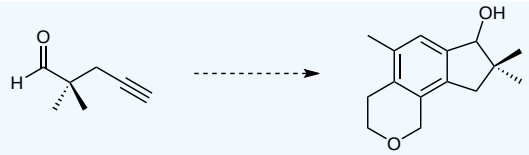
Both of these targets contain cyclopentenones, so we know they can be made using the Pauson-Khand reaction. The answers demonstrate a shorthand target disconnection that leads backwards to the starting enyne. Note that like in all Pauson-Khand reactions, the carbonyl carbon (carbon #1) does not appear in the starting material because it originates as one of the CO ligands on cobalt. Problem A shows that allenes can react successfully in Pauson-Khand reactions (literature reference Journal of Organic Chemistry 2008).





Exercise 2.4.6

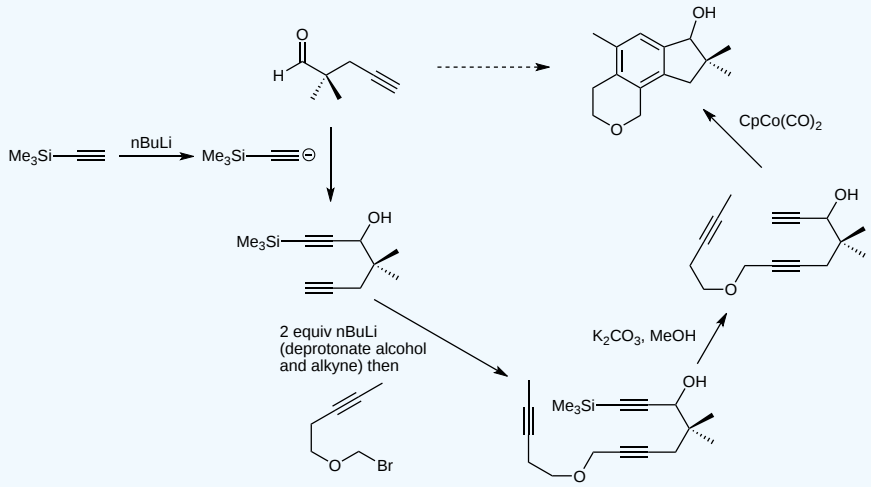
Beginning with the indicated starting material and any other compounds, complete a synthesis of the target (alcyopterosin).



Answer

The keys here are the alkyne in the starting material and the benzene ring in the product. This indicates we will be using a cyclotrimerization reaction as the key step. Using the dimethyl carbon as the anchor, it's possible figure out the pieces that must be added to the starting material. The second alkyne is added as an acetylide anion in the first step. In the second step, a different acetylide anion adds via a substitution reaction to yield the necessary triyne. After an alkyne deprotection step, the final step is the cyclotrimerization reaction to yield the target.

Reference: Organic Letters 2010



Contributors

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CHAPTER OVERVIEW

3: Neighboring Group Participation, Rearrangements, and Fragmentations

3.1: Introduction to Neighboring Group Participation, Rearrangements, and Fragmentations
3.2: Neighboring Group Participation
3.3: Rearrangements
3.4: Fragmentations

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3.1: Introduction to Neighboring Group Participation, Rearrangements, and Fragmentations

Objectives

After completing this section, you should be able to:

1. Understand the general reaction types classified as neighboring group participation, rearrangements, and fragmentations
2. Spot structural fragments that favor neighboring group participation, rearrangements, and fragmentations

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Neighboring group participation
- Rearrangement
- Fragmentation

Study Notes

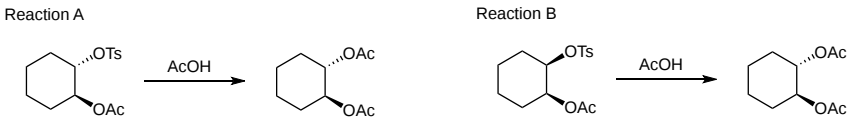
In Intro Orgo, you learned about common substitution and elimination reactions of alkyl halides (and halide equivalents like tosylates) and classified them as S_N1, S_N2, E1, and E2. In this section, we are going to introduce you to more interesting reactions that begin with standard R-X or R-OTs starting materials. Our goal in this introductory chapter is to provide an organizational framework that will help guide your more in depth study in the following three chapters. Don't worry about the lack of problems in this chapter, there will be plenty of problems to come when we talk about neighboring group participation, rearrangements, and fragmentations each in their own specific chapter.

Content

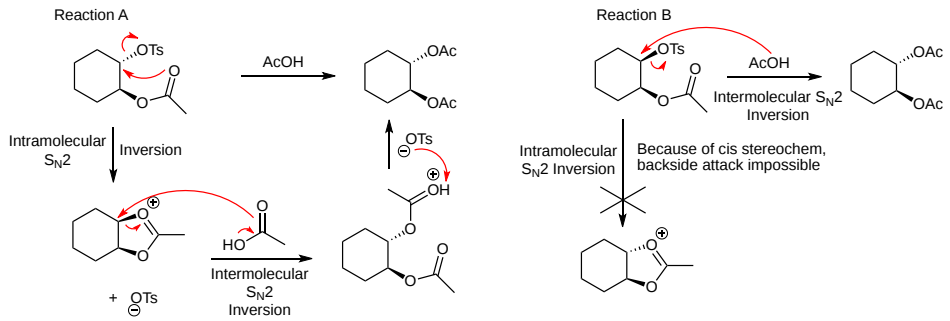
As with many topics in Intro Orgo, we only scratched the surface when introducing reactions of alkyl halides. You learned a variety of useful substitution and elimination reactions but likely haven't met reactions that involve neighboring group participation. When studying carbocations formed in S_N1 and E1 reactions, you probably learned about simple carbocation rearrangements like hydride, methyl, and alkyl shifts. However, it's unlikely that you were introduced to fascinating rearrangements like the pinacol, Favorskii, or Wolff rearrangements. Finally, fragmentation reactions, where key structural carbon-carbon bonds are cleaved to generate a new carbon skeleton, were probably not mentioned. Let's spend this chapter briefly introducing each of these reactions before studying them in depth in the following chapters.

Neighboring Group Participation (NGP)

As the name implies, this class of reactions relies on the influence of a neighboring group to explain what at first seem like incomprehensible reactions. These are generally substitution reactions that have unexpected outcomes. Their mechanisms become clear, however, once you spot the participation of an intramolecular nucleophile on the reaction outcome. Don't forget that intramolecular nucleophiles can be either a lone pair on a heteroatom or an electron rich pi bond. The following pair of reactions illustrates the importance of understanding neighboring group participation. These are substitution reactions of diastereomeric tosylates that yield the identical trans product. These look like straightforward substitution reactions where an acetate nucleophile replaces a tosylate leaving group. Reaction B fits the pattern we learned in Intro Orgo for an S_N2 reaction. The cis starting material reacts with complete inversion to yield the trans product. However, what's happening in Reaction A? This substitution reaction proceeds with complete retention, the trans starting material yields a trans product. This can't be an S_N1 reaction since we learned that will yield a racemic mixture (1:1 mixture of cis and trans products). How do we get only retention? The most straightforward way is if two consecutive S_N2 reactions occur. How is this possible? If the acetate group that starts on the molecule participates in the reaction as the neighboring group, this explains the outcome.

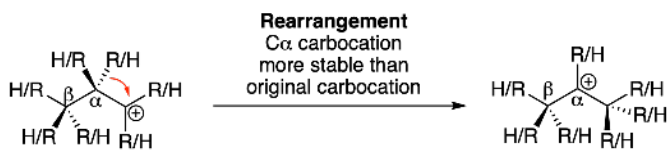


Looking at the mechanisms, we can understand the reactions. In Reaction A, the neighboring acetate group (always draw out the complete functional group structure to spot if NGP is possible) can participate in an intramolecular S_N2 reaction resulting in the first inversion. This is followed by the second S_N2 reaction which is of the intermolecular variety with acetic acid. Deprotonation yields the trans product. The mechanism demonstrates how retention is possible: an intramolecular S_N2 reaction followed by an intermolecular S_N2 reaction. In Reaction B, due to the cis stereochemistry, an intramolecular S_N2 reaction is impossible. The cis acetate can't participate in a backside attack since it is on the same face as the leaving group. So, this reaction can only undergo a standard intermolecular S_N2 reaction to yield the same trans product.

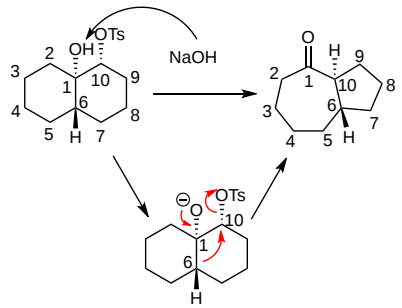


Rearrangements

You have likely already seen carbocation rearrangements in Intro Orgo. When generating a carbocation as part of an S_N1 and/or E1 reaction, you were told to "beware of rearrangement". Thus, you analyzed the structure to determine the type of carbocation generated (primary, secondary, tertiary, and/or resonance stabilized) and looked to the adjacent carbons (the alpha carbons) to see if they would be a more stable carbocation (more highly substituted or resonance stabilized). If so, a group on the adjacent carbon "shifted" to make a new bond to the carbocation. The most common rearrangement being a hydride shift, but you likely also saw alkyl shifts.

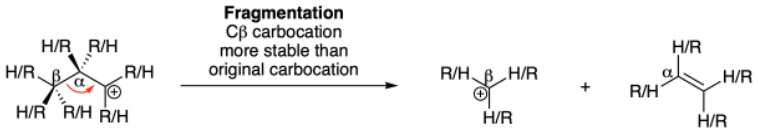


Rearrangements definitely occur from carbocation intermediates (as pictured above); however, the most synthetically useful rearrangements proceed via mechanisms that don't involve true carbocation intermediates. The lack of a carbocation helps control the selectivity of the reaction toward production of only the desired target. To identify a rearrangement that doesn't involve a carbocation, the key is to spot a leaving group next to a group that promotes rearrangement. A common example is an alcohol that can turn into a carbonyl upon rearrangement. For example, the semipinacol rearrangement shown below highlights a rearrangement promoted by the loss of a tosylate and the formation of a carbonyl. Deprotonation by sodium hydroxide generates the negatively charged intermediate that undergoes rearrangement. Formation of the new carbonyl at C1 promotes rearrangement resulting from cleavage of the C1-6 bond to form the new C6-10 bond. This rearranges the original bicyclo[6,6] system into a new bicyclo[5,7] system. We will see many more examples of cationic and anionic rearrangements in an upcoming chapter.

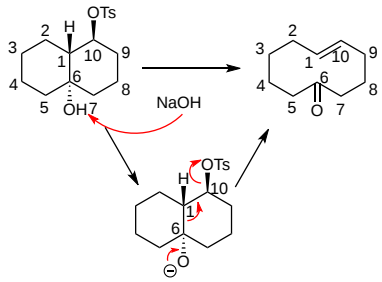


Fragmentations

Fragmentations are related to rearrangements in that the structural fundamentals vary slightly. For cationic intermediates, rearrangements occur when the alpha carbon is a more stable carbocation. Fragmentations occur with the beta carbon is a more stable carbocation. This results in cleavage of the alpha-beta C-C bond, the beta carbon becomes the new carbocation, and formation of a new alkene.



Investigating a substrate similar to our rearrangement example above, we can see that true carbocations aren't necessary for fragmentations either. We just need the fragmentation promoting group, an alcohol in this case, one more bond away from the leaving group. With the OH on C6, formation of the new carbonyl promotes cleavage of the 1-6 bond to form a new alkene upon loss of the tosylate leaving group. This example demonstrates the power of the Grob fragmentation for the production of medium-sized rings, in this case a 10-membered ring, that are often difficult to make.



Contributors

- Prof. Kevin Shea (Smith College)

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3.2: Neighboring Group Participation

Learning Objectives

After completing this section, you should be able to:

1. Understand the power of neighboring group participation to generate unexpected reaction outcomes
2. Spot structural fragments that favor neighboring group participation
3. Draw mechanisms incorporating neighboring group participation to explain reaction outcomes

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Neighboring group participation (NGP)
- Phenonium ion
- Non-classical carbocation

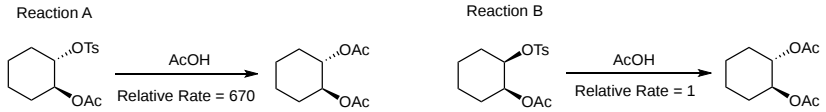
Study Notes

We briefly introduced neighboring group participation (NGP) in the previous chapter. In this chapter we will see more examples that highlight the impact of a nucleophilic neighboring group on reaction rate, regiochemistry, and stereochemistry. Remember, these are all substitution reactions of alkyl compounds containing leaving groups (halide, tosylate, etc.) and some type of internal nucleophile, either a heteroatom with a lone pair or a pi bond. It is good practice to start these types of problems by drawing out the full structure of any abbreviated functional groups and working your way through the mechanism starting with possible intramolecular reactions.

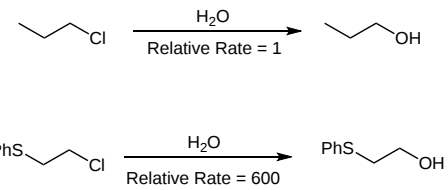
We will separate this chapter into three different types of neighboring groups: 1) Heteroatoms with lone pair electrons, 2) Benzene ring pi bonds, and 3) Alkene pi bonds. Lone pair electrons on heteroatoms are the easiest neighboring groups to spot and are the most common. Pi bonds, either from benzene or an alkene, create very unusual intermediates and generate very surprising results. The alkene neighboring group even created a heated chemical controversy that involved high profile chemists (including one who would later go on to win the Nobel Prize) attempting to determine the correct mechanism for one important reaction.

Heteroatom Nucleophiles as Neighboring Groups

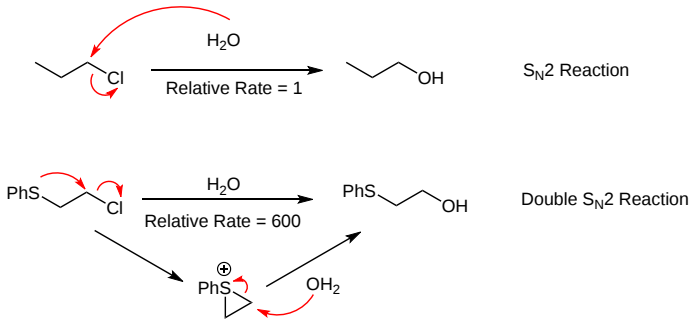
We have already seen an example of this class of reactions in the preceding chapter. As a reminder, the diastereomeric tosylates react with acetic acid to yield the identical trans diacetate product. (For an explanation of this outcome, including the reaction mechanisms, please revisit Chapter 3.1.) We also should note that the relative rates of these reactions vary dramatically, with Reaction A proceeding 670 times faster than Reaction B. This further highlights the power of neighboring group participation; it can dramatically enhance the rate of reactions versus standard nucleophilic substitution reactions. We will see further examples of this throughout the chapter.



We can see another NGP example below with the reactions of the different primary alkyl chlorides with water. In the absence of the rate information, we would assume these are both simple S_N2 reactions. However, the dramatic differences in reaction rates indicate that something unusual is happening. This is when we should look for a neighboring group, hopefully spotting the sulfur in the bottom reaction.

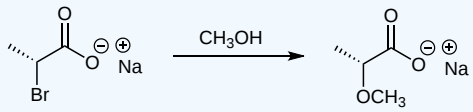


The S can act as an excellent internal nucleophile and promote an intramolecular reaction. As highlighted below in the mechanisms for these two reactions, the top reaction is a straightforward S_N2 reaction. The bottom reaction is much faster because of NGP with the internal S nucleophile. This creates a cyclic sulfonium ion intermediate that reacts much more quickly with water.



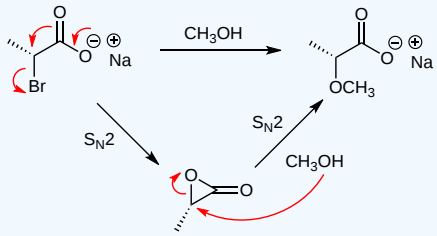
Exercise 3.2.1

Propose a mechanism to explain the outcome of the following reaction.



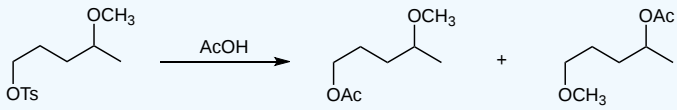
Answer

This is an example of a substitution reaction that proceeds with retention. As we have already seen, this is a hallmark for an NGP mechanism. In this case, the internal nucleophile is a carboxylate that forms an epoxide-type intermediate which reacts quickly with the methanol solvent. These two consecutive S_N2 reactions result in overall retention of configuration.



Exercise 3.2.2

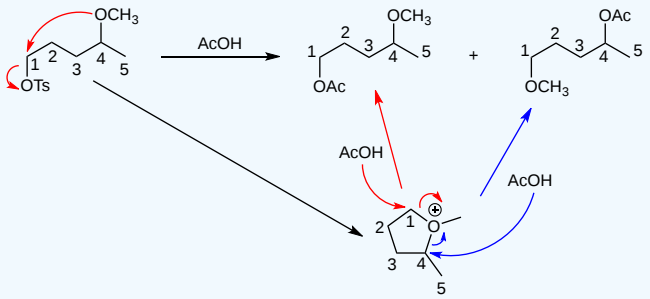
Propose a mechanism to explain how both products are formed in the reaction.



Answer

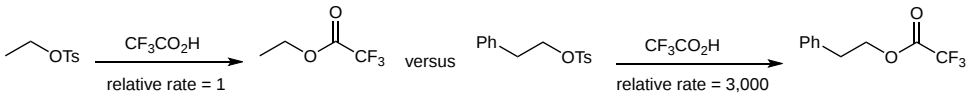
If this was a simple substitution reaction, we would only form the first product. Seeing that two products are formed, including the second one that looks very strange, we should focus on neighboring group participation. The ether O is a very

good internal nucleophile. It can react to form a cationic five-membered ring intermediate. This common intermediate can lead to formation of both of the products depending on which carbon in the intermediate is attacked.

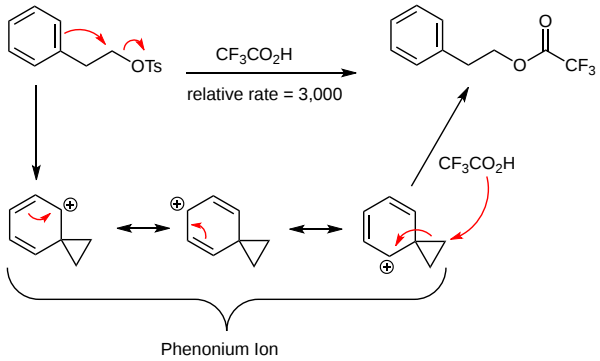


Benzene Ring Pi Bonds as Neighboring Groups

As demonstrated in the following pair of reactions, benzene ring pi bonds are very effective neighboring groups. As we have already seen, without the rate data, we would not know that anything interesting is happening when comparing these two reactions. How is it possible that the second reaction is 3,000 times faster than the first one? With no heteroatom containing a lone pair, it must be the presence of the benzene ring.

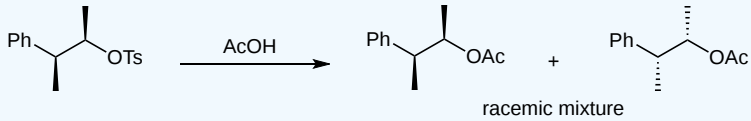


The first reaction is a standard S_N2 reaction while the second one results from two S_N2 reactions, as shown in the mechanism below. Like when doing electrophilic aromatic substitution reactions in Intro Orgo, the phenyl ring acts as a nucleophile to displace the tosylate leaving group. This generates a resonance stabilized three-membered ring phenonium ion intermediate. Addition of the trifluoroacetate nucleophile breaks open the three membered ring and restores aromaticity to the benzene ring.



? Exercise 3.2.3

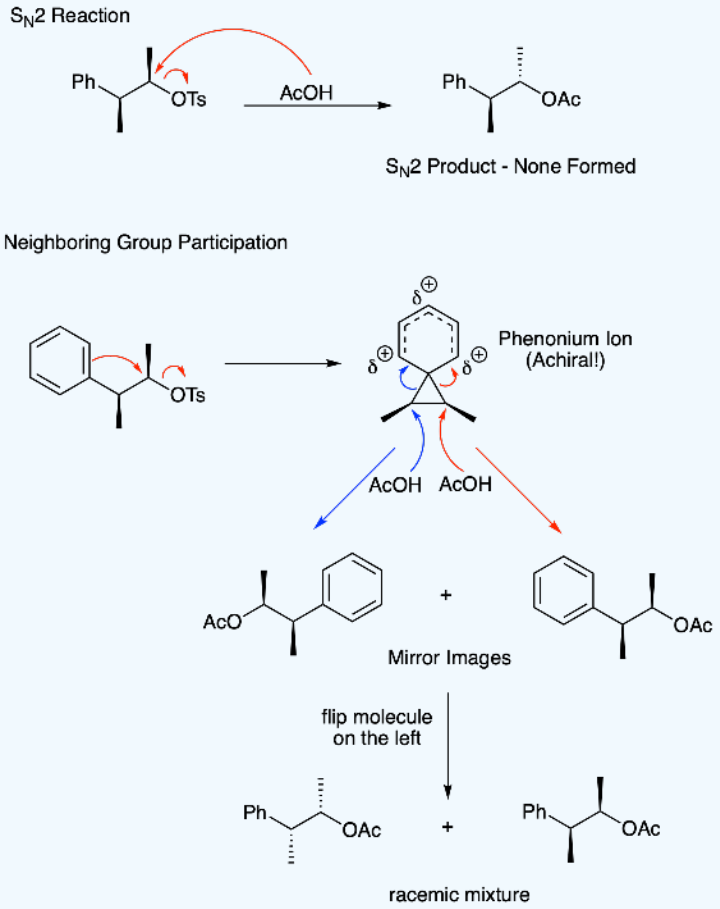
Propose a mechanism to explain the results of the following reaction. Note: You are starting with a single enantiomer of the starting material.



Answer

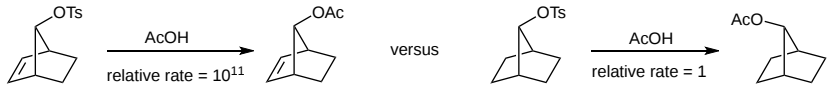
We can verify this isn't an S_N2 reaction by drawing out the product that would result from inversion at the carbon bearing the tosylate. Again, we must look to neighboring group participation. When the benzene ring attacks the tosylate it yields an achiral phenonium ion. The acetate nucleophile can attack either the left or right side of the three membered ring to yield

the product with a restored benzene ring. The two products formed are mirror images and flipping the product on the left demonstrates that we do form the target product mixture.



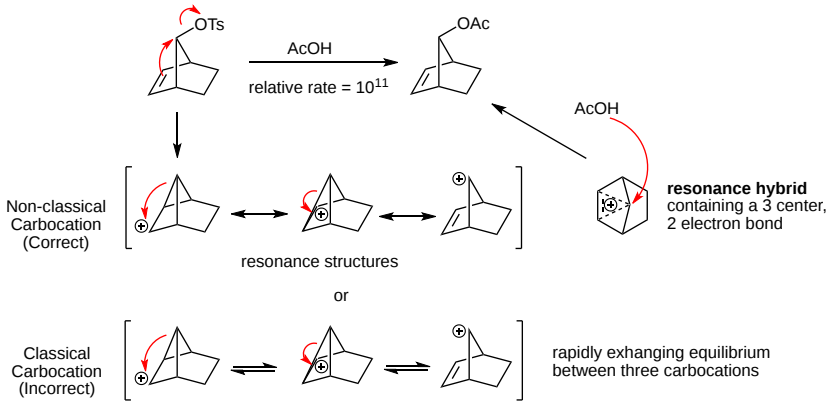
Alkene Pi Bonds as Neighboring Groups

This is, perhaps, the most interesting example of neighboring group participation. It was definitely the most controversial and involved many research groups who investigated whether the key intermediate was a classical or non-classical carbocation. The principal players in this drama were H.C. Brown (Nobel Prize winner for hydroboration reactions) who favored the classical carbocation and Saul Winstein who promoted the non-classical explanation. Winstein's view was ultimately proven correct based on a variety of investigations including NMR and X-ray crystallography. For a detailed explanation of this important historical argument, there is an excellent description in Walling's 1983 paper in *Accounts of Chemical Research*. So, how do we make this fascinating carbocation and what does it have to do with neighboring group participation? The scheme below illustrate the key reactions, and we will see the carbocation when we illustrate the mechanism. First, to the reactions! The second reaction is a straightforward S_N2 reaction. The first reaction has an unbelievable rate enhancement of 10^{11}! This is truly remarkable when compared to the other rate enhancements we've seen in this chapter with the largest being 3,000 for the phenonium ion reaction.



So, what is going on? This is where we wade into the classical versus non-classical carbocation debate. Clearly, the neighboring alkene pi bond is acting as the neighboring group and pushing off the tosylate leaving group. This is our first S_N2 reaction. What is the structure of the cation formed when this happens? We have two options. For both the classical and non-classical carbocation options, the structures look identical. The critical difference is that we are using different types of arrows to connect the structures. For the classical carbocation, we are showing the structures as rapidly interconverting cations that are in equilibrium. They are all distinct intermediates. For the non-classical carbocation, these cations are resonance structures, so there are not intermediates at all.

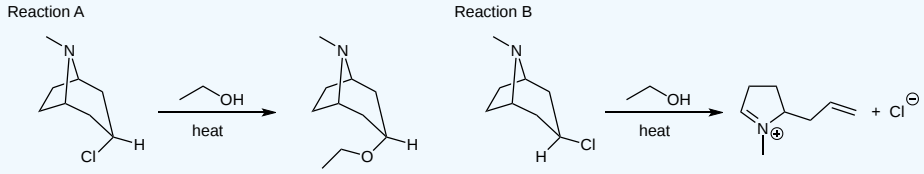
Instead, the intermediate is the hybrid structure (pictured in a top down view making it easier to see). This is a very strange resonance hybrid. The three dashed lines indicate that the two electrons from the original pi bond are shared over three carbon atoms, making this an unusual three center, two electron bond! In the second S_N2 reaction, acetic acid attacks this resonance hybrid to yield the product.



Summary Problems

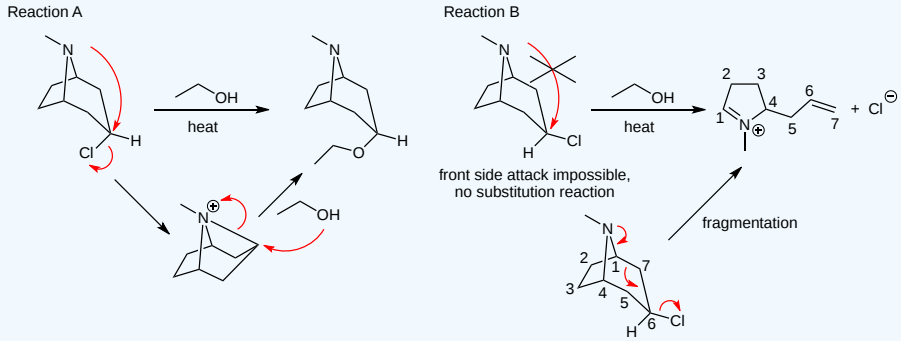
? Exercise 3.2.4

The reactions of the isomeric starting materials produce very different products. Propose a mechanism to explain Reaction A. Why can't the starting material in Reaction B undergo a similar reaction? Reaction B is a preview of what we will see in the fragmentation chapter. Propose a mechanism to explain the product formation.



Answer

Reaction A should look familiar. This is another example of neighboring group participation with the N attacking as the internal nucleophile. Two S_N2 reactions yield the product that is formed with net retention. In Reaction B, backside attack is impossible because the N is attacking the same face where the leaving group already is. Instead, this molecule fragments, breaking the C1-C7 bond to yield the monocyclic product shown.



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3.3: Rearrangements

Objectives

After completing this section, you should be able to:

1. Spot structural fragments that favor rearrangement reactions
2. Draw mechanisms incorporating rearrangements to explain reaction outcomes

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Pinacol rearrangement
- Semipinacol rearrangement
- Payne rearrangement
- Benzilic acid rearrangement
- Favorskii rearrangement
- Tiffeneau-Demjanov rearrangement
- Wolff rearrangement
- Curtius rearrangement
- Baeyer-Villager rearrangement
- Beckmann rearrangement

Study Notes

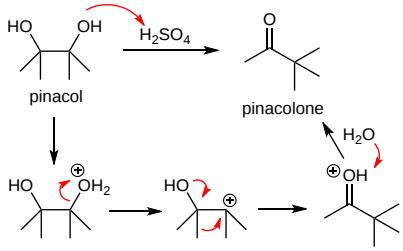
We briefly introduced rearrangements in a previous chapter and you likely learned a little bit about them in Intro Orgo. In this chapter, we will focus exclusively on rearrangements that are synthetically useful. Rearrangements occur readily under strongly acidic conditions, but this leads to uncontrolled decomposition for most substrates. You will see that useful rearrangements occur under both acidic and basic conditions, and our goal is to introduce you to some of the most popular rearrangements for synthesis. This generally involves a leaving group on an atom adjacent to a rearrangement promoting atom, generally an O or N. It is often very challenging to think retrosynthetically for rearrangements, so our focus will be on the forward direction. We will aim to draw mechanisms that explain reaction outcomes, sometimes including interesting stereochemical issues.

Content

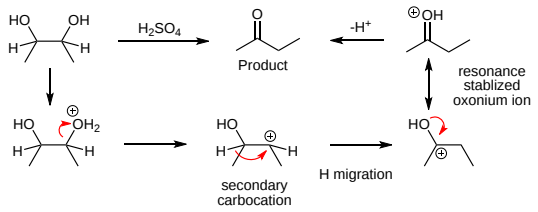
Our goal in this chapter is to introduce the most important rearrangements you will likely encounter in organic synthesis papers. We also know this will provide you with the skills to understand other reactions that you might encounter during your studies. Heteroatom placement in these reactions is critical, with heteroatoms playing the roles of both leaving groups and rearrangement promoting atoms. We will see that substrates rearrange to make new C-C, C-O, and C-N bonds. These reactions also provide opportunities for ring expansions and ring contractions.

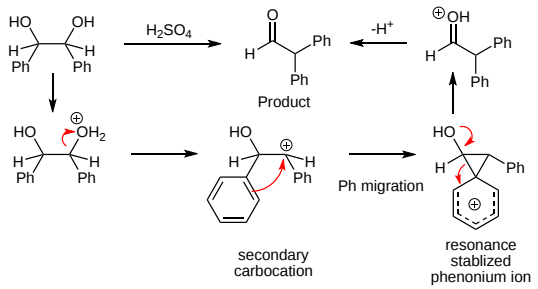
Pinacol Rearrangement

The pinacol rearrangement is the acid catalyzed rearrangement of a 1,2-diol into a ketone. It is named after the molecule pinacol, pictured below, the simplest substrate to undergo the reaction. One of the alcohols is protonated to make the leaving group (water) while the other OH participates as the rearrangement promoting group. After water leaves, generating a tertiary carbocation, the remaining alcohol forms a carbonyl, thus promoting the rearrangement of a methyl group. Deprotonation completes the mechanism to form pincolone and regenerate the catalytic acid.



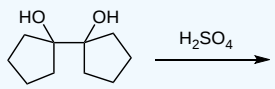
For unsymmetrical diols, not surprisingly, you form the most stable carbocation intermediate. You will see an example of this in the problems below. What about substrates where different groups can migrate? The following examples demonstrate that H migrates faster than R, which is consistent with what you saw previously in Intro Orgo. An H shift yields a more stable cationic intermediate than if an alkyl group migrates. What about Ph vs H? In this case, the benzene ring migrates faster. These seems strange until we remember our previous chapter on neighboring group participation. A migratory phenyl yields a phenonium ion intermediate that is favored over H migration.





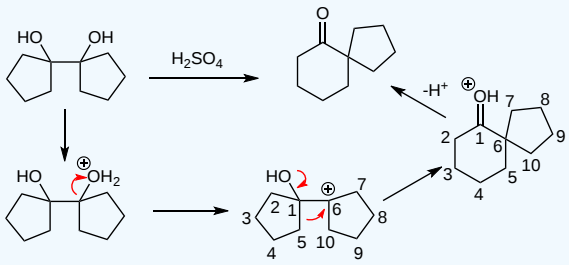
Exercise 3.3.1

For the following reaction, propose a product and a mechanism to explain its formation.



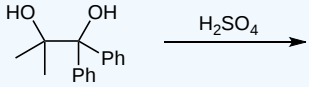
Answer

Using the same strategy as the pinacol rearrangements above, we quickly generate a tertiary carbocation. Formation of the carbonyl that we know will be in the product promotes rearrangement (migration) of one of the ring bonds. This yields a very interesting result. One of the original 5-membered rings expands to form a new 6-membered ring. So, we can use the pinacol rearrangement as a ring expansion reaction!



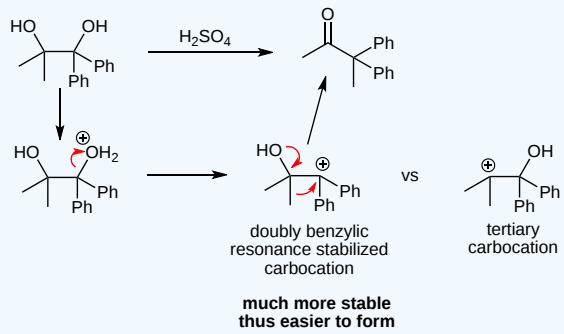
Exercise 3.3.2

For the following reaction, propose a product and a mechanism to explain its formation.

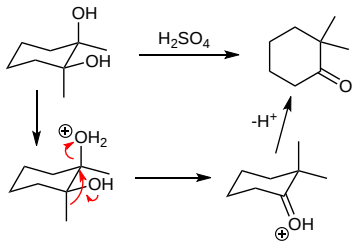


Answer

In this example, the two possible carbocations that can form after water leaves are very different. The tertiary carbocation is low enough in energy to form; however, the doubly benzylic, resonance stabilized carbocation is much lower in energy. So, it forms preferentially, resulting in a methyl shift to form the product ketone.

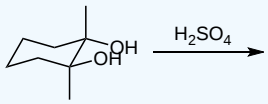


Another interesting aspect of the pinacol rearrangement is the impact of stereochemistry on the migrating group. If you think about this statement, it seems to contradict what we have shown in all of the reactions up to now in this chapter. How can stereochemistry of the diol (cis or trans) matter when we generate a planar carbon as part of the carbocation intermediate? It turns out, like many reactions in organic chemistry, our first look was an oversimplification. The current understanding is that an achiral carbocation does not form. Instead, a chiral ion pair forms, retaining the stereochemistry of the starting material. However, when considering rearrangements of chiral diols, we will sometimes draw the carbocation and sometimes a concerted mechanism depending on what helps most with our understanding. The key is to recognize that what does form is a chiral version of the free carbocation (the ion pair) that promotes the rearrangement. Similar to what you learned in intro orgo for S_N2 and E2 reactions, the migrating group must be antiperiplanar to the leaving group. The example and problem below demonstrate that stereochemistry is critically important when considering reactions of cyclic diols. We will first consider reaction of the cis cyclohexane diol. Axial leaving groups are much more reactive than equatorial leaving groups, so the reaction occurs with the protonated axial OH leaving accompanied by formation of the new carbonyl and rearrangement of the axial methyl group, the anitperiplanar migrating group. What happens if we run the same reaction on the trans isomer of this diol? See if you can come up with an answer as part of the next problem.



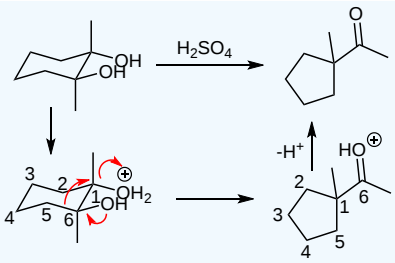
? Exercise 3.3.3

What is the product of this reaction? Also, provide a mechanism for its formation.

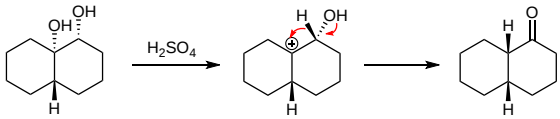


Answer

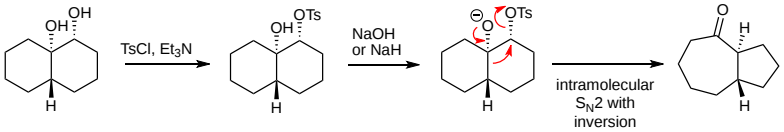
Both of the alcohols are equatorial because they are larger than the axial methyl groups and they can form an intramolecular hydrogen bond to stabilize this conformation. So, when a protonated equatorial alcohol leaves, which group is antiperiplanar to participate in the pinacol rearrangement? It's clearly not one of the methyl groups. Thus, the ring bond is the only alternative. As shown in the mechanism, formation of the new carbonyl promotes cleavage of the 5-6 bond to form a new 1-5 bond. The result is a ring contraction from 6- to 5-members! This demonstrates that the pinacol rearrangement can produce both ring contractions and ring expansions, as we saw previously.



Let's consider one more type of pinacol rearrangement that is very important for complex structures and often appears in total synthesis applications. It is called a **semipinacol rearrangement** and involves rearrangement under basic conditions where it is impossible to form a carbocation. To understand why this is a key reaction, let's first look at the reaction below. This is a standard pinacol rearrangement. As we saw above, with an unsymmetrical diol, we will protonate the tertiary carbocation to form the more stable tertiary carbocation and then do our rearrangement. In this case, a hydrogen shift to yield the ketone product. But, what if we wanted to form the carbocation at the secondary alcohol? It is impossible to do this under acidic conditions.

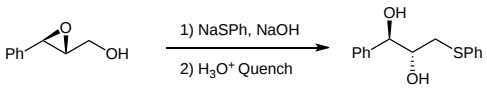


The solution is to move away from acidic conditions and think about reactions we know that occur selectively at secondary alcohols. If we can make the secondary alcohol into a good leaving group, we can force that alcohol to leave, reverse the position of the rearrangement promoting O and generate a different product. How do we put that into practice? The reaction sequence below shows the standard way this is accomplished. Alcohols react selectively with tosyl chloride from least hindered (primary) to most hindered (tertiary), so we can selectively tosylate the secondary alcohol in the presence of the tertiary alcohol. Next, addition of a base results in deprotonation of the alcohol to form an alkoxide that can promote the rearrangement. Formation of the ketone promotes rearrangement of the ring bond to force out the tosylate leaving group. In this fascinating example, that results in a simultaneous ring expansion and ring contraction!

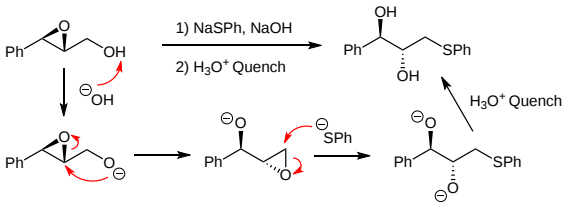


Payne Rearrangement

The Payne rearrangement involves reactions of nucleophiles with epoxy alcohols under basic conditions. Like many rearrangements, at first glance it seems confusing. We can rationalize hydroxide adding to an epoxide, but how does the sulfur nucleophile replace the poor OH leaving group? The key here is to think first about deprotonating the primary alcohol and then to focus on neighboring group participation.

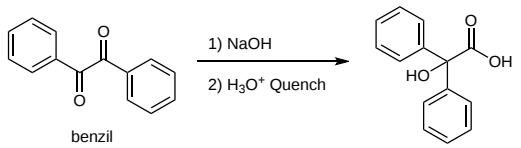


Deprotonating the primary alcohol generates an alkoxide nucleophile that opens the epoxide via an intramolecular S_N2 reaction to form a new epoxide. The sulfur nucleophile can now add to the less hindered side of the new epoxide via an intermolecular S_N2 reaction. The final protonation step yields the target trans diol.

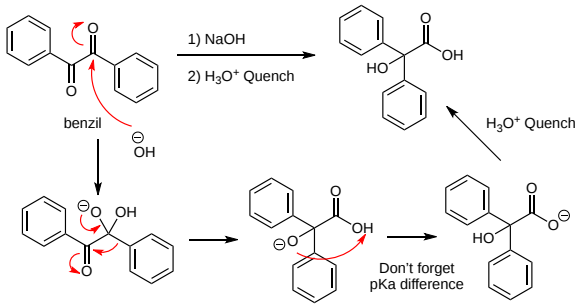


Benzilic Acid Rearrangement

The benzilic acid rearrangement involves conversion of a 1,2-diketone into a carboxylic acid. The conditions are deceptively simple, hydroxide followed by an acid quench, and lead to the migration of a benzene ring.

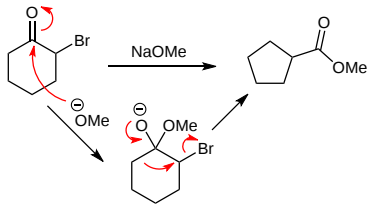


This mechanism is relatively straightforward. Hydroxide adds to one of the ketones to yield a tetrahedral intermediate. Reforming the carbonyl results in rearrangement of the phenyl onto the second carbonyl. The acid quench ultimately generates the target carboxylic acid.



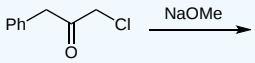
Favorskii Rearrangement

The Favorskii rearrangement transforms an alpha halo ketone into an ester, as shown in the example below. Upon first inspection, this seems to continue the theme we just saw in the benzilic acid rearrangement. Add the nucleophile to the carbonyl, reform the carbonyl, and have the rearrangement occur pushing out the leaving group. For this substrate, that results in a ring contraction reaction. As we will see in the problems below, this is not the only mechanistic possibility.



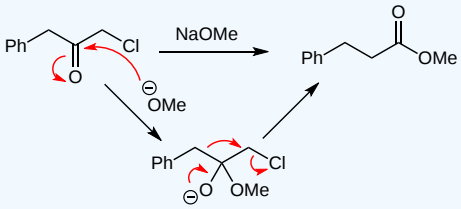
? Exercise 3.3.4

Propose a mechanism and a product for the following reaction.



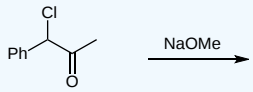
Answer

This reaction appears to behave exactly like the reaction shown above. Rearrangement occurs from the tetrahedral intermediate and yields the ester product. See the answers to Exercise #5 for an alternate mechanism to get the same product.



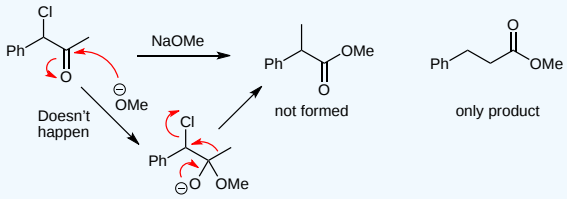
Exercise 3.3.5

Propose a mechanism and a product for the following reaction.

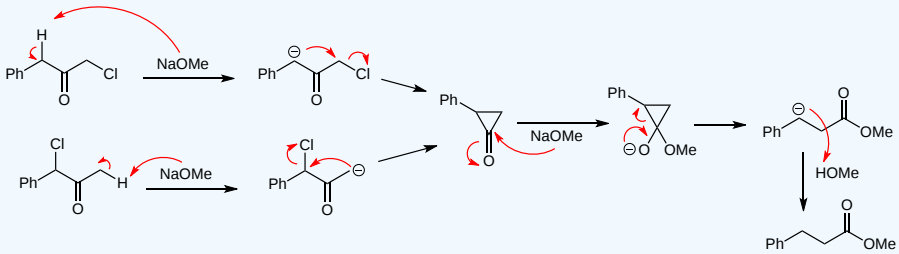


Answer

As shown below, our standard Favorskii mechanism fails for this reaction. We do not form the product predicted by the mechanism used previously. Instead, we form the same product observed in the reaction from Exercise #4. How is this possible? If the two starting materials form the same product, perhaps the reactions proceed through a common intermediate.



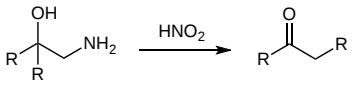
A different way to think about these reactions is to use the methoxide as a base, not a nucleophile. If we deprotonate alpha to the carbonyl on the opposite side of the halogen, something interesting can happen. As shown below, we form two different enolates that can each undergo an intramolecular alkylation reaction to yield the same cyclopropanone intermediate. Due to the ring strain, this is a much more reactive carbonyl that does react with methoxide to yield a tetrahedral intermediate. Reforming the carbonyl breaks open the three-membered ring to selectively yield the resonance stabilized anion that is subsequently protonated by the methanol formed in the first step.



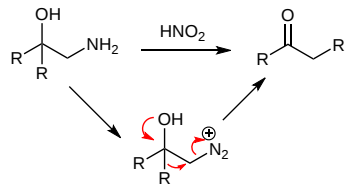
So, we have seen two potential mechanisms for the Favorskii rearrangement. Depending on the substrate, either is possible. So, the best problem solving strategy is to consider both options and then see which one looks most favorable. In the example above, resonance stabilization of an anion adjacent to the benzene ring helps favor this mechanism.

Tiffeneau-Demjanov Rearrangement

In this rearrangement, a 1,2-aminoalcohol is converted into a ketone as shown in the generic example below. The reagent that promotes this transformation is nitrous (not nitric) acid. If you previously studied nucleophilic aromatic substitution reactions, you might recognize that combining an amine and nitrous acid yields a reactive diazonium intermediate. This is a key step in the Sandmeyer reaction where anilines react with nitrous acid to yield a diazo benzene intermediate that reacts with a variety of nucleophiles to make new benzene derivatives.



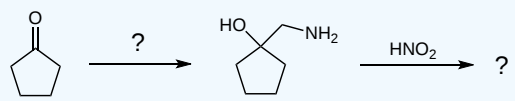
In the Tiffeneau-Demjanov rearrangement, formation of the diazonium intermediate promotes the key rearrangement step. Similar to previous mechanisms, formation of the carbonyl promotes the alkyl shift and loss of the leaving group.



A historical note about this reaction is to recognize the key role played by Bianka Tchoubar in its development. She conducted the critical experiments in Tiffeneau's lab to determine the scope and limitations of the reaction. Bianka was a key figure in the organic chemistry community in France from the 1930s until the 1980s, resulting in 140 publications.

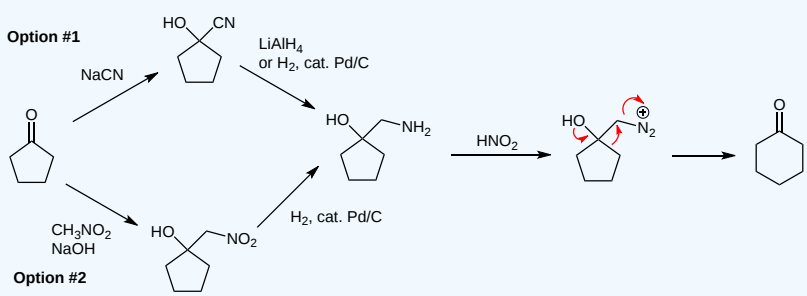
Exercise 3.3.6

First, starting with cyclopentanone, how would you produce the desired aminoalcohol? Second, what product is formed upon exposure of the aminoalcohol to nitrous acid?



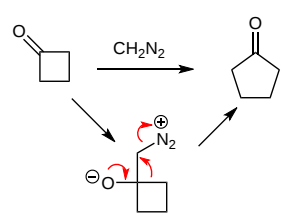
Answer

There are two ways to convert cyclopentanone into the target aminoalcohol. In option #1, we add sodium cyanide to yield a cyanohydrin that can be reduced with either lithium aluminum hydride or hydrogen and catalytic palladium. In option #2, we use a Henry reaction to generate a nitroalcohol that can be reduced with hydrogen and catalytic palladium. Adding nitrous acid promotes the Tiffeneau-Demjanov rearrangement to yield a ring expanded ketone.



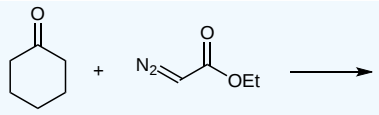
Wolff Rearrangement

The Wolff rearrangement is similar to the Tiffeneau-Demjanov rearrangement because of the key role of a diazo intermediate. The most common variation involves reaction of a ketone with a diazo compound. As shown below, treating cyclobutanone with diazomethane yields a ring expansion reaction to form cyclopentanone via a mechanistic pathway that should look familiar.



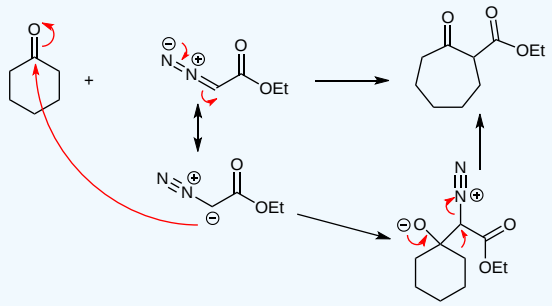
Exercise 3.3.7

Propose a mechanism and the product for the following reaction.

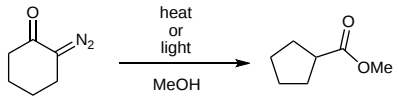


Answer

As with many mechanisms, it helps to draw out the complete Lewis structure for reactive functional groups. There are two common resonance structures for diazo compounds and the one with the negative charge on carbon highlights that this atom is nucleophilic. Using this carbon to form a new carbon-carbon bond yields a tetrahedral intermediate. Reforming the carbonyl leads to the rearrangement, resulting in a ring expansion and the seven-membered ring product.

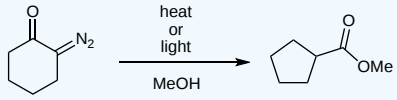


Wolff rearrangements are also useful for ring contraction reactions. As shown below, treating an alpha diazoketone with heat or light in methanol promotes the rearrangement to yield the contracted ester product. We will discuss the mechanism for this reaction in the next problem. Forming the starting alpha diazoketone involves a diazo transfer reaction with a ketone. We will generally not worry about this step and instead start with the alpha diazo ketone.



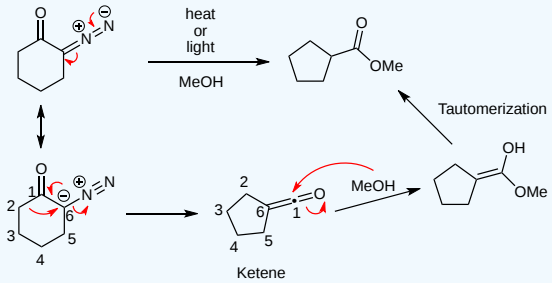
Exercise 3.3.8

Propose a mechanism for this reaction. Hints: The key intermediate is a ketene. The role of heat or light is to promote the loss of nitrogen gas. You don't need to factor that into your mechanism.



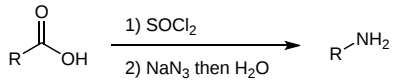
Answer

This is a strange mechanism for us. It actually will make more sense when we study carbenes in a later chapter. For now, let's focus on the resonance structure with the negative charge on carbon. From here, nitrogen can leave, we can form a new carbon-carbon double bond between C1 and C6, and we can rearrange to form a new C2-C6 bond. This yields the ketene intermediate that reacts with methanol to form an enol. Tautomerization yields the 5-membered ring ester product.

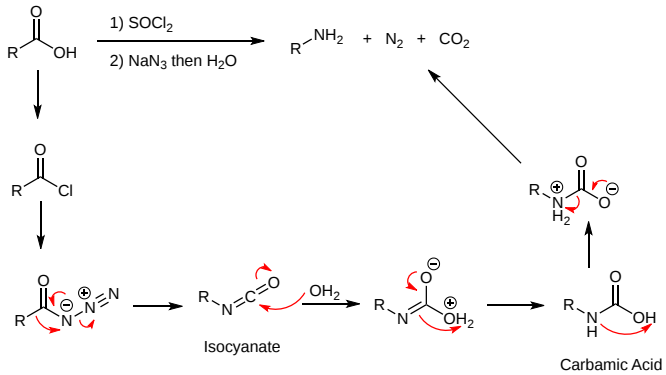


Curtius Rearrangement

The Curtius rearrangement generally involves the conversion of a carboxylic acid into an amine with the loss of one carbon. It is similar to the Wolff rearrangement but in place of diazomethane, this reaction uses an azide nucleophile. A generic example, shown below, involves generation of an acid chloride upon treatment of the carboxylic acid with thionyl chloride followed by reaction with sodium azide to promote the rearrangement then addition of water to generate the amine product. Other products formed include nitrogen gas and carbon dioxide.

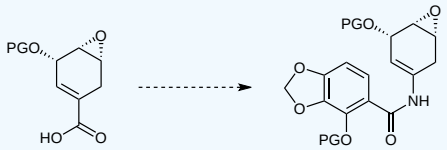


As shown below in the full mechanism, the key intermediate is an isocyanate. This forms upon rearrangement of the azide intermediate resulting in loss of nitrogen gas and formation of a new R-N bond. Addition of water to the isocyanate generates a carbamic acid that loses carbon dioxide under the reaction conditions to complete the reaction and form the product amine. Other nucleophiles can be added to the isocyanate intermediate to yield different products including a substituted amide, as shown in the problem below.



Exercise 3.3.9

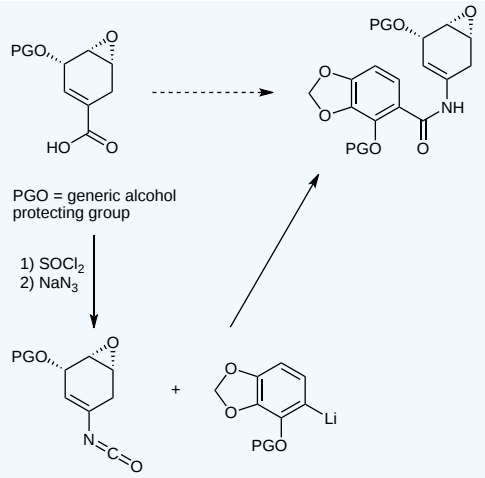
Beginning with the indicated starting material, how could you use a Curtius rearrangement to generate the target amide?



PGO = generic alcohol protecting group

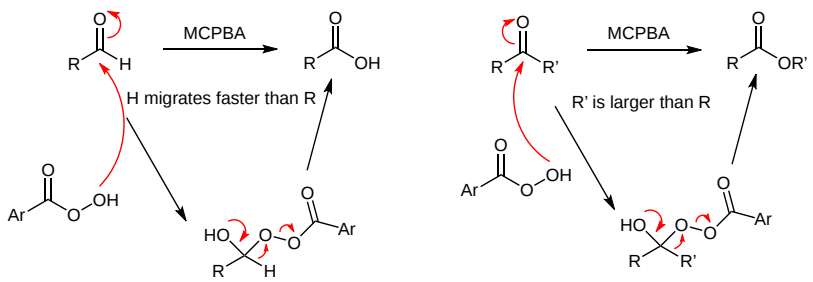
Answer

This reaction has been used in the synthesis of the natural product pancratistatin. Like in our general example, the starting carboxylic acid is treated with thionyl chloride followed by sodium azide. This yields the isocyanate intermediate after a Curtius rearrangement. Adding a functionalized organolithium reagent to the isocyanide yields the target amide. This sequence nicely highlights that isocyanates can participate in more than just hydrolysis reactions.



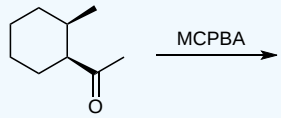
Baeyer-Villager Rearrangement

The Baeyer-Villager rearrangement is the reaction of a peracid with an aldehyde or ketone to yield a carboxylic acid or ester, respectively. There are two possible products for ketones with selectivity generally favoring migration of the larger group. The most common peracid used synthetically is meta-chloroperoxybenzoic acid (MCPBA) which also reacts with alkenes to form epoxides. Beware of this dual reactivity when planning syntheses. The Baeyer-Villager rearrangement mechanism is shown below. The peracid adds to the aldehyde or ketone to produce a tetrahedral intermediate. Reforming the carbonyl promotes the rearrangement with H migrating exclusively in the aldehyde substrate to yield the carboxylic acid product. A similar intermediate is formed in the ketone reaction. In this case, the larger alkyl group migrates (related to which group can better stabilize a partial carbocation on the carbonyl carbon in the transition state) to yield the ester product.



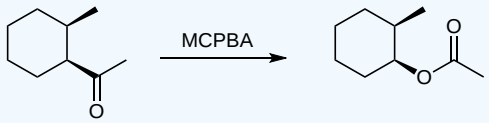
Exercise 3.3.10

Propose a product for the following Baeyer-Villager rearrangement.



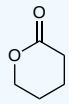
Answer

The left side of the ketone is larger than the methyl group, so this alkyl group migrates onto the new O in the mechanism to yield the product ester. Note that no bonds were formed or broken to the chiral carbon on the cyclohexane ring so this stereochemistry does not change.



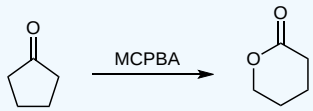
Exercise 3.3.11

Propose a Baeyer-Villager rearrangement that would yield the target lactone.



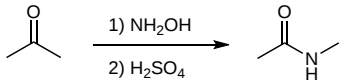
Answer

Thinking about the ketone that led to the formation of the six-membered ring lactone, we should realize that we just need to remove the O in the ring from the product to yield the all-carbon starting material. In this case, it's cyclopentanone. This reaction highlights the ability of the Baeyer-Villager rearrangement to promote a ring expansion reaction.

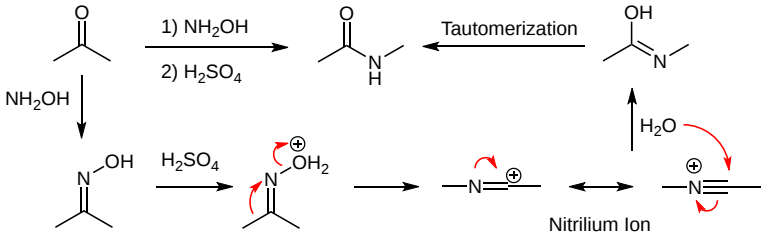


Beckmann Rearrangement

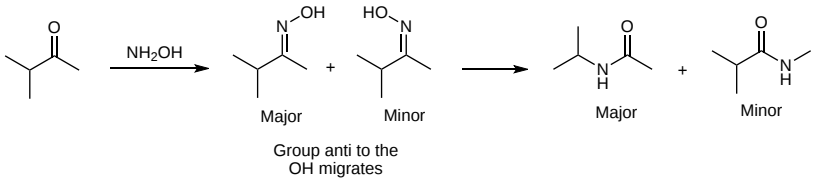
The Beckmann rearrangement converts ketones into amides and is the nitrogen equivalent of the Baeyer-Villager reaction with ketones. The rearrangement is relatively straightforward for reactions of symmetrical ketones, as shown in the example below.



Treatment of the ketone with hydroxylamine yields an oxime that rearranges upon exposure to sulfuric acid to yield a nitrilium ion. Addition of water completes the mechanism to yield the product amide after tautomerization. The details are shown in the scheme below.

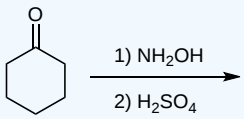


What about reaction of an unsymmetrical ketone? The structure of the oxime leads directly to the rearrangement outcome. Sterically, the OH in the oxime is oriented away from the larger ketone group. This results in the major or only product resulting from rearrangement of the larger ketone substituent.



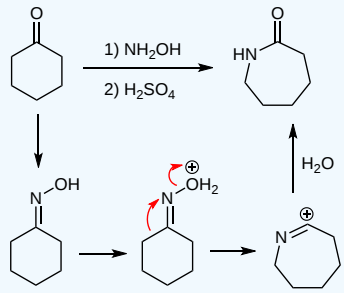
Exercise 3.3.12

What is the product of the following Beckmann rearrangement?

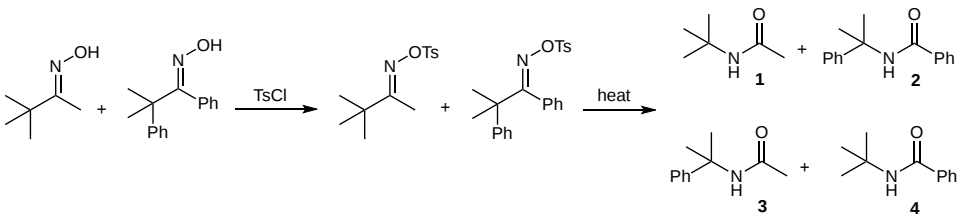


Answer

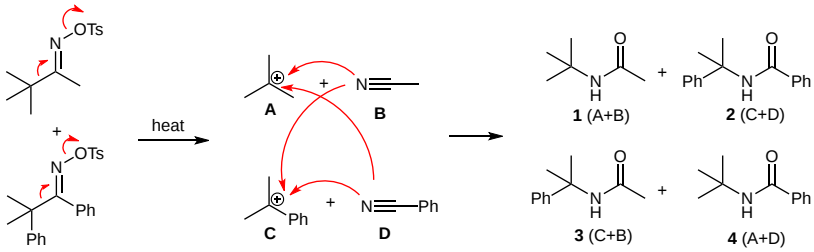
When starting with a cyclic ketone, a Beckmann rearrangement promotes a ring expansion reaction to yield an expanded lactam as shown below.



The Beckmann rearrangement isn't always this straightforward, as the following experiment illustrates. Beginning with a mixture of the two oximes, they are treated with tosyl chloride to yield the corresponding tosylates. Heating the tosylates yields four products. Products **1** and **2** are the standard Beckmann rearrangement products. How did products **3** and **4** form? Clearly, something strange is happening here.



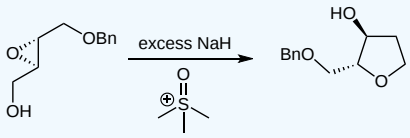
To explain how all four of these products formed simultaneously, we must consider a fragmentation reaction as part of the mechanism. This results when a highly stabilized carbocation intermediate can form which is definitely the case for this substrate. Fragmentation of the tosylates yields tertiary carbocations **A** and **C**. These carbocations can combine with either of the nitriles (**B** or **D**). So, these four recombination possibilities yield the observed products. This experiment highlights another mechanistic possibility for the Beckmann rearrangement and provides a preview of the mechanism we will focus on in our next section (fragmentations!).



Summary Problems

? Exercise 3.3.13

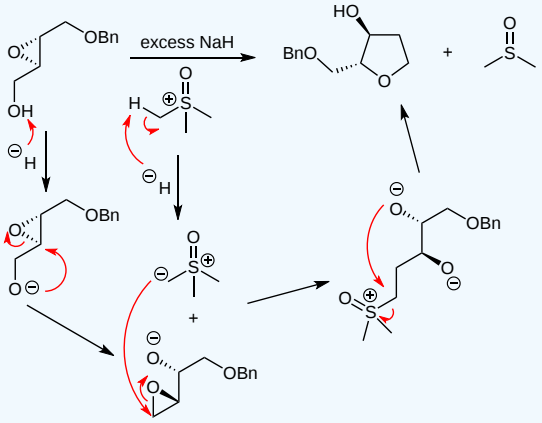
Propose a mechanism for the following transformation.



Answer

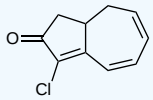
The key step in this mechanism is a Payne rearrangement. This occurs after the primary alcohol is deprotonated. The resulting new epoxide reacts with the sulfur ylide produced upon deprotonation. After forming the new carbon-carbon bond, the new 5-membered ring forms via a substitution reaction with dimethyl sulfoxide as the leaving group.

Reference - *Journal of the American Chemical Society* 2004



Exercise 3.3.14

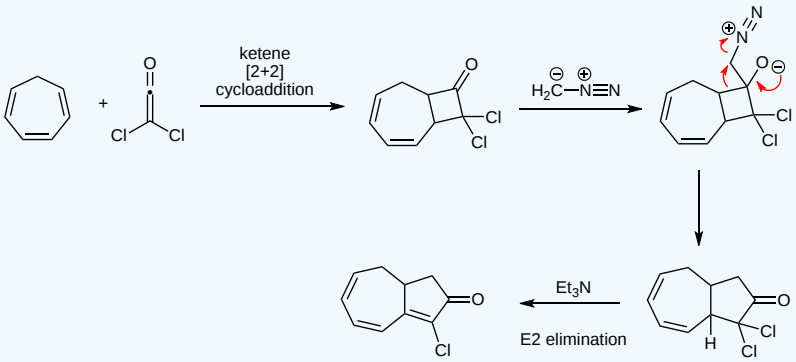
The molecule below can be used to synthesize substituted azulenes. Our goal in this problem is to propose a three-step synthesis of this bicyclic cyclopentenone. One step involves dichloroketene while another is a ring expansion reaction.



Answer

The key step in this synthesis is a Wolff rearrangement. The synthesis begins with a ketene [2+2] cycloaddition between cycloheptatriene and dichloroketene. The resulting bicyclic ketone reacts with diazomethane and then undergoes the Wolff rearrangement. This results in a ring expansion to yield the 5,7-bicycle. The final step in the synthesis is an E2 elimination of HCl promoted by triethylamine.

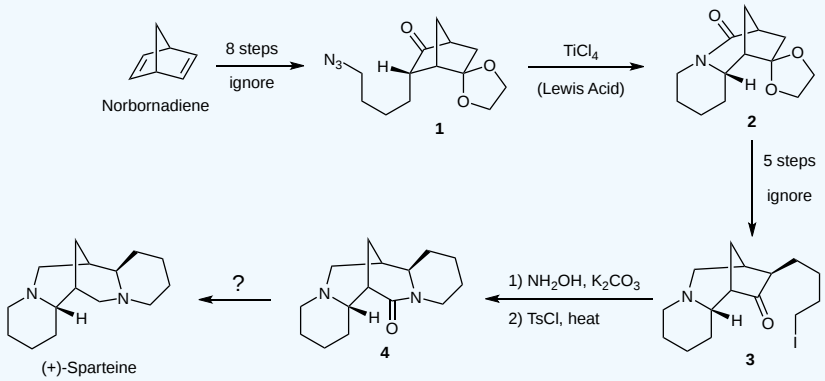
Reference - *Angewandte Chemie International Edition* 2005



Exercise 3.3.15

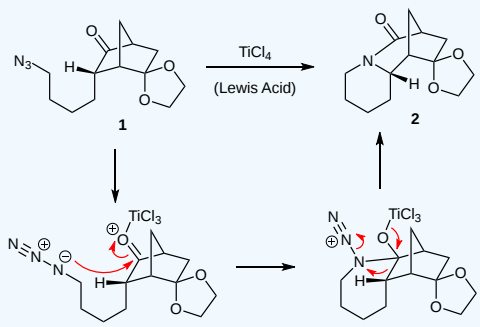
(+)-Sparteine is a natural product that is a very popular chiral ligand for a variety of asymmetric reactions. The first asymmetric total synthesis of this molecule was published in 2002 and it involved several reactions of interest to us. Azide **1** was prepared in eight steps from commercially available norbornadiene. Propose a mechanism for the conversion of **1** into amide **2**. After five steps, **2** was converted into keto iodide **3** which upon treatment with hydroxyl amine and tosyl chloride

yielded amide **4**. (Note: I have modified the reaction conditions for the synthesis of **4** from the literature to make them consistent with material you have learned in this chapter.) Provide a mechanism for this transformation and then indicate how you would convert **4** into (+)-sparteine in one step.

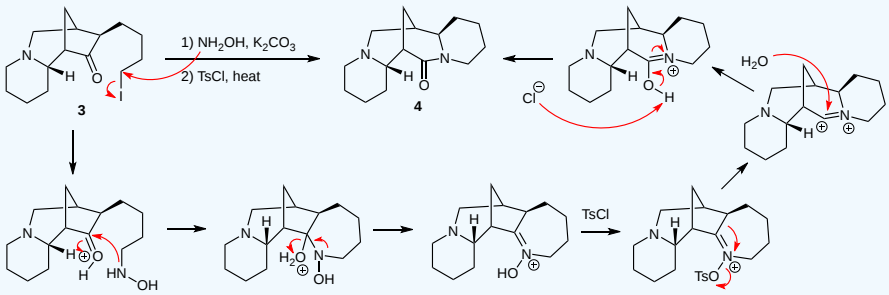


Answer

The key step here is a Schmidt reaction which is similar to a Curtius rearrangement. The Lewis acid activates the carbonyl for attack by the azide. This tetrahedral intermediate undergoes the rearrangement to form the amide product and lose nitrogen gas.

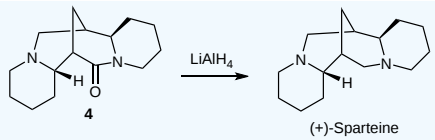


The key step in this sequence is a Beckmann rearrangement. The mechanism starts with a substitution reaction with hydroxylamine following by an intramolecular iminium ion formation. (Note: I have omitted the proton transfer steps to save space.) In the paper cited below, the second step is irradiation with ultraviolet light to promote an unusual photo-Beckmann rearrangement. For consistency with what we learned in this chapter, we will proceed as if TsCl and heat will enable this transformation. Addition of tosyl chloride and heat should promote formation of an N-tosylate that undergoes the Beckmann rearrangement. This yields a very unusual intermediate with positive charges on adjacent atoms (and likely explains why this reaction doesn't work in the lab). It should react quickly with water to yield the amide product after deprotonation.



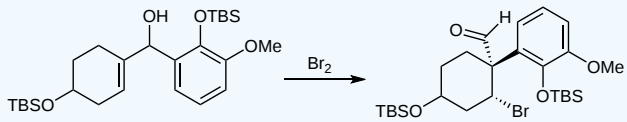
The synthesis of (+)-sparteine concludes with a lithium aluminum hydride reduction of the amide.

Reference - *Organic Letters* 2002



Exercise 3.3.16

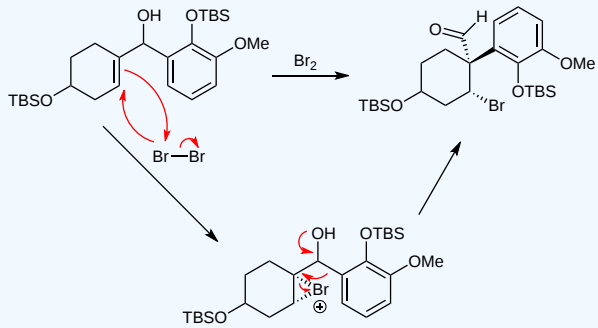
Propose a mechanism for the following transformation.



Answer

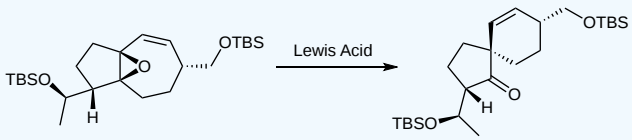
The key step in this mechanism is a semi-pinacol rearrangement. In the first step, bromine reacts with the alkene to yield a cyclic bromonium ion intermediate. This undergoes a semi-pinacol rearrangement to yield the target aldehyde.

Reference - *Organic Letters* 2004



Exercise 3.3.17

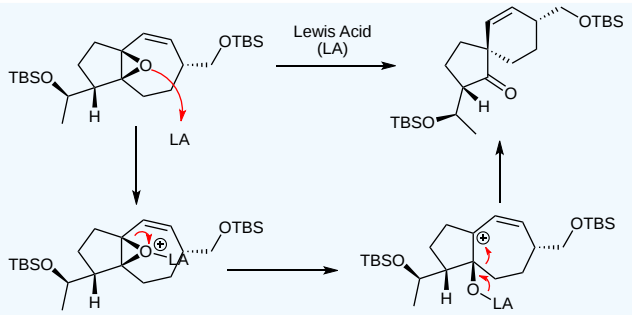
Trost discovered the following transformation while investigating the total synthesis of pseudolaric acid B. Propose a mechanism to explain this reaction.



Answer

The key step in this mechanism is a pinacol rearrangement. The epoxide adds to the Lewis acid, then opens up to form a tertiary allylic carbocation. Next, the pinacol rearrangement yields the bicyclic 5,6-spiro product.

Reference - *Journal of the American Chemical Society* 2008



Contributors

- Prof. Kevin Shea (Smith College)

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3.4: Fragmentations

Objectives

After completing this section, you should be able to:

1. Spot structural fragments that favor fragmentation reactions
2. Draw mechanisms incorporating fragmentations to explain reaction outcomes

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Grob Fragmentation
- Eschenmoser Fragmentation

Study Notes

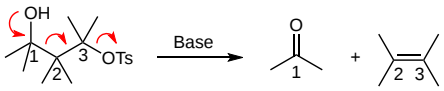
We briefly introduced fragmentations in a previous chapter and you likely did not learn about them in Intro Orgo. We also met the Beckmann fragmentation at the end of the previous chapter on rearrangements. In this chapter, we will focus exclusively on fragmentations that are synthetically useful. Like rearrangements, fragmentations occur readily under strongly acidic conditions, but this leads to uncontrolled decomposition for most substrates. You will see that useful fragmentations occur under conditions similar to rearrangements but with a slightly different arrangement of atoms, one more carbon between the fragmentation promoting atom (generally O or N) and the leaving group. Fragmentations are much less common than rearrangements.

Content

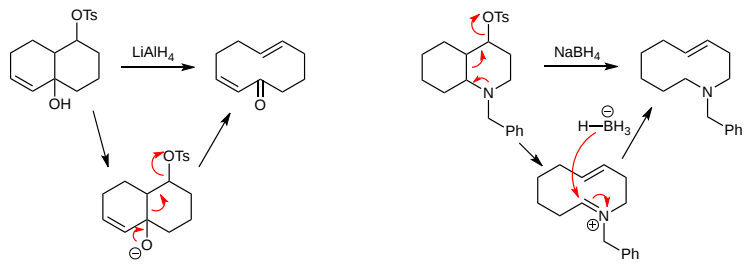
In this chapter, we will introduce the most important fragmentations you will likely encounter in organic synthesis papers. We also know this will provide you with the skills to understand other reactions that you might encounter during your studies. Heteroatom placement in these reactions is critical, with heteroatoms playing the roles of both leaving groups and fragmentation promoting atoms. We will see that substrates fragment to make new C-C bonds and turn cyclic molecules into acyclic targets. Fragmentations also provide a novel method for the synthesis of challenging medium-sized rings upon fragmentation of bicyclic systems.

Grob Fragmentation

The Grob fragmentation is similar to the pinacol rearrangement. Substrates that are 1,2-diols (or 1,2-diol type compounds) undergo the pinacol rearrangement to yield a new ketone or aldehyde. Substrates that are 1,3-diols (or 1,3-diol type compounds) undergo the Grob fragmentation to yield both a new ketone/aldehyde and an alkene, as shown below.

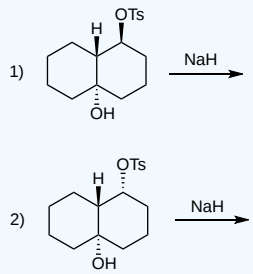


The Grob fragmentation is an excellent method for constructing medium or large rings from bicyclic systems. Two examples for the synthesis of 10-membered rings are shown below. The example on the left is a standard Grob fragmentation. A deprotonated alcohol forms a carbonyl that promotes cleavage of the adjacent C-C bond (the fragmentation) to generate a new alkene and loss of the tosylate leaving group. The example on the right highlights that nitrogen can also function as a fragmentation promoting atom. In this case, fragmentation and loss of tosylate yields a new alkene and an iminium ion. Sodium borohydride reduces the iminium ion to yield the amine product. The example on the left is actually an oversimplification of this reaction because it does not show stereochemistry. Fragmentations are similar to E2 reactions and cyclic pinacol rearrangements in that the reacting groups must be antiperiplanar for constructive orbital overlap to occur. The follow problem explores the importance of stereochemistry for the Grob fragmentation.



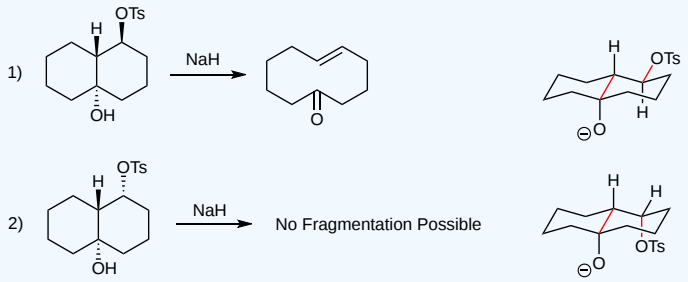
Exercise 3.4.1

Only one of the following two reactions yields a Grob fragmentation. Which reaction is it? Explain. Hint: It is very helpful to draw out these trans decalin molecules in the chair conformation.



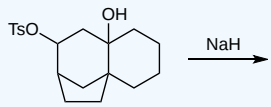
Answer

Reaction #1 undergoes the fragmentation while reaction #2 does not. Focusing on the chair conformation for each molecule, we can explain why. In the first reaction, the fragmenting C-C bond and the bond to the leaving group are anti (both in red). In reaction #2, the fragmenting C-C bond and the leaving group (both in red) are not anti. Instead, a C-H bond is anti to the fragmenting C-C bond so the reaction does not occur.



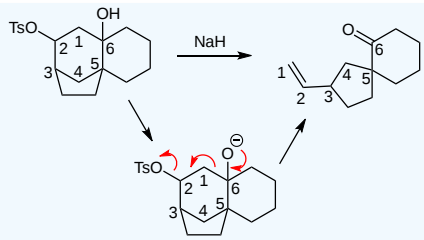
Exercise 3.4.2

Predict the product of the following reaction.



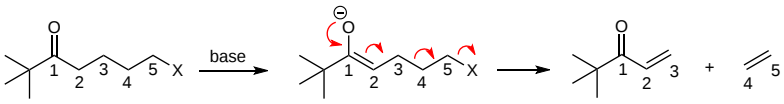
Answer

Following our standard strategy for the Grob fragmentation, we can show how the starting tricycle fragments into the product bicycle. As always, numbering helps keep track of atoms.



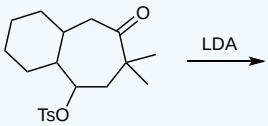
1,5-Fragmentations

Though much less common than Grob fragmentations, 1,5-fragmentations are also possible. These substrates start as ketones or aldehydes and the reaction is promoted by base induced enolate formation. Upon fragmentation, they yield an unsaturated ketone and an alkene, as shown below.



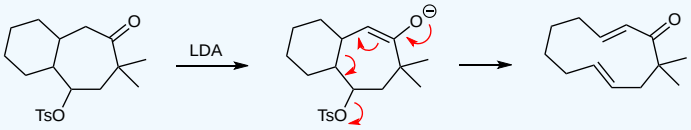
Exercise 3.4.3

Predict the product of the following reaction.



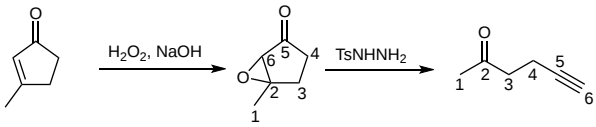
Answer

After formation of the enolate, the molecule can fragment as shown above to yield the 11-membered ring product.

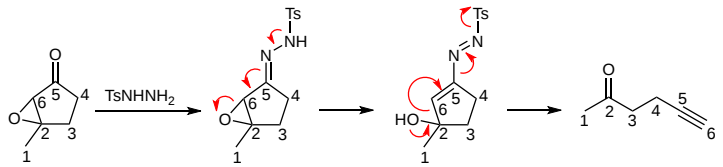


Eschenmoser Fragmentation

The Eschenomser fragmentation (sometimes called the Eschenmoser-Tanabe fragmentation) was discovered in 1967 in the lab of Albert Eschenmoser at the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland. Much of the early work on the scope of this reaction in the Eschenmoser lab was conducted by Dorothee Felix. The reaction begins with the epoxidation of a cyclic conjugated enone to yield an epoxy carbonyl. Treatment of this molecule with tosyl hydrazine promotes fragmentation to remove the ring, generating a new carbonyl and alkyne.

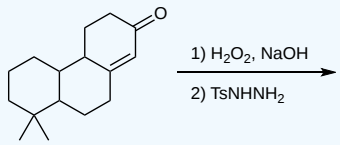


The mechanism of the fragmentation reaction is similar to the Wolff-Kishner reaction (reduction reaction of carbonyls with hydrazine and base) with important differences due to the presence of the epoxide and the tosylate group. After formation of the tosyl hydrazone, the important mechanistic steps begin. Movement of electrons from the nitrogen attached to the tosyl forms a double bond between the nitrogens, creates a C5-C6 alkene, and opens the epoxide. Next, the electrons flow back in the opposite direction. A carbonyl forms which cleaves the C2-C6 bond (the fragmentation) to yield the product alkyne while generating nitrogen gas (N_2) and the tosyl leaving group.



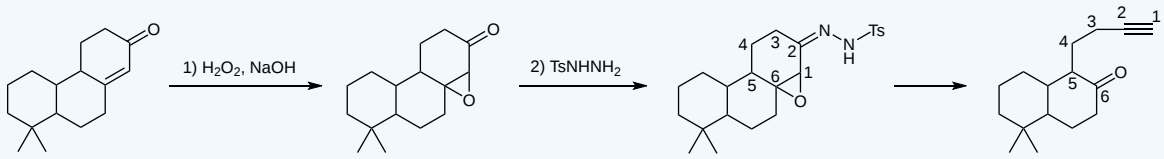
Exercise 3.4.4

What is the product of the following reaction sequence?



Answer

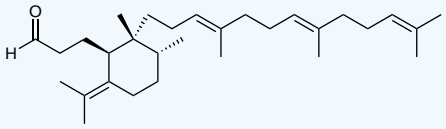
Like all Eschenmoser fragmentations, the reaction will ultimately cleave the alkene bond in the original conjugated enone. The means that the alkene carbon farthest from the carbonyl (the beta carbon) will turn into the product ketone while the other carbon from the alkene and the ketone carbon will turn into the product alkyne. Applying this along with the mechanism show above yields the target, containing one fewer ring than the starting material.



Summary Problems

Exercise 3.4.5

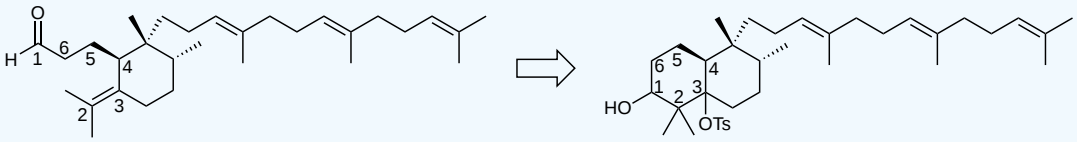
The triterpene shown below was shown to arise biosynthetically via a Grob fragmentation. Propose a reasonable precursor that would participate in this fragmentation to yield the given target.



Answer

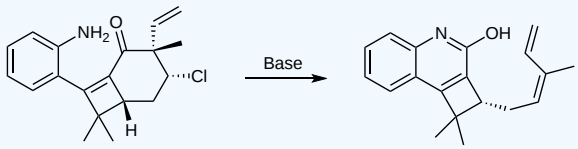
Returning to our introduction of the Grob fragmentation above, we can see that the product has a carbonyl at C1 and an alkene between C2 and C3. This means for our 1,3-diol type starting material, we need the alcohol at C1 and the leaving group at C3. We also need a bond between C1 and C2 that will cleave during the fragmentation reaction. That means our starting material is the bicyclic molecule shown below.

Reference - *Angewandte Chemie* 2006



Exercise 3.4.6

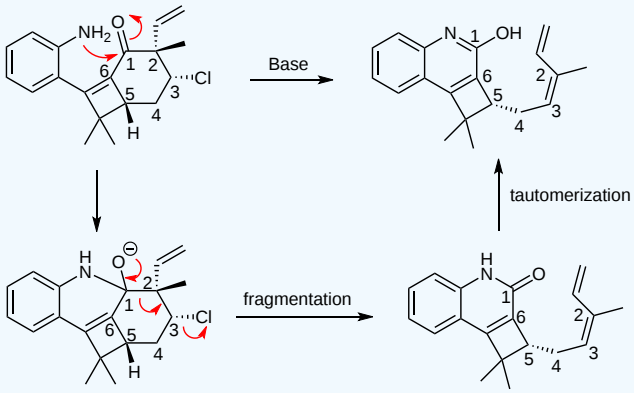
The following undesired reaction occurred during John Wood's synthesis of welwitindolinone. Propose a mechanism to explain this transformation. Hint: The final step of the mechanism is a tautomerization reaction to generate the bicyclic aromatic system from a lactam.



Answer

The mechanism starts with an intramolecular carbonyl addition of the amine to the ketone. (Base removes a proton from the amine after the addition.) The resulting tetrahedral intermediate is set up perfectly for a fragmentation due to the chloride leaving group at the 3-position. So, the carbonyl reforms, the C1-C2 bond cleaves to form the C2-C3 alkene, and chloride leaves. This yields a lactam that tautomerizes to the product quinoline structure.

Reference: *Journal of the American Chemical Society* 2008



Contributors

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4: Radical Reactions

Learning Objectives

After completing this section, you should be able to:

1. Understand radical reactions involved in functional group conversions and carbon-carbon bond formation
2. Understand radical chain reactions and radical combination reactions
3. Draw mechanisms incorporating radicals to explain reaction outcomes
4. Plan syntheses using radical reactions

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Radical initiation
- AIBN
- Radical propagation
- Bu_3SnH
- Radical termination
- Barton-McCombie deoxygenation
- Barton decarboxylation
- Hofmann-Loeffler-Freytag reaction
- Pinacol reaction
- McMurry reaction
- Acyloin reaction

Study Notes

Radical reactions are nearly always covered in Intro Orgo. Students generally learn about radical chain reactions for the bromination of alkanes (with Br_2) and alkenes (with HBr and peroxides). They also often encounter allylic and benzylic bromination with NBS (a very interesting mechanism involving polar steps as part of a radical chain reaction). In this chapter, we will highlight several other useful radical chain reactions for functional group interconversions and, most importantly, for carbon-carbon bond formation. These reactions will proceed by the standard outline you have seen before: initiation with a radical initiator and propagation with a radical propagator. We will also meet synthetically useful radical reactions that proceed by a process called radical combination. These will look like termination steps from a radical chain reaction but they will be the productive pathway yielding our desired product. Radical reactions are currently a very popular research area, with many top synthetic organic labs working to develop useful transformations that are impossible using polar reactions. The information you learn in this chapter will help you understand these recent developments.

Don't forget that all mechanisms in this chapter involve the movement of single electrons (radicals!), so we will use **single-headed arrows** in our mechanisms.

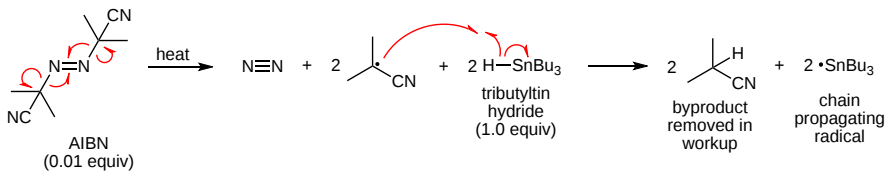
Content

Our goal in this chapter is to introduce fundamental radical reactions that you will likely encounter in organic synthesis papers. This will build on what you have already learned in Intro Orgo about bromination reactions with bromine as the chain propagating radical by demonstrating the power of radical reactions using tributyltin radicals. These transformations will enable dehalogenation, decarboxylation, and deoxygenation reactions. Most importantly, they will demonstrate the utility of radical reactions for the synthesis of carbon-carbon bonds, especially 5- and 6-membered rings. We will also see the power of radical combination reactions for remote functionalization that can lead to the synthesis of heterocyclic ring systems.

Initiation and Propagation Steps

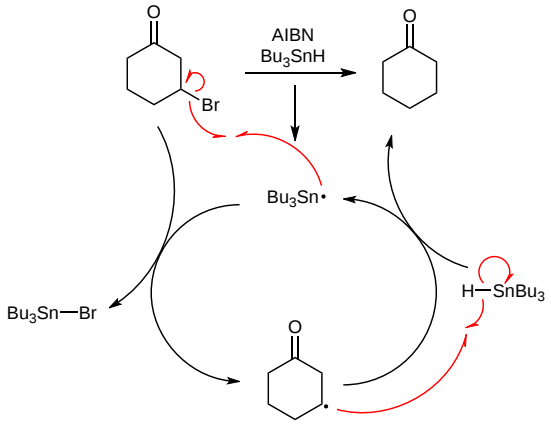
Before getting into the actual radical reactions, we first need to comment on two key reagents: AIBN (AzobisIsoButyroNitrile) and Bu_3SnH (tributyltin hydride). We will use AIBN as our radical initiator and Bu_3SnH as the precursor for our chain propagating radical, tributyltin radical. Upon heating, AIBN cleaves to form nitrogen gas and two radicals that react with Bu_3SnH to yield two tributyltin radicals, as shown below. Tributyltin is our chain propagating radical, so these two radicals can each start a radical chain process (the propagation steps) resulting in the production of our desired molecule. Please remember a few key points about initiation and propagation steps: 1) We only need a small amount of the initiator to begin the chain process. Generally, 1 mol% of AIBN (0.01 equivalents) is sufficient to generate enough tributyltin radicals for the propagation steps. Although not a true catalyst, you can think about AIBN like the catalyst that must be present to make the chain reaction possible. 2) The chain propagating radical, tributyltin radical, must be a reactant in your first propagation step and a product in your last propagation step. Tributyltin radical looks a bit like a catalyst (think Pd(0) in a Stille or Suzuki reaction) but it is different in a key way. Tributyltin hydride is consumed in the reaction and must be present in a stoichiometric amount (at least 1.0 equivalents) or the chain will be broken before all of the starting material reacts. Don't forget, the propagation steps are the only productive steps in a chain reaction. This is where your product is formed. 3) Termination steps break the chain and are undesired. In radical chain reactions, combining two radicals to form a new bond is never a productive reaction. Your product will never come from a termination step. These molecules are undesired byproducts and their formation must be very limited for the radical chain reaction to be synthetically useful.

Initiation Steps with AIBN and Bu_3SnH



Dehalogenation Reactions

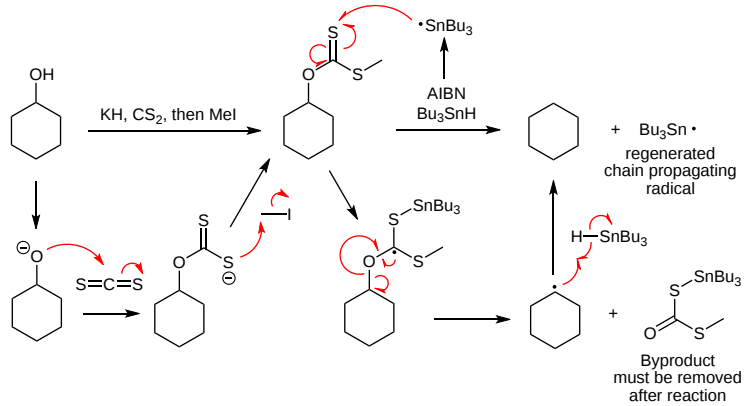
Tributyltin hydride is a useful reagent for the dehalogenation (reduction) of alkyl halides. This illustrates a radical chain mechanism using tributyltin as the chain propagating radical. (As always, AIBN and tributyltin hydride combine in the initiation steps shown above to produce tributyltin radical.) Once the tributyltin radical is formed, it reacts to form a new Sn-Br bond by cleaving the C-Br bond to generate a carbon radical. This forms tributyltin bromide, a byproduct that must be removed after the reaction, and the new carbon radical that is part of our chain process. The carbon radical reacts with tributyltin hydride (remember, we have a very small amount of AIBN, just enough to start the process, and at least 1 equivalent of Bu_3SnH to react completely with the alkyl bromide starting material) to form the new C-H bond in the product and another molecule of tributyltin radical that can participate in another cycle of the chain process.



Barton-McCombie Deoxygenation

Similar to the dehalogenation reaction above, radical reactions can be used to remove an alcohol from a molecule, thus deoxygenating (reducing) the compound. We need to use some unusual chemistry to make the deoxygenation possible, specifically

we need to form a xanthate, a functional group similar to a carbonate that contains two sulfur atoms. One of the sulfurs is part of a thio carbonyl (C=S) which is very reactive toward radical reactions and readily reacts with tributyltin radical to form a Sn-S bond and a carbon radical. To form the xanthate, we react the alcohol with potassium hydride to generate a negatively charged oxygen nucleophile. This reacts with carbon disulfide (the sulfur equivalent of carbon dioxide) and then methyl iodide to generate the xanthate intermediate. Once the xanthate is formed, it can react with tributyltin radical to participate in our radical chain reaction. The first step generates a new S-Sn bond and a carbon radical that decomposes to yield a dithiocarbonate ester (a byproduct that must be removed after the reaction) and a new carbon radical. At this point, the molecule has been successfully deoxygenated and the final step with tributyltin hydride completes the reaction by forming a C-H bond and regenerating the chain propagating tin radical.



Barton Decarboxylation

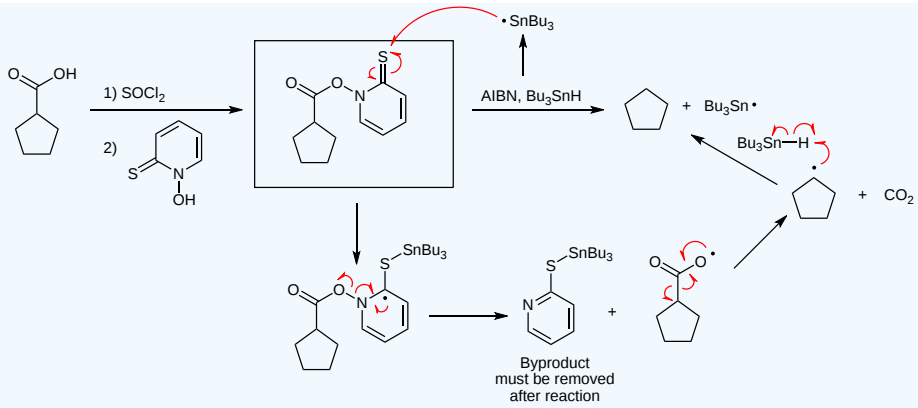
You likely learned about polar decarboxylation reactions in Intro Orgo. These reactions enable the removal of a carboxylic acid in a 1,3-carbonyl acid functional group. The second carbonyl positioned beta to the carboxylic acid carbonyl is critical in the mechanism (either acidic or basic conditions). These polar reactions do not work when the other carbonyl is absent. Thus, a decorboxylation reaction that doesn't require the presence of a second carbonyl at a specific position is highly valuable for synthetic chemists. This example highlights the importance of the Barton decarboxylation, a radical decarboxylation that is similar to the deoxygenation reaction shown above. It relies on a different reagent than the deoxygenation, so a xanthate ester isn't formed, but the steps are very similar, including reaction of tributyltin radical with a thiocarbonyl. In the problem below, you can propose a mechanism for this interesting reaction.

? Exercise 4.1

The reaction scheme below illustrates the multistep Barton decarboxylation reaction. Predict the product of the first two steps. Then, using that product, provide a mechanism for the radical decarboxylation step.

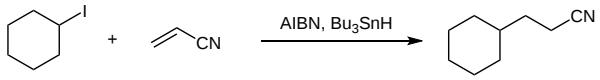
Answer

The first two steps are Intro Orgo reactions. Thionyl chloride converts the carboxylic acid into an acid chloride that reacts withe the hydroxyl amine (fancy alcohol) to generate the hydroxyl amine ester product. As we saw previously, the C=S bond reacts readily with a tributyltin radical. The resulting carbon radical can generate a very stable pyridine byproduct upon cleavage of the weak N-O bond. This generates an oxygen radical that can yield carbon dioxide, thus driving this step, via C-C bond cleavage. This is the key decarboxylation step. The resulting carbon radical combines with tributyltin hydride to yield the product and regenerate the chain propagating radical.

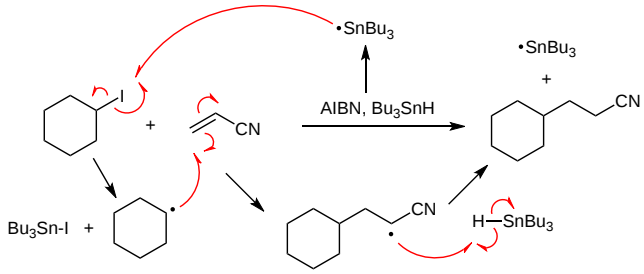


Carbon-Carbon Bond Forming Reactions

Radical chain reactions mediated by Bu_3SnH can also promote the formation of carbon-carbon bonds. These are among the most important radical reactions in synthetic chemistry since they provide us with another option in our toolbox of methods to make critical molecular connections. Key components in these reactions are a carbon-halogen bond that can react with the chain propagating tributyltin radical to generate a carbon radical that combines with an alkene or alkyne to form the new carbon-carbon bond. These reactions occur both inter- and intramolecularly with the latter being favored for higher yields and better regioselectivity. Radical reactions are kinetically controlled so they provide a very useful strategy for the synthesis of 5-membered rings. This is even true for most instances when selecting between the formation of 5- versus 6-membered rings in intramolecular cyclization reactions. (The smaller ring forms faster and, thus, is favored.) In intermolecular reactions, it is often helpful to have an electron poor alkene or alkyne as the radical partner to help favor regioselectivity with the (generally) more substituted radical formed in the first step. An example reaction and mechanism are shown below for a standard intermolecular carbon-carbon bond forming reaction. An intramolecular example is shown in the following problem.

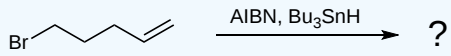


Mechanism



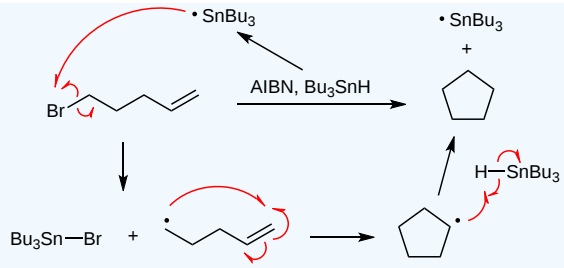
Exercise 4.2

For the following intramolecular C-C bond forming reaction, predict the product and propose a mechanism for its formation.



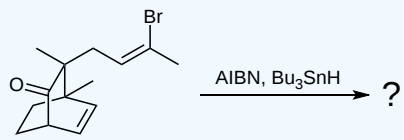
Answer

Like in our intermolecular example above, the tributyltin radical attacks the carbon-halogen bond to yield a carbon radical. This new radical participates in an intramolecular C-C bond forming reaction to form a 5-membered ring radical that reacts in the final step to form the product and regenerate the chain propagating radical. Note, because of ring strain, we won't form the 4-membered ring resulting from addition to the other side of the alkene.



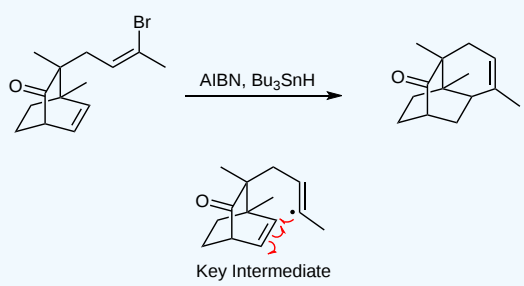
? Exercise 4.3

Predict the product of the following reaction.



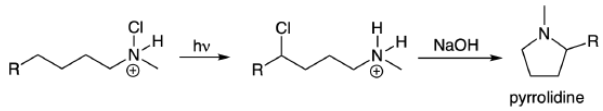
Answer

This problem highlights that radicals can easily form on sp^2 carbons and is a reminder that bond rotation is always important to consider. The key intermediate forms and reacts to yield the new 6-membered ring which forms faster than the 7-membered ring alternative.

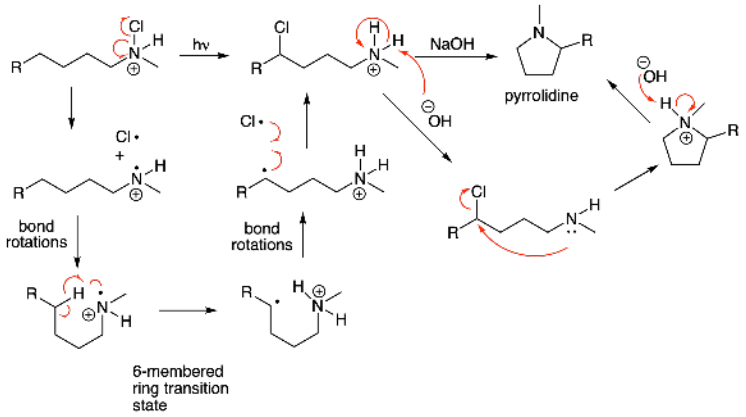


Non-Chain Radical Combination Reactions

Some highly useful radical reactions involve the combination of two radicals to form an important new bond. (These look like a termination step in a radical chain mechanism.) These reactions have become increasingly relevant as new and more mild methods for Hydrogen Atom Transfer (HAT) reactions have recently been developed. We will explore some classic examples in this class of radical reactions which you can then apply to understand more contemporary transformations. The **Hofmann-Loeffler-Freytag** reaction enables remote functionalization of a haloamine that ultimately results in the formation of a new pyrrolidine ring (saturated 5-membered ring containing N). The reaction and mechanism are shown below. The first step in the reaction is the radical portion of the mechanism. (The chloroamine can be formed by treating the amine with t-butyl hypochlorite (tBuOCl).) Light promotes homolytic cleavage of the weak N-Cl bond to yield a Cl radical and an N radical. The next steps help explain the highly selective nature of this reaction. Bond rotation enables a HAT via a highly favored six-membered ring transition state that also transforms the reactive nitrogen radical into a more stable secondary carbon radical. The product of the first portion of the reaction forms via a radical combination reaction of the initially generated Cl radical with the newly formed C radical. This 1,4-chloroamine can undergo an intramolecular S_N2 reaction to yield the pyrrolidine product. A related example of a Hoffmann-Loeffler-Freytag reaction to yield a lactam is shown in the next problem.

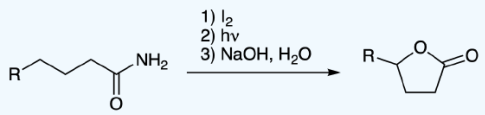


Mechanism



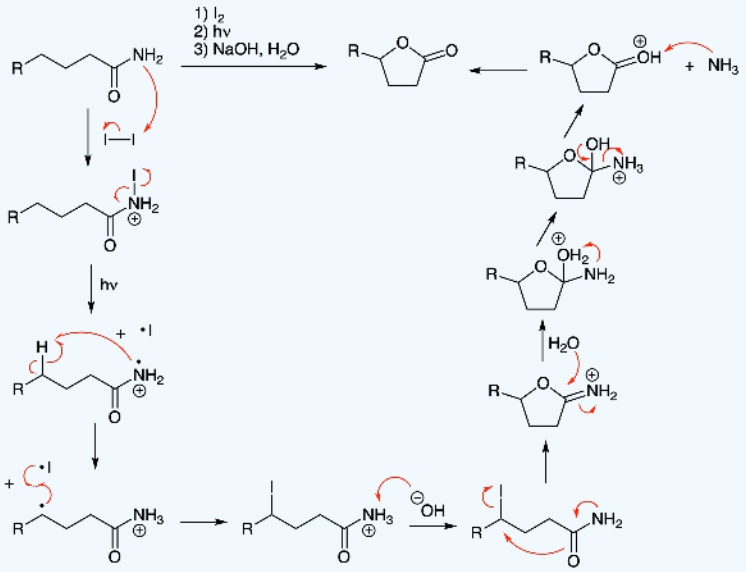
Exercise 4.4

Propose a mechanism for this Hofmann-Loeffler-Freytag reaction.



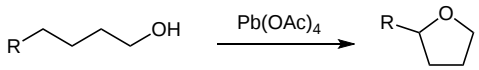
Answer

Iodine promotes formation of the requisite haloamine via a substitution reaction. Light initiates the radical portion of the mechanism which proceeds via the key six-membered ring transition state as shown in the prior example. After the radical combination reaction to yield the iodo amide, hydroxide deprotonates the nitrogen making the amide nucleophilic. Attack by the more reactive O yields the iminium ion-type intermediate that undergoes hydrolysis to ultimately yield the target lactone.

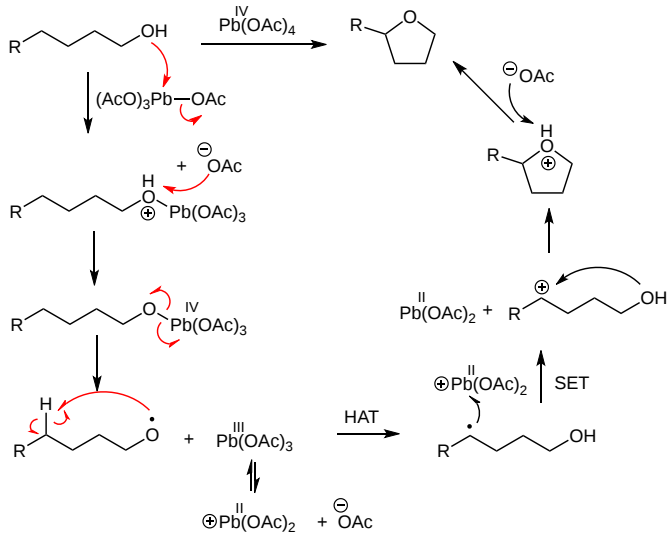


A related reaction promoted by lead tetraacetate ($Pb(OAc)_4$) that proceeds via a key oxygen radical provides a synthetically useful method for the synthesis of tetrahydrofurans. As shown below, treatment of an alcohol with $Pb(OAc)_4$ yields a substituted tetrahydrofuran (THF). The mechanism does not have a radical combination step, instead relying on a Single Electron Transfer (SET) process between a carbon radical and lead to yield a carbocation. The mechanism begins with a substitution reaction on lead with the starting alcohol. The new O-Pb bond is weak and can homolytically cleave to yield Pb(III) and an oxygen radical. Like in the Hofmann-Loefflear-Freytag reaction, the oxygen radical does a Hydrogen Atom Transfer (HAT) step via a 6-membered ring

transition state to yield a carbon radical that reacts with a formally positive Pb(II) via SET. Thus, the lead is reduced and the carbon is oxidized to a carbocation that readily reacts with the intramolecular alcohol to yield the desired THF.

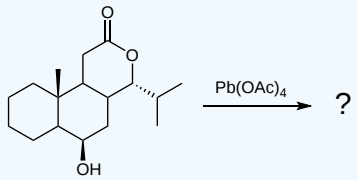


Mechanism



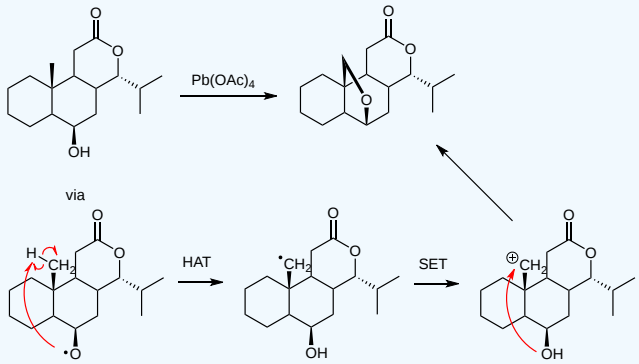
Exercise 4.5

Propose a product for the following reaction.



Answer

Like in the mechanism above, the lead reagent will promote formation of an oxygen radical from the alcohol. This will participate in a HAT reaction with the methyl group, followed by a SET reaction, and finally cyclization to form the new 5-membered ring.

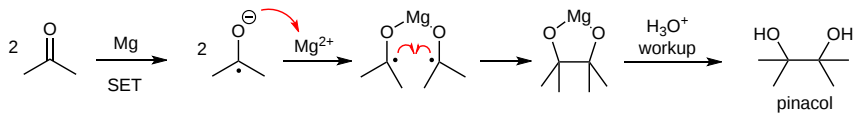


Other useful radical combination reactions involve dimerization of carbonyl starting materials. The three most popular are the **pinacol reaction**, the **McMurry reaction**, and the **acyloin reaction**. These involve starting with ketones (pinacol and McMurry) or

esters (acyloin) and adding a strong metal reducing agent like sodium, magnesium, or titanium to generate ketyl radicals that dimerize and ultimately produce diol (pinacol), alkene (McMurry), or keto alcohol (acyloin) products. Intermolecular examples of each are shown below. Intramolecular reactions are also possible and will occasionally show up in total synthesis papers.

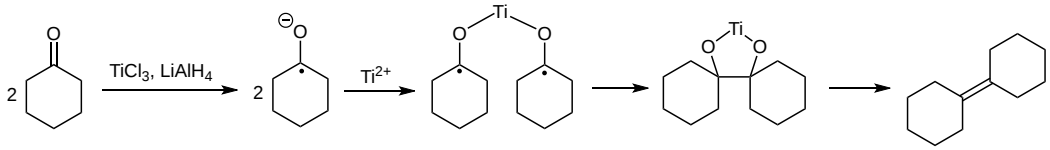
Pinacol Reaction

Two equivalents of acetone react with magnesium metal via Single Electron Transfer (SET) to yield two radical anions (ketyl radical anions). These two anions react with cationic magnesium (+2) to yield the neutral diradical that undergoes a radical combination reaction to form a new carbon-carbon bond. The resulting 5-membered ring breaks down in the acidic workup to yield the diol product. In this case, the product is pinacol, the starting point for the pinacol rearrangement that we saw in Chapter 3.



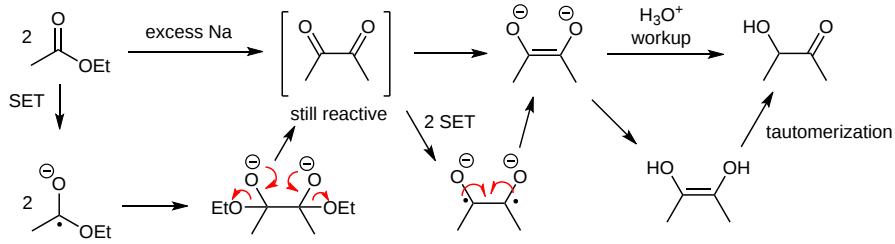
McMurry Reaction

The McMurry reaction is nearly identical to the pinacol reaction except for the final step. The key difference is the use of titanium metal, generated in situ from titanium trichloride and lithium aluminum hydride. Titanium reacts with two ketones to yield two ketal radical anions that react with cationic titanium to yield a neutral diradical. The diradical participates in the radical combination reaction to yield a new 5-membered ring include a new C-C bond. At this point, the McMurry reaction diverges from the pinacol reaction. The titanocycle is not stable, instead it undergoes a deoxygenation reaction to yield an alkene product. Overall, the McMurry reaction acts like a reverse ozonolysis reaction by combining two ketones to yield an alkene.



Acyloin Reaction

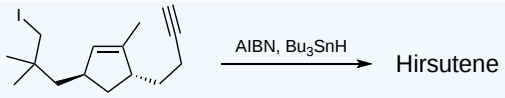
The acyloin reaction begins just like the pinacol reaction with SET reactions to yield two radical anions. Dimerization (radical combination) yields the new carbon-carbon bond and an intermediate that looks like a double tetrahedral intermediate from the carbonyl addition section of Intro Orgo. Accordingly, ethoxide is a good leaving group which promotes formation of a 1,2-diketone. This compound is highly reactive toward reduction, so it will accept two more electrons from sodium to yield a diradical dianion. Radical combination generates a new pi bond. This diradical is stable and is quenched in the workup to produce a diol. Since this is an enol, it will tautomerize to yield the keto alcohol product.



Summary Problems

? Exercise 4.6

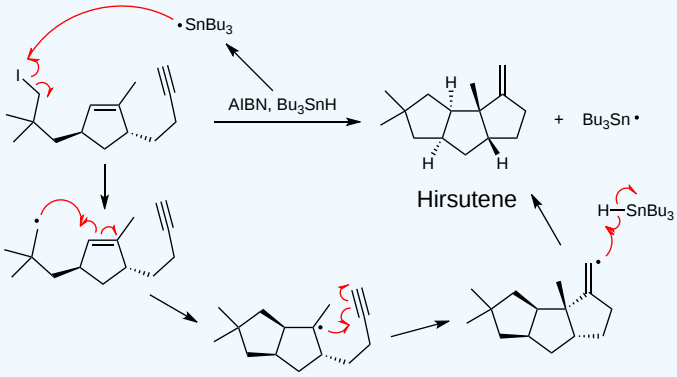
One of the most powerful examples of the utility of carbon-carbon bond forming radical reactions in synthesis is Curran's synthesis of hirsutene published in 1985. The reaction below is the final step in the synthesis. Propose the structure of hirsutene and a mechanism for its formation.



Answer

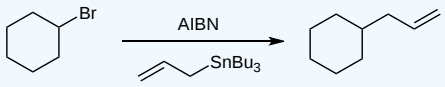
DOI - https://doi.org/10.1021/ja00291a077

This follows the pattern we observed previously. The tin radical reacts with the iodide to form a carbon radical that reacts with the alkene to form a new 5-membered ring. The resulting tertiary radical reacts with the alkyne to form the third 5-membered ring in hirsutene. Note that the stereochemistry in the starting material determines the stereochemistry in the product. The alkyl chain coming out forms a new bond from above the initial 5-membered ring. The alkyl chain going back forms a new bond from beneath the initial 5-membered ring.



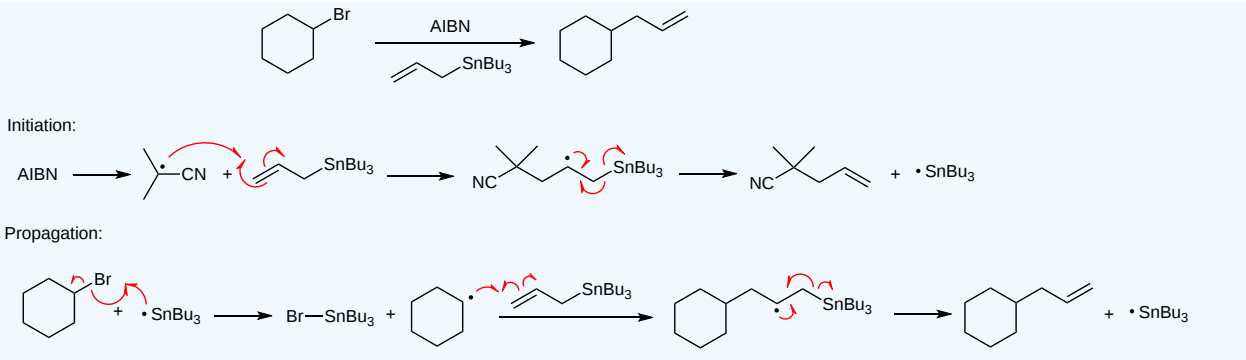
Exercise 4.7

Though much less common, it is possible to use tin reagents other than tributyltin hydride to promote carbon-carbon bond forming reactions. One example is allyl tributyltin. An example of this reaction is shown below. Propose a mechanism for the initiation and propagation steps. Hint: Like in all of our other reactions with tin, tributyltin radical is the chain propagating radical.



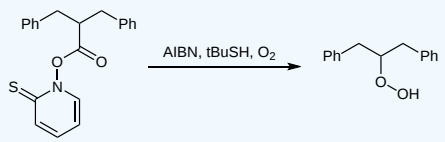
Answer

Without a Sn-H bond, radicals that react with the allyl tin reagent must add to the alkene, like we have seen in other radical reactions in this section. So, for the initiation steps, the initiating radical adds to the alkene then the resulting carbon radical decomposes to yield an allyl group on the initiating group plus the chain propagating tin radical. In the propagation steps, the first step is our standard Sn + Br to yield the first carbon radical. The only option for the new carbon radical is to add to the alkene of the tin allyl group. This generates a secondary carbon radical than decomposes just like in the initiation steps, leaving the allyl group on the product and regenerating the chain propagating tin radical. Note: alkenes are much more reactive that C-C or C-Sn single bonds.



? Exercise 4.8

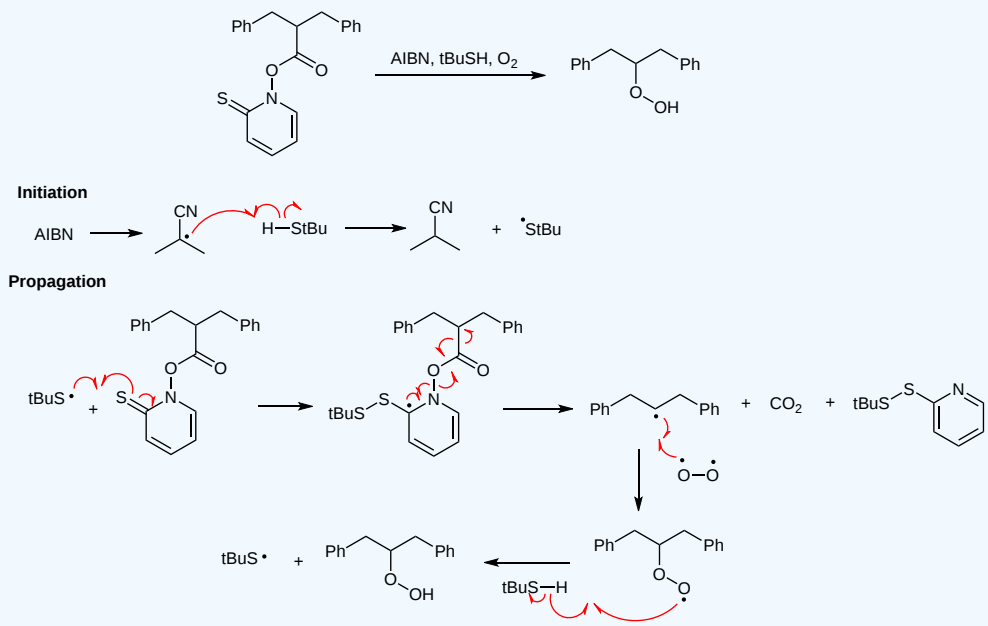
Provide a mechanism for the reaction shown below. Hints: 1) Don't forget about the ground state structure/behavior of oxygen. 2) *t*-BuSH reacts similarly to Bu_3SnH.



Answer

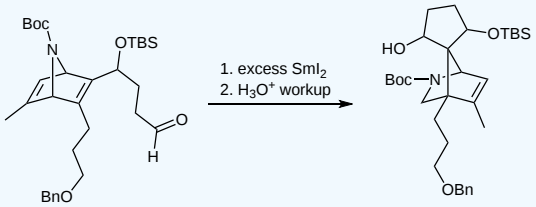
The mechanism begins with standard initiation steps. AIBN generates the initiating carbon radical that reacts with t-butyl thiol to yield the chain propagating S radical. Since this behaves like the tributyltin radical, it will add to the weak C=S making a new S-S bond and carbon radical. This new radical quickly reacts to generate a stable pyridine, gaseous carbon dioxide, and a new secondary carbon radical. Remembering that oxygen exists as a diradical, we see that the next step is a radical combination between the carbon radical and O_2. In the final step, the remaining O radical reacts with the beginning thiol to generate the product and regenerate the chain propagating radical.

Literature Reference: Barton *Tetrahedron* **1985**



Exercise 4.9

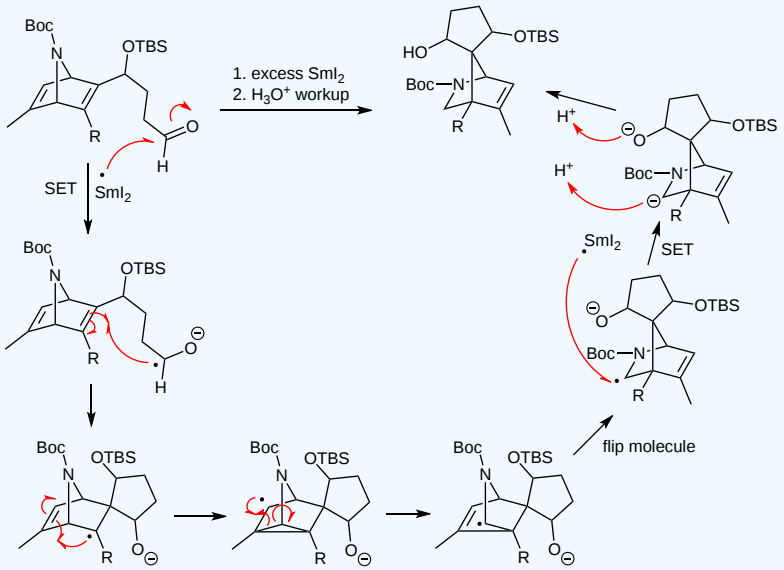
Provide a mechanism for the following transformation. Remember, SmI_2 is an excellent single electron donor. Hint: At some point in the mechanism you will need to form an alpha-N radical (a radical on a carbon next to the N).



Answer

Samarium diiodide starts the reaction by donating an electron (Single Electron Transfer (SET)), to the carbonyl. This yields a radical anion that undergoes a radical cyclization reaction to generate the new 5-membered ring and a tertiary radical. In the next step, this radical adds to the adjacent pi bond to form a transient 3-membered ring and a secondary radical. Regeneration of the alkene enables radical cleavage of the unstable cyclopropane to yield a stabilized alpha-N radical. Another SET mediated by samarium converts the radical into a carbanion. Both anions are quenched in the acidic workup to yield the target molecule.

Literature Reference: Wood *Chemical Science* **2020**



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5: Carbene Reactions

Objectives

After completing this section, you should be able to:

1. Understand the structure of singlet and triplet carbenes
2. Understand how to generate carbenes and carbenoids
3. Understand carbene reactions involved in cyclopropantion and C-H insertion reactions
4. Draw mechanisms incorporating carbenes to explain reaction outcomes
5. Plan syntheses using carbene reactions

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Singlet carbene
- Triplet carbene
- Carbenoid
- Alpha Elimination
- Cyclopropanation
- Simmons-Smith reaction
- C-H Insertion

Study Notes

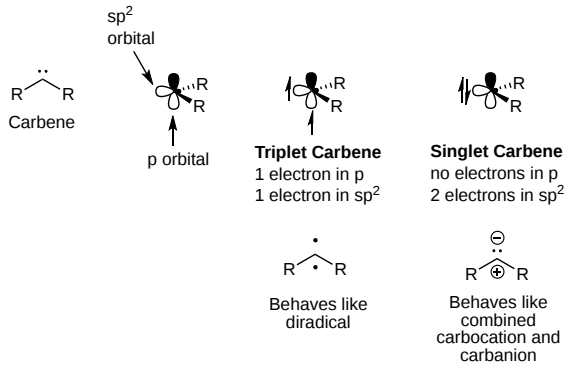
Carbenes are the final member in the four reactive intermediates of carbon, joining carbanions, carbocations, and radicals. It is unusual to meet carbenes in Intro Orgo, so it is often a shock to realize there is a brand new version of reactive carbon that wasn't encountered earlier. Carbenes are much less important that the other three intermediates mentioned above, and we will learn only a few fundamental reactions to make them and two reactions that carbenes participate in. They provide us with one critical synthetic transformation, cyclopropanation. This reaction is the most important transformation of carbenes, and it functions as the carbon equivalent of MCPBA epoxidation. The reactivity of carbenes can be tuned by coordination with a variety of metals to form metal carbenoids. We will mention this briefly and encourage you to learn more about this fascinating research topic if you are interested.

Content

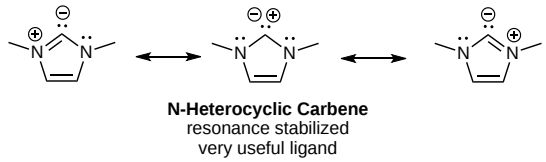
Our goals in this chapter are three-fold: 1) Understand the structure of carbenes. 2) Understand how to make carbenes and carbenoids. 3) Understand carbene cyclopropanation and carbene C-H insertion reactions. These topics cover the fundamentals of carbenes and carbene reactions and will prepare you to use and understand carbenes in the context of organic synthesis.

Carbene Structure

A carbene is a neutral form of carbon that has two bonds and two additional electrons. It is highly reactive because it has an incomplete octet with only six electrons around carbon. Carbenes can exist with their nonbonding electrons as either a lone pair or two radicals. The diradical form is known as a triplet carbene, while the structure with a lone pair is called a singlet carbene. Carbene structure is not always obvious and can depend on the method used to make the carbene. However, since we are often more comfortable thinking about carbocations and carbanions than radicals, we will simplify our analysis of carbenes and assume that they are singlet carbenes. Again, this is an oversimplification, and you are encouraged to learn more about carbenes and their structure if you are interested. Getting back to singlet carbenes, since they contain both a lone pair in a hybrid orbital (sp^2) and an empty p orbital, they behave as if they are simultaneously a carbanion and a carbocation. This strange combination leads to unique reactivity. To help us recognize this type of reactivity, we will draw carbenes with both a positive and negative formal charge, thus indicating that they are neutral but highly reactive.

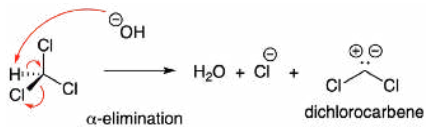


One relatively stable and popular class of carbenes are N-heterocyclic carbenes. These molecules are very useful as organometallic ligands, and they are seen frequently in organic synthesis.

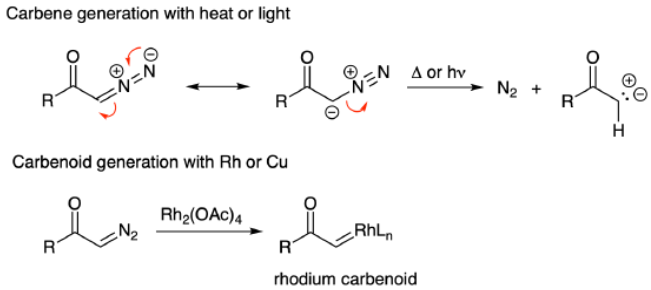


Carbene Synthesis

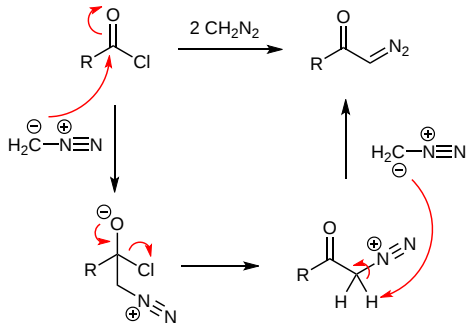
The two most popular methods for the synthesis of carbenes are from **alpha-elimination of a halo compound** and from **decomposition of a diazo compound**. A common example of the alpha-elimination reaction is the deprotonation reaction of chloroform with hydroxide to yield dichlorocarbene.



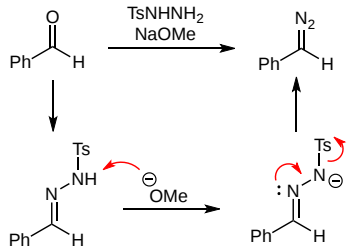
Diazo decomposition is the preferred method for carbene and carbenoid generation and occurs upon exposure to heat, light, or a metal promoter (like Rh or Cu). A standard carbene can be generated from any diazo compound with heat or light with loss of nitrogen gas. Treating a diazo compound with a metal converts the diazo into a metal carbenoid. In the example below, rhodium acetate enables formation of a rhodium carbenoid. (Note: the "L_n" in the structure means some number of acetate ligands are attached to rhodium.) Rhodium and copper carbenoids have very similar reactivity to carbenes; however, the metal carbenoids are often more selective and their reactivity can be tuned based on the ligands present on the metal.



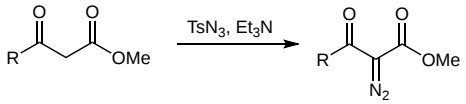
Before continuing on to carbene reactions, it is important to comment on how diazo compounds are generated. The most popular methods start with an acid chloride, an aldehyde, or a 1,3-dicarbonyl. Treating an acid chloride with two equivalents of diazomethane yields an alpha-diazo ketone. The first equivalent of diazomethane participates in a carbonyl substitution reaction. The second equivalent is the base that deprotonates the diazonium intermediate to yield the diazo product.



Treating an aldehyde with tosylhydrazine and base yields a diazo compound. As expected, tosylhydrazine reacts with the aldehyde to yield a tosylhydrazone. Methoxide removes the acidic N-H proton. The resulting anion undergoes loss of tosyl to yield the neutral diazo product.



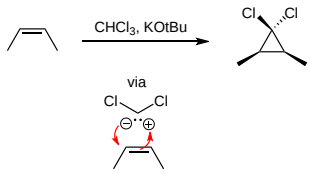
1,3-Dicarbonyl compounds readily undergo diazo transfer reactions where an azide donates two nitrogens to form the diazo product. An example using tosyl azide is shown below. A variety of azides can participate in these reactions.



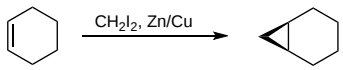
Carbene Reactions

Cyclopropanation Reactions

The most important carbene reactions are ones that enable formation of cyclopropanes. Depending on the structure of the target cyclopropane, different carbene starting materials are employed. If a dihalocyclopropane is the target, then a standard alpha-elimination reaction is used. As shown below, treating the starting alkene with chloroform and a base readily yields a dichlorocyclopropane product. The reaction mechanism is a stereospecific, concerted process.



When the goal is synthesis of a cyclopropane bearing a new CH_2 group, the best option is the **Simmons-Smith reaction**. As shown below, combination of an alkene with diiodomethane and a Zn/Cu metallic couple yields the target cyclopropane. In the mechanism of this reaction, a free carbene is not formed. Instead, zinc first does an oxidative addition with one of the C-I bonds. The resulting organozinc intermediate behaves like a carbene, participating in a concerted reaction with the alkene to yield the cyclopropane and zinc(II) iodide.



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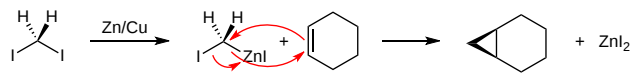
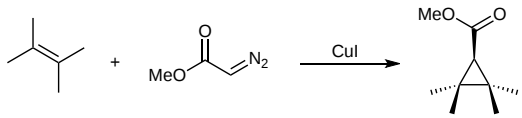
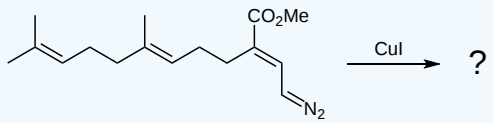


Generating more highly substituted cyclopropanes involves the use of diazo compounds in both inter- and intramolecular reactions. Synthesis applications often take advantage of the increase in structural complexity available with intramolecular cyclopropanation reactions. An intermolecular example is shown below while an intramolecular reaction is featured in the following problem. The example problem below highlights a synthesis that proceeds via a copper carbenoid.



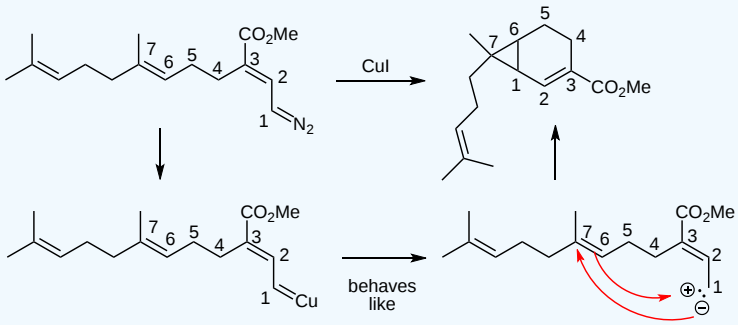
? Exercise 5.1

Propose the product of the following reaction.



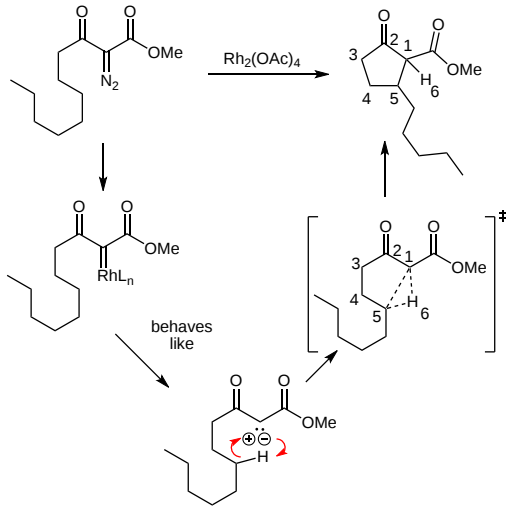
Answer

Copper reacts with the diazo compound to form a copper carbenoid. This reacts like a carbene to enable an intramolecular cyclopropanation reaction. In addition to the 3-membered ring, the reaction is selective for the production of the favored 6-membered ring as part of the bicyclic product.



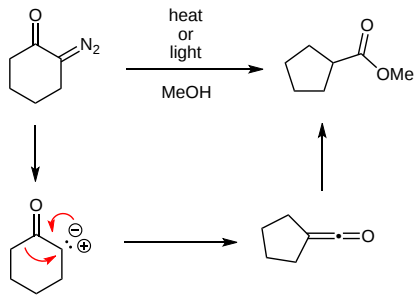
C-H Insertion Reactions

C-H insertion reactions provide another reaction pathway for carbenes. (As we will see shortly, C-H insertion reactions adjacent to the carbene carbon to yield an alkene are a major limitation in carbene applications.) Intramolecular C-H insertion reactions provide another method for the synthesis of 5-membered rings. As we have seen previously, this results from a favorable 6-membered ring transition state. In the example below, a rhodium carbenoid forms first. There is no alkene for a potential cyclopropanation reaction, so a C-H insertion reaction occurs. The most favorable 6-membered ring transition state yields the 5-membered ring product.

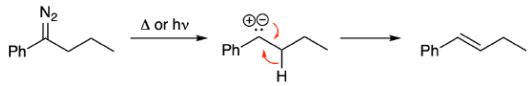


Limitations of Carbene Reactions

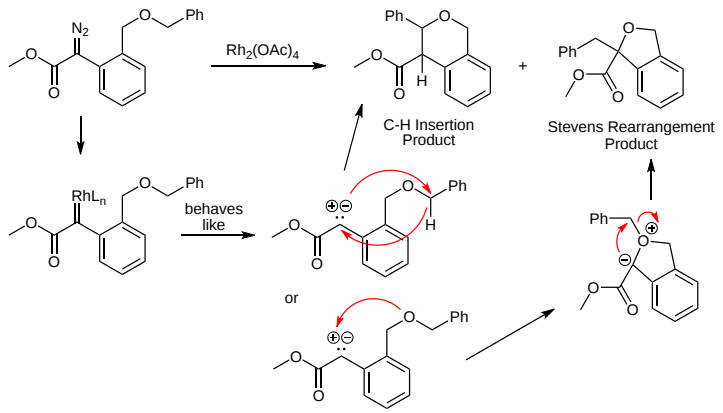
When planning carbene reactions, there are several limitations to be aware of. First, don't forget that alpha-diazo ketones also participate in **Wolff rearrangements** (as we saw in Chapter 3 and mentioned in Exercise 3.3.8). The mechanism introduced in Chapter 3 did not involve a carbene. However, it is possible to draw an alternate mechanism that proceeds via a carbene. Compare the following mechanism to the one provided in the answer to Exercise 3.3.8. Both proceed to a ketene, they just get there in different ways. The preference for the Wolff rearrangement is to draw it as a carbene mechanism.



Second, carbenes with an adjacent C-H bond often undergo **C-H insertions** to yield an alkene before participating in cyclopropanation or C-H insertion to form a ring. This can be mitigated by some metal carbenoids, but it is always important to be wary of this undesired side reaction.



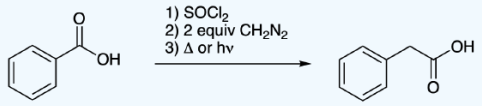
Third, nucleophilic atoms, like oxygens in ethers, can add directly to the carbene and produce rearrangement products. This is called the **Stevens rearrangement** and an example is provided below. The rhodium carbenoid reacts by the expected C-H insertion reaction to yield a new 6-membered ring (the ether O blocks formation of a 5-membered ring since there are no C-H bonds at this position), and it also reacts via a Stevens rearrangement to yield a 5-membered ring cyclic ether. In this mechanism, the ether O adds to the empty p orbital of the carbene then the resulting carbanion participates in a substitution reaction with the oxygen as the neutral leaving group.



Summary Problems

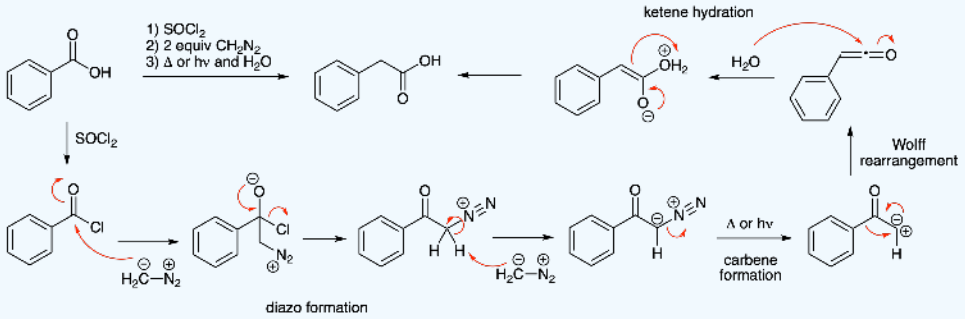
Exercise 5.2

The Arndt-Eistert reaction is useful method for the homologation (extension by one carbon) of carboxylic acids. Propose a mechanism for the second and third steps in this reaction.



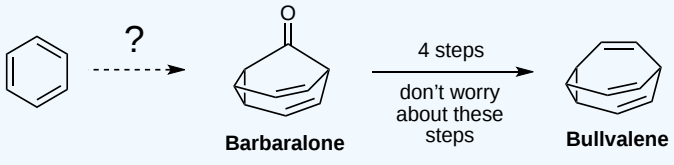
Answer

Thionyl chloride converts the carboxylic acid into an acid chloride. As outlined previously in the chapter, conversion of an acid chloride into a diazo compound happens readily with 2 equivalents of diazomethane. Heat or light will generate the carbene that undergoes a Wolff rearrangement to yield a ketene. Hydration of the ketene yields a carboxylic acid having one more carbon than the starting material.



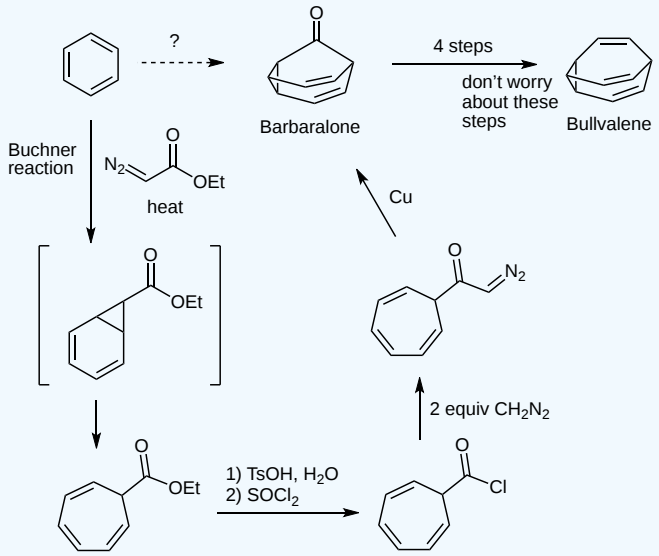
Exercise 5.3

We mentioned the molecule bullvalene in the section on sigmatropic rearrangements in Chapter 1.4. In this problem, we will see several steps in the Doering group's synthesis of bullvalene. A key intermediate in the bullvalene synthesis is barbaralone (named for Barbara Ferrier, the first person to make it). Starting with benzene, how would you make barbaralone? Hint: One reaction in your synthesis should be the Buchner reaction.



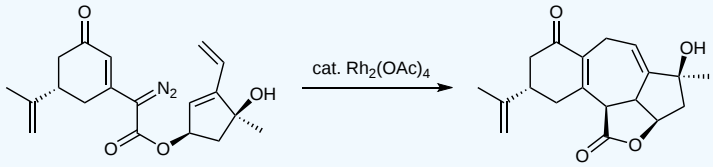
Answer

This synthesis utilizes two carbene steps. In the Buchner reaction, a carbene reacts with benzene to form a cyclopropane that quickly opens via a [3,3] sigmatropic rearrangement to yield a cycloheptatriene. This ethyl ester is hydrolyzed to the carboxylic acid and then the acid chloride. Treatment with 2 equivalents of diazomethane yields an alpha diazo ketone that reacts with copper to furnish a carbenoid that undergoes another cyclopropanation reaction to yield barbaralone.



? Exercise 5.4

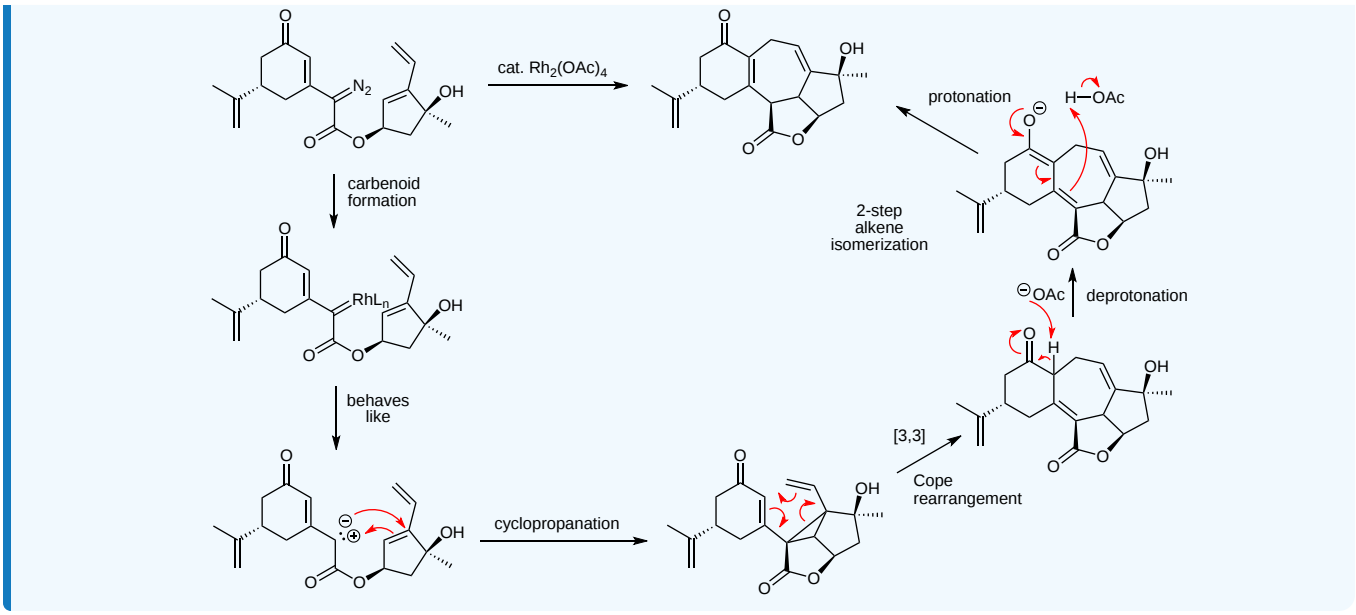
Propose a mechanism for the following transformation.



Answer

Carbenoid formation leads to an intramolecular cyclopropanation that also generates a new 5-membered ring. The cyclopropane fragments via a Cope rearrangement to form the 7-membered ring in the product. The final two steps are a base catalyzed isomerization to yield the desired target.

Literature reference - Stoltz *Chemical Science* **2017**



Contributors

- Prof. Kevin Shea (Smith College)

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