

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

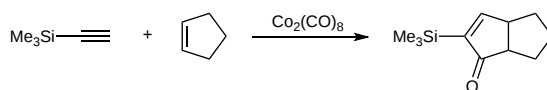
In this chapter, we will learn about two reactions that are commonly promoted by cobalt complexes, the Pauson-Khand reaction for the formation of cyclopentenones and alkyne cyclotrimerization for the synthesis of substituted benzene rings. These transformations are not as common as the Pd-catalyzed bond 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

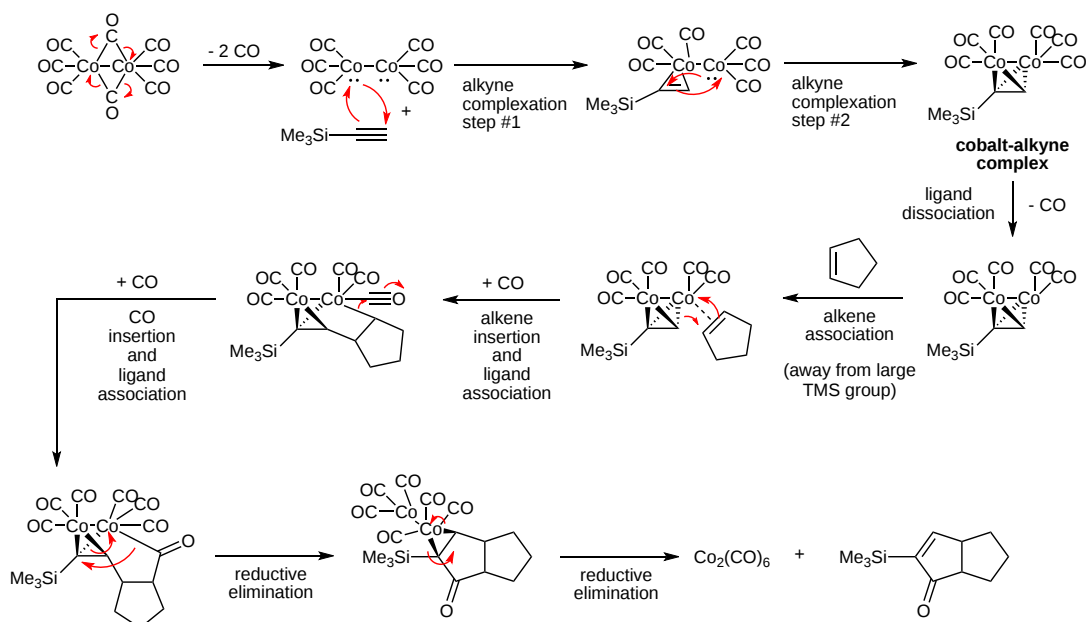
This chapter will focus on ring forming reactions commonly promoted by cobalt. Other metal catalysts or promoters can mediate the Pauson-Khand reaction and alkyne cyclotrimerization reactions. An understanding of the cobalt-mediated reactions will help when you encounter reactions promoted by other metals. 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 site 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 elimination 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.

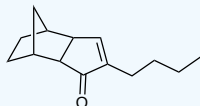


Mechanism



? Exercise 2.4.1

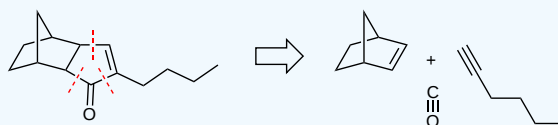
How would you construct the target molecule in one step using a Pauson-Khandt reaction?



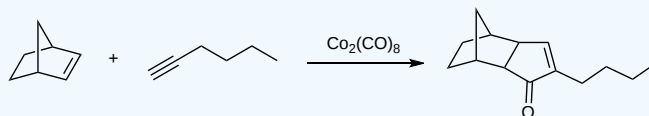
Answer

This molecule contains a cyclopentenone, the Pauson-Khandt 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 materials: 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 $\text{Co}_2(\text{CO})_8$ to yield the target.

Retrosynthetic Analysis

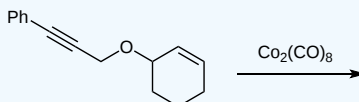


Synthesis



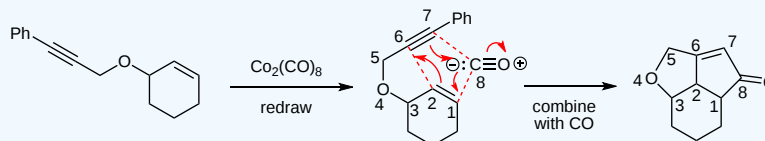
? Exercise 2.4.2

Predict the product of the following reaction.



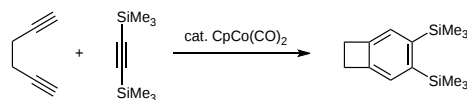
Answer

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.

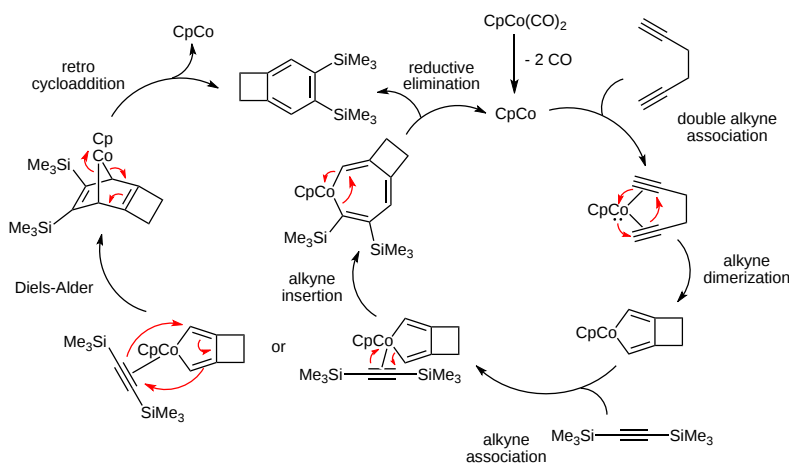


Co-Catalyzed Cyclotrimerization

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.

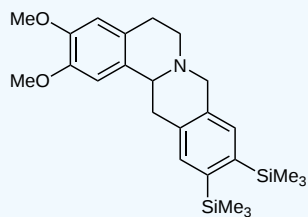


Mechanism



? Exercise 2.4.3

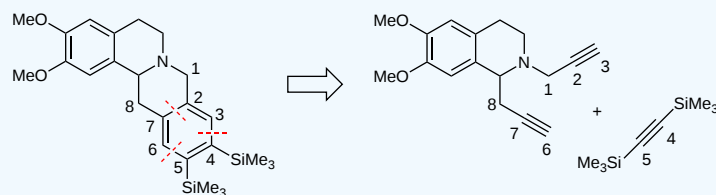
Propose a one step synthesis of the target molecule using a cobalt catalyzed cyclotrimerization reaction.



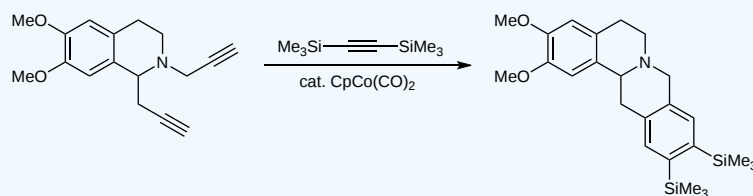
Answer

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.

Retrosynthetic Analysis

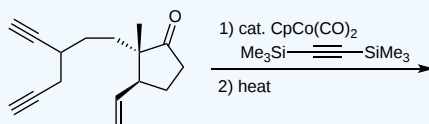


Synthesis



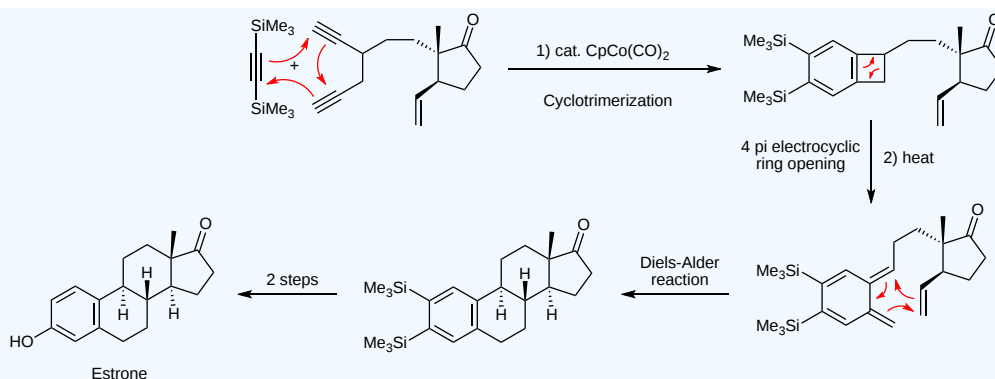
? Exercise 2.4.4

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



Answer

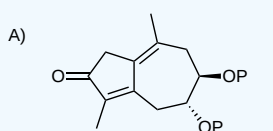
This reaction sequence involves the key steps in Johnson's synthesis of estrone. It begins with a cyclotrimerization to make the cyclobutane-fused benzene. (Note: This is an oversimplified mechanism. The curved arrows do not illustrate the actual mechanism (see above for that). They just help demonstrate 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.



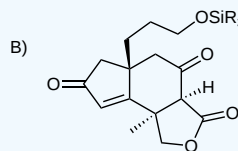
Summary Problems

? Exercise 2.4.5

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

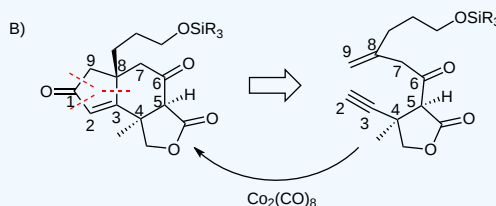
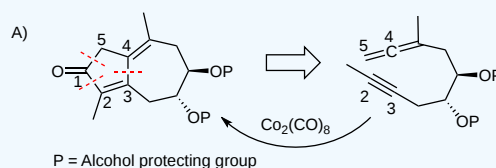


P = Alcohol protecting group



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

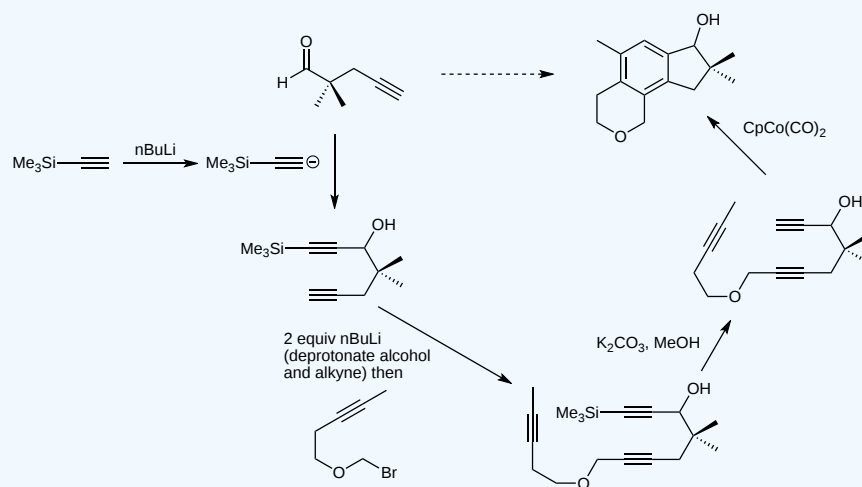
Beginning with the indicated starting material and any other compounds, complete a synthesis of the target (alcyopterosin).



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](#)



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