

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

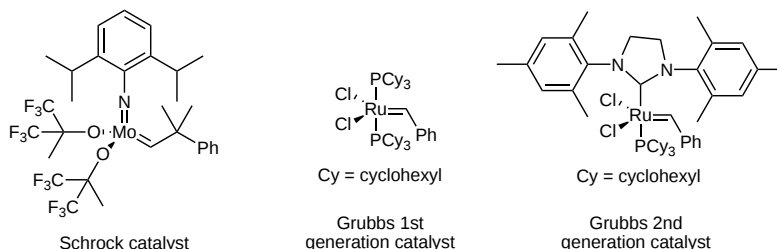
Study Notes

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.

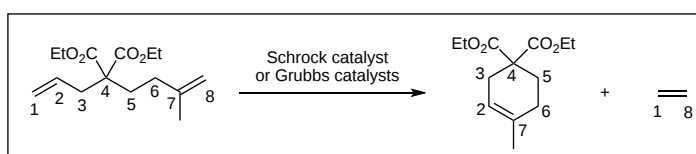
Content

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.

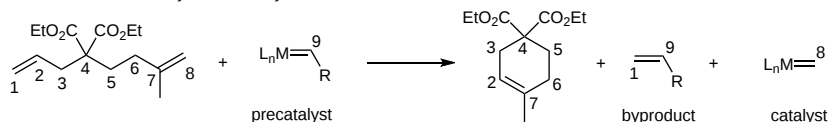
Olefin metathesis catalysts (shown below) are examples of metal-carbene complexes where the reactive metal (either Ru or Mo) contains a double bond to the carbon ligand that participates in the reaction. Furthermore, these highly reactive catalysts are actually examples of what chemists call precatalysts. 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).



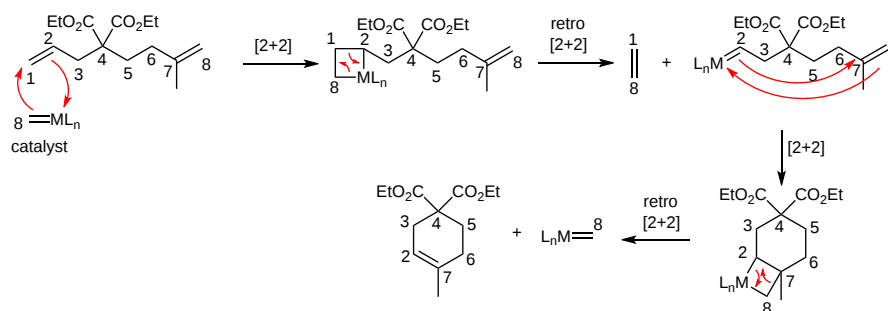
An example ring closing metathesis (RCM) reaction is shown below along with the mechanism. In this case, we are forming a six membered ring. As mentioned above, RCM reactions generate ethylene as a byproduct, meaning that the starting diene has two more carbons than the cyclic product. Don't forget this 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 $\text{L}_n\text{M}=\text{CH}_2$. 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, $\text{L}_n\text{M}=\text{CH}_2$.) 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.



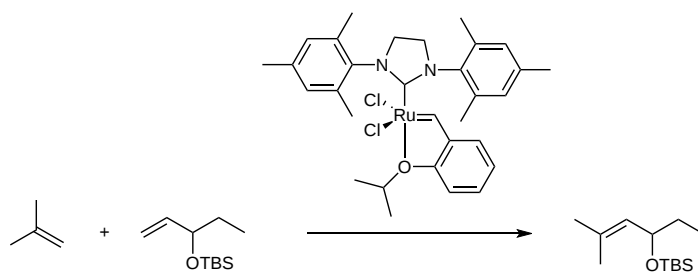
Formation of Active Catalyst - Precatalyst Reaction



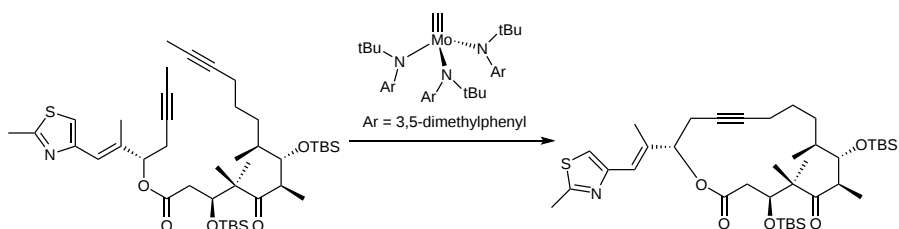
Mechanism



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 known as the Hoveyda-Grubbs catalyst.

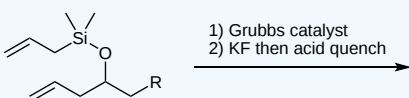


Alkyne metathesis is a useful variant of standard olefin metathesis. Tungsten and molybdenum catalysts have been developed that enable efficient ring closing alkyne metathesis. Not surprisingly, this strategy is only useful for the synthesis of large rings which are able to handle the significant ring 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.



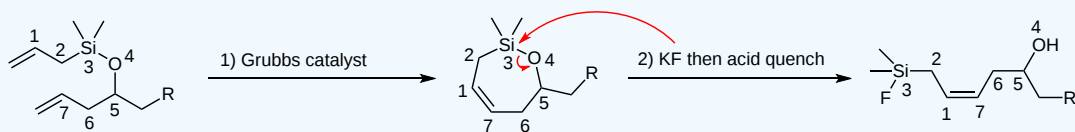
? Exercise 2.3.1

Propose a product for the following reaction sequence.



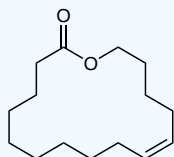
Answer

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.



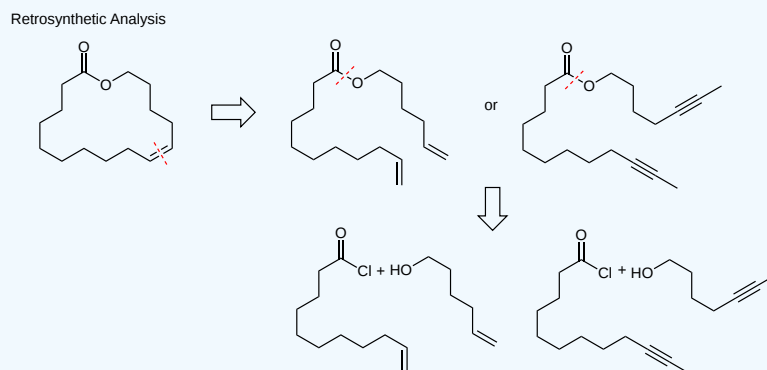
? Exercise 2.3.2

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.



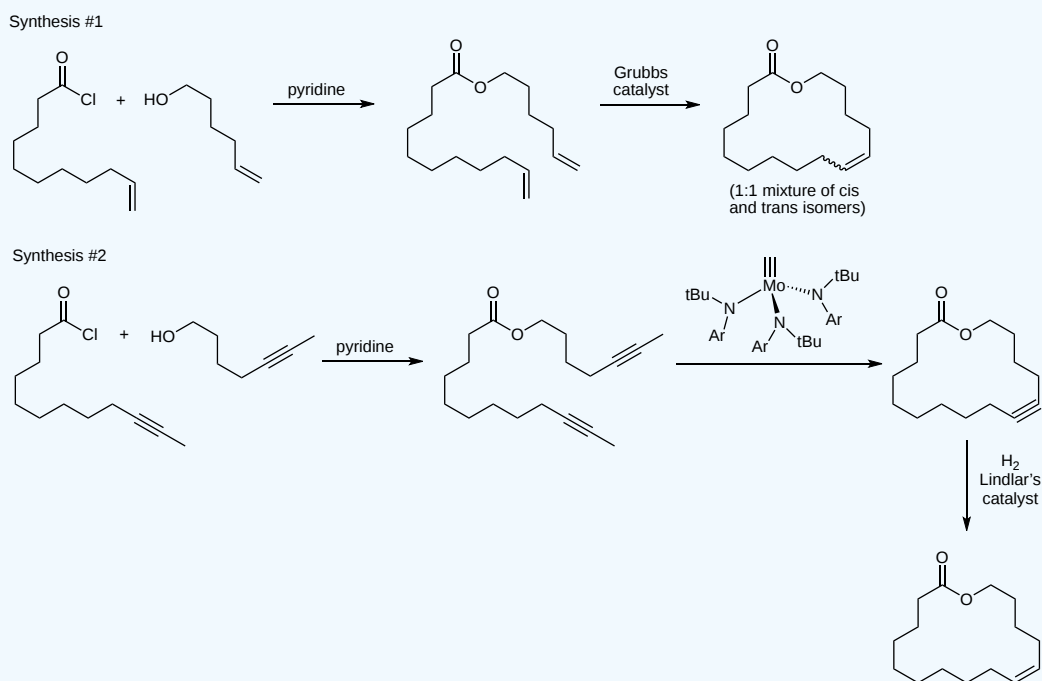
Answer

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.



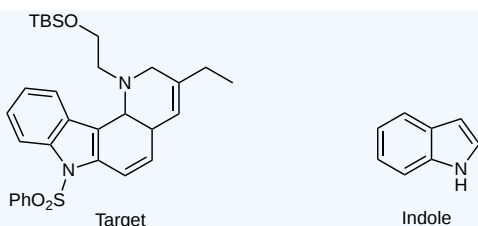
Synthesis #1 is likely the most obvious choice. Form the ester in the first step then use the Grubbs catalyst to form the 16-membered ring. One issue with this synthesis is the unfortunate limitation of alkene RCM for large rings that often generates cis/trans product mixtures. In fact, this reaction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

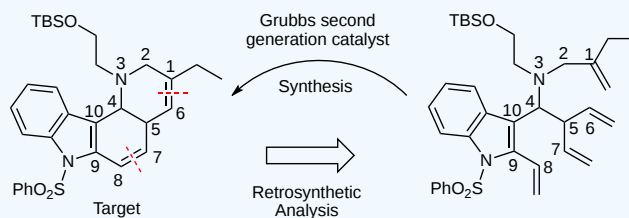
The following target is a key synthetic intermediate in a published synthesis of pseudotabersonine. Propose a one-step synthesis of this tetracycle beginning with a substituted indole as your bicyclic starting material.



Answer

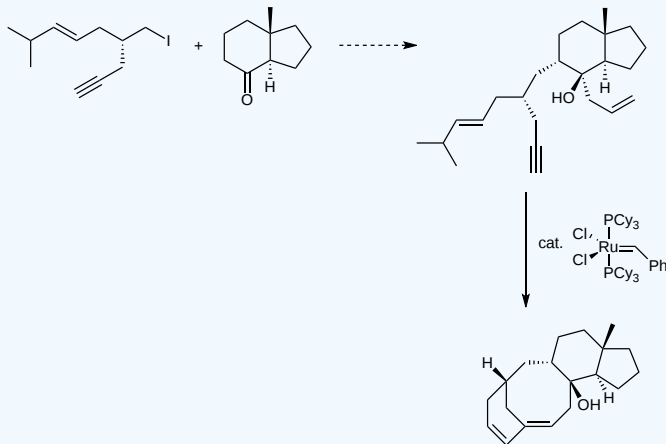
Reference: [Organic Letters 2010](#)

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

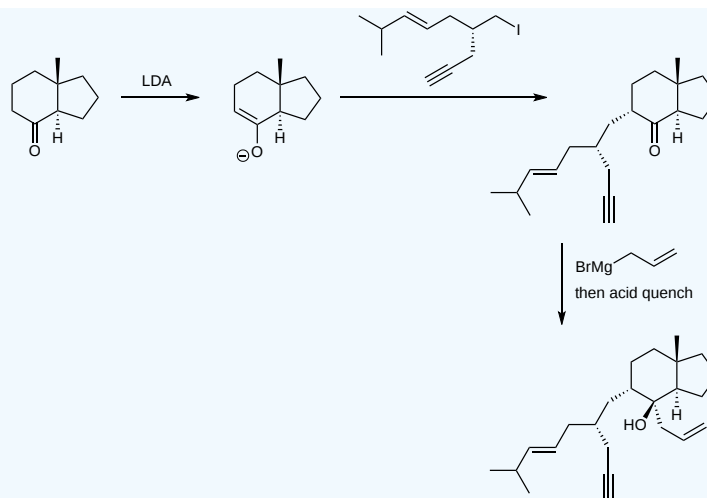
The following synthetic sequence outlines a strategy that can be applied to the synthesis of taxol-like molecules. First, propose a synthesis of the key ring-closing metathesis precursor. Second, propose a mechanism for the ring-closing metathesis reaction.



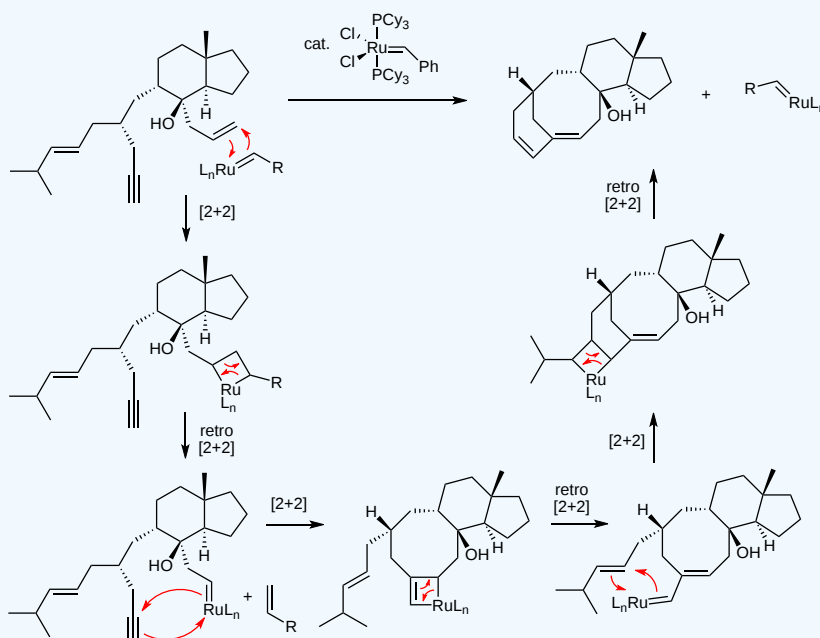
Answer

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.



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