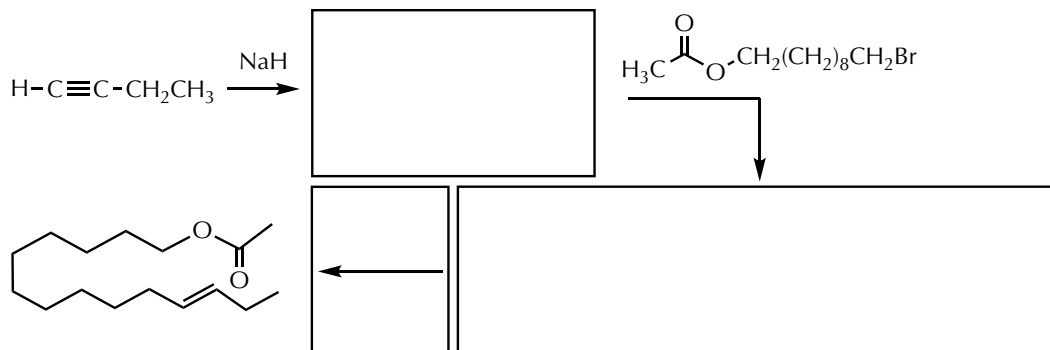


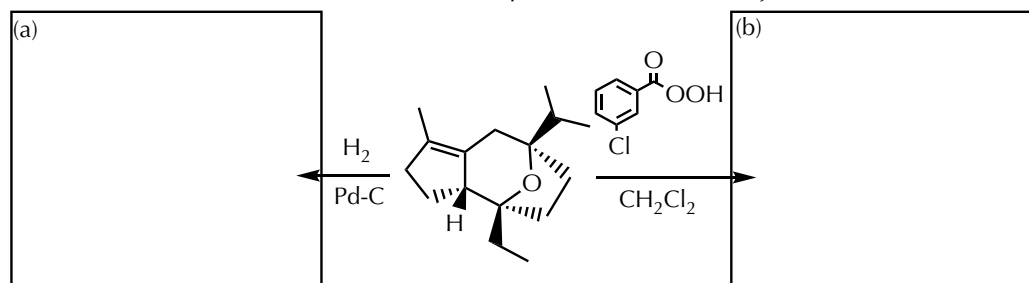
Thinking in Blue #12 - Questions 9.26, 9.27, and 9.30

9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, **1979**, 14, 1).

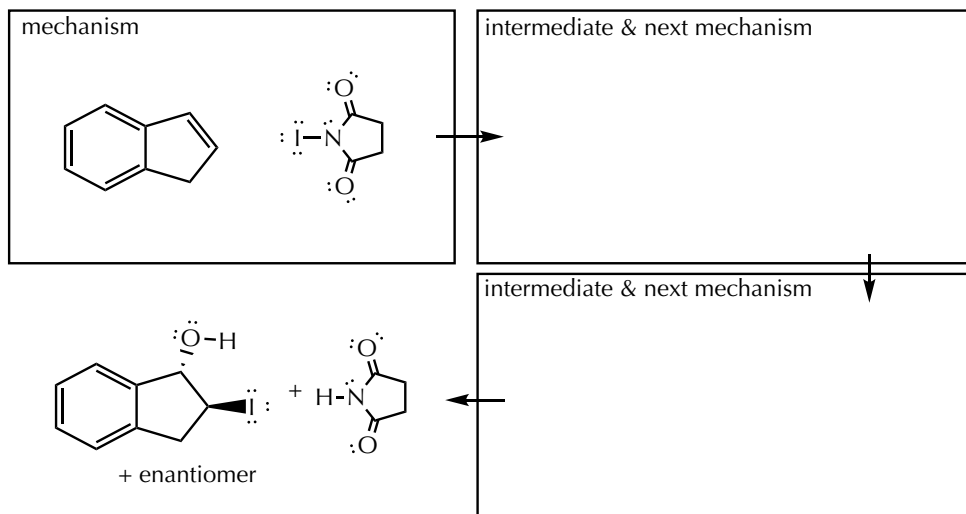
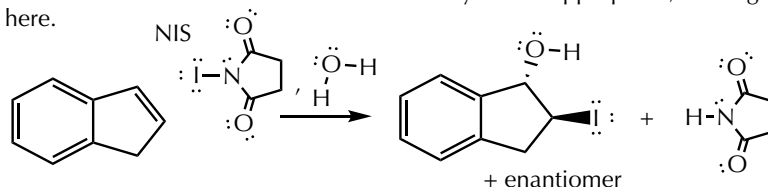


9.27 The following reactions, from the synthesis of an antitumor agent, give two diastereomeric products.

- (a) The major diastereoisomer from the hydrogenation reaction has the (R)-configuration at the new stereocenter bearing a methyl group (adapted from *ACS Med Chem Lett*, **2017**, 8, 746).
- (b) The reaction with mCPBA shows the same stereoselectivity as the hydrogenation reaction (i.e., both occur on the same side/face of the alkene). Draw the complete structure of the major diastereoisomer in each case.



9.30 The synthesis of iodohydrins using N-iodosuccinimide (NIS) as a source of electrophilic iodine was studied on a large series of compounds (*Internat J Cancer*, **2014**, 53B, 1425). Provide the complete, stepwise curved arrow mechanism for this reaction. Include stereochemistry where appropriate, leading to the stereoisomer explicitly shown here.

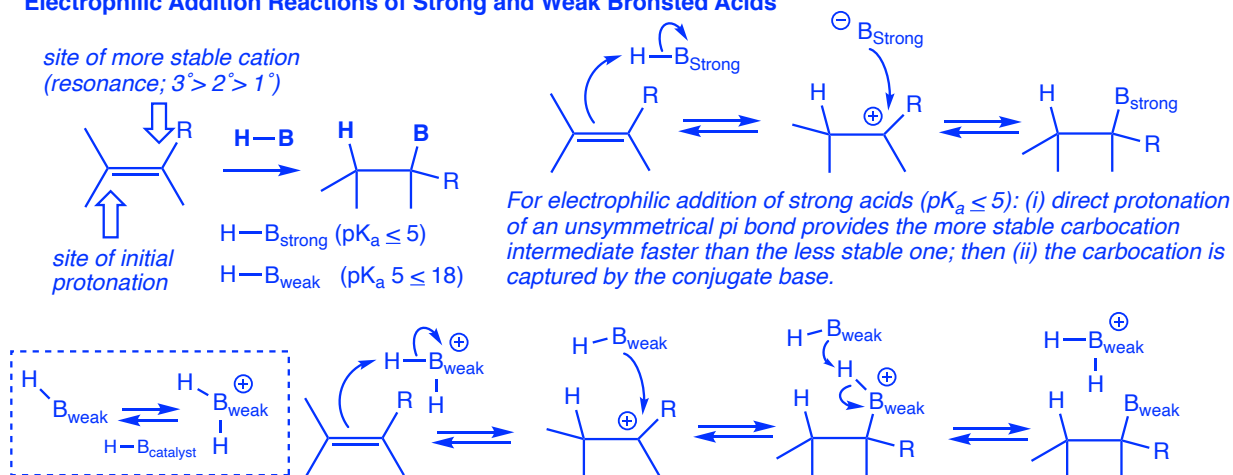


*Reminder! Pay attention to drawing the molecular geometry of hybridized atoms, particularly in reactions where there is a change in geometry.*

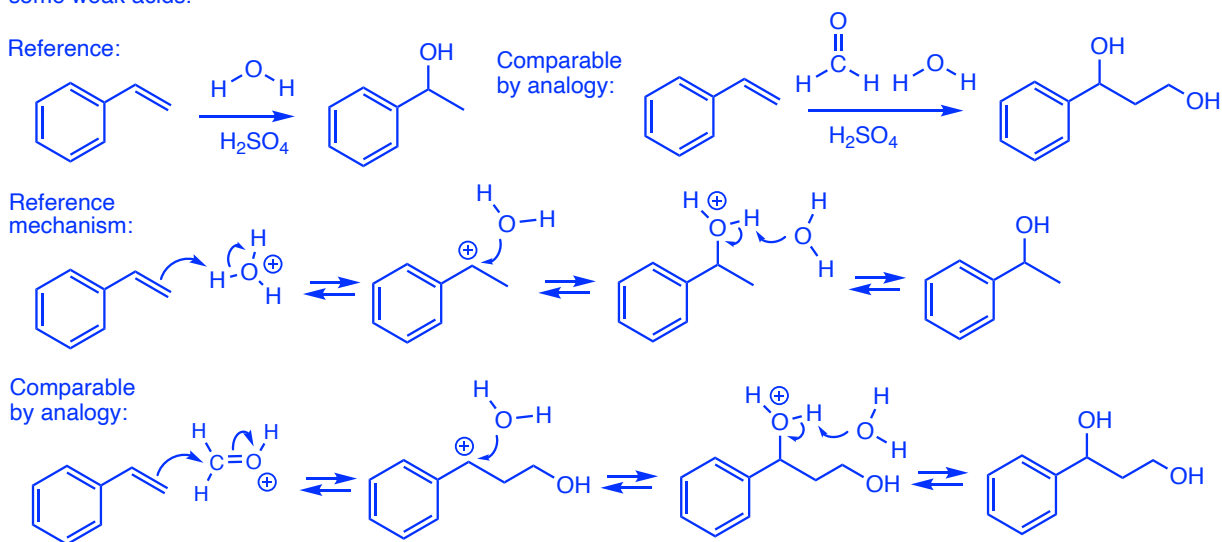
9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, **1979**, 14, 1).

The initial introduction to addition reaction chemistry was limited to the protonation of pi bonds to give carbocation intermediates, with the only sub-classifications being the difference in conditions (and mechanism) for strong versus weak Bronsted acids as reagents (see: Week 6). These generalizations apply to triple bonds and double bonds.

### Electrophilic Addition Reactions of Strong and Weak Bronsted Acids



As a type of reaction, understanding the step-wise addition reaction represented by this category can be extended to first steps, other than protonation, that also proceed through carbocation intermediates with the same logic for the regioselectivity. For example, the protonated C=O can play the same role as the strong acid in the addition reaction of some weak acids.



Stereochemical analysis can now be done on any product or intermediate. In both of these cases, the products have a single tetrahedral stereocenter where none existed before, so a pair of enantiomers is anticipated.

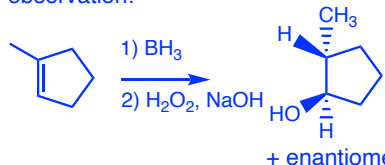
Reminder! Pay attention to drawing the molecular geometry of hybridized atoms, particularly in reactions where there is a change in geometry.

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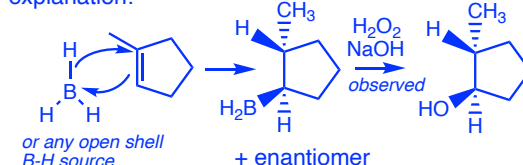
At this point, the introduction to electrophilic addition is broadened to include many other examples where the outcomes form a larger and more diverse set of reactions. The experimental observation for what happens in the addition reaction is needed because nearly all of them cannot be figured out from basic principles, even though they can be subsequently explained by using comparisons with other reactions. This new set of reactions can then, in turn, be used to make analogies for an even broader range of reagents. Specific reference examples are still widely applicable in themselves, and also need to be understood as concepts that can be used for many addition reactions of double and triple bonds.

### Hydroboration-Oxidation (*syn* addition of water)

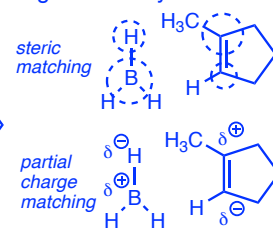
observation:



explanation:

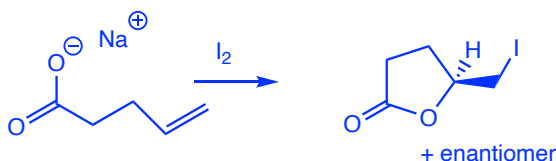
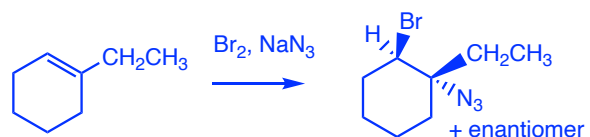
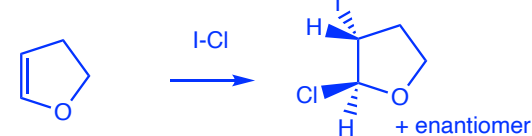
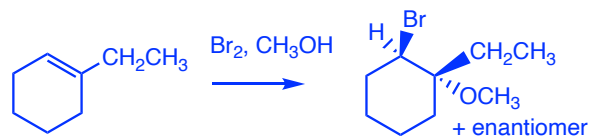
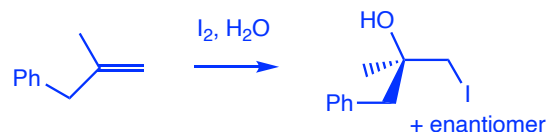
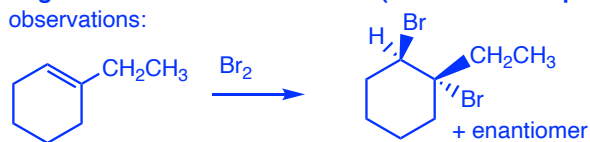


regioselectivity:

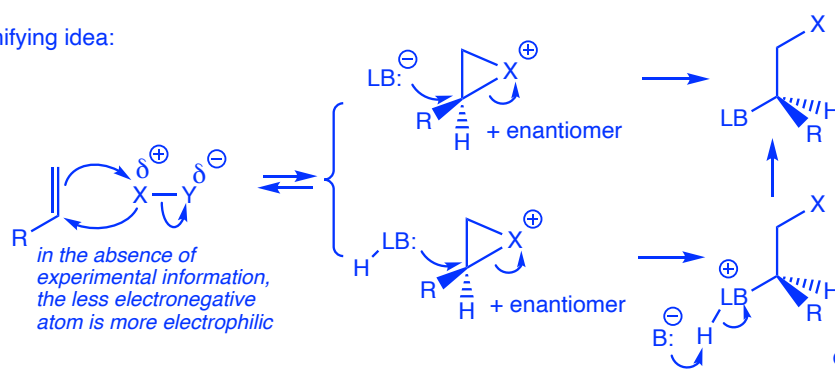


### Halogenation and related additions (formation and opening of cationic 3-membered rings: *trans* addition)

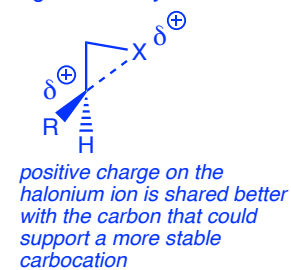
observations:



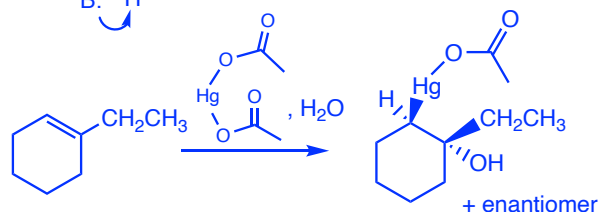
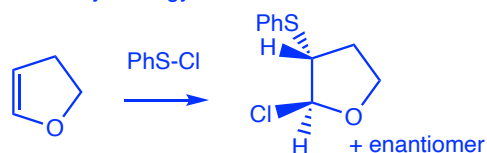
unifying idea:



regioselectivity:



extrapolation by analogy:



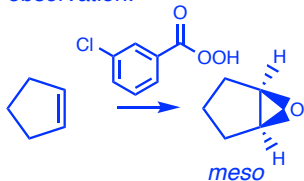
Reminder! Pay attention to drawing the molecular geometry of hybridized atoms, particularly in reactions where there is a change in geometry.

9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, 1979, 14, 1).

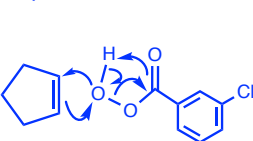
### Oxidation Reactions

Another common set of addition reactions involve reagents that deliver oxygen atoms. As with the other examples in this discussion, the experimental observations are critical because the outcomes from these fundamental cases are impossible to predict based on principles. Once understood, however, they can be used to extrapolate by analogy to other cases.

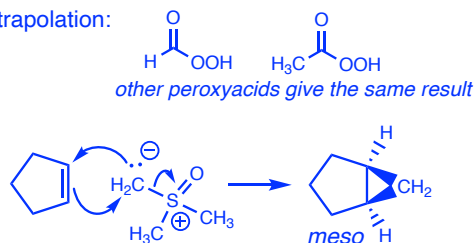
observation:



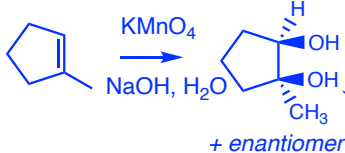
explanation:



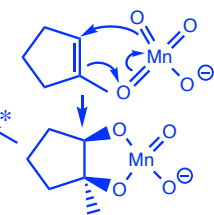
extrapolation:



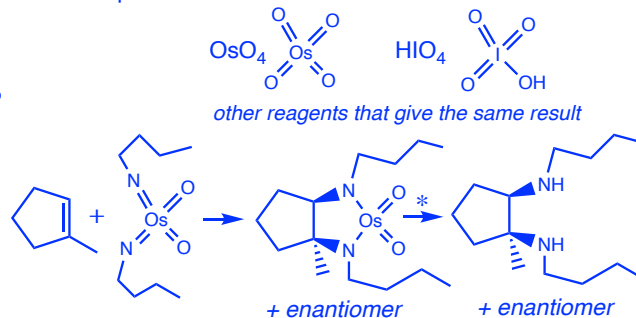
observation:



explanation:

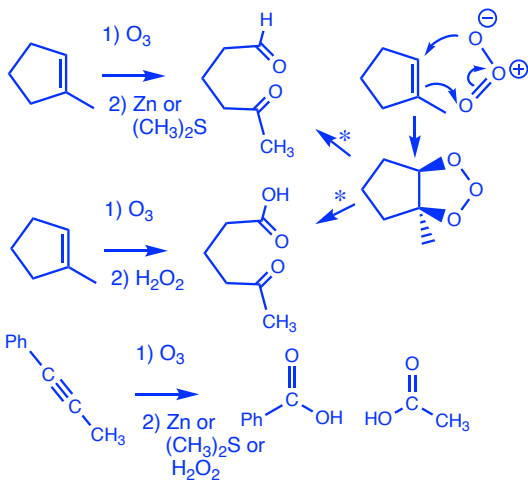


extrapolation:

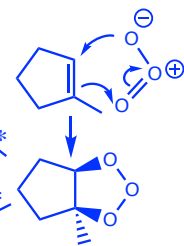


\*a "work-up" or additional experimental step in the lab procedure to hydrolyze, decompose, transform, or neutralize an intermediate

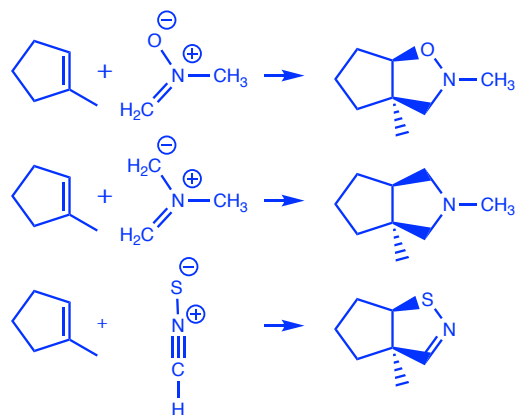
observation:



explanation:



extrapolation: there are hundreds of comparable reagents to  $\text{O}_3$  that give stable 5-membered ring products



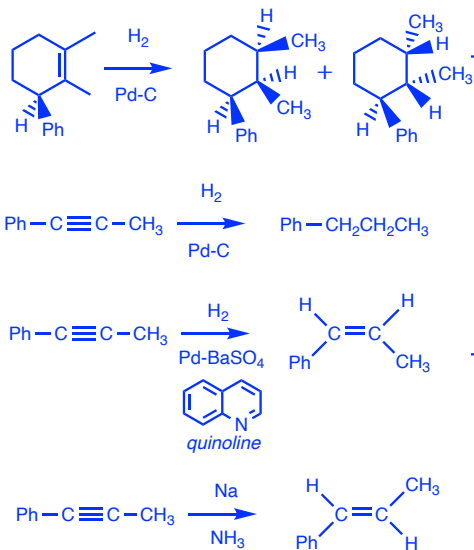
*Reminder! Pay attention to drawing the molecular geometry of hybridized atoms, particularly in reactions where there is a change in geometry.*

9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, **1979**, 14, 1).

### Reduction Reactions

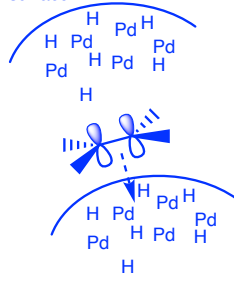
Reduction reactions are often companions to oxidation reactions. The addition reaction of the elements of molecular hydrogen ("H<sub>2</sub>") to pi bonds is the most common reduction reaction in organic chemistry.

observations:



explanation:

*finely divided metals adsorbed on charcoal can react with H<sub>2</sub> and scatter H atoms on the surface*



*pi bonds complex with the surfaces, 2 H's are transferred with syn addition outcome*

*complex mechanism that transfers 2 electrons and 2 protons, giving the sterically preferred outcome*

extrapolation:

many different metals and metal compounds have been observed to catalyze the hydrogenation reaction:

including Pt, Pd, PtO<sub>2</sub>, Ni

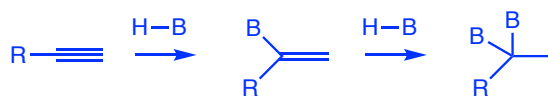
a few different combinations of metal supports and catalyst poisons can be used to give the (Z)-double bond as a product

Pd-CaCO <sub>3</sub>	Pd-CaCO <sub>3</sub>	Pd-BaSO <sub>4</sub>
PbO	quinoline	PbO

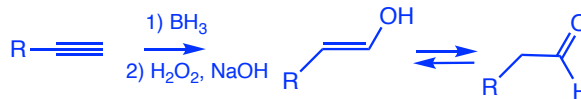
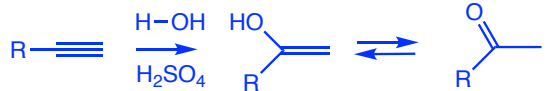
lithium in liquid ammonia (Li/NH<sub>3</sub>) also works as an alternative to Na/NH<sub>3</sub>

### Summary of the common addition reactions with triple bonds:

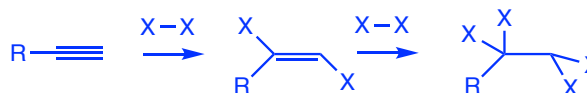
Electrophilic addition of strong and weak Bronsted acids (mono & di-addition possible):



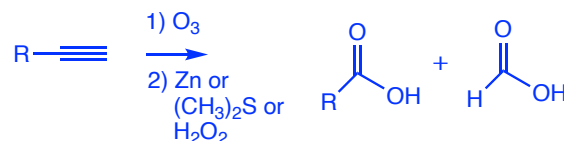
Except for the addition of water (H<sub>2</sub>O/acid or hydroboration-oxidation), which adds once and then an isomerization takes place.



Halogenation (mono-addition less common, di-addition more common):



Oxidation reactions (ozonolysis; see prior examples)



Reduction reactions (see above, on this page)

Reminder! Pay attention to drawing the molecular geometry of hybridized atoms, particularly in reactions where there is a change in geometry.

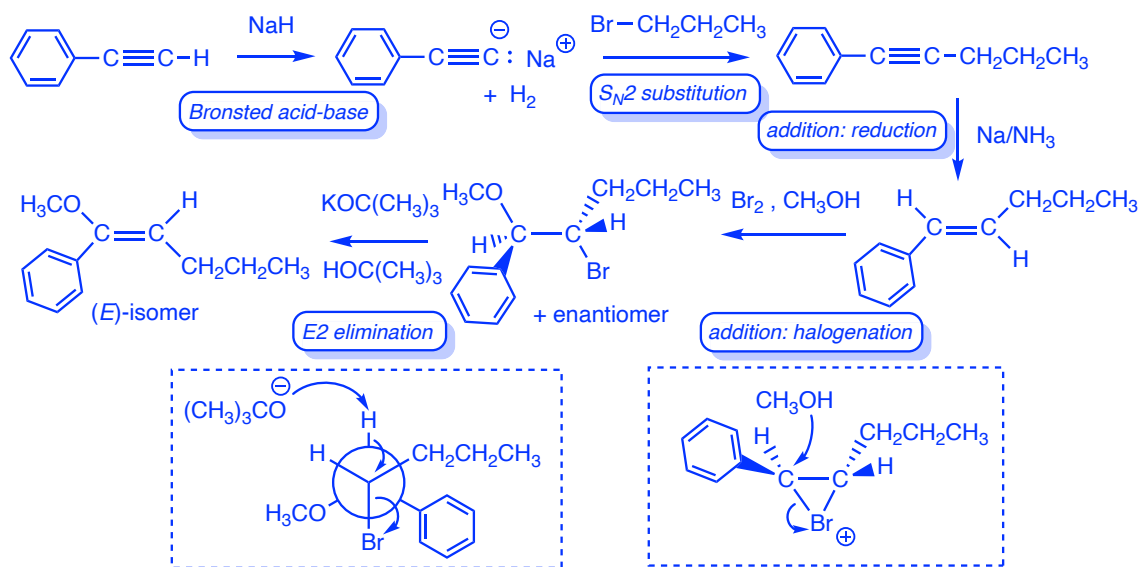
9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, 1979, 14, 1).

It is worth remembering that all of the previous pages represent the understanding that a person needs **BEFORE** trying to work on exam-style questions. It should be clear to you that our exam questions are not aimed at direct recall of information to simply give it back, but instead to have an understanding of the information to the degree that you can (a) know what is needed to approach answering a question and (b) correctly apply the right information to new and unfamiliar experimental results.

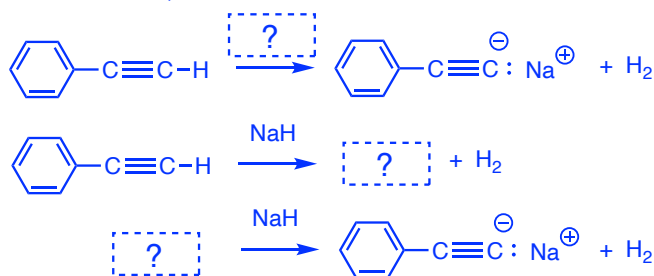
The other thing that should be obvious (and will be more obvious, in a moment, below) is how the information genuinely builds on itself, and how not clearing up earlier errors will create a *debt of misunderstanding* that will continue to plague a learner repeatedly.

*Thinking in Blue* is not a study summary, nor is it pedagogical. This resource is an honest effort to make it clear just what a high achieving learner knows **BEFORE** trying to work on these questions, because none of the questions are asking for this information to be delivered, but rather to be used.

At this point in CHEM 210, the cumulative nature of the subject becomes quite clear. You have all the fundamental reaction types and plenty of representative examples, so perhaps the single most common thing done with organic chemistry can now be illustrated, namely, building new molecules using a linear sequence of chemical reactions. Molecular complexity, including specific stereochemical outcomes, can be built up quite rapidly. Here is an example:



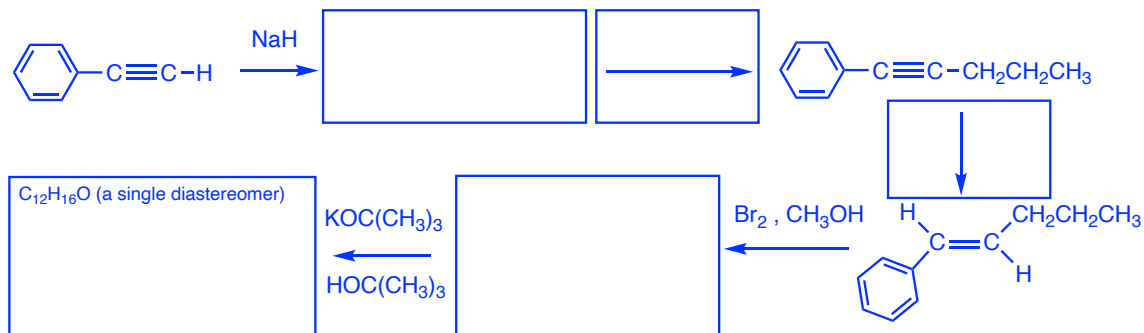
For the easiest type of problem, you need to be comfortable and familiar with all of these "A + B → C" relationships regardless of whether "A", "B", or "C" is missing. Just take the first reaction; it can be legitimately formatted in three ways (note that problems such as this go back to the first day of class! balanced equations... well-behaved atoms...)



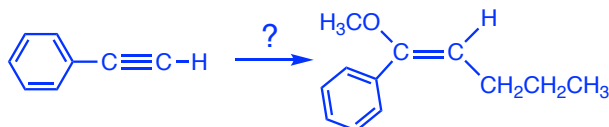
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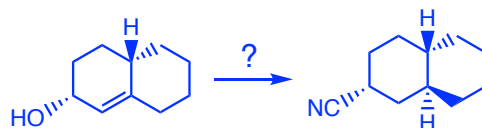
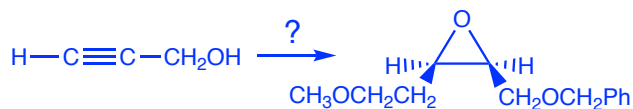
A reaction sequence such as the one on the previous page can be reformatted as an exam question in numerous ways that leave just enough information about the relationships so that those who understand them can deduce what is missing. But if you do not already have the relationships in these reactions understood, there will simply not be enough information in the question, itself, to produce an answer. The information in the question is used to figure out what you need... but then you need to have it!



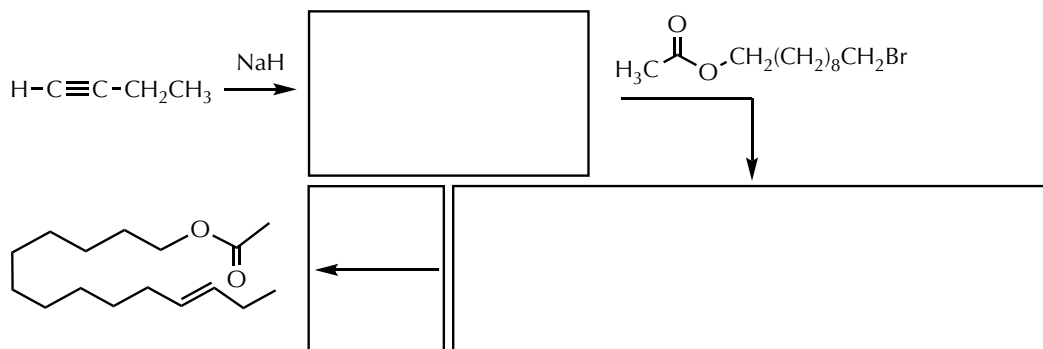
Formatted as above, there is enough information about each step present to be able to identify the exact sequence of reactions, so that you do not need to worry about that. A somewhat more sophisticated version of this question would be to pose it as a transformation, with no information about how many steps and in which order. And although it is a more complex question when formatted this way, the answer relies completely on knowing which kinds of reactions are available and the order in which they can be used.



Formatted this way, given the still-limited number of reactions you have to use, there is likely only the one sequence of reactions that you can be sure would work (because they are predated). But without the full inventory of reactions at your immediate disposal, the question cannot be rationally answered. Perhaps having seen the sequence makes that set of relationships seem reasonable. Here are a few that take a comparable yet completely different sequence to answer; yet all within the realm of CHEM 210 at this point (although admittedly quite difficult).

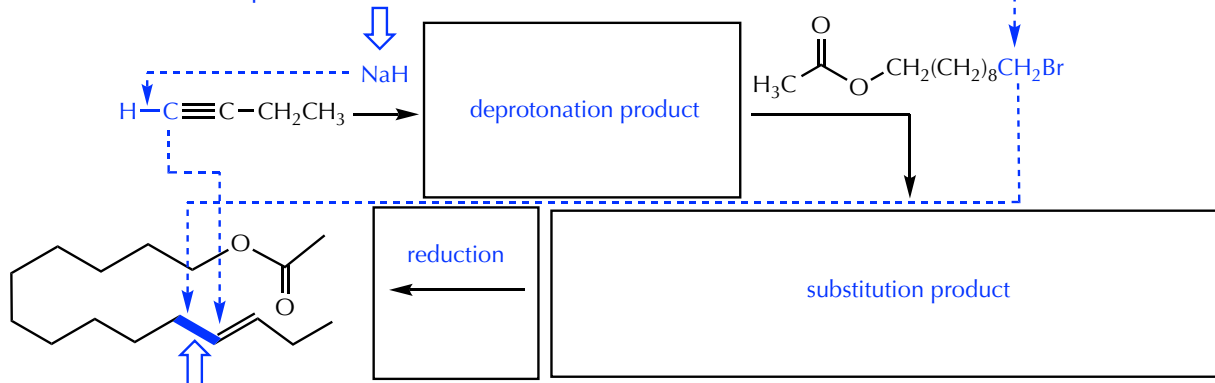


9.26 Fill in the missing intermediates and reagents in this synthesis of one component of the sex attractant pheromone of the Tea Tortrix Moth (*App Ent Zoo*, **1979**, 14, 1).

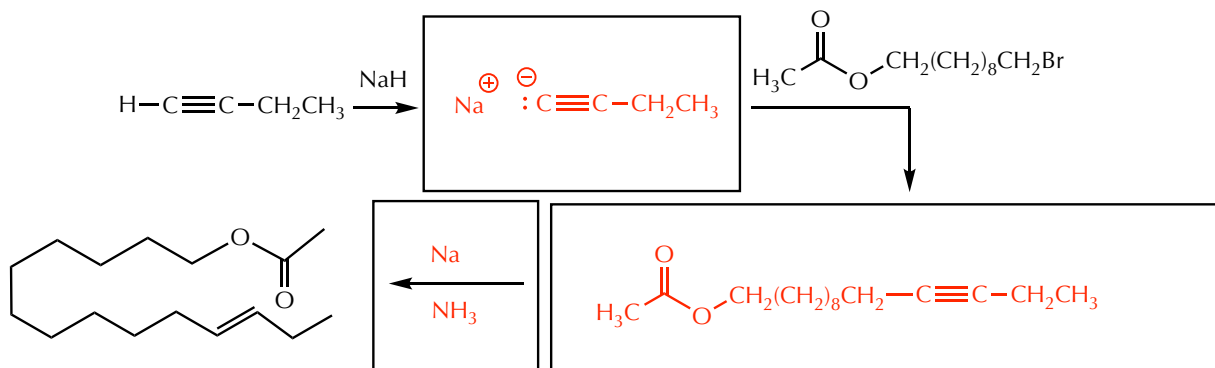


Hopefully you can see the logic of the presentation on the past few pages when you look at this question! There is no strictly linear way to approach answering this question, and you need to have all of the possible types of reactions under your control (but not this specific one, because it is a new example). Rather than simply diving into any question, stepping back to get the information you can about what is presented is always a good strategy because it can create general expectations and maybe even a general solution.

(1) used as a strong Bronsted base, and in combination with the relatively acidic sp CH bond of the triple bond, creates a good nucleophile for  $\text{S}_{\text{N}}2$  reactions when you have a  $1^\circ$  C-LG bond; and there is a molecule in the next step with a  $1^\circ$  C-LG bond



(2) all of the carbons of those two molecules are accounted for in the product, and they are connected through this C-C bond, which is consistent with the proposition for a substitution reaction up above; instead of a triple bond, however, there is now a double bond in the (*E*) configuration, so the last step is the reduction from the triple bond (and that absolutely needs to be recalled as the “dissolving metal reduction” ( $\text{Na}/\text{NH}_3$  or  $\text{Li}/\text{NH}_3$ ))

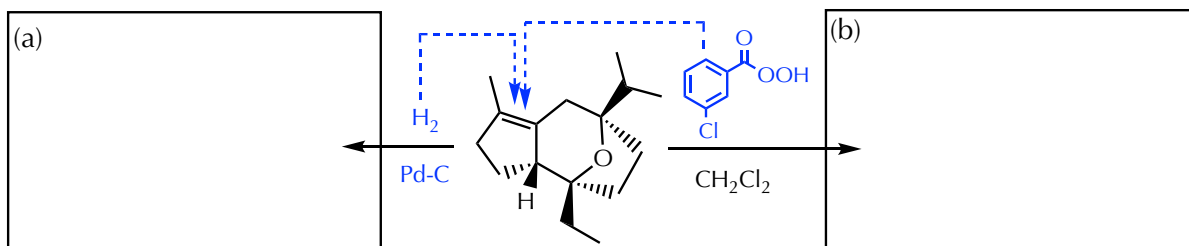




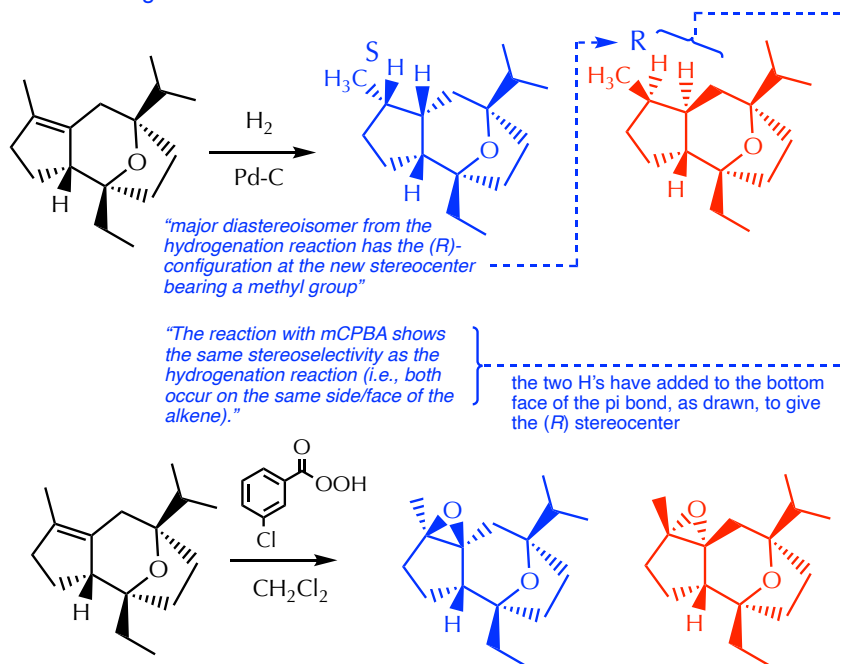
This question has two quite separate parts, where different reactions are carried out on the same starting material, which has been presented in the center (with one reaction, (a), heading to the left, and the other, (b), heading to the right). The first sentence also states explicitly that both reactions give a pair of diastereomers (so anything other than that must be the wrong reaction).

9.27 The following reactions, from the synthesis of an antitumor agent, give two diastereomeric products.

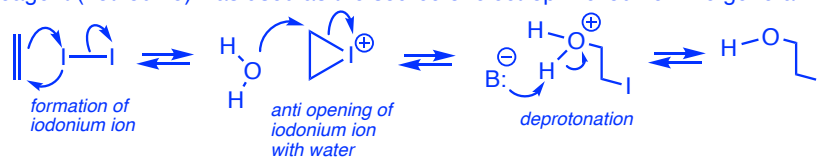
- (a) The major diastereoisomer from the hydrogenation reaction has the (R)-configuration at the new stereocenter bearing a methyl group (adapted from *ACS Med Chem Lett*, **2017**, *8*, 746).
- (b) The reaction with mCPBA shows the same stereoselectivity as the hydrogenation reaction (i.e., both occur on the same side/face of the alkene). Draw the complete structure of the major diastereoisomer in each case.



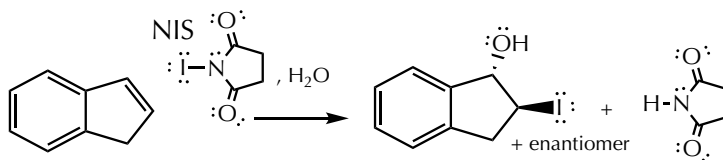
Both of the reactions are additions, and they are formatted in the most familiar way ( $A + B \rightarrow ?$ , that is, to predict the product). In (a), using hydrogen as a reagent with a metal catalyst only signals addition; and in (b), the peroxyacid signals exactly the same thing. There is only one double bond in the molecule, so there is no choice to make. Because the molecule is filled with stereocenters, adding things to the “top face” of the double bond (as drawn) will give a diastereomer relative to adding to the “bottom face” of the double bond, provided that at least one new stereocenter is forming.



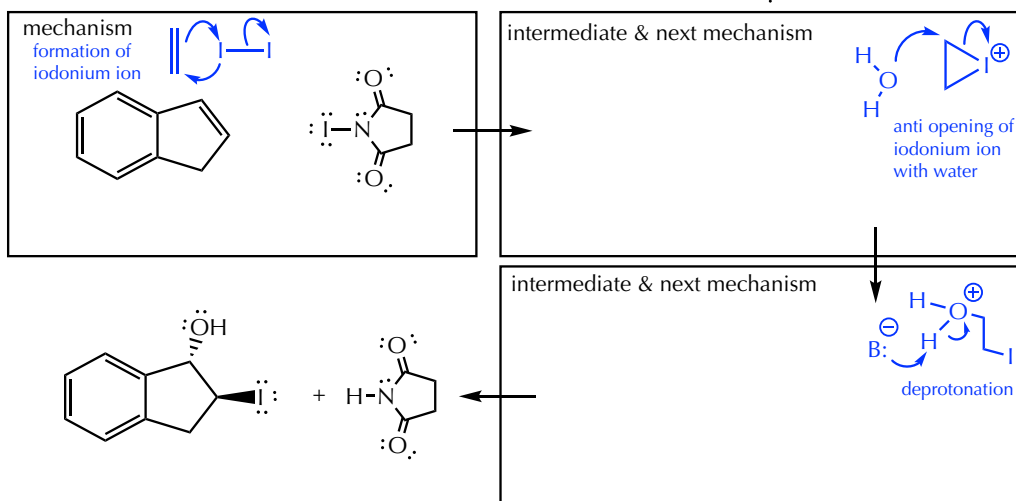
The reaction product looks like the outcome from the " $I_2, H_2O$ " addition reaction. The text of the question states that the NIS reagent (not iodine) was used as the source of electrophilic iodine. The general mechanism is 3 steps:



9.30 The synthesis of iodohydrins using N-iodosuccinimide (NIS) as a source of electrophilic iodine was studied on a large series of compounds (*Internat J Cancer*, **2014**, 53B, 1425). Provide the complete, stepwise curved arrow mechanism for this reaction. Include stereochemistry where appropriate, leading to the stereoisomer explicitly shown here.



The general steps should map onto the specific case of the question!



The general steps should map onto the specific case of the question!

