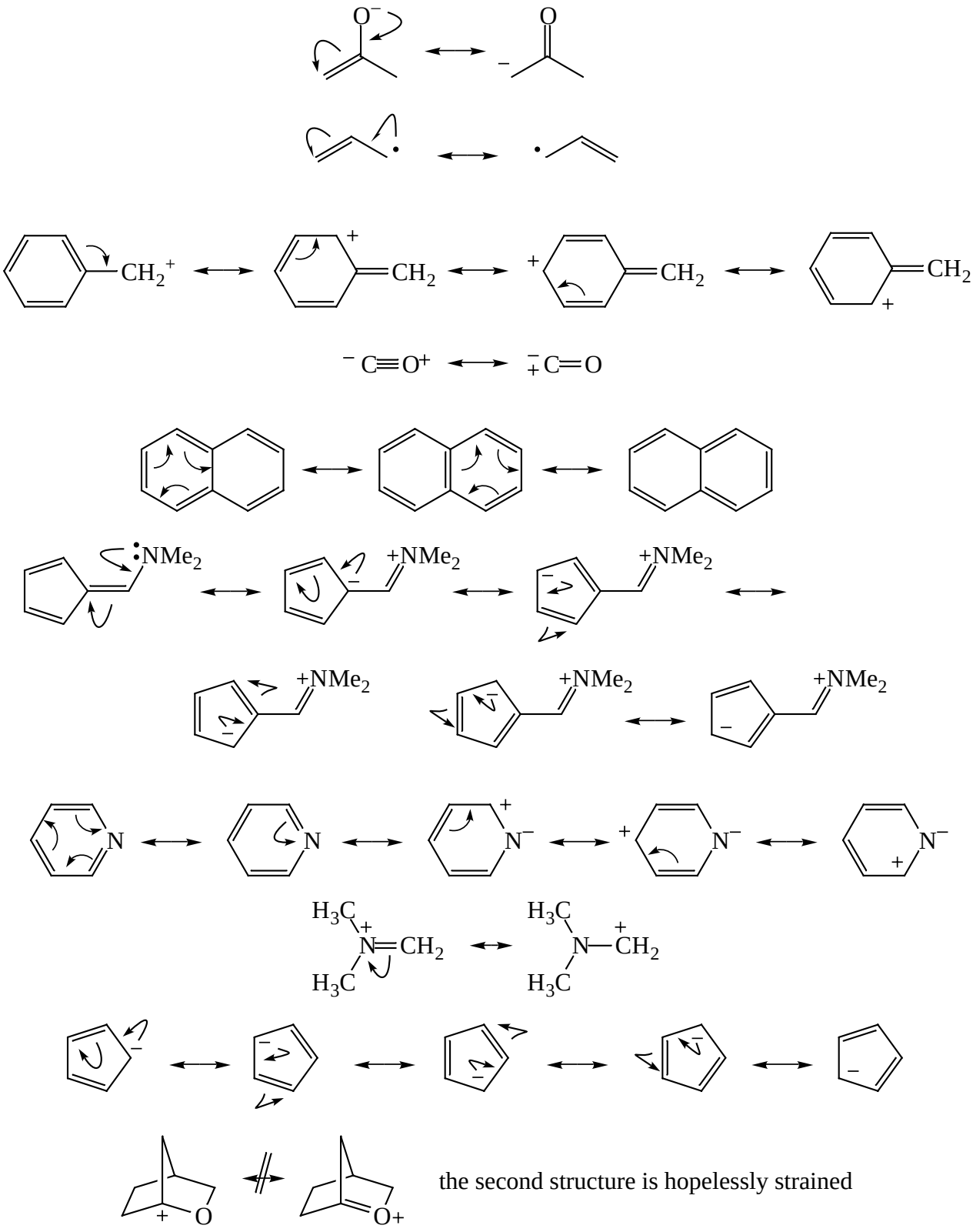
Answers To Chapter 1 In-Chapter Problems.

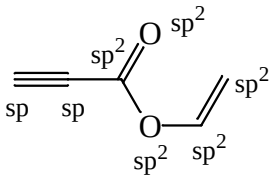
1.1. The resonance structure on the right is better because every atom has its octet.

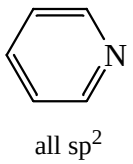
1.2.



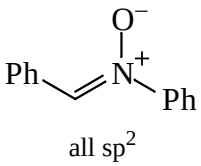
the second structure is hopelessly strained

1.3.

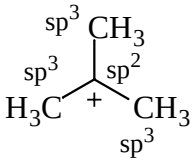


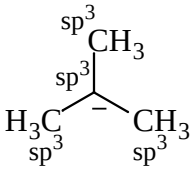


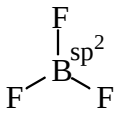
all sp^2

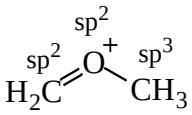


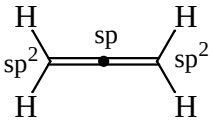
all sp^2







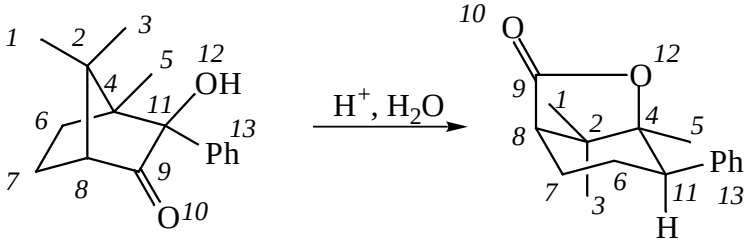




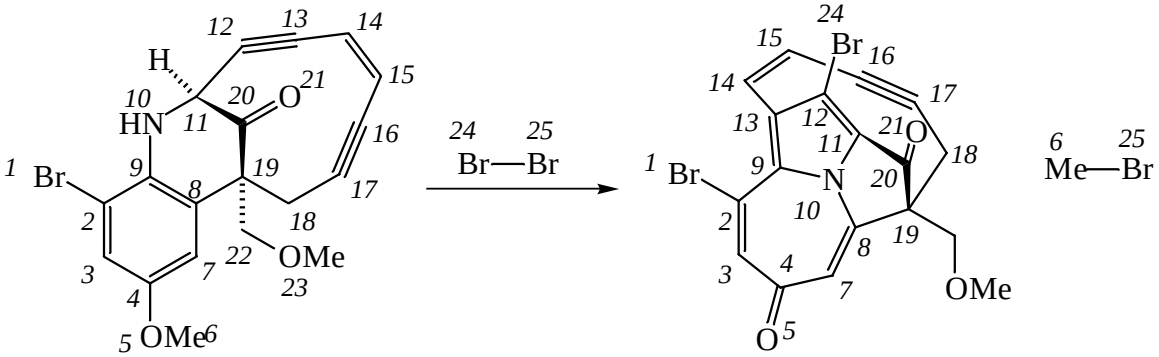
1.4. The O atom in furan has sp^2 hybridization. One lone pair resides in the p orbital and is used in resonance; the other resides in an sp^2 orbital and is not used in resonance.

1.5.

(a) No by-products. C(1–3) and C(6–9) are the keys to numbering.



(b) After numbering the major product, C6 and Br25 are left over, so make a bond between them and call it the by-product.



1.6. (a) Make C4–O12, C6–C11, C9–O12. Break C4–C6, C9–C11, C11–O12.
(b) Make C8–N10, C9–C13, C12–Br24. Break O5–C6, C8–C9.

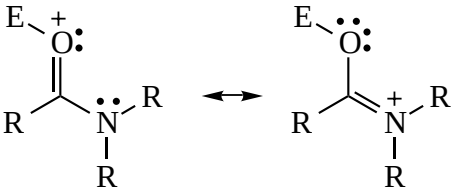
1.7. PhC≡CH is much more acidic than BuC≡CH. Because the pK_b of HO^- is 15, PhC≡CH has a p$K_a \leq$ 23 and BuC≡CH has p$K_a > 23$.

1.8. The OH is more acidic ($pK_a \approx 17$) than the C α to the ketone ($pK_a \approx 20$). Because the by-product of the reaction is H_2O, there is no need to break the O–H bond to get to product, but the C–H bond α to the ketone must be broken.

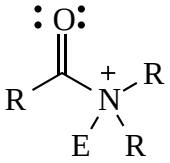
Answers To Chapter 1 End-Of-Chapter Problems.

1. (a) Both N and O in amides have lone pairs that can react with electrophiles. When the O reacts with an electrophile E^+, a product is obtained for which two good resonance structures can be drawn. When the N reacts, only one good resonance structure can be drawn for the product.

reaction on O



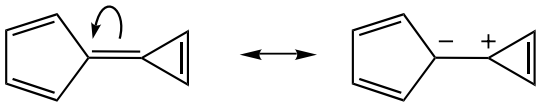
reaction on N



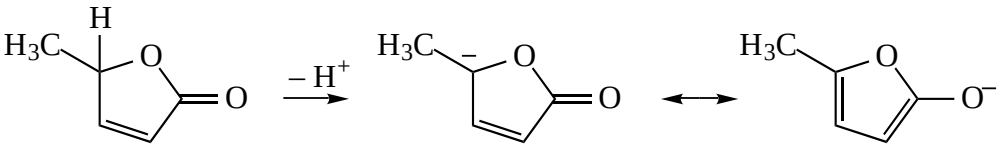
(b) Esters are *lower in energy* than ketones because of resonance stabilization from the O atom. Upon addition of a nucleophile to either an ester or a ketone, a tetrahedral intermediate is obtained for which resonance is not nearly as important, and therefore the tetrahedral product from the ester is nearly the same energy as the tetrahedral product from the ketone. As a result it costs more energy to add a nucleophile to an ester than it does to add one to a ketone.

(c) Exactly the same argument as in (b) can be applied to the acidity of acyl chlorides versus the acidity of esters. Note that Cl and O have the *same* electronegativity, so the difference in acidity between acyl chlorides and esters cannot be due to inductive effects and must be due to resonance effects.

(d) A resonance structure can be drawn for **1** in which charge is separated. Normally a charge-separated structure would be a minor contributor, but in this case the two rings are made aromatic, so it is much more important than normal.

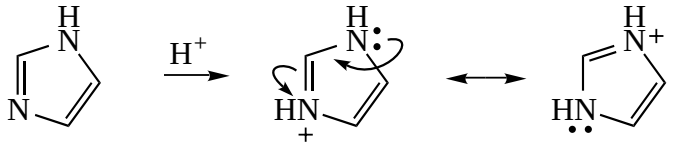


(e) The difference between **3** and **4** is that the former is cyclic. Loss of an acidic H from the γ C of **3** gives a structure for which an aromatic resonance structure can be drawn. This is not true of **4**.

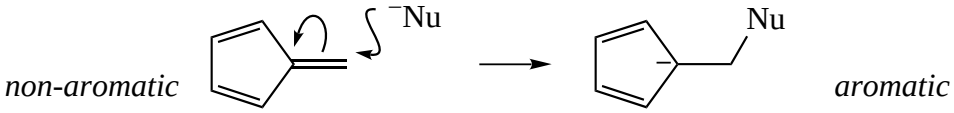


(f) Both imidazole and pyridine are aromatic compounds. The lone pair of the H-bearing N in imidazole is required to maintain aromaticity, so the other N, which has its lone pair in an sp^2 orbital that is perpendicular to the aromatic system, is the basic one. Protonation of this N gives a compound for which two

equally good aromatic resonance structures can be drawn. By contrast, protonation of pyridine gives an aromatic compound for which only one good resonance structure can be drawn.



(g) The C=C π bonds of simple hydrocarbons are usually nucleophilic, not electrophilic. However, when a nucleophile attacks the exocyclic C atom of the nonaromatic compound fulvene, the electrons from the C=C π bond go to the endocyclic C and make the ring aromatic.



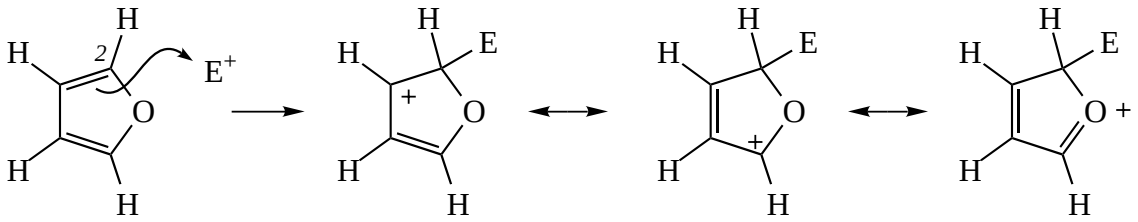
(h) The tautomer of 2,4-cyclohexadienone, a nonaromatic compound, is phenol, an aromatic compound.

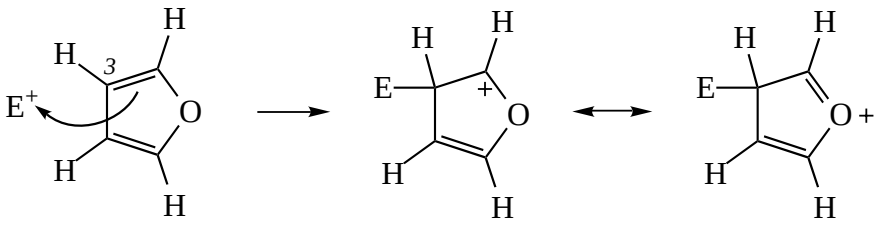
(i) Carbonyl groups C=O have an important resonance contributor $\overset{+}{C}–\overline{O}$. In cyclopentadienone, this resonance contributor is antiaromatic.

[**Common error alert:** Many cume points have been lost over the years when graduate students used cyclohexadienone or cyclopentadienone as a starting material in a synthesis problem!]

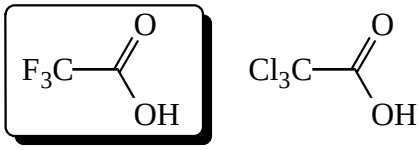
(j) PhOH is considerably more acidic than EtOH (pK_a= 10 vs. 17) because of resonance stabilization of the conjugate base in the former. S is larger than O, so the S(p)–C(p) overlap in PhS^- is much smaller than the O(p)–C(p) overlap in PhO^-. The reduced overlap in PhS^- leads to reduced resonance stabilization, so the presence of a Ph ring makes less of a difference for the acidity of RSH than it does for the acidity of ROH.

(k) Attack of an electrophile E^+ on C2 gives a carbocation for which three good resonance structures can be drawn. Attack of an electrophile E^+ on C3 gives a carbocation for which only two good resonance structures can be drawn.



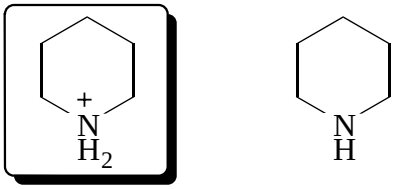


2. (a)



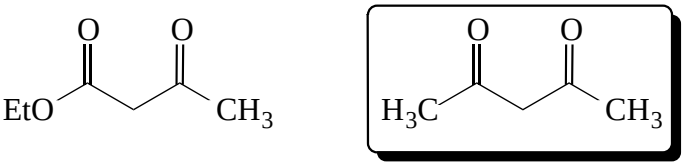
inductive electron-withdrawing effect of F is greater than Cl

(b)



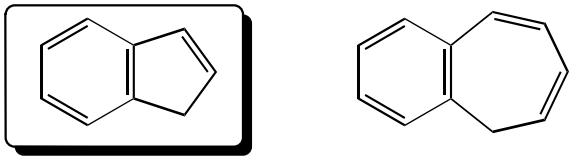
In general, AH^+ is more acidic than AH

(c)



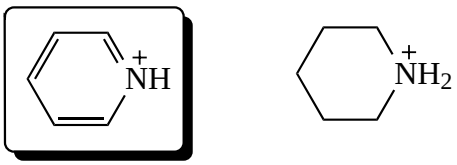
Ketones are more acidic than esters

(d)



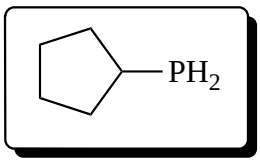
Deprotonation of 5-membered ring gives aromatic anion; deprotonation of 7-membered ring gives anti-aromatic anion.

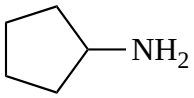
(e)



The N(sp^2) lone pair derived from deprotonation of pyridine is in lower energy orbital, hence more stable, than the N(sp^3) lone pair derived from deprotonation of piperidine.

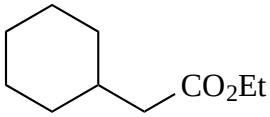
(f)

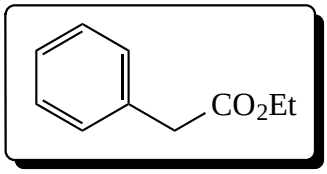




Acidity increases as you move down a column in the periodic table due to increasing atomic size and hence worse overlap in the A–H bond

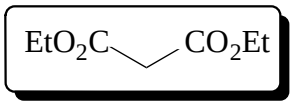
(g)

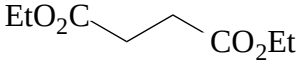




The anion of phenylacetate is stabilized by resonance into the phenyl ring.

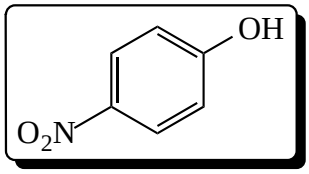
(h)

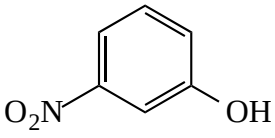




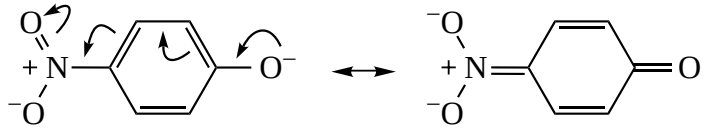
Anions of 1,3-dicarbonyl compounds are stabilized by resonance into *two* carbonyl groups

(i)

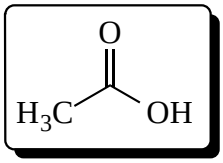


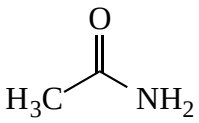


The anion of 4-nitrophenol is stabilized by resonance directly into the nitro group. The anion of 3-nitrophenol can't do this. Draw resonance structures to convince yourself of this.



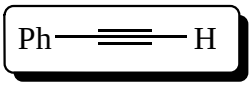
(j)





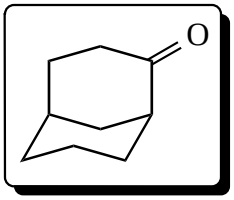
More electronegative atoms are more acidic than less electronegative atoms in the same row of the periodic table

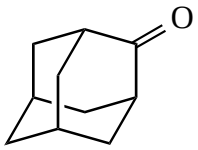
(k)



C(sp) is more acidic than C(sp^3), even when the anion of the latter can be delocalized into a Ph ring.

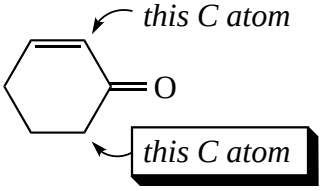
(l)





The anion of the latter cannot overlap with the C=O π bond, hence cannot delocalize, hence is not made acidic by the carbonyl group.

(m)

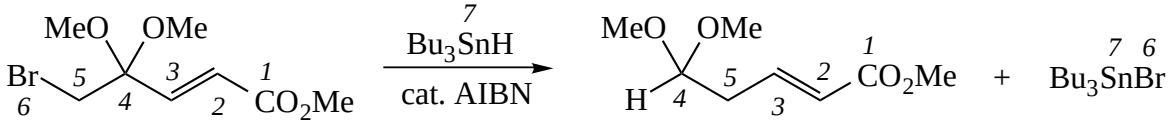


The C(sp^2)–H bond on the upper atom is the plane of the paper, orthogonal to the p orbitals of the C=O bond, so the C=O bond provides no acidifying influence. The C(sp^3)–H bonds on the lower atom are in and out of the plane of the paper, so there is overlap with the C=O orbitals.

3.

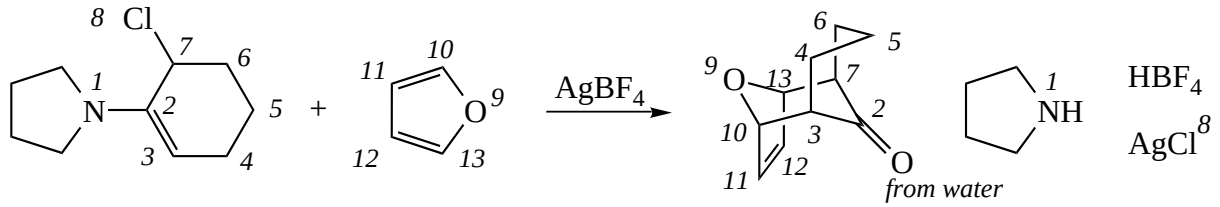
(a) Free-radical. (Catalytic peroxide tips you off.)
(b) Metal-mediated. (Os)
(c) Polar, acidic. (Nitric acid.)
(d) Polar, basic. (Fluoride ion is a good base. Clearly it's not acting as a nucleophile in this reaction.)
(e) Free-radical. (Air.) Yes, an overall transformation can sometimes be achieved by more than one mechanism.
(f) Pericyclic. (Electrons go around in circle. No nucleophile or electrophile, no metal.)
(g) Polar, basic. (LDA is strong base; allyl bromide is electrophile.)
(h) Free-radical. (AIBN tips you off.)
(i) Pericyclic. (Electrons go around in circle. No nucleophile or electrophile, no metal.)
(j) Metal-mediated.
(k) Pericyclic. (Electrons go around in circle. No nucleophile or electrophile, no metal.)
(l) Polar, basic. (Ethoxide base. Good nucleophile, good electrophile.)
(m) Pericyclic. (Electrons go around in circle. No nucleophile or electrophile, no metal.)

4. (a) The mechanism is free-radical (AIBN). Sn7 and Br6 are missing from the product, so they're probably bound to one another in a by-product. Made: C5–C3, Sn7–Br6. Broken: C4–C3, C5–Br6.

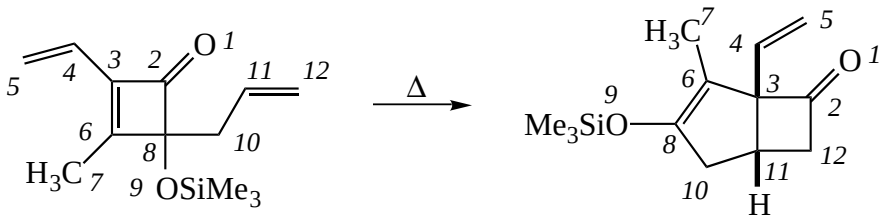


(b) Ag^+ is a good Lewis acid, especially where halides are concerned, so polar acidic mechanism is a

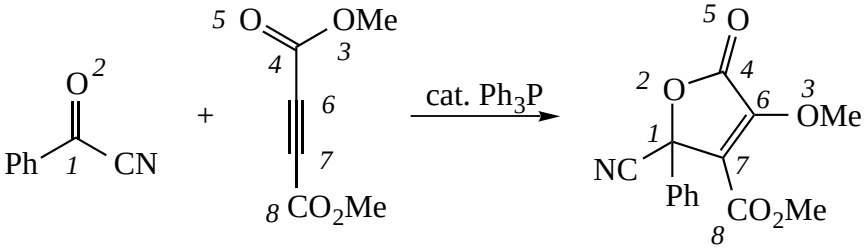
reasonable guess, but mechanism is actually pericyclic (bonds forming to both C10 and C13 of the furan and C3 and C7 of the enamine). Cl8 is missing from the product; it must get together with Ag to make insoluble, very stable AgCl. An extra O appears in the product; it must come from H_2O during workup. One of the H's in H_2O goes with the BF_4^-, while the other is attached to N1 in the by-product. Made: C3–C10, C7–C13, C2–O (water), Ag–Cl. Broken: N1–C2, C7–Cl8.



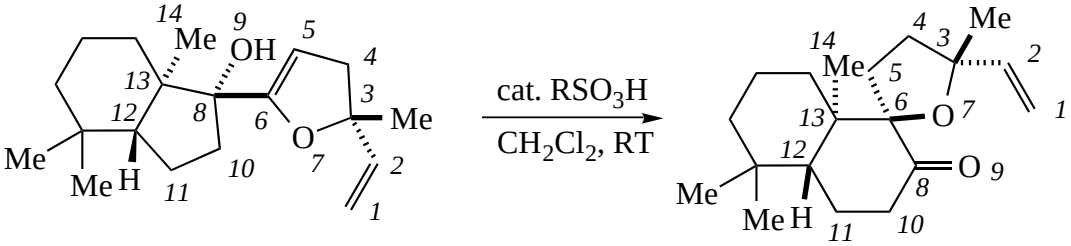
(c) This mechanism is also pericyclic. Use the carbonyl, Me_3SiO, and CH_3 groups as anchors for numbering the atoms. Made: C2–C12, C3–C11. Broken: C2–C8.



(d) Ph_3P is a Lewis base. The mechanism is polar under basic conditions. Made: C1–C7, O2–C4, O3–C6. Broken: O3–C4.

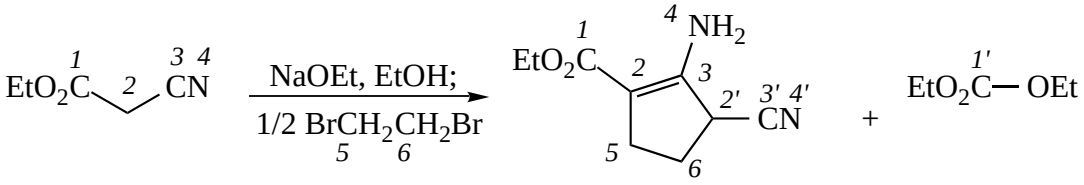


(e) The mechanism is polar under acidic conditions due to the strong acid RSO_3H. Made: C13–C6. Broken: C13–C8.

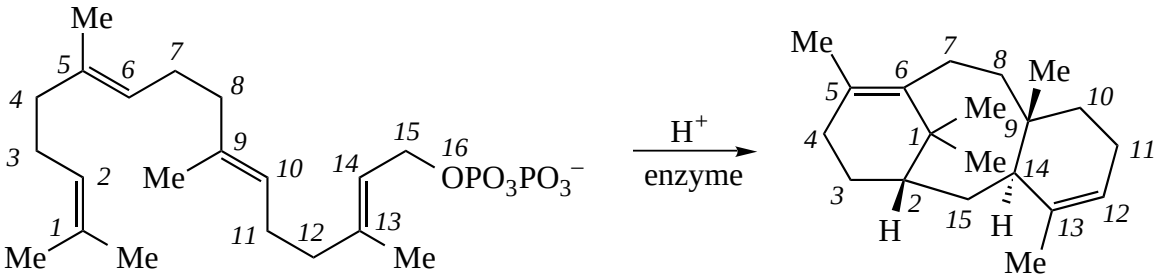


(f) The mechanism is polar under basic conditions (NaOEt). Two equivalents of cyanoacetate react with

each equivalent of dibromoethane. One of the CO_2Et groups from cyanoacetate is missing in the product and is replaced by H. The H can come from EtOH or HOH, so the CO_2Et is bound to EtO or HO. The two products differ only in the location of a H atom and a π bond; their numbering is the same. Made: C2–C5, C2'–C6, C2'–C3, C1'–OEt. Broken: C1'–C2', C5–Br, C6–Br.

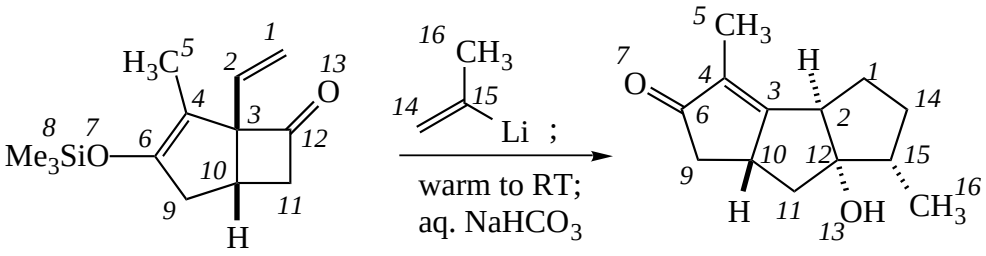


(g) Polar under acidic conditions. The enzyme serves to guide the reaction pathway toward one particular result, but the mechanism remains fundamentally unchanged from a solution phase mechanism. The Me groups provide clues as to the numbering. Made: C1–C6, C2–C15, C9–C14. Broken: C15–O16.

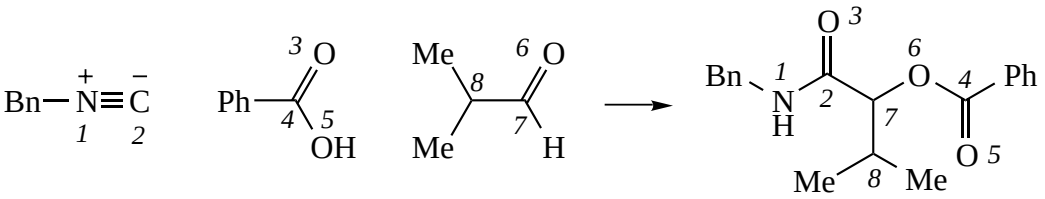


Geranylgeranyl pyrophosphate *A Taxane*

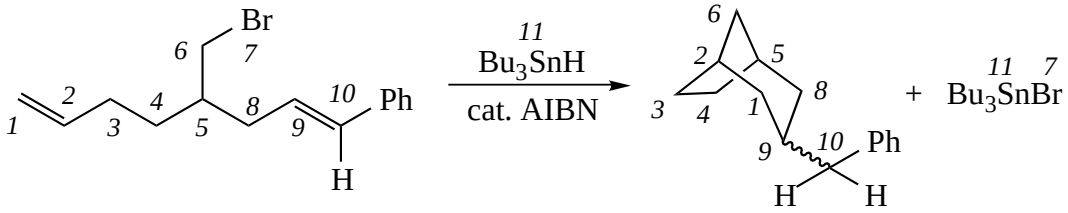
(h) Two types of mechanism are involved here: First polar under basic conditions, then pericyclic. At first the numbering might seem very difficult. There are two CH_3 groups in the starting material, C5 and C16, and two in the product. Use these as anchors to decide the best numbering method. Made: C1–C14, C2–C12, C12–C15. Broken: C3–C12, O7–Si8.



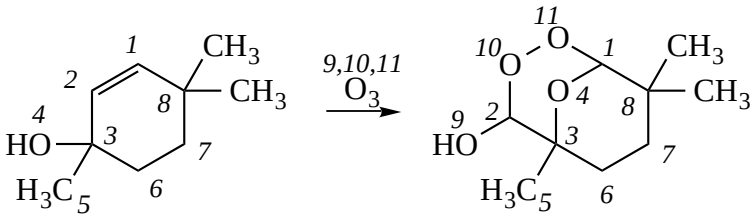
(i) The carboxylic acid suggests a polar acidic mechanism. Made: C2–C7, C2–O3, C4–O6. Broken: O3–C4.



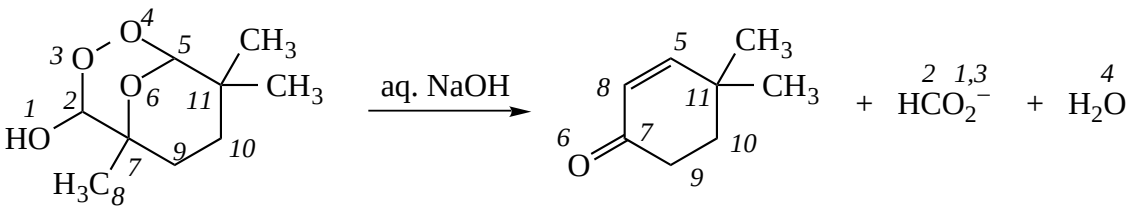
(j) Free-radical mechanism (AIBN). Both Br7 and Sn11 are missing from the product, so they are probably connected to one another in a by-product. H12 appears connected to C10 in the product, as C10 is the only C that has a different number of H's attached in S.M. and product. Made: C1–C9, C2–C6, Br7–Sn11. Broken: C6–Br7.



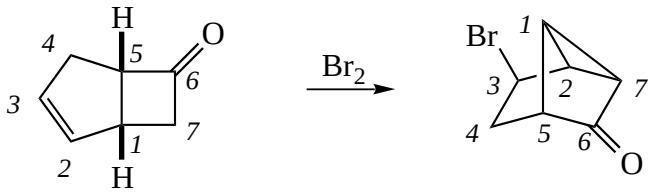
(k) No acid or base is present, and the reaction involves changes in π bonds. This is a pericyclic mechanism. Use C8 with its two Me groups as an anchor to start numbering. Ozone is a symmetrical molecule, but the middle O is different from the end O's; it's not clear which O in ozone ends up attached to which atom in the product. However, it is clear where O4 ends up, as it remains attached to C3. Made: C1–O11, C1–O4, C2–O9, C2–O10. Broken: C1–C2, O9–O10.



(l) Polar mechanism under basic conditions. Again, use C11 with its two Me groups as an anchor to start numbering. C7 remains attached to C8 and O6 in the product. C2 leaves as formate ion; the two O's attached to C2 in the S.M. remain attached to it in the formate product. O4 is still missing; it's probably lost as H_2O, with the two H's in H_2O coming from C8. Made: C5–C8. Broken: C2–C7, O3–O4, O4–C5, C5–O6.



(m) Bromine undergoes electrophilic (polar acidic) reactions in the absence of light. Use C6 as an anchor to begin numbering. In the S.M. there are two CH_2 groups, C4 and C7. The one CH_2 group in the product must be either C4 or C7. C7 is next to C6 in the S.M., while C4 is not; since the CH_2 group in the product is not next to C6, it is probably C4. Made: C2–C7, C3–Br. Broken: Br–Br.



5. N= nucleophilic, E= electrophilic, A= acidic.

(a) E	(b) none*	(c) E	(d) A	(e) A**	(f) E
(g) none†	(h) N	(i) none	(j) N	(k) A	(l) E
(m) none**	(n) E	(o) A	(p) N	(q) none	(r) N
(s) A, N	(t) E	(u) E	(v) none	(w) none	(x) N
(y) A	(z) E	(aa) A	(bb) N	(cc) N, A	(dd) N
(ee) none	(ff) N	(gg) E, A	(hh) N	(ii) none	(jj) N
(kk) N	(ll) E	(mm) slightly A?			

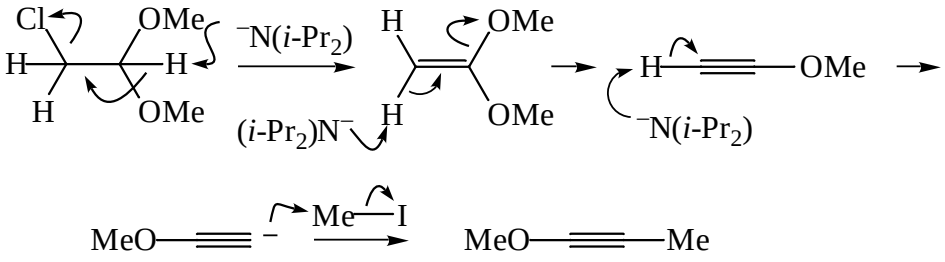
*See text (Section B.1) for an explanation.

**The O atom still has a lone pair, but if it were to use it in a nucleophilic reaction, it would acquire a very unfavorable +2 formal charge.

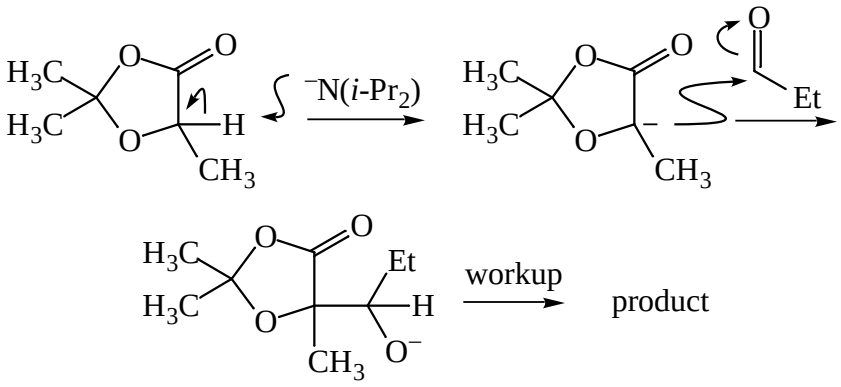
†The fact that an elimination reaction can occur upon removal of H^+ from this atom (with loss of the leaving group next door) is irrelevant to the question of the *acidity* of this atom. Acidity is a measure of the difference in energy between an acid and its conjugate base. The conjugate base formed by removing H^+ from this atom would be very high in energy.

Answers To Chapter 2 In-Chapter Problems.

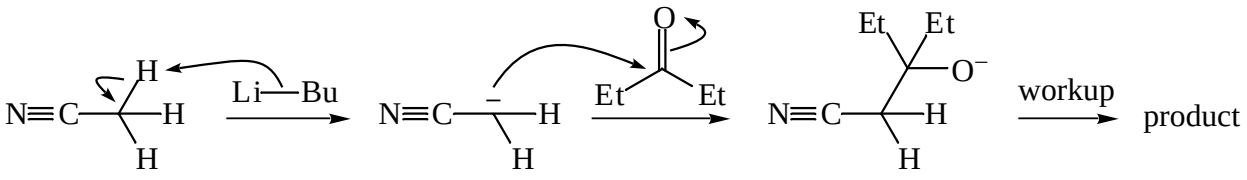
2.1. LDA is a strong base. Two E2 eliminations give an alkyne, which is deprotonated by the excess LDA to give an alkynyl anion. This species then reacts with MeI by an S_N2 process.



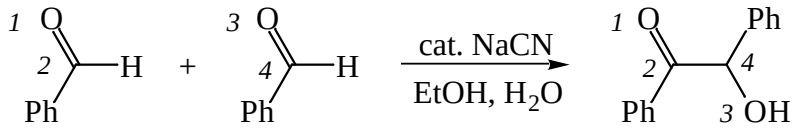
2.2(a). LDA deprotonates the C α to the ester, which adds to the aldehyde to give the aldol product after workup.



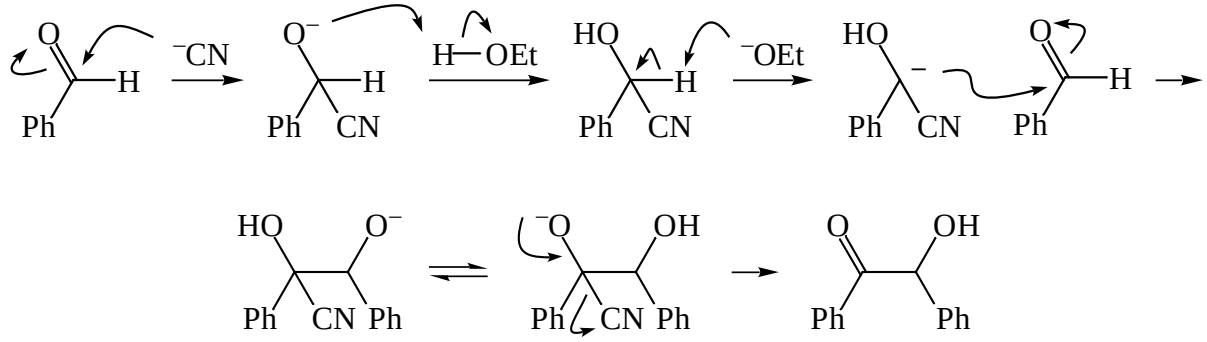
2.2(b). BuLi deprotonates the C α to the nitrile, which adds to the ketone to give the aldol product after workup.



2.3. Make: C2–C3. Break: none. Note that because the NaCN is catalytic, its atoms are not incorporated into the product, and hence there is no need to number them.

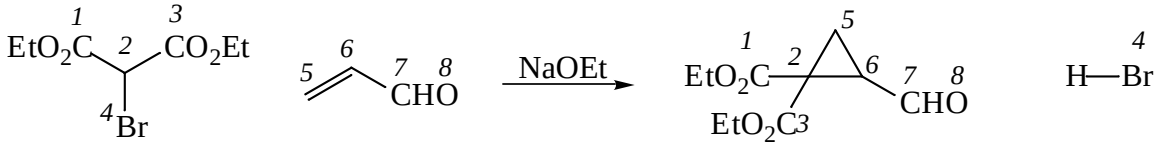


C2 is electrophilic, and C4 is ... electrophilic! To make a bond between them, C2 must be turned into a nucleophile (*umpolung*). This must be the purpose of the $^{-}$CN. Aldehydes are not acidic at the carbonyl C, so the $^{-}$CN cannot simply deprotonate C2. Instead, it must add to C2. Now C2 is α to a nitrile, it is much more acidic, and it can be deprotonated by excess $^{-}$CN to give an enolate, which can add to C4. Finally, deprotonation of O1 and elimination of $^{-}$CN gives the observed product.

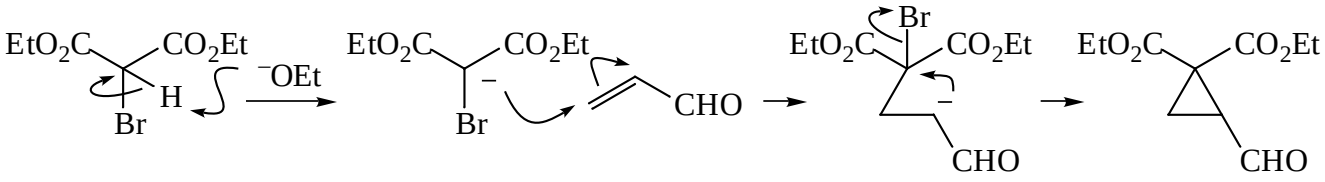


2.4.

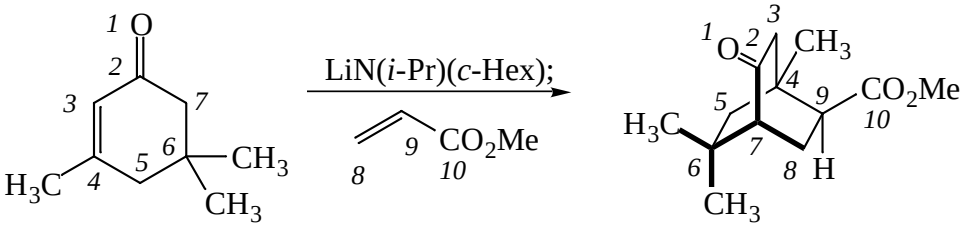
(a) Make: C2–C5, C2–C6. Break: C2–Br4.



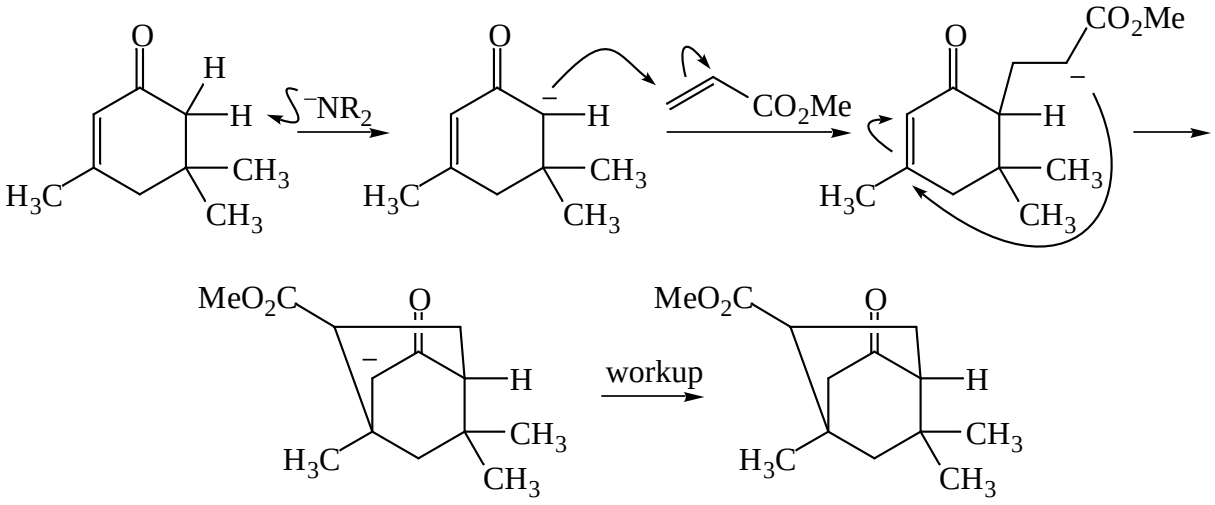
C2 is both electrophilic and particularly acidic. C5 is electrophilic, and C6 has no reactivity, so the first bond to be made must be C2–C5. Therefore, deprotonation of C2 gives a nucleophile, which can attack electrophilic C5 to give an enolate at C6. *Now* C6 is nucleophilic, and intramolecular S_N2 substitution at C2 gives the product. Although C2 is a tertiary alkyl halide and is not normally expected to undergo S_N2 substitution, this reaction works because it is intramolecular.



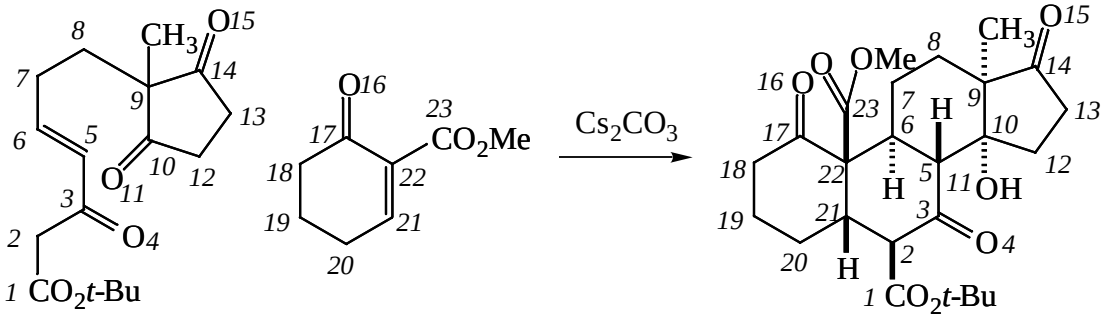
(b) Make: C7–C8, C4–C9. Break: none.



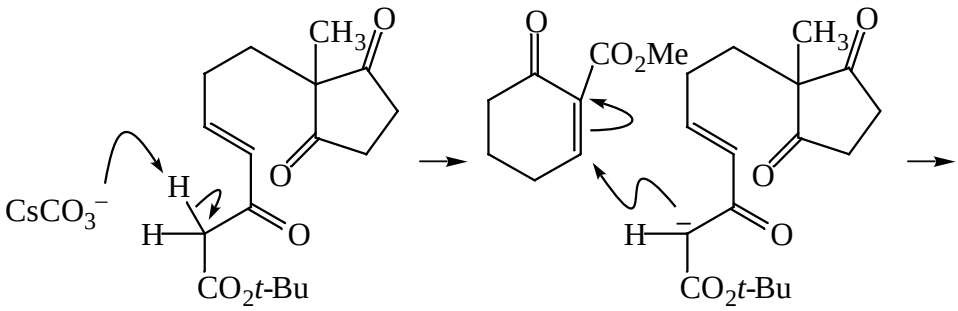
The thing above the arrow is a fancy version of LDA. C4 and C8 are electrophilic, C9 is unreactive, and C7 is acidic, so first step must be to deprotonate C7 to make it nucleophilic. Conjugate addition to C8 generates a nucleophile at C9, which adds to C4 to give a new enolate. Workup then provides the product.

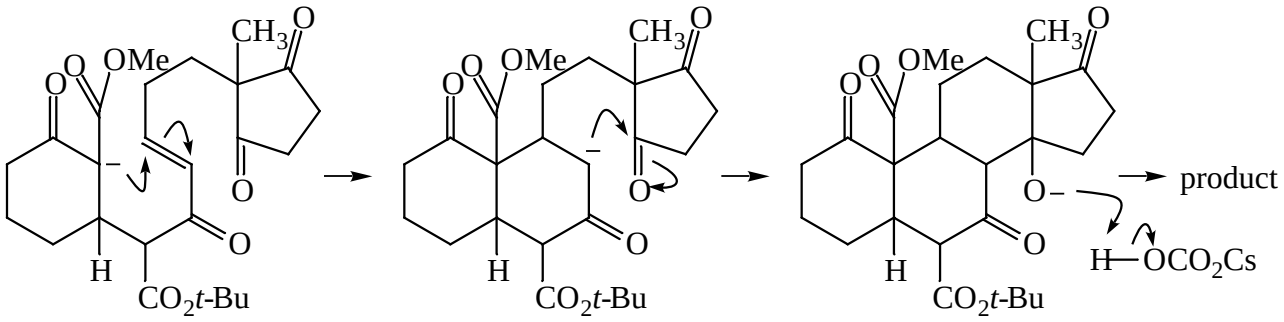


(c) Make: C2–C21, C5–C11, C6–C22. Break: none.



Among the six atoms involved in bond-making, three (C6, C10, C21) are electrophilic, two (C5, C22) are unreactive, and only C2 is acidic, so first step is deprotonation of C2. The nucleophile adds to C21, making C22 nucleophilic. It adds to C6, making C5 nucleophilic. It adds to C10, giving the product.

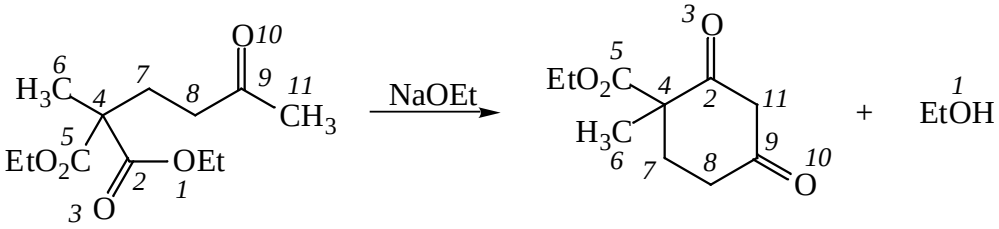




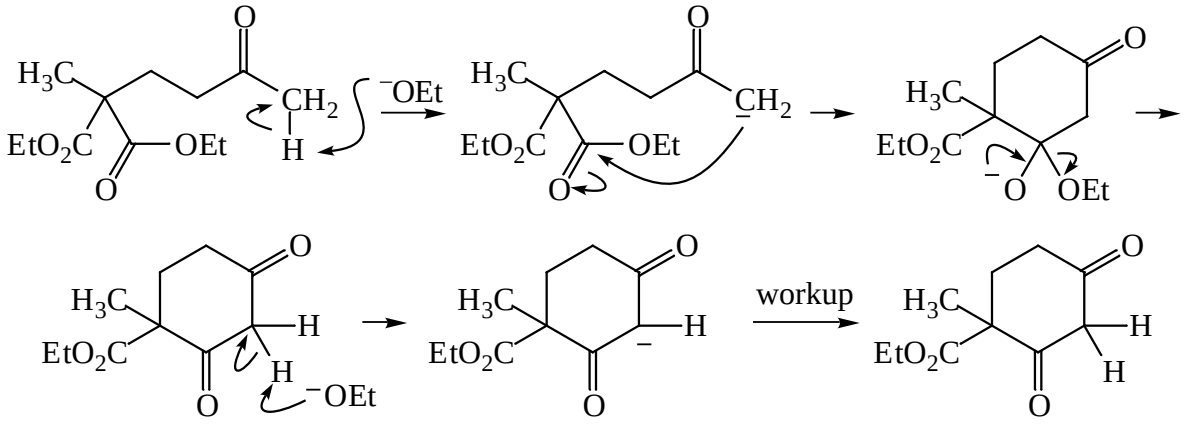
2.5. Because under basic conditions carboxylic acids are deprotonated to the carboxylate ions, which are no longer electrophilic enough that a weak nucleophile like MeO^- can attack them. Upon workup the carboxylate is neutralized to give back the carboxylic acid.

2.6.

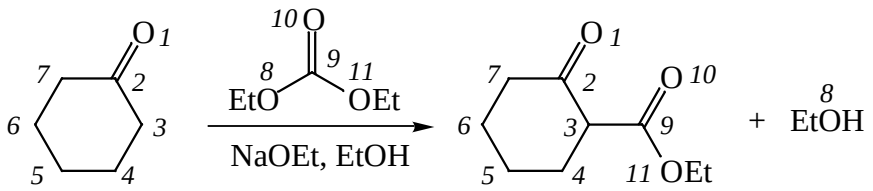
(a) Balancing the equation shows that EtOH is a by-product. Make: C2–C11. Break: O1–C2.



C2 is electrophilic, so first step must be to deprotonate C11 to make it nucleophilic. Addition to C2 followed by elimination of O1 affords the product. Because the product is a very acidic 1,3-diketone, though, it is deprotonated under the reaction conditions to give an anion. Workup then affords the neutral product.



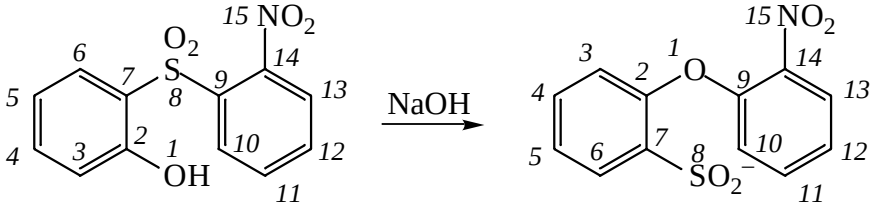
(b) Make: C3–C9. Break: O8–C9.



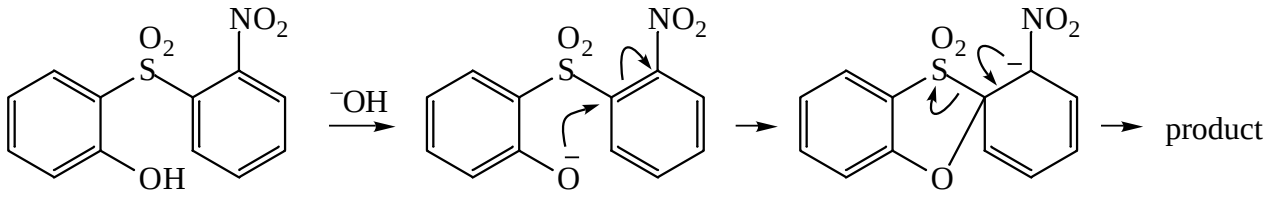
The mechanism is exactly the same as drawn in part (a).

2.7.

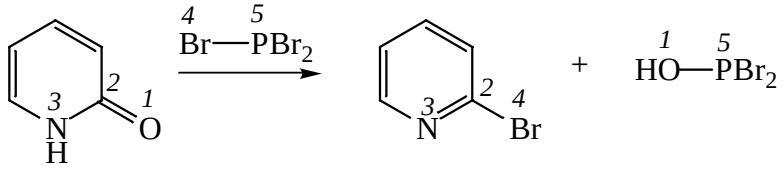
(a) Make: O1–C9. Break: S8–C9.



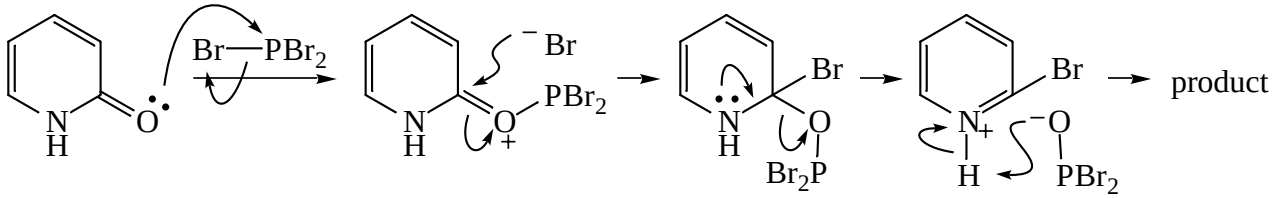
The base deprotonates O1, which adds to C9, giving an anion that is delocalized over C10, C12, C14, and into the NO_2 group. The anion then expels SO_2^- to give the product.



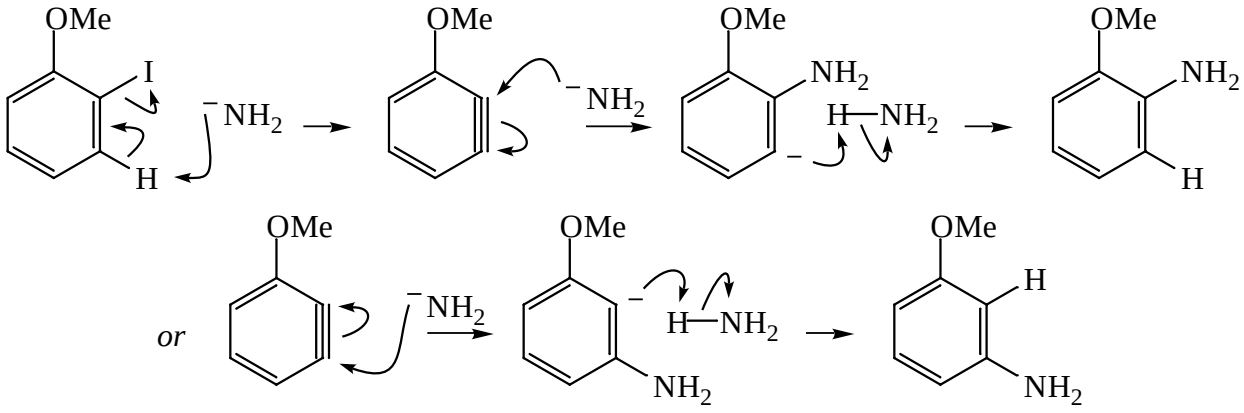
(b) Make: O1–P5, C2–Br4. Break: O1–C2, Br4–P5.



O1 is clearly a nucleophile, and C2 is clearly an electrophile. P5 could be either a nucleophile (lone pair) or an electrophile (leaving group attached), but because it reacts with O1 and because the P5–Br4 bond breaks, in this reaction it must be acting as an electrophile. Attack of O1 on P5 in S_N2 fashion displaces Br4, which can now attack C2 in an addition reaction. Finally, the N3 lone pair is used to expel O1 to give the observed product.



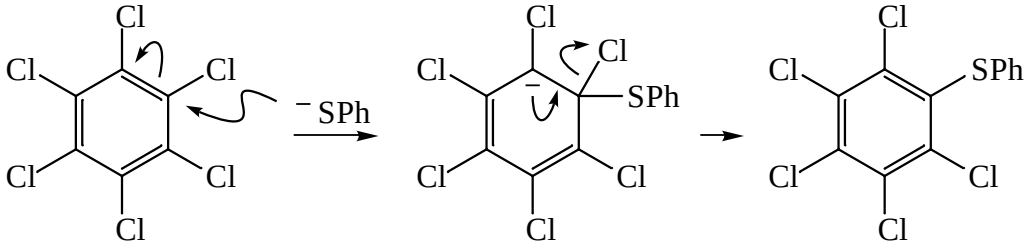
2.8. E2 elimination of HI from the aryl iodide gives a benzyne, which can be attacked at either C of the triple bond to give two different products.



2.9. E2 elimination of HBr from the alkenyl halide gives an alkyne or an allene, neither of which is electrophilic. The only reason benzyne is electrophilic is because of the strain of having two C(sp) atoms in a six-membered ring. Remove the six-membered ring, and the strain goes away.

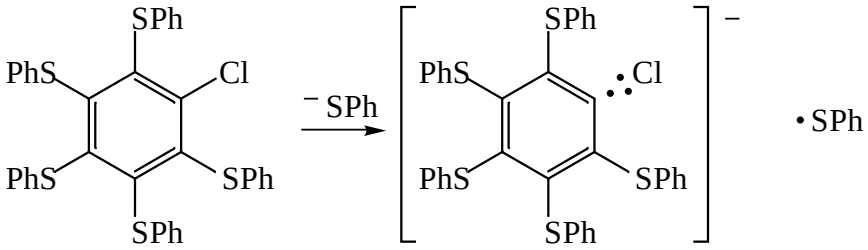
2.10. The first substitution involves attack of PhS^- on C_6Cl_6 to give $C_6Cl_5(SPh)$, and the last involves attack of PhS^- on $C_6Cl(SPh)_5$ to give $C_6(SPh)_6$. The elimination–addition mechanism is ruled out in both cases because of the absence of H atoms adjacent to Cl, so the choices are addition–elimination or $S_{RN}1$. The first reaction involves a very electron-poor arene (all those inductively withdrawing Cl atoms), so addition–elimination is reasonable, although $S_{RN}1$ is not unreasonable. The last substitution, though, is at an electron-rich arene, so only $S_{RN}1$ is a reasonable possibility.

First:

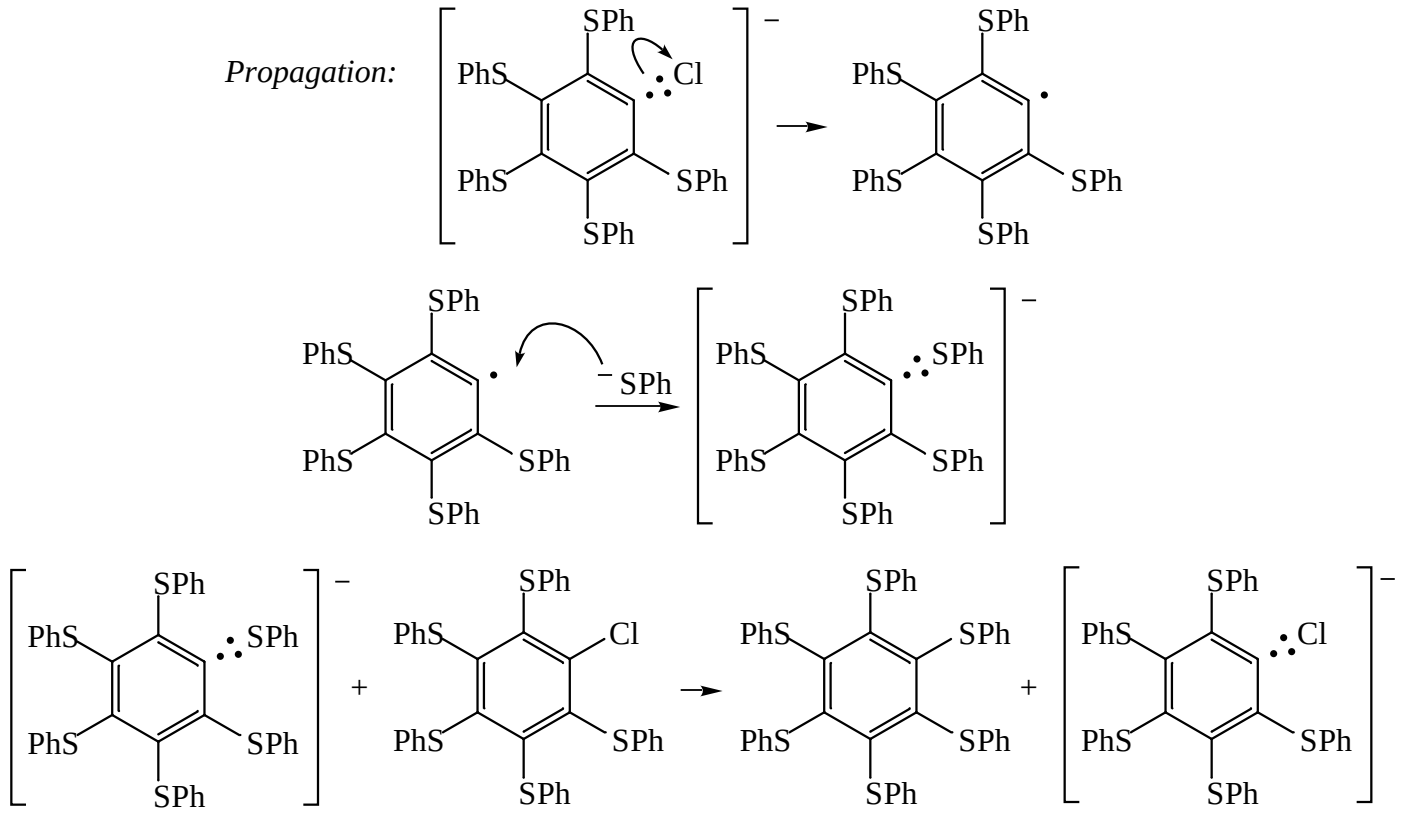


Last:

Initiation:

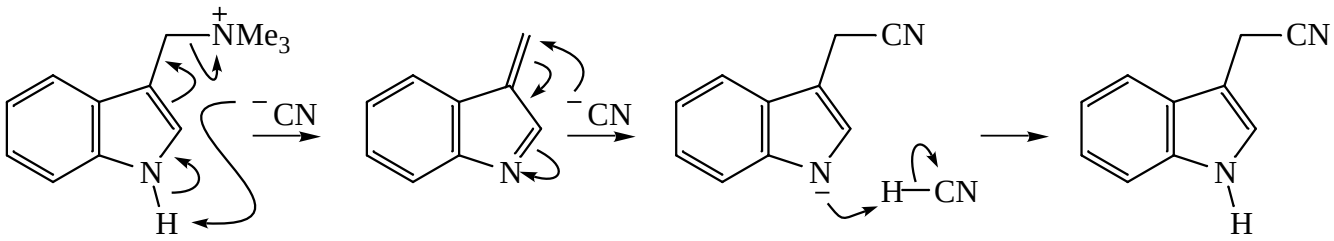


Propagation:



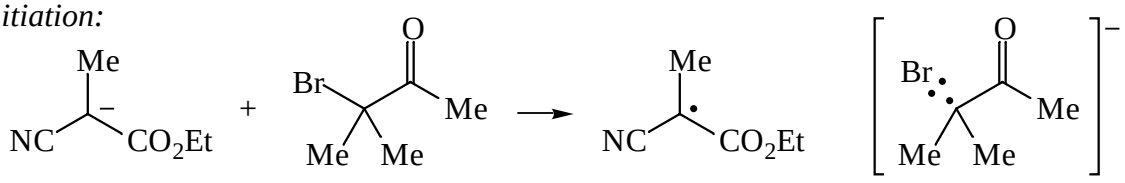
2.11.

(a) An addition–elimination mechanism is reasonable.

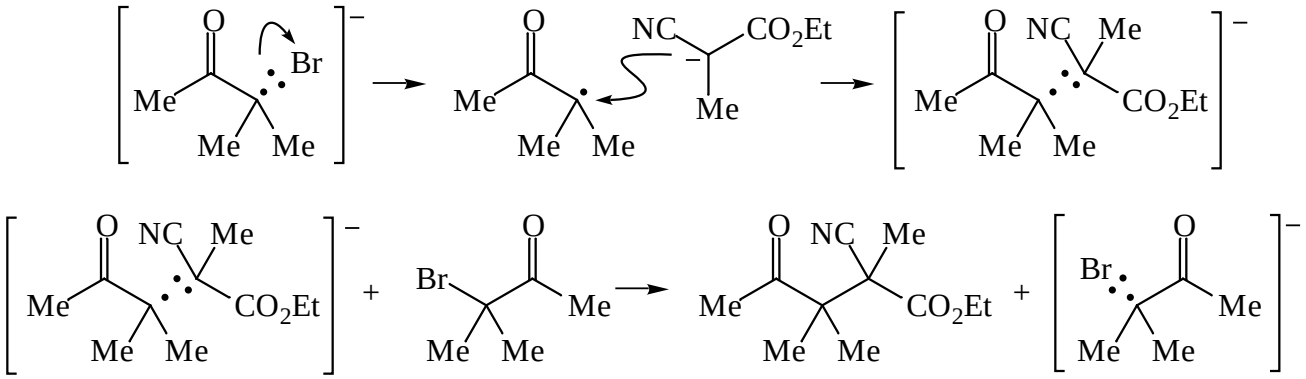


(b) An addition–elimination mechanism is not reasonable. Elimination of HBr from the starting material gives an α,β-unsaturated ketone that is now a π bond electrophile at a C different from the one that originally had the Br attached to it. The only reasonable mechanism is $S_{RN}1$.

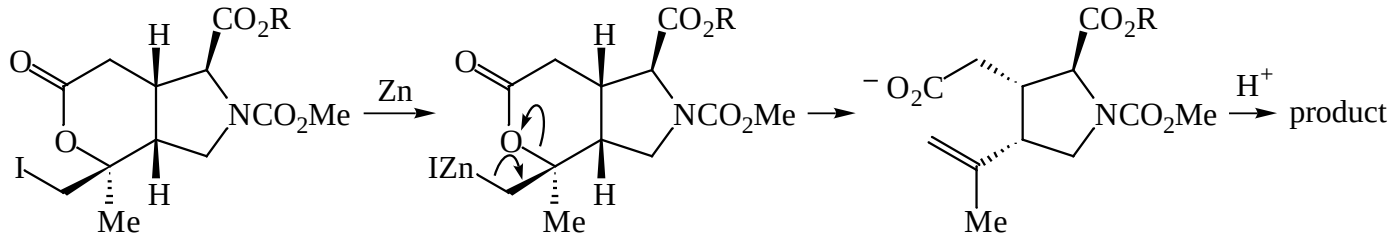
Initiation:



Propagation:

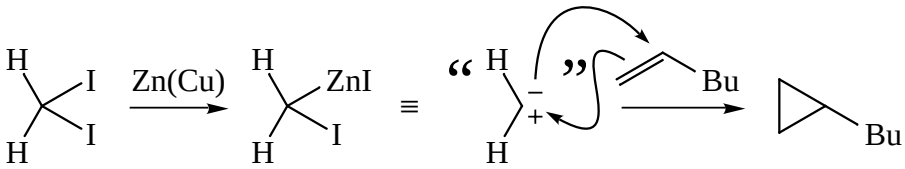


2.12.

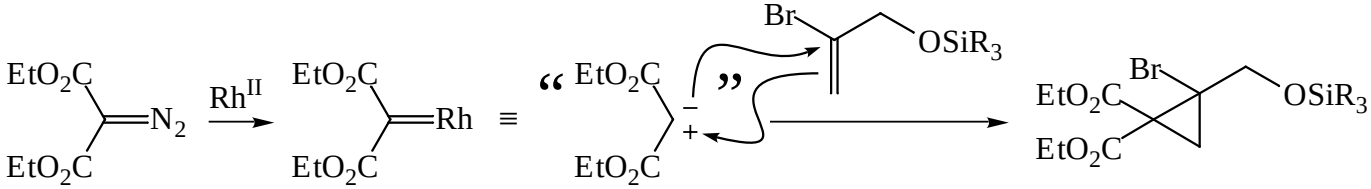


2.13.

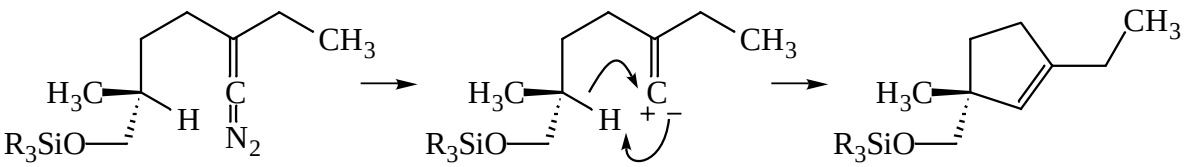
(a)



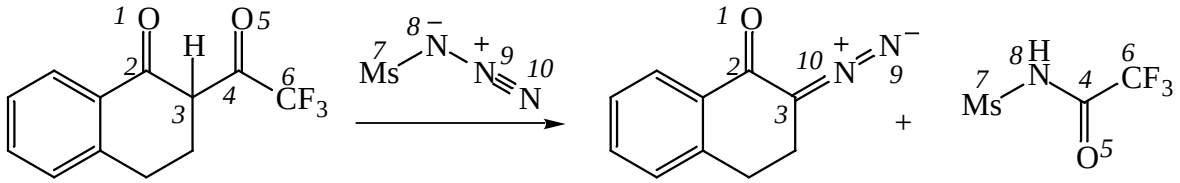
(b)



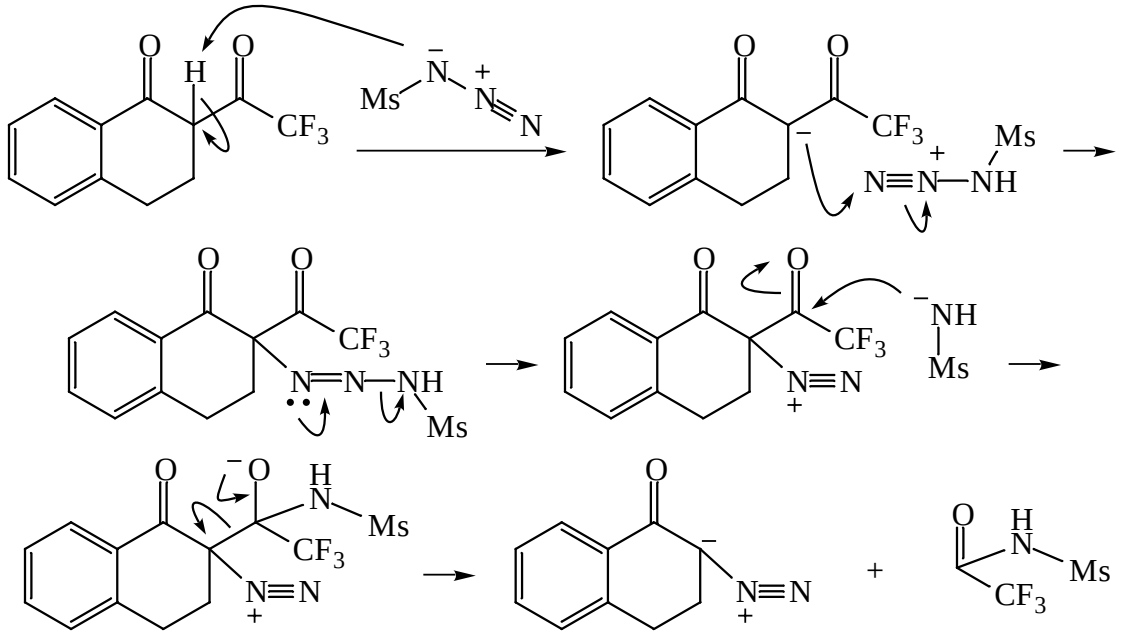
2.14.



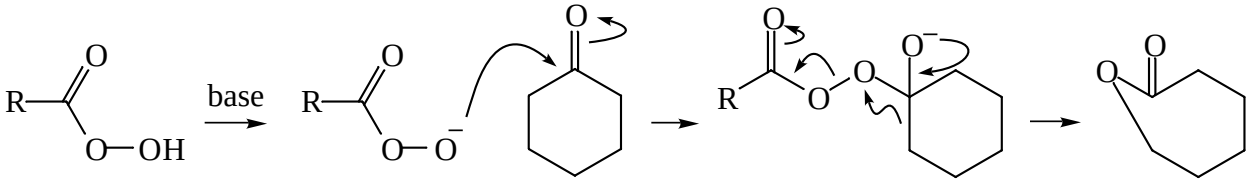
2.15. Numbering correctly is key to this problem. The written product is missing the fragments $COCF_3$ and MsN, so it is likely that they are connected to one another in a by-product. All the numbering in the product is clear except for N8, N9, and N10. N8 is attached to Ms in the starting material and is probably still attached to it in the product. But is N9 or N10 attached to C3 in the product? C3 is very acidic, and when it is deprotonated it becomes nucleophilic. N9 has a formal positive charge, so N10 is electrophilic. Therefore, N10 is most likely attached to C3 in the product. Make: C3–N10, C4–N8. Break: C3–C4, N8–N9.



N8 deprotonates C3 to make the latter nucleophilic, and it adds to N10. The lone pair on N10 is then used to expel N8 from N9. N8 then comes back and adds to C4, and expulsion of C3 from C4 affords the two products.

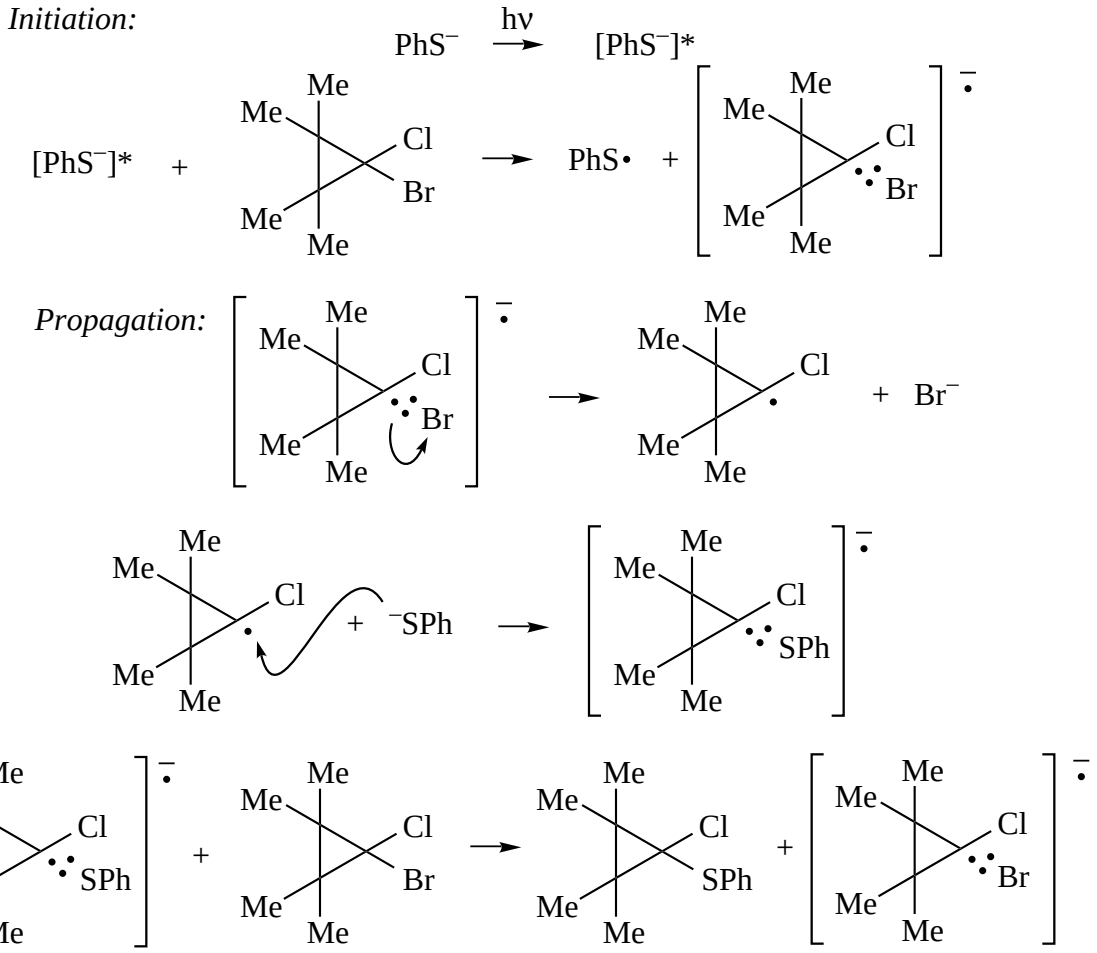


2.16.

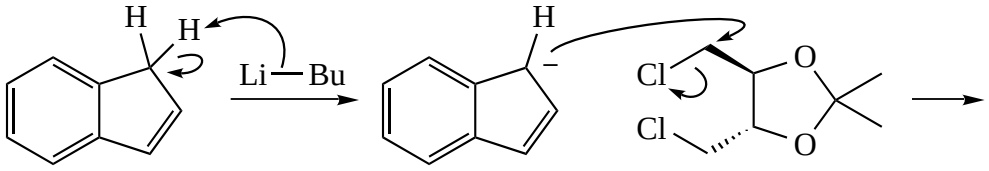


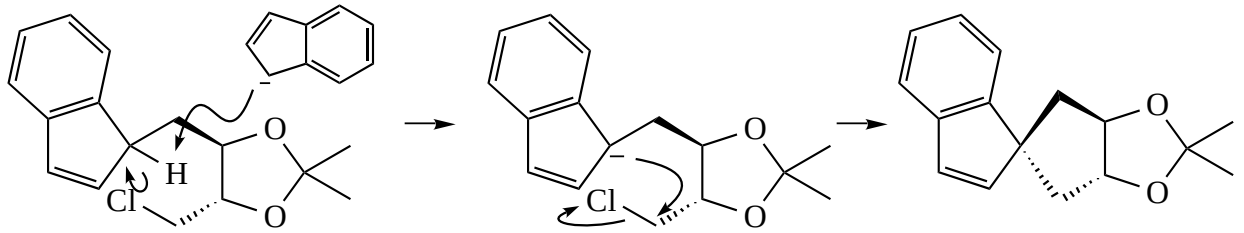
Answers To Chapter 2 End-of-Chapter Problems.

1. (a) Substitution at a 3° alkyl halide rarely proceeds by an S_N2 mechanism, unless the reaction is intramolecular. In this case S_N2 is even less likely because of the highly hindered nature of the electrophile and the fact that the electrophilic C is unlikely to want to expand its bond angles from 109° to 120° on proceeding through the S_N2 transition state. The other possibility in this case is $S_{RN}1$, which is reasonable given the heavy atom nucleophile and the requirement of light.

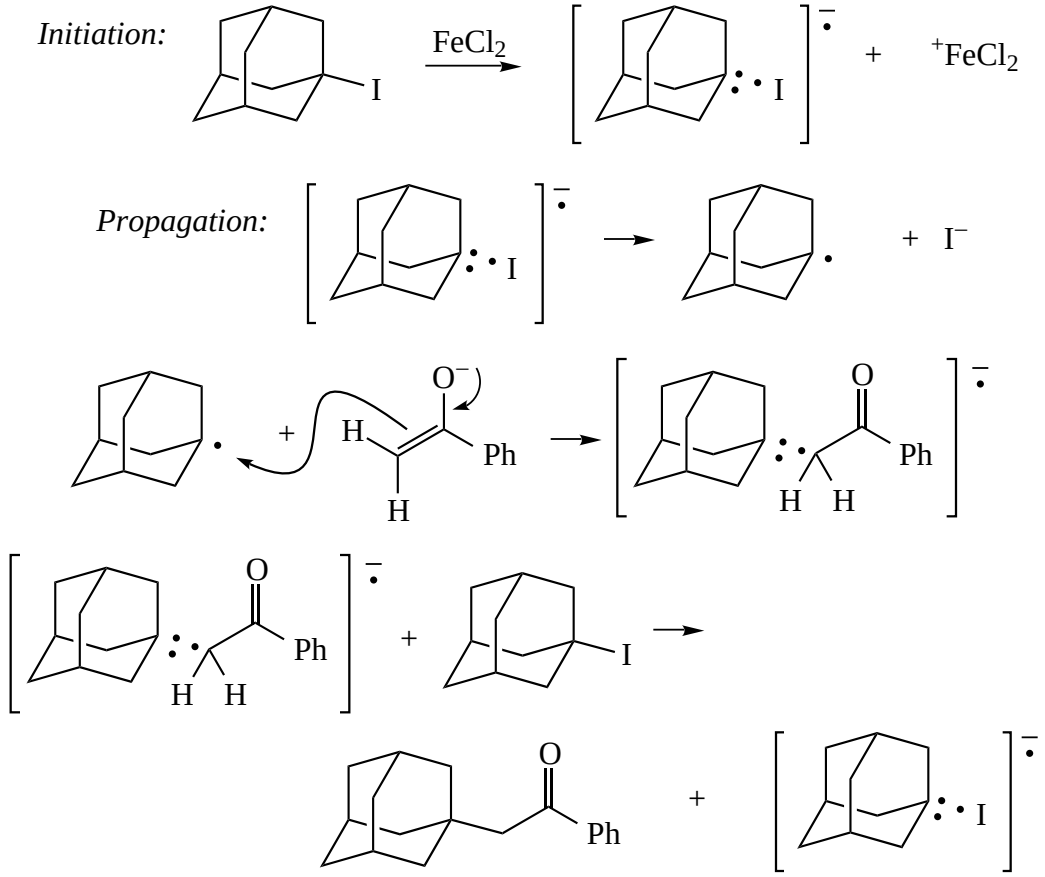


(b) The 1° halide will definitely undergo substitution by an S_N2 mechanism. Indene is a pretty good acid ($pK_a \approx 19$) due to aromatic stabilization of the anion. After deprotonation with BuLi, it attacks the electrophilic C by S_N2. A second equivalent of indenyl anion then redeprotonates the indenyl group of the product, allowing a second, intramolecular S_N2 reaction to proceed to give the observed product.

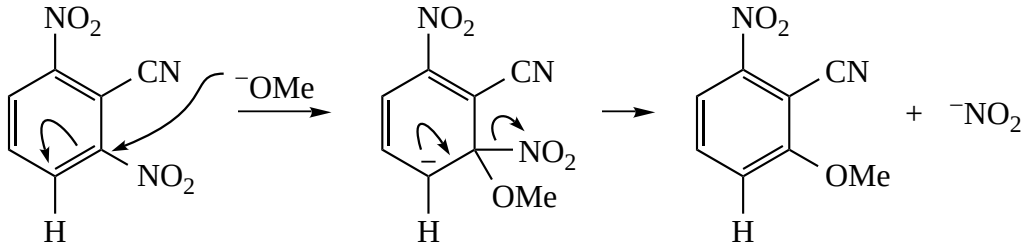




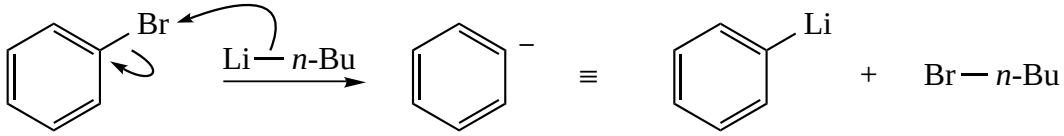
(c) This 3°, uninvertable halide cannot undergo S_N2 substitution. An elimination–addition mechanism is unlikely because the base is not terribly strong and the neighboring C–H bonds are not parallel to the C–I bond. The most likely possibility is $S_{RN}1$. C(sp^3)–I bonds are good substrates for $S_{RN}1$ reactions. The $FeCl_2$ is a one-electron reducing agent ($Fe^{II} \rightarrow Fe^{III}$) that acts as an initiator.



(d) Substitution on arenes with strongly electron-withdrawing groups usually takes place by an addition–elimination mechanism. In this case the leaving group is nitrite, $^-NO_2$.



(e) The first product results from halogen–metal exchange. The mechanism of halogen–metal exchange is not well understood. It may proceed by S_N2 substitution at Br by the nucleophilic C, or it may involve electron transfer steps. (See Chapter 5.)



Small amounts of aromatic substitution product are often formed during halogen–metal exchange. Many mechanisms are possible.

The major product PhLi could react with the by-product *n*-BuBr in an S_N2 reaction.

Addition–elimination could occur. PhBr is not an electrophilic arene, but the very high nucleophilicity of *n*-BuLi may compensate.

An $S_{RN}1$ reaction could occur.

Elimination–addition (benzyne mechanism) could occur.

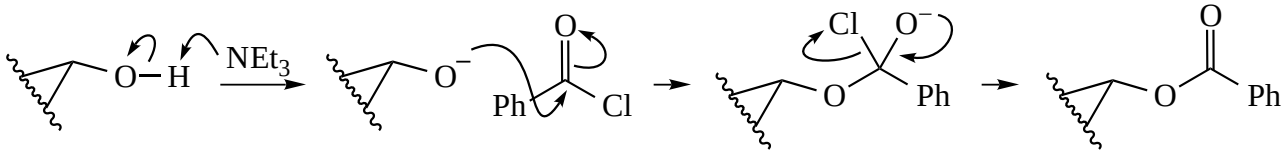
Certain experiments would help to rule these possibilities in or out.

Elimination–addition goes through a benzyne intermediate, and the nucleophile can add to either benzyne C, so both 3- and 4-bromotoluene should give mixtures of products if this mechanism is operative.

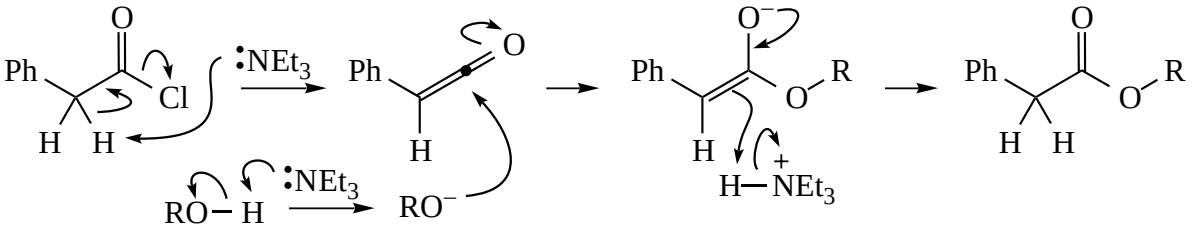
Addition–elimination would accelerate (compared to halogen–metal exchange) with electron-withdrawing groups on the ring and decelerate with electron-donating groups on the ring.

If the S_N2 mechanism is operative, changing *n*-BuLi to *s*-BuLi would reduce the amount of substitution product a lot, and changing it to CH_3Li would increase it. If the $S_{RN}1$ mechanism is operative, changing *n*-BuLi to *s*-BuLi would not change the amount of substitution much, and changing it to CH_3Li would reduce it a lot.

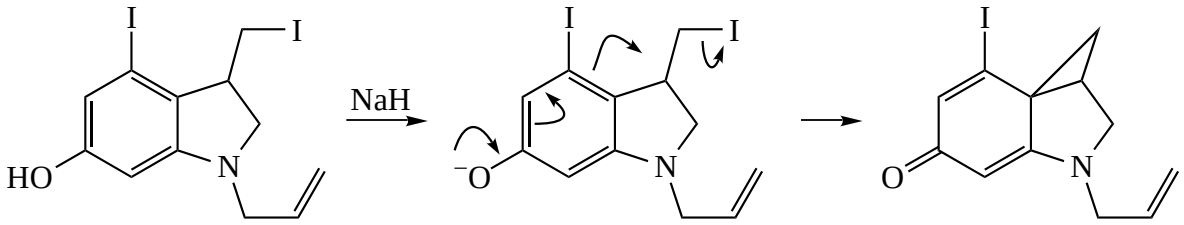
(f) Acyl chlorides can undergo substitution by two mechanisms: addition–elimination or elimination–addition (ketene mechanism). In this case, elimination–addition can't occur because there are no α H's. The mechanism must be addition–elimination.



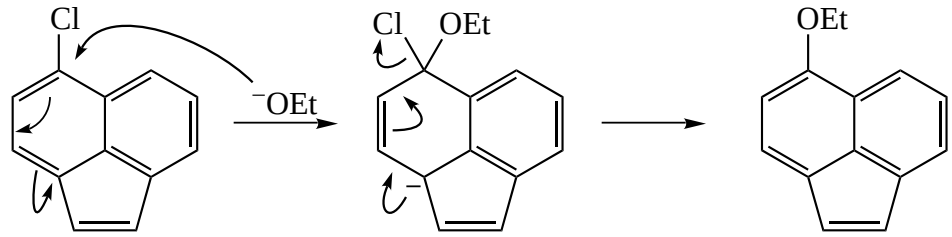
(g) This acyl chloride is particularly prone to elimination because of the acidicity of the benzylic H's. Addition–elimination can't be ruled out, but elimination–addition is more likely.



(h) The reaction proceeds by an S_N2 mechanism. The reaction has a very low entropy of activation, so it proceeds despite the loss of aromaticity. The product is a model of the antitumor agent duocarmycin. DNA reacts with duocarmycin by attacking the CH_2 group of the cyclopropane ring in an S_N2 reaction.

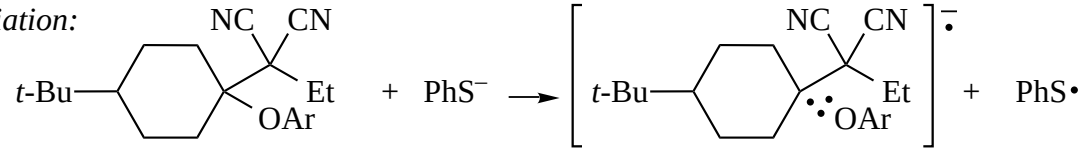


(i) This nucleophilic substitution reaction at aromatic C(sp^2) can proceed by addition–elimination, elimination–addition, or $S_{RN}1$. In this case, addition–elimination is low in energy because of the strong stabilization of the Meisenheimer complex by aromaticity of the five-membered ring.

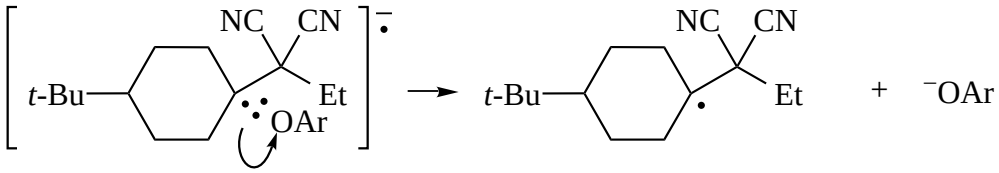


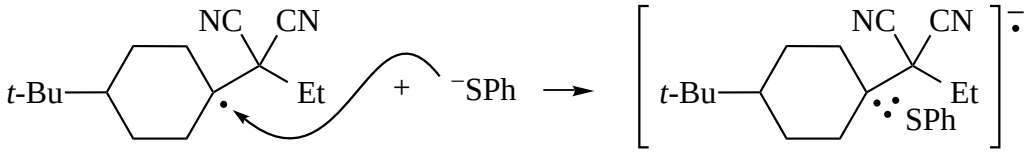
(j) The mechanism cannot be S_N2 because of the 3° alkyl electrophile. The most likely mechanism is $S_{RN}1$, which proceeds through radical anions. The best resonance structure of the radical anion of the starting material puts the odd electron in the aromatic ring, and the best resonance structure of the radical anion of the product puts the odd electron on S, but in both cases it is more convenient to draw the resonance structure in which there is a three-electron, two-center bond.

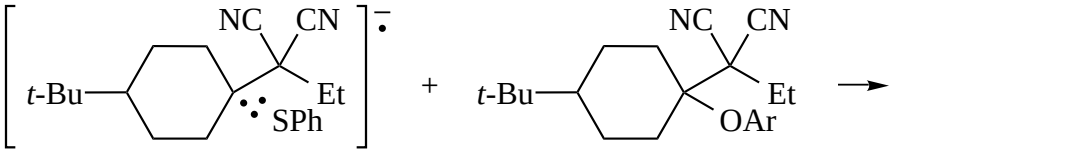
Initiation:

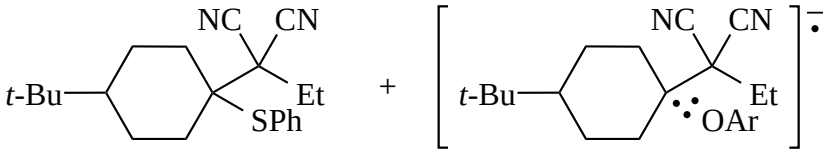


Propagation:



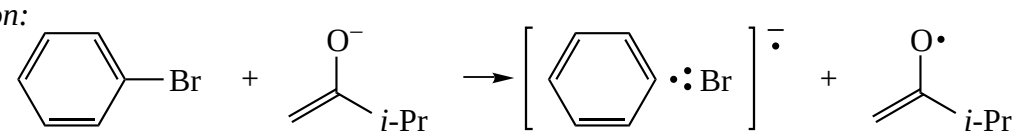




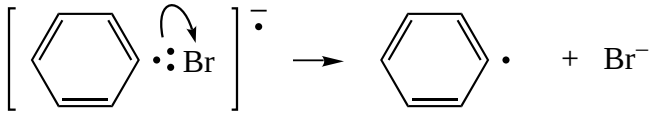


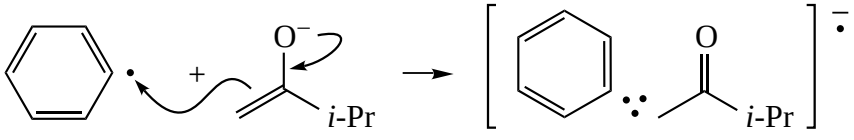
(k) Substitution at aromatic C(sp^2) can occur by one of three mechanisms. Addition–elimination requires that the ring be substituted with electron-withdrawing groups. Elimination–addition requires very strong bases like NH_2^-. The third mechanism, $S_{RN}1$, is operative here; the light is a clue that radicals are involved.

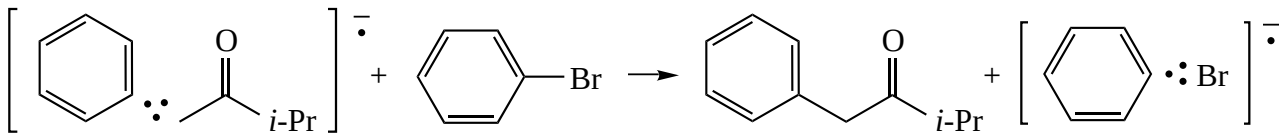
Initiation:



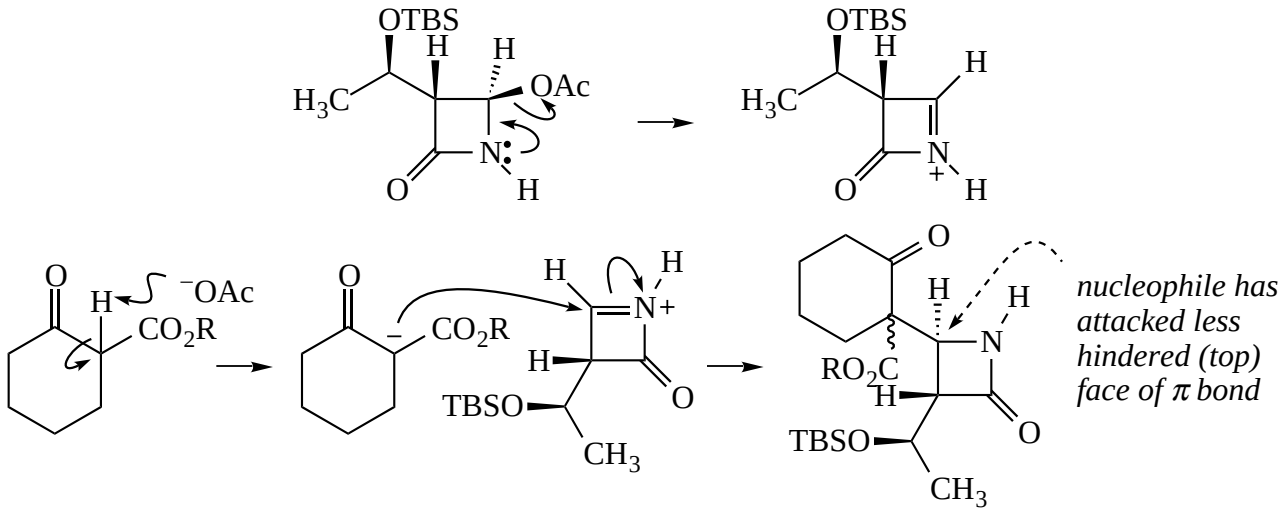
Propagation:



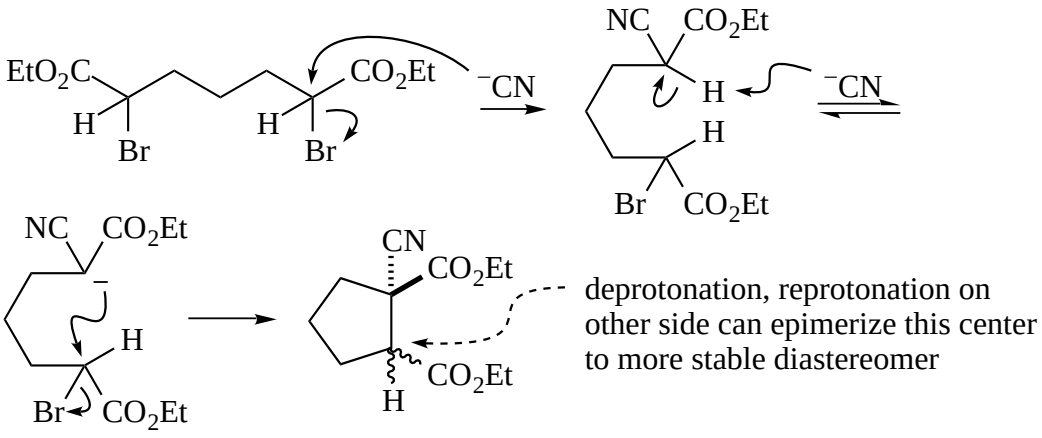




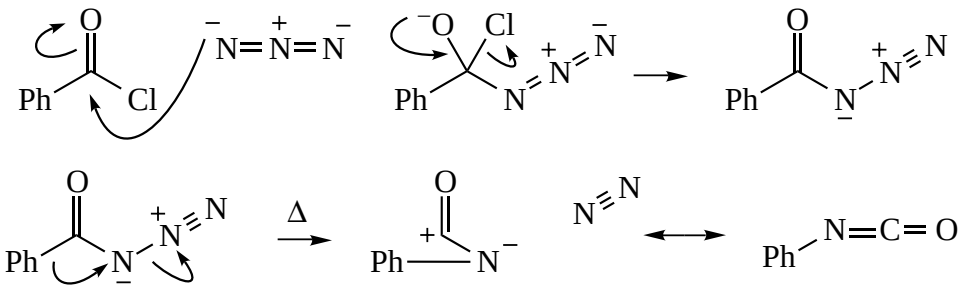
(l) The mechanism clearly cannot be S_N2, because substitution occurs with retention of configuration. Two sequential S_N2 reactions are a possibility, but unlikely, because $^-$OAc is a lousy leaving group in S_N2 reactions. It is more likely that an elimination–addition mechanism operates. The AcO group is α to N, and the lone pair on N weakens and lengthens the C–O bond, making it prone to leave to give an *N*-acyl-iminium ion. The AcO^- deprotonates the ketoester to give an enolate, which adds to the electrophilic C=N π bond from the less hindered face (opposite from the substituent on C2 of the lactam), giving a *trans* product as observed.



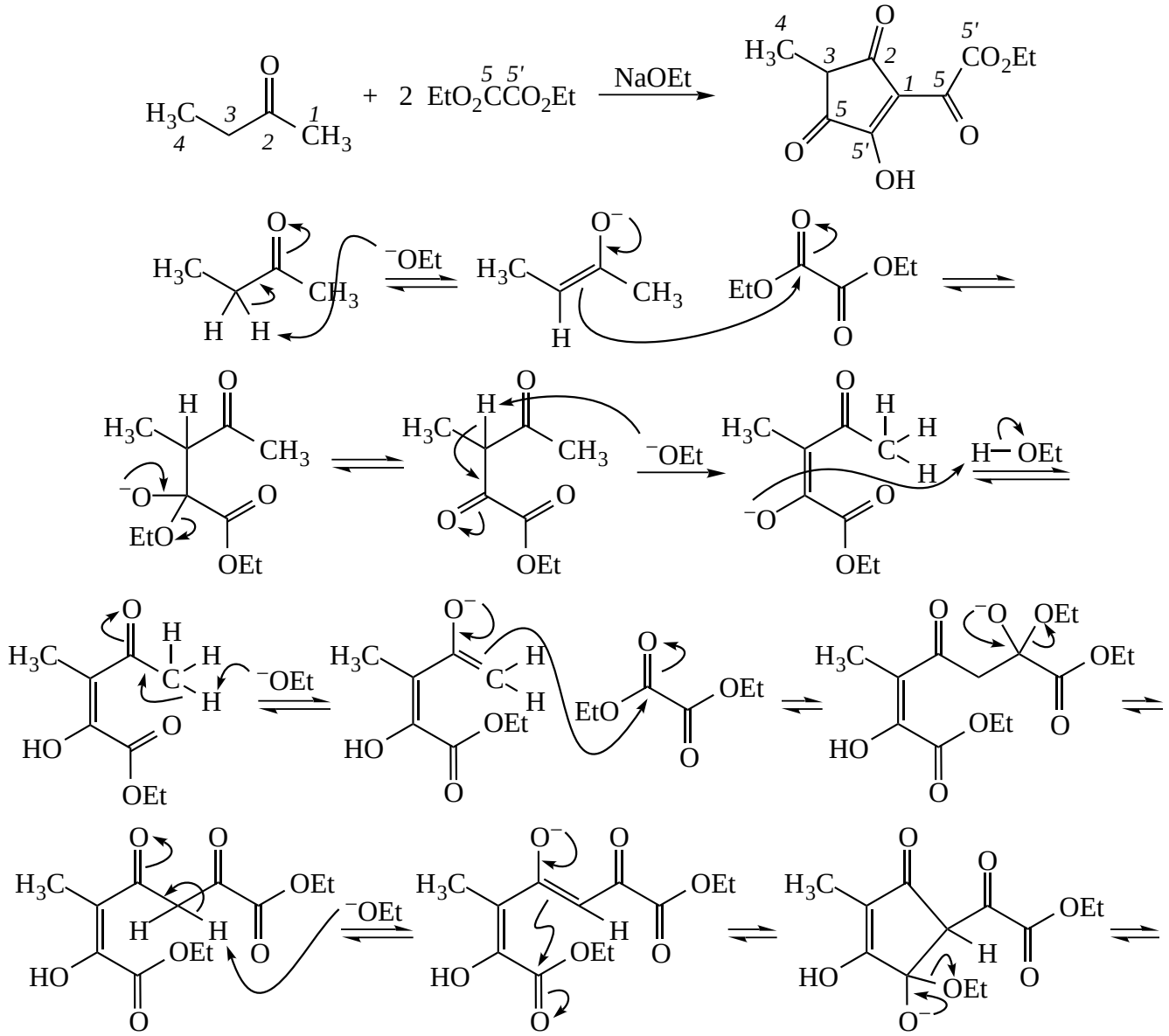
2. (a) Cyanide can act as a nucleophile toward the bromoester, displacing one Br^- in an S_N2 reaction to give a cyanoacetate. The cyanoacetate ($pK_a = 9$) is deprotonated by another equivalent of $^-$CN ($pK_b = 9$) to give an enolate that attacks the *other* bromoester to give the product.

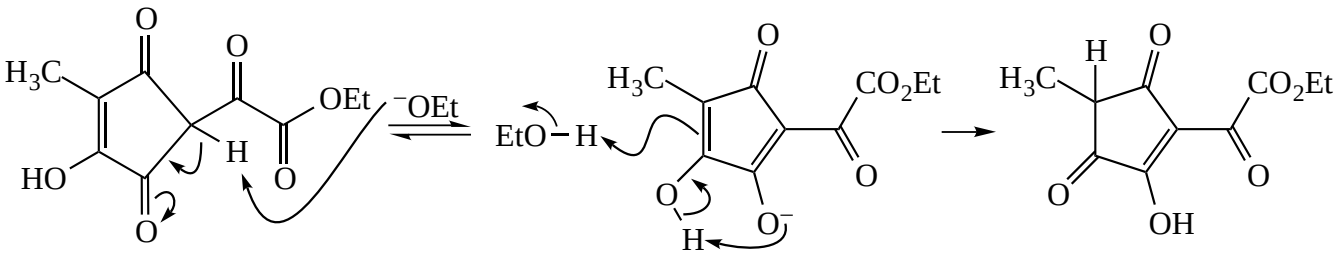


(b) The acyl chloride is a potent electrophile and N_3^- is a nucleophile, so the first part of the reaction involves addition–elimination to make the acyl azide. Upon heating, the Ph–CO bond breaks and a Ph–N bond forms. This suggests a 1,2-shift, promoted by loss of N_2.

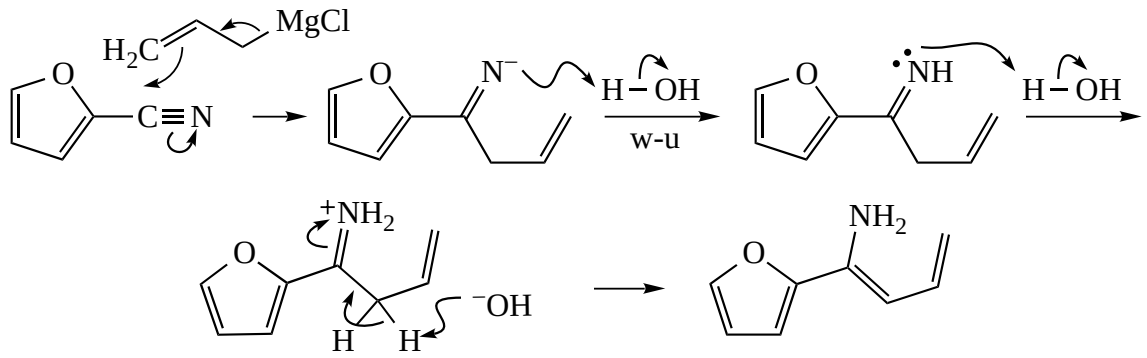


(c) Make: C1–C5, C1–C5', C3–C5. Break: C5–OEt (twice), C5'–OEt (once). Each substitution at C(sp^2) must occur by addition–elimination. The particular order of acylation events can vary from the answer given here.

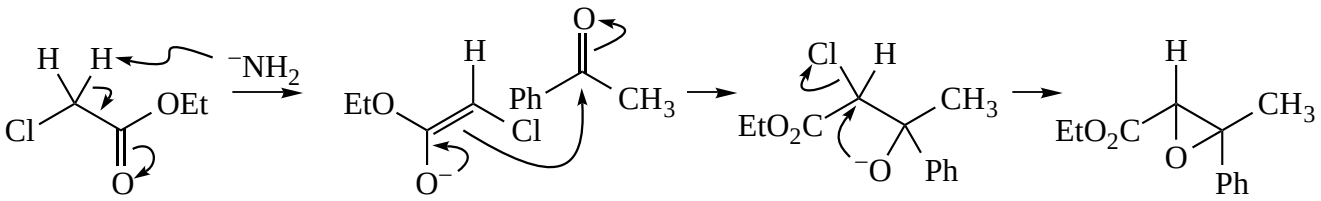




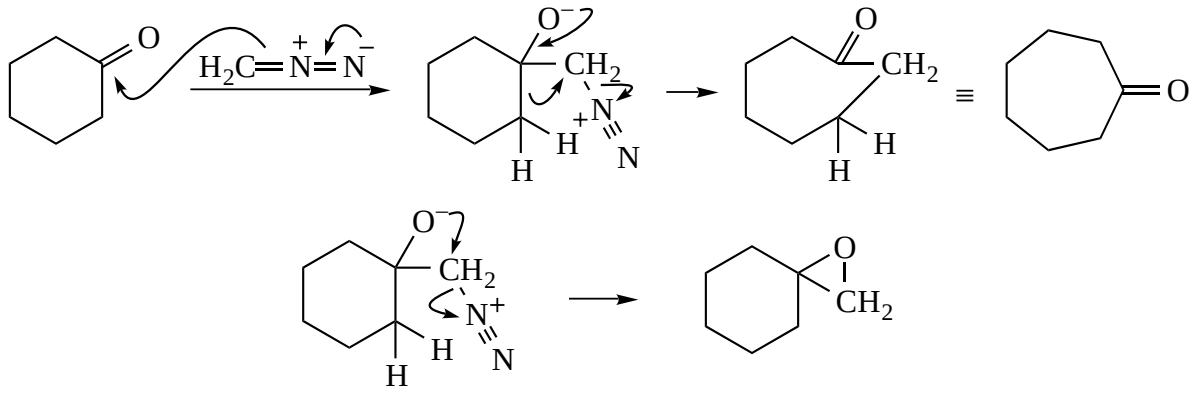
(d) Either the α or the γ carbon of the Grignard reagent can attack the nitrile. Isomerization of the initial product occurs upon workup, probably by protonation–deprotonation (rather than deprotonation–protonation) because of the weak acidity and decent basicity of imines.



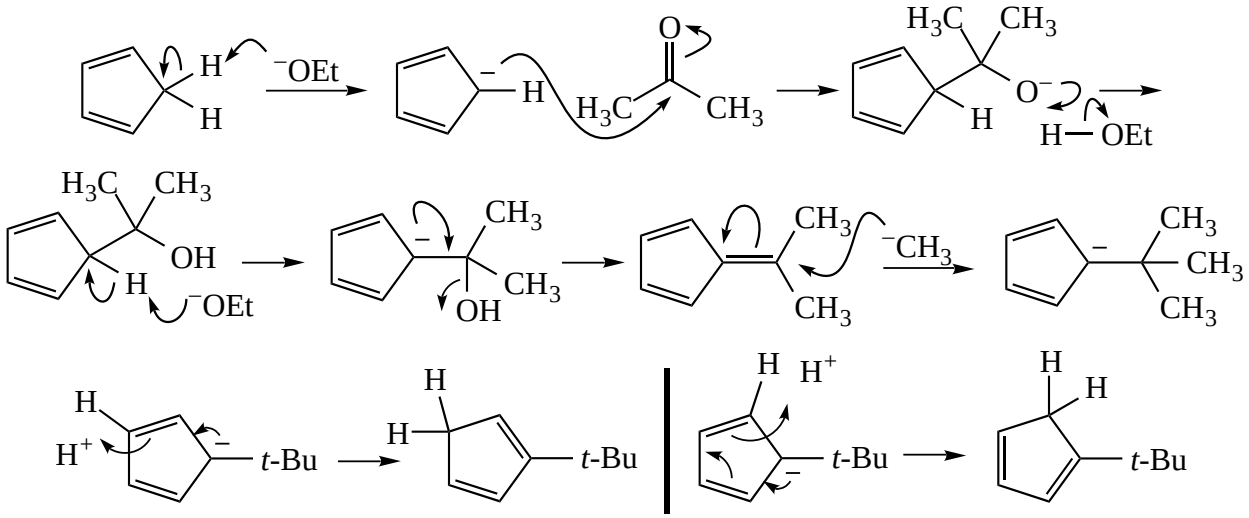
(e) One C–C and one C–O bond are formed. The ketone O is not nucleophilic enough to participate in S_N2 reactions, so the initial event must be attack of the ester enolate on the ketone. Sodium amide acts as a base.



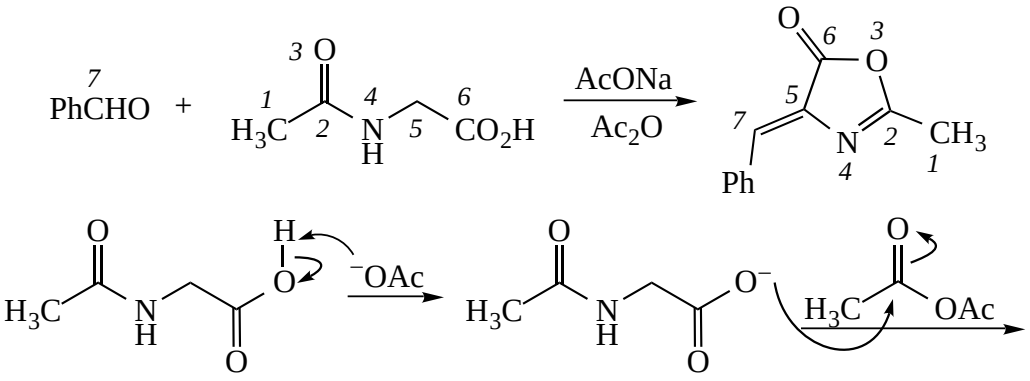
(f) The C in diazomethane is nucleophilic. The product of attack of diazomethane on the carbonyl C has a leaving group α to the alkoxide, so either a 1,2 alkyl shift or direct nucleophilic displacement can occur. The insertion product happens to dominate with $H_2\bar{C}–\overset{+}{N}_2$, but with $H_2\bar{C}–\overset{+}{S}Me_2$ the epoxide dominates.

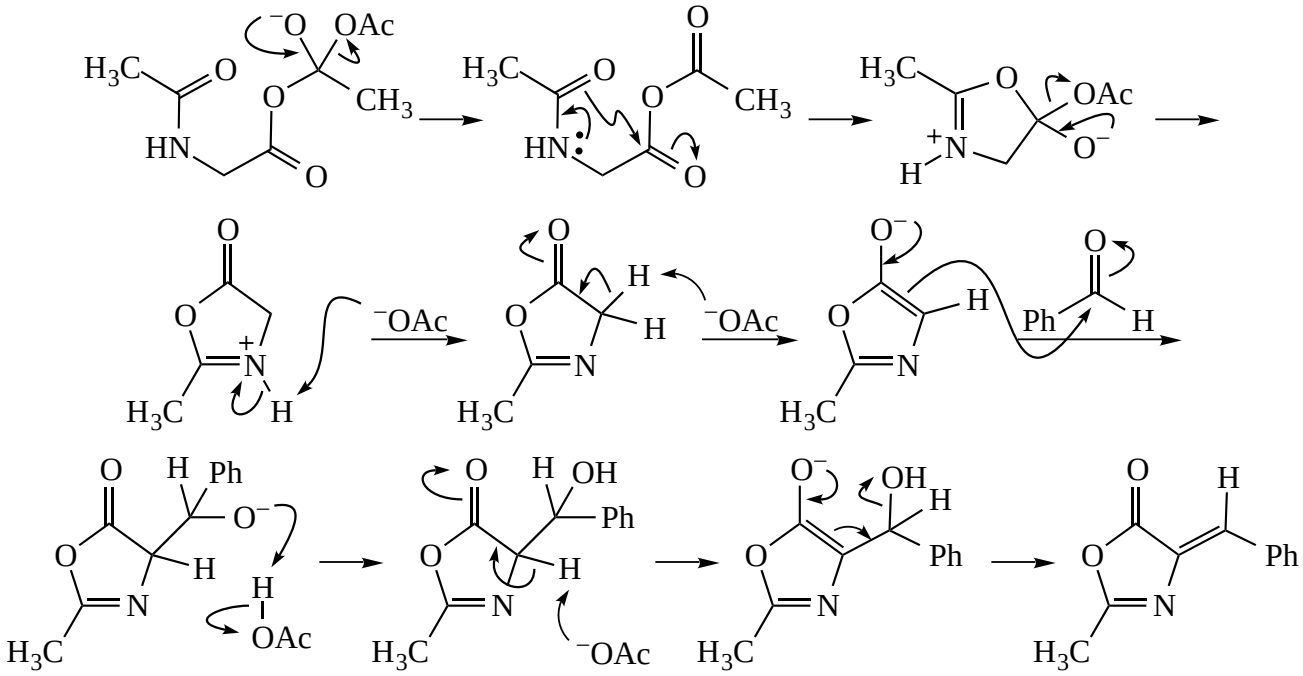


(g) Cyclopentadiene is very acidic, and its conjugate base is very nucleophilic. It can undergo aldol reactions with carbonyl compounds. After dehydration, a *fulvene* is obtained. The fulvene is an electrophile because when a nucleophile adds to the exocyclic double bond, the pair of electrons from that bond makes the five-membered ring aromatic.



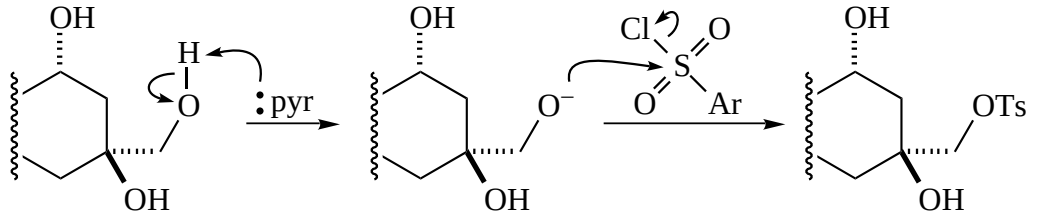
(h) Two new bonds are formed: O3–C6 and C5–C7. O3 is nucleophilic, while C6 is moderately electrophilic; C5 is nucleophilic only after deprotonation, and C7 is quite electrophilic. Under these very mildly basic conditions, it is unlikely that C5 will be deprotonated, so it is likely that the O3–C6 bond forms first. The purpose of the acetic anhydride (Ac_2O) is to convert the weakly electrophilic carboxylic acid into a strongly electrophilic mixed acid anhydride. The mild base deprotonates the carboxylic acid, which makes a weakly nucleophilic carboxylate ion (on O). Reaction of the carboxylate with the electrophilic Ac_2O gives, after addition–elimination, the mixed anhydride, which is strongly electrophilic at C6. O3 can then attack C6 to give, after addition–elimination, the initial cyclic product. At this point C5 becomes particularly acidic because the conjugate base is aromatic. The aldol and dehydration reactions with benzaldehyde then proceed normally.





(i) Overall, the 1° OH is replaced by H. The H is presumably coming from $LiAlH_4$, a good source of nucleophilic H^-, so the 1° OH must be transformed into a good leaving group. The first step must transform the 1° alcohol into a tosylate. The mechanism of reaction of an alkoxide with TsCl is probably S_N2; the purpose of the DMAP is to catalyze the reaction, either by acting as a strong base or by displacing Cl^- from TsCl and then being displaced itself. In the next step, DBU is a nonnucleophilic base; elimination is not possible (no β H's), so it must deprotonate an OH group. This converts the OH into a good nucleophile. In this way, the 3° OH can react with the tosylate to give an epoxide. The epoxide is quite electrophilic due to ring strain, and so it acts as an electrophile toward $LiAlH_4$ to give the observed product.

Step 1:



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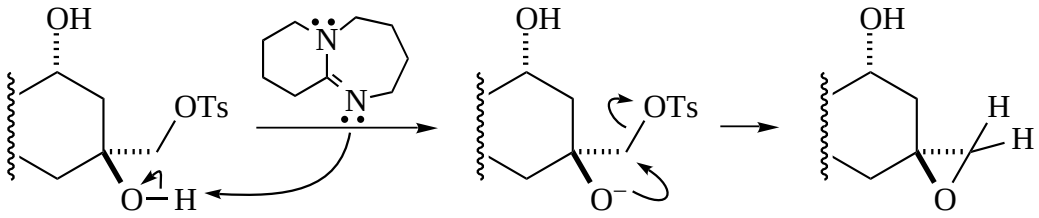
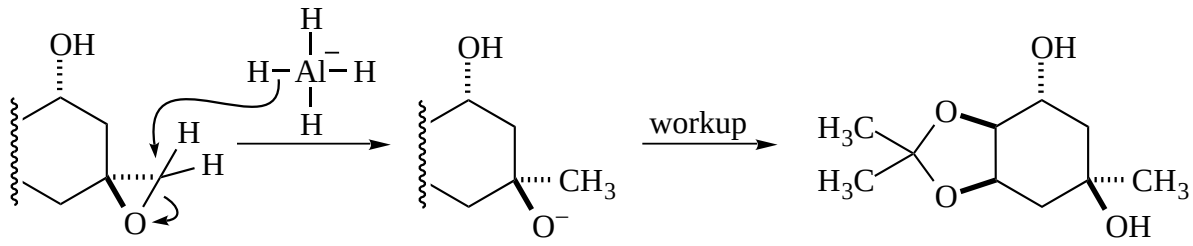
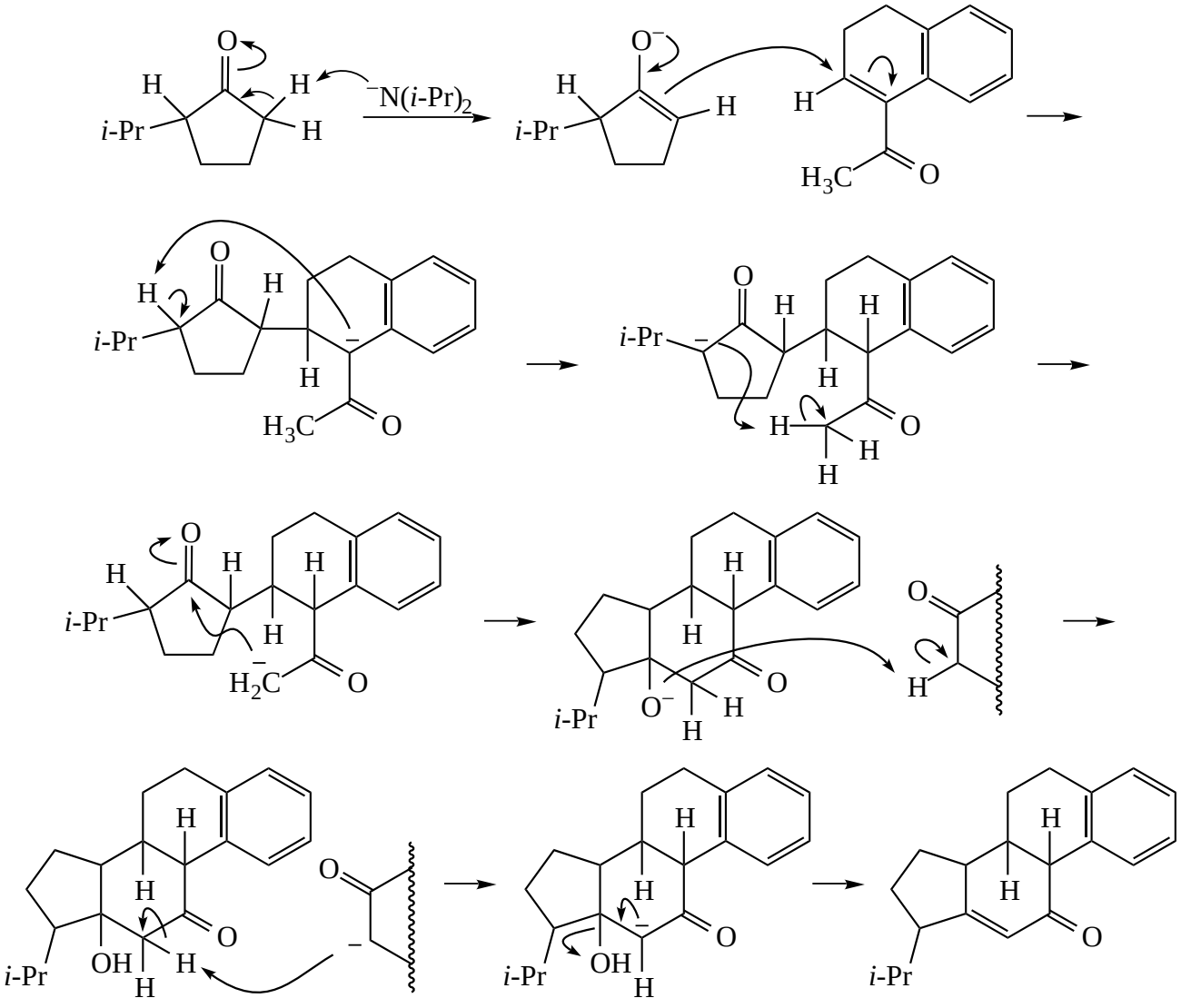


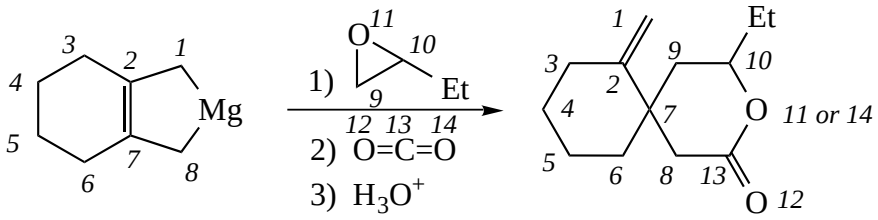
Step 3:



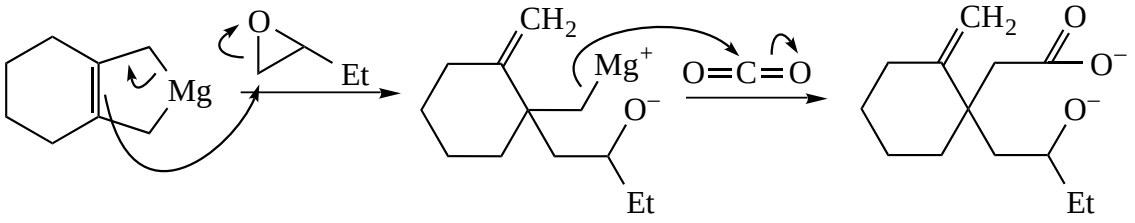
(j) LDA deprotonates the less hindered of the two acidic C atoms. A Robinson annulation then occurs by the mechanism discussed in the text. Two proton transfers are required in the course of the annulation, and both must occur by a two-step mechanism in which the substrate is first protonated, then deprotonated. The most likely proton source is the ketone of starting material or product. (The solvent cannot be a proton source in this particular reaction because it is carried out in THF. The conjugate acid of the LDA used to initiate the reaction cannot be used as a proton source either, because it is not acidic enough.)



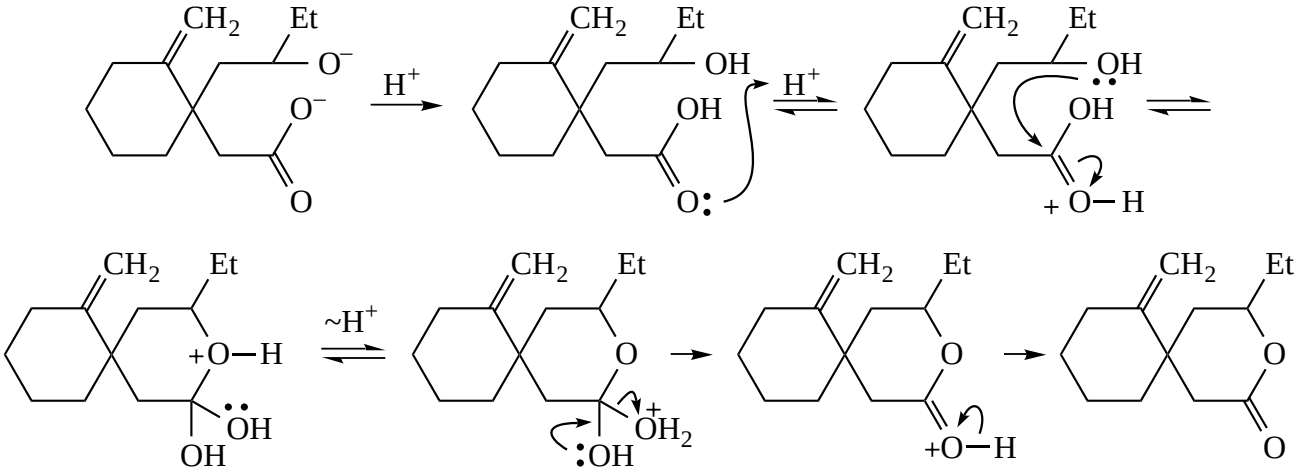
(k) Make: C7–C9, C8–C13, and either O11–C13 or C10–O14. Break: Either C10–O11 or C13–O14.



C9 and C11 are both electrophilic. The cyclic magnesium compound is nucleophilic at C1 and C8, and allylically at C7 and C2. The first step, then is nucleophilic attack of nucleophilic C7 on electrophilic C9 to give an alkoxide. Then when CO_2 is added, the nucleophilic C8 carbanion attacks the electrophilic C11.

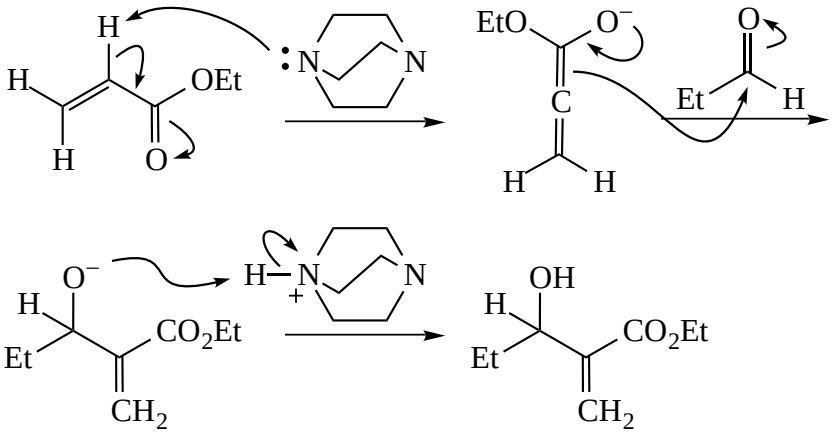


Upon addition of acid, the alcohol reacts with the carboxylic acid to give a lactone (cyclic ester). This acid-catalyzed reaction is discussed in detail in Chapter 3. The reaction is far more likely to occur by attack of O11 on C13 than by attack of O14 on C10.

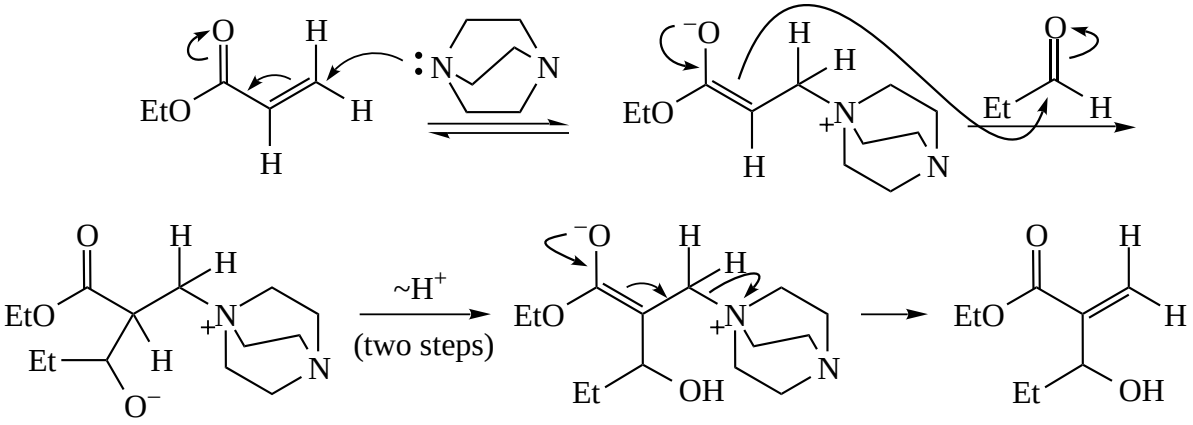


(l) 1,4-Diazabicyclo[2.2.2]octane (DABCO) can act as either a base or a nucleophile. When it acts as a base, it deprotonates C2 to give an enolate, which attacks the aldehyde in an aldol reaction to give the product after proton transfer. When it acts as a nucleophile, it adds to the electrophilic C3 to give an enolate, which attacks the aldehyde in an aldol reaction. Elimination of DABCO by an E2 or E1cb mechanism then gives the product.

Mechanism with DABCO as base:



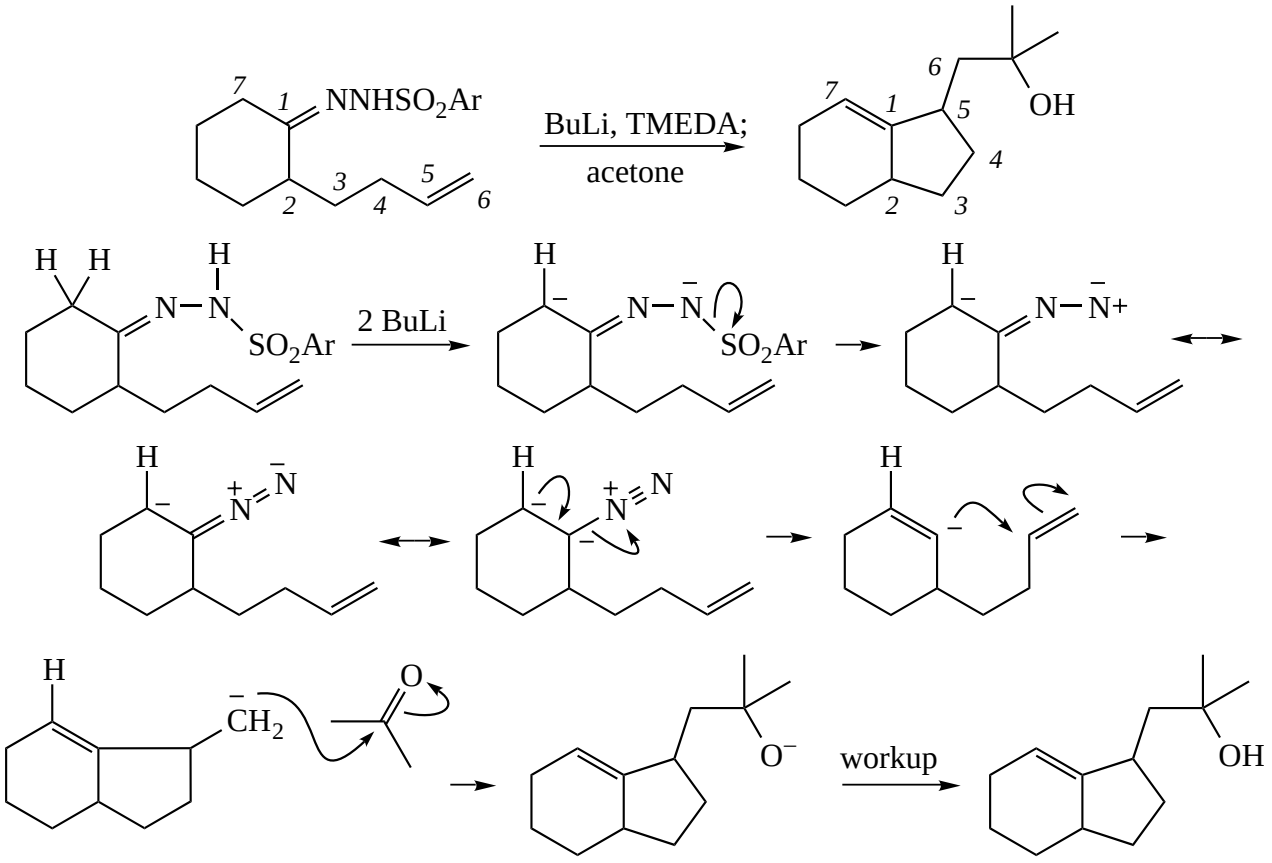
Mechanism with DABCO as nucleophile:



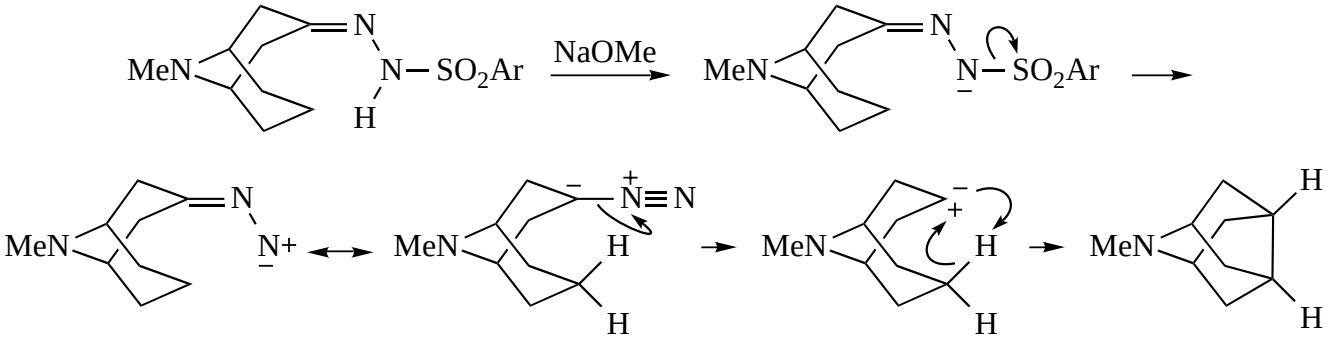
The second mechanism is much more likely, even without the information in problem (m), as C(sp^2)–H bonds α to carbonyls are not very acidic. (See Chapter 1.)

(m) Nucleophilicity is dramatically affected by steric bulk, whereas basicity is only slightly affected. If steric bulk in the amine catalyst affects the rate of the reaction dramatically, then DABCO must be acting as a nucleophile, not a base.

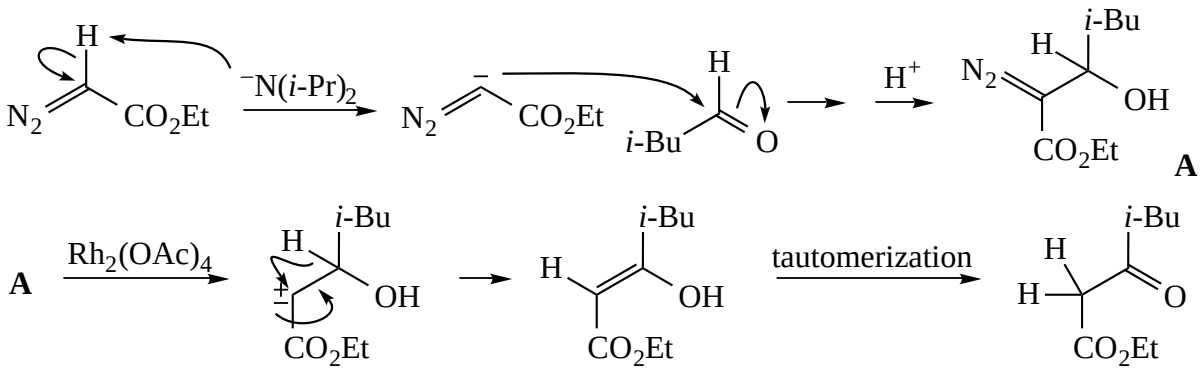
(n) Make: C1–C5, C6–acetone. Break: C1–N. This is a Shapiro reaction. Addition of BuLi to the hydrazone deprotonates N, then deprotonates C7 to give a dianion. α-Elimination of $ArSO_2^-$ gives an intermediate that loses N_2 to give an alkenyl anion. This undergoes intramolecular addition to the pendant π bond to give an alkyl anion, which is quenched with acetone to give the product. The addition of the alkenyl anion to the unactivated π bond occurs because of the low entropy of activation, the very high nucleophilicity of the anion, and the favorable formation of a C–C σ bond, and despite the poor electrophilicity of the π bond and the formation of a higher energy C(sp^3) anion from a lower energy C(sp^2) anion.



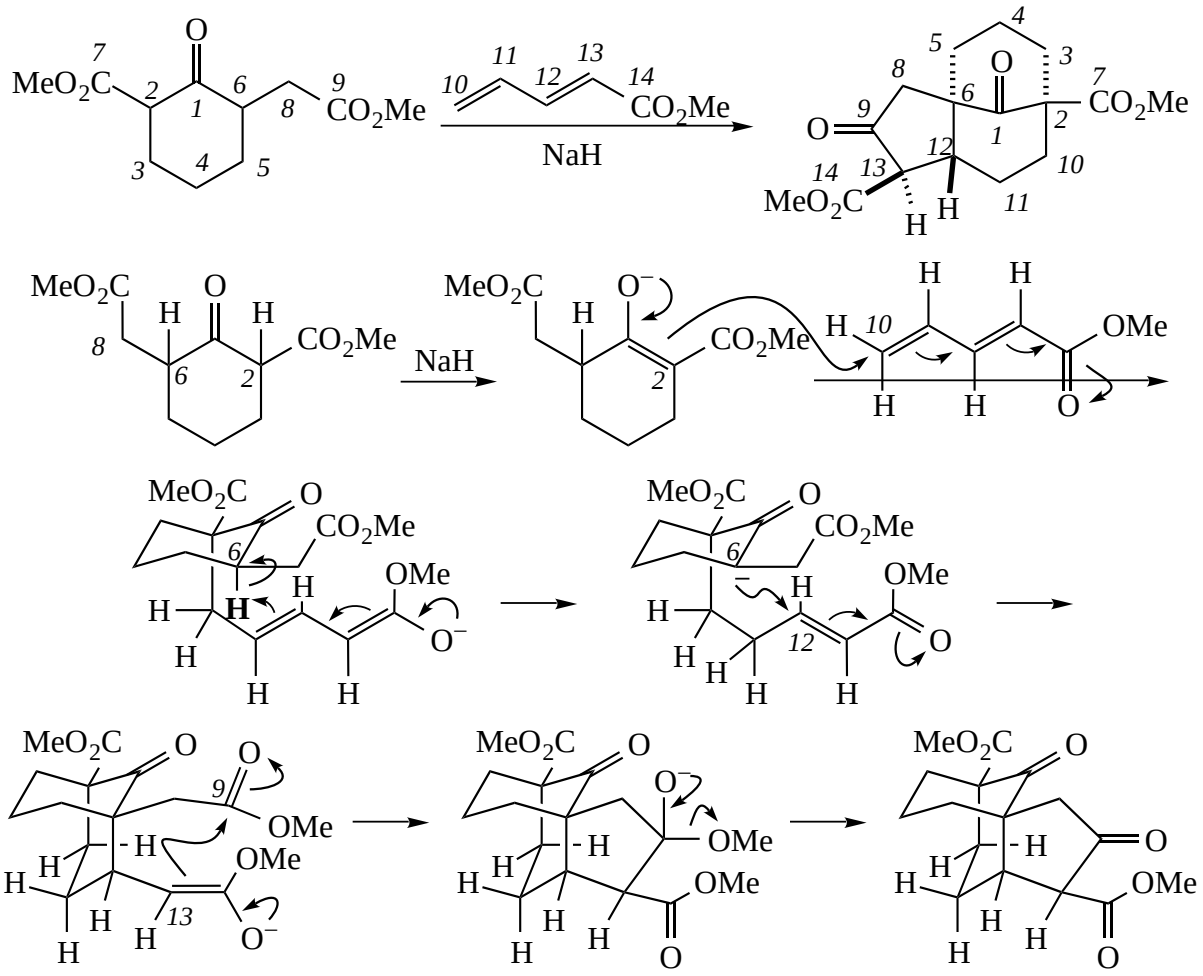
(o) This is a Bamford–Stevens reaction. We are forming a new C–C bond to a remote, unactivated C, suggesting a carbene inserting into a C–H bond. The base deprotonates N. α-Elimination of $ArSO_2^-$ gives the diazo compound, which spontaneously loses N_2 to give the carbene. The carbene inserts into the nearby (in space) C–H bond to give the product.



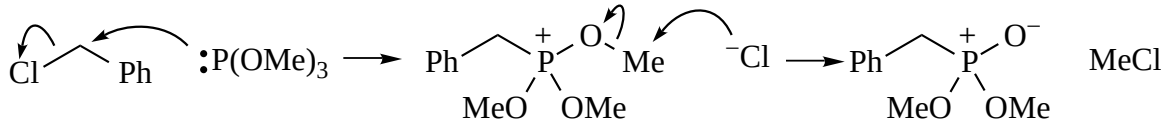
(p) LDA is a strong, nonnucleophilic base. It will deprotonate the diazo compound, turning it into a good nucleophile. Addition to the aldehyde C=O bond and workup gives intermediate **A**. Now, treatment of **A** with Rh(II) generates a carbenoid, which reacts as if it were a singlet carbene. A 1,2-shift gives the enol, which can tautomerize to the observed product.



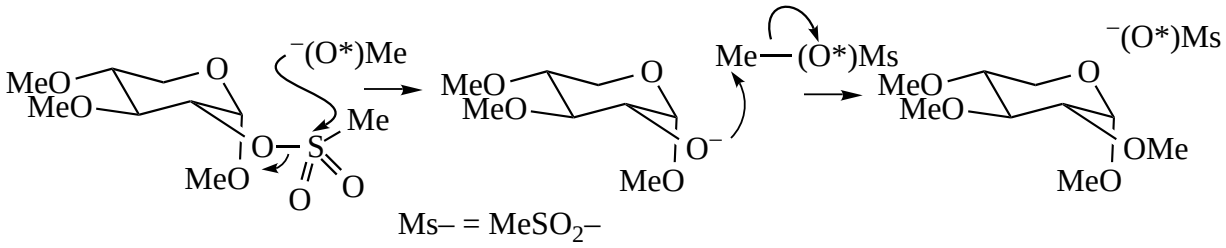
(q) Make: C2–C10, C6–C12, C9–C13. Break: none. C2 and C6 are nucleophilic (once they are deprotonated), while C9, C10 and C12 are electrophilic. C2 is by far the most acidic site, so the C2–C6 bond is probably formed first.



(r) The by-product is MeCl. Make: P–Bn, Me–Cl. Break: O–Me. The first step is attack of nucleophilic P on the electrophilic BnCl. Then Cl^- comes back and attacks a Me group, displacing O^- to give the phosphonate.

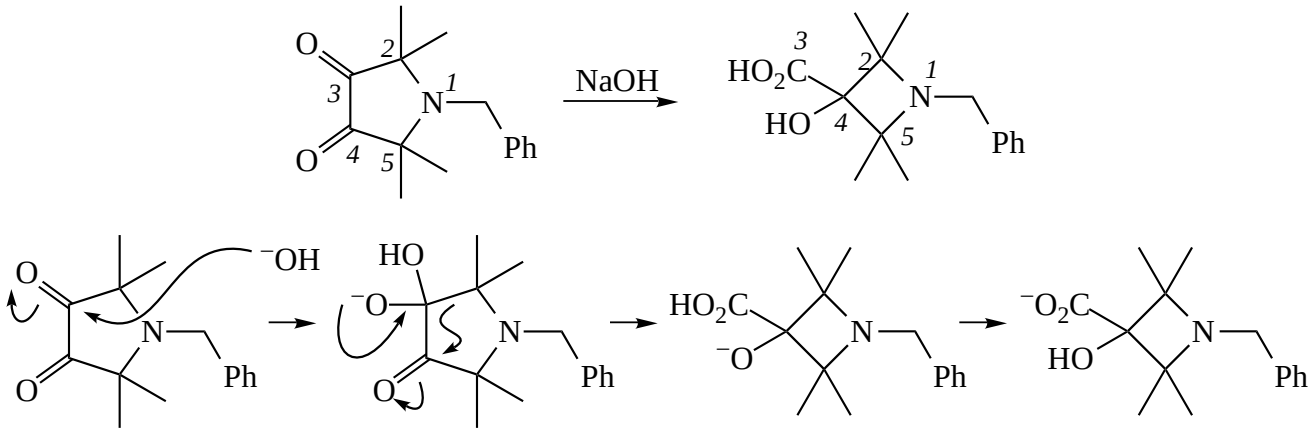


(s) Clearly simple S_N2 can't be the answer, as configuration is retained at C2 and ^{18}O incorporation into the product is not observed. The other electrophilic site in this compound is the S of the Ms group. Cleavage of the Ms–OR bond can occur under these basic conditions. Attack of $Me(*O)^-$ on the S of the Ms group displaces RO^- and gives Me(*O)Ms. Me(*O)Ms is an electrophile at C that can react with the sugar alkoxide to give the observed product.

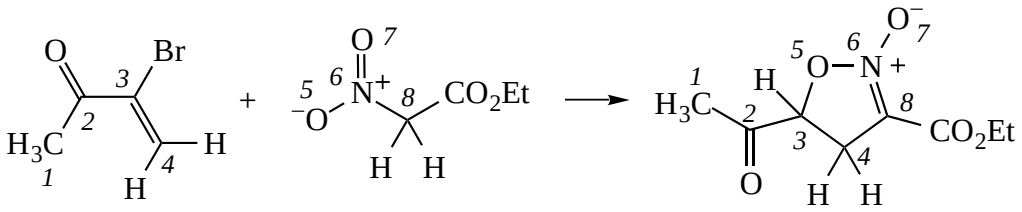


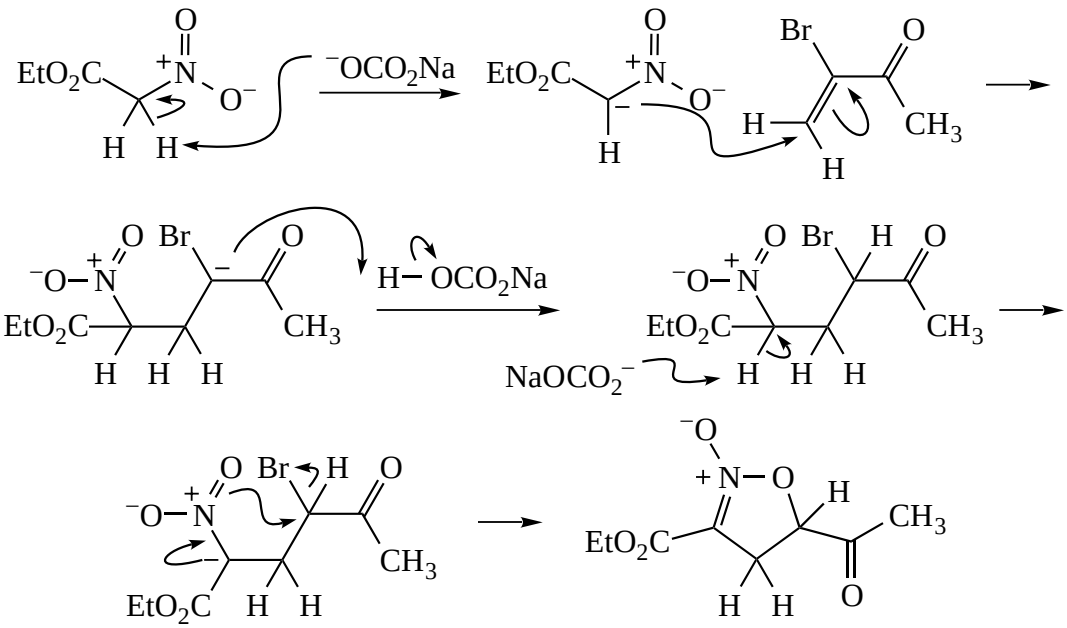
Ms– = $MeSO_2$–

(t) The benzilic acid rearrangement was discussed in the text (Section E.1).

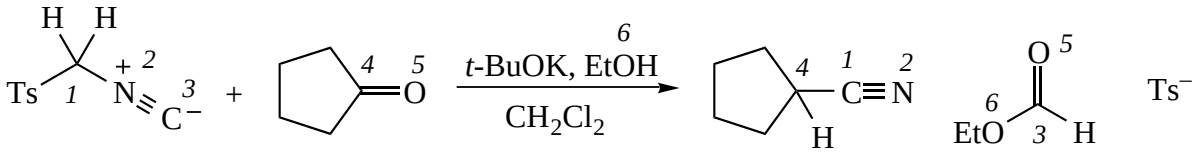


(u) Make: C3–O5, C8–C4. Break: C3–Br. Because C8 is very acidic (between the NO_2 and carbonyl groups) while C4 is electrophilic, the first bond-forming step is likely to form C8–C4. Then displacement of Br from C3 by O5 gives the product.

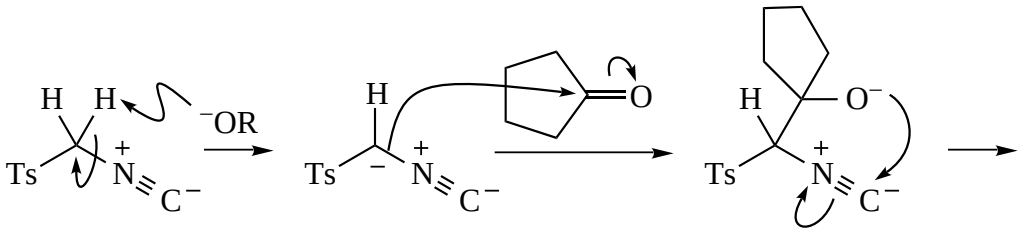


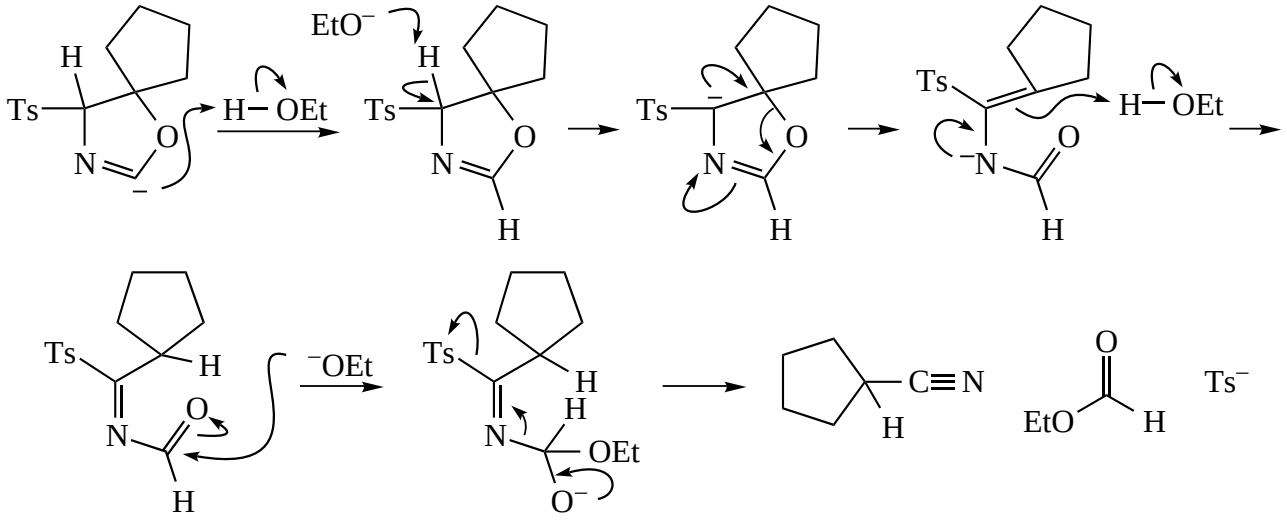


(v) Numbering the atoms correctly is key here. The cyanide C in the product could be C1 and the formate C, C3, or vice versa. How do we tell which? If the cyanide C is C3, this would mean that attack of C3 on C4 would occur. But this reaction would not require base, and we're told that base is required for the first bond-forming reaction to occur. On the other hand, if the cyanide C is C1, then the first step could be deprotonation of the relatively acidic C1 (next to Ts and formally positively charged N) followed by attack of C1 on electrophilic C4. The latter is more reasonable. Make: C1–C4, O5–C3, O6–C3. Break: C3–N2, C4–O5, C1–Ts.

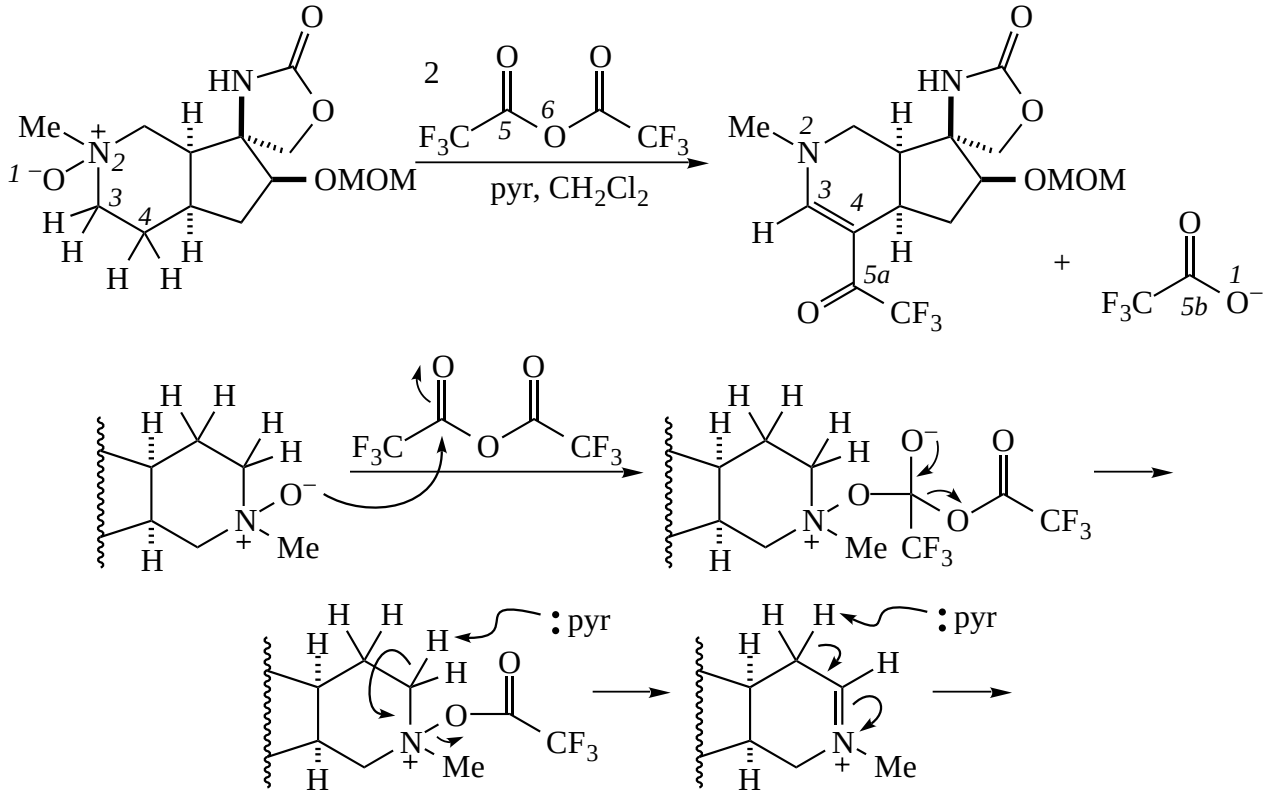


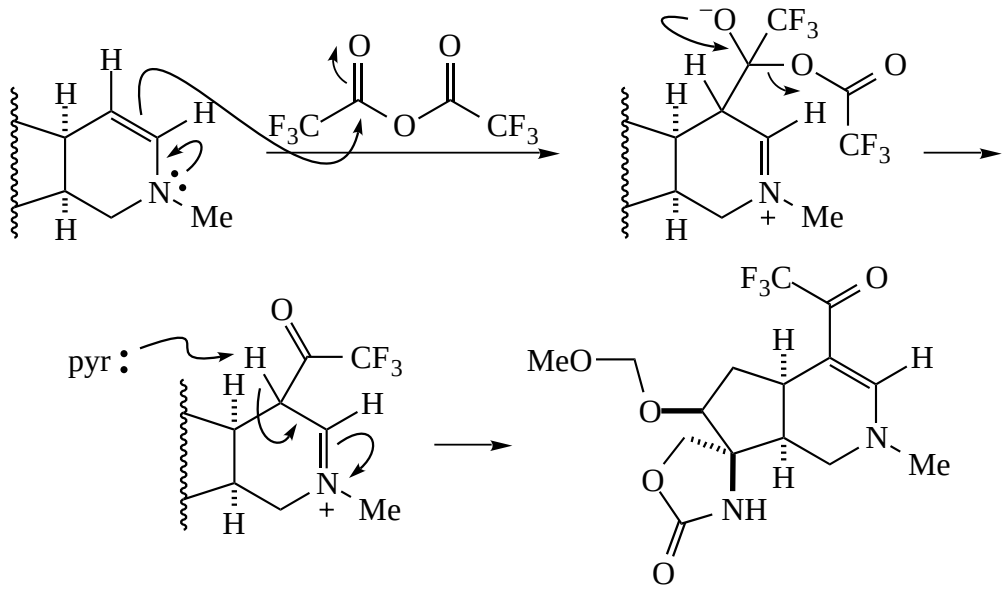
Deprotonation of C1 is followed by attack of C1 on C4 to give an alkoxide at O5. O5 can then attack *electrophilic* C3 (next to a heteroatom with a formal plus charge!) to give a five-membered ring with an anionic C, which is immediately protonated. Deprotonation of C1 again is followed by cleavage of the C4–O5 bond to give an amide.



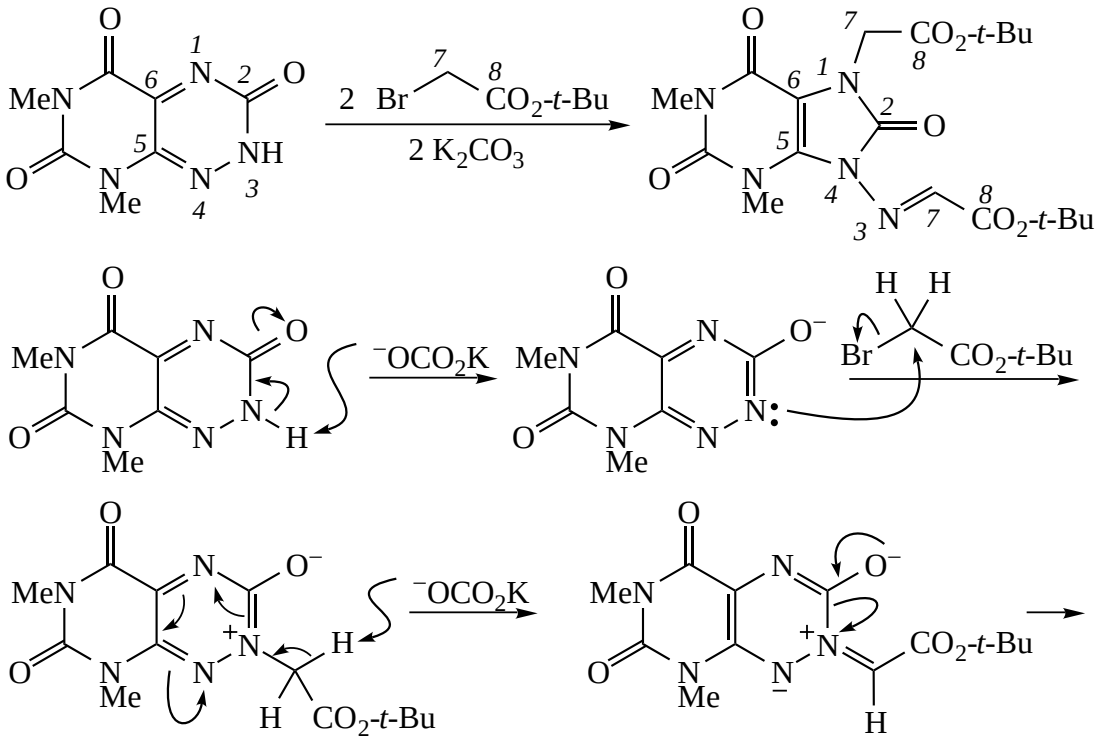


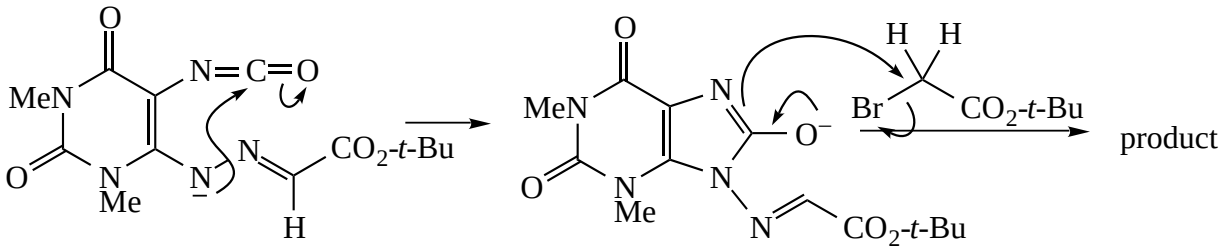
(w) Two equivalents of trifluoroacetic anhydride are required, so there are two C5's and two O6's. One of those C5's, C5a, ends up attached to C4 in the product. The other, C5b, must end up attached to O1, which is absent from the product. Make: O1–C5a, C4–C5b. Break: O1–N2, C5a–O6a, C5b–O6b. O1 is nucleophilic, C5a is electrophilic, so the first step is probably attack of O1 on C5a. Elimination of CF_3CO_2H can now occur to break the O1–N2 bond. This gives an iminium ion, which can be deprotonated at C4 to give an enamine. Enamines are nucleophilic β to the N, so C4 is now nucleophilic and can attack C5b; loss of H^+ from C4 gives the product.



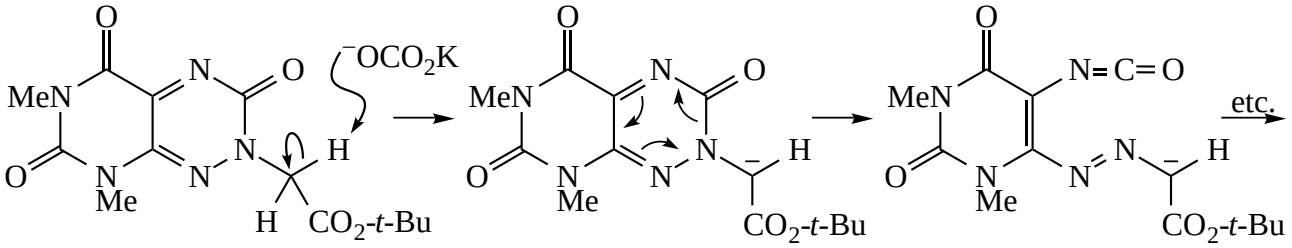


(x) Make: N1–C7a, N3–C7b, N4–C2. Break: C2–N3, C7–Br. The first step is likely deprotonation and alkylation of N3. This makes a σ bond between N3 and C7b, but we need to introduce a π bond. This can be done by an elimination reaction. Deprotonation of C7 gives an enolate, which can be delocalized onto N4 by resonance. Now, the N3–C2 bond can be broken, giving the electrons to N3 and forming an isocyanate out of N1 and C2. These two steps constitute an E1cb elimination. Finally, attack of N4 on C2 gives an amide anion, which can be alkylated again by the bromide to give the product. Note: Cleavage of the N3–C2 bond at the same time as deprotonation of C7, as in a standard E2 elimination, is possible, but this is unlikely: the lone pair that is put on C2 cannot be delocalized as it forms because the orbital in which it resides is orthogonal to the C6=N1 π bond.

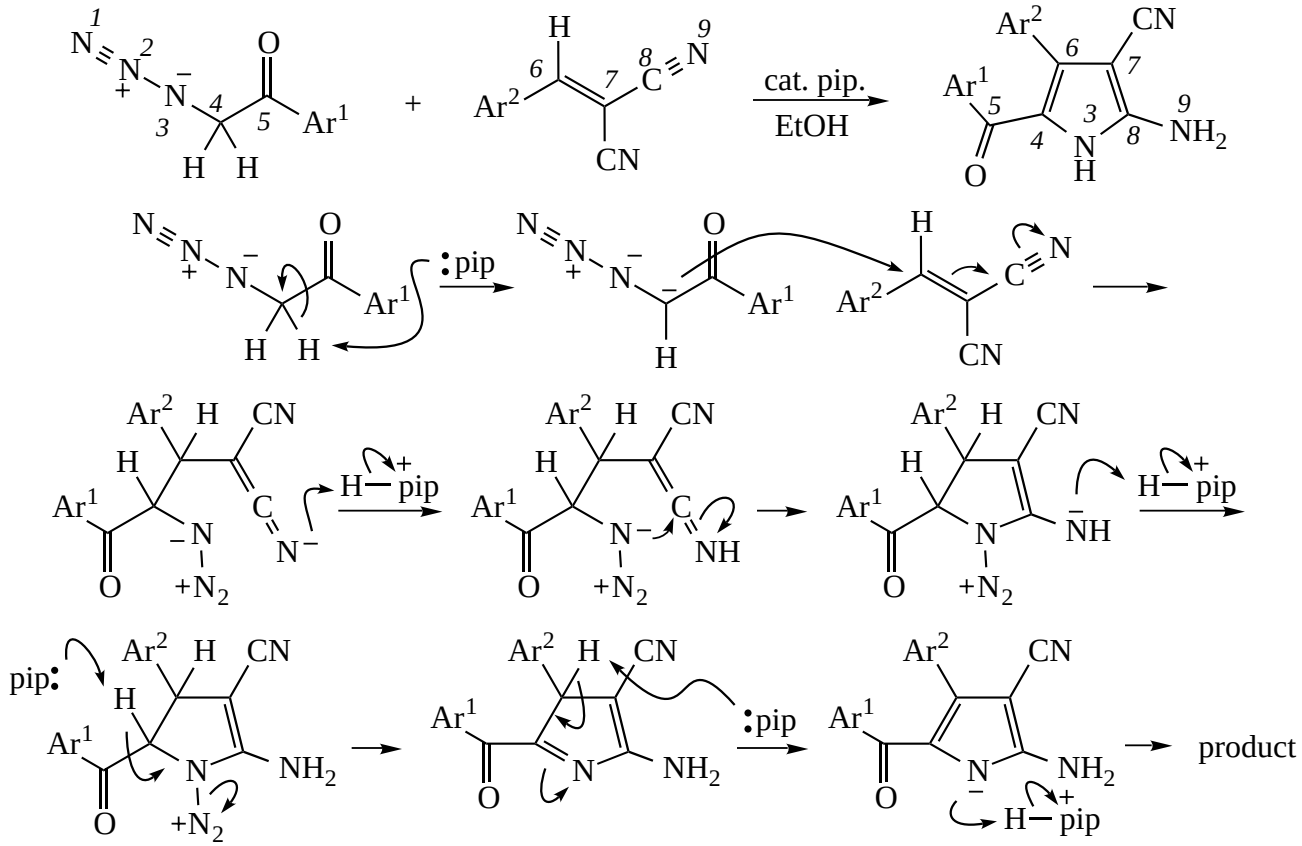




Another way to draw the key N–C ring-cleaving step is as an *electrocyclic ring opening.*

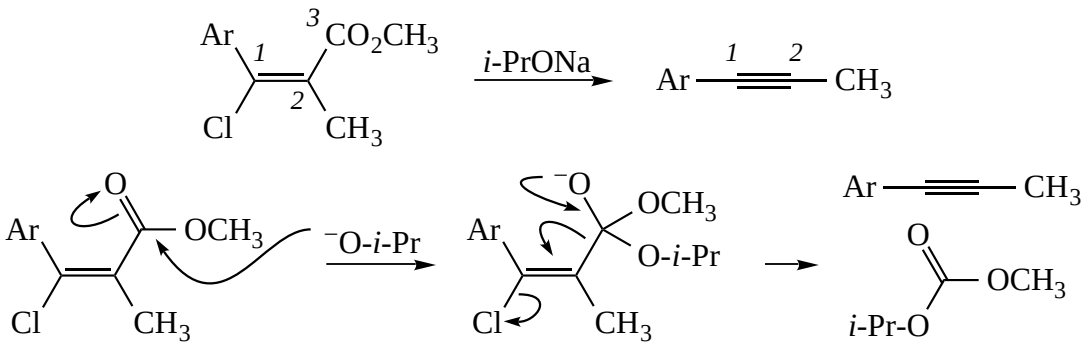


(y) Make: N3–C8, C4–C6. Break: N2–N3. Conditions are basic, and C6 is very electophilic, so first step is likely deprotonation of C4 and addition of the enolate to C6. After protonation of N9, addition of N3 to C8 can occur. Protonation of N9 is followed by loss of H^+ and N_2 by an E2 mechanism. Finally, tautomerization by deprotonation and reprotonation gives the observed product.

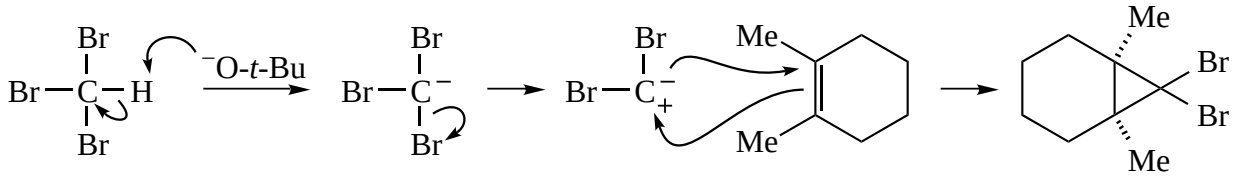


(z) Make: none. Break: Cl–C1, C2–C3. *i*-PrO^- is nucleophilic. There are two electrophilic sites in the

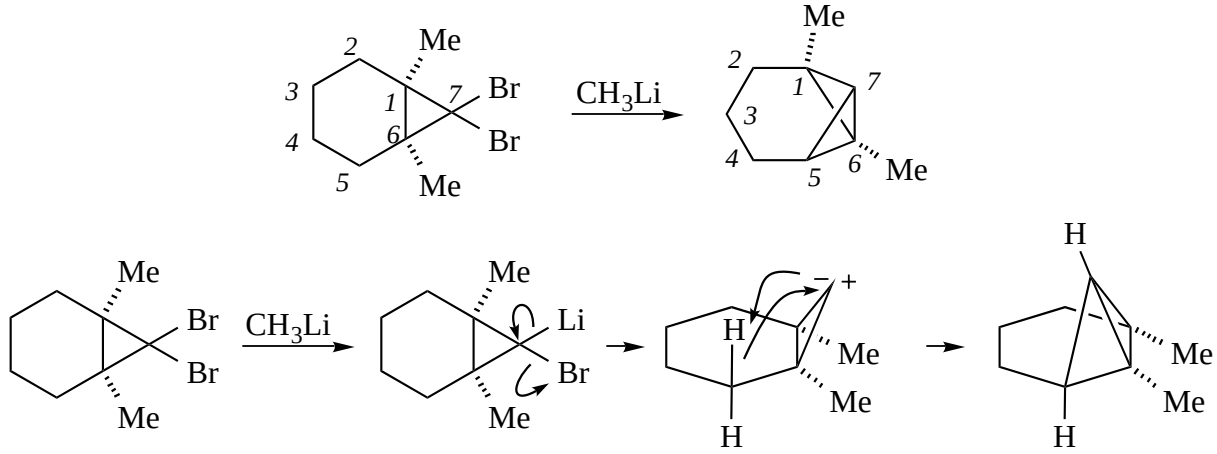
starting material, C1 and C3. Attack of *i*-PrO⁻ at C1 doesn't get us anywhere, since the product does not have a C1–O bond, so the first step is probably addition of *i*-PrO⁻ to the C3=O π bond. In the second step, the O⁻ electrons can move down to form the carbonyl bond again, breaking the C2–C3 bond. The electrons in the C2–C3 bond are used to form a second C2=C1 π bond and to expel Cl⁻.



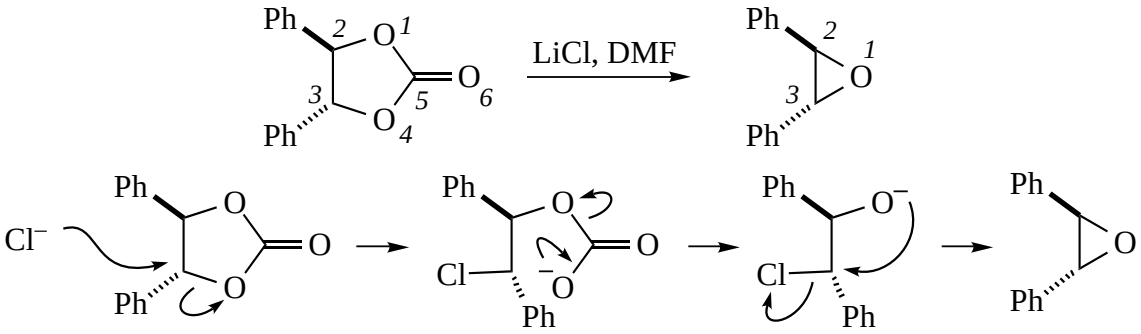
(aa) The first transformation is a standard dibromocarbene addition to an alkene (Section D.4). The strong base deprotonates the bromoform. α-Elimination gives the carbene, which undergoes cyclo-addition to the alkene to give the product.



In the second transformation: Make: C5–C7. Break: C7–Br, C7–Br. Formation of a bond between C7 and the unactivated and remote C5 suggests a carbene reaction. Addition of MeLi to a dihalide can give substitution, elimination, or halogen–metal exchange. Here elimination is not possible and substitution does not occur, so that leaves halogen–metal exchange. (Dibromocyclopropanes are quite prone to undergo halogen–metal exchange.) α-Elimination then occurs to give the carbene, which inserts into the C5–H bond to give the product.

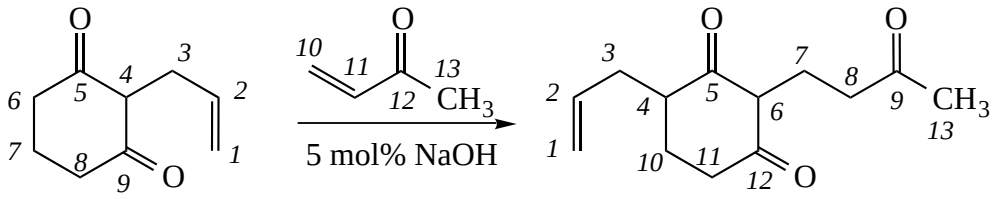


(bb) Make: C3–O1. Break: C3–O4, O1–C5. We are substituting O4 for O1 at C3, and this substitution is occurring with *retention* of configuration, suggesting two sequential S_N2 reactions. What is the role of LiCl? Cl^- is a pretty good nucleophile, especially in a polar aprotic solvent like DMF. The C3–O4 bond can be cleaved by S_N2 substitution with Cl^-. After loss of CO_2 from O1, O1 can come back and do a second S_N2 substitution at C3 to give the product.

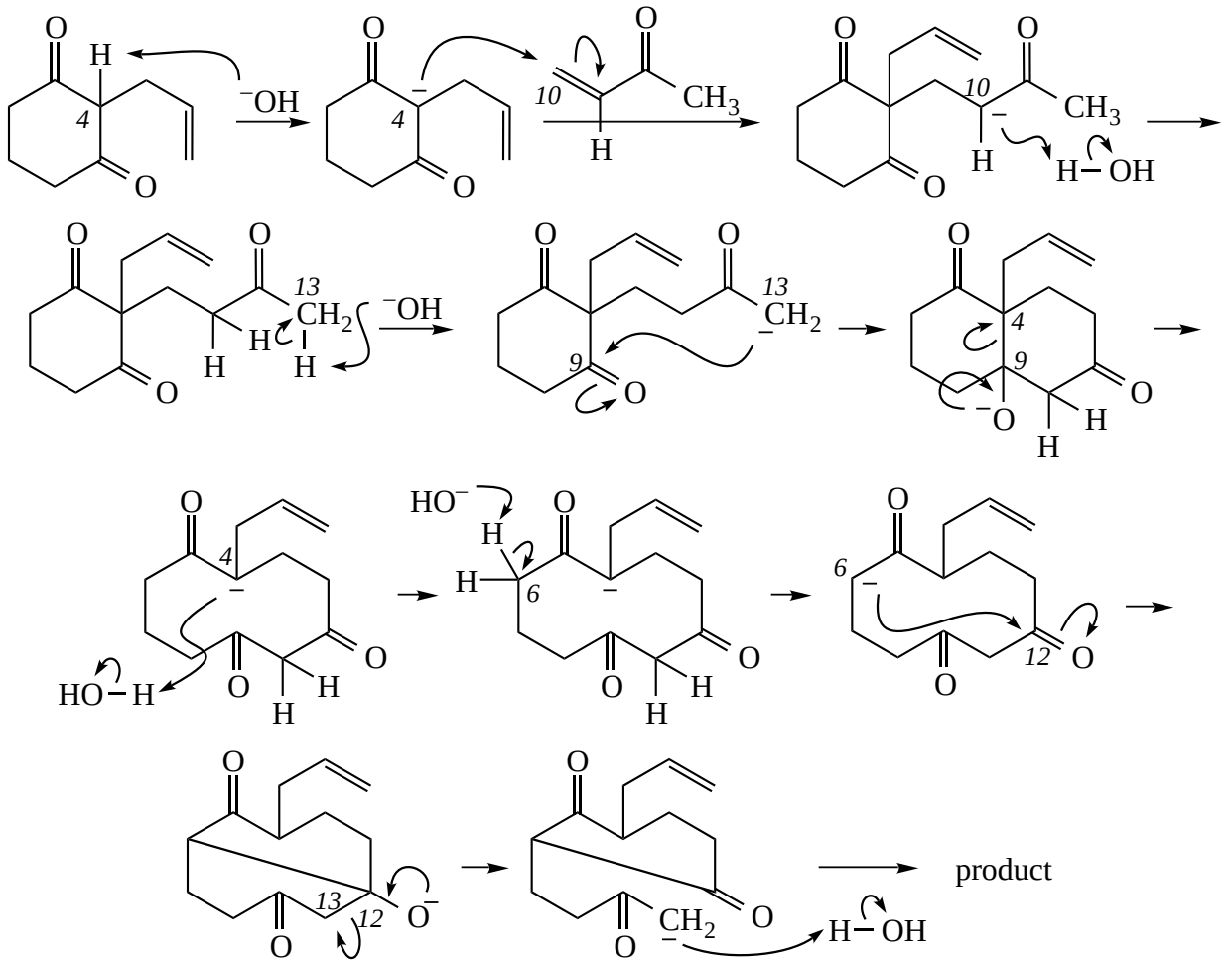


(cc) This reaction is a Robinson annulation. The mechanism was discussed in the text.

(dd) The key to determining this reaction is, as usual, numbering the atoms correctly. Clearly some sort of rearrangement is occurring, and some C–C bonds must break. Bonds between carbonyl C's and α C's can break quite readily in 1,3-dicarbonyl compounds because the carbanion generated at the α C is stabilized by another carbonyl group. Therefore, the C4–C5 or C5–C9 bond in the starting material might break, but it is unlikely that the C3–C4 bond will break. Once you have C4 identified correctly, C5 through C9 should be clear, and that leaves little choice for C10 through C13. *Note:* If you started numbering with C10–C13, you almost certainly would have become confused. Make: C4–C10, C6–C12, C9–C13. Break: C4–C9, C12–C13.

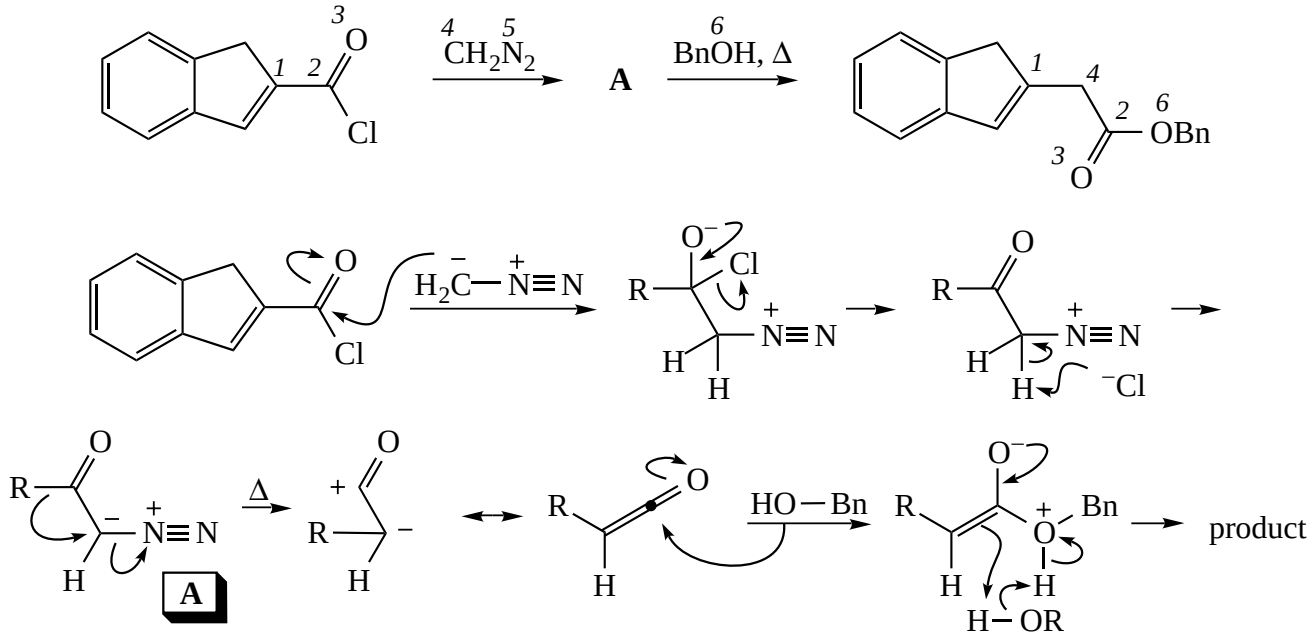


The first steps are the same as in the previous problem. C4 is deprotonated, it undergoes a Michael addition to C10 (making C4–C10), proton transfer occurs from C13 to C11, and C13 adds to C9 (making C9–C13). At this point, though, rather than an E1cb elimination, a fragmentation occurs, breaking C9–C4. We still have to make C6–C12 and break C12–C13. Proton transfer from C6 to C4 occurs, and C6 adds to C12. Then a second fragmentation occurs, breaking C12–C13. Protonation of C13 gives the product.



Why does this pathway occur instead of the Robinson annulation when the seemingly trivial change of increasing the concentration of NaOH is made? Good question. It is not clear. It seems likely that the Robinson annulation *does* occur first (because quick quenching helps to increase the quantity of Robinson product), but the E1cb elimination at the end of the annulation mechanism is reversible in the presence of NaOH as base. It seems likely, then, that if NaOEt were used as base instead, only the Robinson product would be observed regardless of the quantity of catalyst.

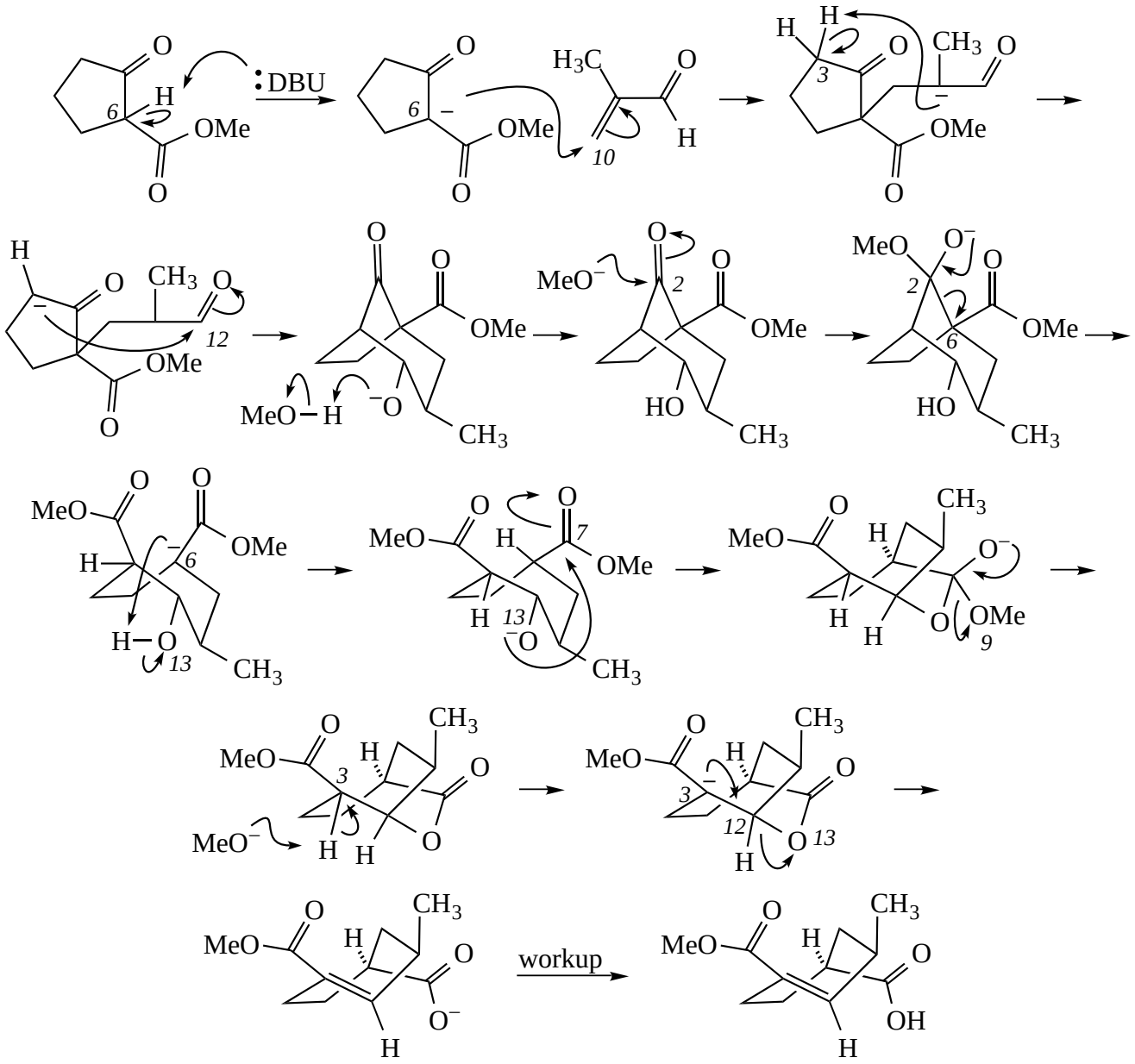
(ee) Make: C1–C4, C4–C2, C2–O6. Break: C1–C2, C2–Cl, C4–N5. The acyl chloride is a potent electrophile at C2. CH_2N_2 is nucleophilic at C4. Addition–elimination occurs, then deprotonation to give a diazoketone. Deprotonation by Cl^- is reasonable because the diazonium ion is a much stronger acid than it appears at first sight. Heating this compound causes it to undergo a 1,2-shift to give a ketene, which is trapped by BnOH to give the product. Under these *neutral* conditions, an awful zwitterionic intermediate must be drawn. It's better not to draw a four-center TS for the proton transfer step to convert the zwitterion into product, so solvent is shown intervening.



(ff) This transformation is an example of the Mitsunobu reaction. The mechanism of the Mitsunobu reaction was discussed in the text (Section F.2).

(gg) Numbering is again key. Identifying C10, C11, C12 in the product is easy. Using the information that the first step is a Michael reaction, C6 must be attached to C10 in the product. From there the numbering is straightforward. Make: C2–O9, C3–C12, C6–C10, C7–O13. Break: C2–C6, C7–O9, C12–O13.

Deprotonation of acidic C6 by DBU gives a carbanion, which undergoes a Michael reaction to C10. The new carbanion at C10 can deprotonate C3 to give a new carbanion, and this can undergo an aldol reaction to C12. Now our two new C–C bonds have been formed. We still have to break C2–C6 and two C–O bonds. The alkoxide at O13 can deprotonate MeOH, which can then add to C2. Fragmentation of the C2–C6 bond follows to give a C6 enolate. The C6 enolate then deprotonates O13, and intramolecular trans-esterification occurs to form the O13–C7 bond and to break the C7–O9 bond. MeO^- then comes back and promotes E1 elimination across the C3–C12 bond to break the C12–O13 bond and give the product. The intramolecular transesterification explains why C7 becomes an acid and C2 remains an ester in the product.



3.

F^- is a lousy leaving group. It leaves only under drastic conditions. These conditions are not strongly basic. No reaction occurs.

In polar aprotic solvents, F^- is a good nucleophile. Benzyl bromide is a good electrophile under all conditions. The product is benzyl fluoride, $PhCH_2F$.

I^- is an excellent nucleophile, but ^-OH is such a lousy leaving group that alcohols are not electrophiles in substitution reactions under basic conditions. No reaction occurs.

3° Alkyl halides normally undergo elimination reactions with hard (e.g., first-row) nucleophiles. If there is a choice of conformers from which anti elimination can take place, the stabler product is usually produced. The product is *E*-PhC(Me)=CHMe.

Thiolate anions RS^- are excellent nucleophiles. The substrate, a 1° alkyl halide, is a good substrate for nucleophilic substitutions under basic conditions. The product is $PhSCH_2CHMe_2$. Ethanol acts merely as a solvent in this case. It is not nearly as nucleophilic as the thiolate, nor is it acidic enough to be deprotonated by the thiolate, so it's unlikely to react with the alkyl halide.

Secondary alkyl halides may undergo substitution or elimination under basic conditions, but with the strong hindered base and lousy nucleophile LDA, elimination is certain to occur. The product is $CH_3CH=CH_2$.

Normally, Me_3COK or *t*-BuOK acts only as a base, giving elimination products from alkyl halides. In the present case, though, the alkyl halide CH_3Br cannot undergo elimination. Moreover, the extremely unhindered CH_3Br is an excellent substrate for nucleophilic substitutions. The product may be Me_3COMe, or no reaction may occur, depending on how strongly the reaction mixture is heated. *t*-Alkyl ethers are better prepared by the acid-catalyzed addition of alcohol to alkenes (Chapter 3).

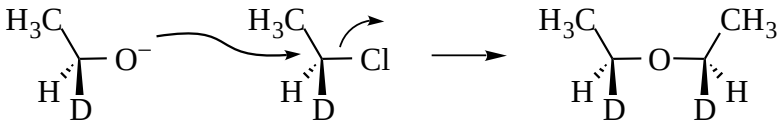
Cyclohexyl halides may undergo elimination or substitution reactions. They are usually more prone to elimination, but the acetate anion $MeCO_2^-$ is not particularly basic, and nucleophiles are particularly nucleophilic in the polar aprotic solvent DMF. More cyclohexyl acetate (substitution) than cyclohexene (elimination) is likely to form.

Thioethers are good nucleophiles, and CH_3I is an excellent electrophile. The product is $Me_3S^+ I^-$.

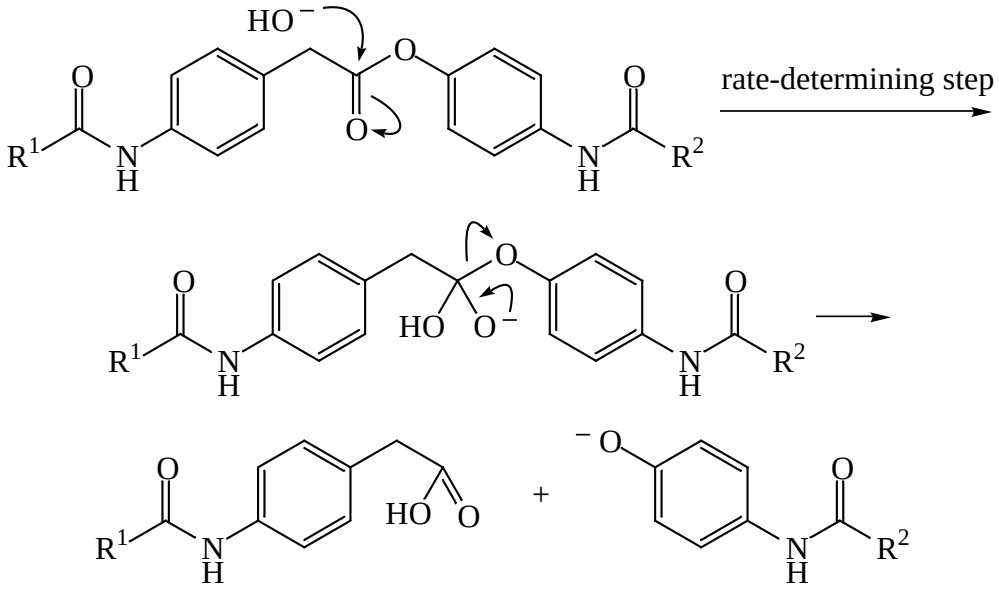
3° Alkyl halides normally undergo elimination with hard nucleophiles. Elimination usually occurs from the conformer in which the leaving group and H are anti to one another. The product is *Z*-PhC(Me)=C(Me)Ph by the E2 mechanism.

1° Tosylates are excellent electrophiles, and ^-CN is an excellent nucleophile, so substitution is likely to occur. The configuration at the electrophilic C inverts with respect to the (*S*) starting material. The product, (*R*)-EtCH(D)CN, is optically active.

The 1° alkyl halide is likely to undergo substitution given the pretty good nucleophile EtO^-. The configuration at the electrophilic C inverts with respect to the starting material, but the configuration at the stereogenic C in the nucleophile remains unchanged. The product is *meso*, achiral, and optically inactive.



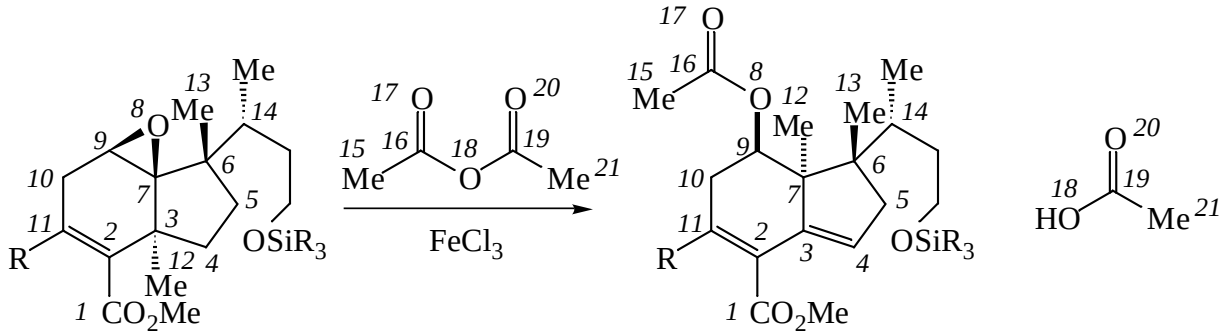
4. (a)



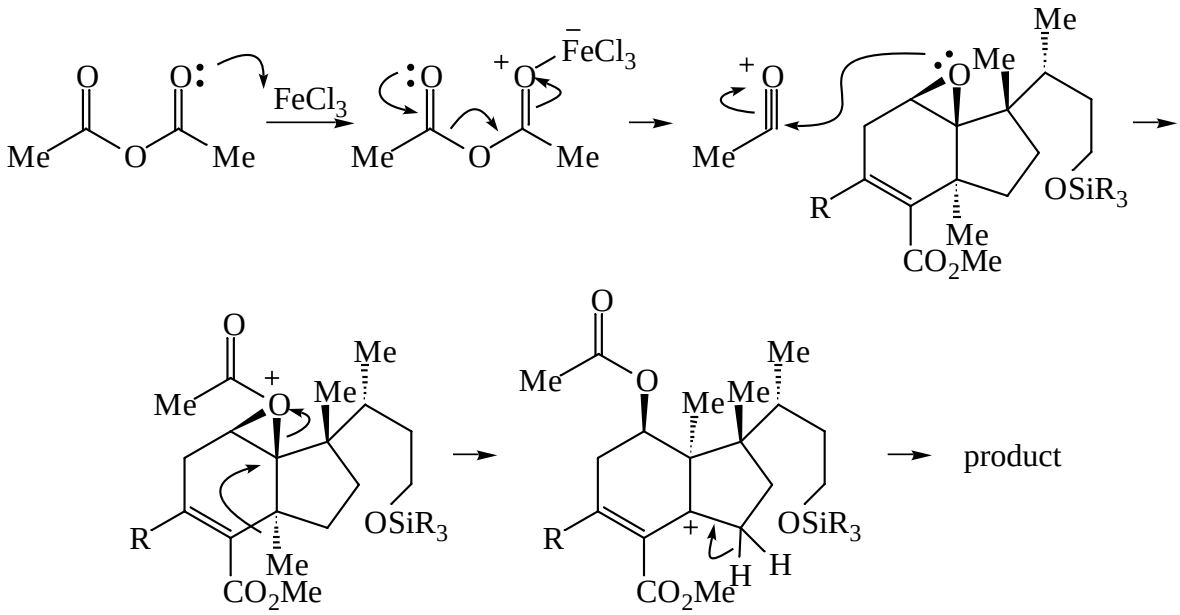
(b) Antibodies to **A** bind strongly to it. Because the tetrahedral intermediate in the RDS of the reaction so strongly resembles **A**, the anti-**A** antibodies bind strongly to it, too, lowering its energy. Because the tetrahedral intermediate is higher in energy than the starting material, the TS leading to it resembles the tetrahedral intermediate, and as a result the anti-**A** antibodies also lower the energy of the TS, increasing the rate of the reaction.

Answers To Chapter 3 In-Chapter Problems.

3.1. The by-product is AcOH. It is important in this problem to draw out the structure of Ac_2O and label all the atoms. Make: C7–C12, O8–C16. Break: C3–C12, C16–O18.



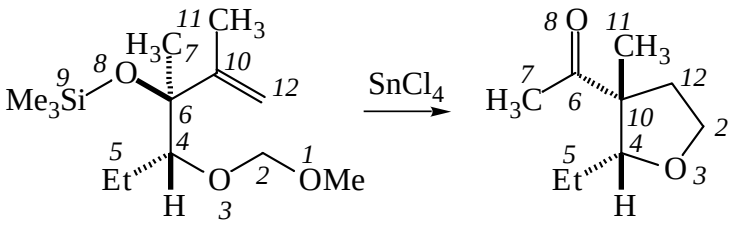
The fact that C12–C3 breaks and C12–C7 makes is a signal that a 1,2-alkyl shift occurs. The shift requires that a carbocation be formed at C7, which could be accomplished by cleaving the C7–O8 bond. Before the C7–O8 bond cleaves, something else must attach to O8 to give it a formal positive charge. Because we need to make an O8–C16 bond, that something could be C16. The role of the $FeCl_3$ is to encourage the ionization of the O18–C16 bond by coordinating to O20. (Alternatively, the $FeCl_3$ can coordinate to O17, and O8 can be acetylated with C16 by an addition–elimination mechanism.)



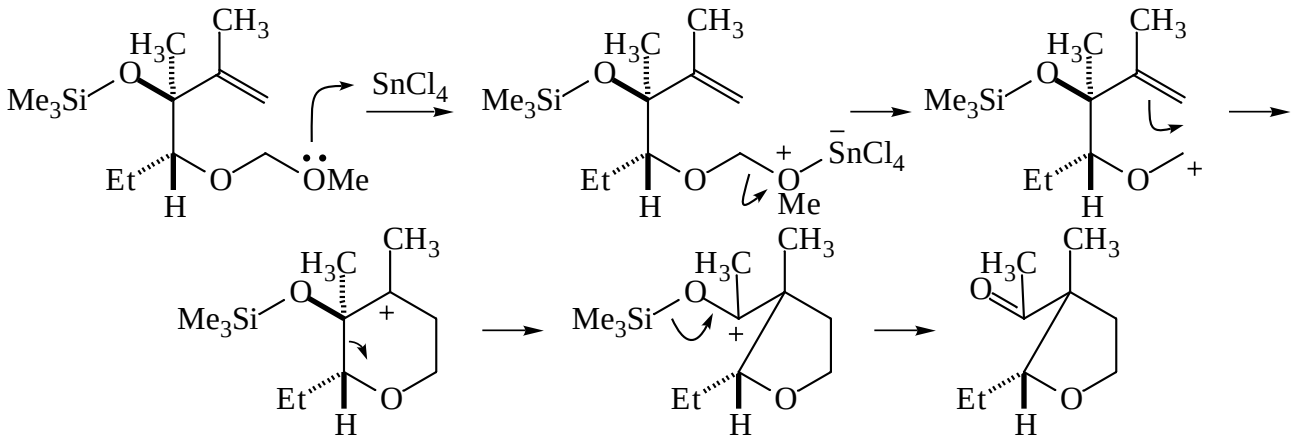
Why do we draw cleavage of the C7–O8 bond concerted with migration of C12? If the two steps were nonconcerted, then a C7 carbocation would intervene, and other 1,2-shifts could occur. For example, C13 or C14 could shift from C6 to C7. In a 1,2-shift that is concerted with leaving group departure, the migrating group must be antiperiplanar to the leaving group, and only C12 fulfills this condition.

3.2. Make: C2–C12, C4–C10. Break: O1–C2, C4–C6, O8–Si9. Neither O1 nor Si9 are incorporated

into the product.

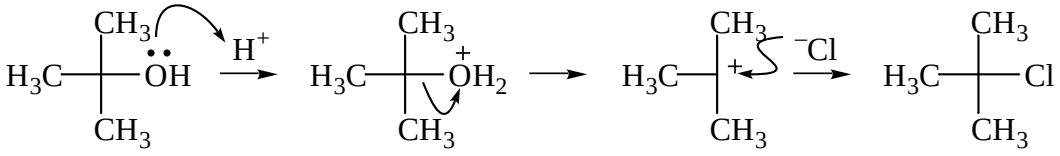


The role of the Lewis acid is either to make a π bond electrophile more electrophilic or to promote the departure of a leaving group. There is no π bond electrophile in the starting material, but O1 is a leaving group, so the first step must be coordination of $SnCl_4$ to O1. Cleavage of the O1–C2 bond gives a carbocation at C2 (although it is primary, it is well-stabilized by O3), and the C2 carbocation is attacked by nucleophilic C12 to give a C10 carbocation. Now a 1,2-shift of C4 from C6 to C10 can occur to give a new carbocation at C6. Finally, fragmentation of the O8–Si9 bond gives the product.

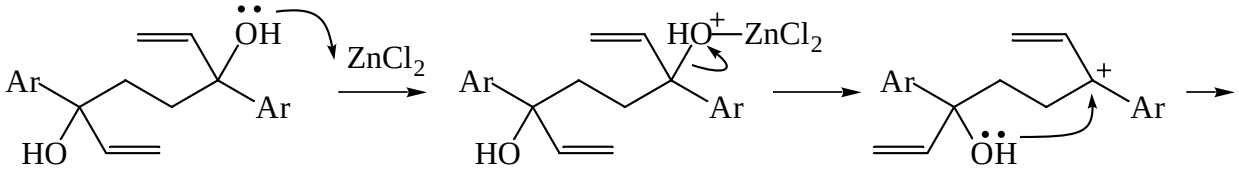


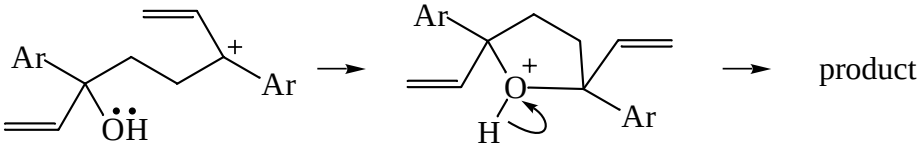
3.3.

(a)



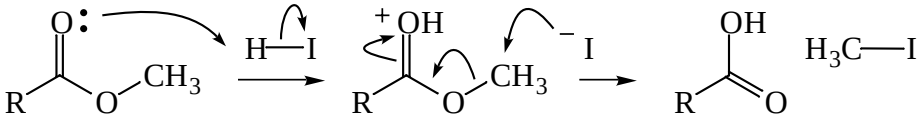
(b)



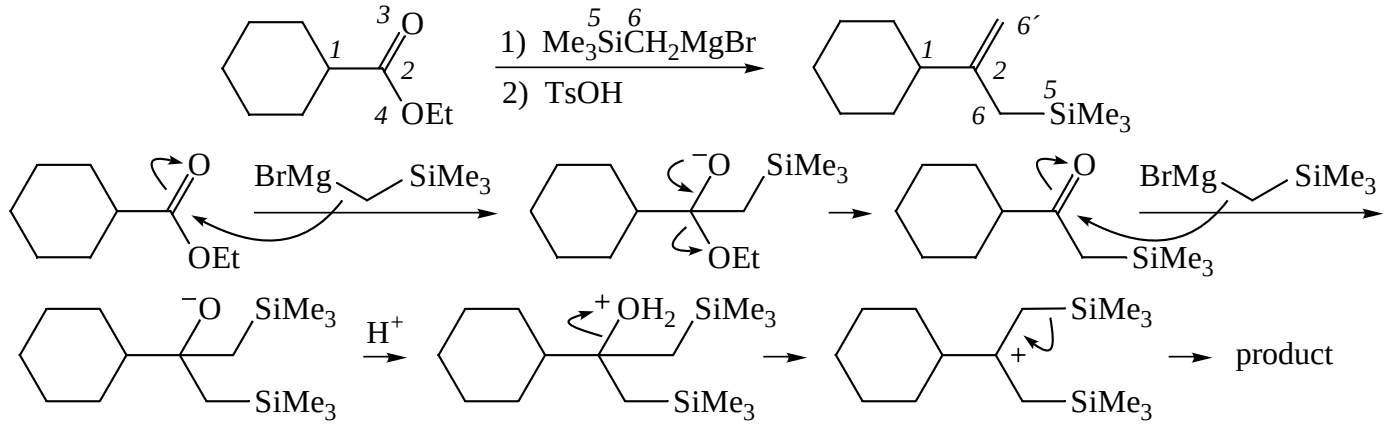


3.4. Because the carbocations derived from aryl and alkenyl halides are extremely high in energy.

3.5. The carbonyl O of esters, amides, and the like is always more nucleophilic than any other heteroatom attached to the carbonyl C. The first protonation occurs at the carbonyl O. An S_N2 attack of I^- on CH_3 then gives the free carboxylic acid.

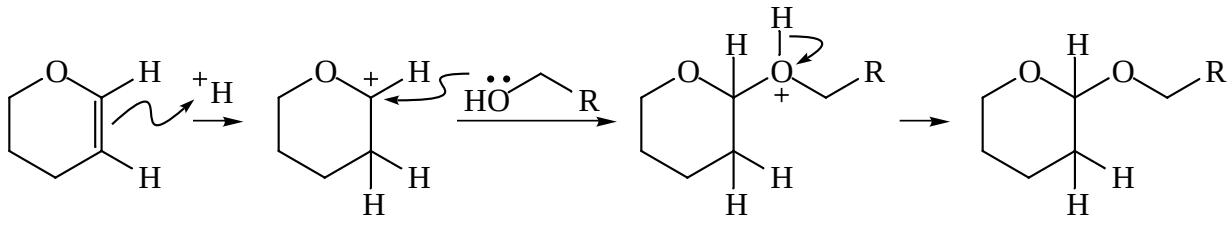


3.6. A few things about this reaction may have caught you off guard. First, the first step is a polar reaction under basic conditions, involving the Grignard reagent; only the second step is a polar reaction under acidic conditions. Second, *two* equivalents of the Grignard are required for the product; the second equivalent explains whence comes the terminal alkene C (labelled C6´) in the product. (Remember that Grignards react with esters by addition–elimination–addition to give tertiary alcohols, and that it is not possible under normal circumstances to stop the reaction after one Grignard adds.) Make: C2–C6, C2–C6´. Break: C2–O3, C2–O4, Si5´–C6´.

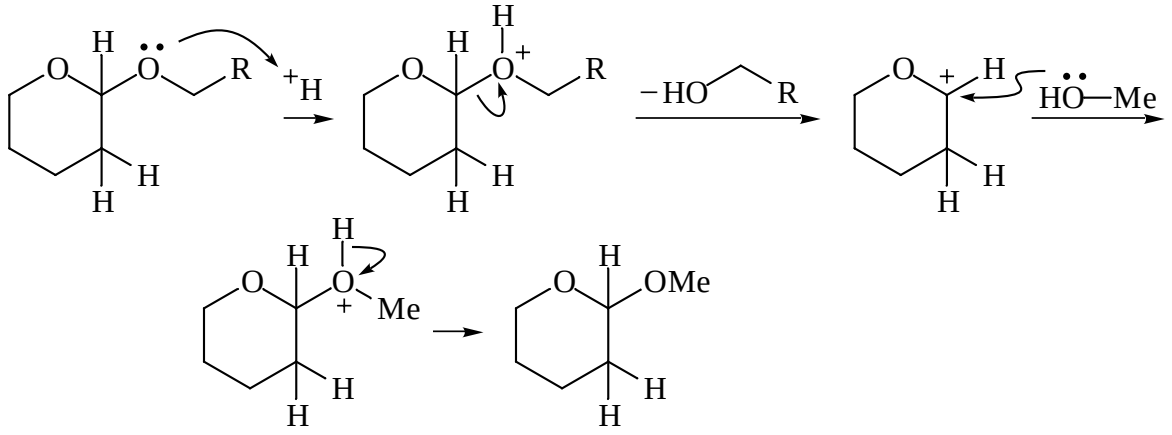


3.7.

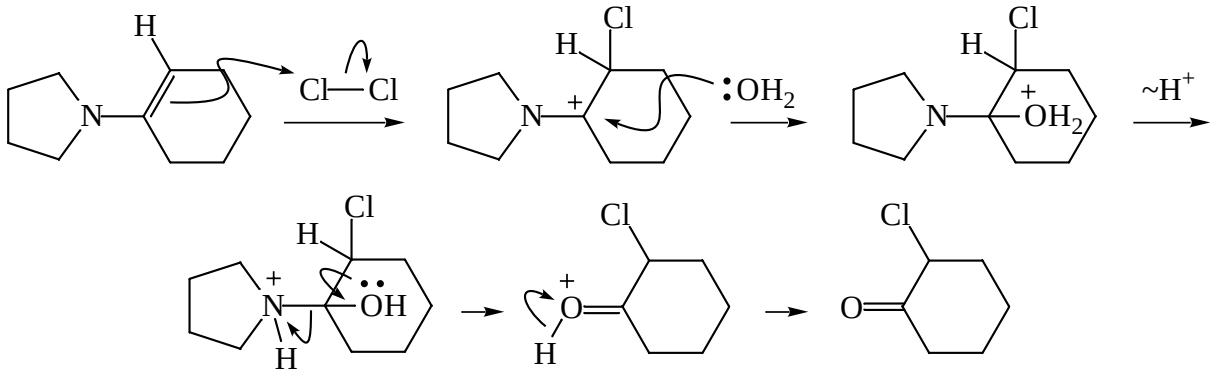
(a)



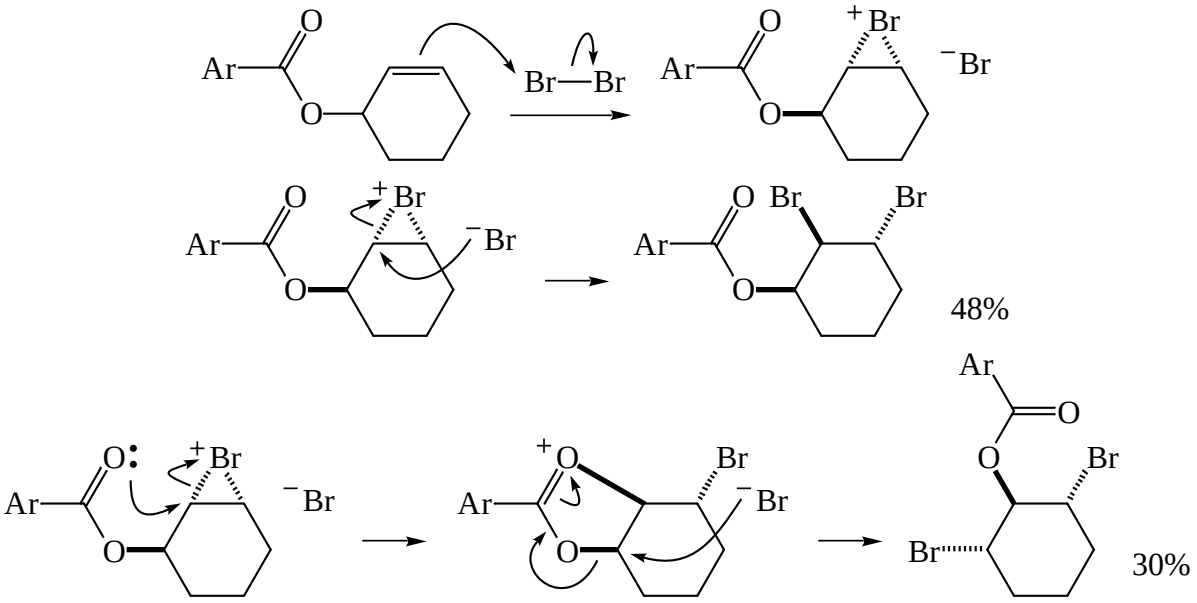
(b) This substitution reaction must proceed by an S_N1 mechanism.

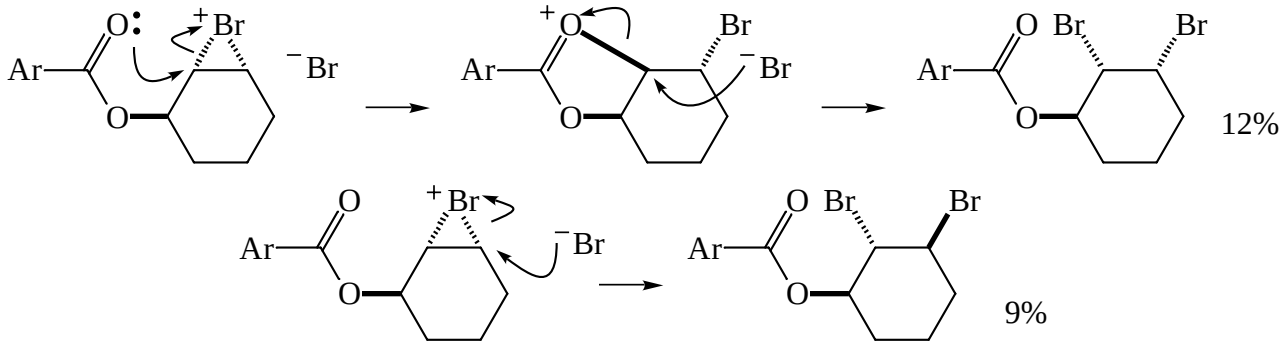


3.8. The N atom so strongly stabilizes cations that a β-halocarbocation is the likely intermediate, not a halonium ion.



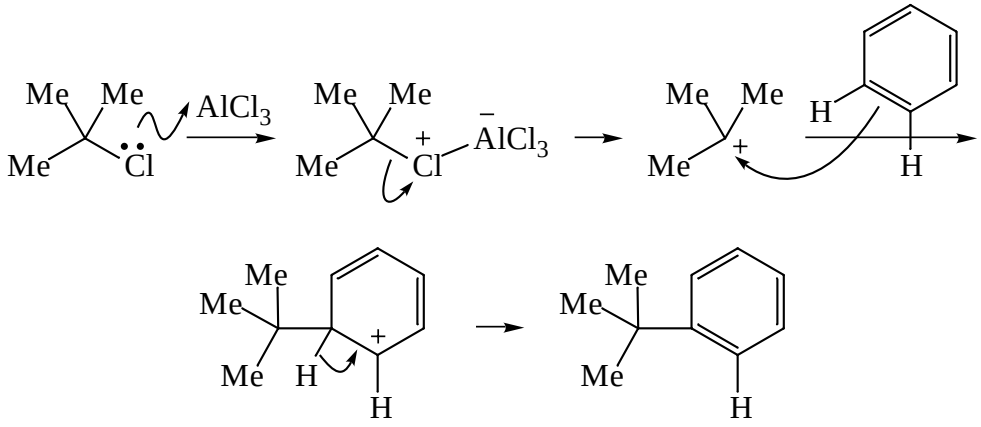
3.9. The products have in common a bromonium ion that is formed by attack of Br_2 on the face of the double bond *opposite* the acyloxy substituent. The two products not consistent with simple anti addition across the π bond are obtained via neighboring group participation of the acyloxy group.



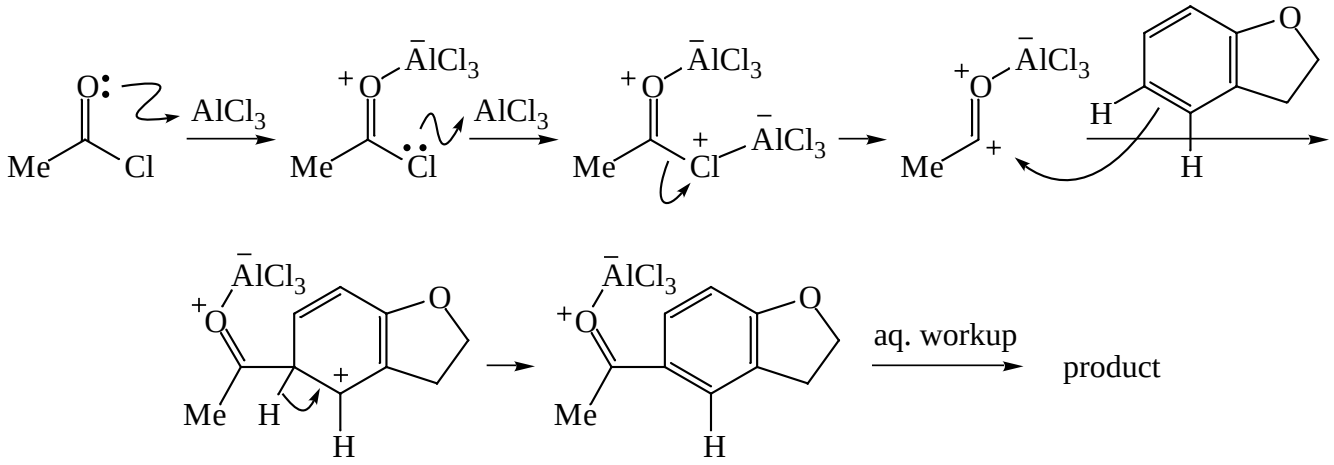


3.10.

(a) The role of $AlCl_3$ is to turn the Cl of *t*-BuCl into a better leaving group. Ionization of the C–Cl bond gives a carbocation, which reacts with benzene by the standard addition–fragmentation mechanism.

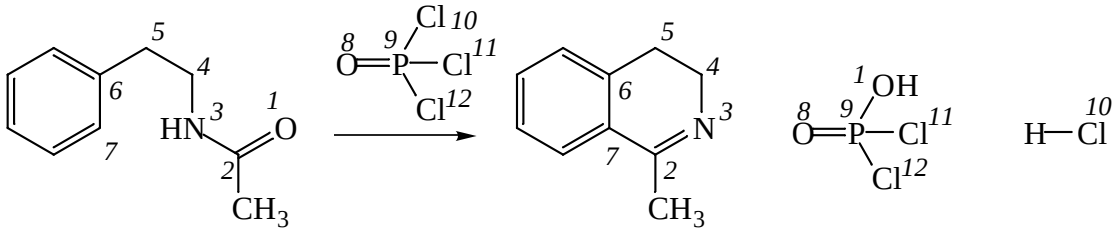


(b) Unlike a Friedel–Crafts alkylation, which requires only a catalytic amount of $AlCl_3$, a Friedel–Crafts acylation requires more than a stoichiometric amount of $AlCl_3$. The first equivalent coordinates to the carbonyl O; the remaining catalytic amount catalyzes the ionization of the C–Cl bond. The final product is obtained after addition–fragmentation and aqueous workup.

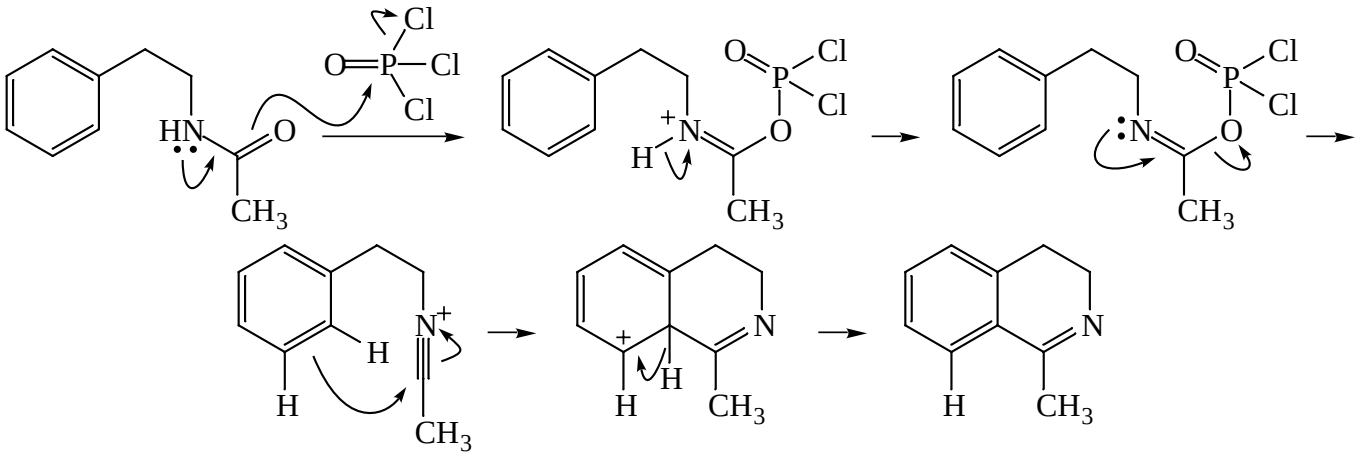


(c) The starting material loses the elements of water, but if water is the by-product, what is the role of the

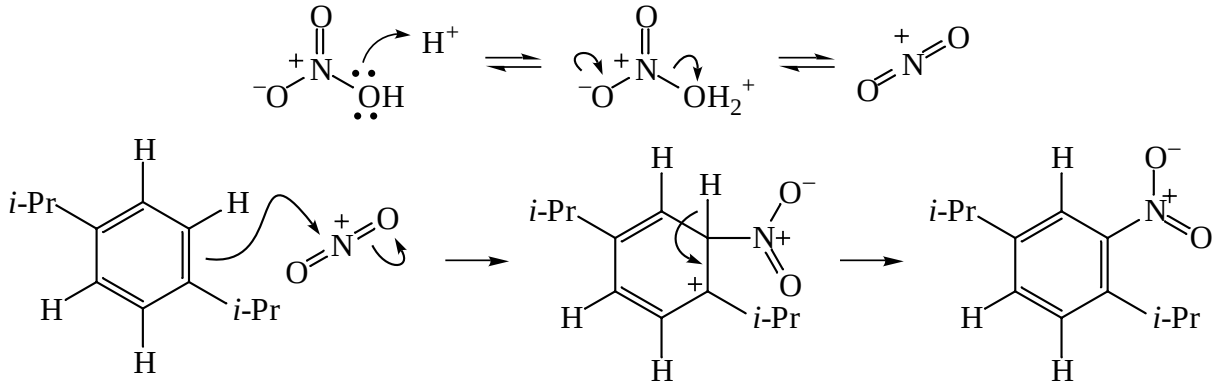
$POCl_3$? It is not a Lewis acid; it is a σ bond electrophile at P. Because P9 is electrophilic and O1 is nucleophilic, the first step must be formation of O1–P4 bond. If this is true, the P-containing by-product has an O–P bond. Make: O1–P9, C2–C7. Break: O1–C2, P9–Cl10.

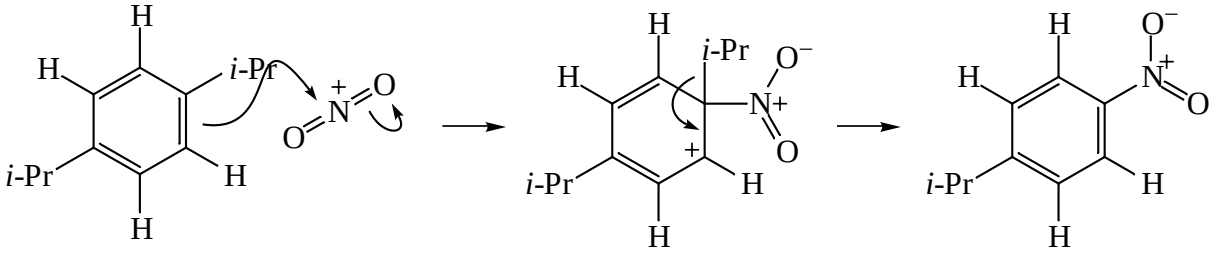


In the first step, O1 attacks P9 and displaces Cl10. After deprotonation of N3, a carbocation at C2 (stabilized by resonance with N4) is formed. Addition–elimination then gives the product. An alternative and reasonable mechanism would have C7 attack C2 before the C2–O1 bond cleaves (addition–elimination type mechanism), but the conventional wisdom is that the reaction proceeds through the nitrlium ion intermediate.



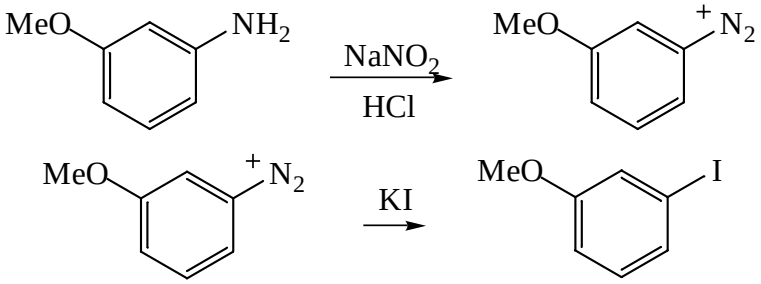
3.11. The first product is derived from a normal electrophilic aromatic substitution reaction of the kind described in the text. The second product is derived from ipso electrophilic aromatic substitution. The mechanism is exactly the same, but in the last step *i*-Pr^+ is lost instead of H^+.



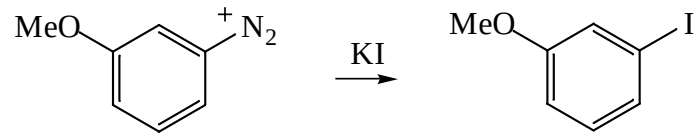


3.12.

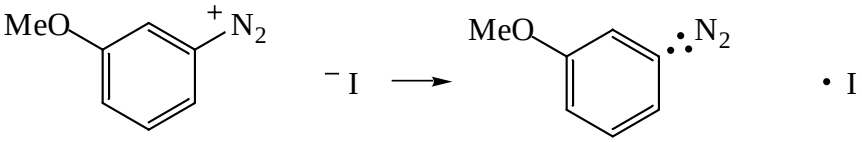
(a) The initial part, formation of a diazonium ion, proceeds by the mechanism described in the book.



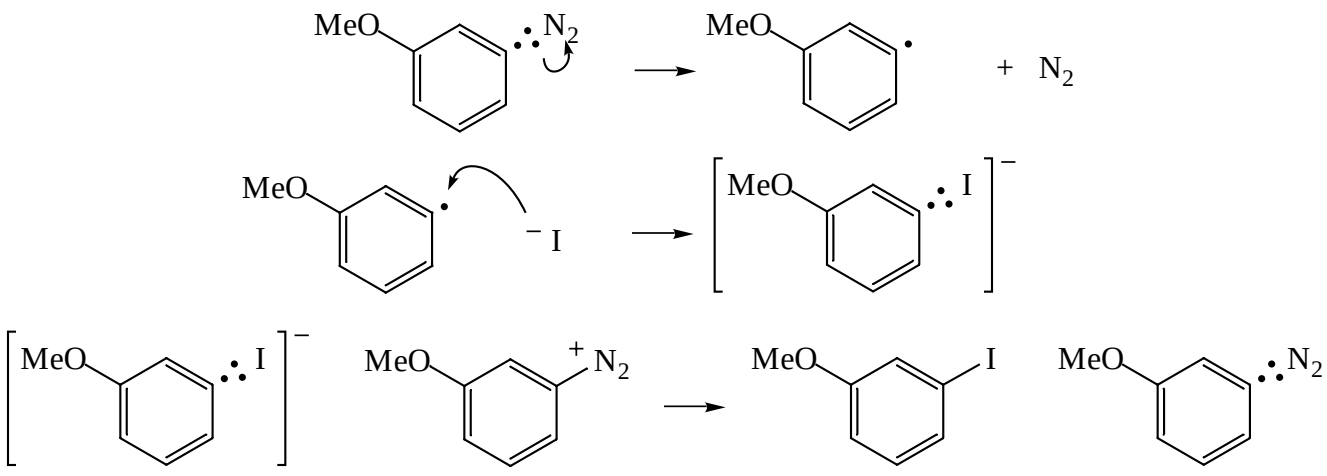
The second part, substitution of N_2 by I^-, proceeds by the $S_{RN}1$ mechanism.



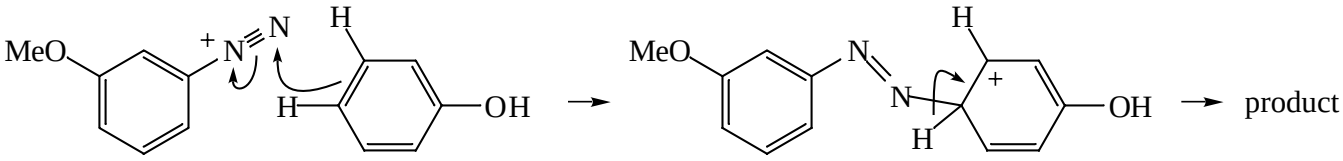
Initiation:



Propagation:

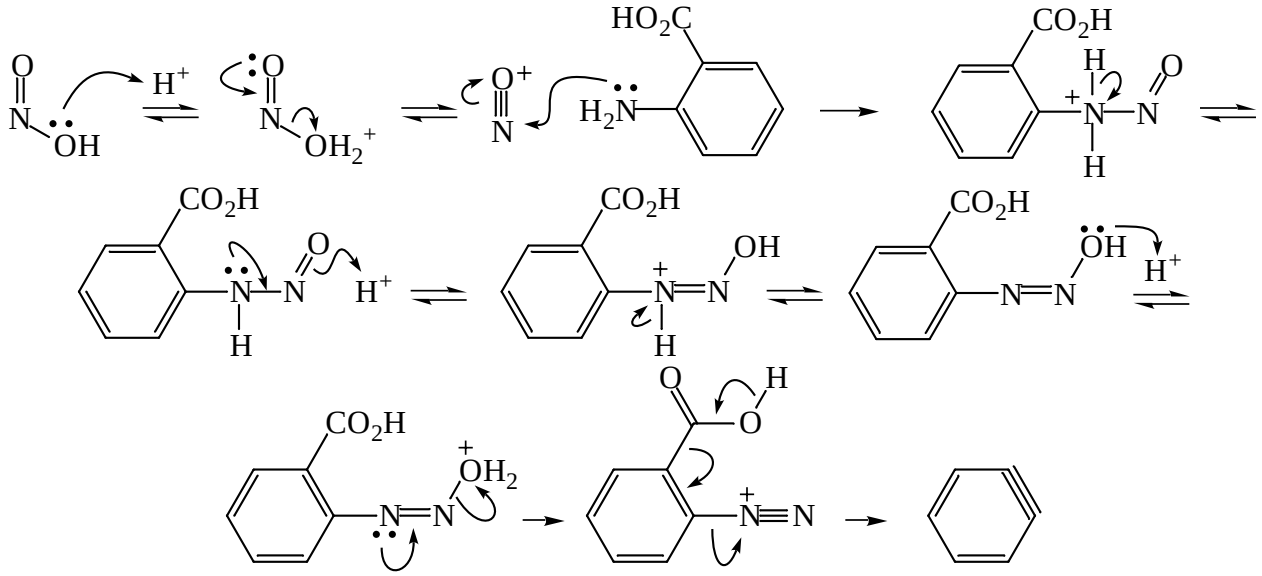


(b) Here the diazonium ion forms again, but now, an electrophilic aromatic substitution occurs, with the terminal N of the diazonium ion acting as the electrophile.

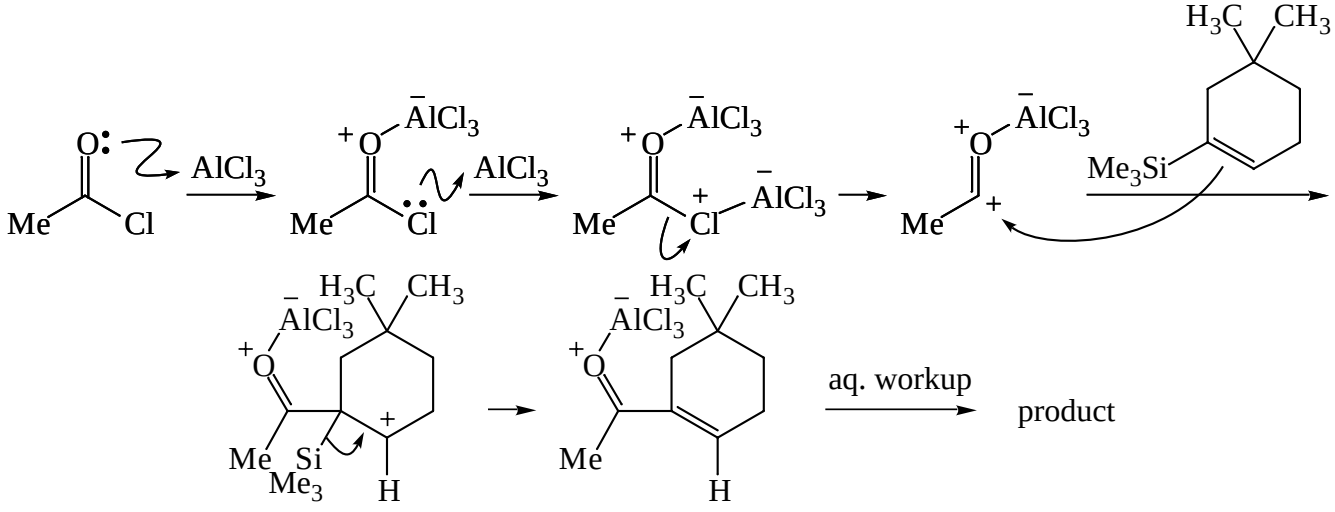


3.13.

(a) Only an N–N bond is made, and one C–C bond is broken. When an amine is combined with $NaNO_2$ and HCl, a diazonium ion is formed. An elimination reaction then ensues with loss of CO_2.



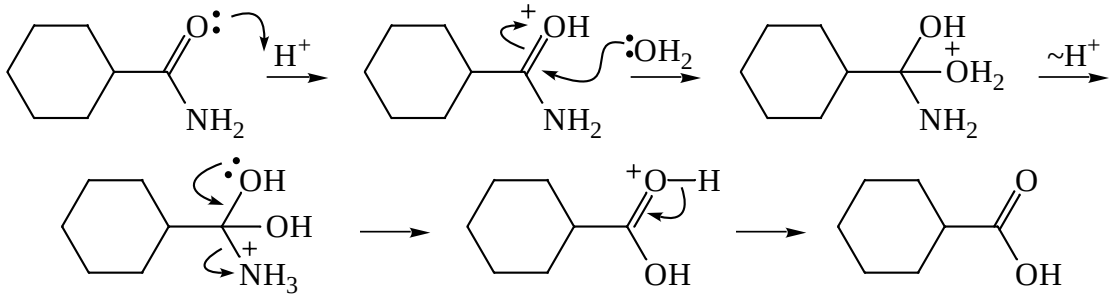
3.14. The mechanism is exactly the same as in 3.10(b).



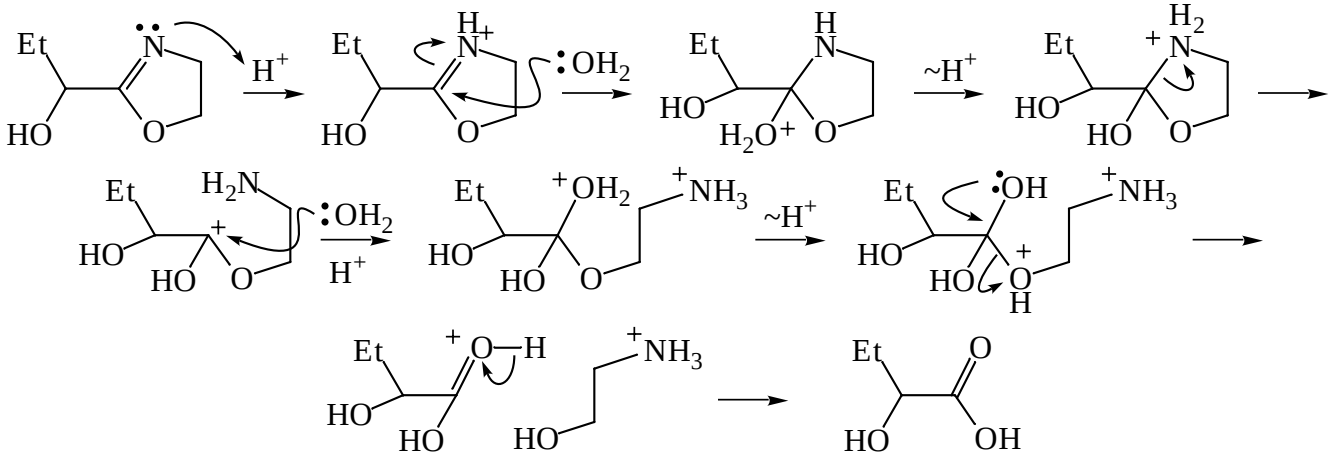
3.15.

(a) The mechanism proceeds by addition–elimination. *However*, both the addition and elimination steps

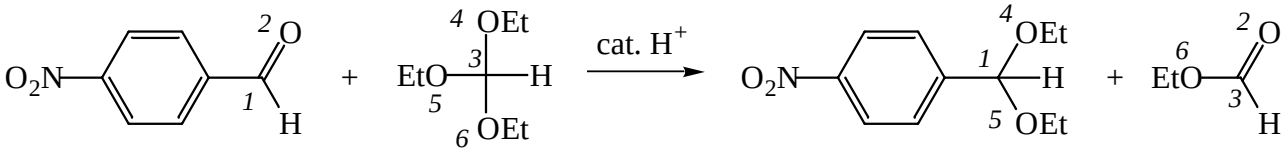
are preceded by protonation and followed by deprotonation. It is very important that these proton transfer steps are drawn properly!



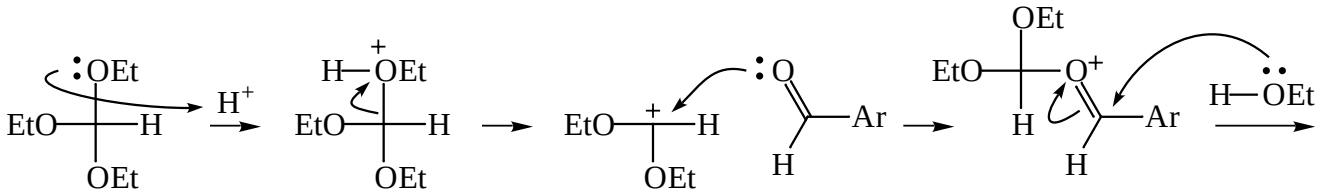
(b) It is unlikely that the CH_2–O bond in the starting material will break under aqueous acidic conditions (can't form a carbocation, and S_N2 is unlikely unless conditions are very harsh). Therefore the CH_2–O bond is preserved in the product, which means that *both* O's of the carboxylic acid product come from H_2O.

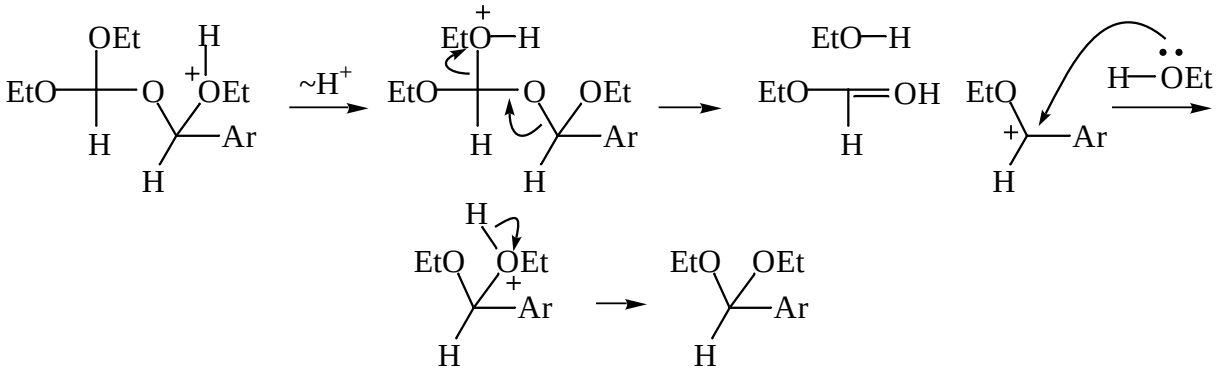


3.16. Make: C1–O4, C1–O5, O2–C3. Break: C1–O2, C3–O4, C3–O5.

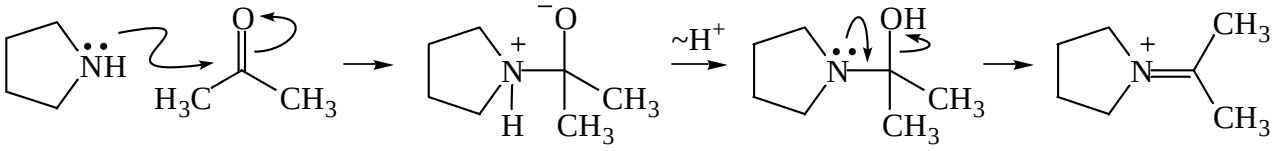


There are a number of ways this reaction could proceed, but the key step in any of them is attack of O2 on a carbocation at C3.

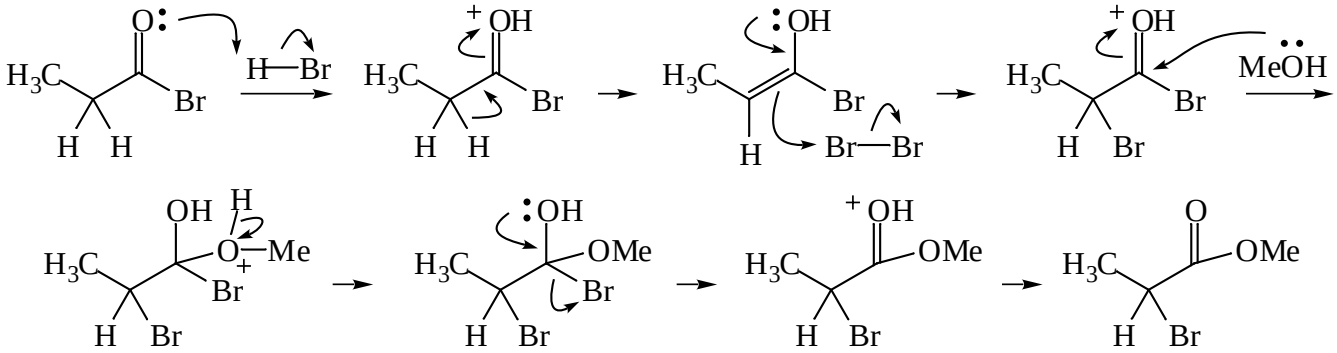




3.17. Under these nearly neutral conditions, it is unclear whether the carbonyl O is protonated before or after attack of N. Either way is acceptable.

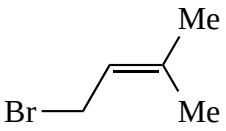


3.18. Two substitutions are occurring here: H to Br, and Br to MeO. Looking at the order of reagents, the first substitution is H to Br. Br_2 is electrophilic, so the α-C of the acyl bromide must be made nucleophilic. This is done by enolization. The substitution of Br with MeO occurs by a conventional addition–elimination reaction under acidic conditions.



Answers To Chapter 3 End-of-Chapter Problems.

1. (a) In order to compare it directly with the other two carbocations, the carbocation derived from the first compound should be drawn in the resonance form in which the empty orbital is located on the 3° C. It can then clearly be seen that the three carbocations are all 3° carbocations that differ only in the third carbocation substituent. The order of substituent stabilizing ability is lone pair > π bond > σ bonds.



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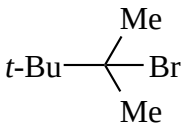

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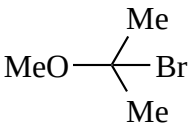
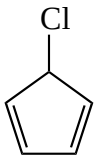


1

(b) The first compound gives an antiaromatic carbocation. Among the other two, the second compound gives a cation with the electron deficiency delocalized across one 2° and two 1° C's, while the third compound gives a cation with the electron deficiency delocalized across three 2° C's.



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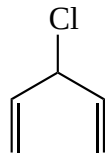

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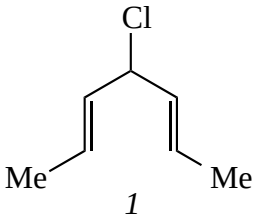
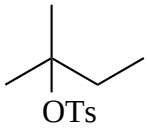


1

(c) The order of stability of alkyl cations is 3° > 2° > 1°.



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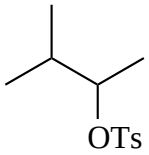

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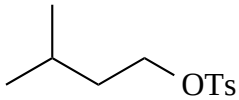
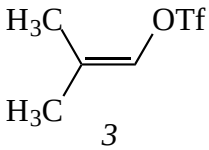


3

(d) The second compound gives a lone-pair-stabilized carbocation. Among the other two, 1° alkyl carbocations are more stable than 1° alkenyl carbocations.



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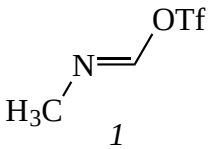
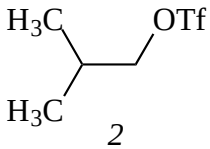
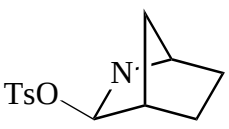


1



2

(e) The first compound generates a cation that can be stabilized by the lone pair on N. The second compound generates a cation that cannot be stabilized by the lone pair on N due to geometrical constraints (would form bridgehead π bond, a no-no). Therefore the *inductive* effect of N *destabilizes* the carbocation derived from the second compound relative to the carbocation from the third compound, in which the N is more remote.



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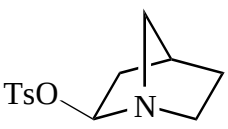

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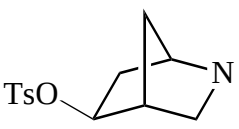

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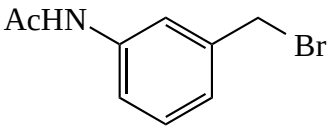
(f) The second and third compounds generate cations that can be directly stabilized by resonance with the lone pairs on the heteroatoms, with N more stabilizing than O, while the cation from the first compound isn't stabilized by resonance with the heteroatom at all.



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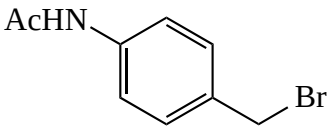

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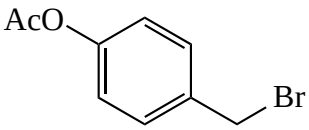

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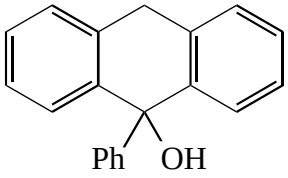
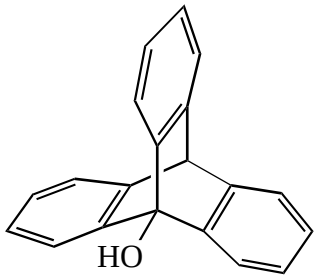
(g) The second compound (a *triptycene*) provides no π stabilization to the corresponding cation, because the p orbitals of the phenyl rings are perpendicular to the empty p orbital. The first compound is more likely to ionize than the third for two reasons. (1) The phenyl rings in first compound are more electron-rich (alkyl-substituted). (2) In the first compound, two of the phenyl rings are held in a coplanar arrangement by the bridging CH_2, so they always overlap with the empty p orbital of the cation. In the third compound, there is free rotation about the C–Ph bonds, so there is generally less overlap between the Ph π clouds and the empty p orbital of the cationic center.



1



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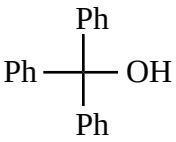


2

2.

(a) Excellent carbocation, nucleophilic solvent, ∴ S_N1. Br^- leaves spontaneously to give a carbocation, which combines with solvent to give a protonated ether, which loses H^+ to give the product.

(b) Excellent carbocation, nucleophilic solvent, ∴ S_N1. First O is protonated, then OH_2 leaves to give carbocation, Next, the carbonyl O of AcOH adds to the carbocation, and then H^+ is lost from O to give the product.

(c) Excellent carbocation, nonnucleophilic solvent, ∴ E1. First O is protonated, then OH_2 leaves to give carbocation. Finally, H^+ is lost from the C adjacent to the electron-deficient C to give the alkene.

(d) Good carbocation, nucleophilic solvent, ∴ S_N1. The product is racemic. Br^- leaves spontaneously to give a planar, achiral carbocation; then the carbonyl O of HCO_2H adds to the carbocation from either enantioface. Finally, H^+ is lost from O to give the product.

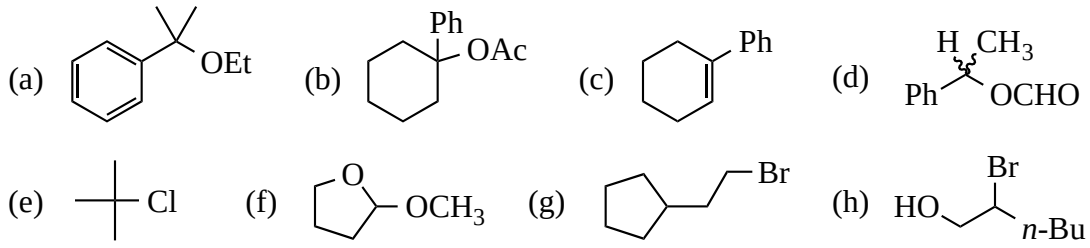
(e) Excellent carbocation, nucleophilic solvent, ∴ S_N1. Here the nucleophile is Cl^-, because addition of H_2O simply gives back starting material. First O is protonated, then OH_2 leaves to give carbocation, then Cl^- adds to carbocation to give the product.

(f) Excellent carbocation, nucleophilic solvent, ∴ S_N1. First the O of the OH group is protonated, then OH_2 leaves to give an O-stabilized carbocation. Next, the O of CH_3OH adds to the carbocation, and finally H^+ is lost from the O of OCH_3 group to give the product. Note that the ring oxygen could also act

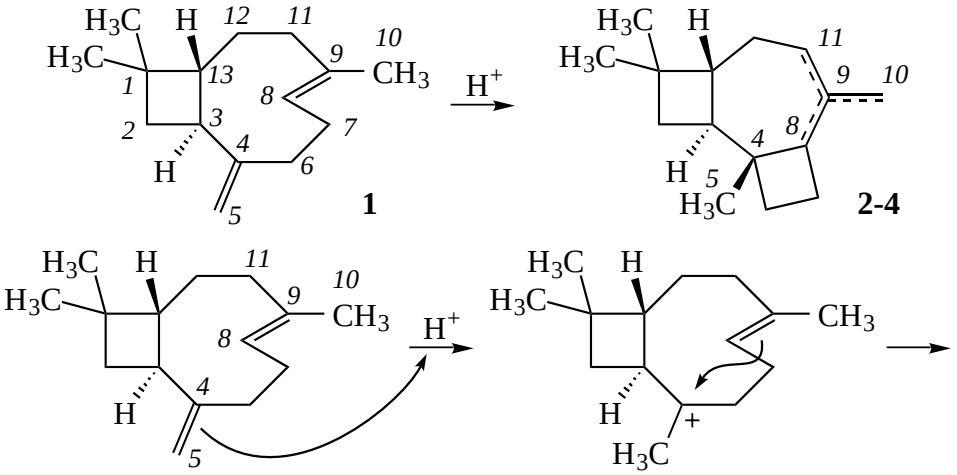
as a leaving group to give an acyclic compound, but entropy favors the loss of the OH group (because two products are formed from one).

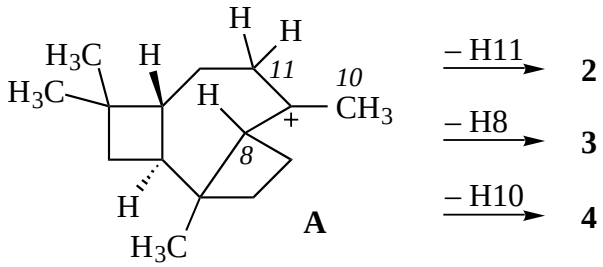
(g) Awful carbocation, so can't be S_N1. Strongly acidic conditions, excellent nonbasic nucleophile, ∴ S_N2. First O is protonated, then Br^- does a nucleophilic displacement of OH_2 to give the product.

(h) So-so carbocation, excellent nonbasic nucleophile. Could be S_N1 or S_N2. First O is protonated; then, *either* Br^- displaces O from C to give product, *or* O leaves to form carbocation, and then Br^- adds to the carbocation. The regiochemistry is determined by the formation of the stabler carbocation. (Even in S_N2 reaction, the central C in the transition state has some carbocationic character, so the more substituted C undergoes substitution under acidic conditions.)

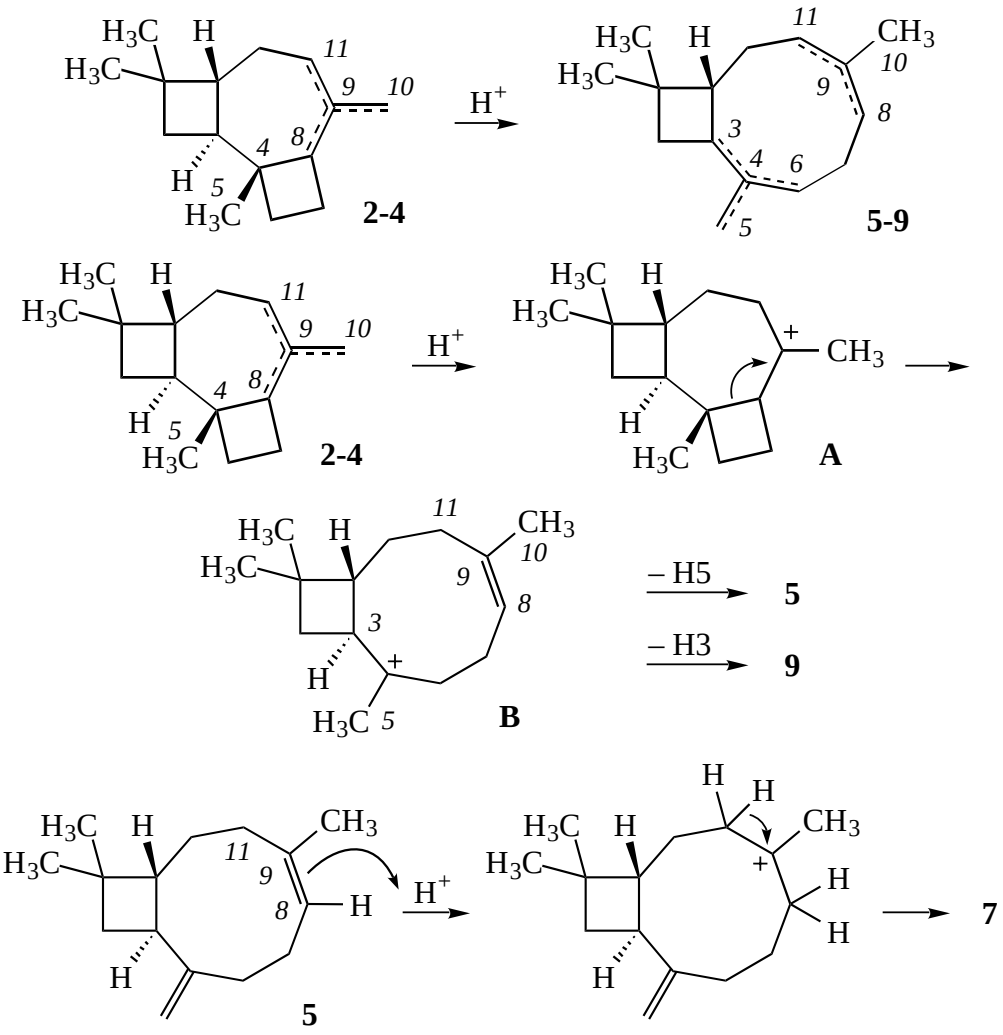


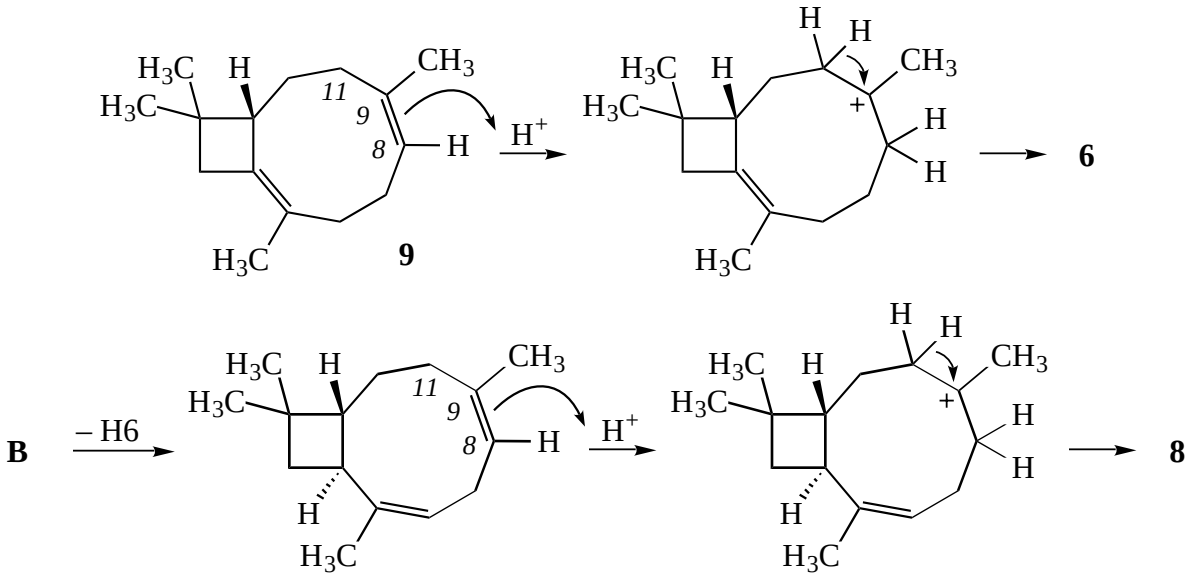
3. Number the C's in **1.** We see that the first set of compounds, **2-4,** are all obtained by formation of a bond between C4 and C8. To make the C4–C8 bond, we could make C4 electrophilic and C8 nucleophilic, or vice versa. If we make C8 electrophilic by protonation of C9, then after attack of C4, we end up with a 1° carbocation on C5 — very unstable and not what we want. On the other hand, if we make C4 electrophilic by protonating C5, then after attack of C8 on C4, we end up with a 3° carbocation on C9. As compounds **2-4** differ only in the location of the π bond to C9, suggesting that loss of H^+ from a C9 carbocation is the last step, this is what we need to do.



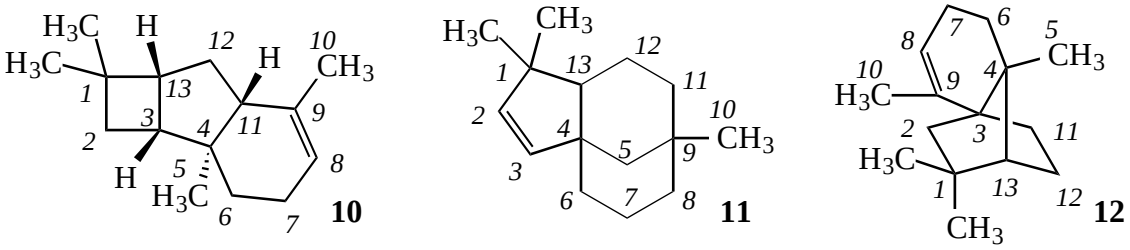


The next set of products, **5-9,** must be formed from **2-4.** To get from **2-4** to **5-9,** we must break the C4–C8 bond again. This is easy to do if we regenerate carbocation **A.** Cleavage of the C4–C8 bond gives a C8=C9 π bond and a carbocation, **B,** at C4. Loss of H^+ from C5 or C3 of **B** gives product **5** or **9**, respectively. Compounds **5** and **9** can then partly isomerize to compounds **7** and **6,** respectively, by protonation at C8 and loss of H^+ from C11. Loss of H^+ from C6 of **B,** followed by protonation at C8 and loss of H^+ from C11, gives product **8.**

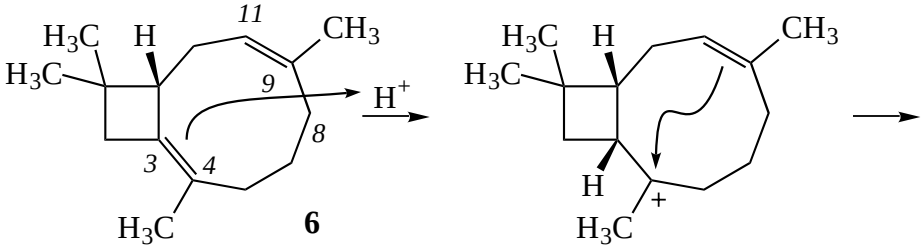


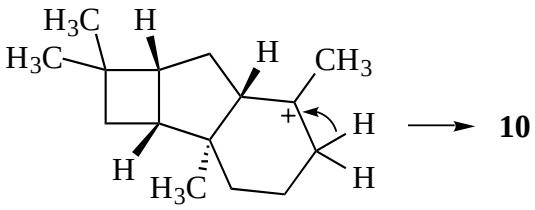


After a while longer, compounds **5-9** are converted into compounds **10-12.** Note that since all of **5-9** are easily interconverted by protonation and deprotonation reactions, any of them could be the precursors to any of **10-12.**



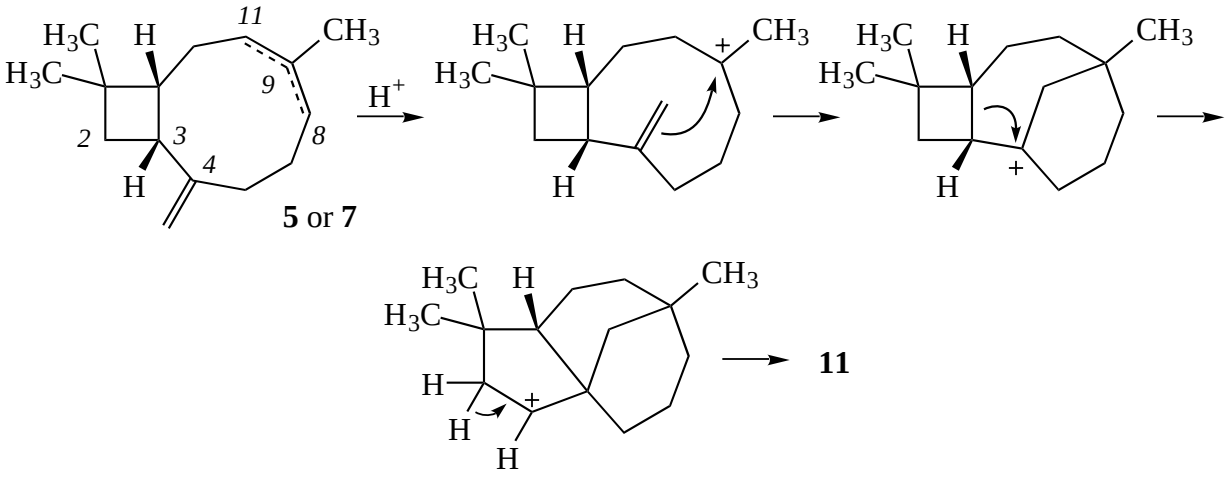
Compound **10** has a new C4–C11 bond. Either C4 is the nucleophile and C11 is the electrophile, or vice versa. Either way, compounds **5** and **9** are excluded as the immediate precursors to **10,** since they both have a saturated C11 that cannot be rendered nucleophilic or electrophilic (except by isomerization to **6, 7,** or **8**). If C11 is the nucleophile, this would put a carbocation at C9, which is where we want it so that we can deprotonate C8 to form the C8=C9 π bond in **10.** So we might protonate **6, 7,** or **8** at C3, C5, or C6, respectively, to make an electrophile at C4. However, note the stereochemistry of the H atom at C3 in **10.** Both **7** and **8** have the opposite stereochemistry at C3. This means that **6** must be the immediate precursor to **10.** Protonation of C3 of **6** from the top face gives a carbocation at C4. Attack of the C11=C9 π bond on C4 gives a new σ bond and a carbocation at C9. Loss of H^+ from C8 gives **10.**





10

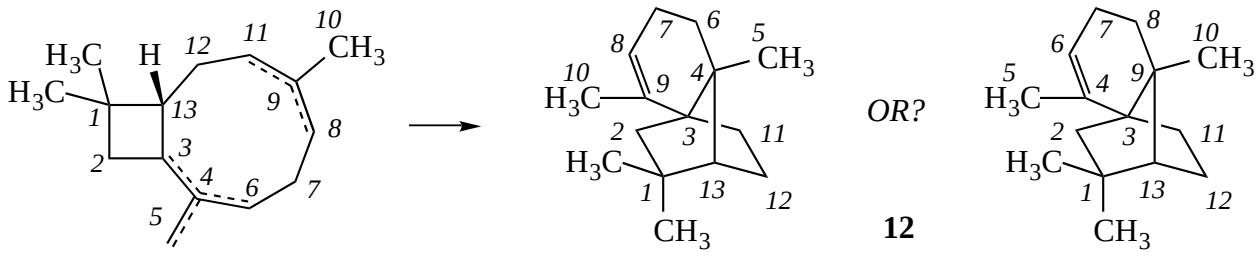
Compound **11** has new bonds at C5–C9 and C13–C4, and the C3–C13 bond is broken. Also, a new C2=C3 π bond is formed. The shift of the C13–C3 bond to the C13–C4 bond suggest a 1,2-alkyl shift. Then loss of H^+ from C2 can give the C2=C3 π bond. So we need to establish a carbocation at C4. We can do this simply by protonating C5 of **5** or **7,** but if we do this, then we can't form the C5–C9 bond. But allowing C5 to be a nucleophile toward a C9 carbocation will give a similar carbocation at C4 and gives the desired bond. The requisite carbocation at C9 might be generated by protonation of C8 of **5** or C11 of **7.** Addition of the C4=C5 π bond to C9 gives the C5–C9 σ bond and a carbocation at C4. A 1,2-alkyl shift of C13 from C3 to C4 gives a carbocation at C3, which is deprotonated to give **11.**



5 or **7**

11

The key to **12** is numbering its C's correctly. It's relatively easy to number the atoms in the bottom of the compound as C1 to C3 and C11 to C13, but the atoms in the top half of the compound could be labelled as C4 to C9 or the other way around, as C9 to C4. If you label the atoms incorrectly, the problem becomes nearly impossible. How do you decide which is correct?



12

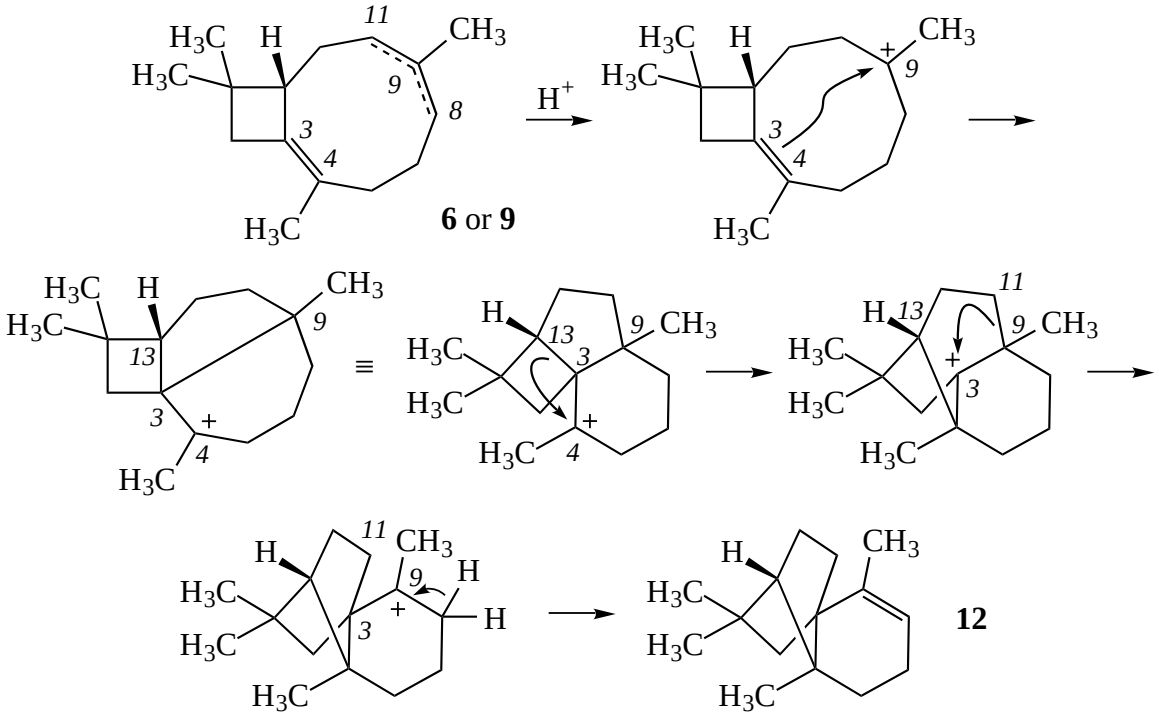
Make a list of make and break for each compound.

Left make: C3–C9, C3–C11, C4–C13. Right make: C3–C9, C3–C11, C9–C13.

Left break: C3–C13, C9–C11. Right break: C3–C13, C9–C11.

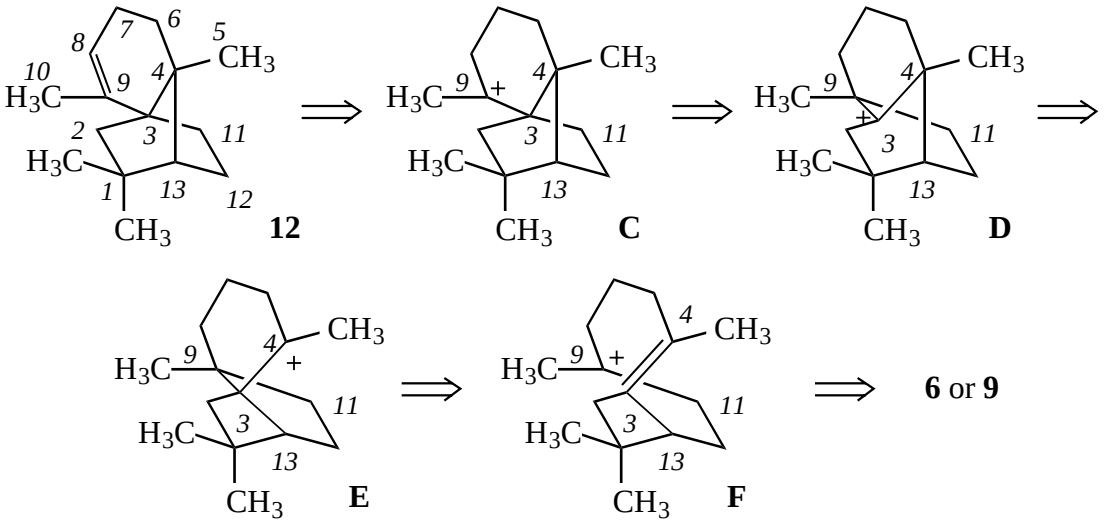
The only difference is that on the right, we need to make C4–C13, while on the left, we need to make C9–C13. Which is better? On the left, the C4–C13 bond can be made and the C3–C13 bond can be broken by a 1,2-shift. This can't be done on the right. Also, in compound **11** we made a C4–C13 bond. Not a lot to go on, but the first numbering seems a little more likely, so we'll go with it. If you were unable to number the atoms correctly, go back and try to solve the problem now.

The broken C13–C3 and new C13–C4 bonds suggest a 1,2-alkyl shift of C13 from C3 to a C4 carbocation, leaving a carbocation at C3. The broken C9–C11 and new C3–C11 bonds suggest a 1,2-shift of C11 from C9 to a C3 carbocation, leaving a carbocation at C9. Since a shift of C11 from C9 to C3 could only occur *after* C3 and C9 were connected, this suggests that the C3–C9 bond is formed *first.* Such a bond would be formed from a C9 carbocation with a C3=C4 π bond. The C9 carbocation could be formed from **6** or **9.** Attack of the C3=C4 π bond on C9 puts a carbocation at C4. Then C13 shifts from C3 to C4. That puts a carbocation at C3. Then C11 shifts from C9 to C3. Finally, deprotonation of C8 gives the product.

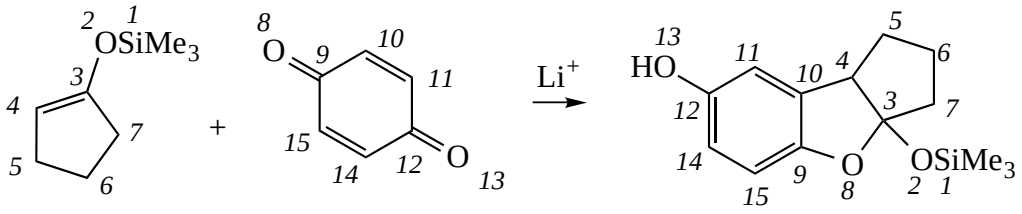


In a deep-seated rearrangement like this, it's sometimes easier to work backwards from the product. The π bond at C8=C9 in **12** suggests that the last step is deprotonation of C8 of a carbocation at C9, **C.** Carbocation **C** might have been formed from carbocation **D** by a 1,2-alkyl shift of C11 from C9 to C3. Carbocation **D** might have been formed from carbocation **E** by a 1,2-alkyl shift of C13 from C3 to C4. Carbocation **E** might have been formed from carbocation **F** by attack of a C3=C4 π bond on a C9

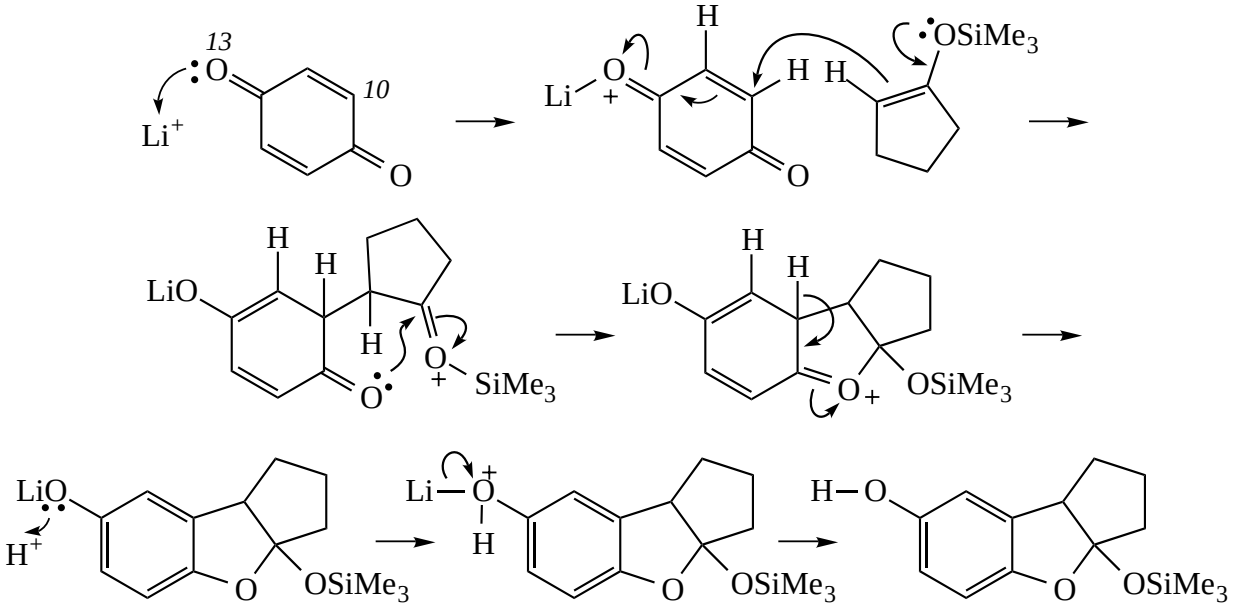
carbocation. The C9 carbocation could have been formed from **6** or **9** by protonation of C11 or C8, respectively.



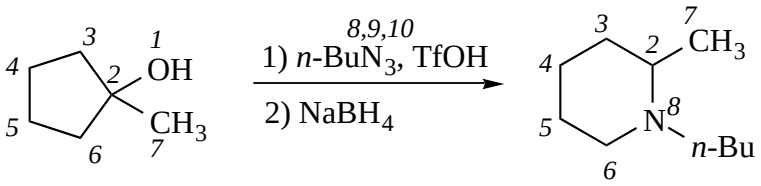
4. (a) Make: C3–O8, C4–C10.



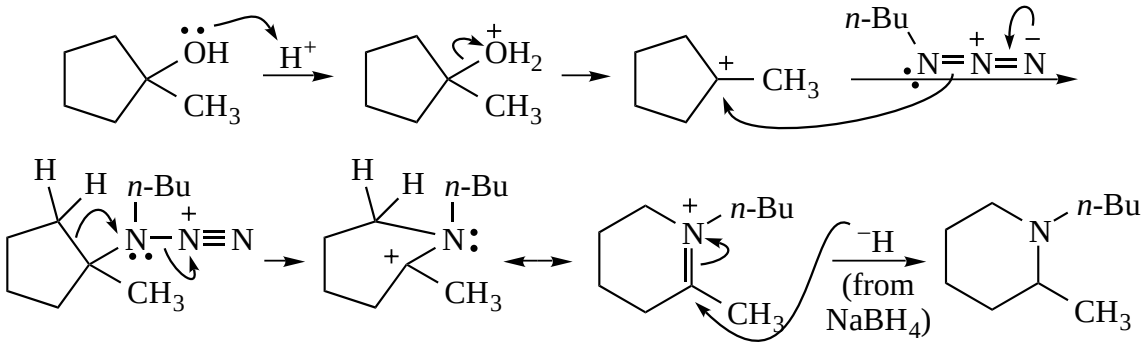
C4 is nucleophilic (enol ether), and C10 is electrophilic. The Lewis acid makes C10 more electrophilic by coordinating to O13. After conjugate addition, O8 traps the C3 carbocation. Proton–Li^+ exchange gives the product.



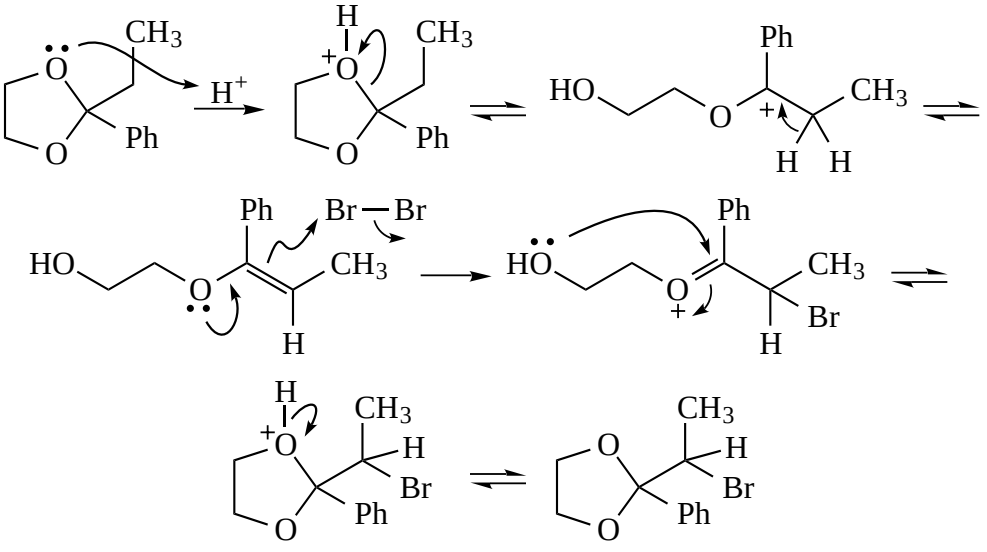
(b) Make: C2–N8, C6–N8. Break: O1–C2, C2–C6.



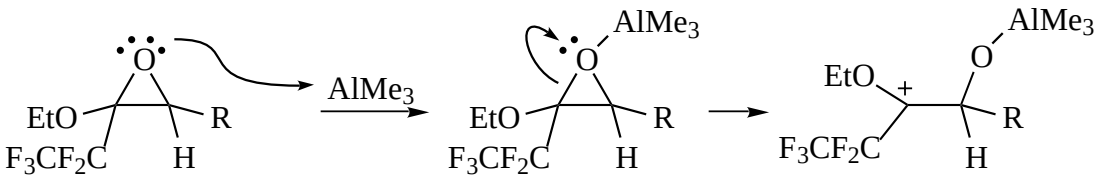
N8 of the azide adds to the carbocation to give an amine with an N_2^+ leaving group attached. Concerted 1,2-migration of C6 from C2 to N8 and expulsion of N_2 gives a N-stabilized carbocation, which is reduced by $NaBH_4$ to give the product.



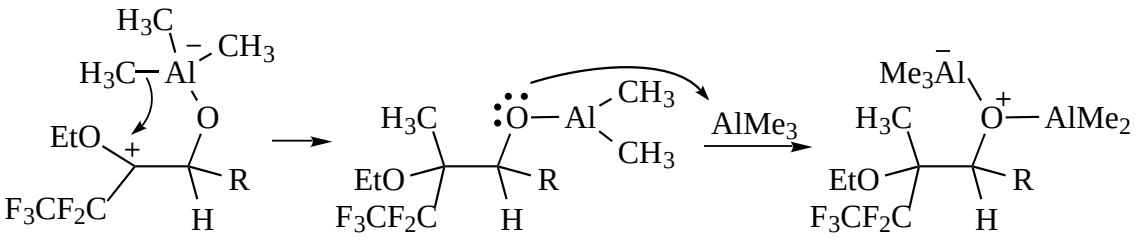
(c) Bromine is an electrophile, so we need to convert the CH_2 group into a nucleophile. This might be done by converting it into an alkene C. There is a leaving group next door, so we can do an E1 elimination to make an enol ether. Another way to look at it: under acidic conditions, acetals are in equilibrium with enol ethers. Either way, after bromination of the enol ether, a new carbocation is formed, which ring-closes to give the product.



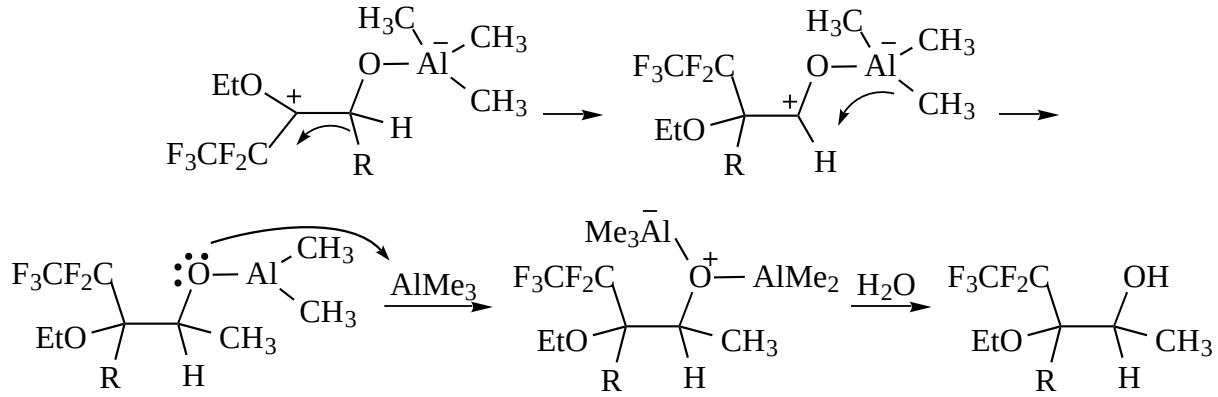
(d) Both reactions begin the same way. $AlMe_3$ is a Lewis acid, so it coordinates to the epoxide O. The epoxide then opens to a carbocation.



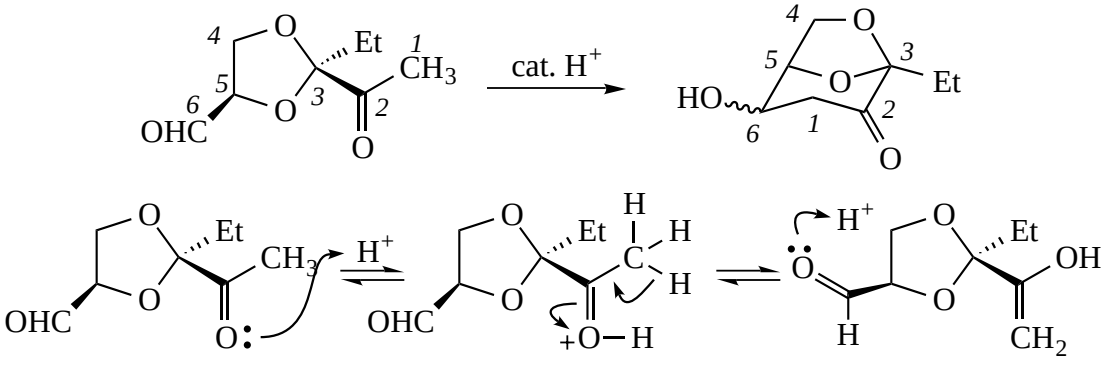
When R= CH_2CH_2Ph, the coordinated Al simply transfers a Me group to the carbocation C (σ bond nucleophile). The O atom then coordinates another equivalent of $AlMe_3$ before the product is obtained upon workup.

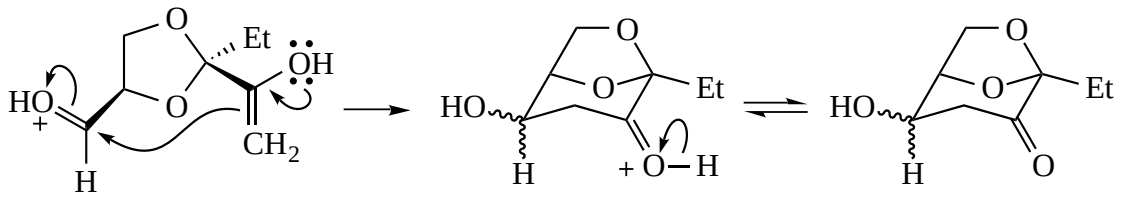


When R= cyclohexyl, the R group migrates (1,2-alkyl shift) to give a new carbocation. (2° Alkyl groups are more prone to migrate than 1° alkyl groups.) After Me transfer to the new carbocation and coordination of another equivalent of $AlMe_3$, workup gives the product.

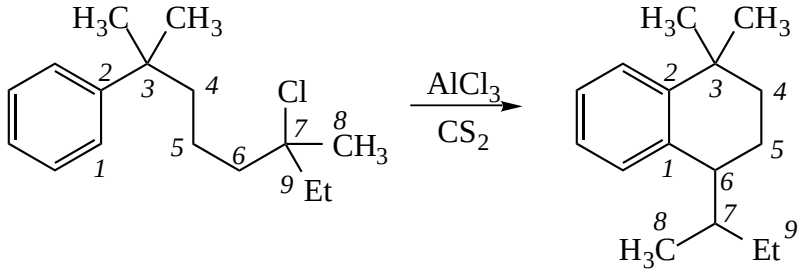


(e) Make: C1–C6. An acid-catalyzed aldol reaction.

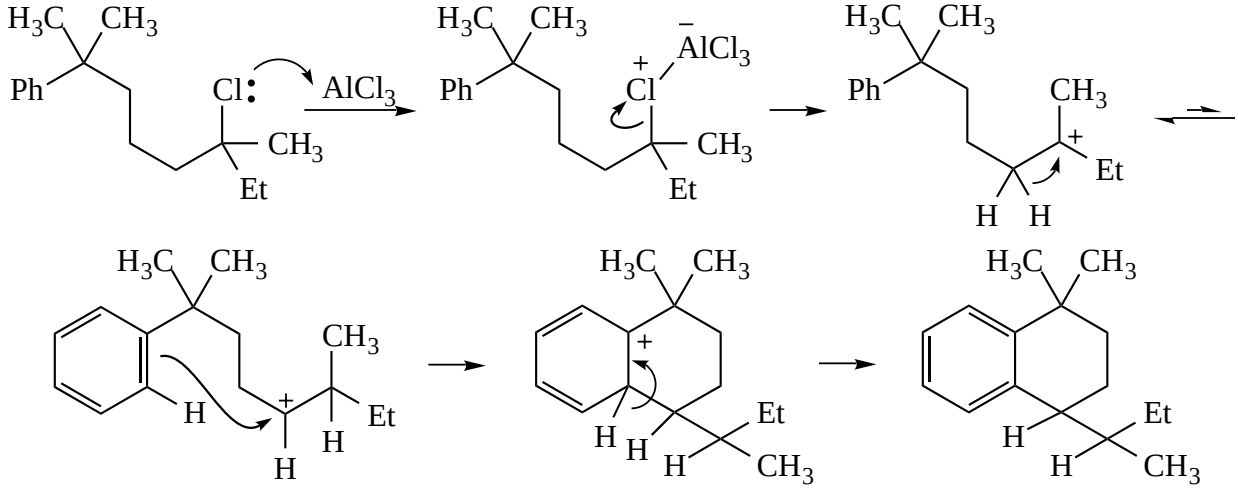




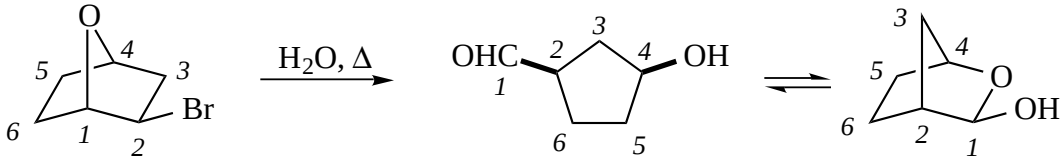
(f) Make: C1–C6. Break: C7–Cl.

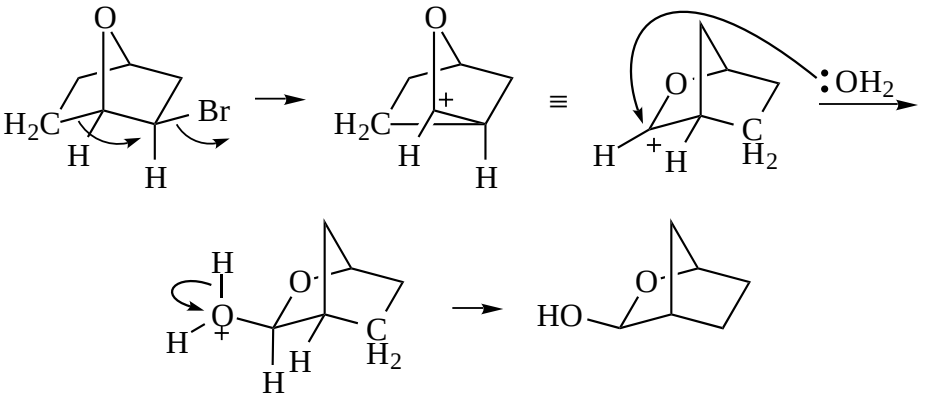


The reaction looks like a simple Friedel–Crafts alkylation, but there is a twist — the leaving group is not on the C which becomes attached to the ring. After formation of the C7 carbocation, a 1,2-hydride shift occurs to give a C6 carbocation. The 1,2-hydride shift is energetically uphill, but the 2° carbocation is then trapped rapidly by the arene to give a 6-6 ring system.



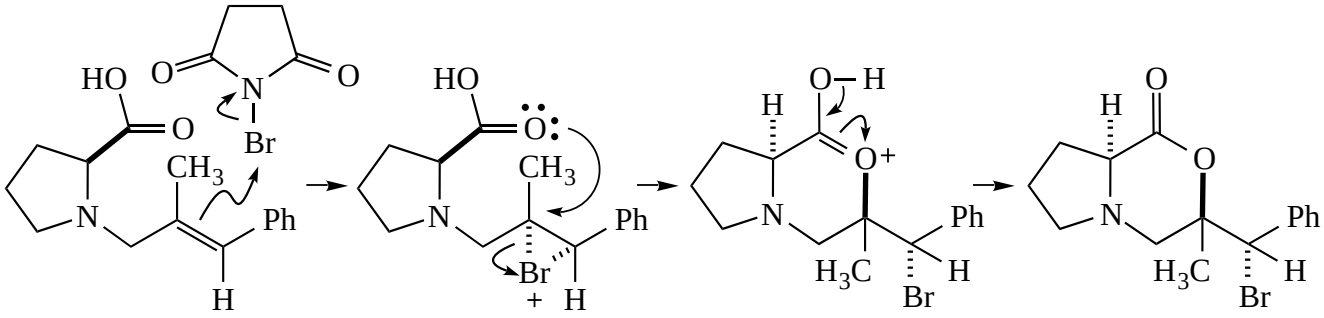
(g) Number the C's! The sequence C2–C3–C4–C5–C6 is identifiable on the basis of the number of H's and O's attached to each C in starting material and product. Make: C2–C6. Break: C1–C6. This pattern is evocative of a 1,2-alkyl shift. The C1–C6 bond is antiperiplanar to the C2–Br bond, so it migrates.



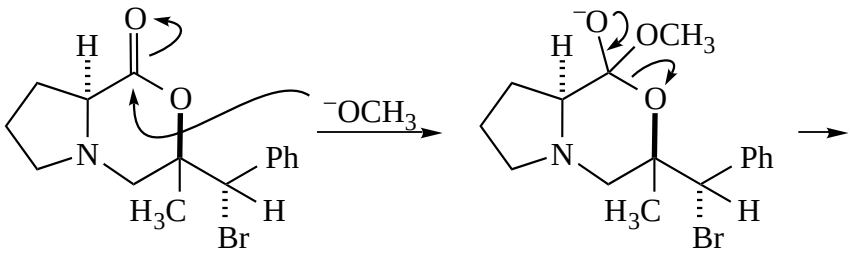


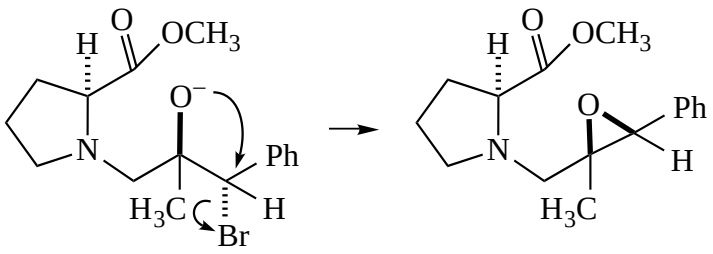
(h) The first step of this two-step reaction takes place under acidic conditions, and the second step takes place under basic conditions. The product from the acidic conditions needs to be a stable, neutral compound.

NBS is a source of Br^+. It reacts with alkenes to give bromonium ions. Then both C–Br bonds need to be replaced by C–O bonds by single inversions, since the *trans* stereochemistry of the double bond is retained in the epoxide. Under these acidic conditions the bromonium ion is opened intramolecularly by the acid carbonyl O, with inversion at one center; loss of H^+ gives a bromolactone.

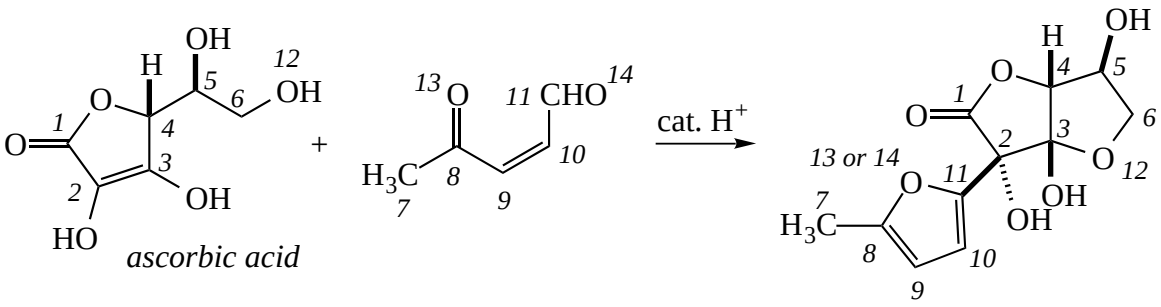


Now MeO^- is added to begin the sequence that takes place under basic conditions. The MeO^- opens the lactone to give a 2-bromoalkoxide, which closes to the epoxide, inverting the other center.

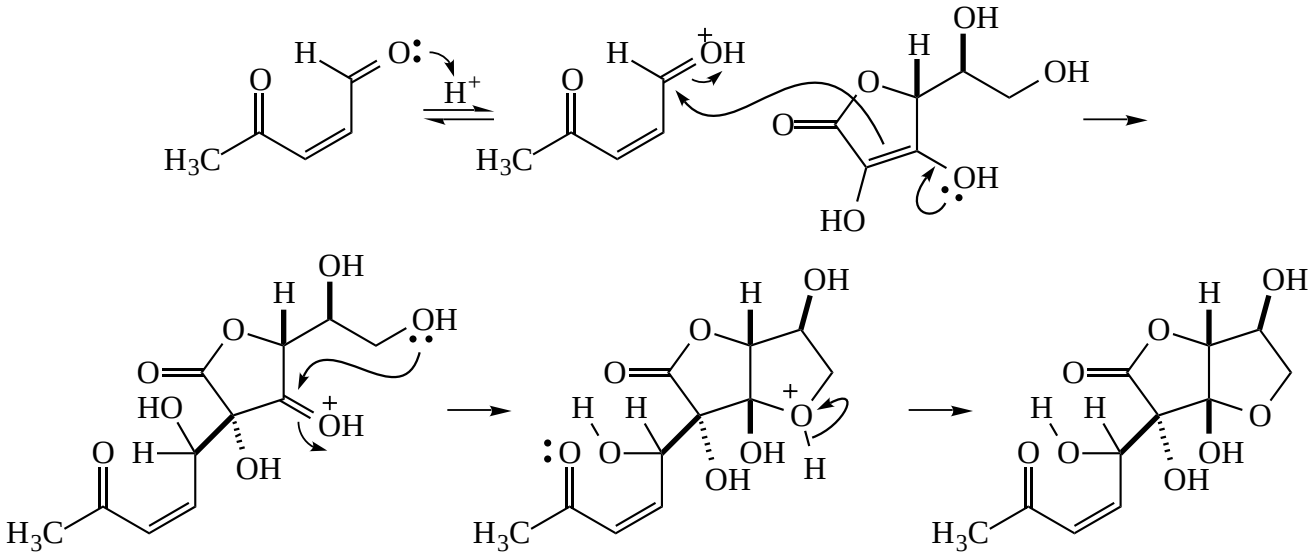




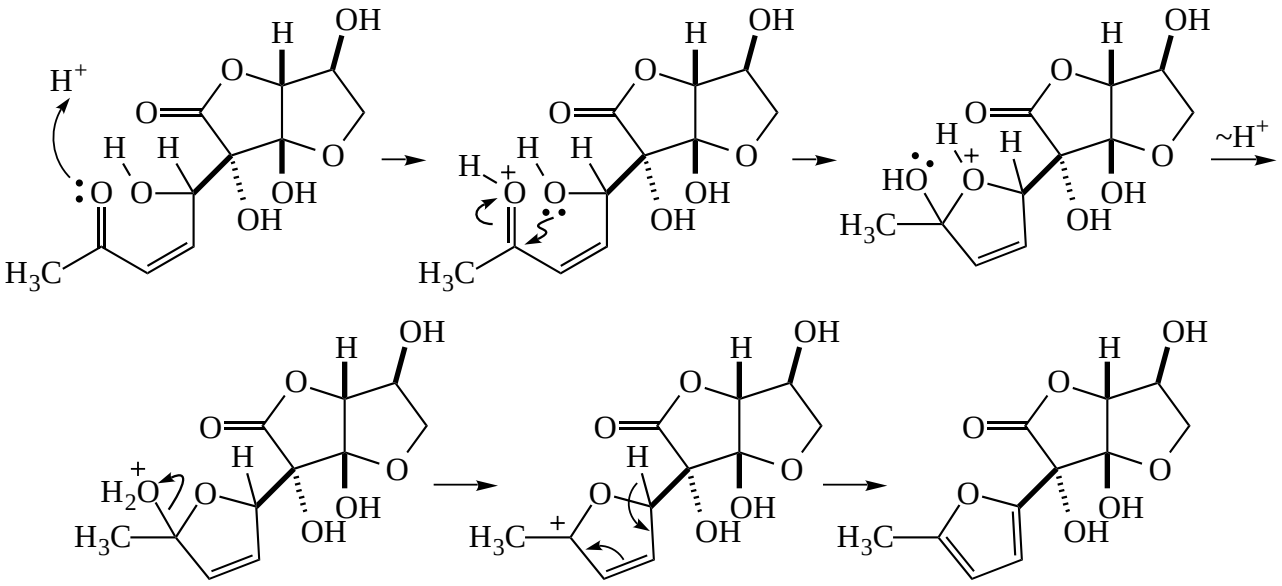
(i) Make: C2–C11, C3–O12, and either C8–O14 or C11–O13. Break: Either C8–O13 or C11–O14.



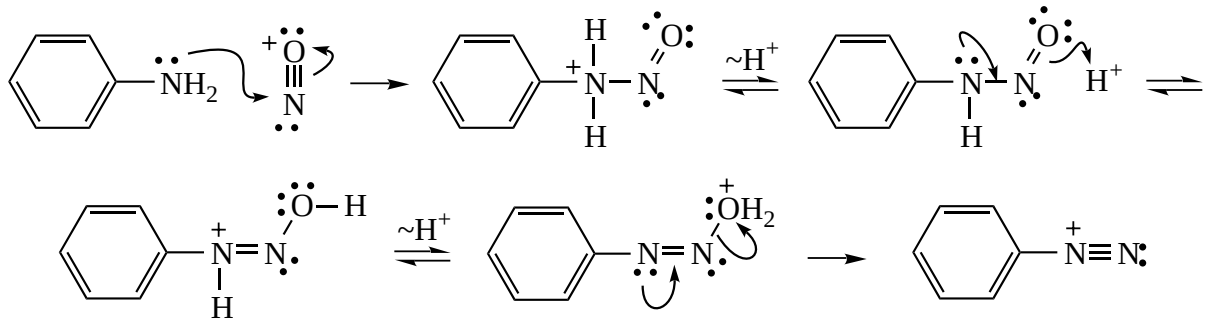
Both C2 and C3 are β to an OH group, and C3 is also β to a carbonyl. Thus C3 is subject to both pushing and pulling, but C2 is subject only to pushing. The first step then is likely attack of nucleophilic C2 on electrophilic C11. Then the C3 carbocation is trapped by O12.



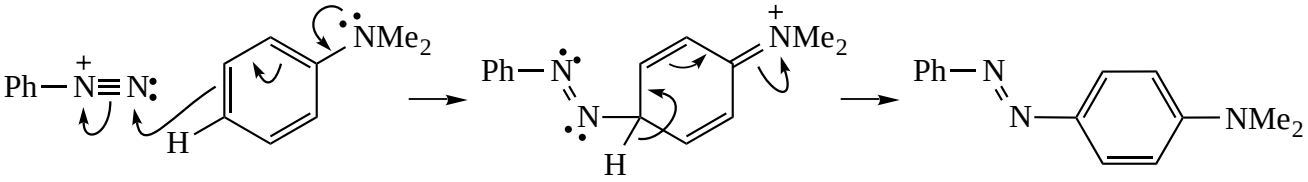
Now the furan ring is formed. Either O13 or O14 must be lost (certainly as H_2O). If O14 is lost, a carbocation at C11 would be required. This carbocation would be destabilized by the electron-withdrawing carbonyl at C18. Better to protonate O14, have O14 attack C8, and then lose O14 as H_2O.



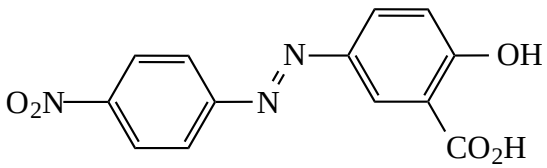
(j) Addition of $NaNO_2$ and HCl to an aniline always gives a diazonium salt by the mechanism discussed in the chapter (Section D.2).



Then the second arene undergoes electrophilic aromatic substitution, with the terminal N of the diazonium salt as the electrophilic atom. When nucleophilic arenes are added to diazonium salts, electrophilic aromatic substitution tends to take place instead of S_N1 substitution of the diazonium salt.

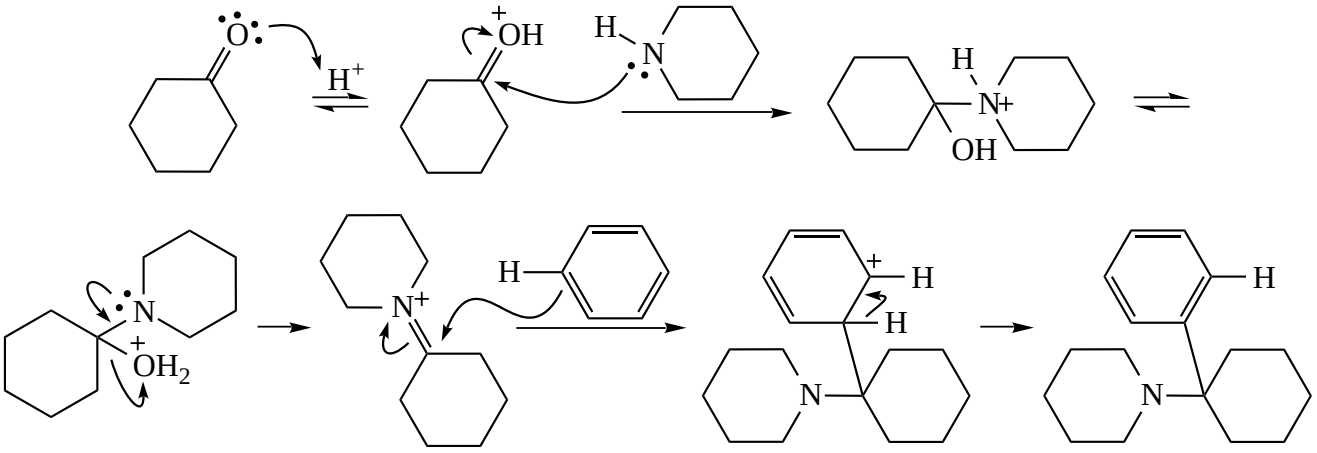


(k) Salicylic acid (as in acetylsalicyclic acid, or aspirin) is 2-hydroxybenzoic acid.

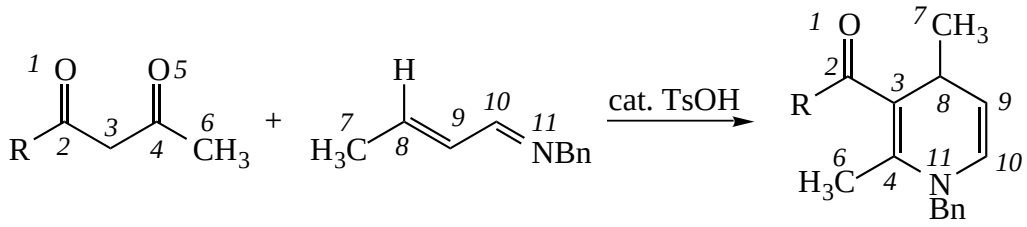


(l) Two new σ bonds are formed in this reaction. In principle either the N–C bond or the C–C bond could

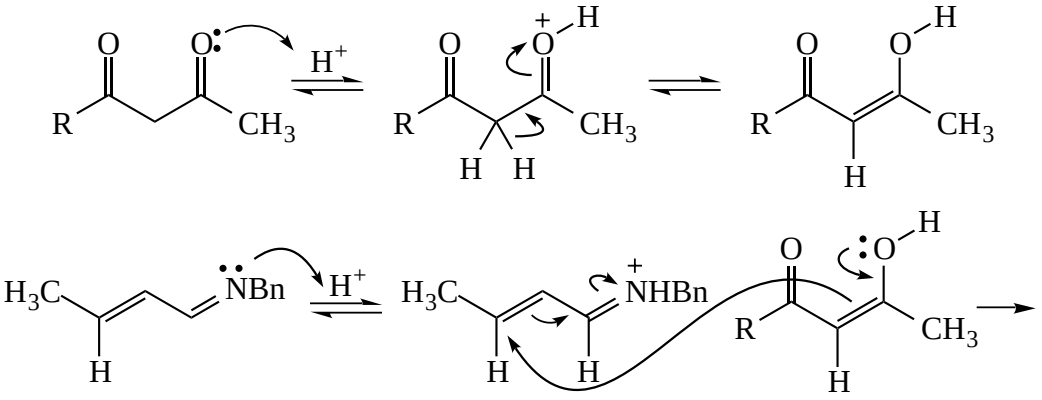
form first. Benzene does not generally react with ketones, while the reaction of an amine with a ketone is very rapid. Therefore the N–C bond forms, and iminium ion is generated, and then electrophilic aromatic substitution occurs to give PCP.

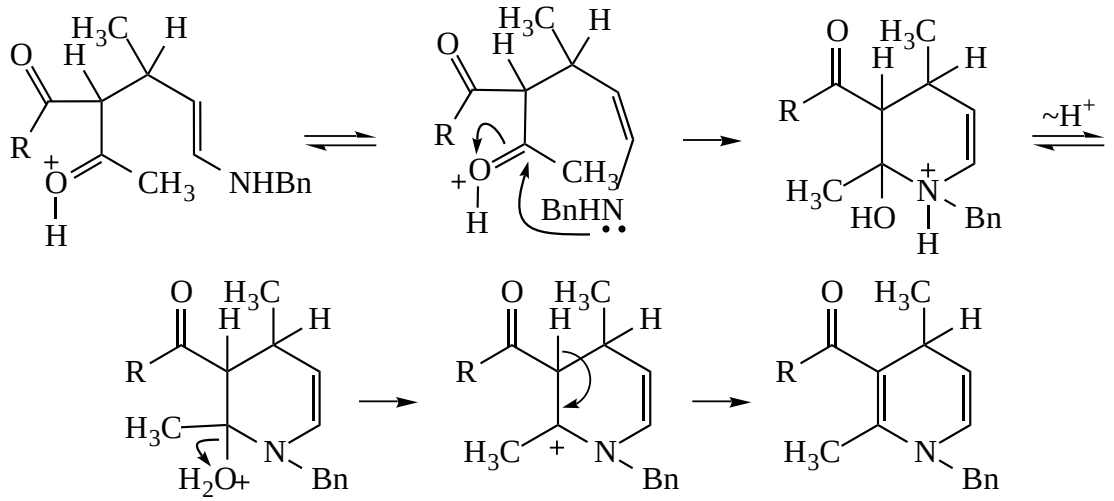


(m) Make: C3–C8, C4–N11. Break: C4–O5.

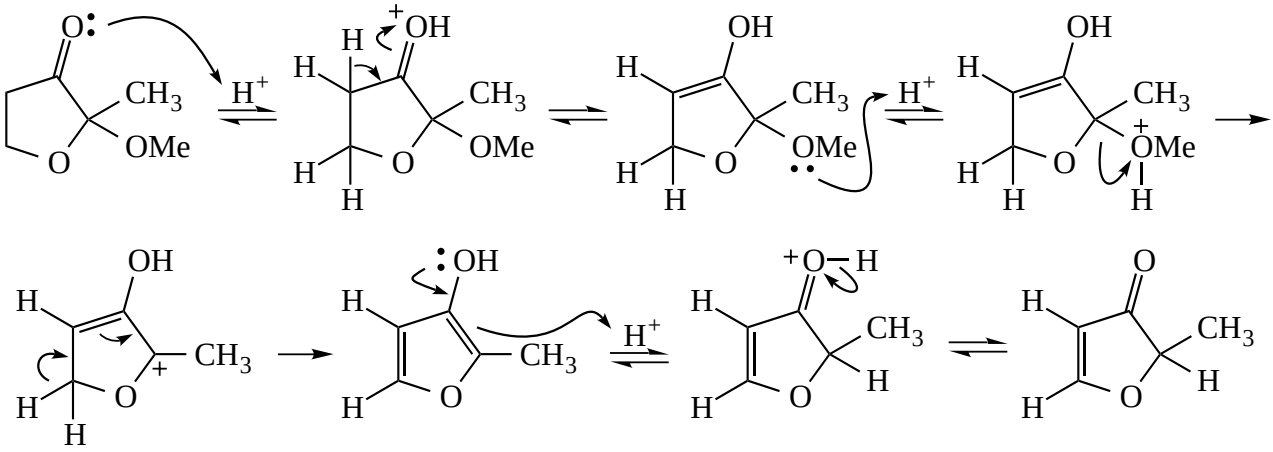


C3 and N11 are nucleophilic, C4 and C8 are electrophilic. Which bond forms first? Once the N11–C4 bond forms, C3 is made much less nucleophilic. So form the C3–C8 bond first (Michael reaction). C3 is made nucleophilic by tautomerization to the enol. The Michael reaction must be preceded by protonation of N11 to make C8 electrophilic enough. After the Michael reaction, the enamine is formed by the mechanism discussed in the text.

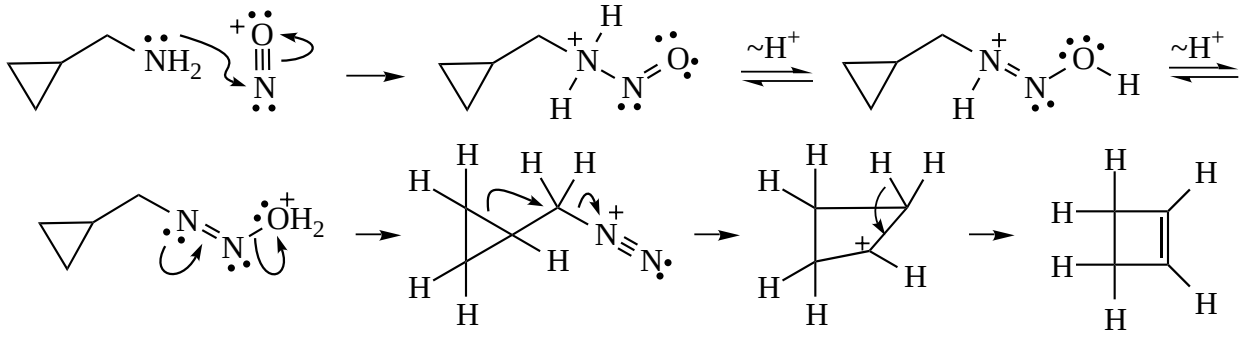




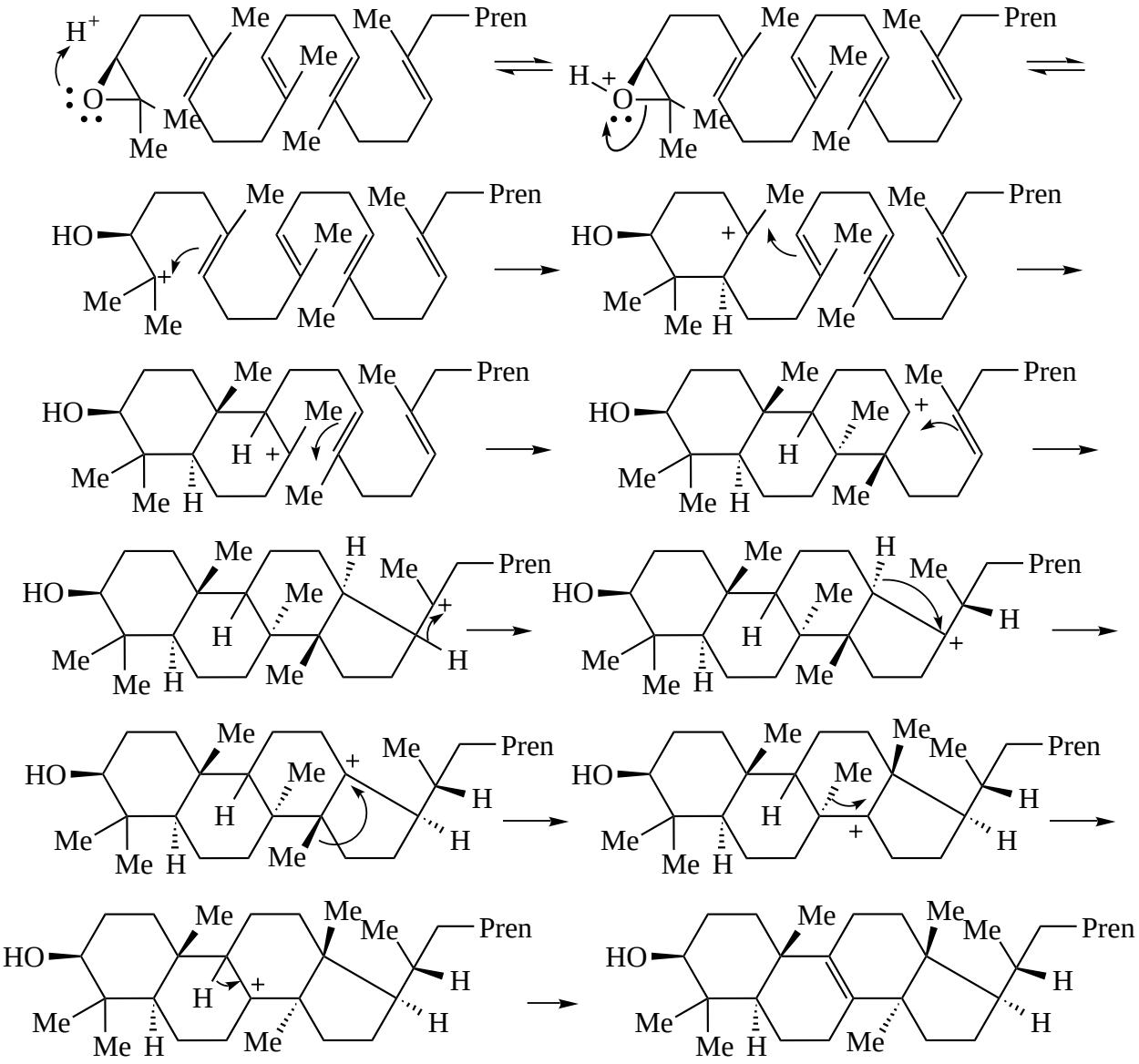
(n) The elements of MeOH are eliminated. However, since there are no H's β to the OMe group, the mechanism must be slightly more complicated than a simple E1. The key is to realize that formation of a carbocation at the acetal C is unlikely to occur with the keto group present. Under acidic conditions, the keto group is in equilibrium with the enol, from which a vinylogous E1 elimination can occur.



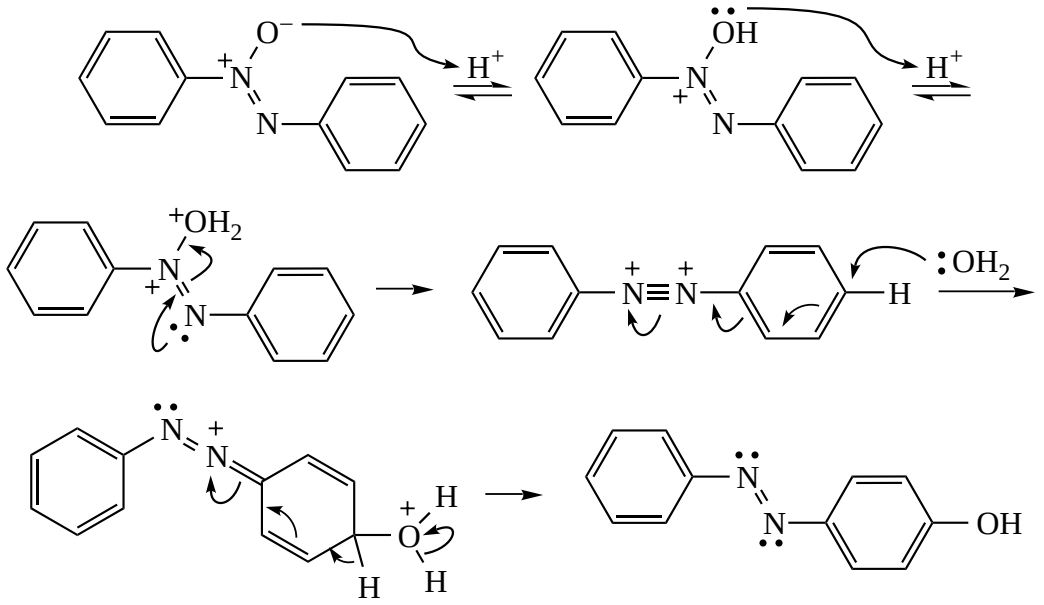
(o) Nitrous acid converts primary amines into diazonium salts RN_2^+. The N_2 group is an excellent leaving group. Formation of the carbocation followd by 1,2-alkyl migration gives a more stable carbocation, which loses H^+ to give cyclobutene. Alternatively, α-elimination could occur from the diazonium ion to give a carbene, which would undergo the 1,2-hydride shift to give the alkene.



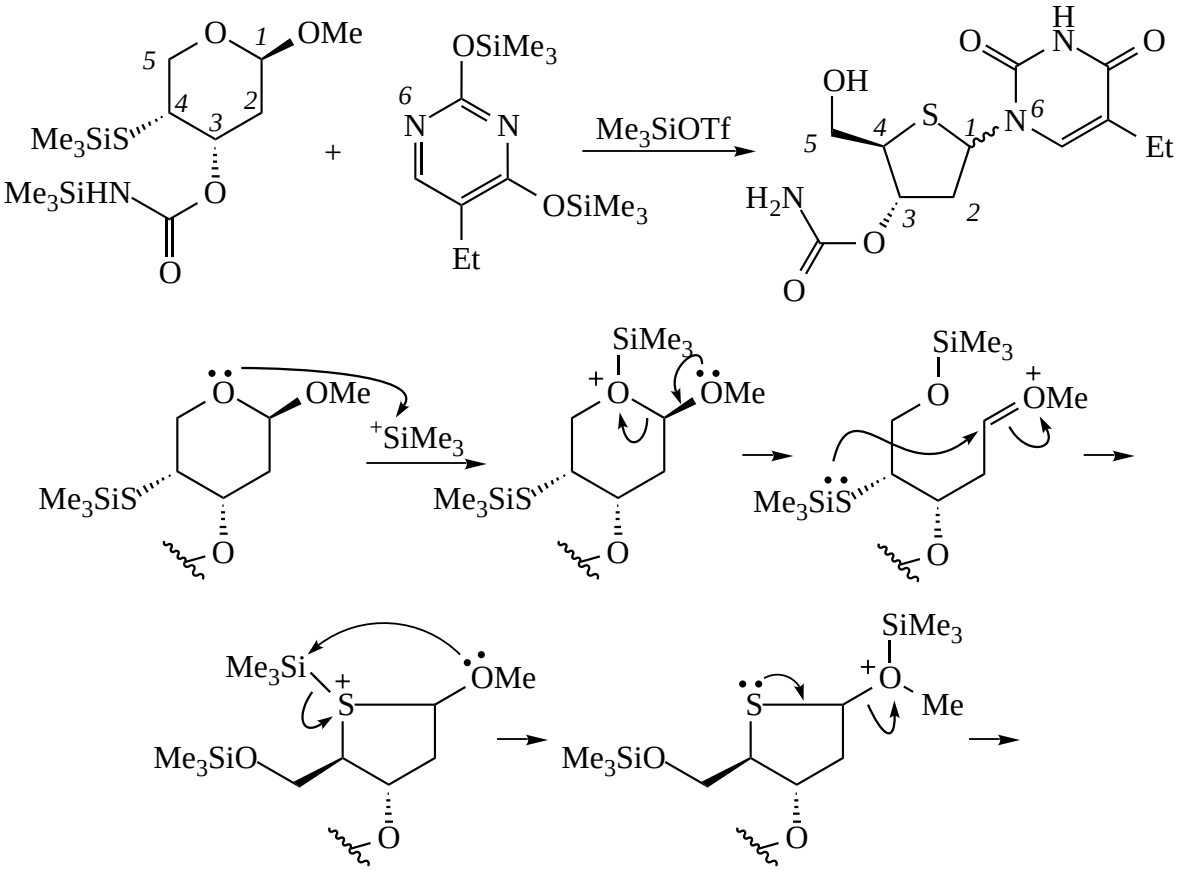
(p) The most basic site is the epoxide O. Protonation followed by a very facile ring opening gives a 3° carbocation. A series of additions of alkenes to carbocations follows, then a series of 1,2-shifts. The additions and 1,2-shifts have been written as if they occur stepwise, but some or all of them might be concerted. In principle, any of the carbocationic intermediates could undergo many other reactions; the role of the enzyme is to steer the reaction along the desired mechanistic pathway.

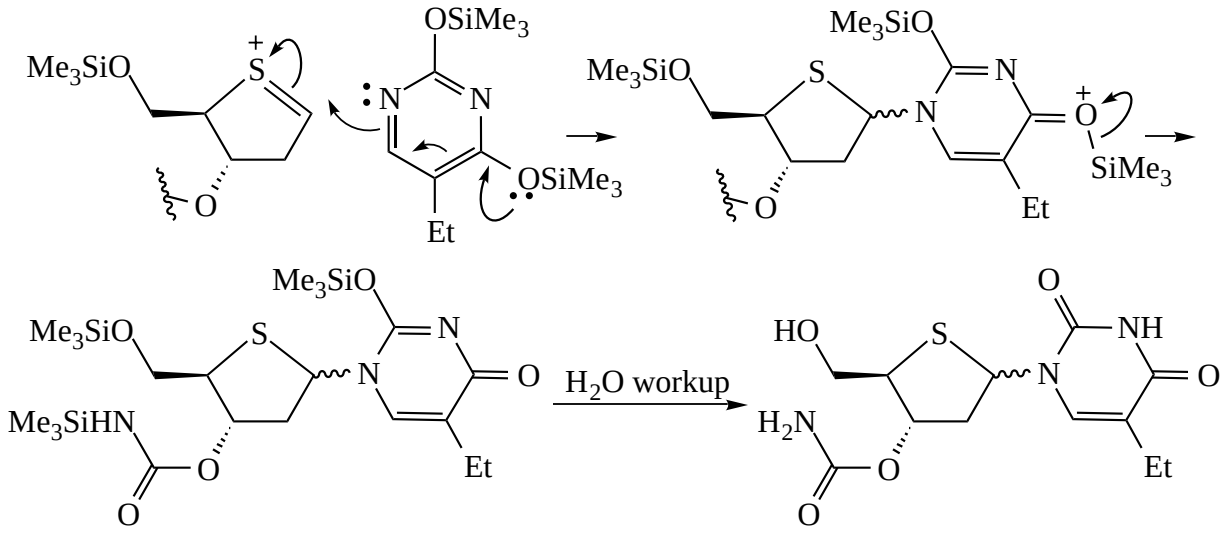


(q) The scrambling of the ^{15}N label suggests a symmetrical intermediate in which the two N's are equivalent. Incorporation of ^{18}O from H_2O suggests that a nucleophilic aromatic substitution is occurring. Double protonation of O followed by loss of H_2O gives a very electrophilic, symmetrical dicationic intermediate. Water can attack the *para* carbon; deprotonation then gives the product.

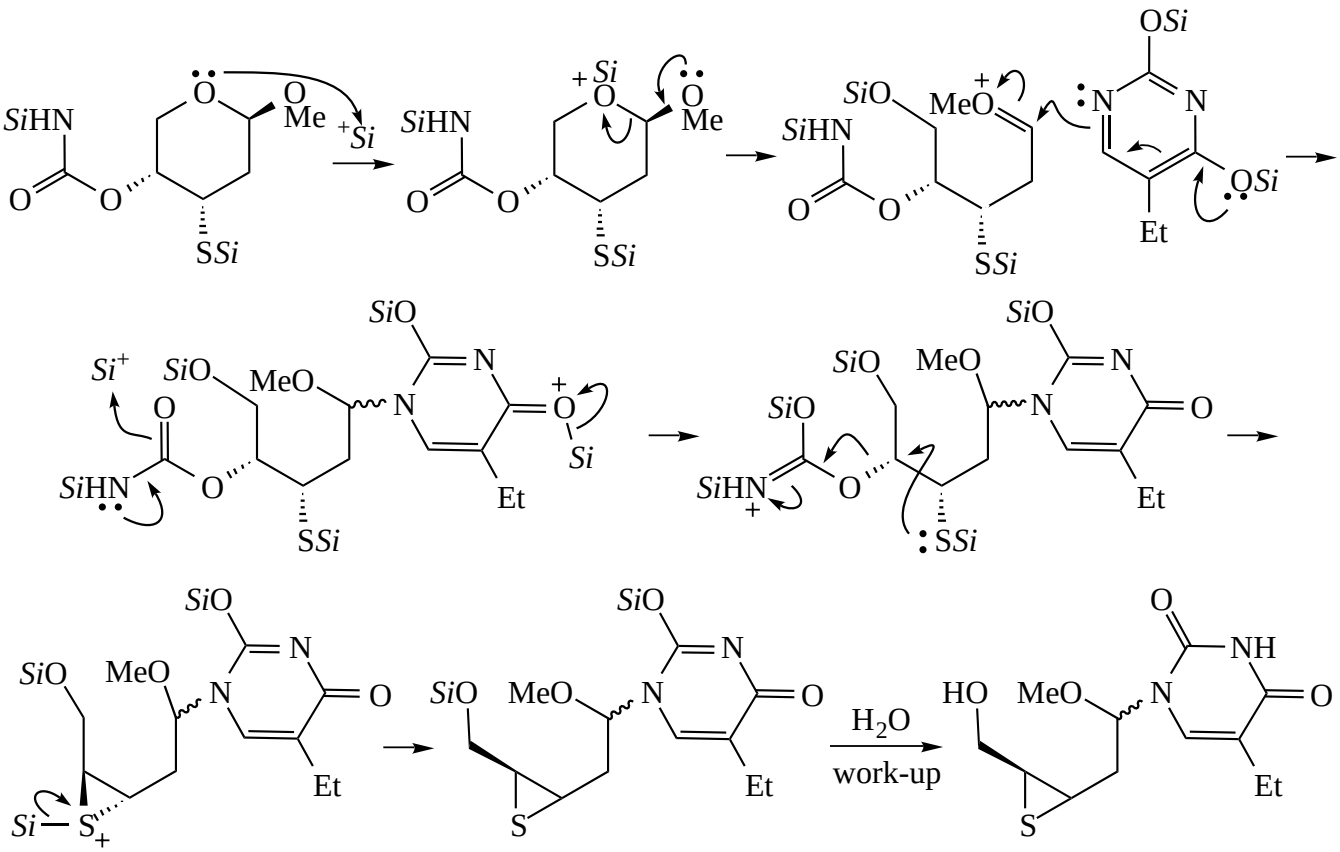


(r) (1) The two C1–O bonds undergo substitution with C1–S and C1–N6 bonds. Under these Lewis acidic conditions, and at this secondary and O-substituted center, the substitutions are likely to proceed by an S_N1 mechanism. The order of the two substitutions is not clear.

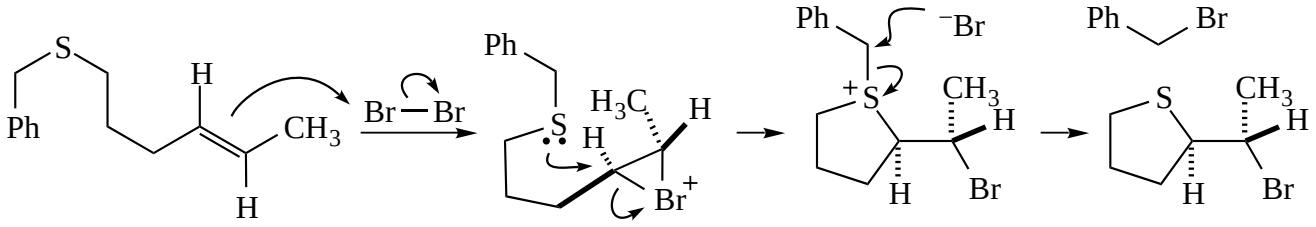




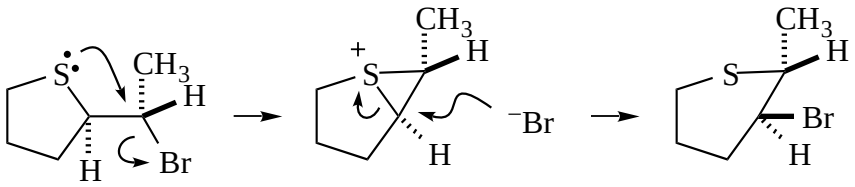
(2) Now only the endocyclic C1–O bond undergoes substitution, but the C4–O bond undergoes substitution with a C–S bond. In the previous problem we had S attack the C1 carbocation to give a five-membered ring. In the present problem, this would result in the formation of a four-membered ring, so the external nucleophile attacks C1 directly. We still need to form the C4–S bond. As it stands, C4 is not terribly electrophilic, but silylation of the urethane carbonyl O makes C4 more electrophilic. Then attack of S on C4 followed by desilylation gives the product. *Si* = $SiMe_3$.



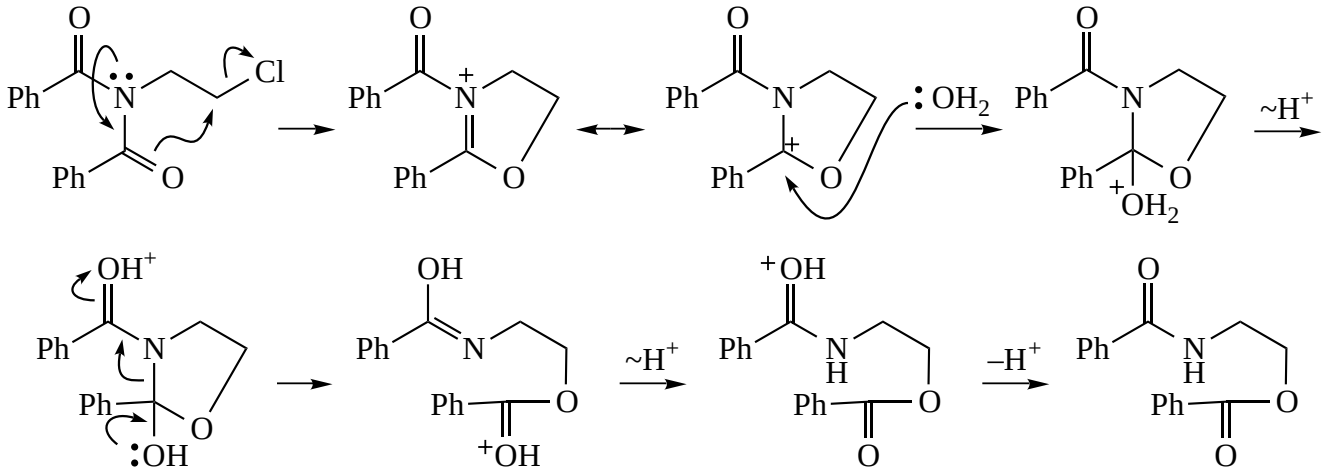
(s) Five-membered ring formation proceeds through a bromonium ion intermediate.



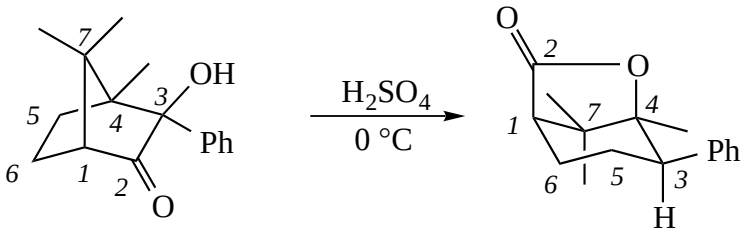
The five-membered ring can convert to the six-membered ring by two S_N2 displacements.



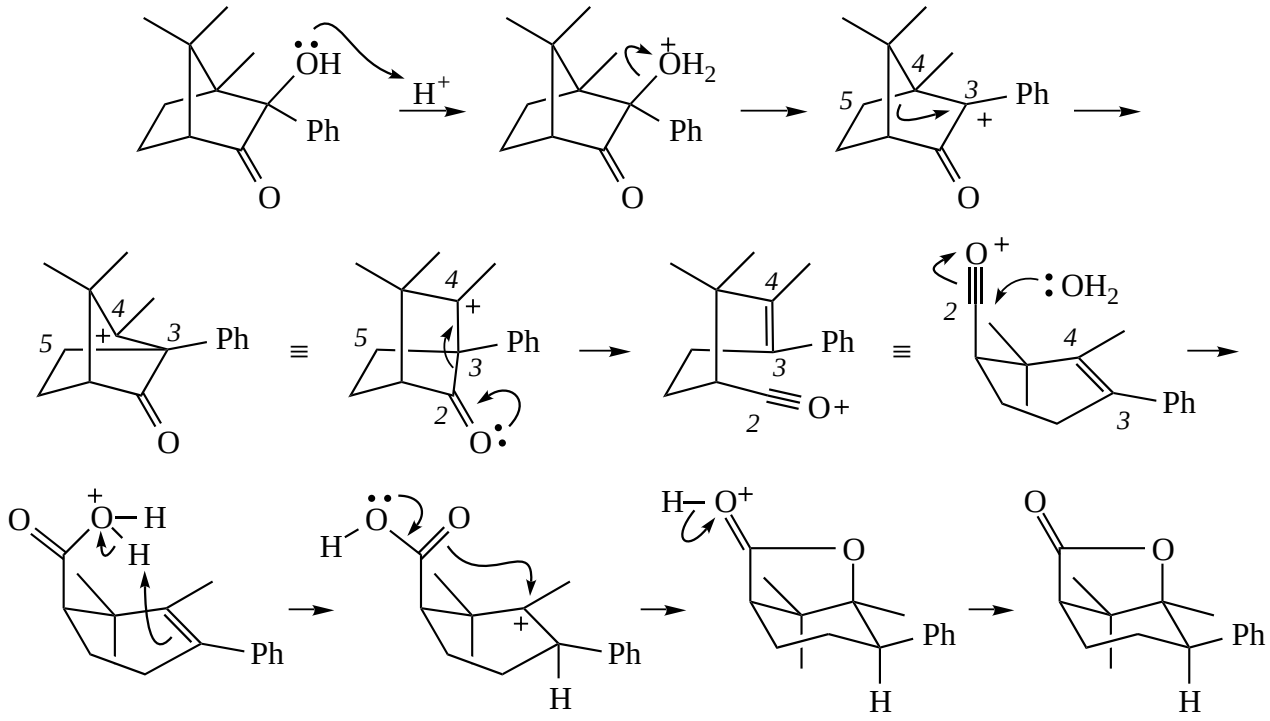
(t) The dependence of the rate of the reaction on the length of the alkyl chain suggests that an *intramolecular* reaction occurs between the nucleophilic O and the electrophilic C attached to Cl.



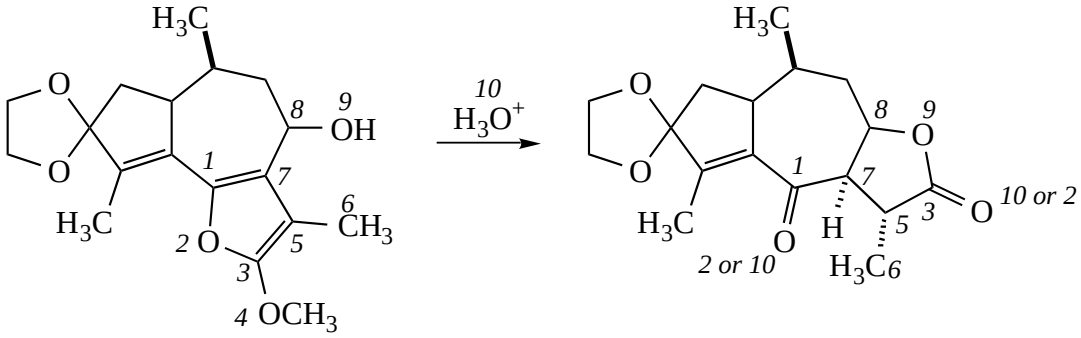
(u) The key atoms to recognize for numbering purposes are C7, C4, and C3. Then the others fall into place. Break: C2–C3, C4–C5. Make: C3–C5.



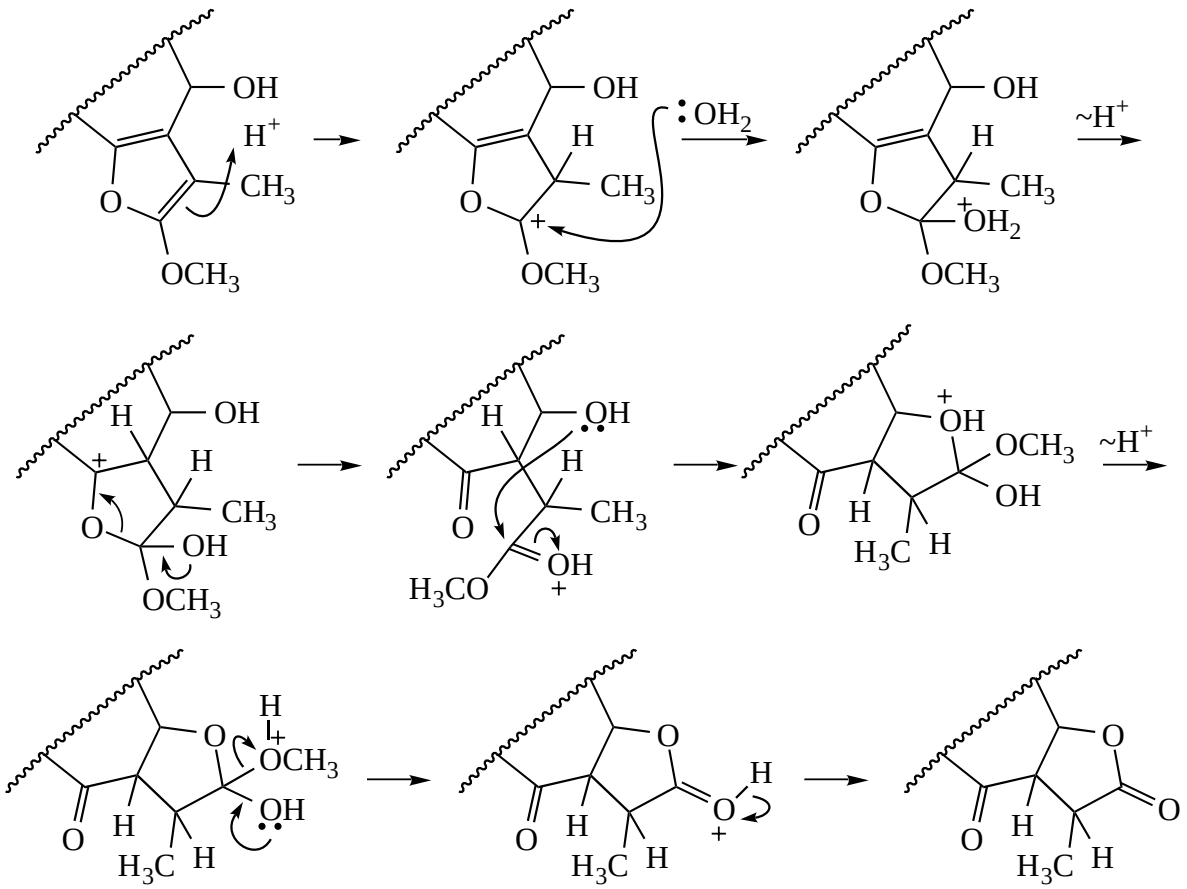
The cleavage of C5–C4 and formation of C5–C3 suggests that we have a 1,2-alkyl migration of C5 from C4 to a cationic C3. Then the electrons in the C2–C3 bond can move to form a new π bond between C3 and C4, leaving a stabilized acylium ion at C2. After addition of H_2O to the acylium ion, an acid-catalyzed electrophilic addition of the resultant carboxylic acid to the alkene occurs to give the final product.



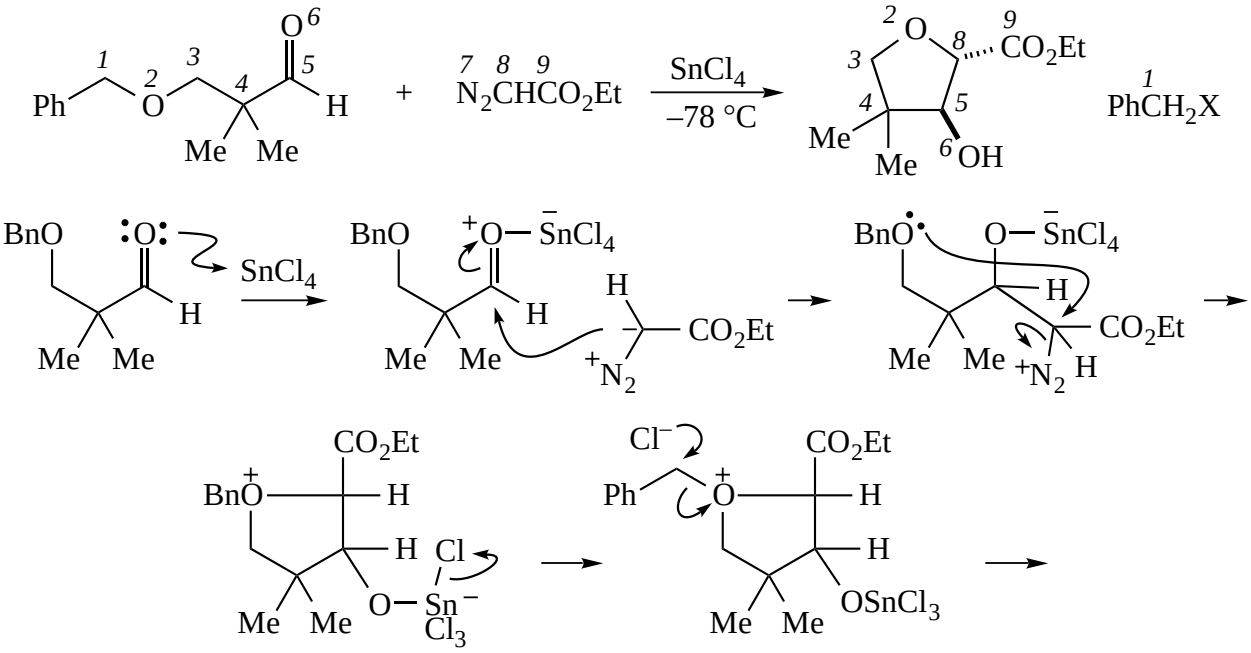
(v) The OCH_3 group is lost, and an OH group is gained. Whereas in the starting material C1 and C3 are attached to the same O, in the product they are attached to different O's. It is not clear whether O2 remains attached to C1 or C3. Make: O9–C3, O10–C3; break: C3–O4, C3–O2. *OR* make: O9–C3, O10–C1; break: C3–O4, C1–O2.

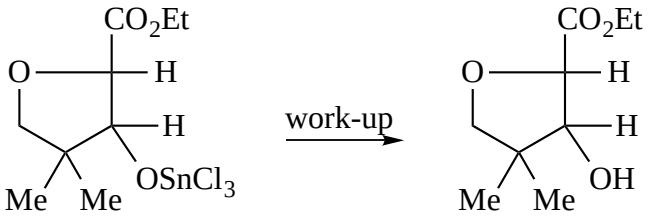


The first step is protonation; since all of the C–O bonds to be broken are C(sp^2)–O bonds, the direct ionization of a C–O bond won't occur, so protonating O is unproductive. Both C5 and C7 need to gain a bond to H; protonation of C5 gives the better carbocation. Water can add to make the C3–O10 bond. The rest of the mechanism follows.

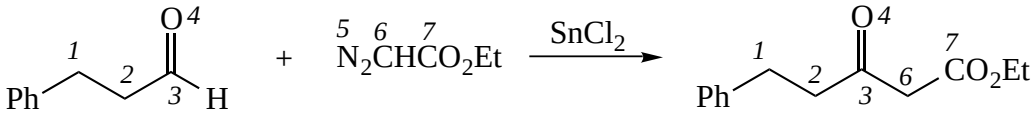


(w) Make: O2–C8, C5–C8. Break: C8–N, C1–O2. C8 is nucleophilic. $SnCl_4$ coordinates to O6 to make C5 more electrophilic, and C8 attacks C5. Then O2 circles around to displace N_2 from C8. Finally, Cl^- from $SnCl_4$ can come back and displace O2 from C1. The stereochemistry of the product is thermodynamically controlled.

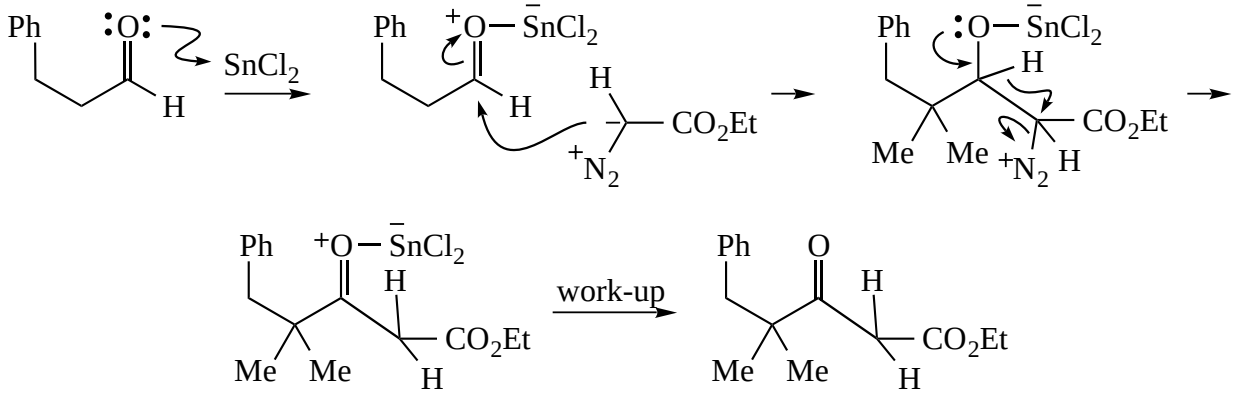




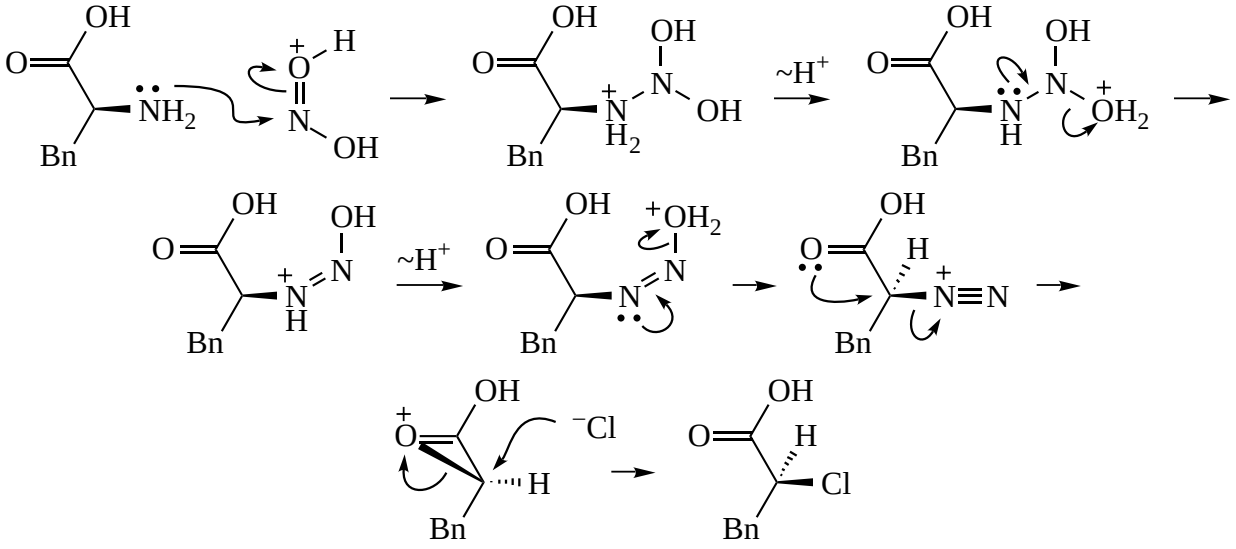
(x) Make: C3–C6. Break: C6–N5.



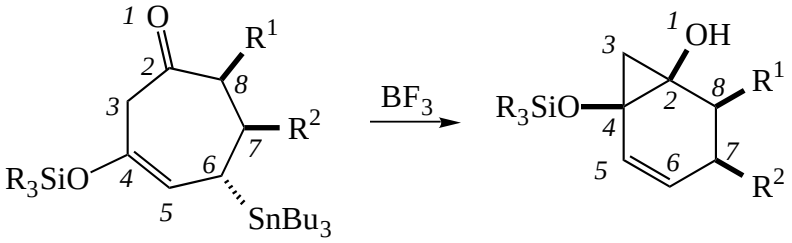
Reaction starts off the same way as last time. After addition to the carbonyl, though, a 1,2-hydride shift occurs with expulsion of N_2 to give the product after workup.



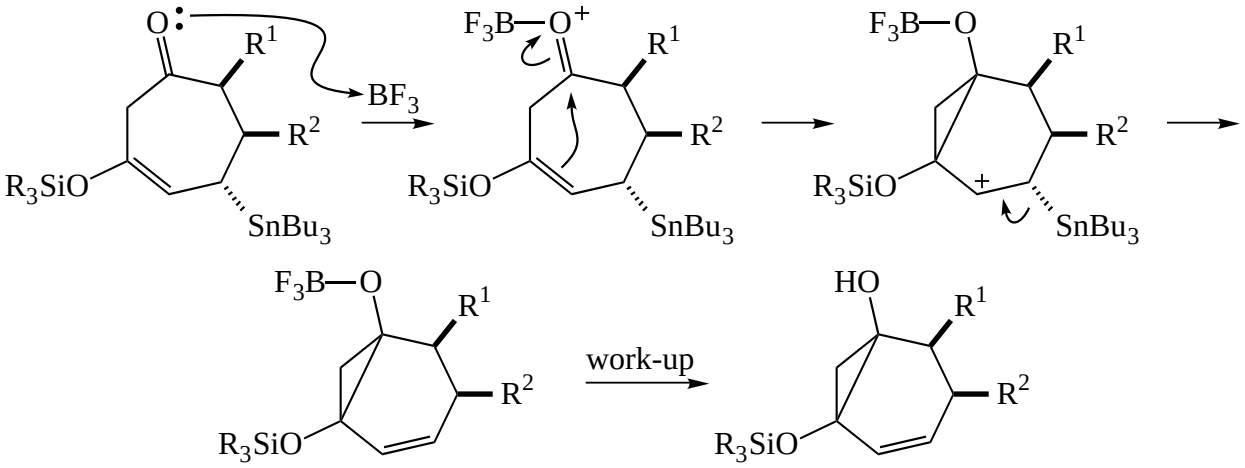
(y) The stereochemistry tells you that neither a simple S_N1 nor an S_N2 mechanism is operative. Two S_N2 substitutions would give the observed result, however. When 1° amines are mixed with HNO_2, a diazonium ion is formed. Intramolecular S_N2 substitution by the carbonyl O gives a lactone, and then a second S_N2 substitution by Cl^- gives the product.



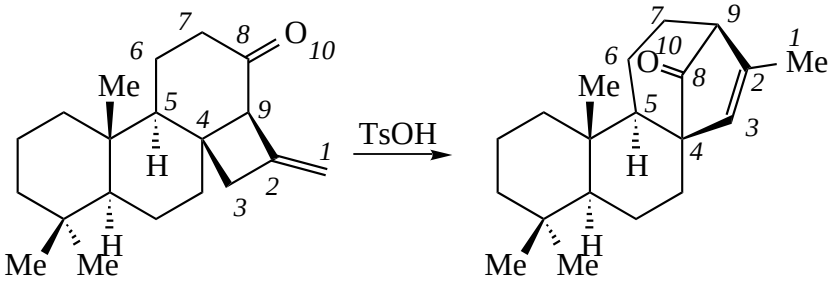
(z) Make: C2–C4. Break: C6–Sn.



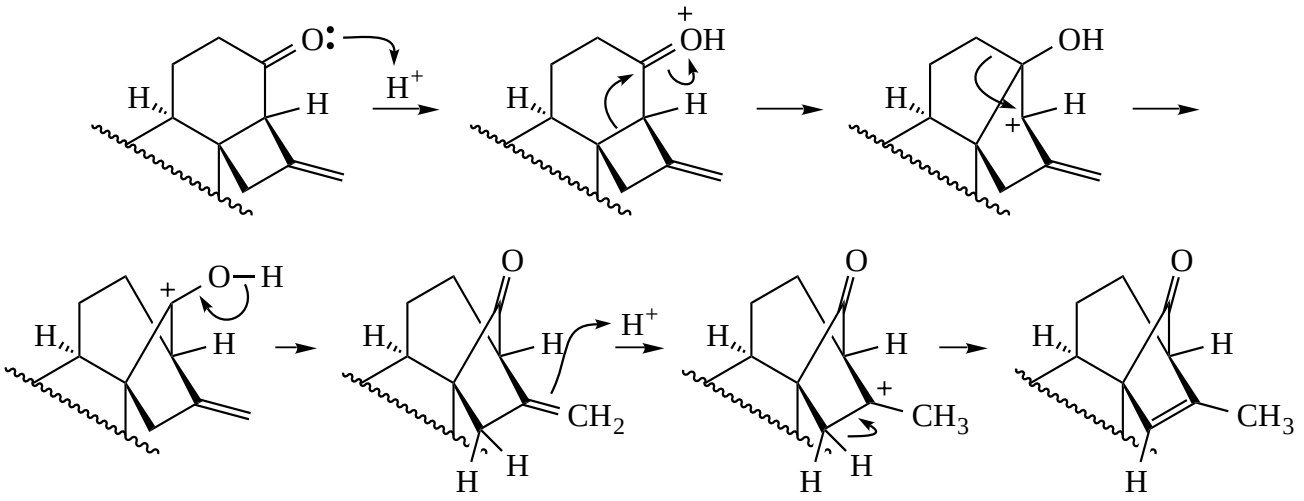
C2 is electrophilic, especially after BF_3 coordinates to it. C4 can then act as a nucleophile, making C5 carbocationic. Fragmentation of the C6–Sn bond gives the product.



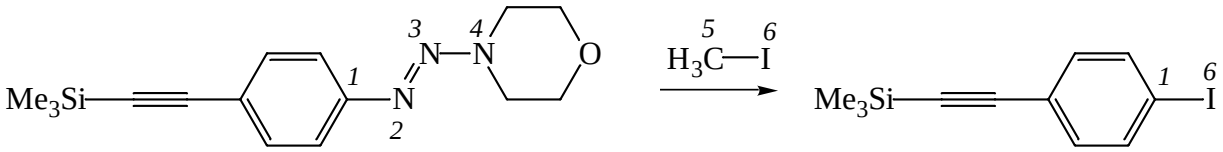
(aa) Numbering correctly is key. C4 through C7 are clear. The Me group in the product must be C1, and it's attached to C2. The rest follow. Make: C7–C9, C4–C8. Break: C7–C8, C4–C9.



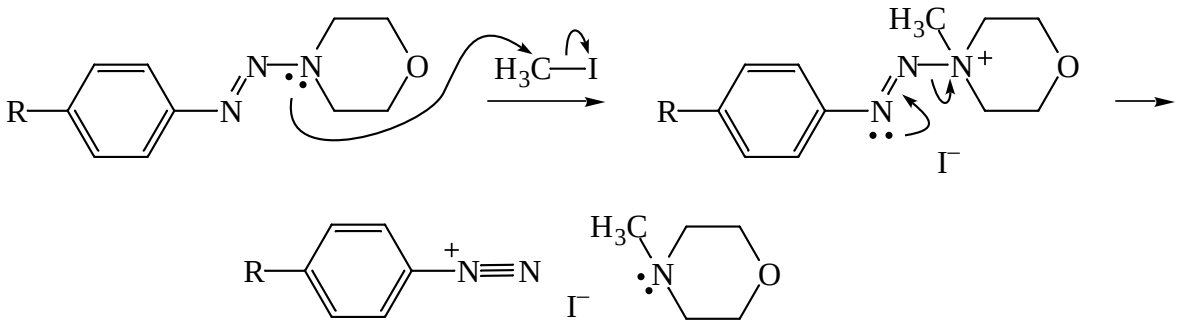
First step is protonation of O10 to make C8 electrophilic. Then a shift of C4 from C9 to C8 occurs to give a cation at C9. This is followed by a shift of C7 from C8 to C9. Deprotonation of O10, protonation of C1, and deprotonation of C3 give the product.



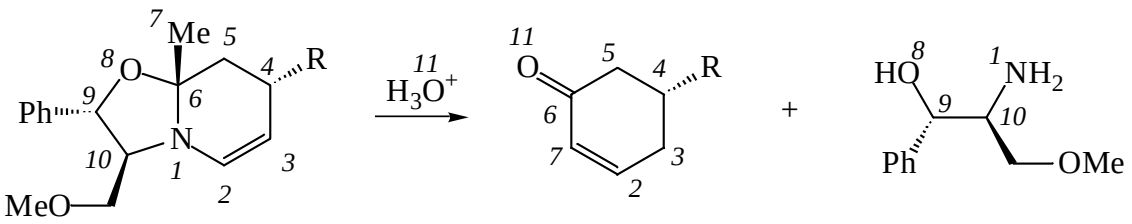
(bb) Make: C1–I6. Break: C1–N2, C5–I6.



Hold on! What happened to N2, N3, N4, and C5? One possibility is that the new product has an N2–C5 bond. But this doesn't seem too likely, because it seems that this compound would want to form N_2. If we assume N_2 is formed, then there must be a new N4–C5 bond. Make: C1–I6, N4–C5. Break: C1–N2, C5–I6. The first step is attack of N4 on C5, displacing I6. Cleavage of the N3–N4 bond then gives a diazonium ion, which undergoes $S_{RN}1$ substitution as in in-chapter problem 3.12.

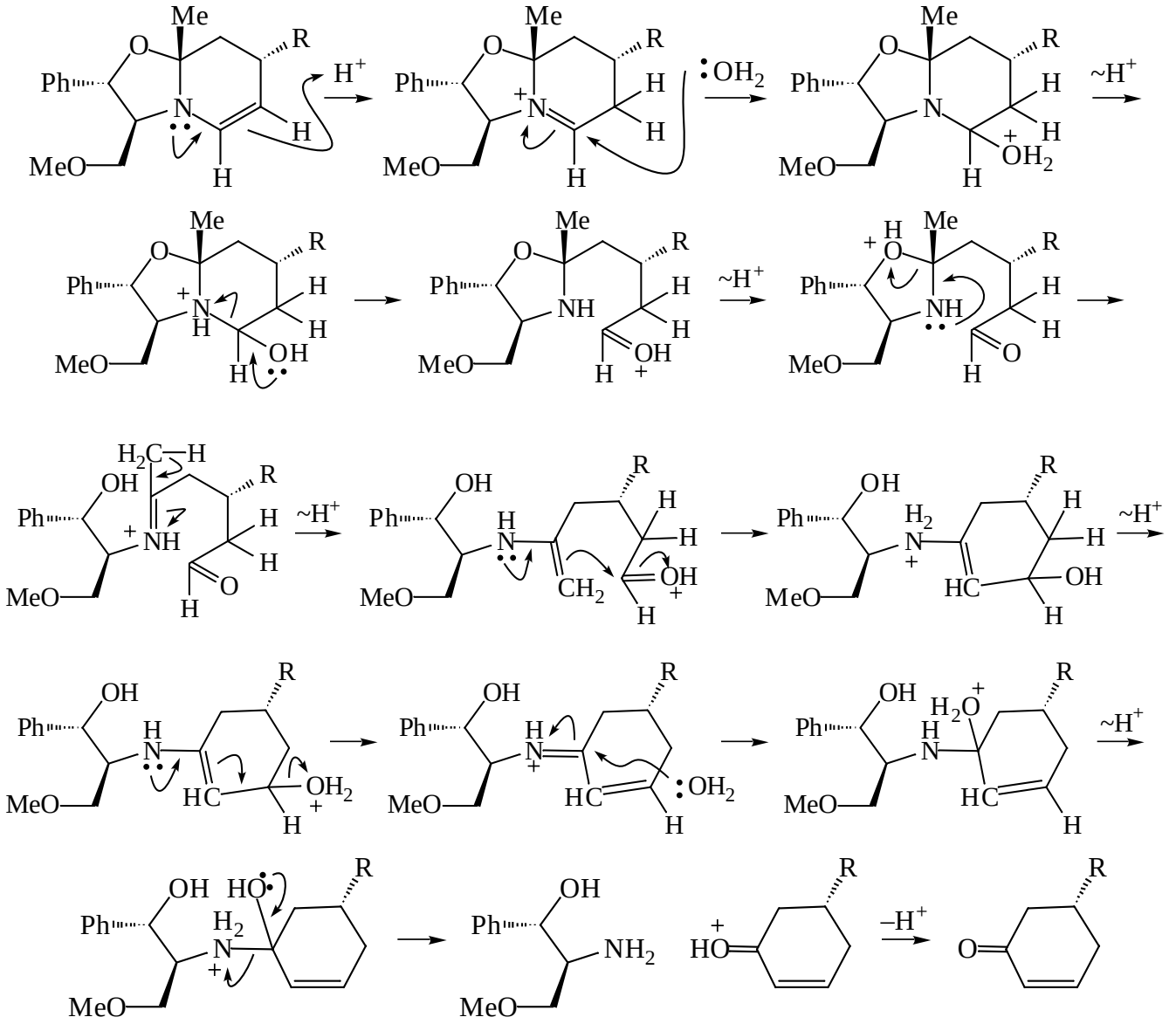


(cc) Make: C2–C7, C6–O11. Break: N1–C2, N1–C6, C6–O8.



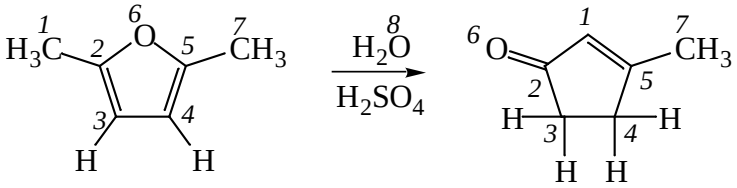
The first step must be protonation to form a nice stable carbocation. The first protonation can occur on C3

to give a C2 carbocation or on O8 so it can leave to form a C6 carbocation. Let's assume the former for now. Protonation on C3 gives a carbocation to which O11 can add. Proton transfer to N1 is followed by cleavage of the N1–C2 bond. Another proton transfer from O11 to O8 is followed by cleavage of the O8–C6 bond to give a C6 carbocation. At this point, we have the opportunity to turn C7 into a nucleophile by H^+ transfer from C7 to O11 to give an enamine. Attack of C7 on C2 is now followed by H^+ transfer from N1 to O11 and cleavage of the O11–C3 bond. Finally, O11 attacks C2, and H^+ transfer from O11 to N1 is followed by cleavage of the N1–C6 bond to give the products.

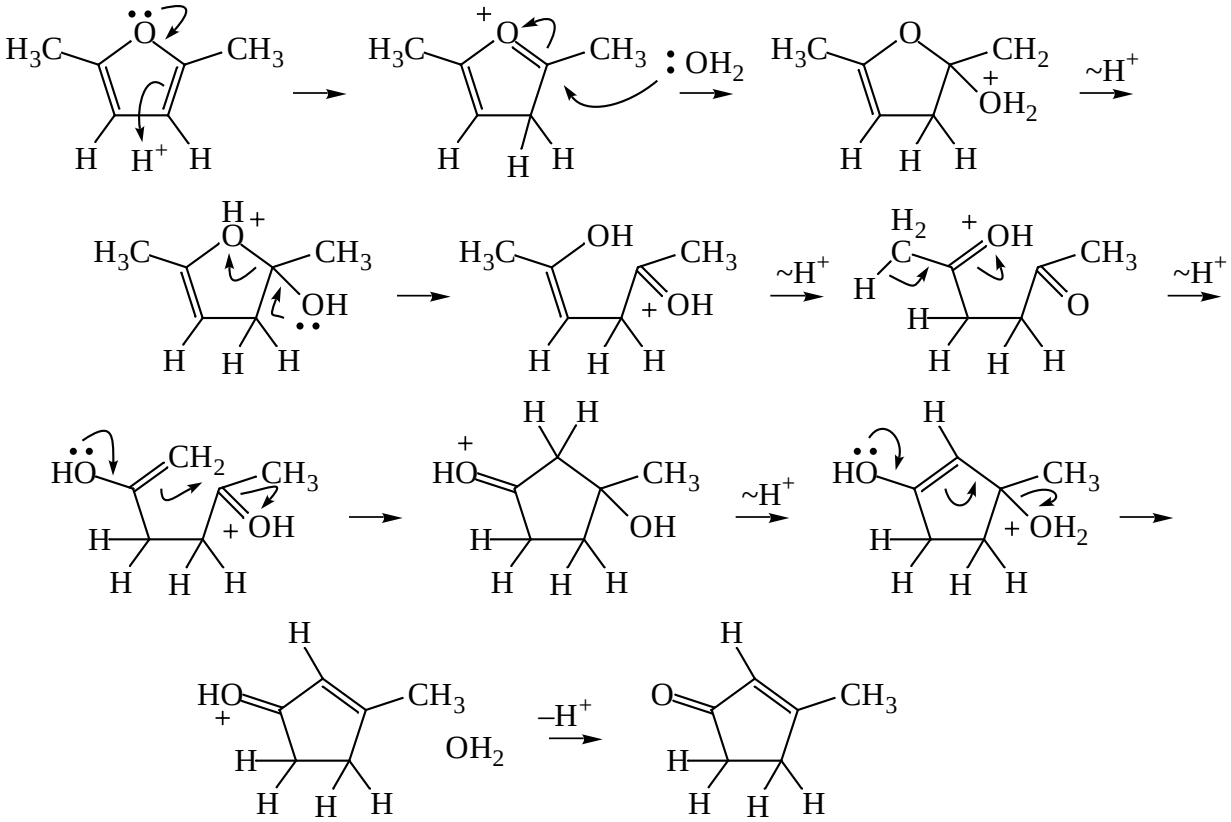


A similar mechanism can be drawn if O8 is protonated first (not shown). Cleavage of the O8–C6 bond gives a C6 carbocation to which O11 adds. After cleavage of the N1–C6 bond, H^+ transfer from C7 to C3 occurs to give an enol and an iminium ion. C7 then attacks C2, and elimination of the amine follows to give the products.

(dd) Make: C1–C5. Break: C5–O6.

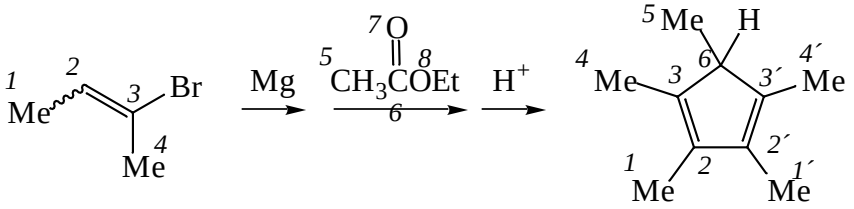


The first step is protonation. Because both C3 and C4 need to pick up protons, we protonate on C4. At this point, there's not much we can do except allow H_2O to add to the carbocation, even though this is not a bond that is in our list of bonds that need to be made; we will need to cleave it later. Addition of O8 to C5, H^+ transfer from O8 to O6, and cleavage of the C5–O6 bond follow. At this point we still need to make the C1–C5 bond. C5 is clearly electrophilic, so C1 needs to be made nucleophilic. Proton transfer from O8 to C3 and another H^+ transfer from C1 to O8 gives the C1 enol, which attacks the C5 carbocation. Another H^+ transfer from C1 to O8 is followed by cleavage of the O8–C5 bond, and loss of H^+ gives the product.

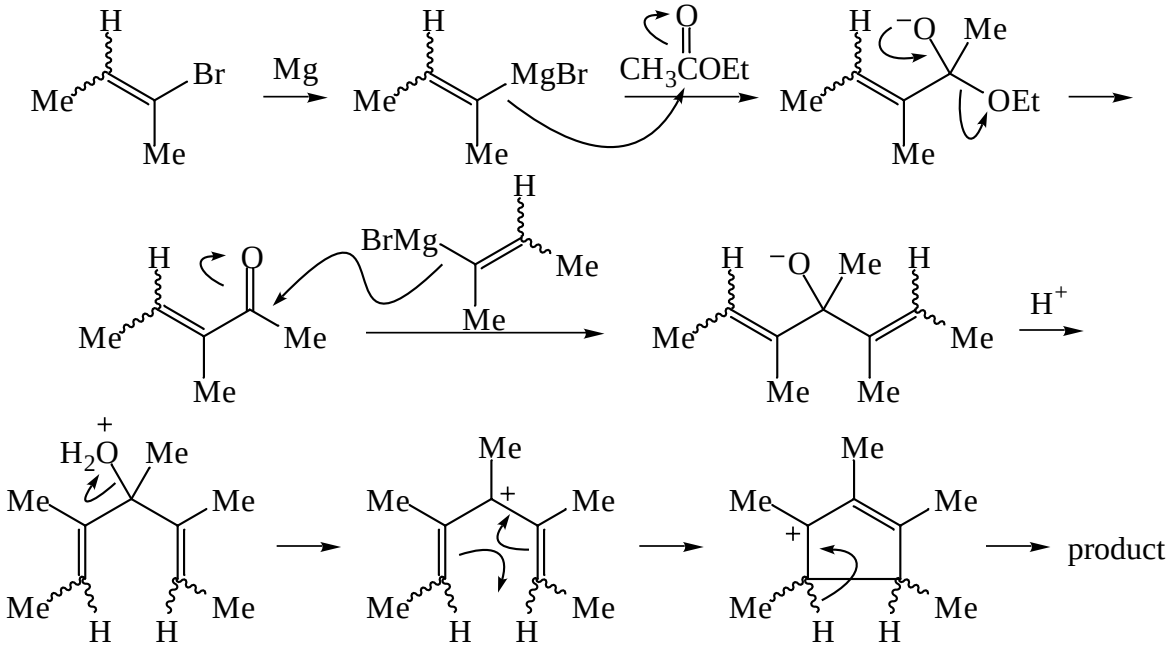


Answers To Chapter 4 In-Chapter Problems.

4.1. The numbering of the atoms is quite difficult in this problem. The number of Me groups in the product suggests that at least two equivalents of the bromide are incorporated into the product. But which ring atoms are C3 and which one is C6? And even if one of the ring carbons is arbitrarily chosen as C6, there is still the question of whether C3 or C2 becomes attached to C6. This problem is solved by noting that step 1 turns the bromide into a Grignard reagent, which is nucleophilic at C3, so it is likely to attack C6, and electrophilic atom. Make: C3–C6, C3´–C6, C2–C2´. Break: C6–O7, C6–O8, C3–Br, C3´–Br.

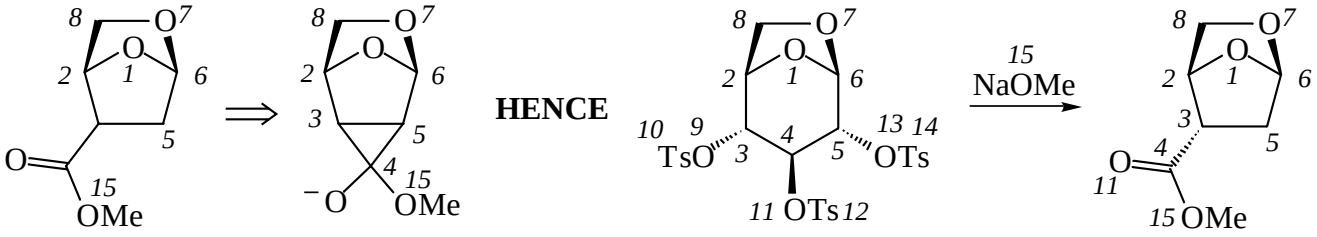


In the first step, the bromide is converted to a Grignard reagent. In the second step, two equivalents of the Grignard reagent react with the ester by addition–elimination–addition. (Remember, the ketone that is initially obtained from reaction of a Grignard reagent with an ester by addition–elimination is more electrophilic than the starting ester, so addition of a second Grignard reagent to the ketone to give an alcohol is faster than the original addition to give the ketone.) In the last step, addition of acid to the tertiary, doubly allylic alcohol gives a pentadienyl cation that undergoes electrocyclic ring closure. Loss of H^+ gives the observed product.



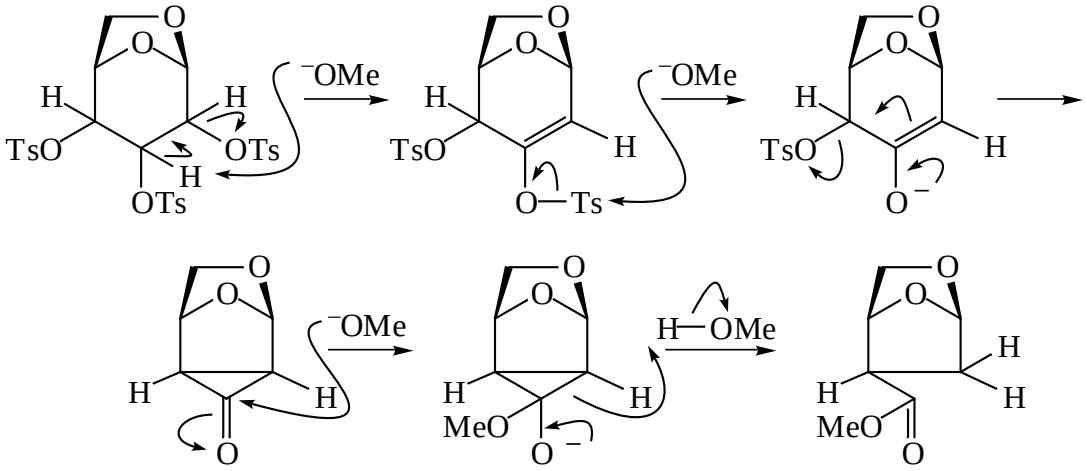
4.2. As usual, the key to this problem is numbering correctly. The main question is whether the ester C in the product is C3 or C4. Because a ring contraction from 6- to 5-membered is likely to proceed by a Favorskii rearrangement, where the last step is cleavage of a cyclopropanone, it makes sense to label the

ester C as C4. Make: C3–C5, C4–C15. Break: C3–O9, C4–C5, C5–O13, O11–Ts12.

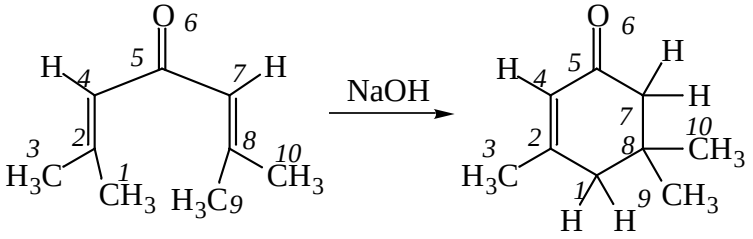


Hold on! If the O11–Ts12 bond is broken, and the electrons go to O (as seems reasonable), what happens to the Ts? Some nucleophile must form a bond to it. The only nucleophile in the mixture is MeO^-, so let's add Ts12–O15 to our make list.

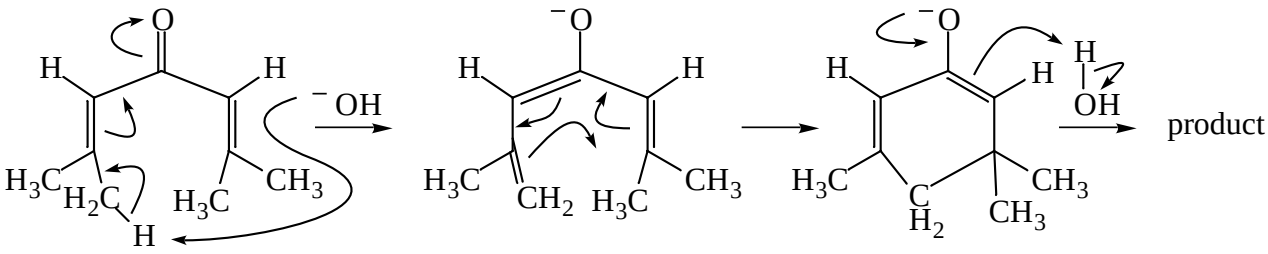
NaOMe is a good base, and with all these TsO groups, an E2 elimination reaction to break a C–OTs bond seems reasonable. Either the C3–O9 or the C5–O13 bond can be cleaved; we choose the C5–O13 bond here, but cleavage of the other bond works, too. The product is an enol tosylate. A second elimination reaction is not possible, but at this point we can form the Ts12–O15 bond and cleave the O11–Ts12 bond by having MeO^- attack Ts 12, displacing O11 to make an enolate. Electrocyclic ring closing with concurrent cleavage of the C3–O9 bond gives a cyclopropanone. Addition of O15 to C4 and then C4–C5 bond cleavage with concurrent protonation of C5 by solvent gives the product.



4.3. Make: C1–C8. Break: none.

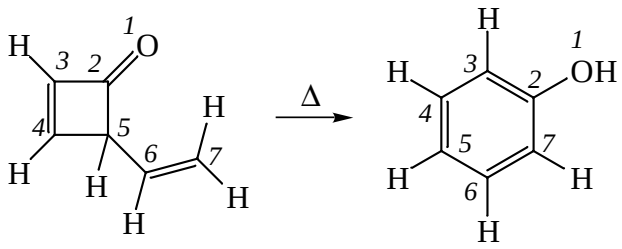


Deprotonation of C1 gives an enolate ion, which in this compound is actually a 1,3,5-hexatriene. As such it can undergo an electrocyclic ring closing. Protonation gives the product.

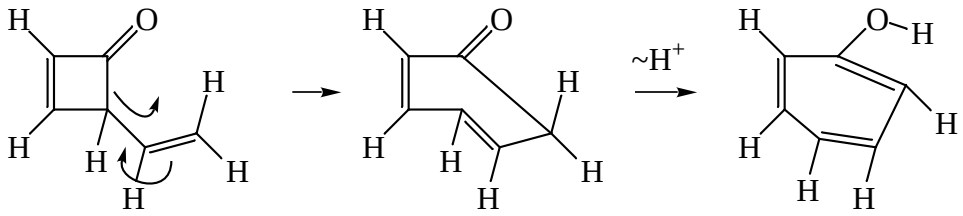


You may have been tempted to draw the C1–C8 bond-forming reaction as a conjugate addition. However, once C1 is deprotonated, the carbonyl group is no longer electrophilic, because it is busy stabilizing the enolate. It is much more proper to think of the bond-forming reaction as an electrocyclic ring closure. This problem illustrates why it is so important to consider *all* the resonance structures of any species.

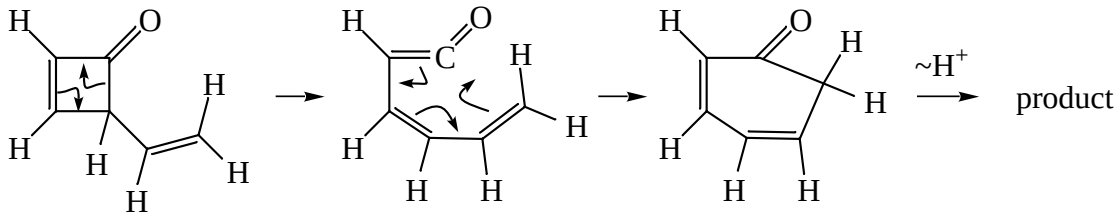
4.4. Make: C2–C7. Break: C2–C5.



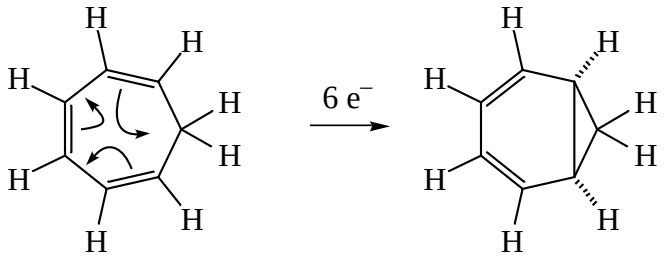
You may be very tempted to draw the following mechanism for the reaction:



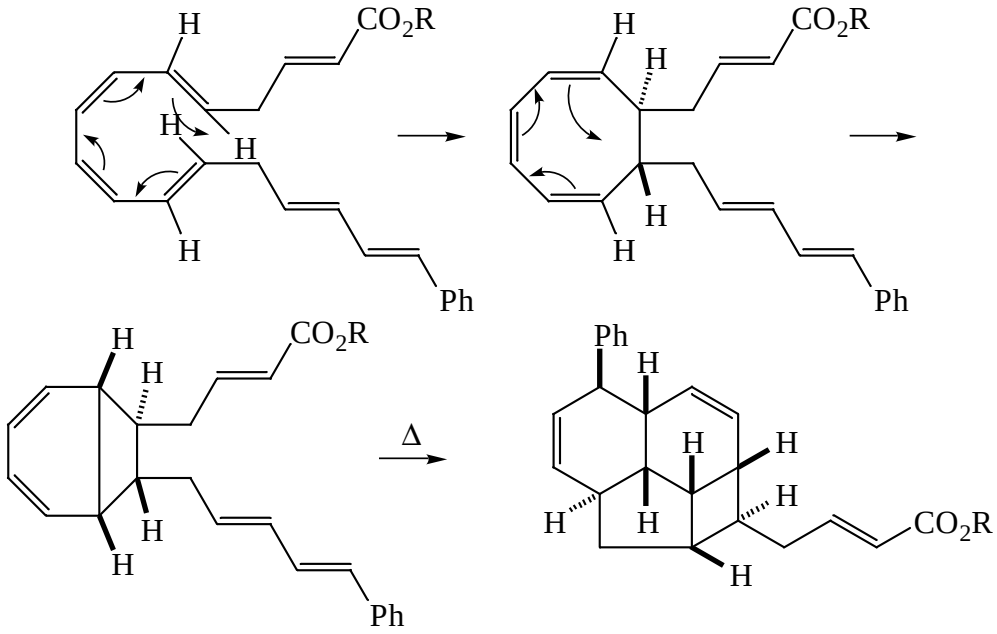
However, this mechanism is not correct. It is a [1,3]-sigmatropic rearrangement, and for reasons which are discussed in Section 4.4.2, [1,3]-sigmatropic rearrangements are very rare under thermal conditions. A much better mechanism can be written. The C2–C5 bond is part of a cyclobutene, and cyclobutenes open very readily under thermal conditions. After the electrocyclic ring opening, a 1,3,5-hexatriene is obtained, and these compounds readily undergo electrocyclic ring closure under thermal conditions. Tautomerization then affords the product.



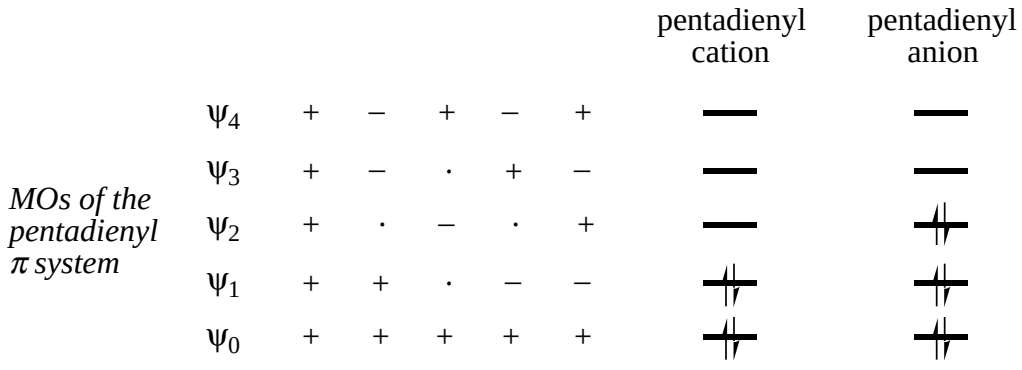
4.5. The product has a cis ring fusion.

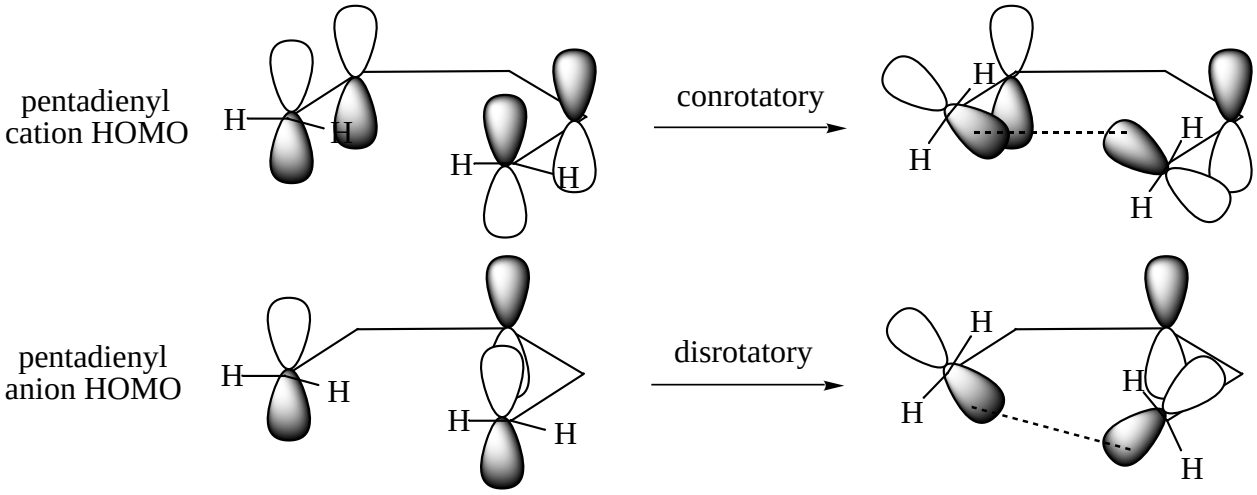


4.6. The first electrocyclic ring closure involves eight electrons, so it is conrotatory under thermal conditions, and the two hydrogen atoms at the terminus of the tetraene, which are both in, become trans. The second electrocyclic ring closure involves six electrons, so it is disrotatory under thermal conditions, and the two hydrogen atoms at the terminus of the triene, which are both out, become cis. This is the arrangement observed in the natural product.

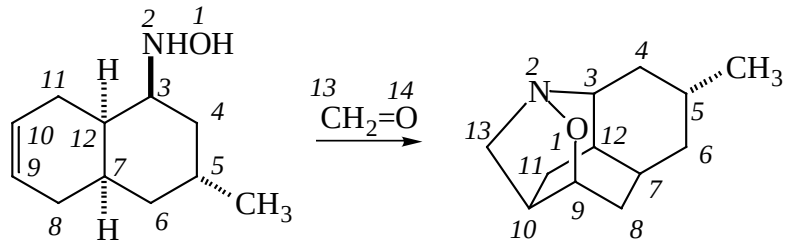


4.7. The HOMO of the pentadienyl cation is ψ_1, which is antisymmetric, so a conrotatory ring closure occurs, consistent with the four electrons involved in this reaction. The HOMO of the pentadienyl anion is ψ_2, which is symmetric, so a disrotatory ring closure occurs, consistent with the six electrons involved in this reaction.

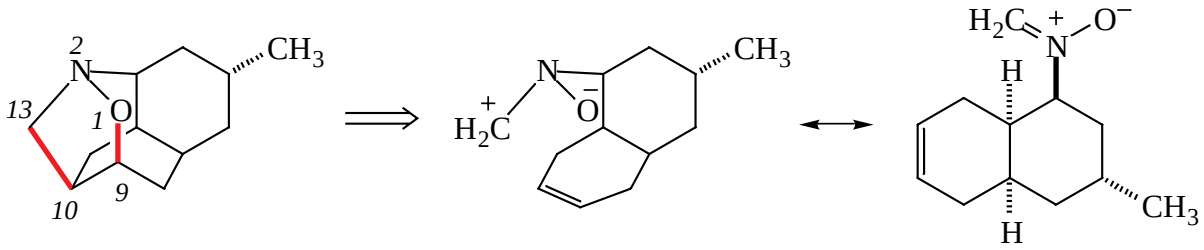




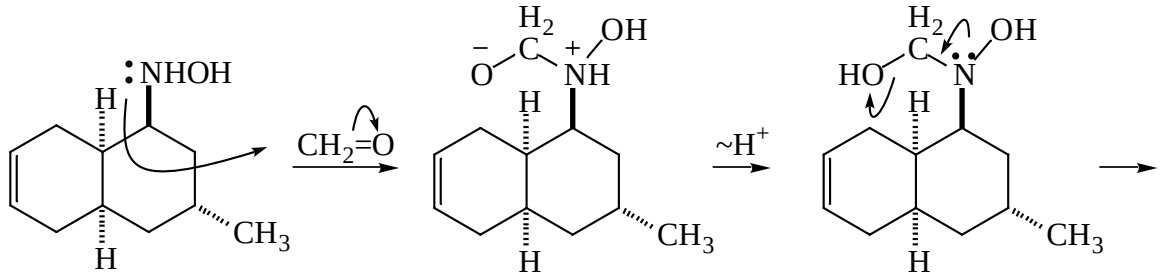
4.8. Make: O1–C9, N2–C13, C10–C13. Break: C13–O14.

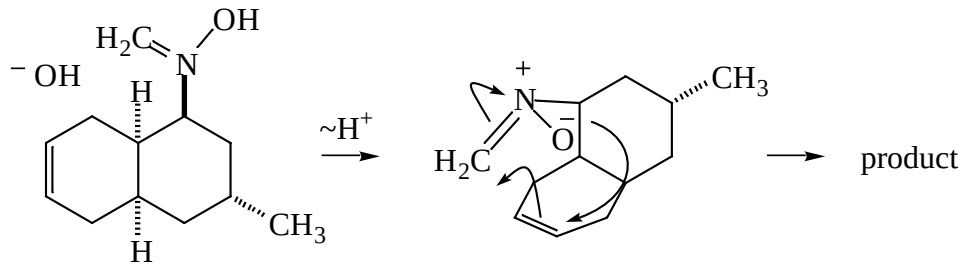


The new five-membered, heterocyclic ring clues you in to the fact that a 1,3-dipolar cycloaddition has occurred here to form bonds O1–C9 and C10–C13. Disconnect these bonds, putting a + charge on C13 and a – charge on O1, to see the immediate precursor to the product.

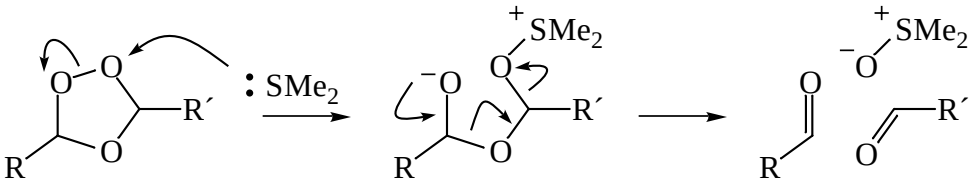


When this disconnection is written in the forward direction along with some curved arrows, it is the last step in the reaction. Now all you have to do is make N2–C13 and break C13–O14. This is easy to do: N2 attacks C13, proton transfer occurs, N2 expels O14, and deprotonation gives the nitrone.

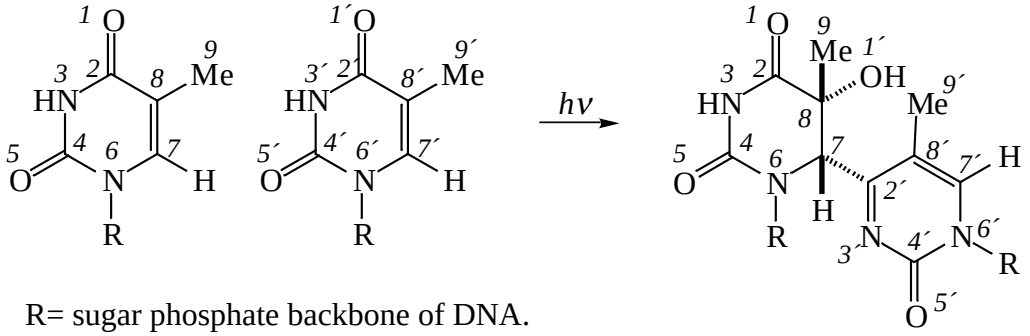




4.9. Me_2S attacks one of the O atoms involved in the O–O bond, displacing O^-. Hemiacetal collapse to the carbonyl compounds then occurs.

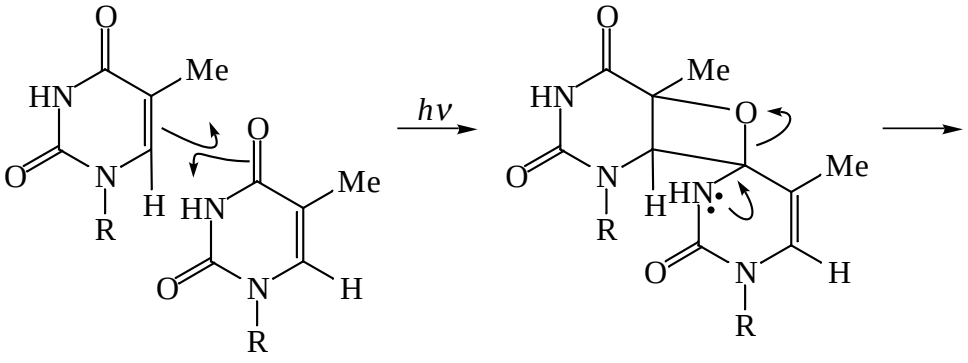


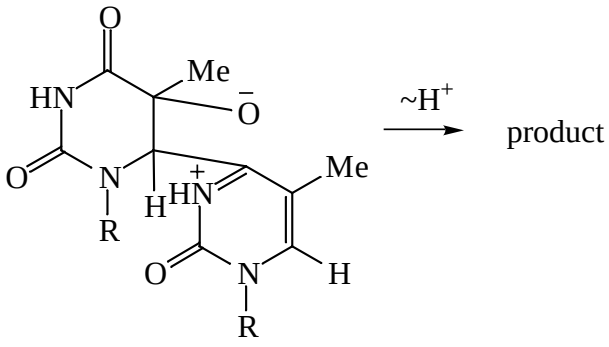
4.10. Make: C7–C2´, C9–O1´. Break: C2´–O1´.



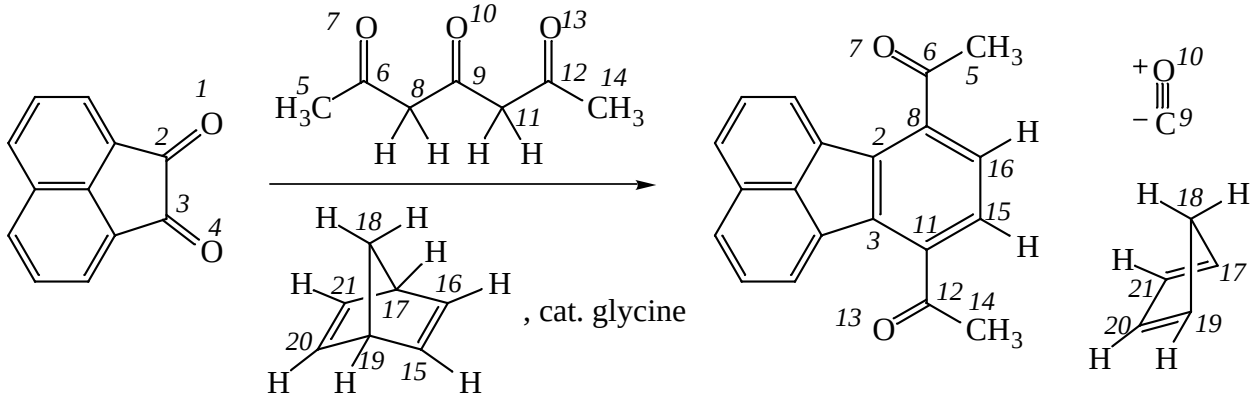
R= sugar phosphate backbone of DNA.

Making the C7–C2´ and C9–O1´ suggests a [2 + 2] photocycloaddition. Then the lone pair on N3´ expels O1´ from C2´ to give the observed product (after proton transfer).

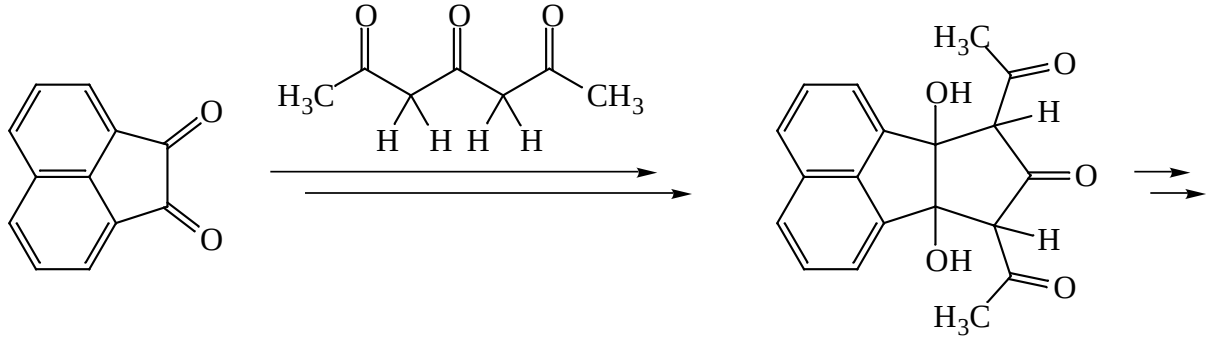


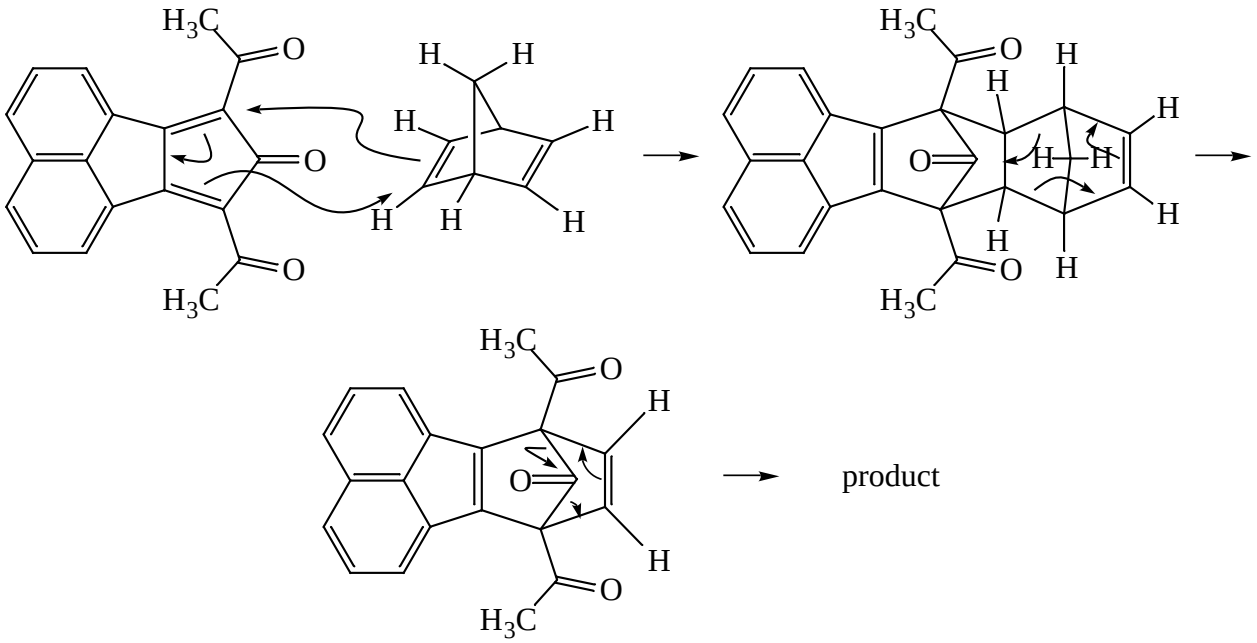


4.11. The numbering is not straightforward in this reaction, but if you draw in the H atoms you can see that the two CH groups in the new benzene ring in the product probably come from two CH groups in norbornadiene. Atoms unaccounted for in the written product include C9 and O10 (can be lost as CO), C17 to C21 (can be lost as cyclopentadiene), and O1 and O4 (can be lost as H_2O). Make: C2–C8, C3–C11, C8–C16, C11–C15. Break: O1–C2, C3–O4, C8–C9, C9–C11, C15–C19, C16–C17.

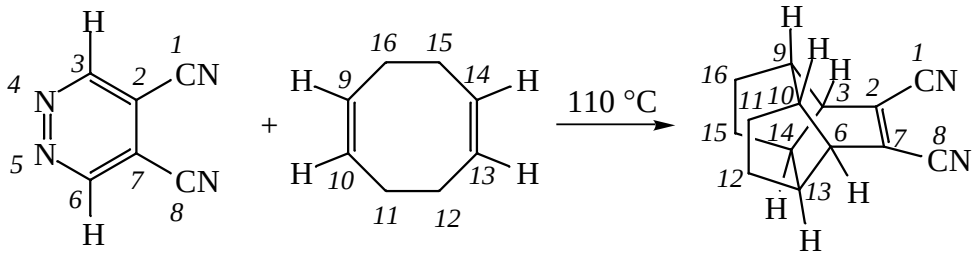


Glycine acts as an acid–base catalyst in this reaction. C8 and C11 are very acidic, and once deprotonated they are very nucleophilic, so they can attack C2 and C3 in an aldol reaction. Dehydration gives a key cyclopentadienone intermediate. (The mechanism of these steps is not written out below.) Cyclopentadienones are antiaromatic, so they are very prone to undergo Diels–Alder reactions. Such a reaction occurs here with norbornadiene. A retro-Diels–Alder reaction followed by a [4 + 1] retrocycloaddition affords the product.

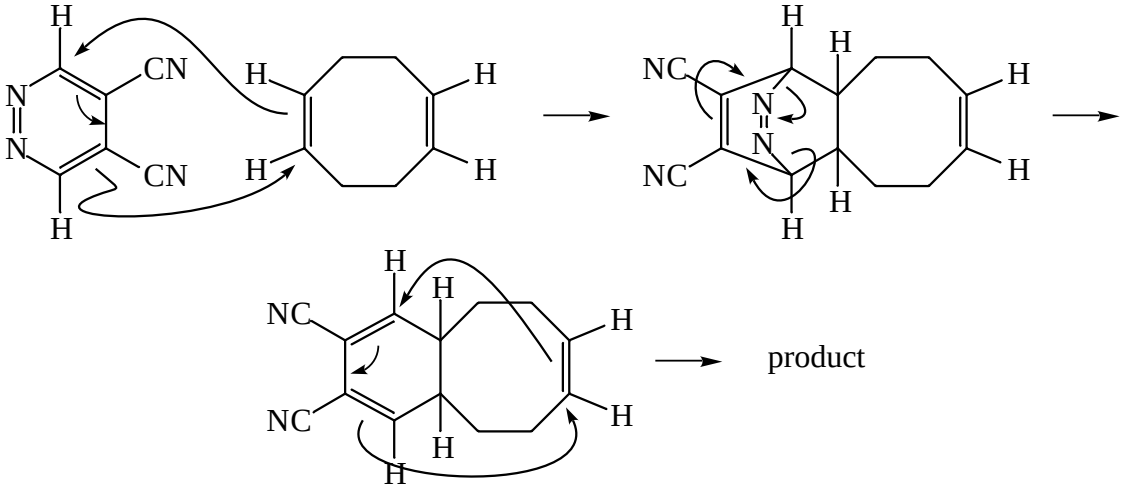




4.12. Make: C3–C9, C3–C14, C6–C10, C6–C13. Break: C3–N4, N5–C6.



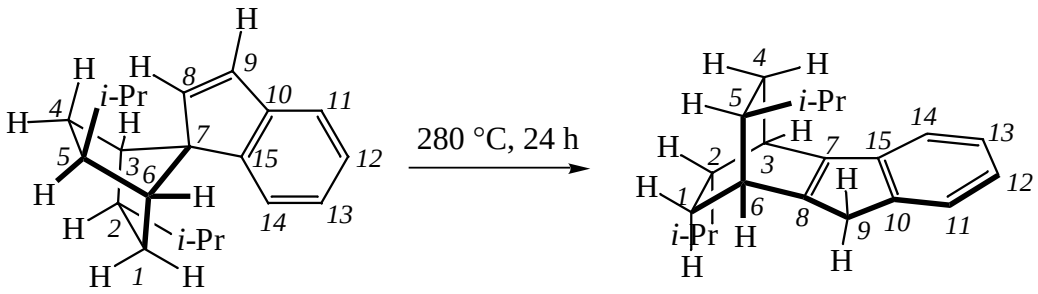
The C3–C9 and C6–C10 bonds can be made by a Diels–Alder reaction. Then loss of N_2 and cleavage of the C3–N4 and N5–C6 bonds can occur by a retro-Diels–Alder reaction. This step regenerates a diene, which can undergo another, intramolecular Diels–Alder reaction with the C13–C14 π bond to give the product.



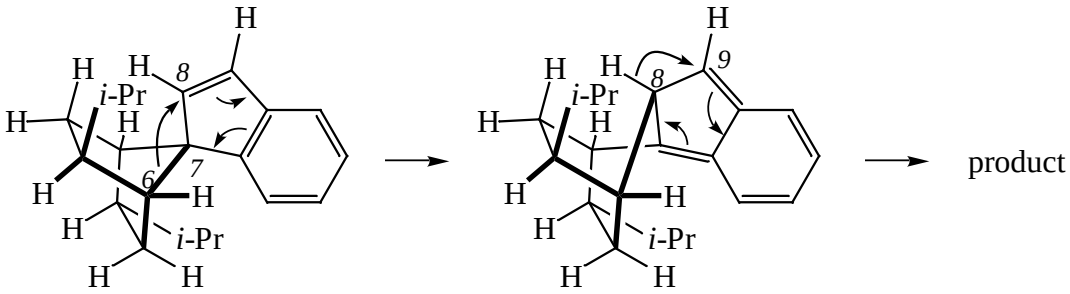
4.13. The [6+4] cycloaddition involves five pairs of electrons (an odd number), so it is thermally

allowed. The [4+3] cationic cycloaddition involves three pairs of electrons, so it is also thermally allowed.

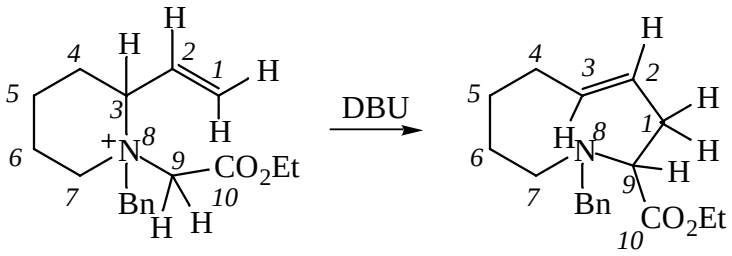
4.14. Make: C6–C8. Break: C6–C7.



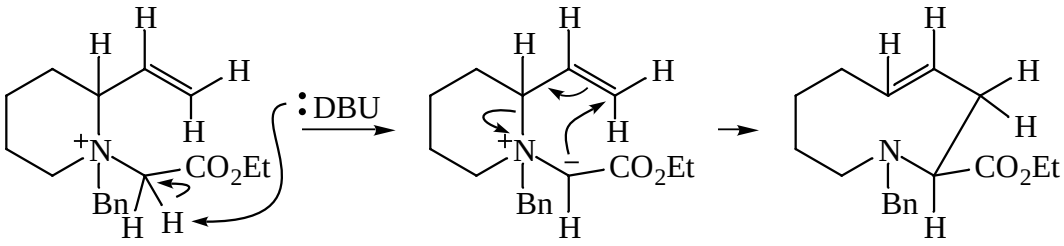
Making and breaking bonds to C6 suggests a [1,n] sigmatropic rearrangement, and a [1,5] sigmatropic rearrangement, one of the most common types, is possible here. Once the rearrangement is drawn, however, the mechanism is not complete, even though all bonds on the make & break list have been crossed off. C8 still has one extra H and C9 has one too few. Both these problems can be taken care of by another [1,5] sigmatropic rearrangement. This step, by the way, reestablishes the aromatic ring.



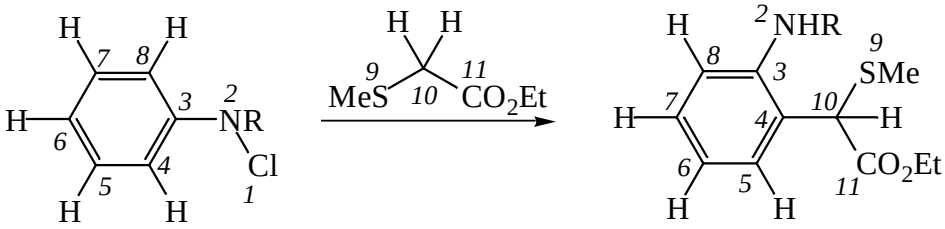
4.15. Make: C1–C9. Break: C3–N8.



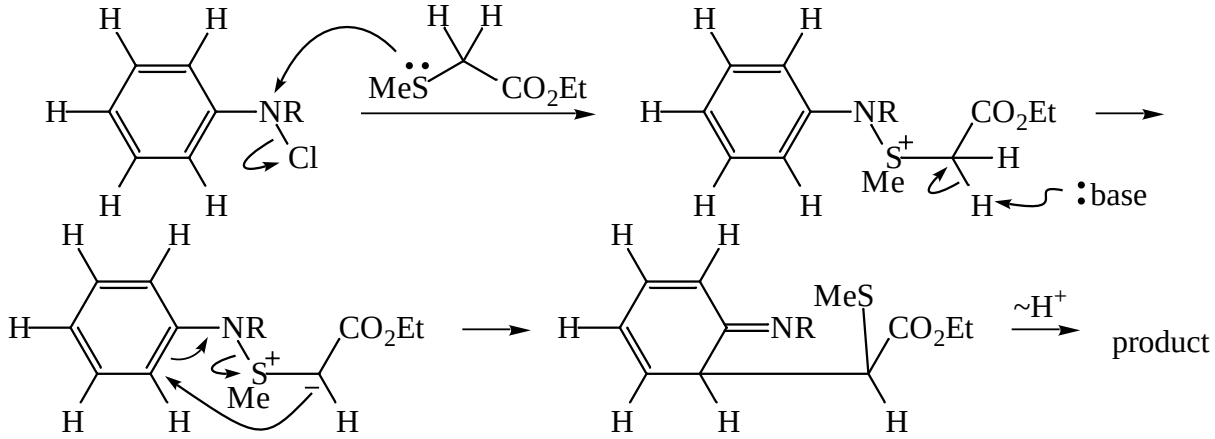
Deprotonation of C9 by DBU gives an ylide (has positive and negative charges on adjacent atoms that cannot quench each other with a π bond), a compound which is particularly prone to undergo [2,3] sigmatropic rearrangements when an allyl group is attached to the cationic center, as is the case here. Esters are not normally acidic enough to be deprotonated by DBU, but in this ester the N^+ stabilizes the enolate by an inductive effect.



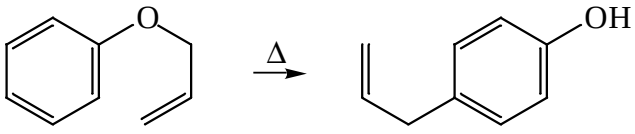
4.16. Make: C4–C10. Break: Cl1–N2.



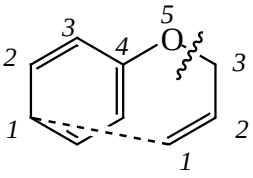
The most unusual bond in this system is the N–Cl bond. The nucleophilic substitution step must involve cleavage of this bond. No base is present, but S is an excellent nucleophile, even in its neutral form, so the first step probably entails formation of an S9–N2 bond. Now we have to make the C4–C10 bond and make the S9–N2 bond. Deprotonation of C4 gives an ylide, which as discussed in problem 4.15 is likely to undergo a [2,3] sigmatropic rearrangement. Tautomerization to rearomatize then gives the product.



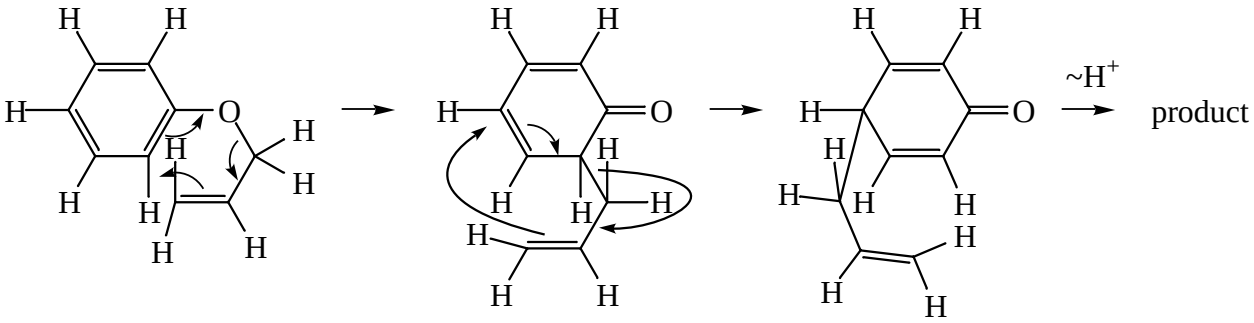
4.17. The reaction in question is:



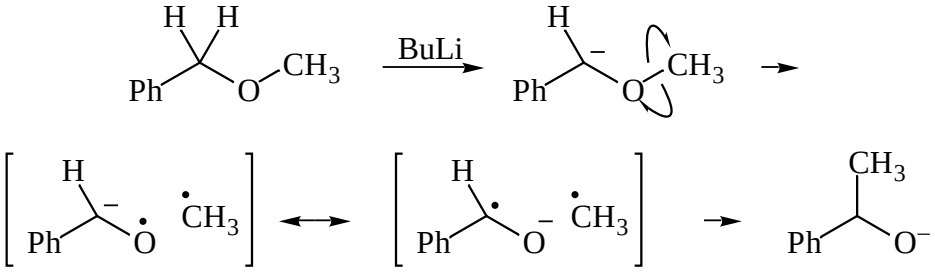
To name the reaction, draw a dashed line where the new bond is made, draw a squiggly line across the bond that is broken, and count the number of atoms from the termini of the dashed bond to the termini of the squiggly bond.



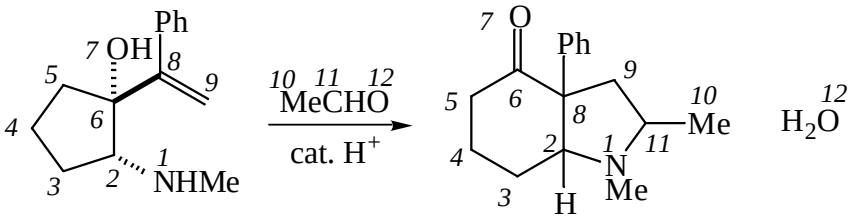
This reaction would be a [3,5] sigmatropic rearrangement, an eight-electron reaction, and hence would require that one component be antarafacial. Not likely! A more reasonable mechanism begins with the same [3,3] sigmatropic rearrangement that gives 2-allylphenol. However, instead of tautomerization to give the aromatic product, a second [3,3] sigmatropic rearrangement occurs. Then tautomerization gives the product.



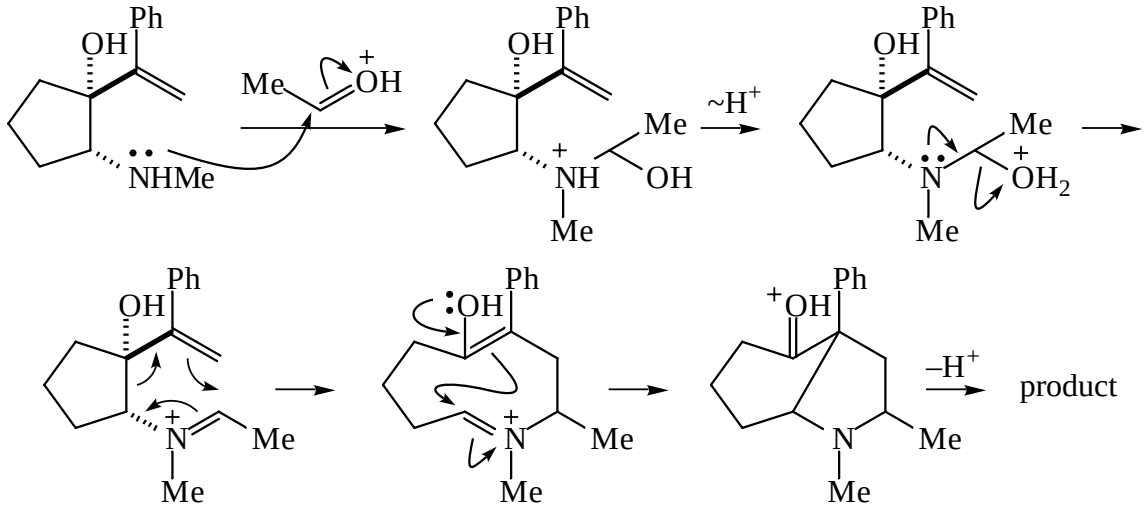
4.18. Both the Stevens rearrangement and the nonallylic Wittig rearrangement begin with deprotonation of the C atom next to the heteroatom followed by an anionic [1,2] sigmatropic rearrangement. Both involve four electrons, an even number of electron pairs, and hence if either is concerted then one of the two components of the reaction must be antarafacial. This condition is extremely difficult to fulfill, and hence it is much more likely that both reactions are nonconcerted. Both the Stevens rearrangement and the nonallylic Wittig rearrangement are thought to proceed by homolysis of a C–S or C–O bond and recombination of the C radical with the neighboring C atom.



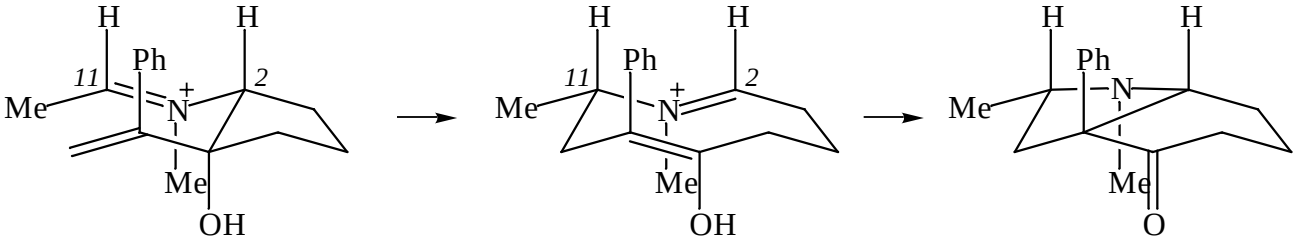
4.19. Make: N1–C11, C2–C8. Break: C2–C6, C11–O12.



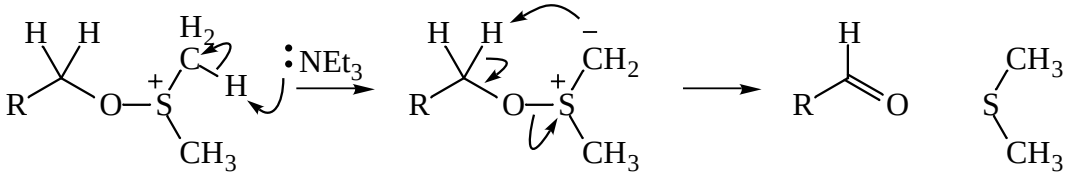
The N1–C11 bond is easily made first. Cleavage of the C11–O12 bond gives an iminium ion that is also a 1,5-(hetero)diene. The Cope rearrangement occurs to give a new iminium ion and an enol. Attack of the enol on the iminium ion (the Mannich reaction) affords the product.



Now the stereochemistry. Assume the thermodynamically more stable iminium ion forms (Me groups cis). The Cope rearrangement occurs from a chair conformation. This puts the Ph, H2, and H11 all pointing up both before and after the rearrangement. Assuming the Mannich reaction occurs without a change in conformation (a reasonable assumption, considering the proximity of the nucleophilic and electrophilic centers), the Ph, H2, and H11 should all be cis in the product.



4.20. Deprotonation of one of the Me groups adjacent to S gives an ylide which can undergo a retro-hetero-ene reaction to give the observed products.



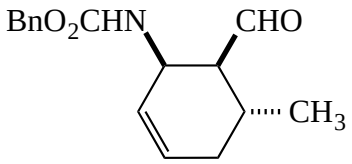
If $(CD_3)_2SO$ (deuterated DMSO) is used for the Swern reaction, the E2 mechanism predicts that the sulfide product should be $(CD_3)_2S$; the retro-hetero-ene mechanism predicts that it should be $(CD_3)S(CHD_2)$. Guess which product is actually found?

Answers To Chapter 4 End-of-Chapter Problems.

1.

(a) An eight-electron [4+4] cycloaddition. It proceeds photochemically.
(b) A four-electron conrotatory electrocyclic ring opening. It proceeds thermally.
(c) A six-electron ene reaction. (Note the transposition of the double bond.) It proceeds thermally.
(d) A six-electron [1,5] sigmatropic rearrangement. It proceeds thermally.
(e) A ten-electron [8+2] cycloaddition. It proceeds thermally.
(f) A six-electron [2,3] sigmatropic rearrangement. It proceeds thermally.
(g) A six-electron disrotatory electrocyclic ring opening. It proceeds thermally.
(h) A four-electron disrotatory electrocyclic ring closing. It proceeds photochemically.
(i) A six-electron disrotatory electrocyclic ring closing. It proceeds thermally.
(j) A six-electron [3+2] (dipolar) cycloaddition. It proceeds thermally.
(k) A four-electron [2+2] cycloaddition. It proceeds photochemically.
(l) A six-electron conrotatory electrocyclic ring opening. It proceeds photochemically.

2.

<table>
<tr>
<td>(a) Regio: RNH and CHO are 1,2. Stereo: CHO and CH_3 remain trans; NHR is out, CHO is endo, so they are cis in product.
 
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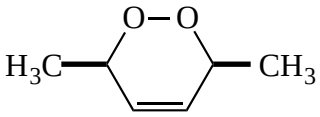
<td>(b) The two CH_3 groups are both out groups, so they are cis in product.
 
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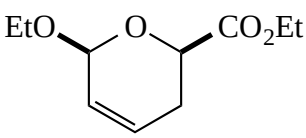
<td>(c) Regio: C4 of diene is nucleophilic, so it makes a bond to electrophilic C of dienophile. Stereo: EtO is out, CO_2Et group is endo, so they are cis in product.
 
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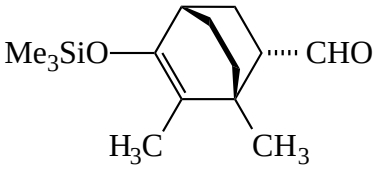
<td>(d) Regio: CHO and $OSiMe_3$ are 1,4. Stereo: the CH_2CH_2 bridge is in at both ends of the diene, CHO is endo, so they are trans in product.
 
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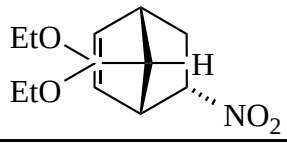
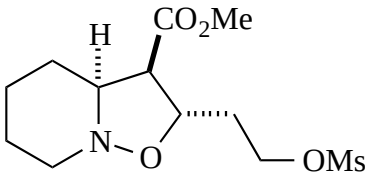
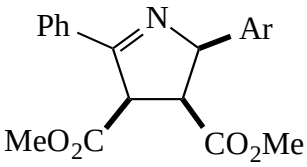
(e) Dienophile adds to less hindered face of diene. C(sp^3) of five-membered ring is *in*, NO_2 is *endo*, so they are *trans* in product.



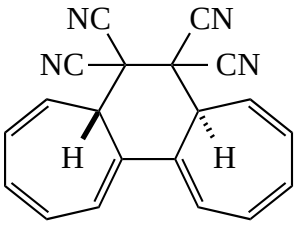
(f) Regio: Nucleophilic O adds to electrophilic β C of unsaturated ester. Stereo: alkyl and CO_2Me groups remain *trans*; H is *in*, CO_2Me is *endo*, so they are *trans* in product.



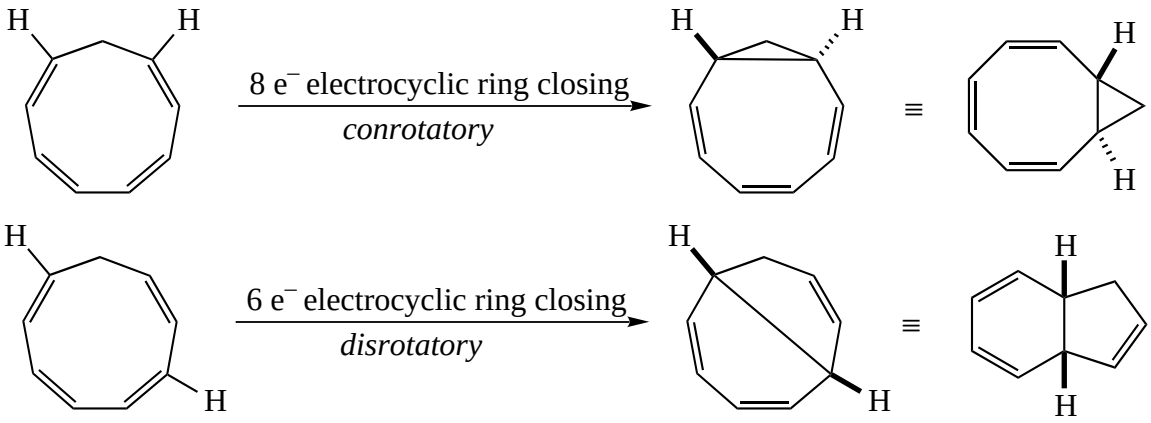
(g) Stereo: CO_2Me groups remain *trans*. Ar group is probably *out* for steric reasons, CO_2Me is *endo*, so the two are *cis* in the product.

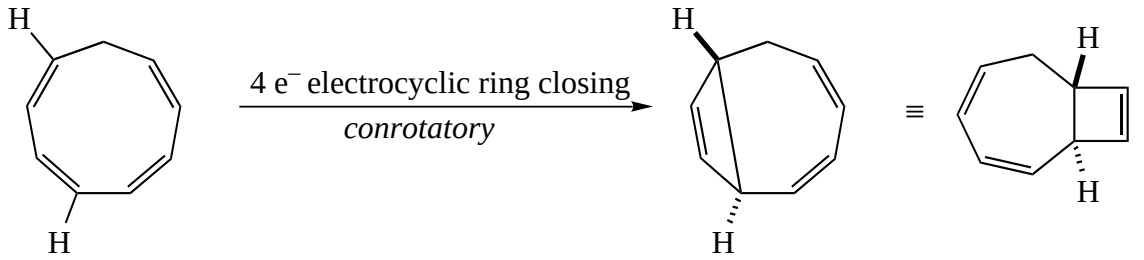


(h) The [14+2] cycloaddition must be antarafacial with respect to one component. The two *in* groups of the 14-atom component become *trans* in the product.



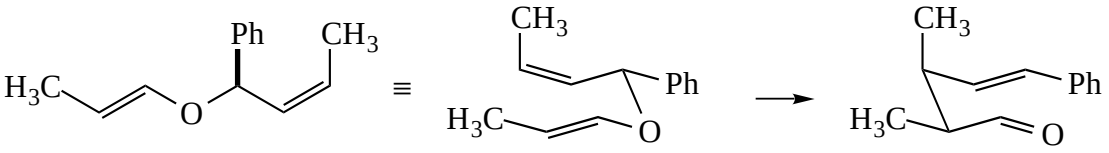
3. 1,3,5,7-Cyclononatetraene can theoretically undergo three different electrocyclic ring closures.



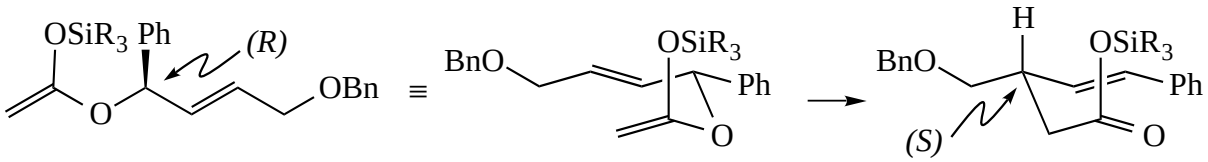


When small rings are fused to other rings, the *cis* ring fusion is almost always much more stable than the *trans* ring fusion. The opposite is true only for saturated 6-6 or larger ring systems. (Make models to confirm this.) The order of stability of the three possible products shown above is: *cis*-6-5 > *trans*-7-4 > *trans*- 8-3.

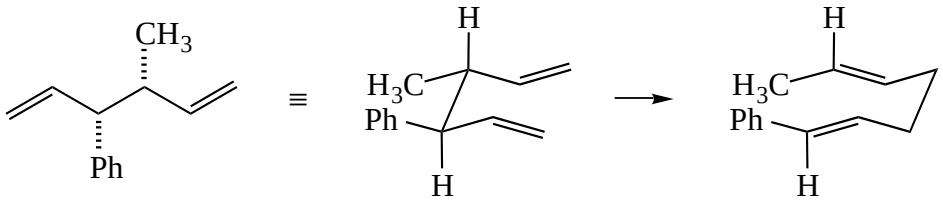
4. (a) Chair TS, with the Me on the C(sp^3) equatorial.



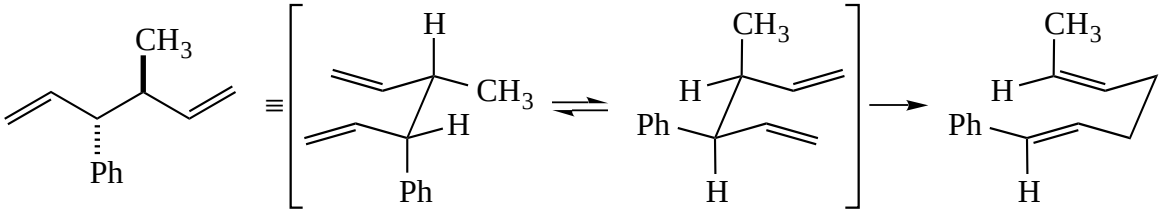
(b) Chair TS, with the Ph equatorial.



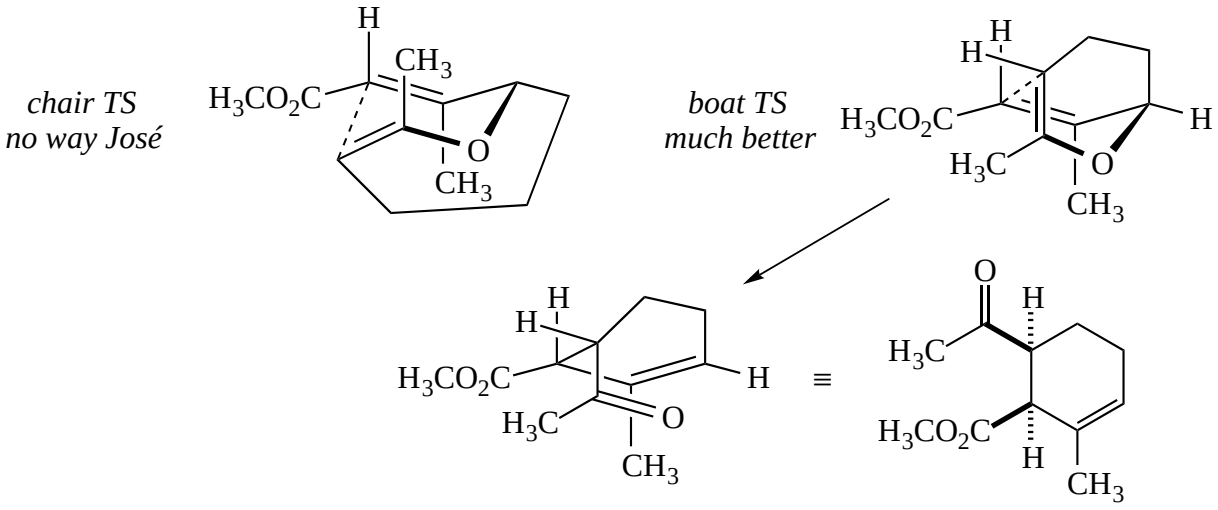
(c) Chair TS, with both substituents equatorial.



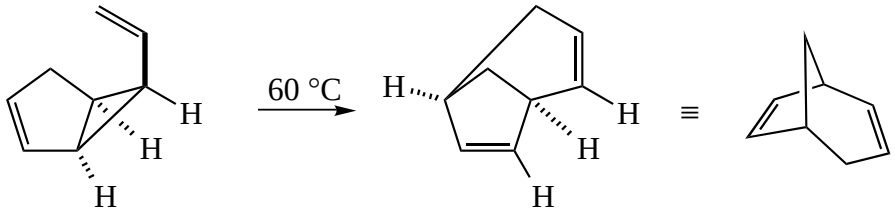
(d) Two different chairs are possible, but one (Ph equatorial) is lower in energy than the other.



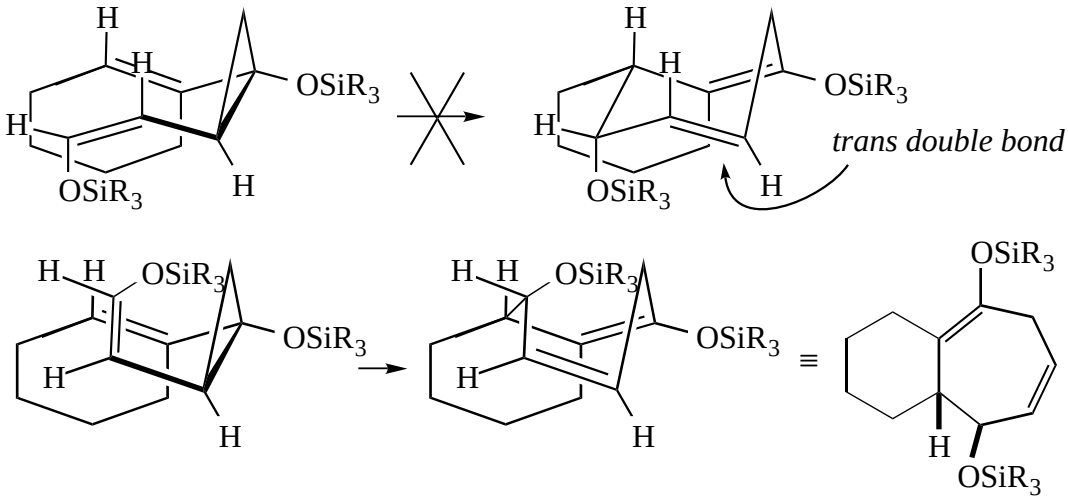
(e) A chair TS is not possible, so it goes through a boat TS.



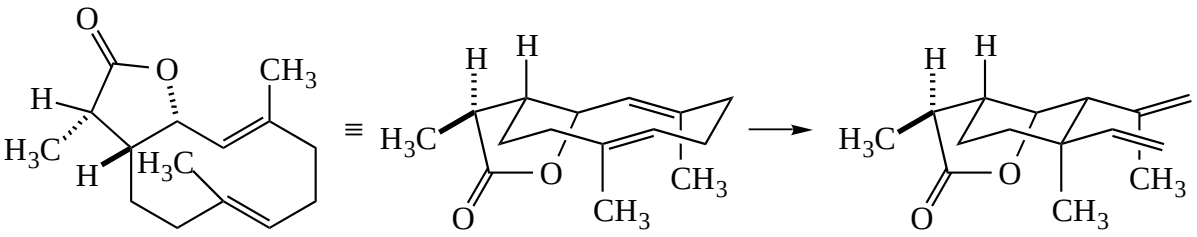
(f) Again, a boat TS is necessary.



(g) A chair TS would produce a trans double bond in the seven-membered ring, so the boat TS is operative, and the H and $OSiR_3$ groups on the two stereogenic atoms are *cis* to one another.



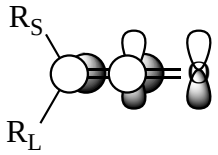
(h) The chair TS is enforced in this macrocyclic compound.



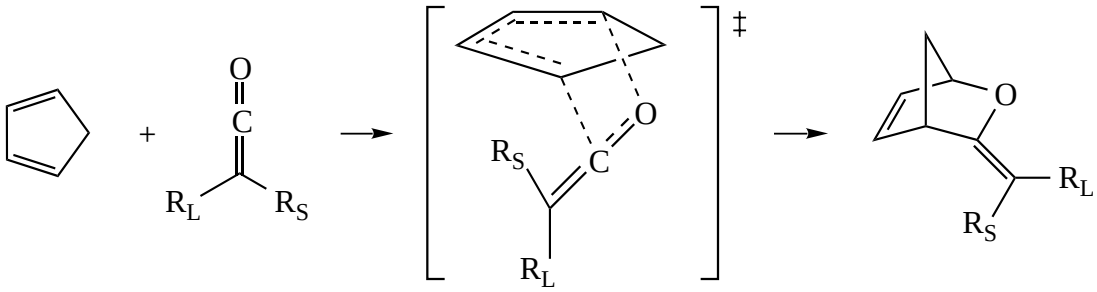
5. (a) First step: hetero-Diels–Alder reaction (six-electron, [4+2] cycloaddition). Second step: Claisen rearrangement (six-electron, [3,3] sigmatropic rearrangement).

(b) The diene is electron-rich, so it requires an electron-poor dienophile for a normal electron demand Diels–Alder reaction. The C=C bond of ketenes is pretty electron-rich, due to overlap with the lone pairs on O: $H_2C{=}C{=}\ddot{O} \leftrightarrow H_2\bar{C}{-}C{\equiv}\overset{+}{O}$. Only the C=O bond of the ketene is of sufficiently low energy to react with the diene at a reasonable rate.

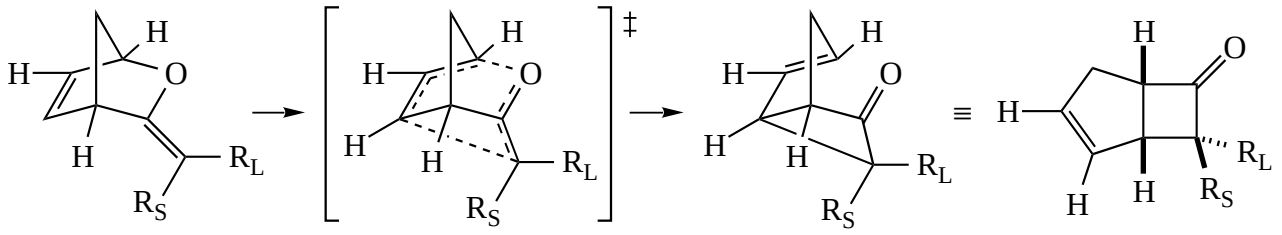
(c) First, it is important to remember that in ketenes, the p orbitals of the C=O bond are coplanar with the substituents on the terminal C.



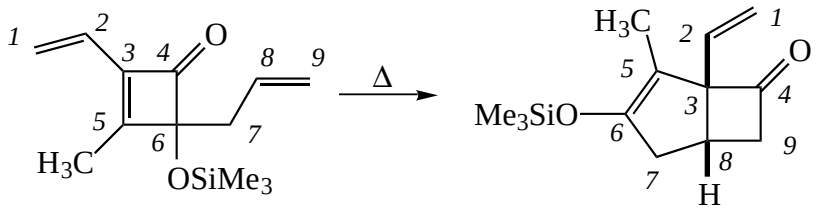
Because of the ketene's geometry, in the TS of the hetero-Diels–Alder reaction, either R_S or R_L must point directly at the diene. The lower energy approach towards R_S is chosen, and the product in which R_S points back toward the former diene portion of the compound is obtained.



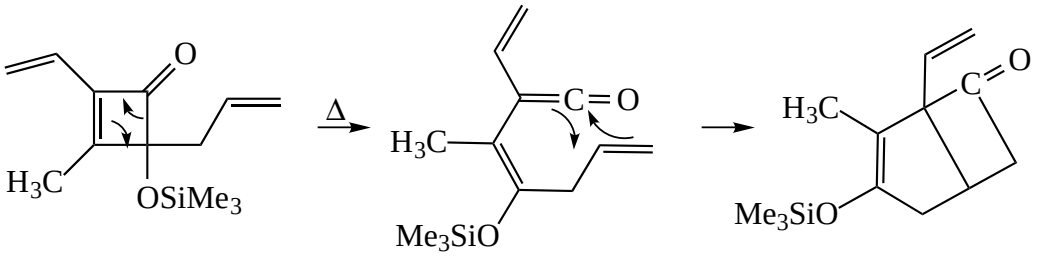
Second step: The new σ bond forms between the bottom face of the double bond on the left and the bottom face of the double bond on the right, giving the observed, less thermodynamically stable product.



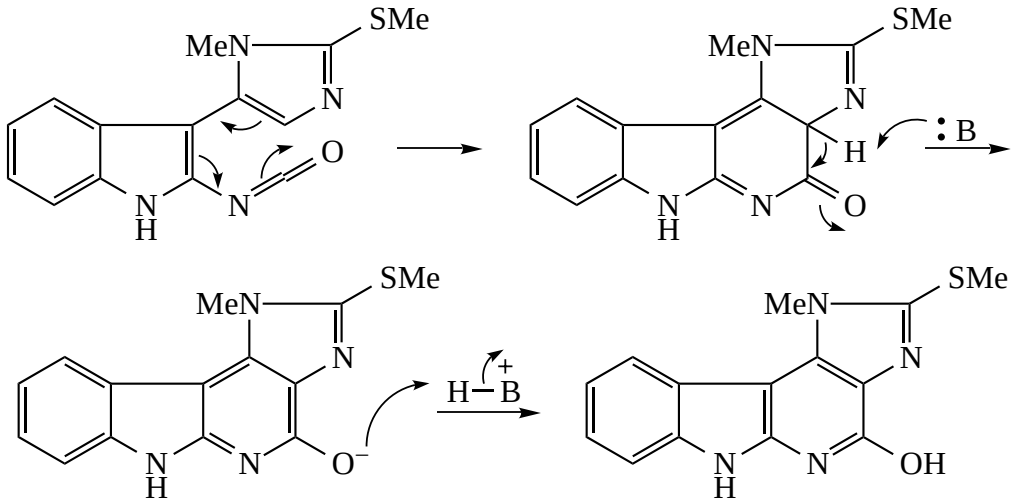
6. (a) Number the C's. C1, C2, C5 and C6 are clear in both starting material and product. The rest follows.



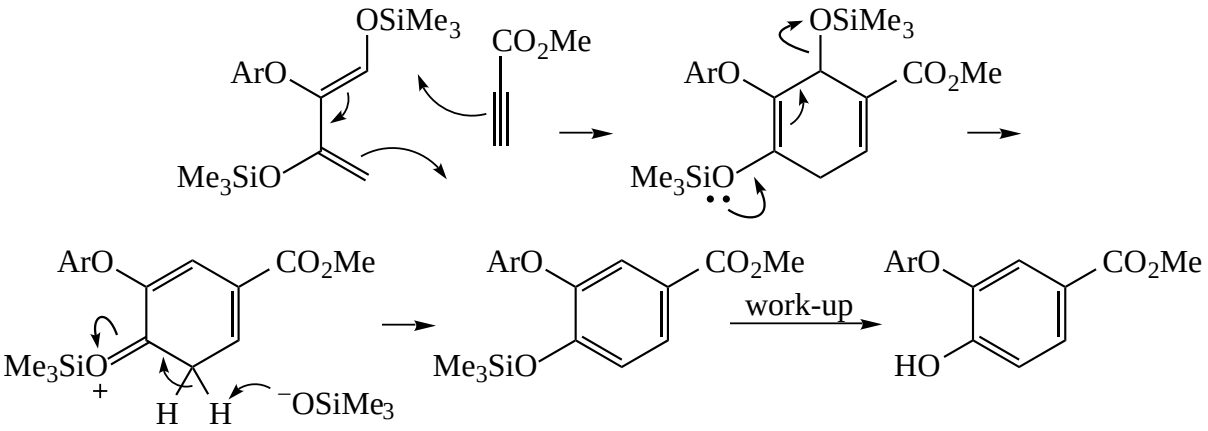
We break the C4–C6 bond, and we form C3–C8 and C4–C9. The formation of the latter two bonds and the fact that we're forming a cyclobutanone suggests a [2+2] cycloaddition between a ketene at C3=C4=O and the C8=C9 π bond. We can generate the requisite C3=C4 π bond by electrocyclic ring opening of the cyclobutene ring in the S.M.



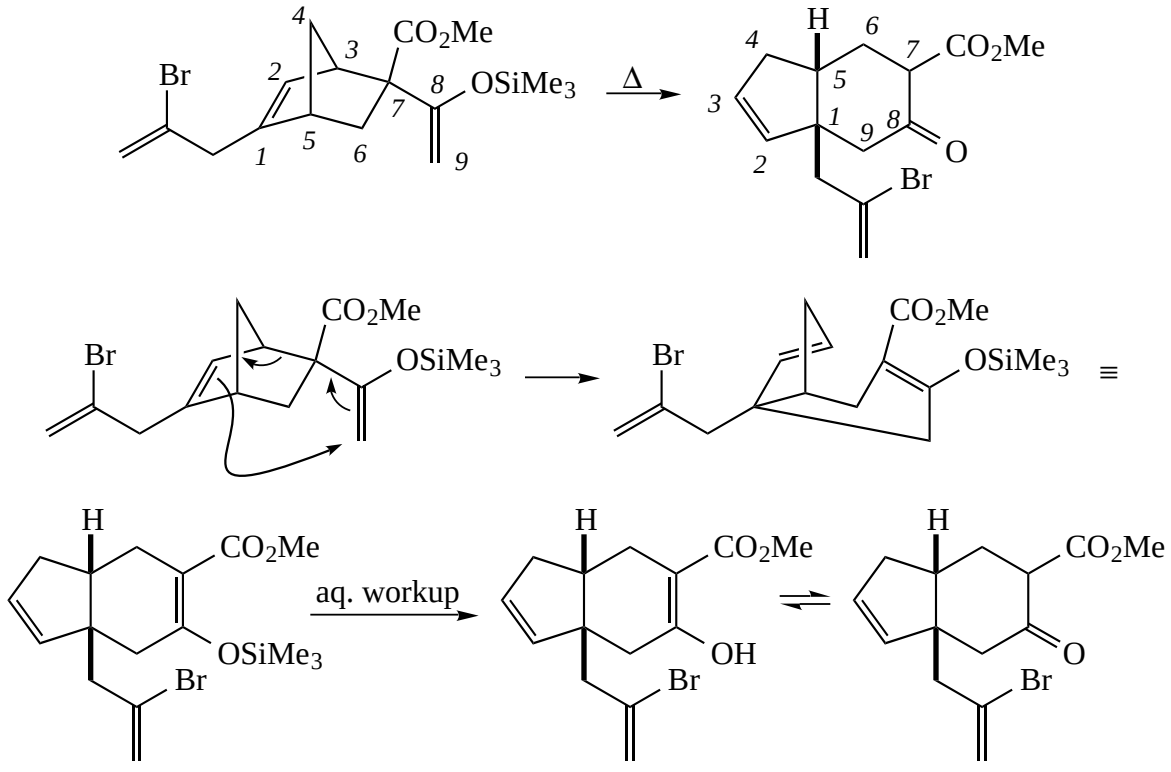
(b) Electrocyclic ring closing followed by base-catalyzed tautomerization (both starting material and product are bases) gives the product.



(c) Diels–Alder reaction followed by spontaneous elimination of Me_3SiO^- and aromatization gives the product. Loss of Me_3SiO^- occurs so readily because the Me_3Si group is a π electron withdrawer like a carbonyl group.

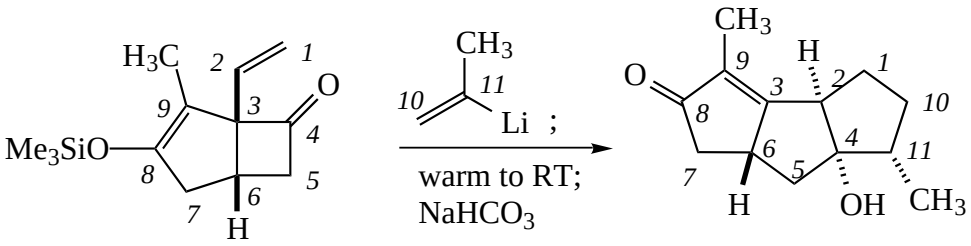


(d) The key atoms for numbering the C's are C1 (with the 2-bromoallyl group attached), C7 (ester group attached), and C8 (O attached). We form bond C1–C9 and break bond C3–C7. Since C3–C7 is the central bond of a 1,5-diene system terminating in C1 and C9, i.e. C1=C2–C3–C7–C8=C9, this must be a Cope rearrangement.

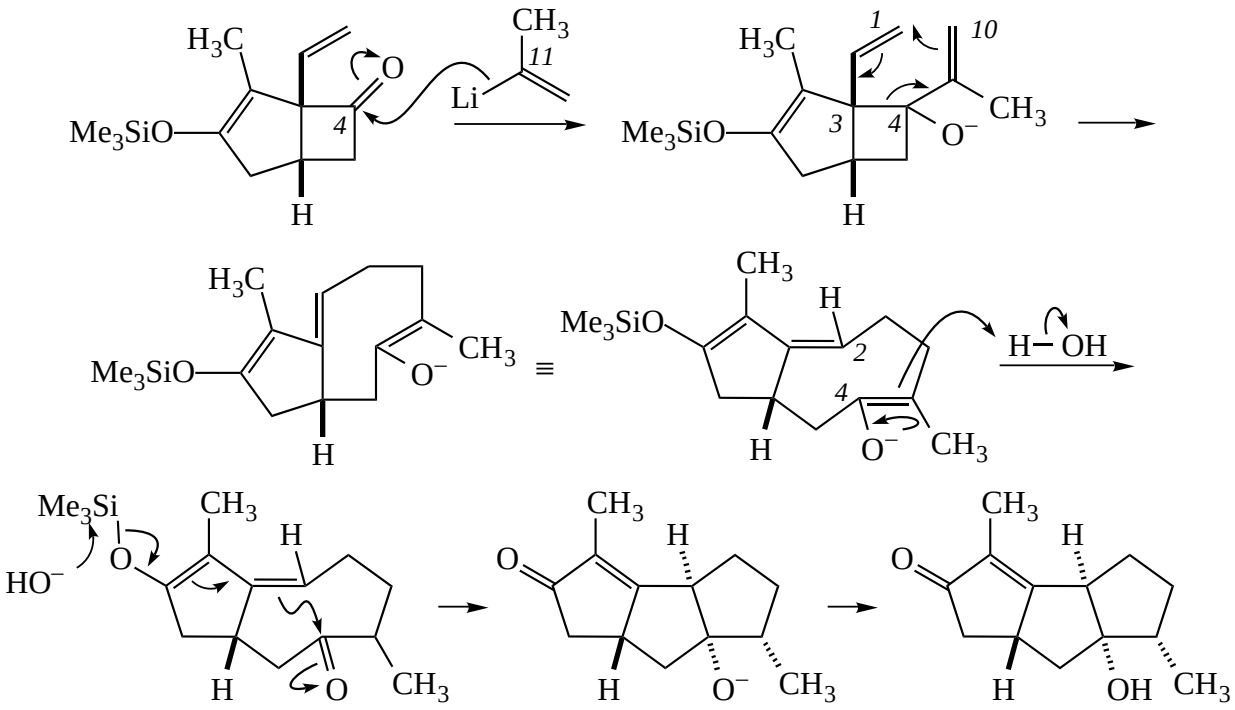


(e) Numbering the carbons is made easier by C9, C8, and C4. These atoms make it easy to label C4 through C9. Since C11 is a carbanion, we can expect that it will add to C4, the only electrophilic C in the starting material, and since C11 has a CH_3 group attached, we can identify it and C10 in the product as the

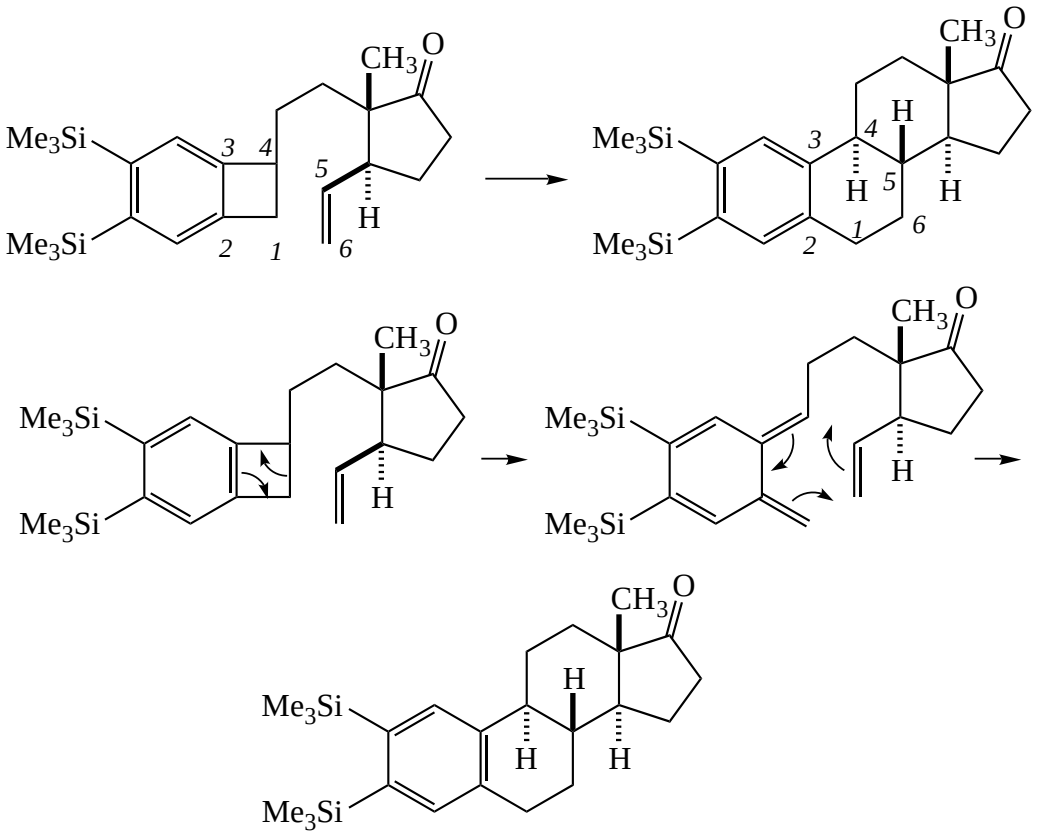
easternmost C's, with C11 attached to C4. For C1 to C3, we preserve the most bonds if we retain the C9–C3–C2–C1 sequence. So overall, we form C4–C11, C4–C2, and C10–C1, and we break C4–C3.



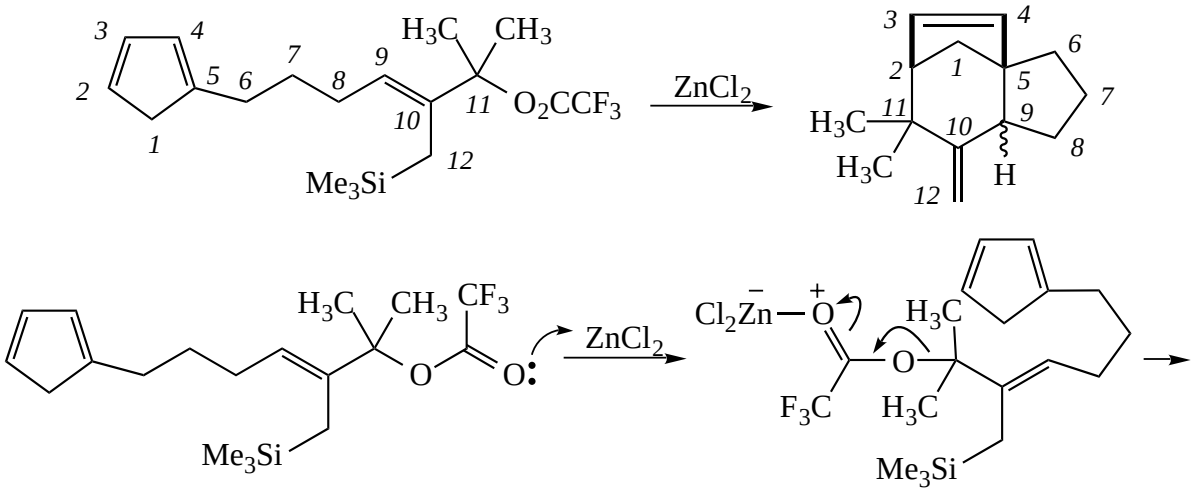
The first step is addition of C11 to C4. We still need to form C10–C1 and break C4–C3. Since we have a 1,5-diene (C11=C10–C4–C3–C2=C1), we can do an oxy-Cope rearrangement. This gives a 5-8 system in which we only have to form the C4–C2 bond. C4 is neither nucleophilic nor electrophilic, while C11 is nucleophilic (conjugation from $OSiMe_3$). Upon quenching with water, however, C4 becomes an electrophilic carbonyl C, whereupon C11 attacks with concomitant desilylation of O to give the product.

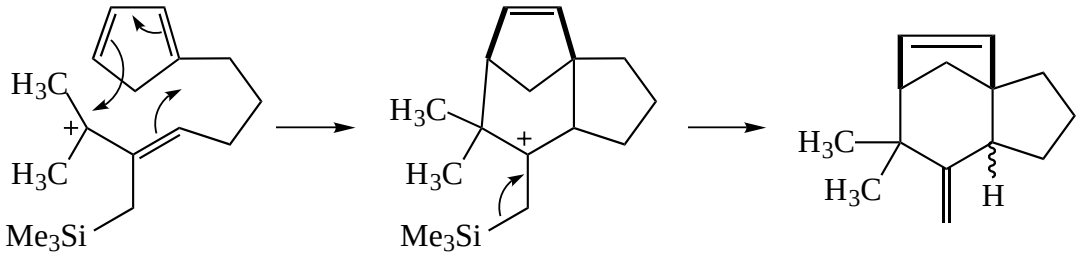


(f) It's clear that we form C4–C5 and C1–C6 bonds, and we break C1–C4. The strained C1–C4 bond can be opened by an electrocyclic ring opening to give an *o*-xylylene, which undergoes an [8+2] cycloaddition to give the observed product.

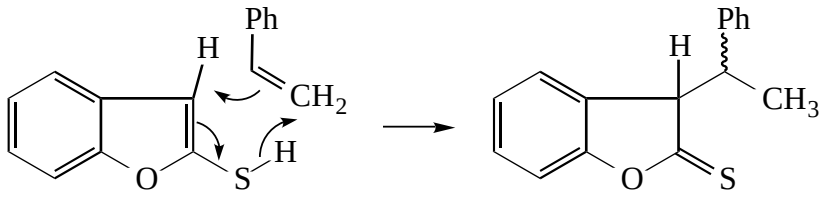


(g) We form C2–C11 and C5–C9 bonds, and we eliminate the elements of $Me_3SiO_2CCF_3$. The $ZnCl_2$ is a Lewis acid, so it coordinates to the carbonyl O and causes the cleavage of the carboxylate–C11 bond to give the nice stable allylic cation C9–C10–C11. This cation can undergo a six-electron, [4+3] cycloaddition with the C2=C3–C4=C5 diene to give a new carbocation at C11. Loss of the Me_3Si^+ group from C12 then gives the product.

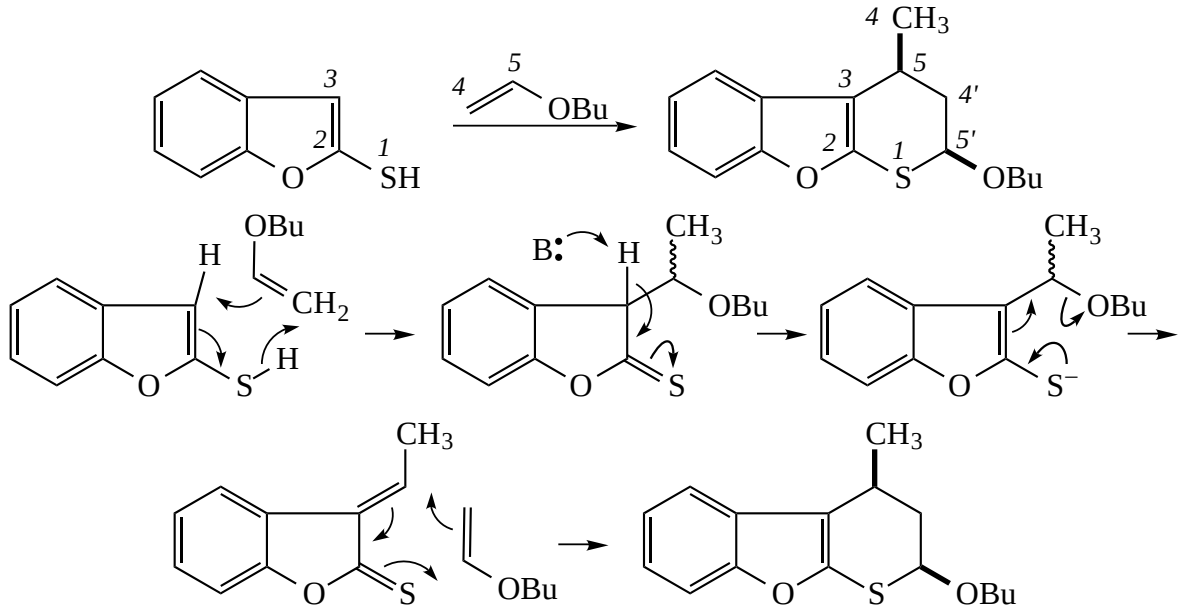




(h) The first product is formed by a hetero-ene reaction, with transfer of the H attached to S to the terminal C of styrene.

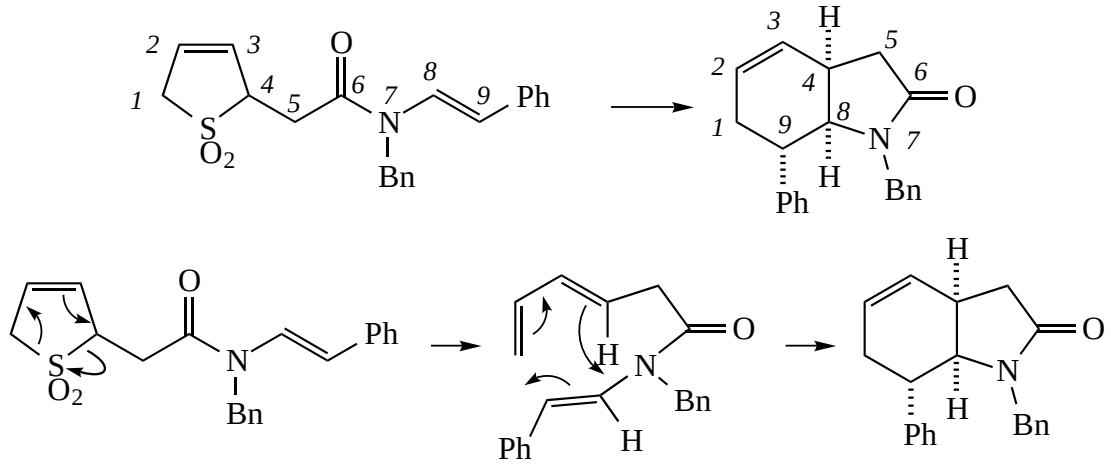


The second product must incorporate two equivalents of the enol ether. We form C3–C5, C5–C4', and C5'–S1 bonds, and we transfer a H from S1 to C4. A hetero-ene reaction forms the C3–C5 bond and transfers the H. As for the other two bonds, since S1 and C5 are at the ends of a four-atom unit, we might expect a Diels–Alder reaction. We can get to the requisite diene by eliminating the elements of BuOH by an E1cb mechanism. The hetero-Diels–Alder reaction gives the product with *endo* stereoselectivity and the expected regioselectivity.

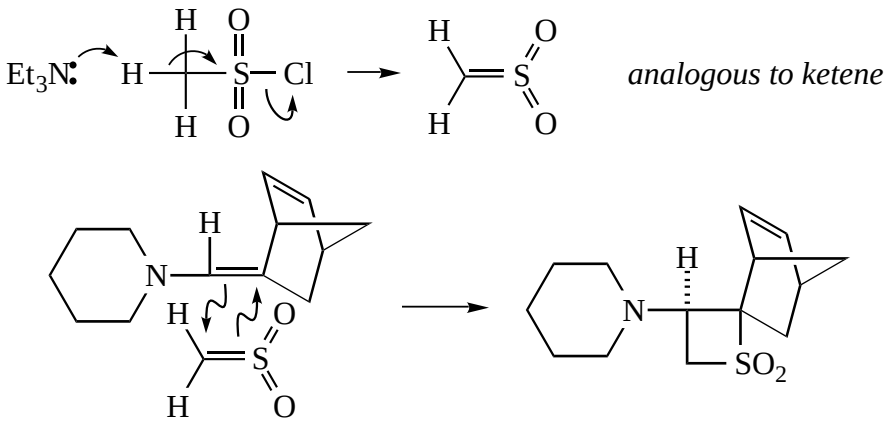


(i) We form C9–C1 and C4–C8 bonds, and we break C1–S and C4–S bonds. Since C1 and C4 are the ends of a four-carbon unit, we can expect a Diels–Alder reaction. The cyclohexene in the product should also tip you off. We can obtain the requisite diene by doing a [4+1] retro-cycloaddition, eliminating SO_2 to give the C1=C2–C3=C4 diene. Stereospecific and *endo*-selective Diels–Alder reaction then gives the

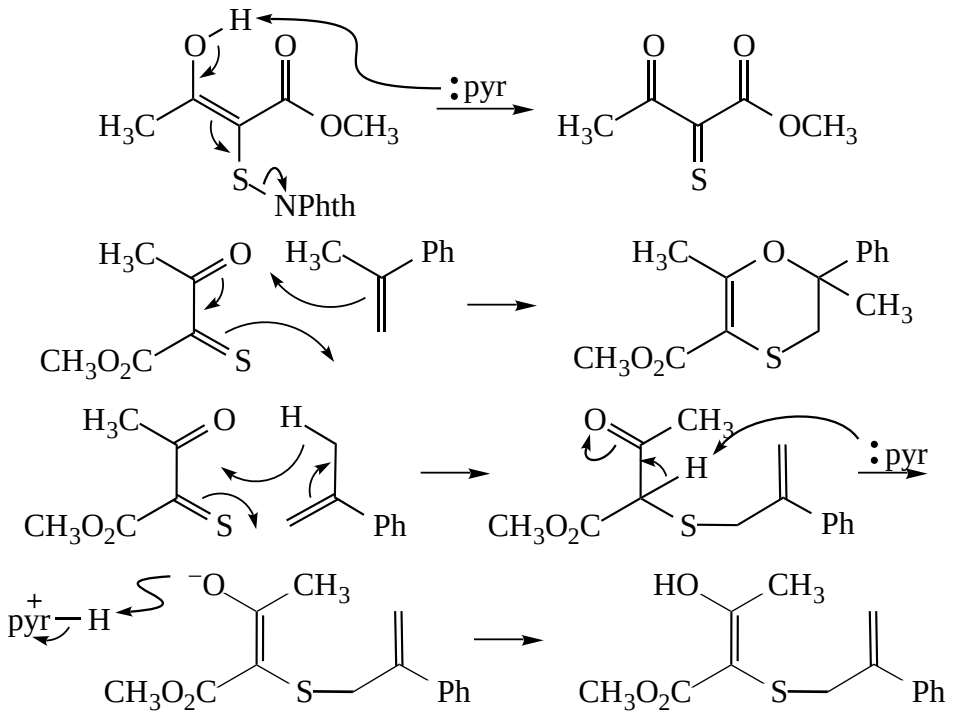
product.



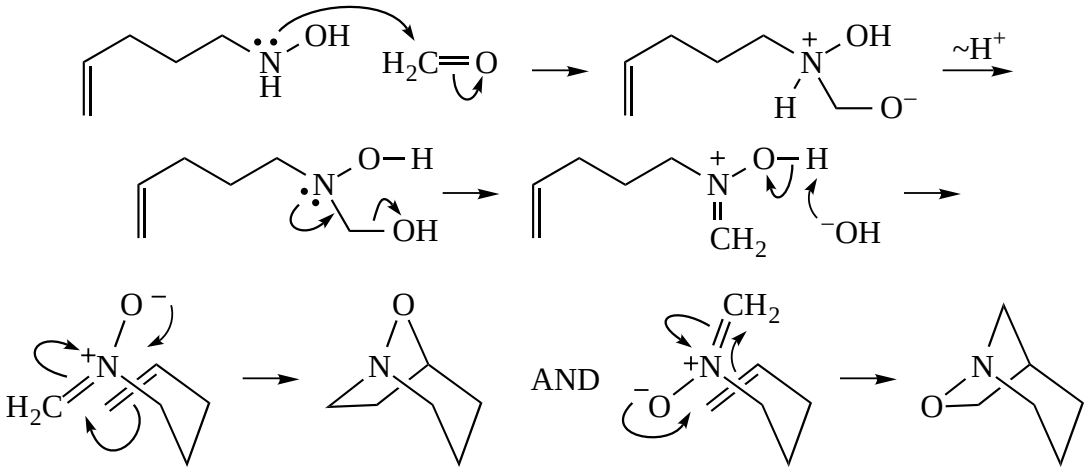
(j) When an acyl chloride is treated with Et_3N, β-elimination takes place to give a ketene. When a sulfonyl chloride is treated with Et_3N, β-elimination takes place in the same way. The intermediate undergoes [2+2] cycloadditions just like ketenes do to give the saturated four-membered ring.



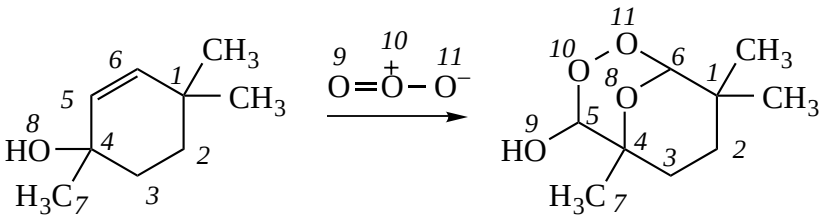
(k) The second product provides the key. It is a six-membered ring with a single double bond, probably the product of a hetero-Diels–Alder reaction. The requisite diene can be made from the starting material by a vinylogous β-elimination, with NPhth as the leaving group. The same diene intermediate can undergo a hetero-ene reaction to give the *other* observed product. An alternative mechanism for formation of the first product, i.e. direct attack of the alkene (nucleophile) on S (electrophile, NPhth as leaving group) to give a carbocation, followed by loss of H^+, is also possible, but is less likely, especially since we know the C=S compound is formed under the conditions. If this mechanism were operative it's also likely that H^+ would be lost from the *other* C of the carbocation to give the more substituted and more stable isomeric alkene.



(l) Whenever you see a five-membered heterocycle, think 1,3-dipolar cycloaddition. The heterocyclic rings shown can be made from an intramolecular cycloaddition of a nitrone and the alkene. The nitrone must be made from the hydroxylamine and formaldehyde.

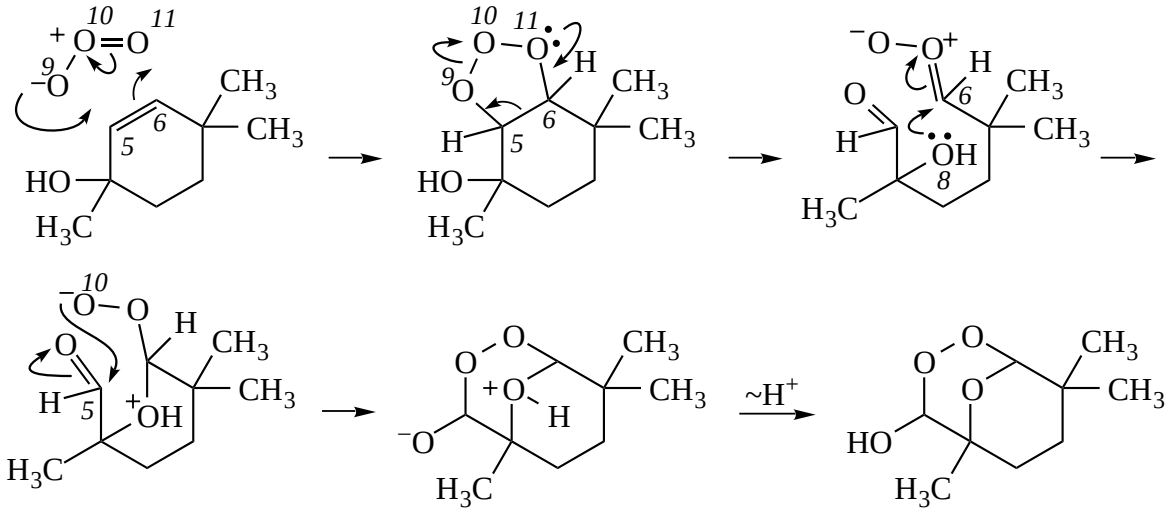


(m) Make: C5–O10, C5–O9, C6–O8, C6–O11. Break: C5–C6, C9–O10.

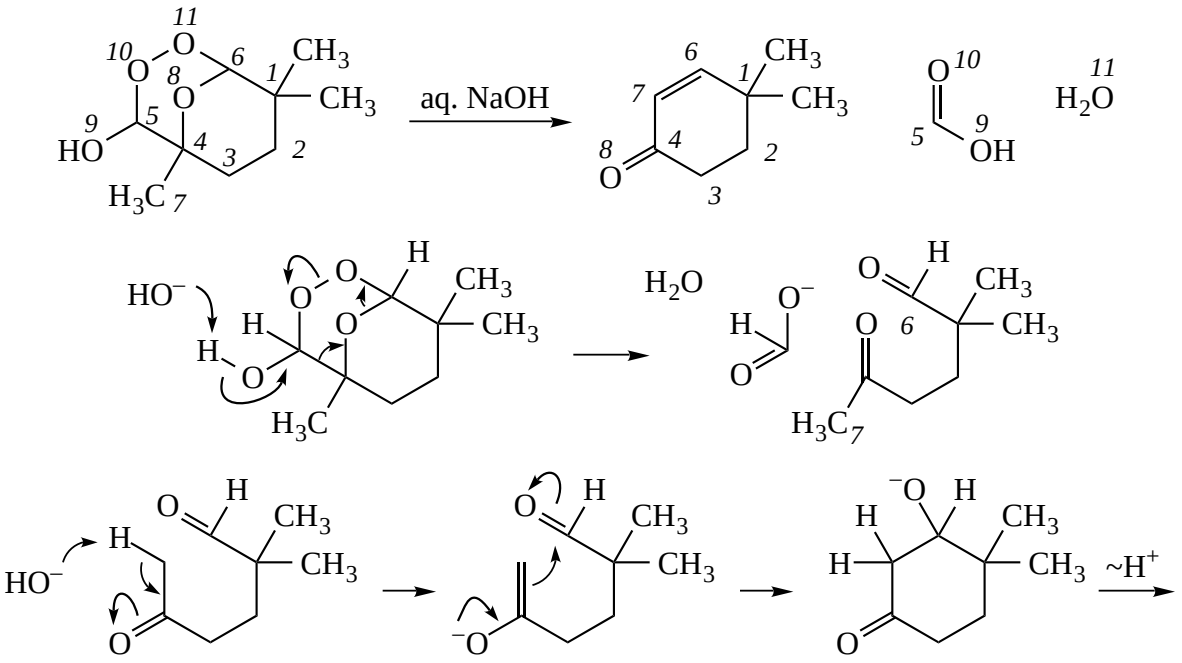


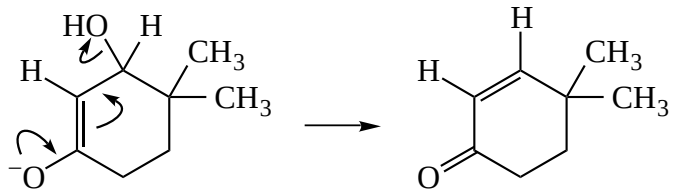
Ozone lives to do 1,3-dipolar cycloadditions. After the cycloaddition to give the C6–O11 and C5–O9

bonds, retro 1,3-dipolar cycloaddition occurs to break the C9–O10 and C5–C6 bonds. Then O8 can attack C6 and O10 can attack C5 to give the observed intermediate (after proton transfer).

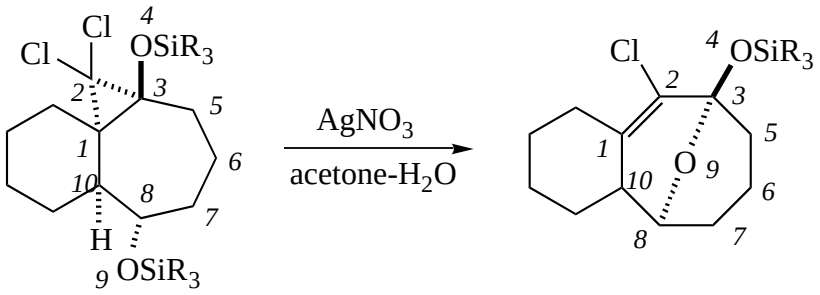


Second step. The elements of CH_4O_3 are eliminated. The most likely by-products are H_2O and HCOOH. Make: None. Break: C4–C5, C6–O8, O10–O11. The base can deprotonate the OH on C5, and the lone pair on O can then push down to form a π bond with C5, causing the C4–C5 bond to break. The electrons keep getting pushed around until they end up on O again and the O–O bond is broken, providing the driving force for the step. A keto-aldehyde and formate anion are obtained. Now C7 (deprotonated) is nucleophilic and C6 is electrophilic, so an aldol reaction followed by dehydration gives the observed product.

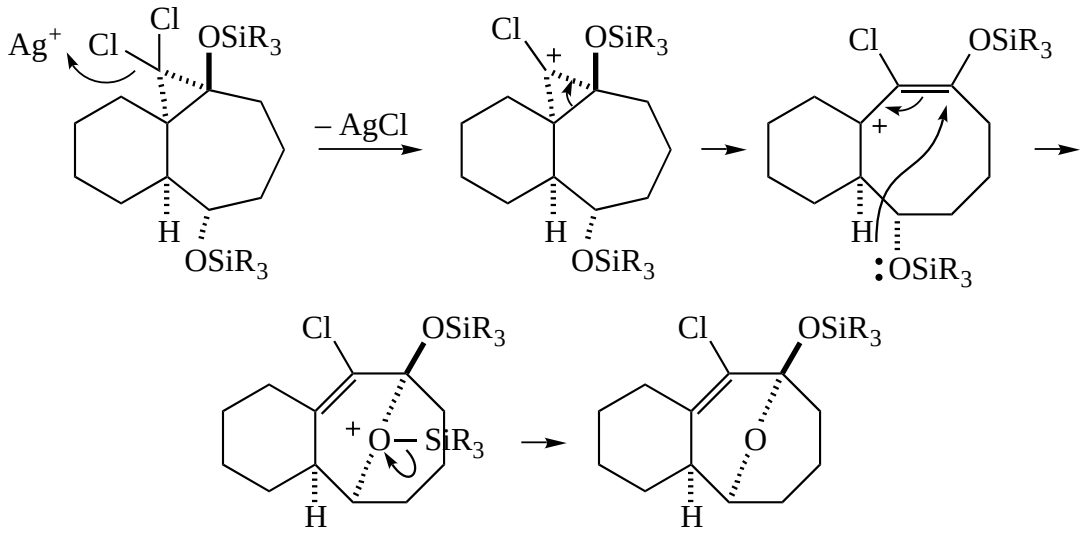




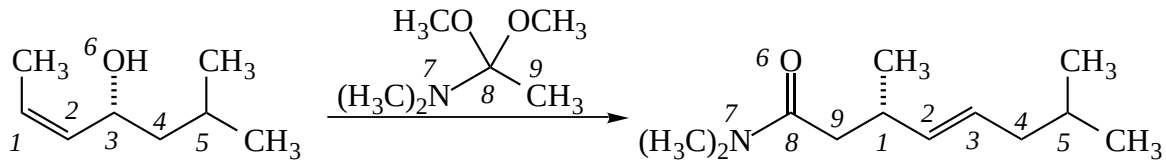
(n) Make: O9–C3. Break: C1–C3. Since O9 is nucleophilic, we must turn C3 into an electrophilic center.

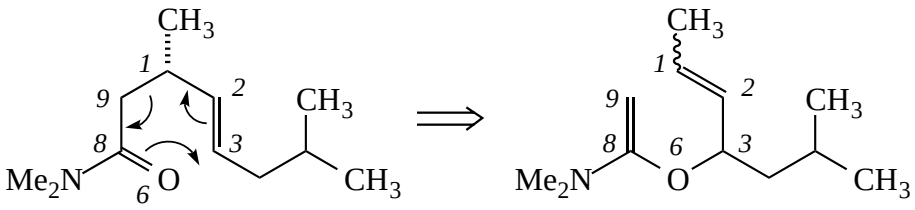


In the first step, Ag^+ promotes the departure of Cl^- to give a cyclopropyl carbocation. This undergoes two-electron disrotatory electrocyclic ring opening to give the chloroallylic cation, in which the empty orbital is localized on C1 and C3. Then O9 can add to C3; desilylation then gives the product.

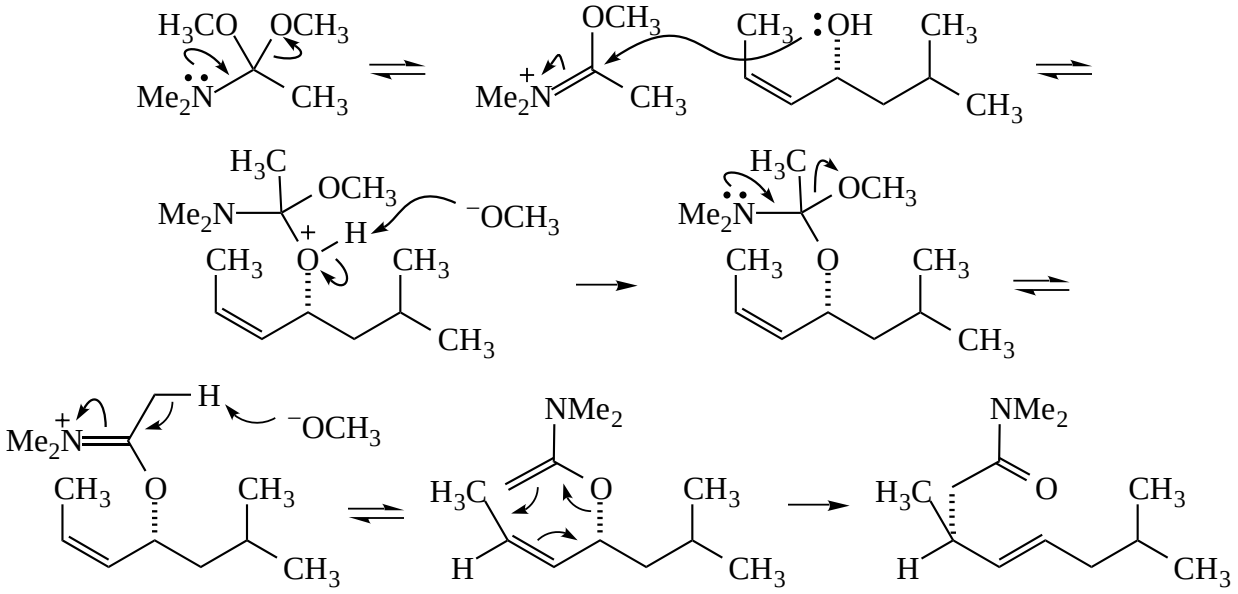


(o) The product is a 1,5-diene, specifically a γ,δ-unsaturated carbonyl, suggesting a Claisen rearrangement. Work backwards one step from the product.

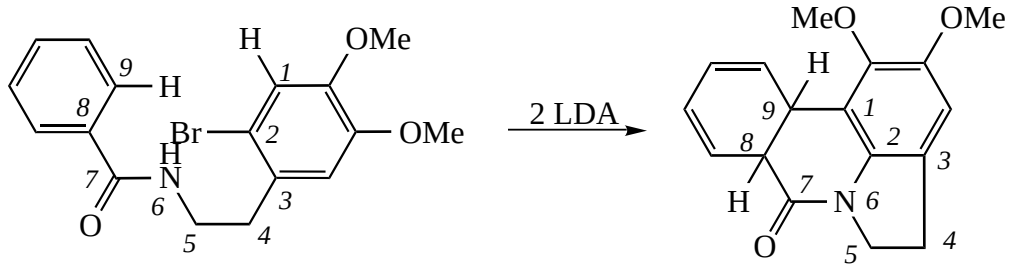




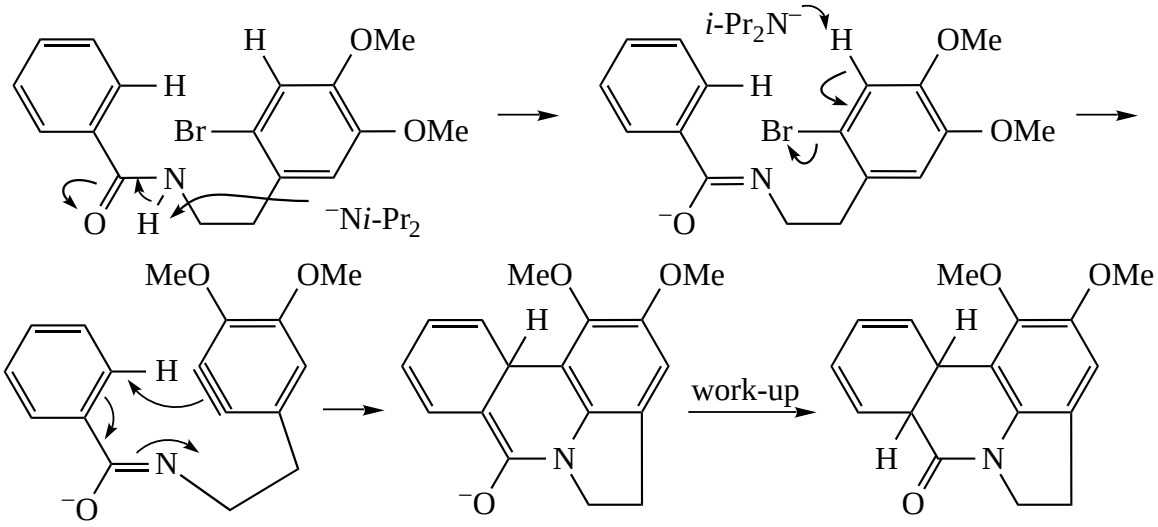
The immediate precursor retains the O6–C3 bond and would have a C8–O6 bond and a C8=C9 π bond. This calls for an S_N1 substitution at C8 to replace the C8–OMe bond with a C8–O6 bond and an E1 elimination to make the C8=C9 π bond. The overall reaction is an orthoamide Claisen rearrangement.



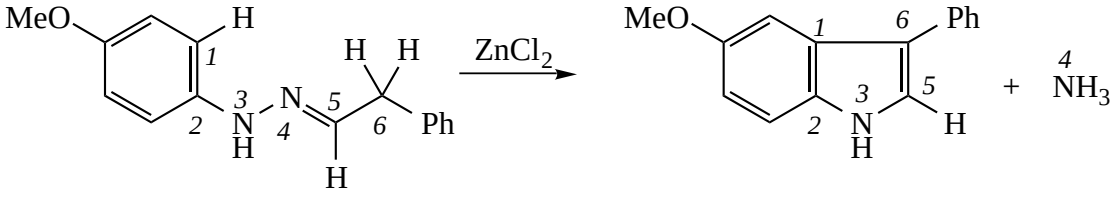
(p) Make: C1–C9, C2–N6.



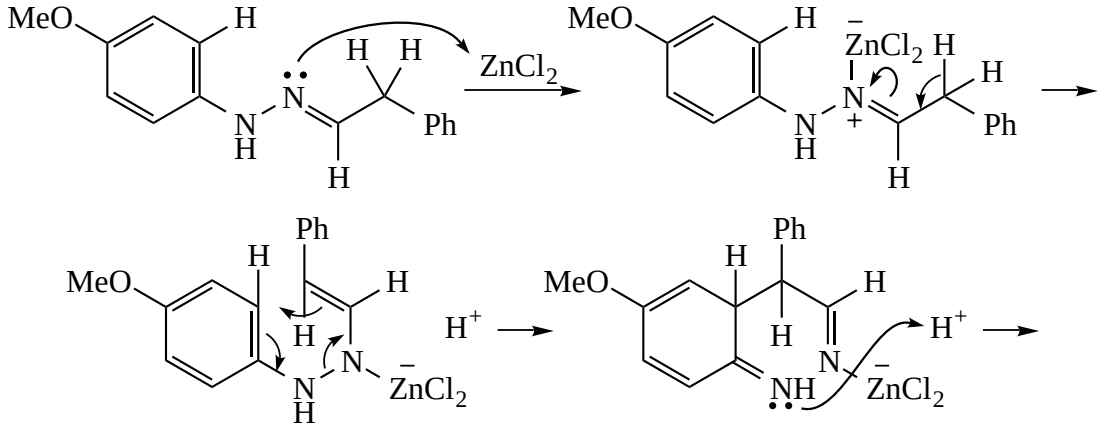
Since N6 and C9 are at the ends of a four-atom chain, we might expect a Diels–Alder reaction. The dienophile in such a reaction would be benzyne; the key is the benzene ring fused to the new six-membered ring and the fact that the H on C1 is gone in the product. (You could alternatively draw the π bond of the aromatic ring participating in the Diels–Alder reaction, but this is unlikely, because the π bonds of aromatic rings are very bad dienophiles.) The first equivalent of LDA deprotonates N to make the 1,3-diene across N6=C7–C8=C9; the second equivalent induces an E2 elimination across C1–C2 to give an aryne. Cycloaddition gives the enolate, which is protonated on C8 to give the observed product. In fact, this compound is not very stable, and it is oxidized by air to give the fully aromatic product.

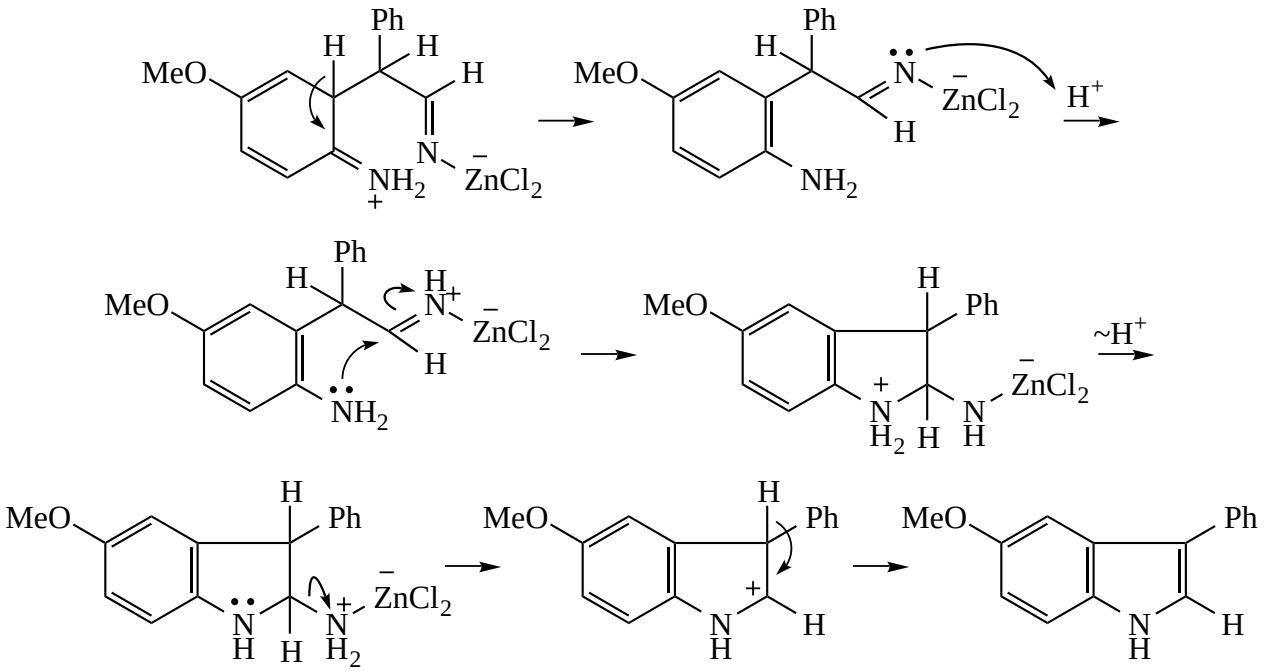


(q) Break: N3–N4, N4–C5. Make: C1–C6, N3–C5. We lose the elements of NH_3.

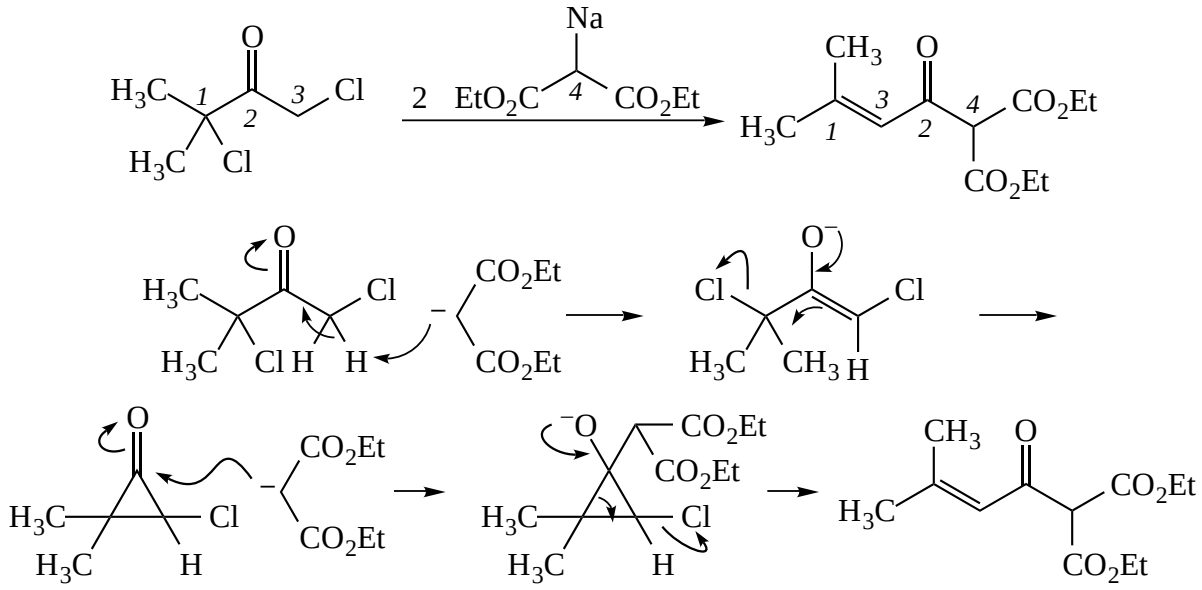


Since we are forming a σ bond at the end of a six-atom chain and breaking the σ bond in the middle, we might expect a Cope rearrangement. To do this, we must make a C5=C6 π bond. We can do this by transposing the N4=C5 π bond. This transposition converts an imine to an enamine, which is exactly analogous to converting a ketone to an enol. The enamine then undergoes Cope rearrangement to give the C1–C6 bond. (Note how this Cope rearrangement is analogous to the Claisen rearrangement of *O*-allyl-phenols.) After reestablishing aromaticity by tautomerization, nucleophilic N3 attacks electrophilic C5 to form the N3–C5 bond. Finally, E1 elimination of NH_3 gives the indole.

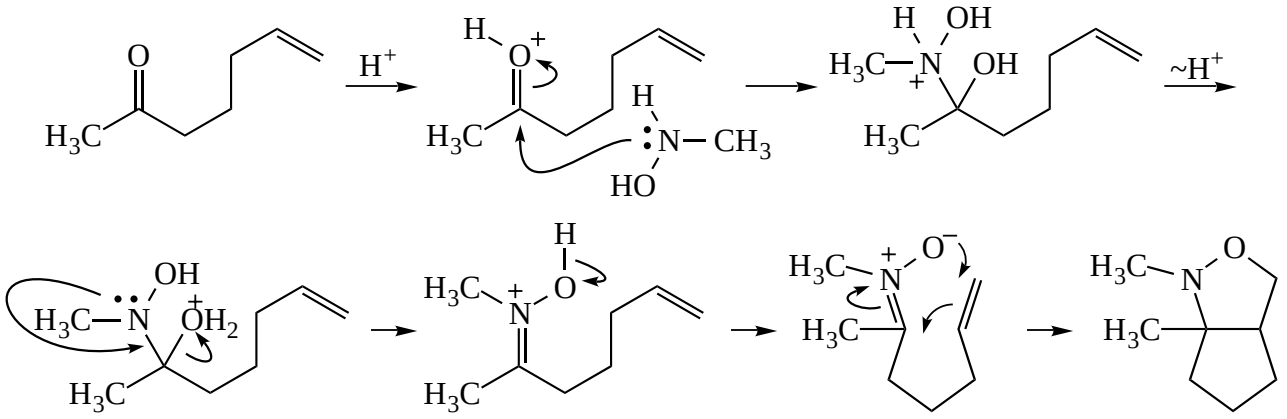




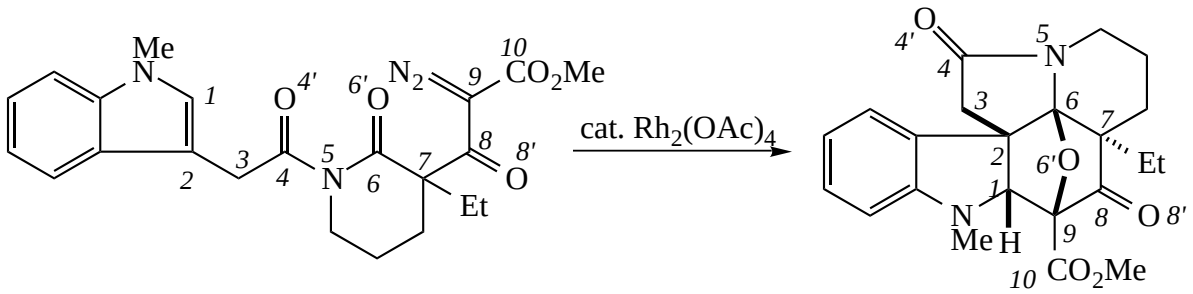
(r) Make: C2–C4, C1–C3. Break: C1–C2. Since only one equivalent of malonate is incorporated into the molecule, the other equivalent must act as a base. The migration of C1 from C2 to C3 is a 1,2-alkyl shift. Under these basic conditions, it is likely to proceed by a Favorskii mechanism. Deprotonation of C3 by malonate gives the enolate. Two-electron electrocyclic ring closing with expulsion of Cl^- gives the cyclopropanone. Attack of malonate on C2 gives a tetrahedral intermediate; fragmentation of this with expulsion of Cl^- gives the observed product. Other reasonable mechanisms can be drawn, some of which do not involve an electrocyclic ring closing.



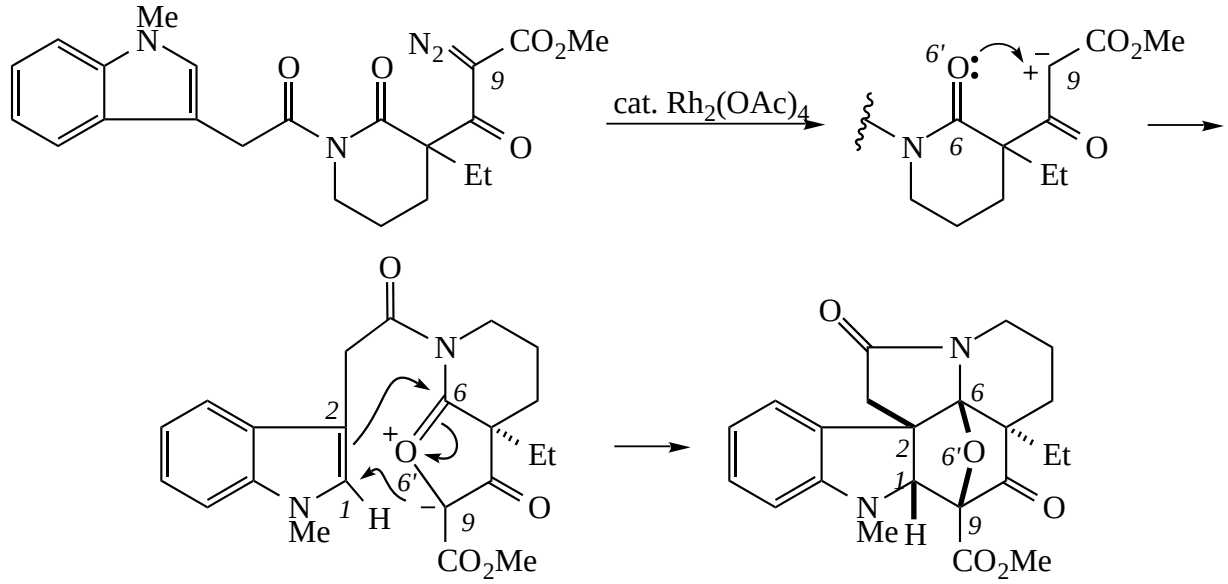
(s) The five-membered heterocycle should alert you to a 1,3-dipolar cycloaddition.



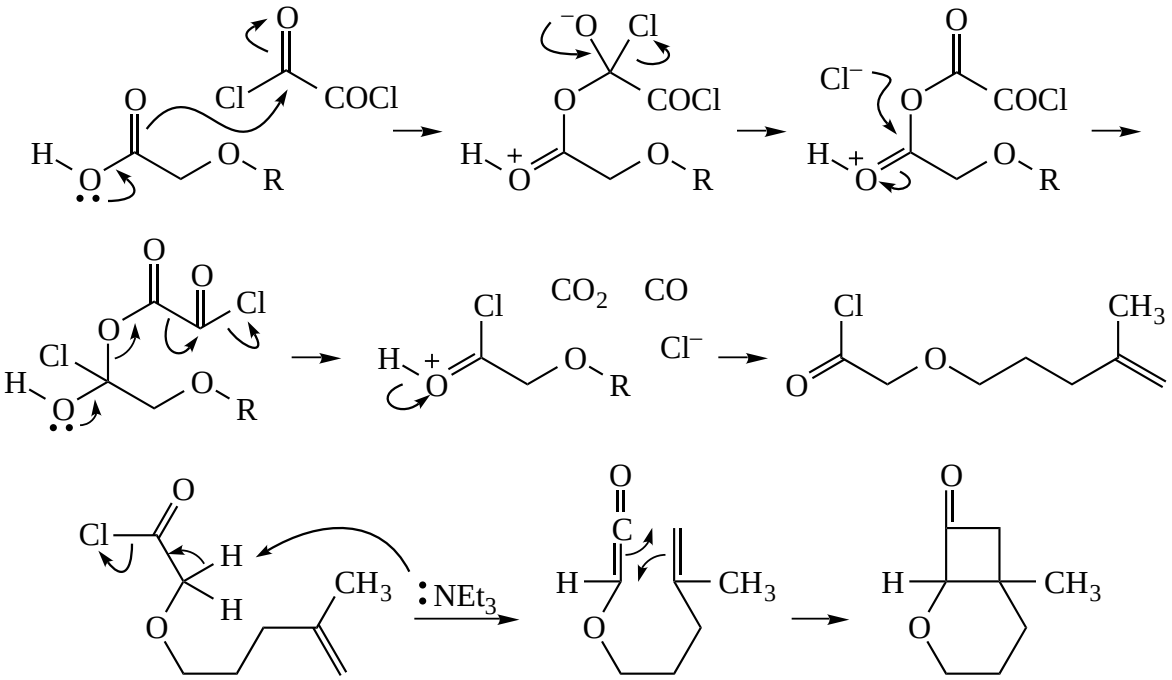
(t) Make: C1–C9, C2–C6, O6'–C9. Break: C9–N_2.



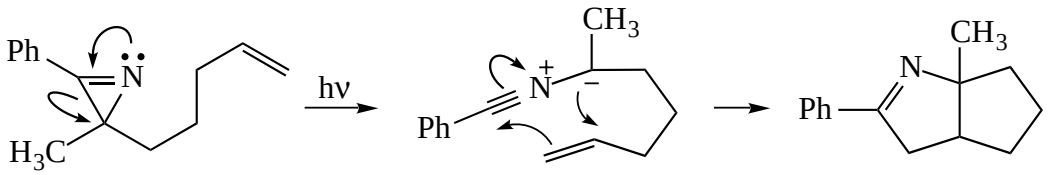
C6 and C9 are at opposite ends of a four-carbon unit, but since one of these atoms (C7) is saturated and quaternary, a Diels–Alder reaction is unlikely (can't make diene). The combination of a diazo compound with Rh(II) generates a carbenoid at C9. The nucleophile O6' can add to the empty orbital at C9, generating the O6'–C9 bond and a carbonyl ylide at C6–O6'–C9. Carbonyl ylides are 1,3-dipoles (negative charge on C9, formal positive charge on O6', electron deficiency at C6), so a 1,3-dipolar cycloaddition can now occur to join C2 to C6 and C1 to C9, giving the product. Note how a relatively simple tricyclic starting material is transformed into a complex hexacyclic product in just one step!



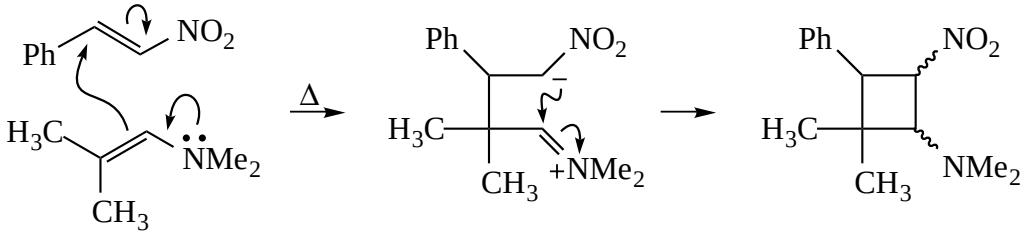
(u) The cyclobutanone should tip you off to a ketene–alkene cycloaddition. Ketenes are generally made by Et_3N-catalyzed elimination of HCl from acyl chlorides. Oxalyl chloride ClCOCOCl serves to convert the acid into an acid chloride.



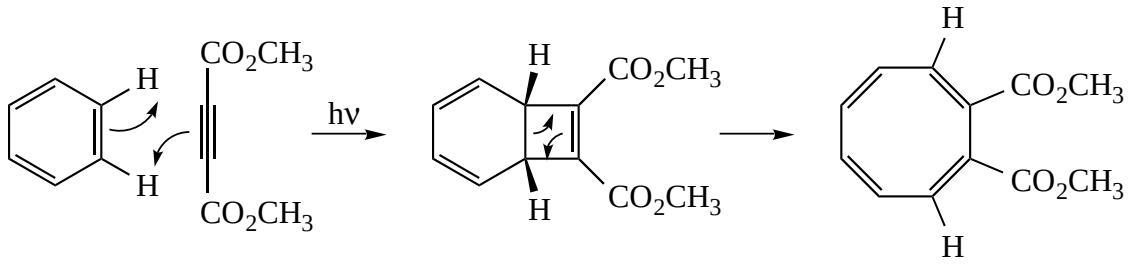
(v) Another five-membered heterocycle, another 1,3-dipolar cycloaddition. The first step is formation of the requisite 1,3-dipole, a nitrile ylide, by a two-electron electrocyclic ring opening. Then dipolar cycloaddition occurs.



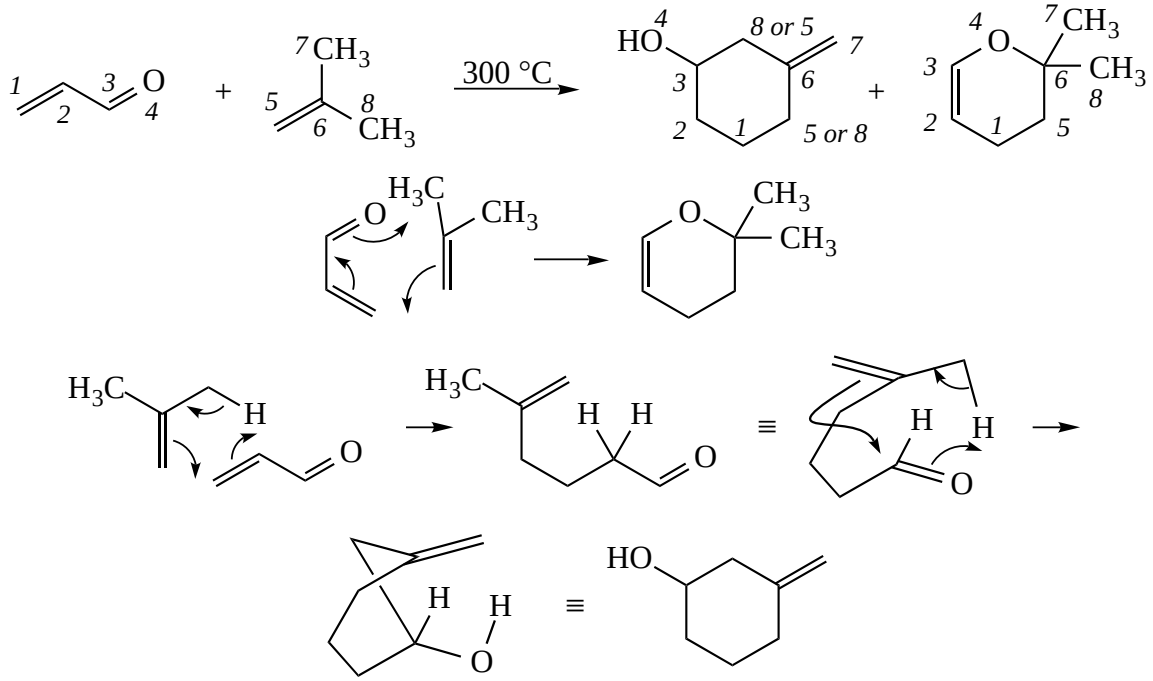
(w) *Formally* this reaction is a [2+2] cycloaddition. In practice, concerted [2+2] cycloadditions occur under thermal conditions *only* when one of the components is a ketene or has a π bond to a heavy element like P or a metal. Neither of the alkenes in this reaction fits the bill. However, one of these alkenes is very electron rich and the other is very electron poor, so a *nonconcerted*, two-step polar mechanism is likely.



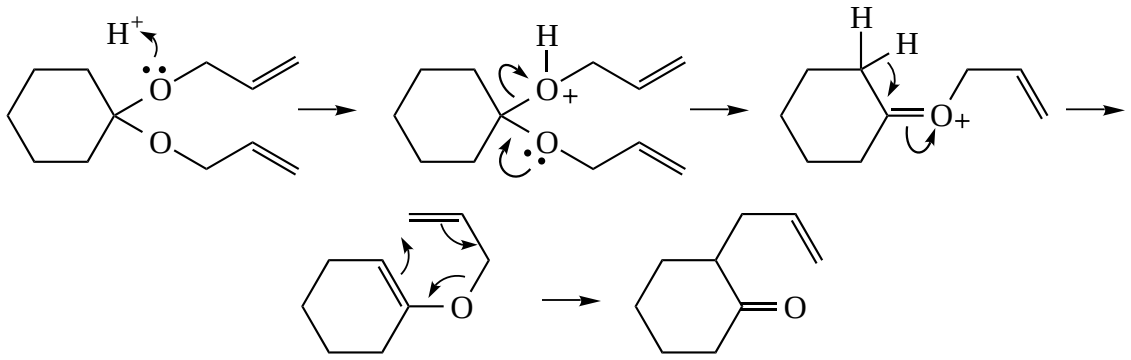
(x) The extra six C's must come from benzene. A photochemically allowed [2+2] cycloaddition between the alkyne and benzene gives an intermediate that can undergo disrotatory electrocyclic ring opening to give the observed product (after bond alternation). (Either two or three arrows can be drawn for the electrocyclic ring opening, but the TS for the reaction involves all eight π electrons, so to be disrotatory the reaction must be promoted photochemically.) Benzene does not usually undergo cycloaddition reactions, but here it evidently does.



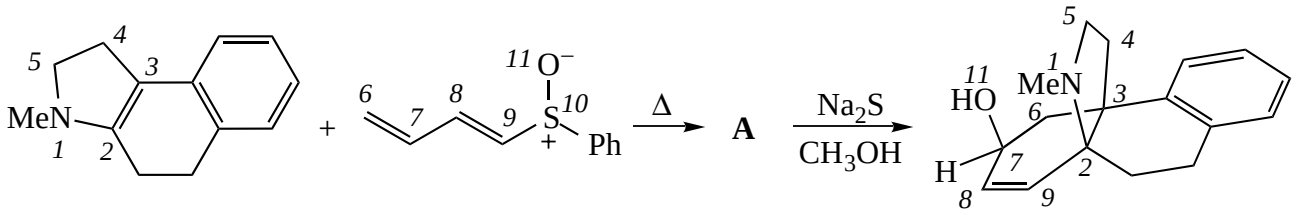
(y) The second product is clearly obtained by a hetero-Diels–Alder reaction between acrolein and isobutylene. The first product is less obvious. Two new C–C bonds are formed, and H atoms are transferred from C7 and C8 to C2 and O4. This suggests two ene reactions.



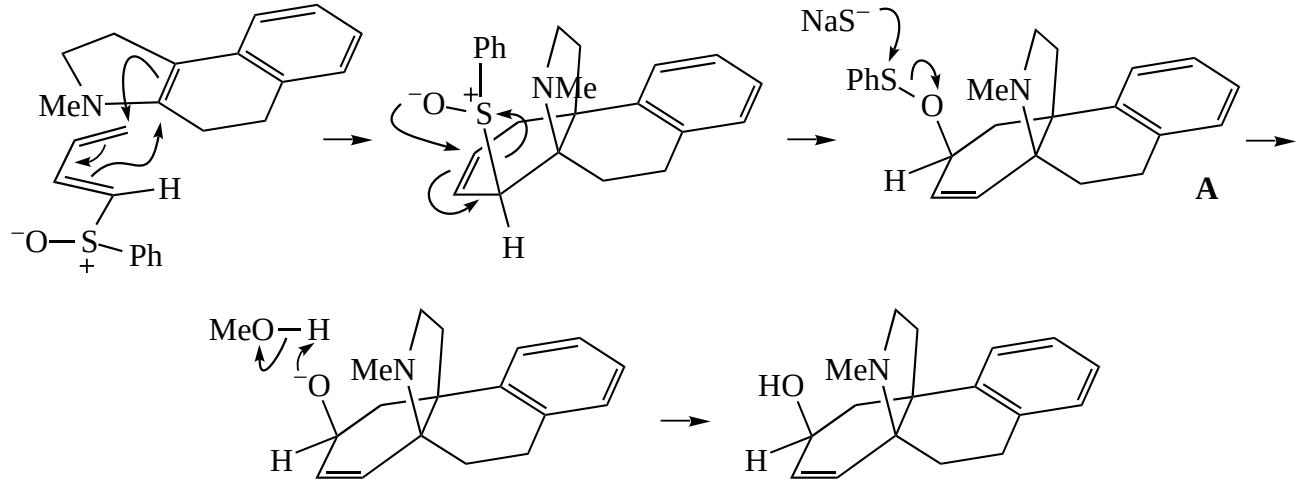
(z) Elimination of allyl alcohol occurs by an E1 mechanism. Then a Claisen rearrangement gives the product.



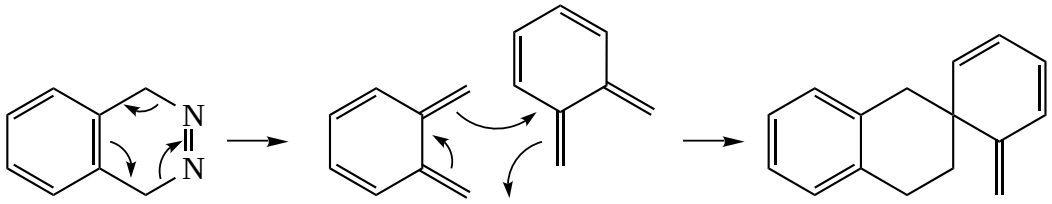
(aa) The C6 to C9 unit in the product is numbered by virtue of the two H's on C6. Make: C2–C9, C3–C6, C7–O11. Break: C9–S10, S10–O11.



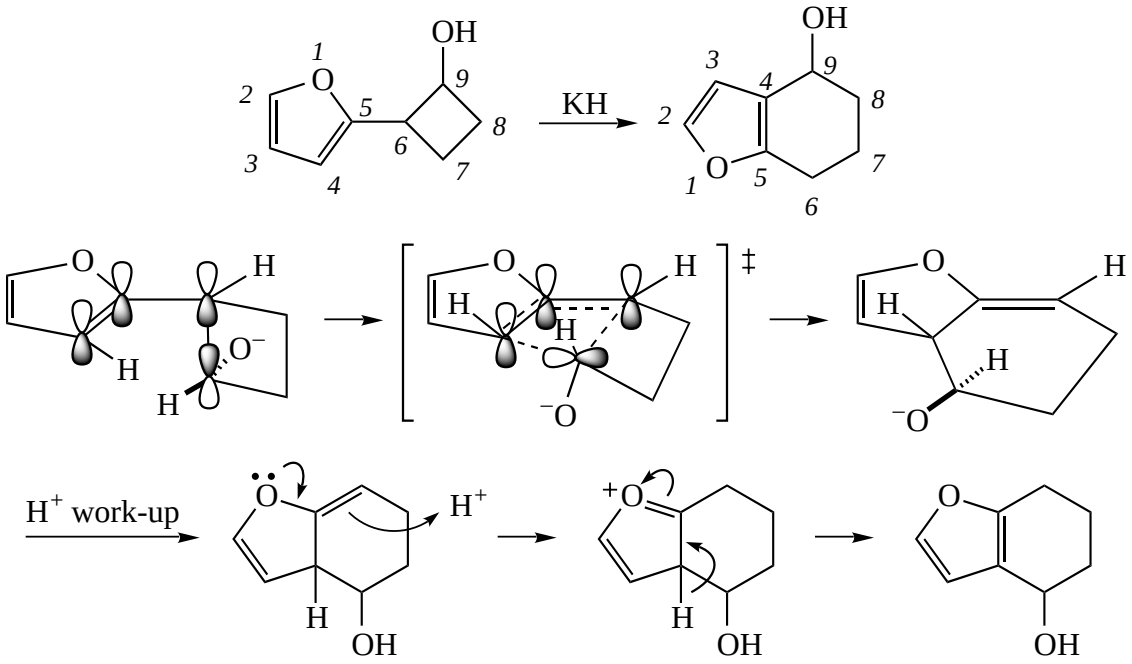
Formation of C2–C9 and C3–C6 suggests a Diels–Alder reaction, this one of the inverse electron demand flavor. The regioselectivity follows the *ortho-para* rule and the stereoselectivity is *endo.* The C7–O11 bond can now be formed and the C9–S10 bond cleaved by a [2,3] sigmatropic rearrangement to give compound **A**. All that is left is to cleave the S10–O11 bond. Na_2S attacks S, with RO^- acting as the leaving group, and protonation gives the final product.



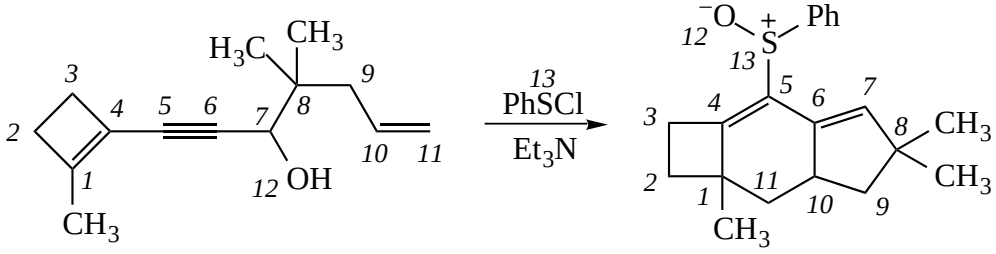
(bb) Retro Diels–Alder reaction gives off N_2 and an *ortho*-xylylene. With no other substrates available, this extremely reactive substance dimerizes in another Diels–Alder reaction to give the product.



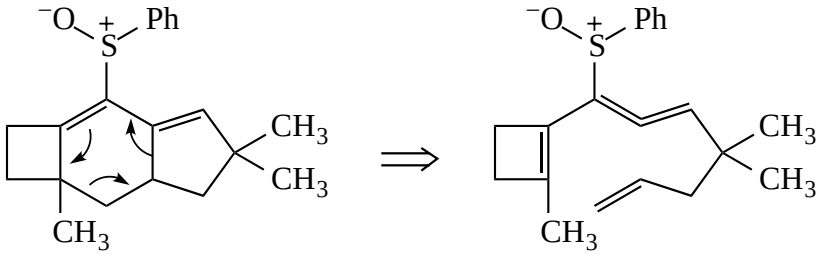
(cc) The product is formally the result of a [1,3] sigmatropic rearrangement. ***STOP!*** [1,3] sigmatroopic rearrangements are very rare, and they should be viewed with suspicion. They are thermally allowed only when one of the components is antarafacial. Sometimes an apparent [1,3] shift is actually the result of two sequential reactions (polar or pericyclic). In this case, the presence of KH suggests an oxyanion-accelerated concerted process. The one-atom component can be antarafacial if the *back* lobe of the sp^3 orbital used to make the old bond to C6 is then used to make the new bond to C4. After workup, aromaticity is reestablished by protonation-deprotonation.



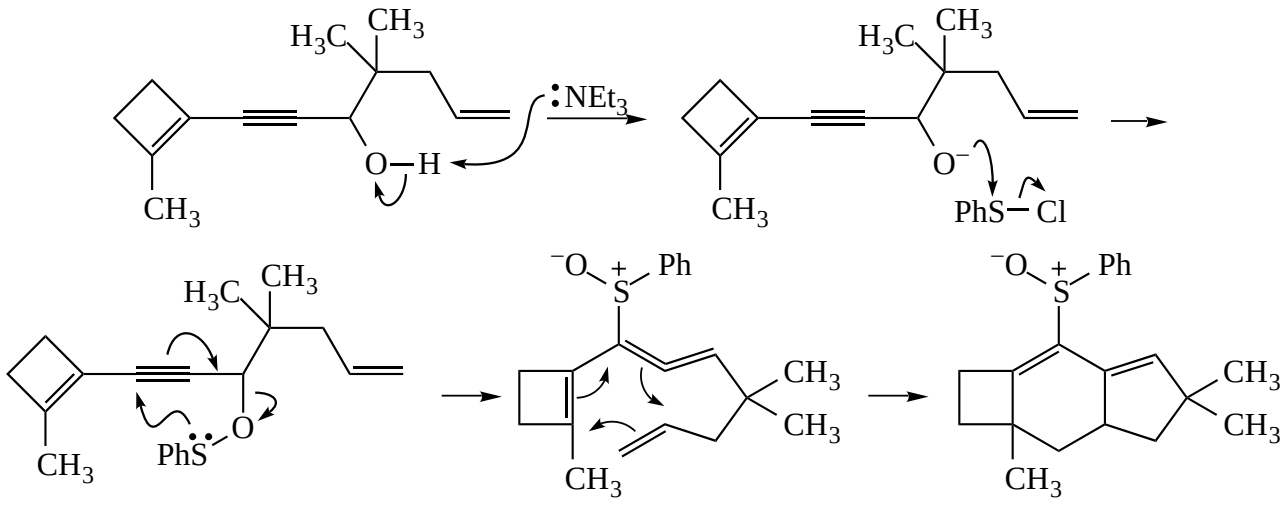
(dd) Make: C1–C11, C5–S13, C6–C10, O12–S13. Break: C7–O12, S13–Cl.



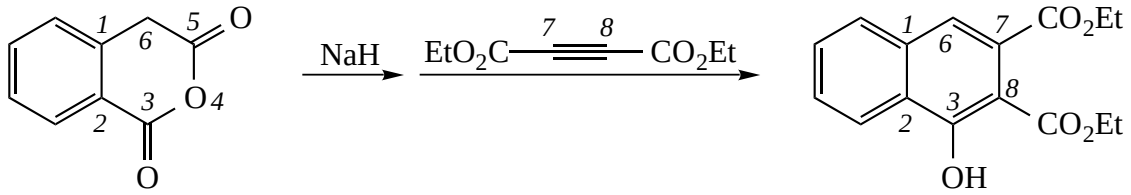
The product looks very much like the result of a Diels–Alder reaction that forms the C1–C11 and C6–C10 bonds. Work backwards one step from the product.



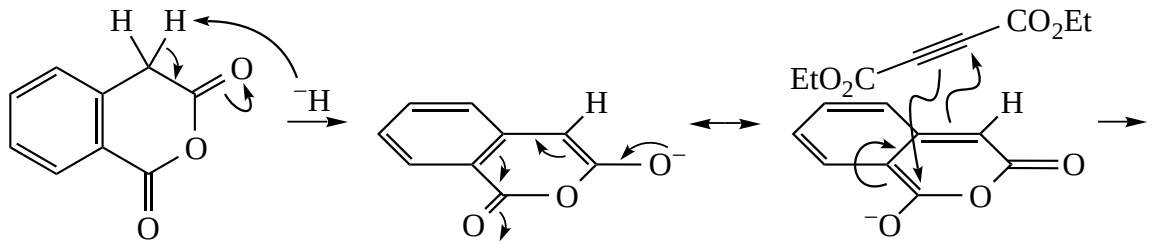
The intermediate might be made by a [2,3] sigmatropic rearrangement of an RO–SPh compound.

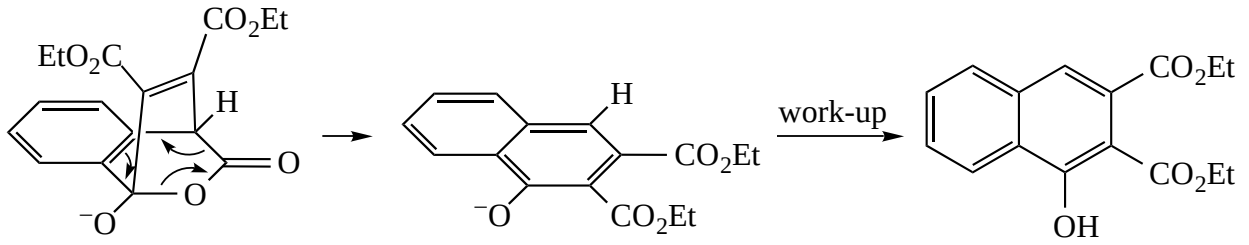


(ee) Make: C6–C7, C3–C8. Break: C5–C6, C3–O4.

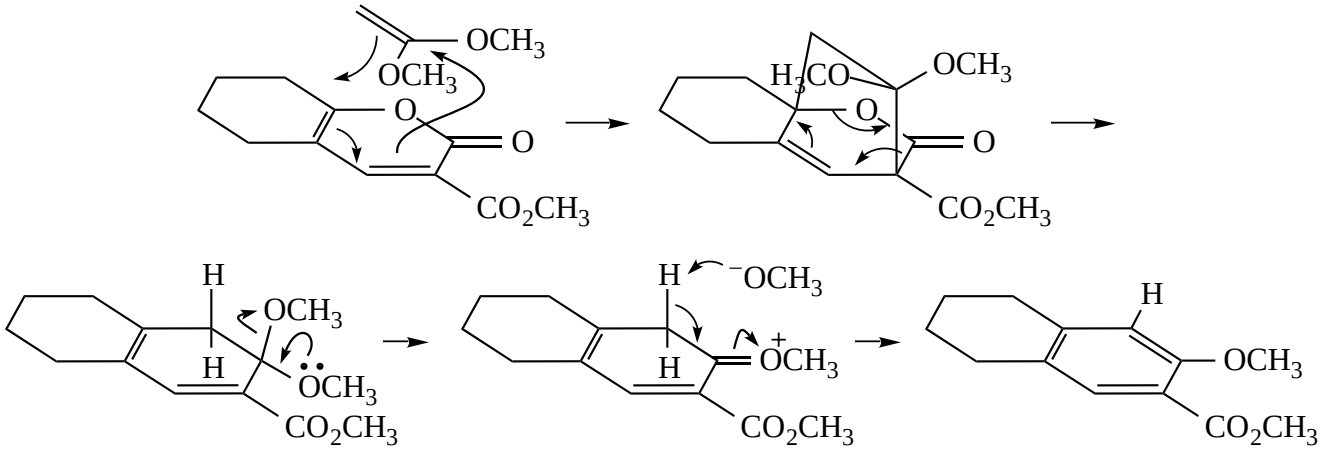


The two new bonds can be obtained by a Diels–Alder reaction. First, deprotonation gives an enolate that has an *ortho*-xylylene resonance structure. Diels–Alder reaction followed by retro-Diels–Alder reaction gives the product.

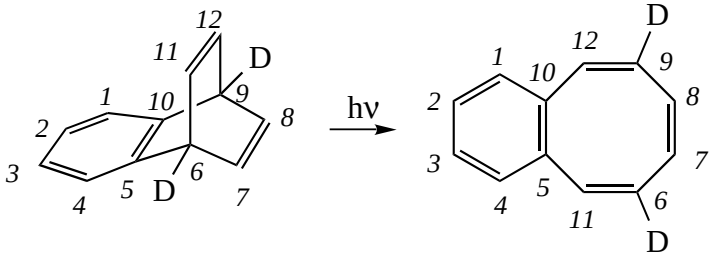




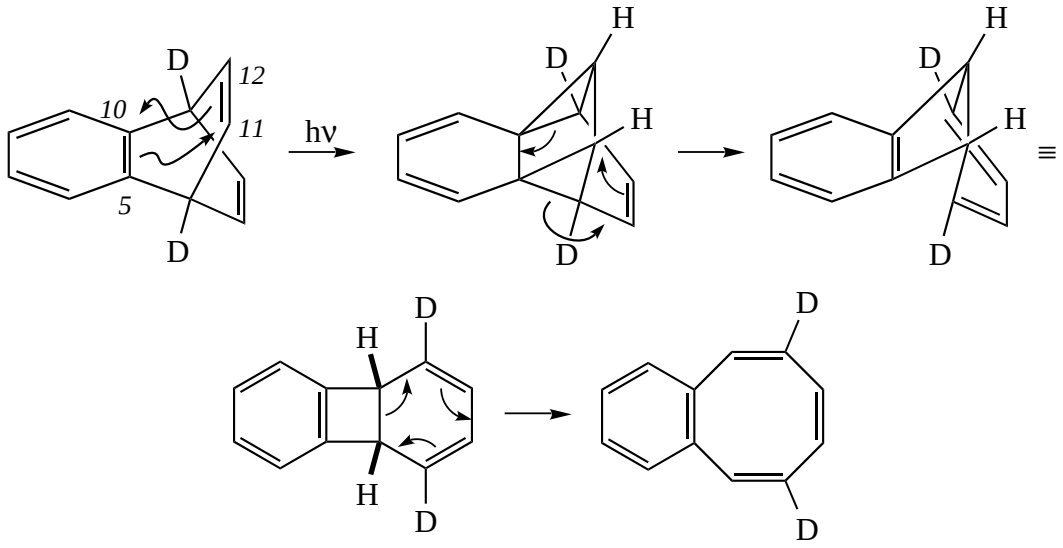
(ff) As in the previous problem, Diels–Alder reaction followed by retro-Diels–Alder reaction establishes the desired C–C bonds. Then E1 elimination of CH_3OH gives the desired product. (An E1cb mechanism for elimination is also reasonable, but less likely in the absence of strong base.)



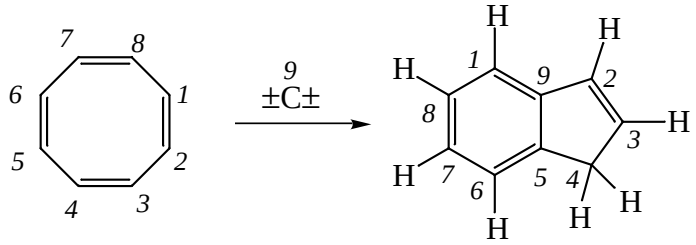
(gg) The D atoms give major clues to the numbering. Break: C5–C6, C9–C10, C11–C12. Make: C5–C11, C10–C12.



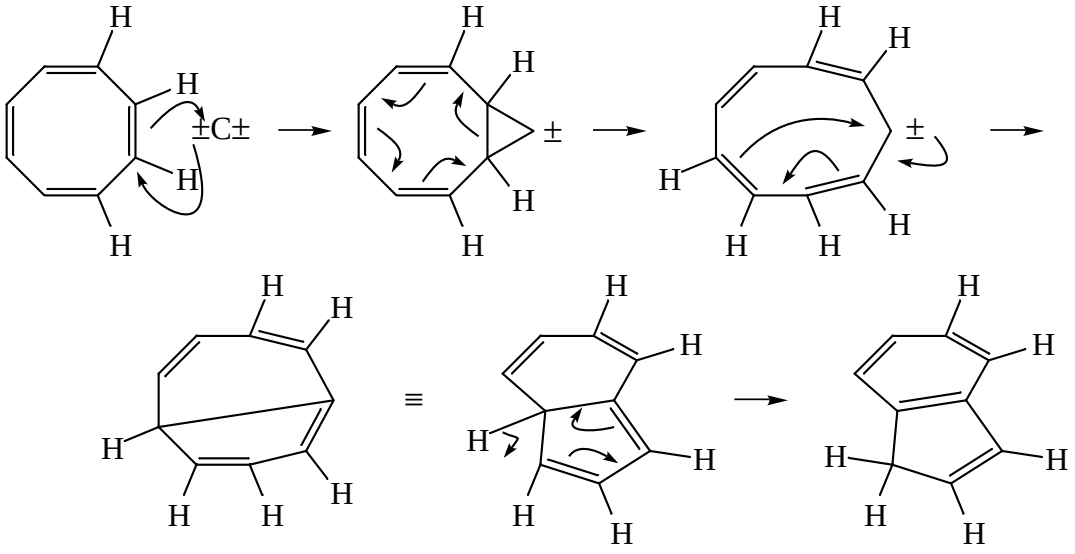
If we break the C5–C6 and C9–C10 bonds by a retro-Diels–Alder reaction first, we get two molecules of benzene. But irradiation of benzene doesn't give the observed product, so this can't be right. Instead, let's form the C5–C11 and C10–C12 bonds first by a (photochemically allowed) [2+2] cycloaddition. This gives the strained polycyclic compound shown. Now the C5–C6 and C10–C9 bonds can be broken by a [4+2] retro-cycloaddition (thermal, supra with respect to both components) to give the tricyclic compound. This compound can then undergo disrotatory six-electron electrocyclic ring opening (thermal) to give the observed product. Note that only the first reaction in this series requires light.



(hh) Numbering the product is difficult. Because C9 in the starting material has no H atoms, let's make it one of the C's in the product that has no H atoms. Make: C1–C9, C2–C9, C5–C9. Break: C1–C2.

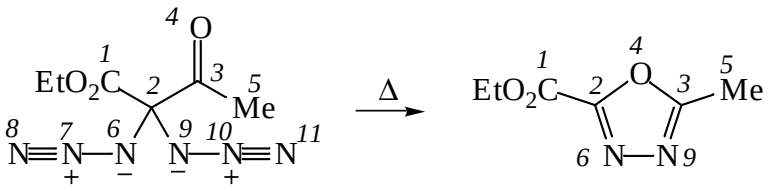


Carbenes like to do [2 + 1] cycloadditions to alkenes. Such a cycloaddition between C9 and the C1=C2 π bond gives a product which can undergo an 8-electron electrocyclic ring opening to cleave the C1–C2 bond, then a 6-electron electrocyclic ring closing to form the C5–C9 bond. All that is left to do is a [1,5] sigmatropic rearrangement to move the C5 H to C4.

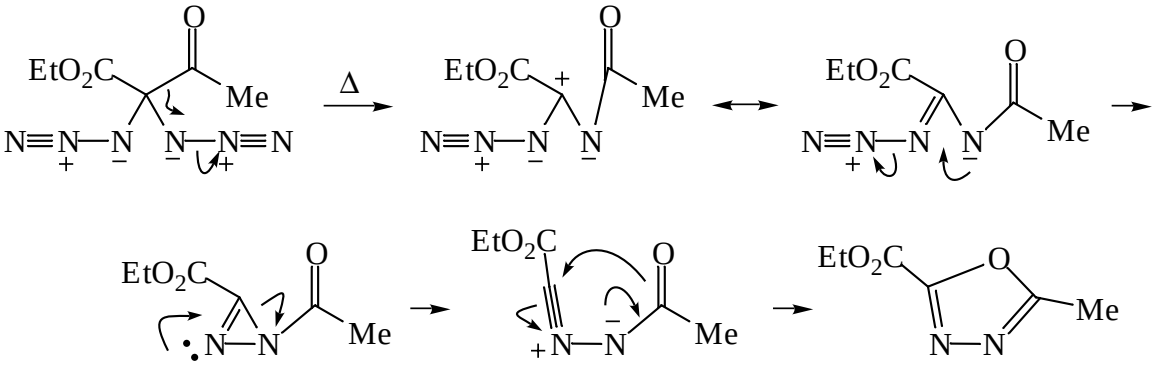


(ii) Following the instructions, we number all the N atoms. The byproducts are 2 N_2. Make: C2–O4,

C3–N9, N6–N9. Break: C2–N9, N6–N7, N9–N10.

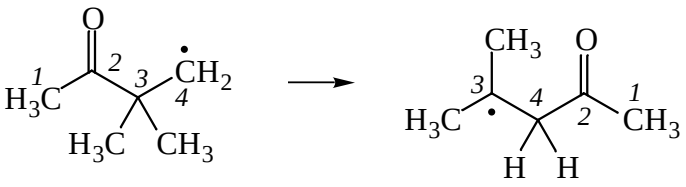


The thermal reaction that azides undergo is the Wolff rearrangement (Chapter 2). In the present case, the Wolff rearrangement allows us to make the C3–N9 bond and cleave the N9–N10 bond. A resonance structure can be drawn in which N9 has a negative charge. This lone pair is used to attack N6, displacing N_2. Next, the C2–N9 bond is cleaved by a 4-electron electrocyclic ring opening to give a nitrilimine, which then undergoes a 6-electron electrocyclic ring closure to give the product.

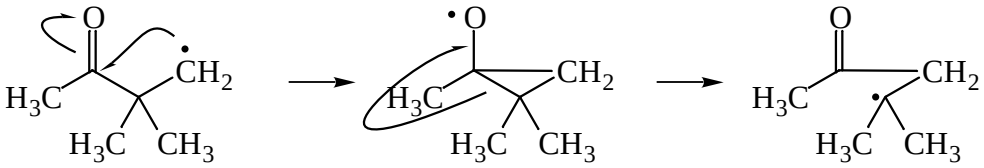


Answers To Chapter 5 In-Chapter Problems.

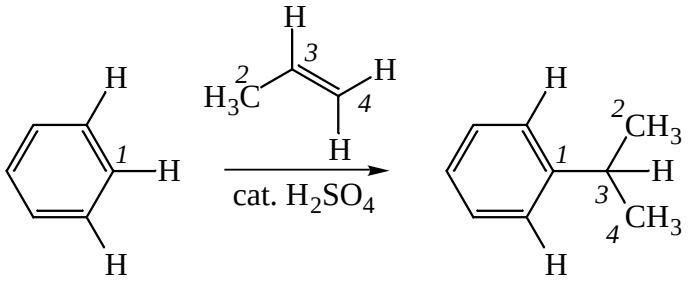
5.1. Make: C2–C4. Break: C2–C3.



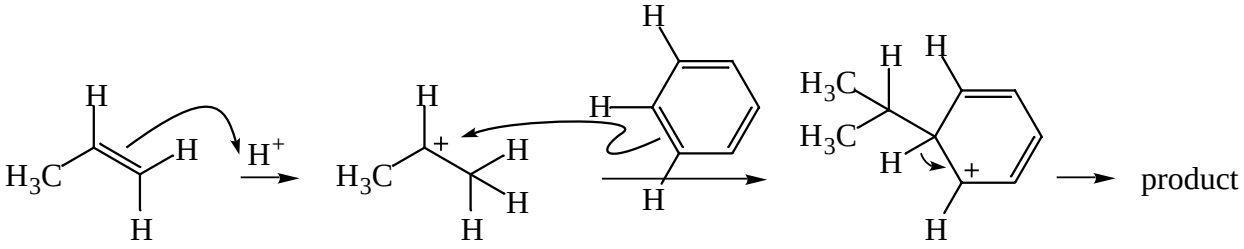
If this compound were not a radical, you might suspect a [1,2] sigmatropic rearrangement. However, radicals do not undergo such rearrangements. The C4 radical can make a bond to C2 by adding to the π bond. Then the C3–C2 bond can break by fragmentation.



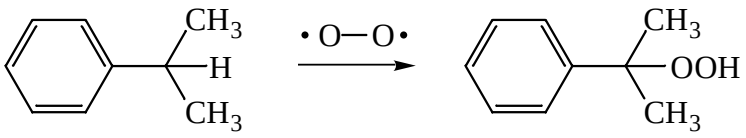
5.2. Step 1. Make: C1–C3. Break: none.



Note: This reaction involves a polar acidic mechanism, not a free-radical mechanism! It is a Friedel–Crafts alkylation, with the slight variation that the requisite carbocation is made by protonation of an alkene instead of ionization of an alkyl halide. Protonation of C4 gives a C3 carbocation. Addition to C1 and fragmentation gives the product.

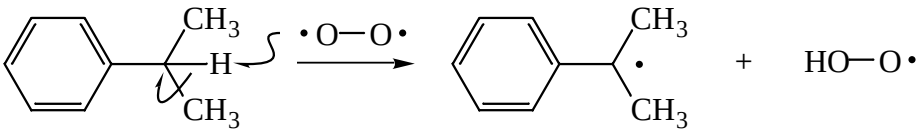


Step 2. Only a C–O bond is made.



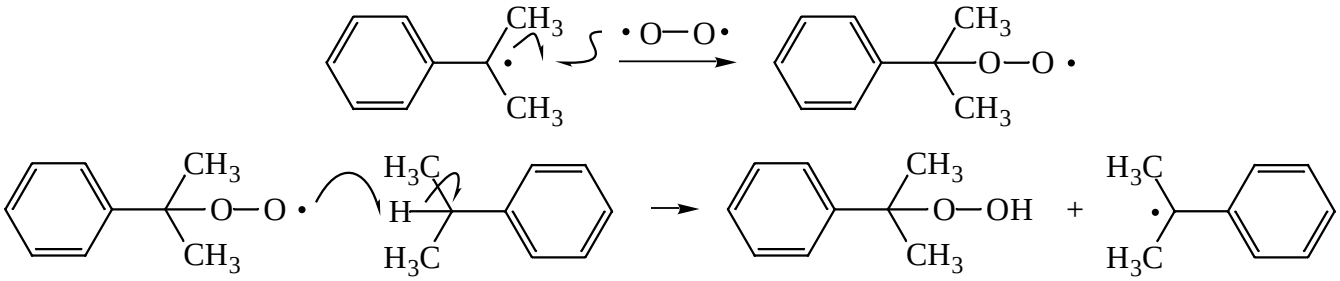
The presence of O_2 clues you in that this is a free-radical mechanism, specifically a free-radical substitution. Because it is an intermolecular substitution reaction, it probably proceeds by a chain mechanism. As such it has three parts: initiation, propagation, and termination. (We do not draw termination parts in this book.) The initiation part turns one of the stoichiometric starting materials into an odd-electron radical. This can be done here by abstraction of H· from C by O_2.

Initiation:

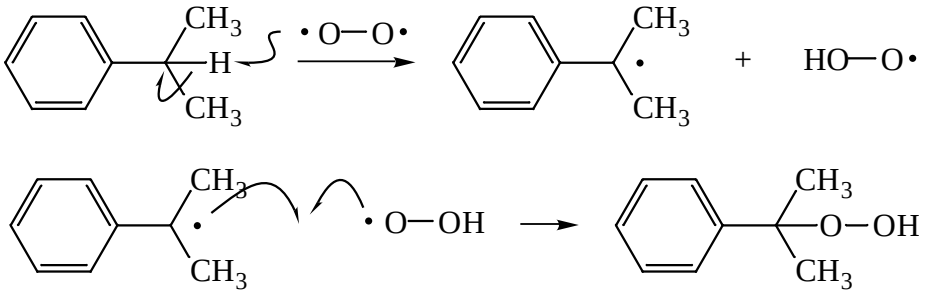


The propagation part begins with the radical generated in the initiation part, and it continues until all the starting materials are converted into products. Every individual step in the propagation part must have an odd number of electrons on each side of the arrow, and the last step must regenerate the radical that was used in the first step. Here the C radical combines with O_2 to give an O radical, and this O radical abstracts H· from starting material to give the product and to regenerate the C radical.

Propagation:

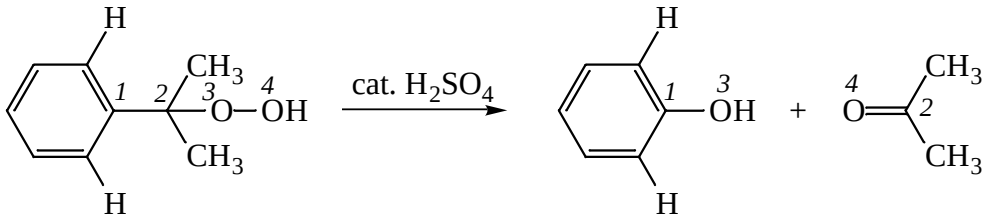


Although it is tempting to draw the following mechanism, the temptation should be resisted because it is not a chain mechanism.

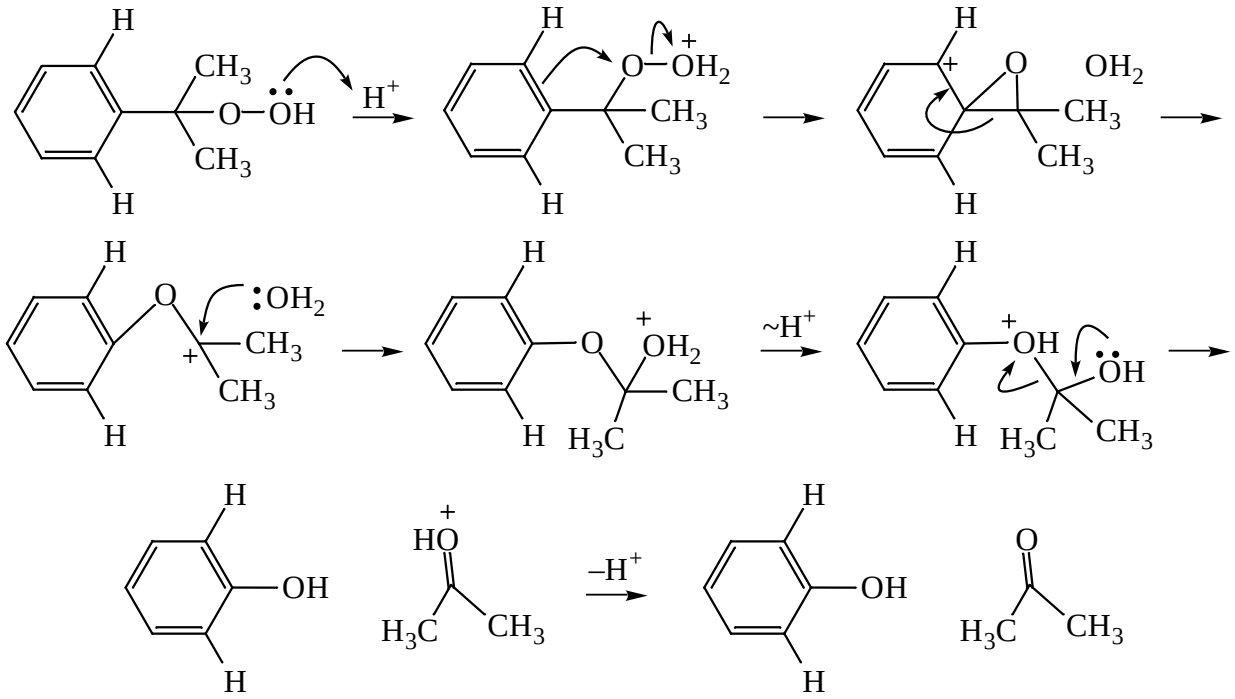


Step 3. The numbering of the atoms in this polar acidic mechanism is not straightforward, because it is

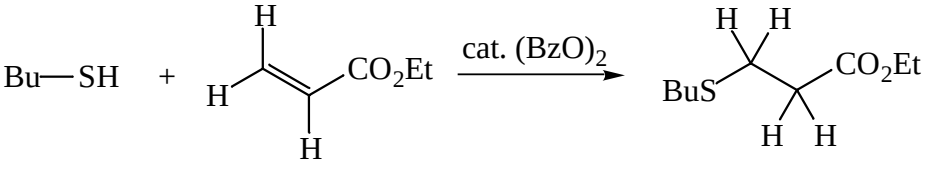
not clear whether C1 ends up bound to O3 or O4. However, if it ends up bound to O3, then we can draw a 1,2-alkyl shift (break C1–C2, make C1–O3) with expulsion of a leaving group (break O3–O4). Then O4 can add to the new C2 carbocation, and the resulting hemiacetal can collapse to phenol and acetone.



Actually, a two-step 1,2-alkyl shift has to be drawn, because Ph groups do not undergo concerted 1,2-shifts; instead their π bonds participate in an addition–fragmentation process.

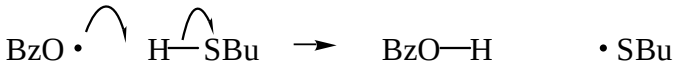


5.3. This addition reaction proceeds by a chain mechanism.



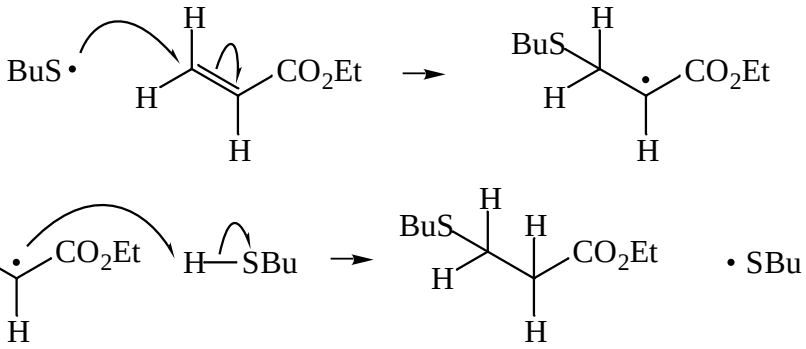
In the initiation part, one of the stoichiometric starting materials is converted into a free radical. The BzO· produced from $(BzO)_2$ can abstract H· from BuSH to give BuS·.

Initiation:

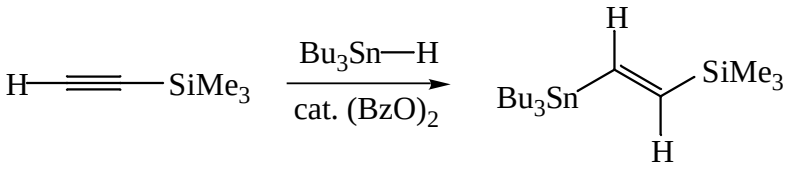


In the propagation part, BuS· adds to the alkene to give an alkyl radical, which abstracts H· from BuSH to give the product and to regenerate the starting radical.

Propagation:

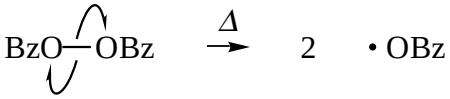


5.4. This addition reaction proceeds by a chain mechanism.



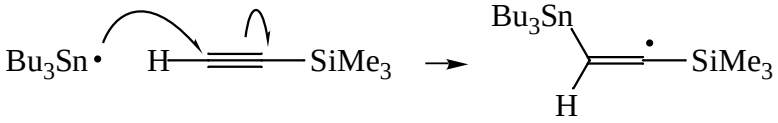
In the initiation part, the BzO· produced from $(BzO)_2$ can abstract H· from Bu_3SnH to give Bu_3Sn·.

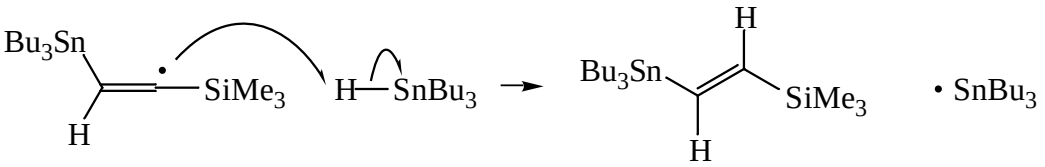
Initiation:



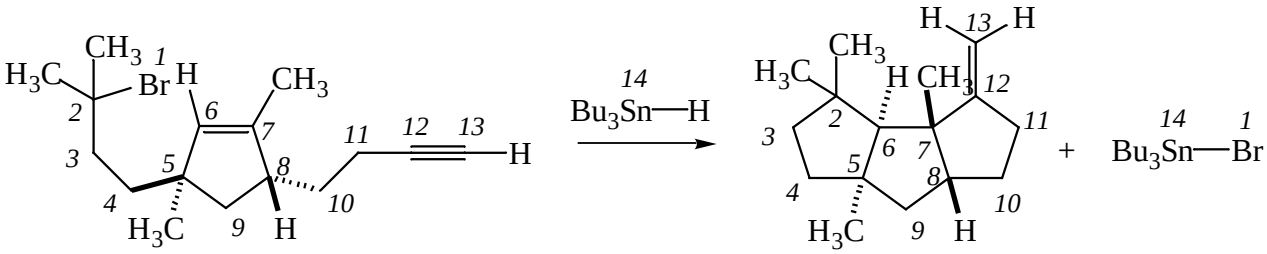
In the propagation part, Bu_3Sn· adds to the alkyne to give an alkenyl radical, which abstracts H· from Bu_3SnH to give the product and to regenerate the starting radical.

Propagation:





5.5(a). Make: Br1–Sn14, C2–C6, C7–C12. Break: Br1–C2.

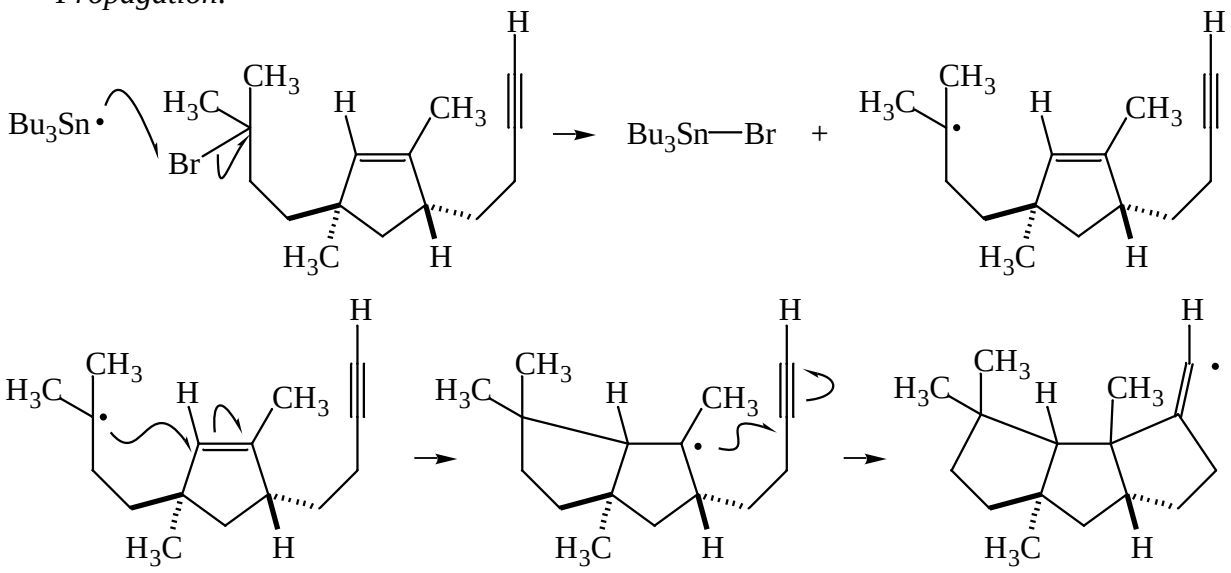


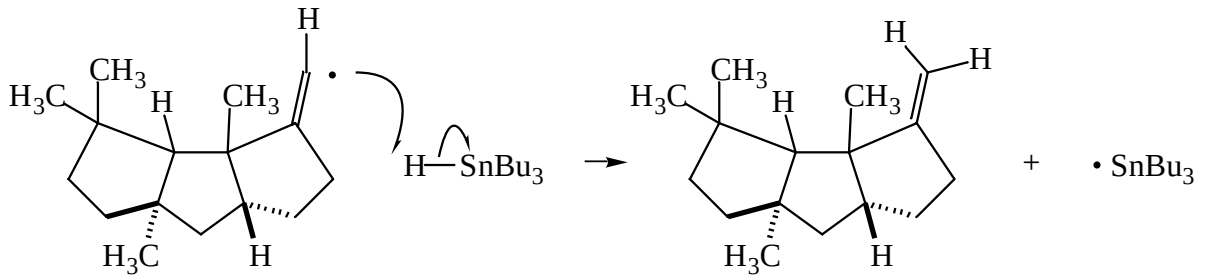
This is overall a substitution reaction — the C2–Br1 and Sn14–H σ bonds are swapped — so it is almost certainly a chain reaction. No initiator is listed, but it is likely that ambient air provides enough O_2 to abstract H· from Sn14.

Initiation:

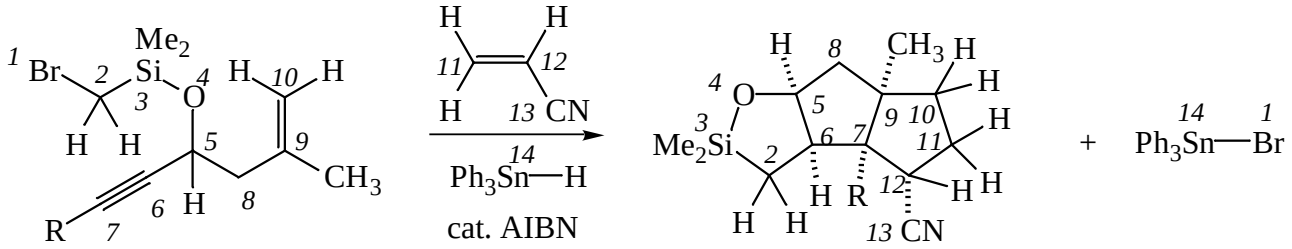
Bu_3Sn· abstracts Br1 from C2. The C2 radical then adds to C6 to give a C7 radical, which adds to C12 to give a C13 radical. The C13 radical abstracts H· from Bu_3SnH to give the product and regenerate Bu_3Sn·.

Propagation:



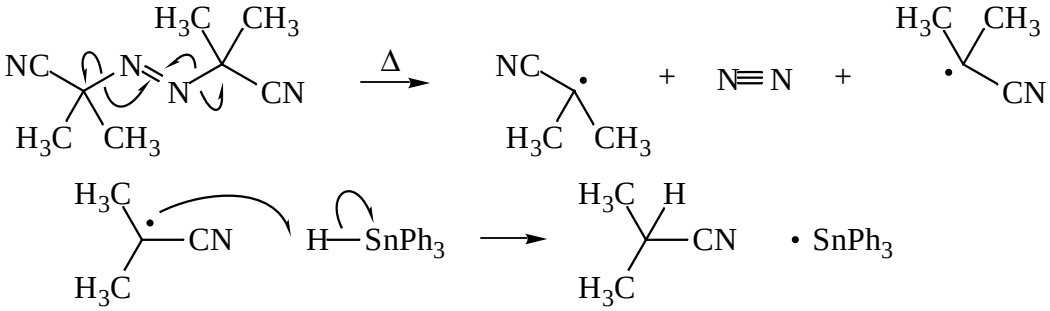


5.5(b). Make: Br1–Sn14, C2–C6, C7–C9, C7–C12, C10–C11. Break: Br1–C2.



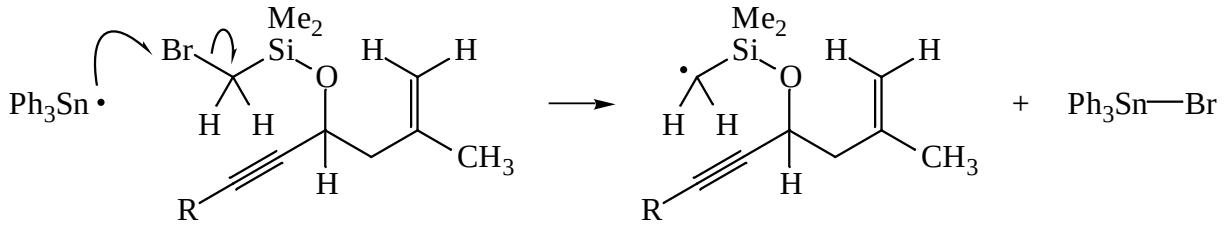
AIBN is a very common initiator of free radical reactions. The radical derived from its fragmentation abstracts H· from Ph_3SnH to give Ph_3Sn·.

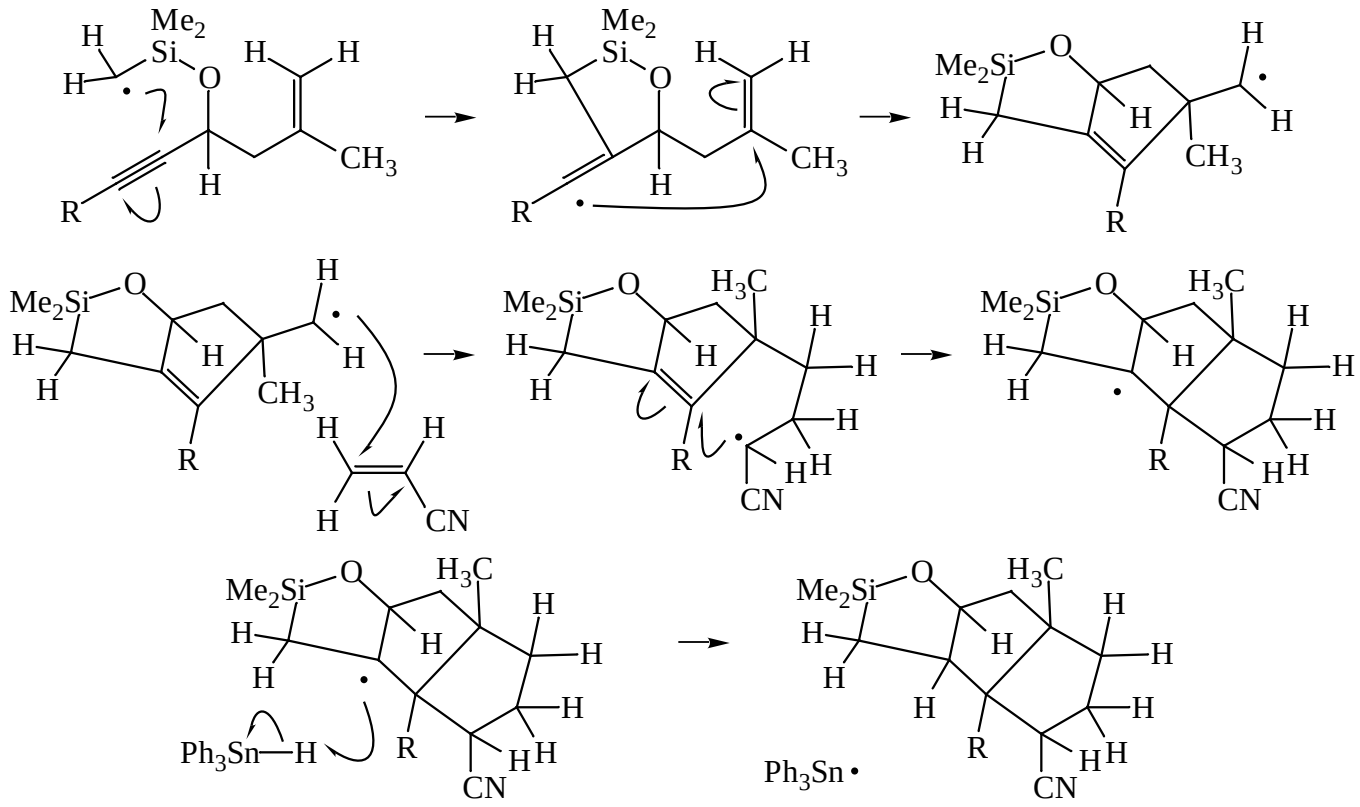
Initiation:



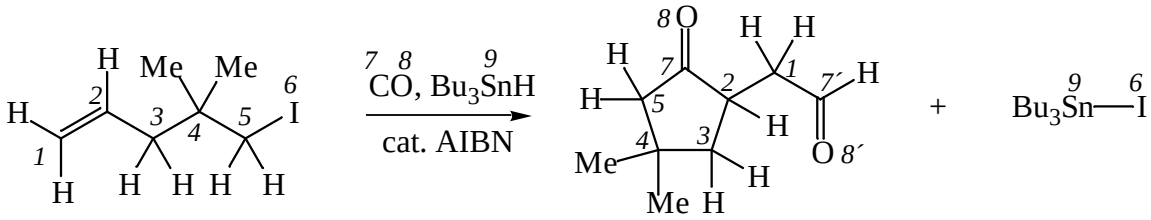
Ph_3Sn· abstracts Br1 from C2. The C2 radical then adds to C6 to give a C7 radical, which adds to C9 to give a C10 radical. (Why not have C7 add to C12 instead of C9 at this point? Because addition to C9 is intramolecular and forms a five-membered ring, making this addition very fast.) Now C10 adds to C11 to give a C12 radical, which can then add to C7 to give a C6 radical. C6 then abstracts H· from Ph_3SnH to give the product and regenerate Ph_3Sn·.

Propagation:



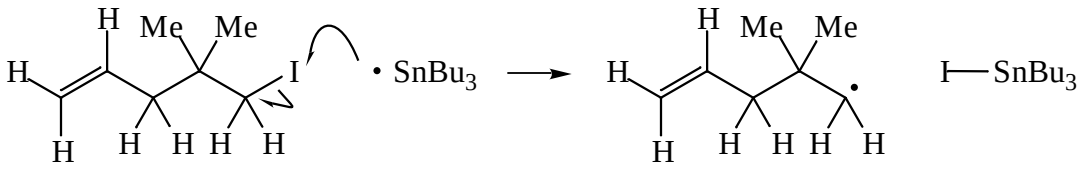


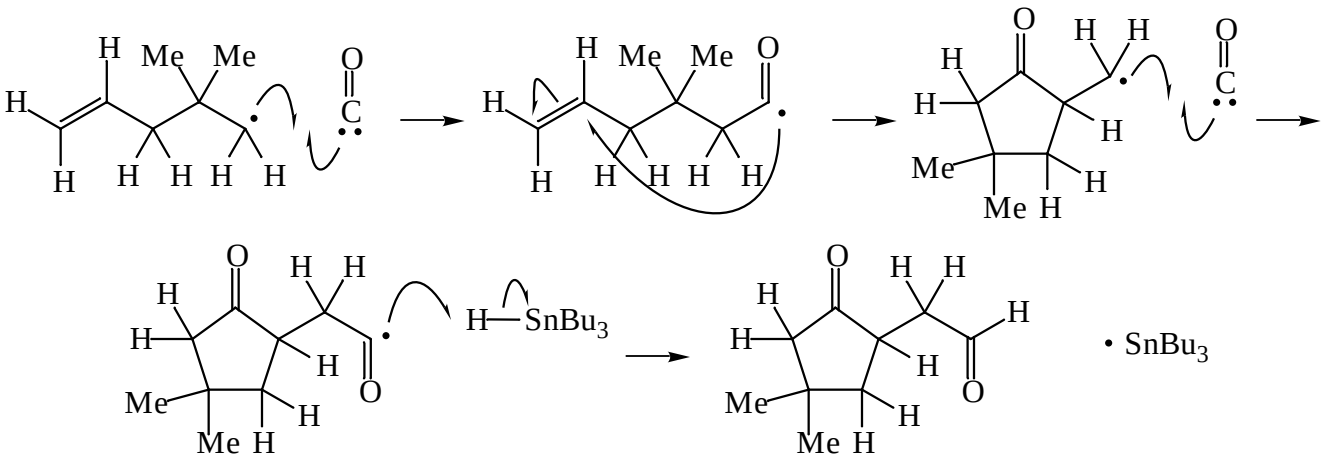
5.6. Make: C1–C7´, C2–C7, C5–C7, I6–Sn9. Break: C5–I6.



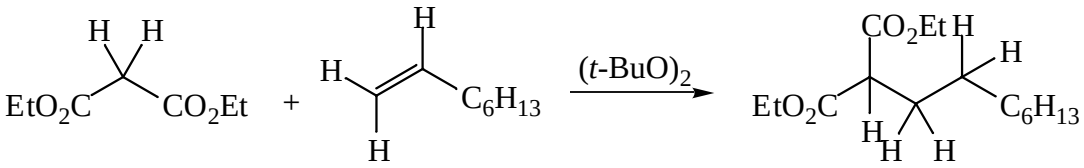
The initiation is the same as for 5.5(b). In the propagation part, Sn· abstracts I· from C5. The C5 radical then adds to C7 of CO to make a new C7 radical. The C7 radical adds to C2 to make a C1 radical, which adds to C7´ of a second equivalent of CO to make a C7´ radical. C7´ then abstracts H· from Bu_3SnH to give the product and regenerate Bu_3Sn·.

Propagation:



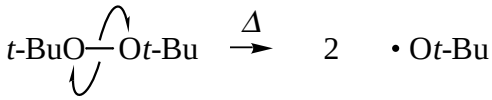


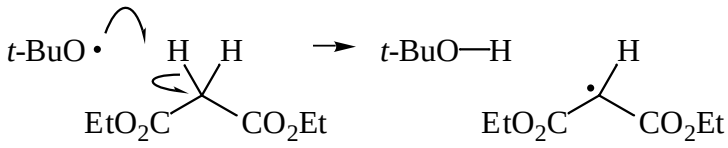
5.7(a). One C–C bond is made, and no bonds are broken.



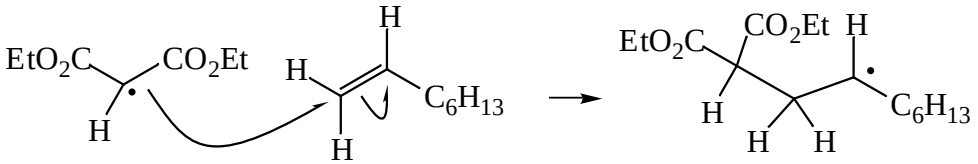
The *t*-BuO· abstracts H· from malonate in the initiation part. A free radical addition mechanism like the one in problem 5.3 ensues.

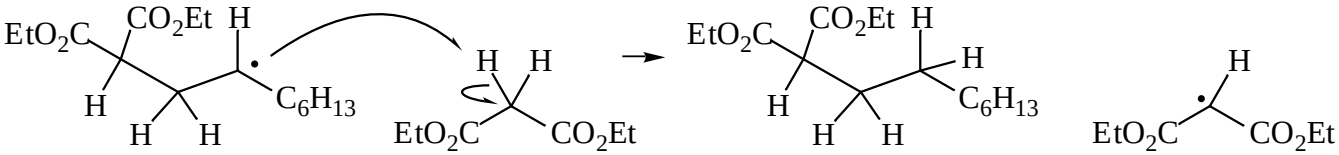
Initiation:



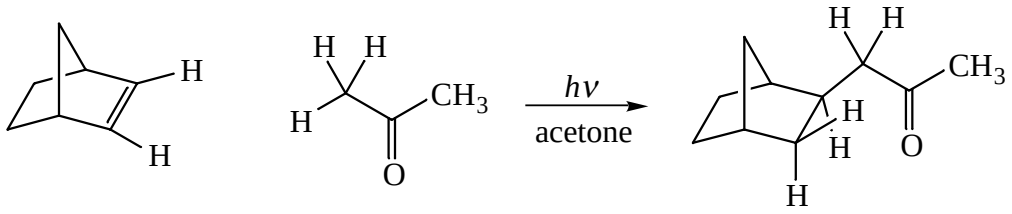


Propagation:



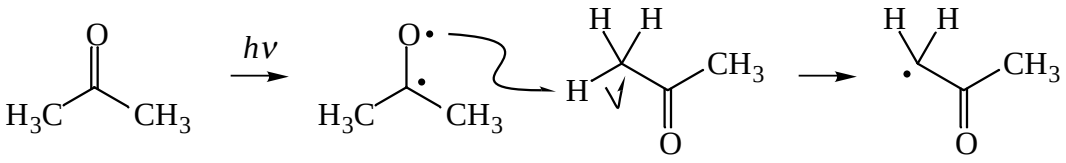


5.7(b). Again, one C–C bond is made, and no bonds are broken.



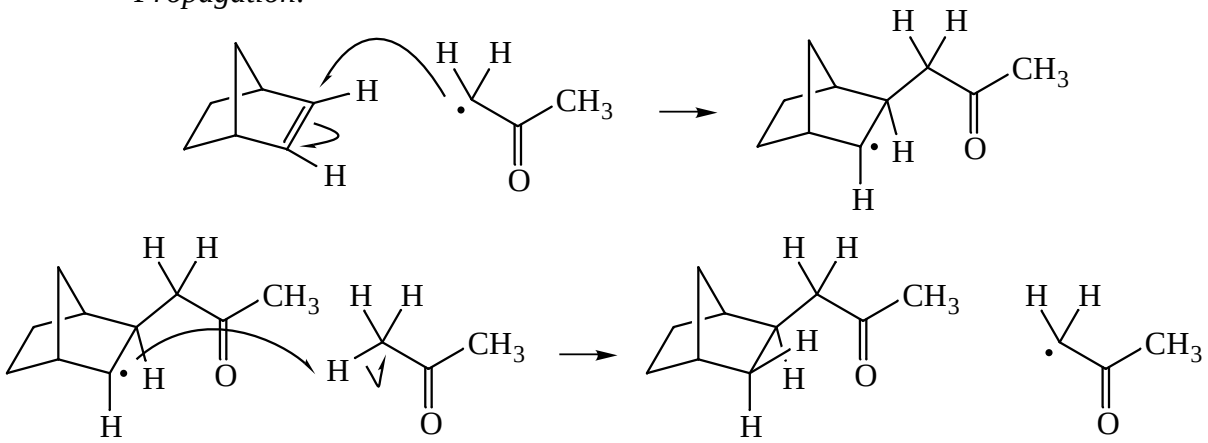
Intermolecular free-radical addition reactions almost always proceed by chain mechanisms. Here light photoexcites acetone, and O· then abstracts H· from the α-position of another molecule of acetone to complete the initiation.

Initiation:

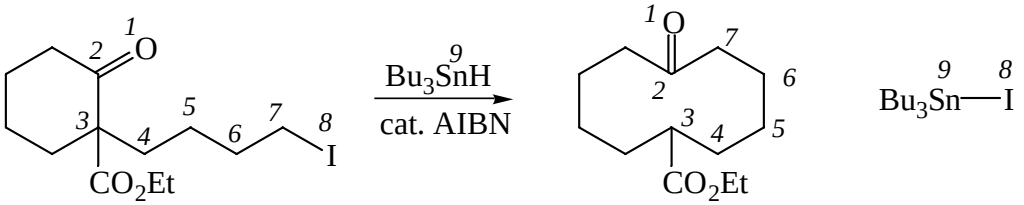


Propagation proceeds as in problem 5.7(a).

Propagation:

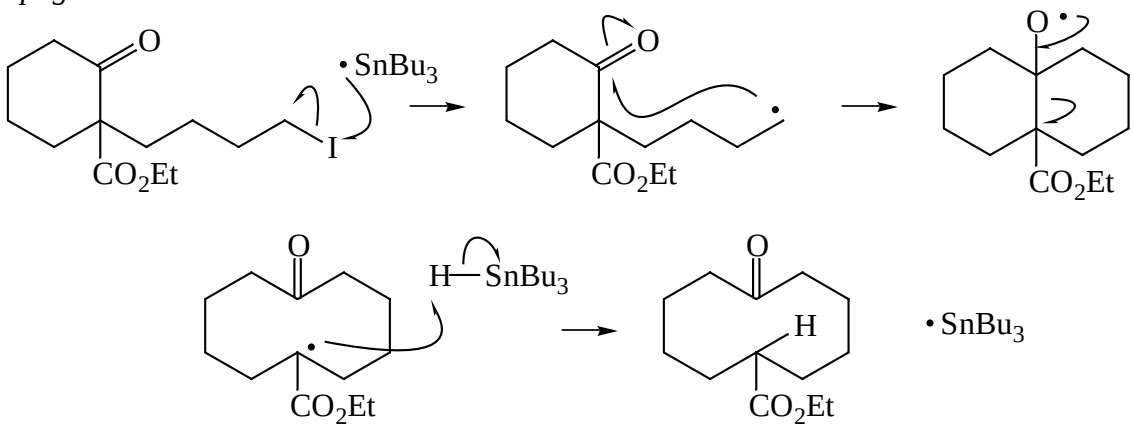


5.8. Make: C2–C7, Sn9–I8. Break: C2–C3, C7–I8.

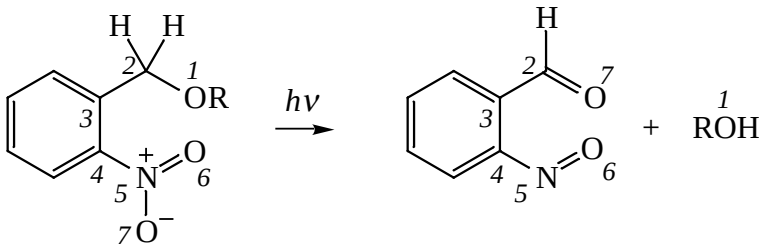


Initiation proceeds as usual. Abstraction by Sn9 of I8 from C7 gives a C7 radical, which adds to the C2 carbonyl. Cleavage of the C2–C3 bond gives a C3 radical, which abstracts H· from Bu_3SnH to give the product and complete the chain.

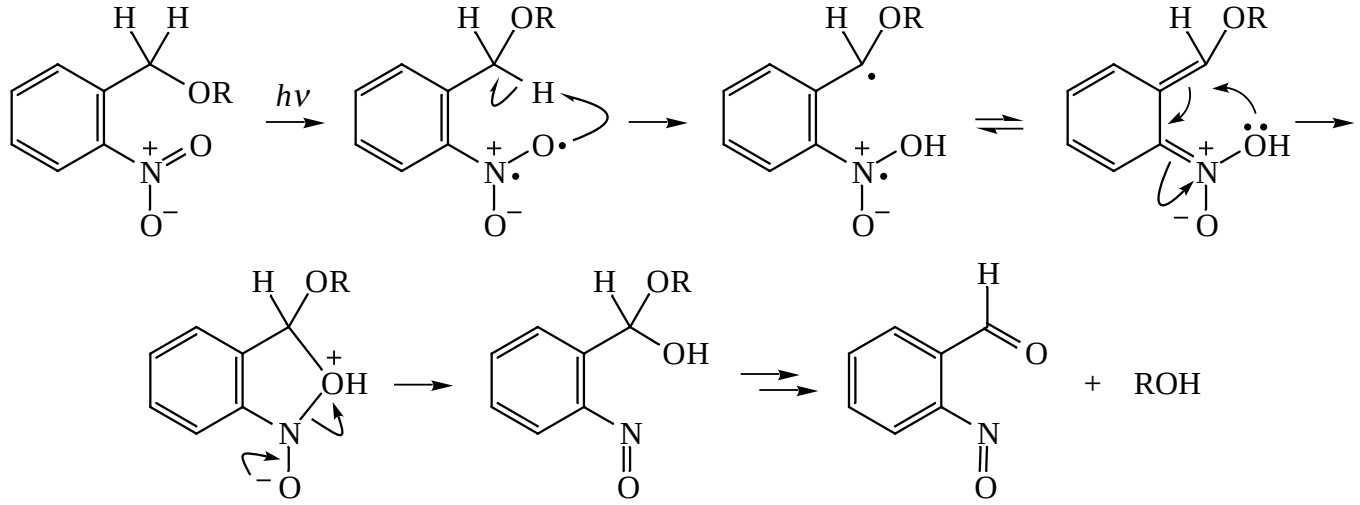
Propagation:



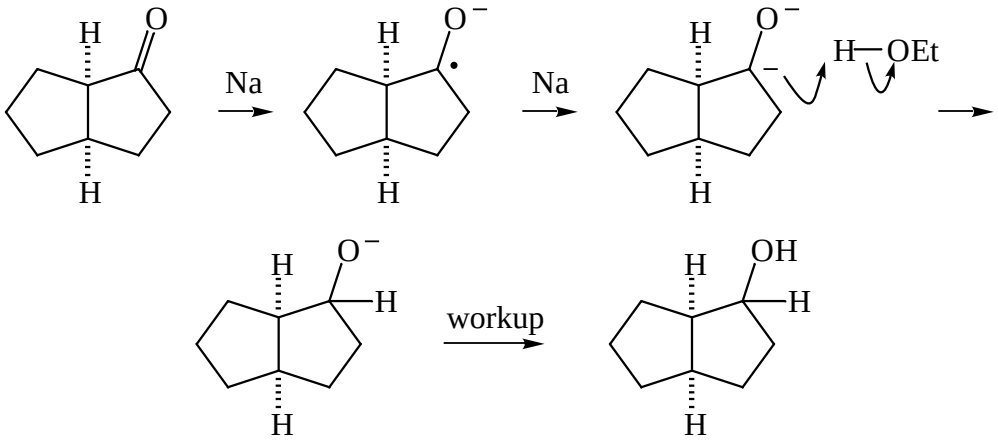
5.9. Make: C2–O7. Break: O1–C2, N5–O7. Note that O6 and O7 are equivalent.



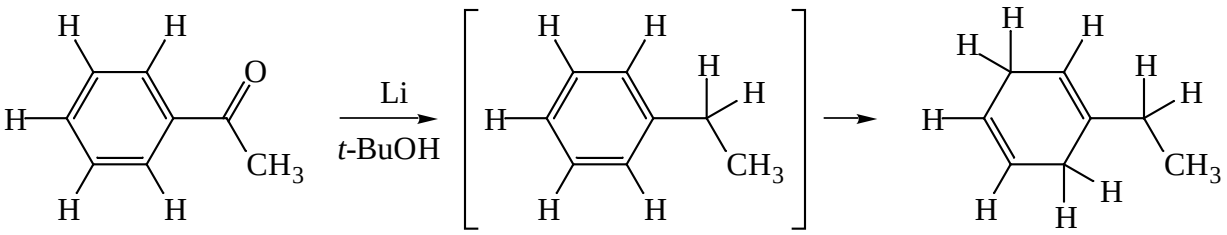
Unimolecular photochemical eliminations usually proceed by nonchain mechanisms. Photoexcitation gives an N5–O6 1,2-diradical. Abstraction of H· from C2 by O6 then gives a 1,4-diradical, which can collapse to an *o*-xylylene type of compound. Electrocyclic ring closure forms the O7–C2 bond and reestablishes aromaticity. Cleavage of the N5–O7 bond then gives a hemiacetal, which undergoes cleavage by the usual acid- or base-catalyzed mechanism to give the observed products.



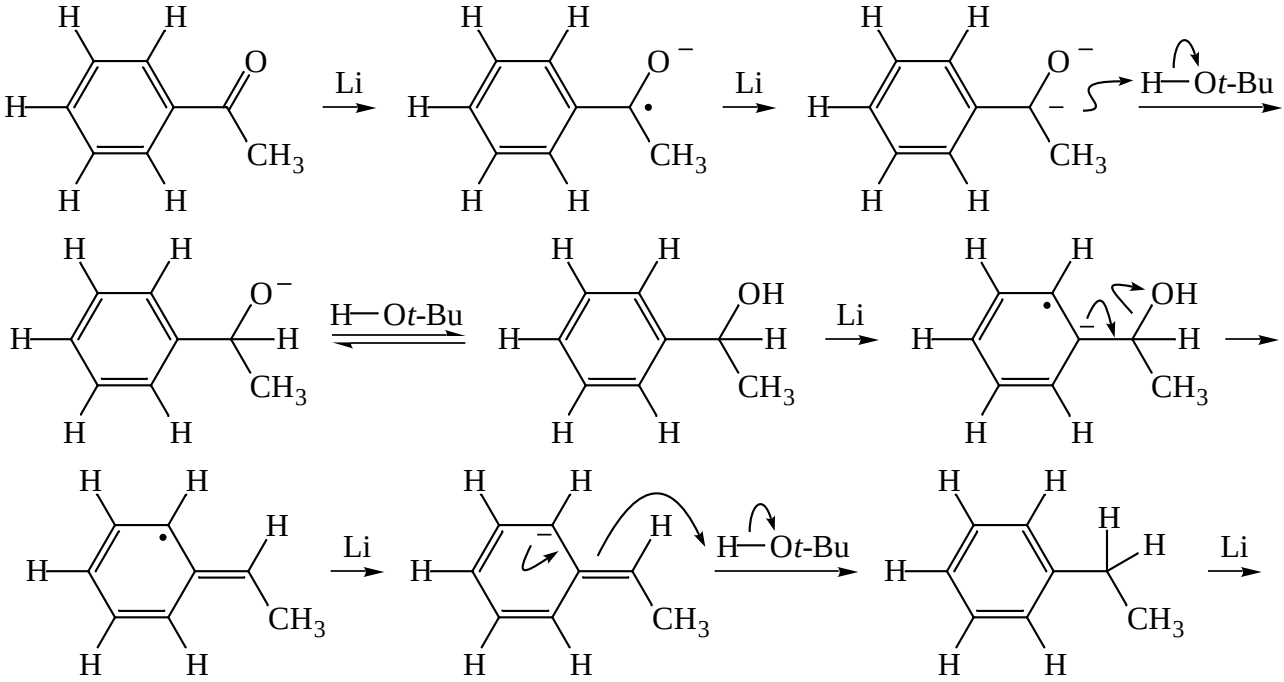
5.10. Addition of one electron to the ketone gives a ketyl (·C–O⁻), and addition of another electron gives a carbanion, which is protonated by EtOH. Workup then gives the reduced compound. Note how curved arrows are *not* used to show the movement of electrons in electron transfer steps.

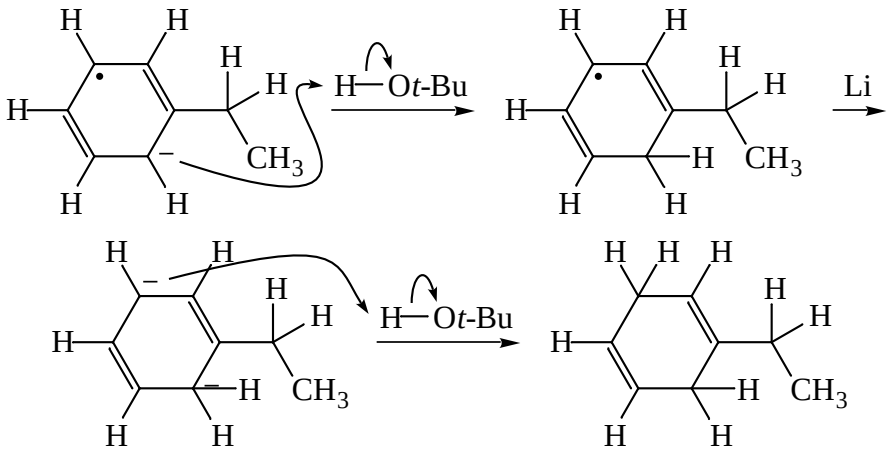


5.11. Only the C–O bond is cleaved, but several C–H bonds are made.

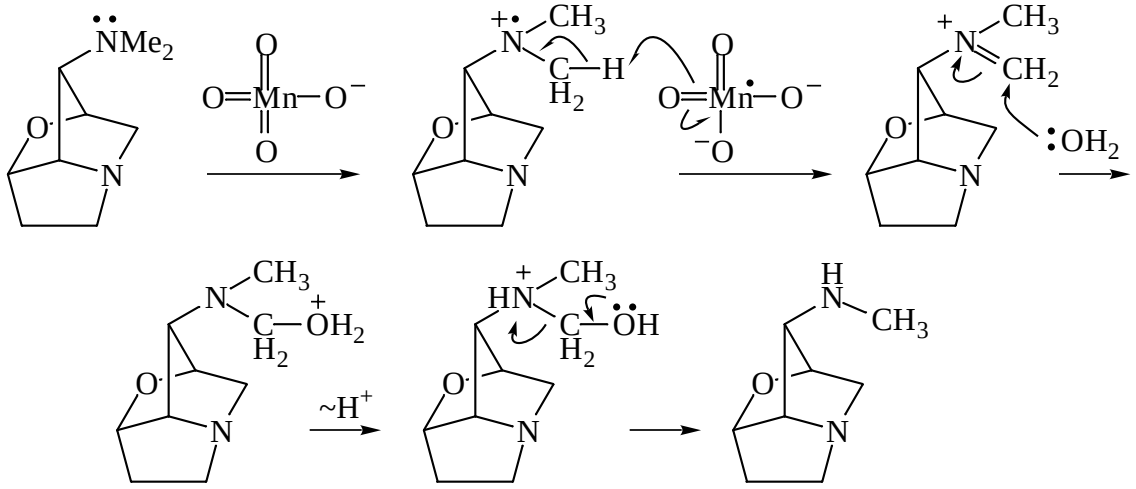


First the ketone is reduced to the alkoxide according to the mechanism shown in problem 5.9. This alkoxide is in equilibrium with the corresponding alcohol. Addition of another electron to the benzene π system gives a radical anion, which expels ⁻OH to give a radical. This radical is reduced again and then protonated to give ethylbenzene. Another electron is added, protonation occurs again, another electron is added, and protonation occurs once more to give the observed product.

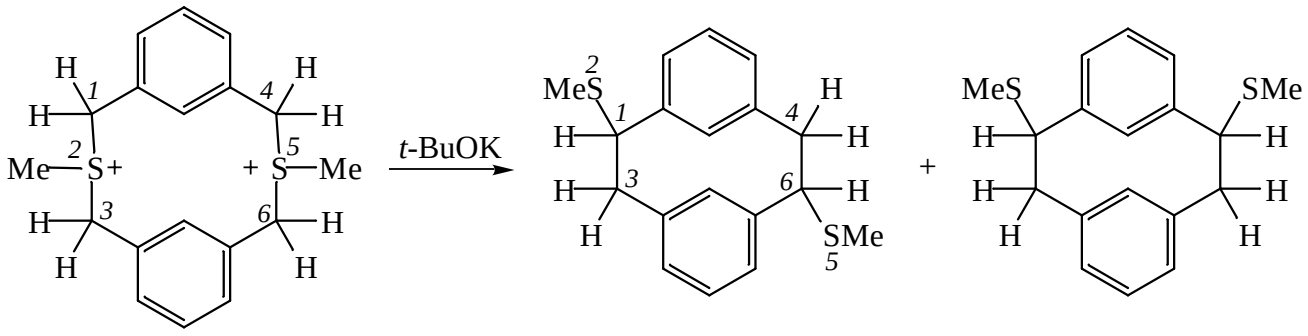




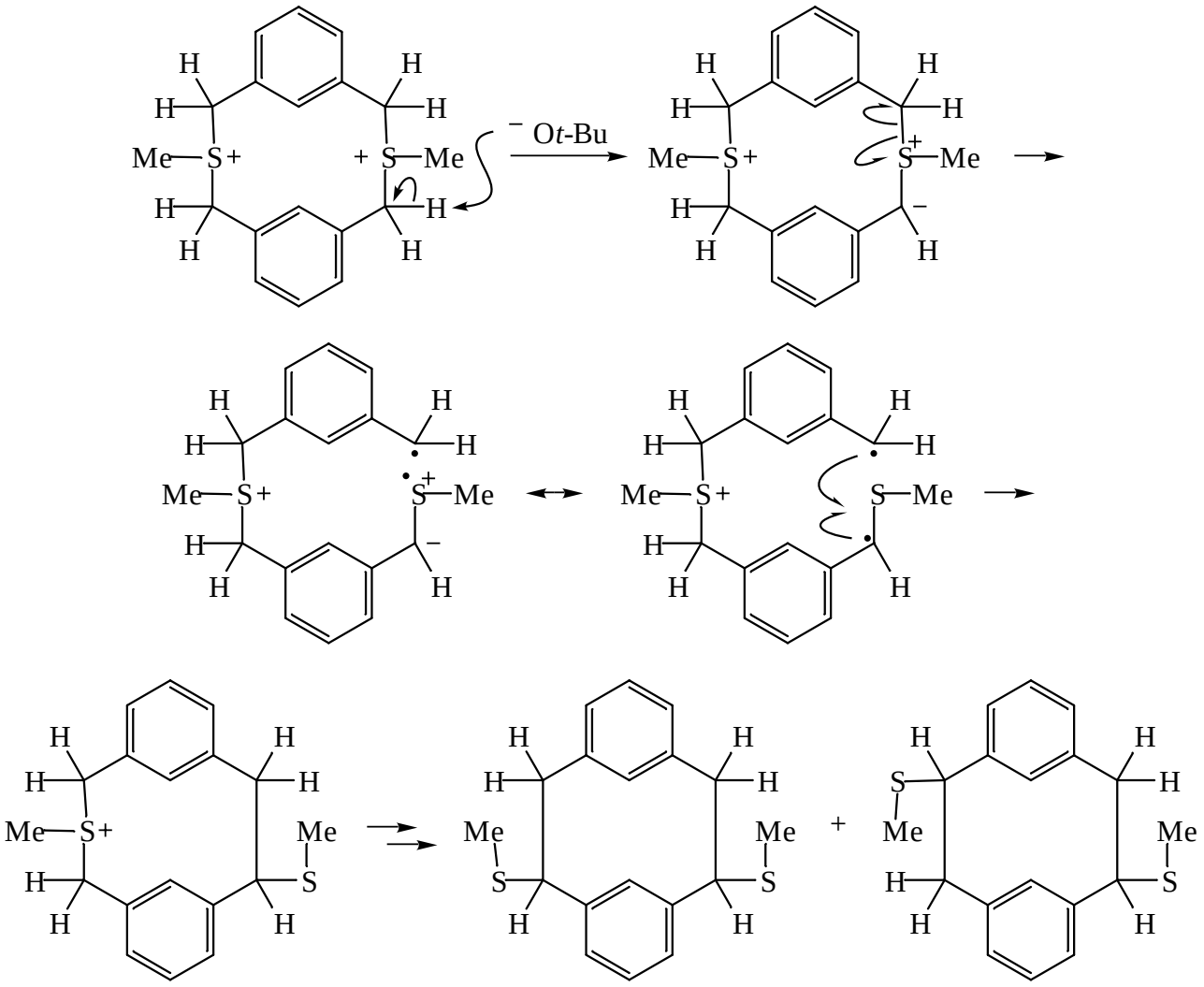
5.12. No need to number: only a N–C bond is cleaved. $KMnO_4$ is a one-electron oxidizing agent, and the HOMO of the starting material is the N lone pair, so the first step is electron transfer to give the N-based radical cation. N is somewhat electronegative, and it is unhappy about being electron-deficient, so it looks to its neighbors for another electron. It can gain such an electron from a neighboring C–H bond, if another species can take care of the H·. The $[MnO_4]^{2-}$ radical dianion can use an O atom and an unpaired electron to abstract H from a CH_3 group to give an iminium ion. Hydrolysis of the iminium ion by a conventional two-electron mechanism gives the secondary amine.



5.13. Make: C1–C3, C4–C6. Break: S2–C3, C4–S5.



Deprotonation of C6 gives an ylide , which undergoes a 1,2-shift (break C4–S5, make C4–C6). This 1,2-shift occurs in two steps: the C4–S5 bond homolyzes to give a radical and a radical cation, and recombination of C4 and C6 occurs to give an intermediate ring-contracted by one atom. The same process is repeated on the other side to give the observed product. Whether one or the other regioisoemr is obtained depends on whether C1 or C3 is deprotonated for the second ring contraction.



Answers To Chapter 5 End-of-Chapter Problems.

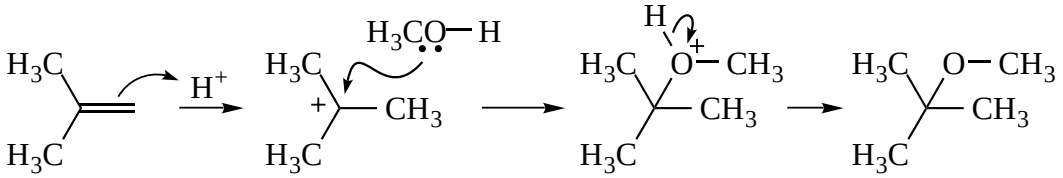
1. (a) MTBE is less prone to autoxidize than ether and THF. In MTBE, only one C attached to O bears H's, and abstraction of one of these H's gives a 1° radical. In ether and THF, both C's bear H's, and abstraction of one of these H's gives a 2° radical. 2° Radicals are much more stable than 1° radicals, so ether and THF are more prone to autoxidize.

(b) ETBE is of less interest than MTBE because it is more prone to autoxidize. Abstraction of H· from the

H-bearing C adjacent to O gives a 2° radical of comparable stability to the radical derived from ether and THF.

Incidentally, MTBE also forms an azeotrope with H_2O (like benzene does), so there is no need to dry it over $MgSO_4$ or 4 Å molecular sieves after an extraction, as must be done with both ether and THF. MTBE also has a much higher flash point than ether.

(c) Acidic conditions are required.



(d) Ethanol is made from corn — hence the name, grain alcohol. If ETBE were required to be used in gasoline, it would mean megabucks for corn producers.

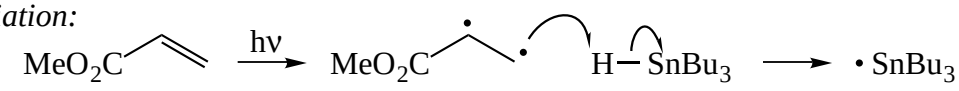
(e) One reason is that MTBE is much more polar and hence more soluble in groundwater than gasoline. The other reason is more subtle. The primary mechanism by which gasoline is degraded is by free-radical processes — either by O_2 in the air, or by bacteria with oxidizing enzymes that proceed by one-electron mechanisms. It is easier to abstract H· from gasoline (which has 2° and 3° C–H bonds) than is it to abstract H· from MTBE.

2. (a) CFCs decompose most readily during the Antarctic spring and in the stratosphere. This suggests that their decomposition is catalyzed by UV light. The action of UV light on CFCs is likely to cause homolysis of a C–Cl bond. In fact, Cl· radicals are the agents that catalyze ozone depletion.

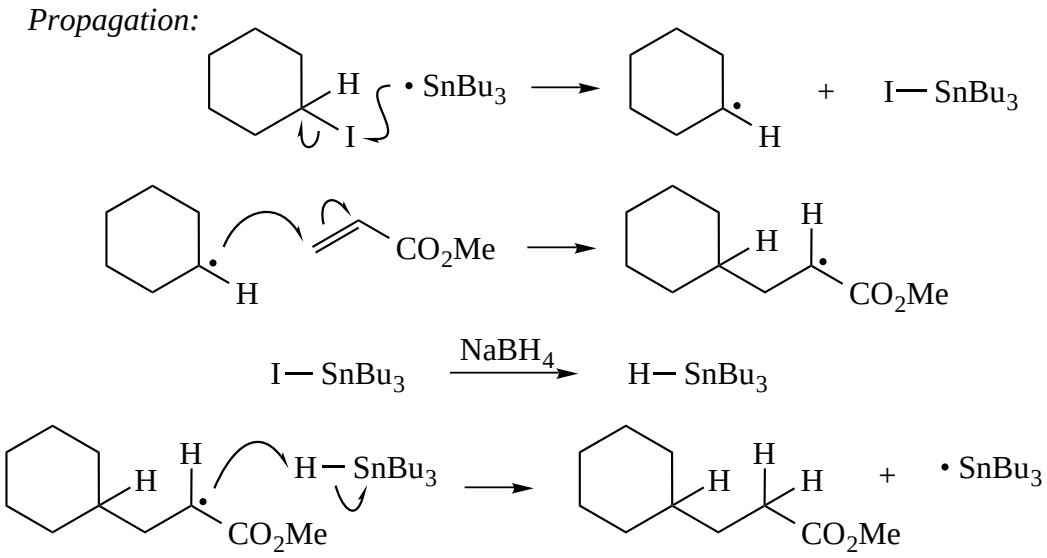
(b) HCFCs have a C–H bond, whereas CFCs don't. In the lower atmosphere, O_2 (actually, HO·) can abstract H· from an HCFC to give an alkyl radical, which can then undergo further reactions. This decomposition pathway is not open to CFCs, so they remain intact until they reach the stratosphere.

3. (a) This is a standard free-radical addition reaction. Bu_3Sn· abstracts I· from the alkyl iodide, the alkyl radical adds to the acrylate ester, and abstraction of H· from $HSnBu_3$ completes the chain. The Bu_3SnI produced in the course of the reaction is reduced by $NaBH_4$ back to $HSnBu_3$. Initiation steps other than the one shown (e.g., C–I bond homolysis) may be envisioned. The termination steps are the usual radical–radical combination and disproportionation reactions.

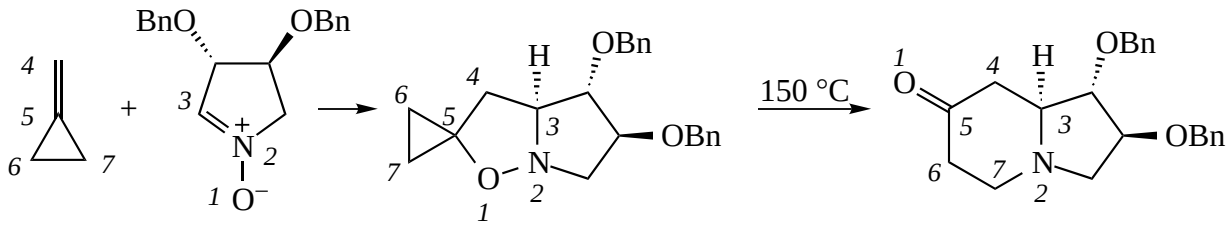
Initiation:



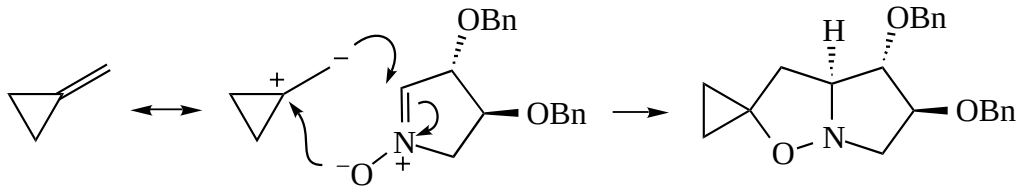
Propagation:



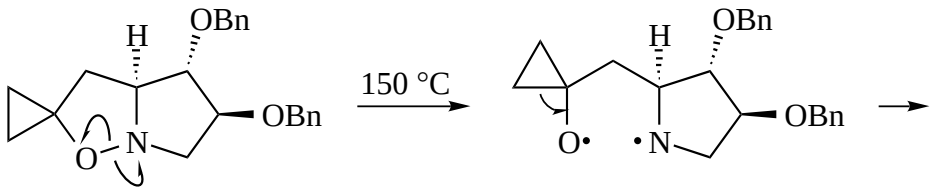
(b) Number the atoms.

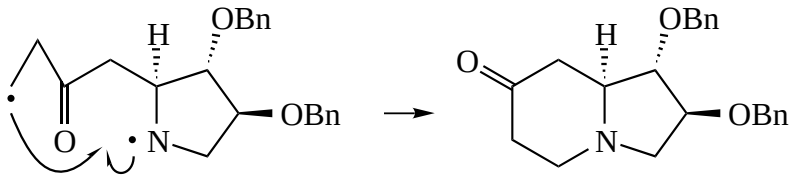


The first reaction is a 1,3-dipolar cycloaddition. The best resonance structure for the dipolarophile puts the positive charge on C5 and the negative charge on C4. This makes C5 most likely to be attacked by O1.

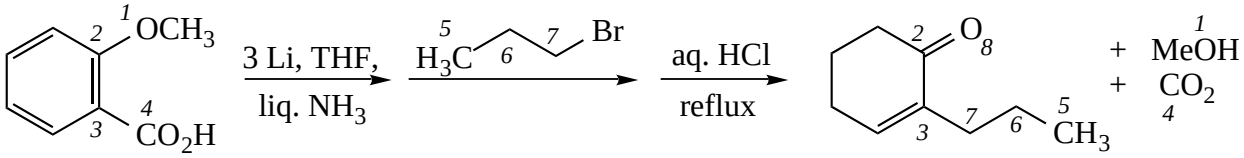


Now the second step. Make: C7–N2. Break: O1–N2, C5–C7. Heating the tricyclic compound causes thermolysis of the weak O1–N2 bond. The cyclopropyloxy radical quickly ring-opens to put the radical center at C7; then radical–radical recombination between C7 and N2 gives the product.

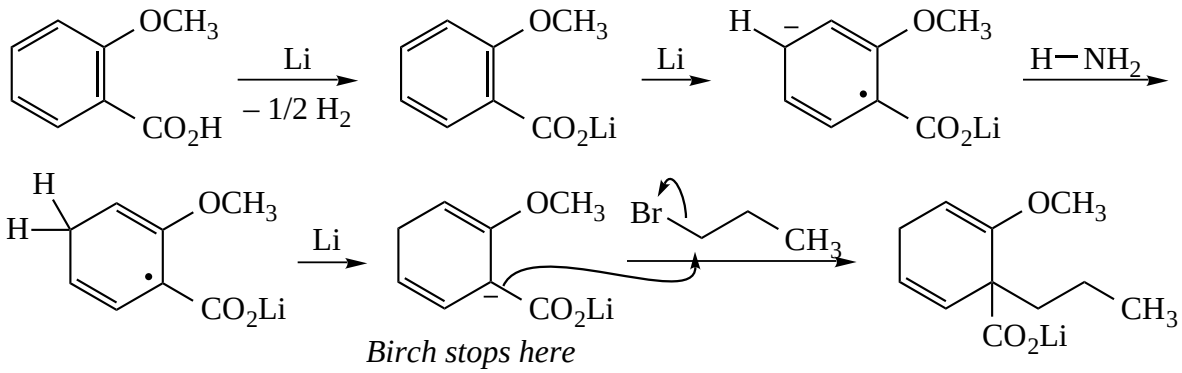




(c) The by-products are MeOH and CO_2, and the O in the product must come from H_2O. Make: C3–C7, C2–O8. Break: O1–C2, C3–C4.

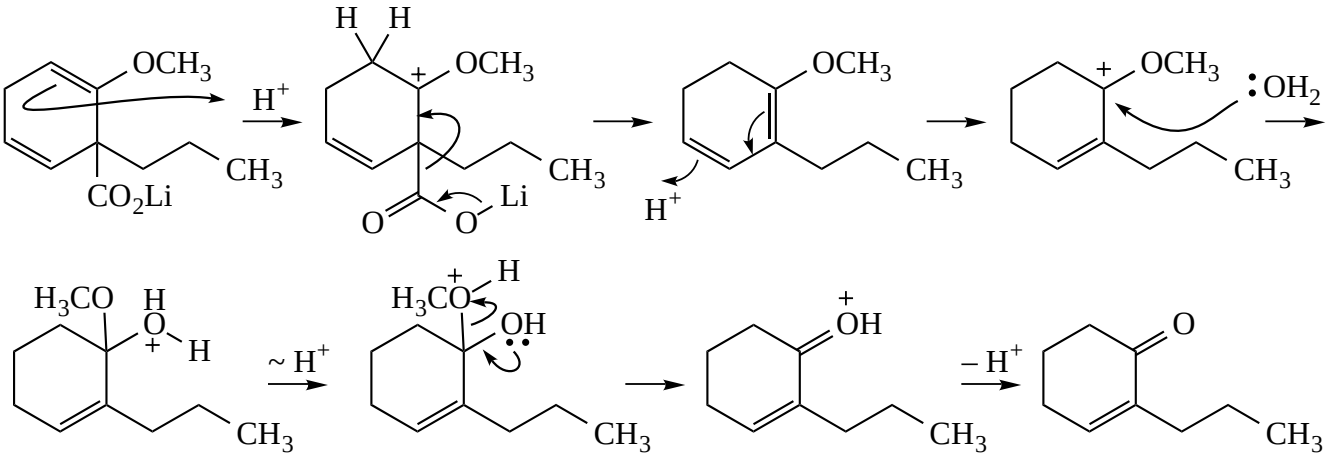


The first part is a Birch reduction, with NH_3 as the proton source. It gives the carboxylate enolate as the initial product. When the alkyl halide is added, the enolate acts as a nucleophile to give the C3–C7 bond in an S_N2 reaction.



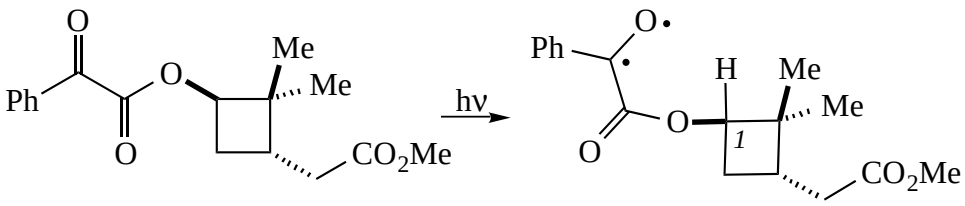
Birch stops here

Refluxing in acid protonates the enol ether to give a nice stable carbocation. Loss of CO_2 from this carbocation gives a new dienol ether. Acidic hydrolysis of this dienol ether gives the product enone in the usual fashion.

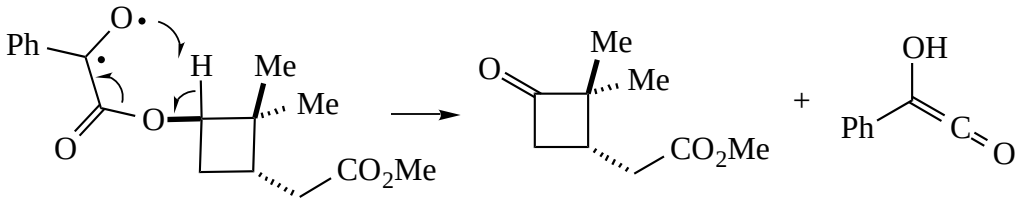


(d) Light promotes an electron from the π to the π* orbital in the aromatic C=O bond to give a 1,2-

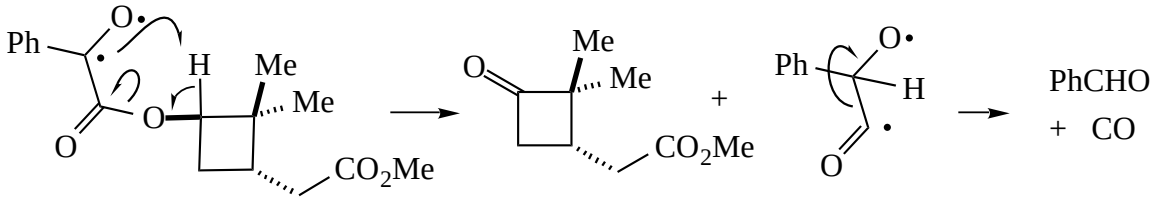
diradical.



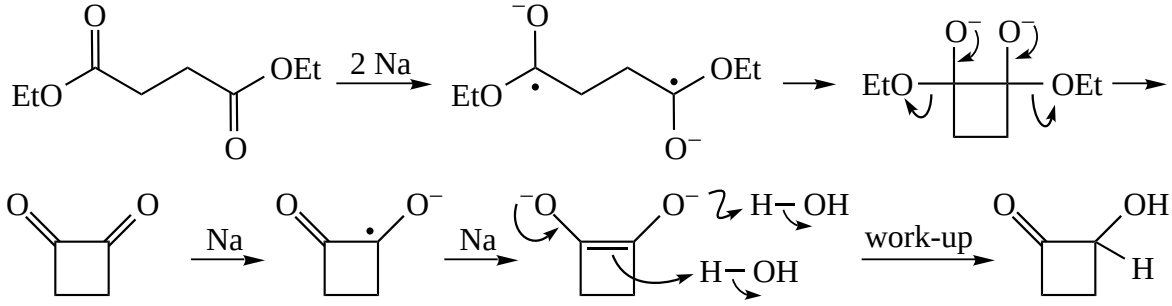
The O radical can then undergo Norrish type II cleavage, abstracting H· from C1 in a six-membered TS, to give the cyclobutanone and the ketenol.



Alternatively, the C radical can abstract H· from C1 in a five-membered TS to give the cyclobutanone, CO, and PhCHO.

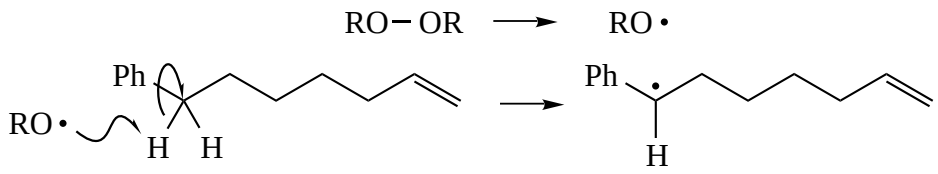


(e) This is an acyloin condensation. The two ketones are reduced to ketyls, which couple and lose EtO^-. The 1,2-dione is then reduced further by Na to give an ene-1,2-diolate, which after workup gives the α-hydroxyketone.

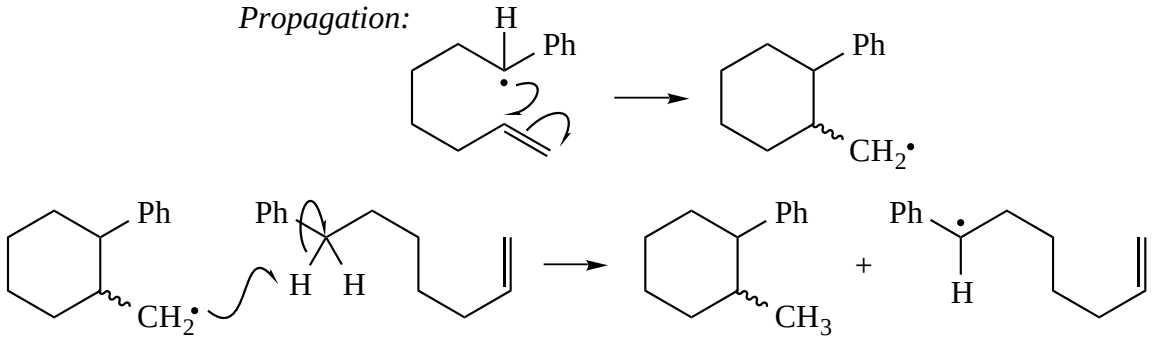


(f) A new C1–C6 bond is formed. Initiation has an alkoxy radical abstract H· form the C1–H bond to make a benzylic radical. Propagation consists of cyclization, then H· abstraction by C7 from a C1–H bond.

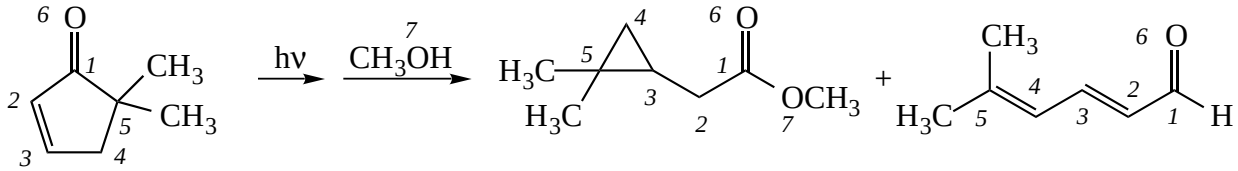
Initiation:



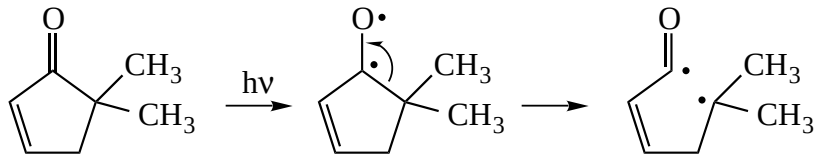
Propagation:



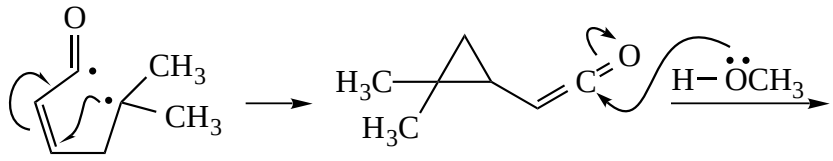
(g) Product 1: Make: C1–O7, C3–C5. Break: C1–C5. Product 2: Make: C1–H. Break: C1–C5. In both compounds, the C1–C5 bond is broken, suggesting that the first step in both cases is Norrish type I cleavage.

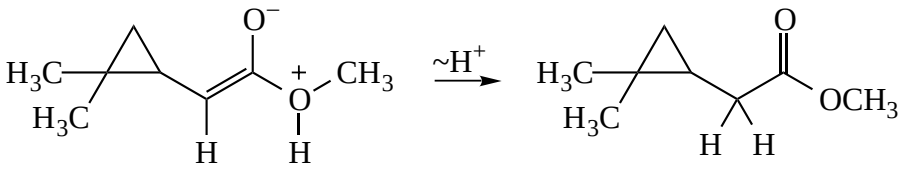


Light induces formation of a 1,2-diradical. Norrish type I cleavage to give the stabler of the two possible 1,5-diradicals then occurs.

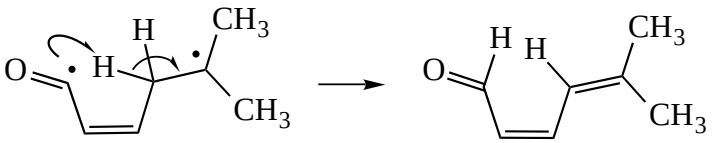


The diradical can undergo radical–radical recombination at C3–C5 to give a ketene, which reacts with CH_3OH to give the ester product via an awful zwitterionic intermediate.

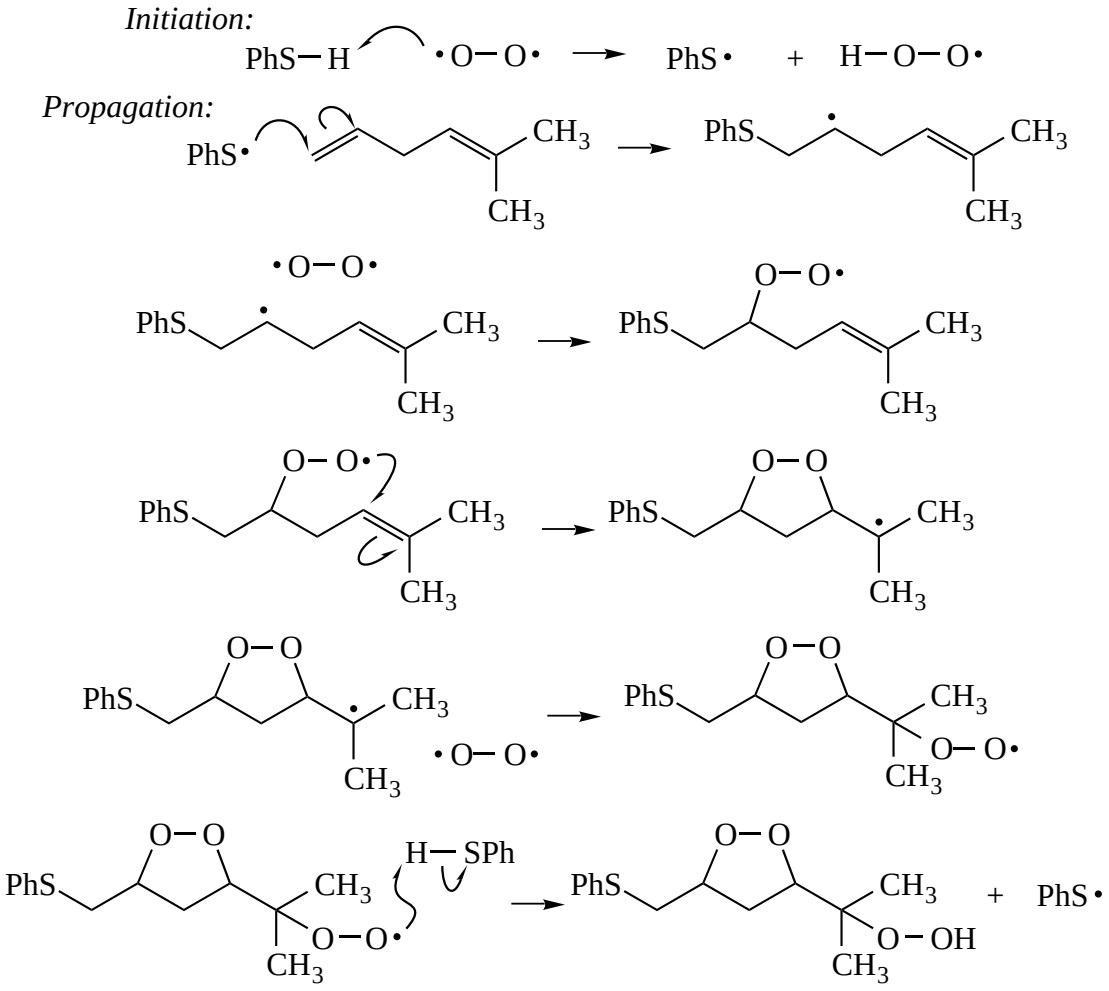




Alternatively, C1 of the diradical can abstract H· from C4 in a disproportionation reaction to give the dienal product.

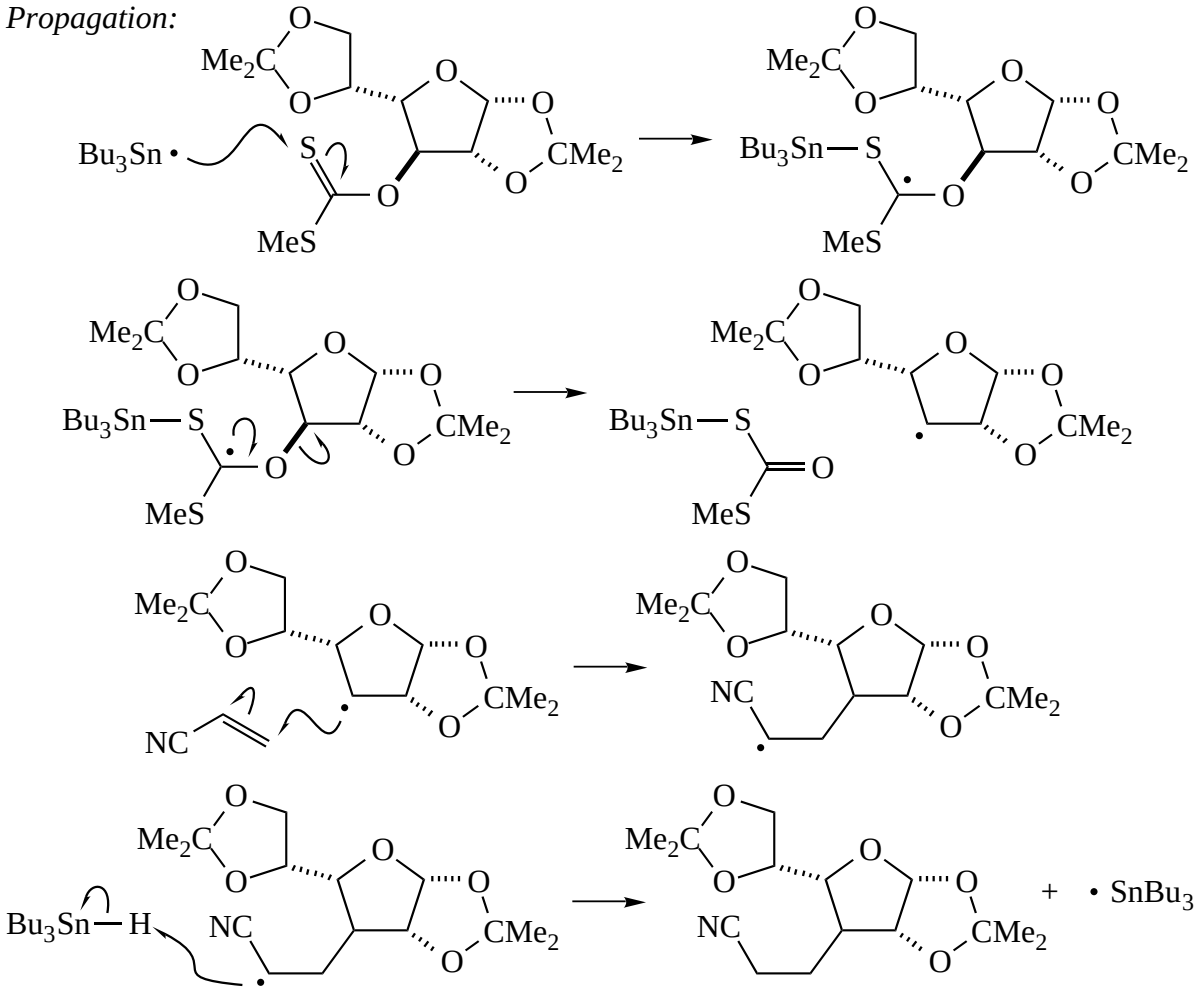


(h) *Two* molecules of O_2 are incorporated into this autoxidation product, in addition to one equivalent of thiophenol. Initiation proceeds by H· abstraction from PhSH by O_2. Propagation has PhS· add to the less substituted alkene to give an alkyl radical, which reacts with O_2 to give a peroxy radical. This adds intramolecularly to the other alkene to give a new alkyl radical, which combines with O_2 again to give a new peroxy radical. The peroxy radical abstracts H· from PhSH to complete the chain.

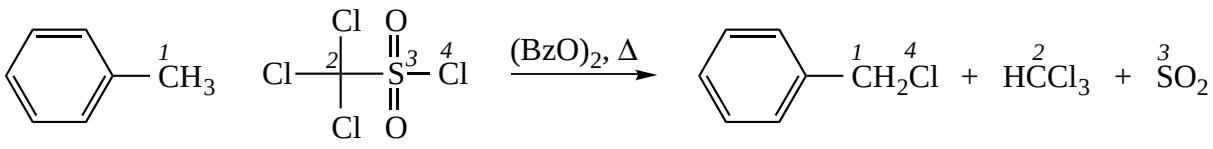


(i) This reaction combines the Barton deoxygenation with an addition reaction. In the propagation part, $Bu_3Sn\cdot$ adds to S of the C=S bond to give an alkyl radical, which fragments to give the dithiocarbonate and a new alkyl radical. The alkyl radical then adds to acrylonitrile to give yet another alkyl radical, which abstracts H· from Bu_3SnH to complete the chain.

Propagation:

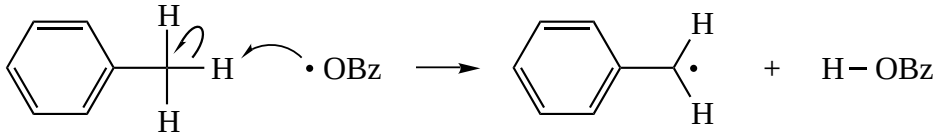


(j) The Cl in the product could come from either the S–Cl bond *or* the C–Cl bond, but since C still has three Cl's attached in the product, it probably comes from the S–Cl bond. Make: C1–Cl4. C2–H. Break: C1–H, C2–S3, S3–Cl4.



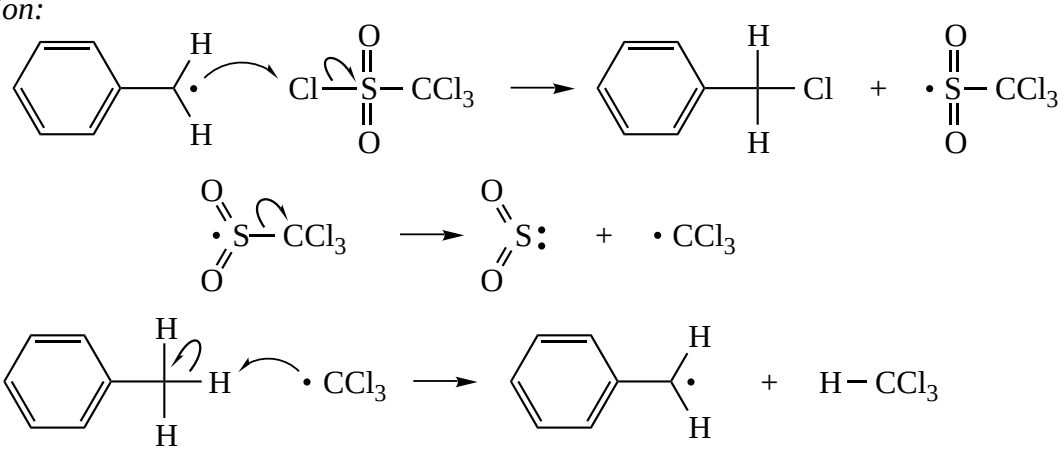
$BzO\cdot$ is generated in the initiation. It abstracts H· from toluene to give a benzyl radical.

Initiation: $BzO{-}OBz \xrightarrow{\Delta} 2\ BzO\bullet$

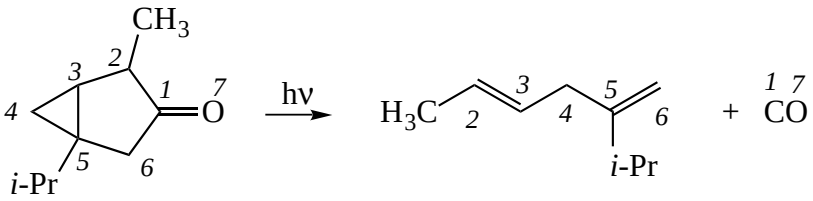


Benzyl radical abstracts Cl4 from S3 to give benzyl chloride and $Cl_3CSO_2\cdot$ radical. This radical then fragments to give SO_2 and $\cdot CCl_3$, which then abstracts H· from toluene to complete the chain.

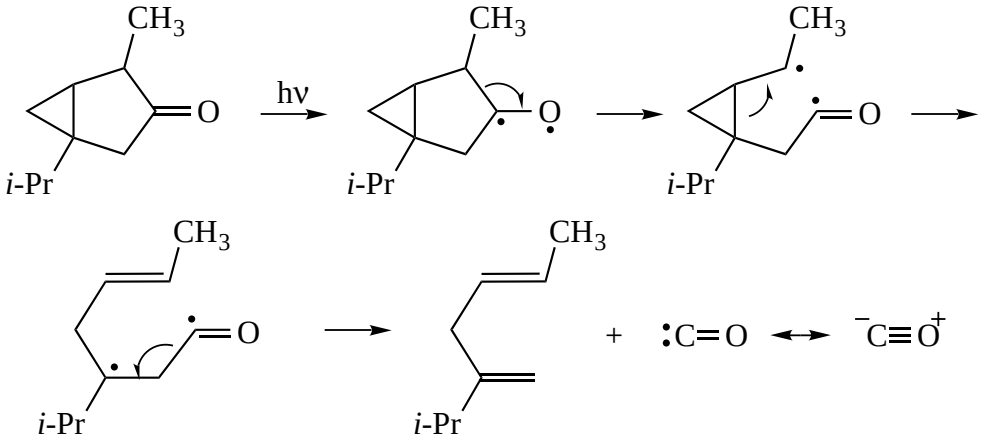
Propagation:



(k) The by-product is CO. Make: none. Break: C1–C2, C1–C6, C3–C5.



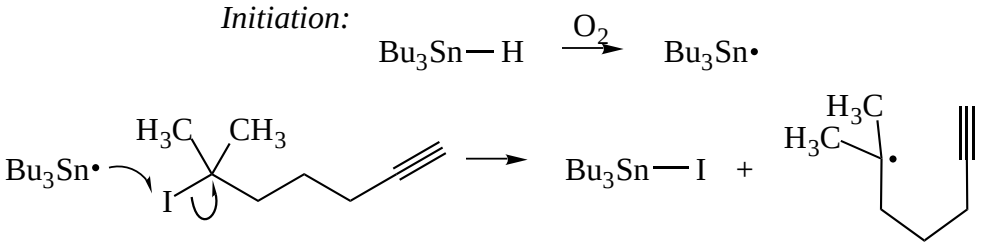
Photoexcitation of the ketone gives a 1,2-diradical, which undergoes Norrish type I cleavage of the C1–C2 bond to give a 1,5-diradical. The cyclopropylcarbinyl radical opens up to give a 1,3-diradical, which finally loses CO to give the observed diene. Some of these steps may be concerted.



(l) This radical-catalyzed isomerization reaction is a variation of the Bu_3SnH-promoted reductive cycliza-

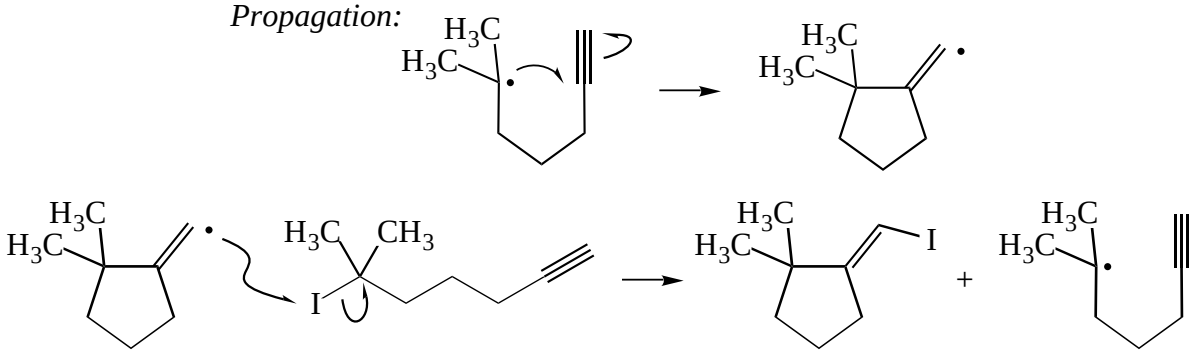
tion of haloalkenes that we've seen before. Bu_3SnH is no longer a stoichiometric starting material, so it cannot appear in the propagation part of the mechanism. Instead, it is an initiator that is used to generate small amounts of the alkyl radical by abstraction of I· from the starting material.

Initiation:



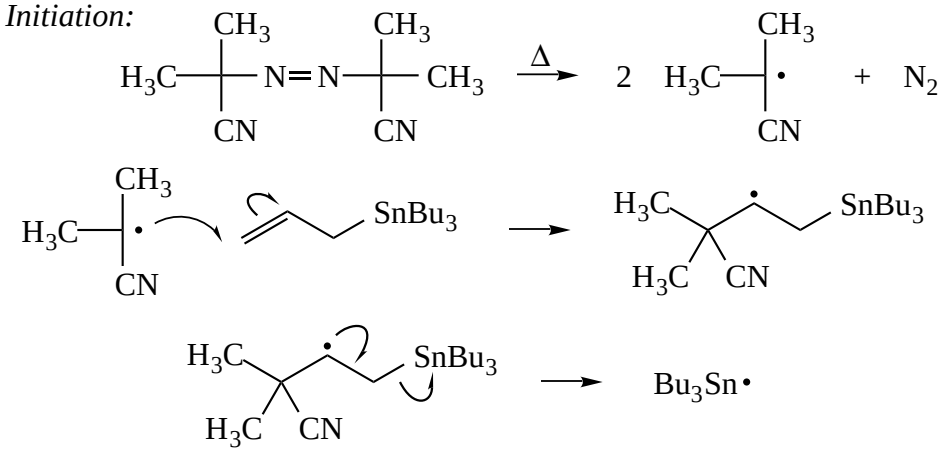
In the propagation part of the mechanism, the alkyl radical adds to the triple bond to give a vinyl radical, which abstracts I· from the starting material to give the product and to complete the chain.

Propagation:

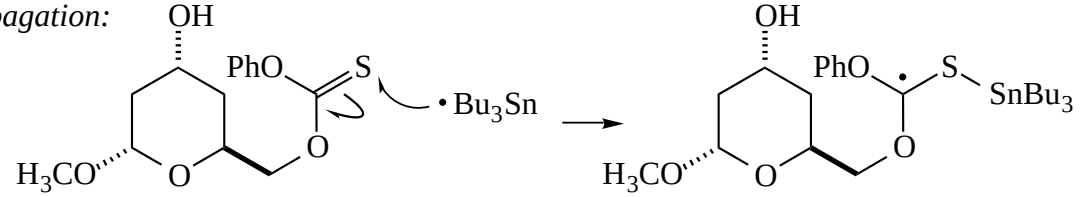


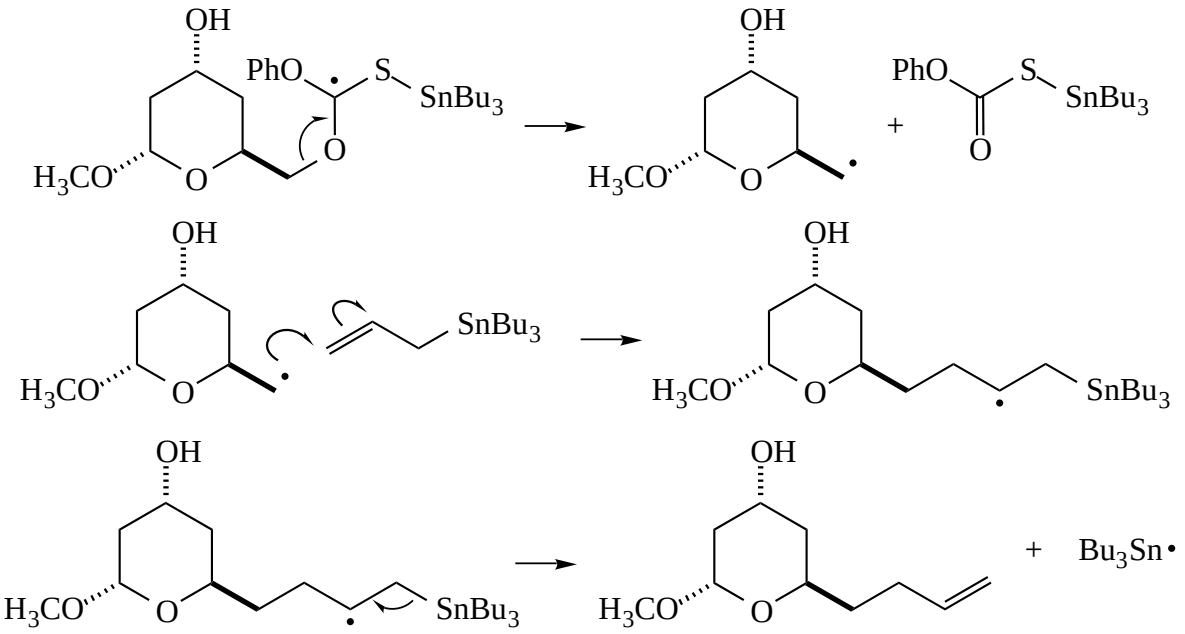
(m) This reaction combines a Barton deoxygenation with a free-radical allylation. Bu_3Sn· is the chain-carrying species.

Initiation:

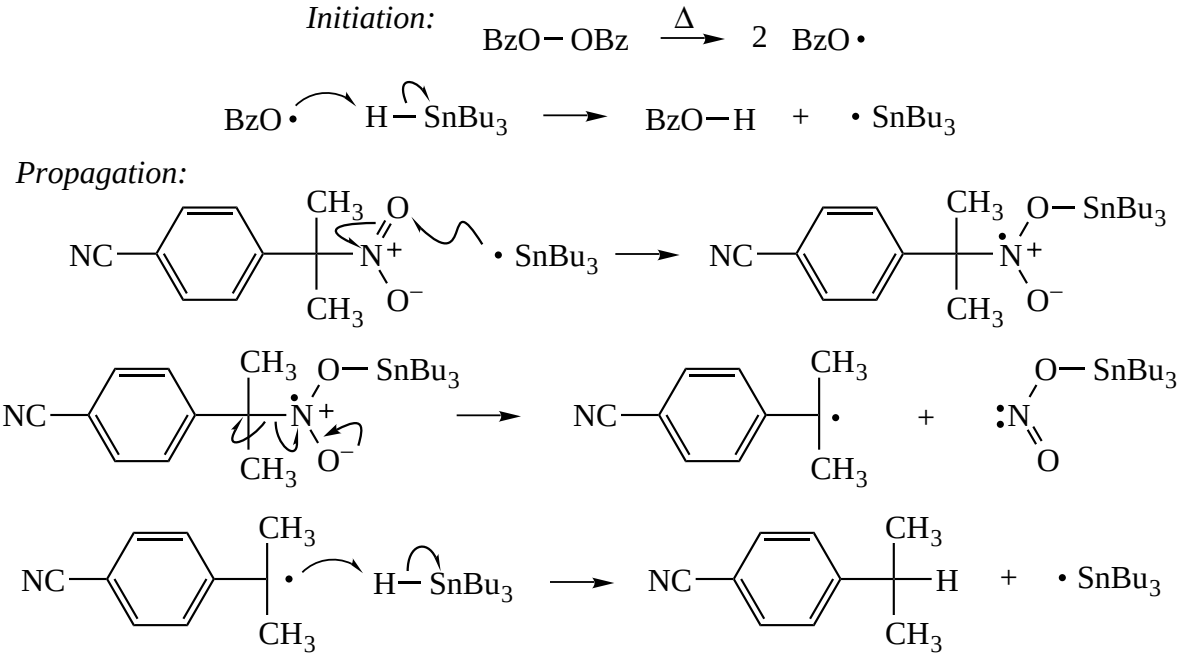


Propagation:

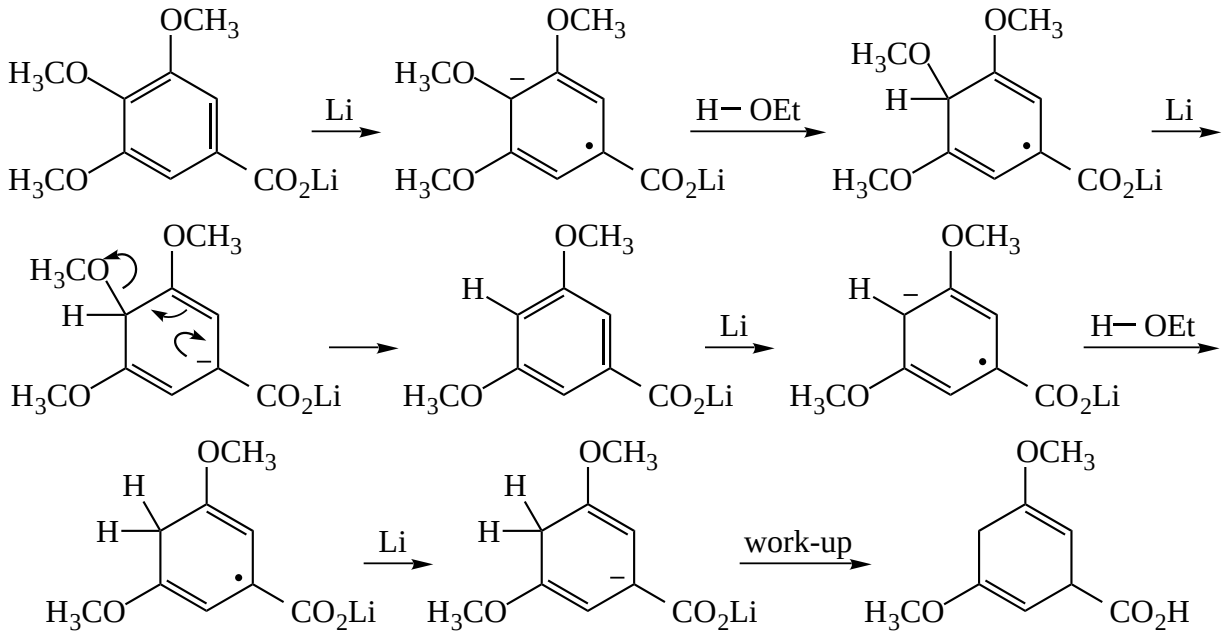




(n) This free-radical substitution appears to proceed by direct attack of $Bu_3Sn\cdot$ on the C–N bond to give a Sn–N bond and a C radical. However, the N atom is quite sterically encumbered, and direct abstraction of a light atom by $Bu_3Sn\cdot$ is quite rare. A better mechanism has the $Bu_3Sn\cdot$ add to O of the N=O π bond to give a N-centered radical. Fragmentation of the C–N bond then gives a nitrite and the requisite alkyl radical, which abstracts H· from Bu_3SnH to complete the chain.

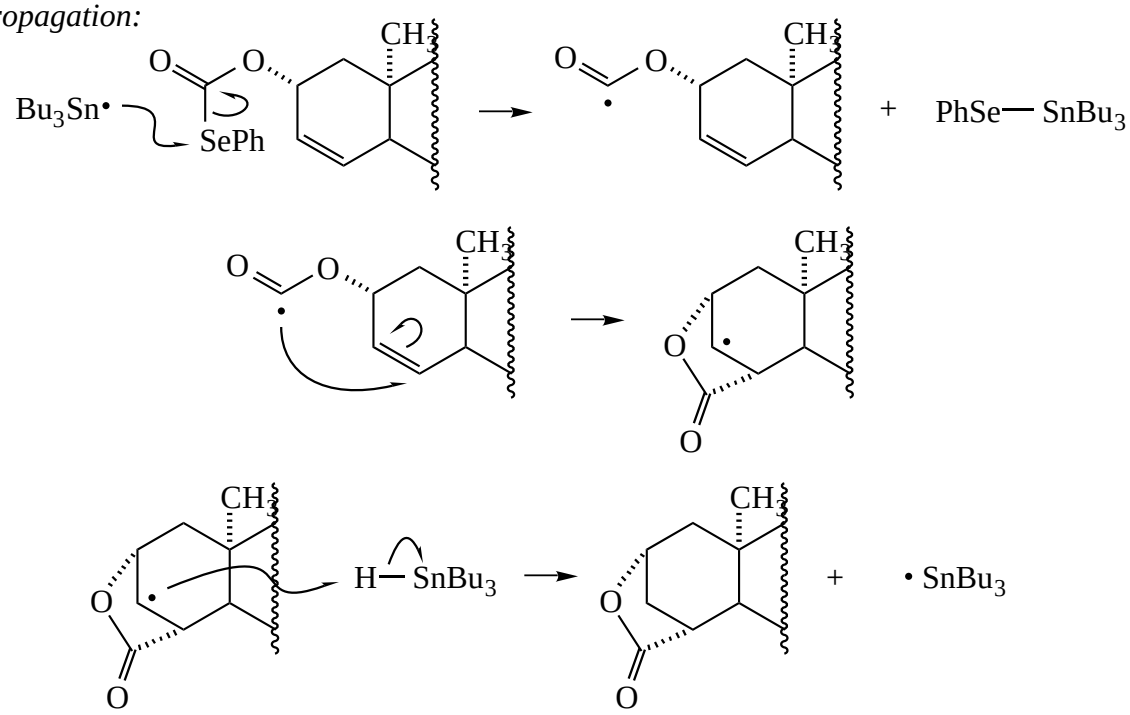


(o) In this Birch reduction, the first equivalent of Li reduces the acid to a carboxylate. The Birch reduction then proceeds normally until after the second electron transfer step, when elimination of MeO^- occurs to give a new aromatic compound. Now Birch reduction proceeds again normally to give the observed product.

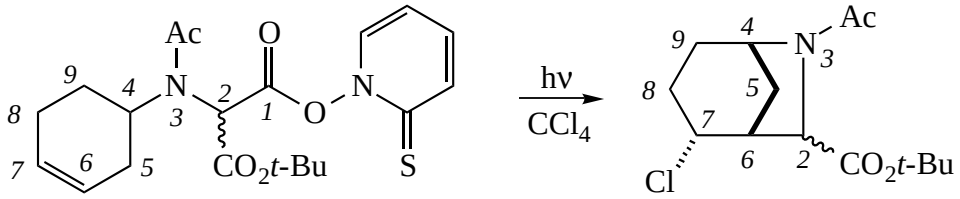


(p) This reaction is a standard free-radical addition reaction, except that the reaction takes place in an intramolecular fashion.

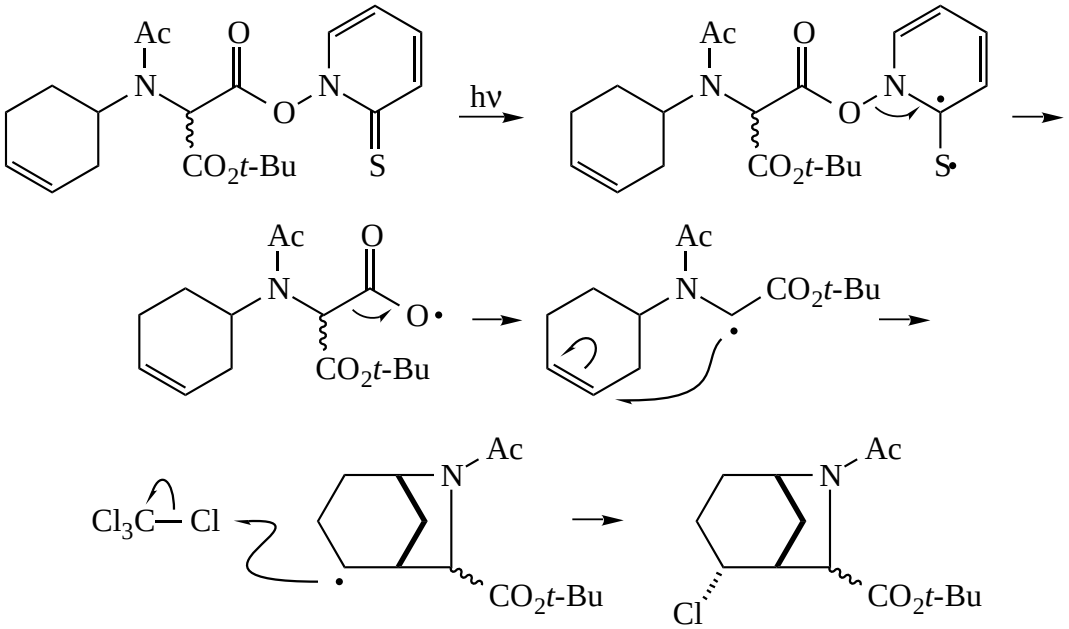
Propagation:



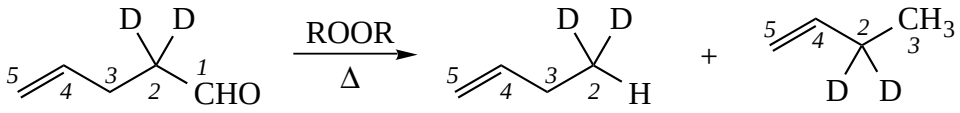
(q) Make: C2–C6, C7–Cl. Break: C1–C2.



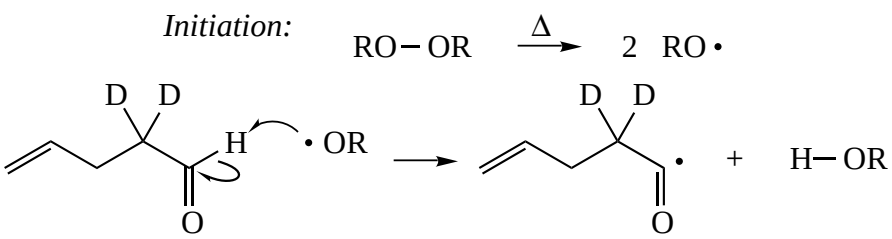
The weakest bond, the C=S π bond, will be selectively photoexcited. Fragmentation of the weak N–O bond (Norrish type I cleavage) gives a carboxy radical, which can fragment to give a C2 radical, which adds to the C6=C7 π bond to give a C7 radical, which abstracts Cl· from CCl_4 to give the product. The reaction may or may not be drawn as a chain reaction, depending on whether the rate of addition of the Cl_3C· radical to S of the C=S π bond is comparable in rate to the Norrish cleavage.



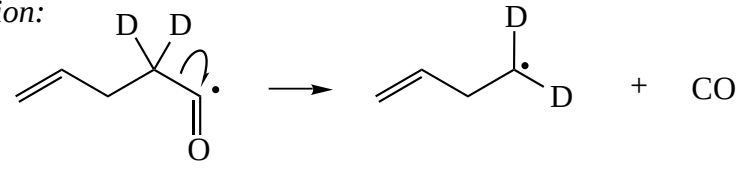
(r) First compound: Make: C2–H. Break: C1–C2. Second compound: Make: C2–C4, C3–H. Break: C1–C2, C3–C4.



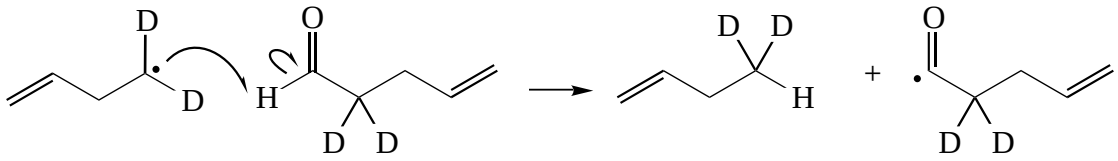
In both products, the C1–C2 bond has cleaved. Cleavage of this bond can occur by fragmentation of the C1 radical to give the C2 radical and CO. The C1 radical is generated by abstraction of H·.



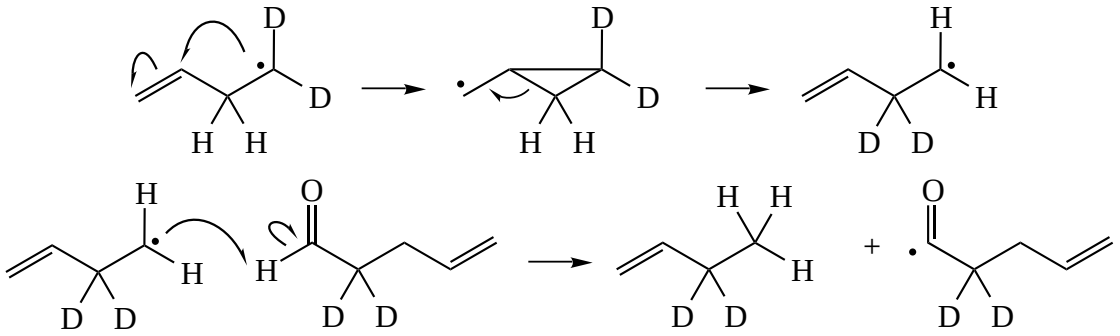
Propagation:



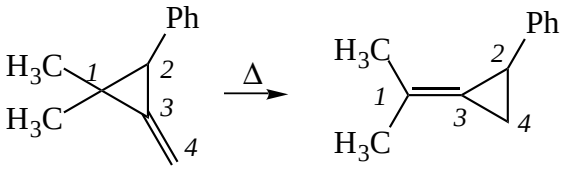
The first product is obtained by abstraction of H· from the starting material to complete the chain.



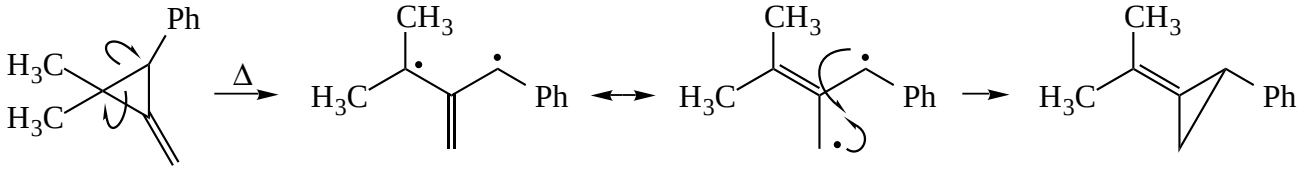
The second product still requires formation of the C2–C4 bond and cleavage of the C3–C4 bond. Addition of C2 to C4 is followed by fragmentation of the C2–C3 bond. The C3 radical then abstracts H· from the starting material to give the second product and to complete the chain.



(s) Make: C2–C4. Break: C1–C2.

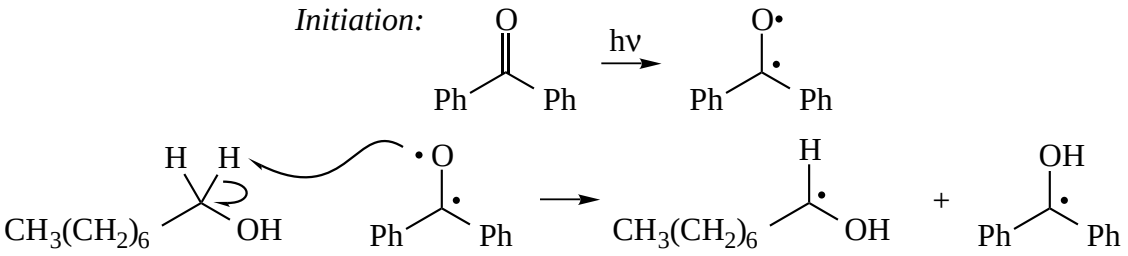


The C1–C2 bond is quite weak. Homolysis of this bond gives a 1,3-diradical at C1 and C2. The C1 radical is allylically delocalized onto C4, also. Combination of the C2 radical with with the C4 radical gives the product.

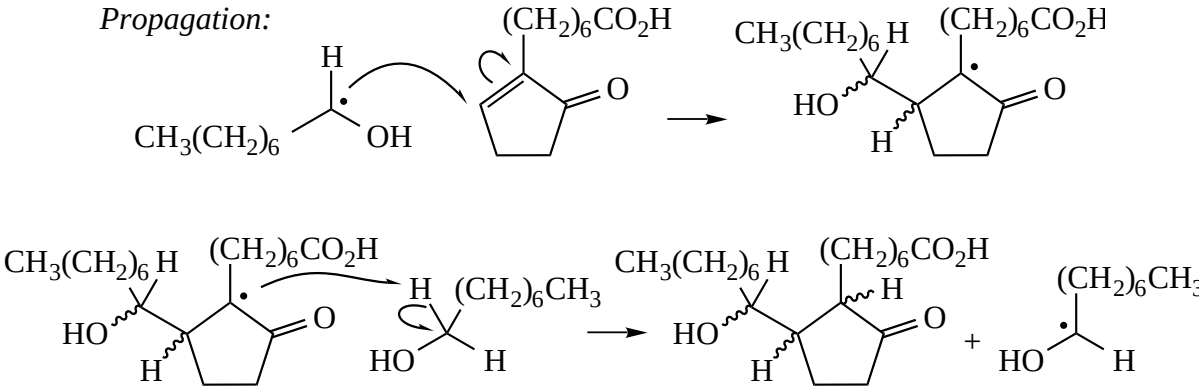


(t) Another free-radical addition reaction. The initiator is benzophenone in its photoexcited state.

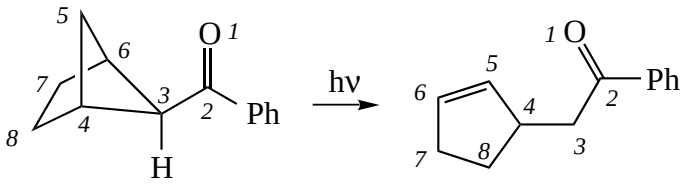
Initiation:



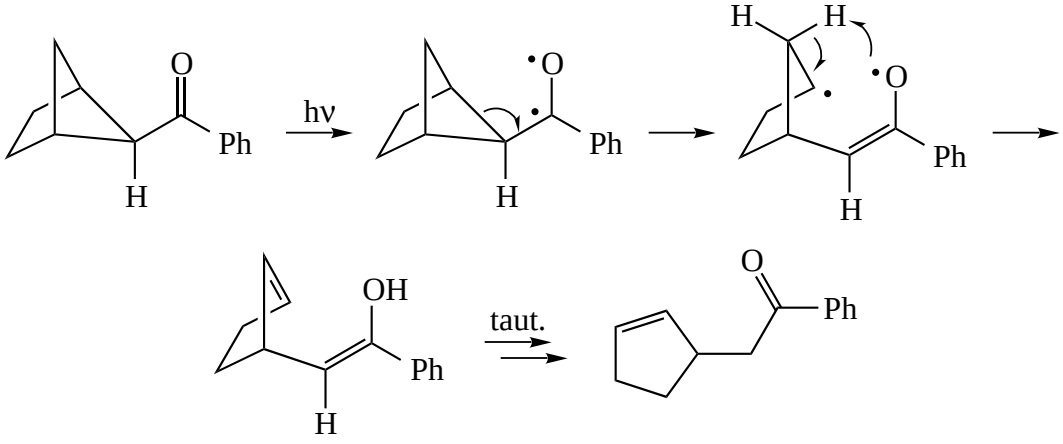
Propagation:



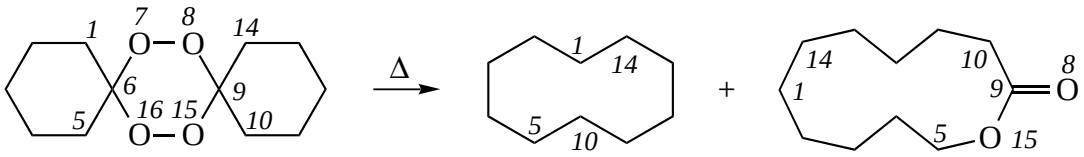
(u) Make: C3–H. Break: C3–C6, C5–H.



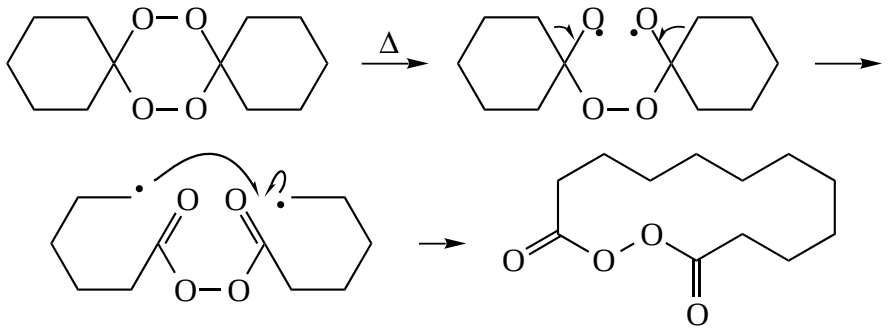
Photoexcitation of the ketone gives a 1,2-diradical. An unusual mode of cleavage for ketones that is neither Norrish type I nor II, cleavage of the C3–C6 bond, then occurs to give a new diradical. The unusual cleavage occurs here in order to relieve strain in the four-membered ring. A disproportionation reaction (six-membered TS) then gives an unsaturated enol, which tautomerizes (acid or base catalysis) to give the observed product.



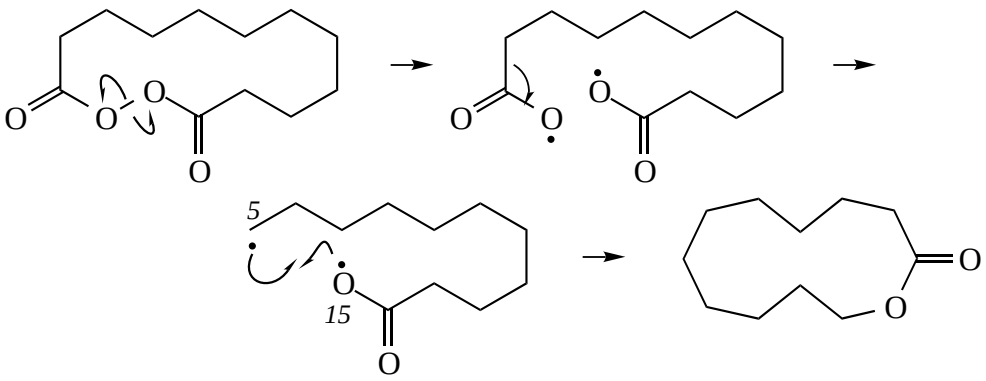
(v) From starting material to first product, two equivalents of CO_2 are missing. First product: Make: C1–C14, C5–C10. Break: C1–C6, C5–C6, O7–O8, C9–C10, C9–C14, O15–O16. From starting material to second product, one equivalent of CO_2 is missing. Second product: Make: C1–C14, C5–O15. Break: C1–C6, C5–C6, O7–O8, C9–C14, O15–O16.



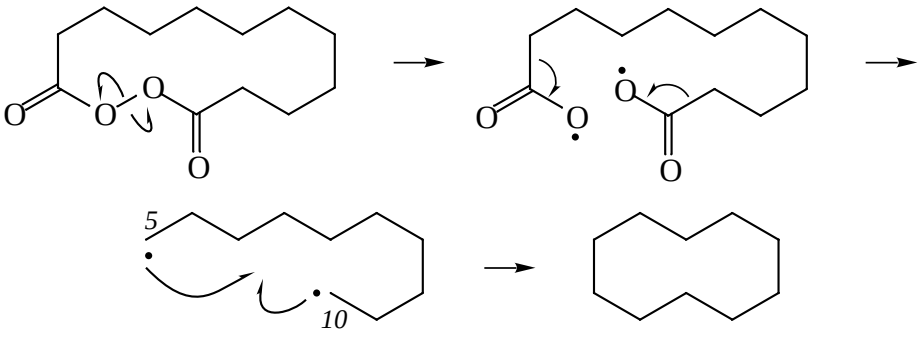
Heating cleaves a weak O–O bond homolytically to give two oxy radicals. Fragmentation of the C1–C6 and C9–C14 bonds gives two radicals which recombine to give a cyclic diacyl peroxide.



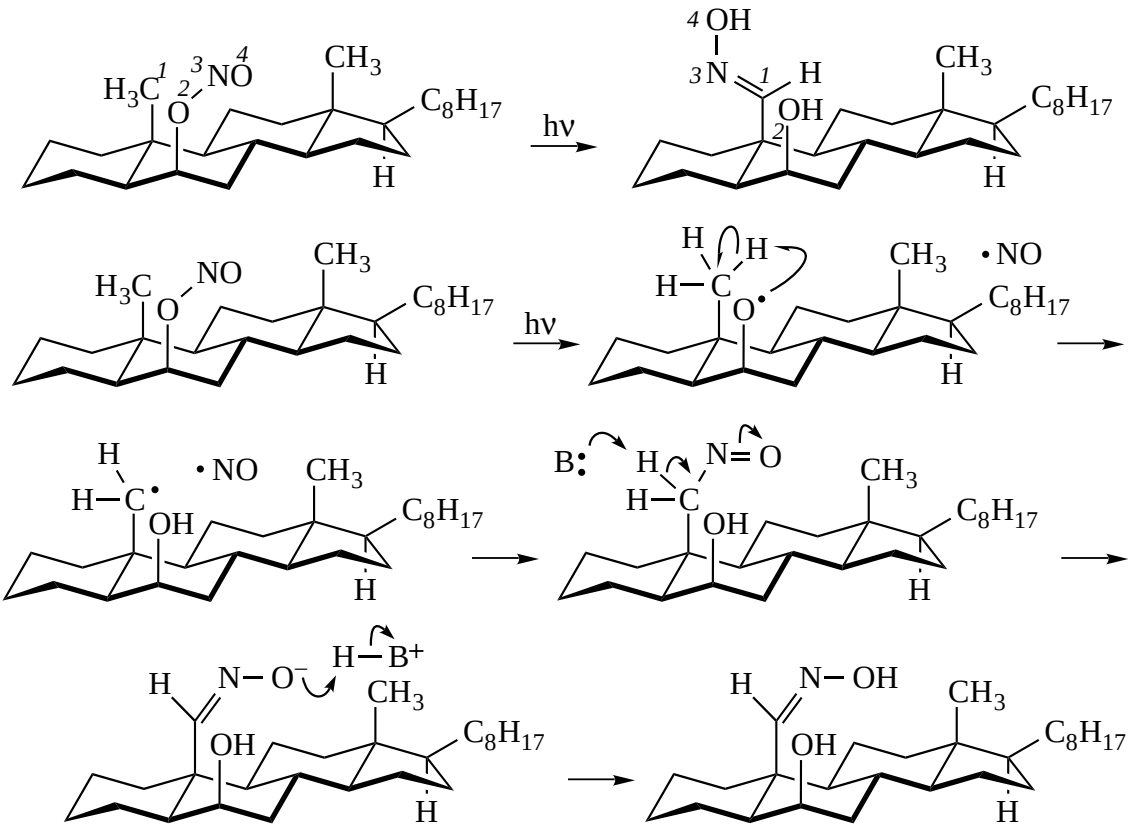
Homolytic cleavage of the O15–O16 bond gives a new diradical. This can lose either one or two equivalents of CO_2 before recombination to give the two observed products.



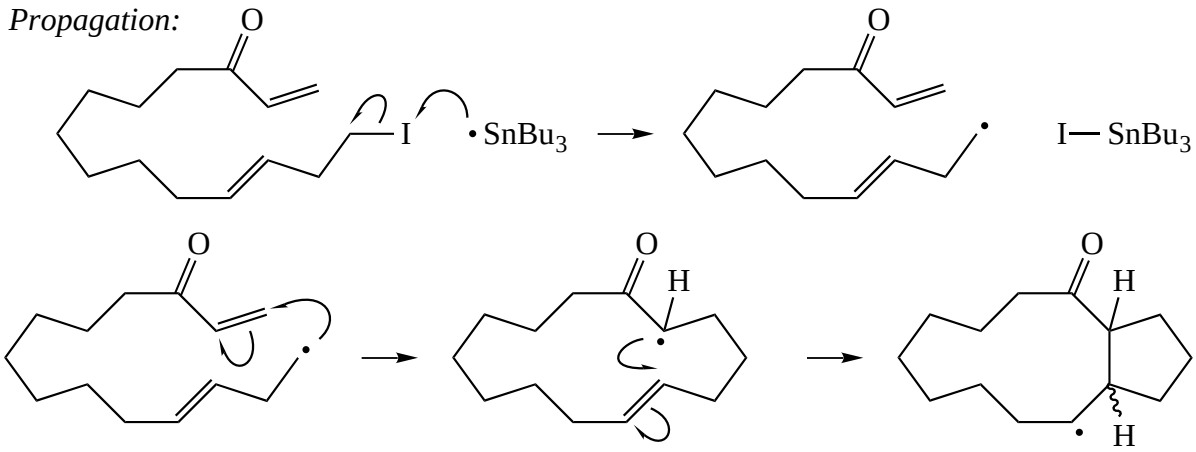
OR

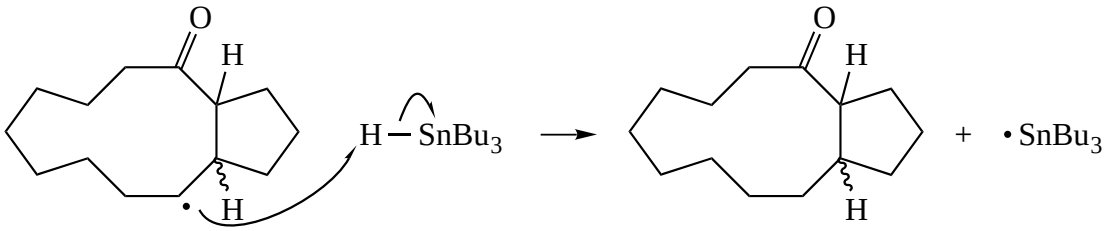


(w) Make: C1–N3. Break: O2–N3. This is a Barton reaction. Homolytic cleavage of the O–NO bond gives an oxy radical which abstracts H· from the nearby C1. Combination of this radical with NO, then tautomerization, gives the oxime.

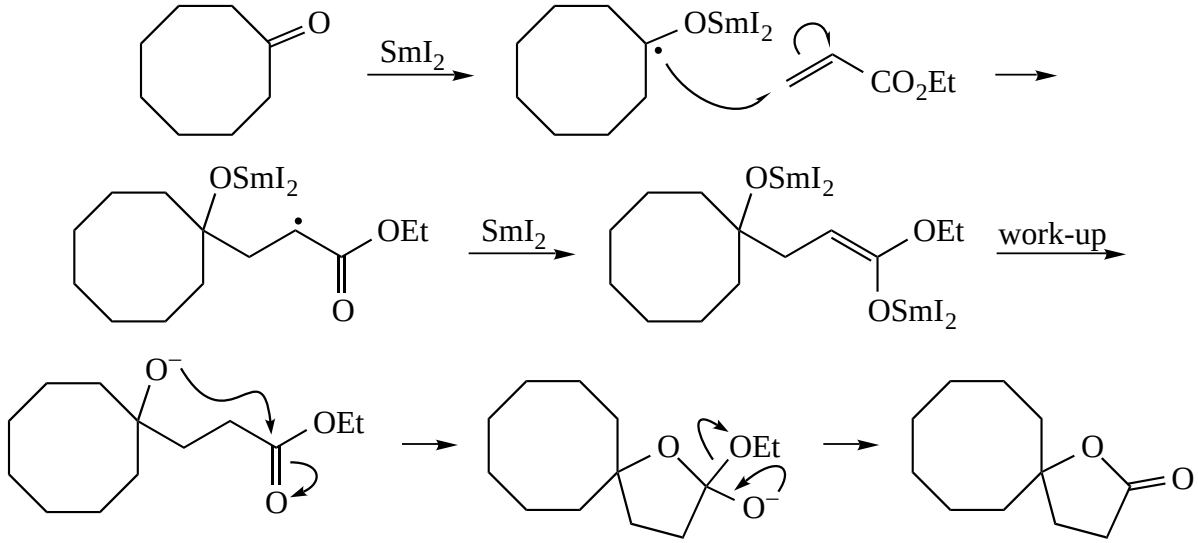


(x) Two sequential free-radical addition reactions occur. They may be stepwise or concerted.



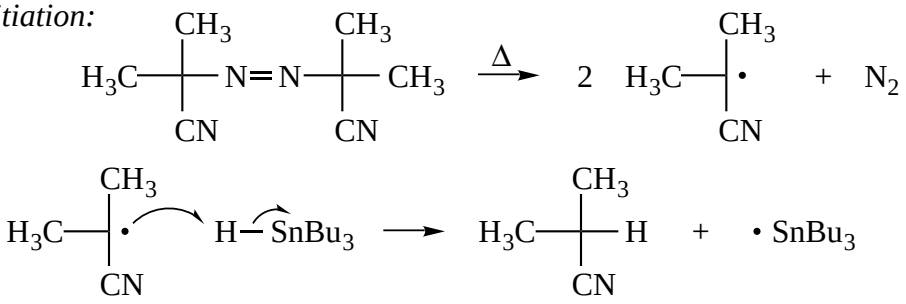


(y) Reduction of the ketone by SmI_2 gives the ketyl. Addition of the C radical to ethyl acrylate gives a new radical, which undergoes further reduction by SmI_2 to give the ester enolate. Workup gives a γ-hydroxyester alcohol, which closes up to the lactone (cyclic ester).

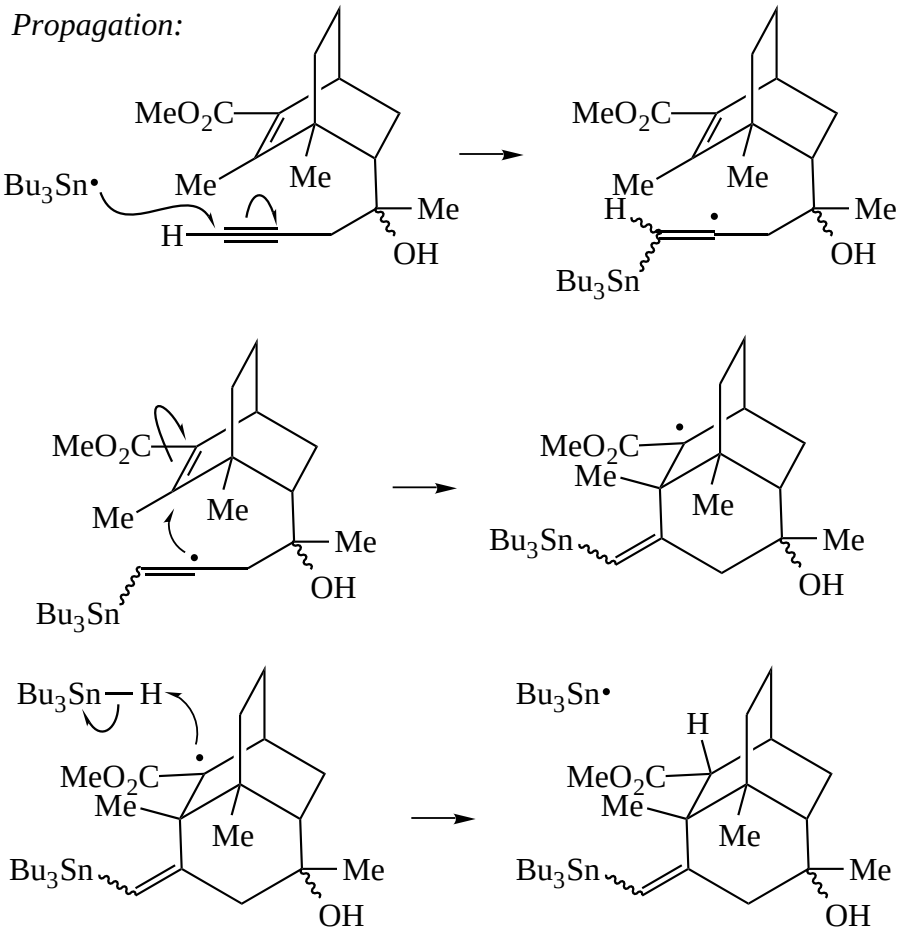


(z) The $Bu_3Sn\cdot$ adds to the alkyne to give an alkenyl radical, which then undergoes intramolecular addition to give an alkyl radical. This radical is quenched from the less hindered side to put the carboxylate group in the more sterically hindered position.

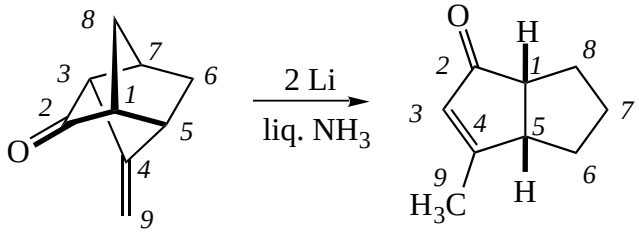
Initiation:



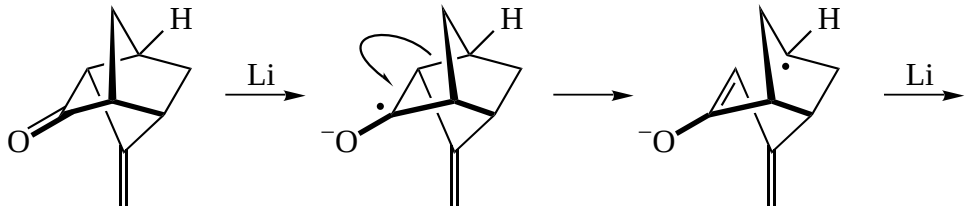
Propagation:

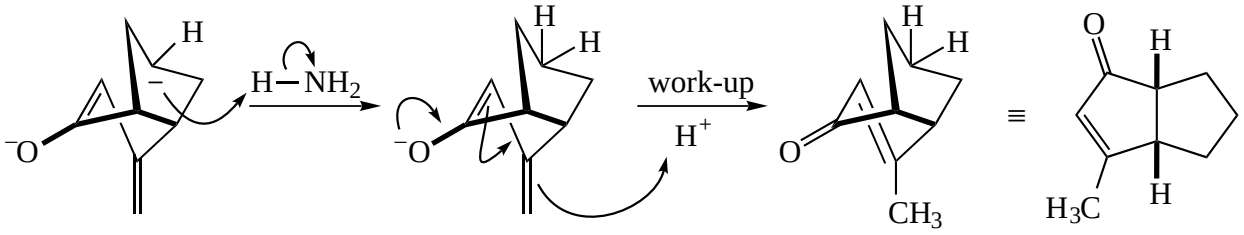


(aa) The easiest atoms to assign in the product are C2, C9 and C4. Break: C3–C7.

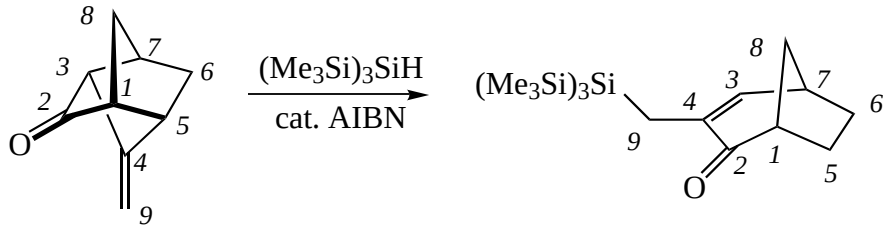


The first step is electron transfer to the C=O π* orbital to make the ketyl. This undergoes homolytic C3–C7 cleavage to give an enolate and a radical at C7. Under the reaction conditions, this radical is reduced by a second equivalent of Li to give a carbanion, which is protonated by NH_3. The enolate is protonated on C9 upon workup.



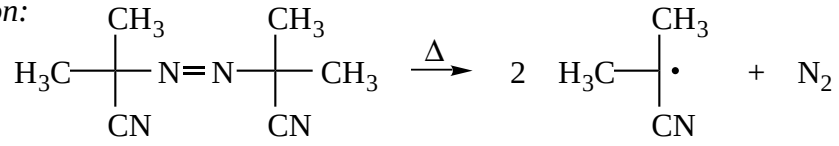


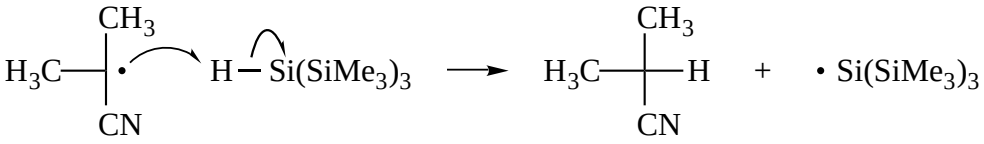
(bb) Again, the easiest atoms to number in the product are C2, C9, and C4. In the product, the bridgehead C next to the carbonyl C2 is going to be either C1 or C3; this C is more likely to be C1, since it is bound to two CH_2's, and in the starting material C1 is bound to one CH and one CH_2 while C3 is bound to no CH_2's. From there the numbering is clear. Make: Si–C9, C4–C2. Break: C2–C3, C4–C5.



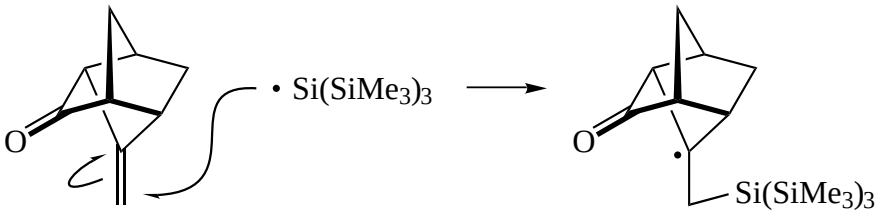
This is an intermolecular reaction, so it's going to be a chain process. Initiation has the AIBN-derived radical remove H from Si. In the propagation, the Si radical adds to C9. From there, two pathways are possible. *Either* we can make C4–C2, then cleave C3–C2, *or* we can cleave C2–C3, then make C4–C2. Either way, the final steps are the cleavage of C4–C5, then abstraction of H· from Si–H to start the propagation again.

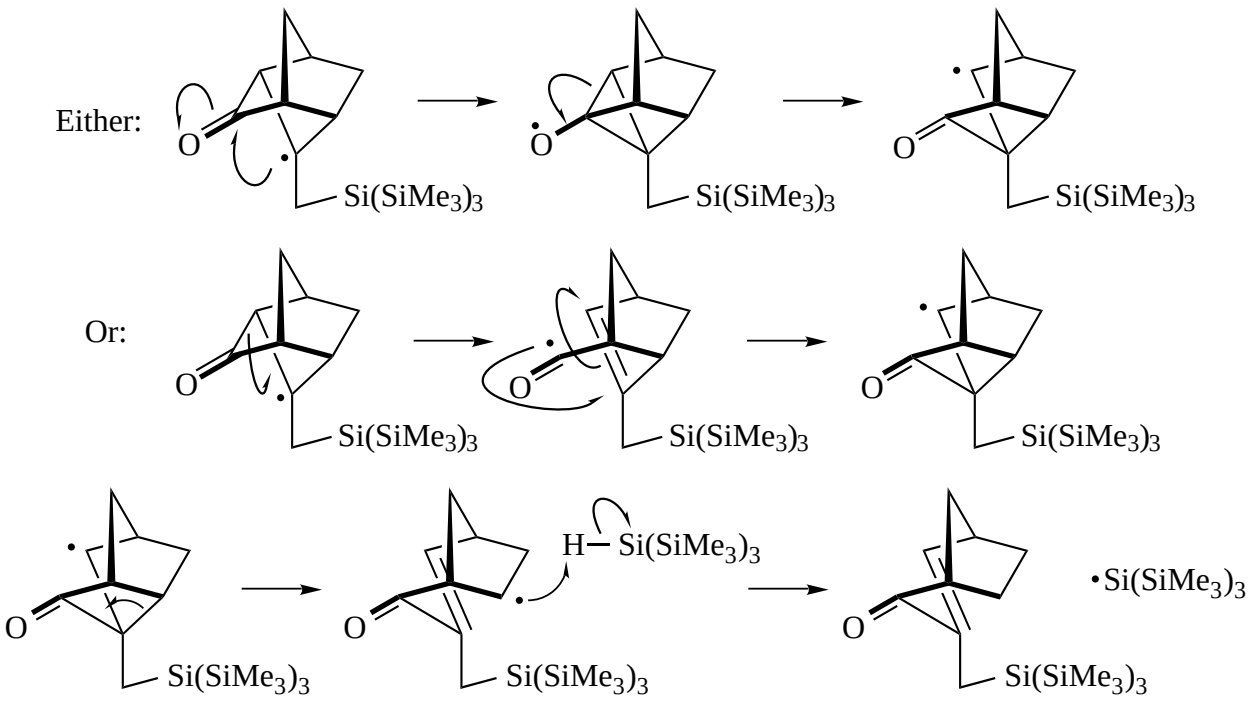
Initiation:



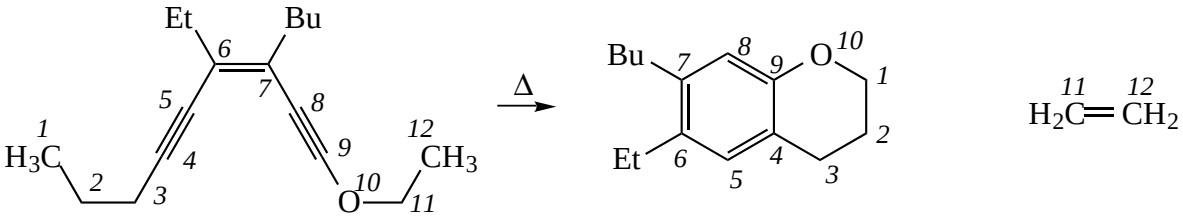


Propagation:

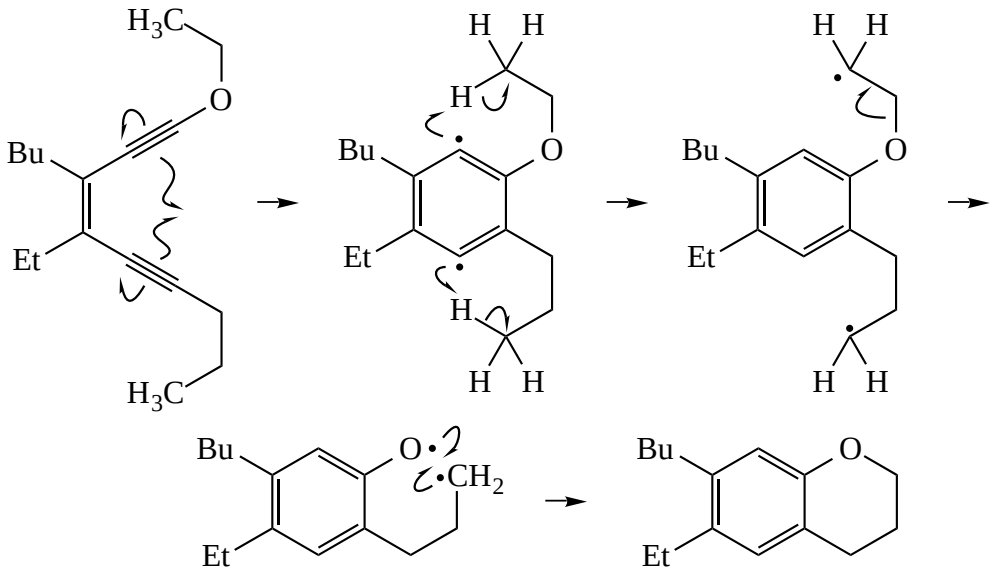




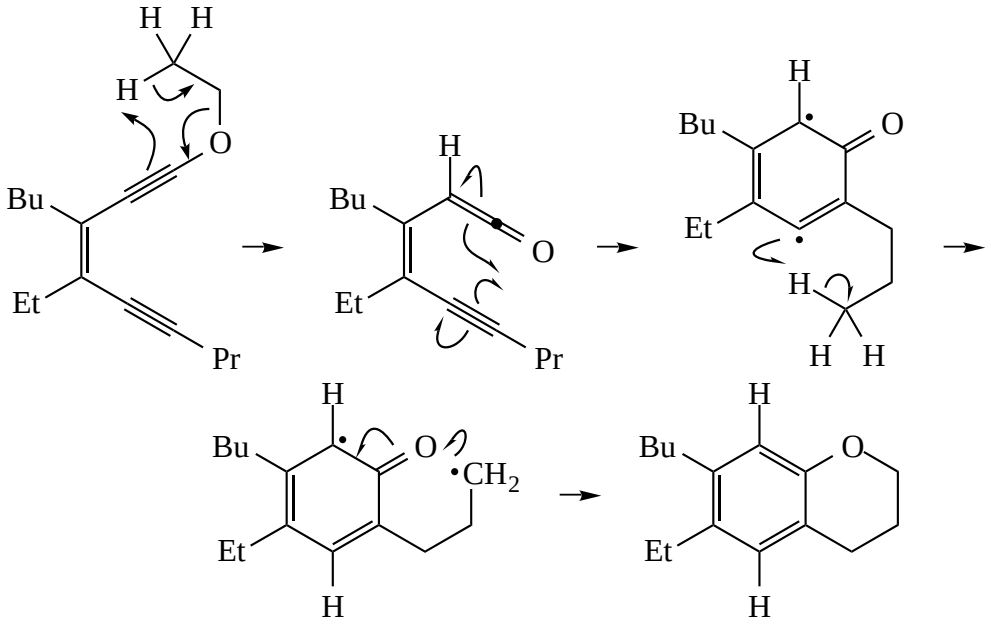
(cc) A molecule of ethylene is lost. Make: C1–O10, C4–C9. Break: O10–C11.



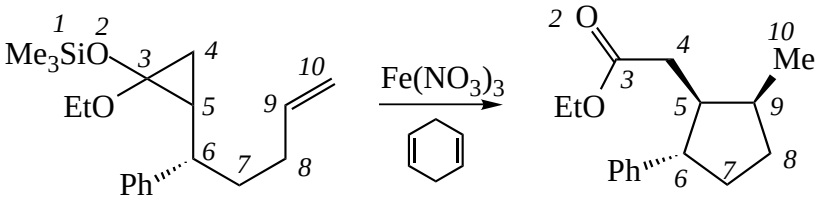
Enediynes tend to undergo Bergman cyclizations, and the C4–C9 bond can be made in this way. The C5 and C8 radicals produced thereby can each abstract H· from C1 and C12, respectively. Fragmentation of the C10–C11 bond, then radical–radical combination gives the product.



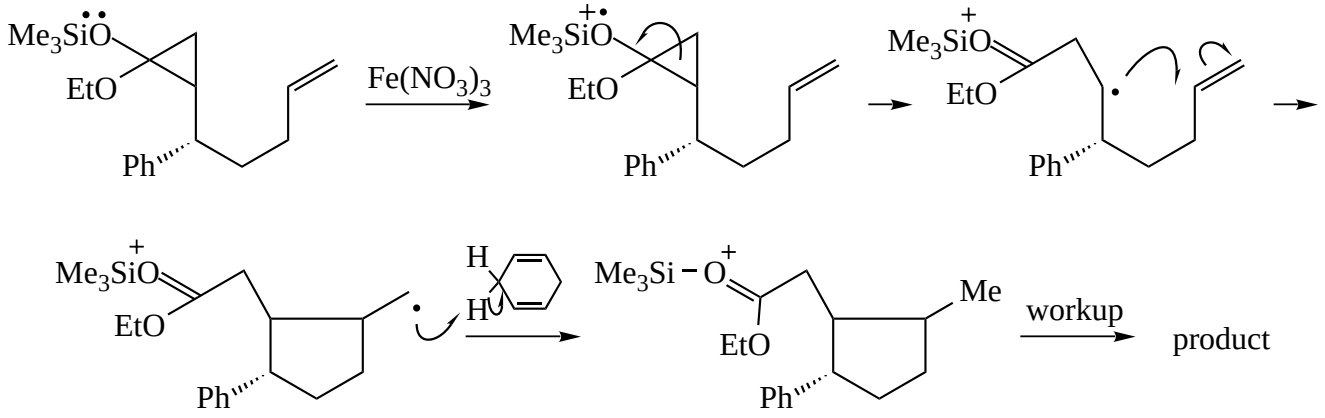
Alternatively, a retro-ene reaction cleaves the O10–C11 bond and gives a highly unsaturated ketene. The ketene can undergo cycloaromatization to give a diradical intermediate. H· abstraction and radical–radical recombination then give the product.



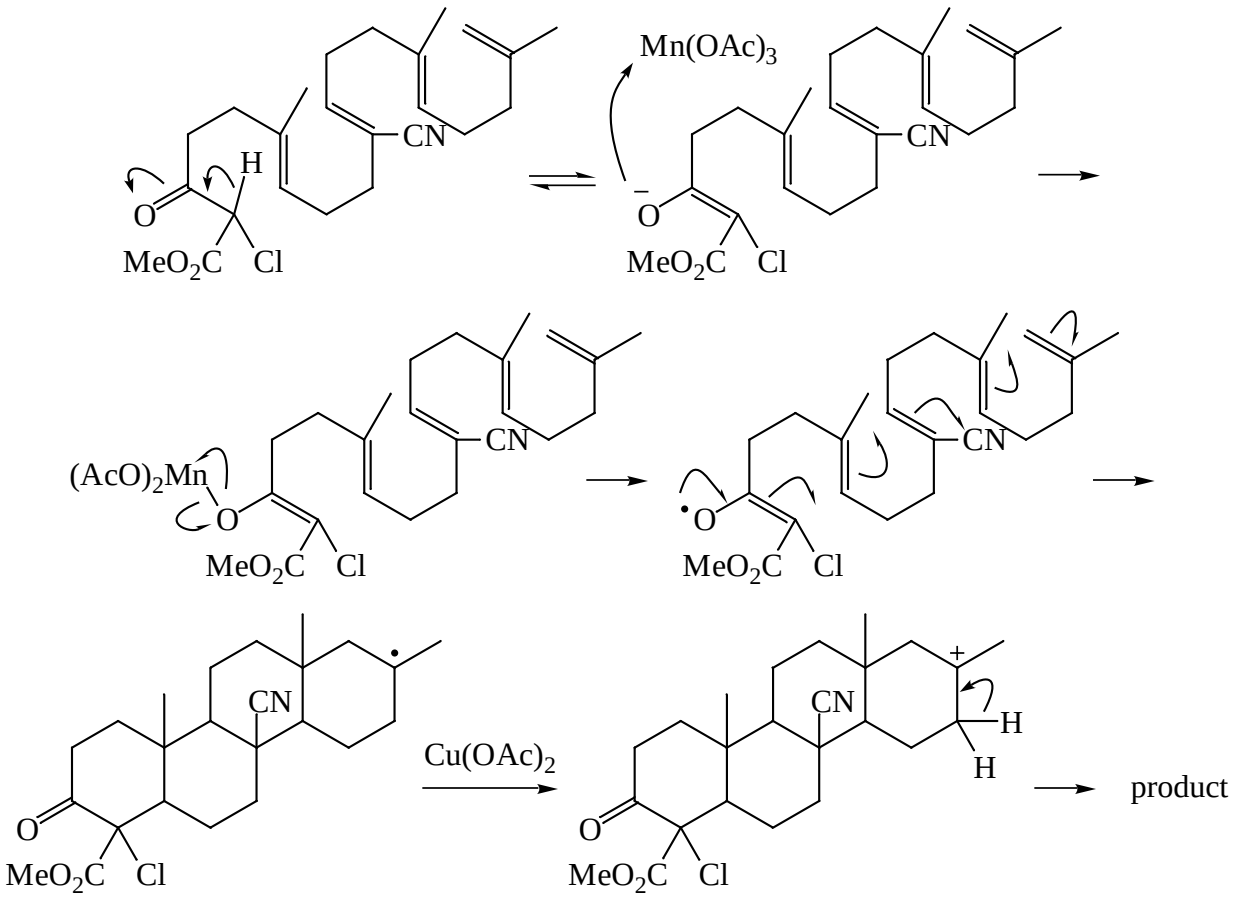
(dd) Make: C5–C9. Break: Si1–O2, C3–C5.



$Fe(NO_3)_3$ has the same reactivity as CAN, a one-electron oxidizing agent. The $Fe(NO_3)_3$ will remove the electron highest in energy from the substrate. Such an electron would have to be one of the unshared electrons of the O atoms. After removal of an electron from O2, the C3–C5 bond can fragment to give a C5 radical, which can add to C9 and generate a new radical at C10. The C10 radical then abstracts H· from 1,4-cyclohexadiene. Si1 is lost from O2 upon aqueous workup.



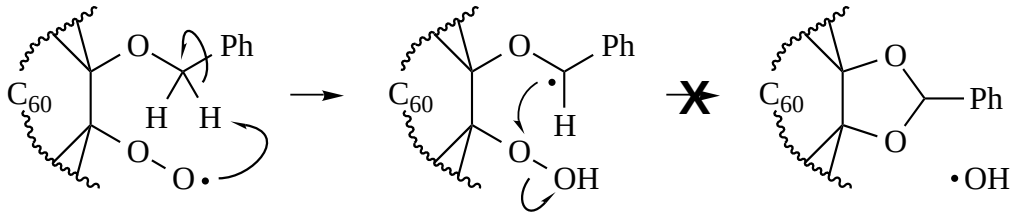
(ee) The purpose of $Mn(OAc)_3$ is to make an enoxy radical. This occurs by formation of the Mn(III) enolate followed by homolytic cleavage of the Mn–O bond. A cascade free-radical cyclization then occurs (either in one step or stepwise) to give the fully cyclized radical. $Cu(OAc)_2$ then promotes another one-electron oxidation to give a carbocation, which loses H^+ to give the product.



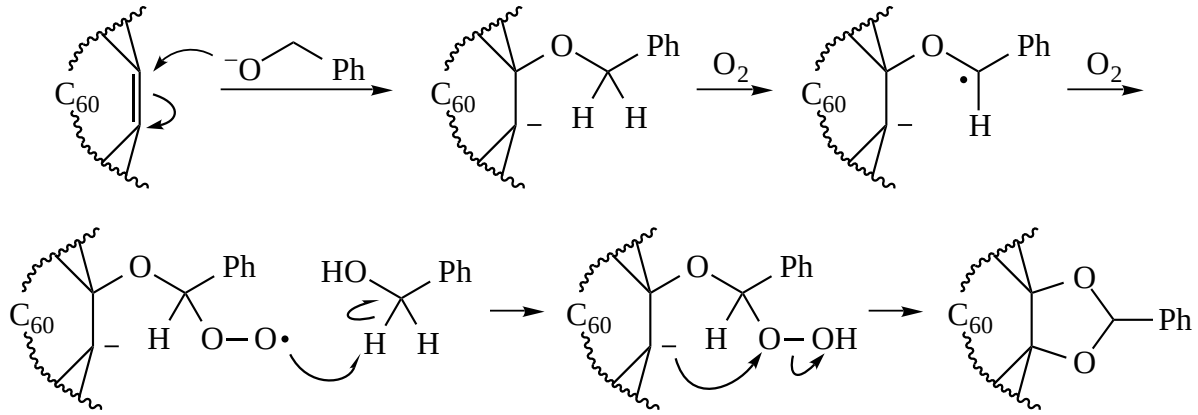
4. (a) The third step, combination of O_2 with a radical, is reasonable. The fourth step, abstraction of H· from an O–H bond by ROO·, is *not* reasonable, because the alkylperoxy radical is much more stable than the alkoxy radical. The radical could abstract H·, but not from an O–H bond. The fifth step is reasonable, assuming that the benzyloxy radical could be formed in the first place. The sixth step, abstraction of RO·

from an RO–OH bond by a stable alkyl radical, is *very doubtful*. HO· is a very high energy species that is only very rarely seen in organic reactions, and reaction mechanisms claiming HO· as an intermediate or by-product must be viewed with great skepticism. (It is, however, an important biological radical.) Also, abstractions of first row atoms are not common, and the proposed ·OH abstraction reaction is expected to be quite slow.

(b) The fourth and fifth steps could be combined to give a reasonable step. That is, the peroxy radical could directly abstract H· from the benzylic bond in an intramolecular fashion to give a benzylic radical and the hydroperoxy compound. This would require a seven-membered TS, but at least the H· would be abstracted from a relatively weak bond. Unfortunately, this would not solve the problem of the sixth step.

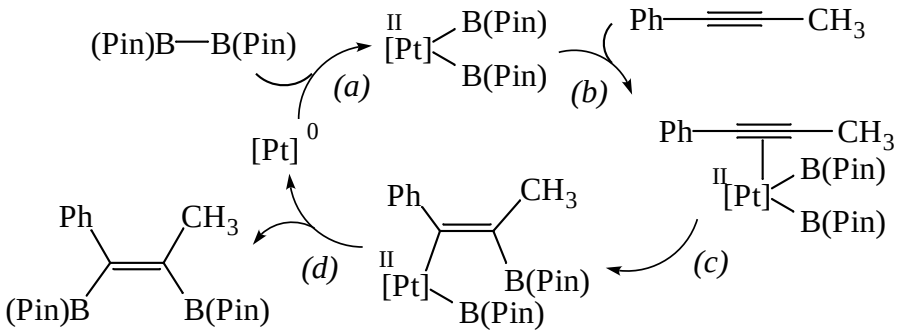


A better possibility: $PhCH_2O^-$ adds to C_{60}. Then autoxidation of a benzylic C–H bond occurs to give the hydroperoxide. Then the C_{60} carbanion displaces OH^- from the hydroperoxide to give the product.



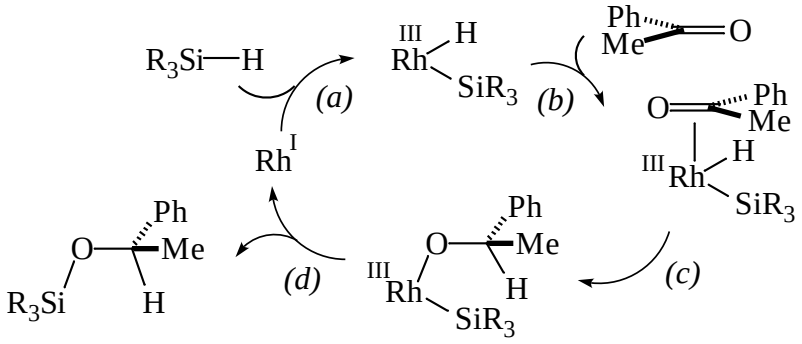
Answers To Chapter 6 In-Chapter Problems.

6.1. The mechanism is identical to hydrogenation, with $[(pin)B]_2$ replacing H_2 and [Pt] replacing Pd. The number of ligands attached to Pt is uncertain, so it is permissible to write [Pt] instead of $(Ph_3P)_2Pt$ or $(Ph_3P)_3Pt$.



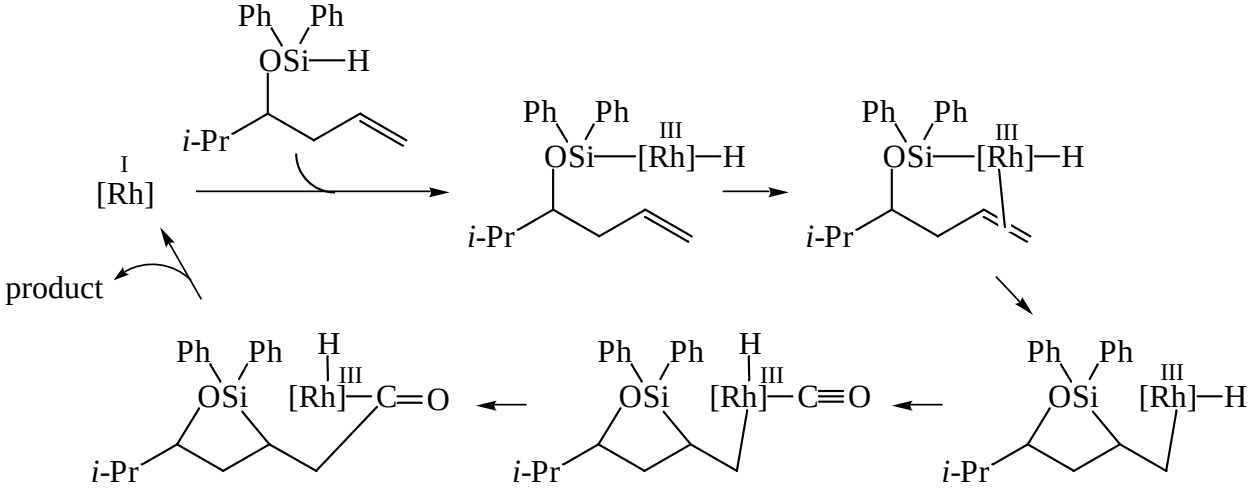
(a) oxidative addition;
(b) coordination;
(c) insertion;
(d) reductive elimination.

6.2. The mechanism begins the same, but after coordination of the C=O π bond to Rh, a Si–Rh–O intermediate is obtained. Reductive elimination gives the identical product.



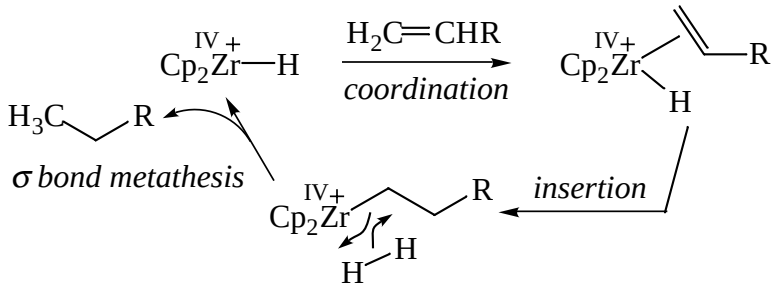
(a) oxidative addition;
(b) coordination;
(c) insertion;
(d) reductive elimination.

6.3. The mechanism proceeds by insertion of Rh(I) into the Si–H bond, coordination of the C=C π bond to Rh(III), insertion of the π bond into the Rh–Si bond, coordination of CO to Rh(III), insertion of CO into the Rh–C bond, and reductive elimination to give the product and regenerate Rh(I).

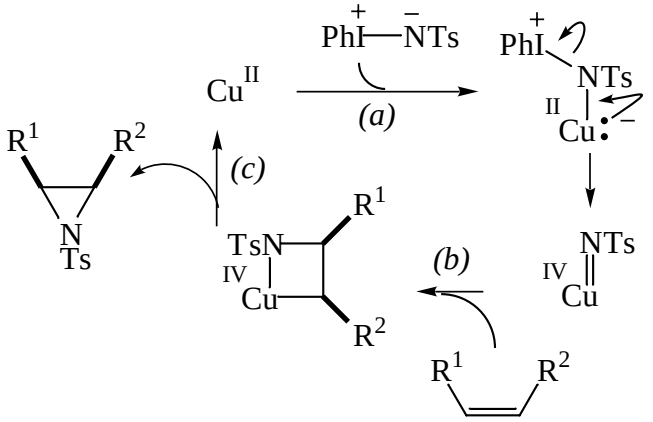


6.4. The isomerization of alkylzirconocenes proceeds by a series of β-hydride eliminations and insertions. Because the C(sp^2)–Zr bond is much stronger than the C(sp^3)–Zr bond, and because the allene product that would be generated by β-hydride elimination from an alkenylzirconocene is high in energy, the β-hydride elimination is uphill in energy.

6.5. An alkylzirconocene undergoes σ-bond metathesis with H_2 gas to give the alkane and Cp_2ZrH^+. Coordination and insertion of the alkene into the Zr–H bond regenerates the alkylzirconocene.



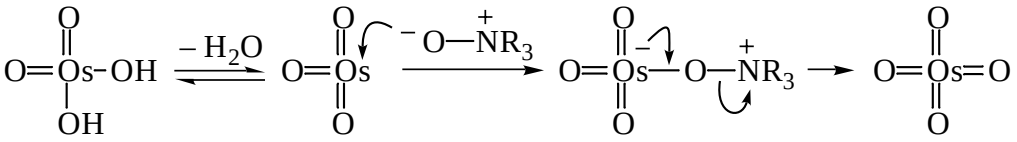
6.6. The reagent PhI=NTs can be drawn in the resonance form $Ph\overset{+}{I}–\overset{-}{N}Ts$, where its resembalnce to ClO^- becomes clear. Moreover, the issues of the square planar coordination sphere of the Mn(salen) complex don't exist with Cu(II), so a very simple mechanism can be drawn: coordination of the N of the reagent to Cu(II), displacement of PhI by a lone pair on Cu to give a Cu(IV)=NTs reagent, [2 + 2] addition to the alkene, and reductive elimination.



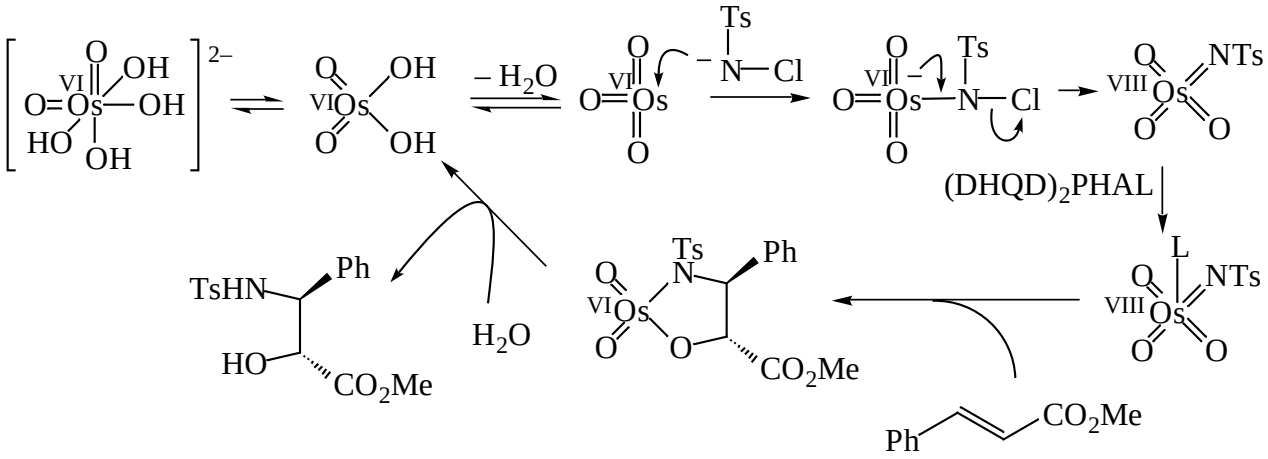
(a) coordination;
(b) [2+2] cycloaddition;
(c) reductive elimination.

Unfortunately, there's a problem with this mechanism, too: Cu doesn't like to be in the IV oxidation state. A more likely mechanism begins with one- or two-electron reduction of Cu(II) to Cu(I) or Cu(0), followed by a Cu(I)/Cu(III) or a Cu(0)/Cu(II) catalytic cycle. The electrons for the reduction would have to come from the PhI=NTs reagent.

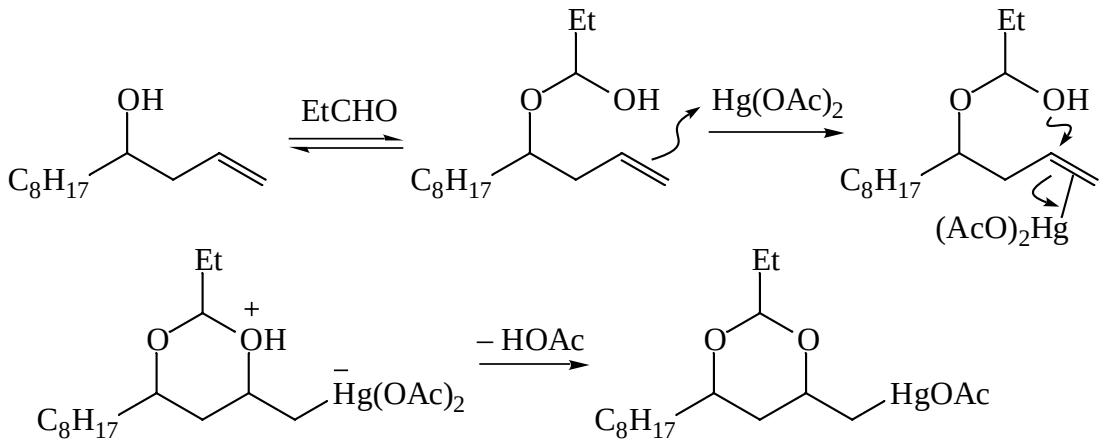
6.7. $OsO_2(OH)_2$ is in equilibrium with OsO_3. Addition of the amine oxide O to Os gives an Os(VI) ate complex, and a lone pair from Os displaces NR_3 to give OsO_4.



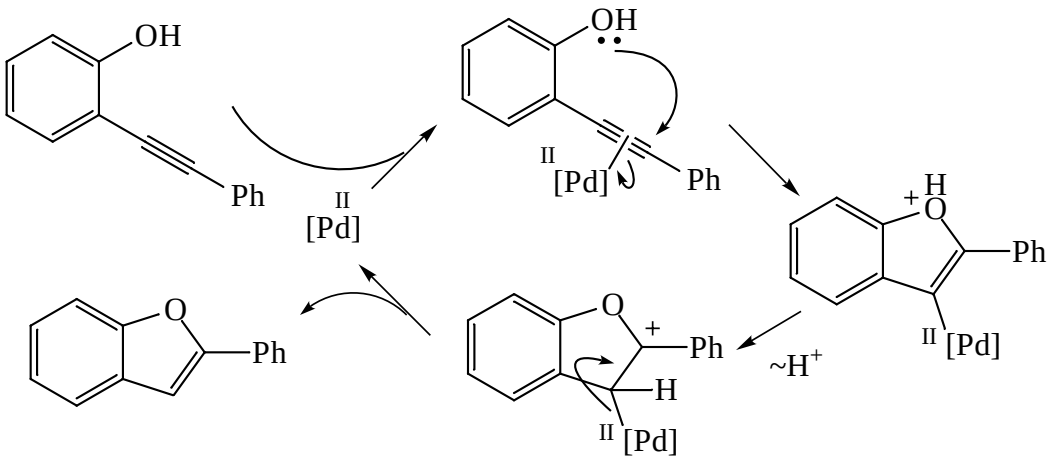
6.8. As before, $K_2OsO_2(OH)_4$ is in equilibrium with OsO_3. TsNCl adds to Os, which uses a lone pair to displace Cl from N and give the key Os(VIII) intermediate. Coordination of the Sharpless ligand creates a complex that adds rapidly to the alkene. Hydrolysis of the Os(VI) product regenerates $OsO_2(OH)_2$ and provides the product.



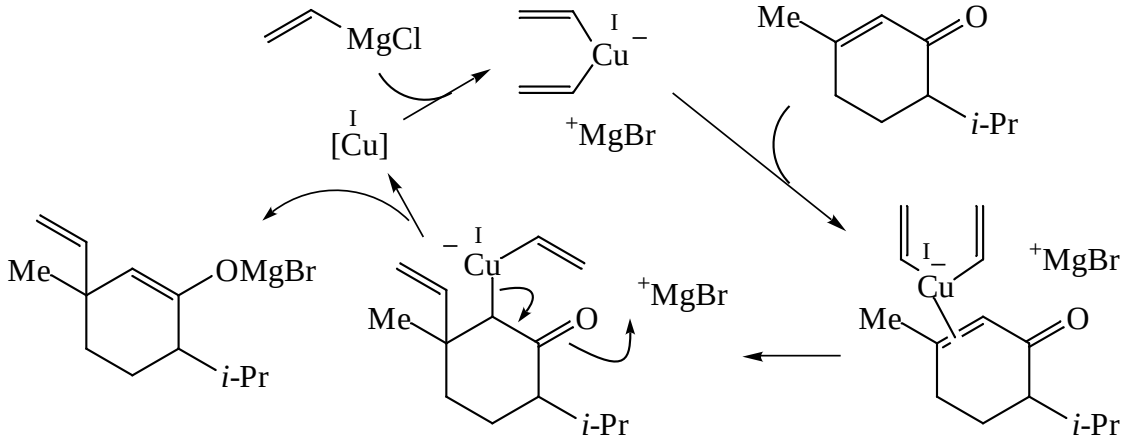
6.9. The alcohol and aldehyde are in equilibrium with the hemiacetal. Coordination of Hg(II) to the alkene is followed by attack of the hemiacetal O on the alkene to give, after loss of AcOH, the product.



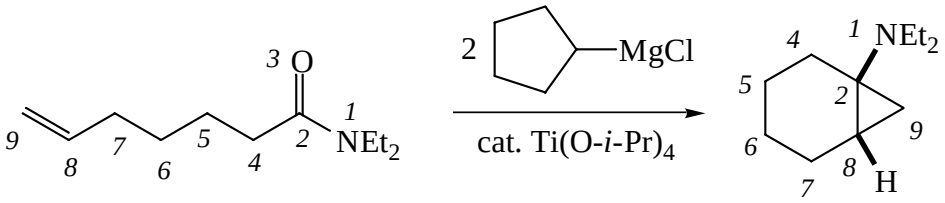
6.10. Coordination of the alkyne to Pd(II) is followed by attack of O on the distal C to give the furan ring with the C–Pd σ bond. Proton transfer from O to the C bearing the Pd is followed by fragmentation of the C–Pd bond to give the product and to regenerate Pd(II). Instead of protonating C, one could protonate Pd and show a reductive elimination to give the same product.



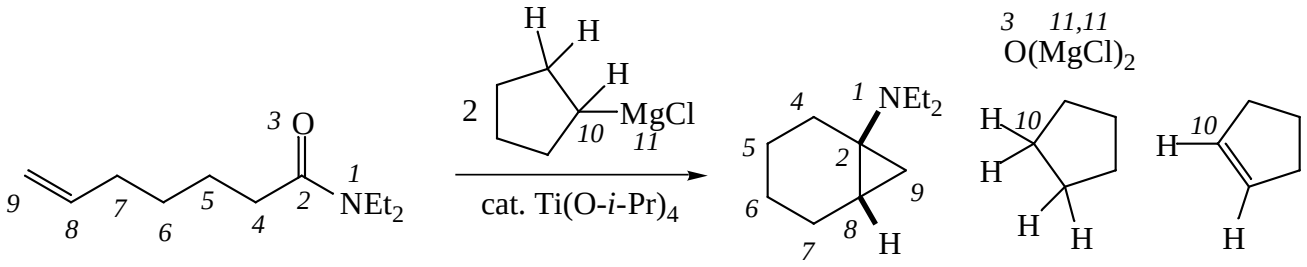
6.11. The mechanism is very similar to the stoichiometric one, except that the key dialkylcuprate reagent is made from transmetallation of the Grignard reagent.



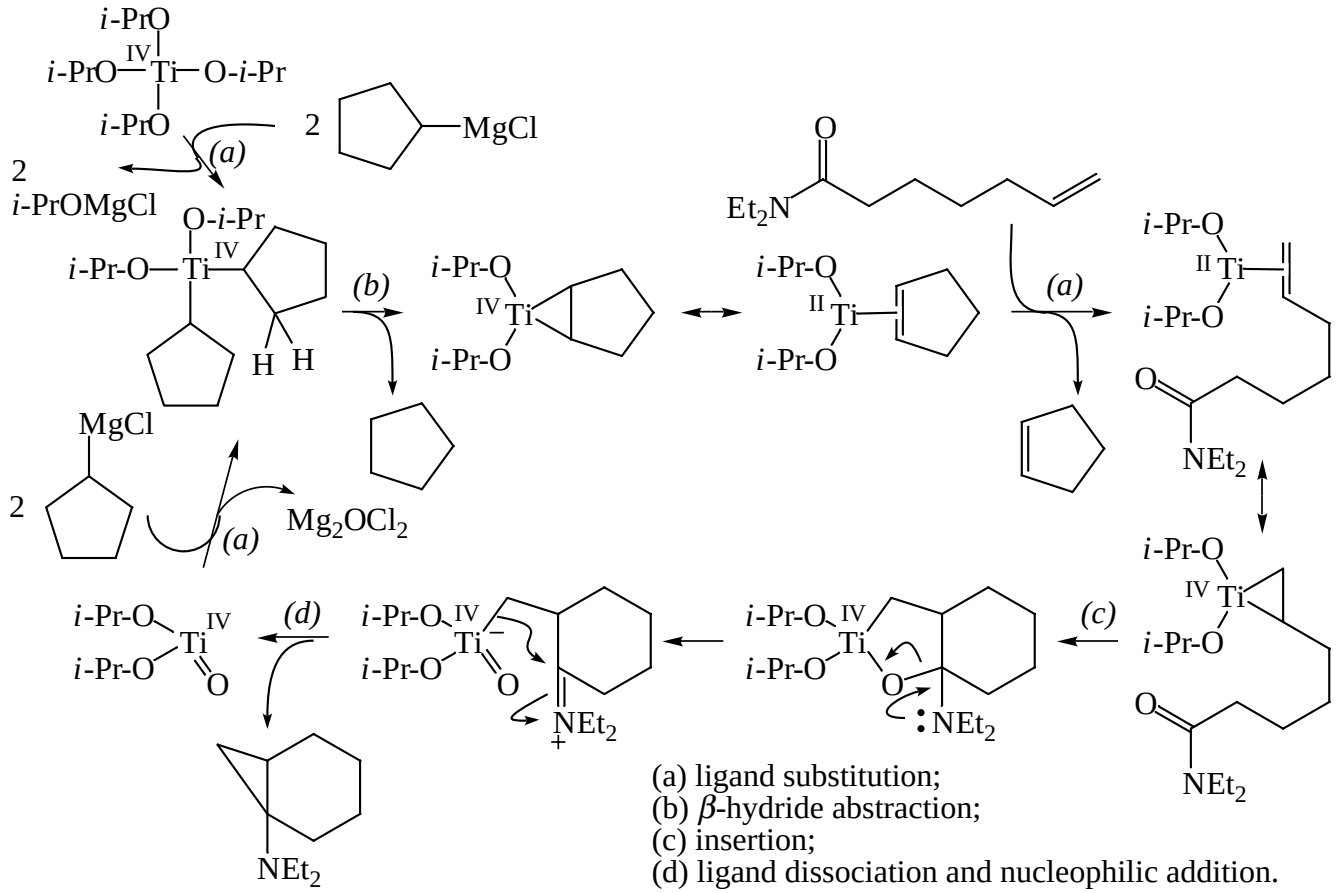
6.12. As usual, we number the heavy atoms.



Hold on! The product is missing O3. Where did it go? Also, what happens to the two equivalents of C_5H_9MgCl? It makes sense that O3 should be bound to two ^+MgCl ions at the end of the reaction. That leaves two C_5H_9 groups to account for. Perhaps they are disproportionated into C_5H_{10} and C_5H_8. Make: C2–C8, C2–C9, O3–Mg11 (twice). Break: C2–O3, C10–Mg11 (twice).



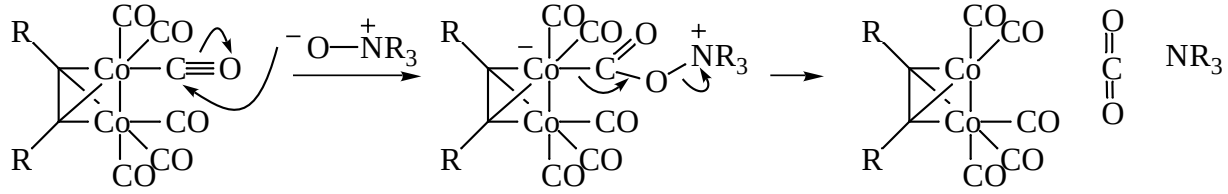
The Grignard reagent is obviously a nucleophile. Although C2 is an electrophile, we do not make a C2–C10 bond, so that is not the first step. The first step is substitution of two *i*-PrO groups on Ti with two C_5H_9 groups. β-Hydride abstraction then occurs to give C_5H_{10} and a titanacyclopropane, which is a resonance form of Ti(II)–C_5H_8 complex. Exchange of the C_5H_8 alkene ligand for the substrate alkene gives a new Ti(II)–alkene complex, which is a resonance form of a Ti(IV) titanacyclopropane. This ligand exchange converts both C8 and C9 into nucleophiles. Insertion of the C2=O3 π bond into the C8–Ti bond gives a titanafuran with a new C8–C2 bond. This compound can also be described as an *O*-titanahemiaminal. The lone pair can be used to cleave the C2–O3 bond and give an iminium ion and a Ti(IV) alkyl ate complex, which is nucleophilic at C9. Attack of C9 on C2 gives the desired product and a Ti(IV) oxide, which undergoes ligand substitution with two equivalents of C_5H_9MgCl to complete the catalytic cycle.



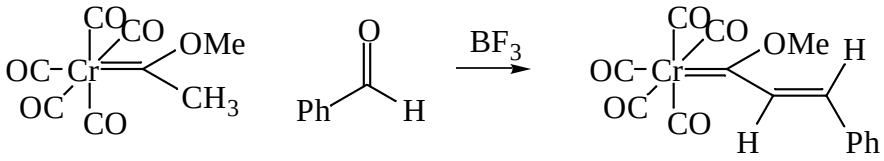
(a) ligand substitution;
(b) *β*-hydride abstraction;
(c) insertion;
(d) ligand dissociation and nucleophilic addition.

6.13. The question should read: NMO oxidizes one CO ligand of the alkyne–$Co_2(CO)_6$ complex to CO_2 and gives an alkyne–$Co_2(CO)_5$ complex. Write a mechanism for this transformation.

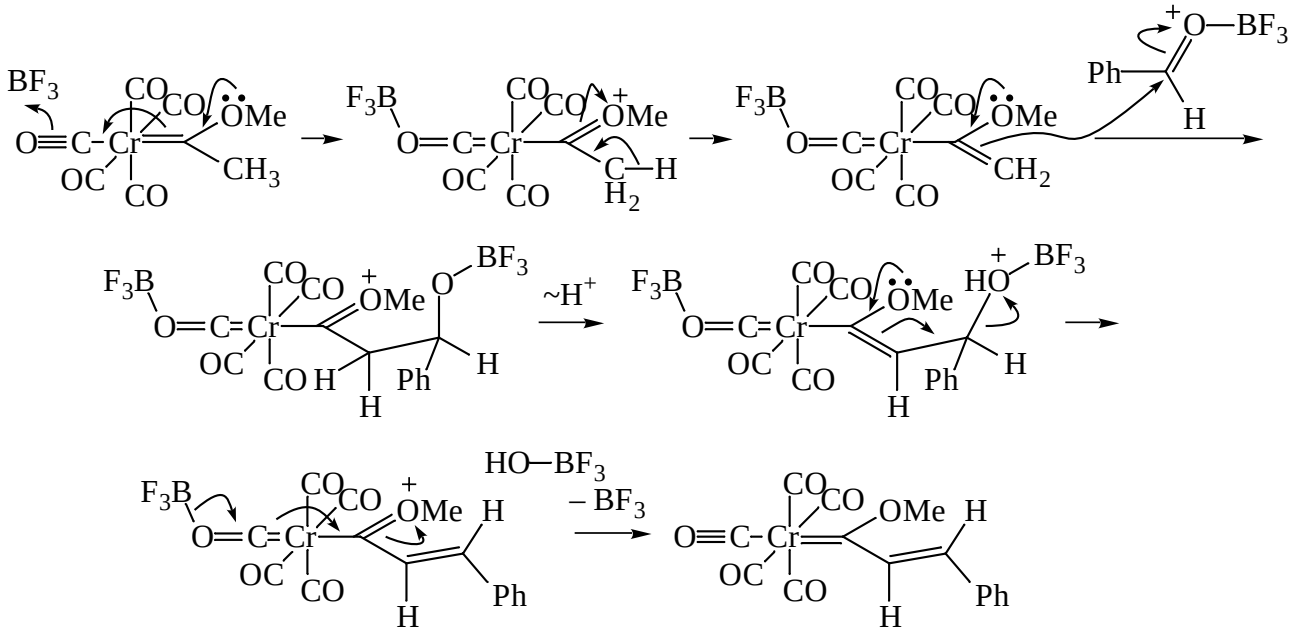
The mechanism begins with nucleophilic attack of the amine oxide O on a CO ligand to give a species that looks something like an ester. The Co–C bond then cleaves, with the electrons being used by C to make a π bond to O and expel NR_3.



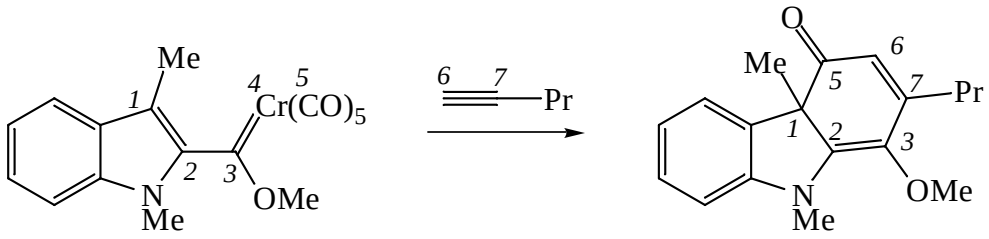
6.14. This reaction can be viewed as an acid-catalyzed aldol reaction between an ester and an aldehyde, where the carbonyl O of the ester is replaced with a $(CO)_5Cr$ group.



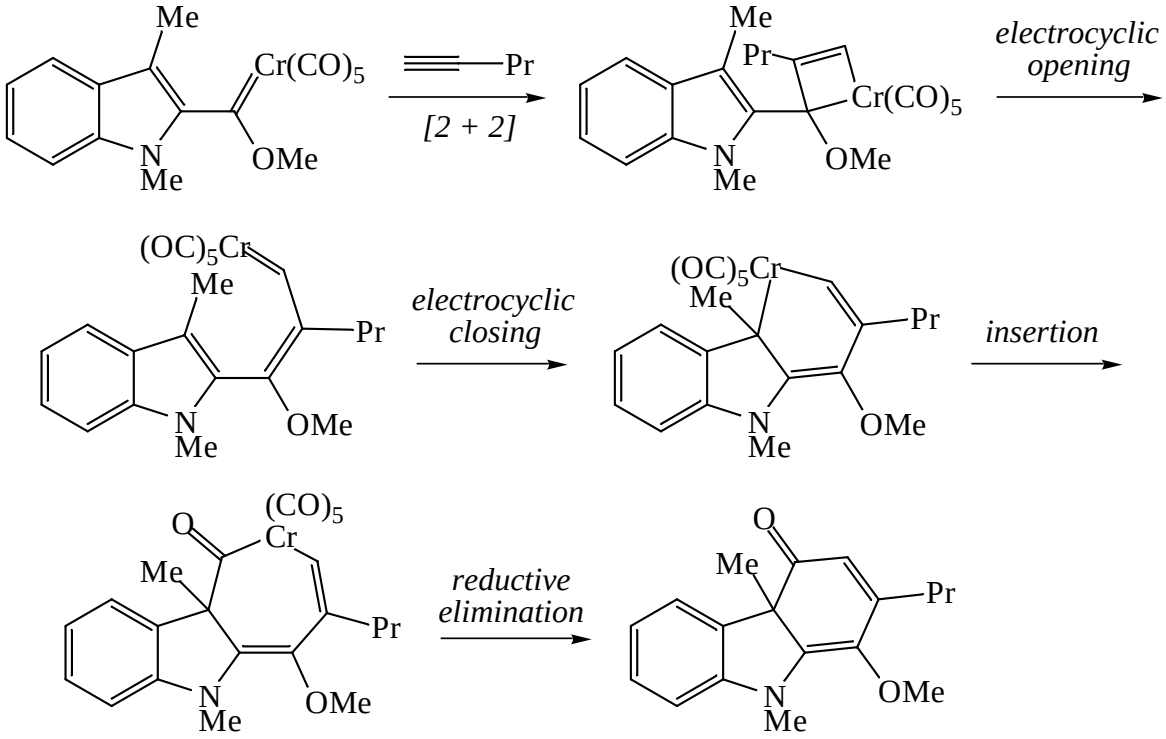
The mechanism proceeds by BF_3-catalyzed conversion of the Cr carbene complex to an "enol", followed by attack on the BF_3-complexed aldehyde.



6.15. Make: C1–C5, C3–C7, C5–C6. Break: C3–Cr4, Cr4–C5.

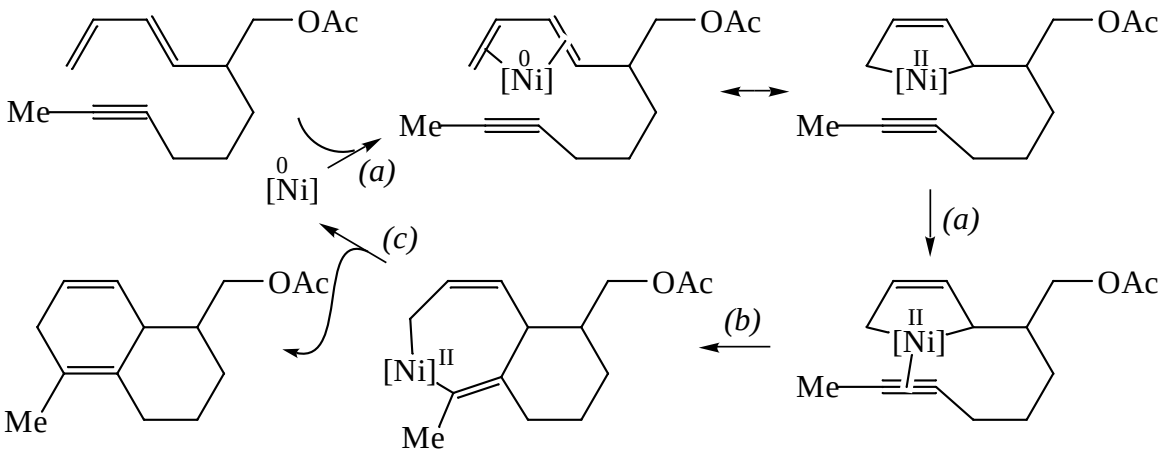


The mechanism begins with a [2 + 2] cycloaddition between the Cr=C bond and the C≡C bond to form the C3–C7 bond and give a chromacyclobutene. Electrocyclic ring opening breaks the Cr4–C3 bond to give an allylidenechromium compound. At this point, several pathways are possible; one is shown below. Electrocyclic ring closing of the 1,3,5-triene system gives a chromacyclohexadiene, insertion of CO into the Cr–C1 bond (or Cr–C6 bond) occurs, and reductive elimination gives the product.



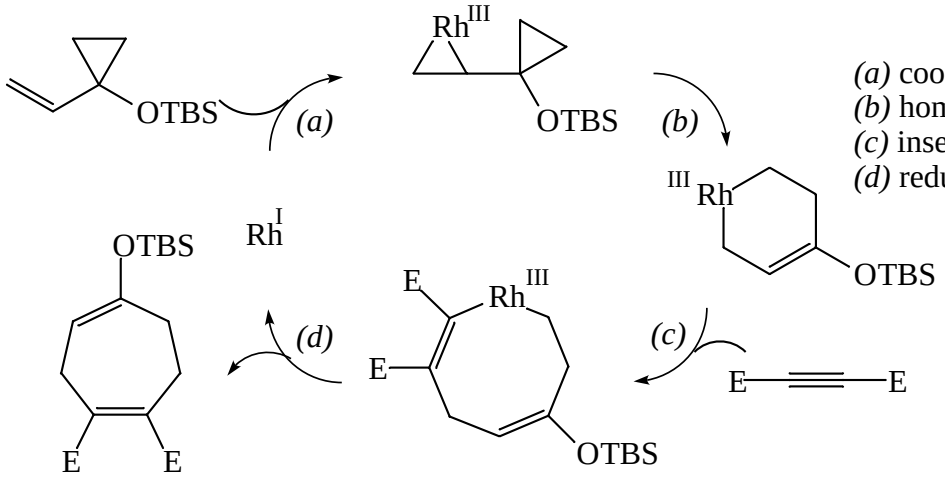
An alternative end-game has the CO insert into the Cr=C bond of the allylidenechromium compound to give a Cr complex of a ketene. Electrocyclic ring closing of the ketene would then give the product.

6.16. The purpose of the P compound is to coordinate to Ni(0) and keep it in solution throughout the course of the reaction. Coordination of the diene to Ni(0) gives a complex that can also be drawn as a Ni(II) nickelacyclopentene complex. Coordination of the alkyne, insertion, and reductive elimination complete the catalytic cycle.



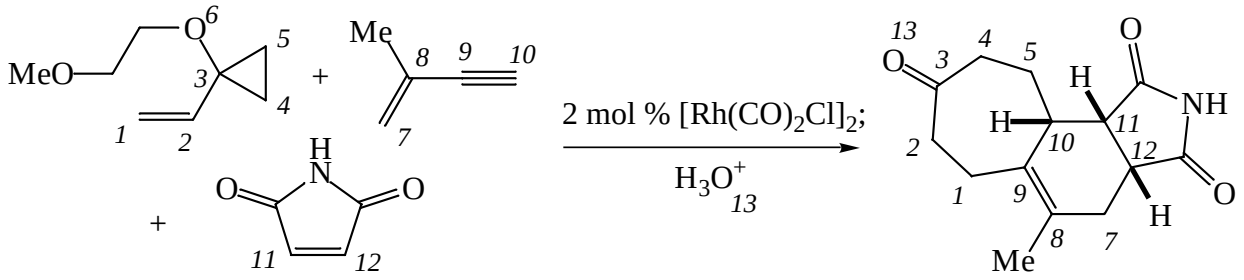
(a) ligand coordination; (b) insertion; (c) reductive elimination.

6.17. Coordination of the Rh(I) to the vinyl group and homoallylic rearrangement gives a rhodacyclohexene. Insertion of the alkyne into a Rh–C bond and reductive elimination completes the catalytic cycle.

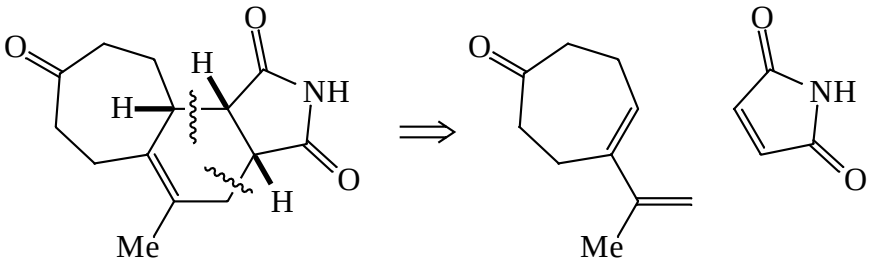


(a) coordination;
(b) homoallylic rearrangement;
(c) insertion;
(d) reductive elimination.

6.18. Make: C1–C9, C3–O13, C5–C10, C7–C12, C10–C11. Break: C3–C5, C3–O6.

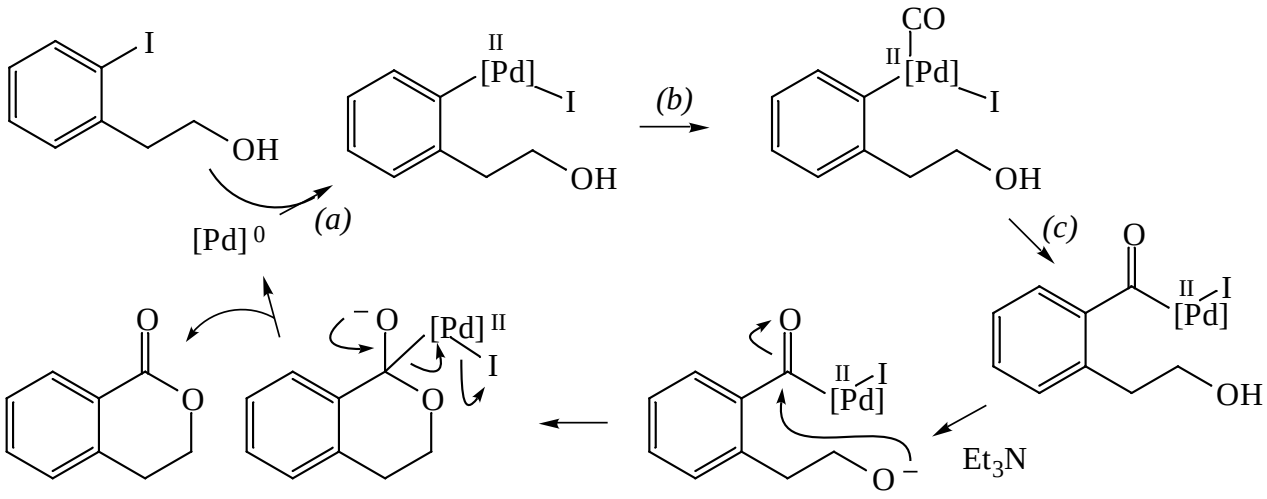


The C7–C12 and C10–C11 bonds can be made by a Diels–Alder reaction (cyclohexene product). This observation simplifies the problem considerably.



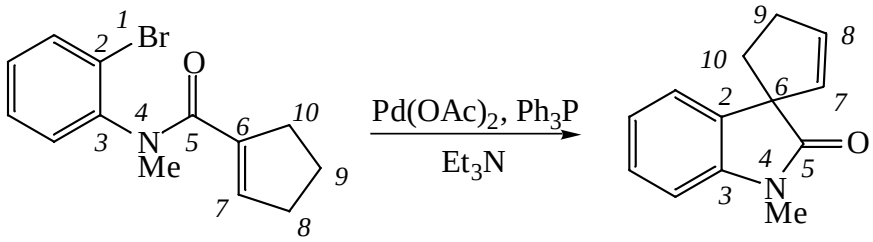
The mechanism for formation of the cycloheptenone is exactly the same as discussed in the book. After a Diels–Alder reaction, the enol ether is hydrolyzed to the ketone by an acid-catalyzed mechanism.

6.19. As is almost always true when when the substrate in a Pd-catalyzed reaction is C(sp^2)–X, the first step is oxidative addition of Pd(0) to the C–I bond to give an arylpalladium(II) intermediate. (Although the Pd compound that is added to the reaction mixture is Pd(II), it is reduced in situ to Pd(0) by the mechanism outlined in the text.) Coordination of CO and insertion into the C–Pd bond gives an acylpalladium(II) intermediate. Deprotonation of the alcohol is followed by nucleophilic attack on the carbonyl C. Expulsion of Pd(0) gives the product and completes the catalytic cycle.



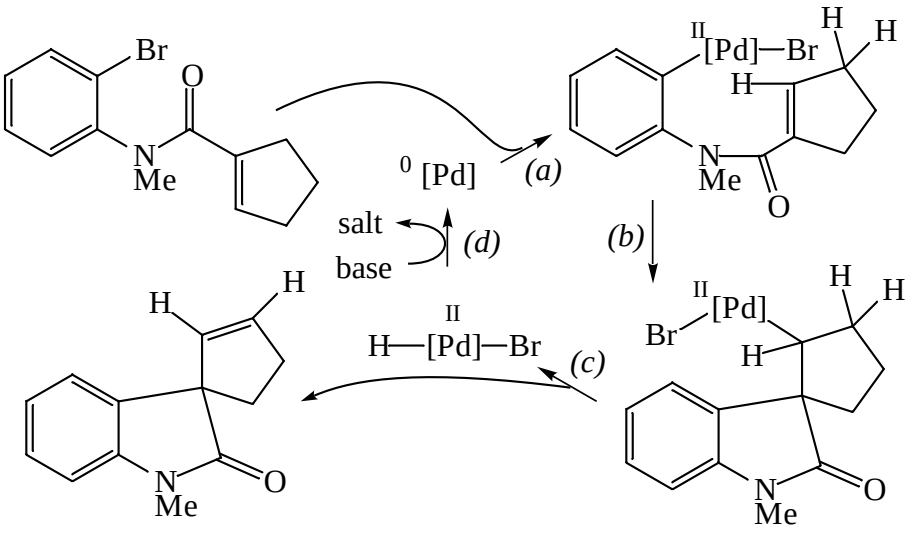
(a) oxidative addition; *(b)* coordination; *(c)* insertion.

6.20. Make: C2–C6. Break: C2–Br. Also, note the loss of one H from C8.



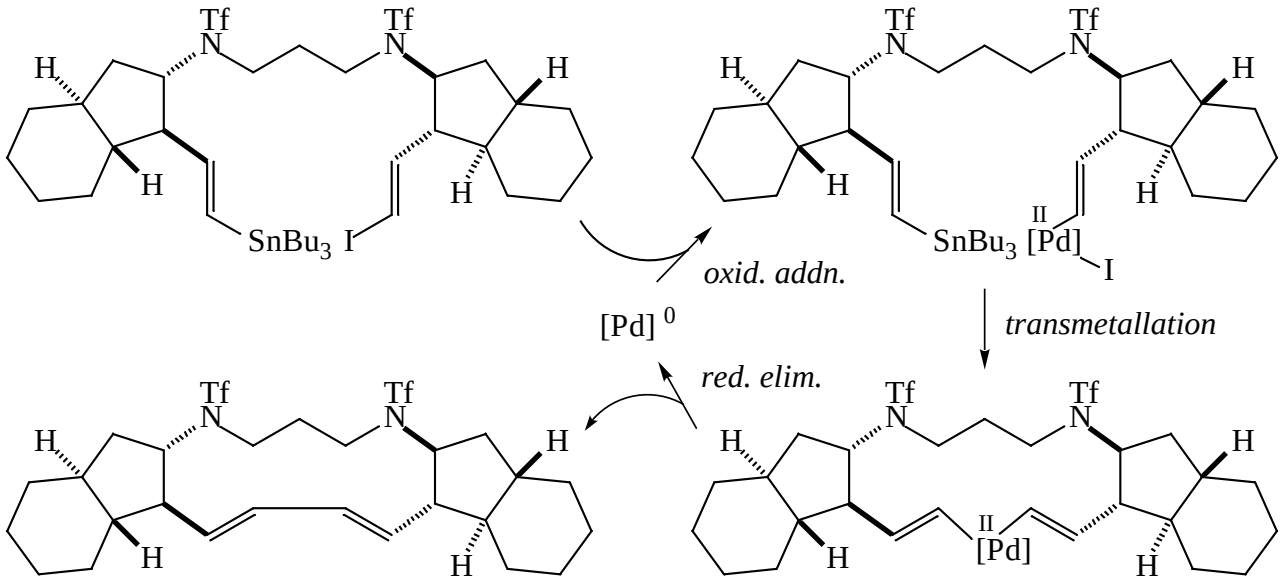
The mechanism begins with oxidative addition of Pd(II) to the C2–Br1 bond to give an arylpalladium(II) compound. (Although the Pd compound that is added to the reaction mixture is Pd(II), it is reduced in situ

to Pd(0) by the mechanism outlined in the text.) Insertion into the C6=C7 π bond is followed by β-hydride elimination, with the H coming from C8, to give the product and H–Pd(II)–Br. Deprotonation of the Pd complex regenerates Pd(0) to complete the catalytic cycle.

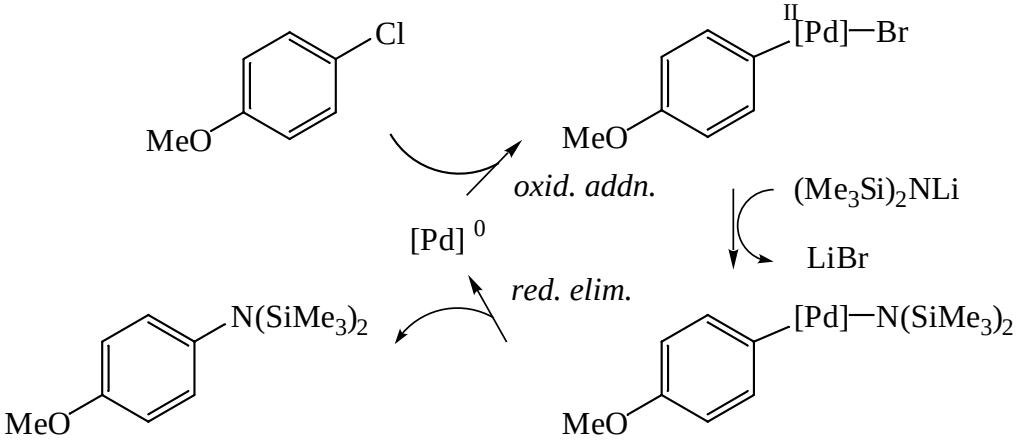


(a) oxidative addition;
(b) coordination, insertion;
(c) β-hydride elimination;
(d) deprotonation, dissociation.

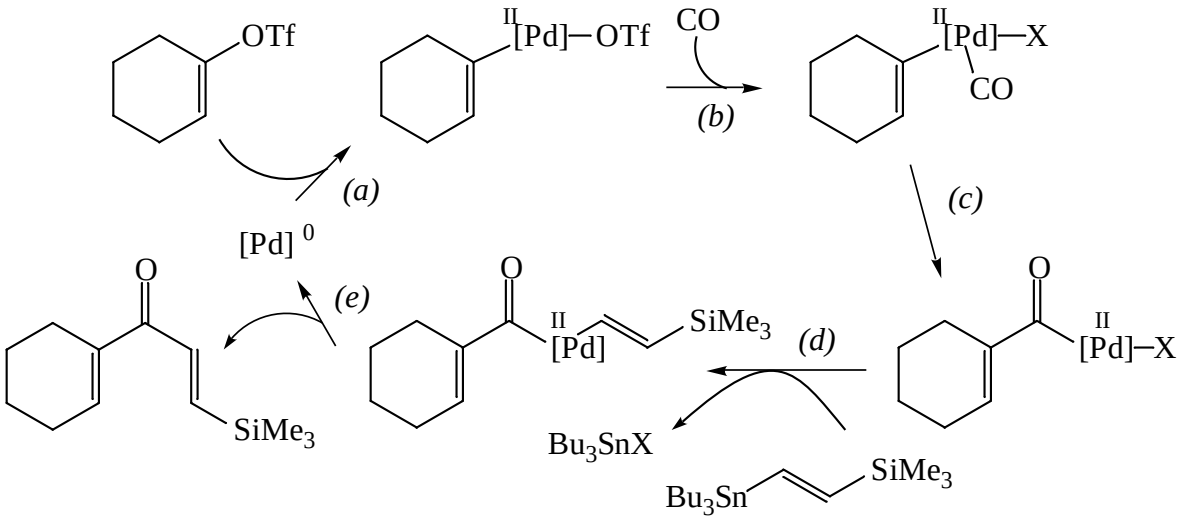
6.21. It proceeds by the standard mechanism for cross-coupling reactions: oxidative addition of Pd(0) to the C–I bond, transmetallation to give the C–Pd(II)–C compound, and reductive elimination.



6.22. Again, it proceeds by the standard mechanism for cross-coupling reactions: oxidative addition of Pd(0) to the C–Cl bond, transmetallation (can also be viewed as ligand substitution) to give the N–Pd(II)–C compound, and reductive elimination.

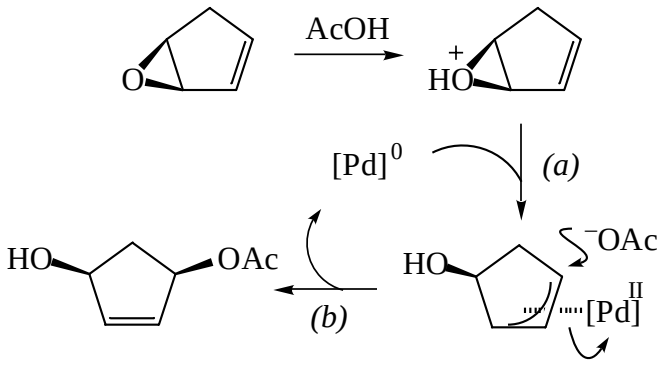


6.23. The mechanism is the same as a regular Stille coupling, except that coordination of CO and insertion into the Pd–C bond intervenes between the oxidative addition and transmetallation steps. At some point the TfO^- group on Pd is exchanged for a Cl^- group.



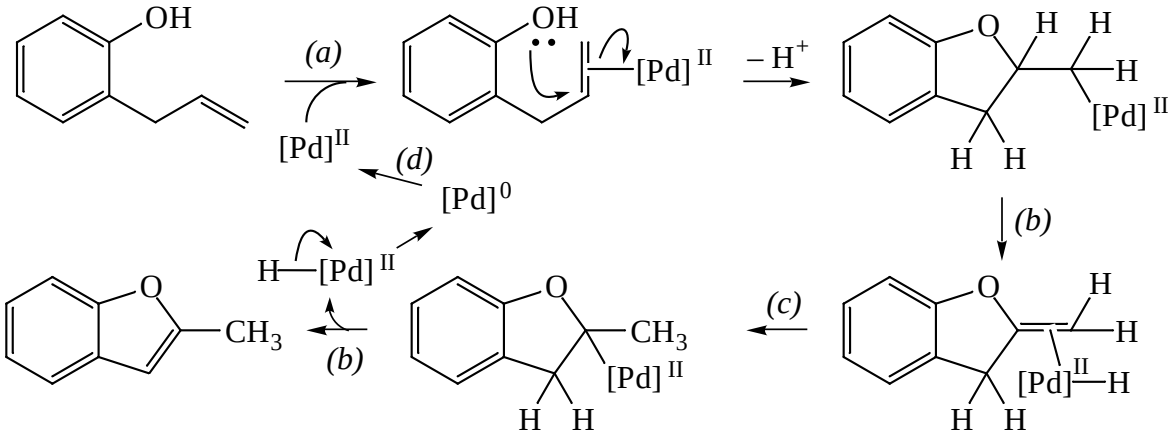
(a) oxidative addition; (b) coordination;
(c) insertion; (d) transmetallation; (e) reductive elimination.

6.24. Protonation of the epoxide by AcOH is followed by nucleophilic ring-opening with Pd(0) (S_N2-type reaction) to give an allylpalladium(II) complex. The AcO^- then attacks the allyl ligand, regenerating Pd(0) and affording the product.



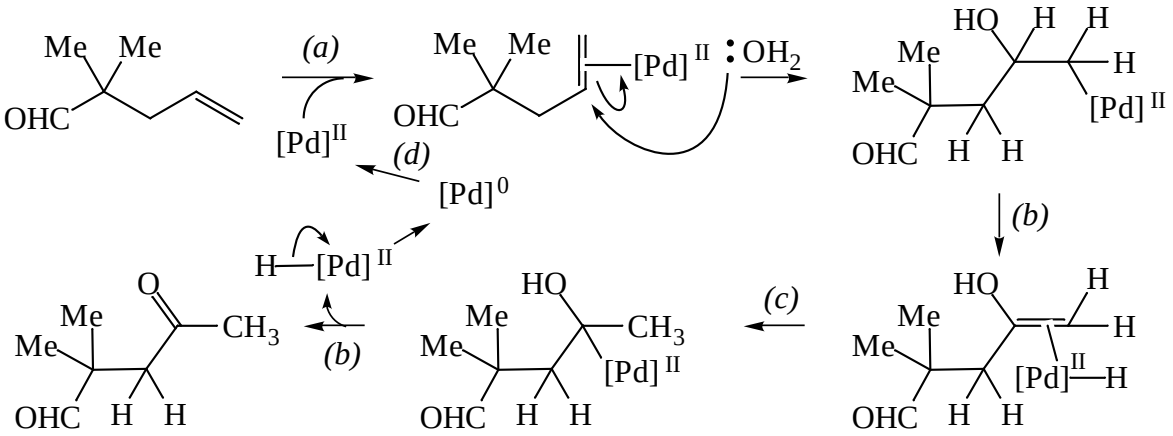
(a) oxidative addition;
(b) nucleophilic displacement ("S_N2").

6.25(a). Coordination of Pd(II) to the alkene converts the alkene into an electrophile, which is attacked by the OH lone pair to give an alkylpalladium(II) complex. β-Hydride elimination, insertion, and a second β-hydride elimination afford the product and a Pd(II) hydride, which is deprotonated to Pd(0). Oxidation of Pd(0) back to Pd(II) is carried out by $Cu(OAc)_2$, and the Cu is then reoxidized by O_2.



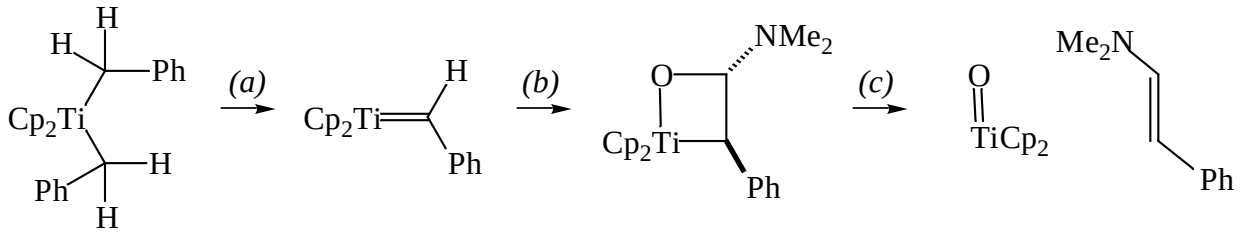
(a) ligand association; (b) β-hydride elimination; (c) insertion; (d) oxidation.

(b) The mechanism is exactly the same as described in (a), except that the nucleophile is H_2O and the last β-hydride elimination removes H from O, not C.



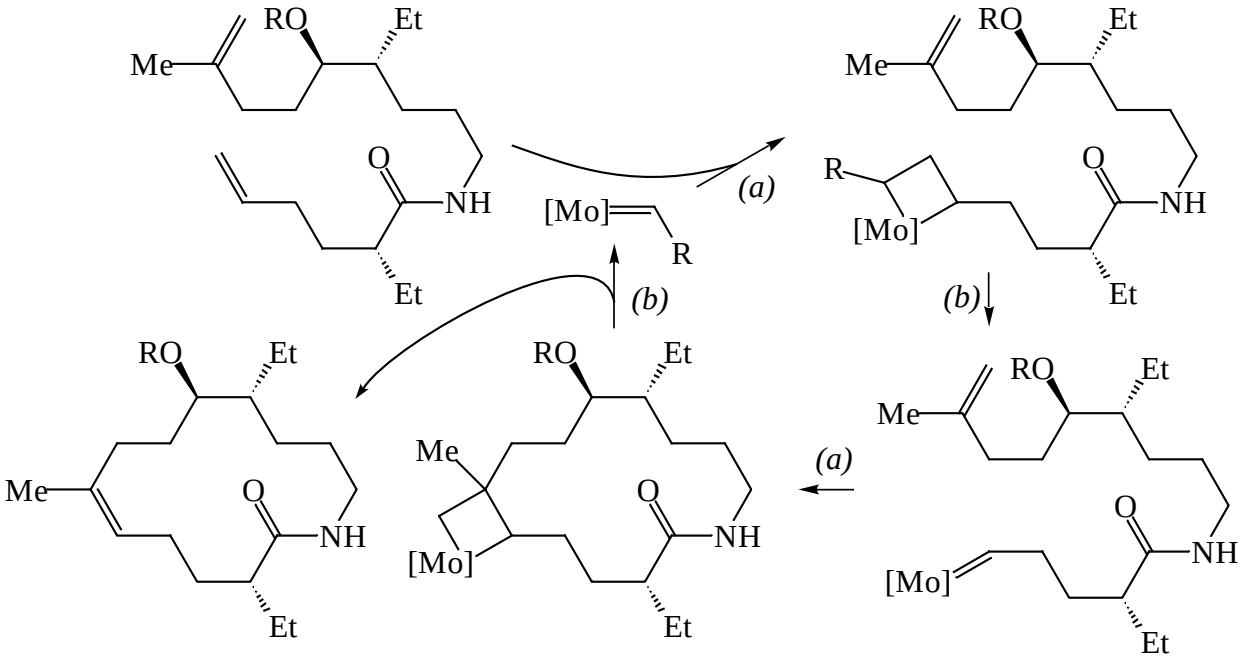
(a) ligand association; (b) β-hydride elimination; (c) insertion; (d) oxidation.

6.26. The mechanism begins with α-hydride elimination to give a benzylidenetitanium complex. A [2 + 2] cycloaddition gives the titanaoxetane, and [2 + 2] retrocycloaddition affords the product and the by-product.



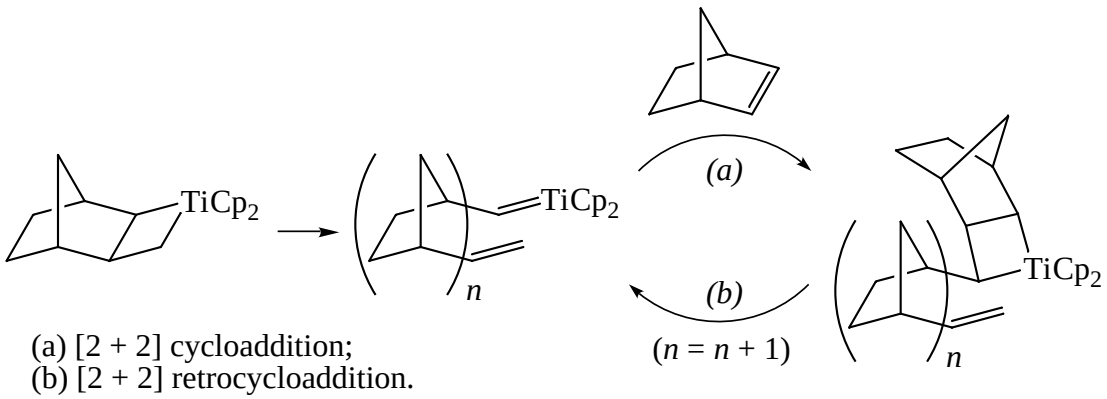
(a) α-hydride elimination; (b) [2 + 2] cycloaddition; (c) [2 + 2] retrocycloaddition.

6.27. The Mo=C π bond of the catalyst (R = *t*-Bu in the first catalytic cycle, R = h subsequently) undergoes a [2 + 2] cycloaddition to the substrate to give a molybdacyclobutane. A [2 + 2] retrocycloaddition affords a new Mo=C π bond, which undergoes intramolecular [2 + 2] cycloaddition with the other C=C π bond in the molecule. A [2 + 2] retrocycloaddition affords the product and regenerates the catalyst.



(a) [2 + 2] cycloaddition; (b) [2 + 2] retrocycloaddition.

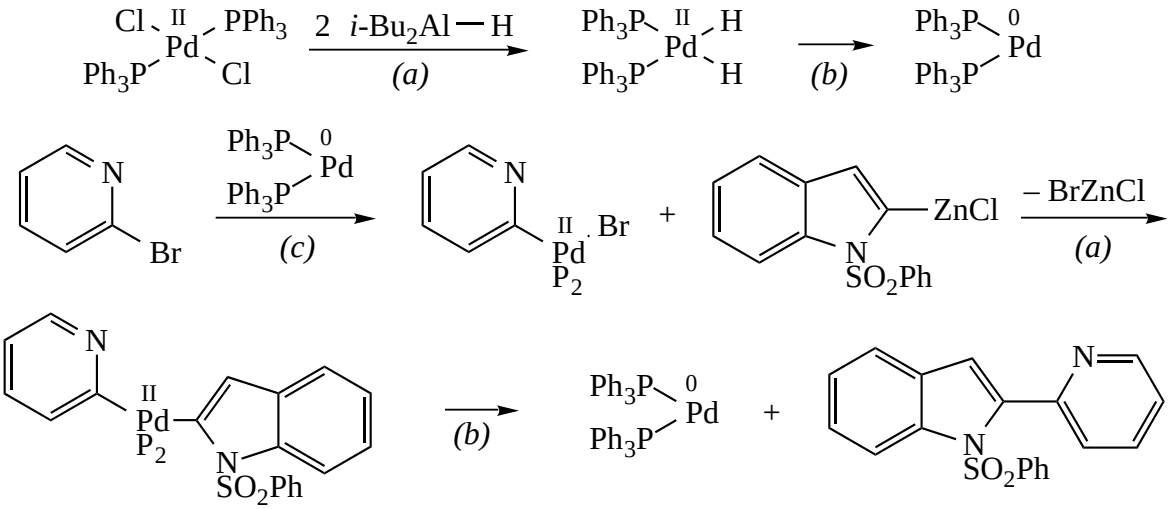
6.28. The mechanism again consists of a series of [2 + 2] cycloadditions and retrocycloadditions.



(a) [2 + 2] cycloaddition;
(b) [2 + 2] retrocycloaddition.

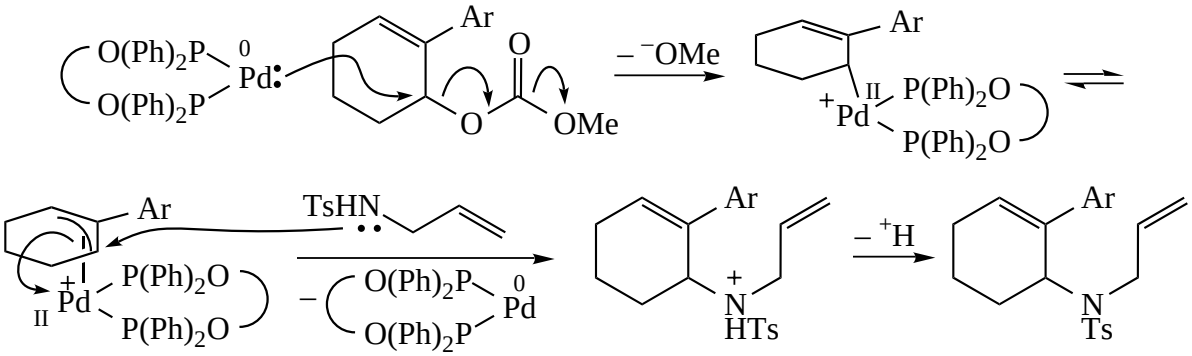
Answers To Chapter 6 End-of-Chapter Problems.

1. (a) A new C–C bond is formed between a nucleophilic C–Zn and an electrophilic C–Br. This Pd-catalyzed reaction proceeds through the standard oxidative addition, transmetallation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The oxidative addition requires Pd(0). The role of the DIBAL is to reduce the Pd(II) to Pd(0) by two transmetallations and reductive elimination of H_2.



(a) transmetallation; *(b)* reductive elimination; *(c)* oxidative addition.

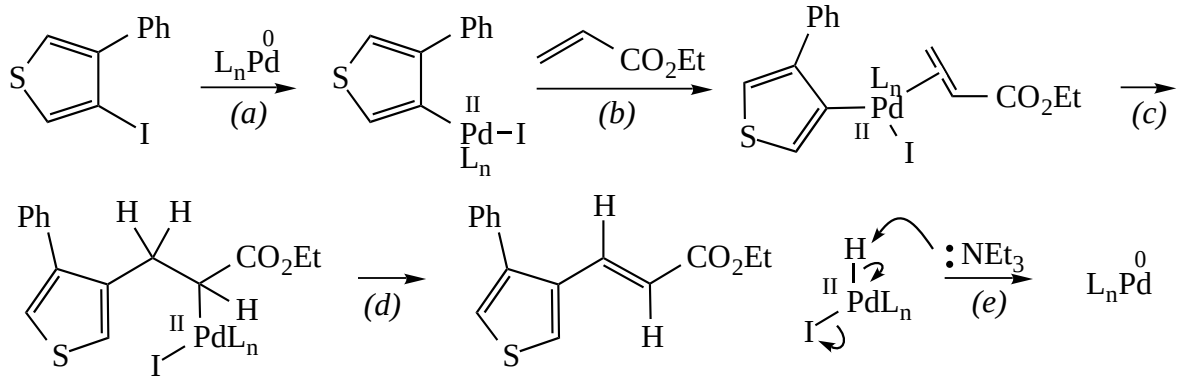
(b) An allylic leaving group is replaced by a nucleophile. This reaction proceeds through the standard sequence for allylic substitutions catalyzed by Pd, i.e. two sequential backside displacements. The chiral ligand causes the nucleophile to attack only one of the two prochiral termini of the *meso* π allyl intermediate. The N may be deprotonated before or after it attacks the π allyl complex.



(c) A new C–C bond is formed between a nucleophilic terminal alkyne PhC≡CH and an electrophilic C–I. This Sonogashira reaction proceeds through the standard oxidative addition, transmetallation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The terminal alkyne is converted to a Cu(I) acetylide before transmetallation to Pd occurs. The mechanism was discussed in the text (Section 6.3.4).

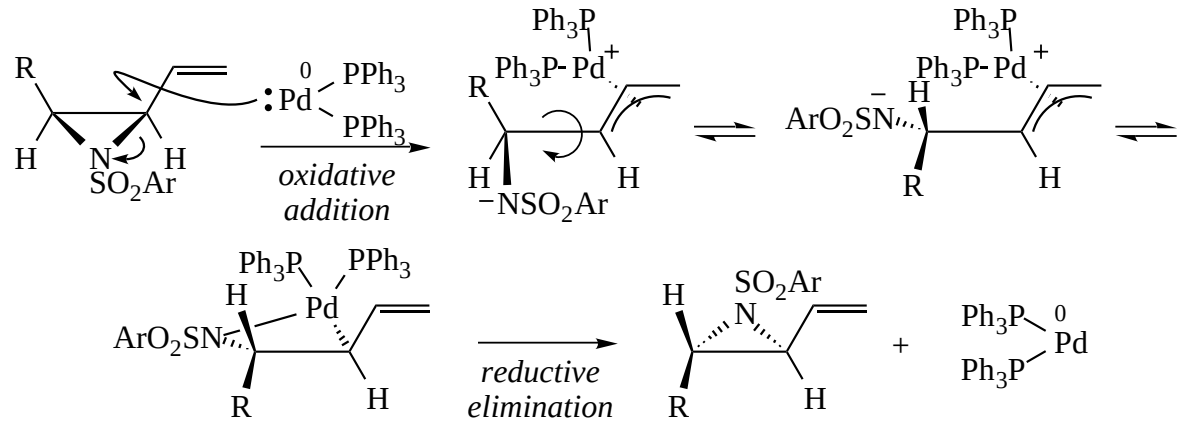
(d) A new C–C bond is formed between a nucleophilic C–B and an electrophilic C–I. This Suzuki coupling proceeds through the standard oxidative addition, transmetallation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The mechanism was discussed in the text (Section 6.3.4).

(e) There is no nucleophile in this Heck reaction. The first step must be oxidative addition of Pd(0) to the Ar–I bond to give a Pd(II) complex. (Before this can occur, the Pd(II) complex that is added to the reaction mixture must be reduced to Pd(0). In this system, it is not clear how it happens. Either the I^- or the S in a small amount of heterocycle might act as a reducing agent.) The crucial C–C bond is then formed by coordination of the π bond of acrylate to the Pd(II) complex and migratory insertion. β-Hydride elimination gives the organic product and I–Pd(II)–H. Deprotonation and dissociation of I^- regenerates the Pd(0).

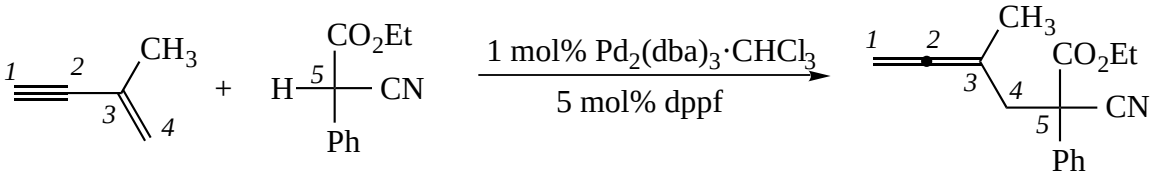


(a) oxidative addition; *(b)* coordination; *(c)* insertion; *(d)* β-hydride elimination; *(e)* deprotonation

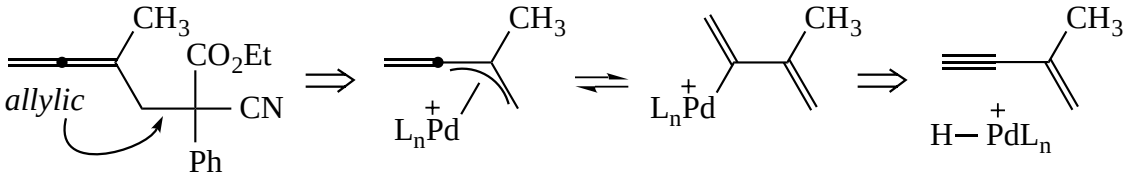
(f) An allylic C with a leaving group is being epimerized by the Pd(0) complex. One possible mechanism is simple displacement of N by Pd(0) to form the π allyl complex, then displacement of Pd(0) by N to reform the ring. The problem with this mechanism is that allylic substitution reactions catalyzed by Pd proceed with *retention* of configuration (two S_N2-type displacements), whereas this reaction proceeds with *inversion* of configuration. In this particular molecule, the anionic N can coordinate to the Pd π allyl intermediate in an intramolecular fashion; reductive elimination from this chelate would give the product with overall *inversion* of configuration.



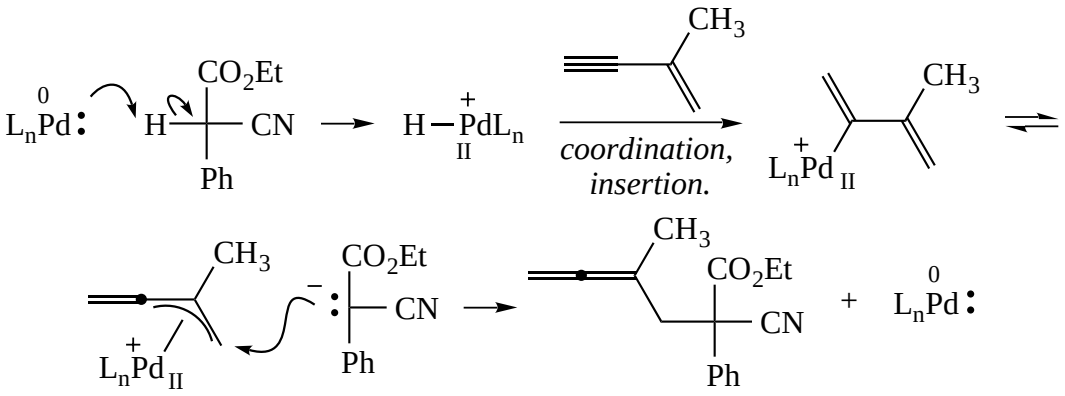
(g) Make: C4–C5, C1–H. Break: C5–H.



C5 is extremely acidic, and once deprotonated it is nucleophilic. C4, though, is not electrophilic, so we need to convert it to an electrophilic C. Looking at the product, one sees that the new C–C bond is allylic. This suggests attack of C5 on a π allyl complex. This complex could be made by insertion of the C1≡C2 π bond into a Pd–H bond. This last could be made by protonation of Pd(0) by C5.

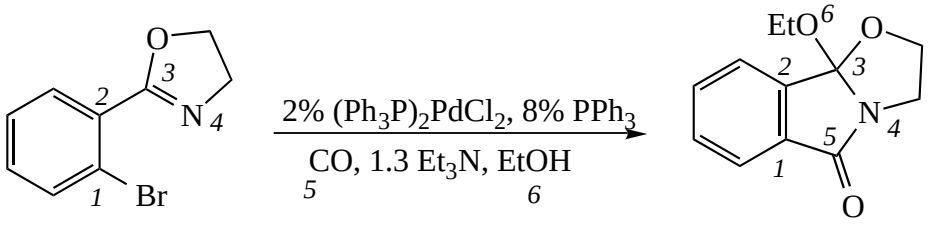


Protonation of Pd(0) gives [Pd(II)–H]$^+$. Coordination and insertion of the C1≡C2 π bond gives the Pd π allyl complex. Attack of the nucleophile on the less hindered terminus gives the observed product.

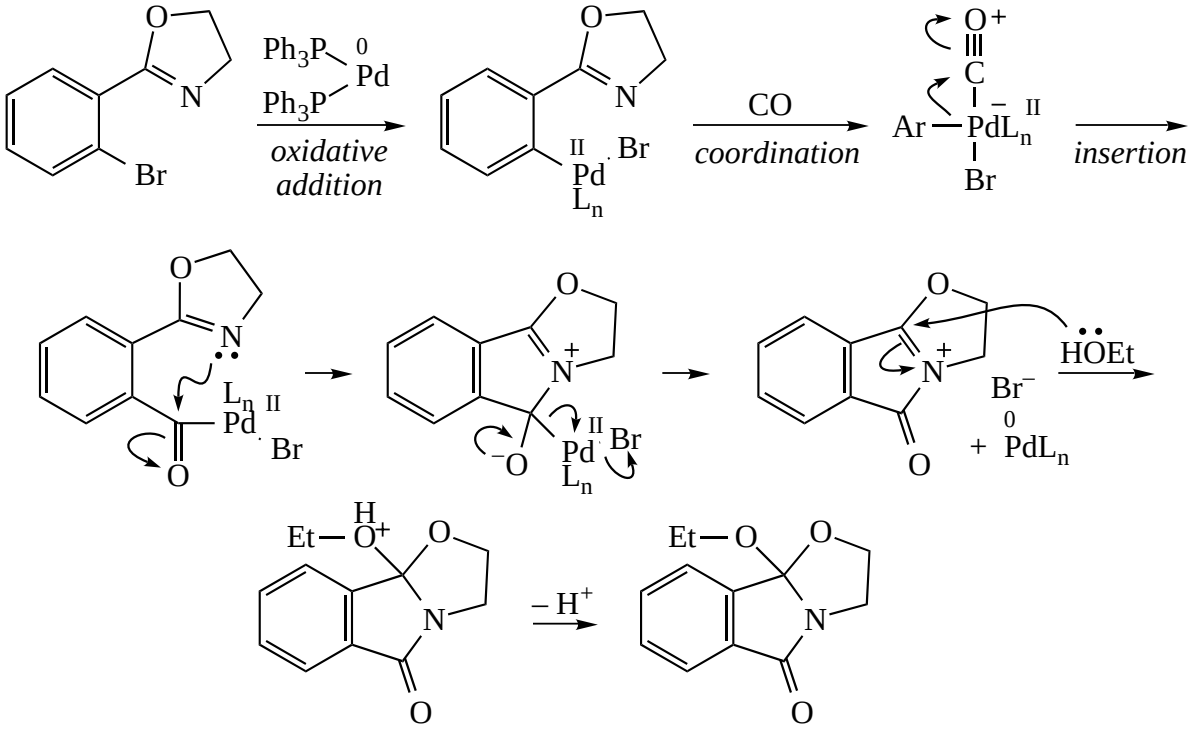


(h) This reaction is simply a Wacker oxidation. Its mechanism was discussed in the text (Section 6.3.6). The key steps are attack of H_2O on an electrophilic Pd–alkene complex, then β-hydride elimination to give the enol.

(i) Make: C1–C5, N4–C5, C3–O6. Break: C1–Br.

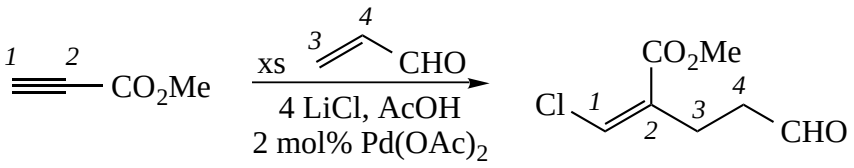


Incorporation of CO into an organic substrate usually occurs by insertion of CO into a C–metal bond. The requisite C1–metal bond is formed by oxidative addition of a Pd(0) species into the C1–Br bond, the normal first step upon combining a Pd(0) compound and an aryl halide. Coordination and insertion of CO follows. Addition of N to the carbonyl and loss of Pd(0) gives an iminium ion, which is trapped by EtOH to give the product.

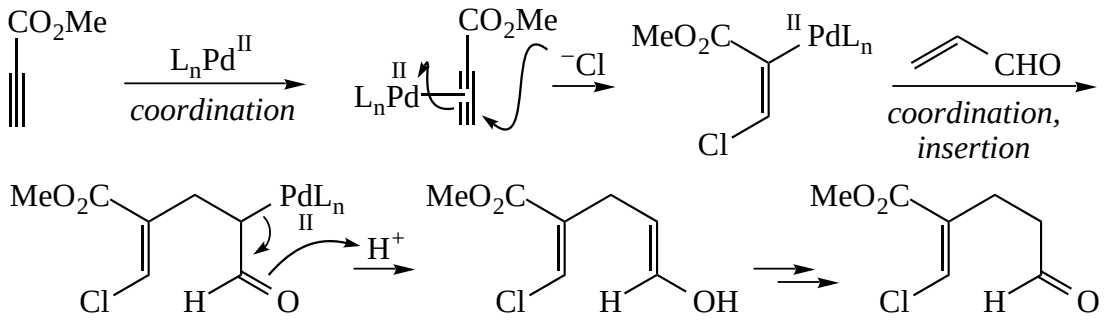


(j) This is another Heck reaction. After the insertion to give the σ bound Pd(II), β-hydride elimination occurs in the direction of the OH to give an enol. The enol tautomerizes to the aldehyde.

(k) Make: C1–Cl, C2–C3. Break: none.

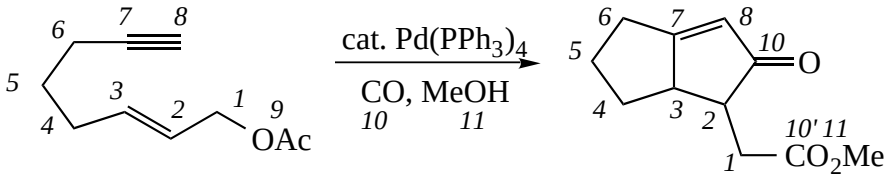


In fact, a mechanism for this reaction can be drawn that does not involve Pd at all, but let's assume that Pd is required for it to proceed. Cl^- must be nucleophilic. It can add to C1 of the alkyne if the alkyne is activated by coordination to Pd(II). (Compare Hg-catalyzed addition of water to alkynes.) Addition of Cl^- to an alkyne–Pd(II) complex gives a σ-bound Pd(II) complex. Coordination and insertion of acrolein into the C2–Pd bond gives a new σ-bound Pd(II) complex. In the Heck reaction, this complex would undergo β-hydride elimination, but in this case the Pd enolate simply is protonated to give the enol of the saturated aldehyde.

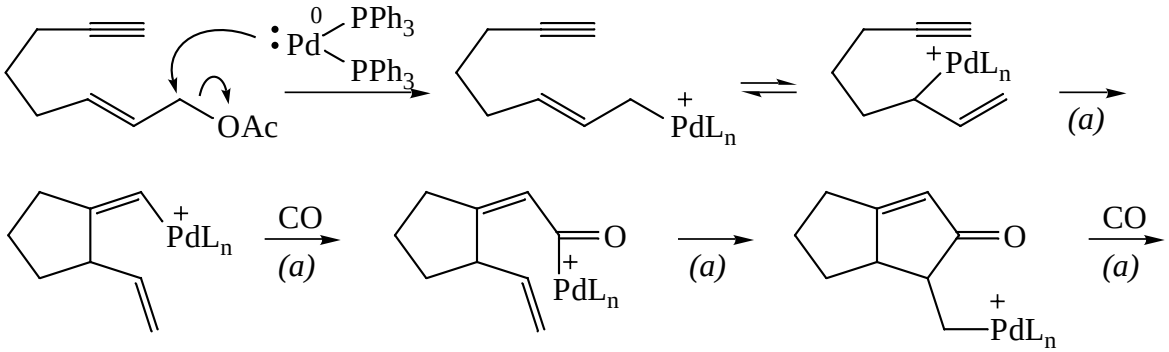


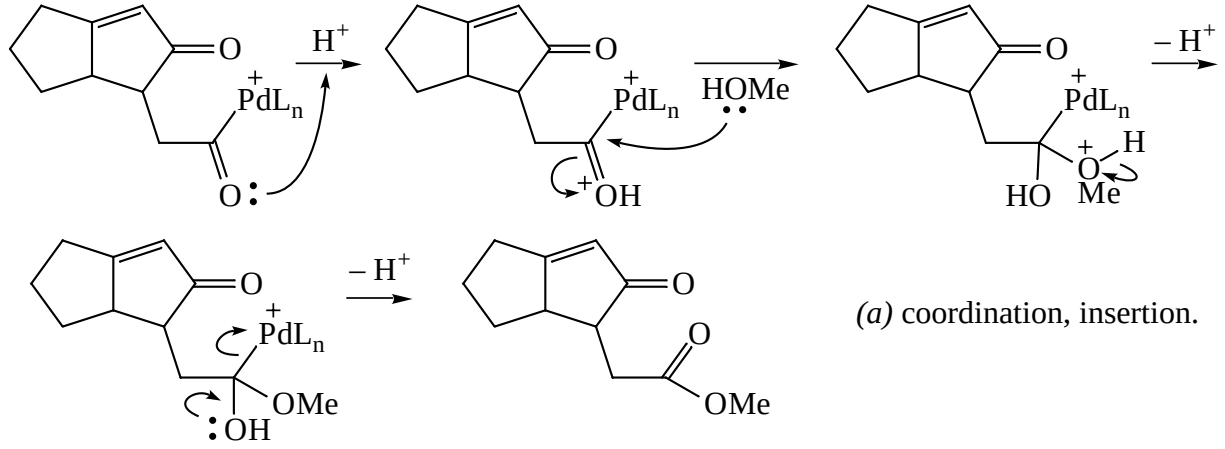
(l) A new C–C bond is formed between a nucleophilic C–Sn and an electrophilic C–Br. This Stille coupling proceeds through the standard oxidative addition, transmetallation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The mechanism was discussed in the text (Section 6.3.4).

(m) Make: C1–C10', C2–C10, C3–C7, C8–C10, C10'–O11. Break: C1–O9.



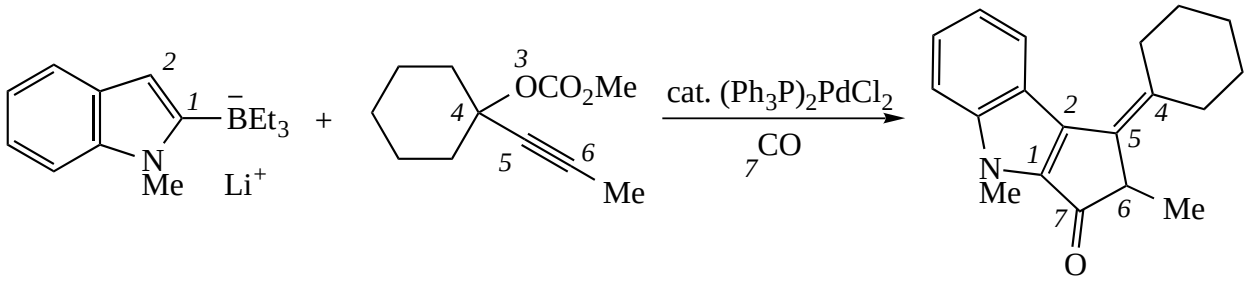
The first step is oxidative addition to the C1–O9 bond to make a Pd π allyl complex. Both C1 and C3 are rendered reactive by this step. At this point, we can either make the C1–C10' bond by CO insertion, or we can make the C3–C7 bond by insertion of the C7=C8 π bond into the C3–Pd bond. The first alternative would be followed by displacement of Pd from C10', requiring a new activation step to incorporate Pd into the substrate and allow the formation of the other bonds. After insertion of the C7=C8 π bond into the C3–Pd bond, though, we get a C8–Pd bond. This can insert CO to give the C8–C10 bond. The C1=C2 π bond can now insert into the C10–Pd bond, giving a C1–Pd bond. A second equivalent of CO then inserts. Finally, displacement of Pd from C10' by MeOH gives the product. The mechanism by which the Pd displacement proceeds is written as acid-promoted because the by-product of the reaction is AcOH.



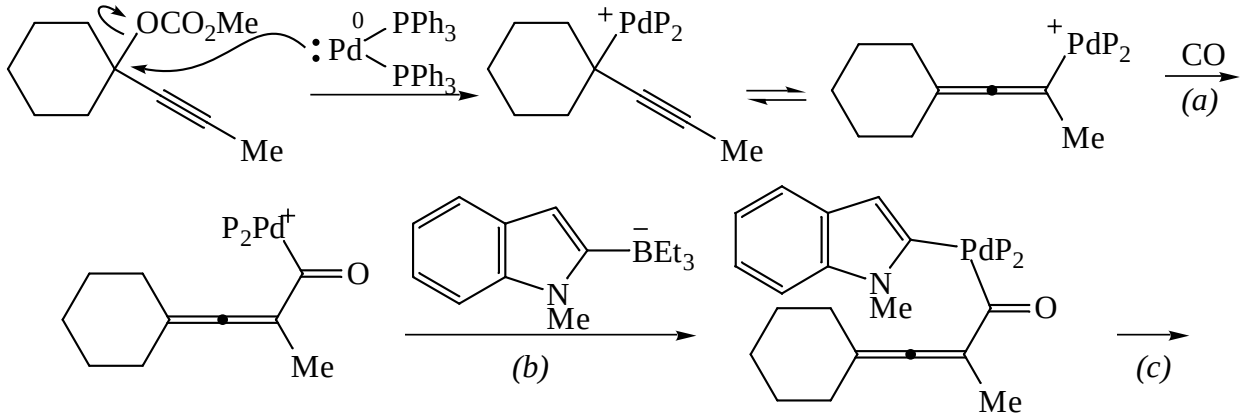


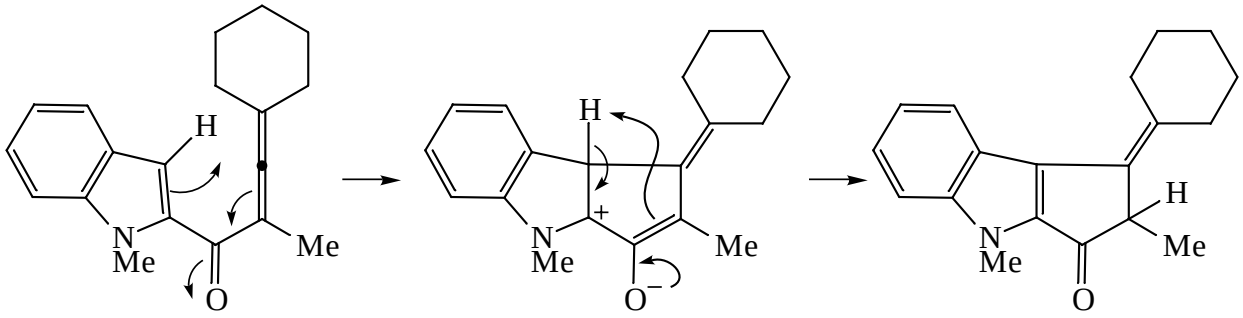
(a) coordination, insertion.

(n) Make: C1–C7, C2–C5, C6–C7. Break: C1–B, O3–C4. C1, with its bond to a negatively charged B, is nucleophilic.



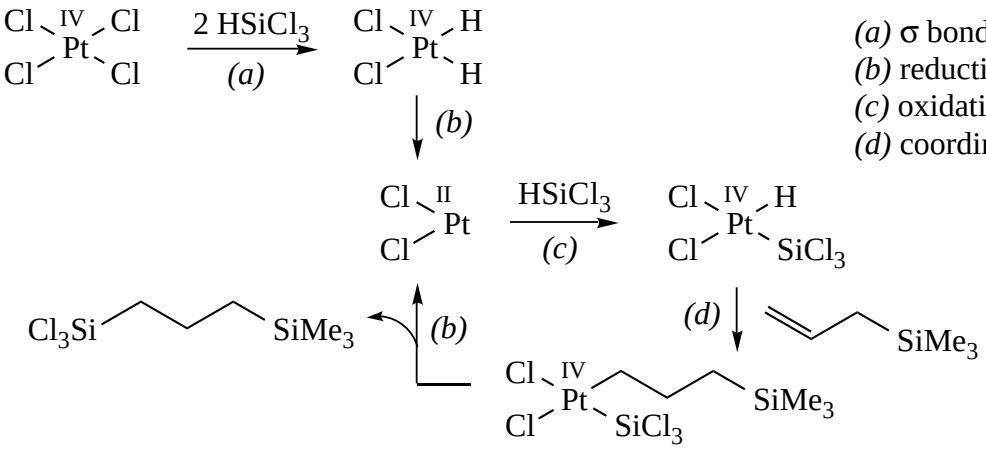
A simple Suzuki-type coupling would form a bond between C1 and either C4 or C6. Obviously that isn't happening here. The O3–C4 bond is propargylic, so Pd(0) can undergo oxidative addition here to make a propargyl–Pd(II) complex. No new bonds are formed to C4, but the propargyl complex is in equilibrium with an allenyl complex with a C6–Pd bond. Insertion of CO into this bond gives the C7–C6 bond. Now transmetallation with the C1–B bond and reductive elimination gives the C1–C7 bond. At this point, the C2–C5 bond still needs to be formed. An electrocyclic ring-closing forms this bond and gives a zwitterionic oxyallyl. Proton transfer from C2 to C6 reestablishes indole aromaticity and completes the sequence.





(a) coordination, insertion; *(b)* transmetallation; *(c)* reductive elimination.

(o) The simplest mechanism that can be drawn for this reaction is as follows. First the Pt(IV) precatalyst needs to be reduced to Pt(II). This can be accomplished by σ bond metathesis of two Pt–Cl bonds with Cl_3Si–H to give a Pt(IV) dihydride, which can undergo reductive elimination to give a Pt(II) species. (The Pt species are shown as $PtCl_4$ and $PtCl_2$, but of course other ligands may be present.) The catalytic cycle then proceeds by oxidative addition of Cl_3Si–H to Pt(II), coordination and insertion of the alkene into the Pt–H bond, and reductive elimination of the product, just like a Pd-catalyzed hydrogenation.

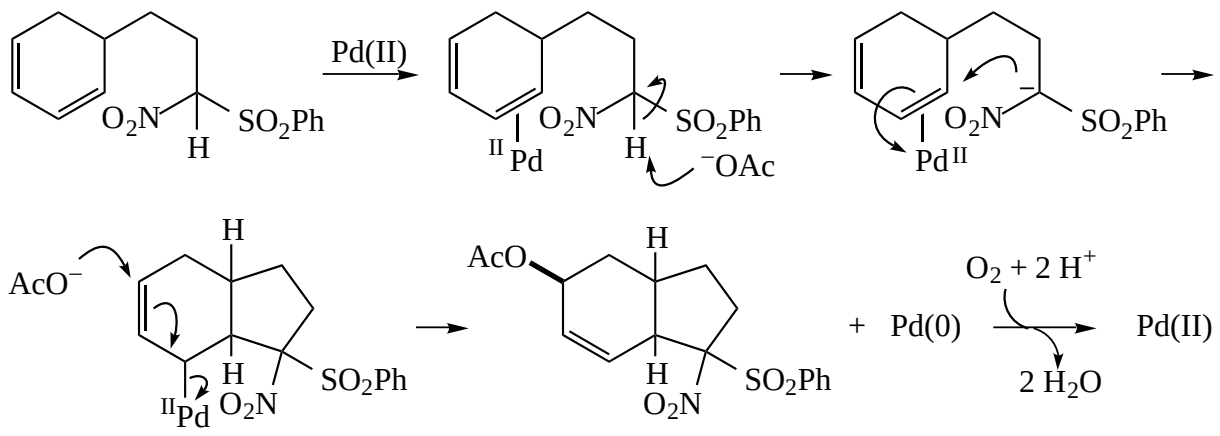


(a) σ bond metathesis;
(b) reductive elimination;
(c) oxidative addition;
(d) coordination, insertion.

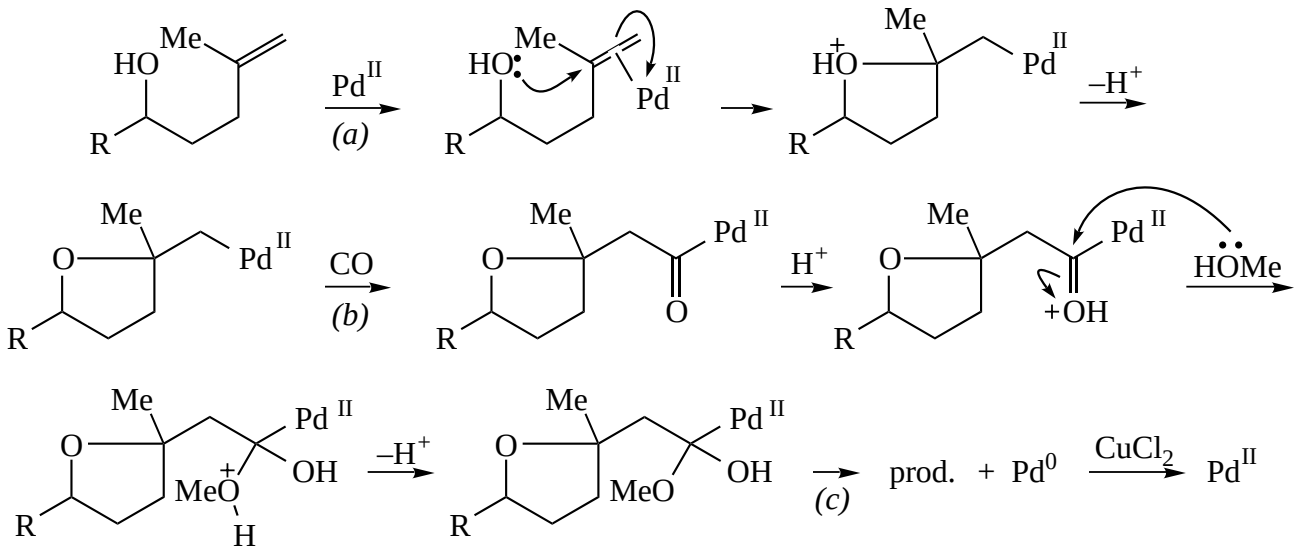
Experiments show that the actual mechanism of this reaction is considerably more complex than the one shown [radicals may be involved, especially in the reduction of Pt(IV) to Pt(II)], but the simple mechanism above provides a starting point for further investigation.

(p) The reaction is a carbonylative Stille coupling. The mechanism was discussed in the text (Section 6.3.4).

(q) Addition of a nucleophile to an alkene is catalyzed by Pd(II) salts. The Pd(II) coordinates to the alkene and makes it electrophilic, and the nucleophile attacks to give a C–Pd bond. In this case, because the substrate is a diene, the product is an allylpalladium(II) complex, a good electrophile. It is attacked by AcO^- to give the organic product plus Pd(0). O_2 then oxidizes the Pd(0) back to Pd(II).

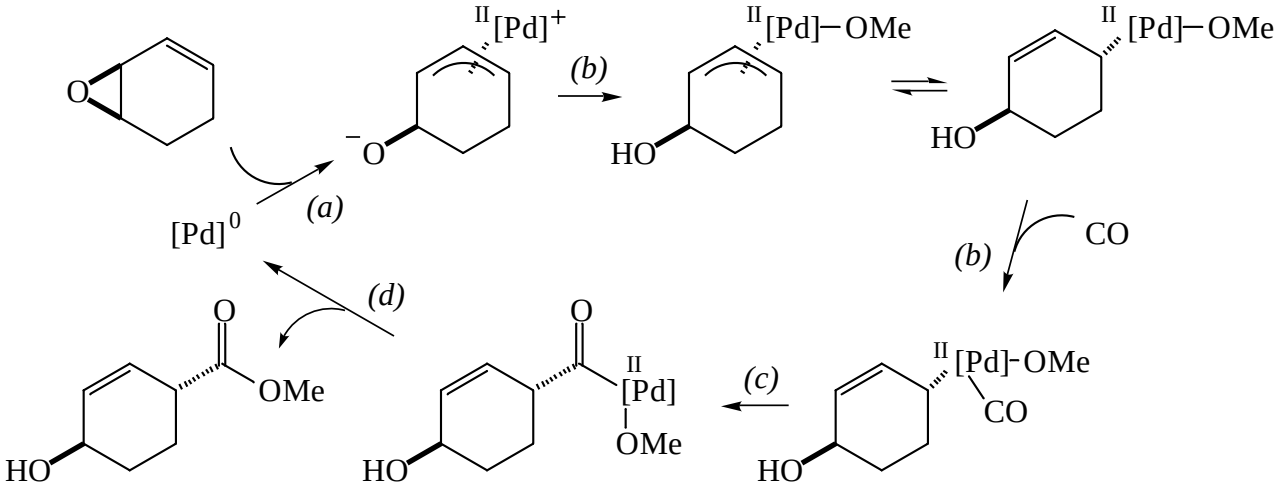


(r) Addition of a nucleophile to an alkene is catalyzed by Pd(II) salts. The product, an alkylpalladium(II) compound, usually undergoes β-hydride elimination, but in this case insertion of CO occurs to give an acylpalladium(II) complex. Displacement of Pd(0) by MeOH gives the product. Pd(0) is reoxidized to Pd(II) by $CuCl_2$.



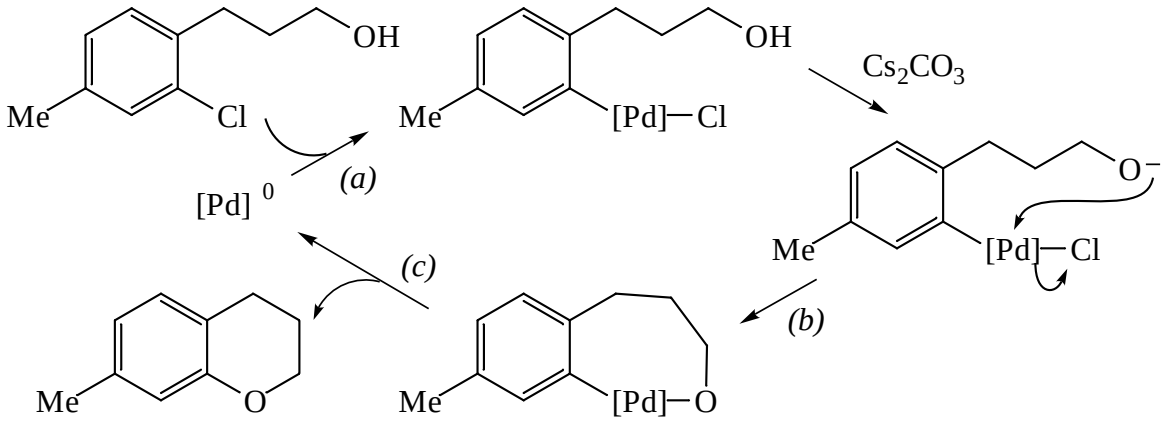
(a) coordination; *(b)* coordination, insertion; *(c)* β-hydride elimination.

(s) This reaction is a neat twist on allylic substitution. Pd(0) (generated in situ, perhaps by oxidation of CO to CO_2) reacts with the allylic epoxide by backside displacement to give a zwitterionic (π-allyl)Pd(II) complex. MeOH protonates the alkoxide, and MeO^- then coordinates to Pd. The π-allyl group is in equilibrium with a σ-allyl group, and coordination and insertion of CO into the Pd–C σ bond provides an acylpalladium(II) complex. Reductive elimination of the ester regenerates Pd(0).



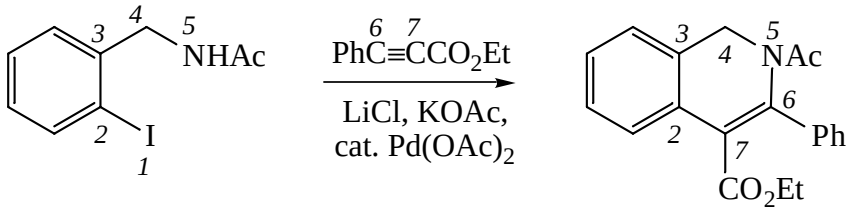
(a) S_N2-type oxidative addition; (b) ligand association; (c) insertion; (d) reductive elimination.

(t) Pd-catalyzed substitutions of aryl halides proceed by an oxidative addition–ligand substitution–reductive elimination mechanism.

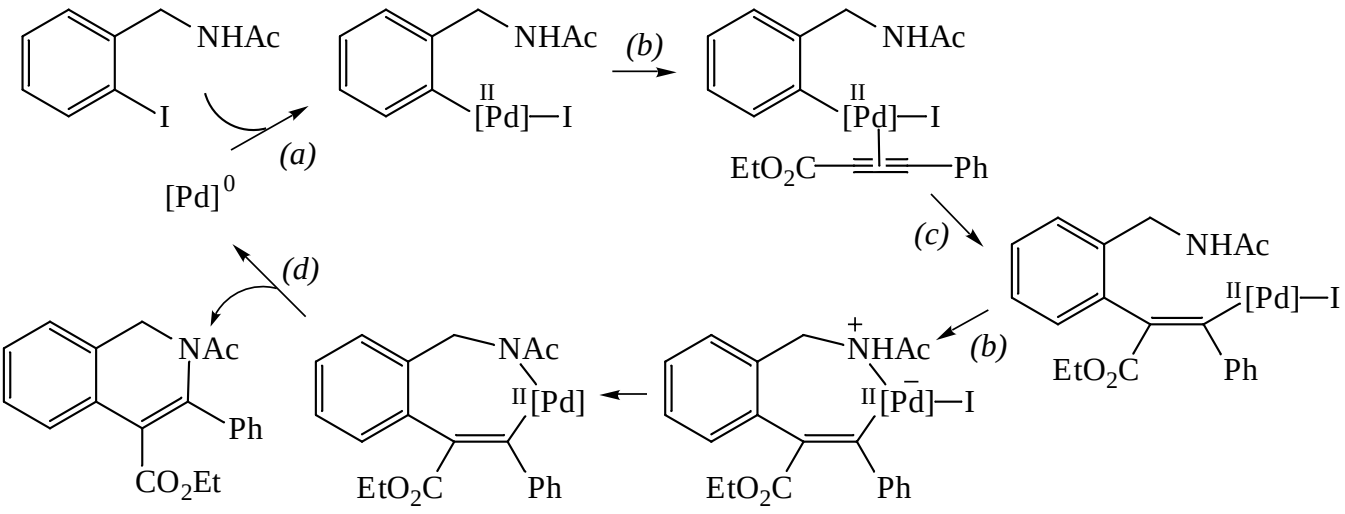


(a) oxidative addition; (b) ligand substitution; (c) reductive elimination.

(u) Make: C2–C7, N5–C6. Break: I1–C2.

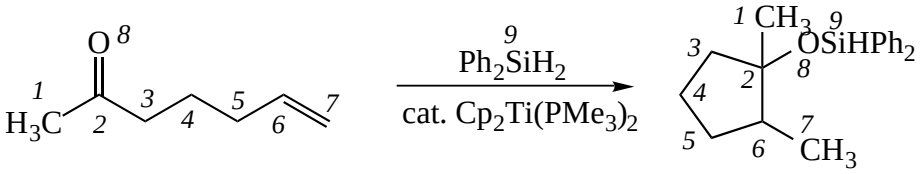


The first step, as usual with aryl halides, is oxidative addition of Pd(0) to the C–I bond. This step makes C2 reactive. Coordination of the alkyne to Pd(II) and insertion makes the C2–C7 bond and gives an alkenylpalladium(II) complex. Finally, coordination of N to Pd(II), removal of HI by the base, and reductive elimination provides the product and regenerates Pd(0).

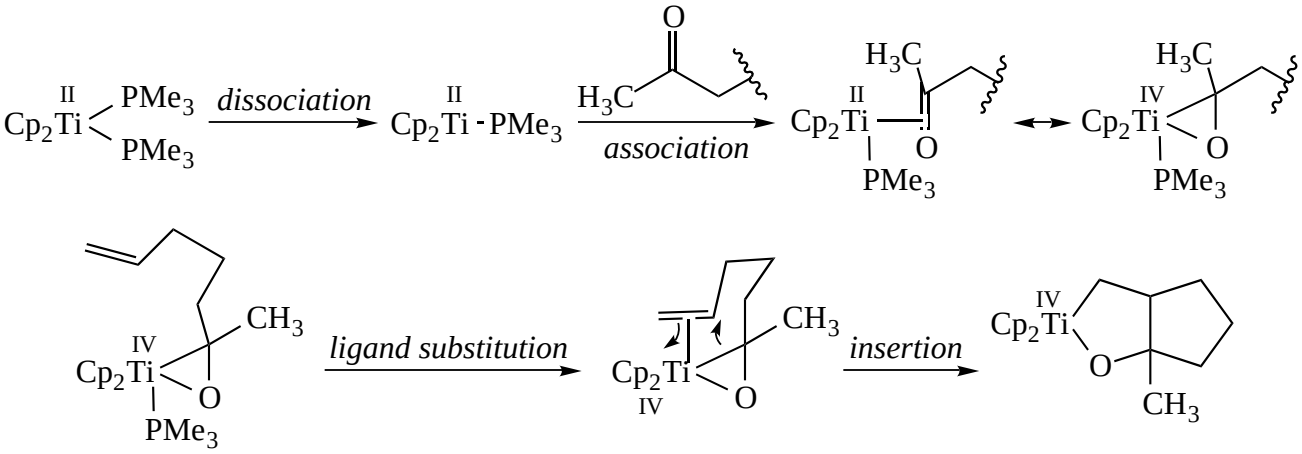


(a) oxidative addition; (b) ligand association; (c) insertion; (d) reductive elimination.

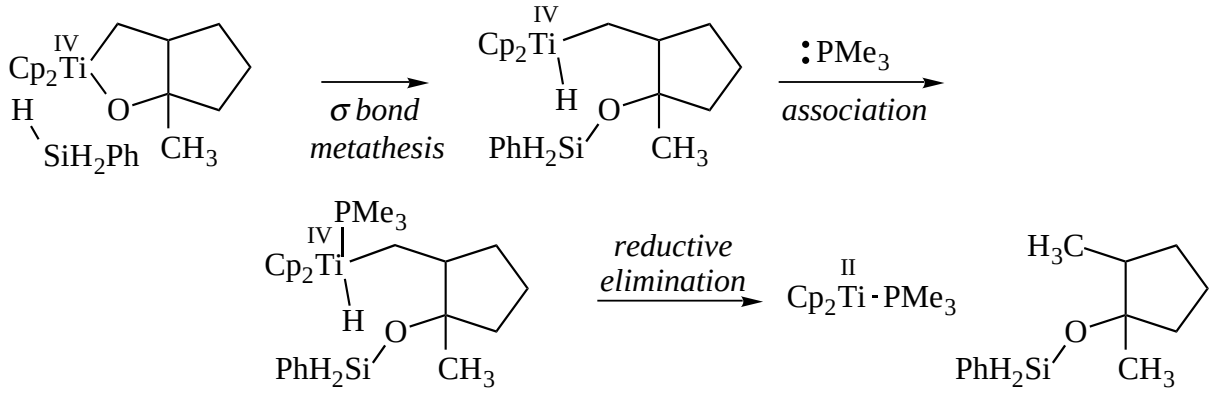
2. (a) Make: C2–C6, O8–Si9. We also remove one H from Si9 and add one to C7. Ti is in the (II) oxidation state. Low-valent Ti compounds are commonly used for reductive coupling reactions. We can form the C6–C2 bond by such a reductive coupling.



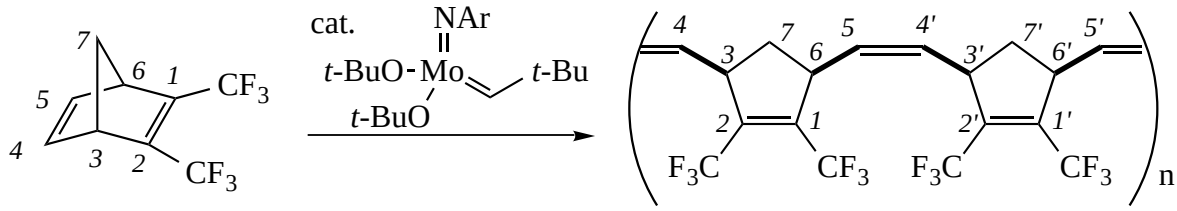
Dissociation of Me_3P from the 18-electron complex gives a 16-electron complex. Association of the carbonyl group gives a Ti(II) π complex that can also be described as a Ti(IV) metallaoxirane. Dissociation of the second Me_3P, association of the alkene, and migratory insertion into the C2–Ti bond gives a five-membered metallacycle.



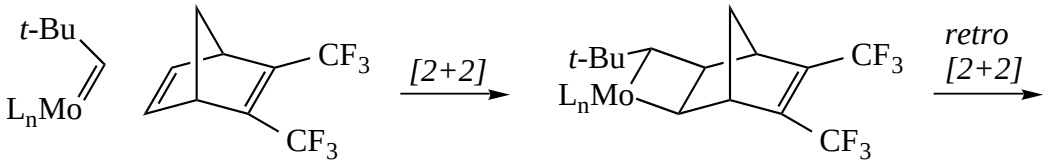
We still need to form the O8–Si9 bond, break the C7–Ti bond, and regenerate Ti(II). A σ bond metathesis between the Si9–H and Ti–O8 bonds can occur to give a very strong Si9–O8 bond and a Ti–H bond. No change in the Ti(IV) oxidation state occurs. Reductive elimination from Ti(IV) gives the product and regenerates Ti(II).

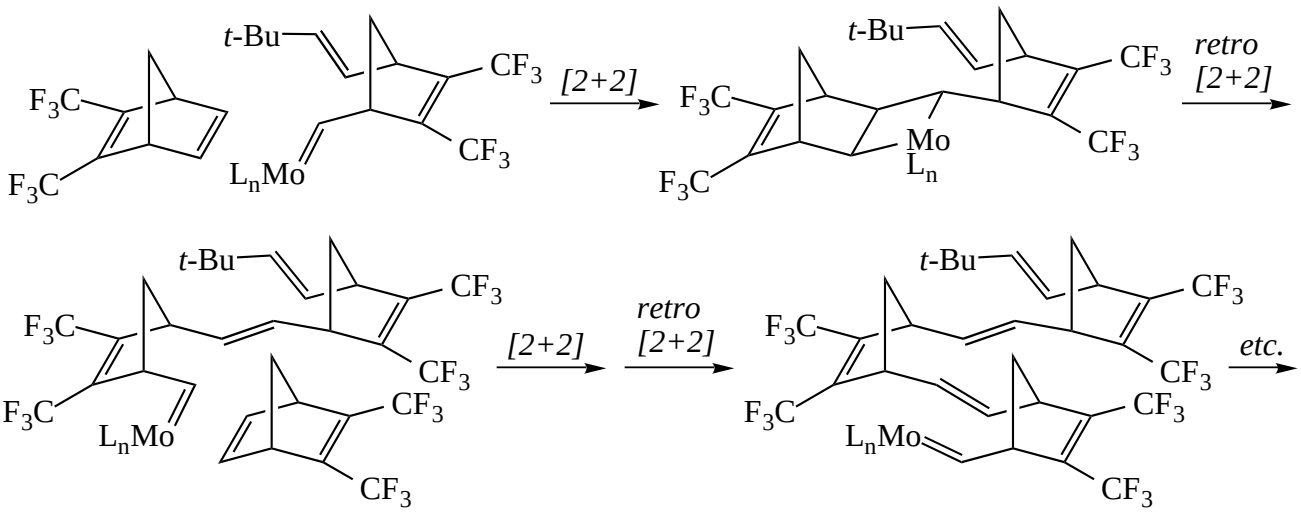


(b) Make: C4=C5' and C4'=C5 (x' indicates that atom in another molecule). Break: C4=C5. Mo is in the (VI) oxidation state, so it is d^0. The complex is a 14-electron complex. (The ArN= group uses the N lone pair to contribute another pair of electrons.) This is a ROMP reaction, i.e. ring-opening metathesis polymerization (Section 6.4.2).

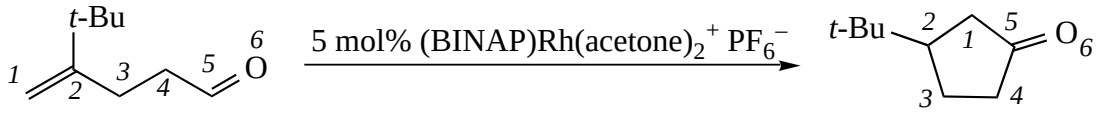


Compounds containing M=C bonds can undergo [2+2] cycloadditions, and this reaction allows olefin metathesis to occur. The Mo=C bond [2+2] cycloadds to the C4=C5 bond to give a metallacyclobutane. A retro [2+2] cycloaddition cleaves the C4=C5 bond and makes a Mo=C4 bond. This new bond cycloadds across another C4'=C5' bond to make a new C4–C5' bond; retro [2+2] cycloaddition cleaves the C4=C5 bond and completes the formation of the C4=C5' bond. The process repeats itself many times over to make the polymer. No change in Mo's oxidation state or d electron count occurs in any step.

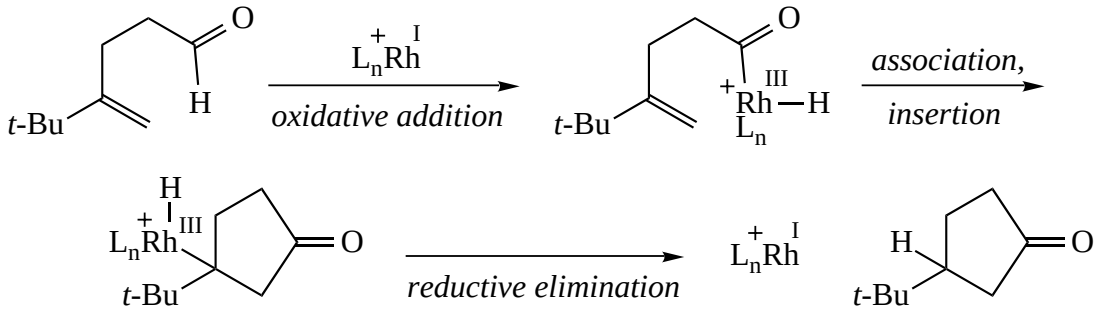




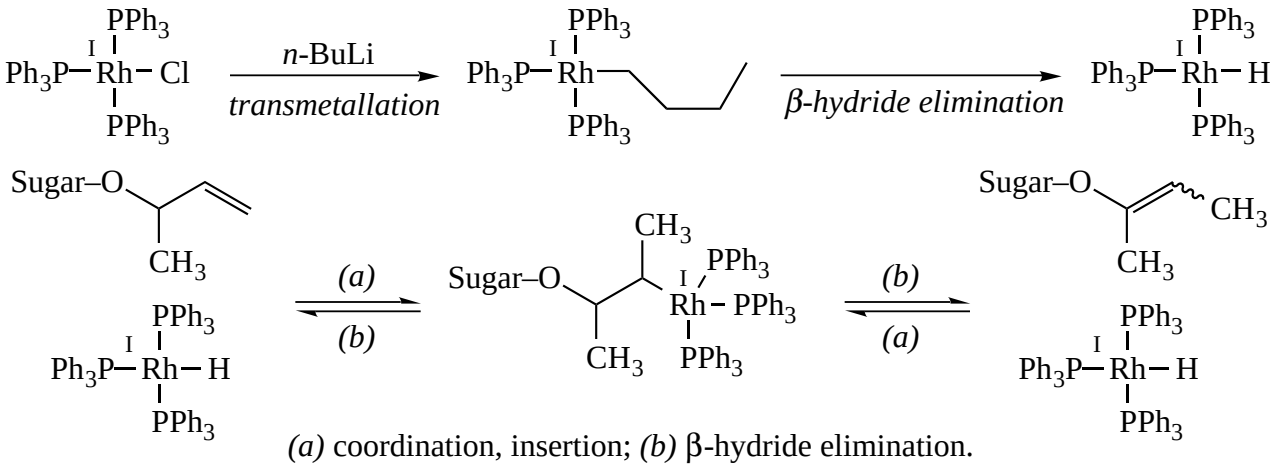
(c) Make: C1–C5, C2–H. Break: C5–H. Rh is in the (I) oxidation state, hence it is d^8; the two acetone molecules are counted as two-electron donors, so it is a 16-electron complex.



Essentially the C1=C2 bond is inserted into the C5–H bond. This suggests that the Rh oxidatively adds across the C5–H bond. Rh can do this with aldehydes. After oxidative addition to the C5–H bond to give a Rh(III) complex, insertion and reductive elimination give the product and regenerate Rh(I). Solvent molecules may be associating or dissociating at any point in the sequence.

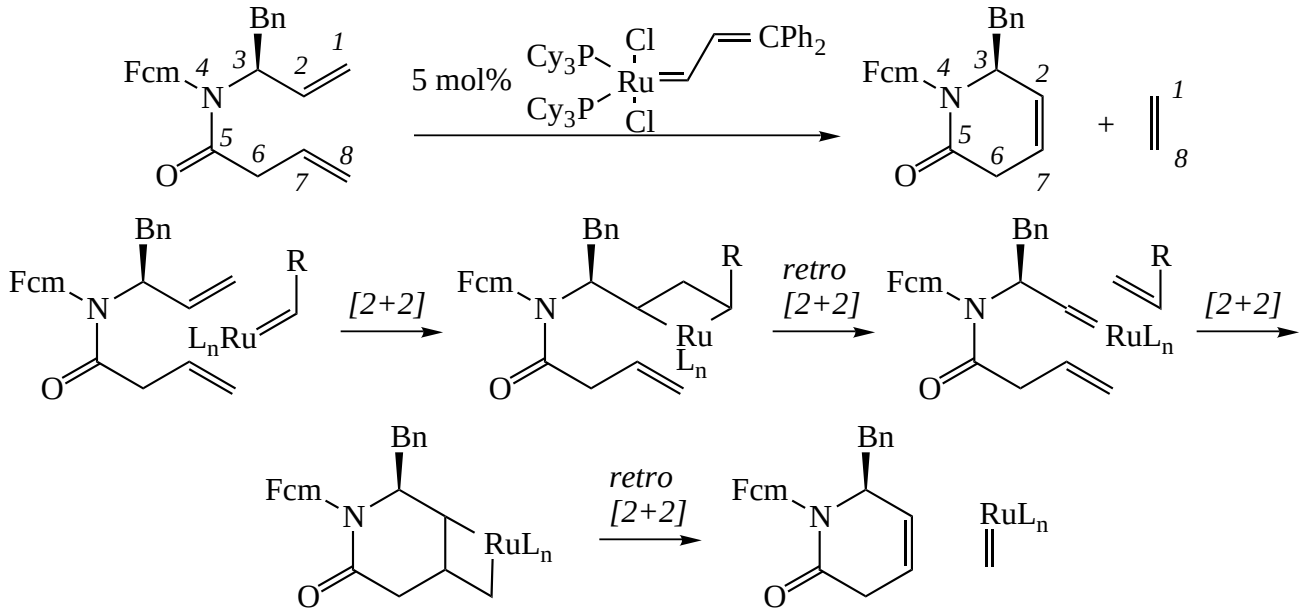


(d) Alkene isomerization can proceed by an oxidative addition (to the allylic C–H bond)/ reductive elimination sequence or by an insertion/ β-hydride elimination sequence. Wilkinson's catalyst normally isomerizes alkenes by the first mechanism. However, in this case BuLi is added to the catalyst first. This will give a Rh–alkyl bond, which can decompose by β-hydride elimination (as many metal alkyls do) to a Rh–H bond. Now the catalyst can carry out the insertion/ β-hydride elimination sequence to isomerize the alkene to a thermodynamic mixture of isomers. The most conjugated alkene is the lowest in energy and is obtained in greatest proportion.



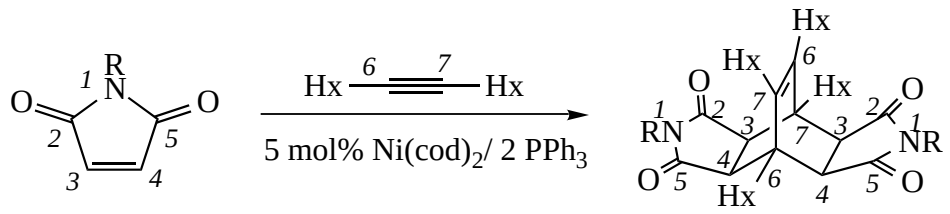
(a) coordination, insertion; *(b)* β-hydride elimination.

(e) The product is missing C1 and C8. They are lost as $H_2C{=}CH_2$. Make: C2=C7, C1=C8. Break: C1=C2, C7=C8. The Ru complex is 16-electron, d^2, Ru(IV). This is another olefin metathesis reaction, except this time it is ring-*closing* metathesis. The mechanism proceeds by a series of [2+2] and retro [2+2] cycloadditions. The R group starts off as $CH{=}CPh_2$, but after one cycle R= H.

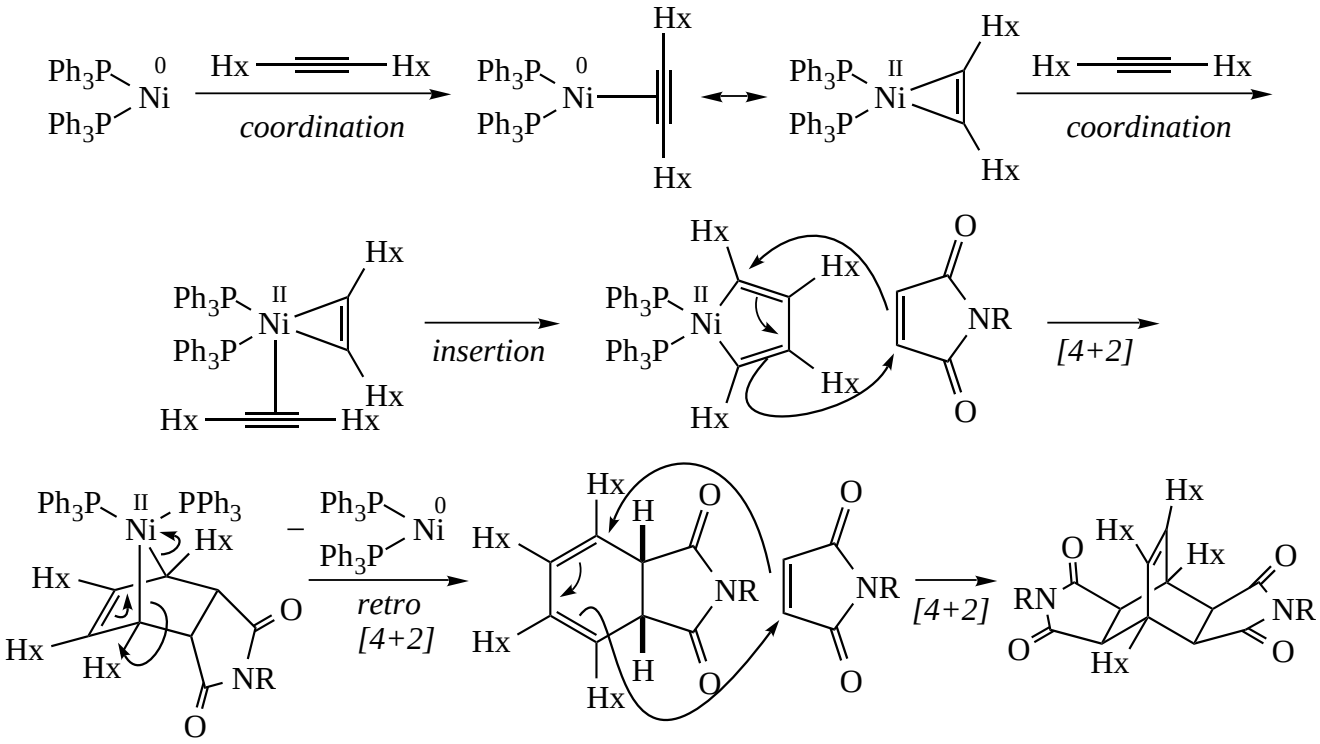


(f) See answer to in-chapter problem 6.6.

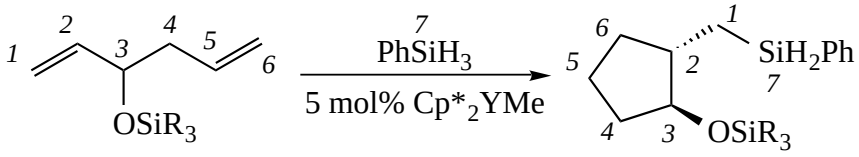
(g) Make: C3–C7 (x2), C4–C6 (x2), C6–C7. Ni is in the (0) oxidation state. $Ni(cod)_2$ is an 18-electron complex. $(Ph_3P)_2Ni(cod)$ is also an 18-electron complex. The fact that we are making six-membered rings from isolated π bonds suggests a cyclotrimerization.



Coordination of Ni(0) to the alkyne gives a π complex, which can be written in its Ni(II) resonance form. Coordination and insertion of another alkyne forms the new C6–C7 bond and gives a nickelacyclopentadiene. Maleimide may react with the metallacycle by coordination, insertion, and reductive elimination to give a cyclohexadiene. Alternatively, [4+2] cycloaddition to the metallacycle followed by retro [4+1] cycloaddtion to expel Ni(0) gives the same cyclohexadiene. The cyclohexadiene can undergo Diels–Alder reaction with another equivalent of maleimide to give the observed product.

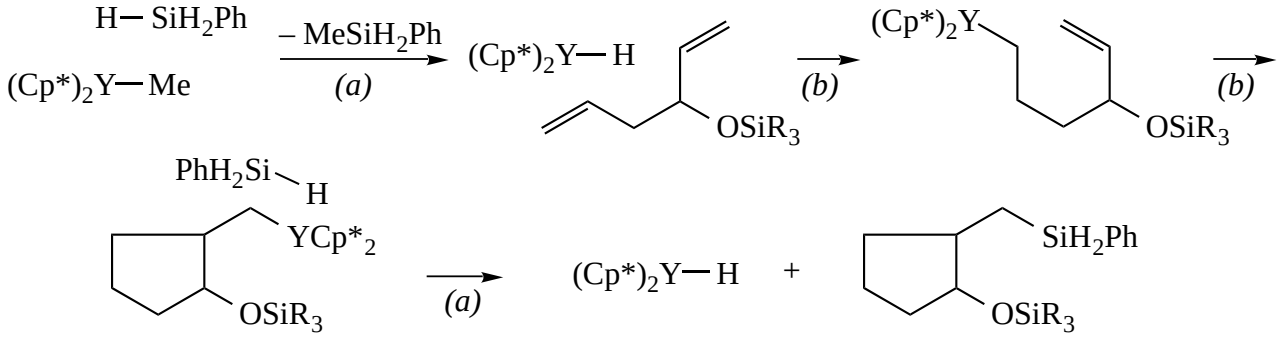


(h) Make: C1–Si7, C6–C2, C5–H. Break: Si7–H. Y is in the (III) oxidation state in the d^0, 14-electron complex.



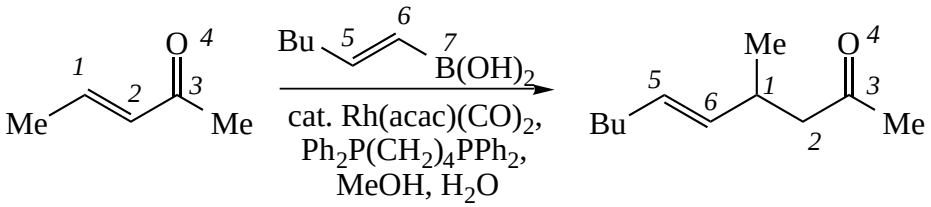
The overall transformation involves insertion of the C5=C6 and the C2=C1 π bonds into the Si7–H bond. An oxidative addition of Si–H to Y, insertion, insertion, reductive elimination sequence might occur. The problem with this is that the d^0 Y complex can't do oxidative addition. The alternative by which the Si–H

bond is activated is a σ bond metathesis process. Cp^*_2Y–Me undergoes σ bond metathesis with the Si–H bond to give Cp^*_2Y–H. Coordination and insertion of the C5=C6 π bond into the Y–H bond gives the C5–H bond and a C6–Y bond. Coordination and insertion of the C1=C2 π bond into the C6–Y bond gives the key C6–C2 bond and a C1–Y bond. Finally, σ bond metathesis occurs once more to make the C1–Si bond and regenerate Cp^*_2Y–H.

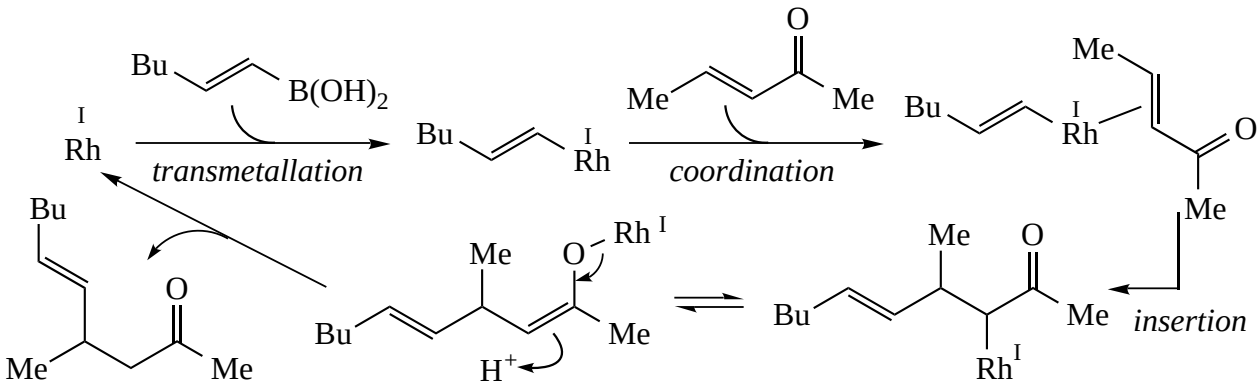


(a) σ bond metathesis; *(b)* coordination, insertion.

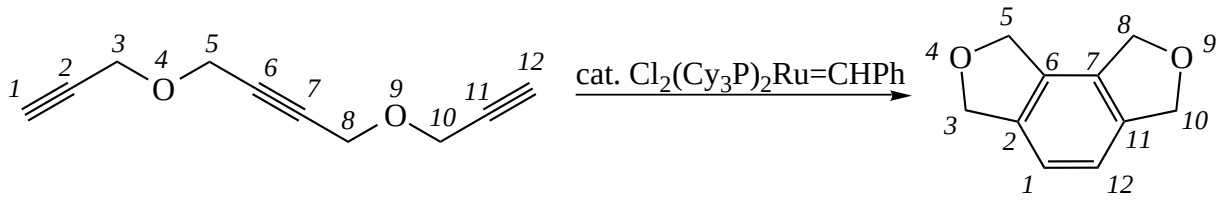
(i) Make: C6–C1. Break: C6–B7.



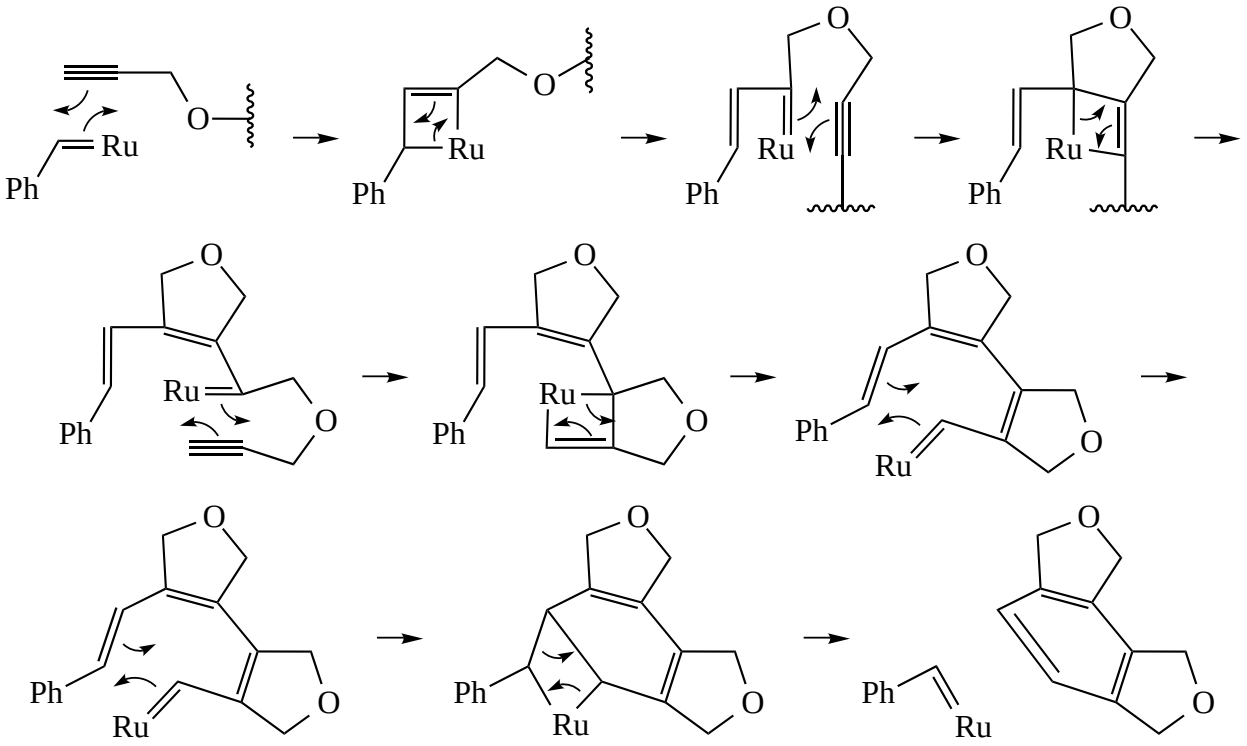
The reaction looks like a conjugate addition. A C6–Rh bond could insert into the C1=C2 π bond. The C6–Rh bond could be made by transmetallation.



(j) Make: C1–C12, C2–C6, C7–C11.

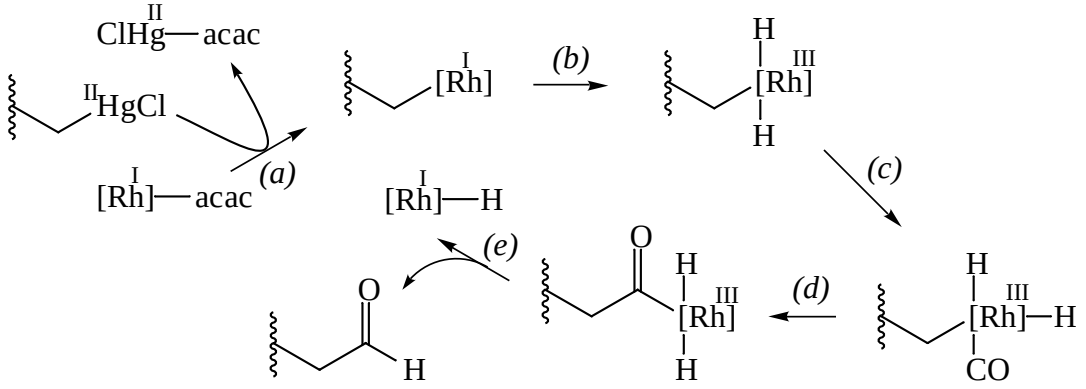


The overall reaction is a cyclotrimerization. Cyclotrimerizations are usually catalyzed by low-valent Co or Ni complexes by a reductive coupling mechanism, but the Ru=C complex lives to do [2+2] cycloadditions, so let it. Cycloaddition to the C1=C2 bond gives a ruthenacyclobutene, which can undergo electrocyclic ring opening to give a Ru=C2 π bond. This π bond can do a [2+2] cycloaddition to the C6=C7 π bond. Another ring opening, another [2+2] cycloaddition, another ring opening, another [2+2] cycloaddition, and a [2+2] retrocycloaddition give the product and regenerate the catalyst.

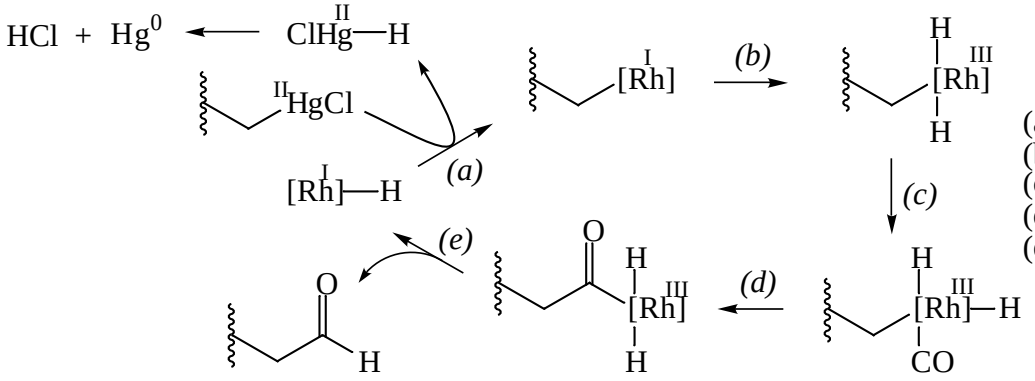


(k) The mechanism of this intramolecular Rh-catalyzed [5 + 2] cycloaddition proceeds by the mechanism shown in Section 6.2.12 (with the alkyne in the text replaced by the vinyl group in the substrate in this problem) or by the one shown in the answer to Problem 6.17.

(l) This reaction is a variation of the hydroformylation reaction. Transmetallation of Rh(I)(acac) with the alkylmercury(I) compound gives ClHg(acac) and an alkylrhodium(I) compound. Oxidative addition of H_2 gives a Rh(III) compound, and coordination and insertion of CO gives the acylrhodium(III) compound. Reductive elimination then gives the product and regenerates Rh(I) — but as a Rh–H, not as Rh(acac).

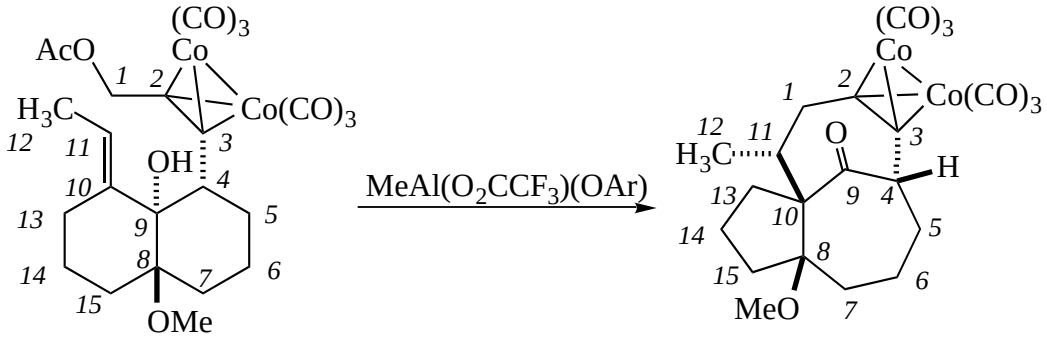


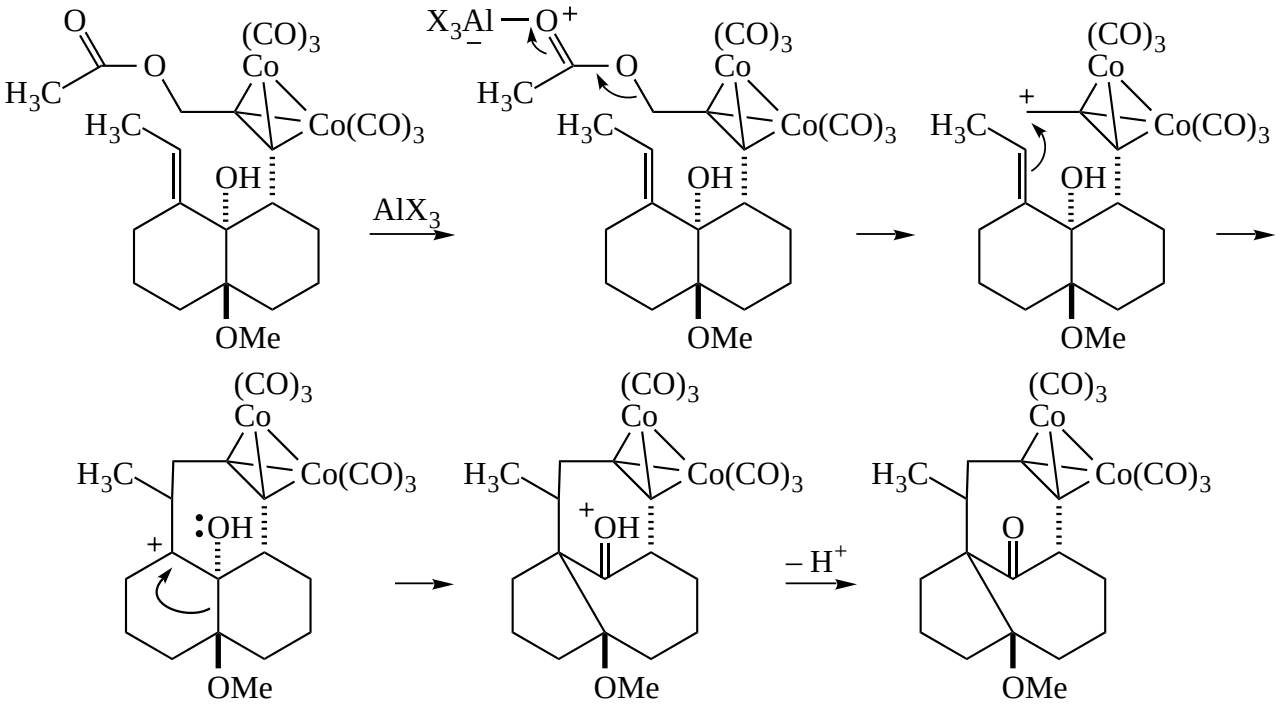
Once Rh(I)–H is generated, the transmetallation between it and R–HgCl gives Rh(I)–R and H–HgCl. The latter compound decomposes to Hg(0) and HCl.



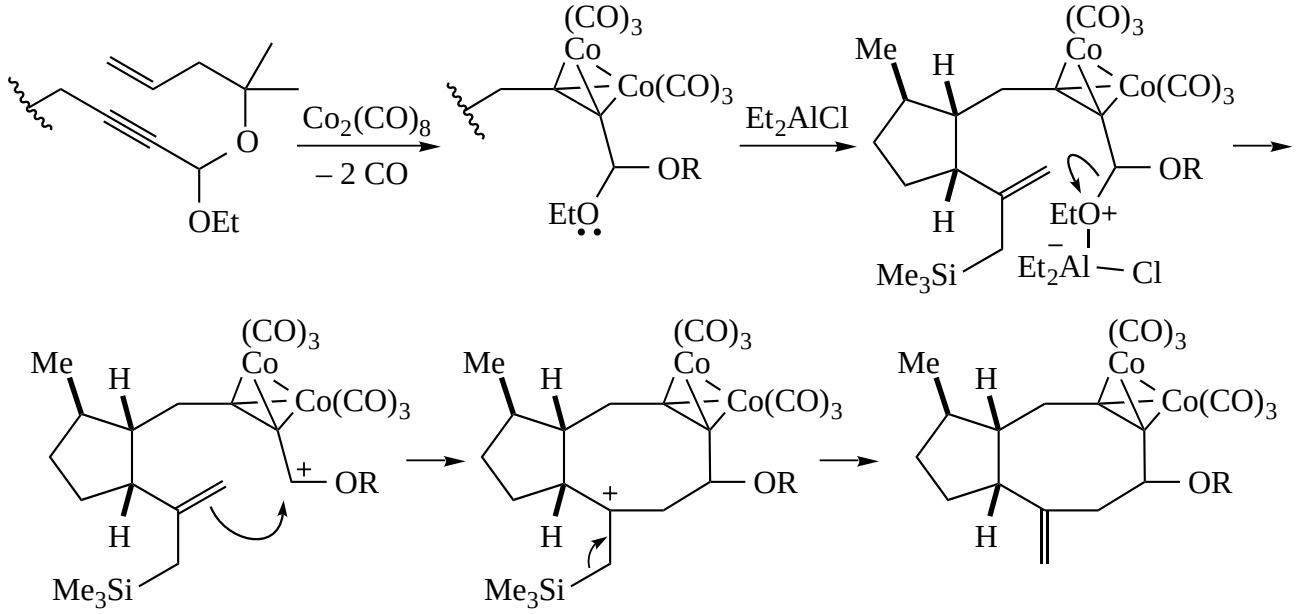
(a) transmetallation;
(b) oxidative addition;
(c) coordination;
(d) insertion;
(e) reductive elimination.

3. (a) Make: C1–C11, C8–C10. Break: C1–OAc, C8–C9. $Co_2(CO)_6$–alkyne complexes are prone to form cations at the propargylic position because the C–Co bonds hyperconjugatively stabilize the cation. The C10=C11 π bond can add to a C1 cation. Pinacol rearrangement (1,2-shift) then breaks the C8–C9 bond. Loss of H^+ from O completes the sequence.

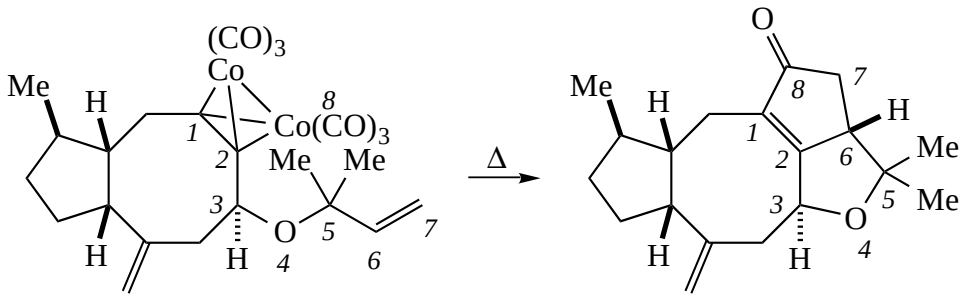




(b) Addition of $Co_2(CO)_8$ to an alkyne forms the $Co_2(CO)_6$–alkyne complex. Propargyl cation formation is thereby enhanced. The Lewis acid coordinates to the less hindered OEt group, converting it into a good leaving group. It leaves to give the propargyl cation, which is attacked by the alkene to form the eight-membered ring. Loss of Me_3Si^+ gives the product. Because of ring strain, the eight-membered ring could not form if the alkyne were not coordinated to $Co_2(CO)_6$. The $Co_2(CO)_6$ both reduces the bond angles around the "alkyne" C's *and* reduces the entropic barrier to eight-membered ring formation by holding the two "alkyne" substituents near one another.

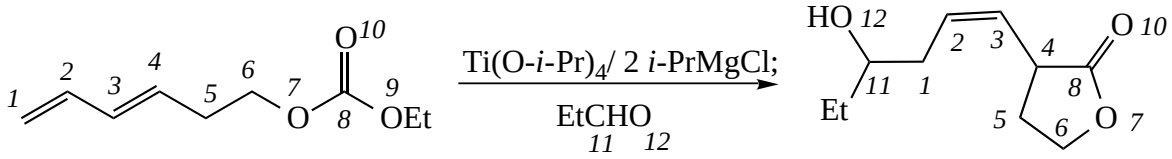


(c) Make: C1–C8, C2–C6, C7–C8. Break: Co–C1, Co–C2, Co–C8.

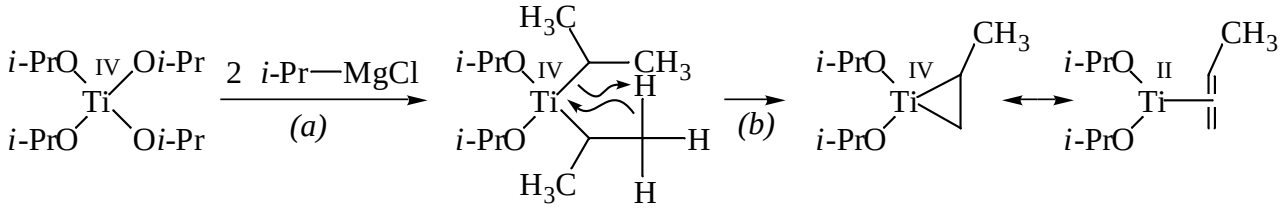


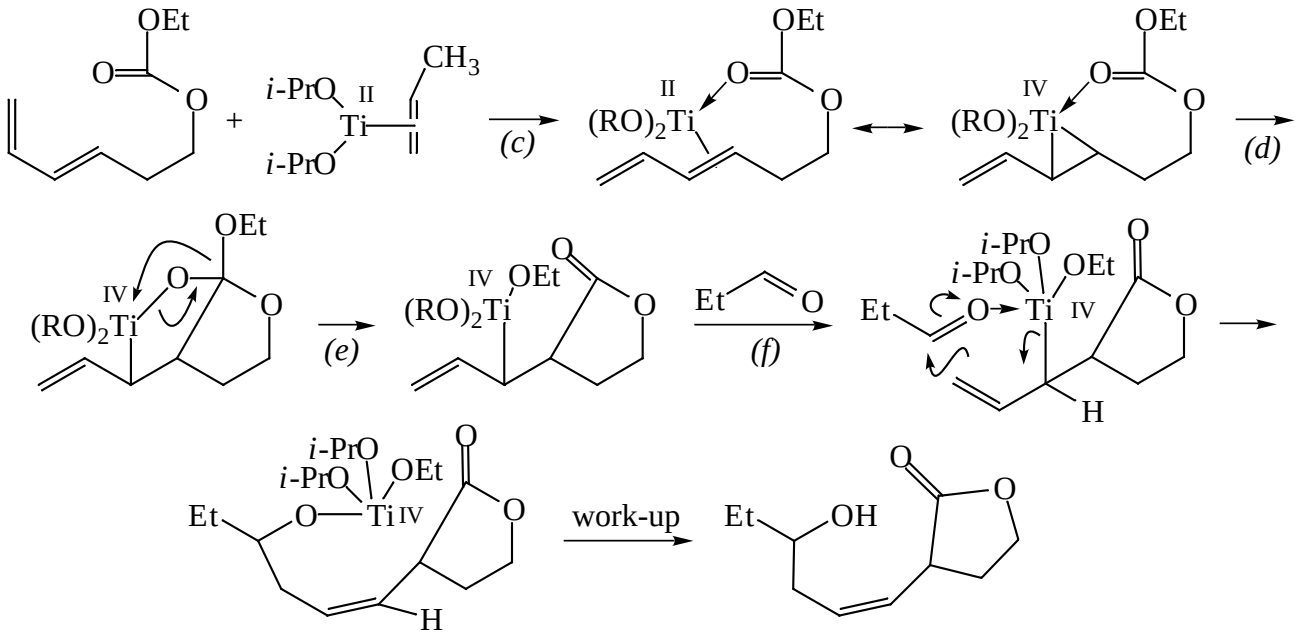
Conversion of a $Co_2(CO)_6$–alkyne complex into a cyclopentenone is the Pauson–Khand reaction. It proceeds by loss of CO from one Co to make a 16-electron complex, coordination and insertion of the C6=C7 π bond into the C2–Co bond to make the C2–C6 bond and a C7–Co bond, migratory insertion of CO into the C7–Co bond to make the C7–C8 bond, reductive elimination of the C1–C8 bond from Co, and decomplexation of the other Co from the C1=C2 π bond. The mechanism is discussed in the text (Section B.1.f).

(d) Make: C1–C11, C4–C8. Break: C8–C9. Ti is in the (IV) oxidation state, so it is d^0. Since we are forming new bonds from C4 to C8 and C1 to C11, and both C8 and C11 are electrophiles, both C1 and C4 must act as nucleophiles Normally in a diene one terminus acts as a nucleophile and one terminus acts as an electrophile. The role of the Ti, then, is to supply the necessary electrons. But Ti(IV) is not a reducing agent, so the role of the Grignard reagent must be to reduce the Ti.



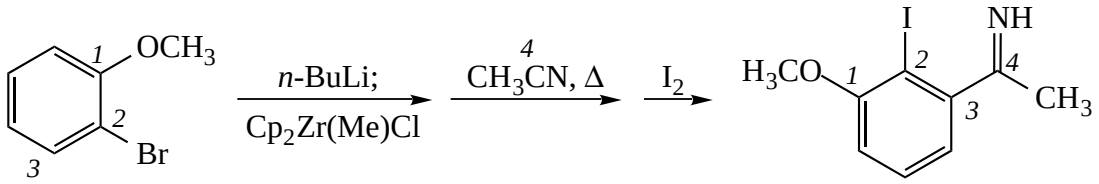
Addition of the Grignard to Ti(O-*i*-Pr)$_4$ will displace two *i*-PrO$^-$ groups and give (*i*-PrO)$_2$Ti(*i*-Pr)$_2$. β-Hydride abstraction (or β-hydride elimination followed by reductive elimination) then gives a Ti(II)–alkene complex ↔ titanacyclopropane. Coordination of the C3=C4 π bond and loss of propene gives a new titanacyclopropane; coordination of O10 promotes the formation of this particular titanacyclopropane. Insertion of the C8=C10 bond into the Ti–C4 bond forms the crucial C4–C8 bond. Expulsion of EtO$^-$ from C8 gives the lactone; the EtO$^-$ can coordinate to Ti(IV). There is still a Ti–C3 bond, so C3 is nucleophilic, as is C1 by vinylology. Nucleophilic addition of C1 to C11 and aqueous workup gives the product.



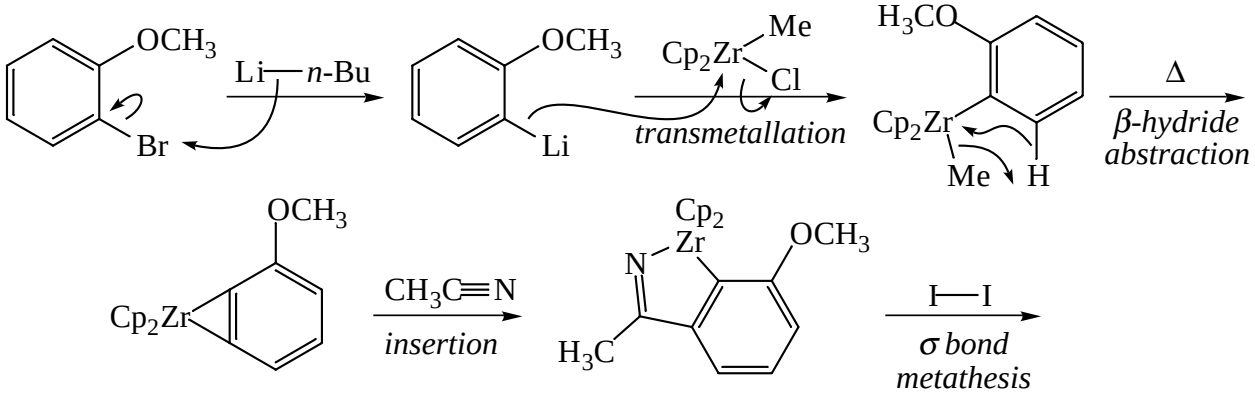


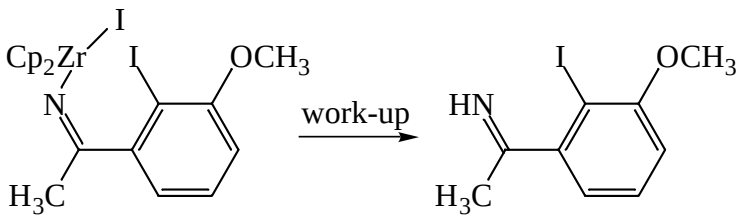
(a) transmetallation; *(b)* β-hydride abstraction; *(c)* ligand substitution; *(d)* insertion; *(e)* β-alkoxy elimination; *(f)* coordination.

(e) Make: C2–I, C3–C4. Break: C2–Br. Since C4 is electrophilic, C3 must be made nucleophilic. This would be the role of the Zr complex.



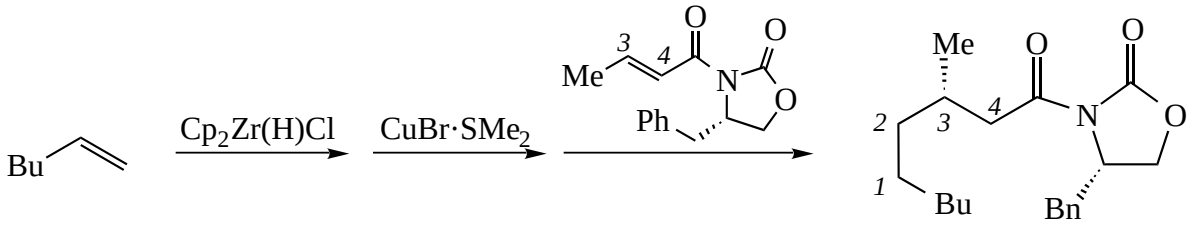
Addition of BuLi to ArBr results in halogen–metal exchange to give ArLi. Addition of $Cp_2Zr(Me)Cl$ to ArLi gives transmetallation to give $Cp_2Zr(Me)Ar$ and LiCl. We need to make a Zr–C3 bond in order to render C3 nucleophilic. This can be done by a β-hydride abstraction reaction to give a zirconacyclopropane. Insertion of the C4≡N bond into the C3–Zr bond gives the crucial C3–C4 bond. We still need to form the C2–I bond. Addition of I_2 cleaves the C2–Zr bond and gives the C2–I bond. Aqueous workup cleaves the N–Zr bond to give the observed product.



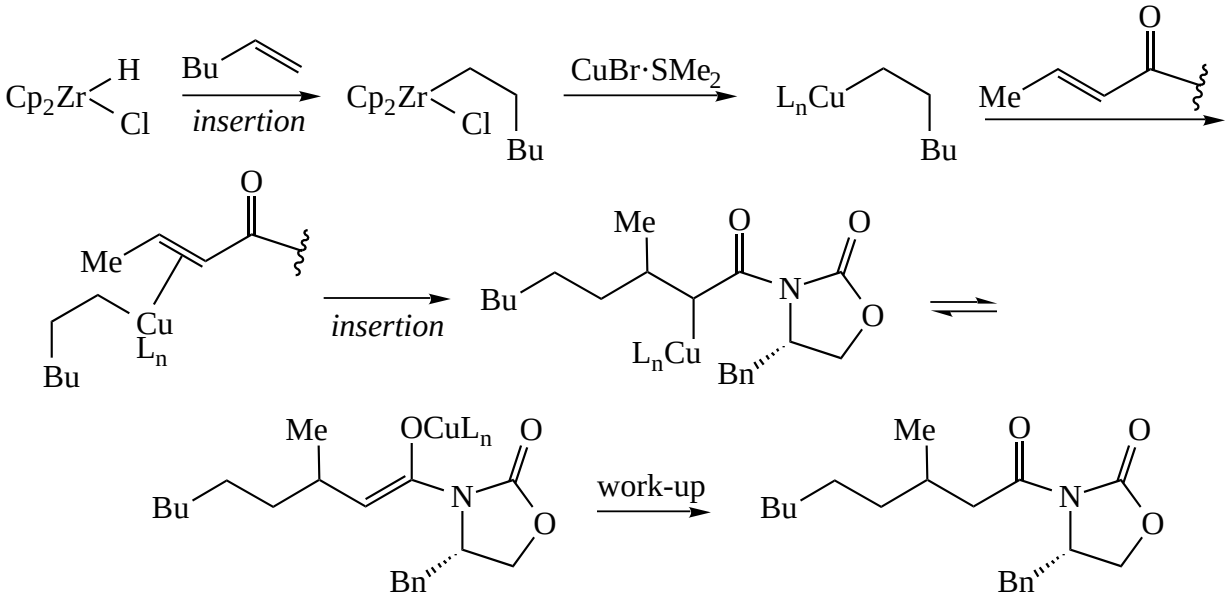


(f) This reaction proceeds via mechanisms similar to the previous two problems. The Grignard reagent reduces Ti(IV) to a Ti(II)–propene complex. Exchange of propene with the imine gives a titanaaziridine complex. Insertion of the alkyne into the C–Ti bond gives a titanapyrrolidine. Addition of I_2 cleaves the C–Ti bond in favor of a C–I bond. Aqueous workup then gives the product.

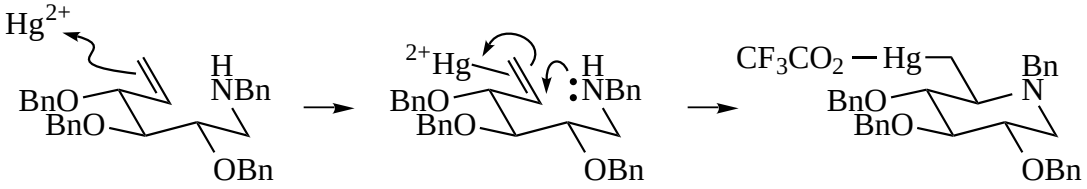
(g) Make: C2–C3. C3 is electrophilic, so C2 must be made nucleophilic.



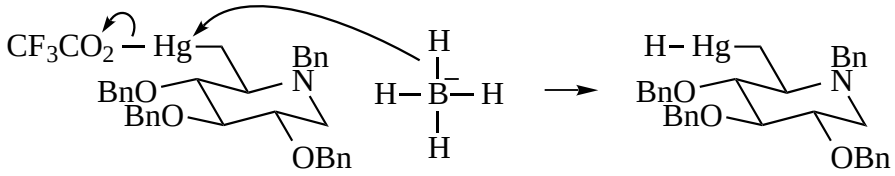
Addition of an alkene to a compound containing a metal–H bond usually results in insertion, and it does in this case, too, to give the stabler 1° alkylmetal. Addition of CuBr to this complex might result in transmetallation, to give a C2–Cu bond. Addition of the copper compound to the unsaturated imide gives conjugate addition, perhaps by coordination of the C3=C4 π bond and insertion into the C2–Cu bond. Workup gives the observed product.



(h) Hg(II) salts coordinate to alkenes and make them more electrophilic. In this case, the N can attack the alkene–Hg complex, giving an alkylmercury intermediate.

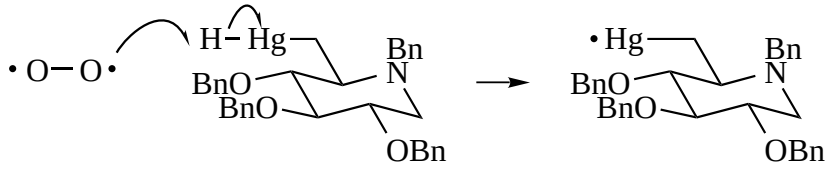


The $NaBH_4$ replaces the Hg–O_2CCF_3 bond with a Hg–H bond.

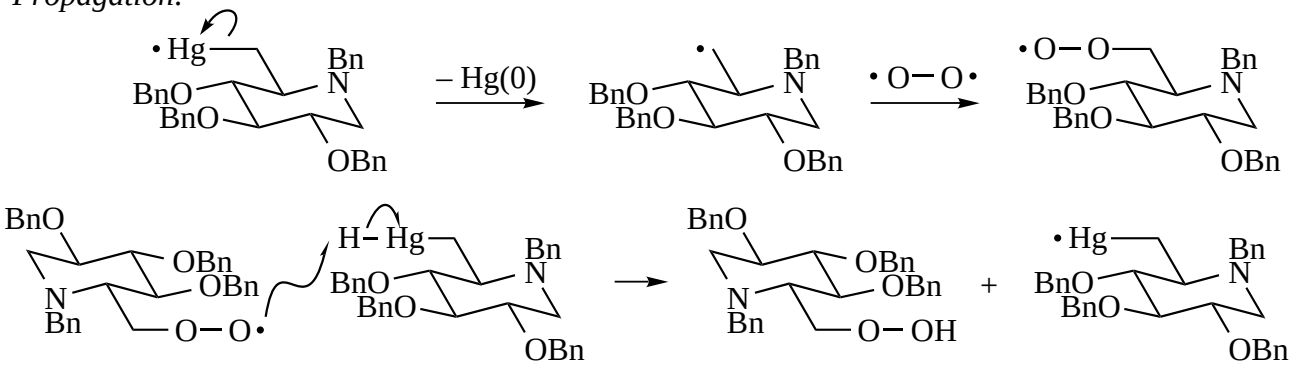


Free-radical decomposition of the alkylmercury hydride then occurs to replace the C–Hg bond with a C–O bond, with the O coming from O_2. The free-radical reaction gives a hydroperoxide C–OOH.

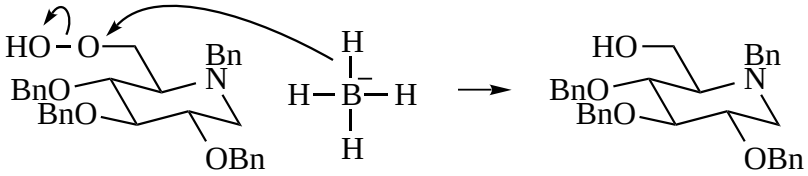
Initiation:



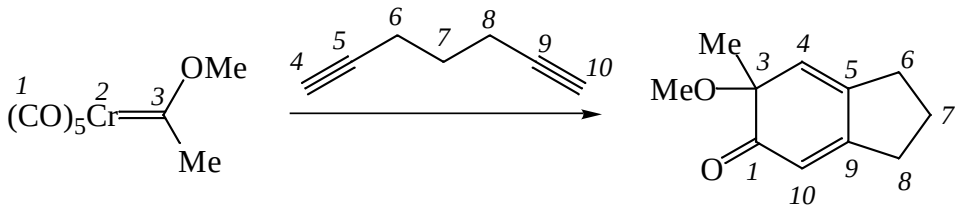
Propagation:



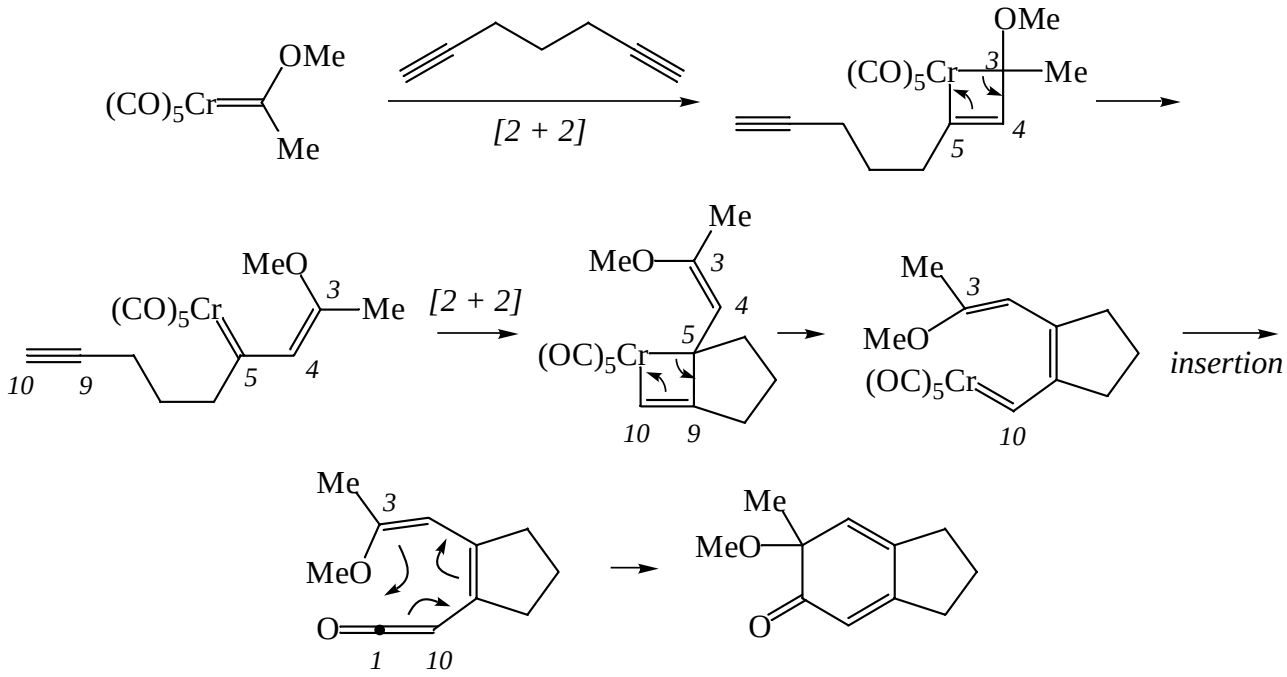
Finally, the hydroperoxide is reduced to the alcohol C–OH by excess $NaBH_4$.



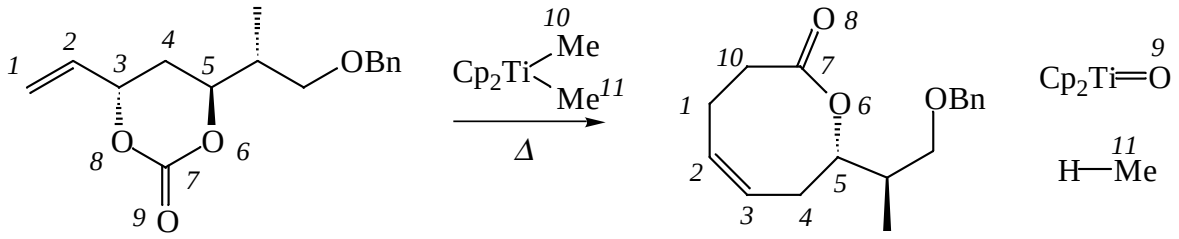
(i) Make: C1–C3, C1–C10, C3–C4, C5–C9. Break: C1–Cr2, C3–Cr2.



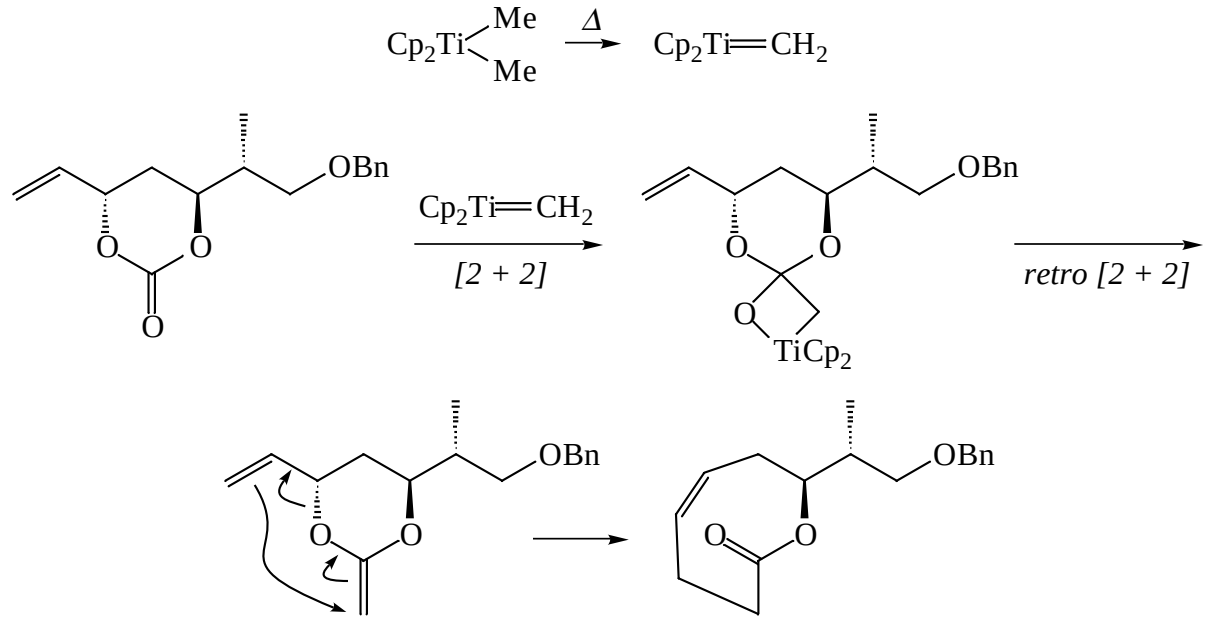
The first step is cycloaddition of the Cr=C3 bond to the alkyne to make the C3–C4 bond. The chromacyclobutene undergoes electrocyclic ring opening to give a new Cr=C3 bond, which undergoes intramolecular [2 + 2] cycloaddition with the other alkyne to form the C5–C9 bond. The new chromacyclobutene undergoes electrocyclic ring opening to give a new Cr=C10 bond. Insertion of CO into the Cr=C10 bond gives the ketene, which undergoes electrocyclic ring closing to give the product.



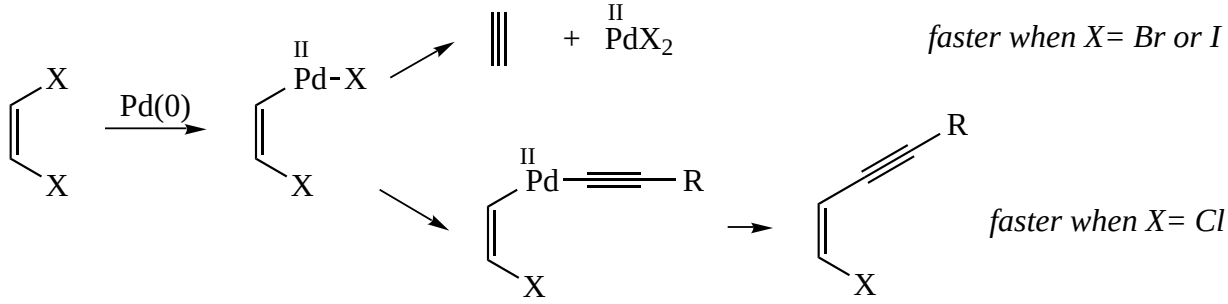
(j) Going from starting material to product, an O is replaced by a CH_2 group. The CH_2 group must come from Cp_2TiMe_2. The missing O must go to Ti. The question is, which O is the missing one: O8 or O9. Even though the product has a carbonyl, that does not mean that the carbonyl O in the product is O9, as in the starting material. In fact, because O9 in the starting material is more reactive, it in fact is the one that reacts with Ti and ends up excised from the starting material. Make: C1–C10, C7–C10, O9–Ti. Break: C3–O8, C7–O9, Ti–C10, Ti–C11.



The first step is α-hydride abstraction in Cp_2TiMe_2 to cleave the C11–Ti bond and give $Cp_2Ti{=}CH_2$. This compound undergoes [2 + 2] cycloaddition with the C7=O9 bond to give new C7–C10 and O9–Ti bonds, and [2 + 2] retrocycloaddition cleaves the Ti–C10 bond. Finally, the diene undergoes a Claisen rearrangement to give the product.



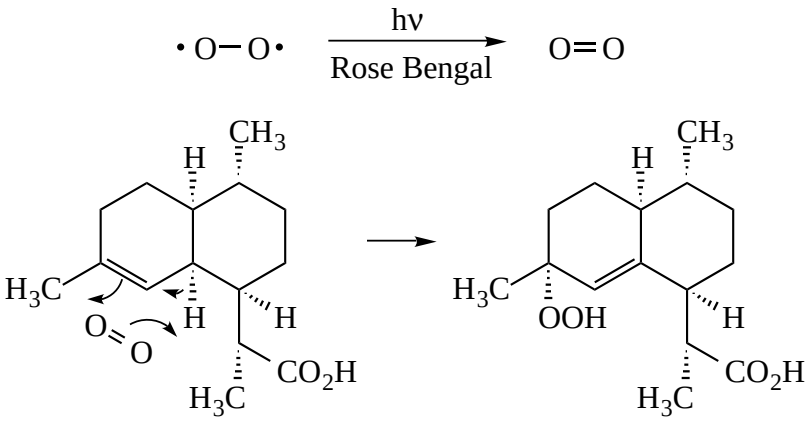
4. Oxidative addition of Pd(0) to a *cis*-dihaloethylene gives an intermediate that can undergo β-halide elimination. The C–Br or C–I bond is more prone to undergo β-elimination than the much stronger C–Cl bond. The transmetallation and reductive elimination steps of the Sonogashira coupling have more time to occur when a C–Cl bond is β to Pd than when a C–Br or C–I bond is β to Pd.



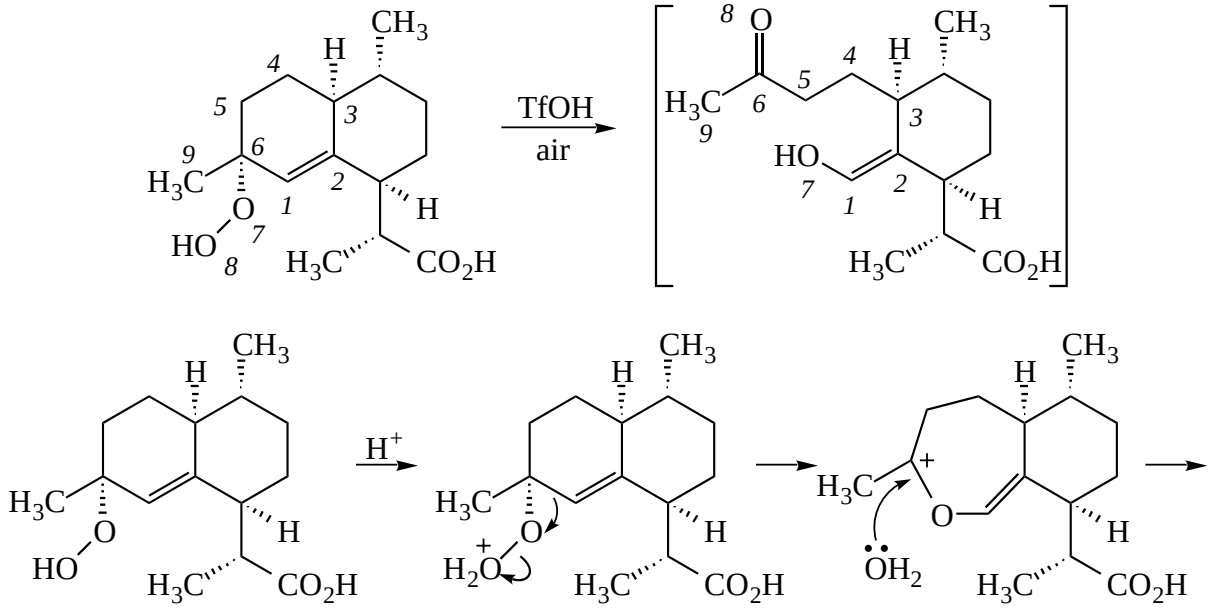
Answers To Chapter 7 Problems.

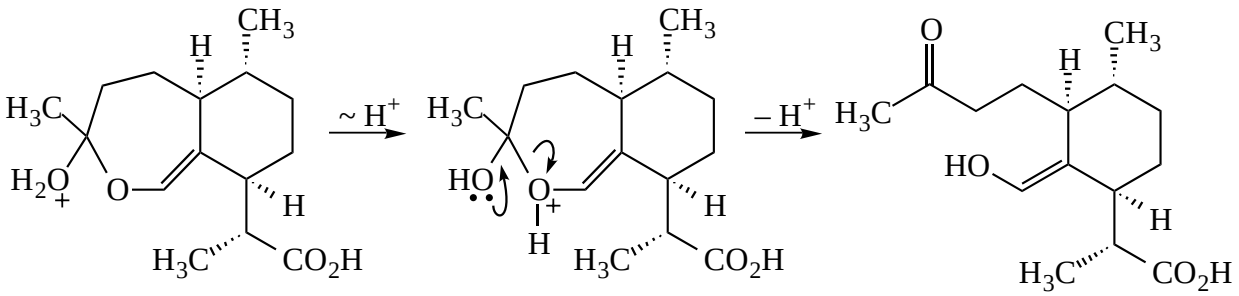
1. Most of the Chapter 1 problems appear as end-of-chapter problems in later chapters.

2. The first reaction is an ene reaction. When light shines on O_2 in the presence of light and Rose Bengal, singlet oxygen is obtained. This compound can do cycloadditions or ene reactions. If the reaction were a free-radical autoxidation, neither light nor Rose Bengal would be required.

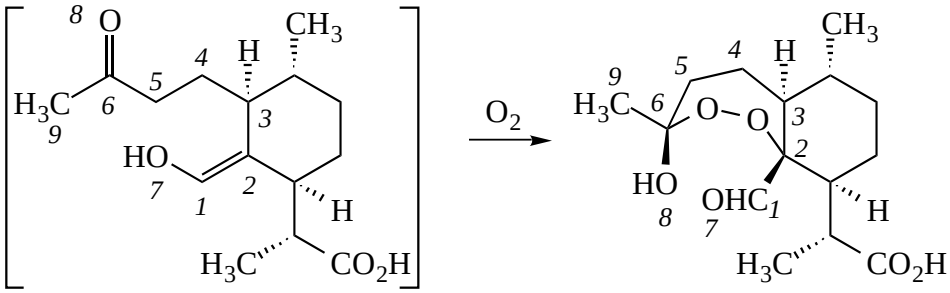


Second reaction. Air is not required for formation of the keto-enol. The C1–C6 and O7–O8 bonds are broken, and a new C1–O bond is made. It makes sense that the driving force for breaking the C1–C6 bond should be provided by migrating C1 from C6 to O7 (note: a 1,2-shift) and expelling O8. Then O8 can add back to C6 to give a hemiketal which can open up to the ketone.

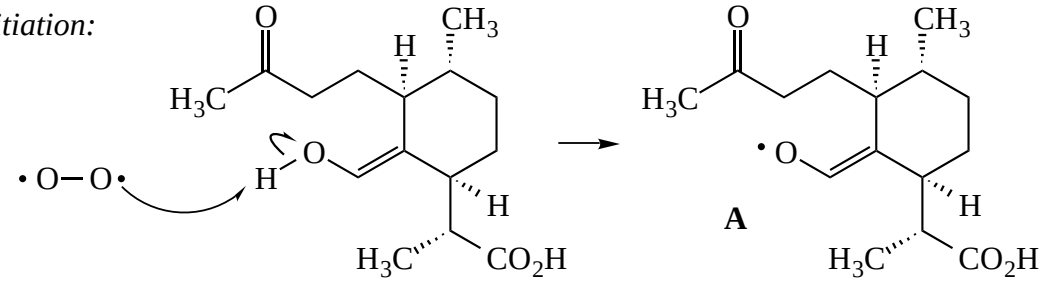




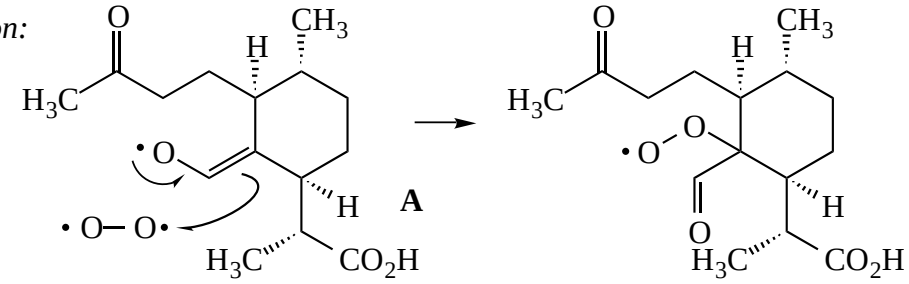
Air is required for conversion of the keto-enol to the endoperoxide. The most likely reaction is autoxidation. The O_2 makes bonds to C2 and C6, neither of which has an H atom attached for abstraction. But abstraction of H· from O7 gives a radical, **A,** that is delocalized over O7 and C2. Addition of O_2 to C2 gives a hydroperoxy radical, which abstracts H· from O7 of the starting material to give a hydroperoxide and **A** again. The hydroperoxide thus obtained can then add to the C6 ketone in a polar fashion to give the observed hemiketal.

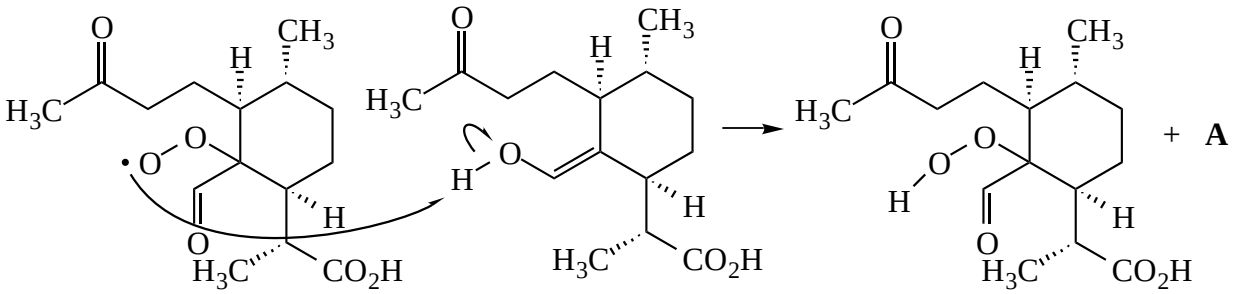


Initiation:

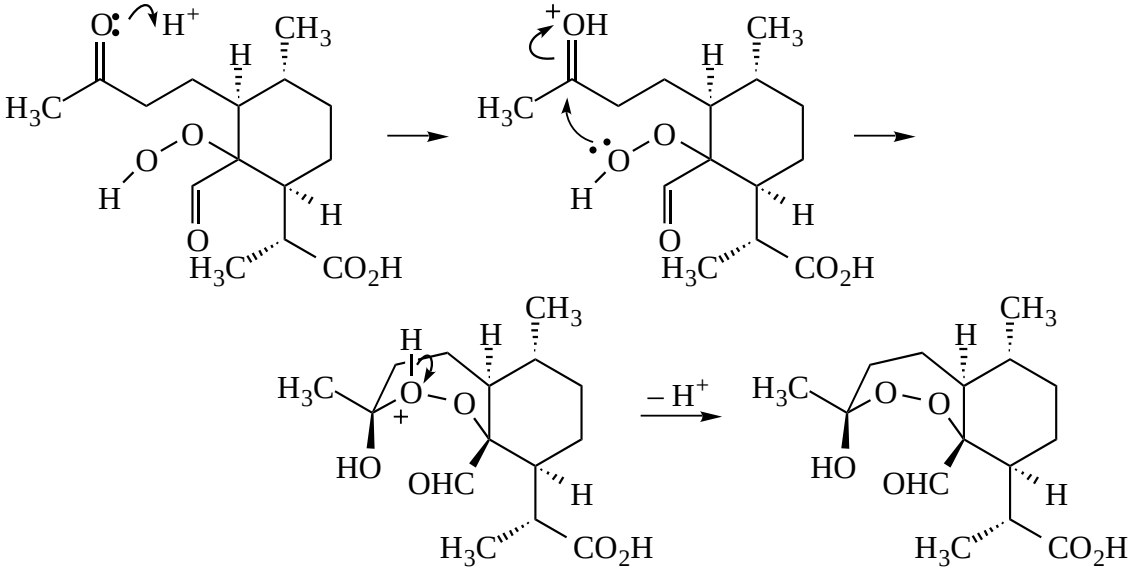


Propagation:

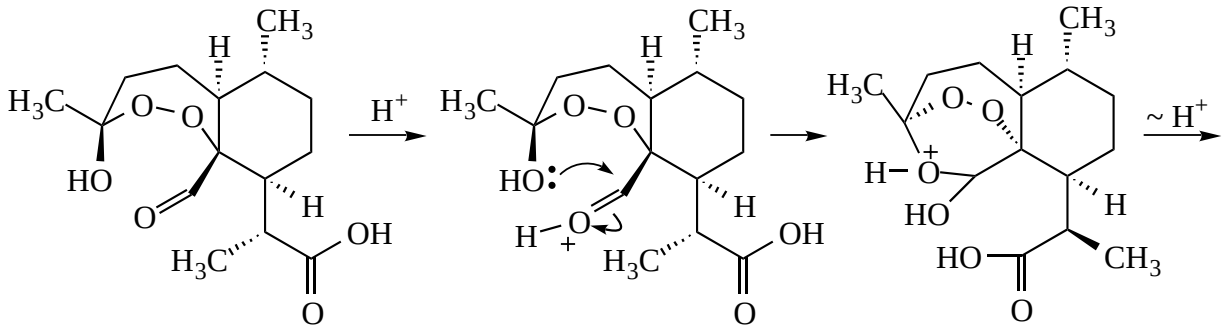


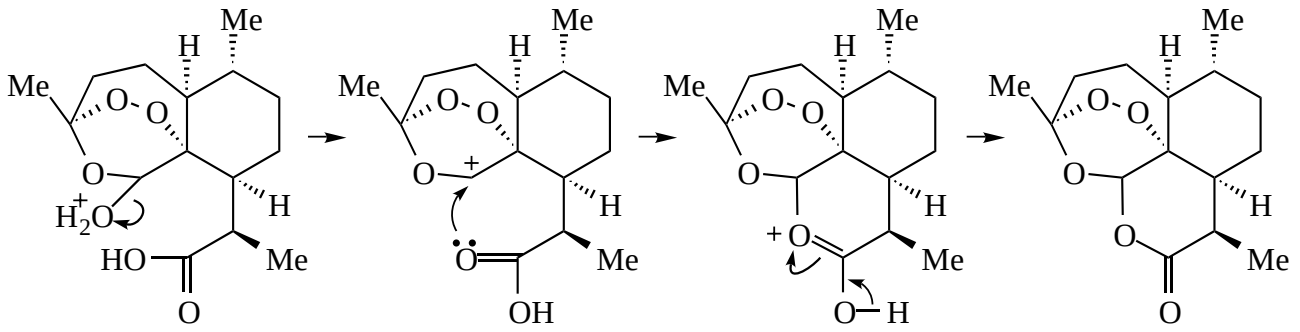


Polar reaction (acid is still present):

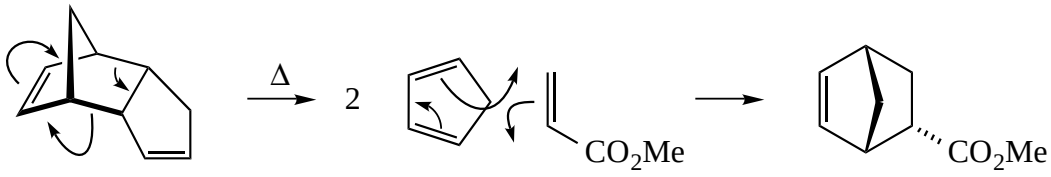


The fourth reaction is transformation of the aldehyde into an acetal. This proceeds by acid-catalyzed addition of an alcohol to the carbonyl, loss of H_2O, and then addition of the acid O to the carbocation. Other perfectly correct sequences of steps could be written here.



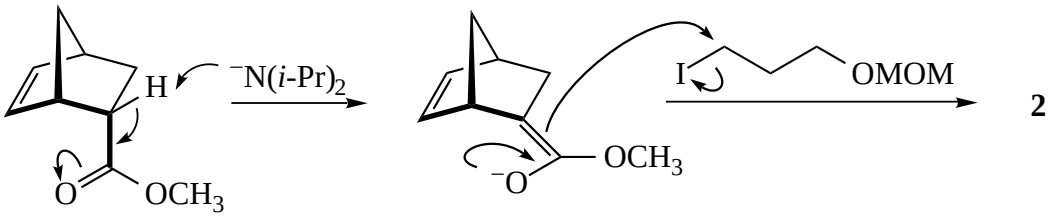


3. (a) Compound **1** is obviously made by a Diels–Alder reaction between cyclopentadiene and methyl acrylate. Cyclopentadiene is made from the starting material by a retro-Diels–Alder reaction. The product is obtained stereoselectively because of *endo* selectivity in the Diels–Alder reaction.

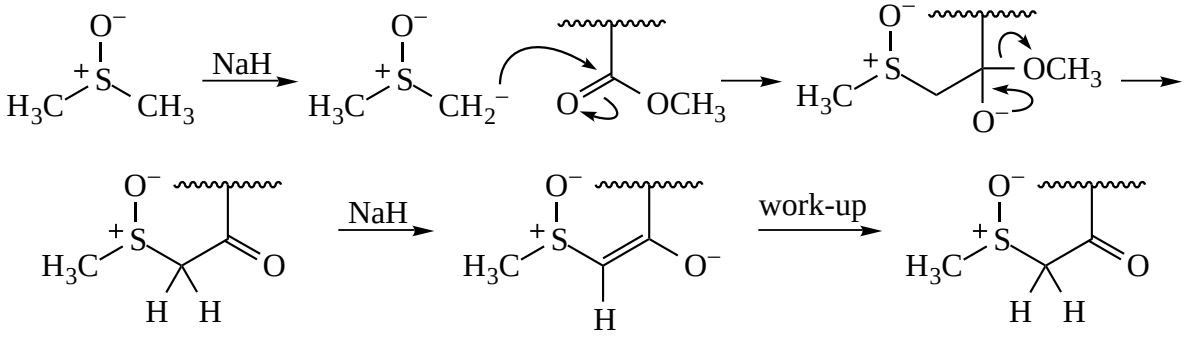


The starting material is called "dicyclopentadiene". Cyclopentadiene itself is not stable: it dimerizes to dicyclopentadiene slowly at room temperature by a Diels–Alder reaction. It does this even though it is not an electron-deficient dienophile, demonstrating the enormous reactivity of cyclopentadiene as a diene in the Diels–Alder reaction.

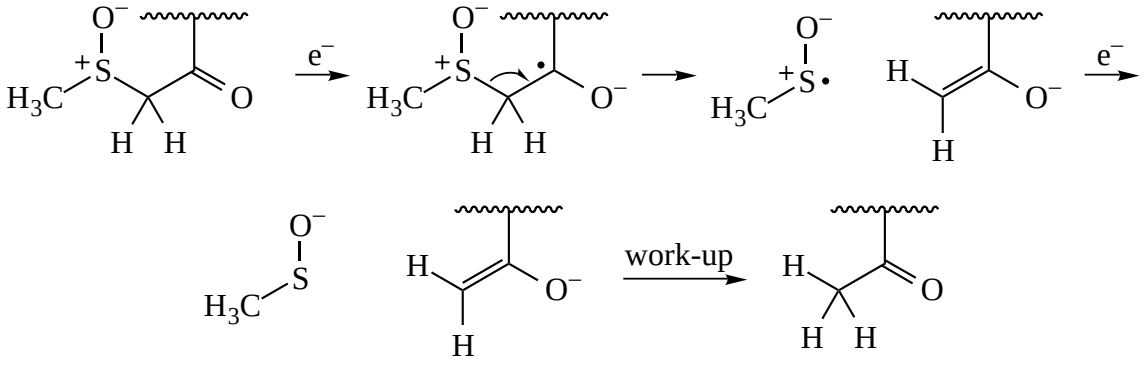
(b) LDA is a strong base. Compound **2** is obtained from the enolate of **1** by a simple S_N2 substitution reaction.



Now DMSO is treated with NaH, then with **2**, then with Zn and NaOH, to give overall substitution of CH_3 for CH_3O. The CH_3 group must come from DMSO, so we need to make a new bond between the DMSO C and the C=O carbon. NaH is a good base; it deprotonates DMSO to give the *dimsyl* anion. This adds to the carbonyl C, and then loss of MeO^- occurs to give the β-ketosulfoxide. This is a very good acid (like a 1,3-dicarbonyl), so it is deprotonated under the reaction conditions to give the enolate. Workup gives back the β-ketosulfoxide. This part of the mechanism is directly analogous to a Claisen condensation.

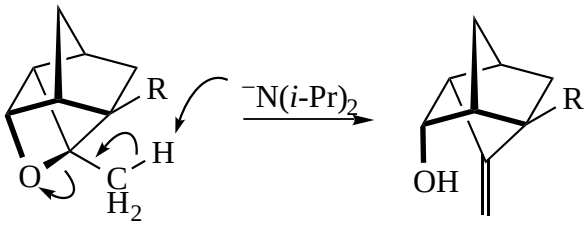


To get to **3**, we need to cleave the S–C bond. Zn is an electron donor, like Na or Li. Electron transfer to the ketone gives a ketyl, which undergoes fragmentation to give the enolate. The second electron from the Zn goes to the S leaving group to give $MeSO^-$. Workup gives the methyl ketone.



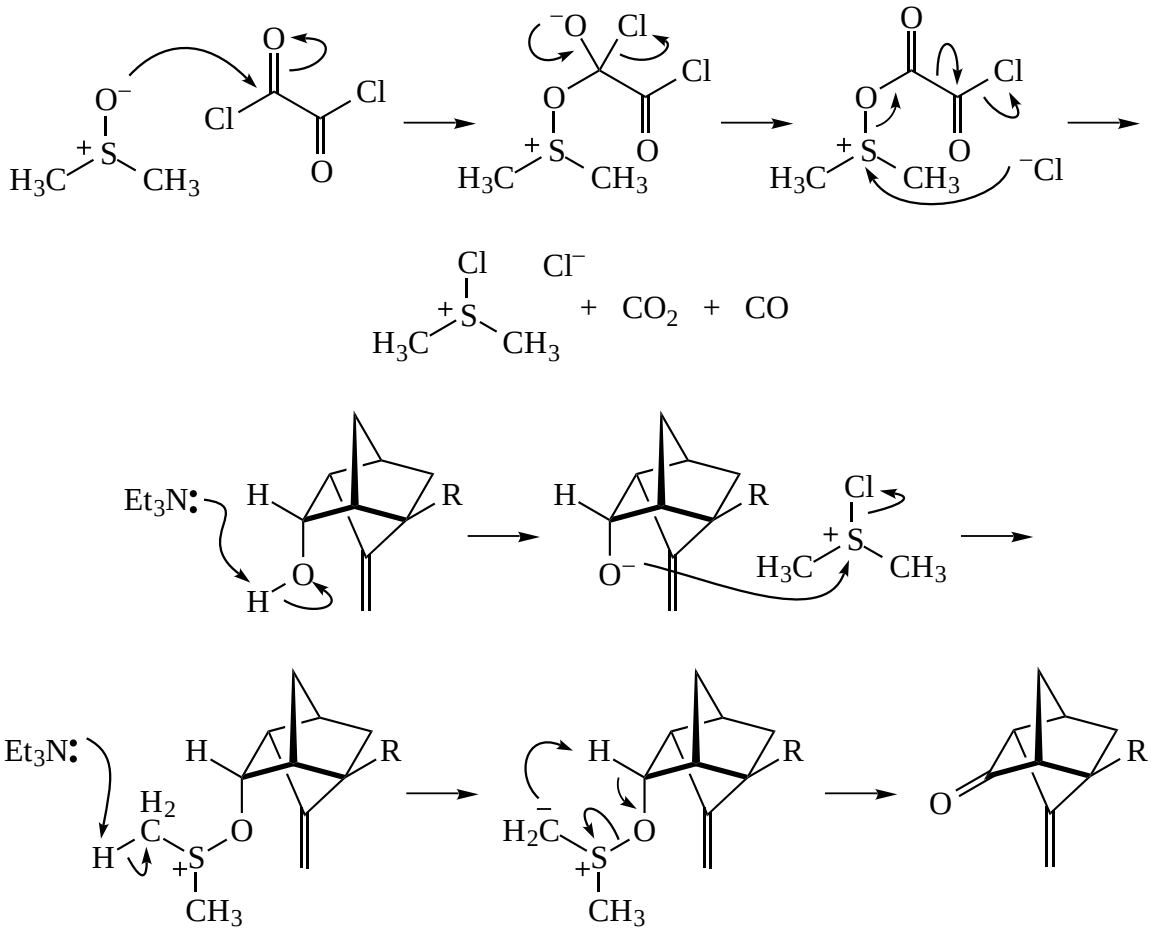
(c) The conversion of **3** to **4** is a [2+2] cycloaddition, the Paterno–Büchi reaction. This four-electron reaction proceeds photochemically.

(d) The conversion of **4** to **5** is an E2 elimination.

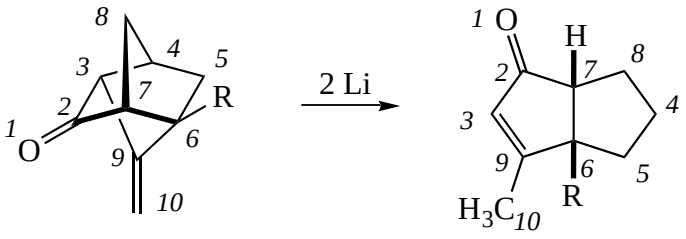


5

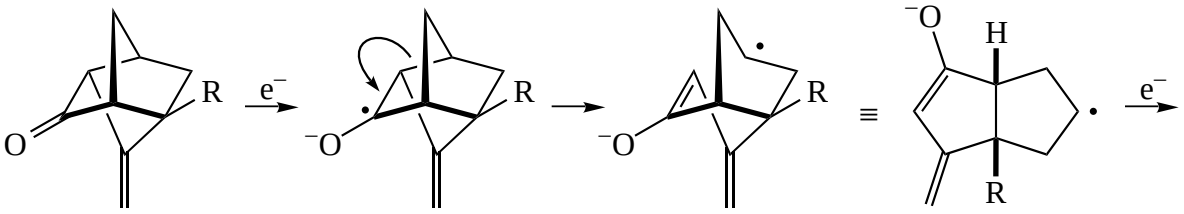
The conversion of **5** to **6** is a Swern oxidation. The O of DMSO is nucleophilic, and it reacts with oxalyl chloride. Cl^- then comes back and displaces O from S to give a S electrophile. The OH of **5** is then deprotonated, whereupon it attacks S, displacing Cl^-. Then deprotonation of a Me group and a retro-hetero-ene reaction occur to give the ketone.

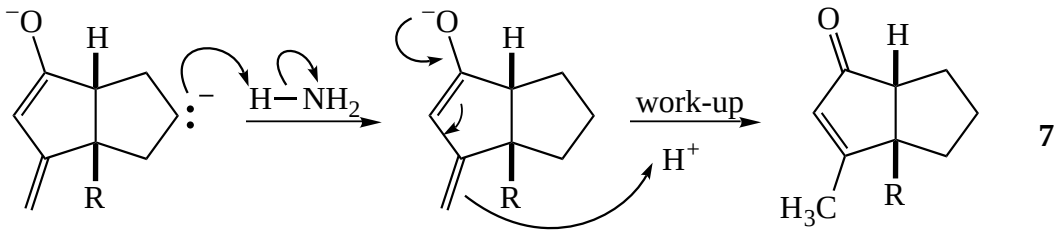


The conversion of **6** to **7** is a dissolving metal reduction. Number the atoms. The key atoms are O1, C2, C6, C10, and C9. Make: none. Break: C3–C4.

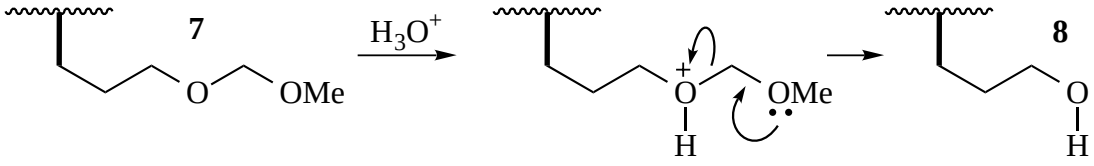


The first step is formation of the ketyl of **6**. This species can undergo fragmentation to form the C2–C3 enolate and a radical at C4. A second electron transfer gives a carbanion at C4, which deprotonates NH_3. Upon workup, C10 is protonated to give **7**.

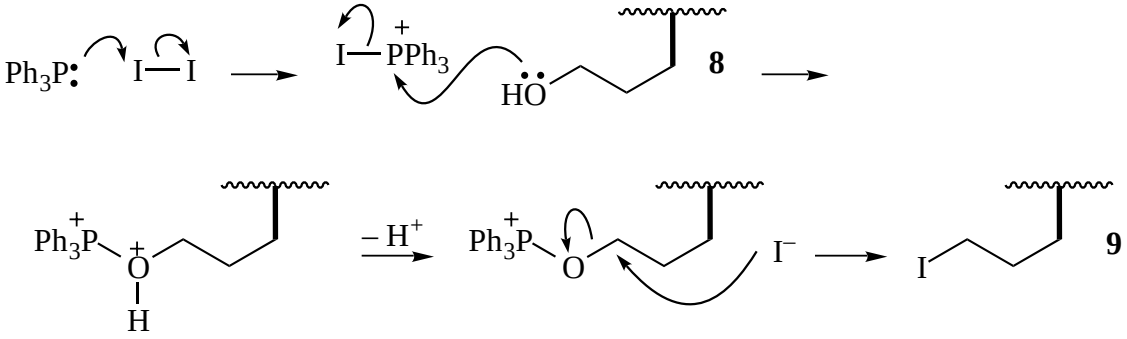




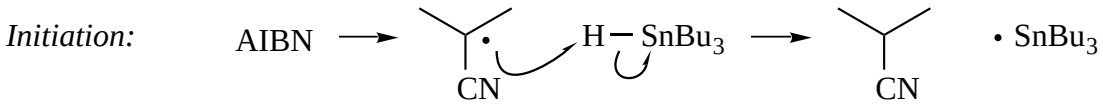
The conversion of **7** to **8** is a simple hydrolysis of an acetal. Acetals are functionally equivalent to alcohols + carbonyls and can be interconverted with them under acidic conditions. Several reasonable mechanisms can be drawn for this transformation, but all must proceed via S_N1 substitutions.



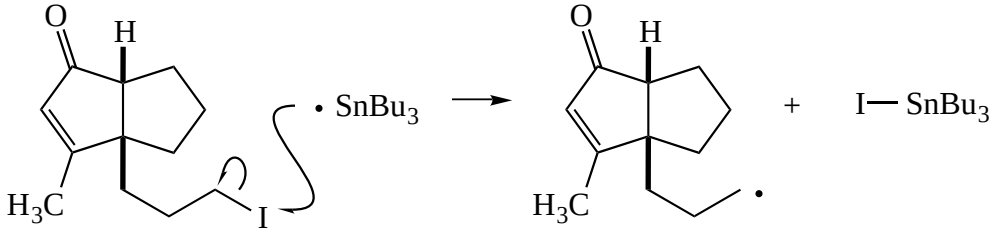
The conversion of **8** to **9** uses PPh_3 and I_2. The former is a nucleophile, the latter is an electrophile, so they react to give $Ph_3\overset{+}{P}–I$. The P is attacked by the alcohol to give an O–P bond, and the I^- then displaces Ph_3PO from C to give the alkyl iodide.

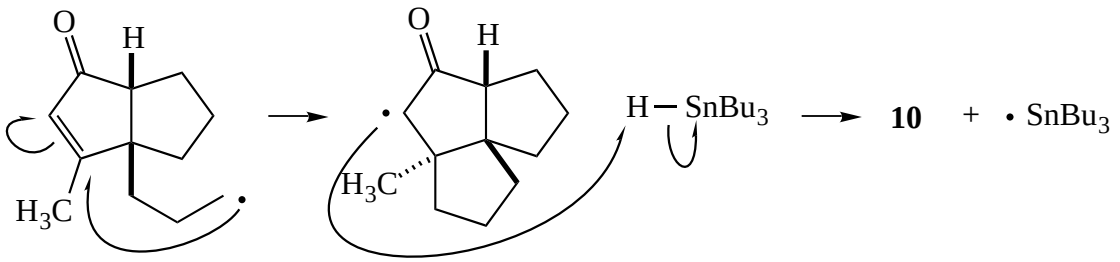


The next reaction is obviously a free-radical chain reaction.

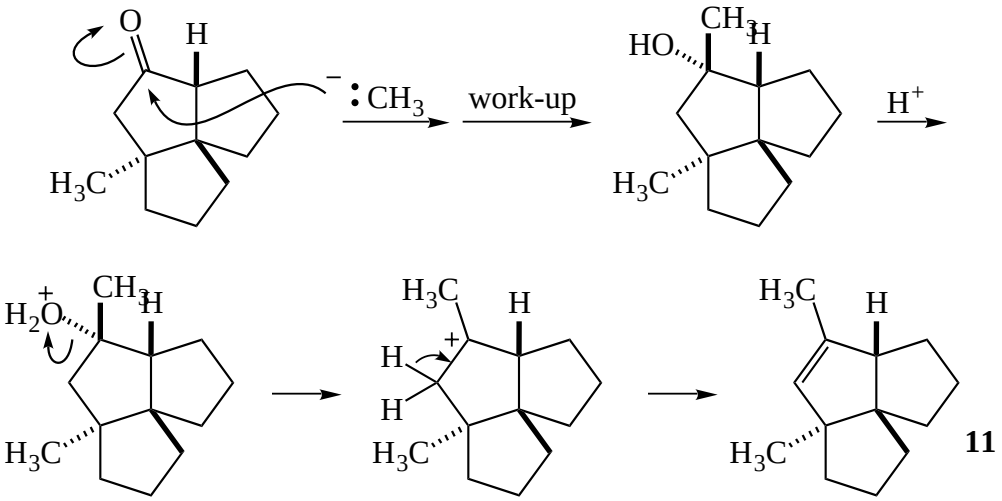


Propagation:



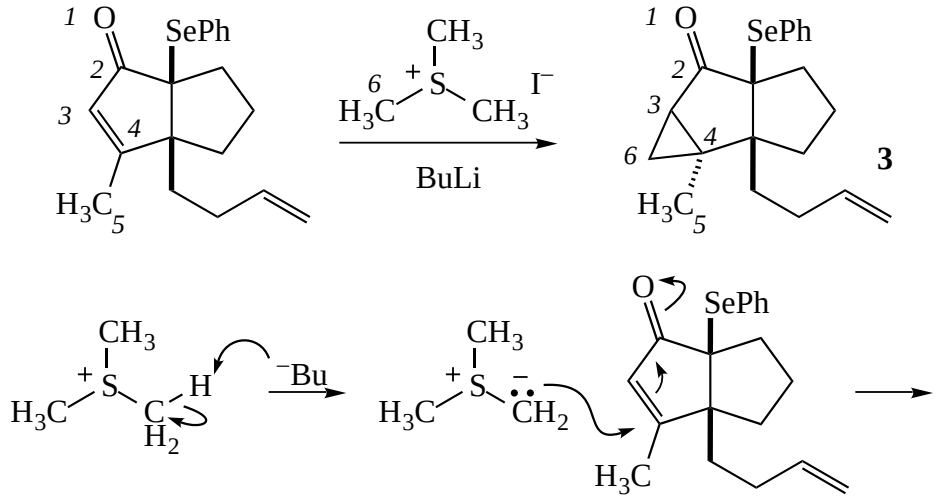


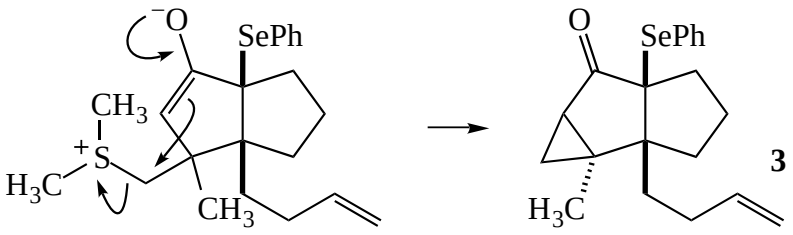
Finally, conversion of **10** to **11** involves addition of the very nucleophilic MeLi to the ketone; workup gives the alcohol. Then E1 elimination promoted by the acid TsOH gives the alkene.



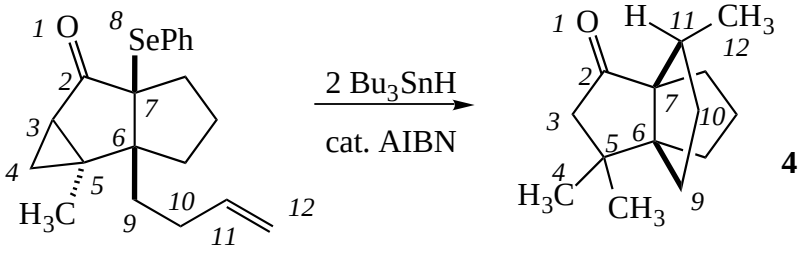
4. (a) The transformation of **1** to **2** (not shown) is a simple deprotonation with LDA, followed by S_N2 substitution on Se, displacing $^-$SePh.

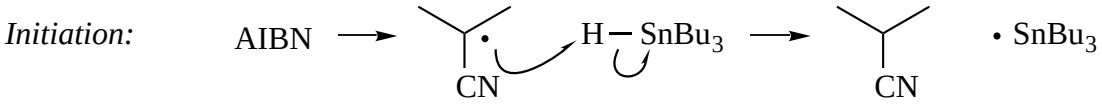
The conversion of **2** to **3** requires making C3–C6 and C4–C6, and breaking C6–S. The BuLi deprotonates C6 to give a sulfur ylide. This makes C6 nucleophilic. It adds to C4, making an enolate and making C3 nucleophilic. The enolate at C3 then attacks C6, displacing Me_2S to give the product.

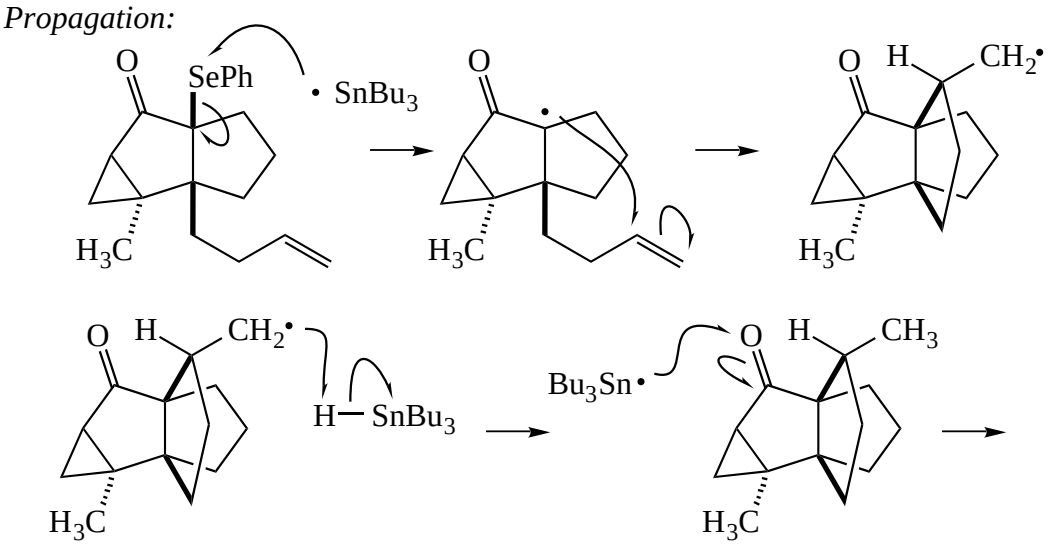


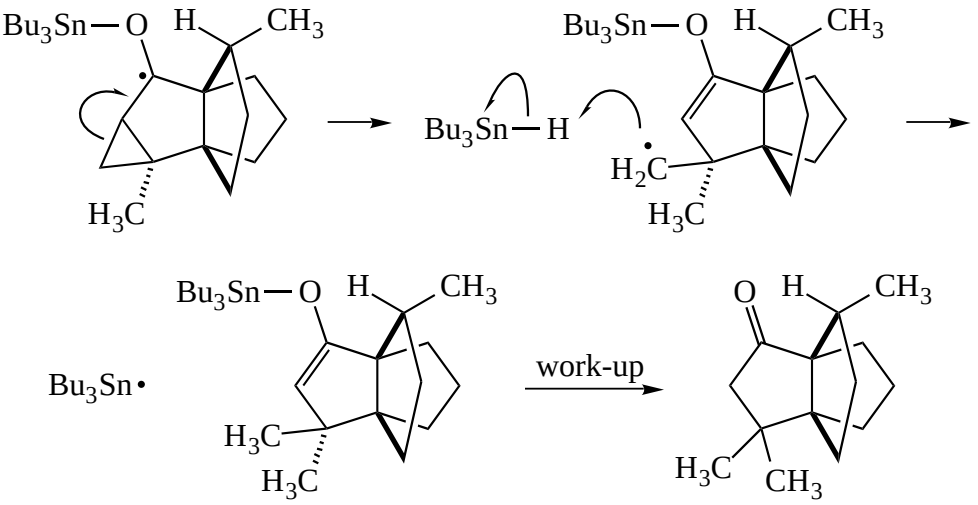


The conversion of **3** to **4** is a free-radical chain process. Note two equivalents of Bu_3SnH are required. Make: C7–C11, Sn–Se8. Break: Se8–C7, C3–C4. Let's deal with the Se first. After initiation, $Bu_3Sn\cdot$ abstracts SePh from C7. The C7 radical then adds to C11, giving a radical at C12 which abstracts H from Bu_3SnH to regenerate $\cdot SnBu_3$. The C3–C4 bond still needs to be broken, and C3 and C4 both need to have H attached to them. We know that a cyclopropane ring cleaves very easily if a radical is generated at a C attached to it, e.g. at C2. We can generate a radical at C2 by having $Bu_3Sn\cdot$ add to O1. Then the C3–C4 bond cleaves, making a C4 radical and a tin enolate at C3–C2–O1. The C4 radical abstracts H from Bu_3SnH to propagate the chain. The tin enolate is protonated upon workup to give **4**.

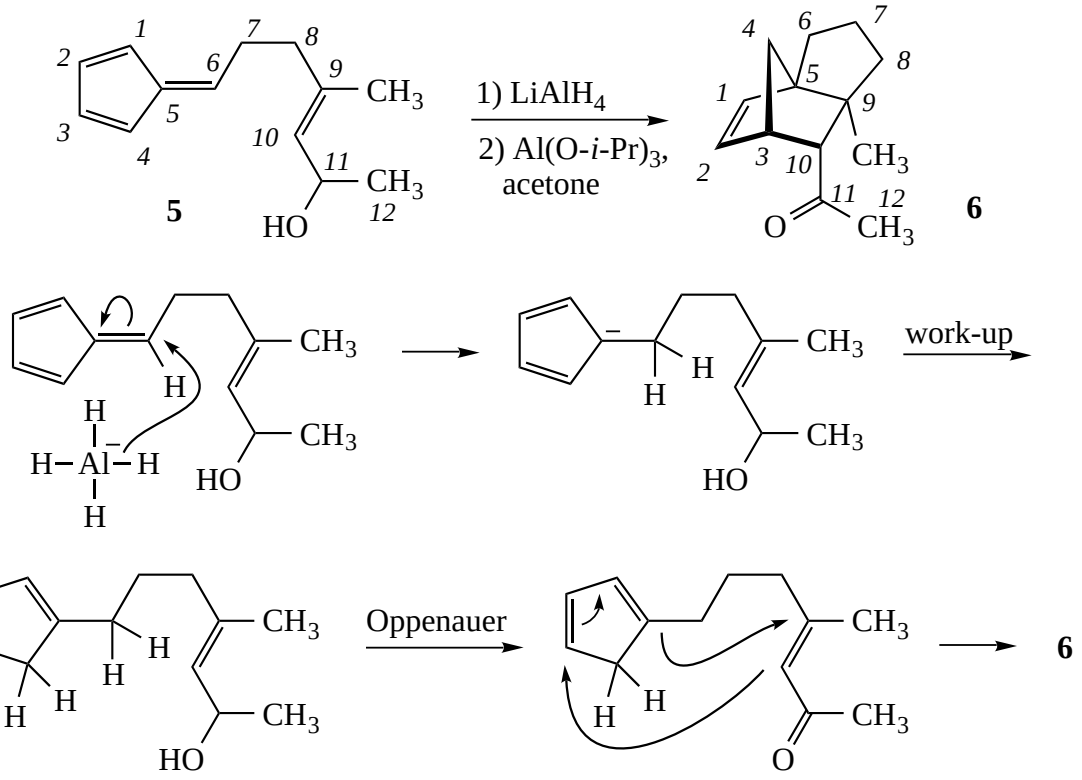




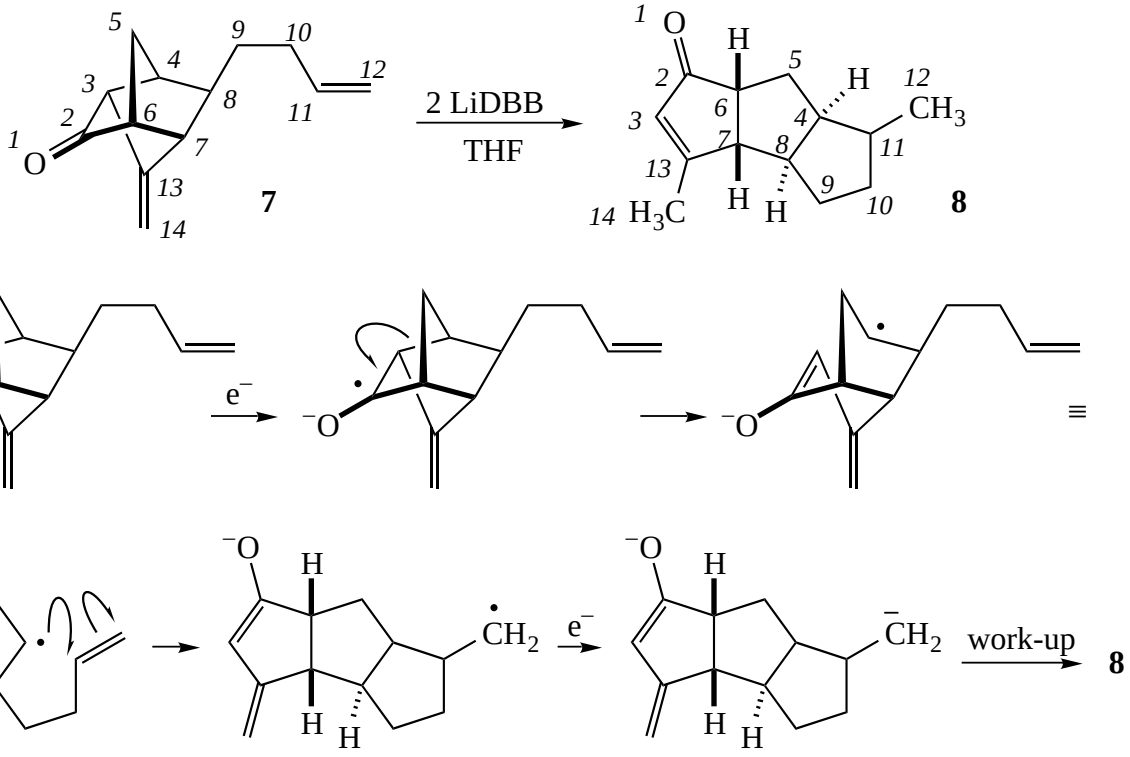




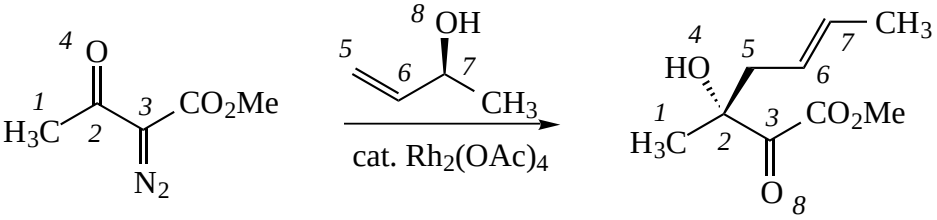
(b) $LiAlH_4$ is a source of very nucleophilic H^-. It must add to an electrophilic C. If you obey Grossman's Rule, you will see that C4 and C6 in the product have extra H's. Of these two only C6 is electrophilic, because when H^- adds to C6, a very stable (aromatic) cyclopentadienyl anion is obtained. This anion is protonated at C4 upon workup to give the alcohol. (Actually, the anion can be protonated on C3, C4, or C5, but all three isomers are in equilibrium with one another, and only the isomer protonated on C4 is able to undergo the subsequent Diels–Alder reaction.) When the alcohol is oxidized to the ketone, the C9=C10 π bond becomes electron-deficient and electronically suitable to undergo an intramolecular Diels–Alder reaction with the cyclopentadiene to give **6**.



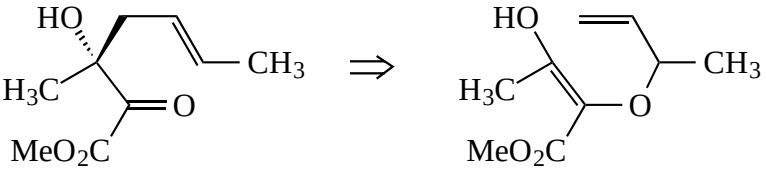
(c) Make: C4–C11. Break: C3–C4. The first step is electron transfer to form the ketyl. Fragmentation of the C3–C4 bond occurs to give a radical at C4, which can add to C11 to make the C4–C11 bond and put the radical on C12. A second electron transfer gives a carbanion at C12. Upon workup it is protonated, as is C14, to give **8**.



5. First step. Make: C3–O8, C2–C5. Break: C7–O8.

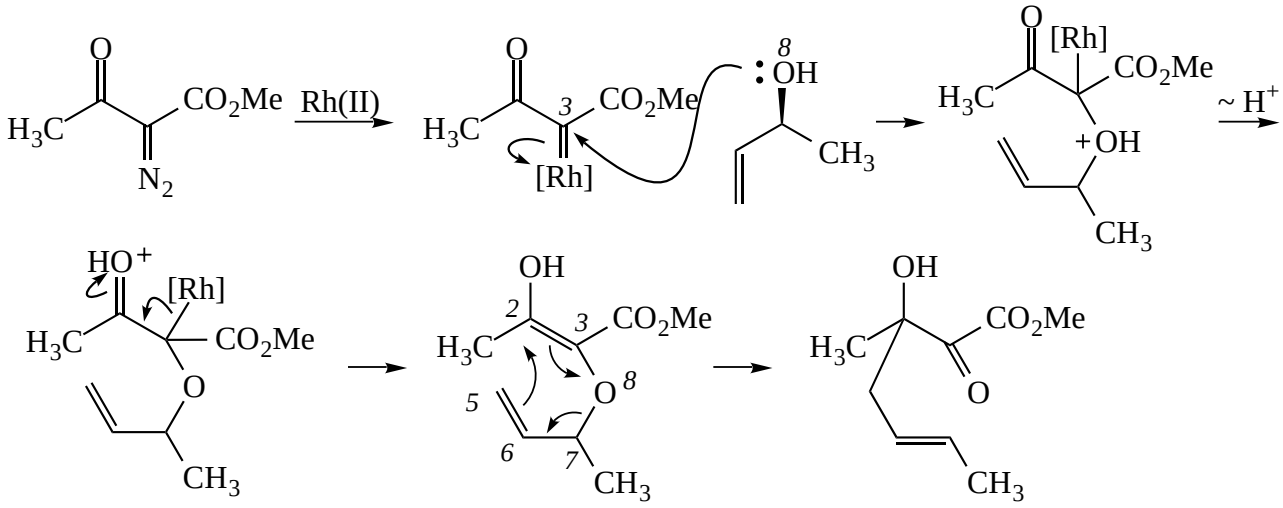


The product is a γ,δ-unsaturated carbonyl compound (a 1,5-diene), hinting that the last step is a Claisen rearrangement.

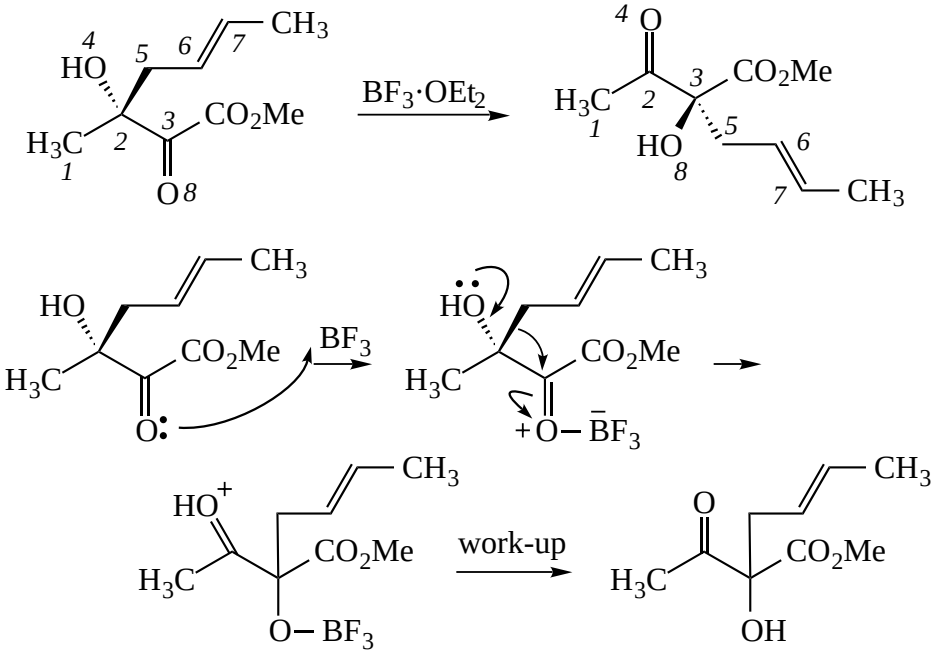


The diazo compound combined with the Rh(II) salt tells you that a carbenoid is involved. The carbenoid can be drawn in the Rh=C form or as its synthetic equivalent, a singlet carbene. In either case, C3 can

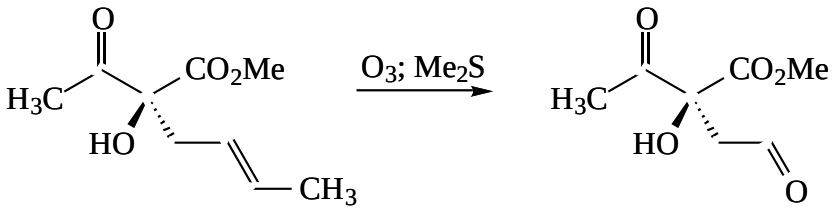
undergo one of the typical reactions of carbenes, addition of a nucleophile, to form the C3–O8 bond. After proton transfer to O4 and loss of [Rh], a Claisen rearrangement can occur to give the product.



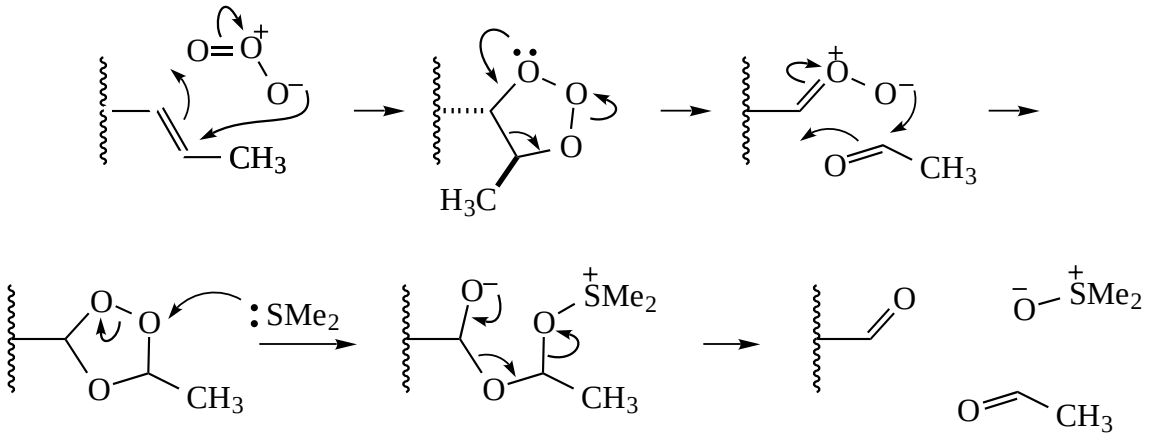
Second step. Make C3–C5. Break C2–C5. The reaction proceeds by a 1,2-shift.



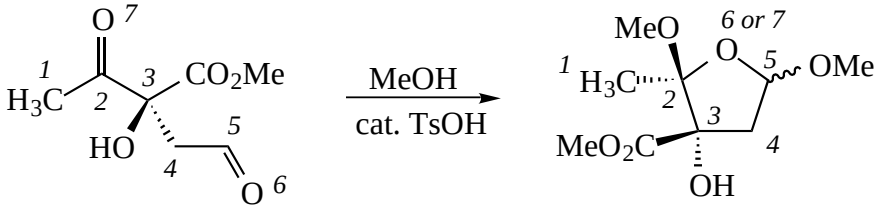
Third step. Standard ozonolysis with Me_2S workup.



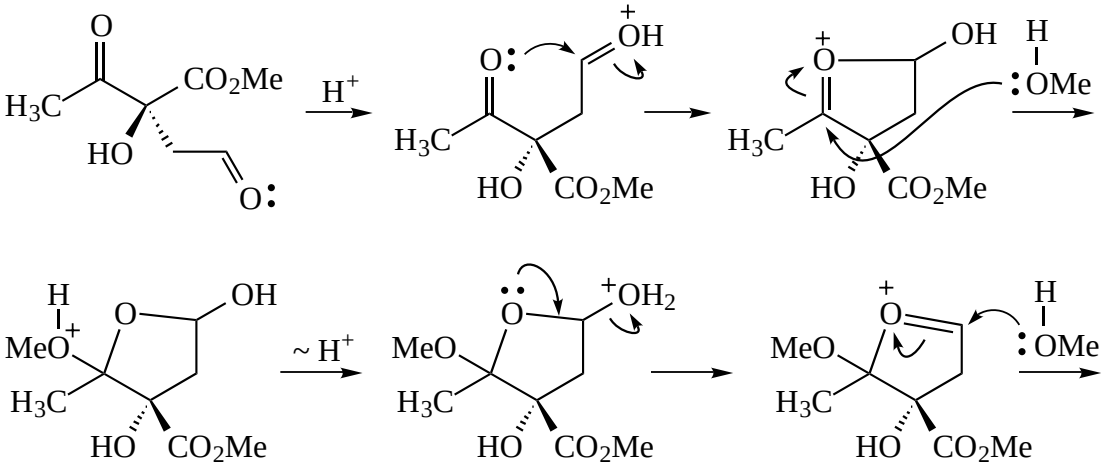
The Criegee mechanism should be drawn. The initially formed 1,2,3-trioxolane can be split up in two ways, one of which gives the desired aldehyde, but the mechanism can't stop there.

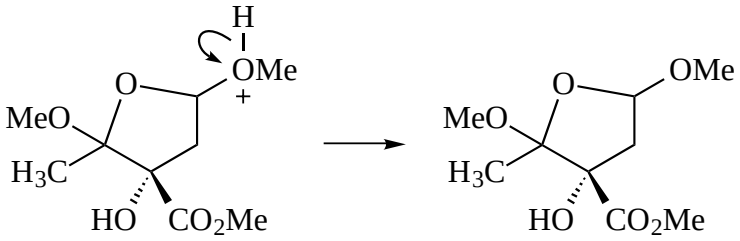


Fourth step. It is not clear whether the ring O is O6 or O7. If the ring O is O6, then make: C2–OMe, C2–O6, C5–OMe, and break: C2–O7. If the ring O is O7, then make: C2–OMe, C5–O7, C5–OMe, and break: C5–O6.



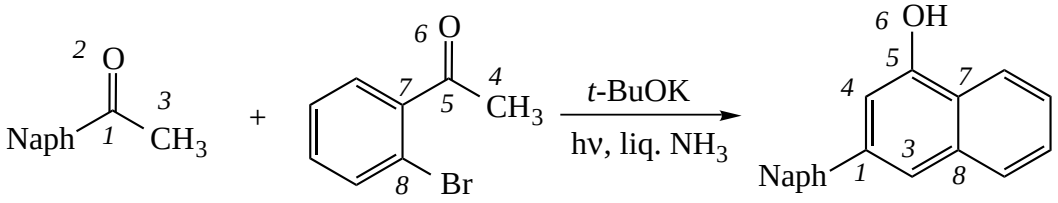
First step is protonation of one of the carbonyl O's. An intramolecular addition is likely to occur faster than an intermolecular one. Because a better carbocation can be formed at C2 than at C5, addition of O7 to O5 is more likely than addition of O6 to C2.



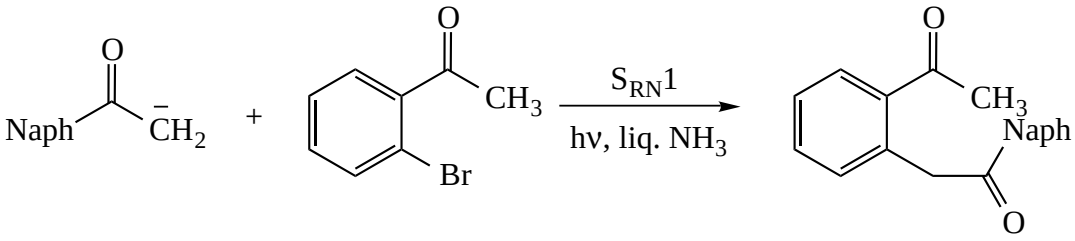


It should be stressed that this mechanism is not the only reasonable one for this reaction. Any reasonable mechanism should avoid an S_N2 substitution, however.

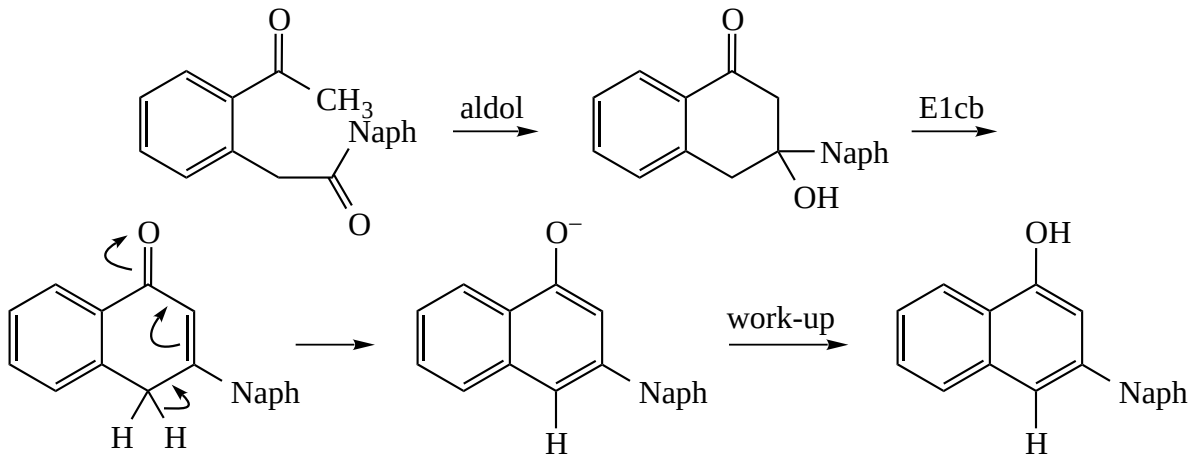
6. Make: C1–C4, C3–C8. Break: C1–O2, C8–Br. The light suggests a free-radical or pericyclic reaction is operative in at least part of the mechanism.



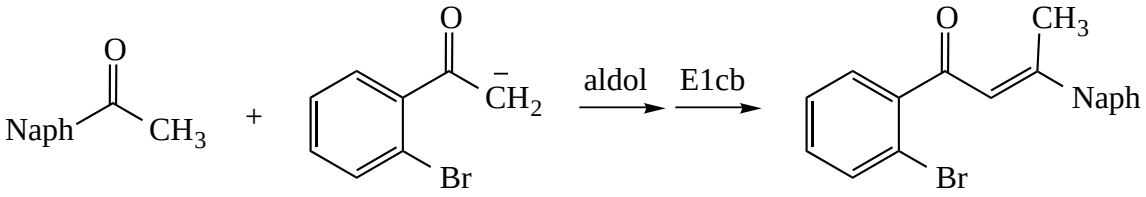
The base may deprotonate either C3 or C4. Deprotonation of C3 makes it nucleophilic. We need to form a new bond from C3 to C8 via substitution. The mechanism of this aromatic substitution reaction could be addition–elimination or $S_{RN}1$. The requirement of light strongly suggests $S_{RN}1$. See Chap. 2, section C.2, for the details of drawing an $S_{RN}1$ reaction mechanism.



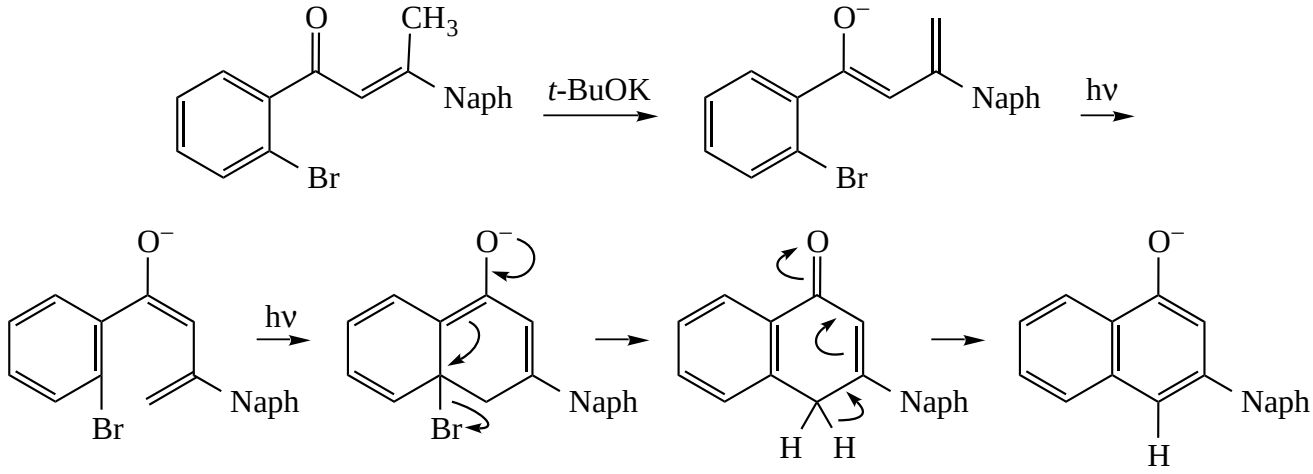
After the substitution is complete, all that is required is an aldol reaction, dehydration by E1cb, and deprotonation. Workup then gives the product.



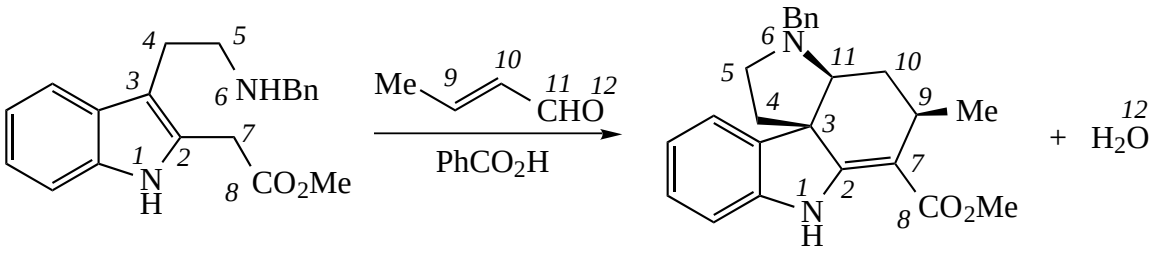
Alternatively, deprotonation of C4 makes it nucleophilic, and an aldol reaction and dehydration by E1cb gives an enone.



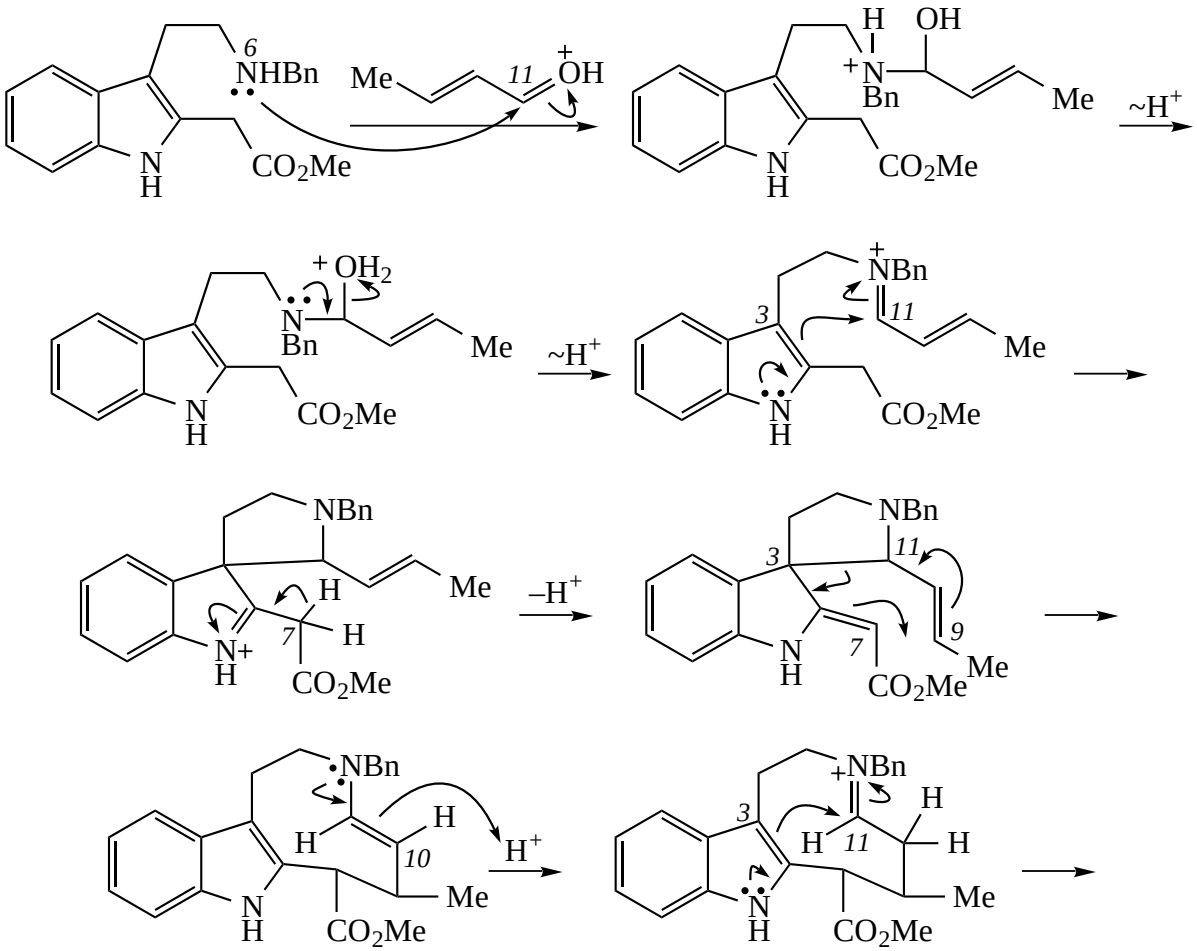
We still need to form C3–C8. Deprotonation of C3 gives a dienolate. The more stable, (*E*) isomer will form. Light causes this isomer to isomerize to the (*Z*) isomer. An electrocyclic ring closing, which may also require light because it destroys aromaticity, gives the C3–C8 bond. Expulsion of Br^- and deprotonation gives the conjugate base of the product.

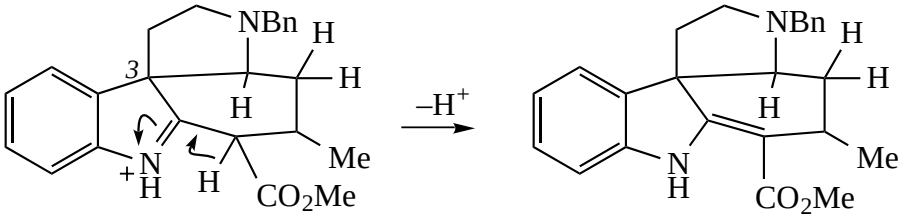


7. Make: C3–C11, N6–C11, C7–C9. Break: C11–O12.

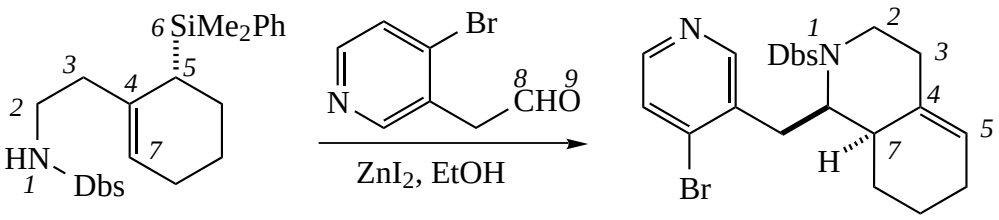


The combination of an amine and an aldehyde under weakly acidic conditions almost always gives an iminium ion very rapidly. Such a reaction forms the N6–C11 bond. Nucleophilic C3 can then attack this iminium ion to give a new iminium ion. We still need to make C7–C9. Deprotonation of C7 gives a neutral enamine and a 1,5-diene. Cope rearrangement of the diene gives the C7–C9 bond, but it breaks the C3–C11 bond that was just formed! However, C11 can be made electrophilic again by protonation of C10. Attack of nucleophilic C3 on C11 gives an iminium ion again, and deprotonation of C7 gives the product.

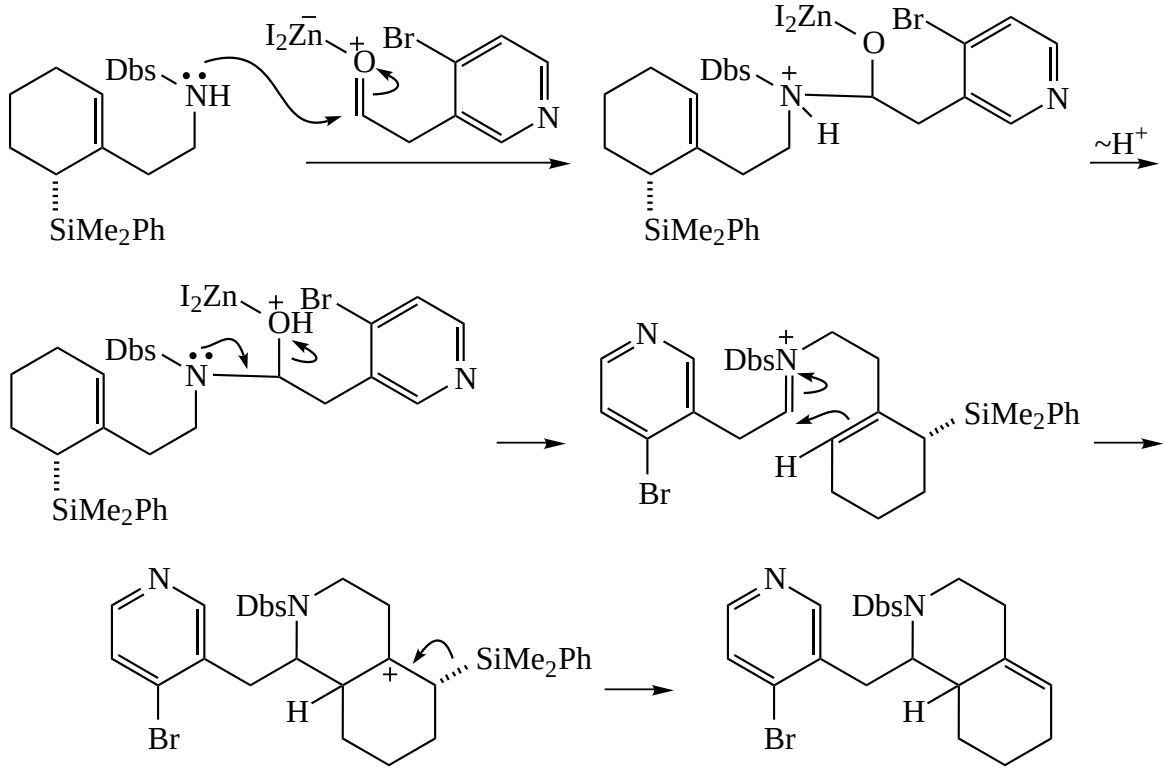




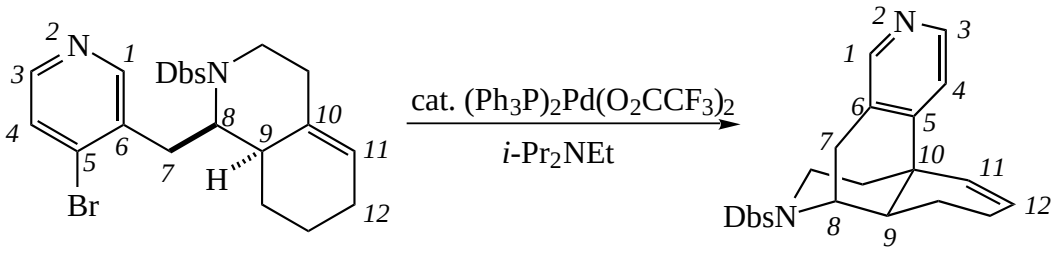
8. First reaction. Make: N1–C8, C7–C8. Break: C5–Si6, C8–O9.



The combination of an amine and an aldehyde under weakly acidic conditions almost always gives an iminium ion very rapidly. Such a reaction forms the N1–C8 bond. Nucleophilic C7 can then attack this iminium ion to give a carbocation. Fragmentation of the C5–Si6 bond gives the product.



Second step. Make: C5–C10. Break: C5–Br.



The catalytic Pd complex and the aryl bromide together suggest the first step is oxidative addition of Pd(0) to the C5–Br bond. (The reduction of Pd(II) to Pd(0) can occur by coordination to the amine, β-hydride elimination to give a Pd(II)–H complex and an iminium ion, and deprotonation of Pd(II)–H to give Pd(0).) The C10–C11 π bond can then insert into the C5–Pd bond to give the C5–C10 bond. β-Hydride elimination then gives the C11–C12 π bond and a Pd(II)–H, which is deprotonated by the base to regenerate Pd(0). The overall reaction is a Heck reaction.