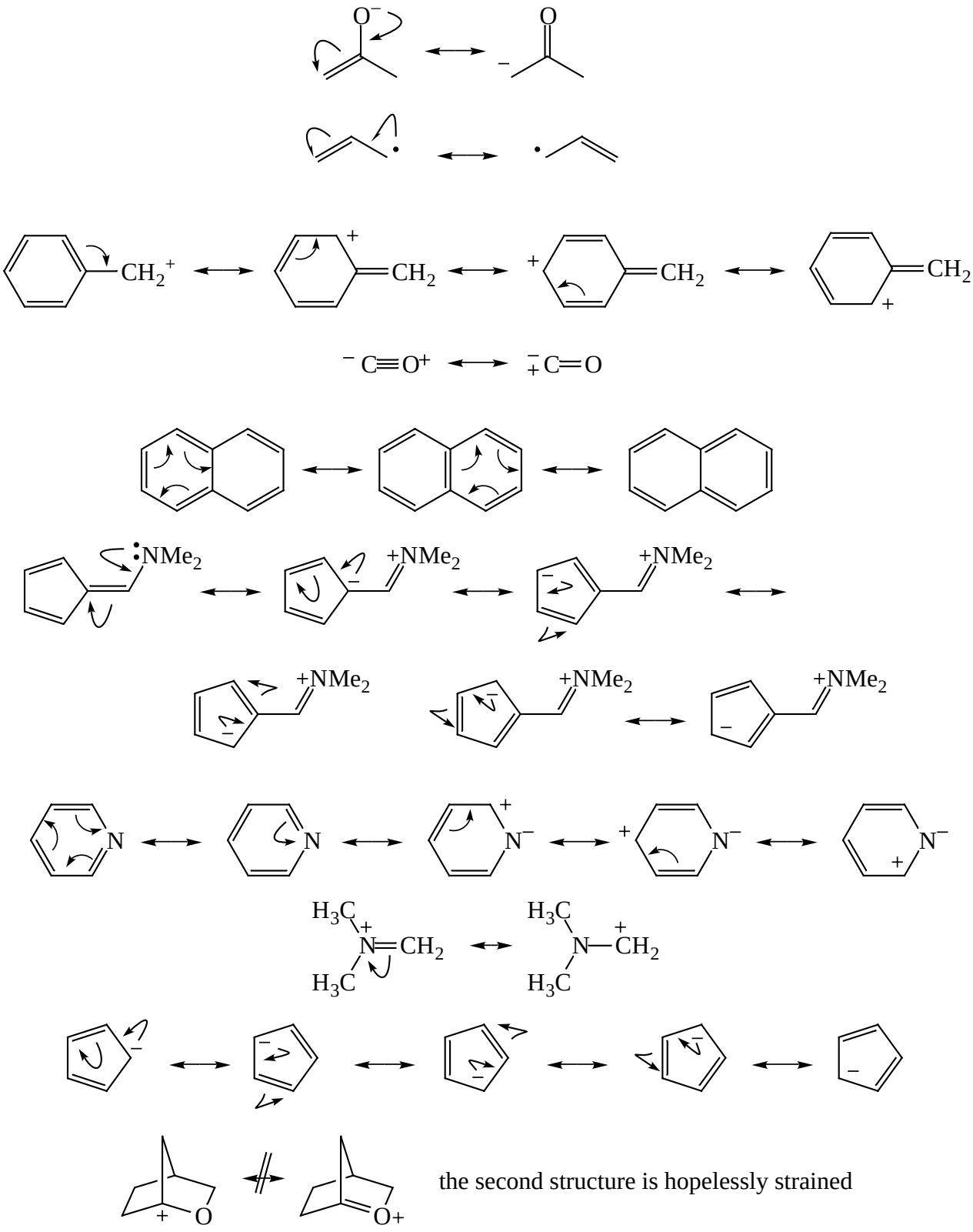
Answers To Chapter 1 In-Chapter Problems.

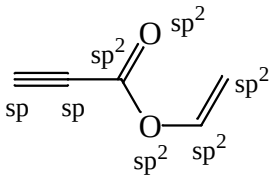
1.1. The resonance structure on the right is better because every atom has its octet.

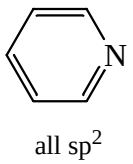
1.2.



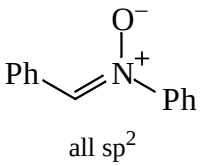
the second structure is hopelessly strained

1.3.

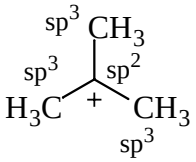


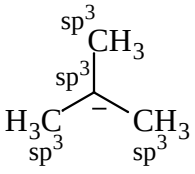


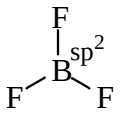
all sp^2

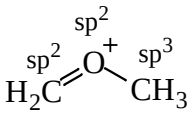


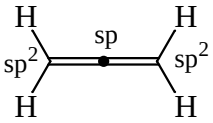
all sp^2







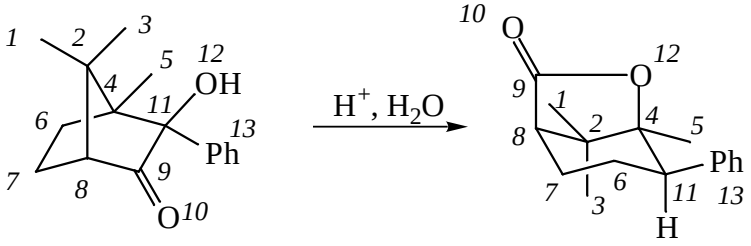




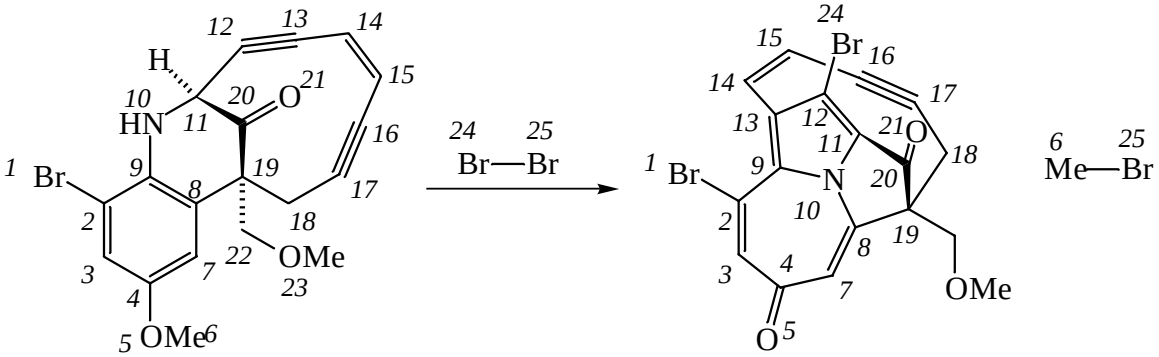
1.4. The O atom in furan has sp^2 hybridization. One lone pair resides in the p orbital and is used in resonance; the other resides in an sp^2 orbital and is not used in resonance.

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.

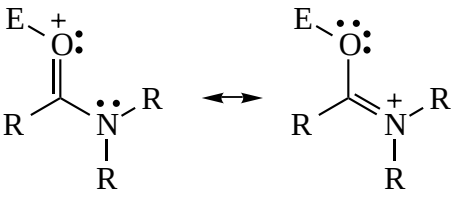
1.7. PhC≡CH is much more acidic than BuC≡CH. Because the pK_b of HO^- is 15, PhC≡CH has a p$K_a \leq$ 23 and BuC≡CH has p$K_a > 23$.

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.

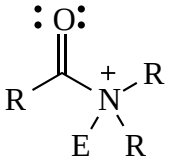
Answers To Chapter 1 End-Of-Chapter Problems.

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



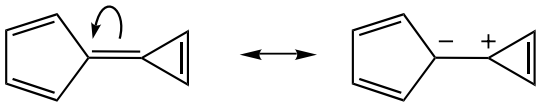
reaction on N



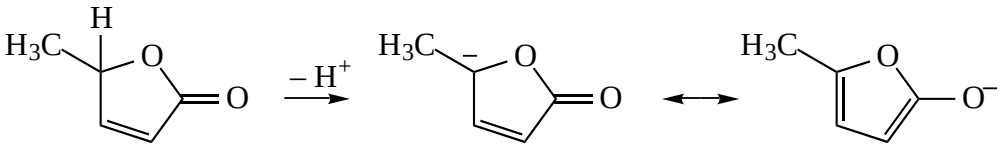
(b) Esters are *lower in energy* than ketones because of resonance stabilization from the O atom. Upon addition of a nucleophile to either an ester or a ketone, a tetrahedral intermediate is obtained for which resonance is not nearly as important, and therefore the tetrahedral product from the ester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

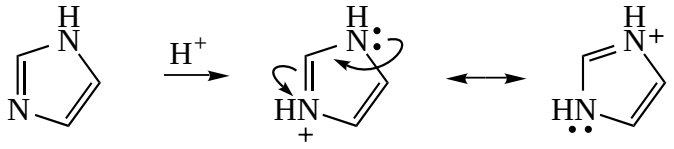


(e) The difference between **3** and **4** is that the former is cyclic. Loss of an acidic H from the γ C of **3** gives a structure for which an aromatic resonance structure can be drawn. This is not true of **4**.

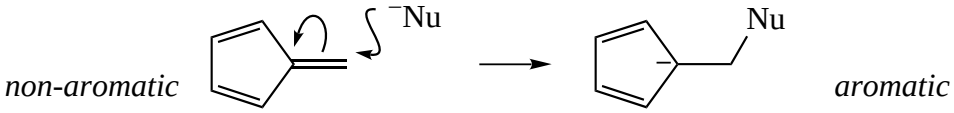


(f) Both imidazole and pyridine are aromatic compounds. The lone pair of the H-bearing N in imidazole is required to maintain aromaticity, so the other N, which has its lone pair in an sp^2 orbital that is perpendicular to the aromatic system, is the basic one. Protonation of this N gives a compound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



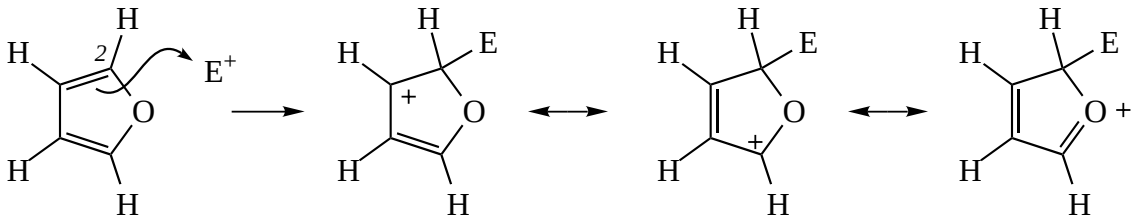
(h) The tautomer of 2,4-cyclohexadienone, a nonaromatic compound, is phenol, an aromatic compound.

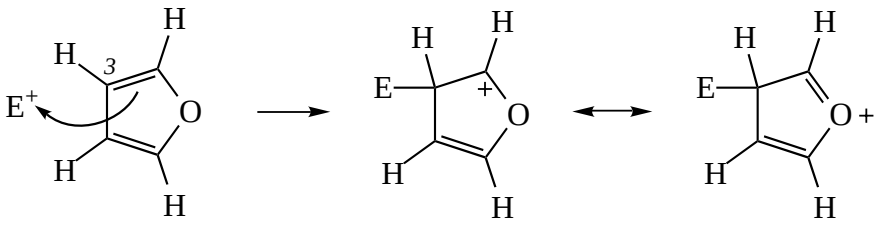
(i) Carbonyl groups C=O have an important resonance contributor $\overset{+}{C}–\overline{O}$. In cyclopentadienone, this resonance contributor is antiaromatic.

[**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!]

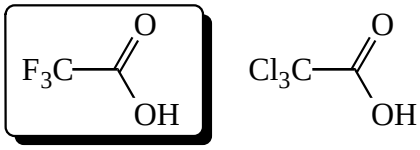
(j) PhOH is considerably more acidic than EtOH (pK_a= 10 vs. 17) because of resonance stabilization of the conjugate base in the former. S is larger than O, so the S(p)–C(p) overlap in PhS^- is much smaller than the O(p)–C(p) overlap in PhO^-. The reduced overlap in PhS^- leads to reduced resonance stabilization, 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.



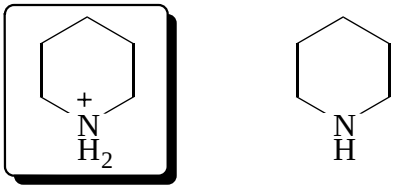


2. (a)



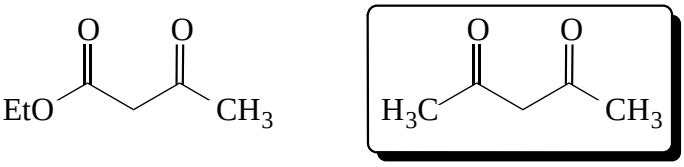
inductive electron-withdrawing effect of F is greater than Cl

(b)



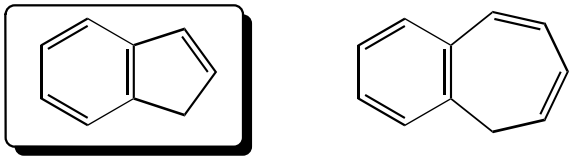
In general, AH^+ is more acidic than AH

(c)



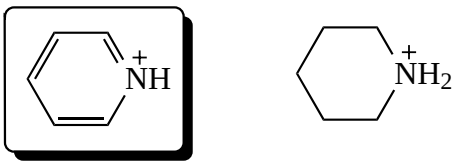
Ketones are more acidic than esters

(d)



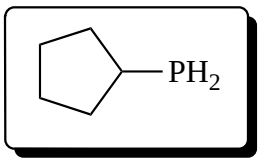
Deprotonation of 5-membered ring gives aromatic anion; deprotonation of 7-membered ring gives anti-aromatic anion.

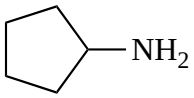
(e)



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.

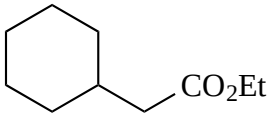
(f)

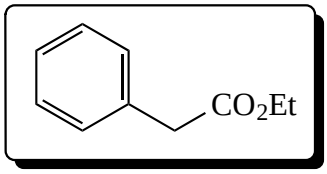




Acidity increases as you move down a column in the periodic table due to increasing atomic size and hence worse overlap in the A–H bond

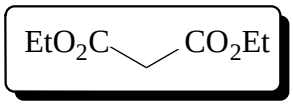
(g)

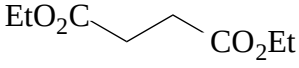




The anion of phenylacetate is stabilized by resonance into the phenyl ring.

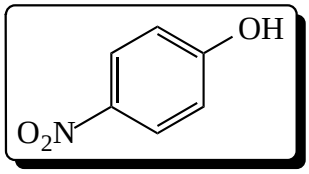
(h)

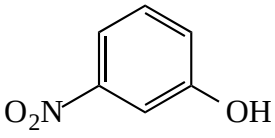




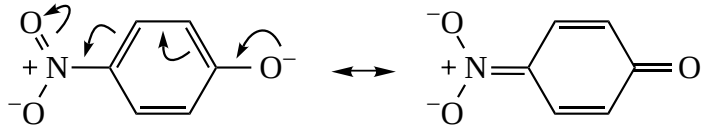
Anions of 1,3-dicarbonyl compounds are stabilized by resonance into *two* carbonyl groups

(i)

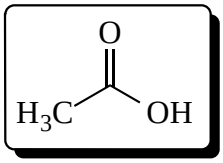


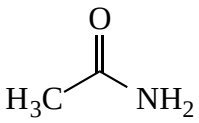


The anion of 4-nitrophenol is stabilized by resonance directly into the nitro group. The anion of 3-nitrophenol can't do this. Draw resonance structures to convince yourself of this.



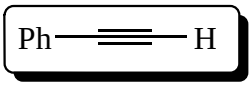
(j)





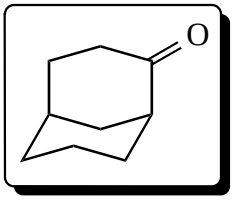
More electronegative atoms are more acidic than less electronegative atoms in the same row of the periodic table

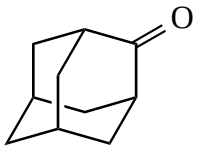
(k)



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

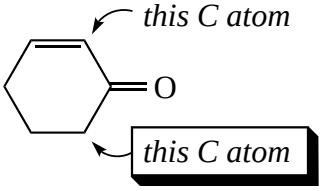
(l)





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)

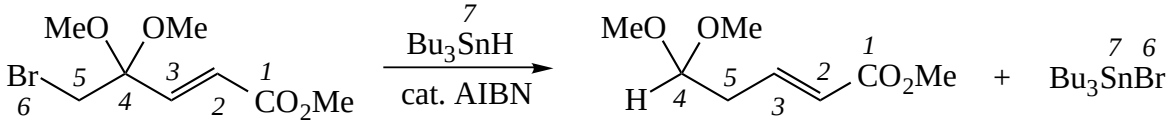


The C(sp^2)–H bond on the upper atom is the plane of the paper, orthogonal to the p orbitals of the C=O bond, so the C=O bond provides no acidifying influence. The C(sp^3)–H bonds on the lower atom are in and out of the plane of the paper, so there is overlap with the C=O orbitals.

3.

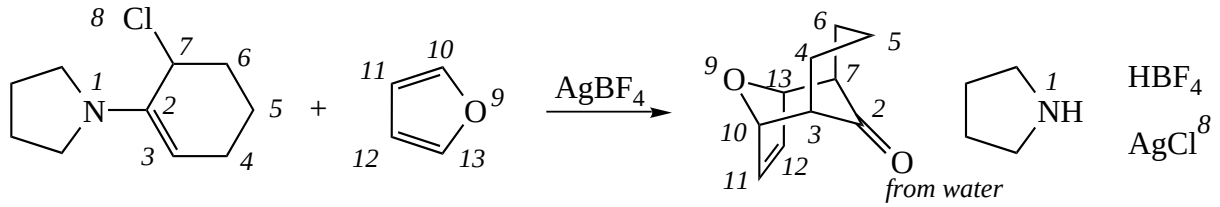
(a) Free-radical. (Catalytic peroxide tips you off.)
(b) Metal-mediated. (Os)
(c) Polar, acidic. (Nitric acid.)
(d) Polar, basic. (Fluoride ion is a good base. Clearly it's not acting as a nucleophile in this reaction.)
(e) Free-radical. (Air.) Yes, an overall transformation can sometimes be achieved 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.

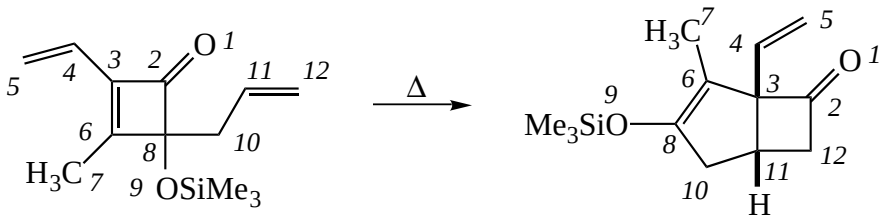


(b) Ag^+ is a good Lewis acid, especially where halides are concerned, so polar acidic mechanism is a

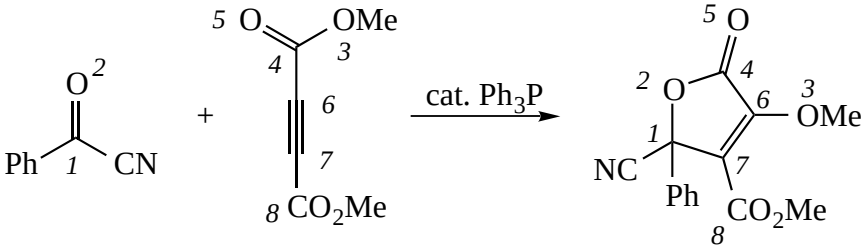
reasonable guess, but mechanism is actually pericyclic (bonds forming to both C10 and C13 of the furan and C3 and C7 of the enamine). Cl8 is missing from the product; it must get together with Ag to make insoluble, very stable AgCl. An extra O appears in the product; it must come from H_2O during workup. 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.



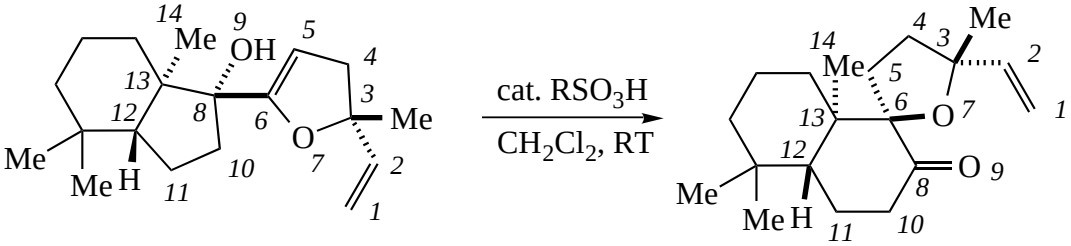
(c) This mechanism is also pericyclic. Use the carbonyl, Me_3SiO, and CH_3 groups as anchors for numbering the atoms. Made: C2–C12, C3–C11. Broken: C2–C8.



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

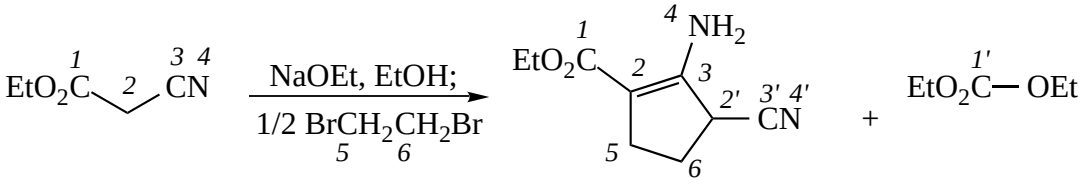


(e) The mechanism is polar under acidic conditions due to the strong acid RSO_3H. Made: C13–C6. Broken: C13–C8.

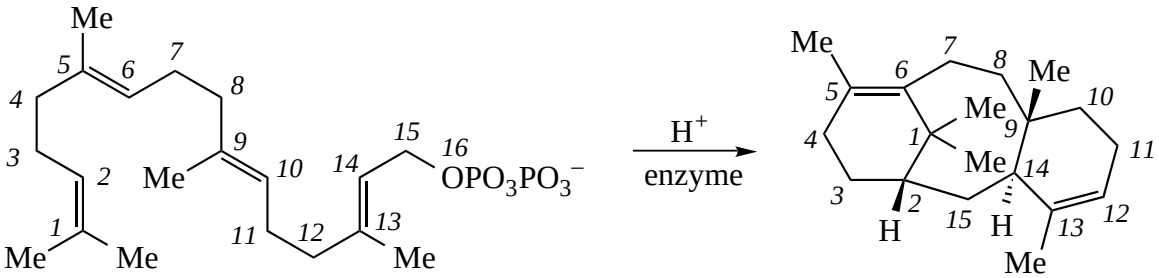


(f) The mechanism is polar under basic conditions (NaOEt). Two equivalents of cyanoacetate react with

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.

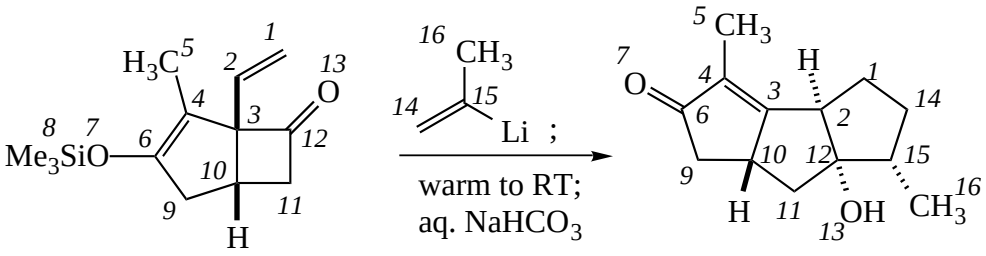


(g) Polar under acidic conditions. The enzyme serves to guide the reaction pathway toward one particular result, but the mechanism remains fundamentally unchanged from a solution phase mechanism. The Me groups provide clues as to the numbering. Made: C1–C6, C2–C15, C9–C14. Broken: C15–O16.

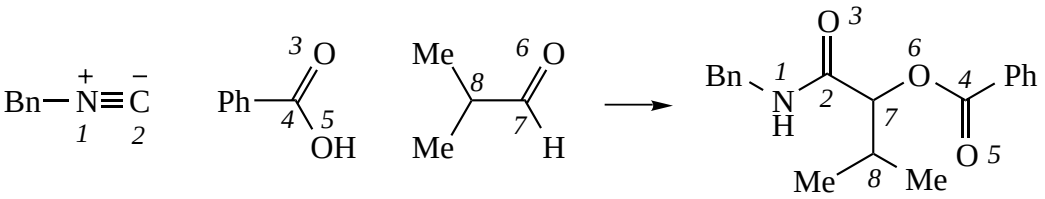


Geranylgeranyl pyrophosphate *A Taxane*

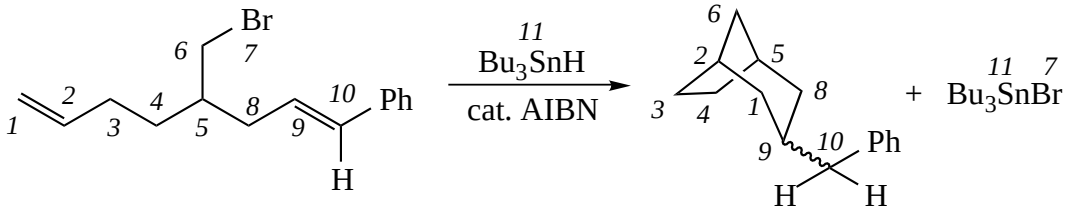
(h) Two types of mechanism are involved here: First polar under basic conditions, then pericyclic. At first the numbering might seem very difficult. There are two CH_3 groups in the starting material, C5 and C16, and two in the product. Use these as anchors to decide the best numbering method. Made: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



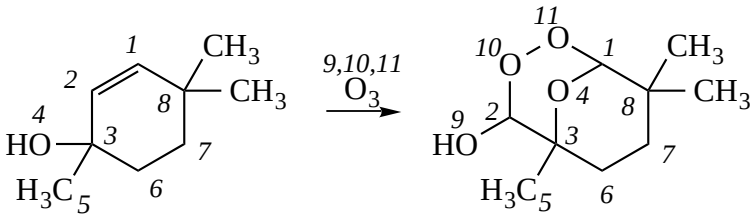
(i) The carboxylic acid suggests a polar acidic mechanism. Made: C2–C7, C2–O3, C4–O6. Broken: O3–C4.



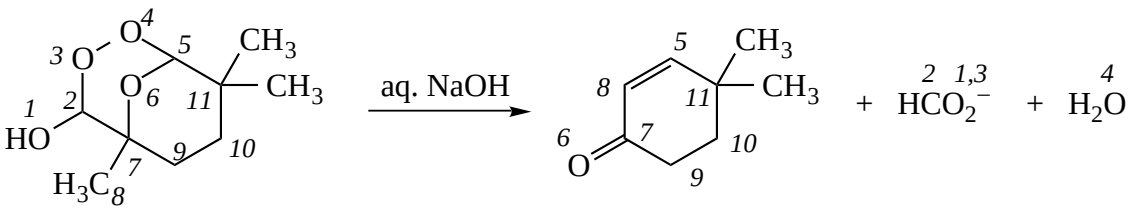
(j) Free-radical mechanism (AIBN). Both Br7 and Sn11 are missing from the product, so they are probably connected to one another in a by-product. H12 appears connected to C10 in the product, as C10 is the only C that has a different number of H's attached in S.M. and product. Made: C1–C9, C2–C6, Br7–Sn11.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



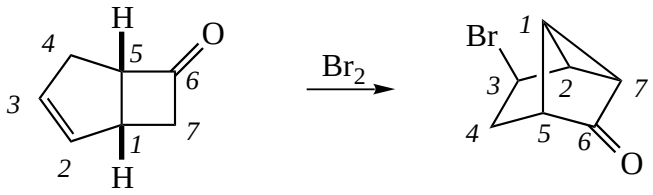
(k) No acid or base is present, and the reaction involves changes in π bonds. This is a pericyclic mechanism. Use C8 with its two Me groups as an anchor to start numbering. Ozone is a symmetrical molecule, but the middle O is different from the end O's; it's not clear which O in ozone ends up attached 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.

http://www.springer.com/0-387-95468-6

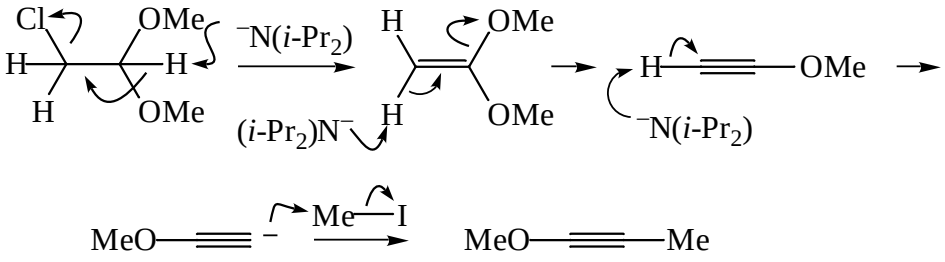
The Art of Writing Reasonable Organic Reaction Mechanisms

Grossman, R.B.

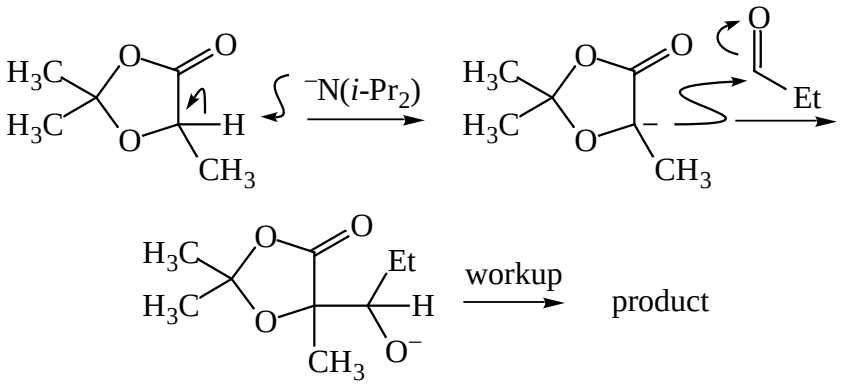
2005, XVI, 355 p. 34 illus., Hardcover
ISBN: 0-387-95468-6

Answers To Chapter 2 In-Chapter Problems.

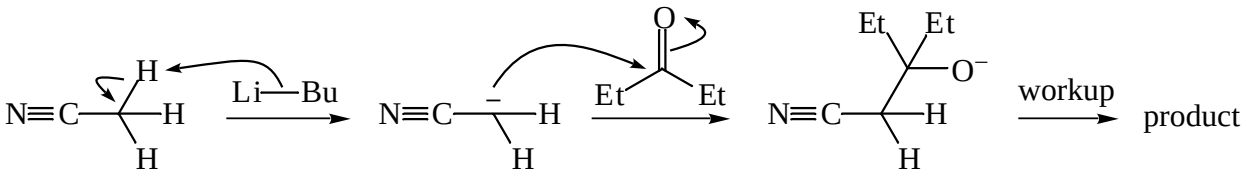
2.1. LDA is a strong base. Two E2 eliminations give an alkyne, which is deprotonated by the excess LDA to give an alkynyl anion. This species then reacts with MeI by an S_N2 process.



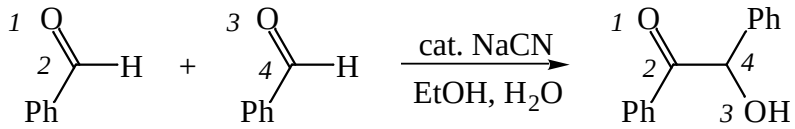
2.2(a). LDA deprotonates the C α to the ester, which adds to the aldehyde to give the aldol product after workup.



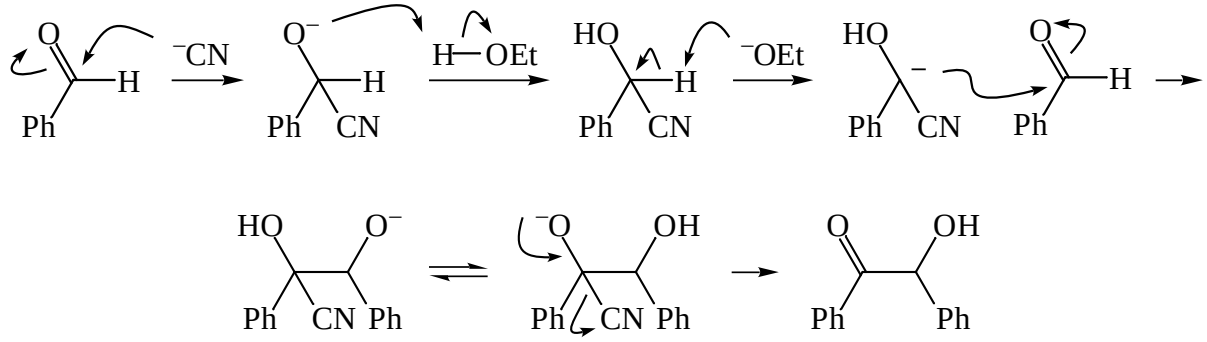
2.2(b). BuLi deprotonates the C α to the nitrile, which adds to the ketone to give the aldol product after workup.



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.

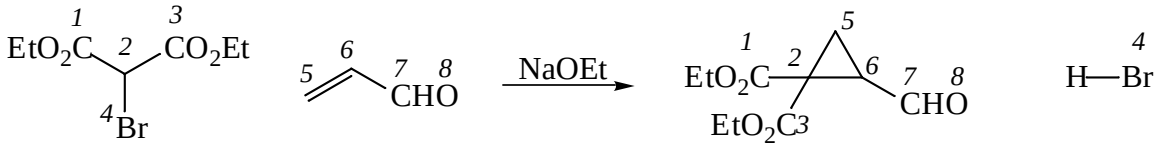


C2 is electrophilic, and C4 is ... electrophilic! To make a bond between them, C2 must be turned into a nucleophile (*umpolung*). This must be the purpose of the $^{-}$CN. Aldehydes are not acidic at the carbonyl C, so the $^{-}$CN cannot simply deprotonate C2. Instead, it must add to C2. Now C2 is α 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.

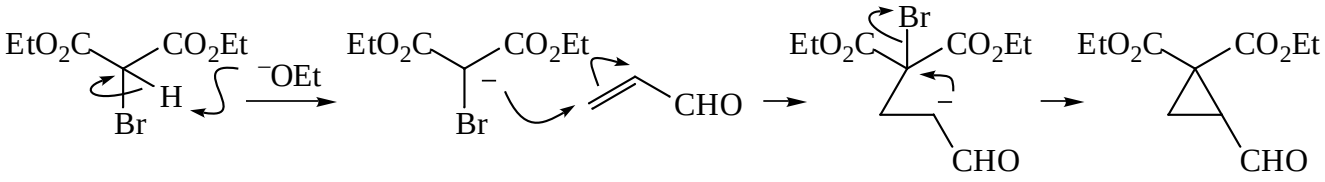


2.4.

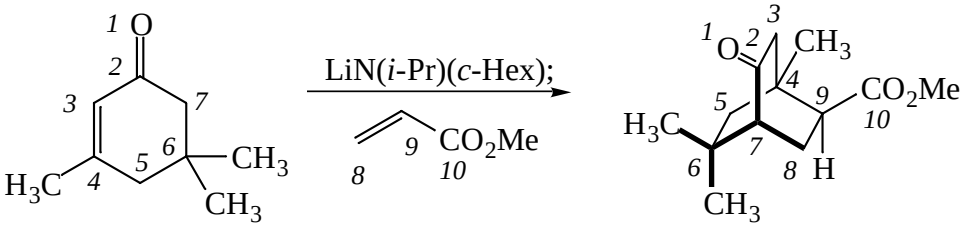
(a) Make: C2–C5, C2–C6. Break: C2–Br4.



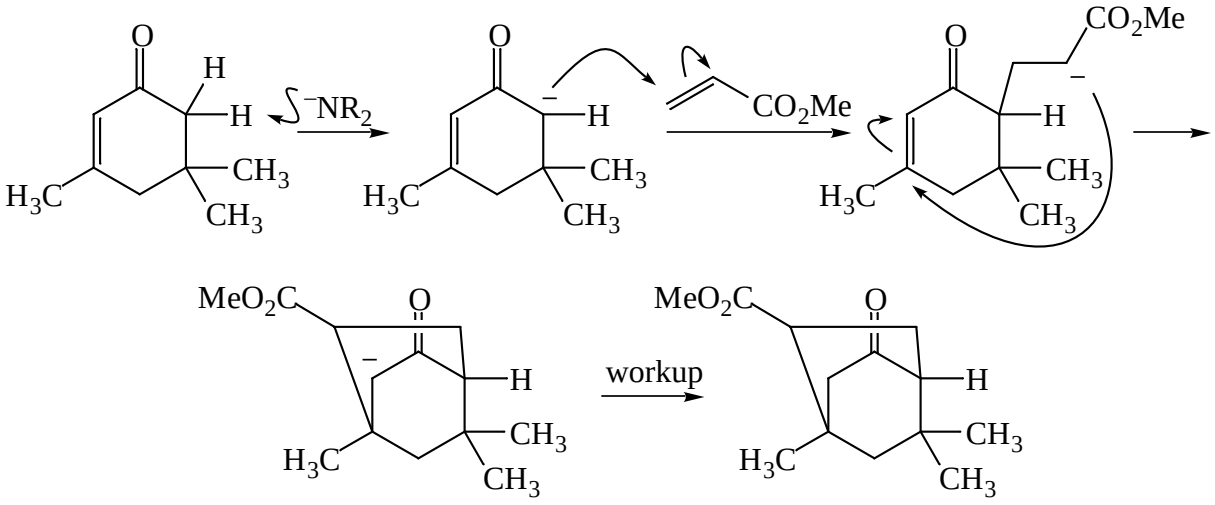
C2 is both electrophilic and particularly acidic. C5 is electrophilic, and C6 has no reactivity, so the first bond to be made must be C2–C5. Therefore, deprotonation of C2 gives a nucleophile, which can attack electrophilic C5 to give an enolate at C6. *Now* C6 is nucleophilic, and intramolecular S_N2 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.



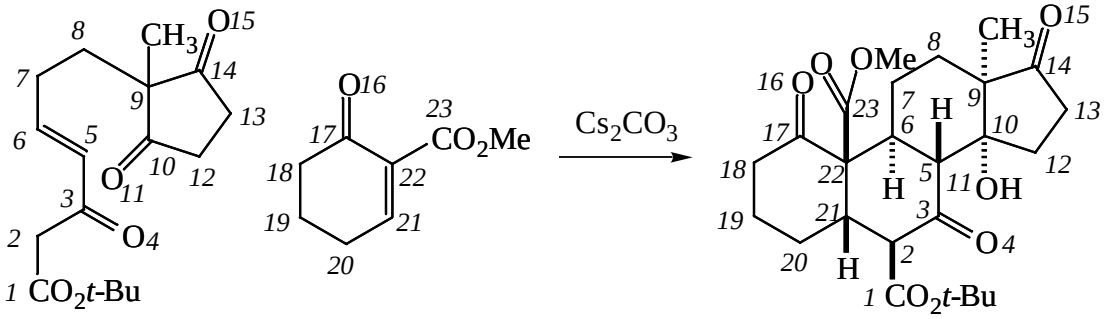
(b) Make: C7–C8, C4–C9. Break: none.



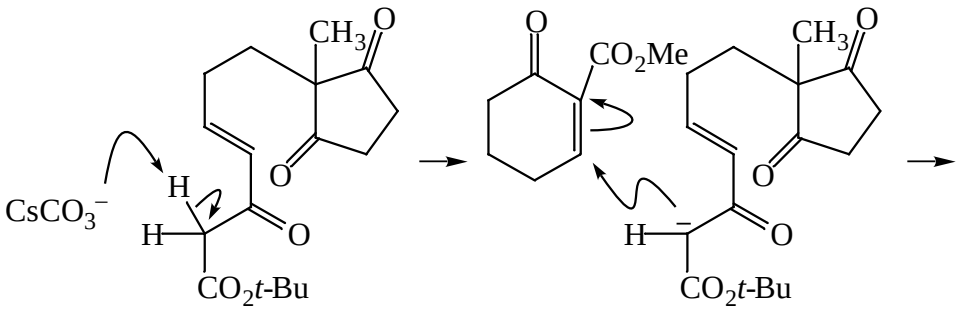
The thing above the arrow is a fancy version of LDA. C4 and C8 are electrophilic, C9 is unreactive, and C7 is acidic, so first step must be to deprotonate C7 to make it nucleophilic. Conjugate addition to C8 generates a nucleophile at C9, which adds to C4 to give a new enolate. Workup then provides the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

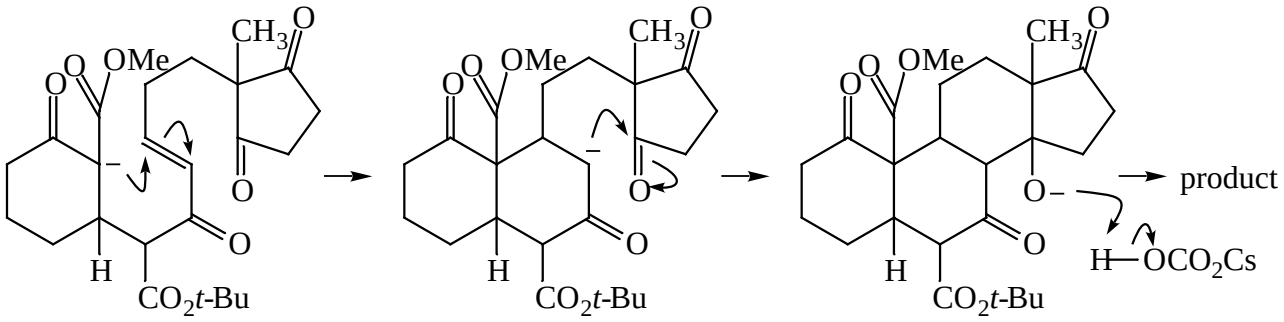


(c) Make: C2–C21, C5–C11, C6–C22. Break: none.



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.

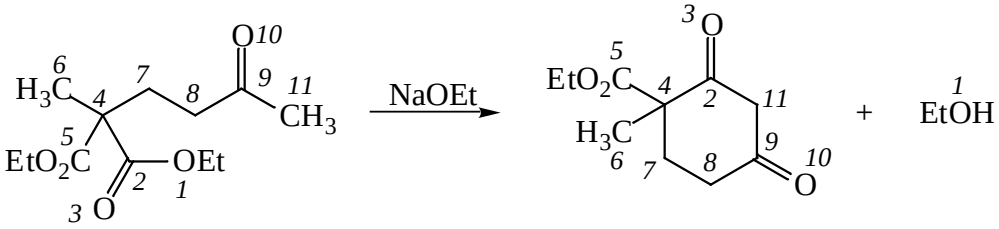




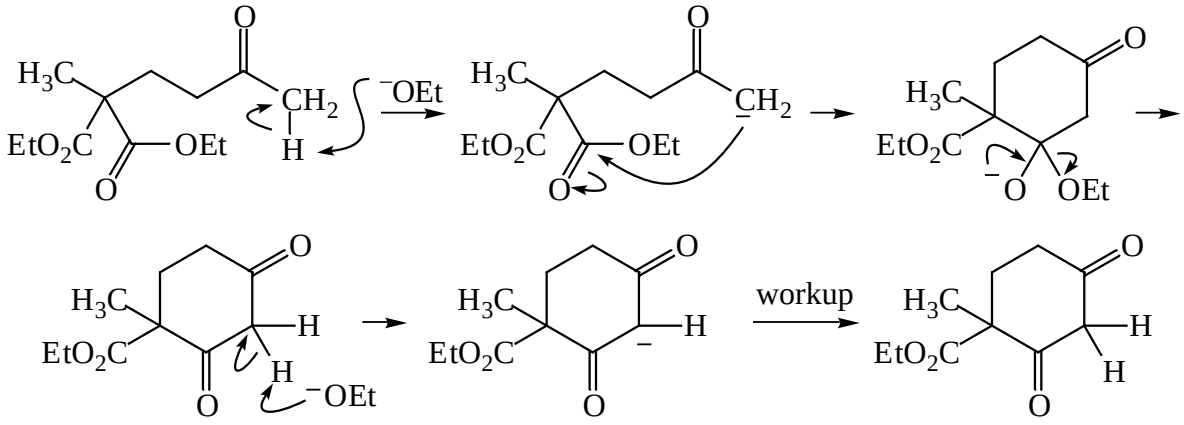
2.5. Because under basic conditions carboxylic acids are deprotonated to the carboxylate ions, which are no longer electrophilic enough that a weak nucleophile like MeO^- can attack them. Upon workup the carboxylate is neutralized to give back the carboxylic acid.

2.6.

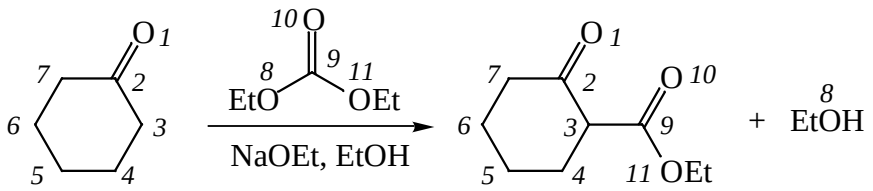
(a) Balancing the equation shows that EtOH is a by-product. Make: C2–C11. Break: O1–C2.



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.



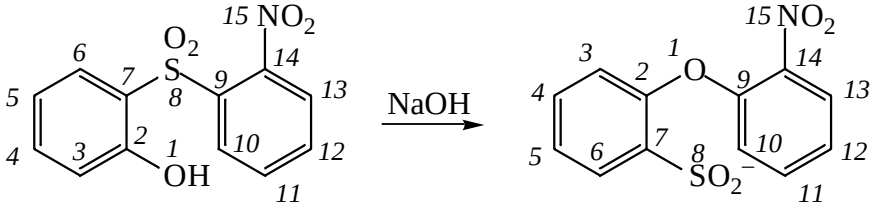
(b) Make: C3–C9. Break: O8–C9.



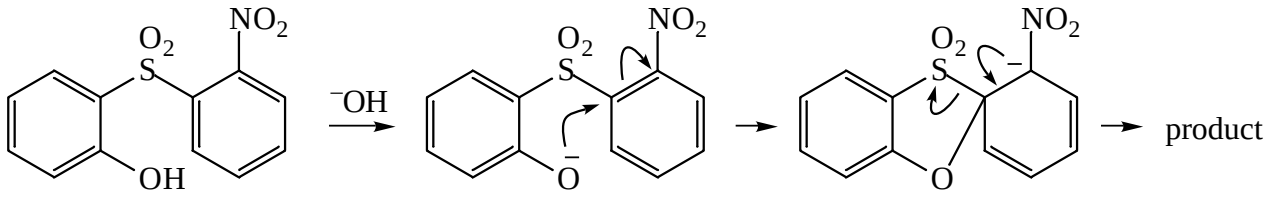
The mechanism is exactly the same as drawn in part (a).

2.7.

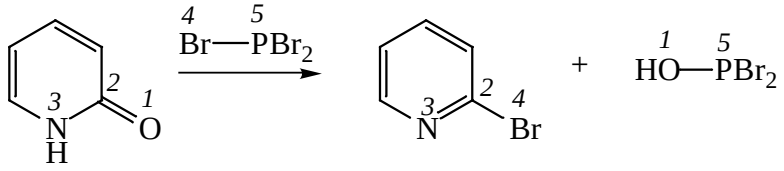
(a) Make: O1–C9. Break: S8–C9.



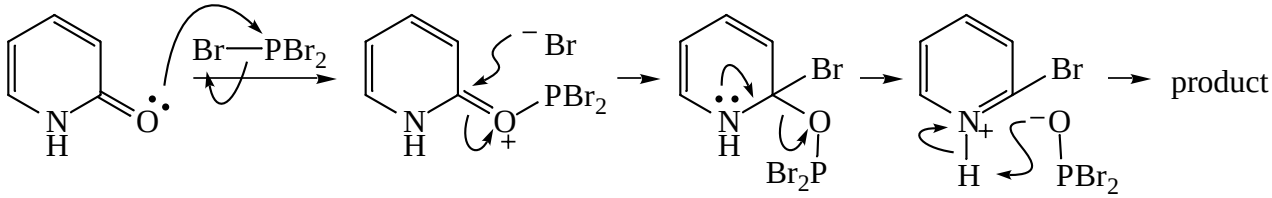
The base deprotonates O1, which adds to C9, giving an anion that is delocalized over C10, C12, C14, and into the NO_2 group. The anion then expels SO_2^- to give the product.



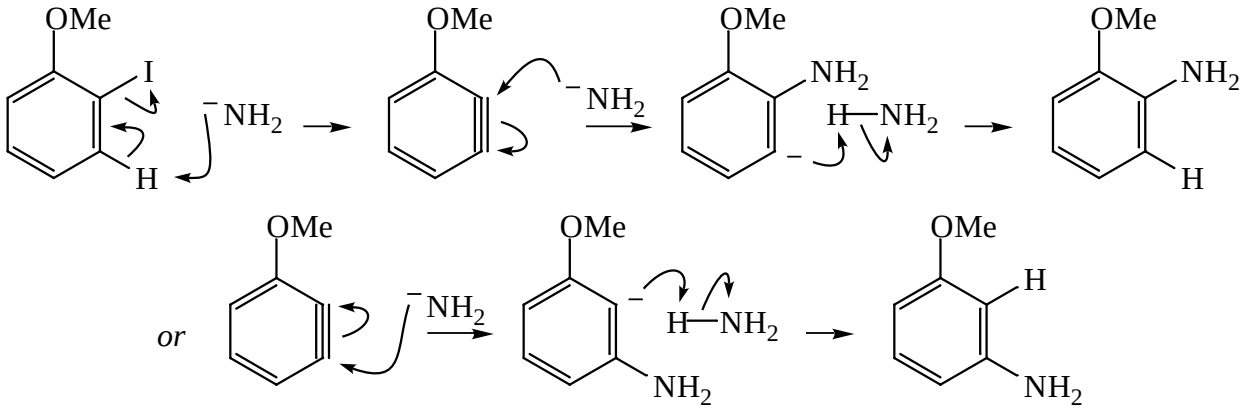
(b) Make: O1–P5, C2–Br4. Break: O1–C2, Br4–P5.



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.



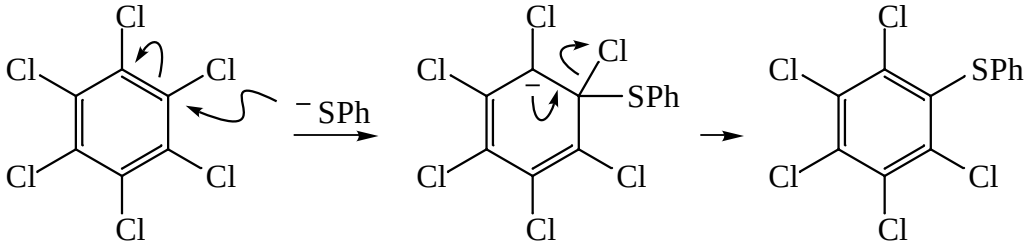
2.8. E2 elimination of HI from the aryl iodide gives a benzyne, which can be attacked at either C of the triple bond to give two different products.



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.

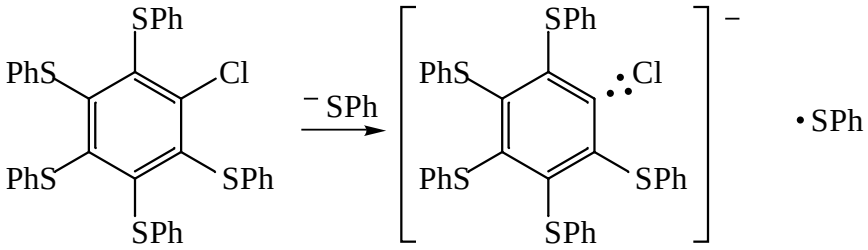
2.10. The first substitution involves attack of PhS^- on C_6Cl_6 to give $C_6Cl_5(SPh)$, and the last involves attack of PhS^- on $C_6Cl(SPh)_5$ to give $C_6(SPh)_6$. The elimination–addition mechanism is ruled out in both cases because of the absence of H atoms adjacent to Cl, so the choices are addition–elimination 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:

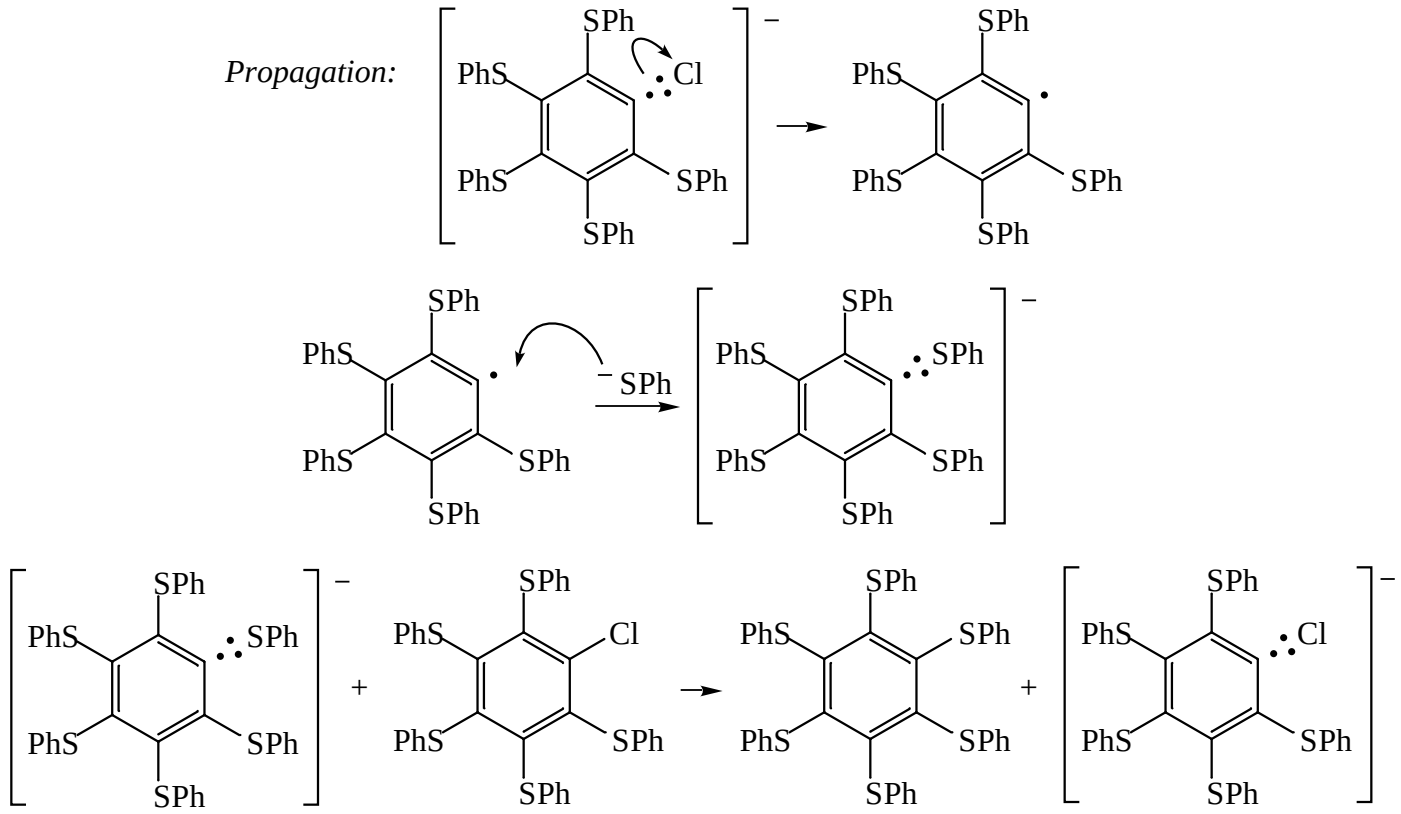


Last:

Initiation:

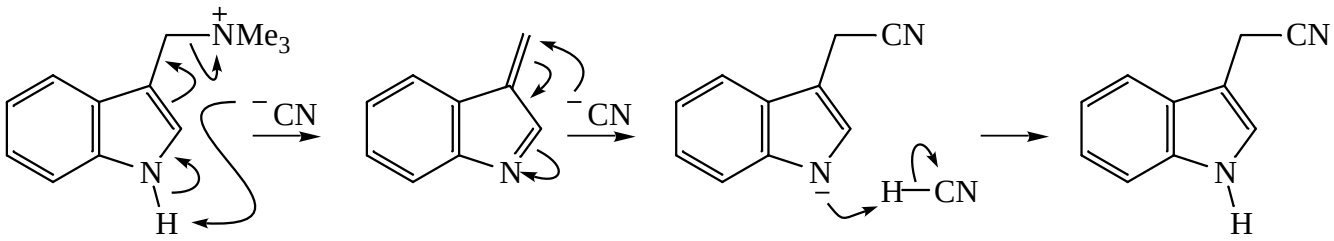


Propagation:



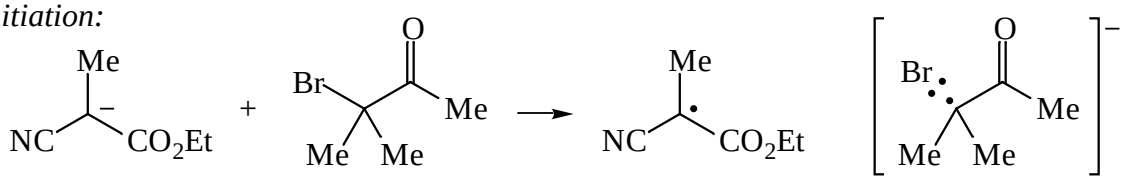
2.11.

(a) An addition–elimination mechanism is reasonable.

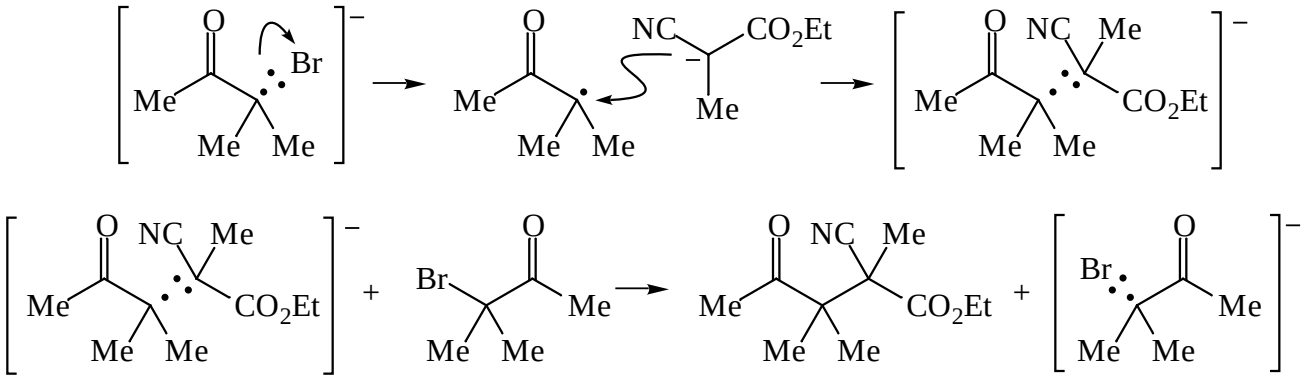


(b) An addition–elimination mechanism is not reasonable. Elimination of HBr from the starting material gives an α,β-unsaturated ketone that is now a π bond electrophile at a C different from the one that originally had the Br attached to it. The only reasonable mechanism is $S_{RN}1$.

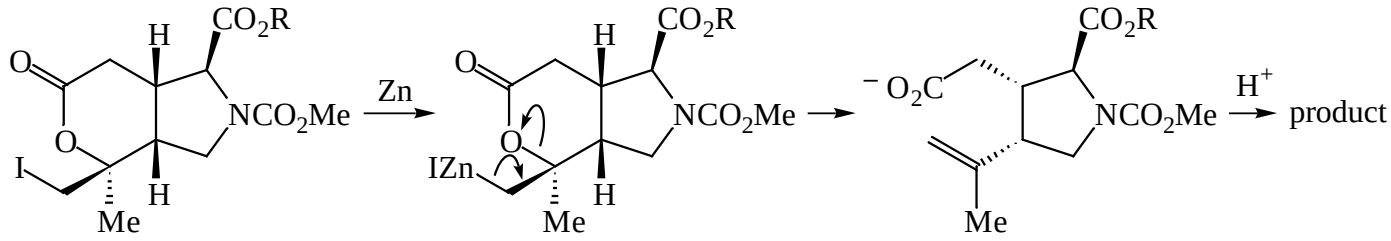
Initiation:



Propagation:

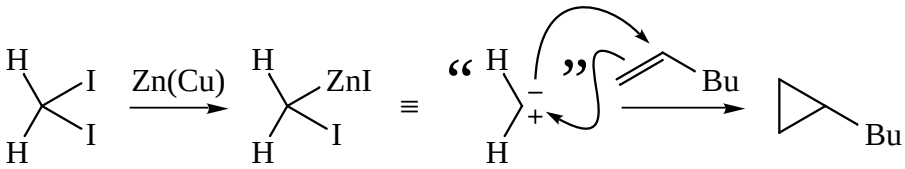


2.12.

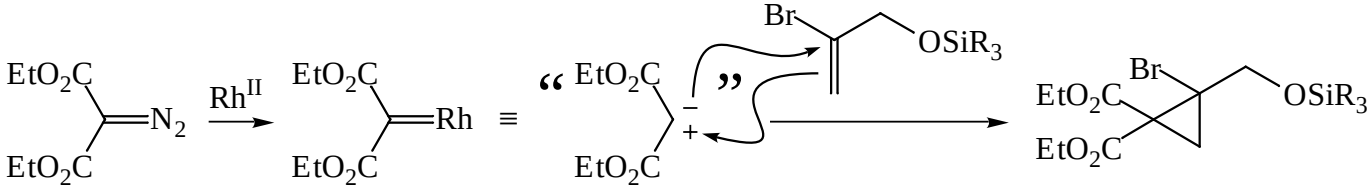


2.13.

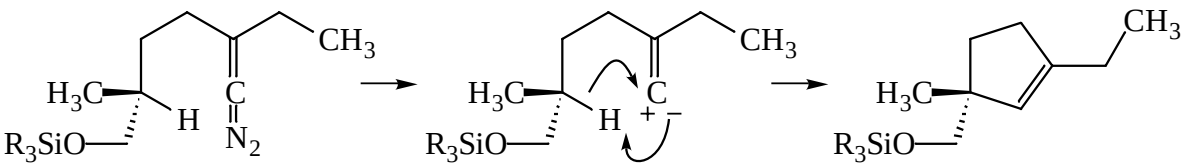
(a)



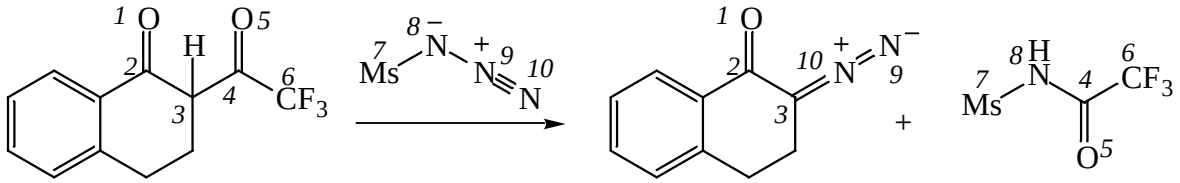
(b)



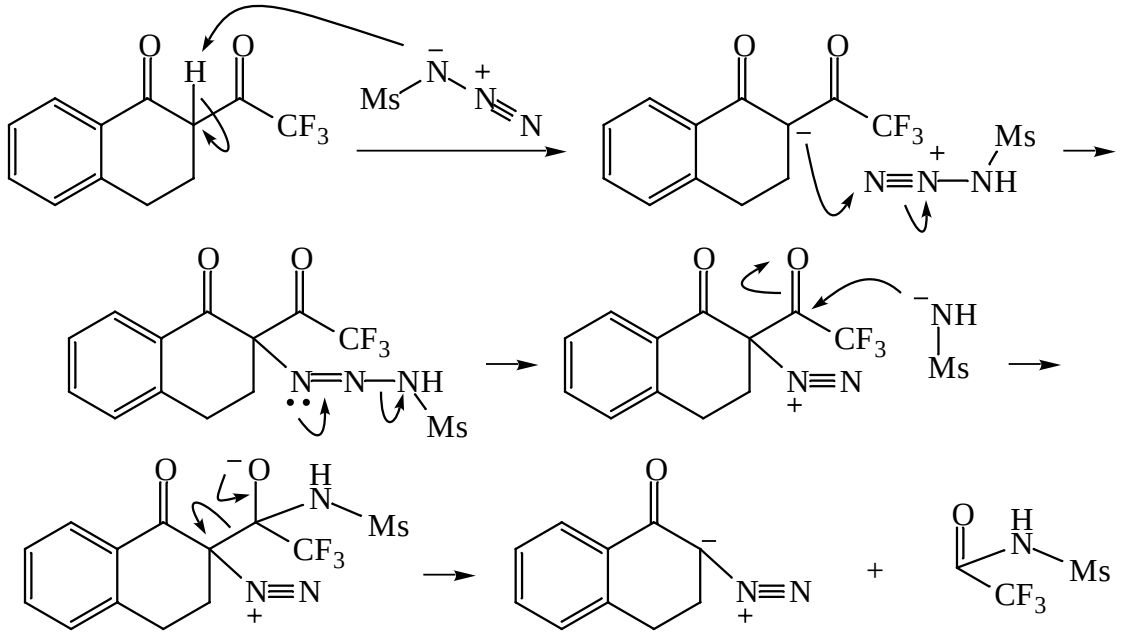
2.14.



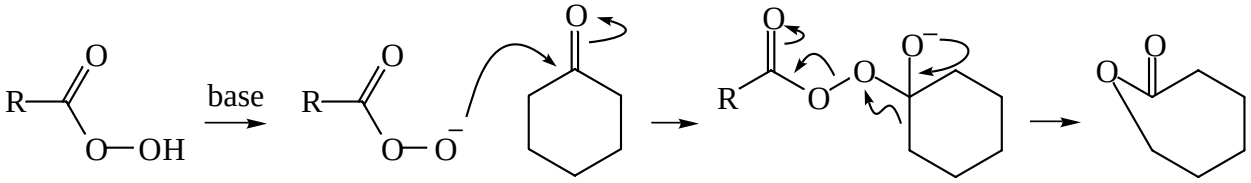
2.15. Numbering correctly is key to this problem. The written product is missing the fragments $COCF_3$ and MsN, so it is likely that they are connected to one another in a by-product. All the numbering in the product is clear except for N8, N9, and N10. N8 is attached to Ms in the starting material 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.

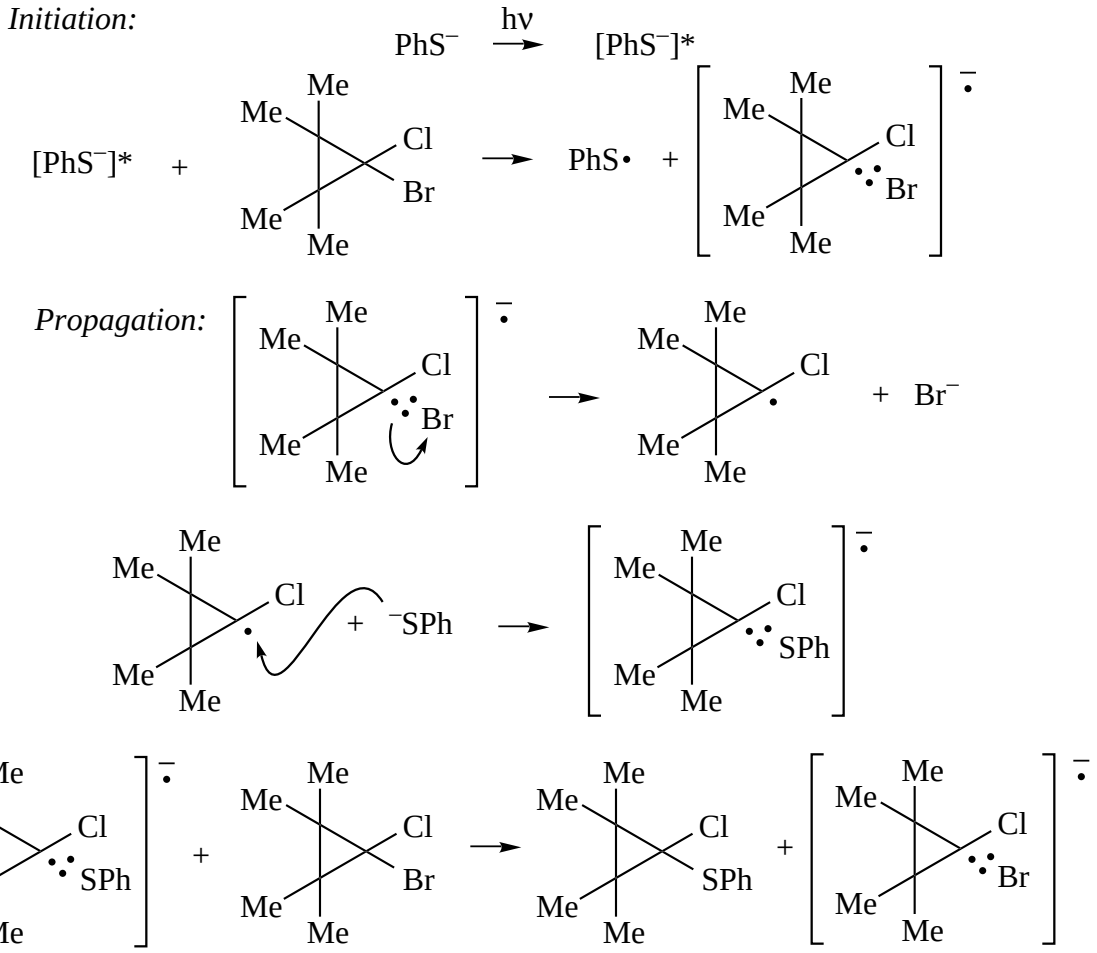


2.16.

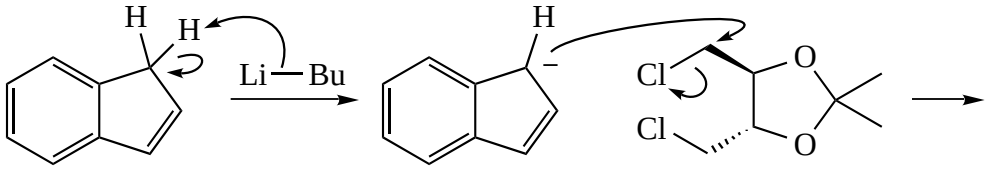


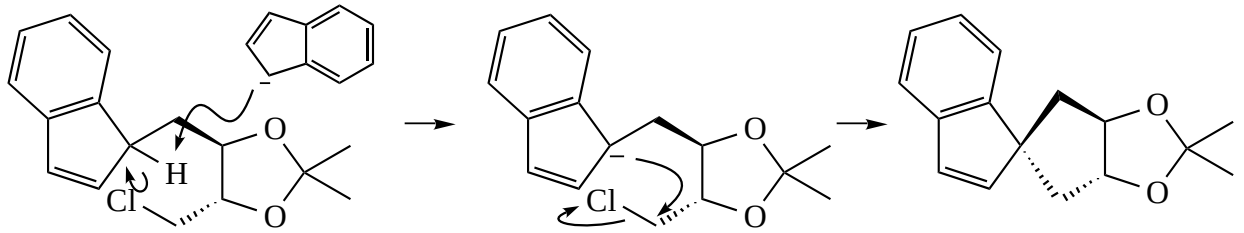
Answers To Chapter 2 End-of-Chapter Problems.

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.

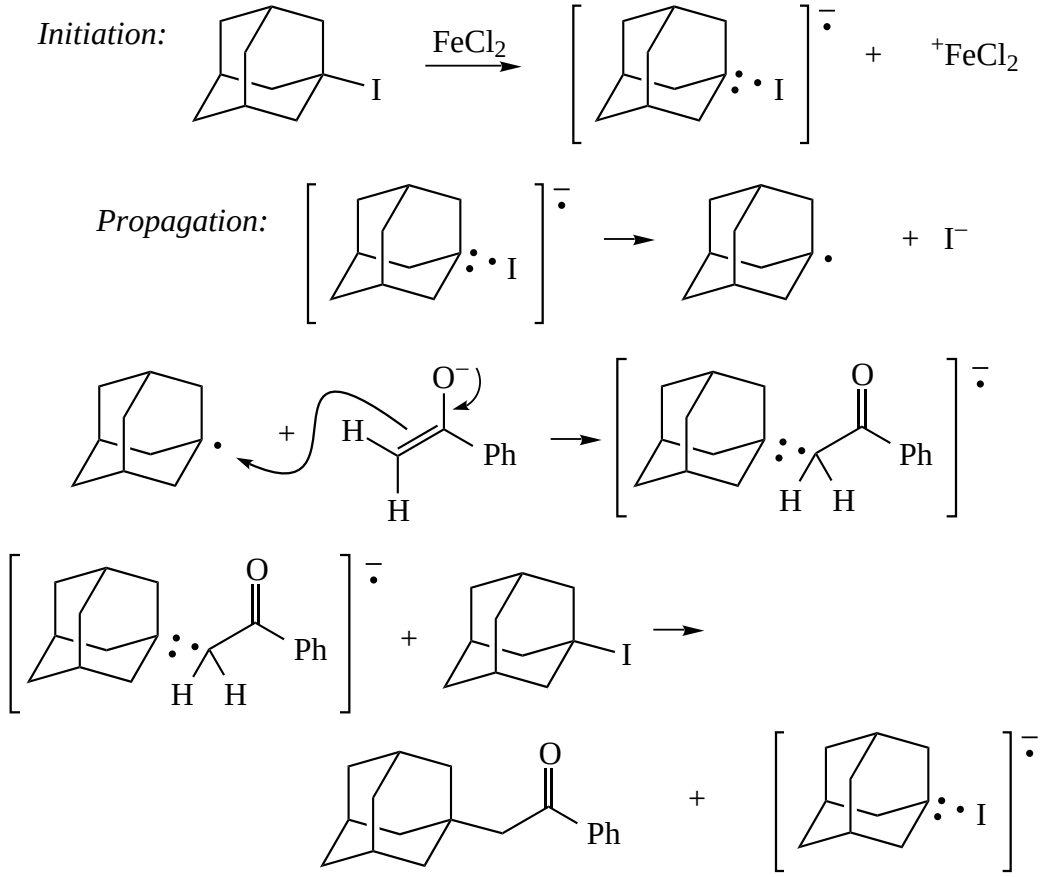


(b) The 1° halide will definitely undergo substitution by an S_N2 mechanism. Indene is a pretty good acid ($pK_a \approx 19$) due to aromatic stabilization of the anion. After deprotonation with BuLi, it attacks the electrophilic C by S_N2. A second equivalent of indenyl anion then redeprotonates the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

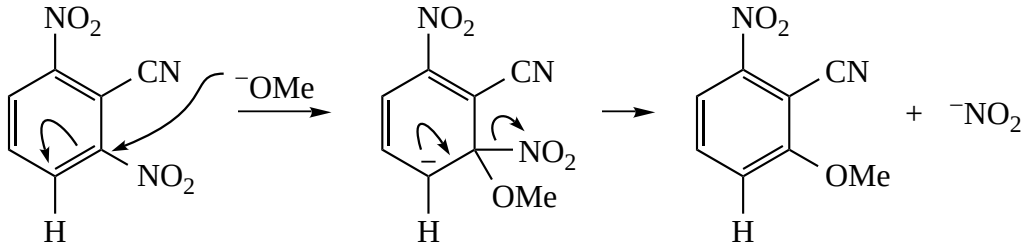




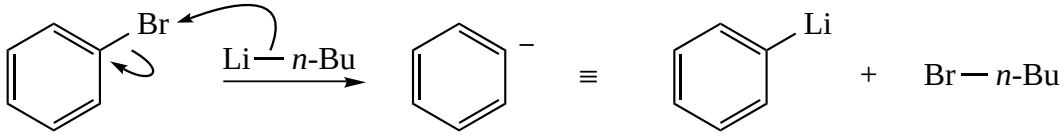
(c) This 3°, uninvertable halide cannot undergo S_N2 substitution. An elimination–addition mechanism is unlikely because the base is not terribly strong and the neighboring C–H bonds are not parallel to the C–I bond. The most likely possibility is $S_{RN}1$. C(sp^3)–I bonds are good substrates for $S_{RN}1$ 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.

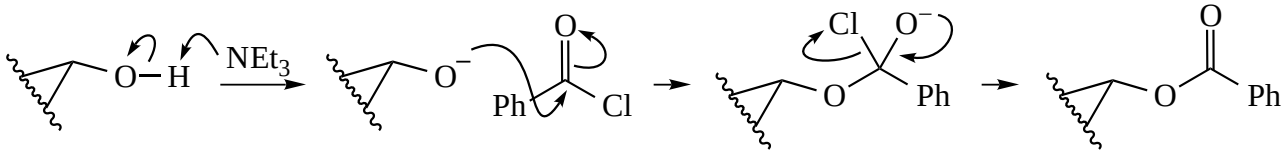
Certain experiments would help to rule these possibilities in or out.

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.

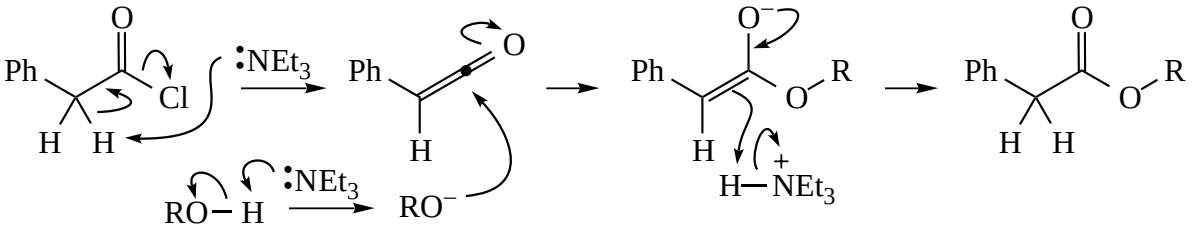
Addition–elimination would accelerate (compared to halogen–metal exchange) with electron-withdrawing groups on the ring and decelerate with electron-donating groups on the ring.

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.

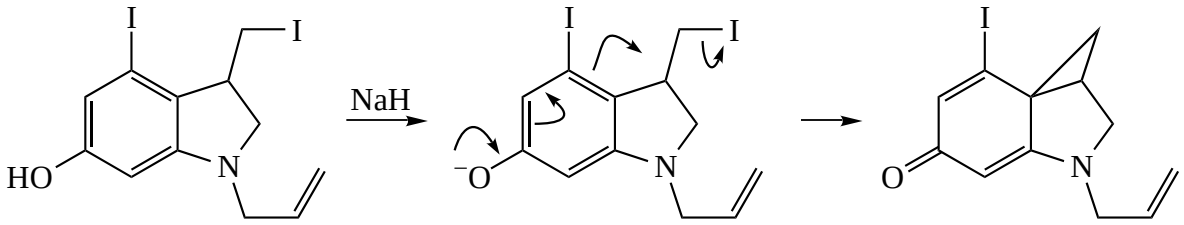
(f) Acyl chlorides can undergo substitution by two mechanisms: addition–elimination or elimination–addition (ketene mechanism). In this case, elimination–addition can't occur because there are no α H's. The mechanism must be addition–elimination.



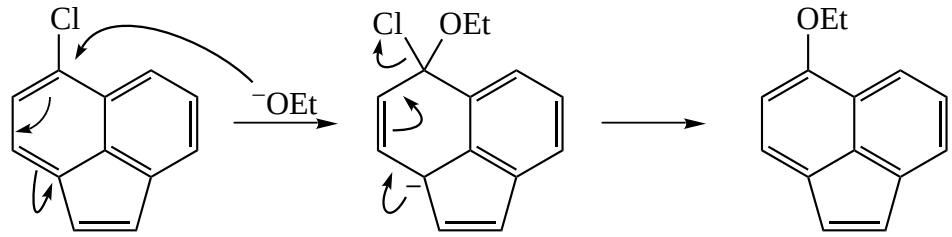
(g) This acyl chloride is particularly prone to elimination because of the acidicity of the benzylic H's. Addition–elimination can't be ruled out, but elimination–addition is more likely.



(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.

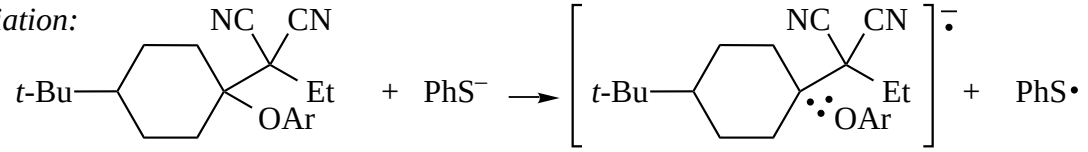


(i) This nucleophilic substitution reaction at aromatic C(sp^2) can proceed by addition–elimination, elimination–addition, or $S_{RN}1$. In this case, addition–elimination is low in energy because of the strong stabilization of the Meisenheimer complex by aromaticity of the five-membered ring.

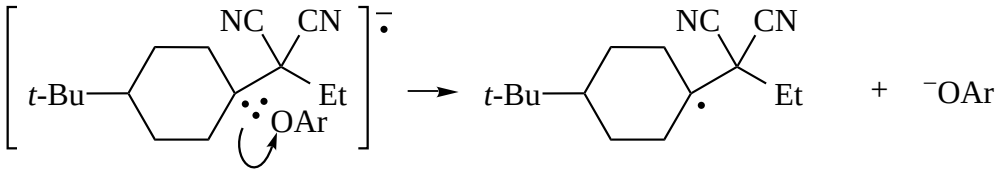


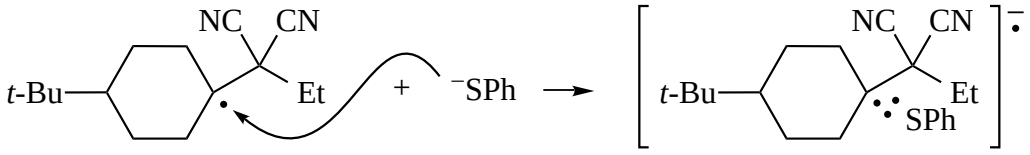
(j) The mechanism cannot be S_N2 because of the 3° alkyl electrophile. The most likely mechanism is $S_{RN}1$, which proceeds through radical anions. The best resonance structure of the radical anion of the starting material puts the odd electron in the aromatic ring, and the best resonance structure 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.

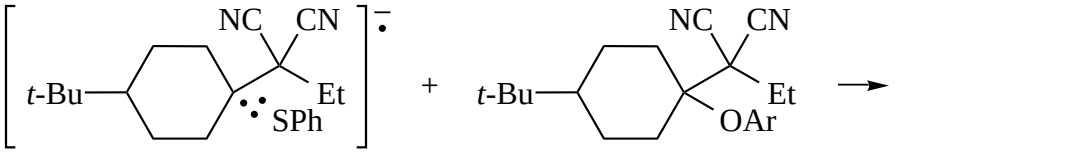
Initiation:

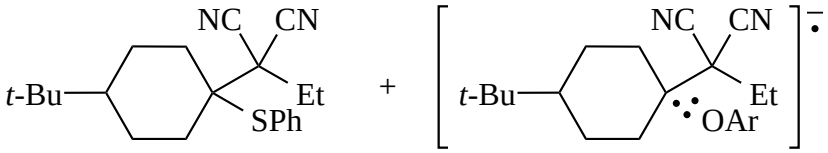


Propagation:



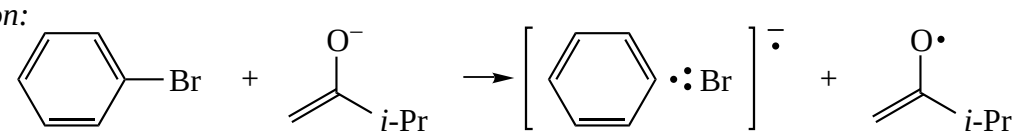




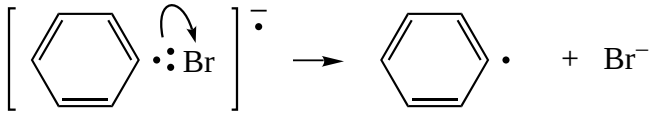


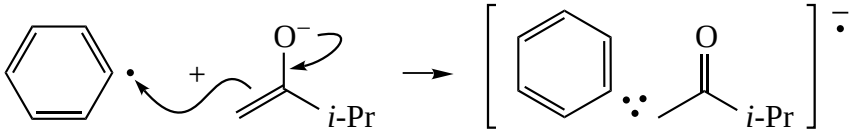
(k) Substitution at aromatic C(sp^2) can occur by one of three mechanisms. Addition–elimination requires that the ring be substituted with electron-withdrawing groups. Elimination–addition requires very strong bases like NH_2^-. The third mechanism, $S_{RN}1$, is operative here; the light is a clue that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

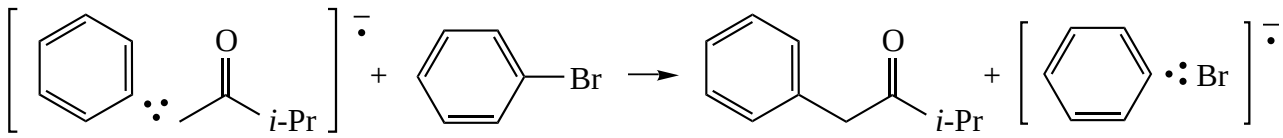
Initiation:



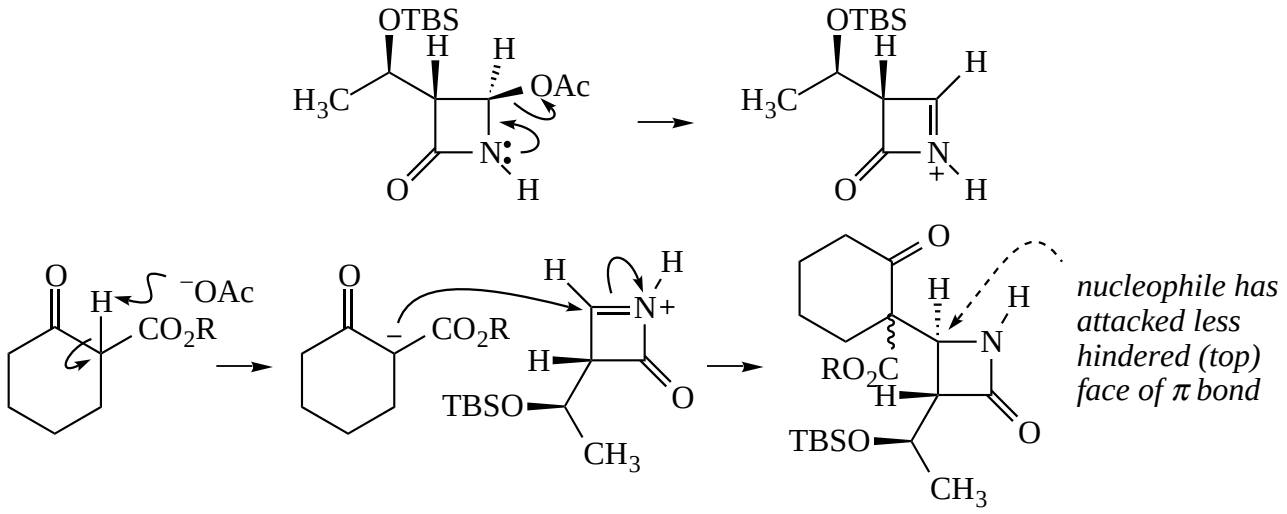
Propagation:



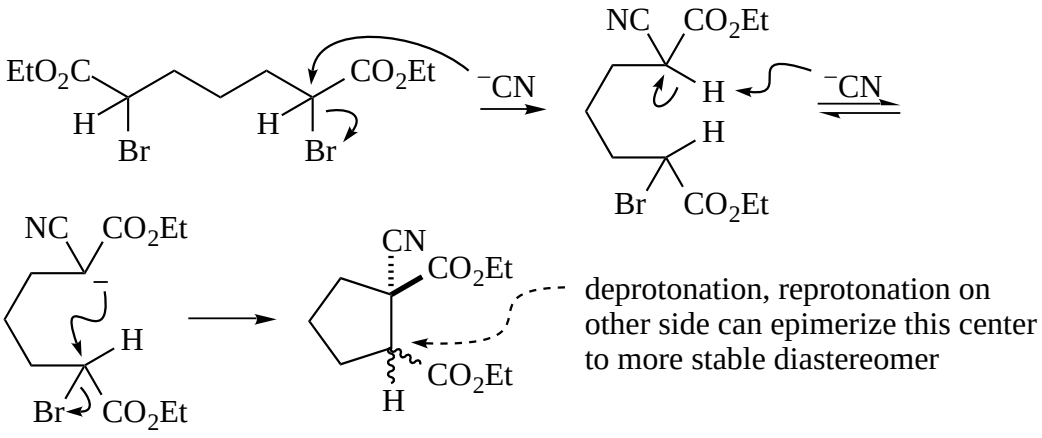




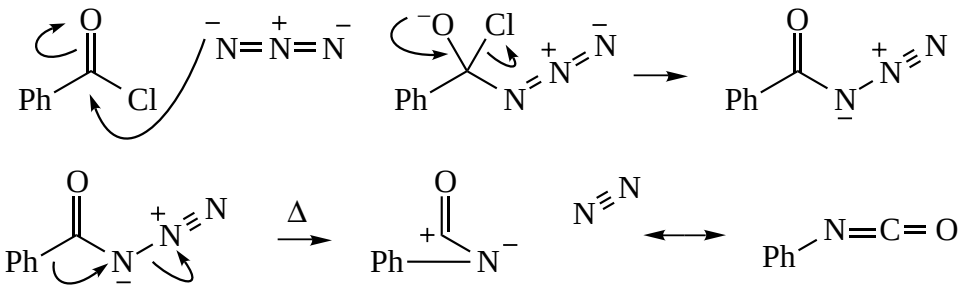
(l) The mechanism clearly cannot be S_N2, because substitution occurs with retention of configuration. Two sequential S_N2 reactions are a possibility, but unlikely, because $^-$OAc is a lousy leaving group in S_N2 reactions. It is more likely that an elimination–addition mechanism operates. The AcO 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.



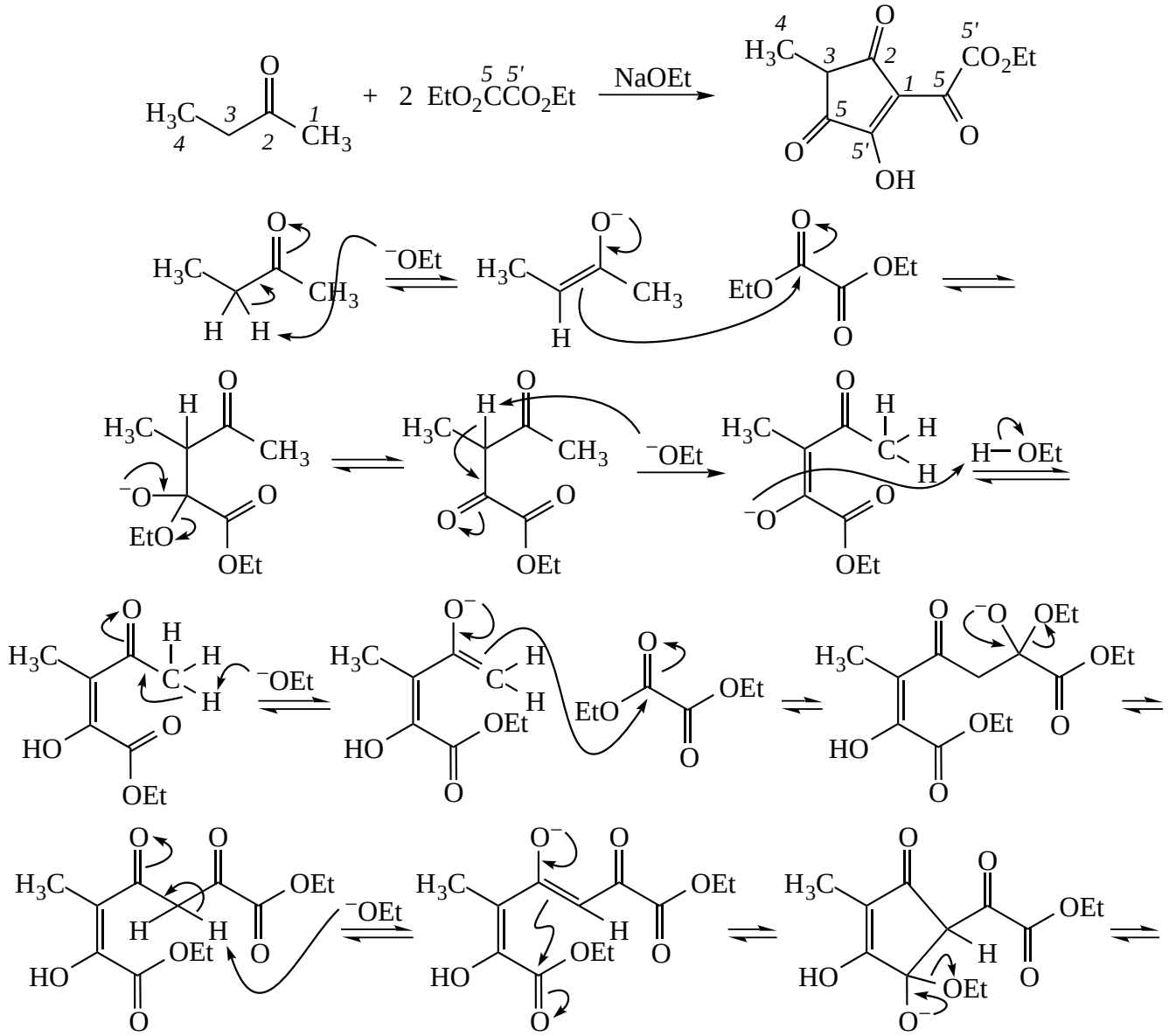
2. (a) Cyanide can act as a nucleophile toward the bromoester, displacing one Br^- in an S_N2 reaction to give a cyanoacetate. The cyanoacetate ($pK_a = 9$) is deprotonated by another equivalent of $^-$CN ($pK_b = 9$) to give an enolate that attacks the *other* bromoester to give the product.

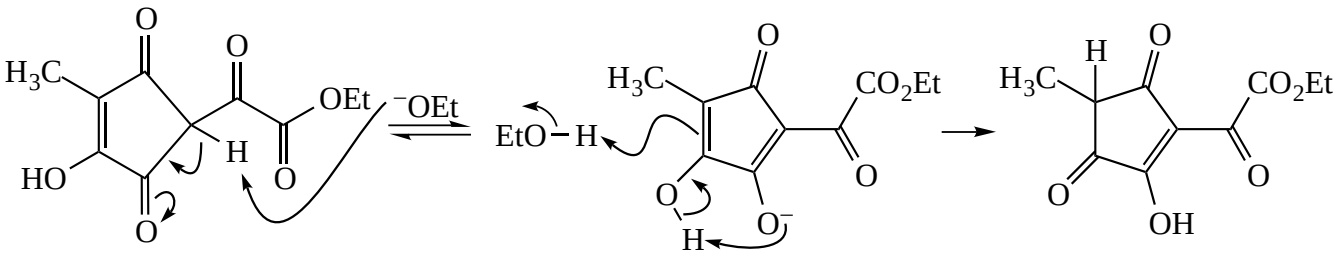


(b) The acyl chloride is a potent electrophile and N_3^- is a nucleophile, so the first part of the reaction involves addition–elimination to make the acyl azide. Upon heating, the Ph–CO bond breaks and a Ph–N bond forms. This suggests a 1,2-shift, promoted by loss of N_2.

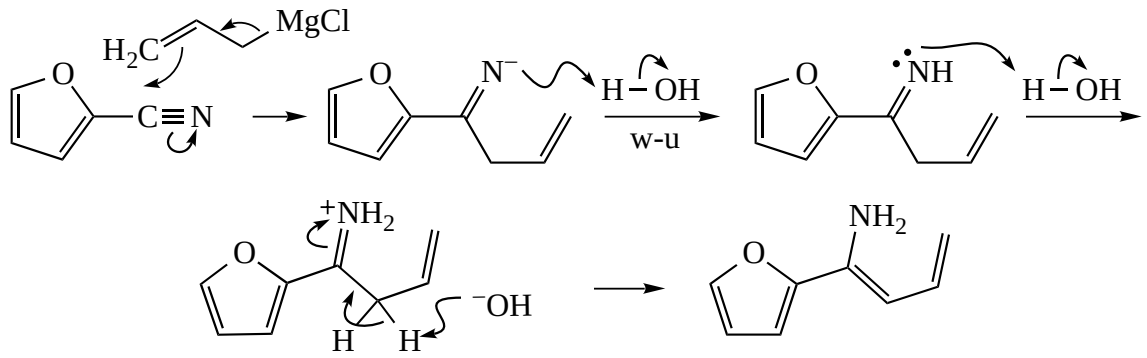


(c) Make: C1–C5, C1–C5', C3–C5. Break: C5–OEt (twice), C5'–OEt (once). Each substitution at C(sp^2) must occur by addition–elimination. The particular order of acylation events can vary from the answer given here.

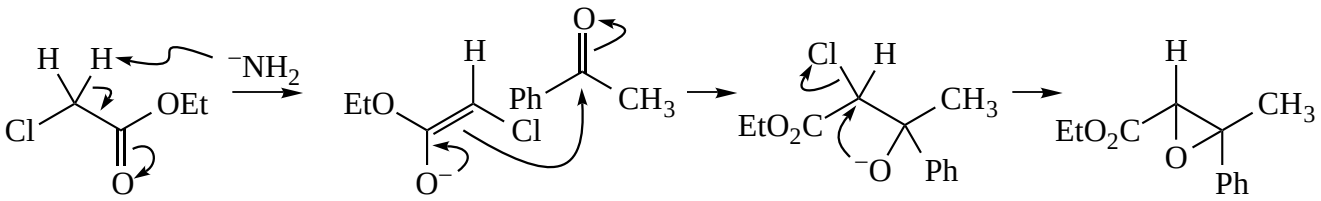




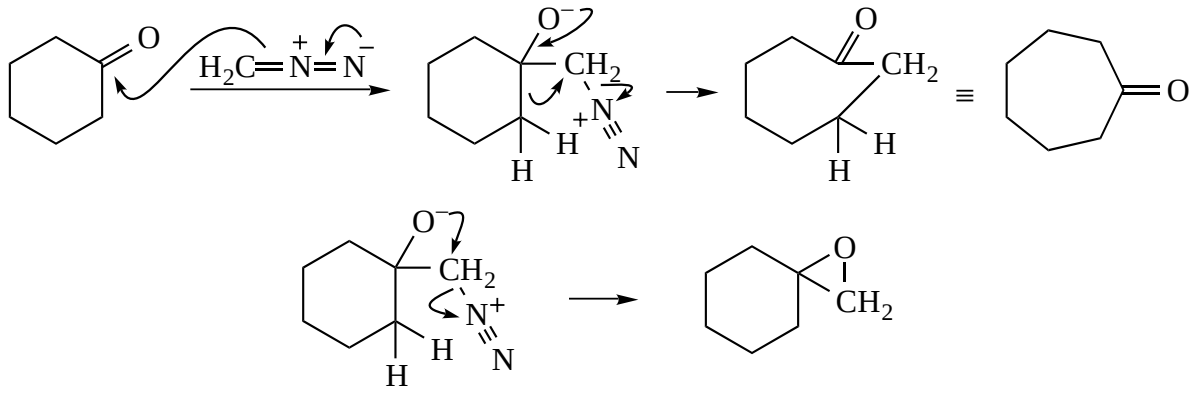
(d) Either the α or the γ carbon of the Grignard reagent can attack the nitrile. Isomerization of the initial product occurs upon workup, probably by protonation–deprotonation (rather than deprotonation–protonation) because of the weak acidity and decent basicity of imines.



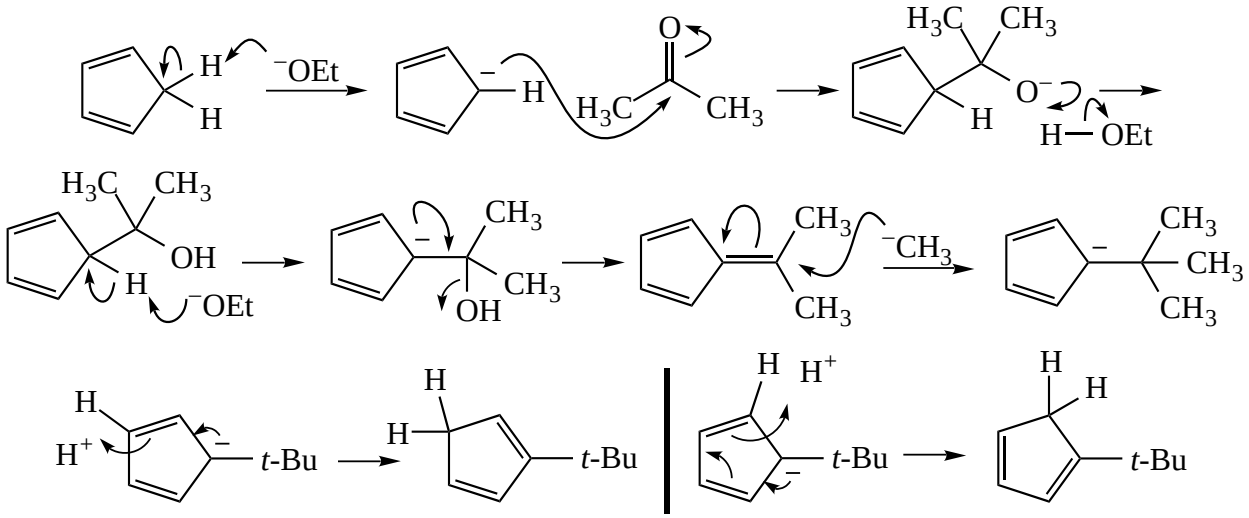
(e) One C–C and one C–O bond are formed. The ketone O is not nucleophilic enough to participate in S_N2 reactions, so the initial event must be attack of the ester enolate on the ketone. Sodium amide acts as a base.



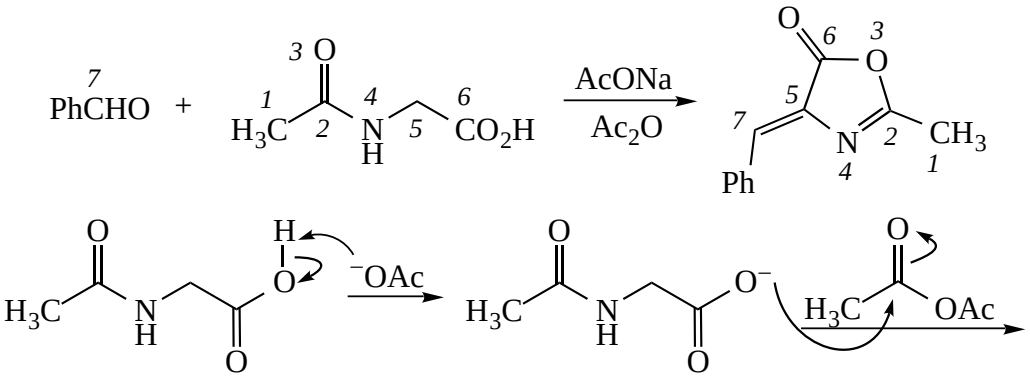
(f) The C in diazomethane is nucleophilic. The product of attack of diazomethane on the carbonyl C has a leaving group α to the alkoxide, so either a 1,2 alkyl shift or direct nucleophilic displacement can occur. The insertion product happens to dominate with $H_2\bar{C}–\overset{+}{N}_2$, but with $H_2\bar{C}–\overset{+}{S}Me_2$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

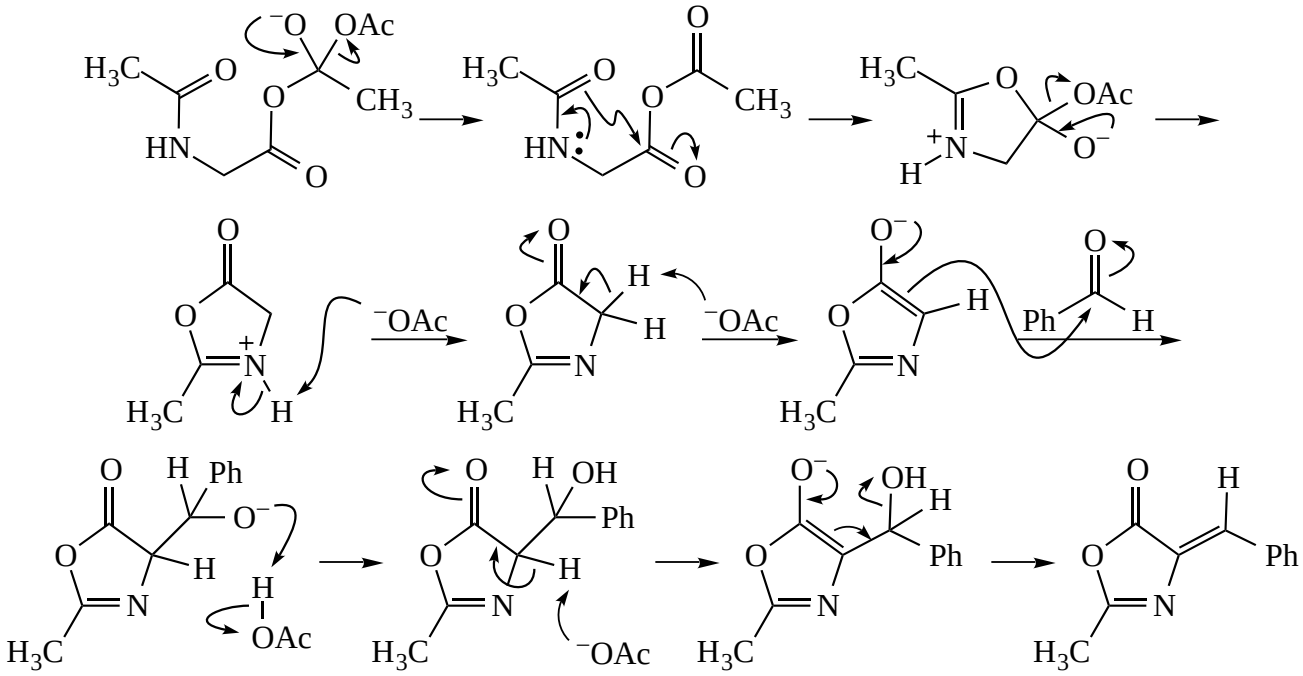


(g) Cyclopentadiene is very acidic, and its conjugate base is very nucleophilic. It can undergo aldol reactions with carbonyl compounds. After dehydration, a *fulvene* is obtained. The fulvene is an electrophile because when a nucleophile adds to the exocyclic double bond, the pair of electrons from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



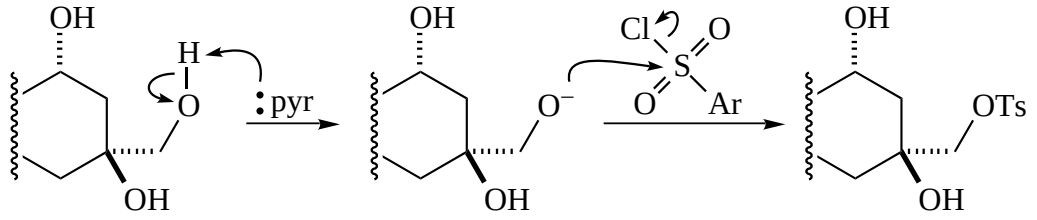
(h) Two new bonds are formed: O3–C6 and C5–C7. O3 is nucleophilic, while C6 is moderately electrophilic; C5 is nucleophilic only after deprotonation, and C7 is quite electrophilic. Under these very mildly basic conditions, it is unlikely that C5 will be deprotonated, so it is likely that the O3–C6 bond 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.



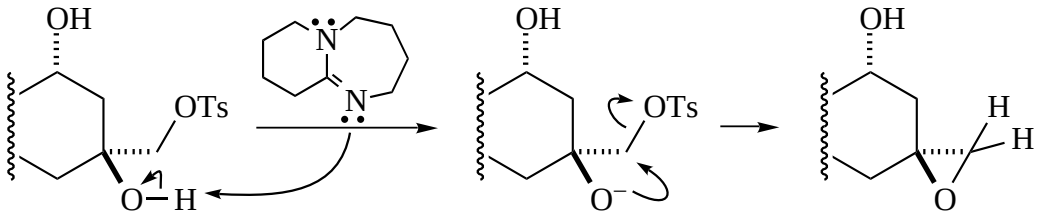


(i) Overall, the 1° OH is replaced by H. The H is presumably coming from $LiAlH_4$, a good source of nucleophilic H^-, so the 1° OH must be transformed into a good leaving group. The first step must transform the 1° alcohol into a tosylate. The mechanism of reaction of an alkoxide with TsCl is probably 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.

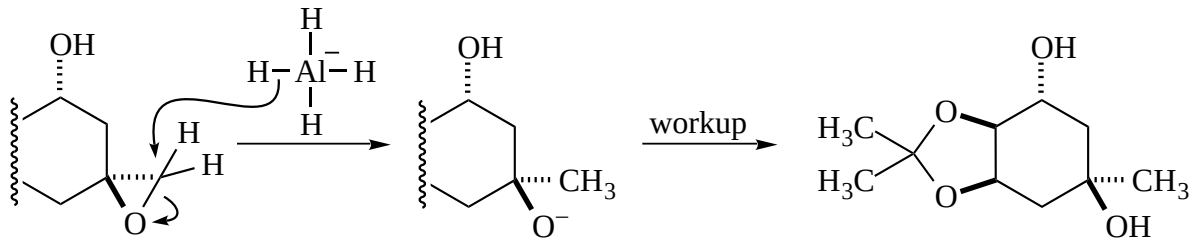
Step 1:



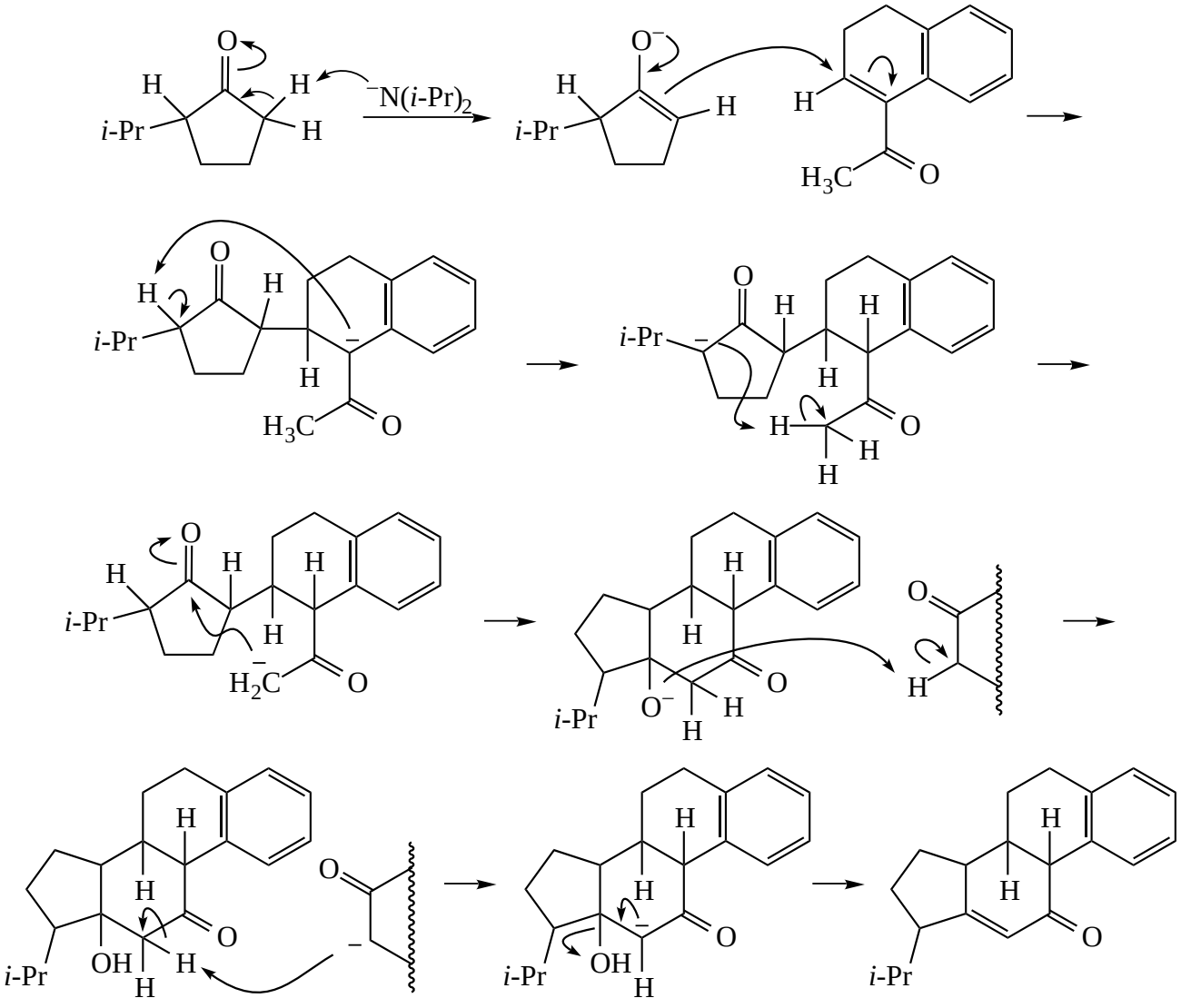
Step 2:



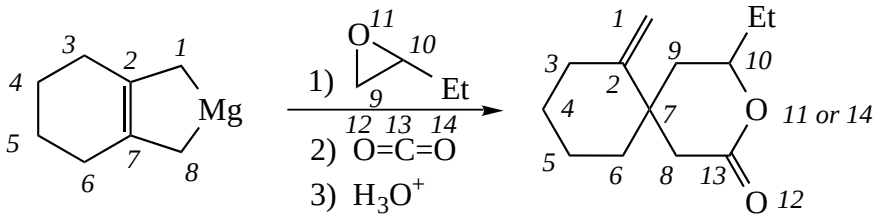
Step 3:



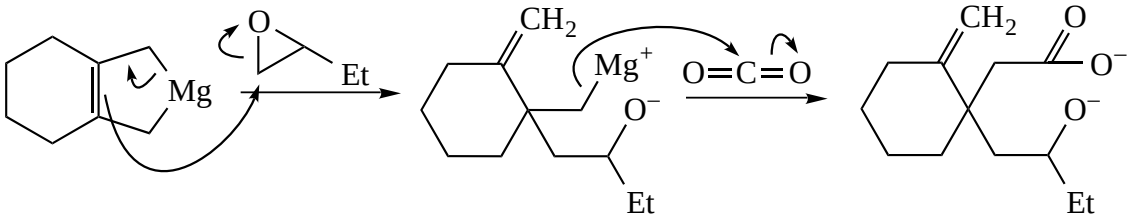
(j) LDA deprotonates the less hindered of the two acidic C atoms. A Robinson annulation then occurs by the mechanism discussed in the text. Two proton transfers are required in the course of the annulation, and both must occur by a two-step mechanism in which the substrate is first protonated, then deprotonated. 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.)



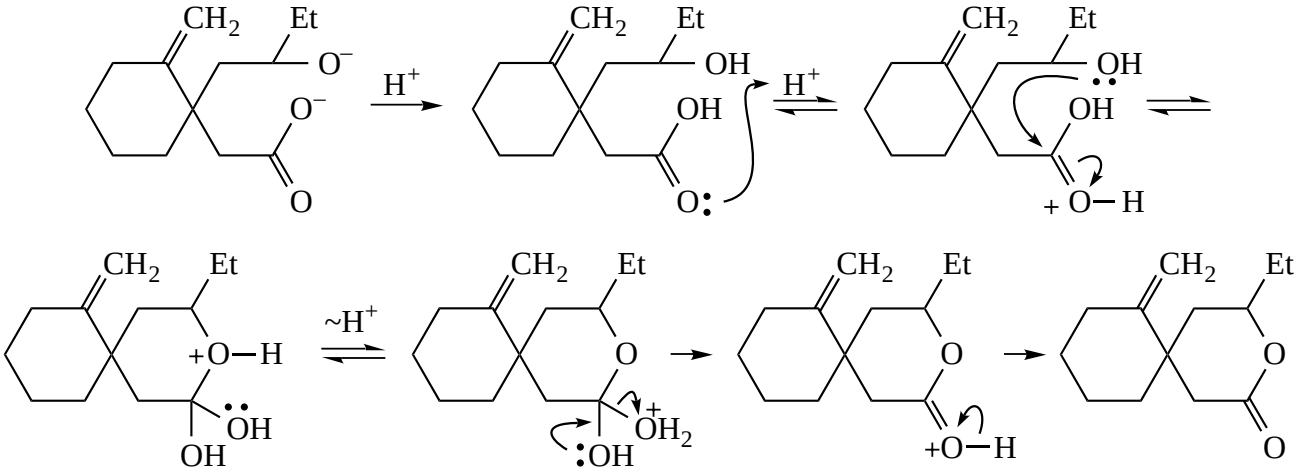
(k) Make: C7–C9, C8–C13, and either O11–C13 or C10–O14. Break: Either C10–O11 or C13–O14.



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.

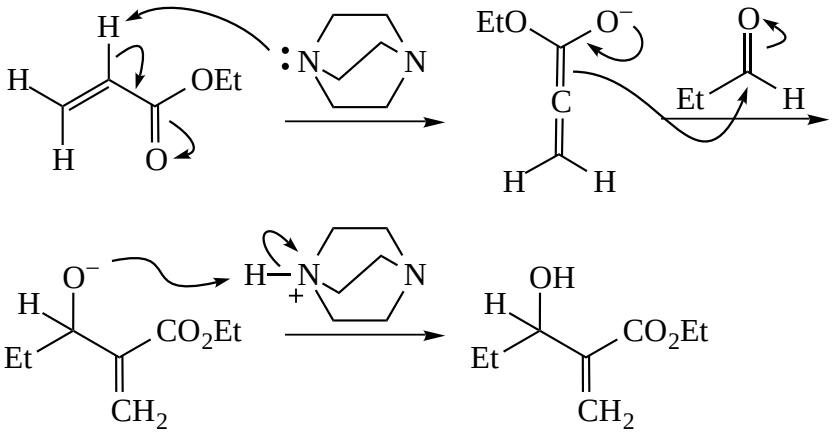


Upon addition of acid, the alcohol reacts with the carboxylic acid to give a lactone (cyclic ester). This acid-catalyzed reaction is discussed in detail in Chapter 3. The reaction is far more likely to occur by attack of O11 on C13 than by attack of O14 on C10.

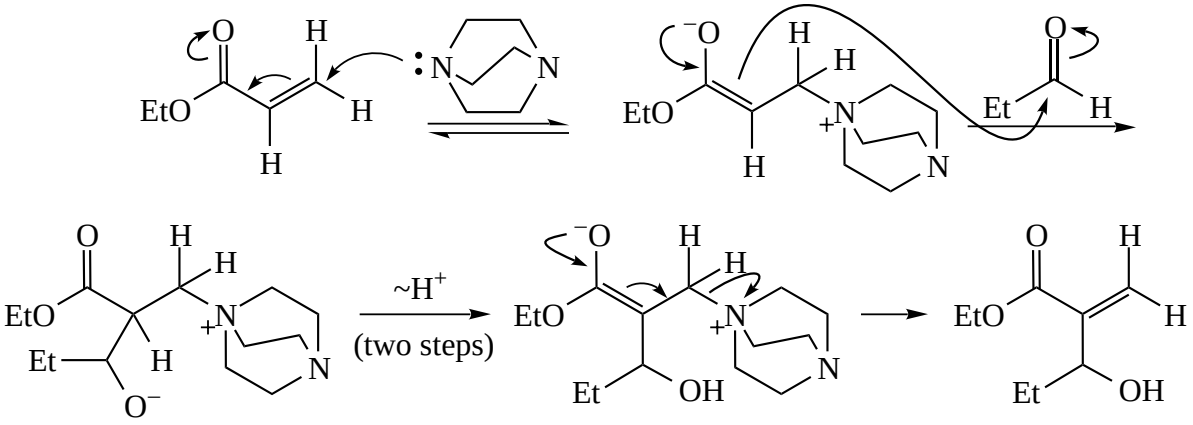


(l) 1,4-Diazabicyclo[2.2.2]octane (DABCO) can act as either a base or a nucleophile. When it acts as a base, it deprotonates C2 to give an enolate, which attacks the aldehyde in an aldol reaction to give the product after proton transfer. When it acts as a nucleophile, it adds to the electrophilic C3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



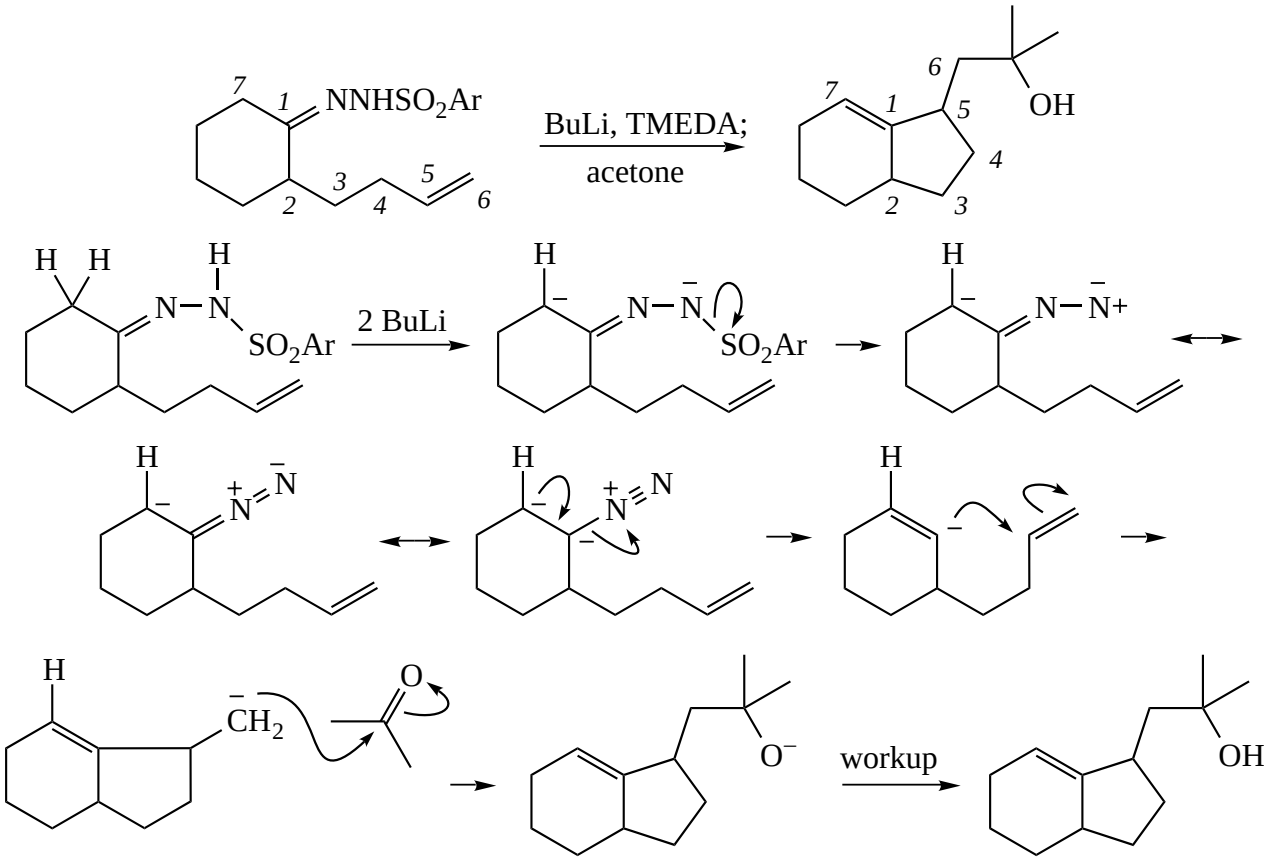
Mechanism with DABCO as nucleophile:



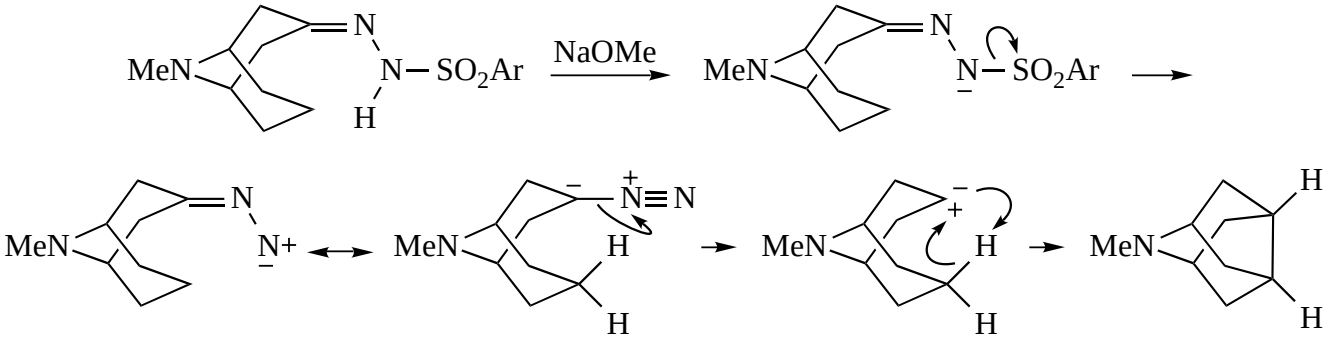
The second mechanism is much more likely, even without the information in problem (m), as C(sp^2)–H bonds α to carbonyls are not very acidic. (See Chapter 1.)

(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.

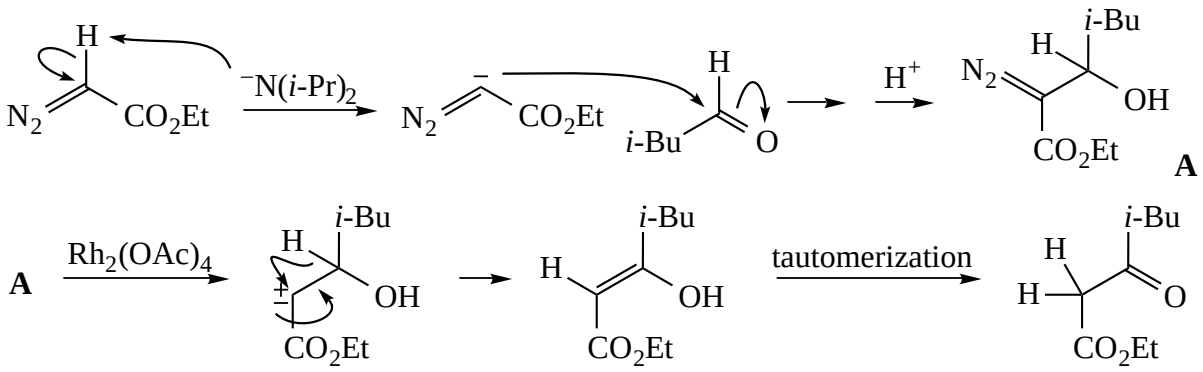
(n) Make: C1–C5, C6–acetone. Break: C1–N. This is a Shapiro reaction. Addition of BuLi to the hydrazone deprotonates N, then deprotonates C7 to give a dianion. α-Elimination of $ArSO_2^-$ gives an intermediate that loses N_2 to give an alkenyl anion. This undergoes intramolecular addition to the pendant 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.



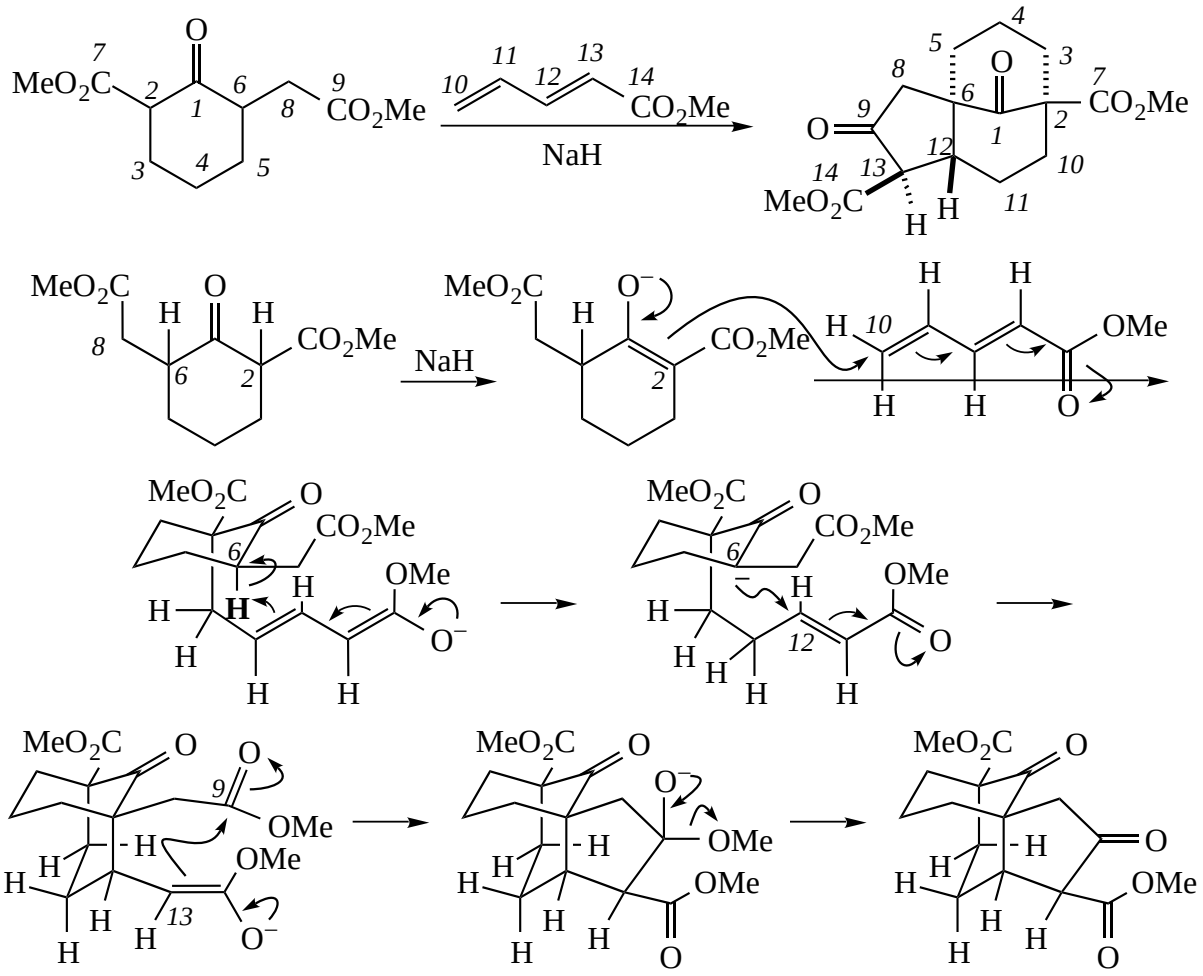
(o) This is a Bamford–Stevens reaction. We are forming a new C–C bond to a remote, unactivated C, suggesting a carbene inserting into a C–H bond. The base deprotonates N. α-Elimination of $ArSO_2^-$ gives the diazo compound, which spontaneously loses N_2 to give the carbene. The carbene inserts into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



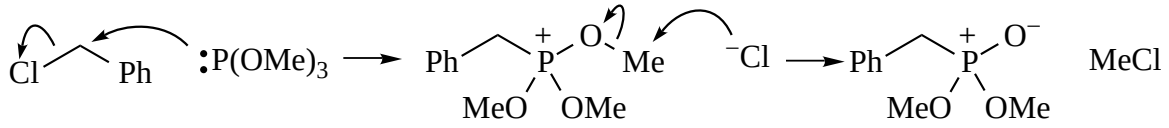
(p) LDA is a strong, nonnucleophilic base. It will deprotonate the diazo compound, turning it into a good nucleophile. Addition to the aldehyde C=O bond and workup gives intermediate **A**. Now, treatment of **A** with Rh(II) generates a carbenoid, which reacts as if it were a singlet carbene. A 1,2-shift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



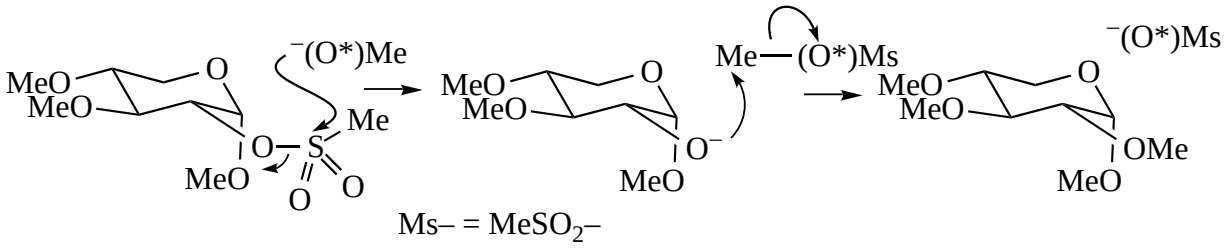
(q) Make: C2–C10, C6–C12, C9–C13. Break: none. C2 and C6 are nucleophilic (once they are deprotonated), while C9, C10 and C12 are electrophilic. C2 is by far the most acidic site, so the C2–C6 bond is probably formed first.



(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.

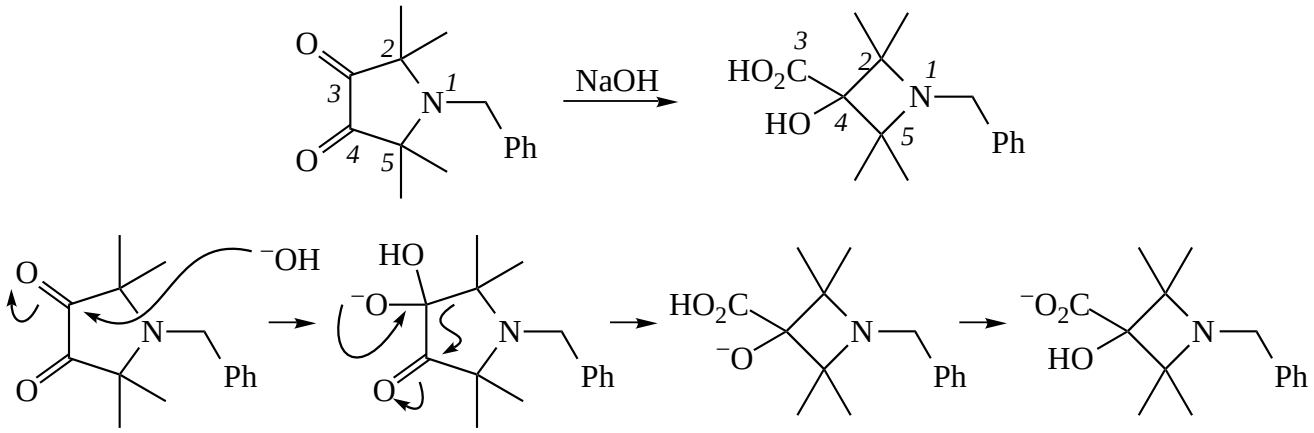


(s) Clearly simple S_N2 can't be the answer, as configuration is retained at C2 and ^{18}O incorporation into the product is not observed. The other electrophilic site in this compound is the S of the Ms group. Cleavage of the Ms–OR bond can occur under these basic conditions. Attack of $Me(*O)^-$ on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

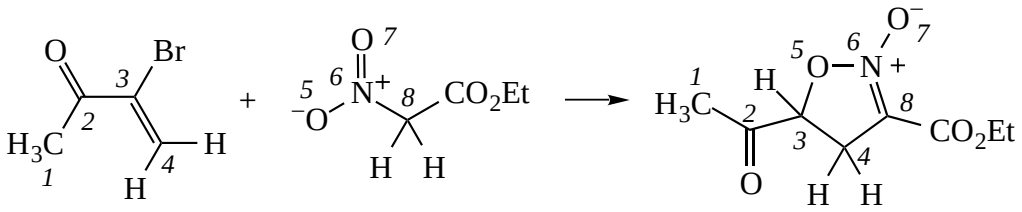


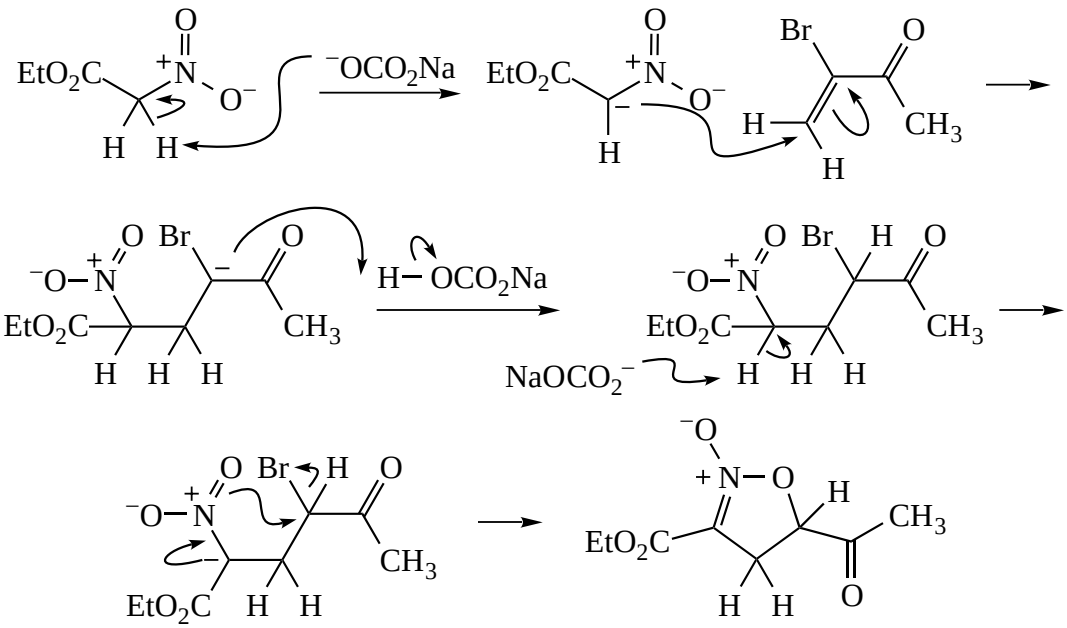
Ms– = $MeSO_2$–

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

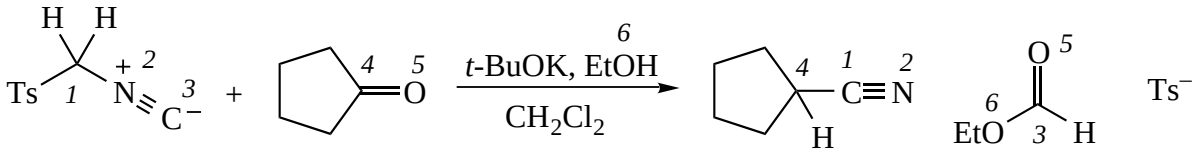


(u) Make: C3–O5, C8–C4. Break: C3–Br. Because C8 is very acidic (between the NO_2 and carbonyl groups) while C4 is electrophilic, the first bond-forming step is likely to form C8–C4. Then displacement of Br from C3 by O5 gives the product.

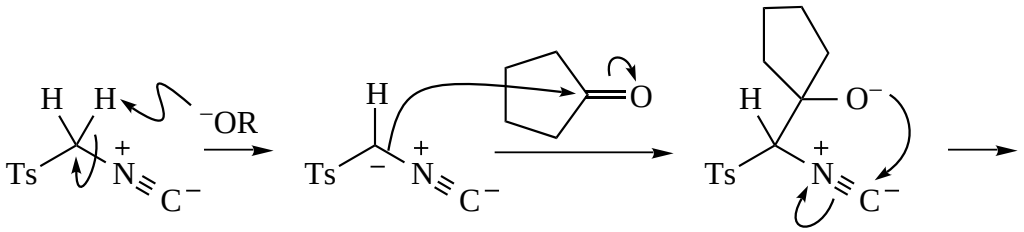


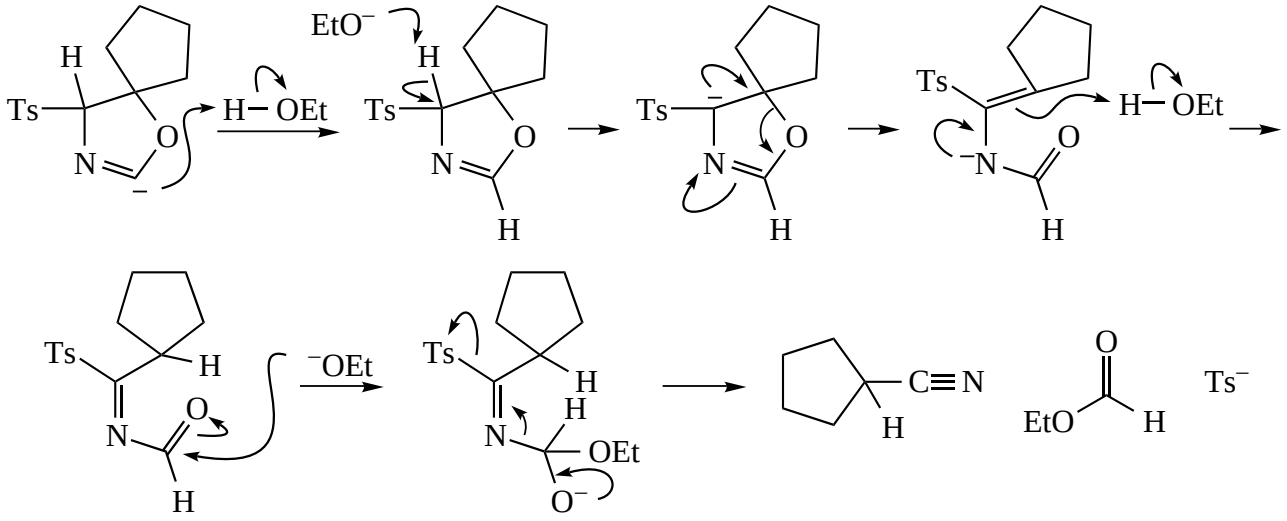


(v) Numbering the atoms correctly is key here. The cyanide C in the product could be C1 and the formate C, C3, or vice versa. How do we tell which? If the cyanide C is C3, this would mean that attack of C3 on C4 would occur. But this reaction would not require base, and we're told that base is required 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.

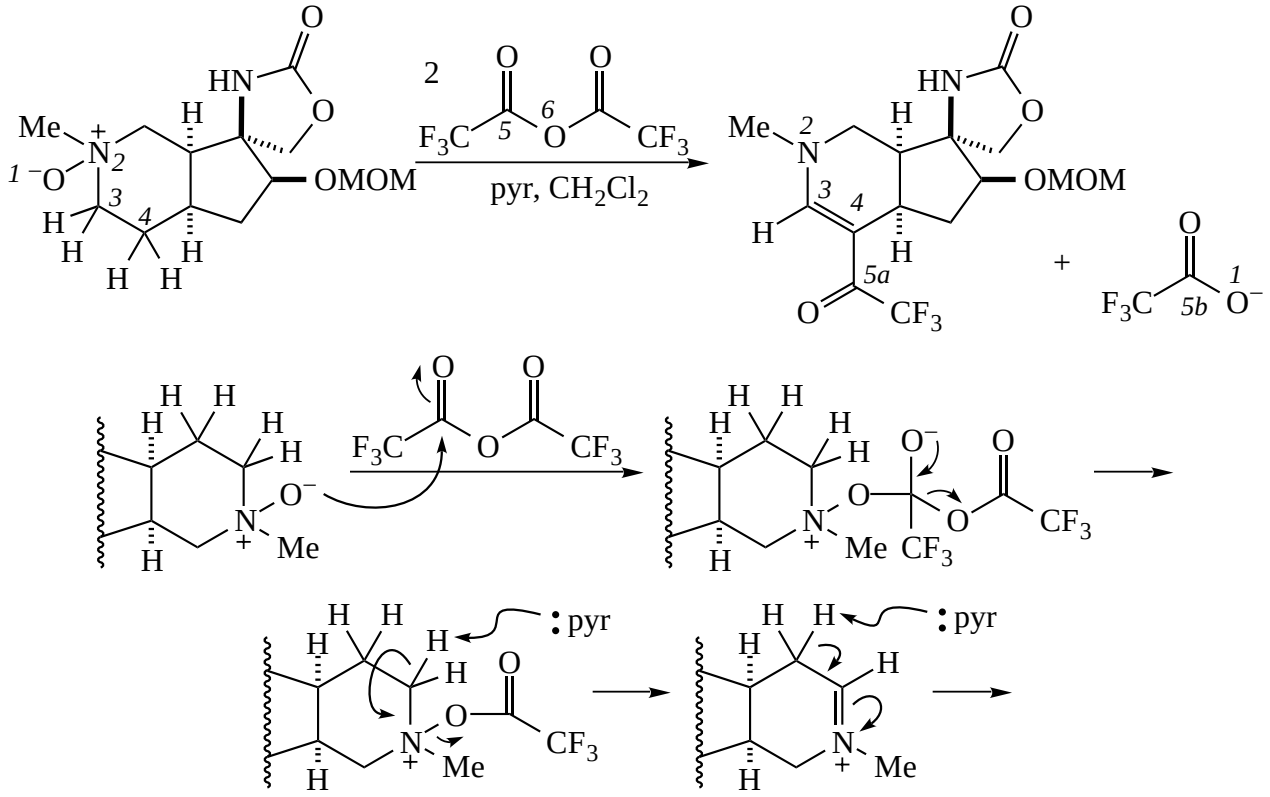


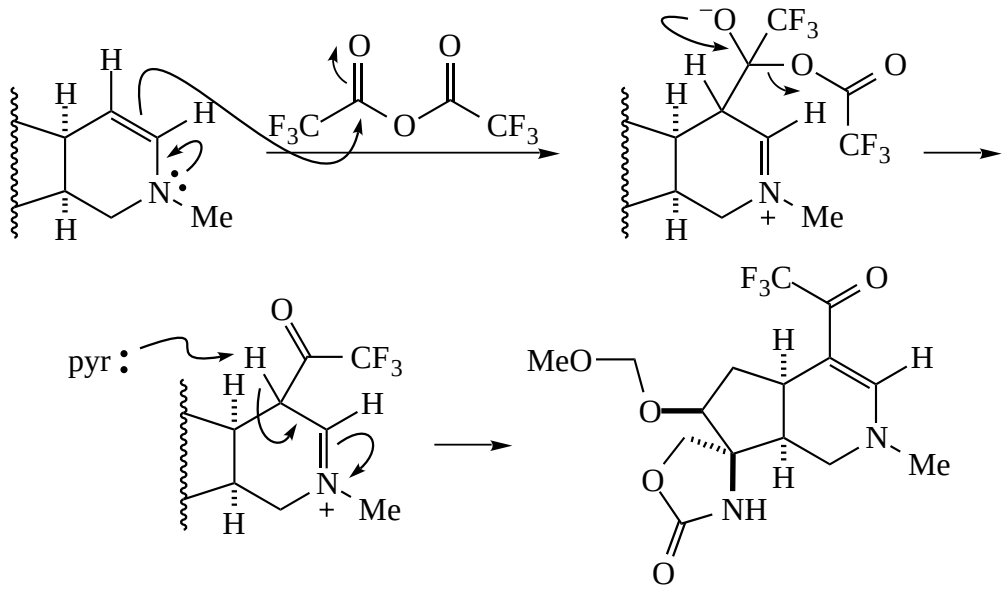
Deprotonation of C1 is followed by attack of C1 on C4 to give an alkoxide at O5. O5 can then attack *electrophilic* C3 (next to a heteroatom with a formal plus charge!) to give a five-membered ring with an anionic C, which is immediately protonated. Deprotonation of C1 again is followed by cleavage of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



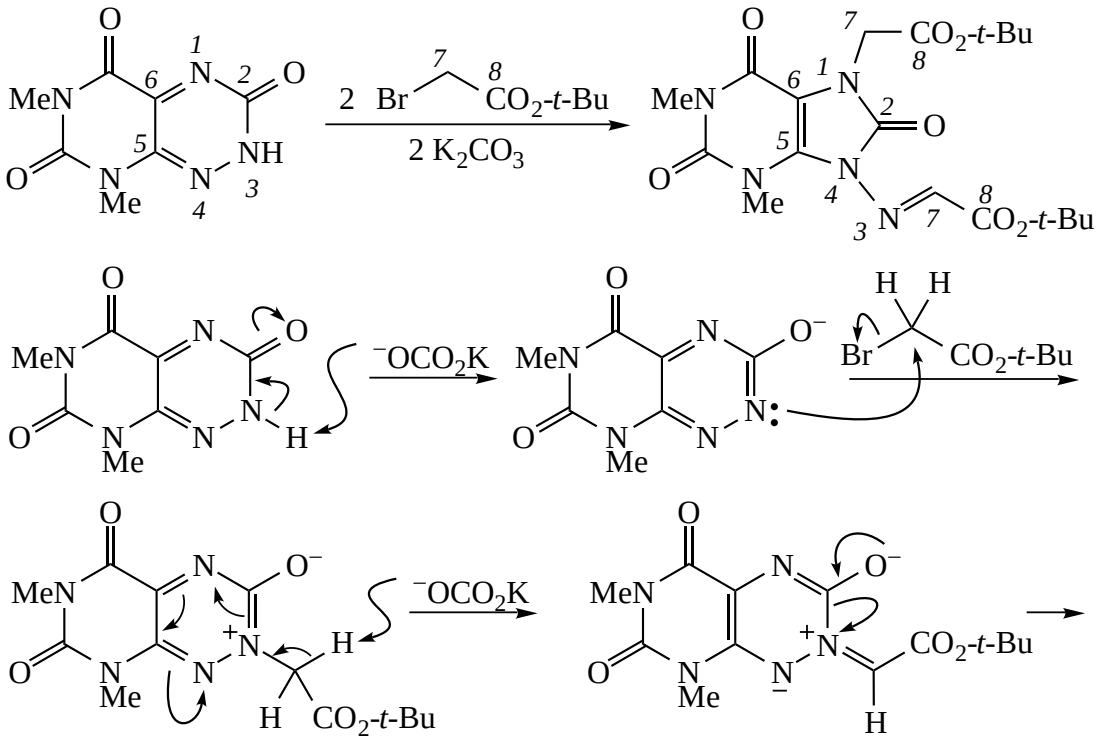


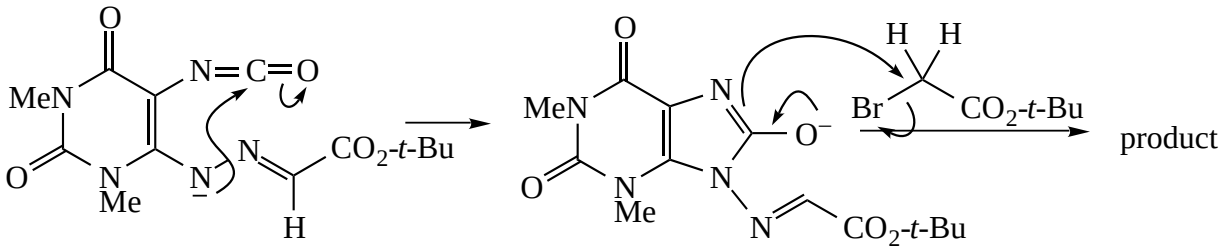
(w) Two equivalents of trifluoroacetic anhydride are required, so there are two C5's and two O6's. One of those C5's, C5a, ends up attached to C4 in the product. The other, C5b, must end up attached to O1, which is absent from the product. Make: O1–C5a, C4–C5b. Break: O1–N2, C5a–O6a, C5b–O6b. O1 is nucleophilic, 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.



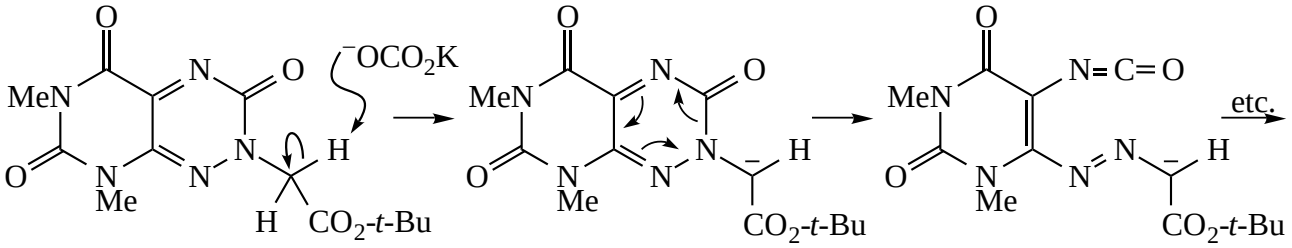


(x) Make: N1–C7a, N3–C7b, N4–C2. Break: C2–N3, C7–Br. The first step is likely deprotonation and alkylation of N3. This makes a σ bond between N3 and C7b, but we need to introduce a π bond. This can be done by an elimination reaction. Deprotonation of C7 gives an enolate, which can be delocalized onto 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.

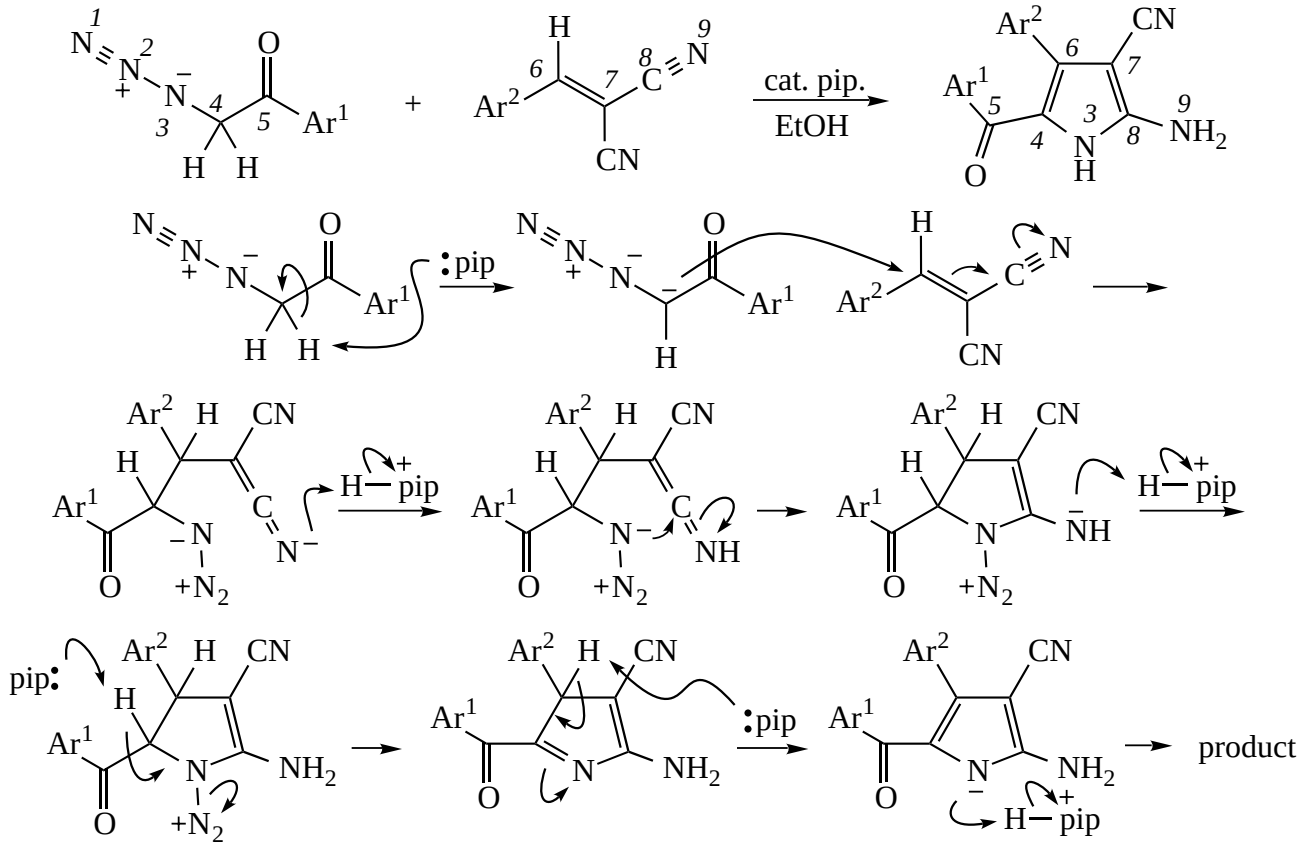




Another way to draw the key N–C ring-cleaving step is as an *electrocyclic ring opening.*

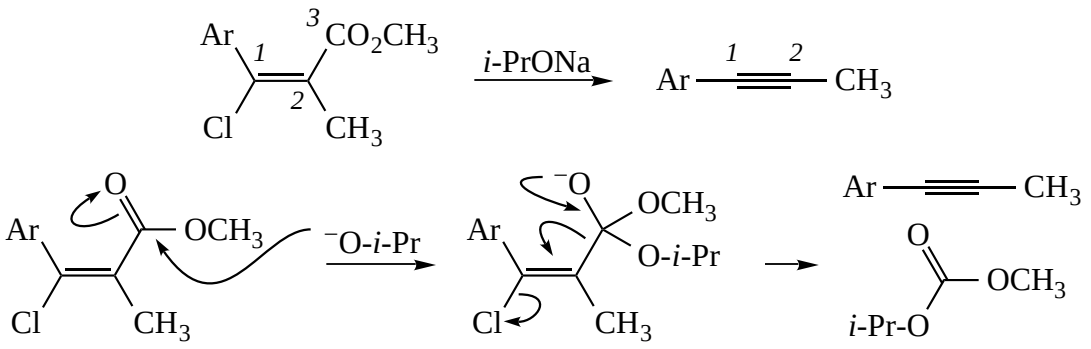


(y) Make: N3–C8, C4–C6. Break: N2–N3. Conditions are basic, and C6 is very electophilic, so first step is likely deprotonation of C4 and addition of the enolate to C6. After protonation of N9, addition of N3 to C8 can occur. Protonation of N9 is followed by loss of H^+ and N_2 by an E2 mechanism. Finally,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

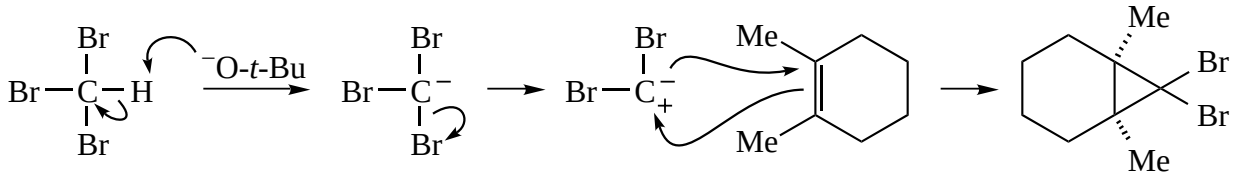


(z) Make: none. Break: Cl–C1, C2–C3. *i*-PrO^- is nucleophilic. There are two electrophilic sites in the

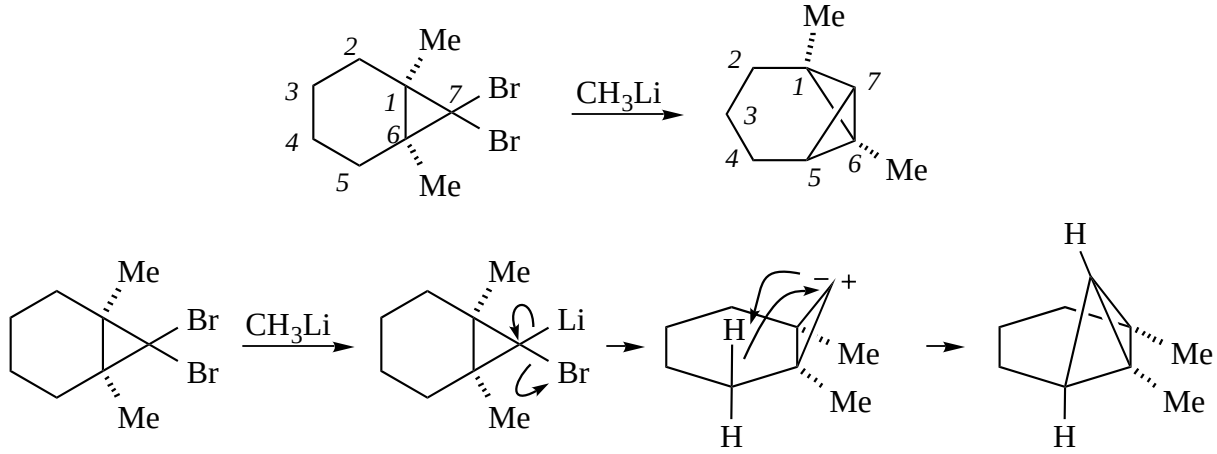
starting material, C1 and C3. Attack of *i*-PrO⁻ at C1 doesn't get us anywhere, since the product does not have a C1–O bond, so the first step is probably addition of *i*-PrO⁻ to the C3=O π bond. In the second step, the O⁻ electrons can move down to form the carbonyl bond again, breaking the C2–C3 bond.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



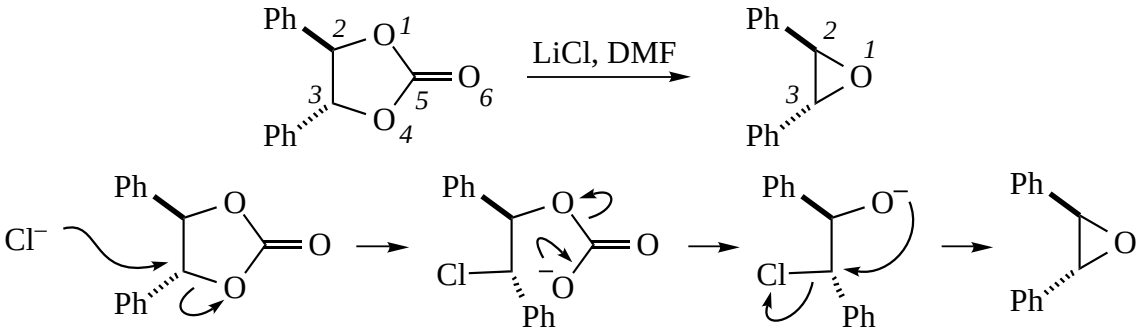
(aa) The first transformation is a standard dibromocarbene addition to an alkene (Section D.4). The strong base deprotonates the bromoform. α-Elimination gives the carbene, which undergoes cyclo-addition to the alkene to give the product.



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.

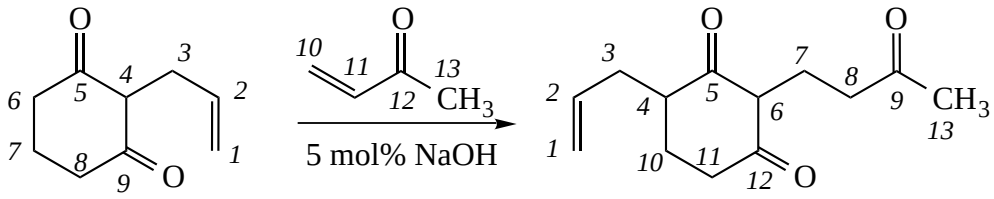


(bb) Make: C3–O1. Break: C3–O4, O1–C5. We are substituting O4 for O1 at C3, and this substitution is occurring with *retention* of configuration, suggesting two sequential S_N2 reactions. What is the role of LiCl? Cl^- is a pretty good nucleophile, especially in a polar aprotic solvent like DMF. The 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.

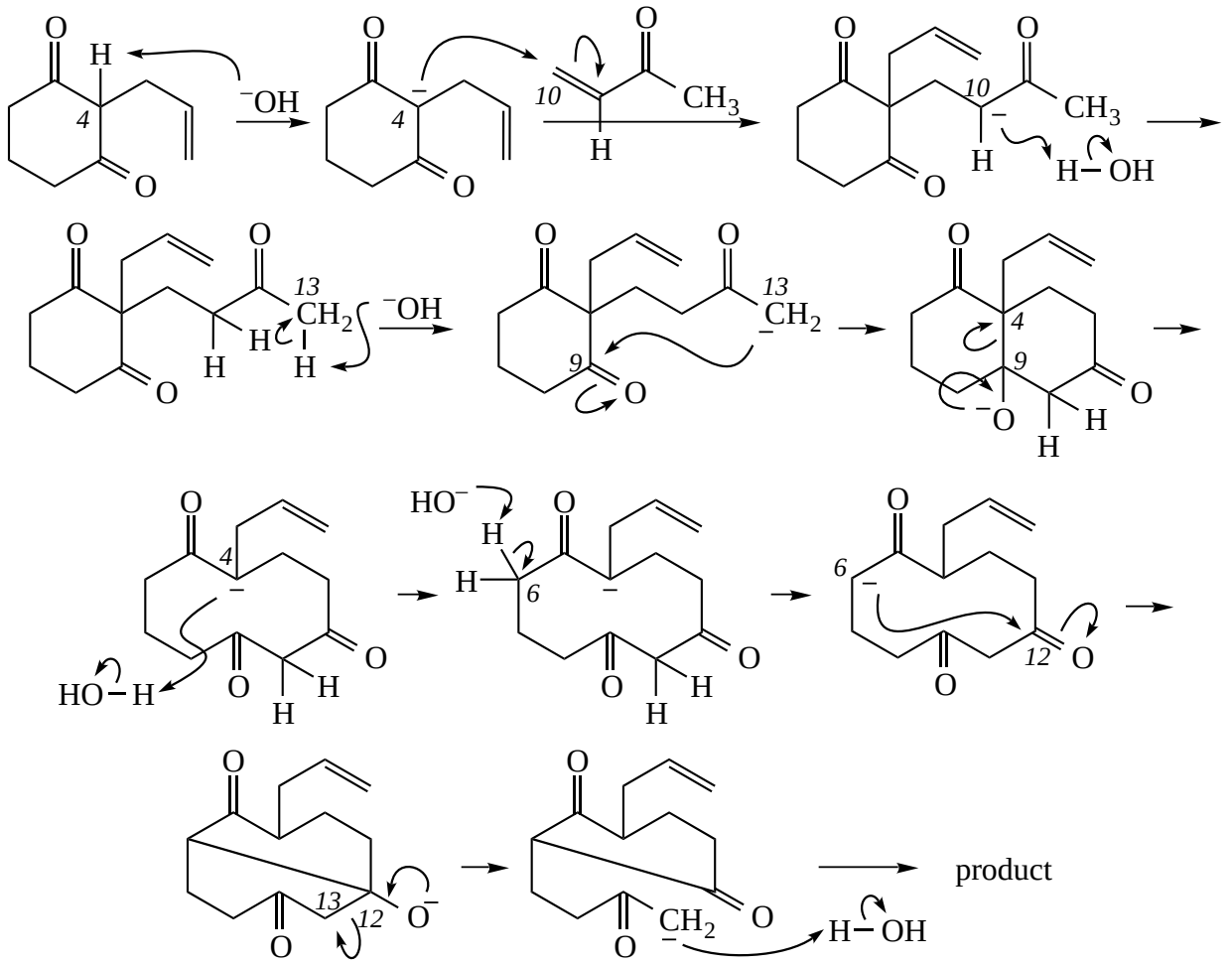


(cc) This reaction is a Robinson annulation. The mechanism was discussed in the text.

(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.

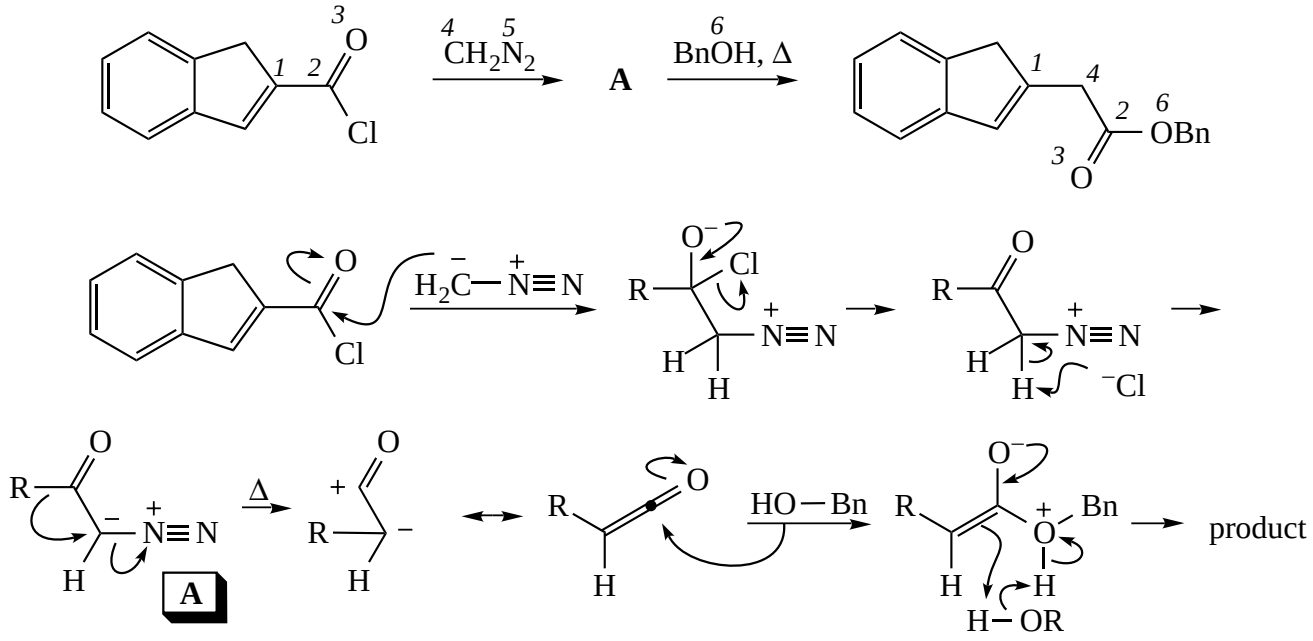


The first steps are the same as in the previous problem. C4 is deprotonated, it undergoes a Michael addition to C10 (making C4–C10), proton transfer occurs from C13 to C11, and C13 adds to C9 (making C9–C13). At this point, though, rather than an E1cb elimination, a fragmentation occurs, breaking C9–C4. 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.

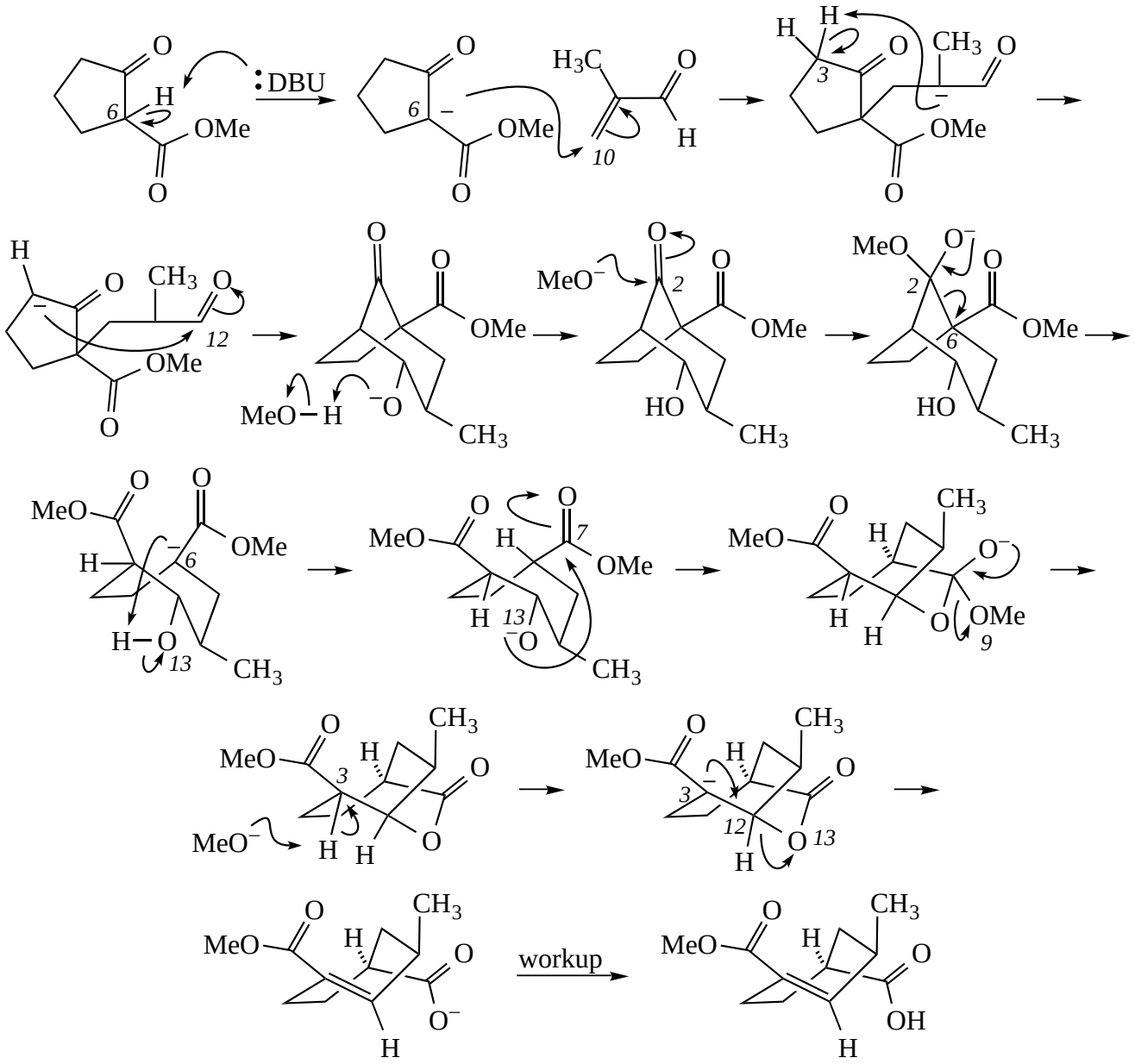
(ee) Make: C1–C4, C4–C2, C2–O6. Break: C1–C2, C2–Cl, C4–N5. The acyl chloride is a potent electrophile at C2. CH_2N_2 is nucleophilic at C4. Addition–elimination occurs, then deprotonation to give a diazoketone. Deprotonation by Cl^- is reasonable because the diazonium ion is a much stronger acid than 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).

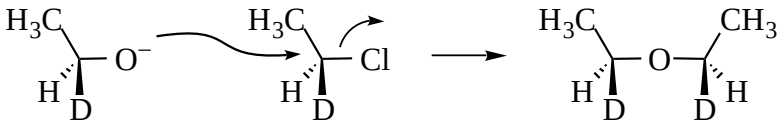
Cyclohexyl halides may undergo elimination or substitution reactions. They are usually more prone to elimination, but the acetate anion $MeCO_2^-$ is not particularly basic, and nucleophiles are particularly nucleophilic in the polar aprotic solvent DMF. More cyclohexyl acetate (substitution) than cyclohexene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

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

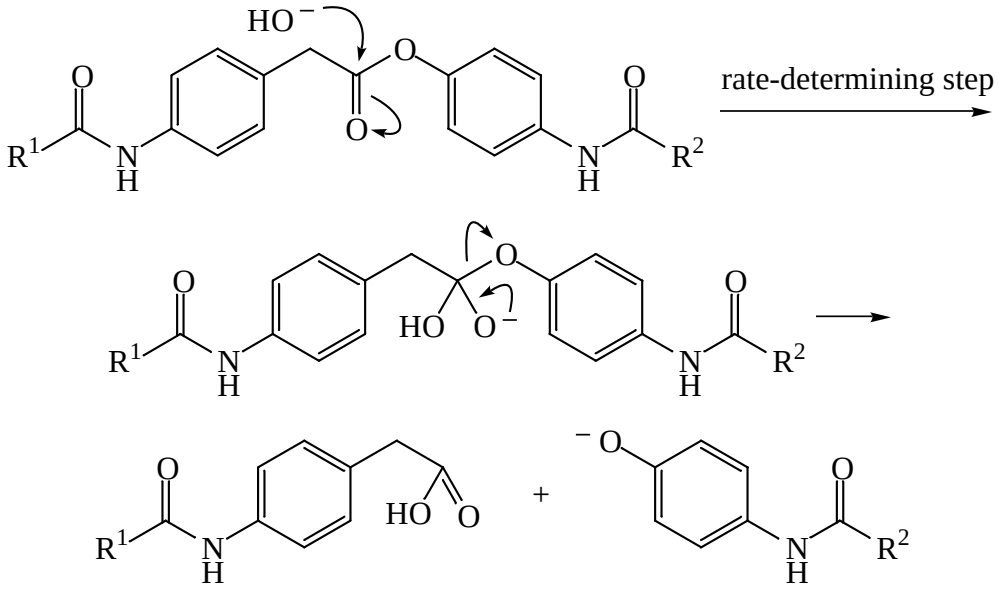
3° Alkyl halides normally undergo elimination with hard nucleophiles. Elimination usually occurs from the conformer in which the leaving group and H are anti to one another. The product is *Z*-PhC(Me)=C(Me)Ph by the E2 mechanism.

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.

http://www.springer.com/0-387-95468-6

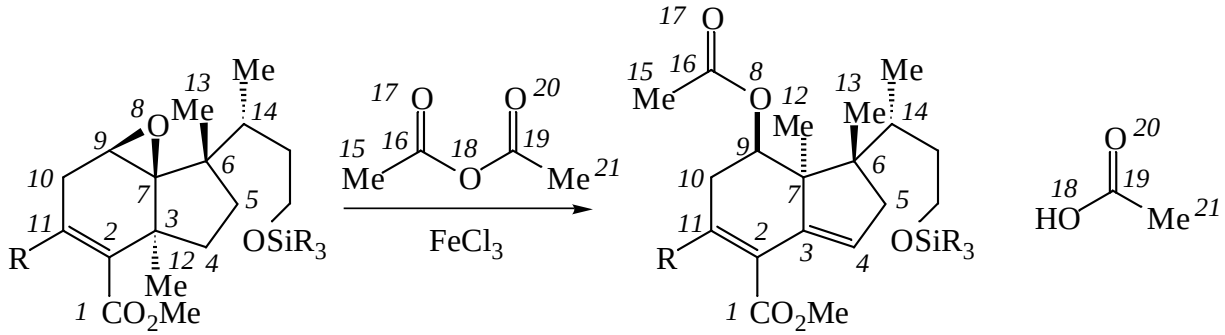
The Art of Writing Reasonable Organic Reaction Mechanisms

Grossman, R.B.

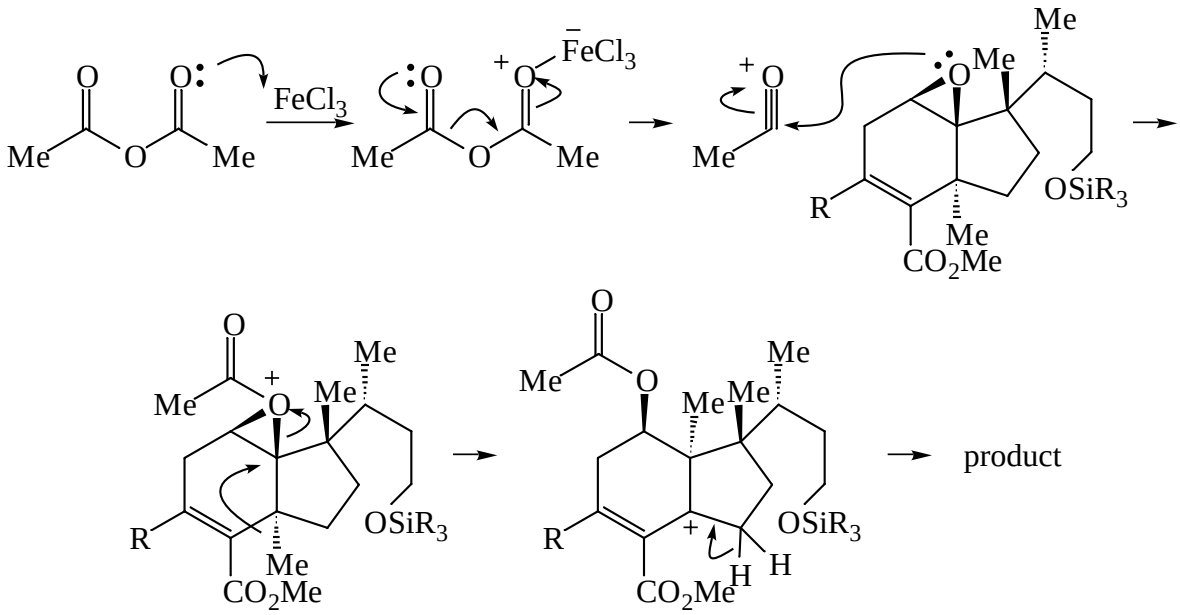
2005, XVI, 355 p. 34 illus., Hardcover
ISBN: 0-387-95468-6

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.



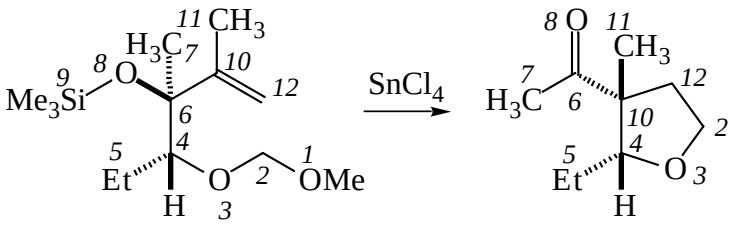
The fact that C12–C3 breaks and C12–C7 makes is a signal that a 1,2-alkyl shift occurs. The shift requires that a carbocation be formed at C7, which could be accomplished by cleaving the C7–O8 bond. Before the C7–O8 bond cleaves, something else must attach to O8 to give it a formal positive charge. Because 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.)



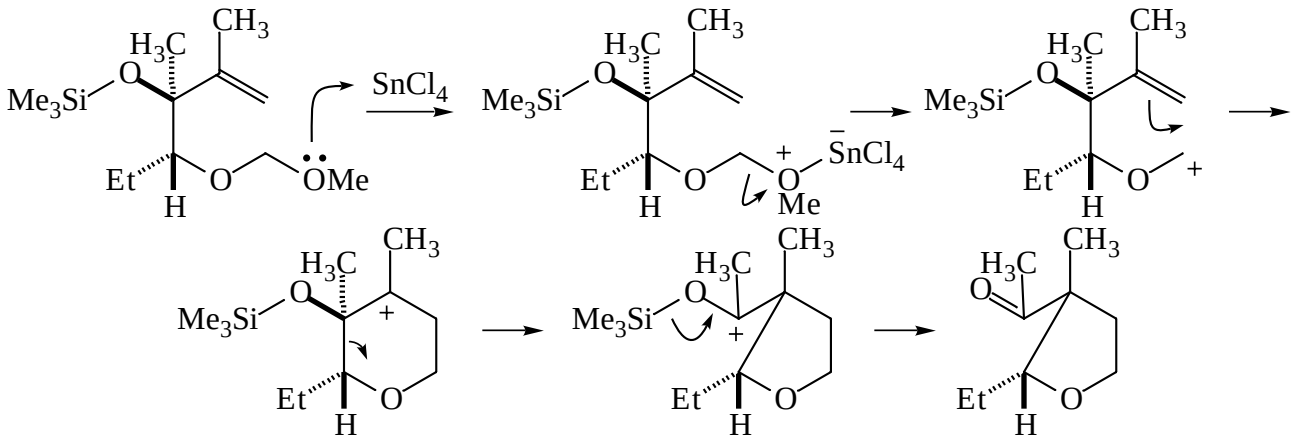
Why do we draw cleavage of the C7–O8 bond concerted with migration of C12? If the two steps were nonconcerted, then a C7 carbocation would intervene, and other 1,2-shifts could occur. For example, C13 or C14 could shift from C6 to C7. In a 1,2-shift that is concerted with leaving group departure, the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

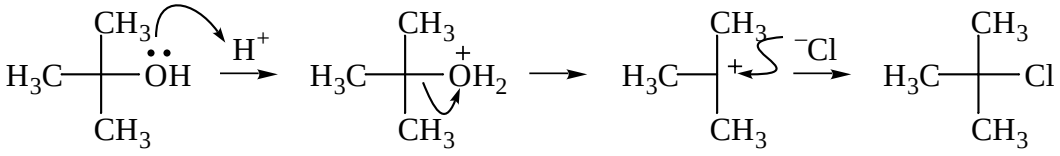


The role of the Lewis acid is either to make a π bond electrophile more electrophilic or to promote the departure of a leaving group. There is no π bond electrophile in the starting material, but O1 is a leaving group, so the first step must be coordination of $SnCl_4$ to O1. Cleavage of the O1–C2 bond 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.

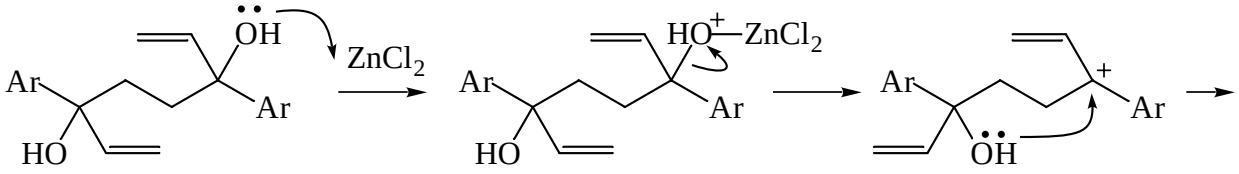


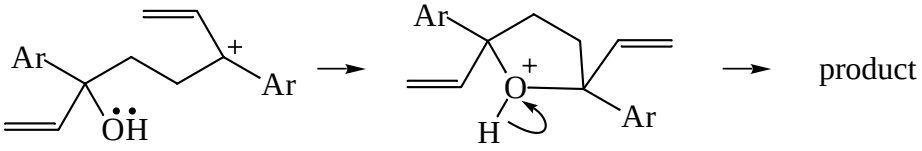
3.3.

(a)



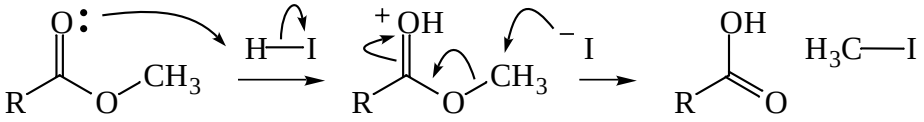
(b)



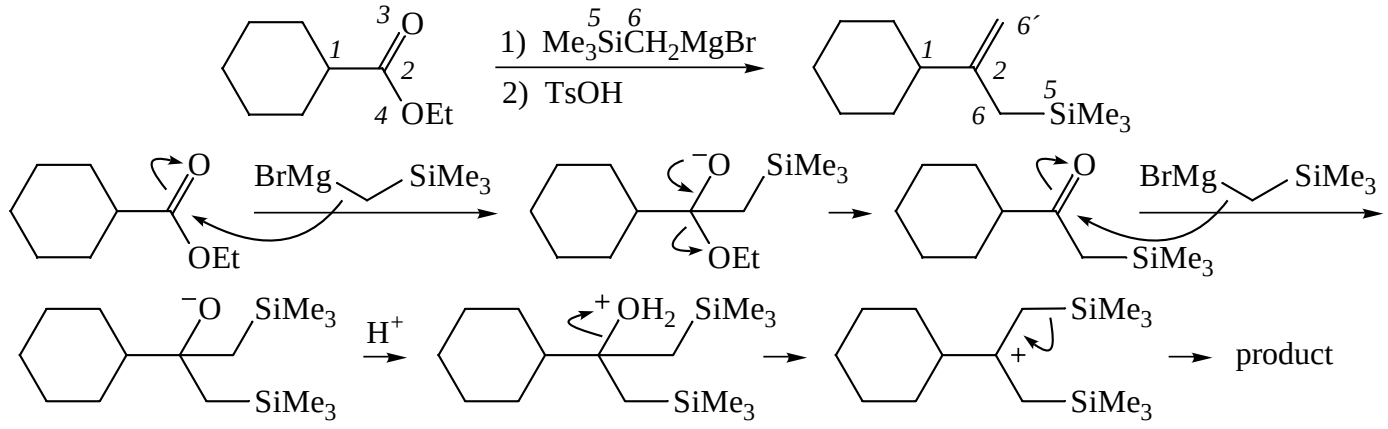


3.4. Because the carbocations derived from aryl and alkenyl halides are extremely high in energy.

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.

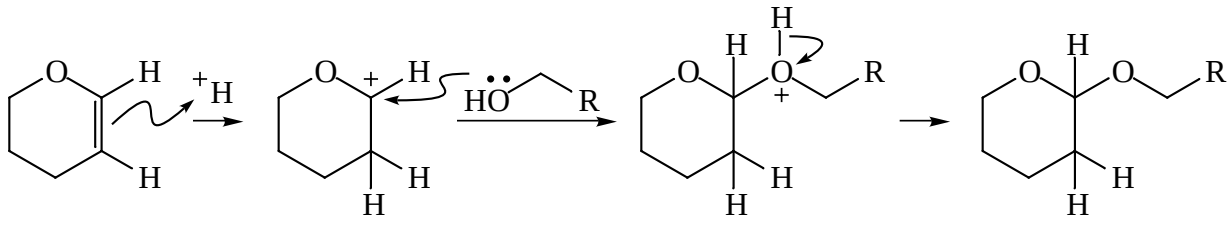


3.6. A few things about this reaction may have caught you off guard. First, the first step is a polar reaction under basic conditions, involving the Grignard reagent; only the second step is a polar reaction under acidic conditions. Second, *two* equivalents of the Grignard are required for the product; 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´.

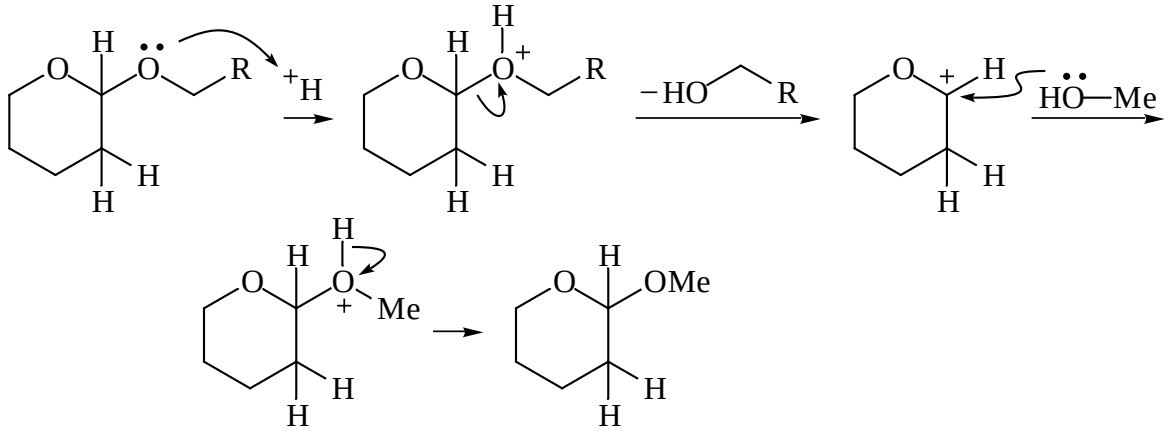


3.7.

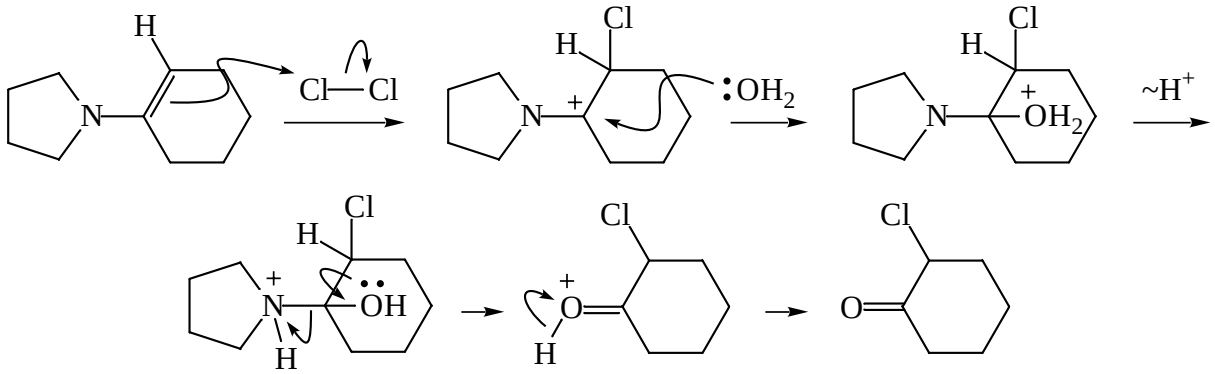
(a)



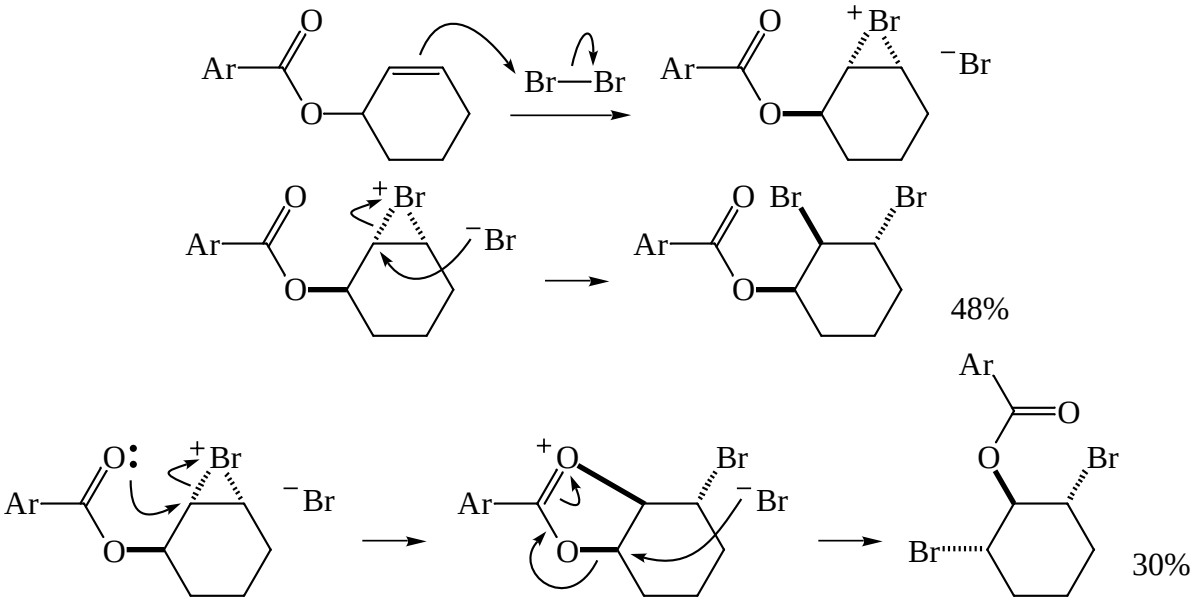
(b) This substitution reaction must proceed by an S_N1 mechanism.

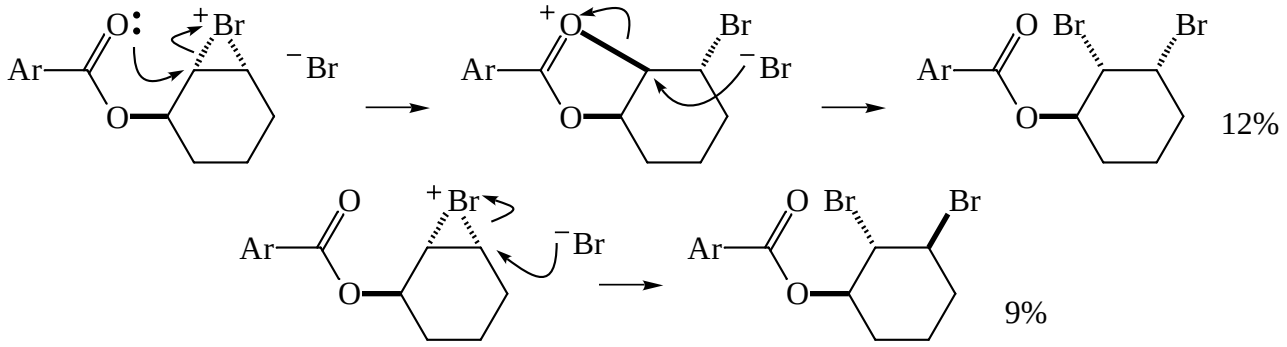


3.8. The N atom so strongly stabilizes cations that a β-halocarbocation is the likely intermediate, not a halonium ion.



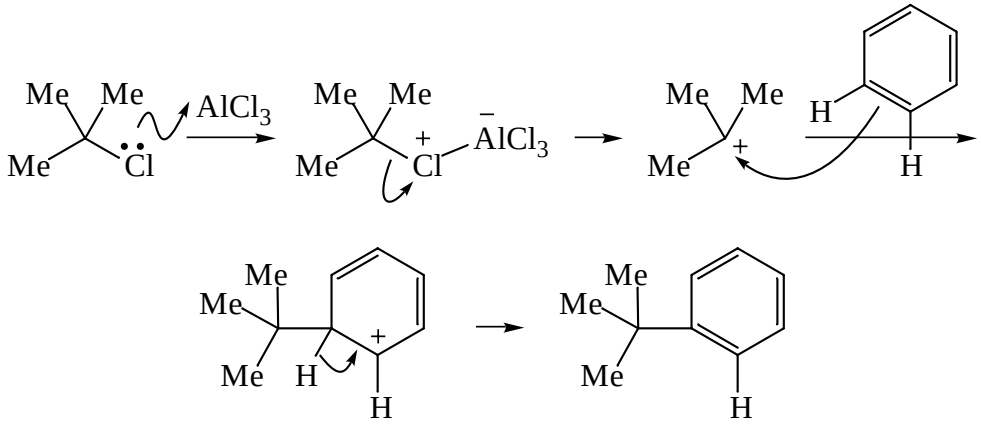
3.9. The products have in common a bromonium ion that is formed by attack of Br_2 on the face of the double bond *opposite* the acyloxy substituent. The two products not consistent with simple anti addition across the π bond are obtained via neighboring group participation of the acyloxy group.



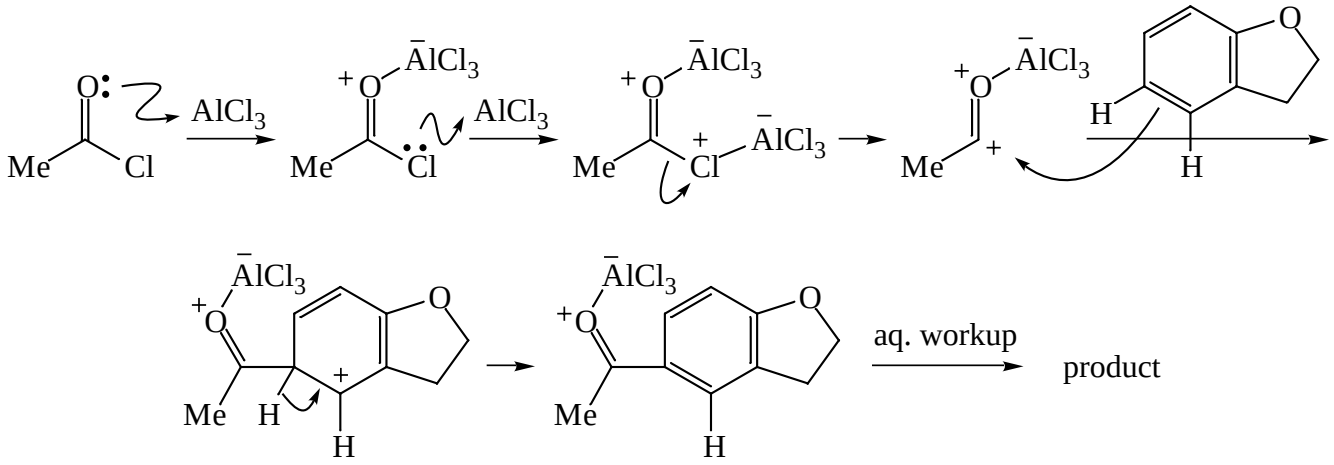


3.10.

(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.

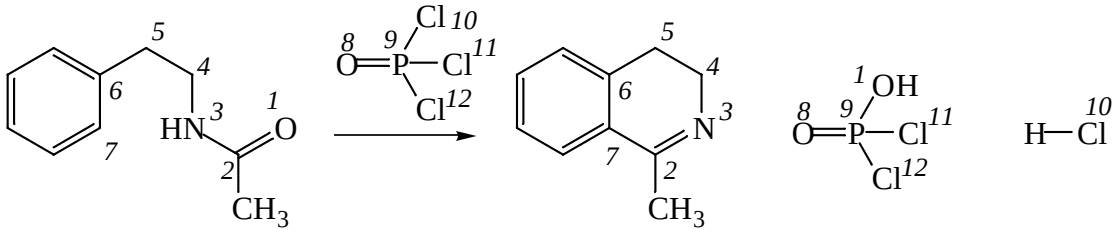


(b) Unlike a Friedel–Crafts alkylation, which requires only a catalytic amount of $AlCl_3$, a Friedel–Crafts acylation requires more than a stoichiometric amount of $AlCl_3$. The first equivalent coordinates to the carbonyl O; the remaining catalytic amount catalyzes the ionization of the C–Cl bond.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

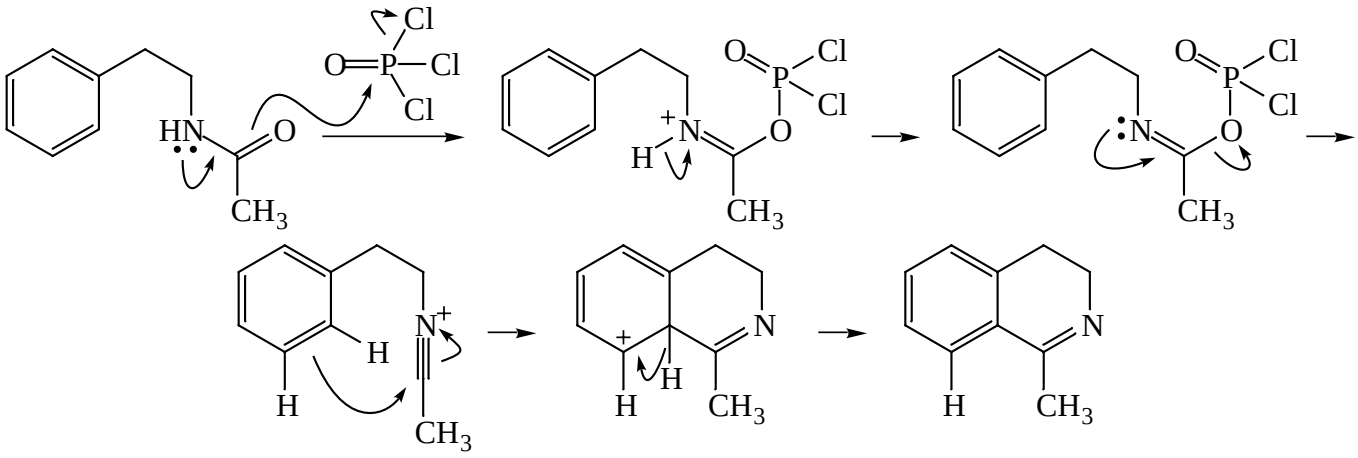


(c) The starting material loses the elements of water, but if water is the by-product, what is the role of the

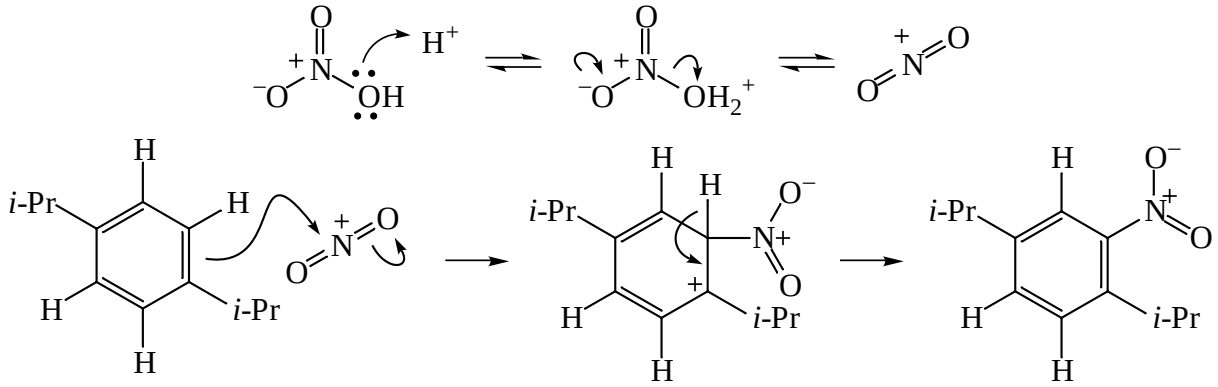
$POCl_3$? It is not a Lewis acid; it is a σ bond electrophile at P. Because P9 is electrophilic and O1 is nucleophilic, the first step must be formation of O1–P4 bond. If this is true, the P-containing by-product has an O–P bond. Make: O1–P9, C2–C7. Break: O1–C2, P9–Cl10.

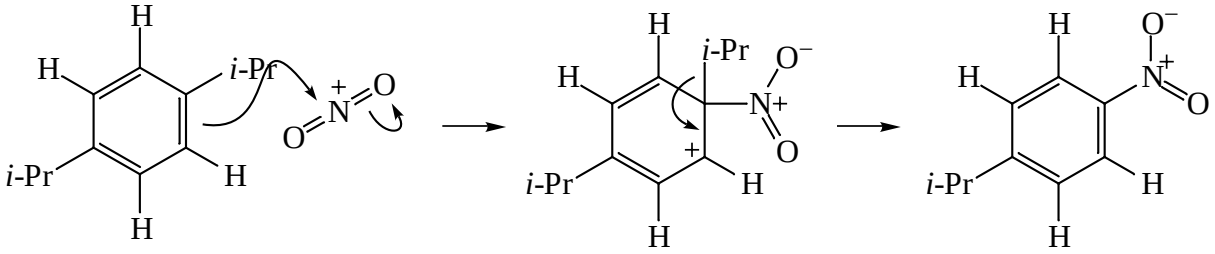


In the first step, O1 attacks P9 and displaces Cl10. After deprotonation of N3, a carbocation at C2 (stabilized by resonance with N4) is formed. Addition–elimination then gives the product. An alternative and reasonable mechanism would have C7 attack C2 before the C2–O1 bond cleaves (addition–elimination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



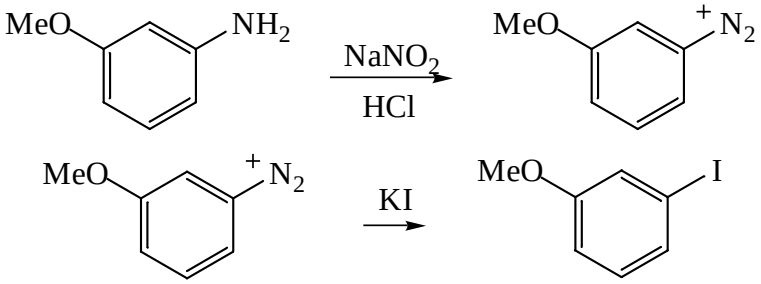
3.11. The first product is derived from a normal electrophilic aromatic substitution reaction of the kind described in the text. The second product is derived from ipso electrophilic aromatic substitution. The mechanism is exactly the same, but in the last step *i*-Pr^+ is lost instead of H^+.



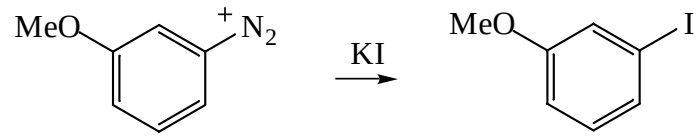


3.12.

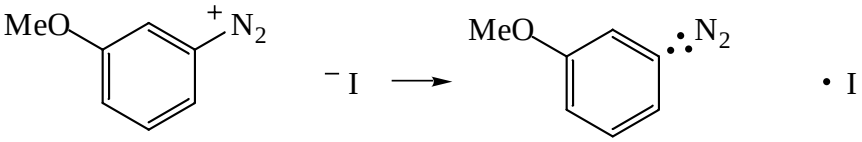
(a) The initial part, formation of a diazonium ion, proceeds by the mechanism described in the book.



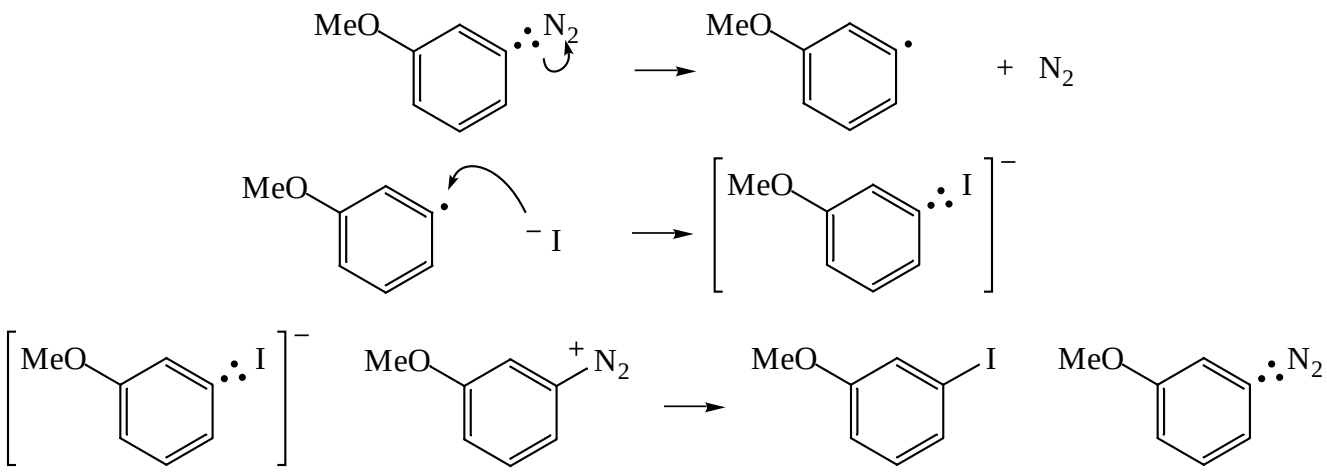
The second part, substitution of N_2 by I^-, proceeds by the $S_{RN}1$ mechanism.



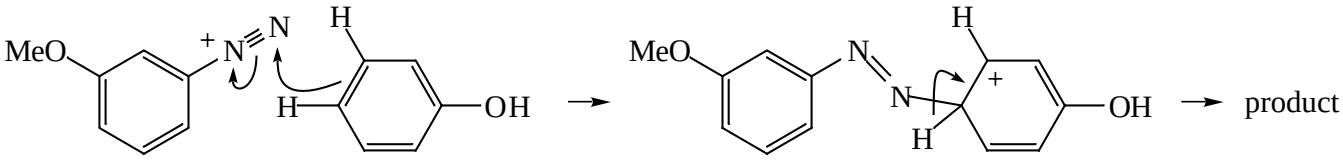
Initiation:



Propagation:

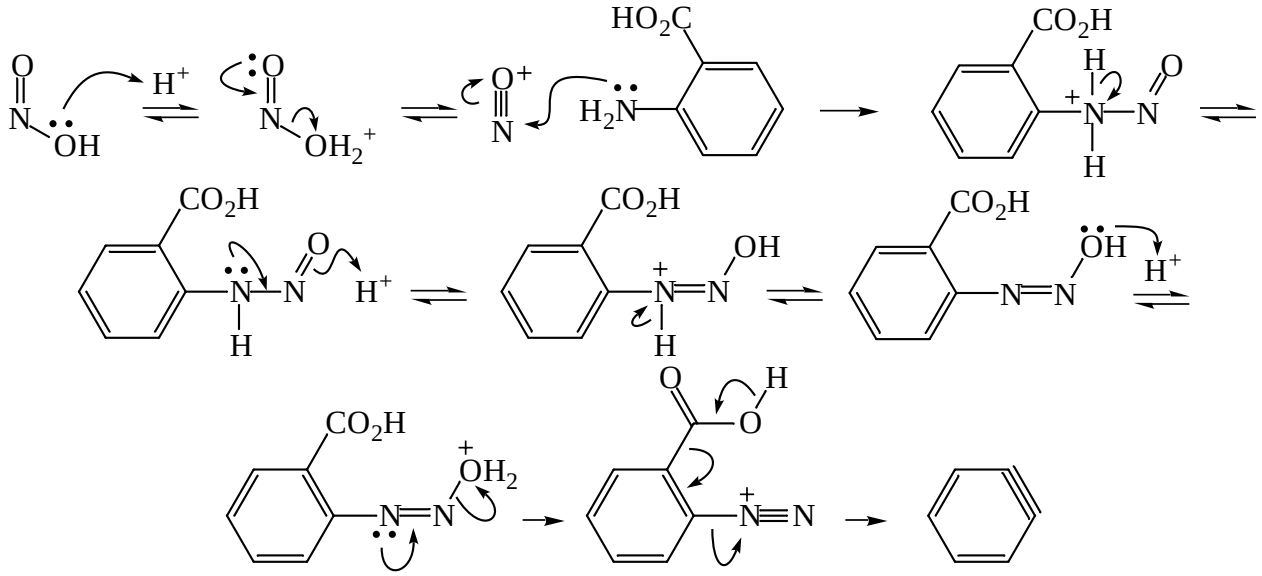


(b) Here the diazonium ion forms again, but now, an electrophilic aromatic substitution occurs, with the terminal N of the diazonium ion acting as the electrophile.

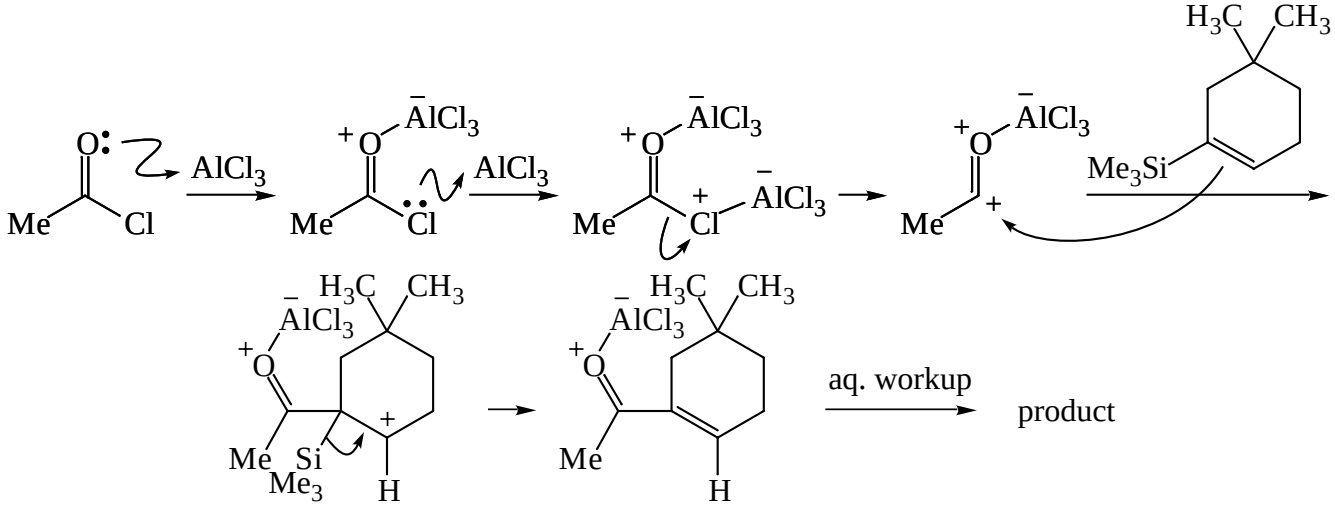


3.13.

(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.



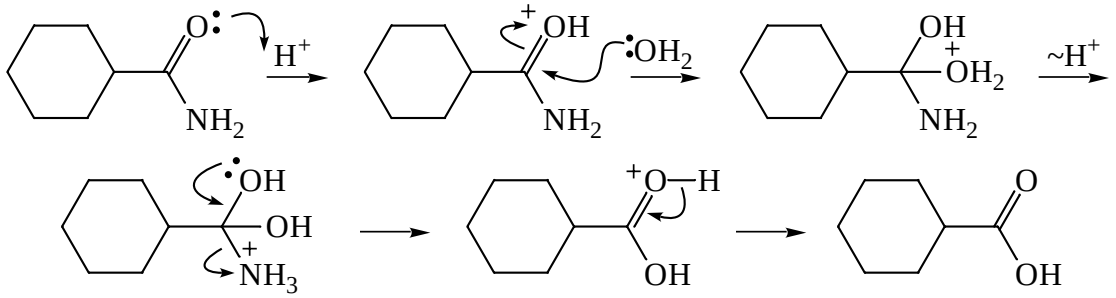
3.14. The mechanism is exactly the same as in 3.10(b).



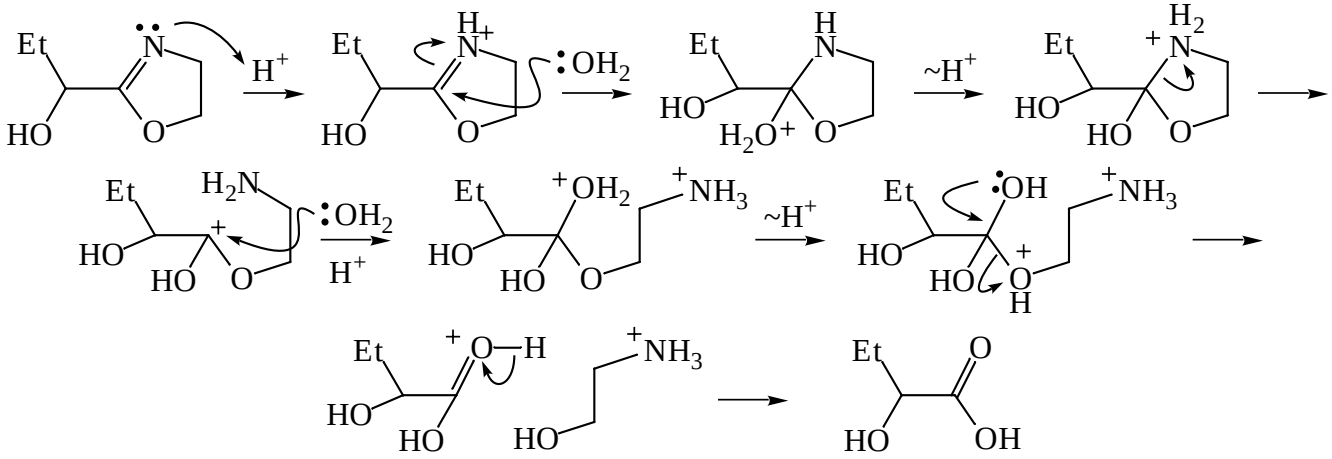
3.15.

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

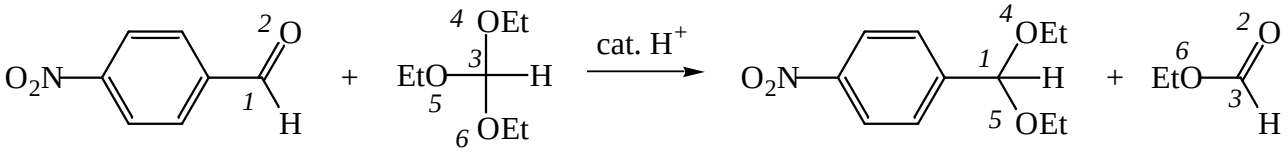
are preceded by protonation and followed by deprotonation. It is very important that these proton transfer steps are drawn properly!



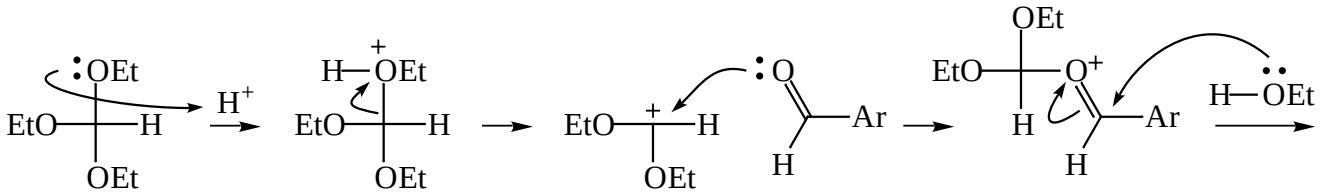
(b) It is unlikely that the CH_2–O bond in the starting material will break under aqueous acidic conditions (can't form a carbocation, and S_N2 is unlikely unless conditions are very harsh). Therefore the CH_2–O bond is preserved in the product, which means that *both* O's of the carboxylic acid product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

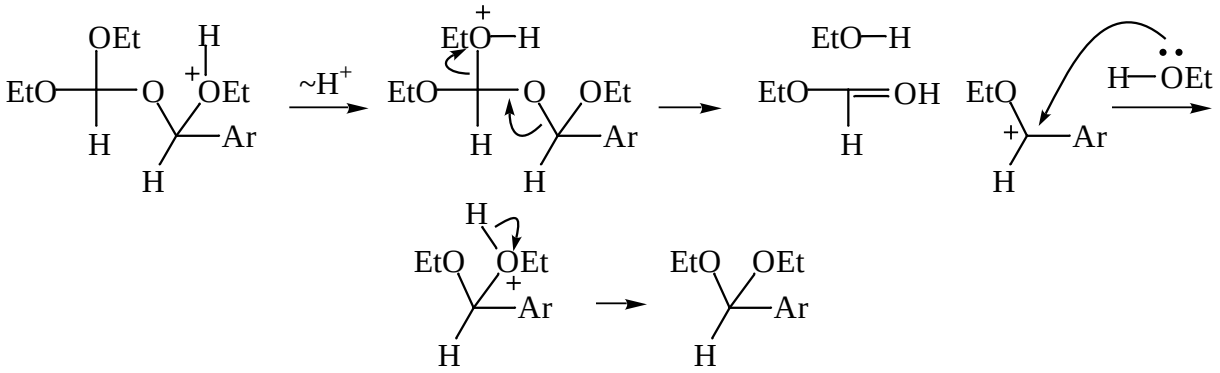


3.16. Make: C1–O4, C1–O5, O2–C3. Break: C1–O2, C3–O4, C3–O5.

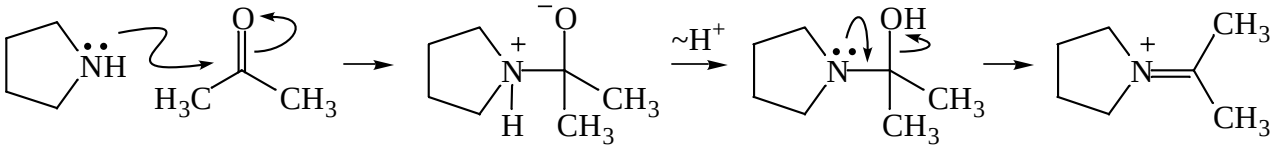


There are a number of ways this reaction could proceed, but the key step in any of them is attack of O2 on a carbocation at C3.

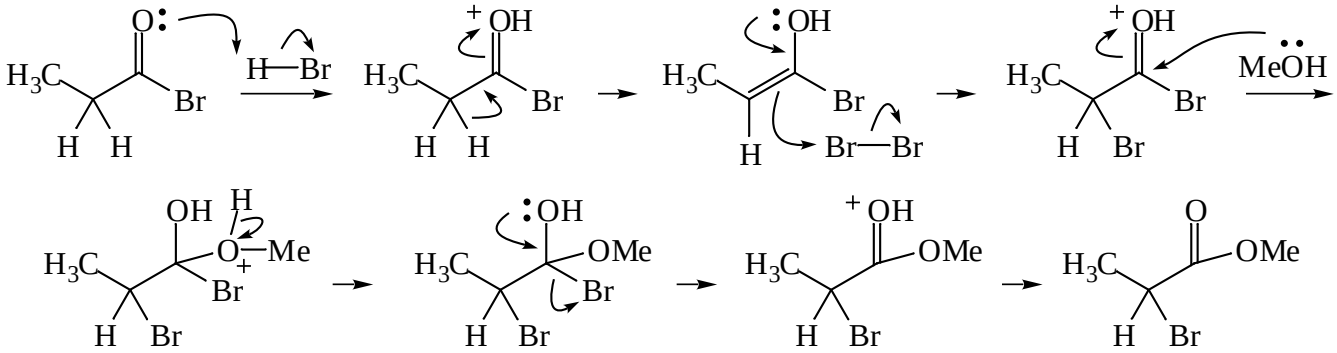




3.17. Under these nearly neutral conditions, it is unclear whether the carbonyl O is protonated before or after attack of N. Either way is acceptable.

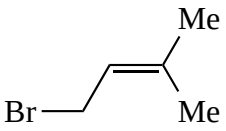


3.18. Two substitutions are occurring here: H to Br, and Br to MeO. Looking at the order of reagents, the first substitution is H to Br. Br_2 is electrophilic, so the α-C of the acyl bromide must be made nucleophilic. This is done by enolization. The substitution of Br with MeO occurs by a conventional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

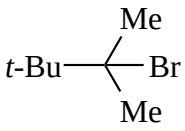


Answers To Chapter 3 End-of-Chapter Problems.

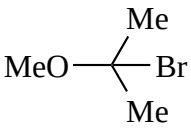
1. (a) In order to compare it directly with the other two carbocations, the carbocation derived from the first compound should be drawn in the resonance form in which the empty orbital is located on the 3° C. It can then clearly be seen that the three carbocations are all 3° carbocations that differ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



2

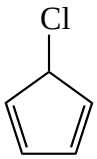


3

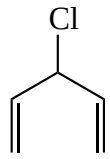


1

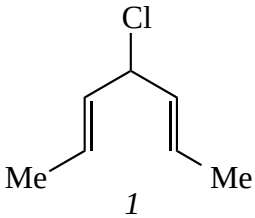
(b) The first compound gives an antiaromatic carbocation. Among the other two, the second compound gives a cation with the electron deficiency delocalized across one 2° and two 1° C's, while the third compound gives a cation with the electron deficiency delocalized across three 2° C's.



3

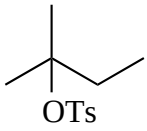


2

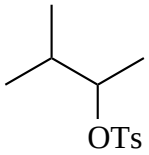


1

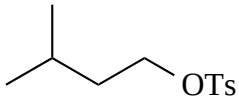
(c) The order of stability of alkyl cations is 3° > 2° > 1°.



1

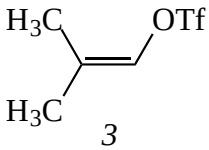


2

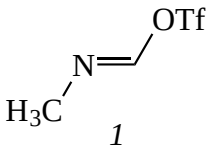


3

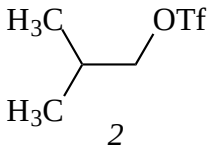
(d) The second compound gives a lone-pair-stabilized carbocation. Among the other two, 1° alkyl carbocations are more stable than 1° alkenyl carbocations.



3

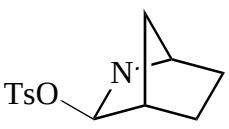


1

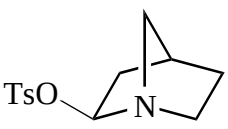


2

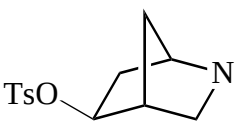
(e) The first compound generates a cation that can be stabilized by the lone pair on N. The second compound generates a cation that cannot be stabilized by the lone pair on N due to geometrical constraints (would form bridgehead π bond, a no-no). Therefore the *inductive* effect of N *destabilizes* the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



1

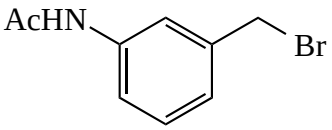


3

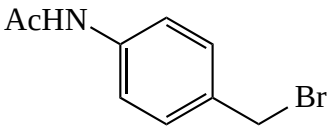


2

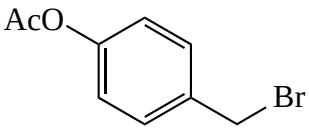
(f) The second and third compounds generate cations that can be directly stabilized by resonance with the lone pairs on the heteroatoms, with N more stabilizing than O, while the cation from the first compound isn't stabilized by resonance with the heteroatom at all.



3

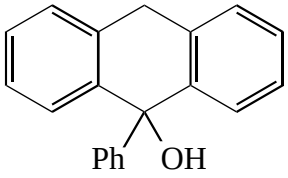


1

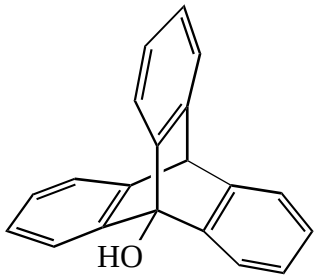


2

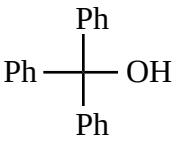
(g) The second compound (a *triptycene*) provides no π stabilization to the corresponding cation, because the p orbitals of the phenyl rings are perpendicular to the empty p orbital. The first compound is more likely to ionize than the third for two reasons. (1) The phenyl rings in first compound are 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



3



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.

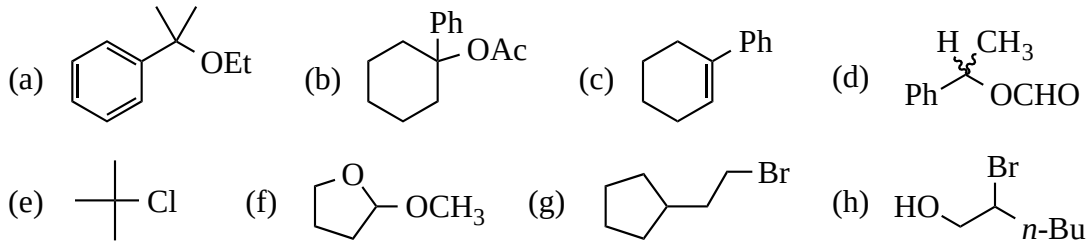
(e) Excellent carbocation, nucleophilic solvent, ∴ S_N1. Here the nucleophile is Cl^-, because addition of H_2O simply gives back starting material. First O is protonated, then OH_2 leaves to give carbocation, then Cl^- adds to carbocation to give the product.

(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

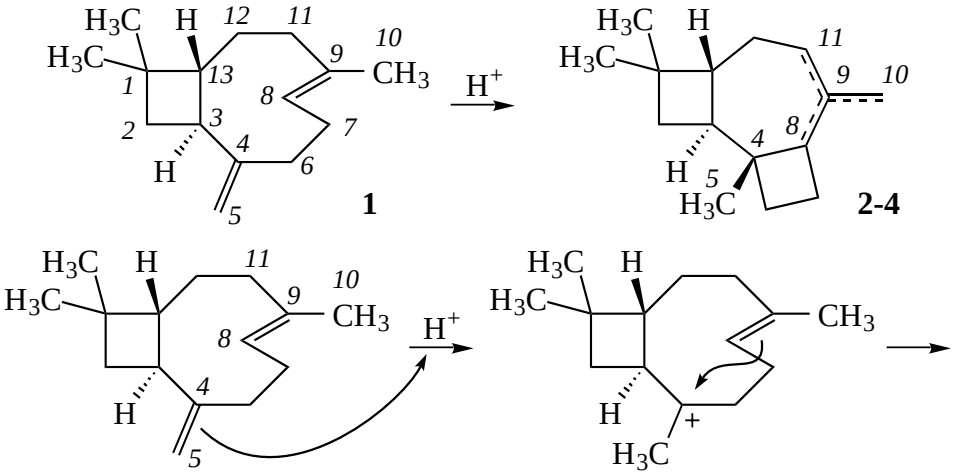
as a leaving group to give an acyclic compound, but entropy favors the loss of the OH group (because two products are formed from one).

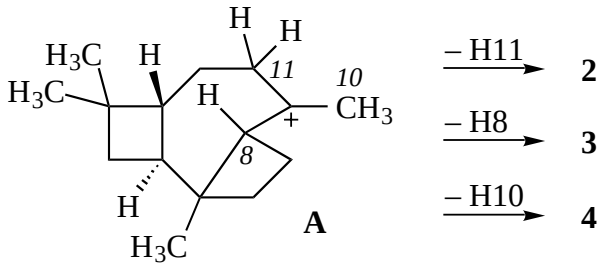
(g) Awful carbocation, so can't be S_N1. Strongly acidic conditions, excellent nonbasic nucleophile, ∴ S_N2. First O is protonated, then Br^- does a nucleophilic displacement of OH_2 to give the product.

(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.)

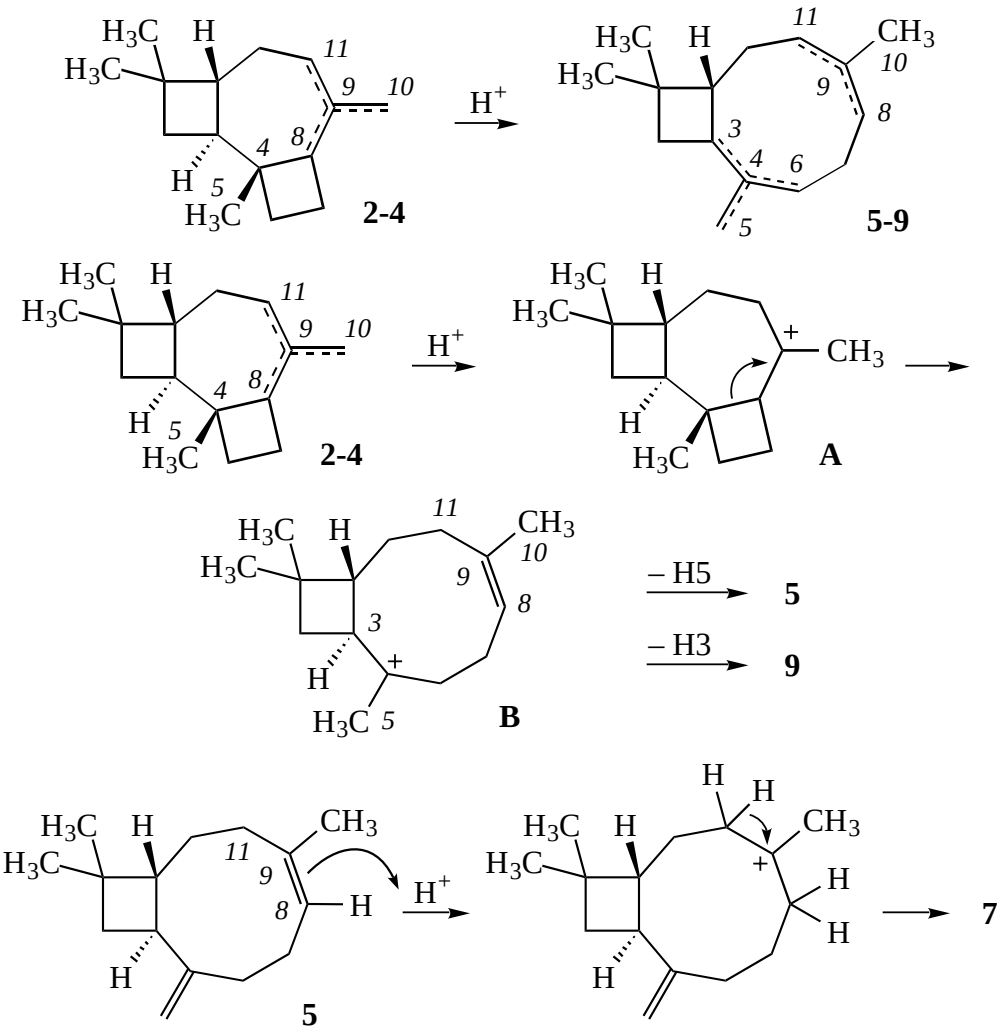


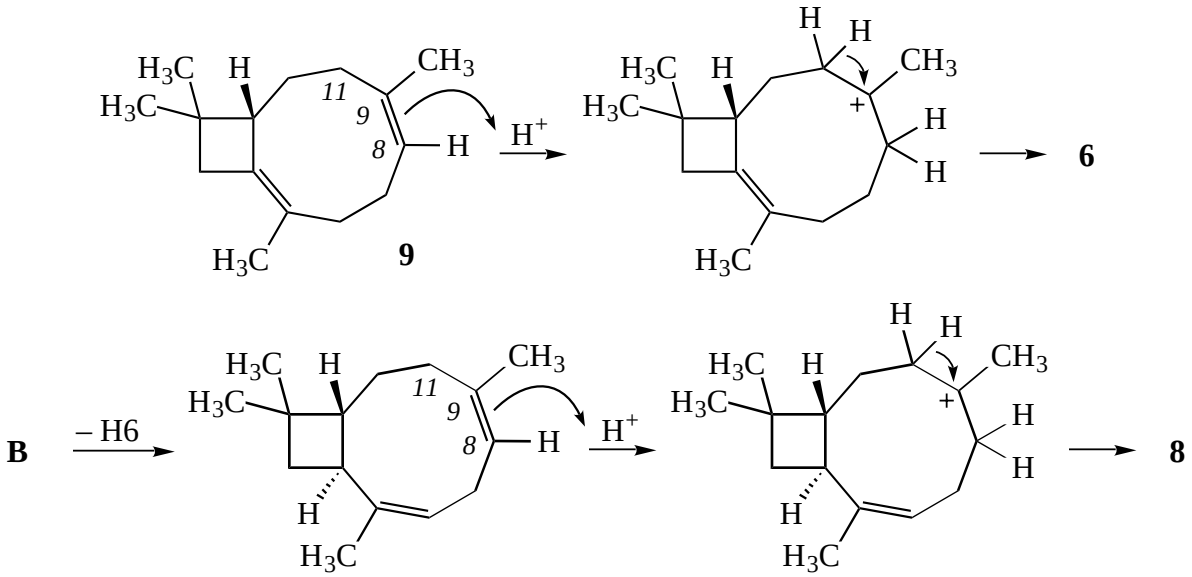
3. Number the C's in **1.** We see that the first set of compounds, **2-4,** are all obtained by formation of a bond between C4 and C8. To make the C4–C8 bond, we could make C4 electrophilic and C8 nucleophilic, or vice versa. If we make C8 electrophilic by protonation of C9, then after attack of C4, 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.



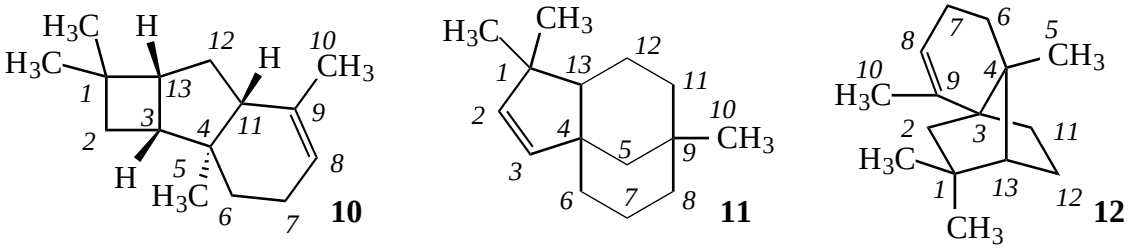


The next set of products, **5-9,** must be formed from **2-4.** To get from **2-4** to **5-9,** we must break the C4–C8 bond again. This is easy to do if we regenerate carbocation **A.** Cleavage of the C4–C8 bond gives a C8=C9 π bond and a carbocation, **B,** at C4. Loss of H^+ from C5 or C3 of **B** 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.**

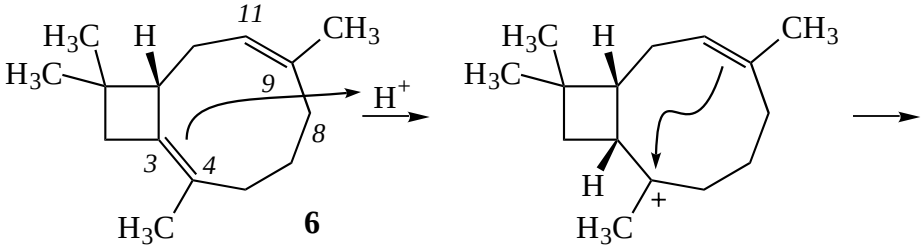


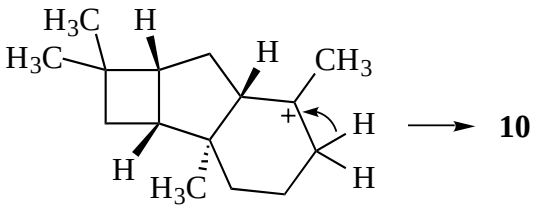


After a while longer, compounds **5-9** are converted into compounds **10-12.** Note that since all of **5-9** are easily interconverted by protonation and deprotonation reactions, any of them could be the precursors to any of **10-12.**



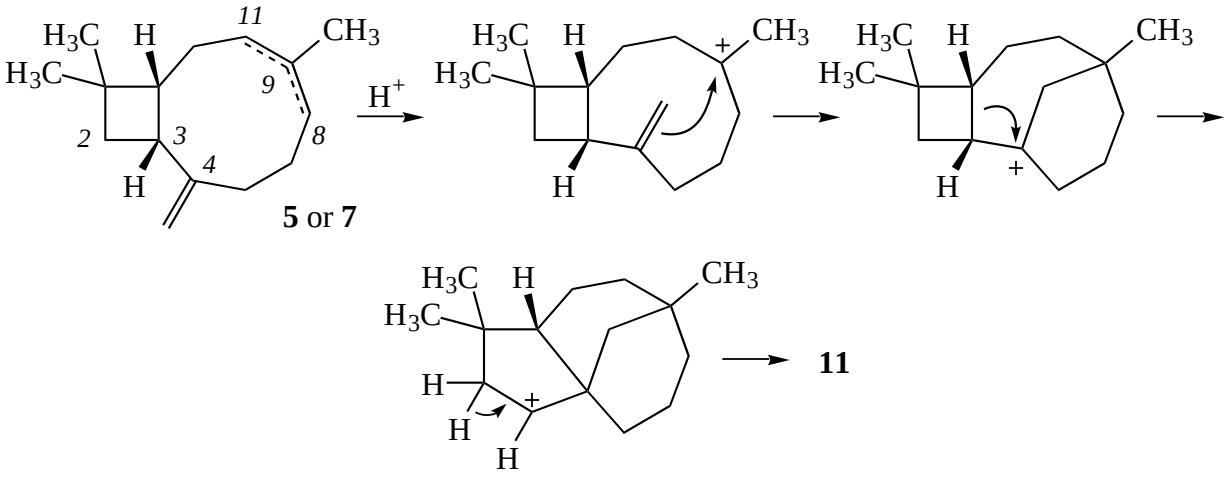
Compound **10** has a new C4–C11 bond. Either C4 is the nucleophile and C11 is the electrophile, or vice versa. Either way, compounds **5** and **9** are excluded as the immediate precursors to **10,** since they both have a saturated C11 that cannot be rendered nucleophilic or electrophilic (except 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

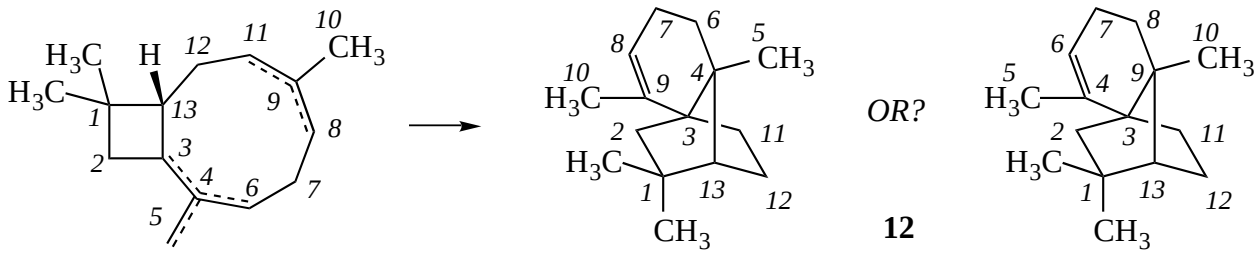
Compound **11** has new bonds at C5–C9 and C13–C4, and the C3–C13 bond is broken. Also, a new C2=C3 π bond is formed. The shift of the C13–C3 bond to the C13–C4 bond suggest a 1,2-alkyl shift. Then loss of H^+ from C2 can give the C2=C3 π bond. So we need to establish a carbocation at C4. We can do this 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

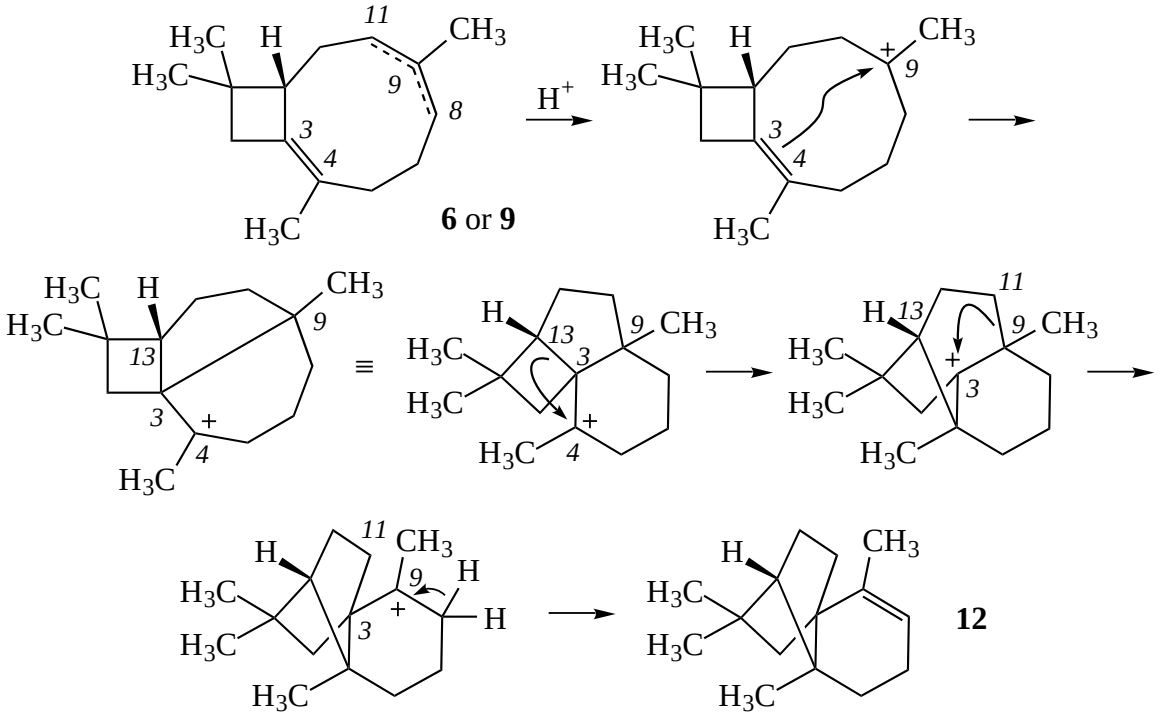
Make a list of make and break for each compound.

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.

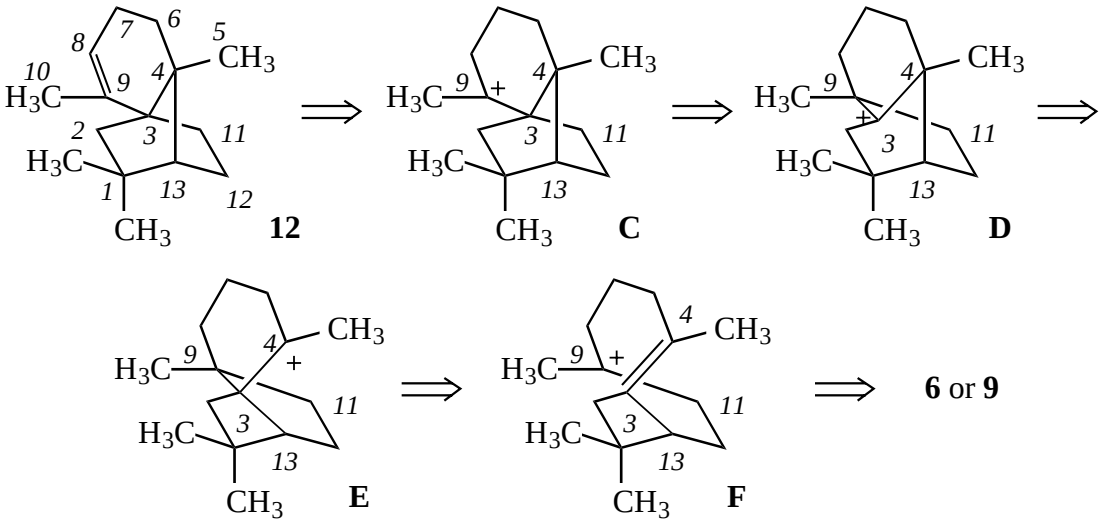
The only difference is that on the right, we need to make C4–C13, while on the left, we need to make C9–C13. Which is better? On the left, the C4–C13 bond can be made and the C3–C13 bond can be broken by a 1,2-shift. This can't be done on the right. Also, in compound **11** we made a C4–C13 bond. Not 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.

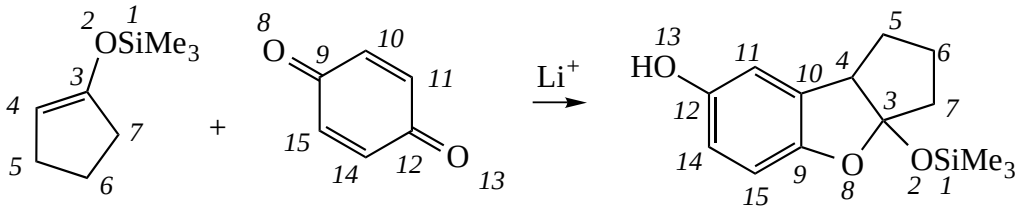


In a deep-seated rearrangement like this, it's sometimes easier to work backwards from the product. The π bond at C8=C9 in **12** suggests that the last step is deprotonation of C8 of a carbocation at C9, **C.** Carbocation **C** might have been formed from carbocation **D** by a 1,2-alkyl shift of C11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

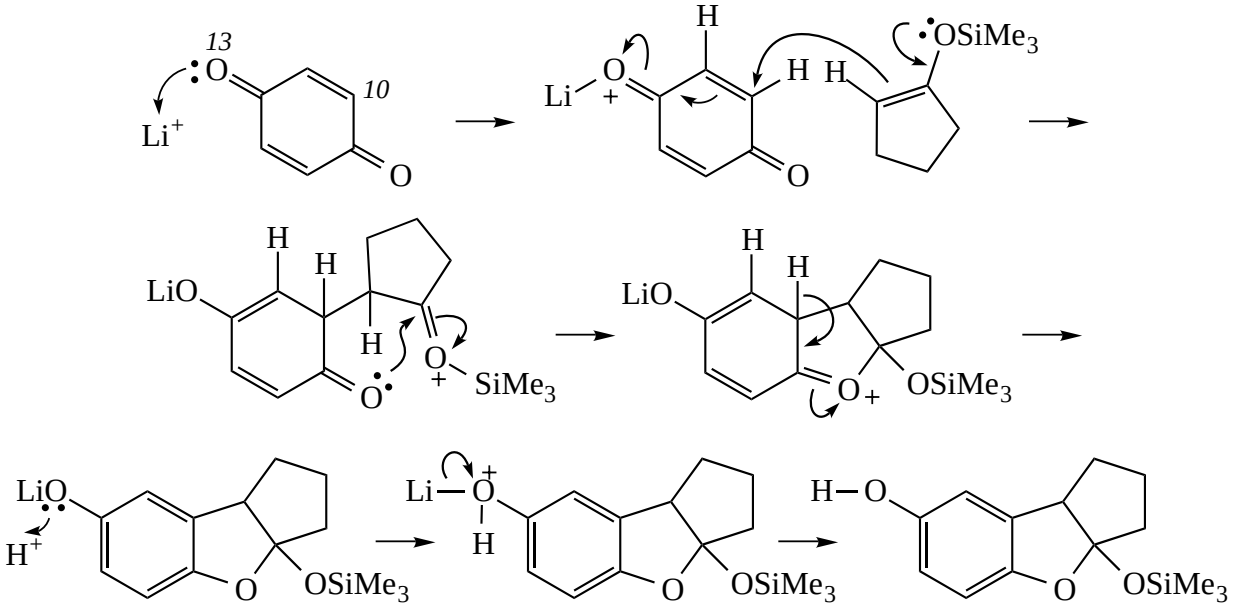
carbocation. The C9 carbocation could have been formed from **6** or **9** by protonation of C11 or C8, respectively.



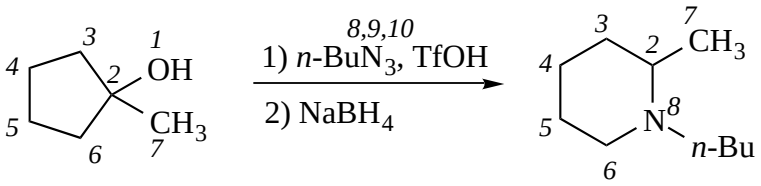
4. (a) Make: C3–O8, C4–C10.



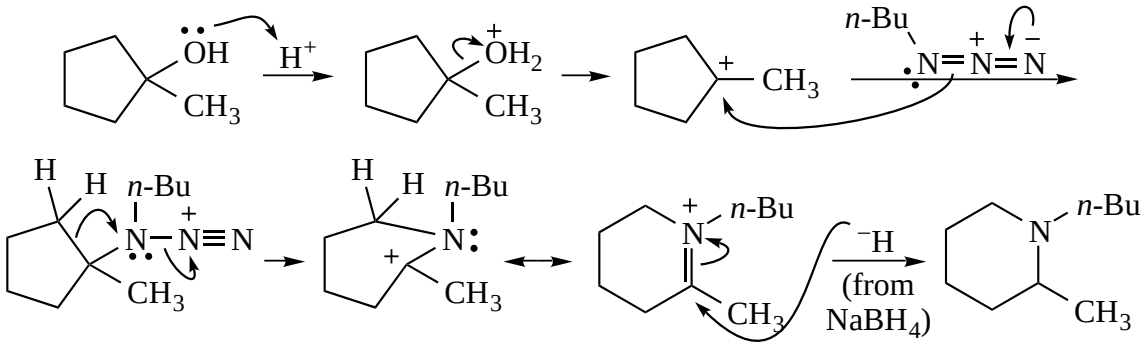
C4 is nucleophilic (enol ether), and C10 is electrophilic. The Lewis acid makes C10 more electrophilic by coordinating to O13. After conjugate addition, O8 traps the C3 carbocation. Proton–Li^+ exchange gives the product.



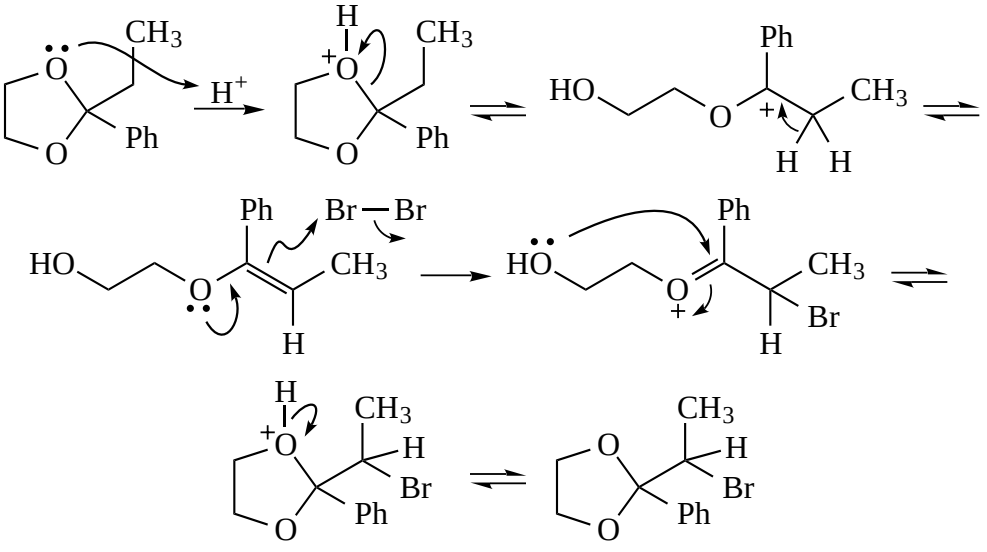
(b) Make: C2–N8, C6–N8. Break: O1–C2, C2–C6.



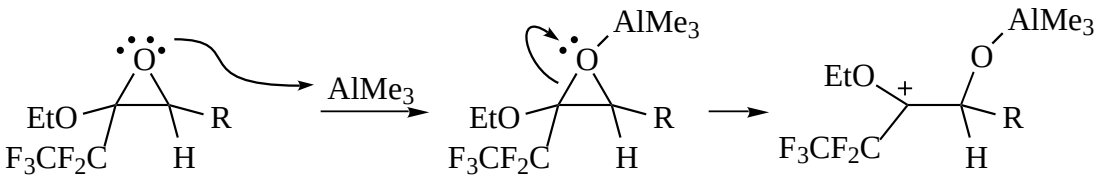
N8 of the azide adds to the carbocation to give an amine with an N_2^+ leaving group attached. Concerted 1,2-migration of C6 from C2 to N8 and expulsion of N_2 gives a N-stabilized carbocation, which is reduced by $NaBH_4$ to give the product.



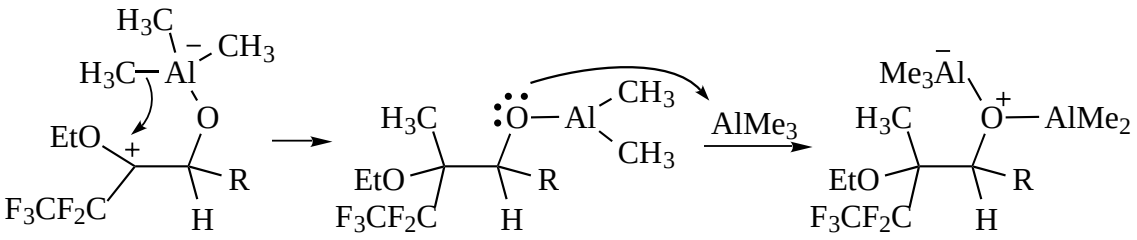
(c) Bromine is an electrophile, so we need to convert the CH_2 group into a nucleophile. This might be done by converting it into an alkene C. There is a leaving group next door, so we can do an E1 elimination to make an enol ether. Another way to look at it: under acidic conditions, acetals are in equilibrium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



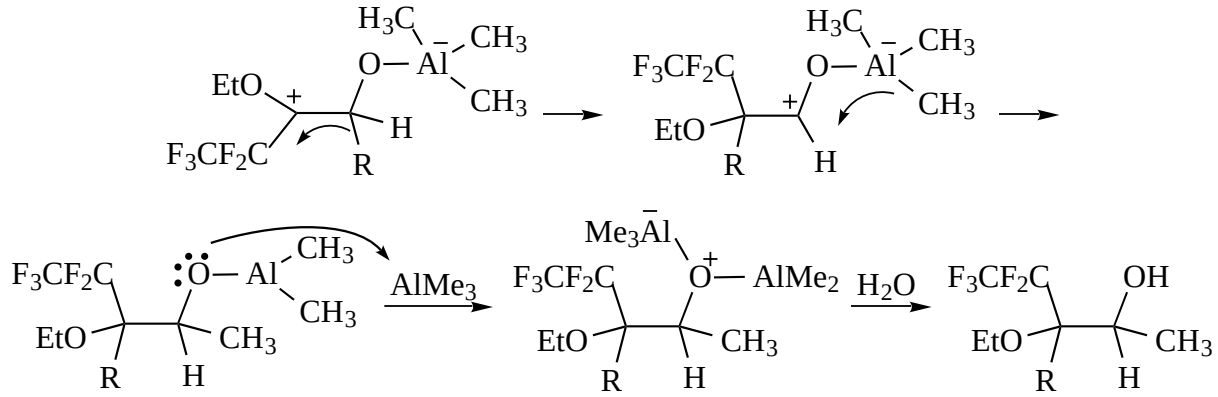
(d) Both reactions begin the same way. $AlMe_3$ is a Lewis acid, so it coordinates to the epoxide O. The epoxide then opens to a carbocation.



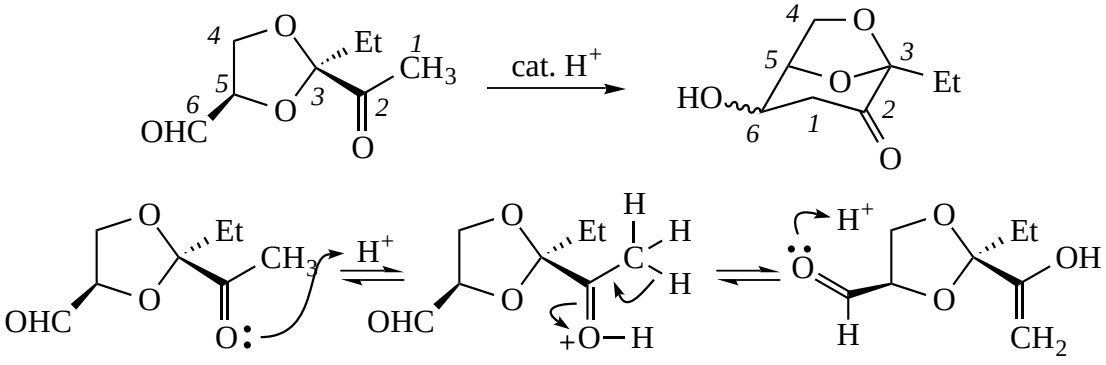
When R= CH_2CH_2Ph, the coordinated Al simply transfers a Me group to the carbocation C (σ bond nucleophile). The O atom then coordinates another equivalent of $AlMe_3$ before the product is obtained upon workup.

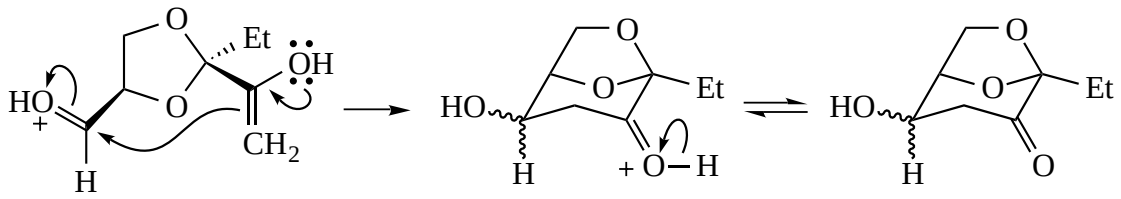


When R= cyclohexyl, the R group migrates (1,2-alkyl shift) to give a new carbocation. (2° Alkyl groups are more prone to migrate than 1° alkyl groups.) After Me transfer to the new carbocation and coordination of another equivalent of $AlMe_3$, workup gives the product.

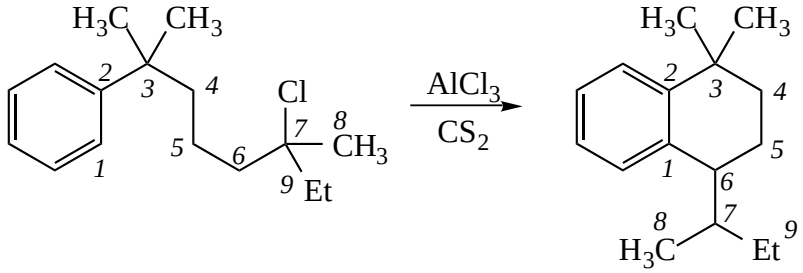


(e) Make: C1–C6. An acid-catalyzed aldol reaction.

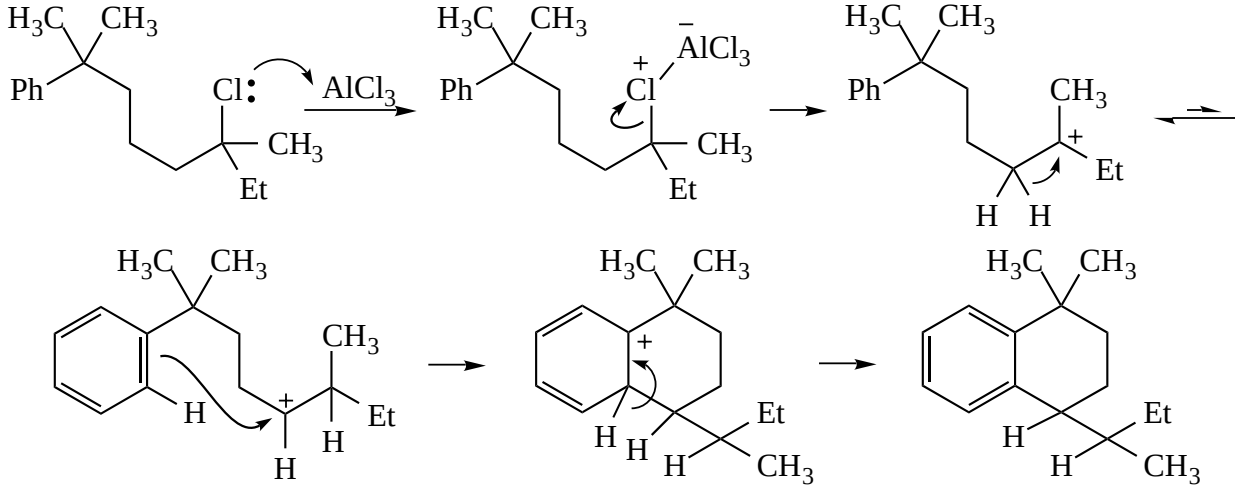




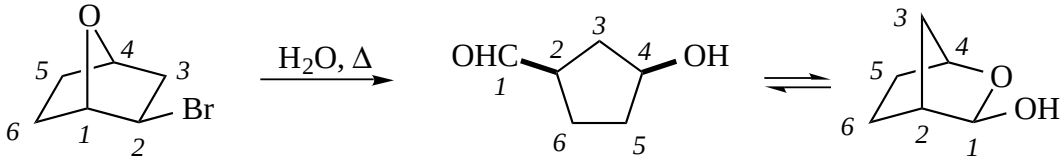
(f) Make: C1–C6. Break: C7–Cl.

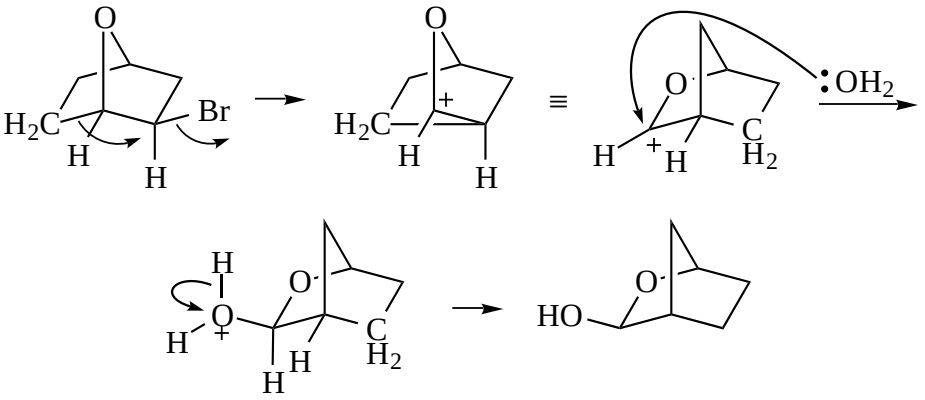


The reaction looks like a simple Friedel–Crafts alkylation, but there is a twist — the leaving group is not on the C which becomes attached to the ring. After formation of the C7 carbocation, a 1,2-hydride shift occurs to give a C6 carbocation. The 1,2-hydride shift is energetically uphill, but the 2°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



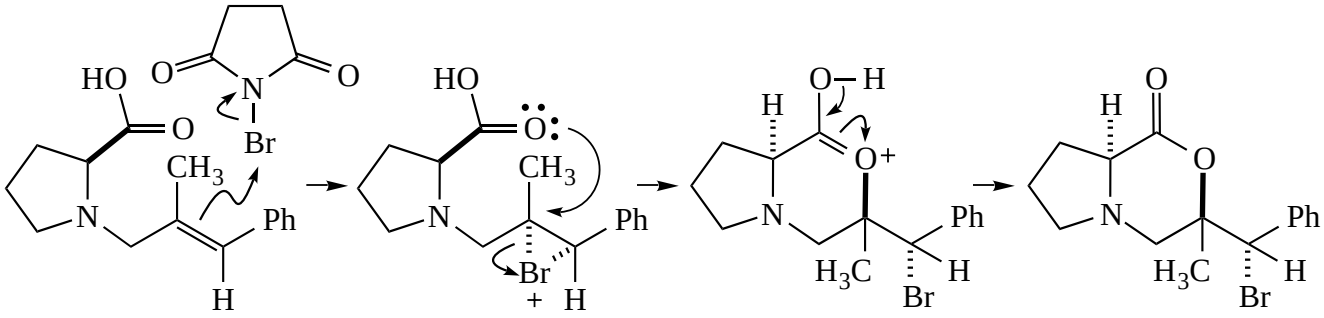
(g) Number the C's! The sequence C2–C3–C4–C5–C6 is identifiable on the basis of the number of H's and O's attached to each C in starting material and product. Make: C2–C6. Break: C1–C6. This pattern is evocative of a 1,2-alkyl shift. The C1–C6 bond is antiperiplanar to the C2–Br bond, so it migrates.



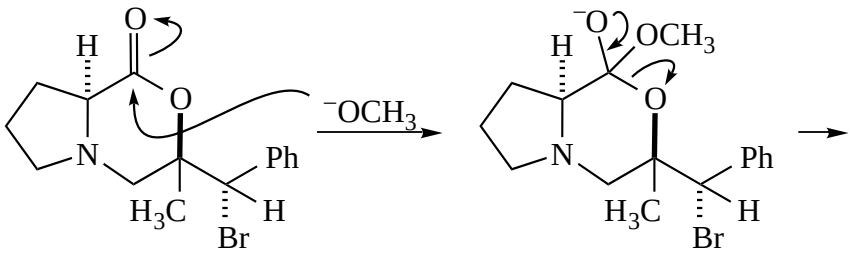


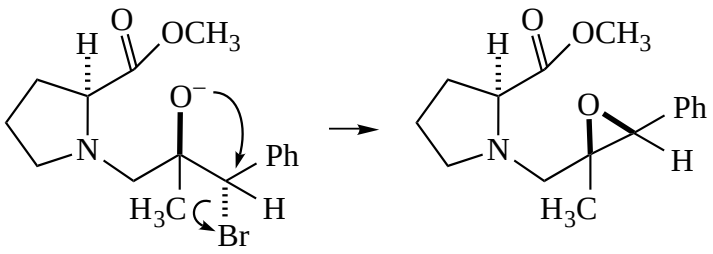
(h) The first step of this two-step reaction takes place under acidic conditions, and the second step takes place under basic conditions. The product from the acidic conditions needs to be a stable, neutral compound.

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.

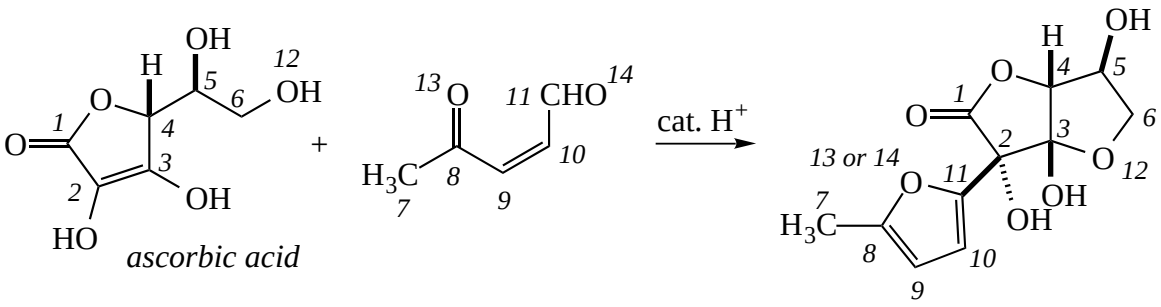


Now MeO^- is added to begin the sequence that takes place under basic conditions. The MeO^- opens the lactone to give a 2-bromoalkoxide, which closes to the epoxide, inverting the other center.

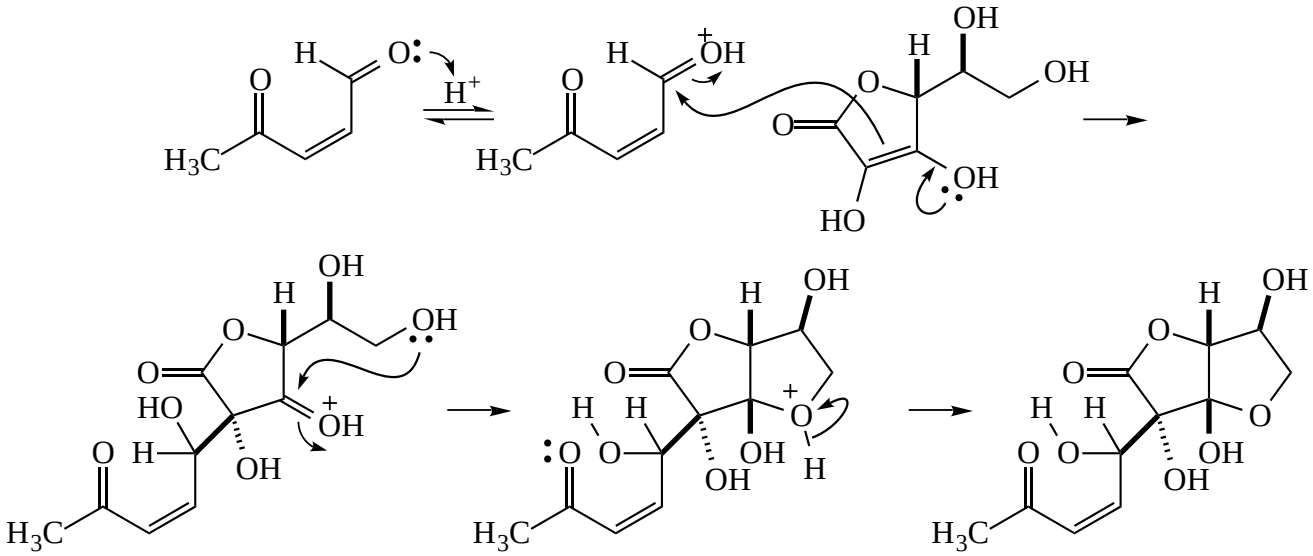




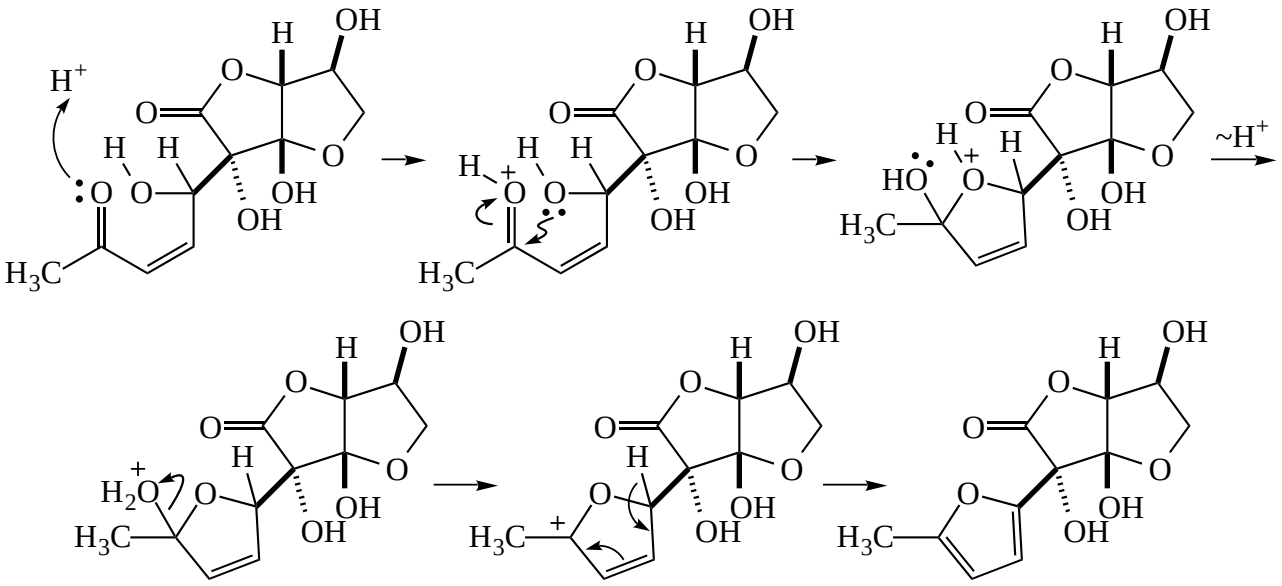
(i) Make: C2–C11, C3–O12, and either C8–O14 or C11–O13. Break: Either C8–O13 or C11–O14.



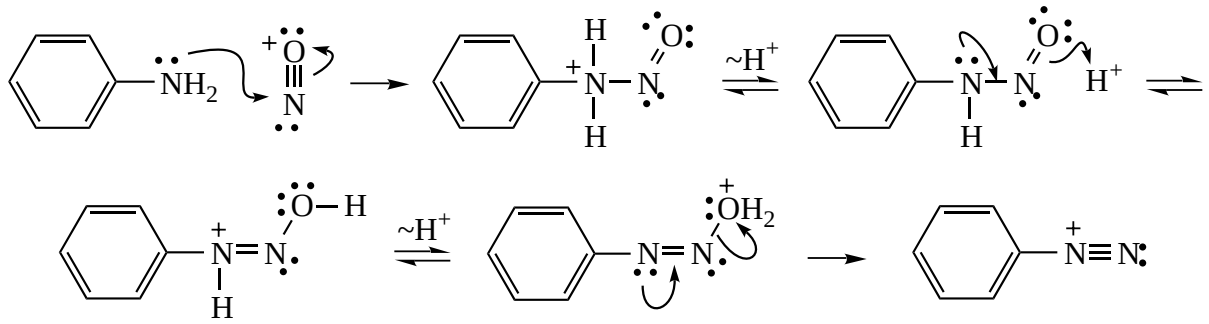
Both C2 and C3 are β to an OH group, and C3 is also β to a carbonyl. Thus C3 is subject to both pushing and pulling, but C2 is subject only to pushing. The first step then is likely attack of nucleophilic C2 on electrophilic C11. Then the C3 carbocation is trapped by O12.



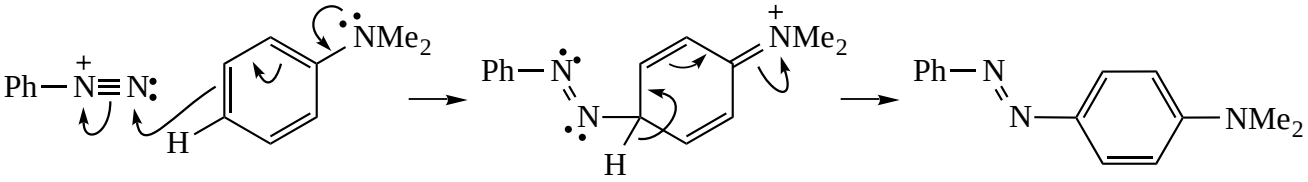
Now the furan ring is formed. Either O13 or O14 must be lost (certainly as H_2O). If O14 is lost, a carbocation at C11 would be required. This carbocation would be destabilized by the electron-withdrawing carbonyl at C18. Better to protonate O14, have O14 attack C8, and then lose O14 as H_2O.



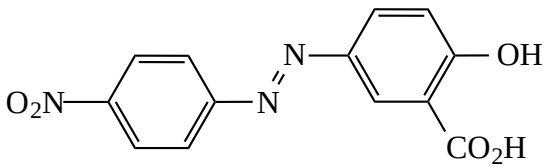
(j) Addition of $NaNO_2$ and HCl to an aniline always gives a diazonium salt by the mechanism discussed in the chapter (Section D.2).



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.

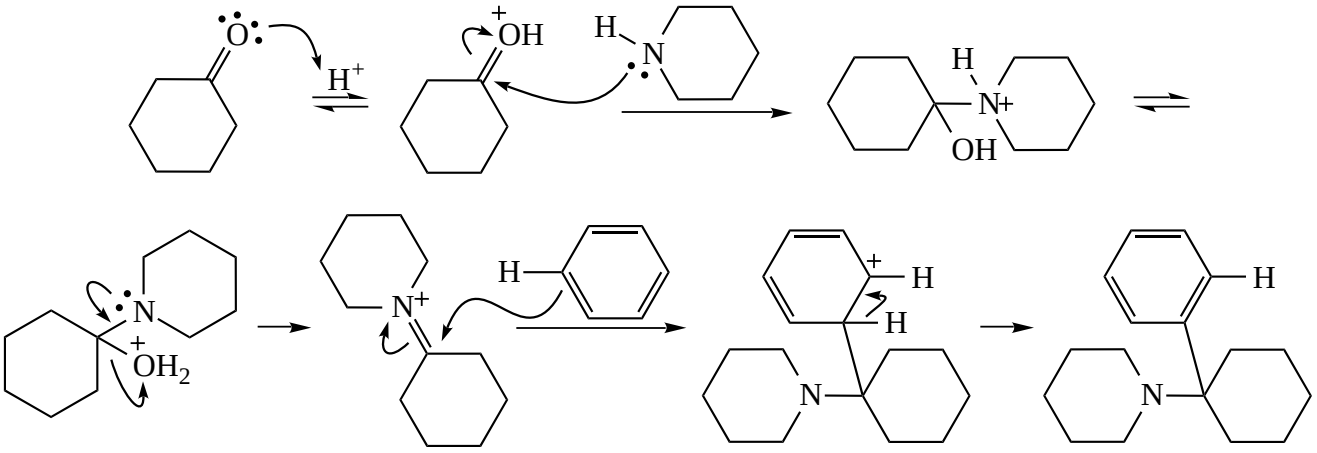


(k) Salicylic acid (as in acetylsalicyclic acid, or aspirin) is 2-hydroxybenzoic acid.

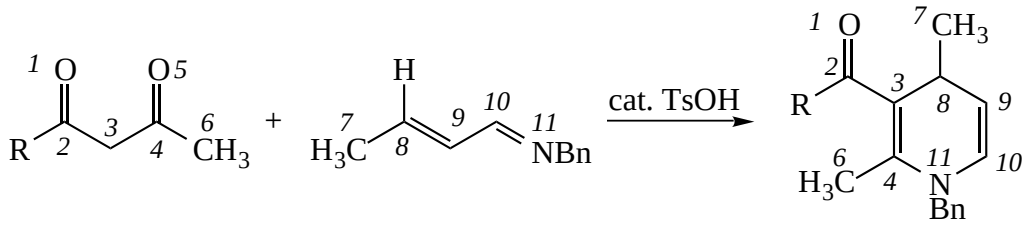


(l) Two new σ bonds are formed in this reaction. In principle either the N–C bond or the C–C bond could

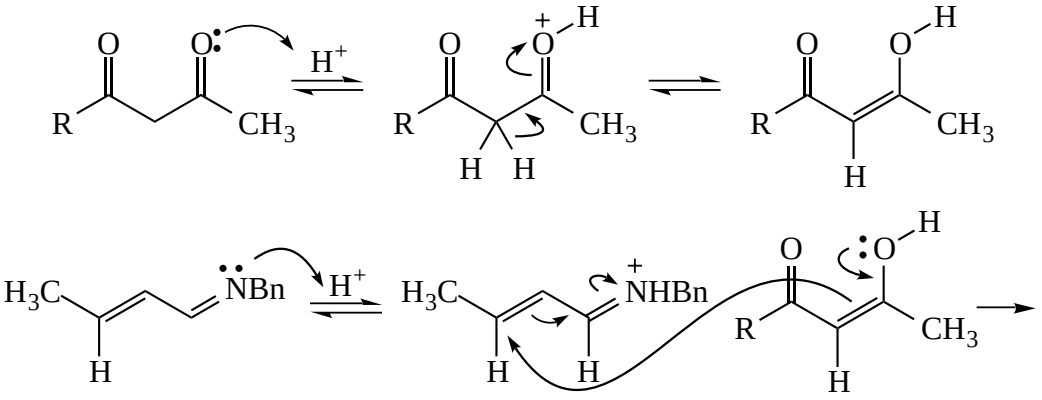
form first. Benzene does not generally react with ketones, while the reaction of an amine with a ketone is very rapid. Therefore the N–C bond forms, and iminium ion is generated, and then electrophilic aromatic substitution occurs to give PCP.

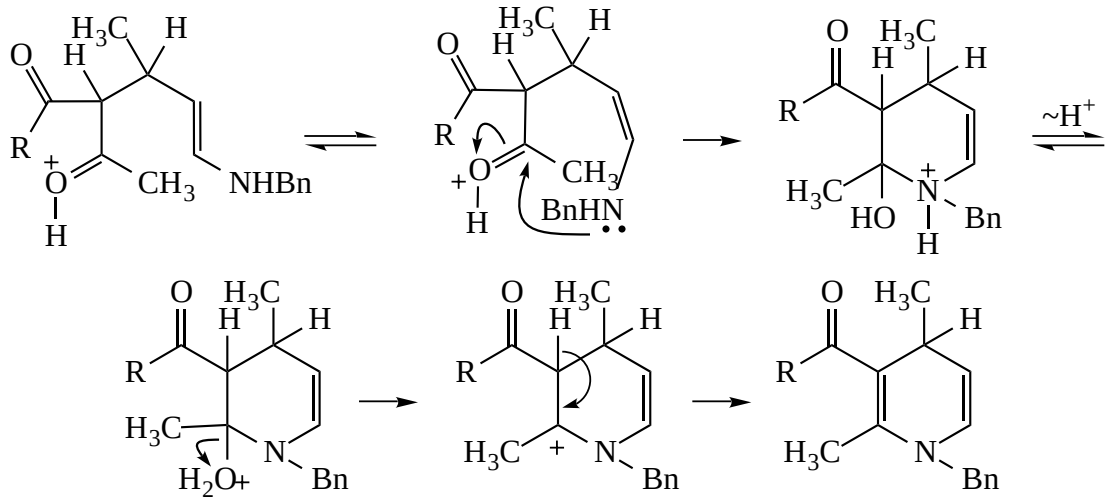


(m) Make: C3–C8, C4–N11. Break: C4–O5.

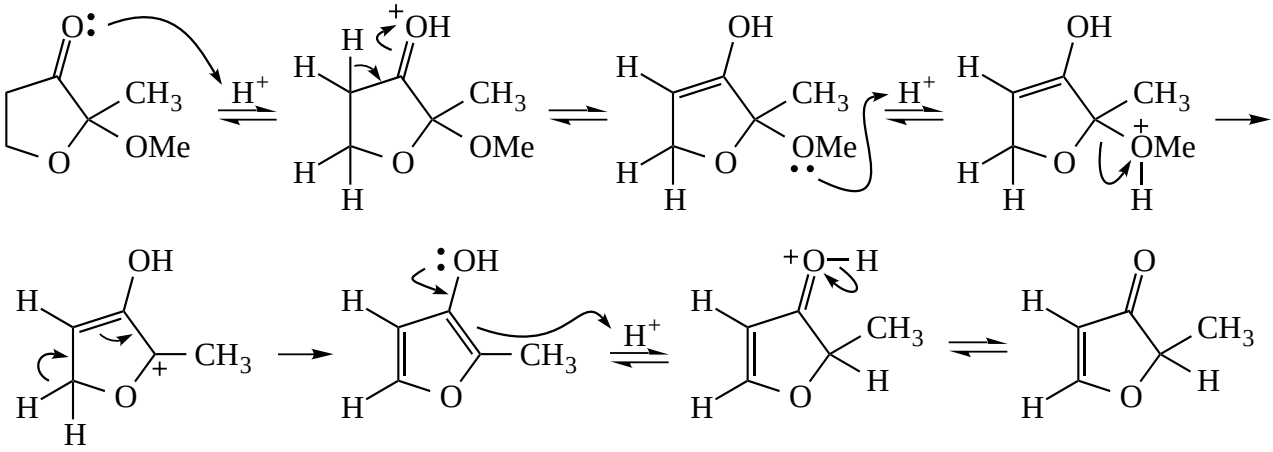


C3 and N11 are nucleophilic, C4 and C8 are electrophilic. Which bond forms first? Once the N11–C4 bond forms, C3 is made much less nucleophilic. So form the C3–C8 bond first (Michael reaction). C3 is made nucleophilic by tautomerization to the enol. The Michael reaction must be preceded by protonation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

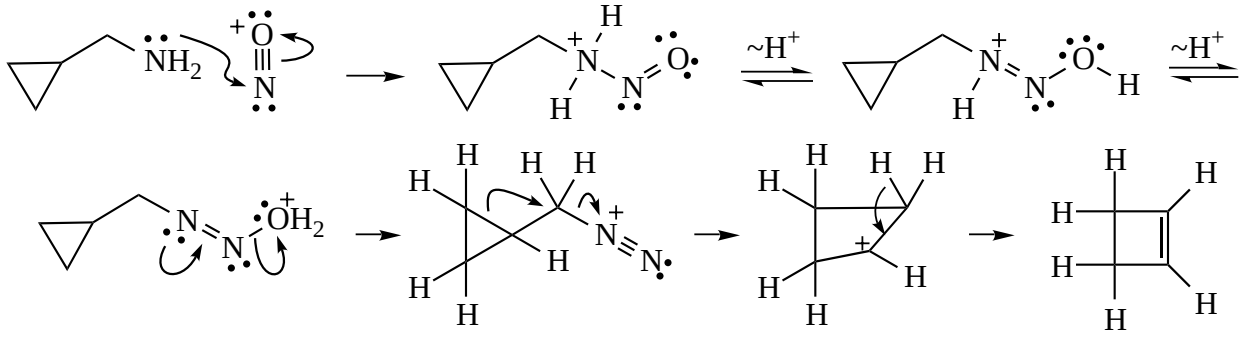




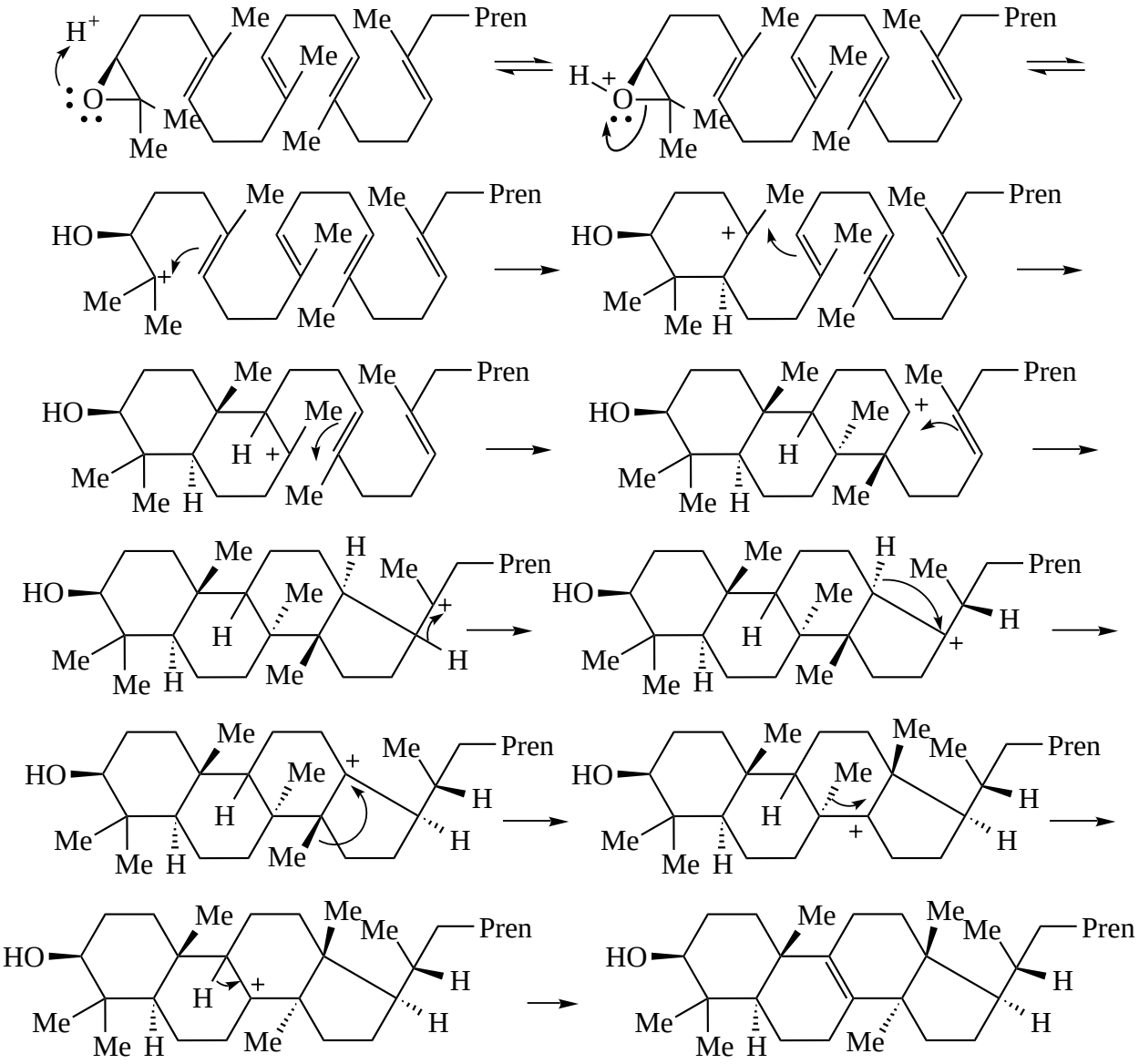
(n) The elements of MeOH are eliminated. However, since there are no H's β to the OMe group, the mechanism must be slightly more complicated than a simple E1. The key is to realize that formation of a carbocation at the acetal C is unlikely to occur with the keto group present. Under acidic conditions,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



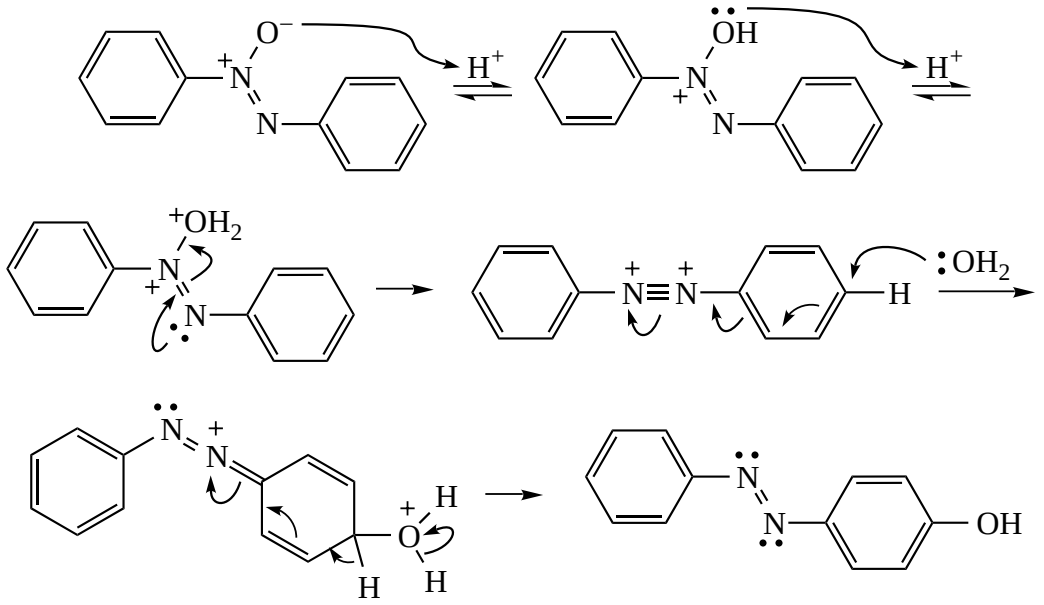
(o) Nitrous acid converts primary amines into diazonium salts RN_2^+. The N_2 group is an excellent leaving group. Formation of the carbocation followd by 1,2-alkyl migration gives a more stable carbocation, which loses H^+ to give cyclobutene. Alternatively, α-elimination could occur from the diazonium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



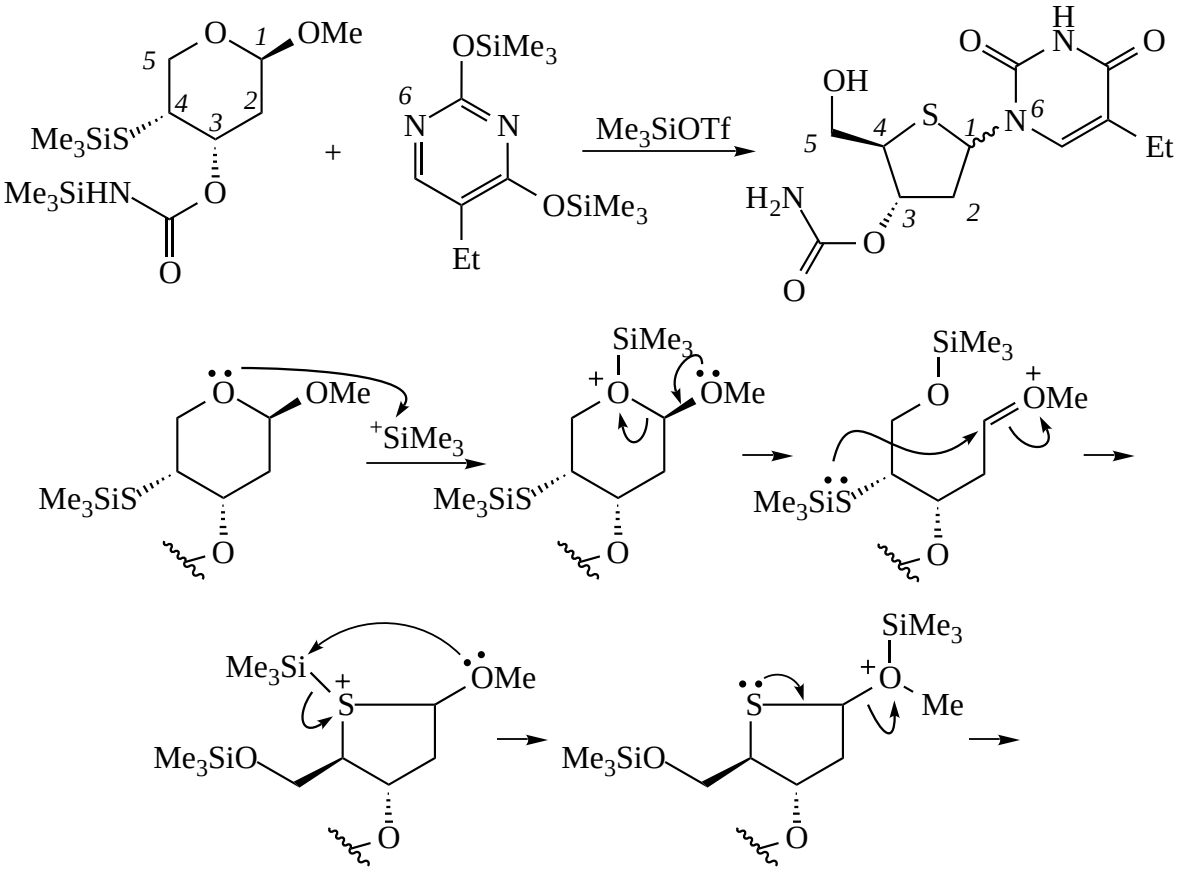
(p) The most basic site is the epoxide O. Protonation followed by a very facile ring opening gives a 3° carbocation. A series of additions of alkenes to carbocations follows, then a series of 1,2-shifts. The additions and 1,2-shifts have been written as if they occur stepwise, but some or all of them 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.

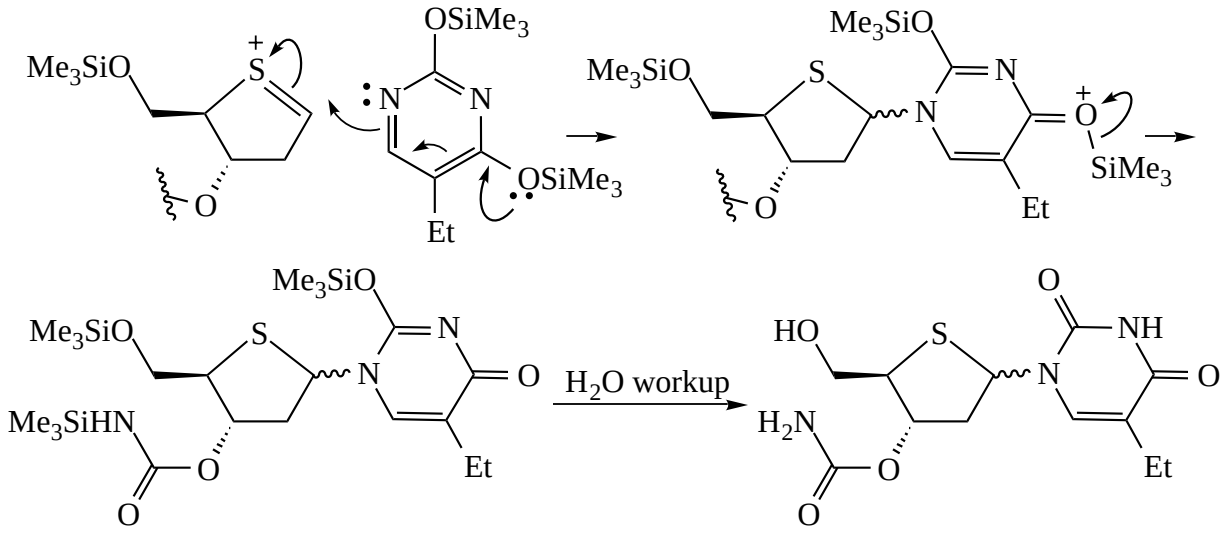


(q) The scrambling of the ^{15}N label suggests a symmetrical intermediate in which the two N's are equivalent. Incorporation of ^{18}O from H_2O suggests that a nucleophilic aromatic substitution is occurring. Double protonation of O followed by loss of H_2O gives a very electrophilic, symmetrical dicationic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

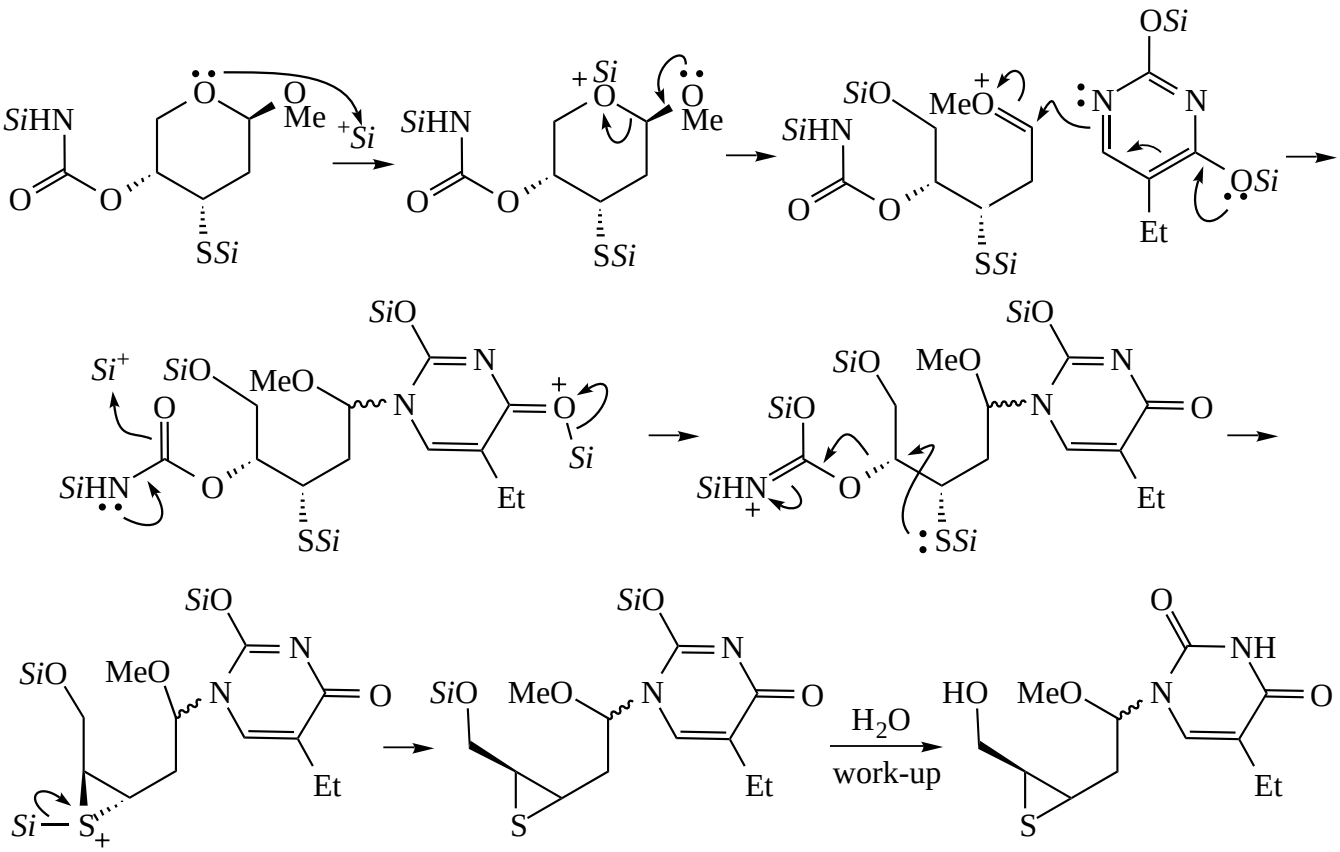


(r) (1) The two C1–O bonds undergo substitution with C1–S and C1–N6 bonds. Under these Lewis acidic conditions, and at this secondary and O-substituted center, the substitutions are likely to proceed by an S_N1 mechanism. The order of the two substitutions is not clear.

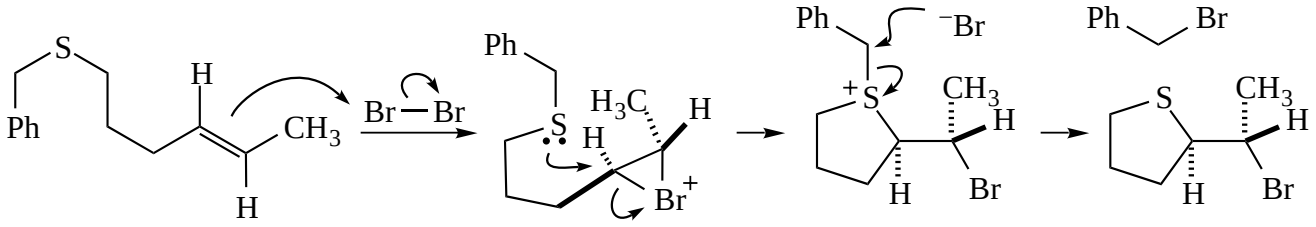




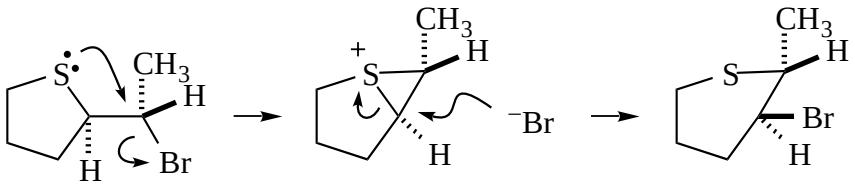
(2) Now only the endocyclic C1–O bond undergoes substitution, but the C4–O bond undergoes substitution with a C–S bond. In the previous problem we had S attack the C1 carbocation to give a five-membered ring. In the present problem, this would result in the formation of a four-membered ring, so the external 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* = $SiMe_3$.



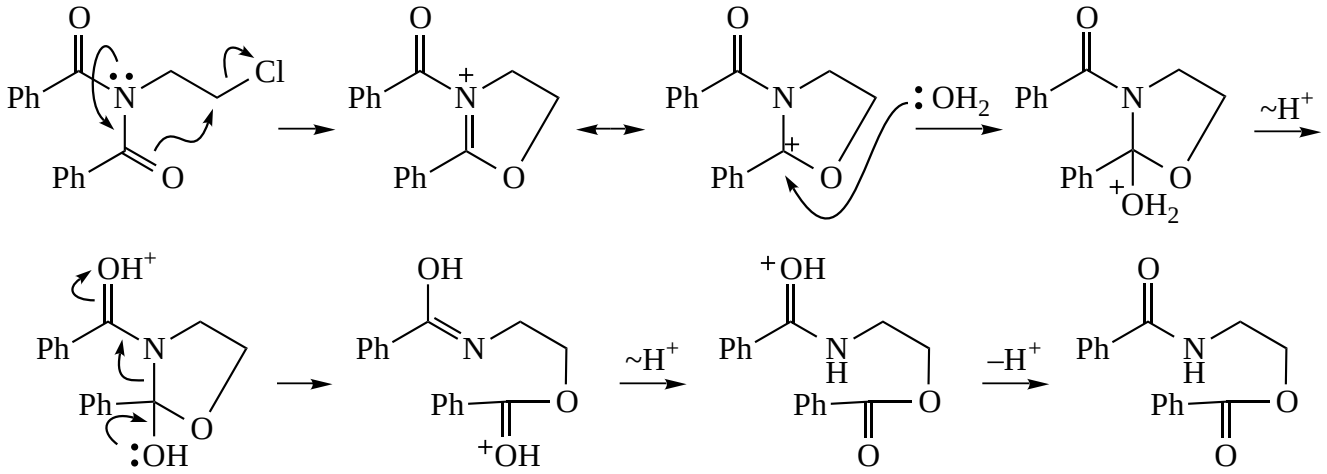
(s) Five-membered ring formation proceeds through a bromonium ion intermediate.



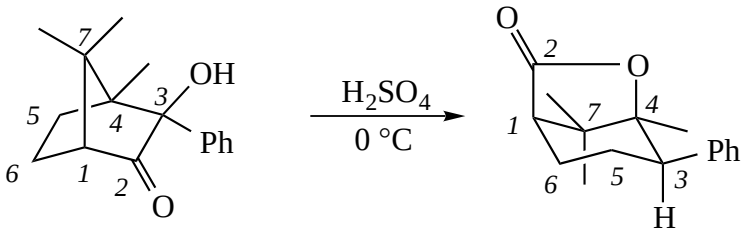
The five-membered ring can convert to the six-membered ring by two S_N2 displacements.



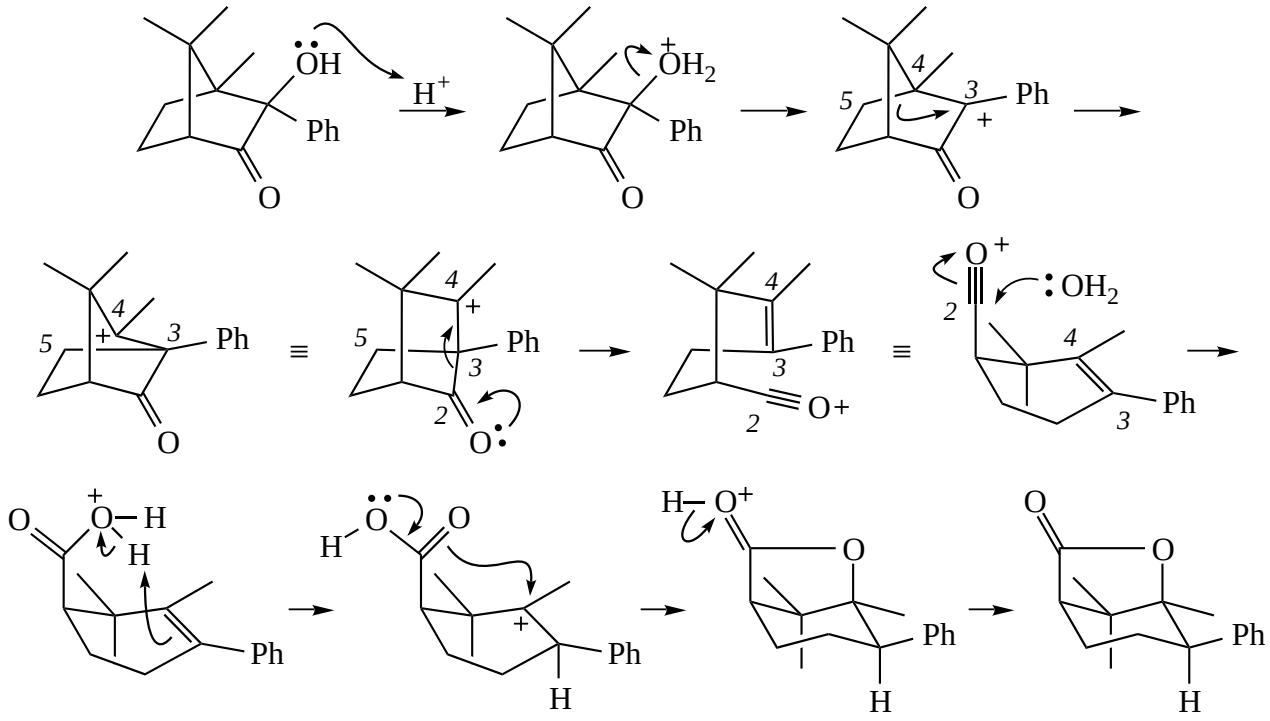
(t) The dependence of the rate of the reaction on the length of the alkyl chain suggests that an *intramolecular* reaction occurs between the nucleophilic O and the electrophilic C attached to Cl.



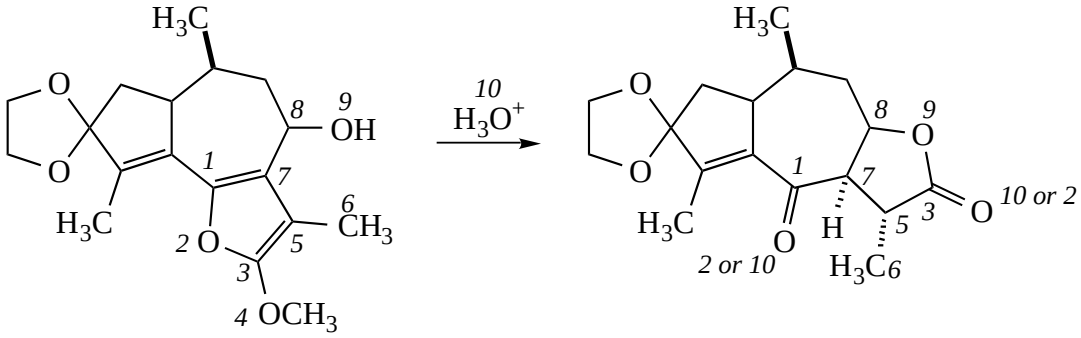
(u) The key atoms to recognize for numbering purposes are C7, C4, and C3. Then the others fall into place. Break: C2–C3, C4–C5. Make: C3–C5.



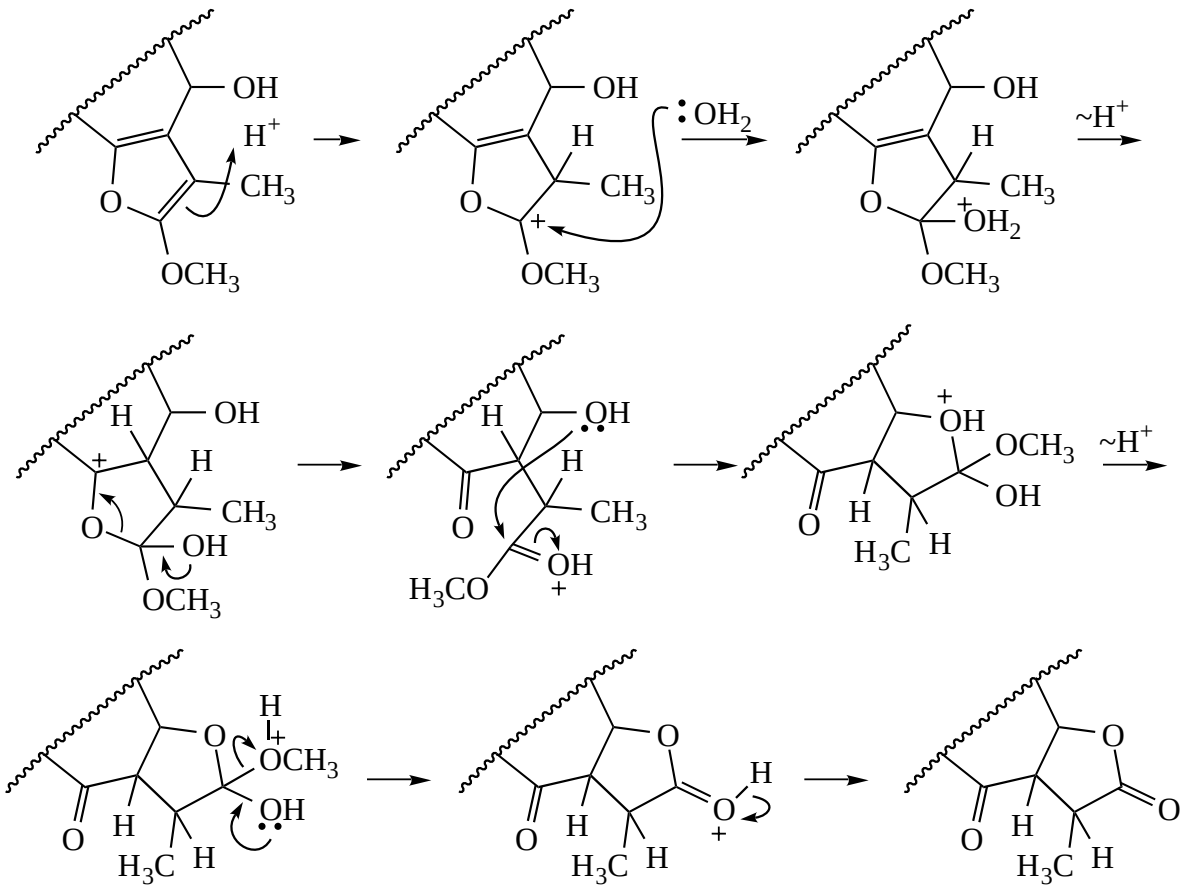
The cleavage of C5–C4 and formation of C5–C3 suggests that we have a 1,2-alkyl migration of C5 from C4 to a cationic C3. Then the electrons in the C2–C3 bond can move to form a new π bond between C3 and C4, leaving a stabilized acylium ion at C2. After addition of H_2O to the acylium ion, an acid-catalyzed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



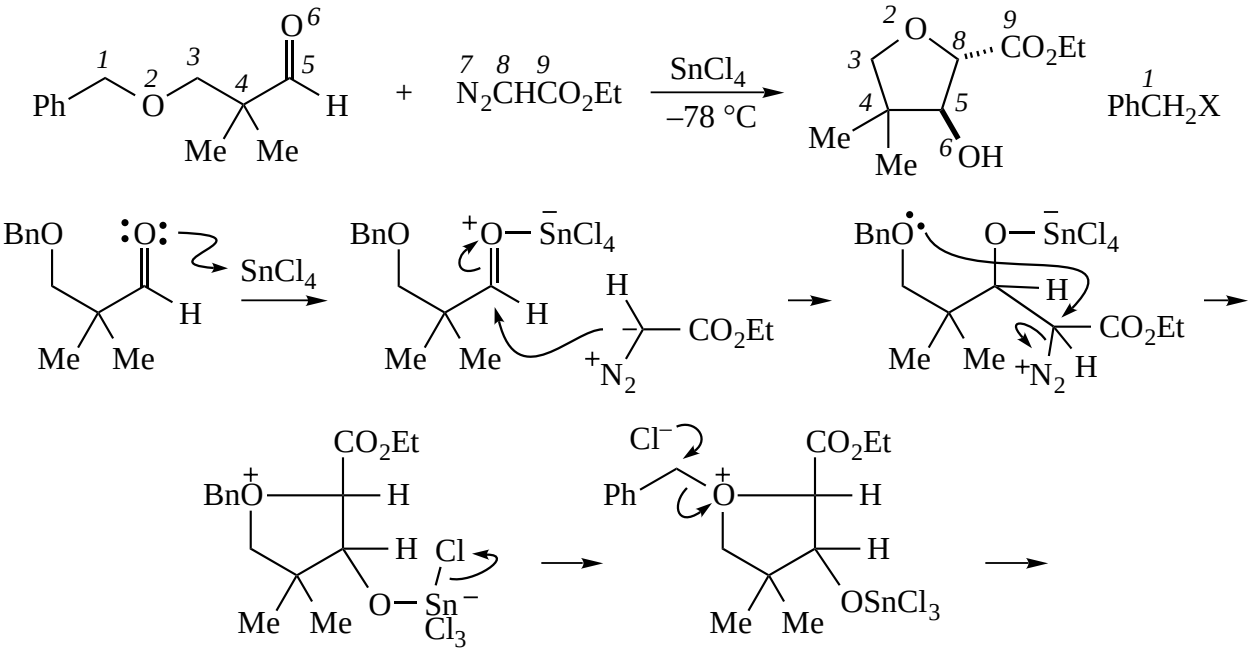
(v) The OCH_3 group is lost, and an OH group is gained. Whereas in the starting material C1 and C3 are attached to the same O, in the product they are attached to different O's. It is not clear whether O2 remains attached to C1 or C3. Make: O9–C3, O10–C3; break: C3–O4, C3–O2. *OR* make: O9–C3, O10–C1;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

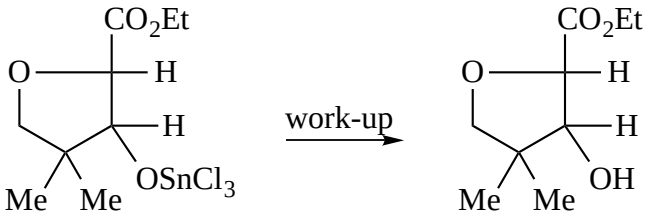


The first step is protonation; since all of the C–O bonds to be broken are C(sp^2)–O bonds, the direct ionization of a C–O bond won't occur, so protonating O is unproductive. Both C5 and C7 need to gain a bond to H; protonation of C5 gives the better carbocation. Water can add to make the C3–O10 bond.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

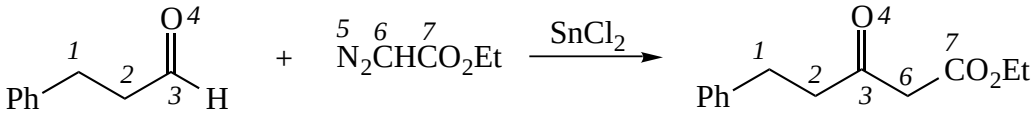


(w) Make: O2–C8, C5–C8. Break: C8–N, C1–O2. C8 is nucleophilic. $SnCl_4$ coordinates to O6 to make C5 more electrophilic, and C8 attacks C5. Then O2 circles around to displace N_2 from C8. Finally, Cl^- from $SnCl_4$ can come back and displace O2 from C1. The stereochemistry of the product is thermodynamically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

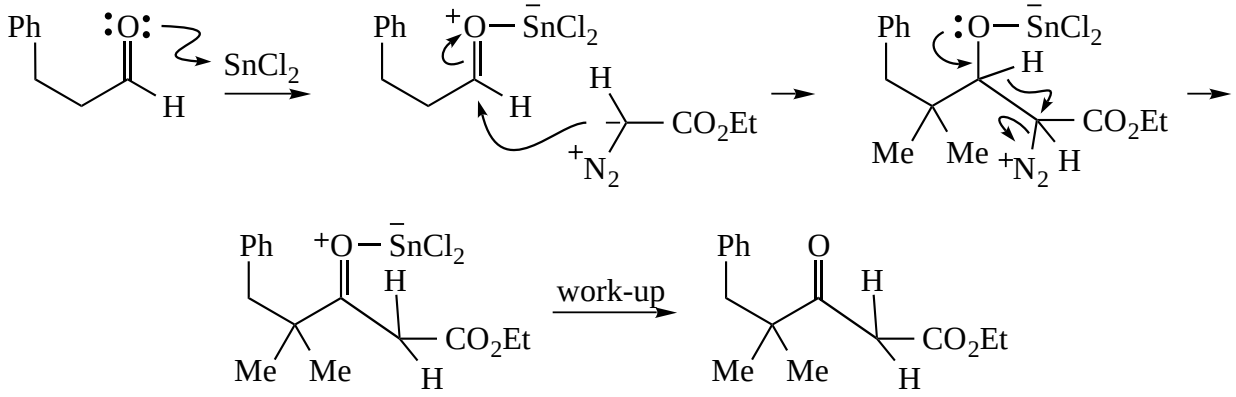




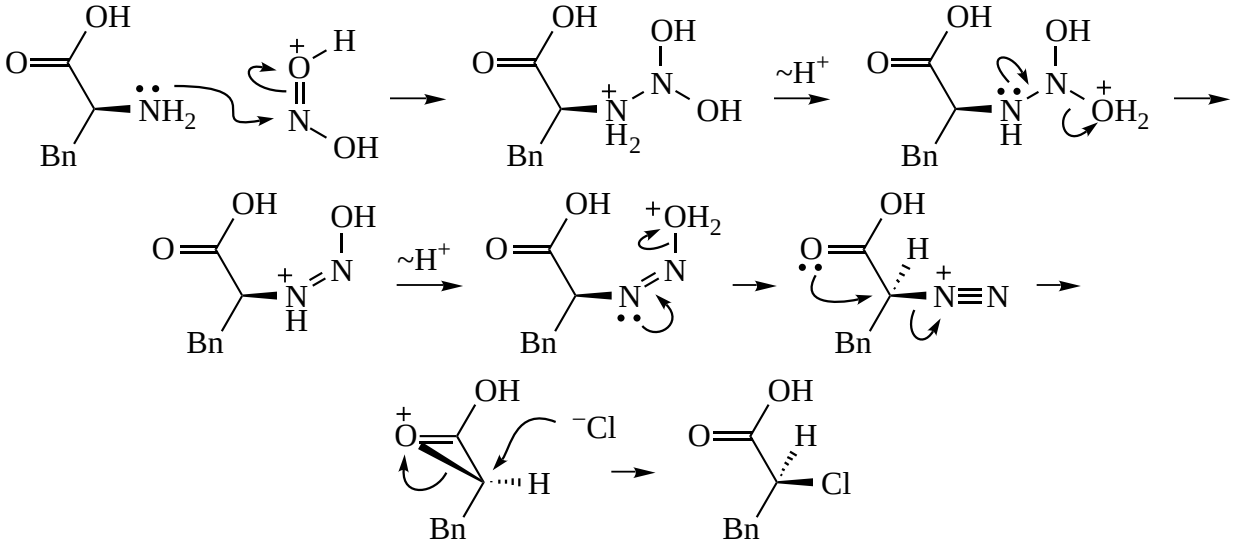
(x) Make: C3–C6. Break: C6–N5.



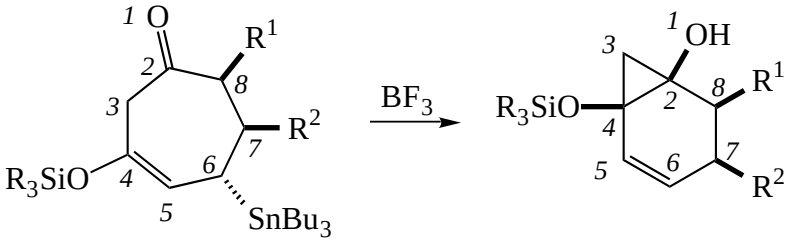
Reaction starts off the same way as last time. After addition to the carbonyl, though, a 1,2-hydride shift occurs with expulsion of N_2 to give the product after workup.



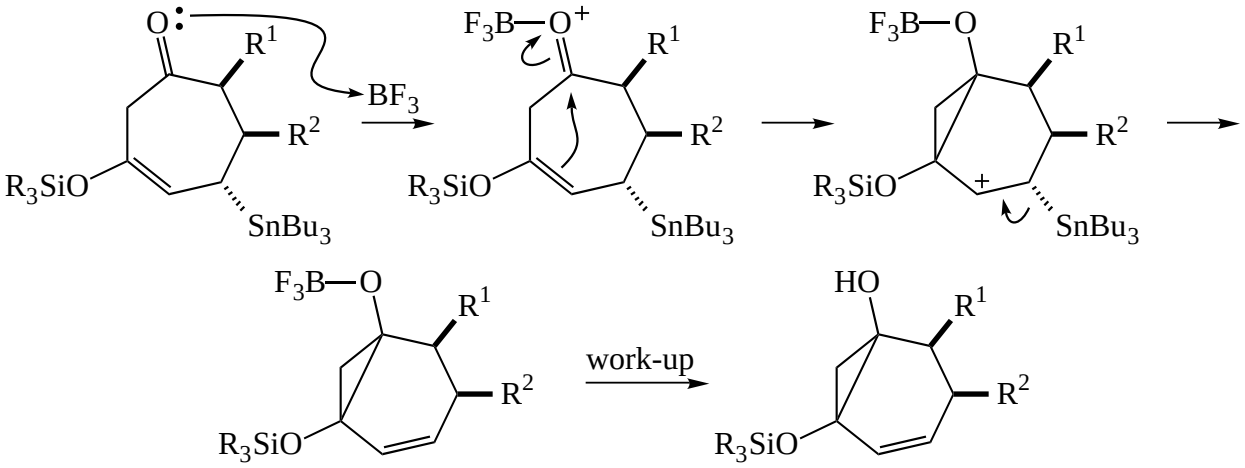
(y) The stereochemistry tells you that neither a simple S_N1 nor an S_N2 mechanism is operative. Two S_N2 substitutions would give the observed result, however. When 1° amines are mixed with HNO_2, a diazonium ion is formed. Intramolecular S_N2 substitution by the carbonyl O gives a lactone, and then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



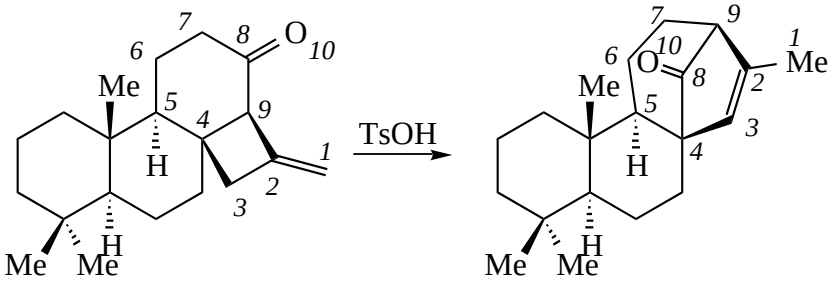
(z) Make: C2–C4. Break: C6–Sn.



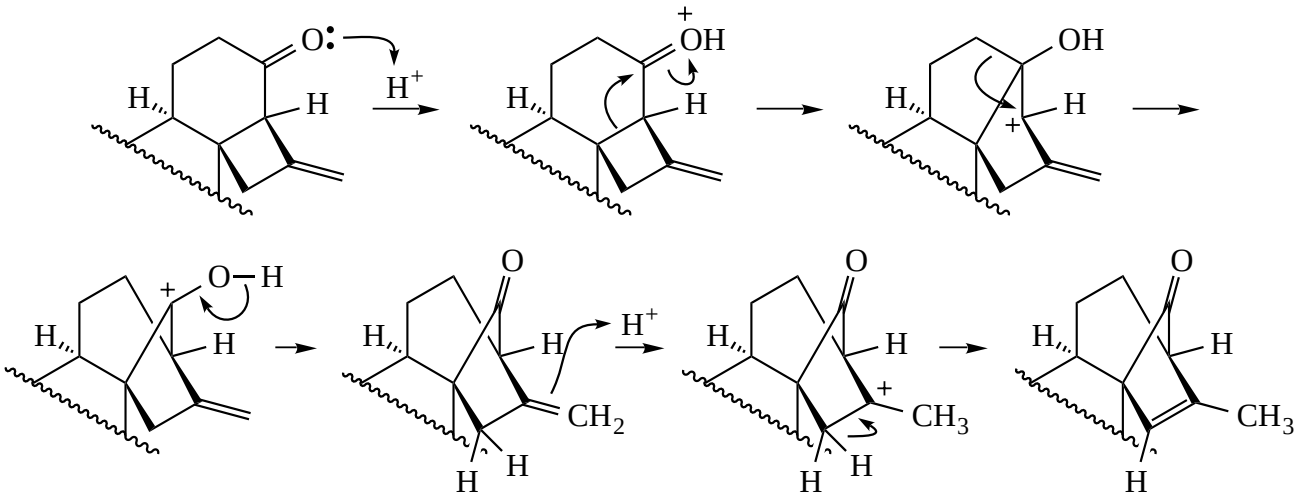
C2 is electrophilic, especially after BF_3 coordinates to it. C4 can then act as a nucleophile, making C5 carbocationic. Fragmentation of the C6–Sn bond gives the product.



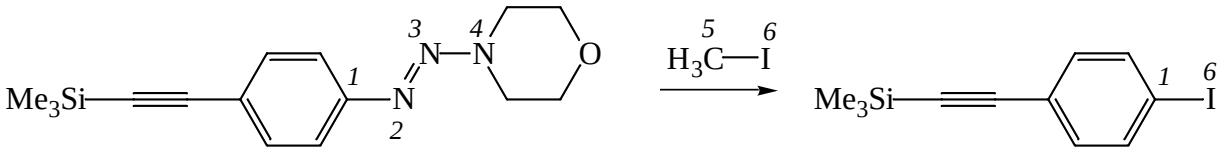
(aa) Numbering correctly is key. C4 through C7 are clear. The Me group in the product must be C1, and it's attached to C2. The rest follow. Make: C7–C9, C4–C8. Break: C7–C8, C4–C9.



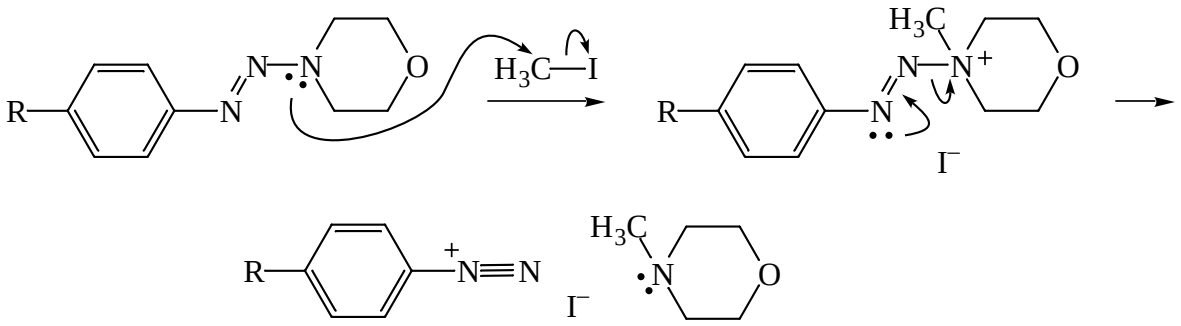
First step is protonation of O10 to make C8 electrophilic. Then a shift of C4 from C9 to C8 occurs to give a cation at C9. This is followed by a shift of C7 from C8 to C9. Deprotonation of O10, protonation of C1, and deprotonation of C3 give the product.



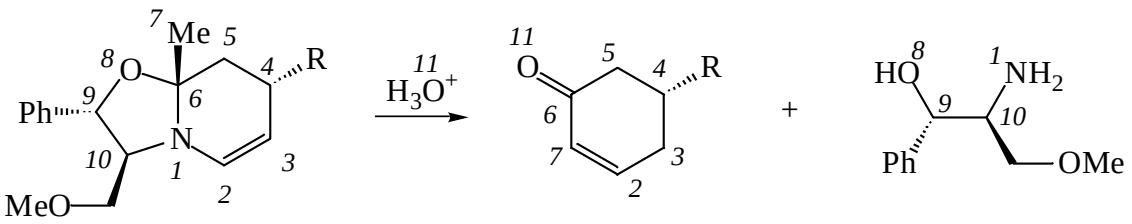
(bb) Make: C1–I6. Break: C1–N2, C5–I6.



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.

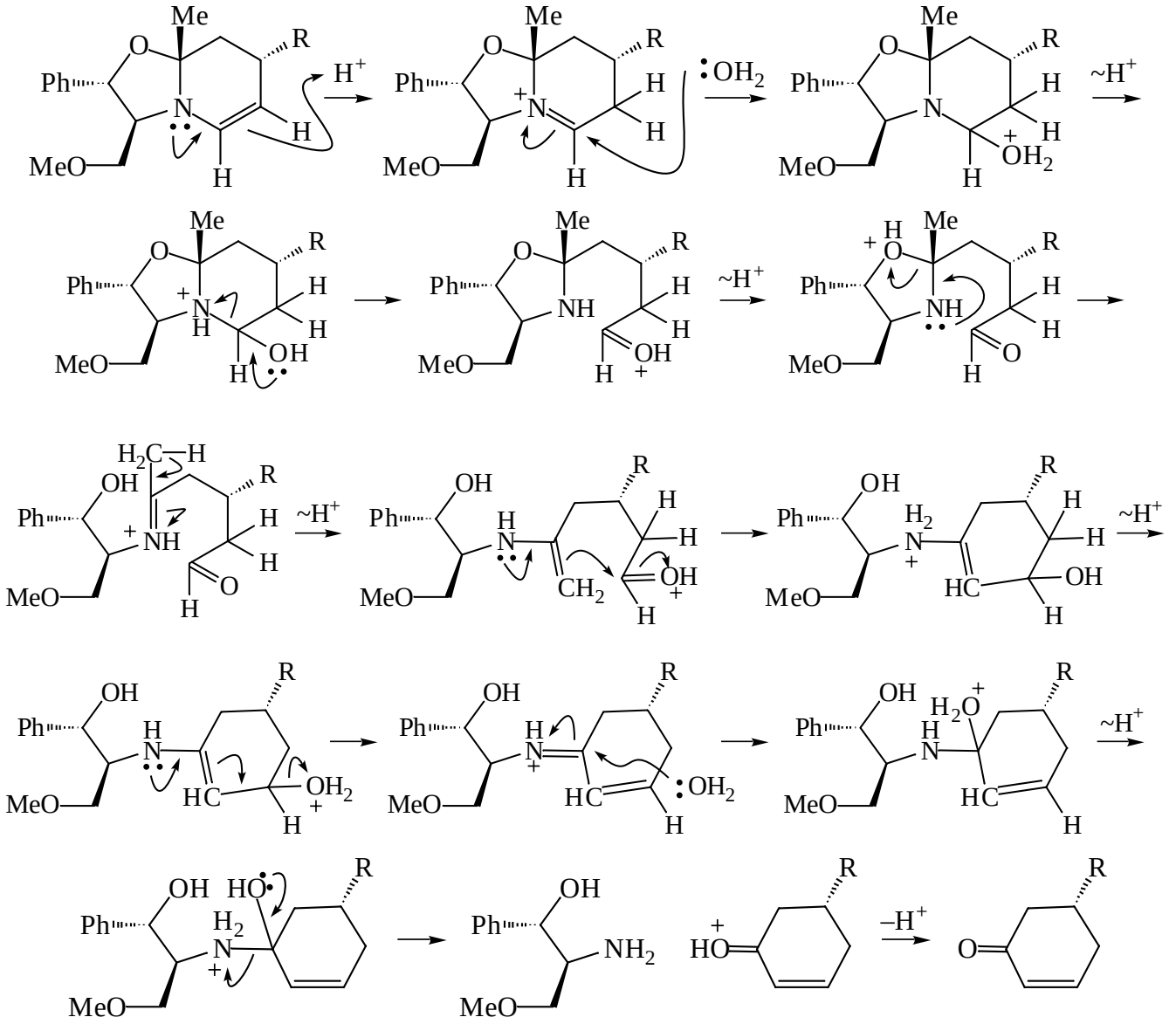


(cc) Make: C2–C7, C6–O11. Break: N1–C2, N1–C6, C6–O8.



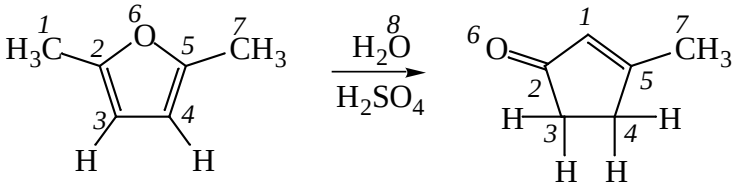
The first step must be protonation to form a nice stable carbocation. The first protonation can occur on C3

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.