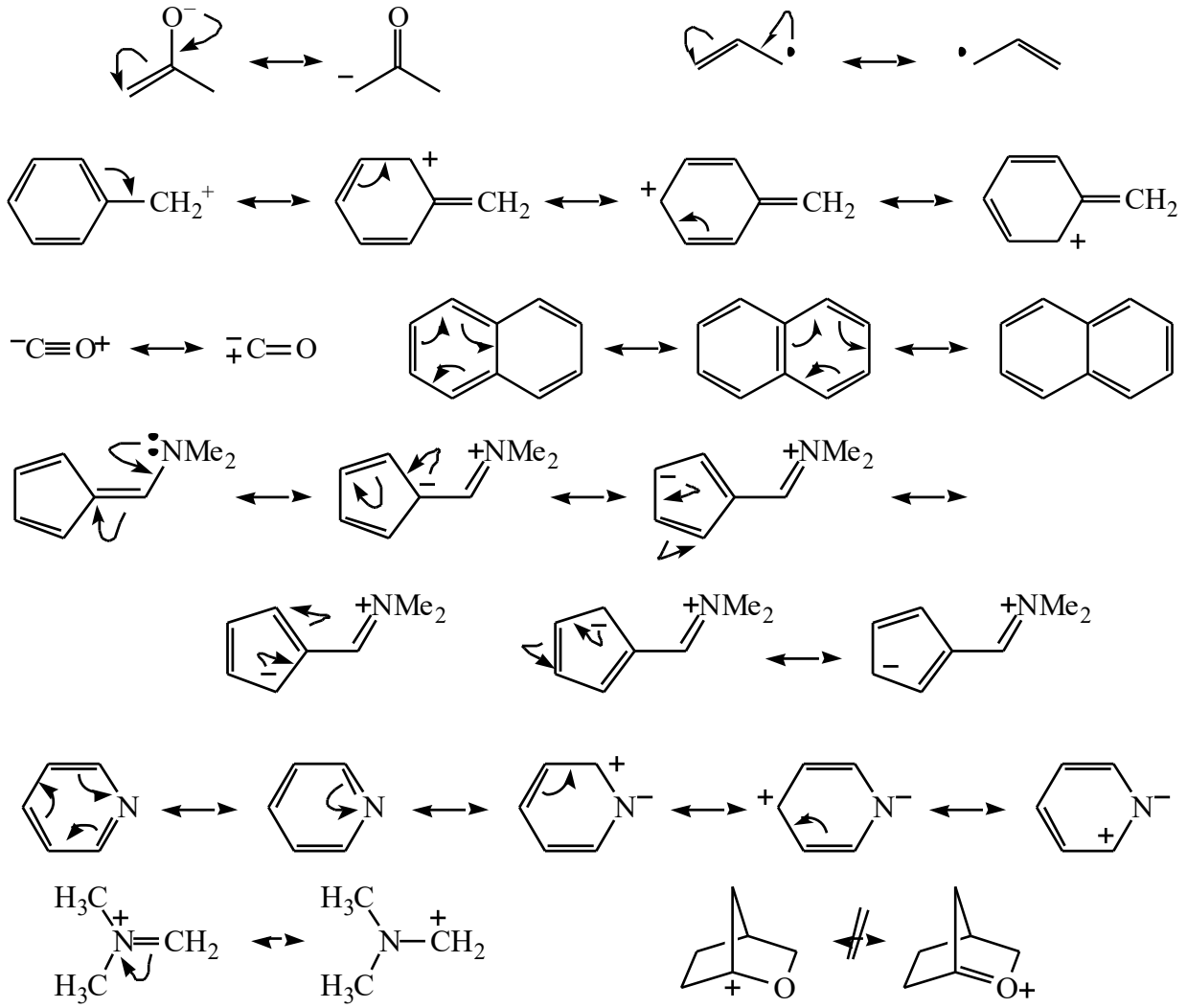
ANSWERS TO PROBLEMS IN BODY OF CHAPTER 1.

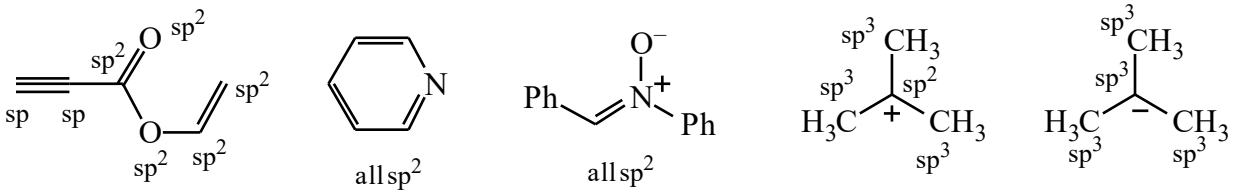
1.1. The resonance structure on the right is better because every atom has its octet.

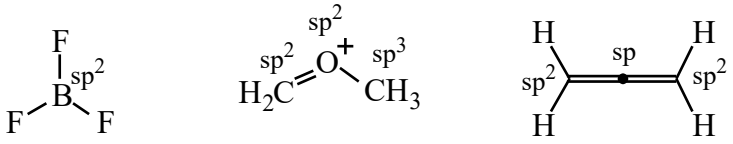
1.2.



the second structure is hopelessly strained

1.3.

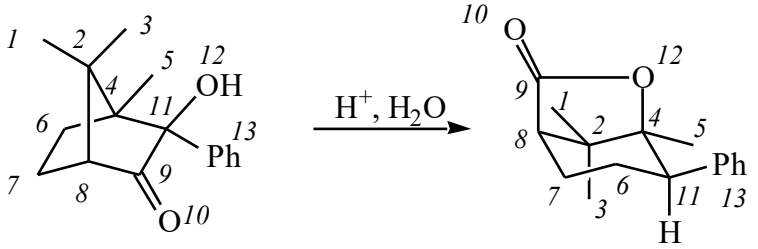




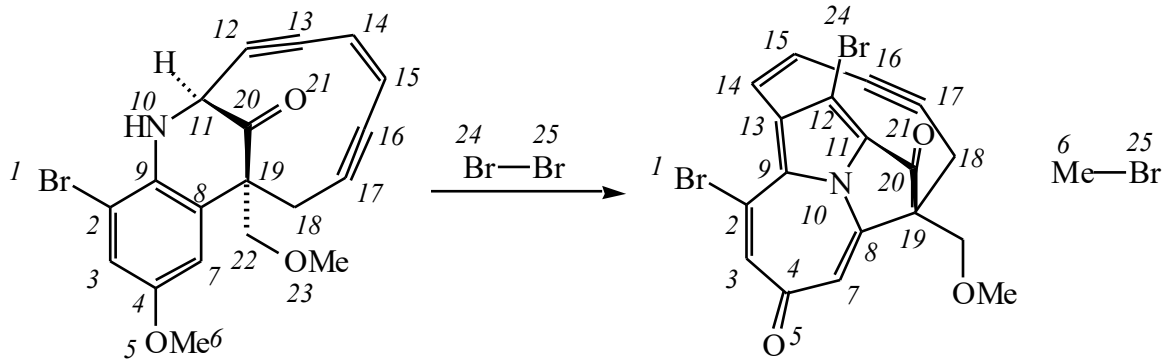
1.4. Furan has sp^2 hybridization. One of the lone pairs is in a *p* orbital, and the other is in an sp^2 orbital. Only the lone pair in the *p* orbital is used in resonance.

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.

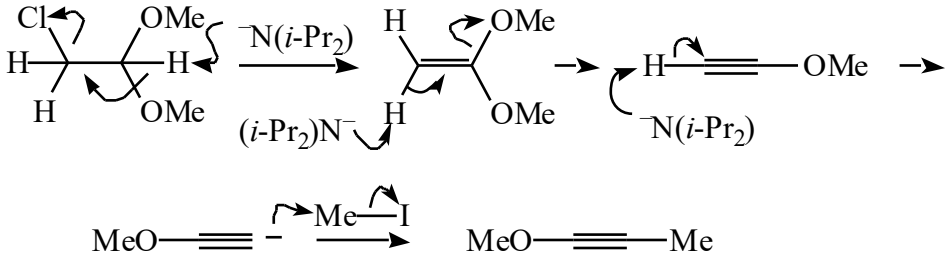
(b) Make C8–N10, C9–C13, C12–Br24. Break O5–C6, C8–C9.

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.

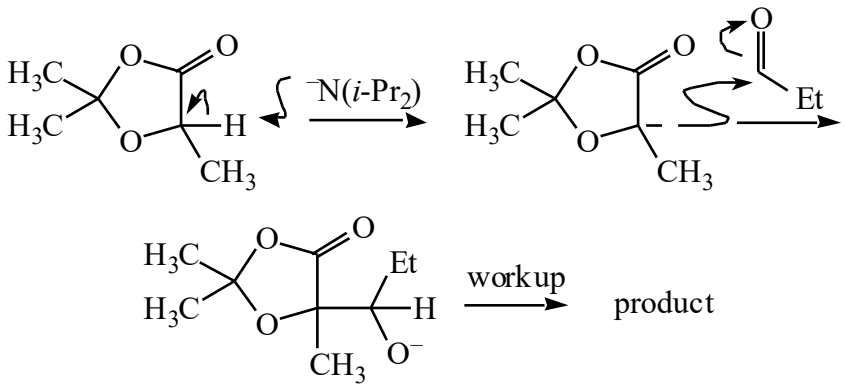
ANSWERS TO PROBLEMS IN BODY OF CHAPTER 2.

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.

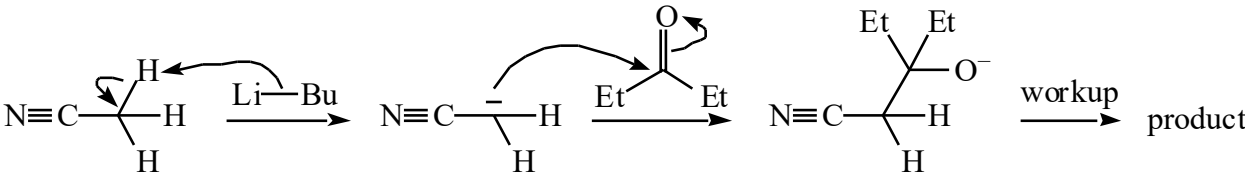


2.2. The difference between the two reactions is found in the electrophile. In the second case, the base/nucleophile can promote an E2 elimination by removing the allylic H atom; in the first case, the H atom that needs to be removed is not homoallylic. To improve the yield of the second reaction, run it in a polar aprotic solvent such as DMF, a measure that increases nucleophilicity more than basicity.

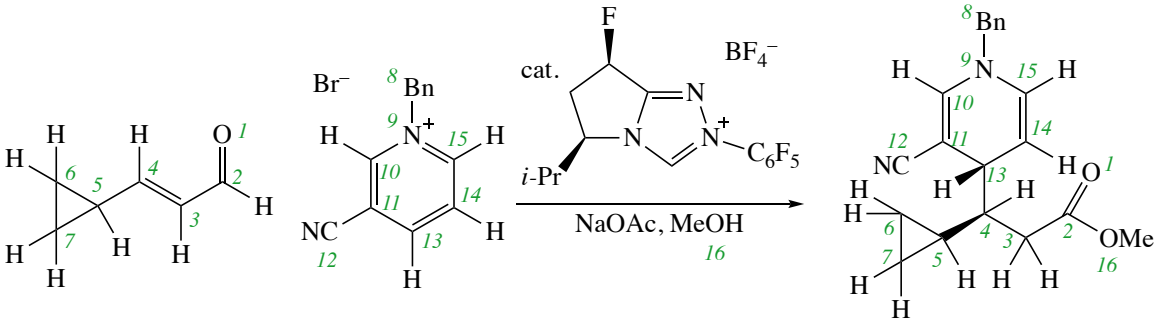
2.3(a). LDA deprotonates the C α to the ester, which adds to the aldehyde to give the aldol product after workup.



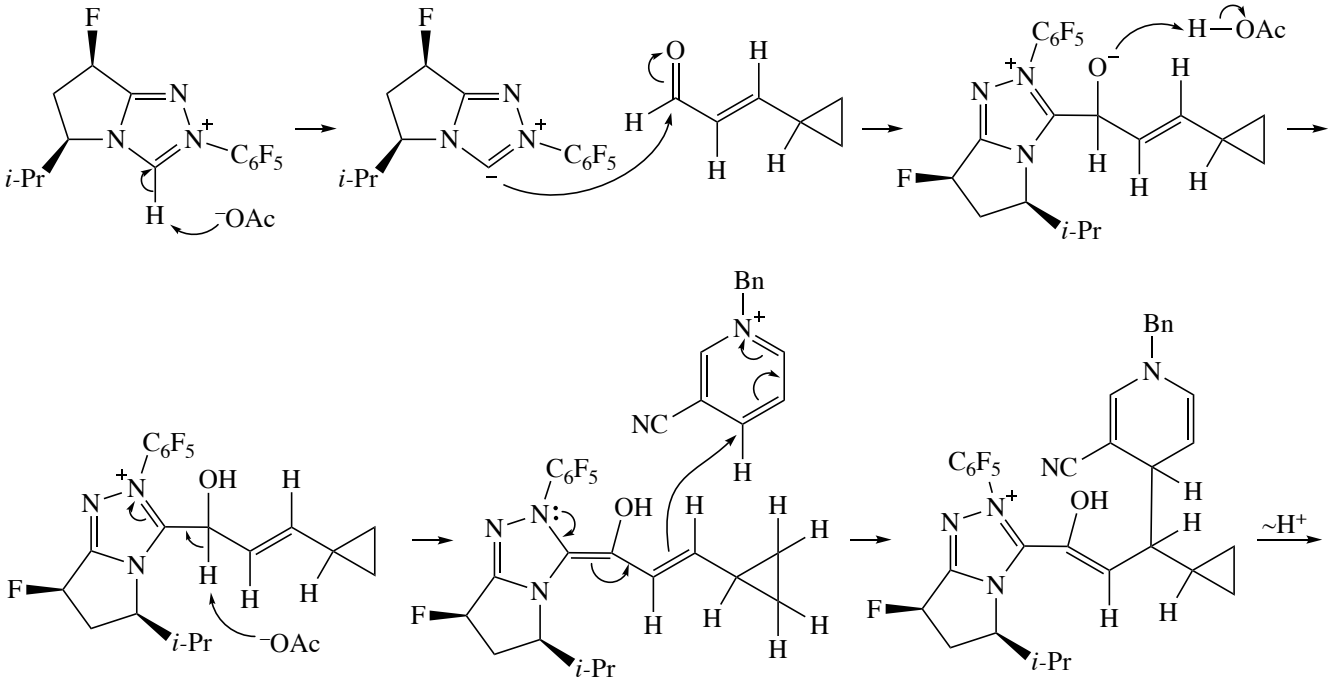
2.3(b). BuLi deprotonates the C α to the nitrile, which adds to the ketone to give the aldol product after workup.

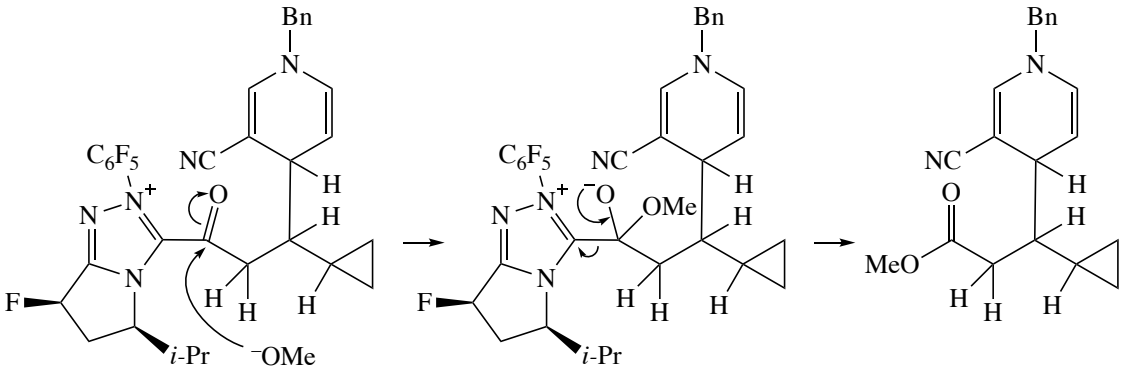


2.4. Make: C2–O16, C4–C13. Break: none.



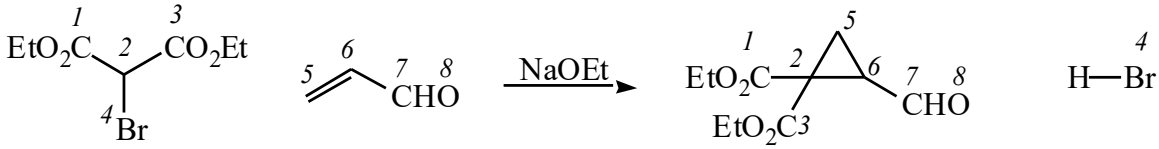
C4 is an electrophile, and so is C13. One of them must be converted to a nucleophile in order for them to react. That is the role of the catalyst. After the C atom between the two N atoms is deprotonated, it adds to C2, which converts C2 from being electrophilic to being acidic. Deprotonation of C2 then makes C2 nucleophilic, which also makes C4 nucleophilic, so C4 can now add to C13. Finally, after base-catalyzed tautomerization of the enol (two steps shown as ~H^+), MeO^- does nucleophilic substitution at C2 to give the product and regenerate the catalyst.



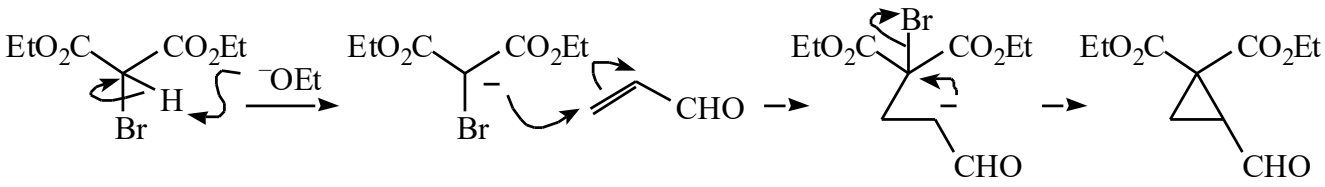


2.5.

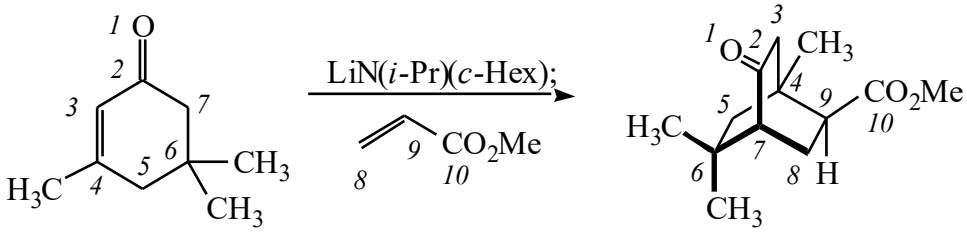
(a) Make: C2–C5, C2–C6. Break: C2–Br4.



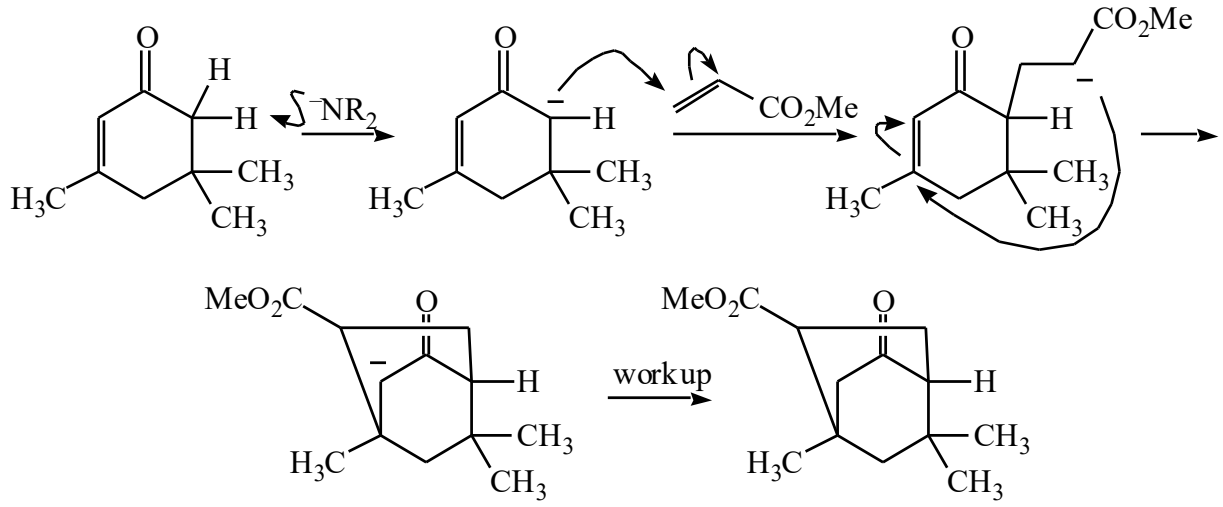
C2 is both electrophilic and particularly acidic. C5 is electrophilic, and C6 has no reactivity, so the first bond to be made must be C2–C5. Therefore, deprotonation of C2 gives a nucleophile, which can attack electrophilic C5 to give an enolate at C6. *Now* C6 is nucleophilic, and intramolecular S_N2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



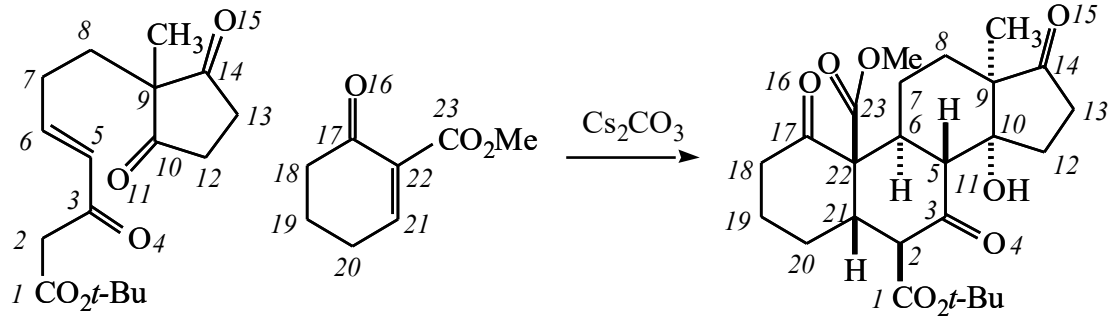
(b) Make: C7–C8, C4–C9. Break: none.



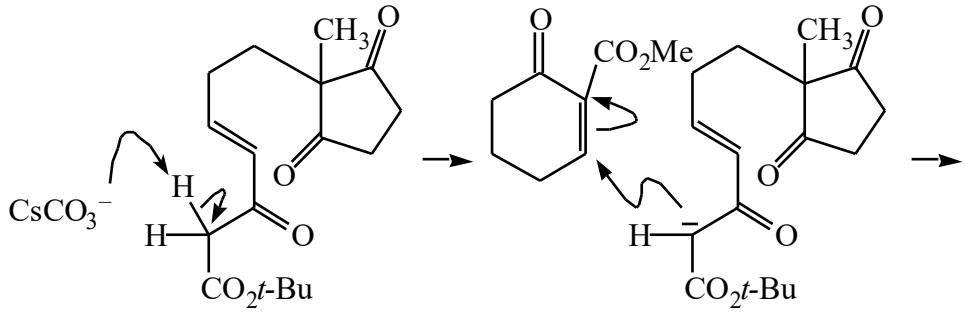
The thing above the arrow is a fancy version of LDA. C4 and C8 are electrophilic, C9 is unreactive, and C7 is acidic, so first step must be to deprotonate C7 to make it nucleophilic. Conjugate addition to C8 generates a nucleophile at C9, which adds to C4 to give a new enolate. Workup then provides the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

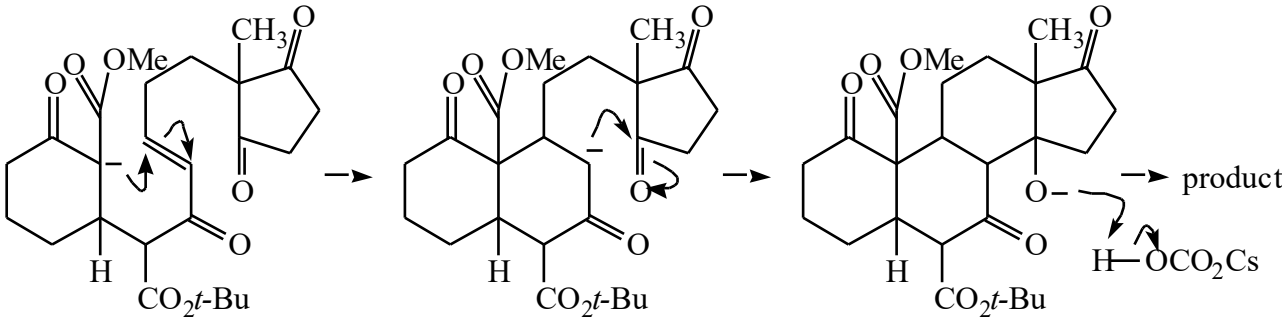


(c) Make: C2–C21, C5–C11, C6–C22. Break: none.



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.

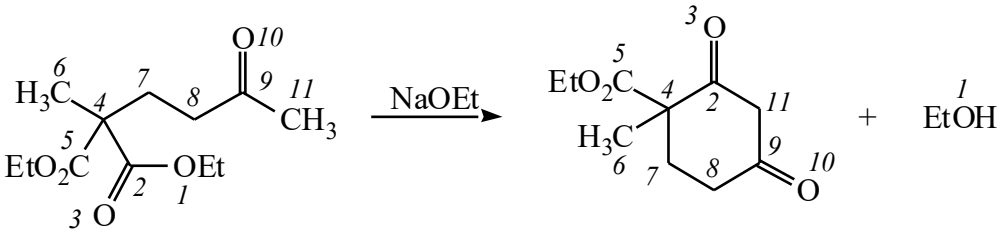




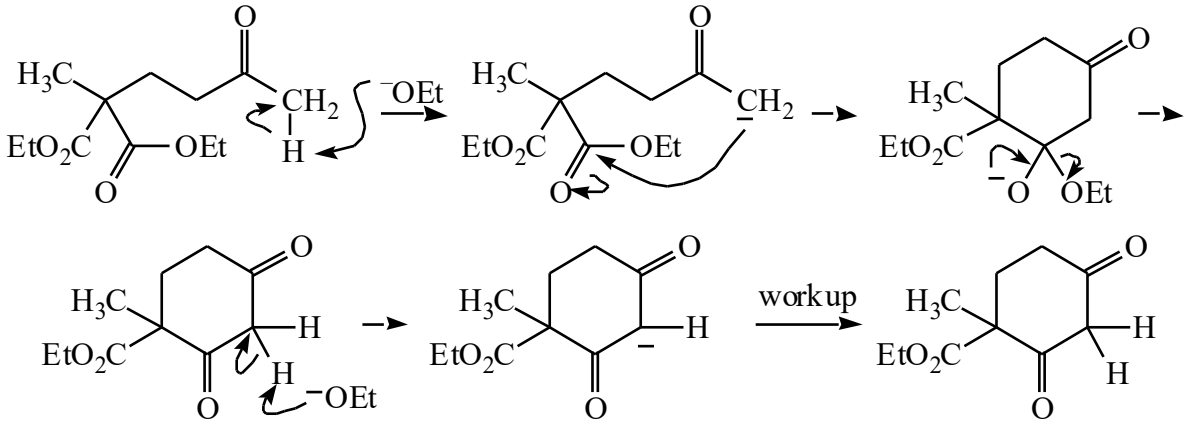
2.6. Because under basic conditions carboxylic acids are deprotonated to the carboxylate ions, which are no longer electrophilic enough that a weak nucleophile like MeO^- can attack them. Upon workup the carboxylate is neutralized to give back the carboxylic acid.

2.7.

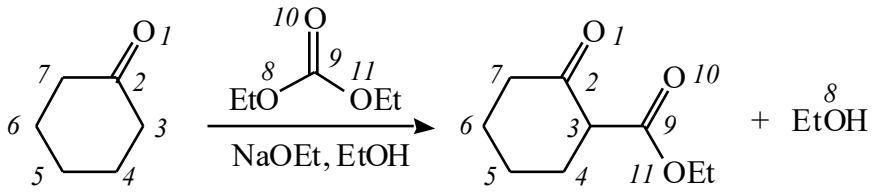
(a) Balancing the equation shows that EtOH is a by-product. Make: C2–C11. Break: O1–C2.



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.



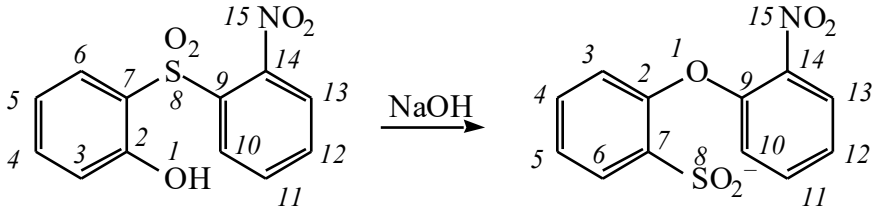
(b) Make: C3–C9. Break: O8–C9.



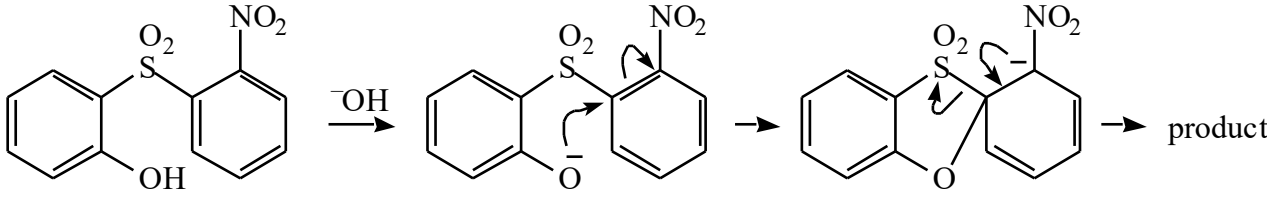
The mechanism is exactly the same as drawn in part (a).

2.8.

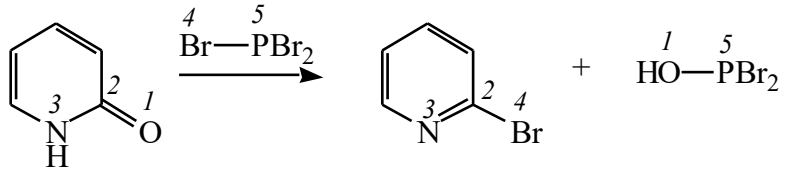
(a) Make: O1–C9. Break: S8–C9.



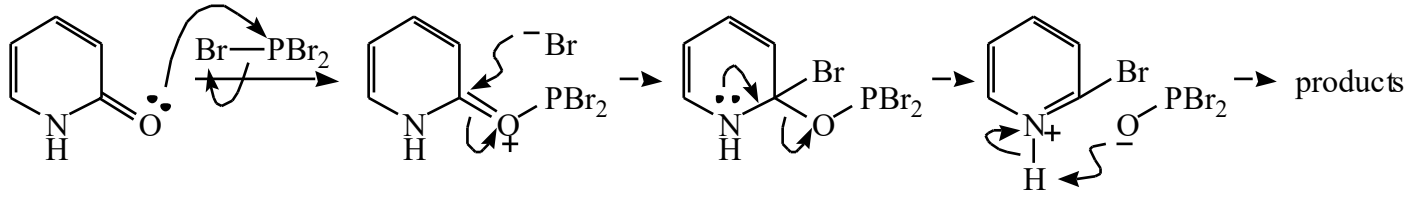
The base deprotonates O1, which adds to C9, giving an anion that is delocalized over C10, C12, C14, and into the NO_2 group. The anion then expels SO_2^- to give the product.



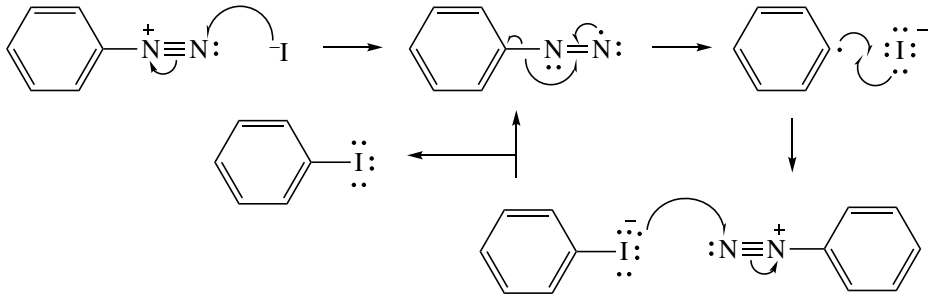
(b) Make: O1–P5, C2–Br4. Break: O1–C2, Br4–P5.



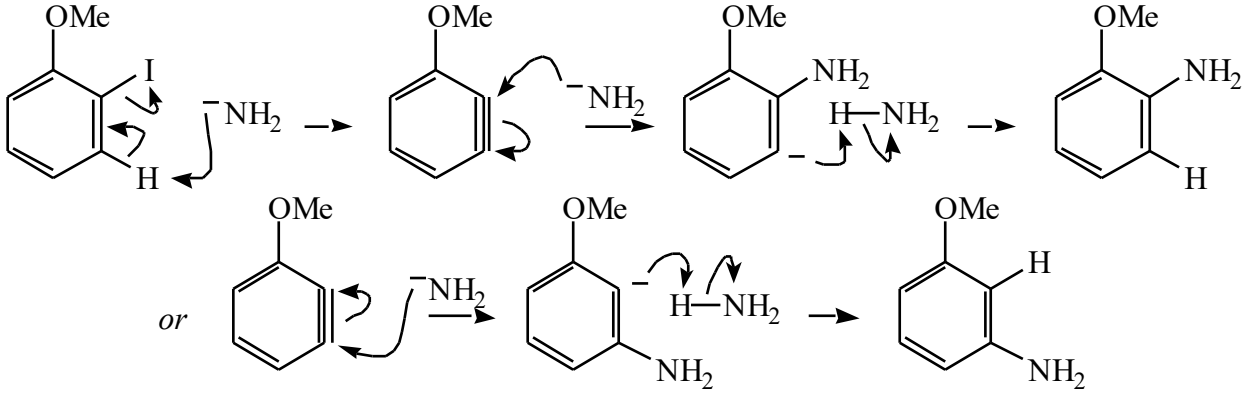
O1 is clearly a nucleophile, and C2 is clearly an electrophile. P5 could be either a nucleophile (lone pair) or an electrophile (leaving group attached), but because it reacts with O1 and because the P5–Br4 bond breaks, in this reaction it must be acting as an electrophile. Attack of O1 on P5 in S_N2 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.



2.9. The $S_{RN}1$ mechanism begins with electron transfer from the very oxidizable I^- to the terminal N of $PhN^+{\equiv}N$. Homolytic cleavage of the C–N bond then gives a phenyl radical, which forms a new σ bond to I^- to give the radical anion $[PhI]^-$. (I have placed the unpaired electron of $[PhI]^-$ on I as a ninth electron, but one could instead draw other resonance structures involving the ring π bonds.) The chain is completed by electron transfer from $[PhI]^-$ to $PhN^+{\equiv}N$ to give PhI and to regenerate the PhN=N· radical.



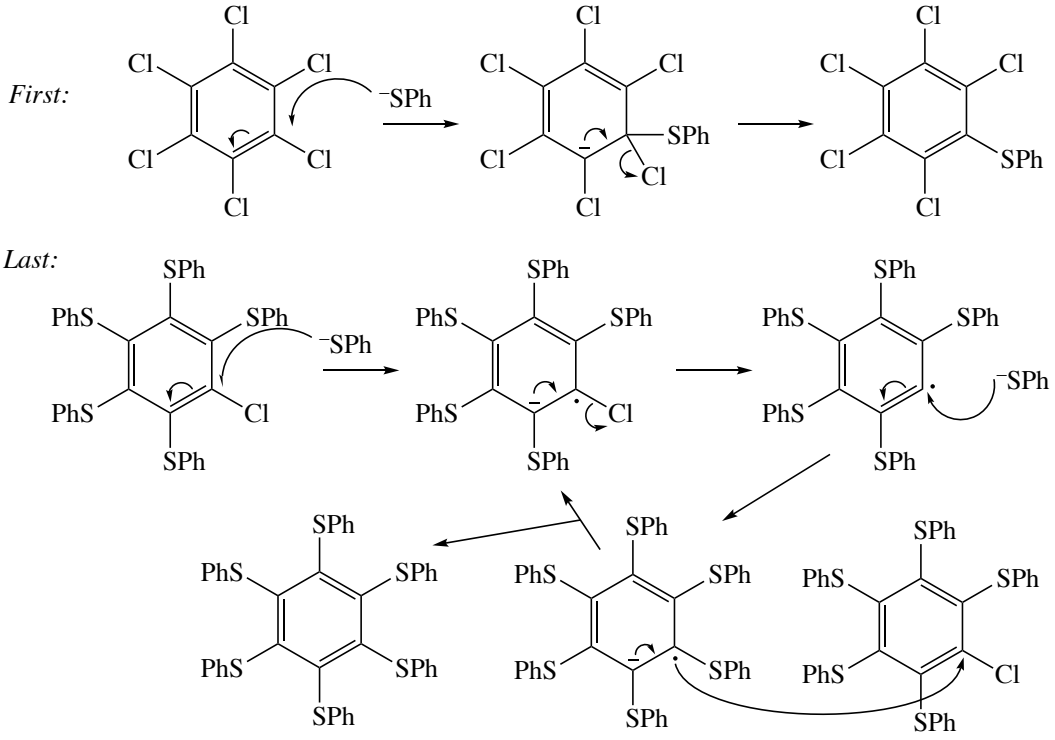
2.10. E2 elimination of HI from the aryl iodide gives a benzyne, which can be attacked at either C of the triple bond to give two different products.



2.11. 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.

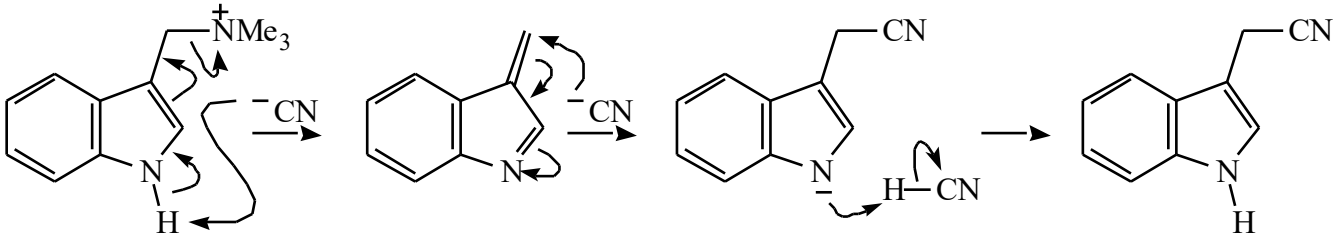
2.12. The first substitution involves attack of PhS^- on C_6Cl_6 to give $C_6Cl_5(SPh)$, and the last involves attack of PhS^- on $C_6(SPh)_5Cl$ to give $C_6(SPh)_6$. The elimination–addition mechanism is ruled out in both cases because of the absence of H atoms adjacent to Cl, so the choices are addition–elimination 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.



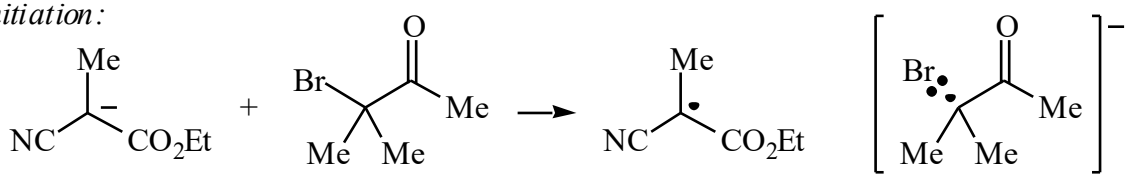
2.13.

(a) An addition–elimination mechanism is reasonable.

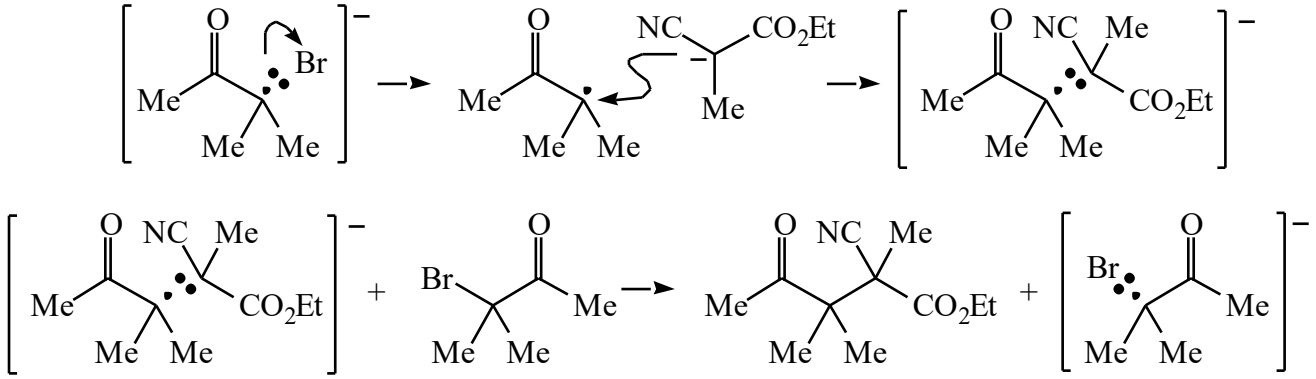


(b) An addition–elimination mechanism is not reasonable. Elimination of HBr from the starting material gives an α,β-unsaturated ketone that is now a π bond electrophile at a C different from the one that originally had the Br attached to it. The only reasonable mechanism is $S_{RN}1$.

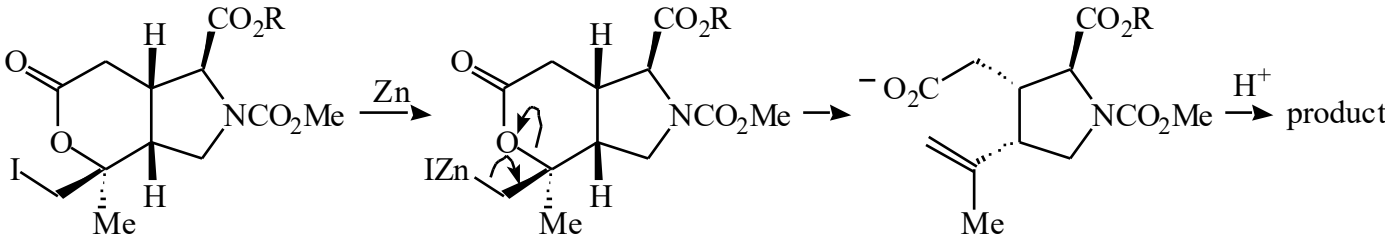
Initiation:



Propagation:

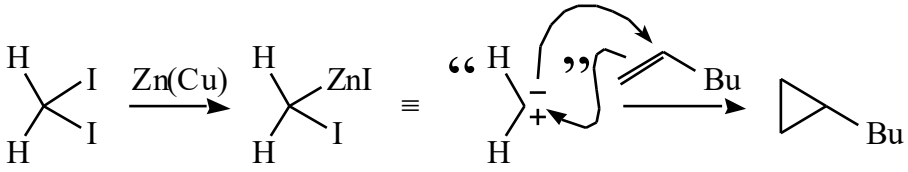


2.14.

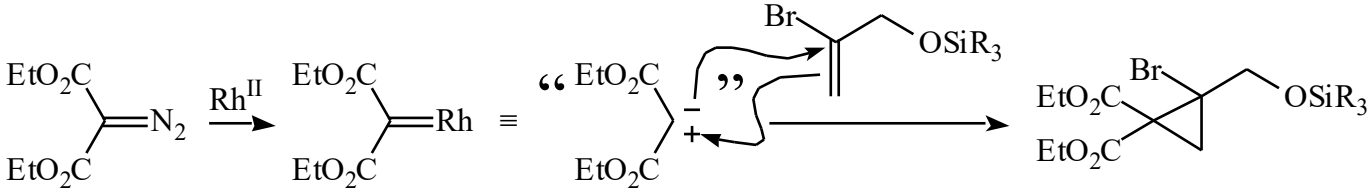


2.15.

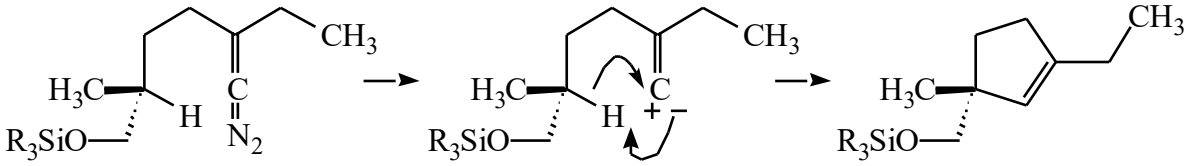
(a)



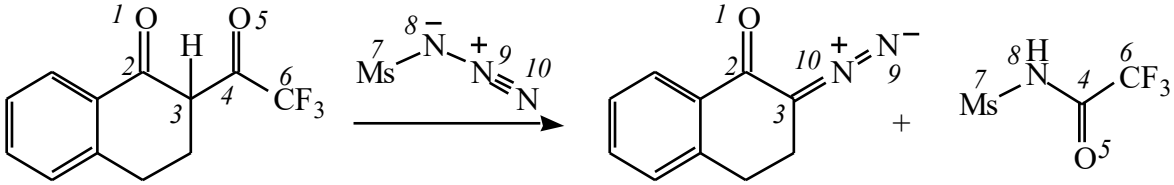
(b)



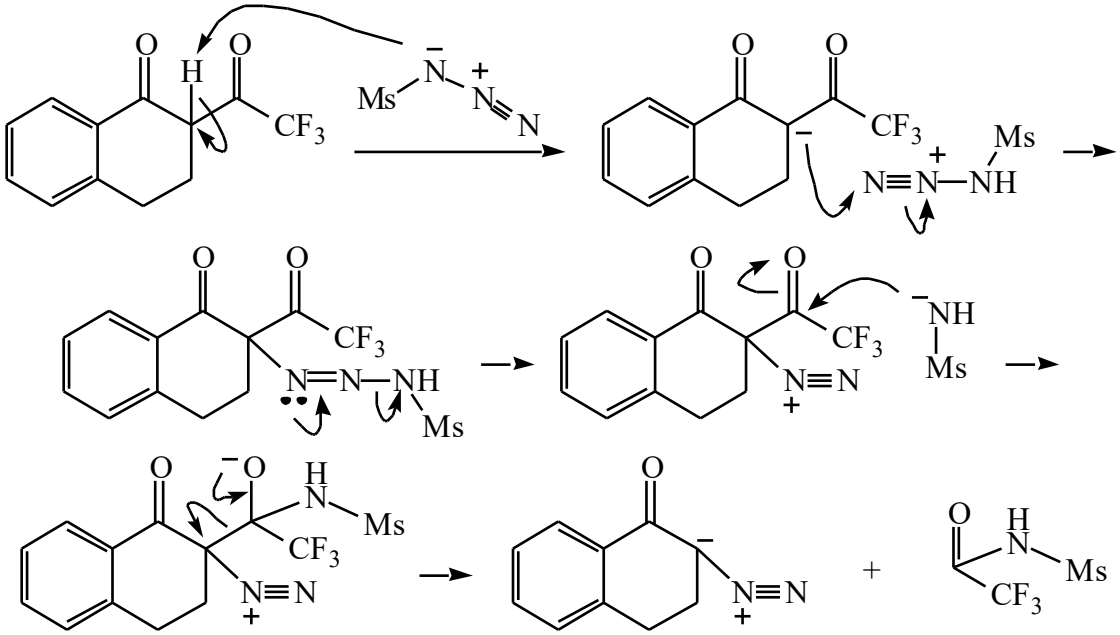
2.16.



2.17. 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.

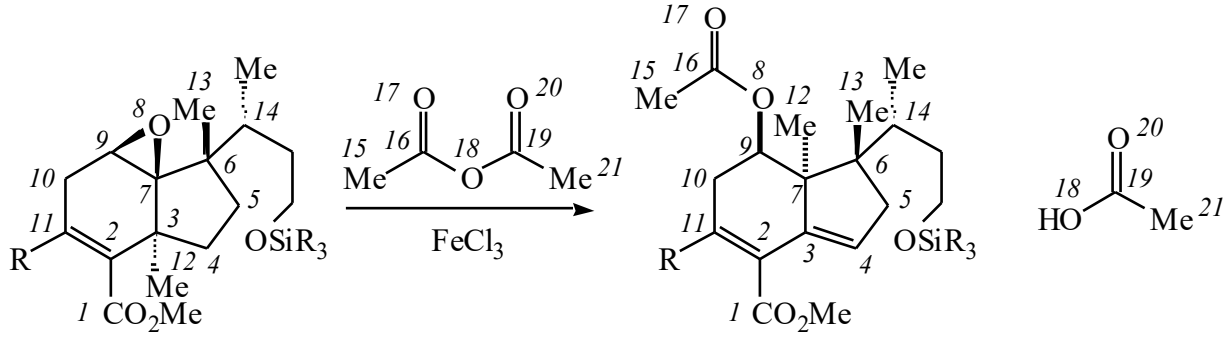


N8 deprotonates C3 to make the latter nucleophilic, and it adds to N10. The lone pair on N10 is then used to expel N8 from N9. N8 then comes back and adds to C4, and expulsion of C3 from C4 affords the two products.

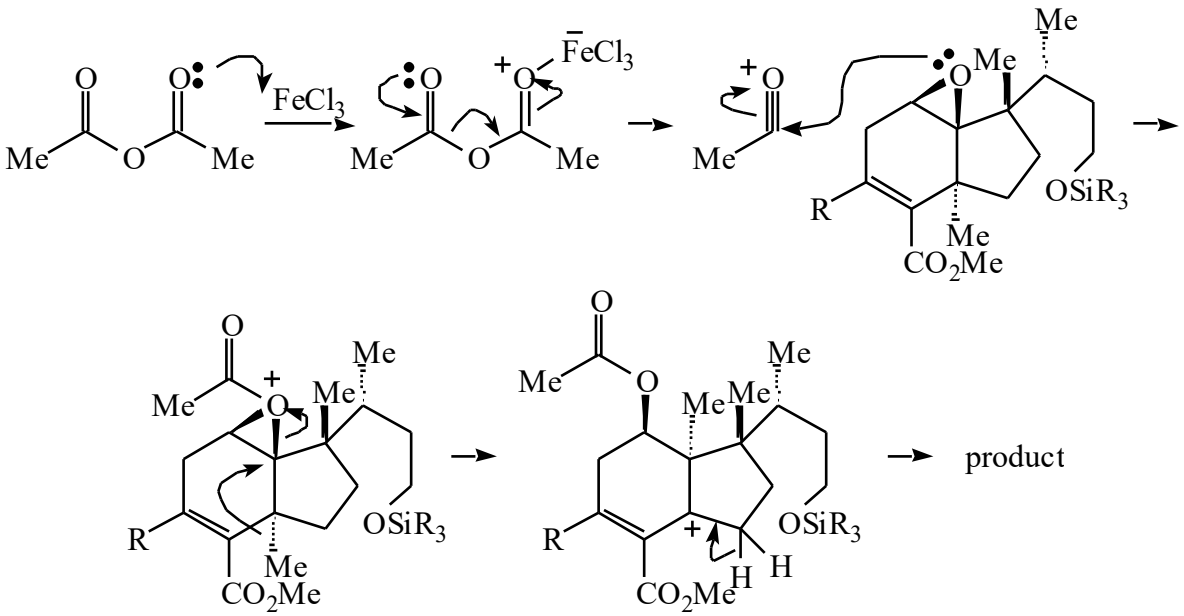


ANSWERS TO PROBLEMS IN BODY OF CHAPTER 3.

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.



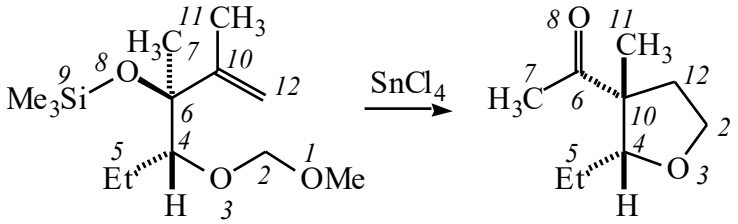
The fact that C12–C3 breaks and C12–C7 makes is a signal that a 1,2-alkyl shift occurs. The shift requires that a carbocation be formed at C7, which could be accomplished by cleaving the C7–O8 bond. Before the C7–O8 bond cleaves, something else must attach to O8 to give it a formal positive charge. Because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



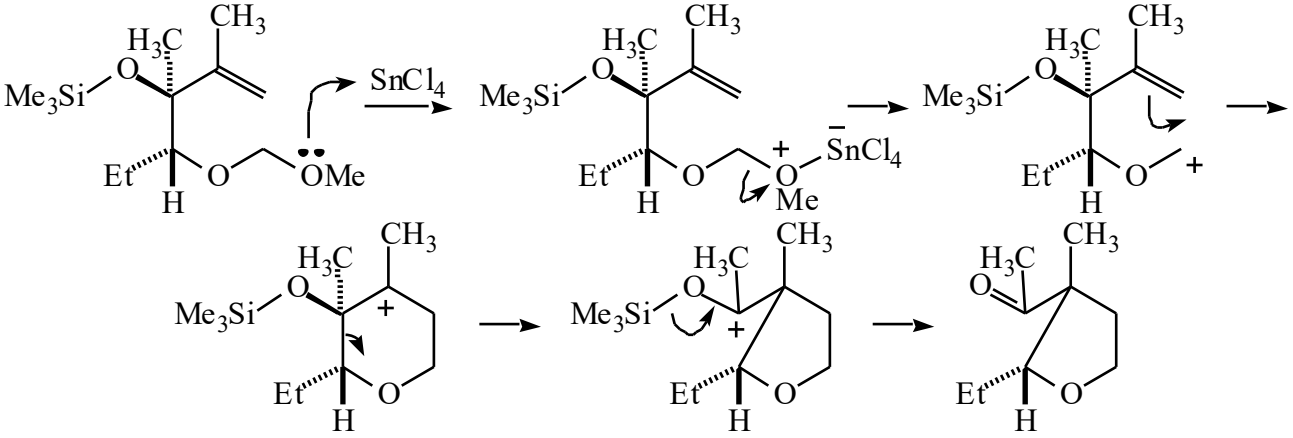
Why do we draw cleavage of the C7–O8 bond concerted with migration of C12? If the two steps were nonconcerted, then a C7 carbocation would intervene, and other 1,2-shifts could occur. For example, C13 or

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.

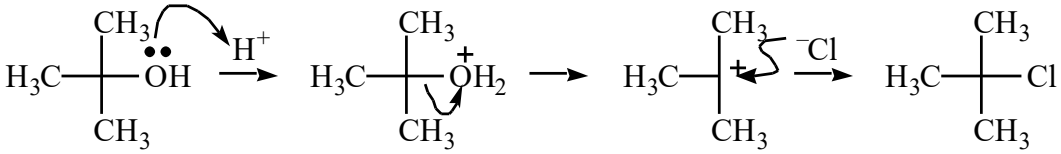


The role of the Lewis acid is either to make a π bond electrophile more electrophilic or to promote the departure of a leaving group. There is no π bond electrophile in the starting material, but O1 is a leaving group, so the first step must be coordination of $SnCl_4$ to O1. Cleavage of the O1–C2 bond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

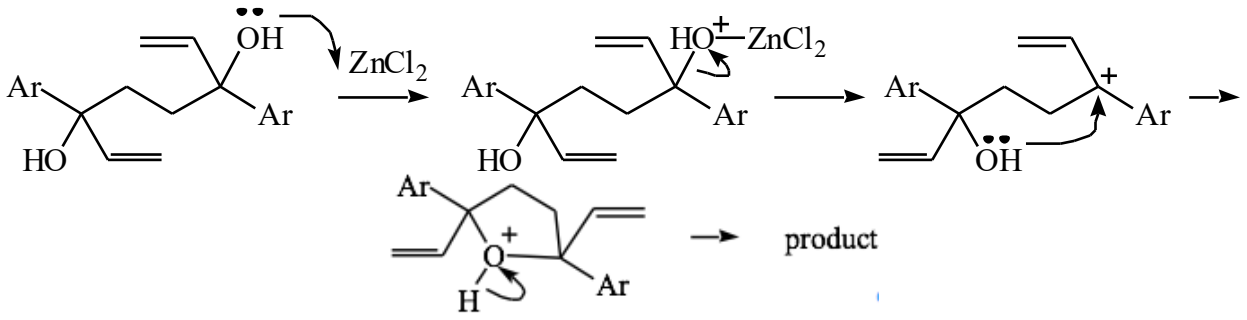


3.3.

(a)

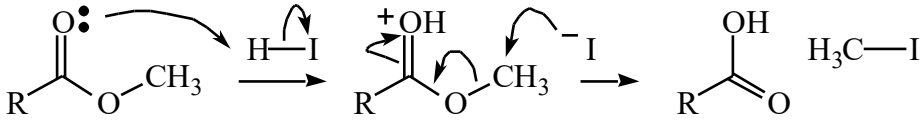


(b)

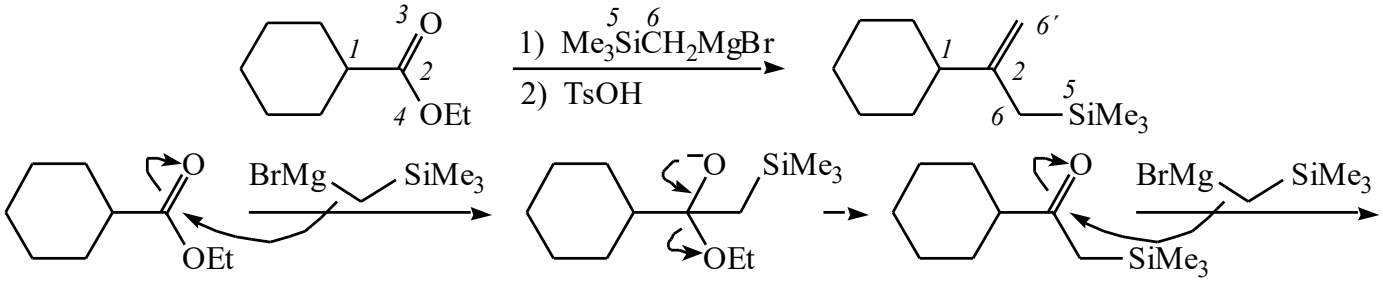


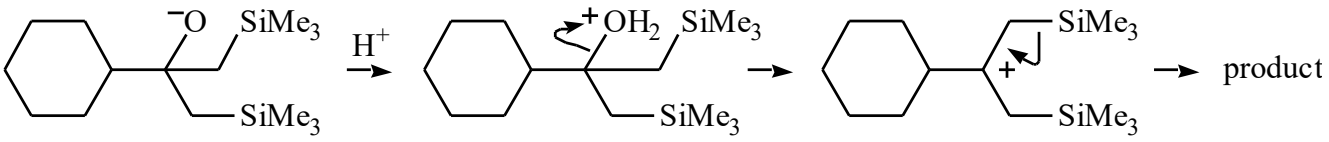
3.4. Because the carbocations derived from aryl and alkenyl halides are extremely high in energy.

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.



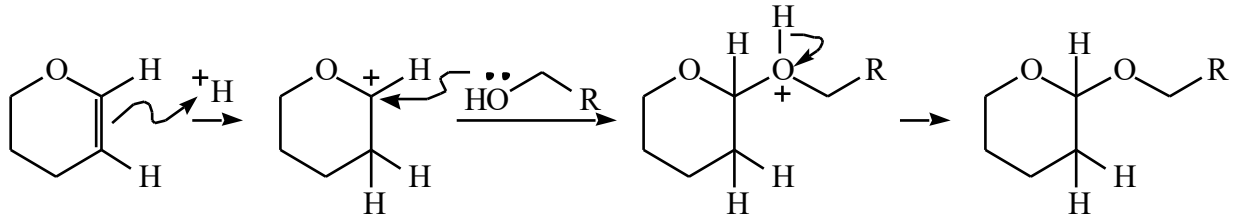
3.6. A few things about this reaction may have caught you off guard. First, the first step is a polar reaction under basic conditions, involving the Grignard reagent; only the second step is a polar reaction under acidic conditions. Second, *two* equivalents of the Grignard are required for the product;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



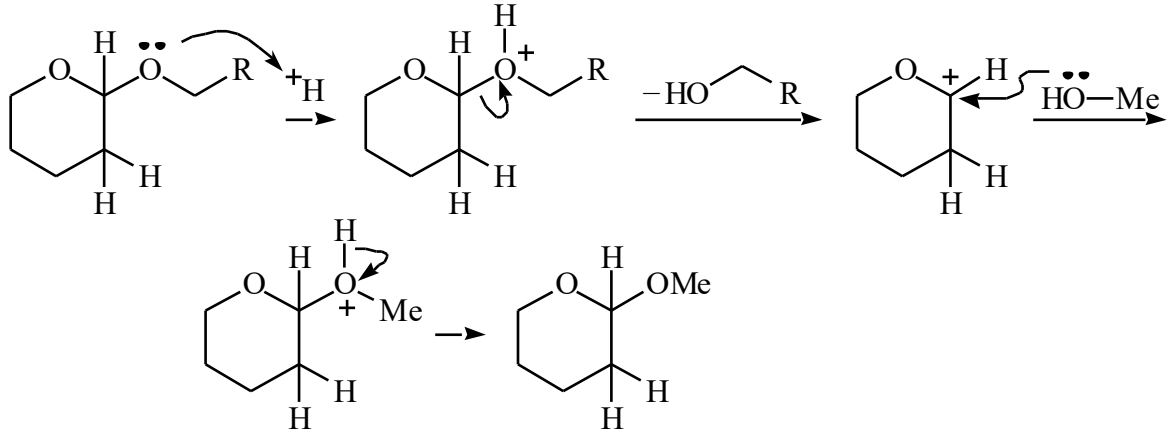


3.7.

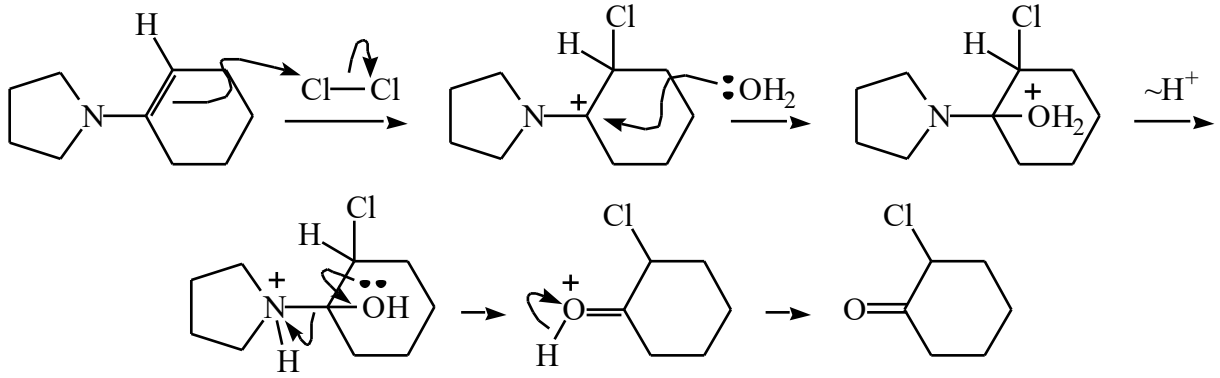
(a)



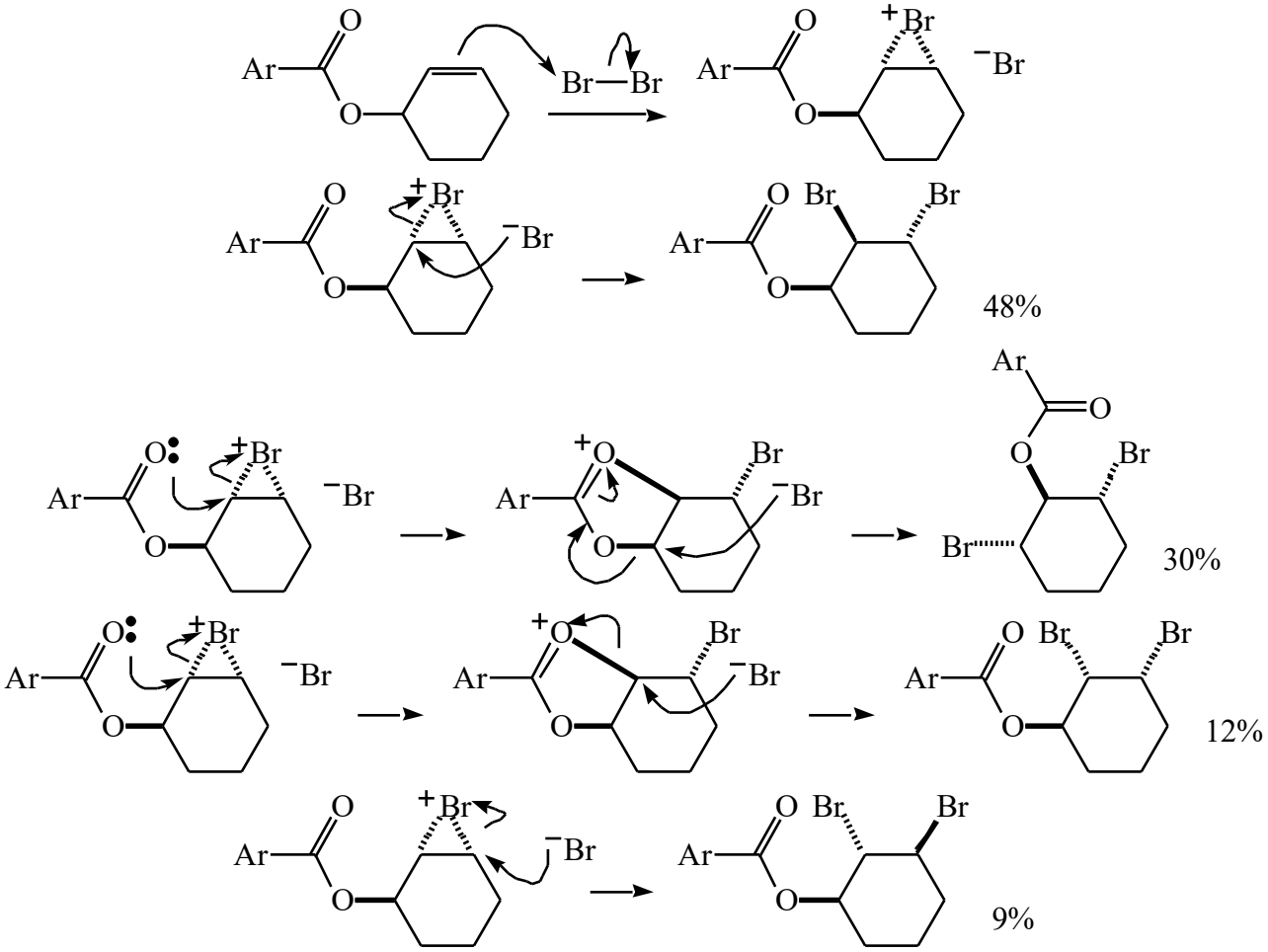
(b) This substitution reaction must proceed by an S_N1 mechanism.



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

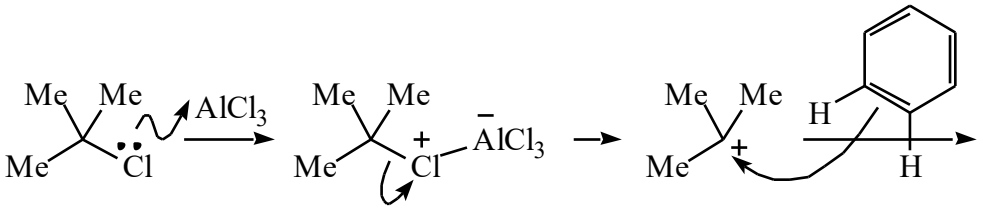


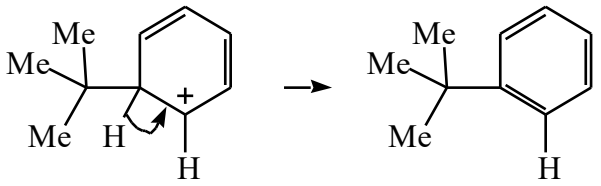
3.9. The products have in common a bromonium ion that is formed by attack of Br_2 on the face of the double bond *opposite* the acyloxy substituent. The two products not consistent with simple anti addition across the π bond are obtained via neighboring group participation of the acyloxy group.



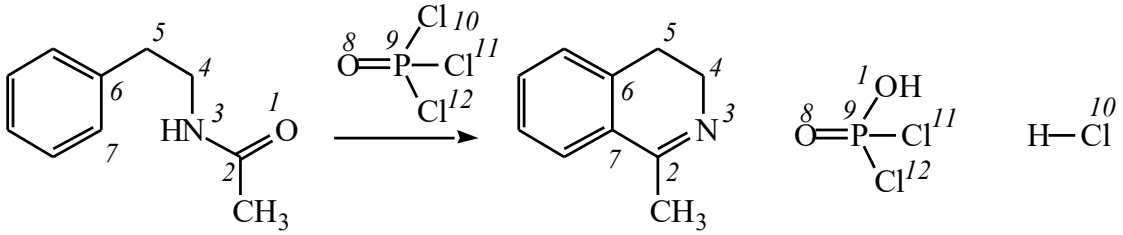
3.10.

(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.

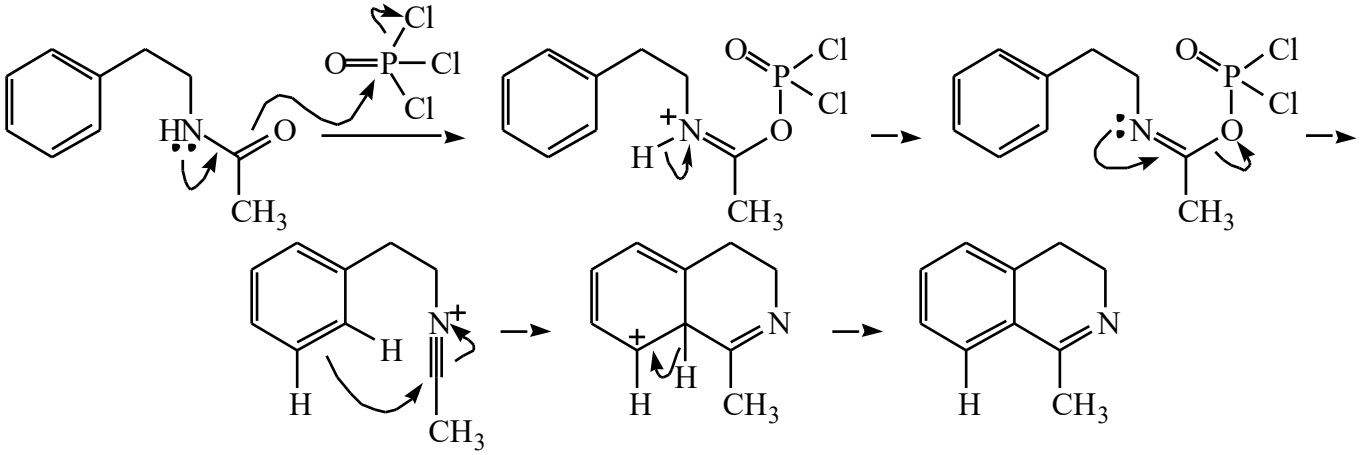




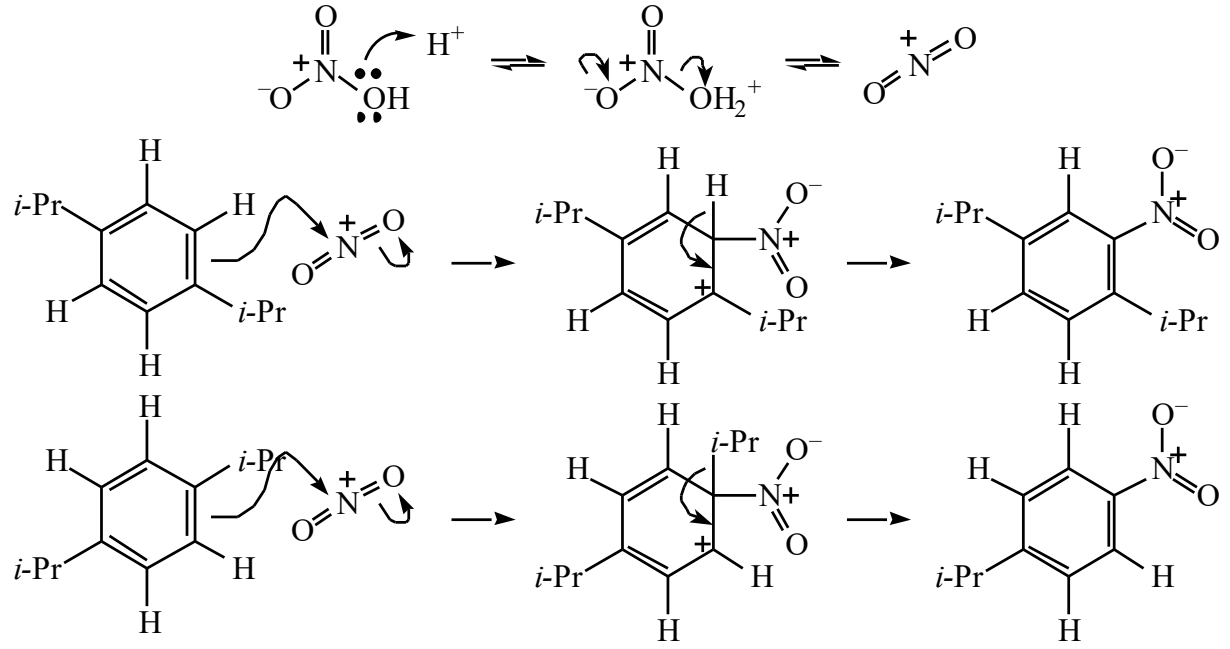
(b) The starting material loses the elements of water, but if water is the by-product, what is the role of the $POCl_3$? It is not a Lewis acid; it is a σ bond electrophile at P. Because P9 is electrophilic and O1 is nucleophilic, the first step must be formation of O1–P4 bond. If this is true, the P-containing by-product has an O–P bond. Make: O1–P9, C2–C7. Break: O1–C2, P9–Cl10.



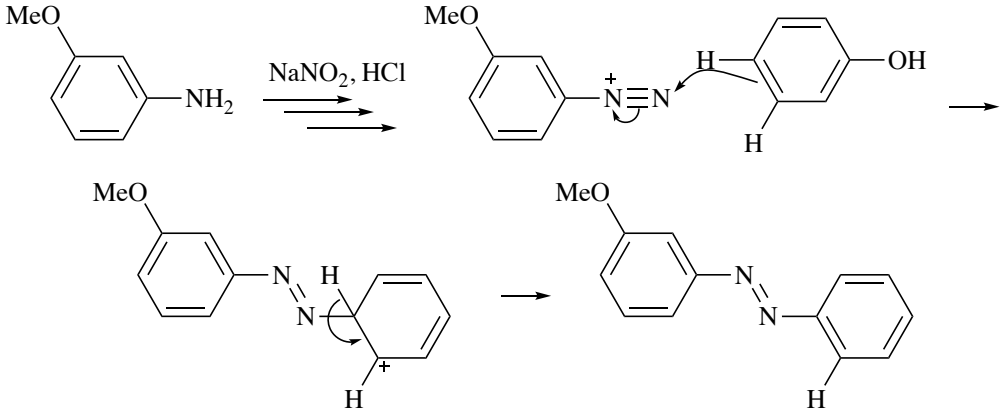
In the first step, O1 attacks P9 and displaces Cl10. After deprotonation of N3, a carbocation at C2 (stabilized by resonance with N4) is formed. Addition–elimination then gives the product. An alternative and reasonable mechanism would have C7 attack C2 before the C2–O1 bond cleaves (addition–elimination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



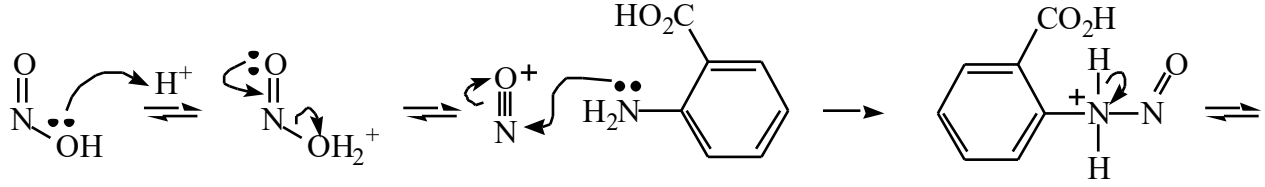
3.11. The first product is derived from a normal electrophilic aromatic substitution reaction of the kind described in the text. The second product is derived from ipso electrophilic aromatic substitution. The mechanism is exactly the same, but in the last step *i*-Pr^+ is lost instead of H^+.

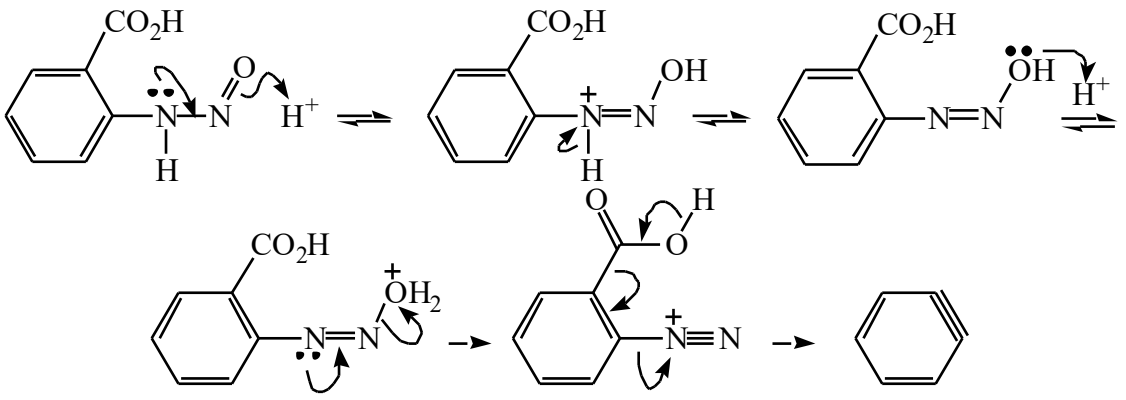


3.12. You should be able by now to draw the first part of the mechanism, the conversion of the amine to a diazonium ion. Electrophilic aromatic substitution, with the terminal N of the diazonium ion acting as the electrophile, then gives the observed diazo compound.

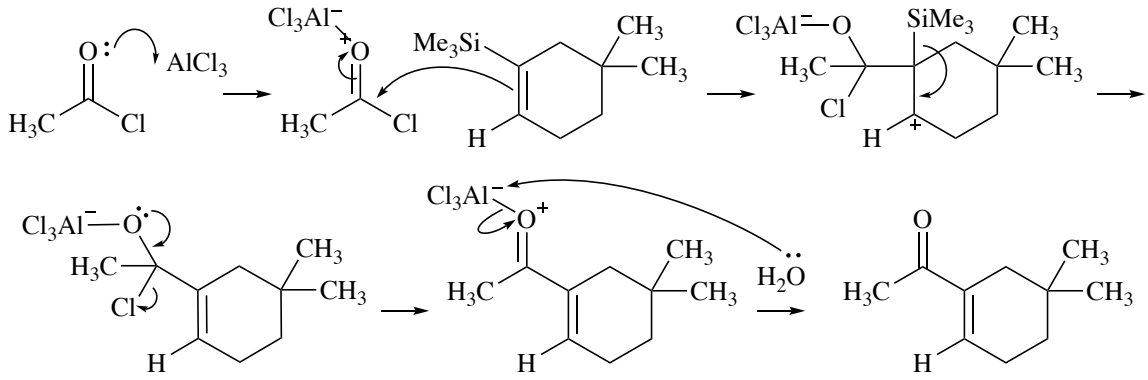


3.13. Only an N–N bond is made, and one C–C bond is broken. When an amine is combined with $NaNO_2$ and HCl, a diazonium ion is formed. An elimination reaction then ensues with loss of CO_2.



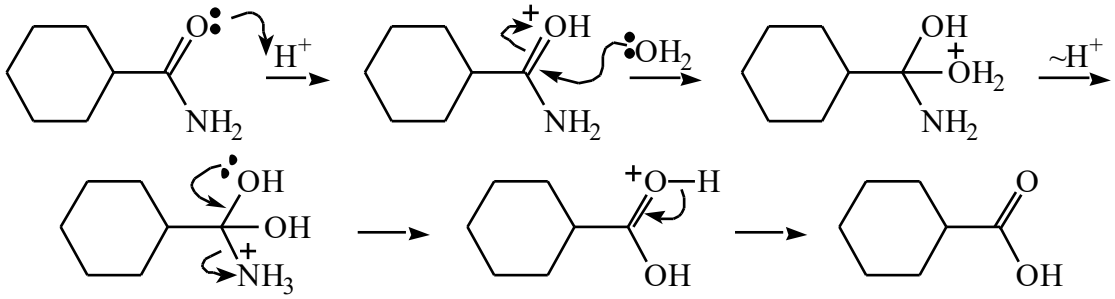


3.14. The mechanism is exactly the same as the mechanism for Friedel–Crafts acylation with an acyl chloride.

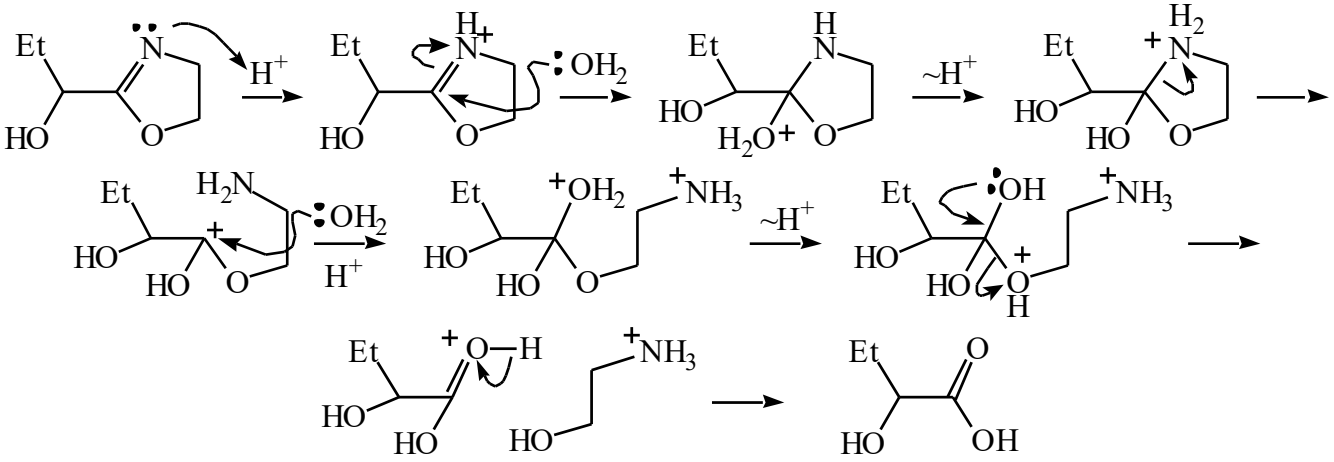


3.15.

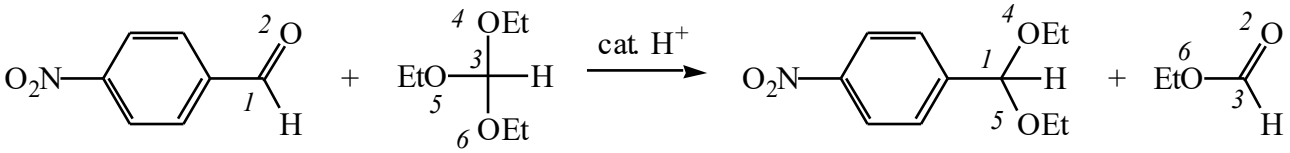
(a) The mechanism proceeds by addition–elimination. *However*, both the addition and elimination steps are preceded by protonation and followed by deprotonation. It is very important that these proton transfer steps are drawn properly!



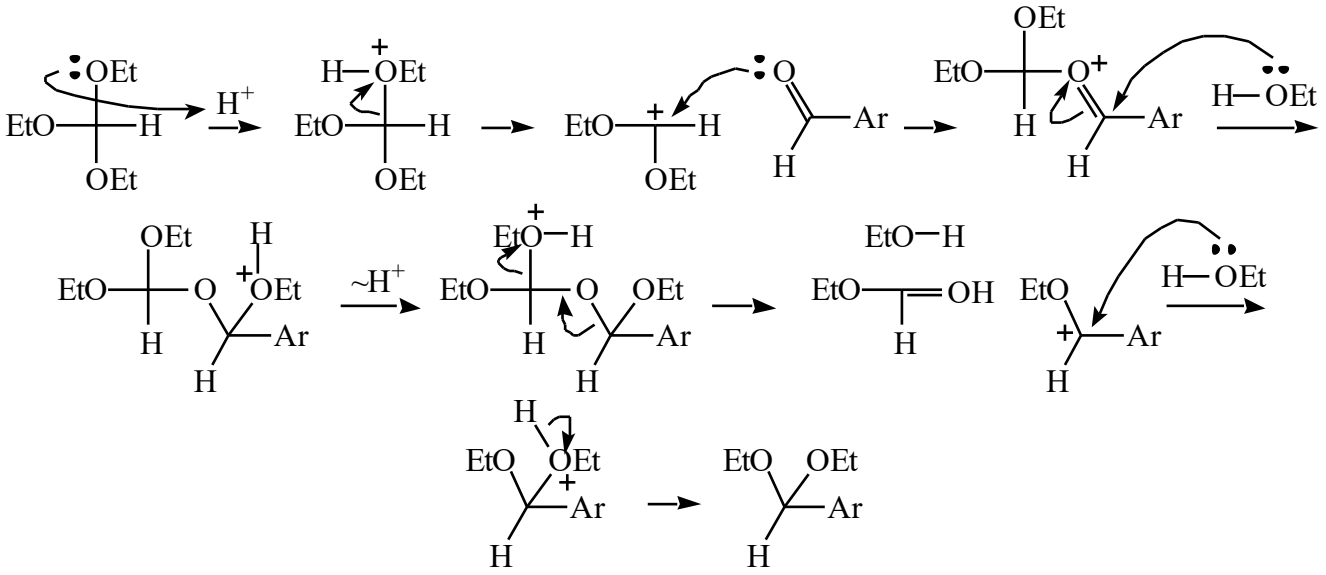
(b) It is unlikely that the CH_2–O bond in the starting material will break under aqueous acidic conditions (can't form a carbocation, and S_N2 is unlikely unless conditions are very harsh). Therefore the CH_2–O bond is preserved in the product, which means that *both* O's of the carboxylic acid product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



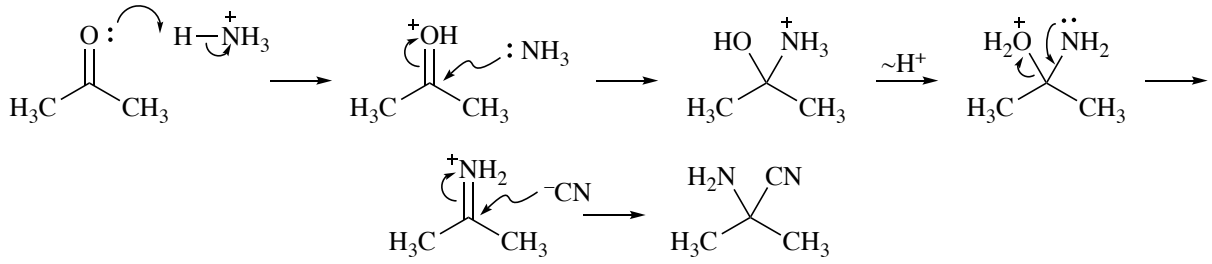
3.16. Make: C1–O4, C1–O5, O2–C3. Break: C1–O2, C3–O4, C3–O5.



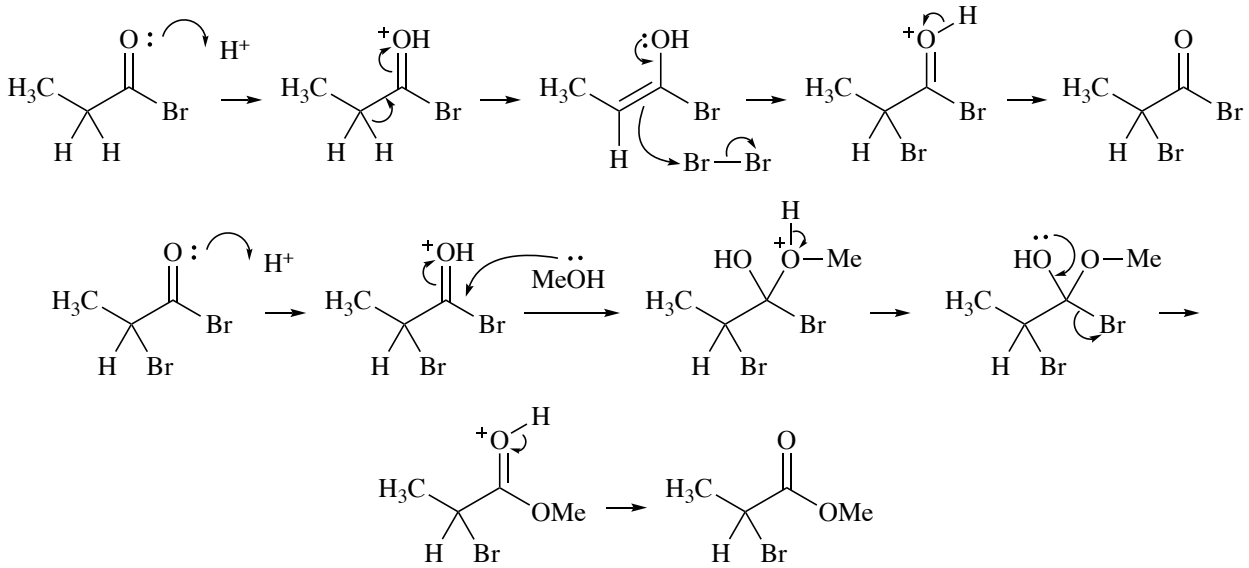
There are a number of ways this reaction could proceed, but the key step in any of them is attack of O2 on a carbocation at C3.



3.17. Under these mildly acidic conditions, the carbonyl O atom is protonated before NH_3 attacks. Proton transfer followed by loss of H_2O gives the iminium ion. Addition of ^-CN gives the α-amino nitrile. The reason why the pH shouldn't be made very acidic is that ^-CN will be protonated, giving HCN, a poisonous gas.

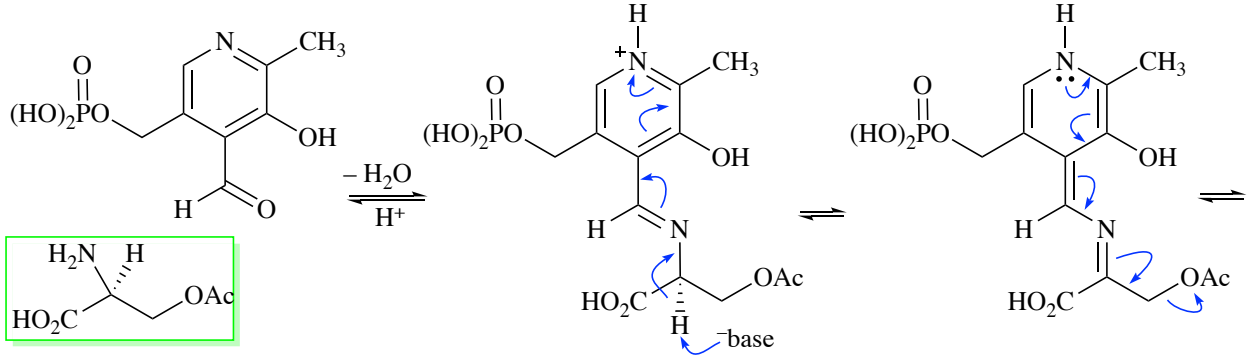


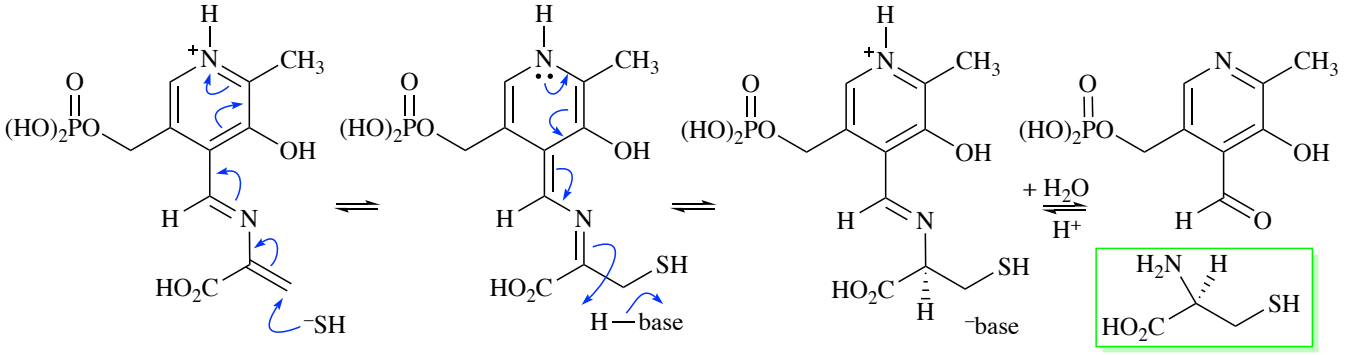
3.18. The acyl bromide tautomerizes to an enol, which reacts with Br_2. The MeOH reacts with the acyl bromide product by the regular addition–elimination method, with appropriate protonations and deprotonations.



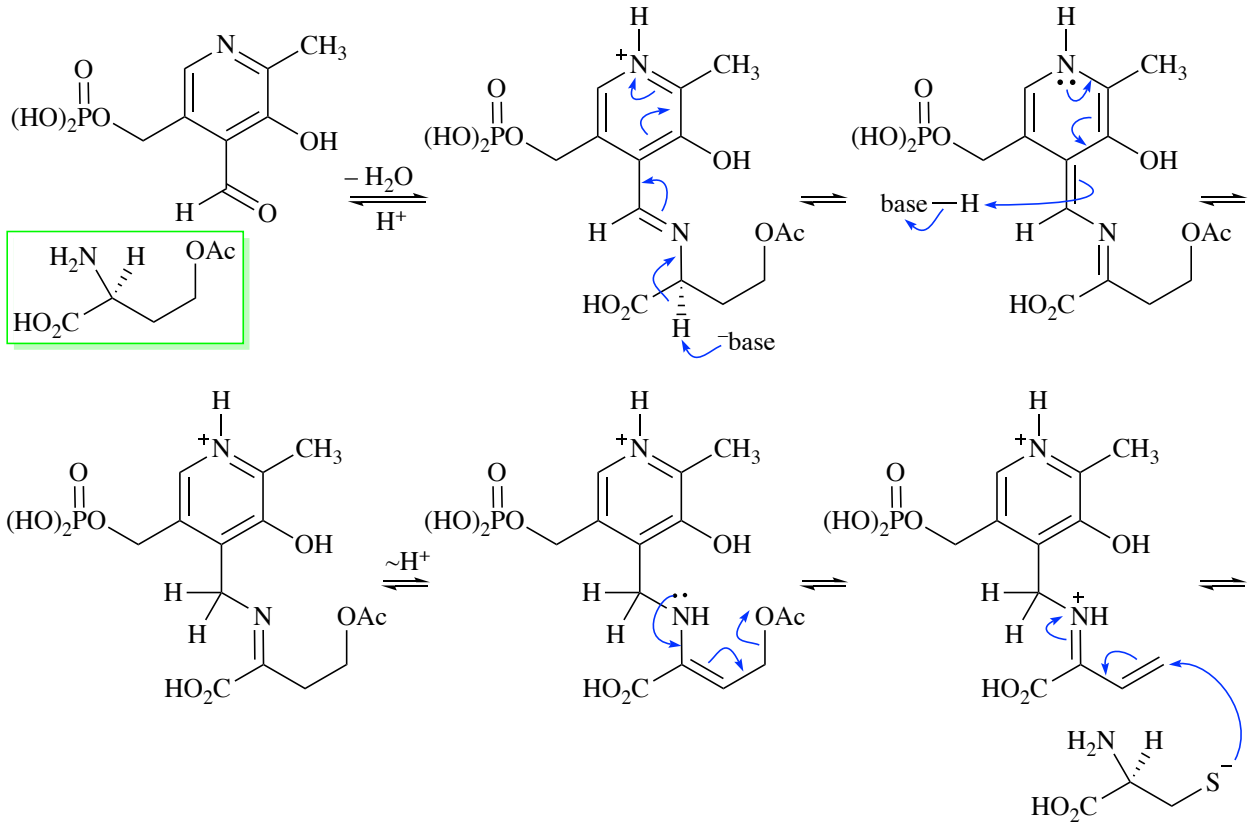
3.19.

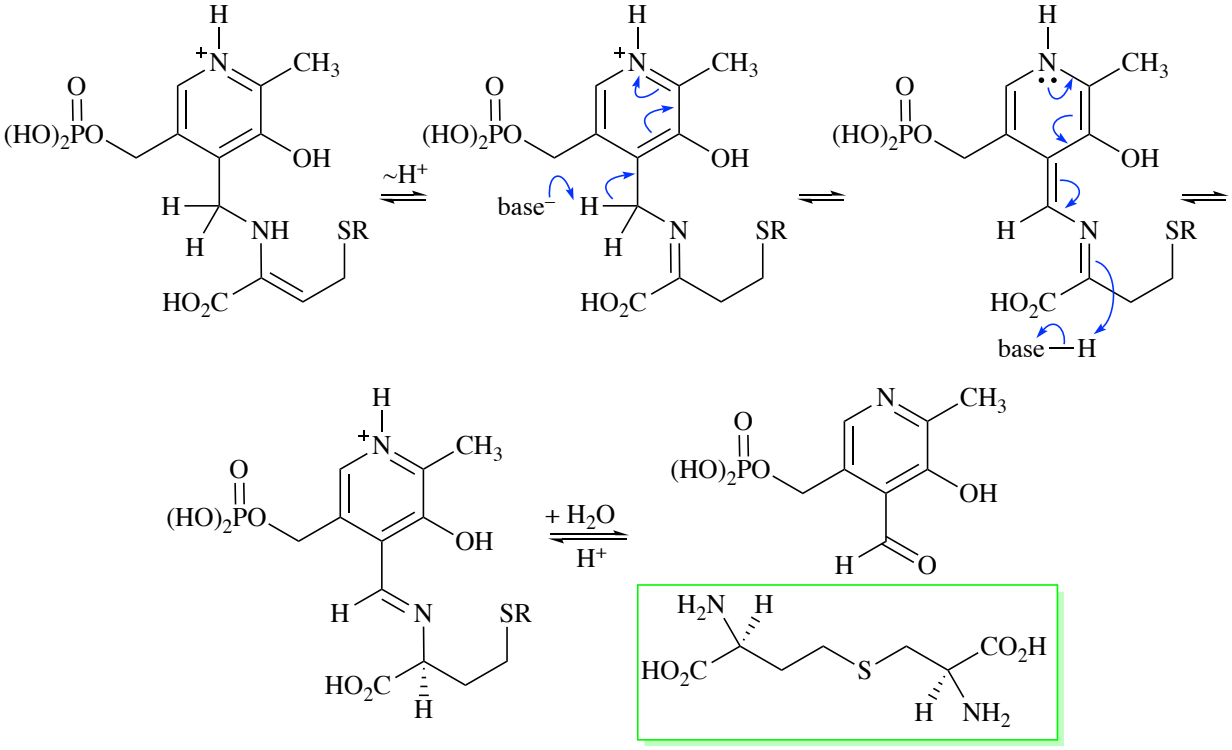
(a) After formation of the PLP imine of *O*-acetylserine, the elements of AcOH are eliminated by an E1cb mechanism to give an electrophilic alkene (conjugated to the pyridinium ion). The HS^- can then add to this alkene, and protonation of the α-C followed by hydrolysis gives cysteine.





(b) After formation of the PLP imine of *O*-acetylhomoserine, the imine is tautomerized to give an α-imino acid. The imine tautomerizes to the enamine. A substitution by the elimination–addition then occurs, replacing $^{-}$OAc with the thiolate. The enamine tautomerizes back to the imine, which then tautomerizes to a new imine. Hydrolysis of this new imine gives the diamino diacid and regenerates pyridoxal phosphate.




H
N
CH3
O
(HO)2PO
OH
H
H
NH
SR
HO2C
~H+
base−
base
+ H2O
H+
H2N
CO2H
S
NH2