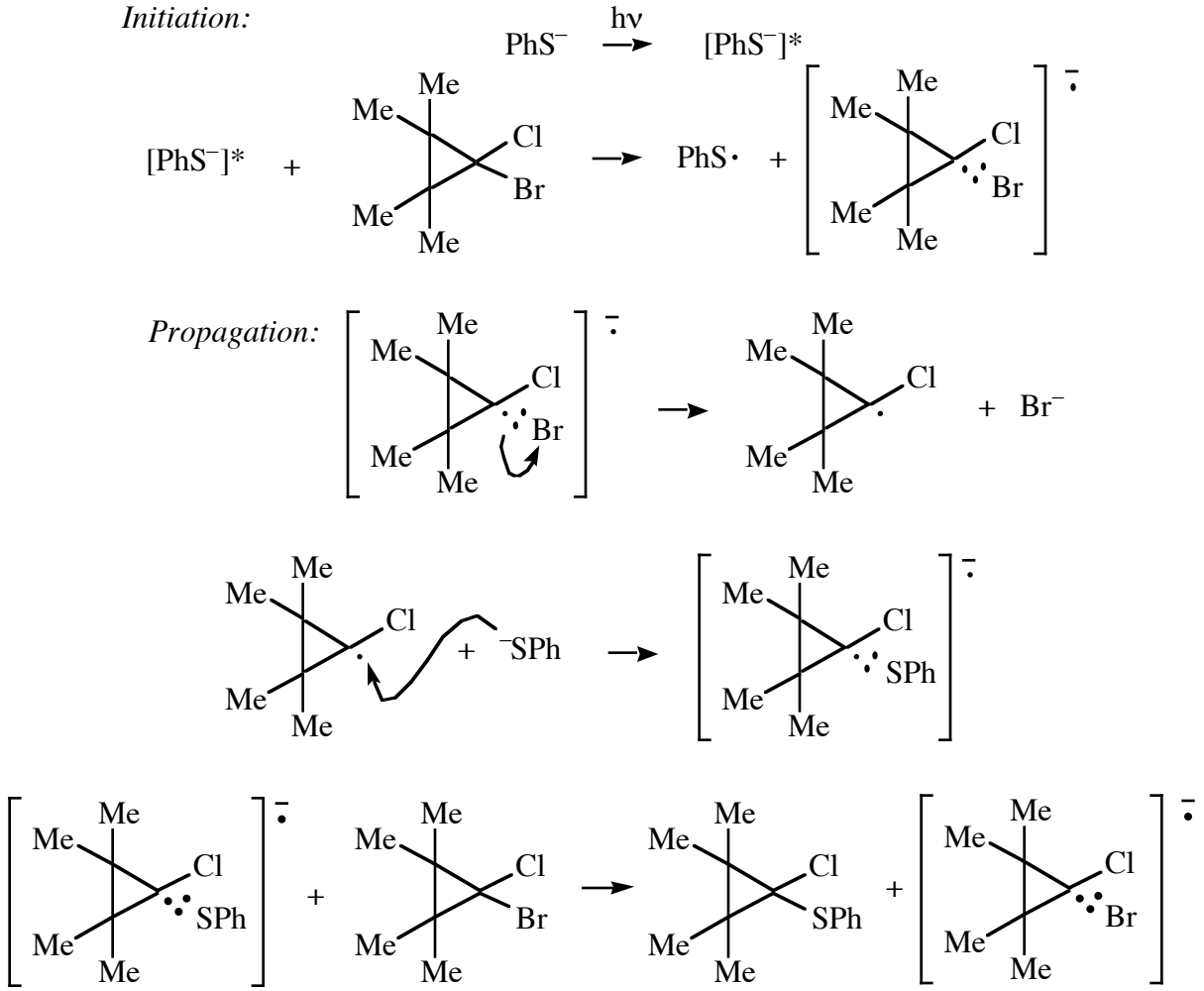
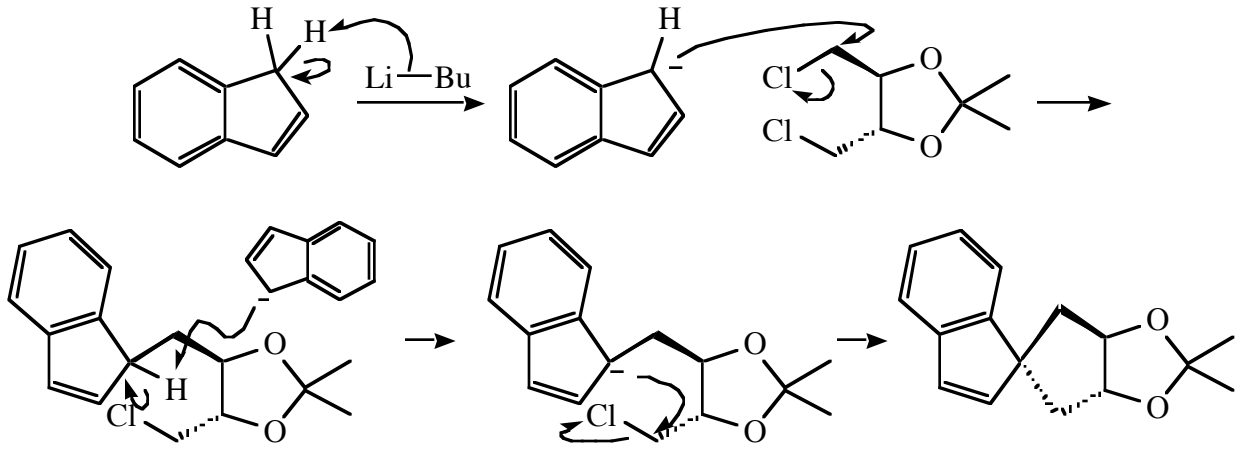
Answers To Chapter 2 Problems.

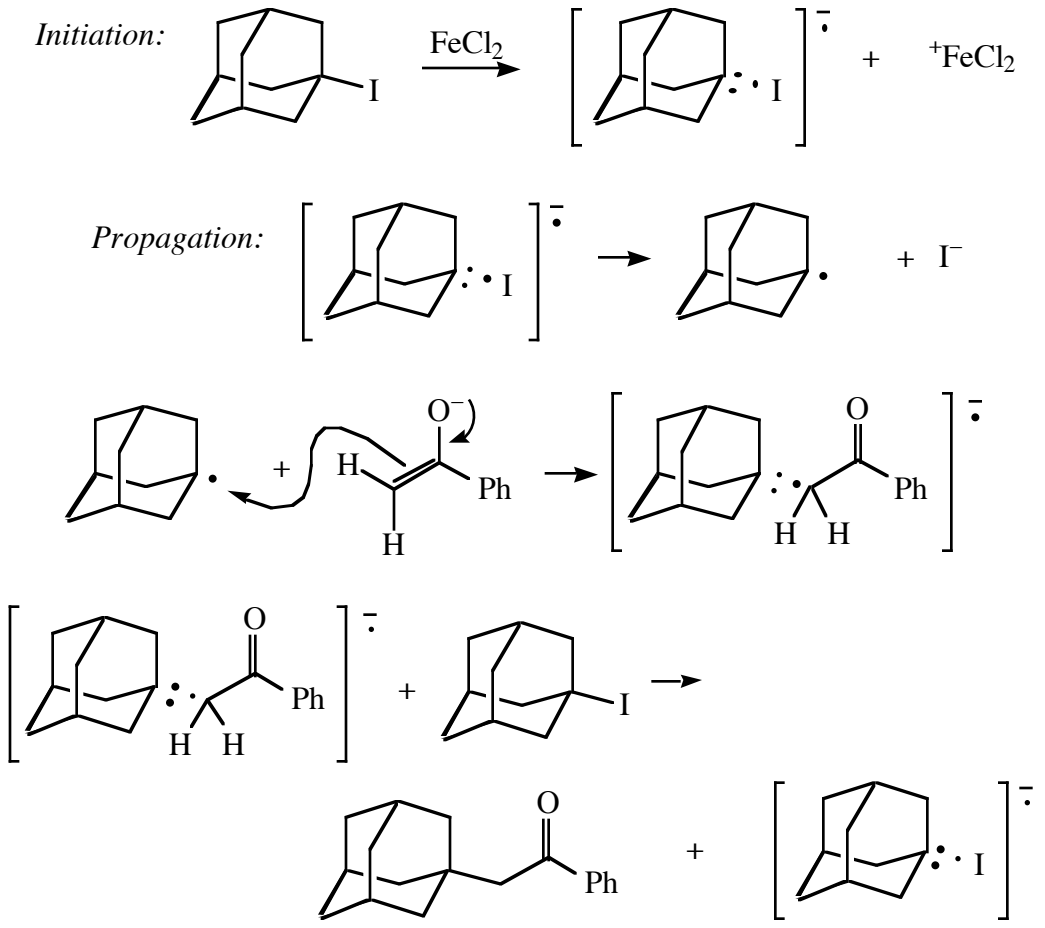
1. (a) Substitution at a 3° alkyl halide rarely proceeds by an S_N2 mechanism, unless the reaction is intramolecular. In this case S_N2 is even less likely because of the highly hindered nature of the electrophile and the fact that the electrophilic C is unlikely to want to expand its bond angles from 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.



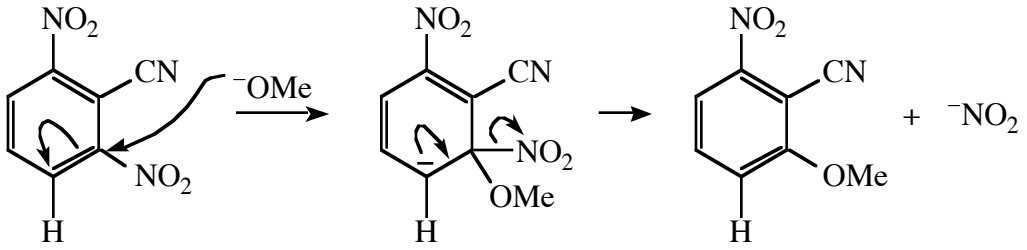
(b) The 1° halide will definitely undergo substitution by an S_N2 mechanism. Indene is a pretty good acid ($pK_a \approx 19$) due to aromatic stabilization of the anion. After deprotonation with BuLi, it attacks the electrophilic C by S_N2. A second equivalent of indenyl anion then redeprotonates the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



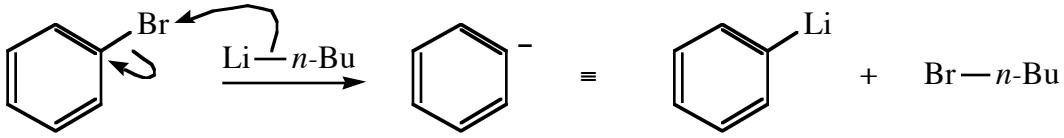
(c) This 3°, uninvertable halide cannot undergo S_N2 substitution. An elimination–addition mechanism is unlikely because the base is not terribly strong and the neighboring C–H bonds are not parallel to the C–I bond. The most likely possibility is $S_{RN}1$. C(sp^3)–I bonds are good substrates for $S_{RN}1$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

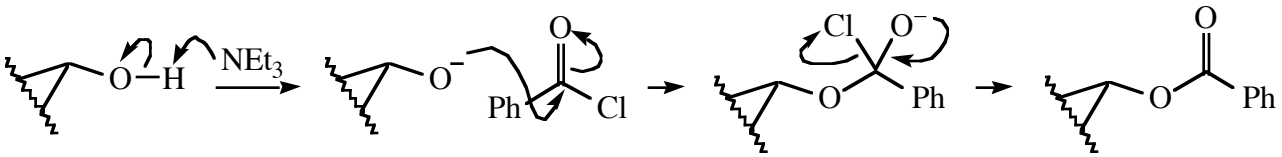
- The major product PhLi could react with the by-product *n*-BuBr in an S_N2 reaction.
- Addition–elimination could occur. PhBr is not an electrophilic arene, but the very high nucleophilicity of *n*-BuLi may compensate.
- An $S_{RN}1$ reaction could occur.
- Elimination–addition (benzyne mechanism) could occur.

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

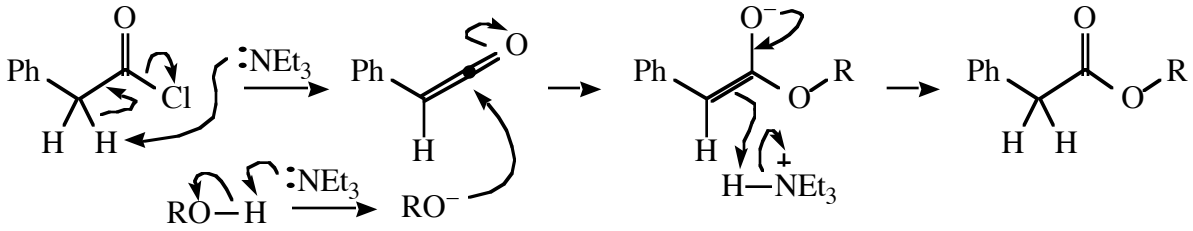
- Elimination–addition goes through a benzyne intermediate, and the nucleophile can add to either benzyne C, so both 3- and 4-bromotoluene should give mixtures of products if this mechanism is operative.
- Addition–elimination would accelerate (compared to halogen–metal exchange) with electron-withdrawing 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 substi-

tution 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.

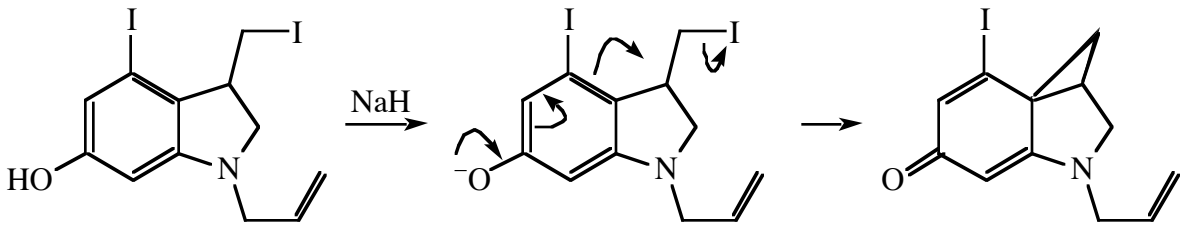
(f) Acyl chlorides can undergo substitution by two mechanisms: addition–elimination or elimination–addition (ketene mechanism). In this case, elimination–addition can't occur because there are no α H's. The mechanism must be addition–elimination.



(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.

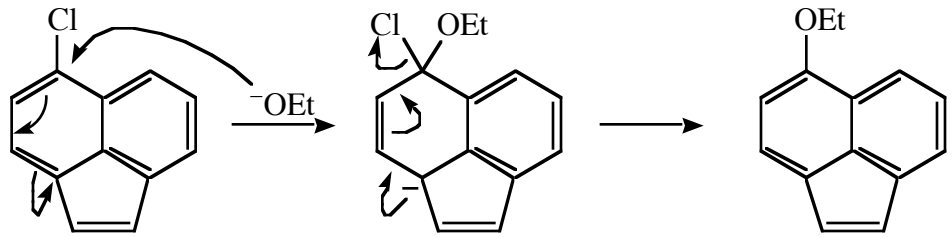


(h) The reaction proceeds by an S_N2 mechanism. The reaction has a very low entropy of activation, so it proceeds despite the loss of aromaticity. The product is a model of the antitumor agent duocarmycin. DNA reacts with duocarmycin by attacking the CH_2 group of the cyclopropane ring in an S_N2 reaction.

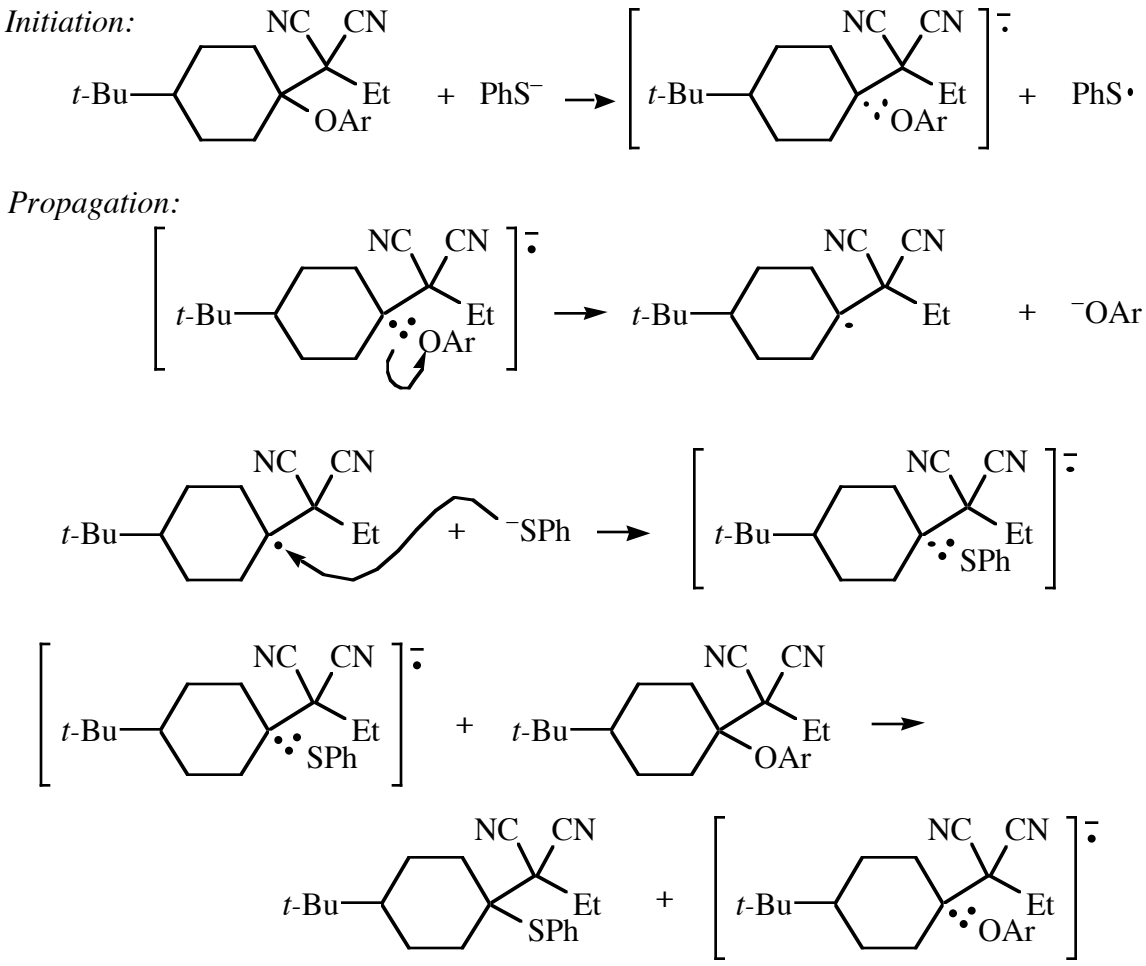


(i) This nucleophilic substitution reaction at aromatic C(sp^2) can proceed by addition–elimination, elimination–addition, or $S_{RN}1$. In this case, addition–elimination is low in energy because of the strong

stabilization of the Meisenheimer complex by aromaticity of the five-membered ring.

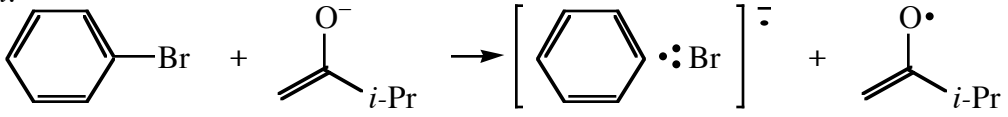


(j) The mechanism cannot be S_N2 because of the 3° alkyl electrophile. The most likely mechanism is $S_{RN}1$, which proceeds through radical anions. The best resonance structure of the radical anion of the starting material puts the odd electron in the aromatic ring, and the best resonance structure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

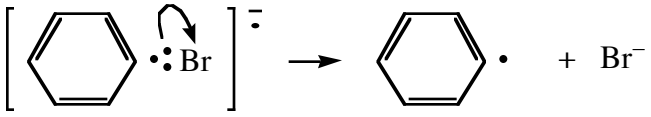


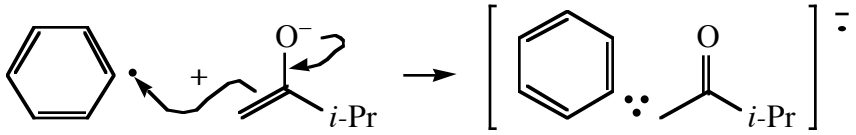
(k) Substitution at aromatic C(sp^2) can occur by one of three mechanisms. Addition–elimination requires that the ring be substituted with electron-withdrawing groups. Elimination–addition requires very strong bases like NH_2^-. The third mechanism, $S_{RN}1$, is operative here; the light is a clue that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

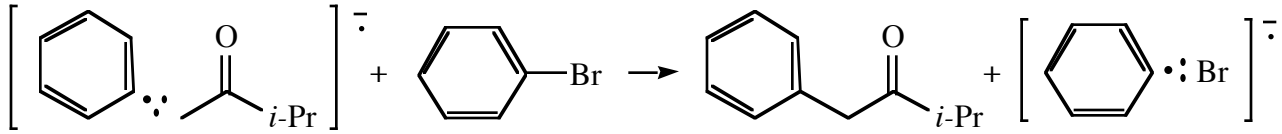
Initiation:



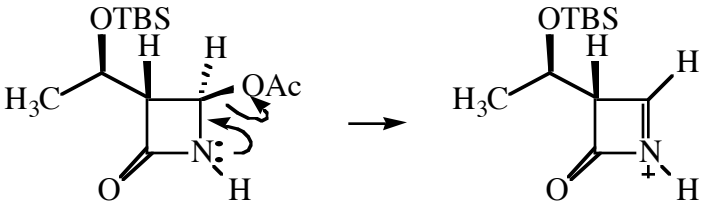
Propagation:

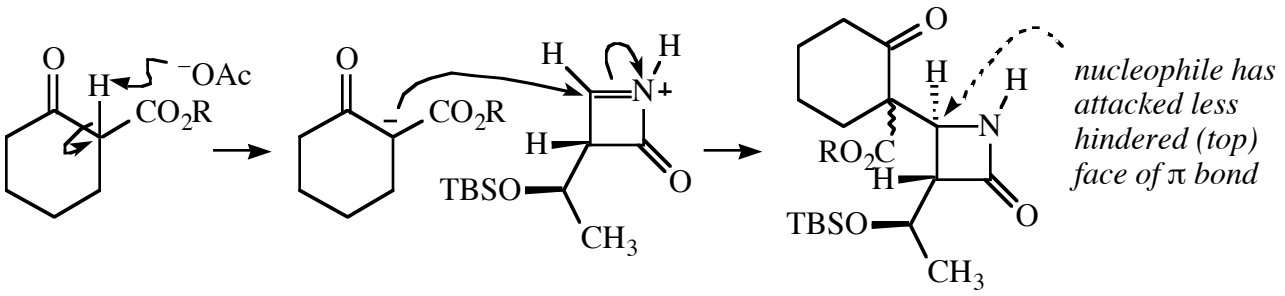




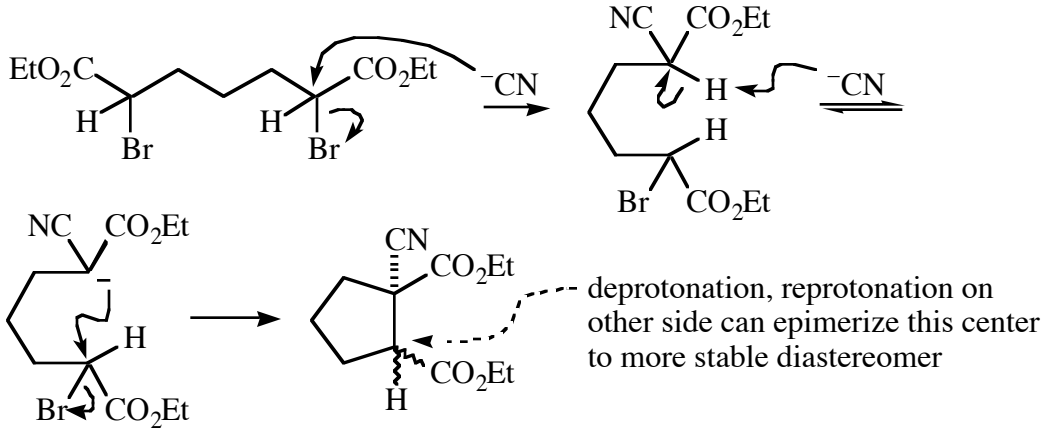


(l) The mechanism clearly cannot be S_N2, because substitution occurs with retention of configuration. Two sequential S_N2 reactions are a possibility, but unlikely, because $^-$OAc is a lousy leaving group in S_N2 reactions. It is more likely that an elimination–addition mechanism operates. The AcO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

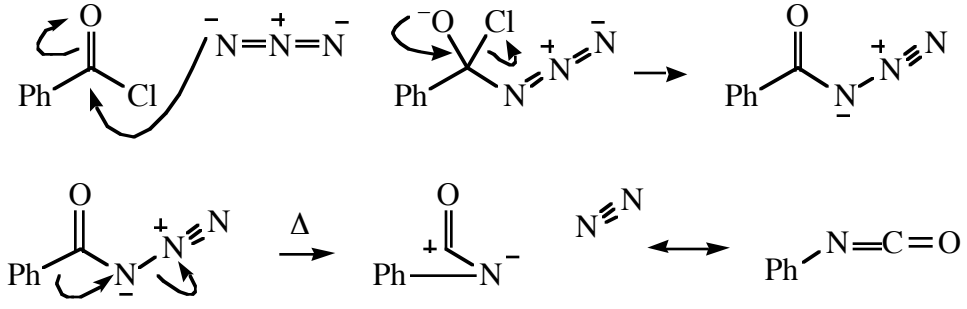




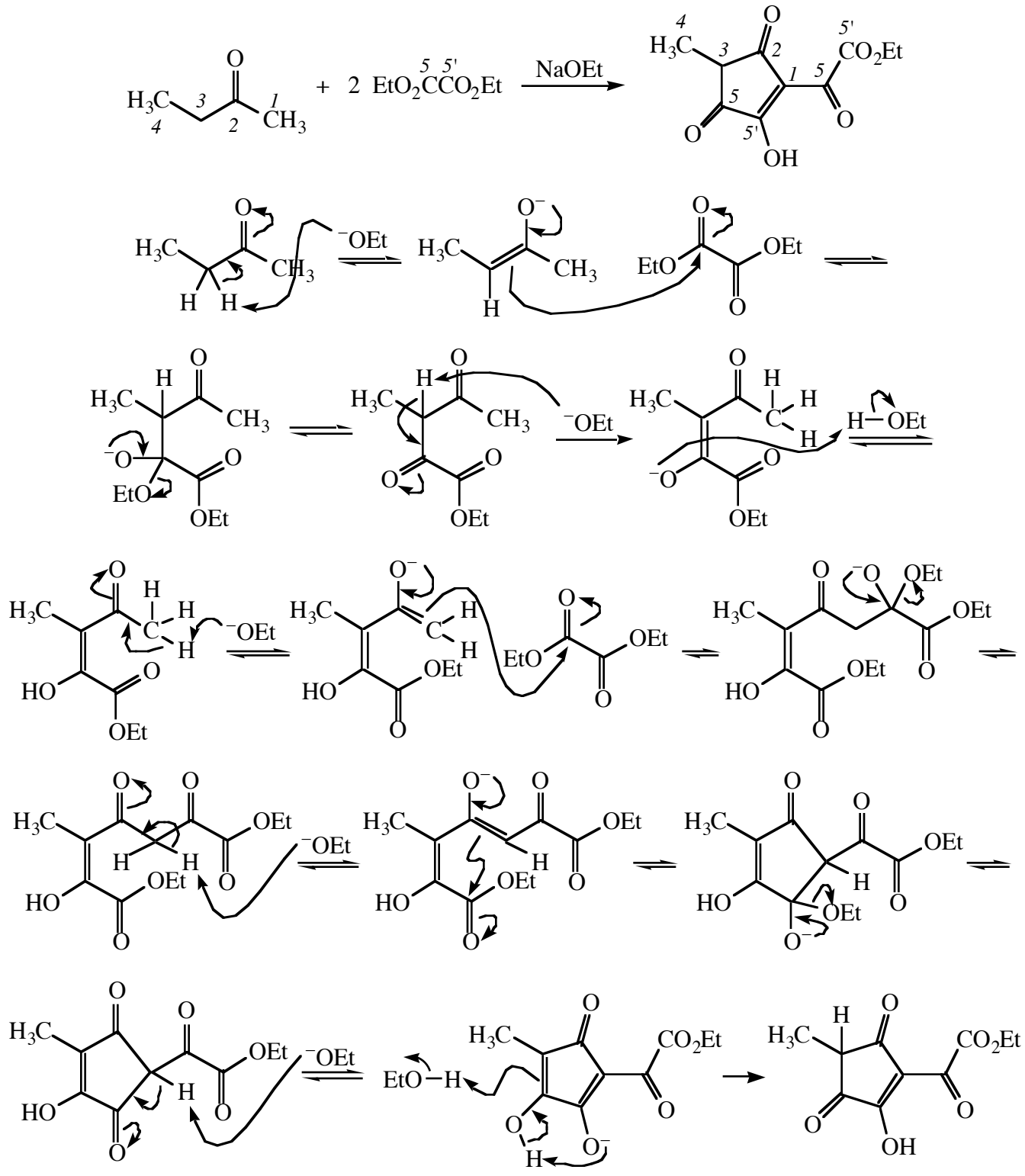
2. (a) Cyanide can act as a nucleophile toward the bromoester, displacing one Br^- in an S_N2 reaction to give a cyanoacetate. The cyanoacetate ($pK_a = 9$) is deprotonated by another equivalent of ^-CN ($pK_b = 9$) to give an enolate that attacks the *other* bromoester to give the product.



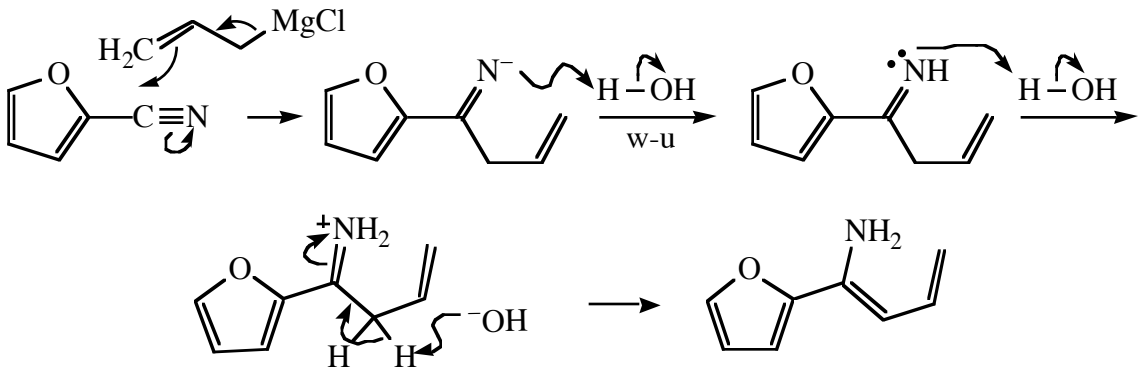
(b) The acyl chloride is a potent electrophile and N_3^- is a nucleophile, so the first part of the reaction involves addition–elimination to make the acyl azide. Upon heating, the Ph–CO bond breaks and a Ph–N bond forms. This suggests a 1,2-shift, promoted by loss of N_2.



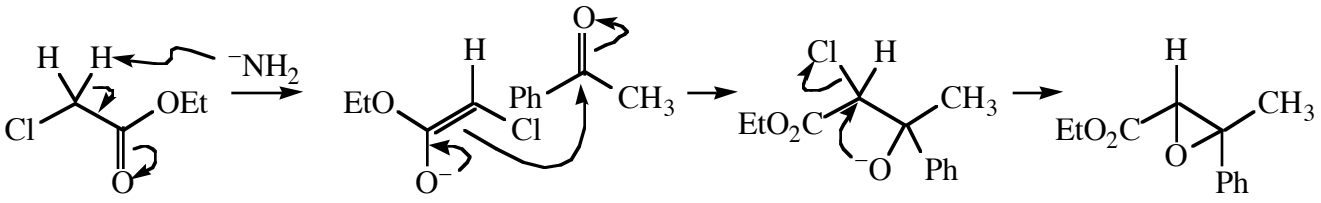
(c) Make: C1–C5, C1–C5', C3–C5. Break: C5–OEt (twice), C5'–OEt (once). Each substitution at C(sp^2) must occur by addition–elimination. The particular order of acylation events can vary from the answer given here.



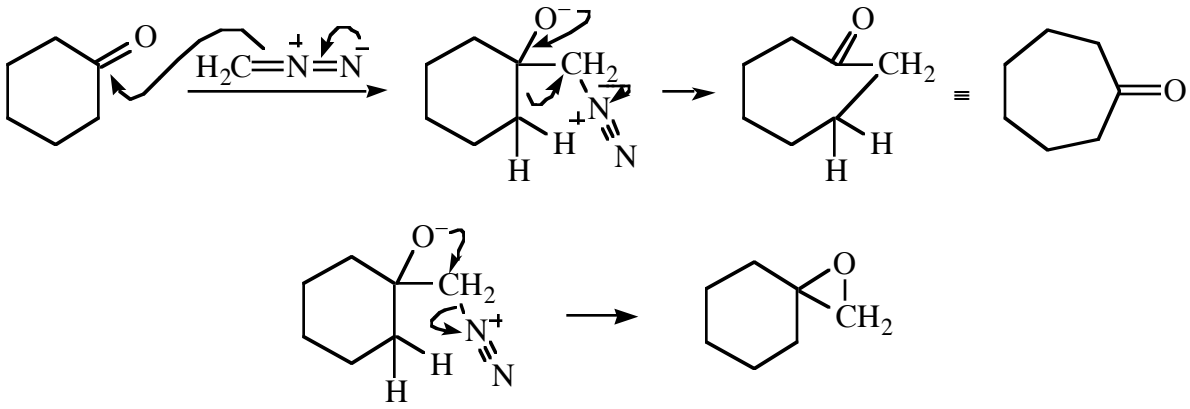
(d) Either the α or the γ carbon of the Grignard reagent can attack the nitrile. Isomerization of the initial product occurs upon workup, probably by protonation–deprotonation (rather than deprotonation–protonation) because of the weak acidity and decent basicity of imines.



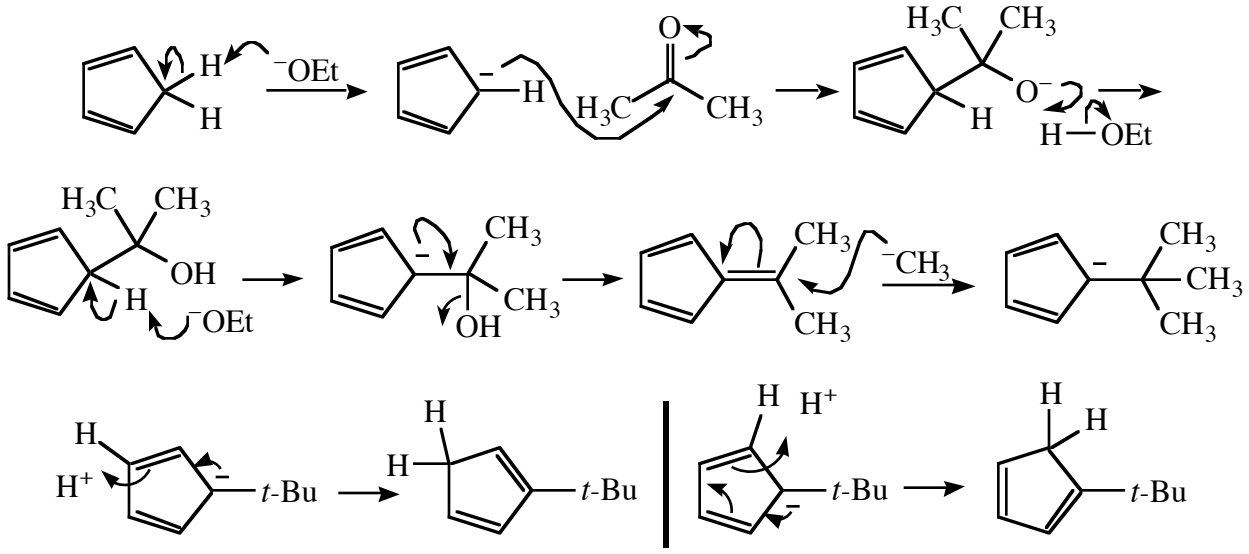
(e) One C–C and one C–O bond are formed. The ketone O is not nucleophilic enough to participate in S_N2 reactions, so the initial event must be attack of the ester enolate on the ketone. Sodium amide acts as a base.



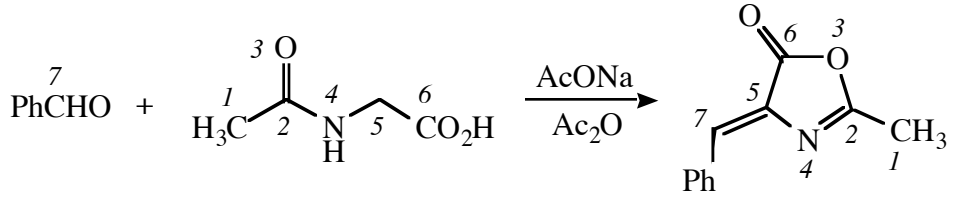
(f) The C in diazomethane is nucleophilic. The product of attack of diazomethane on the carbonyl C has a leaving group α to the alkoxide, so either a 1,2 alkyl shift or direct nucleophilic displacement can occur. The insertion product happens to dominate with $H_2\bar{C}–\overset{+}{N}_2$, but with $H_2\bar{C}–\overset{+}{S}Me_2$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

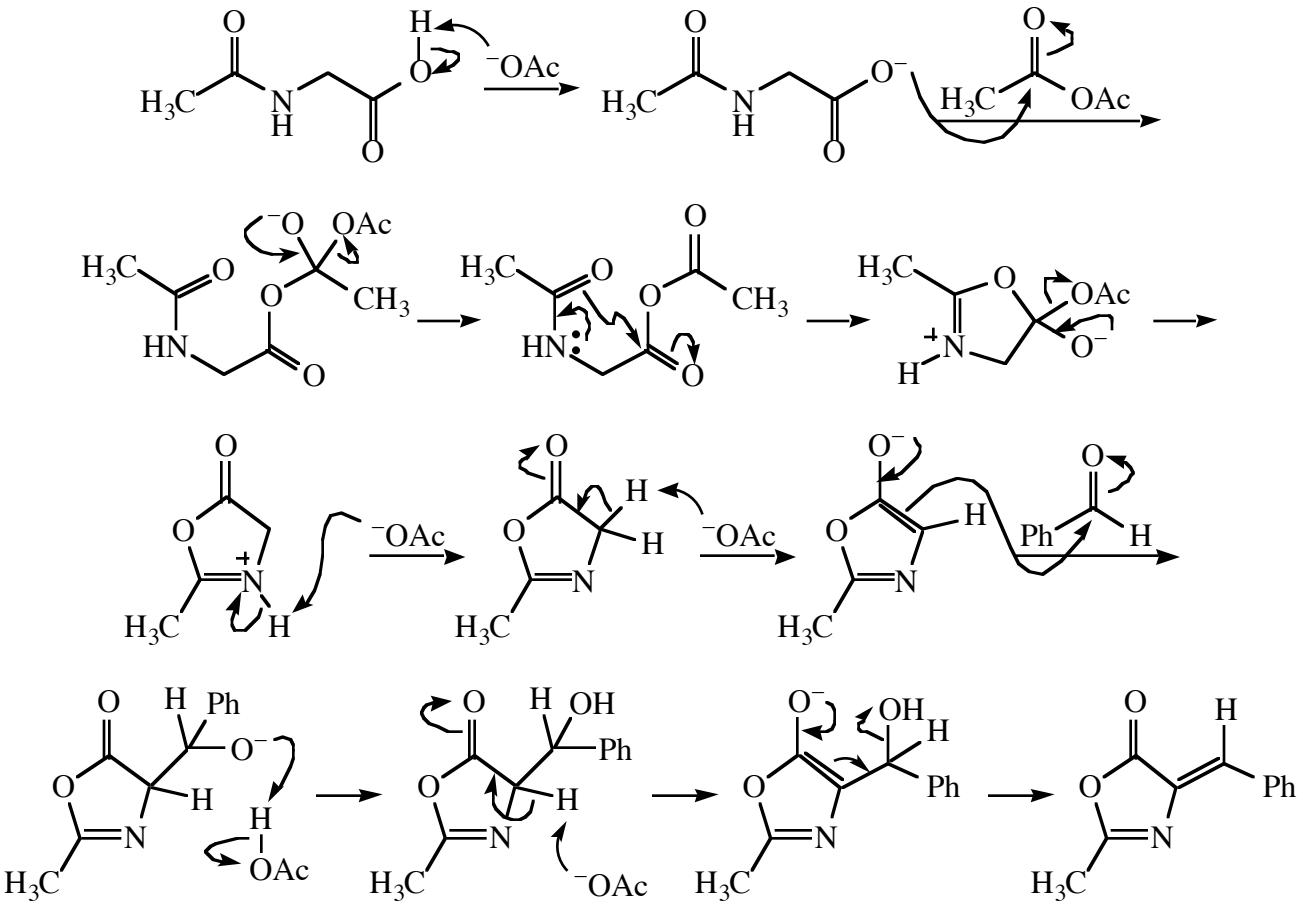


(g) Cyclopentadiene is very acidic, and its conjugate base is very nucleophilic. It can undergo aldol reactions with carbonyl compounds. After dehydration, a *fulvene* is obtained. The fulvene is an electrophile because when a nucleophile adds to the exocyclic double bond, the pair of electrons from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



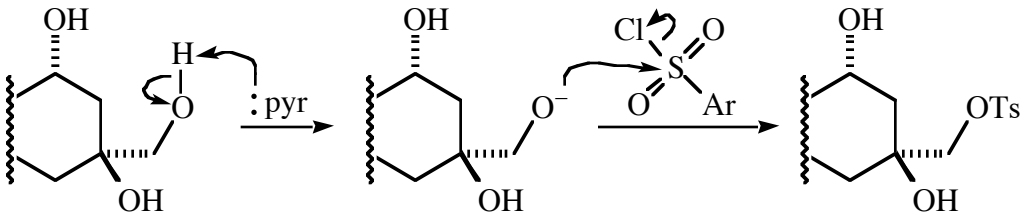
(h) Two new bonds are formed: O3–C6 and C5–C7. O3 is nucleophilic, while C6 is moderately electrophilic; C5 is nucleophilic only after deprotonation, and C7 is quite electrophilic. Under these very mildly basic conditions, it is unlikely that C5 will be deprotonated, so it is likely that the O3–C6 bond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



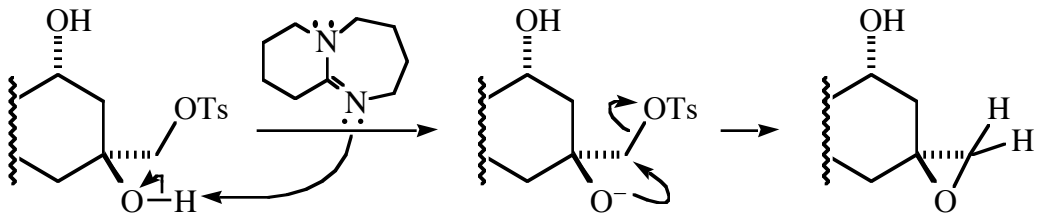


(i) Overall, the 1° OH is replaced by H. The H is presumably coming from $LiAlH_4$, a good source of nucleophilic H^-, so the 1° OH must be transformed into a good leaving group. The first step must transform the 1° alcohol into a tosylate. The mechanism of reaction of an alkoxide with TsCl is probably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

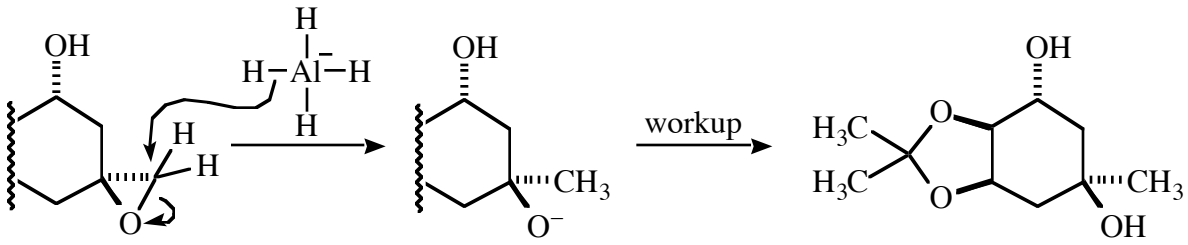
Step 1:



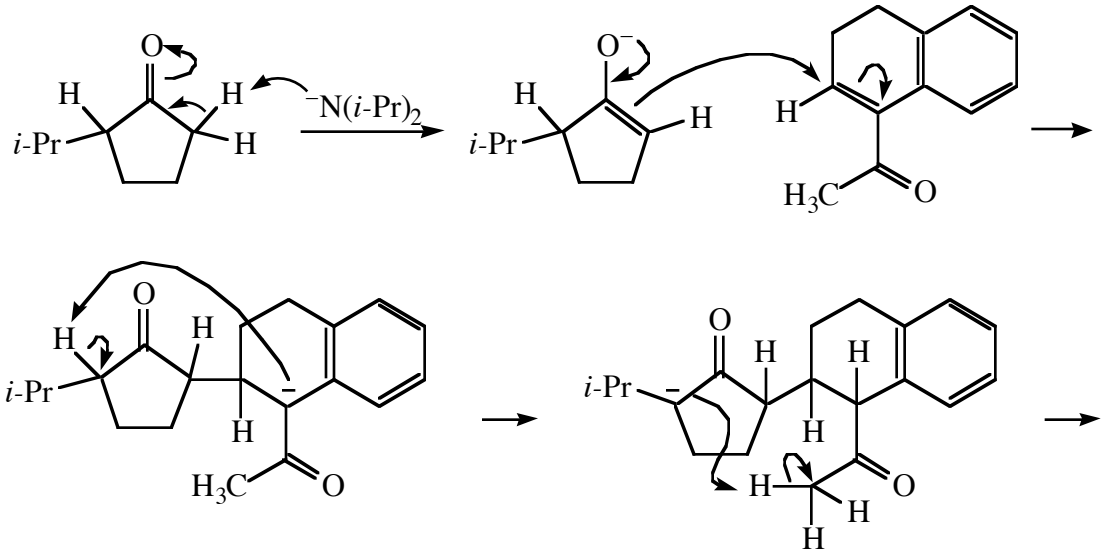
Step 2:

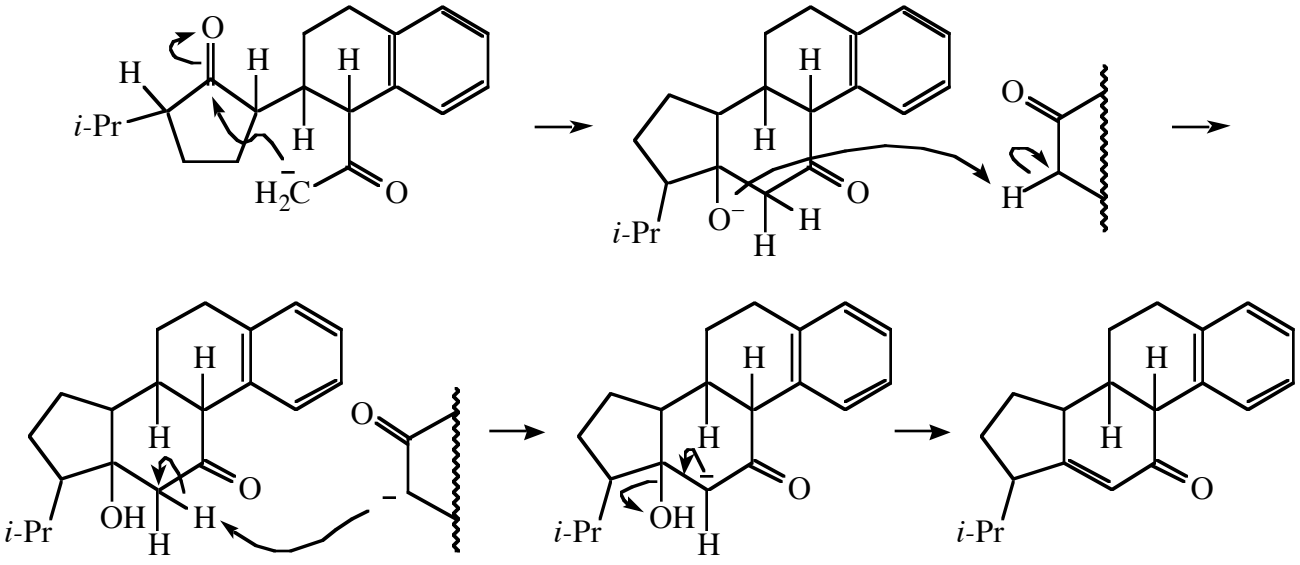


Step 3:

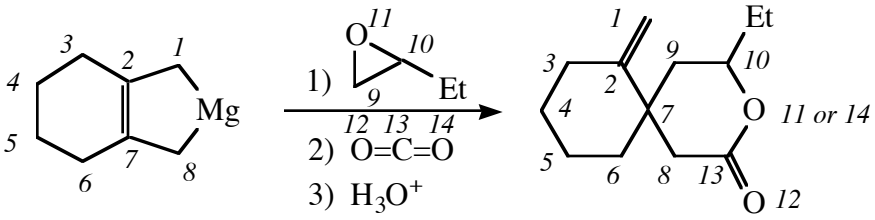


(j) LDA deprotonates the less hindered of the two acidic C atoms. A Robinson annulation then occurs by the mechanism discussed in the text. Two proton transfers are required in the course of the annulation, and both must occur by a two-step mechanism in which the substrate is first protonated, then deprotonated.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

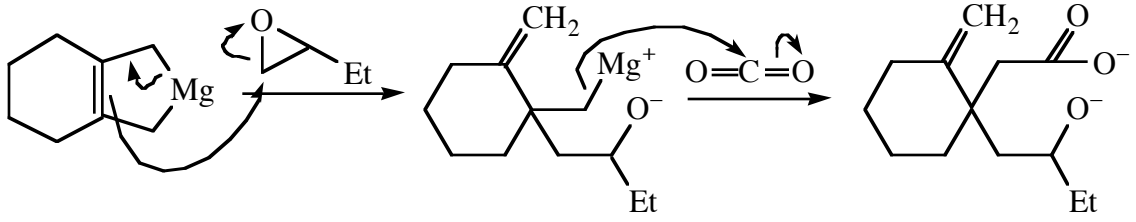




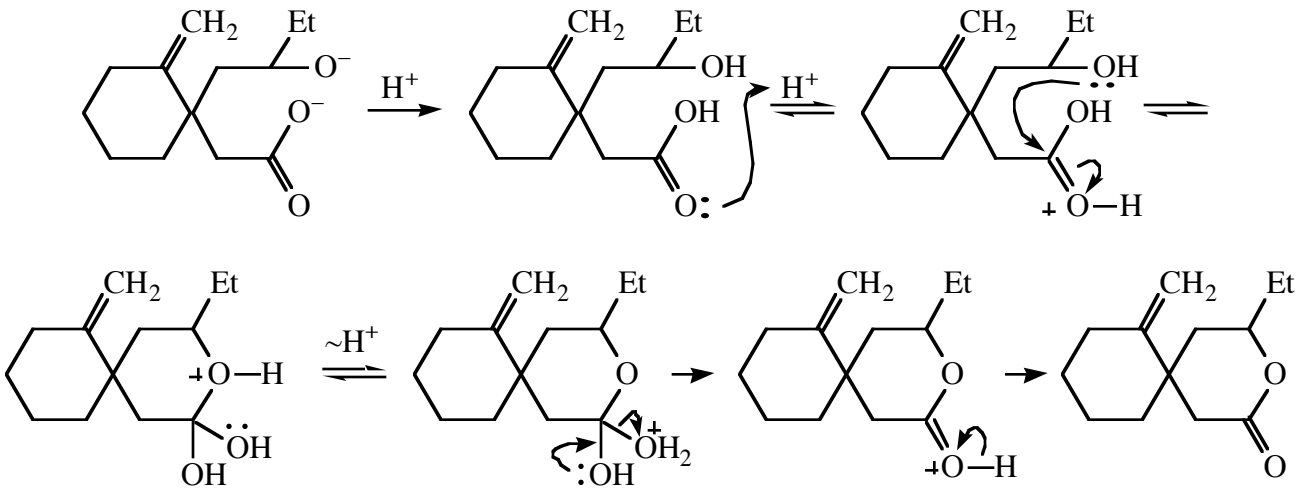
(k) Make: C7–C9, C8–C13, and either O11–C13 or C10–O14. Break: Either C10–O11 or C13–O14.



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.

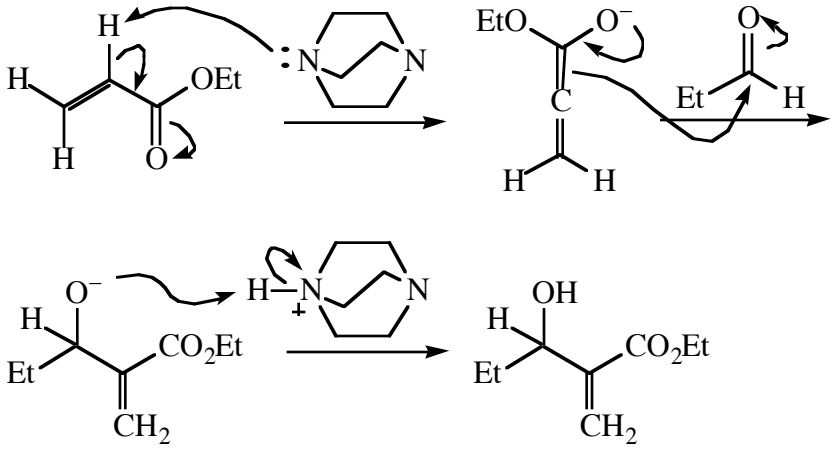


Upon addition of acid, the alcohol reacts with the carboxylic acid to give a lactone (cyclic ester). This acid-catalyzed reaction is discussed in detail in Chapter 3. The reaction is far more likely to occur by attack of O11 on C13 than by attack of O14 on C10.

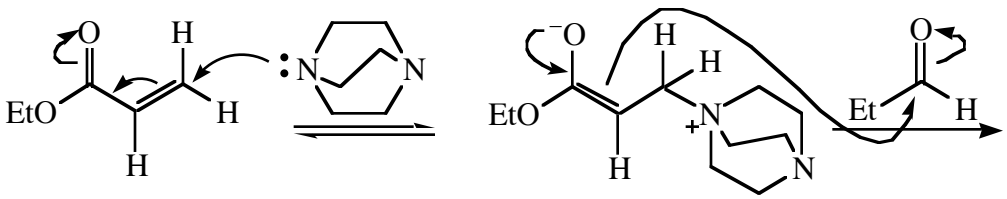


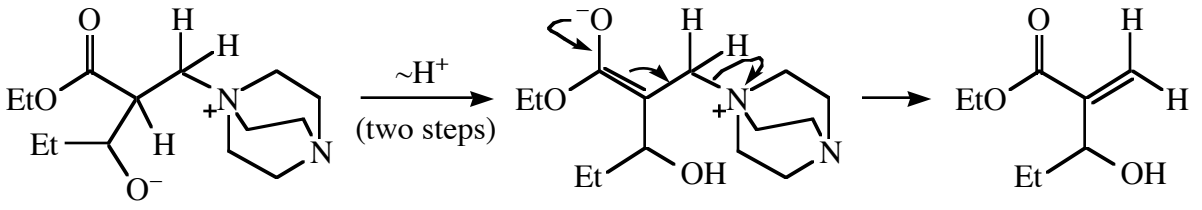
(ℓ) 1,4-Diazabicyclo[2.2.2]octane (DABCO) can act as either a base or a nucleophile. When it acts as a base, it deprotonates C2 to give an enolate, which attacks the aldehyde in an aldol reaction to give the product after proton transfer. When it acts as a nucleophile, it adds to the electrophilic C3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

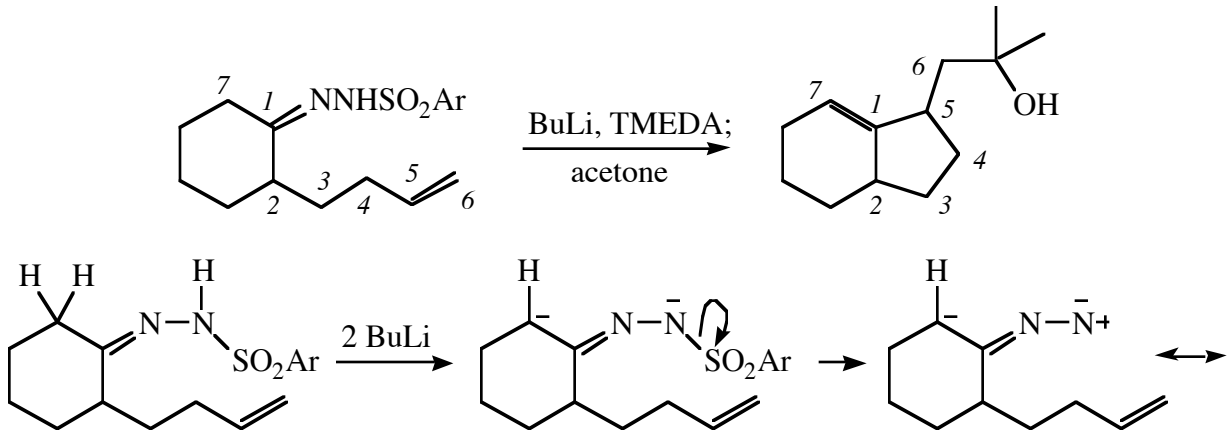


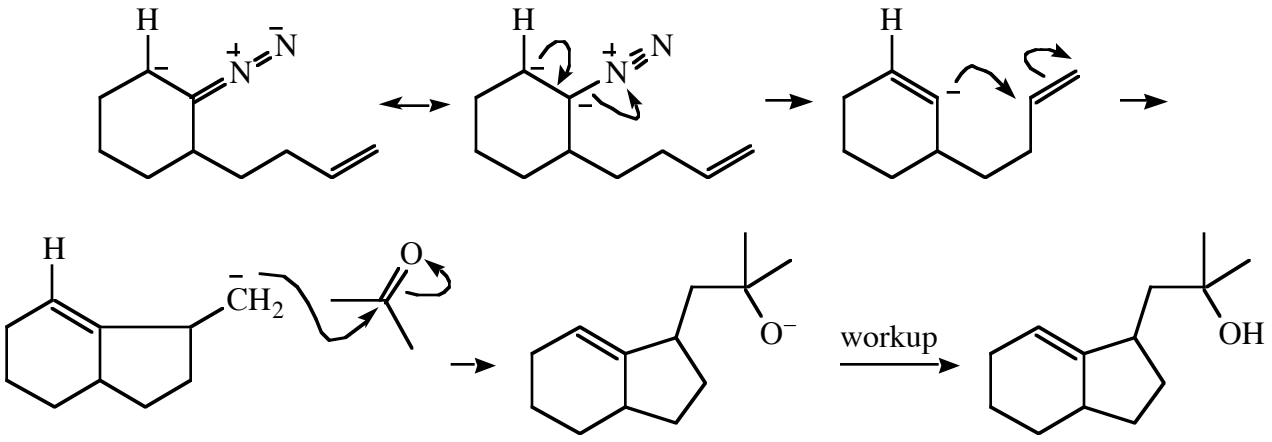


The second mechanism is much more likely, even without the information in problem (m), as C(sp^2)–H bonds α to carbonyls are not very acidic. (See Chapter 1.)

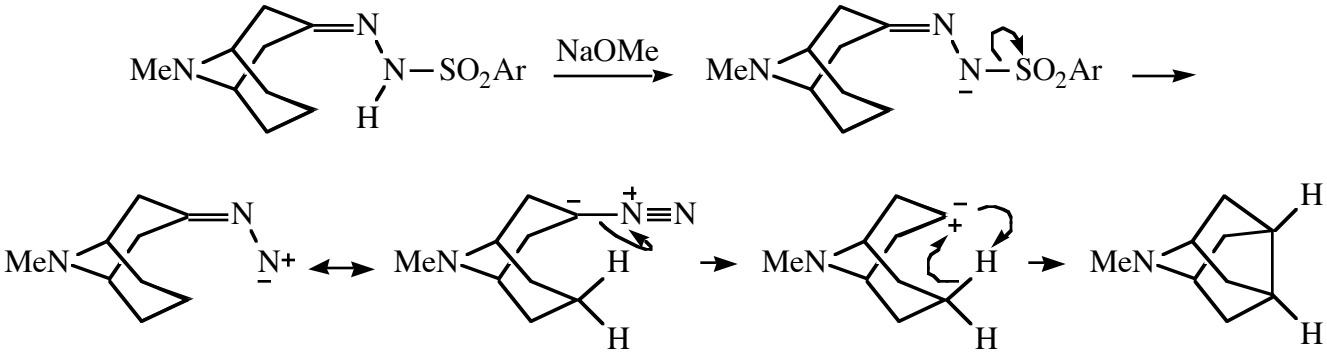
(m) Nucleophilicity is dramatically affected by steric bulk, whereas basicity is only slightly affected. If steric bulk in the amine catalyst affects the rate of the reaction dramatically, then DABCO must be acting as a nucleophile, not a base.

(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.

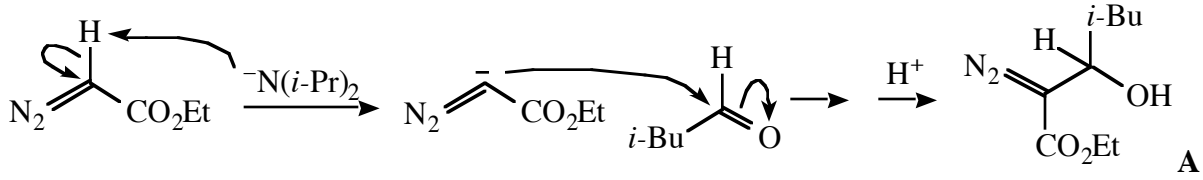




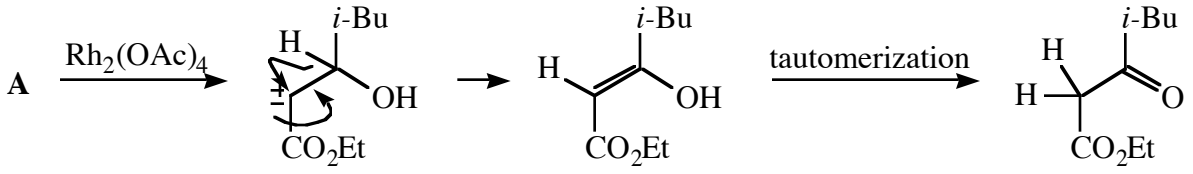
(o) This is a Bamford–Stevens reaction. We are forming a new C–C bond to a remote, unactivated C, suggesting a carbene inserting into a C–H bond. The base deprotonates N. α-Elimination of $ArSO_2^-$ gives the diazo compound, which spontaneously loses N_2 to give the carbene. The carbene inserts into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



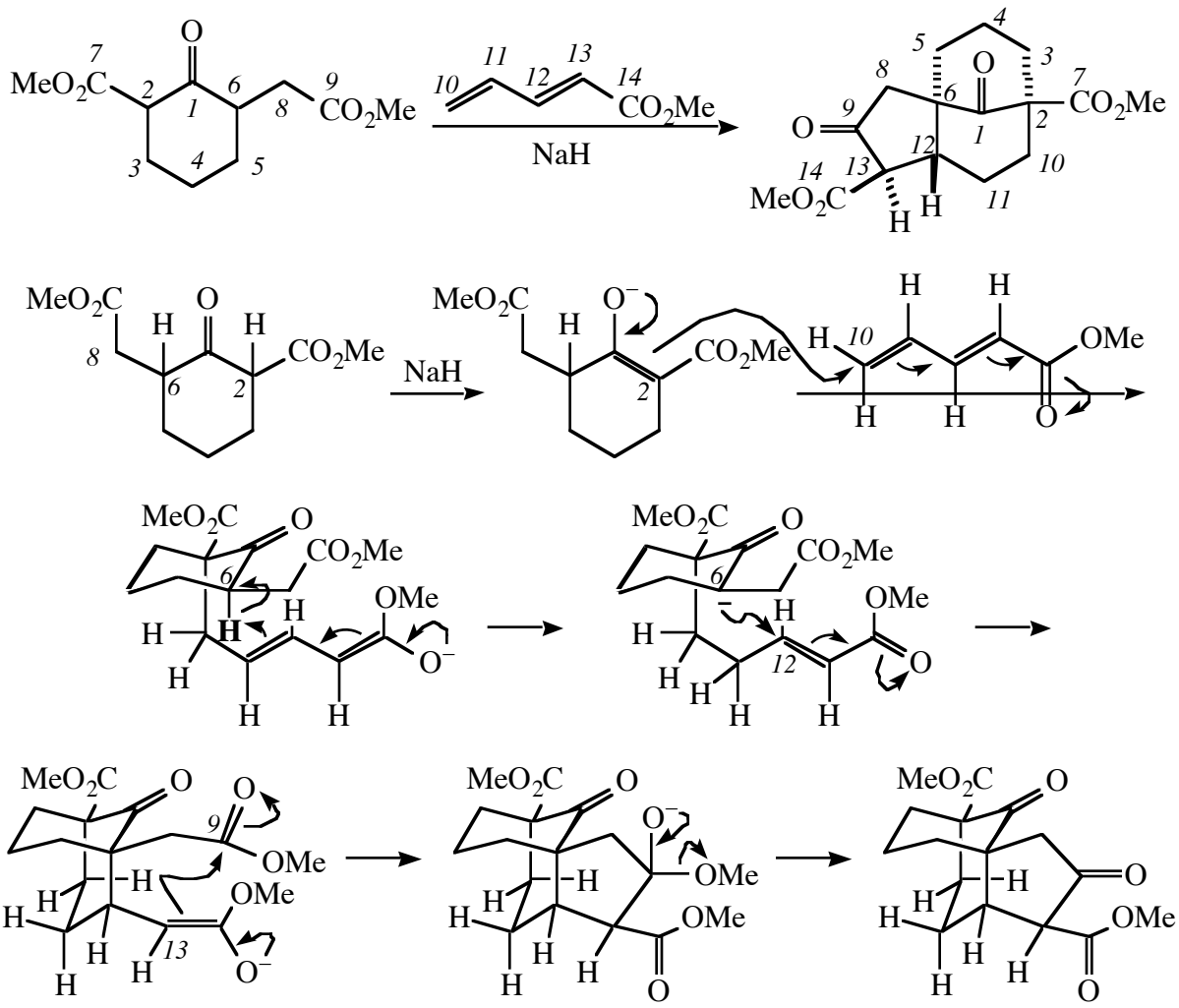
(p) LDA is a strong, nonnucleophilic base. It will deprotonate the diazo compound, turning it into a good nucleophile. Addition to the aldehyde C=O bond and workup gives intermediate **A**. Now, treatment of **A** with Rh(II) generates a carbenoid, which reacts as if it were a singlet carbene. A 1,2-shift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



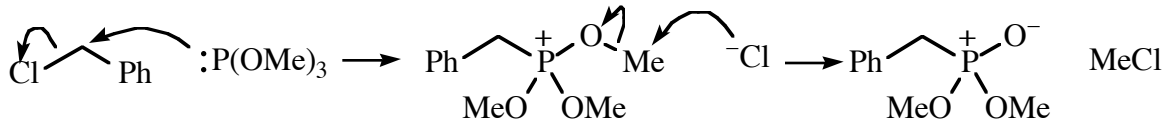
A



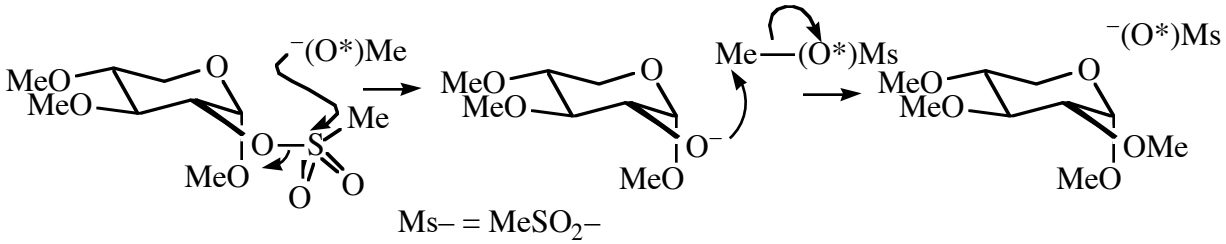
(q) Make: C2–C10, C6–C12, C9–C13. Break: none. C2 and C6 are nucleophilic (once they are deprotonated), while C9, C10 and C12 are electrophilic. C2 is by far the most acidic site, so the C2–C6 bond is probably formed first.



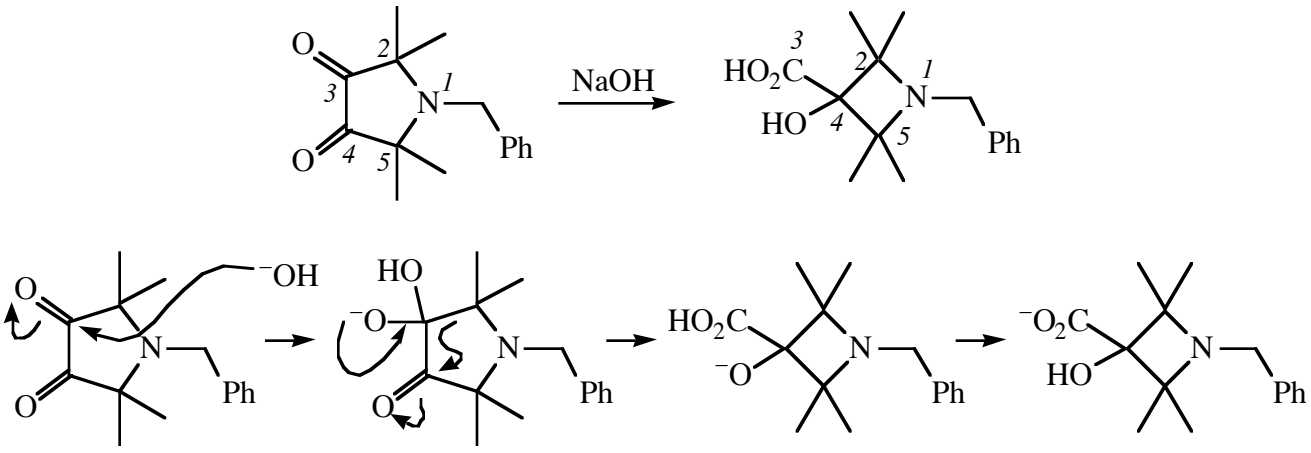
(r) The by-product is MeCl. Make: P–Bn, Me–Cl. Break: O–Me. The first step is attack of nucleophilic P on the electrophilic BnCl. Then Cl^- comes back and attacks a Me group, displacing O^- to give the phosphonate.



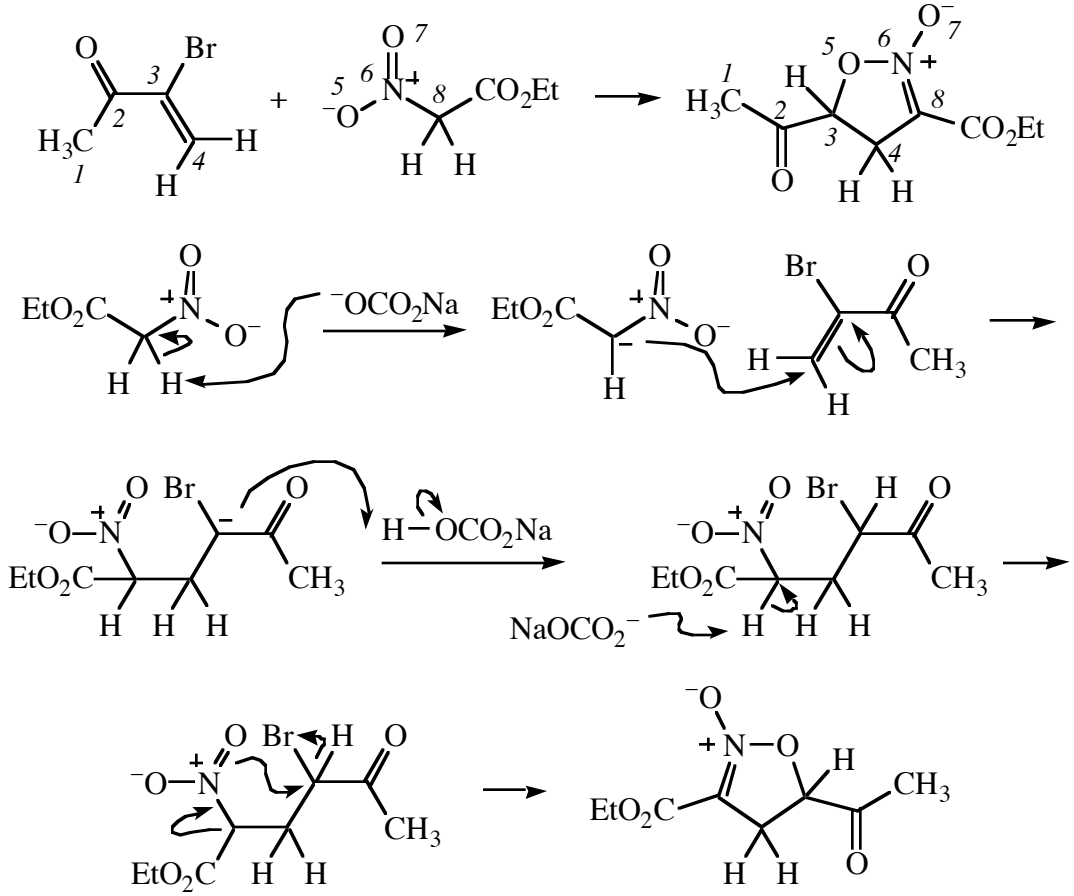
(s) Clearly simple S_N2 can't be the answer, as configuration is retained at C2 and ^{18}O incorporation into the product is not observed. The other electrophilic site in this compound is the S of the Ms group. Cleavage of the Ms–OR bond can occur under these basic conditions. Attack of Me(*O)$^-$ on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



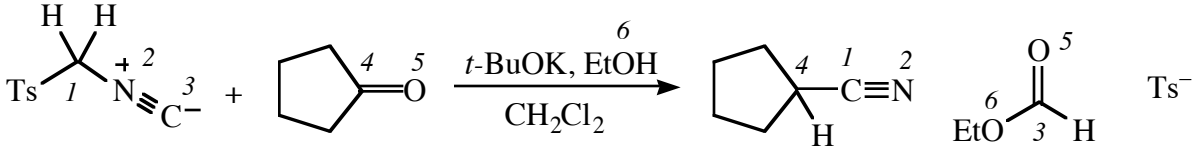
(t) The benzilic acid rearrangement was discussed in the text (Section E.1).



(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.

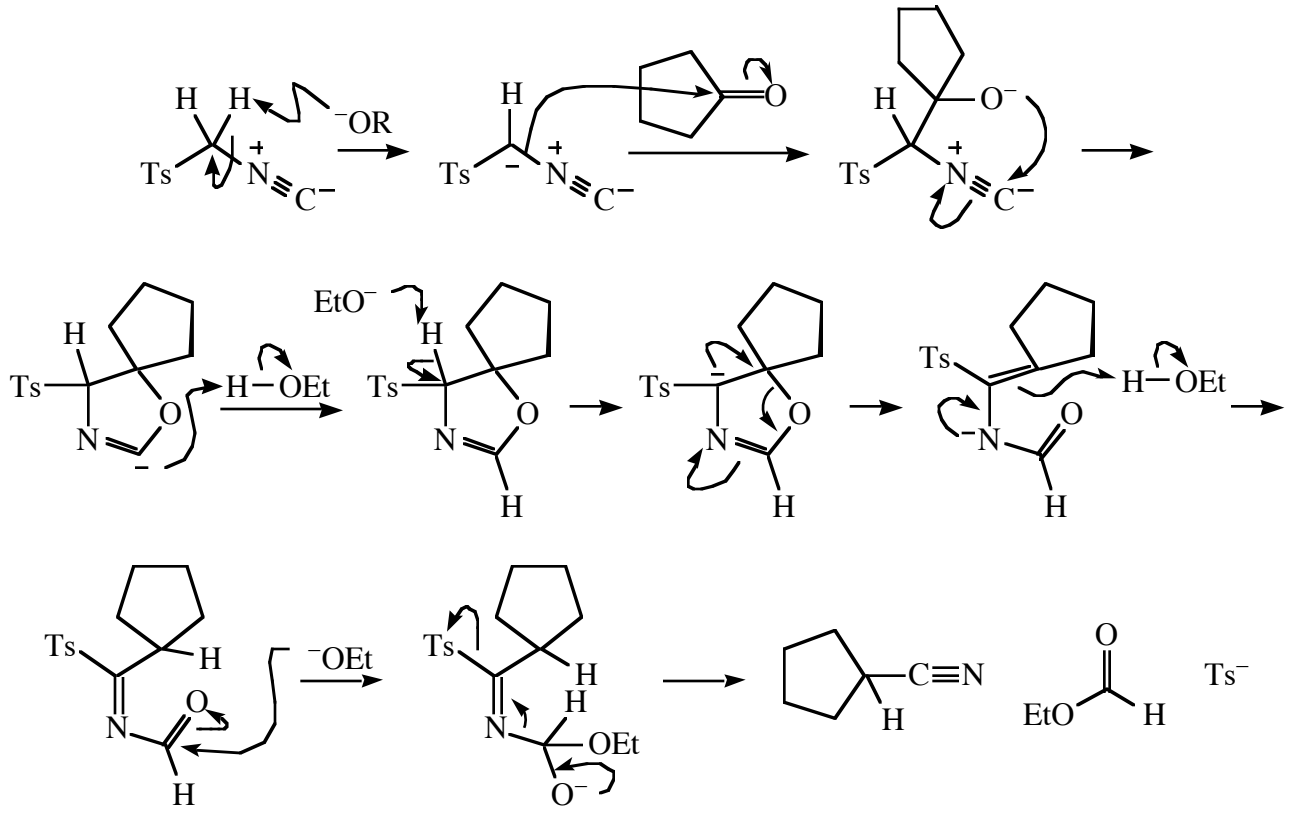


(v) Numbering the atoms correctly is key here. The cyanide C in the product could be C1 and the formate C, C3, or vice versa. How do we tell which? If the cyanide C is C3, this would mean that attack of C3 on C4 would occur. But this reaction would not require base, and we're told that base is required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

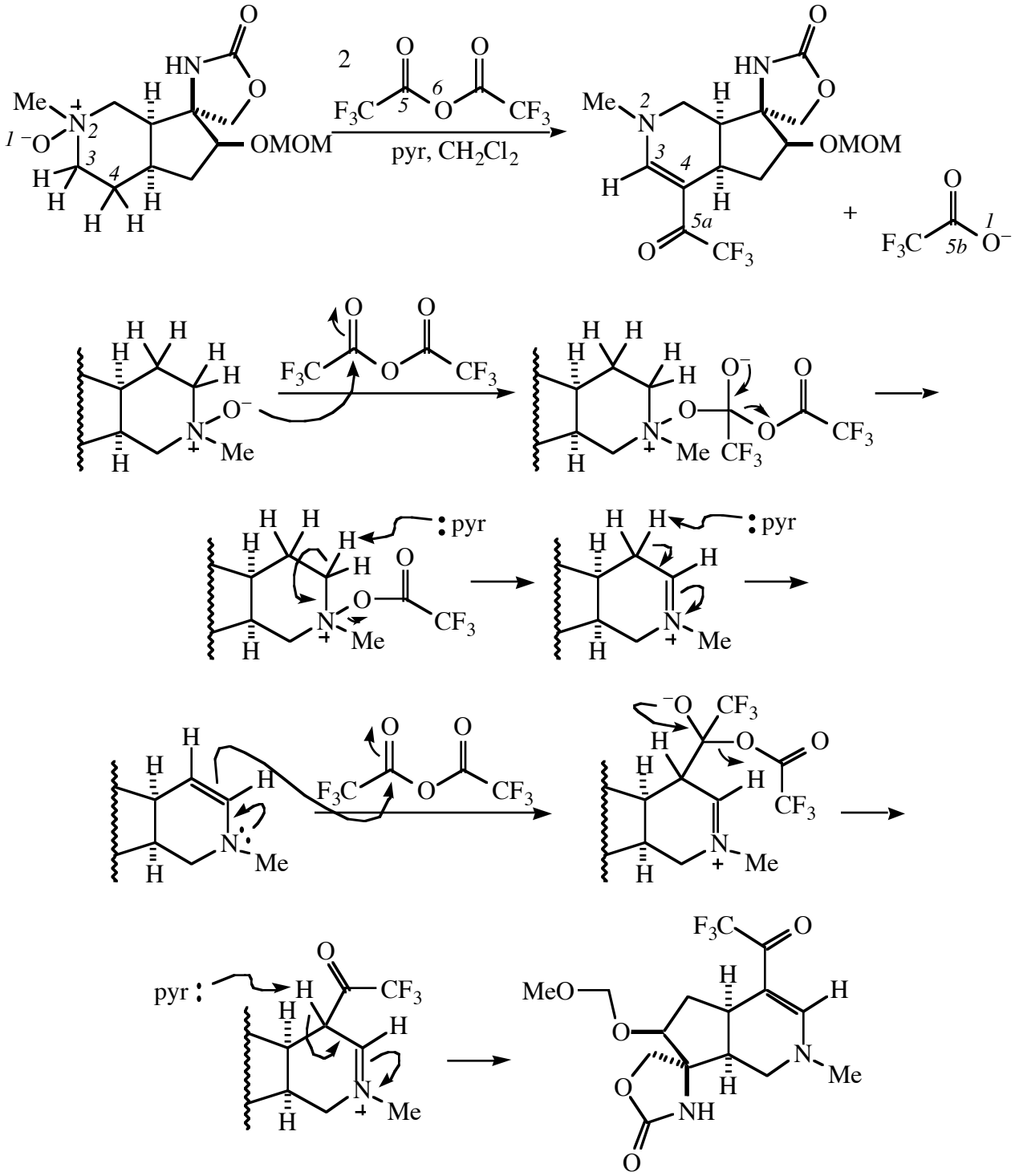


Deprotonation of C1 is followed by attack of C1 on C4 to give an alkoxide at O5. O5 can then attack *electrophilic* C3 (next to a heteroatom with a formal plus charge!) to give a five-membered ring with an

anionic C, which is immediately protonated. Deprotonation of C1 again is followed by cleavage of the C4–O5 bond to give an amide.

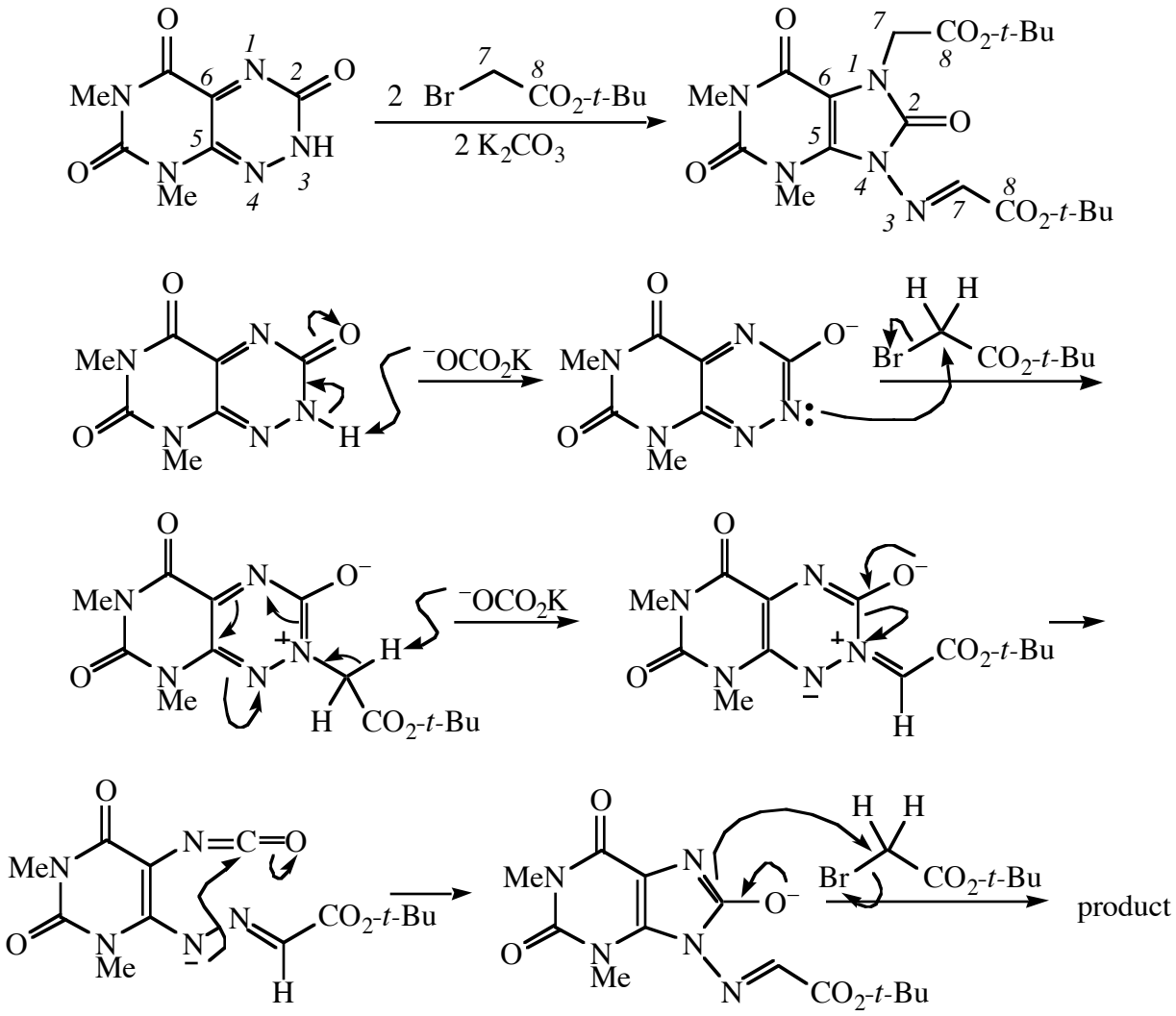


(w) Two equivalents of trifluoroacetic anhydride are required, so there are two C5's and two O6's. One of those C5's, C5a, ends up attached to C4 in the product. The other, C5b, must end up attached to O1, which is absent from the product. Make: O1–C5a, C4–C5b. Break: O1–N2, C5a–O6a, C5b–O6b. O1 is nucleophilic,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

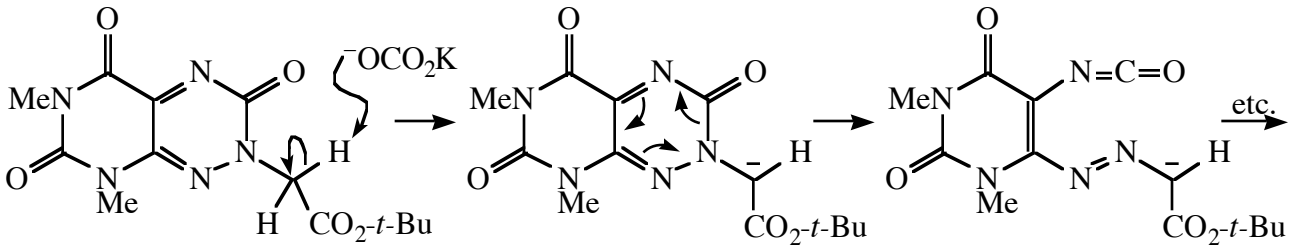


(x) Make: N1–C7a, N3–C7b, N4–C2. Break: C2–N3, C7–Br. The first step is likely deprotonation and alkylation of N3. This makes a σ bond between N3 and C7b, but we need to introduce a π bond. This can be done by an elimination reaction. Deprotonation of C7 gives an enolate, which can be delocalized onto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

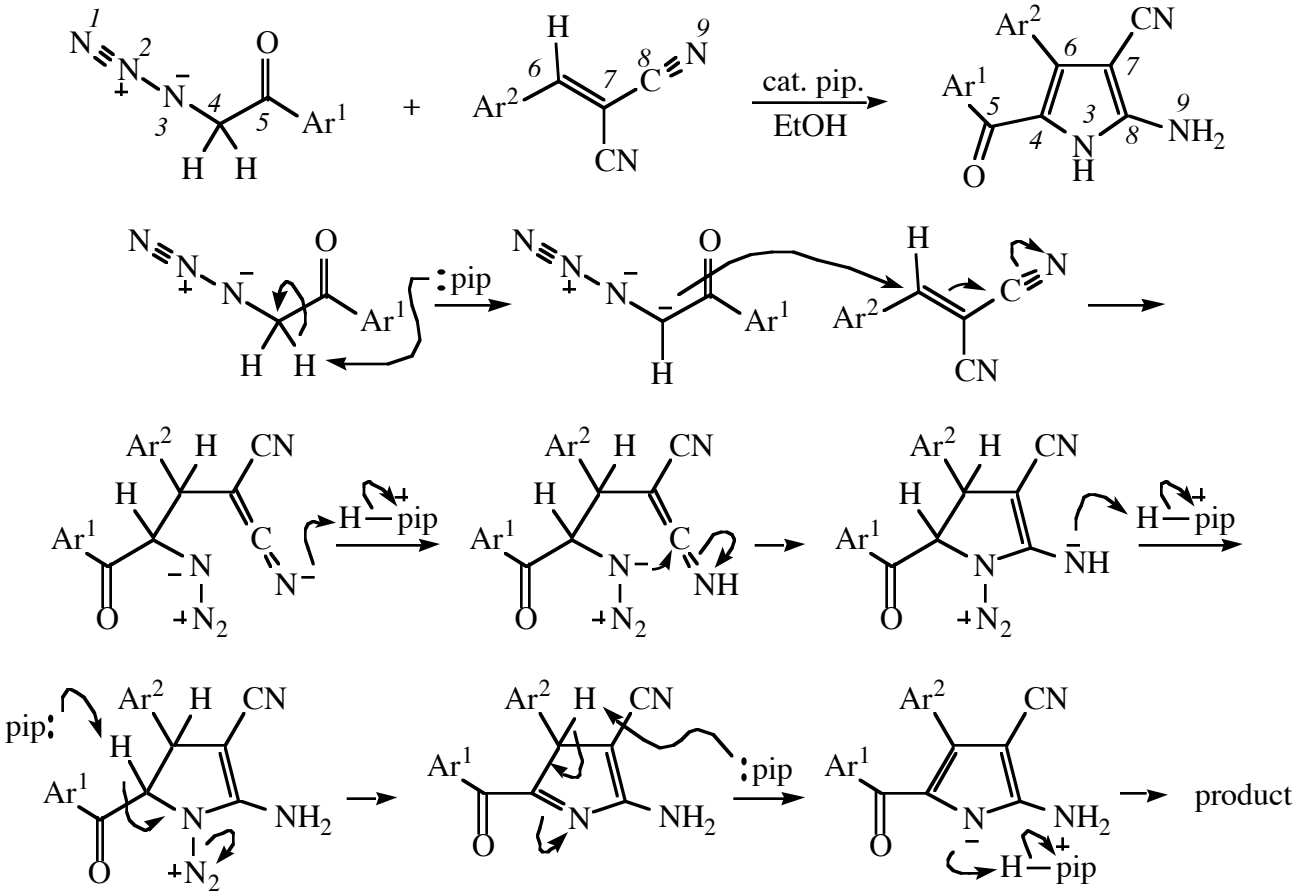
isocyanate out of N1 and C2. These two steps constitute an E1cb elimination. Finally, attack of N4 on C2 gives an amide anion, which can be alkylated again by the bromide to give the product. Note: Cleavage of the N3–C2 bond at the same time as deprotonation of C7, as in a standard E2 elimination, is 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*.

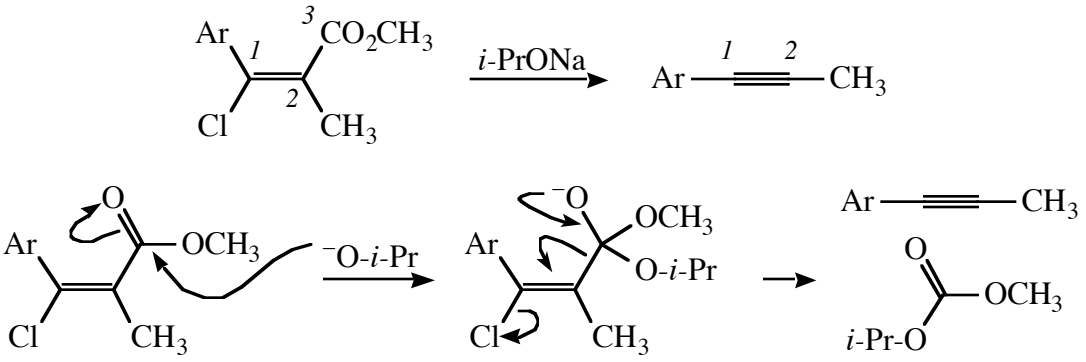


(y) Make: N3–C8, C4–C6. Break: N2–N3. Conditions are basic, and C6 is very electophilic, so first step is likely deprotonation of C4 and addition of the enolate to C6. After protonation of N9, addition of N3 to C8 can occur. Protonation of N9 is followed by loss of H^+ and N_2 by an E2 mechanism. Finally,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

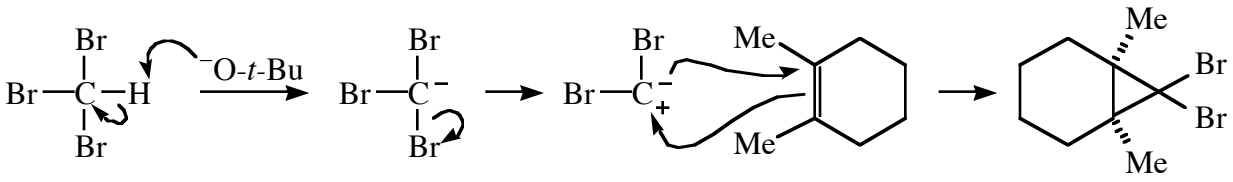


(z) Make: none. Break: Cl–C1, C2–C3. *i*-PrO$^-$ is nucleophilic. There are two electrophilic sites in the starting material, C1 and C3. Attack of *i*-PrO$^-$ at C1 doesn't get us anywhere, since the product does not have a C1–O bond, so the first step is probably addition of *i*-PrO$^-$ to the C3=O π bond. In the second step, the O$^-$ electrons can move down to form the carbonyl bond again, breaking the C2–C3 bond. The

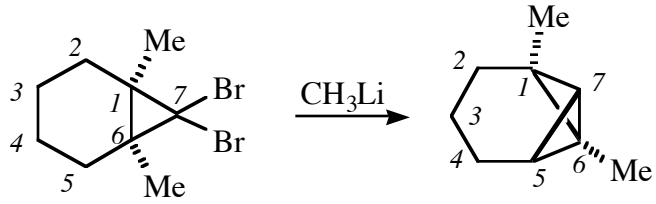
electrons in the C2–C3 bond are used to form a second C2=C1 π bond and to expel Cl^-.

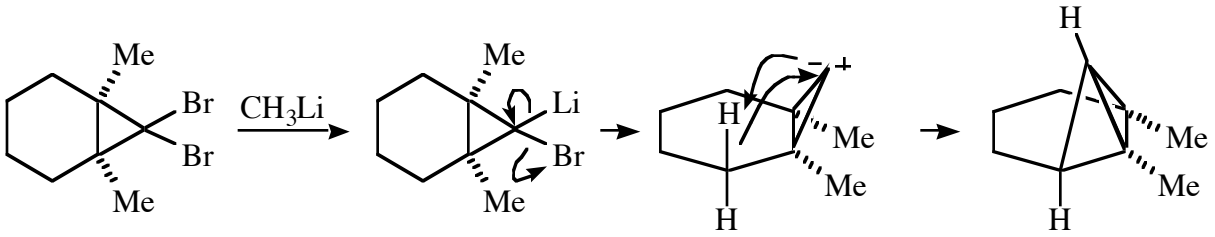


(aa) The first transformation is a standard dibromocarbene addition to an alkene (Section D.4). The strong base deprotonates the bromoform. α-Elimination gives the carbene, which undergoes cycloaddition to the alkene to give the product.

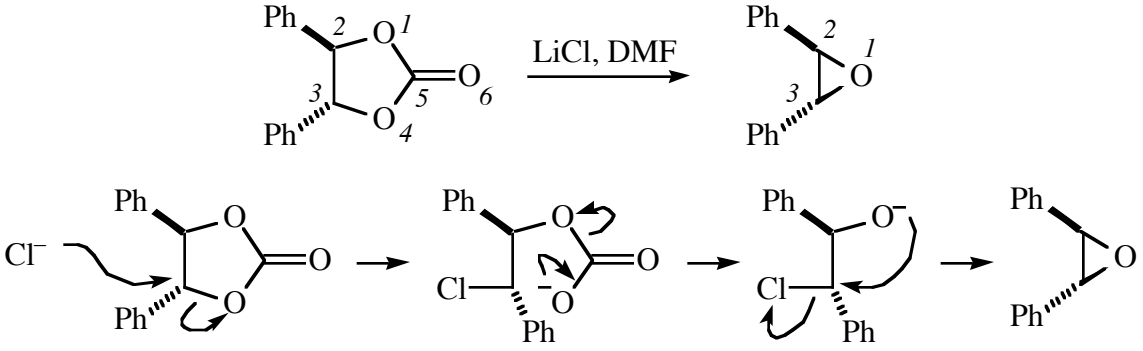


In the second transformation: Make: C5–C7. Break: C7–Br, C7–Br. Formation of a bond between C7 and the unactivated and remote C5 suggests a carbene reaction. Addition of MeLi to a dihalide can give substitution, elimination, or halogen–metal exchange. Here elimination is not possible and substitution 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.



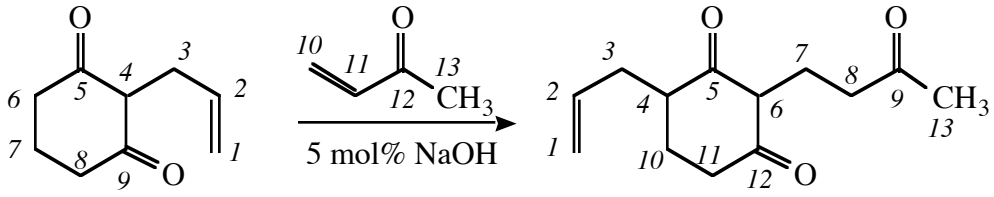


(bb) Make: C3–O1. Break: C3–O4, O1–C5. We are substituting O4 for O1 at C3, and this substitution is occurring with *retention* of configuration, suggesting two sequential S_N2 reactions. What is the role of LiCl? Cl^- is a pretty good nucleophile, especially in a polar aprotic solvent like DMF. The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

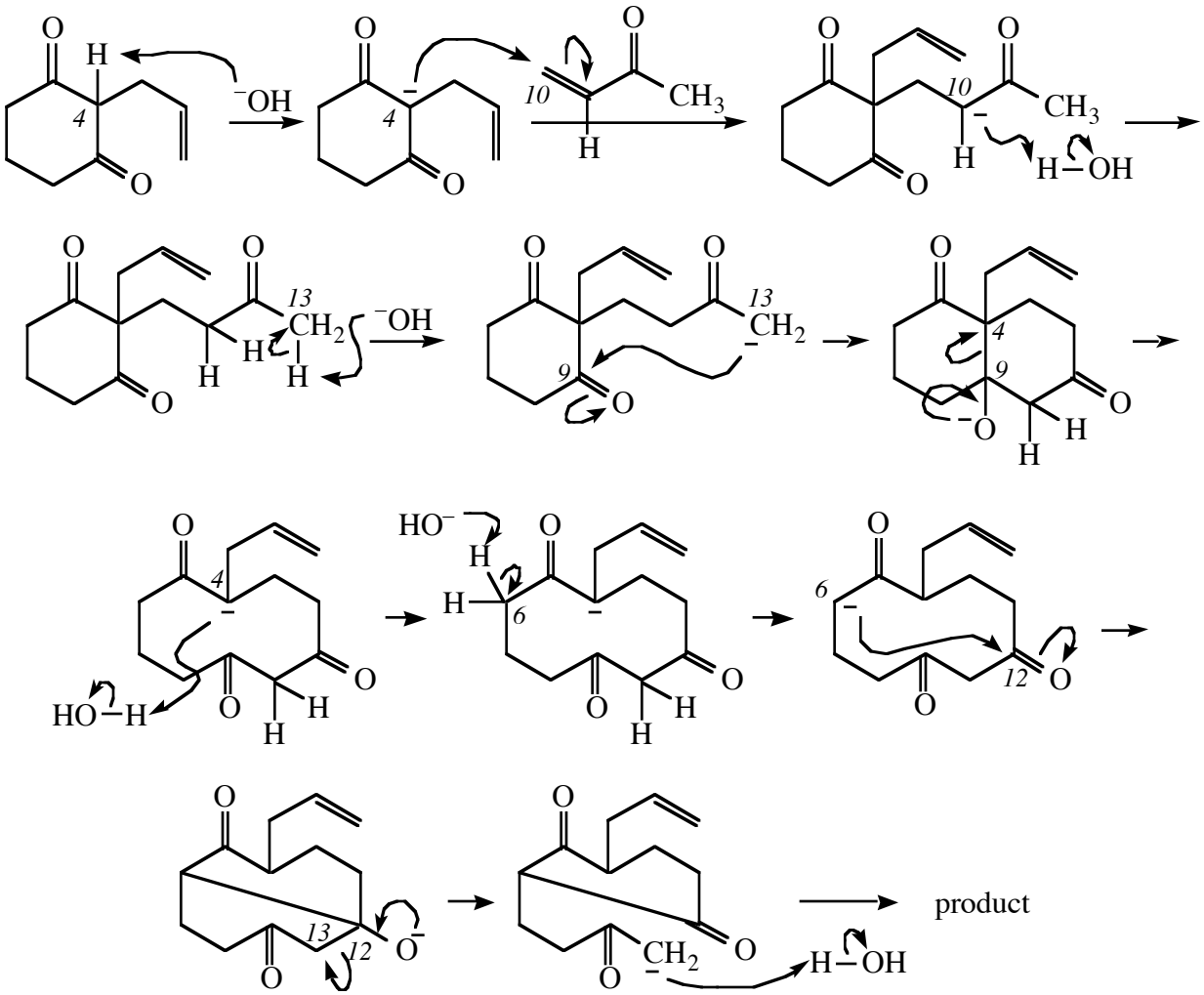


(cc) This reaction is a Robinson annulation. The mechanism was discussed in the text.

(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.



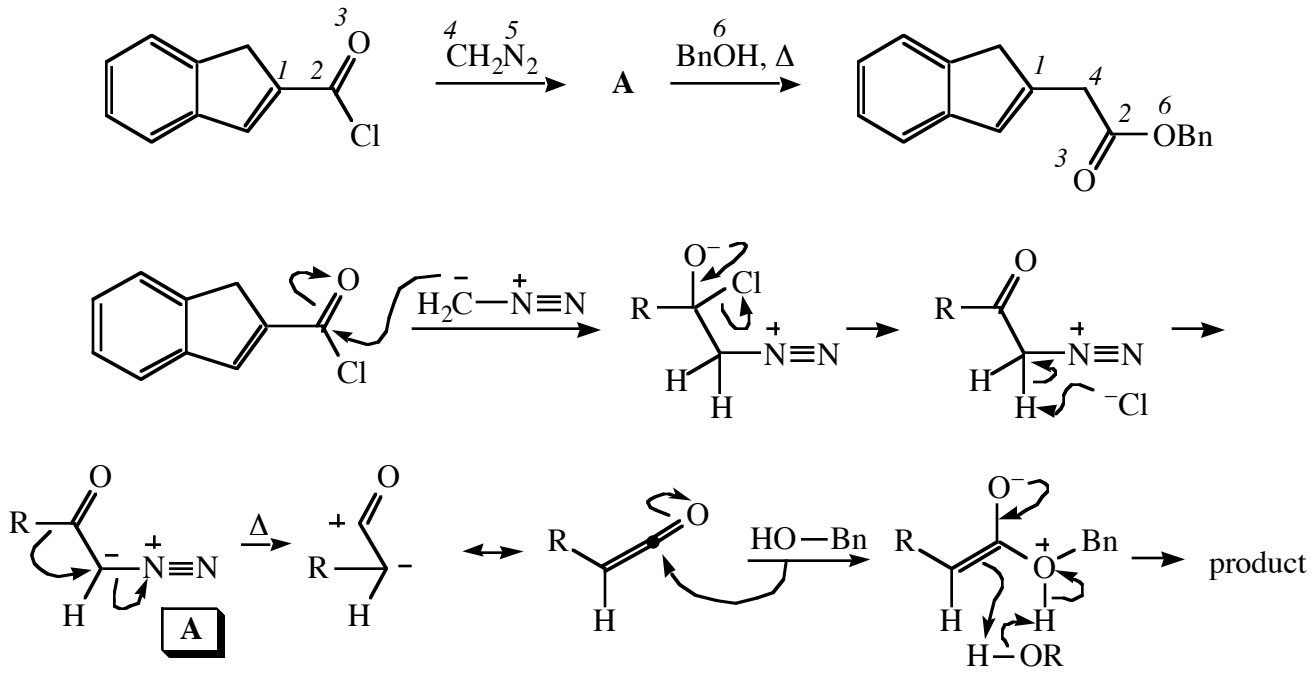
The first steps are the same as in the previous problem. C4 is deprotonated, it undergoes a Michael addition to C10 (making C4–C10), proton transfer occurs from C13 to C11, and C13 adds to C9 (making C9–C13). At this point, though, rather than an E1cb elimination, a fragmentation occurs, breaking C9–C4.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

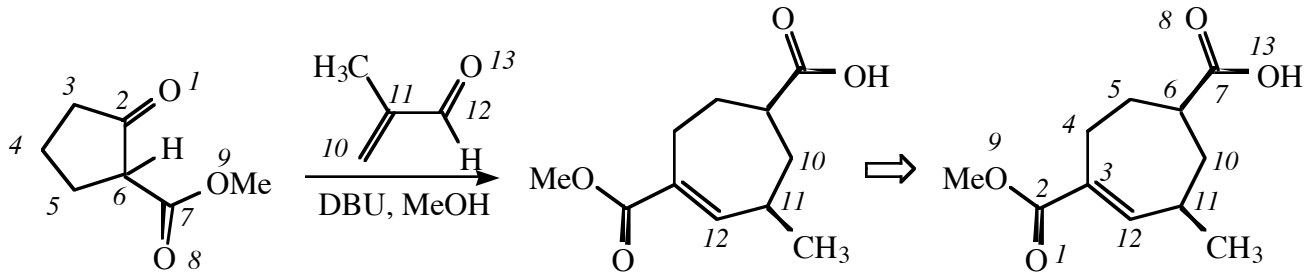
(ee) Make: C1–C4, C4–C2, C2–O6. Break: C1–C2, C2–Cl, C4–N5. The acyl chloride is a potent electrophile at C2. CH_2N_2 is nucleophilic at C4. Addition–elimination occurs, then deprotonation to give a diazoketone. Deprotonation by Cl^- is reasonable because the diazonium ion is a much stronger acid than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



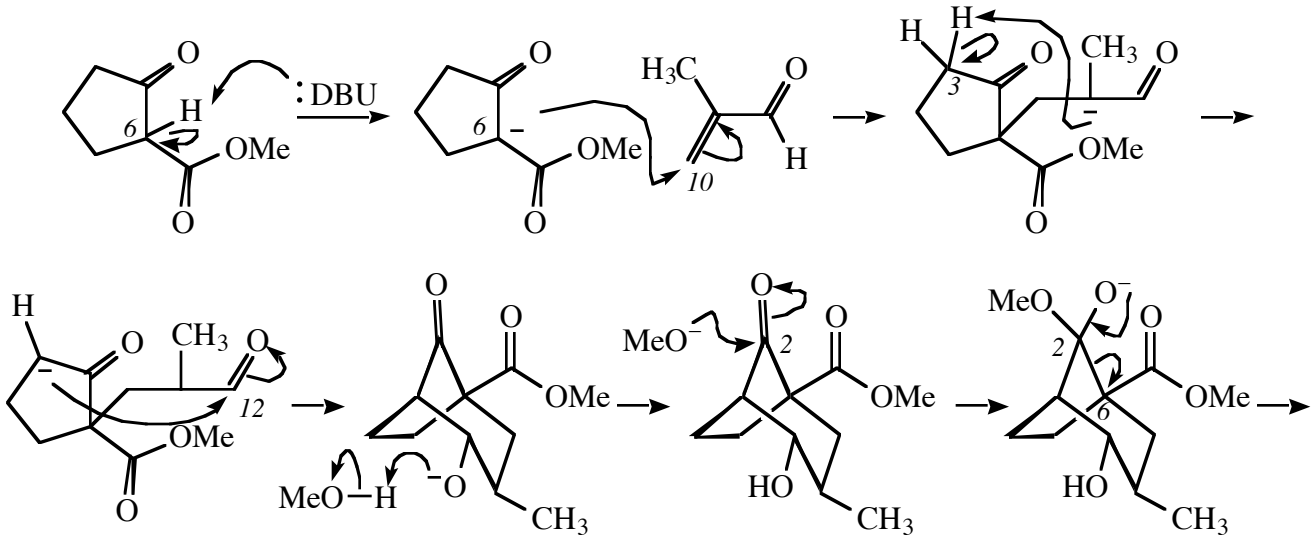
(ff) This transformation is an example of the Mitsunobu reaction. The mechanism of the Mitsunobu reaction was discussed in the text (Section F.2).

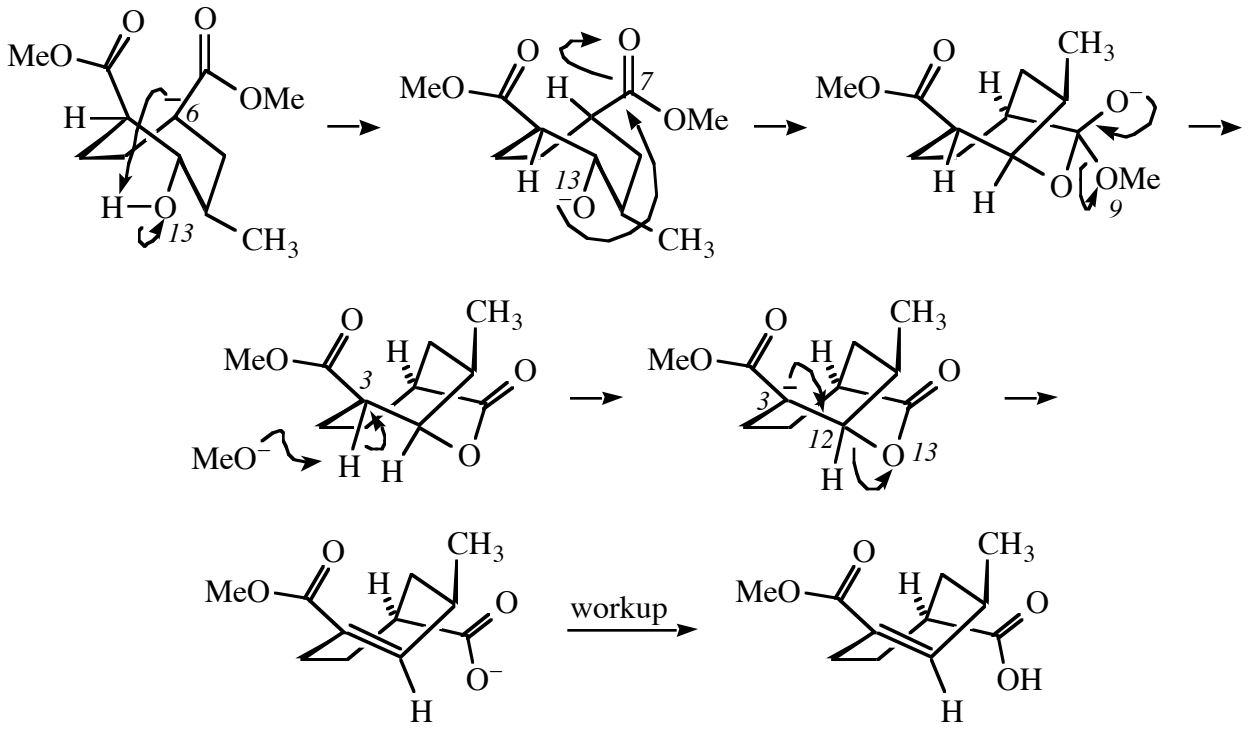
(gg) Numbering is again key. Identifying C10, C11, C12 in the product is easy. Using the information

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 transesterification 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.

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

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

(c) 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.

(d) 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.

(e) 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.

(f) 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

$CH_3CH{=}CH_2$.

(g) 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).

(h) 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.

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

(j) 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.

(k) 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.

(l) 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.