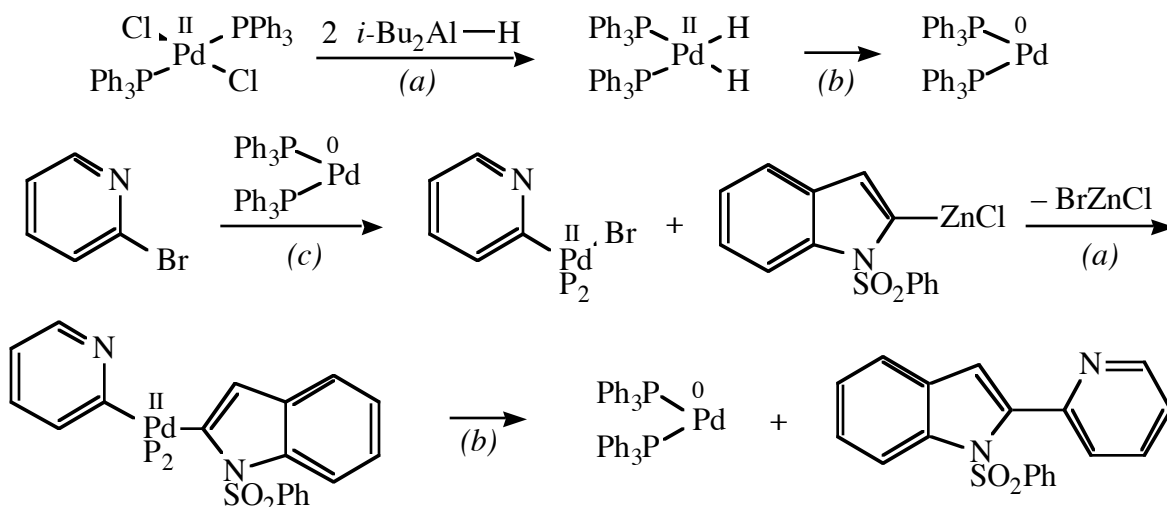
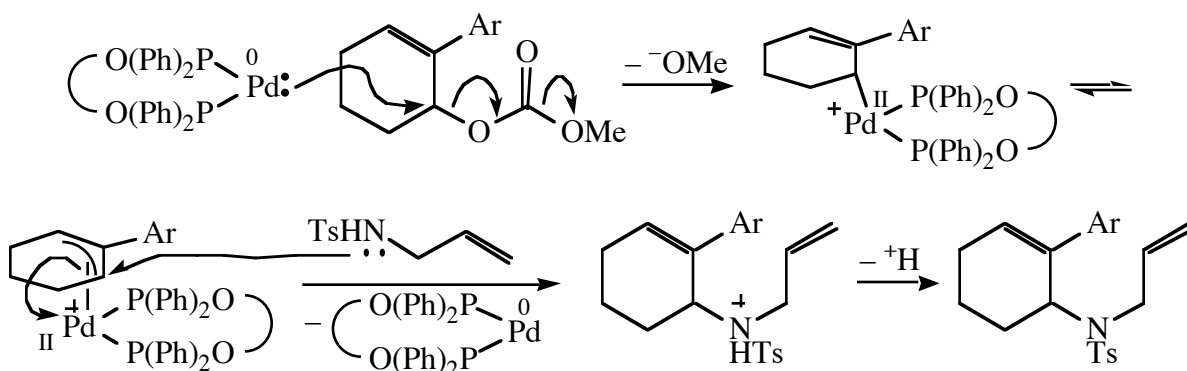


Answers To Chapter 6 Problems.

1. (a) A new C–C bond is formed between a nucleophilic C–Zn and an electrophilic C–Br. This Pd-catalyzed reaction proceeds through the standard oxidative addition, transmetalation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The oxidative addition requires Pd(0). The role of the DIBAL is to reduce the Pd(II) to Pd(0) by two transmetalations and reductive elimination of H₂.



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

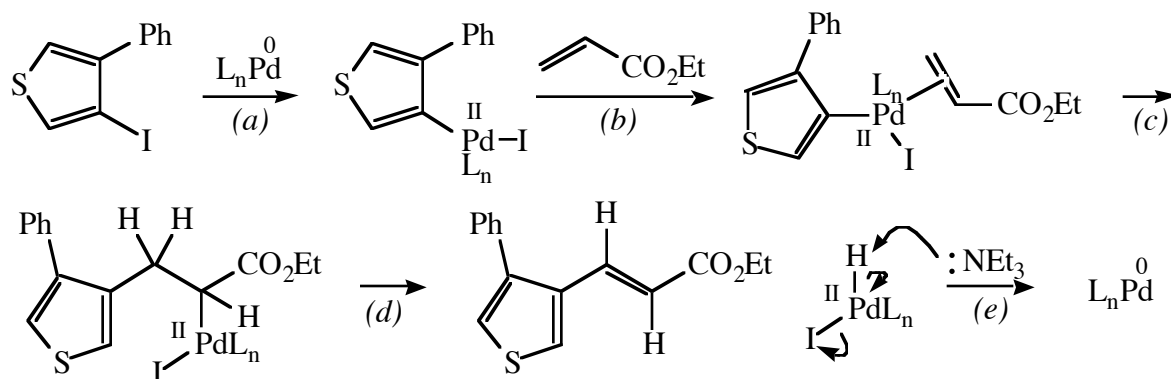


(c) A new C–C bond is formed between a nucleophilic terminal alkyne PhC≡CH and an electrophilic C–I.

This Sonogashira reaction proceeds through the standard oxidative addition, transmetalation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The terminal alkyne is converted to a Cu(I) acetylide before transmetalation to Pd occurs. The mechanism was discussed in the text (Section C.2.d).

(d) A new C–C bond is formed between a nucleophilic C–B and an electrophilic C–I. This Suzuki coupling proceeds through the standard oxidative addition, transmetalation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The mechanism was discussed in the text (Section C.2.d).

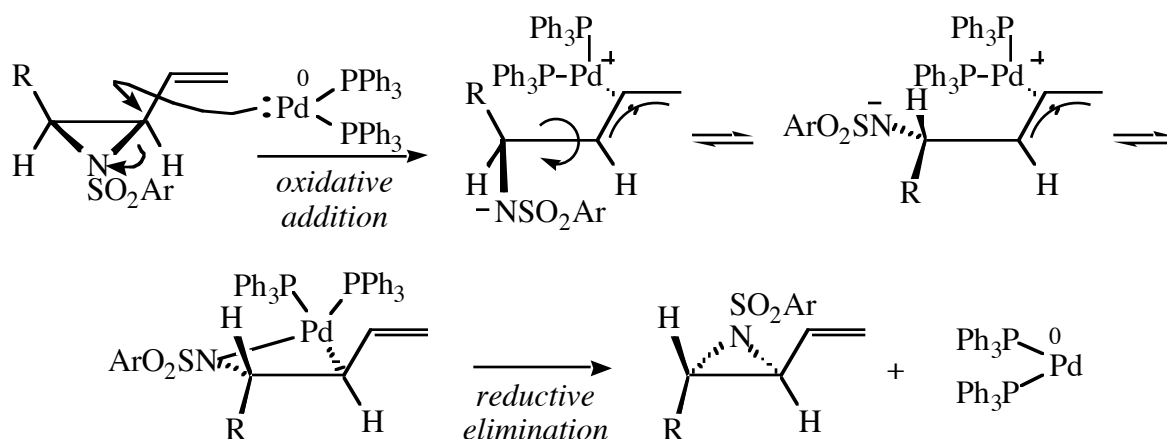
(e) There is no nucleophile in this Heck reaction. The first step must be oxidative addition of Pd(0) to the Ar–I bond to give a Pd(II) complex. (Before this can occur, the Pd(II) complex that is added to the reaction mixture must be reduced to Pd(0). In this system, it is not clear how it happens. Either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



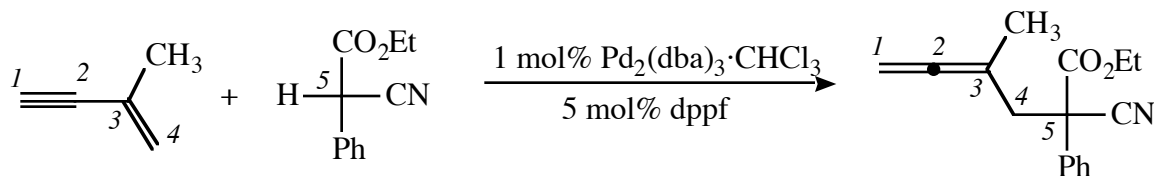
(a) oxidative addition; (b) coordination; (c) insertion; (d) β -hydride elimination; (e) deprotonation.

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

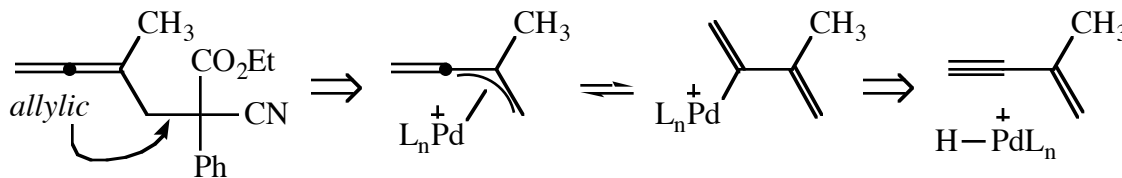
intermediate in an intramolecular fashion; reductive elimination from this chelate would give the product with overall *inversion* of configuration.



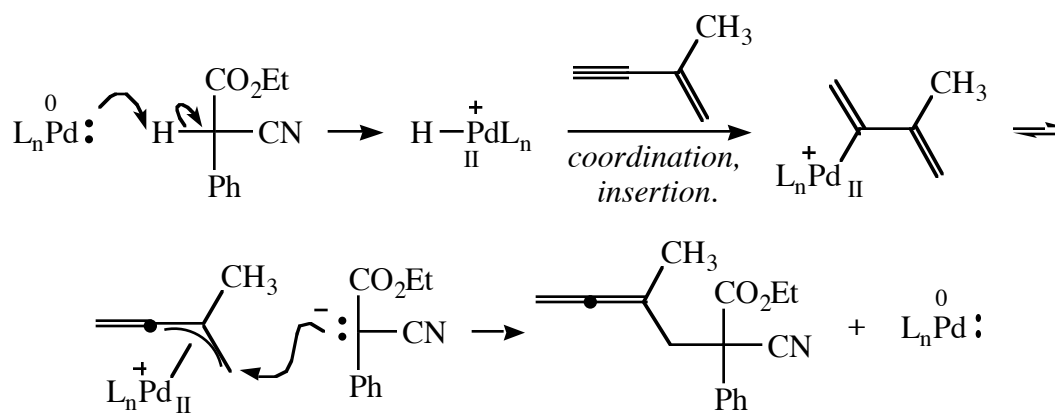
(g) Make: C4–C5, C1–H. Break: C5–H.



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

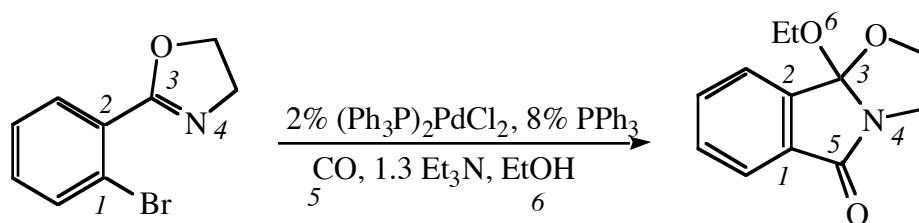


Protonation of Pd(0) gives [Pd(II)–H]⁺. Coordination and insertion of the C1=C2 π bond gives the Pd π allyl complex. Attack of the nucleophile on the less hindered terminus gives the observed product.

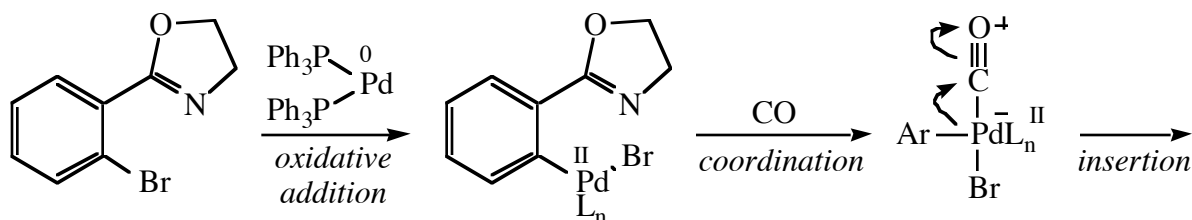


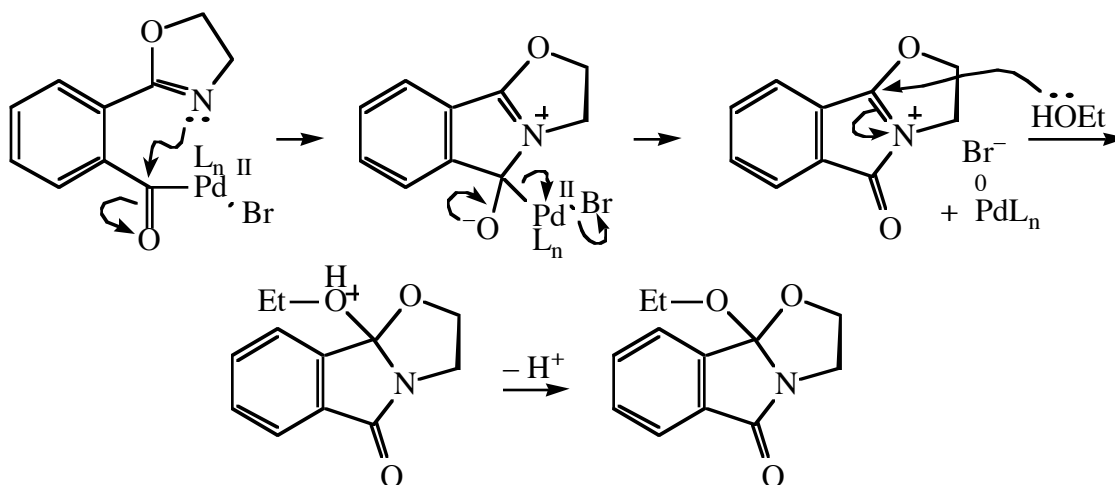
(h) This reaction is simply a Wacker oxidation. Its mechanism was discussed in the text (Section C.2.f). The key steps are attack of H_2O on an electrophilic Pd-alkene complex, then β -hydride elimination to give the enol.

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



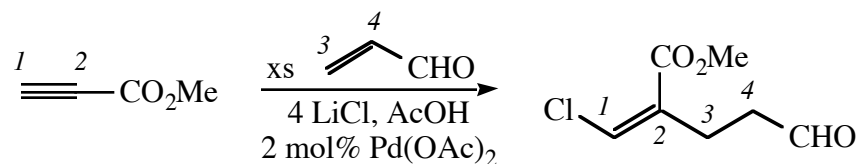
Incorporation of CO into an organic substrate usually occurs by insertion of CO into a C–metal bond. The requisite C1–metal bond is formed by oxidative addition of a Pd(0) species into the C1–Br bond, the normal first step upon combining a Pd(0) compound and an aryl halide. Coordination and insertion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



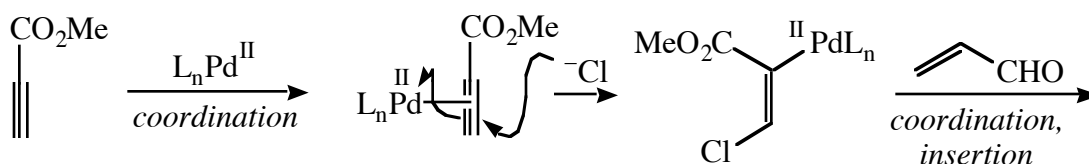


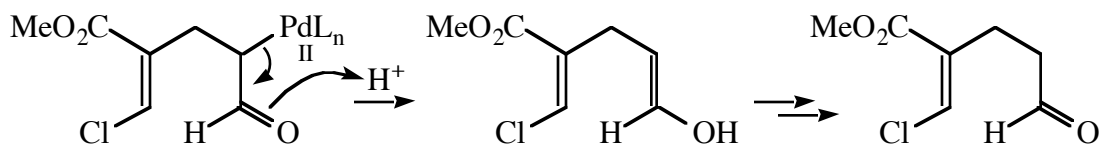
(j) This is another Heck reaction. After the insertion to give the σ bound Pd(II), β -hydride elimination occurs in the direction of the OH to give an enol. The enol tautomerizes to the aldehyde.

(k) Make: C1–Cl, C2–C3. Break: none.



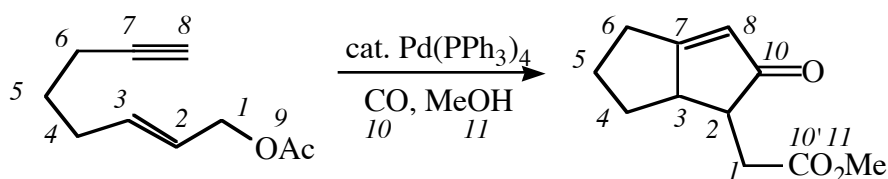
In fact, a mechanism for this reaction can be drawn that does not involve Pd at all, but let's assume that Pd is required for it to proceed. Cl^- must be nucleophilic. It can add to C1 of the alkyne if the alkyne is activated by coordination to Pd(II). (Compare Hg-catalyzed addition of water to alkynes.)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



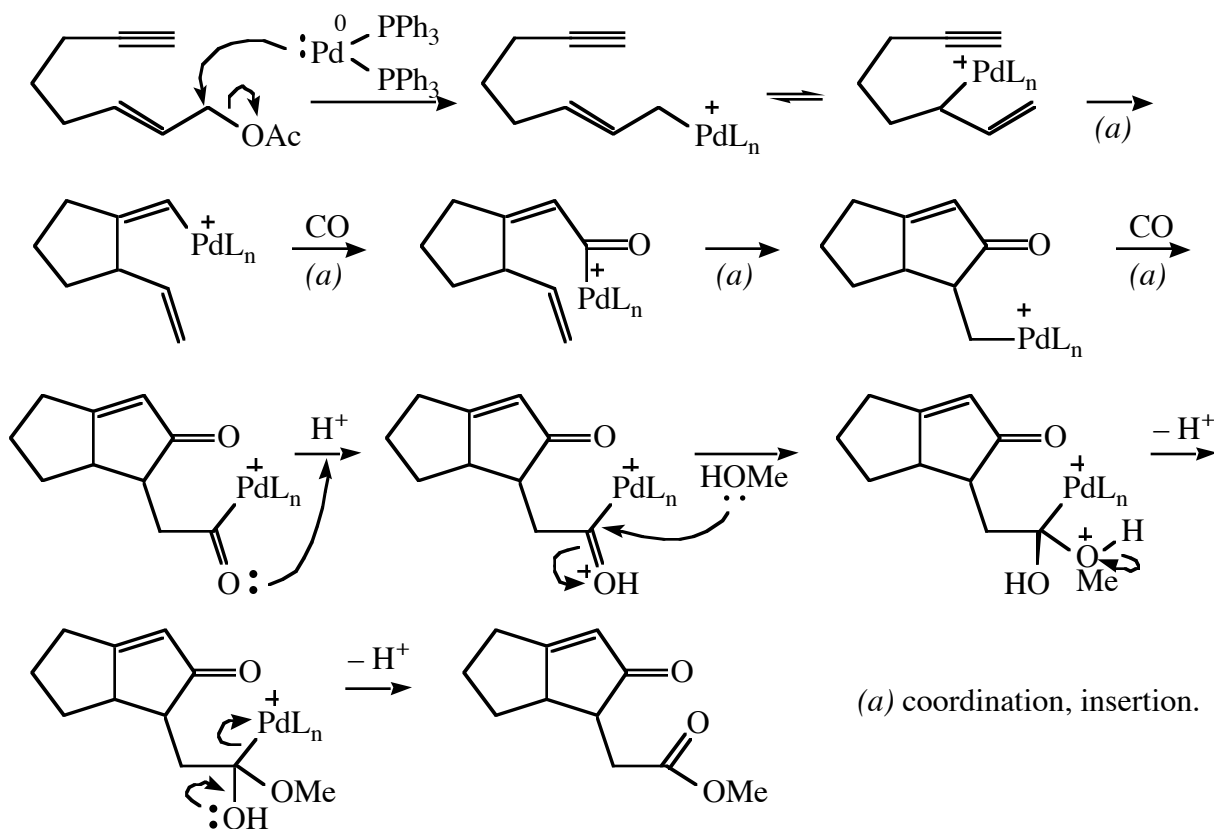


(l) A new C–C bond is formed between a nucleophilic C–Sn and an electrophilic C–Br. This Stille coupling proceeds through the standard oxidative addition, transmetalation, reductive elimination process characteristic of Pd-catalyzed cross-couplings. The mechanism was discussed in the text (Section C.2.d).

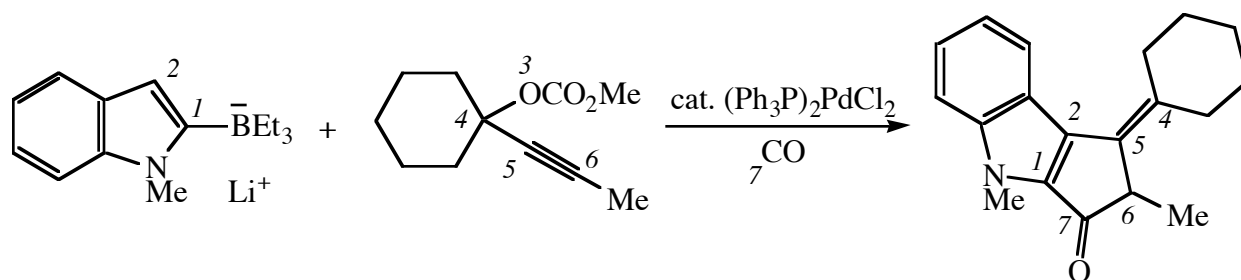
(m) Make: C1–C10', C2–C10, C3–C7, C8–C10, C10'–O11. Break: C1–O9.



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

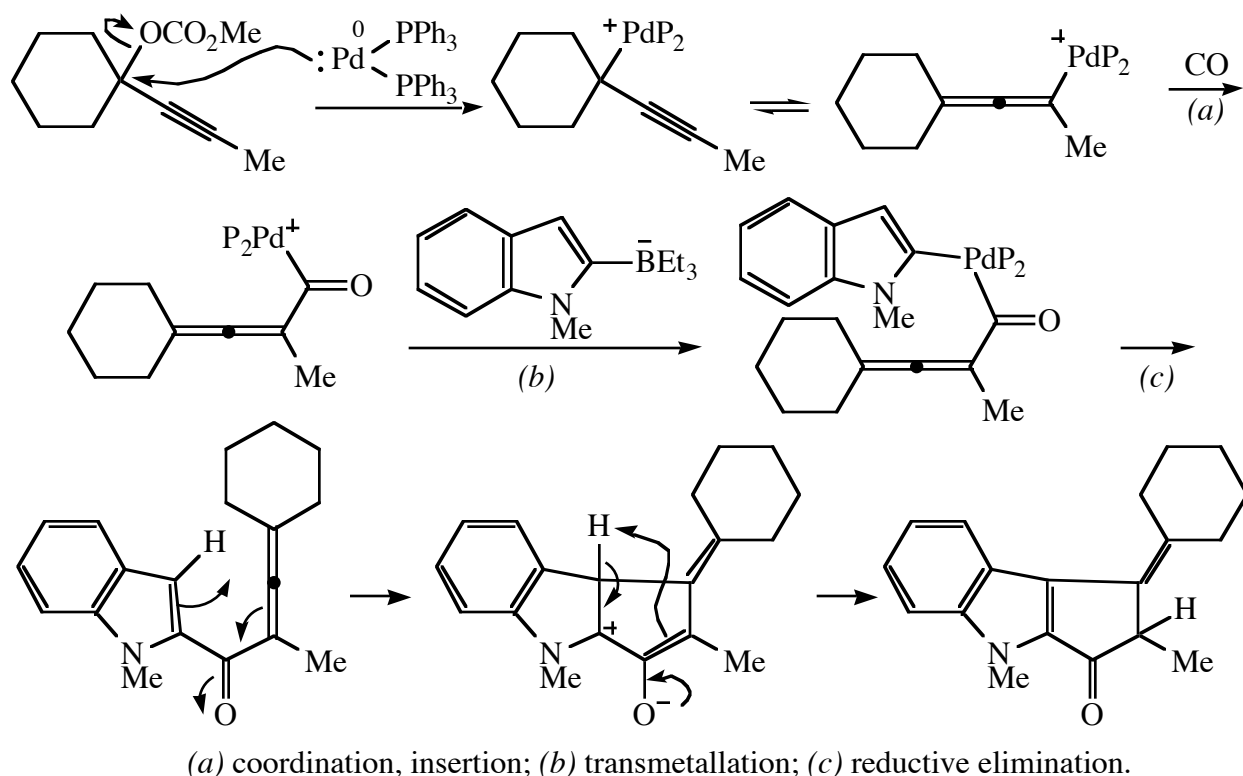


(n) Make: C1–C7, C2–C5, C6–C7. Break: C1–B, O3–C4. C1, with its bond to a negatively charged B, is nucleophilic.

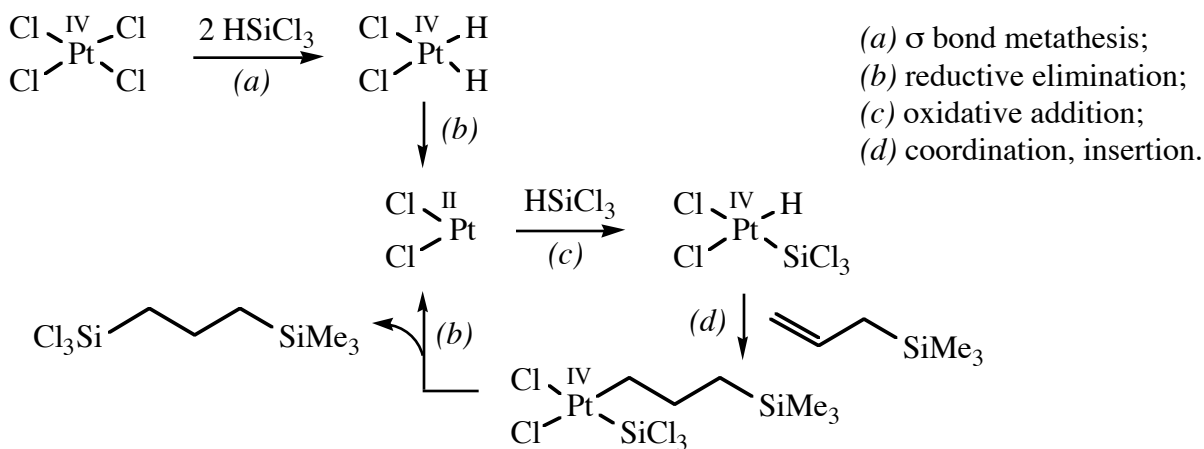


A simple Suzuki-type coupling would form a bond between C1 and either C4 or C6. Obviously that isn't happening here. The O3–C4 bond is propargylic, so Pd(0) can undergo oxidative addition here to make a propargyl–Pd(II) complex. No new bonds are formed to C4, but the propargyl complex is in equilibrium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

ionic oxyallyl. Proton transfer from C2 to C6 reestablishes indole aromaticity and completes the sequence.



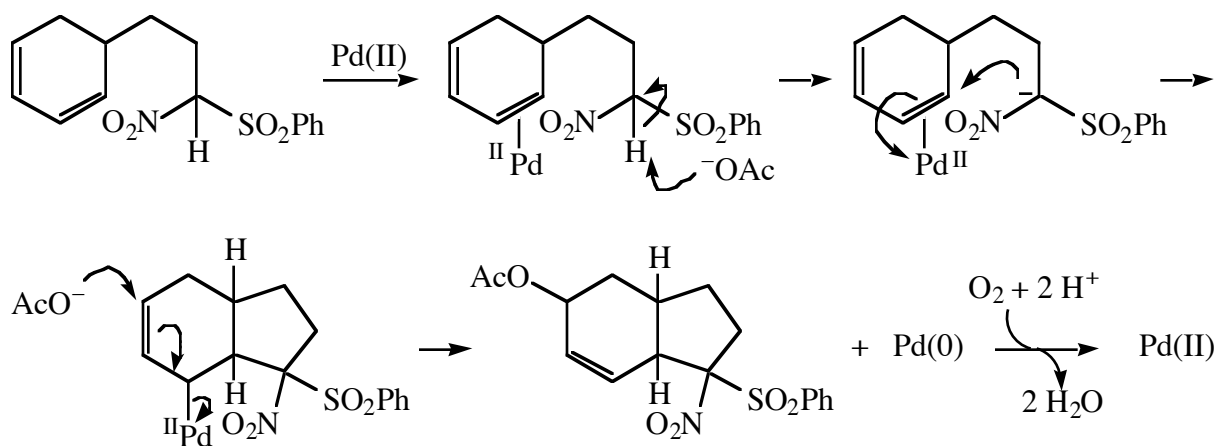
(o) The simplest mechanism that can be drawn for this reaction is as follows. First the Pt(IV) precatalyst needs to be reduced to Pt(II). This can be accomplished by σ bond metathesis of two Pt–Cl bonds with $\text{Cl}_3\text{Si-H}$ to give a Pt(IV) dihydride, which can undergo reductive elimination to give a Pt(II) species. (The Pt species are shown as PtCl_4 and PtCl_2 , but of course other ligands may be present.) The catalytic cycle then proceeds by oxidative addition of $\text{Cl}_3\text{Si-H}$ to Pt(II), coordination and insertion of the alkene into the Pt–H bond, and reductive elimination of the product, just like a Pd-catalyzed hydrogenation.



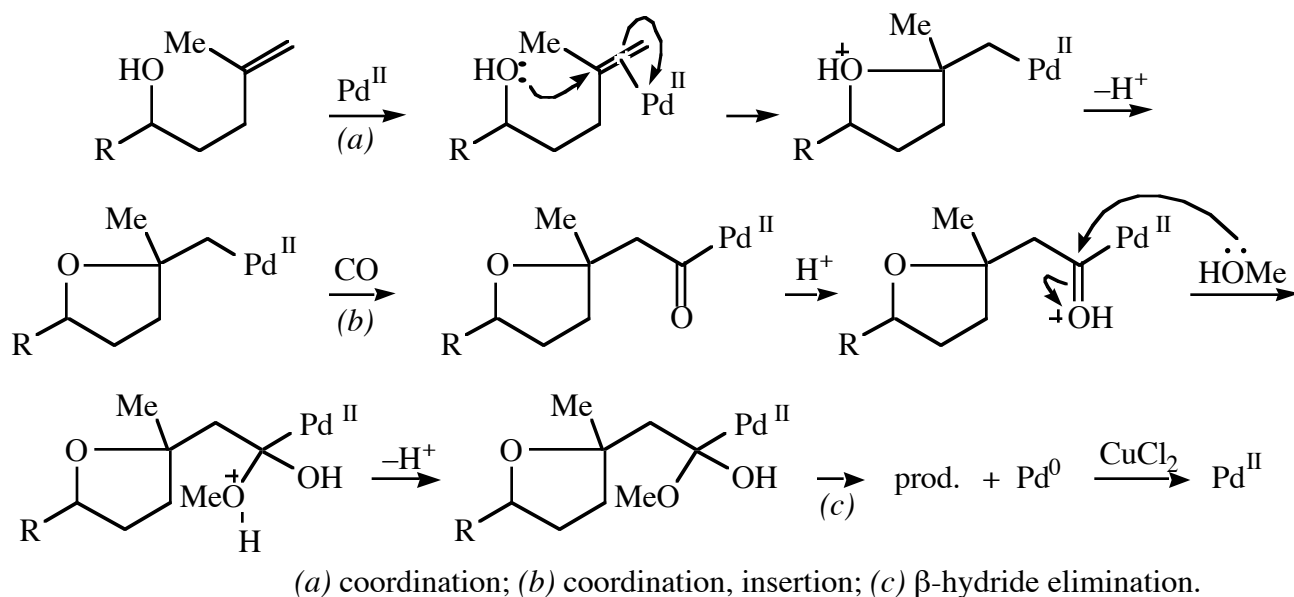
Experiments show that the actual mechanism of this reaction is considerably more complex than the one shown [radicals may be involved, especially in the reduction of Pt(IV) to Pt(II)], but the simple mechanism above provides a starting point for further investigation.

(p) The reaction is a carbonylative Stille coupling. The mechanism was discussed in the text (Section C.2.d).

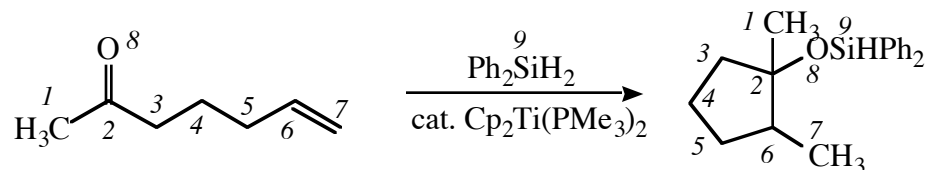
(q) Addition of a nucleophile to an alkene is catalyzed by Pd(II) salts. The Pd(II) coordinates to the alkene and makes it electrophilic, and the nucleophile attacks to give a C–Pd bond. In this case, because the substrate is a diene, the product is an allylpalladium(II) complex, a good electrophile.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



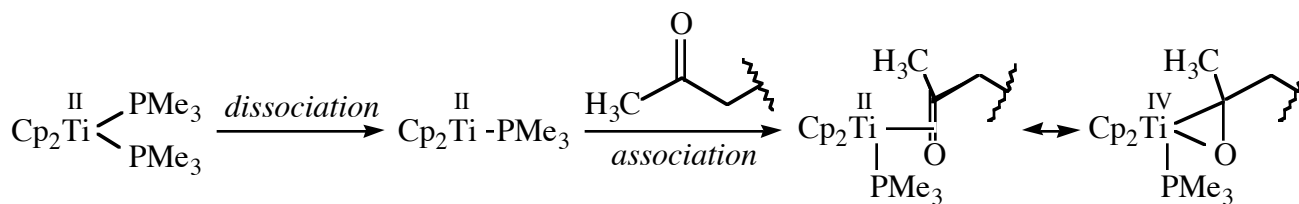
(r) Addition of a nucleophile to an alkene is catalyzed by Pd(II) salts. The product, an alkylpalladium(II) compound, usually undergoes β -hydride elimination, but in this case insertion of CO occurs to give an acylpalladium(II) complex. Displacement of Pd(0) by MeOH gives the product. Pd(0) is reoxidized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

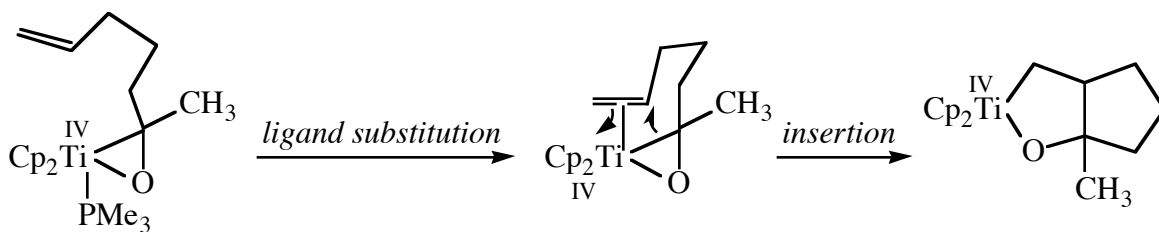


2. (a) Make: C2–C6, O8–Si9. We also remove one H from Si9 and add one to C7. Ti is in the (II) oxidation state. Low-valent Ti compounds are commonly used for reductive coupling reactions. We can form the C6–C2 bond by such a reductive coupling.

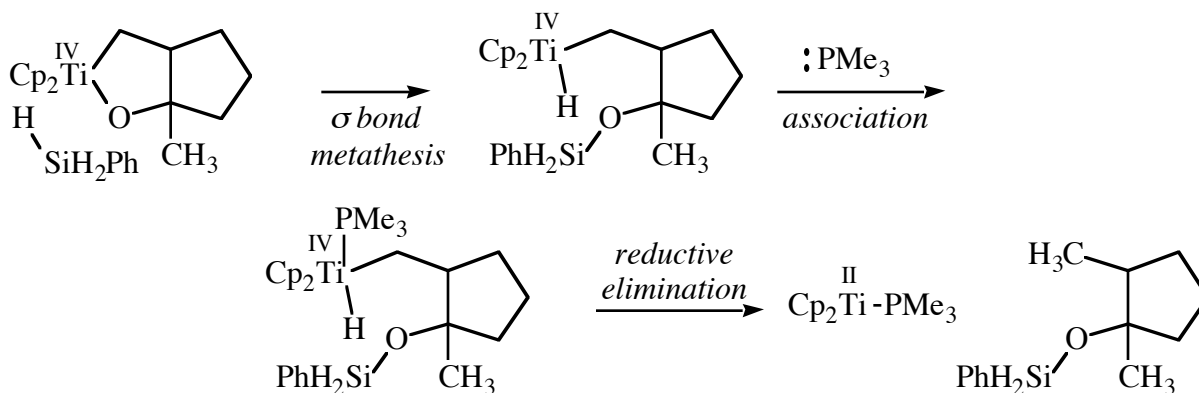


Dissociation of Me_3P from the 18-electron complex gives a 16-electron complex. Association of the carbonyl group gives a Ti(II) π complex that can also be described as a Ti(IV) metalla-oxirane. Dissociation of the second Me_3P , association of the alkene, and migratory insertion into the C2–Ti bond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

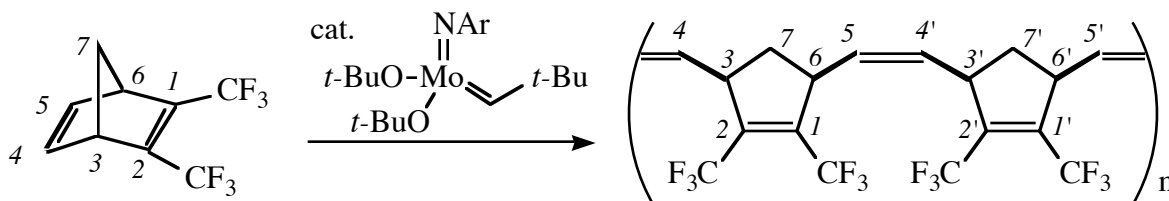




We still need to form the O8–Si9 bond, break the C7–Ti bond, and regenerate Ti(II). A σ bond metathesis between the Si9–H and Ti–O8 bonds can occur to give a very strong Si9–O8 bond and a Ti–H bond. No change in the Ti(IV) oxidation state occurs. Reductive elimination from Ti(IV) gives the product and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

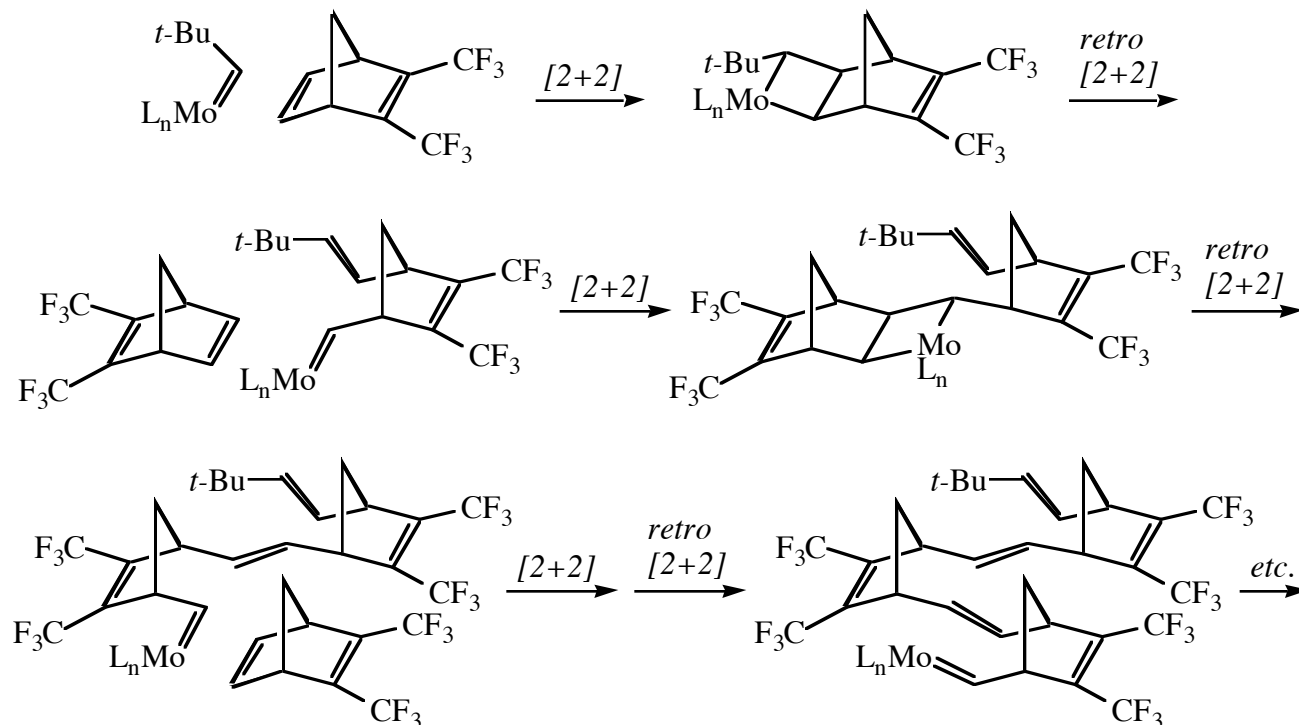


(b) Make: C4=C5' and C4'=C5 (x' indicates that atom in another molecule). Break: C4=C5. Mo is in the (VI) oxidation state, so it is d^0 . The complex is a 14-electron complex. (The ArN= group uses the N lone pair to contribute another pair of electrons.) This is a ROMP reaction, i.e. ring-opening metathesis polymerization (Section C.3.c).

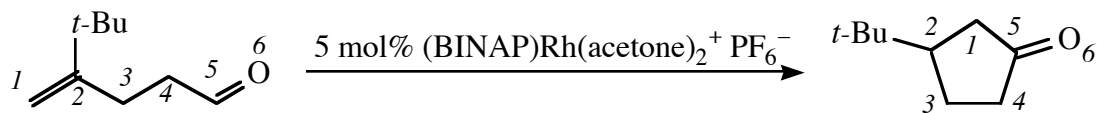


Compounds containing M=C bonds can undergo [2+2] cycloadditions, and this reaction allows olefin metathesis to occur. The Mo=C bond [2+2] cycloadds to the C4=C5 bond to give a metallacyclobutane. A retro [2+2] cycloaddition cleaves the C4=C5 bond and makes a Mo=C4 bond. This new bond cyclo-

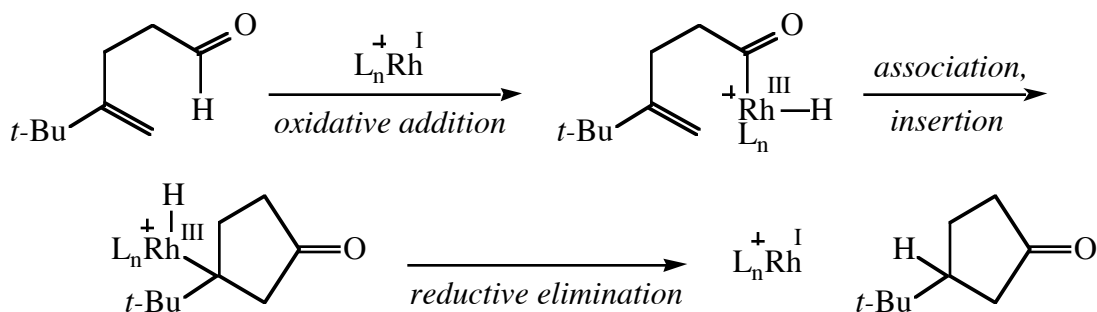
adds across another C4'=C5' bond to make a new C4–C5' bond; retro [2+2] cycloaddition cleaves the C4=C5 bond and completes the formation of the C4=C5' bond. The process repeats itself many times over to make the polymer. No change in Mo's oxidation state or d electron count occurs in any step.



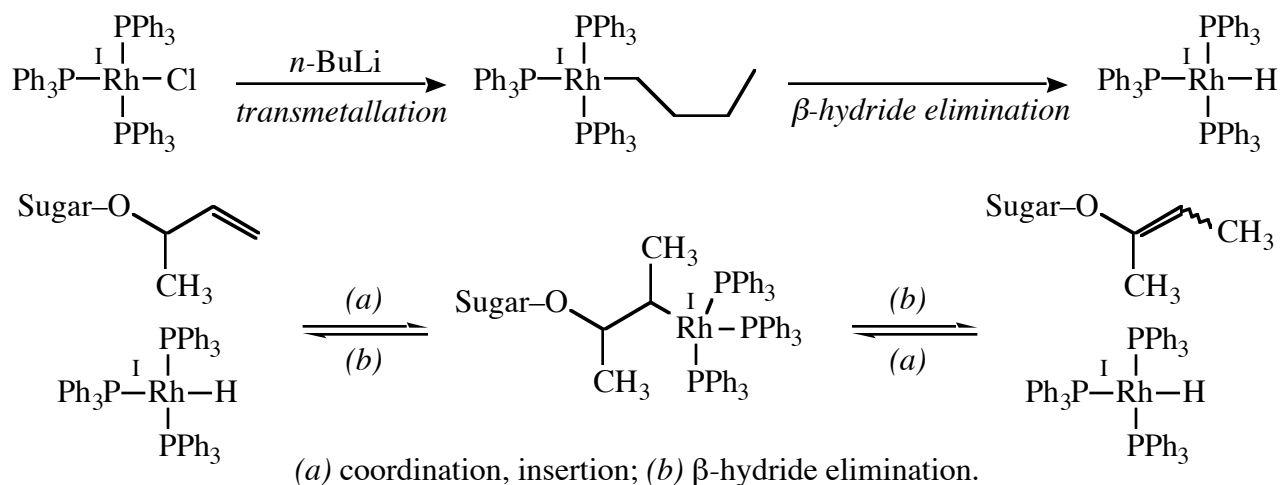
(c) Make: C1–C5, C2–H. Break: C5–H. Rh is in the (I) oxidation state, hence it is d⁸; the two acetone molecules are counted as two-electron donors, so it is a 16-electron complex.



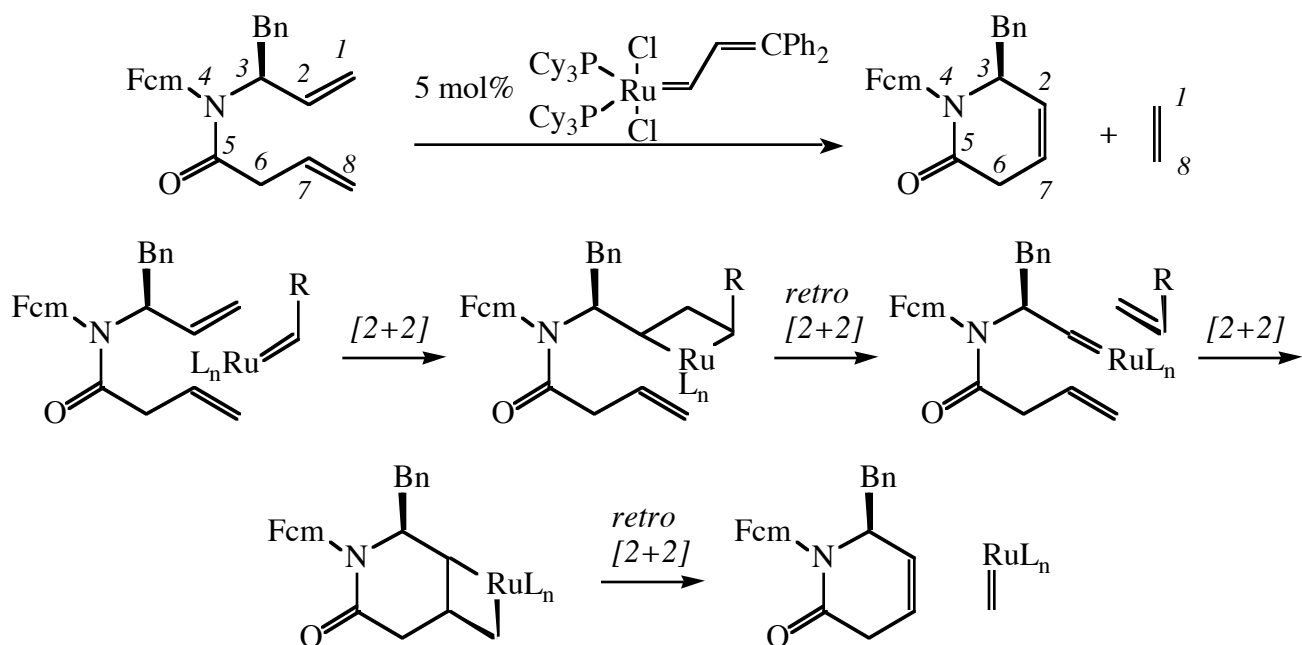
Essentially the C1=C2 bond is inserted into the C5–H bond. This suggests that the Rh oxidatively adds across the C5–H bond. Rh can do this with aldehydes. After oxidative addition to the C5–H bond to give a Rh(III) complex, insertion and reductive elimination give the product and regenerate Rh(I). Solvent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



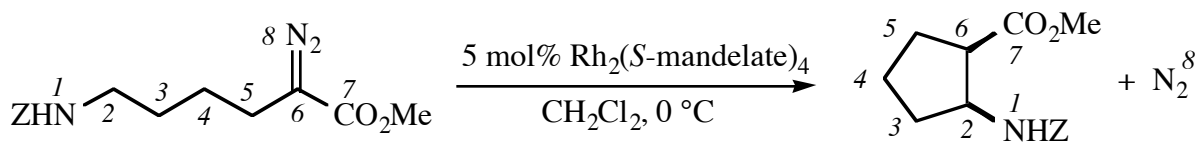
(d) Alkene isomerization can proceed by an oxidative addition (to the allylic C–H bond)/ reductive elimination sequence or by an insertion/ β -hydride elimination sequence. Wilkinson's catalyst normally isomerizes alkenes by the first mechanism. However, in this case BuLi is added to the catalyst first.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



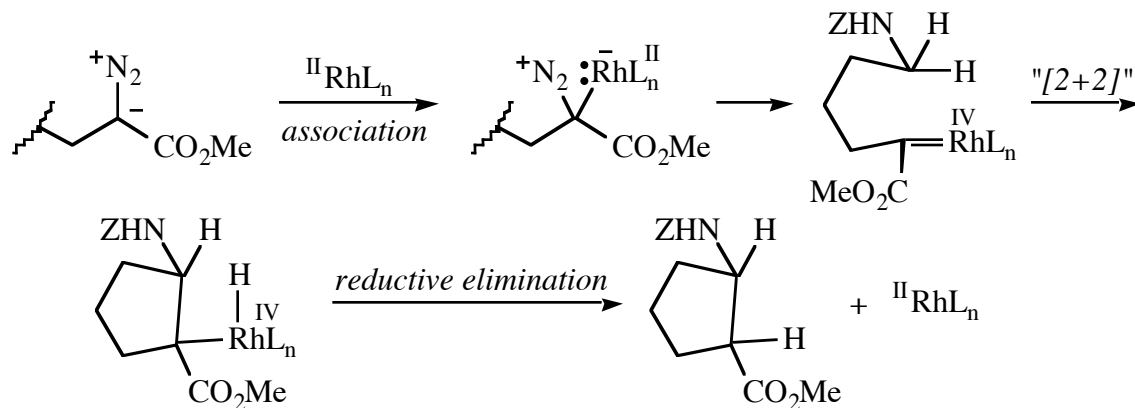
(e) The product is missing C1 and C8. They are lost as $H_2C=CH_2$. Make: $C_2=C_7$, $C_1=C_8$. Break: $C_1=C_2$, $C_7=C_8$. The Ru complex is 16-electron, d^2 , Ru(IV). This is another olefin metathesis reaction, except this time it is ring-closing metathesis. The mechanism proceeds by a series of [2+2] and retro [2+2] cycloadditions. The R group starts off as $CH=CPh_2$, but after one cycle $R=H$.



(f) Make: C6–C2, C6–H. Break: C6–N8, C2–H.

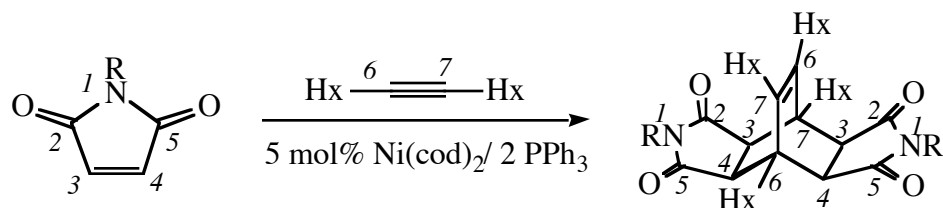


The interaction of diazo compounds with Rh(II) complexes produces carbenoids, L_nRh=CR₂, with Rh in the (IV) oxidation state. The carbenoids do typical reactions such as C–H insertion. The mechanism of C–H insertion involves [2+2] cycloaddition with the C–H σ bond, followed by reductive elimination. The *S*-mandelate ligands on Rh ensure that the insertion reaction is enantioselective.

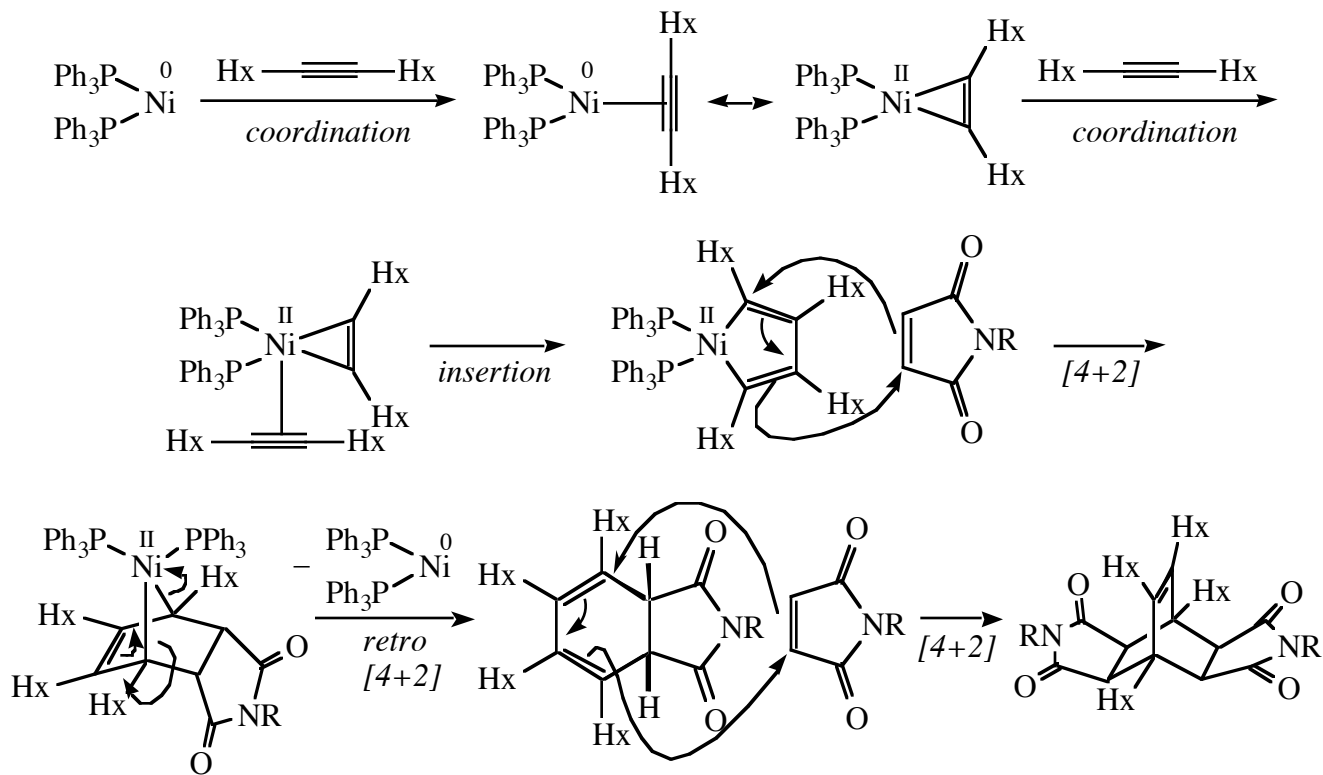


(g) Make: C3–C7 (x2), C4–C6 (x2), C6–C7. Ni is in the (0) oxidation state. Ni(cod)₂ is an 18-electron

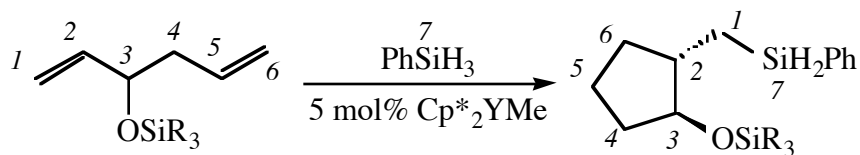
complex. $(\text{Ph}_3\text{P})_2\text{Ni}(\text{cod})$ is also an 18-electron complex. The fact that we are making six-membered rings from isolated π bonds suggests a cyclotrimerization.



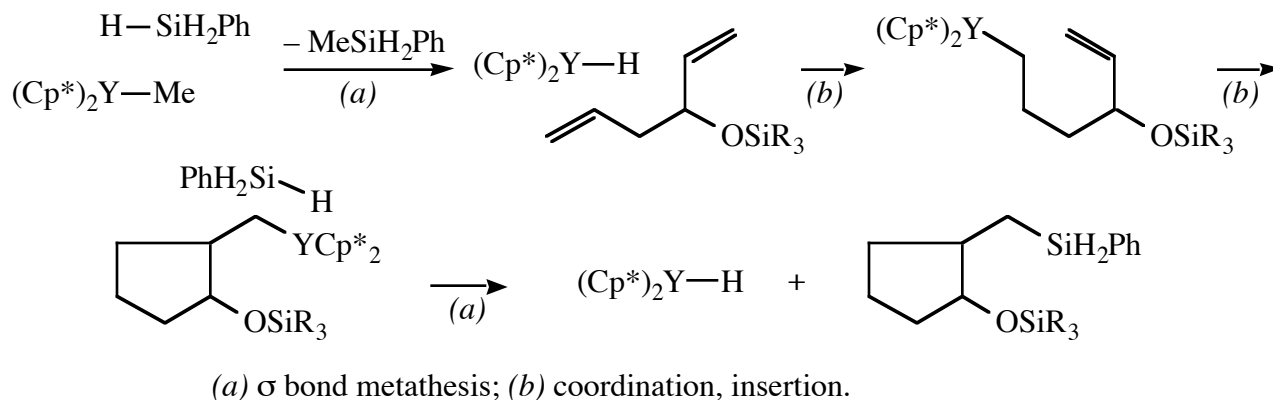
Coordination of Ni(0) to the alkyne gives a π complex, which can be written in its Ni(II) resonance form. Coordination and insertion of another alkyne forms the new C6–C7 bond and gives a nickelacyclopentadiene. Maleimide may react with the metallacycle by coordination, insertion, and reductive elimination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



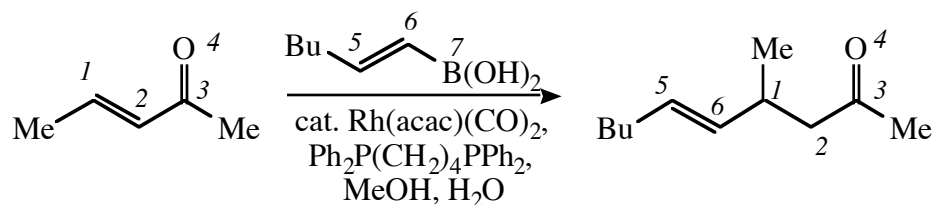
(h) Make: C1–Si7, C6–C2, C5–H. Break: Si7–H. Y is in the (III) oxidation state in the d^0 , 14-electron complex.



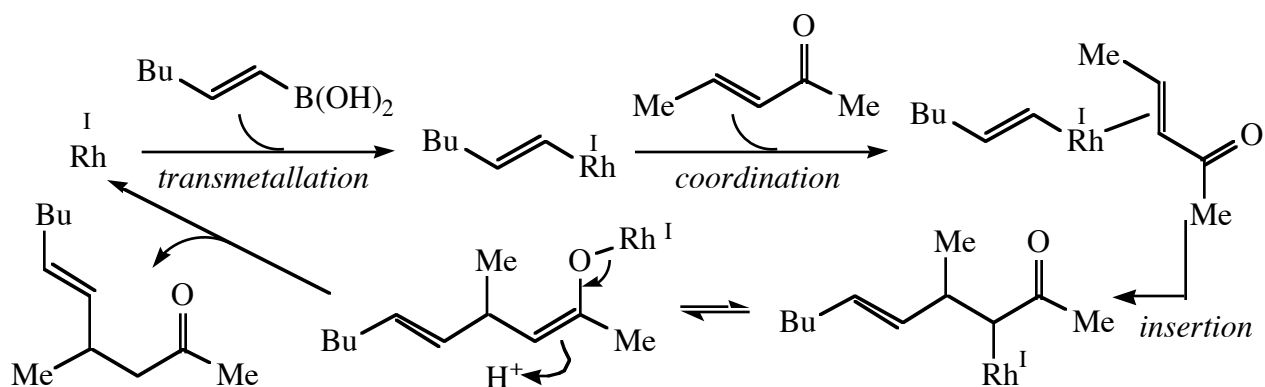
The overall transformation involves insertion of the C5=C6 and the C2=C1 π bonds into the Si7-H bond. An oxidative addition of Si-H to Y, insertion, insertion, reductive elimination sequence might occur. The problem with this is that the d^0 Y complex can't do oxidative addition. The alternative by which the Si-H bond is activated is a σ bond metathesis process. $\text{Cp}^*_2\text{Y-Me}$ undergoes σ bond metathesis with the Si-H bond to give $\text{Cp}^*_2\text{Y-H}$. Coordination and insertion of the C5=C6 π bond into the Y-H bond gives the C5-H bond and a C6-Y bond. Coordination and insertion of the C1=C2 π bond into the C6-Y bond gives the key C6-C2 bond and a C1-Y bond. Finally, σ bond metathesis occurs once more to make the C1-Si bond and regenerate $\text{Cp}^*_2\text{Y-H}$.



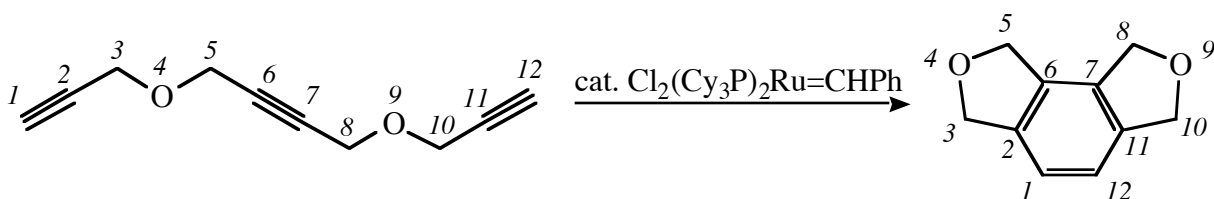
(i) Make: C6-C1. Break: C6-B7.



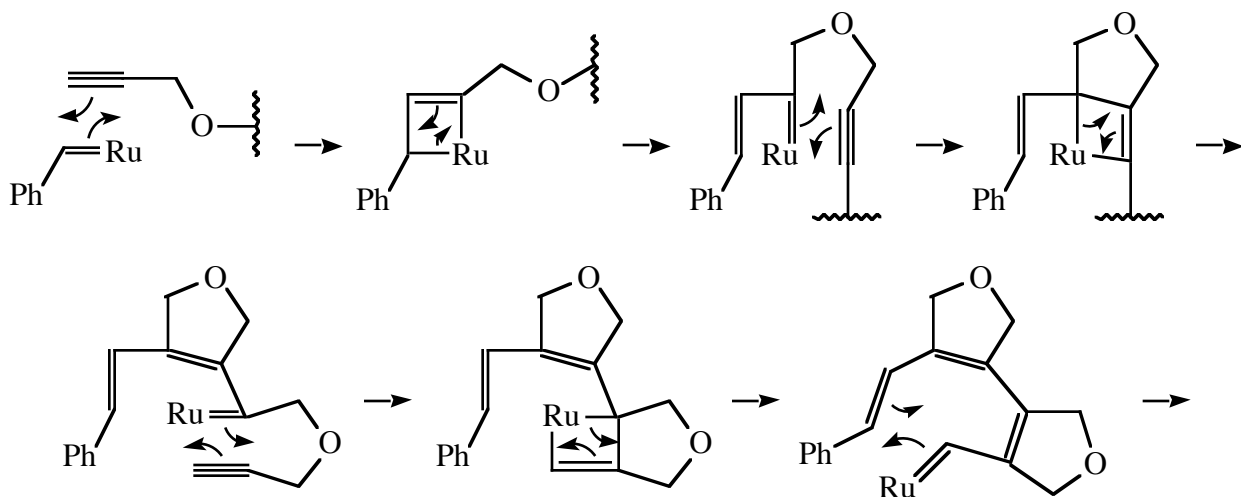
The reaction looks like a conjugate addition. A C6-Rh bond could insert into the C1=C2 π bond. The C6-Rh bond could be made by transmetalation.

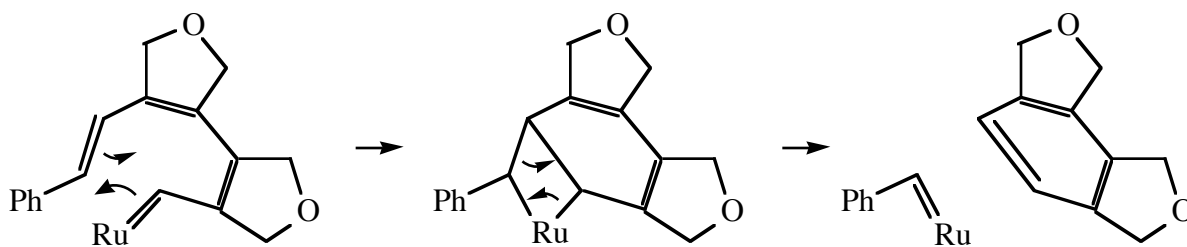


(j) Make: C1–C12, C2–C6, C7–C11.

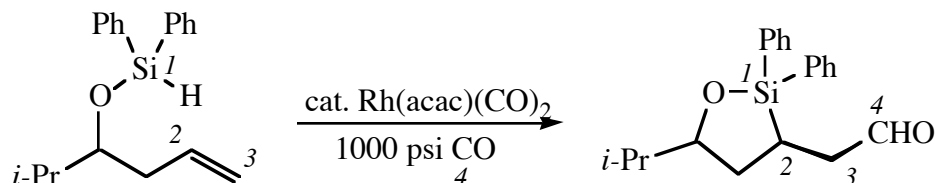


The overall reaction is a cyclotrimerization. Cyclotrimerizations are usually catalyzed by low-valent Co or Ni complexes by a reductive coupling mechanism, but the Ru=C complex lives to do [2+2] cycloadditions, so let it. Cycloaddition to the C1=C2 bond gives a ruthenacyclobutene, which can undergo electrocyclic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

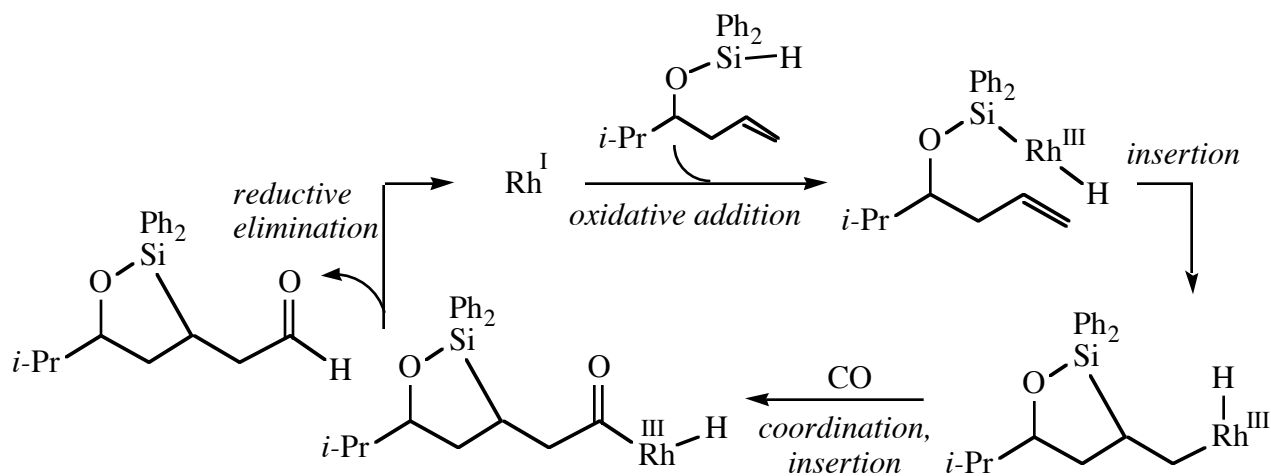




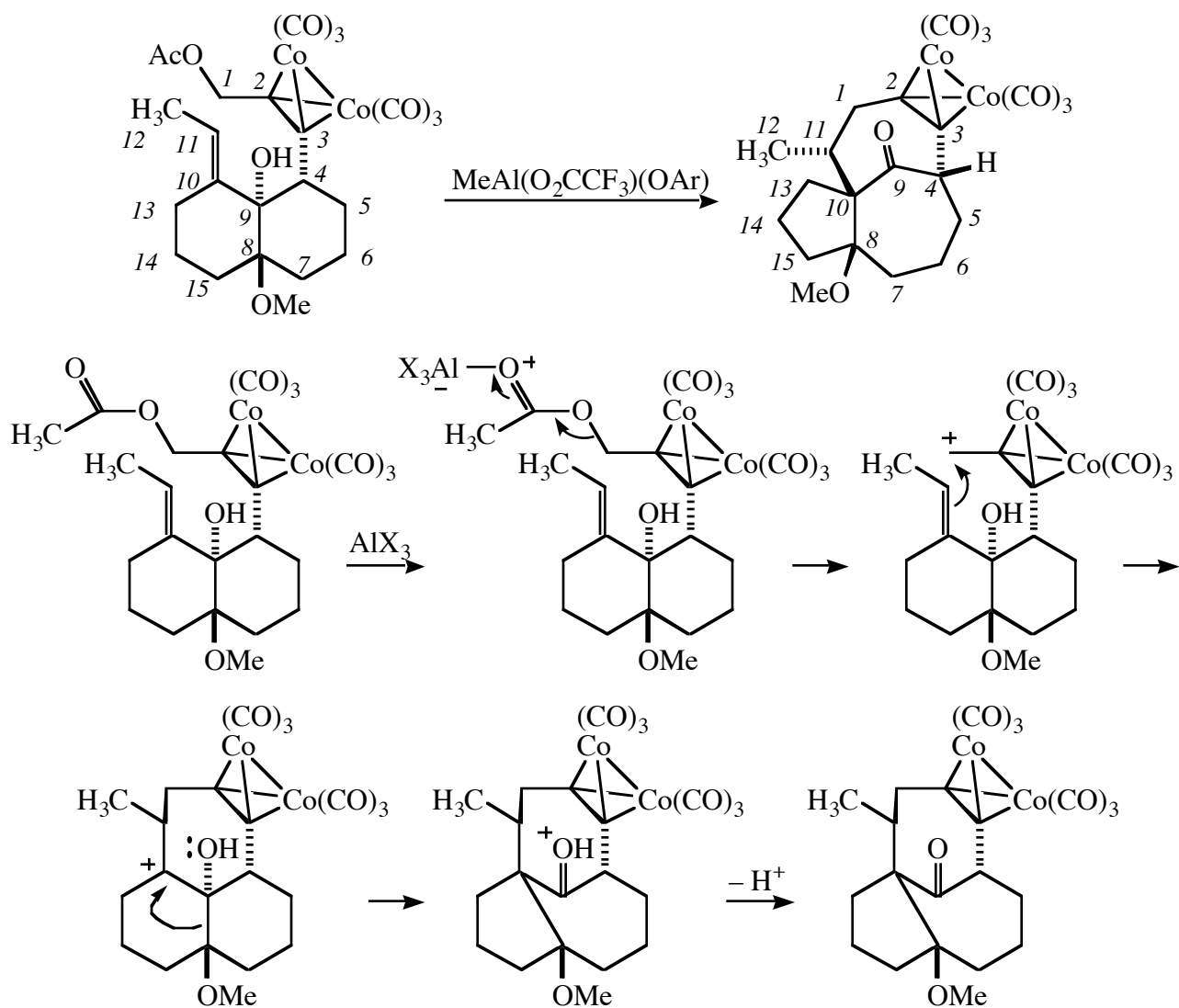
(k) Make: Si1–C2, C3–C4. Break: None.



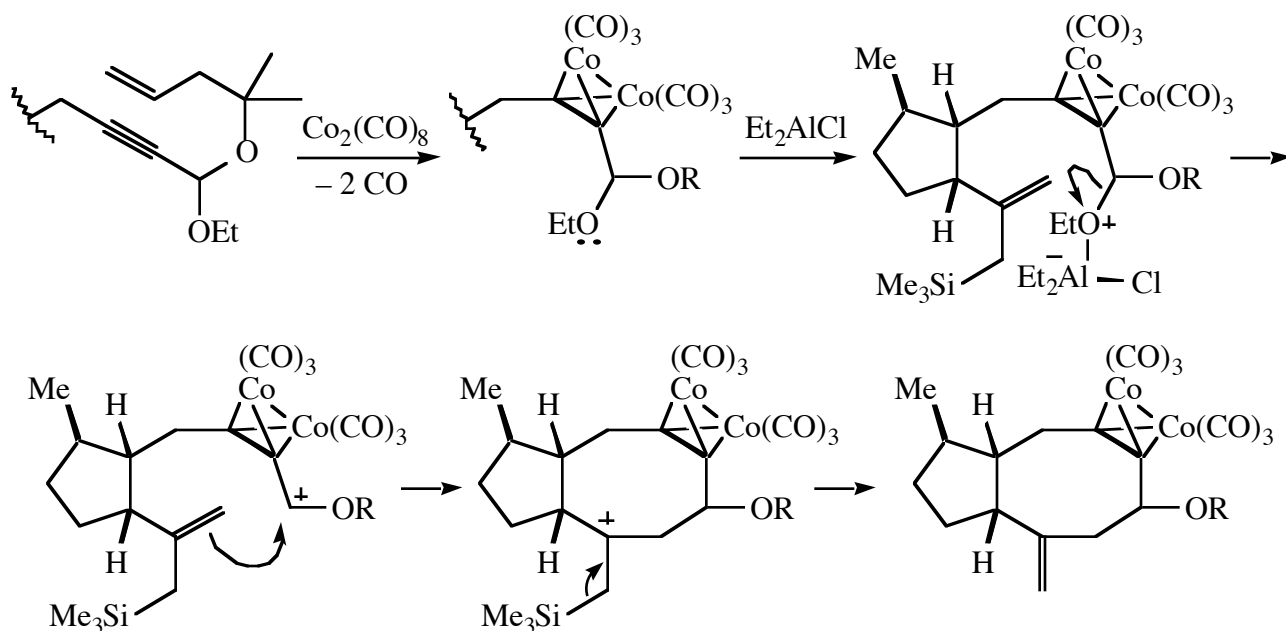
Insertion of a Rh–Si bond into the C2=C3 π bond will give the Si1–C2 bond. The requisite Si–Rh bond can be made by oxidative addition of Rh(I) to the Si–H bond. After the insertion, coordination of CO to Rh, insertion of CO into the Rh–C3 bond, and reductive elimination give the product.



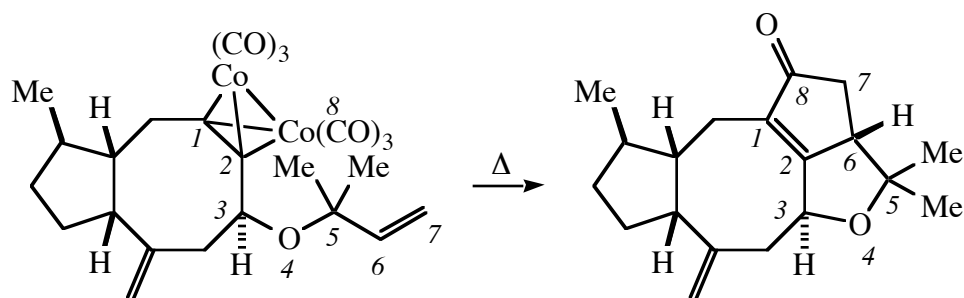
3. (a) Make: C1–C11, C8–C10. Break: C1–OAc, C8–C9. $\text{Co}_2(\text{CO})_6$ -alkyne complexes are prone to form cations at the propargylic position because the C–Co bonds hyperconjugatively stabilize the cation. The C10=C11 π bond can add to a C1 cation. Pinacol rearrangement (1,2-shift) then breaks the C8–C9 bond. Loss of H^+ from O completes the sequence.



(b) Addition of $\text{Co}_2(\text{CO})_8$ to an alkyne forms the $\text{Co}_2(\text{CO})_6$ -alkyne complex. Propargyl cation formation is thereby enhanced. The Lewis acid coordinates to the less hindered OEt group, converting it into a good leaving group. It leaves to give the propargyl cation, which is attacked by the alkene to form the eight-membered ring. Loss of Me_3Si^+ gives the product. Because of ring strain, the eight-membered ring could not form if the alkyne were not coordinated to $\text{Co}_2(\text{CO})_6$. The $\text{Co}_2(\text{CO})_6$ both reduces the bond angles around the "alkyne" C's and reduces the entropic barrier to eight-membered ring formation by holding the two "alkyne" substituents near one another.



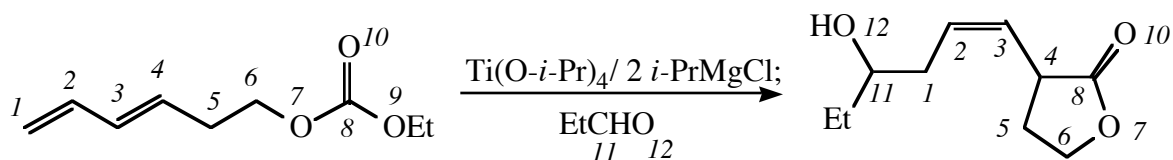
(c) Make: C1–C8, C2–C6, C7–C8. Break: Co–C1, Co–C2, Co–C8.



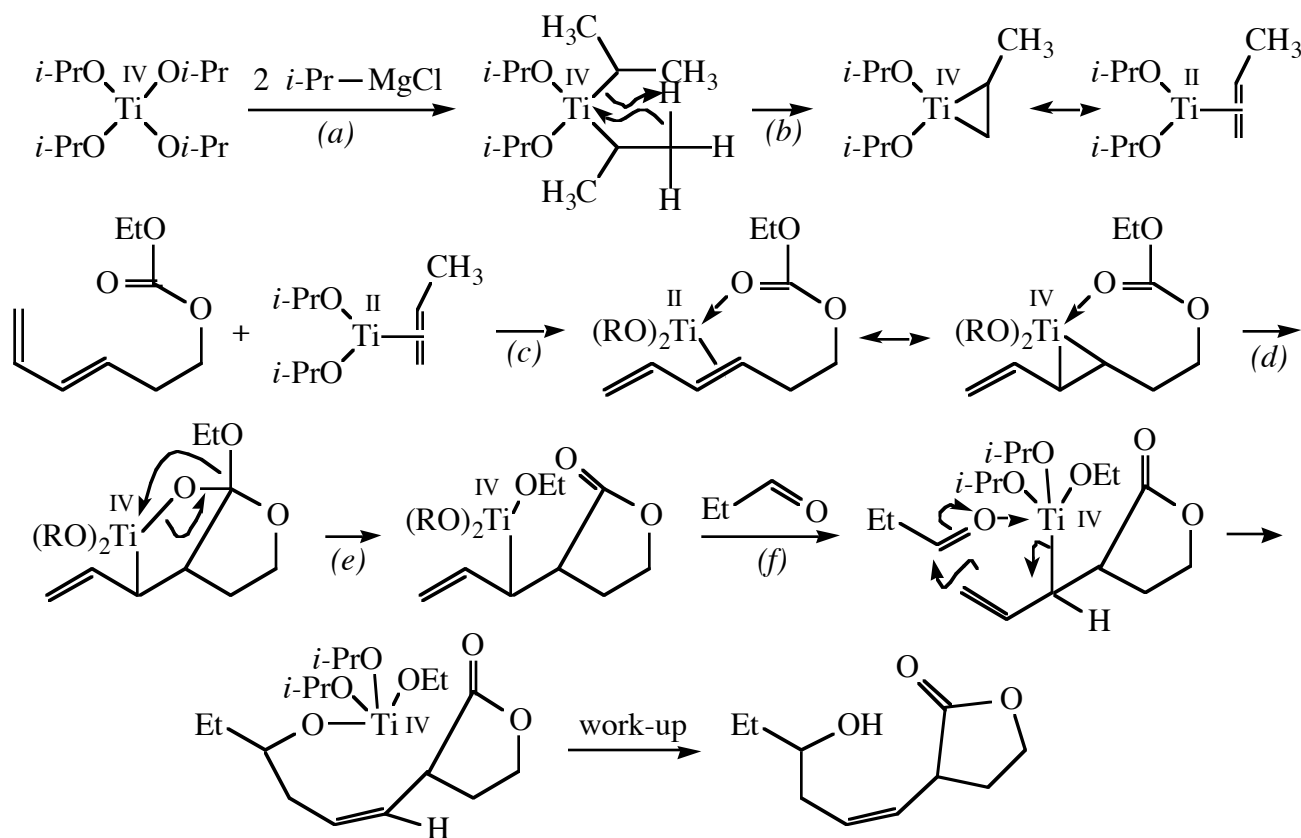
Conversion of a $\text{Co}_2(\text{CO})_6$ -alkyne complex into a cyclopentenone is the Pauson–Khand reaction. It proceeds by loss of CO from one Co to make a 16-electron complex, coordination and insertion of the $\text{C}_6=\text{C}_7$ π bond into the $\text{C}_2\text{--Co}$ bond to make the $\text{C}_2\text{--C}_6$ bond and a $\text{C}_7\text{--Co}$ bond, migratory insertion of CO into the $\text{C}_7\text{--Co}$ bond to make the $\text{C}_7\text{--C}_8$ bond, reductive elimination of the $\text{C}_1\text{--C}_8$ bond from Co, and decomplexation of the other Co from the $\text{C}_1=\text{C}_2$ π bond. The mechanism is discussed in the text (Section B.1.f).

(d) Make: C1–C11, C4–C8. Break: C8–C9. Ti is in the (IV) oxidation state, so it is d^0 . Since we are forming new bonds from C4 to C8 and C1 to C11, and both C8 and C11 are electrophiles, both C1 and C4 must act as nucleophiles. Normally in a diene one terminus acts as a nucleophile and one terminus acts as

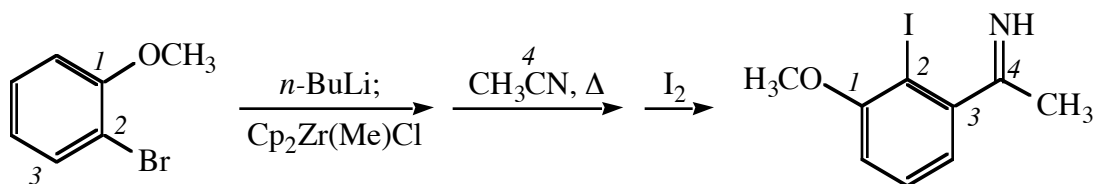
an electrophile. The role of the Ti, then, is to supply the necessary electrons. But Ti(IV) is not a reducing agent, so the role of the Grignard reagent must be to reduce the Ti.



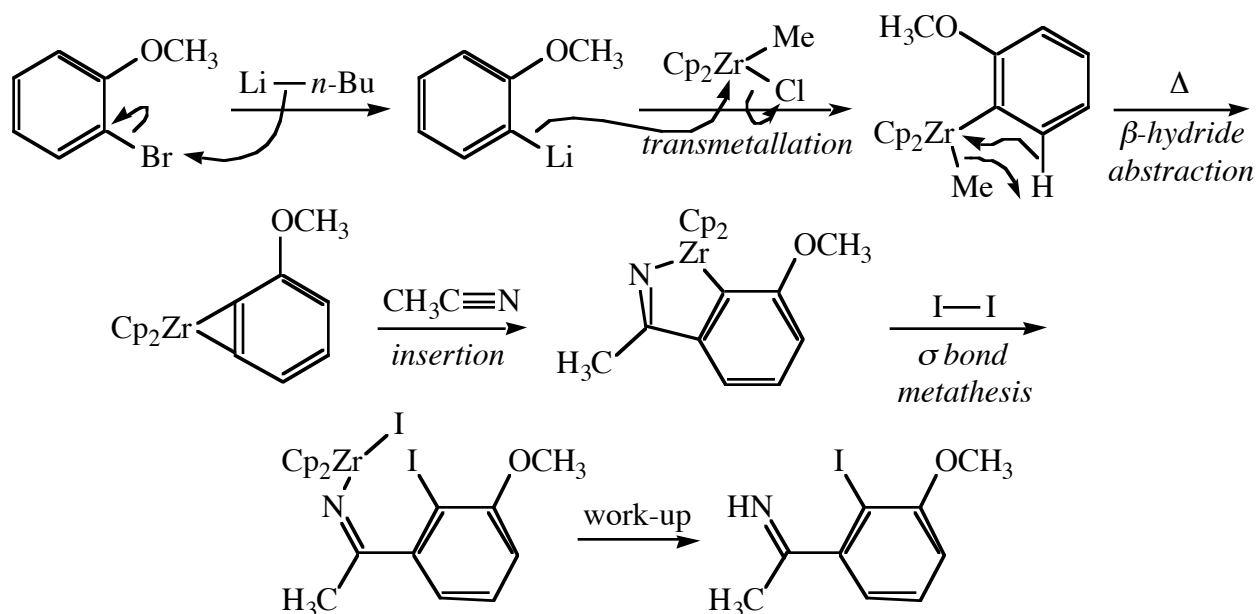
Addition of the Grignard to $\text{Ti}(\text{O-}i\text{-Pr})_4$ will displace two $i\text{-PrO}^-$ groups and give $(i\text{-PrO})_2\text{Ti}(i\text{-Pr})_2$. β -Hydride abstraction (or β -hydride elimination followed by reductive elimination) then gives a Ti(II)-alkene complex \leftrightarrow titanacyclopropane.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



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

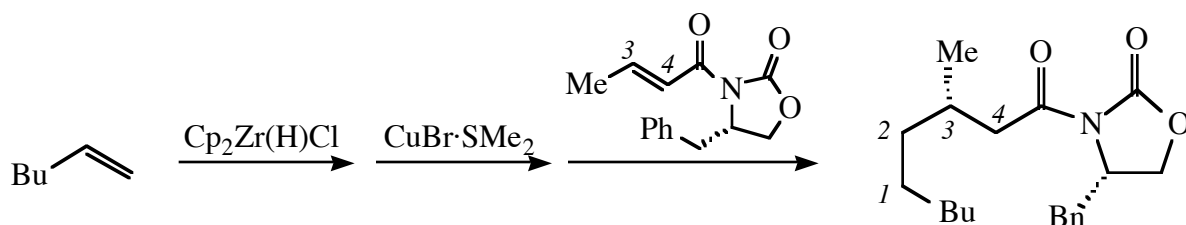


Addition of BuLi to ArBr results in halogen–metal exchange to give ArLi. Addition of $\text{Cp}_2\text{Zr}(\text{Me})\text{Cl}$ to ArLi gives transmetalation to give $\text{Cp}_2\text{Zr}(\text{Me})\text{Ar}$ and LiCl. We need to make a Zr–C3 bond in order to render C3 nucleophilic. This can be done by a β -hydride abstraction reaction to give a zirconacyclopropane. Insertion of the C4 \equiv N bond into the C3–Zr bond gives the crucial C3–C4 bond. We still need to form the C2–I bond. Addition of I_2 cleaves the C2–Zr bond and gives the C2–I bond. Aqueous workup cleaves the N–Zr bond to give the observed product.

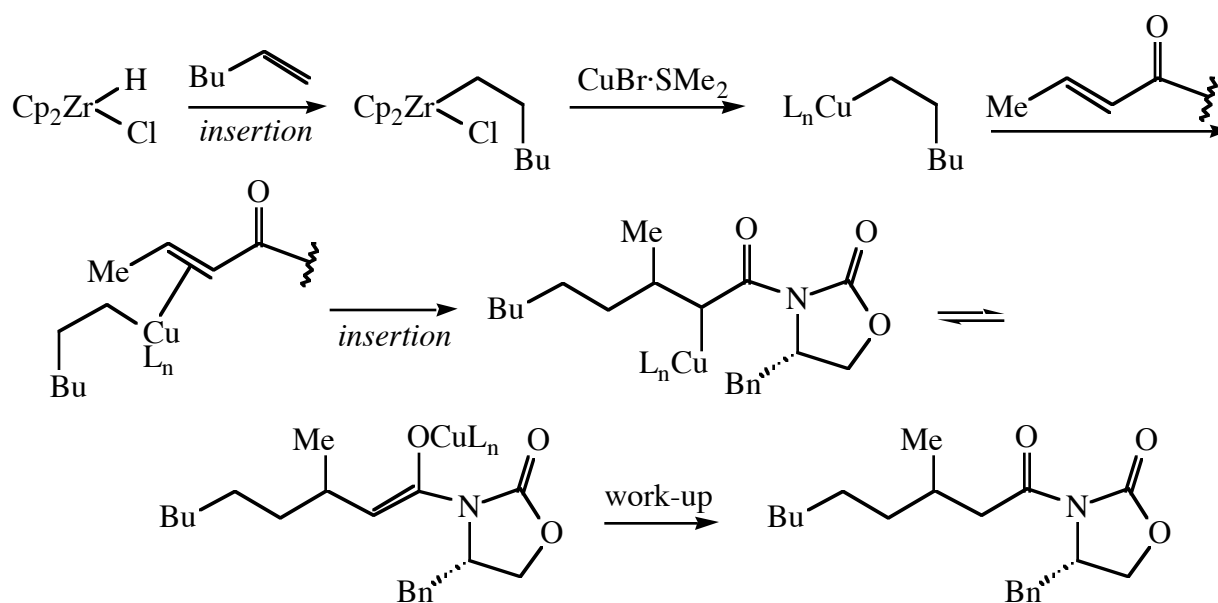


(f) This reaction proceeds via mechanisms similar to the previous two problems. The Grignard reagent reduces Ti(IV) to a Ti(II)–propene complex. Exchange of propene with the imine gives a titanaaziridine complex. Insertion of the alkyne into the C–Ti bond gives a titanapyrrolidine. Addition of I_2 cleaves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

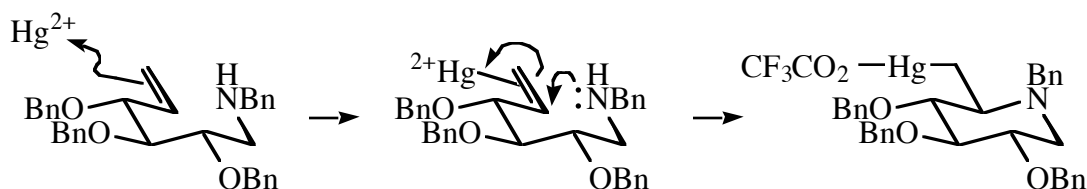
(g) Make: C2–C3. C3 is electrophilic, so C2 must be made nucleophilic.



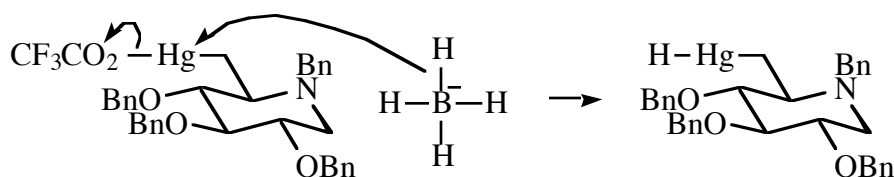
Addition of an alkene to a compound containing a metal–H bond usually results in insertion, and it does in this case, too, to give the stabler 1° alkylmetal. Addition of CuBr to this complex might result in transmetalation, to give a C2–Cu bond. Addition of the copper compound to the unsaturated imide gives conjugate addition, perhaps by coordination of the $\text{C}3=\text{C}4$ π bond and insertion into the C2–Cu bond. Workup gives the observed product.



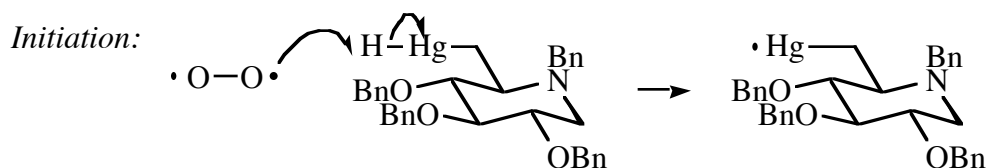
(h) Hg(II) salts coordinate to alkenes and make them more electrophilic. In this case, the N can attack the alkene–Hg complex, giving an alkylmercury intermediate.



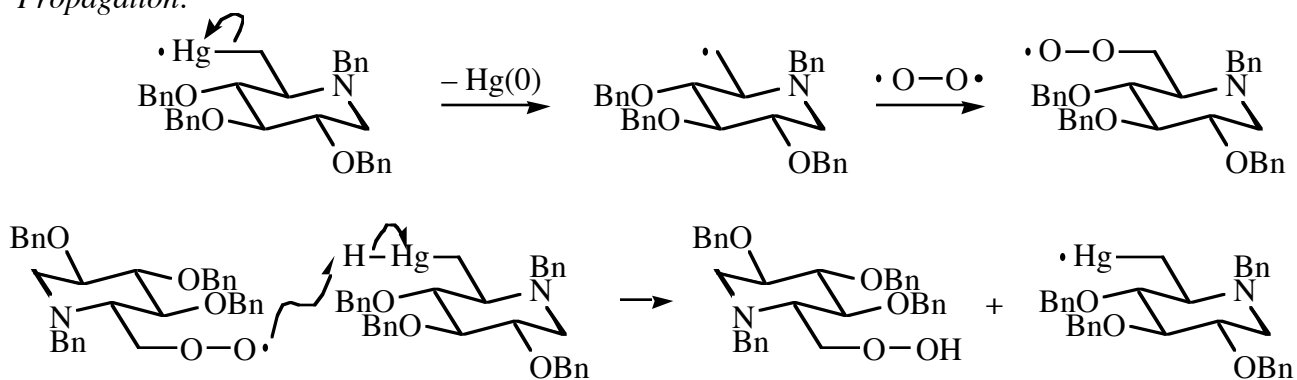
The NaBH_4 replaces the $\text{Hg}-\text{O}_2\text{CCF}_3$ bond with a $\text{Hg}-\text{H}$ bond.



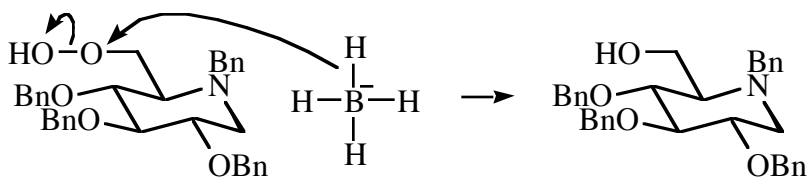
Free-radical decomposition of the alkylmercury hydride then occurs to replace the C–Hg bond with a C–O bond, with the O coming from O_2 . The free-radical reaction gives a hydroperoxide C–OOH.



Propagation:



Finally, the hydroperoxide is reduced to the alcohol $\text{C}-\text{OH}$ by excess NaBH_4 .



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

