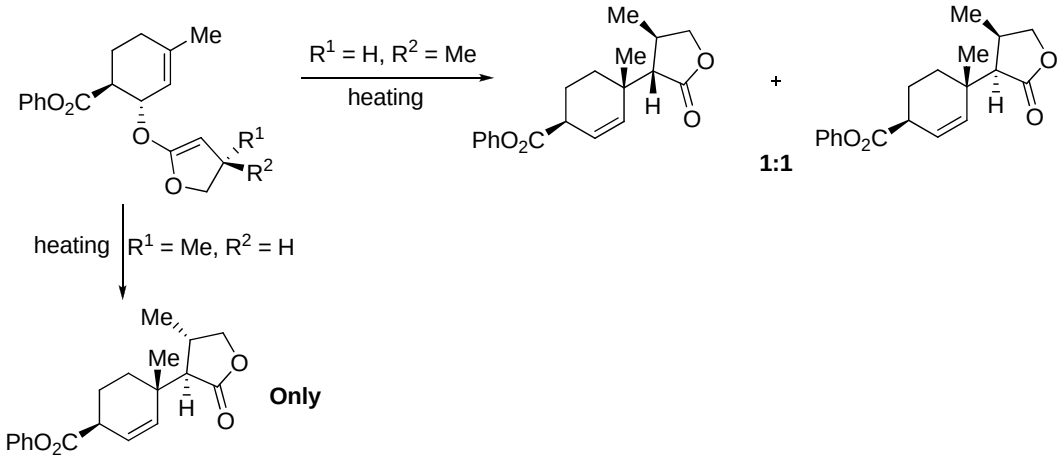
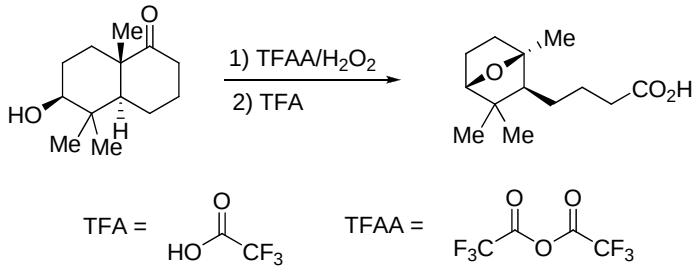
Series 1

Exercise 1



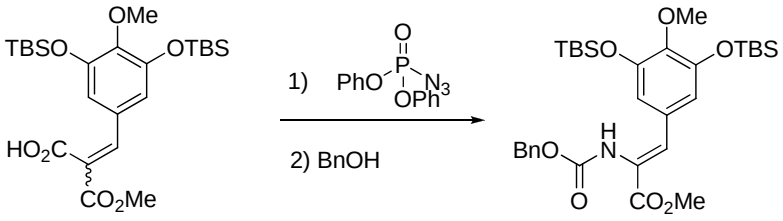
Give a mechanism for the reaction and explain the stereoselectivity observed. Why is the diastereoselectivity changing with the stereochemistry of the center on the dihydrofuran ring?

Exercise 2



Give a mechanism for the reaction and explain the selectivity observed.

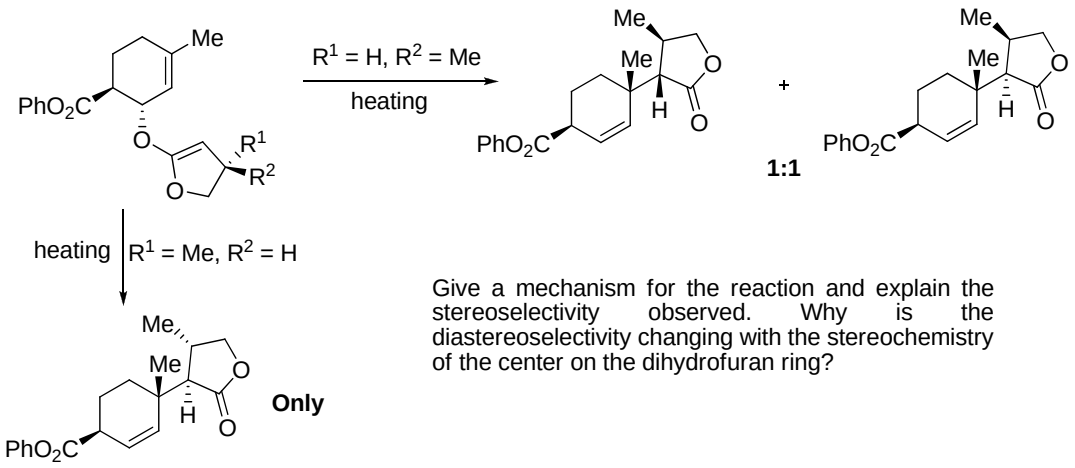
Exercise 3 (Exam question 2008)



Give a mechanism for the reaction. The starting material is a mixture of double bond isomers, but the product is only one isomer: how is it possible?

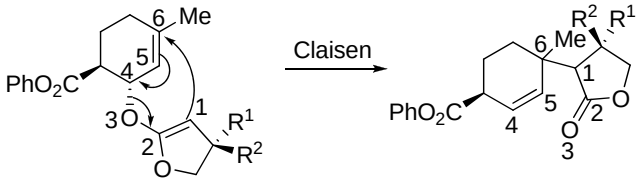
Series 1- Solutions

Exercise 1



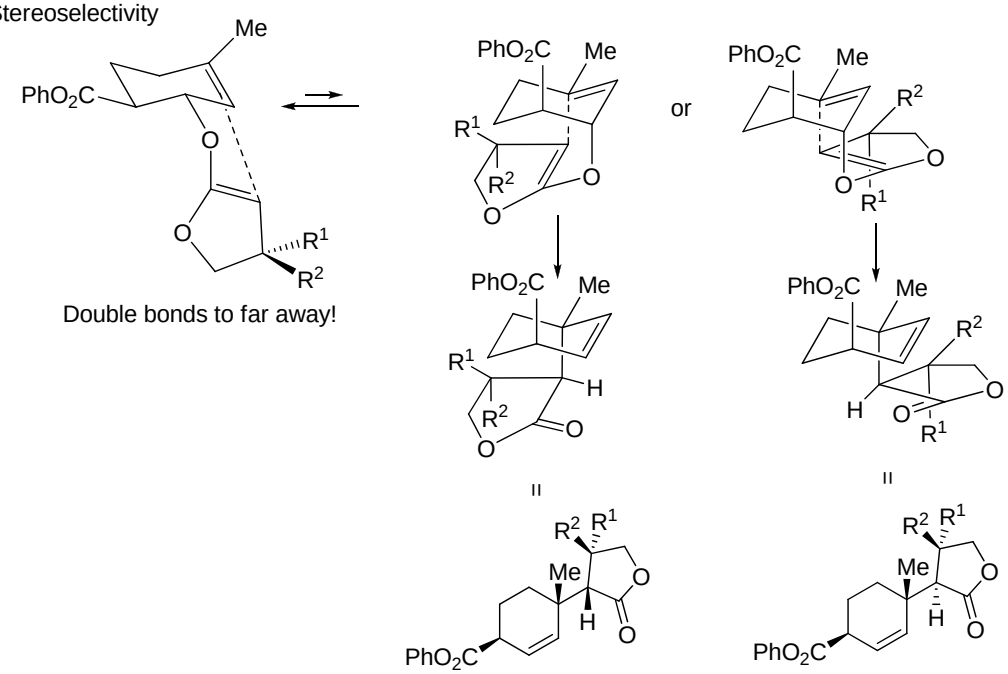
Give a mechanism for the reaction and explain the stereoselectivity observed. Why is the diastereoselectivity changing with the stereochemistry of the center on the dihydrofuran ring?

1) Mechanism



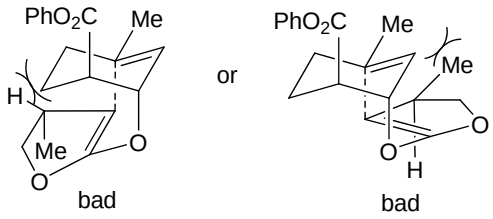
The reaction is a Claisen [3,3] sigmatropic rearrangement. It can be identified by the array of 6 atoms with two terminal double bonds. Numbering starting material and product starting from an easily recognizable group also helps to find the mechanism.

2) Stereoselectivity



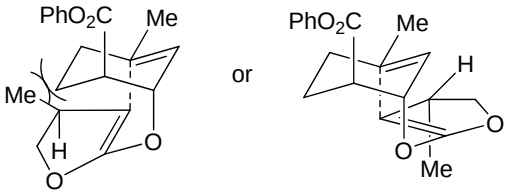
Double bonds to far away!

R^1 = H, R^2 = Me



bad bad

R^1 = Me, R^2 = H



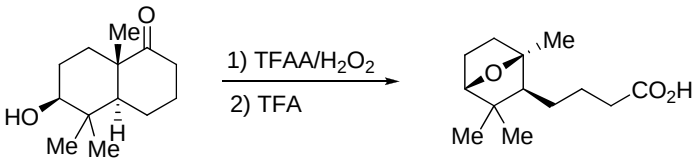
very bad OK

For the Claisen reaction, a chair or a boat transition state are possible. For acyclic systems, the chair is usually preferred, but here, a second 6-membered ring is present. The best way to start is to draw the first 6-membered ring as a chair. The most stable conformation with the groups in equatorial position does not allow the reaction, as the double bonds are two far away for the cyclic transition state. The reaction proceeds from the less stable conformer, via either a chair or a boat transition state, which lead to the observed products.

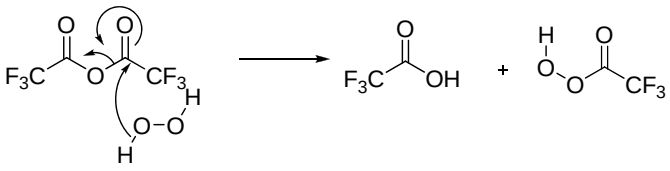
When R^1 = H, R^2 = Me, steric interaction are present in both transition states, and a mixture is obtained. When R^1 = Me, R^2 = H, the boat transition state is much less sterically hindered, and only one product is obtained.

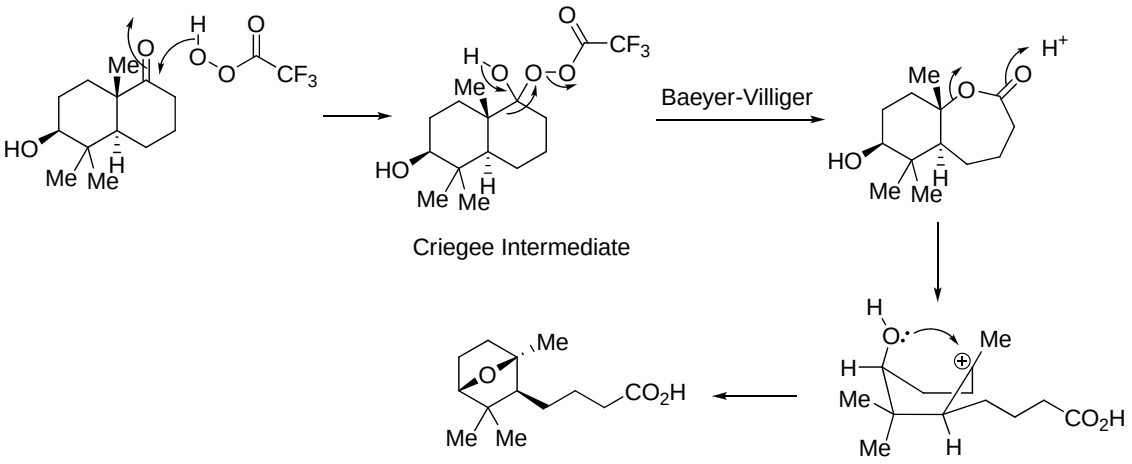
Reference: *J. Chem. Soc. Perkin Trans. 1* **1977**, 1211.

Exercise 2



Give a mechanism for the reaction and explain the selectivity observed.

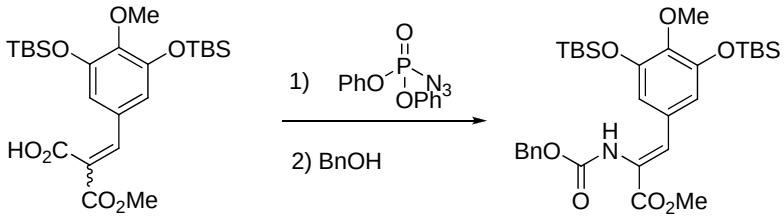




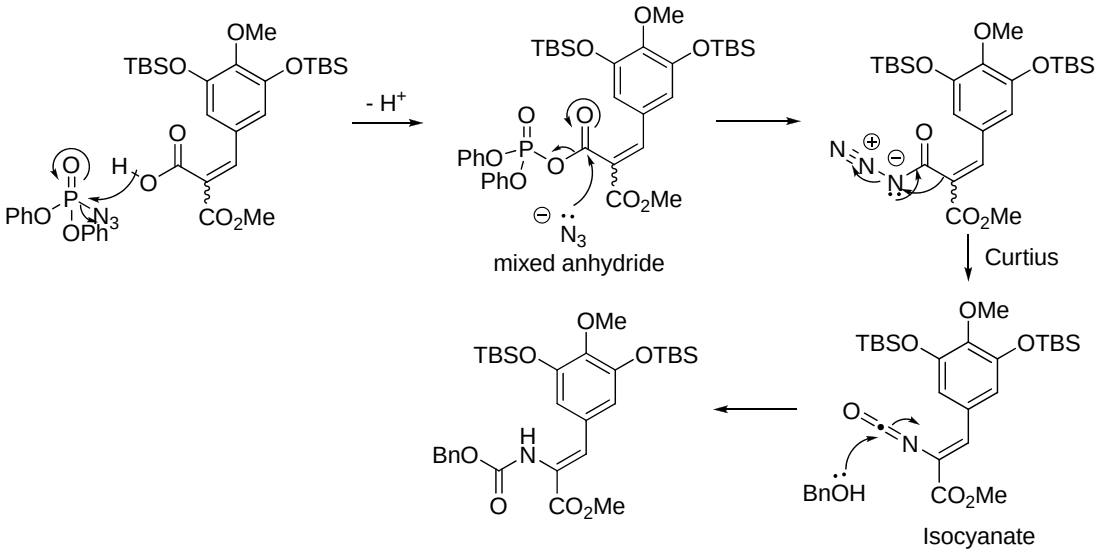
In the first step, hydrogen peroxide reacts with the trifluoroacetic anhydride to form the peracid. The peracid then reacts with the ketone to form an acetal intermediate (Criegee intermediate). A 1,2 shift of the more substituted alkyl subsituent (better cation stabilization) to the electron-defficient oxygen then occurs under release of trifluoro acetic acid (Baeyer-Villiger rearrangement). In the last step, a carbocationic intermediate is formed, which reacts intramolecularly with the alcohol (SN^1 reaction). Only the attack from the same side as the alcohol is possible.

Reference: *J. Org. Chem.* **1995**, *60*, 5114.

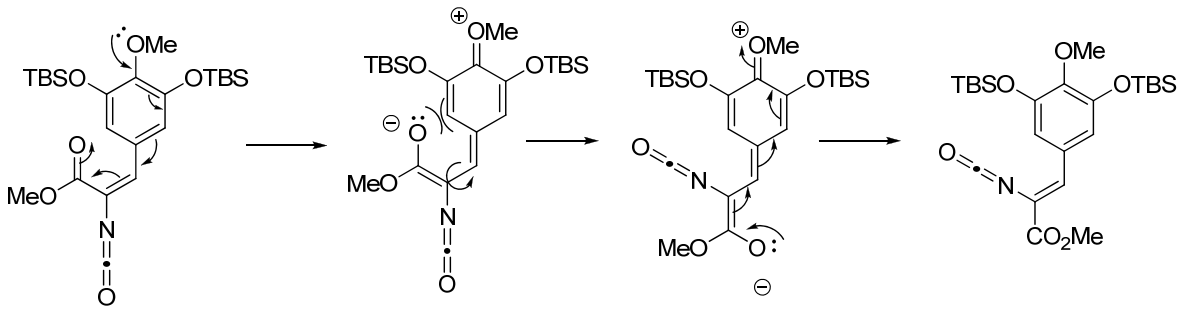
Exercise 3 (Exam question 2008)



Give a mechanism for the reaction. The starting material is a mixture of double bond isomers, but the product is only one isomer: how is it possible?



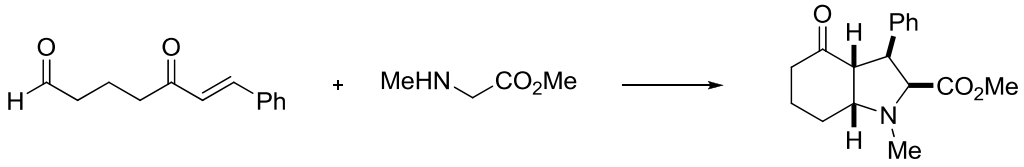
In the first step, the acid is activated by the phosphorous reagent in the form of a mixed anhydride. Addition of the azide and elimination of the phosphate then gives the acyl azide. 1,2-alkyl shift with lost of nitrogen (Curtius) lead to the isocyanate. Finally, benzyl alcohol attacks the electrophilic carbon to form the carbamate product



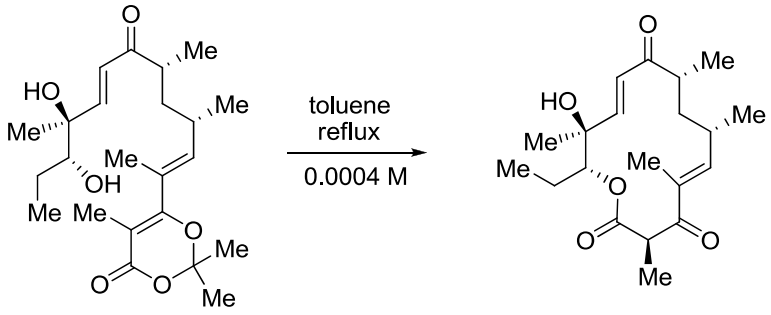
To isomerize the mixture of starting material to a single product, it is necessary to "remove" the double bond. The most probable mechanism is at the stage of the isocyanate: Electron-donation from the para methoxy group allows the formation of a zwitterionic structure, in which bond rotation is possible. The driving force is the smaller size of the isocyanate when compared with the ester.

Series 2: Cyclizations and Cycloadditions

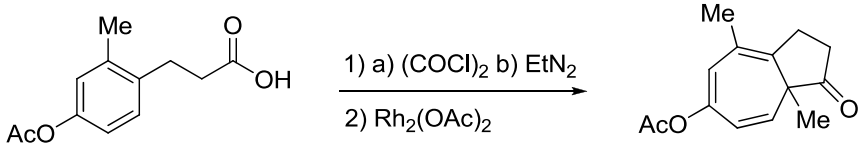
Exercise 1



Exercise 2

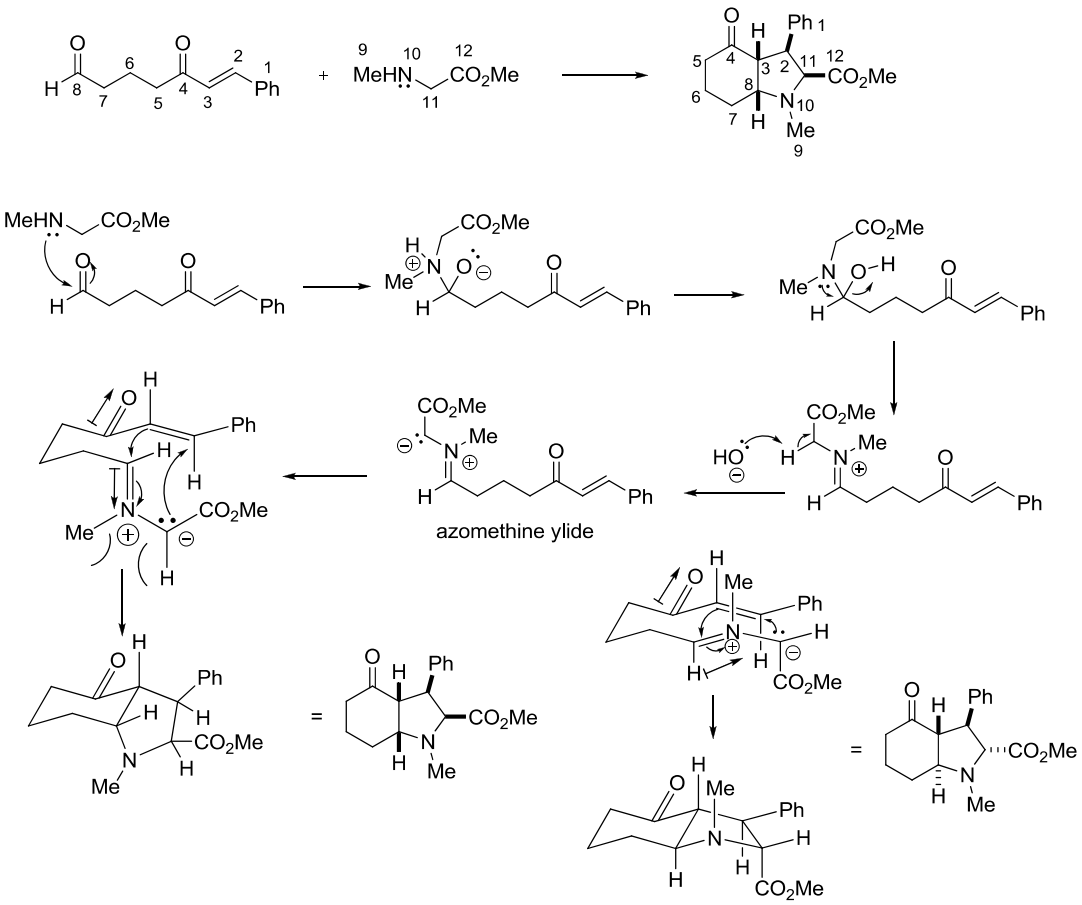


Exercise 3



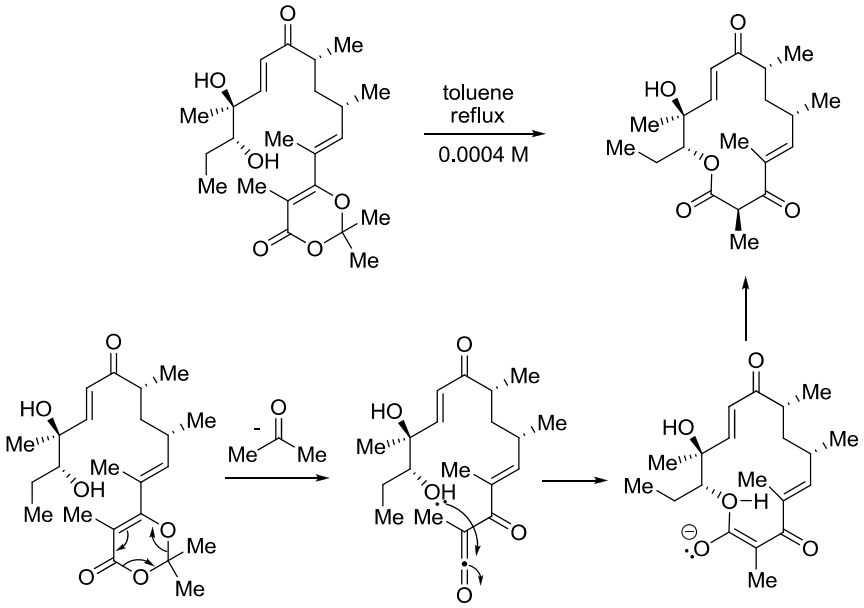
Series 2: Cyclizations and Cycloadditions- Solutions

Exercise 1



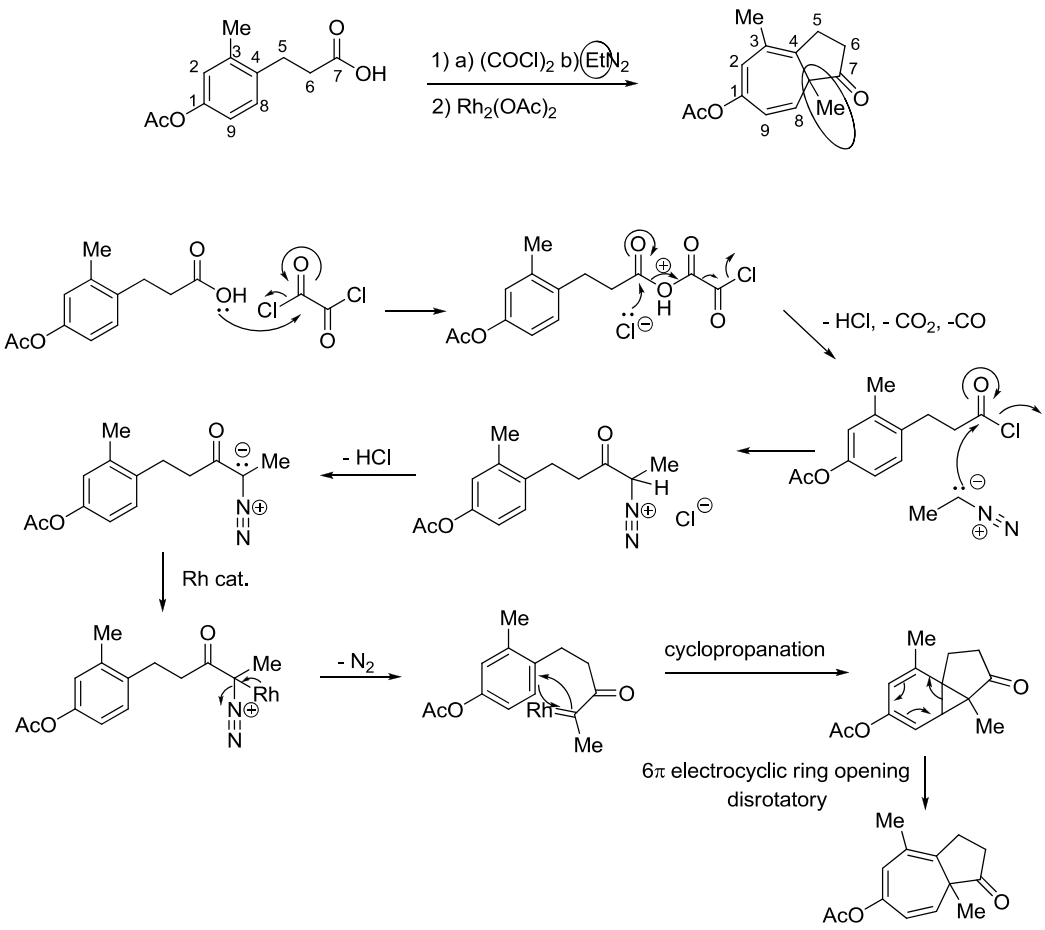
The first step of the reaction is a condensation between the amine and the most electrophilic carbonyl group, the aldehyde, to give an iminium. The condensation between amines and aldehydes is a very important reaction in organic chemistry, which occurs easily. The ester group in alpha position to the nitrogen makes the alpha proton acidic, and deprotonation to form an azomethine ylide is relatively easy. The next step is an intramolecular [3+2] cycloaddition with the alkene. The rationalization of the high diastereoselectivity observed in this step is not trivial. As often when a 6-membered saturated ring is obtained in the product, a good method to obtain a reasonable transition state is to draw the product in a chair conformation. The positioning of the iminium in the pseudo axial position and avoiding the steric interactions between the ester group and the methyl group on the nitrogen leads to the observed product. The potentially sterically more favored transition state with the iminium in equatorial position would have given another diastereoisomer. A possible explanation is that the dipoles are better minimized if the iminium is in axial position.

Exercise 2



The macrolactonization method described here proceeds under perfectly neutral conditions. Consequently, an acid catalyzed process cannot be proposed. Upon heating under reflux in toluene (110 °C) , a retro hetero Diels-Alder reaction occurs under formation of acetone (which is a gas at this temperature). The formed ketene is very electrophilic and reacts spontaneously with the free alcohol. In the last step, a proton transfer occurs. The stereochemistry of the formed center is determined by the thermodynamic stability, as equilibration is easy at a beta-keto ester position. It cannot be predicted easily without determination of the most favourable conformation (for example with a minimization software). The low concentration is essential to prevent intermolecular reactions.

Exercise 3

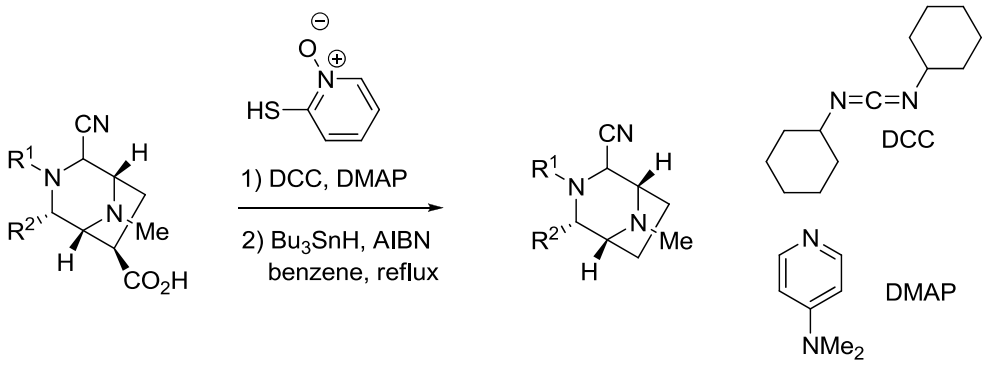


The first step in this exercise is to realize a problem when numbering: there are two carbons more in the product then the starting material, and the benzene ring has reacted! The only possible source of the two new carbons is the diazoethane added in step 1b. The best way is then to proceed stepwise, using the known reactivity of the reagents. The reaction of acids with oxalyl (or sulfonyl) chloride is a classical method for the formation of acid chlorides, in this case via the formation of a mixed anhydride, followed by fragmentation with liberation of carbon monoxide, carbon dioxide and hydrogen chloride. In 1b), it is important to remember the relative nucleophilicity of diazo compounds on the carbon, visible in the drawn resonnance structure, and the strong electrophilic character of acid chlorides. After addition-elimination, the formed salt is unstable and eliminate hydrogen chloride to form a new diazo compound, which is more stable.

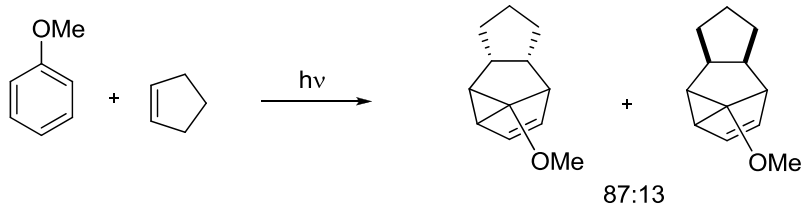
The reaction of diazo compounds with rhodium catalysts is a classical way to generate rhodium carbenoids under nitrogen gas release. Rhodium carbenoids reacts very fast with double bonds, even the one of benzene to give a cyclopropane. The formed cyclohexadiene undergoes then a 6-pi electrons electrocyclic ring opening, which is favored by the release of ring strain, to give the final product.

Series 3: Radicals, photochemistry and Umpolung

Exercise 1

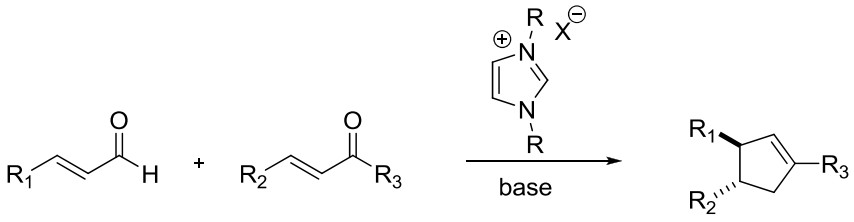


Exercise 2



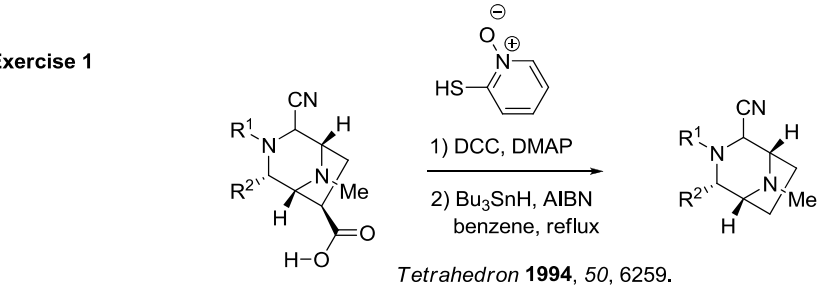
87:13

Exercise 3

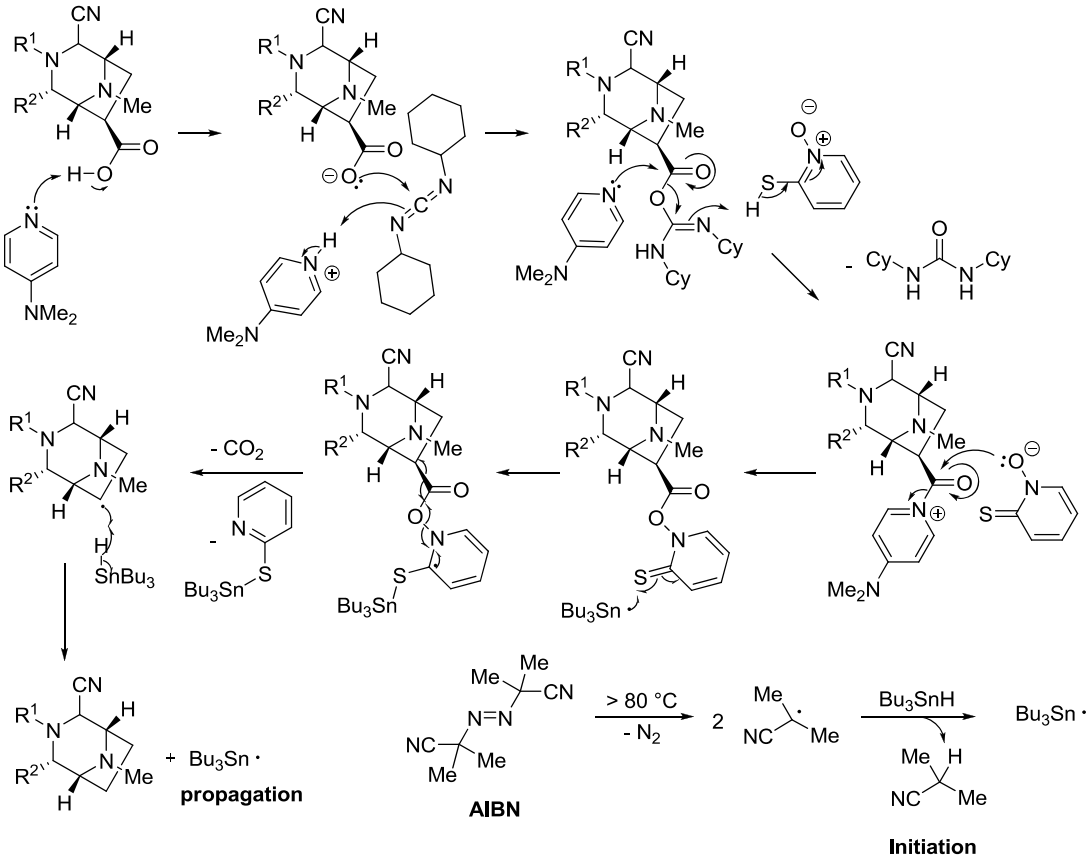


Series 3: Radicals, photochemistry and Umpolung- Solutions

Exercise 1



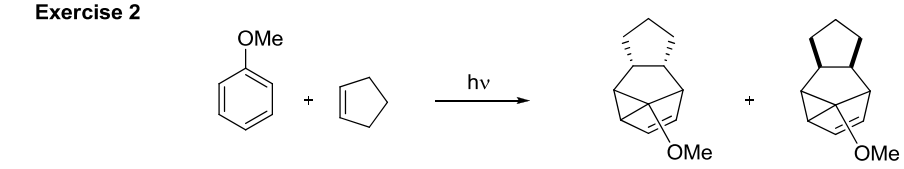
Tetrahedron **1994**, *50*, 6259.

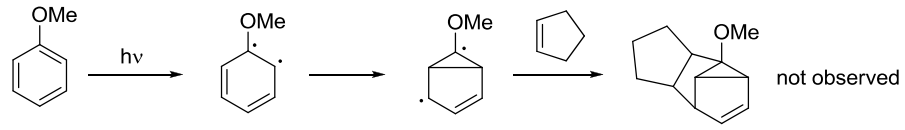


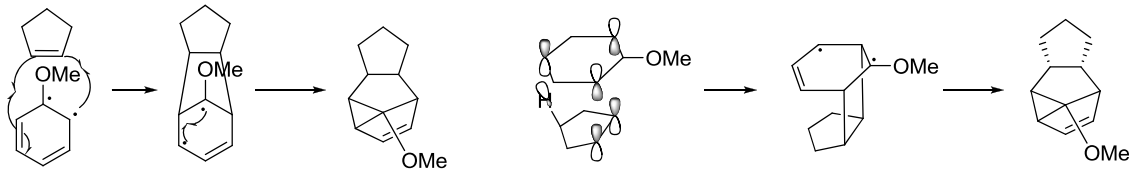
The first step of the reaction is the classical activation of an acid with dicyclohexylcarbodiimide. The role of DMAP is first as a base to form the carboxylate, then as a nucleophilic catalyst to form a very reactive pyridinium ester. After this activation, attack of the thiopyridine oxide is easy and gives an hydroxamate ester. The second step begins with the thermal decomposition of AIBN to form two isobutyryl radicals, which then abstract a hydrogen from tributylin hydride to form a tributyltin radical. The tributyltin radical is thiophilic and adds to the C=S double bond to form a new radical, which can fragment under rearomatization of the pyridine ring and release of carbon dioxide to form a secondary alkyl radical. The secondary alkyl radical is very reactive and can abstract the hydrogen of tributyltin hydride to propagate the radical chain reaction. This is an example of the Barton method for the decarboxylation of acids.

Series 3: Radicals, photochemistry and Umpolung

Exercise 2





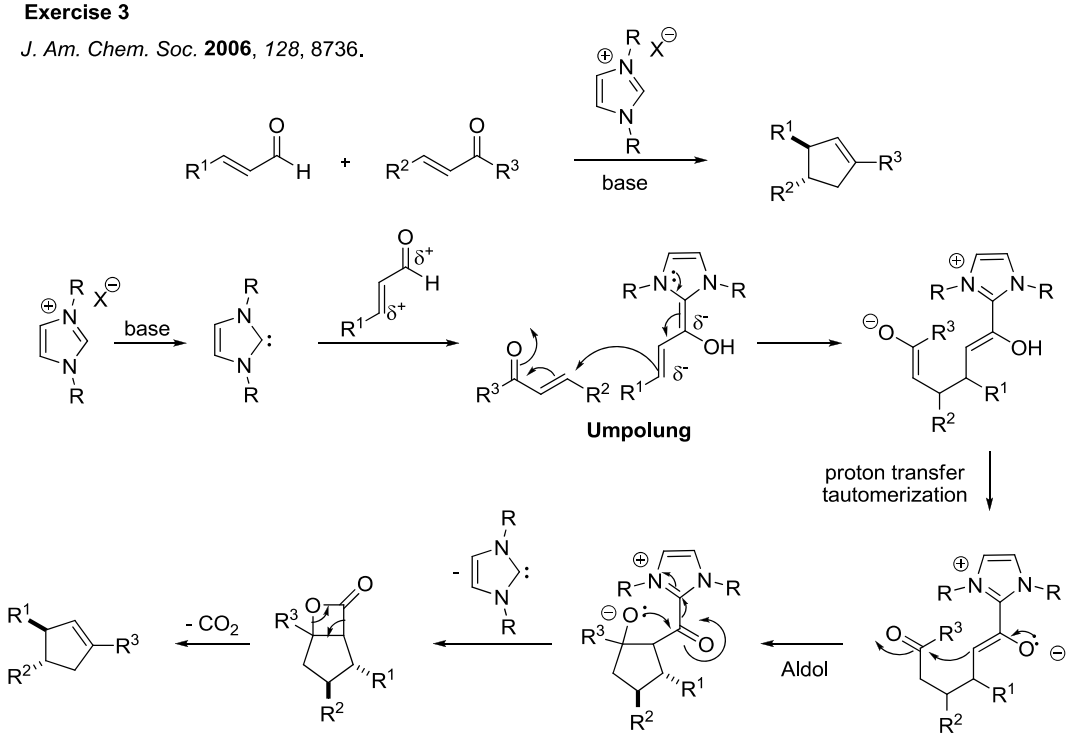


The photochemical reaction between anisole and cyclopentene is initiated by the excitation of the benzene ring. In principle, it would be favorable to have one of the radical next to the stabilizing oxygen. Using the mechanism proposed for benzene, it is difficult to rationalize the regioselectivity, as another product would be expected. It is possible to obtain the right product with this mechanism, but not with a radical next to oxygen. Consequently, it has been proposed that the more stable biradical allows another reaction pathway via [5+2] cycloaddition. The obtained biradical has then still a radical next to oxygen. Final recombination gives the observed product. For the diastereoselectivity, secondary orbital interactions between the orbitals of the C-H bonds on the cyclopentene and the pi orbital of the benzene diradicals have been proposed to favor the *endo* product.

Series 3: Radicals, photochemistry and Umpolung

Exercise 3

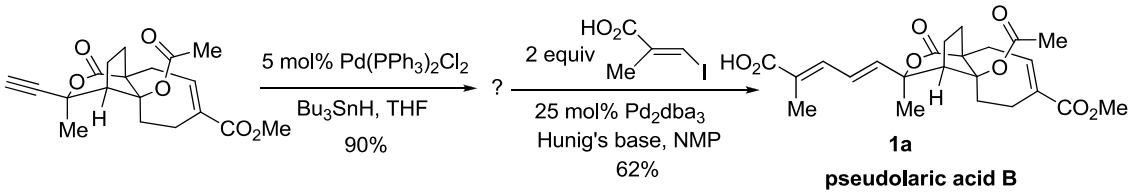
J. Am. Chem. Soc. **2006**, *128*, 8736.



The active catalyst is generated by deprotonation of the imidazolium salt to form the nucleophilic heterocyclic carbene. The carbene adds then to the most electrophilic position: the carbonyl of the aldehyde. The formed Breslow intermediate has now an inversed reactivity when compared with the starting material (Umpolung). The attack at the gamma position is favored for bulky R group on the catalyst. Michael type additon to the conjugated ketone is favored (softer position). After proton transfer and tautomerization, an intramolecular aldol reaction gives the cyclopentyl ring. Lactonization with release of the carbene catalyst is occurring next. Finally, decarboxylation of the beta lactone gives the observed product. The reaction is probably under thermodynamical control, leading to the less sterically hindered *trans* product.

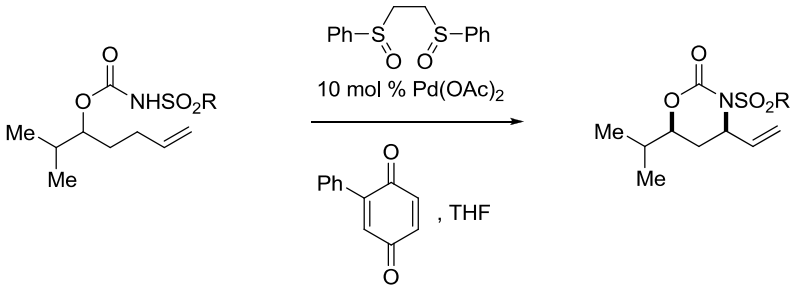
Series 4: Transition metals in organic synthesis

Exercise 1



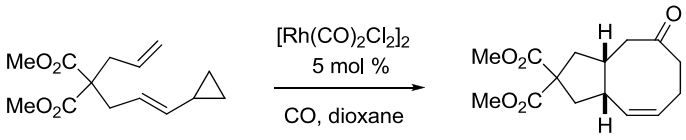
Propose a detailed mechanism for this two steps reaction.

Exercise 2



Propose a detailed mechanism for this reaction.

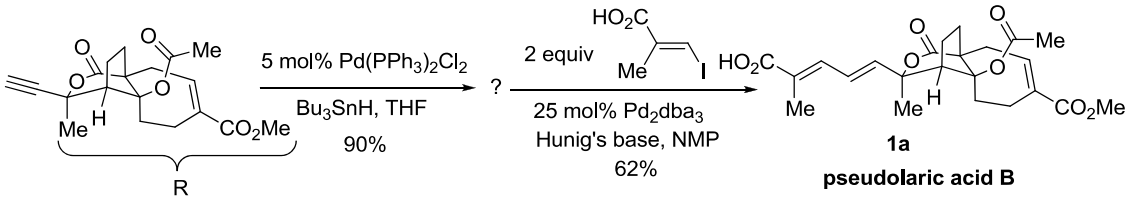
Exercise 3



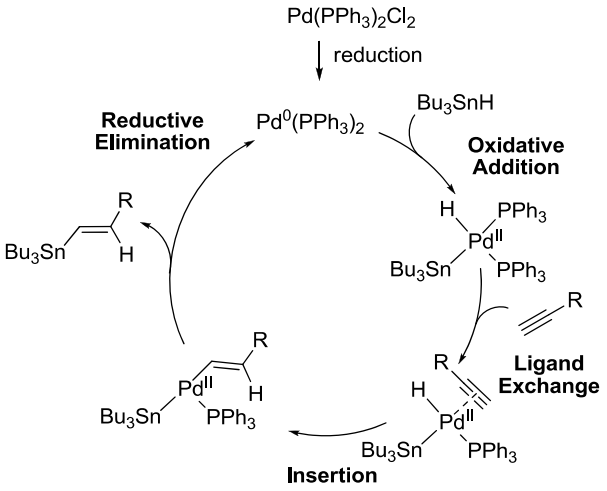
Propose a detailed mechanism for this reaction.

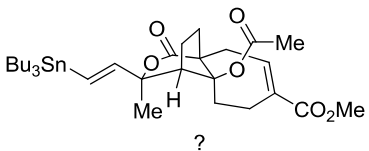
Series 4: Transition metals in organic synthesis - Solutions

Exercise 1



J. Am. Chem. Soc. **2008**, *130*, 16424.





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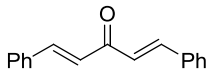
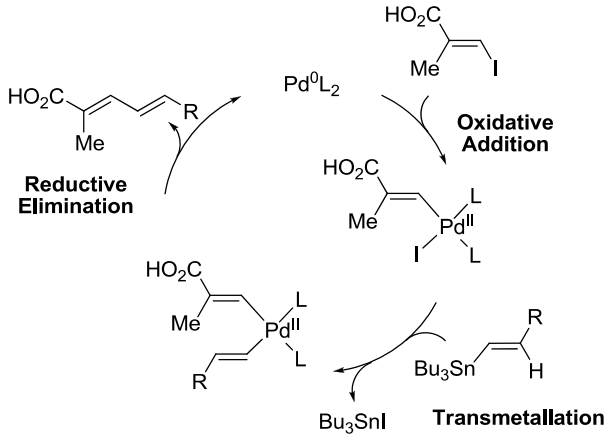


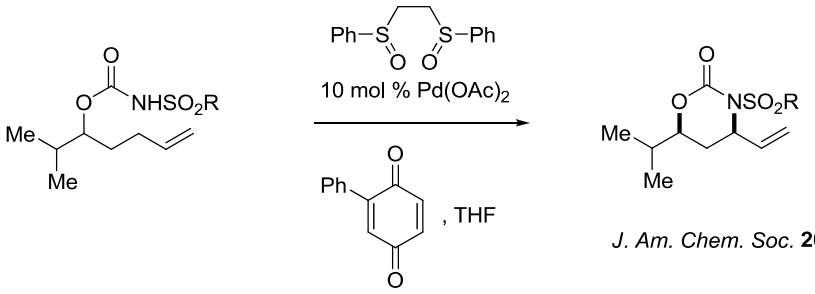


The first step in the reaction is a Pd-catalyzed hydrostannylation of the alkyne, very similar to the general addition to olefins in the script (page 106). The Pd(II) precatalyst is first reduced to Pd(0), either by the phosphine or through the tributyltin hydride. After oxidative addition of the tributyltin hydride, coordination and insertion of the acetylene occurs. The insertion into the Pd-H bond is probably favored because of steric reasons. The reaction generates the *trans* olefin with high selectivity. Finally, reductive elimination gives the vinyl stannane, which is the product obtained after the first step.

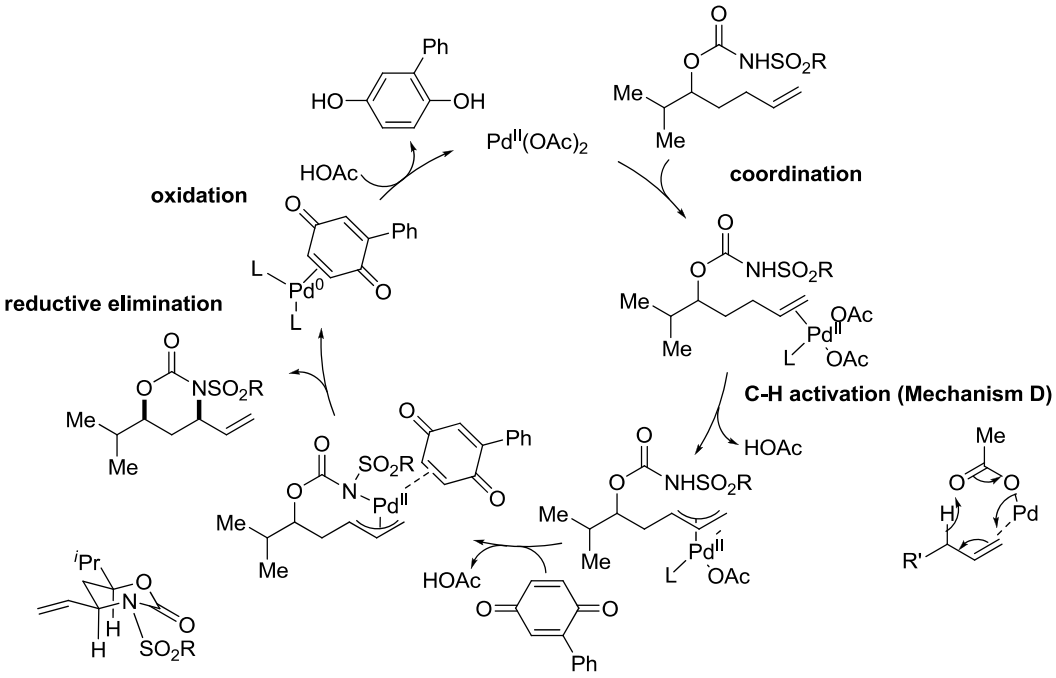
The second step is a classical Stille coupling, proceeding via oxidative addition, transmetallation and reductive elimination. The base was probably required to prevent protodematallation promoted by the acid. dba (dibenzylidene acetone) is a useful ligand for Pd(0). The mild conditions allows to construct the side chain of the complex natural product with good selectivity.

Series 4: Transition metals in organic synthesis - solutions

Exercise 2



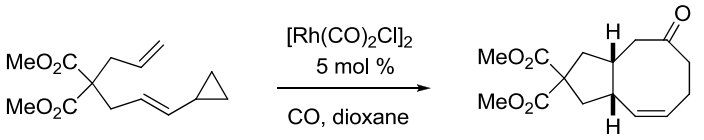
J. Am. Chem. Soc. **2009**, *131*, 11707.



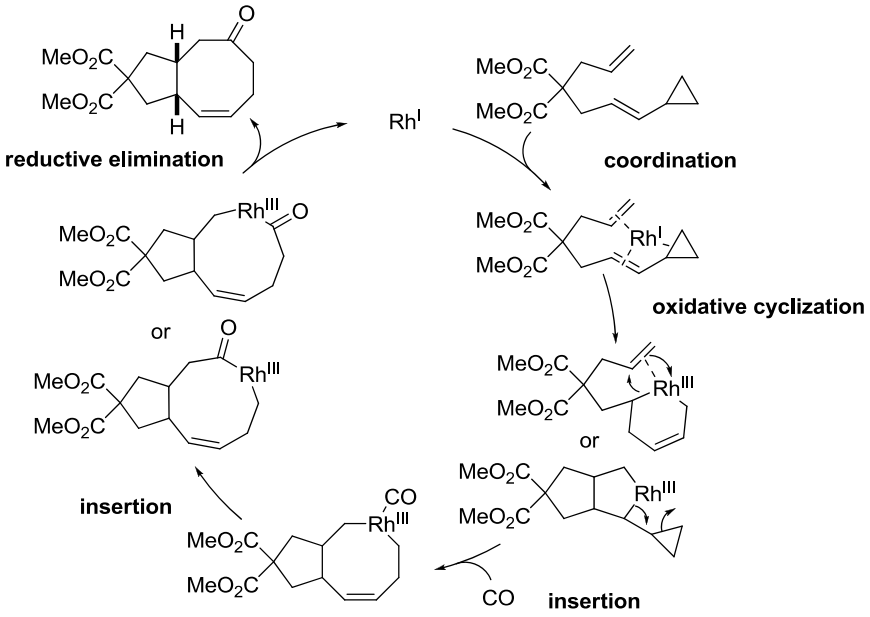
This reaction is an intramolecular variation of the allylic C-H oxidation developed by C. White (script p. 112). The reaction starts with coordination of Pd to the double bond, followed by allylic C-H bond functionalization, probably via a concerted deprotonation mechanism to form a pi-allyl complex. At this point, deprotonation and coordination of the nitrogen is possible. The benzoquinone oxidant also play a role as ligand to promote the following reductive elimination step to form Pd(0). Finally, oxidation to Pd(II) occurs. The phenyl group on benzoquinone allowed to modulate his oxidation potential. The disulfoxide ligands was essential for the success of the reaction, but it is still unclear what its exact role is. The observed diastereoselectivity can be explained by the favorable equatorial position of the two substituents in the chair conformation of the product.

Series 4: Transition metals in organic synthesis - solutions

Exercise 3



J. Am. Chem. Soc. **2007**, *129*, 10060.



This example by Wender demonstrates the capacity of Rh catalysts for cyclization reactions. After coordination of the diene system, two oxidative cyclizations are possible: Via reaction of the two olefins, to form a metalacyclopentane or via reaction with the vinylcyclopropane, to form a metalacyclohexene. In the latter case, the cyclopropane is behaving like an olefin, due to the high energy of the ring strain. In the next step, insertion of the olefin or on the cyclopropane gives a metalacyclooctene. Under CO pressure, CO insertion is faster than reductive elimination and two different rhodium acyl complexes can be formed. Finally, reductive elimination gives the observed product. The diastereoselectivity observed is difficult to rationalize in this case.