Suggested solutions for Chapter 40

PROBLEM 1
Suggest mechanisms for these reactions, explaining the role of palladium in the first step.

Purpose of the problem
Revision of enol ethers and bromination, the Wittig reaction, and, of course, first steps in palladium chemistry.

Suggested solution
The first step is a reaction of an enol with an allylic acetate catalysed by palladium(0) via an \( \eta^3 \) allyl cation. There is no regiochemistry to worry about as the diketone and allylic acetate are both symmetrical.

\[
\begin{align*}
\text{AcO} & \underset{\text{Ph}_3P} \rightarrow \text{AcO} \\
\text{OEt} & \underset{\text{PdLn}} \rightarrow \text{L}_n\text{Pd} \\
\text{OEt} & \underset{\text{NBS}} \rightarrow \text{OEt}
\end{align*}
\]

NBS in aqueous solution is a polar brominating agent, ideal for reaction with an enol ether. The intermediate is hydrolysed to the ketone by the usual acetal style mechanism.

You might have drawn the \( \eta^3 \) allyl cation complex in various satisfactory ways—some are mentioned on p. 1089 of the textbook.
Finally, an intramolecular Wittig reaction. This is a slightly unusual way to do what amounts to an aldol reaction but the 5,5 fused enone system is strained and the Wittig went under very mild conditions ($K_2CO_3$ in aqueous solution). The stereochemistry of the new double bond is the only possible and Wittig reactions with stabilised ylids generally give the most stable of the possible alkene.

PROBLEM 2
This Heck-style reaction does not lead to regeneration of the alkene. Why not? What is the purpose of the formic acid (HCO$_2$H) in the reaction mixture?

Purpose of the problem
Making sure you understand the steps in the mechanism of the Heck reaction.

Suggested solution
The reaction must start with the oxidative addition of Pd(0) into the Ph–I bond. The reagent added is Pd(II) so one of the reduction methods on page 1081 of the textbook must provide enough Pd(0) to start the reaction going. The oxidative addition gives PhPdI and this does the Heck reaction on the alkene. Addition occurs on the less hindered top (exo-) face and the phenyl group is transferred to the same face.
Normally now the alkyl palladium(II) species would lose palladium by β-elimination. This is impossible in this example as there is no hydrogen atom syn to the Pdi group. Instead, an external reducing agent is needed and that is the role of the formate anion: it provides a hydride equivalent by ‘transfer hydrogenation’ when it loses CO₂.

PROBLEM 3
Cyclization of this unsaturated amine with catalytic Pd(II) under an atmosphere of oxygen gives a cyclic unsaturated amine in 95% yield. How does the reaction work? Why is the atmosphere of oxygen necessary? Explain the stereochemistry and regiochemistry of the reaction. How would you remove the CO₂Bn group from the product?

Purpose of the problem
Introducing you to ‘aminopalladation’: like oxypalladation, nucleophilic attack on a palladium π-complex.

Suggested solution
The π-complex between the alkene and Pd(II) permits nucleophilic attack by the amide on its nearer end and in a cis fashion because the nucleophile is tethered by a short chain of only two carbon atoms. Nucleophilic attack and elimination of Pd(0) occur in the usual way. The removal of the CO₂Bn group would normally be done by hydrogenolysis but in this case ester hydrolysis by, say, HBr would be preferred to

avoid reduction of the alkene. The free acid decarboxylates spontaneously.

![Chemical reaction diagram]

**PROBLEM 4**

Suggest a mechanism for this lactone synthesis.

![Chemical reaction diagram]

**Purpose of the problem**

Introducing you to carbonyl insertion into a palladium (II) σ-complex.

**Suggested solution**

Oxidative insertion into the aryl bromide, carbonylation, and nucleophilic attack on the carbonyl group with elimination of Pd(0) form the catalytic cycle. No doubt the palladium has a number (1 or 2?) of phosphine ligands complexed to it during the reaction and these keep the Pd(0) in solution between cycles.

![Chemical reaction diagram]
**PROBLEM 5**

Explain why enantiomerically pure lactone gives syn but racemic product in this palladium-catalysed reaction.

Purpose of the problem

Helping you to understand the details of palladium-catalyzed allylation.

Suggested solution

Following the usual mechanism, the palladium complexes to the face of the alkene opposite the bridge. The ester leaves to give an allyl cation complex. This is attacked by the malonate anion from the opposite face to the palladium. So the overall result is retention of configuration, the syn starting material giving the syn product.

The racemization comes from the structure of the allyl cation complex. It is symmetrical with a plane of symmetry running vertically through the complex as drawn. Attack by the malonate anion occurs equally at either side of the plane giving the two enantiomers of the syn diastereoisomer in equal amounts.

PROBLEM 6

Explain the reactions in this sequence, commenting on the regioselectivity of the organometallic steps.

Purpose of the problem

Revision of allylic Grignard reagents, the synthesis of pyridines, and the mechanism of the Wacker oxidation.

Suggested solution

The allylic Grignard reagent does direct addition from the end remote to the magnesium atom, as often happens. Hydrolysis of the silyl enol ether reveals an aldehyde.

Now the Wacker oxidation, by whatever detailed mechanism you prefer, must involve the addition of water to a Pd(II) π-complex of the alkene and β-elimination of palladium to give Pd(0) which is recycled by oxidation with oxygen mediated by copper.
Finally, the pyridine synthesis is simply a double enamine/imine formation between ammonia and the two carbonyl groups. Probably the aldehyde reacts first.

PROBLEM 7
Give a mechanism for this carbonylation reaction. Comment on the stereochemistry and explain why the yield is higher if the reaction is carried out under a carbon monoxide atmosphere.

Hence explain this synthesis of part of the antifungal compound pyrenophorin.

Purpose of the problem
More carbonylation with a Stille coupling.
Suggested solution

The tin-palladium exchange (transmetallation) occurs with retention of configuration at the alkene. The exchange of the benzyl group for the benzoyl group is necessary to get the reaction started.

Now the coupling can take place on the palladium atom producing the product and Pd(0) which can insert oxidatively into the C–Cl bond. Transmetallation sets up a sustainable cycle of reactions. It is better to have an atmosphere of carbon monoxide because the acyl palladium complex can give off CO and leave a PdPh σ-complex. The atmosphere of CO reverses this reaction.

The second sequence starts with a radical hydrostannylation (chapter 37) giving the E-vinyl stannane preferentially if a slight excess of Bu₃SnH is used.

Now the coupling with the acid chloride takes place as before though this time we have an aliphatic carbonyl complex. There is no problem with β-elimination as that would give a ketene. Again, the stereochemistry of the vinyl stannane is retained in the product.
PROBLEM 8
The synthesis of an antifungal drug was completed by this palladium-catalysed reaction. Give a mechanism, explaining the regio- and stereochemistry.

Purpose of the problem
A simple example of amine synthesis using palladium.

Suggested solution
The palladium forms the usual allyl cation complex and the nitrogen nucleophile attacks the less hindered end thus also retaining the conjugation. Attack at the triple bond would give an allene. The E stereochemistry of the palladium complex is retained in the product.
PROBLEM 9

Work out the structures of the compounds in this sequence and suggest mechanisms for the reactions, explaining any selectivity.

B has IR: 1730, 1710 cm\(^{-1}\), \(\delta_H\) 9.4 (1H, s), 2.6 (2H, s), 2.0 (3H, s), and 1.0 (6H, s).

C has IR: 1710 cm\(^{-1}\), \(\delta_H\) 7.3 (1H, d, \(J\) 5.5 Hz), 6.8 (1H, d, \(J\) 5.5 Hz), 2.1 (2H, s), and 1.15 (6H, s).

**Purpose of the problem**

An intramolecular aldol reaction (p. 636) and a Wacker oxidation (p. 1096).

**Suggested solution**

B clearly has aldehyde and ketone functional groups with nothing but singlets in the NMR. On the other hand C has a *cis* disubstituted alkene with a small (and therefore *cis*) \(J\) value and is a cyclopentenone.
PROBLEM 10
A synthesis of the Bristol-Meyers Squibb anti-migraine drug Avitriptan (a 5-HT receptor antagonist) involves this palladium-catalysed indole synthesis. Suggest a mechanism and comment on the regioselectivity of the alkyne attachment.

Purpose of the problem
A new reaction for you to try – a palladium-catalysed indole synthesis.

Suggested solution
Although palladium(II) is added to the solution, the aryl iodide tells you that this is an oxidative insertion of Pd(0) produced by one of the methods described on p. 1081 of the textbook. The resulting Pd(II) species complexes to the alkyne and the amine can now attack the triple bond. This gives a heterocycle with the Pd(II) in the ring. Coupling of the two organic fragments extrudes Pd(0) to start a new cycle. The nitrogen attacks the more hindered end of the alkyne so that the palladium can occupy the less hindered end.