Suggested solutions for Chapter 38

PROBLEM 1
Suggest mechanisms for these reactions.

Purpose of the problem
Two simple carbene reactions initiated by base.

Suggested solution
Going to the right we must remove the rather acidic proton from CHBr₃ to give the carbanion. This loses bromide to give dibromocarbene and insertion into cyclohexene gives the product.

The second reaction is very similar. α-Elimination of HCl gives a carbene that inserts into an alkene. These are the simplest reactions of carbenes and are very common.
PROBLEM 2
Suggest a mechanism for this reaction and explain the stereochemistry.

![Reaction mechanism diagram]

Purpose of the problem
Another important carbene method used in the synthesis of a natural antibiotic.

Suggested solution
The diazo compound decomposes to gaseous nitrogen and a carbene under catalysis by Cu(II). Insertion into the exposed alkene gives the three-membered ring. The stereochemistry partly comes from the 'tether'—the linkage between the carbene and the rest of the molecule that delivers the carbene to the bottom face of the alkene. The rest comes from the inevitable cis fusion between the five- and three-membered rings.

![Styerechemistry diagram]

PROBLEM 3
Comment on the selectivity shown in these reactions.

![Reaction diagrams]

Purpose of the problem
A study in chemoselectivity during carbene insertion into alkenes.
Suggested solution

The first reaction is a variation on Simmons-Smith cyclopropanation. Though strictly a carbenoid rather than a carbene, it delivers a CH₂ group from an organozinc compound bound to an oxygen atom, in this case the OMe group. Only that alkene reacts.

The second cyclopropanation occurs at the only remaining alkene with a carbene generated from a diazoester. The stereoselectivity comes from attack on the opposite side of the ring from the already established cyclopropane.

There is little selectivity for the stereochemistry of the CO₂Et group but this fortunately did not matter in the synthesis of a natural defence substance from a sponge by G. A. Schieser and J. D. White, *J. Org. Chem.*, 1980, **45**, 1864.

**PROBLEM 4**

Suggest a mechanism for this ring contraction.

**Purpose of the problem**

Drawing mechanisms for a rearrangement involving a carbene formed photochemically.
Suggested solution

The carbene formed by loss of nitrogen from the diazoketone rearranges with the migration of either C–C bond to give a ketene picked up by methanol.

\[
\begin{align*}
\text{N}_2 & \xrightarrow{h\nu} \text{MeOH} \\
\text{MeOH} & \xrightarrow{\text{HOMe}} \text{CO}_2\text{Me}
\end{align*}
\]

**PROBLEM 5**

Suggest a mechanism for the formation of this cyclopropane.

\[
\begin{align*}
\text{Cl} & + \text{OH} \xrightarrow{t-\text{BuOK}} \text{OH}
\end{align*}
\]

**Purpose of the problem**

An unusual type of carbene but it behaves normally.

**Suggested solution**

There is no doubt that \( t\text{-BuO}^- \) is a base, but which proton does it remove? The OH proton perhaps, but that doesn’t lead to a carbene. The proton on the alkyne? That molecule has a leaving group, but is it too far away?

\[
\begin{align*}
\text{Cl} & \xrightarrow{t\text{-BuO}^-} \text{Cl} \\
\text{Cl} & \xrightarrow{\text{Cl}} \text{C}
\end{align*}
\]

Not if you push the electrons through the molecule in a \( \gamma\)-elimination. Normal elimination is \( \beta\)-elimination: both \( \alpha\)- and \( \gamma\)-elimination can produce carbenes. The arrows are easy to make sense of if you think of a carbene as a carbon with both a + and a – charge. The carbene is an
Allenyl carbene with no substituent at the carbene centre. It inserts into the alkene in the other molecule.

PROBLEM 6
Decomposition of this diazo compound in methanol gives an alkene A (C₈H₁₄O) whose NMR spectrum contains two signals in the alkene region: δ_H 3.50 (3H, s), 5.50 (1H, dd, J 17.9, 7.9), 5.80 (1H, ddd, J 17.9, 9.2, and 4.3), 4.20 (1H, m) and 1.3-2.7 (8H, m). What is its structure and geometry?

When you have done that, suggest a mechanism for the reaction using this extra information: Compound A is unstable and even at 20 °C isomerizes to B. If the diazo compound is decomposed in methanol containing a diene, compound A is trapped as the adduct shown. Account for all these reactions.

Purpose of the problem
Revision of structural analysis, alkene geometry, and cycloadditions with carbenes as a mechanistic link.

Suggested solution
The starting material is C₇H₁₀N₂ so it has lost nitrogen and gained CH₄O—one molecule of methanol. We can see the MeO group at δ_H 3.50 and the four CH₂ groups in the ring are still there (8H m at 1.3-2.7). All that is left is a multiplet at δ_H 4.2, obviously next to OMe, and a pair of alkene protons at δ_H 5.5 and 5.8, coupled with J 17.9—obviously a trans alkene. That at δ_H 5.5 is coupled to one proton and the one at 5.8 is coupled to two. We now have these fragments:
But these add up to $C_2H_3$ too much! Clearly the CH attached to OMe and the CH attached to the alkene are the same atom and the CH$_2$ at the other end of the alkene must be one end of the chain of four CH$_2$s. We now have a structure but it doesn’t join up!

This is the test of your belief in spectroscopy—the dotted ends must join up to give A. Yes, this does put an $E$-alkene in a seven-membered ring, and it is difficult to draw, but you were warned that A is unstable. The CH$_2$ group next to the CHOMe group is diastereotopic so the coupling constants are different.

Now that we know the structure of A, it is easy enough to find a mechanism. Loss of nitrogen produces a carbene that gives an allene in a pericyclic process and this twisted compound (the two alkenes are at $90^\circ$ to each other) and protonation gives the trans alkene as a cation that reacts with methanol to give A.

The twisted alkene is unstable and rotates to the much more stable cis alkene even at 20 °C. It can rotate because the overlap between the p orbitals is weak as they are not parallel. Trapping in a Diels-Alder reaction preserves the trans stereochemistry.
PROBLEM 7

Give a mechanism for the formation of the three-membered ring in the first of these reactions and suggest how the ester might be converted into the amine with retention of configuration.

\[
\text{Ph} + \text{N}_2 \xrightarrow{\text{Cu(I)}} \text{Ph} + \xrightarrow{?} \text{NH}_2
\]

Purpose of the problem

A routine carbene insertion and a reminder of nitrenes as analogues of carbenes.

Suggested solution

The diazoester gives the carbene under Cu(I) catalysis and insertion into the alkene follows its usual course. The only extra is stereoselectivity: the insertion happens more easily if the two large groups (Ph and CO\(_2\)Et) keep as far apart as possible.

Conversion of acid derivatives into amines with the loss of the carbonyl group can be done in various ways. In chapter 36 we recommended the Curtius and the Hofmann. The Hofmann degradation is the easier if we start with an ester, converting into the amide with ammonia and then treating with bromine in basic solution. The N-bromo amide undergoes \(\alpha\)-elimination to a nitrene that rearranges to an isocyanate.
PROBLEM 8
Explain how this highly strained ketone is formed, albeit in very low yield, by these reactions. How would you attempt to make the starting material?

Purpose of the problem
To show that intramolecular carbene insertion is a powerful way to make cage compounds.

Suggested solution
Oxalyl chloride makes the acid chloride, and diazomethane converts this into the diazoketone.

Now the carbene chemistry. Treatment with Cu(I) removes nitrogen and forms the carbene. Remarkably, this is able to reach across the molecule and insert into the alkene, thus forming one three- and two new four-membered rings in one step. You will not be surprised at the yield: 10%.

How would you attempt to make the starting material? The original workers used another carbene reaction—the Cu(I) catalysed inserttion of a diazoester into bis-trimethylsilyl acetylene.
PROBLEM 9
Attempts to prepare compound A by phase-transfer catalysed cyclization required a solvent immiscible with water. When chloroform (CHCl₃) was used, compound B was formed instead and it was necessary to use the more toxic CCl₄ for success. What went wrong?

Purpose of the problem
Carbene chemistry is not always what is wanted: how do you avoid it?

Suggested solution
Product B is clearly the adduct of product A and dichlorocarbene which must have come from the chloroform and base. The good news is that product A was evidently formed in the basic reaction mixture so, if we simply avoid a solvent that is also a carbene source, all is well.

[Insert diagram showing the reaction and adduct formation]

PROBLEM 10
Revision content. How would you carry out the first step in this sequence? Propose mechanisms for the remaining steps explaining any selectivity.

Purpose of the problem
Revision of specific enol formation, rearrangement reactions, electrocyclic reactions and conjugate addition plus some carbene chemistry.

Suggested solution
The first step requires a specific enol from an enone. Treatment with LDA achieves kinetic enolate formation by removing one of the more acidic hydrogens immediately next to the carbonyl group. The lithium enolate is trapped with Me₃SiCl to give the silyl enol ether.

The next step is dichlorocarbene insertion into the more nucleophilic of the two akenes. Dichlorocarbene is an electrophilic carbene so the main interaction is between the HOMO (π) of the alkene and the empty p orbital of the carbene. The carbene is formed by decarboxylation, a process that needs no strong base.
You can draw the ring expansion in a number of ways. All start with the removal of the Me₃Si group with water. You might then simply use a one-step mechanism (a) but an electrocyclic process via the cyclopropyl cation (b) might be better. This is allowed since the inevitable cis ring junction requires H and OH to rotate outwards.

Finally, a double conjugate addition of MeNH₂ to the dienone forms the bicyclic amine. Conjugate addition probably occurs first on the more electrophilic chloroenone, though it doesn’t much matter. There is some stereoselectivity in that the remaining chlorine prefers the equatorial position on the new six-membered ring but this is thermodynamic control as that position is easily enolized.

PROBLEM 11
How would you attempt to make these alkenes by metathesis?
**Purpose of the problem**

Applications of this important and powerful method.

**Suggested solution**

Metathesis is usually $E$-selective and these are both $E$-alkenes so prospects are good. We must disconnect each compound at the alkene and add something to the end of each, probably just CH$_2$ as the by-product will then be volatile ethylene.

Each starting material must now be made. The stereochemistry of the first tells us that we should add an allyl metal compound to an epoxide. The metathesis catalyst will be one of those mentioned in the chapter.

The second molecule is not symmetrical but this is all right as it will be an intramolecular (ring-closing) metathesis so we can expect few cross-products. There are many ways to make the starting material: alkylation of a ketone is probably the simplest though conjugate addition would have its advantages. The same catalyst can be used and very little would be needed.
PROBLEM 12
Heating this acyl azide in dry toluene under reflux for three hours gives a 90% yield of a heterocycle. Suggest a mechanism, emphasizing the role of any reactive intermediates.

Purpose of the problem
Demonstrating the practical nature of nitrene chemistry in the context of heterocyclic synthesis.

Suggested solution
Heating an azide liberates nitrogen gas and forms a nitrene. In this case, rearrangement to an isocyanate is followed by intramolecular nucleophilic attack by the ortho amino group.

PROBLEM 13
Give mechanisms for the steps in this conversion of a five- into a six-membered aromatic heterocycle.

Purpose of the problem
It is the turn of carbene chemistry to show its usefulness in that most practical of all subjects: heterocyclic synthesis.
**Suggested solution**

Decomposition of trichloroacetate ion releases the \( \text{Cl}_3\text{C}^- \) carbanion. Loss of chloride gives dichlorocarbene and addition to one of the double bonds in the pyrrole gives a bicyclic intermediate.

\[
\text{Cl}_3\text{C}^- + \text{Cl}_2\text{C}=\text{O} \rightarrow \text{CO}_2 + \text{Cl}_2\text{C}^=\cdot \rightarrow :\text{Cl}
\]

Ring expansion can be drawn in various ways. There is a direct route from the neutral amine, or its anion, that doesn't look very convincing, or you can ionize one of the chlorides first and open the cyclopropyl cation in an electrocyclic reaction. However you explain it, this is a good way to make 3-substituted pyridines.