1) Careful choice of solvent is essential for the successful generation and reaction of a Grignard reagent.

a) Explain why anhydrous diethyl ether and tetrahydrofuran (THF) are common solvents for the generation of Grignard reagents.

Anhydrous (water-free) solvent needed in order to generate Grignard reagent.

Diethyl ether and THF are non-protic solvents so do not undergo an acid-base reaction with RMgX.

Diethyl ether and THF are able to coordinate to the Mg atom via O-atom lone pairs. Coordination improves solubility of RMgX and stabilizes the RMgX species in solution.

See Loudon Chapter 8 pages 361-364.
b) Show the major product(s) of the reaction of 4-methylphenylmagnesium bromide (prepared in anhydrous diethyl ether) with benzophenone (dissolved in either ethanol, acetone, or diethyl ether). Assume acidic workup in each case.

See Loudon Chapter 8 pages 361-364 and Chapter 19 pages 918-920.
2) The reaction of PhMgBr with cyclohexanone (C₆H₁₀) followed by addition of sulfuric acid produces 1-phenylcyclohexene (C₁₂H₁₄) as shown below.

The crude reaction mixture was analyzed by GC-mass spectrometry. Use the GC-MS data on the next page to identify the components of the crude product mixture and assess its purity.

**Component 1 = biphenyl (m/z = 154), minor product (~5.3 % on GC trace)**

**Component 2 = 1-phenylcyclohexene (m/z = 158), major product (~94.7% on GC trace)**

The desired product is impure due to the side reaction shown above.

Draw a plausible mechanism for the formation of the major and minor products starting from bromobenzene.

**Biphenyl is formed via coupling of two phenyl radicals. The radicals are produced by homolytic bond cleavage of the C-Br bond in bromobenzene in the presence of Mg metal. Coupling of the phenyl radical with [MgBr] radical leads to formation of the Grignard reagent. The major product is obtained via nucleophilic addition of the Grignard reagent to the C=O group of cyclohexanone, followed by acidic work-up.**
3) Show the product and justify the chemoselectivity of each of the following oxidative addition reactions. Show the oxidation state of the metal in the product. The table of C-X bond dissociation enthalpies of halobenzenes may be useful.

See Loudon Chapter 18 page 840-841.

![Chemical structures and reactions](image)

### C–X Bond Dissociation Enthalpies

<table>
<thead>
<tr>
<th>Ph–X</th>
<th>ΔH(^{c-x}) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>127</td>
</tr>
<tr>
<td>Cl</td>
<td>97</td>
</tr>
<tr>
<td>Br</td>
<td>84</td>
</tr>
<tr>
<td>I</td>
<td>67</td>
</tr>
<tr>
<td>H</td>
<td>113</td>
</tr>
</tbody>
</table>
4) Transmetallation can be described by the following equilibrium:

\[ \text{M-X} + \text{M'-R} \rightleftharpoons \text{M-R} + \text{M'-X} \]

The process is thermodynamically favorable for the production of M-R if \( X_M > X_M' \) (\( X = \) Pauling electronegativity, M/M' = metal, R = organic group, X = halide).

*Show both products of the following transmetallation reactions. Label the starting materials as either M-X or M'-R, and the products as either M-R or M'-X. Draw a box around the transmetallation product that would be relevant to the catalytic cycle. For extra insight, you could calculate the % ionic character of the C-M bonds of M'-R and M-R.*

\[
\% \text{ ionic character} = \left( \frac{X_C - X_M}{X_C} \right) \times 100 \%
\]

**Hints:** Think about the relative polarities of the C-M bond in the starting material and the main product. Recall that the Pauling electronegativity of carbon, \( X_C \), is 2.55. The periodic table of electronegativity values for each element attached to this problem set may be useful. The rate of migration of groups from \( R_3SnX \) compounds is alkenyl > aryl > allyl > alkyl.

**Example:**

\[
\text{Me} \quad \text{Ph-Pd(PPh}_3\text{)}_2 \quad \text{Ph-Pd(PPh}_3\text{)}_2 \quad \text{ZnClBr}
\]

\[
\begin{array}{llll}
\text{M'-R} & \text{M-X} & \text{M-R} & \text{M'-X} \\
X_{\text{Zn}} = 1.65 & X_{\text{Pd}} = 2.20 & & \\
\end{array}
\]

\[
\% \text{ ionic character C-Zn bond} = \left[ \frac{2.55 - 1.65}{2.55} \right] \times 100 = 35\%
\]

\[
\% \text{ ionic character C-Pd bond} = 14\%
\]

a)

\[
\text{MgBr} + \text{Bu}_3\text{SnBr} \rightleftharpoons \text{SnBu}_3 + \text{MgBr}_2
\]

\[
\begin{array}{llll}
\text{M'-R} & \text{M-X} & \text{M-R} & \text{M'-X} \\
X_{\text{Mg}} = 1.31 & X_{\text{Sn}} = 1.96 & & \\
\end{array}
\]

\[
\% \text{ ionic character C-Mg bond} = 49\% \quad \% \text{ ionic character C-Sn bond} = 23\%
\]
b) 

\[
\text{PhPd}^- + \text{SnBu}_3 \text{C} \rightarrow \text{PhPd} = \text{SnBu}_3
\]

\[
\begin{align*}
\text{M-X} & \quad \text{M'-R} \\
\text{M-R} & \quad \text{M'-X}
\end{align*}
\]

\[
X_{\text{Pd}} = 2.20 \quad X_{\text{Sn}} = 1.96
\]

allyl group transfers faster than alkyl

% ionic character C-Sn bond = 23%

% ionic character C-Pd bond = 14%

c) 

\[
\text{O} \quad \text{MgCl} \quad \text{Me} \quad \text{NiBr}
\]

\[
\begin{align*}
\text{M'-R} & \quad \text{M-X} \\
\text{M-R} & \quad \text{M'-X}
\end{align*}
\]

\[
X_{\text{Mg}} = 1.31 \quad X_{\text{Ni}} = 1.91
\]

% ionic character C-Mg bond = 49%

% ionic character C-Ni bond = 25%

d) 

\[
\text{O} \quad \text{PdBr} \quad \text{MeO} \quad \text{B(OH)}_2
\]

\[
\begin{align*}
\text{M-X} & \quad \text{M'-R} \\
\text{M-R} & \quad \text{M'-X}
\end{align*}
\]

\[
X_{\text{Pd}} = 2.20 \quad X_{\text{B}} = 2.04
\]

% ionic character C-B bond = 20%

% ionic character C-Pd bond = 14%

e) 

\[
2 \quad \text{Li} + \text{CuBr} \rightarrow \text{Li}^{\oplus} \quad \text{Cu}^{\ominus}
\]

\[
\begin{align*}
\text{M'-R} & \quad \text{M-X} \\
\text{M-R} & \quad \text{M'-X}
\end{align*}
\]

% ionic character C-Li bond = 61%

% ionic character C-Cu bond = 25%
5) Suzuki-Miyaura coupling reactions typically occur between aryl or alkenyl halides and an aryloboronic acid. An example of such a reaction is shown below for the synthesis of the food flavoring compound *trans*-anethole (*trans*-1-methoxy-4-(1-propenyl)benzene). The process involves the reaction of 4-methoxyphenylboronic acid and (E)-1-bromo-1-propene.

![Reaction Scheme]

a) Propose a synthesis of 4-methoxyphenylboronic acid starting from phenol. Recall that trimethylborate, B(OMe)_3, reacts as an electrophile toward Grignard reagents. Show all isolated intermediates/products formed. You do not need to give a mechanism for the individual steps.

**Retrosynthesis**

**Forward Synthesis (including reagents and conditions)**

*Anisole is ~10^6 x more reactive toward E*⁺ than benzene, so FeBr₃ promotor is not required.

See Loudon Chapter 18 page 849
b) Complete the catalytic cycle for the Suzuki-Miyaura coupling reaction to form *trans*-anethole (shown on the previous page), drawing the appropriate reagents and products for each of the three labeled steps.

![Catalytic cycle diagram]

- **Reductive elimination**
  - **Oxidative addition**
  - **Ligand association/dissociation**

**c)** A researcher used \((E)-1\)-chloro-1-propene in place of \((E)-1\)-bromo-1-propene in the above reaction. Explain whether the oxidative addition of \(\text{Pd(PPh}_3\text{)}_2\) into the C-Cl bond of \((E)-1\)-chloro-1-propene will be faster or slower than the corresponding insertion into \((E)-1\)-bromo-1-propene.

The C-Cl bond is stronger than the C-Br bond, so oxidative addition step would be slower for \((E)-1\)-chloro-1-propene. See Q3.

d) What is one of the main driving forces for the transmetallation process?

Formation of a new C-M bond of lower polarity/lower %ionic character in the organometallic transmetallation product. The C-B bond has \(~20\%\) ionic character whereas the new C-Pd bond of the transmetallation product has \(~14\%\) ionic character. See Q4.
6) The Negishi reaction is a Pd-catalyzed cross-coupling between an organozinc reagent and an organic halide. The catalytic cycle of the Negishi coupling is similar to that of the Suzuki-Miyaura reaction. The preparation of organozinc reagent 3 via reaction of the organolithium species 2 (a lithiated N-methylimidazole) with ZnCl₂ is outlined below.

\[
\begin{array}{c}
\text{tBu} \quad \text{N} \quad \text{Me} \\
\text{N} \quad \text{H} \\
1 \\
\text{n-BuLi} \quad \rightarrow \quad \text{tBu} \quad \text{N} \quad \text{Me} \\
\text{N} \quad \text{Li} \\
2 \\
\text{ZnCl}_2 \\
\rightarrow \\
\text{3}
\end{array}
\]

a) Draw an electron-pushing mechanism to show the formation of 2 by reaction of the N-methylimidazole precursor 1 with n-BuLi. Display the polarization of the C–Li bond in 2. Is the carbon atom of the C–Li bond nucleophilic or electrophilic?

b) Show all products of the reaction of compound 2 with ZnCl₂ to produce compound 3. What is the general name of this process? Rationalize the outcome of the reaction using Pauling electronegativity values and draw a box around the transmetallation product that would be relevant to the catalytic cycle.

\[
\begin{array}{c}
\text{tBu} \quad \text{N} \quad \text{Me} \\
\text{N} \quad \text{Li} \\
2 \\
\text{ZnCl}_2 \\
\rightarrow \quad \text{transmetallation} \\
\text{Me} \\
3 \\
\text{M'-R} \quad \text{M-X} \\
\chi_{\text{Li}} = 0.98 \quad \chi_{\text{Zn}} = 1.65 \\
% \text{ionic character C-Li bond} = 61 \% \\
% \text{ionic character C-Zn bond} = 35 \%
\end{array}
\]
c) A Negishi coupling reaction between the organozinc reagent 3 and 2-bromobiphenyl was performed in the presence of \([\text{Pd}(\text{PPh}_3)_4]\). Show the products of the Negishi coupling reaction.

\[
\text{Br} \quad \text{Ph} + \quad \text{tBu} \quad \text{N} \quad \text{ZnCl}\quad \xrightarrow{\text{Pd}(\text{PPh}_3)_4} \quad \text{solvent} \quad \text{Me} \quad \text{N} \quad \text{ZnCl} \quad \rightarrow \quad \text{tBu} \quad \text{N} \quad \text{Ph} \quad \text{Me} \quad \text{Ph} \quad \text{or} \quad \text{tBu} \quad \text{N} \quad \text{Ph} \quad \text{Me} \quad \text{Ph}
\]

either conformer is OK for now

d) Complete the catalytic cycle for the Pd-catalyzed Negishi cross-coupling reaction shown below. Clearly label each step, draw the appropriate reagents and products, and show the oxidation state of Pd in each step.
7) The Pd-catalyzed Stille cross-coupling allows for the preparation of thiophene-based liquid crystalline materials \((J. \ Org. \ Chem. \ 2008, \ 73, \ 830-839)\). Draw and label the complete catalytic cycle for the reaction shown below. The reactivity of organic groups in \(R_3SnX\) compounds is vinyl > aryl > allyl > alkyl.