CHEM 344 Organometallic Chemistry Practice Problems (**not for credit**)

Name (print): **ANNE SURKEY**

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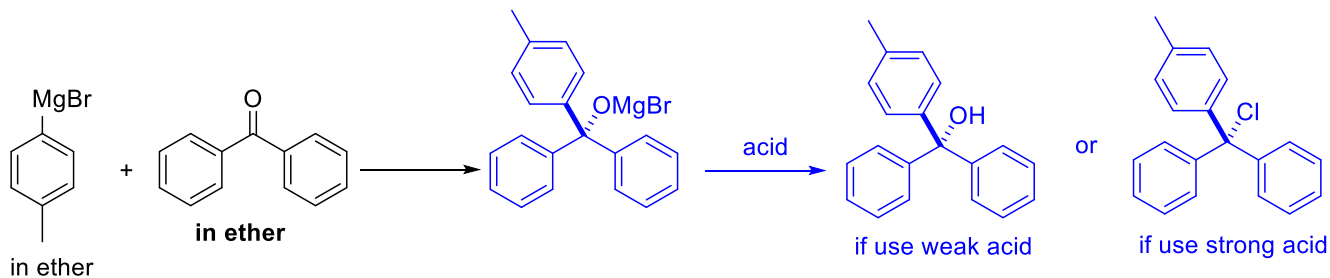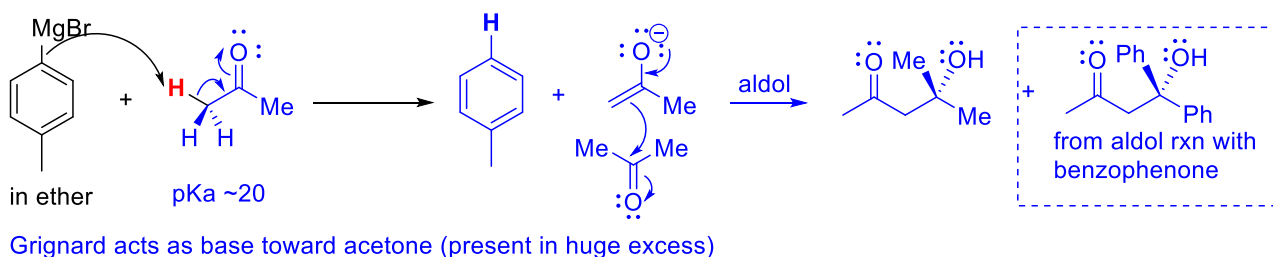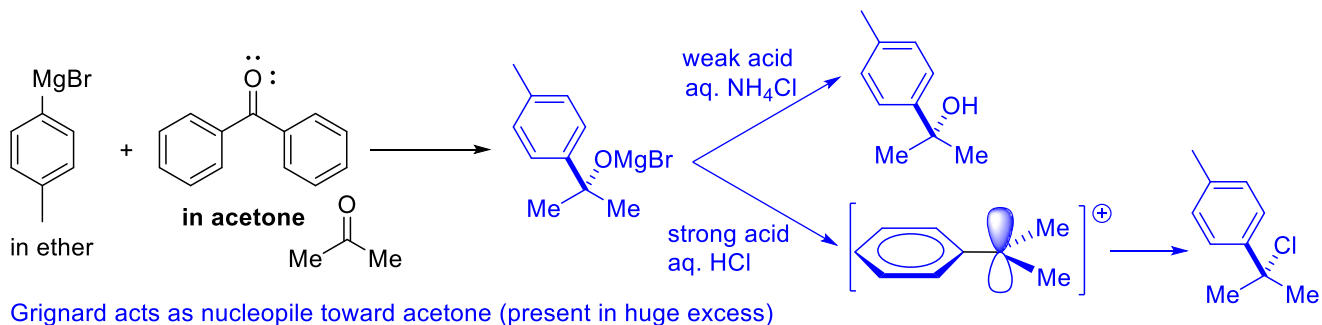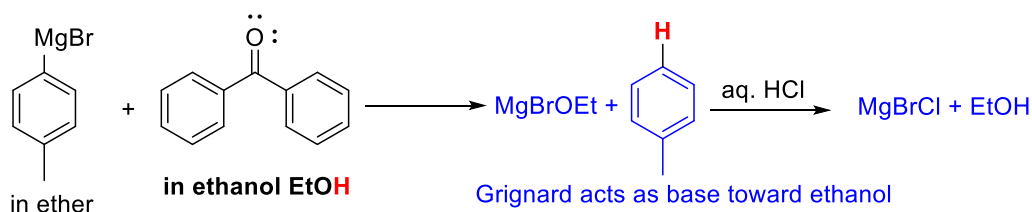
Anhydrous (water-free) solvent needed in order to generate Grignard reagent.

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.

MgBr

in ether

+

Ö:

in ethanol EtOH

→ MgBrOEt +

H

aq. HCl → MgBrCl + EtOH

Grignard acts as base toward ethanol

MgBr

in ether

+

Ö:

in acetone

Me   Me

→

OMgBr

Me   Me

weak acid
aq. NH₄Cl →

OH

Me   Me

strong acid
aq. HCl →

[Me
       Me]⊕

→

Cl

Me   Me

Grignard acts as nucleopile toward acetone (present in huge excess)

MgBr

in ether

+

H

H H

Ö:

Me

pKa ~20

→

H

+

:Ö⊖

Me

Me   Me

:Ö:

aldol →

:Ö Me :ÖH

Me

+

:Ö Ph :ÖH

Ph

from aldol rxn with
benzophenone

Grignard acts as base toward acetone (present in huge excess)

MgBr

in ether

+

O

in ether

→

OMgBr

acid →

OH

if use weak acid

or

Cl

if use strong acid

See Loudon Chapter 8 pages 361-364 and Chapter 19 pages 918-920.

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2) The reaction of PhMgBr with cyclohexanone (C_6H_{10}) followed by addition of sulfuric acid produces 1-phenylcyclohexene ($C_{12}H_{14}$) as shown below.
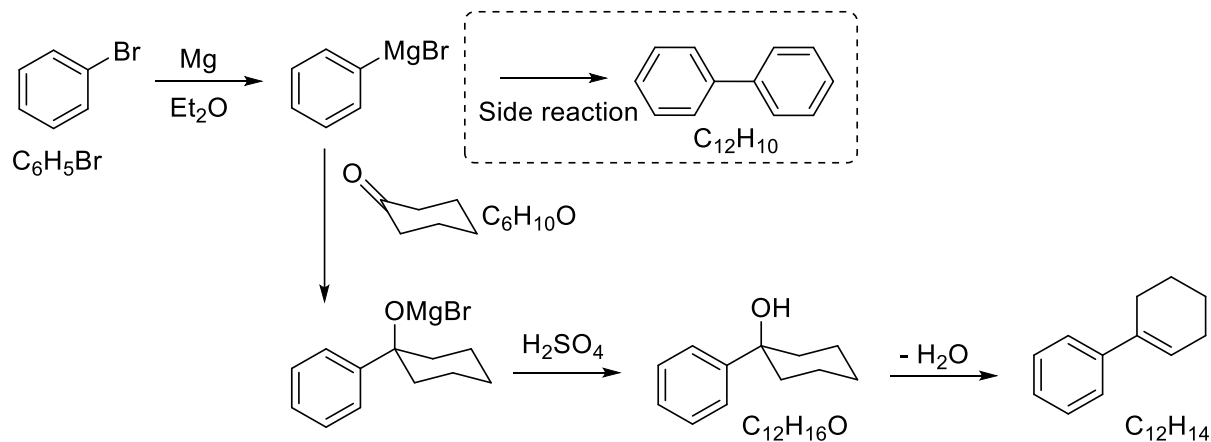

The crude reaction mixture was analyzed by GC-mass spectrometry. Use the GC-MS data on the next page to identify the components of the crude product mixture and assess its purity.

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.
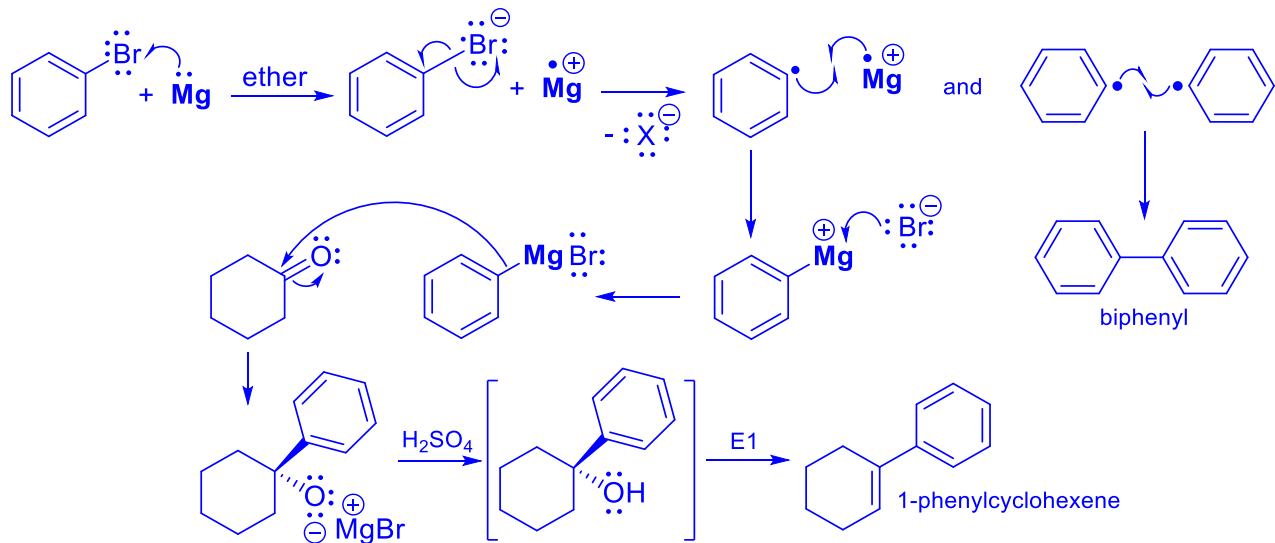
Biphenyl is formed via coupling of two phenyl radicals. The radicals are produced by homolytic bond cleavage of the C-Br bond in bromobenzene in the presence of Mg metal. Coupling of the phenyl radical with [MgBr] radical leads to formation of the Grignard reagent. The major product is obtained via nucleophilic addition of the Grignard reagent to the C=O group of cyclohexanone, followed by acidic work-up.
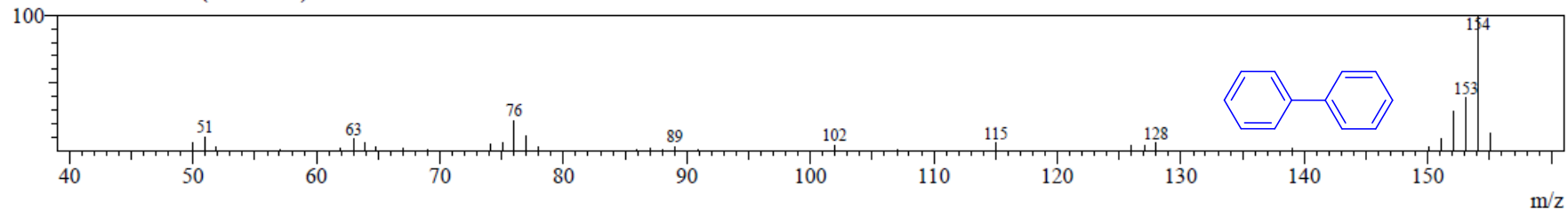
3

romatogram Steve Phenylcyclohexene C:\GCMSsolution\Data\Project1\Steve's resarch\Steve Phenylcyclohexene_1_47.c

970,920
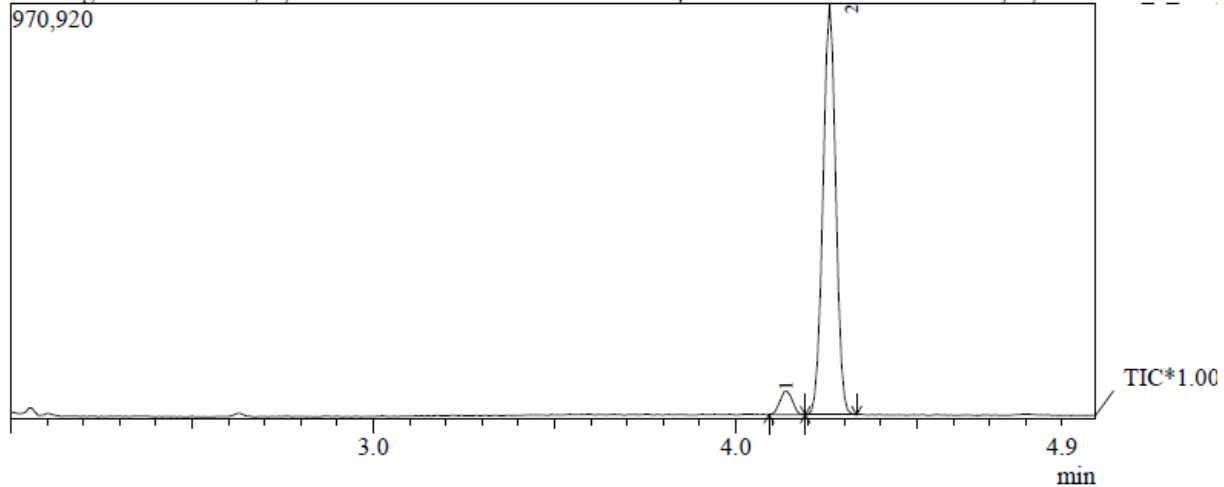
Peak Report TIC		
Peak#	R.Time	Area	Area%
1	4.138	132097	5.32
2	4.258	2351497	94.68
		2483594	100.00

TIC*1.00

3.0   4.0   4.9
min
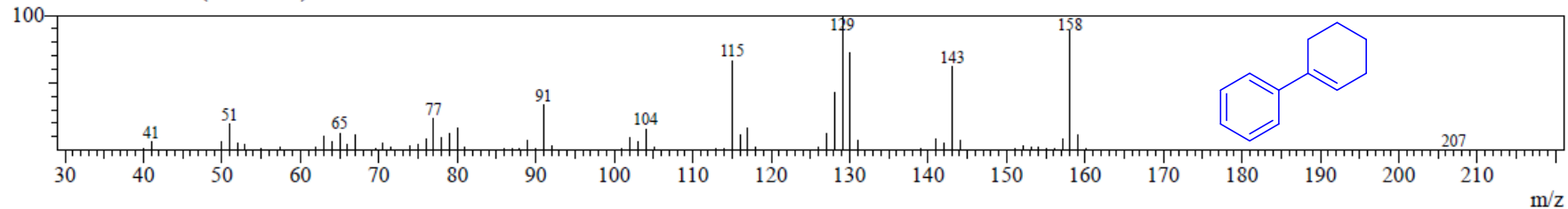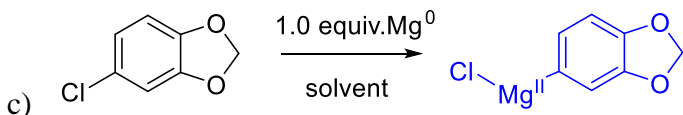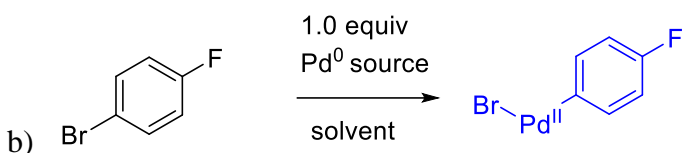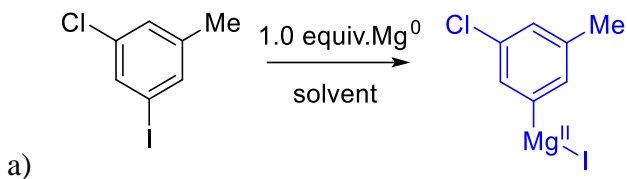
Spectrum

Peak#:1 R.Time:4.1(Scan#:258) MassPeaks:35

Peak#:2 R.Time:4.3(Scan#:272) MassPeaks:89

4
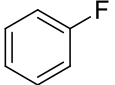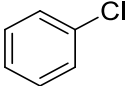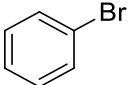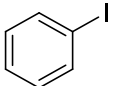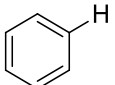
3) Show the product and justify the chemoselectivity of each of the following oxidative addition reactions. Show the oxidation state of the metal in the product. The table of C-X bond dissociation enthalpies of halobenzenes may be useful.

See Loudon Chapter 18 page 840-841.

a)

Cl–(arene)–Me, with I substituent $\xrightarrow[\text{solvent}]{\text{1.0 equiv.Mg}^0}$ Cl–(arene)–Me, with Mg^{II}–I substituent

b)

Br–(arene)–F $\xrightarrow[\text{solvent}]{\substack{\text{1.0 equiv} \\ \text{Pd}^0 \text{ source}}}$ Br–Pd^{II}–(arene)–F

c)

Cl–(benzodioxole) $\xrightarrow[\text{solvent}]{\text{1.0 equiv.Mg}^0}$ Cl–Mg^{II}–(benzodioxole)

C–X Bond Dissociation Enthalpies

Ph–X	$\Delta H^{\circ}_{\text{C–X}}$ (kcal/mol)
Ph–F	127
Ph–Cl	97
Ph–Br	84
Ph–I	67
Ph–H	113

4) Transmetallation can be described by the following equilibrium:

$$\text{M-X} \quad + \quad \text{M'-R} \quad \rightleftharpoons \quad \text{M-R} \quad + \quad \text{M'-X}$$
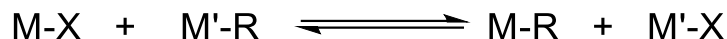
The process is thermodynamically favorable for the production of M-R if $X_M > X_{M'}$ (X = Pauling electronegativity, M/M' = metal, R = organic group, X= halide).

*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.*

$$\% \ ionic \ character = \left(\frac{X_C - X_M}{X_C}\right) * 100 \ \%$$

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:
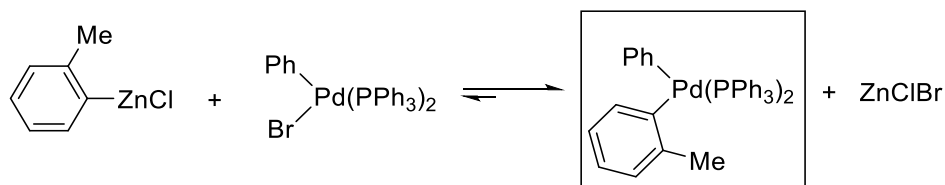
M'-R	**M-X**	**M-R**	**M'-X**
$X_{Zn} = 1.65$	$X_{Pd} = 2.20$		

% ionic character C-Zn bond = [2.55- 1.65 / 2.55] x 100 = 35%

% ionic character C-Pd bond = 14 %

a)
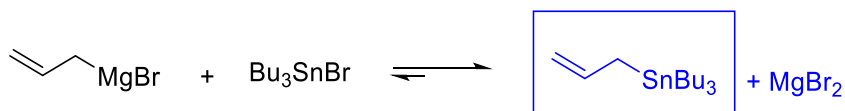
M'-R	**M-X**	**M-R**	**M'-X**
$X_{Mg} = 1.31$	$X_{Sn} = 1.96$		

% ionic character C-Mg bond = 49 %   % ionic character C-Sn bond = 23 %

b)

M-X   **M'-R**   **M-R**   **M'-X**

$X_{Pd} = 2.20$ $X_{Sn} = 1.96$ *allyl group transfers faster than alkyl*

% ionic character C-Sn bond = 23 %   % ionic character C-Pd bond = 14 %

c)

M'-R   **M-X**   **M-R**   **M'-X**

$X_{Mg} = 1.31$ $X_{Ni} = 1.91$

% ionic character C-Mg bond = 49 %   % ionic character C-Ni bond = 25 %

d)

M-X   **M'-R**   **M-R**   **M'-X**

$X_{Pd} = 2.20$ $X_B = 2.04$

% ionic character C-B bond = 20 %   % ionic character C-Pd bond = 14 %

e)

M-X   **M'-R**   **M-R**   **M'-X**

% ionic character C-Li bond = 48 %   % ionic character C-Cu bond = 25 %
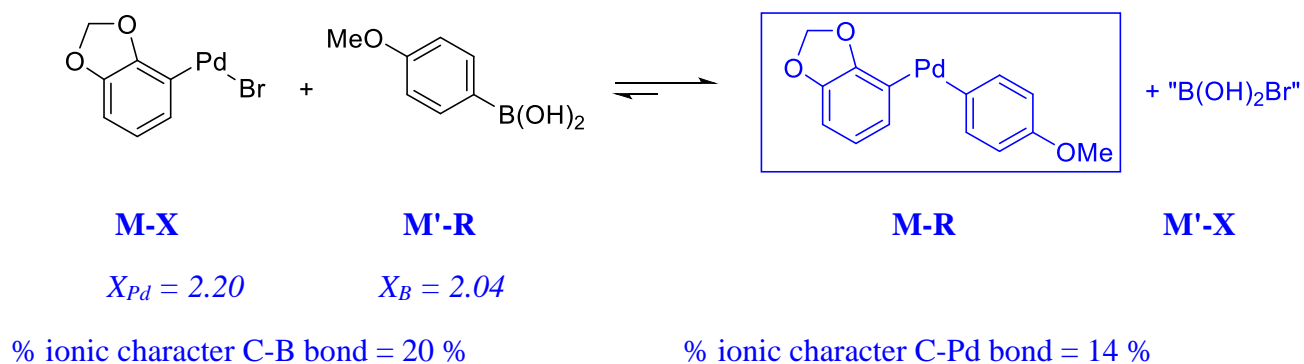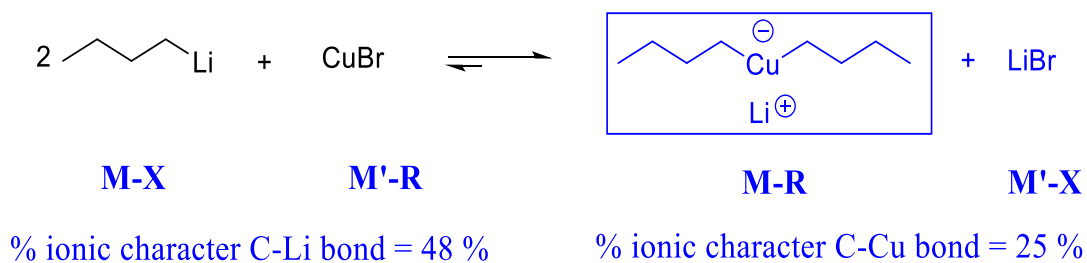
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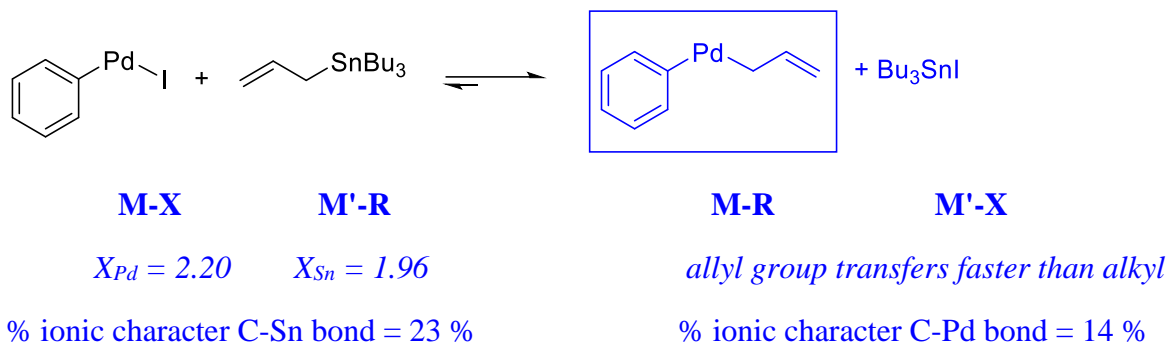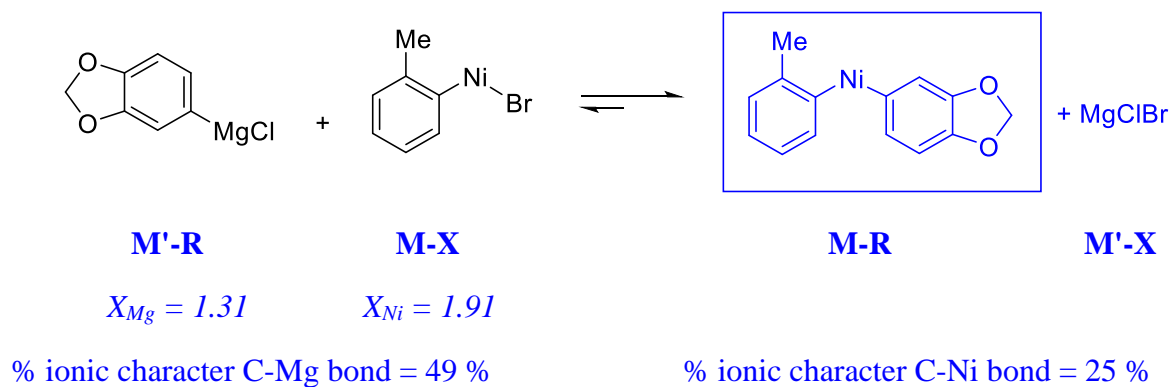
5) Suzuki-Miyaura coupling reactions typically occur between aryl or alkenyl halides and an arylboronic acid. An example of such a reaction is shown below for the synthesis of the food flavoring compound *trans*-anethole (*trans*-1-methoxy-4-(1-propenyl)benzene). The process involves the reaction of 4-methoxyphenylboronic acid and (*E*)-1-bromo-1-propene.

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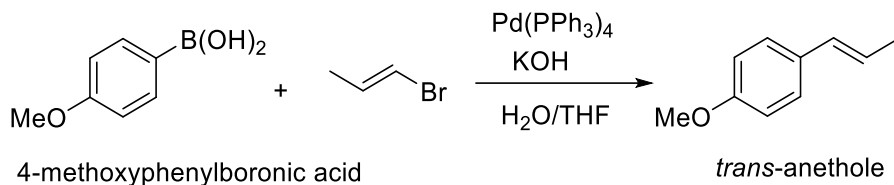
a) Propose a synthesis of 4-methoxyphenylboronic acid starting from phenol. Recall that trimethylborate, B(OMe)$_3$, reacts as an electrophile toward Grignard reagents. Show all isolated intermediates/products formed. You do not need to give a mechanism for the individual steps.

Retrosynthesis
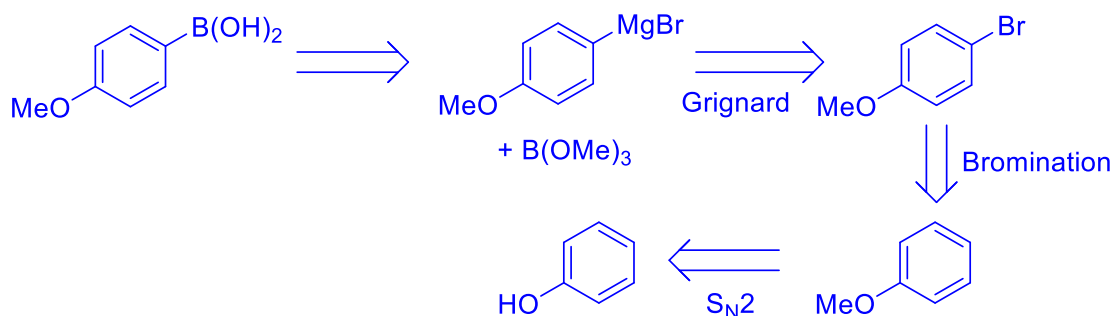
Forward Synthesis (including reagents and conditions)
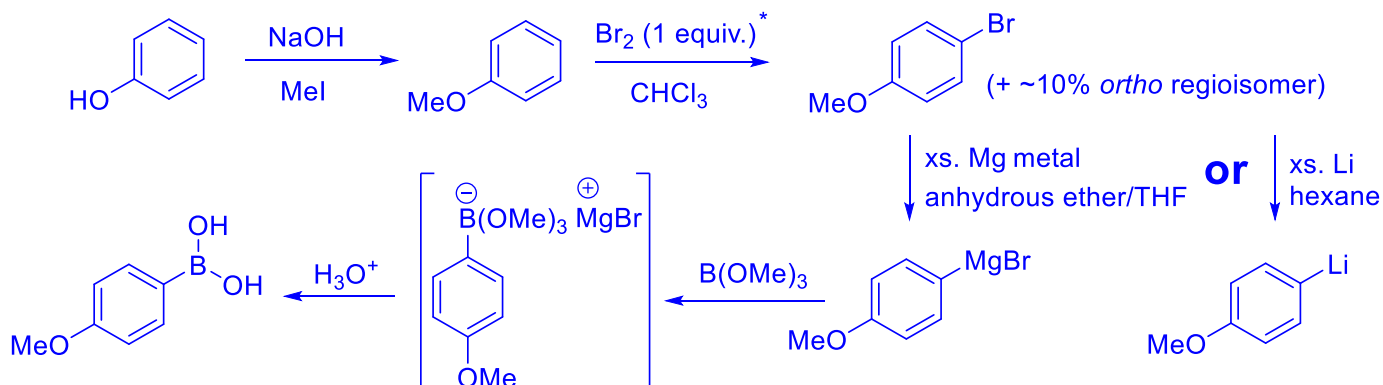
*Anisole is ~10^6 x more reactive toward E$^+$ than benzene, so FeBr$_3$ promotor is not required.

See Loudon Chapter 18 page 849

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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.

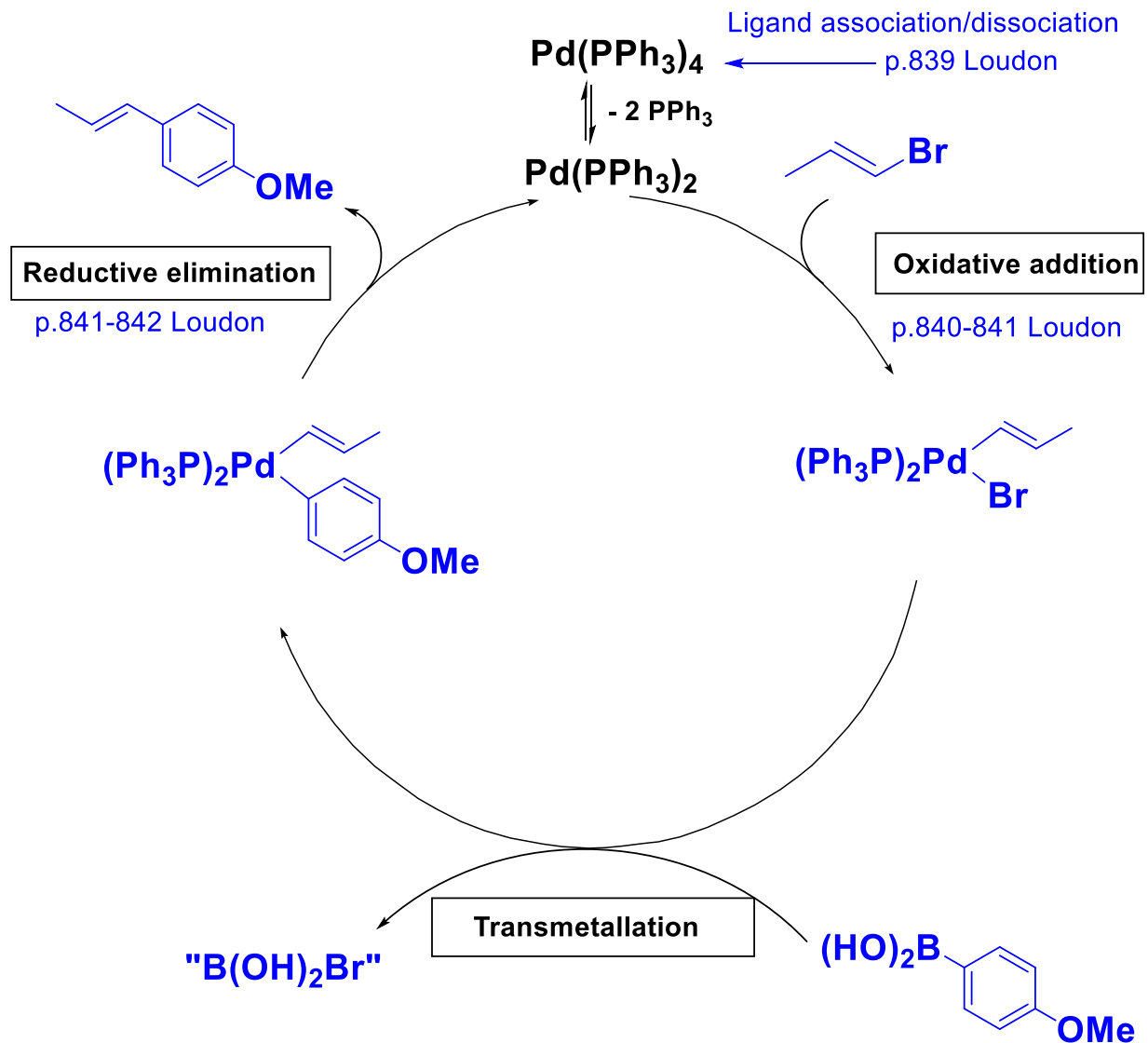c) A researcher used (*E*)-1-chloro-1-propene in place of (*E*)-1-bromo-1-propene in the above reaction. Explain whether the oxidative addition of Pd(PPh$_3$)$_2$ into the C-Cl bond of (*E*)-1-chloro-1-propene will be faster or slower than the corresponding insertion into (E)-1-bromo-1-propene.

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.

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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 pr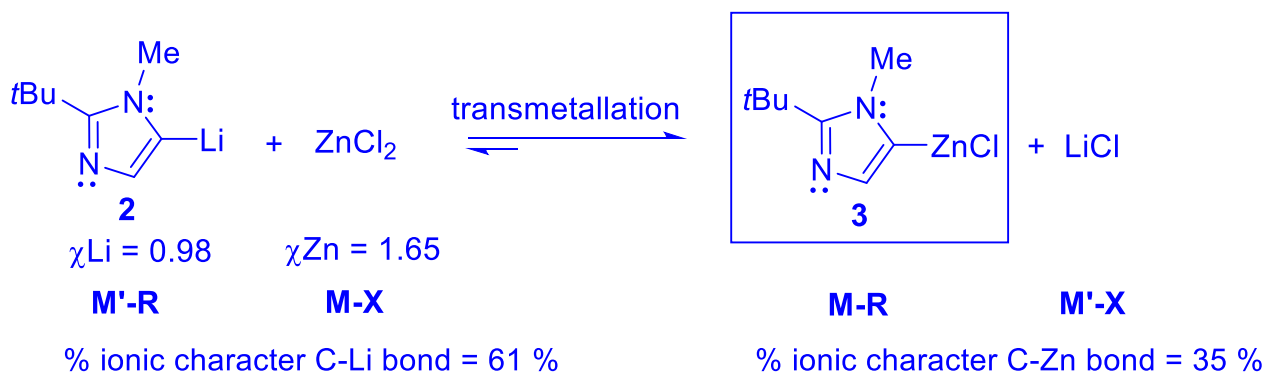eparation of organozinc reagent **3** via reaction of the organolithium species **2** (a lithiated *N*-methylimidazole) with $ZnCl_2$ is outlined below.
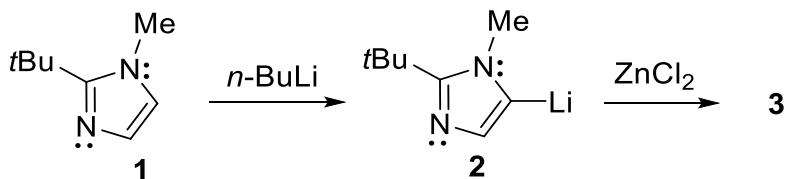
a) Draw an electron-pushing mechanism to show the formation of **2** by reaction of the *N*-methylimidazole precursor **1** with *n*-BuLi. Display the polarization of the C–Li bond in **2**. Is the carbon atom of the C–Li bond nucleophilic or electrophilic?

C-atom of any C-Li bond is nucleophilic
Acts as a base toward **red H-atom.**
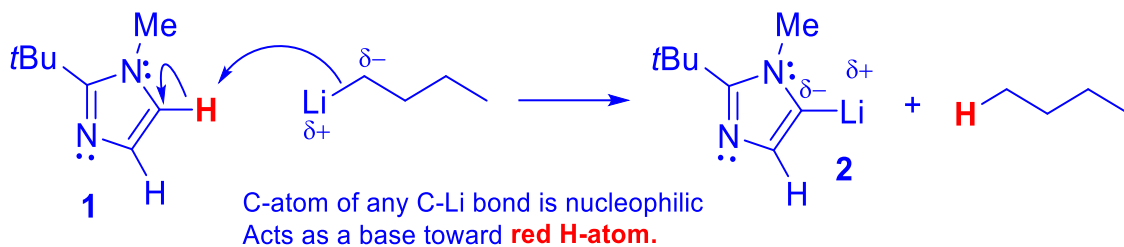
b) Show all products of the reaction of compound **2** with $ZnCl_2$ to produce compound **3**. What is the general name of this process? Rationalize the outcome of the reaction using Pauling electronegativity values and draw a box around the transmetallation product that would be relevant to the catalytic cycle.

χLi = 0.98 χZn = 1.65

M'-R   **M-X**   **M-R**   **M'-X**

% ionic character C-Li bond = 61 %   % ionic character C-Zn bond = 35 %

c) A A Negishi coupling reaction between the organozinc reagent **3** and 2-bromobiphenyl was performed in the presence of [Pd(PPh$_3$)$_4$]. Show the products of the Negishi coupling reaction.

either conformer is OK for now
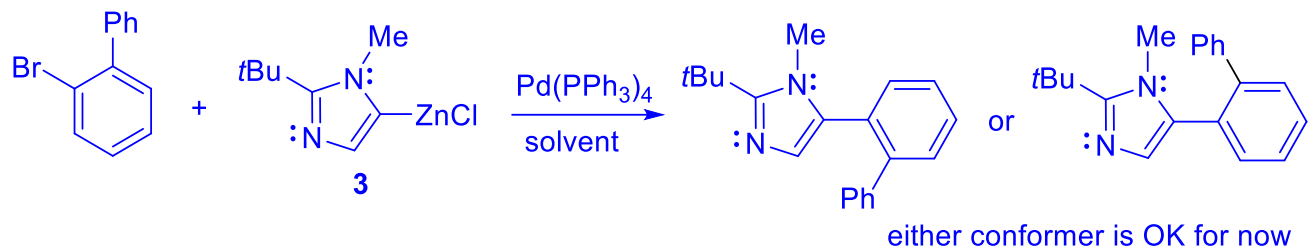
d) Complete the catalytic cycle for the Pd-catalyzed Negishi cross-coupling reaction shown below. Clearly label each step, draw the appropriate reagents and products, and show the oxidation state of Pd in each step.

Ligand association/dissociation
p.839 Loudon

Pd(PPh$_3$)$_4$

- 2 PPh$_3$

Pd(PPh$_3$)$_2$

Pd^0 species

Reductive elimination

p.841-842 Loudon

ionic character C-Pd bond = 14 %

Pd^{II} species

Oxidative addition

p.840-841 Loudon

(Ph$_3$P)$_2$Pd

Pd^{II} species

ZnClBr

Transmetallation

ionic character C-Zn bond = 35 %

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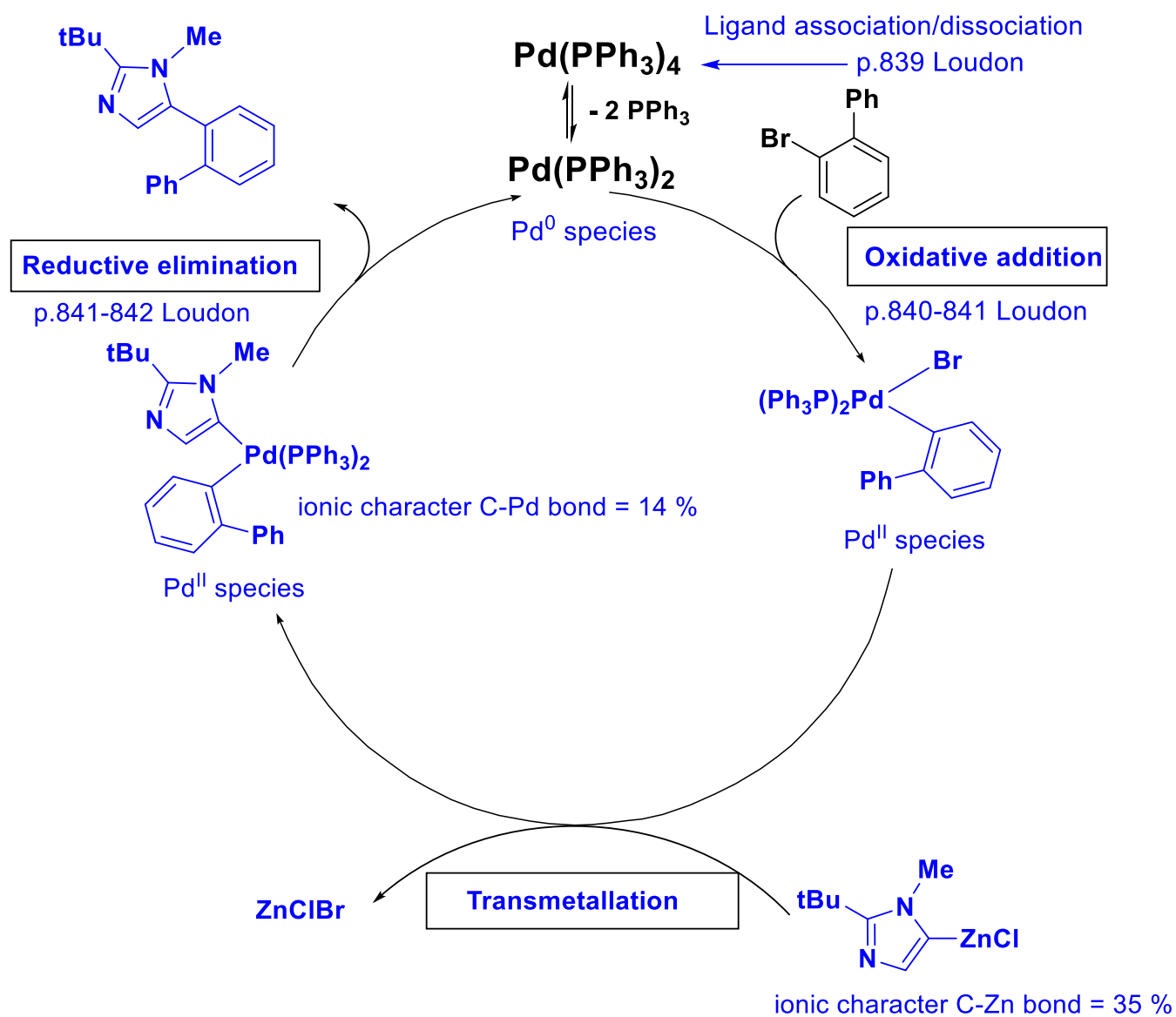
7) The Pd-catalyzed Stille cross-coupling allows for the preparation of thiophene-based liquid crystalline materials (*J. Org. Chem.* **2008**, *73*, 830-839)**.** Draw and label the complete catalytic cycle for the reaction shown below. The reactivity of organic groups in R_3SnX compounds is vinyl> aryl > allyl > alkyl.

Bu_3Sn—⟨aryl⟩—⟨thiophene-S⟩—C_8H_{17} + Br—⟨thiophene-S⟩—C_6H_{13} $\xrightarrow[\text{DMF, 130 °C}]{Pd(PPh_3)_4}$

Pd(PPh₃)₄ $Pd(PPh_3)_4$

⇅ **- 2 PPh₃**

Pd(PPh₃)₂ $Pd(PPh_3)_2$

Pd⁰ species

Br—⟨thiophene-S⟩—C_6H_{13}

Oxidative addition

C_8H_{17}—⟨thiophene-S⟩—⟨aryl⟩—⟨thiophene-S⟩—C_6H_{13}

Reductive elimination

⟨C_6H_{13}—thiophene-S⟩—$Pd(PPh_3)_2$ ... ⟨aryl⟩—⟨thiophene-S⟩—C_8H_{17}

ionic character C-Pd bond = 14 %

Pd^{II} species

(Ph₃P)₂Pd—Br / —⟨thiophene-S⟩—C_6H_{13}

Pd^{II} species

Transmetallation

Bu₃SnBr

$SnBu_3$—⟨aryl⟩—⟨thiophene-S⟩—C_8H_{17}

ionic character C-Sn bond = 23 %