CHEM 344 Organometallic Chemistry Practice Problems (not for credit)

Name (print): **ANSWER KEY** TA name (print): _____

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.

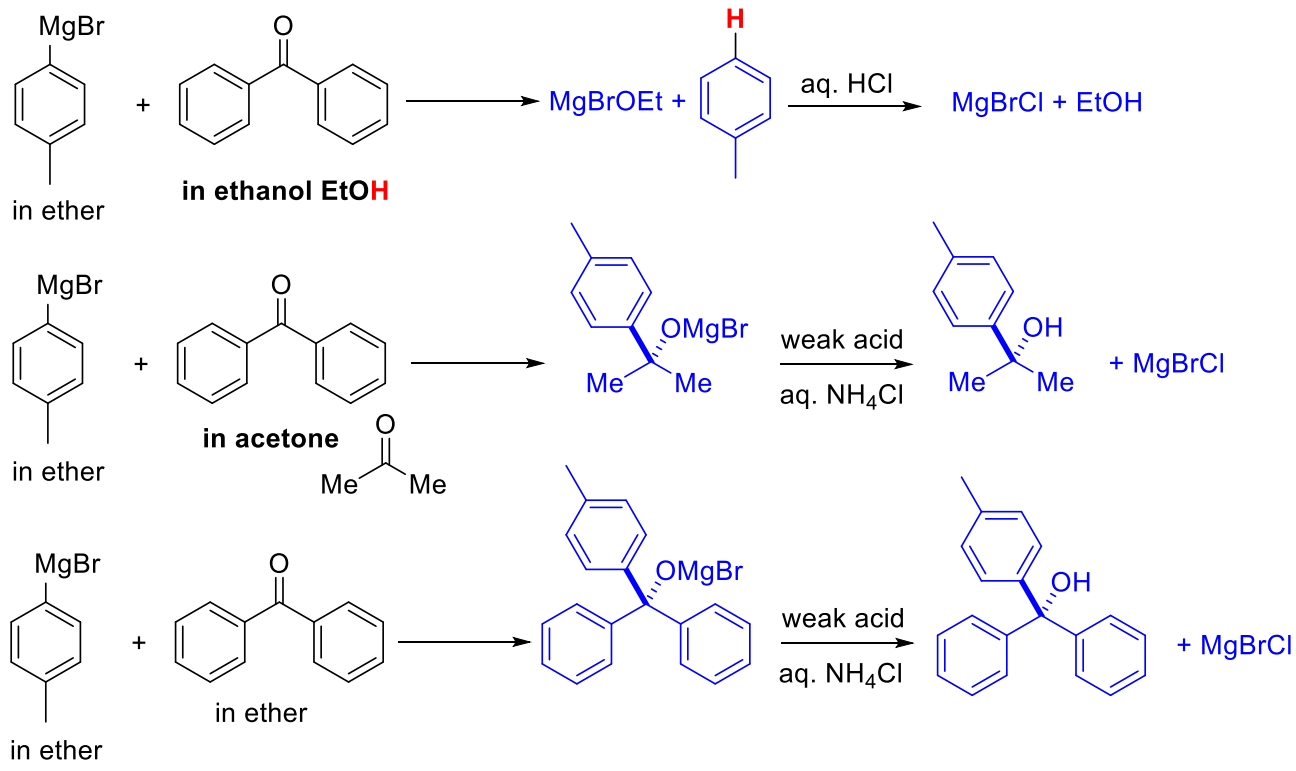
Anhydrous (water-free) solvent needed in order to generate Grignard reagent.

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

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

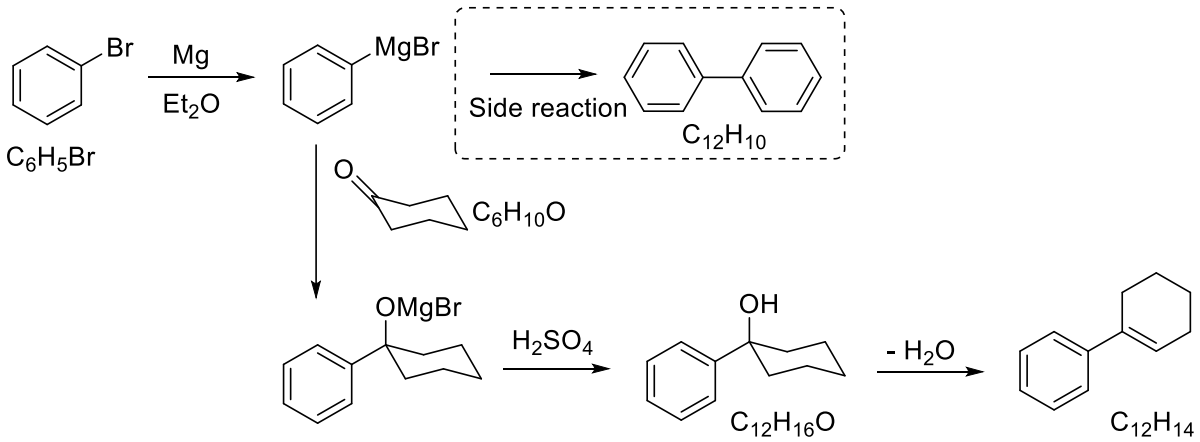
See Loudon Chapter 8 pages 361-364.

b) Show the major product(s) of the reaction of *p*-tolylmagnesium bromide (prepared in anhydrous diethyl ether) with benzophenone (dissolved in either ethanol, acetone, or diethyl ether).



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

2) The reaction of PhMgBr with cyclohexanone followed by addition of acid produces 1-phenylcyclohexene as shown below.



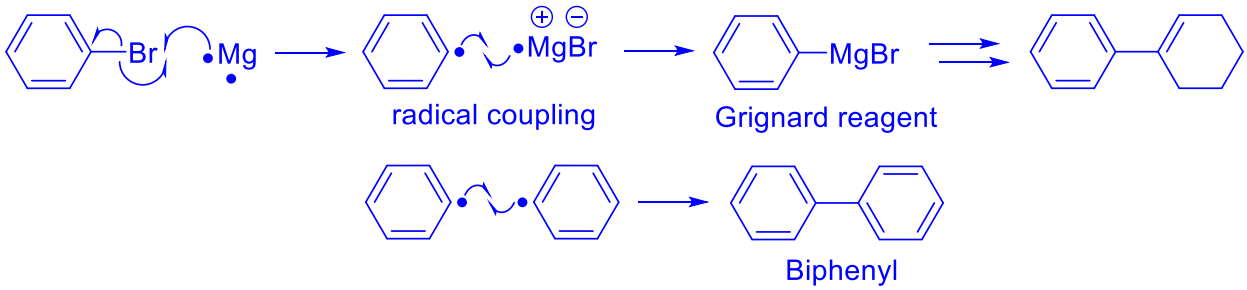
The crude reaction mixture was analyzed by GC-mass spectrometry. Use the GC-MS data on the next page to identify the components of the crude product mixture and assess its purity.

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

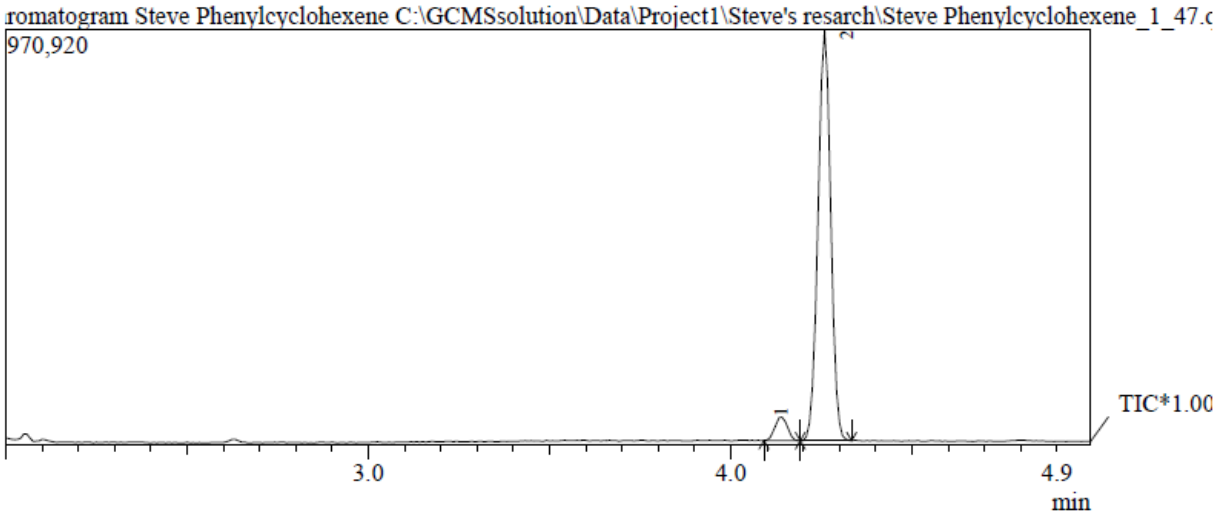
Component 2 = 1-phenylcyclohexene (*m/z* = 158), major product (~94.7% on GC trace)

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

Draw a plausible mechanism for the formation of the minor product. What does the formation of this product imply about the mechanism of formation of the Grignard reagent?



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] leads to formation of the Grignard reagent.



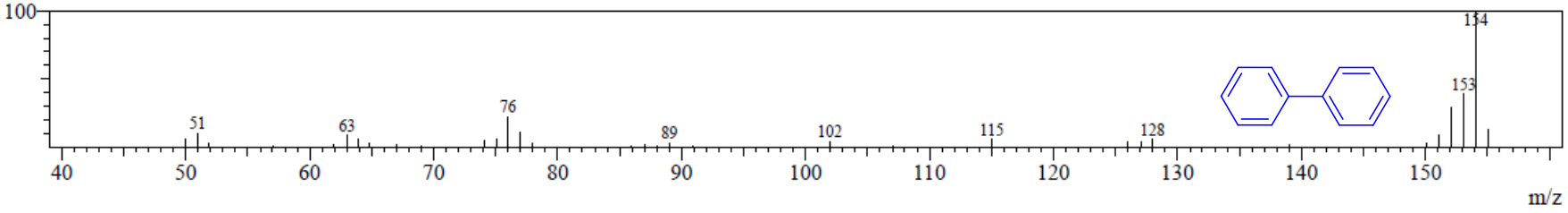
Peak#
1
2

Peak Report TIC

R.Time	Area	Area%
4.138	132097	5.32
4.258	2351497	94.68
	2483594	100.00

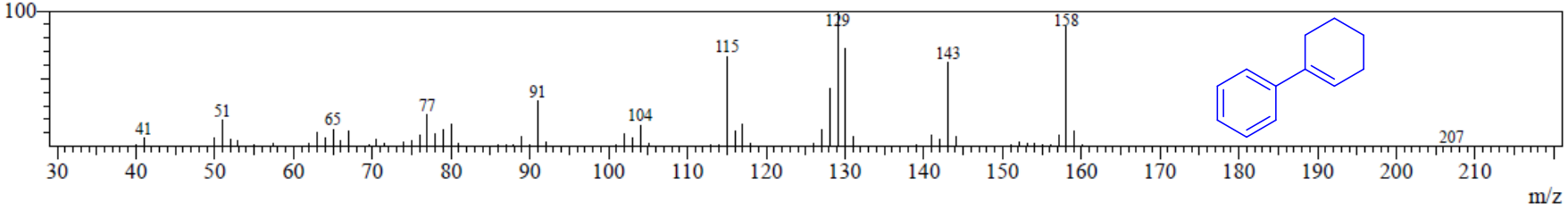
Spectrum

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



Spectrum

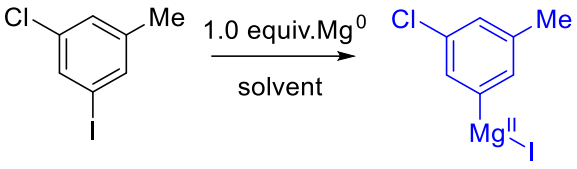
Peak#:2 R.Time:4.3(Scan#:272) MassPeaks:89



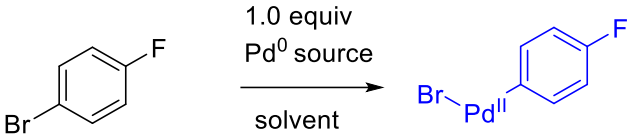
3) Show the product and justify the chemoselectivity of each of the following oxidative addition reactions. Show the oxidation state of the metal in the product. The table of C-X bond dissociation enthalpies of halobenzenes may be useful.

See Loudon Chapter 18 page 840-841.

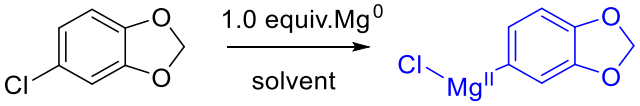
a)



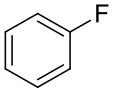
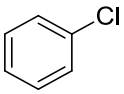
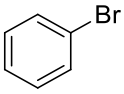
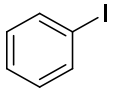
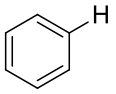
b)



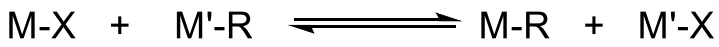
c)



C–X Bond Dissociation Enthalpies

Ph–X	ΔH°_{C-X} (kcal/mol)
	127
	97
	84
	67
	113

4) Transmetallation can be described by the following equilibrium:



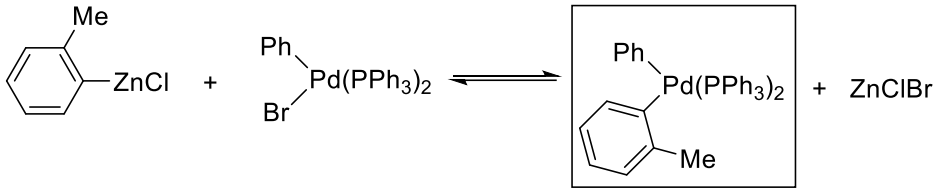
The process is thermodynamically favorable for the production of M-R if $X_M > X_{M'}$ (X = Pauling electronegativity, M/M' = metal, R = organic group, X= halide).

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:



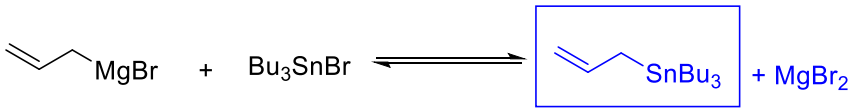
M'-R **M-X** **M-R** **M'-X**

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)

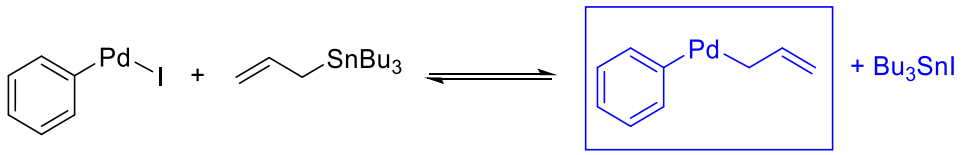


M'-R **M-X** **M-R** **M'-X**

X_{Mg} = 1.31 *X_{Sn} = 1.96*

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

b)

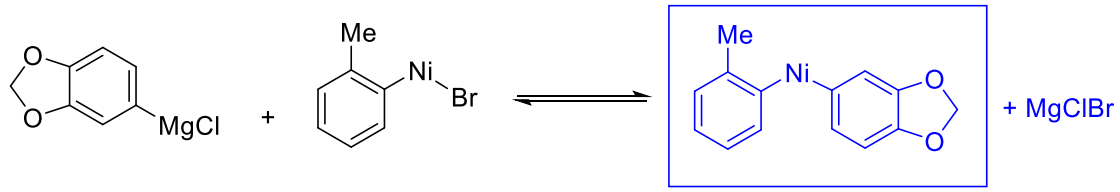


M-X **M'-R** **M-R** **M'-X**

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)

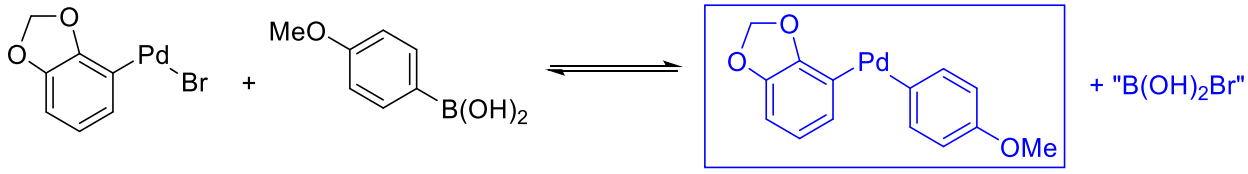


M'-R **M-X** **M-R** **M'-X**

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

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

d)

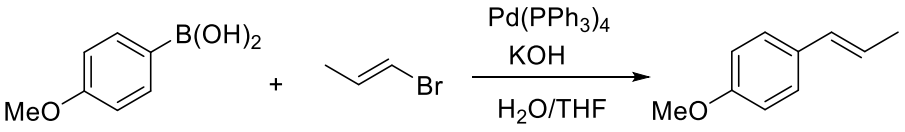


M-X **M'-R** **M-R** **M'-X**

X_{Pd} = 2.20 *X_{B} = 2.04*

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

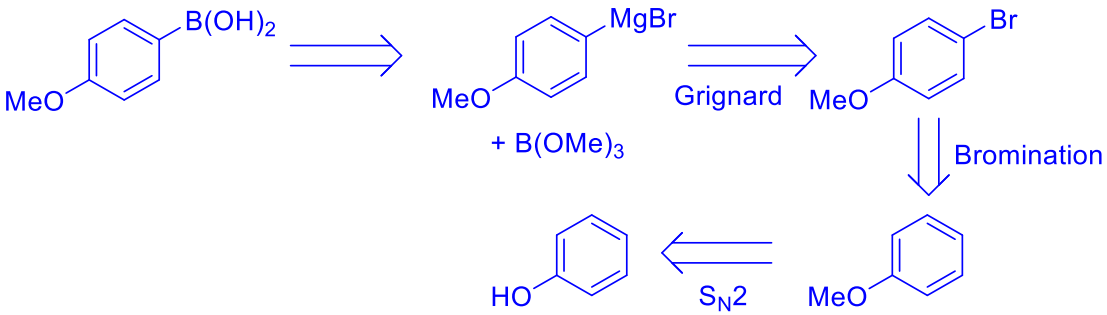
5) Suzuki-Miyaura coupling reactions typically occur between aryl or alkenyl halides and an arylboronic acid. An example of such a reaction is shown below for the synthesis of the food flavoring compound *trans*-anethole (*trans*-1-methoxy-4-(1-propenyl)benzene). The process involves the reaction of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



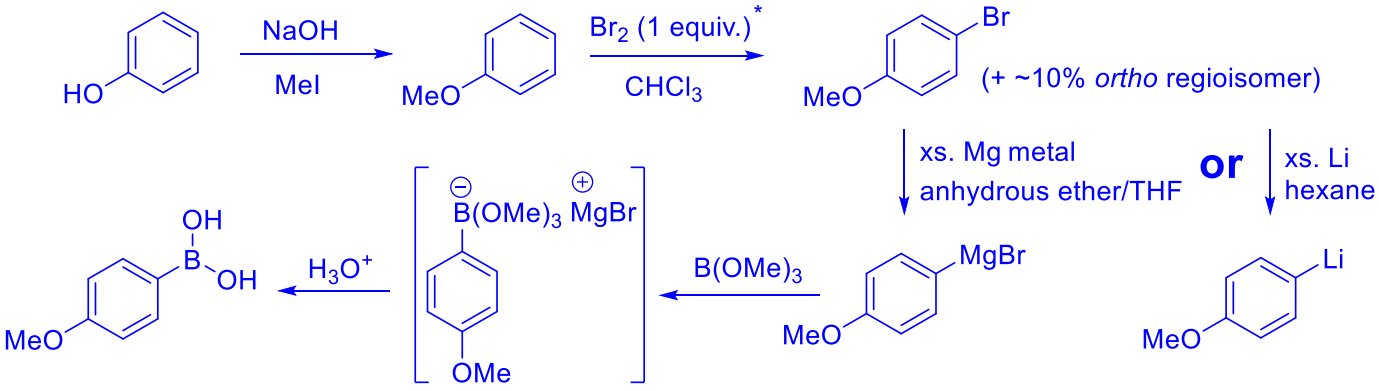
4-methoxyphenylboronic acid *trans*-anethole

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



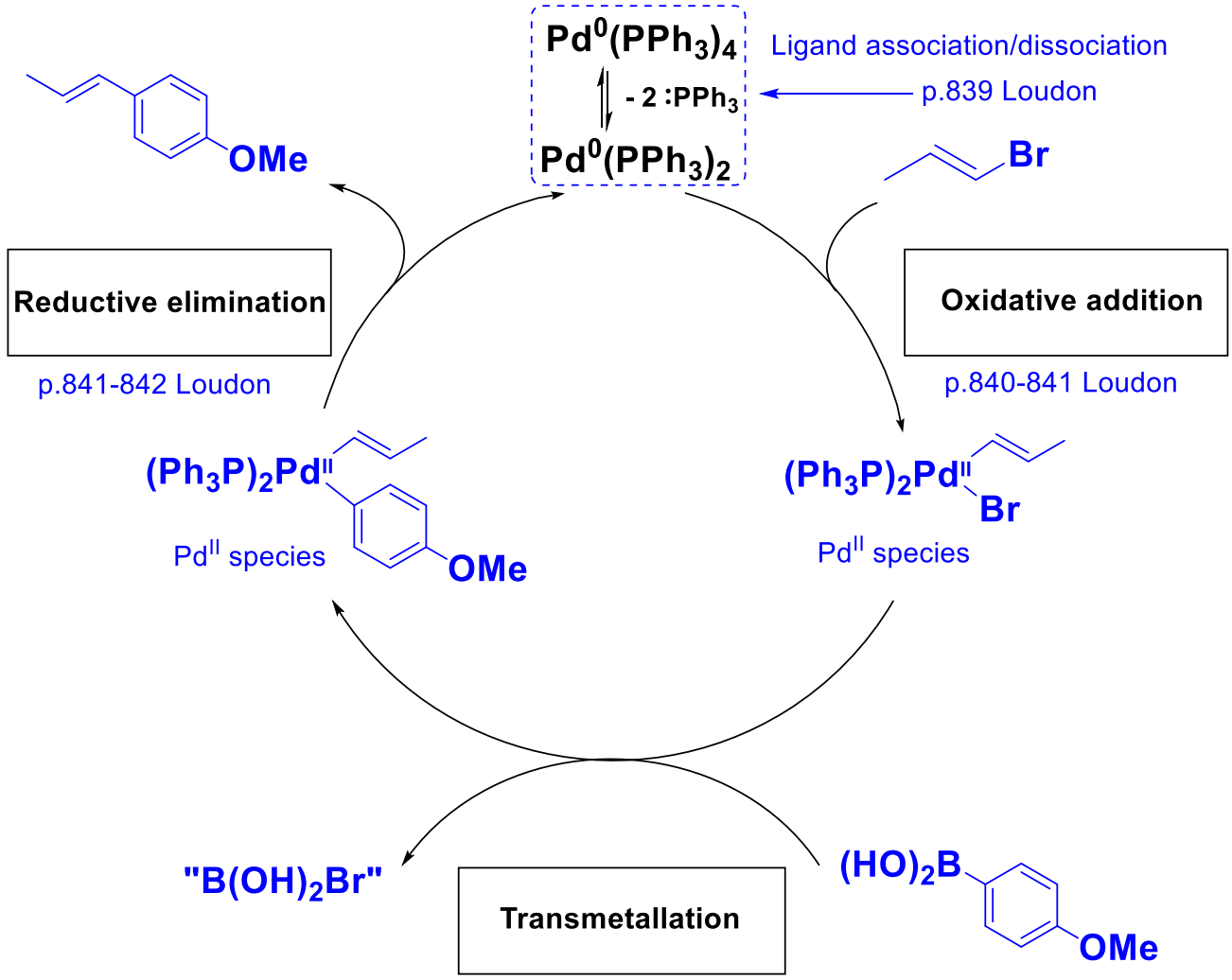
Forward Synthesis (including reagents and conditions)



*Anisole is ~10^6 x more reactive toward E^+ than benzene, so $FeBr_3$ promotor is not required.

See Loudon Chapter 18 page 849

b) Complete the catalytic cycle for the Suzuki-Miyaura coupling reaction shown on page 7, drawing the appropriate reagents and products for each of the three labeled steps. The role of KOH in the reaction will be discussed in the Suzuki pre-lab session next week.



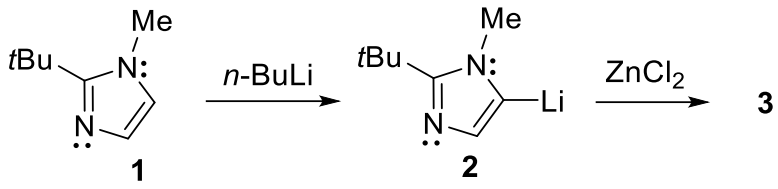
c) A researcher used (*E*)-1-chloro-1-propene in place of (*E*)-1-bromo-1-propene in the above reaction. Explain whether the oxidative addition of $Pd(PPh_3)_2$ into the C-Cl bond of (*E*)-1-chloro-1-propene will be faster or slower than the corresponding insertion into (E)-1-bromo-1-propene.

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

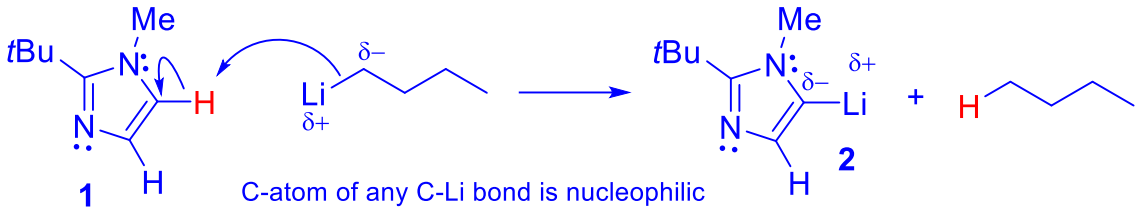
d) What is the driving force for the transmetallation process?

Formation of a less ionic C-M bond.

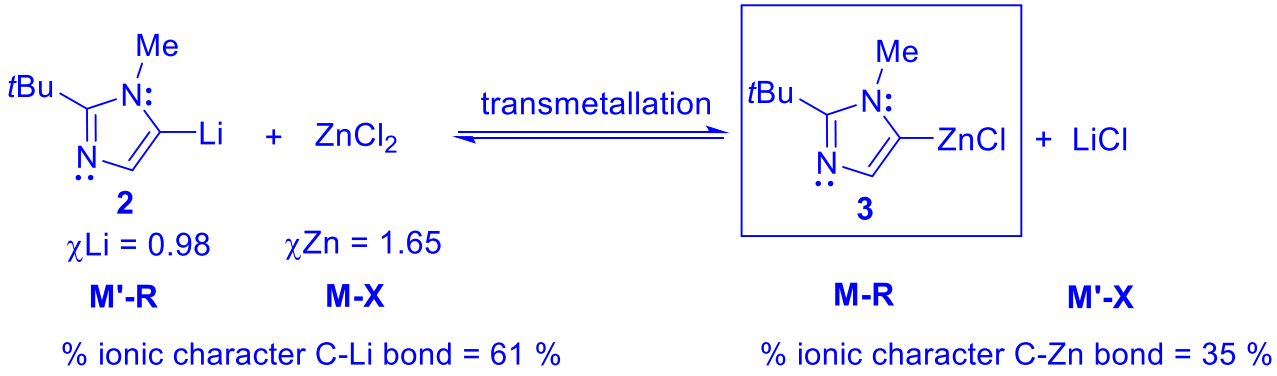
6) The Negishi reaction is a widely used Pd-catalyzed cross-coupling between an organozinc reagent and an organic halide. The catalytic cycle of the Negishi coupling is broadly similar to that of the Suzuki-Miyaura reaction. The preparation of organozinc reagent **3** (a lithiated *N*-methylimidazole) via reaction of **2** with $ZnCl_2$ is outlined below.



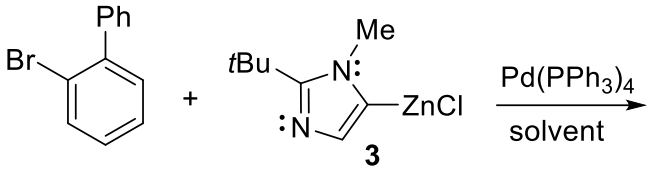
a) Draw an electron-pushing mechanism to show the formation of the organolithium species **2** by reaction of the *N*-methylimidazole precursor **1** with *n*-BuLi. Display the polarization of the C–Li bond in **2**. Is the carbon atom of the C–Li bond nucleophilic or electrophilic?



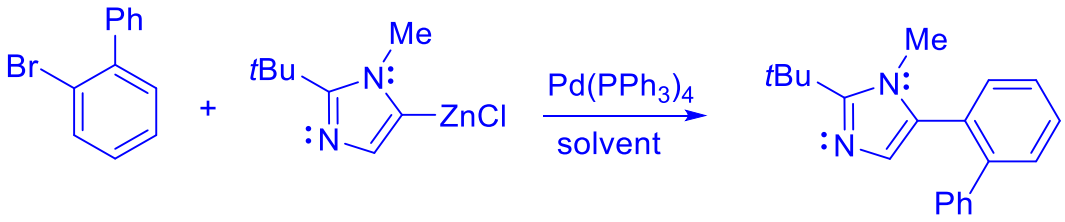
b) Show all products of the reaction of compound **2** with $ZnCl_2$ to produce compound **3**. What is the general name of this process? Rationalize the outcome of the reaction using Pauling electronegativity values and draw a box around the transmetallation product that would be relevant to the catalytic cycle.



c) A Negishi coupling reaction between the organozinc reagent **3** and 2-bromobiphenyl was performed in the presence of the coordination complex [$Pd(PPh_3)_4$].



i) Show the organic product of the Negishi coupling reaction.



ii) List 3 reasons why metal-ligand coordination complexes such as [$Pd(PPh_3)_4$] are often more useful than elemental metals for organometallic catalysis.

- **Metal-ligand complexes are soluble in a wide range of organic solvents, thus allowing homogeneous catalysis (catalysis in solution).**

  Homogeneous catalysis is more attractive than heterogeneous b/c it allows easier access to and control of the active site, easier alteration of the system in general, milder conditions and also easier study of the system leading to fuller understanding of the mechanism. One advantage of heterogeneous catalysis is that the metal catalyst quite easy to separate from the product – this can sometimes be a problem for the purification of pharmaceuticals etc. made via homogeneous catalysis.

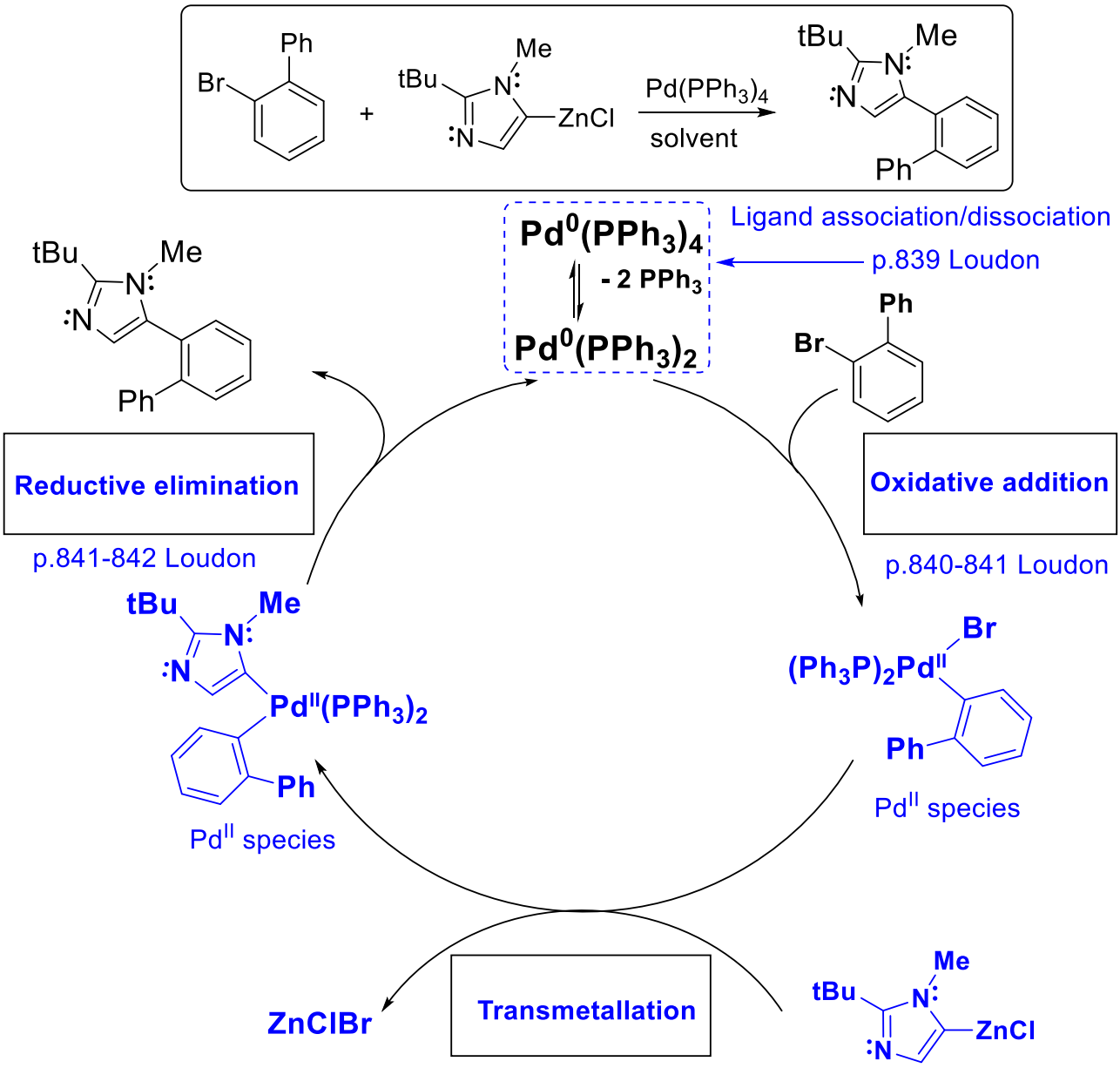
- **Ligands can dissociate from the metal atom to open an active site(s) for catalytic cycle to begin/continue.**

  This is the "just right" bonding referenced in the slides. For example, $Pd(PPh_3)_4$ is a yellow solid that can be stored indefinitely under N_2 (i.e. is "stable") but, in solution in the presence of an aryl bromide, a Pd-P bond will break and create an active site for oxidative addition, thus beginning the catalytic cycle.

- **Ligands control the size and shape of the active site of the metal catalyst.**

  This allows improved selectivity for a particular product. In many cases, a specific ligand or set of ligands can control the size and shape of the reactive pocket on the metal to such an extent that only one enantiomer of a chiral product is produced – this is more difficult to achieve with heterogeneous catalysts.

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.



6) Draw and label the complete catalytic cycle for the Pd-catalyzed Stille cross-coupling of 2-iodotoluene and tributyl(vinyl)stannane shown below. The rate of migration of groups from R_3SnX compounds is alkenyl > aryl > allyl > alkyl.