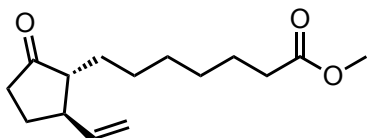


**CHM 3120 Midterm 2**  
**Friday Nov. 11, 2016**

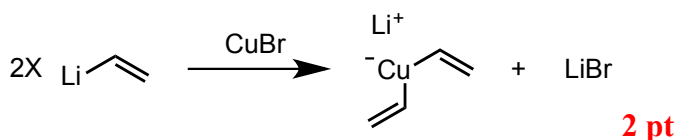
Instructions: Give the answers for all questions neatly in the booklet provided.

1) a) Predict the product(s) of the following reaction (include stereochemistry):



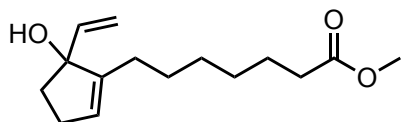
**2 pt (1,4 addition) 1pt (product) 1pt (stereochem)**

b) From which reagents would you prepare the organocuprate reagent?



**2 pt**

c) Would you expect a different product if you treated the starting material with the nucleophile used to make the organocuprate in (b)? If so, what is its structure?

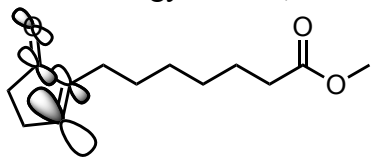


**2 pt**

d) Does MO theory help you account for the product formation under these reaction conditions? If yes, draw the relevant MO. If no, why not?

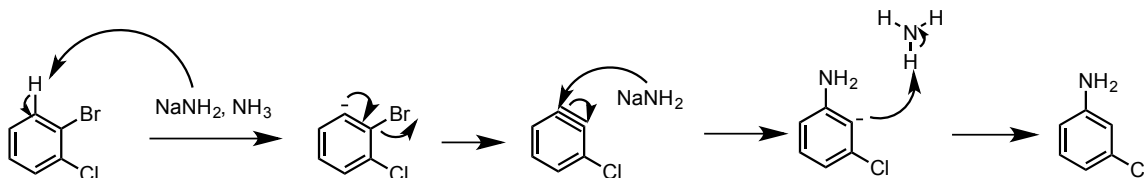
**3 pt (explain 1,4 or 1,2 addition)**

- Yes, the organocuprate reagent in (a) is a softer nucleophile than the organolithium reagent in (c) since Cu is less electropositive than Li.
- In the case of the organocuprate reagent the soft nucleophile (cuprate) will have a high energy HOMO, and the soft electrophile (Michael acceptor) will have a low energy LUMO, this favours a HOMO-LUMO interaction, as shown below.



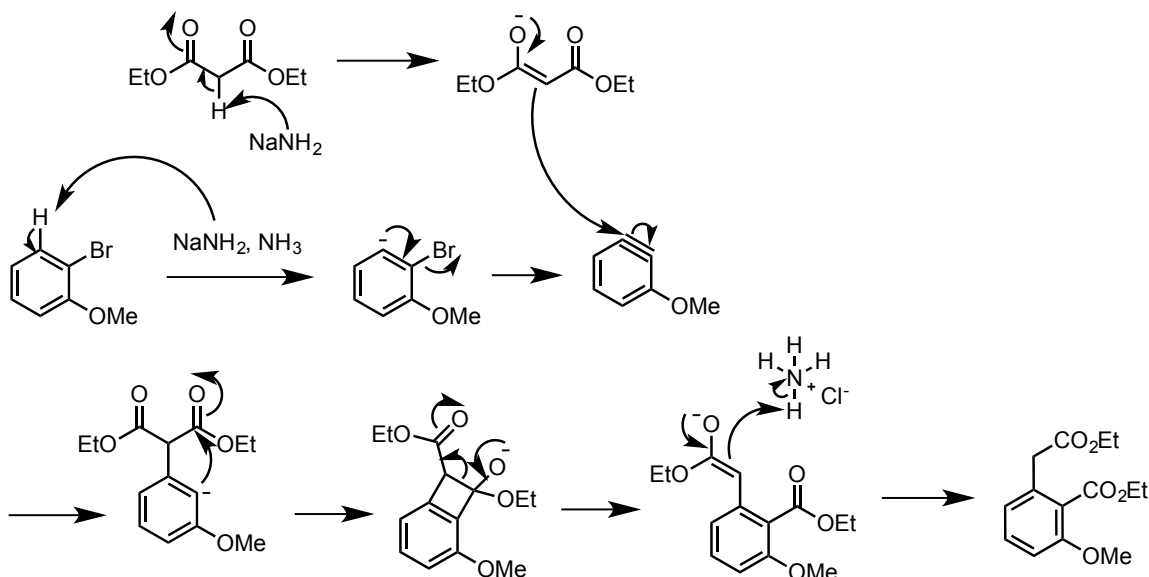
In the case of the organolithium reagent, Li is a small ion and more electropositive as a result it is a hard nucleophile. This results in a direct 1,2-addition product, where the difference in HOMO and LUMO energies is too large, favouring an electrostatic attraction, where the organolithium species directly attacks the carbonyl carbon.

- 2) a) Give the structure of the product you expect would arise in the following reaction, and provide a reasonable (and complete!) mechanism for the transformation:



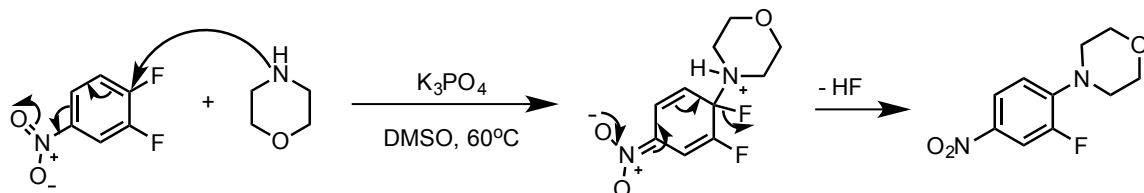
**2 pt (product) 3 pt (benzyne mechanism)**

- b) Draw a reasonable (and complete!) mechanism for the following transformation:



**7 pt**

- 3) a) The pharmaceutical industry loves simple chemistry! The key step in the Novartis synthesis of Zyxiphenazine, a hepatitis C drug, is shown below. Draw the product (which is a couple of trivial steps from Zyxiphenazine) and provide the mechanism for the reaction.



**4 pt**

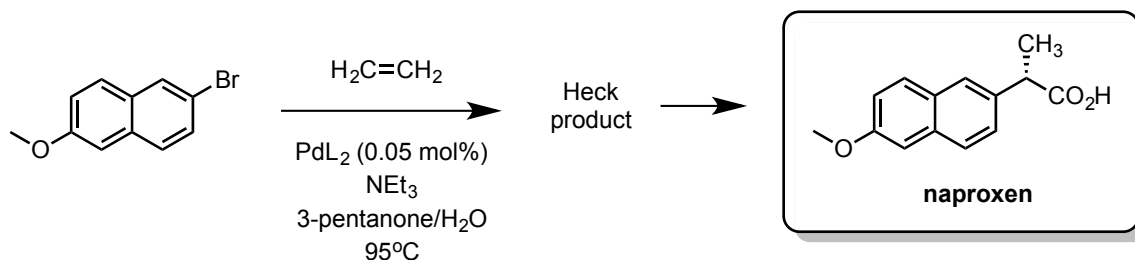
- b) Using your mechanism, explain why fluoride is a better leaving group in nucleophilic aromatic substitutions than other halides.

The addition of the nucleophile to the aromatic ring is the rate determining step, not the departure of the leaving group. Fluoride is the most electronegative atom

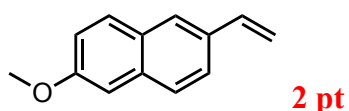
and activates the aromatic ring towards nucleophilic aromatic substitution as the adjacent carbon is highly electrophilic. Going down the periodic table results in a decrease in electronegativity and as a result decreases the electrophilicity of the carbon. Hence, fluoride is the best halogen when it comes to nucleophilic aromatic substitution.

**1 pt (rate determining step) 1 pt (activates carbon to nucleophilic attack)**

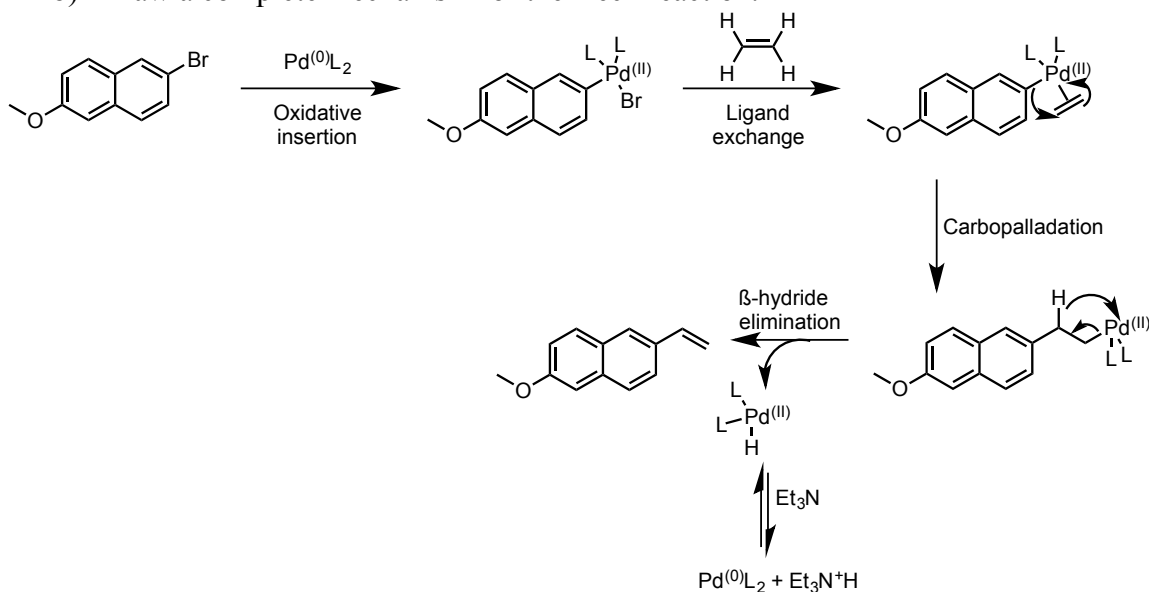
- 4) Albemarle produces 500 tonnes per year of naproxen, a popular non-steroidal anti-inflammatory drug, using a Heck reaction for the penultimate step in the process:



- a) Give the product of this Heck reaction.



- b) Draw a complete mechanism for the Heck reaction.



- c) Albemarle was able to minimize the catalyst required to carry out this reaction with the ligand shown below. Suggest at least one reason that this ligand performed better than the 'standard'  $\text{PPh}_3$  ligand you saw most regularly in class?

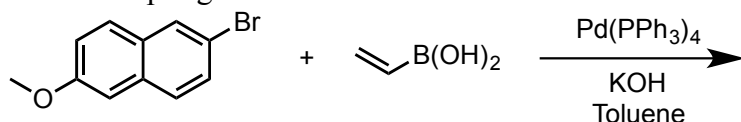
Alkyl substituents on the phosphine ligand make it more electron rich than the regularly used  $\text{PPh}_3$  ligand allowing the palladium to more easily insert into the carbon-halogen bond. Having a more electron rich phosphine ligand stabilizes the electron poor Pd(II) species which results after oxidative insertion.

**2 pt**

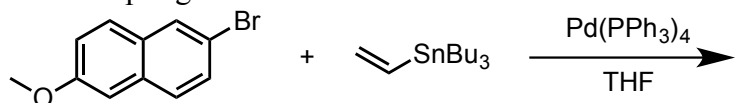
- d) Provide reagents and reaction conditions under which you could carry out Suzuki and Stille couplings to make the same product; why do you think the Heck reaction is preferred from an industrial perspective?

**4 pt**

Suzuki coupling



Stille coupling



**2 pt**

The Heck reaction is preferred from an industrial perspective since it makes use of ethylene gas as its alkene source. Suzuki and Stille couplings would require additional synthesis in order to obtain the organoboron and organotin reagents, respectively.

- 5) Predict the products of the following transformations. Hint: Both reactions proceed via the same type of mechanism. Draw it for each example. **6 pt**

