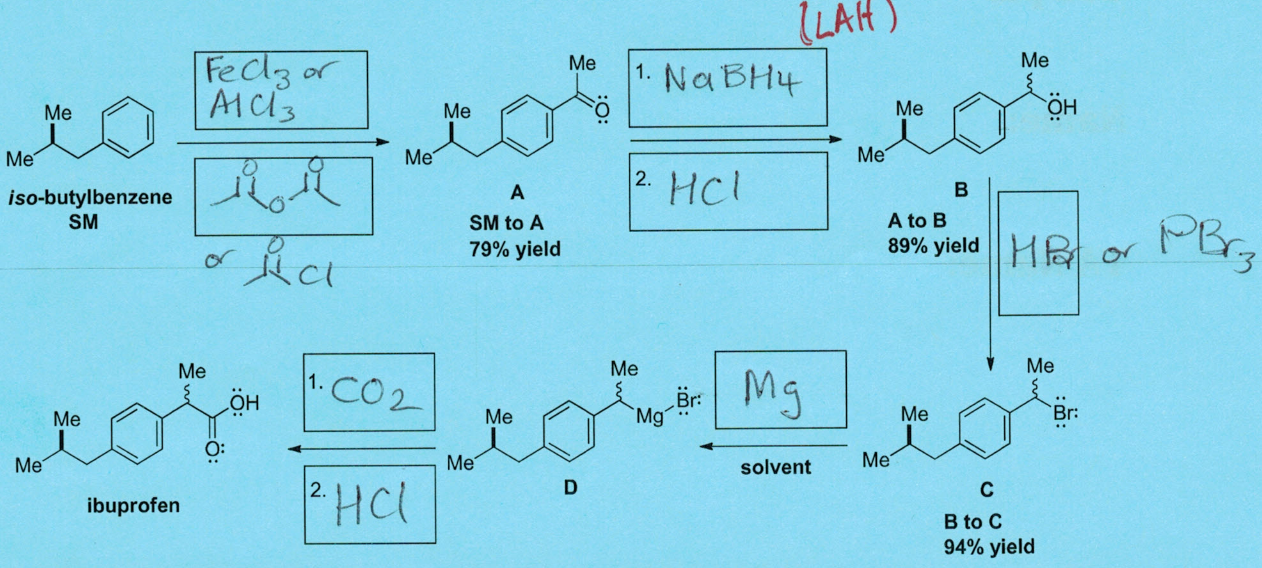
CHEM 344 Final Quiz Fall 2013 **100 pts**

1) A multi-step synthesis of the NSAID ibuprofen is shown below.



a) Fill in the boxes with the appropriate reagent(s) for each step of the synthetic route. (8 pts)

1 pt per correct box

b) 2.81 g of ibuprofen was obtained from 3.78 g of compound C. Showing all work, calculate the % yield of ibuprofen. (4 pts)

Compound C = $C_{12}H_{17}Br$ = 241.19 $g\,mol^{-1}$

3.78 g compound C ÷ 241.19 $g\,mol^{-1}$ = 15.67 mmol

Ibuprofen = $C_{13}H_{18}O_2$ = 206.31 $g\,mol^{-1}$

Theo. yield ibuprofen = 15.67 mmol x 206.31 $g\,mol^{-1}$ = 3.23 g

2.81 g ibuprofen = $\frac{2.81 g}{206.31 g\,mol^{-1}}$ = 13.62 mmol

% yield = $\left(\frac{2.81\,\cancel{g}}{3.23\,\cancel{g}}\right) \times 100$ = 87% or $\left(\frac{13.62\,\cancel{mmol}}{15.67\,\cancel{mmol}}\right) \times 100$ = 87%

2 pts correct theo. yield
2 pts — " — % yield

−2 pts if correct numbers but work not shown

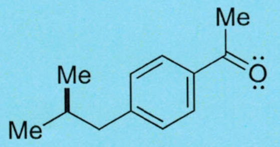
c) Based upon your answer to part b) calculate the overall %yield of ibuprofen starting from *iso*-butylbenzene (SM) (2 pts).

$0{\cdot}79 \times 0{\cdot}89 \times 0{\cdot}94 \times 0{\cdot}87$

$= \underline{57\%}$

this number may vary but if math is correct then give full credit.

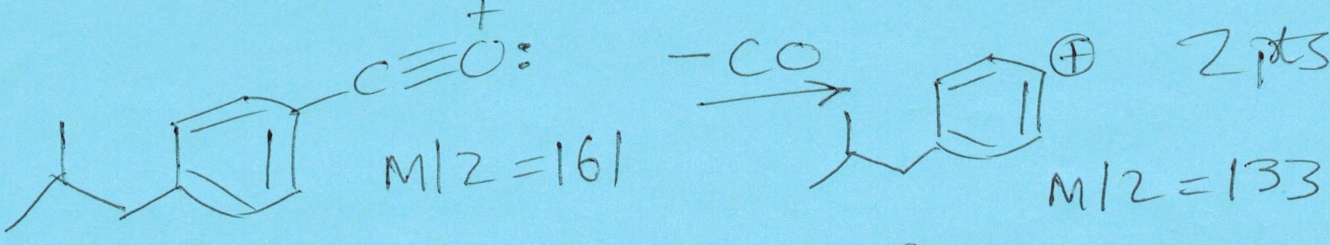
d) The EI-MS data for compound A feature the following important peaks:



A

EI-MS: *m/z* 161 (100 %), 133 (42 %)

For each peak, draw the most likely ion in its major resonance form. Show all formal charges and lone pairs (4 pts).



2 pts

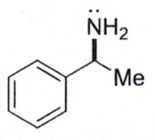
2 pts

anything else = 0 pts

(There are no resonance structures)

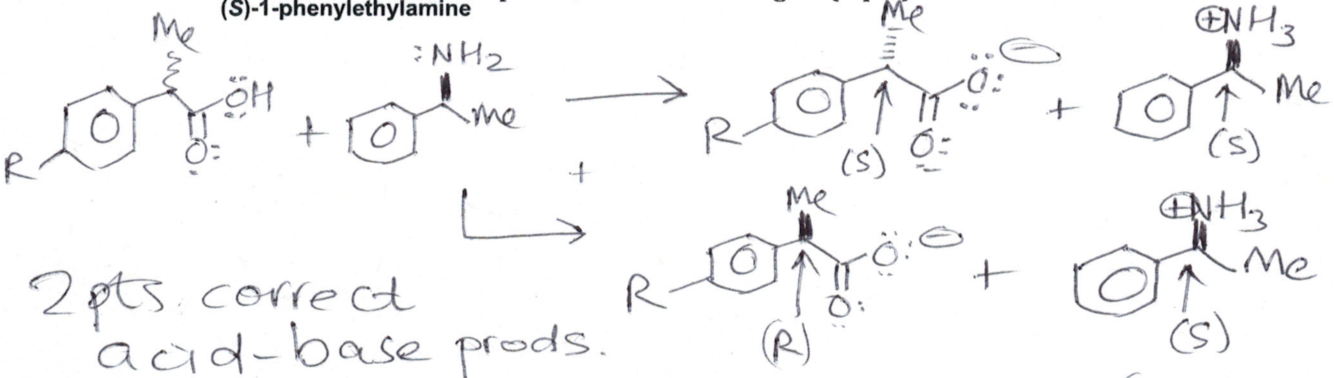
anything else = 0 pts

e) Pure ibuprofen is isolated from the above synthetic route as a racemic mixture. The enantiomers of ibuprofen can be separated by using a chiral reagent such as (*S*)-1-phenylethylamine (shown below).



(*S*)-1-phenylethylamine

Draw the diastereomeric salts produced by reaction of (*S*)-1-phenylethylamine with racemic ibuprofen. Assign the configuration of any chiral atoms as either *R* or *S*. Show all lone pairs and formal charges. (4 pts)



2 pts. correct acid-base prods.

1 pt per correct stereochem. on salts

(4 pts total)

f) The *R,S* salt is soluble in water but the *S,S* salt is insoluble. Suggest a procedure to separate the salts and isolate the two enantiomers of ibuprofen. (4 pts)

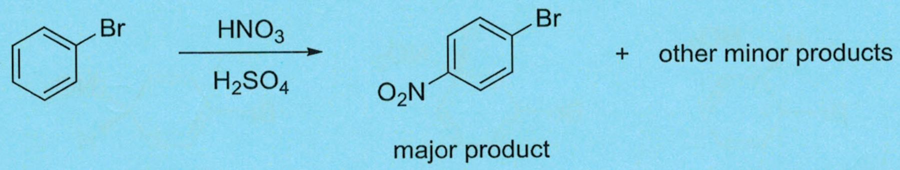
- Add mixture to water → (R,S) soluble, (S,S) not
- Filter suspension to isolate (S,S) salt, add salt to acid soln to reprotonate $RCO_2^{\ominus}$, collect ppt → (S)-ibuprofen (2 pts)
- Acidify original filtrate containing R,S salt, ~~R~~ collect ppt

↓

(R)-ibuprofen

(2 pts).

2) The nitration of bromobenzene with H_2SO_4/HNO_3 results in *p*-bromonitrobenzene as the major product along with (at least) two other organic products. This question will consider the formation of possible products, the ratio of products in the crude material, and the identity of each product.



a) What are the *m/z* values of the two highest abundance molecular ions of the major product? (1 pt)

M|2 = 201 + M/2 = 203

1 pt both correct

b) What is the directing effect of a bromo substituent on a benzene ring? Does a bromo substituent activate or deactivate the benzene ring toward an electrophile? (Do not explain, just identify.) (1 pt)

Deactivating, o/p directing

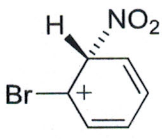
1 pt both correct

c) What is the directing effect of a nitro (NO_2) substituent on a benzene ring? Does a nitro substituent activate or deactivate the benzene ring toward an electrophile? (Do not explain, just identify.) (1 pt)

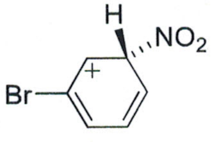
Deactivating, meta directing.

1 pt both correct

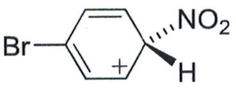
d) Use the structures of the possible arenium intermediates, the potential energy surface shown below, Hammond's postulate, and any other necessary chemical concepts to fully explain why *p*-bromonitrobenzene is the major product of the nitration of bromobenzene. (10 pts)



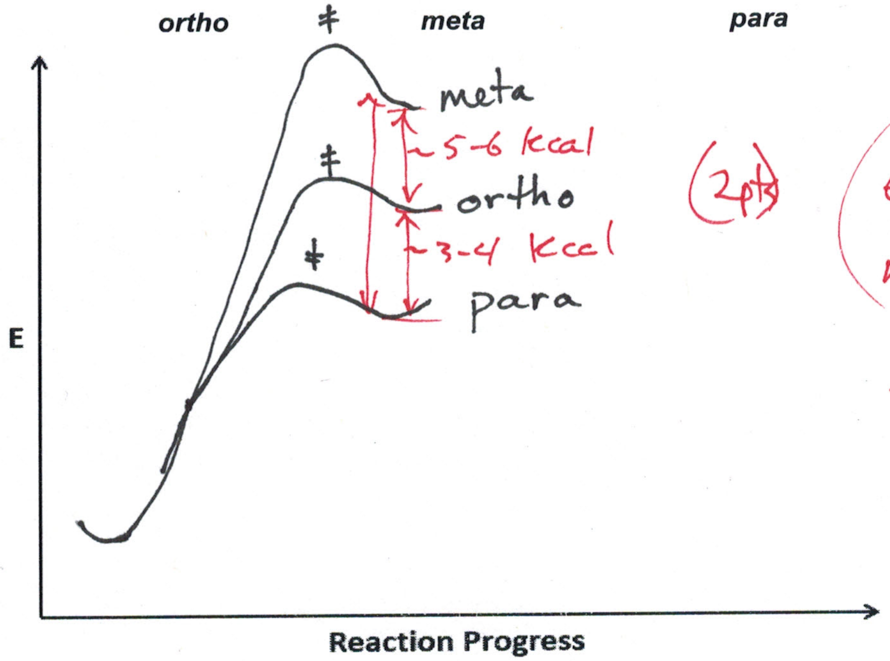
ortho



meta

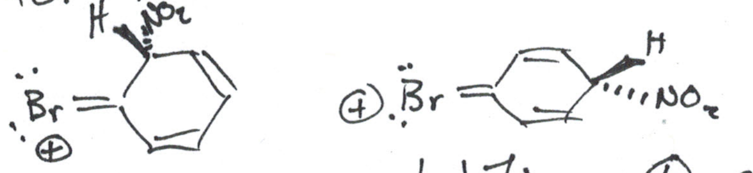


para



(2pts) (energies not needed) order critical

- This reaction is kinetically controlled. (2pts)
  (‡ determines reactivity)
- Hammond's Postulate allows the intermediate energy differences to serve as a proxy for the transition state energies. (2pts)
-



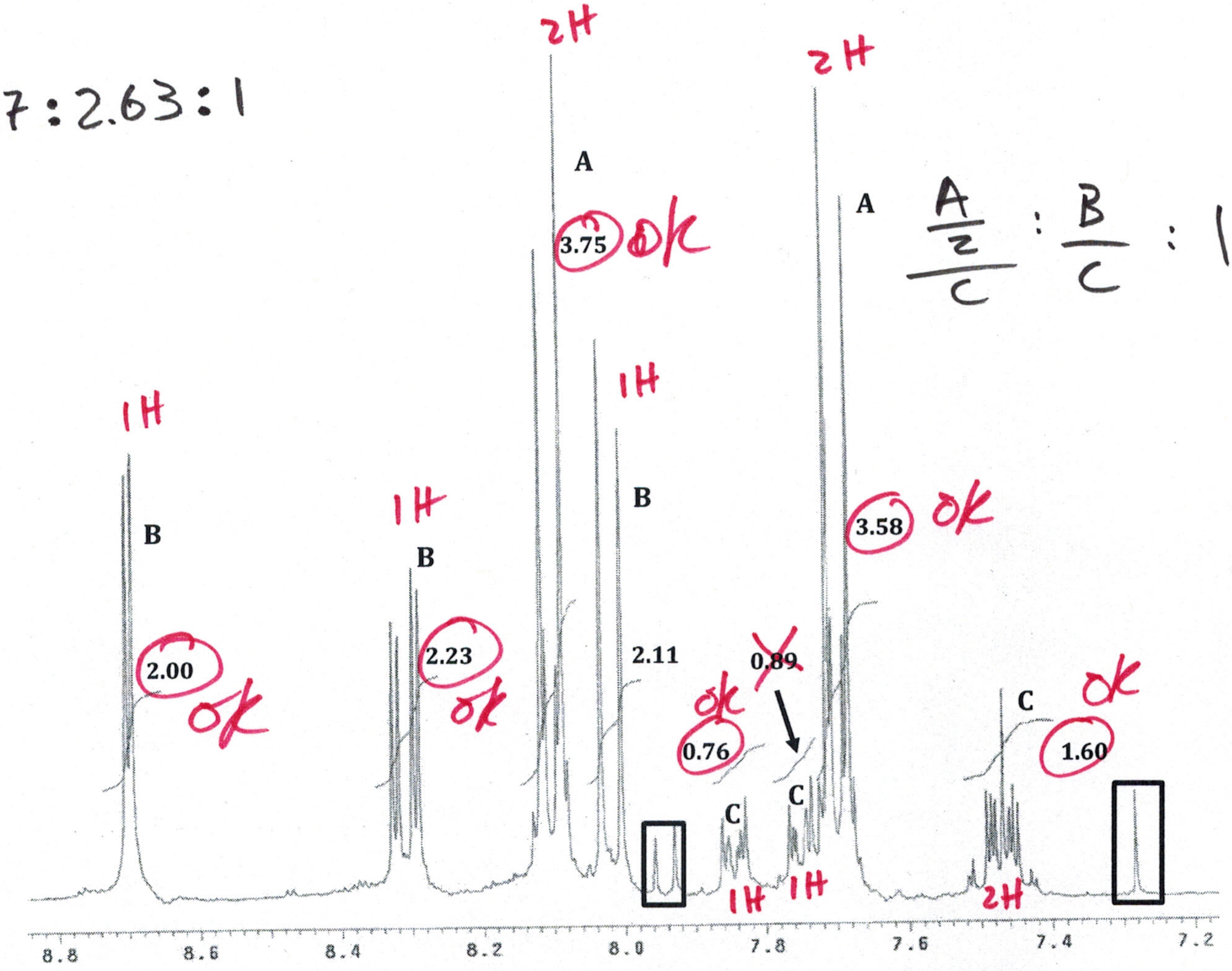
ortho and para areniums allow -Br to stabilize ⊕ charge. (2 pts)

- ortho is higher energy than para due to dipole and/or steric issues. (2pts) true on some versions.

e) The ^{1}H-NMR spectrum of the crude product of the nitration of bromobenzene is shown below. The crude mixture contains 3 organic products (NMR signals labeled A, B, and C). Showing all work, calculate the relative ratios of the 3 products in terms of A:B:C (i.e. A is the most abundant and C is the least abundant of the three products, normalized to C= 1). The raw integrals are displayed next to each signal. Each product contains a single aromatic ring. Ignore the signals in the black boxes. (4 pts) (oops.)

A scratch spectrum is provided at the end of the exam packet but all work for grading must be included on the spectrum on this page.

2.47 : 2.63 : 1



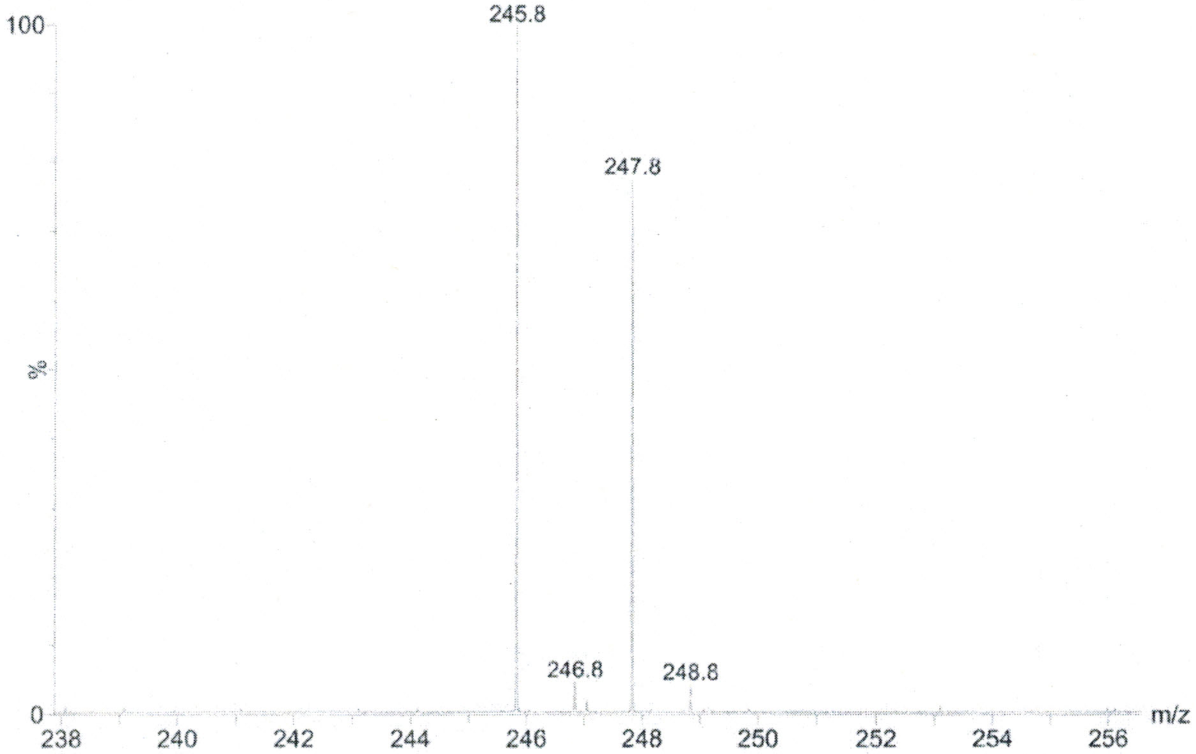
$\frac{A/2}{C} : \frac{B}{C} : 1$

4 pts = good math and ratios; good integrals

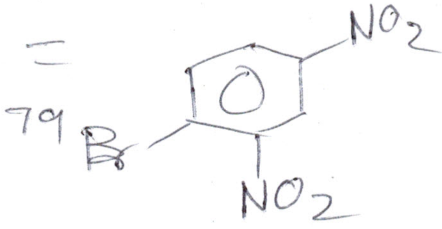
2 pts = any ratio with good math

0 pts = bad math

f) In addition to the ^{1}H-NMR spectrum, an EI-mass spectrum of product B was obtained. Use the EI-MS data shown below and your answer to part a) to deduce and draw the structure of product B. Show all work. (3 pts)

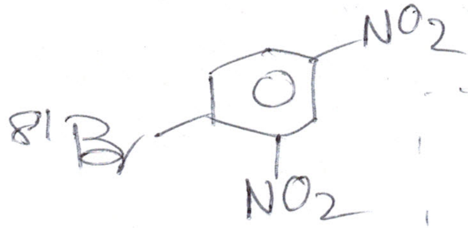


M/z = 246 =



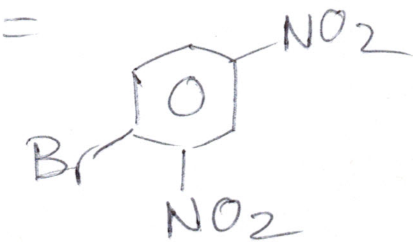
M/z = 248

=



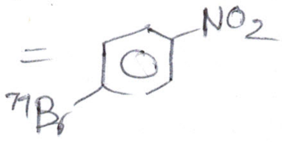
Product B

=

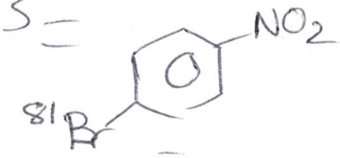


part a)

201 =



203 =



246 - 201 = 45

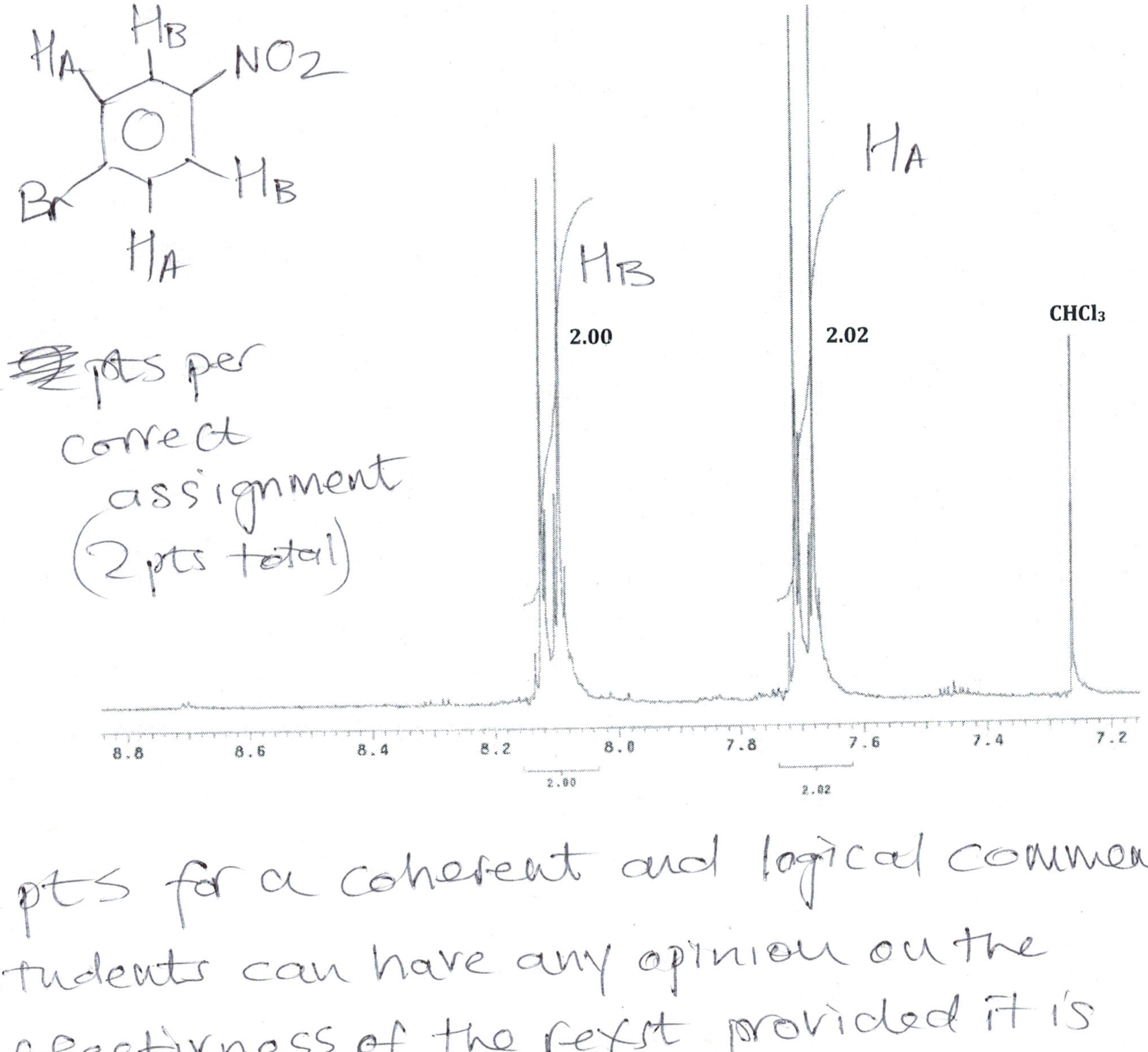
= "+ NO_2, - H"

~~248~~

248 - 203 = 45

= "+ NO_2, - H".

g) The crude nitration product was recrystallized from dichloromethane. The ^{1}H-NMR spectrum of the recrystallized product is shown below. Assign each of the signals in the spectrum using the H$_a$, H$_b$, etc. system. Additionally, comment upon the effectiveness of the recrystallization and explain your reasoning. (4 pts)

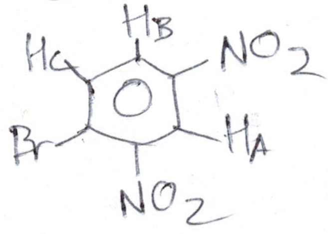


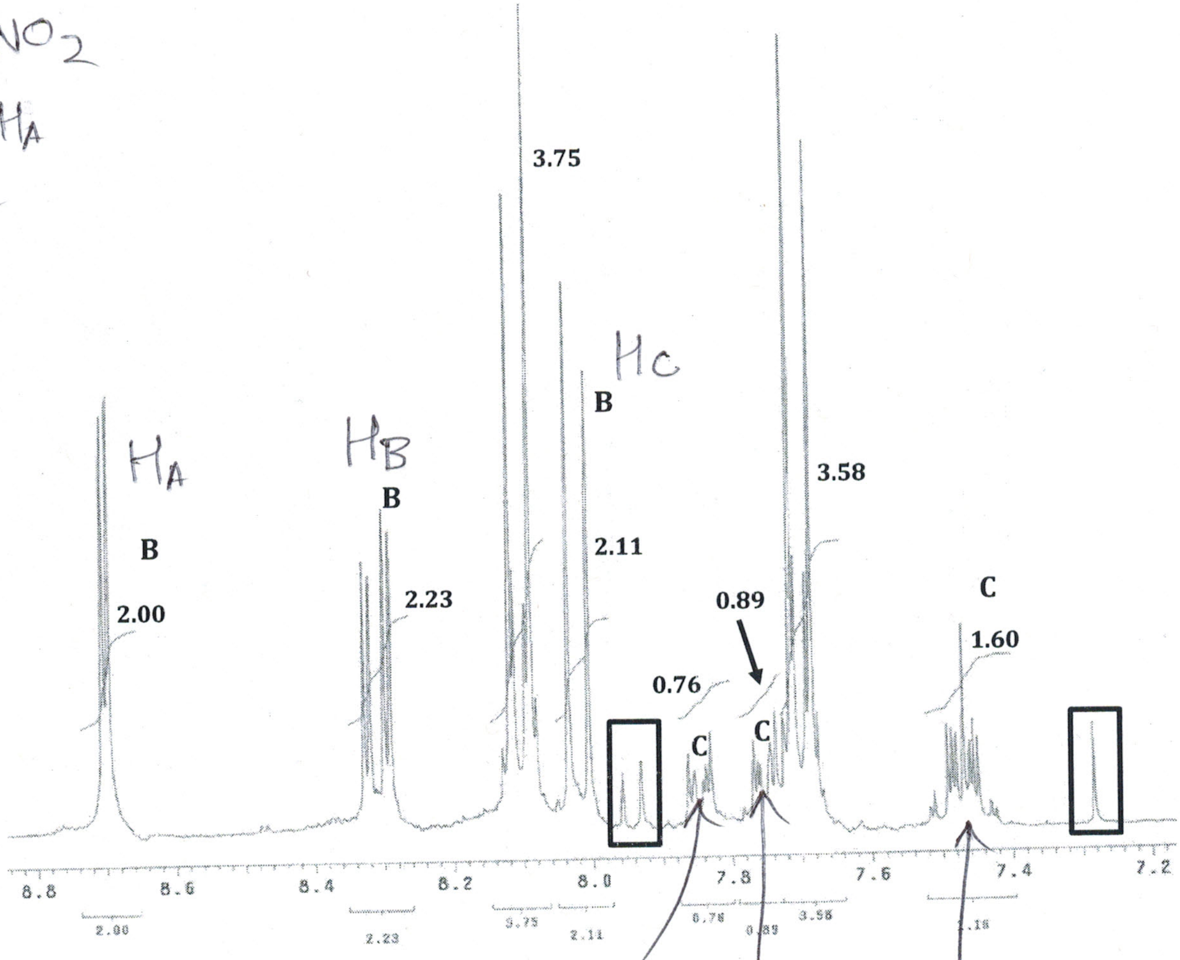
1 ~~2~~ pts per correct assignment (2 pts total)

2 pts for a coherent and logical comment. Students can have any opinion on the effectivness of the rexst provided it is explained.

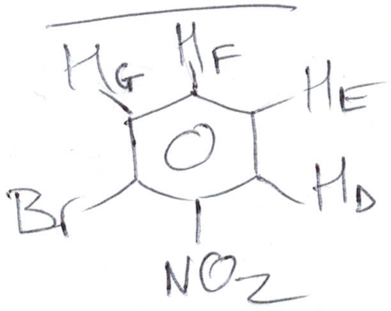
h) Based upon the preceding NMR and MS data draw the structures of the minor products B and C. Justify your answers based upon your chemistry knowledge and the spectra provided. Fully assign the NMR spectrum of the crude product provided below using the Ha, Hb, etc. system. (8 pts)

Product B:





Product C

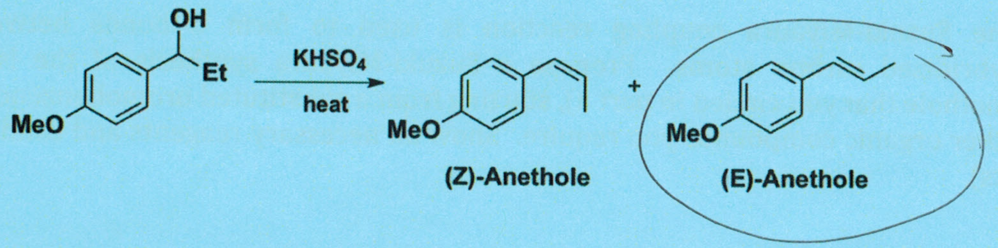


1 pt per correct signal assignment = 6 pts

1 pt per correct structure = 2 pts

8 pts

3) Antheole is an aromatic compound isolated from Anise, Fennel and Star Anise oils. It is commonly used in liqours such as Ouzo. A synthetic route to a mixture of (*Z*)- and (*E*)-Antheole is shown below:



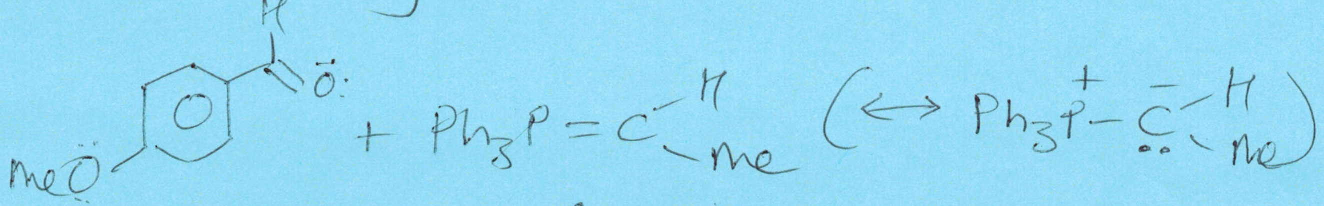
1 pt

a) Name the type of reaction taking place and draw a circle around the major product (2 pts).

Elimination (1pt)

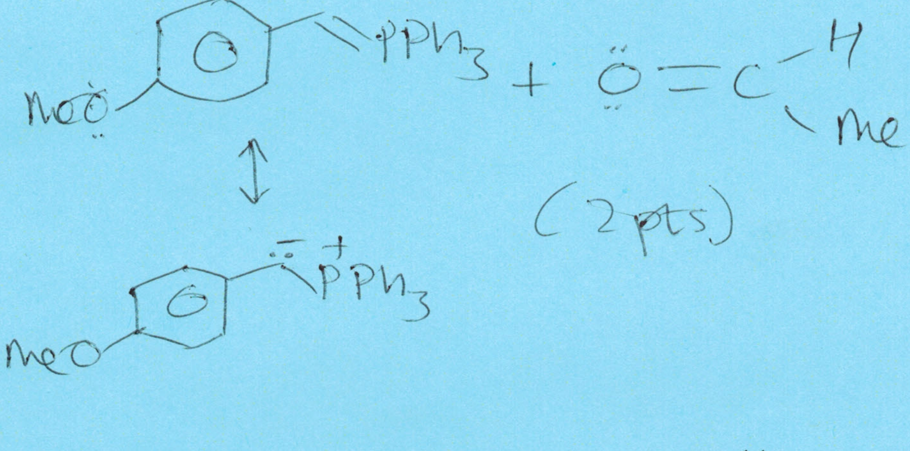
b) Suggest another reaction that you have studied in CHEM 344 that might produce a mixture of (*Z*)- and (*E*)-Antheole. Show all necessary starting materials, reagents, and conditions. (3 pts)

Wittig rxn (1pt)



(2pts)

OR

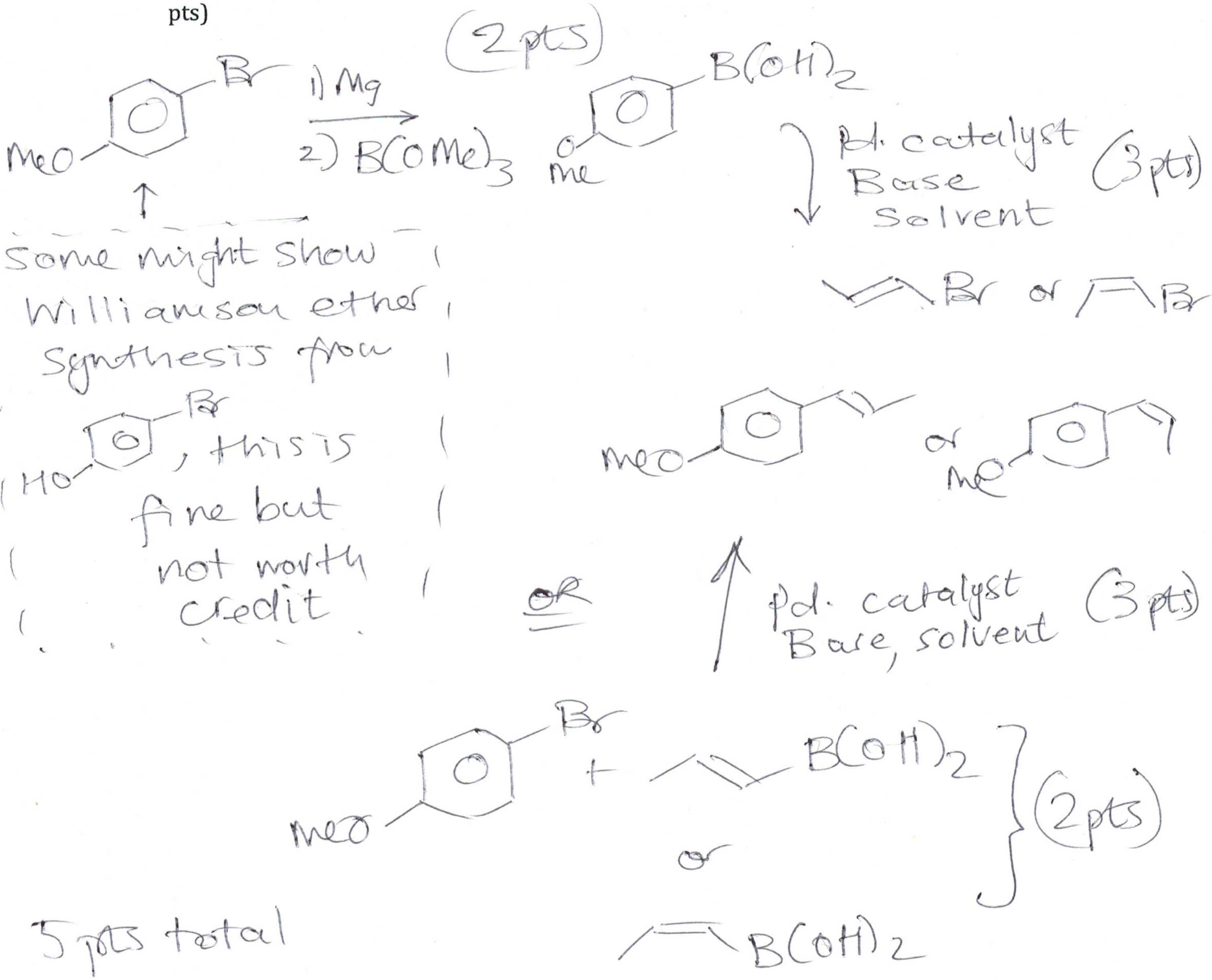


(2pts)

don't need to show resonance structures or formation of ylide

c) The above reactions generate a mixture of (*Z*)- and (*E*)-Anethole. The near identical properties of the isomers makes separation difficult and so there is need for a synthetic route that is selective for each individual isomers.

The Suzuki-Miyaura coupling reaction is used to form σ–bonds between sp^2-hybridized carbon atoms. Propose a Suzuki-Miyaura synthesis of the isomer of Anethole that you circled in part a), starting from a substituted bromobenzene and any other organic compounds you require. Show all necessary reagents and conditions. (5 pts)



Some might show Williamson ether synthesis from HO–C₆H₄–Br, this is fine but not worth credit

5 pts total

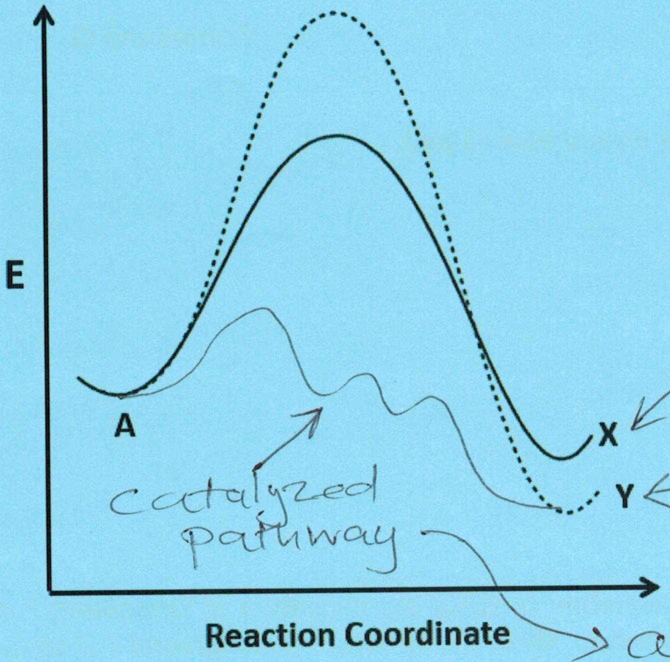
4) The potential energy surfaces a) and b) show the uncatalyzed conversions A → X+Y and B → G+H respectively.

i) On each PE surface, clearly identify the thermodynamic and kinetic product.

ii) on PE surface a), draw and label a possible pathway for the catalyzed process A→ X.

(6 pts total)

a)



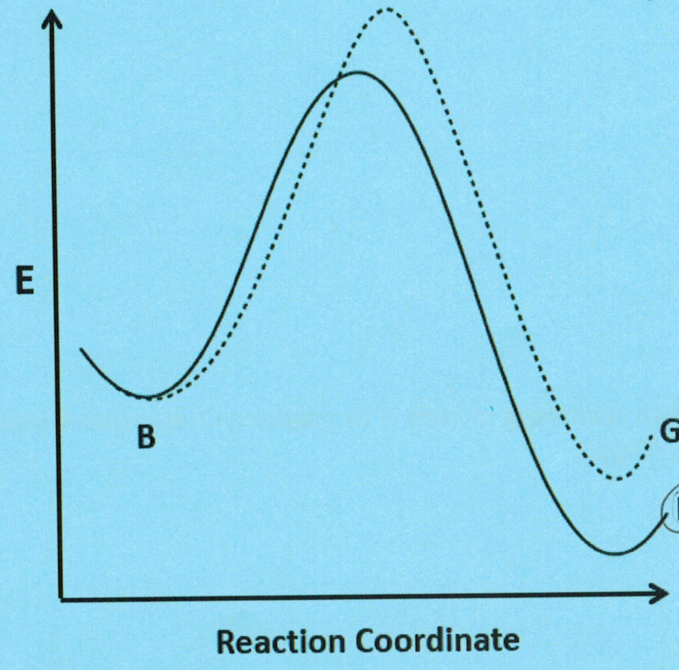
catalyzed pathway

Kinetic (1 pt) product

Thermodynamic product (1 pt)

anything that resembles this = 2pts

b)



Thermodynamic and Kinetic product (2 pts)

5) The Negishi reaction is a widely used Pd-catalyzed cross coupling that uses an organozinc reagent. The preparation of an organozinc reagent Compound G from the substituted imidazole precursor Compound E is shown below.

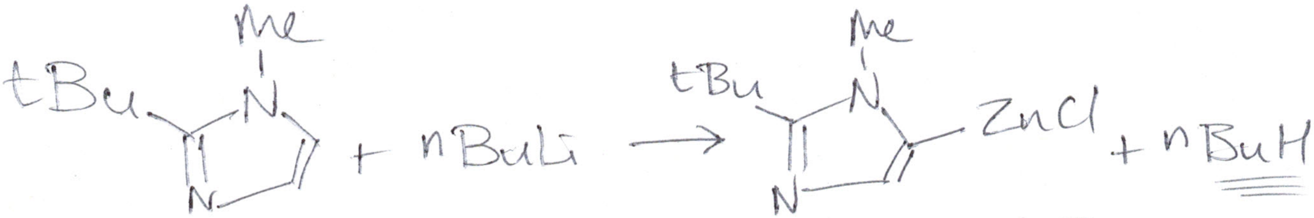
Compound E

Compound G

a) Explain why *n*-BuLi is a very strong base (3 pts).

Strongly polarized $\overset{\delta-}{C}-\overset{\delta+}{Li}$ with high carbanion character

b) Draw a balanced chemical equation to show the formation of Compound F *via* the reaction of *n*-BuLi with Compound E. Show the structure of Compound F (3 pts).



Compound F (2 pts)

1pt correct balanced eqn.

c) State the name of the process occurring in step B to produce Compound G and draw the byproduct of the reaction. (2 pts)

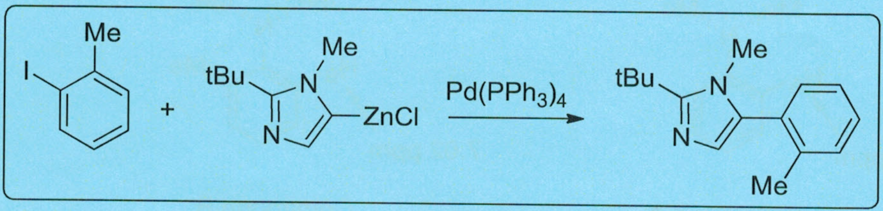
Transmetallation (1 pt)

LiCl (1pt)

↑ anything = 0 pts

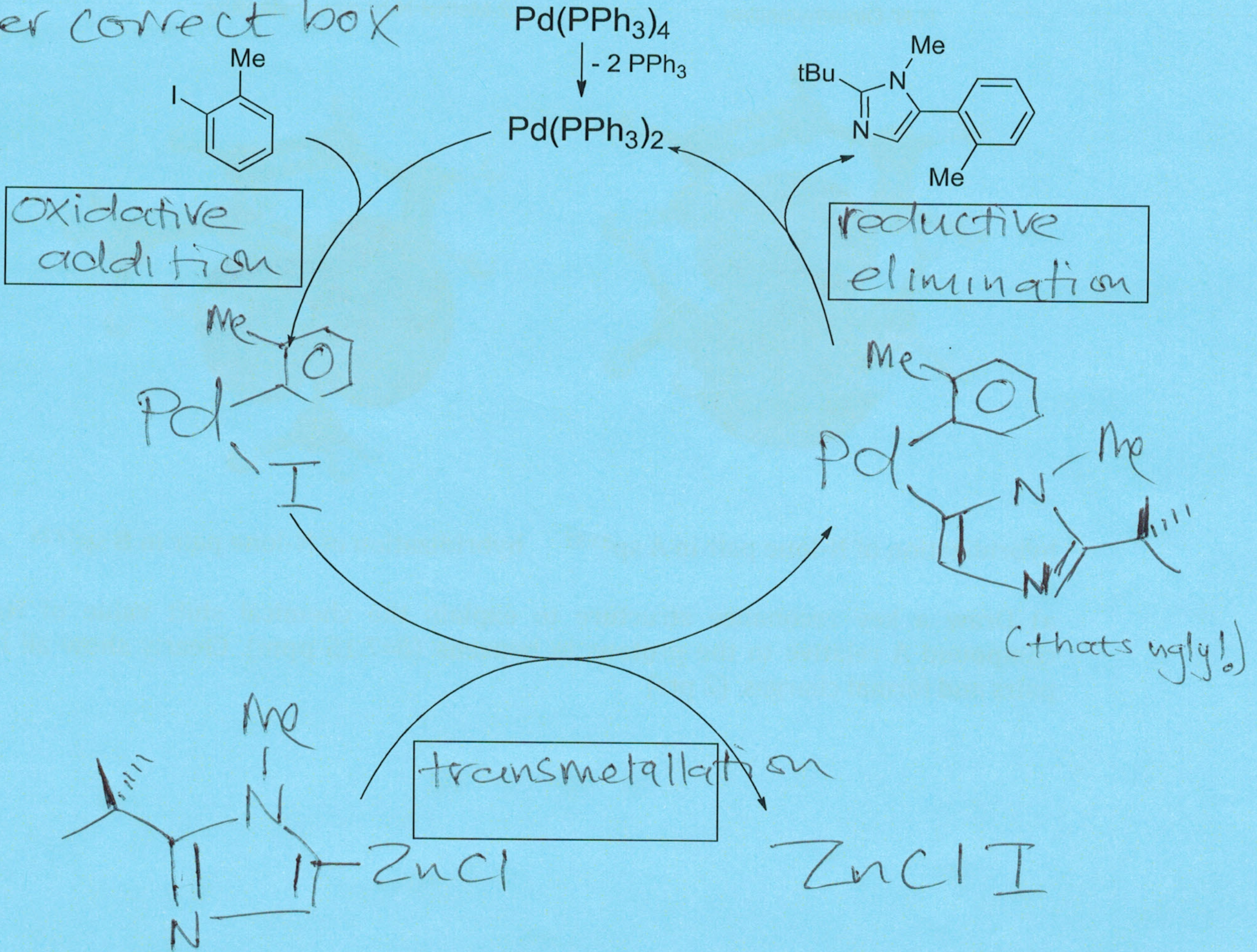
correctly words/describing the TM process without stating the word = 1 pt

d) Complete the catalytic cycle for the Negishi coupling reaction shown below, labeling each step in the blank boxes and drawing the appropriate reagents and products of each of step. (10 pts)

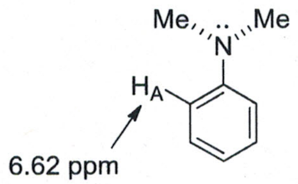


2 pts per correct box

1 pt per correct structure

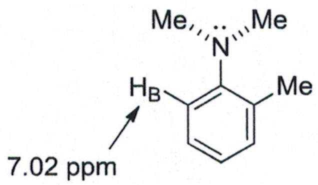


6) The aromatic amines *N,N'*-dimethylaniline (**A**) and 2-methyl-*N,N'*-dimethylaniline (**B**) are shown below. The ^{1}H-NMR chemical shift of the proton *ortho* to the NMe_2 group is given below each structure. The N-atom lone pairs are shown in the color images.



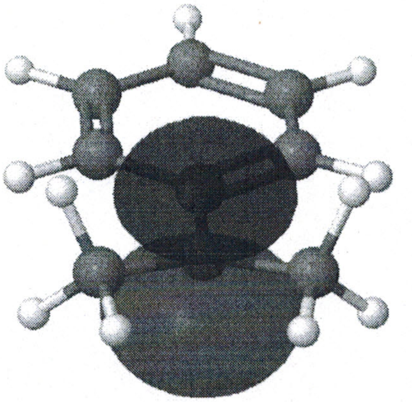
Compound A

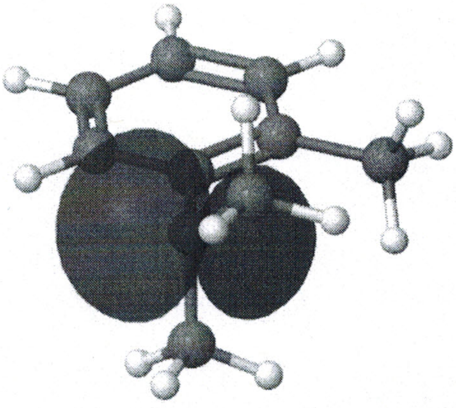
N,N'-Dimethylaniline



Compound B

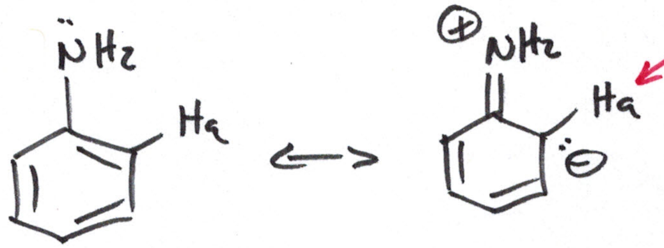
2-Methyl-N,N'-dimethylaniline





hybridization of N-lone pair in **A** $sp^{33.31}$ hybridization of N-lone pair in **B** $sp^{12.26}$

a) Draw a key resonance structure to explain the chemical shift value of H_A in compound **A** relative to the protons in benzene (δ=7.15 ppm). Clearly show all lone pairs and formal charges. (2 pts)



shielded by extra e⁻ density

* lone pairs, resonance arrows, formal charges are required.

b) explain why the proton H_B in compound **B** is deshielded relative to the corresponding proton H_A in compound **A** (4 pts).

The twist caused by the steric bulk of the $-\ddot{N}\text{-}Me_2$ groups removes the N-atom lone pair from conjugation. This changes the shielding caused by the EDG $-\ddot{N}H_2$ substantially.

c) Using your answers in parts (a) & (b), explain whether **A** or **B** has the more basic nitrogen atom (2 pts).

B has the more basic or more reactive lone pair. It is not stabilized by conjugation to the aromatic ring.