

Initials: _____

1

Name: Key

Chem 633: Advanced Organic Chemistry 2011 ... Final Exam

Please answer the following questions *clearly and concisely*. In general, use pictures and less than 10 words in your answers.

Write your answers in the space provided.

Write your initials on each page you want graded.

There are 17 total pages to this exam. The last 2 pages were intentionally left blank and may be used for scratch paper. Please be sure your copy has 17 pages before you begin.

Molecular models are allowed.

Calculators are unnecessary and prohibited.

Potentially Useful Information

$$k_B/h = 2.083 \times 10^{10} \text{ s}^{-1}\text{K}^{-1}$$

$$\kappa = 1 \text{ (kappa)}$$

$$R = 1.98 \text{ cal/mol}\cdot\text{K}$$

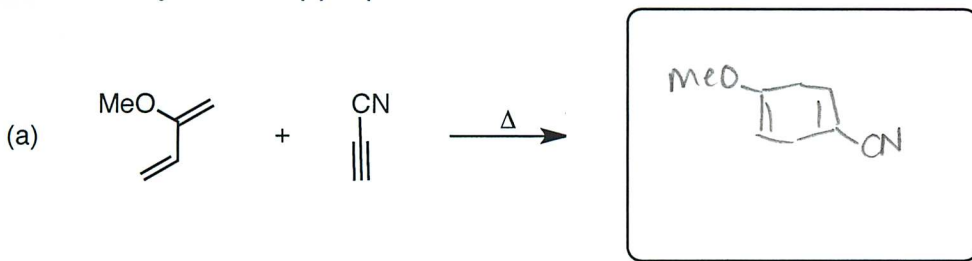
$$\log (X^n) = n \log X$$

$$\log (X \cdot Y) = \log X + \log Y$$

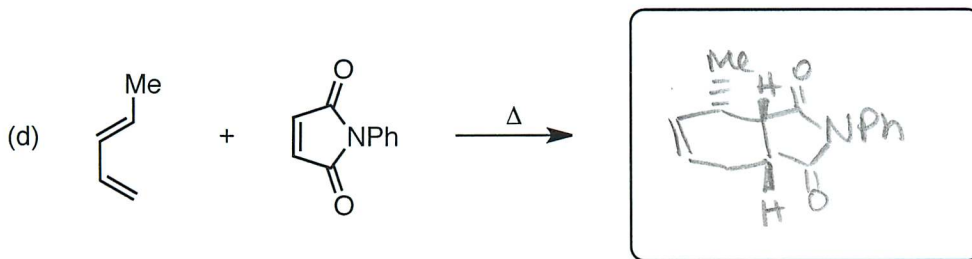
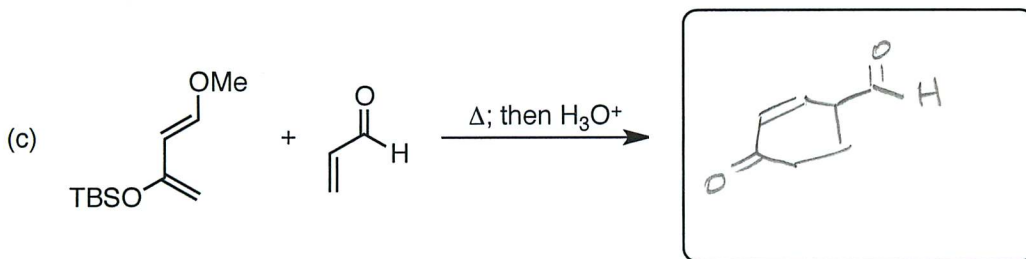
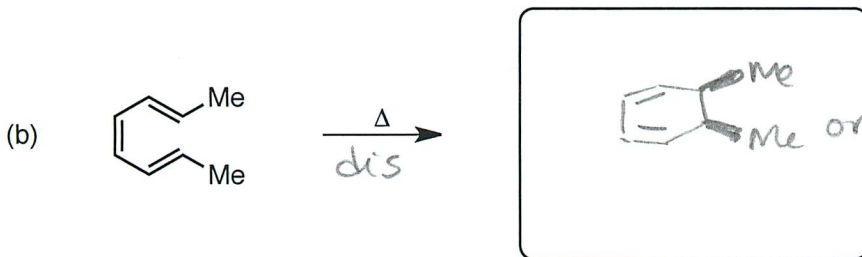
Problem	Points
1	____/15
2	____/8
3	____/10
4	____/12
5	____/24
6	____/16
7	____/15
TOTAL	____/100

3 pts each

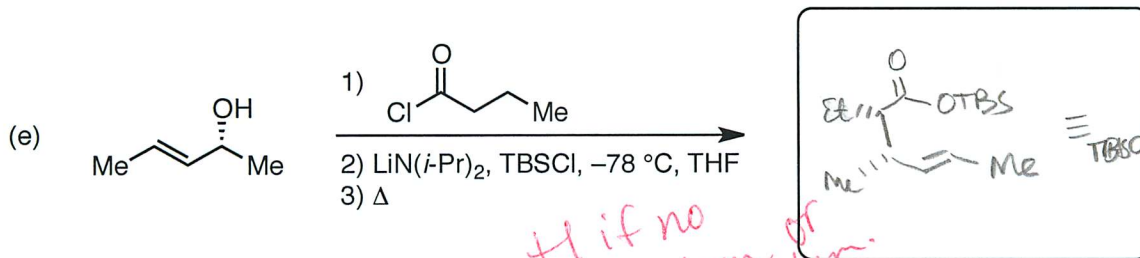
1. (15 points) Predict the major product of the following reactions. Clearly indicate the stereochemistry where appropriate.



+1 if wrong regiochem

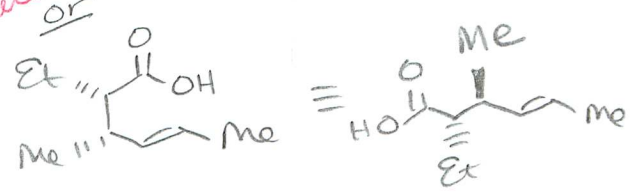


+1 for exo

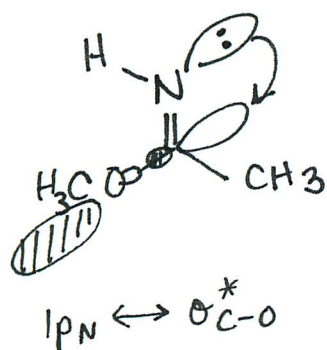
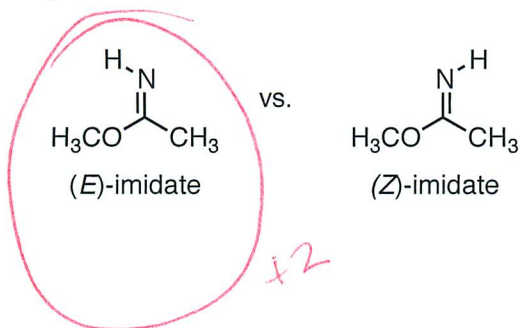


+1 if no stereochem or wrong stereochem.

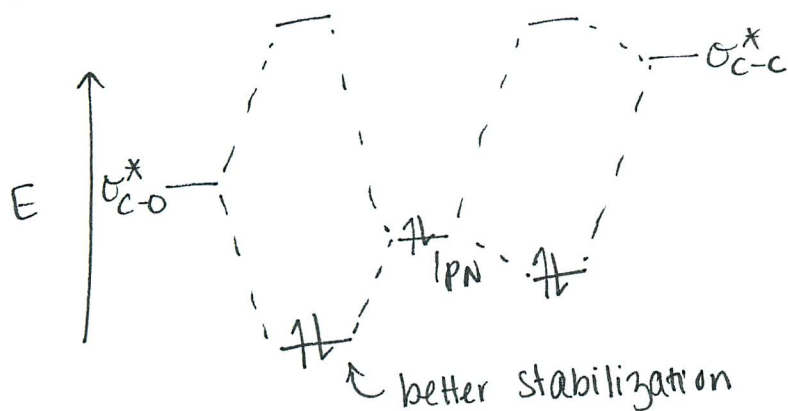
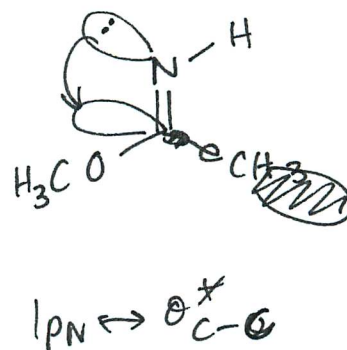
+2 if product not right.



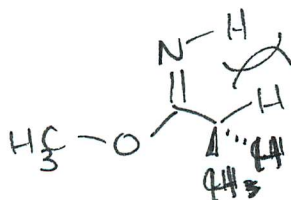
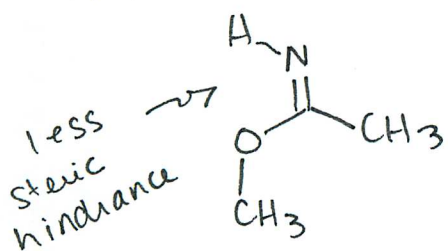
2. (8 points) Which configuration of the imide will be favored: *E* or *Z*? Please briefly, but clearly, rationalize your prediction.



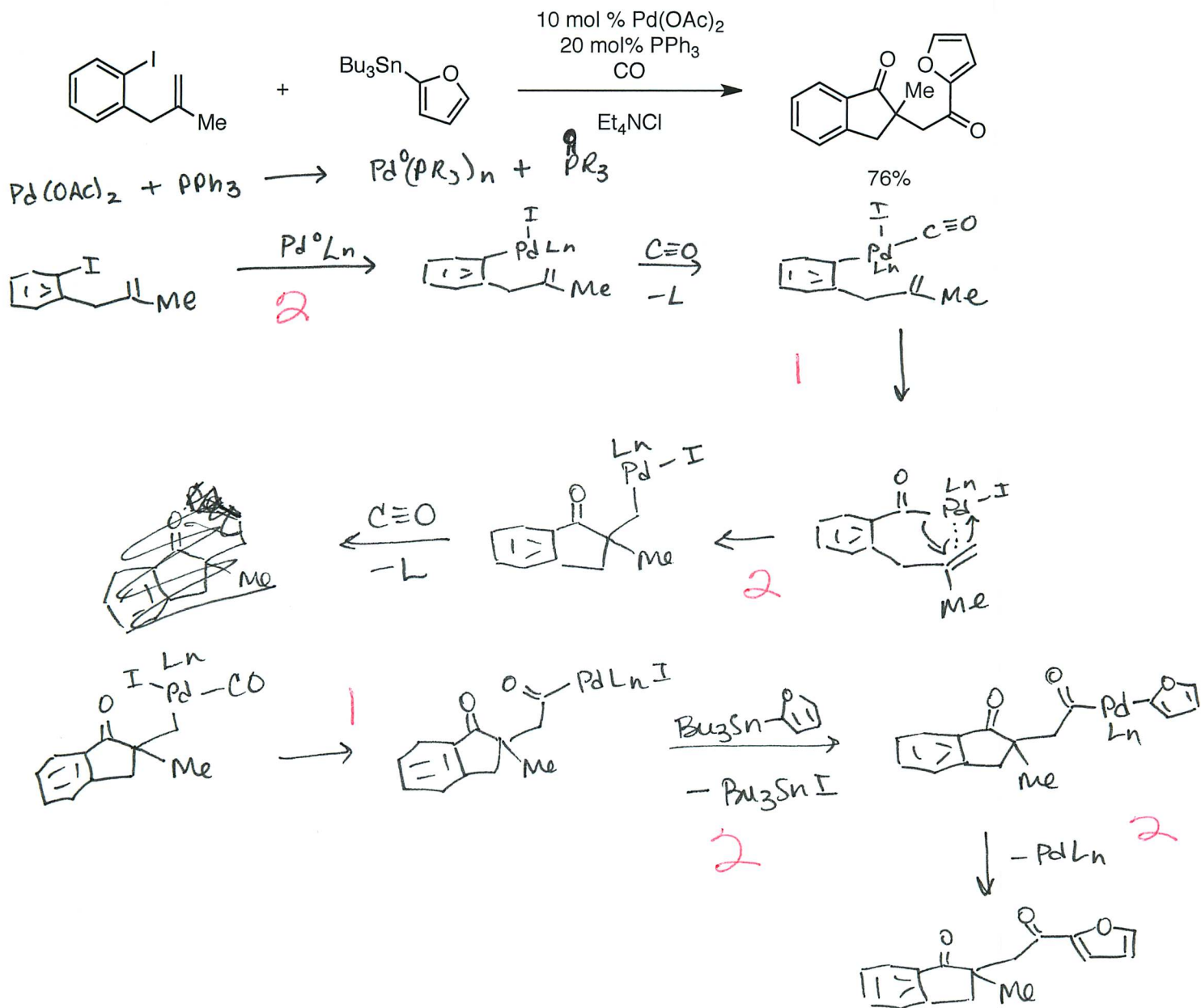
vs.



Also:

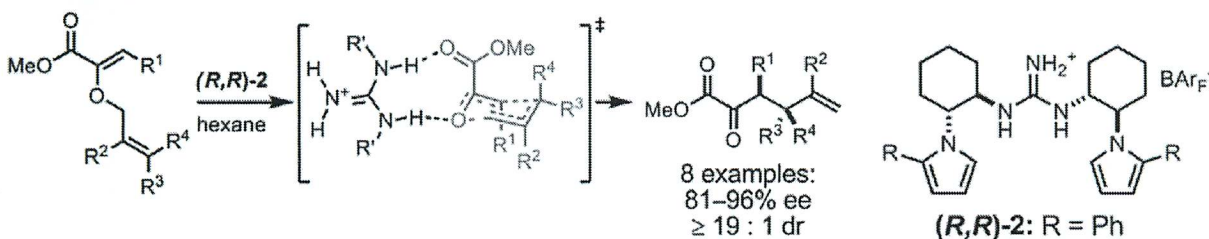


3. (10 points) Please draw a reasonable mechanism for the following transformation (Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, 35, 7661).



4 pts each.

4. (12 points) Jacobsen and Uyeda published the following enantioselective, guanidinium-catalyzed reaction (Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062).



(a) What type of rearrangement is this? Please characterize it as is appropriate for this reaction class.

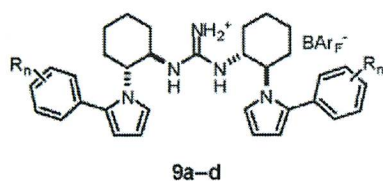
[3,3]-sigmatropic rearrangement (Claisen)

+ 2 for sigmatropic

(b) What types of interactions are shown between the guanidinium catalyst and the substrate in the transition state structure above?

Hydrogen-bonding

(c) The authors found that the enantioselectivity of the reaction depended on substituents on the catalyst, as shown in the table below. Please suggest a rationale for these results.



catalyst	catalyst substituent	exptl er ^a	exptl $\Delta\Delta G^\ddagger$ (kcal/mol) ^b
2	—	6.33 ± 0.05	1.15 ± 0.01
9a	R = 4-fluoro	5.05 ± 0.12	1.01 ± 0.01
9b	R = 4-dimethylamino	8.01 ± 0.20	1.29 ± 0.02
9c	R = 3,4,5-trifluoro	2.61 ± 0.01	0.597 ± 0.002
9d	R = 2,3,4,5,6-pentafluoro	3.80 ± 0.01	0.830 ± 0.001

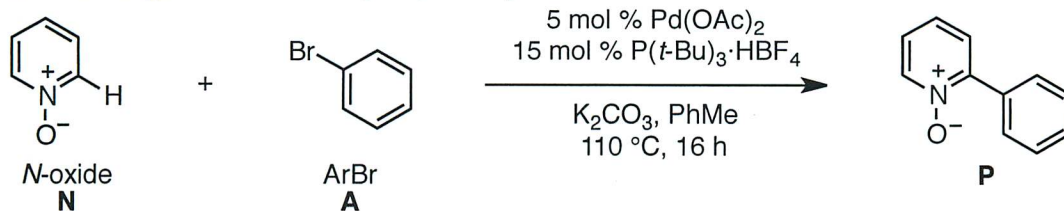
+ 3
cation- π interaction between Ar of catalyst + developing δ^+ of substrate.

More electron-rich π -systems \rightarrow better π -donors \rightarrow higher er.

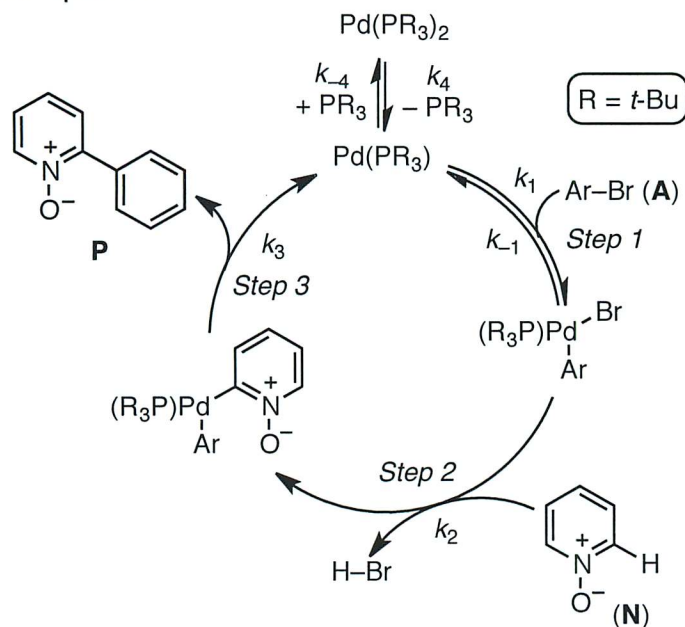
+ 1

3 pts each.

5. (24 points) Fagnou et al. developed an interesting arylation using pyridine *N*-oxides via C–H activation and undertook detailed mechanistic experiments to gain insight into how this reaction works (Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180).



(a) Below was the generally accepted mechanism for this transformation before Fagnou’s studies. Write a rate law for this catalytic cycle in “one plus” format, assuming Step 2 is rate-limiting and subsequent steps to regenerate Pd(PR₃) are fast and irreversible. You may also assume that steps prior to the rate-limiting step are rapid and reversible compared with the rate-limiting step. For now, assume that Pd(PR₃)₂ may be a catalytically relevant species.



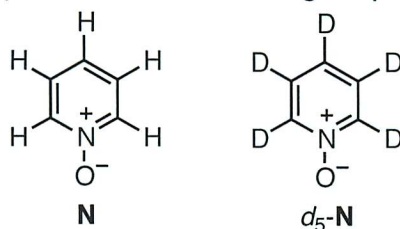
$$\text{rate} = \frac{k_1 k_2 [\text{Pd}]_T [\text{A}][\text{N}]}{1 + \frac{k_{-1}[\text{Ar}]}{k_1} + \frac{k_{-4}[\text{PR}_3]}{k_4}}$$

- 1/mistake.

OK if used Steady State.

(5 – continued)

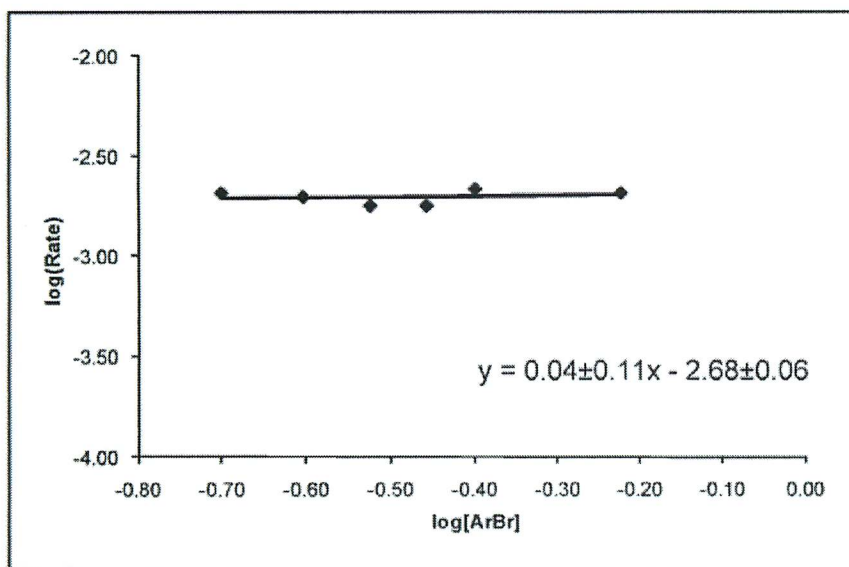
(b) Fagnou measured the relative rates of the reactions of **N** and d_5 -**N** and found $k_H/k_D = 3.3$. Is this consistent with Step 2 as the rate-limiting step? Please *briefly* explain.



Yes: Primary KIE consistent w/ rate-limiting C-H bond cleavage.

3pt.

(c) What do the following graphs tell you? Please note that these are log plots of the initial rate dependence on the concentrations of the various reactants.

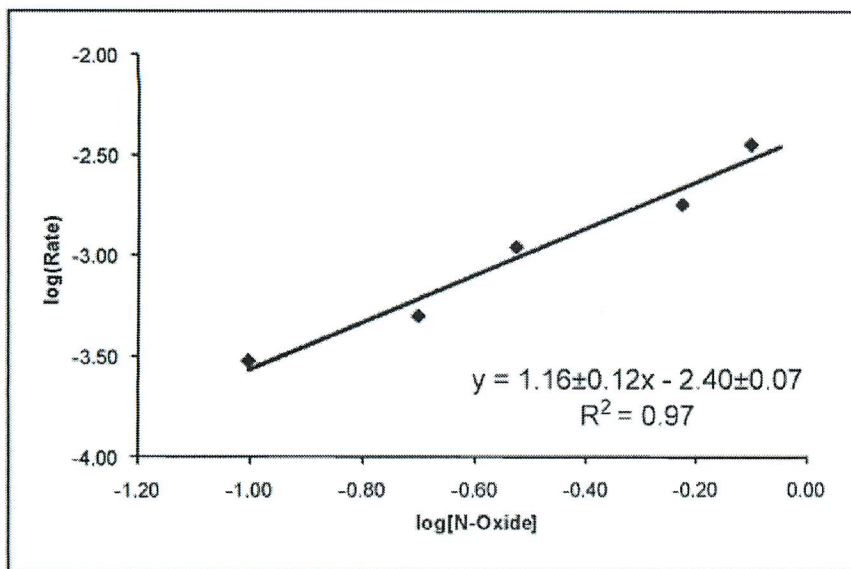


Zero order in [A]

1pt.

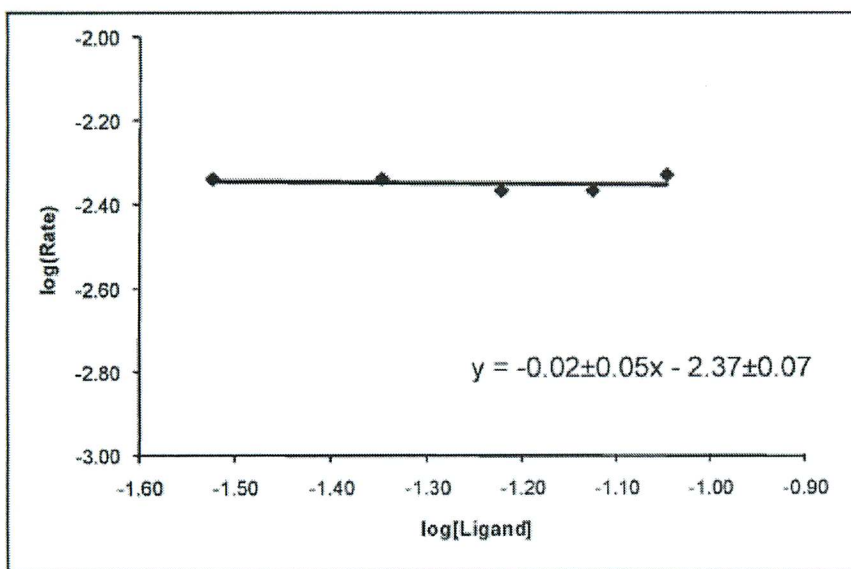
Initials: _____

(5c – continued)



First order in [N]

+1



Zero order in [PR₃]

x 0

(5 - still going)

+3

(d) Please simplify your proposed "one-plus" rate law in Part A to show that it is consistent with the data in Part B.

Only Catalyst resting state = oxidative addn pdt.

$$\text{rate} = \frac{k_1 k_2 [\text{Pd}]_T [\text{A}][\text{N}]}{1 + \frac{k_1 [\text{A}]}{k_{-1}} + \frac{k_{-2} [\text{PR}_3]}{k_4}} = \frac{k_1 k_2 [\text{Pd}]_T [\text{A}][\text{N}]}{\frac{k_1 [\text{A}]}{k_{-1}}} = k_{-1} k_2 [\text{Pd}]_T [\text{N}]$$

↑
1st order in N.
No rate dependence
on [A] or [PR₃]

-1/mistake

(e) Based on the data, what is the catalyst resting state? (No explanation is necessary.)

+3

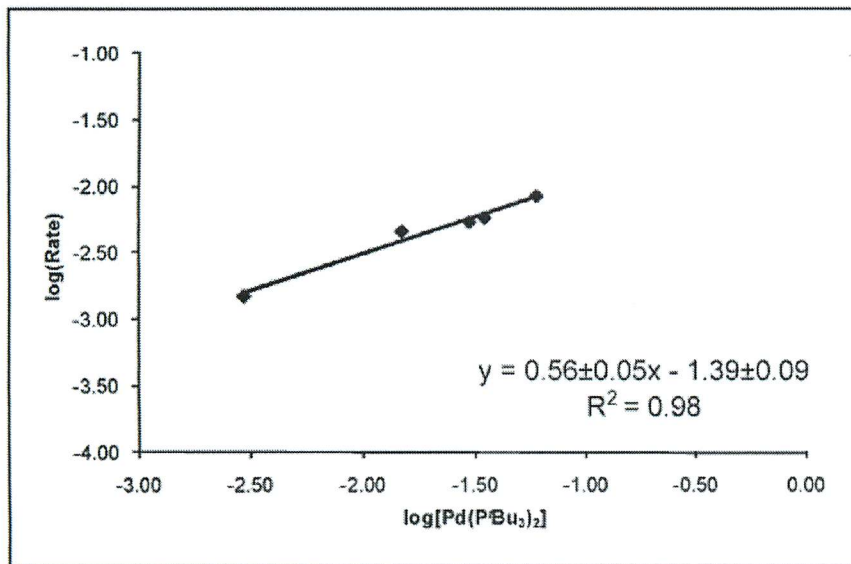


(all or nothing)

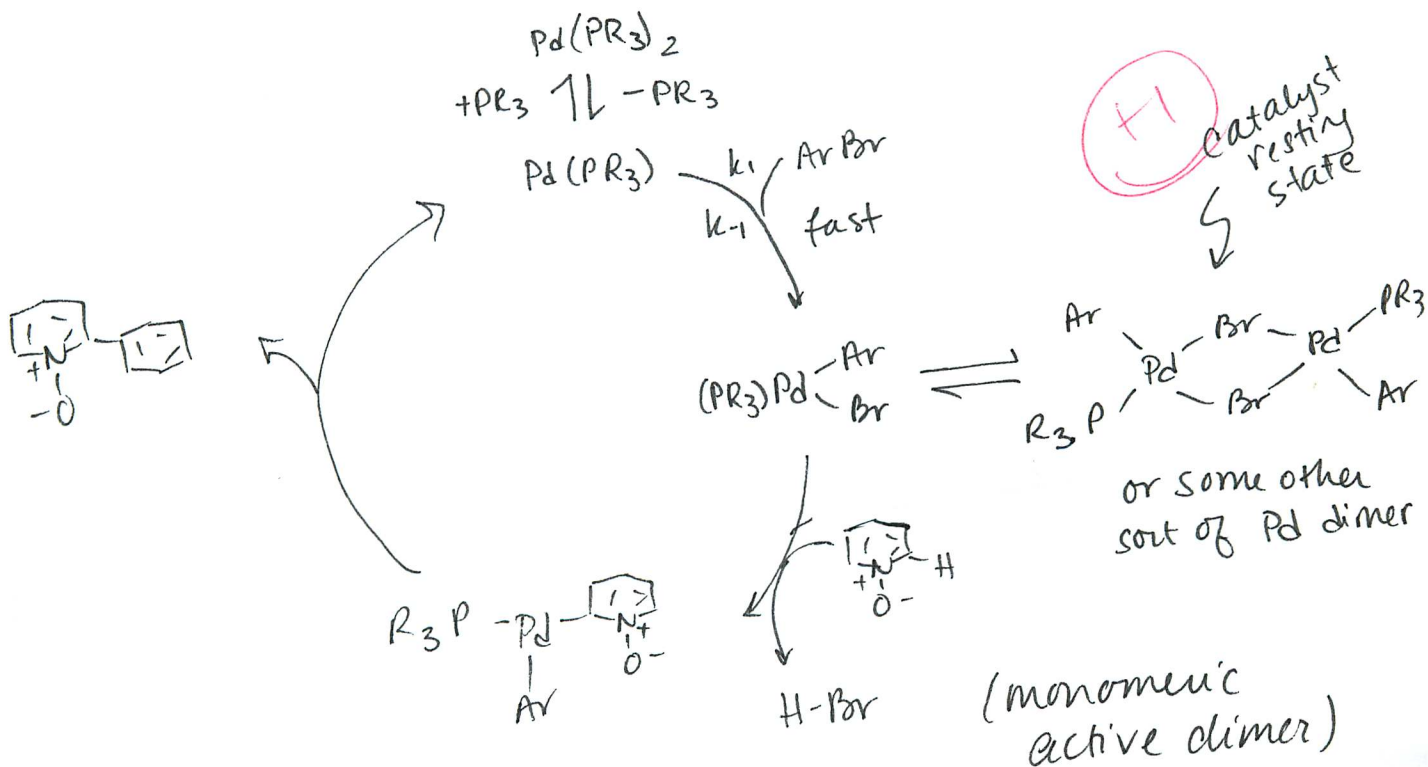
3 pts.

(5 - almost there)

(f) Fagnou also determined the initial rate dependence on the concentration of $\text{Pd}(\text{PR}_3)_2$ (shown in the following plot). What does this data tell you? Is it consistent with the proposed mechanism? If not, please provide a revised catalytic cycle that accounts for all data.

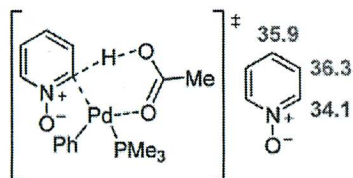


Slope ≈ 0.5 +1
 Half order in $[\text{Pd}]_T$
 Inconsistent +1



(5 – last bit)

(g) Fagnou went on to study the specifics of the C–H activation step (Step 2). Using computational and stoichiometric studies, he found that the bromide exchanges for acetate (OAc), and the acetate participates in the C–H activation via the transition state shown below. The numbers shown represent the computationally predicted energy barriers for C–H activation at each of the 3 sites of the aromatic ring. Based on these energies, **predict the ratio of the three regioisomers** you expect from this reaction.



Ortho C-H activation: $\Delta G^\ddagger = 34.1$ kcal/mol
 Meta C-H activation: $\Delta G^\ddagger = 36.3$ kcal/mol
 Para C-H activation: $\Delta G^\ddagger = 35.9$ kcal/mol

$\Delta \Delta G_{o-m}^\ddagger = 2.2$ kcal/mol

$\Delta \Delta G_{p-m}^\ddagger = 0.4$ kcal/mol

$R = 1.98$ cal/mol·K ≈ 2 cal/mol·K

$T = 110^\circ\text{C} = 383\text{K} \approx 400\text{K}$

$\frac{k_o}{k_m} = e^{\Delta \Delta G_{o-m}^\ddagger / RT}$

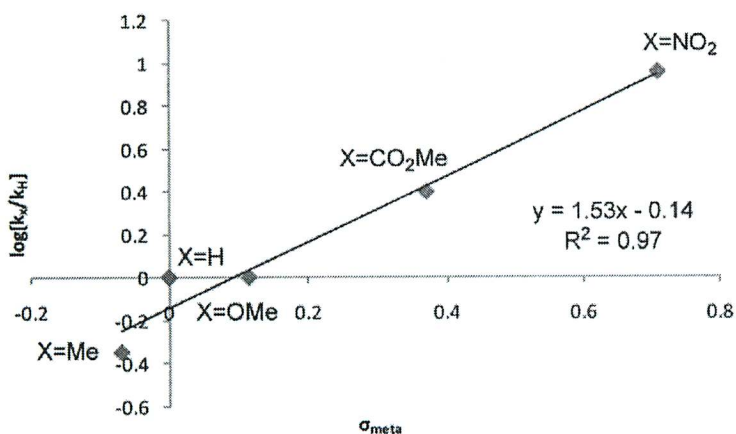
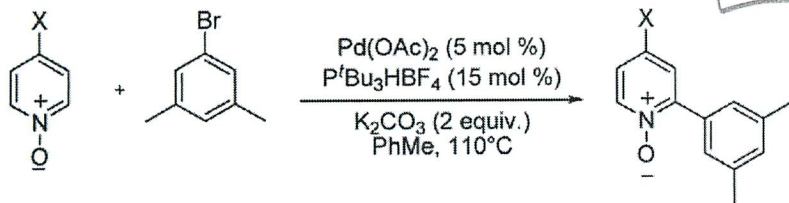
$\frac{k_p}{k_m} = e^{\Delta \Delta G_{p-m}^\ddagger / RT}$

$\frac{k_o}{k_m} = e^{(2200 \text{ cal/mol}) / (2 \text{ cal/mol}\cdot\text{K})(400 \text{ K})}$
 $\approx e^3 \approx 20$

$\frac{k_p}{k_m} = e^{(400 \text{ cal/mol}) / (2 \text{ cal/mol}\cdot\text{K})(400 \text{ K})}$
 $\approx e^{1/2} \approx 1.6$

$o:p:m \approx 20:1.6:1$

(h) What does the following data tell you?



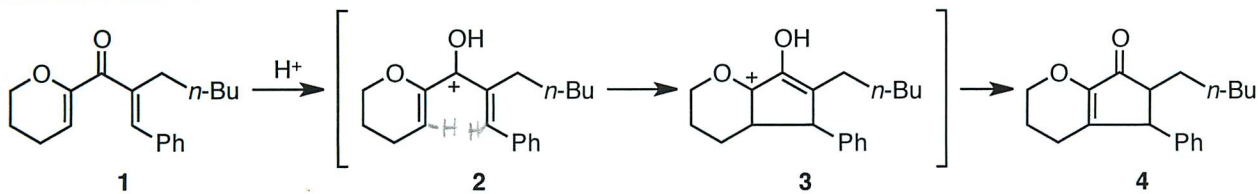
$\rho > 0$ (slope)



Build-up of negative charge in transition state of rate-limiting step.

x2

6. (16 points) (a) What type of reaction is the transformation of intermediate **2** to intermediate **3**?



x 2

electrocyclization (or electrocyclic ring closure)

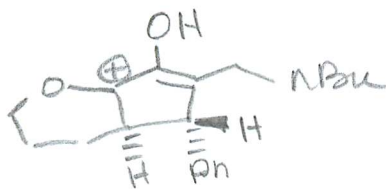
(b) Please characterize the transformation of **2** to **3**, as is appropriate for this type of reaction.

x 2

4e⁻

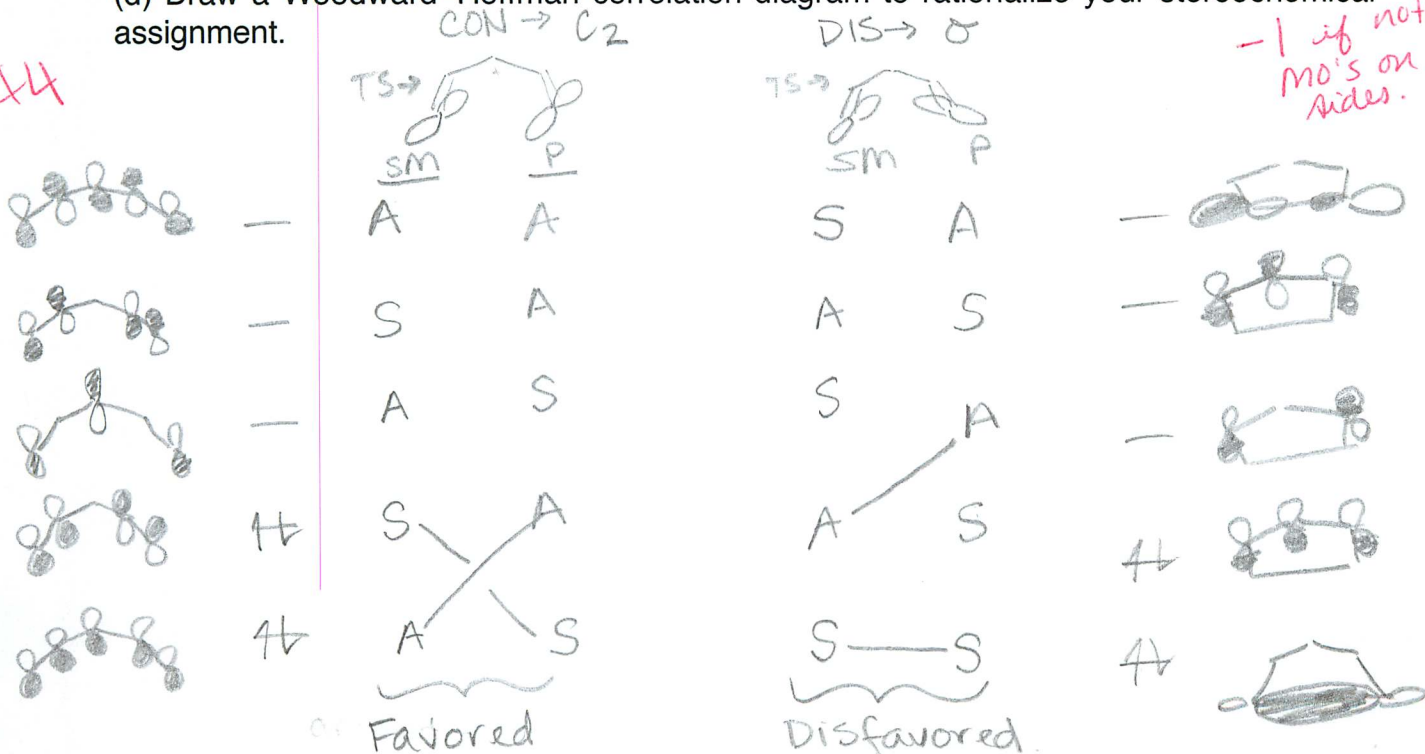
(c) Please clearly draw the stereochemistry of intermediate **3**. → conrotatory

x 4



(d) Draw a Woodward-Hoffman correlation diagram to rationalize your stereochemical assignment.

x 4

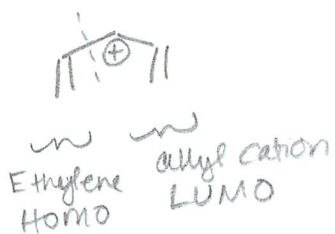


(6 – continued)

(e) Show that Fukui's Frontier Molecular Orbital Theory is also consistent with your stereochemical assignment.

Break SM into Homo + LUMO...

x4

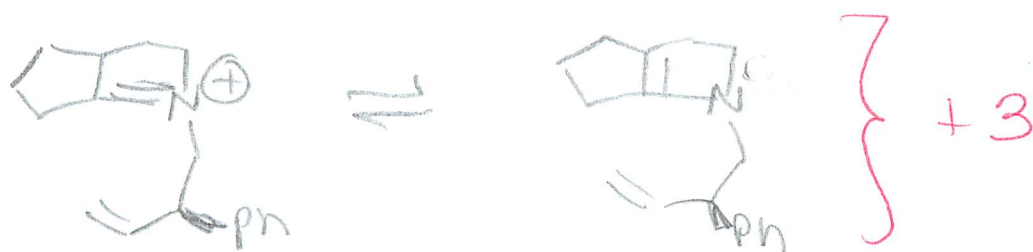


conrotatory ring closure → Net bonding.

(7 – continued)

(b) Despite using mixture of diastereomers of **1**, 99% ee of product **2** was obtained. Please rationalize this result.

Stereocenter epimerizes via enamine:



+4

cis is favored. +1

(c) Using clearly drawn, three-dimensional structures, rationalize the observed stereochemistry and olefin geometry of the product.

cis-5,5 is favored.

+4

