

Initials: _____

1

Name: Answer Key

**Chem 633: Advanced Organic Chemistry
Midterm 2**

Please answer the following questions *clearly and concisely*.

Write your answers in the space provided.

Write your initials on each page you want graded.

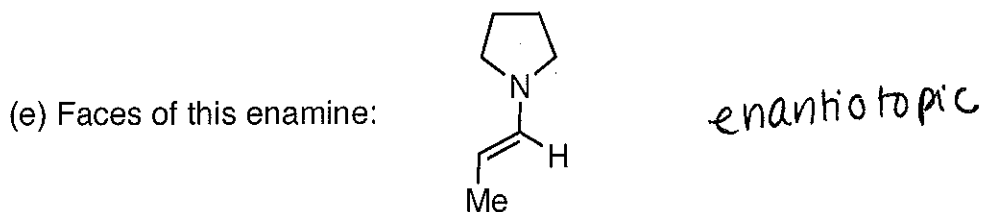
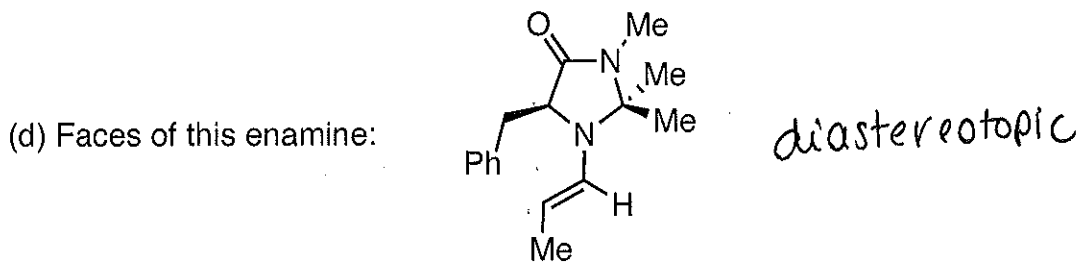
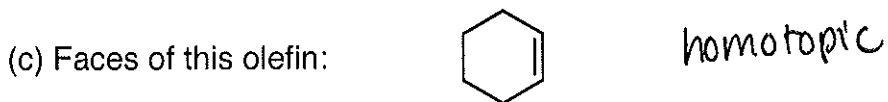
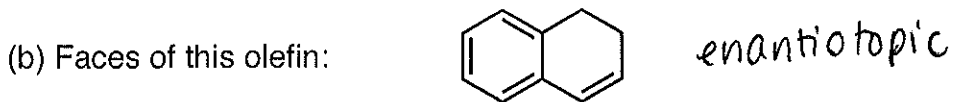
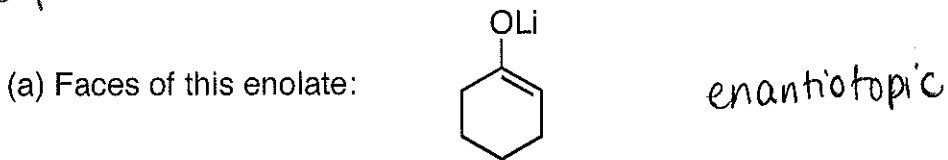
There are 15 total pages to this exam. Please be sure your copy has 15 pages before you begin.

Molecular models are allowed.

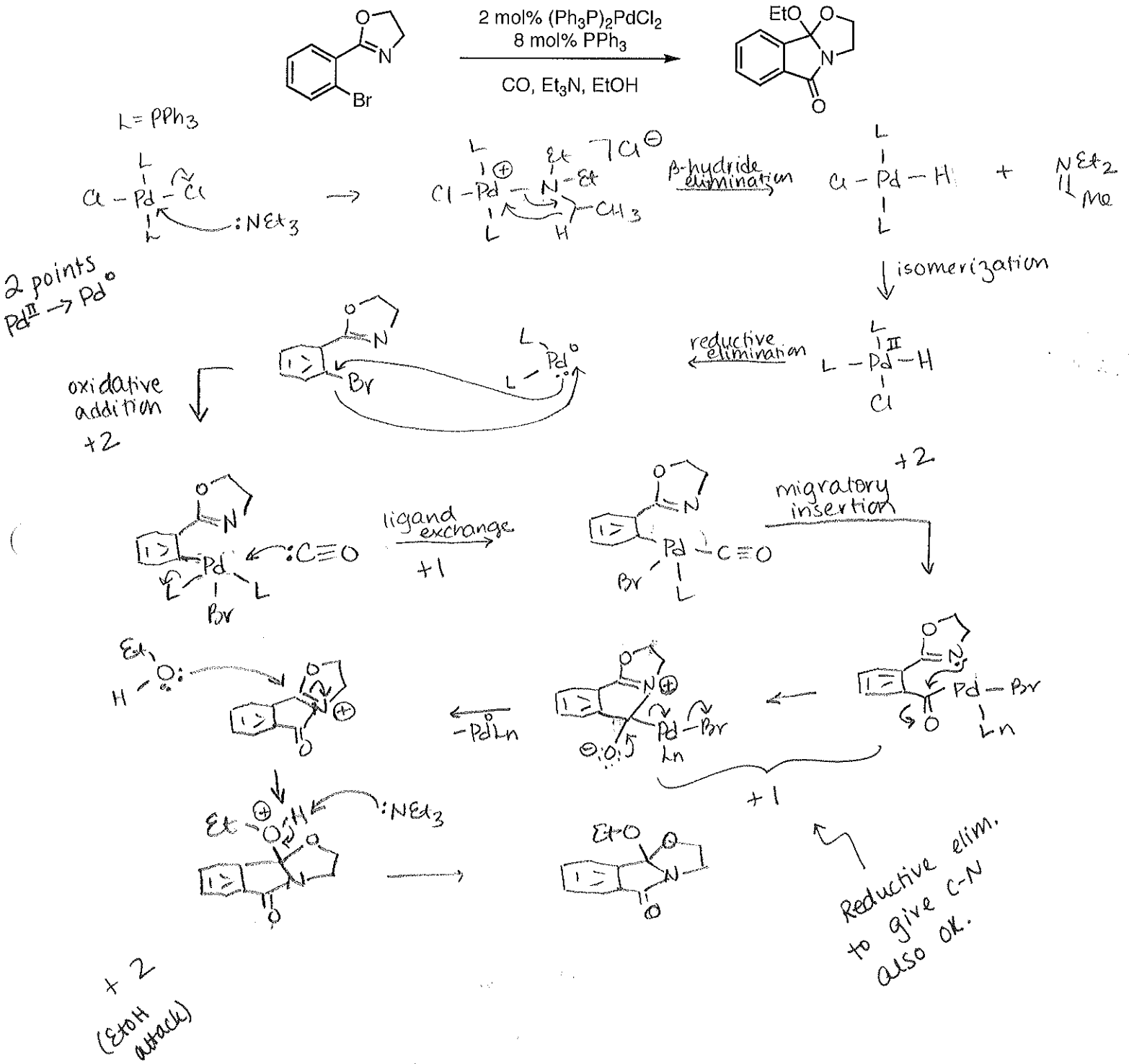
Calculators are unnecessary and prohibited.

Problem	Points	
1	<u>9</u> / 10	} Averages
2	<u>6</u> / 10	
3	<u>7</u> / 10	
4	<u>13</u> / 20	
5	<u>10</u> / 22	
6	<u>19</u> / 28	
TOTAL	<u>64</u> / 100	

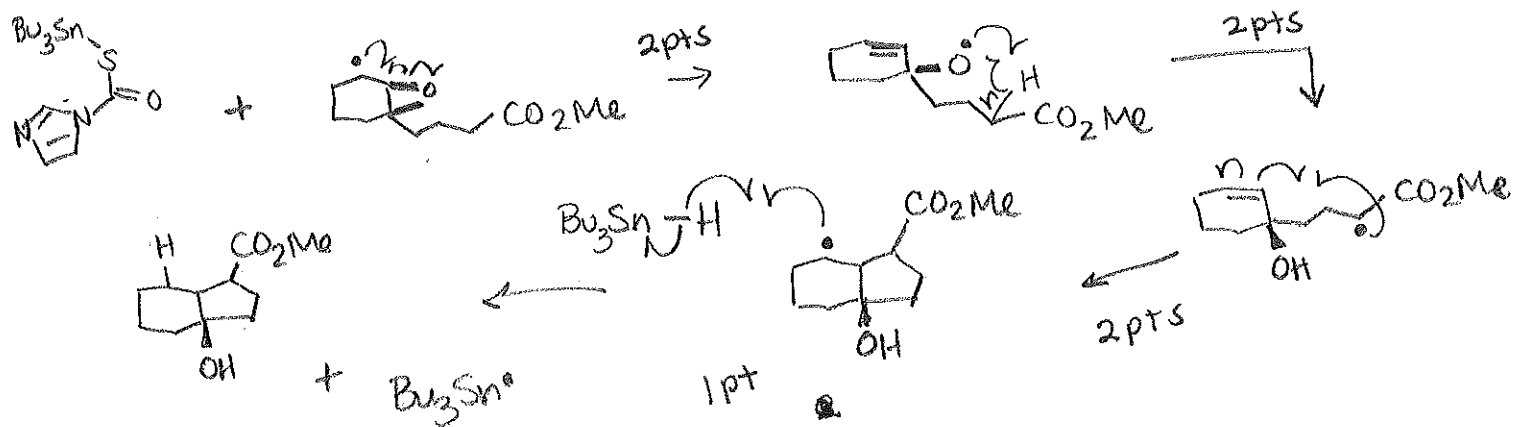
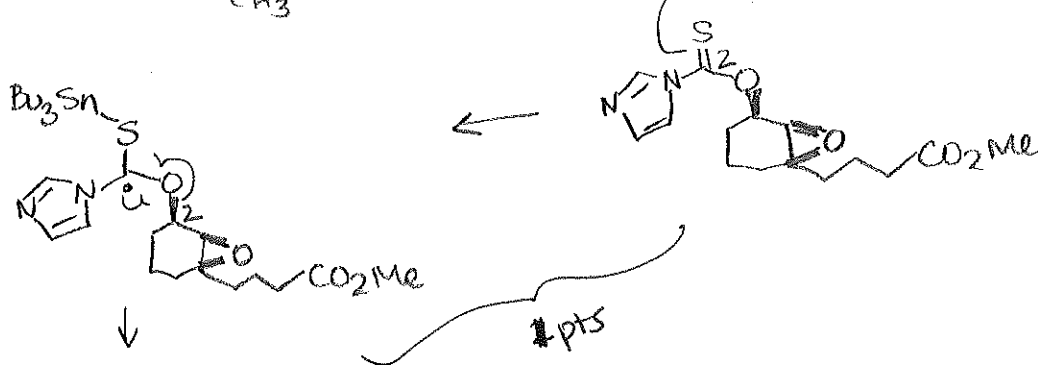
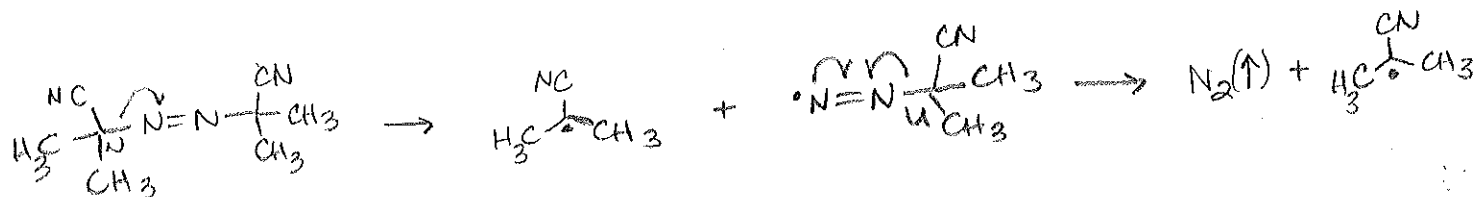
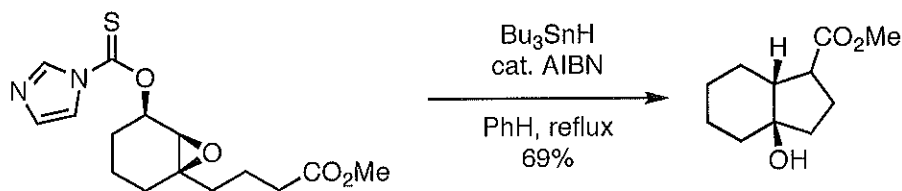
1. (10 points) Please state whether the following groups are homotopic, enantiotopic or diastereotopic. (No explanation necessary)
2 points each.



2. (10 points) Please draw a reasonable arrow-pushing mechanism for the following transformation (Grossman, p. 329).

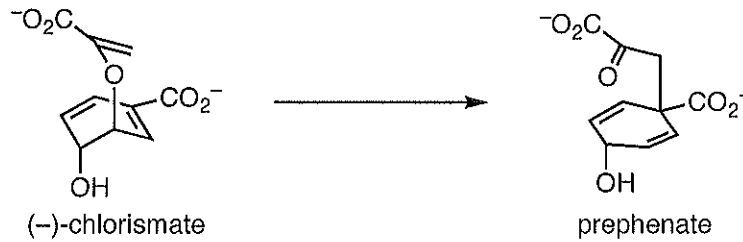


3. (10 points) Please draw a reasonable arrow-pushing mechanism for the following transformation (Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181).



1pt
 Awarded if quenched
 any radical
 w/ HSnBu3
 to generate SnBu3

4. (20 points) Please consider the rearrangement of (-)-chlorismate to prephenate in answering the following questions (Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* 1973, 12, 3492).



5 points

(a) Is this reaction endothermic or exothermic? (No explanation necessary)

exothermic

5 points

(b) Do you expect the transition state of this reaction to be early or late? (No explanation necessary)

early (Hammond Postulate)

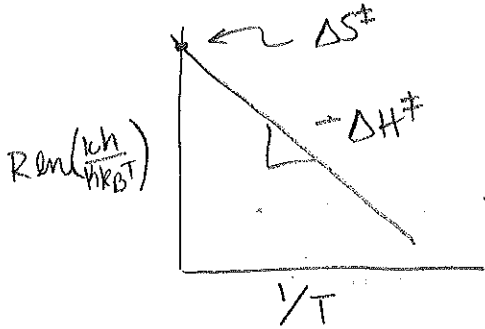
*Gave credit for correct answer based on (a).

5 points

(c) Explain how one can experimentally determine ΔH^\ddagger and ΔS^\ddagger of this process. Include all equations and graphs that are necessary for analyzing the data.

- ① Measure rate constant (k_{obs}) at various rxn temperatures.
- ② Plot $\ln\left(\frac{kh}{k_B T}\right)$ vs. $1/T$

+2



$$\ln\left(\frac{kh}{k_B T}\right) = -\frac{\Delta H^\ddagger}{T} + \Delta S^\ddagger$$

+3 (all or nothing)

5 points

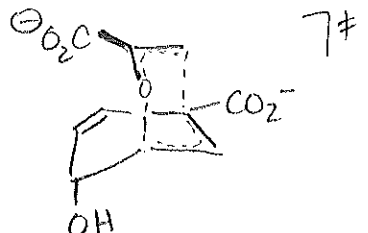
(d) The experimentally determined entropy of this rearrangement is given below. Provide an explanation of the magnitude and sign of entropy.

$$\Delta S^\ddagger = -12.9 \pm 0.4 \text{ e.u.}$$

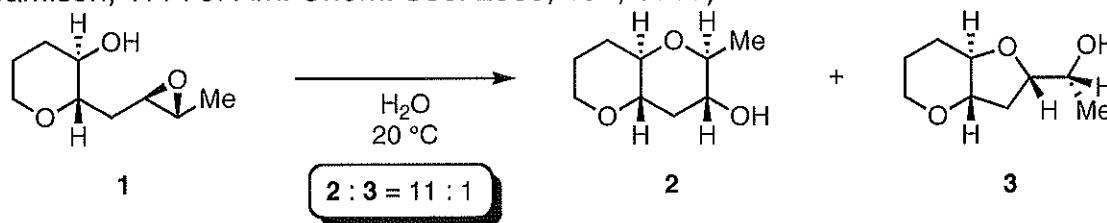
$\Delta S^\ddagger < 0 \Rightarrow$ TS is more ordered than GS +2

Consistent w/ 6-membered chair-like TS +1

Magnitude is not huge so GS has significant order (1 molecule \rightarrow 1 molecule) +2
 GS TS

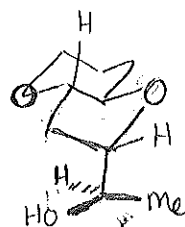
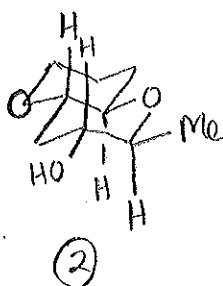


5. (22 points) As a model for highly regioselective epoxide-opening cascades that form ladder polyethers, Byers and Jamison examined the cyclization of epoxide **1** (Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383).



(a) Please draw clear 3-dimensional representations of the lowest energy conformations of **2** and **3**.

4 pts



2 pts each
 (can be wrong)
 (+1 if wrong enantiomer)

(b) The researchers compared the rates of this reaction in H_2O vs. D_2O and found that $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.33$. What does this suggest about the mechanism of this reaction? (Answer in less than 20 words.)

4 pts

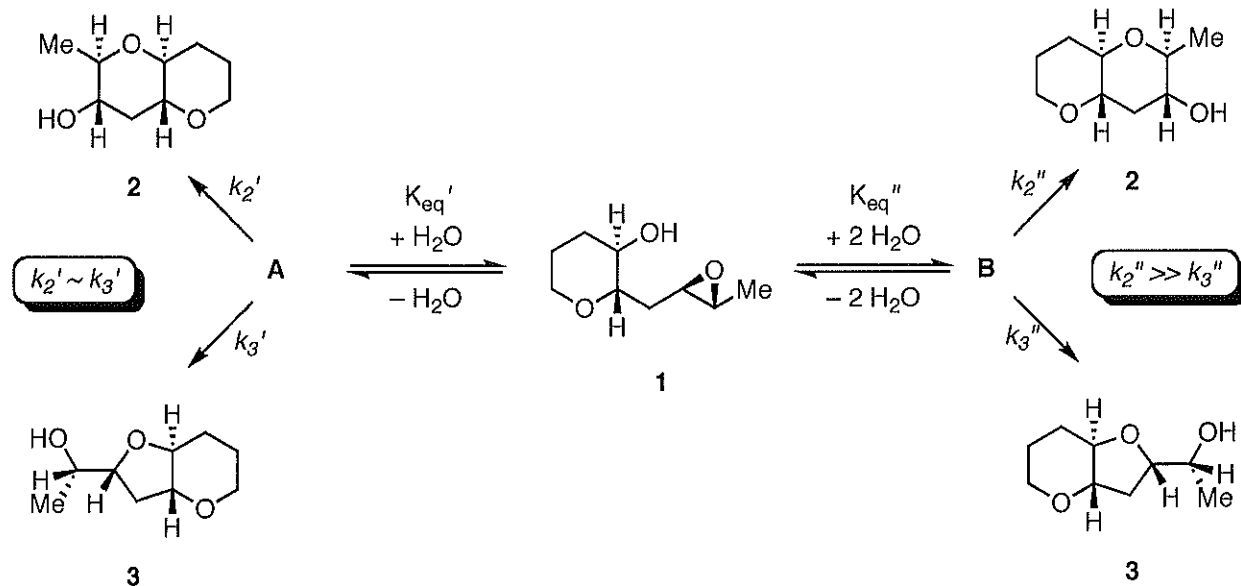
H-O (or D-O) bond of water partially broken in or before rate-determining step.

* Cannot rehybridize ~~H₂O~~ oxygen in H_2O .
 You needed to think about the reactivity of H_2O (not just memorize KIE ranges) to answer this question.

+1 if said breaking O-H/D bond.

(5 – continued)

(c) Jamison proposes that two pathways lead to products **2** and **3**, of which the pathway via intermediate **A** is unselective and the pathway via intermediate **B** is highly selective.



Derive rate laws for the formation of **2** and **3**. You may assume that the equilibrium between **1**, **A** and **B** is fast. Use the constants depicted in the scheme above. Express your rate laws in terms of **[1]** and **[H₂O]**.

4 pts

$$\text{rate}_2 = k_2' [A] + k_2'' [B]$$

$$\text{2 pts } \text{rate}_2 = k_2' K_{eq}' [1][H_2O] + k_2'' K_{eq}'' [1][H_2O]^2$$

$$K_{eq}' = \frac{[A]}{[1][H_2O]}$$

$$[A] = K_{eq}' [1][H_2O]$$

$$K_{eq}'' = \frac{[B]}{[1][H_2O]^2}$$

$$[B] = K_{eq}'' [1][H_2O]^2$$

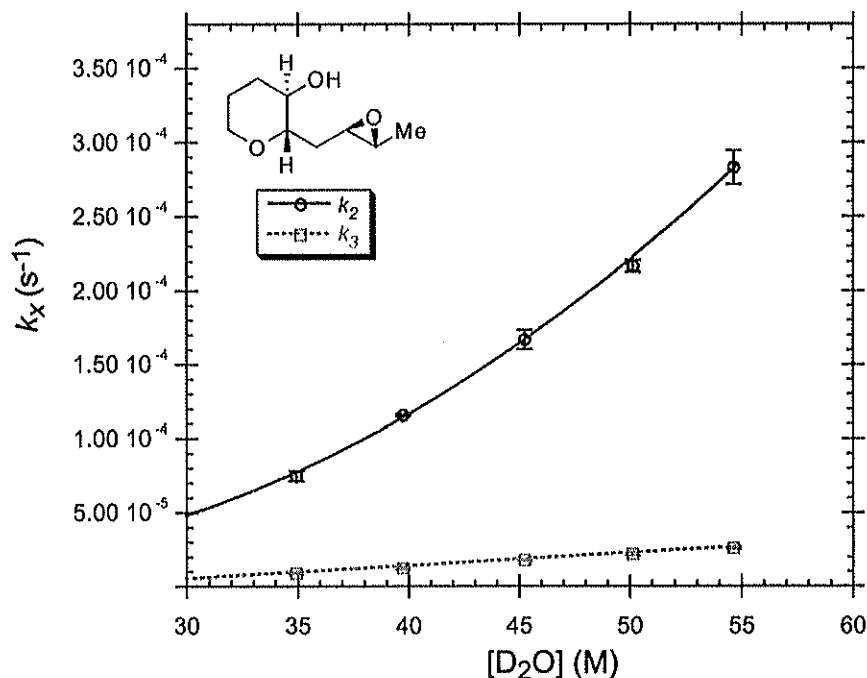
$$\text{rate}_3 = k_3' [A] + k_3'' [B]$$

$$\text{2 pts } \text{rate}_3 = k_3' K_{eq}' [1][H_2O] + k_3'' K_{eq}'' [1][H_2O]^2$$

negligible.

(5 – continued)

(d) This reaction could also be performed in DMSO with a large excess of D_2O relative to epoxide **1**. Under these conditions, the following data was collected. In these graphs, k_2 is the overall observed rate constant for the formation of **2**, and k_3 is the overall observed rate constant for the formation of **3**.



In the formation of **2**, what is the kinetic order in $[D_2O]$?

3pts

> 1st order

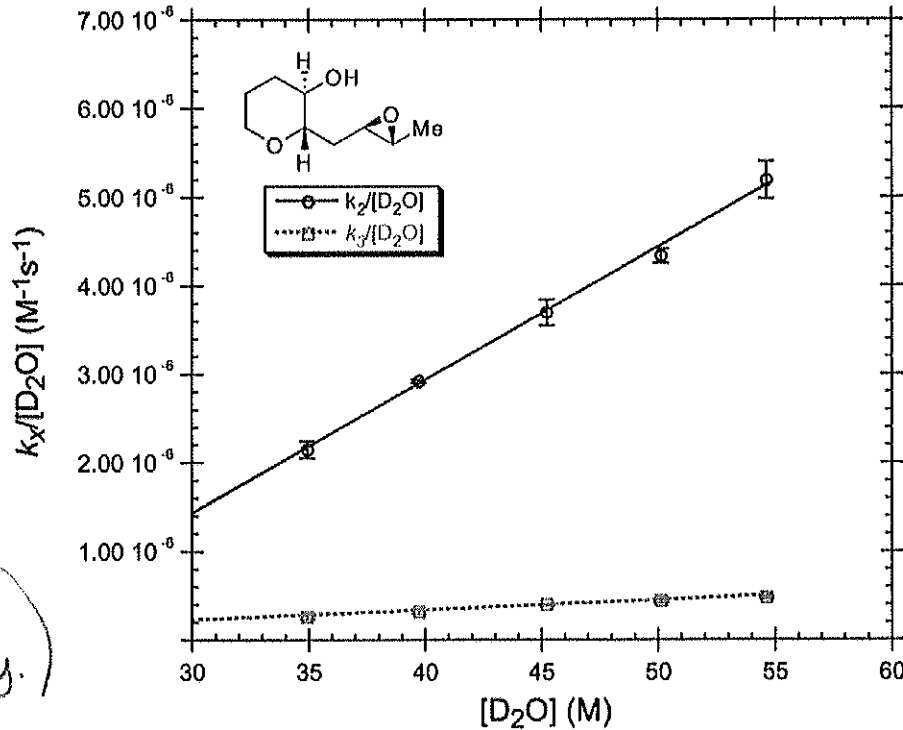
In the formation of **3**, what is the kinetic order in $[D_2O]$?

3pts

first order

(5 - continued)

(e) Please show that the linear behavior in the following graph is consistent with the rate laws you derived for Jamison's proposed mechanism.



4 pts

(H₂O / D₂O can be used interchangeably.)

from (c):

$$\text{rate}_2 = k_2' K_{eq}' [I][H_2O] + k_2'' K_{eq}'' [I][H_2O]^2$$

$$\text{rate}_2 = (k_2' K_{eq}' [H_2O] + k_2'' K_{eq}'' [H_2O]^2) [I] = k_2 [I]$$

$$\frac{k_2}{[H_2O]} = \frac{k_2' K_{eq}' [H_2O] + k_2'' K_{eq}'' [H_2O]^2}{[H_2O]}$$

$$\boxed{\frac{k_2}{[H_2O]} = \underbrace{k_2' K_{eq}'}_{\text{y-intercept}} + \underbrace{k_2'' K_{eq}'' [H_2O]}_{\text{slope}}}$$

} linear equation
+1 if $\frac{\text{rate}}{[H_2O]}$ 2pts

$$\text{rate}_3 = k_3' K_{eq}' [I][H_2O] + k_3'' K_{eq}'' [I][H_2O]^2$$

$$k_3 = k_3' K_{eq}' [H_2O] + k_3'' K_{eq}'' [H_2O]^2$$

$$\boxed{\frac{k_3}{[H_2O]} = k_3' K_{eq}' + k_3'' K_{eq}'' [H_2O]}$$

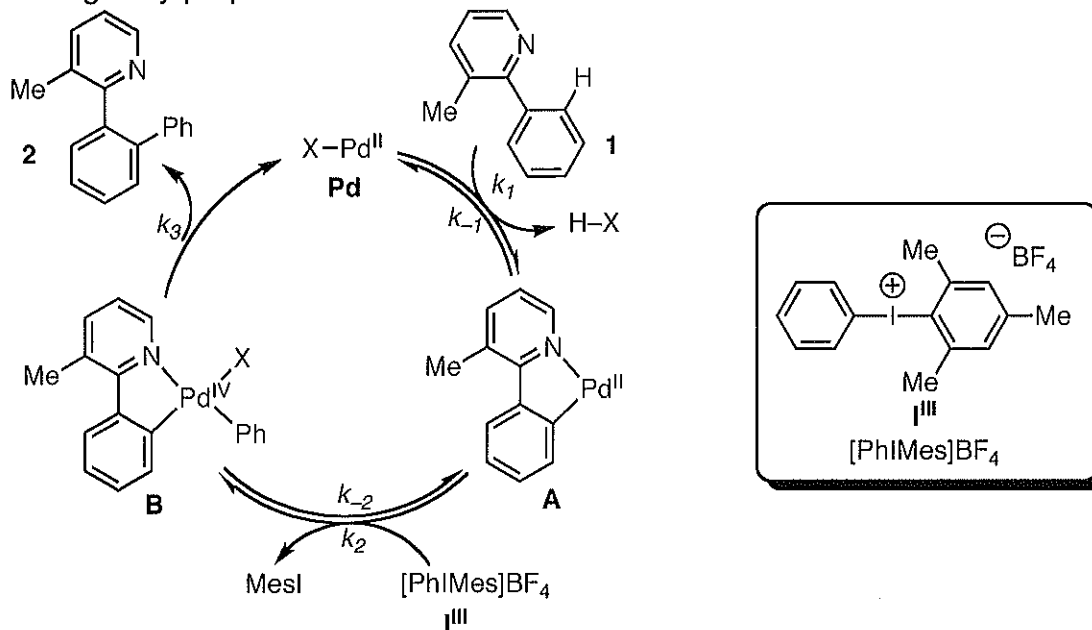
} linear equation
+1 if $\frac{\text{rate}}{[H_2O]}$ 2pts

Note: Difference in slopes reflects $k_2'' \gg k_3''$

4 points each

6. (28 points) Deprez and Sanford have recently reported the careful mechanistic study of the palladium-catalyzed C–H arylation reaction (Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234).

(a) The originally proposed mechanism for this reaction is shown below.



Please write a “one plus” catalytic rate expression for this catalytic cycle. You may use generic observable constants for each of the terms in the rate law (C_1 , C_2 , etc.).

4pts

$$\text{rate} = \frac{C_1 C_2 k_3 [\text{Pd}]_{\text{total}} [1] [\text{I}^{\text{III}}]}{1 + C_1 [1] + C_1 C_2 [1] [\text{I}^{\text{III}}]} \quad -1/\text{mistake}$$

(b) Assuming that the second step ($\text{A} \rightarrow \text{B}$) is rate-limiting and all subsequent steps to regenerate Pd are rapid and irreversible, write a simplified “one plus” catalytic rate expression. Use the rate constants depicted in the catalytic cycle above, and assume that any steps prior to the rate-limiting step are rapid and reversible compared with the rate-limiting step. Express your rate law in terms of $[1]$, $[\text{I}^{\text{III}}]$, and $[\text{Pd}]_{\text{total}}$.

4pts

$$\text{rate} = \frac{k_2 \left(\frac{k_1}{k_{-1} [\text{HX}]} \right) [1] [\text{Pd}]_{\text{total}} [\text{I}^{\text{III}}]}{1 + \left(\frac{k_1}{k_{-1} [\text{HX}]} \right) [1]}$$

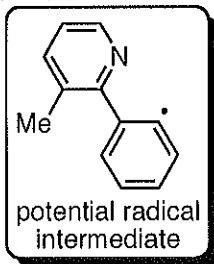
-1/mistake

(-2 for not defining C_1)

(6 - continued)

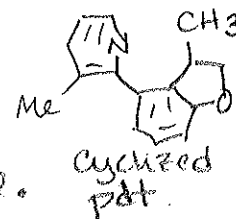
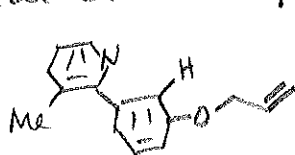
4 points

(c) The authors wondered if this reaction proceeds via a radical intermediate. Please propose 2 experiments to test for the existence of such an intermediate.



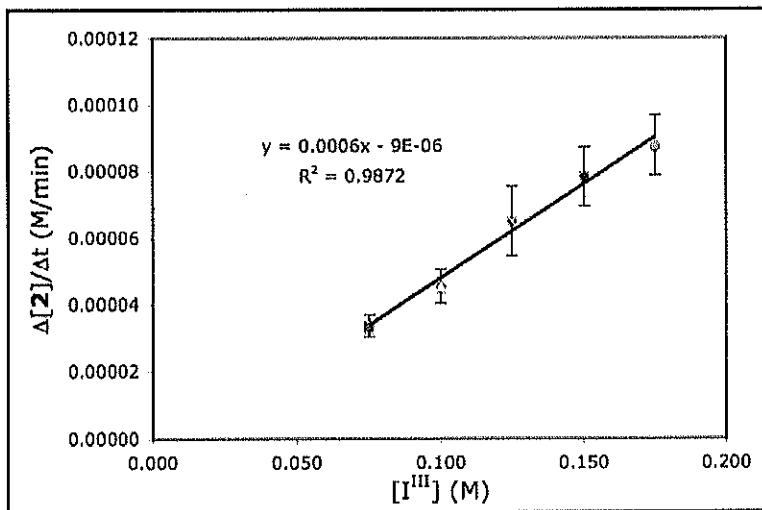
1) Radical Clock Experiment:

+2 Use
(+1 if didn't show substrate)
If it cyclizes, radical is intermediate.



+2 2) Radical trap: Add radical trap. If rxn doesn't work, radical intermediates may be involved.

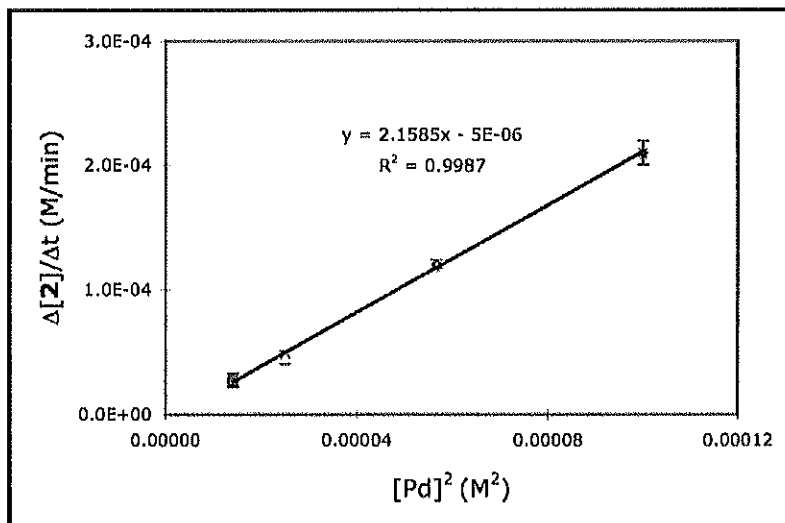
(d) Using initial rate experiments, the following correlations between rate and the concentrations of I^{III} , Pd, and 1 have been determined. Please state the rate dependence (first order, second order, etc.) on each of these species.



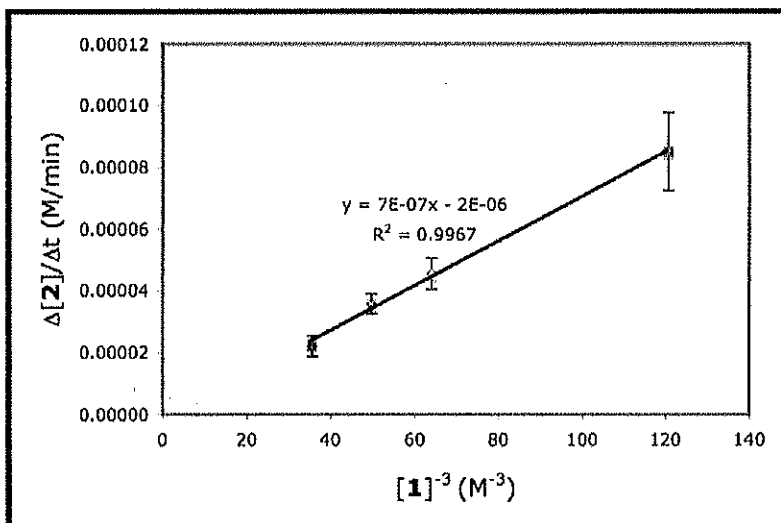
1st order in [I^{III}]

2 pts.

(6d – continued)



2nd order in [Pd]
(1 pt)

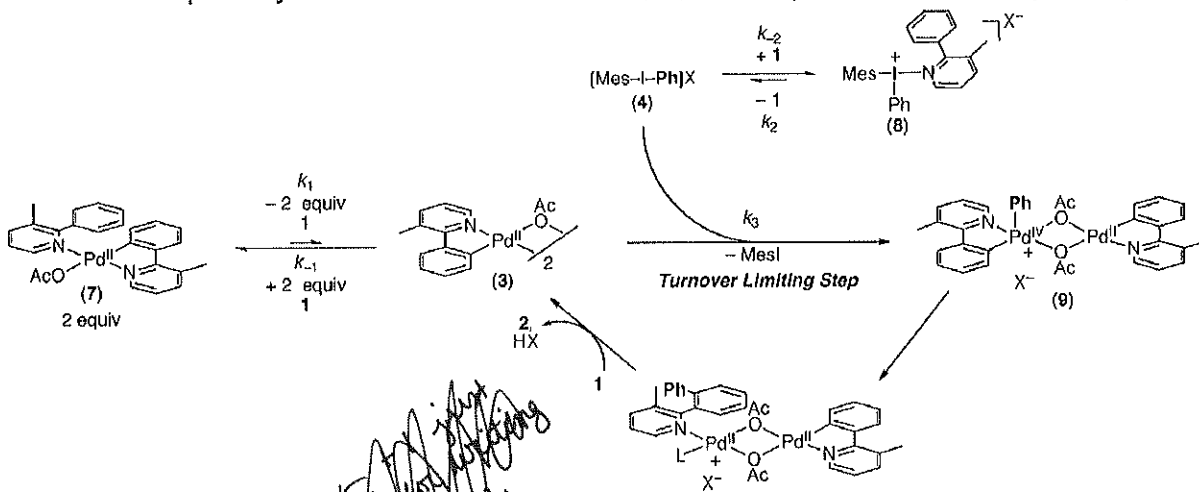


Inverse 3rd order
in [I]
(1 pt)

(6 – continued)

(e) Based on these results and the observation that **7** was the catalyst resting state and **8** was the iodine resting state, Sanford proposed a new mechanism for this reaction (shown below). **Write a rate law for this transformation.** You may assume any steps prior to the rate-limiting (or turnover limiting) step are rapid and reversible compared with the rate-limiting step and that subsequent steps to regenerate **3** are rapid and irreversible. Express your rate law in terms of **7**, **8**, and **1** (the observable species).

4 points



~~Handwritten scribbles~~

rate = $k_3 [3][4]$

$$K_{eq1} = \frac{[3][1]^2}{[7]^2} = \frac{k_1}{k_{-1}}$$

$$[3] = \frac{k_1 [7]^2}{k_{-1} [1]^2}$$

$$K_{eq2} = \frac{[4][1]}{[8]} = \frac{k_2}{k_{-2}}$$

$$[4] = \frac{k_2 [8]}{k_{-2} [1]}$$

$$\text{rate} = \frac{k_1 k_2 k_3 [7]^2 [8]}{k_{-1} k_{-2} [1]^3}$$

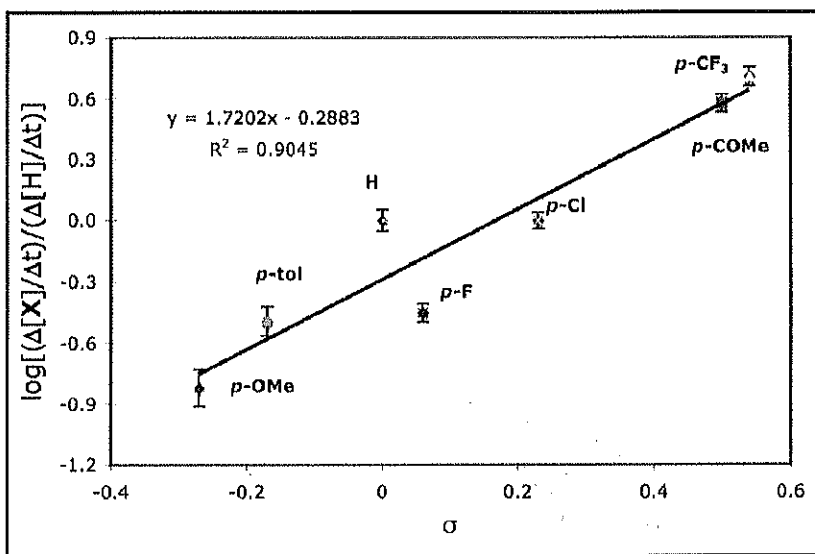
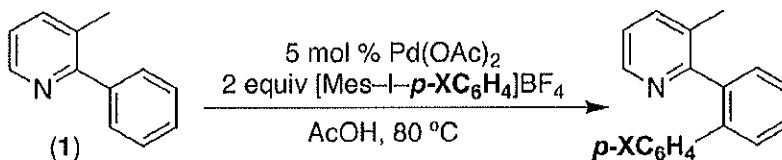
↳ 2nd order in $[7] = [Pd]$
 1st order in $[8] = [I^{III}]$
 Inverse 3rd order in $[1]$ ✓

-1/mistake
 (gave 1 pt if wrote
 rate = $k_3 [3][4]$ but
 did not get to
 right rate equation.)

(6 – continued)

(f) The authors also performed a Hammett study with substituted iodonium reagents in place of I^{III} . What does the following data tell you?

4 pts



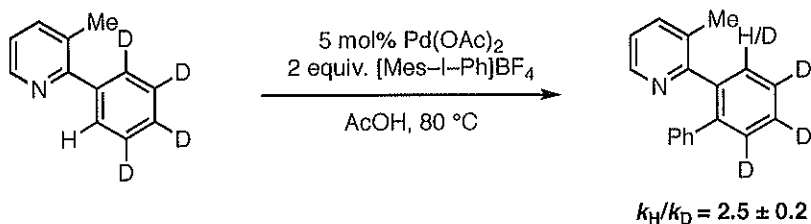
Slope = ρ is positive \Rightarrow Build-up of negative charge in TS.
 Rxn accelerated by electron-withdrawing groups on the iodine reagent.

(6 – continued)

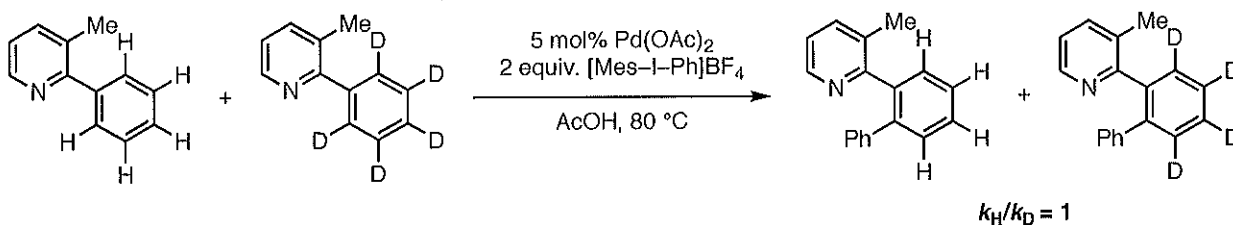
4 points

(g) In a final set of experiments, the authors performed isotope effect experiments. Why are the isotope effects different in these two experiments? (Answer in less than 20 words.)

Experiment 1



Experiment 2



Expt 1 = intramolecular KIE
 Expt 2 = intermolecular KIE] 2 points

2 pts [C-H/D cleaved after rate-determining step.
 undetectable by intermol. KIE expt,
 but detectable by intramol KIE expt.