

Initials: \_\_\_\_\_

1

Name: Answer Key

**Chem 633: Advanced Organic Chemistry 2011 ... Midterm 2**

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 16 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 16 pages before you begin.

Molecular models are allowed.

Calculators are unnecessary and prohibited.

Problem	Points	
1	<u>11</u> / <del>10</del> - 15	(Averages in red)
2	<u>6</u> / <del>18</del> - 10	
3	<u>9</u> / <del>6</del> - 10	
4	<u>9</u> / <del>6</del> - 15	
5	<u>19</u> / <del>10</del> - 25	
6	<u>14</u> / <del>10</del> - 25	
<b>TOTAL</b>	<u>68</u> / 100	

ST DEV = 13

Initials: Key

1. (15 points) Please state whether the following groups are homotopic, enantiotopic or diastereotopic. (No explanation is necessary.)

(a) Faces of this olefin:



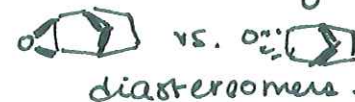
Diastereotopic



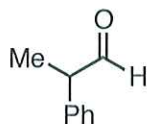
(b) Faces of this olefin:



Enantiotopic

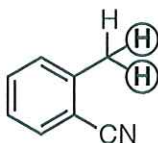


(c) Faces of this aldehyde:



Diastereotopic

(d) Circled hydrogens:

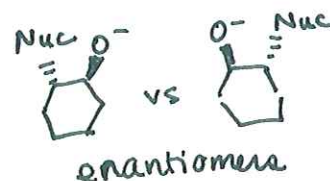


Homotopic

(e) Noted carbons of this epoxide:



Enantiotopic

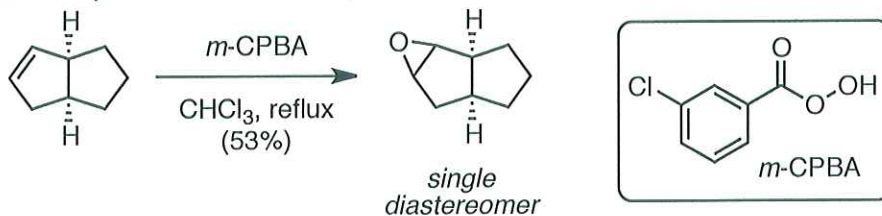


(3 pts each)

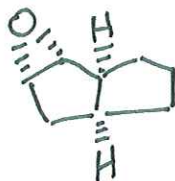
Initials: Key

3

2. (10 points) (a) Only one diastereomer is formed in the following epoxidation (Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294). Please predict the stereochemistry of the product and clearly draw the predicted diastereomer.

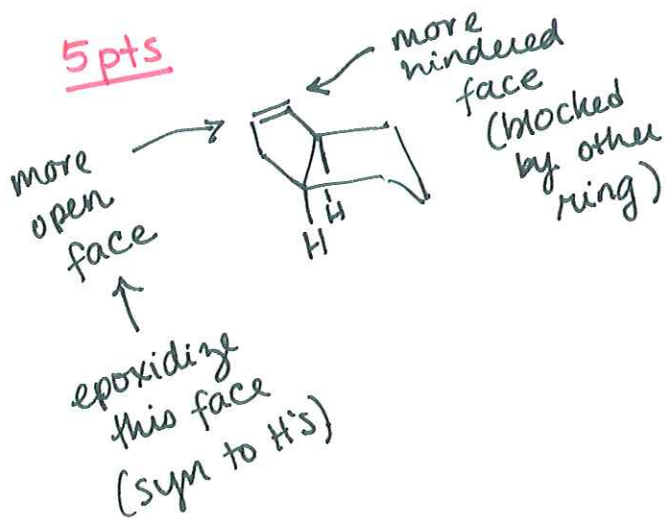


5 pts



(b) Using clearly drawn pictures and few words, explain your prediction in part (a).

5 pts



4 pts for product stability argument.

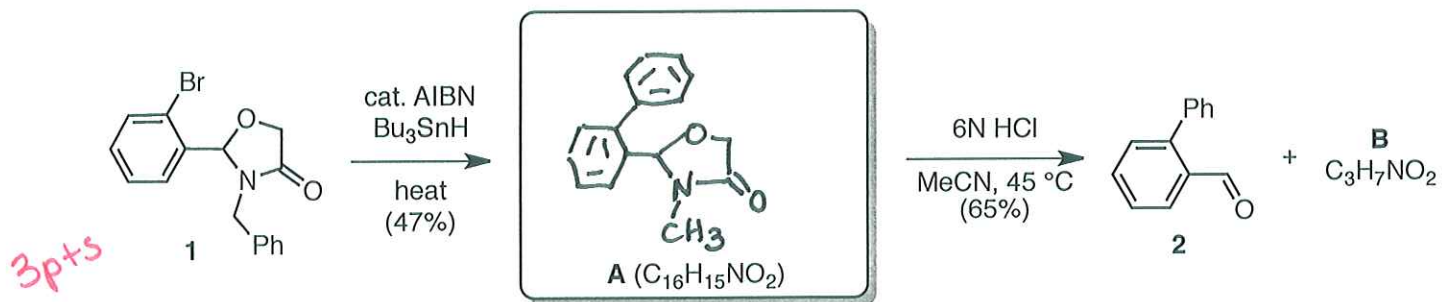
1 pt for wrong answer but ok picture.



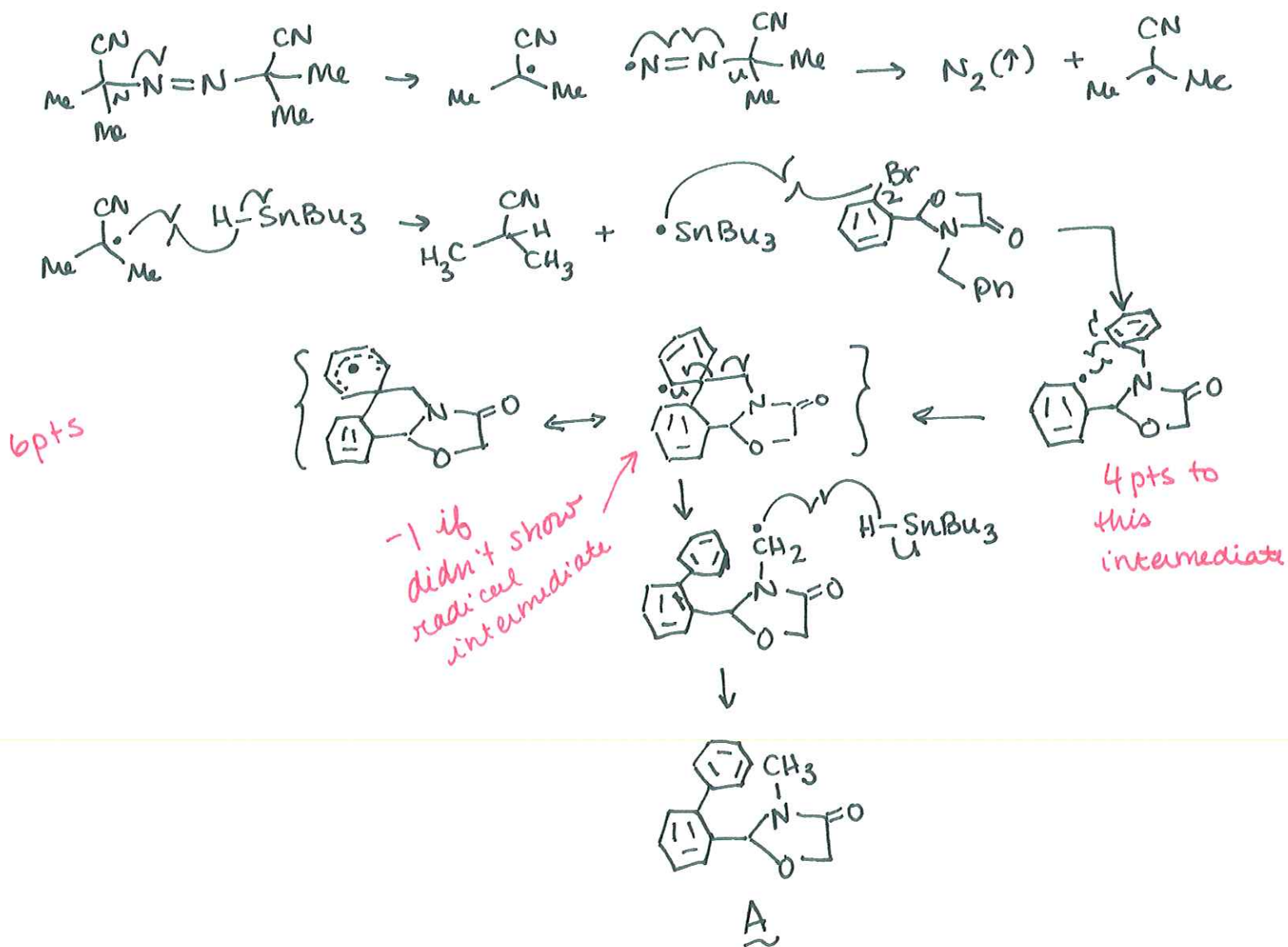
Initials: \_\_\_\_\_

5

4. (15 points) 5 (a) Please propose a structure for **A** in the following scheme (Giraud, L.; Lacote, E.; Renaud, P. *Helv. Chim. Acta* **1997**, *80*, 2148).



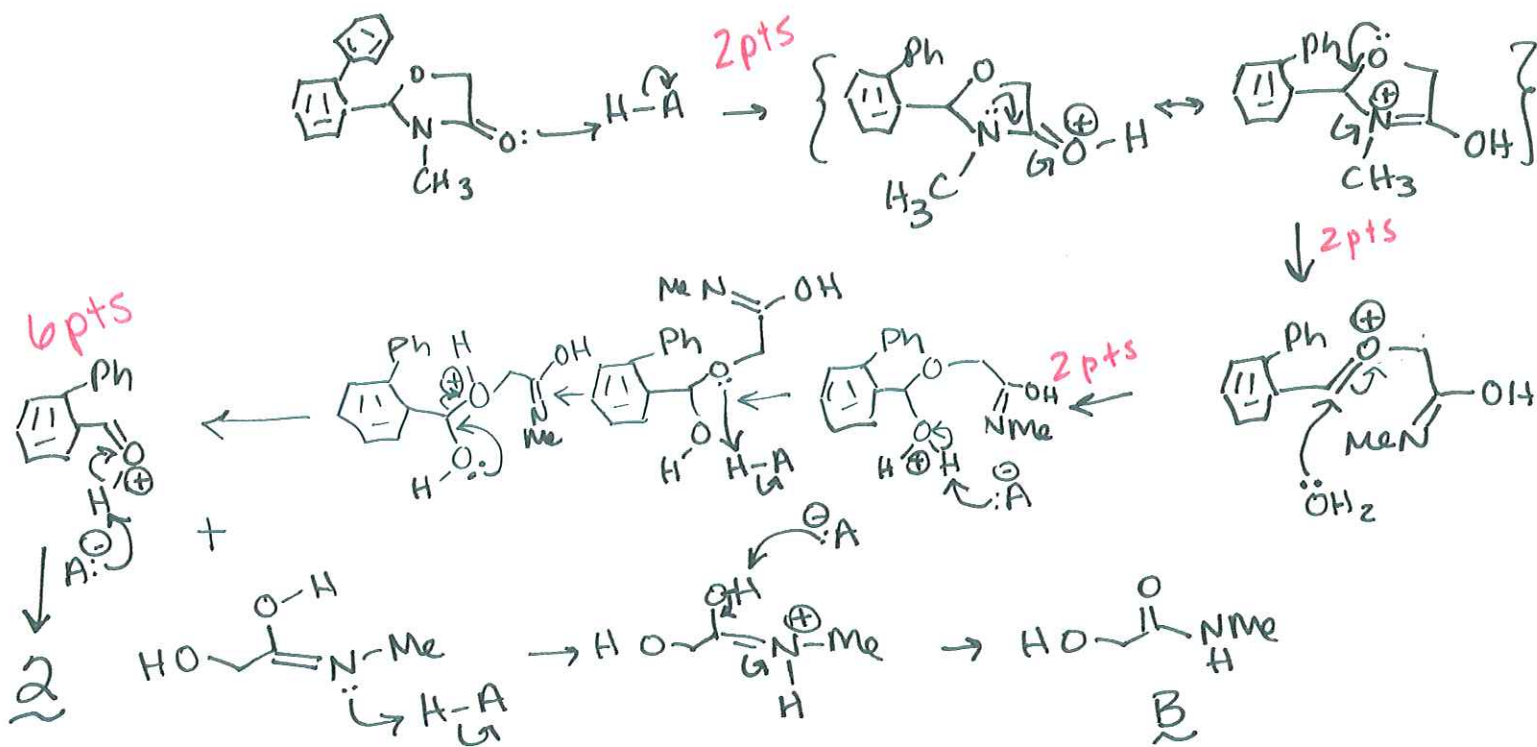
(b) Please propose a reasonable arrow-pushing mechanism for the transformation of **1** to **A**.



Initials: \_\_\_\_\_

(4 - continued)

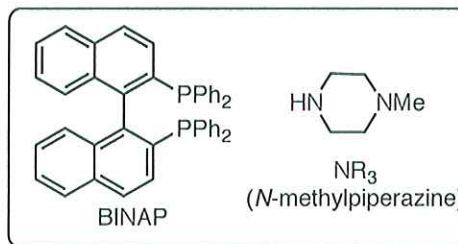
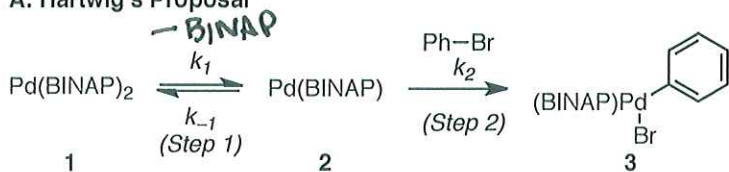
(c) Please propose a reasonable arrow-pushing mechanism for the transformation of A to 2.



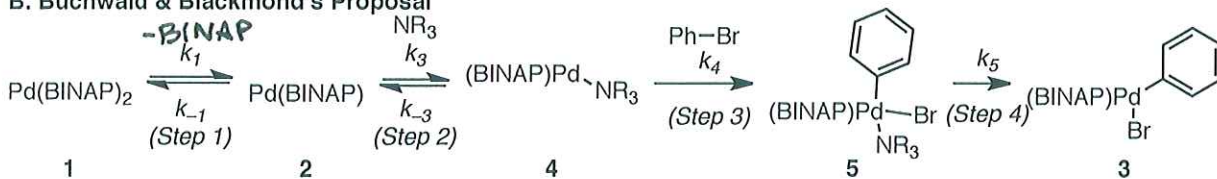
Initials: 5pts each.

5. (25 points) In the early 2000's, Hartwig and Buchwald & Blackmond debated whether amine accelerated the rate of oxidative addition of palladium into C-Br bonds. Hartwig proposed mechanism A, in which amine is not involved in the oxidative addition. Buchwald & Blackmond proposed mechanism B, in which amine accelerates the oxidative addition. (Shekhar, S.; Ryberg, P.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 851)

A. Hartwig's Proposal



B. Buchwald & Blackmond's Proposal



(a) Please write the predicted rate law for Mechanism A, assuming step 2 is rate-determining and step 1 is rapid and reversible in comparison to step 2.

$$\text{rate} = \frac{k_1 k_2 [\text{Pd}(\text{BINAP})_2][\text{PhBr}]}{k_{-1} [\text{BINAP}]} = \frac{k_1 k_2 [1][\text{PhBr}]}{k_{-1} [\text{BINAP}]}$$

-1/mistake

(b) Please write the predicted rate law for Mechanism B, assuming step 3 is rate-determining and all prior steps are rapid and reversible.

$$\text{rate} = k_4 [4][\text{BINAP}]$$

what is [4]? Pre-equilibrium:  $K_3 = \frac{k_3}{k_{-3}} = \frac{[4]}{[2][\text{NR}_3]}$

$$[4] = \frac{k_3 [2][\text{NR}_3]}{k_{-3}}$$

what is [2]?  $K_1 = \frac{k_1}{k_{-1}} = \frac{[2]}{[1][\text{BINAP}]}$

$$[2] = \frac{k_1 [1][\text{BINAP}]}{k_{-1}}$$

$$\text{rate} = \frac{k_1 k_3 k_4 [\text{PhBr}][\text{NR}_3][1]}{k_{-1} k_{-3} [\text{BINAP}]}$$

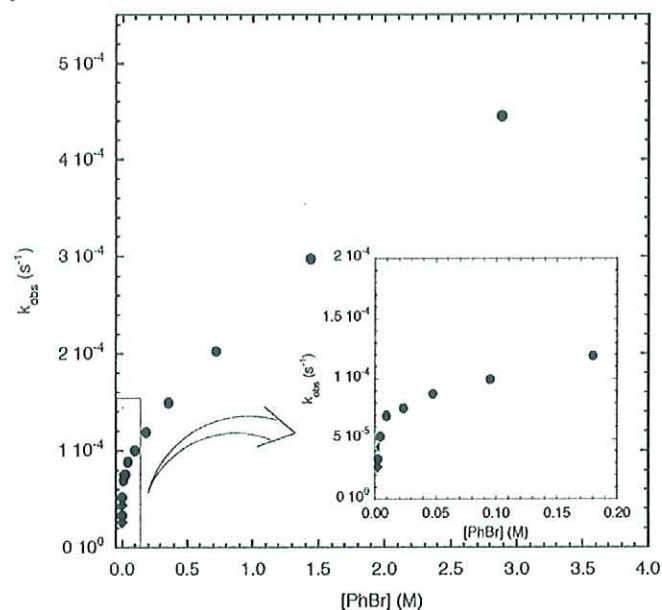
5pts

5pts

Initials: \_\_\_\_\_

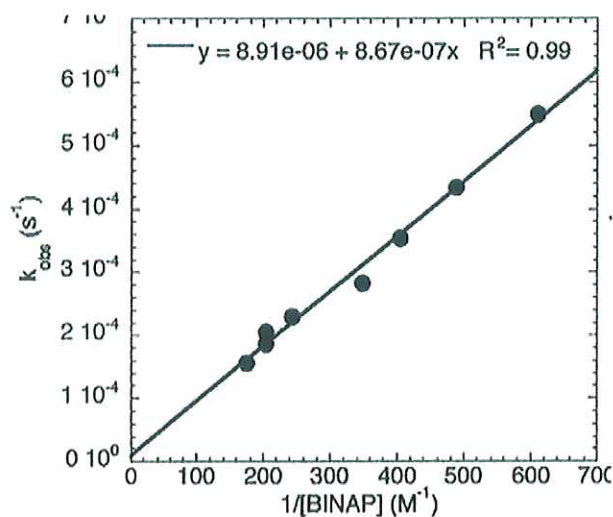
(5 – continued)

(c) Hartwig determined the kinetic order of each of the reactants for the stoichiometric addition of  $\text{Pd}(\text{BINAP})_2$  to phenyl bromide. He reported the following data. What does the following data tell you about the reaction?



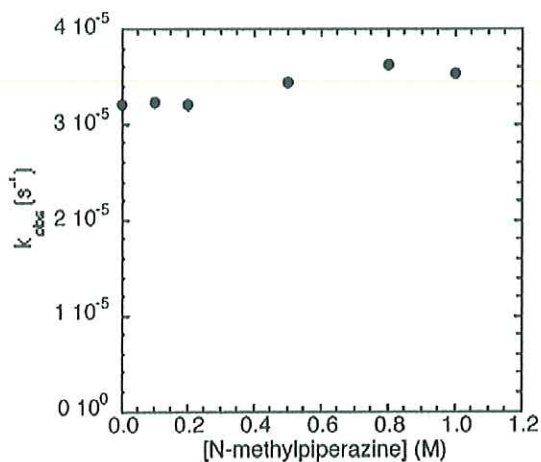
saturation behavior for PhBr.  
1<sup>st</sup> order @ low [PhBr] &  
0 order @ high [PhBr]

2pts



Inverse 1<sup>st</sup> order in [BINAP]

2pt



0 order in  $[\text{NR}_3]$

1pt



Initials: \_\_\_\_\_

9

(5 - continued)

(d) Based on this data, which pathway (A or B) is the dominant pathway?

A

(e) Based on this data, revise your proposed rate law for the dominant pathway, if necessary, to show that the kinetic data supports the dominant mechanistic pathway you picked in part (d).

Saturation w/ PhBr, so PhBr must appear in denominator...  
Pre-equilibrium approx was not appropriate!

$$\text{rate} = \frac{k_1 k_2 [I][\text{PhBr}]}{k_{-1}[\text{BINAP}] + k_2[\text{PhBr}]}$$

} Consistent w/ 0 order in amine.

At low [PhBr],  $k_{-1}[\text{BINAP}] \gg k_2[\text{PhBr}]$

$$\text{rate} = \frac{k_1 k_2 [I][\text{Ph-Br}]}{k_{-1}[\text{BINAP}]}$$

(Plot #2 in part c must have been @ low [PhBr])

At high [PhBr],  $k_{-1}[\text{BINAP}] \ll k_2[\text{PhBr}]$

$$\text{rate} = \frac{k_1 k_2 [I][\text{PhBr}]}{k_2[\text{PhBr}]} = k_1 [I]$$

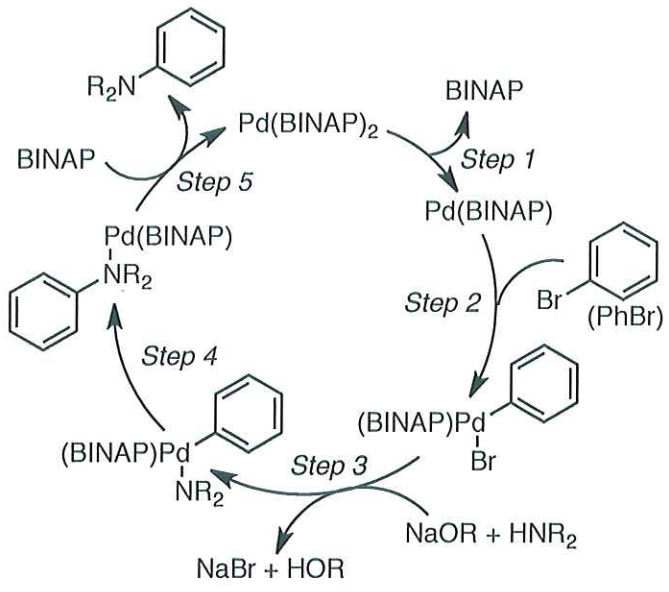
Note: Saturation curve never makes it to being truly flat; so [BINAP] still impacted all those rxns.

+2 if said Pathway B in (d), but showed saturation behavior is consistent.

Initials: \_\_\_\_\_

6. (25 points) The Buchwald/Blackmond vs. Hartwig debate extended far beyond the role of amine in oxidative addition. Each research team had conducted mechanistic experiments to understand the mechanism of Pd-catalyzed C–N cross-coupling reactions. Their mechanistic data conflicted, as did their proposed mechanisms. (Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584)

(a) Hartwig originally proposed the following catalytic cycle. In his initial experiments, he thought that the reaction was zero order in phenyl bromide and zero order in BINAP. Pd(BINAP)<sub>2</sub> was the only Pd resting state in these reactions. Based on this data, which step of Hartwig’s catalytic cycle must be the rate-limiting step?



3pts

Step 1

(b) Based on the data in part (a), write a rate law for Hartwig’s catalytic cycle in terms of observable species. For rate constants, please number them according to the appropriate step, i.e.,  $k_1$  and  $k_{-1}$  for Step 1.

3pts

$$\text{rate} = k_1 [\text{Pd}]_T \quad [\text{Pd}]_T = [\text{Pd}(\text{BINAP})_2]$$

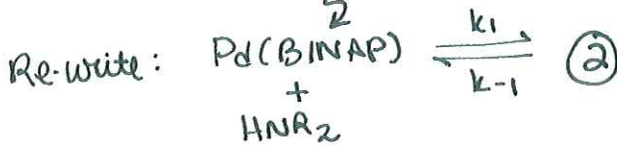
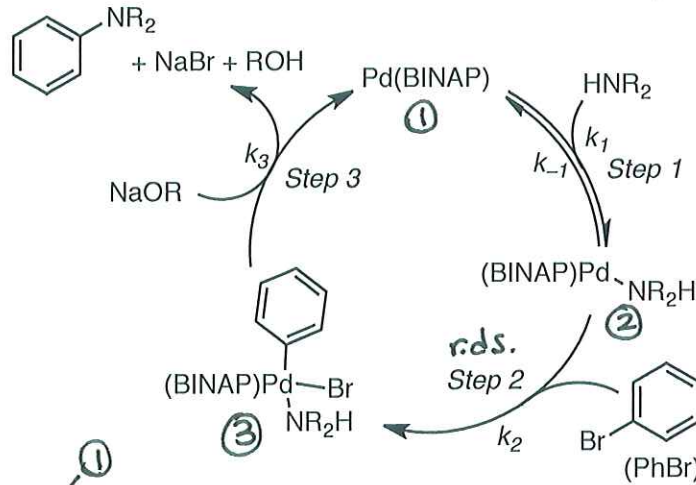
$\approx$   
 only catalyst resting state

-1/mistake

Initials: \_\_\_\_\_

(6 – continued)

(c) In contrast, Buchwald & Blackmond proposed a different mechanism (shown below), in which Pd(BINAP)<sub>2</sub> was not in the catalytic cycle. They based their proposal on the observation that the reaction proceeded more quickly with higher concentrations of amine. Write a rate law for this catalytic cycle in “one plus” format, assuming Step 2 is rate-limiting and subsequent steps to regenerate Pd(BINAP) are fast and irreversible. Use specific rate constants (k<sub>1</sub>, k<sub>2</sub>, etc.).



Possible resting states for Pd:  
 ① & ②



rate = 
$$\frac{k_1 k_2 [\text{Pd}]_T [\text{HNR}_2] [\text{PhBr}]}{k_{-1} + k_2 [\text{PhBr}]}$$

$$1 + \frac{k_1 [\text{HNR}_2]}{k_{-1} + k_2 [\text{PhBr}]}$$

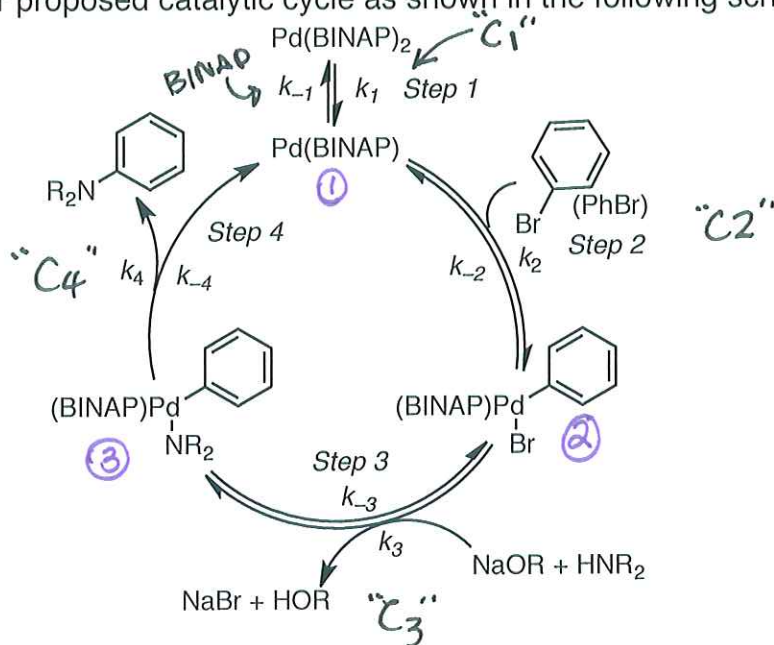
3 pts

~~forget~~ Using PEA instead of SSA → missing this term in numerator & denominator → (-)

Initials: \_\_\_\_\_

(6 - continued)

(d) During the debate, it became clear that both research teams had made mistakes either in their experiments or in their interpretation of the data. Working together, Hartwig, Buchwald and Blackmond revised their proposed catalytic cycle as shown in the following scheme.



Write a general rate law for this catalytic cycle in "one plus" format. You may use generic observable rate constants for each of the terms in the rate law ( $C_1$ ,  $C_2$ , etc.)

$$\text{rate} = \frac{k_4 C_2 C_3 \cdot [Pd]_T [PhBr] [NaOR] [HNR_2]}{1 + C_2 [PhBr] + C_2 C_3 [PhBr] [NaOR] [HNR_2] + C_1 [BINAP]}$$

4pts

① → Pd(BINAP)<sub>2</sub>  
 ② → Pd(BINAP)  
 ③ → (BINAP)Pd-NR<sub>2</sub>

or

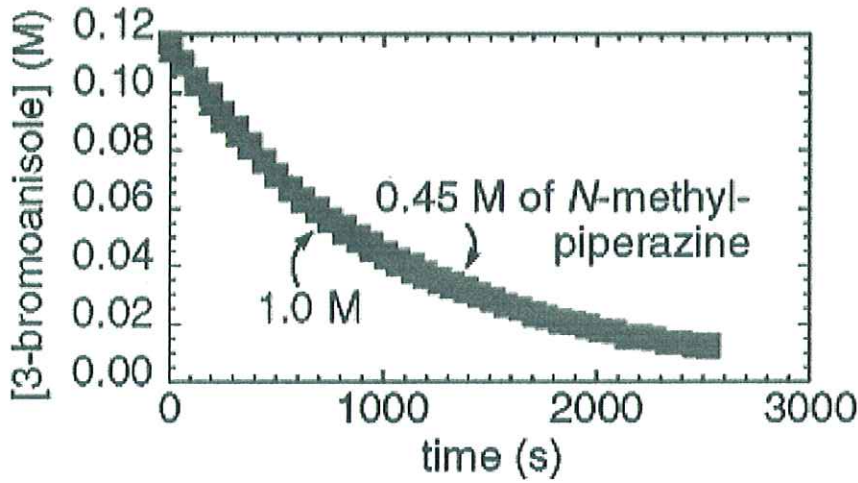
$$\text{rate} = \frac{C_1 [Pd]_T [PhBr] [NaOR] [HNR_2]}{1 + C_2 [PhBr] + C_3 [PhBr] [NaOR] [HNR_2] + C_4 [BINAP]}$$

-1/mistake

Initials: \_\_\_\_\_

(6 – continued)

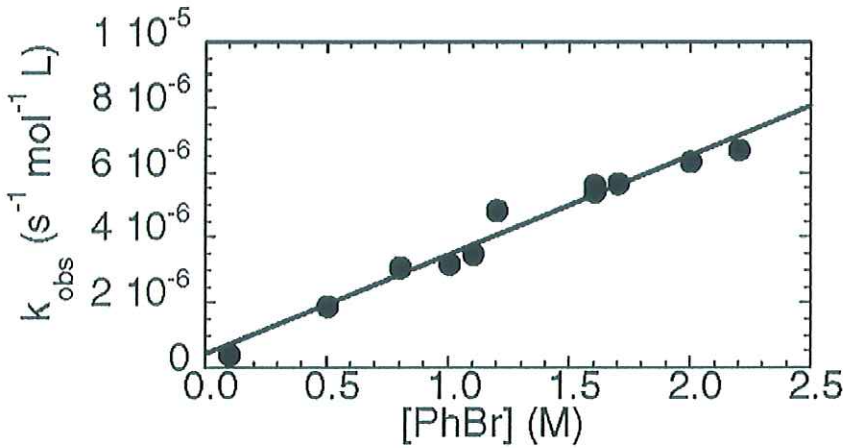
(e) What do the following plots tell you?



$\emptyset$  order in  $\text{HNR}_2$

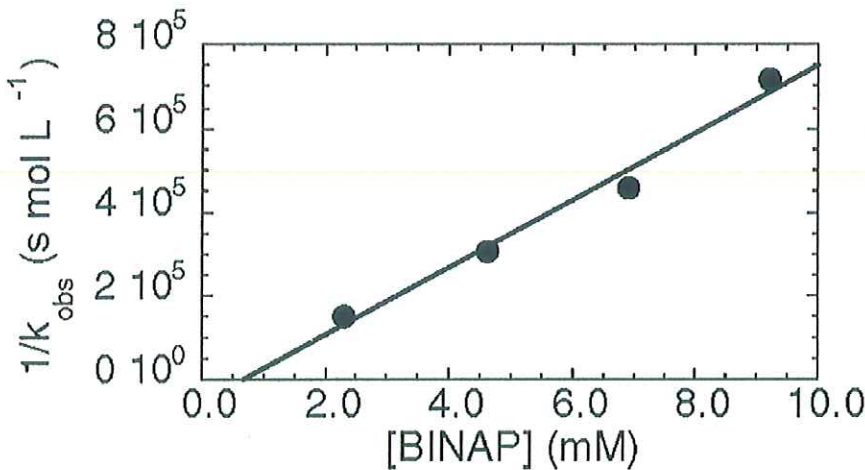
1pt

(Note: For the above plot, 3-bromoanisole was used in place of PhBr and *N*-methylpiperazine was used as  $\text{HNR}_2$ .)



1<sup>st</sup> order in PhBr

1pt



Inverse 1<sup>st</sup> order in BINAP.

1pt

Initials: \_\_\_\_\_

(6 - continued)

(f) Based on the data in part (e), which step is likely to be the rate-limiting step?

### Step 2

3pts

(g) By using <sup>31</sup>P NMR, the researchers were able to observe only Pd(BINAP)<sub>2</sub> throughout the course of the reaction and therefore assert that Pd(BINAP)<sub>2</sub> is the only catalyst resting state. Based on this information and the information in parts (e) and (f), please write the rate equation for this catalytic cycle in terms of [Pd]<sub>T</sub>, [ArBr], [HNR<sub>2</sub>], [NaOR], and [BINAP], using the rate constants shown in the catalytic cycle in part (d).

$[ArBr] = [PhBr]$

Simplify "1+":

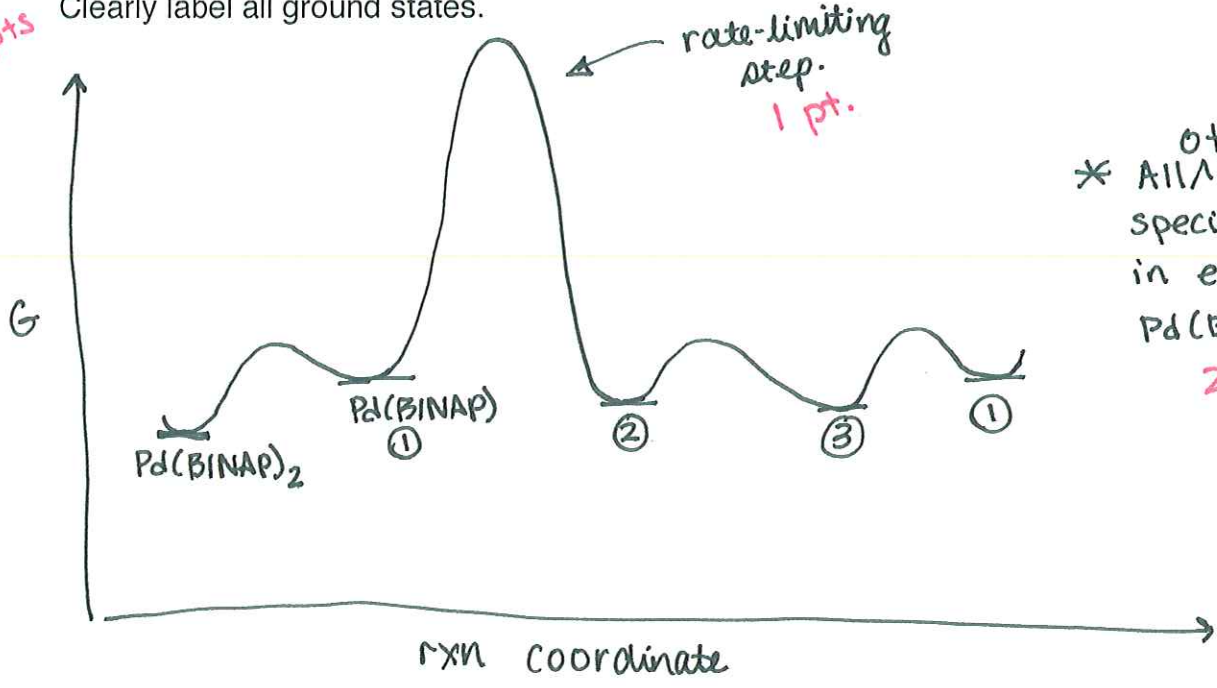
$$rate = \frac{k_2 [Pd]_T [PhBr]}{\cancel{k_1} + \frac{k_{-1} [BINAP]}{k_1}} = \frac{k_1 k_2 [Pd]_T [PhBr]}{k_{-1} [BINAP]}$$

3pts

Pd does not sit @ Pd(BINAP)

(h) Draw a reaction coordinate diagram consistent with the proposed mechanism and rate law. Clearly label all ground states.

3pts



\* All Pd-containing species higher in energy than Pd(BINAP)<sub>2</sub> \*

2 pts.