**CHEM 633: Advanced Organic Chem: Physical**
**Problem Set 6 (Due Thurs, 12/8/16)**
Please do not look up references until after you turn in the problem set unless otherwise noted.
For the following problems, please use Excel (or another graphing program), when necessary. Please submit your graphs with your problem set.
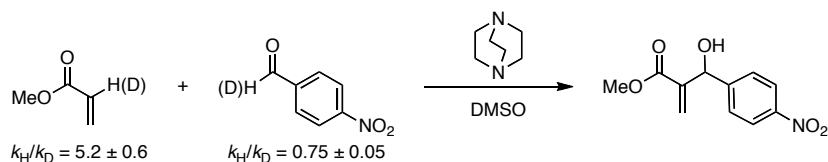
1. One proposed mechanistic sequence for the Baylis-Hillman reaction is shown below (e.g., *J. Org. Chem.* **2003**, *68*, 692). This reaction has recently been studied using the initial rates method (*Org. Lett*, **2005**, *7*, 147). You considered the kinetics of this reaction on Problem Set 5.
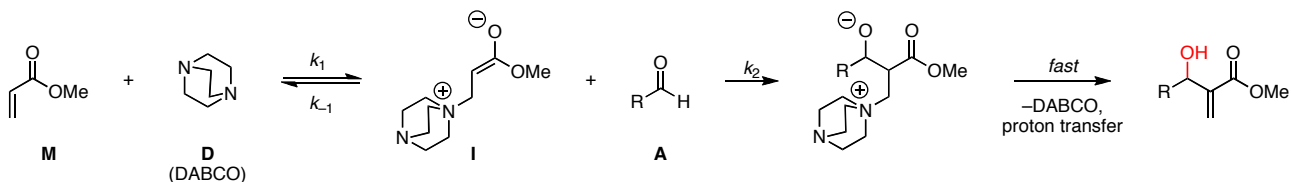
(a) The authors also evaluated this reaction by analyzing isotope effects. For the illustrated mechanism below (the generally accepted mechanism), please predict the isotope effects that should be observed at the indicated positions.
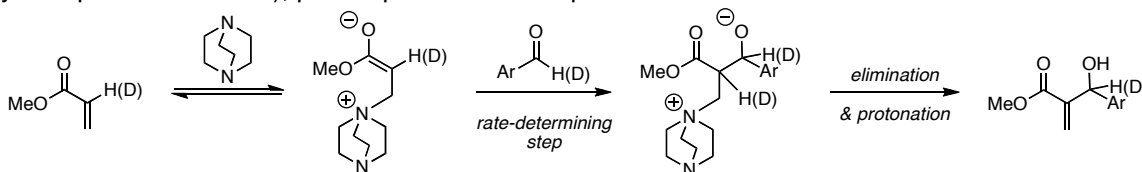

(b) In a recent study, the following isotope effects were measured. What do these isotope effects suggest about the rate-determining step?

$k_H/k_D = 5.2 \pm 0.6$ $k_H/k_D = 0.75 \pm 0.05$

(c) Propose an alternative mechanistic sequence that accounts for the kinetic and isotope effect data.

2. Is there a linear free energy relationship between enantioselectivity and the size of the substituent (R) in the following aziridination reaction (*ACIE* **1998**, *37*, 3392)? Please propose an explanation for why or why not.

| R	ee (%)
H	41
Me	85
n-Pr	90
i-Pr	94
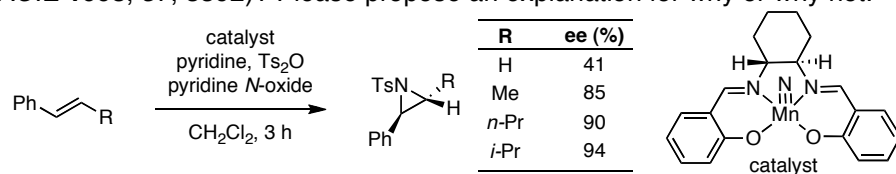
3. Please read this article: Resek & Beak. *J. Am. Chem. Soc.* **1994**, *116*, 405.
   (a) What is an intramolecular kinetic isotope effect experiment?

(b) Why are the values of the intramolecular and intermolecular kinetic isotope effects different?

4. Hayashi and co-workers developed a Wacker cyclization to convert achiral **1** into chiral benzofuran **2** in high enantioselectivity (*J. Am. Chem. Soc.* **2004**, *126*, 3036).
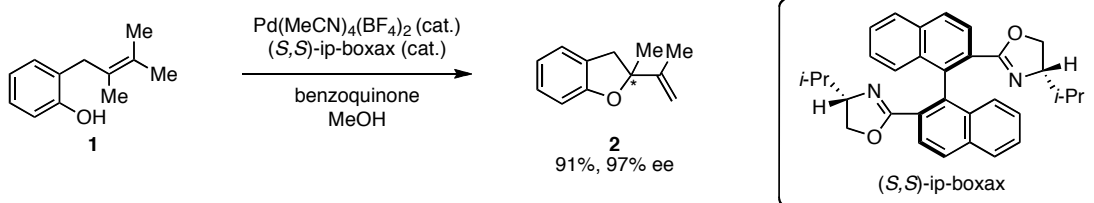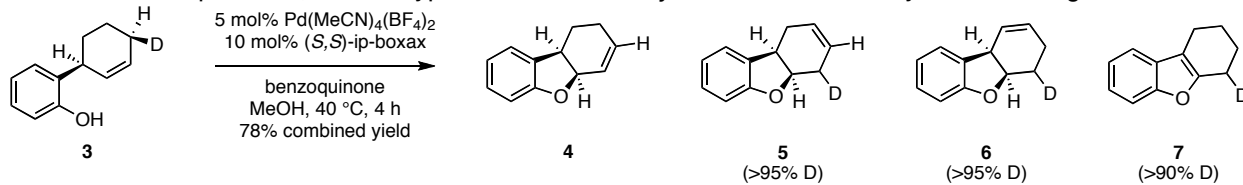

   (a) Please draw a reasonable arrow-pushing mechanism for this transformation.

(b) The researchers wanted to understand whether the reaction proceeds via an *anti* or *syn* oxypalladation step.

Pd(II)

vs.

anti   *syn*
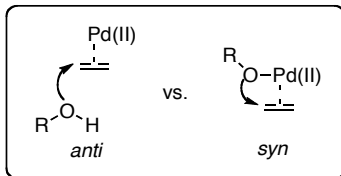
To answer this question, they designed deuterated substrate **3**. Cyclization of **3** gave the 4 products shown below. Based on these products, is the oxypalladation *anti* or *syn*? Please illustrate your reasoning.

5 mol% Pd(MeCN)$_4$(BF$_4$)$_2$
10 mol% (*S*,*S*)-ip-boxax

benzoquinone
MeOH, 40 °C, 4 h
78% combined yield

3

4

5
(>95% D)

6
(>95% D)

7
(>90% D)

5. Please draw a Woodward–Hoffmann molecular orbital correlation diagram for the following reaction and use it to predict the stereochemistry of the product (stereocenters are starred).

Δ

R   R   R   R

4
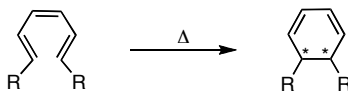
6. Please propose an arrow-pushing mechanism for the following transformation. Please predict the stereochemical outcome (What is the stereochemistry of the starred carbons?) and explain your prediction.
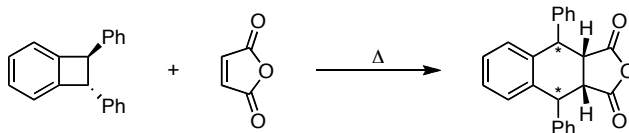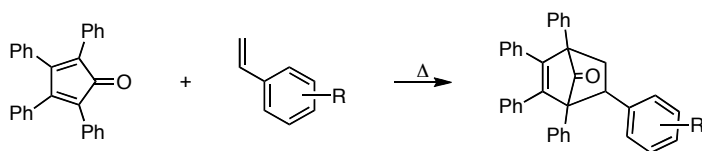

7. (a) Please draw a reasonable arrow-pushing mechanism for the following reaction.

exo
favored

endo
disfavored
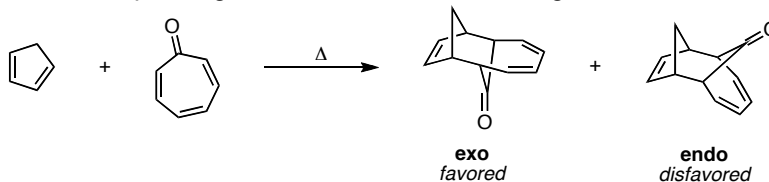
(b) Please explain why the product named "exo" above is favored.

8. Please explain the following trend in reaction rates based on substitution of the styrene dienophile:

R	k (x 10^6 mol^{-1}s^{-1})
p-NMe$_2$	338
p-OMe	102
H	73
p-Cl	78
m-NO$_2$	79
p-NO$_2$	88

9. Using Dewar–Zimmerman theory, please explain why Diels–Alder cycloadditions proceed suprafacially on both the diene and dienophile.

10. (A&D, Ch 3, #1) Chloroform shows a significant bonding interactions with benzene, but carbon tetrachloride does not. Predict the preferred geometry for the interaction and describe the physical nature of the attraction between the two molecules. *Limit your answer to pictures and less than 10 words.*

6

11. The diastereoselectivity of the following Schmidt reaction depends on the R substituent.
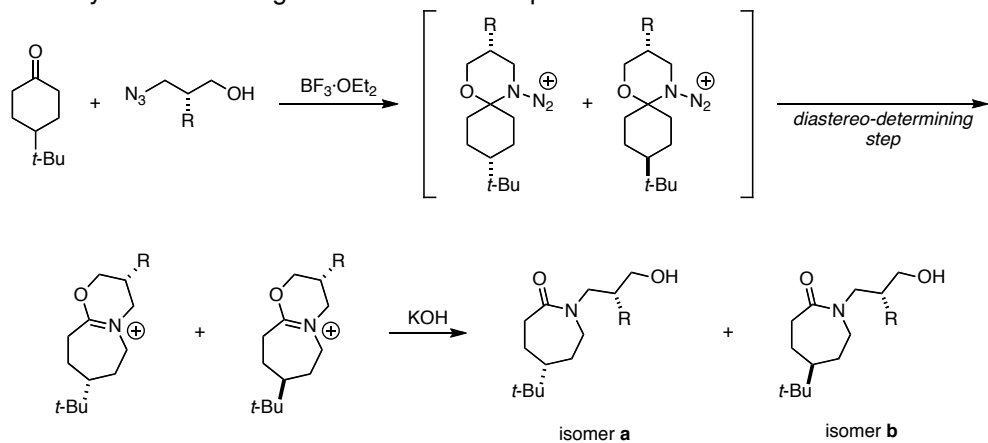
(a) Propose an arrow-pushing mechanism for this Schmidt reaction.

(b) What effect is likely responsible for the increased selectivity for isomer **a** when R = *i*-Pr vs. R = Me? *Limit your answer to less than 5 words.* Please draw 3D representations of the aminal intermediates to illustrate your answer.
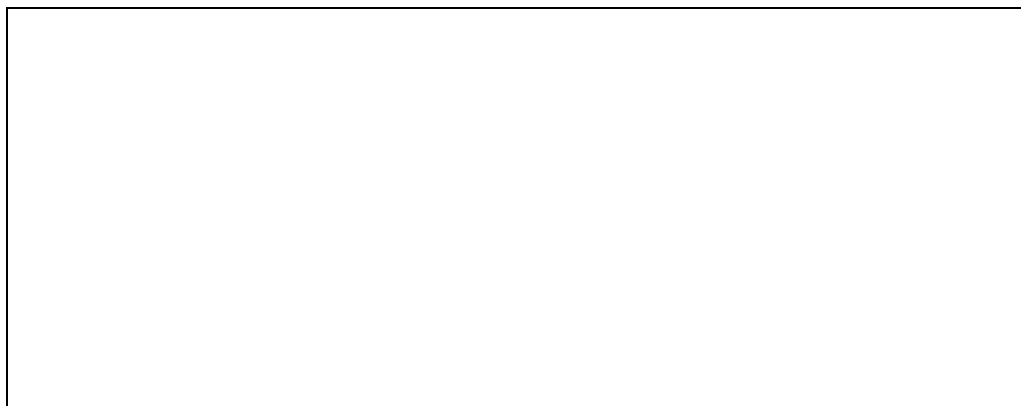
| R	isomer **a** : isomer **b**
Me	74 : 26
i-Pr	88 : 12
4-nitrophenyl	76 : 24
Ph	64 : 36
4-methoxyphenyl	47 : 53
3,4,5-trimethoxyphenyl	43 : 57
OMe	4 : 96

(c) When R = aryl, selectivity for isomer **a** decreases. It has been proposed that this is due to stabilizing cation–π interactions in the transition state that leads to isomer **b**. Please illustrate this cation–π interaction in a 3D representation of the aminal intermediate.
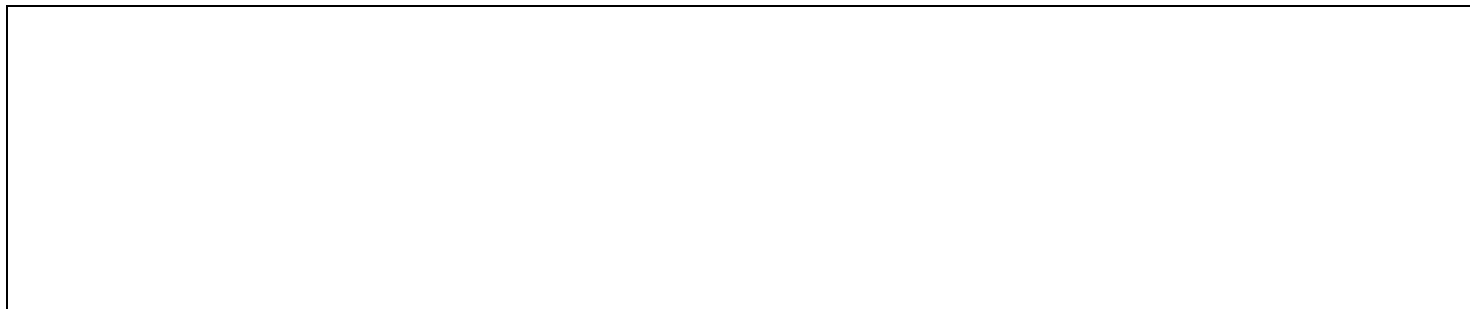
(d) When R = OMe, the reaction is highly selective for isomer **b**. Please illustrate the noncovalent interaction responsible in a 3D representation of the aminal intermediate.
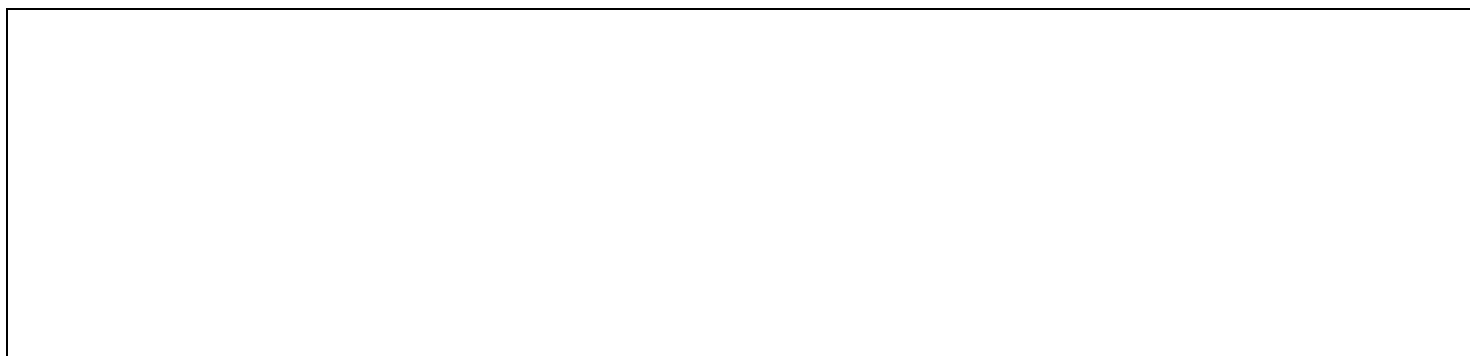
12. Noncovalent interactions are important in enzyme active sites, such as that of squalene-hopene cyclase, which catalyzes the concerted transformation of a linear polyene substrate to hopene and hopanol (Hoshino, T.; Sato, T. *Chem. Commun.* **2002**, 291). In the transition state for this transformation, partial positive charge builds up on the numbered carbons (shown below).
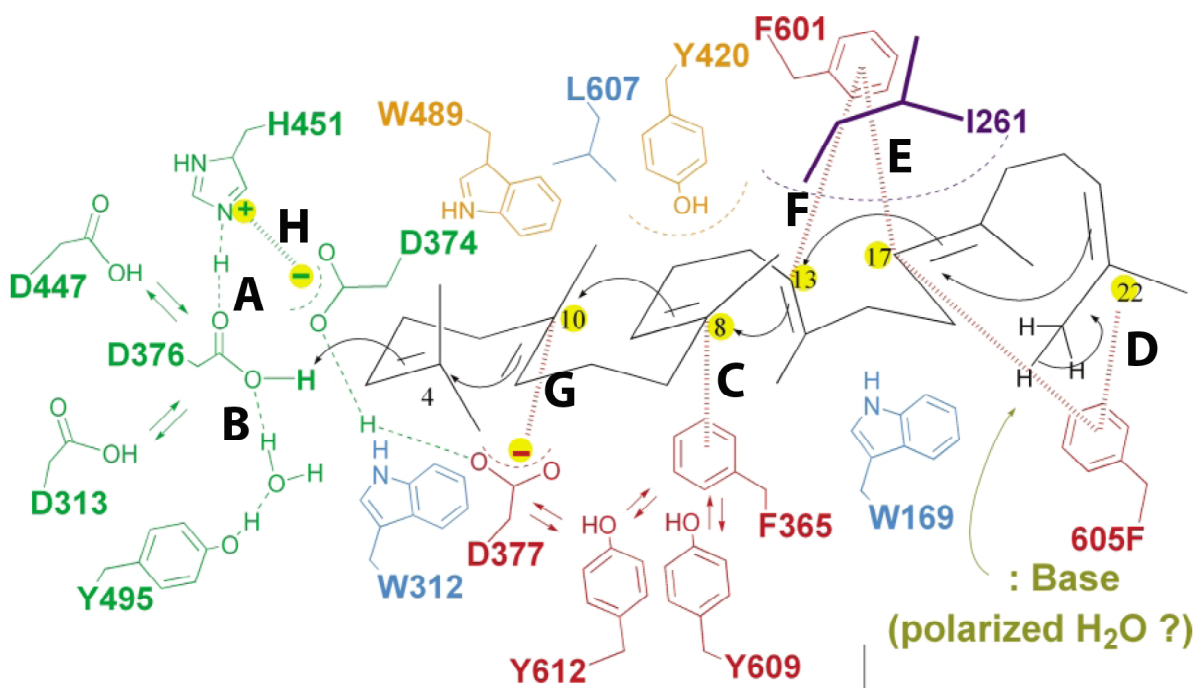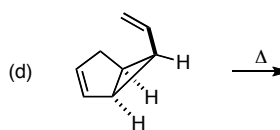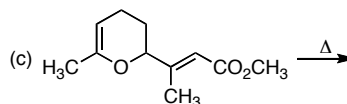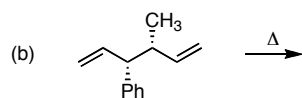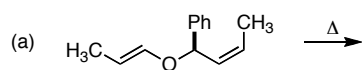
(a) Please label each noncovalent interaction (A–H) by its type (i.e., hydrogen bond, π–π, etc.).
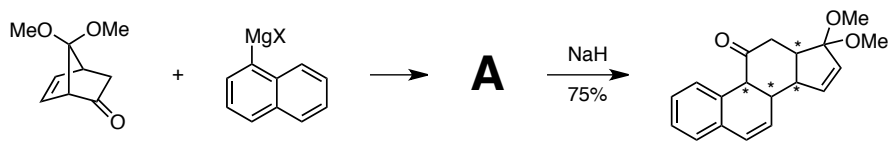
(b) Why do you think there are multiple tryptophans (the amino acids with indole side chains) near this active site?

From Grossman, Chapter 4

13. Draw the product of each of the following [3,3] rearrangements, including its stereochemistry.

(a)

(b)

(c)

(d)

14. (a) Please propose a reasonable arrow-pushing mechanism for the following transformation (Jung *JACS* **1980**, *102*, 2463).

(b) Predict the relative stereochemistry at each of the starred carbons and explain your prediction using clearly drawn structures.