

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

1

Name: ANSWER KEY

### Chem 633: Advanced Organic Chemistry 2011 ... Midterm 1

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 11 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 11 pages before you begin.

Molecular models are allowed.

Calculators are unnecessary and prohibited.

Problem	Points	
1	<u>12</u> /20	
2	<u>9</u> /18	
3	<u>4</u> /6	
4	<u>4</u> /6	
5	<u>4</u> /10	<i>Averages shown</i>
6	<u>5</u> /10	
7	<u>2</u> /10	
8	<u>10</u> /20	
<b>TOTAL</b>	<u>49</u> /100	



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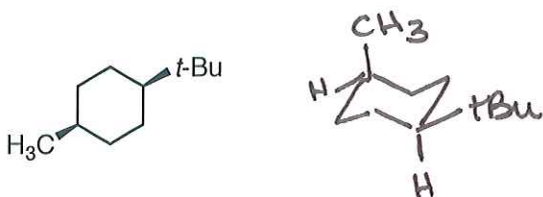
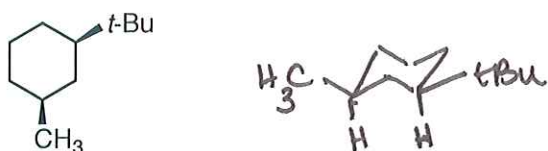
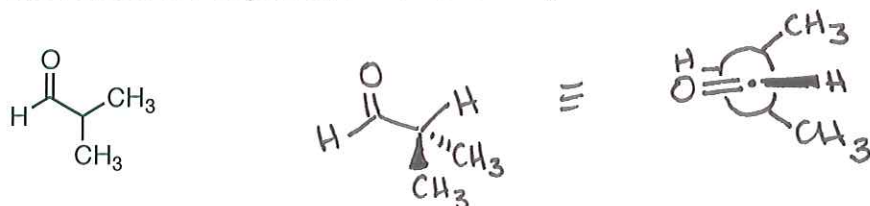
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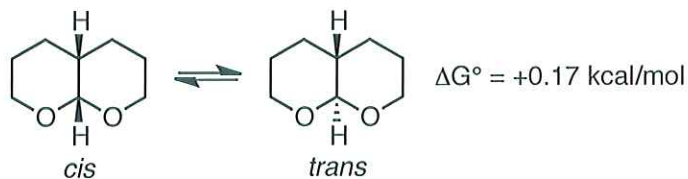
2

4 pts each.

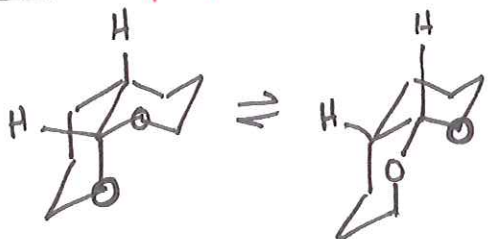
1. (20 points) Please clearly depict the lowest energy conformations of the following molecules. No explanation is necessary.



2. (18 points) (a) Please draw the lowest energy conformations for both the *cis* and *trans* configurations of the following acetal. If there is more than one lowest energy conformation, please draw both.

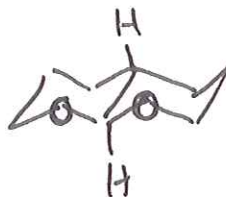


cis (6 pts):



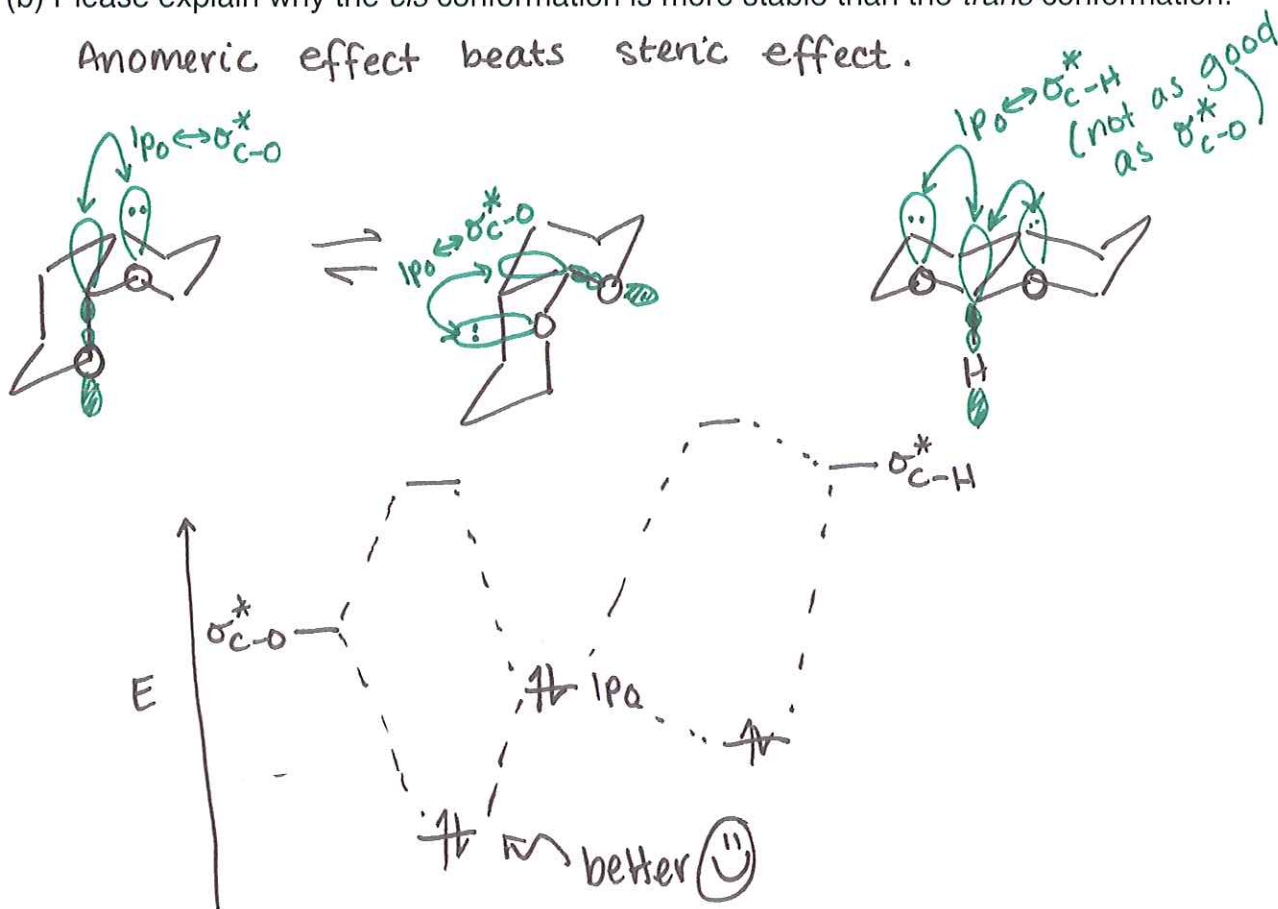
(2 equal lowest energy conformations)

trans (6 pts):



(6 pts) (b) Please explain why the *cis* conformation is more stable than the *trans* conformation.

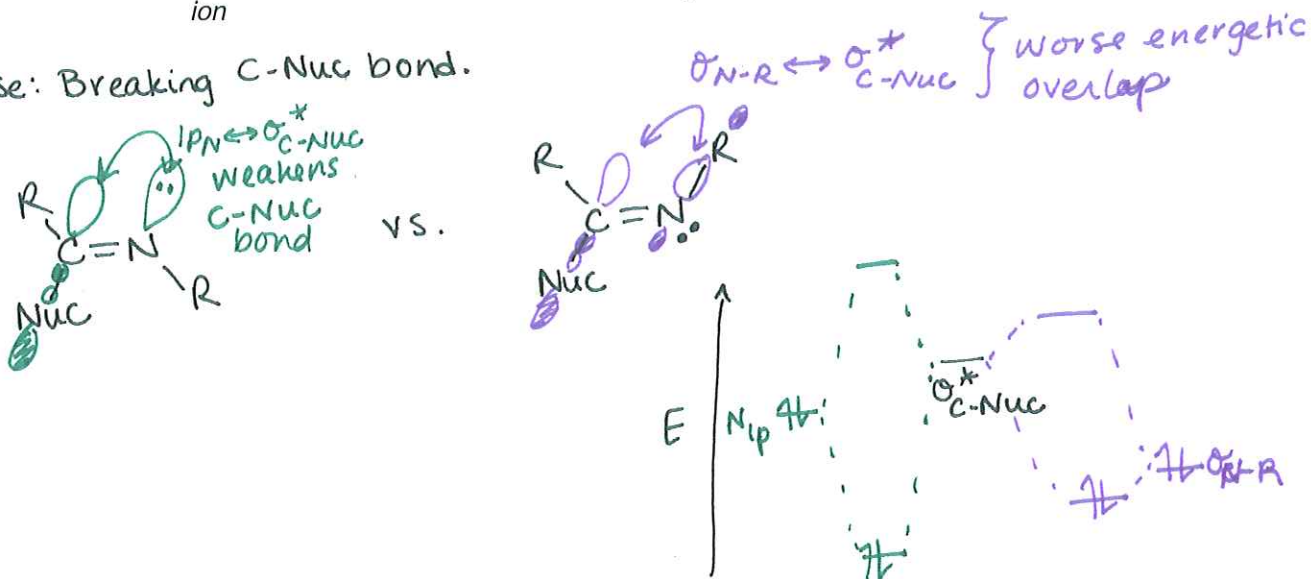
Anomeric effect beats steric effect.



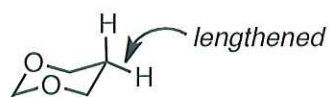
3. (6 points) In nucleophilic additions to nitrilium ions (e.g., 1), the major product is the one in which the nitrogen substituent is *cis* to the incoming nucleophile. Please rationalize why the *cis* product is favored. Hint: You may find it easier to consider the reverse of the reaction, which is a reasonable approach given the Principle of Microscopic Reversibility.



Reverse: Breaking C-Nuc bond.



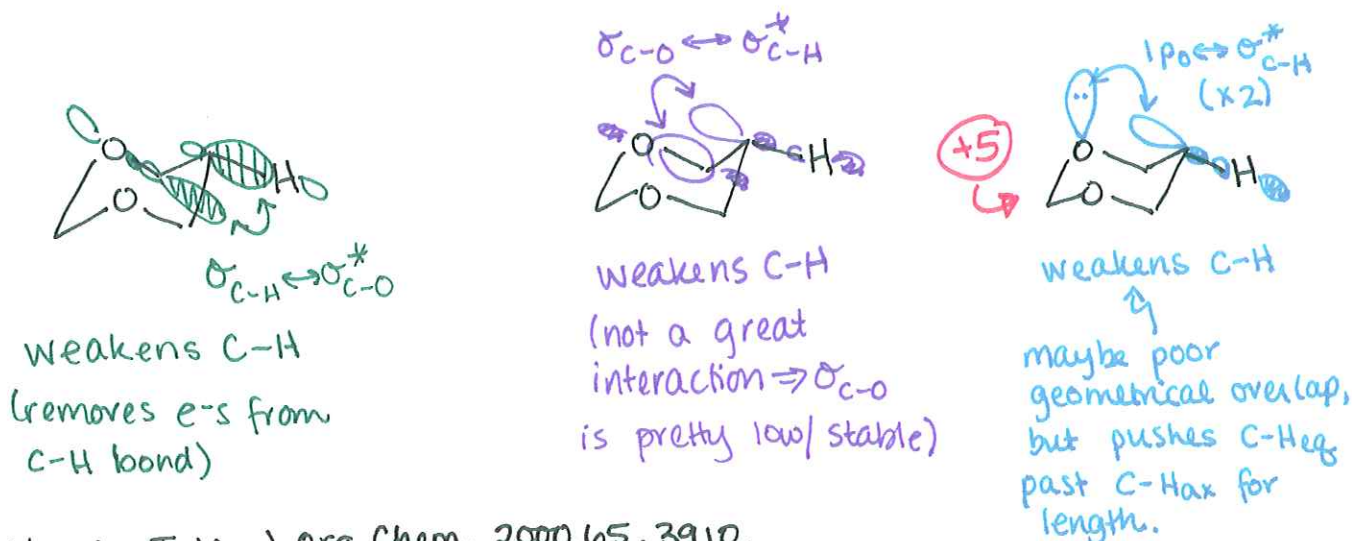
4. (6 points) Please explain why the equatorial C-H bond is longer than the axial one in 1,3-dioxalane.



3 effects on Equatorial C-H:

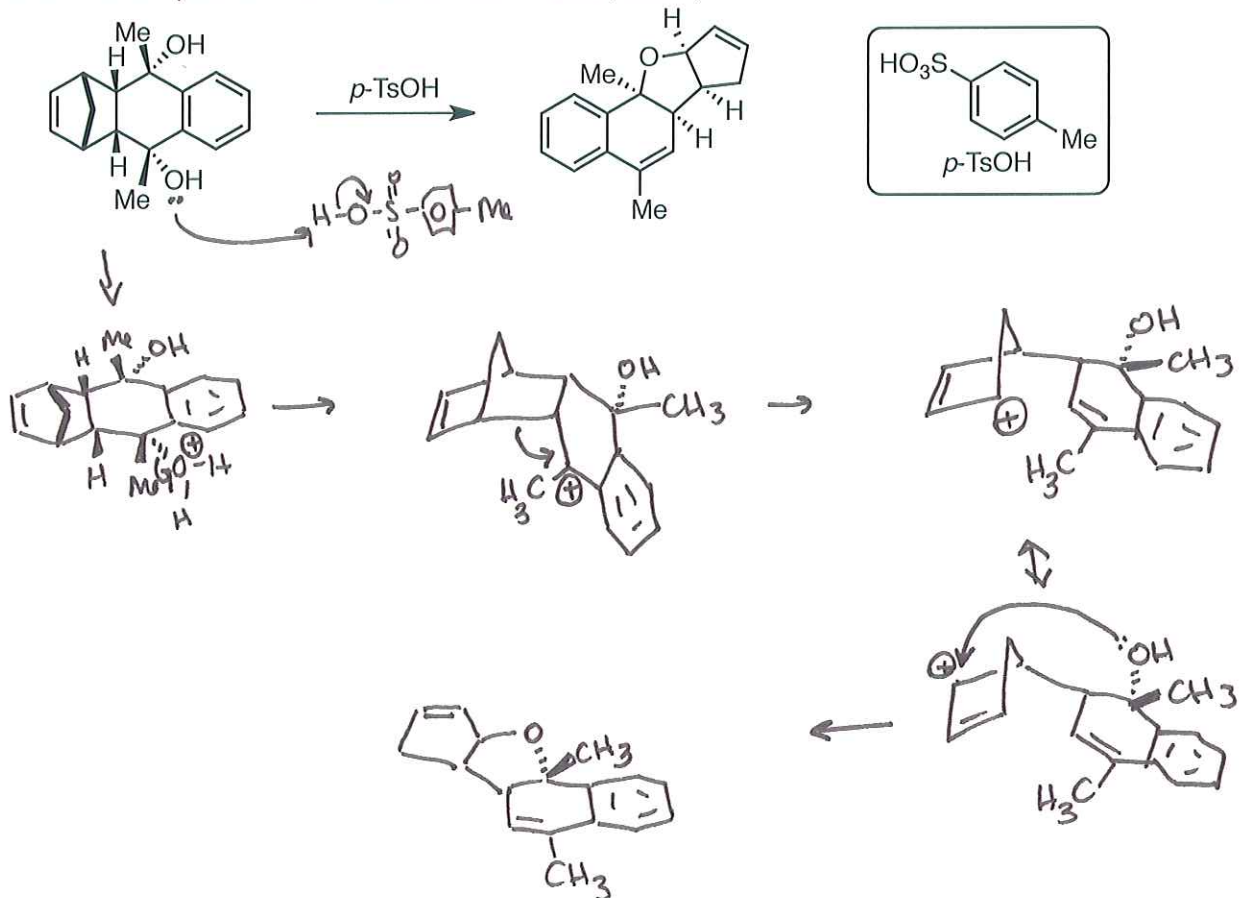
Axial:

Not huge interaction;  $\sigma_{\text{C-H}}$  is pretty stable.  $\sigma_{\text{C-H}} \leftrightarrow \sigma_{\text{C-H}}^*$  vice versa



5. (10 points) (a) Please draw a reasonable arrow-pushing mechanism for the following transformation (Coxon *Tetrahedron Lett.* **1990**, 5357).

(8 pts)



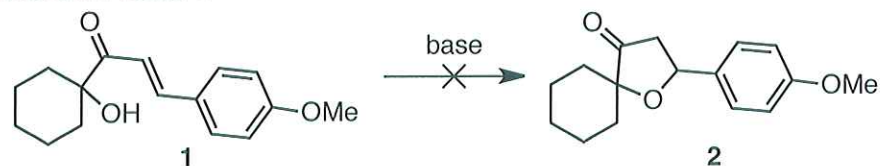
(2 pts)

(b) Is the starting material chiral or achiral?

achiral

6. (10 points) (a) Baldwin has reported that under a variety of basic conditions, alcohol **1** does not cyclize to form ether **2** (Baldwin et al. *JCS Chem. Commun.* **1976**, 736). Why doesn't this reaction occur?

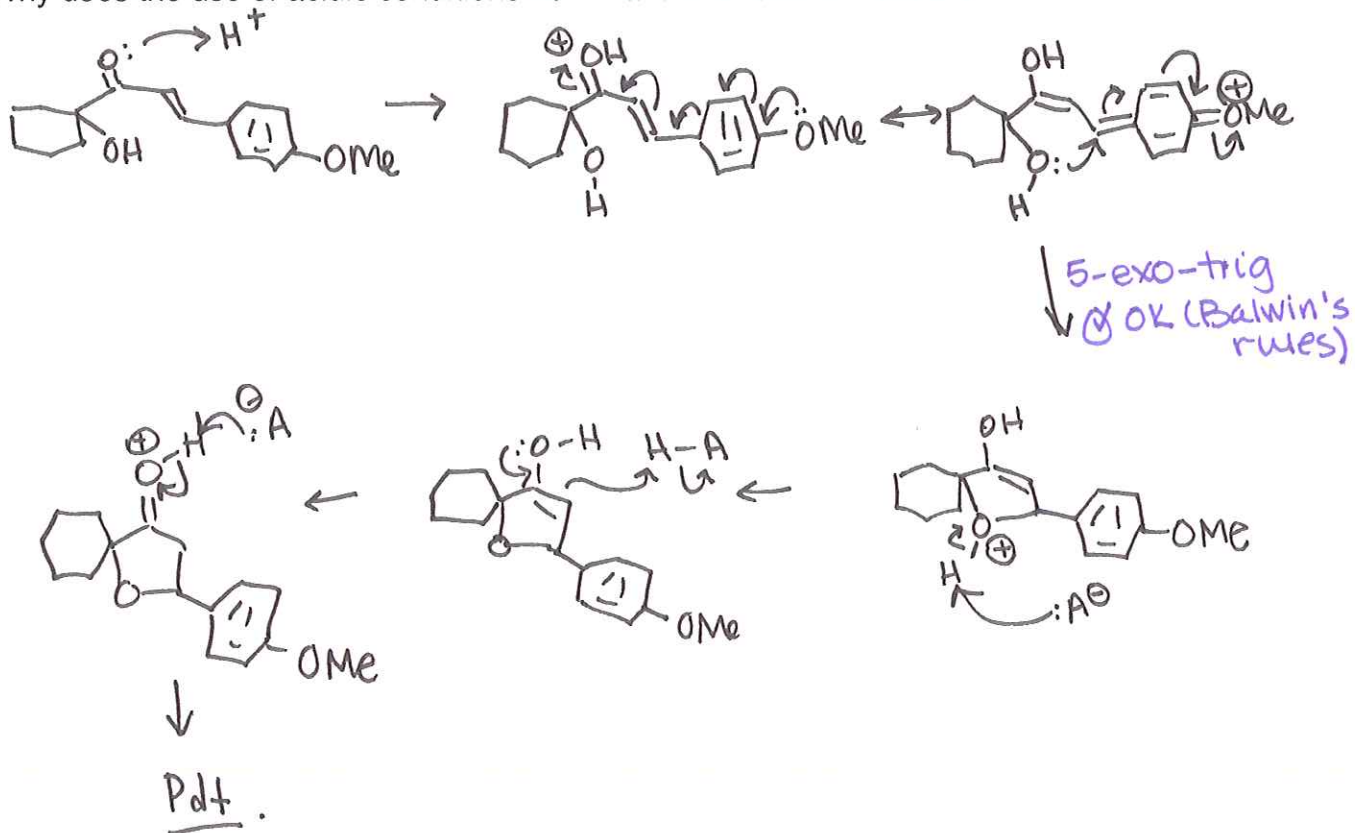
(5 pts)



5-endo-trig - disfavored by Baldwin's Rules.

(b) In contrast, this reaction does occur under acidic conditions (*p*-toluene sulfonic acid). Why does the use of acidic conditions now make this reaction feasible?

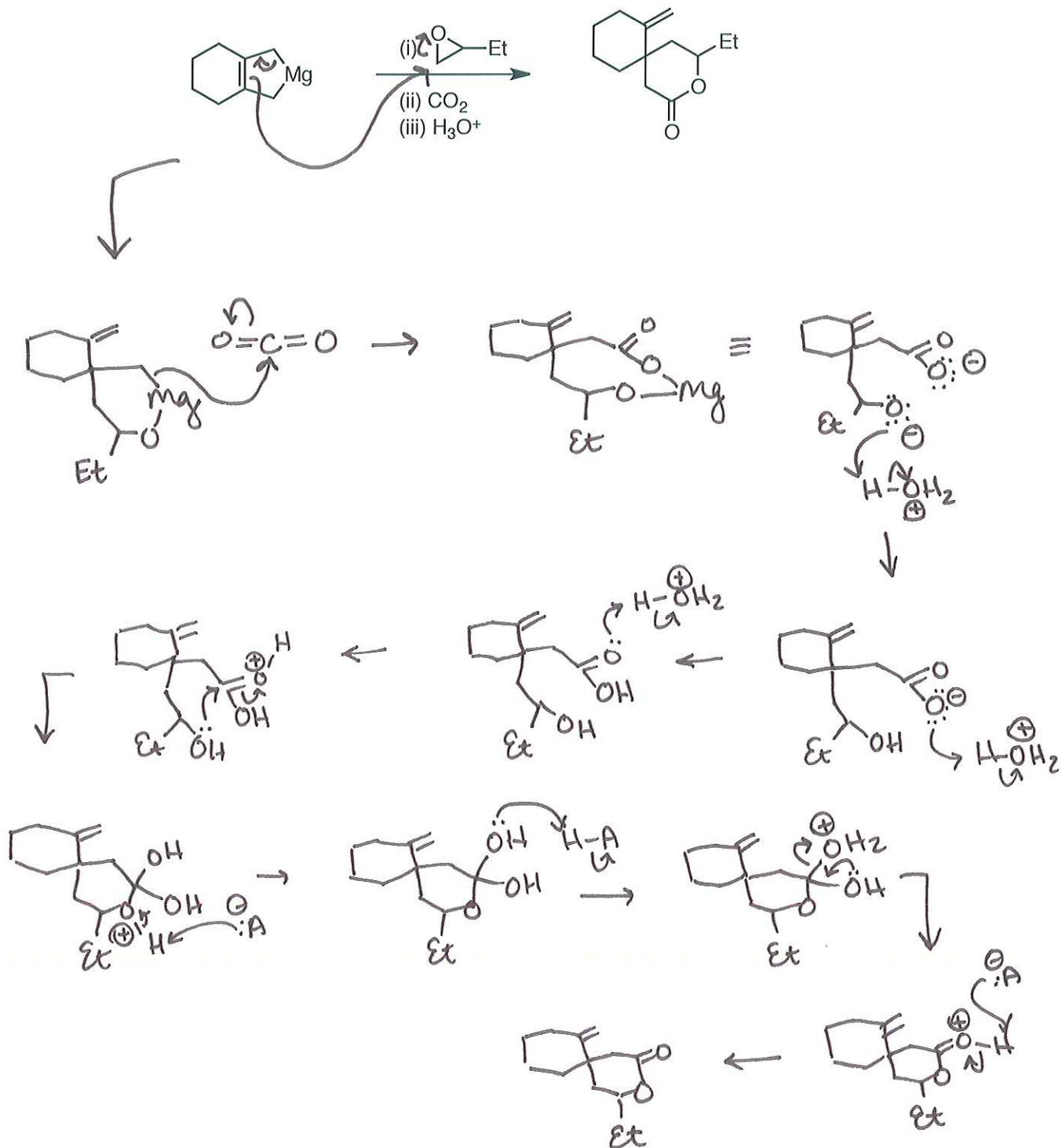
(5 pts)



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7. (10 points) Please propose a reasonable arrow-pushing mechanism for the following transformation. Please note that there is no work-up between steps. (Grossman, Ch 2, #2k)



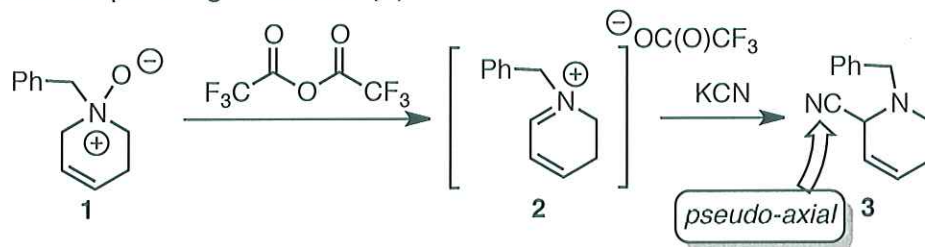
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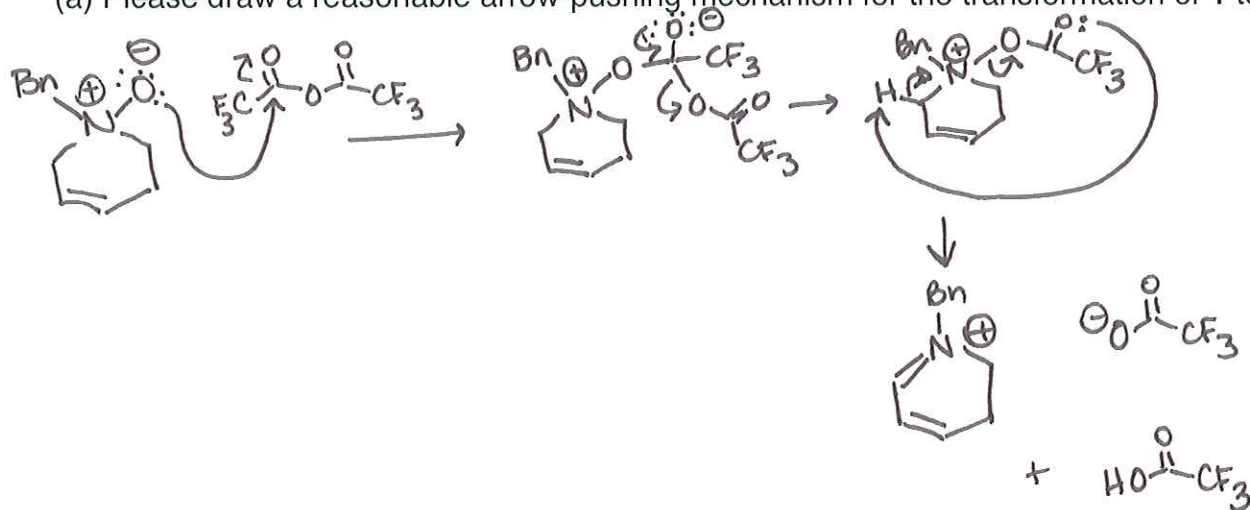
Ref: Bonin, M.; Romero, J.R.; Grierson, D.S.; Husson, H.-P. J. Org. Chem 1984, 49, 2392.

8. (20 points) Husson has reported a method for the preparation of 2-cyanopiperidineines (3) from the corresponding *N*-oxides (1).

(4 pts each)

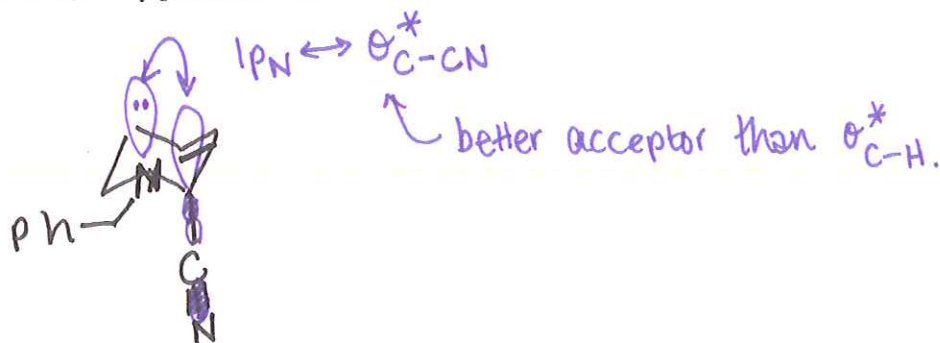


(a) Please draw a reasonable arrow-pushing mechanism for the transformation of **1** to **3**.



(b) Surprisingly, in the observed conformation of **3**, the nitrile (CN) substituent is pseudo-axial, although the A-value of CN predicts a slight equatorial preference (A value = 0.2 kcal/mol). Please explain why the conformation with a pseudo-axial nitrile is more stable.

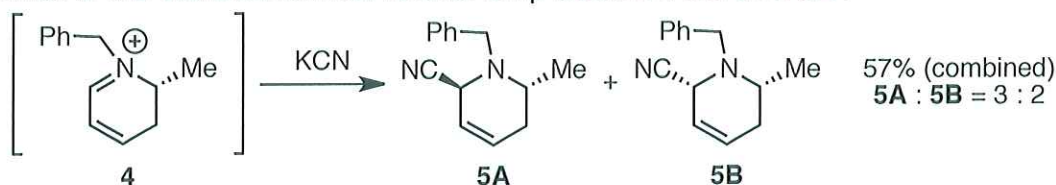
Anomeric effect! ("α-amino nitrile anomeric effect")  
CN  $\approx$  halide or heteroatom.





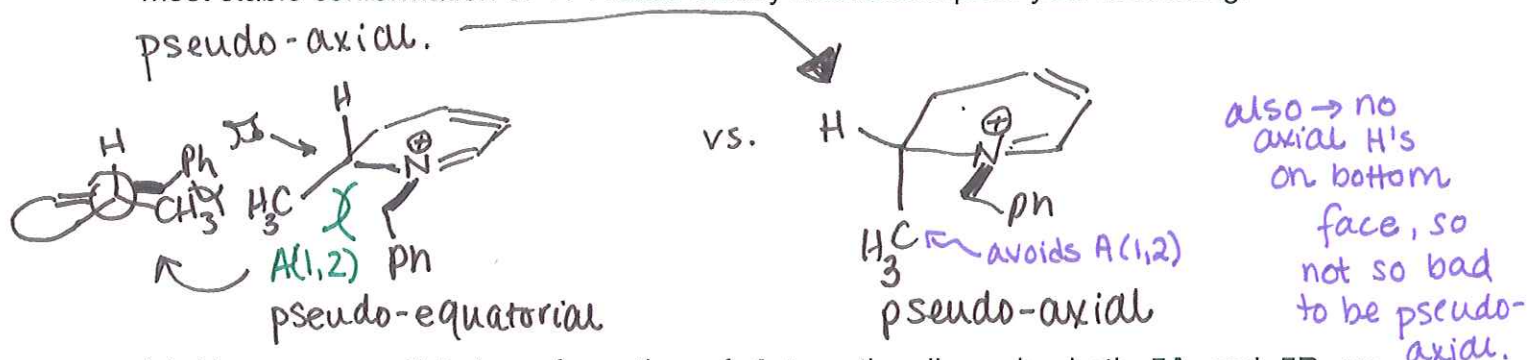
(8 – continued)

(c) In the cyanation of iminium ion **4**, two products (**5A** and **5B**) are observed in a 3:2 ratio. What is the stereochemical relationship between **5A** and **5B**?



Diastereomers

(d) Will the Me substituent be in a pseudo-equatorial or pseudo-axial position in the most stable conformation of **4**? Please clearly illustrate/explain your reasoning.



(e) Use your predicted conformation of **4** to rationalize why both **5A** and **5B** are observed. Hint: You may assume that stabilizing effects present in the products will also be present in the transition states leading to the products.

$\ominus CN$  wants to be axial in transition state ( $\alpha$ -amino nitrile anomeric effect)

But  $CH_3$  is on bottom face.

so...

