

**Name and Signature:**

Part I \_\_\_\_\_ / 14

Part II \_\_\_\_\_ / 16

Part III \_\_\_\_\_ / 21

Part IV \_\_\_\_\_ / 49

Bonus \_\_\_\_\_ / 04

There are 100 points on the exam.

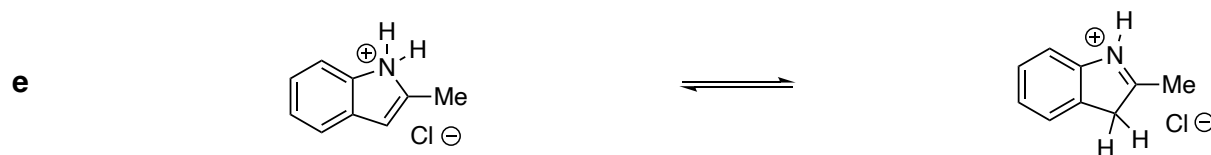
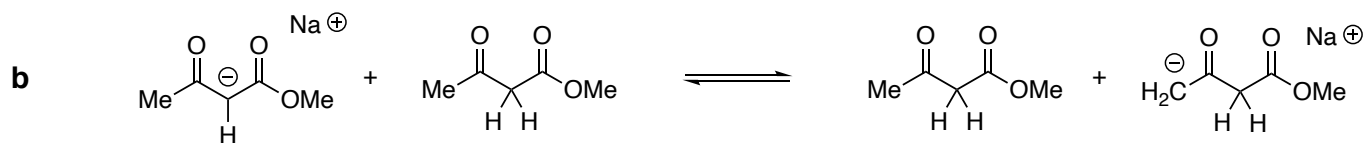
There are four questions (and six pages to this PDF).

Total \_\_\_\_\_ /100

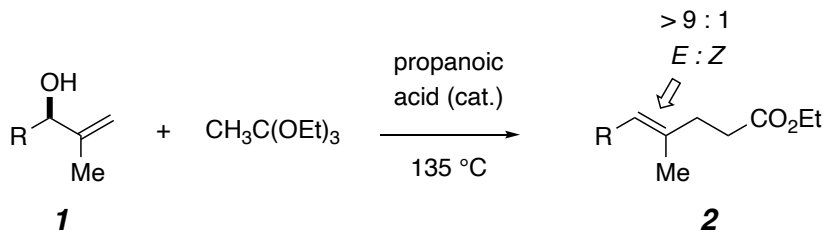
**Instructions**

- Print your name at the top of your first sheet of answers **and add your signature**.
- Your **signature will attest** to the following statement:  
*"I have not communicated with any other person about this exam during the exam period."*
- Answer all questions either on
  - i) blank sheets of paper  
 or, if you are comfortable doing so,
  - ii) by electronically entering your answers directly on this PDF.
- **If i)**, please clearly label the number of each of your answers the same as that of the problem (e.g., III.b.).
- Refrain from the temptation to provide long answers just because you have unlimited room.
- This exam is "open book" and "open resource." That is, you may consult books, the internet, your notes, previous problem sets and answers, Reaxys, etc. – but not another human.
- The only exception is that you may consult with Dorian by email (snedd011@umn.edu) if you have a question about the clarity or meaning of any of the questions themselves.
- When finished, please number all pages of your answer sheets in the top-right corner (e.g., 1 of 5, 2 of 5, etc.).
- **If i)** scan (if possible) or carefully photograph each page (check the readability of those images) of your answers and assemble into a PDF or  
**if ii)** simply save the PDF in which you have inserted your answers.
- Assemble all electronic files into a single PDF, if possible, naming it YOURLASTNAME\_Midterm-II.
- Upload your answers to the Midterm-II folder Dorian has placed in your Google Drive home folder by 8:15 pm.

I. (14 points) Decide whether each of the following equilibria lies predominantly to the **left** or to the **right**. Answer “**right**” or “**left**” for each of **Ia–Ig** on the exam answer sheet you are creating (or simply circle your answer on the PDF itself).



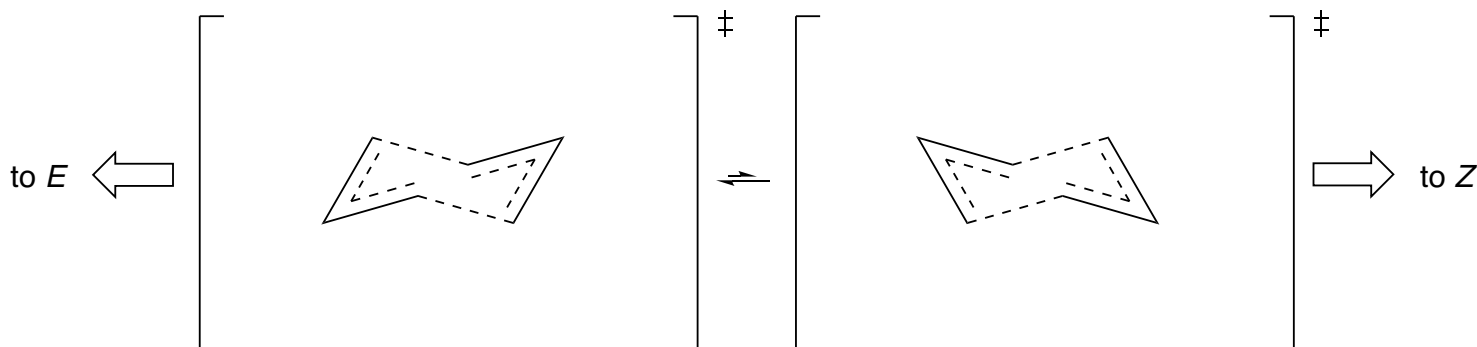
**II. (16 points)** The Johnson orthoester Claisen rearrangement of appropriate allylic alcohol substrates is an excellent method for stereoselective formation of trisubstituted alkenes. For example, chiral, secondary alcohol substrates like **1** show a preference for formation of the product **2** in which the major alkene product has the *E*-geometry. When **1** is treated with triethyl orthoacetate and an acid catalyst, the product ratio of *E*:*Z* alkenes is typically >9:1.



- a) Provide the structure of the key reaction intermediate within which the [3,3]-sigmatropic (Claisen) rearrangement occurs during the conversion of **1** to **2**.



- b) Show the geometry of two transition states, one that leads from the structure of the intermediate you answered in a) to the *E*-alkene and a second that leads from that same intermediate to the *Z*-alkene. Use the chair-like templates provided below. Think carefully about where to place the stereogenic allylic carbon atom (and its H and R substituents) in substrate **1** onto these transition state structures.

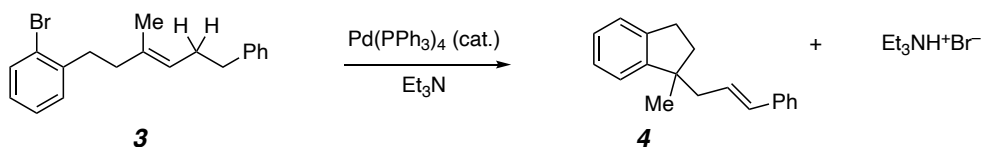


- c) In 1-2 sentences, suggest the specific reason for preferential formation of the *E*-alkene (i.e., what structural feature(s) render(s) one of the two transition states to be more stable?).

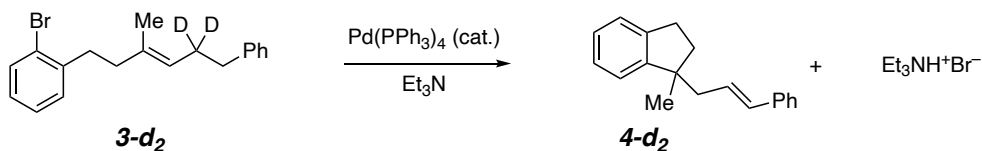
**III. (21 points)** Consider the Heck cyclization reaction that converts **3** into **4** (and triethylammonium bromide).

**a.** Draw each of the key, palladium-containing intermediates. These correspond to species produced by, in no particular order,  $\beta$ -hydride elimination (twice), oxidative addition, carbo-palladation (or 1,2-migratory insertion), alkene association with palladium (as a neutral ligand), and hydropalladation (another type of migratory insertion). There are six such intermediates. Alkene dissociation from Pd releases **4**, allowing the palladium to then turnover additional copies of **3**.

You do not need to show any (and, therefore, how many) of the triphenylphosphine ligands, L, that are present in these intermediates. Do show all of the ligands on palladium that originate from the substrate/reactant.



**b.** Now consider the outcome of performing the same reaction on the dideuterated analog **3-d<sub>2</sub>**. The product, **4-d<sub>2</sub>**, contains both of the original deuterium atoms. Clearly indicate the location of those two deuterium atoms (*hint*: they are no longer attached to the same carbon atom).



- c.** Finally, when the experiment is performed starting with a 1:1 mixture of **3** and **3-d<sub>2</sub>**,
- both substrates react at (and products are formed at) the same rate and
  - 4** and **4-d<sub>2</sub>** are the only products formed; that is, there is no mono-deuterated product observed (i.e., no **4-d<sub>1</sub>**).

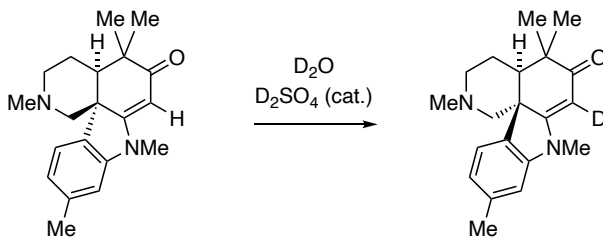
What can you conclude about the mechanism of the reaction from each of these facts?

from i)

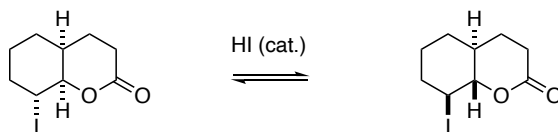
from ii)

IV. (49 pts) Provide a *detailed mechanism* to account for each of the following four reactions. Show *ALL* intermediates, equilibria, and bond-making and -breaking steps.

- a) (18) The epimerization of this cis-fused tetracyclic enone to the trans-fused diastereomer. (*hint*: a retro-vinylogous-Mannich process)



- b) (10) The epimerization of this cis-fused iodolactone to the trans-fused diastereomer.



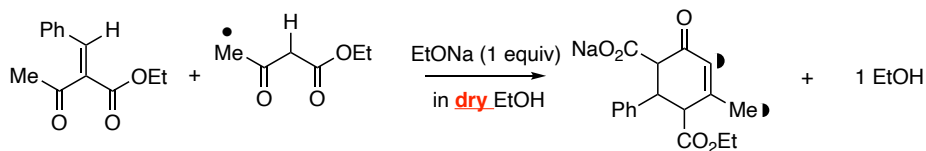
- c) (21) The conversion of ethyl acetoacetate and ethyl benzylideneacetoacetate by the action of sodium ethoxide to the indicated cyclic sodium carboxylate and one equivalent of ethanol.

Notes:

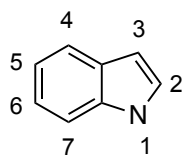
i) There is no water present in this reaction mixture.

ii) One full equivalent of NaOEt is used.

iii) If ethyl acetoacetate bearing a carbon-13 labeled methyl group (see ●) is used, the label shows up equally (i.e., 50% each) at the two indicated positions (see ◐) in the product.



**Reaxys Bonus (4 points)** Provide a search query that you could use to identify *all* indole derivatives that have no additional fused rings in the Reaxys database that (i) bear a non-hydrogen substituent at N1 and C2 (ii) have no substituent at C3, and (iii) may or may not have a non-hydrogen substituent at each of C4–C7.



FYI: Indole numbering