

Name: _____ **ANSWERS**

Please clearly print your name above.

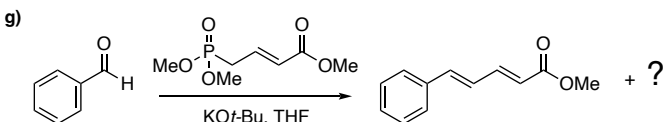
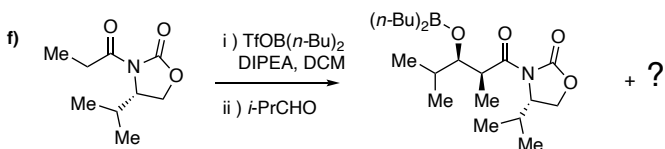
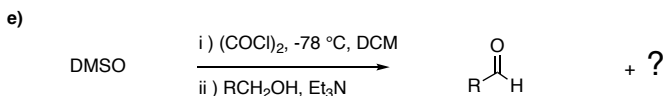
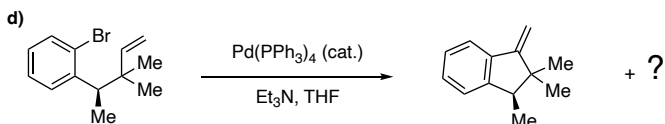
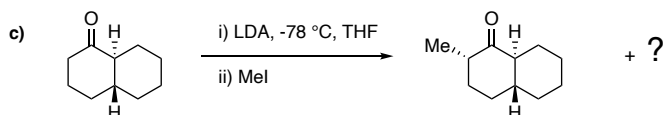
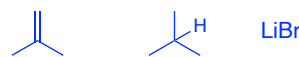
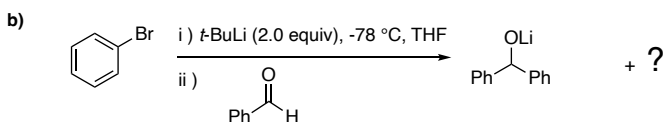
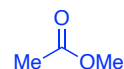
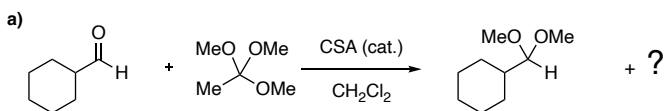
There are 100 points and six questions on the exam.

Answer all questions directly in the space provided on the five exam pages.

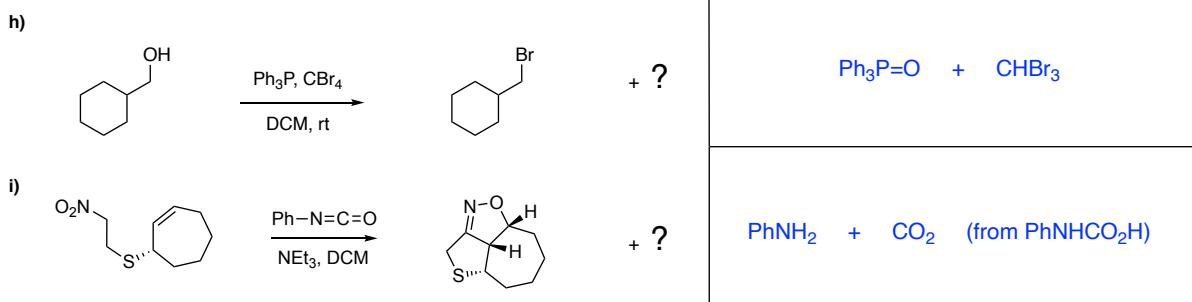
You may not use books, notes, phones, etc.

Part I 27 / 27**Part II** 12 / 12**Part III** 12 / 12**Part IV** 8 / 8**Part V** 37 / 37**Part VI** 4 / 4**Total** 100 / 100

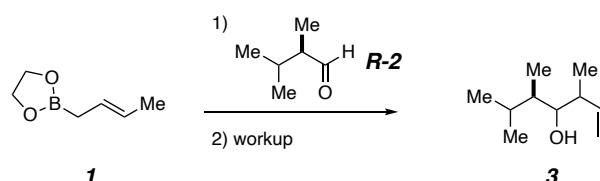
- I. (27) Provide the structure(s) of the byproduct(s) that, together with the indicated main product, constitute(s) a stoichiometrically and fully balanced reaction equation for each of the following nine (a-i) transformations. Note that in many instances, there is more than one byproduct.



I. (cont.)

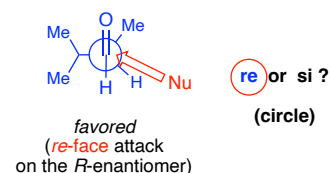


II. (12) The alkene in allylic boronates such as **1**, an *E*-2-butenyl (or crotyl) boronate, are nucleophilic. They will add to aldehydes through a process that can be rationalized using a chair-like transition state geometry similar to that invoked to describe boron enolate aldol addition reactions. Addition of **1** to the chiral aldehyde **R-2** produces the homoallylic alcohol **3**.

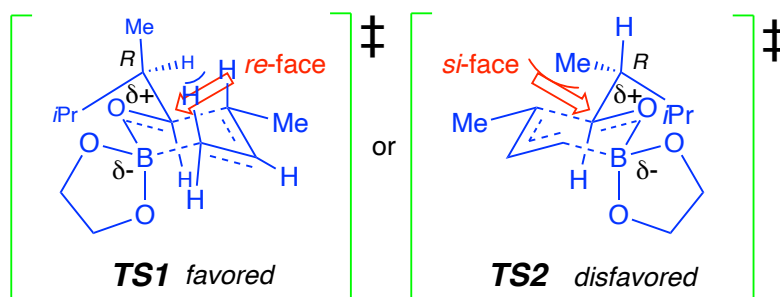


- a) (5) Provide a (short) Felkin-Ahn analysis to deduce which diastereotopic face of **R-2** will be preferentially attacked by a nucleophile. Briefly describe your reasoning; use a Newman projection to support your explanation. Is it the re- or the si-face of the aldehyde in **R-2** that is more easily attacked?

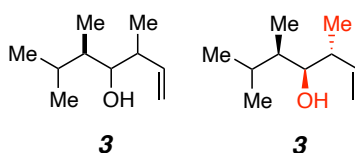
With the large isopropyl group orthogonal to aldehyde carbonyl and in the rotamer shown in the Newman projection, the preferred Bürgi-Dunitz approach angle for the nucleophilic attack brings the nucleophile past the smallest group on the back alpha carbon, the hydrogen atom. This is attack on the re-face of the aldehyde.



- b) (5) Choose one or the other of the two chair-like templates **TS1** or **TS2** to show the orientation of all of the relevant substituents on the six core atoms to depict the most stable transition state geometry. Add all of the missing groups/substituents or atoms.

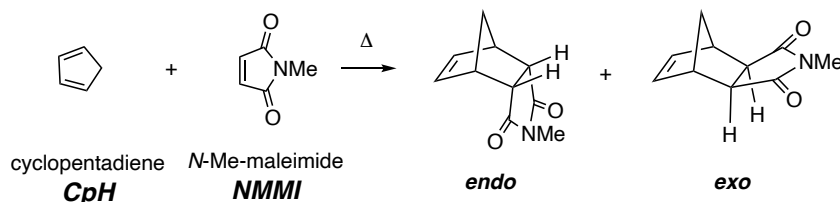


- c) (2) On the structure below clearly indicate the configuration of the two newly created stereocenters in the major stereoisomer of the product **3**; your answer should be consistent with the drawing of the transition state geometry that you created in answer b).

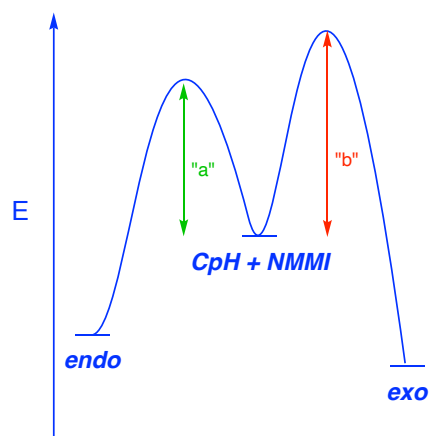


- III. (12 points)** Discuss the concept of kinetic vs. thermodynamic control as it applies to the energetics of the following Diels-Alder reaction. When *N*-methylmaleimide (NMMI) is allowed to react with cyclopentadiene (CpH) at room temperature, the ratio of the *endo* and *exo* products is 19 : 1. When the reaction is performed at 90 °C (or if the solution of the initial 19 : 1 mixture is subsequently heated to 90 °C), the ratio of *endo* to *exo* becomes 1 : 9, regardless of whether that ratio is measured after one day or one week.

Limit your answer to the space inside the box below. Use an energy diagram. Three–five sentences should suffice for your answer. There is no need to explain the origin of the selectivity (i.e., the secondary orbital interactions in the transition states or steric features of the products). I am looking for a qualitative description that compares the relative energies of the products and transition states leading to them, not a description that converts ratios into quantitative energy differences in ΔG° or $\Delta\Delta G^\ddagger$.



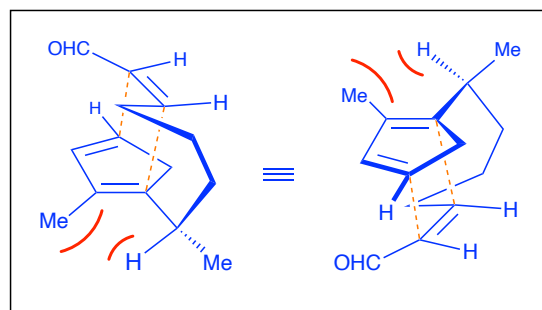
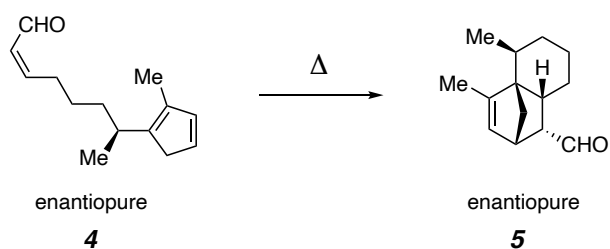
This is an example of a reaction that can lead to two products where the less stable of the two (the *endo* isomer) is formed more rapidly than the more stable counterpart (the *exo* isomer). As shown in the simple potential energy diagram to the right, the activation barrier for formation of *endo* from **CpH** + **NMMI** is lower than barrier leading to *exo*, even though G° of *exo* is below that of *endo*. Under conditions where the reverse reaction of *endo* back to **CpH** + **NMMI** is sufficiently slow, the product ratio will reflect the relative heights of the two activation barriers (i.e., *endo* will be the predominate product). At higher temperature and/or longer times, the system will approach its equilibrium state, and the product ratio will reflect the relative free energies of the two products (i.e., *exo* will predominate to the extent dictated by $\Delta G^\circ_{endo/exo}$).



Alternative language for an explanation:

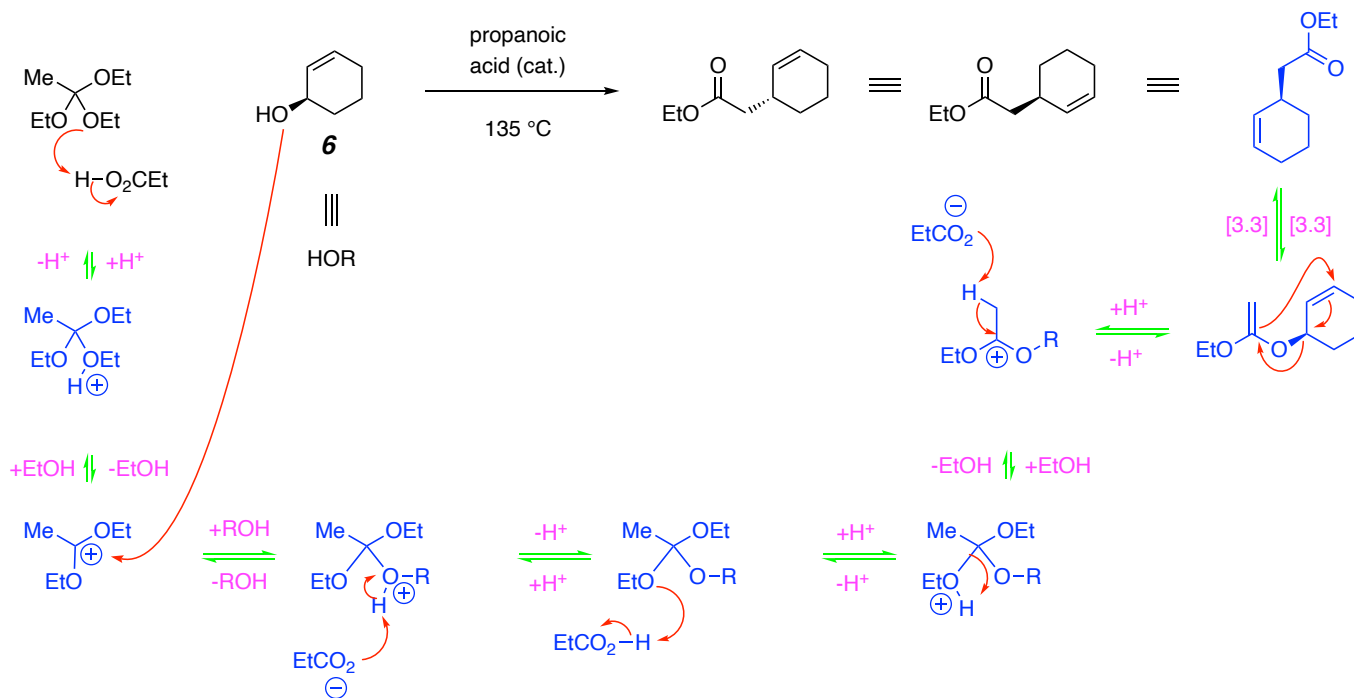
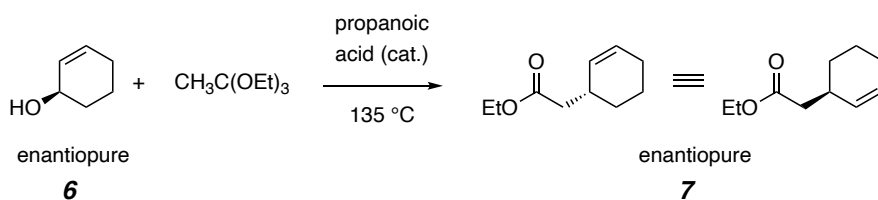
The energy of activation for the cycloaddition of **CpH** with *N*-methylmaleimide (**NMMI**) to give *endo* ("a"), is lower than that to give *exo* ("b"). Therefore, *endo* is the kinetically favored product. The *exo* is more stable than *endo*. Given enough time and energy, the system will equilibrate to give a preponderance of *endo*. The overall rate limiting step for the equilibration is cycloreversion of *endo* back to **CpH** and **NMMI**.

- IV. (8)** Heating enantioenriched trienal **4** results in an intramolecular Diels-Alder reaction to give the tricyclic product **5** with the same level of enantiopurity as that of **4**. In the box provided, carefully draw a transition state structure that is consistent with the formation of the four new stereocenters in **5**. Make clear the $A^{1,3}$ -strain interaction that is important in leading to the high level of diastereoselectivity observed in this reaction.

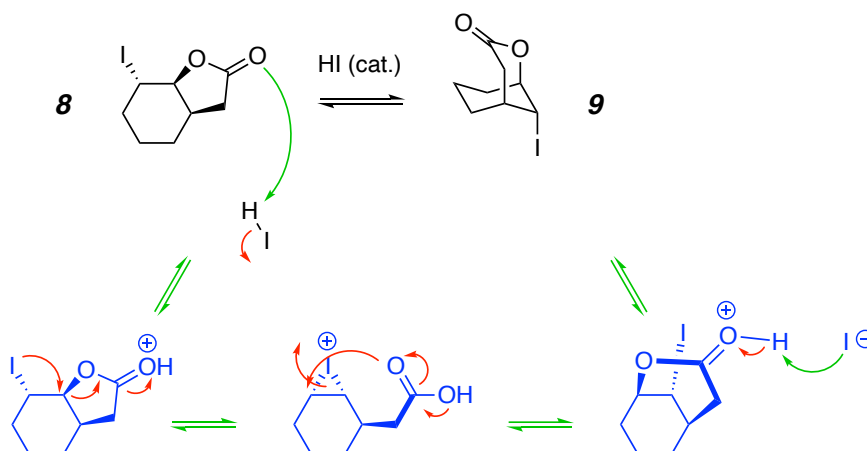


V. (37) Provide a *detailed mechanism* to account for each of the following three reactions. Show *ALL* intermediates, equilibria, and bond-making and -breaking steps. For species that have more than one significant resonance contributor, you only need to show one of them.

a) (16) The Johnson orthoester Claisen rearrangement of **6** to **7**.

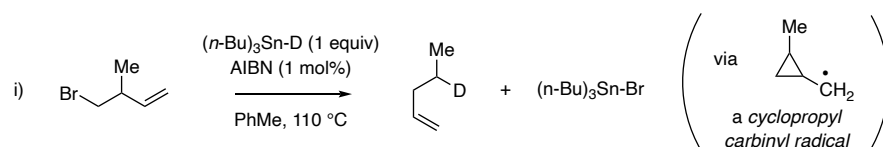


b) (9) The equilibration of the isomeric iodolactones **8** and **9**, catalyzed by hydroiodic acid.

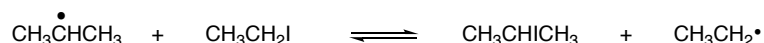


c) (12) Here is some relevant and new information that we have not specifically discussed and that should help you deduce the detailed mechanism for the reaction of **10** to give **11** (below).

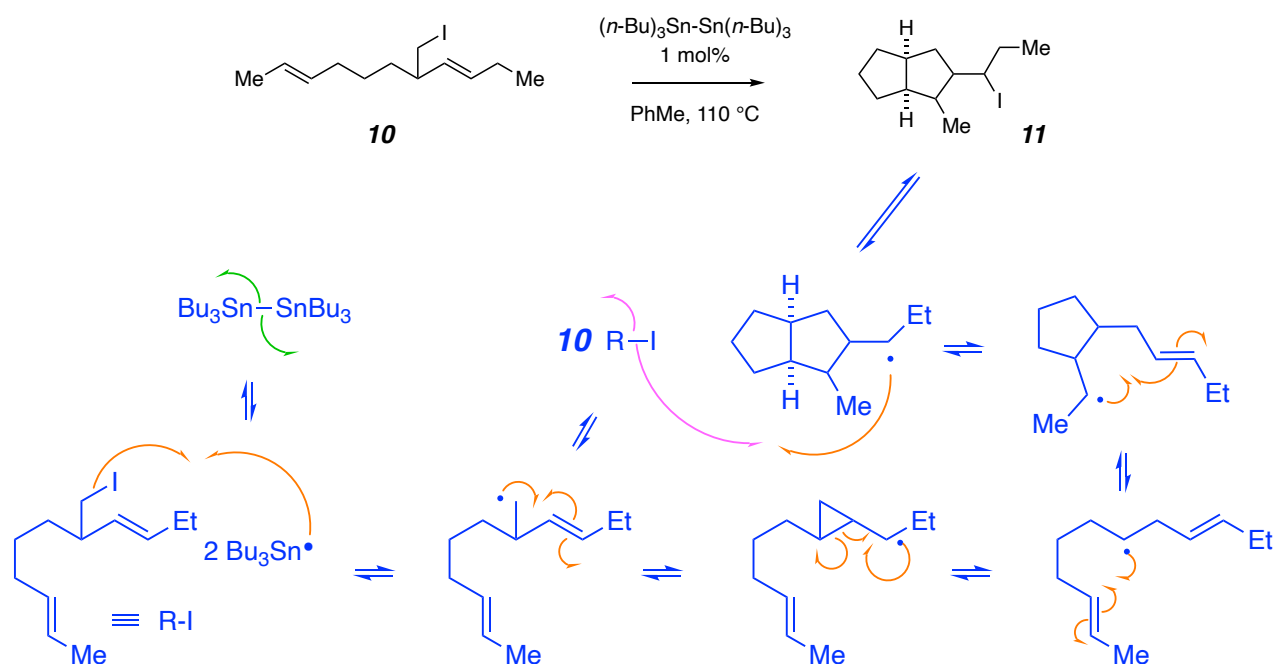
i) cyclopropyl carbinyl radicals form, reversibly and rapidly, from homoallylic radicals as seen in the outcome of this deuteration reaction:



ii) equilibrations such as the following are facile (i.e., fast):

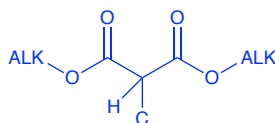


The conversion of the iodide **10** to **11** is an example of an "atom-transfer radical cyclization." Notice that **10** and **11** are isomeric. Only a small amount of the tin reagent (a distannane) is used; no tin hydride reducing agent is present. The tin-tin bond in hexabutyldistannane is weak and homolyzes relatively easily in refluxing toluene to initiate this transformation. Ignore the stereochemical features of the reaction.



VI. Reaxys (4)

Provide the query you would use to answer the following question: How many structures of dialkyl esters of malonic acid (propanedioic acid) that are mono-substituted (with a carbon substituent) at C2 are contained in the Reaxys® database?



* * * end of exam * * *