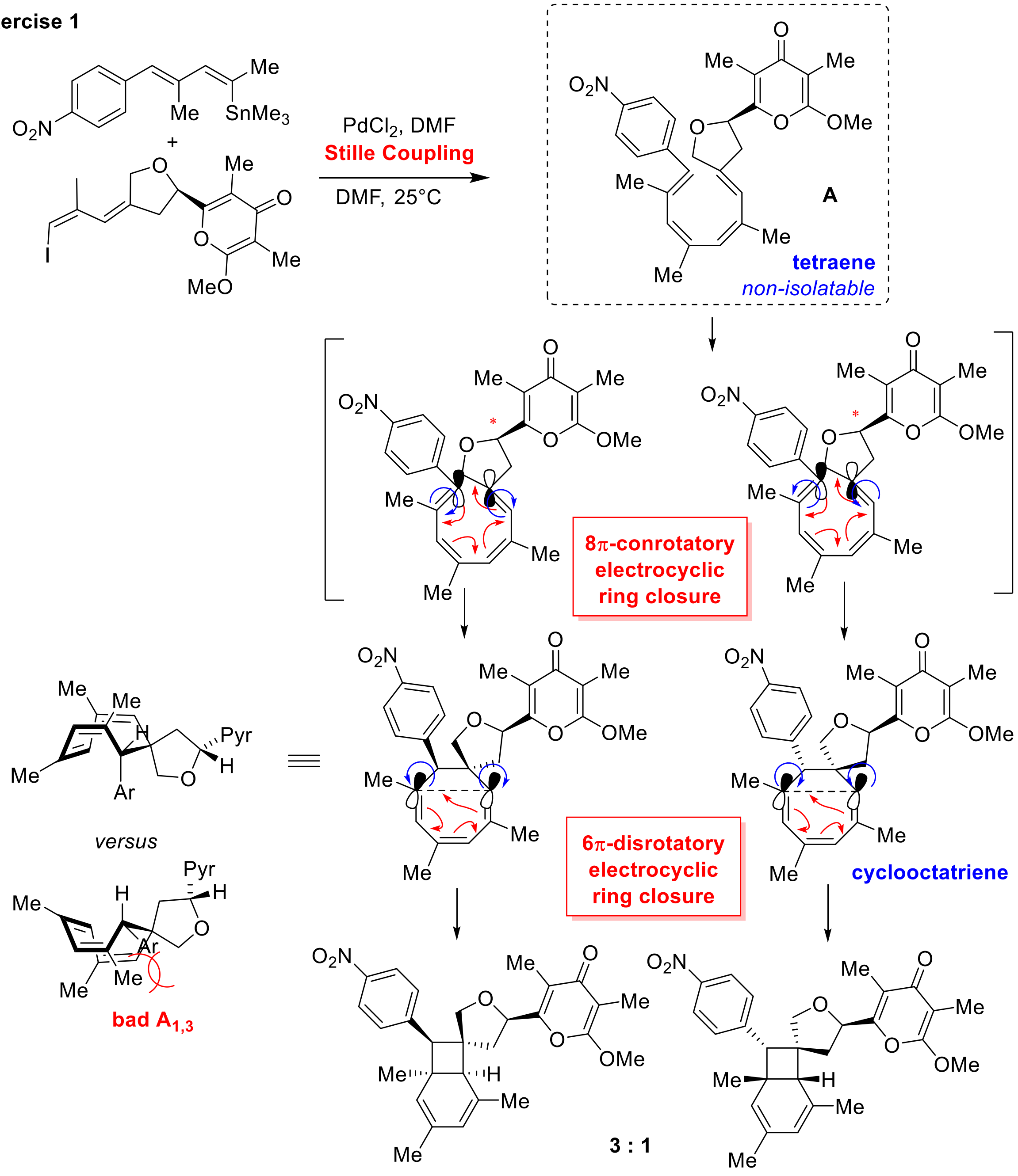
Structure and Reactivity 2025 - Ex Session 2: Cyclizations & Cycloadditions

Exercise 1

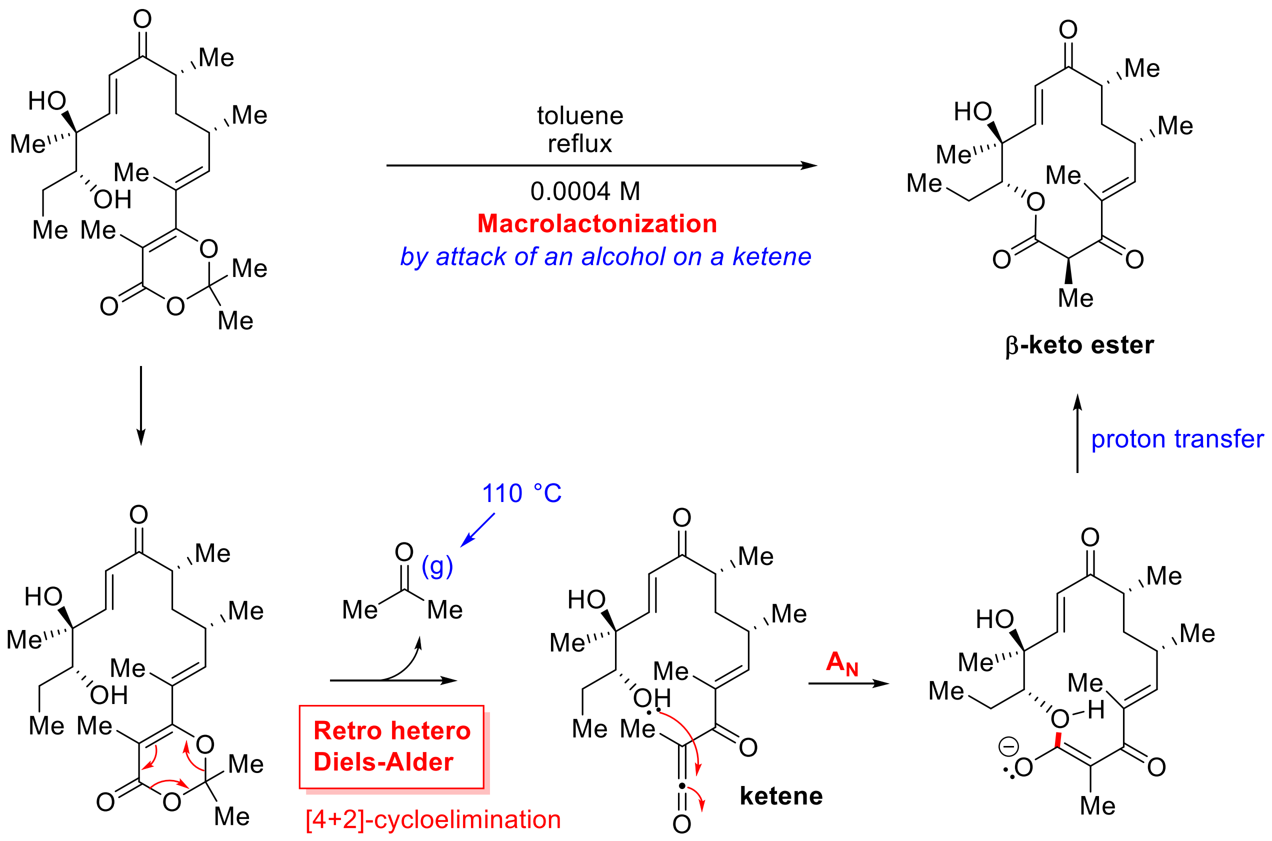


The first step is a palladium-catalyzed cross-coupling reaction (Stille coupling) that gives the shown tetraene intermediate. The drawn intermediate is so reactive that it cannot be isolated, and reacts directly to the products.

The second step is a 8-pi electron conrotatory electrocyclic ring closure that gives the cyclooctatriene. Two ways of conrotatory cyclization are possible leading to the two shown diastereomers (observable because there is already the indicated stereogenic center in the starting material).
This stereocenter also slightly directs the reaction to give the observed 3:1 product ratio.

In the third step, both cyclooctatrienes undergo a 6-pi electron disrotatory ring closure to give the final product.
In principle, again two sense of rotation would be possible, leading to four potential products.
However, two of them would have bad interactions and are not observed (as shown once for the left diastereomer).

Exercise 2



The shown macrolactonization method proceeds under perfectly neutral conditions.
Consequently, an acid-catalyzed process cannot be proposed.

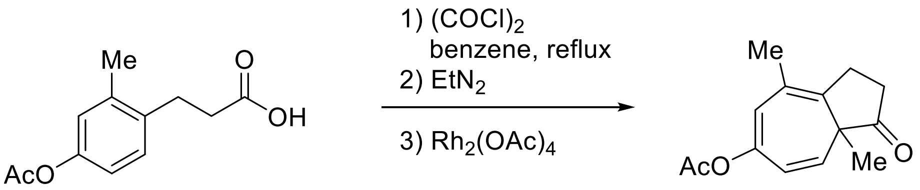
Upon heating under reflux in toluene (110 °C), a retro hetero Diels-Alder reaction
(hence, a [4+2]-cycloelimination) occurs under formation of acetone (which is a gas at this temperature,
and thus the driving force of the reaction).

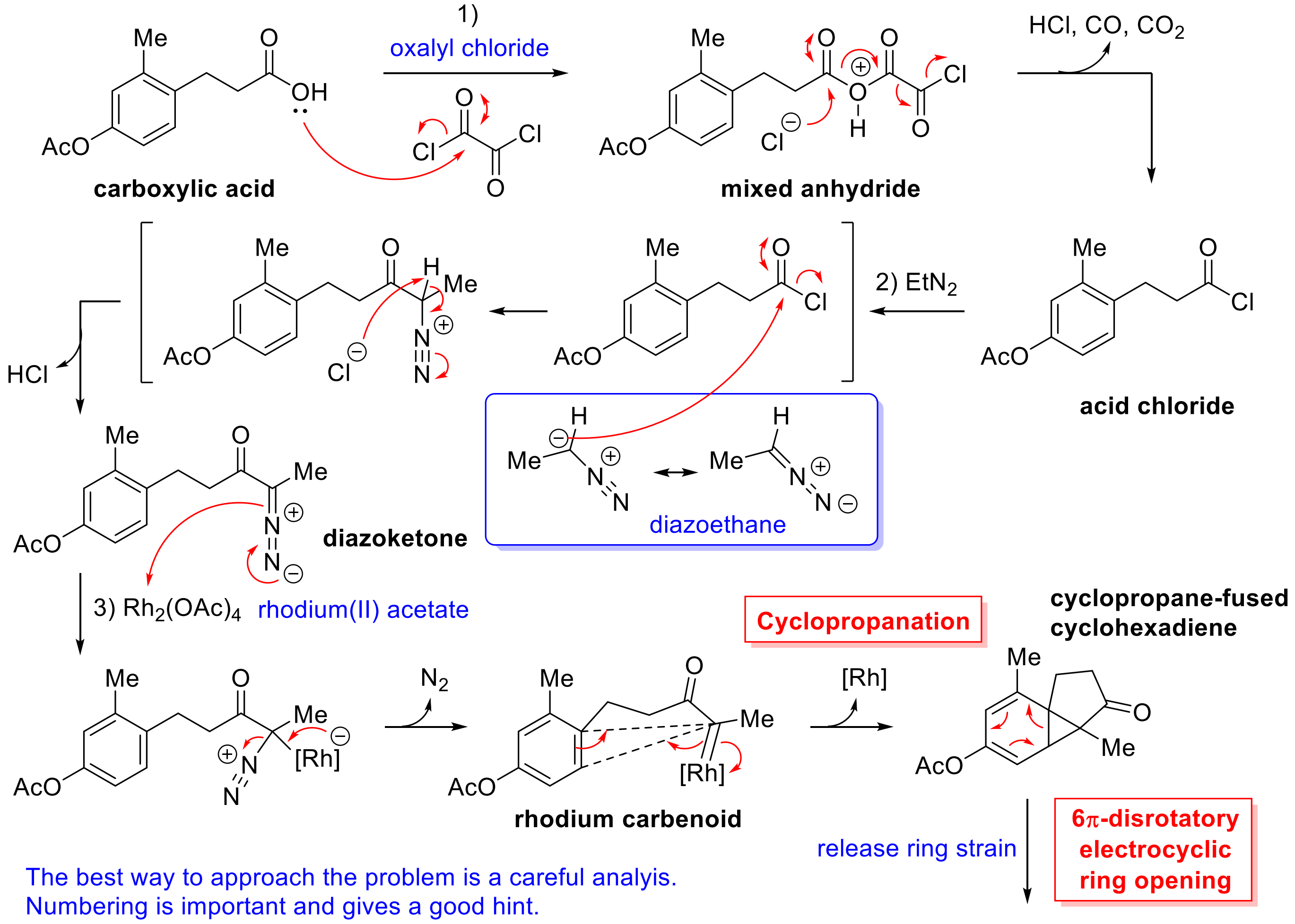
Secondly, the formed ketene is a very powerful electrophile and reacts spontaneously with the free alcohol.

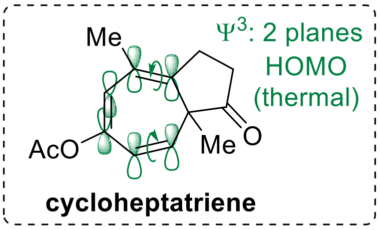
In the last step, a proton transfer occurs. The stereochemistry of the formed center is determined by the
thermodynamic stability, as facile epimerisation occurs for substituents on acidic beta-keto esters.
The stereochemistry, however, cannot be predicted with simple models.

The low concentration of the reaction is essential to prevent intermolecular (dimerization or polymerization) reactions.

Exercise 3:







The best way to approach the problem is a careful analyis.
Numbering is important and gives a good hint.

There are two carbon atoms more in the product then the starting material, and the benzene ring has reacted! The only possible source of the two new carbons is the diazoethane added in step 2. Then it is best to proceed stepwise, using the known reactivity of the reagents.

The reaction of acids with oxalyl chloride (or alternatively thionylchloride) is a classical method for the formation of acid chlorides. In this case, it proceeds via the formation of a mixed anhydride, followed by fragmentation with liberation of carbon monoxide, carbon dioxide and hydrogen chloride.
Note that this reaction is usually DMF-catalyzed (and proceeds via the so-called Vilsmeier reagent).

For step 2, it is important to remember the relative nucleophilicity of diazo compounds on the carbon, apparent in the drawn resonance structure, and the strong electrophilic character of acid chlorides.
Elimination of hydrogen chloride forms then the new diazoketone, which is moderately stable.

The reaction of diazo compounds with rhodium(II)-catalysts such as Rh$_2$(OAc)$_4$ is the classical way to generate rhodium carbenoids, while releasing dinitrogen gas.
Rhodium carbenoids react fast with double bonds - even the poorly reactive ones of a benzene ring - to give cyclopropanes.

Lastly, the formed strained cyclohexadiene undergoes then a 6-pi electron disrotatory electrocyclic ring opening, which is driven by the release of ring strain, to give the final product.