Exam 5: 2013 mean ... 74
2014 mean ... 0 8 0
median 83

Recap:

Amines:

~as bases: basicity determined by
1) stability of conj. acid
2) energy of lone pair

Synth. of amines

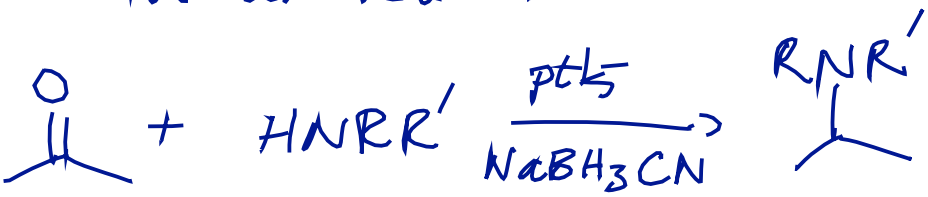
1) Reduction of azides

$$R-N_3 \xrightarrow[Pd/C]{H_2} R-NH_2$$

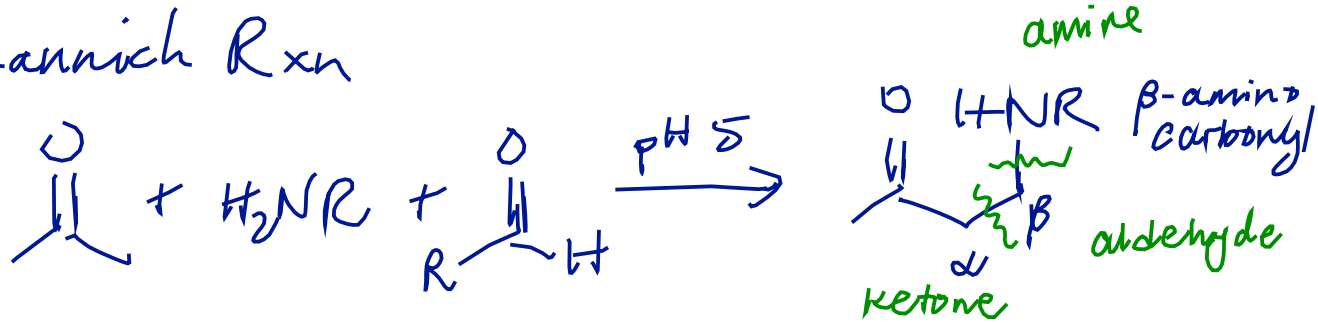
2) Reduction of nitriles

$$R-C\equiv N \xrightarrow[\text{1) LiAlH}_4\text{, 2) H}^+\text{ w/up}]{H_2,\ Pd/C} R-CH_2-NH_2$$

3) Reductive amination



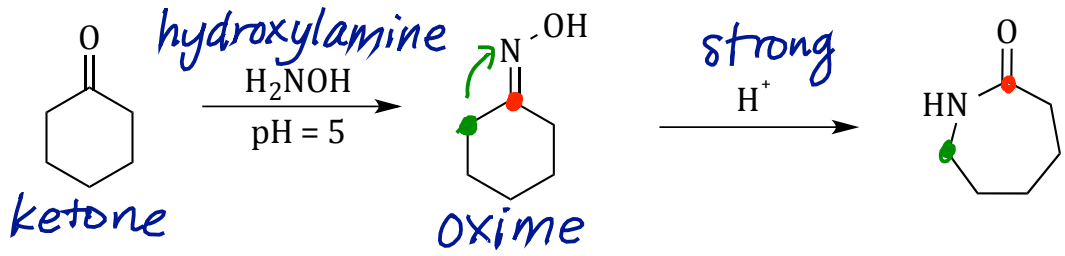
4) Mannich Rxn



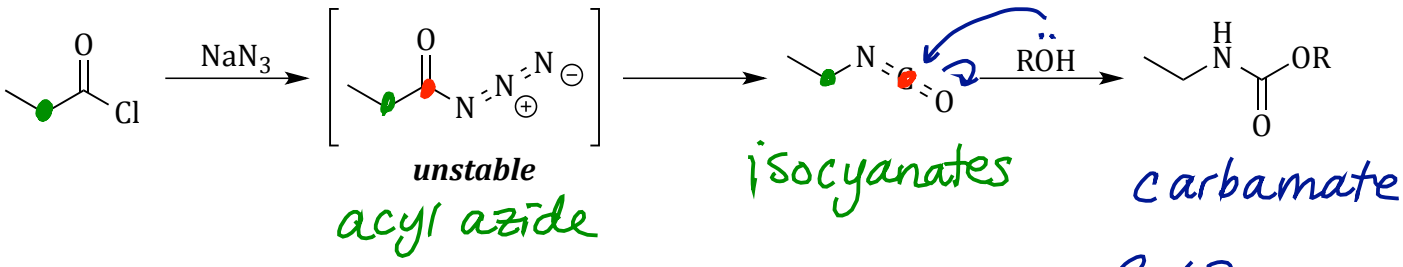
1,2-Alkyl Migration to Nitrogen

There are three similar reactions in which an **alkyl group** undergoes a migration (shift) onto a nitrogen atom. These reactions are:

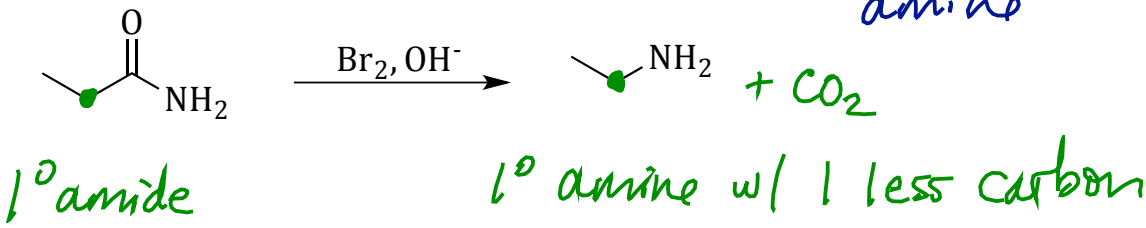
The **Beckmann Rearrangement:**



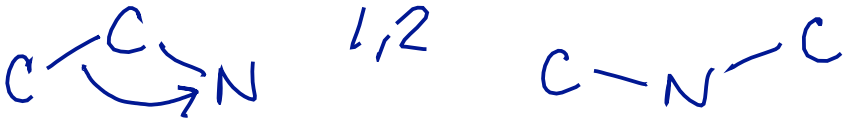
The **Curtius Rearrangement:**



The **Hofmann Rearrangement:**



What is the common feature of the mechanisms of all three of these reactions?

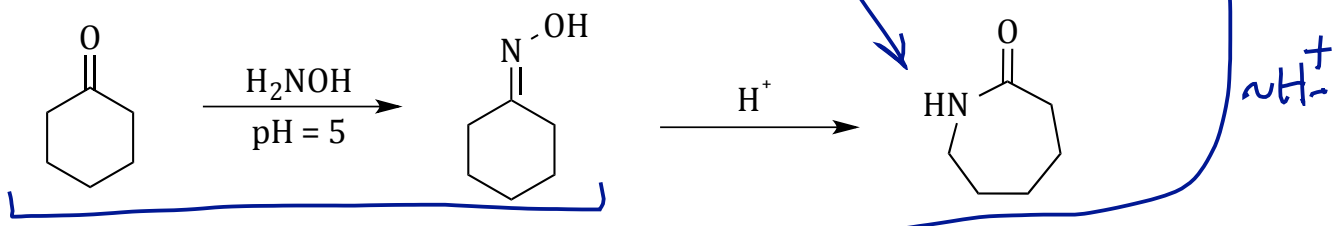


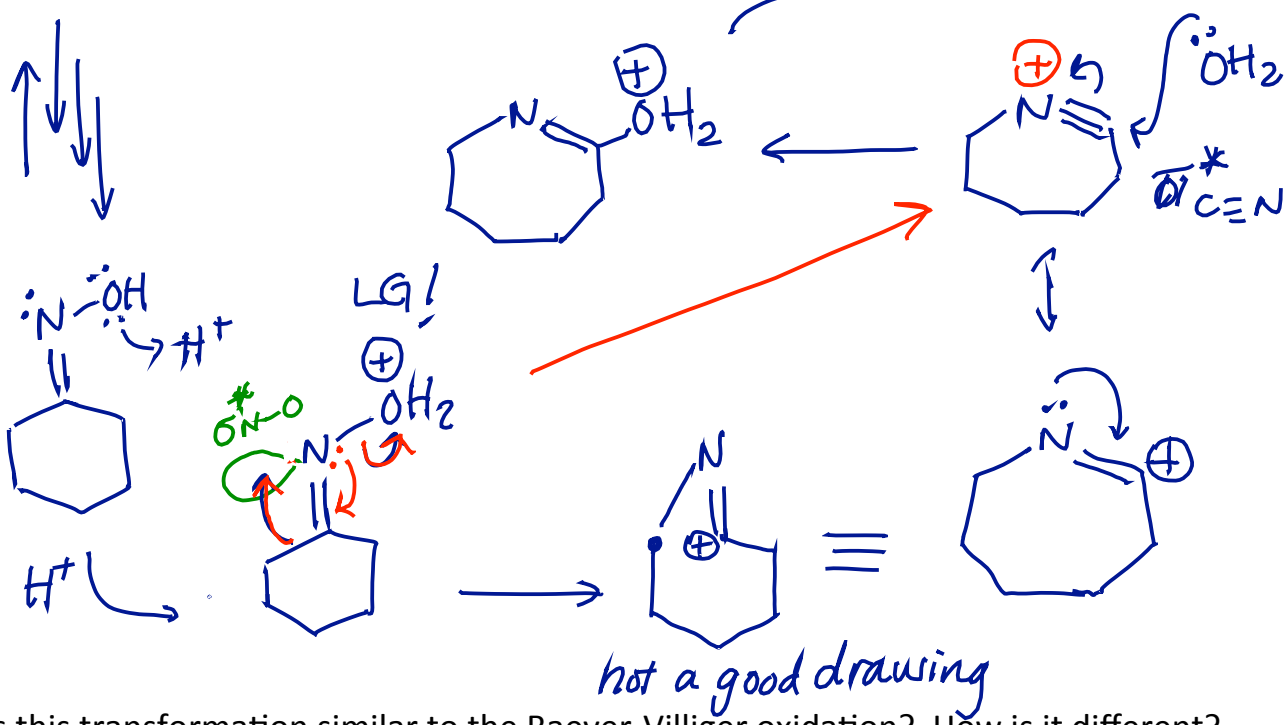
Reading: Section 23.11D

Week 6 July 29, 2014

The Beckmann Rearrangement

Show the mechanism of the following reaction:

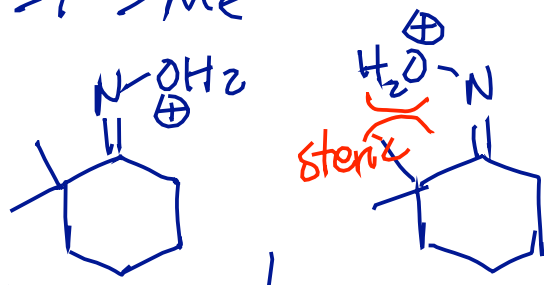




How is this transformation similar to the Baeyer-Villiger oxidation? How is it different?

both ketone oxidation ⟶ CAD

migration: 3° > 2° > Ph > 1° > Me

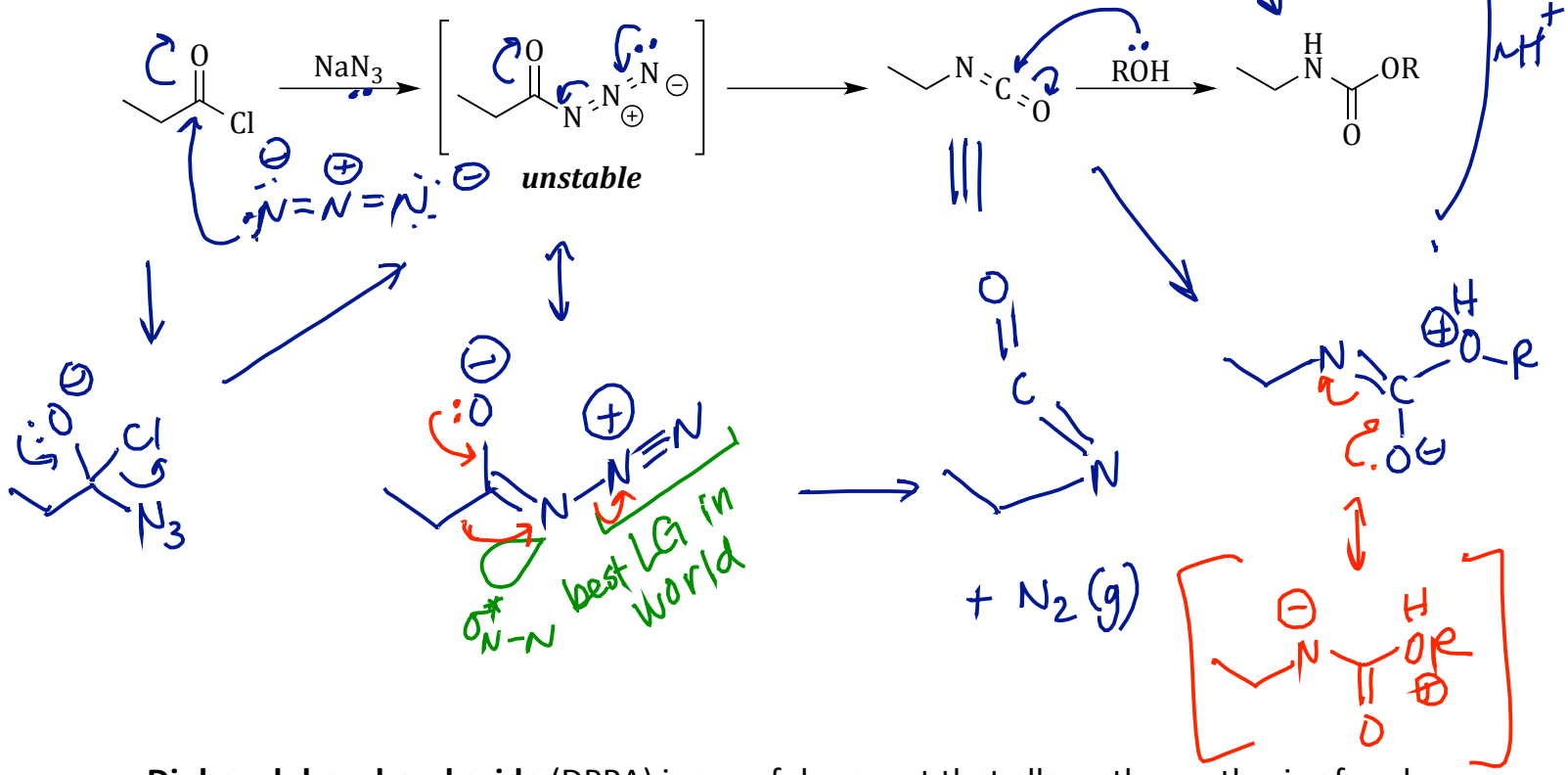


Reading: Section 23.11D

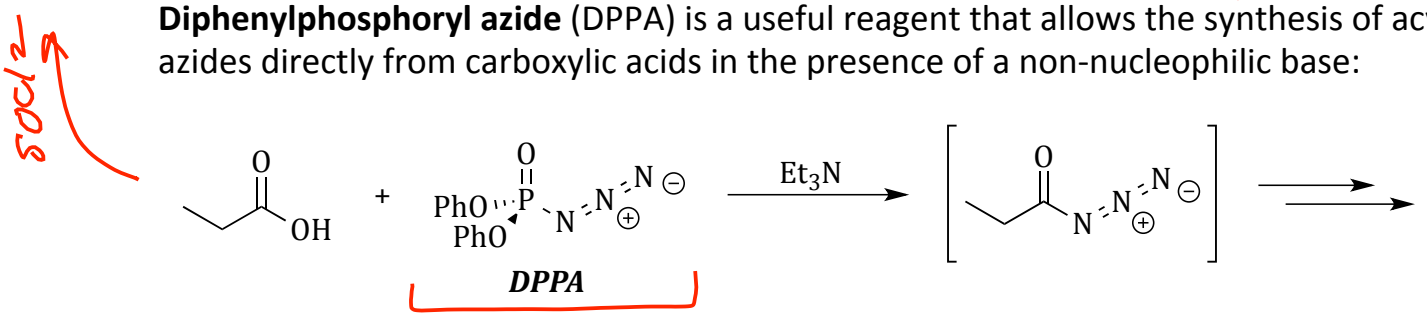
Mechanisms are different!

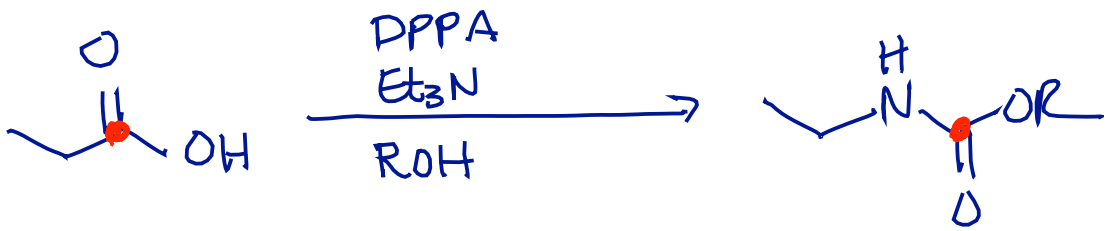
The Curtius Rearrangement

Show the mechanism of the following reaction:



Diphenylphosphoryl azide (DPPA) is a useful reagent that allows the synthesis of acyl azides directly from carboxylic acids in the presence of a non-nucleophilic base:



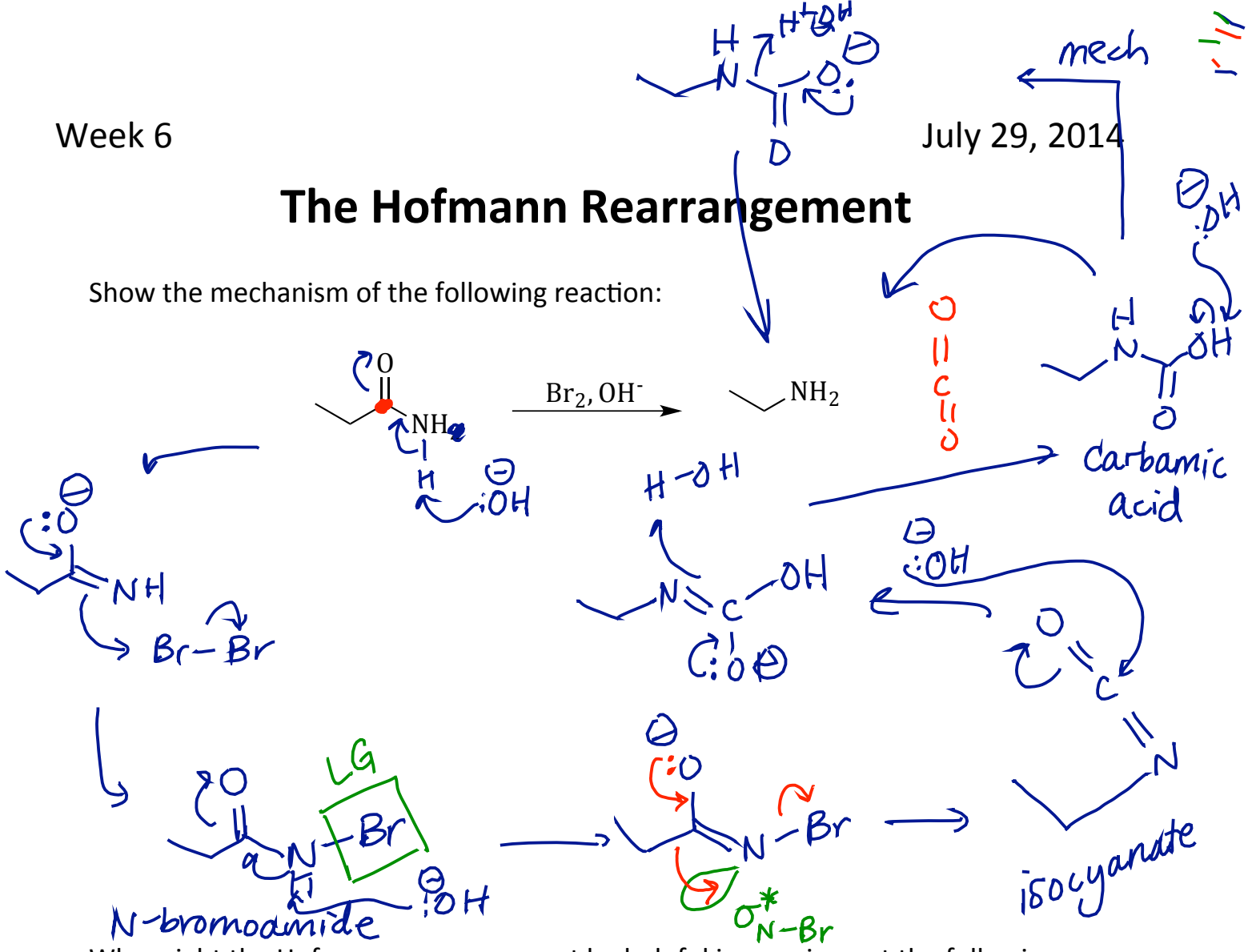


Reading: Section 23.11D

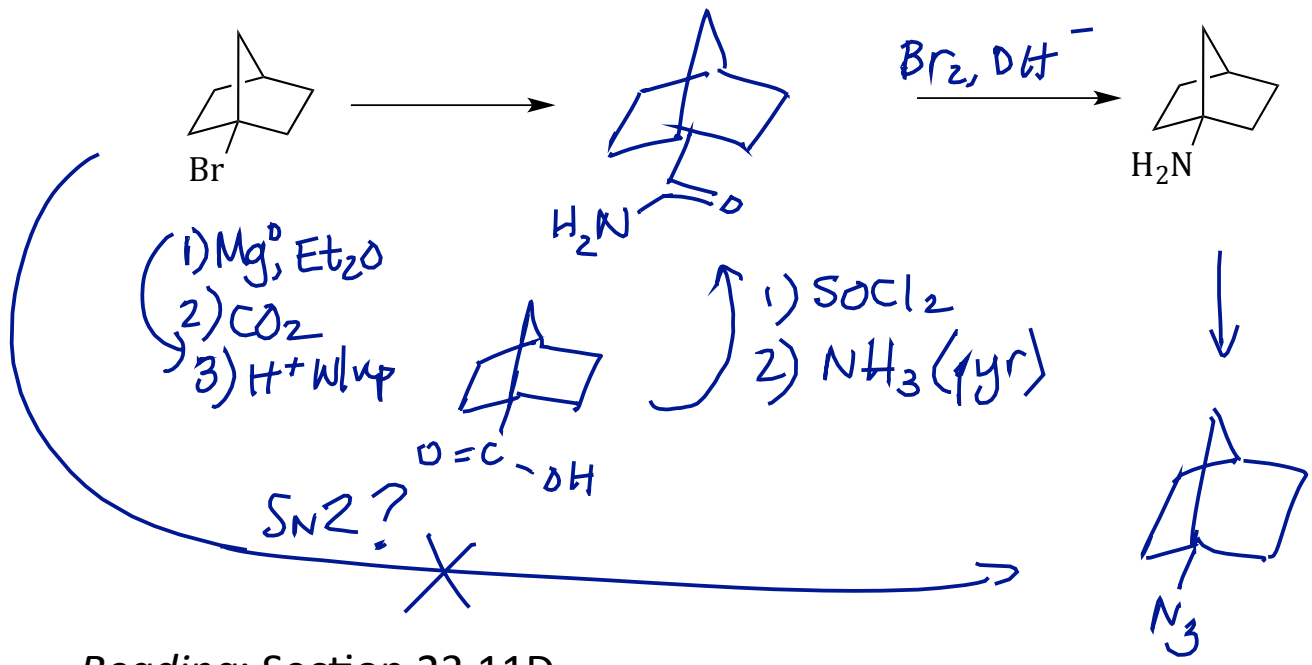
Week 6 July 29, 2014

The Hofmann Rearrangement

Show the mechanism of the following reaction:

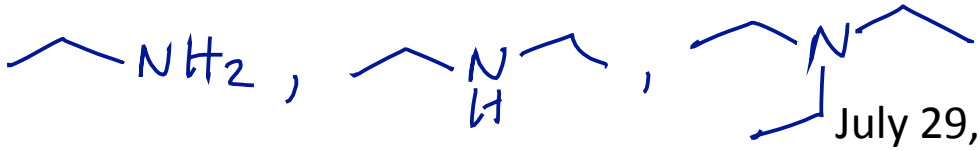


Why might the Hofmann rearrangement be helpful in carrying out the following transformation?



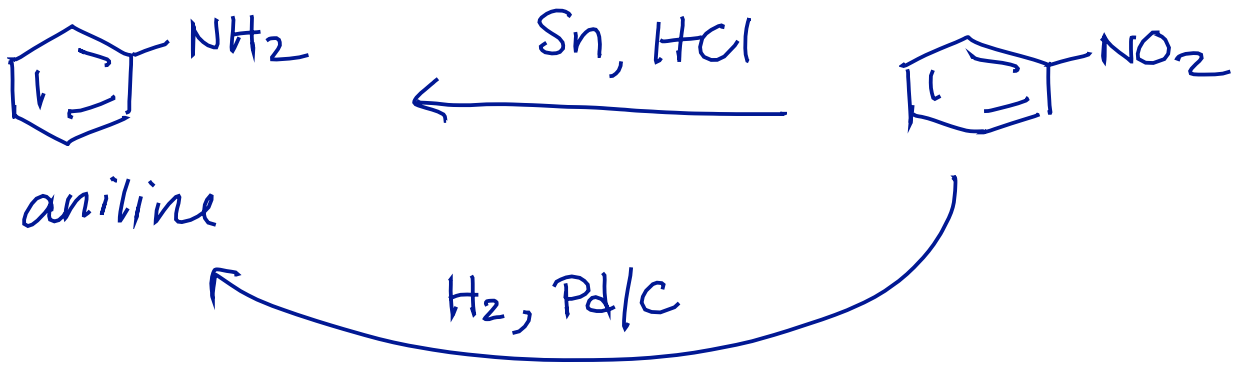
Reading: Section 23.11D

DCC doesn't work w/ NH_3

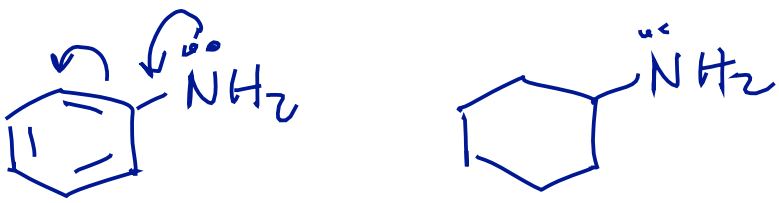


Aromatic Amines: Synthesis & Reactivity

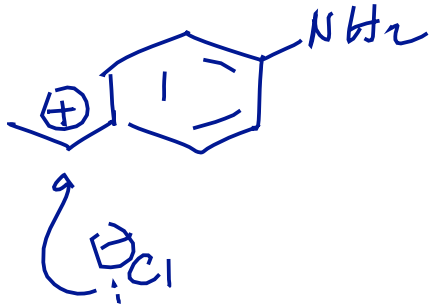
Aniline is an example of an aromatic amine. What is the structure of aniline. How can you synthesize aniline from benzene?



What reactivity is exhibited by aniline and other aromatic amines?



Sn, HCl

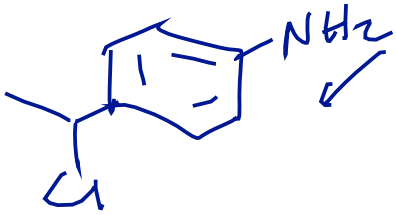


bases

nucleophiles

stabilized lp

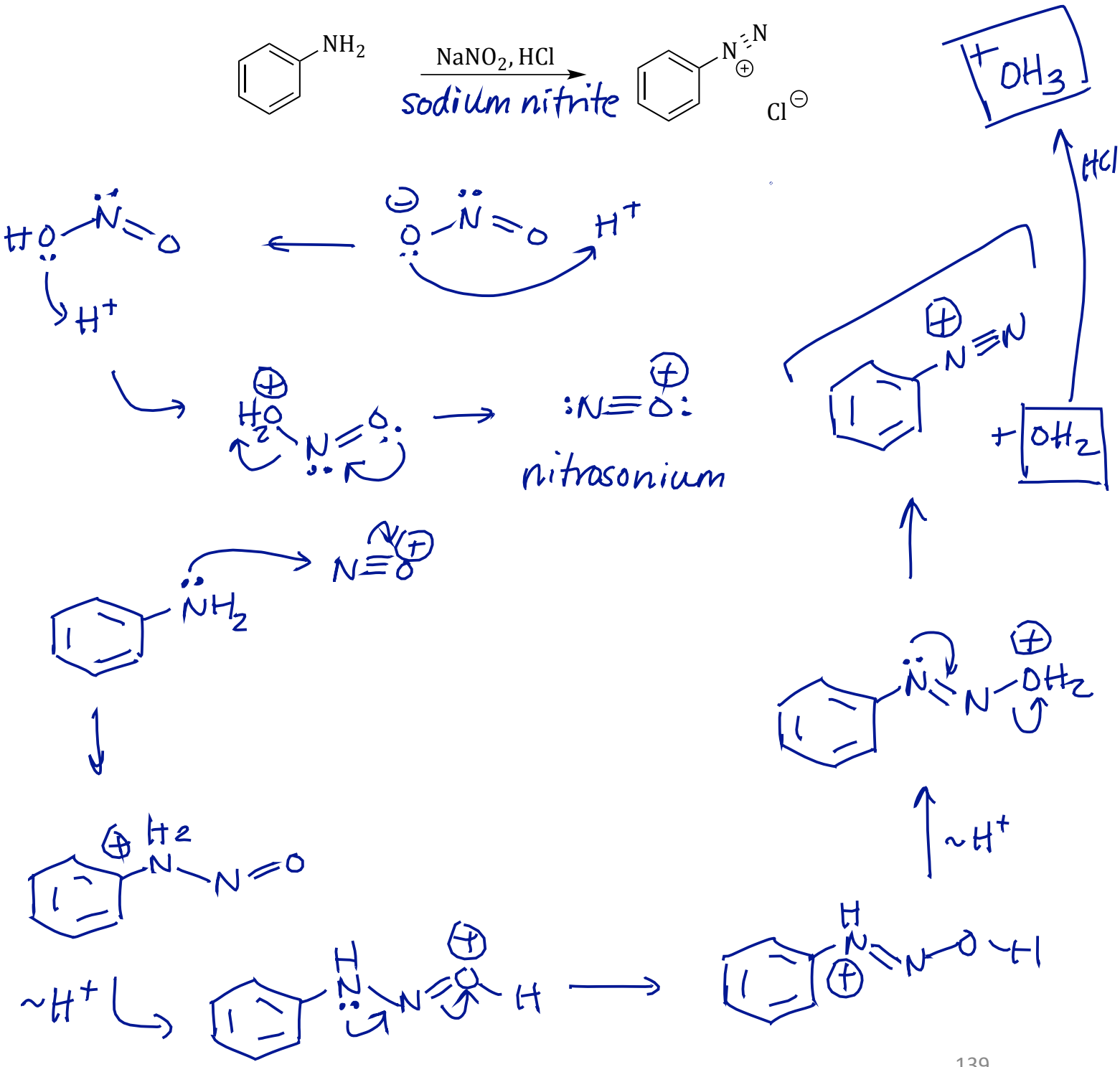
∴ less reactive



Reading: Section 23.10

Aryl Diazonium Salts: Synthesis

Show how aniline can be converted into an **aryl diazonium salt:**

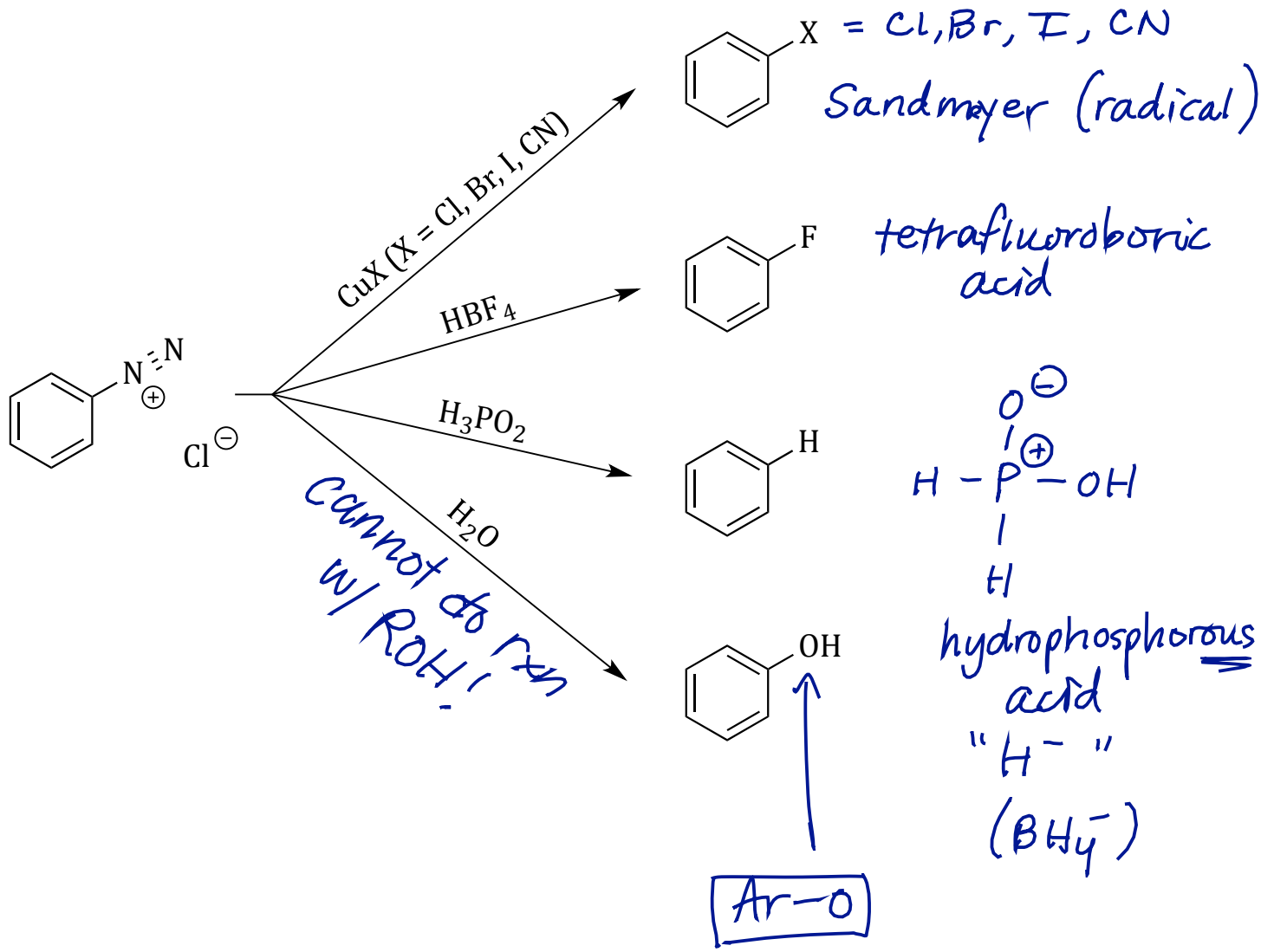


Reading: Section 23.10

Aryl Diazonium Salts:
Reactivity

Aryl diazonium salts are very useful for organic synthesis: the N_2 group (which is just about the best leaving group there is!) can be replaced by many other functional groups. Here are several examples:

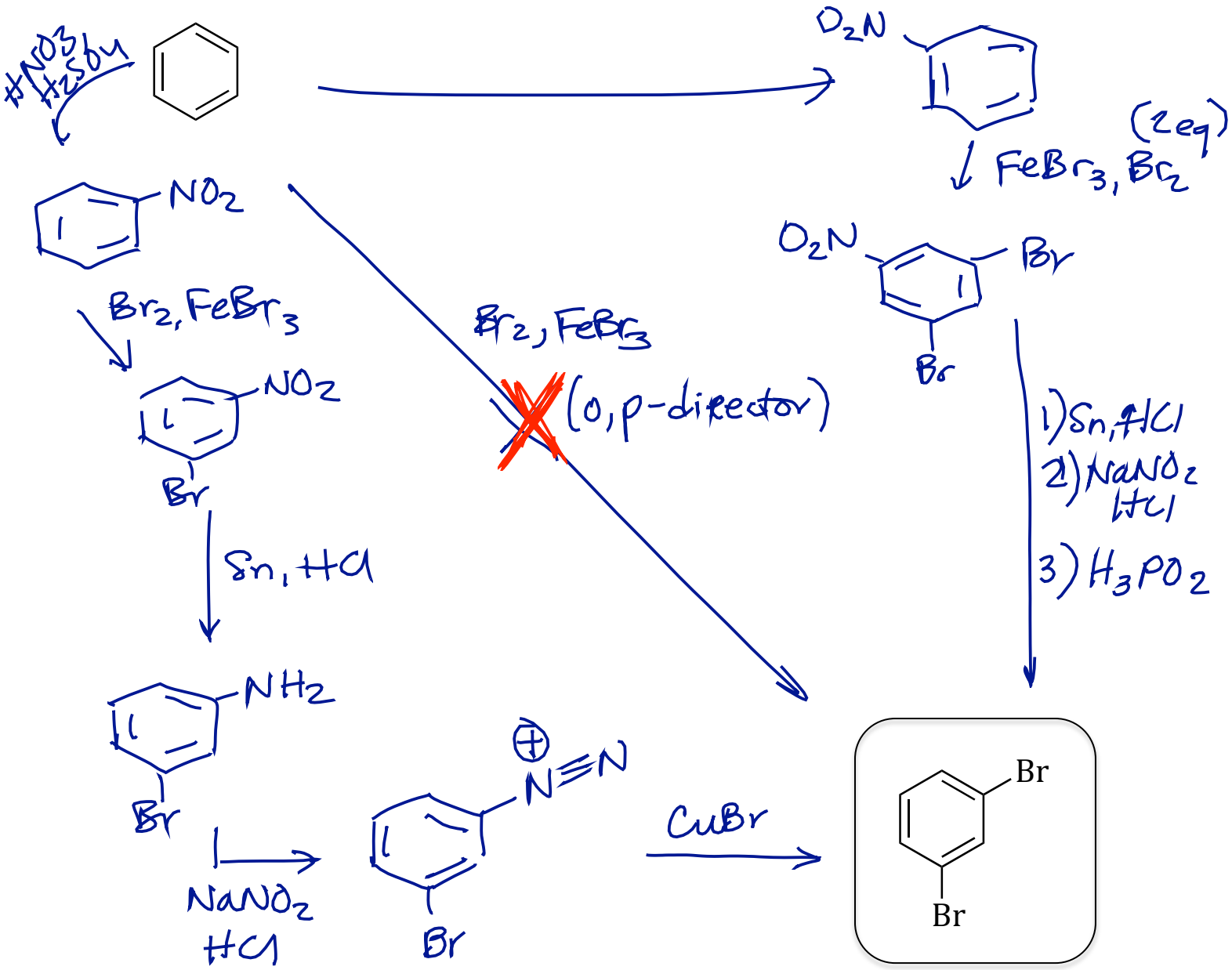
Not know mechanisms!



Reading: Section 23.10

Aryl Diazonium Salts:
Synthetic Utility

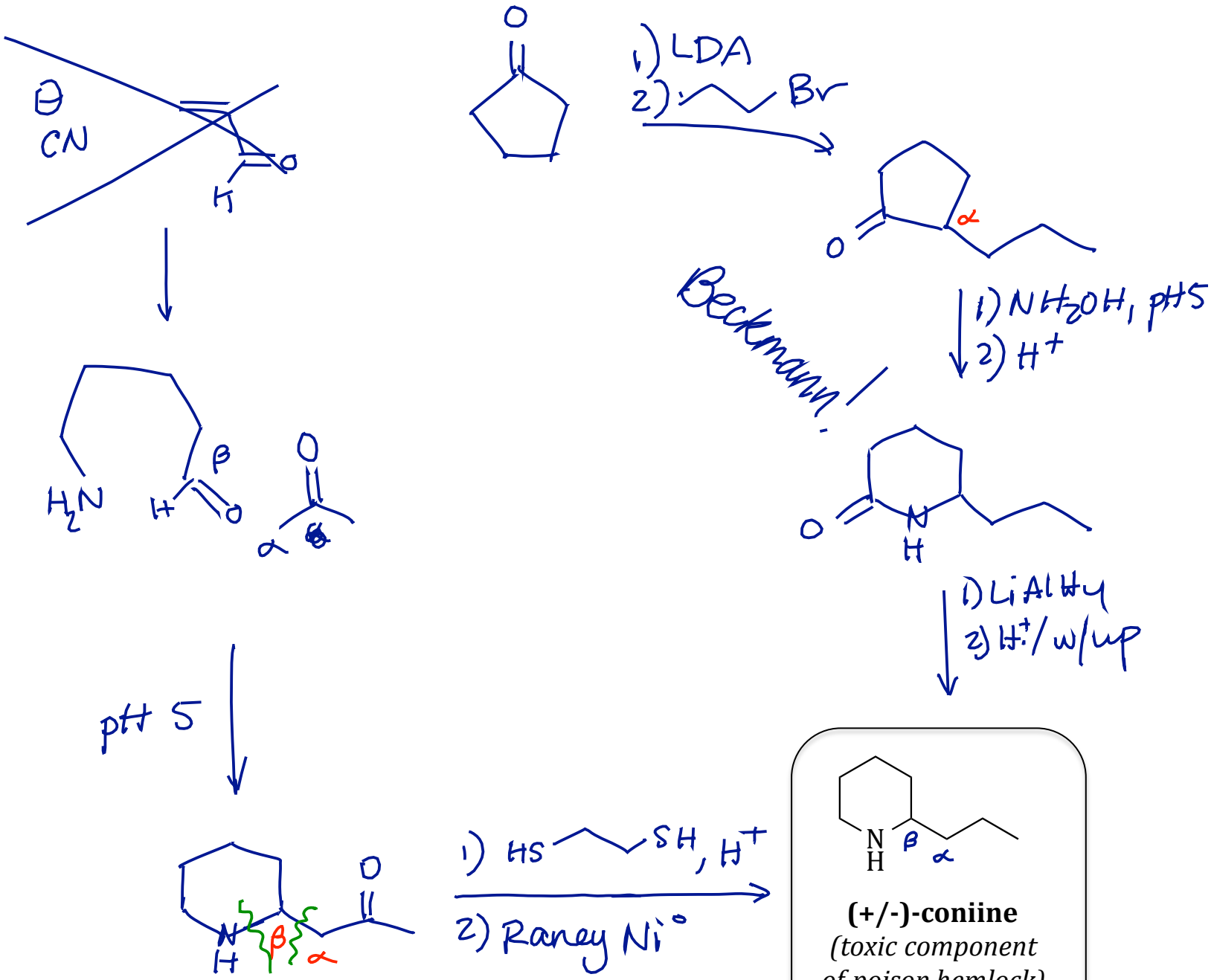
Aryl diazonium salts introduce a new set of strategies for the synthesis of aromatic compounds. Here is an example; design a synthesis of 1,3-dibromobenzene, starting only with benzene. You may use any inorganic reagents you wish.



Reading: Section 23.10

Test Yourself Now

Provide a multistep synthesis of the following natural product; you may use any reagents containing **five or fewer carbons.**



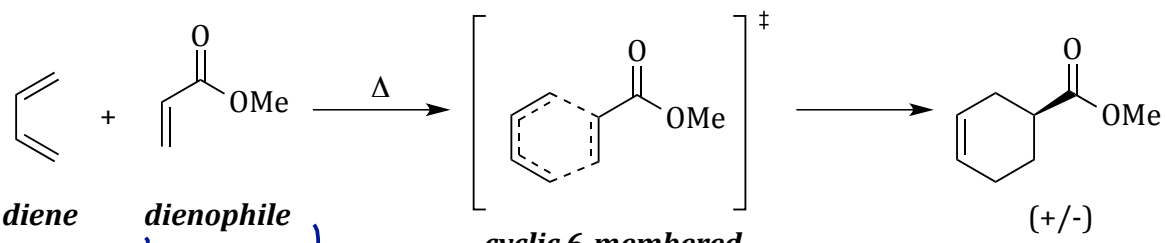
(+/-)-coniine
(toxic component of poison hemlock)

Otto Diels, Kurt Alder

Week 6 — cyclic motion of e^- — July 29, 2014

Intro to Pericyclic Reactions:
The Diels-Alder Reaction

One of the most powerful reactions in organic synthesis is known as the **Diels-Alder reaction**, after Otto Diels and Kurt Alder. Here is an example; can you "push arrows"?

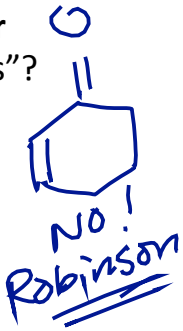


diene — conjugated

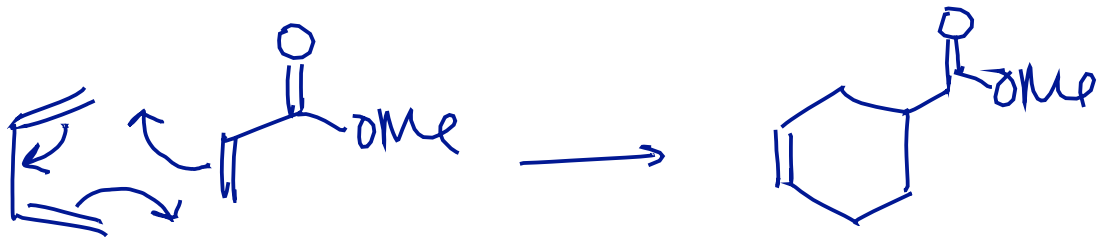
dienophile — alkene (EWG)

cyclic 6-membered transition state

cyclohexene



What are the **frontier orbital interactions** involved in the Diels-Alder reaction?



Diels-Alder 3π bonds → 2σ bonds & 1π bond

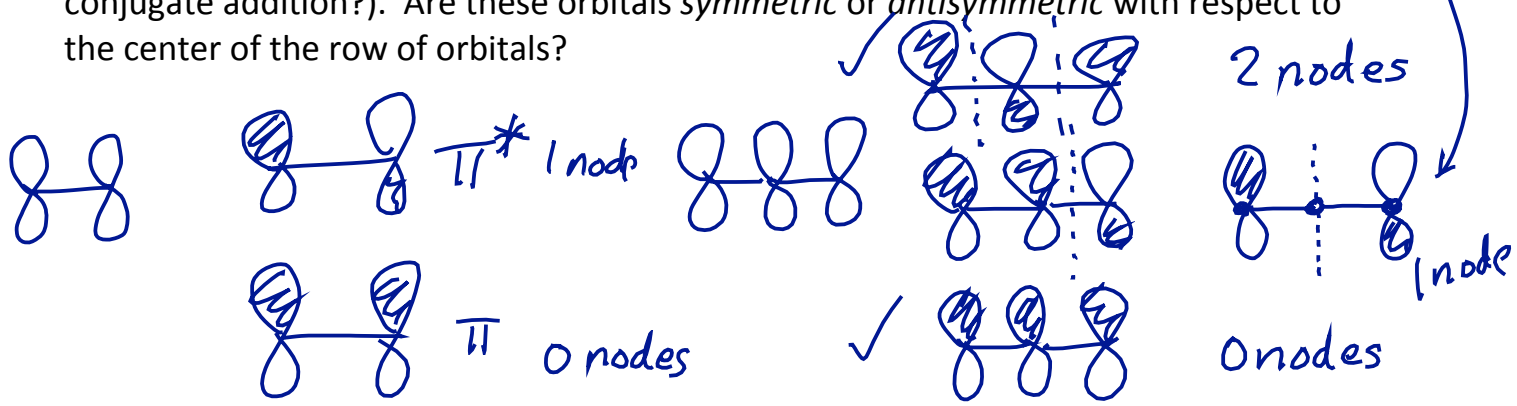
FMO: primarily HOMO of diene & LUMO of dienophile

Reading: Section 15.3

Molecular Orbitals of Conjugated Systems:
2- and 3-Orbital Systems

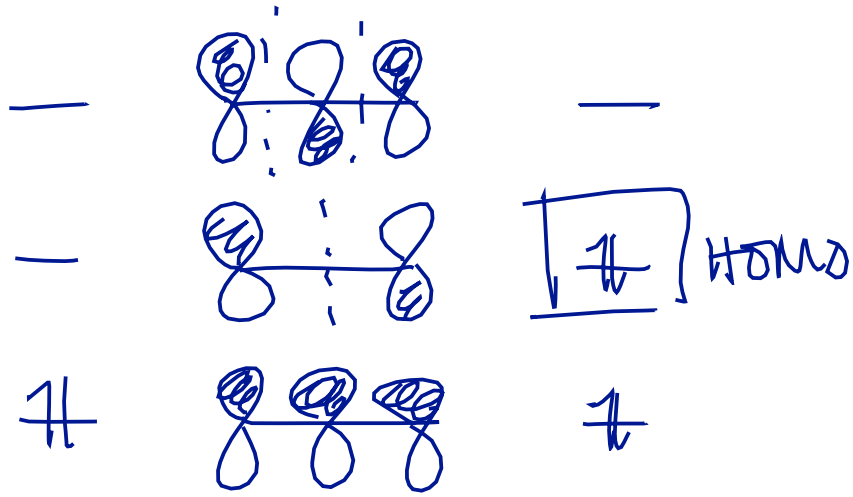
antisymmetric wrt center

Show the molecular orbitals for 2 and 3 conjugated *p*-orbitals (remember this from conjugate addition?). Are these orbitals *symmetric* or *antisymmetric* with respect to the center of the row of orbitals?



symmetric wrt the center

What kind of systems would have 3 conjugated p-orbitals?

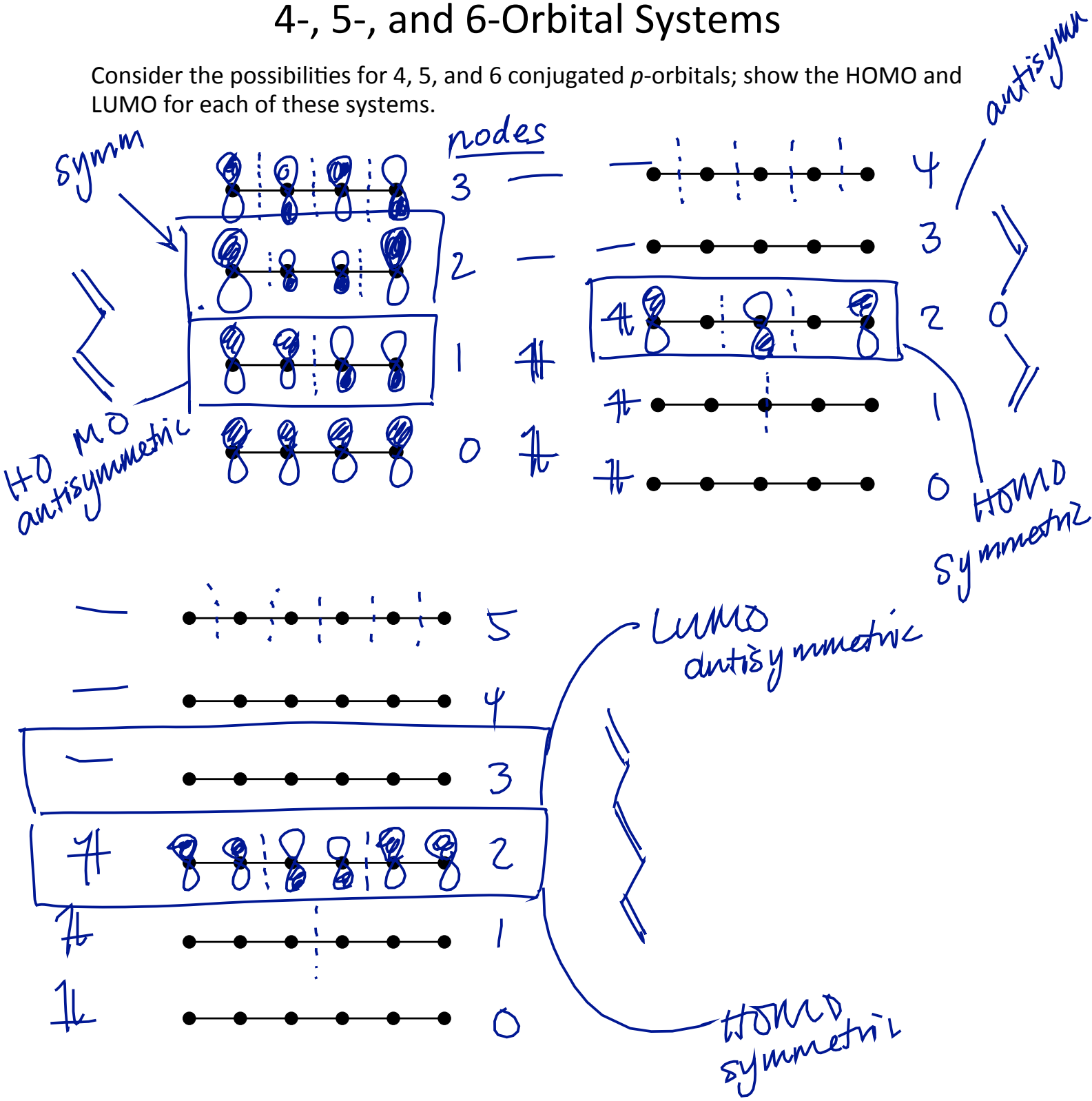


Remember:* n *conjugated p-orbitals* → n *molecular orbitals!

Reading: Section 27.1

Molecular Orbitals of Conjugated Systems:
4-, 5-, and 6-Orbital Systems

Consider the possibilities for 4, 5, and 6 conjugated *p*-orbitals; show the HOMO and LUMO for each of these systems.



Reading: Section 27.1

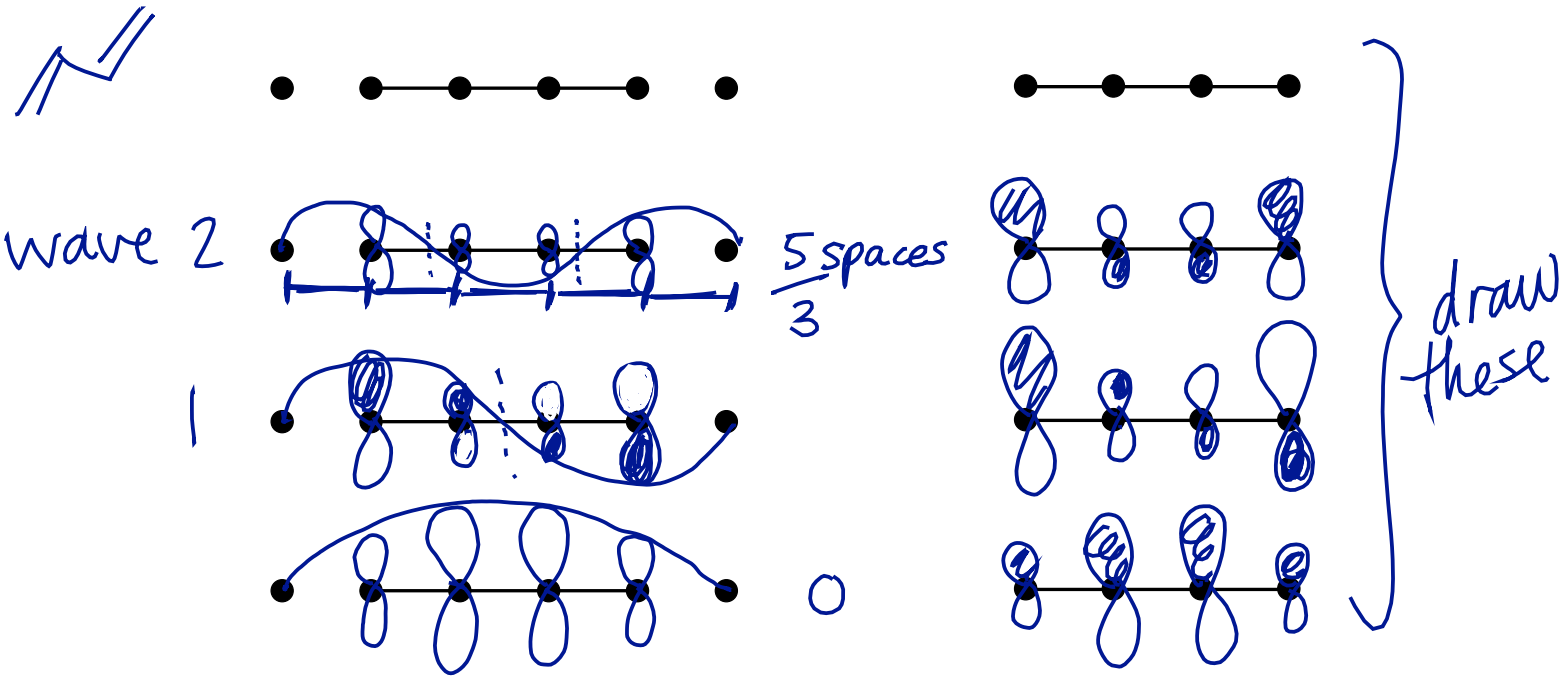
even # nodes — symm., odd — antisymm

MO's are wavefunction ψ

Week 6 July 29, 2014 psi

Molecular Orbitals of Conjugated Systems:
Where are the Nodes? Where are the Electrons?

Is there any way to figure out precisely where the nodes will be in these conjugated systems? Let's find out where the nodes are in a 4-orbital system:



Consider the *allyl anion*. Where will the allyl anion react with an electrophile? Can you explain that pattern of reactivity by using resonance structures? By using MO Theory?

Reading: Section 27.1

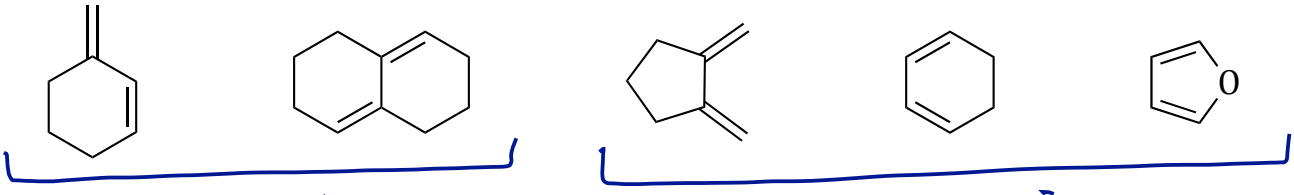
The Diels-Alder Reaction:
Dienes and Dienophiles

The **diene** in the Diels-Alder reaction must react in the *s*-cis conformation. Why?

no DA on s-trans

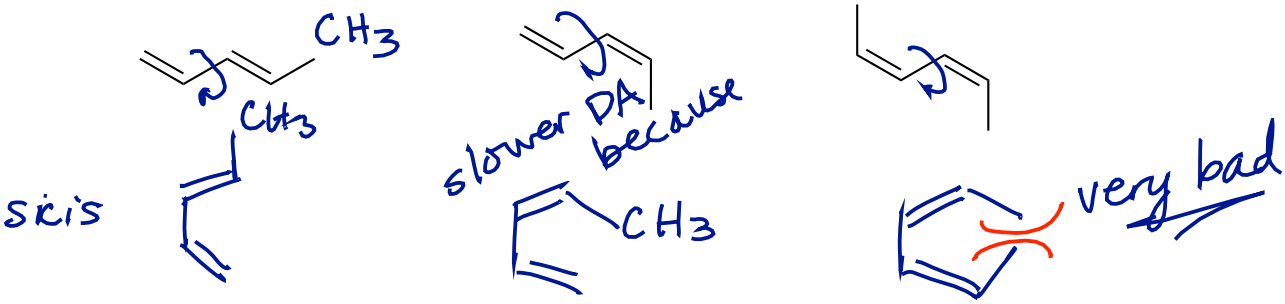
s-trans s-cis

What can you say about the reactivity of the following dienes in Diels-Alder reactions?

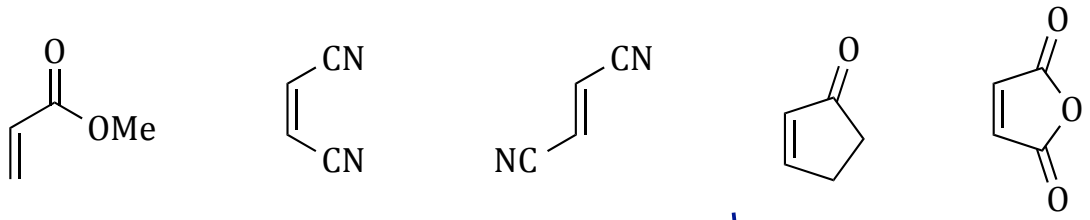


locked in s-trans
No DA-rxn

locked in s-cis
FAST DA rxns



The **dienophile** in a Diels-Alder reaction is usually conjugated with an electron-withdrawing group: a carbonyl or nitrile. These are excellent dienophiles:

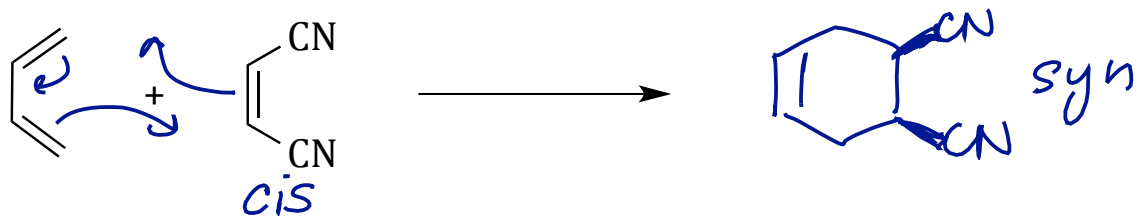


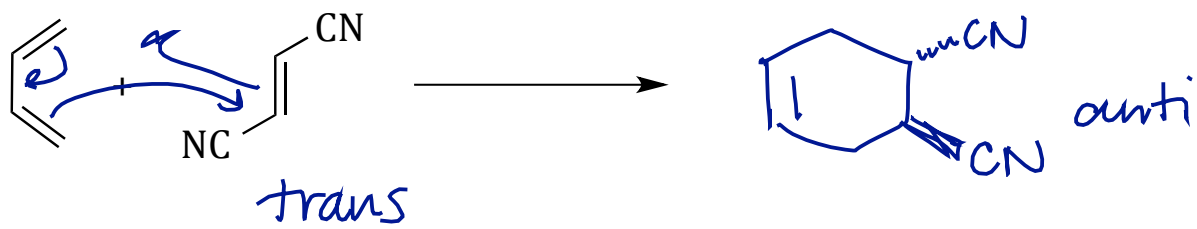
Good EWG!

Reading: Section 15.3

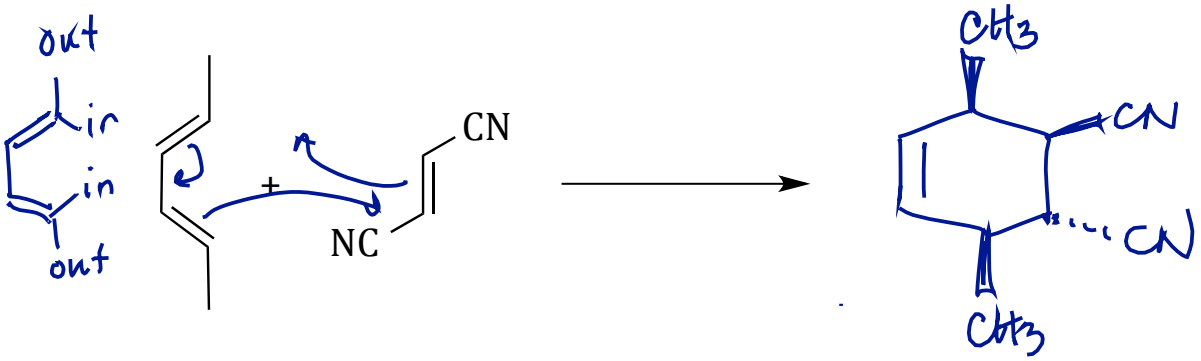
The Diels-Alder Reaction:
Stereochemistry

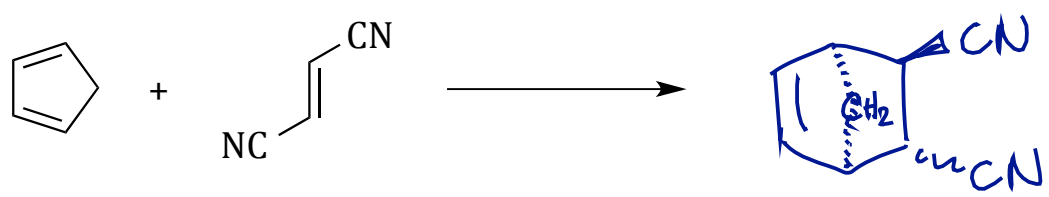
The stereochemistry of the **dienophile** is preserved in the reaction. Predict the products of the following reactions:



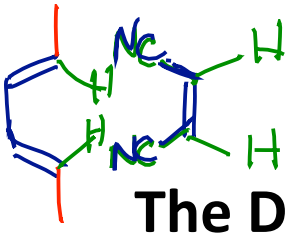


The stereochemistry of the **diene** is also preserved in the reaction. Predict the products of the following reactions:



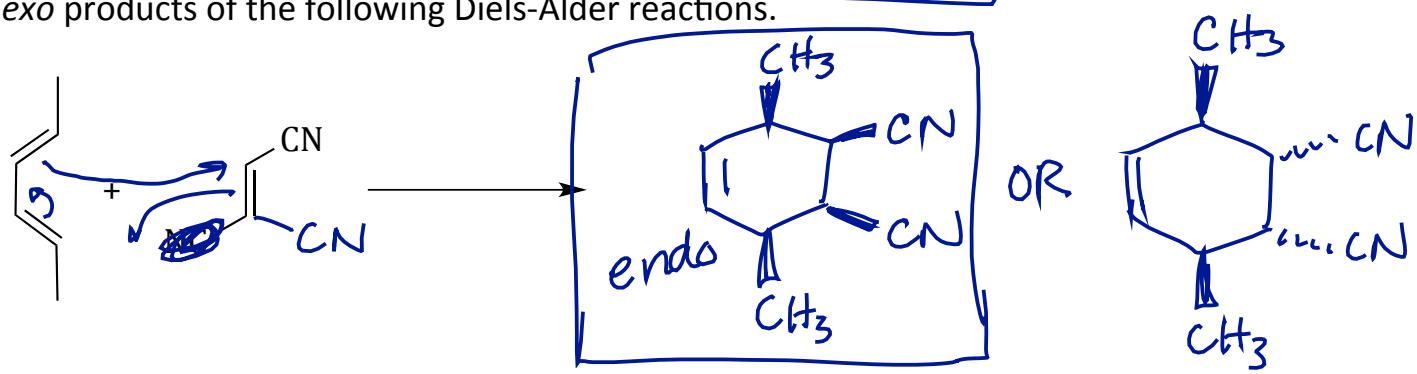


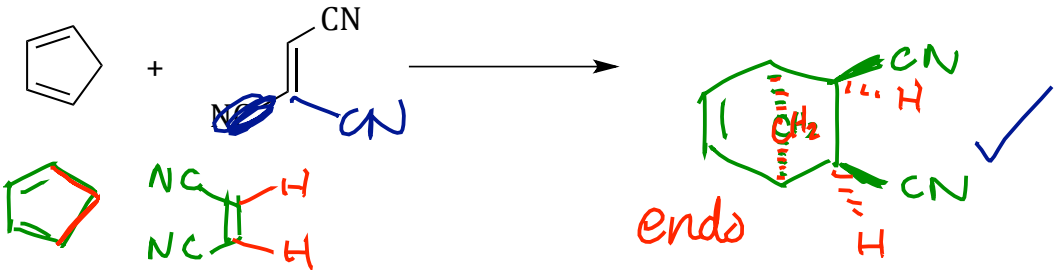
Reading: Section 15.3

Week 6  → right = same side July 29, 2014

The Diels-Alder Reaction:
Stereo- and Regiochemistry

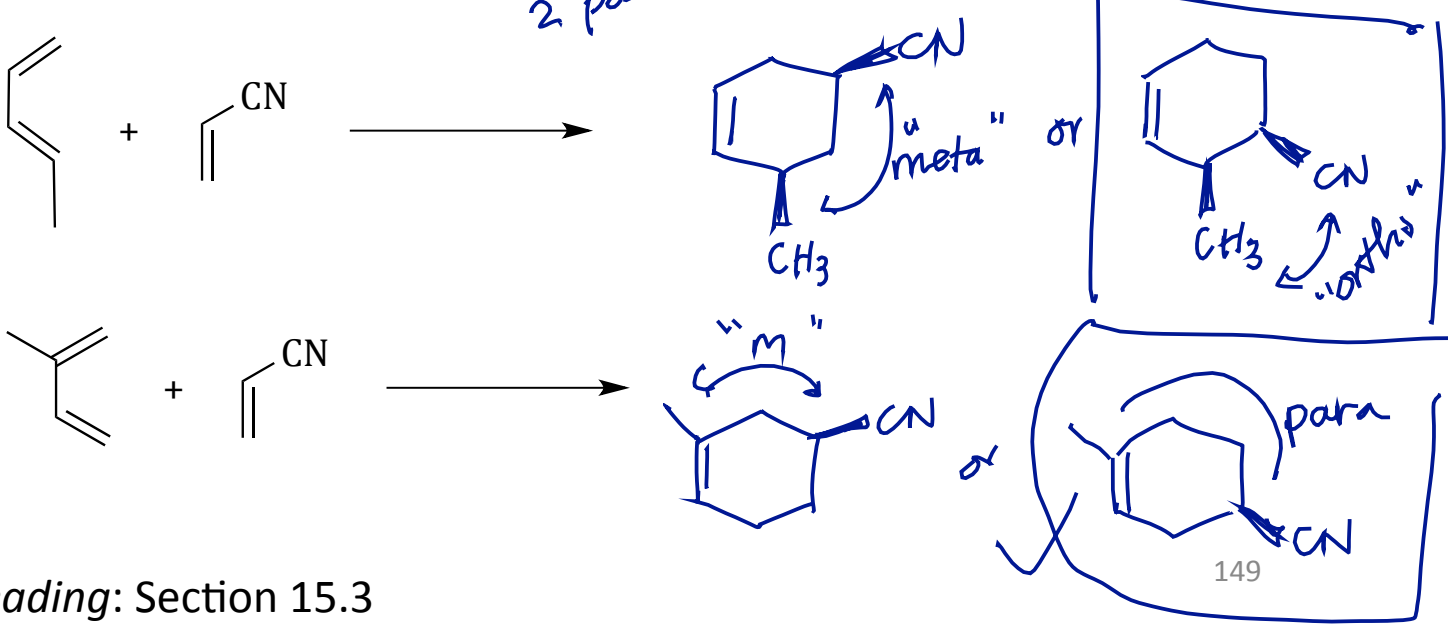
When relevant, the *endo* diastereomer is favored (the "*endo rule*"). Show the *endo* and *exo* products of the following Diels-Alder reactions.





Finally, when there are two possible regioisomers that can be formed, the preferred isomers usually have the substituents in a 1,2 ("ortho") or 1,4 ("para") relationship. Show both possible regioisomers for the following reactions, and indicate the preferred isomer:

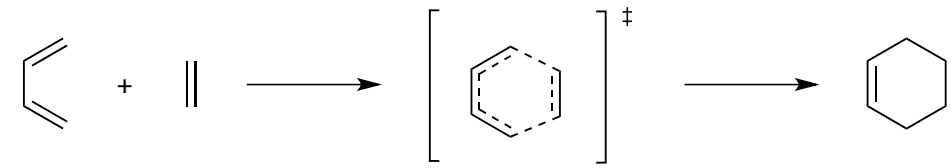
2 possibilities:



Reading: Section 15.3

The Diels-Alder Reaction:
Molecular Orbitals

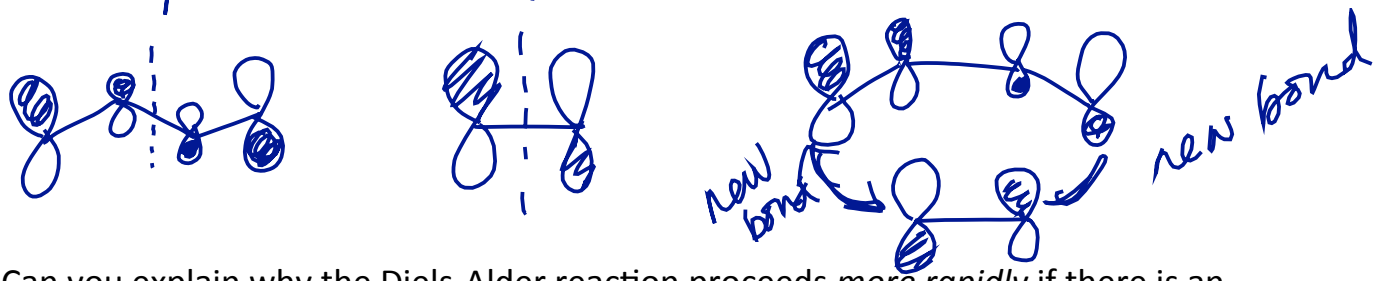
Let's revisit the simplest Diels-Alder reaction:



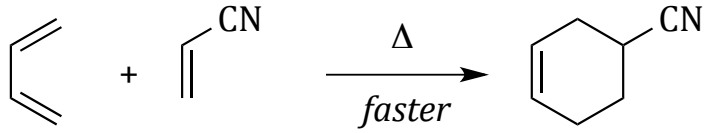
diene ***dienophile*** ***cyclic 6-membered transition state***

What are the **frontier orbital interactions** involved in the Diels-Alder reaction?

diene — 4-p-orbital — HOMO
dienophile — 2 p-orbital — LUMO



Can you explain why the Diels-Alder reaction proceeds *more rapidly* if there is an electron-withdrawing substituent on the dienophile?

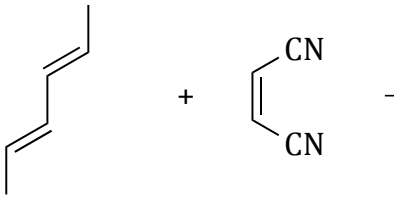
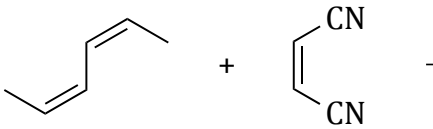
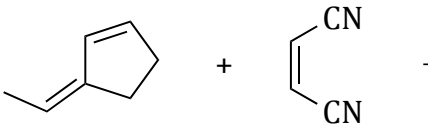
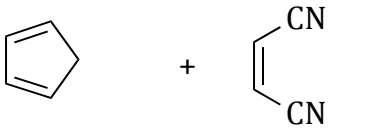


diene ***dienophile*** (+/-)

EWG – lower energy LUMO – making better acceptor
better match HOMO diene

Reading: Section 27.3

The Diels-Alder Reaction:
Test Yourself Now!

Consider the following dienes. Each one is heated with the dienophile *cis*-dicyanoethylene. For each diene, provide the product of the reaction; be sure to indicate **stereochemistry** where relevant. If no reaction will take place, write "no reaction" in the box. Then, **rank** the four dienes in terms of their rate of reaction with the dienophile, with 1 = fastest and 4 = slowest.

Ranking of reaction rate (1 = fastest)