



# CHEMISTRY 4000

---

Topic #3: Skeleton Oriented Bond-Sets

Spring 2022

Dr. Susan Findlay



# Skeleton Oriented Bond Sets

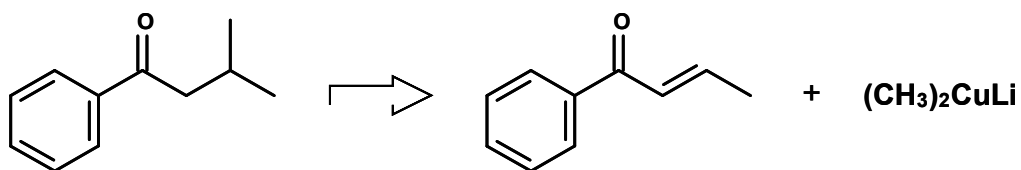
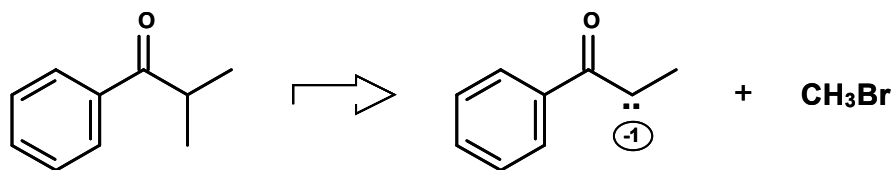
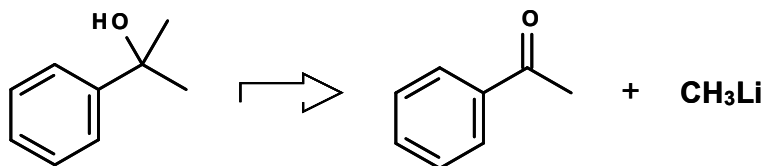
---

- If a target contains one or more branches, each branch is either
  - present in one of the starting materials ('building block' approach), or
  - attached through a bond-forming reaction.
- If there is no functional group at all near the site at which you want to attach a branch, you can consider:
  - an  $S_N2$  (or  $S_N2$ -like) reaction to make a single bond:
  
  
  
  
  
  
  
  
  
  
  - a Wittig reaction (or similar) to make a double bond:

Wittig reactions will be discussed at the end of this set of lecture notes.

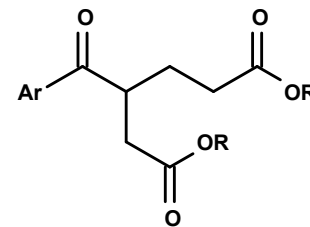
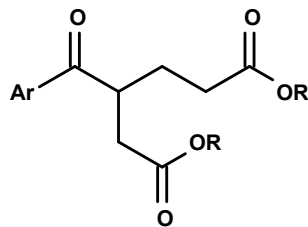
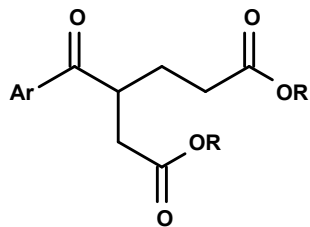
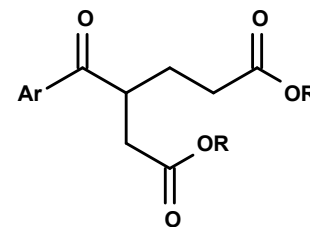
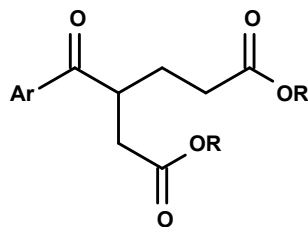
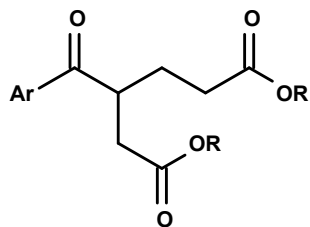
# Skeleton Oriented Bond Sets

- But functional groups are useful! If you have the option, look for nearby functional groups to see if it is possible to use one of the natural synthons ( $a^1$ ,  $d^2$  or  $a^3$ ) to attach the branch:



# Skeleton Oriented Bond Sets

- Where three chains meet, it isn't always obvious which to choose as the "branch" and which two to consider as the main chain. In those cases, consider all the available options:





# Auxiliary Functional Groups

---

- Sometimes, the forward reaction corresponding to a desired retrosynthetic disconnection works better in the presence of an 'extra' functional group that is not present in the final target. A functional group that is used to facilitate a bond-forming reaction then removed is an **auxiliary functional group**.
- For example, we know that it is easier to form an enolate between two carbonyl groups (instead of next to one) because the proton is more acidic. This can be used to regioselectively form an enolate:



# Auxiliary Functional Groups

---

- The second carbonyl also results in a softer nucleophile. This can be desirable if the proposed electrophile is soft.
- Hoffmann refers to the use of an auxiliary functional group to help direct bond formation as a **functional group addition** strategy. 6



# Auxiliary Functional Groups

---

- In order to use a functional group addition strategy, it is necessary that the auxiliary functional group be easy to remove. As long as the extra carbonyl group is an ester that is  $\beta$  to another carbonyl, this is the case. It takes two steps:
  - Hydrolyze the ester to a carboxylic acid by heating with aqueous acid.
  - Decarboxylate (remove  $\text{CO}_2$ ) by heating.
- These can be accomplished in one flask by heating the compound with aqueous acid:



# Auxiliary Functional Groups

---

- What else should you watch out for if you want to use aqueous acid and heat to remove an auxiliary carbonyl group?





# Auxiliary Functional Groups

---

- Mechanism for decarboxylation of a  $\beta$ -keto ester:



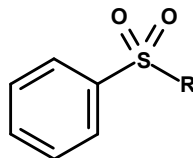
# Auxiliary Functional Groups

---

For more on this reaction, see section 22.4c of Sorrell or section 17.7.2 of Ogilvie

# Auxiliary Functional Groups

- Another class of fairly popular auxiliary functional group is the arylsulfonyl group:



- Reaction of an arylsulfone with a strong base ( $\text{CH}_3\text{Li}$ ,  $\text{BuLi}$ ,  $t\text{-BuLi}$ ,...) results in deprotonation of the carbon bonded to the sulfur, generating a strongly nucleophilic carbon atom:



# Auxiliary Functional Groups

---

- Once the arylsulfone has done its job, it is easily removed.
  - If the carbon bonded to  $-\text{SO}_2\text{Ar}$  is adjacent to a carbon bonded to  $-\text{OH}$ , an elimination reaction gives an *E*-alkene (Julia-Lythgoe olefination):



# Auxiliary Functional Groups

---

- Otherwise, reductive cleavage replaces  $-\text{SO}_2\text{Ar}$  with  $-\text{H}$ :



## Sidenote – Wittig (and Related) Reactions

---

- When you want to attach a bond with a double bond, one option is nucleophilic addition to a ketone or aldehyde followed by elimination of water:
  
  
  
  
  
  
  
  
  
  
- There is often at least one significant problem with this approach...



## Sidenote – Wittig (and Related) Reactions

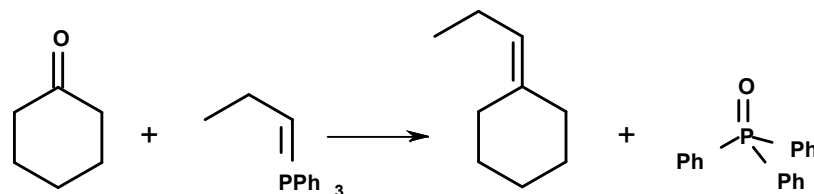
---

- To avoid this problem, you could use the Julia-Lythgoe olefination reaction from page 12 of these notes:

- This reaction gives an *E*-alkene (where stereochemistry applies).

# Sidenote – Wittig (and Related) Reactions

- Another popular alternative is the Wittig reaction (and variants thereof):



- A phosphonium salt can be made by reacting PPh<sub>3</sub> (or other phosphine) with an alkyl halide:

Some simple phosphonium salts can also be bought.





## Sidenote – Wittig (and Related) Reactions

---

- The phosphonium salt is then reacted with a strong base (usually alkyllithium or  $\text{NaNH}_2$ ) to make a phosphonium ylide:



## Sidenote – Wittig (and Related) Reactions

---

- Finally, the phosphonium ylide reacts with a ketone or aldehyde to give the corresponding alkene and  $\text{OPPh}_3$ :



## Sidenote – Wittig (and Related) Reactions

---

- The stereochemistry of this reaction depends on the type of ylide:
  - If the negative charge of the ylide is not stabilized by additional resonance, the major product is a *Z* alkene.
  
  
  
  
  
  
  
  
  
  
  - If the negative charge of the ylide is stabilized by additional resonance, the major product is an *E* alkene.



## Sidenote – Wittig (and Related) Reactions

---

- Horner-Wadsworth-Emmons reactions are very similar to Wittig reactions except that they involve a more highly oxidized phosphorus species:

- These reactions give *E*-alkenes (where stereochemistry applies). 20