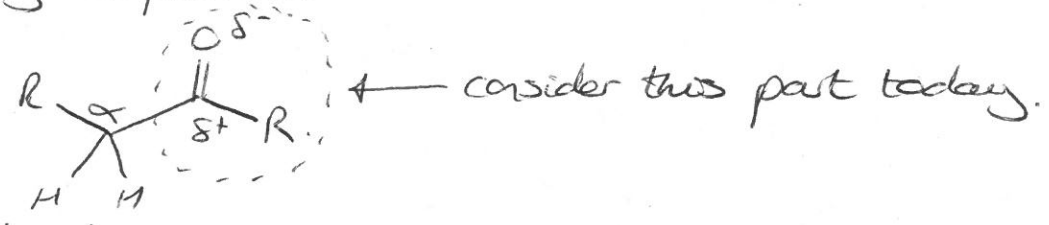
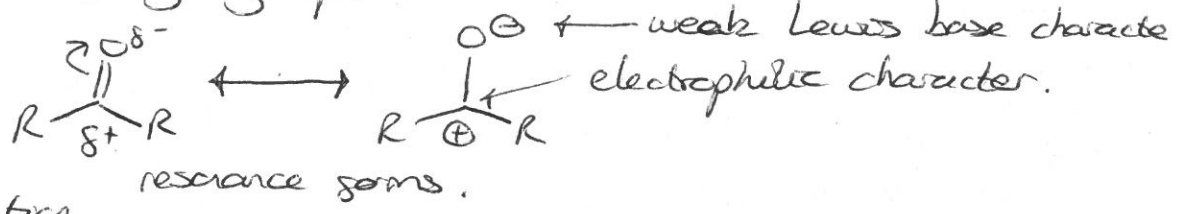


Lecture 1

- Reading CH4103, unit 4; Clayden Ch 6, 11.
- Reactions of carbonyl compounds.



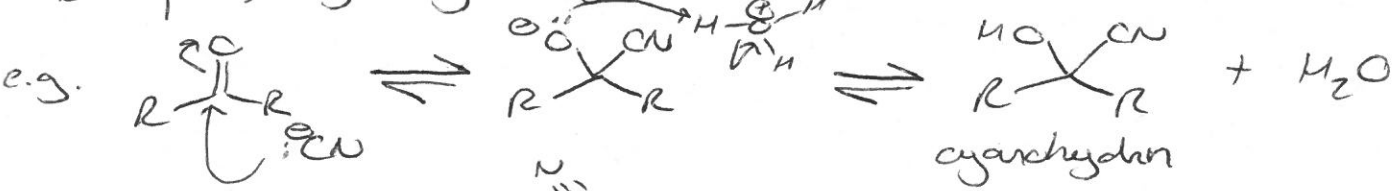
- Reactions of the carbonyl group:



- i) oxidation/reduction.
- ii) acid/base reactions (the oxygen atom is basic)
- iii) addition reactions (the carbon atom is electrophilic)

• The carbon atom can react with nucleophiles while the oxygen atom interacts with a Lewis or Brønsted acids.

- Example) Cyanohydrin formation. (reversible reaction).

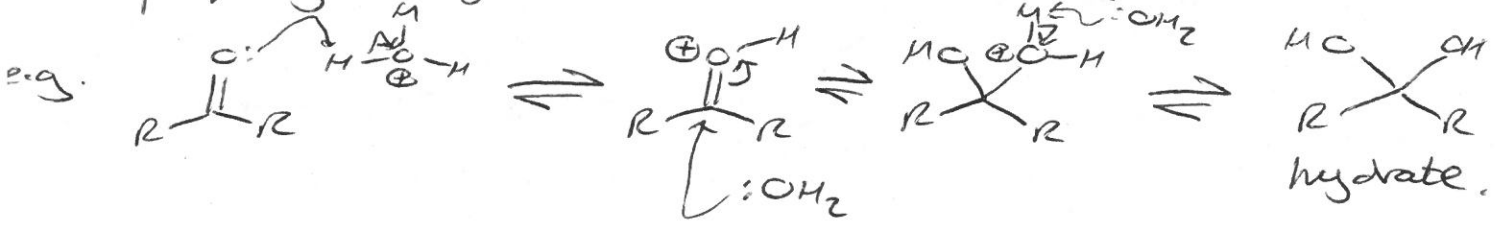


Bürgi-Dunitz angle of nucleophilic attack = 107°

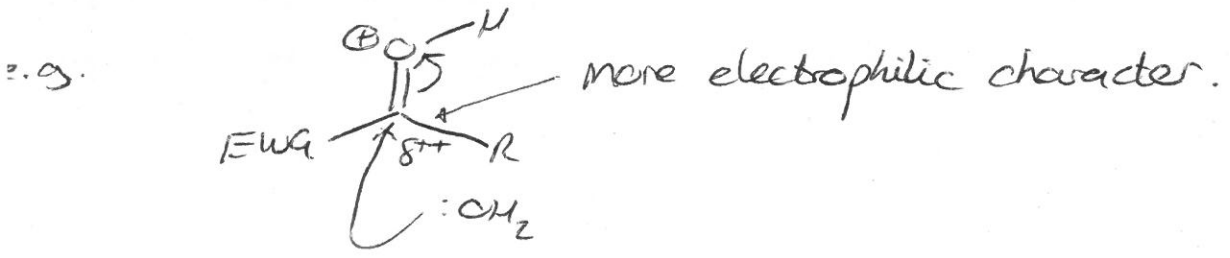


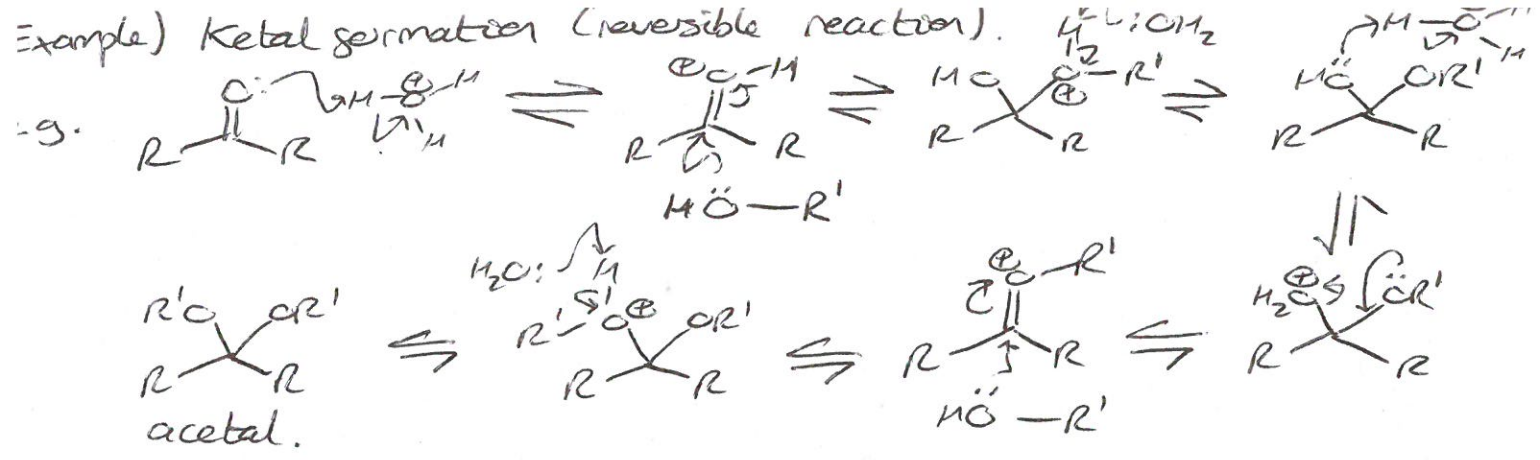
HOMO = filled C sp orbital
LUMO = empty π* orbital

- Example) Hydrate formation (reversible reaction)



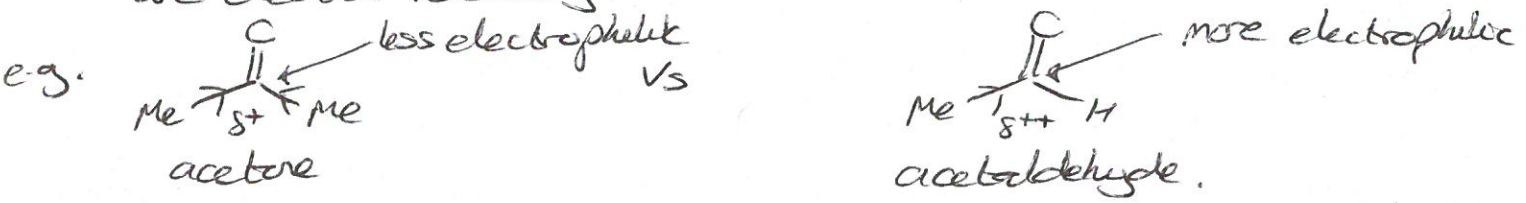
Note: EWG attached to the carbonyl carbon atom make addition more favourable





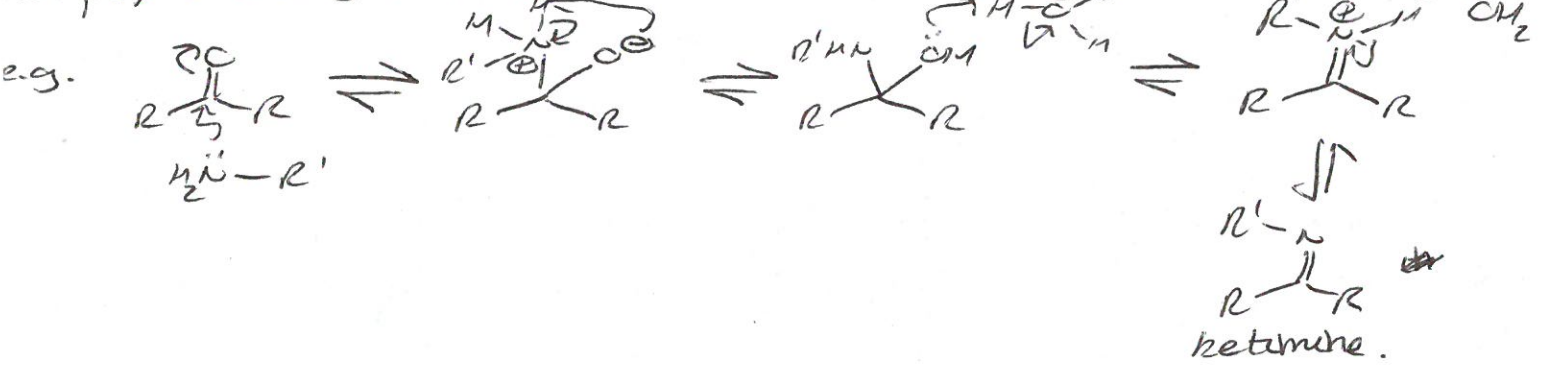
H^+ cat = TsOH or H_2SO_4 .

Note: Ketones are less electrophilic than aldehydes as alkyl groups are electron-releasing.

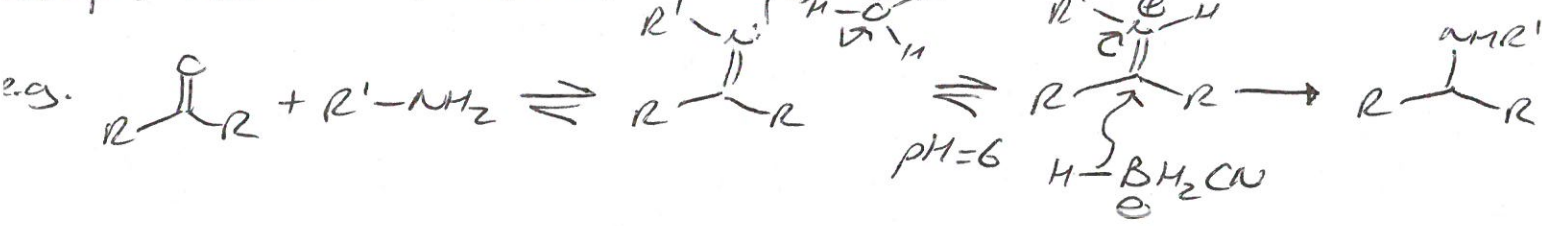


Note: Removal of H_2O favours acetal/ketal formation (Dean-Stark apparatus, molecular sieves, $MgSO_4$ etc.).

Example) Imine formation (reversible reaction).



Example) Reductive amination

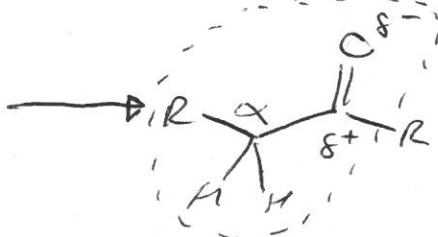


Note: $Na(CN)BH_3$ is a milder hydride donor compared to $NaBH_4$ due to the CN EWG. This reagent is selective toward reduction of iminium ions and it prevents reduction of starting aldehydes or ketones.

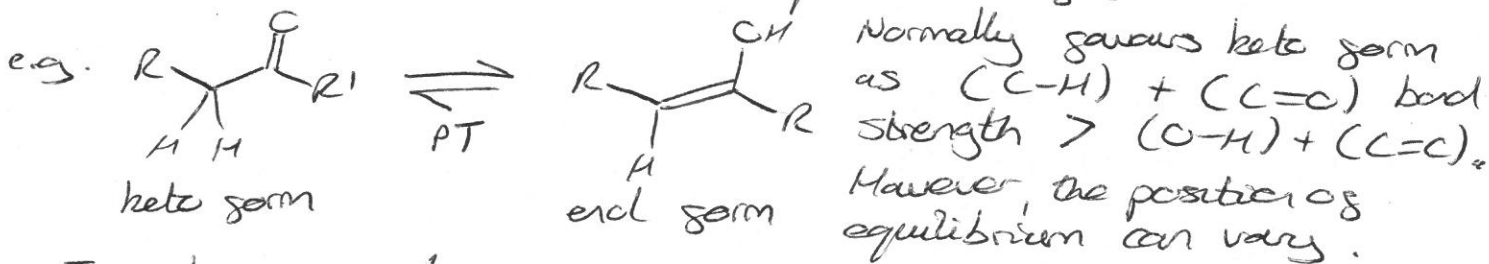
Lecture 2

- Reading CH4103, unit 4; Clayden Ch 8, 20, 26.
- Reactions of carbonyl compounds.

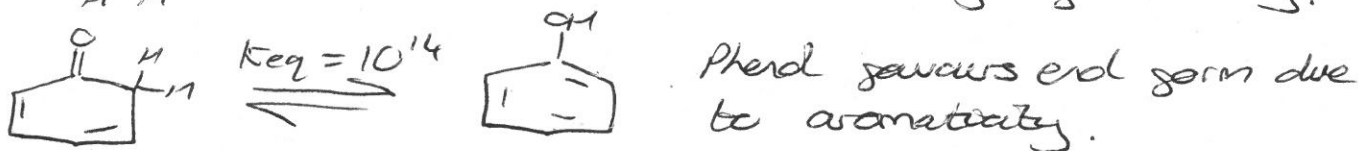
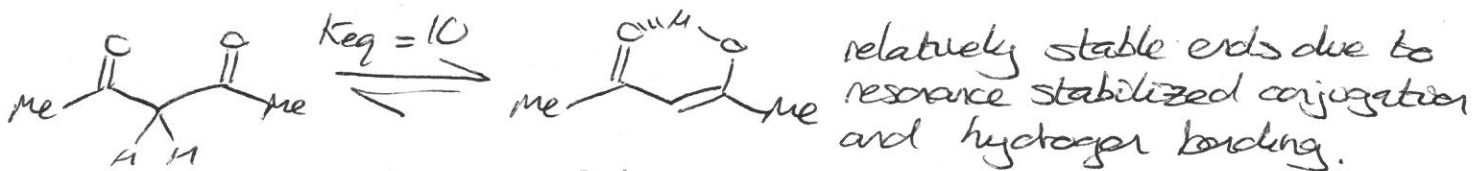
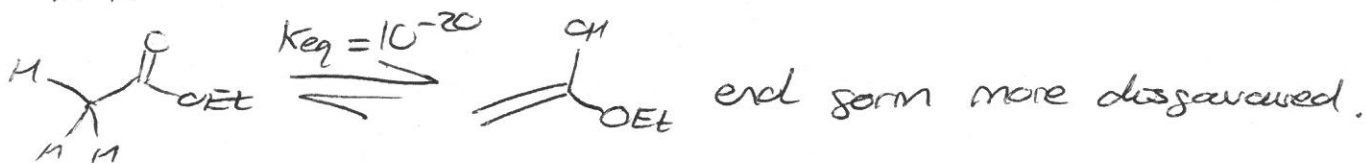
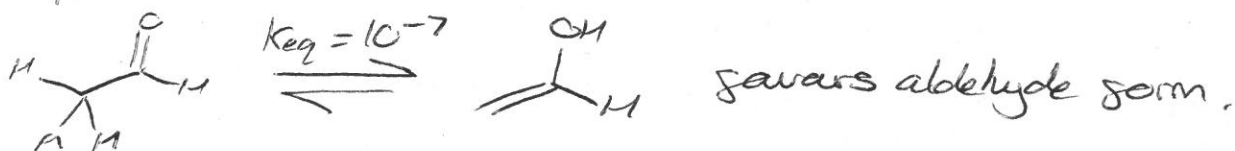
consider this part next



- Enol tautomers (intramolecular proton transfer)



- Examples of enols.



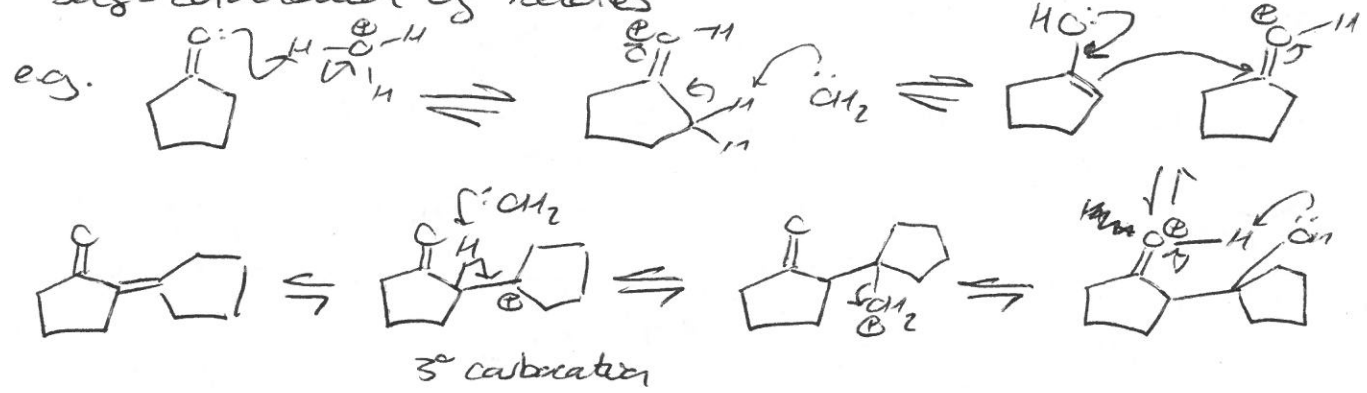
- The hydrogen atoms attached to the α -carbon of a carbonyl compound are weakly acidic as deprotonation gives rise to an anion stabilized through delocalization over the π system, and is ultimately placed on an electronegative oxygen atom.



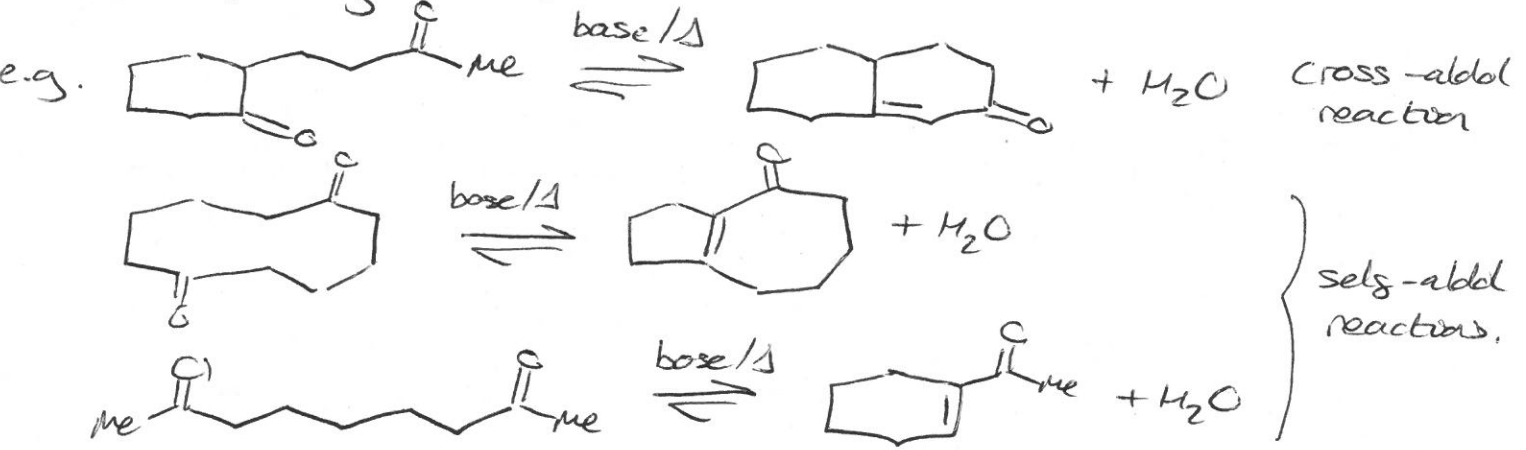
Note: Reactions which are dominated by charges and electrostatic interactions (hard) occur at oxygen, whereas reactions that are dominated by orbital interactions (soft) occur at the α -carbon.

Lecture 3

- Reading Clayden Ch 26.
- Self-condensation of ketones

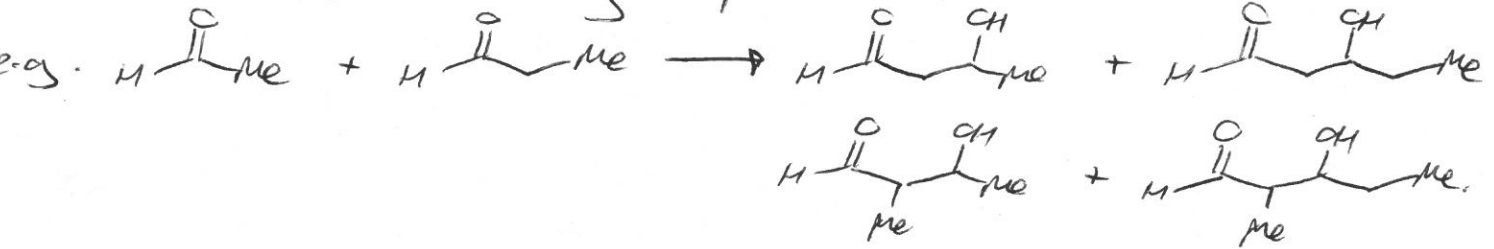


- Intramolecular ~~aldol~~ aldol condensation.
- If a molecule has 2 carbonyl functions, an intramolecular aldol condensation may occur.



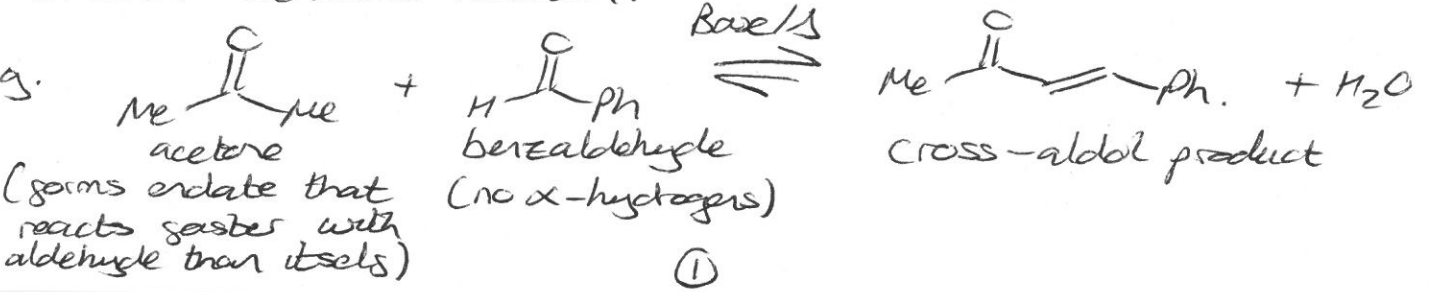
Note: Reversibility of all steps in the aldol condensation means that the most stable product is formed \Rightarrow five or six-membered rings typically favored.

- Crossed-aldol reactions.
- What happens if an aldol condensation/addition reaction is carried out with two different carbonyl compounds?

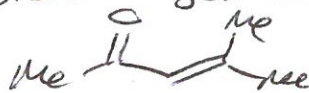


- If only one of the two carbonyl compounds has α -hydrogens (enolizable), only one can form the enolate ion.

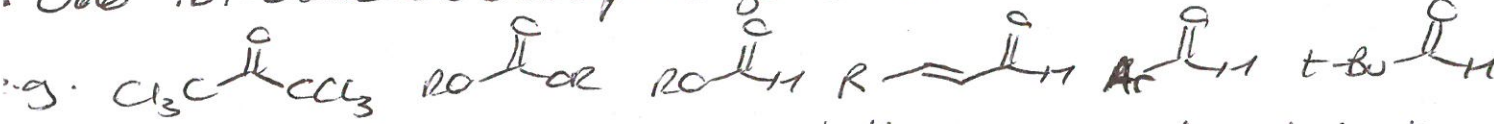
Claisen-Schmidt reaction.



Aldehydes are more electrophilic than ketones and all steps in the mechanism are reversible and the product formed is more thermodynamically stable than

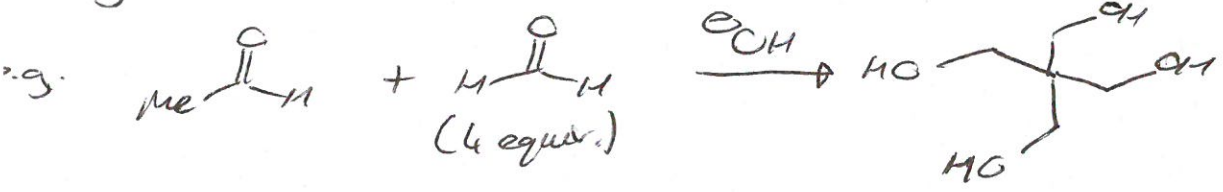


Other non-enolizable electrophiles for cross-aldol reactions.



Note: None have α -hydrogens. Also bulky groups adjacent to the $C=O$ bond slow down the addition reaction.

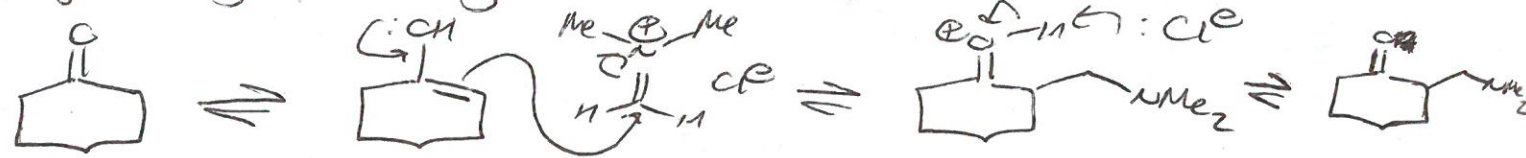
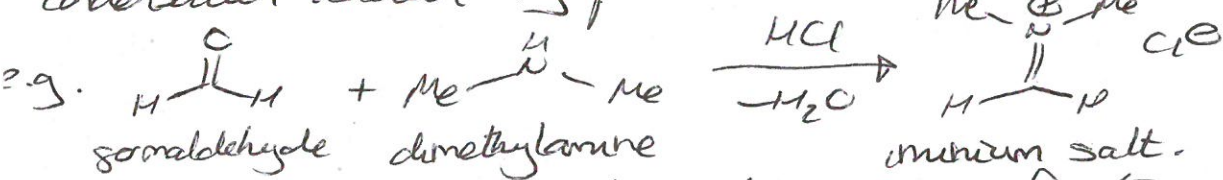
Why not use formaldehyde as non-enolizable acceptor?



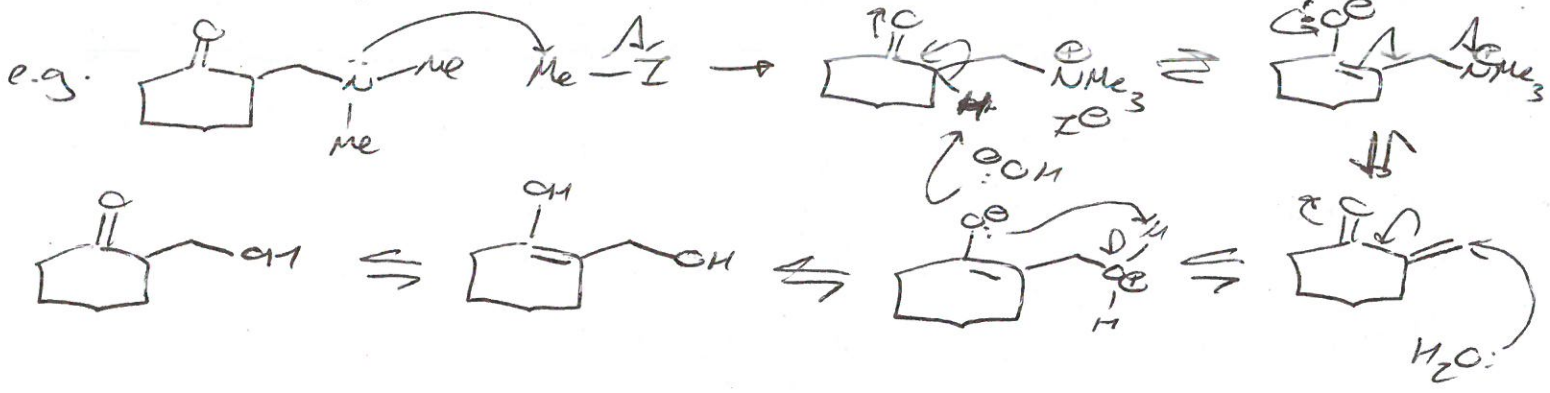
Note: Formaldehyde is very reactive and the aldol reaction proceeds until all enolizable α -hydrogens have been substituted. A final Cannizzaro reaction (hydride transfer to the $C=O$) gives the final product.

The Mannich reaction.

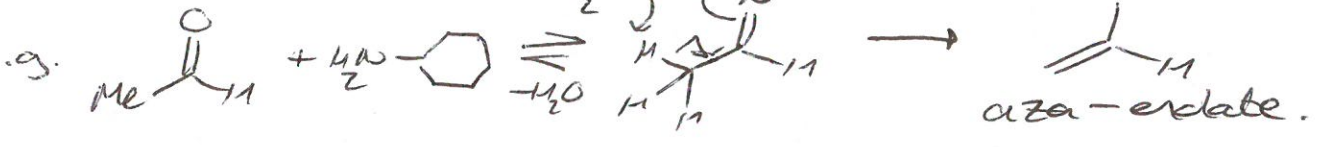
Generates a less reactive formaldehyde analogue so that condensation reaction only proceeds once:



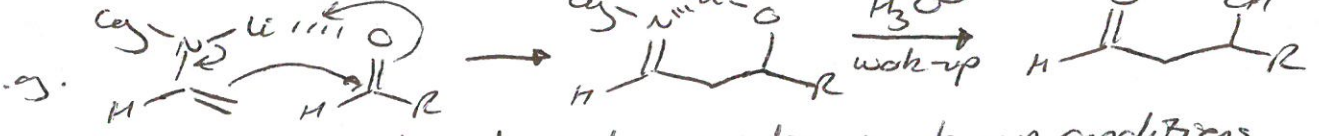
Note: To get the β -hydroxyketone, activate amine to be a good LG, elimination, then add H_2O via Michael addition (Unit 2)



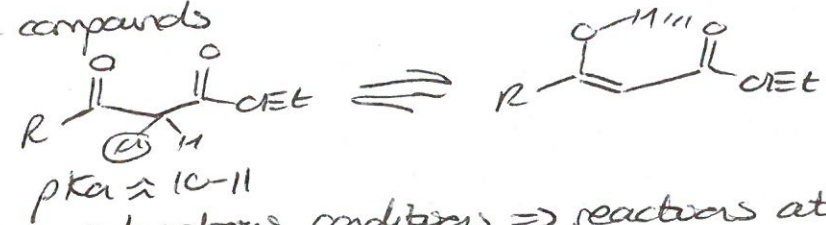
• Enamines



• Aldol reaction.

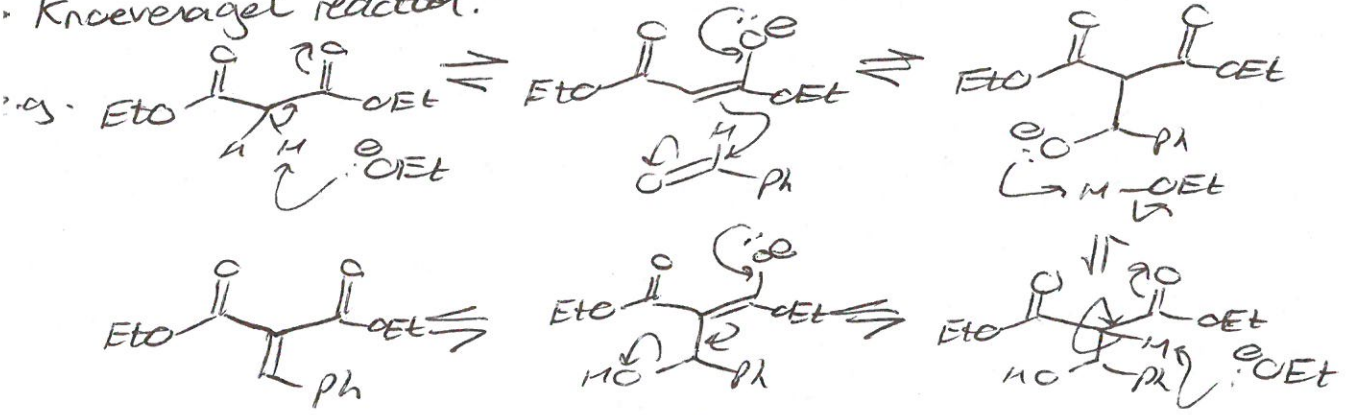


• 1,3-dicarbonyl compounds

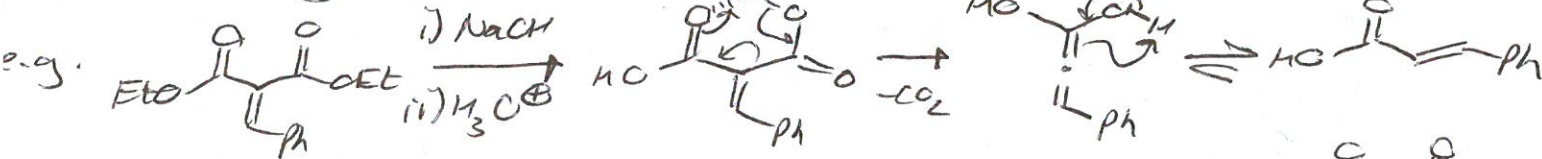


Note: No need for anhydrous conditions \Rightarrow reactions at rt or higher. Enol form stable due to H-bonding. Simple way to activate carbon atoms adjacent to esters.

• Knoevenagel reaction.



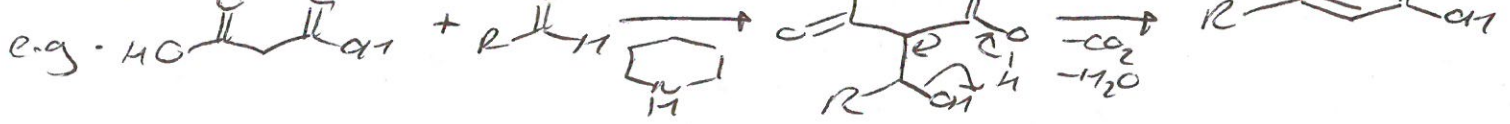
Note: Decarboxylation can be used to remove one of the carbonyl groups.



Note: This procedure can also be used with β -ketoesters e.g. R-C(=O)C(=O)OEt

• Doebner Modification.

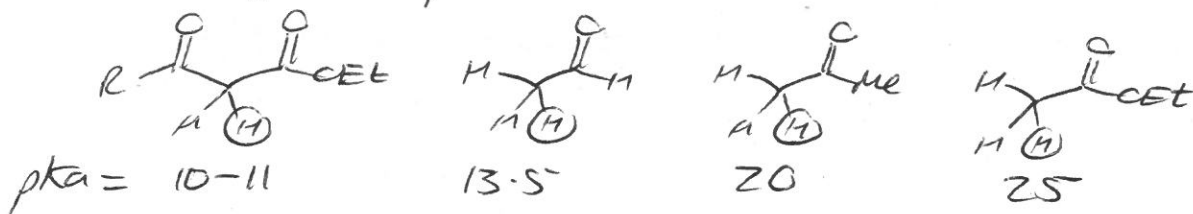
Can access the monoacid in a single step using malonic acid as the end equivalent.



Note: Decarboxylation can also take place using β -ketoacids e.g. R-C(=O)C(=O)OH

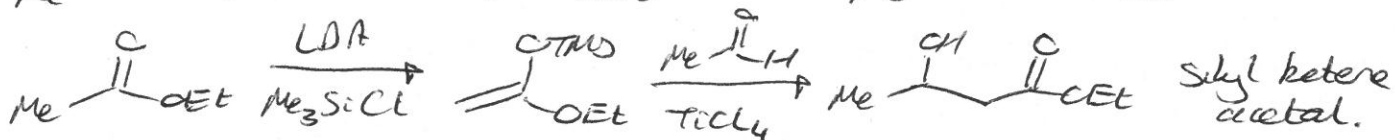
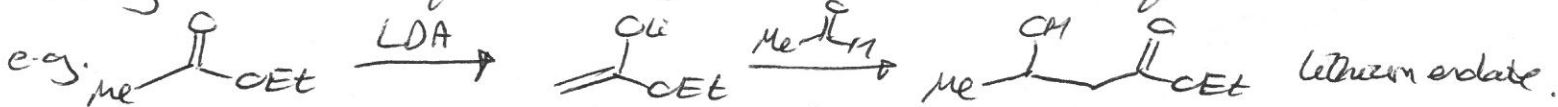
Lecture 5

- Reading Clayden Ch 25, 26.
- A reminder of some pKas.

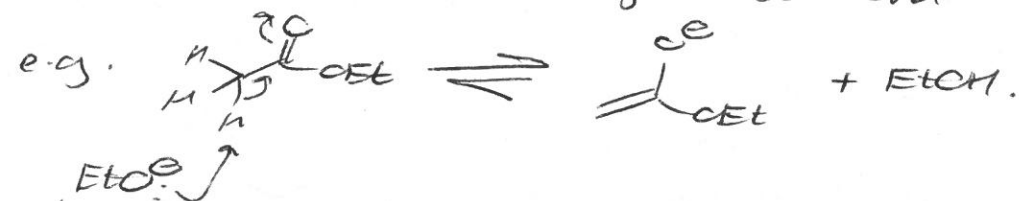


Note: The α -hydrogens in esters are less acidic than others.

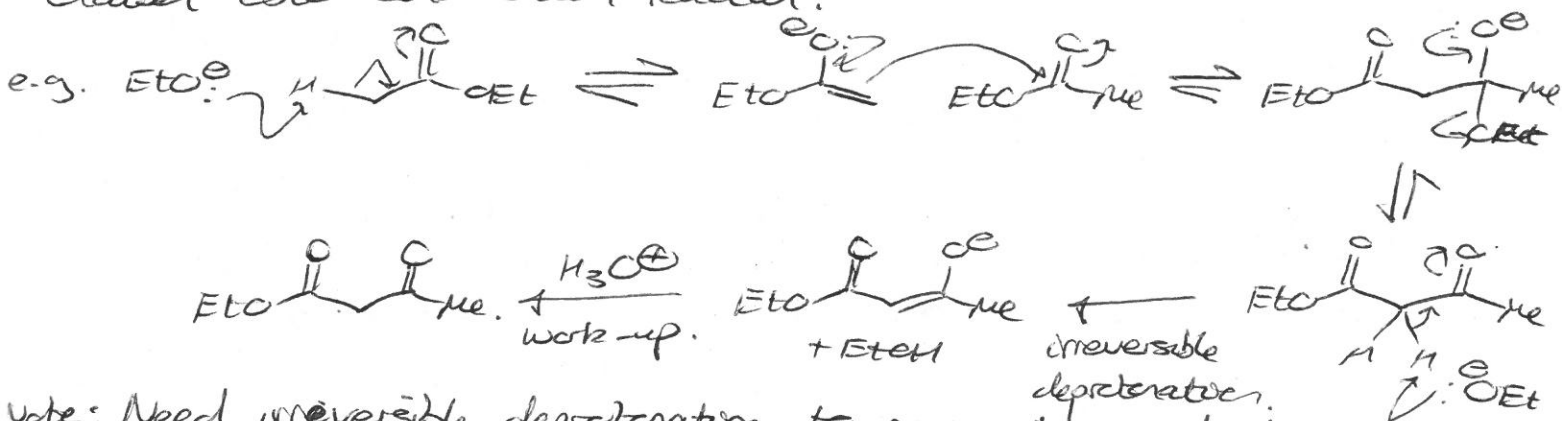
- Strong bases are required to form ester enolate equivalents.



Note: Weaker bases like NaOEt can be used but the solution will exist as a mixture of the ester and the enolate anion.



- Claisen ester condensation reaction.



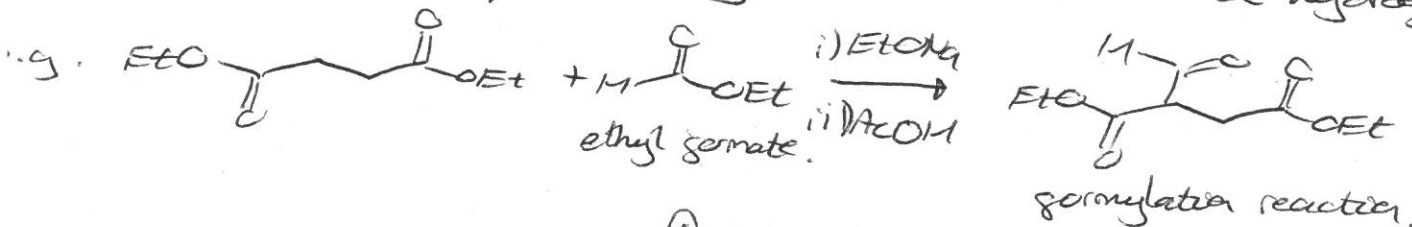
Note: Need irreversible deprotonation to form the product \Rightarrow requires 1 equivalent of base.

- Intramolecular Claisen condensation.



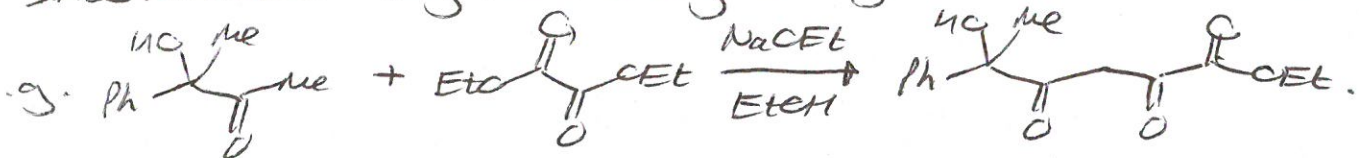
- Cross-Claisen condensations

Either one ester is particularly reactive or has no α -hydrogens.

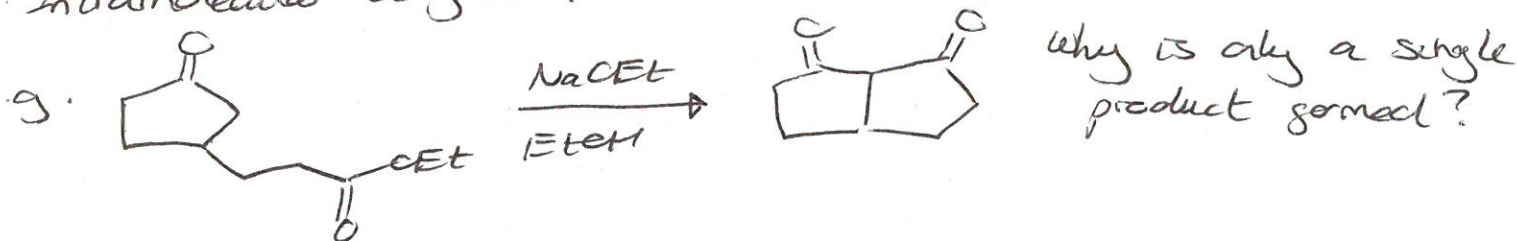


Some related enolate transformations.

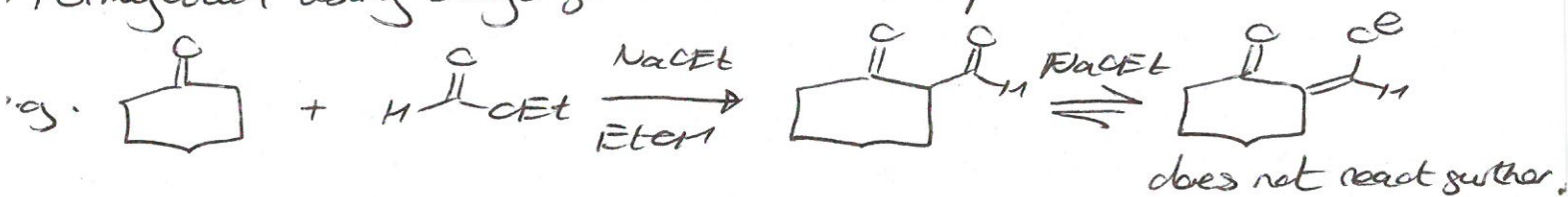
Intermolecular acylation using diethyl oxalate as electrophile.



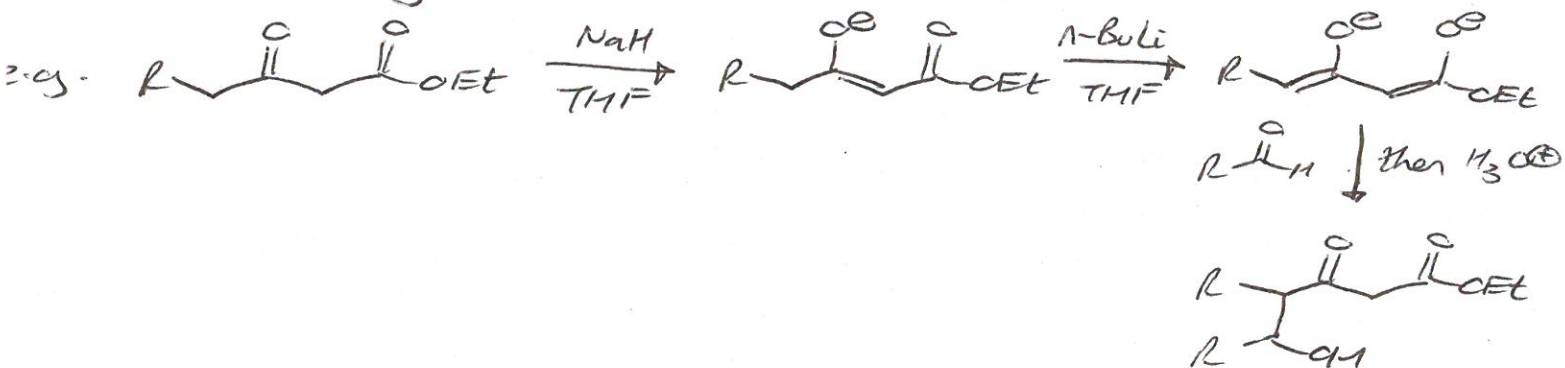
Intramolecular acylation



Formylation using ethyl formate as electrophile.



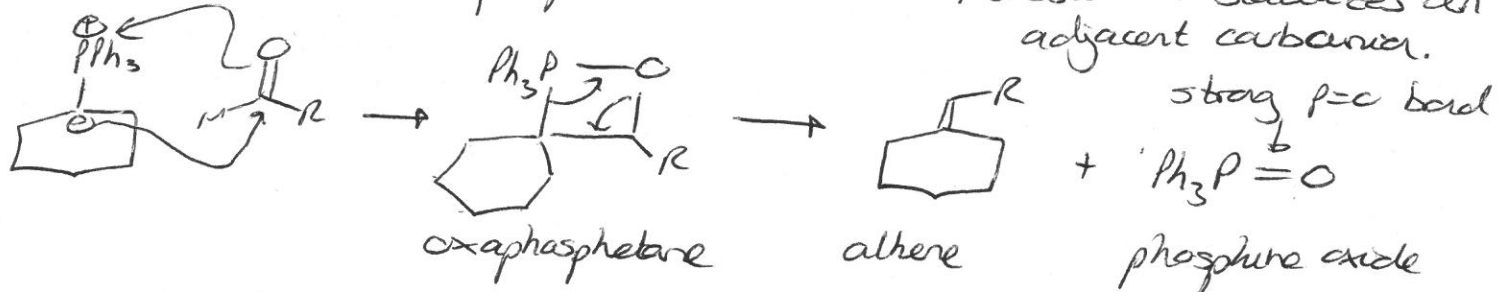
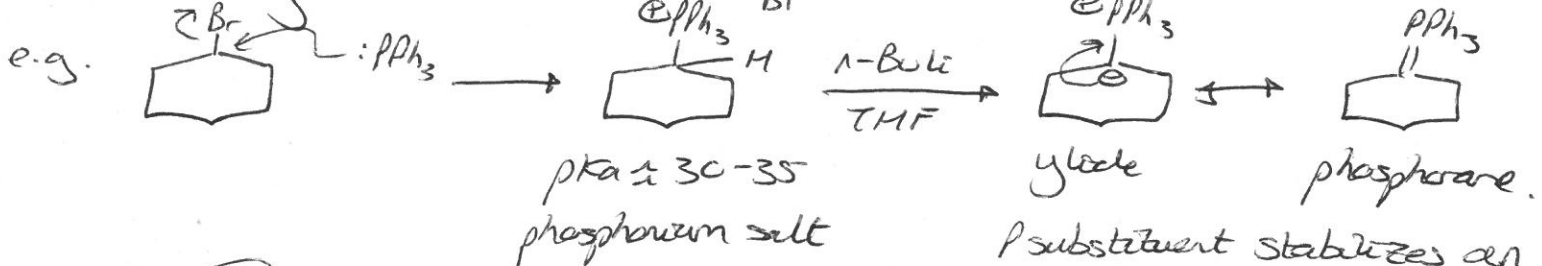
Dianion chemistry (acetoacetate dianion).



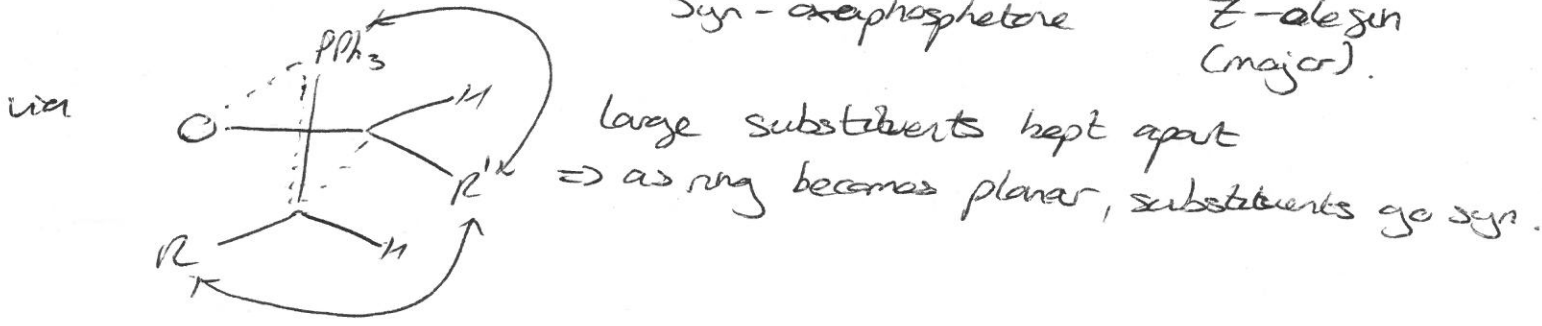
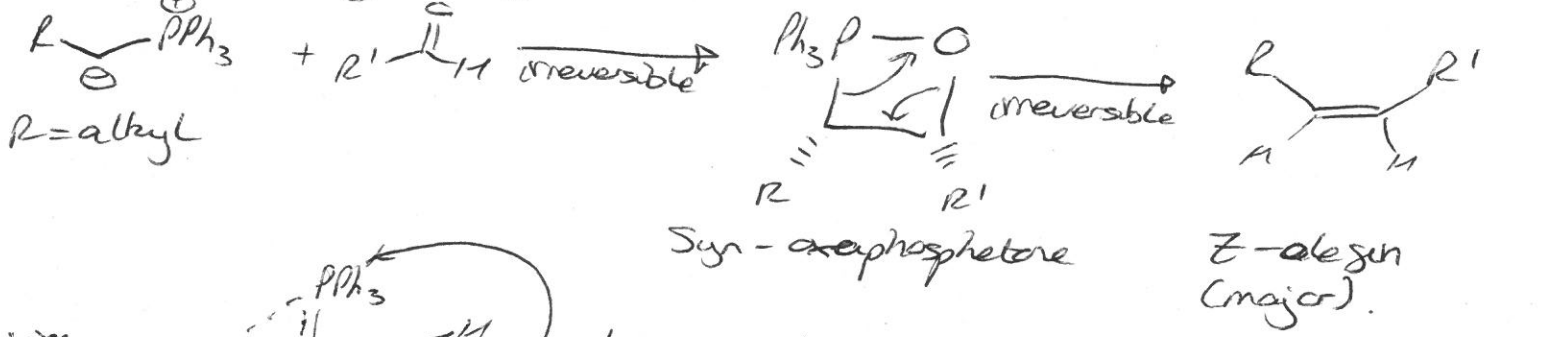
Note: Dianion reacts through less stable anion (kinetic control).
Can favour less stable kinetic product if reactions are irreversible or low T is used.

Lecture 6

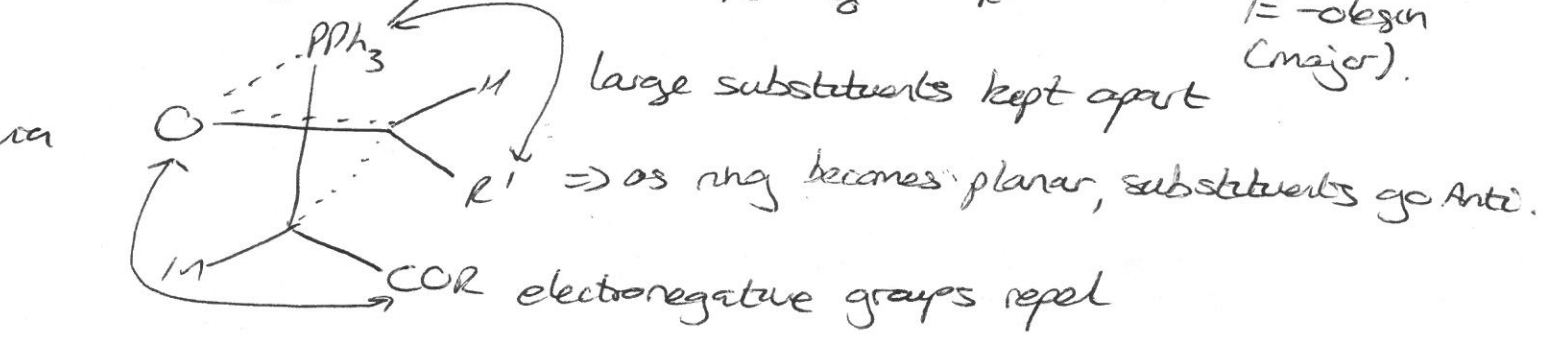
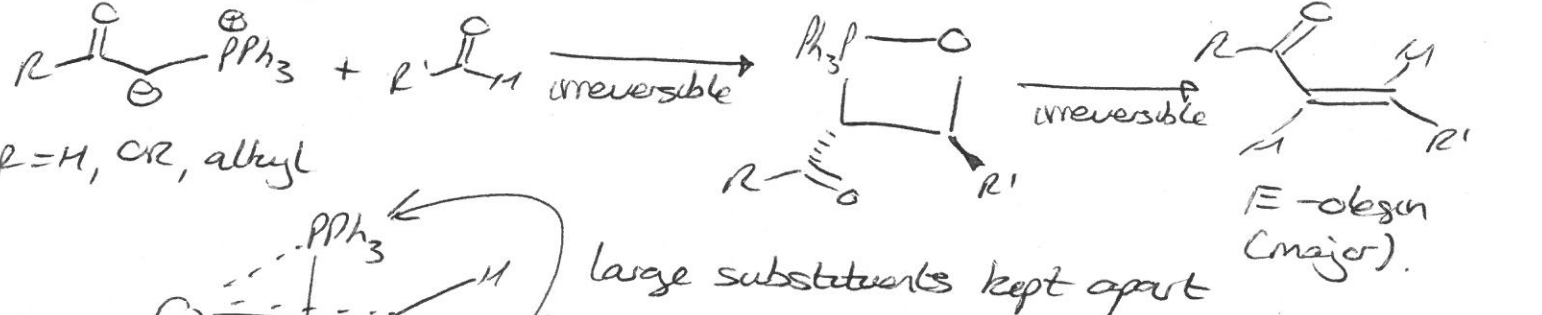
- Reading Clayden Ch 27
- The Wittig reaction.



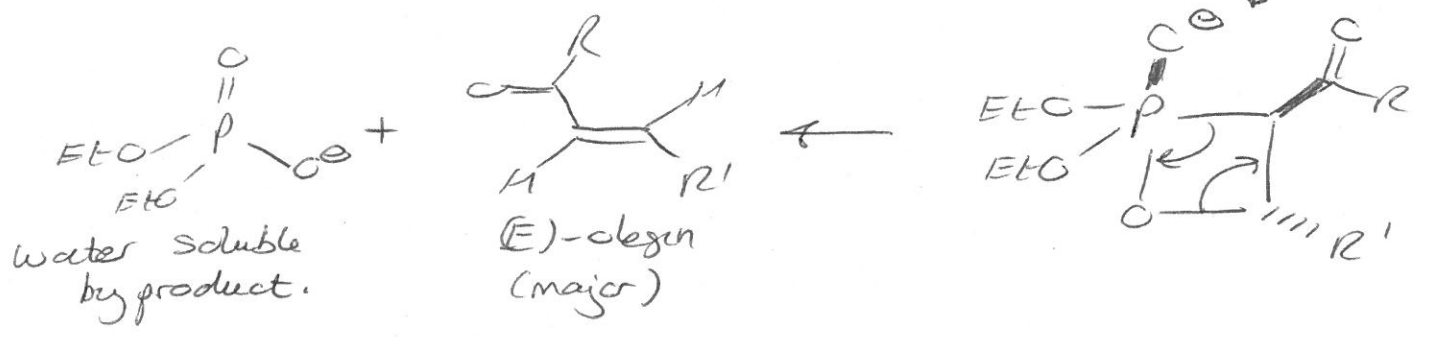
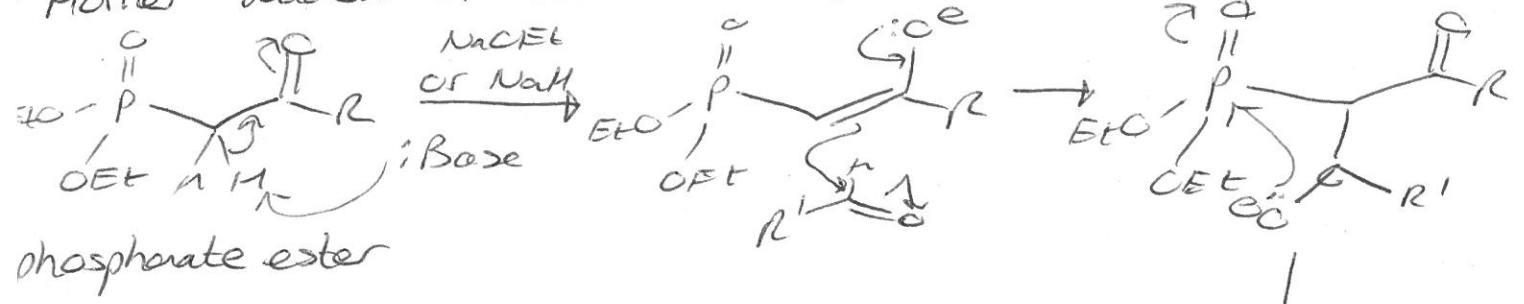
- Unstabilized ylides give Z-olefins.



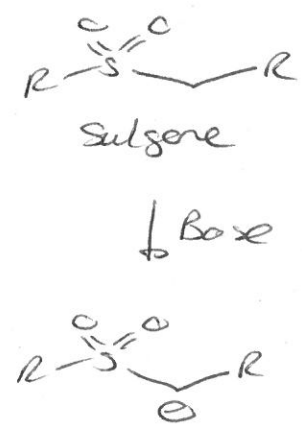
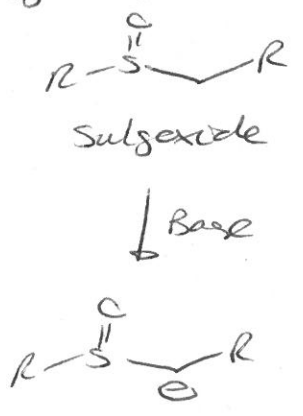
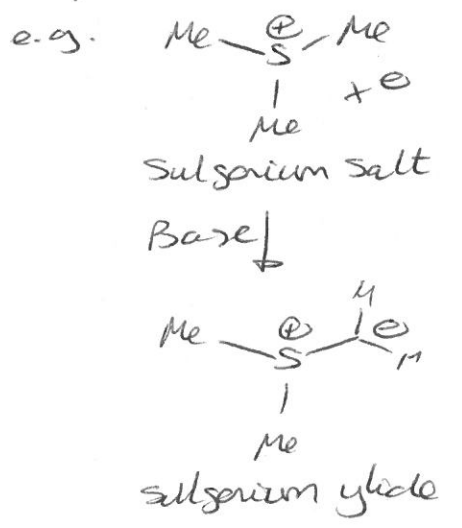
- Stabilized ylides give E-olefins.



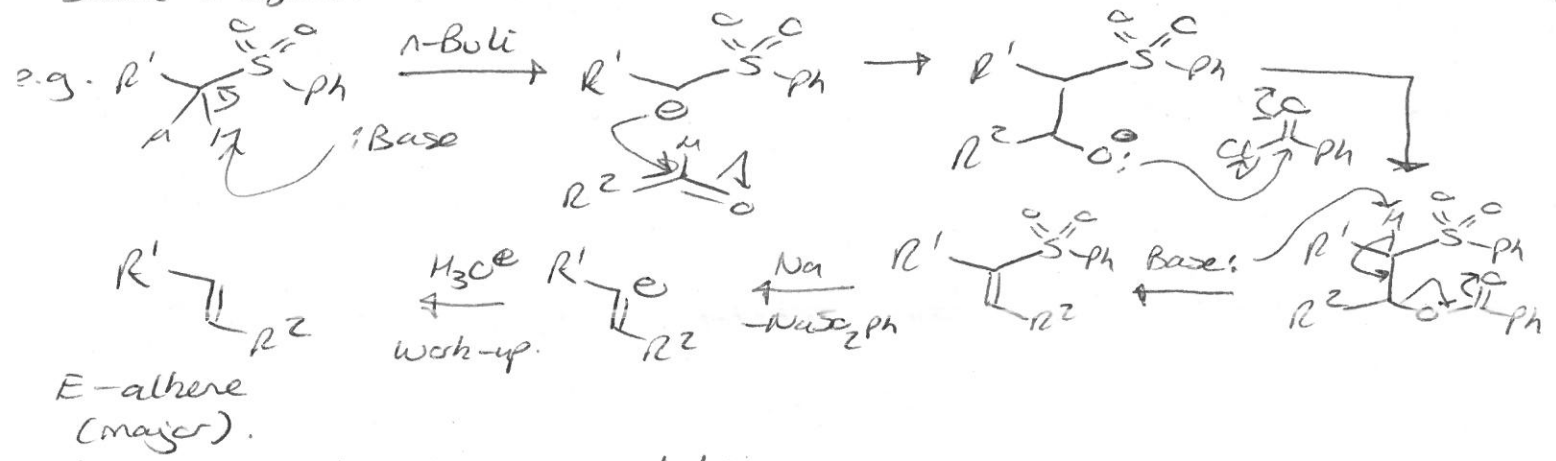
• Horner-Wadsworth-Emmons (HWE) reaction.



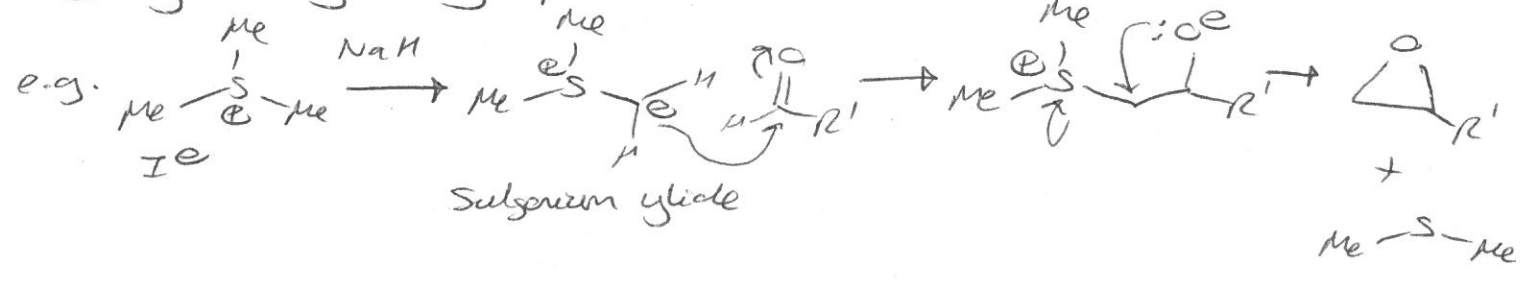
• Deprotonation α to sulfur atoms.



• Julia Olefination.

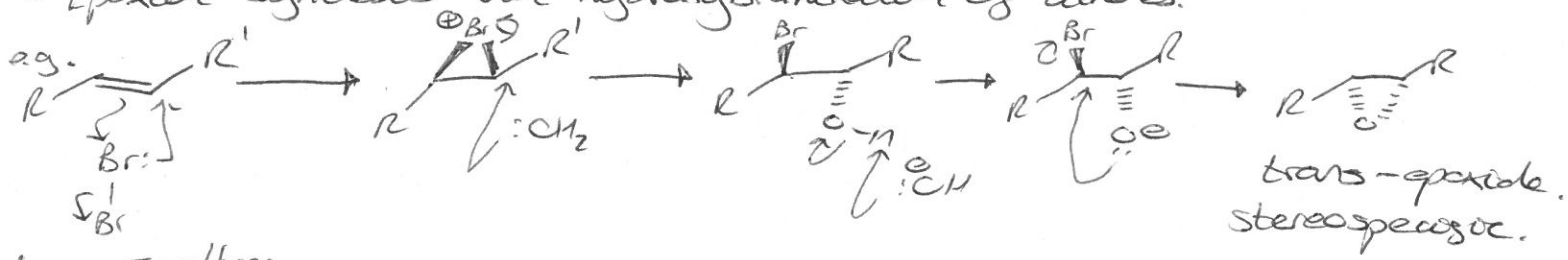


• Corey-Chaykovsky epoxidation.

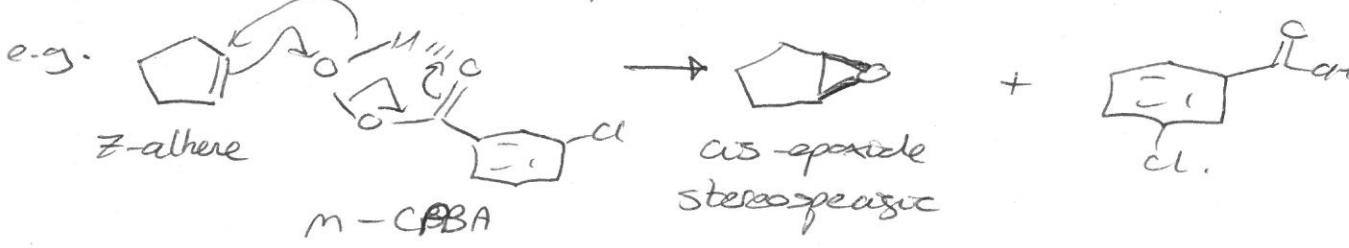


Lecture 7

- Reading CH4103, unit 3; Clayden Ch. 19.
- Epoxide synthesis via hydroxybromination of alkenes.

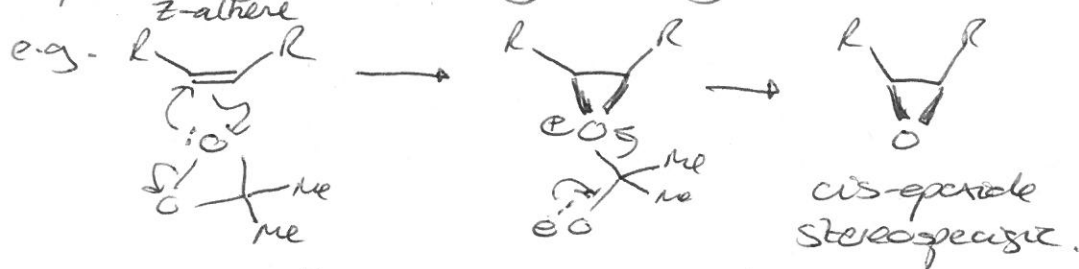


- Epoxide synthesis using peracids.



Note: The reaction rate increases as the olefin becomes more substituted (more nucleophilic).

- Epoxide synthesis using dimethyldioxirane (DMDO)

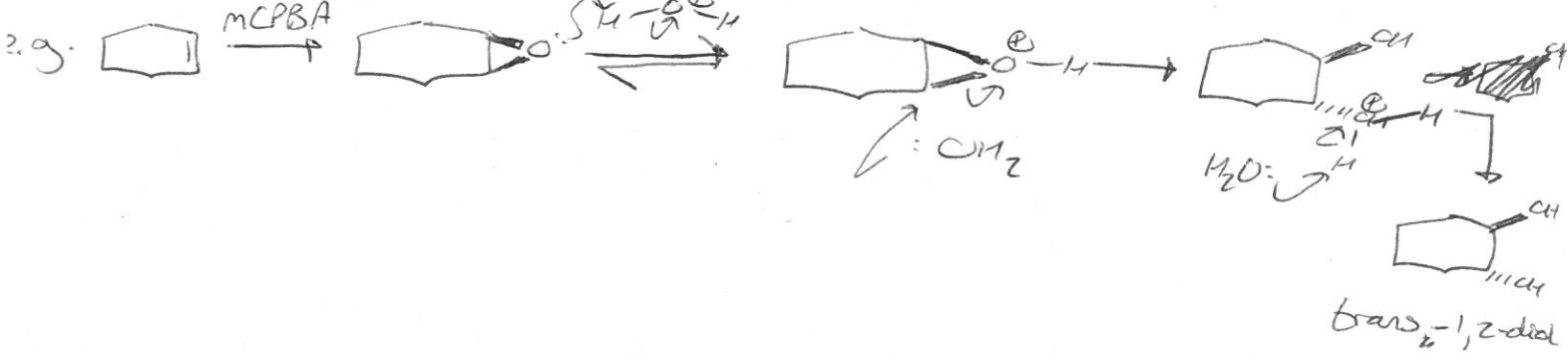


- Epoxide synthesis of e⁻ poor olefins using H₂O₂. (see unit 2 sources)

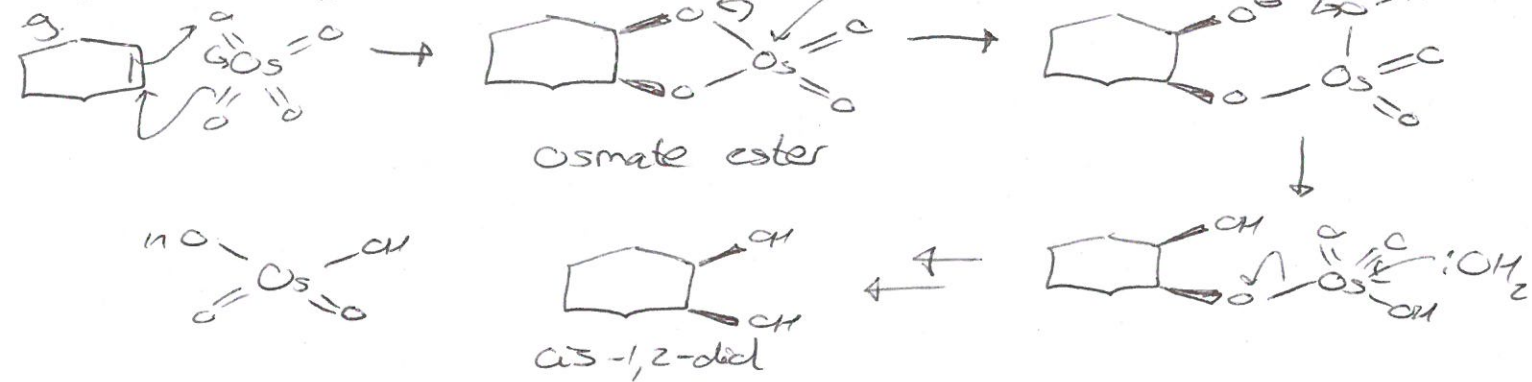


Note: pKa(CH₂O₂) = 11.8 pKa(CH₂O) = 15.7 therefore hydroxide can deprotonate perhydrogen peroxide.

- Anti-dihydroxylation of alkenes.

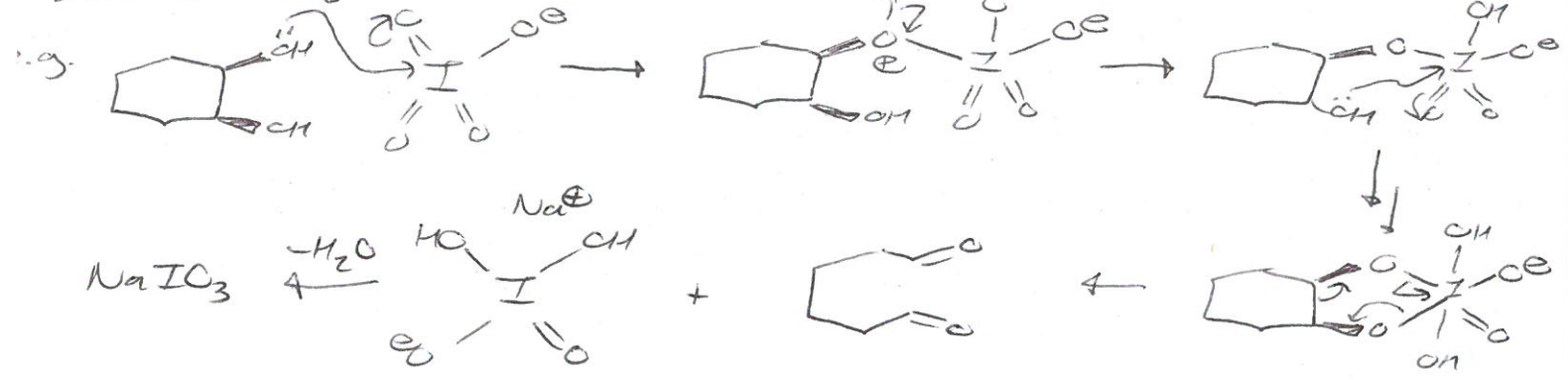


• Syn-dihydroxylation.

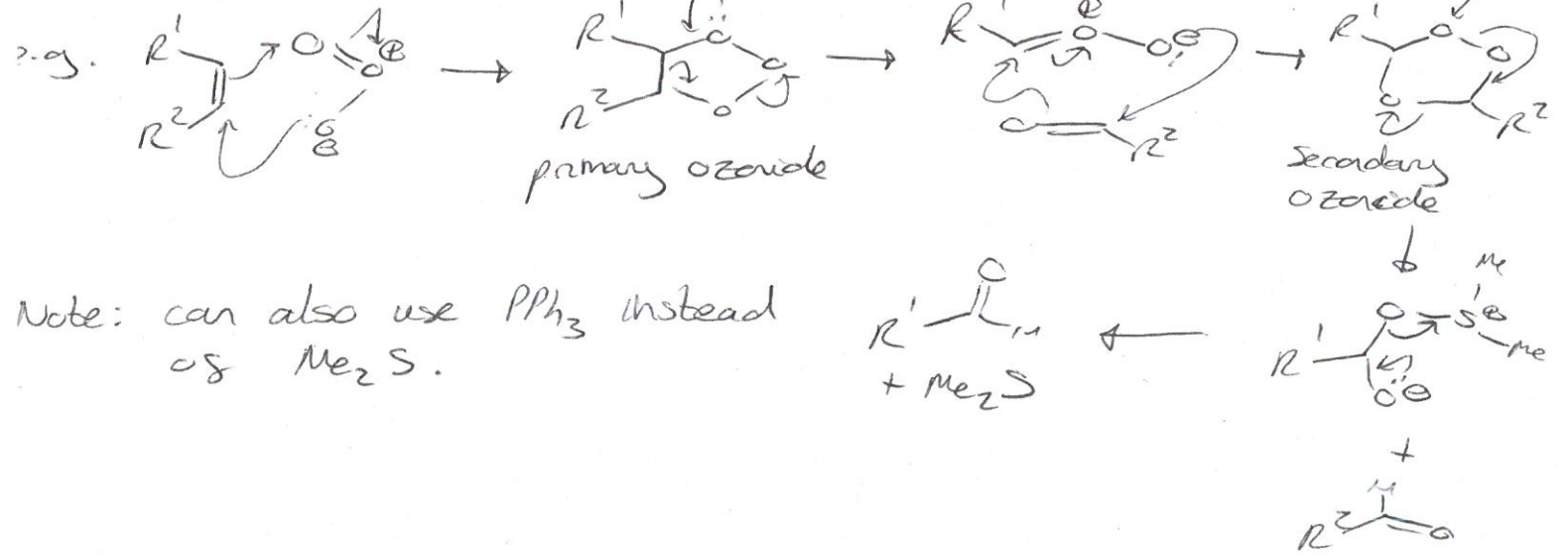


Note: can use oxidizing agents (e.g. $t\text{-BuOOH}$ or $[\text{NMO}]$) alongside catalytic OsO_4

• Diol cleavage.

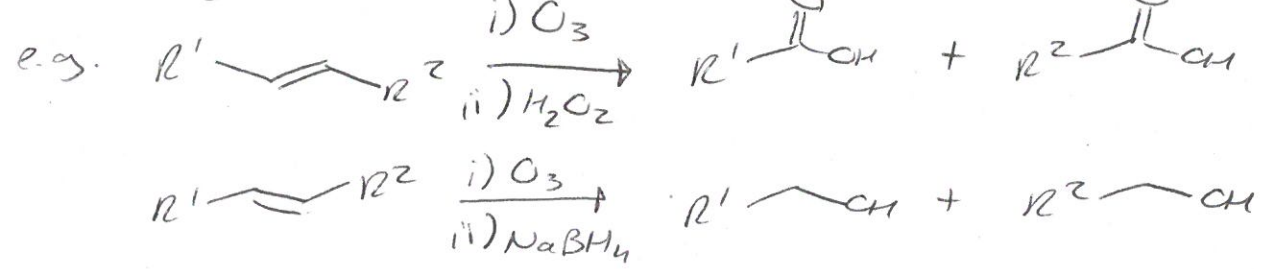


• Ozonolysis.



Note: can also use PPh_3 instead of Me_2S .

• Ozonolysis (oxidative + reductive quenches).

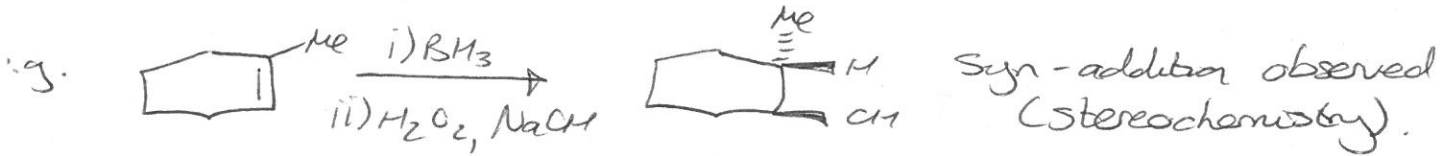
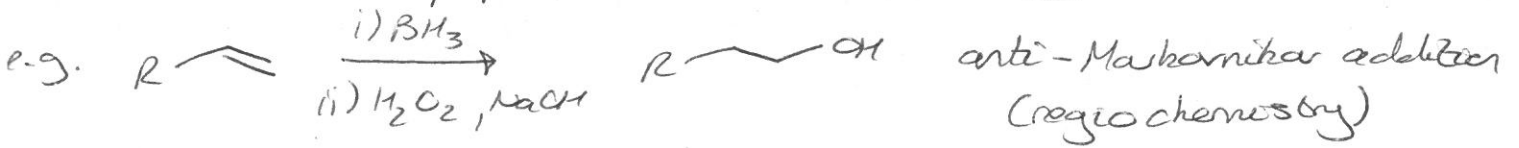


Lecture 8

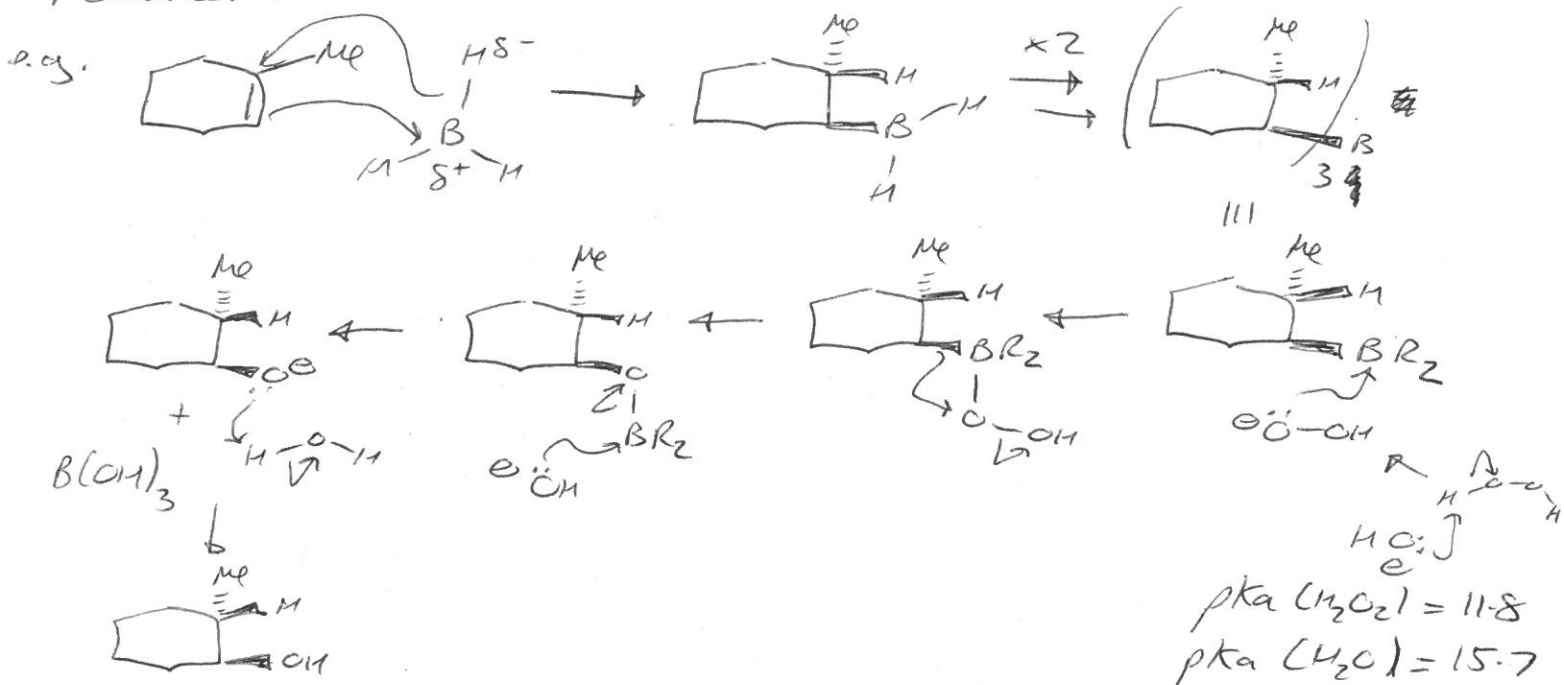
• Reading Clayden Ch. 19.

• Hydroboration/oxidation.

Alcohols can be prepared in two steps using borane chemistry.



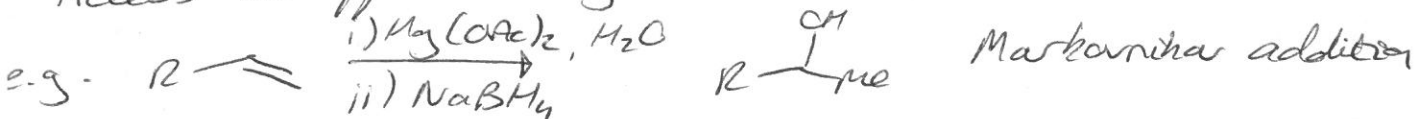
• Mechanism.



Note: Boron (EN = 2.0) and Hydrogen (EN = 2.2) polarises B-H bond. + BH2 larger than H. BH2 adds to least hindered end. Also, C=C π bond adds to B $2p$ orbital so +ve charge on more substituted carbon atom. The oxidation proceeds with retention of configuration.

• Oxymercuration

Access the opposite regioisomer.



• Mechanism.

