Retrosynthetic Analysis 1

Retrosynthetic analysis (retrosynthesis) is a technique for planning a synthesis, especially of complex organic molecules, whereby the complex target molecule (TM) is reduced into a sequence of progressively simpler structures along a pathway which ultimately leads to the identification of a simple or commercially available starting material (SM) from which a chemical synthesis can then be developed. Retrosynthetic analysis is based on known reactions (e.g the Wittig reaction, oxidation, reduction etc). The synthetic plan generated from the retrosynthetic analysis will be the roadmap to guide the synthesis of the target molecule.

The transformation of a molecule to a synthetic precursor is accomplished by

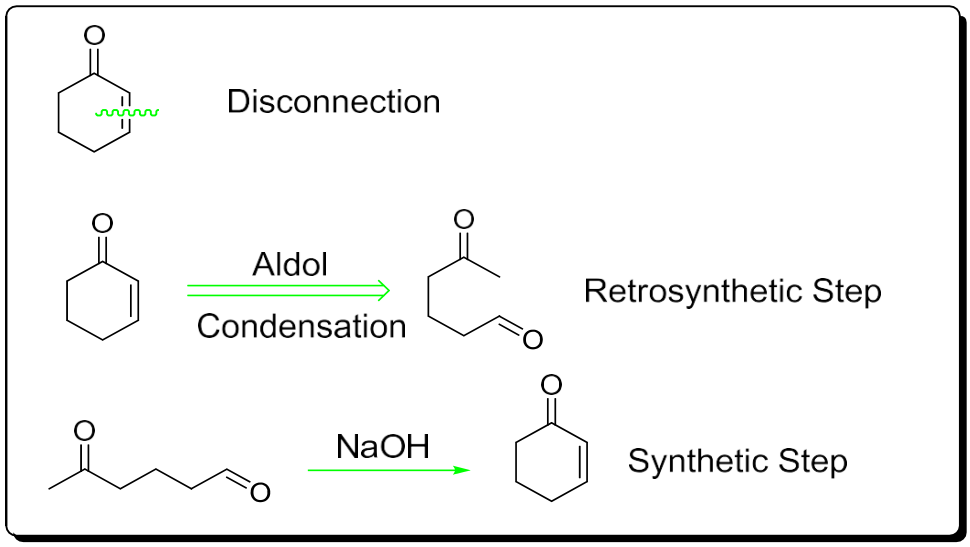
- ***Disconnection***: The term disconnection relates to breaking a carbon-carbon bond of a molecule to generate shorter or simpler fragments. A good disconnection must achieve the greatest simplification of the target molecule. For a complex molecule, this basic disconnection process is repeated until the target is reduced to simple starting materials. The complete set of disconnections and functional group interconversions for a specified target molecule is what constitutes a retrosynthetic pathway or plan.
- ***Functional Group Interconversion (FGI)***: the process of converting one functional group into another by substitution, addition, elimination, reduction, or oxidation. Although FGI doesn't offer much gain to a synthesis, it sets the stage for subsequent disconnection of the intermediate. Revisit the retrosynthetic analysis of Muscalure to identify the disconnections and Functional group interconversions.
- ***Synthetic Strategies***: Choosing the way along the retrosynthetic tree, synthetic planning.
- ***Synthetic Tactics***: How a specific bond or set of bonds at a given site can be efficiently created.

Symbols of Retrosynthetic Analysis

A disconnection is represented by a wavy (≀) line through the¬ bond being disconnected.

A retrosynthetic arrow (⇒): This open arrow represents¬ going from the target molecule "backwards" to simpler molecules (retrons).

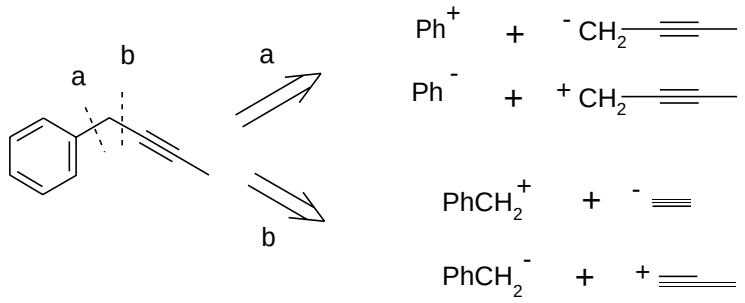
A synthetic arrow (→): This closed arrow represents going in¬ the forward direction.



Disconnections

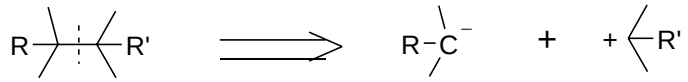
Basic Guidelines:

1. Use disconnections corresponding to known reliable reactions, choose disconnection corresponding to the highest yielding reaction.

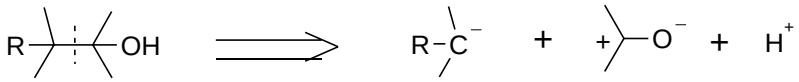


2. Disconnect C-C bond according to the present FGs in the molecule, few examples:

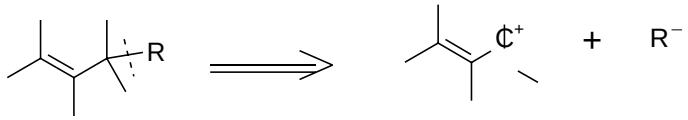
a. C-C bond with no neighbouring functional groups



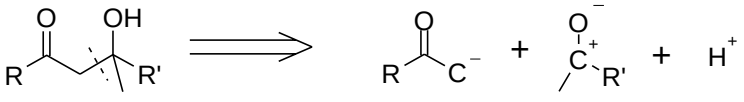
b. C-C bond with one oxygen substituent



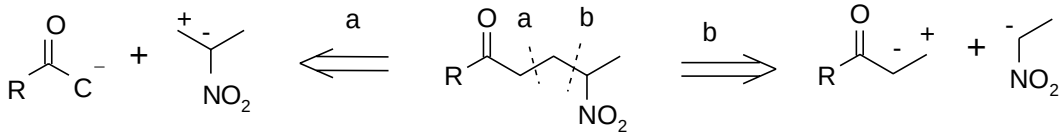
c. Allylic C-C bond



d. C-C bond with two oxygen substituents in positions 1,3

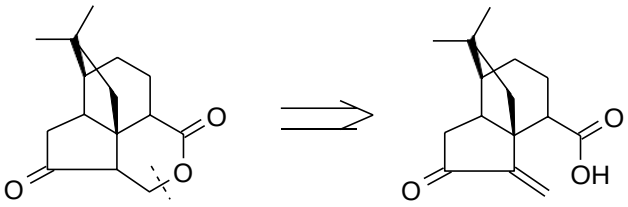


e. C-C bond with two heteroatom substituents in positions 1,2 or 1,4. Umpolung methods.



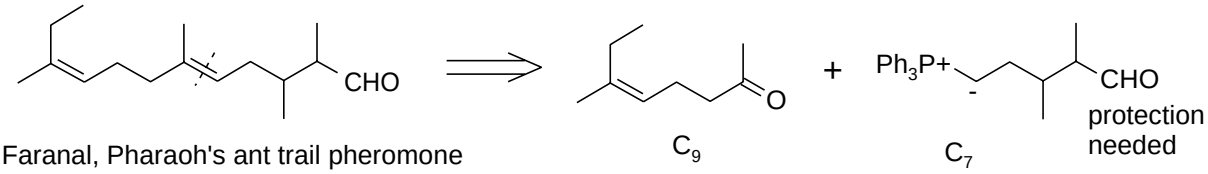
3. Aim for simplification:

a) Disconnect C-X bond (RCO-X)



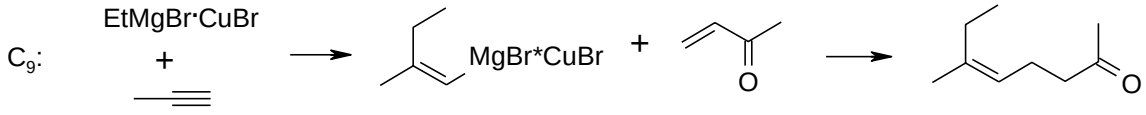
Quadrone

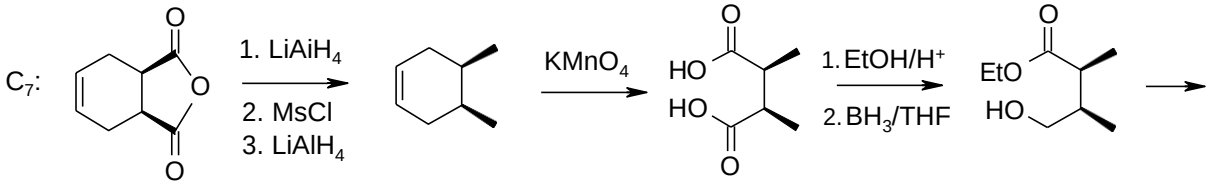
b) disconnect in the middle of the molecule

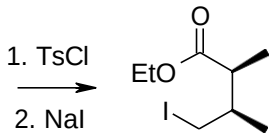


Faranal, Pharaoh's ant trail pheromone

C_9 C_7



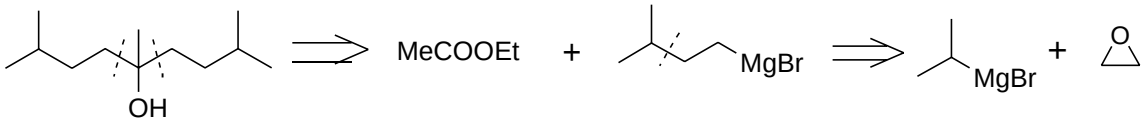




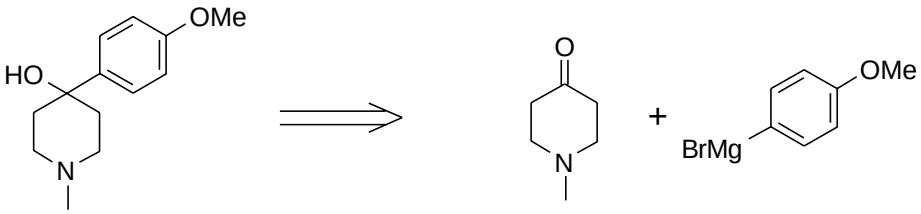
Tetrahedron Lett. **1981**, *22*, 5001

c) disconnect at a branch point

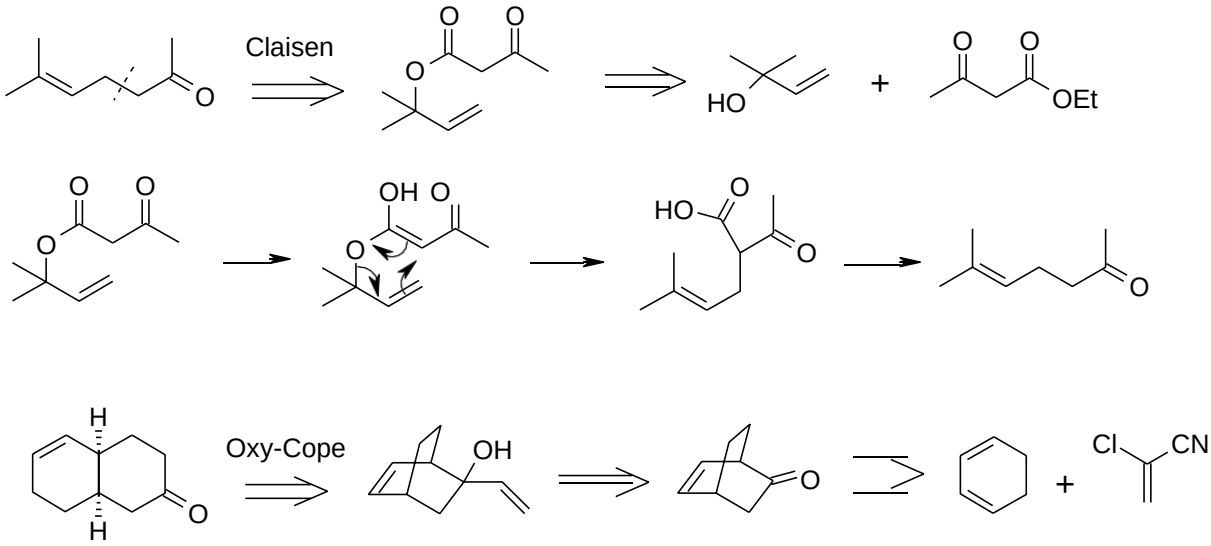
d) use symmetry



e) disconnect rings from chain



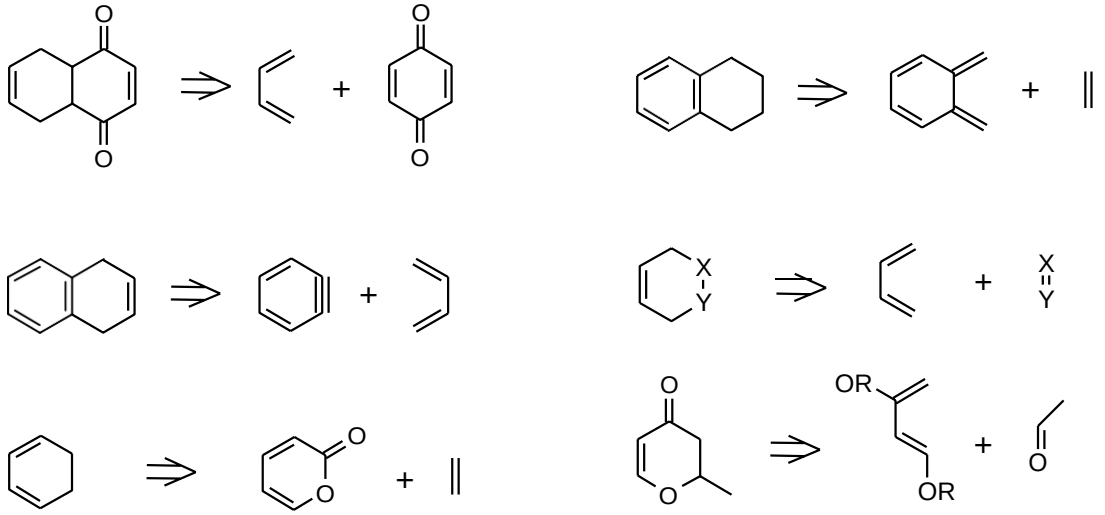
f) use rearrangements



4. Carbocyclic Rings:

If one or more *6-membered carbocyclic* unit present in the molecule consider a set of disconnection available for construction of 6-membered rings: Diels-Alder, Robinson annulation, aldol, Dieckmann, internal S_N2, Birch reduction, etc.

Some types of Diels-Alder disconnections:



5. Examples of cleavage of C-C bond as a retrosynthetic ***reconnection***