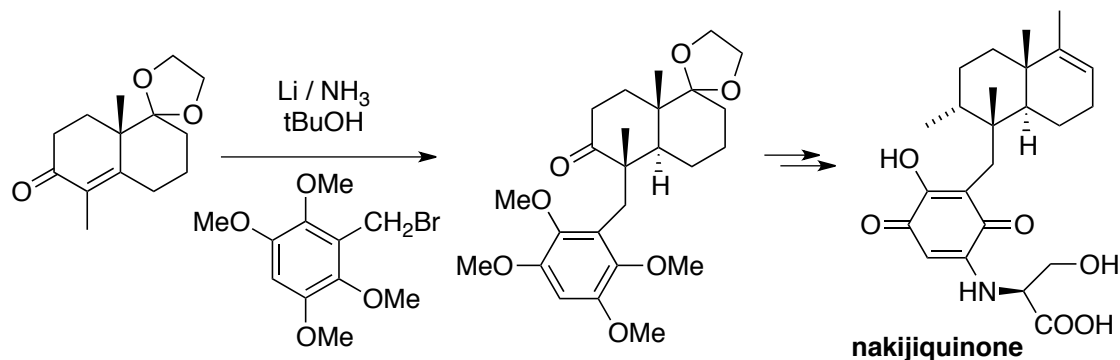


## CHEM 330

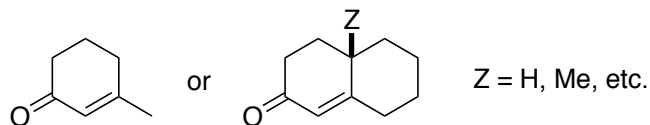
### Topics Discussed on Oct 26

Application of the principles discussed on Oct 21 to the synthesis of nakijiquinone

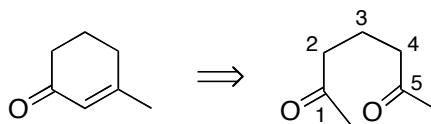


**note:** nakijiquinone is a natural product that inhibits a particular tyrosine kinase (= an enzyme that transfer a phosphoryl group from ATP to the phenolic OH of a tyrosine residue in an particular protein), which is overactive in various breast, ovary, and gastric cancers. Inhibitors of this kinase are useful probes of biological function and candidate anticancer drugs.

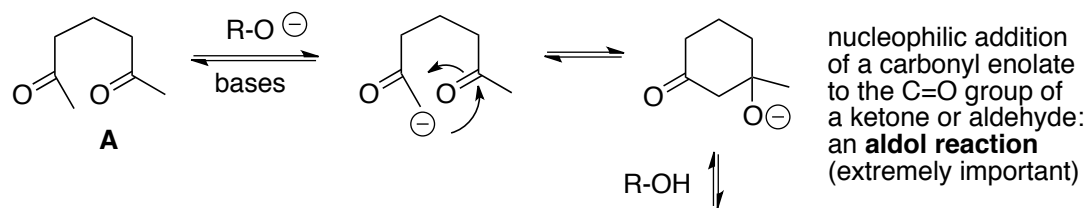
The preparation of enones of the type shown below as a significant objective in contemporary synthetic organic chemistry:

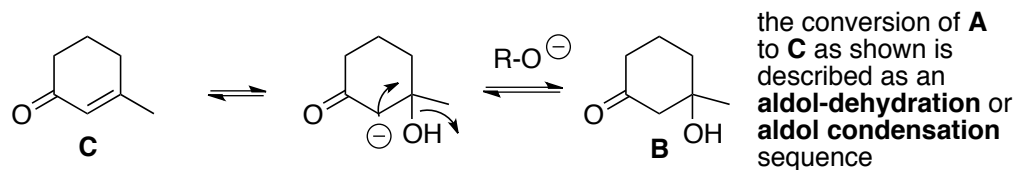


1,5-Dicarbonyl compounds as precursors of the target cyclic systems:

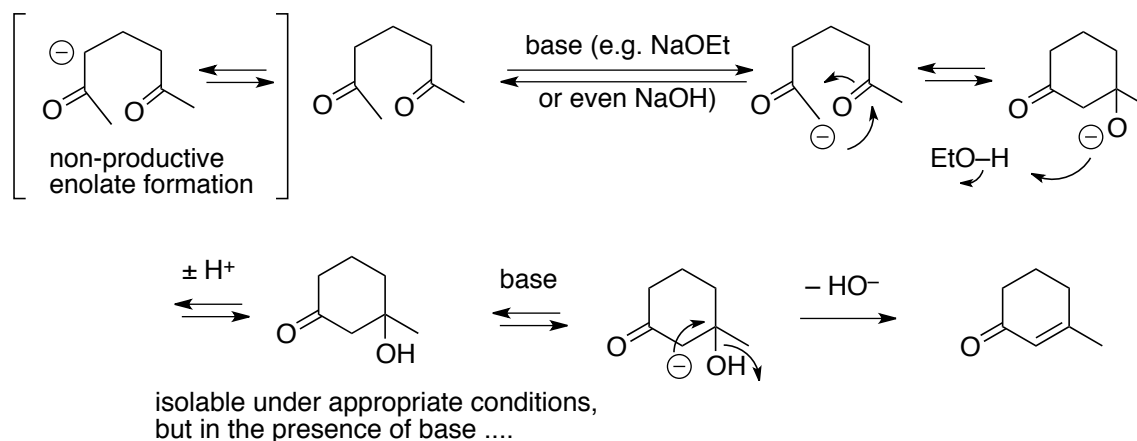


Principle: a 1,5-dicarbonyl compound of the above type may be advanced to the desired enone (also described as a conjugated carbonyl or an  $\alpha,\beta$ -unsaturated ketone) by an aldol – dehydration (aldol condensation) sequence:



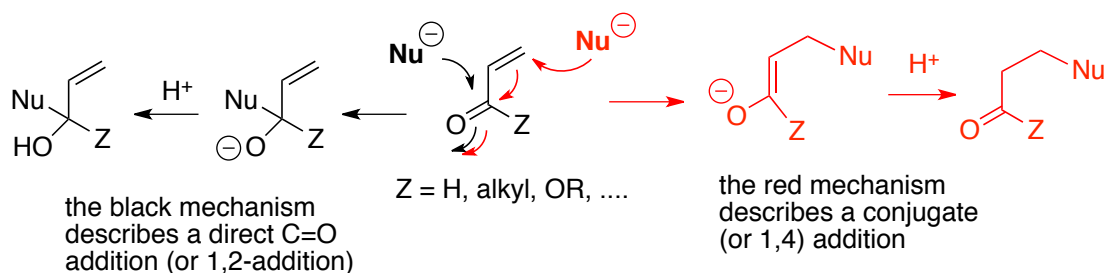


Principle: an aldol-dehydration sequence is best carried out with bases that deprotonate the 1,5-dicarbonyl substrate reversibly, e.g., an alkoxide (or even  $\text{HO}^-$ )"

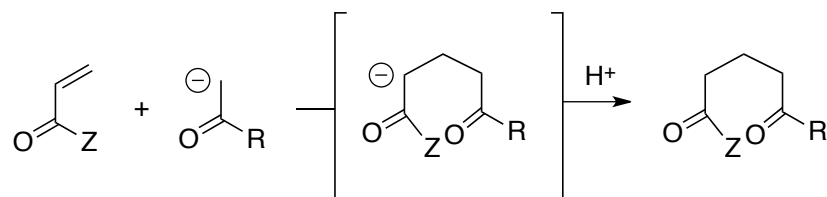


The base-promoted cyclization (= aldol-dehydration) of 1,5-dicarbonyls as a general, extremely useful method for the construction of 6-membered rings

Conjugate addition (also called 1,4-addition) reactions: processes in which a nucleophile reacts with a conjugated carbonyl compound (of any kind) not at the  $\text{C}=\text{O}$  group ("1,2-addition"), but at the distal olefinic center:



Preparation of 1,5-dicarbonyls through the conjugate addition of a carbonyl enolate to an  $\alpha,\beta$ -unsaturated carbonyl substrate: the **Michael** reaction:



Michael donor: a generic nucleophile, such as a carbonyl enolate, that shows a propensity to add in a 1,4-mode to a conjugated carbonyl substrate.

Michael acceptor: the conjugated carbonyl compound that undergoes 1,4-addition upon treatment with an appropriate nucleophile, e.g., an enolate.

Principle: it is not easy to predict whether a given nucleophile will add to a conjugated carbonyl compound in a 1,2 or a 1,4 mode. Therefore, in this class we shall rely on precedent. Intellectual constructs that allow one to formulate *a priori* predictions are beyond the scope of CHEM 330.

Concerning the scope of Michael additions with respect to the **donor**:

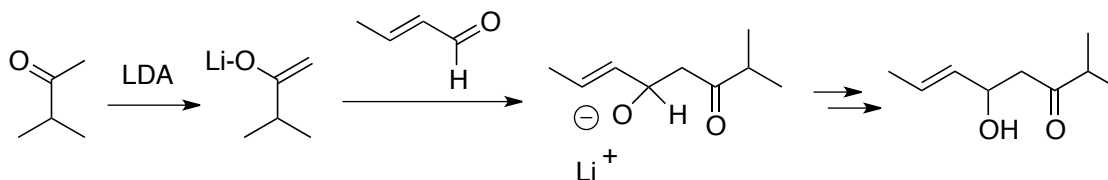
Enolates of carbonyl (ketone, ester, 1,3-dicarbonyl ...) and carbonyl-like (nitrile, nitro ...) compounds as generally effective Michael donors

Enolates of active methylene and related compounds ("stabilized enolates") as especially effective nucleophiles in Michael reactions

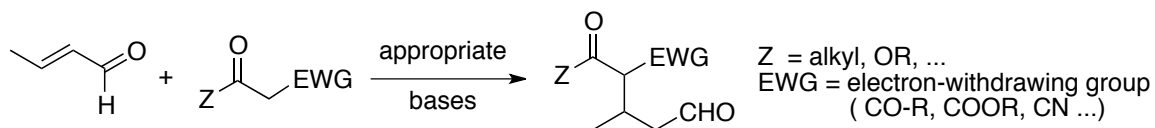
Concerning the scope of Michael additions with respect to the **acceptor**:

(i) Conjugated ketones, esters, nitriles, etc. generally undergo efficient Michael reaction with carbonyl enolates of all types (= unstabilized and stabilized)

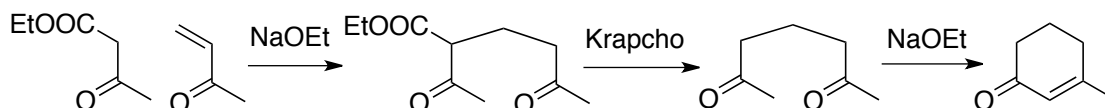
(ii) Conjugated aldehydes tend to react with non-stabilized carbonyl enolates in a 1,2-mode, i.e., they participate in aldol, rather than Michael, reactions, with such nucleophiles. Example:

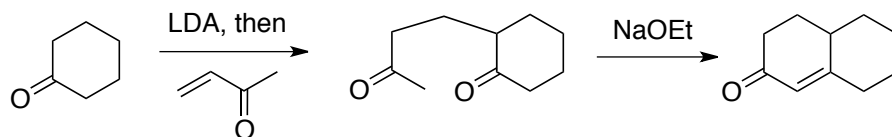


(iii) **however**, conjugated aldehydes do react in a Michael mode with stabilized enolates (anions of active methylene compounds and related substances):

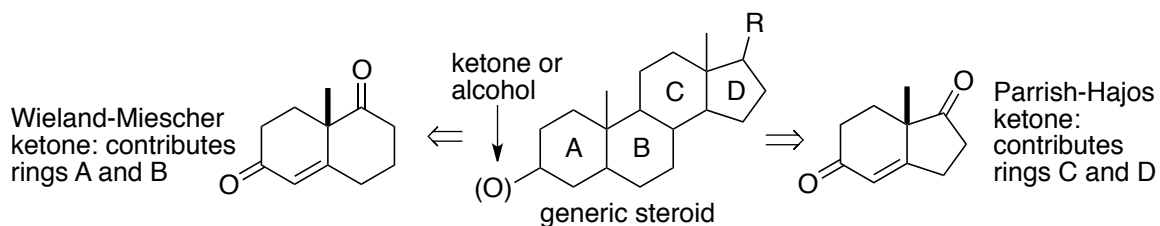


Possible routes to the above enones via Michael reaction / aldol / dehydration:





Application of Michael additions and aldol-dehydration sequences in the preparation of enones useful for the synthesis of steroids:



The Wieland-Miescher ketone as an exceedingly important intermediate for the synthesis of steroids, antibiotics, and other biomedically significant compounds.

Annulation reaction: a process that forms a ring through a multistep sequence.

**Robinson annulation:** a technique for the construction of 6-membered cyclic enones through a multistep sequence that involves a Michael addition followed by aldol-dehydration

Retrosynthetic logic for the synthesis of the above enones:

