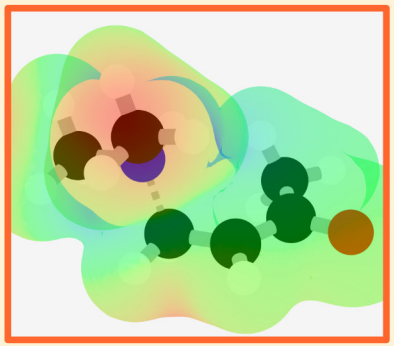
HIGHLIGHTS

- Conjugate addition requires the an activated alkene or Michael acceptor.
- Good activating groups include aldehydes, ketones, esters, amides, nitro groups, nitriles, and sulfones.
- Carbonyl-containing activating groups have two electrophilic centers, direct addition to the carbonyl group is 1,2-addition. Attack on the alkene is 1,4-addition.
- Choice of nucleophile (or Michael donor) can influence 1,2- versus 1,4-addition.
- Nucleophiles with a strong conjugate base, or small, concentrated charge, are hard nucleophiles. They favor 1,2-addition and include organolithium or Grignard reagents.
- Nucleophiles with weak conjugate bases or a diffuse charge are soft nucleophiles. These favor 1,4-addition and include heteroatoms and organocopper compounds.



Conjugate addition reactions involve a nucleophile adding to an activated alkene. A conjugated electron withdrawing group polarizes the alkene, activating it and allowing electrons to flow out onto an electronegative atom. Alkenes conjugated to these groups are often known as ***Michael acceptors***. When the activating group contains a carbonyl group there are two electrophilic centers within the acceptor. Nucleophiles can add directly to the carbonyl group (1,2-addition) or to the ß-carbon of the alkene (1,4-addition). The choice of nucleophile can make a big difference. Nucleophiles that have a strong conjugate base, or have a small, concentrated charge, are known as hard nucleophiles and they favor direct addition. Nucleophiles with weak conjugate bases or those that have a diffuse charge are soft nucleophiles. These favor the 1,4-addition.

CHEMISTRY CLASSICS

CONJUGATE ADDITION

THE MICHAEL REACTION OR 1,4-ADDITION

Conjugate Addition

Making MOLECULES
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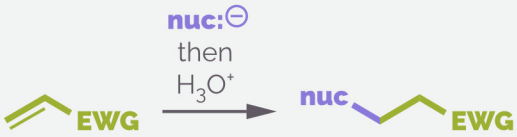
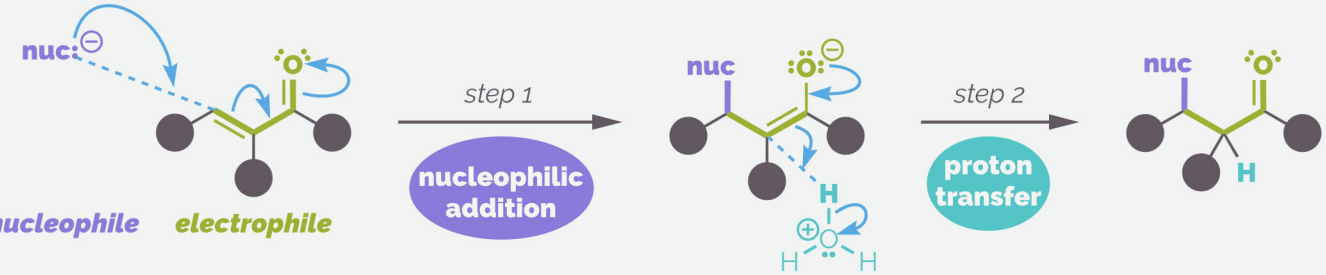
1. General reaction



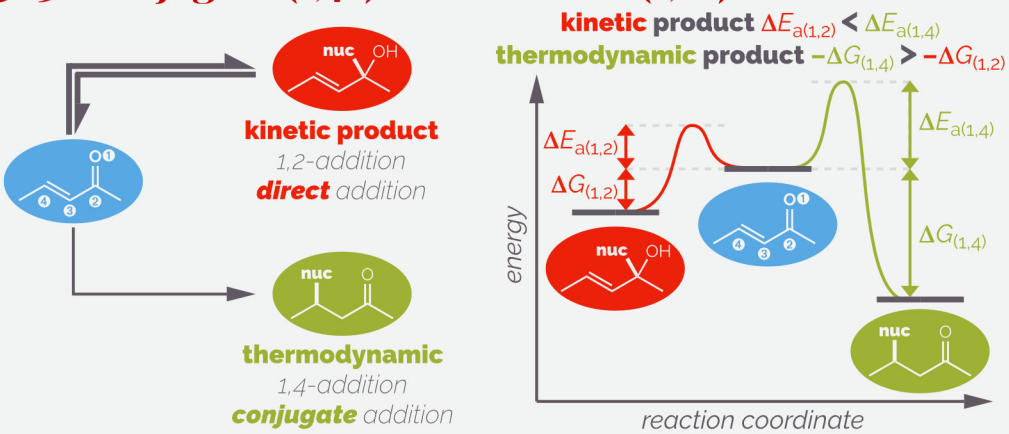
EWG = conjugated electron withdrawing group *e.g.* -C(O)R, -NO_2, -CN
nuc = R_2NH, ROH, NC, organocopper

2. Mechanism (shown for ketone but identical for all conjugated EWG)



Depending on the nature of the nucleophile there may be additional proton transfer steps (e.g. if nuc = R_2NH)
Step 2 can be a second nucleophilic addition if you replace the proton source, H_3O^+, with an electrophile E^+ (e.g. aldehyde)

3. Conjugate (1,4-) *versus* direct (1,2-) addition



The kinetic product forms faster while the thermodynamic product is more stable.
Reaction conditions important if reaction reversible - otherwise look at reactants.

direct (C=O) *or 1,2-addition*
reversible reactions: **kinetic** product
low temperature, **short** reaction

hard nucleophiles attack **LUMO** at ❷

hard nucleophiles - strong bases, charge concentrated on small atom, organolithiums & Grignards

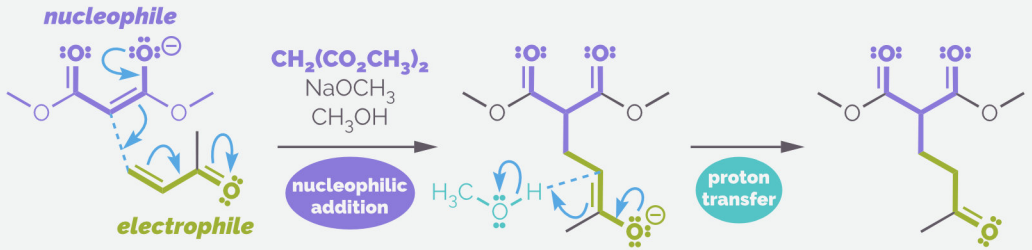
conjugate (C=C) *or 1,4-addition*
reversible reactions: **thermodynamic** product, **high** temperature, **long** reaction

soft nucleophiles attack **LUMO** at ❹

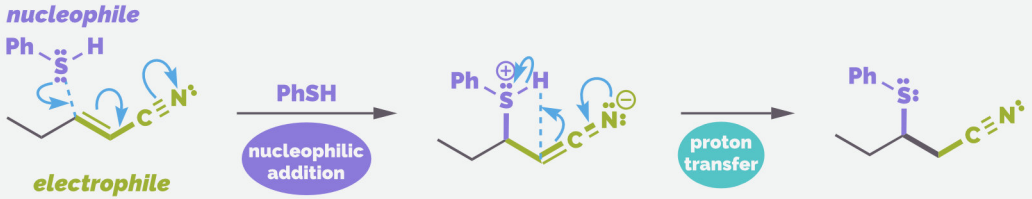
soft nucleophiles - weak bases, diffuse or delocalized charge organocopper/cuprates

4. Examples of conjugate addition

Conjugate addition of enolate to α,β-unsaturated ketone (Michael Addition)



Conjugate addition of thiol it activated alkene (conjugated alkene)



Addition of organocopper reagent followed by aldol reaction (tandem reaction)