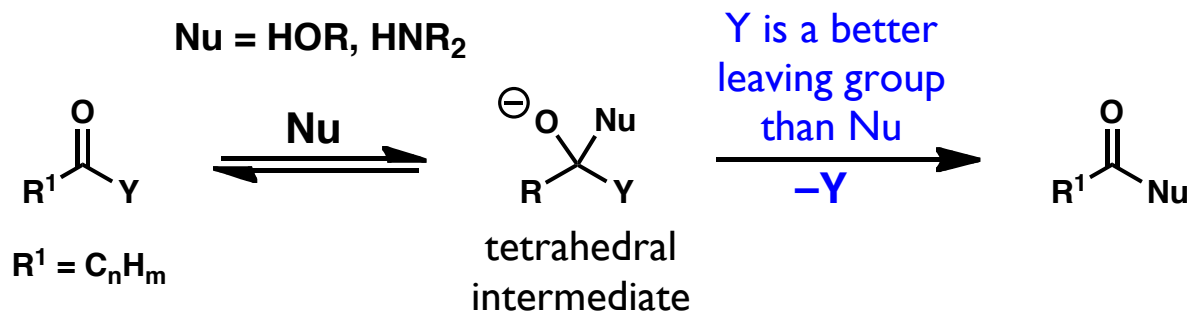


Notes About PS 8

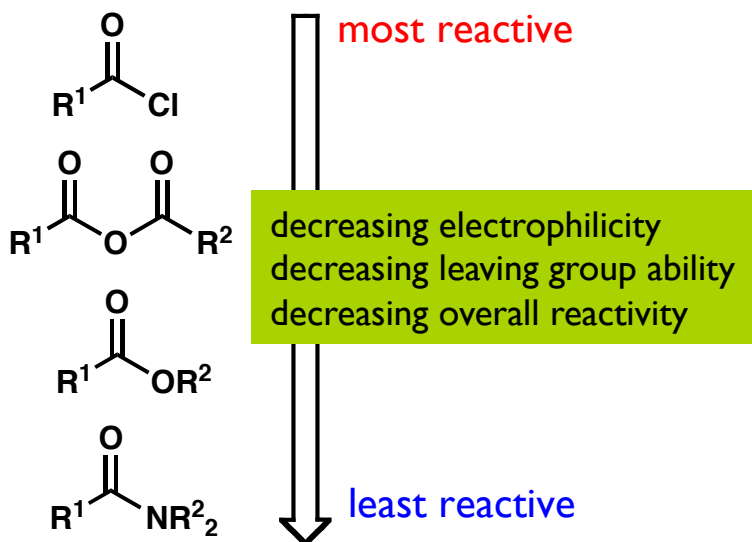
Question 4: The water is more appropriately classified as an “initiator,” not a catalyst, since it is consumed in the reaction.

Question 5: You do not need to show the arrow pushing mechanism for each step of the synthesis, you just need to provide the starting materials, reagents, and products for each step. You can use a general “base” for any Fmoc protection reactions.

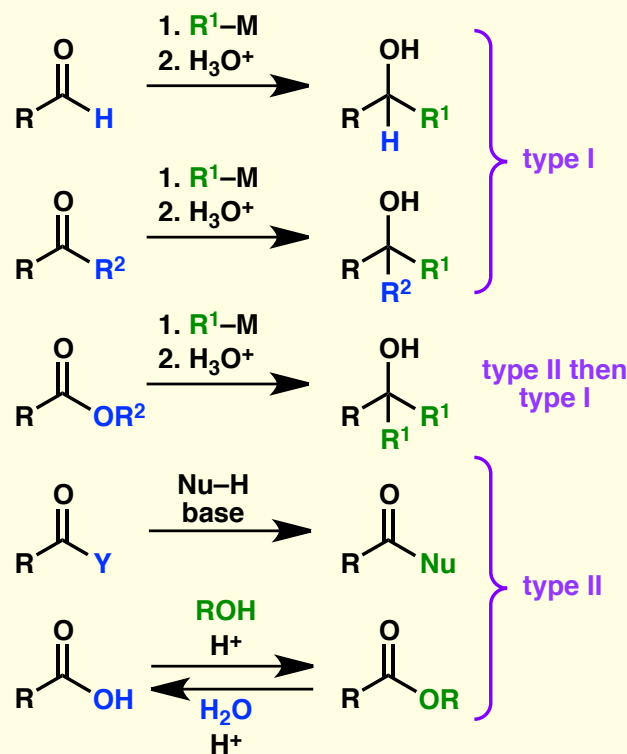
From Last Time: Nucleophilic *Substitution* at the Carbonyl



reactions proceed down the hierarchy of carboxylic acid derivatives

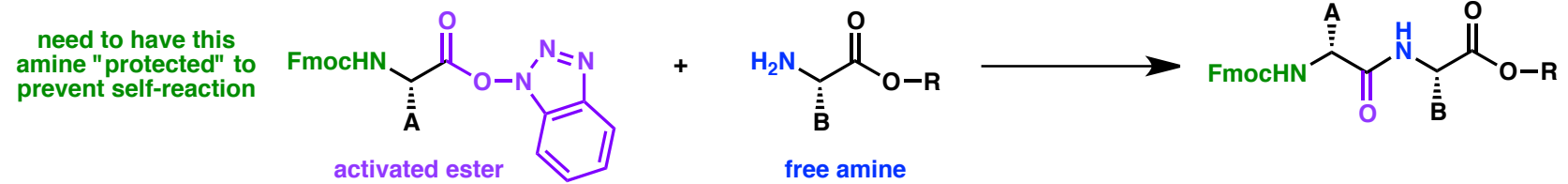


What reactions have we learned so far?



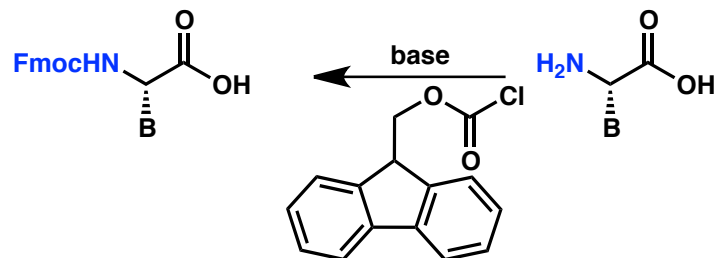
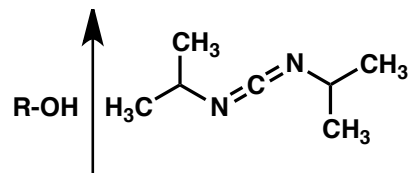
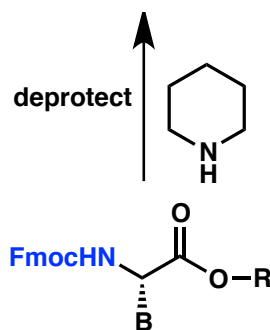
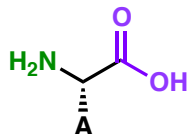
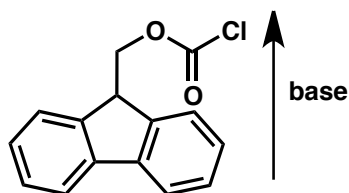
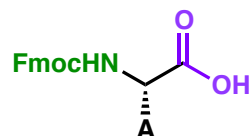
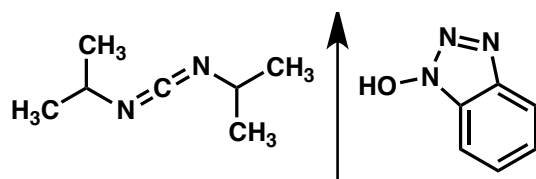
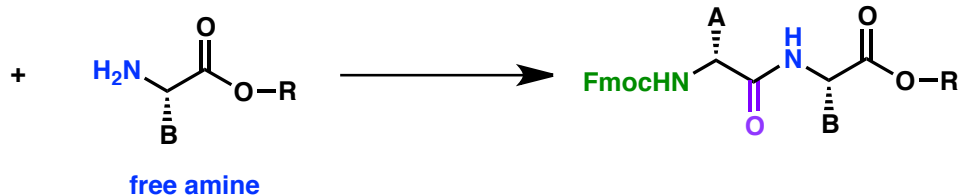
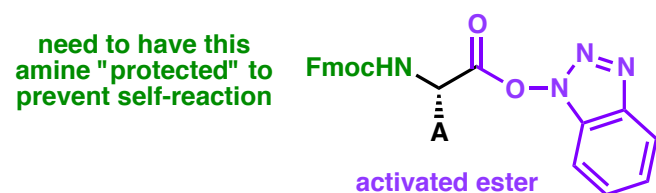
Peptide Synthesis

How to make a simple dipeptide:



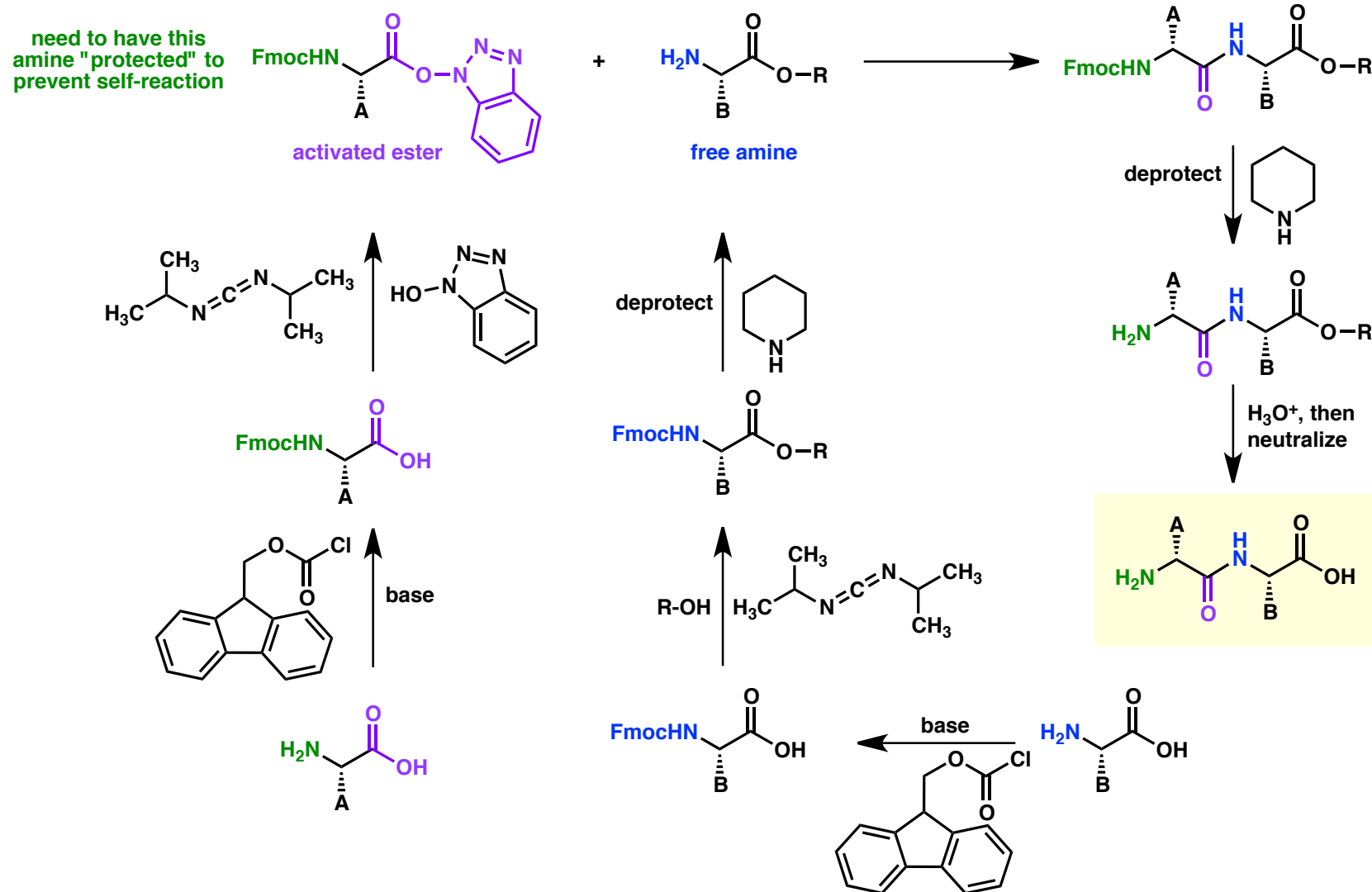
Peptide Synthesis

How to make a simple dipeptide:



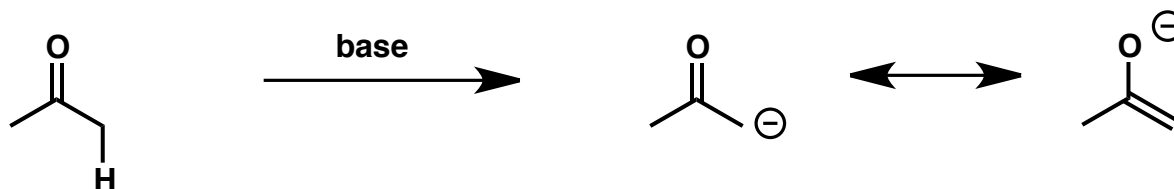
Peptide Synthesis

How to make a simple dipeptide:

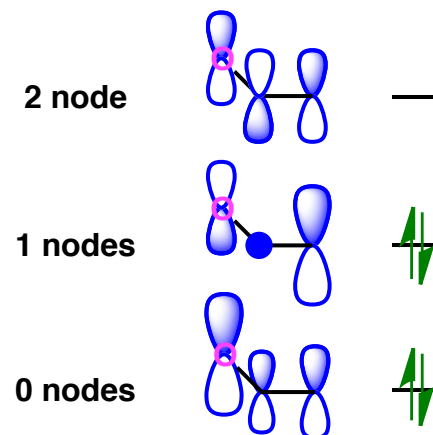
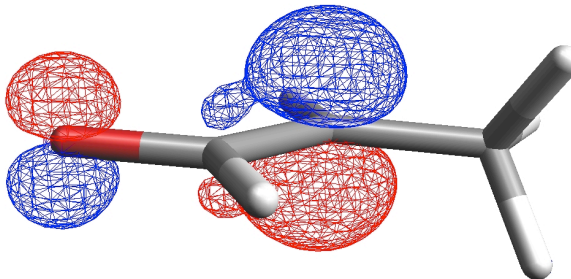


Enolates: Another Type of Carbon Nucleophile

The protons on the carbons α to the carbonyl groups are acidic

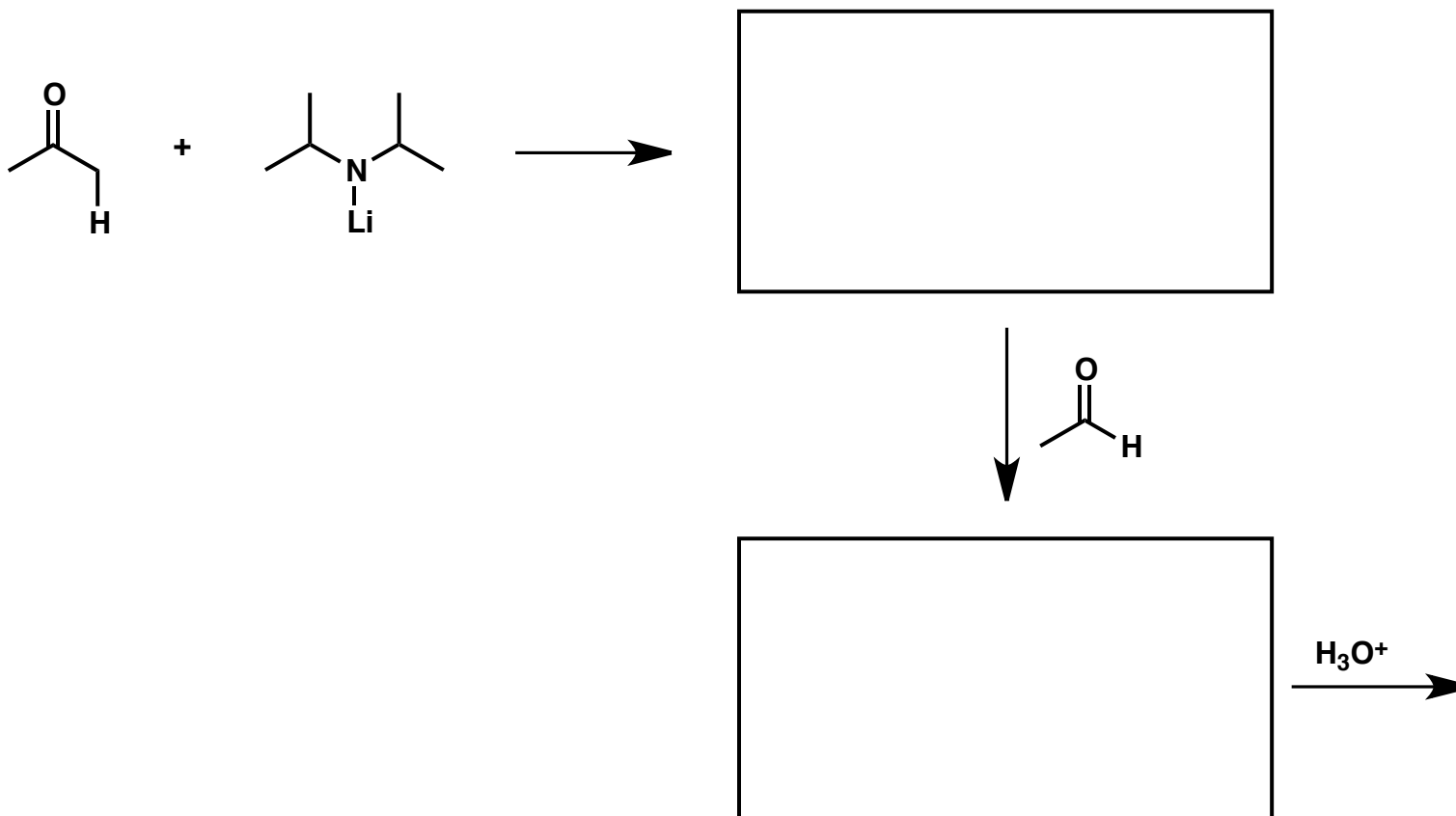
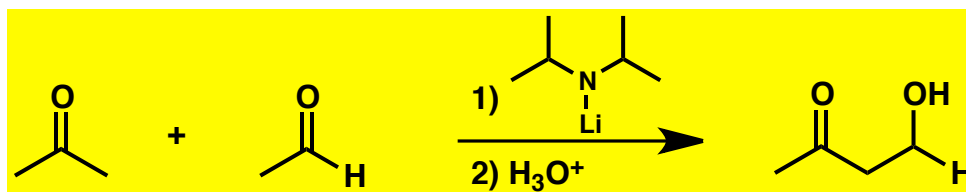


MO considerations

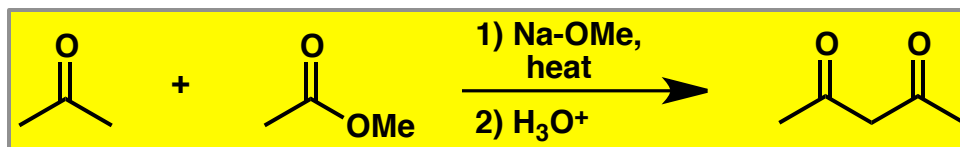


Enolates typically react with electrophiles at carbon

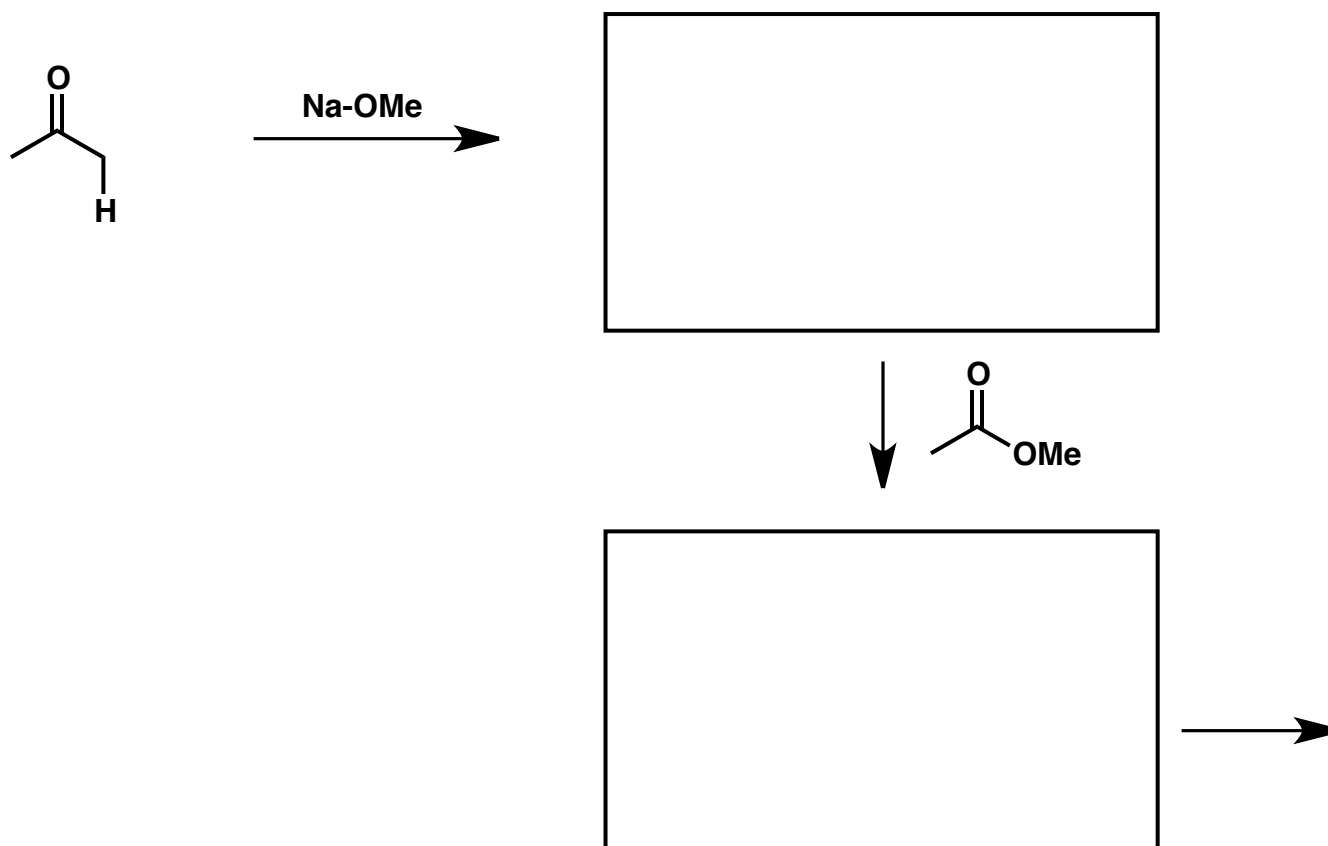
The Aldol Reaction: Reaction of a Ketone with an Aldehyde



The Claisen Condensation: Reaction of a Ketone with an Ester



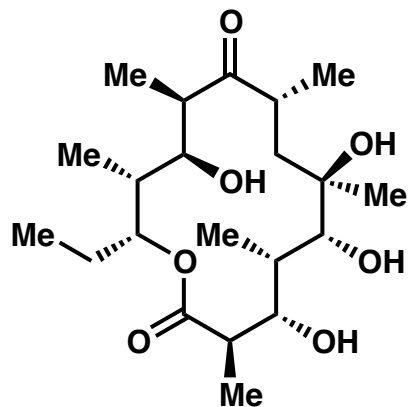
Let's think about the mechanism:



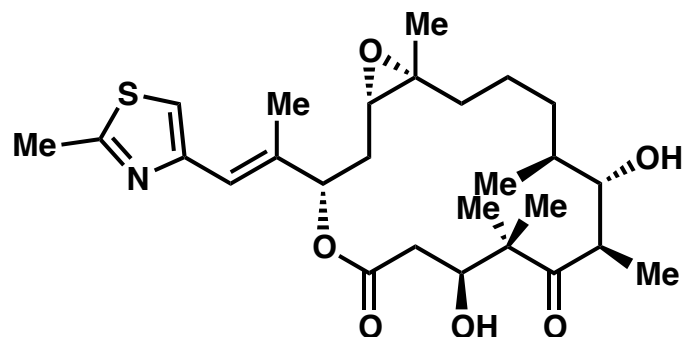
Polyketide Natural Products: Assembled in Nature by an Enolate Substitution at the Carbonyl

The polyketides below are biologically active small molecules produced by bacteria.

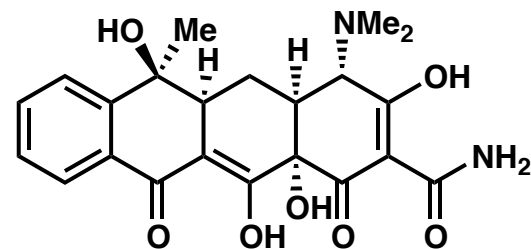
- These are agents of **bacterial chemical warfare**.
- These compounds, or their derivatives, have been developed into drugs



erythronolide B



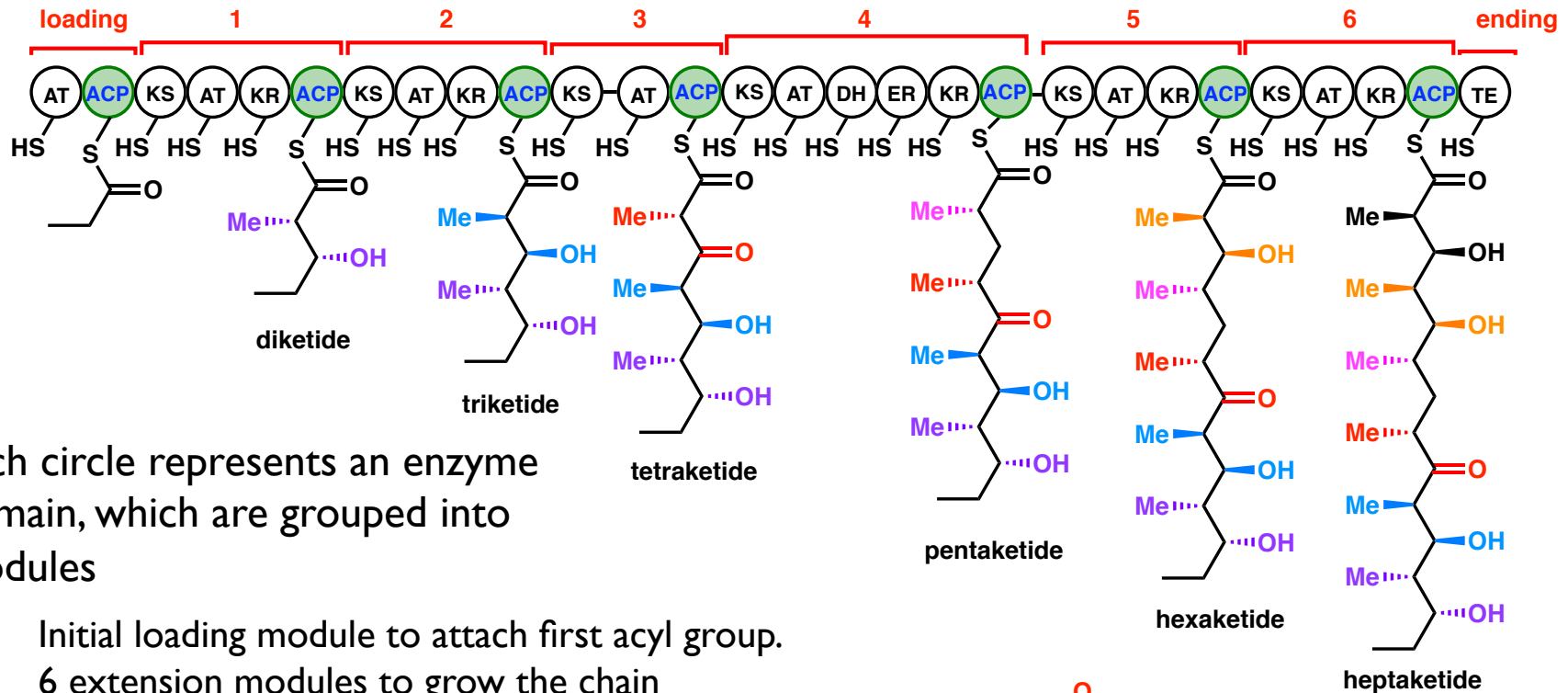
epothilone B



tetracycline

Bacterial Polyketide Synthesis: A Modular Assembly Line

The 6-deoxyerythronolide polyketide synthase schematically:



Each circle represents an enzyme domain, which are grouped into modules

- Initial loading module to attach first acyl group.
- 6 extension modules to grow the chain
- Ending module to release the polyketide

Key:

AT: acyl transferase

ACP: acyl carrier protein

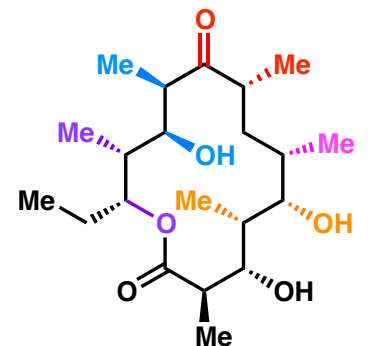
KS: ketoacyl synthase

KR: ketoacylreductase

DH: dehydratase

ER: enoyl reductase

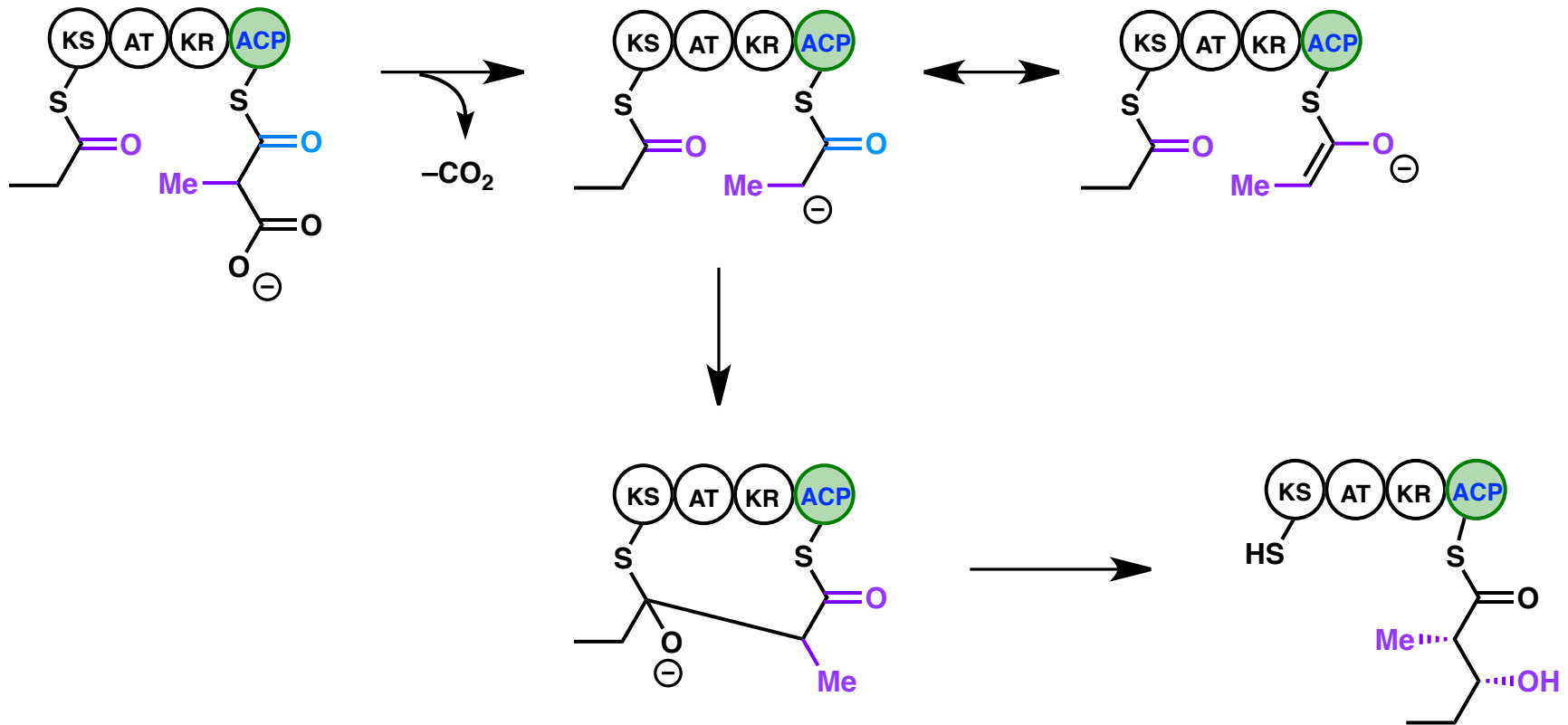
TE: thioesterase



6-deoxyerythronolide B

Polyketide Synthase Employs the Claisen Condensation of a Thio Ester

A decarboxylation reaction – the loss of CO_2 generates an enolate (or enolate equivalent) under mild conditions



Sulfurs are Good Nucleophiles For Nucleophilic Substitution Reactions

The polyketide is propagated from enzyme to enzyme by a series of nucleophilic substitution reactions.

