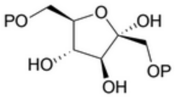
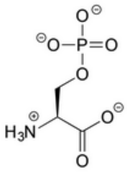
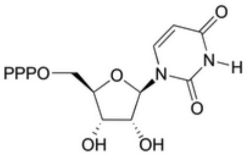
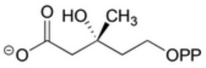
Exercise 8.1. Terms and abbreviations of phosphate

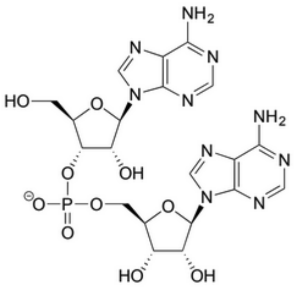
Consider the biological compounds below, some of which are shown with abbreviated structures:


I


II


III


IV


V

a) Which contain one or more phosphate anhydride linkages? Specify the number of phosphate anhydride linkages in your answers.

b) Which contains one or more phosphate monoesters? Again, specify the number for each answer.

c) Which contains a phosphate diester?

d) Which could be described as an organic diphosphate?

e) For each compound, specify the number of bridging and non-bridging oxygens in the phosphate group.

a) Compound III contains two phosphate anyhydride linkages, compound IV contains one.

b) Compound I contains two phosphate monoesters; compoundsII, III, and IV contain one each.

c) Compound V contains a phosphate diester.

d) Compound IV is an organic diphosphate (in contrast, compound I would be called an organic bisphosphate as it has two separate single phosphate groups).

e) I: two bridging, six nonbridging

II: one bridging, three nonbridging

III:three bridging, seven nonbridging

IV: twobridging, five nonbridging

V: two bridging, two nonbridging

Exercise 8.2. Role of Phosphates in Biological Systems

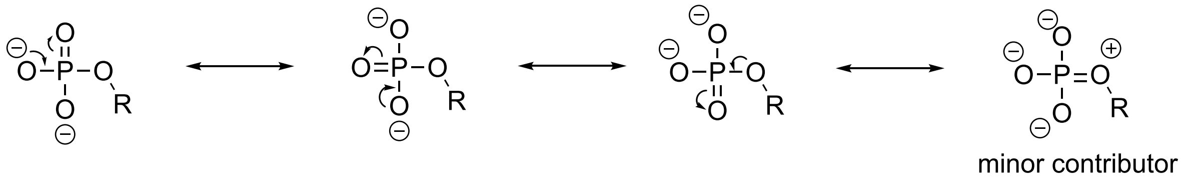
Phosphates have various important roles in biological systems, including the installment of post-translational modifications, activation in biochemical pathways or as bridging links for DNA.

a) Show the different resonance structures that an organic monophosphate has. The organic rest can be depicted as R. Are all four P-O bonds equal?

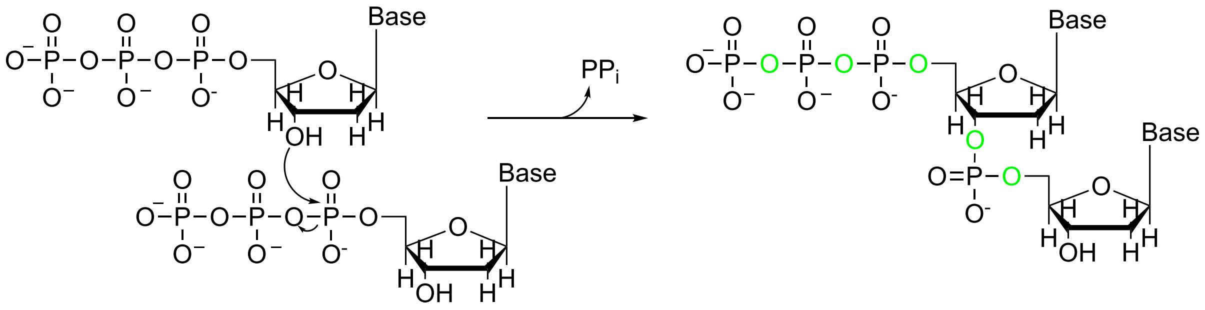
b) Show the mechanism for the linkage of two nucleotide triphosphates, draw the according arrows and name the different bridging and non-bridging oxygens and highlight the phosphate diester. The base can be abbreviated.

c) The amino acid serine can be phosphorylated, can you name a substrate that is willing to donate a phosphate to the amino acid? Draw the phosphorylated product.

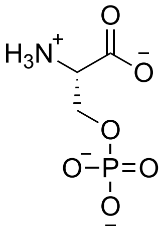
a) Not all equal – Phosphoester bond has more single bond character, while the double bond is mainly distributed through the other three oxygens.



b) Green bridging oxygens, phosphodiester is in between the two sugars

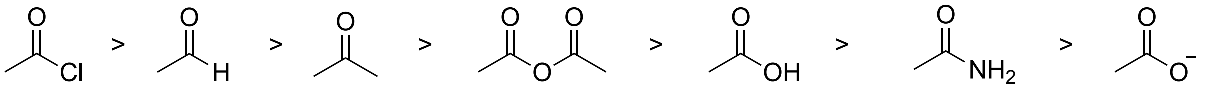


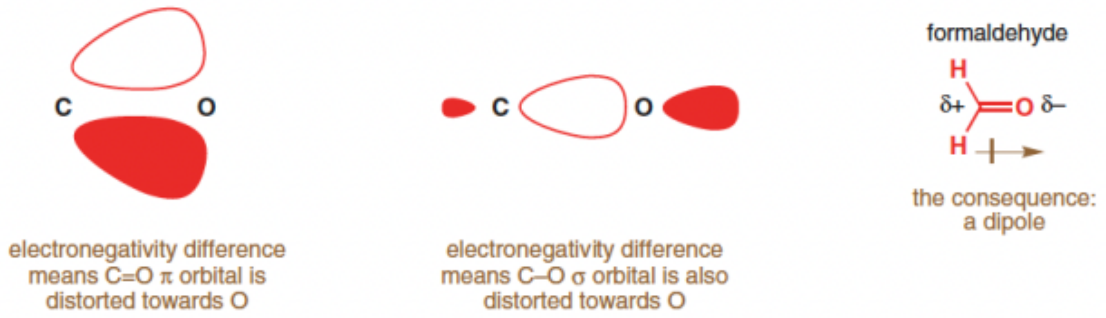
c) ATP is phosphate donor



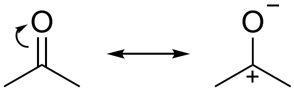
Exercise 8.3. Carbonyl Chemistry – The basics

The carbonyl functional group is essential in chemistry and also highly abundant in molecules of life. Can you name five functional groups that contain a carbonyl group and sort them by their reactivity. Choose one of the five and explain where the reactivity is coming from.



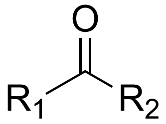


While this resonance structure is only a minor contributor to the actual electronic structure (octett rule is not fullfilled!), it clearly shows that the carbonyl has a deficiency in electrons → electrophile!



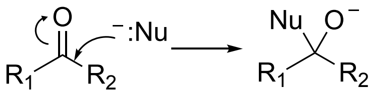
Exercise 8.4. Carbonyl Addition

For the generic keton shown:

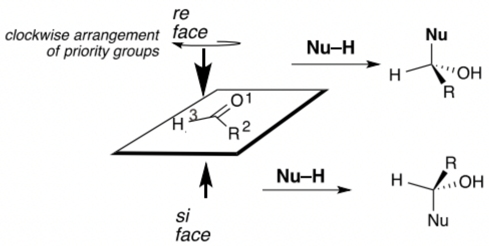


a) Can you draw a generic nucleophilic addition using “:Nu$^-$”
b) If $R_1 \neq R_2$, what enantiomeric products can you expect? Explain why.
c) Carbonyl additions also play a role in nature, draw an enzyme that could catalyze this reaction. Do you think enzymes can control the stereochemistry? If yes, any idea how?

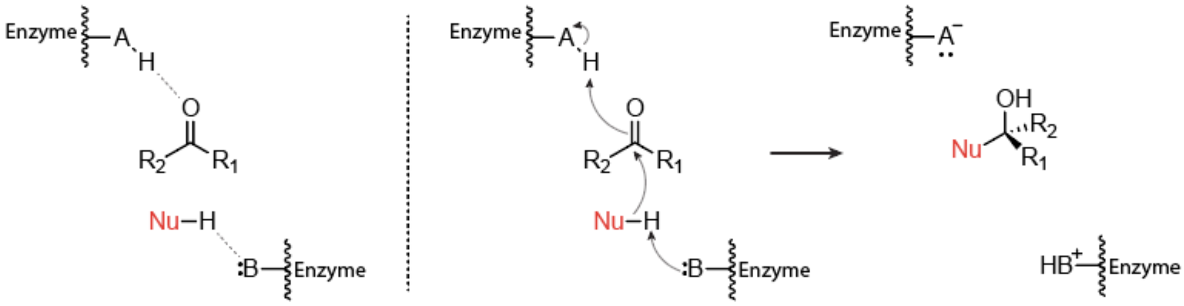
a)



b) lecture 8, slide 36



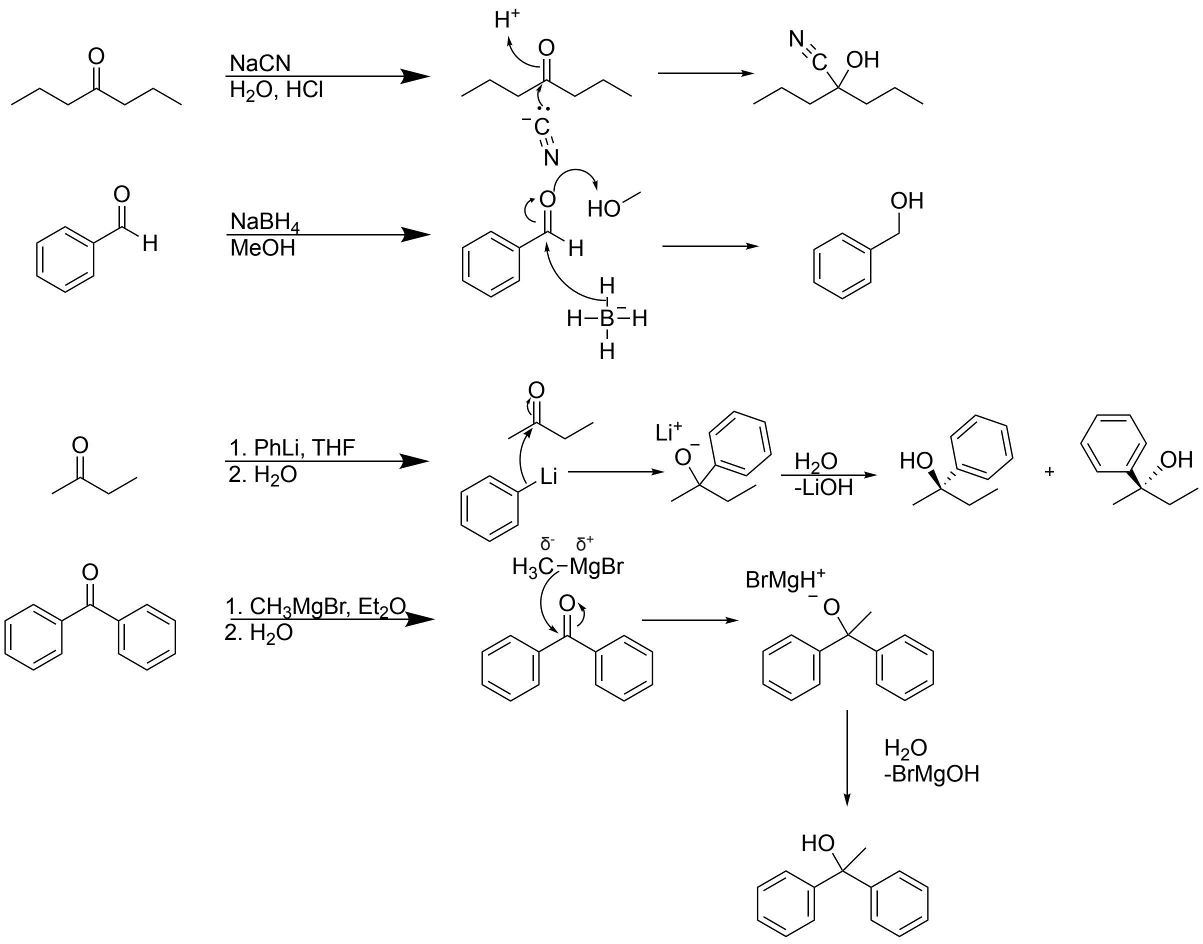
c)



The enzymatic pocket has to provide an acidic and a basic sidechain to catalyze the addition reaction. The base (B:) will polarize the hydrogen of the nucleophile (Nu). This favors deprotonation of the nucleophile. Thus, the nucleophilicity of the nucleophile will increase and as result the nucleophile will be more reactive. On the other side of the carbonyl the acidic side chain (A) positions an acidic proton right above the oxygen. This will favor protonation of the carbonyl oxygen. In the enzymatic pocket the educts will be recruited in a very specific orientation. Thus, the nucleophilic attack will occur from only one specific side of the carbonyl (either re or si face). Therefore, we expect that the product of the enzymatically catalyzed reaction will be either S or R, but not a racemate.

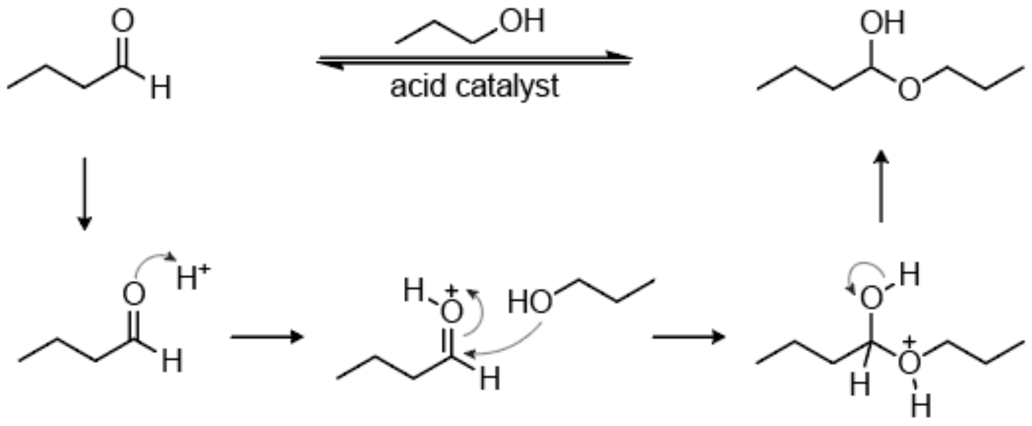
Exercise 8.5. Some Carbonyl Reactions

Show the expected products for the reaction examples below. Mark electrophile and nucleophile. (Drawing arrows and step by steps mechanisms is not required but can definitely help.)



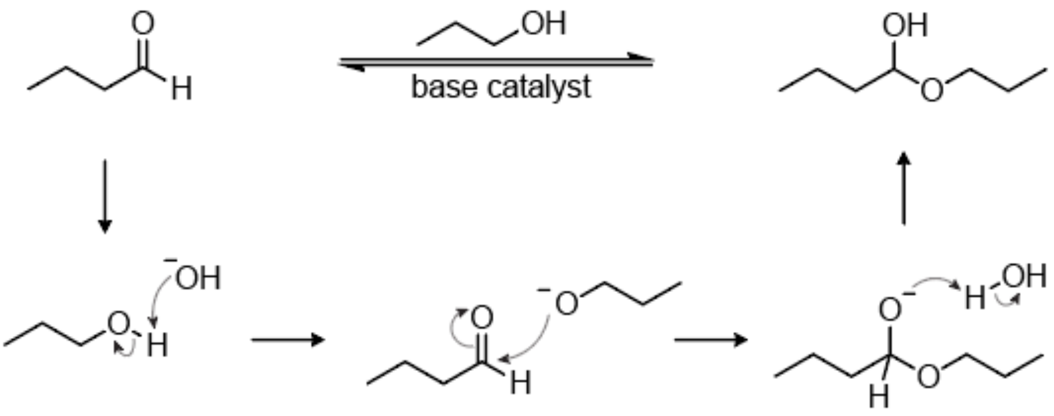
Exercise 8.6. Acid base reactions on Carbonyls

a) Addition of an alcohol to an aldehyde or ketone results in the formation of a hemiacetal and hemiketal. Draw the reaction mechanism of acid catalyzed formation of a hemiacetal below. How does the acid catalyze the reaction?



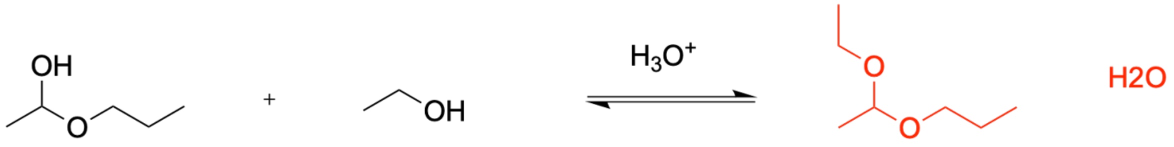
The acid increases electrophilicity of the carbonyl carbon

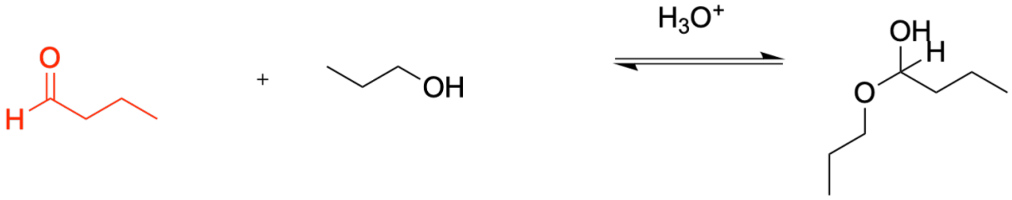
b) The formation of a hemiacetal or hemiketal can also be catalyzed by a base. Draw the reaction mechanism for the reaction below and explain how the base catalyzes the reaction

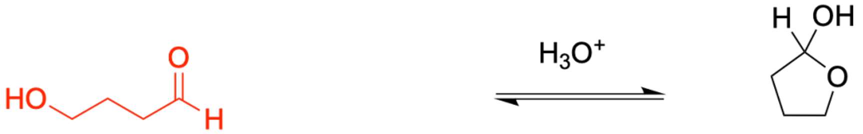


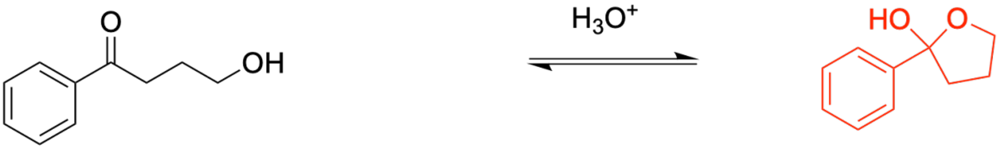
The base increases nucleophilicity of the alcohol

c) Provide the missing starting materials or products.



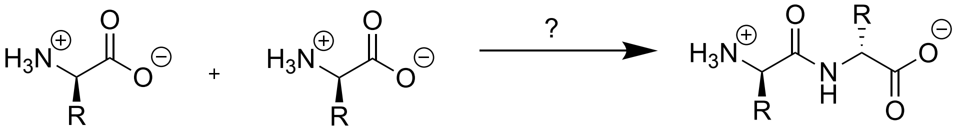




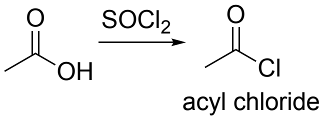


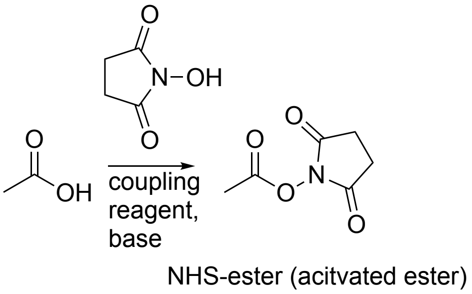
Exercise 8.6. Protein/Peptide Synthesis

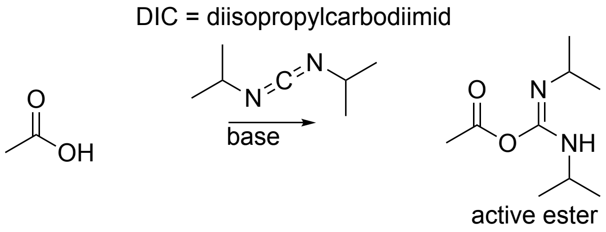
All amino acids have an amino and a carboxylic acidfunctional group, these are used to build long strands of amino acids, which we know as proteins. Nature has developed enzymes which are specialized in creating amide bonds between two amino acids. Do you think the reaction between the acid and the amine forms spontaneous in the lab? Do you have any idea how a chemist can achieve the formation of amides? (Hint: compare addition vs. substitution.)

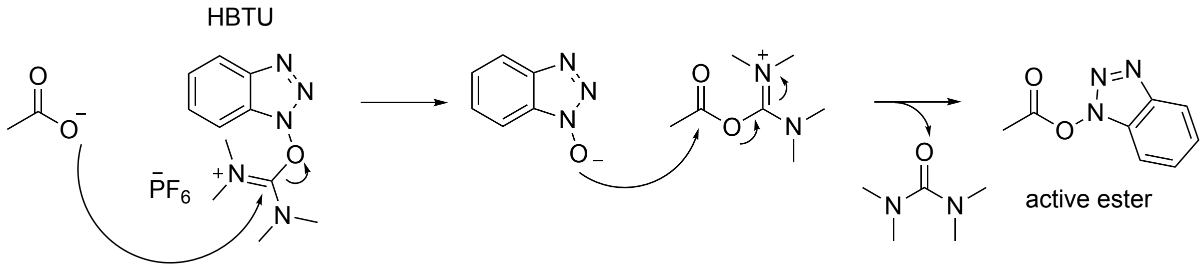


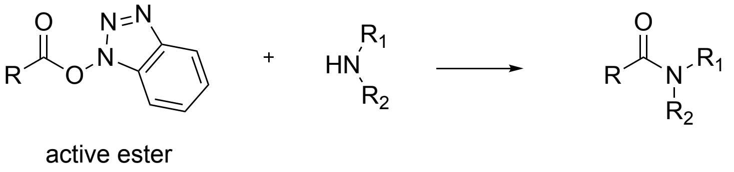
To form amide bonds a substitution has to occur at the carbonyl. However, -OH or -O^- are terrible leaving groups. To still achieve the amide coupling, chemists have modified the carboxylic acids moiety into different functionalities, that allow for efficient substitution. A method would be the creation of acylchloride or activated esters. In peptide synthesis epimerization (changing of one diastereomer) is a big problem, so alternative reagents have been made (carbodiimids and amidinium salts) to reduce the amount of epimerization. Today uronium derivatives such as HBTU are most commonly used in peptide synthesis. Here are a few examples of how to achieve this:







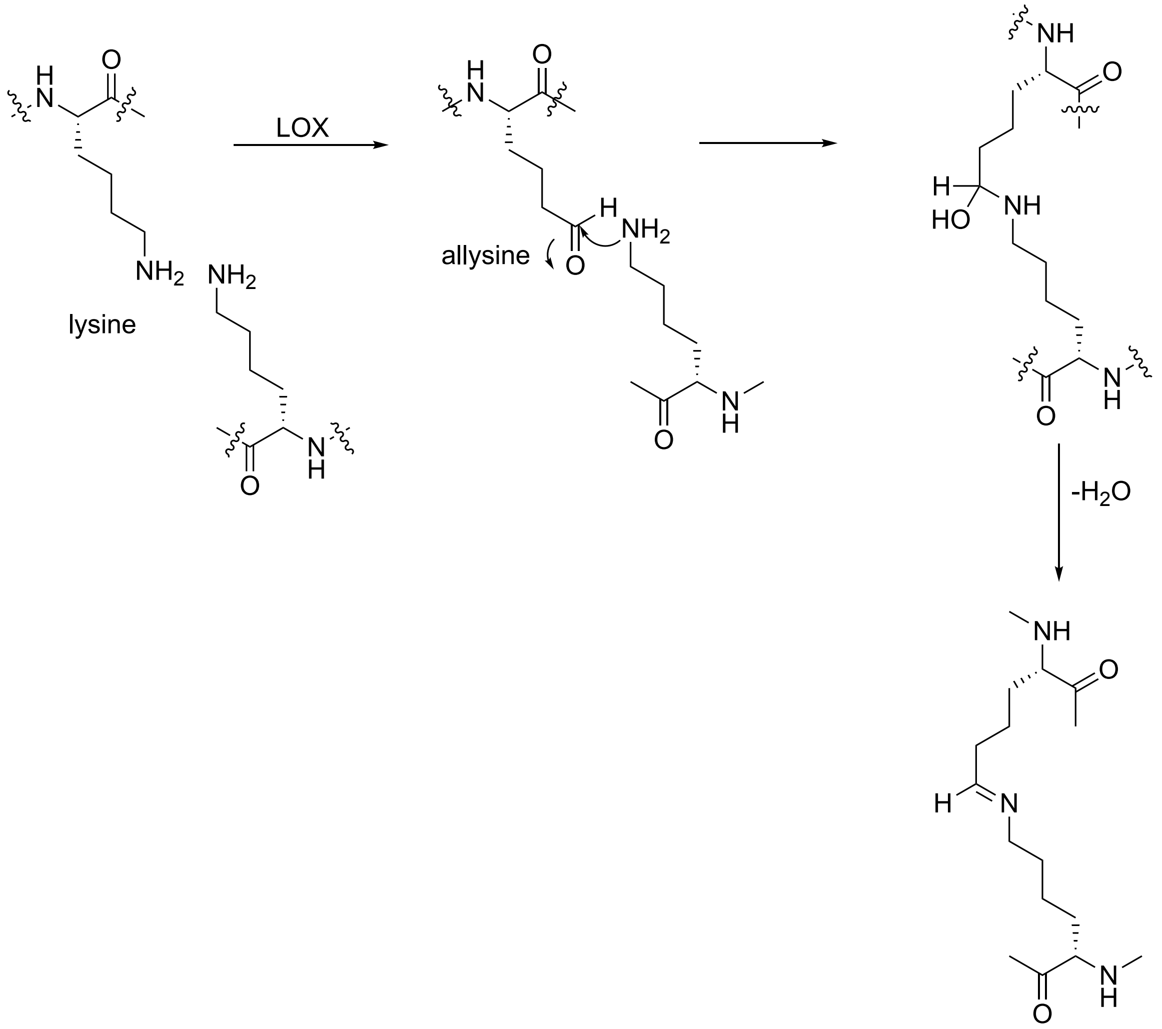




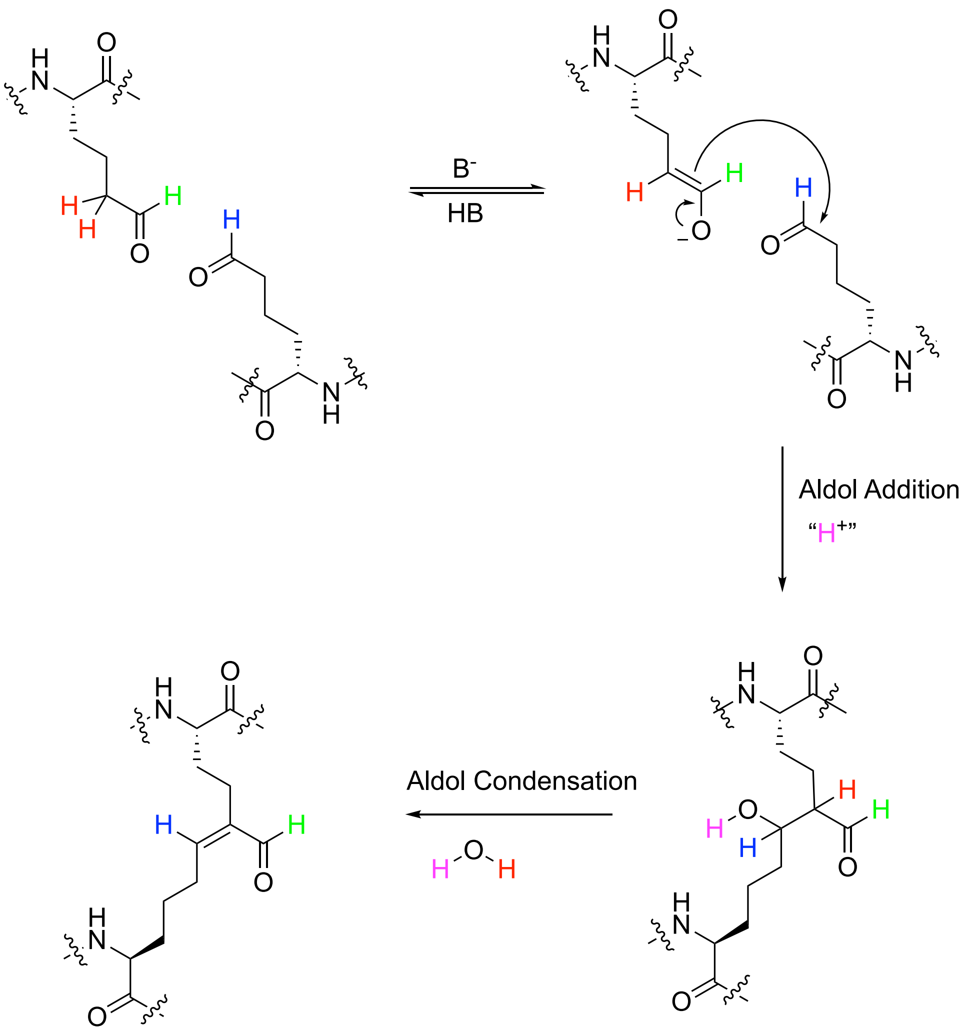
Exercise 8.7. Protein Crosslinks through oxidation

Lysine can by oxidased to an aldehyde by the enzyme lysyl oxidase (LOX), creating a terminal aldehyde that is known as allysine. Propose potential crosslinks that can form between an allysine and a lysine and show the mechanism. Bonus: There is also the possibility of two allysine reacting together, try figuring out what could happen there.

Formation of Schiff base

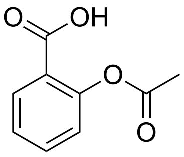


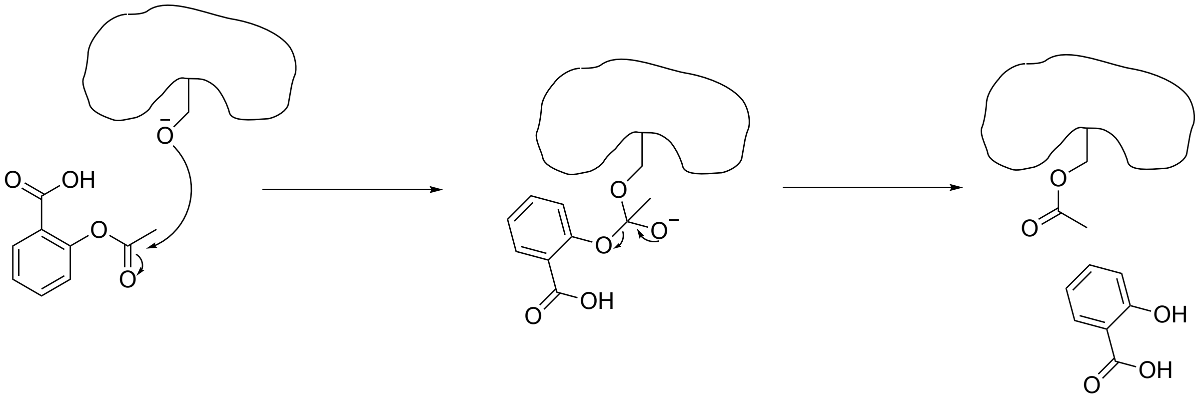
Bonus: Aldol condensation



Exercise 8.9. Acetylsalicylic acid

The compound acetylsalicylic acid, better known as Aspirin, is a widely used painkiller and blood thinner. The compound was already discovered in 1897, but its mechanism of action was not known until 1971 (*Nature New Biology* **1971**, nobel price 1982), when it was shown to interfere with the synthesis of prostaglandins, mainly by inhibiting the enzyme cyclooxygenase (COX). This inhibition comes through a covalent modification of a serine in the substrate binding pocket, can you propose a mechanism of how aspirin is modifying COX?





Cystein gets acetylated and can thereby not bind its natural substrates anymore, leading to the loss of function for COX.