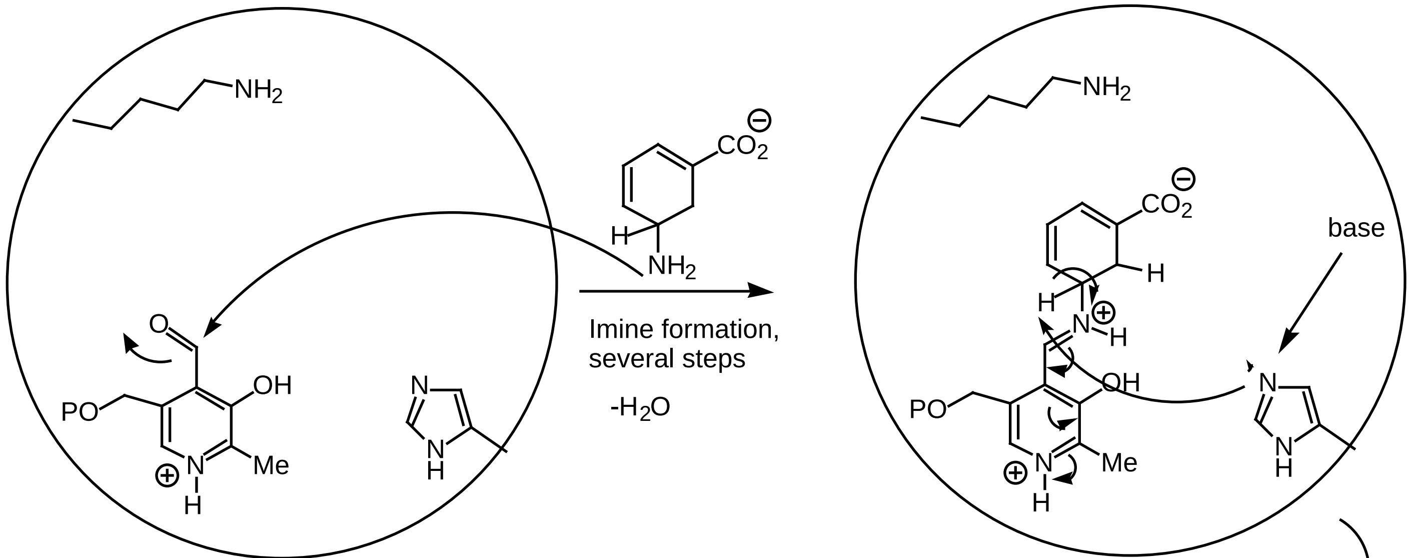
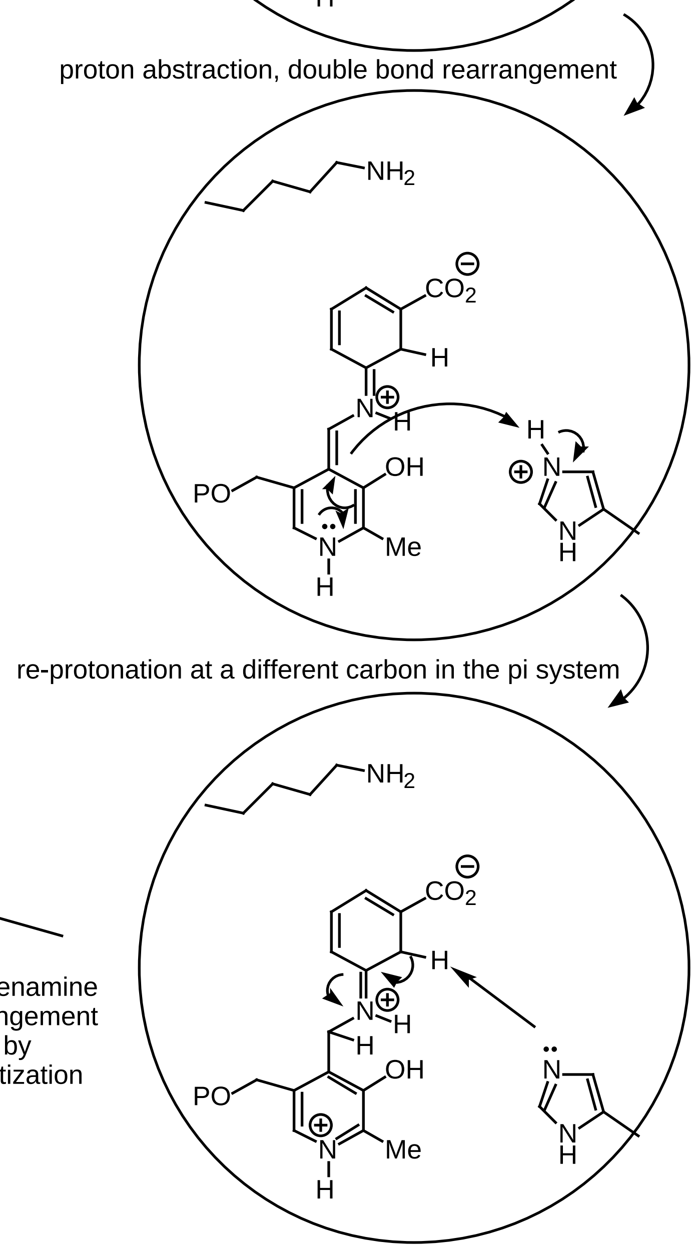
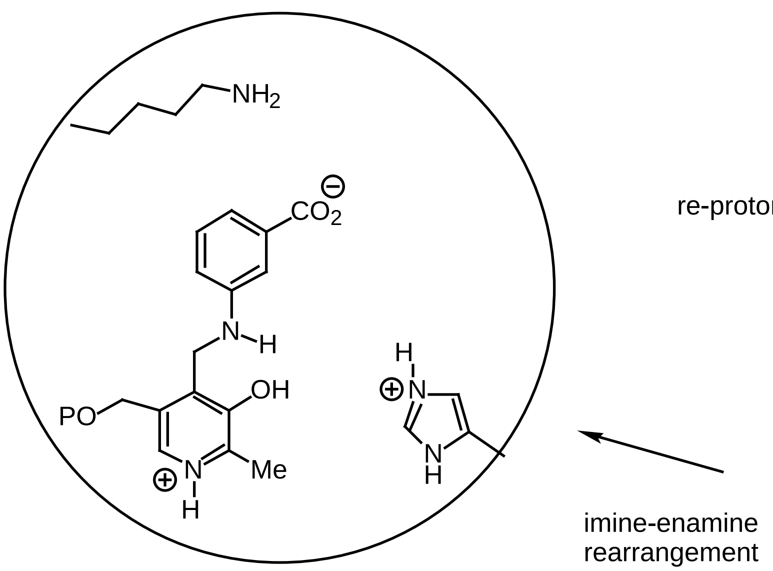
Clarification from last lecture:



Reverse of amino acid synthesis steps, same enzymes

Clarification of the enzyme inhibition by **gabaculine**, a suicide substrate





Cannot regenerate active form of enzyme/cofactor complex

Exam in 11 days!!! Will cover the the last few weeks especially, but that also includes all the carbonyl group chemistry which we emphasized for the Second exam.

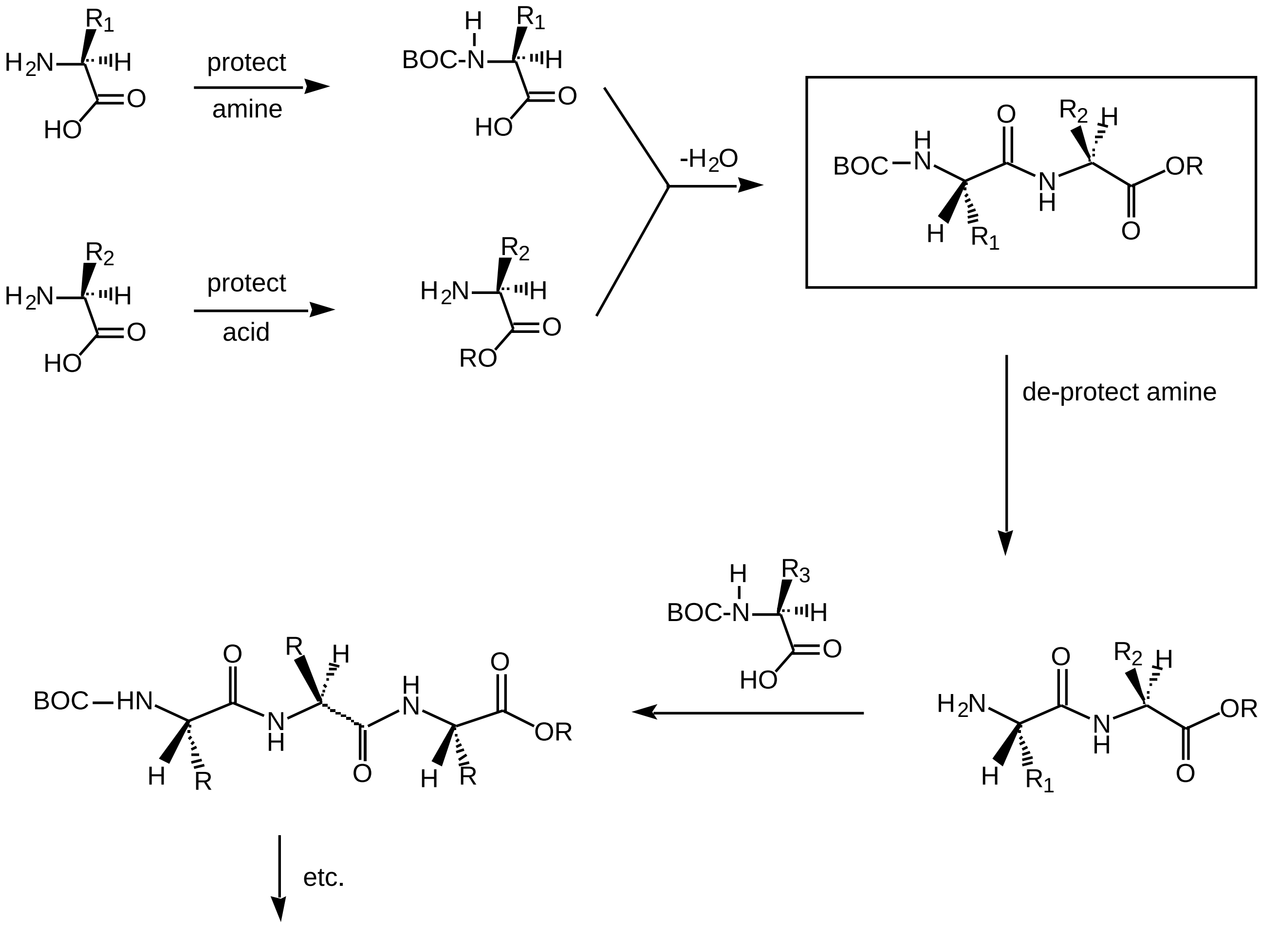
The chemical synthesis of proteins:

Problems: protecting group needed.
create amide bonds.

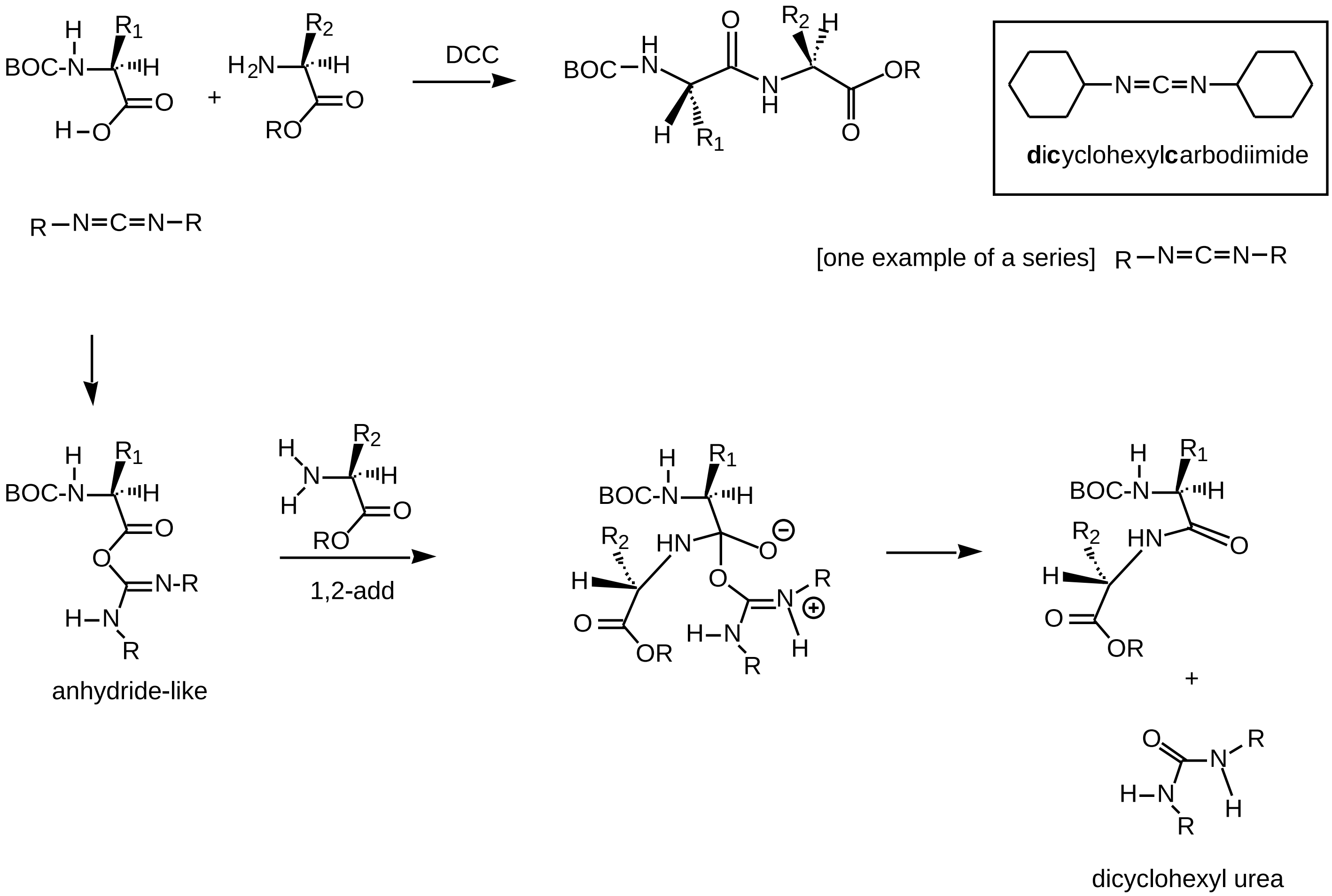
H_2N-**AA₁**-CO_2H + H_2N-**AA₂**-CO_2H → H_2N-**AA₁**-CONH-**AA₂**-CO_2H

Protect NH_2 on **AA₁**, and protect -CO_2H on **AA₂**

P_1-HN-**AA₁**-CO_2H + H_2N-**AA₂**-CO_2P_2 → P_1-HN-**AA₁**-CONH-**AA₂**-CO_2P_2



How induce loss of water and amide bond formation? Many reagents. Most common is complicated: DCC

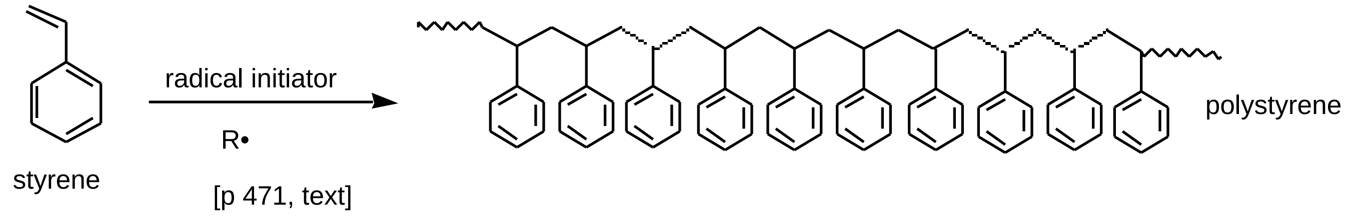


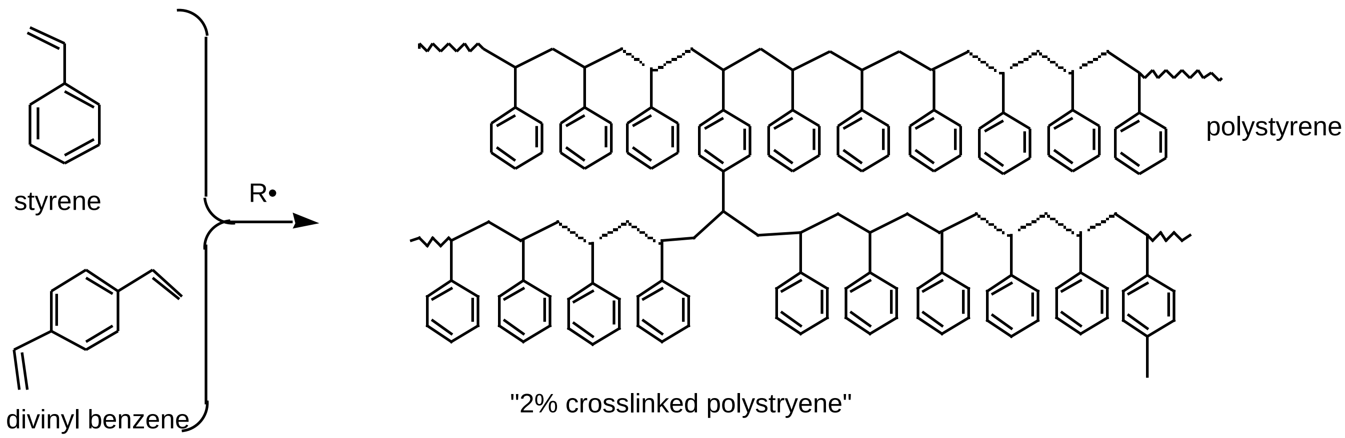
The "Peptide Synthesizer" Automated peptide synthesis. Repeated amide bond formation with different AA
Technical problem: how separate the byproducts from DCC coupling and deprotection steps?

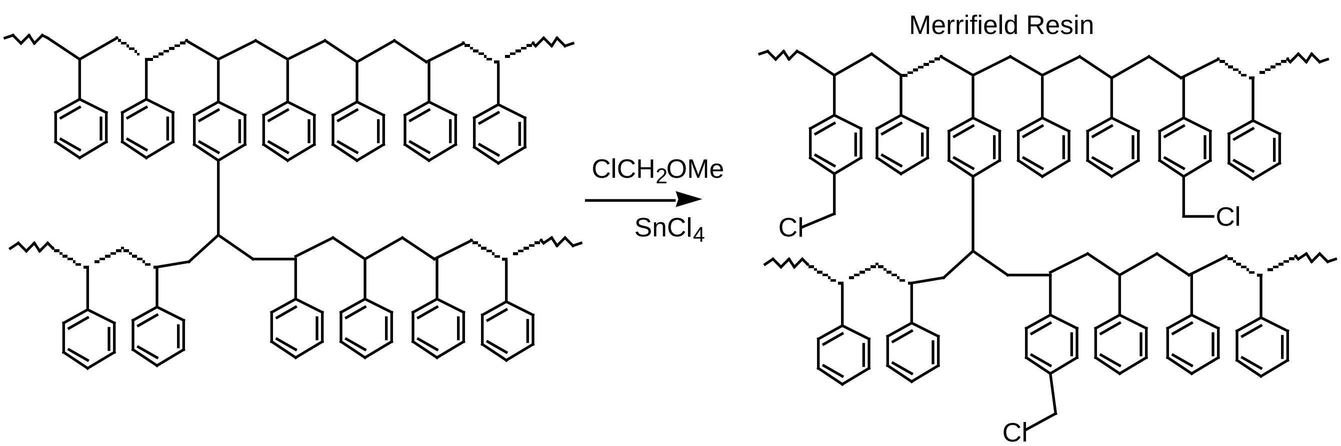
Solid phase synthesis: Easy separation of byproducts by filtration R. Bruce Merrifield, Nobel prize 1986

1. Attach AA_1-NH-BOC to an insoluble polymer via carboxylate (as ester). Deprotect the amino group
2. Add AA_2 (free $-CO_2H$) + DCC in solution.
3. Reaction occurs to couple AA_2 to AA_1 on the polymer
4. Filter away the solution and byproducts
5. Add CF_3CO_2H to deprotect amino group on AA_2, filter, rinse
6. Add AA_3 (free CO_2H) DCC in solution
7. Reaction occurs to couple AA_3 with AA_1-AA_2 at AA_2 amino group
8. Filter
9. Cleave ester linkage to polymer: HO_2C-AA_1-AA_2-AA_3-NH-BOC

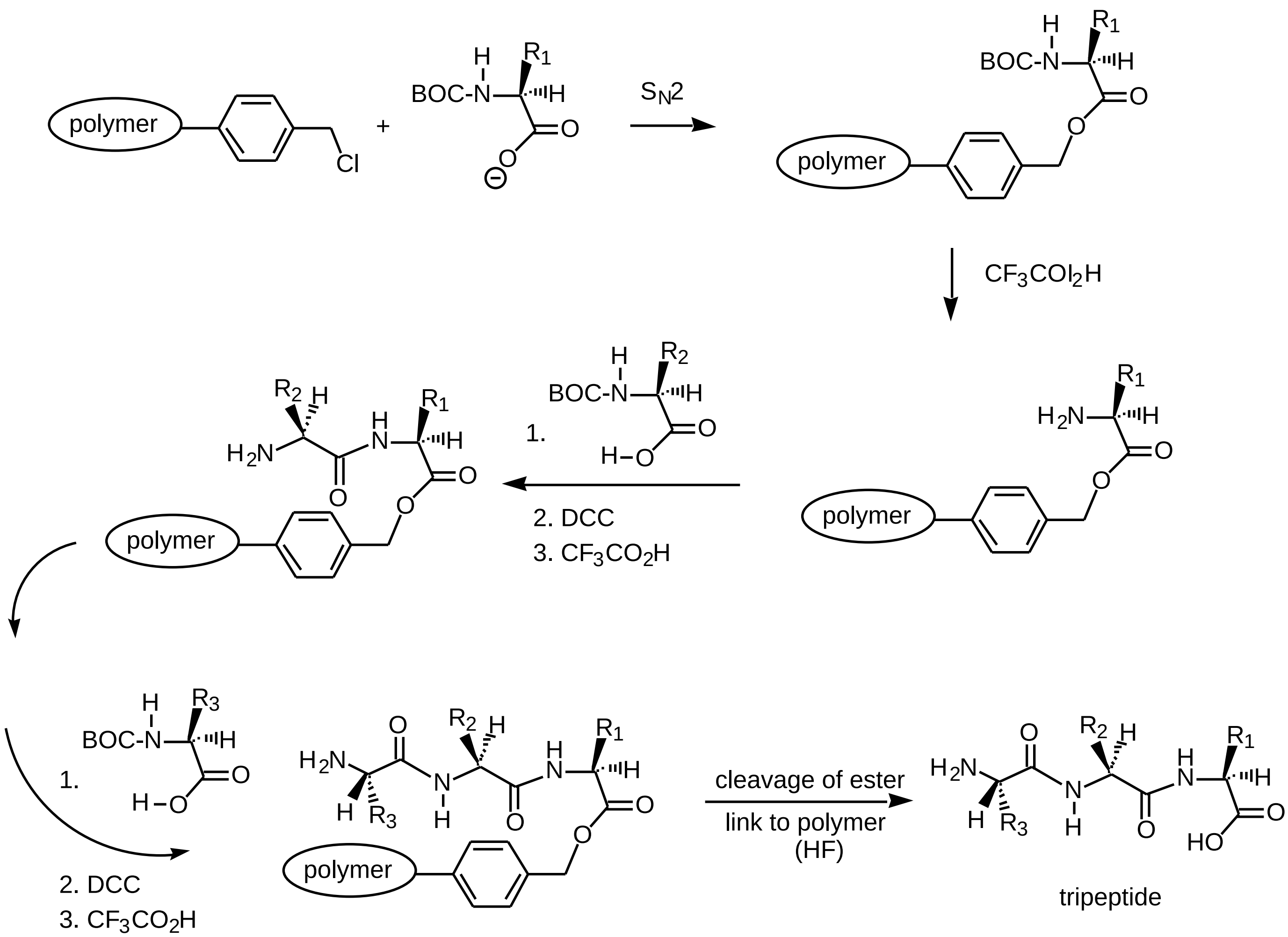
Details:

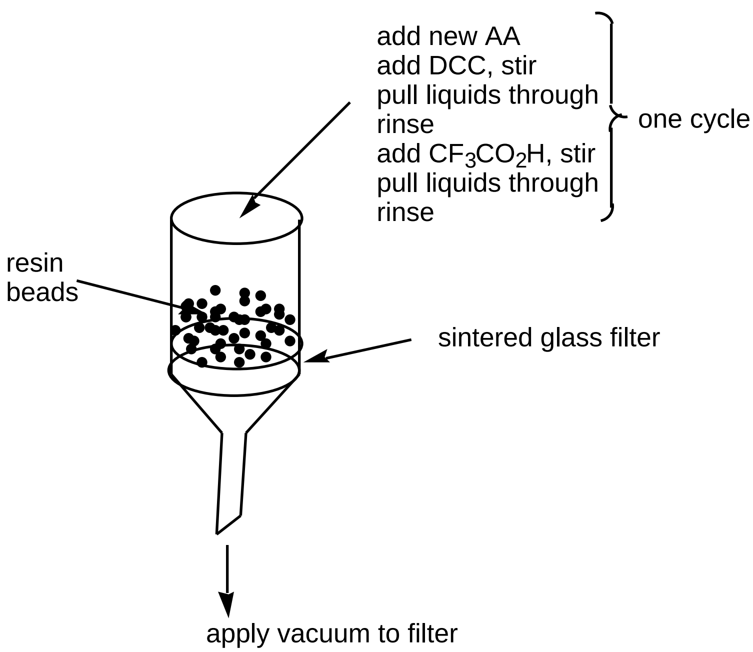






Polypeptide Synthesis:

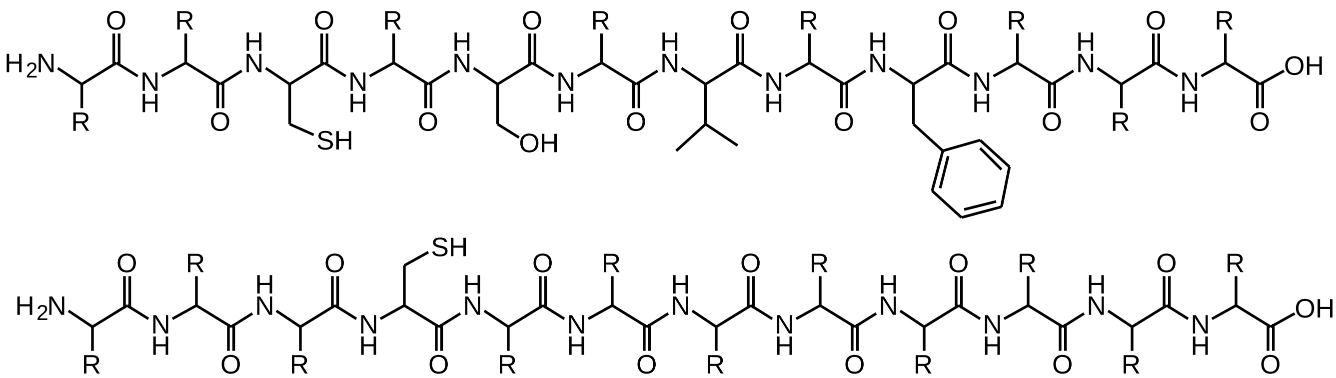




Very effective for polypeptides of 10-30 size.
Enzymes of 100-150 AA have been synthesized by techniques such as this.

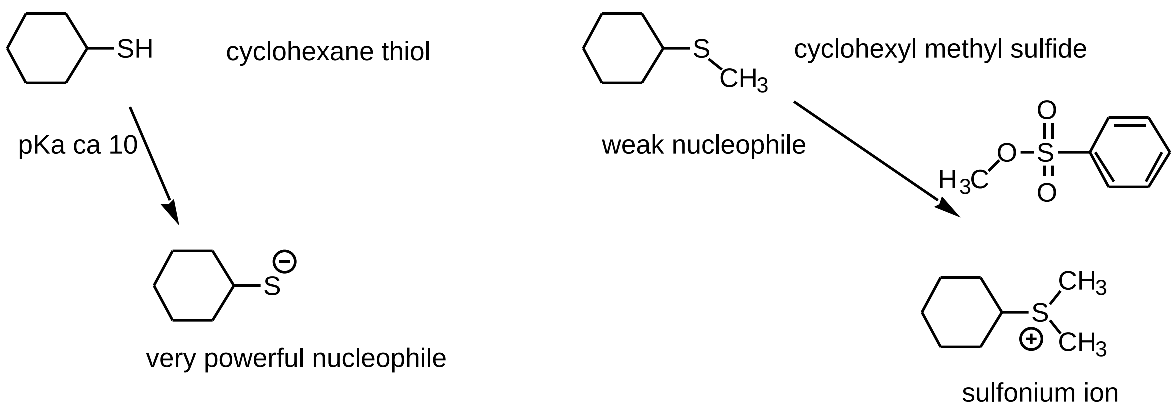
A. Primary structure e.g., a dodecapeptide (proteins can have thousands of AA units)

R = side chain from any one of the 20 essential amino acids

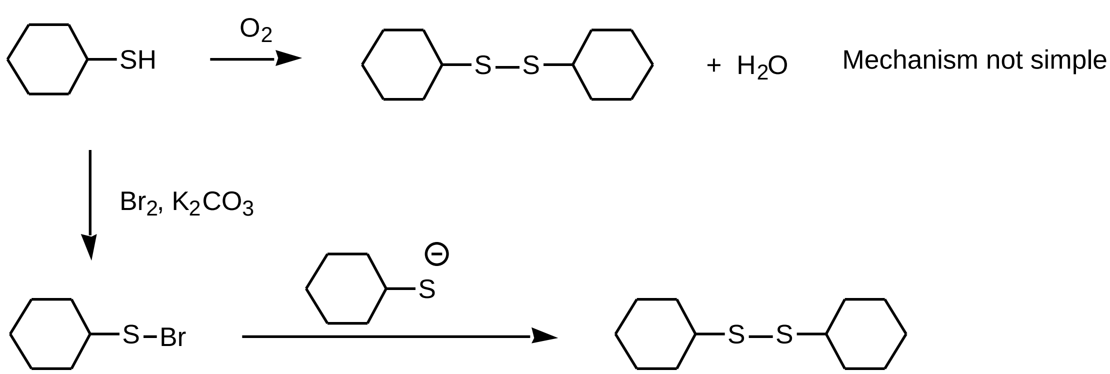


Digression: Text 856-863

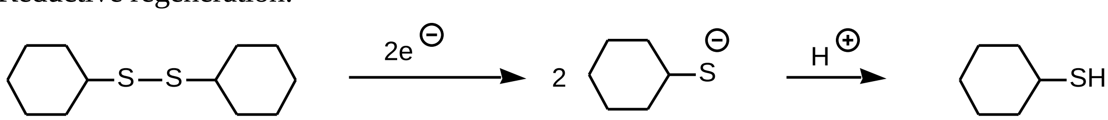
Thiols and thioethers

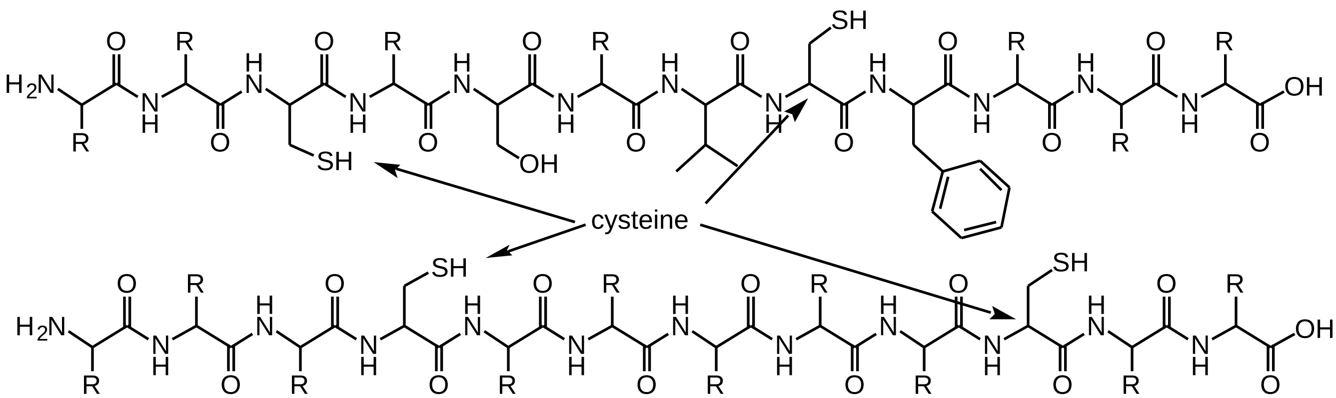


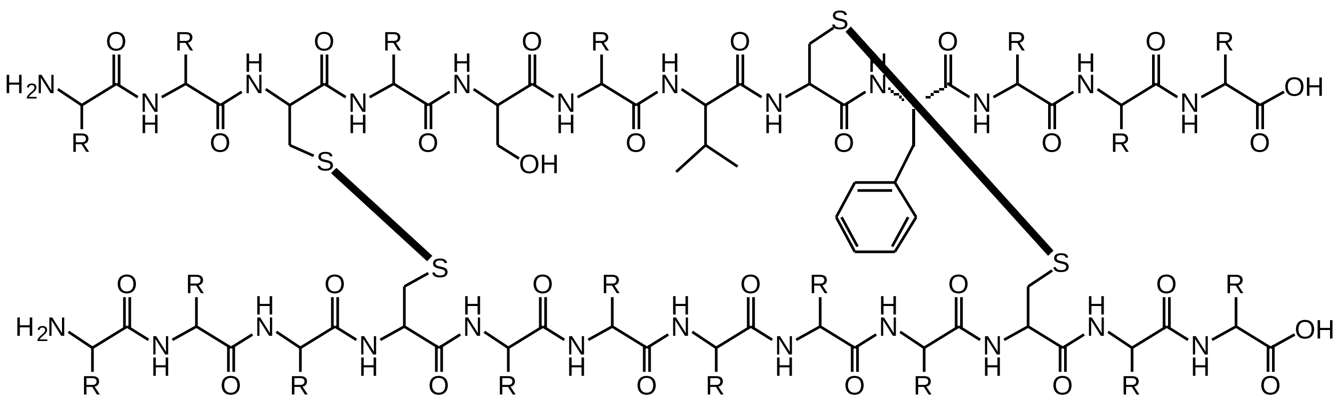
Special reaction, different from the chemistry of ethers: oxidative formation of disulfides



Reductive regeneration:







disulfide crosslinking of peptide chains

Primary sequence of lysozyme, showing disulfide bonds. Supplementary handout

Now: Secondary structure

Alpha helix: Supplementary handout

Beta-Sheet: Supplementary handout

Random coil: essentially a noon-conformation, as the name implies. The polypeptide units adopt a random coil with no discernible pattern: e.g., cooked spagetti. But specific inter-chain interactions support the randon coil.

Hair and wool: α−helix

Silk: β-sheet

Enzymes: mixture of all three, "globular" and soluble

Tertiary Structure: additional local structural features holding chains near each other in a complex fold

ionic interactions (ammonium cations/carboxylate anions)

specific H-bonds between certain side chains

van der Waals forces (hydrophobic bonds)

Quarternary Structure: Protein chains can fold together with other chains (e.g., dimers)