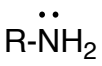
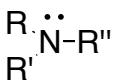
Amines (McM chapt 24)

(**R: alkyl, aryl**)

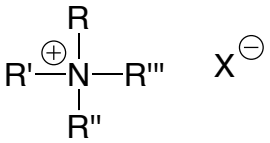


Primary amine

Secondary amine

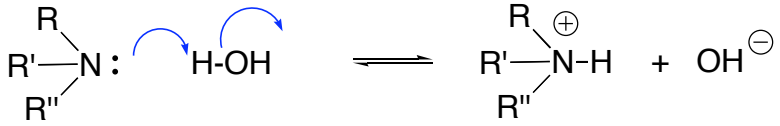


Tertiary amine



Quartenary ammonium salts

Basic compounds



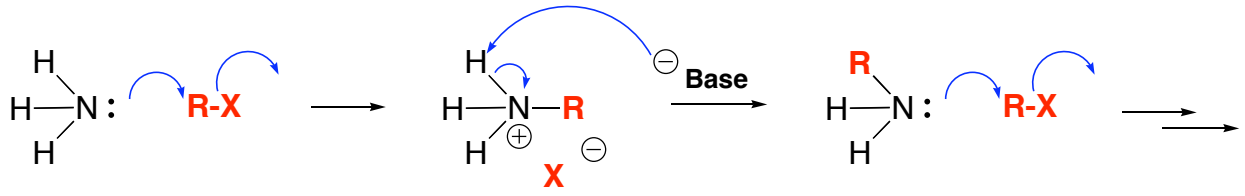
(**R: H, alkyl, aryl**)

pKa Alkylamines: ca 9-11
Arylamines: ca 4-5
(anilines)

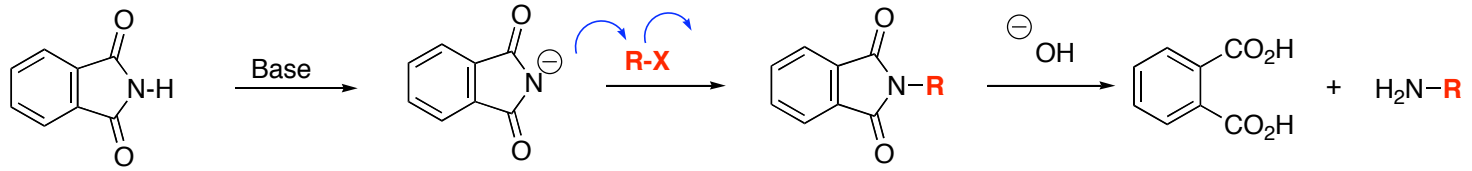
Synthesis (McM 24.6)

Known react. from KJM10xx

Alkylation (ammonia or amine, phtalimide)

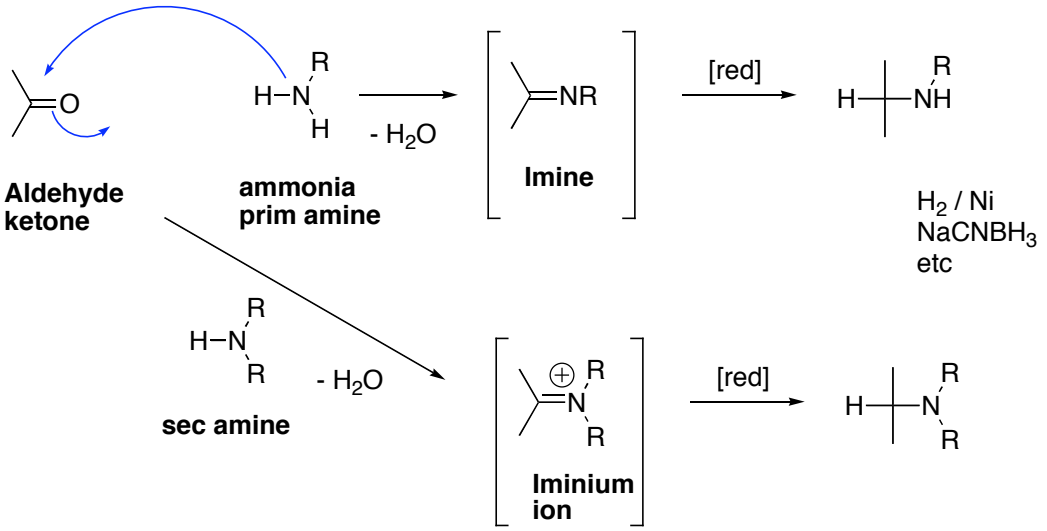


(R: H, alkyl, aryl)



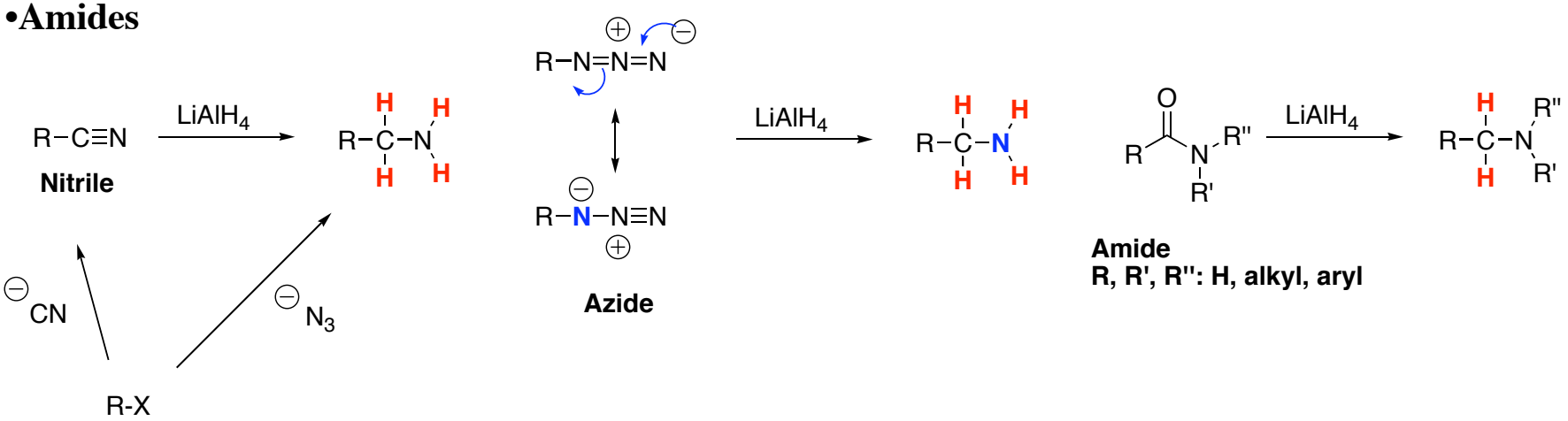
Acidity
c.f. 1,3-dicarbonyls

Reductive amination

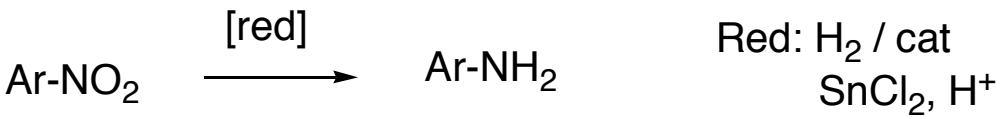


Reductions

- **Nitriles**
- **Azides**
- **Amides**

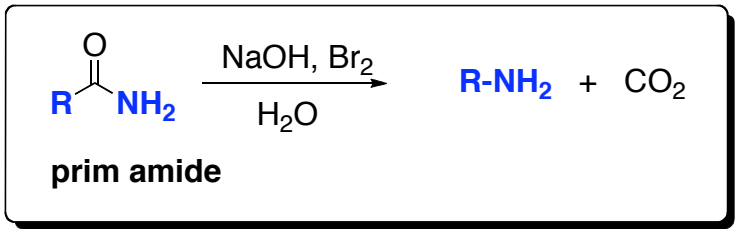


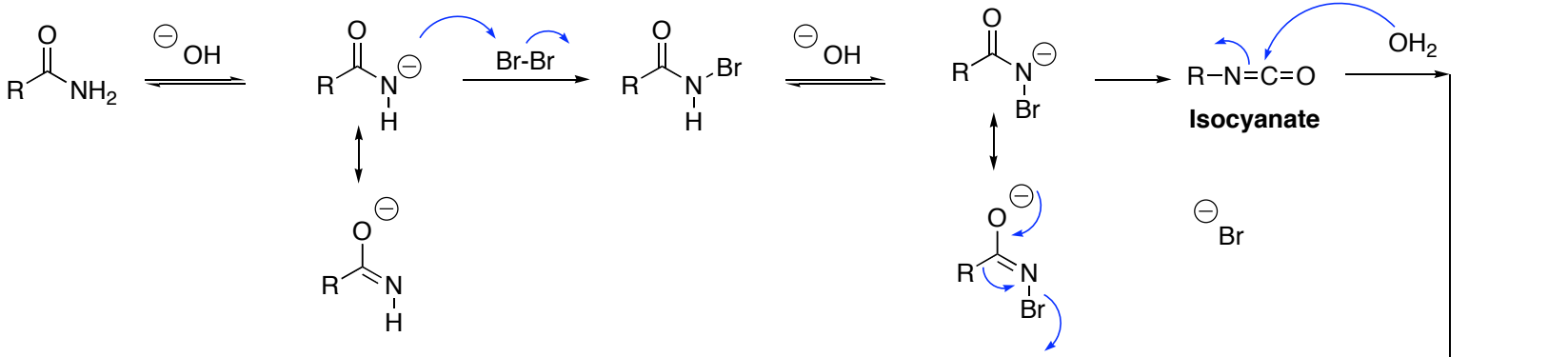
- **Aromatic nitro compounds**



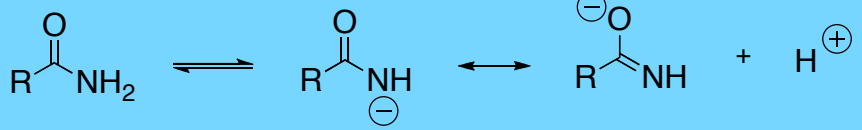
Synthesis (McM 24.6): "New" reactions

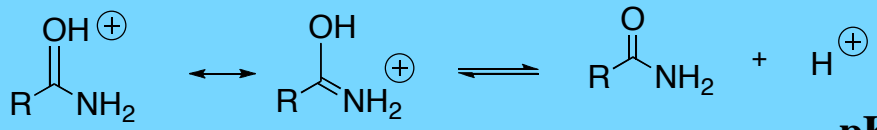
Hofmann rearrangement

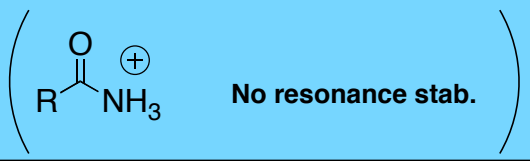




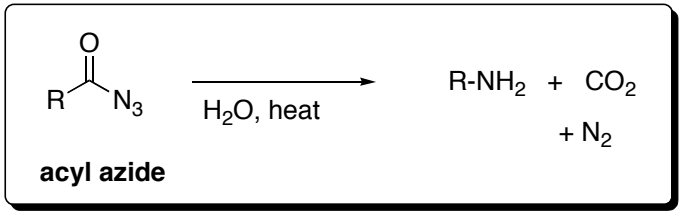
Acid / base properties amides

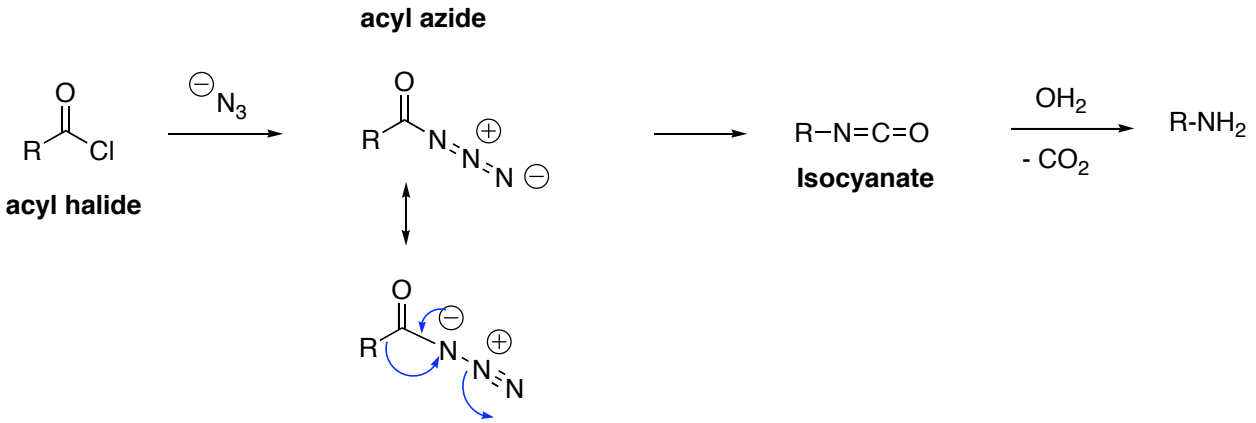




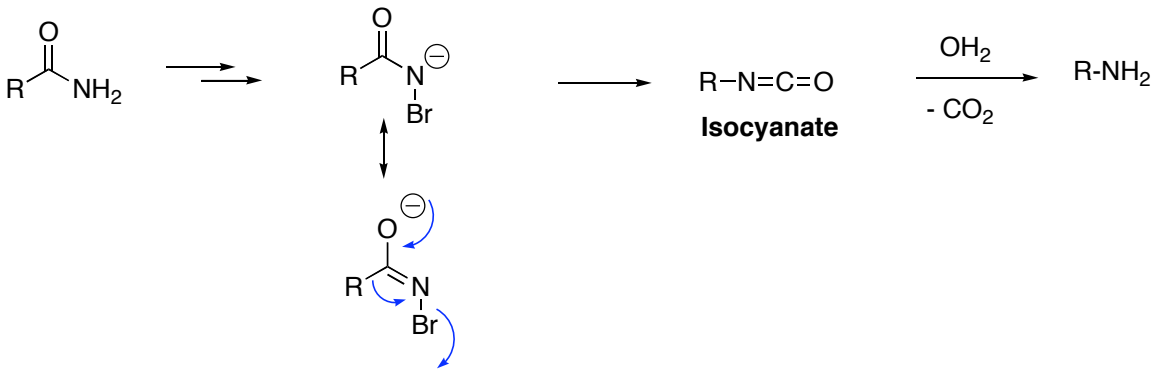


Curtius rearrangement





Mechanistic. related to Hofmann rearrang.



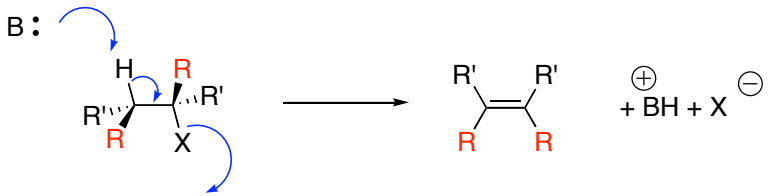
Reactions of amines (Alkylamines) (McM 24.7)

Alkylamines:

- **Alkylation (McM 24.7)**
- **Acylation / synth of amide (McM 21.4, 21.5)**
- **Hofmann elimination (≠ Hofmann rearrangement)**

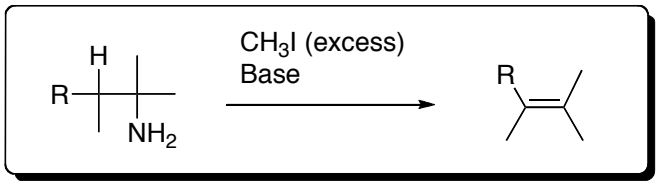
E2 elimination to form alkene

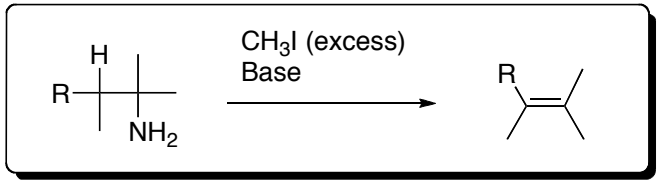
E2: mechanism



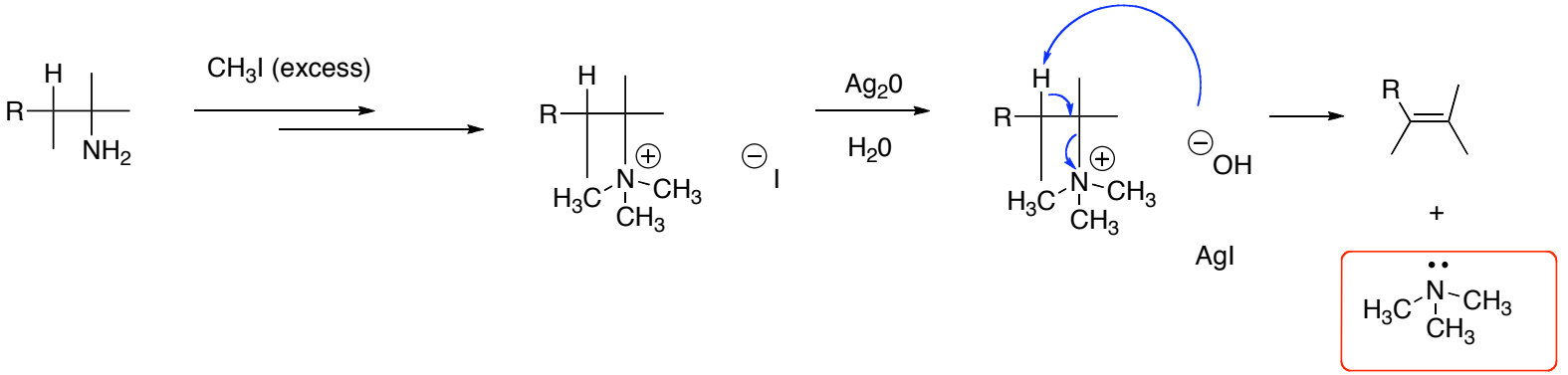
X= halogen, (OH)

X ≠ NR_2 Strong base / bad leaving group



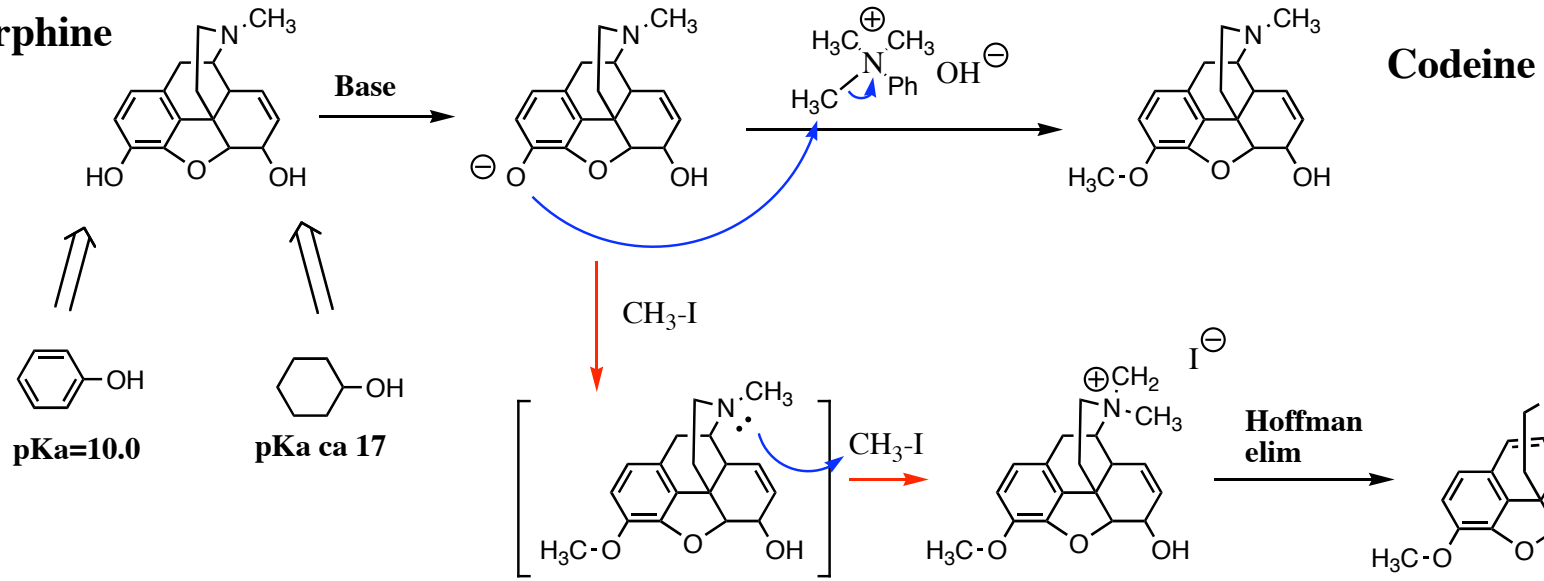


Removal of less sterically hindered H
Not necessarily most stable alkene formed



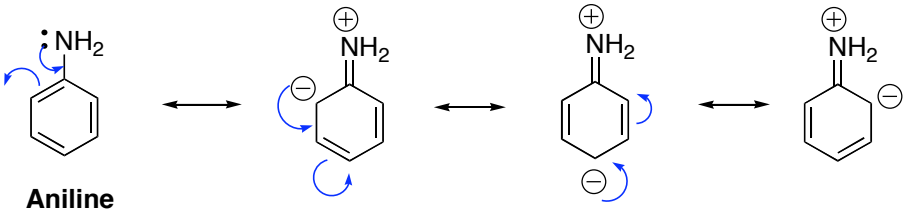
Much better leaving group than $R_2N^{\ominus}$

Morphine



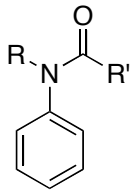
Codeine

Reactions of Arylamines (aniline derivatives) (McM 24.8)

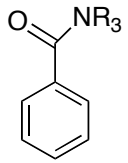


Aniline

- **Weak base (pKa ca 4.6)**
- **Highly Activated for E-fil Ar Subst (o/p)**
- **Protect. as amide: Less activated, still o/p**



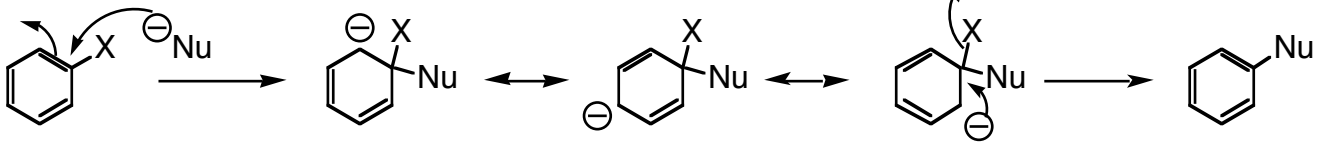
o/p directing



m-directing

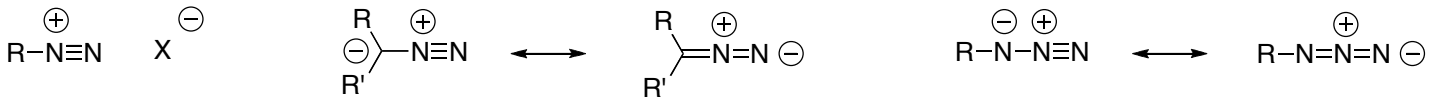
Nucleophilic Aromatic Substitution - Mechanisms

- S_NAr √

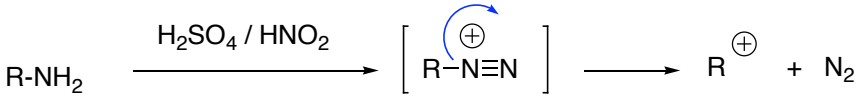


- **S_N1**
- Benzyne √
- **SRN1: Involves radicals**
- (VNS: Vicarious Nucl. Subst.)

Formation of Diazonium Salts and the Sandmeyer Reaction

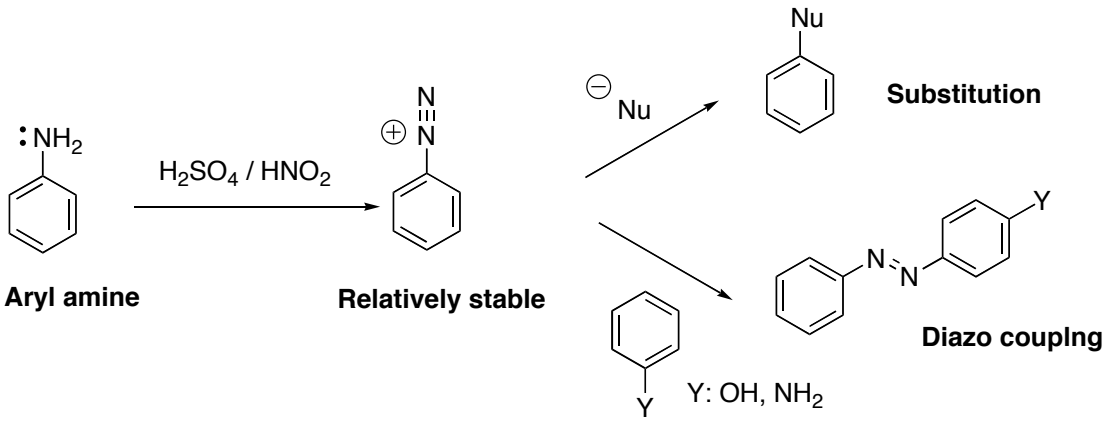


Diazonium salt **Diazo compound** **Azide**



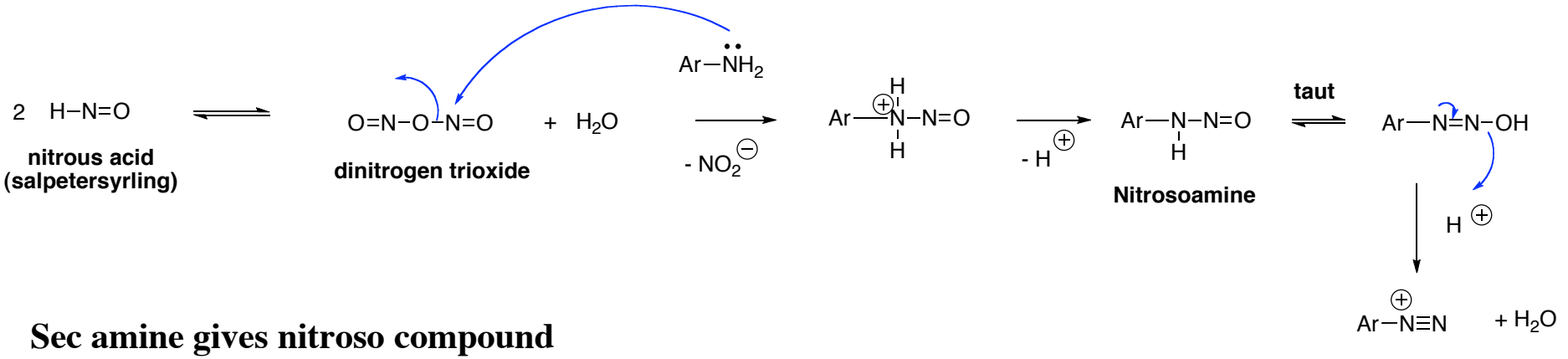
prim alkylamine **very unstable**

Synthetically seldom useful

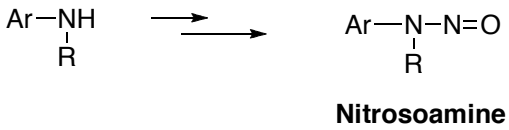


Aryl amine **Relatively stable**

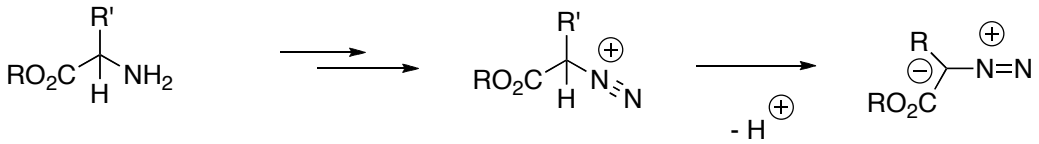
Diazotation of primary amine



Sec amine gives nitroso compound

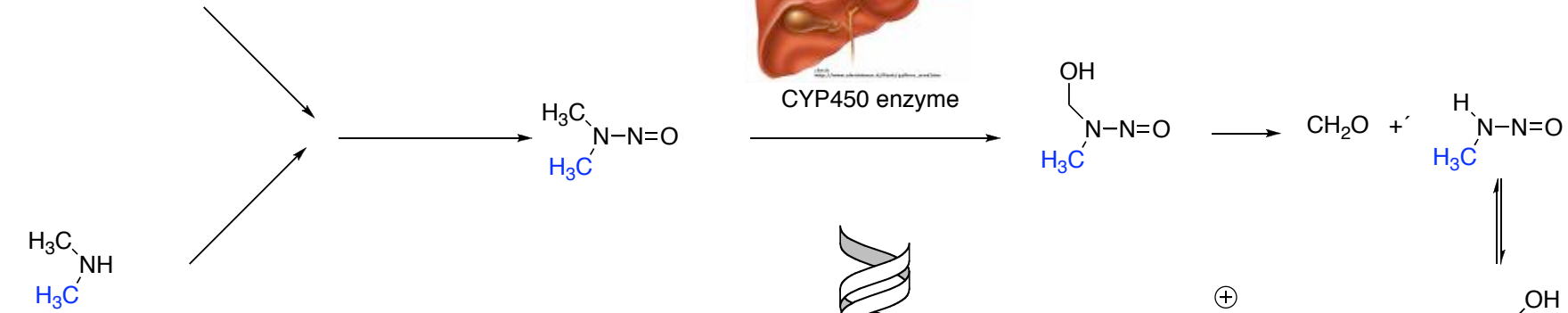


Amines with acidic a-H may give diazo compounds

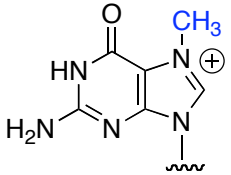


Toxicity nitroso compounds (not in McM) - Alkylation of biomolecules

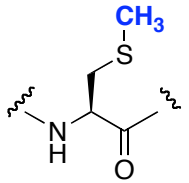
$NO_2^{\ominus}$ / $NO_3^{\ominus}$



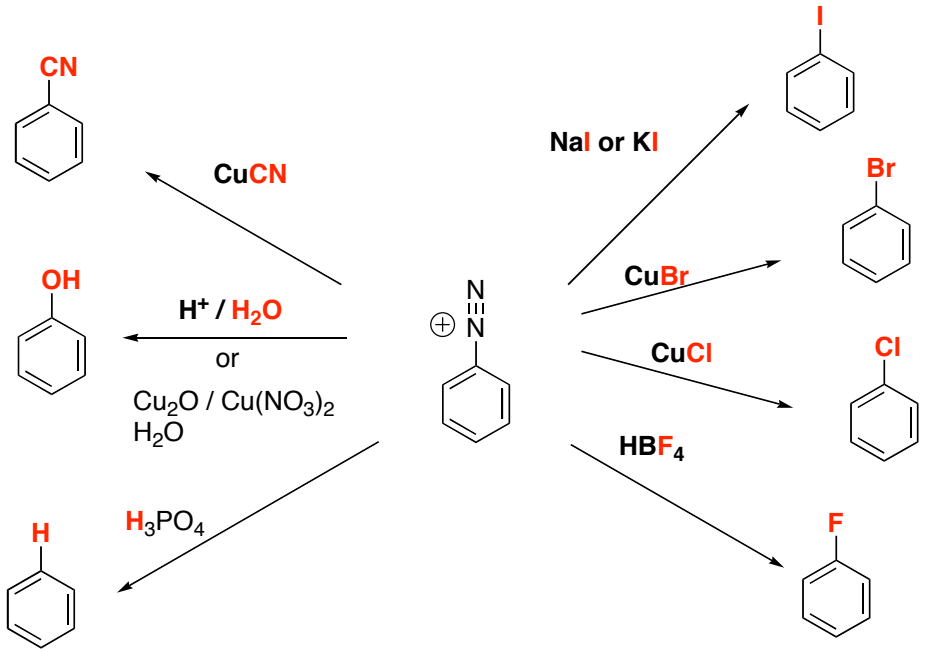
sec alkylamine



N-7 alkylation of guanine in DNA

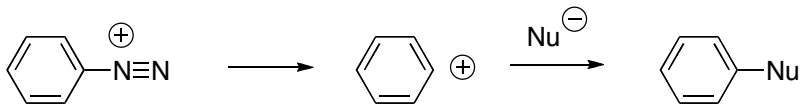


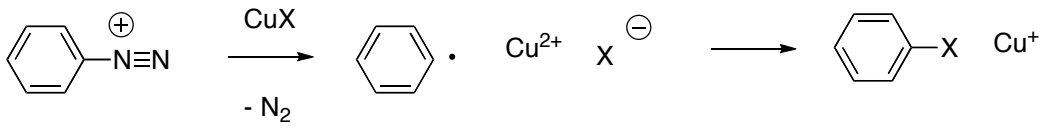
S-methylated cysteine in a peptide/protein



N_2 as leaving group

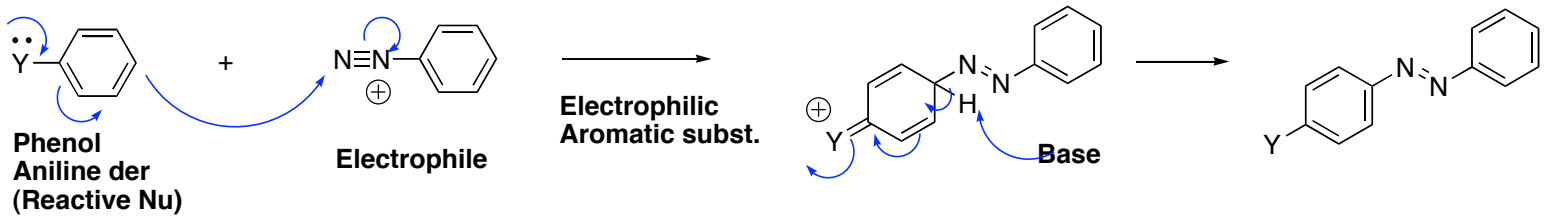
SN1 like mechanism or radical mechanism



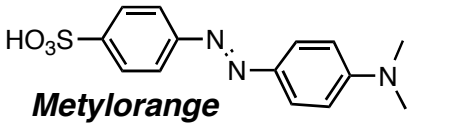


Cu-salt mediated react.
Sandmeyer react.
(radical mech.)

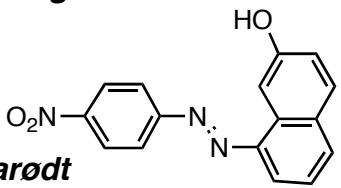
Diazo coupling



Azo dyes
Bayer etc
Late 1800-century, ex.

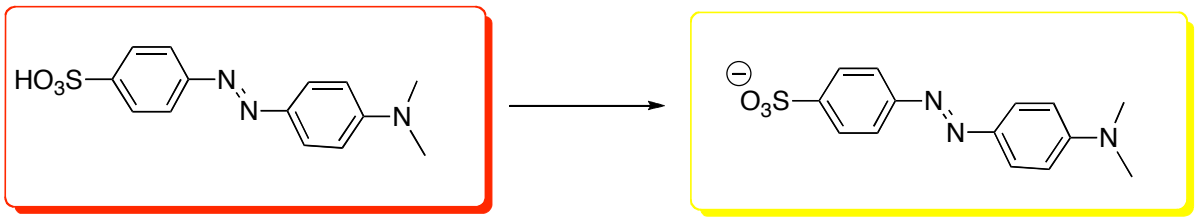


Metylorange



Pararødt

Metylorange

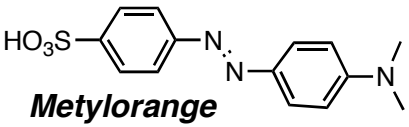


pH < 3.1

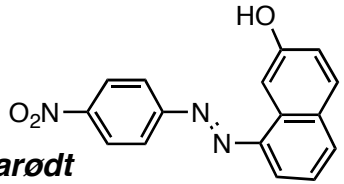
pH >4.4

OH

Azo dyes
Bayer etc
Late 1800-century, ex.

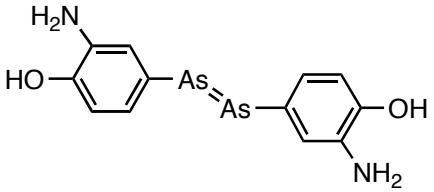


Metylorange



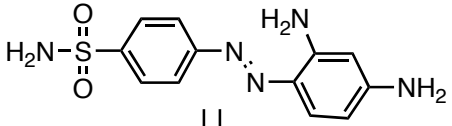
Pararødt

Salvarsan
1. antisyphilis drug 1912

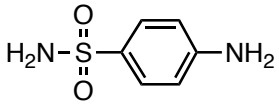


Screening of dyes as antibacterials

1932: ***Prontocil*** active against Streptoccocces infection
no activity on bacterial cultures



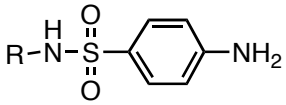
1935: Prontocil metabilized (azoreductase) to ***Sulfanilamid*** *in vivo*



(rel. toxisk)

Antibacterial sulfonamides

Modern sulfa drugsr

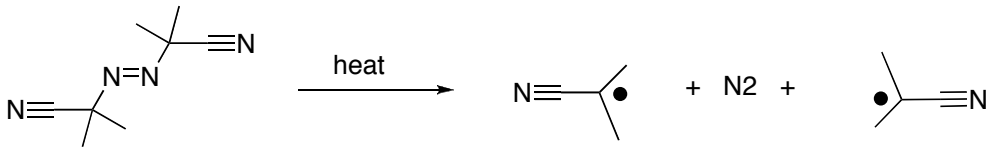


R: Aryl or hetroaryl

Dialkyl azo compounds less stable (explosive)
Not in McM

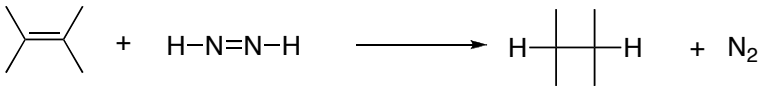
Radical initiator (alternative to benzoyl peroxide, lab. ex. 1)

AIBN: Azobisisobutyronitrile



AIBN

Diimide reductions

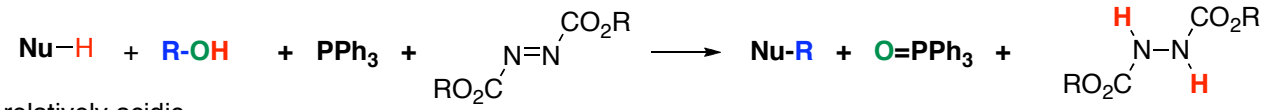


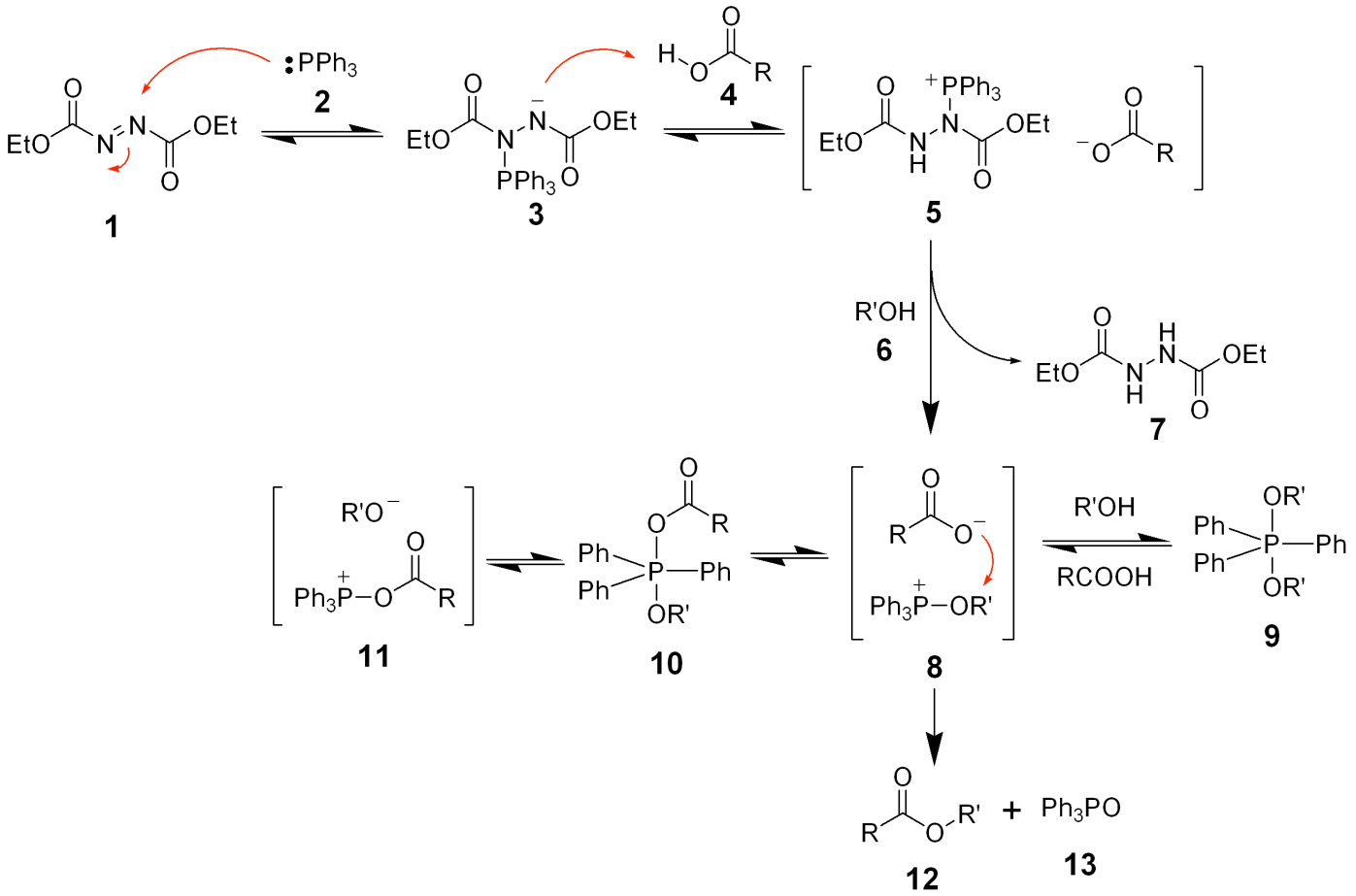
alkene **diimide**

generated in situ,
various precursors

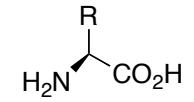
azo, from azote (old french for nitrogen), a (not) zoe (to live) c.f. kvelstoff (old No for nitrogen)

Azo dicarboxylates in Mitsunobu reactions

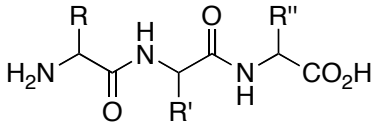




Amino Acids, Peptides etc (McM chapt 26)



L–α-aminoacids
(S)



N-terminal

Tripeptide

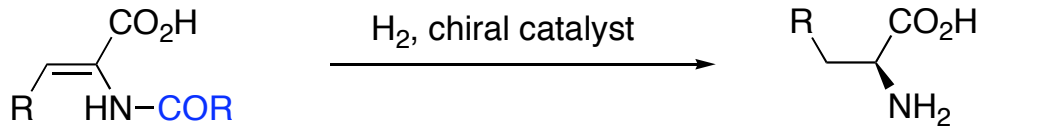
C-terminal

20 essential AA, table 26.1

Synthesis

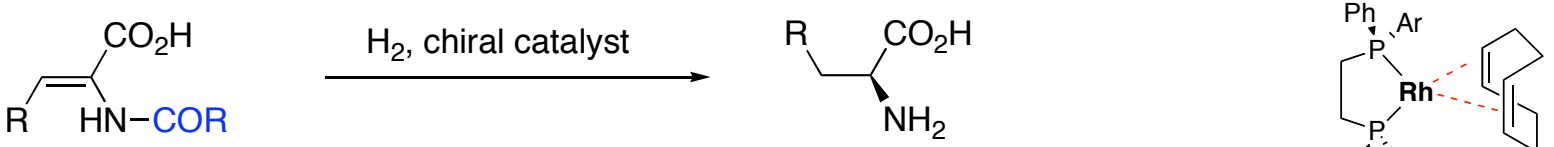
-Resolution of racemic mixt. (synth see chapt 24.3)

-Enantioselective synthesis (26.4)



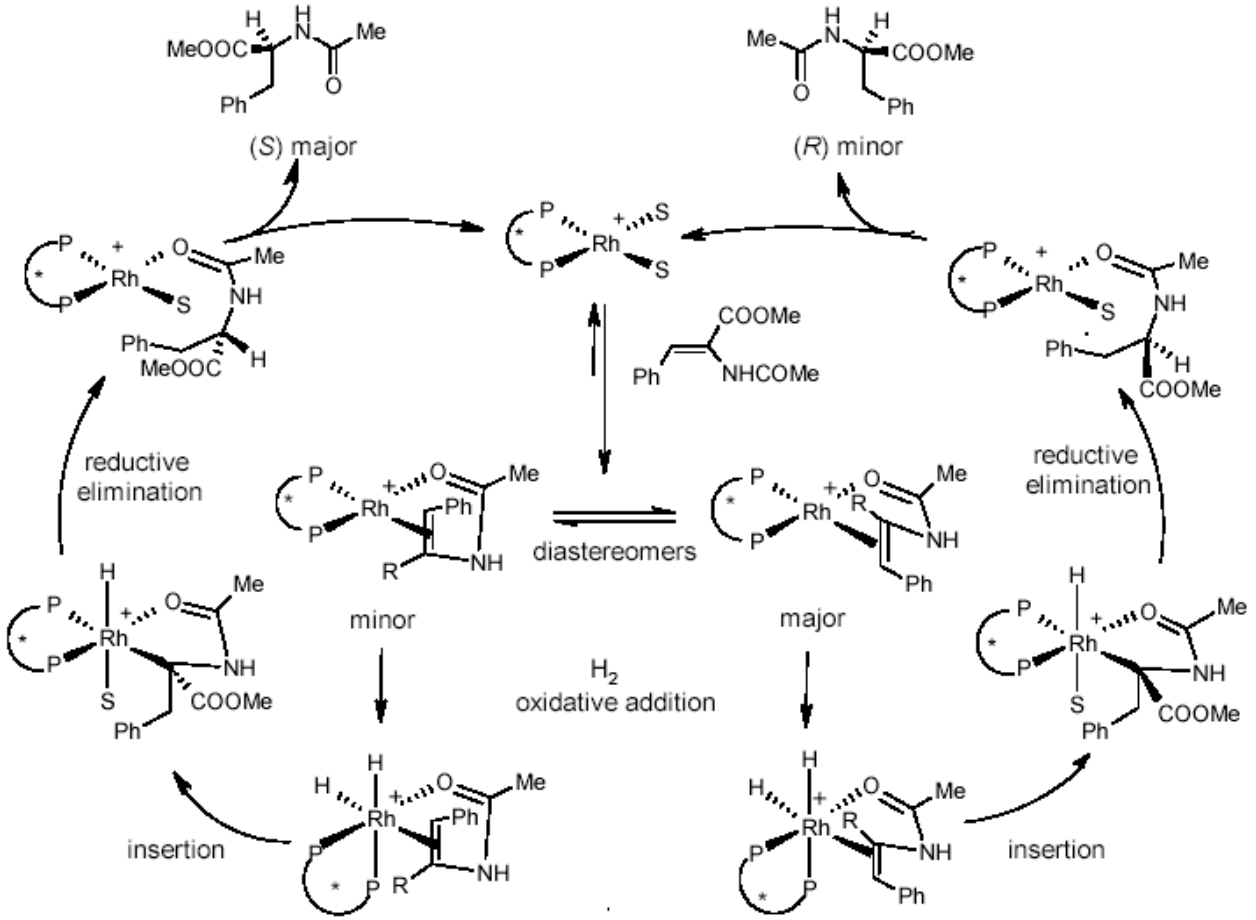
-NH_2 potected as amide

after deprotect.

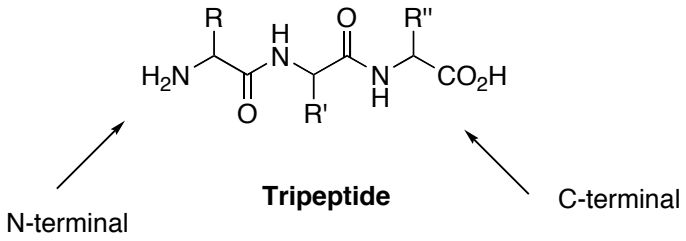


-NH_2 potected as amide

after deprotect.



Determination of peptide structure - Sequensing



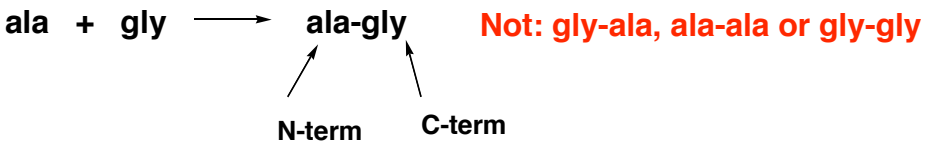
-NMR
-MS
-X-Ray

Chemical methods (only primary structure)

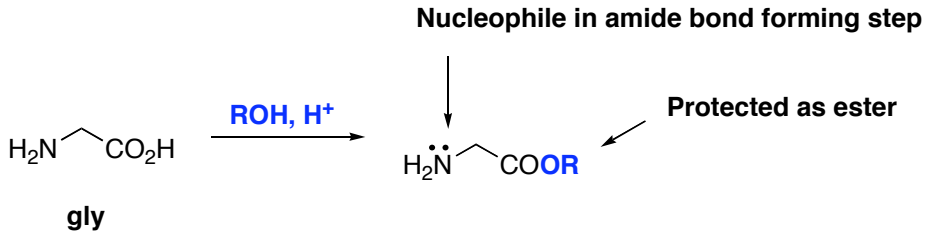
-Edman Degradation: Removes - determines N-terminal AA (26.8)

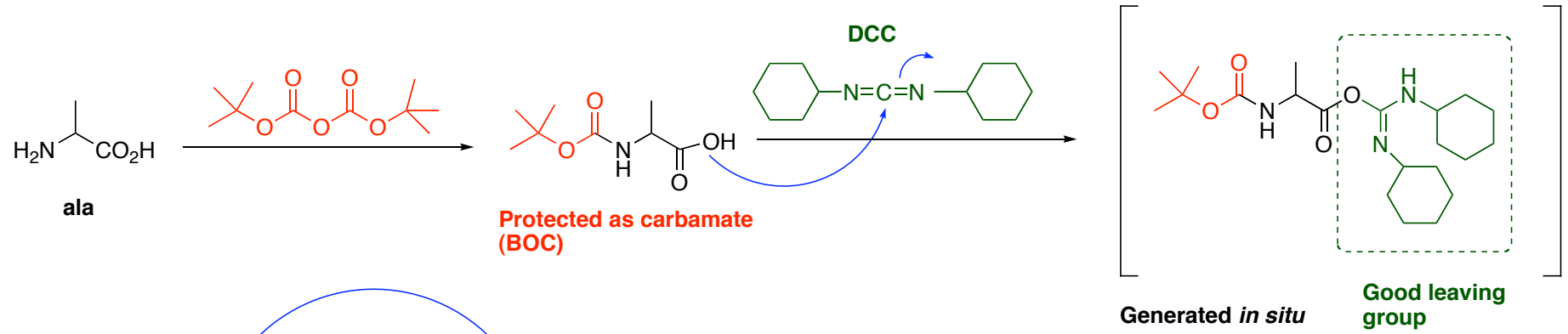
-Carboxypeptidase: Cleaves of C-terminal AA (26.9)

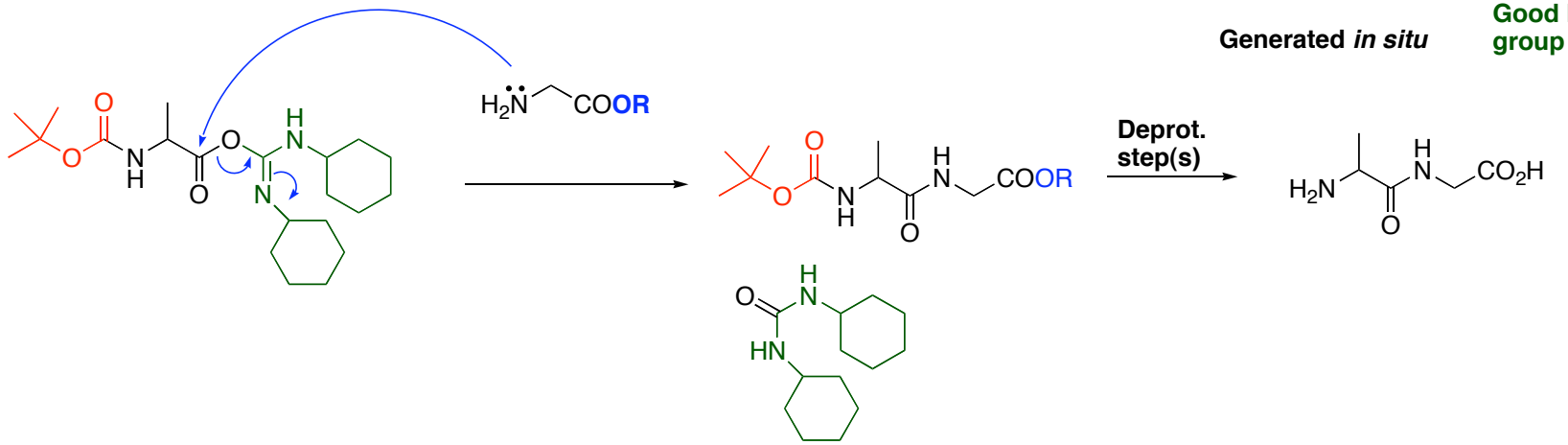
Peptide Synthesis (McM 26.9 - 10)



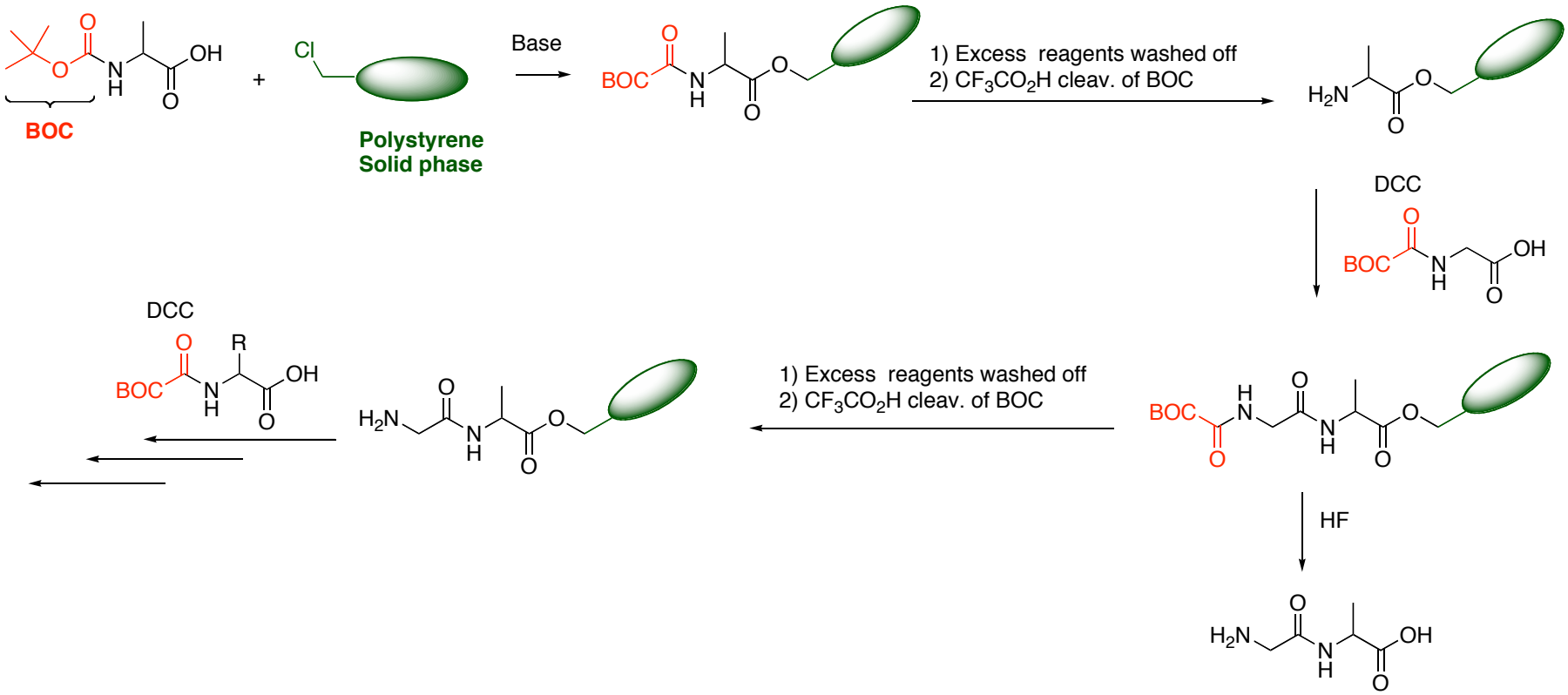
- Selectivity
- Protecting groups
- Solution chemistry
- Solid phase / automatization



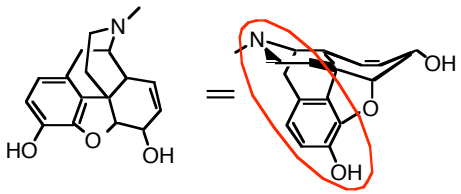




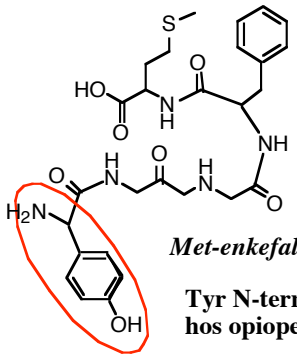
Merrifield:



Synthesis of: peptides,
peptidomimetica; mimics bioactivity of a peptide
more stabe, better bioavail. etc.



Morfin



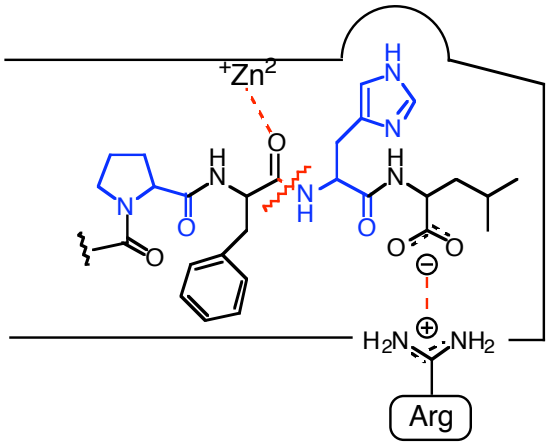
Met-enkefalin

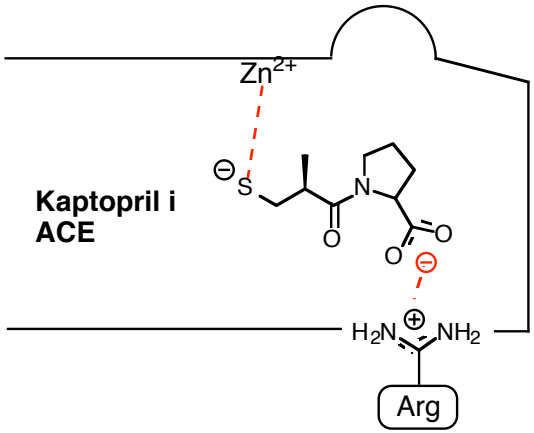
Tyr N-terminal hos opiopeptider

N-term C-term

Asp-Arg-Val-tyr-Ile-His-Pro-Phe-His-Leu —ACE→ Asp-Arg-Val-tyr-Ile-His-Pro-Phe + His-Leu

Angiotensin I ***Angiotensin II***





Peptide / Protein

Proteins are larger and may also contain non-peptide parts, has a biological function

Functions:

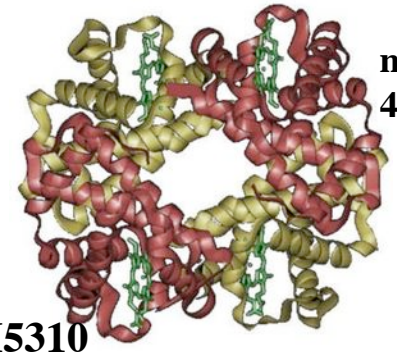
- **Enzymes, biocatalysts, metabolism**
- **Cell signaling; hormones (i.e. insulin), reseptors**
- **Imune system; antibodies**
- **Transport; hemoglobin etc**
- **Structure; ie keratin (hair, nails etc)**

Insulin: 51 AA,
Titin: 26.926 AA (in muscle tissue)

Structure

- **Primary: AA-sequence**
- **Secondary: 3D structure of segment of the protein (α-helix, β-sheets etc)**
- **Tertiary: 3D structure of the whole protein**
- **Quartenary: 3D stucture of an agregate of several proteins**

"a peptide is an amino acid molecule
without secondary structure;
on gaining defined structure, it is a protein."



mammalian hemoglobine
4 protein subunits, each with one heme

Protein crystallography KJM3350/4350
+ Structure of biological macromolecules KJM5310