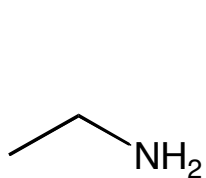


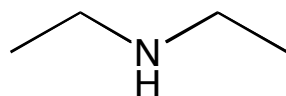
## Amines

Amines are organic compounds containing a nitrogen functionality

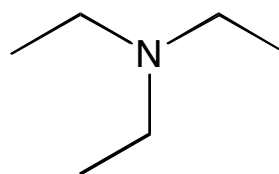
Depending upon the number of alkyl, or aryl, groups attached to nitrogen determines its classification, or order



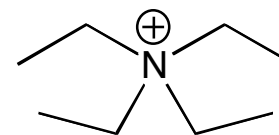
primary



secondary



tertiary



quaternary

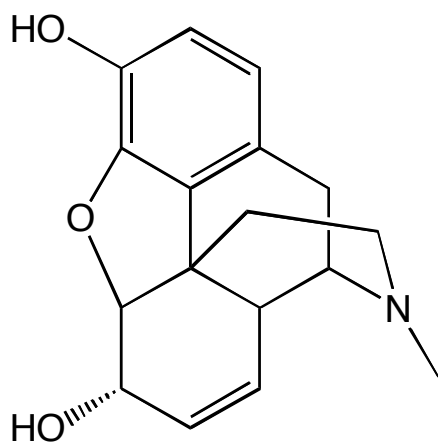
the order also affects the number of hydrogens attached to nitrogen  
(and charge with a quaternary nitrogen)

## Alkaloids

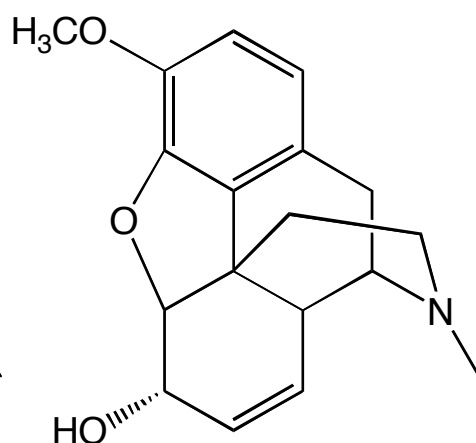
Alkaloids refer to amines that are produced by plants

They are often used for medicinal or physiological purposes

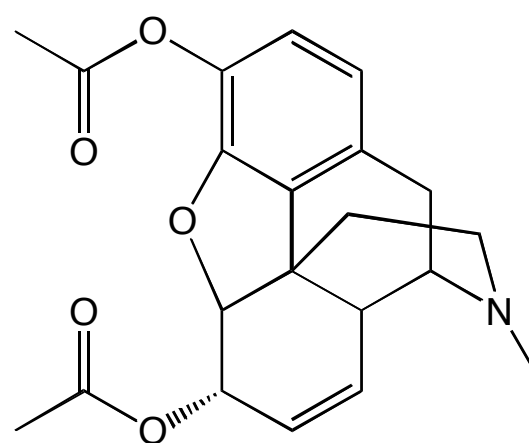
(the plant makes them to cause an effect when an animal eats them for protection)



morphine



codeine

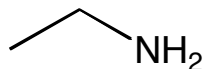


heroin

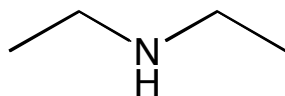
examples of opium alkaloids - compounds bind to receptor sites in the brain

## Nomenclature

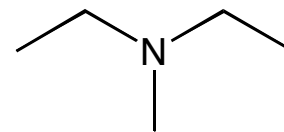
Common names - name the amine by indicating each alkyl substituent with amine suffix



ethylamine

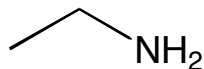


diethylamine

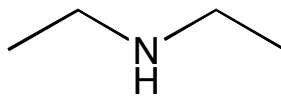


diethylmethylamine

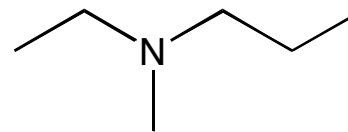
IUPAC names - similar to alcohol names, find longest continuous chain  
and name amine as suffix



ethylamine



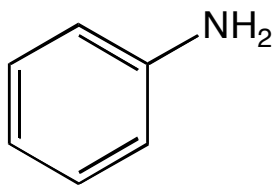
N-ethylethylamine



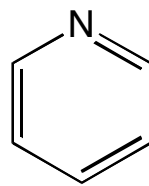
N-ethyl-N-methyl-1-propanamine

## Other Common Names

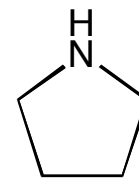
There are a number of compounds with historic common names



aniline



pyridine



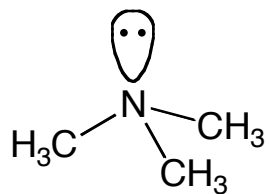
pyrrolidine

these compounds and others seen in aromatic compounds use common names

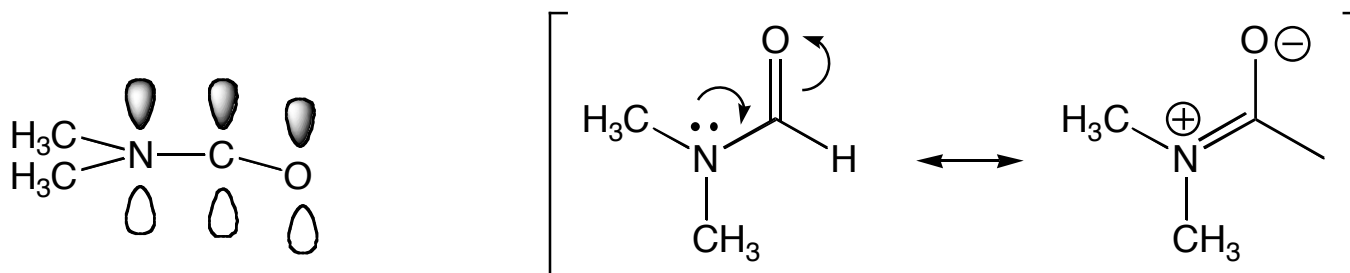
substituents are named as simple substituents with the common name as the root

## Structure

With a saturated amine the lone pair resides in a  $sp^3$  hybridized orbital

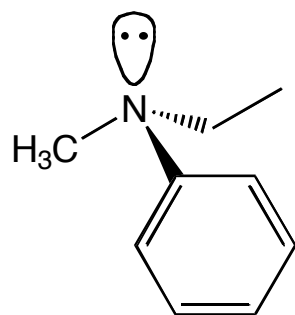


With conjugation the lone pair will reside in a p orbital to allow overlap



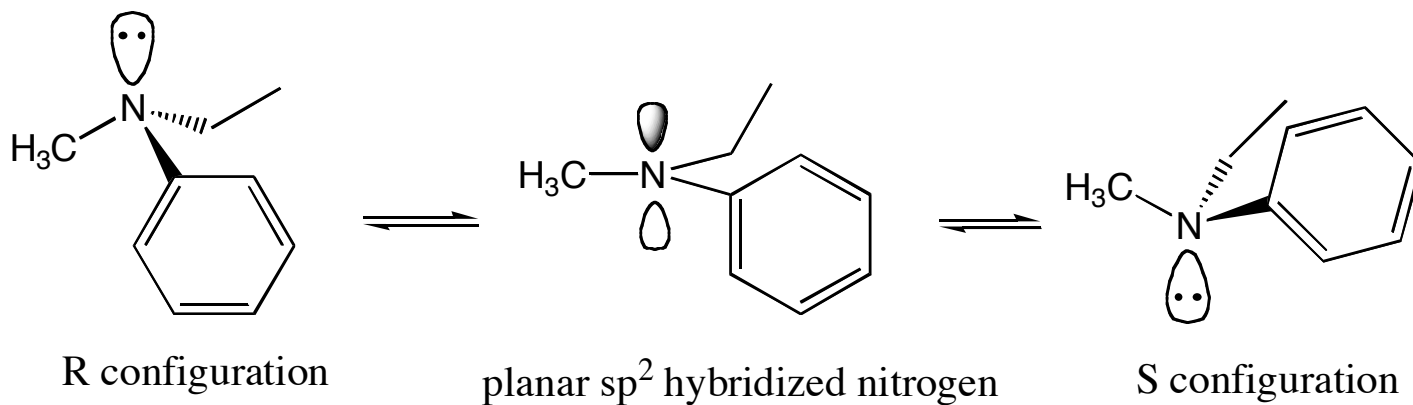
## Nitrogen Inversion

Any  $sp^3$  hybridized center is chiral with four different substituents



R-(N-ethyl-N-methyl)aniline

with nitrogen, however, we usually cannot isolate stereoisomers due to nitrogen inversion

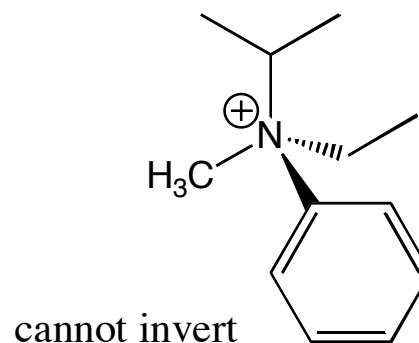
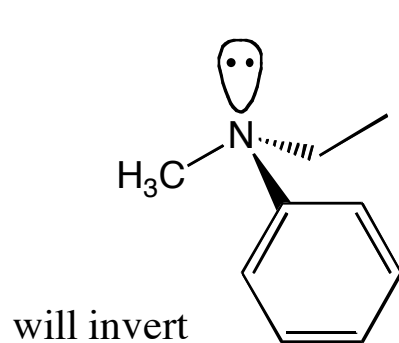


The nitrogen inversion changes the chirality

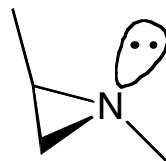
Since this inversion happens at room temperature for nitrogen  
cannot isolate pure form of either enantiomer

can prevent nitrogen inversion in two ways:

1. create quaternary nitrogen - nitrogen is prevented to invert with four covalent bonds



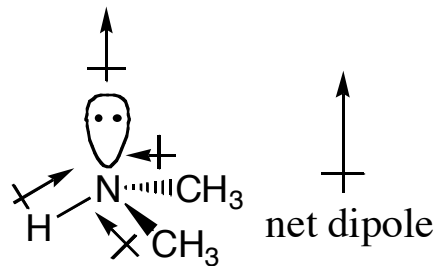
2. strain prevents formation of  $sp^2$  hybridized nitrogen



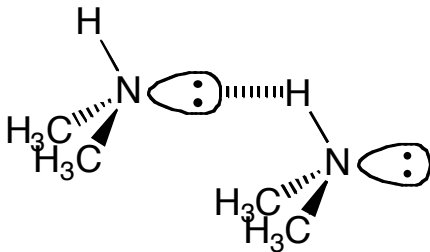
strain of ring hinders  $sp^2$  hybridization

## Properties of Amines

Amines typically have a relatively high dipole



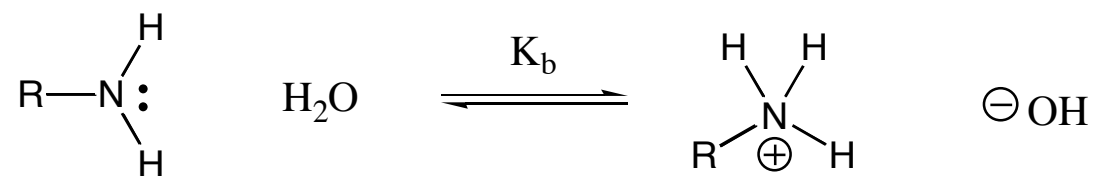
in addition, H-bonding causes amines to have a relatively higher boiling point



## Basicity

Another major factor with amines is the basicity

The lone pair of electrons on nitrogen can act as an acceptor  
(hence Brønsted-Lowry base)



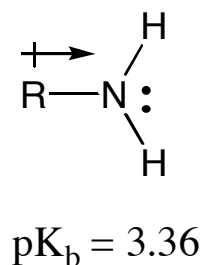
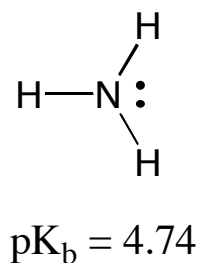
can determine  $\text{p}K_b$  values (just like  $\text{p}K_a$  values for acids)

$$\text{p}K_a + \text{p}K_b = 14$$

therefore strong bases are weak conjugate acids, and vice versa

## Effects of Basicity

The base strength for amines follow many of the same trends as already observed



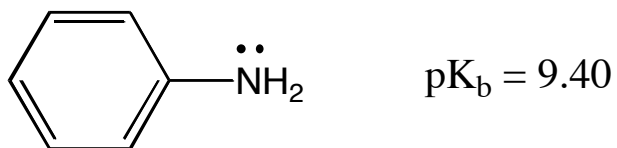
primary amines are more basic than unsubstituted amines

electron donating alkyl groups stabilize ammonium compound after protonation

a difference with these amines though is that secondary and tertiary amines are approximately the same basicity as primary amines - due to hydration effects

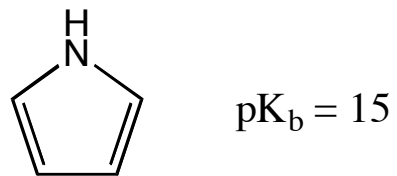
## Resonance Effects

Amines in resonance are less basic than saturated amines



Protonation prevents the lone pair from conjugation

Also remember resonance considerations



protonation makes aromatic compound nonaromatic

## Hybridization

As the percent s character increases the electrons are held more closely to the positively charged nucleus

therefore an  $sp^2$  hybridized amine hold the electrons closer than  $sp^3$  hybridized amine

thus the  $sp^2$  hybridized amine relatively does not want to donate the electron density

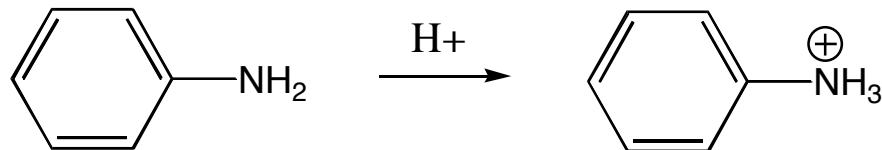
$sp^3$  amines are therefore more basic than  $sp^2$  amines

(other factors being equal)

## Amine Salts

There are many advantageous uses of amine salts

First the salt form of aniline changes the substituent from strongly activating to strongly deactivating - therefore changes regiochemistry and reactivity



Second, the amine salt changes solubility

Amines are soluble in organic phase, salts are soluble in aqueous phase

## Phase Transfer Catalysis (PTC)

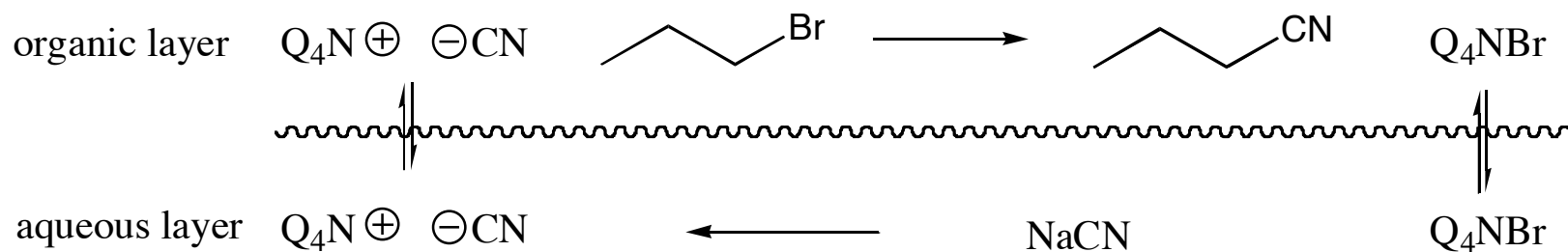
Amine salts are also used to catalyze a variety of organic reactions that feature two components that are soluble in different liquid phases (e.g. organic and aqueous)



high organic solubility  
low aqueous solubility

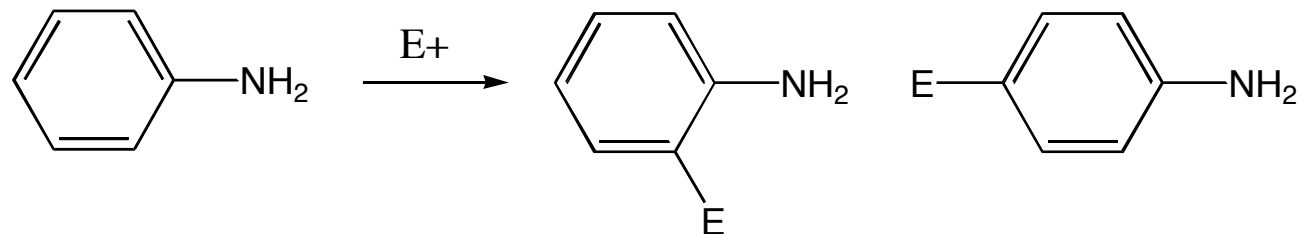
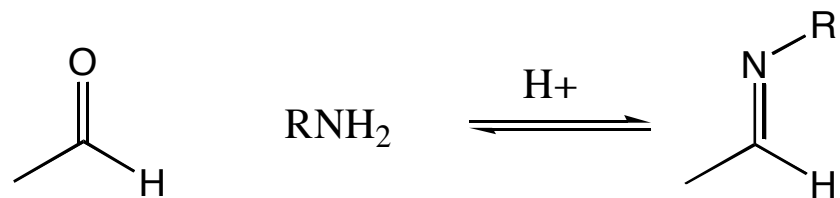
low organic solubility  
high aqueous solubility

adding a phase transfer catalyst will accelerate the rate (often use quaternary amine salts)



## Reactions of Amines

Some reactions we have already seen in the chapters covering ketones and aromatic

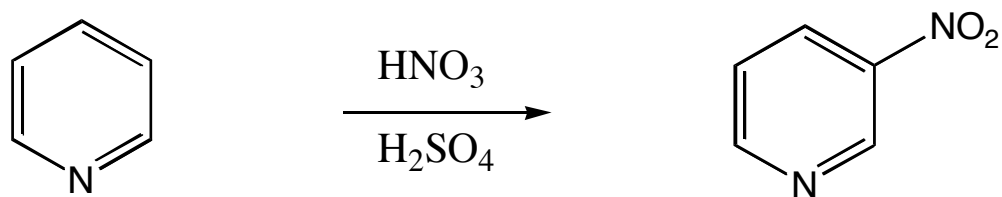


## Pyridine

Pyridine is a strongly deactivating ring system

Many reactions do not work with pyridine due to the strongly deactivating system

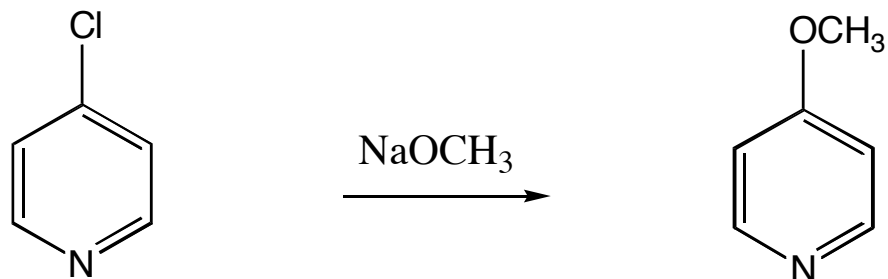
Those that do react occur with meta substitution



consider the arenium ion to understand this regioselectivity

## Nucleophilic Aromatic Substitution

Since pyridine is a strong deactivating group, leaving groups ortho or para to nitrogen will leave in a nucleophilic substitution



again consider charged intermediate for this reaction for regioference

also remember leaving group ability for these nucleophilic substitution reactions

follow electronegativity trends (F > Cl > Br > I)

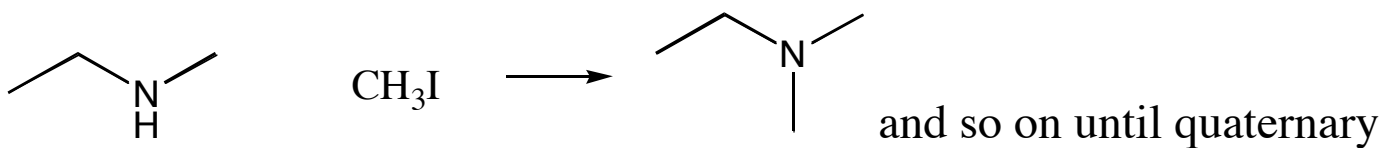
## Alkylation of Amines

The lone pair of electrons on amines can react in a nucleophilic manner

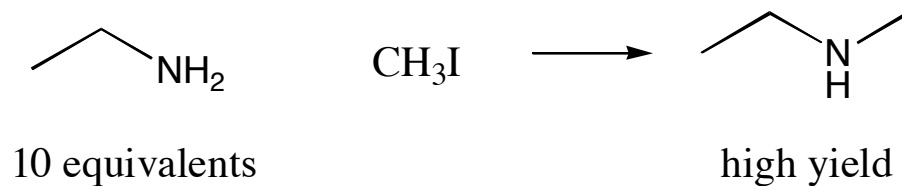


yield is best with primary halide (this is a S<sub>N</sub>2 reaction)

one problem with this reaction is often polyalkylation occurs



To prevent "overalkylation" reaction is run with excess of amine



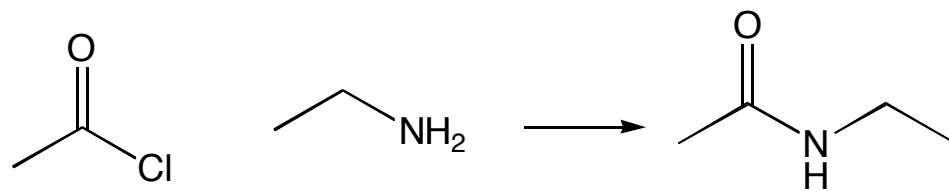
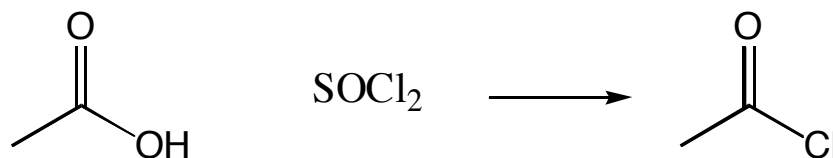
the other option is to run the reaction with excess of alkyl halide

in that case the product will be the quaternary salt

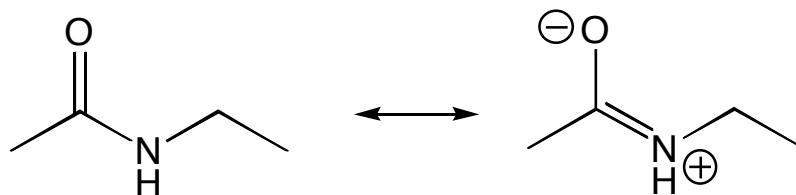
where the amine has been fully alkylated

## Acylation

The amines can also be reacted with acid chlorides to generate amides

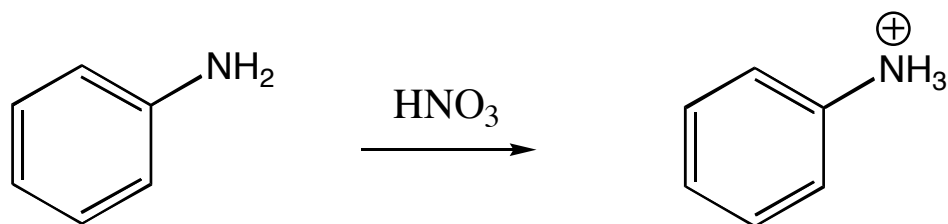


the amide does not generally react further because the lone pair is delocalized

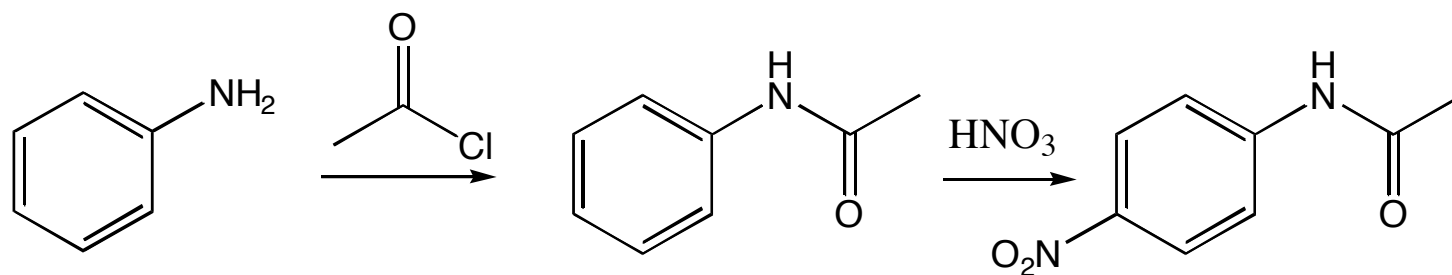


## Acylation to Modify Aromatic Reactivity

Remember aniline is highly reactive and the amine is basic

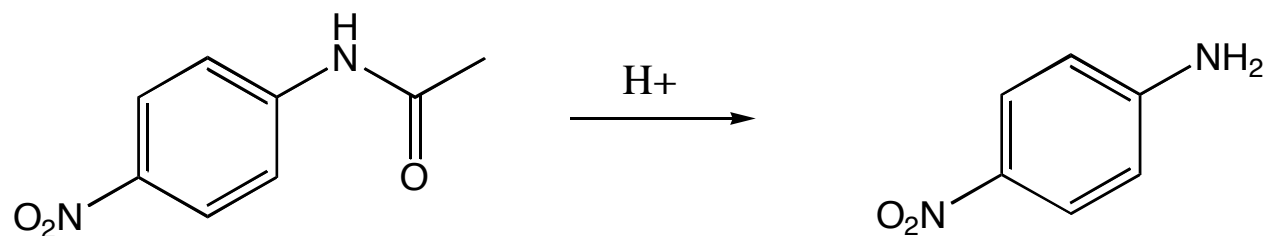


with acylation, however, the compound can be reacted



## Hydrolysis of Aryl Acetyl Group

Once used the acetyl group can be hydrolyzed off in either acidic or basic conditions



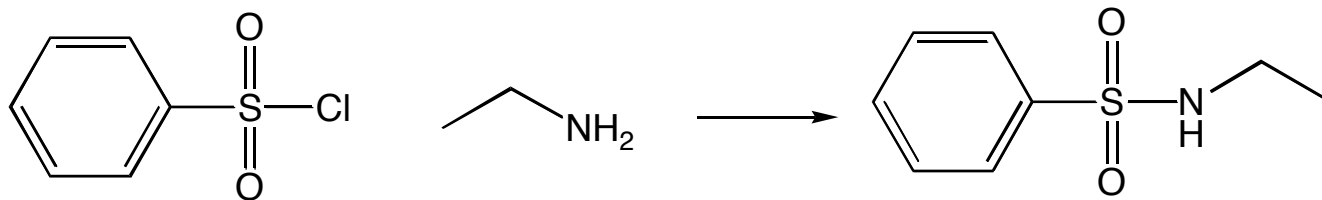
thus the acylation of aniline derivatives are quite useful to modify reactivity

## Sulfonamides

Sulfonamides are widely used as antibacterial agents (called "sulfa drugs")

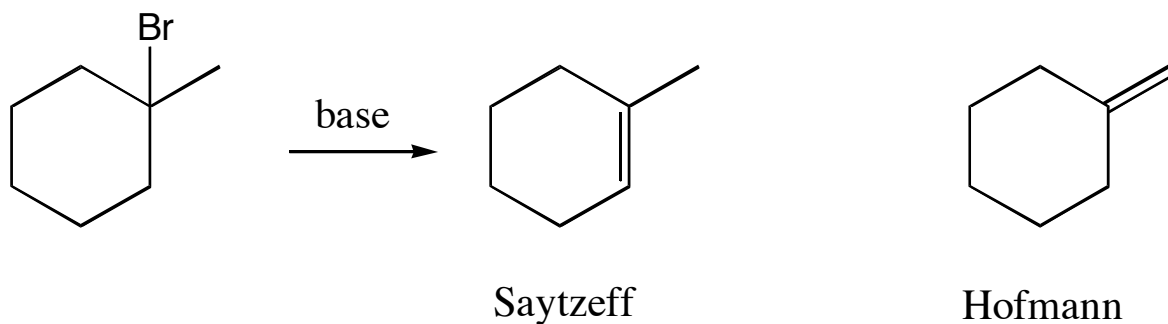
Very similar reactivity as acylation reactions

Use sulfonyl chloride instead of acid chloride



## Hofmann Elimination

Remember E2 mechanisms where eliminations occurred  
with either Saytzeff or Hofmann preference



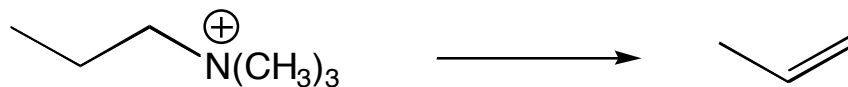
for these reactions the Saytzeff was generally favored due to the more stable product  
Hofmann was observed when the base was too bulky to abstract hydrogen from more  
substituted carbon

The Hofmann product in these E2 is named after amine elimination reactions

When an amine is alkylated with excess alkyl halide a quaternary amine is obtained

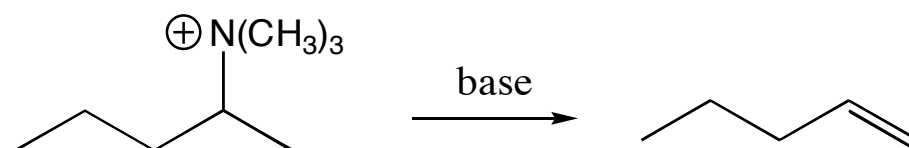


This amine is now a good leaving group



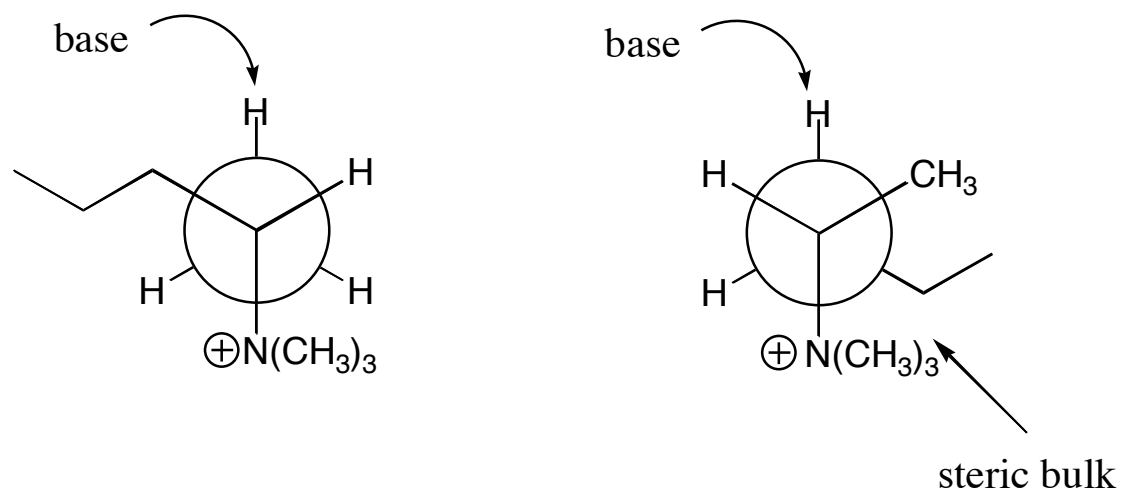
When heated the amine can leave to generated an alkene

When two different alkenes can form the less substituted alkene is preferred



the reason for this difference compared to other E2 reactions is the bulkiness of the quaternary amine leaving group

E2 reactions must be anticoplanar!



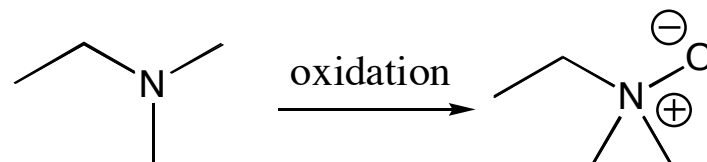
## Cope Elimination

Another method to remove the amine from a compound is the Cope elimination

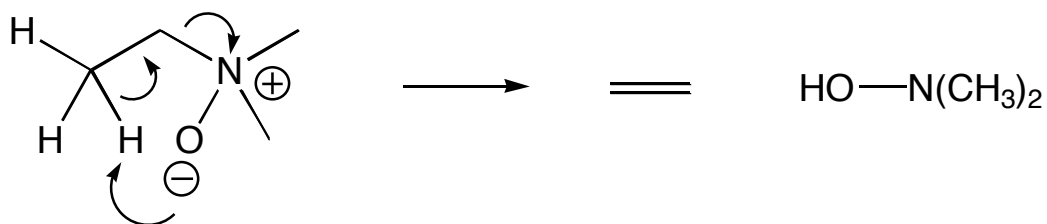
Instead of an E2 base mechanism, the Cope occurs through an oxidation mechanism

A tertiary amine is oxidized to an amine oxide

(primary amines to nitro and secondary amines to hydroxylamines)

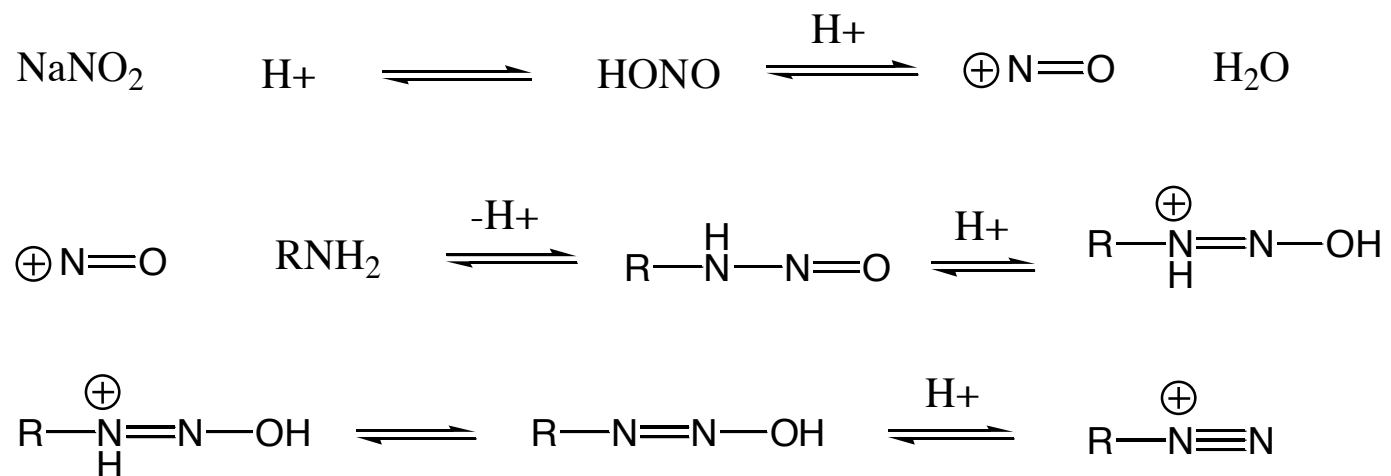


amine oxides will eliminate without base



## Diazonium Salts

Primary amines will react with nitrous acid to form diazonium salts



the key is that nitrogen will leave to generate a carbocation

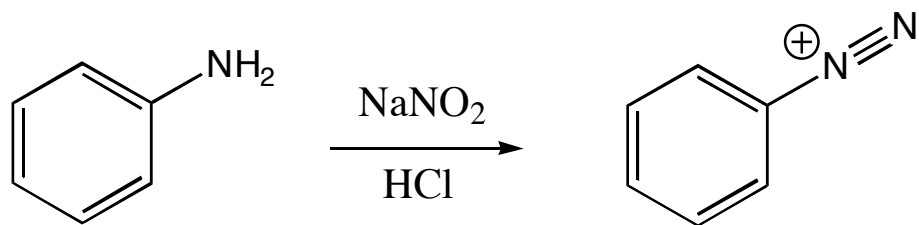


## Arenediazonium Salts

While the generation of alkyl carbocations with this method is unnecessary (there are many other more efficient ways to generate alkyl carbocations),

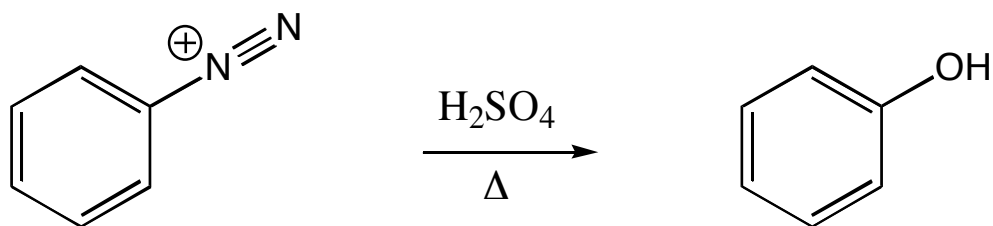
It is a unique method to generate many aryl substituted products

First the arenediazonium salt is generated from an aniline derivative



The nitrogen leaving group ( $\text{N}_2$ ) can then be replaced

Unique products formed:

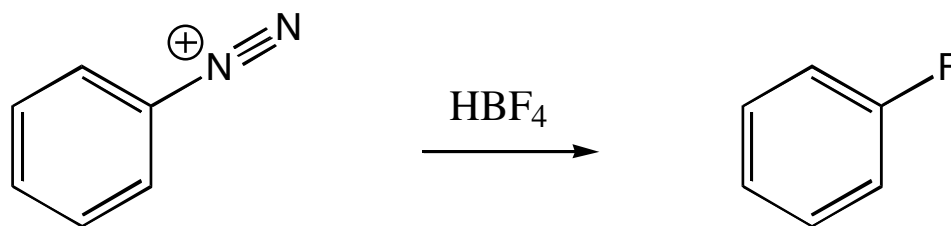


one of the most convenient ways to generate phenol derivatives

it is difficult to generate an oxygen electrophile  
to do a normal electrophilic aromatic substitution

## Generation of Aryl Fluorides

We already saw how arenediazonium salts can be used to add a fluorine substituent

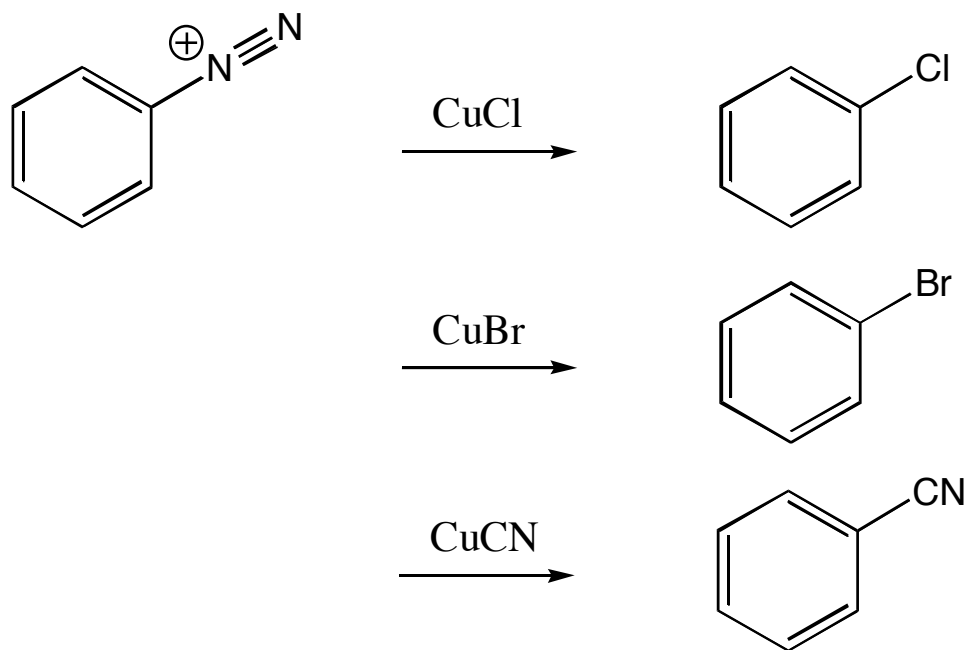


once again this is one of the only ways to add fluorine to the aromatic ring

## Sandmeyer

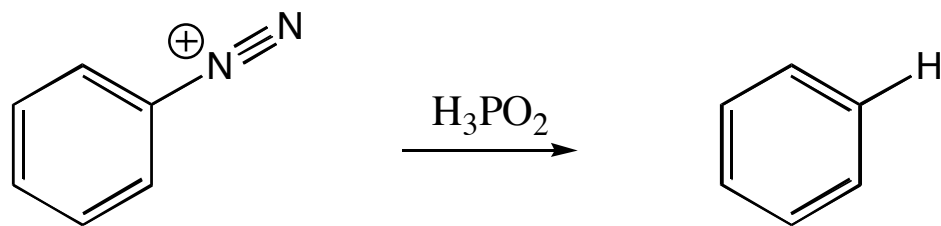
Arenediazonium salts are often reacted with Cu(1) salts

This reaction is called a Sandmeyer reaction

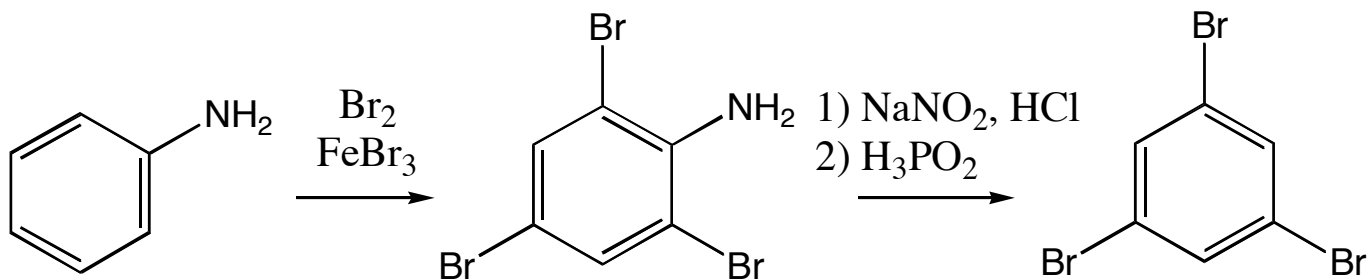


common substituents to add are chlorine, bromine or cyano with this route

## Replacement of Diazonium group with Hydrogen



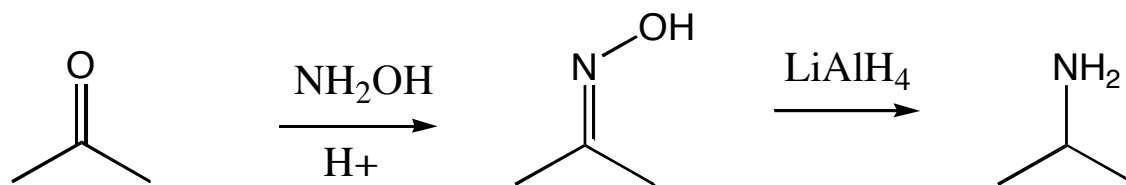
this allows an amine to be used as a directing group and then subsequently removed



would not be able to synthesize bromines meta to each other otherwise

## Synthesis of Amines

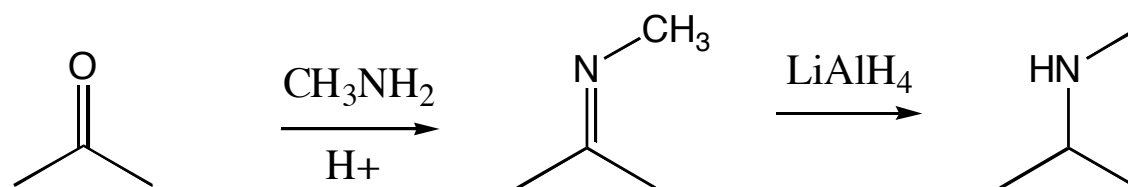
Instead of alkylating amines, which lead to overalkylation problems, amines can be created from imine sources



for primary amines usually use the hydroxylamine to generate an oxime  
once generated the oxime can be reduced to form the amine

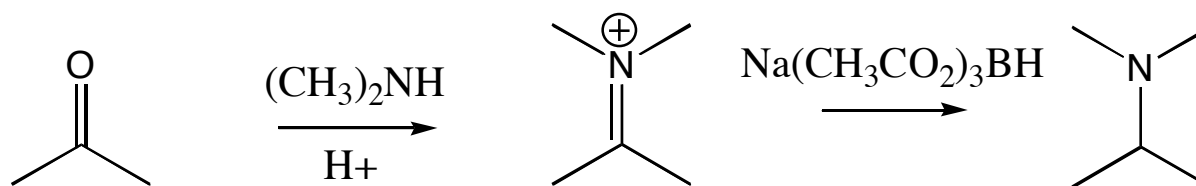
use different ketones or aldehydes to add different alkyl groups to amine

## Secondary Amines



just form imine and then reduce

## Tertiary amines

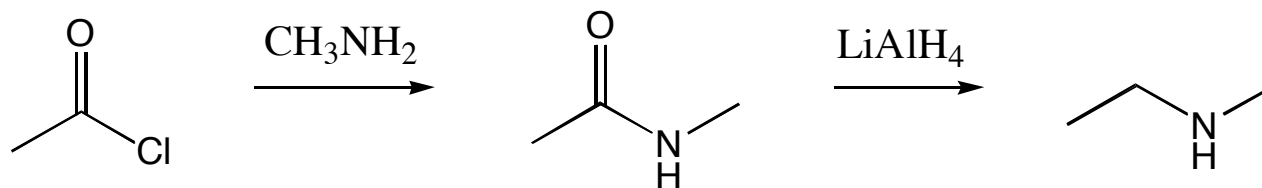


iminium salt

the iminium salt is unstable and must be reduced in situ,  
therefore use weaker reducing agent

## Acylation-Reduction

Another route to substituted amines is to first acylate then reduce



with the amide functionality, reduction with LAH yields the amine

can therefore generate either a 1°, 2°, or 3° amine

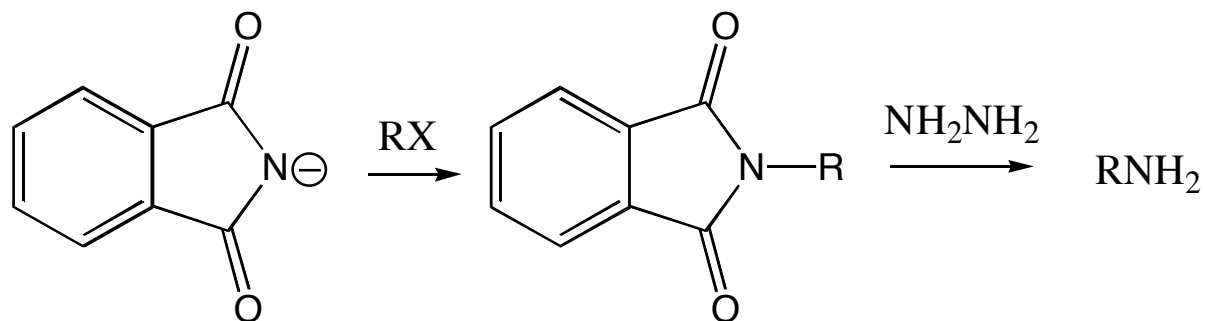
depending upon amine used in acylation step

## Gabriel Synthesis

Sometimes it is just easier to use an alkyl halide than to obtain the necessary ketone, aldehyde, or acid chloride needed for the previous steps

The problem with alkyl halides again was the issue of polyalkylation

Gabriel synthesis uses a phthalimide to prevent overalkylation

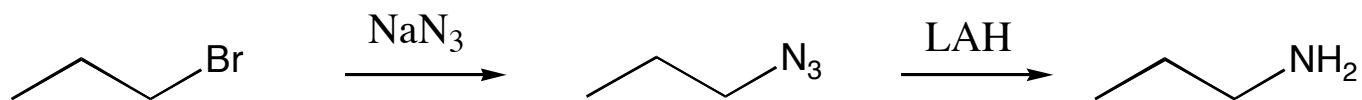


the hydrazine reacts with the phthalimide carbonyls to free the substituted amine

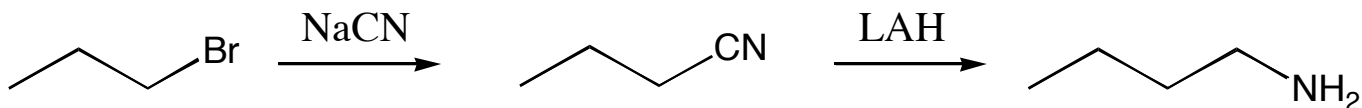
## Another Synthetic Route: Reduce other Nucleophiles

There are a couple of strong nucleophiles that can be reduced to an amine

azides



nitriles

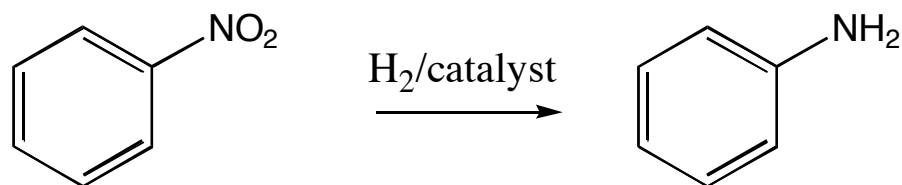


both of these routes allow a  $\text{S}_{\text{N}}2$  reaction to be performed followed by reduction to amine

realize that cyano (nitrile) adds one additional carbon to the framework

## Reduction of Nitro Group

Both alkyl and aryl nitro groups can be reduced to an amine



this reduction can occur under a wide variety of conditions

usually use either  $\text{H}_2$  and a catalyst (Pt, Pd, Ni are common)

or

use active metal with  $\text{H}^+$  source (e.g.  $\text{Sn}/\text{H}_2\text{SO}_4$ ,  $\text{Zn}/\text{HCl}$ )

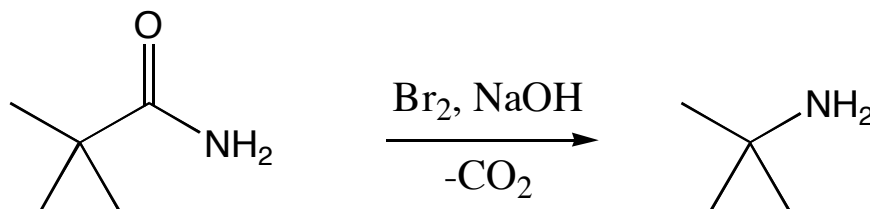
## Hofmann Rearrangement

The main advantage of this method is to generate 3° amines

Realize that with  $S_N2$  methods cannot place amine on 3° carbon

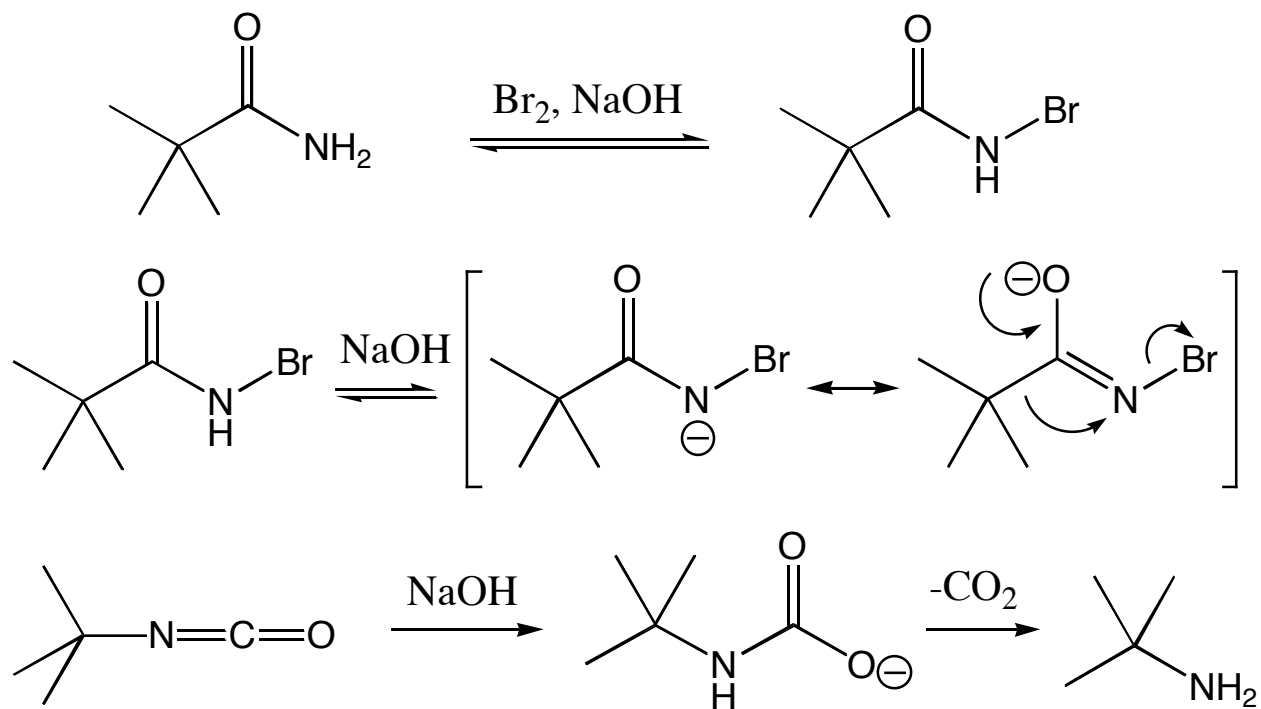
Hofmann starts with a primary amide that can be generated from the acid chloride

Upon introduction of basic halide solution ( $Br_2$  or  $Cl_2$ ) an amine is obtained



the reaction is driven by loss of carbon dioxide

## Mechanism



key is the formation of the isocyanate ( $\text{R-N=C=O}$  structure) which reacts in basic conditions to form carbamic acid which decarboxylates to amine