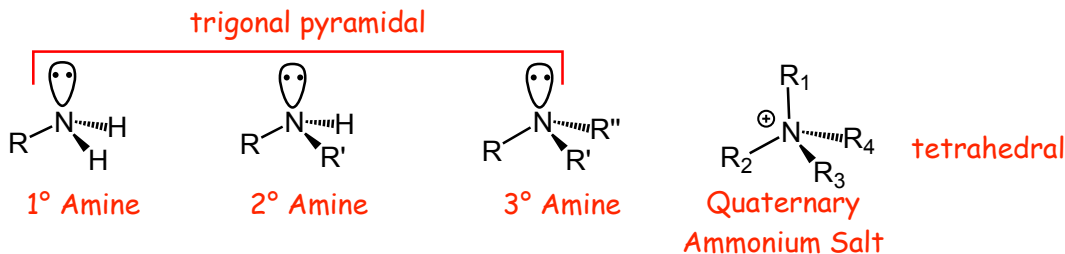


• Amines are trivalent, with a tetrahedral electron pair geometry, although the geometry of a neutral amine is a trigonal pyramidal, since unlike nuclei, the exact positions of an electron pair cannot be defined. An exception is an ammonium salt that is surrounded by 4 atoms (nuclei).

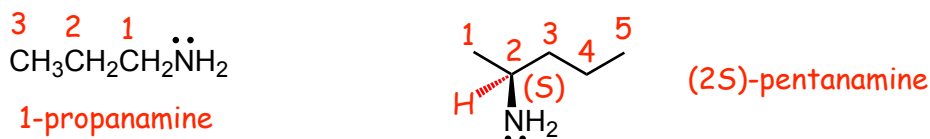


1 Nomenclature

IUPAC priority: acid > ester > amide > nitrile > aldehyde > ketone > alcohol > **amine** > alkene > alkyne > halide

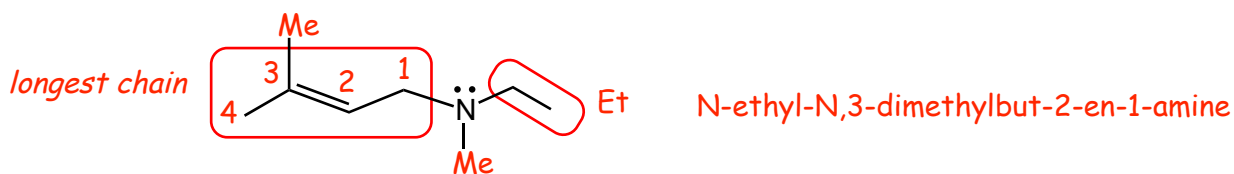
• Amines are named as for alcohols, except that you replace -ol with -amine, **amine suffix**.

• When an amine is a **substituent** it is an **amino substituent**.



• Number the chain as usual to give the amine functional group the lowest number.

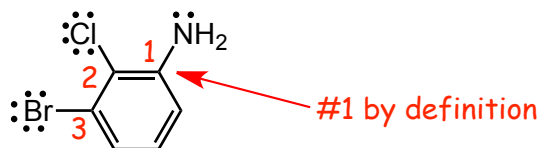
• As mentioned above, amines are named as alcohols except that "amine" is used in place of "ol" and so instead of propan-ol we have propan-**amine** (above), instead of pentanol we have pentan**amine**, etc.



• Find the longest chain that contains the maximum number of functional groups (alkene and amine) = four.

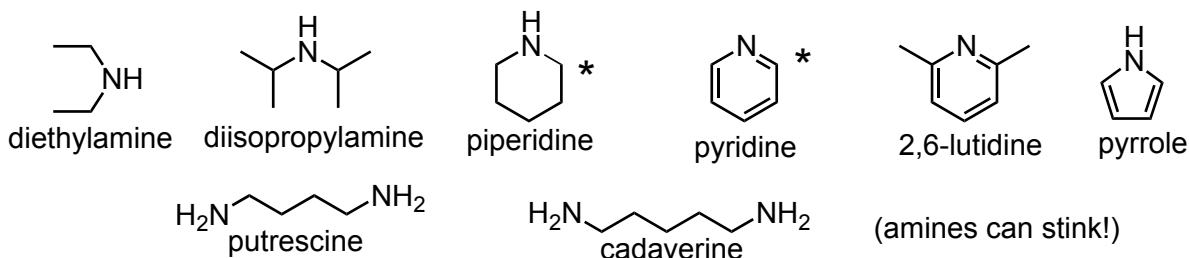
• Number to give the highest priority functional group **amine** the lowest number.

• N comes **before** 3 when specifying the two methyl substituents.



• **Remember**, the common name aniline has been incorporated into IUPAC nomenclature, for example, aniline (above).

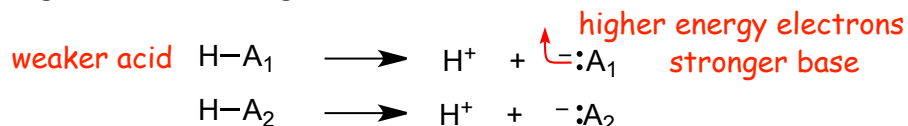
• Some common names for amines



* You should know these two, piperidine seen in the Stork reaction, pyridine a common organic base.

2 Amines as Bases

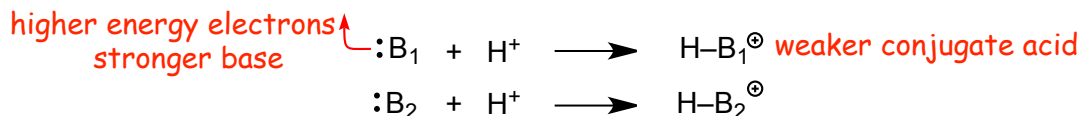
- Deciding the stronger of two acids, e.g. H-A₁ and H-A₂:



- The stronger acid has the more stable conjugate base anion, lower energy electrons in the base.
- The stronger acid corresponds to the more favorable "reaction", left to right.

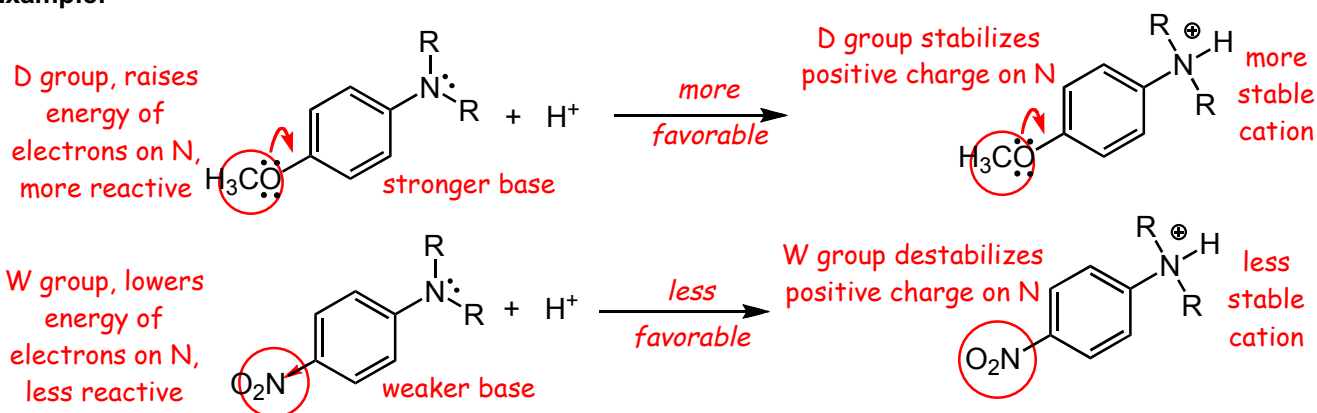
:

- Deciding the stronger of two bases, e.g. B₁ and B₂



- There are no anions here, but the stronger base still has the higher energy, more chemically reactive electrons.
- The stronger base is stronger because the energy of the electrons go down more by getting into a bond.
- The stronger base has the weaker conjugate acid since it has the stronger bond.

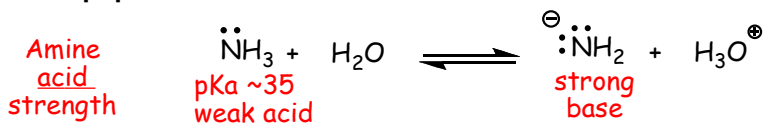
Example:



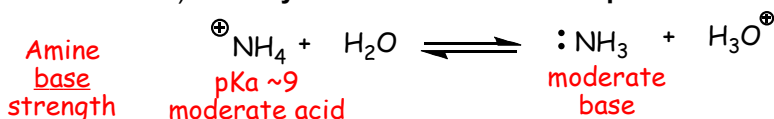
Acidity is Measured in terms of pKa, How is Basicity Measured?

- Basicity can be measured in terms of the corresponding pK_b, however, in organic chemistry we often don't do that, we specify basicity in terms of the acidity of the conjugate acid.

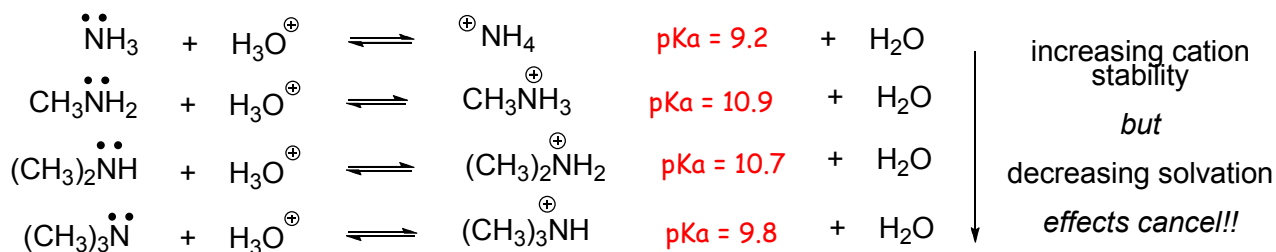
Acidity of an Amine in terms of pKa:



Compare with (and don't confuse with) Basicity of an Amine in terms of pKa of the conjugate acid.

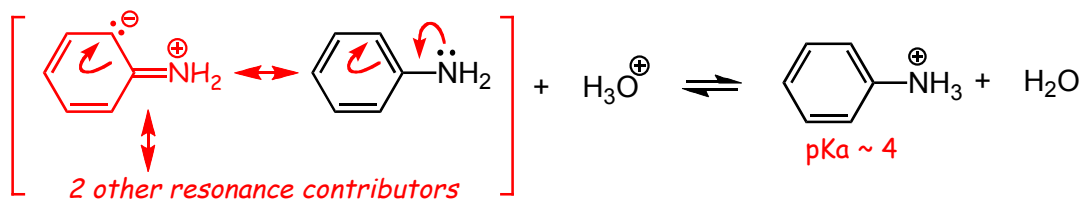


Trends in Basicity?

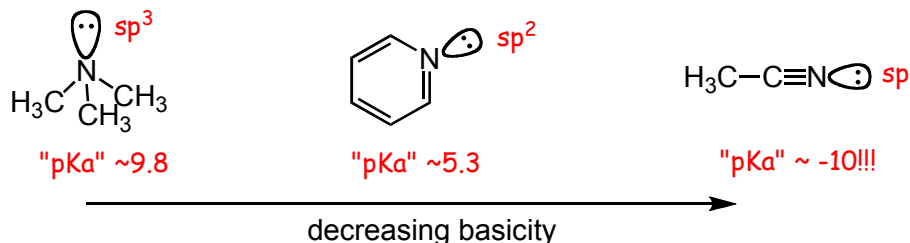


- There are **no clear trends** among the aliphatic amines because of the competing effects of alkyl group donation and reduced solvation of the larger cations.

But



- Minor resonance delocalization (i.e. partial bonding) stabilizes (lowers energy) of the non-bonding electrons in aromatic N, these electrons are less reactive.
- **Aromatic amines are thus much less basic than aliphatic amines:**



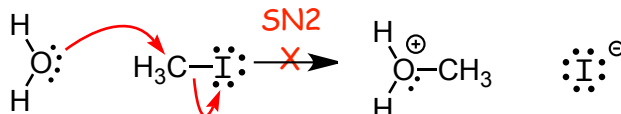
- There is a clear decrease in basicity with decreasing energy of non-bonding electrons as the hybridization of the orbitals gains more s character and less p character.
- The protonated nitrile is about the strongest acid that we discuss this entire course!

4 Reactions of Amines

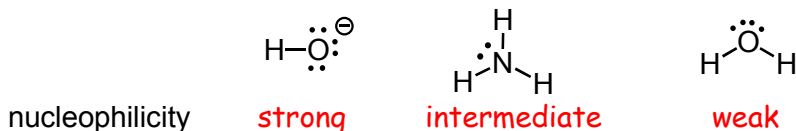
4.1 Amines a Nucleophiles

Recall:

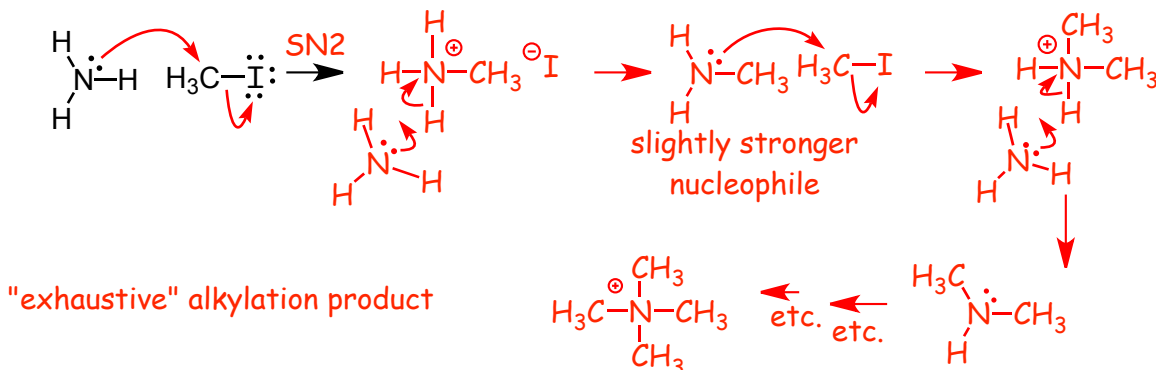
- The reaction below does **not** go, H_2O is not a strong enough nucleophile.



Reminder:



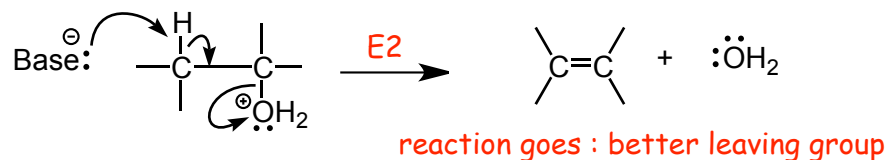
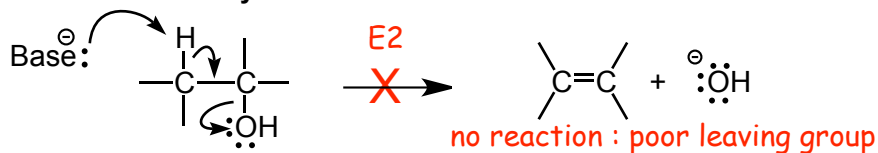
However:



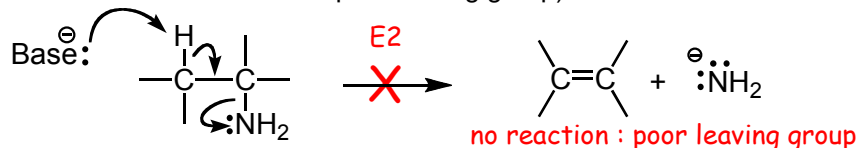
- NH_3 is a strong enough nucleophile that this SN_2 reaction goes!
- MeNH_2 is an even stronger nucleophile, the reaction keeps going!
- On its own, this is clearly not very useful, due to "over-alkylation", except in the Hofmann elimination (see next reaction).

4.2 Hofmann Elimination

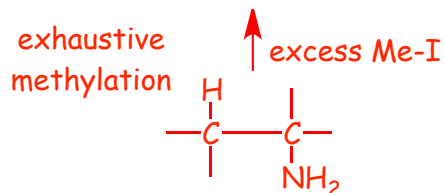
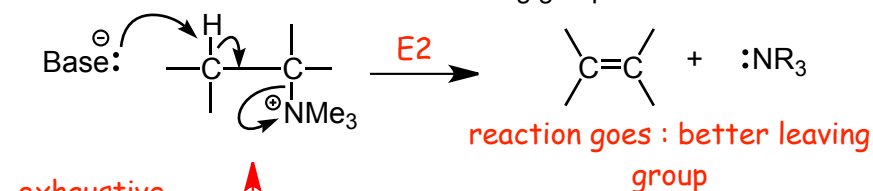
Revisit a Concept we Have Seen Many Times Now:



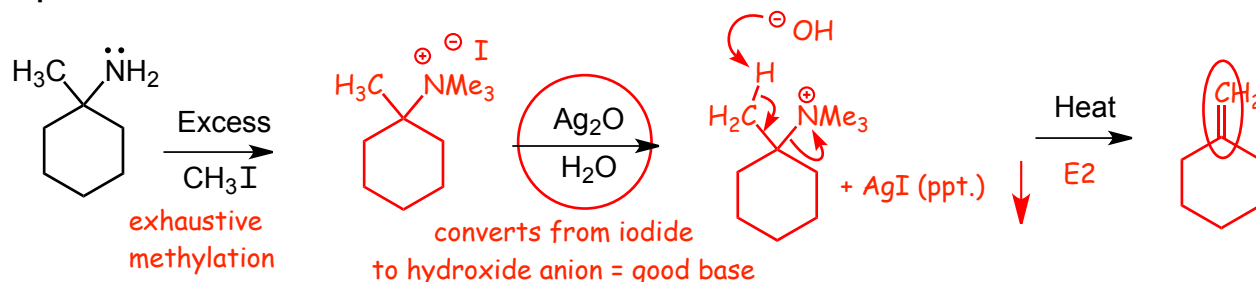
This reaction also doesn't work because of the poor leaving group):



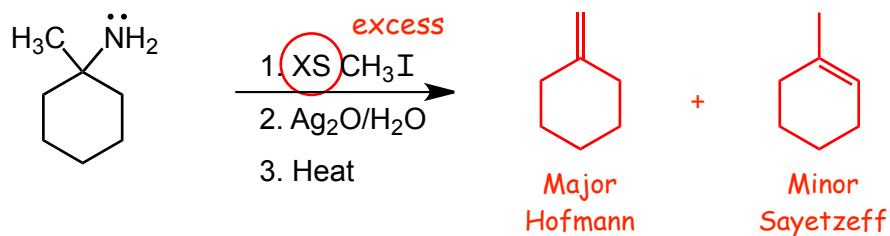
However, this one does because we have a much better leaving group:



Example:

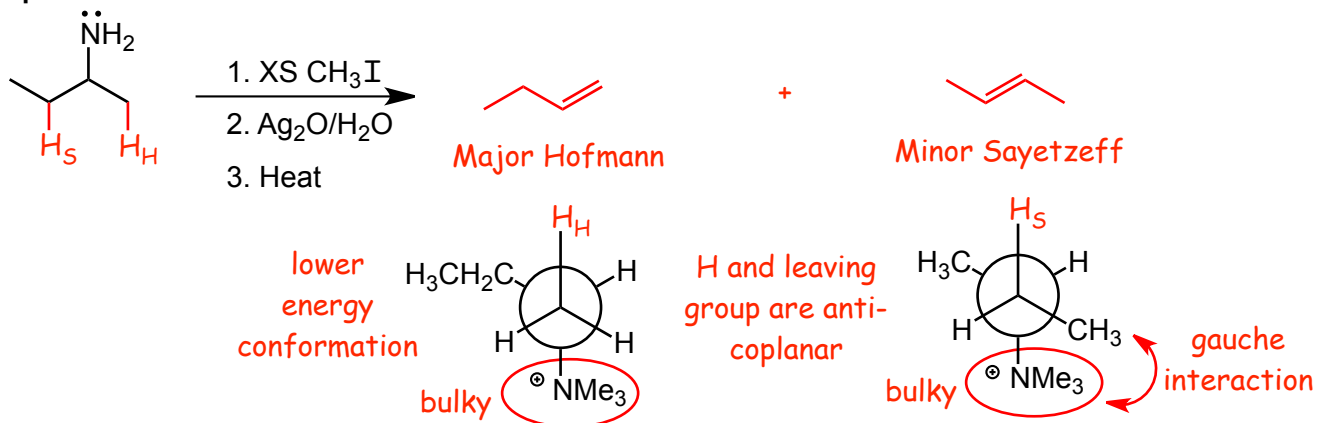


Overall:



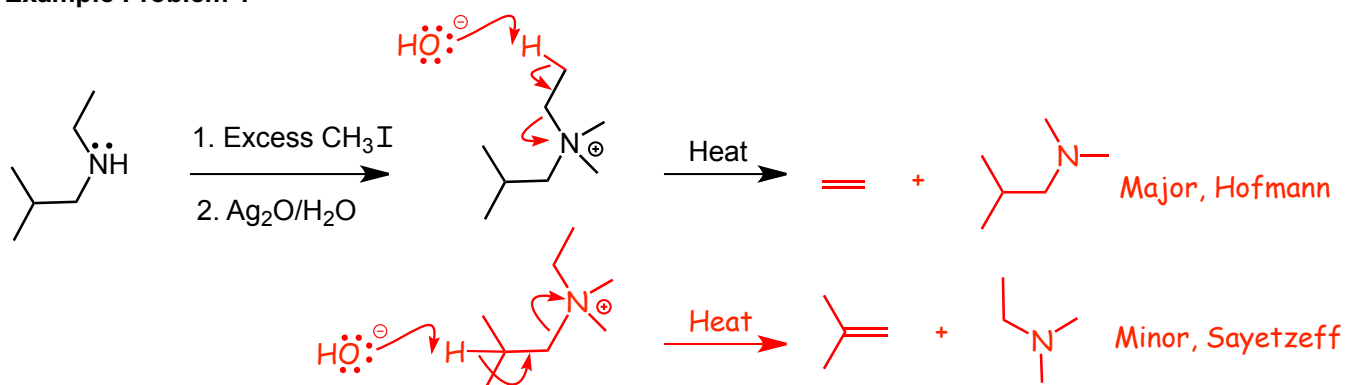
- The reaction is overall **E2 elimination**, forming an alkene with a neutral amine as the leaving group.
- **However**, the **least** substituted alkene is the major product (Hofmann product), not the more substituted Saytzeff (Zaitsev) alkene.
- "XS" is a commonly used abbreviation for "excess".

Explanation for Hofmann Product: A steric effect.



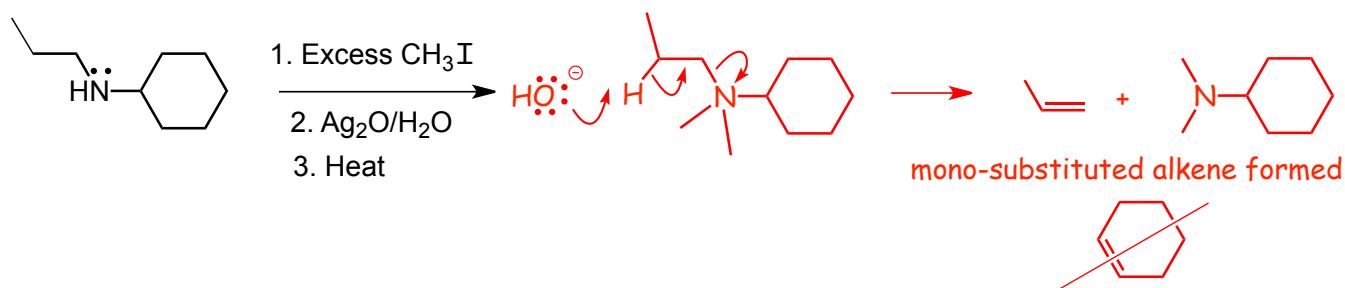
- The $-\text{NMe}_3^+$ group is **large** (bulky), it is roughly the same size as a t-butyl group
- Therefore the E2 conformation for Hofmann elimination is lower in energy than the E2 conformation for Saytzeff elimination for steric reasons (there are fewer higher energy gauche interactions).
- Therefore elimination in the Hofmann conformation is more likely because the structure spends more time in that lower energy conformation.

Example Problem 1

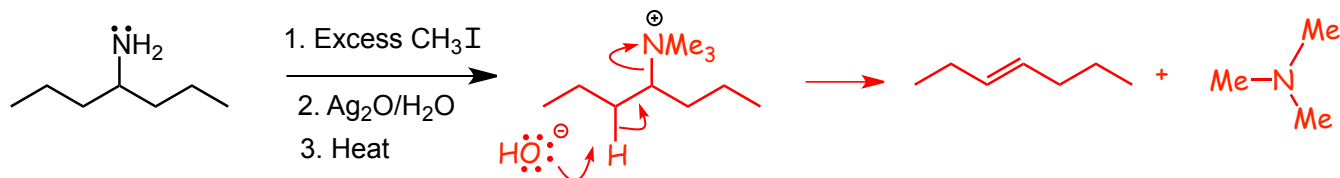


- There are **two** possible elimination products once the ammonium ion has been formed in the reaction with $\text{CH}_3\text{-I}$, the reaction that forms the least substituted (Hofmann) alkene is fastest, the Hofmann alkene is the major alkene product, together with its associated amine.
- In some cases the amine leaving group will be a substantial major organic structure on its own.

Example Problem 2

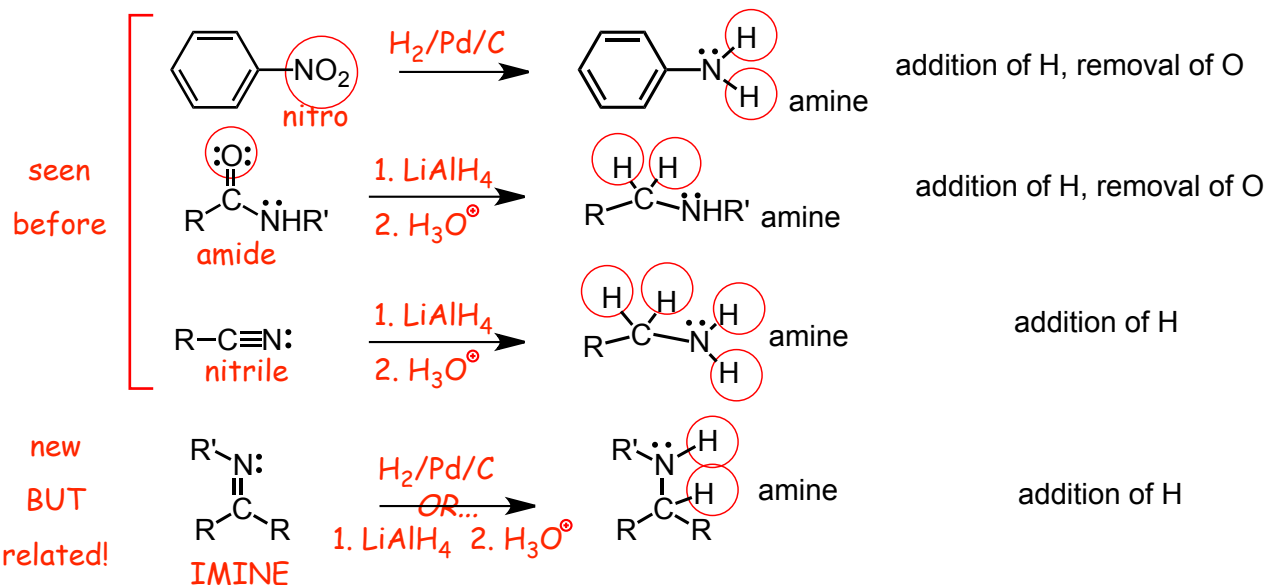


Example Problem 3



3 Synthesis of Amines

Amines are synthesized in **Reduction Reactions**, several of which we have **already seen**:



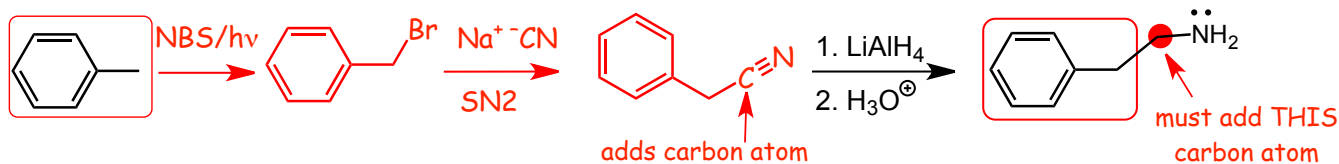
• In reality there are lots of different ways of doing these reductions (many different sets of reagents/conditions work), but here we use reagents/conditions that we already know for simplicity. There is no need to learn even more new reagents at this point (except one!).

3.1 Synthesis of amines using methods we know

Again, we are now using reactions we already know in a synthetic context.

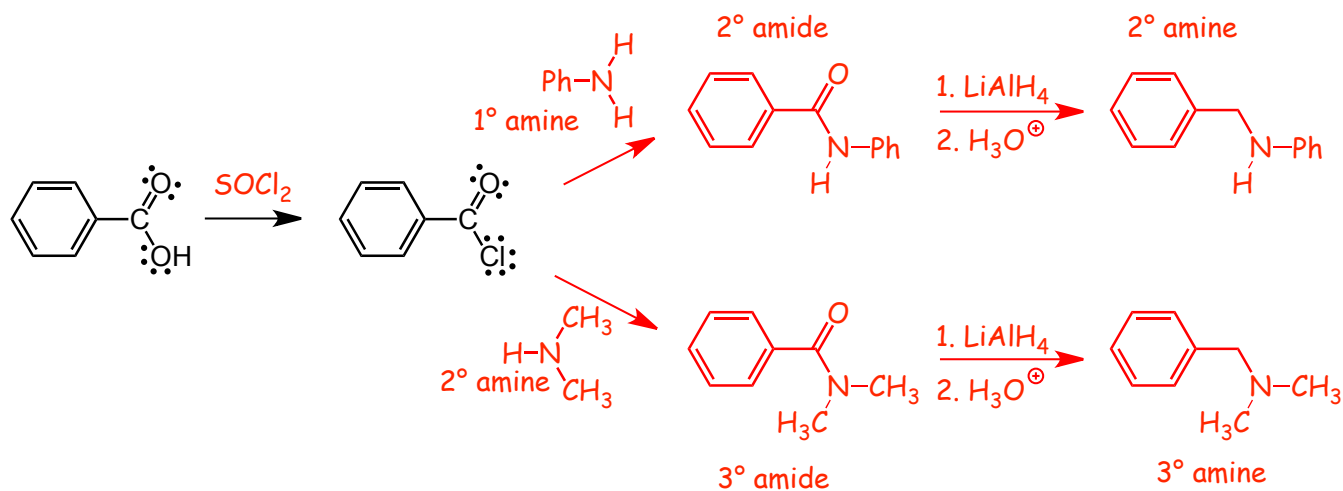
Examples

• As we have now seen many times, bromides are very convenient starting materials to start building new molecules, here we combine an $\text{S}_{\text{N}}2$ reaction with reduction of a nitrile to make a **primary amine**.



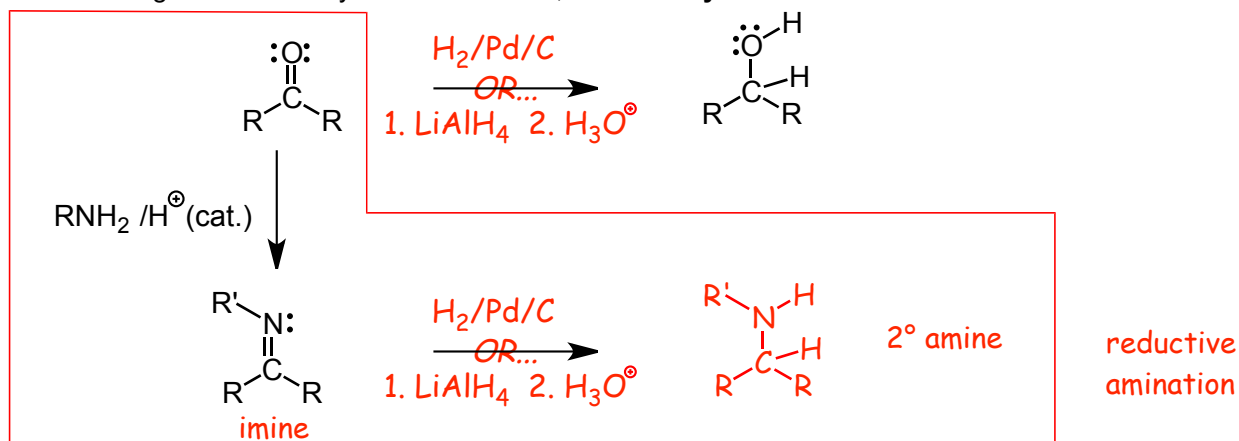
• A 1° amine can therefore be made from a nitrile, where **one carbon atom is added compared to the starting alkyl bromide**.

• 1° , 2° or 3° amines can be made by reducing an amide, which in turn comes from an acid chloride, which in turn comes from a carboxylic acid.



3.2 Synthesis of Substituted Amines by Reduction of an Imine: Reductive Amination

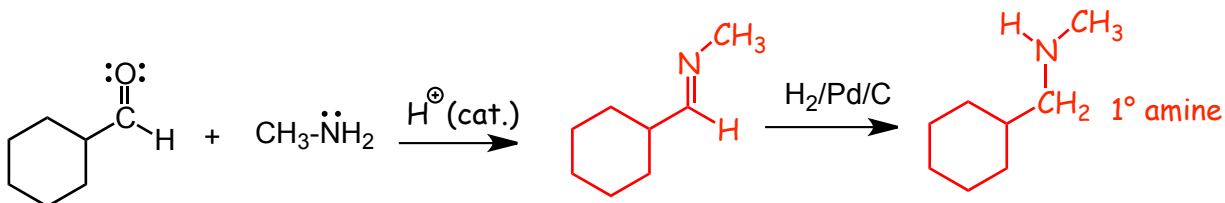
- Addition of nitrogen to a carbonyl to form an imine, **followed by** reduction forms an amine:



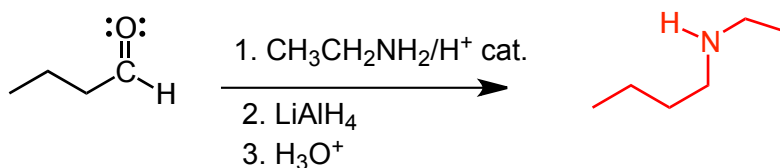
- So now we have a new reaction name: Reductive Amination, but is basically chemistry we already know
- We already knew that we could react an amine with an aldehyde/ketone to form an imine (also known as a Schiff base), and it is no great surprise that the C=N bond of the imine (Schiff base) can be reduced by addition of H₂ addition similarly to a C=O bond, we can even use the **same reducing agents** we already know!
- Reduction of C=N is actually somewhat easier than reduction of C=O, N is less electronegative and the C-N pi-bond is thus a bit weaker than the C-O π-bond.

Indirect Reductive Amination combines these reactions in sequence:

Example 1



Example 2

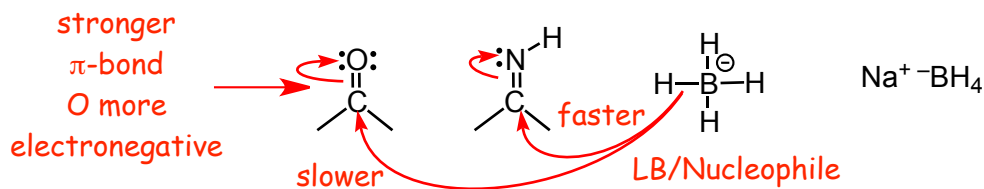


Direct Reductive Amination combines formation of the imine and the reduction **in one reaction**:

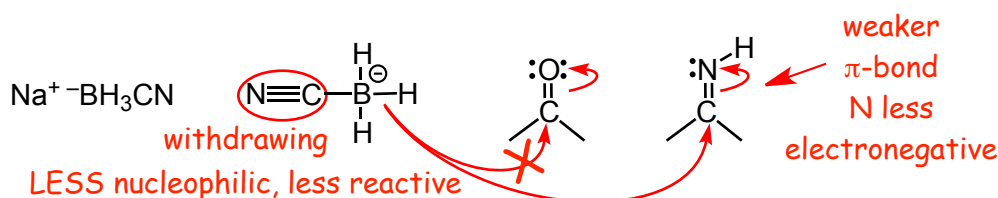


- "In Situ" means formed in the reaction, reaction "in situ" means that the imine reacts as it is formed.
- Here is a final new reducing agent, NaBH_3CN

Recall NaBH_4 :

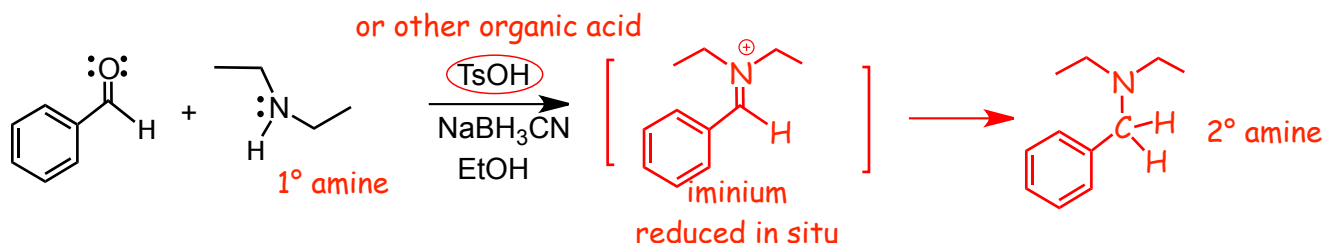
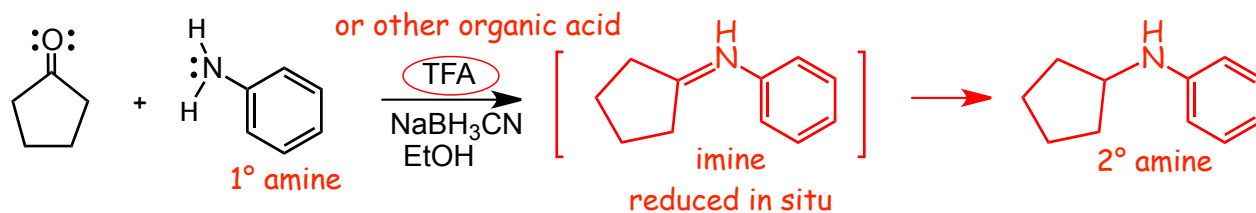


Compare NaBH_3CN :



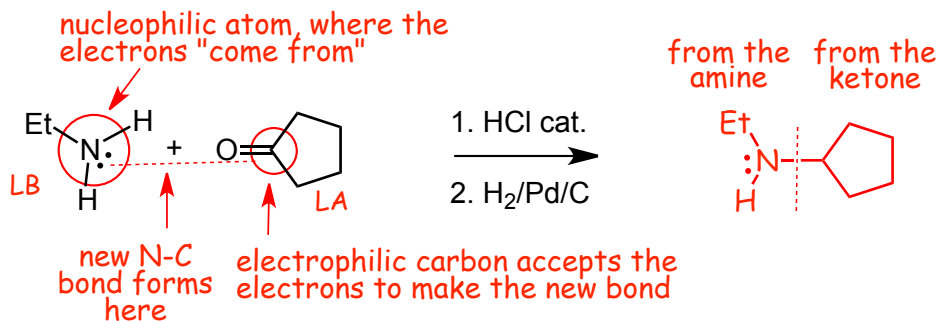
- The $-\text{CN}$ withdrawing group makes the BH_3CN^- anion less nucleophilic, it reacts slower with carbonyls ($\text{C}=\text{O}$) and imines ($\text{C}=\text{N}$), but the reaction with $\text{C}=\text{O}$ is slow enough that it does not happen under reductive amination conditions, $\text{Na}^+ \text{BH}_3\text{CN}^-$ is a selective reducing agent for imines.
- Remember, "no reaction" doesn't really mean no reaction at all, reactivity is not black and white, it means that the reaction with the $\text{C}=\text{O}$ is now slow enough and the reaction with $\text{C}=\text{N}$ fast enough to be useful in the reaction.
- Another subtle point, EtOH may not be required as a solvent to provide the protons that go with the hydride, since the acid that is used to catalyze the reaction may also supply these protons.

Examples



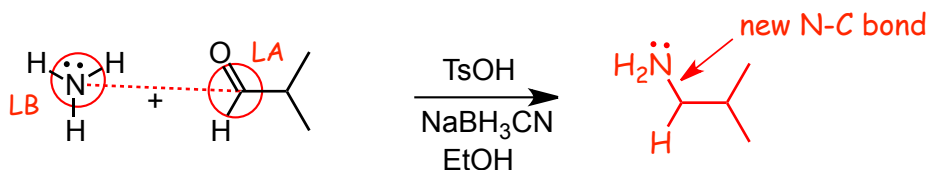
- **Recall:** Heuristics are skills students develop that allow them to solve the problems more quickly than by working them out from first principles, by skipping steps that become obvious.
- **Heuristics can't be taught**, but here we will point you in the right direction to develop heuristics for reductive aminations.

Example 1: Give the product of the following **indirect** reductive amination:



- **Identify** the atoms involved in the bond-forming reaction, don't forget basic Lewis acid/base nucleophile/electrophile principles! The electrons come from the nitrogen and make the new bond to the C=O carbon.
- A **N-C single bond forms** so eliminate the oxygen.

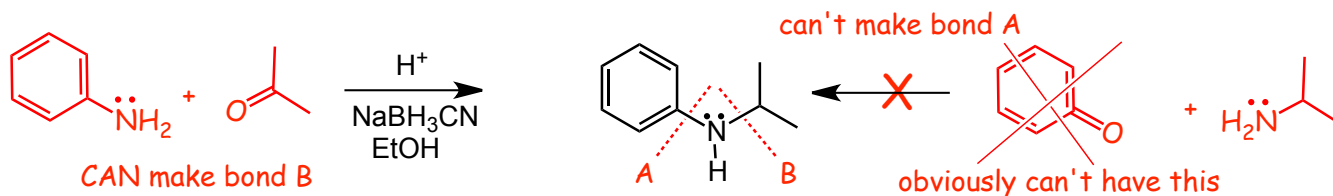
Example 2: Give the product of the following **direct** reductive amination:



- Note that the selective reducing agent NaBH₃CN is included in the reagent/conditions in a "one pot" reaction.

Example in Reverse

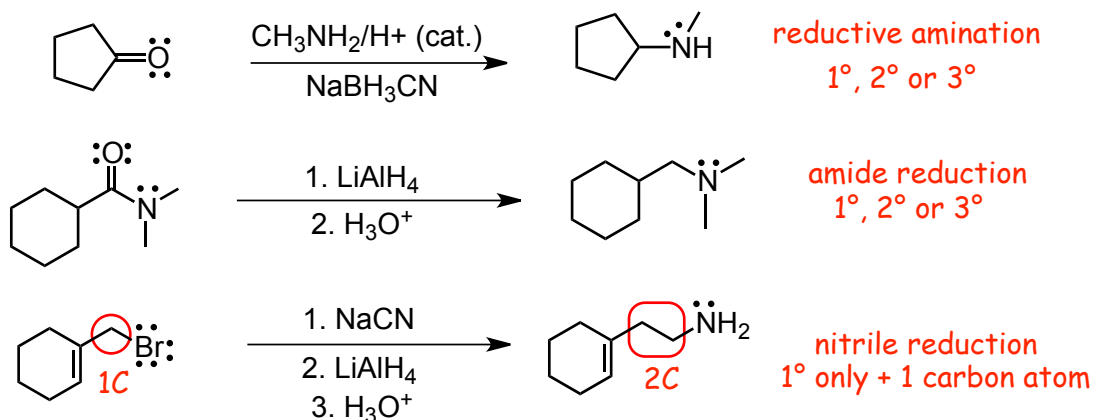
- How can we make the provided amine using a reductive amination?



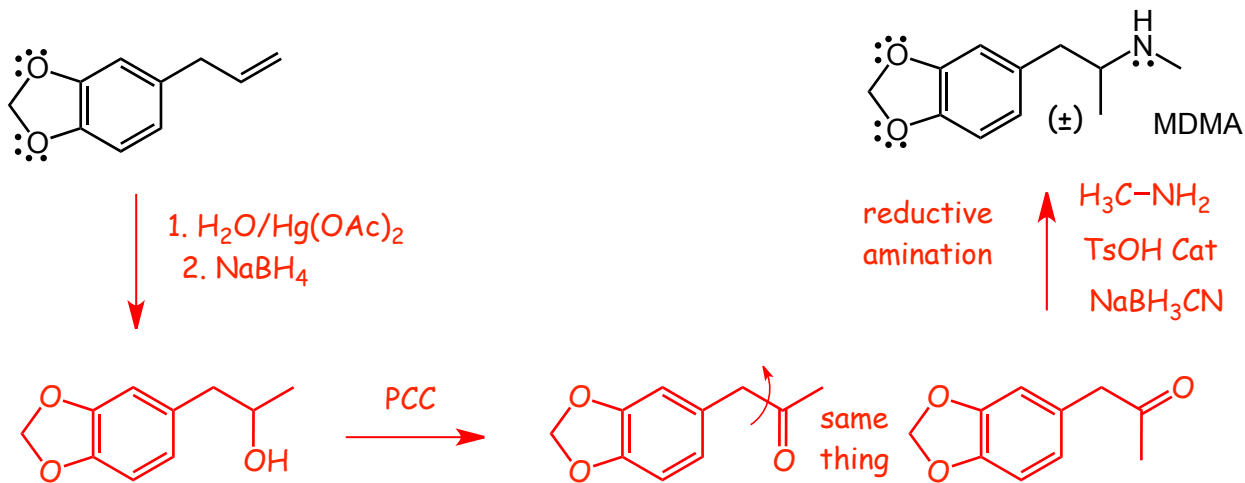
- Break bond "backwards", the benzene ring cannot carry a C=O, the carbonyl must be the fragment on the "right"
- You can use **either** the **direct** or the **indirect** reductive amination methods in a synthesis problem.

5 Some Final Synthesis Problems

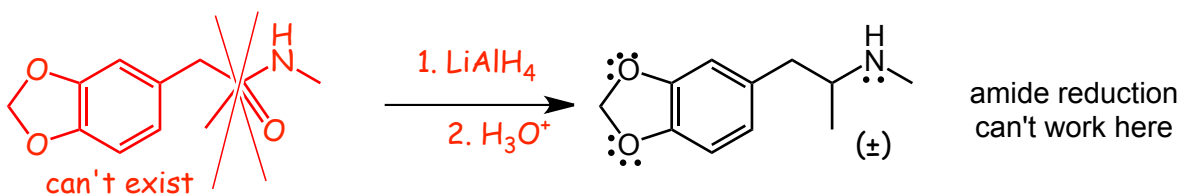
Common Methods of Synthesizing Amines:



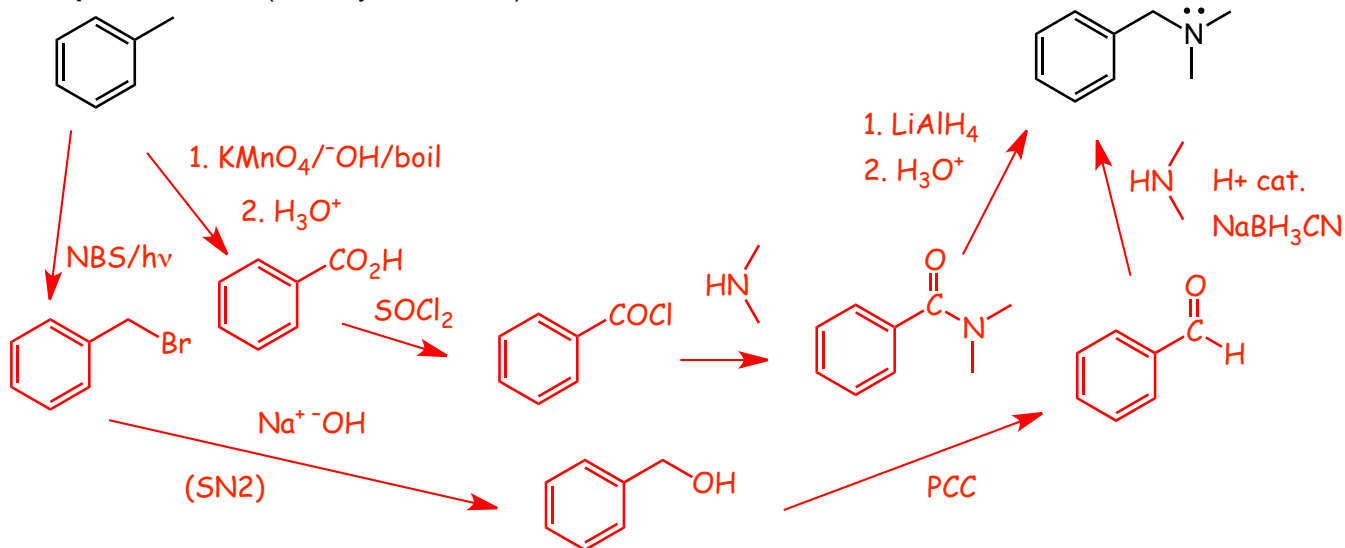
Example Problem 1 (difficulty = moderate):



- Many amines are biologically active, many act on the central nervous system, many drugs contain amine functional groups.
- MDMA = N, α -dimethyl-1,3-benzodioxole-5-ethenamine = Ecstasy : 5g ~ 20 years!!
- This is a secondary amine, which can in principle be synthesized either by reduction of an amide or by reductive amination, however, in this case **only reductive amination would work**.
- Trying to make the amine via amide reduction in this case obviously doesn't work because the relevant amide can't exist.

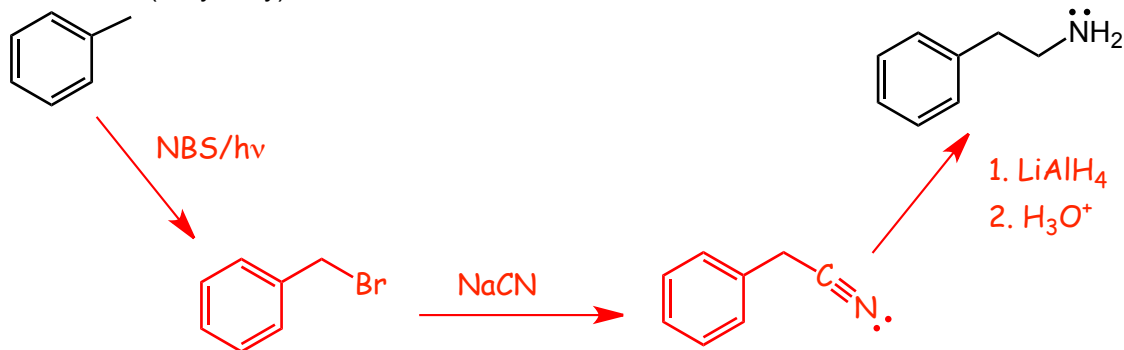


Example Problem 2 (difficulty = moderate):



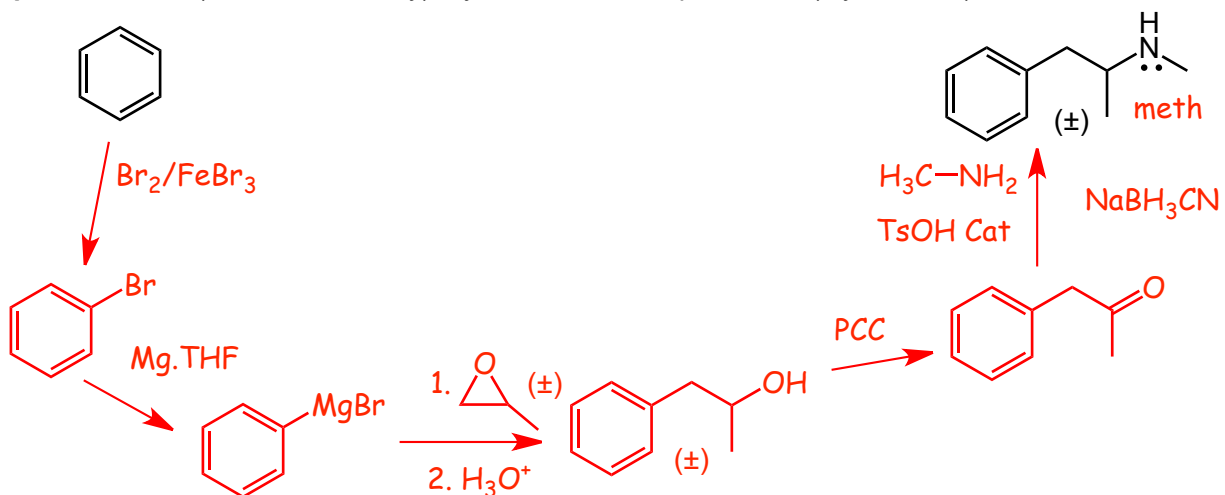
- In this case the strategy again is to identify that we **need to make a tertiary amine**, which requires either a **reductive amination** or **reduction of a tertiary amide**, in this case **either** of these two routes would work, as shown.

Example Problem 3 (fairly easy):



• In this case we need to make a **primary amine** and we need to **add one carbon atom** compared to the starting structure, the **nitrile reduction** method works well here

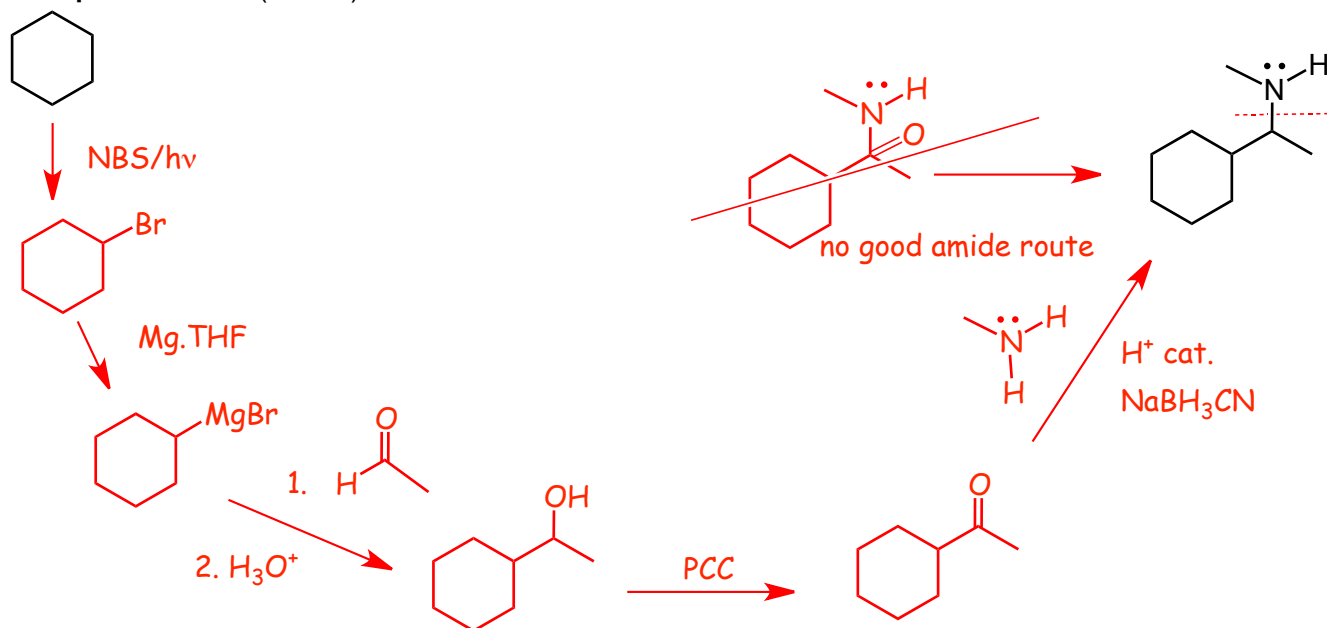
Example Problem 4 (moderate difficulty): Synthesize methamphetamine (crystal meth) from benzene



• Again, the strategy again is to note that we need to make a **tertiary amine**, which requires either a reductive amination or reduction of a tertiary amide, in this case **only the reductive amination works**.

• This is not the synthesis that Walter White used, this is just an organic chemistry exercise!

Example Problem 5 (difficult)

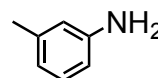
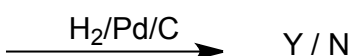
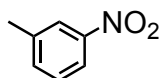
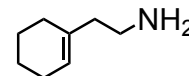
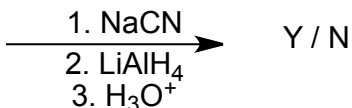
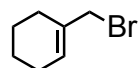
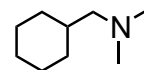
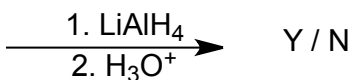
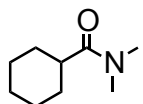


- This one is difficult mainly because it includes many steps, but the strategy is actually quite straightforward.
- We need to make a secondary amine, and there is no obvious amide reduction route, therefore we should think about reductive amination.
- We learned to do reductive aminations "backwards", and the obvious N-C bond to make is the one indicated by the dashed line.
- After that, it is straightforward reactions we learned earlier in the course.

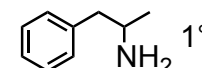
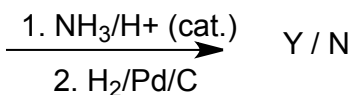
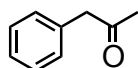
6 Summary of Reactions Involving Amines

You have seen **parts** of some of these reactions in earlier sections!

amine synthesis

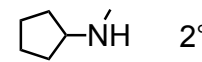
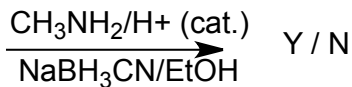


INDIRECT reductive amination

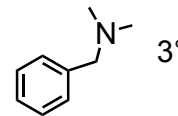
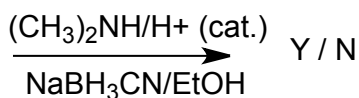
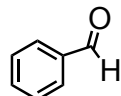


amphetamine

DIRECT reductive amination



2°



3°

Hofmann elimination

