Lecture # 9

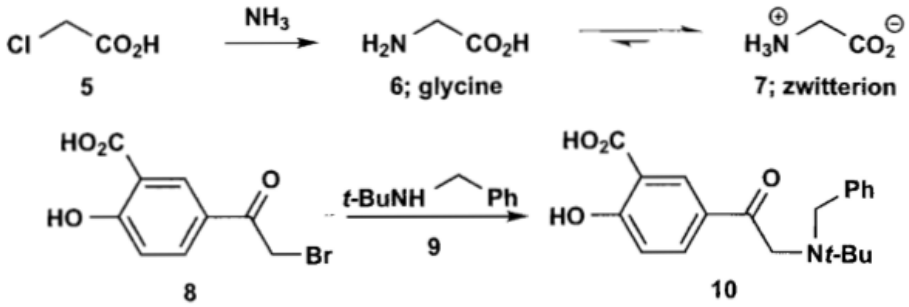
Amine Synthesis

Background Needed for this Chapter

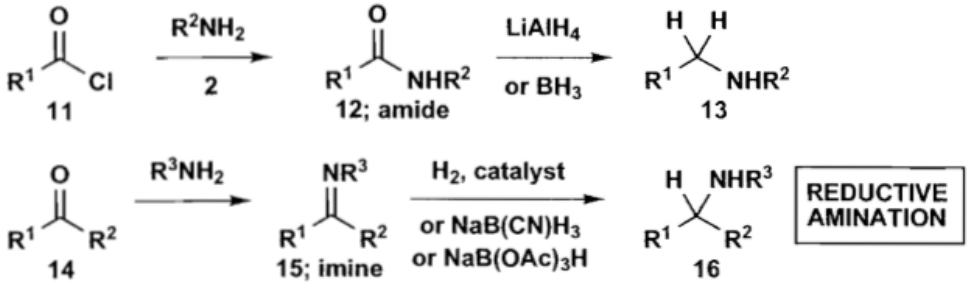
Nucleophilic Substitution at C=O with Loss of Carbonyl Oxygen.

Amine synthesis needs a separate chapter because the C–X disconnection **1a** used for ethers, sulfides and the like in chapter 4 is not suitable for amines. The problem is that the product of the first alkylation **2** is at least as nucleophilic as the starting material **1** (if not more so because of the electron-donating effect of each alkyl group) and further alkylation occurs giving the tertiary amine **3** or even the quaternary ammonium salt **4**. It is no use adding just one equivalent of MeI as the first formed product **1** will compete with the starting material **2** for MeI.

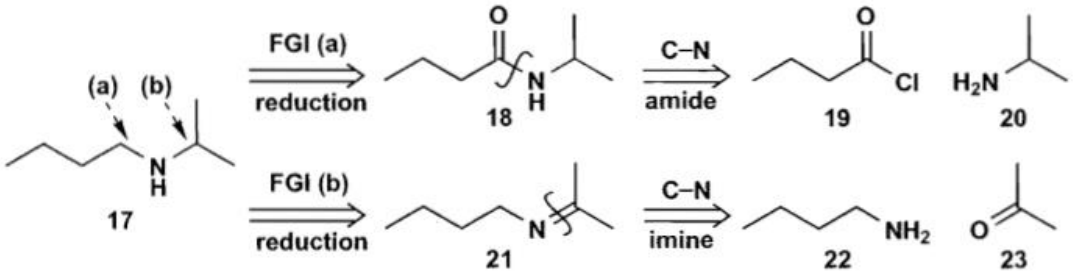
The simple alkylation of an amine with an alkyl halide can occasionally be used if the product is *less* nucleophilic than the starting material. This may be for electronic reasons: glycine **6** can be made by alkylation of ammonia with **5** as it exists mostly as the zwitterion **7** which no longer has a nucleophilic nitrogen. It may be for steric reasons: the alkylation of the α-bromoketone **8**, mentioned at the end of chapter 7, with the sterically hindered amine **9** gives a good yield of the even more sterically hindered amine **10** and no quaternary salt is formed. If the reaction is a cyclisation (chapter 7) it may also work well.



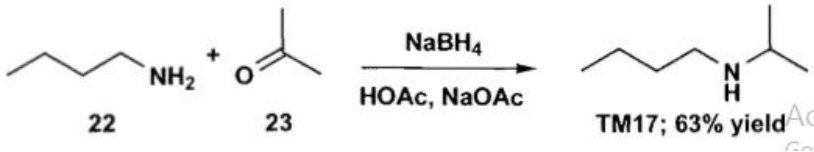
More general solutions come from the replacement of alkylations by reactions with carbonyl compounds. These generally occur once only and in many cases cannot occur twice as the products—amides **12** or imines **15** for example—are much less nucleophilic than the starting amine. The products are reduced to the target amines. The amide route is restricted to amines with a CH_2 group next to nitrogen **13** but the imine route is very general and is known as reductive amination.[1] It is the most important way to make amines and a recent survey showed that the majority of amines made in the pharmaceutical industry are made this way.



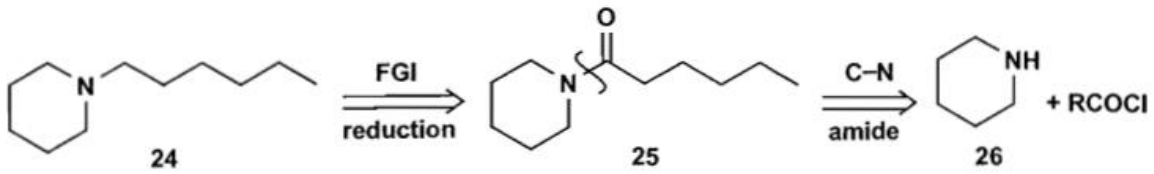
A preliminary FGI is needed before we apply the C–N disconnection. Amine **17** could be made from amide **18** or imine **21** and hence from two different primary amines **20** or **22** and two different carbonyl compounds **19** or **23**. These methods are very versatile.



One published synthesis of this amine **17** is by reductive amination.[2] Note that it is not necessary, nor usually desirable, to isolate the rather unstable imine as reduction with $NaB(CN)H_3$ or $NaB(OAc)_3H$ occurs under the conditions of imine formation.[3] Since the imine is in equilibrium with the starting materials, slightly acidic conditions must be used so that the protonated imine is reduced more rapidly than the aldehyde or ketone. These two reducing agents are stable down to about pH 5.

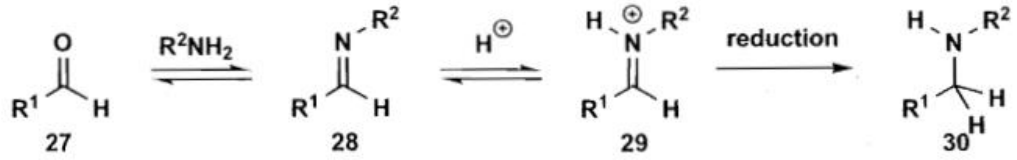


An example that has been made by the amide route is the cyclic amine **24**. Putting the carbonyl group on the side chain **25** allows us to use readily available piperidine **26** as a starting material. The synthesis[4] uses catalytic reduction to give **24** in 92% yield from the amide **25**.



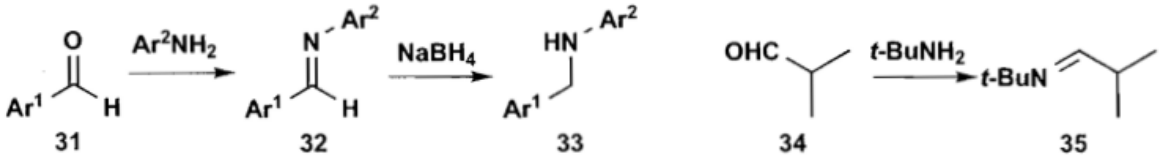
Reductive Amination

This most versatile of amine syntheses can be used to make primary, secondary or tertiary amines providing only that an imine can be formed with an aldehyde or ketone. But tertiary carbon atoms cannot be joined to nitrogen by reductive amination as a tertiary carbon atom cannot have a carbonyl group. The method works by selective reduction of the imine **28** in the presence of the aldehyde **27** or ketone. Catalytic hydrogenation reduces the imine **28** preferentially as the C=N bond of the imine is weaker than the C=O bond of the aldehyde or ketone.



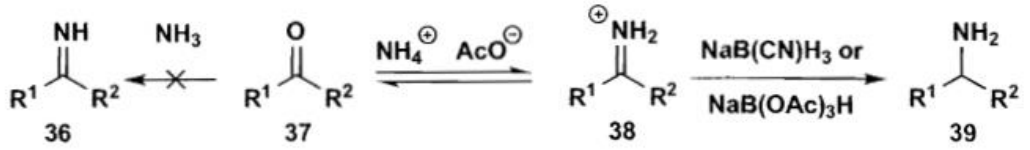
Normal nucleophilic reducing agents like $NaBH_4$ would reduce the more electrophilic aldehyde **27** in preference to the imine **28**. They must be used in slightly acidic solution (pH 5–6) so that the more electrophilic imine salt **29** is reduced. But reducing agents like $NaBH_4$ are unstable in acidic solution, decomposing to hydrogen gas. That is why modified borohydrides [$NaB(CN)H_3$ or $NaB(OAc)_3H$] are used. The electron-withdrawing CN or OAc groups reduce the nucleophilicity of the hydride(s) attached to boron, making it more selective towards the imine salt **29** and stabilising it in acid.

If the imine is stable enough to be isolated,[5] as with diaryl imines **32** or crowded aliphatic amines such as **35**, then $NaBH_4$ can be used for the reduction as there is no competition with unreacted aldehyde.



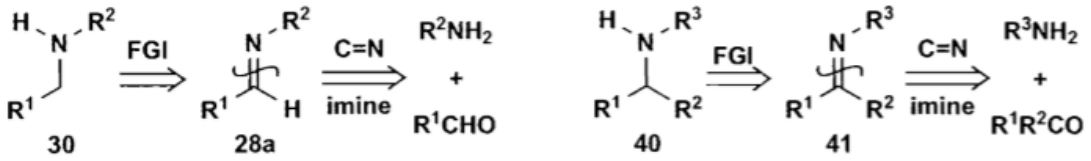
Primary Amines by Reductive Amination

The amine needed would be ammonia but unsubstituted imines **36** are very unstable. Ammonium acetate is usually used as the source of ammonia and to get the right pH for reductive amination with $NaB(CN)H_3$ or $NaB(OAc)_3H$. Either aldehydes **37**; $R^2 = H$ or ketones **37** can be used.



Secondary Amines by Reductive Amination

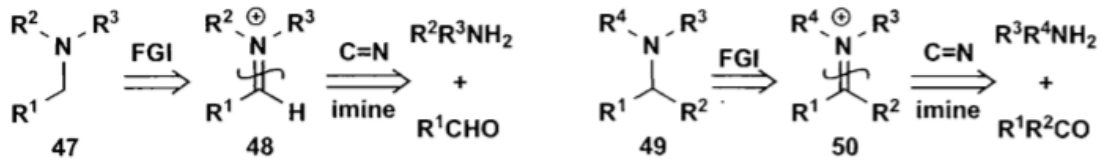
Examples **17, 30** and **33** show how this works with aldehydes. Ketones give amines such as **40** and both can be discovered just by using the disconnections **28a** and **41**. If one of the two carbon atoms joined to nitrogen is tertiary, that must be R^2 in **30** or R^3 in **40** as a tertiary centre cannot be set up by reduction.



Tertiary Amines by Reductive Amination

It may appear at first sight that tertiary amines cannot be made by reductive amination as an imine cannot be made. If a secondary amine such as piperidine **42** reacts with an aldehyde, the product is an enamine **44** not an imine. But reflect: the enamine **44** is formed by deprotonation of the imine salt **45** and that is the species we need for reaction with $NaB(CN)H_3$ or $NaB(OAc)_3H$ to give the tertiary amine **46**. So there is no problem.

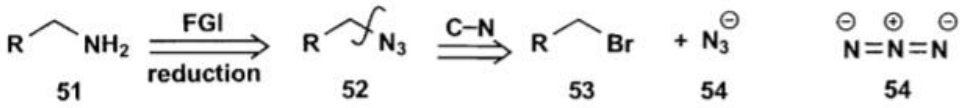
The disconnections are straightforward: just draw the iminium salt **48** or **50** after FGI on the tertiary amine **47** or **49** and disconnect the C=N bond in the usual way. You will often have three choices as to which iminium salt you draw. Only if one of the substituents on nitrogen is tertiary is that option not available. We explore that problem soon.



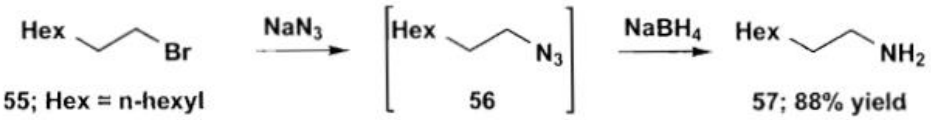
Other Ways to Make Amines

Primary Amines by Alkylation with Alkyl Halides

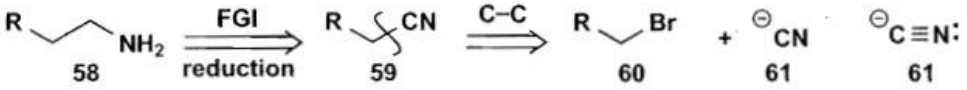
There is one method of direct alkylation of a nitrogen nucleophile. Preliminary FGI (with reduction in mind again) to an alkyl azide **52** allows C–N disconnection to the alkyl halide and azide ion **54**. This interesting species is linear and can slip into crowded molecules like a tiny dart. But there is a drawback: all azides are toxic and POTENTIALLY EXPLOSIVE.



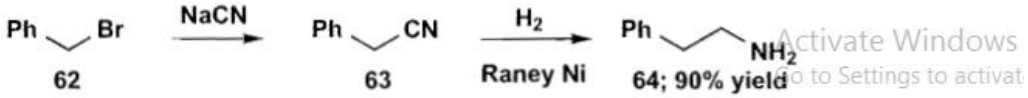
A salt such as sodium azide is used and the reduction can be carried out catalytically, with $NaBH_4$ or with Ph_3P in protic solution. Simple amines such as octylamine **57** can be made this way.[6] The azide **56** is not isolated but the whole reaction sequence carried out in the same aqueous solution to reduce the danger of an explosion.



A more deep-seated disconnection comes from a different FGI (using reduction yet again) with the idea that cyanide ion **61** should be the nucleophile. This makes a C–C bond rather than a C–N bond but does at least disconnect two atoms. Cyanide is an interesting structure: it has to be linear and it has a lone pair on nitrogen and a negative charge on carbon making it one of the rare genuine carbanions. There is again a drawback: cyanides are very toxic.

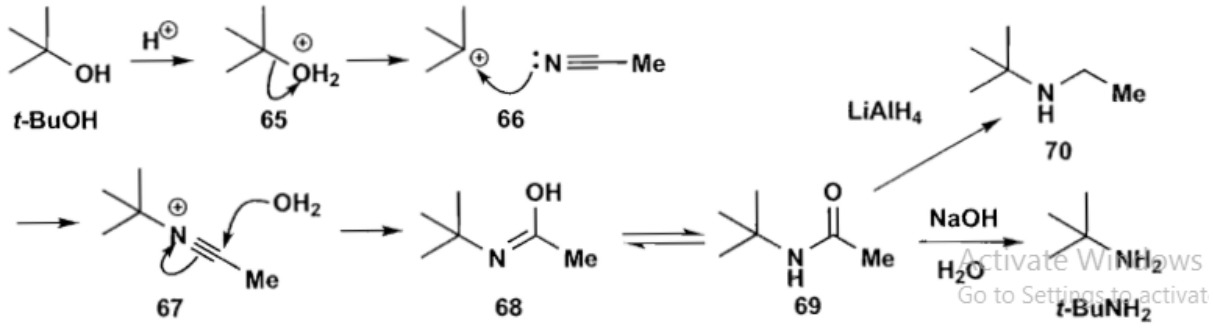


This method is particularly useful if the S_N2 reaction with cyanide is favourable as with benzyl bromide **62**. The reduction can be carried out with a variety of reagents: here hydrogenation over Raney nickel gives a good result.[7]



Joining Tertiary Carbon to Nitrogen

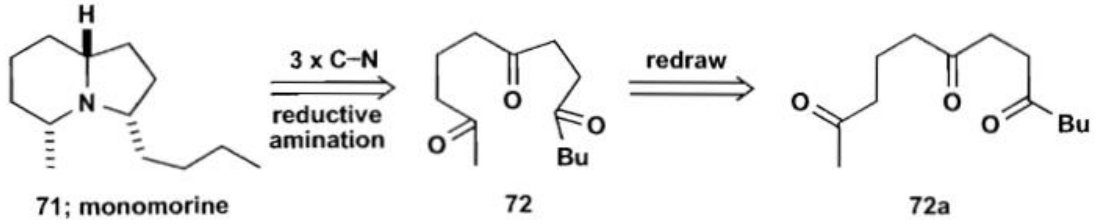
One way to do this uses aliphatic nitro compounds and is discussed in chapter 22. One direct method is the Ritter reaction[8] successful only for tertiary alkyl groups as it involves an S_N1 reaction. The nitrogen nucleophile is a nitrile—a notoriously weak nucleophile that needs a carbocation for reaction. If *t*-butanol and acetonitrile are mixed in acidic solution, the tertiary cation is attacked by the nitrile **66** and the amide **69** is formed. Hydrolysis of the amide gives *t*-$BuNH_2$ or reduction of the amide gives the secondary amine **70**. The nitrile is chosen according to the other alkyl group needed.



The Synthesis of Monomorine I

We end with an example that includes methods from this chapter as well as some revision and a reminder of stereochemistry. Monomorine I **71** is the trail pheromone of Pharaoh's ant (*Monomorium pharaonis*). These ants are pests in hospitals as they spread infections and they follow a trail of monomorine as they go about their evil work. Synthetic monomorine might be

used to lure the ants to their doom. It is a bicyclic amine and disconnection at all the C–N bonds with reductive amination in mind reveals a linear triketone, drawn more clearly as **72a**.



71; monomorine 72 72a

The chemists decided[9] that reacting **72** with ammonia was asking a bit much so they selected the nitro compound **73** as their starting material. The idea is that the nitro group will provide the central nitrogen atom after reduction. As we shall see in chapters 22 and 24 nitro groups stabilise carbanions well and conjugate addition of such anions works well. Hence the disconnection of **73**. Nitropentane **75** might be made by alkylation of the anion of nitropropane **75b** or by the method chosen, an S_N2 reaction of nitrite anion on bromopentane **75a**.

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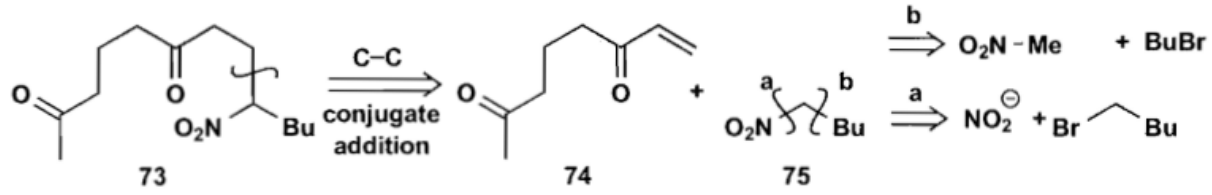
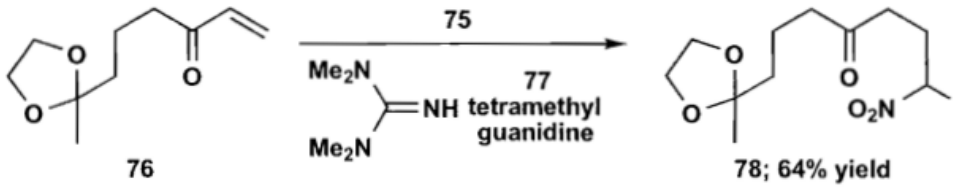


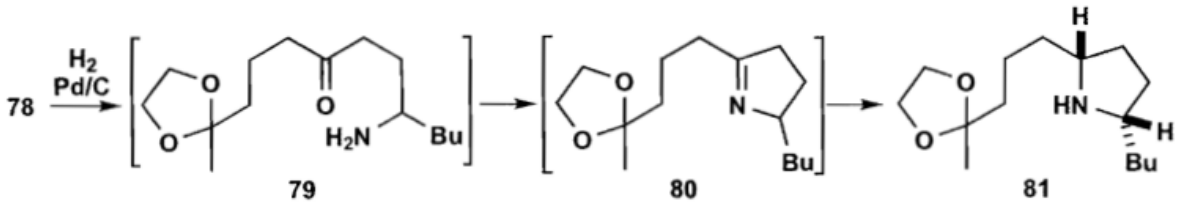
73 74 75

Now for the synthesis. The nitro compound **75** was made from bromopentane and a nitrite in DMSO, a good solvent for S_N2 reactions, and added to the enone **76**, an acetal derived from the diketone **74** with the strong base tetramethyl guanidine **77** as catalyst to give the partly protected form **78** of **73**. Now all is ready for the various reductions.



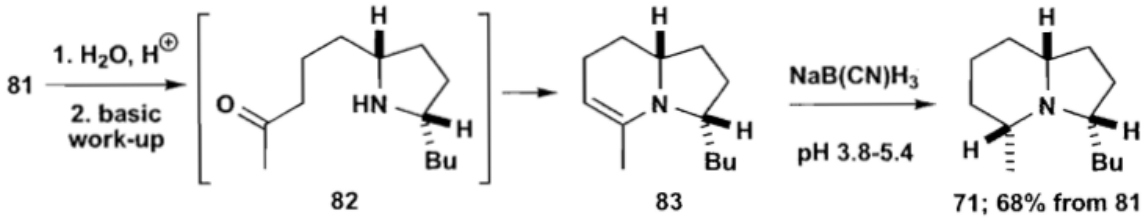
76 78; 64% yield

Catalytic reduction of the nitro group gives the amine **79** that cyclises instantly (chapter 7) to the imine **80** reduced in its turn to the cyclic amine **81**. When the virtually planar five-membered ring of the imine settles on the surface of the Pd/charcoal catalyst it can choose between the side of the ring with a hydrogen atom or the side with the butyl group. It chooses the less hindered side and so the second hydrogen atom is *cis* to the first and the stereochemistry is correct (compare **81** with **71**).



Now the acetal is hydrolysed to reveal the ketone **82** which again cyclises spontaneously to the enamine **83** forming a stable six-membered ring. This cyclic enamine can be isolated and

treated with $NaB(CN)H_3$ in slightly acidic solution. The enamine is thus in equilibrium with the iminium salt (compare **44** and **45**) and reduction again occurs on the less hindered side of the molecule, i.e. *cis* to the other two hydrogen atoms.



This elegant synthesis uses some of the methods of amine synthesis from this chapter and looks forward to the next chapter on protecting groups as well as later discussion of nitro group chemistry.