

Figure 23.3 Phase-transfer catalysis by a quaternary phosphonium salt. (a) At the beginning of the reaction, the ionic nucleophile (red) is soluble in the aqueous layer. (b) Rapid equilibration of the nucleophile with the counterion of the quaternary salt brings the nucleophile into the organic phase. (c) The nucleophile, now in the organic phase, can come into contact with the organic reactant, and a reaction occurs, forming the product and regenerating the phase-transfer catalyst.

23.7 ALKYLATION AND ACYLATION REACTIONS OF AMINES

The previous section showed that amines are *Brønsted bases*. Amines, like many other *Brønsted bases*, are also *nucleophiles* (Lewis bases). Three reactions of nucleophiles are:

1. S_N2 reaction with alkyl halides, sulfonate esters, or epoxides (Secs. 9.1, 9.4, 10.3, and 11.4)
2. addition to aldehydes, ketones, and α,β -unsaturated carbonyl compounds (Secs. 19.7, 19.11, and 22.8A)
3. nucleophilic acyl substitution at the carbonyl groups of carboxylic acid derivatives (Sec. 21.8)

This section covers or reviews reactions of amines that fit into each of these categories.

A. Direct Alkylation of Amines

Treatment of ammonia or an amine with an alkyl halide or other alkylating agent results in alkylation of the nitrogen.

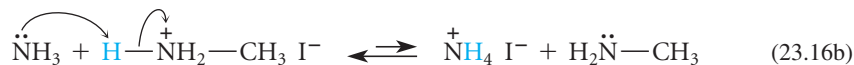
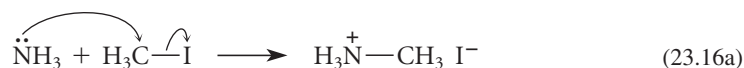


This process is an example of an S_N2 reaction in which the amine acts as the nucleophile.

The product of the reaction shown in Eq. 23.14 is an alkylammonium ion. If this ammonium ion has N—H bonds, further alkylations can take place to give a complex product mixture, as in the following example:

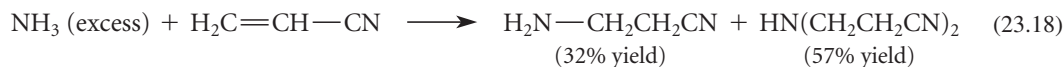
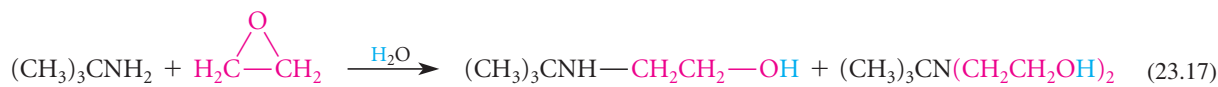


A mixture of products is formed because the methylammonium ion produced initially is partially deprotonated by the ammonia starting material. Because the resulting methylamine is also a good nucleophile, it too reacts with methyl iodide.



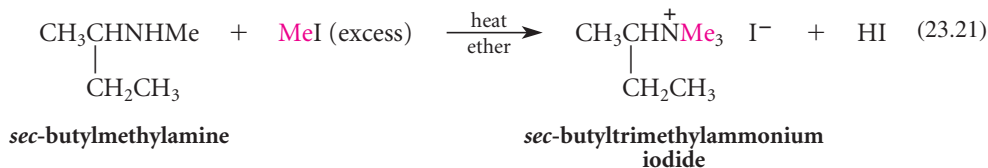
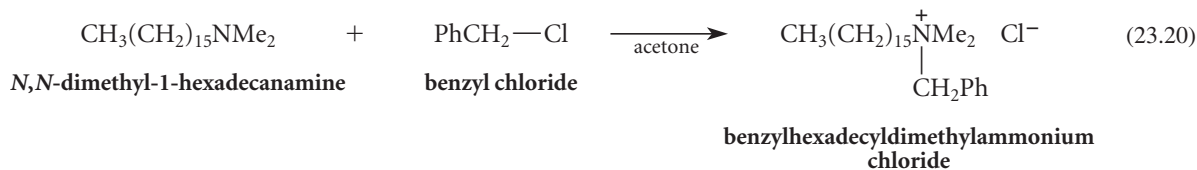
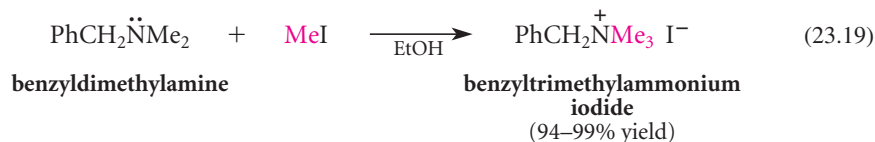
Analogous deprotonation–alkylation reactions give the other products of the mixture shown in Eq. 23.15 (see Problem 23.17).

Epoxides, as well as α,β -unsaturated carbonyl compounds and α,β -unsaturated nitriles, also react with amines and ammonia. As the following results show, multiple alkylation can occur with these alkylating agents as well.



In an alkylation reaction, the exact amount of each product obtained depends on the precise reaction conditions and on the relative amounts of starting amine and alkyl halide. Because a mixture of products results, the utility of alkylation as a preparative method for amines is limited, although, in specific cases, conditions have been worked out to favor particular products. Section 23.11 discusses other methods that are more useful for the preparation of amines.

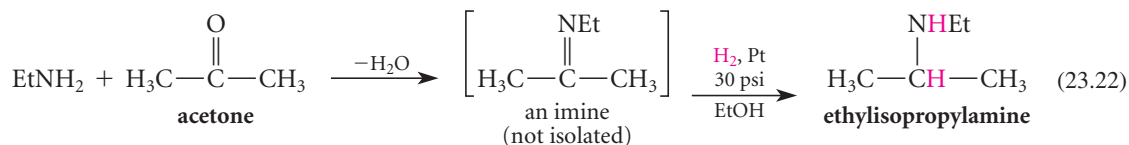
Quaternization of Amines Amines can be converted into quaternary ammonium salts with excess alkyl halide. This process, called **quaternization**, is one of the most important synthetic applications of amine alkylation. The reaction is particularly useful when especially reactive alkyl halides, such as methyl iodide or benzylic halides, are used.



Conversion of an amine into a quaternary ammonium salt with excess methyl iodide (as in Eqs. 23.19 and 23.21) is called **exhaustive methylation**.

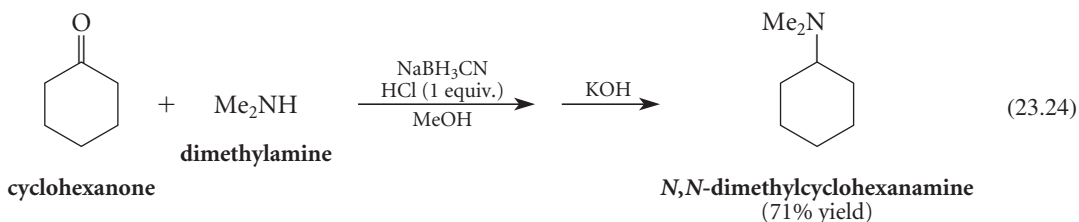
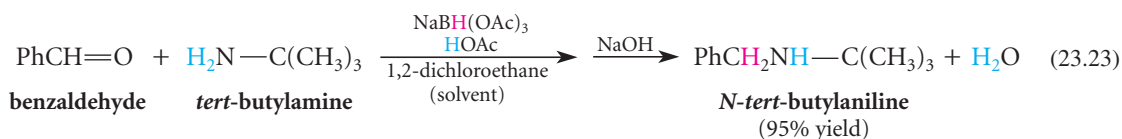
B. Reductive Amination

When primary and secondary amines react with either aldehydes or ketones, they form imines and enamines, respectively (Sec. 19.11). In the presence of a reducing agent, imines and enamines are reduced to amines.



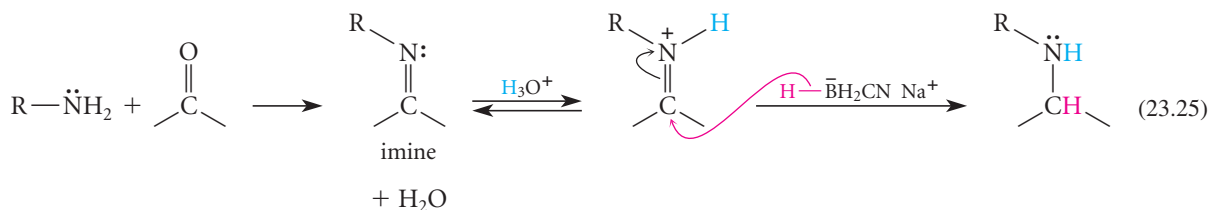
Reduction of the C=N double bond is analogous to reduction of the C=O double bond (Sec. 19.8). Notice that the imine or enamine does not have to be isolated, but is reduced within the reaction mixture as it forms. *Because imines and enamines are reduced more rapidly than carbonyl compounds*, reduction of the carbonyl compound is not a competing reaction.

The formation of an amine from the reaction of an aldehyde or ketone with another amine and a reducing agent is called **reductive amination**. Two hydride reducing agents, sodium triacetoxyborohydride, NaBH(OAc)₃, and sodium cyanoborohydride, NaBH₃CN, find frequent use in reductive amination.



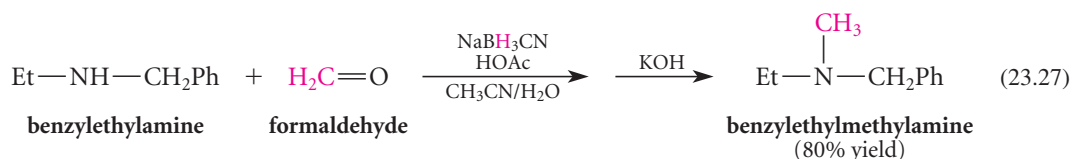
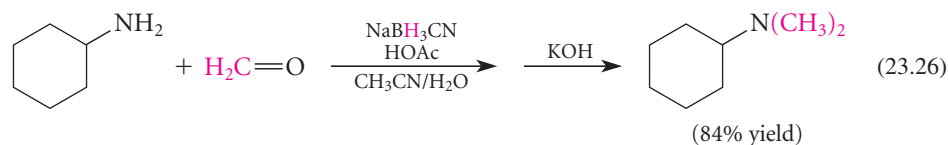
Both sodium triacetoxyborohydride and sodium cyanoborohydride are commercially available, easily handled solids, and sodium cyanoborohydride can even be used in aqueous solutions above pH > 3. Reductive amination with NaBH₃CN is known as the **Borch reaction**, after Richard F. Borch, a professor of medicinal chemistry and molecular pharmacology at Purdue University, who discovered and developed the reaction while he was a professor of chemistry at the University of Minnesota in 1971. Like NaBH₄ reductions, the Borch reduction requires a protic solvent or one equivalent of acid. A proton source is also required for reduction with sodium triacetoxyborohydride. In some cases, the water generated in the reaction is adequate for this purpose, and in other situations, a weak acid can be added. (Acetic acid serves this role in Eq. 23.23.)

Reductive amination, like catalytic hydrogenation, typically involves the imines or enamines and their conjugate acids as intermediates.



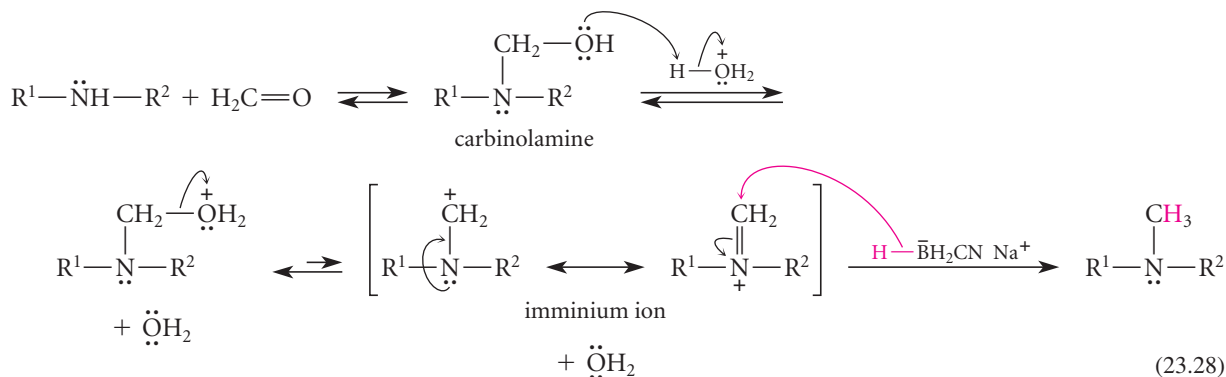
The success of reductive amination depends on the discrimination by the reducing agents between the imine intermediate and the carbonyl group of the aldehyde or ketone starting material. Each reagent is a sodium borohydride (NaBH_4) derivative in which one or more of the hydrides have been substituted with electron-withdrawing groups ($-\text{OAc}$ or $-\text{CN}$). The polar effect of these groups reduces the effective negative charge on the hydride and, as a result, each reagent is less reactive than sodium borohydride itself. Each reagent is effectively “tuned” to be just reactive enough to reduce imines, but not reactive enough to reduce aldehydes or ketones. When NaCNBH_3 is used in protic solvents, hydrogen-bond donation by the solvent to the imine nitrogen (which is more basic than a carbonyl oxygen) catalyzes the reduction.

Formaldehyde can be reductively aminated with primary and secondary amines using the Borch reaction. This provides a way to introduce methyl groups to the level of a tertiary amine:

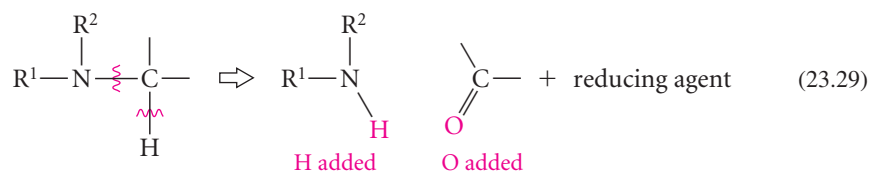


(Quaternization does not occur in these reactions. Why?)

Neither an imine nor an enamine can be an intermediate in the reaction of a secondary amine with formaldehyde (Eq. 23.27). (Why?) In this case a small amount of a cationic intermediate, an *iminium ion*, is formed in solution by protonation of a carbinolamine intermediate and loss of water. The iminium ion, which is also a carbocation, is rapidly and irreversibly reduced by its reaction with hydride.



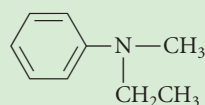
Suppose you want to prepare a given amine and want to determine whether reductive amination would be a suitable preparative method. How do you determine the required starting materials? Adopt the usual strategy for analyzing a synthesis: Start with the target molecule and mentally reverse the reductive amination process. Mentally break one of the C—N bonds and replace it on the nitrogen side with an N—H bond. On the carbon side, drop a hydrogen from the carbon and add a carbonyl oxygen.



As this analysis shows, the target amine must have a hydrogen on the “disconnected” carbon. This process is applied in Study Problem 23.3.

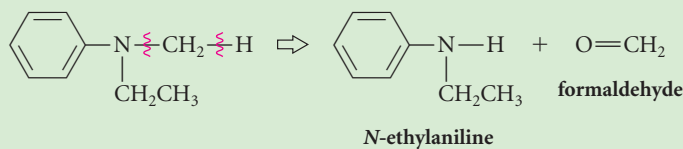
Study Problem 23.3

Outline a preparation of *N*-ethyl-*N*-methylaniline from suitable starting materials using a reductive amination sequence.



N-ethyl-*N*-methylaniline

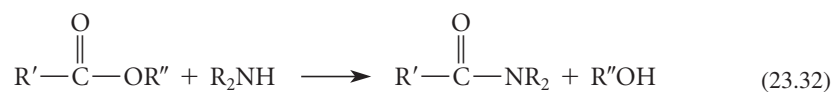
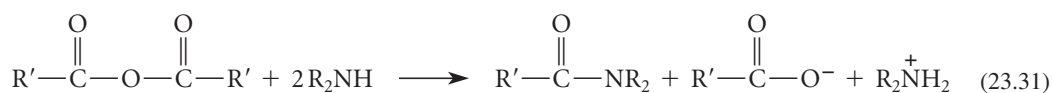
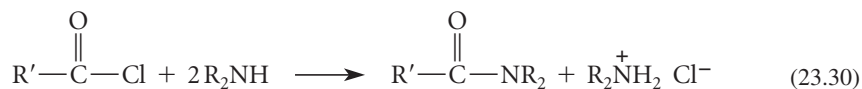
Solution Either the *N*-methyl or *N*-ethyl bond can be used for analysis. (The *N*-phenyl bond cannot be used because the carbon in the C—N bond has no hydrogen.) We arbitrarily choose the N—CH₃ bond and make the appropriate replacements as indicated in Eq. 23.29 to reveal the following starting materials:



Thus, treatment of *N*-ethylaniline with formaldehyde and NaBH₃CN should give the desired amine. (See Problem 23.14 on p. 1136.)

C. Acylation of Amines

Amines can be converted into amides by reaction with acid chlorides, anhydrides, or esters. These reactions are covered in Sec. 21.8.



In this type of reaction, a bond is formed between the amine and a carbonyl carbon. These are all examples of *acylation*: a reaction involving the transfer of an *acyl group*.

Recall that the reaction of an amine with an acid chloride or an anhydride requires either *two equivalents* of the amine or one equivalent of the amine and an additional equivalent of another base such as a tertiary amine or hydroxide ion. These and other aspects of amine acylation can be reviewed in Sec. 21.8.

PROBLEMS

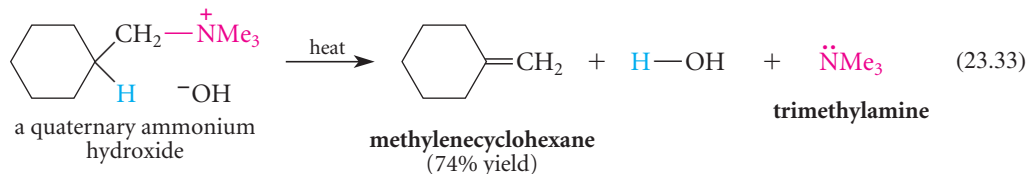
- 23.13 Suggest two syntheses of *N*-ethylcyclohexanamine by reductive amination.
- 23.14 Outline a second synthesis of *N*-ethyl-*N*-methylaniline (the target molecule in Study Problem 23.3) by reductive amination.
- 23.15 Outline a synthesis of the quaternary ammonium salt $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{Ph} \text{ Br}^-$ from each of the following combinations of starting materials.
 (a) dimethylamine and any other reagents (b) benzylamine and any other reagents
- 23.16 (a) A chemist Caleb J. Cookbook heated ammonia with bromobenzene expecting to form tetraphenylammonium bromide. Can Caleb expect this reaction to succeed? Explain.
 (b) What type of catalyst might be used to bring about this reaction under relatively mild conditions? (See Sec. 23.11C.)
- 23.17 Continue the sequence of reactions in Eqs. 23.16a–c to show how trimethylammonium iodide is formed as one of the products in Eq. 23.15.
- 23.18 Outline a preparation of each of the following from an amine and an acid chloride.
 (a) *N*-phenylbenzamide (b) *N*-benzyl-*N*-ethylpropanamide

23.8

HOFMANN ELIMINATION OF QUATERNARY AMMONIUM HYDROXIDES

The previous section discussed ways to *make* carbon–nitrogen bonds. In these reactions, amines react as *nucleophiles*. The subject of this section is an elimination reaction used to *break* carbon–nitrogen bonds. In this reaction, which involves *quaternary ammonium hydroxides* ($\text{R}_4\text{N}^+ \text{ } ^-\text{OH}$) as starting materials, amines act as *leaving groups*.

When a quaternary ammonium hydroxide is heated, a β -elimination reaction takes place to give an alkene, which distills from the reaction mixture.



This type of elimination reaction is called a **Hofmann elimination**, after August Wilhelm Hofmann (1818–1892), a German chemist who became professor at the Royal College of Chemistry in London and later, at the University of Berlin. Hofmann was particularly noted for his work on amines.

A quaternary ammonium hydroxide used as the starting material in Hofmann eliminations is formed by treating a quaternary ammonium salt with silver hydroxide (AgOH), which is essentially a hydrated form of silver (I) oxide (Ag_2O).

