Chapter 8

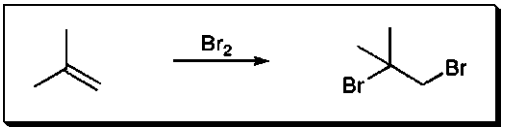
Moving Forward

Organic chemistry is a very mature science upon which numerous disciplines depend. These disciplines range from pharmaceuticals and food science to agrochemicals and material science. In approaching organic chemistry, the chapters thus far focused on utilizing the acid/base properties of organic molecules, in conjunction with the electronic properties of associated functional groups, to rationalize chemical reactions through the movement of electrons. This technique of arrow pushing was presented as an alternative to the memorization of the numerous **name reactions** available to organic chemists today. However, along with the treatments of various **mechanistic components** of organic reactions, this book includes introductions to many of the fundamental reactions studied in introductory organic chemistry courses. In this chapter, these reactions are revisited in order to emphasize that, through the application of arrow pushing, a broader and deeper understanding of organic chemistry can be derived.

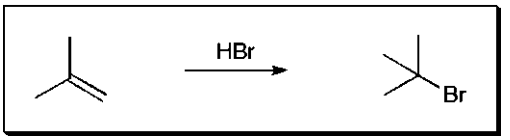
8.1 FUNCTIONAL GROUP MANIPULATIONS

Functional group manipulations involve the transformation of one functional group to another with no additional changes to the core molecular structure. Throughout this book, many different functional groups were presented beginning with those illustrated in Figure 1.3 and continuing through each chapter and their associated problem sets. Considering olefins, among the simplest of functional groups, transformations into alkyl halides were presented in Chapter 7. Specific examples, illustrated in Schemes 8.1 and 8.2, included both the addition of halogens across double bonds as well as the application of Markovnikov's rule when adding acids across double bonds.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 8.1 *Addition of bromine across a double bond.*



Scheme 8.2 *Markovnikov addition of hydrobromic acid across a double bond.*

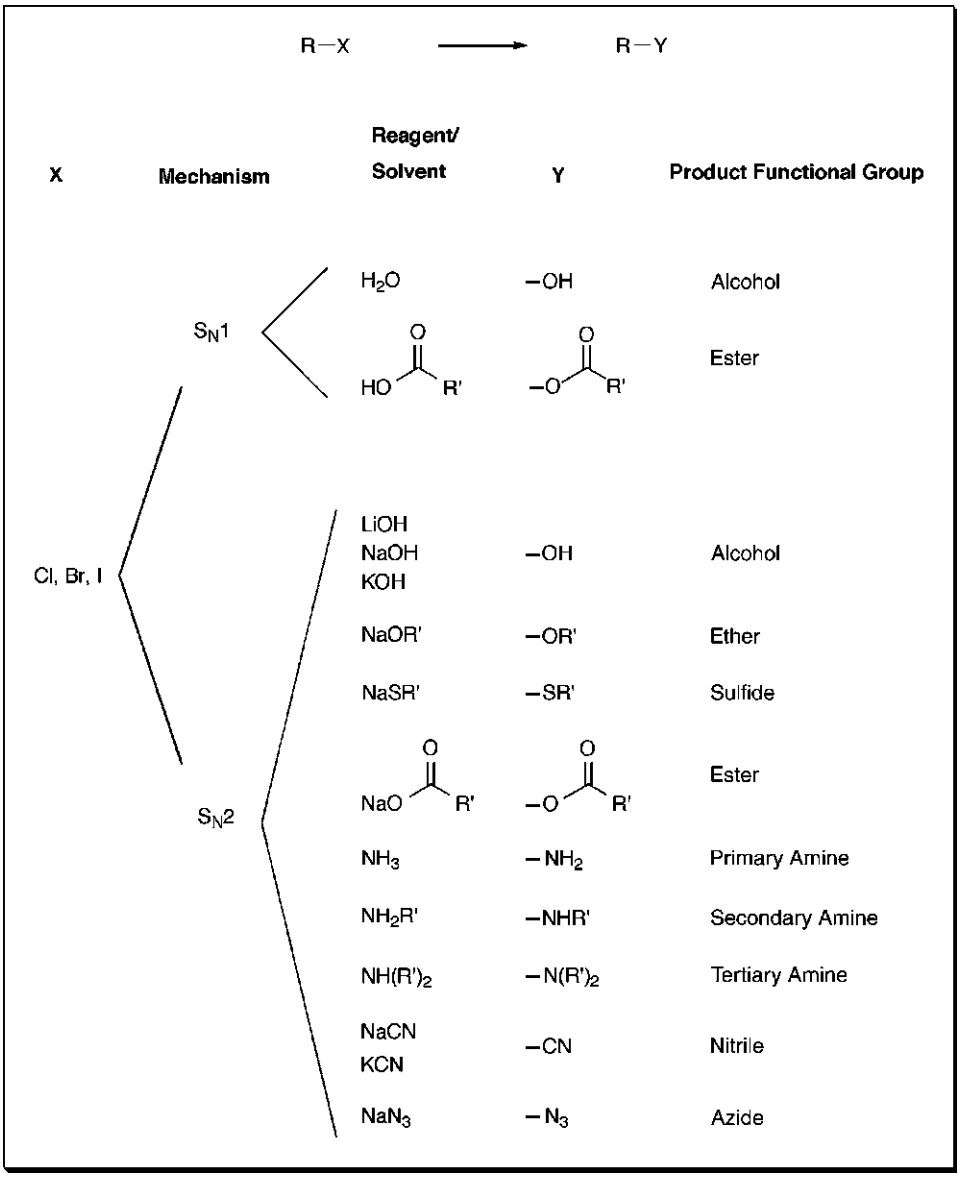
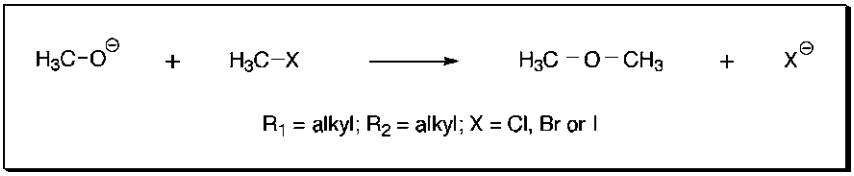


Figure 8.1 *Functional groups available from alkyl halides via S_N1 and S_N2 mechanisms.*



Scheme 8.3 *Conversion of alcohols to ethers—the Williamson ether synthesis.*

While the examples presented in Schemes 8.1 and 8.2 illustrate only the formation of **alkyl bromides**, it is important to recognize that halogens can be replaced through **nucleophilic displacements**. These displacements can occur via either S_N1 or S_N2 mechanisms. Regarding S_N1 reactions, ionization generally occurs under **solvolytic conditions**, limiting the nucleophile to the solvent used. In the case of S_N2 reactions, the only limiting factors relate to the relative nucleophilicities of the incoming nucleophiles compared to those of the leaving groups. Thus, as illustrated in Figure 8.1, alkyl halides can be converted into a wide variety of useful functional groups.

Upon further examination of the **functional group transformations** summarized in Figure 8.1, there are a number of additional conversions applicable to the product functional groups. Among these are the conversions of alcohols to ethers illustrated in Scheme 8.3.

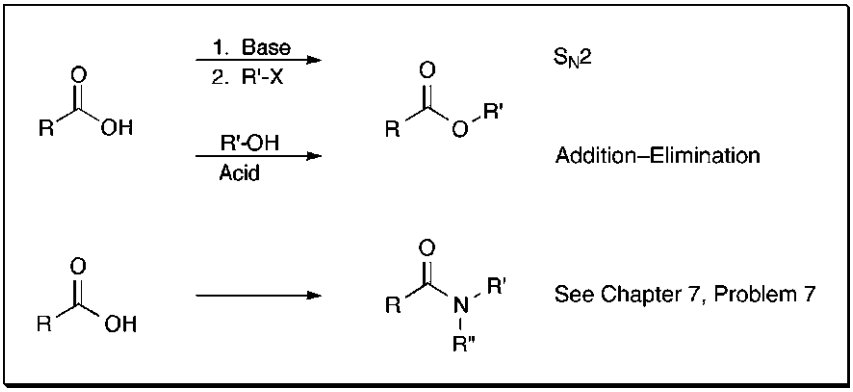


Figure 8.2 *Transformations of carboxylic acids to esters and amides.*

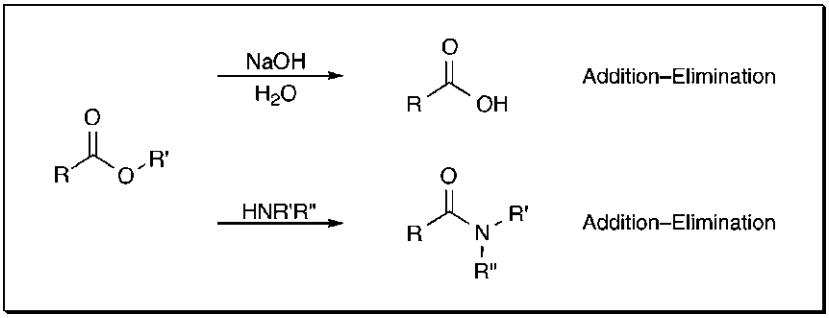


Figure 8.3 *Transformations of esters to carboxylic acids and amides.*

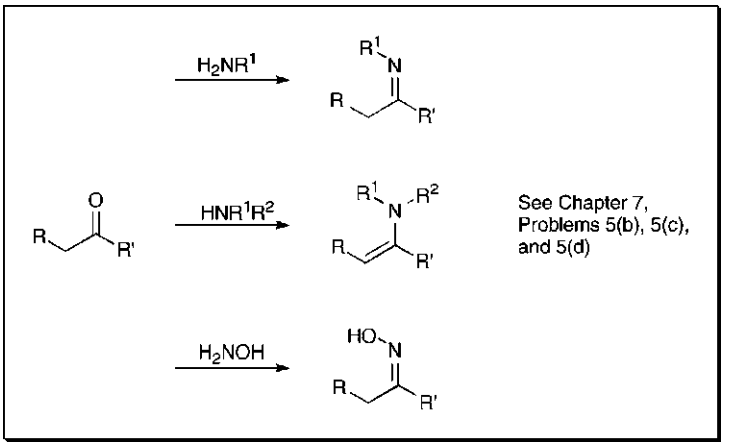


Figure 8.4 *Transformations of aldehydes and ketones to imines, oximes, and enamines.*

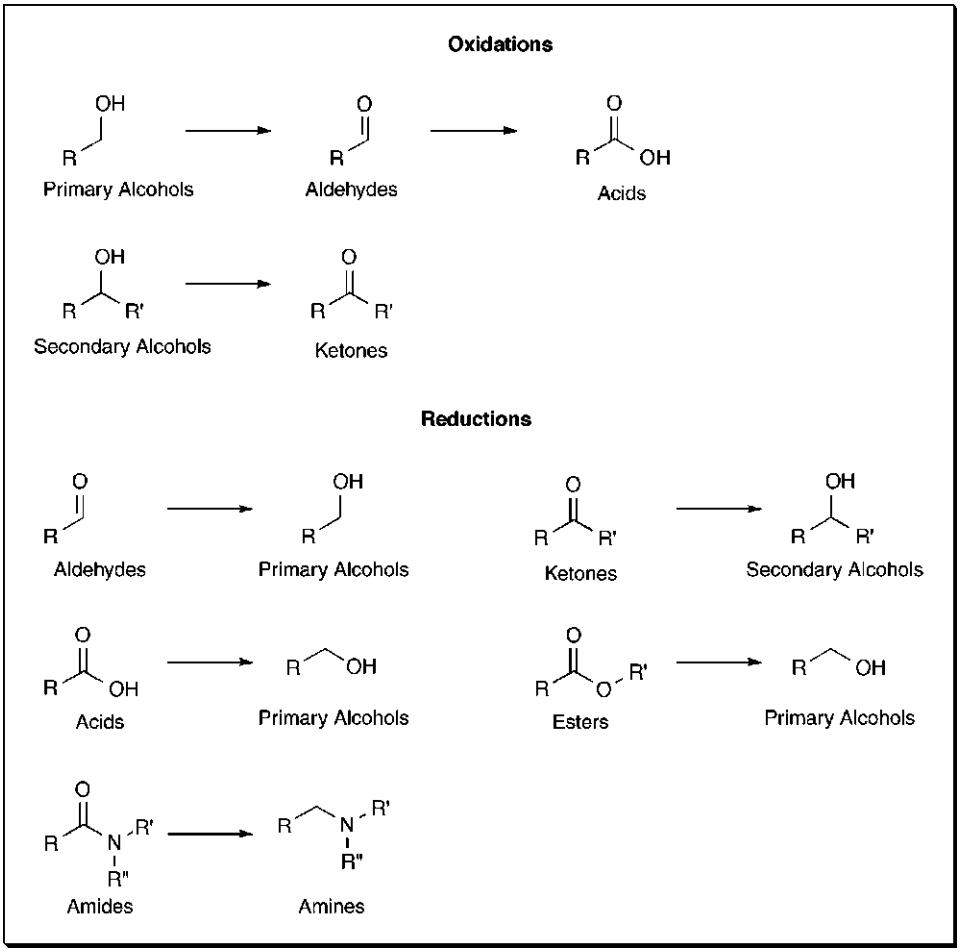


Figure 8.5 *Oxidative and reductive conversions of functional groups.*

Additionally, transformation of carboxylic acids to esters and amides are illustrated in Figure 8.2. The related conversions of esters to acids and amides are shown in Figure 8.3. Finally, transformations of aldehydes and ketones to **imines**, **oximes**, and **enamines** are summarized in Figure 8.4.

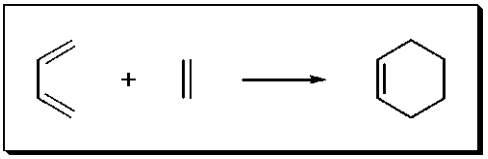
In addition to the functional group transformations discussed in this book, there are many more that depend on **oxidative** and **reductive mechanisms**. These mechanisms are covered in depth in introductory organic chemistry courses and will not be presented here in detail. As an introduction, Figure 8.5 summarizes such transformations, which include the **oxidation** of alcohols to aldehydes, ketones, and carboxylic acids. Likewise, Figure 8.5 introduces the reductive transformations of aldehydes, ketones, and carboxylic acids to alcohols as well as amides to amines. As will be revealed through further coursework, additional functional group manipulations are available and rationalized utilizing the principles of arrow pushing discussed throughout this book.

8.2 NAME REACTIONS

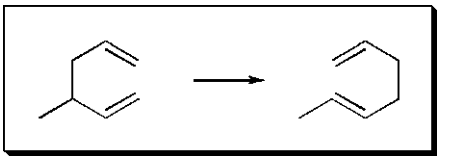
While the focus of the chapters to this point was to introduce the technique of arrow pushing as a strategy for understanding the general principles of organic chemistry, some name reactions were mentioned. These name reactions were presented for two reasons. First, their underlying mechanisms highlight the principles of focus in the chapters in which they were presented. Second, they represent important and fundamental tools for general organic chemistry transformations. While the focus of this book advocates development of a full understanding of organic reaction mechanisms as a means of learning the subject, once this understanding is achieved, recognition of these reactions by name presents a significant shortcut to the description of synthetic processes. The name reactions presented in this book are reviewed in the following paragraphs.

In the introductory chapters of this book, **electrocyclic reactions** were presented as early examples utilizing arrow pushing techniques. These were selected because of their simplicity relating to the nonionic character of the reactions. Specifically, the acid–base properties of the starting molecules are of lesser importance as the reactions illustrated proceed through the movement of electrons through the existing systems. The reactions illustrated include the **Diels–Alder reaction** (Scheme 8.4), the **Cope rearrangement** (Scheme 8.5), and the **Claisen rearrangement** (Scheme 8.6). These and related electrocyclic reactions, depending upon the same mechanistic principles, are covered in depth in introductory organic chemistry coursework.

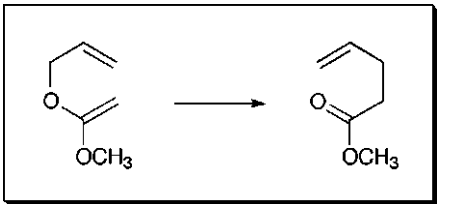
The above-described rearrangement reactions are not the only ones presented within this book. In addition to electrocyclic rearrangements, some rearrangements dependent upon ionic mechanisms were presented. These include the pinacol rearrangement



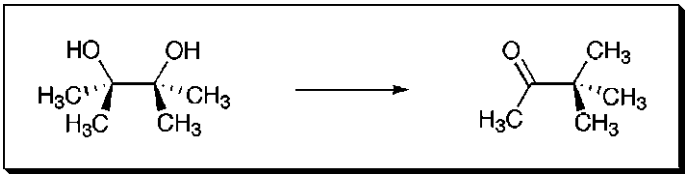
Scheme 8.4 *Diels–Alder reaction.*



Scheme 8.5 *Cope rearrangement.*



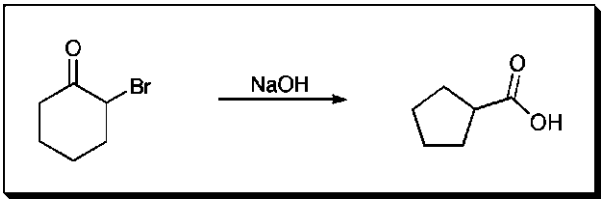
Scheme 8.6 *Claisen rearrangement.*



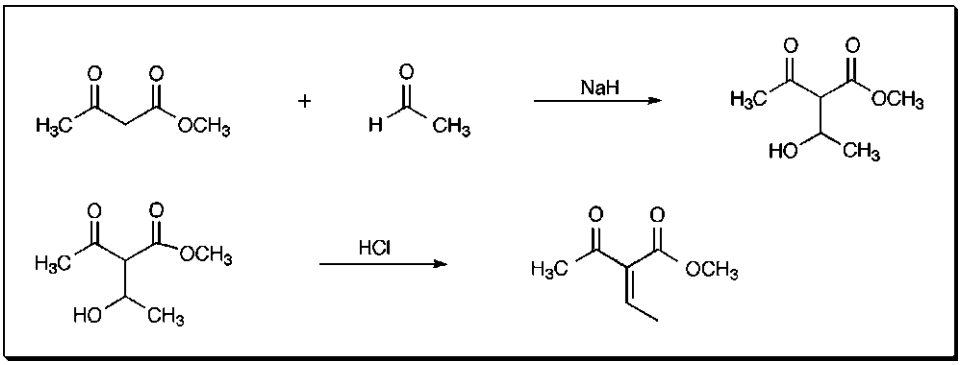
Scheme 8.7 *Pinacol rearrangement.*

(Scheme 8.7) and the **Favorskii rearrangement** (Scheme 8.8). These examples were presented within the context of alkyl shifts and the related hydride shifts. Through these examples, the concepts of **ionic stability** and **spontaneous ionic transformations** to more stable ionic species were explored. These concepts are especially prevalent when examining solvolysis-mediated processes where S_N1 and E1 mechanisms are involved.

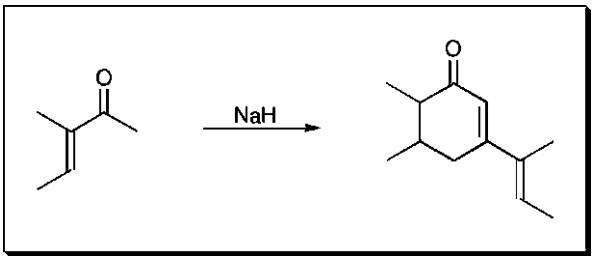
Moving from rearrangements, condensation reactions were also presented. Condensation reactions occur when two reactive species condense with one another forming a new compound. The first was the **aldol condensation** (Scheme 8.9). Later, a more complex application of the aldol condensation was presented in the form of the **Robinson annulation** (Scheme 8.10). For both of these reactions, the underlying lessons relate to the ability to induce reactions and incorporate substitutions at carbon atoms adjacent to carbonyl groups. Similar reactivities of such carbon atoms can be utilized for **alkylation** (S_N2) and **acylation** (addition–elimination) reactions as illustrated in Scheme 8.11.



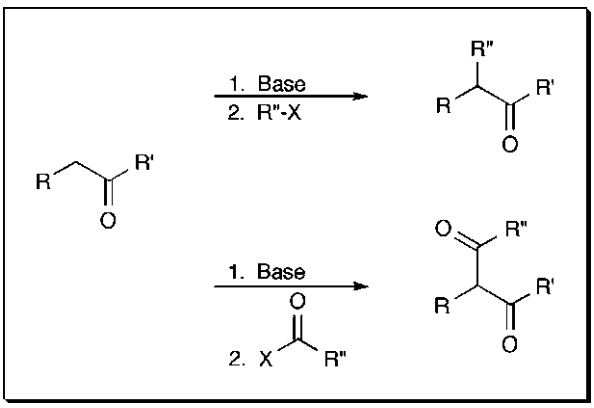
Scheme 8.8 *Favorskii rearrangement.*



Scheme 8.9 *Aldol condensation.*

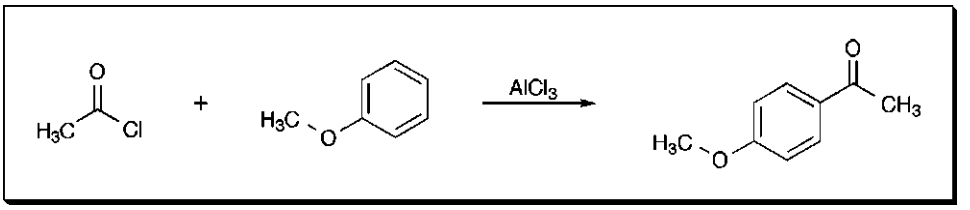


Scheme 8.10 *Robinson annulation.*



Scheme 8.11 *Alkylation and acylation reactions adjacent to carbonyls.*

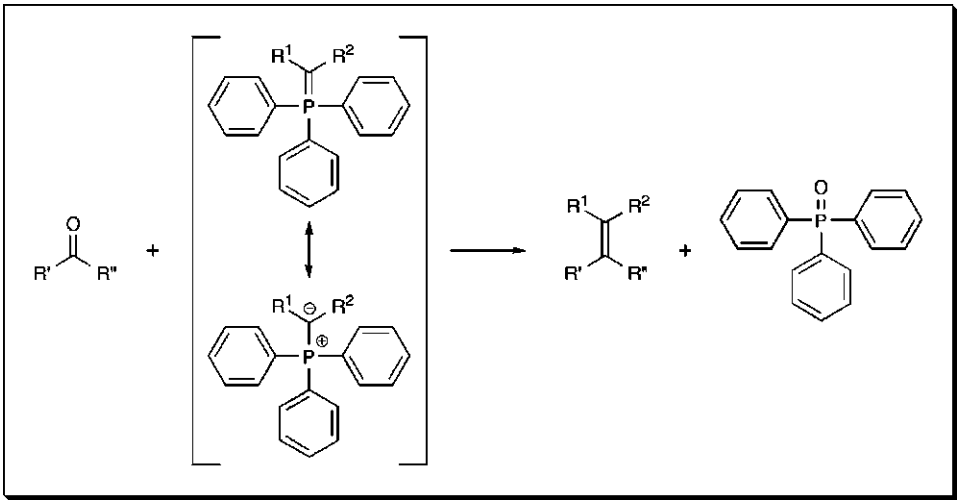
Regarding acylation reactions, acylation of alcohols produces esters and acylation of amines produces amides Both of these transformations are illustrated in Figure 8.2. These, in addition to the introduction of **acyl groups** adjacent to carbonyls (Scheme 8.11), only hint at the breadth of related acylation reactions available and useful in organic synthesis. One additional reaction is the **Friedel–Crafts acylation** illustrated in Scheme 8.12. Through this transformation, extended functionalization of **aryl groups** becomes accessible.



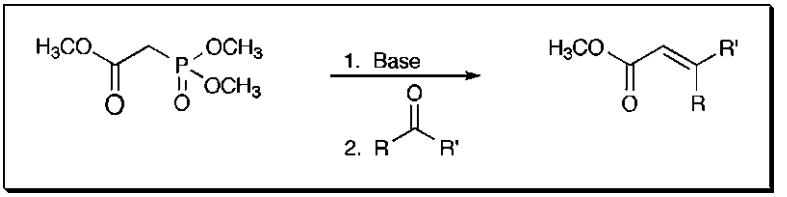
Scheme 8.12 *Friedel–Crafts acylation*

While mechanistically distinct, the aldol condensation and the Friedel–Crafts acylation result in the incorporation of additional carbon atoms to the starting structure. This type of extension is extremely important when planning the synthesis of more complex organic molecules. To this end, the greater the number of available reactions, the greater the versatility in synthetic planning.

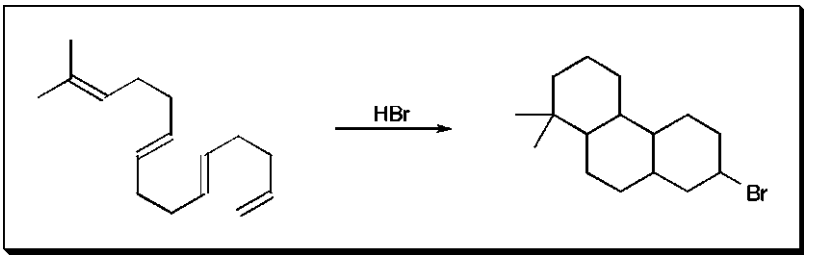
Thus far, the aldol condensation was presented as a method for adding carbon atoms adjacent to carbonyl groups, and the Friedel–Crafts acylation was presented as useful for the addition of carbon atoms to **aromatic rings**. In addition to these reactions, the **Wittig reaction** (Scheme 8.13) and the **Horner–Emmons reaction** (Scheme 8.14) were



Scheme 8.13 *Wittig reaction.*



Scheme 8.14 *Horner–Emmons reaction.*



Scheme 8.15 *Cation–π cyclization.*

presented as capable of replacing the carbon–oxygen double bond of aldehydes and ketones with carbon–carbon double bonds. The new extensions can be simple or functionalized. Additionally, the newly formed double bonds can be modified through addition of halogens or acids.

One final example of a name reaction presented within the text of this book is the **cation–π cyclization**. This reaction, illustrated in Scheme 8.15, returns to the previously described reaction classes that include electrocyclic reactions and rearrangements. Inclusion of this reaction complements the various nucleophiles used throughout the examples of this book by highlighting the nucleophilic nature of double bonds.

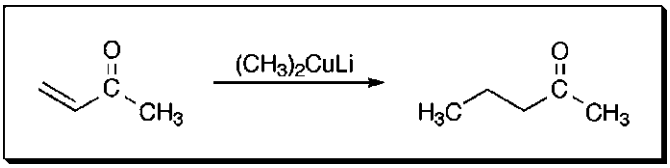
As will be revealed through further coursework, many more name reactions are available. Furthermore, new reactions, yet to be named, are continually being discovered. In approaching all of these reactions, it is imperative to develop mechanistic understandings in order to correctly apply the reactions within the scope of their utilities and limitations. In this respect, arrow pushing presents a valuable approach to the derivation of mechanistic understanding prior to committing the reaction names to memory.

8.3 REAGENTS

Throughout this book, and in association with the various reactions presented, various **reagents** were presented that, due to their specific properties, react in very specific ways. These reagents differ in their basicity, nucleophilicity, and preferred sites of reaction. Table 8.1 summarizes the various properties of the reagent classes presented.

Of the reagents listed in Table 8.1, dialkyllithiocuprates stand out because of their unique ability to participate in 1,4-addition reactions. Such reactions, also known as **conjugate additions**, are generally referred to as **Michael additions**. This name reaction is illustrated in Scheme 8.16 with the reaction of dimethyllithiocuprate with methyl vinyl ketone.

When considering the reagents listed in Table 8.1, it is important to remember that this table is not inclusive. There are many permutations of the reagents listed in the table as well as innumerable additional reagents that have been made useful to various aspects of organic chemistry. In fact, many research groups focus exclusively on the design and preparation of novel reagents capable of solving difficult synthetic problems. It is through this aspect of organic chemistry that some of the most significant advances have been realized.



Scheme 8.16 *Michael addition.*

TABLE 8.1 Reagent Classes and Associated Properties

Reagent Class (Class Name)	Examples	Properties	Uses
R-Li (alkyllithium)	Methyllithium Butyllithium *sec*-Butyllithium *tert*-Butyllithium	Strong base Strong nucleophile when R is not bulky.	Deprotonation of weak organic acids, E2 eliminations S_N2/S_N2' displacements, addition reactions, addition–elimination reactions
R-MgBr (alkylmagnesium bromide, alkyl Grignard)	Methylmagnesium bromide (methyl Grignard)	Strong nucleophile when R is not bulky.	S_N2/S_N2' displacements, addition reactions, addition–elimination reactions
R_2CuLi (dialkyl lithiocuprate)	Dimethyl lithiocuprate	General reactive nucleophile	1,4-Addition reactions
R_2N-Li (lithium dialkylamide)	Lithium diisopropylamide	Strong base, not nucleophilic when R is bulky.	Deprotonation of weak organic acids with acidities as high as $pK_a = 35$
M-H (metal hydride)	Sodium hydride Potassium hydride	Strong, not nucleophilic base	Deprotonation of weak organic acids with acidities as high as $pK_a = 25$
RO-K (potassium alkoxide)	Potassium *tert*-butoxide	Not nucleophilic base	Deprotonation of organic acids with acidities as high as $pK_a = 18$
M-OH (metal hydroxide)	Sodium hydroxide Potassium hydroxide	Nucleophilic bases	Deprotonation of organic acids with acidities as high as $pK_a = 16$, hydrolysis of esters, amides, and nitriles
R_3N (trialkylamine)	Triethylamine Diisopropylethylamine	Not nucleophilic base	Deprotonation of organic acids, acid scavenger

8.4 FINAL COMMENTS

By now, having worked through the material in this book, readers should be well acquainted with the fundamental principles of arrow pushing. Furthermore, through the examples

presented herein, the reader should have acquired an understanding of how to apply arrow pushing to explain reaction processes and to predict reaction products. While this book was intended to serve solely as a supplement to introductory organic chemistry texts, the content was designed to move from the basic foundation of organic chemistry to the direct application of arrow-pushing techniques, thus enabling the reader to begin to advance through the study of organic chemistry. Finally, in closing, readers should endeavor to understand the underlying principles of organic chemistry in order to embrace the full substance of this mature and continually relevant discipline.

PROBLEMS

1. Describe the following functional group transformation in mechanistic terms. Show arrow pushing.

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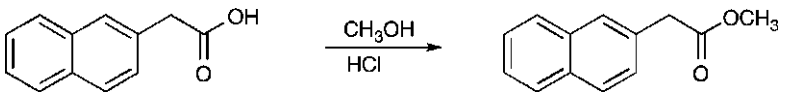

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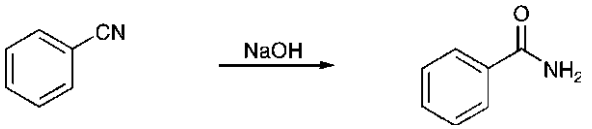

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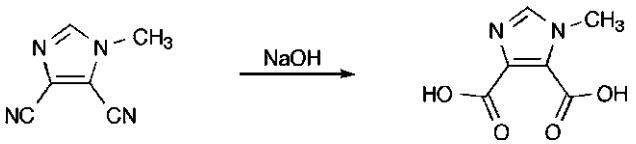

2. Explain the following reactions in mechanistic terms. Show arrow pushing and describe the reaction as a name reaction.

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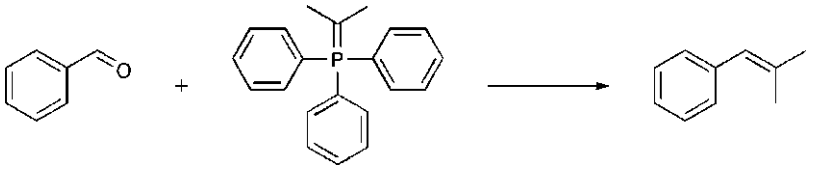

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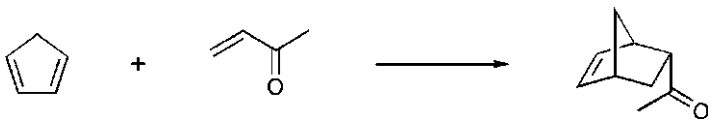

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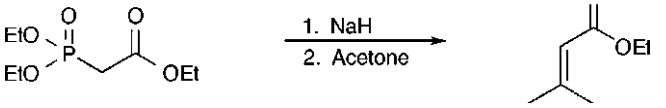

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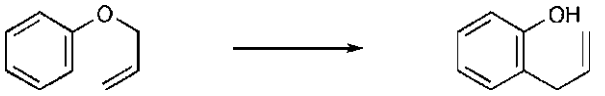
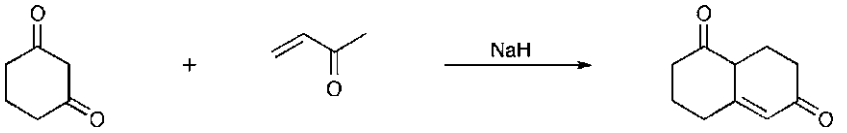
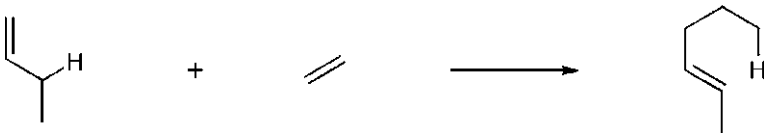


e.



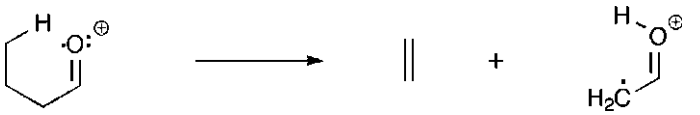
3. Explain the following name reactions in mechanistic terms. Show arrow pushing.

a. The ene reaction



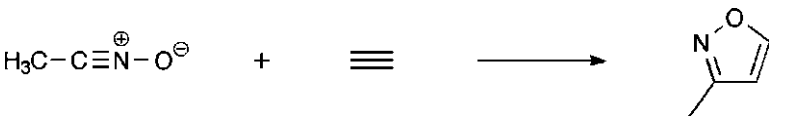
Note: Only the hydrogen involved in the reaction is shown.

b. The McLafferty rearrangement

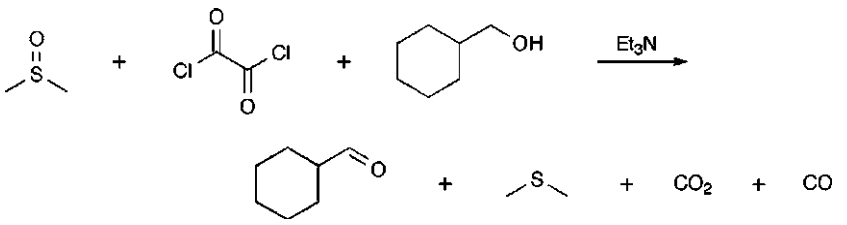


Note: The radical cation present in the starting material is the result of the carbonyl oxygen losing a single electron. This reaction is generally observed during electron impact mass spectrometry.

c. 1,3-Dipolar cycloaddition



d. The Swern oxidation

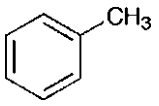


Hint: The oxygen atom in dimethyl sulfoxide is nucleophilic.

4. The Friedel–Crafts acylation, illustrated in Scheme 8.12, shows the formation of one product. However, the reaction, as illustrated, actually forms a mixture of two products. Using the arguments presented in the solution set for Chapter 7, identify the second product. Show partial charges and arrow pushing.

5. Predict all products formed from a Friedel–Crafts acylation on the following compounds with acetyl chloride. Rationalize your answers using partial charges.

a.



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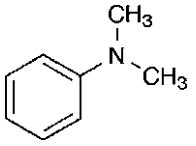

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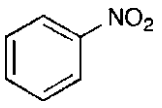
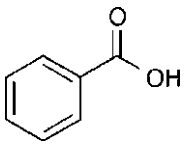
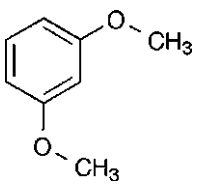


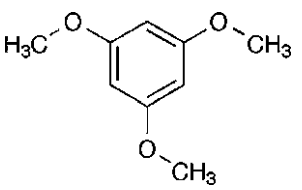
d.



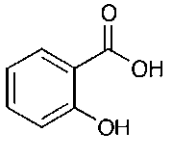
e.

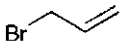
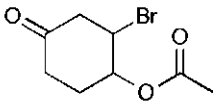


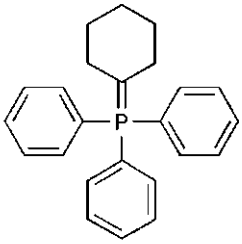
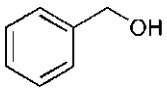
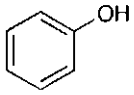
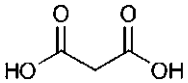
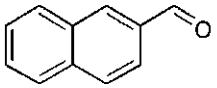
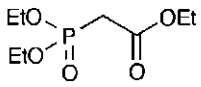
f.



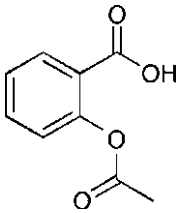
6. From the following list of compounds propose a synthetic strategy for the specified compounds. Up to four synthetic steps may be required. Any chemical reagents may be used. Show all arrow pushing.



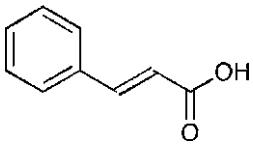







a.



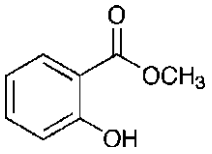
(acetylsalicylic acid, aspirin)

b.



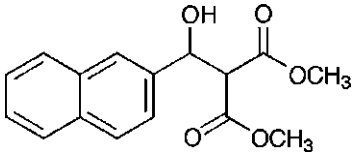
(cinnamic acid)

c.

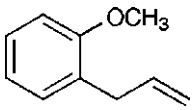


(methyl salicylate, oil of wintergreen)

d.



e.



f.