
Science of Synthesis Version 3.10

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Organometallics

, in *Science of Synthesis*, **1** (), p.1

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Organometallics

1






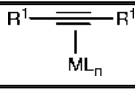
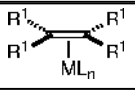
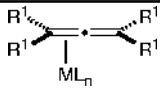
Volume 1:**Compounds with Transition Metal–Carbon σ -Bonds and Compounds of Groups 10 - 8 (Ni, Pd, Pt, Co, Rh, Ir, Fe, Ru, Os)**Lautens, M., in *Science of Synthesis*, 1 (2001), p.1

This volume of *Science of Synthesis* describes compounds with transition-metal σ -carbon bonds for groups 10–8. It is the first volume in the category "Organometallics" and the first volume of the *Science of Synthesis* series. The elements covered are nickel, palladium, platinum, cobalt, rhodium, iridium, iron, ruthenium, and osmium.

The goal of *Science of Synthesis* is to be selective in its coverage rather than comprehensive. Each author has critically evaluated the literature and found the most general and useful methods for the synthesis of a particular target class of σ -complex. In general, one author, or one senior author and coauthors, has written on each product class in order to ensure uniform coverage of the topic. In two instances, i.e. Sections 1.2 and 1.7 (Pd and Fe, respectively), the sheer volume of information required that an additional author contribute to a subsection of the topic.

The parent structures of representative complexes containing σ -bonds that are covered in this volume are shown in **Table 1**.

Table 1 σ -Bonded Complexes Covered in Volume 1

Product Subclass	Representative Structure(s)	Hapticity
arene complexes		6
pentadienyl complexes		5
cyclopentadienyl complexes		5
diene complexes		4
cyclobutadiene complexes		4
allyl complexes		3
alkyne complexes		2
alkene complexes		2
allene/cummulene complexes		2

The organization of the volume follows the general pattern **x.y.z.**, where **x**: volume number = 1, **y**: product class, and **z**: product subclass (methods and variations are described under the subclass heading).

These are now discussed in turn in order to show how the volume can be used.

The product class **y** refers to the individual chapters on each metal. The relative size of each product class is roughly proportional to the proven importance of this metal in synthetically useful processes. Thus, the discussion of Product Class 2 (Organometallic Complexes of Palladium) comprises more than 30% of the volume and reflects the widespread use of palladium complexes and catalysts in organic synthesis.

The product classes appear in the following order:

1.1 Organometallic Complexes of Nickel

1.2 Organometallic Complexes of Palladium

1.3 Organometallic Complexes of Platinum

1.4 Organometallic Complexes of Cobalt

1.5 Organometallic Complexes of Rhodium

1.6 Organometallic Complexes of Iridium

1.7 Organometallic Complexes of Iron

1.8 Organometallic Complexes of Ruthenium

1.9 Organometallic Complexes of Osmium

The product subclass descriptor **z** refers to the metal—carbon σ -bonds of a specific subtype (see [Table 1](#)) listed in order of descending hapticity of the ligand.

The number of subclasses varies from metal to metal and reflects the range of complexes that are known or were judged to be important species in synthetically important reactions. As a result, the subclass designator is *not* connected to a particular class of σ -bond. Two examples are shown below for palladium (Product Class 2) and ruthenium (Product Class 8). It can be easily seen that for palladium, Subclass 1 refers to diene complexes, but for ruthenium, Subclass 1 refers to arene complexes.

1.2.1 Palladium—Diene Complexes

1.2.2 Palladium—Allyl Complexes

1.2.3 Palladium—Alkyne Complexes

1.2.4 Palladium—Alkene Complexes

and

1.8.1 Ruthenium—Arene Complexes

1.8.2 Ruthenium –Pentadienyl Complexes

1.8.3 Ruthenium –Diene Complexes

1.8.4 Ruthenium –Allyl Complexes

1.8.5 Ruthenium –Alkyne Complexes

1.8.6 Ruthenium –Alkene Complexes

Within each product subclass, methods for the synthesis of a particular member of the subclass are described. Charged complexes are ordered within the methods in the following way: (1) neutral, (2) anionic, (3) cationic. For example, in Product Class 1 (Organometallic Complexes of Nickel), Synthesis of Product Subclass 2 (Nickel –Allyl Complexes), the use of Ni(0) is presented before Ni(II) complexes:

1.1.2.1 Method 1: Oxidative Addition of Nickel(0) with Allylic Electrophiles

1.1.2.2 Method 2: Addition of Allylmagnesium Halides to Nickel(II) Salts

The number of these methods varies widely depending on the metal and the particular subclass of –complex. For instance, in the case of palladium –allyl complexes there are 66 methods described covering all of the important processes for generating this important subclass of –complexes.

Within each method an introduction is included followed by a comparison with other methods, a discussion of the scope of the method with representative examples, safety concerns (when warranted), a table of examples (for selected methods), and reaction schemes. Finally, selected experimental procedures are provided along with spectroscopic or physical data.

Each method is further subdivided into variations of the method. An example of the method and variation systems is shown for ruthenium –arene complexes.

1.8 Product Class 8: Organometallic Complexes of Ruthenium

1.8.1 Product Subclass 1: Ruthenium –Arene Complexes

Synthesis of Product Subclass 1

1.8.1.1 Method 1: Preparation of Ruthenium(II) –Arene Complexes

1.8.1.1.1 Variation 1: From Dienes

1.8.1.1.2 Variation 2: By Ligand Exchange

1.8.1.2 Method 2: Preparation of Ruthenium(0) –Arene Complexes

1.8.1.2.1 Variation 1: From Ruthenium(II) Complexes

1.8.1.2.2 Variation 2: By Ligand Exchange

Applications of Product Subclass 1 in Organic Synthesis

1.8.1.3 Method 3: Reactions Involving Ruthenium –Arene Complexes

As can be seen from this example, methods and their variations are discussed for both the Synthesis of the Product Subclass and Application of the Product Subclass in Organic Synthesis. The former category falls directly within the scope of *Science of Synthesis* (which is based on products), whereas the latter category has been created in order to include metal-catalyzed processes in which a π -complex is a proposed and likely intermediate species, but is not isolated. The need to capture the multitude of catalytic reactions where the organic product is not the key feature, but rather an intermediate, differentiates Volumes 1 –8 of *Science of Synthesis* from the other volumes in the series. This point warrants further discussion and expansion of the principles underlying this approach are described below.

For some metals and classes of π -bond, the synthesis of the π -complex generates a stable entity that can be used in a subsequent reaction where the π -bond is apparently unchanged at the end of the reaction. In other words, the product contains a π -bond of a certain subclass as does the starting material. These transformations fit precisely within the scope of *Science of Synthesis*. Many examples illustrating this point are found in Section 1.7.8 (Ferrocenes) and a few are abstracted below to illustrate the point (**Scheme 1**).^[1,2] It is important to note that while some of the transformations in this section undoubtedly occur through the π -bond (in analogy with electrophilic aromatic substitution) the product still contains the cyclopentadienyl ring and is grouped under cyclopentadienyl complexes.

Scheme 1 Reactions of Ferrocene Complexes^[1,2]

Many of the ferrocene complexes described in this section are useful in the synthesis of ligands for catalytic reactions and subsequently appear under the heading Application of the Product Subclass in Organic Synthesis. For example:

1.7.8.12 Method 12: Catalytic Enantioselective Hydrogenation

1.7.8.13 Method 13: Catalytic Enantioselective Hydroboration

1.7.8.14 Method 14: Catalytic Enantioselective Hydrosilylation

1.7.8.15 Method 15: Catalytic Enantioselective Allylic Substitution

1.7.8.16 Method 16: Catalytic Enantioselective Aldol Reactions

In other examples, a metal π -bonded complex can be easily isolated and reacted in a subsequent stoichiometric process to generate a new class of metal π -bond. The reactions of iron π -arene complexes with a nucleophile are illustrative of this class of reactions (**Scheme 2**).^[3,4] In this instance, methods for the preparation of the iron π -arene complex are included in the volume (as a method, under Synthesis of Product Subclass) as are examples of making diene π -pentadienyl complexes by reaction with the nucleophile (also a method, under Synthesis of Product Subclass). Subsequent reactions and demetalation produces purely organic products and these results are discussed under the heading of Application of the Product Subclass in Organic Synthesis.

Scheme 2 Reactions at the π -Bond Generating a New Class of π -Bond^[3,4]

The final category of transformations include those reactions where the π -bonded metal complex is never isolated and is only assumed based on mechanistic studies using known π -complexes and their reactions as a point of reference. The majority of catalytic reactions fall into this category where an organic substrate is converted into an organic product through the auspices of a metal. More than one type of π -complex is typically formed during a cycle, but the reaction is classified based on the π -complex of highest priority that is proposed ($\pi^6 > \pi^5 > \pi^4 \dots$).

An example to illustrate the point is the palladium-catalyzed functionalization of allylic acetates and carboxylates (**Scheme 3**). The most likely mechanism involves complexation of the alkene with palladium (π^2 -complex) followed by ionization to form a π -allyl palladium species (π^3 -complex). Subsequent reaction with a nucleophile to form a σ -bonded palladium product (π^2 -complex) ensues. The complex of highest priority in this cycle is the π^3 -allyl species and so reactions of this type are found in Section 1.2.2 (Palladium π -Allyl Complexes).

Scheme 3 Mechanism of the Catalytic Reaction of an Allylic Acetate with a Nucleophile

It is important to note that the organic products of each catalytic reaction will also appear in the appropriate volume of *Science of Synthesis* dedicated to that product class. For example, palladium-catalyzed allylic amination of an allylic acetate would appear in Volume 1 under Product Class 2, Subclass 2 Palladium –Allyl Complexes and also in *Science of Synthesis*, Vol. 40 (Amines, Ammonium Salts, Haloamines, Hydroxylamines, Hydrazines, Triazines, and Tetrazanes).

In the following section, selected examples abstracted from the individual chapters are presented in order to highlight the diversity of important reactions of π -complexes covered in this volume.

Section 1.1.1 covers the general topic of nickel π -diene complexes and in Section 1.1.1.4.2 a nickel π -diene species is proposed to be involved in a reductive-coupling process promoted by nickel(0). (2*E*,4*E*)-Hexa-2,4-dienoate reacts with an aldehyde in the presence of triethylborane to give the hydroxy ester in 91% yield (**Scheme 4**).^[5]

Scheme 4 Reductive Coupling with Triethylborane^[5]

As mentioned above, Section 1.2 covers the π -complexes of palladium. Section 1.2.4.3.1 outlines the formation and reactions of alkene π -complexes including one of the most important synthetic transformations, the Wacker oxidation. A specific example to highlight the chemoselectivity and synthetic utility is shown below (**Scheme 5**).^[6]

Scheme 5 The Chemoselective Palladium-Catalyzed Oxidation of an Isopropyl-Substituted 2-Allylcyclohexanone to a 1,4-Dicarbonyl Compound^[6,20]

Section 1.3.4 is devoted to the synthesis of alkyne complexes of platinum as well as catalytic processes where a platinum–alkyne species is a likely intermediate. In Section 1.3.4.5.2, a carbonylative process is described where a terminal alkyne reacts with an alkylthiol and carbon monoxide in the presence of tetrakis (triphenylphosphine)platinum(0) to yield the product arising from addition to the internal position of the alkyne (**Scheme 6**).^[7]

Scheme 6 Platinum-Catalyzed Carbonylative Thiolation of an Alkyne^[7]

Cobalt –complexes are important in both stoichiometric and catalytic processes. In Section 1.4.2.2.2, a reaction between a cationic dienecobalt complex and a bis(silyl) enol ether is reported which provides access to fused ring systems in good to excellent yield (**Scheme 7**).^[8]

Scheme 7 Addition of Bis(trimethylsiloxy)dienes to Tricarbonyl(η^4 -diene)cobalt(I) Tetrafluoroborate Complexes^[8]

Rhodium –complexes (Section 1.5) are widely used as catalysts for laboratory and industrial-scale processes of many different types. Among the most useful are diene complexes where norbornadiene or cycloocta-1,5-diene are the ligands. Section 1.5.4.6 outlines the most direct approach to chiral diene complexes of rhodium which are then used in catalytic amounts for hydrogenation, hydroacylation, cycloaddition, and isomerization processes (**Scheme 8**).^[9,10]

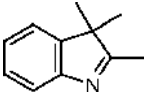
Scheme 8 Synthesis of Cationic Chiral Diene Complexes^[9,10]

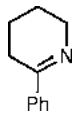
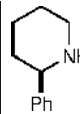
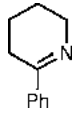
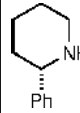
Rhodium –allyl complexes are becoming increasingly important species in a variety of catalytic processes. One such reaction is the "metallo-ene" process which is known for palladium, nickel, and, more recently, rhodium, (Section 1.5.5.7 and [Scheme 9](#)).^[11]

Scheme 9 Metallo-Ene Cyclization^[11]

Iridium –complexes (Section 1.6) are valuable species as precatalysts in organic synthesis and are frequently proposed as intermediates in catalytic cycles involving iridium. An iridium –diene complex, $[\text{Ir}_2(\mu\text{-Cl})_2(\text{ }^4\text{-cod})_2]$, reacts with chiral ligands to form complexes that enantioselectively reduce ketones, alkenes, and imines. Some examples of imine reduction are illustrated in Section 1.6.3.6.4 ([Table 2](#)).^[12-15]

Table 2 Asymmetric Hydrogenation of Imines with $[\text{Ir}_2(\mu\text{-Cl})_2(\text{ }^4\text{-cod})_2]$ and Chiral Phosphine Ligands as the Catalyst Precursors^[12-15]

Substrate	Ligand	Additive	Solvent, Temp	Product	Config	ee (%)	Yield (%)	Ref
	(2 <i>S</i> ,4 <i>S</i>)-BCPM	BiI_3	MeOH, benzene, –30 °C		(+)	91	92	[12]
	(2 <i>S</i> ,4 <i>S</i>)-BCPM	phthalimide	toluene, 2 –5 °C		S	>85	95	[15]
	(2 <i>S</i> ,4 <i>S</i>)-BPPM	BiI_3	MeOH, benzene, –10 °C		S	90	96	[13]

	(S)-Tol-BINAP	BnNH ₂	MeOH, 20 °C		R	90	100	[14]
	(R)-BINAP	BnNH ₂	MeOH, 20 °C		S	87	100	[14]

^a Ligand structures:

Section 1.7 covers a multitude of iron π -complexes which have been synthesized and reacted, among them conjugated dienes and heterodienes. In Section 1.7.3.7, iron π -azadiene synthesis is discussed (**Scheme 10**), [16] while in Section 1.7.3.9.1, the use of chiral azadienes in the synthesis of chiral cyclohexadienes is outlined. [17]

Scheme 10 Preparation of an Iron π -Azadiene Complex [16]

Ruthenium π -complexes are discussed in detail in Section 1.8. Many classes of π -complexes are isolable species that are subsequently used in catalytic processes due to the high cost of ruthenium. For example, in Section 1.8.5.2 a π -ruthenium complex is used as a precatalyst in the regio- and stereoselective anti-Markovnikov addition of acetic acid to a terminal alkyne (**Scheme 11**). [18] Complexation of the alkyne is proposed as a key step in the reaction.

Scheme 11 The Ruthenium-Catalyzed Anti-Markovnikov Addition of Carboxylic Acids to Terminal Alkynes [18]

The synthesis of osmium π -arene and π -heteroarene complexes is discussed in Sections 1.9.1.1 and 1.9.1.2. The most direct method for simple pentaammineosmium π -arene complexes is shown below (**Scheme 12**). [19]

Scheme 12 Synthesis of Pentaammineosmium(II) π -Arene Complexes [19]

In addition, other methods for the conversion of these compounds into more highly substituted derivatives such

as electrophilic aromatic substitution and electrophilic addition are presented in this section of the volume.

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2 **Organometallics**
 Volume 2:
 Compounds of Groups 7-3 (Mn..., Cr..., V..., Ti..., Sc..., La..., Ac...)

Imamoto, T., in *Science of Synthesis*, **2** (2002), p.1

This volume of *Science of Synthesis* describes the synthesis of organometallic complexes of groups 7 –3. It constitutes both the second volume in the category "Organometallics" and also the second volume of the *Science of Synthesis* series. The elements covered include manganese, technetium, rhenium, chromium, molybdenum, tungsten, vanadium, niobium, tantalum, titanium, zirconium, hafnium, scandium, yttrium, the lanthanides, and the actinides.

The synthesis of organometallic complexes of manganese, rhenium, chromium, molybdenum, tungsten, vanadium, niobium, tantalum, titanium, zirconium, and hafnium are discussed in *Houben –Weyl*, Vols. 13/7 and 13/9a. The synthesis, structure, reactivity, and applications of organometallic complexes of groups 7 –3 (Mn, Tc, and Re,^[1,2] Cr, Mo, W, V, Nb, and Ta,^[3,4] and Ti, Zr, Hf, Sc, Y, the lanthanides, and the actinides^[3,5]) have also been collectively reviewed. In addition, several review articles and books dealing with organometallic complexes of specific metals have appeared, and these references are listed in the individual sections of this volume.

A major aim of this volume in the *Science of Synthesis* series is to provide the most useful and reliable methods for the preparation of the target organometallic complexes rather than to provide an exhaustive and comprehensive coverage of all types of complexes. Description of the application of these complexes in organic synthesis is another important goal. Thus, this volume is organized such that these aims are achieved.

This volume follows the organizational principles of *Science of Synthesis*. Thus, each metal, in general, constitutes a separate product class. However, metals with closely related chemistry are described as one product class to avoid redundancy of the methods. As a result, this volume consists of 13 product classes covering groups 7 to 3 in the following order:

2.1 Organometallic Complexes of Manganese

2.2 Organometallic Complexes of Technetium

2.3 Organometallic Complexes of Rhenium

2.4 Arene Organometallic Complexes of Chromium, Molybdenum, and Tungsten

2.5 Organometallic π -Complexes of Chromium, Molybdenum, and Tungsten Excluding Arenes

2.6 Organometallic Complexes of Chromium, Molybdenum, and Tungsten without Carbonyl Ligands

2.7 Carbonyl Complexes of Chromium, Molybdenum, and Tungsten with π -Bonded Ligands

2.8 Organometallic Complexes of Vanadium

2.9 Organometallic Complexes of Niobium and Tantalum

2.10 Organometallic Complexes Titanium

2.11 Organometallic Complexes of Zirconium and Hafnium

2.12 Organometallic Complexes of Scandium, Yttrium, and the Lanthanides

2.13 Organometallic Complexes of the Actinides

Each product class is divided into product subclasses based on the ligand types, and the subclasses are generally placed in an order from higher hapticity to lower. If the complexes contain more than two kinds of ligands, the higher priority is given to the ligand that is most relevant to the main subject of the section. According to this general principle, the table of contents of each product class generally takes the following format, except Section 2.12 in which product subclasses are classified mainly by the formal oxidation state of the complexes. If there are no complexes corresponding to the product subclass, the section is omitted and the next product subclass is described (**x**: volume number = 2; **y**: product class).

x.y Product Class Y: Organometallic Complexes of Metal Y

x.y.1 Product Subclass 1: Metal –Cyclooctatetraenyl Complexes

x.y.2 Product Subclass 2: Metal –Cycloheptatrienyl Complexes

x.y.3 Product Subclass 3: Metal –Arene Complexes

x.y.4 Product Subclass 4: Metal –Triene Complexes

x.y.5 Product Subclass 5: Metal –Dienyl Complexes

x.y.6 Product Subclass 6: Metal –Diene Complexes

x.y.7 Product Subclass 7: Metal –Allyl Complexes

x.y.8 Product Subclass 8: Metal –Alkyne Complexes

x.y.9 Product Subclass 9: Metal –Alkene Complexes

x.y.10 Product Subclass 10: Metal –Carbene Complexes

x.y.11 Product Subclass 11: Metal –Carbyne Complexes

x.y.12 Product Subclass 12: Metal – -Alkyl Homoleptic Complexes

x.y.13 Product Subclass 13: Metal – -Alkyl Non-homoleptic Complexes

x.y.14 Product Subclass 14: Miscellaneous Complexes (i.e., carbonyl complexes, hydride complexes, alkoxide and phenoxide complexes, calcogenide complexes, amine complexes, phosphine complexes, etc.)

Each product subclass, in general, has introductory text and Synthesis of Product Subclass and Applications of Product Subclass in Organic Synthesis sections. The Synthesis of Product Subclass and Applications of Product Subclass in Organic Synthesis sections are ordered into methods and, when relevant, variations of a method. The relative size of each section largely depends on the synthetic importance of the product subclass, and, in some cases, the Applications of Product Subclass in Organic Synthesis is omitted.

This introduction will present very short abstracts of the individual product classes together with some highlighted synthetic methods.

Organometallic complexes of manganese are described in Section 2.1. Many complexes of this class have unique reactivity and are potentially useful as reagents in synthetic reactions since they are prepared from relatively inexpensive manganese compounds. Section 2.1.6 covers the synthesis and characteristic reactivity of manganese –carbene complexes together with their application in organic synthesis. A typical example is shown in **Scheme 1**.^[6]

Scheme 1 Reaction of a Manganese –Carbene Complex with an Enyne^[6]

Manganese "ate" complexes also have unique reactivity: they reduce –acetoxo ketones to generate manganese enolates that are trapped by electrophiles such as aldehydes to give aldols.^[7] The "ate" complexes react with (dibromomethyl)silanes to give silylalkenes stereoselectively (**Scheme 2**).^[8] These topics are discussed in Section 2.1.8.3.

Scheme 2 Reaction of Lithium Tributylmanganate with *tert*-Butyl(dibromomethyl)dimethylsilane^[8]

The element technetium is prepared artificially and is radioactive; its chemistry is relatively undeveloped compared with other transition elements because of special regulations for handling radioactive technetium compounds. Nevertheless, almost all classes of organometallic complexes of technetium have been prepared, although the total number of the characterized complexes is relatively small. Section 2.2 surveys representative organometallic complexes of technetium. It is noted that some technetium isocyanide complexes containing metastable isotope ^{99m}Tc are important as imaging agents in nuclear medicine.

The chemistry of organometallic complexes of rhenium is discussed in Section 2.3. The discussion focuses on the synthesis and reactions of high-valent organometallic complexes. Methyltrioxorhenium(VII) (**1**), a typical example of such complexes, catalyzes the coupling between aldehydes and diazoalkanes to give alkenes (**Scheme 3**).^[9] The proposed mechanism of this interesting reaction is depicted in **Scheme 4**, in which high-valent rhenium –carbene complexes **2** are involved as key intermediates (Section 2.3.7.5).

Scheme 3 Aldehyde Alkenation Catalyzed by Methyltrioxorhenium(VII)^[9]

Scheme 4 Proposed Mechanism of the Methyltrioxorhenium(VII)-Catalyzed Aldehyde Alkenation Reaction^[9]

Organometallic complexes of group 6 elements, chromium, molybdenum, and tungsten, are roughly classified based on the bonding styles into (1) arene complexes, (2) π -complexes excluding arene complexes, (3) complexes without carbonyl ligands, and (4) carbonyl complexes with π -bonded ligands. These complexes are discussed in separate product classes.

Section 2.4 is devoted to the synthesis and reactions of arene complexes. The emphasis is on diastereoselective and enantioselective transformations of chiral chromium π -arene complexes. **Scheme 5** shows a typical example of the synthesis of a natural product using an arene complex as the intermediate.^[10,11] This reaction sequence clearly presents the synthesis of optically pure arene complexes [i. e., (+)-(1*S*)-**3** and (–)-(1*R*)-**3**], the planar chirality directed, highly diastereoselective reaction (aza-Diels –Alder reaction), the compatibility of the tricarbonylchromium group during the reactions, and the facile removal of that group in the final step.

Scheme 5 Synthesis of (–)-Lasubine(I) via Optically Active Chromium π -Arene Complexes^[10]

In sharp contrast to the tremendous applications of many π -complexes of the late transition metals in organic synthesis, the use of the corresponding π -complexes of group 6 elements in synthesis is still quite limited. Therefore, Section 2.5 discusses the synthesis and reactions of structurally interesting π -complexes, but the potential utility of this class of π -complexes in organic synthesis is mentioned only briefly in a few sections (e.g., Section 2.5.1.6).

Section 2.6 covers mainly carbene and carbyne complexes and π -organo complexes of group 6. The development of alkene metathesis catalyzed by transition-metal π -carbene complexes is discussed in Section 2.6.1.5. A highlighted example using a molybdenum π -carbene complex is shown in **Scheme 6**, in which an *E*-alkene is formed stereoselectively by the cross coupling between two different alkenes. Chromium π -organo complexes generated in situ react with aldehydes chemo- and stereoselectively. The utility of this reaction (the Nozaki π -Hiyama π -Kishi reaction) and the use of a modified catalytic system (**Scheme 7**) are discussed in Sections 2.6.4.5.2 and 2.6.4.5.3, respectively.

Scheme 6 Cross-Coupling Alkene Metathesis^[12]

Scheme 7 The Catalytic Nozaki π -Hiyama π -Kishi Reaction^[13]

Section 2.7 surveys carbonyl complexes with σ -bonded ligands. The first two sections (Sections 2.7.1 and 2.7.2) deal with representative carbene and carbyne complexes, respectively, focusing on their preparation and use in organic synthesis. A highlighted example is shown in **Scheme 8**.^[14] Synthesis and reactions of other carbonyl complexes containing isocyanide, phosphine, halide, and hydride ligands are also discussed in detail in other sections.

Scheme 8 Synthesis of a Fischer-Type Chromium π -Carbene Complex and Its Use in a Stereoselective π -Lactam-Forming Reaction^[14]

Among a number of organovanadium complexes, there are many complexes that are structurally interesting and exhibit unique reactivity. For example, hexacarbonylvanadium is a 17-electron, low-spin d^5 , paramagnetic complex, and also the only isolable homoleptic carbonyl radical. On treatment with Lewis bases or arenes, it readily undergoes disproportionation reactions involving redox processes to form an 18-electron vanadium species (**Scheme 9**, see Section 2.8.7).^[15-17]

Scheme 9 Reactions of Hexacarbonylvanadium with Lewis Bases or Arenes^[15-17]

Section 2.9 describes organometallic complexes of niobium and tantalum. Emphasis is on the synthesis and reactions of alkyne and alkene complexes, alkyl complexes, and alkylidene complexes (Schrock-type carbene complexes). These complexes, especially high-valent species, are coordinately unsaturated and react readily with carbonyl compounds, alkenes, and alkynes to give functionalized organic substrates or polymerization products.

The role of organotitanium complexes in organic synthesis is immense, hence the largest page numbers in this volume are allotted to the titanium product class (Section 2.10). Of note is the development of sophisticated catalytic systems that allow highly efficient catalytic asymmetric C—C bond-forming reactions to take place. Two highlighted examples are shown in Schemes 10 and 11.^[18,19]

Scheme 10 Catalytic Asymmetric Pauson–Khand-Type Cyclization^[18]

Scheme 11 Catalytic Enantioselective Aldol Additions of Alkyl Acetate Ketene Acetals^[19]

Titanium –alkene complexes and titanium –carbene species are also extremely useful and chemistry with such complexes is discussed in Sections 2.10.11 and 2.10.12, respectively. Schemes 12 and 13 show two representative examples of reactions induced by such reactive titanium complexes.^[20-23] Alkene polymerizations catalyzed by titanium complexes are also presented in several sections.

Scheme 12 An Example of the Generation of a Titanium –Alkene Complex and Its Reaction with an Alkyne^[20,21]

Scheme 13 An Example of the Chemoselective Methylenation of Carbonyl Compounds with Dibromomethane/Zinc/Titanium(IV) Chloride^[23]

Section 2.11 discusses zirconium and hafnium complexes and also occupies a considerable part of this volume, since organozirconium complexes have widespread utility in organic synthesis. A notable topic is the Negishi – Takahashi protocol for the generation of three-membered zirconacycles via β -hydrogen abstraction (**Scheme 14**, see also Section 2.11.5.2.2).^[24]

Scheme 14 The Negishi –Takahashi Protocol for the Generation of Three-Membered Zirconacycles via β -Hydrogen Abstraction^[24]

The resulting zirconacycles react with a variety of alkenes, alkynes, and enynes to form five-membered zirconacycles that are converted into useful organic substrates. The nickel-complex-mediated reaction of zirconacyclopentadiene with an alkyne forming aromatic compounds is another notable topic (Section 2.11.5.6.4). This protocol enables the synthesis of substituted benzene derivatives from three different alkynes by regiocontrolled cyclizations (**Scheme 15**).^[25,26] Section 2.11.4.7.6.2 describes zirconium-catalyzed enantioselective alkylaluminum of simple alkenes (**Scheme 16**).^[27]

Scheme 15 Nickel-Complex-Mediated Reaction of Zirconacyclopentadienes with Substituted Alkynes^[25,26]

Scheme 16 Enantioselective Zirconium-Catalyzed Alkylaluminum of Simple Terminal Alkenes^[27]

Section 2.12 covers organometallic complexes of group 3 elements, the chemistry of which has made spectacular progress since the 1980s with the development of a novel class of complexes. One prominent complex is bis(η^5 -pentamethylcyclopentadienyl)samarium(II) that undergoes many unprecedented organic transformations (Section 2.12.4). The reaction of bis(η^5 -pentamethylcyclopentadienyl)samarium(II) with 1,2-di(2-pyridyl)ethene under carbon monoxide is a typical example, in which two molecules of carbon monoxide are inserted into the C=C bond (**Scheme 17**).^[28]

Scheme 17 Bis(η^5 -pentamethylcyclopentadienyl)samarium(II)-Mediated Reaction of 1,2-Di(2-pyridyl)ethene with Carbon Monoxide^[28]

Cerium(III) chloride/organolithium or Grignard reagent systems are useful for the preparation of alcohols from carbonyl compounds, even though the substrates are prone to enolization on contact with organolithiums or Grignard reagents (Section 2.12.7.3).^[29,30] An example of this type of reaction is shown in **Scheme 18**.^[31] no addition product is obtained when the reaction is carried out in the absence of cerium(III) chloride. Samarium(II) iodide is a versatile reagent in organic synthesis and its applications are numerous. However, due to space considerations, Section 2.12 only discusses the preparation of the reagent and gives a few representative examples.

Scheme 18 Reaction of a Readily Enolizable Ketone with Butylmagnesium Chloride/Cerium(III) Chloride^[31]

Sections 2.12.10.4 to 2.12.10.6 describe the catalytic activity of group 3 metallocene complexes in organic transformations. Bis(η^5 -pentamethylcyclopentadienyl) rare earth hydride or alkyl complexes exhibit extraordinarily high catalytic activity in the hydrogenation of alkenes.^[32] Similar complexes are also effective for the cyclization of 1,5- and 1,6-dienes^[33] and aminoalkenes,^[34] and the dimerization of alkynes.^[35]

Lanthanide metallocene complexes and lanthanide aryloxide complexes are also highly efficient catalysts for

polymerization reactions (Sections 2.12.4.4, 2.12.5.2, 2.12.6.4, and 2.12.10.7). In contrast with the d-block transition metal Ziegler–Natta and Kaminsky polymerization catalysts, organolanthanide catalysts do not generally require a cocatalyst or activator to enhance their activity. The stereoselective living polymerization of methyl methacrylate,^[36] block copolymerization of nonpolar monomers with polar monomers,^[37] and one-step block copolymerization of ethene with styrene (**Scheme 19**)^[38,39] are highlighted examples.

Scheme 19 One-Step Copolymerization of Ethene and Styrene^[38]

Optically active hetero-bimetallic complexes $\text{LnM}^1_3(\text{BINOL})_3$ [Ln = rare earth metal; M^1 = alkali metal; BINOL = (*R*)- or (*S*)-1,1'-bi-2-naphthol] are successfully used as catalysts for asymmetric C—C bond forming reactions such as the nitroaldol reaction and the Michael reaction (e.g., **Scheme 20**, see also Section 2.12.13.4). In these reactions, the central lanthanide metal acts as a Lewis acid activating the carbonyl component and the binaphthol unit acts as a Brønsted base.

Scheme 20 An Asymmetric Michael Reaction Catalyzed by $\text{LaNa}_3[(R)\text{-BINOL}]_3$ ^[40]

Finally, Section 2.13 describes organometallic complexes of the actinides. In addition to many interesting actinide organometallic complexes, unique organic transformations based on the characteristic reactivity of 5f block elements are described. For example, terminal alkynes react with primary amines in the presence of a catalytic amount of dimethylbis(5-pentamethylcyclopentadienyl)uranium(IV) to give imines in good to high yields (**Scheme 21**, see Section 2.13.5.4).^[41]

Scheme 21 Intermolecular Hydroamination of Terminal Alkynes

In another highlighted example, uranium –alkyl complexes, including metallacyclic uranium complexes, such as **4**, react with carbonyl compounds, including readily enolizable ketones or nitriles, to give alcohols or methylenation products (**Scheme 22**).^[42]

Scheme 22 Synthesis of a Uranium Metallacycle Complex and Its Reaction with 3,4-Dihydronaphthalen-1(2H)-one^[42]

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Organometallics**Volume 3:****Compounds of Groups 12 and 11 (Zn, Cd, Hg, Cu, Ag, Au)**

O'Neil, I. A., in *Science of Synthesis*, **3** (2003), p.1

General Introduction

This volume of *Science of Synthesis* describes the organometallic and organic chemistry of the metals in groups 12 and 11, namely zinc, cadmium, mercury, copper, silver, and gold. The breadth of chemistry displayed in this volume is remarkable and, characteristic of the series, the authors have given a selective and critical evaluation of the recent developments in their areas. Emphasis has been placed on the applications of the compounds synthesized and, wherever appropriate, relevant experimental procedures have been incorporated into the text.

The organization of the sections follows the priority rules of *Science of Synthesis* with the exception of organometallic complexes of gold (Section 3.6).

Organozinc chemistry has undergone a renaissance in the last 15 years, resulting in organozincs being one of the most commonly used class of organometallic reagents in synthesis (see Section 3.1). This is a result of both the developments in methods for their preparation and the use of transition metals, both catalytic and stoichiometric, to enhance their reactivity. Advances in synthesis have enabled the preparation of organozinc intermediates containing a wide range of reactive functionality. This can be typified by the use of hydroboration, followed by boron–zinc exchange, and the insertion of highly activated zinc into carbon—halogen bonds. The use of transition-metal catalysts has then enabled the selective coupling of these organozinc reagents in good yield. Particularly notable is the use of palladium and copper catalysts in such reactions (e.g., **Scheme 1**).^[1,2]

Scheme 1 Selective Coupling Using Organozinc Reagents with Palladium and Copper Catalysts^[1,2]

The addition of $\text{CuCN} \cdot 2\text{LiCl}$ to an alkylzinc iodide or bromide produces a species that has been formulated as $\text{R}^1\text{Cu}(\text{CN})\text{ZnX}$. These compounds exhibit reactivity typical of organocopper reagents, but as they are prepared from the corresponding organozinc reagent they often possess reactive functionality. Should these be regarded as organozinc or organocopper reagents? In order to ensure full coverage, these types of reagents have been included in both the zinc and copper contributions (Sections 3.1 and 3.4, respectively), and are cross-referenced accordingly. In order to avoid unnecessary repetition, the authors in the organozinc and organocopper sections

have illustrated the chemistry of these reagents with different examples, thus, giving a broader coverage of this important family of reagents. Zinc organometallic compounds have also been widely used in asymmetric synthesis, particularly in 1,2- and 1,4-addition reactions.

The use of organocadmium compounds in synthesis is not widespread, mainly due to the toxicity associated with them (see Section 3.2). However, dimethylcadmium(II) is widely used in the deposition of cadmium-containing materials by metal organic chemical vapor deposition (MOCVD).

Due to their rich and varied chemistry, organomercury compounds still continue to attract the attention of synthetic chemists (Section 3.3). As with organocadmium compounds, there is always a concern regarding their toxicity; however, many organomercury compounds can be manipulated under normal laboratory conditions without any special precautions. A wide variety of structural types incorporating a Hg—C bond are available, including hydrides, aromatics, alkynes, alkenes, and alkanes. Several common methods are used to prepare Hg—C bonds including transmetalation, oxymercuration and its variants, and electrophilic aromatic substitution. Synthetic uses involving further functionalization of the Hg—C bond in these compounds are dealt with in each of the product subclasses (Sections 3.3.1–3.3.6). Organomercury compounds have also been widely used in Heck and other palladium-mediated reactions.

Developments in organocopper chemistry continue unabated. Organocopper reagents are amongst the most widely used in organic synthesis. The sheer volume of material has necessitated a highly selective coverage in this contribution (Section 3.4); despite this, the section contains over 500 schemes and 1660 references! One of the most distinguishing features of organocuprates is their reluctance to add into carbonyl groups and the facility with which they add into α,β -unsaturated carbonyl compounds in a 1,4-fashion. This has been exploited on numerous occasions and has been used with great elegance in the three-component synthesis of prostaglandins by Noyori (**Scheme 2**, see also Section 3.4.3.3).^[3]

Scheme 2 Three-Component Synthesis of a Prostaglandin Involving the Conjugate Addition of an Organocopper Reagent to an α,β -Unsaturated Carbonyl Compound^[3]

The section follows the normal *Science of Synthesis* priority rules and starts with monoarylcopper(I) complexes followed by monoalkynylcopper(I), monoalkenylcopper(I), and monoalkylcopper(I) compounds, cyanocuprates (higher-order cuprates), mixed cyanocuprates, and Gilman cuprates (lower-order cuprates) (Sections 3.4.1–3.4.7,

respectively). This order has been adopted on the basis of synthetic considerations. Frequently, the nature and structure of the organocopper species is unknown. Many factors such as solvent, additives (e.g., Lewis acids and bases), and temperature play a role in determining the reagent structure and reactivity. Indeed, there is much debate concerning the nature of organocopper reagents and this has been discussed in some depth in the introduction to the chapter. Many of the recent developments in organocopper chemistry have been driven by natural and nonnatural product synthesis. For example, there has been much effort spent on improving aryl–aryl couplings using organocopper chemistry, resulting in the total syntheses of natural products such as ellagitannin^[4] and (S)-(+)-gossypol^[5] (see also Section 3.4.1.3.2). The syntheses of the enediyne antibiotics^[6] and cyclic and linear polyacetylene structures^[7] have relied heavily on the development of dramatically improved procedures for the sequential coupling of functionalized alkynes and alkenes using organocopper chemistry.

Organosilver and organogold complexes are not yet widely used in synthesis. In the case of organosilver compounds (Section 3.5), this is most likely due to their sensitivity to light and their ready reduction to the metal. Organogold chemistry is more extensive and the gold can exist in the +1, +2, and +3 oxidation states (Section 3.6). The predominant chemistry is that of the Au—C σ -bond. The dominance of organogold compounds with substituted alkyl ligands led to a reversal of the normal *Science of Synthesis* priority ordering in this chapter. Thus, alkyl ligands are dealt with first (Sections 3.6.1 and 3.6.2), followed by alkenyl, alkynyl, and aryl ligands (Sections 3.6.4–3.6.6, respectively). A brief section on carbon in gold clusters has been included (Section 3.6.10); coverage of gold nanoparticles has been omitted.

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Organometallics

4

Volume 4:**Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds**

Fleming, I., in *Science of Synthesis*, **4** (2001), p.1

The order in which the sections in this volume are presented, both the order of the four elements (As, Sb, Bi, Si), and the order of their compounds within the sections devoted to each element, is determined by the rules used throughout the series *Science of Synthesis*. Although admirably logical in itself, it is not designed to reveal underlying patterns in the chemistry of the four elements. The synthesis of the different classes of compounds, which is the main focus of the volume, is rarely an end in itself, although there are organoarsenic and organosilicon compounds in commercial production. More often than not, the main reason for making the compounds is their application in synthesis, for which an overview may be helpful.

The Organic Chemistry of Arsenic, Antimony, and Bismuth

The first three sections in this volume (Sections 4.1 –4.3) record the major methods by which the compounds of the three group 15 elements (As, Sb, Bi) are synthesized, and each section includes a section or sections on their applications in organic synthesis. They are not, in fact, all that often used in organic synthesis, rarely having any advantage over the elements with which they can best be compared, and having the disadvantage of frequently being more expensive, toxic, and smelly.

Arsenic, Antimony, and Bismuth Compared with Phosphorus

A useful comparison for each of the three elements arsenic, antimony, and bismuth is with the more familiar chemistry of the element immediately above them in the periodic table, phosphorus. Each of these elements allows Wittig-like chemistry to be carried out, with subtle shifts in selectivity from that seen with phosphorus. Thus, stabilized ylides of arsenic and antimony, on the one hand, give Wittig-like reactions with carbonyl compounds,^[1,2] but unstabilized ylides based on arsenic react like sulfonium ylides and undergo the Corey – Chaykovsky reaction with carbonyl compounds (**Scheme 1**).^[3] In between, partly stabilized ylides can be fine-tuned to react either way. These trends are of great fundamental interest, but it is rare in synthesis for there to be any advantage over the phosphorus- and sulfur-based reactions.

Scheme 1 Wittig-like and Corey –Chaykovsky-like Reactions of Arsenic and Antimony Ylides^[1-3]

On the other hand, the triorgano derivatives of arsenic(III), and to a lesser extent antimony and bismuth, do have useful differences in their capacities as ligands for transition metals, allowing fine tuning in the stability and reactivity of catalysts derived from their coordination compounds.

Arsenic, Antimony, and Bismuth Compared with Metals

There is an orderly decrease in electronegativity and an increase in metallic character down the series arsenic, antimony, bismuth, and a corresponding increase in effectiveness as substitutes for metals. Like silicon they all have rather feeble metallic properties, but that can be a virtue in controlling reactivity.

Alkylantimony(V) compounds react directly with acid chlorides,^[4] and allylantimonium salts react directly with aldehydes in the same way as alkyl- and allylmethyl compounds in general (**Scheme 2**).^[5] Similarly, allylbismuth reagents, prepared in situ, react with aldehydes like other allylmethyl compounds.^[6] In these reactions the alkyl and allyl groups are nucleophilic, and the antimony or bismuth is behaving as a mild electrofugal group.

Scheme 2 Alkylantimony, Allylantimony, and Allylbismuth Reagents as Carbon Nucleophiles^[4-6]

Triorganoarsenic(III) compounds react with bromine to give dibromotriorganoarsenic(V) products, which readily undergo reductive elimination (in transition-metal terminology) to give organic bromides and the bromodiorganoarsenic(III) compound (**Scheme 3**).^[7] Sometimes, as when one of the organic groups is a vinyl or substituted vinyl group, the intermediate is not observed. Again, the arsenic is behaving overall as an electrofugal group.

Scheme 3 Bromodealkylation of Triorganoarsenic Compounds^[7]

Arsenic, Antimony, and Bismuth in Redox Chemistry

All three elements arsenic, antimony, and bismuth have a rich redox chemistry. In the first place, they have several subclasses with one or more bonds to oxygen, in addition to the (III) and (V) coordination levels, leading, with arsenic, for example, to families of arsanes, arsinous acids, arsonous acids, arsinic acids, and arsonic acids. These, and their counterparts with antimony and bismuth, are handled separately in the various sections devoted to each of the three group 15 elements.

Redox reactions with a change, one way or the other, between the element(III) and element(V) oxidation states are easy with these three elements, as can be seen in the large number of methods for the synthesis of the various subclasses of compounds which involve a change from (III) to (V), or the reverse. The compounds of arsenic, antimony, or bismuth are rarely used simply as reducing or oxidizing agents. Two exceptions might be

the use of bismuth(V) reagents as selective oxidants for converting acyloins into 1,2-diketones, and for converting alcohols in general into ketones in the presence of such easily oxidizable groups as thiols and indoles. [9]

A more obvious application using the easy change of oxidation state, in addition to the reductive elimination mentioned above, is to take advantage of the capacity of a bismuth(V) compound to deliver one of its five ligands, effectively as an electrophile, with concomitant lowering of the oxidation state from bismuth(V) to bismuth(III) (**Scheme 4**).^[10] In this property, bismuth resembles lead(IV) and thallium(III), with the metal center being nucleofugal, characteristic of elements low in the periodic table in high oxidation states.

Scheme 4 An Arylbismuth(V) Compound as an Electrophilic Arylating Agent^[10]

The Organic Chemistry of Silicon

The organic chemistry of silicon lacks the redox capacities of the three elements arsenic, antimony, and bismuth, but is considerably more diverse in the influence it has on the chemistry of the functional groups present in silicon-containing molecules, with substantial chemistry from the many different arrangements by which the silicon atom may be connected to the organic functionality. These principles are best revealed by successively comparing silicon with carbon, the obvious first choice, with metals in general, since silicon is a metalloid, and finally, and in some ways most tellingly, with hydrogen.

Silicon Compared with Carbon

In one sense the chemistry of silicon, relative to that of its vertical neighbor in the periodic table, carbon,^[11] is simple. Silicon chemistry is dominated by the chemistry of *single* bonds to silicon, whereas a high proportion of the chemistry of carbon is based on its functional groups having *double* bonds. Kipping's disappointment that the silicon equivalent of acetone is an unreactive polymer is well-known (**Scheme 5**).^[12]

Scheme 5 A Ketone and Silicone Compared^[12]

The chemistry of double bonds to silicon has comparatively little application in organic synthesis, but this topic is included briefly in this volume (Sections 4.4.1 and 4.4.2), because it is interesting, because it illustrates the difficulty in making and handling compounds with double bonds, and because there are potential applications. Similarly, Section 4.4.3 on the chemistry of silylenes, that is, silicon(II), is brief. These sections concentrate on the preparation of the stable silenes and silylenes, but there is a substantial chemistry hardly mentioned, mostly high-temperature, gas-phase chemistry, in which they are reactive intermediates. This, too, might have substantial importance for organic synthesis, but this possibility, largely studied so far to unravel mechanistic complexities, has had little development as a synthetic method as yet.

Silicon Compared with a Metal

In another sense, the chemistry of silicon is not so simple, since, as an element more electropositive than carbon, and as a second-row element, it can easily accept more than the usual four ligands. This capacity to be a Lewis acid gives it a chemistry quite unlike that of carbon. Thus tetrachlorosilane (Section 4.4.12) is a moderately strong, and selectively oxophilic Lewis acid, allowing it to be used to make trichlorosilyl enol ethers, and function as a bridge in Mukaiyama-like aldol reactions (**Scheme 6**). The silicon in the bridge is able to accept yet another ligand, which gives an opportunity to use a chiral Lewis base with which to induce high levels of enantiocontrol.^[13]

Scheme 6 The Trichlorosilyl Group as a Lewis Acid in an Aldol Reaction

Trimethylsilyl trifluoromethanesulfonate (Section 4.4.14) is a rather weaker but still useful Lewis acid, and there is much scope for tailoring the Lewis acidity to achieve intermediate levels of reactivity by changing ligands. The Lewis acidity of silicon compounds is usually noticeable only when the silicon atom carries one or more electronegative ligands, but the ease with which a β -oxy anion and a trialkylsilyl group undergo *syn* elimination, sometimes known as the Peterson elimination (Section 4.4.37), is another consequence of Lewis acidity detectable even without the presence of electronegative substituents.^[14]

As well as being oxophilic, silyl groups are halophilic, and, most unlike carbon, fluorophilic, making fluoride ion a highly selective nucleophile for silicon, a property that stems in part from the extraordinarily strong bond fluorine makes to silicon.

Another manifestation of its Lewis acidity is the easy nucleophilic substitution that takes place at silicon (**Scheme 7**), much easier than at carbon, a property it shares with all the second-row elements.^[15]

Scheme 7 Comparison of an S_N2 Reaction at Silicon with Carbon

Thus, at one extreme, a silyl triflate (Section 4.4.14) is an aggressive silylating agent, and, at the other extreme, even carbon groups can sometimes be displaced as anions from silicon, even if they have no anion-stabilizing groups attached. Naturally, this is much easier if they do have anion-stabilizing groups, with the result that β -silyl carbonyl compounds (Section 4.4.35), and cyano- (Section 4.4.24), ethynyl- (Section 4.4.30), aryl- (Section 4.4.33), vinyl- (Section 4.4.34), benzyl- (Section 4.4.39), and allylsilanes (Section 4.4.40), can often be persuaded to react as carbon nucleophiles when fluoride ion is used to displace the silyl group (**Scheme 8**).

Scheme 8 Fluoride Ion as a Powerful Nucleophile for Silicon

Similarly, fluoride ion attack on a trimethylsilylmethyl group attached to an iminium ion (Section 4.4.28) is a source of azomethine ylides for 1,3-dipolar cycloadditions. Another application is the Brook rearrangement (**Scheme 9**) found in the chemistry of α -silyl alcohols (Section 4.4.28) and acylsilanes (Section 4.4.25), where an α -alkoxide attacks the silyl group, rendering the β -carbon nucleophilic.^[16] Such behavior in the carbon series is almost unimaginable, just as the Peterson elimination has no carbon counterpart.

Scheme 9 The Brook Rearrangement^[16]

As electropositive elements go, however, silicon is one of the least metallic. This weakness as a metal allows it to be joined to a more metallic metal comparatively easily, and then used as a nucleophile, with considerable potential to tailor the reactivity by the choice of metal. There is significant silicon-anion chemistry found for its compounds with lithium, copper, zinc, aluminum, boron, and tin (Sections 4.4.6 –4.4.11), and even to another silicon atom (Section 4.4.5).

A high proportion of its properties used in organic synthesis can be identified with silicon being the least metallic of metals. In this context, the comparison of silicon with carbon is less illuminating than the comparison with fully metallic elements. Thus silyl enol ethers (Section 4.4.16), both those derived from esters and those derived from ketones and aldehydes, are used as carbon nucleophiles in many of the same reactions as metal enolates [reactions such as the Mukaiyama aldol (**Scheme 10**),^[17] Mannich, and Michael reactions, and similar manifestations of d^2 reactivity] except that the silyl enol ethers need more powerful electrophiles than metal enolates, a condition usually achieved by coordinating the electrophile to a Lewis acid.^[18] Similarly, the *O*-silyl ethers of secondary amides, and their aromatic counterparts such as 2-pyridone, are also useful nitrogen nucleophiles (Section 4.4.15), conspicuously in nucleoside synthesis.^[19]

Scheme 10 Silyl Enol Ethers as d^2 Synthons

A silicon hydride (Section 4.4.4) is a hydride source less powerful than a metal hydride, but more powerful than elemental hydrogen. Silicon hydrides do not reduce carbonyl groups, unless activated by fluoride ion, but they do reduce such cationic electrophiles as carbocations and protonated carbonyl groups (**Scheme 11**). Unlike the hydrides of more metallic elements, silicon hydrides react relatively slowly with protic acids, allowing acids to be used to generate cations in the presence of the silicon hydride reducing agent.^[20] Silicon hydrides are also less effective as hydrogen-atom donors than most metal hydrides, but this, too, can be used when it is important to slow down the hydride-transfer process in radical cyclizations.^[21,22]

Scheme 11 Silicon Hydrides as Reducing Agents

The comparatively metallic properties of a silyl group also show up in the way a silyl group stabilizes a β -carbocation by hyperconjugation, the well-known β -effect (**Scheme 12**),^[23] which is also manifest in such thermodynamically stabilized compounds as β -silyl carbonyl compounds (Section 4.4.35) and silylketenes (Section 4.4.31).

Scheme 12 The β -Effect^[23]

Nevertheless, all these properties are muted relative to those found for metals such as lithium, magnesium, and even zinc, allowing most silicon-containing organic compounds to be handled with ease, without special precautions for avoiding protic solvents or oxygen, and to be carried through many steps in an organic synthesis without the silicon—carbon bond being disturbed.^[24] Silicon appears to be comparatively benign in its environmental impact, and ways of using silicon in organometallic chemistry, as an alternative to tin and other more troublesome metals, are constantly being sought and found, as in the palladium-catalyzed cross coupling of organic halides and triflates with ethynylsilanes (Section 4.4.30) and vinylsilanes (Section 4.4.34) (**Scheme 13**).^[25] This reaction, the Hiyama coupling, has been improved recently by the discovery that aryl- and vinylsilanes which are also silanols are excellent substrates.^[26,52]

Scheme 13 Electrofugal Silyl Groups in Cross-Coupling Reactions^[25]

A less obvious way in which silicon can be compared with a metal is in its capacity to be a σ -electron-withdrawing group, stabilizing β -anions (Section 4.4.23). This is not a property most organic chemists readily associate with an electropositive element, but in fact most metals, when they have an empty p orbital, have this capacity. In the case of silicon, it is not an empty p orbital that provides the stabilization, but the bonds from the silicon to its other ligands, since they are almost always polarized away from silicon towards ligands less electropositive than silicon (**Scheme 14**).^[27]

Scheme 14 Stabilization of an β -Anion by a Silyl Group

This polarization achieves, by negative hyperconjugation, the same effect as an empty p orbital, but to a reduced extent, and an β -silyl group is therefore mildly anion-stabilizing. This property shows up in the comparative stability of diazo(trimethylsilyl)methane (Section 4.4.26), an apparently benign substitute for diazomethane itself,^[28] in the capacity of vinylsilanes (Section 4.4.34) to be attacked by nucleophiles leading to addition, in the increased acidity of silanols,^[29] and in the reduced Lewis basicity of silyl ethers and silylamines relative to free alcohols, ethers and amines.^[30] Silyl groups on oxygen and nitrogen reduce, but do not remove, the nucleophilicity of the oxygen and nitrogen atom, and silyl ethers (Section 4.4.17) are less nucleophilic than either the free alcohol or its metal alkoxide. The residual nucleophilicity allows silyl ethers to be used as oxygen nucleophiles in the absence of protons, which can have considerable advantages, and comparable chemistry is found for silylamines (Section 4.4.21), silyl azides (Section 4.4.20), silyl sulfides and selenides (Section 4.4.19), and silylphosphorus compounds (Section 4.4.22).

Silicon Compared with Hydrogen

Perhaps the most telling of all comparisons is between silicon and hydrogen, where having a silyl group in place of a hydrogen atom provides chemo-, regio-, and stereocontrol that the presence of a hydrogen atom does not allow. There are two contrasting ways in which this property shows up: one when the silicon is on an electronegative atom, and another when it is on carbon.

In general, a silyl group on oxygen can be thought of as a large, greasy, but rather feeble proton.^[15] Silyl ethers, for example, are commonly used as protected versions of the corresponding alcohols, because the silyl group is more difficult to remove from an oxygen atom than a proton is (**Scheme 15**).

Scheme 15 The Silyl Group as a Feeble Proton on Oxygen

The silyl group does not indulge so significantly in bonding analogous to hydrogen bonding; therefore, silylated alcohols are more volatile than the free alcohols. By varying the degree of steric hindrance around the silicon atom, a large family of protecting groups, well classified with respect to their acid and base stability, has been developed (Section 4.4.17).^[31] It is also easy to assemble two different groups attached by oxygen atoms to silicon, allowing a silicon diether (Section 4.4.13) to be an easily disassembled bridge between reacting partners.^[32] Silyl ethers are important not only for alcohols but also for enols, as already seen with silyl enol ethers. The comparison with metal enolates is only one way of thinking about silyl enol ethers; another equally valid comparison is with enols themselves. The nucleophilicity of a silyl enol ether in its d^2 reactions is close to that of an enol. The difference is that it is not, in general, possible to have specific enols, and so the reactions of enols are not regiocontrolled in the way that metal enolate reactions can be.^[33] The only easily handled specific enols are those made from 1,3-dicarbonyl compounds, and even they are not always present in high concentration. In contrast, it is relatively easy to form specific silyl enol ethers; they do not need extra functional groups, and they retain the regiochemistry with which they were generated. Furthermore, silyl enol ethers can react with a number of electrophiles such as tertiary alkyl halides, and acetals in the presence of Lewis acids, these being electrophiles incompatible with other d^2 synthons.^[34,35]

A silyl group on carbon is still large and greasy, but, provided that it is not much more hindered than a trimethylsilyl group, it can be thought of, in contrast to an oxygen-bonded silyl group, as a super-proton.^[15] If the nucleophile is a halogen- or oxygen-based nucleophile, a trimethylsilyl group is more easily removed from carbon than a proton with the same functional relationship (**Scheme 16**).

Scheme 16 The Silyl Group as a Super-Proton on Carbon

Thus, any pathway that leads to a carbocation to a trimethylsilyl group is controlled in its outcome by the loss of the silyl group, placing a double bond specifically between the carbon atom carrying the positive charge and the carbon atom carrying the silyl group. This *kinetic* instability (**Scheme 16**), taken with the *thermodynamic* stability of β -silyl ethyl cations (**Scheme 12**), gives rise to a large amount of highly controlled carbocation chemistry,

especially in the electrophilic substitution reactions of aryl- (Section 4.4.33), vinyl- (Section 4.4.34), allyl- (Section 4.4.40), allenyl- (Section 4.4.32), and propargylsilanes (Section 4.4.38).^[36-38] These compounds show enhanced levels of nucleophilicity relative to their counterparts with a hydrogen atom in place of the silyl group, they show a high tendency to give alkene products rather than those of nucleophilic capture, and they show a high level of regiocontrol in where the double bond is located in the product. Furthermore, some of these reactions show a high level of stereocontrol stemming from the size, and possibly the electropositive nature, of the silyl group. Thus, illustrating all these points, allylsilanes react with electrophiles, not only regioselectively because of the β -effect, but stereospecifically *anti*, and the result is substitution, because of the ease with which the silyl group is lost (**Scheme 17**).^[39-41] There is comparable chemistry with allenylsilanes^[42] and propargylsilanes.^[43]

Scheme 17 The Stereochemistry of the S_E2 Reaction of Allylsilanes^[39-41]

Similarly, vinylsilanes react regioselectively with most electrophiles, again because of the β -effect, with retention of configuration for the same reason, and with overall substitution, because of the ease with which the silyl group is lost (**Scheme 18**).^[37] There is comparable chemistry, without the stereochemical component, with aryl- and ethynylsilanes.^[36]

Scheme 18 The Stereochemistry of Electrophilic Substitution of Vinylsilanes^[37]

Similarly, the enolates of α -silyl carbonyl compounds (Section 4.4.41) are alkylated *anti* with a high level of stereoselectivity.^[44] Other examples of cationic chemistry controlled by silicon are the conversion of silyl epoxides into aldehydes or ketones,^[45] the Stork–Colvin reaction (Section 4.4.29), and the ease of alkene formation from α -silyl alkyl halides (Section 4.4.36), as well as the ease of controlling cationic rearrangements in α -silyl alkyl halides and alcohols (Section 4.4.42).^[46]

Silicon in Redox Chemistry

Finally, the capacity of a silyl group to remain bonded to carbon, allowing it to be carried through many steps of an organic synthesis, especially when the functionality is not such as to provide a pathway for the loss of the silyl group, can be put to powerful, and essentially unique, use by the oxidation of silyl groups carrying at least one electronegative substituent to give alcohols (Section 4.4.18) (**Scheme 19**).^[47-49] Since a phenyl group, and a number of other groups, can be easily removed from the silicon by electrophilic substitution to create the electronegative substituent on silicon, a group such as dimethylphenylsilyl can be used as a masked hydroxy, despite its being, in almost every respect, the chemical opposite: It is large, electropositive, Lewis acidic (if anything), nonpolar in the sense that its being tetrahedral contributes almost no dipole, and is not involved in hydrogen bonding. In contrast, a hydroxy group is small, electronegative, Lewis basic, polar, and a hydrogen-bonding donor and acceptor.

Scheme 19 Silyl-to-Hydroxy Conversion: The Tamao–Fleming Reaction^[47-49]

The organic chemistry of silicon is orderly, highly predictable, and remarkably versatile. It goes from strength to strength, showing little sign of falling from favor as a weapon in the organic chemist's armory.^[50,51]

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Organometallics
Volume 5:
Compounds of Group 14 (Ge, Sn, Pb)

Moloney, M. G.; Thomas, E. J., in *Science of Synthesis*, **5** (2002), p.1

General Introduction

The organometallic chemistry of the main group IV metals germanium, tin, and lead has been dominated by the widespread commercial exploitation of the latter two for antifungal agents (tributyltin oxide) and antiknock agents (tetraethyllead). Apart from its use as a doping agent in semiconductors, germanium has not found a similar bulk organometallic application, principally for reasons of cost. However, the long-term use of tin and lead has resulted in environmental contamination, and as a result of these legitimate environmental concerns, the use of these metals is increasingly restricted. For the synthetic chemist, however, organometallic compounds derived from all three of these metals are both readily accessible and synthetically valuable. Organometallic derivatives of germanium, tin, and lead are generally derived from the +4 oxidation state and are quadrivalent, but divalent germynes, stannynes, and plumbynes are also known. Electronegativity decreases (Ge, 2.02; Sn, 1.72; Pb, 1.55) and atomic size increases (for example, for the +4 oxidation state, ionic radii are: Ge, 53 pm; Sn, 71 pm; Pb, 78 pm) down the group, as expected, and organometallic derivatives from each of these metals participate in both single-electron (radical) and two-electron (ionic) processes. Their order of reactivity increases down the group, reflecting the stronger nature of Ge—H, Ge—O, Ge—Cl, and Ge—C bonds relative to the same bonds with tin and lead, respectively, and this gradation of reactivity has been exploited in synthesis. Further control of reactivity of these organometallic derivatives is achievable by careful manipulation of ligands on the metal, in particular making use of steric effects. Germanium, tin, and lead all exhibit the ability to expand their coordination environment (so-called "hypervalency") and this has been turned to synthetic advantage particularly for organotin compounds. The lower reactivity of organogermanium compounds has recently been put to good effect in the development of selective reducing agents and in combinatorial chemistry applications, but organolead compounds, with a few exceptions, have not found widespread use. All three organometallics display the so-called " σ -effect", in which a carbocationic center to the metal is stabilized; this is responsible for some very useful synthetic reactivity. Indeed, these organometallic compounds exhibit considerable synthetic versatility, and they find application ranging from reducing agents to coupling partners for palladium-mediated reactions and many other transmetalation processes. However, all these main group organometallic derivatives should be handled with care, due to their known or potential toxicity and high fat solubility; such concerns are mitigated to some extent by the fact that these compounds are relatively nonvolatile, although methylstannanes are exceptional in this regard.

In this volume, an attempt has been made to give a realistic overview of the preparation and synthetic value of the relevant organometallic compounds in a systematic manner. As might be expected, there are both synthetic gaps, in which methods giving access to some compound classes are unknown, and gaps in applications, since many organometallic compounds have not been evaluated for useful synthetic reactivity. As a result, many compound classes might be considered to be esoteric and of little value; we hope that the systematic classification of this volume will highlight these gaps and provide justification for their further development.

Note that since the volume is concerned with organometallic compounds, many important inorganic compounds [e.g., tin(IV) chloride, lead(IV) acetate] which find wide and varied application in synthetic organic

chemistry are not included in any detail.

Organization of the Product Subclasses of Germanium, Tin, and Lead Compounds

The organization of the product subclasses of germanium, tin, and lead compounds follows the priority rules of *Science of Synthesis*. Thus, the highest order ligand determines to which product subclass any particular compound is assigned with the metal hydrides being assigned the highest preference, followed by dimetals and metalated germanium, tin, and lead compounds (except for metal —arsenic, -antimony, -bismuth, and -silicon compounds where the other metal has preference). Double-bonded germanium, tin, and lead compounds are treated next, followed by compounds with germanium-, tin-, and lead —halogen, -oxygen, -sulfur, -selenium, -tellurium, -nitrogen, and -phosphorus bonds. Finally, compounds in which the germanium, tin, or lead is attached to four carbon ligands are discussed, with the functionality of the highest order carbon ligand determining the product subclass. Synthesis of each of the classes of compounds is covered in detail and, where relevant, synthetic applications are also given.

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Kaufmann, D. E., in *Science of Synthesis*, **6** (2004), p.1

General Introduction

This volume describes the organometallic and organic chemistry of boron. Despite covering just a single element, an extremely broad spectrum of chemistry is discussed within. As for other volumes of *Science of Synthesis*, the authors are experts in their respective fields and have covered the most important developments selectively and critically. Applications of the compounds synthesized are emphasized and, wherever appropriate, experimental procedures are provided in the text.

Old manuscripts indicate that the Arabs and Persians knew of the mineral borax (sodium tetraborate decahydrate), the first and still the most important natural boron source, over 2000 years ago. Boron oxide has been detected in Chinese enamels from the 4th century B.C. Elemental boron was discovered as a gray powder independently in 1808 by Gay-Lussac and Thenard in France, and by Davy in England as the main reduction product of boric acid by means of potassium. Davy suggested the name "boron", formed from the first syllable from borax and the second from carbon, recognizing important similarities with the latter. The green flame of burning triethylborane, the first representative of the group of organoboron compounds, was reported by Frankland and Duppa in 1860. It then took 50 more years before Stock,^[1] working on this task during 1912–36, and later Lipscomb (Nobel Prize 1976)^[2] investigated the synthesis, structures, and bonding properties of the novel class of hydroboranes. Subsequently, hydridopolyborates were discovered, followed by heteroboranes, with carboranes being the most important subclass of the latter. The important field of organic synthesis via organoboranes was, broadly, developed first by Brown (Nobel Prize 1979)^[3] and co-workers since the middle of the 20th century, strongly accelerated by the discovery of the hydroboration reaction of alkenes and alkynes in 1956.^[4] In 1959, the first diastereoselective,^[5] and 2 years later a highly enantioselective,^[6] hydroboration reaction by means of chiral, terpene-based hydroboranes developed by Brown and Zweifel marked the beginning of practical asymmetric synthesis.

Boron reagents have become very important standard tools for the synthetic chemist^[7,8] because boron compounds combine a unique mixture of interesting properties such as Lewis acidity and facile though highly stereoselective oxidizability.^[9] The boron atom is slightly larger than carbon. All trivalent boron compounds are planar, whereas tetravalent boron compounds assume tetrahedral or nearly tetrahedral geometry. The B—C bond ($-323 \text{ kJ} \cdot \text{mol}^{-1}$)^[10,11] is not much weaker than a C—C bond ($-358 \text{ kJ} \cdot \text{mol}^{-1}$); this situation is also reflected by similar bond lengths (B—C 156 pm). These two classes of compounds are closely related; neutral tricoordinate boron compounds such as trimethylborane are isoelectronic with carbenium ions such as the corresponding *tert*-butyl cation, whereas boronic acids $[\text{R}^1\text{B}(\text{OH})_2]$ are isoelectronic with carboxylic acids, and negatively charged tetracoordinate borates such as the borohydride anion are isoelectronic with neutral hydrocarbons such as methane.^[12]

Boron forms even stronger bonds with nitrogen, oxygen, fluorine, and chlorine. The B—H bond ($-375 \text{ kJ} \cdot \text{mol}^{-1}$) is also slightly weaker than the C—H bond. By means of three-center bonds, monoorganohydroboranes and diorganohydroboranes form dimers, which always display hydride bridges rather than alkyl bridges, as illustrated in **Scheme 1**.^[13-15]

Scheme 1 Hydride Bridging in Monoorganohydroboranes and Diorganohydroboranes

In contrast to hydroboranes, trialkylboranes are monomeric, which may be traced to hyperconjugation with the alkyl substituents. In organoboranes, the B—C bond has largely single σ -bond character. Electron-rich π -systems such as vinyl or aryl groups provide the adjacent B—C bond with partial double-bond character. In small-ring boron heterocycles such as the 2 π -systems, 1*H*-borirenes (e.g., **1**), structural and spectroscopic data point to extensive π -electron delocalization.^[16] The four-membered dihydrodiboretes exist in two isomers, a planar 1,2-dihydro-1,2-borete **2** with two localized π -electrons and a "butterfly" shaped 1,3-dihydro-1,3-borete **3** with delocalized π -electrons.^[17] The 4 π -antiaromatic 1*H*-borole is labile, even in perarylated form **4** (**Scheme 2**).^[18]

Scheme 2 Boron Heterocycles^[16-18]

Substituents with electron lone pairs act similarly while the strength of the boron—heteroatom σ -bonds decreases in the order nitrogen > fluorine > oxygen > sulfur > chlorine. All mesomeric interactions lead to a distinct stabilization of the particular organoboranes.

Boron generally functions as a Lewis acid. In particular, the stable complexes of boron trifluoride with diethyl ether and of the parent hydroborane with amines, ethers, and dimethyl sulfide are of high preparative value. Complexation of less-stable organoboron intermediates with Lewis bases is a proven method of stabilization and storage. Boronic acids also react as Lewis and not as protic acids.

The feasibility of both the highly stereoselective introduction of a boryl group (e.g., by means of a hydroboration reaction) and its subsequent substitution by either a proton or a carbon or heteroatom electrophile is an extremely important prerequisite for its manifold successful applications in stereodirected

syntheses. In particular, the ready oxidizability of boryl groups brings about a high preparative potential. It also means that, in general, uncomplexed organoboron compounds of a low oxidation state have to be handled strictly under inert gas (nitrogen or argon) using Schlenk techniques or a glove box.^[19,20] Boronic acids and their esters are usually quite stable in air and can therefore be handled as ordinary organic compounds without any special precautions. Frequently, the purification of cyclic boronates by column chromatography is also feasible. Because of the low polarity of the B—C bond, many organoboranes are stable in deoxygenated water.

The most important industrial source of boron compounds is still borax. Acidification with carbon dioxide yields boric acid which, together with its anhydride, is the key compound for most of the commercially available boron compounds important for organic synthesis, such as hydroborane—amine, —ether, and —sulfide adducts, metal borohydrides, the haloboranes, boric acid esters, boronic acids and esters, trialkylboranes, and diboron(4) compounds. The main routes to organoboron compounds are transmetalation reactions, boration reactions of unsaturated compounds, and ligand-exchange reactions.^[21]

The most important analytical tool for organoboron compounds is NMR spectroscopy. Of the two boron isotopes, ^{10}B (20%, $I = 3$) and ^{11}B (80%, $I = 3/2$), the latter possesses superior NMR properties. The ^{11}B NMR chemical shifts cover a broad range of about 250 ppm; they depend on the charge, the coordination number, and the substituents at boron.^[22-25]

Vibrational spectroscopy is especially valuable for the structural elucidation of hydroboranes with strongly differing B—H stretching frequencies for bridging and terminal positions (1500–2600 cm^{-1}).^[12,23]

Molecular ions of organoboron compounds are frequently of low abundance or absent in EI mass spectra. Thermally unstable compounds such as boronic acids tend to form decomposition or condensation products under the evaporation conditions. ESI mass spectrometry has proven to be a mild and, therefore, valuable modern tool in many cases.

The effects of boron compounds on biological systems have been reviewed extensively.^[26] Diborane is a toxic hazard (industrial exposure limit 0.1 ppm) as it is not oxidized in air immediately.^[27] The highly volatile lower trialkylboranes (BR^1_3 , $\text{R}^1 = \text{Me, Et, Pr}$) have noxious and lachrymatory properties and they tend to ignite spontaneously. The higher trialkylboranes should also be handled in a closed system. Parallel to their higher oxidation state, boronic acids and esters can be handled as typical organic compounds. During boron neutron capture therapy (BNCT) studies, indications were gathered that water soluble boronic acids tend to have low toxicity while fat-soluble boronic acids are moderately toxic.^[28] In addition, it should be noted that some boronic acids and related compounds are specific enzyme inhibitors.^[29] Up to 350 ppm, boric acid is tolerated well in the diet of rats and dogs; toxic effects are apparent at higher doses.^[30] The lethal dose of boric acid for human adults is estimated to be 15–20 g.^[27] Natural boron-containing compounds occur in plants, algae, and microorganisms.^[31] Boric acid is known to be an essential micronutrient for plants; there is some evidence that traces of boron may also be important for animals.^[32]

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Organometallics

7

Volume 7:**Compounds of Groups 13 and 2 (Al, Ga, In, Tl, Be ... Ba)**

Yamamoto, H., in *Science of Synthesis*, **7** (2004), p.1

This volume describes the organometallic, metalloorganic, and organic chemistry of the elements in groups 13 and 2, namely aluminum, gallium, indium, thallium, beryllium, magnesium, calcium, strontium, and barium. Boron is not included here as its compounds will be discussed in an independent volume [*Science of Synthesis*, Vol. 6 (Boron Compounds)]. The objective of this volume is to detail reliable synthetic procedures for compounds of the elements of groups 13 and 2 already known to be valuable synthetic intermediates or subjects of current research work. The breadth of chemistry displayed here is remarkable and, as is characteristic of the series, each author is an expert in their particular field of chemistry and provides a truly selective and critical evaluation of recent and previous developments. Emphasis has been placed on the applications of the compounds synthesized and, wherever appropriate, reliable experimental procedures are described in the text.

Generally, the organization of the sections follows the rules used throughout the series. However, some metalloorganic and inorganic compounds, such as aluminum aryloxides and aluminum oxide (alumina) (Sections 7.1.4 and 7.1.8, respectively), are included in the text.

Aluminum, the most abundant metal in the lithosphere, is widely used either as the metal itself, or is present in numerous compounds that are important in daily life and represent valuable tools for chemists, e.g. alkylaluminum derivatives and aluminum aryloxides and amides. Recent results of organic syntheses involving various aluminum catalysts are also included in this volume, such as the conjugate addition of a nucleophile to benzaldehyde or benzoyl chloride using aluminum tris(2,6-diphenylphenoxide) (ATPH, **1**) as catalyst (**Scheme 1**).
[1,2]

Scheme 1 Conjugate Addition to Benzaldehyde or Benzoyl Chloride Using an Aluminum Catalyst^[1,2]

Gallium and indium have attained considerable importance in material science; their compounds are discussed in Sections 7.2 and 7.3, respectively. Section 7.4 deals with thallium. Due to their transmission of long-wavelength light, thallium halides have become highly useful in several special infrared techniques. Aqueous solutions of thallium esters have also been used for small-scale mineral separation because of their high density. The unique chemical and physical properties of all these metals are still very interesting not only for material science, but also for the design of catalysts. For example, gallium sodium bis(1,1'-bi-2-naphthoxide) (**2**) has been found to be an excellent catalyst for the asymmetric Michael addition of malonates to cycloalk-2-enones, such as in the formation of **3** (**Scheme 2**).^[3]

Scheme 2 Asymmetric Michael Addition of a Malonate to Cyclohex-2-enone Using a Gallium Catalyst^[3]

Among the organometallic compounds of group 2, organomagnesium compounds (Section 7.6) are of prime importance because of their manifold applications in preparative chemistry. Therefore, they are discussed in great detail in comparison to those compounds of calcium and heavier alkali earth metals. Over 100 years have passed since Grignard published his historic paper on the preparation of ethereal solutions of compounds in which carbon is directly bonded to magnesium.^[4] Even now, Grignard reagents are an obvious choice for organic chemists in many molecule preparations. Although the wide range of applications of the Grignard reagent is truly impressive, the actual mechanistic details of this well-known organometallic compound are still vague. We have had to wait for recent advances in various analytical techniques to understand, even partly, the true details of reactions using this classical reagent. Now that its various mechanisms are understood, the role of the Grignard reagent in organic synthesis is recognized to be even greater than previously anticipated. Accordingly, magnesium is used far more in preparative chemistry, and its compounds are described in detail in this volume.

In contrast, the heavier elements form bonds with a more pronounced ionic character, providing unique synthetic opportunities. Barium compounds, for example, show contrasting regioselectivity to the magnesium derivatives (**Scheme 3**).^[5]

Scheme 3 Regioselectivity of the Carboxylation Reactions of Organobarium and Organomagnesium Compounds^[5]

It should also be emphasized that the reagents mentioned here are both useful and safer than most of the transition-metal compounds. This is an advantageous feature of compounds of the main group of elements with respect to the issue of green chemistry.

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Organometallics
Volume 8:
Compounds of Group 1 (Li ... Cs)

Majewski, M.; Snieckus, V., in *Science of Synthesis*, **8** (2005), p.1

Introduction to Volume 8a

In this Volume 8 of *Science of Synthesis*, 41 authors (M. Barbero, L. Brandsma, D. Caine, J. V. Comasseto, R. L. O. R. Cunha, R. K. Dieter, T. Durst, J. Eames, R. W. Friesen, R. E. Gawley, J. R. Green, G. W. Gribble, F. Hasanayn, A. Jończyk, E. Juaristi, R. M. Kellogg, M. Khodaei, R. Klein, A. Kowalkowska, A. P. Krapcho, R. Łańny, S. MacNeil, M. Majewski, R. Melgar-Fernández, C. Metallinos, A. Mordini, O. Muñoz-Muñoz, C. Nájera, S. O'Connor, N. Ono, J. N. Reed, C. C. Silveira, V. Snieckus, A. Streitwieser, C. F. Sturino, M. Valacchi, P. Venturello, U. Wietelmann, L. Xie, M. Yus, and J. W. Zwikker) describe formation and use of a variety of compounds of the group 1 elements (Li, Na, K, Rb, and Cs) in organic synthesis. Lithium compounds are described in Volume 8a, while compounds of the other group 1 elements are covered in Volume 8b. This volume concludes the eight-part series in Category 1 (Organometallics) following in the elegant footsteps of the alkali metal coverage in *Houben–Weyl*, Vols. 13/1 (1970) and E 19d (1993). For the presentation of methods in chemical synthesis, the major difference between *Houben–Weyl* and *Science of Synthesis* is the comprehensive and exhaustive nature of the former and the selective, critically evaluated, and most useful and reliable methods presented in the latter.

A major challenge in planning the volume concerned the ubiquitous nature of alkali metal compounds in organic synthesis. Ranging from very simple reagents, such as sodium hydroxide, used to generate organometallic intermediates or as sources of cations designed to involve themselves in coordination (e.g., lithium and cesium salts) to "true organometallics" such as alkyllithium compounds, alkali metal derivatives are encountered in a plethora of experimental procedures. As may be appreciated, due largely to their simplicity, many useful alkali metal reagents are difficult to search using standard databases. Therefore, we decided near the beginning that Volume 8 shall depart from the pure "organometallics" theme and that some simple compounds used either for generation of polar organometallics, in situ or otherwise, will also be covered. Similarly, the alkali metal enolates are covered although arguably they are not organometallic species. This choice of coverage resulted in a rather sizeable two-part volume that nonetheless is rather selective in nature. As a consequence of a multiauthor work of this nature, overlap of content is inevitable and, we would argue, desirable for the completeness of a given topic, in order to provide individual flavor and perspective by a given author, and therefore to offer a different appreciation by the reader. For example, the generation of vinyl lithium compounds may be viewed from the perspectives of applications of lithium metal (Section 8.1.1), of deprotonation of alkenes (Section 8.1.8), and of synthesis of α -lithio vinyl ethers (Section 8.1.27). Thus, by way of illustration, the chemist in search of selecting the best method for alkylation of a C—H acid is advised to consult the sections on the corresponding lithium, sodium, and potassium derivatives, and also the relevant sections on the most likely bases for the deprotonation step (inter alia, sections covering lithium amides, lithium and sodium hydride, sodium hydroxide, and phase-transfer catalysis.)

A number of major and distinct differences of Volume 8 compared to most *Science of Synthesis* volumes are readily identified. In particular, a product subclass is defined as follows:

- (a) A reagent that acts upon organic molecules to generate alkali metal species, e.g. lithium hydride for the synthesis of lithium carboxylates (Section 8.1.2.1).
- (b) A carbanionic, normally unstable and fleeting, organometallic intermediate and *not* an isolated product, e.g. sodium acetylide (Section 8.2.8). There are exceptions of alkali metal organics which may be isolated,

characterized, and stored for certain periods of time.

(c) An inorganic reagent based on a group 1 metal that is useful in synthesis but has a tenuous connection to polar organometallics (e.g., sodium halides, Section 8.2.3).

With one exception, the compounds of each metal constitute a separate product class (Section 8.1: lithium, Section 8.2: sodium, Section 8.3: potassium, Section 8.4: rubidium and cesium). Within each product class are given the methods for particular members of the subclasses. The various synthetic intermediates of the given alkali metal are presented in a logical order in which inorganic reagents (e.g., sodium hydride, sodium cyanate) precede organometallic species (e.g., sodium cyclopentadienide) as outlined in the table of contents.

Therefore, the center of attention is the preparation of the intermediate species as emphasized in the discussion of each category, in the tables, and especially in the delineation of experimental procedures in the methods and variations sections. After all, a stated aim of *Science of Synthesis*, in both printed and, for the computer-reliant chemists of the future, electronic forms is to be the first-call source for synthetic practitioners.

Information on the scope and limitations of reactions of the intermediate species is abundantly but selectively provided in the discussion, tables, and experimental procedures. In the procedures, either the generation of the organometallic species only is given and its reactions are referred to in the text or the formation of the species is outlined, as is its treatment with a selected reagent, the workup of a reaction mixture, and the isolation of a product. Generally, physical, but not spectroscopic, properties are given for the products. Mechanistic discussion is minimal but references to original sources are provided.

Applications of product subclass sections follow the order of methods and, where relevant, variations of methods. Some product subclasses concerning reagents and generated organometallic species lend themselves well to presentation of applications for the preparation of specific classes of organic compounds (e.g., Section 8.1.27) whereas others are sufficiently defined in terms of their synthetic utility within the synthesis of the product subclass sections (e.g., Section 8.1.23) and therefore require no applications sections.

Perusal of this volume will clearly demonstrate the dominance of organolithium reagents and intermediates in organic synthesis compared to the other alkali metals. As a consequence, and not surprisingly, the previous extensive studies on structure, acidity (pK_a), reactivity, mechanism, and theory of the "Polare Organometalle",^[1] originally concentrating on organosodium and organopotassium compounds, have been superseded by extensive research on organolithium compounds. Thus, *Houben –Weyl*, Vol. E 19d, the theoretical –experimental treatment by Sapse and Schleyer,^[2] the pedagogic and colossal review by Schlosser,^[3] and the monumental volumes of Rappoport and Marek^[4] are rich sources for increasing our understanding of these highly basic and nucleophilic organometallics and thereby lead to greater ability to devise new base/ligand combinations, improve established reactions, and predict new ones. "For those who seek to discover new reactions, the most insightful lessons come from trying to trace important reactivity principles back to their origins."^[5]

Unfortunately, structural information has been by and large insufficiently assimilated by synthetic chemists perhaps due to the lack of easily appreciated and widely encompassing predictive rules which would allow direct experimental tests. Analogous to the area of synthetic radical chemistry, which was illuminated by preceding physical organic studies, the pioneering efforts of Bauer,^[6] Beak,^[7] Boche,^[8] Collum,^[9,10] Fraenkel,^[11] Hoppe,^[12] Lappert,^[13] Meyers,^[14] Schleyer,^[15] Seebach,^[16] Streitwieser,^[15] and Williard^[17] have significantly advanced our understanding of organolithium compounds with the consequent impact on synthesis.

In the area of polar organometallics, in spite of the lack of detailed knowledge of the species involved, their state of aggregation, and the mechanism of reaction with organic molecules, organolithium chemistry continues its positive march in synthesis, providing new valuable reactions, including increasing numbers which are applicable on very large scale. For example, the Merck –DuPont Merck synthesis of the angiotensin II inhibitor Losartan is a

significant demonstration. Similarly, the synthetic chemistry of enolates continues to grow, and although great advances have been made in unraveling enolate structure, the pithy comment made by Seebach in 1988, pointing out that considering our poor understanding of the nature of the species involved, it is remarkable how many reactions can actually be run with predictable results, continues to be relevant.^[22] Undoubtedly as a result of the strong basicity and high coordination and aggregation properties of organolithium compounds, their use in enantioselective synthesis has witnessed the most spectacular advance in this field since the mid-1990s.^[23,24] For the future, in view of the expense of lithium, breakthroughs in catalytic reactions of organolithiums may be anticipated.

The sections dealing with sodium and potassium compounds give unique overviews of the use of inorganic salts of these alkali metals in organic synthesis. The wide use of sodium hydroxide and potassium hydroxide, especially in phase-transfer catalysis, and the corresponding sodium and potassium alkoxides for deprotonation of C—H acids having moderate pK_a values reflects the availability and low cost of these materials. The use of sodium and potassium amides in organic synthesis has nearly disappeared from the literature since the 1970s, these strong bases being superseded by lithium dialkylamides and alkyllithiums. Organosodium and organopotassium compounds derived from sp^2 (aromatic, vinyl) and sp^3 organic compounds have not, in spite of lower cost, enjoyed general applicability owing to the difficult handling of these unstable and pyrophoric substances. In small-scale chemistry, the highly powerful Lohmann–Schlosser base combinations (R^1Li – R^2OK) are widely used.

From the rubidium/cesium product class, the special characteristics of cesium salts in certain organic reactions (such as the "cesium effect" in macrocyclization and cesium bases in Suzuki–Miyaura cross coupling) are recognized by synthetic chemists.

Finally, perhaps an unnecessary statement is that this volume, as all others in the *Science of Synthesis* series, will make its profound impact via the periodic electronic updates.

Introduction to Volume 8b

Volume 8b is the second part of the review of alkali metal chemistry from the perspective of organic synthesis and deals with sodium, potassium, cesium, and rubidium, and their selected derivatives. Organolithium compounds and other lithium species are described in *Science of Synthesis*, Volume 8a. Taken together, Volumes 8a and 8b conclude the eight-part series in Category 1 (Organometallics) following in the elegant footsteps of the alkali metal coverage in *Houben–Weyl*, Vols. 13/1 (1970) and E 19d (1993). For the presentation of methods in chemical synthesis, the major difference between *Houben–Weyl* and *Science of Synthesis* is the comprehensive and exhaustive nature of the former and the selective, critically evaluated, and most useful and reliable methods presentation of the latter.

As has been already pointed out in the introduction to Volume 8a, a major challenge in planning the volume concerned the ubiquitous nature of alkali metal compounds in organic synthesis. Broadly speaking, Volume 8 covers the alkali metals in diverse and arguably unusual categories: (a) their elemental form; (b) a number of simple derivatives such as hydrides, hydroxides, and halides; (c) "true organometallic compounds" bearing metal—carbon bonds such as alkylmetals; and (d) metal enolates. Hence, Volume 8 departs to some extent from the purely organometallics focus of the eight-part series. From the above defined categories, the simple alkali metal derivatives are most difficult in terms of information retrieval for a review because they do not appear as keywords, are too common to be abstracted, and represent a daunting number of reagents and compounds. "Simple" derivatives (category b) are encountered in a plethora of experimental procedures and are undoubtedly used in the most diverse ways. They are also among the oldest reagents of organic chemistry; sodium hydroxide, for example, was in use during the Berzelius/Woehler era.^[1]

Chemical properties and the consequent synthetic applications of derivatives of alkali metals overlap to a large degree, i.e. the behavior of sodium hydride and potassium hydride can be expected to be similar. As a result, and

also owing to the nature of multiple authorship, overlap of content between chapters is inevitable and, we would argue, desirable for the completeness of a given topic, in order to provide individual flavor and perspective by a given author, and therefore to afford a different appreciation by the reader. However, a cautionary note regarding the perceived overlap of expected chemistry is in order: selecting sodium hydroxide instead of potassium hydroxide or, similarly, a sodium enolate instead of the analogous lithium enolate for a given reaction might be a nontrivial issue. Some comments on differences in reactivity depending on the metal involved are provided in the overview of Volume 8b below.

Clearly, the chemist consulting *Science of Synthesis* is expected to be primarily interested in finding methods and procedures for the synthesis of defined targets. For this purpose, the broader the perspective, the better and therefore, as a reference source, Volumes 8a and 8b should be consulted side by side. To illustrate, the chemist in search of selecting the best method for alkylation of a C—H acid is advised to consult the sections on the lithium, sodium, and potassium species corresponding to the C—H acid, as well as the relevant sections on the most likely bases to be used for the deprotonation step (inter alia, lithium amides, lithium and sodium hydride, sodium hydroxide, and phase-transfer catalysis). In addition, organomagnesium and organozinc compounds should be considered as they are a part of the polar organometallic landscape and, in some reactions, such as nucleophilic addition to carbonyls, are synthetically equivalent to alkyllithium, alkylsodium, or alkylpotassium reagents. The reader is referred to *Science of Synthesis*, Vol. 7 [Compounds of Groups 13 and 2 (Al, Ga, In, Tl, Be ... Ba) (Section 7.6)] and Vol. 3 [Compounds of Groups 12 and 11 (Zn, Cd, Hg, Cu, Ag, Au) (Section 3.1)] for discussion of these compounds.

A number of major and distinct differences of Volume 8 compared to most *Science of Synthesis* volumes are readily identified. In particular, a product subclass is defined as follows:

- (a) A reagent that acts upon organic molecules to generate alkali metal species, e.g. sodium hydride for the synthesis of sodium alkoxides (Section 8.2.2).
- (b) A carbanionic, normally unstable and fleeting, organometallic intermediate and *not* an isolated product, e.g. vinylsodium (Section 8.2.7). There are exceptions of alkali metal organics which may be isolated, characterized, and stored for certain periods of time.
- (c) An inorganic reagent based on a group 1 metal that is useful in synthesis but has a tenuous connection to polar organometallics (e.g., sodium halides, Section 8.2.3).

With one exception, each metal constitutes a separate product class: [Section 8.1: lithium (see Vol. 8a); Section 8.2 sodium, Section 8.3: potassium, Section 8.4: rubidium and cesium]. Within each Product Subclass are given the methods of preparation of particular members of the subclass. The various synthetic intermediates of the given alkali metal are presented in a logical order in which inorganic reagents (e.g., NaH, NaCN) precede organometallic species (e.g., sodium cyclopentadienide) as outlined in the table of contents.

Therefore, the center of attention is always the preparation of an intermediate species for a given reaction as emphasized in the discussion of each category, in the tables, and especially in the delineation of experimental procedures in the methods and variations sections. After all, a stated aim of *Science of Synthesis*, in both printed and, for the computer-reliant chemists of the future, electronic form is to be the first-call source for synthetic practitioners.

Information on the scope and limitations of reactions of intermediate species is abundantly but selectively provided in the discussion, tables, and experimental procedures. In the procedures, either the generation of the organometallic species only is given and its reactions are referred to in the text, or a complete procedure in which the generation of a species, its treatment with a selected reagent, the workup of the reaction mixture, and the isolation of a product are fully elaborated. Generally, physical, but not spectroscopic, properties are given for the

products. Mechanistic discussion is minimal but references to original sources are provided.

Application of product subclass sections follow the order of methods and, where relevant, variations of methods. Some product subclasses concerning reagents and generated organometallic species lend themselves well to presentation of applications for the preparation of specific classes of organic compounds whereas others are sufficiently defined in terms of their synthetic utility within the synthesis of the product subclass sections and therefore require no separate applications sections; this is often the case for reactive intermediates.

Volume Perspective

To provide the reader with a perspective on Volume 8b, the major features are summarized below. Details can be found in the relevant sections.

The discussion in each subclass begins by consideration of the metal in the elemental state (Sections [8.2.1](#), [8.3.1](#), and [8.4.1](#)). The chemistry of group 1 metals is dominated by their low ionization energy, a feature that is responsible for their major use in reduction reactions ([Scheme 1](#)).

[Scheme 1](#) Typical Reductive Processes with Elemental Alkali Metals

All of the alkali metals in dry ammonia or in an ether solvent establish an equilibrium of a solvated electron and the corresponding solvated cation with the electron ready for transfer to a variety of functional groups. In general, the heavier the metal, the greater the reducing power of the solution. Even though a large number of other reduction protocols such as those based on catalytic hydrogenation or metal hydrides are now available, methods that rely on alkali metals are still eminently useful, being often less expensive and frequently proceeding with high chemo- and stereoselectivity. Perhaps most popular in this class is reduction involving sodium metal in liquid ammonia, which is applicable to a great variety of functional groups, and includes dearomatization (the "sodium" Birch reduction) and reductive (pinacol and McMurry) coupling procedures (**Scheme 2**).^[2–6]

Scheme 2 Examples of Reductions with Alkali Metals

A classical expression of stereoselectivity of this procedure, which is controlled by thermodynamics, is

encountered in reduction of alkynes to *E*-alkenes, and the observations on the differences between lithium and sodium in this reaction now constitute a timeless contribution to chemistry (**Scheme 3**).^[7] As evident from the experimental procedures in the appropriate sections, some effort has been expended toward developing special forms of alkali metals with altered reactivity such as "sodium sand", "micronized sodium", potassium intercalated in graphite or absorbed on alumina, and derivatives such as superactive alkali metal hydrides.^[8] Clearly, selection of the appropriate reagent is important. Common reductive processes encompass reduction of aldehydes and ketones (including reductive coupling protocols), reduction of alkenes and alkynes, and also reductive cleavage of C—O, C—N, carbon—halogen, and C—S bonds.

Scheme 3 Reduction of Alkynes with Lithium and Sodium^[7]

Sodium and potassium hydrides are used primarily as bases to generate alkoxides, enolates and, if the term may be accepted,^[9] various "carbanions". Carbanions can be used further as bases better suited to the specific system, e.g. the dimethyl anion $[\text{MeS}(\text{O})\text{CH}_2^-]$. Use of sodium hydride and potassium hydride in the generation of borohydride reagents deserves special mention {see *Science of Synthesis*, Vol. 6 [Boron Compounds (Section 6.1.2)]}. Typically, the use of an alkali metal hydride results in the formation of a polar intermediate and this is followed by a reaction with an electrophile (e.g., alkylation of carbonyl compounds, addition to a carbon—heteroatom double bond, etc.) or with a proton donor (e.g., the Nef reaction), or, less frequently, by a rearrangement or fragmentation (e.g., fragmentation of homoallylic alkoxides or oxy-Cope and other rearrangements, **Scheme 4**).^[10] Virtually every nucleophile—electrophile reaction has an intramolecular variant, e.g. the Dieckmann condensation. Often the reacting system is complex and the alkali metal hydride is used in one of several steps or as a component in a mixed reagent, e.g. metal-containing complexes used as reducing agents (Section 8.2.2) and potassium hydride/oxygen/crown ether systems used in oxidation (Section 8.3.2). An example of a multistep process that involves the hydride only in one step is the palladium(0)-catalyzed deconjugative allylation of malonates,^[11] which can be viewed from the perspective of a reaction involving sodium hydride (this point of view highlights the choice of the base used in generation of the nucleophile), as one of many reactions of metal enolates (focusing on the structure of the enolate), or by considering it as a part of the more general landscape of organopalladium chemistry (*vide infra*).

Scheme 4 Tandem [2,3]-Wittig—Anionic Oxy-Cope Rearrangement^[10]

While the selection of sodium hydride over potassium hydride might be dictated by safety factors (KH is much more reactive and more of a safety hazard), there may be better reasons for selecting one of these two seemingly very similar reagents. For example, dimsylvpotassium (generated with KH) is superior to dimsylv sodium (generated with NaH) in Hakomori methylation of carbohydrates.^[12] The basicities of sodium hydride and potassium hydride appear to be harder to quantify than, for example, those of alkoxides and may be somewhat dependent on the means of preparation of the hydride.^[13] Major applications of alkali metal hydrides are summarized in **Scheme 5**. Details, examples, and specialized applications of hydrides are found in Sections **8.2.2** and **8.3.2**. Sodium and potassium hydrides are also used in generation of metal enolates and, for these, the reagent might have a bearing on the process (*vide infra*).

Scheme 5 Typical Uses of Alkali Metal Hydrides

Alkali metal hydroxides, alkoxides, carbonates, and acetates comprise a large group of reagents that can be classified as metal –oxygen derivatives. These reagents are primarily used as bases and a number of special protocols have been developed, of which phase-transfer catalysis (PTC) is the most important. Applications of these compounds as bases for deprotonation (generation of nucleophilic anions) are rather analogous to reactions of sodium hydride and potassium hydride and follow the schematic presented in **Scheme 5**. A number of well-known reactions, such as condensations involving carbonyl compounds (aldol, Claisen, Dieckmann, Darzens, Robinson annulation, inter alia), C –C bond-forming reactions via phosphorus, sulfur, or nitrogen ylide intermediates (e.g., the Wittig, Horner –Wadsworth –Emmons, Ramberg –B äcklund reactions), addition of carbanions or other anions to multiple C –C bonds (Michael reaction and its variants), and elimination reactions (e.g., dehydrohalogenation) rely on the use of hydroxides and alkoxides as bases. Unlike the hydrides, the alkali metal –oxygen reagents are also useful as nucleophiles and participate in such textbook reactions as nucleophilic aliphatic substitution (e.g., Williamson ether synthesis, cleavage of epoxides), vinylic nucleophilic substitution, addition to carbonyl groups (e.g., ester hydrolysis, transesterification, ring opening), nucleophilic aromatic substitution, and others.

Two special subgroups of reactions involving alkoxides and hydroxides are cross-coupling processes, where alkoxides can act as activators and have a great influence on the reaction outcome,^[14] and cleavage of silyl enol ethers, where alkoxides can be used to generate the alkali metal enolate from the silyl derivative.^[15] Typical reactions of alkoxides and hydroxides acting as nucleophiles are shown in a generalized format in **Scheme 6**, which is meant to be illustrative rather than exhaustive.

Scheme 6 Typical Reactions of Alkoxides and Hydroxides as Nucleophiles, and Use in Cross-Coupling and Desilylation Reactions

While the popularity of sodium ethoxide and potassium *tert*-butoxide may be a matter of tradition (i.e., why not potassium ethoxide and sodium *tert*-butoxide?) or another reflection of safety issues, it should be noted that alkoxides of different metals tend to have different aggregate structures,^[16,17] that mixed alkoxides involving lithium and heavier alkali metals are known,^[18] and that, in several systems, different behavior of lithium, sodium, and potassium alkoxides is observed. Thus, the catalytic effects of alkali metal *tert*-butoxide clusters on the rates of ester interchange reactions are reflected in differences in reactivity as a function of the cation ($\text{Li}^+ < \text{Na}^+ < \text{K}^+ < \text{Rb}^+ < \text{Cs}^+$).^[19] Furthermore, a new variation on the classical Williamson ether synthesis, involving the preparation of *tert*-alkyl ethers via the reaction of alkyl halides with alkali metal phenoxides, has shown a variable substitution to elimination ratio depending on the metal.^[20] Also notable are the differences in the outcome of stereoselective hydrogenation of ketones catalyzed by ruthenium complexes in the presence or absence of *tert*-butyl alkoxides (sodium or potassium).^[21,22] In another illustration of metal alkoxide reactivity differences, the mechanistically interesting 1,4-dithiin to 1,3-dithiole rearrangement, which proceeds upon deprotonation with alkoxide bases, shows major differences in efficiency depending on the base: potassium *tert*-butoxide leads to quantitative rearrangement, whereas sodium and lithium *tert*-butoxides are effective only in the presence of crown ethers and conversions are low.^[23] A classic and well-recognized reaction involving different reactivity of alkoxides is the anionic oxy-Cope rearrangement where the rates depend on the degree of cation coordination and follow the order $\text{K}^+ > \text{Na}^+ > \text{Li}^+$.^[13] The alkyllithium –potassium *tert*-butoxide combination (Lochmann –Schlosser "superbase"^[24,25]) is highly useful, especially in benzylic and allylic deprotonation reactions (*vide infra*).^[26]

Outside the area of synthetic organic chemistry, several important differences in polymerization processes have been identified as resulting from using either sodium or potassium *tert*-butoxide, for example, one involving a marked change in the tacticity of the polymer.^[27]

The advent of phase-transfer catalysis (PTC, see Section 8.2.4) signaled major changes in the development of the chemistry of C –H acids, and progress in the area of enantioselective synthesis have been especially striking.^[28] While, for good reasons both in terms of concentration and nature of base, 50% sodium hydroxide solution is by far the most commonly used reagent, other systems for phase-transfer catalysis have been devised and developments in the area of solid –liquid phase-transfer catalysis, with applications of solid potassium hydroxide in dimethyl sulfoxide being especially useful, augur well for the future application of phase-transfer catalysis in organic synthesis.^[29] Although the method now seems to be relegated to textbooks as "classical", applications abound, e.g. dihalocarbene generation and Wittig reaction (Scheme 7).^[30–32] Newer extensions include solid supports preloaded with hydroxide, in which potassium hydroxide seems to be emerging as the most promising base.^[33] In the more classical liquid –liquid media, the replacement of sodium hydroxide by potassium hydroxide can lead to major differences in reactivity and selectivity.^[34]

Scheme 7 Use of Phase-Transfer Catalysis in a Wittig Reaction and in Carbene Addition^[30–32]

Following up on the theme of derivatives of alkali metals used as bases, it is noteworthy that the use of unsubstituted sodium and potassium amides as reagents in organic synthesis has nearly disappeared from the literature since the mid-1970s, these strong bases being superseded by lithium dialkylamides, alkyllithium compounds, and, to some extent, sodium and potassium hexamethyldisilazides. It may be questioned if this is actually scientifically valid and if there is truly no potential in developing dialkylamides of sodium and potassium for organic synthesis. Sodium and potassium derivatives of N—H acids include the amides, hexamethyldisilazides, mono- and disodium cyanamide, and the azides. The amides acting as nucleophiles are encountered in reactions involving alkyl- and arylamines and alkanamides, for example in N-alkylation of such compounds. In this respect, it should be noted that although most of these reactions are simple and can be performed efficiently under phase-transfer catalysis conditions, the choice of base and the experimental protocol may be critical. For example, alkylation of a derivative of tetraazacyclododecane (four N—H centers) with *tert*-butyl bromoacetate in the presence of potassium carbonate yields the corresponding tetraalkylated derivative, whereas the analogous reaction performed in the presence of solid sodium hydrogen carbonate provides the trialkylated product. These observations were exploited in synthesis of DOTA ligands.^[35] Significant applications of potassium dialkylamides include the "acetylenic walk" reaction,^[36] the palladium-catalyzed α -enolate arylation,^[37] and the sulfur ylide into epoxide transformations^[38] (**Scheme 8**).

Scheme 8 Alkyne Isomerization and Palladium-Catalyzed Arylation with Potassium Hexamethyldisilazide^[36,37]

Several product subclass sections give unique overviews of the use of inorganic salts of alkali metals in organic synthesis (Sections 8.2.3–8.2.6, 8.3.3, 8.4.2, and 8.4.3). Halides of sodium, potassium, rubidium, and cesium, and also cyanides, carbonates, and other salts, appear in a great many diverse reactions and this rich chemistry is difficult to summarize in a concise fashion. For example, sodium halides (Section 8.2.3) are used as nucleophiles in many aliphatic and aromatic substitution reactions, such as the classical Finkelstein reaction (**Scheme 9**),^[39] or the extremely useful dealkoxycarbonylation with sodium chloride (the Krapcho reaction), conditions of which tolerate the presence of many functional groups (**Scheme 10**),^[40] but sodium chloride is also used as the source of molecular chlorine for addition reactions, for reductive dehalogenation of α -halo ketones, and for oxidative transformation of alcohols into carbonyl compounds.

Scheme 9 The Finkelstein Reaction^[39]

Scheme 10 The Krapcho Dealkoxycarbonylation

Sodium iodide and sodium bromide are used in combination with transition metals, or their salts, and with lanthanides, or their salts, in a variety of applications, e.g. Suzuki –Miyaura cross coupling^[41] (**Scheme 11**), Heck coupling,^[42] and indium-mediated allylation of 1,2-diones.^[43] Selective bromo for iodo exchange in heterocycles using sodium bromide (**Scheme 12**),^[44] and cyano for halo exchange with sodium cyanide^[45] are widely applicable synthetic processes. Sodium fluoride is well-known as, inter alia, a useful reagent in cleavage of C —Si and O —Si bonds. The classical S_N2 displacement of alkyl halides and other corresponding leaving groups is augmented by the possibility to effect the equivalent of this reaction on aryl and vinyl halides under transition-metal catalysis.^[46]

Scheme 11 Suzuki –Miyaura Coupling^[41]**Scheme 12** Selective Halide Replacement with Sodium Iodide^[44]

Cesium halides and cesium carbonate are important reagents in organic synthesis with diverse applications, highlights of which include the "cesium templating effect" in macrocyclization, use as activators in numerous reactions, such as addition of nucleophiles to carbonyl groups, Michael and aldol reactions, and transition-metal-catalyzed cross coupling and related reactions, and use of cesium carbonate to generate nucleophiles (Sections 8.4.2 and 8.4.3).

In **Scheme 13**, some additional examples of reactions involving alkali metal salts are provided only to pique the reader's curiosity and entice him or her to visit the appropriate sections, since providing a general picture in one scheme is not feasible.

Scheme 13 Examples of Use of Sodium Halides in Synthesis^[47 –52]

Although enjoying relatively special synthetic application (and odors), potassium –sulfur, –selenium, and, much less, –tellurium chemistry finds utility in transformations leading to organochalcogen compounds. Potassium sulfide, selenide, and telluride, as well as the corresponding thiocyanate, selenocyanate, and tellurocyanate, are commercially available or readily prepared reagents. The most widely used reactions of potassium thiocyanate and selenocyanate are alkylations with alkyl halides in which their ambident nucleophilicity to form either C —N or carbon —chalcogen bonds is evidenced,^[53] in the synthesis of significant heterocycles (**Scheme 14**),^[54] and in stereoselective alkene inversions^[55] and epoxide to alkene transformations.^[56] In general, the corresponding sodium –sulfur, –selenium, and –tellurium derivatives are also readily prepared and are, perhaps, more widely used.

Scheme 14 Heterocycles from Thiocyanate^[54]

Polar organometallic organosodium and organopotassium compounds derived from sp^2 (aromatic, vinyl) and sp^3 organic compounds have not, in spite of lower cost, enjoyed general applicability owing to the difficulty in handling of these unstable and pyrophoric substances. The lower stability of sodium and potassium organometallics in solution compared to similar organolithium compounds has been documented.^[57]

When use of these compounds is considered during synthetic planning "metal effects", elegantly summarized by Schlosser,^[57] and also use of organomagnesium compounds (Grignard reagents) must be considered. Briefly, different metals may cause a different reaction to be favored, e.g. proton abstraction over addition to a carbon — heteroatom multiple bond or vice versa, and may be responsible for differences in regio- or stereoselectivity.

Mechanistically, the moniker "carbanions" tends to be misleading and a number of mechanisms may operate.

While benzyllithiums have seen numerous uses in organic synthesis (cf., Section 8.1.13), the analogous sodium or potassium species are not popular, perhaps also for instability reasons, and because, under conditions for their generation, side reactions such as ring metalation occur, which can also be a function of the choice of sodium or potassium base used for deprotonation (Section 8.2.11). Perhaps predictably, benzyllithium, benzylnsodium, and benzylnpotassium show different reactivity as reflected in yields and selectivities. To illustrate, varying efficiency and diastereoselectivity in reactions of isoindolinones metalated at the benzylic position using either lithium hexamethyldisilazane, sodium hexamethyldisilazane, or potassium hexamethyldisilazane in the synthesis of 3-alkylisoindolin-1-ones has been observed.^[58]

The important field of directed *ortho*-metalation of aromatics and heteroaromatics (DoM and HetDoM) has no counterpart in sodium and potassium chemistries due to such species being pyrophoric, unstable, and often unselective, although attempts to change this situation are ongoing.^[59]

Derivatives of the heaviest alkali metals, cesium and rubidium, show marked differences in chemical behavior and in structure compared to the corresponding lithium compounds (Section 8.4.1). In ether solvents, fluorenyllithium exists predominantly in the form of solvent-separated ion pairs, whereas analogous cesium compounds show contact ion pair structures. A brief discussion of the aggregation phenomena comparing lithium species with heavier alkali metals derivatives is clearly presented in Section 8.4.1. Many useful organorubidium and -cesium compounds can be prepared by proton removal from the hydrocarbon by the metal, in contrast to organolithium chemistry where this is usually not promising and the use of alkyllithium or lithium amide bases is required. Synthetic applications of organorubidium and -cesium compounds, such as in addition reactions of these nucleophilic species to carbonyl groups, are not popular (Section 8.4.4), perhaps due to the much greater instability of such reagents.

In small-scale chemistry, the highly powerful Lochmann –Schlosser superbase combinations are reasonably widely used and a number of synthetic applications have been reported (Section 8.3.7). Some illustrative examples are shown in **Scheme 15**.^[60,61]

Scheme 15 Synthetic Applications of Superbases^[60,61]

Organosodium compounds stabilized by an adjacent heteroatom, such as metalated sulfoxides (of which dimethylsodium is the most popular), sulfones, sulfoximines, and nitronates, as well the corresponding , -

disubstituted species (metalated disulfones, -nitro sulfones, and dinitronates) have found broad application in organic synthesis (Sections 8.2.12 and 8.2.13). The derived species are used in synthetic methods of alkylation or addition to a carbonyl group, or addition–elimination protocols; amongst the latter, the aromatic vicarious nucleophilic substitution (VNS) of hydrogen deserves special mention as it provides a new approach to functionalization of aromatic compounds (Scheme 16).^[62] Some reagents in this class provide a convenient source of carbonyl synthetic equivalents with reactivity umpolung; for example methyl (methylsulfanyl)methyl sulfoxide metalated twice (in two separate steps) constitutes a carbonyl dianion equivalent (Scheme 17).^[63]

Scheme 16 The Aromatic Vicarious Nucleophilic Substitution of Hydrogen^[62]

Scheme 17 Synthesis of a Ketone by Double Alkylation of Methyl (Methylsulfanyl)methyl Sulfoxide^[63]

Alkali metal enolates are now well established as the most important class of reactive intermediates for C—C bond formation. Briefly, their reactions include nucleophilic displacement (alkylation, silylation, and replacement of the α -hydrogen with a heteroatom-based functional group, such as hydroxy), addition to carbonyl groups (aldol and related reactions), addition to C=N bonds (Mannich reaction), and addition to electron-deficient C=C bonds (Michael reaction). An abbreviated "cartoon" summary of reaction types is presented in Scheme 18. Most of these reaction types have intramolecular variants and many strategies for enantioselective and diastereoselective synthesis of chiral compounds have been developed (see Section 8.1.17).

In the area of enolate chemistry the sentiment that sodium enolates are superfluous or, at least, overshadowed by lithium enolates surfaces occasionally. The synthetic community would be, however, poorly served if sodium enolates were to be forgotten. The major difference in overall lithium and sodium (or potassium) enolate chemistry is that the former is dominated by kinetically controlled protocols while the latter involves mostly reactions under thermodynamic control.^[64] The predominance of thermodynamic protocols in chemistry of sodium and potassium enolates is more a consequence of tradition than necessity. Teachers of organic synthesis often observe students falling in love with lithium diisopropylamide and hurriedly suggesting its use for all deprotonation reactions, with the obvious unnecessary complications in such reactions as the venerable malonate and acetoacetate condensations. Bases that are typically used for generation of sodium and potassium enolates involve the corresponding alkali metal hydrides, alkoxides, and hexamethyldisilazanides, the latter allowing the reactions to be performed under kinetic control. Because the hydrides are non-nucleophilic, carrying out certain types of multiple reactions, such as polyalkylation of ketones, in "one pot" by using excess of the base and excess of the electrophile is possible, in contrast to protocols involving lithium amides as bases.^[65]

There are numerous significant differences in reaction outcomes between lithium, sodium, and potassium enolates including control of O- vs C-alkylation of enolates (sodium enolates give a greater proportion of O- vs C-alkylation; Section 8.2.15). Another instructive reaction is the alkylation of aldehydes; α -alkylation of aldehydes via

deprotonation using lithium amides is not a viable synthetic protocol due to intervening side reactions such as hydride transfer from the amide to the carbonyl group, addition of the amide to the carbonyl group, and, to a smaller extent, self-aldolization,^[66] but potassium enolates of aldehydes, generated using potassium hydride, can be smoothly alkylated.^[67] In addition, alkylation and aldol reactions of ketone enolates can differ substantially in regioselectivity depending on the cation (lithium, sodium, or potassium).^[68,69] The enolization process itself can be affected by the choice of base and thus, for example, regioselectivity differences using lithium bases vs sodium hydride or potassium alkoxide bases are known.^[57] A synthetically very valuable hydroxylation of enolates using 2-sulfonyloxaziridines proceeds in much higher yields with potassium enolates than with lithium enolates.^[70]

Scheme 18 Typical Reactions of Alkali Metal Enolates

The importance of structural studies on lithium enolates, especially concerning aggregation phenomena, has led to similar investigation of sodium enolates but not of potassium enolate aggregates. In the solid-state crystal structures, lithium, sodium, and potassium enolates show certain similarities but also differences in aggregation numbers.^[71,72]

This brief overview only touches on some of the multitude of methods and reactions that comprise Volume 8b. To conclude, perhaps an unnecessary statement is that Volume 8, as all others in the *Science of Synthesis* series, will make its profound impact via the periodic electronic updates. The reader may be richly rewarded in making comparisons especially between the organometallic chemistry of lithium and that of potassium and sodium in solving his or her synthetic problems.

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Hetarenes

, in *Science of Synthesis*, **9** (), p.1

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



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Hetarenes**Volume 9:****Fully Unsaturated Small Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom**

Maas, G., in *Science of Synthesis*, **9** (2000), p.1

This volume covers the synthesis of three- and four-membered heterocycles with maximum unsaturation and five-membered hetarenes with one oxygen, sulfur, selenium, tellurium, nitrogen, or phosphorus atom. The parent ring systems treated in this volume are shown in **Table 1** together with the sections in which they appear. Obviously, this collection does not include ring systems incorporating heteroatoms of elements with metallic character such as arsenic, lead, or silicon and its higher homologues. Such heterocycles will appear in volumes devoted to organoelement compounds.

Table 1 Structures and Numbering Schemes of the Heterocycles Covered in Volume 9

Product Class	Ring System
oxirenes	 oxirane Section 9.1
thiirenes	
selenirenes	 selenirane Section 9.3
tellurirenes	 tellurirane Section 9.4
1 <i>H</i> -azirines	 1 <i>H</i> -azirine Section 9.5
phosphirenes	
three-membered rings with P and one or more heteroatoms	
four-membered rings with one or more heteroatoms	





furans	 furan Section 9.9
thiophenes	
selenophenes	 selenophene Section 9.11
tellurophenes	 tellurophene Section 9.12
pyrroles	 1H-pyrrole Section 9.13
phosphaoles	

Table 1 also illustrates how the individual product classes are further divided into product subclasses. While the subclasses associated with thiirenes, phosphirenes, thiophenes, and phosphaoles all embrace a group of chemically closely related molecules, this is not always so for the ring systems registered in Sections 9.7 and 9.8. In these cases, practical considerations, such as the low number of different synthetic pathways to these systems and the avoidance of having too many product classes with only a couple of members, have led to the chosen system.

This volume deals mostly with the *synthesis* of the heterocyclic ring systems shown in **Table 1**. For furans, thiophenes, and pyrroles, in contrast to all other systems, the wealth of available methods does not allow a comprehensive coverage to be given here, and only selected methods are presented. The *chemistry* of these

heterocycles is only discussed insofar as it is relevant to their synthesis (examples: subsequent reactions of oxirenes and azirines, formed only as reactive intermediates; generation of some of the three- and four-membered phosphorus-containing heterocycles in the coordination sphere of transition metals or trapping by metal complexation); for the five-membered heteroarenes, reactions of substituents at the α -position of the ring are also addressed briefly.

The synthesis of furans, thiophenes, and pyrroles was discussed in a comprehensive manner in *Houben –Weyl*, Vol. E 6.^[1] Azetes have been covered in *Houben –Weyl*, Vol. E 16c,^[2] and 1,2-dithietes in *Houben –Weyl*, Vol. E 11/2.^[3] The structure, synthesis, chemistry, and applications of many heterocyclic ring systems covered in this volume have also collectively been reviewed.^[4,5] References to reviews on specific heterocyclic systems are given in each article. The major part of this volume is devoted to the synthesis of furans, thiophenes, and pyrroles. Readers who wish to obtain the most important facts on the synthesis, reactivity, and properties in particular of these three product classes in condensed form are recommended to consult some recent textbooks on heterocyclic chemistry.^[6-9]

The synthetic methods for each ring system are arranged in general according to the following scheme, which applies strictly only for the five-membered heteroarenes, although not all subheadings are relevant in all cases. For the three- and four-membered rings, this scheme is applied appropriately.

x: volume number = 9; **y:** product class; **z:** product subclass

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Formation of Two Heteroatom —Carbon Bonds and One C —C Bond

x.y.z.1.1.1 Fragment X and Two C —C Fragments

x.y.z.1.1.2 Fragments C —C —C, X, and C Although this is a possible disconnection, no associated methods are given in this volume.

x.y.z.1.2 By Formation of One Heteroatom —Carbon and Two C —C Bonds

x.y.z.1.2.1 Fragments X —C, C —C, and C

x.y.z.1.2.2 Fragments X —C —C and Two C Fragments Although this is a possible disconnection, no associated methods are given in this volume.

x.y.z.1.3 By Formation of Three C —C Bonds

x.y.z.1.3.1 Fragment C —X —C and Two C Fragments

x.y.z.1.4 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.4.1 Fragments C —C —C —C and X

x.y.z.1.5 By Formation of One Heteroatom —Carbon and One C —C Bond

x.y.z.1.5.1 Fragments X —C —C and C —C

x.y.z.1.5.2 Fragments X —C and C —C —C

x.y.z.1.5.3 Fragments X —C —C —C and C

x.y.z.1.6 By Formation of Two C —C Bonds**x.y.z.1.6.1** Fragments C —X —C and C —C**x.y.z.1.6.2** Fragments C —X —C —C and C**x.y.z.1.7** By Formation of One Heteroatom —Carbon Bond**x.y.z.1.7.1** Fragment X —C —C —C —C**x.y.z.1.8** By Formation of One C —C Bond**x.y.z.1.8.1** Fragment C —X —C —C —C**x.y.z.1.8.2** Fragment C —C —X —C —C**x.y.z.2** Synthesis by Ring Transformation

x.y.z.3 Aromatization (e.g., by Oxidation of Dehydro Compounds or Elimination Reactions) In this volume, the term "aromatization" should be interpreted as "introduction of maximum unsaturation", since the target ring systems can be aromatic, antiaromatic, or nonaromatic.

x.y.z.4 Synthesis by Substituent Modification

The fragment headings in the list given above are a useful categorization scheme whenever a chosen strategy to assemble a ring system by formation of one or more heteroatom —carbon or C —C bonds can be achieved with different building blocks. For example, assembly of a thiophene ring by formation of one S —C and one C —C bond can be effected by three different combinations of building blocks or fragments as shown in [Scheme 1](#). In cases where a ring is assembled from two or more fragments, the fragment headings which include fragments of similar size and contain the heteroatom in the larger fragment are mentioned first. However, some minor deviations from this general rule of *Science of Synthesis* can be found in this volume. Thus, the author of Sections [9.13.1.5](#) and [9.13.1.6](#) arrived at a different order by "working around the ring" with one C —C disconnection, which is, of course, another reasonable approach.

Scheme 1 Three Ways To Construct a Thiophene Ring by Formation of One S —C and One C —C Bond

While fragment headings are especially useful for the five-membered rings (see Sections [9.10](#) and [9.13](#) for graphical representations of the fragment approach to the synthesis of thiophenes and pyrroles, respectively), they are applied for systematic reasons throughout this volume, even in cases where this is redundant information, as for example in the cases of ring closure by formation of two heteroatom —carbon bonds or of one heteroatom —carbon bond.

After the fragment headings, a further subdivision into methods is given. In the sections on furans, thiophenes, and pyrroles, selected methods are presented which are considered the most useful and versatile ones to obtain the respective ring system with a certain substituent pattern. For all other ring systems, only a small number of different methods exist, partly because the chemistry of particular ring systems is still under active development, and therefore the given list of methods is more or less complete. In selected cases, methods are further subdivided into variations on a method. The presentation of methods and variations is generally given to include:

1. An introduction, in which some (historical) background information is given, the scope of the method/variation is described, and a comparison with other methods/variations is eventually made; safety information is given when necessary, and mechanistic information is provided where relevant to the use of the method in synthesis.
2. Reaction schemes associated with a short list of representative examples.
3. Representative experimental procedures.

Within each article, the organizational principle is based on the synthetic methods used, not on the functional groups or substitution patterns of the heterocyclic product. Related methods, e.g. those involving the simultaneous formation of two C—C bonds, are grouped together, not necessarily the methods of synthesis of similarly substituted heteroarenes. However, the index can be used to locate methods recommended for the synthesis of a particular type of heteroarene with specific substituents.

The term "fully unsaturated ring systems" in the title of this volume also deserves a short comment. It is applied here to heterocycles with the maximum possible number of double bonds, or of C=C bonds in the ring, or of other double bonds, depending on which criterion is applicable. It follows from this definition that 1*H*-azirines **1** and 1*H*-phosphirenes **3** (Scheme 2) are covered in this volume while the respective isomers, 2*H*-azirines **2** and 2*H*-phosphirenes **4**, are not. By the same principle, 2*H*- and 3*H*-pyrroles and 2*H*-phospholes do not appear as product subclasses in this volume.

Scheme 2 1*H*- and 2*H*-Isomers of Azirines and Phosphirenes

From a structural point of view, three-membered and some of the four-membered heterocyclic ring systems reach the level of full unsaturation when they carry heteroatoms with an unshared pair of electrons that can eventually conjugate with the π -orbitals of the ring double bond. For the sake of completeness, however, it was decided to also include some subclasses of unsaturated heterocycles where this unshared pair of electrons was involved in further bonding. Thus, thiirene 1,1-dioxides were included as a subclass of thiirenes; as subclasses of phosphirenes, not only derivatives of trivalent phosphorus (3 -1*H*-phosphirenes) but also of quinquivalent phosphorus (5 -1*H*-phosphirenes) as well as the 1 -metal complexes of 3 -1*H*-phosphirenes are given. As the only exception in the group of five-membered heteroarenes, the thiophene 1,1-dioxides were included as a subclass of thiophenes although they are clearly not heteroaromatic compounds. This was done because of their close relationship to thiophenes and in order to complete the presentation of their syntheses, which is addressed in part already in the preceding section on substituent modification of thiophenes.

The ring systems covered in this volume embrace a wide range of stabilities as well as physical and chemical properties. This is in part connected to the question of whether or not cyclic π -conjugation exists in these heterocycles and, if so, whether it leads to an antiaromatic destabilization or aromatic stabilization of the molecule. Oxirenes, 1*H*-azirines, thiirenes, and selenirenes (see Table 1) are prototypes of Hückel-type antiaromatic compounds with a 4 π -electron system. In fact, no stable representatives of these systems have been isolated so far, but low-temperature matrix-isolation studies gave spectroscopic evidence of their formation in a few cases,^[10] including the parent thiirene^[11] and selenirene.^[12] Thus, these species represent, in general, highly reactive intermediates and their participation in a reaction must be concluded from product analysis and isotope labelling studies [for this reason, the style of the articles on oxirenes (Section 9.1), thiirenes (Section 9.2), selenirenes (Section 9.3), and 1*H*-azirines (Section 9.5) is different from the others; since the synthetic approach does not give these species as stable products but rather leads to other products formed subsequently, detailed arguments

supporting the intermediacy of the reactive species are also described]. For example, oxirenes may be involved in the enzymatic or chemical oxidation of alkynes with sources of oxygen atoms (Section 9.1.1), and there are indications that they interconvert with α -oxo carbenes. Azirines and thiirenes are assumed to take part in a similar rearrangement (Scheme 3).

Scheme 3 Oxirenes, Azirines, and Thiirenes as Intermediates
in Carbene –Carbene Rearrangements

The S-oxides of thiirenes, the thiirene 1-oxides and thiirene 1,1-dioxides, are both more stable than thiirene itself. Several compounds of this type have been synthesized, and 2,3-diphenylthiirene 1-oxide (5) has been found to be more stable thermally than the 1,1-dioxide 6. It is assumed that this difference is due to the fact that sulfur dioxide is a better leaving group than sulfur monoxide, which is also reflected in the different thermolysis pathways of both compounds (Scheme 4). The chemistry of thiirene 1-oxides and 1,1-dioxides is characterized by nucleophilic opening of the strained ring and cycloaddition reactions across the C=C bond.

Scheme 4 Thermolysis Pathways of 2,3-Diphenylthiirene 1-Oxide (5)^[13]
and 1,1-Dioxide 6^[14]

Thiirenium ions are sulfur analogues of the Hückel-aromatic cyclopropenylum ions, and it is therefore not surprising that several dialkyl- and alkyl-aryl-substituted derivatives of this ring system could be isolated as stable salts with non-nucleophilic counterions (Section 9.2.4).

The synthesis of the first 3 -1*H*-phosphirene was reported in 1982; since then, the chemistry of these systems and of the related 5 -1*H*-phosphirenes, and 3 -1*H*-phosphirenium and 5 -1*H*-phosphirenium salts as well, has been under intense investigation.^[15,16] 3 -1*H*-Phosphirenes, in contrast to 1*H*-azirines, are not antiaromatic compounds since the phosphorus atom has a distorted pyramidal configuration which prevents the unshared pair of electrons from conjugation with the σ -bond in the ring, also, the large barrier to inversion at phosphorus prevents a planar C_{2v} transition state which would generate an antiaromatic situation. 3 -Phosphirenes can occur as 1*H*- or 2*H*-tautomers. Ab initio calculations show that, for the parent compound, the 2*H*-tautomer is more stable, while substitution at phosphorus with a halogen, especially fluorine, reverses the stabilities (Scheme 5).

Scheme 5 1*H*- and 2*H*-Tautomers of 3 -Phosphirenes

In practice, the parent 1*H*-phosphirene is not known, and a 1-unsubstituted phosphirene, 2-*tert*-butyl-3-phenyl- ³-1*H*-phosphirene, readily decomposes in solution to give the alkyne and presumably a phosphinidene (PH) (Section 9.6.5.3.4.1). On the other hand, a good number of ³-1*H*-phosphirenes are known which are substituted at phosphorus not only with halogen but also with various other groups. 1-Chloro- ³-1*H*-phosphirenes **7** are key compounds to generate other phosphirenes by nucleophilic substitution of the chlorine atom (**Scheme 6**).^[17-19]

Scheme 6 Substitution Reactions with 1-Chloro- ³-1*H*-Phosphirenes^[18,19]

⁵-1*H*-Phosphirenium ions **8** (**Scheme 7**) are stabilized energetically by π aromaticity according to ab initio calculations,^[20] and the parent ³-1*H*-phosphirenylium ion **9** is an aromatic 2 π -delocalized system with a resonance energy of 34–38 kcal·mol⁻¹. In practice, the ions **8** are much easier to prepare than **9** as stable salts. A number of phosphirenium salts **8** have been isolated in the form of their tetrachloroaluminate and triflate salts, whereas the presence of chloride ions (as well as of better nucleophiles such as water) tends to induce ring opening. ³-1*H*-Phosphirenylium ions have been postulated as intermediates in various nucleophilic substitution reactions of 1-halo- ³-1*H*-phosphirenes. However, no stable salt of type **9** has been isolated so far, and the first species to be characterized by NMR in solution [**9**, R¹ = *t*-Bu; R² = Ph; X = B(OTf)₄; generated in liquid sulfur dioxide] was only reported in 1994.^[21]

Scheme 7 ⁵-1*H*-Phosphirenium **8** and ³-1*H*-Phosphorenylium Salts **9**

Among the fully unsaturated four-membered heterocycles, azetes (azacyclobutadienes) have probably attracted

most attention from both a synthetic and a theoretical point of view. According to theory, they are antiaromatic compounds similar to cyclobutadienes. While the parent azete is still unknown, thermodynamic stabilization (by amino substituents or benzannulation) and kinetic stabilization (by bulky substituents) leads to isolable azetes. By far the best investigated azete so far is tri-*tert*-butylazete (**10**), which is readily obtained by thermolysis of tri-*tert*-butylcyclopropenyl azide.^[22] In spite of its kinetic stabilization, it is a highly reactive compound which is easily oxidized and hydrolyzed and undergoes a broad range of addition and cycloaddition reactions (**Scheme 8**).^[2,23]

Scheme 8 Generation and Selected Transformations of Tri-*tert*-butylazete (**10**)^[23]

In contrast to azetes, derivatives of ⁵-phosphete and ³-phosphete are much less known. ⁵-Phosphetes have been isolated so far only in benz- or naphthannulated form **11**^[24] and ³-phosphetes have been obtained only as ⁴-ligands of transition-metal complexes. For the whole set of fully unsaturated four-membered phosphorus heterocycles (see **Table 1**), it appears that the presence of a ⁵-phosphorus rather than a ³-phosphorus atom gives a better chance of isolating such a ring system. Thus, compounds **11**–**18** (**Scheme 9**), all of which contain at least one ⁵-phosphorus atom, have been isolated, whereas all other phosphetes of **Table 1**, containing only ³-phosphorus, have so far been generated only in the coordination sphere of transition metals. It should be mentioned that, for some of the compounds shown in **Scheme 9**, crystal structure analyses, spectroscopic data, and chemical behavior suggest that the ring double bonds are highly polarized and that an ylide description is more appropriate.^[38] In contrast to the other compounds in **Scheme 9**, 1 ⁵,3 ⁵-diphosphetes constitute a well-investigated subclass with many compounds, the chemistry of which is dominated by the strong carbanionic nature of the ring carbon atoms and the ability to form six-membered ring systems by insertion of π -systems such as alkynes and isocyanates (see Section **9.8.7**).

Scheme 9 Fully Unsaturated Four-Membered Phosphorus Heterocycles Which Have Been Isolated^[24-37]

1,2-Dithietes **19** and the less-studied 1,2-diselenetes are π -isoelectronic with benzene. The parent 1,2-dithiete has been generated by pyrolysis of 1,3-dithiol-2-one and was shown to exist at 620 °C in the gas phase.^[39] 1,2-Diselenete has been generated analogously and was characterized by photoelectron spectroscopy in the gas phase and by IR spectroscopy in an argon matrix.^[40] A variety of 3,4-disubstituted 1,2-dithietes have also been isolated and were shown to have an interesting chemistry. A typical feature of these compounds is the valence equilibrium with 1,2-dithiones (**Scheme 10**); electron-attracting or sterically demanding substituents stabilize the cyclic form whereas electron-donating substituents favor the 1,2-dithione form.

Scheme 10 The Valence Equilibrium between 1,2-Dithietes **19** and 1,2-Dithiones **20**

Furan, thiophene, selenophene, tellurophene, and pyrrole are five-membered heteroaromatic compounds; they are also called π -excessive heteroarenes since their π -electron density at each atom is higher than in benzene. Although quantification of their relative aromaticities is difficult owing to the variety of different criteria to define and to evaluate aromaticity, most of the presently available criteria point to an order of decreasing aromaticity of benzene > thiophene > selenophene > pyrrole > tellurophene > furan.^[6]

Furans, thiophenes, and pyrroles occupy a major role among heteroaromatic compounds. They are both synthetic targets and building blocks for further transformations which do not leave the heteroaromatic ring intact. Only a few aspects of their synthesis and reactivity will be mentioned here.

The majority of substituted furans, thiophenes, and pyrroles are synthesized from acyclic precursors, and it is therefore helpful to know which particular pattern of substituents and functionalities can be achieved with a certain synthetic method. For the major ring-closure procedures, readily accessible starting materials can be used in many

cases, and the same general strategy can often be applied to synthesize all three ring systems. Some selected examples are shown in **Scheme 11** together with the sections in which they appear. Additional flexibility of a certain synthetic method often results from the replacement of a functional group by a similar one, e.g. a carbonyl function may be replaced by an imine function or a cyano group, and α -halo ketones may be replaced by other α -electrophilic carbonyl compounds and their synthetic equivalents.

Scheme 11 Some General Methods for the Synthesis of Furans, Thiophenes, and Pyrroles from Acyclic Precursors

Fragments $\text{C} - \text{C} - \text{C} - \text{C}$ and X , or Fragment $\text{X} - \text{C} - \text{C} - \text{C} - \text{C}$

(**a**₁) From 1,4-diketones: Paal–Knorr ($\text{X} = \text{O}$, NR) or Paal ($\text{X} = \text{S}$) synthesis

(**a**₂) From buta-1,3-diynes

Fragments $\text{X} - \text{C} - \text{C}$ and $\text{C} - \text{C}$

(**b**₁) From 3-oxocarboxylic esters and α -halocarbonyl compounds

(b₂) From α -hydroxy (-sulfanyl, -amino) ketones and activated alkynes

(b₃) From α -hydroxy (-sulfanyl, -amino) ketones and active methylene compounds

Fragments C —X —C and C —C

(c₁) From bis(acceptor-substituted methyl)amines (ethers, sulfides) and 1,2-diketones (Hinsberg synthesis)

Electrophilic-substitution reactions are typical for the introduction of substituents at preformed furan, thiophene, and pyrrole rings. Because of the π -excessive character of these heteroarenes, the reaction rates are higher than in the case of benzene. For the electrophilic bromination of the α -position, relative rates of 3×10^{18} (pyrrole), 6×10^{11} (furan), 5×10^9 (thiophene), and 1 (benzene) have been calculated from rate and isomer distribution data, but the

differences are not always so expressed. It is interesting to note that pyrrole reacts substantially faster than furan in spite of its higher degree of aromaticity, mainly because of better stabilization of the intermediate σ -complex. As will be discussed in the respective articles, electrophilic substitution reactions, such as halogenation, nitration, acylation, and alkylation, can be carried out under much milder conditions than in the case of benzene, and less-electrophilic reagents can often be used. The latter possibility sometimes turns into a necessity, for example in order to avoid unselective and multiple halogenation reactions of pyrroles or to circumvent the sensitivity of the most electron-rich heteroarenes, pyrroles and furans, towards strong proton Lewis acids, from which ring opening and polymerization often results.

In solution reactions, electrophiles preferentially attack the 2-position rather than the 3-position, the 2-directing effect being highest for furan and lowest for pyrrole.^[6,41] General trends for the directing effect of substituents are also known.^[6] Five-membered heteroarenes with 2- and 2,5-substitution are readily obtained by direct electrophilic-substitution reactions, but selective introduction of substituents in the 3- and 4-position requires blocking of the 2-position(s) and eventually removal of these substituents after manipulation of the 2-position(s), as illustrated in the synthesis of 3-bromothiophene (**21**) (Scheme 12).^[42] In pyrroles, strongly electron-withdrawing or sterically demanding removable substituents at nitrogen favor 3-substitution. Thus, pyrroles **23**^[43,44] and **24**^[45] could be synthesized from 1-phenylsulfonyl- and 1-(triisopropylsilyl)pyrrole, respectively. It must be mentioned, however, that in contrast to the Friedel–Crafts acylation of 1-(phenylsulfonyl)pyrrole, softer electrophiles still react almost exclusively by 2-substitution (e.g., Vilsmeier formylation with *N,N*-dimethylformamide/phosphoryl chloride, cyanation with cyanogen bromide/aluminum trichloride^[43]).

Scheme 12 Directed Synthesis of 3-Substituted Thiophenes **21**^[42] and **22**^[46] and Pyrroles **23**,^[43,44] **24**,^[45] and **25**^[45]

Highly regioselective and efficient substitution reactions are possible when a metalated furan, thiophene, or N-substituted pyrrole is exposed to electrophilic reagents. If no other substituent is present, metalation at the 2-position is usually achieved by hydrogen–lithium exchange. A bromine–lithium exchange using butyllithium or *tert*-butyllithium allows selective metalation at the corresponding ring position. The syntheses of 3-acetylthiophene (**22**)^[46] and of 3-substituted pyrroles **25** (Scheme 12) illustrate these selective transformations.

The ring systems of furan, thiophene, and pyrrole occur in many compounds of natural or synthetic origin. Since it is not in the scope of this volume to give an overview on these compounds, it may suffice to single out two compounds, lamellarin L (**26**) and ningalin B (**27**), from two closely related classes of marine natural products which are currently under active investigation as new antitumor agents and as nontoxic modulators of the multidrug-resistant phenotype. Both **26** and **27** (Scheme 13) are highly substituted and functionalized pyrrole derivatives and, in both cases, the pyrrole ring was constructed with most of the functionality already present in the precursors. The total synthesis of **26** used two different arylpyruvic acid units with a Paal–Knorr-type ring-closure step (i.e., two C—C fragments and an N fragment),^[47] and the pyrrole ring of **27** was generated by a reductive ring-contraction of a tetrasubstituted 1,2-diazine.^[48] Another approach to the lamellarin class of alkaloids used an intramolecular azomethine ylide cycloaddition reaction (i.e., fragments C—N—C and C—C).^[49]

Scheme 13 Lamellarin L (**26**) and Ningalin B (**27**)

Derivatives of furan, thiophene, and pyrrole can also be found in a number of pharmaceuticals. The thiophene ring is often introduced because it is considered to be bioisosteric with the benzene ring; however, this does not prevent the synthesis of a compound with modified biological activity. The following pharmacologically active compounds are listed in Scheme 14: ranitidine (**28**), one of the most successful drugs ever developed (histamine H₂-receptor antagonist; treatment of gastrointestinal disorders and of gastric and duodenal cancer), furosemide (**29**; diuretic), nitrofurantoin (**30**; bacteriostatic and bactericide; used for wound treatment), nitrofurantoin (**31**; treatment of infections of the urinary tract), articain or carticain (**32**; local anesthetic), pyrantel (**33**; anthelmintic), thenalidin (**34**; histamine H₁-receptor antagonist), tiagabine (**35**; anticonvulsant), tiaprofenic acid (**36**; anti-inflammatory), tioconazol (**37**; local antimycotic), ketorolac (**38**; analgesic, anti-inflammatory; alleviation of postoperative pain), atorvastatin (**39**; lowering of cholesterol levels), and zomepirac (**40**; analgesic, anti-inflammatory).

Scheme 14 Selected Examples of Pharmacologically Active Compounds with Furan, Thiophene, and Pyrrole Units

Some agrochemicals also contain furan and pyrrole rings as the central structural unit. Formecyclox (**41**) and related furancarboxamides are components of formulations of seed-disinfectant fungicides and wood preservatives. Several 5-substituted 2-nitrofurans are known for their fungicidal, insecticidal, or plant growth-regulatory activities (**Scheme 15**). The 4-aryl-1*H*-pyrrole-3-carbonitriles **42** and **43** (fempiclonil) are fungicides used in cereal seed treatment.^[50] The fully substituted pyrrole **44** (Pirate) has recently been registered in the US and in Japan as an agricultural insecticide and miticide;^[51,52,66] it is interesting to note that this compound was developed from the lead structure of dioxapyrrolomycin (**45**), which was isolated from fermentation broths of streptomyces fungi and displayed a moderate broad-band insecticidal activity.

Scheme 15 Selected Examples of Agrochemicals with Furan, Thiophene, and Pyrrole Units

In materials science, oligo- and polythiophenes have met considerable interest due to their conductivity, electroactivity, and long-term chemical stability, and they play an important role in the design of functional conducting polymers with a broad range of possible applications.^[53,54] Polypyrroles, including simple substituted ones, and polypyrrole copolymers have also been evaluated as conducting polymers for many applications,^[54] for instance as solid electrolytes in capacitors,^[55] in electrocatalysis on modified electrodes,^[56,57] and as electrodes in chemical sensor and biosensor devices.^[58]

³-1*H*-Phospholes are only weakly aromatic because the high intrinsic inversion barrier of the pyramidal phosphorus cannot be overcome by the substantial stabilization by π -electron delocalization in the planar form. Since the unshared pair of electrons at phosphorus cannot overlap efficiently with the π -orbitals of the diene system, 1*H*-pyrroles behave like a combination of a 1,3-diene and a phosphine, and they resemble cyclopentadienes more than 1*H*-pyrroles.^[16,59] Typical for the reactivity of 1*H*-phospholes **46** is the easy cleavage of the exocyclic P—R bond with alkali metals leading to phospholide ions **47**, and the rearrangement into 2*H*-phospholes by an initial [1,5]-sigmatropic shift of the P-substituent, e.g. **48** \rightarrow **49** (**Scheme 16**). The 2*H*-phospholes undergo dimerization but can be trapped in a Diels–Alder reaction with dienophiles,^[60,61] e.g. **49** \rightarrow **50**, and 1,3-dienes.^[60] P—H phospholes undergo the [1,5]-*H* shift readily at low temperature and therefore the parent compound was observed in solution only at 173 K.^[61] Heating of 1*H*-phospholes in the presence of potassium *tert*-butoxide is another route to generate phospholide ions (e.g., **48** \rightarrow **51**, via deprotonation of intermediate 2*H*-phospholes), and the latter can be alkylated to give other 1-substituted phospholes (**51** \rightarrow **52**).^[62] Furthermore, the 1*H*-phosphole system can act as a 1,3-diene in Diels–Alder reactions and as a 2 π -component in photochemical [2 + 2]-cycloaddition reactions.

Scheme 16 Reactivity Patterns of ³-1*H*-Phospholes^[60-62]

In contrast to 1*H*-phospholes, phospholides are without doubt aromatic planar rings with a fully delocalized 6 π -electron system. Their chemistry seems to take place exclusively at phosphorus, but this is no longer the case with the π -phospholyl metal complexes; for example, phosphoferrocenes undergo Friedel–Crafts acylation and Vilsmeier formylation at the phospholyl ligand (see Section 9.14.3).

Some phosphole derivatives have recently emerged as promising phosphine-type ligands in transition metal-catalyzed organic transformations (Scheme 17). Palladium complex 53, containing a tetraphosphole macrocycle as ligand, was found to be a robust catalyst in cross-coupling reactions of the Stille and Heck type.^[63] Starting from 1*H*-phospholes, 1-phosphanorbornadienephosphonates 54^[64] and 2,2'-bis(1-phosphanorbornadienyl) 55, as well as some related compounds,^[65] were synthesized. The water-soluble compounds 54 can serve as ligands for the biphasic rhodium-catalyzed hydroformylation of alkenes, and enantiopure 55 (BIPNOR) displays high efficiency in the rhodium- or ruthenium-catalyzed asymmetric hydrogenation of C=C and C=O bonds.

Scheme 17 Novel Phosphole Derivatives Used in Homogeneous Catalysis^[63-65]

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10 **Hetarenes**
Volume 10:
Fused Five-Membered Hetarenes with One Heteroatom

Thomas, E. J., in *Science of Synthesis*, **10** (2000), p.1

This volume covers the synthesis of five-membered heterocyclic compounds with either an oxygen-, sulfur-, nitrogen-, selenium-, tellurium-, or phosphorus-containing heterocycle fused to one or two benzenoid rings. The parent ring structures of the heterocycles covered in this volume are shown in **Scheme 1** together with the numbering schemes used.

Scheme 1 Structures and Numbering Schemes for the Parent Heterocycles Covered in Volume 10

The synthesis of the *O*-, *S*-, and *N*-heterocycles was discussed in *Houben-Weyl*, Vol. E 6^[1] and their structure, synthesis, and chemistry has also collectively been reviewed.^[2,3] References to reviews on specific heterocyclic systems are given in each chapter.

This volume presents selected procedures for the *synthesis* of benzo-fused five-membered hetarenes. The *chemistry* of these heterocycles is only presented insofar as it is relevant to their synthesis, e.g. by modification of substituents. The discussions of each class of hetarene generally follow the following pattern, although some chapters follow a slightly different order to emphasize the most useful approaches to the hetarene in question and not all subsections are relevant to all hetarenes:

x: volume number = 10; **y**: product class; **z**: product subclass

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Annulation to an Arene

x.y.z.1.1.1 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.1.2 By Formation of One Heteroatom —Carbon Bond and One C —C Bond

x.y.z.1.1.3 By Formation of Two C —C Bonds

x.y.z.1.1.4 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.1.5 By Formation of One C —C Bond

x.y.z.1.2 By Annulation to the Heterocyclic Ring

x.y.z.1.2.1 By Formation of Three C —C Bonds

x.y.z.1.2.2 By Formation of Two C —C Bonds

x.y.z.1.2.3 By Formation of One C —C Bond**x.y.z.2** Synthesis by Ring Transformation**x.y.z.3** Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)**x.y.z.4** Synthesis by Substituent Modification

The sections listed above are further subdivided into methods which have been selected as the most useful for the preparation of the hetarene in question. Each method is presented separately as follows:

1. Introduction; comparison with other methods.
2. Presentation of the scope of the method to include: background, discussion of representative examples, safety; mechanistic information where relevant to the use of the method in synthesis; a table of examples (for selected methods); reaction schemes.
3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format.

The coverage is not meant to be exhaustive. Rather, the most useful and reliable methods for each hetarene have been selected. In some cases, methods which are recommended for limited use or which have not yet been fully developed are listed at the end of a section for reference.

Synthetic routes to heterocycles with a specific functionality, e.g. 3-alkylindoles, are not grouped together. Within each chapter, the organizational principle is based on the synthetic methods used, not on the functionality of the heterocyclic product. Related methods, e.g. those involving the simultaneous formation of two C —C bonds, are juxtaposed, not necessarily the methods of synthesis of similarly substituted hetarenes. However, the index can be used to locate all methods recommended for synthesis of a particular type of hetarene with specific substituents.

This volume covers the synthesis of heterocyclic compounds with widely different stabilities and chemical and physical properties ranging from unstable hetarenes such as benzo[c]furans, e.g. the parent system **1** which is normally generated and trapped in situ (see **Scheme 2**),^[4] to very stable dibenzohetarenes such as dibenzothiophene (**2**), which undergoes decomposition at only 1% per hour when heated at 545 °C.^[5]

Scheme 2 Stabilities of Benzo[c]furans and Dibenzothiophenes

Benzo[*b*]furans, benzo[*b*]thiophenes, and indoles can generally be isolated and show chemistry typical of electron-rich heterocyclic compounds. However, indoles tend to be unstable in the presence of acid. They are weak bases with pK_a values of ca. -3 . Protonation occurs at C3 to generate 3*H*-indolium cations, e.g. **3** (**Scheme 3**). These are reactive species and are susceptible toward nucleophilic attack, leading to oligomerization under acidic conditions.^[6,7]

Scheme 3 Protonation of Indoles

Electrophilic substitution of benzo[*b*]furans, -thiophenes, and indoles occurs preferentially at C3, the 3-position in indole being 5.5×10^{13} more reactive toward tritium exchange than a position in benzene.^[8] However, electrophilic substitution of benzo[*b*]furans and indoles is hampered by their acid sensitivity and susceptibility to oxidation. Nevertheless, procedures have been developed for the electrophilic substitution of indoles at C3, as exemplified in **Scheme 4**.^[9-12] If a substituent is already present at the 3-position in an indole, initial attack still takes place at this site to give 3,3-disubstituted intermediates which often rearrange to give 2,3-disubstituted indoles.^[13-16]

Scheme 4 Examples of Electrophilic Substitution of Indole^[9-12]

Indoles with functionalized alkyl groups at the 3-position are reactive towards nucleophilic substitution. For example, the quaternary ammonium salt of gramine (**4**) reacts with cyanide to give 3-cyanomethylindole (**5**; **Scheme 5**).^[17] 1-Substituted indoles are regioselectively deprotonated at C2 by alkyllithium or lithium amide bases to give 2-lithio derivatives which can be trapped by electrophiles to yield 2-substituted indoles, as illustrated by the generation of the 2-lithioindole **7** from 1-methoxyindole (**6**) and its reactions with a range of electrophiles, e.g. *N,N*-dimethylformamide.^[18]

Scheme 5 Representative Reactions of Functionalized Indoles^[17,18]

Benzo[*b*]thiophene (**8**) also undergoes electrophilic substitution, e.g. bromination, at C3 (**Scheme 6**).^[19] As with *N*-substituted indoles, deprotonation at C2 can be carried out using strong bases and subsequent reaction of the metalated intermediate with an electrophile gives 2-substituted benzo[*b*]thiophenes, e.g. the preparation of the 2-carboxylic acid **10** by carboxylation of the lithiated intermediate **9**.^[20]

Scheme 6 Some Reactions of Benzo[*b*]thiophene

Benzo[*c*]furans and benzo[*c*]thiophenes are less stable than their benzo[*b*] isomers. Benzo[*c*]furans can only be isolated if they are substituted at the 1- and 3-positions with aryl or electron-withdrawing substituents, e.g. 1,3-diphenylbenzo[*c*]furan (**12**) can be obtained as a crystalline solid, mp 129 –130 °C, by reduction of 1,2-dibenzoylbenzene (**11**) followed by elimination (**Scheme 7**).^[21] Otherwise, benzo[*c*]furans are generated as reactive intermediates which are intercepted by other reagents (see **Scheme 2**).

Scheme 7 Synthesis of 1,3-Diphenylbenzo[*c*]furan^[21]

Benzo[*c*]thiophenes tend to be more stable than their benzo[*c*]furan counterparts. The parent benzo[*c*]thiophene (**13**; **Scheme 8**) has been isolated as a crystalline solid by vacuum sublimation and can be stored under nitrogen at –30 °C, although it quickly decomposes in air.^[22] The 1,3-diaryl derivatives, e.g. **14**, once again are much more stable, as are the 1-methoxycarbonyl and 1,3-bis(methoxycarbonyl) derivatives **15** and **16**.

Scheme 8 Representative Benzo[*c*]thiophenes

The position of equilibrium between 1*H*- and 2*H*-isoindoles (**Scheme 9**) is quite finely balanced and the ratio is influenced by substituents and by solvent, hydroxylic solvents favoring the 1*H*-tautomer whereas dipolar aprotic solvents seem to favor the 2*H*-isomer.^[23] The kinetic instability of isoindoles in solution may reflect the presence of both isomers, allowing condensation between the 1*H*- and 2*H*-isomers to take place since *N*-alkylisoindoles, e.g. 2-phenylisoindole (**17**), which must exist as 2*H*-isomers, are kinetically much more stable than their *N*-unsubstituted counterparts. Electron-deficient isoindoles are more stable than electron-rich ones. Electrophilic substitution tends to occur at C1 and 2*H*-isoindoles are reactive dienes in Diels –Alder reactions.

Scheme 9 Isoindoles

The dibenzo-fused five-membered hetarenes are typically stable, aromatic compounds which undergo electrophilic substitution in a benzene ring *para* to the heteroatom. Representative examples are given in **Scheme 10**.^[24-26]

Scheme 10 Representative Electrophilic Substitution of Dibenzo-Fused Five-Membered Hetarenes^[24-26]

Deprotonation of dibenzohetarenes also provides useful regioselective access to substituted derivatives. Examples include the sequential metalation of dibenzofuran (**18**), trapping the 4-lithiated derivative with *N,N*-dimethylformamide, repeated metalation, and finally quenching with methyl iodide to give 4-formyl-6-methyldibenzofuran (**19**; **Scheme 11**).^[27] This chemistry is particularly applicable to the preparation of functionalized dibenzothiophenes, e.g. the conversion of dibenzothiophene (**2**) into its 4-trimethylsilyl derivative **20**.^[28]

Scheme 11 Regioselective Metalation of Dibenzo-Fused Hetarenes^[27,28]

Many compounds covered in this volume have considerable importance, both commercially and from an environmental point of view. Understandably, the longest chapter is devoted to the synthesis of indoles. These are of fundamental importance biologically since the proteinogenic amino acid tryptophan (**21**; **Scheme 12**) is a 3-substituted indole. The biosynthetic incorporation of tryptophan into secondary metabolites means that thousands of natural products are known which have incorporated an indole fragment into their structure. ^[29] Many of these play crucial metabolic roles and others exhibit a wide range of biological activities. Examples include 5-hydroxytryptamine (serotonin, a neurotransmitter; **22**), lysergic acid diethylamide (**23**), the tranquilizer reserpine (**24**), and, vincristine (**25**), which is used in cancer chemotherapy. Many important pharmaceuticals have been developed which are substituted indoles. These include indomethacin (**26**; anti-inflammatory), ondansetron (**27**; antiemetic), pindolol (**28**; antihypertensive), and, sumatriptan (**29**; antimigraine).

Scheme 12 Biologically Active Indoles

Benzo[*b*]thiophenes are used for the synthesis of thioindigo dyes and, in the pharmaceutical and agrochemical industries, as isosteres for indoles with increased lipid solubility. They have been used in a wide variety of pharmaceuticals including contraceptives, laxatives, and anti-influenza, antihypertensive, anti-inflammatory, antiviral, and anticancer drugs.

Benzo[*c*]thiophenes are important for the preparation of conducting polymers. Electrochemical oxidation of benzo[*c*]thiophene (**13**) in polar aprotic solvents leads to the formation of an oxidized polymer **30** (**Scheme 13**) which is both electrically conducting and optically transparent.^[30] The reduced form **31** is a blue insulator. Aspects of the preparation of polybenzo[*c*]thiophene are discussed in the chapter on benzo[*c*]thiophenes.

Scheme 13 Benzo[*c*]thiophene Polymers

The isoindole moiety is found in the phthalocyanines, e.g. **32** (**Scheme 14**), metal complexes of which are of importance as dyes. Unsymmetric derivatives have nonlinear optical properties and they have found applications as liquid crystals and chemical sensors.

Scheme 14 Isoindole-Containing Phthalocyanine

Because of their wide range of structures and biological activities, the precautions which have to be taken in handling benzo-fused five-membered hetarenes vary widely. However, because so many indoles show pronounced biological activities which can be mimicked and modulated by close isosteres, caution is recommended in handling these compounds until their toxicity has been established. Most are relatively nonvolatile, however, so good laboratory practice normally suffices for handling these compounds on a small scale in a well-ventilated chemical laboratory.

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11 **Hetarenes**
 Volume 11:
 Five-Membered Hetarenes with One Chalcogen and One Additional Heteroatom

Schaumann, E., in *Science of Synthesis*, **11** (2001), p.1

General Introduction

In this volume, the syntheses of five-membered heterocyclic compounds with one oxygen, sulfur, selenium, or tellurium ring atom and a second ring atom are discussed. The second ring atom may again be a chalcogen, or nitrogen, or phosphorus. The heterocycles under consideration are fully conjugated and can be regarded as aromatic systems, i.e. hetarenes, at least, in a formal sense. The parent ring structures of the heterocycles **1–48** covered in this volume are shown in **Scheme 1**, together with the method of numbering and their nomenclature.

Scheme 1 Structures, Numbering Schemes, and Nomenclature for the Parent Heterocycles Covered in Volume 11

The synthesis of the *O*-, *S*-, and/or *N*-heterocycles has been discussed in *Houben –Weyl*, Vol. E 8a^[1] and E 8b.^[2] Information on the tellurium-containing ring systems can be found in *Houben –Weyl*, Vol. E 12b,^[3] and the phosphorus-containing ring systems are surveyed in *Houben –Weyl*, Vol. E 2.^[4] Comprehensive compilations of reviews on specific heterocyclic systems can be found in each chapter.

In this volume the *syntheses* of hetarenes is emphasized. Their *transformations* are covered only in so far as is relevant to their synthesis, e.g. by modification of substituents. However, a general description of the reactivity of

the heterocycles is given in the introductory section of each chapter. For each class of heteroarenes, the discussion of the methods of synthesis follows a general pattern, which is outlined below. However, occasionally adjustments have been made to highlight the best procedures. This formal organization allows the identification of gaps in the methods used to synthesize specific ring systems and this may encourage future work to rectify these omissions.

For the monocyclic ring systems, the following general organization is applied:

x: volume number = 11; **y:** product class; **z:** product subclass

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Formation of Three Bonds

x.y.z.1.2 By Formation of Two Heteroatom—Heteroatom Bonds

x.y.z.1.3 By Formation of One Heteroatom—Heteroatom and One Heteroatom—Carbon Bond

x.y.z.1.4 By Formation of Two Heteroatom—Carbon Bonds

x.y.z.1.5 By Formation of Two C—C Bonds

x.y.z.1.6 By Formation of One Heteroatom—Heteroatom Bond

x.y.z.1.7 By Formation of One Heteroatom—Carbon Bond

x.y.z.1.8 By Formation of One C—C Bond

x.y.z.2 Synthesis by Ring Transformation

x.y.z.3 Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)

x.y.z.4 Synthesis by Substituent Modification

Similarly, the following general arrangement for an annulated heteroarene is used:

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Annulation to an Arene

x.y.z.1.1.1 By Formation of Three Bonds

x.y.z.1.1.2 By Formation of Two Heteroatom—Heteroatom Bonds

x.y.z.1.1.3 By Formation of One Heteroatom—Heteroatom and One Heteroatom—Carbon Bond

x.y.z.1.1.4 By Formation of Two Heteroatom—Carbon Bonds

x.y.z.1.1.5 By Formation of Two C—C Bonds

x.y.z.1.1.6 By Formation of One Heteroatom—Heteroatom Bond

x.y.z.1.1.7 By Formation of One Heteroatom—Carbon Bond

x.y.z.1.1.8 By Formation of One C —C Bond**x.y.z.1.2** By Annulation to the Heterocyclic Ring**x.y.z.2** Synthesis by Ring Transformation**x.y.z.3** Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)**x.y.z.4** Synthesis by Substituent Modification

For each section listed above, the most important synthetic methods are given and their scope and limitations are discussed, and compared with other methods. Tables and representative experimental procedures illustrate the applicability of each approach. Often the methods are further subdivided into variations, and each variation is again fully exemplified. Less important methods, or modes, of formation with the potential for future elaboration are also documented.

The formalized arrangement of the methods of synthesis concerns the ring framework only. Thus, for example, there are no special sections dealing with thiazolamines. However, the pertinent information on the syntheses of these compounds may be found in other sections. To extract this information use of the electronic product is advised (substructure and text searches).

Heterocycles **1**–**23** are cations that are isoelectronic with the tropylium cation. An indication of some aromatic character can be derived from their ¹H NMR spectra, which indicate the presence of a ring current, at least for **1** and **2**,^[5] although there is some controversy about this interpretation. In spite of their formal aromaticity, neither the 1,2-dioxolium cation **49**, nor its derivatives have been described (**Scheme 2**).

Scheme 2 1,2-Dioxolium Cation

Potential precursors of type **50** have been made, but they are highly unstable and undergo ready isomerization to diastereomeric oxiranes **51** (**Scheme 3**).^[6]

Scheme 3 3*H*-1,2-Dioxole Decomposition^[6]

In contrast to **49** which contains a peroxide unit, the corresponding system **1**, which contains an 1,3-arrangement of oxygen atoms is known. Even so, compounds of type **1** are extremely unstable and can only be synthesized if additional stabilization by donor substituents, or by benzoannulation is present.^[7] Apparently, the cationic ring is perturbed by the two highly electronegative oxygen atoms, but this perturbation is reduced, if one ring oxygen is replaced by a sulfur and 1,2-derivatives **3** can be isolated. Similarly, donor-substituted 1,3-oxathiolium salts **4** are moderately stable.

The inclusion of two ring sulfur atoms, as in the heterocycles **10**–**13**, leads to stable and generally crystalline salts.

In line with the aromatic character of these ring systems, X-ray data confirm the presence of a planar five-membered ring and of bond delocalization. The formation of triheterapentalenes **52** represents a special case, in which the bicyclic system contains a three-coordinated d^4 -sulfur (or selenium, or tellurium) atom Y and vicinally disposed heteroatoms X and Z (**Scheme 4**). These compounds are heterocyclic analogues of the bicyclic pentalene dianion.

Scheme 4 Heteropentalenes

The introduction of selenium or tellurium atoms into five-membered hetarenium systems results in reduced stability. Thus, simple 1,2-ditellurolium salts are known only in solution. Structurally, hypervalent selenium (or tellurium) with three-center, four-electron bonding appears to be involved in systems with a vicinal oxygen ring atom (**Scheme 5**, **53B**). Nevertheless, the nomenclature used to describe them is based upon the resonance structure **53A**.

Scheme 5 Structural Representation of Oxaselenolium and Oxatellurolium Systems

1,2-Thiaselenolium, 1,2-thiatellurolium, and 1,2-selenatellurolium salts appear to be unknown. However, the selenatellurolium fragment can be found in the nonaromatic heterocycle **54** (**Scheme 6**).^[8]

Scheme 6 The Selenatellurolium Fragment in a Nonaromatic Heterocycle^[8]

In contrast to the charged systems **1–23**, the heterocycles **24–48** show features of more typically aromatic compounds, i.e. the ease by which electrophilic substitution occurs, and little tendency to undergo addition reactions. The monocycles are formally derived from benzene and all, including isoselenazoles, are stable under normal conditions. The corresponding bicyclic systems may be considered as derivatives of naphthalene, but two sets of heteronaphthalenes are possible, depending on whether a chalcogen atom (**55A**) replaces a formal lateral ethene unit, or whether this formal exchange affects the C1—C2 unit (**55B**) (**Scheme 7**). The former type displays an efficient aromatic 10- electron delocalization with a quinoid double bond arrangement in the carbocyclic ring.

Scheme 7 Heteronaphthalenes

There has been some controversy about applying the principles of aromaticity to heterocycles, but even from a qualitative standpoint the systems in question differ widely in double-bond delocalization and reactivity. **Scheme 8** shows a rough order of resonance stabilization and stability.

Scheme 8 Order of Increasing Resonance Stabilization and Stability

The presence of a ring nitrogen makes the hetarenes basic but, with the exception of benzothiazole (**35**, pK_a 7.84), ^[9] the parent ring systems are all less basic than pyridine (pK_a 5.22) as shown in **Scheme 9**. As none of the systems have a pronounced sensitivity to acid, their basic character allows their extraction and isolation from mixtures by treatment with acid.

Scheme 9 Parent Ring Systems in Order of Increasing Basicity

Hetarenes **24** –**48** are also weak acids. For the 1,2-diheteroatom systems, metalation and H/D exchange occur in

different positions (**Scheme 10**). In the 1,3-systems, the proton at C2, located between the heteroatoms, is the most acidic (pK_a of oxazole 20 ± 2).

Scheme 10 Most Acidic Sites

In spite of their aromatic character, the heteroatom—heteroatom bond reduces the stability of hetarenes **24**–**26**, **31**–**33**, **36**, **37**, **40**, **41**, **45**, and **46**. This bond is usually the point of fission, both on thermolysis and photolysis, but in most cases it is also readily cleaved under reductive, and even oxidative, conditions. This bond cleavage is exploited in synthesis, particularly for derivatives of isoxazole (**24**), where it allows ready access to 4-amino-3-en-2-ones and further to 1,3-diketones.^[10,11] In derivatives of 2,1-benzisoxazole (**26**) a similar bond cleavage is used to form 2-acylarylnitrenes,^[12] or 2-(aminoaryl)ketones, both of which are important intermediates for the syntheses of 1,4-benzodiazepines (cf. Scheme 11).^[13]

Scheme 11 Isoxazoles – Bond Cleavage^[10-12]

The presence of an acidic hydroxy, sulfanyl, or amino substituent next to a ring nitrogen allows two tautomeric forms **56A** and **56B**.^[46] By analogy, a vinylogous arrangement leads to the alternatives **57A** and **57B** and, in addition, **57C** (**Scheme 12**). In most cases, when $X = O$ or S , the (thio)lactam form **56B** predominates, i.e. the possibility of amide or thioamide resonance overrules aromatic resonance stabilization. However, in the crystalline state or in nonpolar solvents either form may be preferred, or an equilibrium is established (as in the case of isoxazoles).^[14] Compounds with an exocyclic primary or a secondary amino group ($X = NR^1$) usually exist in form **56A**, rather than as imino derivatives **56B**, although exceptions such as **58** are known.^[15] In this volume, tautomeric preferences are ignored when the syntheses of compounds **56** and **57** are considered.

Scheme 12 Substituent Tautomerism in Azahetarenes^[14,15]

Among the reactions of the uncharged hetarenes, electrophilic substitution reactions deserve special interest as being typical of aromatic compounds. In fact, the majority of these hetarenes undergo smooth displacement of hydrogen when reacted with electrophiles, usually halogen or nitrating agents. An exception is oxazole (**27**), which has a particularly low tendency to participate in S_E reactions. The preferred site of electrophilic attack depends on the hetarene and also on the presence of other substituents. Benzo derivatives are normally attacked at the carbocyclic ring, but an exception is observed in the chlorination of benzothiazole (**35**), which is attacked at C2 as well as C6 (**Scheme 13**).

Scheme 13 Regioselectivity of Electrophilic Substitution Reactions

All the cationic hetarenes **1**–**23** react readily with nucleophiles, implying that the counterion should be a non-nucleophilic species, such as tetrafluoroborate or trifluoromethanesulfonate. The primary addition product may be unstable. For example, in most cases when 1,2-dithiolium systems **59** are the starting materials, sulfur-containing **61** or sulfur-free ring-opened products **62** are formed via **60**.^[16] The addition of nucleophiles to 1,3-dithiolium salts **63** gives useful derivatives **64**, making the salts **63** valuable synthetic intermediates (**Scheme 14**).^[17]

Scheme 14 Reactions of Hetarenium Systems with Nucleophiles^[16,17]

Halogen-substituted uncharged heteroarenes normally undergo smooth displacement reactions with nucleophiles. Alternatively, the nucleophile may form an adduct that may subsequently undergo ring opening. Addition is favored when the substrates are N-alkylated heterocycles, e.g. 2-alkylisoxazolium salts (**Scheme 15**).^[18] The same activation to addition applies to oxazoles,^[19] although oxazoles already show a pronounced tendency to take part in addition reactions, including cycloadditions. Thus, a Diels –Alder reaction with singlet oxygen allows the use of oxazoles as masked triacylamines (**Scheme 16**).^[20,47]

Scheme 15 Addition Reactions of Organometallics to Isoxazoles^[18]

Scheme 16 Oxazoles as Masked Triacylamines^[20]

Derivatives of 2,1-benzisoxazole (**26**) and -benzisothiazole (**33**), containing quinoid carbocycles, seem ideally suited as dienes in Diels –Alder cycloadditions. However, 10- aromatic resonance makes **26** and, in particular, **33** poor dienes. By contrast, derivatives of 1,2-thiaphosphole (**36**) do behave as dienes, although dienophilic reactivity is observed for derivatives of 1,3-benzoxaphosphole (**30**).

The family of *ortho*- and *peri*-fused naphthalene derivatives **65** includes representatives where X and Y are both

chalcogen atoms, or a chalcogen atom and a nitrogen. However, a description of their chemistry is beyond the scope of this volume. **Scheme 17** serves as a guide to the literature.^[21-45]

Scheme 17 *ortho* and *peri*-Fused Naphthalenes with a Chalcogen-Containing Heterocyclic Component^[21-45]

Ring Atom X	Ring Atom Y	Synthesis Ref	Chemical or Physical Properties Ref
O	S(O)	[21]	[22]
O	SO ₂	[23]	[24]
S	S	[25-32]	[22,33]
S	S(O)	[22,33]	[22,32]
S	SO ₂	[26]	[27]
SO ₂	SO ₂	[34]	[32]
S	Se	[31,35]	—
S	Te	[36]	—
Se	Se	[29-31,37-39]	—
Se	Te	[36]	—
Te	Te	[31,35,40-42]	—
SO ₂	NH	[43]	[44]
Si	Si	[45]	—

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Hetarenes

12

Volume 12:**Five-Membered Hetarenes with Two Nitrogen or Phosphorus Atoms**

Neier, R., in *Science of Synthesis*, **12** (2002), p.1

This volume covers the synthesis of five-membered heterocyclic compounds with either two nitrogen or two phosphorus ring atoms, as well as five-membered heterocycles containing one nitrogen and one phosphorus ring atom, or one nitrogen and one arsenic ring atom. The five-membered heterocycles of this category fused to a six-membered aromatic carbocyclic or heterocyclic ring are also treated. For the fused systems, the heteroatoms can be located exclusively in the five-membered ring or one of the heteroatoms can be part of the five-membered ring as well as part of the six-membered ring. The parent ring structures of the heterocycles covered in this volume are shown in **Scheme 1**, together with the numbering schemes and nomenclature used (based on CAS).

Scheme 1 Structures, Numbering Schemes, and Nomenclature for the Parent Heterocycles Covered in Volume 12

The heterocycles are treated according to the classification principles developed for *Science of Synthesis*. In the section covering the diphospholes (Section 12.7), the classification scheme was slightly modified for this young and special class of compounds in a similar way as was done for the phospholes, see *Science of Synthesis*, Vol. 9 [Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Heteroarenes with One Heteroatom (Section 9.14, p 553)]. The deprotonated forms of the 1,2-diphospholes and of the 1,3-diphospholes, the corresponding 1,2-diphospholides and 1,3-diphospholides, possess a greater stability than their protonated parent compounds due to their higher aromaticity. Diphospholyls belong to the phosphacyclopentadienyl family and, therefore, easily form π -complexes (**Scheme 2**). Some of these complexes, especially the phosphaferrrocene complexes, are also treated in Section 12.7.

Scheme 2 General Structures of Phosphacyclopentadienyl Complexes Covered in Volume 12

The section dealing with the imidazopyridines and pyrazolopyridines (Section 12.5) embraces a group of closely related molecules, which are often synthesized using similar methodologies. For this section the classification scheme has also been modified, taking into account the low number of synthetic pathways and the high number of structurally related heterocycles. Heterocycles containing additional nitrogen atoms in the six-membered ring are also treated in Section 12.5, as long as the synthesis of these compounds uses a ring-closure reaction to build up the five-membered ring. The compounds shown in **Scheme 3** are known,^[1-5] and some aspects of their chemistry are discussed in Section 12.5, but their synthesis generally proceeds via ring closure of the six-membered ring; they are, therefore, described in *Science of Synthesis*, Vol. 17 [Six-Membered Heteroarenes with Two Unlike or More than

Two Heteroatoms and Fully Unsaturated Larger-Ring Heterocycles (Section 17.2)].

Scheme 3 Structures of Heterocycles of the Imidazotriazine and Pyrazolotriazine Type which are Partially Covered in Volume 12

The synthesis of pyrazoles, indazoles, imidazoles, and benzimidazoles was discussed in *Houben –Weyl*, Vols. E 8b and E 8c. The structure, synthesis, and chemistry of these heterocycles, as well as of the phosphorus-containing heterocycles, has been reviewed.^[8,9] References treating specific heterocycles or specific subjects relating to these heterocycles are given in each section of this volume.

Since their detection in the 19th century, an impressive number of syntheses has been reported for pyrazoles, indazoles, imidazoles, and benzimidazoles. Only a selection of all the published methods can be presented. Many of the classical syntheses of these heterocycles still belong to the selection of the best methods available. Newer developments have also been incorporated, in particular methods for functionalizing these heterocycles via metalation. Palladium-catalyzed cross-coupling reactions are also mentioned. The chemistry of these heterocycles is discussed with a strong focus on synthesis. The use of these heterocycles as ligands in the coordination sphere of metals is not treated. Reactions of substituents directly linked to the heterocycles and reactions at the -position of the ring are addressed. Direct deprotonation has become an important synthetic methodology, also in heterocyclic chemistry, which allows the achievement of many important functionalizations. In *Science of Synthesis*, these methods are comprehensively treated in volumes dedicated to the chemistry of organometallic compounds and, therefore, only selected examples are covered in this volume. Carbon —carbon coupling reactions using transition metals have been increasingly applied to heterocycles. Again, the chemistry related to these carbon —carbon coupling reactions is discussed in a more comprehensive manner in the volume dedicated to the organometallic compounds involved. For the imidazopyridines and pyrazolopyridines (Section 12.5), and especially for the phosphorus-containing heterocycles (Sections 12.6 and 12.7), a more comprehensive approach has been possible. Some of these heterocycles have only been synthesized for the first time during the past 10 years. For these heterocycles, adjustments have been made that allow a more comprehensive approach, and not only presentation of the best synthetic methods.

For each class of heterocycle the discussion generally follows the following pattern: The formal organization has been created in order to assist the reader to find a specific methodology and to allow comparison of similar synthetic methods for different heterocycles. The organization of *Science of Synthesis* is based on a formalism which allows unequivocal classification of the reported synthetic methods.^[10] The scheme developed for *Science of*

Synthesis is a very useful guide for organizing the vast published knowledge about heterocyclic chemistry. The organizational scheme applies strictly only for five-membered heteroarenes with one heteroatom in the ring and clearly not all the subheadings are relevant in all cases.

For heteroarenes containing more than one heteroatom, very specific synthetic methods have been developed. It has, therefore, been necessary to slightly adapt the organizational scheme of *Science of Synthesis* to the needs and knowledge of the specific heterocyclic system treated.

For the imidazoles (Section 12.3), the section is organized according to the following scheme:

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Formation of Four Heteroatom —Carbon Bonds

x.y.z.1.1.1 Fragments C —C, C, and Two X Fragments

x.y.z.1.2 By Formation of Three Heteroatom —Carbon Bonds

x.y.z.1.2.1 Fragments X —C, C —C, and X

x.y.z.1.2.2 Fragments X —C —C, X, and C

x.y.z.1.3 By Formation of Two Heteroatom —Carbon Bonds and One C —C Bond

x.y.z.1.3.1 Fragments X —C, X —C, and C

x.y.z.1.4 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.4.1 Fragments X —C —X and C —C

x.y.z.1.4.2 Fragments X —C —C and X —C

x.y.z.1.4.3 Fragments X —C —C —X and C

x.y.z.1.4.4 Fragments C —X —C —C and X

x.y.z.1.5 By Formation of One Heteroatom —Carbon and One C —C Bond

x.y.z.1.5.1 Fragments C —X —C and X —C

x.y.z.1.5.2 Fragments X —C —X —C and C

x.y.z.1.6 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.6.1 Fragment X —C —C —X —C

x.y.z.1.6.2 Fragment X —C —X —C —C

x.y.z.1.7 By Formation of One C —C Bond

x.y.z.1.7.1 Fragment C —X —C —X —C

x.y.z.2 Synthesis by Ring Transformation

x.y.z.3 Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)**x.y.z.4 Synthesis by Substituent Modification**

The fragment headings given above allow the different schemes for synthesizing imidazoles to be categorized. They also allow recognition of the different strategies that can be used to assemble imidazoles by the formation of one or more heteroatom —carbon or C —C bonds. The different combinations of building blocks are illustrated in **Scheme 4**.

Scheme 4 Fragments Used to Construct Imidazoles

Slight adjustments also had to be made for the section on pyrazoles (Section 12.1):

x.y.z.1 Synthesis by Ring-Closure Reactions**x.y.z.1.1 By Formation of One Heteroatom —Carbon Bond and Two C —C Bonds****x.y.z.1.1.1 Fragments X —X —C, C, and C****x.y.z.1.2 By Formation of Two Heteroatom —Carbon Bonds****x.y.z.1.2.1 Fragments C —C —C and X —X****x.y.z.1.3 By Formation of One Heteroatom —Carbon and One C —C Bond****x.y.z.1.3.1 Fragments X —X —C and C —C****x.y.z.1.3.2 Fragments X —X —C —C and C****x.y.z.1.4 By Formation of One Heteroatom —Heteroatom Bond**

x.y.z.1.4.1 Fragment $X-C-C-X$

x.y.z.1.5 By Formation of One Heteroatom—Carbon Bond

x.y.z.1.5.1 Fragment $X-X-C-C$

x.y.z.1.6 By Formation of One $C-C$ Bond

x.y.z.1.6.1 Fragment $C-X-X-C$

x.y.z.2 Synthesis by Ring Transformation

x.y.z.3 Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)

x.y.z.4 Synthesis by Substituent Modification

These adjustments are a consequence of the different arrangements of the two heteroatoms in the hetarene. The starting materials available are obviously different and, thereby, the reasonable retrosynthetic dissection of the product into fragments is changed (**Scheme 5**).

Scheme 5 Fragments Used to Construct Pyrazoles

Finally, the general arrangement is slightly modified for the annulated hetarenes (Sections 12.2 and 12.4):

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Annulation to an Arene

x.y.z.1.1.1 By Formation of Three Bonds

x.y.z.1.1.2 By Formation of Two Heteroatom—Heteroatom Bonds

x.y.z.1.1.3 By Formation of One Heteroatom—Heteroatom and One Heteroatom—Carbon Bond

x.y.z.1.1.4 By Formation of Two Heteroatom—Carbon Bonds

x.y.z.1.1.5 By Formation of Two $C-C$ Bonds

x.y.z.1.1.6 By Formation of One Heteroatom —Heteroatom Bond

x.y.z.1.1.7 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.1.8 By Formation of One C —C Bond

x.y.z.1.2 By Annulation to the Heterocyclic Ring

x.y.z.2 Synthesis by Ring Transformation

x.y.z.3 Aromatization (by Oxidation of Dehydro Compounds or Elimination Reactions)

x.y.z.4 Synthesis by Substituent Modification

The fragment headings are further subdivided into methods and variations. In the sections on pyrazoles (Section 12.1), indazoles (Section 12.2), imidazoles (Section 12.3), and benzimidazoles (Section 12.4) selected methods are presented. The methods which are considered to be the most useful and versatile for the synthesis of a specific ring system are discussed in more detail. The presentation generally contains the following components:

1. An introduction containing some background information, the scope and limitation of the method/variation described, mechanistic information, and, where relevant, a comparison with other methods.
2. Reaction schemes, most of the time associated with a table of representative examples, and a short specific description of the reaction in general. Safety indications and experimental precautions necessary for a specific reaction are noted.
3. Representative experimental procedures.

For all other ring systems, especially for the phosphorus-containing heterocycles (Sections 12.6 and 12.7), only a small number of methods exist, primarily because the chemistry of these ring systems is still very young and under active development. For these ring systems, the given list of methods is more or less exhaustive.

The organizational principles are based on the synthetic methods applied, not on the functionality of the heterocyclic product. Methods with related retrosyntheses are juxtaposed, e.g. those involving the formation of two heteroatom —carbon bonds. Therefore, heterocycles possessing a specific functional group are not grouped together. If all the syntheses of a heterocycle containing a specific functionality need to be found, these can be located using the index, as well as structure and text searches in the electronic product.

The heterocycles described in this volume have widely different stabilities and chemical and physical properties. To date, the parent compound of the 1,2-diphospholes has not been isolated and only one derivative **1** of 1,2-diphosphole (**Scheme 6**) has been well characterized.^[11]

Scheme 6 Synthesis of a 1,2-Diphosphole Derivative^[11]

Imidazoles and pyrazoles and their benzoannulated derivatives are stable compounds with a considerable aromatic

character. Imidazole (bp 256 °C) and pyrazole (bp 187 °C) may be distilled at normal pressure without destruction. Pyrolysis of pyrazoles often leads to ring-opened products.^[12] Imidazoles, however, can be pyrolyzed at temperatures above 600 °C, inducing the migration of an alkyl group into the 2-position without destruction of the heteroaromatic ring (**Scheme 7**).^[13]

Scheme 7 Pyrolysis of 1-Methyl-1*H*-imidazole^[13]

The two heterocycles imidazole and pyrazole resemble a pyrrole –pyridine combination. Pyridine is a moderate nitrogen base, whereas pyrroles often function as hydrogen bond donors. By formal combination of these two properties into one heteroarene, the amphoteric nature of these molecules is predicted (**Scheme 8**).

Scheme 8 Acidity and Basicity of Imidazole and Pyrazole^[14,15]

The acidity of the two heterocycles is very similar (pK_a 14.21 for pyrazole, compared to pK_a 14.4 for imidazole). In contrast, the basicity of the two heterocycles is quite different, with pyrazole being considerably less basic than imidazole (pK_a 2.53 for pyrazole,^[14] compared to pK_a 6.99 for imidazole^[15]). This enhanced basicity plays a crucial role in the catalytic triad (also called charge relay system) which includes an imidazole ring stemming from the active site histidine used by the serine proteases such as chymotrypsin (**Scheme 9**).^[16]

Scheme 9 "Charge Relay System" in the Catalytic Triad of Serine Proteases^[16]

Electrophilic substitution of 1*H*-imidazole occurs preferentially at C4. Many of the classical electrophilic substitution reactions using 1*H*-imidazole probably first introduce the substituent on nitrogen. Many of the electrophilic

substitutions, however, are hampered by the fact that strongly acidic conditions are necessary, so that the imidazole ring would be protonated and the reactivity toward electrophilic reagents strongly reduced. Nevertheless, procedures have been reported for the electrophilic substitution of imidazole at C4, as shown in **Scheme 10**.^[17-19]

Scheme 10 Electrophilic Substitution of 1*H*-Imidazole^[17-19]

Addition of electrophiles to imidazoles can be achieved by direct metalation or metal –halogen exchange, followed by trapping with an adequate electrophile (**Scheme 11**). The ease of metalation is usually C2 > C5 > C4.^[20,21]

Scheme 11 Functionalization of Imidazoles by Direct Metalation or by Metal –Halogen Exchange^[20,21]

1*H*-Pyrazole also undergoes electrophilic substitution preferentially at C4. This regioselectivity is in accordance with the results of deuterium exchange experiments, which show that the 4-position is 1.6×10^4 times more reactive than the 3- and 5-positions if 1-methyl-1*H*-pyrazole is reacting as its free base.^[22] The difference in rate is even greater if the deuterium exchange rate is measured for the conjugate acid (2.5×10^5). Representative examples of electrophilic substitutions of pyrazoles are given in **Scheme 12**.^[23-26]

Scheme 12 Representative Electrophilic Substitutions of Pyrazoles^[23-26]

In the metalation of 1-methyl-, 1-benzyl-, or even 1-phenyl-1*H*-pyrazole, side reactions can occur, such as deprotonation at the methyl or at the benzyl group, or even *ortho* lithiation. Using optimized conditions, these side reactions can be avoided and metalation at C5 occurs cleanly. The so-obtained 5-lithiopyrazoles can be trapped with carbon electrophiles.^[27] An elegant method for avoiding these problems is the introduction of the hydroxymethyl protecting group (**Scheme 13**).^[28] The doubly deprotonated pyrazole can be obtained and trapped with electrophiles; during the acidic workup, the hydroxymethyl protecting group is removed.

Scheme 13 Functionalization of Pyrazoles by Direct Metalation^[27,28]

The benzo analogues, benzimidazole and indazole, react preferentially on the nitrogen atoms. Functionalization of the single carbon atom available for reactions in the five-membered ring is often in competition with reactions on the annulated aromatic ring (**Scheme 14**).^[29] For indazole, conditions have been reported where the five-membered heterocycle is attacked preferentially.^[6,7]

Scheme 14 Electrophilic Substitution Reactions of Benzimidazole and Indazole^[6,7,29]

Many members of the family of heterocycles presented in this volume have considerable importance. The imidazole ring is present in the proteinogenic amino acid histidine, and also in histamine, azomycin, and pilocarpine (**Scheme 15**). The imidazole ring has important functions as a ligand for metal ions and, especially, as a proton-donor and proton-acceptor unit in the charge relay mechanism of many hydrolytic enzymes (see **Scheme 9**). Pyrazole derivatives have been far less frequently identified as natural products; two examples are given in **Scheme 15**.

Scheme 15 Biologically Active Imidazoles and Pyrazoles

The heterocycles covered in this volume are ideal building blocks for introducing hydrogen-bond donating and accepting capacities into small drug molecules. It is, therefore, not surprising that many drug molecules contain these heterocycles. Some representative examples are indicated in **Scheme 16**.

Scheme 16 Representative Examples of the Use of Imidazole- or Pyrazole-Derived Compounds as Drugs

Pyrazole rings have also been incorporated into agrochemicals, which find use as herbicides and as plant growth regulators (**Scheme 17**).

Scheme 17 Pyrazole Derivatives Used as Agrochemicals

1*H*-Pyrazol-5-ols are in equilibrium with their pyrazolone tautomer. They react with diazonium salts forming azo dyes, which have been widely used technically (**Scheme 18**). Tartrazin, for example, has been used to color paper, leather, cosmetics, and even food. In color photography, 1-aryl-1*H*-pyrazol-5-ols are used as magenta couplers.

Scheme 18 Dyes Derived from Pyrazolones

The hydrotris(pyrazolyl)borato ligand has been widely used in chemistry. The coordination chemistry with many different metals, as well as the structure and chemistry of the metal complexes, have been intensively studied. The ligand proved to be especially suited for obtaining model compounds that allow the function of metal ions in enzymes to be imitated. Finally, 1,1-carbonyldiimidazole, the Staab reagent, is a mild and very useful condensation

reagent (**Scheme 19**).

Scheme 19 Application of Pyrazole and Imidazole Derivatives in Chemistry

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13 **Hetarenes**
Volume 13:
Five-Membered Hetarenes with Three or More Heteroatoms

Storr, R. C.; Gilchrist, T. L., in *Science of Synthesis*, **13** (2003), p.1

General Introduction

Nearly a hundred different ring systems are included in this volume: a clear indication of the variety of possible structures that can be formed by including three or more heteroatoms in a five-membered ring. Some of these rings systems, such as the thiadiazoles, triazoles, and tetrazoles, are common and stable structures with hundreds of known derivatives, whereas others, such as the thia-triazoles and pentazoles, are thermally unstable species with little known chemistry. All can loosely be classified as "aromatic"^[1] on the basis of the Hückel rule in that each can formally be regarded as containing six π -electrons made up of four electrons from two double bonds and two electrons from the lone pair on a heteroatom.

The chemistry of many of the product classes included in this volume is described in *Houben –Weyl*, Vol. E 8, in *Comprehensive Heterocyclic Chemistry*, Vols. 5 and 6, and in *Comprehensive Heterocyclic Chemistry II*, Vol. 4. References to these volumes for individual product classes are given in each section. The series *Progress in Heterocyclic Chemistry* provides an annual survey of newly published work on many of these ring systems.

Structures of the parent ring systems included in each product class are shown in **Scheme 1**. Where ring systems are known only as cations or anions these are shown, otherwise the neutral form of the parent ring is listed. The list is limited to monocyclic ring systems and simple benzo analogues, but in the sections covering individual product classes several other fused ring systems, mostly with a bridgehead nitrogen atom, are also included. No attempt has been made to provide comprehensive coverage of such fused ring systems.

Scheme 1 Structures of the Parent Heterocycles Covered in Volume 13

Procedures for the preparation of each member of the product class are included in this volume. The methods of preparation listed are not necessarily comprehensive; the ones selected are mostly those with some general application. These include ring syntheses from acyclic precursors, syntheses involving transformations of other ring systems, and functional group manipulation, although methods involving standard functional group transformations are not covered in detail. Reaction mechanisms are also not routinely discussed. The purpose of the volume is to describe useful methods of preparation, hence the physical and chemical properties of the ring systems are outlined only briefly. The order of presentation of the material is generally as follows. A similar order is followed for benzo-fused heteroarenes.

x: volume number = 13; **y:** product class; **z:** product subclass (not always relevant)

x.y Product Class y

x.y.z Product Subclass z

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Formation of Three Bonds (subdivided further if different bonds are formed; order: Heteroatom — Heteroatom Bond, Heteroatom —Carbon Bond, C —C Bond)

x.y.z.1.1.1 Method 1

x.y.z.1.1.1.1 Variation 1 (only some methods are subdivided into variations)

x.y.z.1.1.1.2 Variation 2, etc.

x.y.z.1.1.2 Method 2, etc.

x.y.z.1.2 By Formation of Two Heteroatom —Heteroatom Bonds

x.y.z.1.2.1 Method 1, etc.

x.y.z.1.3 By Formation of One Heteroatom —Heteroatom and One Heteroatom —Carbon Bond

x.y.z.1.4 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.5 By Formation of Two C —C Bonds

x.y.z.1.6 By Formation of One Heteroatom —Heteroatom Bond

x.y.z.1.7 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.8 By Formation of One C —C Bond

x.y.z.2 Synthesis By Ring Transformation**x.y.z.3 Aromatization****x.y.z.4 Synthesis By Substituent Modification**

x.y.z.4.1 Modification of Existing Substituents (order: substitution of hydrogen, of metals, of carbon functionalities, of heteroatoms)

x.y.z.4.2 Addition Reactions**x.y.z.4.3 Rearrangement of Substituents****x.y.z.4.4 Modification of Substituents** (usually, reactions at the -atom)

The nomenclature used for most of these ring systems is systematic, the suffix -ole indicating a five-membered unsaturated ring and the number and type of heteroatoms being indicated by prefixes. A feature of several of the ring systems in this volume is that many of the known examples are ones that are represented by dipolar valence bond forms. This is true for 1,2,3-oxadiazoles and 1,2,3,4-oxatriazoles among others, for which the conventional fully unsaturated ring systems are hardly known and unstable whereas the dipolar compounds are much more stable. Some examples of these compounds, which are known collectively as mesoionic compounds,^[2,3] are shown in **Scheme 2**.

Scheme 2 Examples of Mesoionic Compounds^[2,3]

The degree to which some of these structures can be regarded as aromatic is questionable, since nonaromatic structures are often the major contributors to the various resonance forms that can be written. This is illustrated for the best known of this group of compounds, the so-called sydnones **1**, resonance structures of which are shown in **Scheme 3**. The structural and spectroscopic properties of sydnones point to the nonaromatic resonance hybrid **1B** as being the major contributor.^[4] Such compounds are nevertheless represented in this volume by structures such as **1A** with two internal double bonds in order to preserve the theme of the hetarenes volumes. No system of nomenclature for mesoionic compounds is as yet universally accepted; however, the IUPAC recommendations have been used throughout this volume. The nomenclature "-ium-olate" (and related nomenclature for species with exocyclic sulfur and nitrogen atoms in place of oxygen) is adopted in this volume; thus, structure **2** ($R^1 = \text{Me}$) is named as 3-methyl-1,2,3,4-oxatriazol-3-ium-5-olate. The only exception is for structures of type **1** for which the commonly accepted trivial name "sydnone" is retained.

Scheme 3 Resonance Structures for Sydnones^[4]

Many of the ring systems in Product Class 13 exhibit tautomerism.^[5,6] One type of tautomeric equilibrium occurs in five-membered heteroarenes with NH as part of the ring. For example, 1,2,3-triazoles can exist as 1*H*-tautomers **3** or as 2*H*-tautomers **4** (**Scheme 4**); (there is also a nonaromatic tautomer possible, structure **5**). The barrier to interconversion of tautomers such as **3** and **4** is extremely low. It is sometimes possible to predict which tautomer will predominate on the basis of the substitution pattern but they are chemically indistinguishable.

Scheme 4 Annular Tautomerism in 1,2,3-Triazoles^[5,6]

The second important type of tautomeric equilibrium exists in heterocycles with a C-amino, C-hydroxy, or C-sulfanyl substituent. If such substituents are attached to the 2- or 5-positions the major tautomeric form can be confidently predicted. This is illustrated for 1,2,4-triazoles with a C5 substituent. The amino tautomer is strongly favored over the imino form but the oxo and thioxo tautomers predominate over the alternative hydroxy and sulfanyl forms (**Scheme 5**). On the other hand equilibria between hydroxy and oxo tautomers in some C3 substituted heterocycles can be much more finely balanced; for example, the enol tautomer **6** is the preferred form of 5-phenyl-1,2,4-oxadiazol-3-ol in protic solvents.^[7]

Scheme 5 Tautomeric Equilibria in Amino-, Hydroxy-, and Sulfanyl-Substituted 1,2,4-Triazoles and 1,2,4-Oxadiazoles^[5-7]

The existence of such tautomeric forms can complicate the pattern of reactivity of the substituted heterocycles; for example, 1,2,4-triazol-3-amine can be acylated on C1, on the exocyclic amino group, or on both, under different reaction conditions.^[8,9]

With so many possible structures it is not surprising that heterocycles in this product class are commonly found as components of pharmaceuticals, agrochemicals, and dyestuffs, and have many other practical applications. The types of heteroatoms and their positions allow for subtle changes in the electronic properties of the ring systems; in general the rings become more electron deficient as the number of heteroatoms is increased. A further degree of control can be achieved by the choice of substituents on carbon atoms in the ring. Since many of the ring systems are also thermally stable, they can be designed to provide robust functional groups with predictable properties when they form components of larger structures. The acidity and basicity of the ring systems can similarly be controlled to a large degree by the choice and placement of heteroatoms and of functional groups: this is illustrated in **Scheme 6** by the variation in the acid pK_a values for some triazoles and tetrazoles.

Scheme 6 Comparative pK_a Values (in Water or Aqueous Alcohol) for Some Triazoles and Tetrazoles^[10,11]

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14 **Hetarenes**
Volume 14:
Six-Membered Hetarenes with One Chalcogen

Thomas, E. J., in *Science of Synthesis*, **14** (2003), p.1

General Introduction

Six-membered oxygen containing heterocycles are an important group of compounds widely dispersed throughout the plant kingdom. They are components of many biologically active compounds including drugs. This volume of *Science of Synthesis* covers the synthesis of six-membered hetarenes with one chalcogen, i.e. oxygen, sulfur, selenium, or tellurium, in the heterocyclic ring, including pyrylium salts and pyranones together with their benzo-fused analogues.

These compounds are included in a hetarene volume of *Science of Synthesis* because the parent pyrylium heterocycle **1** (**Scheme 1**) has physical properties which indicate that some delocalization is present although aromatic stabilization is low, and pyrylium salts are susceptible to nucleophilic attack. Pyran-2- and -4-ones **2** and **4** also have resonance structures **3** and **5** which could be regarded as being aromatic with pyrylium salt character, although much of the chemistry of these systems, e.g. the Diels –Alder reactivity of pyran-2-ones, is not representative of aromatic behavior.

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Scheme 2 Structures of the Parent Heterocycles Covered in Volume 14

This volume presents selected procedures for the *synthesis* of monochalcogen containing six-membered hetarenes. The *chemistry* of these heterocycles is only presented in so far as it is relevant to their synthesis, e.g. by modification of substituents, or where the heterocycle is used in a generally useful synthetic process, e.g. the cycloaddition chemistry of 3-oxidopyrylium salts. Discussions of each hetarene generally follow the same pattern although some sections have a slightly different order to emphasize the more useful approaches to the hetarene in question and not all sections are relevant to all hetarenes. For some benzo-fused systems, annulation onto an arene is separated from annulation onto the hetarene. The usual order of presentation is as follows.

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x.y Product Class y

Introductory Text

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x.y.z.1.1.1.2 Method 2

x.y.z.1.1.1.2.1 Variation 1 (the division of methods into variations is optional)

x.y.z.1.1.1.2.2 Variation 2

x.y.z.1.1.1.2.3 Variation 3, etc.

x.y.z.1.1.2 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.1.2.1 Method 1, etc.

x.y.z.1.1.3 By Formation of One Heteroatom —Carbon and One C —C Bond

x.y.z.1.1.4 By Formation of Two C —C Bonds

x.y.z.1.1.5 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.1.6 By Formation of One C —C Bond

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Pyrylium salts with non-nucleophilic counterions can generally be isolated although no monocyclic pyrylium salt has been identified as a natural product. Chemically they behave as cyclic oxonium salts but are more stable, e.g. to hydrolysis in aqueous solution, than simple oxonium salts, indicative of some aromatic character.^[1] The presence of a diamagnetic ring current is supported by NMR, see **Scheme 3**, and UV data.^[2-5] Thiopyrylium salts are more stable than their oxygen or selenium analogues.^[6-8]

Scheme 3 Selected ¹H and ¹³C NMR Data for Pyrylium Salts^[2,4,5]

Pyrylium salts are susceptible to base-catalyzed hydrolysis giving OH adducts **7** and enediones **8** via attack at the 2- or 6-positions, see **Scheme 4**; substituents at these positions lead to increased stability.^[9] Reactions with primary amines or organometallic reagents also involve attack at C2 (C6) followed by ring-opening, tautomerism, and ring closure, to give benzenoid compounds or pyridinium salts, e.g. **9**. NMR and UV data for benzopyrylium and xanthylum salts confirm the presence of diamagnetic ring currents in these systems with extensive charge delocalization over all rings,^[2,3] but nucleophilic attack occurs in the heteroarene ring to preserve the integrity of the benzenoid rings, e.g. the addition of morpholine to xanthylum salt **10** at C9.^[10]

Scheme 4 Hydrolysis of Pyrylium Salts and Related Reactions

Whether pyranones should be regarded as aromatic has been investigated extensively both theoretically and experimentally.^[2,3] The ^1H and ^{13}C NMR spectra of 2*H*-pyran-2-one (**2**) (**Scheme 5**) give little evidence of a diamagnetic ring current and coupling constant data are consistent with bond localization.^[11-13] The IR carbonyl stretching absorptions of 2*H*-pyran-2-ones (ca. 1720–1740 cm^{-1}) are typical of six-membered lactones implying a limited contribution from the betaine structure **3**. However, NMR and IR data for 4*H*-pyran-4-ones, e.g. a C=O stretch in the region of 1660–1678 cm^{-1} , are consistent with a small ring current and some delocalization. 4*H*-Pyran-4-one is more basic than simple ketones with a $\text{p}K_{\text{a}}$ of 0.1 and 4*H*-1-benzopyran-4-one (**12**), with a $\text{p}K_{\text{a}}$ 2.0, is even more basic. For 4*H*-pyran-4-thione (**13**), microwave spectroscopy shows a further shortening of the C3—C4 bond and lengthening of the C2—C3 bond indicative of enhanced aromaticity.^[14]

Scheme 5 NMR Data for 2*H*-Pyran-2-ones and 4*H*-Pyran-4-ones^[11-13]

Tautomerism of hydroxypyranones is complex with different tautomers sometimes being observed in solution and in the solid state. The 4-hydroxy-2*H*-pyran-2-one tautomer (**14**) predominates in the equilibrium with 2-hydroxy-4*H*-pyran-4-one (**15**) and the diketone **16**, see **Scheme 6**.^[2] In the benzo-fused series, 4-hydroxy-2*H*-1-benzopyran-2-one (**17**) is the dominant tautomer in solution in chloroform, dioxane, or dimethyl sulfoxide, although tautomers **17** and **18** are both trapped in certain reactions, e.g. with diazomethane.^[15]

Scheme 6 Tautomerism of Hydroxypyranones^[2,15]

The chemistry of 2*H*-pyran-2-ones generally reflects both diene and enol lactone character. Bromination of 2*H*-pyran-2-one (**2**) gives 2*H*-3-bromopyran-2-one (**20**) via addition of bromine across the 3,4-double bond followed by dehydrobromination.^[16] However, electrophilic substitution is possible, nitration of 2*H*-6-phenylpyran-2-one (**21**) giving the 3-nitroproduct **22** if 67% nitric acid is used. With stronger nitric acid, nitration takes place in the phenyl ring because carbonyl protonation reduces the reactivity of the pyranone towards electrophilic attack.^[17] Treatment of 2*H*-pyran-2-one **2** with trimethyloxonium tetrafluoroborate gives 2-methoxypyrylium tetrafluoroborate (**19**). Nucleophiles react with 2*H*-pyran-2-ones at the carboxy group leading to ring opening, but perhaps their most useful reactions are Diels –Alder reactions, which can give benzenoid derivatives by subsequent loss of carbon dioxide.^[18] For example, methyl 2-oxo-2*H*-pyran-6-carboxylate (**23**) gives trimethyl benzene-1,2,3-tricarboxylate (**24**) on heating with dimethyl acetylenedicarboxylate. Photolysis of 2*H*-pyran-2-ones has been widely studied with cyclization to cyclobutenes, e.g. **25**, observed under singlet conditions (**Scheme 7**).^[19,20]

Protonation or reaction with methylating agents, converts 4*H*-pyran-4-one (**4**) into 4-hydroxy- or 4-methoxypyrylium salts, e.g. **26**. Reactions with organometallic reagents take place at C4 giving 4-alkylpyrylium salts after subsequent dehydration, e.g. **27**, or 4*H*-4,4-dialkylpyrans (e.g., conversion of 2,6-dimethyl-4*H*-pyran-4-one **28** into the 4,4-dipropyl derivative **29**) if an excess of the organometallic reagent is used. 4*H*-Pyran-4-ones react with O- and N-nucleophiles at both C2, with ring opening, and at C4 and can give mixtures of products. Photolysis of 4*H*-pyran-4-one (**4**) gives 2*H*-pyran-2-one (**2**) via a γ -dimethane type of rearrangement (**Scheme 7**).^[21]

Scheme 7 Some Reactions of 2*H*-Pyran-2-ones and 4*H*-Pyran-4-ones^[2,3,16-20]

The main uses of monocyclic pyrylium salts utilize their optical properties. For example, the strong fluorescence of 2,4,6-triphenylpyrylium tetrafluoroborate (**30**) (**Scheme 8**), which is commercially available, has been known for a long time, and this salt is widely used as a photosensitizer in electron-transfer reactions.^[22] 1-Benzopyrylium salts have been of considerable interest since it was discovered that most of the colors of flowers are due to the 3-*O*-glycosides of polyhydroxy flavylum (i.e., 2-aryl-1-benzopyrylium) salts, i.e. anthocyanines.^[23] Thiopyrylium salts and their selenium and now tellurium analogues have also been developed because of their photochemical properties and improved stability of the thiopyrylium system.^[6-8]

Pyranone rings are found in many biological natural products including relatively simple compounds such as the antibiotic kojic acid (31) to more complex examples, such as bufotalin (32). Many of these compounds, and their analogues with the other chalcogens in the heterarene rings, have the potential to be developed into useful pharmaceuticals, such as warfarin (33), which is used to reduce the tendency of blood to clot (Scheme 8). Many more natural products, e.g. the polycyclic marine natural products, have reduced pyran and pyranone substructures, and can be accessed from the heterarenes discussed in this volume.

Scheme 8 Examples of Commercially Important and Naturally Occurring Pyrylium Salts and Pyranones^[22,23]

SAFETY: Many of the heterocycles discussed in this volume have biological activity and should be regarded as toxic. Therefore they should be handled with care although, as they tend to be involatile, good laboratory practice should suffice. However, particular care must be taken when handling perchloric acid and perchlorate salts. The isolation of pyrylium salts as perchlorates is widespread because of the non-nucleophilic nature of the perchlorate anion and the often excellent crystallinity of the perchlorates. However, perchloric acid is also a powerful oxidizing agent and its reaction with organic substrates can lead to explosions. Any organic perchlorate must therefore be handled with the greatest care behind a secure safety screen and treated as a potential explosive. It is recommended that tetrafluoroborate salts are used whenever possible.

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Whether pyranones should be regarded as aromatic has been investigated extensively both theoretically and experimentally.^[2,3] The ^1H and ^{13}C NMR spectra of 2*H*-pyran-2-one (**2**) (**Scheme 5**) give little evidence of a diamagnetic ring current and coupling constant data are consistent with bond localization.^[11-13] The IR carbonyl stretching absorptions of 2*H*-pyran-2-ones (ca. 1720–1740 cm^{-1}) are typical of six-membered lactones implying a limited contribution from the betaine structure **3**. However, NMR and IR data for 4*H*-pyran-4-ones, e.g. a C=O stretch in the region of 1660–1678 cm^{-1} , are consistent with a small ring current and some delocalization. 4*H*-Pyran-4-one is more basic than simple ketones with a $\text{p}K_{\text{a}}$ of 0.1 and 4*H*-1-benzopyran-4-one (**12**), with a $\text{p}K_{\text{a}}$ 2.0, is even more basic. For 4*H*-pyran-4-thione (**13**), microwave spectroscopy shows a further shortening of the C3—C4 bond and lengthening of the C2—C3 bond indicative of enhanced aromaticity.^[14]

Scheme 5 NMR Data for 2*H*-Pyran-2-ones and 4*H*-Pyran-4-ones^[11-13]

Tautomerism of hydroxypyranones is complex with different tautomers sometimes being observed in solution and in the solid state. The 4-hydroxy-2*H*-pyran-2-one tautomer (**14**) predominates in the equilibrium with 2-hydroxy-4*H*-pyran-4-one (**15**) and the diketone **16**, see **Scheme 6**.^[2] In the benzo-fused series, 4-hydroxy-2*H*-1-benzopyran-2-one (**17**) is the dominant tautomer in solution in chloroform, dioxane, or dimethyl sulfoxide, although tautomers **17** and **18** are both trapped in certain reactions, e.g. with diazomethane.^[15]

Scheme 6 Tautomerism of Hydroxypyranones^[2,15]

The chemistry of 2*H*-pyran-2-ones generally reflects both diene and enol lactone character. Bromination of 2*H*-pyran-2-one (**2**) gives 2*H*-3-bromopyran-2-one (**20**) via addition of bromine across the 3,4-double bond followed by dehydrobromination.^[16] However, electrophilic substitution is possible, nitration of 2*H*-6-phenylpyran-2-one (**21**) giving the 3-nitroproduct **22** if 67% nitric acid is used. With stronger nitric acid, nitration takes place in the phenyl ring because carbonyl protonation reduces the reactivity of the pyranone towards electrophilic attack.^[17] Treatment of 2*H*-pyran-2-one **2** with trimethyloxonium tetrafluoroborate gives 2-methoxypyrylium tetrafluoroborate (**19**). Nucleophiles react with 2*H*-pyran-2-ones at the carboxy group leading to ring opening, but perhaps their most useful reactions are Diels –Alder reactions, which can give benzenoid derivatives by subsequent loss of carbon dioxide.^[18] For example, methyl 2-oxo-2*H*-pyran-6-carboxylate (**23**) gives trimethyl benzene-1,2,3-tricarboxylate (**24**) on heating with dimethyl acetylenedicarboxylate. Photolysis of 2*H*-pyran-2-ones has been widely studied with cyclization to cyclobutenes, e.g. **25**, observed under singlet conditions (**Scheme 7**).^[19,20]

Protonation or reaction with methylating agents, converts 4*H*-pyran-4-one (**4**) into 4-hydroxy- or 4-methoxypyrylium salts, e.g. **26**. Reactions with organometallic reagents take place at C4 giving 4-alkylpyrylium salts after subsequent dehydration, e.g. **27**, or 4*H*-4,4-dialkylpyrans (e.g., conversion of 2,6-dimethyl-4*H*-pyran-4-one **28** into the 4,4-dipropyl derivative **29**) if an excess of the organometallic reagent is used. 4*H*-Pyran-4-ones react with O- and N-nucleophiles at both C2, with ring opening, and at C4 and can give mixtures of products. Photolysis of 4*H*-pyran-4-one (**4**) gives 2*H*-pyran-2-one (**2**) via a γ -dimethane type of rearrangement (**Scheme 7**).^[21]

Scheme 7 Some Reactions of 2*H*-Pyran-2-ones and 4*H*-Pyran-4-ones^[2,3,16-20]

The main uses of monocyclic pyrylium salts utilize their optical properties. For example, the strong fluorescence of 2,4,6-triphenylpyrylium tetrafluoroborate (**30**) (**Scheme 8**), which is commercially available, has been known for a long time, and this salt is widely used as a photosensitizer in electron-transfer reactions.^[22] 1-Benzopyrylium salts have been of considerable interest since it was discovered that most of the colors of flowers are due to the 3-*O*-glycosides of polyhydroxy flavylum (i.e., 2-aryl-1-benzopyrylium) salts, i.e. anthocyanines.^[23] Thiopyrylium salts and their selenium and now tellurium analogues have also been developed because of their photochemical properties and improved stability of the thiopyrylium system.^[6-8]

Pyranone rings are found in many biological natural products including relatively simple compounds such as the antibiotic kojic acid (31) to more complex examples, such as bufotalin (32). Many of these compounds, and their analogues with the other chalcogens in the heterarene rings, have the potential to be developed into useful pharmaceuticals, such as warfarin (33), which is used to reduce the tendency of blood to clot (Scheme 8). Many more natural products, e.g. the polycyclic marine natural products, have reduced pyran and pyranone substructures, and can be accessed from the heterarenes discussed in this volume.

Scheme 8 Examples of Commercially Important and Naturally Occurring Pyrylium Salts and Pyranones^[22,23]

SAFETY: Many of the heterocycles discussed in this volume have biological activity and should be regarded as toxic. Therefore they should be handled with care although, as they tend to be involatile, good laboratory practice should suffice. However, particular care must be taken when handling perchloric acid and perchlorate salts. The isolation of pyrylium salts as perchlorates is widespread because of the non-nucleophilic nature of the perchlorate anion and the often excellent crystallinity of the perchlorates. However, perchloric acid is also a powerful oxidizing agent and its reaction with organic substrates can lead to explosions. Any organic perchlorate must therefore be handled with the greatest care behind a secure safety screen and treated as a potential explosive. It is recommended that tetrafluoroborate salts are used whenever possible.

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16 **Hetarenes**
Volume 16:
Six-Membered Hetarenes with Two Identical Heteroatoms

Yamamoto, Y., in *Science of Synthesis*, **16** (2003), p.1

General Introduction

This volume covers the synthesis of six-membered heterocyclic compounds with two identical heteroatoms, i.e. oxygen, sulfur, selenium, tellurium, nitrogen, or phosphorus ring atoms. Six-membered heterocycles of this category fused to a six-membered aromatic carbocyclic or heterocyclic ring, or to a five-membered heterocyclic ring with two nitrogen atoms, are also discussed. The parent ring structures of the heterocycles covered in this volume are shown in **Scheme 1**, together with the numbering schemes and nomenclature used.

Scheme 1 Structures, Numbering Schemes, and Nomenclature for the Parent Heterocycles Covered in Volume 16

The synthesis of 1,2- and 1,4-dioxins, 1,2- and 1,4-dithiins, and pyridazines (1,2-diazines) and their annulated derivatives was discussed in *Houben –Weyl*, Vol. E 9a. The synthesis of pyrimidines (1,3-diazines) and pyrazines (1,4-diazines), and of their annulated derivatives together with purines, was discussed in *Houben –Weyl*, Vol. E 9b/Part 1 and Vol. E 9b/2, respectively. Bicyclic six-membered ring systems each with one to two nitrogen atoms were discussed in *Houben –Weyl*, Vol. E 9c. The structure, synthesis, and chemistry of these heterocycles have been reviewed.^[1,2] References treating specific heterocycles or specific subjects relating to these heterocycles are given in each section of this volume.

This volume presents selected procedures for the *synthesis* of six-membered hetarenes with two identical heteroatoms. The *chemistry* of these heterocycles is only presented insofar as it is relevant to their synthesis, e.g. by modification of substituents. The discussions of each class of compound generally follow the pattern shown below, although not all subsections are relevant to every hetarene. Some sections follow a slightly different order to emphasize the most useful approaches to the hetarene in question. The most notable case is the chapter on

purines (see Section 16.17). The chapter on diazinodiazines (Section 16.22), which are also bicyclic systems where both rings contain heteroatoms, has additional headings under the ring-closure sections to complement this class of compounds.

x: volume number = 16; **y:** product class; **z:** product subclass

x.y.z.1 Synthesis by Ring-Closure Reactions

x.y.z.1.1 By Annulation to an Arene

x.y.z.1.1.1 By Formation of Four Heteroatom —Carbon Bonds and One C —C Bond

x.y.z.1.1.2 By Formation of Four Heteroatom —Carbon Bonds

x.y.z.1.1.3 By Formation of Three Heteroatom —Carbon Bonds and One C —C Bond

x.y.z.1.1.4 By Formation of Two Heteroatom —Carbon and Two C —C Bonds

x.y.z.1.1.5 By Formation of Three Heteroatom —Carbon Bonds

x.y.z.1.1.6 By Formation of Two Heteroatom —Carbon Bonds and One C —C Bond

x.y.z.1.1.7 By Formation of One Heteroatom —Carbon and Two C —C Bonds

x.y.z.1.1.8 By Formation of One Heteroatom —Heteroatom and One Heteroatom —Carbon Bond

x.y.z.1.1.9 By Formation of One Heteroatom —Heteroatom and One C —C Bond

x.y.z.1.1.10 By Formation of Two Heteroatom —Carbon Bonds

x.y.z.1.1.11 By Formation of One Heteroatom —Carbon and One C —C Bond

x.y.z.1.1.12 By Formation of Two C —C Bonds

x.y.z.1.1.13 By Formation of One Heteroatom —Heteroatom Bond

x.y.z.1.1.14 By Formation of One Heteroatom —Carbon Bond

x.y.z.1.1.15 By Formation of One C —C Bond

x.y.z.1.2 By Annulation to the Heterocyclic Ring

x.y.z.2 Synthesis by Ring Transformation

x.y.z.3 Aromatization

x.y.z.4 Synthesis by Substituent Modification

The sections listed above are further subdivided into methods that have been selected as the most useful for the preparation of the heteroarene in question. Each method is presented separately as follows:

1. An introduction containing some background information, the scope and limitation of the method described,

mechanistic information, and, where relevant, a comparison with other methods.

2. Reaction schemes, most of the time associated with a table of representative examples, and a short specific description of the reaction in general. Safety indications and experimental precautions necessary for a specific reaction are noted.

3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format.

The coverage is not meant to be exhaustive. Rather, the most useful and reliable methods for each heteroarene have been selected. In some cases, especially for ditellurins and diphosphinines (Sections 16.7 and 16.23, respectively), only a small number of methods exist, primarily because the chemistry of these ring systems is still very young.

The organizational principles are based on the synthetic methods applied, not on the functionality of the heterocyclic product. Methods with related retrosyntheses are juxtaposed, e.g. those involving the formation of two heteroatom—carbon bonds. Therefore, heterocycles possessing a specific functional group are not grouped together. If all the syntheses of a heterocycle containing a specific functionality need to be found, these can be located using the index, as well as structure and text searches in the electronic product.

This volume covers the synthesis of heterocyclic compounds with widely different stabilities and chemical and physical properties. For example, 1,4-diphenyl-2,3-benzodioxin (**1**) is unstable and not isolated, but trapped in situ (see **Scheme 2**);^[3] the parent compound 2,3-benzodioxin is not yet known (see Section 16.1).

Scheme 2 Synthesis of an Unstable 2,3-Benzodioxin^[3]

Other dioxins, such as 1,2-dioxin, 1,2-benzodioxin, and dibenzo[*c,e*][1,2]dioxin, are not known. Similarly, 1,2-dithiins and 1,2-diselenins are relatively unstable in comparison with their corresponding 1,4-analogues, and 1,2-ditellurins are not known (Sections 16.3–16.7). Compared to the oxygen, sulfur, selenium, tellurium, and phosphorus heterocycles, so many different types of nitrogen heterocycles (1,2-, 1,3-, and 1,4-diazines and their annulated derivatives) are known and most of them are stable and exhibit certain biological activities.

The resonance structures of pyridazine (Section 16.8) indicate that there is no "unactivated" ring carbon with respect to nucleophilic attack (**Scheme 3**). However, Chichibabin-type aminations of unsubstituted pyridazine^[4] and substitution of nucleophilic carbon-centered radicals, e.g. alkoxycarbonylation,^[5,6] occurs at C4/C5 (**Scheme 4**, Sections 16.8.4.1.1.2.6 and 16.8.4.1.1.2.2.1, respectively).

Scheme 3 Resonance Structures of Pyridazine

Scheme 4 Chichibabin-Type Amination and Radical Alkoxy carbonylation of Unsubstituted Pyridazine^[4-6]

The addition of Grignard reagents to pyridazine also takes place at C4/C5, while that of organolithium reagents is at C3/C6.^[7] The electron-deficient character of the pyridazine ring makes it susceptible toward (partial) reduction, e.g. with lithium aluminum hydride. It should be noted that the reaction behavior of substituted pyridazines strongly depends on the nature of the substituents. For example, electrophilic substitution reactions can take place with pyridazines bearing (preferably at least two) electron-donating groups or with various pyridazine *N*-oxides. Pyridazin-3(2*H*)-one (**2**) and pyridazine-4(1*H*)-one (**3**) exist in the oxo form in the solid state and in solution (**Scheme 5**). An equilibrium between the oxo (lactam) form and its tautomer (lactim form) has been revealed for dilute solutions in dioxane, and the equilibrium shifts more to the lactim form on further dilution. For "maleic hydrazide", the preferred tautomeric form is the monolactam –monolactim structure **4**. The tautomeric behavior of pyridazinethiones (sulfanylpuridazines) is essentially the same as for the oxygen analogues, but pyridazinamines generally exist in the amino form.

Scheme 5 Tautomerism of Pyridazinones

Pyrimidine (Section 16.12) is an electron-deficient heteroarene and significant electron depletion is observed at C2, C4, and C6, but only relatively minor depletion at C5. Therefore, nucleophiles generally attack at the 2-, 4-, or 6-

positions, whereas electrophiles attack either C5 or the ring nitrogen atoms. For example, amination of 4-methylpyrimidine with sodium amide gives 4-methylpyrimidin-2-amine, 6-methylpyrimidine-2,4-diamine, and other products.^[8,9] Pyrimidines bearing a strongly electron-withdrawing group undergo hydration, e.g. formation of adduct **5** from 5-nitropyrimidine (**Scheme 6**),^[10] and in acidic media, 5-mesyl- and 5-(methylsulfinyl)pyrimidine behave similarly.^[11] Simple pyrimidines undergo addition of Grignard or alkyllithium reagents usually across the N3—C4 bond; thus, pyrimidine gives the adduct **6** upon treatment with phenylmagnesium bromide or phenyllithium, and subsequent oxidation gives 4-phenylpyrimidine (**Scheme 6**).^[12] Electrophilic attack on pyrimidines can only occur under normal conditions if at least one electron-donating group is present. In this case, halogenation, nitration, nitrosation, diazocoupling, sulfonation, formylation, and related reactions are possible at the 5-position.

Scheme 6 Hydration of Pyrimidine Bearing an Electron-Withdrawing Group and Arylation of Pyrimidine Using a Metal Reagent^[10,11]

Resonance structures of pyrimidine can be written with charge-separated structures in a similar manner to that shown with pyridazine (see **Scheme 3**). Tautomerism occurs in pyrimidines that are substituted by hydroxy, sulfanyl, or amino groups. In most cases, 2-, 4-, and 6-hydroxy-substituted pyrimidines exist not as pyrimidinols, but as pyrimidin-2(1*H*)-one (**8**), pyrimidin-4(3*H*)-one (**7**), and pyrimidin-6(1*H*)-one, respectively. Similarly, the sulfur analogue of pyrimidin-4(3*H*)-one, pyrimidine-4(3*H*)-thione (**9**) forms a thiolactam structure (**Scheme 7**). On the other hand, the amino-substituted pyrimidines exist as aromatic pyrimidinamines rather than favoring the imino form.

Scheme 7 Tautomerism of Pyrimidinones and Pyrimidinethiones

The resonance structures of pyrazine (Section 16.14) are represented in **Scheme 8**, and pyrazine is also an electron-deficient heteroaromatic compound, similar to pyridazine and pyrimidine. Electrophilic substitution reactions of unsubstituted quinoxaline or phenazine (Sections 16.15 and 16.16, respectively) are unusual under ordinary reaction conditions. When activating substituents are present on the benzenoid ring, substitution usually becomes more facile. Nucleophilic substitution takes place through the direct displacement of hydrogen, as observed in the reaction of pyridazine (**Scheme 4**), but this type of reaction is rare with pyrazine. The ease of displacement of the substituents varies depending on the substitution pattern. There is a tendency to formulate nucleophilic substitution as simple addition/elimination reactions (**Scheme 8**).

Scheme 8 Resonance Structures and Reactivity of Pyrazine

Tautomerism exists in pyrazines when they are substituted by a hydroxy group. There is overwhelming evidence to suggest that in these cases the molecules exist largely in the amide form **10** (**Scheme 9**). However, in the case of pyrazinamine and quinoxalin-2-amine, the amino tautomer is favored rather than the imino form.

Scheme 9 Tautomerism of Pyrazinone

Purines (Section 16.17) are one of the most ubiquitous heterocycles; the quantity of naturally occurring purines is enormous as 50% of ribonucleic acid and deoxyribonucleic acid bases are purines. There are various forms of tautomerism that operate in the different purine species. Four NH-tautomeric forms exist depending on the site of attachment of the proton at the ring nitrogens (**Scheme 10**); the CH-tautomers, e.g. **11**, are of minor importance. Amine –imine tautomerism can be considered for amino-substituted purines such as adenine (**12A** and **12B**, **Scheme 10**), guanine, isoguanine, or purinediamine. Lactam –lactim tautomers exist in hypoxanthine (**13A** and **13B**), guanine, isoguanine, or xanthine. Similar structures can be discussed for sulfanylpurines. The purine ring system can undergo both electrophilic and nucleophilic reactions. The anionic form of purine is readily attacked by electrophiles, such as alkylating or glycosylating agents, to produce, in general, the N9-substituted derivatives (**Scheme 11**). In the neutral form, the products may vary. The large movement of negative charge in purines from the π -electron-excessive five-membered ring to the π -electron-deficient six-membered ring results in the C8 atom becoming the most electron-deficient site in the nonionized molecule. Therefore, nucleophilic substitution at this position occurs easily, and the order for displacement is C8 > C6 > C2. On the other hand, purine anion formation causes nucleophilic attack predominantly at C6 in the pyrimidine ring and the order for replacement of appropriate substituents is C6 > C2 > C8. Electrophilic attack is rare, but if one or more strongly electron-donating groups exist in the ring system, electrophiles may attack the C8 atom. In the presence of substrates capable of producing acyl radicals, purines give the 8-acyl derivatives.

Scheme 10 Purine Tautomers

Scheme 11 Anionic Form of Purine

Pyridopyridazines are compounds in which a pyridine ring is attached directly to a pyridazine (Section 16.18). The benzo-fused derivatives of pyridazines are cinnolines and phthalazines (see Sections 16.9 and 16.10, respectively). Similarly, pyridopyrimidines and pyridopyrazines (Sections 16.19 and 16.20, respectively) are compounds with a pyridine ring fused to a pyrimidine or pyrazine, respectively. Among these three classes of pyrido-fused 1,2-diazines, pyridopyrimidines are the most investigated. Reduction of their ring system takes place readily. Upon catalytic reduction, the tetrahydro derivatives in the pyridine ring are obtained,^[13] but borohydride reduction gives pyrimidine ring reduced derivatives.^[13] Lithium aluminum hydride reduction often proceeds further with reductive ring opening to the aminomethyl-substituted pyridine derivatives.^[13] In general, nucleophilic attack of pyridopyrimidines occurs at the pyrimidine ring and the pyridine ring is stable under ordinary nucleophilic conditions. For example, Grignard reagents add to pyrido[2,3-*d*]pyrimidine to give 4-substituted derivatives^[14] (**Scheme 12**). Electrophilic attack at ring nitrogen, e.g. protonation, occurs at the pyrimidine nitrogen because of favorable resonance considerations and is accompanied by covalent hydration and/or ring opening (**Scheme 12**).

Scheme 12 Reactivity of Pyridopyrimidines^[14]

Pteridine (pyrazino[2,3-*d*]pyrimidine, Section 16.21) is the pyrimidine derivative to which a pyrazine ring is fused. Tautomerism is possible in heteroatom-substituted pteridines, as observed with pyrimidines and pyrazines. For example, tautomeric structures of pteridines substituted at the 4-position by a heteroatom are shown in **Scheme 13**. The character of the heteroatom X determines which tautomer is preferred. As mentioned for pyrimidine (*vide supra*), when X is nitrogen, the amino form is favored over the imino form, whereas the amide or thioamide form is the more stable tautomer when X is oxygen or sulfur, respectively. Accordingly, pterin (**14**) mainly exists in the 2-amino-4-oxo form, rather than as the 2-amino-4-hydroxy derivative (**Scheme 13**). Pteridine is attacked by nucleophiles such as water, alcohols, and amines to form "covalent adducts", especially at the highly reactive 4- and 7-positions, e.g. **15**.^[15] Heating of the covalent hydrate **15** under acidic conditions causes ring cleavage to give 3-aminopyrazine-2-carbaldehyde (**Scheme 14**).^[16]

Scheme 13 Tautomerism of Heteroatom-Substituted Pteridines

Scheme 14 Covalent Hydration of Pteridine and Ring Cleavage^[15,16]

Many compounds covered in this volume have considerable importance from a commercial point of view and, in particular, the nitrogen heterocycles are extremely important since most of them exhibit a wide range of biological activities. Accordingly, the longer chapters are devoted to the synthesis of nitrogen heterocycles. **Scheme 15** illustrates the structures of some pyridazine-derived drug molecules that have made their way onto the market: antibiotic cefozopran, antidepressant minaprine, and analgesic/anti-inflammatory agent emorfazone. Phthalazine-derived drug molecules, hydralazine and budralazine, which are currently on the market, are also shown in the **Scheme 15**.

Scheme 15 Pyridazine- and Phthalazine-Derived Drug Molecules

Pyrimidines play an important role in nature. Uracil, thymine, and cytosine (**Scheme 16**) are the main components of the nucleosides uridine, deoxythymidine, and cytidine, respectively. A nonproteinogenic α -amino acid containing a pyrimidine ring is lathyrine, which can be isolated from the seeds of *Lathyrus tingotanus*. Variolin B was discovered in the antarctic sponge *Kirkpatrickia variolosa* and is an example of a pyrimidine-based alkaloid that shows some cytostatic and antiviral activity (**Scheme 16**).

Scheme 16 Pyrimidine-Based Natural Products

One of the most widely used pyrimidine-based drugs is trimethoprim, which is active against many gram-positive and -negative bacteria by inhibiting their dihydrofolate reductase. Another dihydrofolate reductase inhibitor is pyrimethamine. 5-Fluorouracil is a clinically established anticancer drug and component of various multidrug regimes for the treatment of tumors (**Scheme 17**). The pyrimidine moiety is also present in a variety of pesticides.

Scheme 17 Pyrimidine-Based Drug Molecules

Pyrazinecarboxamide is a well-known synthetic antimycobacterial agent and is used for the treatment of tuberculosis. Glipizide is a 5-methylpyrazine-2-carboxamide derivative and is an oral antidiabetic agent (**Scheme 18**).

Scheme 18 Pyrazine-Based Drug Molecules

Purine itself has not been found in nature, but purine derivatives are one of the most ubiquitous natural products. The purine heterocycle is a constituent of nucleosides and nucleotides. Adenosine 5'-triphosphate (ATP) is used for the storage of energy, and nicotinamide adenine dinucleotide (NAD) is involved in cellular redox processes (**Scheme 19**).

Scheme 19 Important Purine Derivatives in Metabolism

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17 **Hetarenes**
Volume 17:
Six-Membered Hetarenes with Two Unlike or More Than Two Heteroatoms and Larger Hetero-Rings

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General Introduction

In this volume the synthesis of six-membered hetarenes with two unlike or more than two heteroatoms and of fully unsaturated larger-ring heterocycles is discussed. The parent ring structures of the heterocycles covered in this volume are shown in **Scheme 1**, together with the numbering schemes used.

Scheme 1 Structures and Numbering Schemes of the Parent Heterocycles Covered in Volume 17

The synthesis of these oxygen-, sulfur-, and/or nitrogen-containing heterocycles was discussed in *Houben –Weyl*, Vol. E 9a, Vol. E 9c, and Vol. E 9d, and their structure, reactivity, and chemistry has also been extensively reviewed.^[1,2] References to previous reviews on specific heterocycles can be found in each section.

This volume presents selected procedures for the *synthesis* of the diverse group of heterocycles shown in **Scheme 1**. The *chemistry* of these heterocycles is, in most cases, presented only when relevant to their synthesis, e.g. by modification of substituents. There are a few exceptions such as Section 17.8.4 which discusses reactions around the porphyrin periphery. The discussions of each subclass generally adhere to the following pattern, although some chapters follow a slightly different order to emphasize the most useful approaches to the heterocycle in question. Note that not all subsections are relevant to all heterocycles:

x: volume number = 17; **y**: product class; **z**: product subclass

x.y.z Product Subclass z

Introductory Text

x.y.z.1 Synthesis by Ring-Closure Reactions**x.y.z.1.1 By Formation of Three Heteroatom —Carbon Bonds****x.y.z.1.2 By Formation of Two Heteroatom —Carbon Bonds****x.y.z.1.3 By Formation of One Heteroatom —Carbon and One C —C Bond****x.y.z.1.4 By Formation of Two C —C Bonds****x.y.z.1.5 By Formation of One Heteroatom —Carbon Bond****x.y.z.1.6 By Formation of One C —C Bond****x.y.z.2 Synthesis by Ring Transformation****x.y.z.2.1 By Ring Enlargement****x.y.z.2.2 Formal Exchange of Ring Members with Retention of the Ring Size****x.y.z.2.3 By Ring Contraction****x.y.z.3 Aromatization (or Synthesis by Introduction of a Double Bond)**

In this volume the term "aromatization" should be interpreted as "introduction of maximum unsaturation", since the target ring systems can in some cases be aromatic, antiaromatic, or nonaromatic.

x.y.z.4 Synthesis by Substituent Modification**x.y.z.4.1 Substitution of Existing Substituents****x.y.z.4.2 Addition Reactions****x.y.z.4.3 Rearrangement of Substituents****x.y.z.4.4 Modification of Substituents**

The sections listed above are further subdivided into methods which have been selected as the most useful for the preparation of the particular heterocycle. Each method is presented separately as follows:

1. An introduction with some background information is given, the scope of the method/variation is described, and a comparison with other variations is eventually made; safety information is given when significant, and mechanistic information is provided when relevant to the use of the method in synthesis.
2. Reaction schemes associated with a short list of representative examples.
3. Representative experimental procedures.

Within each chapter, the organizational principle is based on the synthetic methods used, and not on the functional groups or substitution patterns of the heterocyclic product. Related methods, e.g. all those involving the simultaneous formation of two heteroatom—carbon bonds, are grouped together, rather than the methods of synthesis of similarly substituted heterocycles. However, the index can be used to locate methods recommended for the synthesis of a particular type of heterocycle with specific substituents.

The ring systems covered in this volume embrace a wide range of stabilities, as well as physical and chemical properties. This is in part related to whether or not cyclic π -conjugation exists in the heterocycles and, if so, whether it leads to antiaromatic destabilization or aromatic stabilization of the molecule. 1,4-Oxathiins, 1,4-thiazines, and 1,4-oxazines are nonaromatic, electron-rich heterocycles that undergo oxidation and hydrolysis reactions with considerable ease, demonstrating their relative instability. The parent 1,4-oxathiin and 1,4-thiazine can be isolated but are stable only under inert atmosphere at $-60\text{ }^{\circ}\text{C}$ and at room temperature, respectively.^[3,4] On exposure to air at room temperature, 1,4-oxathiin rapidly decomposes to form a white insoluble polymer. Furthermore, it has not been possible to isolate 1,4-oxazine in pure form.^[5] The annulated 1,4-thiazine and 1,4-oxazine analogues are aromatic when they exist as the N-substituted isomers and thus are more stable to oxidizing and hydrolytic conditions. In the benzo-fused ring systems, the heterocyclic ring is still more reactive than the carbocyclic ring toward electrophilic substitution. However, dibenzo-fused compounds undergo clean electrophilic substitution and metalation reactions at different positions on the carbocyclic rings depending on the nature of the heteroatoms. In the case of phenoxathiin (**1**) (Scheme 2), electrophilic attack introduces the first substituent at the C2-position and the second substituent at the C8-position, as observed in bromination and sulfonation reactions.^[6] However, in acylation reactions, the C2,C7-disubstituted product is predominantly formed over the C2,C8-disubstituted product.^[7] In the case of 10*H*-phenoxazine (**2**), the nitrogen atom directs the first electrophilic attack to the C3-position and the second to the C7-position in the case of bromination;^[8,9] however, under standard acylation conditions, an acetyl group was introduced at the C2-position, *para* to the oxygen atom, a seemingly unusual site at first glance. This change in the substitution pattern is due to acetylation of the nitrogen atom prior to that of the carbocyclic ring. The *N*-acyl group is then removed under hydrolytic workup conditions to give the observed products.^[10] The acyl-group-directing tendency of 10*H*-phenothiazines **3** (Scheme 2) depends on the nature of the substituent on the nitrogen atom, where alkyl substituents lead to the formation of 3,7-disubstituted compounds while acyl substituents lead to 2,8-disubstituted products.

Scheme 2 Regioselectivity of Electrophilic Substitution Reactions of Phenoxathiin, 10*H*-Phenoxazine, and 10*H*-Phenothiazine

In metalation reactions of phenoxathiin, 10*H*-phenoxazine, and 10*H*-phenothiazine, chelation plays an important role in determining the substitution pattern. The oxygen atom of phenoxathiin (**1**) acts as a directing group resulting in metalation *ortho* to the oxygen atom, as is seen in the formation of acid **4** (Scheme 3).^[11] However, this directing effect of the oxygen atom can be overcome by oxidation of phenoxathiin to phenoxathiin 10,10-dioxide, which is metalated *ortho* to the sulfone moiety.^[12] 10*H*-Phenoxazine (**2**) and 10*H*-phenothiazine (**6**) bear an acidic proton on the nitrogen atom that is removed in the first step by the organometallic reagent. Subsequent treatment of the anion with carbon dioxide leads to a lithio carbamate salt that can be metalated *ortho* to the nitrogen atom with another equivalent of organolithium reagent. Addition of the electrophile and subsequent workup leads to the introduction of a substituent only at the position *ortho* to the nitrogen atom. This effect has been used with various electrophiles to prepare derivatives **5** and **7** (Scheme 3).^[13,14]

Scheme 3 Metalation Reactions of Phenoxathiin, 10*H*-Phenoxazine, and 10*H*-Phenothiazine

Triazines and tetrazines are highly electron-deficient heterocycles, and, therefore, are resistant to electrophilic substitution reactions, even though 1,3,5-triazine is aromatic in nature. The 1,2,3-triazines cannot be subjected to the usual methods of nucleophilic substitution because, after attack of a nucleophile at the 4-position, the 1,2,3-triazine ring opens and nitrogen is evolved (see *Houben –Weyl*, Vol. E 9c, p 561). The parent 1,3,5-triazine is also a very labile compound and undergoes cleavage to afford hydrogen cyanide easily in the presence of nucleophiles.^[15] However, this instability of 1,3,5-triazine, in fact, makes it a convenient source of hydrogen cyanide, as exemplified by its use in the Gattermann aldehyde synthesis.^[16] On the other hand, 1,2,4-triazines are stable to nucleophilic attack and the low electron density in the ring helps in site-specific substitution. The vast majority of carbon, nitrogen, and sulfur nucleophiles preferentially add to C5, eventually leading to 5-substituted 1,2,4-triazines. The preferred attack at the C5-position is probably due to a 1,4-quinonoid contribution to the intermediate anion when a formal negative charge is placed at N2. On the other hand, attack at the C3- or C6-position leads to a comparatively more energetic intermediate that requires less stable 1,2-quinonoid contributions in order to place the negative charge upon a nitrogen atom.^[17] However, once attack at C5 has occurred, subsequent substitution does take place at C3, while reaction at C6 is only rarely observed. Only Grignard reagents possess a differing reactivity pattern, wherein substitution at C6 is known to occur prior to substitution at C3 (**Scheme 4**).^[18]

Scheme 4 Sequential Reactions of 1,2,4-Triazine with Grignard Reagents^[18-21]

The highly electron-deficient nature of triazines and tetrazines makes them good dienes in inverse-electron-demand Diels –Alder cycloadditions with electron-rich dienophiles, such as alkenes, alkynes, or enamines, to form a wide range of condensed heterocyclic ring systems such as pyrimidines **8**, pyridines **9**, and pyridazines **10** (**Scheme 5**).^[22] The pyridazine products can act as dienophiles for a second hetero-Diels –Alder reaction to form carbocyclic compounds. 1,2,4-Triazines rapidly undergo inverse-electron-demand Diels –Alder cycloadditions across C3/C6 with many electron-rich dienophiles and systems containing strained double bonds. Similarly, 1,3,5-triazines participate in Diels –Alder addition reactions where the positions of attack on the ring depend on the nature of the substituents present. Both inter- and intramolecular cycloadditions of these systems have been reported, providing, after expulsion of nitrogen or nitriles, pyridines and pyrimidines (or sometimes pyrazines). This methodology, combined with the ability to functionalize the triazine core easily and selectively through nucleophilic substitution, provides an attractive route to condensed heterocycles, whose synthesis would otherwise be quite laborious. Of additional importance is the construction of dihydropyridines through cycloaddition reactions of 1,2,4-triazines with ketenes, enol ethers, enamines, imidates, and similar compounds.^[22,23] Here the products may react further and eliminate a substituent to form the corresponding pyridines. 1,2,4,5-Tetrazines undergo Diels –Alder addition reactions with electron-rich alkenes and, after nitrogen extrusion, form dihydropyridazine derivatives which either tautomerize to the stable 1,4-dihydro derivative or eliminate HX to form pyridazines **10**.

Scheme 5 Hetero-Diels –Alder Reactions of Triazines and Tetrazines with Electron-Rich Dienophiles^[22,23]

Azepines, thiepins, and oxepins have attracted attention due to their close relation to cycloheptatriene and their potentially antiaromatic 8 π -electron nature. The most important feature of the oxepin structure is its ability to undergo valence isomerization to benzene oxide (**11**, X = O) (**Scheme 6**). The equilibrium between the two valence isomers can also be shifted in either direction by different methods such as by increasing solvent polarity that moves the equilibrium toward benzene oxide,^[24] or by introducing substituents at the C2- and C7-positions that, according to ab initio calculations, can destabilize the benzene oxide form.^[25] Isolation of the parent thiepin has not been possible, perhaps due to the decomposition of thianorcaradiene (**11**, X = S) to benzene and elemental sulfur; however, it is possible to suppress this decomposition pathway by introducing bulky substituents such as *tert*-butyl groups at the C2- and C7-positions, which inhibit the electrocyclic reaction leading to the formation of the corresponding thianorcaradiene.

Scheme 6 Instability of Oxepins and Thiepins

Arene oxides are postulated to be biosynthetic intermediates in the monooxygenase-catalyzed formation of phenolic metabolites from aromatic substrates, based upon an observation of substituent migration. Other evidence includes the isolation of some arene oxides from natural sources such as methyl oxepin-2-carboxylate (cf. **15**, **Scheme 7**) obtained from the fungus *Phellinus tremulae*.^[26,27] Labeling experiments in *Phellinus ribis* using methyl benzoate-2,6- d_2 (**12**) led to the isolation of methyl oxepin-2-carboxylate (**15**) with 70% deuterium incorporation, along with two differently labeled salicylates **16** and **17** which were proposed to be formed via intermediates **13** and **14**, respectively (**Scheme 7**).^[28] In addition, studies on the mechanism of catechol dioxygenase induced C—C cleavage reactions that lead to ring-opened products indicate that these reactions may also proceed via oxepins/arene oxides.^[29] Hence, the formation of oxepin may be a critical step in the conversion of benzene into carcinogenic products by photooxidation in the environment,^[30] or through metabolism inside the body.

Scheme 7 Oxepins as Products of Enzymatic Arene Oxidations^[28]

While monocyclic oxepins, as well as their sulfur and nitrogen analogues, are of considerable theoretical interest, their annulated derivatives have practical importance due to their pharmacological activity. Different methods

have been developed to introduce various functional groups at the C10-position owing to the pharmaceutical interest in dibenz[*b,f*]oxepins with diverse side chains at this position. In one such approach, treatment of dibenz[*b,f*]oxepin-10(11*H*)-one derivatives **18** with a nucleophile, in the presence of a Lewis acid, leads to formation of C10-substituted dibenz[*b,f*]oxepins **19** (Scheme 8).^[31]

Scheme 8 Introduction of Nucleophiles into Dibenz[*b,f*]oxepins^[31]

Along with studies to understand their aromatic properties, diazepines (seven-membered heterocycles containing two nitrogen atoms) are interesting because of their pharmacological properties. The diazepines can exist in different tautomeric forms, and the equilibrium ratios are highly dependent on the ability of the ring substituents to stabilize a particular isomer. Although most systems favor one tautomer, in some cases it is possible to interconvert the tautomers by chemical transformations. An example of the chemical interconversion of annulated 1*H*- and 3*H*-1,2-diazepines **20** and **21**, respectively, is shown in Scheme 9.^[32-34]

Scheme 9 Interconversion of Annulated 1*H*- and 3*H*-1,2-Diazepines^[32-34]

Cyclazines are planar conjugated cyclic molecules with either $(4n+2)$ or $4n$ π -electrons and a central nitrogen atom which is covalently bonded to three of the peripheral carbon atoms. Cyclazines are very interesting from both a theoretical and chemical point of view and have been widely studied, particularly to evaluate their degree of aromaticity. Of the different types of cyclazines, the [2.2.3]cyclazines having a planar 10 π -electron system are most widely studied with respect to their stability and chemical behavior.^[35] The parent [2.2.3]cyclazine is the best known and most important compound in the cyclazine series because of its novel structural properties, as well as for the fact that its partially saturated framework occurs in some natural products.^[35,36] Along with [2.2.3]cyclazines, the [2.2.4]cyclazinium ion is an example of an "odd-membered" annulene, consisting of a $(4n+2)$ π -electron system and exhibiting aromatic properties.

On the other hand, cyclazines bearing a peripheral π -electron system related to the [12]annulenes have been shown to be paratropic. [3.3.3]Cyclazine (**22**) was found to be highly reactive, having a propensity toward both

oxidation and reduction. [3.3.3]Cyclazine (**22**) is readily oxidized by halogens initially to produce a stable radical cation and eventually to the dication **23** (**Scheme 10**), indicating a small energy gap between the frontier orbitals of [3.3.3]cyclazine.^[37,38]

Scheme 10 Oxidation of [3.3.3]Cyclazine by Bromine^[37,38]

Like the cyclazines, heterocyclic compounds containing eight-membered and larger-membered fully unsaturated rings have been studied to probe their aromatic or nonaromatic nature. The interest in azocines (i.e., azacyclooctatetraenes) is primarily due to their structural similarity to cyclooctatetraene and hence their stability and valence isomerization have been studied. Similar to cyclooctatetraene, azocines adopt a tub-shape conformation lacking conjugative stability and are nonaromatic systems. However, planar dianions (e.g., **24**) (**Scheme 11**) can be generated by two-electron reduction of 2-alkoxyazocines, and are aromatic 10⁻electron systems.^[39] The ¹H NMR spectra of the stable dipotassium salts of 2-methoxyazocines reveal substantial deshielding of their methyl and vinyl protons, indicating extensive charge delocalization and the presence of an appreciable ring current. In diheterocines, 1,4-dioxocin with 10⁻electrons is polyalkenic in nature, whereas 1,4-dihydro-1,4-diazocines are planar and probably aromatic. N-Substituted 4*H*-1,4-oxazocines behave similarly to the 1,4-dihydro-1,4-diazocines in that the nitrogen substituent dictates the degree of π -delocalization. More specifically, the incorporation of electron-withdrawing substituents (e.g., *N*-tosyl) into 4*H*-1,4-oxazocine systems leads to derivatives with twisted, nonplanar conformations, while hydrogen substitution or electron-donating groups (e.g., *N*-alkyl) lead to highly delocalized, planar molecules.

Scheme 11 Large-Ring Heterocycles with Aromatic Character

In heteronines, the nine-membered ring heterocycles that are isoelectronic with the cyclononatetraenyl anion, oxonin (**25**) and 1*H*-azonines **26** where the R¹ substituents are electron-withdrawing groups (e.g., acyl, sulfinyl), have puckered, polyalkenic constitutions (**Scheme 11**). Conversely, the parent 1*H*-azonine (**26**, R¹ = H) and 1-alkyl-1*H*-azonines **26** (R¹ = alkyl) are planar, aromatic compounds that satisfy Hückel's (4*n* + 2)⁻electron rule. Therefore, they exhibit more thermodynamic stability and are diatropic.^[40-42] Similarly, alkali metal azonides (azonine salts) **27** are also planar, π -delocalized, aromatic compounds.

Unlike heterocycles with smaller rings, eight- and larger-ring compounds are mainly synthesized through valence isomerizations of suitable precursors. The valence isomerizations can often be induced under thermal or photolytic conditions, as can be seen from the two examples in **Scheme 12**.^[43,44]

Scheme 12 Preparation of Larger-Ring Heterocycles via Valence Isomerization^[43,44]

Porphyrins are macrocyclic compounds made up of four pyrrole-type subunits joined by methylene bridges. The macrocycle contains 22 π -electrons of which 18 π -electrons form a delocalized aromatic system according to Hückel's rule for aromaticity. The aromaticity of porphyrins has been confirmed on the basis of their heat of combustion and the X-ray structures of numerous porphyrin derivatives. The high aromatic stabilization of porphyrins and metalloporphyrins is relevant in the various roles they play in biological systems as the core of various macromolecules (e.g., heme, chlorophylls, bacteriochlorophylls). The method of synthesis of particular porphyrins depends on the substitution patterns desired. The oligomerization of the 2-(aminomethyl)pyrrole **28** leads to a simple, symmetrical porphyrin **29** (**Scheme 13**).^[45]

Scheme 13 Synthesis of 2,3,7,8,12,13,17,18-Octaethylporphyrin^[45]

The chemical reactivity of porphyrins is closely related to that of large aromatic hydrocarbons. The reactivity of porphyrins can be altered by the introduction of metals into the inner core, influencing the conjugated π -system by inductive effects. Vilsmeier formylation of the porphyrin core has long been one of the most effective methods for introducing carbon substituents onto the periphery (**Scheme 14**).^[46] The formyl group can then be converted into various other functional groups, such as alcohols using Grignard or organolithium reagents, nitriles via oxime formation, and *E*- and *Z*-(2-substituted vinyl)porphyrins using Wittig reagents, making formylporphyrins very versatile synthetic intermediates.

Scheme 14 Formylation of a Porphyrin Derivative^[46]

Phthalocyanines are planar macrocycles consisting of four isoindole-type units joined together by aza bridges to form an 18 π -electron system. Although they are similar to porphyrins, these heterocycles do not occur in nature. Phthalocyanines have been extensively investigated owing to their properties as dyes. More recently, these compounds have been exploited commercially for optical data storage, as catalysts, and as photoconductors in xerography. A large number of methods exist for the synthesis of phthalocyanines based on cyclooligomerization of suitably substituted precursors such as the phthalimide derivative **30** (Scheme 15).^[47]

Scheme 15 Preparation of a Metal π -Phthalocyanine Complex^[47]

Although many compounds covered in this volume have been synthesized mainly to study their physical properties, some of the ring systems have also been found in naturally occurring compounds. A few examples of such natural products include C-1027 (an enediyne antibiotic possessing a 1,4-benzoxazine unit that is responsible for its DNA binding ability, **31**), trichochrome F (a natural pigment found in red hair and feathers, **32**), the 2*H*-azepine chalciporone (a pungent component isolated from the common mushroom *Chalciporus piperatus*, **33**), perilloxin (a cyclooxygenase-1 inhibitor, **34**), aranotin (a metabolite of *Arachniotus aureus*, **35**), LL-Z1220 [a fungal metabolite possessing antibiotic and antimicrobial activity that occurs as a mixture of two valence tautomers: the *syn*-benzene dioxide **36** ($R^1 = 4\text{-oxo-4H-pyran-2-yl}$) and 2-(1,4-dioxocin-6-yl)-4*H*-pyran-4-one (**37**, $R^1 = 4\text{-oxo-4H-pyran-2-yl}$)],^[48] and chlorophyll a (**38**) and chlorophyll b (**39**) (Scheme 16).

Scheme 16 Naturally Occurring Compounds

Derivatives of 1,4-thiazine, 1,2,3- and 1,2,4-triazine, oxepins, and azepines are also found in a number of pharmaceuticals. **Scheme 17** shows the following pharmaceutically active compounds: chlorpromazine (inhibits prion cellular infections, **40**), lamotrigine (a novel anticonvulsant for the treatment of epilepsy, **41**), temozolomide (an antitumor agent, **42**), CGP 3466 (protects neuronal cells from apoptotic cell death and shows neuroprotective effects, **43**), doxepin (an antidepressant drug, **44**), opipramol (an antidepressant and antipsychotic agent, **45**), and chlordiazepoxide (Librium, a tranquilizer, **46**).

Scheme 17 Selected Examples of Pharmacologically Active Compounds

Some agrochemicals have also been developed based on the triazine or tetrazine ring skeleton, such as azinphos-methyl (a nonsystemic insecticide and acaricide of lasting persistence, chiefly effective against biting and sucking pests, mainly used on citrus, cotton, grapes, maize, some ornamentals, fruit, and vegetables, [47](#)), metribuzin (Sencor, a herbicide, [48](#)), atrazine (a herbicide based on the 1,3,5-triazine skeleton, which acts as an inhibitor of photosynthesis in plants by interrupting the light-driven flow of electrons from water to NADP⁺, [49](#)), and clofentezine (highly effective against mites and used as an acaricide, [50](#)) (**Scheme 18**).

Scheme 18 Selected Examples of Agrochemicals

Along with compounds having significant biological activity, some of the heterocyclic compounds in this volume have also found industrial, analytical, and synthetic applications (**Scheme 19**). For example, 1,3,5-triazine-2,4,6-triamine (melamine, [51](#)), 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, [52](#)), and 1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (cyanuric acid, [53](#)) are starting materials for the preparation of polymers with a wide range of applications including the formation of high-pressure laminates, coatings, fiber-reactive dyes, and optical brighteners. In chemical analysis, methylene blue ([54](#)) is widely used as an oxidation–reduction indicator. Ferene ([55](#)), an iron (II) chelator, is used both as a colorimetric indicator as well as a corrosion inhibitor. Along with their use as dienophiles in hetero-Diels–Alder reactions, triazines such as 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HODhbt, [56](#)) and 3-[(diethoxyphosphoryl)oxy]-1,2,3-benzotriazin-4(3*H*)-one (DEPBT, [57](#)) are used as reagents in the formation of amide bonds with negligible racemization in the coupling of protected α -amino acids.

Scheme 19 Selected Examples of Commercially and Synthetically Useful Compounds

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Compounds with Four and Three Carbon–Heteroatom Bonds

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Compounds with Four and Three Carbon–Heteroatom Bonds

18

Volume 18:

Four Carbon—Heteroatom Bonds: $X-C-X$, $X=C=X$, $X_2C=X$, CX_4 Knight, J. G., in *Science of Synthesis*, **18** (2005), p.1

This volume covers the synthesis of compounds containing four carbon—heteroatom bonds. These are shown in **Table 1** together with the sections in which they appear.

Table 1 Structures and Nomenclature of the Four Carbon—Heteroatom Bond Containing Compounds Covered in Volume 18

Product Class	Structural Formula(e)	Section
cyanogen halides, cyanates and their sulfur, selenium, and tellurium analogues, sulfinyl and sulfonyl cyanides, cyanamides, and phosphalkynes	$XC=N$, $XC=P$ ($X = \text{halo}$, OR^1 , SR^1 , SeR^1 , TeR^1 , NR^1R^2)	18.1
carbon dioxide, carbonyl sulfide, carbon disulfide, isocyanates, isothiocyanates, carbodiimides, and their selenium, tellurium, and phosphorus analogues	$X=C=Y$ ($X, Y = O, S, Se, Te, NR^1, PR^1$)	18.2
carbonic acid halides	$XC(O)Y$ ($X = \text{halo}$; $Y = \text{halo}$, OR^1 , SR^1 , SeR^1 , NR^1R^2 , PR^1R^2)	18.3
carbonic acids and esters, and their sulfur, selenium, and tellurium analogues	$XC(O)Y$ ($X, Y = OR^1$, SR^1 , SeR^1 , TeR^1)	18.4
polymeric carbonic acids and esters, and their sulfur analogues	polymers based on $XC(O)Y$ ($X = Y = OR^1$, SR^1)	18.5
carbamic acids and esters, and their sulfur, selenium, tellurium, and phosphorus analogues	$XC(O)NR^1R^2$, $XC(O)PR^1R^2$ ($X = OR^3$, SR^3 , SeR^3 , TeR^3)	18.6
polymeric carbamic acids and esters, and their sulfur analogues	polymers based on $XC(O)NR^1R^2$ ($X = OR^3$, SR^3)	18.7
ureas	$R^1R^2NC(O)NR^3R^4$	18.8
polymeric ureas	polymers based on $R^1R^2NC(O)NR^3R^4$	18.9
thiocarbonic acids and thiocarbamic acids and esters, ureas, and their sulfur, selenium, tellurium, and phosphorus analogues	$XC(S)Y$ ($X, Y = \text{halo}$, OR^1 , SR^1 , SeR^1 , TeR^1 , NR^1R^2 , PR^1R^2)	18.10
seleno- and tellurocarbonic acids and derivatives	$XC(Se)Y$, $XC(Te)Y$ ($X, Y = \text{halo}$, OR^1 , SR^1 , SeR^1 , TeR^1 , NR^1R^2 , PR^1R^2)	18.11
imidic acids, isoureas, and their sulfur, selenium, and phosphorus analogues	$XC(=NR^1)Y$, $XC(=PR^1)Y$ ($X, Y = \text{halo}$, O , SR^2 , SeR^2 , TeR^2 , NR^2R^3 , PR^2R^3)	18.12
guanidines	$R^1R^2NC(=NR^3)NR^4R^5$	18.13
phosphorus analogues of guanidine	$XC(=NR^3)PR^1R^2$, $XC(=PR^1)Y$ ($X, Y = NR^1R^2$, PR^1R^2)	18.14
tetraheterosubstituted methanes with a carbon—halogen bond	XCX_3 ($X = \text{halo}$; $Y = \text{halo}$, OR^1 , SR^1 , SeR^1 , TeR^1 , NR^1R^2 , PR^1R^2)	18.15
other tetraheterosubstituted methanes	CX_4 ($X = OR^1$, SR^1 , SeR^1 , TeR^1 , NR^1R^2 , PR^1R^2)	18.16

References to reviews on these specific functional groups are given in each section. Discussions of each specific group are generally subdivided into methods that have been selected as the most useful for the preparation of the product class in question. Where possible, each method is presented separately as follows:

1. Introduction: comparison with other methods.
2. Presentation of the scope of the method to include background, discussion of representative examples, safety; mechanistic information where relevant to the use of the method in synthesis; a table of examples (for selected

methods); reaction schemes.

3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format. The coverage is not exhaustive, rather the most useful and reliable methods for the synthesis of each functional group have been selected. In some cases, methods that are recommended for limited use, or that have not yet been fully developed, are listed at the end of a section for reference. Tables and representative experimental procedures are given to illustrate the applicability of each approach.

This introduction will outline the individual product classes together with highlighted synthetic methods.

Section **18.1** covers compounds containing the $\text{XC}=\text{N}$ or $\text{XC}=\text{P}$ unit. Many of these are thermally and hydrolytically unstable toxic compounds. Cyanogen fluoride (FCN) is explosive and decomposes to give polymeric species at room temperature. In contrast, cyanogen bromide (BrCN) and chloride (ClCN) are commercially available. All of the cyanogen halides are electrophilic and react with both heteroatom and carbon nucleophiles. These reactions can be used to produce many of the other derivatives covered in Section **18.1**; for example, reaction with alcohols leads to cyanates **1** (**Scheme 1**).^[1-3]

Scheme 1 Cyanates by Alcoholysis of Cyanogen Halides^[1-3]

Because of the electronegativity of oxygen, cyanates (R^1OCN) are more electrophilic than normal nitriles. Alkyl cyanates rearrange to the more thermodynamically stable isocyanates (R^1NCO).^[2] Alkyl thiocyanates (R^1SCN) rearrange in a similar way, but are thermally and hydrolytically more stable than the corresponding cyanates. In contrast, seleno- and especially tellurocyanates are more labile and difficult to handle due to the weakness of the $\text{C}-\text{Se}$ or $\text{C}-\text{Te}$ bond.

Sulfonyl cyanides **2** may be obtained by oxidation of thiocyanates,^[4] but the method of choice is nucleophilic substitution of a cyanogen halide by a sulfinate anion **3** (**Scheme 2**).^[5] Sulfonyl cyanides have similar electrophilicity to cyanogen halides but are less volatile, less toxic, and easier to handle. They can be used to transfer the cyano group to a host of nucleophiles such as thiols, alcohols, amines, and carbon nucleophiles such as enolates and organometallic species.^[6]

Scheme 2 Synthesis of Sulfonyl Cyanides^[4,5]

Cyanamide itself (H_2NCN) is highly toxic and polymerizes violently above its melting point. Monosubstituted cyanamides (R^1HNCN) may act as either nucleophiles or electrophiles, as indicated by the resonance forms in **Scheme 3**. They are commonly used as precursors to a range of other classes of compound found in this volume (ureas, carbamates, guanidines, and related heterocycles).^[7-10]

Scheme 3 Resonance Forms of Cyanamides

The most commonly used cyanophosphonate is diethyl cyanophosphonate (**4**, diethyl phosphorocyanidate, DEPC), which is made by the Arbuzov reaction between triethyl phosphite and cyanogen bromide (**Scheme 4**).^[11] Diethyl cyanophosphonate is used as a coupling reagent for acylation reactions, for example in peptide synthesis under mild conditions.^[12]

Scheme 4 Arbuzov Reaction To Form Diethyl Cyanophosphonate^[11]

Few heteroatom-substituted phosphalkynes ($\text{XC}\equiv\text{P}$) have been reported. They are usually prepared, in low yield, by elimination reactions. The $\text{C}\equiv\text{P}$ bond undergoes cycloaddition reactions to form phosphaheterocycles.

Heterocumulenes ($\text{X}=\text{C}=\text{Y}$) are the subject of Section **18.2**. Due to removal of electron density from the central carbon by the electronegative atoms X and Y, these compounds are normally electrophilic at carbon and are susceptible to attack by a range of heteroatom and carbon nucleophiles. Attack by heteroatom nucleophiles typically gives rise to other classes of compound found in this volume (**Scheme 5**). They also undergo cycloaddition across one of the π -bonds, especially when reacting with π -systems which have some nucleophilic character.

Scheme 5 Nucleophilic Attack on Heterocumulenes

Supercritical carbon dioxide has become an important reaction medium for green chemistry.^[13,14] Carbon disulfide is more reactive than carbon dioxide due to the $\text{C}=\text{S}$ bonds being longer and having weaker π -overlap than the corresponding $\text{C}=\text{O}$ bonds. The initial adducts of nucleophilic addition are also less prone to undergo the reverse reaction to re-form carbon disulfide. Carbon diselenide tends to polymerize easily, but it does react with oxygen, nitrogen, and carbon nucleophiles.

Isocyanates (R^1NCO) are produced industrially by reaction of phosgene (COCl_2) with primary amines (R^1NH_2). On a small scale, the Curtius rearrangement of acyl azides **5** is a more convenient method (**Scheme 6**).^[15-17] Isothiocyanates (R^1NCS) are less electrophilic than the corresponding isocyanates and many are relatively hydrolytically stable. Reaction with oxygen, sulfur, and nitrogen nucleophiles gives rise to thiocarbamates, dithiocarbamates, and thioureas respectively.^[18]

Scheme 6 Isocyanates from Curtius Rearrangement of Acyl Azides^[15-17]

The stability of carbodiimides ($R-N=C=NR$) is dependent on the nature of the nitrogen substituents. Most are stable at room temperature but decompose or polymerize on heating. Carbodiimides are important reagents for the activation of carboxylic acids in peptide-coupling reactions, which are often catalyzed by a hypernucleophilic acylation catalyst such as 1*H*-benzotriazol-1-ol (1-hydroxybenzotriazole, BtOH) (**Scheme 7**).^[19,20]

Scheme 7 Peptide Coupling by Carbodiimide and 1*H*-Benzotriazol-1-ol^[19,20]

The heterocumulenes containing a C=P bond are less stable than the corresponding oxygen or nitrogen species. The oxaphosphapropadienes ($R^1P=C=O$) and azaphosphapropadienes ($R^1P=C=NR^2$) undergo nucleophilic attack at the carbon atom. In contrast, the 1,3,5-diphosphapropadienes (carbodiphosphoranes) **6** are strongly basic on the carbon due to the importance of the ylidic resonance forms (**Scheme 8**). Diphosphapropadienes ($R^1P=C=PR^2$) are less highly polarized and undergo both electrophilic and nucleophilic attack at phosphorus.

Scheme 8 Resonance Forms of Carbodiphosphoranes

Section **18.3** covers carbonic acid halides. Due to the electronegativity of both the halogen and the other heteroatom, these compounds all display electrophilic character at the central carbon and the principal reaction involves nucleophilic attack by heteroatom nucleophiles such as alcohols, phenols, thiols, and amines (**Scheme 9**).

Scheme 9 Nucleophilic Substitution of Carbonic Acid Halides

Phosgene ($COCl_2$) is commercially available and is the best-known member of this product class. Despite its high toxicity, it is widely used as a versatile, powerful electrophile for a wide range of nucleophiles. Reaction with alcohols is the most widely used method for the synthesis of chloroformates ($R^1OCOC(=O)Cl$), which are commonly used for the protection of amines as carbamates **7** (**Scheme 10**).^[21] Reaction of phosgene with thiols leads to chlorothioformate *S*-esters ($R^1SCOC(=O)Cl$).^[22]

Scheme 10 Carbamate Protection of Amines by Chloroformate Esters^[21]

Reaction of phosgene with secondary amine hydrochlorides gives the corresponding carbamoyl chlorides **8** which can then react by further nucleophilic substitution with alcohols, thiols, and amines, to give carbamates, thiocarbamates, and ureas respectively (**Scheme 11**).^[22]

Scheme 11 Stepwise Nucleophilic Substitution of Phosgene via a Carbamoyl Chloride^[22]

The synthesis and applications of carbonic acids and esters are covered in Section **18.4**. Monoesters of carbonic acid (R^1OCO_2H) are highly unstable with respect to decarboxylation to give alcohols and carbon dioxide. The corresponding metal salts (R^1OCO_2M), which are most simply prepared by the addition of a metal alkoxide to carbon dioxide, are much more stable. The most widely studied class of organocarbonates is the diesters ($R^1OCO_2R^2$). These are classically produced by the reaction of phosgene and an alcohol in the presence of an organic base to give a chloroformate **9**, which may be reacted with a second alcohol to form the carbonate diester **10** (**Scheme 12**).

Scheme 12 Organocarbonate Diesters from Alcohols and Phosgene

Bis(trichloromethyl) carbonate (**11**), which is known as triphosgene, is formed by photochemical chlorination of dimethyl carbonate. Triphosgene displays similar reactivity to phosgene itself but has the advantage of being a solid, thus making it significantly safer and easier to handle.^[23] Reaction with nucleophiles leads to loss of trichloromethanol, which forms phosgene by loss of hydrogen chloride (**Scheme 13**).

Scheme 13 Synthesis of Triphosgene and Reaction with Nucleophiles To Liberate Phosgene^[23]

Dialkyl dicarbonates [dialkyl pyrocarbonates, $(R^1OCO)_2O$] such as di-*tert*-butyl dicarbonate (**12**) are used as acylating agents, as alternatives to chloroformates. They are widely used in amino acid chemistry as protecting groups (**Scheme 14**).^[24]

Scheme 14 Carbamate Protection of Amino Acids Using Di-*tert*-butyl Dicarbonate^[24]

Seleno- and tellurocarbonates are photosensitive and are less stable than the corresponding carbonates.

Selenocarbonic acid O,Se-diester **13** can be prepared by reaction of a selenol with an alkyl chloroformate

(**Scheme 15**).^[25] Reduction of selenocarbonic acid diesters **13** by tributylstannane leads to the corresponding alkoxy-carbonyl radical **14**, which may cyclize onto an appropriately placed radical acceptor, such as an alkene, or decarboxylate to form an alkyl radical (**Scheme 15**).^[25]

Scheme 15 Formation of Selenocarbonic Acid O,Se-Diesters and Homolysis To Form an Alkoxy-carbonyl Radical
^[25]

Polycarbonates (Section **18.5**) are most commonly synthesized by the reaction of a diol (or diphenol) with phosgene (**Scheme 16**). They are commercially extremely important due to their high stability and excellent physical properties such as toughness, electrical insulation, and flame resistance.

Scheme 16 Polycarbonates from the Polycondensation of a Diol and Phosgene

Section **18.6** outlines the synthesis and applications of carbamic acid derivatives. The parent compound, carbamic acid ($\text{H}_2\text{NCO}_2\text{H}$), is unstable with respect to decarboxylation and has not been isolated. Carbamate salts ($\text{R}^1\text{R}^2\text{NCO}_2^- \text{X}^+$; $\text{X} = \text{NH}_4$, metal) are readily formed and may be used for elaboration to carbamate esters ($\text{R}^1\text{R}^2\text{NCO}_2\text{R}^3$). The most common application of carbamate esters is as protecting groups for the amine function.^[26] The basis for this protection is the conjugation between the nitrogen lone pair and the carbamate carbonyl group which renders the nitrogen less nucleophilic. Carbamate protection is most often accomplished by reaction of an amine with either a chloroformate ester (**Scheme 10**) or a dialkyl dicarbonate (**Scheme 14**).^[21,24] In peptide-coupling reactions between amino acid derivatives, the use of carbamate protecting groups is found to lead to less racemization during base-catalyzed coupling of carboxy-activated acids.^[20,26]

Carbamate esters are also prepared by nucleophilic attack of an alcohol on a suitable electrophile such as an isocyanate **15** (**Scheme 17**). This reaction is often catalyzed by either base (to activate the alcohol) or a Lewis acid (to activate the isocyanate).

Scheme 17 Synthesis of Carbamate Esters by Nucleophilic Addition of Alcohols to Isocyanates

Cyclic carbamate esters are synthesized by reaction of the corresponding amino alcohol with phosgene or a phosgene equivalent such as bis(trichloromethyl) carbonate (**11**), trichloromethyl chloroformate (diphosgene, **16**), ^[27] 1,1 -carbonyldiimidazole (**17**), ^[28] or a dialkyl carbonate **18** (**Scheme 18**). Chiral oxazolidinones, especially *N*-acyl derivatives **19** ($R^5 = COR^7$), have found widespread use as chiral auxiliaries for asymmetric reactions such as aldol reactions, ^[29] enolate alkylation, ^[30] and Diels–Alder cycloadditions. ^[31] Achiral *N*-acyloxazolidinones **19** ($R^5 = COR^7$) have also been extensively employed as metal-chelating substrates in a variety of asymmetric metal-catalyzed transformations. ^[32-37]

Scheme 18 Synthesis of Oxazolidinones from Amino Alcohols by Reaction with Phosgene Equivalents ^[27,28]

Free thiocarbamic S-acid (H_2NCOSH) is unstable but metal and ammonium thiocarbamates **20**, which can be conveniently formed by addition of amines or metal amides to carbon monoxide in the presence of sulfur, are much more stable. Thiocarbamate salts are used as intermediates for the synthesis of ureas, thiocarbamate S-esters **21**, carbamic acid esters, and isocyanates. Alkylation of thiocarbamate anions occurs preferentially on sulfur, the soft nucleophilic center (**Scheme 19**). ^[38]

Scheme 19 Synthesis of Thiocarbamate S-Esters ^[38]

Selenocarbamates ($R^1R^2NCOSer^3$) are used as precursors to carbamoyl radicals which may subsequently react with a suitable radical trap, e.g. by cyclization onto a pendant alkene to form a lactam. This is directly analogous to the reaction of selenocarbonates (**Scheme 15**). ^[39]

Section **18.7** is focused on polyurethanes, which are the only industrially important class of carbamic acid based polymer. The synthesis of polyurethanes is normally achieved by condensation of a diol with a diisocyanate (**Scheme 20**). The sulfur analogues, polythiocarbamates, which are synthesized by addition of thiols to isocyanates, are much less important due to the unpleasant odor of the thiol monomers and the lower thermal stability of the polymers.

Scheme 20 Synthesis of Polyurethanes by Polycondensation of Diols and Diisocyanates

The synthesis of ureas is covered in Section 18.8. The direct synthesis of ureas by reaction between an amine and carbon dioxide requires high temperatures and pressures, or the use of expensive or toxic dehydrating agents to remove the water which is formed as a byproduct. The simplest synthesis involves the condensation of an amine with phosgene, which can be used to form unsymmetrical ureas **23** ($R^1 \quad R^2$) if the stoichiometry of the first addition is controlled in order to produce the isocyanate intermediate **22** (Scheme 21).^[40,41] In fact, the wide availability of isocyanates by a range of methods makes them the most commonly used precursors for large scale urea synthesis.

Scheme 21 Synthesis of Ureas by Reaction of Amines with Phosgene^[40,41]

Dihydropyrimidines **24** are cyclic ureas which display a range of important pharmacological properties. They can be synthesized by the Biginelli reaction, an acid-catalyzed, one-pot, three-component coupling between an aldehyde, a α -dicarbonyl compound, and a urea (Scheme 22).^[42,43] Cyclic ureas **25** have also been produced by a variation of the Ugi reaction, involving a five-component coupling (Scheme 22).^[44]

Scheme 22 Synthesis of Dihydropyrimidines by Biginelli, Three-Component Coupling, and Ugi, Five-Component Coupling Reactions^[42-44]

Polymeric ureas are covered in Section 18.9 and are most commonly formed by nucleophile-initiated polymerization of isocyanates **26** or by the copolymerization of diisocyanates **27** and diamines (Scheme 23). Polyureas find widespread use as elastomers, foams, fibers, and spray coatings. Condensation of urea with formaldehyde produces urea-formaldehyde resins which are industrially very important, and are used in particular for the manufacture of adhesives.

Scheme 23 Synthesis of Polyureas

Thiocarbonic acid derivatives are the focus of Section 18.10. The principle differences between the thiocarbonyl species and the corresponding carbonyl compounds result from the weaker C=S vs C=O bond, the softer nature of the sulfur as a nucleophile, and the greater ease of oxidation of the sulfur. Thiophosgene (CSCl_2) reacts readily with a range of heteroatom nucleophiles to form other thiocarbonic acid derivatives. These reactions may be controlled in a stepwise manner to give access to the chlorocarbonothioyl species 28, thus allowing the synthesis of unsymmetrical thiocarbonic acid derivatives 29 (Scheme 24).^[45]

Scheme 24 Synthesis of Thiocarbonic Acid Derivatives by Stepwise Nucleophilic Substitution of Thiophosgene^[45]

Conversion of 1,2-diols into 1,3-dioxolane-2-thiones 30 is the basis for the Corey–Winter alkenation reaction. Heating the thiones 30 in the presence of a thiophile such as trimethyl phosphite leads to stereospecific reductive decarboxylation to give the corresponding alkene 31 (Scheme 25).^[46]

Scheme 25 Corey–Winter Alkenation Reaction^[46]

Dithiocarbonate O,S-diester 33 are commonly termed xanthates. They are often prepared by reaction of an alkoxide with carbon disulfide and trapping of the resulting xanthate anion 32 with an alkyl halide (Scheme 26). Thiocarbonate O,O-diester 34 (X = O) and dithiocarbonate O,S-diester 34 (X = S) may both be used in the Barton–McCombie deoxygenation of alcohols under radical reducing conditions (Scheme 26).^[47,48]

Scheme 26 Synthesis of Dithiocarbonate O,S-Diesters (Xanthates) and the Barton–McCombie Deoxygenation Reaction^[47,48]

Seleno- and tellurocarbonic acid derivatives are covered in Section 18.11. Although some selenocarbonic acid derivatives are stable, many are thermally and photolytically unstable. The increased bond length and poorer π -overlap makes the corresponding tellurocarbonic acid derivatives less stable still. Selenocarbonyl difluoride is known, but the dichloride (selenophosgene) has only been reported once. In contrast, selenocarbonates $[R^1OC(Se)XR^2; X = O, S, Se]$ have been more widely studied. Cyclic selenocarbonates, selenocarbamates, and selenoureas can all be made by reaction of carbon diselenide with a difunctional nucleophile such as a diol, amino alcohol, or diamine but this approach is restricted by the limited availability of carbon diselenide and its tendency to polymerize. Cyclic 1,3-dioxolane-2-selones can be converted by reductive decarboxylation into the corresponding alkenes in a similar reaction to that of the thiones shown in Scheme 25.^[49]

The Woollins reagent (35), which is analogous to the well-known thionating agent, Lawesson's reagent, has been developed for the conversion of carbonyl compounds into the corresponding selenocarbonyl species.^[50] As shown in Scheme 27, *N,N*-diethylurea reacts with the Woollins reagent to give the selenourea 36.^[51]

Scheme 27 Oxygen–Selenium Exchange of *N,N*-Diethylurea Using the Woollins Reagent^[51]

Section 18.12 deals with imidic acids, based on the $XC(=NR^1)Y$ unit, and the corresponding $C=P$ species. Carbonimidic dihalides $[XC(=NR^1)Y; X = Y = \text{halo}]$ and the related iminium salts $[XC(=N^+R^1R^2)Y; X = Y = \text{halo}]$ are highly electrophilic and one or both halides may be displaced by heteroatom nucleophiles to give either other imide derivatives 37 or heterocumulenes 38, such as carbodiimides, isocyanates, and isothiocyanates (Scheme 28).^[52,53]

Scheme 28 Nucleophilic Substitution of Carbonimidic Dihalides^[52,53]

The corresponding phosphaaalkenes ($X_2C=PR^1$) are often unstable, depending on the nature of the substituent on

phosphorus. Stable species commonly bear a very large phosphorus substituent which provides steric protection.

Guanidines are covered in Section **18.13**. They are among the strongest organic bases ($pK_{aH} \approx 12$) due to the powerful resonance stabilization of the protonated form (**Scheme 29**). The synthesis of guanidines is often hampered by their strong basicity and polarity, which can be sufficient to make them water soluble, especially if the nitrogens are not alkylated or protected with an electron-withdrawing group. Substituted guanidines can be prepared by the addition of substituents to a pre-existing guanidine core, e.g. by alkylation or condensation with carbonyl compounds, but the most common methods for guanidine synthesis involve reaction of an amine with an amidine derivative bearing a leaving group. Typical amidine equivalents include cyanogen bromide (BrCN), carbodiimides ($\text{R}^1\text{N}=\text{C}=\text{NR}^2$), and thioureas [$\text{R}^1\text{NHC}(\text{S})\text{NHR}^2$].^[54]

Scheme 29 Resonance Stabilization of Guanidinium Cation

Section **18.14** deals with analogues of guanidine in which one or more of the nitrogen atoms is replaced by a phosphorus. The most widely used method for the formation of phosphaguanidines **39** is by addition of a phosphine nucleophile to a carbodiimide (**Scheme 30**).^[55] Addition of phosphorus(III) nucleophiles to carbonimidic dichlorides ($\text{Cl}_2\text{C}=\text{NR}^1$) is used to prepare imines with two phosphorus substituents, and the use of phosphite esters leads to the phosphorus(V) species **40** by an Arbuzov-type reaction.^[56] There are no general methods for the synthesis of phosphorus analogues of guanidines which contain the phosphalkene ($\text{C}=\text{P}$) group, although many such compounds have been prepared.

Scheme 30 Synthesis of Phosphaguanidines^[55,56]

Compounds with four single bonds to heteroatoms are discussed in Sections **18.15** and **18.16**. Section **18.15** covers those compounds in which at least one of the heteroatoms is a halogen. Tetrahalomethanes include simple one-carbon chlorofluorocarbons (CFCs), which have been used as refrigerants and aerosol propellants, and compounds such as carbon tetrachloride, which has been used as a relatively stable nonflammable solvent. The use of highly halogenated alkanes has been drastically reduced in view of their potential for damage to the environment through ozone depletion. Many tetrahalomethanes can be prepared by decarboxylative halogenation of trihaloacetates **41** (**Scheme 31**).

Scheme 31 Synthesis of Tetrahalomethanes by Decarboxylative Halogenation of Trihaloacetates

Trifluoromethyl hypofluorite (F_3COF) has been used as an electrophilic fluorinating agent for reaction with aromatic rings and silyl enol ethers derived from a variety of carbonyl compounds.^[57] Perhaps the best-known series of trifluoromethyl compounds is that based on the sulfonic acid and its derivatives. Trifluoromethanesulfonic acid (triflic acid) is very powerfully acidic and hence, the trifluoromethanesulfonate (triflate) anion (CF_3SO_3^-) is an excellent leaving group. In fact, solvolysis of alkyl trifluoromethanesulfonates is 10^5 – 10^7 times faster than that of alkyl halides or 4-toluenesulfonates.^[58] Trifluoromethanesulfonic anhydride is a powerful hard electrophile and reacts with a wide range of heteroatom nucleophiles to give the corresponding trifluoromethanesulfonates. Conversion of alcohols into trifluoromethanesulfonate esters allows displacement of the hydroxy group by nucleophiles.^[59] Vinyl and aryl trifluoromethanesulfonates **43**, prepared by reaction of trifluoromethanesulfonic anhydride with enolates or phenols respectively, have found widespread use in transition metal mediated coupling reactions due to the ease of oxidative addition into the C—O bond of the trifluoromethanesulfonate (**Scheme 32**). *N*-Phenylbis(trifluoromethanesulfonamide) (**42**), McMurry's reagent, is also an excellent trifluoromethanesulfonyl donor and has the advantages of being much more stable than trifluoromethanesulfonic anhydride, being less reactive and therefore more selective, and being a crystalline solid and hence easier to handle.^[60,61]

Scheme 32 Synthesis of Vinyl and Aryl Trifluoromethanesulfonates and Oxidative Addition to Coordinatively Unsaturated Transition-Metal Complexes

Section **18.16** covers compounds with four single bonds to heteroatoms, none of which are halogen. Most of the many possible permutations involving oxygen, nitrogen, sulfur, and phosphorus have in fact been reported. Orthocarbonic acid tetraesters [$\text{C}(\text{OR}^1)_4$] have found use in the synthesis of polymers for biodegradable plastics, resins, and dental restoratives. Their reaction with Lewis acids, such as boron trifluoride–diethyl ether complex, leads to the formation of trialkoxycarbenium salts **44**. The triethyl derivative **45**, Meerwein's reagent, is commercially available and is used as powerful, hard electrophilic alkylating agent (**Scheme 33**).^[62,63]

Scheme 33 Synthesis of Trialkoxycarbenium Salts and Reaction of Meerwein's Reagent with Diethyl Ether^[62,63]

Orthocarbonates have been used as protecting groups for alcohols, amines, and carbonyl groups.^[26] As expected for an acetal-like species, they are stable under basic conditions, but may be hydrolyzed in acid. Thermal decomposition of dihydrooxadiazoles **46** has been used in the study of dialkoxycarbenes **47** (**Scheme 34**).^[64]

Carbenes **47** are also produced by thermolysis of dialkoxydiazirines **48**.

Scheme 34 Formation of Dialkoxycarbenes by Thermolysis of Dihydrooxadiazoles and Dialkoxydiazirines^[64,65]

Orthocarbonic acid diester diamides [urea acetals, $(R^1O)_2C(NR^2R^3)_2$] undergo a variety of reactions, often involving nucleophilic displacement of either an alkoxy or an amino group depending on the nature of the nucleophile.^[66] Tetrathioorthocarbonates $[C(SR^1)_4]$ are stable and have been used as monomers for polymer synthesis. In contrast, the corresponding tetrakis(dialkylamino)methanes $[C(NR^1R^2)_4]$ may be isolated but are thermally unstable and hydrolyze readily to form hexaalkylguanidinium salts.^[67]

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Compounds with Four and Three Carbon–Heteroatom Bonds

Volume 19:

Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives

19

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General Introduction

This volume covers the synthesis of compounds with three carbon —heteroatom bonds which include nitrile oxides, nitrile sulfides, nitrile imines, nitrilium salts, nitrile ylides, nitriles, phosphalkynes, and carbon- and heteroatom-bound isocyanides. These are shown in [Table 1](#), together with the sections in which they appear.

Table 1 Structures and Nomenclature for the Three Carbon —Heteroatom Bond Containing Compounds Covered in Volume 19

Product Class	Structural Formula	Section
nitrile oxides	$R^1C \ N^+ \text{---} O^-$	19.1.1
nitrile sulfides	$R^1C \ N^+ \text{---} S^-$	19.1.2
nitrile imines	$R^2C \ N^+ \text{---} N^-R^1$	19.2
nitrilium salts	$R^2C \ N^+ \text{---} R^1$	19.3
nitrile ylides	$R^2C \ N^+ \text{---} C^-R^1$	19.4
nitriles	$R^1C \ N$	19.5
phosphalkynes	$R^1C \ P$	19.6
isocyanides	$R^1N=C$	19.7.1
heteroatom-bound isocyanides	$YN=C$ (Y = N, S, O, P)	19.7.2

References to reviews on these specific functional groups are given in each section. Discussion of each specific group is generally subdivided into methods that have been selected as the most useful for the preparation of the product class or subclass in question. Each method is presented separately as follows:

1. Introduction: comparison with other methods.
2. Presentation of the scope of the method to include background, discussion of representative examples, safety; mechanistic information where relevant to the use of the method in synthesis; a table of examples (for selected methods); reaction schemes.
3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format.

The coverage is not exhaustive, rather the most useful and reliable methods for the synthesis of each functional group have been selected. In some cases, methods that are recommended for limited use, or that have not yet been fully developed, are listed at the end of a section for reference. Tables and representative experimental procedures are given to illustrate the applicability of each approach.

This introduction will outline the individual product classes together with highlighted synthetic methods.

Nitrile oxides are 1,3-dipoles containing the same array of atoms in the functional group as nitrones, but at one

oxidation level higher. Nitrile oxides **2** are readily prepared, mainly from hydroximoyl halides **1**, which are obtained through the halogenation of aldoximes with a variety of halogenating reagents^[1] or by treatment of activated nitroalkanes with thionyl chloride in the presence of triethylamine (**Scheme 1**).^[2] As they are difficult to isolate and store, nitrile oxides are normally generated in the presence of a reactive dipolarophile, giving the appropriate adduct directly; however, some nitrile oxides with bulky substituents are stable. Cycloaddition to a substituted ethene proceeds regioselectively, and the products are highly useful as precursors for a variety of other compounds and their functionality is readily unmasked. Typically, metal ion promoted cycloadditions to give dihydroisoxazoles **3** are highly useful reactions (**Scheme 1**). Stereospecific syntheses of dihydroisoxazoles can be achieved using effective chiral auxiliaries and metal ions. Typically, in the presence of magnesium ions the cycloaddition of nitrile oxides to allylic alcohols proceeds in a highly *syn*-selective manner when *-*-chiral dipolarophiles are used.^[3]

Scheme 1 Synthesis of Nitrile Oxides from Hydroximoyl Halides and Stereospecific 1,3-Dipolar Addition to Alkenes^[2-4]

Nitrile oxides can also be prepared directly by oxidation of aldoximes with sodium hypochlorite or *N*-bromosuccinimide in the presence of a base such as triethylamine. Such oxidations are normally combined with cycloaddition reactions with a suitable dipolarophile already present in the same pot. One typical example is the intramolecular cycloaddition of an aldoxime to give tricycle **4**, which contains the ring skeleton of natural product streptazolin (**Scheme 2**).^[5]

Scheme 2 Direct Synthesis of a Nitrile Oxide and Its Application in the Partial Synthesis of Streptazolin^[5]

Nitrile sulfides are unstable and it is impossible to isolate them. Nitrile sulfides are generated by the thermal decomposition of five-membered heterocyclic compounds, such as 1,3,4-oxathiazol-2-one, and trapped immediately with a suitable dipolarophile, thereby providing access to several classes of heterocycles that are obtained only with difficulty by other means.

Nitrile imines **6**, which can be generated by the base-induced dehydrohalogenation of stable hydrazoneyl halides **5**, are trapped by a variety of 1,3-dipolarophiles such as alkenes and alkynes to afford 4,5-dihydropyrazoles and pyrazoles, respectively (**Scheme 3**).^[6,7]

Scheme 3 Generation of Nitrile Imines from Hydrazoneyl Halides and Entrapment with Alkenes and Alkynes^[6,7]

Nitrilium salts are intermediates in a number of reactions that include the Beckmann rearrangement producing amides from oximes,^[8,9] the Ritter reaction producing amides from alcohols and nitriles,^[10-12] the von Braun amide degradation reaction producing alkyl halides and nitriles,^[13] the Bischler –Napieralski reaction producing dihydroisoquinolines and related ring-fused imines from amides and arenes,^[13] the Hoesch acylation reaction from arenes and nitriles,^[14] the Gattermann formylation reaction of arenes and heteroarenes,^[15] and the Schmidt reaction producing amides from ketones and hydrazoic acid.^[16] In most cases, the nitrilium ions are formed and reacted instantly, but stable nitrilium salts can be isolated. The acid-mediated dehydration of oximes is better known as the Beckmann rearrangement. N-Alkylation of nitriles provides one of the most convenient and direct routes to nitrilium salts. Nitrilium salts are also prepared by the interaction of alkyl chloroformates with Lewis acid complexes of nitriles.

Nitrile ylides are 1,3-dipoles and can be prepared by several methods^[7,17] including the elimination of hydrogen chloride from imidoyl chlorides, the reaction of carbenes and carbenoids with nitriles, and the photochemical ring opening of aziridines. Pyrroles and dihydropyrroles are obtained by the 1,3-dipolar cycloaddition of nitrile ylides with alkynes and alkenes.

Nitriles are an extremely important class of compounds in organic synthesis. Nitriles have a strong dipole, oriented with the negative end toward the nitrogen, and the cyano group is recognized as a powerful electron-withdrawing substituent. Nitriles have unique properties, and thus various reactions for the synthesis and the unique transformations of nitriles have been developed.

A typical method for the synthesis of nitriles is the construction of the cyano group by functional group transformation from various starting materials, such as aldehydes, carboxylic acids and their derivatives, hydrazones, aldoximes, carboxamides, and thioamides.^[18-20]

The oxidation of hydrazones and aldoximes are important synthetic routes to nitriles, although the direct conversion of aldehydes in a one-pot reaction can be carried out by oxidation of the in situ formed aldimines. One of the most typical transformations is the preparation of nitriles by nucleophilic substitution of alkyl, allyl, and benzyl halides (at the sp^3 -carbon —halogen bonds) with various cyanide reagents.^[21,22] Substitution at the sp^2 -carbon —halogen bonds is very difficult; however, the palladium-catalyzed coupling reaction of *Z*- and *E*-vinyl halides with sodium cyanide in the presence of 18-crown-6 was introduced in 1977 as the first transition-metal-catalyzed cyanation reaction of sp^2 -carbon —halogen bonds to give *Z*- and *E*-vinyl cyanides stereospecifically.^[23] This reaction led to the discovery of palladium- and nickel-catalyzed cyanations of aryl halides and vinyl and aryl trifluoromethanesulfonates. The conversion of the aryl chlorides into aryl cyanides is very convenient.^[24]

Aromatic and heteroaromatic nitriles can be prepared by direct cyanation of aromatic and heteroaromatic compounds with cyanogen bromide or trichloroacetonitrile in the presence of Friedel –Crafts catalysts.^[25] Heterocyclic *N*-oxides such as pyridine, quinone, pyrazine, pyrimidine, quinoxaline, or isoquinoline *N*-oxide undergo reaction with trimethylsilyl cyanide in the presence of a base to give the cyanation products directly. The reactions of pyridine 1-oxide with dimethylcarbamoyl chloride and trimethylsilyl cyanide give the corresponding carbonitriles in excellent yields (modified Reissert –Henze reaction).^[26] Catalytic asymmetric Reissert-type reactions of quinoline and isoquinoline derivatives using a Lewis acid –Lewis base bifunctional catalyst are highly useful; for example, with a catalyst obtained from ligand **7** and diethylaluminum chloride,^[27] 1-(2-furylcarbonyl)-6,7-dimethoxy-1,2-dihydroquinoline-2-carbonitrile (**8**) is obtained in 91% ee (**Scheme 4**).

Scheme 4 Aluminum-Catalyzed Asymmetric Reissert-Type Reaction of a Quinoline^[27]

Direct cyanation of the sp³-C –H bond of acetylenes is performed by treatment with copper(I) cyanide and chlorotrimethylsilane,^[28] or butyllithium and phenyl cyanate.^[29] Direct cyanation of the sp³-C –H bond is extremely difficult; however, aerobic oxidative cyanation of tertiary amines with sodium cyanide has been demonstrated. Thus, the treatment of *N,N*-dimethylaniline with catalytic ruthenium(III) chloride hydrate and sodium cyanide under molecular oxygen (1 atm) gives *N*-cyanated amine **9** (**Scheme 5**), which is the precursor of amino acids and 1,2-diamines, in excellent yields. The direct C –H activation of an amine to nitrogen with a ruthenium catalyst forms the intermediate iminium ion and this is the key step of this interesting reaction.^[30]

Scheme 5 Aerobic Ruthenium-Catalyzed Oxidative Cyanation of a Tertiary Amine with Sodium Cyanide^[30]

Introduction of the cyano group by substitution of the metals in organometallic compounds can also be used for nitrile synthesis. Typically, the substitution reaction of organozinc or copper compounds with tosyl cyanide is highly useful.^[31]

Nitriles can also be synthesized by the transformation of other substrates such as amines, alcohols, and nitro compounds. The oxidative transformation of primary amines to nitriles is performed by aerobic oxidation of primary amines in the presence of a hydroxyapatite-bound ruthenium complex [Ru-HAP(II)], which is prepared by mixing calcium hydroxyapatite [Ca₁₀(PO₄)₆(OH)₂] with aqueous ruthenium(III) chloride.^[32]

The synthesis of cyanohydrins and especially the asymmetric synthesis of these compounds are extremely important; therefore, many methods have been developed.^[33] The cyanohydrins of aldehydes are prepared upon

treatment with potassium or sodium cyanide/18-crown-6, acetone cyanohydrins with a metal complex catalyst, and trimethylsilyl cyanide with a catalyst. The most significant advances in the area of cyanohydrin chemistry since 1985 have been the development of catalysts for the asymmetric addition of cyanide to aldehydes. The reaction can be induced by a variety of catalysts, of which enzymes, synthetic peptides, and chiral metal complexes are the three most common.^[34-38]

The cyclic dipeptide containing histidine residue catalyzes the asymmetric addition of hydrogen cyanide to benzaldehyde, giving optically active mandelonitrile with up to 90% ee.^[39] A number of organometallic reagents based on chiral complexes of titanium,^[40-42] aluminum, lanthanide,^[41,43,44] and other metals^[45] have been found to catalyze the asymmetric addition of hydrogen cyanide or trimethylsilyl cyanide to aldehydes. Typically, the chiral titanium –salen complex **10** catalyzes the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes affording the cyanohydrin acetates **11** with high enantioselectivities (**Scheme 6**).

Scheme 6 Titanium-Catalyzed Asymmetric Addition of Potassium Cyanide and Acetic Anhydride to Aldehydes^[43,44]

The Strecker reaction is a three-component condensation reaction between a carbonyl compound, an amine, and a cyanide to produce an α -aminonitrile. The reaction proceeds via in situ formation of an imine, followed by addition of cyanide to the imine.

The asymmetric addition of cyanide to imines is important in organic synthesis.^[46-50] The enantioselective addition of hydrogen cyanide or trimethylsilyl cyanide to imines in the presence of a chiral catalyst such as a cyclic dipeptide,^[51] or an aluminum,^[52,53] titanium,^[54] or zirconium^[55] complex is very important in the synthesis of optically active α -aminonitriles. Typically, enantioselective addition of hydrogen cyanide to imines gives aminonitriles **13** using 5 mol% of the chiral aluminum –salen complex **12** (**Scheme 7**).^[52]

Scheme 7 Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral Aluminum –Salen Complex^[52]

Hydrocyanation of α,β -unsaturated carbonyl compounds and related compounds is performed upon treatment with diethylaluminum cyanide (prepared from HCN and Et_3Al), trimethylsilyl cyanide and a Lewis acid, or acetone cyanohydrin. Hydrogen cyanide itself is normally incapable of adding to Michael acceptors.

The hydrocyanation of alkynes is a very important and useful process since it generates highly versatile α,β -unsaturated nitriles from easily accessible starting materials. The tetrakis(triphenyl phosphite)nickel(II)-catalyzed hydrocyanation of diphenylacetylene gives 1,2-diphenylethanenitrile selectively.^[56,57]

The Dupont process for the synthesis of adiponitrile (hexanedinitrile, **14**) from buta-1,3-diene is the most important application of hydrocyanation. The overall reaction consists of three stages, the first being the synthesis of a mixture of pent-3-enenitrile and 2-methylbut-3-enenitrile (7:3) by the nickel-catalyzed addition of 1 equivalent of hydrogen cyanide to buta-1,3-diene. The isomeric nitriles are separated by distillation, and the unwanted branched product is isomerized in a second step using a similar nickel(0) catalytic system in the presence of a Lewis acid. In the final part of the process, the mixture of unbranched pentenenitriles is isomerized and concomitantly hydrocyanated resulting in the product adiponitrile (**14**) with selectivities of up to 90% (**Scheme 8**).^[58-60]

Scheme 8 Nickel-Catalyzed Hydrocyanation of Buta-1,3-diene To Give Adiponitrile^[58-60]

There are many methods for the synthesis of nitriles from other nitriles with retention of the cyano group. The reactions of α -cyano carbanions with electrophiles are one of the fundamental synthetic routes to nitriles, which include reaction with alkyl halides, epoxides, the aldol reaction, the Knoevenagel reaction, the Michael reaction, and the Thorpe–Ziegler reaction. Usually α -cyano carbanions can be generated upon treatment of nitriles with strong bases such as lithium diisopropylamide and potassium *tert*-butoxide; however, C–H activation to the nitrogen of nitriles with a low-valent transition-metal catalyst such as dihydridotetrakis(triphenylphosphine) ruthenium(II) is highly useful. The aldol reaction, the Knoevenagel reaction, and the Michael reaction of nitriles can be carried out in a highly selective manner with low-valent transition-metal complexes such as dihydridotetrakis(triphenylphosphine)ruthenium(II) as the redox Lewis acid catalyst under neutral and mild reaction conditions.^[61,62] Typically, the reaction of ethyl cyanoacetate with 4-hydroxybenzaldehyde gives the product **15** in 98% yield (**Scheme 9**). The reaction can be carried out under neutral conditions and acidic substrates are tolerated in the reaction. Another example is the Michael addition of ethyl 2-cyanopropanoate (**16**) to a base-sensitive substrate of prop-2-enal to give **17** (**Scheme 9**). These reactions provide nonsalt processes that are environmentally benign.^[63]

Scheme 9 Ruthenium-Catalyzed Aldol Condensation and Michael Addition^[61,62]

The Thorpe –Ziegler reaction has been carried out using a stoichiometric amount of a strong base, such as sodium hydride, to give aminonitriles from dinitriles; however, pentahydridobis(triisopropylphosphine)iridium(V) can be used instead of a strong base, and the catalytic reaction of **18** can be carried out to give **19** under neutral conditions (**Scheme 10**).^[64]

Scheme 10 Iridium-Catalyzed Thorpe –Ziegler Condensation of a Nitrile^[64]

Conjugate additions of reactive nucleophiles to alkenes or alkynes are important C —C and carbon —heteroatom bond-forming reactions for making a variety of nitriles.^[65,66] Various nucleophiles such as oxo enolates, ester enolates, enamines, metalated nitriles, metalated nitroalkanes, organometallic compounds, allylsilanes, thiols, and amines add to alkenenitriles selectively to give numerous nitrile compounds.

[2+2] Cycloaddition, 1,3-dipolar cycloaddition, and the Diels –Alder reaction are convenient for the stereoselective synthesis of cyclic compounds bearing a nitrile. Iminoacetonitriles, which are readily prepared from alcohols, are useful azodienophiles for intramolecular hetero-Diels –Alder reactions (**Scheme 11**).^[67]

Scheme 11 Aza-Diels –Alder Reaction of an Iminoacetonitrile^[67]

The Heck –Mizoroki reaction, palladium- and nickel-catalyzed cross-coupling reactions with various organometallic compounds, and palladium-catalyzed reactions of allyl esters are extremely useful for the synthesis of nitrile compounds, especially alkenenitriles.

Nitriles have unique properties, and, therefore, various transformations of nitriles have been developed. Functional group transformations of nitriles to amines, imines, aldehydes, ketones, amides, amidines, amidrazones, imidates, and carboxylic acids are widely known, and these transformations have been described in sections of other volumes within *Science of Synthesis*.

The applications of nitriles in the construction of more complex molecules are also described in this volume.

Three-component reactions, one-pot cyclization, cycloaddition, and domino reactions are often used for the synthesis of various heterocyclic compounds. Typically, the reaction of **20** with trimethylsilyl trifluoromethanesulfonate, followed by disiloxydiene **21** affords the open-chain product **22**. Treatment of **22** with triethylamine affords the benzopyrano[2,3-*b*]pyridine **23** (**Scheme 12**).^[68]

Scheme 12 Reaction of 4-Oxo-4*H*-1-benzopyran-3-carbonitrile with a Disiloxy-1,3-diene^[68]

One of the unique properties of nitriles is their ability to strongly coordinate to metals. Using this property, new types of practical catalytic reactions of nitriles have been developed. Typically, the ruthenium-catalyzed reaction of amines, nitriles, and water under neutral reaction conditions to give amides and ammonia is an extremely useful reaction which can also be applied to the synthesis of polyamides from diamines and dinitriles (**Scheme 13**).^[63,69]

Scheme 13 Ruthenium-Catalyzed Amidation of Nitriles with Amines and Water^[69]

A novel three-component reaction involving nitriles, alkenenitriles, and water in the presence of pentahydridobis (triisopropylphosphine)iridium(V) as a Lewis acid and base ambiphilic catalyst affords glutarimides **24**, which are versatile intermediates in the synthesis of biologically active compounds (**Scheme 14**).^[64]

Scheme 14 Iridium-Catalyzed Three-Component Reaction of Nitriles, Alkenenitriles, and Water To Give Glutarimides^[64]

A wide range of pyridines have been prepared by the [2+2+2] cyclotrimerization of nitriles and alkynes. Cobalt complexes are the most common catalysts.^[70] The complex fused heterocycles can be prepared using cobalt-catalyzed cycloaddition reactions.^[71]

Two alternative approaches to the cyclotrimerization were reported, although both result in the formation of a stoichiometric transition-metal species. Thus, titanium(II) alkoxide [prepared in situ from $\text{Ti}(\text{OiPr})_4$ and iPrMgCl]^[72] and bis(η^5 -cyclopentadienyl)(diethyl)zirconium(IV)^[73] promote this type of reaction (**Scheme 15**).

Scheme 15 Zirconium-Mediated Pyridine Synthesis^[73]

Demko and Sharpless demonstrated the formation of substituted tetrazoles from nitriles and azides by heating neat tosyl cyanide with an unhindered azide, giving quantitative conversion into the 1-substituted 5-tosyltetrazole **25** (**Scheme 16**), which can be readily elaborated by nucleophilic substitution of the tosyl group.^[74] This is a "click chemistry" transformation in that no solvent is required.

Scheme 16 The "Click Chemistry" Approach to Tetrazoles^[74]

Phosphaalkynes are unstable molecules, and their chemistry resembles that of alkynes rather than nitriles. The P-C bond system shows a pronounced tendency to undergo cycloaddition and cyclooligomerization reactions.

Methylidynephosphine (**26**), ethylidynephosphine (**27**), and fluoromethylidynephosphine (**28**) (**Scheme 17**) can be generated and characterized, but must be stored under dry argon at low temperature.^[75]

Scheme 17 Typical Phosphaalkynes^[75,76]

However, (2,2-dimethylpropylidyne)phosphine (**29**) is prepared and isolated as a stable colorless liquid (bp 61 °C) and has been employed preferentially in model studies concerning the reactivity of this product class. The most important methods for synthesis of phosphalkynes are β -elimination reactions. The application of phosphalkynes in organic synthesis is well documented in many reviews.^[75,77-83] In analogy to the use of acetylene in cycloaddition reactions, phosphalkynes are also predominant reaction partners in mainly [2+1], [2+2], [3+2], and [4+2] cycloadditions.^[77,79,80,84]

The [2+1] cycloadditions of electron-deficient species allows the synthesis of unsaturated three-membered phosphorus heterocycles such as **30** (**Scheme 18**) {see also Science of Synthesis, Vol. 9 [Fully Unsaturated Small Ring Heterocycles and Monocyclic Five-Membered Heteroarenes with One Heteroatom (Section 9.6)]}.^[85] The cycloaddition of phosphalkynes, e.g. **29**, with 1,3-dipoles provides access to a wide range of five-membered heterocyclic systems such as **31**.^[86,87]

Scheme 18 [2+1]- and [3+2]-Cycloaddition Reactions of Phosphalkynes^[85-87]

Isocyanides have a unique and rather unusual electronic structure. The carbon atom of the isocyano group often exhibits carbene-like reactivity that can be represented by a resonance structure $\text{RN}=\text{C}:$; therefore, isocyanides undergo a variety of β -addition reactions with reagents of the type $\text{X}-\text{Y}$, which can be regarded as insertion into the $\text{X}-\text{Y}$ bond. On the other hand, the linear structure of isocyanides is well represented by the resonance structure $\text{RN}^+=\text{C}^-$, in which the isocyano nitrogen is sp -hybridized.

Isocyanides are usually stable and, hence, distillation and chromatographic separation can be used for isolation of these compounds. The characteristic odor of isocyanides, and in particular of low-boiling isocyanides, is extremely unpleasant, so all experiments should be carried out in a well-ventilated fume hood.

Aliphatic and aromatic isocyanides are synthesized and utilized as reactive synthetic intermediates for organic synthesis.^[88,89] The nucleophilic substitution of halides or equivalents with metal cyanides such as silver cyanide^[90] and trimethylsilyl cyanide with a Lewis acid^[91,92] are typical synthetic routes to these compounds (**Scheme 19**). Isocyanates can be transformed into isocyanides by deoxygenation with appropriate reagents such as triethyl phosphite^[93] (**Scheme 19**) or by reduction of a carbamate with trichlorosilane/triethylamine.^[94]

The dehydration of formamides by acylating reagents, such as phosgene,^[95] trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), thionyl chloride, and tosyl chloride, and bases, such as triethylamine, is now recognized as the most general method for the preparation of isocyanides due to the ready availability of the starting materials (**Scheme 19**).^[96]

Scheme 19 Typical Syntheses of Isocyanides^[90-95]

Reactions of isocyanides can be classified into three categories. The first involves the isocyano carbon atom formally behaving like a carbene, undergoing α -addition reactions. Three- or four-component reactions involving the α -addition process have also been developed, leading to development of combinatorial syntheses of amino acid derivatives. The second classification involves generation of a carbanion α to the isocyano group, which is trapped with alkyl halides, epoxides, carbonyl compounds, or Michael acceptors, leading to products in which the isocyano group is retained or converted into other functionalities. Finally, the last category involves cleavage of the C—NC bond, that is reductive removal of the isocyano group and isocyanide α -nitrile rearrangement.

α -Addition of organometallic compounds to isocyanides seems to be the most direct way to compounds such as imidoyllithiums **32**, which have been proven to be synthetically useful. The imidoyllithiums **32** are prepared by the reaction of isocyanides with organolithiums (**Scheme 20**).^[97,98] It is necessary to use isocyanides that do not carry β -hydrogens to avoid hydrogen abstraction at their β -positions. *tert*-Alkyl isocyanides and aryl isocyanides are suitable for use in the generation of imidoyllithiums.

Scheme 20 Generation and Reactions of Imidoyllithiums^[97,98]

The Passerini reaction and the Ugi reaction are highly useful for multicomponent couplings via α -addition reactions. The reaction of isocyanides with carbonyl compounds in the presence of carboxylic acids gives α -acyloxy-carboxamides (Passerini reaction).

In addition to the three components used in the Passerini reaction, an amine is used as the fourth component in the Ugi reaction. The condensation of the amines and carbonyl compounds generates imine intermediates, which react with acids and isocyanides to give synthetically useful α -acylamino-carboxamides. Since the Ugi coupling reaction is suitable for combinatorial synthesis of peptide derivatives, e.g. **33** (**Scheme 21**), much effort has been devoted to expansion of the reaction scope, application to solid-phase synthesis, and increasing the reaction's efficiency.^[99,100]

Scheme 21 The Ugi Reaction^[99,100]

Asymmetric dihydrooxazole synthesis has been achieved by using a gold catalyst bearing a chiral ferrocenylphosphine ligand **34** in the reaction of isocyanoacetate with aldehydes (**Scheme 22**). Enantioselectivity as high as 95% ee is recorded with high *trans* diastereoselectivity in the reaction of benzaldehyde.^[101]

Scheme 22 Gold-Catalyzed Aldol Reaction of Isocyanoacetates^[101]

Polymerization systems using transition-metal catalysts are commonly utilized, leading to the synthesis of poly(isocyanides) with high stereoregularity. The polymerization mechanism is supposed to involve successive insertion of the isocyano carbon atoms into the transition metal—carbon bond during the propagation stage. Efforts have also been made to develop asymmetric polymerizations that afford optically active helical polymers. Using chiral organopalladium complex **35** as an initiator for asymmetric polymerization^[102,103] gives a highly stereoselective construction of a helical structure with a single screw-sense. The helical structures of poly(quinoxaline-2,3-diyls) **36** are exceptionally stable (**Scheme 23**).

Scheme 23 Asymmetric Polymerization of a 1,2-Diisocyanobenzene with a Chiral Palladium Initiator^[103]

Nitrogen-, oxygen-, sulfur-, and phosphorus-bound isocyanides are covered in Section **19.7.2**. There are not many

known compounds of this class due to the instability of these compounds. Among the heteroatom-bound isocyanides, nitrogen-bound isocyanides have been studied most extensively.

Typically, diazoisocyanide is prepared from the corresponding 1-substituted 3-formyltriaz-1-ene by dehydration with thionyl chloride. The products exhibit exceptional thermal as well as chromatographic stability.

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Compounds with Four and Three Carbon–Heteroatom Bonds

20

Volume 20:


Three Carbon—Heteroatom Bonds: Acid Halides; Carboxylic Acids and Acid Salts; Esters, and Lactones; Peroxy Acids and R(CO)OX Compounds; R(CO)X, X = S, Se, Te

Panek, J. S., in *Science of Synthesis*, **20** (2006), p.1

This volume covers the preparation of carboxylic acid derivatives, all of which have a carbon forming three formal bonds to heteroatoms, including acid halides, carboxylic acids, and carboxylic acid salts (Vol. 20a). Also covered are esters, lactones, peroxy acids, and $R^1(CO)OX$ compounds, as well as structural types of $R^1(CO)X$ (X = S, Se, Te) (Vol. 20b). **Table 1** summarizes graphically the carboxylic acid derivatives covered in Volume 20.

Table 1 Classes of the Three Carbon —Heteroatom Bond Containing Carboxylic Acid Derivatives Covered in Volume 20

Product Class	Structural Formula(s)	Section
acid halides	$R^1C(O)X$ (X = halo)	20.1
carboxylic acids	R^1CO_2H	20.2
alkanoic acids	R^1CO_2H (R^1 = alkyl)	20.2.1
arenedicarboxylic acids	$Ar^1(CO_2H)_2$	20.2.2
butenedioic acids, acetylenedicarboxylic acid	$HO_2CCR^1=CR^2CO_2H$, $HO_2CC \equiv CCO_2H$	20.2.3
alkanedioic acids	$HO_2C(CR^1R^2)_nCO_2H$	20.2.4
2-oxo- and 2-imino-substituted alkanoic acids	$R^1C(=X)CO_2H$ (X = O, N)	20.2.5
2,2-diheteroatom-substituted alkanoic acids	$R^1CX(Y)CO_2H$	20.2.6
2-aminoalkanoic acids (-amino acids)	$R^1R^2C(NH_2)CO_2H$	20.2.7
2-heteroatom-substituted alkanoic acids	$R^1CH(X)CO_2H$ (X = halo, O, S, Se, Te)	20.2.8
alk-2-ynoic acids	$R^1C \equiv CCO_2H$	20.2.9
arenecarboxylic acids	Ar^1CO_2H	20.2.10
alk-2-enoic acids	$R^1CH=CHCO_2H$	20.2.11
3-oxoalkanoic and 3,3-dioxyalkanoic acids	$R^1C(O)CH_2CO_2H$, $R^1C(OR^2)_2CH_2CO_2H$	20.2.12
3-heteroatom-substituted alkanoic acids	$R^1CHXCH_2CO_2H$ (X = halo, O, S, N, P)	20.2.13
carboxylic acid salts	R^1CO_2M , $R^1CO_2NR^2_4$, $R^1CO_2PR^2_4$	20.3
carboxylic acid anhydrides	$(R^1CO)_2O$	20.4
carboxylic acid esters	$R^1CO_2R^2$	20.5
alkyl alkanoates	$R^1CO_2R^2$ (R^1 = alkyl)	20.5.1
arenedicarboxylic acid esters	$Ar(CO_2R^1)_2$	20.5.2
butenedioic acid esters/butyndioic acid esters	$R^1O_2CCR^2=CR^3CO_2R^4$, $R^1O_2CC \equiv CCO_2R^2$	20.5.3
alkanedioic acid esters	$R^3O_2C(CR^1R^2)_nCO_2R^4$	20.5.4
alkynyl alkanoates	$R^1CO_2C \equiv CR^2$	20.5.5
aryl alkanoates	$R^1CO_2Ar^1$	20.5.6
alkenyl alkanoates	$R^1CO_2CR^2=CR^3R^4$	20.5.7
2-oxo- and 2-imino-substituted alkanoic acid esters, and related compounds	$R^1C(=X)CO_2R^2$	20.5.8
2,2-diheteroatom-substituted alkanoic acid esters	$R^1CX(Y)CO_2R^2$	20.5.9
2-aminoalkanoic acid esters (-amino acid esters)	$R^1R^2C(NH_2)CO_2R^3$	20.5.10

2-heteroatom-substituted alkanolic acid esters	$R^1 R^2 CXCO_2R$	20.5.11
alk-2-ynoic acid esters	$R^1 C \equiv CCO_2R^2$	20.5.12
arenecarboxylic acid esters	$Ar^1 CO_2R^1$	20.5.13
alk-2-enoic acid esters	$R^1 CH=CHCO_2R^2$	20.5.14
3-oxo- and 3,3-diheteroatom-substituted alkanolic acid esters	$R^1 C(O)CH_2CO_2R^2$, $R^1 CX(Y)CH_2CO_2R^2$	20.5.15
3-heteroatom-substituted alkanolic acid esters	$R^1 CHXCH_2CO_2R^2$ (X = halo, O, S, N, P)	20.5.16
lactones		20.6
peroxy acids and derivatives	$R^1 CO_2OR^2$	20.7
thiocarboxylic S-acids, selenocarboxylic Se-acids, tellurocarboxylic Te-acids, and derivatives	$R^1 C(O)X$ (X = S, Se, Te): $R^1 C(O)XH$, $R^1 C(O)XM$, $R^1 C(O)XR^2$, $R^1 C(O)XZ$	20.8

The product subclasses dealing with alkanolic acids (Section 20.2.1) and alkyl alkanooates (Section 20.5.1) are further subdivided according to how the product is obtained from its precursor (Sections 20.2.1.1 –20.2.1.8 and 20.5.1.1 –20.5.1.7, respectively). These sections cover general methods that are sometimes also applicable to subsequent special classes of carboxylic acids or esters covered in Volume 20.

Each section contains a brief introduction to the specific class and discussion of the most useful and reliable methods for the preparation of each functional group, including background, safety, representative examples, and general experimental procedures. Some sections are further divided into variations according to transformations from different reagents.

This introduction will outline the individual product classes together with highlighted synthetic methods.

Section 20.1 pertains to the preparation and chemistry of acid halides. Acid halides are used widely as acylating agents for nucleophilic species in organic synthesis. Among them, acid iodides are some of the best acylating agents because of the iodide's competency as a leaving group. Acid halides are also moderate to powerful electrophiles and participate in highly efficient addition –elimination reactions through a tetrahedral transition state. These reactions proceed even with relatively weak nucleophiles. The most common method for the synthesis of acid halides is halogenation of carboxylic acids. Synthesis from acid chlorides is another frequently used method (Scheme 1).^[1–3]

Scheme 1 Synthesis of Acid Halides from Acid Chlorides^[1–3]

Carboxylic acids, characterized by the presence of a carboxy group (written as CO_2H), are widespread in nature and are typically weak acids. Ester hydrolysis is one of the most fundamental approaches to carboxylic acid synthesis. Many of the chemical reactions used for their preparation are oxidations, as the carbon atom of the carboxy group has a high oxidation state. Other common synthetic procedures involve hydrolysis of

nitriles and carboxylation of organometallic intermediates.

Arenedicarboxylic acids (Section [20.2.2](#)) are versatile monomers and components for high-performance polymers and liquid-crystalline compounds. The easiest way to obtain arenedicarboxylic acids is by the hydrolysis of arenedicarboxylic acid esters. Other reactions, such as replacement of hydrogens and halo groups with carboxylic acid ([Scheme 2](#)),^[4] as well as other functional-group transformations and metal-catalyzed carboxylation reactions, have also contributed largely to the synthesis of arenedicarboxylic acids.

Scheme 2 Palladium-Catalyzed Carbonylation of 2,5-Dibromobicyclo[4.2.0]octa-1,3,5-triene^[4]

Section [20.2.3](#) covers butenedioic acids and acetylenedicarboxylic acid (butynedioic acid), which are frequently used in a variety of organic reactions, such as Diels –Alder reactions, conjugate additions, and hydrogenations. The synthesis of these substrates includes oxidations of furfural, furan, or crotonaldehyde using vanadium(V) oxide, rearrangements from acetoacetic acid esters, aldol condensation ([Scheme 3](#)),^[5] carboxylation of organometallic species, elimination protocols, and other oxidative methods.

Scheme 3 Synthesis of a Butenedioic Acid through Aldol Condensation^[5]

Alkanedioic acids (Section [20.2.4](#)) are most commonly synthesized by oxidative protocols, e.g. from lactones, nitroalkanes, cyclobutanones, halocyclobutenes, or dihalocyclobutanones ([Scheme 4](#)).^[6] The protocol in [Scheme 4](#) is stereospecific with regard to the substituents of the starting dichlorocyclobutanones (and the alkenes from which they are prepared by cycloaddition). Other synthetic methods to alkanedioic acids are oxidative couplings of carboxylate dianions, anhydride cleavage, and allylic alkylation.

Scheme 4 Alkanedioic Acids from Dichlorocyclobutanones^[6]

Section **20.2.5** introduces α -heteroatom-substituted carboxylic acids of the type $R^1C(=X)CO_2H$. They are found in essential biochemical systems and therefore play a central role in major metabolic pathways, and also are important synthetic intermediates toward biologically active compounds. Hydrolysis of the corresponding esters is the most common method for the synthesis of this product subclass (**Scheme 5**). Hydrolysis of other compounds, such as nitriles, can also be used for the synthesis. Other valuable methods include oxidation, Friedel–Crafts acylation, and aldol condensation of pyruvic acid with benzaldehydes.

Scheme 5 2-Oxo- and 2-(Oxyimino)alkanoic Acids by Hydrolysis of Esters

The chemistry of 2,2-diheteroatom-substituted alkanoic acids is covered in Section **20.2.6**. The conditions for synthesis of these compounds are typically very harsh, often involving high acidity, high refluxing temperatures, or strongly oxidizing conditions. The synthesis can be achieved by the following methods: hydrolysis of 2,2-diheteroatom-substituted esters or amides, hydrolysis of thiazoles or α,α -dihalo acid halides, oxidation of α -hydroxycarboxylic acids, 2,2-diheteroatom-substituted aldehydes, or 2,2-dihaloalkan-1-ols, oxidative cleavage of an alkynol, addition to various substrates, [3,3]-sigmatropic rearrangement of allyl trihaloacetates (**Scheme 6**),^[7,8] or nucleophilic substitution at the α -carbon of 2,2-diheteroatom-substituted acetic acids.

Scheme 6 2,2-Dihalopent-4-enoic Acids by Claisen-Type Rearrangements^[7,8]

The synthesis of α -amino acids is covered in Section 20.2.7. They are among the most common motifs in nature and show a wide range of biological, chemical, and material properties. Numerous nonnatural α -amino acids have been synthesized as probes of protein structure, as catalysts, and as pharmaceutical and agricultural agents from the study of the 20 proteogenic amino acids. There are many methods for the preparation of α -amino acids, and the most reliable and experimentally well-described syntheses of 2-aminoalkanoic acids and 2-alkyl-2-aminoalkanoic acids are discussed in detail. The challenge for the diastereoselective synthesis of 2-alkyl-2-aminoalkanoic acids lies in the construction of a fully-substituted carbon center. One of the most extensively used methods for the preparation of 2-alkyl-2-aminoalkanoic acids is alkylation of a chiral α -amino acid enolate equivalent (**Scheme 7**).^[9,10]

Scheme 7 Synthesis of 2-Alkyl-2-aminoalkanoic Acids by Alkylation of Oxazinones^[9,10]

Section 20.2.8 discusses methods for the synthesis of 2-heteroatom-substituted alkanoic acids with an emphasis on methods for their enantioselective synthesis. This subclass of compounds is widely used in total synthesis and medicinal chemistry. Deaminative substitution of optically enriched amino acids is a frequently used method for the synthesis of chiral alkanoic acids (**Scheme 8**).^[11,12] This reaction occurs with net retention of configuration.

Scheme 8 Synthesis of 2-Hydroxyalkanoic Acids from Amino Acids^[11,12]

Alk-2-ynoic acids (Section 20.2.9) serve as important building blocks in various fields, including total synthesis of biologically active compounds and other complex molecules. In addition, they are valuable substrates for exploring a wide range of reactions, such as cycloadditions and reactions with nucleophiles, as their reactivity is enhanced by the electron-withdrawing carboxy group. The most widely reported synthesis of alk-2-ynoic acids involves the addition of metalated alk-1-ynes to solid or gaseous carbon dioxide (**Scheme 9**).

Scheme 9 Synthesis of Alk-2-ynoic Acids by Carboxylation of Alk-1-ynylmetal Reagents with Carbon Dioxide

Methods for the synthesis of aromatic carboxylic acids (Section 20.2.10) are generally similar to those of aliphatic acids (e.g., oxidation, hydrolysis). However, arenes are more susceptible to oxidation than alkenes. Unwanted reactions of the aromatic group may occur under strongly oxidizing conditions. One of the simplest methods for synthesis of aromatic carboxylic acids involves addition of a nucleophilic aryl organometallic species to carbon dioxide (**Scheme 10**).^[13,14] The organometallic compounds most often used are lithium or

magnesium aryl carbanions.

Scheme 10 Synthesis of Arenecarboxylic Acids by Carboxylation of Arylmatal Species^[13,14]

The synthesis of alk-2-enoic acids is covered in Section **20.2.11**. This product subclass is ubiquitous in many classes of natural products and the most common method for the synthesis of the unsaturated acid functionality is hydrolysis of a corresponding ester. Other important and powerful methods for the direct synthesis include carboxylation of alkenyl organometallics, elimination reactions, carbonyl alkenations (**Scheme 11**),^[15,16] reduction of alk-1-ynoic acids, cycloaddition of alkynoic acids, palladium-catalyzed cross coupling to α -halogen-substituted alk-2-enoic acids, Heck reaction, and alkene metathesis.

Scheme 11 Synthesis of Alk-2-enoic Acids by Carbonyl Alkenations^[15,16]

Section **20.2.12** discusses the chemistry of 3-oxoalkanoic and 3,3-dioxyalkanoic acids. They are valuable intermediates in total synthesis as well as convenient precursors of ketones and α -oxo esters. The two main synthetic methods employ the acidic or basic hydrolysis of α -oxo esters, which are described in Section **20.5.15**. Other important methods are acylation of bis(trimethylsilyl) malonate, acylation of trimethylsilyl acetates (**Scheme 12**),^[17] carboxylation of methyl ketones, electrocarboxylation of chloroacetone, electrocarboxylation of vinyl trifluoromethanesulfonates, hydration of alk-2-ynoic acids, and hydroxyacylation and oxidation of alkenes.

Scheme 12 Synthesis of 3-Oxoalkanoic Acids by Acylation of Trimethylsilyl Acetate^[17]

The synthesis of α -heteroatom-substituted alkanolic acids is outlined in Section **20.2.13**. Common synthetic methods are ring opening of cyclic precursors (**Scheme 13**),^[18] addition to α,β -unsaturated compounds, or oxidations of a range of substrates, including haloalkanoic acids, hydroxy- and sulfanylalkanoic acids and derivatives, and amino- and phosphonoalkanoic acids and derivatives.

Scheme 13 α -Heteroatom-Substituted Alkanolic Acids by Ring Opening of Oxiranes^[18]

Section **20.3** covers the chemistry of carboxylic acid salts. They are reactive intermediates and isolable species in organic synthesis and medicinal chemistry. They often have better stability, crystallinity, and water solubility than the corresponding carboxylic acids. These properties make them valuable to the synthetic purification and administration of orally bioavailable medicines (e.g., penicillin antibiotics, **Scheme 14**).

Scheme 14 Penicillin Antibiotics as Carboxylic Acid Salts

Carboxylic acid salts are commonly prepared by the reaction of an appropriate base with the corresponding carboxylic acids (**Scheme 15**).

Scheme 15 Preparation of Common Carboxylic Acid Salts

Synthetic methods toward carboxylic acid anhydrides (Section 20.4) are generally through the activation of the carboxylic acids followed by attack of a second carboxylate unit to produce the anhydrides. The most common method for the synthesis of anhydrides is the removal of one molecule of water (dehydration) from the carboxylic acids (Scheme 16).^[19]

Scheme 16 Anhydride Synthesis from Carboxylic Acids^[19]

Carboxylic acid esters are covered in Section 20.5. They are one of the most important classes of organic compounds. The most general preparation of esters is performed by the reaction of a carboxylic acid and an alcohol, conventionally under acid catalysis (Scheme 17). Other important methods for the synthesis of alkyl alkanoates, including alcoholysis, oxidation of acetals, ozonolysis of alkenes, Baeyer –Villiger oxidation of ketones, Favorskii rearrangement, Wolff rearrangement, and so on, are depicted with specific examples in Section 20.5.1

Scheme 17 Brønsted Acid Catalyzed Esterification

The synthesis of arenedicarboxylic acid esters is covered in Section 20.5.2. There are two common methods for the easy access to this class of compounds: direct esterification of arenedicarboxylic acid esters using various reagents and the Diels –Alder reaction of precursor dicarboxylic acid esters and dienes followed by aromatization (Scheme 18).^[20]

Scheme 18 Synthesis of Arenedicarboxylic Acid Esters by Diels –Alder Reaction^[20]

The synthesis of butenedioic and acetylenedicarboxylic (butynedioic) acid esters is covered in detail in Section 20.5.3. There are many different methods leading to this subclass, generally including the following types: anhydride cleavage, organometallic-catalyzed carbenoid dimerization, phosphorus-based alkenations,

1,4-additions of alcohols, elimination protocols, semihydrogenation of the corresponding acetylenedicarboxylate, and other methods. One of the classical approaches is the elimination of an activated leaving group from a succinic acid ester derivative (**Scheme 19**).^[21]

Scheme 19 Synthesis of a Butenedioic Acid Ester by Elimination^[21]

Section **20.5.4** covers the synthesis of alkanedioic acid esters. The simplest and most common approaches to succinate esters are esterification of succinic acid and reduction of butenedioates. Asymmetric alkylations using *N*-acyloxazolidinones (Evans' asymmetric alkylation) is perhaps the most general and widely used method for the synthesis of enantiomerically pure α -alkylsuccinates (**Scheme 20**).^[22]

Scheme 20 Synthesis of α -Alkylsuccinates by Asymmetric Alkylation^[22]

For asymmetric synthesis of amino- or hydroxy-substituted succinates, a common strategy is aldol condensation of ester enolate derivatives to α -imino or α -oxo esters using either a chiral auxiliary or chiral Lewis acids (**Scheme 21**).^[23] Other methods and examples presented in this section include alkene dimerization, rearrangements, carbonylation of alkenes catalyzed by transition metals, conjugate addition, Stobbe condensations, and stereoselective sigmatropic rearrangements.

Scheme 21 Synthesis by Aldol Condensation^[23]

The synthesis of alkynyl alkanoates is described in Section [20.5.5](#). There are three general pathways to alkynyl esters; these are shown in [Scheme 22](#). The most straightforward pathway is esterification of a carboxylic acid derivative with an ynolate. Another widely used method is the S_N2 reaction of a carboxylate anion nucleophile with a suitable alkynyl electrophile, such as an alkynyliodonium salt. Lastly, iodobenzene dicarboxylates react with acetylide anions to afford alkynyl alkanoates.

Scheme 22 Common Strategies for the Synthesis of Alkynyl Alkanoates

Aryl alkanoates (Section [20.5.6](#)) are both important core structures of many biologically active natural products and important intermediates in organic synthesis. The most straightforward route is O-acylation of phenols ([Scheme 23](#), route a). Acyl halides are the most commonly used acylating agents. A more widely used strategy is the activation and direct oxidation of arene C—H bonds ([Scheme 23](#), route b), since arenes are more widely available than the corresponding phenols. Displacement of diazonium groups by nucleophiles (the Sandmeyer reaction) is another useful method for the synthesis of aryl alkanoates.

Scheme 23 Synthesis of Aryl Alkanoates by Activation and Oxidation of Arenes

Alkenyl alkanoates (Section [20.5.7](#)) can be regarded as masked enols ([Scheme 24](#)), which makes them very useful in a number of synthesis activities. For example, alkenyl alkanoates participate in many reactions including alkene addition reactions ([Scheme 24](#)), cycloadditions, aldol reactions, and acylation reactions.

Scheme 24 Alkenyl Alkanoates as Masked Enol Equivalents

Methods for the synthesis of alkenyl alkanoates include enolate O-acylation, O-acylation of alkynolate-derived enolates, catalyzed alkyne alkoxycarbonylation, alkenylmercury and alkenyl halide coupling with metal acetate salts, Fischer carbene coupling with acid chlorides, elimination, and Wittig-type alkenation reactions.

2-Oxo- and 2-imino-substituted alkanoic acid esters, and related esters with a C=X bond at the α -carbon (Section 20.5.8), are important intermediates in biological pathways. They find use in the syntheses of numerous natural products, α -amino- α -oxo acids, fluorinated amino acids, and a range of heterocycles. One of the most widely applied procedures for the synthesis of this subclass is oxidation of various precursors including α -hydroxy esters and α -diazo esters, as well as 3-oxo-2-(triphenylphosphoranylidene)propanoates (Scheme 25). Other methods involve esterification, hydrolysis, alcoholysis, and rearrangements, and these are also presented in this section.

Scheme 25 Synthesis of 2-Oxoalkanoic Acid Esters by Oxidation

2,2-Diheteroatom-substituted alkanoic acid esters (Section 20.5.9) are versatile intermediates in natural product synthesis. A classical method to prepare this product subclass is esterification of the corresponding acids, because this method is generally reliable and high yielding, requires only simple reaction techniques, and has a variety of available reaction conditions. Acetal formation is a long-developed method, as it is commonly used as a protective protocol for ketones. Other synthetic methods include alcoholysis, oxidative cleavage of an alkene, nucleophilic attack at an α -carbon, radical reactions, and rearrangements.

Section 20.5.10 covers the chemistry and synthesis of α -amino acid esters. They have similar functions and applications to the corresponding α -amino acids, and they can also be divided into three types according to their

structures: α , β -didehydroamino acid esters, 2-aminoalkanoic acid esters and 2-alkyl-2-aminoalkanoic acid esters. Many of the methods described for the synthesis of α -amino acids in Section 20.2.7 are also applicable to α -amino acid esters; as such this section is written as a complement to the carboxylic acid section described earlier. One of the examples using Schmidt rearrangement of α -oxo esters is depicted in **Scheme 26**.^[24]

Scheme 26 Synthesis of α -Amido Esters by Schmidt Rearrangement^[24]

2-Heteroatom-substituted alkanoates find their principal use in organic synthesis and medicinal chemistry. The preparation of this subclass of compounds is discussed in Section 20.5.11, with an emphasis on their enantioselective synthesis. The heteroatoms covered in this section are halogen, oxygen (hydroxy, alkoxy, and epoxide), sulfur, selenium, and tellurium. General methods for enantioselective synthesis are asymmetric catalysis, use of a transient chiral auxiliary, and kinetic resolution. One such example is shown below in **Scheme 27**.^[25] In addition, methods that are applied in industry are highlighted in this section.

Scheme 27 Catalytic Asymmetric Hetero-Diels –Alder Reactions of 2-Oxoalkanoates^[25]

Alk-2-ynoic acid esters (Section 20.5.12), like alk-2-ynoic acids, are valuable candidates to explore a large number of reactions, due to their improved reactivity as a result of the electron-withdrawing group. They are also the most common precursors for the preparation of alk-2-enoic acid esters by partial reduction or nucleophilic addition to the triple bond. Typically, the most straightforward method is esterification of alk-2-ynoic acids, usually in the presence of catalysts. One of the best and most widely used methods is carboxylation of terminal alkynes (**Scheme 28**), since they are generally either commercially available or can be easily accessed through well-established procedures.

Scheme 28 Synthesis by Carboxylation of Terminal Alkynes

Section [20.5.13](#) is focused on the synthesis of arenecarboxylic acid esters. The general methods can be divided into two major reaction types: the arene –carbon bond formation and the construction of the aromatic ring. The aromatic-ring construction can be achieved by anionic methods, by radical cyclizations of α -oxo esters, by cycloadditions, by electrocyclization and elimination, through oxidative rearrangement of hydrazone derivatives, or lithiation and alkylation of benzoate esters. The most straightforward strategy is utilizing a Friedel –Crafts acylation approach ([Scheme 29](#)).^[26] Other methods for the synthesis of arenecarboxylic acid esters through arene –carbon bond formation include oxidation of benzylic ethers, radical benzyloxylation, metalation, or carbonylation of various substrates.

Scheme 29 Friedel –Crafts Approach to an Arenecarboxylic Acid Ester^[26]

Alk-2-enoic acid esters (Section [20.5.14](#)) can often be found in natural products and medicinal agents. They are also important synthetic intermediates in organic synthesis. The α,β -unsaturated ester functionality can undergo reactions such as conjugate additions and cycloadditions, in which the ester group can be further modified building in additional complexity. There are four major methods for the synthesis of this class of compounds: alkoxycarbonylation of alkenyl organometallics, elimination reactions, aldol-type condensation, and, lastly, Wittig reaction (and related alkenylations), which is one of the most reliable methods for the introduction of the α,β -unsaturated ester functionality ([Scheme 30](#)).^[27,28]

Scheme 30 Alk-2-enoic Acid Esters from Wittig and Peterson Reactions^[27,28]

3-Oxoalkanoic acid esters (Section [20.5.15](#)), also referred to as α -oxo esters or α -keto esters, are valuable intermediates in a large pool of molecular synthesis. Literature reports regarding the synthesis of this subclass are numerous. Among them, the most direct method is oxidation of 3-hydroxyalkanoic acid esters. In addition, acylation of 3-oxoalkanoic acid esters is a very efficient and amenable strategy for large-scale syntheses (**Scheme 31**).^[29]

Scheme 31 Acylation of Methyl Acetoacetate with Acid Chlorides^[29]

Section [20.5.16](#) outlines the synthesis of α -heteroatom-substituted alkanoic acid esters. Most of the general synthetic methods for the synthesis of α -heteroatom-substituted alkanoic acids are also applicable to the corresponding esters. For instance, addition to α,β -unsaturated esters, cycloaddition reactions, and ring opening of cyclic precursors are typical examples.

Lactones (Section [20.6](#)) are frequently found in chemistry and nature, and many of them are important synthetic intermediates and building blocks because of their bifunctionality. In addition, chiral lactones are potential templates for the diastereoselective construction of additional stereocenters. General strategies for the synthesis of lactones are shown in **Scheme 32**. The most obvious synthetic pathway for the synthesis of lactones is to construct the two C—O bonds directly (routes a and b). The lactone ring can also be obtained from an ester precursor by a C—C bond formation reaction (route c), such as intramolecular Wittig—Horner reaction, alkylation, cross coupling, cycloaddition, or ring-closing metathesis. In addition, lactones may be prepared from other cyclic compounds such as ketones or cyclic anhydrides (route d).

Scheme 32 General Strategies for the Synthesis of Lactones

Organic peroxides (Section [20.7](#)) are widely used in research laboratories because of their exceptional reactivity and utility as oxidizing agents. Because of the weak peroxide bond, peroxides are exceptionally prone to violent decomposition, which can be initiated by heat, mechanical shock, or friction, especially in the presence of certain catalysts and promoters. As a class, they are among the most hazardous substances handled in the laboratories. The synthesis of peroxy acids and derivatives frequently begins with hydrogen peroxide (**Scheme 33**).^[30] They are also widely used as a source of free radicals to initiate a number of addition and polymerization reactions. The chemistry and synthesis of O-acylhydroxylamine and related sulfur, selenium, and tellurium compounds, acyl hypohalites, and peroxy acid esters are also discussed in this section.

Scheme 33 Preparation of Phthaloyl Peroxide^[30]

Section [20.8](#) reviews the synthesis of thiocarboxylic S-acids and their derivatives. There are a large number of methods leading to thiocarboxylic S-acids and related compounds. One example for the direct synthesis of thioesters from carboxylic acids and thiols is described in **Scheme 34**.^[31] Selenocarboxylic Se-acids, tellurocarboxylic Te-acids, and related compounds are also discussed briefly at the end of the section. The chemistry and synthesis of each product subclass is discussed separately.

Scheme 34 Synthesis of Thiocarboxylic S-Acid Esters from Carboxylic Acids and Thiols^[31]

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Compounds with Four and Three Carbon–Heteroatom Bonds

21

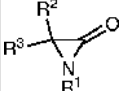

Volume 21:

Three Carbon—Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams

Mahajan, Y. R.; Weinreb, S. M., in *Science of Synthesis*, **21** (2005), p.1

This volume covers the synthesis of compounds containing an amide moiety, including peptides and lactams. These compounds have been divided into groups depending on the type of amide and the nature of the substituents around the amide functionality. These groups are shown in **Table 1**, together with the sections in which they appear.

Table 1 Classes of the Amide-Bond-Containing Compounds Covered in Volume 21

Product Class	Structural Formula(s)	Section
simple amides	$R^1C(O)NH_2$, $R^1C(O)NHR^2$, $R^1C(O)NR^2R^3$	21.1
triacylamines and diacylamines	$R^1C(O)NC(O)R^2C(X)R^3$, $R^1C(O)NR^2C(O)R^3$	21.2
<i>N</i> -[-(heteroatom)alkyl]-substituted alkanamides	$R^1C(O)NR^2CX_2R^3$, $R^1C(O)NR^2CXR^3R^4$	21.3
<i>N</i> -arylalkanamides, ynamides, enamides, dienamides, and allenamides	$R^1C(O)NR^2Ar^1$, $R^1C(O)NR^2C=CR^3$, $R^1C(O)NR^2CR^3=CR^4R^5$	21.4
-heteroatom-substituted alkanamides	$R^1C(X)C(O)NR^2R^3$, $R^1CX_2C(O)NR^2R^3$, $R^1CHXC(O)NR^2R^3$	21.5
alk-2-ynamides, arenecarboxamides, and alk-2-enamides	$R^1C=CC(O)NR^2R^3$, $Ar^1C(O)NR^1R^2$, $R^1R^2C=CR^3C(O)NR^4R^5$	21.6
-heteroatom-substituted alkanamides	$R^1C(X)CH_2C(O)NR^2R^3$, $R^1CX_2CH_2C(O)NR^2R^3$, $R^1CHXCH_2C(O)NR^2R^3$	21.7
-lactams		21.8
-lactams		21.9
-lactams and larger ring lactams		21.10
peptides		21.11
metal amides and imides	$R^1C(O)NMR^2$, $R^1C(O)NMC(X)R^2$	21.12
<i>N</i> -heteroatom-substituted alkanamides	$R^1C(O)NX_2$, $R^1C(O)NXR^2$	21.13
acylphosphorus compounds	$R^1C(O)P(O)(OR^2)_2$, $R^1C(O)PR^2R^3$	21.14

References to reviews on the different classes of compounds are given within each section. The discussion of each specific group is generally subdivided into methods that have been selected as the most useful for the preparation of the product class or subclass in question. Each method is presented separately as follows:

1. Introduction: comparison with other methods.

2. Presentation of the scope of the method including background, discussion of representative examples, safety, mechanistic information where relevant to the use of the method in synthesis, a table of examples (for selected methods), and reaction schemes.

3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, with each variation being presented according to the above format.

The coverage in this volume is not meant to be exhaustive, rather the most useful and reliable methods for the synthesis of each compound class have been selected by the respective authors. In some cases, methods that are apparently of only limited utility, or that have not yet been fully developed, are listed at the end of a section for reference. Tables and representative experimental procedures are given to illustrate the applicability of each approach.

It is important to note that amide polymers are not included, even though they certainly constitute an important class of amido compounds. This omission is mainly due to the fact that these macromolecules are not traditional targets for chemists working in the field of organic synthesis, and hence a thorough and comprehensive treatment of polymers is beyond the scope of the *Science of Synthesis* series.

This introduction outlines the individual product classes, together with highlighted synthetic methods.

The synthesis of simple amides (i.e., those without any other functional groups directly attached) is described in Section 21.1. The primary methods of amide synthesis discussed here are condensation processes and are classified depending on the nature of the precursor used: carbonic acids and derivatives, carboxylic acids and derivatives, aldehydes and ketones, and amines. Along with these sections, rearrangement reactions leading to amides are also discussed.

The synthesis of amides from carbonic acids and derivatives involves either a reduction or the formation of a C—C bond. Depending on the carbonic acid derivative, the synthesis may also involve the formation of a C—N bond. Phosgene and phosgene surrogates, chloroformates, carbonates, and carbon monoxide have been utilized for the simultaneous trapping of both a nitrogen and a carbon atom to afford amides. The preparation of amides from carbamates, carbamoyl chlorides, isocyanates, and urea derivatives involves the formation of a C—C bond. Generally, urea derivatives are not used in intermolecular amide synthesis due to the fact that the amide bond formed in this process is more reactive than the starting urea derivative, and thus can react further to form ketones. Hence, urea derivatives are mainly used in intramolecular reactions, as exemplified in **Scheme 1** for the formation of amides 1.^[1]

Scheme 1 Synthesis of Amides from Urea Derivatives by Intramolecular Cyclization^[1]

Formation of an amide bond by the coupling of carboxylic acids and derivatives with amines is one of the most popular methods in the synthesis of both amides and peptides. Owing to their wide application in peptide synthesis, methods employing carbodiimides, mixed anhydrides, and other condensation reagents are discussed in detail in Section 21.11. Along with carboxylic acids and derivatives, amides can also be prepared from thiocarboxylic acids and esters, nitriles, and imidates. Furthermore, significant progress has been made in the synthesis of amides from isocyanides via Ugi and Passerini multicomponent reactions.

In general, amides are prepared by the coupling of higher oxidation state compounds, such as carboxylic acid derivatives, with amines; however, synthetic methods starting with precursors in lower oxidation states, such as aldehydes, ketones, imines, and related compounds, are also available. As the products are therefore in a low oxidation state, an oxidation step must be included to obtain the desired amides. A variety of oxidizing agents such as *N*-bromosuccinimide, peroxides, sodium perborate, manganese(IV) oxide, and permanganate, as well as electrochemical techniques, have been employed to obtain the amides.

Rearrangement reactions comprise some of the most useful methods of converting non-nitrogenous compounds into amides. This reaction class contains very commonly used methods in amide and lactam synthesis, including the Beckmann and the Favorskii rearrangements, as well as the still-growing family of Schmidt reactions. These rearrangement reactions usually begin with ketones or ketone derivatives. As α -substituted ketones can be synthesized in enantiomerically pure form in numerous ways, and since most of these rearrangement reactions permit a migrating group bearing a stereogenic center to retain its stereochemical integrity, these reactions can also be employed for the asymmetric synthesis of amides, e.g. 2 (Scheme 2).^[2]

Scheme 2 Asymmetric Amide Synthesis by an Intramolecular Schmidt Rearrangement^[2]

The last part of Section 21.1 deals with substitution reactions and functional group manipulations of amide-containing compounds such as *N*-heteroatom-substituted alkanamides, formamides, diacyl- and triacylamines, ynamides, and enamides, without affecting the amide bond.

The synthesis of triacylamines, diacylamines, and related compounds is discussed in Section 21.2. More recently, imides have gained popularity as valuable synthetic intermediates due to their effectiveness as components of chiral auxiliaries such as Oppolzer's sultam and Evans' oxazolidines.^[3,4] Furthermore, the utilization of amino acids and their derivatives as chiral templates, and their ready conversion into imides, has enabled the preparation of versatile chiral synthons for a number of applications. One of the reagents commonly used for *N*-phthaloyl protection of sensitive amino acids is *N*-(ethoxycarbonyl)phthalimide (ethyl 1,3-dioxo-1,3-dihydro-2*H*-isoindole-2-carboxylate, **3**; Scheme 3). This compound can be easily prepared either by treating phthalimide with ethyl chloroformate in the presence of triethylamine or by treating potassium phthalimide with ethyl chloroformate in dimethylformamide.^[5]

Scheme 3 Preparation and Application of *N*-(Ethoxycarbonyl)phthalimide^[5]

The synthesis and applications of *N*[-(heteroatom)alkyl]-substituted alkanamides are reviewed in Section 21.3. These compounds are excellent electrophiles and readily undergo displacement reactions with a wide range of heteroatom and carbon nucleophiles. The latter case provides a convenient method for the formation of new C—C bonds. Most of the oxygen-, sulfur-, nitrogen-, and phosphorus-containing amido compounds are relatively stable and moisture-insensitive, whereas *N*-(1-haloalkyl) amides are not sufficiently stable for purification. Hence these compounds are usually generated in situ and used immediately in subsequent transformations. Of the different *N*[-(heteroatom)alkyl]-substituted alkanamides, the oxygen- and chlorine-containing compounds have been widely used for in situ generation of highly reactive *N*-acyliminium ions. The ability of these compounds to act as effective α -amidoalkylating agents allows the convenient introduction of other heteroatom functionalities, as well as the formation of new C—C bonds (Scheme 4). *N*-(1-Hydroxyalkyl) amides are classically prepared by the addition of *N*-unsubstituted amides to highly electrophilic aldehydes; however, these compounds can also be prepared using methods that can be broadly classified into two categories: addition of reducing agents or organometallic compounds to imides, and oxidation of amides.

Scheme 4 Generation and Reactions of *N*-Acyliminium Ions

N-(1-(Sulfur)alkyl)-substituted alkanamides possess inherent versatility, as each of the three different oxidation levels (sulfide, sulfoxide, sulfone) is readily available and suitable for subsequent elaboration. These sulfur-substituted amides participate in several synthetically useful transformations including a diverse range of *N*-acyliminium chemistry, free-radical cyclizations, and couplings of α -amido carbanions with electrophiles. The α -(alkylsulfanyl) and α -(arylsulfanyl) substituents can be easily introduced into amides and carbamates by displacement of suitable leaving groups such as halo, alkoxy, and sulfonyl functionalities with a thiol. Subsequent oxidation of the sulfides provides the corresponding sulfoxide and sulfone derivatives. The synthesis and application of *N*-(1-sulfonylalkyl)alkanamides is exemplified in [Scheme 5](#).^[6]

Scheme 5 Synthesis and Application of *N*-(1-Sulfonylalkyl) Amides^[6]

Alkanamides possessing aryl, alkynyl, and alkenyl substituents directly connected to the amide nitrogen are discussed in Section [21.4](#). Of the different routes available for the synthesis of *N*-arylalkanamides, the one involving formation of a C(aryl)—N bond is the most difficult to effect, often requiring harsh conditions, which has previously limited the applicability of this strategy. Significant progress, however, has now been made in this area and has led to the development of efficient palladium-mediated, as well as copper-mediated, *N*-arylations of amides ([Scheme 6](#)).^[7,8] These methods complement each other in that electron-rich or *ortho*-substituted electronically neutral aryl halides that are difficult to amidate using palladium catalysts can, in most cases, be

amidated using a copper catalyst.

Scheme 6 Synthesis of *N*-Aryl Amides by C—N Bond Formation^[7,8]

The enhanced stability of ynamides relative to ynamines has led to extensive studies of their participation in Pauson–Khand cycloadditions, Suzuki, Sonogashira, and Negishi cross couplings, and other reactions. A revival of interest in the chemistry of ynamides began soon after the report of an efficient and general method for the synthesis of ynesulfonamides using iodonium trifluoromethanesulfonates (e.g., preparation of ynesulfonamide **4**; **Scheme 7**).^[9] Subsequently, other synthetic methods starting from simple terminal alkynes and amides, employing the palladium and copper catalysts used for the synthesis of *N*-arylalkanamides, as well as those used for Sonogashira and Negishi couplings, were developed (e.g., preparation of ynamide **5**; **Scheme 7**).^[10]

Scheme 7 Synthesis of an Ynesulfonamide and an Ynamide Using Alkynyl Derivatives^[9,10]

Enamides are an important class of compounds due to their occurrence as substructures in a number of natural products and as potential drugs, as well as their utility as intermediates in the synthesis of various heterocycles. Owing to the inherent reactivity of enamides, this functionality is generally introduced in the final stages of a natural product synthesis. The *N*-acylation of imines and formation of C—N bonds employing transition-metal-catalyzed methods similar to those used for the synthesis of *N*-arylalkanamides are now common strategies for the synthesis of enamides. Formation of the C=C bond is also an important approach for the synthesis of

enamides and can be achieved in different ways, such as alkenation reactions (Wittig, thio-Wittig, Horner–Wadsworth–Emmons, and Peterson alkenations), elimination reactions, and condensation of amides with aldehydes (e.g., formation of **6**; **Scheme 8**).^[11]

Scheme 8 Synthesis of an Enamide by a Horner–Wadsworth–Emmons Alkenation^[11]

Dienamides have mainly been studied due to their ability to participate in Diels–Alder reactions. Many of the methods used for the synthesis of enamides are also applicable to the synthesis of dienamides. Developments in ring-closing enyne metathesis have led to applications in the synthesis of dienamides, as shown in **Scheme 9**.^[12]

Scheme 9 Synthesis of Dienamides by Ring-Closing Enyne Metathesis^[12]

Allenamides have been studied in various types of cyclization reactions (anionic, palladium-catalyzed, and iodine-promoted), as well as in different types of cycloadditions. Allenamides are generally prepared by base-induced isomerization of *N*-propargyl amides. This process can be terminated by protonation, as depicted in **Scheme 10**, or by the addition of an electrophile, leading to the formation of a C—C bond.^[13]

Scheme 10 Synthesis of an Allenamide by Base-Induced Isomerization of an *N*-Propargyl Amide^[13]

Section **21.5** covers the synthesis of α -heteroatom-substituted alkanamides. α -Haloalkanamides are primarily synthesized either by mono- or di- α -halogenation of amides, or by displacement of the heteroatom from other α -heteroatom-substituted alkanamides. A large variety of reagents is available for electrophilic halogenations, such as Selectfluor, *N*-fluorobis(trifluoromethylsulfonyl)amine, *N*-chlorosuccinimide, hypochlorite salts, elemental bromine, hypobromite, and iodine. Nucleophilic displacement of nonactivated heteroatoms is generally achieved using *N,N*-dimethylaminosulfur trifluoride, phosphorus pentachloride, thionyl chloride, or phosphorus tribromide. Displacement of chloride by iodide to prepare the corresponding α -iodoalkanamides (i.e., the Finkelstein reaction) is widely used in order to increase the reactivity of the starting chloro compounds toward nucleophiles. Further modifications can be achieved by alkylation/aldol reactions of the enolates generated from the α -haloalkanamides.

-Oxygen-, -sulfur-, or -selenium-substituted alkanamides are generally prepared by treatment of the corresponding amide enolates with a variety of reagents, such as lithium *tert*-butyl peroxide, 2-tosyloxaziridines, disulfides, *S*-phenyl benzenethiosulfonate, diphenyl diselenide, *N*-(phenylselanyl)phthalimide, and phenyltellurenyl iodide (**Scheme 11**). The -hydroxyalkanamides can subsequently be oxidized to the corresponding -oxoalkanamides using standard oxidizing agents such as the Dess–Martin periodinane, pyridinium dichromate, or the Jones reagent.

Scheme 11 Synthesis of -Hydroxy-, -Sulfanyl-, -Selanyl-, and -Tellanylalkanamides

-Nitrogen- and -phosphorus-substituted alkanamides are also prepared by electrophilic amination of enolates [using azodicarboxylates, *N*-(*tert*-butoxycarbonyl)-*O*-tosylhydroxylamine, or diphenylphosphoryl azide with di-*tert*-butyl carbonate or diphenylphosphoryl chloride], or by nucleophilic displacement from the corresponding -heteroatom-substituted alkanamides (using amines, azides, nitrosoarenes, oximes, trialkyl phosphites, or trialkylphosphines). -Diazoalkanamides are accessed by diazo-transfer reactions using diphenylphosphoryl azide, methanesulfonyl azide, or arenesulfonyl azides (**Scheme 12**), or by diazotization of -aminoalkanamides.

Scheme 12 Synthesis of -Diazoalkanamides via Diazo Transfer

The synthesis of , -unsaturated amides is discussed in Section **21.6**. , -Unsaturated amides are present in several natural products, as well as some biologically important molecules, and are valuable synthetic intermediates in the construction of alkaloids. Alkene-forming reactions of silanes (Peterson alkenation), phosphoranes (Wittig reaction), and phosphonates (Horner–Wadsworth–Emmons reaction) have been successfully employed for the synthesis of , -unsaturated amides (e.g., amides **7**; **Scheme 13**).^[14,15] Isomerization or elimination reactions of suitably substituted amides are also capable of yielding unsaturated and polyunsaturated amides.

Scheme 13 Synthesis of , -Unsaturated Weinreb Amides by the Horner–Wadsworth–Emmons Reaction^[15]

The synthesis of -heteroatom-substituted alkanamides, including asymmetric methods, is reviewed in Section **21.7**. The most straightforward way of constructing these -heteroatom-substituted alkanamides is by introducing

substituents at the α -position via a conjugate addition. Considerable progress has been made in the preparation of enantiomerically pure systems by the addition of heteroatoms to α,β -unsaturated amides, whereby the stereochemistry is controlled using chiral reagents, auxiliaries, or catalysts. The different heteroatoms which can be introduced include halogen, oxygen, selenium, sulfur, and phosphorus; however, α -nitrogen-substituted alkanamides are by far the best known subclass of such compounds. Various sources of nucleophilic nitrogen can be used in the process, depending on the nature of subsequent transformations that are planned. Enantioselective conjugate addition of azides to alkenamides affords useful intermediates which can be further elaborated to the corresponding α -amino acids by reduction, or can be used as dipoles in [3+2] cycloadditions, as shown in **Scheme 14**.^[16]

Scheme 14 Enantioselective 1,4-Addition of Azidotrimethylsilane and Intramolecular Cycloaddition^[16]

The synthesis and reactions of β -lactams are discussed Section **21.8**. The high strain energy (41 kcal \cdot mol⁻¹) of β -lactams profoundly influences their structure and reactivity. In such compounds there is minimal overlap between the nitrogen lone pair and the carbonyl group. These lactams are generally prepared by one of two different strategies: cyclization by dehydrohalogenation of α -halo-substituted amides, or the cycloelimination reaction of *N*-(sulfonyloxy)-substituted amides, such as **8** (**Scheme 15**). Due to their high ring strain, β -lactams undergo facile reactions with nucleophiles to yield ring-opened products.^[17]

Scheme 15 Conversion of *N*-(Mesyloxy)-Substituted Amides into 2-Substituted Amides via β -Lactams^[17]

The synthesis of γ -lactams is reviewed in Section **21.9**. The chemistry and biology of γ -lactams have been extensively studied owing to the presence of this functionality in various important antibiotics such as penicillins, cephalosporins, penems, and monobactams. [2+2] Cycloaddition of an imine with a ketene is one of the most versatile and efficient routes for the construction of the γ -lactam skeleton. The *cis/trans* ratio of the γ -lactam formed in this reaction depends on various factors such as order of addition of the reagents, method of generation and structure of the ketene, nature of the imine, solvent, and temperature. Enantiomerically enriched γ -lactams can be obtained when the cycloaddition is carried out in the presence of chiral Lewis acids, chiral nucleophiles such as cinchona alkaloids (e.g., quinine), or chiral ferrocene **9** (**Scheme 16**).^[18]

Scheme 16 Catalytic Enantioselective [2+2] Cycloaddition of an Imine with a Ketene in the Presence of a Chiral Ferrocene Derivative^[18]

The synthesis and reactivity of γ -lactams and larger ring lactams are discussed in Section **21.10**. These compounds are generally prepared using standard amide-bond-forming protocols from the corresponding amino acids or related derivatives such as nitriles, azides, or nitro compounds. Furthermore, methods based on C—C bond formation, such as radical reactions and ring-closing metathesis (for an example, see **Scheme 17**), have also been used for the synthesis of such lactams.^[19]

Scheme 17 Macrocyclic Lactam Synthesis via Metathesis Using a Second Generation Grubbs Catalyst^[19]

Section **21.11** presents an overview of the synthesis of peptides along with a discussion of related issues such as protecting groups, racemization, and the different supports and linkers that are available for solid-phase synthesis. The peptide bond is generally accessed by activation of a carboxylic acid component in the form of an acid halide, anhydride (symmetrical, cyclic, or mixed), or active ester, or by in situ activation achieved using reagents such as those shown in **Scheme 18**.

Scheme 18 Reagents Used for the Activation of Carboxylic Acids in Peptide Synthesis

The abbreviations commonly used by peptide chemists, and thus in Section 21.11, differ slightly to those used for the same groups and reagents found elsewhere in *Science of Synthesis*. The main differences are for the benzyl (Bzl rather than Bn), benzyloxycarbonyl (Z rather than Cbz), and trityl (Trt rather than Tr) protecting groups, and for dicyclohexylamine (DCHA rather than Cy₂NH). The abbreviations have been defined in the text the first time they are used and are also defined in an extra abbreviations list at the end of the volume. A comprehensive list of abbreviations used in peptide chemistry can also be found in *Houben–Weyl*, Vol. E 22.

Acid halides are mainly used for coupling hindered systems and for weakly nucleophilic amines. With appropriate protecting groups on the amine terminus and the side chains, acid chlorides and fluorides of amino acids can often be isolated and stored. Alternatively, acid halides can also be prepared in situ using bis(trichloromethyl) carbonate (triphosgene) or tetramethylfluoroformamidinium hexafluorophosphate (TFFH). Symmetrical anhydrides are often used in solid-phase peptide synthesis as they afford the desired peptides in higher yield and with higher purity than achieved using carbodiimide procedures. Activation of carboxylic acids can also be effected by condensation with electron-deficient hydroxy compounds to form active esters. Commonly used reagents include substituted phenols (e.g., pentafluorophenol), *N*-hydroxysuccinimide, 1,2,3-benzotriazol-1-ol (HOBt), 7-aza-1,2,3-benzotriazol-1-ol (HOAt), and 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HODhbt). In solution synthesis, carbodiimides, such as *N,N*-dicyclohexylcarbodiimide (DCC), *N,N*-diisopropylcarbodiimide (DIC), and *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (EDC), are commonly used due to their efficiency, tolerance to a wide variety of solvents, and low cost. A major byproduct in these coupling reactions is the urea derivative of the carbodiimide reagent, which in most cases can be easily separated from the desired product. Superior reagents which have been developed are phosphonium and uronium/guanidinium salts, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU), and *N*-[(dimethylamino)(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU), that are effective in difficult couplings between sterically hindered substrates. The utilization of different coupling reagents, depending on the steric hindrance of the coupling partners, is seen in the synthesis of the tetrapeptide fragment 10 of the Ser-Thr phosphatase inhibitor microcystin LA (Scheme 19).^[20]

Scheme 19 Application of Different Coupling Reagents in the Synthesis of a Tetrapeptide Fragment^[20]

Metal amides and imides are reviewed in Section **21.12**. Metal imides, in particular those of group 1 elements and silicon, have shown utility in organic synthesis as intermediates for the generation of *N*-substituted amides and imides, imines, sulfur-substituted amides, and transmetalated amides and imides. In general, metal amides or imides are prepared through deprotonation using a metal–base complex, or by a ligand-exchange process. Metal amides of group 1 elements are highly reactive and hence are generated in situ and immediately used in subsequent transformations, as depicted in **Scheme 20**.^[21]

Scheme 20 *N*-Methylation of Amides via Sodium Amides Generated In Situ^[21]

Silicon amides and imides are versatile reagents and have been used to generate *N*-substituted amides from lactones, epoxides, and ketones. These species can be oxidized to *N*-hydroxy-substituted amides and can be employed in aza-Peterson alkenations. One of the most common methods for preparing *N*-silyl-substituted amides and imides is through exchange of a silyl moiety with compounds such as hexamethyldisilazane (e.g., the synthesis of **11**; **Scheme 21**), tetramethyldisilazane, and *N*-silyl-substituted carboxamides.^[22]

Scheme 21 Synthesis of a *N*-Silyl-Substituted Amide by Silicon Exchange with Hexamethyldisilazane^[22]

Section **21.13**, which covers *N*-heteroatom-substituted amides, encompasses a wide variety of systems. One important subclass included in this section is the acyl azides, which have been known since the late 1800s and have been studied extensively owing to their useful synthetic applications. Acyl azides undergo a rearrangement

(i.e., the Curtius rearrangement) to give isocyanates that can be subsequently converted into amines, ureas, and carbamates. The nucleofugacity of the azide anion makes acyl azides good acylating agents and these species were formerly used in peptide synthesis prior to the development of carbodiimide methodology. Traditionally, acyl azides are prepared from activated carboxylic acids such as acid chlorides, or by nitrosation of acylhydrazines in the case of compounds prone to α -epimerization. With the introduction of diphenylphosphoryl azide, acyl azides can be prepared directly from unactivated carboxylic acids, e.g. **12** (**Scheme 22**).^[23]

Scheme 22 Synthesis of an Acyl Azide from a Carboxylic Acid with Diphenylphosphoryl Azide^[23]

N-Halo-substituted amides are versatile oxidants. For example, *N*-bromosuccinimide has been used in oxidations of aldehydes to acid bromides and various *N*-haloalkanamides have also been used in halogenation reactions as a source of chlorine, bromine, or iodine. These compounds are typically prepared by direct *N*-halogenation of amides with reagents such as perfluorinated hypofluorites (e.g., CF_3OF), hypochlorite, bromine, hypobromite, and iodine. *N*-Bromoalkanamides are prone to Hofmann rearrangement under basic conditions and the temperature during *N*-bromination reactions should be monitored carefully.

Both cyclic and acyclic *N*-hydroxy-substituted amides (hydroxamic acids) have been studied extensively from both medicinal chemistry and pharmacological points of view. A number of molecules having this functionality have been developed for the treatment of ailments such as cardiovascular disease, cancer, HIV/AIDS, malaria, and tuberculosis. These compounds can be prepared by acylation of hydroxylamine, oxidation of amides, deprotection of hydroxamates, and also by an ene reaction of acyl nitroso compounds (**Scheme 23**).^[24]

Scheme 23 Synthesis of a Cyclic Hydroxamic Acid via an Ene Reaction of an Acyl Nitroso Compound^[24]

N-Methoxy-*N*-methyl amides, introduced by Weinreb, are widely used in organic synthesis as acylating agents as they react with only 1 equivalent of a variety of nucleophilic reagents to produce ketones or aldehydes in high

yield. Multiple addition is usually not encountered, even if excess nucleophile is used, due to the formation of a stable metal-chelated tetrahedral intermediate which collapses only upon aqueous acidic workup. An example of the synthesis and application of Weinreb amides is depicted in **Scheme 24**.^[25]

Scheme 24 Synthesis of a Ketone from *N*-*tert*-Butyloxycarbonyl-Protected (S)-Phenylalanine via the Corresponding Weinreb Amide^[25]

Finally, Section **21.14** discusses the synthesis of acylphosphorus compounds. These compounds have been widely employed for the generation of phosphorus-containing analogues of biologically active compounds and the formation of C—C bonds with elimination of the phosphorus-containing moiety. The broad applicability of the acylphosphonate subclass of acylphosphorus compounds in organic synthesis is mainly due to their reactivity, which can be attributed to the low pK_a of the proton to the carbonyl group and the rapid cleavage of the C—P bond under aqueous acidic conditions. The commonest methods for assembling acylphosphonates are the Arbuzov-type reaction of an acyl chloride with a trialkyl phosphite, and the oxidation of α -hydroxy phosphonates (**Scheme 25**).^[26]

Scheme 25 Synthesis of Acylphosphonates by Oxidation of the Corresponding α -Hydroxy Phosphonates^[26]

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Compounds with Four and Three Carbon–Heteroatom Bonds

22

Volume 22:

Three Carbon–Heteroatom Bonds: Thio-, Seleno- and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives

Charette, Andr B., in *Science of Synthesis*, **22** (2005), p.1

This volume of *Science of Synthesis* covers the synthesis of carboxylic acid derivatives that do not contain a C=O group. The various classes of compounds include a wide range of different functional groups with various unique properties and synthetic utilities. **Table 1** lists the classes of carboxylic acid derivatives covered in Volume 22.

Table 1 Classes of Carboxylic Acid Derivatives Covered in Volume 22

Product Class	Structural Formula	Section
thiocarboxylic acids and derivatives		22.1
-substituted sulfur ylides		22.1.1
thioacyl halides	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{X} \end{array}$ <p>X = halo</p>	22.1.2
thiocarboxylic O-acid esters	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{OR}^2 \end{array}$	22.1.3
dithiocarboxylic acid esters	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{SR}^2 \end{array}$	22.1.4
selenothiocarboxylic Se-acid esters	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{SeR}^2 \end{array}$	22.1.5
tellurothiocarboxylic Te-acid esters	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{TeR}^2 \end{array}$	22.1.6
thioamides	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^1-\text{C}-\text{N}(\text{R}^2)(\text{R}^3) \end{array}$	22.1.7
selenocarboxylic acids and derivatives		22.2
tellurocarboxylic acids and derivatives		22.3
imidic acids and derivatives		22.4
N-carbon-substituted iminium salts		22.4.1
C-heteroatom-substituted nitrones		22.4.2
imidoyl halides	$\begin{array}{c} \text{NR}^2 \\ \parallel \\ \text{R}^1-\text{C}-\text{X} \end{array}$ <p>X = halo</p>	22.4.3

imidates		22.4.4
thioimidates		22.4.5
selenoimidates (imidoselenoates)		22.4.6
telluroimidates (imidotelluroates)		22.4.7
<i>N</i> -carbon-substituted amidines (imidamides)		22.4.8
<i>N</i> -heteroatom-substituted amidines		22.4.9
alkylidenephosphines	 <i>X = halo</i>	22.5
arsaalkenes and arsonium ylides	 <i>X = halo</i>	22.6
ortho acid derivatives		22.7
1,1,1-trihalomethyl compounds		22.7.1
ortho esters	 <i>X = halo, O</i>	22.7.2
trithioortho esters	 <i>X = halo, S</i>	22.7.3
triselenoortho esters	 <i>X = halo, Se</i>	22.7.4
tritelluroortho esters	 <i>X = halo, Te</i>	22.7.5
ortho amides		22.7.6
tris(diorganophosphino)methanes		22.7.7

Each section includes a brief introduction to the class of compound, a description of the most important and useful methods for the synthesis of the product class, including safety concerns, and references to reviews describing the preparation and chemistry of each specific functional group. In addition, some representative experimental procedures are also provided. The section may be further divided into variations, if, for example, different reagents may be used for the transformation.

The coverage has been limited to the description of the most important and most widely used methods for the synthesis of each functional group. Tables and representative experimental procedures are provided on a case-

to-case basis when important methods with newer developments are reported.

Section **22.1.1** provides a general introduction to α -substituted sulfur ylides and the general methods for their preparation. Substituents include silyl, stannyl, germyl, halo, alkoxy, sulfanyl, selanyl, amino, phosphorus(III), and phosphorus(V) moieties. Although there are several methods available, the most general approach to these compounds involves deprotonation of the parent sulfonium^[1] or sulfoxonium^[2] salt, since the pK_a of the α -proton is significantly lowered by the presence of the heteroatom (**Scheme 1**). Furthermore, the presence of the substituent generally prevents problems associated with the regioselectivity of the deprotonation.

Scheme 1 Deprotonation of α -Substituted Sulfur Ylides

The most important applications of these compounds in synthesis include Peterson-type alkenations ($Y = \text{TMS}$),^[3] cyclopropanation (**Scheme 2**),^[4] 1,3-dipolar cycloaddition,^[5] [2,3]-sigmatropic rearrangement,^[6] and carbonyl addition, followed by intramolecular ring closure, giving synthetically valuable α -substituted oxiranes (**Scheme 2**), which are generally not isolated and are converted into ring-opened products.^[7]

Scheme 2 Applications of α -Substituted Sulfur Ylides^[4,7]

The preparation of thioacyl halides is presented in Section **22.1.2**. These compounds are rather important since they can be used as starting materials to generate a wide range of thiocarboxylic acid derivatives (see Sections 22.1.3–7). Of the various methods available for their preparation, the conversion of dithiocarboxylic acids into thioacyl halides is the most generally useful (**Scheme 3**).^[8]

Scheme 3 Preparation of Thioacyl Chlorides^[8]

The reactivity of thioacyl halides parallels that of acyl halides but the products are often less stable. These reagents can be used in thioacylation reactions when treated with a wide range of nucleophiles. In addition, they can be used in Friedel–Crafts and thioacylation reactions^[9] to produce thioketones and in [4+2]-cycloaddition reactions^[10] with dienes. Oxidation leads to unstable chlorosulfines.^[11]

Section **22.1.3** describes the preparation and chemistry of thiocarboxylic O-acid esters. Typically, this compound class can be prepared from alcohols and an activated thioacyl reagent (e.g., chloride, benzotriazole), by treating esters with Lawesson's reagent,^[12] by thiolysis of imino ethers, or by alkoxythiocarboxylation of enolates using

appropriate thiocarboxylation reagents such as *O*-alkyl *S*-methyl dithiocarbonates (**Scheme 4**).

Scheme 4 General Approaches to Thiocarboxylic *O*-Acid Esters

Thiocarboxylic *O*-acid esters are highly useful and versatile starting materials for carrying out further synthetic transformations. They can be used as electrophiles in thioacylation processes involving organolithium reagents.^[13] Trapping of the tetrahedral intermediate with alkylating agents (such as iodomethane), followed by hydrolysis, leads to ketones.^[14] These compounds can also be used in the Claisen rearrangement,^[15] and as nucleophiles in aldol^[16] and Michael reactions.^[17] In addition, these compounds participate in several cycloaddition processes either by acting as an activating group to decrease the energy of the LUMO of dienophiles (Diels–Alder reaction)^[18] or in hetero-Diels–Alder-type reactions that involve addition onto the C=S moiety.^[19]

Very important applications also include desulfurization reactions to reduce thioesters to ethers or the Barton–McCombie-type deoxygenation of secondary alcohols.^[20] Finally, these compounds are good starting materials to generate difluoro derivatives through a fluorodesulfurization process.

The preparation of the related dithiocarboxylic acid esters and its synthetic applications, which are more or less parallel to those of the thioester, are described in Section 22.1.4. Section 22.1.5 and 22.1.6 describe the chemistry of the more exotic thiocarboxylic Se- and Te-acid esters.

Section 22.1.7 deals with the synthesis of thioamides; these are a very important functional group, which are found in a number of biologically active compounds, including active pharmaceutical ingredients, plant protection agents, and flotation and vulcanization agents.^[21] The reactivity of thioamides is quite different from that of amides, due to the unique properties of the sulfur atom. Thioamides are indeed versatile precursors for the synthesis of a variety of heterocyclic compounds.^[22] Three retrosynthetic disconnections may be envisioned for the preparation of thioamides: (1) addition of the sulfur atom to the substrate; (2) addition of the nitrogen atom to the substrate; (3) addition of a carbon nucleophile to isothiocyanates.^[23] The most widely used method is the replacement of an oxygen atom from an amide functionality by a sulfur atom using either tetraphosphorus decasulfide or Lawesson's-type reagents (**Scheme 5**).^[24] Alternative methods have been developed to overcome potential problems, as the sulfurization reaction is also possible using other substrates. For instance, the activation of *N*-mono- or *N,N*-disubstituted amides with pyridine and trifluoromethanesulfonic acid leads to pyridinium imidates which are susceptible to thiolysis using ammonium sulfide, providing *N*-mono- or *N,N*-disubstituted thioamides in high yields.^[25] *N*-Unsubstituted thioamides are easily obtained from the thiolysis of nitriles using, for instance, thioacetic acid.^[26] For the synthesis of more elaborate thioamides containing other functional groups which are also susceptible to reaction with the thioacylating agent, other synthetic routes are possible. The addition of a variety of carbon nucleophiles, including enamines, ketene acetals, enolates, Grignard reagents, organolithium reagents, trimethyl(trifluoromethyl)silane, aryl groups, organosamarium reagents, and radicals, to isothiocyanates is efficient for the synthesis of such thioamides. Furthermore, electrophilic thioacyl reagents readily react with amine nucleophiles to give thioamides in good yields.

Scheme 5 General Approaches to Thioamides

Section **22.2** concerns the chemistry of selenocarboxylic acids and derivatives, and the large body of work done on these compounds is quite impressive both from a preparative and application standpoint. In contrast to the other selanyl derivatives, the selenocarbonyl halides, are relatively rare and the methods available are quite specific to certain appropriately substituted compounds. Selenocarboxylic O-, S-, and Se-acid esters have been prepared quite efficiently using several methods (**Scheme 6**).

Scheme 6 General Approaches to Selenocarboxylic Acids

The methods for the preparation of selenocarboxylic acid amides follow closely those described for the corresponding O-, S-, and Se-esters and are discussed in Section **22.2.4** (**Scheme 7**). In addition, it is also possible to prepare selenocarboxylic acid amides from 1,1-dihaloalkenes and elemental selenium in the presence of an amine.^[27]

Scheme 7 General Approaches to Selenocarboxylic Acid Amides

In contrast to the selenocarboxylic acid derivatives very little work has been done on the corresponding telluro compounds (Section **22.3**). The main reason is that the compounds are generally quite unstable due to their light- and oxygen-sensitivity. However, it is possible to synthesize tellurocarboxylic O-acid esters from various activated amides.^[28,29]

Section **22.4.1** deals with the formation of carbon-substituted iminium salts. This is an extremely important topic since it includes Vilsmeier-type reagents which are still widely used today. Although there are numerous reagents that allow conversion of amides into Vilsmeier reagents, there are few other approaches to this product class (**Scheme 8**).

Scheme 8 General Approaches to Vilsmeier-Type Reagents

The preparations of alkoxymethaniminium salts and sulfanylmethaniminium salts involve similar approaches that usually best employ amides or thioamides as starting materials (**Scheme 9**).

Scheme 9 General Approaches to Alkoxy- and Sulfanylmethaniminium Salts

Imidazolium salts, which are among the most important precursors to *N*-heterocyclic carbene ligands,^[30] are usually prepared by the condensation of secondary amines with ortho esters or from Vilsmeier salts or other activated amides or nitrilium salts and amines.

The synthesis of *C*-heteroatom-substituted nitrones and other related dipoles is described in Section 22.4.2. The chloro derivative can be prepared by the rearrangement of α -chloro nitroso compounds. The products can be used for the preparation of the oxygenated analogues upon alcohol addition. A general approach for the generation of *C*-oxygenated nitrones is shown in Scheme 10. In addition, the *C*-sulfanyl and *C*-sulfonyl analogues are prepared similarly. The methods for the preparation of *C*-nitrogen derivatives are numerous but are typically quite specific for various compounds. The oxidation of imidamides (amidines) is an efficient process.

Scheme 10 A General Approach to *C*-Heteroatom-Substituted Nitrones from Hydroxamic Acids

Finally, the chemistry of *C*-heteroatom-substituted azomethine ylides is described from a preparative standpoint. These, and related derivatives, are of course excellent dipolar moieties for use in 1,3-dipolar cycloaddition reactions. The dipole is usually prepared from the corresponding trimethylsilyl derivative through desilylation or by the alkylation of nitrogen by a rhodium carbenoid.

Sections 22.4.3 to 22.4.7 deal with the preparation and chemistry of imidate derivatives. The imidoyl halides that can be prepared by activation of the corresponding *N*-monosubstituted amides with various reagents often serve as precursors to generate the other derivatives. Alternatively, the halide can be prepared from the corresponding isocyanide, nitrile, or ketenimine. Alternatively, *O*- and *S*-alkylation of the corresponding amide can be used for the direct preparation of these product classes. The direct addition of alcohols and thiols to nitriles and isocyanides is also an efficient method to access this product class.

In Sections 22.4.8 and 22.4.9 the preparation of amidines and their derivatives is described; these sections are quite important and comprehensive due to the importance and role that these compounds play in pharmaceuticals. The strategies that are used for their synthesis are intimately related to the preparation and reactions of the reactive precursors described in the previous sections. Although the amidines are not often used as intermediates in organic synthesis, these compounds are widely found in natural products.

Section 22.5 describes the preparation of (2-halomethylene)phosphines, which have a high propensity to undergo dimerization. These phosphorus(III) compounds can be efficiently prepared in a number of ways including those illustrated in Scheme 11. The preparation of alkoxy derivatives ($X = OR^1$) is reminiscent of those described for the imidate. The preparation of other highly exotic phosphorous derivatives is also described. The preparation of related arsenic derivatives is presented in Section 22.6.

Scheme 11 General Approaches to (2-Halomethylene)phosphines

Although 1,1,1-trihaloalkanes are considered to be carboxylic acid derivatives by virtue of having the same oxidation state, their physical properties are quite different. Section [22.7.1](#) describes the synthesis of this extremely important class of organic compounds ([Scheme 12](#)). These compounds are widely found in the pharmaceutical industry as well as in materials science and agrochemistry. Several different strategies can be used to incorporate trihaloalkyl units into an organic molecule. Direct halogenation is sometimes possible as long as the position to be halogenated is activated (such as a benzylic position). Alternatively, there are several available sources of either nucleophilic or electrophilic CX₃ groups that can be used to introduce this group into organic molecules. It is also possible to employ a halogen-exchange reaction to convert one 1,1,1-trihalo derivative into another.

[Scheme 12](#) General Approaches to 1,1,1-Trihaloalkanes

Section [22.7.2](#) describes the preparation of ortho esters and their halogenated acetal and ether derivatives. Ortho esters are important protecting groups for carboxylic acids since they are easily hydrolyzed back to the acid under mild acidic conditions but they are quite resistant to basic conditions. [Scheme 13](#) illustrates two of the various methods for their preparation.

[Scheme 13](#) General Approaches to Ortho Esters and Related Derivatives

Closely related syntheses of the sulfur (Section [22.7.3](#)), selenium (Section [22.7.4](#)), and tellurium analogues (Section [22.7.5](#)) of ortho esters are also described. Although the trithioortho esters are widely used, the selenium and tellurium analogues are not very common.

Section [22.7.6](#) deals with the preparation of ortho amides. The main application of these compounds is as reagents for the incorporation of a formyl unit. They can be prepared using various methods but the most useful and important of these involve displacement of a leaving group (cyano, halide) from a suitable precursor ([Scheme 14](#)). In addition, it is also possible to add nucleophiles to guanidinium salts.

[Scheme 14](#) General Approaches to Ortho Amides

Section [22.7.7](#) describes the preparation of tris(diorganophosphino)methanes and their derivatives. Only five methods have been described, including the alkylation of lithium tris(dimethylphosphino)methanides or the phosphorylation of a suitably substituted organolithium. It is also possible to oxidize tris(diorganophosphino)

methanes with oxygen or sulfur to generate related derivatives.

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Compounds with Four and Three Carbon–Heteroatom Bonds
Volume 23:
Three Carbon—Heteroatom Bonds: Ketenes and Derivatives

23

Danheiser, R. L., in *Science of Synthesis*, **23** (2006), p.1

General Introduction

This volume covers the synthesis and applications of ketenes and ketenimines, as well as sulfur, selenium, and tellurium analogues of ketenes. The nature of the substituents attached at the C2 carbon of ketenes has a dramatic effect on the chemistry of these compounds, and consequently this volume is divided into 17 product classes based on the type of substituent at this position. **Table 1** lists the classes of ketenes and related compounds discussed in the volume, together with the sections in which they appear.

Table 1 Structures and Nomenclature for Classes of Ketenes Covered in Volume 23

Product Class	Structural Formula	Section
ketene	$\text{=}\cdot\text{=O}$	23.1
silylketenes	$\text{R}^1_3\text{Si}-\text{CH}=\text{O}$	23.2
halogen-substituted ketenes	$\text{X}-\text{CH}=\text{O}$ X = F, Cl, Br, I	23.3
oxygen-substituted ketenes	$\text{R}^1\text{O}-\text{CH}=\text{O}$	23.4
sulfur- and selenium-substituted ketenes	$\text{R}^1\text{X}-\text{CH}=\text{O}$ X = S, Se	23.5
nitrogen- and phosphorus-substituted ketenes	$\text{R}^1_2\text{X}-\text{CH}=\text{O}$ X = N, P	23.6
alkylideneketenes	$\text{=}\cdot\text{=}\cdot\text{=O}$	23.7
cyanoketenes	$\text{NC}-\text{CH}=\text{O}$	23.8
acylketenes	$\text{R}^1-\text{C}(=\text{O})-\text{CH}=\text{O}$	23.9
imidoylketenes	$\text{R}^1-\text{C}(\text{NR}^2)=\text{CH}=\text{O}$	23.10
alk-1-ynylketenes	$\text{C}\equiv\text{C}-\text{CH}=\text{O}$	23.11
aryl- and hetarylketenes	$\text{Ar}^1-\text{CH}=\text{O}$	23.12
alkenylketenes	$\text{CH}_2=\text{CH}-\text{CH}=\text{O}$	23.13
alkyl- and cycloalkylketenes	$\text{R}^1-\text{CH}_2-\text{CH}=\text{O}$	23.14
1,2-bisketenes	$\text{O}=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{O}$	23.15
sulfur, selenium, and tellurium analogues of ketenes	$\text{=}\cdot\text{=X}$ X = S, Se, Te	23.16
ketenimines	$\text{=}\cdot\text{=NR}^1$	23.17

Each section includes an introduction to the product class covered followed by a description of the most important

methods for the synthesis of the several subclasses into which the product class is divided. This discussion is not exhaustive, and only the most useful and reliable methods for the synthesis of each product subclass are included. Examples are provided illustrating each method, as well as representative experimental procedures. In some cases, methods are further subdivided into variations on the method, typically when alternative tactics have been reported for effecting a particular transformation.

Most ketenes are reactive species and readily undergo dimerization and polymerization. For this reason, many of the most important methods for the preparation of ketenes do not lead to an isolable ketene product, but rather generate a reactive ketene intermediate that is intercepted in situ by further reaction with a nucleophile or with a ketenophilic π -bond. In this volume, considerable attention is therefore devoted to the discussion of the applications of each product subclass in organic synthesis.

The remainder of this introduction summarizes the most important synthetic methods and applications for each product class. The single most widely employed strategy for the synthesis of ketenes involves elimination reactions based on carboxylic acid derivatives. Nearly every class of ketene can be generated by one or another variation of this basic strategy. In this introduction, attention is therefore focused on methods that are unique to each product class of ketene derivatives.

Section **23.1** discusses the chemistry of ketene itself. Ketene (**1**) is a pungent gas, which undergoes dimerization on standing to form a 19:1 mixture of dimers **2** and **3** (**Scheme 1**).^[1] Ketene was first prepared in 1907 by the pyrolysis of acetic anhydride, ethyl acetate, or acetone over a hot platinum wire,^[2] and the pyrolysis of acetic acid is in fact used today for the industrial preparation of ketene.^[3] The pyrolysis of acetone over a hot metal filament in a Hurd lamp is a popular method for the generation of ketene in the laboratory.^[4,5] Other methods that have been employed for the synthesis of ketene include the dehydrohalogenation of acetyl halides, the reductive 1,2-dehalogenation of 2-haloacetyl halides, and the retro-ene reaction of alkynyl ethers.

Scheme 1 Dimerization of Ketene

Ketene has found wide application in organic synthesis. This highly reactive carbonyl compound acetylates a variety of nucleophilic compounds under mild conditions and combines in [2 + 2] cycloadditions with alkenes, alkynes, and aldehydes. The scope of these cycloadditions is limited, however, due to the propensity of ketene to undergo dimerization. For this reason, more reactive ketenes such as dichloroketene are often employed as ketene equivalents in [2 + 2] cycloadditions, as discussed in Section **23.3**

Silylketenes are the subject of Section **23.2**. This class of ketenes exhibits dramatically different behavior as compared to other classes. Hyperconjugative and inductive effects suppress the tendency of silylketenes to undergo dimerization and to participate in uncatalyzed [2 + 2] cycloadditions with π -bonds. As a result, and in marked contrast to members of other classes of ketenes, silylketenes are usually isolable substances that can even be purified by distillation and chromatography.

A variety of preparative methods provide convenient access to silylketenes. The most popular method for the synthesis of (trimethylsilyl)ketene (**4**) involves the thermolysis of 1-ethoxy-2-(trimethylsilyl)acetylene (**Scheme 2**).^[6] This transformation proceeds via a retro-ene reaction and furnishes the ketene in 65% overall yield from ethoxyacetylene, the precursor to the alkynylsilane. (Trimethylsilyl)ketene is a stable liquid that is purified by distillation (bp 81 –82 °C). Other silylketenes have been prepared by various elimination methods, including the

dehydrohalogenation of acyl halides, the dehydration of silylacetic acids, and the thermolysis of silylacetic anhydrides. The Wolff rearrangement of α -diazo- α -silyl ketones provides another useful method for the synthesis of several subclasses of silylketenes.

Scheme 2 Synthesis of (Trimethylsilyl)ketene^[6]

Silylketenes function as valuable building blocks in a number of methods for the synthesis of carbocyclic and heterocyclic compounds. Particularly useful is the [2 + 2] cycloaddition of silylketenes with aldehydes to furnish α -lactones (**Scheme 3**).^[7,8] This process is catalyzed by Lewis acids, and enantioselective variants have been developed based on chiral Lewis acid catalysts. Silyl(vinyl)ketenes are an especially valuable class of synthons, and these ketenes function as versatile synthetic building blocks in a number of important transformations, including Diels–Alder and hetero-Diels–Alder reactions, and [4 + 1] annulations leading to highly substituted cyclopentenones (**Scheme 4**).^[9,10]

Scheme 3 Synthesis of α -Lactones by Lewis Acid Catalyzed Cycloaddition of Silylketenes and Aldehydes

Scheme 4 Synthesis of Cyclopentenones by [4 + 1] Annulation of (Trialkylsilyl)vinylketenes and Carbenoid Reagents^[9,10]

Section **23.3** covers the chemistry of halogen-substituted ketenes. Included are fluoro-, chloro-, bromo-, and iodoketenes, as well as dihalo derivatives. Computational studies reveal that ketenes are destabilized by electron-withdrawing substituents, and members of this product class are predicted to be highly reactive substances. From the perspective of organic synthesis, dichloroketene stands out as the most important member of this class of ketenes. This highly reactive ketene cannot be isolated, and is typically generated in situ for reaction with a suitable ketenophile. The most widely employed methods for the generation of dichloroketene are the dehydrochlorination of dichloroacetyl chloride with a base (usually triethylamine), and the reductive 1,2-dechlorination of trichloroacetyl chloride, which is most commonly effected using activated zinc.^[11,12] **Scheme 5** presents these methods in the context of their application to the synthesis of cyclobutanones and cyclobutenones. Dichloroketene is much more reactive in [2 + 2] cycloadditions than ketene itself, and combines in good yield with many alkenes and alkynes that do not react with ketene in satisfactory yield. The products of these cycloadditions can be dechlorinated by exposure to reducing agents such as zinc and tributyltin hydride,

and this two-step sequence thus provides access to cyclobutanones and cyclobutenones that are not available by direct cycloaddition reactions involving ketene itself.

Scheme 5 Synthesis of Cyclobutanones and Cyclobutenones via [2 + 2]-Cycloaddition Reactions of Dichloroketene

Haloketenes function as useful synthetic intermediates in a number of other synthetic applications, among which the Bellus –Claisen (ketene –Claisen) rearrangement is particularly notable (**Scheme 6**).^[13,14]

Scheme 6 Bellus –Claisen Rearrangement

Oxygen-substituted ketenes are discussed in Section 23.4. This product class includes alkoxyketenes, (aryloxy)ketenes, siloxyketenes, (acyloxy)ketenes, and (sulfonyloxy)ketenes. In general, these ketenes are unstable substances that readily undergo dimerization and polymerization, and consequently they must usually be generated in situ as transient intermediates for reaction with suitable ketenophilic compounds. As in the case of most other classes of ketenes, elimination reactions involving carboxylic acid derivatives provide the most

common methods for the generation of oxygen-substituted ketenes. A method with particular utility for the preparation of this class of ketenes is the photolysis of Fischer-type chromium carbene complexes.^[15] **Scheme 7** illustrates this method as applied to the synthesis of α -lactams. Irradiation of the chromium α -carbene complex **5** furnishes the ketene complex **6**, which then undergoes [2 + 2] cycloaddition with an imine (the Staudinger α -lactam synthesis) to produce the desired product **7**.

Scheme 7 Synthesis of α -Lactams by Cycloaddition of Imines with Oxygen-Substituted Ketenes Generated by Photolysis of Chromium α -Carbene Complexes

Section **23.5** focuses on the synthesis and applications of sulfur- and selenium-substituted ketenes. Although predicted to be somewhat more stable as compared to halogen- and oxygen-substituted ketenes, members of this product class are rarely isolable substances and are usually generated in situ to participate in further transformations. The most commonly employed methods for the synthesis of sulfur-substituted ketenes involve elimination reactions of carboxylic acid derivatives. Complementing these standard approaches is the Wolff rearrangement of α -diazo thioesters. **Scheme 8** presents an example of a particularly useful variant of this process, in which the thia-Wolff rearrangement is catalyzed by dirhodium tetraacetate. The highly reactive (arylsulfanyl)ketenes generated in this fashion can be trapped in situ with alkenes, alkynes, and imines to afford four-membered-ring products in good yield.^[16,17]

Scheme 8 [2 + 2] Cycloaddition of a Sulfur-Substituted Ketene Generated by Wolff Rearrangement^[16]

Nitrogen- and phosphorus-substituted ketenes are covered in Section **23.6**. The principal methods employed for the synthesis of this product class parallel those of oxygen-substituted ketenes. Particularly useful are elimination reactions of α -amino acid derivatives and the photolysis of Fischer-type chromium α -aminocarbene complexes. The application of the latter method to generate an aminoketene derivative, which is trapped in situ with an amino acid ester to form a dipeptide, is shown in **Scheme 9**.^[18]

Scheme 9 Synthesis of Peptides by Addition of Amino Acid Esters to Nitrogen-Substituted Ketenes Generated by Photolysis of Chromium α -Carbene Complexes^[18]

Section **23.7** is concerned with the chemistry of alkylideneketenes. Two subclasses are included in this class of ketenes: substituted methyleneketenes and carbon suboxide. The most widely used method for generating alkylideneketenes involves the thermolysis of alkylidene derivatives of Meldrum's acid (**Scheme 10**), a wide variety of which are available by the condensation of Meldrum's acid with aldehydes and ketones.^[19]

Scheme 10 Generation of Alkylideneketenes by Thermolysis of Meldrum's Acid Derivatives^[19]

Carbon suboxide (**8**) is a lachrymatory and irritant gas (bp 7 °C) that is stable in solution for short term storage. One of the most convenient methods for synthesizing this compound involves heating a mixture of malonic acid and phosphorus pentoxide, and distilling out the carbon suboxide as it forms (**Scheme 11**).^[20]

Scheme 11 Synthesis of Carbon Suboxide from Malonic Acid^[20]

Methods for the synthesis of cyanoketenes are described in Section **23.8**. The most useful routes to these ketenes employ a strategy involving zwitterazido cleavage.^[21] For example, thermolysis of 4-azido-3-chloro-5-methoxyfuran-2(5*H*)-one (**9**) provides access to chloro(cyano)ketene, which is a highly reactive ketene that readily undergoes in situ [2 + 2] cycloadditions with a variety of alkenes, such as cyclohexene (**Scheme 12**).^[22] Heating 2,5-diazido-3,6-di-*tert*-butylbenzo-1,4-quinone (**10**) in benzene leads to the formation of *tert*-butyl(cyano)ketene, which is a relatively stable cyanoketene that can be stored in solution in aromatic solvents such as benzene and toluene.

Scheme 12 Generation of Chloro(cyano)ketene and *tert*-Butyl(cyano)ketene by Zwitterazido Cleavage Reactions^[22-24]

Section **23.9** deals with the preparation and synthetic applications of acylketenes, i.e. ketenes with a carbonyl group directly attached to the terminal carbon of the ketene moiety. Members of this class are often generated by elimination reactions starting from carboxylic acid derivatives. The Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds serves as another particularly useful method for the synthesis of acylketenes. An exceptionally important method, which is unique for this class of ketenes, involves thermolysis of 2,2-dimethyl-4*H*-1,3-dioxin-4-one derivatives. Heating these compounds at 100 –150 °C triggers a [4 + 2] cycloreversion (retro-Diels –Alder reaction), which produces an acylketene and acetone. This process is usually carried out in the presence of a ketenophile that traps the unstable acylketene as it forms in a subsequent [2 + 2] or [4 + 2] cycloaddition.

Scheme 13 illustrates this strategy as applied to the preparation of acetylketene. The starting material in this case, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**11**), is easily prepared by the acid-catalyzed addition of acetone to diketene.

Scheme 13 Generation of Acetylketene by Thermolysis of 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one

The chemistry of imidoylketenes (iminoketenes) is the subject of Section **23.10**. **Scheme 14** presents several of the subclasses into which this product class is divided. Included are *N*-alkyl-, *N*-aryl-, and *N*-hetaryl-substituted imidoylketenes **12**. (*N*-Acylimidoyl)ketenes **13**, acyl(imidoyl)ketenes **14**, and 6-(oxomethylene)cyclohexa-2,4-dien-1-imines **15** constitute other subclasses of imidoylketenes discussed in this section. Many of the methods used for the generation of these ketenes involve the thermolysis of heterocyclic compounds. In some cases, equilibration of the imidoylketene products with acylketenimines **16** via a [1,3] rearrangement takes place at the elevated temperatures required for these reactions (**Scheme 15**).

Scheme 14 Imidoylketene Product Subclasses

Scheme 15 Rearrangement of Imidoalkynes to Acylketenimines

Section **23.11** discusses the synthesis of alk-1-enylketenes. Very little has been reported to date concerning this class of unsaturated ketenes. Alk-1-enylketenes have been generated by retro Diels –Alder reactions and by thermolysis of alkoxydienes, and alkynyl(cyano)ketenes have been prepared by thermolysis of 2,5-dialkynyl-3,6-diazidobenzo-1,4-quinones.

Product Class 12, aryl- and hetarylketenes (Section **23.12**), represents one of the most extensively studied classes of ketenes. Diphenylketene was isolated by Staudinger in 1905 and was the first persistent ketene to be characterized.^[25] Many arylketenes are stable in solution and a number of diarylketenes are isolable solids. The preparation of members of this product class is usually accomplished using the standard methods for ketene synthesis introduced in earlier sections. Elimination reactions involving carboxylic acid derivatives and the Wolff rearrangement of α -diazo aryl ketones constitute particularly important methods. Aryl- and hetarylketenes have found wide application in organic synthesis, especially as acylating agents and as partners in [2 + 2] cycloadditions with alkenes and imines leading to cyclobutanones and β -lactams, respectively. The stability of many arylketenes in solution permits their use in transformations not possible with less stable ketenes. This has been exploited, for example, in a method for the catalytic asymmetric synthesis of 2-arylalkanoic acid ester derivatives (**Scheme 16**).^[26] The stereochemical course of this reaction is believed to be controlled by the enantioselective protonation of the enolate intermediate formed by addition of the phenol to the ketene. The chiral Brønsted acid involved in this key step is the conjugate acid of the catalyst **17**.

Scheme 16 Catalytic Asymmetric Synthesis of 2-Arylalkanoic Acid Esters from Arylketenes^[26]

Section **23.13** covers the chemistry of alkenylketenes. The several subclasses included in this product class are

illustrated by structures **18**–**21** as shown in **Scheme 17**. Many alkenylketenes readily undergo [4 + 2] dimerization by a hetero-Diels–Alder reaction pathway, and thus must be generated in situ for trapping when they are employed as synthetic intermediates. Vinylketenes **18** can be prepared by standard methods such as elimination reactions of α,β - and α,γ -unsaturated carboxylic acid derivatives, and by the Wolff rearrangement of α -diazo- β -unsaturated ketones. A unique method for the synthesis of vinylketenes involves the four-electron electrocyclic ring opening of cyclobutenones, a process that can be effected either by heating or photochemically by irradiation. **Scheme 18** shows an example of this process in the context of a [4 + 4] annulation method for the synthesis of eight-membered carbocyclic compounds.^[27]

Scheme 17 Alkenylketene Product Subclasses

Scheme 18 [4 + 4]-Annulation Strategy Based on Reaction of 1,3-Dienes with Vinylketenes Generated by Electrocyclic Ring Opening of Cyclobutenones^[27]

1,3-Dienylketenes **19** and (2-arylvinyl)ketenes **20** are especially valuable subclasses of alkenylketenes that function as intermediates in several annulation strategies for the construction of highly substituted benzenoid aromatic rings. **Scheme 19** outlines one such benzannulation strategy based on the reaction of an alkyne with a cyclobutenone or diazo ketone.^[28,29] Mechanistically, this process proceeds via a cascade of several pericyclic reactions. Firstly, thermolysis or irradiation generates a transient vinylketene intermediate **22**, which reacts with the alkyne in a [2 + 2] cycloaddition. Electrocyclic ring opening of the resulting cyclobutenone **23** furnishes a 1,3-dienylketene **24**, which immediately undergoes six-electron electrocyclic ring closure and then tautomerization to produce the phenolic product **25**. As shown in **Scheme 20**, a variant of this process leading to benzo-1,4-quinones **27** has also been developed that involves the thermolysis of 4-alkenyl-4-hydroxycyclobutenones **26**. Cyclobutenones of type **26** are available by addition of organometallic compounds to cyclobutene-1,2-diones.^[30,31]

Scheme 19 Benzannulation Strategy Based on the Reaction of Alkynes with Cyclobutenones or Diazo Ketones^[28,29]

Scheme 20 Benzannulation Strategy Based on the Thermolysis of 4-Alkenyl-4-hydroxycyclobutenones^[30,31]

Section **23.14** focuses on alkylketenes and cycloalkylketenes. This product class is divided into several subclasses: monoalkylketenes **28**, dialkylketenes **29** and (oxomethylene)cycloalkanes (cycloalkylketenes) **30**, cyclopropylketenes **31** and oxiranylketenes **32**, and (fluoroalkyl)ketenes (e.g., **33** and related compounds), as shown in **Scheme 21**. The chemistry of alkylketenes has been the subject of extensive investigation since the first member of this class, dimethylketene, was prepared in 1906. Many alkylketenes are stable in solution, although the pure compounds often dimerize rapidly and most also react rapidly with moisture to give carboxylic acids. Dialkylketenes are typically more stable than monoalkylketenes, and some sterically shielded derivatives such as di-*tert*-butylketene are quite stable as neat liquids. Elimination reactions, beginning with various carboxylic acid derivatives, and the Wolff rearrangement of diazo ketones constitute the most common methods for the synthesis of alkylketenes.

Alkylketenes serve as valuable intermediates in numerous important synthetic transformations. For example, a key step in the venerable Arndt –Eistert method for the chain extension of carboxylic acids involves the Wolff

rearrangement of a diazo ketone **34** to produce an alkylketene **35**, which is trapped by the nucleophilic solvent to afford the homologated product (**Scheme 22**).^[32] [2 + 2] Cycloadditions of alkylketenes with alkenes, imines, and aldehydes provide access to cyclobutanones, -lactams, and -lactones, respectively.

Scheme 21 Subclasses of Alkylketenes

Scheme 22 Alkylketenes as Intermediates in the Arndt –Eistert Reaction

Bisketenes are the subject of Section **23.15**. Covered in this section are 1,2-bisketenes **37**, as well as higher order bisketenes in which the two ketene moieties are separated by tethers composed of two or more carbon and/or heteroatoms. The most important method for the synthesis of 1,2-bisketenes involves the thermal or photochemical electrocyclic ring opening of cyclobutene-1,2-diones **36** (**Scheme 23**). In the case of many substituents R¹ and R², the cyclobutenediones are thermodynamically favored, and ring closure to regenerate **36** may occur if the ketene is not trapped as it forms in an appropriate addition reaction.

Scheme 23 Generation of 1,2-Bisketenes by Electrocyclic Ring Opening of Cyclobutenediones

Section **23.16** is concerned with the chemistry of sulfur, selenium, and tellurium analogues of ketenes. This product class includes thioketenes **38** and cumulated thioketenes **39** (and their derivatives); carbon subsulfide (**40**, propadienedithione) is a member of the latter subclass (**Scheme 24**). Also discussed in this section are thioketene S-oxides **41**, selenoketenes **42**, and the elusive telluroketenes **43**. At the present time, no truly general methods exist for the synthesis of members of this product class, and the best synthetic routes to a specific thioketene or selenium or tellurium analogue must be determined on a case by case basis.

Scheme 24 Product Subclasses for Sulfur, Selenium, and Tellurium Analogues of Ketenes

The final section, Section **23.17**, discusses the chemistry of ketenimines, the nitrogen analogues of ketenes. These compounds tend to exhibit greater stability as compared to the analogous ketenes; therefore, this section focuses on methods for the preparation of ketenimines, with little attention devoted to their application in organic synthesis. The most popular method for the synthesis of ketenimines involves the reaction of secondary carboxamides with triphenylphosphine and bromine in the presence of triethylamine (**Scheme 25**). This transformation is believed to proceed via the formation of oxyphosphonium salt **44**, which is converted into the imidoyl bromide **45**. Dehydrobromination by the amine base then furnishes the ketenimine.

Scheme 25 Synthesis of Ketenimines by Dehydration of Secondary Carboxamides

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Compounds with Four and Three Carbon–Heteroatom Bonds

24

Volume 24:

Three Carbon–Heteroatom Bonds: Ketene Acetals and Yne–X Compounds

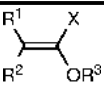
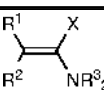
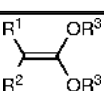
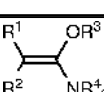
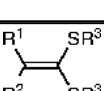
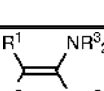
de Meijere, A., in *Science of Synthesis*, **24** (2005), p.1

General Introduction

This volume of *Science of Synthesis* covers the syntheses of compounds formally having three carbon — heteroatom bonds, i.e. those with the oxidation state of carboxylic acid derivatives. These include a wide range of functionalities as outlined in **Table 1**. Accordingly, the various product subclasses have a variety of applications in organic synthesis, the most important of which are summarized in each section.

Table 1 Classes of Compounds Covered in Volume 24

Product Subclass	Structural Formula	Section
1,1-dihaloallenes		24.1.1
1-heteroatom-functionalized 1-haloallenes		24.1.2 – 24.1.5
1,1-bis(organooxy)allenes	$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^2 \end{array} \quad \begin{array}{c} \text{OR}^3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{OR}^3 \end{array}$	24.1.6
1-heteroatom-functionalized 1-(organooxy)allenes		24.1.7 – 24.1.9
1,1-bis(organochalcogeno)allenes		24.1.10
1-heteroatom-functionalized 1-(organochalcogeno)allenes		24.1.11, 24.1.12
1,1-bis(nitrogen-functionalized) allenes	$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^2 \end{array} \quad \begin{array}{c} \text{NR}^3_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NR}^3_2 \end{array}$	24.1.13
1-nitrogen-functionalized 1-phosphorus-functionalized allenes		24.1.14
1,1-bis(phosphorus-functionalized) allenes		24.1.15

1,1-dihaloalk-1-enes		24.2.1
1-halo-1-(organooxy)alk-1-enes	 $\begin{array}{c} R^1 \quad X \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad OR^3 \end{array}$ <p>X = F, Cl, Br, I</p>	24.2.2
1-halo-1-(organochalcogeno)alk-1-enes		24.2.3
1-nitrogen-functionalized 1-haloalk-1-enes	 $\begin{array}{c} R^1 \quad X \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad NR^3_2 \end{array}$ <p>X = F, Cl, Br, I</p>	24.2.4
1-phosphorus-functionalized 1-haloalk-1-enes		24.2.5
1,1-bis(organooxy)alk-1-enes (ketene O,O-acetals)	 $\begin{array}{c} R^1 \quad OR^3 \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad OR^3 \end{array}$	24.2.6
1-(organochalcogeno)-1-(organooxy)alk-1-enes (ketene O,S-, O,Se-, O,Te-acetals)		24.2.7, 24.2.8
1-nitrogen-functionalized 1-(organooxy)alk-1-enes (ketene O,N-acetals)	 $\begin{array}{c} R^1 \quad OR^3 \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad NR^4_2 \end{array}$	24.2.9
1-phosphorus-functionalized 1-(organooxy)alk-1-enes		24.2.10
1,1-bis(organosulfanyl)alk-1-enes (ketene S,S-acetals)	 $\begin{array}{c} R^1 \quad SR^3 \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad SR^3 \end{array}$	24.2.11
1-heteroatom-functionalized 1-(organosulfanyl)alk-1-enes		24.2.12 – 24.2.14
1,1-bis(organoselanyl)- and 1,1-bis(organotellanyl)alk-1-enes		24.2.15 – 24.2.16
1,1-bis(nitrogen-functionalized) alk-1-enes (ketene N,N-acetals)	 $\begin{array}{c} R^1 \quad NR^3_2 \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^2 \quad NR^3_2 \end{array}$	24.2.17
1-nitrogen-functionalized 1-phosphorus-functionalized alk-1-enes		24.2.18
1,1-bis(phosphorus-functionalized) alk-1-enes		24.2.19

dihaloacetylenes	$\text{X}^1\text{—}\equiv\text{—X}^2$ $\text{X}^1 = \text{F, Cl, Br, I}$ $\text{X}^2 = \text{F, Cl, Br, I}$	24.3.1
1-heteroatom-functionalized 2-haloacetylenes		24.3.2
bis(organooxy)acetylenes	$\text{R}^1\text{O—}\equiv\text{—OR}^1$	24.3.3
1-heteroatom-functionalized 2-(organooxy)acetylenes		24.3.4 – 24.3.6
bis(organochalcogeno)acetylenes	$\text{Z—}\equiv\text{—Z}$ $\text{Z} = \text{SR}^1, \text{SO}_2\text{R}^1, \text{SeR}^1, \text{TeR}^1$	24.3.7
1-phosphorus-functionalized 2-(organochalcogeno)acetylenes and 1-nitrogen-functionalized 2-(organochalcogeno)acetylenes		24.3.8, 24.3.9
bis(nitrogen-functionalized) acetylenes	$\text{R}^1_2\text{N—}\equiv\text{—NR}^1_2$	24.3.10
1-nitrogen-functionalized 2-phosphorus-functionalized and bis (phosphorus-functionalized) acetylenes		24.3.11
1-haloalk-1-ynes and alk-1-yn-1-ols	$\text{R}^1\text{—}\equiv\text{—X}$ $\text{X} = \text{F, Cl, Br, I, OH}$	24.4.1
1-(organooxy)alk-1-ynes and 1-(heterooxy)alk-1-ynes	$\text{R}^1\text{—}\equiv\text{—OR}^2$	24.4.2
1-(organochalcogeno)alk-1-ynes	$\text{R}^1\text{—}\equiv\text{—Z}$ $\text{Z} = \text{SR}^2, \text{SeR}^2, \text{TeR}^2$	24.4.3
1-nitrogen-functionalized alk-1-ynes		24.4.4
1-phosphorus-functionalized alk-1-ynes		24.4.5

Each section provides references to previously published reviews concerning the preparation and chemistry of each subclass with its specific functional group(s), a brief introduction, and the most important and practical methods for the synthesis of the product subclass, including safety concerns wherever applicable. The scope of each method is presented with a discussion of the background, mechanistic information whenever relevant, reaction schemes, and tables of examples (for selected methods). In addition, some representative experimental procedures are provided to guide the user.

In many cases, the methods are further subdivided into variations on a method, and a variation can imply different conditions, different reagents, or different starting materials to approach the same target compounds. Each variation is presented according to the same format. The coverage is not exhaustive, but comprehensive as far as the most useful and reliable methods for the synthesis of each subclass are concerned.

This introduction will briefly outline the individual product subclasses and will highlight the major synthetic approaches as well as possible applications in organic synthesis.

1,1-Dihaloallenes **3**, as covered in Section **24.1.1**, can be prepared by any of four basic methods (**Scheme 1**): (1) substitution of a halogen or metal in allene **1** by a halogen; (2) acetylene –allene isomerization of acetylene derivatives **2** (Z = OH, halo); (3) dehydrohalogenation (Z = H) or dehalogenation (Z = halo) of oligohalogenated propene derivatives **5**; (4) thermal ring-opening isomerization of 3,3-dihalocyclopropenes **4**.

Scheme 1 Synthesis of 1,1-Dihaloallenes

In general, fluoroallenes are best prepared from allenes **1**, acetylenes **2**, or propenes **5**; chloro- and bromoallenes can be synthesized from acetylenes **2**, cyclopropenes **4**, or propenes **5**; and iodoallenes are prepared from allenes **1** or acetylenes **2**. 1,1-Difluoro- and 1,1-dichloroallene rapidly dimerize by [2 + 2] cycloaddition at room temperature, and tetrafluoro- as well as tetrachloroallene are even more prone to dimerization. With proper handling, however, they can be used as halogenated building blocks in organic synthesis, as they rapidly undergo addition of nucleophiles as well as electrophiles, [2 + 2] cycloadditions with alkenes, [2 + 3] cycloadditions with 1,3-dipoles, as well as [2 + 4] cycloadditions with 1,3-dienes.

Allenes carrying one halogen and one other heteroatom substituent [OR^1 , SAr^1 , SR^1 , S(O)R^1 , SO_2R^1 , $\text{N}(\text{CF}_3)_2$, $\text{P}(\text{O})(\text{OR}^1)_2$] at the same carbon atom are rather rare (Sections 24.1.2 –24.1.5), and for several of them only a single example has been reported, e.g. 1-iodo-1-methoxyallene can be prepared from methoxyallene by deprotonation and subsequent iodination in 95% yield,^[1] but must be handled with care at low temperature. Several 1-halo-1-(organochalcogeno)allenes have been prepared, and they are more stable. Although they may be considered as oligofunctional C_3 building blocks, reports on their actual use in organic synthesis are scarce. This also applies to allenes containing a halogen and an amino or a phosphorus substituent at the same carbon, and there is a single report on the application of a 1-phosphorus-functionalized 1-bromoallene in a palladium-catalyzed cross-coupling reaction (Sonogashira type).^[2] Bis(organooxy)- **6** and 1-(organooxy)-1-siloxyallenes as well as tetraalkoxyallenes **7** (**Scheme 2**), all of which are easily accessible, have been applied as substrates for cycloadditions (see Section 24.1.6).

Scheme 2 Convenient Approaches to 1,1-Bis(organooxy)allenes^[3,4]

Allenes with an organooxy and a nitrogen or a phosphorus functionality at the same carbon can be prepared in good yields, as can 1,1-bis(organochalcogeno)allenes; however, all of these compounds have limited synthetic use. This also applies to the other subclasses covered in Sections 24.1.7 –24.1.15.

1,1-Bis(heteroatom-functionalized) alk-1-enes, which are covered in Sections 24.2.1 –24.2.19, are much more common; in fact, quite a number of these are very useful reagents or intermediates in organic synthesis. 1,1-Dihaloalk-1-enes, either with a combination of halogens or with two identical halogens, can be prepared by a wide variety of methods (Section 24.2.1), and usually in good yields, e.g. substitution of a silyl or a halo group in **8** by another halo group to yield **9**. Dehydrohalogenation of oligohaloalkanes, e.g. **10**, offers another route to 1,1-dihaloalk-1-enes, e.g. **11**. Wittig-type dihaloalkenations of carbonyl compounds with tetrahalomethanes and triphenylphosphine present a third, highly versatile route to 1,1-dihaloalk-1-enes **12** (X = Cl, Br, I) (**Scheme 3**). Bearing in mind that 1,1-dihaloalk-1-enes can easily be converted into acetylenes, the latter methodology offers a route from aldehydes and even ketones to terminal and 1,2-disubstituted acetylenes, including 1-halo-substituted alkynes. It is also possible to prepare 1,1-dihaloalk-1-enes by addition of halogens to 1-haloacetylenes, but in practice this is less important.

Scheme 3 Syntheses of Various 1,1-Dihaloalk-1-enes

1,1-Dihaloalk-1-enes are also the most important precursors to other 1-heteroatom-substituted 1-haloalk-1-enes, as one of the two halogen substituents can often be selectively replaced by an oxygen (Section **24.2.2**), a nitrogen (Section **24.2.4**), a chalcogen (Section **24.2.3**), a phosphorus (Section **24.2.5**), or another heteroatom functionality. Halogen –metal exchange on a 1,1-dihaloalk-1-ene in general leads to an alkylidenecarbenoid, which can undergo dimerization to yield a butatriene, cheletropic addition to an alkene to give an

alkylidenecyclopropane, or a Fritsch –Butenberg –Wiechell rearrangement (1,2-migration of an alkyl or an aryl group) to furnish a 1,2-disubstituted alkyne. Zinc carbenoids of this type can be cross coupled under palladium catalysis with aryl halides to furnish α -halostyrenes, or with alkenyl halides to give di- or oligohaloalka-1,3-dienes. In short, 1,1-dihaloalk-1-enes are important assets in the toolbox of synthetically oriented organic chemists.

1-Halo-1-(organooxy)alk-1-enes (Section 24.2.2), which are formally the enol ethers of acid halides, can also be regarded as synthetic equivalents of ketene O,O-acetals. Due to the electron-withdrawing effect of the halogen substituents (if chlorine or fluorine), they are usually more reactive toward nucleophiles. 1-Bromo- and 1-iodo-1-(organooxy)alk-1-enes, on the other hand, are electron-rich alkenes and are thereby more reactive toward electrophiles. The most versatile preparations of 1-halo-1-(organooxy)alk-1-enes **15** are by addition of alcohols across the triple bond of a 1-haloalk-1-yne, e.g. **14**, generated in situ from a 1,1-dihaloalk-1-ene, e.g. **13**, or by formal nucleophilic substitution occurring by a sequence of nucleophilic addition and elimination on a tetrasubstituted 1,1-dihaloalk-1-ene **16**, to give **18** via **17** (Scheme 4). A third practical method is by elimination of hydrogen halides or halogens from α -haloalkyl alkyl ethers or α,α -dihaloalkyl alkyl ethers, respectively. Additions of hydrogen halides, halogens, or other electrophiles to alkynyl ethers to give 1-halo-1-(organooxy)alk-1-enes are definitely less important.

Scheme 4 Two Approaches to 1-Halo-1-(organooxy)alk-1-enes

Like 1,1-dihaloalk-1-enes, 1-halo-1-(organooxy)alk-1-enes are versatile reagents for various synthetic applications. The halogen can, for example, be selectively substituted by halogen –lithium exchange and subsequent trapping with a variety of electrophilic reagents. Under palladium catalysis, cross coupling with alkynes and vinylzinc halides leads to alkoxy-substituted 1,3-enynes and 1,3-dienes, which in turn have been used as building blocks for the construction of complex organic skeletons.

1-Halo-1-(organochalcogeno)alk-1-enes (Section 24.2.3) are mostly prepared by substitution of one heteroatom substituent on a 1,1-bis(heteroatom-functionalized) alk-1-ene, e.g. a metal for a halogen, a halogen for a chalcogen, an oxygen for a halogen, or by elimination of hydrogen halides or halogens from oligohaloalkyl alkyl thioethers. Wittig- and Horner –Wadsworth –Emmons-type alkenations of carbonyl compounds with appropriately substituted ylides and phosphorus-stabilized carbanions can also be favorably applied (Scheme 5).

Scheme 5 Five Important Methods for the Preparation of 1-Halo-1-(organochalcogeno)alk-1-enes^[5–11]

Additions of hydrogen halides or halogens to a 1-(organochalcogeno)acetylene as well as addition of chalcogenides to haloacetylenes constitute another type of route to this subclass of compounds. Since they contain at least three different functionalities, they play a definite role as building blocks for the construction of more complex organic molecules. They can be incorporated into other molecules by way of halogen–metal exchange with subsequent trapping by electrophiles, palladium- and other transition-metal-catalyzed cross-coupling reactions, nucleophilic displacement of the halogen, cycloadditions, and other methods. Dehydrohalogenations and dehalogenations lead to 1-(organochalcogeno)alk-1-ynes (see Section 24.3.4).

Basically, the same methodologies are applied to prepare and to utilize 1-nitrogen-functionalized 1-haloalk-1-enes, which are covered in Section 24.2.4, and 1-phosphorus-functionalized 1-haloalk-1-enes (Section 24.2.5).

1,1-Bis(organooxy)alk-1-enes (Section 24.2.6), on the other hand, commonly known as ketene O,O-acetals, are most frequently and best prepared by dehydrohalogenation of α -halo acetals, by elimination from other functionalized acetals, by O-alkylation of ester enolates, or by Wittig and Horner–Wadsworth–Emmons alkenations of carbonyl compounds, i.e. methods which are also applied toward the synthesis of other 1,1-bis(heteroatom-functionalized) alk-1-enes. Ketene O,O-acetals **19A** are electron-rich alkenes, with a nucleophilicity intermediate between that of enols and enamines. They have an energetically high-lying HOMO with the highest electron density at the β -carbon as expressed by resonance structure **19B** (Scheme 6). This causes electrophiles (e.g., halogens, alkyl halides, acyl halides, silyl trifluoromethanesulfonates) to attack at this position, and the initial adducts **20** typically undergo either elimination of hydrogen halide to provide β -substituted ketene O,O-acetals **21** or elimination of an alkyl halide to yield β -substituted esters **22**. In reactions with electron-deficient α,β -systems, such as electron-poor alkenes and dienes as well as aldehydes and ketones, regular ketene O,O-acetals usually form [2 + 2] and [2 + 4] cycloadducts. These adducts can undergo ring opening again to give acyclic products, frequently with a restored and more highly substituted ketene O,O-acetal subunit.

Scheme 6 General Reaction Pathways of Ketene O,O-Acetals with Electrophilic Reagents

The mixed ketene acetals with one organooxy (OR^1) and one organochalcogeno group (SR^1 , SeR^1 , TeR^1), as presented in Sections 24.2.7 and 24.2.8, are less important than the ketene *O,O*-acetals, and can also be prepared by the same methods as the other 1,1-bis(heteroatom-functionalized) alk-1-enes. Due to the number of examples and the richness of their chemistry, the 1-nitrogen-functionalized 1-(organooxy)alk-1-enes, commonly called ketene *O,N*-acetals, as presented in Section 24.2.9, are the most important among these mixed acetals. There are 55 methods discussed for the synthesis of this subclass, a few with additional variations, and they vary with respect to different starting materials and reagents, as well as differing reaction principles. Among the most generally applicable methods are the nucleophilic substitution of a halogen in a 1-nitrogen-functionalized 1-haloalk-1-ene (an α -haloamine) 23 by an organooxy group, the reaction of 2-acceptor-substituted ketene *O,O*-acetals 24 with nitrogen nucleophiles, the treatment of *O,O*-dialkyl dithiomalonates 25 with 2 equivalents of ammonia or a primary or a secondary amine, as well as the deprotonation with appropriate bases of [alkoxy(alkyl) (dialkylamino)]carbenium salts 26 (Scheme 7), which are readily accessible by alkylation of carboxamides or carboximidates. Elimination from aldehyde *O,N*-acetals with an appropriate leaving group in the α -position, or from *N,N*-dialkylcarboxamide acetals, additions of CH_2 -acidic compounds to dialkoxy(amino)carbenium salts, to dialkoxymethanediamines, to (trialkoxy)methanediamines, or to alkyl cyanates, constitute other reasonably general routes to ketene *O,N*-acetals. Such moieties have also been generated in a large variety of heterocyclic environments as exemplified in Section 24.2.9.

Scheme 7 Ketene *O,N*-Acetals from Various Precursors

Naturally, ketene *O,N*-acetals are even more nucleophilic than ketene *O,O*-acetals and, as a consequence, they rapidly react with a variety of electrophiles. Among the notable transformations are the substitutions of a β -hydrogen in a β -unsubstituted ketene *O,N*-acetal by, for example, trichloro-1,3,5-triazine, ortho esters, isocyanates, ketenes, α,β -unsaturated carbonyl compounds, alkynes, and other carbon as well as heteroatom electrophiles, which all give additionally functionalized ketene *O,N*-acetals.

While 1-phosphorus-functionalized 1-(organooxy)alk-1-enes (see Section 24.2.10) are of minor importance, except that those bearing a phosphonate substituent are synthetic equivalents of β -aminophosphonic acids, the ketene *S,S*-acetals (see Section 24.2.11), systematically named 1,1-bis(organosulfanyl)alk-1-enes, constitute one of the more common subclasses of the whole category covered in this volume. Most of the methods for the synthesis of ketene *S,S*-acetals are analogous to those for other 1,1-bis(heteroatom-substituted)alk-1-enes, yet there are some unique routes too. The alkylation of dithiocarboxylic acids and their derivatives (including trithioortho esters) is one such method, which has several variations (Scheme 8). Another peculiar approach to ketene *S,S*-acetals is by direct or indirect elimination of water from 2-hydroxyalkanal *S,S*-acetals, which are easily prepared by addition of metalated formaldehyde *S,S*-acetals or 1,3-dithianes and analogues to carbonyl compounds. When a trimethylsilyl group is present in the initial *S,S*-acetal, as in 27, this corresponds to a Peterson alkenation of the carbonyl compound 28, leading to 29 in good to very good yields for many examples. The most versatile synthesis of ketene *S,S*-acetals, however, is by twofold alkylation of the adducts obtained from deprotonated weakly or strongly CH-acidic compounds 30 and carbon disulfide (Scheme 9).

Scheme 8 Methods for the Preparation of Ketene *S,S*-Acetals

Scheme 9 Ketene *S,S*-Acetals from Carbanions of CH-Acidic Compounds and Carbon Disulfide

Since their discovery in 1910,^[12] these compounds have become well-established versatile intermediates in organic synthesis. Apart from the fact that they contain a masked carbonyl group, their main value originates from the stabilizing effect that sulfur exerts on both positively and negatively charged adjacent centers. This makes the double bond in ketene S,S-acetals prone to either nucleophilic or electrophilic attack. Thus, ketene S,S-acetals have served as precursors to many classes of organic compounds.

Just like the other 1,1-bis(heteroatom-functionalized) alk-1-enes with two different heteroatom substituents, the analogues of ketene S,S-acetals with one organosulfanyl and one other heteroatom substituent such as organoselanyl, organotellanyl (see Section 24.2.12), diorganoamino (see Section 24.2.13), diorganophosphoryl, and bis(organooxy)phosphoryl (see Section 24.2.14), as well as Se,Se-, Se,Te-, and Te,Te-analogues of the ketene S,S-acetals (Sections 24.2.15 and 24.2.16), in some case have certain features that may be advantageous for synthetic applications, but all of these subclasses are less important. Basically, the synthetic approaches are the same as those established for many of the other 1,1-bis(heteroatom-functionalized) alk-1-enes.

Ketene *N,N*-acetals, which are dealt with in Section 24.2.17, by far outnumber any of the other ketene acetals and their analogues. Unless they are substituted with electron-withdrawing groups, ketene *N,N*-acetals are extremely electron rich and are thereby nucleophilic alkenes; however, they can be easily prepared and handled. Although several of the more than 75 methods listed in this section do have close similarities, their sheer number indicates the broad accessibility of the members of this subclass. Again, there are basic methods which are analogous to those that have already been discussed for other subclasses in the corresponding sections, but there are also several which are specific for ketene *N,N*-acetals. The more general and therefore important are the transformations of anhydrides, esters, or amides **31** by treatment with tetrakis(dimethylamino)titanium, the addition of amines to various 2-substituted alkynamines **32**, the reaction of chloroformamidinium chlorides **33** (prepared from tetraalkylureas or tetraalkylthioureas and phosgene) or other formamidinium cation derivatives with CH-acidic compounds (including cyclopentadiene) or with methyllithium (Scheme 10). Since a wide range of ketene S,S-acetals **34** are so conveniently prepared by addition of carbanions and carbanion equivalents to carbon disulfide with subsequent twofold alkylation, facile transformation to ketene *N,N*-acetals by treatment with primary or secondary amines is also a versatile and quite general method.

Scheme 10 The Four Most General and Important Methods for the Preparation of Ketene *N,N*-Acetals

In addition to ketene *N,N*-acetals, there are various other 1,1-bis(nitrogen-functionalized) alk-1-enes with two azo, two azido, or two nitro functionalities. Their preparations and chemical and physical properties are described in subsection [24.2.17.3](#). All are rather hazardous compounds; in fact, the 1,1-dinitroalk-1-enes are explosives and therefore their chemistry has only been studied more recently. Among them, 2,2-dinitroethene-1,1-diamine **35** also known as Fox-7 or DADNE, is a high-performance explosive. It is prepared in 2 steps from the imidazolidinedione derivative **35** ([Scheme 11](#)).^[13] Except for this application, this product subclass has had very limited practical use in organic synthesis.

Scheme 11 Preparation of 2,2-Dinitroethene-1,1-diamine^[13]

On the other hand, alkenes carrying both a nitrogen and a phosphorus (Section [24.2.18](#)) or two phosphorus substituents (Section [24.2.19](#)) at the same carbon atom, can be valuable synthetic intermediates en route to other phosphorus-containing compounds. The most common nitrogen functionalities in such alkenes are acylamino, diorganoamino, and isocyanato groups, while the most popular phosphorus substituents are diethoxyphosphoryl, triphenylphosphonium, and diphenylphosphoryl. The best approach to such compounds is by Wittig- or Horner –Wadsworth –Emmons-type alkenations of aldehydes or ketones with the appropriate reagent ([Scheme 12](#)).

Scheme 12 Synthesis of a 1,1-Bis(phosphorus-functionalized) Ethene by a Horner –Wadsworth –Emmons-Type Alkenation^[14]

Of the 1,2-bis(heteroatom-functionalized) acetylenes, one of the dihaloacetylenes, namely diiodoacetylene, is the longest known (dating back to 1865) compound,^[14] but all of the dihaloacetylenes have only limited use. Several of them have only been prepared for spectroscopic and structural characterization, and all of them are explosive

and highly toxic substances (see Section 24.3.1). Preparative syntheses are usually by elimination or pyrolytic fragmentation. Dichloroacetylene is rather easily obtained from trichloroethene (upon treatment with an appropriate base) and it can be reasonably safely handled when diluted with diethyl ether.

1-Heteroatom-functionalized 2-haloacetylenes with trialkylsilyl, alkoxy, organosulfonyl, organosulfanyl, and phosphoryl groups (see Section 24.3.2) have their specific applications as functionalized two-carbon building blocks in organic synthesis. In particular, the silylated haloacetylenes have been used to prepare nucleophilic acetylene reagents by halogen–metal exchange, and have also been applied in transition-metal-catalyzed cross-coupling reactions for the assembly of oligoacetylene frameworks. The trialkylsilyl-substituted 1-haloacetylenes are temporarily protected terminal acetylenes; they are best prepared by halogenation of (trialkylsilyl)acetylenes, e.g. 37, via their metal (silver, magnesium, copper, lithium, sodium) derivatives (Scheme 13). Other 1-heteroatom-functionalized 2-haloacetylenes, e.g. 38, 39, and 40, can be prepared in the same way or by elimination from 1-heteroatom-functionalized oligohaloalk-1-enes.

Scheme 13 Preparation of 1-Heteroatom-Functionalized 2-Haloacetylenes^[15–18]

Bis(organooxy)acetylenes, as covered in Section 24.3.3, comprise only a few examples, and all of them are symmetrically disubstituted. Except for di-*tert*-butoxyacetylene, all of the dialkoxyacetylenes are extremely unstable compounds, but diphenoxyacetylene can be prepared and handled. Acetylenes with one organosulfanyl and a *tert*-butoxy substituent (Section 24.3.4) can be prepared, but are not very stable either. A 1-amino-2-(organooxy)acetylene (Section 24.3.5) has only been generated and identified by ionization–neutralization–reionization mass spectrometry. Only a rather limited number of 1-phosphorus-functionalized [with $P(OR^1)_2$, $P(O)(OR^1)_2$, PPh_3 and $P(S) t-Bu_2$ groups] have been reported in the literature (see Section 24.3.6).

Compounds with two identical organochalcogeno groups on the triple bond have received slightly more attention than those with two different groups (Section 24.3.7). Bis(organosulfanyl)acetylenes 41 can be obtained in high yields by the reaction of thiols with in situ generated dichloroacetylene^[19] or by treatment of disodium ethynediide (from acetylene and metallic sodium) in liquid ammonia with organo thiocyanates^[20,21] (Scheme 14). The selenyl and tellanyl analogues are accessible by similar methods. Acetylenes with one organochalcogeno and one other heteroatom functionality (NR^1_2 , PR^1_3) are even less important (Sections 24.3.8 and 24.3.9).

Scheme 14 Preparation of 1,2-Bis(organosulfanyl)acetylenes^[19–21]

N,N,N,N-Tetraalkylacetylenediamines, which can be prepared from trichloroethene and secondary amines in the presence of sodium amide, have found some applications in cycloaddition reactions (Section 24.3.10). Their key feature is their electron richness, which can be carried over into the cycloadducts. Acetylenes with one nitrogen and one phosphorus functionality, or with two phosphorus functionalities, (see Section 24.3.11) make up a significantly larger and more diverse group of compounds (Section 24.3.11). Bis(diphenylphosphino)acetylene (42) is best prepared from tetrachloroethene and lithium diphenylphosphide (Scheme 15).^[22] This compound has predominantly served as a ligand to form bridged bi- and oligonuclear metal complexes, while the bis(phosphine oxide) 43 derived from it has been applied as a dienophile in Diels –Alder reactions with dienes leading to a whole family of new ligands for transition metals.

Scheme 15 Preparation and Synthetic Application of Bis(phosphorus-functionalized) Acetylenes^[22,23]

Monoheteroatom-functionalized acetylenes comprise a much larger group of compounds than the difunctionalized acetylenes, and they correspondingly have much more importance for organic synthetic applications. 1-Haloalk-1-yne (Section 24.4.1) are easily prepared by any one of about 12 methods and further variations thereof. The direct halogenation of terminal acetylenes with alkali metal hypohalites or with *N*-halosuccinimide or elemental bromine or iodine is also convenient, as are dehydrohalogenations of 1,1-dihaloalk-1-ynes.

1-Haloalk-1-yne are important intermediates in transition-metal-catalyzed cross-coupling reactions for the straightforward synthesis of conjugated diynes, enynes, and enediynes, as well as larger arrays consisting of arene, alkene, and alkyne moieties. Hydroboration and hydrostannation reactions of 1-bromo- as well as 1-iodoalk-1-yne lead to stereodefined bifunctional alkene building blocks for stereoselective organic syntheses. 1-Haloalkynes are also precursors to a broad range of other functionalized alkynes.

1-(Organooxy)alk-1-yne and 1-(heterooxy)alk-1-yne (see Section 24.4.2) attract far less attention than 1-haloalk-1-yne, although they can undergo regioselective additions of either electrophiles or nucleophiles, and can serve as useful dienophiles in Diels –Alder reactions. The known compounds of this subclass comprise alkynyl *N,N*-diisopropylcarbamates, carboxylates, ethers, sulfonates, and dialkyl phosphonates, as well as siloxyacetylenes.

Obviously, 1-(organosulfanyl)alk-1-yne are the most important representatives among the subclass of 1-(organochalcogeno)alk-1-yne presented in Section 24.4.3. Since organochalcogeno groups can be easily removed after any synthetic transformation of such an alkyne, they not only serve as specific functionalities, but also as protecting groups that reveal terminal alkynes after deprotection. Organochalcogeno groups may best be

attached to terminal alkynes by treating metal acetylides with elemental chalcogens with subsequent alkylation, or with organochalcogeno halides or organo thiocyanates. Dehydrohalogenations of dihaloalkyl alkyl (or aryl) sulfides can also be applied to prepare (organosulfanyl)acetylenes. Oxidation of (organosulfanyl)acetylenes gives (organosulfinyl)- and (organosulfonyl)acetylenes, which are versatile intermediates in organic synthesis.

A reliable access to *N,N*-disubstituted acetylenamines, as discussed in Section 24.4.4, has only been known since 1963,^[24] but ever since, new methods have been developed that rely on substitution, elimination, isomerization, or fragmentation reactions (Scheme 16). These acetylenamines are extremely electron-rich compounds, yet reasonably stable, and thus they have been used in a broad range of addition and cycloaddition reactions, all leading to enamines, which can be favorably employed in further organic synthetic transformations.

Scheme 16 Four Major Routes to *N,N*-Disubstituted Ynamines^[25,26]

N-Acyl and *N*-sulfonyl derivatives of ynamines, which had been neglected for a long time, have more recently become available and turn out to be extremely versatile building blocks for organic synthesis (see Section 24.4.4.2). These *N*-functionalized ynamines, e.g. 44, 45, and 46 (Scheme 17) are electron-deficient analogues of *N,N*-dialkylalk-1-yn-1-amines, and they are much more stable toward hydrolysis than the latter. Compounds of this sort can therefore be favorably employed in cycloaddition reactions including transition-metal-catalyzed cascade oligocyclizations leading to heterocycles and heterooligocycles.

Scheme 17 *N*-Sulfonyl- and *N*-Acylalk-1-yn-1-amines^[27]

Among the other conceivable nitrogen-functionalized alk-1-ynes (see Section 24.4.3), i.e. alk-1-ynediazonium salts, 1-azidoalk-1-ynes and 1-nitroalk-1-ynes, the diazonium salts and azidoalkynes are extremely unstable and thus mainly of theoretical interest. 1-Nitroalk-1-ynes have been prepared and applied in cycloaddition reactions, but their importance is also limited.

Finally, 1-phosphorus-functionalized alk-1-ynes, (see Section 24.4.5) are accessible according to the same basic methods as the ynamines. The phosphorus substituents present in the known compounds comprise nearly all of the possible phosphorus functionalities. Notably, compounds with an electron-withdrawing phosphorus substituent have been employed in metal-catalyzed cross-coupling and cycloaddition reactions.

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Compounds with Two Carbon–Heteroatom Bonds

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Compounds with Two Carbon–Heteroatom Bonds
Volume 25:
Aldehydes

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General Introduction

Aliphatic and alicyclic aldehydes on one side and arenecarbaldehydes on the other are ubiquitous in organic chemistry. The manifold of methods available for their preparation comprises the major part of this volume. Product Class 1 (aliphatic and alicyclic aldehydes) is subdivided into 16 subsections and Product Class 6 (arenecarbaldehydes) is divided into 9 subsections. Each subsection discusses a particular group of synthetic approaches. They are ordered from degradative methods, through functional group interconversions, to C—C bond-forming reactions. Arguably, Product Classes 8 (α,β-unsaturated aldehydes) and 4 (2-heteroatom-substituted aldehydes) are next with respect to importance and volume. Further types of aldehydes considered worthy of treatment in their own right are 2-oxoaldehydes and heteroatom analogues (Product Class 2), 2,2-diheteroatom-substituted aldehydes (Product Class 3), ynals (Product Class 5), polyenals (Product Class 7), and 3-heteroatom-substituted aldehydes (Product Class 9).

Section **25.1.1** describes the synthesis of aliphatic and alicyclic aldehydes by oxidative cleavage. Ozonolysis of alkenes is a well-known method for the preparation of aldehydes. It can be used whenever no sensitive groups, in particular electron-rich arenes, are present in the substrate, e.g. **1** (**Scheme 1**).^[1]

Scheme 1 Oxidative Cleavages of C=C Bonds Introduced by the Allylation of an Enamine or the Allylboration of an Aldehyde^[1,2]

In the presence of such functionality in the alkene, dihydroxylation of the C=C bond by a catalytic amount of osmium(VIII) and stoichiometric quantities of a co-oxidant followed by periodate cleavage is the route of choice for

degrading alkenes, e.g. **2**, to aldehydes (**Scheme 1**). Often, the latter transformations can be combined in a one-pot reaction, the Lemieux –Johnson oxidation.^[3]

Section **25.1.2** focuses on syntheses of aldehydes by the oxidation of primary alcohols. The use of chromium(VI) oxidants for this purpose has been on the decline because of their carcinogenicity and because there are powerful alternatives. As demonstrated in **Scheme 2**, these include the Swern oxidation, i.e. the successive addition of activated dimethyl sulfoxide and triethylamine to the substrate,^[4] a low-temperature variant that is particularly effective for making polymerizable aldehydes, e.g. **3**,^[5] use of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and a co-oxidant (e.g., the preparation of aldehyde **4**),^[6] 1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess –Martin periodinane;^[7] e.g., the preparation of aldehyde **5**),^[8] 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX; e.g., the preparation of aldehyde **6**),^[9] tetrapropylammonium perruthenate/4-methylmorpholine *N*-oxide (TPAP/NMO),^[10] and dimethyl sulfoxide/*N*-chlorosuccinimide (Corey –Kim method).^[11]

Scheme 2 Oxidation of Primary Alcohols To Give Sensitive Aldehydes: Swern Oxidation, 2,2,6,6-Tetramethylpiperidin-1-oxyl/Sodium Hypochlorite, Dess –Martin Oxidation, and 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-Oxide Oxidation^[5,6,8,9]

Section **25.1.2** also describes the oxidation of other singly bonded functional groups including silyl ethers and sulfoxides. The former saves a deprotection step, whereas the latter is interesting because it links to possibilities such as introducing the sulfur atom as a metalated sulfoxide or as a benzenethiolate anion into the substrate, e.g. into the sulfide precursor of the substrate **7** (**Scheme 3**).^[12]

Scheme 3 Pummer Rearrangement of a Sulfoxide as a Conversion of an Aromatic Sulfide into an Aldehyde^[12]

The synthesis of aldehydes by rhodium- or ruthenium-catalyzed isomerization reactions is possible starting from allylic alcohols or allylic amines (the latter procedure requiring a subsequent hydrolysis step). This is the subject of Section 25.1.3. If a stereocenter results at C3 of the substrate, its absolute configuration can be controlled up to a value of 86% ee using allylic alcohols^[13,14] and perfectly starting from allylic amines with the use of chiral rhodium catalysts **8** (Scheme 4).^[15] The *R*-configured enamine (*R*)-**9** provides (+)-citronellal upon hydrolysis with dilute sulfuric acid and, in another two steps, (–)-menthol in the famous Takasago process (>4000 tons annually).

Scheme 4 Enantioselective Isomerizations of *N,N*-Diethylgeranylamine and *N,N*-Diethylnerylamine^[15]

Section 25.1.4 discusses the many methods available for the preparation of aliphatic aldehydes by the reduction of carboxylic acid derivatives (acid chlorides, esters, amides, nitriles, and others), one of the most common synthetic routes to these compounds. Notable examples for carrying out this transformation without overreduction include the diisobutylaluminum hydride reduction of *N*-methoxy-*N*-methylamides (Weinreb amides), which is the most reliable access to aliphatic aldehydes from carboxylic acid derivatives (see, for example, Scheme 5),^[16] and of nitriles, followed by hydrolysis of the resulting imine.^[17] Weinreb amides can be prepared under fairly mild conditions, and chemoselective reductions in the presence of esters or nitriles are possible.

Scheme 5 Reduction of a Weinreb Amide^[16]

Section **25.1.5** presents syntheses of aliphatic aldehydes via elimination or rearrangement reactions starting from glycols, epoxides, and halohydrins, as exemplified in **Scheme 6** by the pinacol rearrangement of 1,2-diphenylethane-1,2-diol^[18] and the semipinacol rearrangement of a steroid-based epoxide.^[19]

Scheme 6 Pinacol Rearrangement of a Glycol and Semipinacol Rearrangement of an Epoxide^[18,19]

The preparation of aliphatic aldehydes by methods involving protonation are detailed in Sections **25.1.6**. Asymmetric protonation of enols furnishes enantiomerically enriched aldehydes (**Scheme 7**).^[20]

Scheme 7 Enantioselective Protonation of an Enol^[20]

Aldehydes are formed by the hydrolysis of imines, acetals, enol ethers, and derivatives thereof. Conditions for these reactions are reviewed in Section **25.1.7**. Many of them are mild, using catalytic amounts of a Brønsted or Lewis acid,^[21] but non-acidic alternatives generally exist that enable the reactions to be performed in the presence of acid-sensitive functional groups. This allows, for example, the selective hydrolysis of enol ethers in the presence of acid-sensitive functional groups (**Scheme 8**).^[22]

Scheme 8 Hydrolysis of Enol Ethers Using Pyridinium 4-Toluenesulfonate/Water or Chlorotrimethylsilane^[21,22]

Most transition-metal-catalyzed additions of water across the C—C bond of a terminal alkyne provide a methyl ketone (Markovnikov addition). However, the formation of an aldehyde by the analogous anti-Markovnikov addition can also be achieved using ruthenium catalysts. This is described in Section 25.1.8 as a two-step procedure comprised of the regioselective hydrometalation of the terminal alkyne followed by oxidation of the carbon—metal bond. The first strategy is exemplified by the hydration of **Scheme 9**; it is based on the unique design of a bidentate ligand, which self-assembles.^[23]

Scheme 9 Ruthenium(II)-Catalyzed Anti-Markovnikov Hydration of a Steroidal Alkyne^[23]

The formylation of enolates and enols (see Section [25.1.9](#)) is a standard approach for the preparation of α -oxoaldehydes, which are valuable 1,3-bifunctional building blocks in organic synthesis. Enolates, which are commonly used, are formylated by alkyl formates (in crossed-Claisen condensations). For enols, the formylating agents include chloroformamidine salts (Vilsmeier reagents) or, as a milder alternative, dimethylformamide acetals ([Scheme 10](#)).^[24]

Scheme 10 Formylation of an Enolizable Ketone with Dimethylformamide Dimethyl Acetal^[24]

A variety of strategies are available for the one-carbon homologation of aldehydes, as presented in Section [25.1.10](#). Several of these are two-step processes that proceed via intermediates (e.g., nitriles, enol ethers) that are presented here for convenience, but are also discussed as single-step methods in other sections of the volume. One strategy is the combination of an aldehyde with nitromethane via a nitro-aldol reaction followed by a dehydration to give a nitroalkene (Henry reaction). This is transformed into the homologated aldehyde (Nef reaction) either directly or after reduction of the C=C bond. This homologation is applicable to highly functionalized substrates such as the aminosugar shown in [Scheme 11](#).^[25]

Scheme 11 Homologation of an Aldehyde via the Nef Reaction^[25]

Section [25.1.11](#) discusses the hydroformylation of alkenes, focusing in particular on laboratory-scale applications of this industrially important process. A mixture of hydrogen and carbon monoxide is the formylating agent and a rhodium complex is the catalyst. The rate and regioselectivity of these reactions are highly influenced by the catalyst and the substituents on the alkene substrate. Yet, the most remarkable property of these substituents is their great compatibility with the reaction conditions. An example, in which stereoselectivity of the hydroformylation is directed by a phosphine-containing substituent, as an elaboration of an Evans aldol addition product [10](#), is shown in [Scheme 12](#).^[26] [Scheme 12](#) also features the first general hydroformylation procedure working at room

temperature and ambient pressure.

Scheme 12 Regioselective Hydroformylations of Alkenes^[26,27]

Section **25.1.12** illustrates the preparation of aliphatic aldehydes by one-carbon extensions of alkyl halides through "nucleophilic formylation". The oldest and arguably still most common formyl anion equivalent is lithiated 1,3-dithiane, but there are many others. In any case, a deprotection step is required to unmask the aldehyde function. If unmasking an alkylated 1,3-dithiane is impossible because of the presence of labile functional groups elsewhere in the molecule, one can employ lithiated 5-methyl-1,3,5-dithiazinane as a reagent because its alkylation products can be unmasked under particularly mild conditions (**Scheme 13**).^[28]

Scheme 13 C₁-Extension of an Alkyl Halide Delivering an Acid-Labile Aldehyde^[28]

A complementary C₁-elongation approach to aldehydes is the one-carbon extension of organometallic compounds, mostly alkyllithium compounds or their Grignard analogues, by an appropriate derivative of formic acid (Section **25.1.13**). This strategy is probably the most frequently used chain-extending synthesis of aliphatic and alicyclic aldehydes of all. Its feasibility hinges upon the stability of the initially formed tetrahedral intermediate

under the reactions conditions; if it were not resistant to expulsion of the leaving group, the subsequent addition of a second molecule of the organometallic reagent would result in the formation of a secondary alcohol. Usually, N,N-disubstituted formamides are employed as formylating reagents (see, for example, **Scheme 14**)^[29] including the Weinreb amide derived from formic acid.^[30]

Scheme 14 C₁-Extension of an Organolithium Compound, Obtained with 96% ee by Hoppe's Lithiation, with Dimethylformamide^[29]

The C-alkylation of enolates derived from aldehydes is not a simple process. Generally, it suffers from competing aldol reactions, and sometimes from competing O-alkylation. Techniques to overcome or circumvent these undesired reactions are described in Section **25.1.14**. Most of the literature examples for direct alkylations describe the C2 alkylation of 2-branched aldehydes (see, for example, **Scheme 15**),^[31] in which the rate of aldolization is slowed down.

Scheme 15 Regio- and Diastereoselective C2-Alkylation of an Aldehyde^[31]

Aldehydes without branching at C2 can be 2-alkylated after transforming them into the corresponding silyl enol ethers, enamines, imines, or imine derivatives, and this is also discussed. A textbook reaction of the latter class is Enders' SAMP/RAMP technology,^[32] an example of which is shown in **Scheme 16**.^[33] "Newcomers" with respect to enantioselective C—C bond formations at C2 of aldehydes, namely organocatalytic intramolecular alkylations^[34,35] and Michael additions,^[36] are also mentioned.

Scheme 16 Reagent-Controlled Stereoselective C2-Methylation of an Aldehyde-Derived SAMP Hydrazone^[33]

Section **25.1.15** reviews conjugate addition reactions to α,β -unsaturated aldehydes to give three-carbon extended products. The conjugate addition of organometallic species is dominated by organocuprates, which generally provide very good regioselectivity in 1,4-additions to α,β -unsaturated carbonyl compounds, although examples using aldehydes are relatively rare and may be complicated by competing side reactions (**Scheme 17**).^[37] Organozinc and organoboron reagents represent valuable alternatives.

Scheme 17 Michael Addition to an α,β -Unsaturated Aldehyde^[37]

Section **25.1.15** also covers Claisen and oxy-Cope rearrangements as means of elongating aldehydes and α,β -unsaturated aldehydes by a three-carbon unit. **Scheme 18** illustrates this by a regioselective Claisen rearrangement^[38] and by the chirality transfer from a modified Evans aldol product in a siloxy-Cope rearrangement.^[39]

Scheme 18 C₃-Elongation of Aldehydes by Claisen or Cope Rearrangement^[38,39]

α,β -Unsaturated aldehydes are electron-deficient dienophiles. Accordingly, they undergo [4 + 2]-cycloaddition reactions with a wide range of 1,3-dienes, particularly those bearing electron-donating substituents, giving

cyclohexenecarbaldehydes, as presented in Section 25.1.16. A variety of different reaction conditions and catalysts have been used to promote these reactions. Particularly intriguing are organocatalytic enantioselective intermolecular^[40,41] and intramolecular Diels –Alder reactions (Scheme 19).^[42]

Scheme 19 An Organocatalytic Enantioselective Intramolecular Diels –Alder Reaction of an α,β -Unsaturated Aldehyde^[42]

Section 25.4, covering 2-heteroatom-substituted aldehydes, comprises considerably more space than one would have found appropriate in the 1990s. This is because it now features one of the showcases of asymmetric catalysis, namely the enantiocontrolled organocatalytic C2-heterofunctionalization of aldehydes. Fascinating developments comprise enantioselective C2-aminations,^[43,44] C2 oxygenations,^[45–47] C2 chlorinations,^[48] and even C2 fluorinations^[49] using this approach. Scheme 20 highlights this approach embellished as a tandem 1,4-reduction/enolate fluorination.^[50]

Scheme 20 Stereodivergent, Enantioselective Organocatalytic Syntheses of α,β -Fluorinated Aldehydes^[50]

Arenecarbaldehydes are occasionally synthesized by oxidative cleavage reactions (see Section 25.6.1), several of which are also applicable to aliphatic aldehydes, but this is not the case for the example selected in Scheme 21.^[51] There, an arenecarbaldehyde is prepared from an enamine by a dihydroxylation/oxidative diol cleavage protocol; because the C=C bond to be cleaved belongs to an enamine, bond scission can be effected using sodium periodate and no osmium(VIII) catalyst at all. Oxidative decarboxylations of arylacetic acids including arylglycines and mandelic acid derivatives yield arenecarbaldehydes too.^[52]

Scheme 21 Synthesis of a 2-Nitrobenzaldehyde by the Formation and Oxidative Cleavage of a C=C Bond^[51]

Section [25.6.2.1](#) compiles oxidants for obtaining arenecarbaldehydes by attacking a benzylic methyl group. Included are cerium(IV) and hypervalent iodine compounds as well as 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone for the laboratory scale and dihalogenation/hydrolysis as the classical procedure, or anodic oxidation as an innovative process on an industrial scale. A multitude of reagents effects the oxidation of arylmethanols to yield arenecarbaldehydes (Section [25.6.2.2](#)). Many of them have precedence in the chemistry of aliphatic aldehydes, whereas particularly mild oxidants are usually also known to oxidize allylic alcohols to α,β -unsaturated aldehydes. Catalysts making oxygen a viable oxidant for this transformation have been under intense investigation on the laboratory scale (see, for example, [Scheme 22](#)),^[53] aiming at making such systems amenable to the production scale. Benzylic halides give aldehydes by the Kornblum or the Sommelet reactions. Electron-rich benzylic amines provide aldehydes after a base-catalyzed rearrangement of *N*-benzylimines, giving *N*-benzylideneamines, followed by hydrolysis.

Scheme 22 Polymer-Supported Perruthenate Catalyzed Oxidation of an Arylmethanol to an Arenecarbaldehyde
^[53]

Reduction of arenecarboxylic acids and their derivatives to aldehydes (Section [25.6.4](#)) has the inherent challenge of avoiding overreduction to the corresponding benzylic alcohol. This is generally possible by the same reagents that effect the analogous oxidations in the aliphatic series (see Section [25.1.4](#)). In contrast, hydrogenation and hydrogenolysis are much more useful techniques in the aromatic vs aliphatic series, particularly starting from nitriles or aroyl chlorides (Rosenmund reduction). [Scheme 23](#) shows a dihydrooxazole moiety as one of the many other carboxylic acid derivatives that are suitable, in principle, for proceeding to an arenecarbaldehyde by reduction (this motif came into the molecule because it controlled the absolute configuration of its biaryl axis); in spite of the considerable steric hindrance in this example, reduction is possible without affecting the ester group.
^[54]

Scheme 23 Reduction of a Dihydrooxazole-Derived Iminium Salt to an Arenecarbaldehyde Using L-Selectride^[54]

Hydrolysis of arenecarbaldehyde derivatives (Section 25.6.4), such as (dihalomethyl)arenes, acetals, and oximes, is commonly used for establishing an aldehyde function, particularly in protecting-group chemistry. Many methods that avoid the highly acidic conditions used in many traditional procedures have been developed. For example, the silver(I)-mediated hydrolysis of (dihalomethyl)arenes leaves the hydrolysis-prone aryl acetate groups intact in the example shown in **Scheme 24**.^[55] Often, this kind of hydrolysis terminates two-step syntheses of arenecarbaldehydes initiated by the *gem*-dihalogenation of substituted toluenes according to Section 25.6.2.1.4

Scheme 24 Silver-Assisted Hydrolysis of a (Dibromomethyl)arene^[55]

Section 25.6.5 is entitled "Synthesis by Formylation of Arylmethyl Reagents" and focuses with equal weight on aryllithium and aryl Grignard compounds. The formylating agent is almost invariably dimethylformamide even if the analogous Weinreb amide appears to be slightly superior.^[30] The virtue of this method cannot be overestimated. It stems very fundamentally from the variety of ways by which arylmetal reagents of both series can be prepared: (a) By deprotonation of an arene ring using an alkyllithium or a magnesium amide as the base; in the former case this is well-established technology (*ortho*-lithiation), while in the latter case the method is just emerging.^[56] (b) By the reduction of aryl halides using lithium metal (alone or in the presence of electron acceptors such as 4,4'-di-*tert*-butylbiphenyl) or magnesium turnings. (c) By the long-known bromine – or iodine –lithium exchange reactions relying mostly on butyllithium, occasionally on *tert*-butyllithium, or in special cases on mesityllithium^[57] as the metalating agent, or by the increasingly important halogen –magnesium exchange reactions (iodine –magnesium exchange with isopropylmagnesium bromide^[58] or diisopropylmagnesium;^[58] bromine –magnesium exchange using the isopropylmagnesium chloride –lithium chloride complex^[59] or lithium tributylmagnesate;^[60] bromine or iodine –magnesium exchange using the 1:1 complex formed from diisopropylmagnesium and lithium chloride).^[61] The main attraction of employing aryl Grignard compounds prepared by routes (a) or (c) is their outstanding tolerance for electrophilic groups in the substrate, as emphasized by the examples displayed in **Scheme 25**.^[56,62]

Scheme 25 Generation of Functionalized Aryl Grignard Compounds by Substituent-Directed Deprotonation or Iodine –Magnesium Exchange^[56,62]

Schlosser's base (potassium *tert*-butoxide/butyllithium) permits the efficient metalation even of unactivated arenes (**Scheme 26**).^[63]

Scheme 26 Metalation/Formylation of an Unactivated Arenecarbaldehyde Using Schlosser's Base Followed by

Dimethylformamide

Besides aryl C—M bonds, aryl C—H bonds can be formylated as discussed in Section 25.6.6. There are very few Friedel–Crafts-type formylations of arenes because formyl halides are quite labile, but formyl fluoride can be used, and formyl chloride is generated in situ from hydrogen chloride and carbon monoxide during the well-established Gattermann–Koch reaction. However, formyl halide surrogates have found wide application, notably in the Vilsmeier–Haack reaction ($\text{ClCH}=\text{NR}^1_2^+$). Modifications of the classical protocol have improved yields, shortened reaction times, broadened range of successful substrates, simplified product isolation, and reduced the environmental impact. They include the use of microwave irradiation, solid-supported substrates and/or reagents (Scheme 27),^[64] solvent-free conditions, or a fluorinated solvent.

Scheme 27 Vilsmeier–Haack Formylation of Arenes Using a Polystyrene-Bound Reagent^[64]

The importance of salicylaldehyde-based imines as "privileged ligands" in transition-metal complex catalysis has spurred great interest in the *ortho*-formylation of phenols. Traditional approaches such as the Reimer–Tiemann or Gattermann reaction have essentially given way to the Duff^[65] and related reactions,^[66] as exemplified in Scheme 28.

Scheme 28 Formylations Providing Substituted Salicylaldehydes^[65,66]

Conversion of an aryl halide (or trifluoromethanesulfonate) into an arenecarbaldehyde is readily achieved by palladium-catalyzed carbonylation (see Section 25.6.7). Quite low catalyst loadings (0.25–0.33 mol%) and carbon monoxide/hydrogen pressures (5 atm) are possible under the conditions documented in Scheme 29.^[67]

Scheme 29 Palladium-Catalyzed Formylation of Aryl Bromides^[67]

The final parts on arenecarbaldehyde preparations are Sections [25.6.8](#) and [25.6.9](#), which summarize how one can process pre-existing arenecarbaldehydes through C—C or C—X bond formations, respectively. Coverage in both cases is confined to the transformation of unprotected arenecarbaldehydes. The scope of what is reported is therefore limited and would be considerably larger if one included the chemistry of protected arenecarbaldehydes. If "third-party" substituents, which would overrule aldehyde function in dominating the reactivity, are absent, arenecarbaldehydes can be manipulated by either of two widely applicable strategies: (a) *ortho*-lithiation by Comins' method,^[68] i.e. via in situ formed aminoalkoxide intermediates as directing groups, followed by electrophilic functionalization (see, for example, [Scheme 30](#)),^[69] or (b) palladium-catalyzed substitution of arene-bound halogen atoms or trifluoromethanesulfonate groups by an organometallic or heteroatom nucleophile (see, for example, [Scheme 31](#)).^[70]

Scheme 30 *ortho*-Formylation of an Arenecarbaldehyde^[69]

Scheme 31 Palladium-Catalyzed Bromine –Phosphorus Exchange Reaction of an Arenecarbaldehyde^[70]

Volume 25 treats the preparations of polyenals and α,β -unsaturated aldehydes in Sections [25.7](#) and [25.8](#), respectively. Of the many reactions presented there, two stand out as being truly highlights: Hoffmann's C₆-extension of aldehydes by addition of a functionalized allylboronate, which provides $\alpha,\beta,\gamma,\delta,\epsilon$ -unsaturated aldehydes in a total of two steps ([Scheme 32](#)),^[71] and the "Russian synthesis" of vitamin A aldehyde by the acetal variant of Mukaiyama's aldol addition by a C₁₅ + C₅ strategy, which also consists of two steps ([Scheme 33](#)).^[72]

Scheme 32 Extension of an Aldehyde by a C₆-Reagent Delivering a Conjugated Trienal^[71]

Scheme 33 Extension of an Aldehyde by a C₄-Reagent Delivering the Conjugated Dienal Moiety of Vitamin A^[72]

The closing Section **25.9** is devoted to the synthesis of 3-heteroatom-substituted aldehydes. The most common route, i.e. the aldol addition, to the most important subclass of this family of compounds, i.e. to 3-hydroxyaldehydes, is exempted: In the *Science of Synthesis* system this reaction is classified as an alcohol synthesis. However, Section **25.9** is a goldmine for non-aldol accesses to 3-hydroxyaldehydes, and a comprehensive source of information on the synthesis of aldehydes with C—B, C—Si, C—Sn, C—S, C—N, C—P, and C—Hal bonds at C3.

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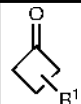

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Compounds with Two Carbon–Heteroatom Bonds
Volume 26:
Ketones

Cossy, J., in *Science of Synthesis*, **26** (2004), p.1

Ketones are among the most important organic compounds in terms of their occurrence and utility in chemical and biochemical transformations. This volume of *Science of Synthesis* covers the synthesis of ketones. Each author has described the most general and useful methods for the synthesis of a particular class of ketones. The parent ketones that are covered in this volume are shown in **Table 1** together with the sections in which they appear.

Table 1 Classes of Ketones Covered in Volume 26

Product Class and Method	Structural Formula	Section
aliphatic and alicyclic ketones	$R^1C(=O)R^2$	26.1
by oxidation of heterosubstituted alkanes R^1CHXR^2		26.1.1
by oxidation of alkanes and alkenes		26.1.2
by reduction of 1,2-diketones and derivatives $R^1C(=O)C(=X)R^2$, , - diheterosubstituted ketones $R^1C(=O)CX_2R^2$, -heterosubstituted ketones $R^1C(=O)CHXR^2$, enones, and ynones		26.1.3
from carboxylic acids and derivatives $R^1C(=X)Y$		26.1.4
from aldehydes R^1CHO		26.1.5
from thioketones $R^1C(=S)R^2$, acetals $R^1C(OR^3)_2R^2$, cyanohydrins, enol ethers $R^1C(OR^2)=CR^3R^4$, enamines, other ene derivatives, and related compounds		26.1.6
from alkynes, allenes, and ketenes		26.1.7
by fragmentation or rearrangement of epoxides, diols, and allyl alcohols		26.1.8
from ketones $R^1C(=O)R^2$		26.1.9
from enones $R^1R^2C=C(R^3)C(=O)R^4$		26.1.10
cyclobutanones		26.2
cyclopropanones		26.3
1,2-diketones and related compounds	$R^1C(=O)C(=X)R^2$	26.4
, -diheterosubstituted ketones	$R^1C(=O)CX_2R^2$	26.5
-heterosubstituted ketones	$R^1C(=O)CHXR^2$	26.6
ynones	$R^1C \quad CC(=O)R^2$ and $R^1C \quad C(CH_2)_nC(=O)R^2$	26.7
aryl ketones	$Ar^1C(=O)R^1$	26.8
enones	$R^1CH=CC(=O)R^2$ and $R^1CH=C(CH_2)_nC(=O)R^2$	26.9
- and more remotely functionalized cyano ketones, oxo ketones, and carboxy ketones and derivatives	$R^1C(=O) \text{---} (C)_n \text{---} C \quad N$, $R^1C(=O) \text{---} (C)_n \text{---} C(=X)R^2$, and $R^1C(=O) \text{---} (C)_n \text{---} C(=X)Y$; $n > 1$	26.10
- and more remotely functionalized ketones	$R^1C(=O) \text{---} (C)_n \text{---} CHXR^2$; $n > 1$	26.11

Within each product class, the synthetic methods are described and the number of methods vary depending on

the ketone class. The scope of the methods are described with representative examples, safety concerns, reaction schemes, and selected experimental procedures. Many methods are further subdivided into variations.

Section **26.1** is an introduction dealing with the general chemical properties of aliphatic and alicyclic ketones; the synthesis of these ketones is covered in Sections 26.1.1 –26.1.10. Topics covered in the introduction of Section 26.1 include thermochemistry, acid/base properties, hydrogenation, oxidation, hydration, the oxa-ene and Diels –Alder reactions, the frangomeric effect, regioselective pinacol-type coupling, bond dissociation energies, and radical chemistry, including Norrish type I and II processes.

The synthesis of ketones by oxidation of secondary alcohols is described in Section **26.1.1**. The most frequently used reagents are chromium(VI) oxide, pyridinium chlorochromate (**Scheme 1**),^[1] pyridinium dichromate, manganese(IV) oxide, tetrapropylammonium perruthenate, the Dess –Martin periodinane, and oxidants based on dimethyl sulfoxide (Swern oxidation). Also covered in Section **26.1.1** are oxidations of other functions such as halide, nitro (Nef reaction), and amino.

Scheme 1 Oxidation of Cycloheptanol to Cycloheptanone by Pyridinium Chlorochromate^[1]

The focus of Section **26.1.2** is on oxidation of alkenes and alkanes, excluding allylic and benzylic oxidations. The oxidation of alkenes to ketones can be achieved without the cleavage of the skeleton as in the Wacker oxidation or by the cleavage of the skeleton by using ozone or the osmium(VIII) oxide/sodium periodate procedure. The use of molecular oxygen for the oxidation of alkanes is important in both industrial and synthetic aspects. Substituted porphyrins can be used for the aerobic oxidation of alkanes in the presence of acetaldehyde (**Scheme 2**).^[2]

Scheme 2 Oxidation of an Alkane Using a Porphyrin –Metal Complex^[2]

Section **26.1.3** describes reduction of α -heterosubstituted ketones, enones, and ynones. 1,2-Diketones and related compounds can be transformed to ketones by reduction under acidic conditions, while reductive processes for α -hetero- and β , γ -diheterosubstituted ketones include the use of active metals, low-valent metal ions, electrolysis, or hydride reagents. Enones and ynones are transformed into ketones by catalytic hydrogenation, by conjugate reduction using transition-metal hydrides, or by dissolving metals. The synthesis of ketones from carboxylic acids and derivatives is covered in Section **26.1.4**. Substrates include acyl halides, carboxylic acids, acid anhydrides, esters, lactones, amides, nitriles, and dihydroimidazoles and, with careful selection of the organometallic reagent and control of the reaction conditions, ketones can be obtained in good yields without double addition of the nucleophile (**Scheme 3**).^[3]

Scheme 3 Preparation of Ketones from Acyl Chlorides and Grignard Reagents^[3]

Synthesis from aldehydes by substitution of the aldehyde hydrogen is discussed in Section **26.1.5**. This substitution is achieved mainly either by generating an acyl radical which then undergoes addition to an alkene, or by transition-metal-catalyzed hydroacylation. Syntheses from chalcogenoketones, acetals, enol ethers, enamines, and derivatives are found in Section **26.1.6**. These compounds often function as protected ketones and/or valuable reactive "umpolung" synthons. Formation of ketones by transformation of alkynes, allenes, and ketenes is described in Section **26.1.7**. Alkynes and allenes can be transformed to ketones by metal-catalyzed hydration or by a hydroboration–oxidation sequence, and ketenes to ketones by nucleophilic addition followed by hydrolysis. Methods involving fragmentation and rearrangement (Section **26.1.8**) are important due to the large number of applications of these transformations in the synthesis of natural products. Chemical transformations such as oxidative cleavage of alkenes and glycol derivatives, fragmentation of 1,3-dihetero-functionalized compounds (e.g., the Grob fragmentation,^[4] **Scheme 4**), the Eschenmoser fragmentation, and some photochemical fragmentations such as the Norrish type II are described. Important rearrangement reactions covered include the Claisen, oxy-Cope, pinacol, and semi-pinacol transformations, as well as

isomerizations of allylic alcohols and epoxides.

Scheme 4 Synthesis of a Medium-Sized-Ring Ketone by Grob Fragmentation^[4]

In Section **26.1.9**, dealing with the synthesis of ketones from other ketones, the emphasis is on the formation of C—H and C—C bonds with chemo-, regio-, stereo-, and enantioselectivity. The synthesis of ketones from enones by formation of C—C bonds in a 1,4-addition process is covered in Section **26.1.10**. Suitable Michael donors include Grignard reagents, cuprates, malonates (and derivatives), α -oxo esters, α -diketones, nitroalkanes, sulfones, and phosphonates. In this section, emphasis is placed upon asymmetric conjugated addition which has been dominated by metal catalysis as well as upon organocatalysis (**Scheme 5**).^[5]

Scheme 5 Enantioselective Conjugate Addition of Organosiloxanes^[5]

Sections **26.2** and **26.3** deal respectively with the synthesis of cyclobutanones and cyclopropanones as well as their derivatives. Cyclobutanones are synthetically useful building blocks for the synthesis of a wide range of natural and nonnatural complex molecules, and can be synthesized by cyclodialkylation of protected carbonyl groups or by carbonylation of metallacyclobutane complexes, but the most common methodology is probably the [2+2] cycloaddition between a ketene and an alkene (**Scheme 6**).^[6] In general, cyclopropanones are not isolated since they readily undergo ring opening or polymerization in the presence of acids, bases, electrophiles, or nucleophiles. Commonly, cyclopropanone chemistry has been performed from intermediates such as cyclopropanone hemiacetals and acetals, and Section **26.3** focuses on the preparation of such compounds. In contrast, cyclopropenones, also covered here, are stable compounds.

Scheme 6 [2+2] Cycloaddition of a Ketene to Cyclopenta-1,3-diene^[6]

The synthesis of ketones with an α -heteroatom such as 1,2-diketones (and derivatives), α,β -diheterosubstituted ketones, and α -monoheterosubstituted ketones are covered in Sections **26.4**, **26.5**, and **26.6**, respectively. Symmetrical 1,2-diketones are efficiently prepared reductively from carboxylic acids, while

the unsymmetrical compounds can be prepared by nucleophilic acylation of acid derivatives by acylmetal reagents. Syntheses of α,β -diheterosubstituted ketones covered in Section 26.5 include direct replacement of one or two hydrogens adjacent to the carbonyl, as well as more specific methods such as the Pummerer rearrangement, a very useful method of introducing a sulfur and an oxygen at the α -position of a ketone (Scheme 7).^[7] Section 26.6 focuses principally upon indirect methods of preparation of α -substituted ketones, many of which are extremely important synthetic intermediates, notably from acetate enol ethers, enols, enolates, silyl ethers, enamines, or enamides.

Scheme 7 A Pummerer Rearrangement^[7]

Ynones (Section 26.7) are valuable intermediates for heterocycle synthesis. Important methods covered include the acylation of metalated alkynes and the oxidation of alkynyl alcohols, as well as the Eschenmoser fragmentation of α,β -epoxyketones. The most important synthesis of aryl ketones (Section 26.8) is probably the Friedel–Crafts acylation but acylation of organometallic reagents is an attractive alternative. Other useful routes to aryl ketones include benzylic oxidation and aromatization of various cycloadducts. Section 26.9 deals with enones which appear as structural motifs in a diverse range of naturally occurring molecules. α,β -Unsaturated ketones, in particular, are widely used as building blocks in synthesis and comprise the main body of this section. Methods covered include allylic oxidation (Scheme 8),^[8] oxidation of allylic alcohols, acylation of organometallic reagents, as well as the aldol, Wittig, Baylis–Hillman, and Pauson–Khand reactions.

Scheme 8 Allylic Oxidation with a Selenium Reagent^[8]

In Sections 26.10 and 26.11, which cover the synthesis of γ,δ - and more remotely functionalized ketones, only the formation of the ketone function is described. Section 26.10 reviews the synthesis of ketones with an additional carbonyl, nitrile, or carboxy substituent, or equivalent, while Section 26.11 covers halo, hydroxy, sulfanyl, amino, and phosphono ketones, and derivatives. An overview of the more popular methods is presented without neglecting routes that can bring solutions to specific problems. For example, the ring opening of 1-methylpiperidin-4-one affords an α,β -unsaturated ketone with an amino group at a remote position (Scheme 9).^[9]

Scheme 9 Ring Opening of Cyclic Amino Ketones^[9]

The R^1 and R^2 groups in ketones (R^1COR^2) can be alkyl, alkenyl, alkynyl, or aryl. The simplest member is named trivially as acetone. Higher ketones can be named using functional class nomenclature, indicating the alkyl, alkenyl, alkynyl, and aryl groups associated with the carbonyl function in alphabetical order, e.g. methyl propyl ketone (MeCOPr). However, the preferred IUPAC nomenclature is substitutive, in which ketones are named as a derivative of the appropriate hydrocarbon by adding the suffix "one", e.g. pentan-2-one (MeCOPr). If a higher priority substituent is also present, the prefix "oxo" is used, e.g. 2-oxopropanoic acid (MeCOCO₂H).

Acetone is present in blood and urine and in large amounts in the urine of diabetics. It can be obtained by pyrolysis of tartaric and citric acids and of carbohydrates. It can be made from wood alcohol, from acetic acid, or by fermentation processes. Industrial methods to produce acetone include: (a) the catalytic dehydrogenation of propan-2-ol which is available from propene,^[10,11] (b) processes based on acetylene which, with steam, is passed over a heated mixed oxide catalyst, (c) the cumene hydroperoxide route to phenol,^[12] and (d) hydrolysis of an alkene –palladium salt complex with reoxidation of the palladium.^[13]

Acetone is also formed by hydration of propyne, by hydrolysis of 2-bromopropene, by hydrolysis of 2,2-dihalopropanes, from 2-hydroxy-2-methylpropanoic acid by oxidation, from acetyl chloride by action of zinc or dimethylcadmium(II), or from calcium acetate by heating.

Acetone is a colorless, water-soluble liquid (bp 56.2 °C, mp –94.9 °C, d^{20} 0.796, n_D 1.3602) of characteristic smell. It is highly inflammable and forms explosive mixtures with air or oxygen. It is miscible in all proportions with other organic solvents such as alcohols and ethers. Acetone is a good organic solvent and can dissolve some inorganic salts such as potassium iodide and potassium manganate(VII).

Acetone gives, with sodium nitroprusside solution followed by the addition of alkali, a red color which changes to violet on addition of acetic acid.^[14] Acetone and other ketones can be detected by chromatography as derivatives such as the 2,4-dinitrophenylhydrazone.^[15]

The simplest ketones are water-soluble liquids with pleasant odors and the higher members are low-melting solids. The physical properties of the simpler aliphatic symmetrical ketones, are listed in [Table 2](#), those of cyclic ketones in [Table 3](#), those of unsymmetrical ketones in [Table 4](#), those of aryl ketones in [Table 5](#), and those of unsaturated ketones in [Table 6](#).

The unsaturation can be a C=C or C–C bond conjugated with the ketone functionality.

Table 2 Physical Properties of Symmetric Aliphatic Ketones^[16]

Compound	Formula	mp (°C)	bp (°C)	d (g · mL ^{–1})	Refractive Index n_D^{20}	Ref
pentan-3-one	EtCOEt	–42	102	d^{20} 0.8138	1.3922	[16]
heptan-4-one	PrCOPr	–33	144	d^{20} 0.8145	1.4069	[16]
2,4-dimethylpentan-3-one	iPrCOiPr	–	124	d^{20} 0.8108	1.4001	[16]

nonan-5-one	BuCOBu	–6	186	d 0.818	1.4210	[16]
2,6-dimethylheptan-4-one	iBuCOiBu	–	168	d^{20} 0.8053	1.4121	[16]
3,5-dimethylheptan-4-one	s-BuCOs-Bu	–	162	d^{14} 0.8260	1.4193	[16]
2,2,4,4-tetramethylpentan-3-one	t-BuCOt-Bu	–	152	d^{18} 0.8240	1.4195	[16]
undecan-6-one	Me(CH ₂) ₄ CO(CH ₂) ₄ Me	14	226	d^{20} 0.8262	–	[16]
2,8-dimethylnonan-5-one	iPr(CH ₂) ₂ CO(CH ₂) ₂ iPr	–	226	–	–	[16]
3,3,5,5-tetramethylheptan-4-one	EtMe ₂ CCOCMe ₂ Et	–	196	–	–	[16]
3,5-diethylheptan-4-one	Et ₂ CHCOCH ₂ Et ₂	–	203	–	–	[16]
tridecan-7-one	Me(CH ₂) ₅ CO(CH ₂) ₅ Me	31	264	d^{30} 0.825	–	[16]
pentadecan-8-one	Me(CH ₂) ₆ CO(CH ₂) ₆ Me	41	–	–	–	[16]
heptadecan-9-one	Me(CH ₂) ₇ CO(CH ₂) ₇ Me	53	–	–	–	[16]
nonadecan-10-one	Me(CH ₂) ₈ CO(CH ₂) ₈ Me	58	–	–	–	[16]
tricosan-12-one	Me(CH ₂) ₁₀ CO(CH ₂) ₁₀ Me	69	–	d^{90} 0.7888	–	[16]
heptacosan-14-one	Me(CH ₂) ₁₂ CO(CH ₂) ₁₂ Me	78	–	d^{81} 0.7986	–	[16]
hentriacontan-16-one (palmitone)	Me(CH ₂) ₁₄ CO(CH ₂) ₁₄ Me	83	–	d^{90} 0.7947	–	[16]
pentatriacontan-18-one (stearone)	Me(CH ₂) ₁₆ CO(CH ₂) ₁₆ Me	88	–	d^{95} 0.7932	–	[16]

Table 3 Physical Properties of Symmetric Cyclic Ketones^[16]

Ketone	mp (°C)	bp (°C)	d^{20} (g · mL ^{–1})	Refractive Index n_D^{20}	Ref
cyclobutanone	–	99	0.938	1.4210	[16]
cyclopentanone	–51	130 –131	0.997	1.4370	[16]
cyclohexanone	–47	155	0.947	1.4500	[16]
cycloheptanone	–	179	0.951	1.4610	[16]
cyclooctanone	39 –41	195 –197	0.958	–	[16]

Table 4 Physical Properties of Unsymmetric Aliphatic Ketones^[16]

Compound	Formula	mp (°C)	bp (°C)	d (g · mL ^{–1})	Refractive Index n_D	Ref
ethyl methyl ketone (butan-2-one)	MeCOEt	–86	79.6	d^{20} 0.8058	n_D^{20} 1.7880	[16]
pentan-2-one	MeCOPr	–78	102	d^{20} 0.8089	n_D^{20} 1.3902	[16]
3-methylbutan-2-one	MeCOiPr	–	95	d^{16} 0.8046	n_D^{16} 1.3879	[16]
hexan-2-one	MeCOBu	–57	127	d^{20} 0.8095	n_D^{20} 1.4007	[16]
hexan-3-one	EtCOPr	–	125	d^{20} 0.8118	n_D^{20} 1.4007	[16]
4-methylpentan-2-one	MeCOiBu	–85	117	d^{20} 0.7908	n_D^{20} 1.3956	[16]
3-methylpentan-2-one	MeCOs-Bu	–	118	d^{20} 0.8145	n_D^{20} 1.4002	[16]
3,3-dimethylbutan-2-one	MeCOt-Bu	–	106	d^{16} 0.7999	–	[16]
heptan-2-one	MeCO(CH ₂) ₄ Me	–35	151	d^{20} 0.8111	n^{20} 1.4086	[16]
3-ethylpentan-2-one	MeCOCH ₂ Et ₂	–	138	–	–	[16]
4-methylhexan-2-one	MeCOCH ₂ s-Bu	–	146	–	–	[16]
heptan-3-one	EtCOBu	–39	149	–	–	[16]
octan-2-one	MeCO(CH ₂) ₅ Me	–16	173	d^{20} 0.8179	n_D^{20} 1.4154	[16]
nonan-2-one	MeCO(CH ₂) ₆ Me	–15	194	d^{22} 0.8188	n_D^{22} 1.4175	[16]
decan-2-one	MeCO(CH ₂) ₇ Me	14	209	d^{22} 0.8230	n_D^{22} 1.4263	[16]
undecan-2-one	MeCO(CH ₂) ₈ Me	15	225	d^{17} 0.8295	n_D^{17} 1.4300	[16]
dodecan-2-one	MeCO(CH ₂) ₉ Me	21	246/100 Torr	–	–	[16]
tridecan-2-one	MeCO(CH ₂) ₁₀ Me	29	250/100 Torr	d^{28} 0.8229	–	[16]

tetradecan-2-one	MeCO(CH ₂) ₁₁ Me	34	207/100 Torr	–	–	[16]
pentadecan-2-one	MeCO(CH ₂) ₁₂ Me	39	294	d^{39} 0.8182	–	[16]
hexadecan-2-one	MeCO(CH ₂) ₁₃ Me	43	230/100 Torr	–	–	[16]
heptadecan-2-one	MeCO(CH ₂) ₁₄ Me	48	246/110 Torr	d^{48} 0.8140	–	[16]
octadecan-2-one	MeCO(CH ₂) ₁₅ Me	52	251/100 Torr	–	–	[16]
nonadecan-2-one	MeCO(CH ₂) ₁₆ Me	55	266/110 Torr	d^{56} 0.8180	–	[16]

Table 5 Physical Properties of Aryl Ketones^[16]

Compound	mp (°C)	bp (°C)	d^{20} (g · mL ⁻¹)	Refractive Index n^{20}	Ref
acetophenone	20.5	202	1.030	1.5320	[16]
propiophenone	18	218	1.009	1.5250	[16]
benzophenone	48 –49	305	–	–	[16]
4-(dimethylamino)benzophenone	88 –90	–	–	–	[16]
4,4'-bis(dimethylamino)benzophenone (Michler's ketone)	174 –176	–	–	–	[16]

Table 6 Physical Properties of Unsaturated Ketones^[16]

Compound	mp (°C)	bp (°C)	d^{20} (g · mL ⁻¹)	Refractive Index n^{20}	Ref
but-3-en-2-one	–	36.5 –36.8/145 Torr	0.842	1.4110	[16]
pent-3-en-2-one	–	121 –124	0.862	1.4370	[16]
cyclopent-2-enone	–	64 –65/19 Torr	0.980	1.4810	[16]
cyclohex-2-enone	–53	168	0.993	1.4880	[16]
cyclohept-2-enone	–	–	0.993	1.4940	[16]
but-3-yn-2-one	–	85	0.870	1.4060	[16]

The length of the C=O bond in ketones is about 1.20 Å according to the determination by electron diffraction and by microwave spectroscopy. The length of the bond increases as its polarity decreases.^[17] The conjugation of the C=O bond with a C=C, C–C, or C–N bond has only a small influence on the C=O distance. For example the C=O bond length in acetone is 1.22 Å^[17] and that in 2-oxopropanenitrile is 1.226 Å.^[18]

The strong C=O bonds have relatively short lengths. In acetone the bond energy is 160.0 kcal · mol⁻¹.^[19]

Dipole moments are usually determined by studying the dielectric constant of solutions and by measurement of the Stark effect on microwave transitions.^[20] The dipole moments of some carbonyl compounds are reported in **Table 7**.^[21-23]

Table 7 Dipole Moments of Ketones^[21-23]

Compound	Dipole Moment	Method	Ref
acetone	2.90	Stark effect on microwave spectra	[21]
acetophenone	2.97	dielectric-constant method	[22]
cyclohexanone	3.08	computation from experimental values	[23]

Adjacent alkyl groups increase the polarity of the C=O bond. The conjugation of the carbonyl bond with a C=C or C–C bond has only a small influence on the C=O dipole moment as in the case of the bond lengths. As a first approximation, one might expect that the dipole moment of an aromatic ketone and that of the corresponding aliphatic compound would be nearly the same but, because of the greater polarizability of the

phenyl group in the near neighborhood of a dipolar group, the dipole moment of the aromatic compound is slightly larger. This is true for *meta*-directing substituents, but not for *ortho*- and *para*-directing substituents.

Ionization energies can be determined by extrapolation of the Rydberg series in the vacuum ultraviolet spectra of the molecules, or from the appearance potentials of the ions in a mass spectrometer, or by studying the photoionization efficiency curves.^[24] The first of these methods yields the energy difference between the ground states of the ion and of the molecule, both of these states being at the zeroth vibrational level; this spectroscopic value is an adiabatic ionization energy. In the second method the transition is considered to be so fast that the nuclei do not change their position during the transition. The ion is in a vibrational level frequently above that of the zeroth level; the electron-impact method is supposed to yield the ionization energy. The vertical ionization energies (I_v) are equal or greater in magnitude than the adiabatic energies (I_a). Both I_v and I_a for different ketones are reported in **Table 8**.

Table 8 Ionization Energies of Ketones^[25-30]

Compound	Ionization Energy (eV) ^a	Method	Ref
acetone	9.69	photoionization	[25,26]
	9.89	impact	[27]
	9.92	impact	[28]
ethyl methyl ketone	9.58	impact	[29]
	$I_v = 9.52, I_a = 9.48$	photoionization	[30]
pentan-2-one	$I_v = 9.41, I_a = 9.37$	photoionization	[30]

^a I_v = vertical ionization energy; I_a = adiabatic ionization energy.

Only the carbonyl stretching vibration, which is typical of infrared spectra of ketones, will be considered here. All compounds containing a carbonyl group show a very strong band in the region 1650–1850 cm⁻¹ (**Table 9**). The region in which this vibration appears is very narrow for a series of similar compounds. The position of the C=O band depends on the physical state of the compound, the inductive effect, electronic effects of neighboring substituents, ring strain, vibrational coupling between neighboring carbonyl groups, hydrogen bonding, enolization, and solvent effects.

Groups with a strongly electron-attracting inductive effect decrease the negative charge on the oxygen and the vibrational frequency increases relative to that of other ketones. The electron-repelling inductive effect of the ethyl group is larger than that of the methyl group and increases the negative charge on oxygen. This effect is responsible for the shift in stretching vibration from 1689 cm⁻¹ for acetophenone to 1694 cm⁻¹ for propiophenone. Other effects can add their influence to the inductive effect such as the variation of the force constant of adjacent bonds or the action of an electrostatic field created by a neighboring electronic cloud.

The mesomeric effect occurs when the C=O bond is conjugated either with another double bond or with a lone pair of electrons. Usually in this case, the carbonyl bond is more polarized, the force constant is smaller, and the stretching bands are shifted toward lower frequencies. For example, the carbonyl stretching frequency shifts from 1717 cm⁻¹ in cyclohexanone to 1675 cm⁻¹ in cyclohex-2-enone. If partial enolization occurs in a saturated ketone, the C=O stretching band intensity decreases and O—H and C=C stretching bands appear. A new C=O stretching band might also appear as a consequence of hydrogen bonding between the ketonic and enolic species. It should be pointed out that solvent effects are important and are characteristic for each ketone. Carbonyl stretching frequencies of some ketones in solution are reported in **Table 9**.

Table 9 Carbonyl Stretching Frequencies of Ketones^[31-36]

--	--	--

Compound	ν (C=O) (cm ⁻¹)	Ref
2,2,4,4-tetramethylpentan-3-one	1685	[31]
2,4-dimethylheptan-4-one	1695	[31]
cyclohexanone	1717	[32,33]
cyclopentanone	1750	[34]
cyclobutanone	1775	[31]
acetophenone	1689	[35]
propiophenone	1694	[35]
4-aminoacetophenone	1677	[36]
4-methylacetophenone	1687	[36]
4-fluoroacetophenone	1692	[36]
4-nitroacetophenone	1700	[36]
diaryl ketones	1665	[31]
cyclohex-2-enone	1675	[31]
-diketones	1720–1760	[31]
enolized -diketones	1675	[31]
-diketones	1720	[31]
-diketones enol form	1650	[31]

Simple carbonyl compounds present several regions of absorption below the Rydberg bands in the ultraviolet region. The first band is located near 4000 Å and corresponds to a very weak absorption ($\epsilon_{\text{max}} \sim 10^{-3}$), the second band near 3000 Å corresponds to a weak absorption ($\epsilon_{\text{max}} \sim 10$). The third and the fourth bands have a moderate to strong intensity and are near 1800 Å, and the fifth band with a very strong intensity is at shorter wavelength (1600 Å). The first two bands correspond to a transition from an oxygen 2p lone-pair orbital to the carbonyl antibonding π^* -orbital. The third and the fourth bands correspond to a transition of an oxygen 2p lone-pair electron to the carbonyl antibonding π^* -orbital. The fifth band corresponds to a transition of a σ electron to the antibonding σ^* -orbital.

The band around 4000 Å is due to a $n \rightarrow \pi^*$ transition where the ground state is a singlet and the excited state is a triplet. The intensity of this first band is small since these bands involve two states of different multiplicity and are therefore "forbidden". If the C=O bond is conjugated with a double bond or with a conjugated system, both the singlet–singlet and singlet–triplet $n \rightarrow \pi^*$ transitions will shift to longer wavelengths (red shift). In contrast to the effect of a double bond, alkyl groups cause a blue shift of the $n \rightarrow \pi^*$ transition of carbonyl compounds. It must be noted that these $n \rightarrow \pi^*$ bands have a very low intensity and that their wavelengths depend very much on the solvent. There is a large blue shift on going from a nonpolar solvent to a polar one. [37] The singlet–singlet $n \rightarrow \pi^*$ transitions and singlet–triplet $n \rightarrow \pi^*$ of some ketones are reported in Table 10.

The promotion of an n-orbital electron to a π^* -antibonding orbital leaves one electron in the n-orbital, so the $n \rightarrow \pi^*$ excited state may have a radical-like behavior. For example, ketones are well-known for their rearrangement, reduction, or cycloaddition on irradiation. Many other examples show that the photochemistry arising from the $n \rightarrow \pi^*$ excited states demands interpretation based on radical-like intermediates.

Table 10 Singlet and Triplet $n \rightarrow \pi^*$ Transitions [38–41]

Compound	Singlet–Singlet $n \rightarrow \pi^*$	Singlet–Triplet $n \rightarrow \pi^*$	Ref				
	Transition Wavelength (Å)	ϵ_{max}	Solvent	Transition Wavelength (Å)	ϵ_{max}	Solvent	
acetone	2750	22	cyclohexane	–	–	–	[38]

cyclopentanone	2780	18	MeOH	–	–	–	[39]
cyclohexanone	2820	15	MeOH	–	–	–	[39]
cycloheptanone	2838	20	MeOH	–	–	–	[39]
acetophenone	3628	78	hexane	3885	0.03	hexane	[40]
benzophenone	3787	337	hexane	4121	0.03	hexane	[40,41]

The absorption at about 1500 Å in the spectra of simple ketones is very strong ($\epsilon_{\text{max}} \sim 20000$). This band corresponds to a $n \rightarrow \pi^*$ transition. An electron-donating substituent shifts the absorption to longer wavelengths, owing to resonance interaction between the π -electron system and the substituent. The conjugation of a double bond with a carbonyl group leads to intense absorption ($\epsilon_{\text{max}} \sim 15000$) and to an important red shift. This band corresponds to the transfer of a π -electron from a π -molecular orbital to a π^* -molecular orbital and this band has a charge-transfer character. The prediction of the maxima of the $n \rightarrow \pi^*$ of α, β -unsaturated ketones can be made by Woodward's rules or by an extension of these rules.^[42]

A main difference between the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ bands consists in the solvent effect. In going from nonpolar solvent to polar solvent, the $\pi \rightarrow \pi^*$ bands shift to longer wavelengths. The interaction with the solvent stabilizes the ground and the excited states in a different way and induces the red shift of the $\pi \rightarrow \pi^*$ transition. Singlet $n \rightarrow \pi^*$ transitions for some ketones are reported in **Table 11**.

Table 11 Singlet $n \rightarrow \pi^*$ Transitions^[43-46]

Compound	Transition Wavelength (Å)	ϵ	Phase	Ref
acetone	1800	900	vapor	[43]
but-2-en-3-one	2190	3600	EtOH	[44]
1-methylpent-2-en-4-one	2490	2490	EtOH	[44]
but-3-yn-2-one	2150	5000	EtOH	[45]
benzophenone	2600	–	EtOH	[46]

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Compounds with Two Carbon–Heteroatom Bonds
Volume 27:
Heteroatom Analogues of Aldehydes and Ketones

Padwa, A., in *Science of Synthesis*, **27** (2004), p.1

This volume covers the synthesis of compounds containing two carbon —heteroatom bonds which are heteroatom analogues of aldehydes and ketones. These are shown in **Table 1** together with the sections in which they appear.

Table 1 Structures and Nomenclature for the Two Carbon —Heteroatom Bond Containing Compounds Covered in Volume 27

Product Class	Structural Formula	Section
sulfur ylides	$R^1R^2C=S=CR^3R^4$	27.1
alkylidenesulfonium salts	$R^1R^2C=S^+R^3$	27.2
thioaldehyde and thioketone S,S-dioxides (sulfenes)	$R^1R^2C=SO_2$	27.3
thioaldehyde and thioketone S-oxides (sulfines)	$R^1R^2C=S=O$	27.4
thioaldehydes	$R^1CH=S$	27.5
thioketones	$R^1R^2C=S$	27.6
imines	$R^1R^2C=NR^3$	27.7
iminium salts	$R^1R^2C=N^+R^3R^4$	27.8
N-acylimines	$R^1R^2C=NCOR^3$	27.9
N-acyliminium salts	$R^1R^2C=N^+(R^3)COR^4$	27.10
azomethine ylides	$R^1R^2C=N^+(R^3)C^-R^4R^5$	27.11
N-haloimines	$R^1R^2C=NX$	27.12
nitrones	$R^1R^2C=N^+(R^3)O^-$	27.13
nitronic acids	$R^1R^2C=N^+(O^-)OH$	27.14
oximes	$R^1R^2C=NOR^3$	27.15
azines	$R^1R^2C=N-N=CR^3R^4$	27.16
hydrazones	$R^1R^2C=N-NR^3R^4$	27.17
hydrazonium compounds	$R^1R^2C=N-N^+R^3_3$	27.18
azomethine imines	$R^1R^2C=N^+(R^3)-N^-R^4$	27.19
N-nitroimines	$R^1R^2C=N-NO_2$	27.20.1
N-nitrosoimines	$R^1R^2C=N-NO$	27.20.2
diazo compounds	$R^1R^2C=N_2$	27.21
alkylidenephosphines	$R^1R^2C=PR^3$	27.22
alkylidenephosphonium salts	$R^1R^2C=P^+R^3R^4$	27.23
alkylidenephosphoranes	$R^1R^2C=PR^3_3$	27.24

References to reviews on these specific functional groups are given in each section. Discussions of each specific group are generally subdivided into methods that have been selected as the most useful for the preparation of the product class in question. Each method is presented separately as follows:

1. Introduction: comparison with other methods.
2. Presentation of the scope of the method to include background, discussion of representative examples,

safety; mechanistic information where relevant to the use of the method in synthesis; a table of examples (for selected methods); reaction schemes.

3. Representative experimental procedures.

In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format.

The coverage is not exhaustive, rather the most useful and reliable methods for the synthesis of each functional group have been selected. In some cases, methods that are recommended for limited use, or that have not yet been fully developed, are listed at the end of a section for reference. Tables and representative experimental procedures are given to illustrate the applicability of each approach. Many of the classical syntheses for these carbon—heteroatom—bonds still belong to the selection of the best methods available; however, newer developments are also incorporated. The relative size of each section largely depends on the synthetic importance of the product's functional group.

This introduction will outline the individual product classes together with highlighted synthetic methods.

The synthesis and chemistry of sulfur ylides are described in Section 27.1. Stabilization of the anionic center adjacent to the positively charged sulfur atom is believed to be mainly due to an electrostatic interaction, with a small contribution from negative hyperconjugation (i.e., overlap of the lone pair on carbon with a σ^* -orbital on sulfur). Sulfoxonium salts are more acidic than the corresponding sulfonium salts. The increased stability of sulfoxonium ylides is due to the removal of electron density from sulfur by the oxygen atom.

As nucleophiles, sulfur ylides show similar behavior to carbanions, but since there is no net negative charge there are also significant differences. Sulfur ylides are often highly reactive compounds and, as such, are nonisolable species that are generally prepared in situ. However, a significant number of sulfur ylides bearing anion-stabilizing groups have been isolated and characterized, although these ylides tend to be of limited synthetic utility due to their low reactivity. The two most popular methods for the synthesis of sulfur ylides are deprotonation of the corresponding onium salt or reaction of a sulfide, sulfoxide, or thiocarbonyl compound with a carbene.

Sulfonium ylides have become the most popular class of sulfur ylides due to the relatively high reactivity of monosubstituted ylides and the ease with which they can be obtained from sulfides. It is this nucleophilic behavior that dominates the chemistry of sulfur ylides and makes them versatile reagents for a variety of synthetic transformations. Sulfur ylides undergo reactions with a wide range of electrophiles and Lewis acids, forming adducts that can sometimes be isolated or collapse to afford new products. Most commonly, sulfoxonium or sulfonium ylides are employed in the synthesis of three-membered ring compounds from aldehydes and ketones, e.g. the formation of oxirane **1** (Scheme 1),^[1] imines, Michael acceptors, and, less commonly, thiocarbonyl compounds.

Scheme 1 Formation of an Oxirane from a Sulfonium Ylide and a Ketone^[1]

Significant attention has also been paid to thiocarbonyl ylides **2**, which are reactive intermediates that are

isoelectronic with the allyl anion. Several procedures are utilized for the preparation of these ylides including deprotonation of alkylidenesulfonium salts, the 1,3-dipolar cycloaddition reaction of diazo compounds with thiocarbonyl compounds followed by extrusion of nitrogen (**Scheme 2**), and the direct addition of a carbene to thiocarbonyl compounds.^[2-7] 1,3-Elimination reactions represent another useful method for the generation of relatively unsubstituted thiocarbonyl ylides from simple starting materials, and are also employed for the synthesis of thiocarbonyl ylide analogues such as oxonium and azomethine ylides.

Scheme 2 Formation of Thiocarbonyl Ylides

The major focus of Section 27.2 is on the application of thionium (alkylidenesulfonium) ion intermediates in organic synthesis. Sulfur has the distinct ability to stabilize the positive charge on a neighboring carbon center. Therefore, carbocations that are stabilized by an adjacent sulfur atom can be isolated as salts. This is particularly true for those cases where the positive charge is further stabilized by additional heteroatoms. Some of the major methods employed for the preparation of alkylidenesulfonium ions involve the direct alkylation of thiocarbonyl compounds, α -halogen elimination from α -halogen sulfides, and α -alkylsulfanyl elimination from dithioacetals. Dimethyl(methylsulfanyl)sulfonium tetrafluoroborate is frequently used as a chemoselective initiator of thionium ion formation from dithioketals. One of the more versatile and important methods for the generation of thionium ions is via the Pummerer reaction. The Pummerer reaction involves the formation of thionium ions from a sulfoxide precursor bearing at least one α -hydrogen atom. In general, as shown in **Scheme 3**, this transformation requires (1) an electrophile (E^+) to activate the sulfoxide and to transform the oxygen into a good leaving group, (2) a general base to remove a proton to give the thionium ion intermediate **3**, and (3) a nucleophile (Nu^-) to trap the unstable thionium ion **3**.^[8]

Scheme 3 Pummerer Reaction Involving a Thionium Ion from a Sulfoxide Precursor^[8]

The S,S-dioxides of thioaldehydes and thioketones are referred to as "sulfenes" and are reviewed in Section 27.3. So far, no stable sulfene or its imide has been isolated as these reactive intermediates are simply generated in situ and trapped by a variety of nucleophilic reagents. The synthetic importance of sulfenes lies in these trapping reactions, which permit the preparation of many four-membered ring compounds that are difficult to obtain otherwise. The elimination of hydrogen chloride from alkanesulfonyl chlorides is the most common method for the generation sulfenes. The reaction is performed in the presence of a suitable trapping agent, e.g. an electron-rich alkene such as an enamine, which ultimately furnishes the four-membered thietane 1,1-dioxide ring system **4** (**Scheme 4**).^[9-22]

Scheme 4 Formation of a Thietane 1,1-Dioxide via a Sulfene

Generation of the parent sulfene under neutral conditions is also achieved by fluoride-induced elimination of chlorotrimethylsilane from (trimethylsilyl)methanesulfonyl chloride followed by trapping with a reagent such as an enamine, ynamine, or cyclopentadiene.^[23]

The reaction of diazoalkanes with sulfur dioxide is another general method for the in situ preparation of sulfenes (**Scheme 5**).^[24-27] The usefulness of the method is limited by the reaction of the initially generated sulfene with the diazoalkane, which is still present in the reaction mixture, to produce symmetrical thiirane 1,1-dioxides **5**.

Scheme 5 Formation of Sulfenes by the Reaction of Diazoalkanes and Sulfur Dioxide^[24-27]

Vinyl ethers, ketene *N,N*-acetals, and ynamines are all used as trapping reagents with sulfenes giving alkoxythietane 1,1-dioxides **6** and 3-(dialkylamino)thiete 1,1-dioxides **7** and **8** (**Scheme 6**).^[28-32]

Scheme 6 Reaction of Sulfenes with Vinyl Ethers, Ketene *N,N*-Acetals, and Ynamines^[28-32]

The S-oxides of thioaldehydes and thioketones are known as sulfines. These reactive intermediates correspond to derivatives of sulfur dioxide in which one oxygen atom is replaced by a functionalized carbon atom and these compounds are described in Section 27.4. The stability of sulfines is predominantly determined by the nature of the substituents at the sulfine carbon atom. Although aliphatically substituted sulfines are rather unstable, the aromatically substituted ones are usually stable at room temperature and can be stored in the refrigerator for a considerable length of time. Sulfines bearing one heteroatom at the carbon atom are thermally stable.

The three principle modes of synthesis of sulfines **9** are shown in **Scheme 7** and involve (1) formation of the C=S bond in an alkylidenation reaction, (2) oxidation of thiocarbonyl-containing compounds, and (3) dehydrochlorination of appropriate sulfinyl chlorides. The oxidation method is by far the most general. The other two methods are of importance when the starting thiocarbonyl compound is not stable and when reactive sulfines are to be prepared in situ.

Scheme 7 Synthesis of Sulfines

Reaction of (diarylmethylene)triphenylphosphoranes with an excess of sulfur dioxide in an apolar solvent affords the corresponding diarylsulfines **9** in good yield (**Scheme 8**).^[33] In analogy with the Wittig reaction, it is assumed that initially these ylides react with sulfur dioxide to give a sulfobetaine **10**, which then fragments into the sulfine **9** and triphenylphosphine oxide.

Scheme 8 Formation of Sulfines from a (Diarylmethylene)triphenylphosphorane and Sulfur Dioxide^[33]

The reaction of α -silyl carbanions with sulfur dioxide constitutes another general method for the synthesis of a variety of sulfines. This method is a modification of the Peterson alkenation reaction. An alternative approach to the preparation of α -silyl carbanions used in the synthesis of sulfines, e.g. **11**, makes use of the α -addition of appropriate nucleophiles to vinylsilanes (**Scheme 9**).^[34]

Scheme 9 Synthesis of Sulfines from α -Silyl Carbanions^[34]

The chemical behavior of sulfines has been investigated in considerable detail. The major applications in synthesis involve (1) nucleophilic reactions at the sulfine sulfur atom and (2) [4+2]-cycloaddition chemistry. Sulfines undergo a ready Diels–Alder reaction with various 1,3-dienes and 1,3-dipoles. The Diels–Alder reaction is particularly useful to trap unstable sulfines. The reaction of various nucleophiles with sulfines readily occurs and leads to thiophilic addition products.

Studies on the preparation and reactivity of thiocarbonyl groups are described in Sections 27.5 and 27.6. There are many general similarities between the chemistry of carbonyl and thiocarbonyl groups. A significant increase in reaction rate is often observed for thiocarbonyl compounds due to the inherent instability of the C—S σ -bond. The higher reactivity of thiocarbonyl compounds is associated with the poor orbital overlap of this σ -bond. Only a few examples of stable, isolable thioaldehydes and thioketones are available and the even greater reactivity of thioaldehydes has delayed the isolation of the first examples. As a result of their high reactivity, thioaldehydes, such as **12**, are generally generated and trapped in situ (see **Scheme 10**). In the absence of trapping agents, trimerization and polymerization are common reaction pathways. Bulky substituents in the α -position can sterically protect the thioaldehyde group and permit their isolation. The Diels–Alder reaction of thioaldehydes with dienes is often reversible and the [4+2] cycloreversion of the adducts is also used to regenerate the reactive thioaldehyde upon heating.

Scheme 10 Generation and Trapping of Thioaldehydes

The ene reactions of thioaldehydes have also been studied in detail. Both intermolecular reactions with enophiles and intramolecular reactions with tethered alkenes are known.

A range of thiating agents are used to prepare thioaldehydes **12** from their more common oxygen analogues. In most cases, the products undergo further reactions in situ either with themselves (**Scheme 11**) or with trapping reagents. The early syntheses of thioaldehydes involved the treatment of aldehydes with hydrogen sulfide under acidic conditions. Some other methods involve the use of metal and metalloid sulfides such as hexamethyldisilathiane, hexaalkyl- or hexaaryldistannathianes, and bis(dimethylaluminum) sulfide. Phosphorus-based thiating agents such as phosphorus pentasulfide and Lawesson's reagent are also used to prepare both transient and stable thioaldehydes from the corresponding carbonyl precursors.^[35]

Scheme 11 Preparation of Thioaldehydes with a Thiating Agent

The Norrish type-II photolytic cleavage of phenacyl sulfides is another mild and useful method of preparing thioaldehydes that bear a wide range of functionalities. In most cases, the thioaldehydes **12** are trapped in situ by dienes to give Diels –Alder adducts (**Scheme 12**),^[36] provided that the dienes are transparent to the wavelength of light used and are sufficiently reactive to trap the thioaldehyde at near to room temperature.

Scheme 12 Thioaldehydes by Norrish Type-II Photolytic Cleavage of Phenacyl Sulfides^[36]

A further method for preparing thioaldehydes **12** is through a 1,2-elimination reaction of thiol derivatives that bear a leaving group on the sulfur atom and often have an acidic proton in the α -position (**Scheme 13**). Examples of common substrates used include Bunte salts **13** ($X = \text{SO}_3\text{Na}$),^[37,38] sulfonyl chlorides **13** ($X = \text{Cl}$),^[39-41] thiosulfinates **13** [$X = \text{S(O)R}^2$],^[42-46] and phthalimide derivatives **13** ($X = \text{NPhth}$).^[47,48] Several other miscellaneous eliminations have also been reported.

Scheme 13 Thioaldehydes by 1,2-Elimination of Thiol Derivatives Bearing a Leaving Group on Sulfur

Aliphatic low-molecular-weight thioketones have a tendency to undergo spontaneous dimerization or oligomerization unless there is electronic or steric stabilization in the molecule. Thioketones need bulky substituents in order for them to be isolable and are often tricky to handle because oligomerization and polymerization, formation of stable tautomeric enethiols, and ready conversion into the corresponding ketones must be prevented. A convenient way of storing unstable and transient thioketones **14** is by transforming these compounds into thermally labile [4+2] cycloadducts (**Scheme 14**), which can be submitted to a retro-Diels – Alder reaction or to thermolysis of their dimers to regenerate the thioketones when desired.

Scheme 14 Formation and Transformation of Thioketones

The most widely used method for the synthesis of thiocarbonyl groups depends upon the conversion of a carbonyl compound into the corresponding thiocarbonyl compound by reaction with hydrogen sulfide gas in the presence of an acid.^[49,50] Despite the difficulties associated with the use of hydrogen sulfide gas, this approach is still in use. The inorganic reagent most commonly used to transform non-enolizable ketones into thioketones is phosphorus pentasulfide, and this reagent has found extensive application in the synthesis of thioketones and related thiocarbonyl compounds. The procedure generally involves boiling a suspension of phosphorus pentasulfide in toluene or xylene, using an excess of reagent and long reaction times, and results in quite variable yields. Thioketones containing alkyl or aryl substituents are also obtained in good yield by direct thionation of the corresponding carbonyl compounds with Lawesson's reagent.^[51,52] Hydrazones are transformed into stable thioketones containing alkyl or aryl substituents by reaction with reagents such as sulfur dichloride or sulfur monochloride in the presence of a base such as triethylamine. This method seems to be of synthetic value in view of the experimental simplicity and ready availability of hydrazones from ketones. 1,3-Dithiolanes, which are readily obtained from ketones by reaction with ethane-1,2-dithiol in the presence of a catalyst such as boron trifluoride – diethyl ether complex, are used as precursors of thioketones by treatment with *N,N*-diisopropylethylamine or another base. 1,3-Dithiolane 1,1-dioxides, which are readily accessible by oxidation of the parent dithiolanes, also offer particularly facile access to thioketones. Thioketones, like thioaldehydes, are also prepared from noncarbonyl precursors via the elimination of HX from sulfenyl halides, Bunte salts, or phthalimide derivatives. Different reactions are available for the synthesis of thioketones using other noncarbonyl precursors such as monohalides and geminal dibromides.

The synthesis and reactions of imines are covered in Section 27.7. Compounds with the general structure $R^1R^2C=NR^3$ were first obtained by Schiff by condensation of ketones and aldehydes with primary amines. Since imines are analogues of carbonyl compounds, many of their chemical properties are markedly similar to ketones or aldehydes. Imines are used synthetically to make new C — C bonds and the C=N moiety is known to undergo reactions with various electrophiles. The presence of a C=N bond allows for the possibility of *E/Z* isomerism (*syn/anti*). However, the geometrical isomers of aliphatic imines are easily interconverted. *N*-Silylimines are stable imine derivatives that possess high nucleophilic activity at the nitrogen atom and that are widely used as masked N — H imines. The formation of a wide variety of *N*-substituted imines from primary amines and aldehydes or ketones is the most general method for the preparation of this functional group. Both

the addition of the amine and the subsequent elimination of water are acid catalyzed. The most general procedure for the synthesis of N—H ketimines is the addition of Grignard reagents to a nitrile group, which can be stopped at the imine stage by decomposition of the initially formed complex with anhydrous ammonia. An improvement of this method involves the decomposition of the magnesium complex with anhydrous methanol, thus leading to higher yield of imines, fewer side products, and also the isolation of less-stable N—H ketimines.

Iminophosphoranes **15** can react with carbonyl compounds and, thus, this reaction constitutes an excellent method for the construction of C=N bonds via inter- and intramolecular aza-Wittig reactions (**Scheme 15**).^[53] This method provides one of the best procedures for imine formation under mild and neutral reaction conditions. The intramolecular version attracts considerable attention because of its high potential for the synthesis of nitrogen-containing heterocycles.

Scheme 15 Formation of Imines by Reaction of Iminophosphoranes with Carbonyl Compounds^[53]

The deprotonation of imines with a non-nucleophilic base such as lithium diisopropylamide is the most frequently used method for the generation of 1-azaallyl anions; these anions are used for the preparation of a large variety of functionalized imines. The lithium counterion of the 1-azaenolates is generally represented as nitrogen coordinated. The stereo- and regiochemistry of the formation of imine anions has been extensively investigated. There are at least three points of interest: (1) the stereochemistry of the C—N bond, (2) the stereochemistry of the C=C bond, and (3) regiochemistry of deprotonation. In most cases, the least substituted carbon atom is deprotonated.

Section 27.8 covers the chemistry of the related iminium salts. This class of reactive intermediates can be divided into methaniminium salts derived from formaldehyde, terminal iminium salts derived from aldehydes, and quaternary iminium salts derived from ketones. Iminium salts are more electrophilic than the corresponding imines because of their highly polarized C=N bond and are extensively used for the synthesis of heterocyclic ring systems. They react as electrophiles in C—C bond-forming reactions, not only with organometallic reagents, but also with electron-rich systems such as enamines, indoles, and amino- and hydroxy-substituted arenes. Iminium salts **16** are commonly prepared by the reaction of amines with aldehydes and ketones under acidic catalysis (**Scheme 16**). The reaction of non-enolizable aliphatic and aromatic aldehydes with 1-(trimethylsilyl)pyrrolidines represents an alternative for the synthesis of terminal iminium chlorides. The alkylation of imines is a useful method for the synthesis of iminium salts. Electrophilic attack on the nitrogen atom of an enamine is also used as a method for the preparation of vinylammonium salts. In addition, iminium salts can be prepared by the elimination of cyanide from α -amino cyanides or by the cleavage of hemiaminals (**Scheme 16**).

Scheme 16 The Formation of Iminium Salts

N-Acylimines, which are synthetically useful intermediates utilized in a wide variety of transformations, are

discussed in Section 27.9; they are generally generated and used in situ from amines containing a good leaving group. *N*-Acylimines themselves are rather unstable and, if it is possible, they rapidly undergo tautomerization into the corresponding enamides. Only those *N*-acylimines bearing electron-withdrawing substituents or tetrasubstituted groups on the imino carbon atom are isolated. The general method for the synthesis of stable *N*-acylimines consists of the acylation of readily available *N*-silyl-substituted imines, e.g. formation of **17** in **Scheme 17**,^[54] or imidate hydrochlorides. The reactivity of the C=N bond in *N*-acylimines is greatly enhanced relative to simple *N*-alkylimines and their stability toward water is also increased. *N*-Acylimines also possess the characteristics of both hetero-1,3-dienes and dienophiles for [4+2] cycloadditions.

Scheme 17 *N*-Acylimines by Acylation of *N*-Silylimines^[54]

Section 27.10 reviews *N*-acyliminium salts, which represent versatile electrophilic species with many applications for the synthesis of nitrogen-containing compounds. *N*-Acyliminium salts are significantly more electrophilic than the corresponding iminium species due to the presence of the electron-withdrawing acyl group at the iminium nitrogen atom. For most synthetic applications they are generated in situ, although a few cyclic and acyclic salts have been isolated and characterized by NMR spectroscopy and X-ray analyses. For synthetic applications, *N*-acyliminium ions, such as **18**, are frequently formed from α -haloalkyl-, α -hydroxyalkyl-, α -alkoxyalkyl-, or α -acyloxyalkyl-substituted amines, lactams, or carbamates. Lewis acids and silylating agents are routinely used to assist formation of the electrophilic intermediate. The generation of the *N*-acyliminium ion, which is generally assumed to be the rate-determining step, is followed by in situ trapping by the nucleophile, which includes aromatic and heteroaromatic compounds, alkenes (e.g., reaction of **18** to give the bicyclic system **19**; **Scheme 18**), acetylenes, ketenes, and organometallic species. The overall process is known as the α -amidoalkylation reaction.

Scheme 18 Formation of an *N*-Acyliminium Ion and Intramolecular Trapping by an Alkene

Azomethine ylides belong to the allyl-type class of 1,3-dipoles and are described in Section 27.11. Most azomethine ylides cannot be isolated under normal conditions. Only in cases where the 1,3-dipole bears several electron-withdrawing groups is the reactive dipole isolated. The main application of azomethine ylides in organic synthesis is based on their potential for 1,3-dipolar cycloaddition chemistry and for electrocyclization reactions. Aziridines bearing conjugating groups undergo thermolysis to give azomethine ylides by C—C bond cleavage of the three-membered heterocyclic ring. The generation of azomethine ylides by valence isomerization of 2,3-dihydrooxazoles is another common method for the preparation of these reactive 1,3-dipoles. 1,2-Prototropic shift in imines gives azomethine ylides with a hydrogen attached to the central nitrogen, e.g. the formation of **21** from imine **20** (**Scheme 19**);^[55-59] the facility with which the proton migration occurs depends on the basicity of the nitrogen and especially on the acidity of the α -hydrogen. Closely related

to the 1,2-hydrogen migration route, aryl-substituted *N*-[(trimethylsilyl)methyl]imines undergo thermal 1,2-silyl shift affording azomethine ylides. One of the most important methods for generating azomethine ylides involves condensation of carbonyl compounds with α -amino esters, or related aminoalkyl derivatives containing an electron-withdrawing group, followed by deprotonation to give the azomethine ylide, e.g. **22** (Scheme 19).^[60-62] A further useful procedure involves alkylation of an imine with trimethylsilylmethyl trifluoromethanesulfonate and subsequent desilylation of the resulting iminium salt **23** with fluoride ion giving azomethine ylides **24**.^[63] This method is particularly appropriate and frequently utilized for the generation of nonstabilized azomethine ylides. A particularly powerful and widely used method for the generation of azomethine ylides involves condensation of α -amino acids with carbonyl compounds. The resulting iminium carboxylate undergoes a subsequent decarboxylation with formation of the dipole.

Scheme 19 The Formation of Azomethine Ylides^[55-63]

The synthesis and reactions of *N*-haloimines are discussed in Section 27.12. The popular methods of preparation include oxidation of 4-aminophenol with sodium hypohalites, oxidation of *N,N*-bis(benzylidene) arylmethanediamines and *tert*-butyl hypochlorite, and the reaction of carbonyl compounds with chloroamine. The latter reaction is one of the most convenient ways of making *N*-chloroimines.

The role of nitrones in organic synthesis is substantial and, hence, a significant number of pages in this volume are allotted to this important functional group (Section 27.13). Nitrones are isoelectronic with allyl anions and are stabilized by resonance. They are also 1,3-dipoles and the enormous potential of the 1,3-dipolar cycloaddition reaction has been the driving force for most research in the field of nitrone chemistry. Nitrones undergo cycloaddition with a wide range of substituted alkenes, often proceeding with a very high degree of regio- and stereochemical control. The construction of isoxazolidines, such as **25** (Scheme 20),^[64] using nitrone cycloaddition has received considerable attention because of the wide application of these heterocycles in organic synthesis, including the preparation of 1,3-amino alcohols. A number of excellent procedures exist for the synthesis and isolation of nitrones including the oxidation of the corresponding amines or hydroxylamines. Nitrones derived from aldehydes are readily prepared by condensation methods. In the case

of ketonitrone, some activation of the carbonyl group may be required. The reaction of an oxime with an alkylating agent represents a further method for nitrone generation (**Scheme 20**).

Scheme 20 Formation of Nitrone and Further Cycloaddition to Isoxazolidines^[64]

Nitronic acids (and their derivatives) are related to the nitrone family and are reviewed in Section 27.14. These structures are more commonly referred to in the literature as *aci*-nitro compounds, nitronic acids, and, less frequently, by the IUPAC name alkylideneazinic acids. With regard to applications in synthesis, nitronic acid is an intermediate in the Nef reaction, which is traditionally used to convert nitroalkanes into carbonyl compounds.^[65] Nitronate salts, on the other hand, serve as nucleophiles in nitroaldol condensation reactions (the Henry reaction).^[66] More importantly for organic synthesis, alkyl and silyl nitronates are widely used in 1,3-dipolar cycloaddition reactions with various dipolarophiles. The resulting [3+2] cycloadducts provide a useful entry to heterocycles.

Section 27.15 discusses the synthesis and chemistry of oximes. The most general method for the preparation of oximes involves the condensation of various carbonyl compounds with hydroxylamine, e.g. the formation of cyclohexanone oxime (**26**) (**Scheme 21**).^[67] Nitrosation, oxidation of amino compounds, and the reduction of nitro compounds are also used to prepare this useful functional group. Generally, oximes are stable, easily crystallized, and exhibit high melting points. There are two stereoisomers (*E/Z*) possible for an aldoxime as well as for an unsymmetrical ketoxime that can be distinguished by NMR spectroscopy. Oximes are extensively utilized for the synthesis of a variety of nitrogen-containing compounds. By employing the Beckmann rearrangement, the Beckmann fragmentation, and the Neber reaction, many different ring systems can be prepared. Selective 1,2-migration of an alkyl group located *anti* to the oxime hydroxy group generally occurs to produce rearranged amides. The Neber reaction of *O*-sulfonyloximes **27** with base is used to prepare α -amino ketones **28** (**Scheme 21**);^[68] the reaction is believed to proceed via a 2*H*-azirine intermediate.

Scheme 21 Formation and Further Reaction of Oximes^[67,68]

Section 27.16 is devoted to a survey of the chemistry of azines. These compounds correspond to nitrogen analogues of aldehydes and ketones derived by condensation with hydrazine. Reaction of carbonyl compounds with preformed primary hydrazones is used to prepare monosubstituted and geminally disubstituted azines **29**, as well as tri- and tetrasubstituted systems (**Scheme 22**). Azines undergo both oxidation and reduction, with the former reaction most frequently resulting in oxidative hydrolysis to give the parent carbonyl compound. Under strongly reducing conditions, azines react to give the corresponding hydrazines, which are readily reoxidized to the related azo derivatives. Intramolecular cyclization reactions of azines bearing pendant functional groups are well precedented. Cycloaddition reactions across azines are also known producing four- and five-membered ring cycloadducts.

Scheme 22 Formation of Azines by Reaction of Carbonyl Compounds with Primary Hydrazones

Hydrazones are useful intermediates for organic synthesis and are surveyed in Section 27.17. These compounds are widely used for the derivatization, protection, C—C bond formation, and functional group transformation of aldehydes and ketones, and for the synthesis of a variety of nitrogen-containing heterocyclic compounds. Hydrazones are ambident nucleophiles that can react with electrophiles either at the nitrogen atom or at the azomethine carbon. Strong bases can deprotonate hydrazones to form hydrazone anions, whereas nucleophiles generally attack the azomethine carbon to give addition products. Hydrazones can be converted into alkanes, alkenes, and amines, and are also precursors of reactive diazo compounds and carbenes. Hydrazones exist in *E* and *Z* isomeric forms and their preparation normally leads to the formation of the more stable isomer, which equilibrates with the less stable form. The formation of hydrazones is generally a facile reaction and the equilibrium for the majority of cases involving the reaction of aldehydes and ketones with hydrazines favors the product hydrazones. Coupling of diazonium compounds with active methylene compounds is another well-established method for the introduction of *N*-aryldiazo groups at the enolizable carbon atom. An important use of *N*-arylhydrazones is in the Fischer indole synthesis. This synthesis involves the cyclization of enolizable *N*-arylhydrazones in the presence of an acid catalyst with the loss of ammonia to furnish substituted indoles.

Hydrazonium compounds are generally divided into two subclasses: 1,1,1-trialkyl-2-alkylidene- and 1,2,2-trialkyl-1-alkylidenehydrazinium compounds. Section 27.18 surveys this class of hydrazone derivatives. Alkylation of hydrazones with alkyl halides is the oldest and most generally used method for the preparation of this functional group and mainly occurs at the terminal nitrogen atom. Condensation of carbonyl compounds and hydrazine derivatives represents an alternative method for the preparation of hydrazonium compounds. Azirines **30** are prepared in good yield by modified Neber rearrangement reactions of 1,1,1-trimethylhydrazinium compounds in the presence of base catalysts (**Scheme 23**).^[69,70] The reaction of Grignard reagents with 1,1,1-trimethylhydrazinium iodides provides a good method for the synthesis of secondary aziridines, especially for aziridines that cannot be prepared by the Hoch–Campbell procedure.^[71-73]

Scheme 23 Modified Neber Rearrangement of 1,1,1-Trimethylhydrazinium Compounds To Give Azirines

Section 27.19 covers the generation and application in organic synthesis of azomethine imines. The azomethine imine class of 1,3-dipoles are normally not isolable and readily undergo cycloaddition with a variety of dipolarophiles. *N*-Monosubstituted hydrazones are capable of reacting as azomethine imines upon 1,2-prototropic shift from the terminal nitrogen to the central nitrogen atom. Intermolecular cycloaddition reactions of aldo- and ketohydrazones with a variety of dipolarophiles afford pyrazolidine cycloadducts **31** (**Scheme 24**).^[74,75] Condensation of 1,2-disubstituted hydrazines with aldehydes or aldehyde-derived acetals and hemiacetals is an alternative method for the preparation of azomethine imines. In the absence of a suitable trapping reagent, the in situ generated azomethine imine usually dimerizes to give hexahydro-1,2,4,5-tetrazines. Addition of nucleophilic reagents across the iminium moiety of the azomethine imine affords isolable hydrazinoacetals, which, in turn, are precursors for the parent azomethine imine dipole. A 1,4-silotropic shift of -silylnitrosamines is also utilized as a method for the generation of the azomethine imine dipole. Another synthetic approach involves the deprotonation of the exocyclic amino group of *N*-amino-substituted azolium salts.

Scheme 24 Pyrazolidines by Intermolecular Cycloaddition Reactions of Hydrazones with Dipolarophiles^[74,75]

The chemistry of *N*-nitro- and *N*-nitrosoimines is reviewed in Section 27.20. The most predominant method for the synthesis of *N*-nitroimines involves nitrosation of the corresponding oximes; many different nitrosation conditions are used. Traditionally, *N*-nitroimines serve as intermediates for the transformation of oximes into the corresponding aldehydes or ketones. Aminolysis of *N*-nitroimines gives imines, providing a unique method for the preparation of sterically hindered imines. The products from the reactions of *N*-nitroimines and nucleophiles frequently undergo elimination reactions to give exchange products. The most prominent examples are exchange reactions with ammonia and hydrazine. The strong activating nature of the nitro group on the imino π -bond makes *N*-nitroimines excellent recipients for cycloaddition reactions. Relatively little is known about *N*-nitrosoimines, although there are some reports in the literature where they are believed to be intermediates generated during the decomposition of nitrogen-containing compounds. *N*-Nitrosoimines are formed by the nitrosation of the corresponding ketimines with acidified sodium nitrite, nitrosyl chloride, dinitrogen tetroxide, or nitrosonium tetrafluoroborate.

Section 27.21 is devoted to the methods for preparing diazo compounds, which have, indeed, played a very important role in synthetic organic chemistry. Their catalytic decomposition reactions afford a reliable method for the generation of reactive metallo carbenoids. Among the more synthetically useful processes of these carbenoid intermediates are intramolecular C—H insertion, cyclopropanation, and ylide generation. Beside the carbene and carbenoid chemistry of diazo compounds, there exists a substantial amount of 1,3-dipolar cycloaddition chemistry of the intact diazo group with π -bonds of alkenes. Numerous methods for the synthesis

of individual classes of diazo compounds have been developed over the years. One of the best methods for the preparation of diazo compounds, such as **32** (**Scheme 25**), consists of the direct introduction of both nitrogen atoms in a single reaction step.^[76,77] The entire azo group is transferred from an activated azide to a CH-acidic compound by a process known as the diazo-group transfer. The diazo-transfer reaction, which proceeds best with sulfonyl azides, is quite general, but is limited by the requirement that the methylene hydrogens of the substrate must be sufficiently acidic. Direct diazo transfer to ketone enolates is very difficult to carry out. Instead, an indirect strategy in which the ketone is first formylated and then treated with a sulfonyl azide reagent is frequently used.

Scheme 25 Formation of Diazo Compounds by Diazo-Transfer Reaction

Because of the close structural similarity of the diazonium group to the diazo group, it is possible to prepare diazo compounds by diazotization reactions. Systematic investigation of this methodology shows that it is most suitable for the synthesis of diazo-substituted heterocycles from the corresponding amino-substituted heterocycles. The diazo group can also be directly introduced onto a heterocyclic ring. The reaction proceeds by the intermediate formation of a nitroso compound, which is subsequently converted into the diazo heterocycle, e.g. **33** (**Scheme 26**), via the diazonium salt.

Scheme 26 Diazo-Substituted Heterocycles by Diazotization Reactions

The Staudinger reaction of azides with triphenylphosphine yields phosphine imides, which have, in turn, been subjected to nitrosation with nitrosonium tetrafluoroborate to provide various diazo compounds.

Condensation of oximes with chloroamines (Forster reaction) as well as the dehydrogenation of hydrazones are simple methods for the synthesis of diazo compounds **34** (**Scheme 27**), especially α -diazo ketones. The limiting factor of the latter method is often the formation of azines as side products.

In addition to the dehydrogenation of hydrazones, the elimination of sulfinates from *N*-sulfonylhydrazones (Bamford –Stevens reaction) is an alternative method for the conversion of carbonyl compounds into diazo compounds **34** (**Scheme 27**). The *N*-sulfonylhydrazones are synthesized from carbonyl compounds and

arylsulfonohydrazides and then converted into the corresponding lithium or sodium salts. The diazo compounds are generated from these salts by photolysis, vacuum pyrolysis, or thermolysis of a suspension in a suitable solvent. The preferred starting compounds for the Bamford –Stevens reaction are tosylhydrazones, which are prepared from commercially available 4-toluenesulfonohydrazide (tosylhydrazine) and the appropriate carbonyl compound.

The generation of diazenolates from suitable precursors is another useful method for the synthesis of diazoalkanes **34** (**Scheme 27**). *N*-Nitrosoamides, *N*-nitrosocarbamates, and *N*-nitrosoureas are all used as diazo precursors. Treatment of the nitroso starting materials with a base such as potassium hydroxide or sodium methoxide is traditionally used for the cleavage reaction.

Scheme 27 Methods for the Formation of Diazo Compounds

The ability to generate diazoalkanes by photolysis of suitably substituted 2,5-dihydro-1,3,4-oxadiazoles **35** has the advantage that the diazo compound **34** can be generated at low temperature in an inert solvent and that the formation of azines is prevented (**Scheme 28**).

Scheme 28 Diazoalkanes by Photolysis of 2,5-Dihydro-1,3,4-oxadiazoles

Diazo compounds are also prepared by substitution at the diazo carbon atom and this method is referred to as "electrophilic diazoalkane substitution". This term is used to describe reactions of a diazomethyl compound or its metalated derivatives, in which the diazo function remains intact. Although the exchange reactions between a hydrogen atom bonded to the diazo carbon atom and mercury or acyl halides have been known for some time, the synthetic scope of this method has only been developed since the late 1970s. The diazoalkane plays the part of the nucleophile with which the appropriate electrophile reacts. In most cases, the reactions are substitution reactions of acceptor-substituted diazo compounds, such as diazocarbonyl compounds or diazoacetic esters **36** in which the electron-withdrawing group has both a proton-activating and an anion-

stabilizing function (**Scheme 29**).

Scheme 29 Electrophilic Diazoalkane Substitution

Alkylidenephosphines are trivalent phosphorus derivatives with a P=C bond and are reviewed in Section 27.22. The closely related alkylidenephosphonium salts are described in Section 27.23. Although many synthetic pathways are known for the preparation of alkylidenephosphines, the choice of method often depends on the availability of the starting materials. Primary phosphines, bis(silyl)-substituted phosphines, or dihalophosphines are frequently used as precursors for the generation of the P=C bond species. *P*-Hydrogen-substituted alkylidenephosphines can be prepared by the alcoholysis of *P*-(trimethylsilyl)-substituted alkylidenephosphines and are suitable precursors for the preparation of further alkylidenephosphine derivatives. Due to the high reactivity of the phosphorus–halogen bond, *P*-halo-substituted alkylidenephosphines are excellent synthons for other alkylidenephosphine derivatives by reaction with nucleophiles such as organolithium or Grignard reagents. The principle of silatropic rearrangement to give (1-siloxyalkylidene)(trimethylsilyl)phosphines **37** (**Scheme 30**) combined with an addition reaction is utilized for the synthesis of *P*-carbon-substituted alkylidenephosphines.^[78]

Scheme 30 Silatropic Rearrangement To Give (1-Siloxyalkylidene)(trimethylsilyl)phosphines^[78]

Finally, Section 27.24 describes the preparation and chemistry of phosphorus ylides [trialkyl(alkylidene)phosphoranes]. These highly useful compounds are employed in a host of natural product syntheses. The most general method of ylide generation is the formation of a quaternary phosphonium salt by reaction of a phosphine with an alkyl halide, followed by removal of an α -proton by a base to give the phosphorus ylide, e.g. **38** (**Scheme 31**).^[79] The ylide can also be liberated from the salt by electrolysis and pyrolytic elimination. Phosphorus ylides are sufficiently nucleophilic to react with most electrophiles. The Wittig reaction between alkylidenephosphoranes and carbonyl compounds affords phosphine oxide and alkenes with a predictably positioned double bond.

Scheme 31 Generation of an (Alkoxymethylene)triphenylphosphorane and Its Subsequent Reaction with a Carbonyl Compound^[79]

The reaction dates back to 1953 and is one of the most widely used C=C bond-forming processes in organic synthesis. The rate as well as *E/Z* selectivity of the Wittig reaction depend on, among other factors such as solvent polarity and the presence or absence of lithium salts, the particular combination of ylide and carbonyl components. Phosphorus ylides are also used as nucleophiles with alkyl halides, epoxides, nitriles, alkenes, and alkynes, or as precursors to more reactive species such as carbenes. Phosphorus ylides featuring elements from almost all groups of the periodic table directly bound to the α -carbon are prepared and used in organic synthesis. α -Silylated phosphoranes have become a cornerstone of modern preparative ylide chemistry due to their availability and multi-faceted applicability. α -Silylated phosphorus ylides are generally prepared by treating the parent ylide with a suitable silylating agent to give the respective α -silylalkylphosphonium salts, which are then easily manipulated to yield more complex ones. *Z*-Selective alkenation of aldehydes generally occurs with unstabilized ylides by deprotonation with a base. The hydrogen atom on the ylidic carbon is relatively mobile and can be replaced with a large number of substituents. Hence, the reaction of simple phosphorus ylides is easily modified by using salt-free low-temperature conditions. However, the complementary *E*-alkenation was problematic until the advent of the Wittig–Schlosser reaction, which eventually solved this stereochemical issue. In this procedure, the unstabilized ylide is prepared from its salt and a lithium base. Then, it is treated with the carbonyl compound and the resulting mixture of *erythro*- and *threo*-betaines **39** are deprotonated –lithiated by adding a second equivalent of the same lithium base at low temperature to give predominantly the lithiated *threo*-isomer. Its reprotonation with a mineral acid then regenerates exclusively the *threo*-configured starting betaine, which collapses to give the corresponding *E*-alkene (**Scheme 32**).^[80]

Scheme 32 The Wittig –Schlosser Reaction^[80]

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Compounds with Two Carbon–Heteroatom Bonds

28

Volume 28:

Quinones and Heteroatom Analogues

Griesbeck, A. G., in *Science of Synthesis*, **28** (2006), p.1

This volume covers modern synthetic methods to quinones and their heteroatom analogues. Quinones constitute a large and important class of organic compounds that show rich and fascinating chemistry.^[1] These structures are common constituents of biologically relevant molecules often serving as electron acceptors in electron transport chains, thus playing a vital role in electron transport in the respiratory and photosynthetic elements as well as a number of redox processes in nature. Quite often they serve as versatile intermediates in organic synthesis, biological chemistry, inorganic chemistry, and materials science. While biological processes and applications in materials science often make use of the redox properties of the *p*-quinone/hydroquinone or *o*-quinone/catechol systems, in coordination chemistry these compounds act as redox active, strongly electron-accepting ligands. In organic synthesis, *p*- and *o*-quinones offer a class of highly versatile building blocks as well as excellent one-electron acceptors and mild oxidants. A number of compounds containing benzo-1,4-quinone as well as benzo-1,2-quinone moieties have been isolated from nature and are found to be biologically and pharmaceutically active.^[2–4] The literature on the synthesis of quinones until 1978 has been reviewed in *Houben–Weyl*, Vols. 7/3a, 7/3b, and 7/3c.

The three major compound classes, benzo-, naphtho-, and anthraquinones are described in Sections 28.1–28.5. The isomeric *p*- and *o*-quinones are discussed in separate sections when appropriate. Phenanthrenediones and related ring assemblies are discussed in Section 28.6, while quinones fused with hetarenes containing nitrogen or oxygen, and the carbonyl heteroatom analogues containing sulfur and nitrogen are covered in Sections 28.7, 28.8, 28.9, and 28.10, respectively. Finally, diazocyclohexadienones (quinone diazides, Section 28.11) and quinomethanes (Section 28.12) are described as separate compound classes. The chemical and physical properties of the different product classes are extremely diverse and are therefore not discussed here; detailed descriptions of their distinct properties are described in the individual sections (Table 1).

Table 1 Classes of Quinones Covered in Volume 28

Product Class	Section
benzo-1,4-quinones	28.1
benzo-1,2-quinones	28.2
naphtho-1,4-quinones	28.3
naphtho-1,2-quinones and positional isomers	28.4
anthra-9,10-quinones and positional isomers	28.5
phenanthrene-9,10-diones and related ring assemblies	28.6
nitrogen- and oxygen-containing hetarene quinones	28.7
sulfur analogues of quinones	28.8
benzo- and naphthoquinone imines and diimines	28.9
anthraquinone and phenanthrene-9,10-dione imines and diimines	28.10
diazocyclohexadienones	28.11
<i>o</i> - and <i>p</i> -quinomethanes	28.12

Naphtho-1,4-quinones are widely distributed in nature, mainly in plants, fungi, and bacteria. The various properties and applications of this product class have been extensively reviewed.^[2] They can be isolated as yellow, orange, red, or purple solids, and are sparingly soluble in water but readily soluble in most organic

solvents. Due to their molecular structure and their redox properties, they exhibit interesting physical properties as well as a wide range of biological activities. Extracts from plants containing mixtures of naphtho-1,4-quinone derivatives have been used for centuries not only as dyes or ingredients for cosmetics but also in traditional medicine for the treatment of a great number of diseases. A number of naphtho-1,4-quinones, such as atovaquone, plumbagin, lapachol, and shikonin, are now being used in medical drugs or ointments. Although the exact mode of action of these compounds has not been completely elucidated, their biological activity is usually due to their redox properties, involving the formation of unstable oxygen reactive species such as free radicals, which can take part in various biosynthetic pathways.

Anthra-9,10-quinones are important industrial compounds and are widely distributed as natural products in plants and microorganisms. Their importance as dyestuffs has been known from ancient times, and they were also among the first industrially produced light-stable pigments. In more recent times they have gained increasing importance as organic dyes with multiple applications, for example in the printing industry, as fluorescent enzyme substrates, and as tags for biomolecules. The role of anthraquinones in hydrogen peroxide production is also of great economic importance.

The chemistry of *o*-quinones has been a subject of great interest both from the synthetic and theoretical standpoints because they are unique conjugated 1,2-diones that can elicit diverse modes of cycloaddition. Phenanthrene-9,10-diones are important intermediates in the formation of metabolites responsible for the carcinogenic character of some polycyclic aromatic hydrocarbons. Many of the synthetic approaches have been developed to gain access to these metabolites.

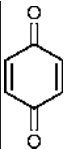
Imines derived from benzoquinones and higher annulated quinones constitute an old class of compounds. Although there are no previous specific sections in the *Houben –Weyl* series, related information can be found in the volumes dealing with quinones (*Houben –Weyl*, Vols. 7/3a, 7/3b, and 7/3c). The driving force behind the early studies on these compounds was their use as azomethine dyes, and the patent literature of the time contains a large number of compounds belonging to these groups. Among them only the so-called indoaniline dyes are mentioned here as an example. These compounds are one of the more important classes of cyan color dyes and have widespread commercial applications, including photography and print systems.

The nomenclature of quinones and quinone derivatives in the chemical literature was, and still is, largely nonsystematic. Over the years the practice and the rules for naming these compound has changed. The IUPAC recommendations from 1979 state that: "Diketones and tetraketones derived from aromatic compounds by conversion of two or four CH groups into CO groups with any necessary rearrangement of double bonds to a quinonoid structure are named by adding the suffix "-quinone" or "-diquinone" to the name of the aromatic compound (this name sometimes being modified)." In the IUPAC recommendations from 1993 only acenaphthoquinone, anthraquinone, benzoquinone, and naphthoquinone are listed in the appendix of retained trivial names. CAS uses systematic names for quinones and quinone imines. In **Table 2**, the nonsystematic names for some common quinones from the IUPAC recommendations of 1979, the names used in *Science of Synthesis*, and the CAS names are collected.

The terms "quinoid" and "quinonoid" are both used to mean "of, or resembling, a quinone." "Quinoid" is used slightly more often in the chemical literature and is thus the preferred form used in Volume 28 of *Science of Synthesis*.


Table 2 Background to Quinone Nomenclature

Structure	Nomenclature		
	IUPAC (1979)	Science of Synthesis	CAS

	<i>p</i> -benzoquinone	benzo-1,4-quinone	cyclohexa-2,5-diene-1,4-dione
	1,4-naphthoquinone	naphtho-1,4-quinone	naphthalene-1,4-dione
	anthraquinone	anthra-9,10-quinone	anthracene-9,10-dione
	5,6-chrysenequinone	chrysene-5,6-quinone	chrysene-5,6-dione

The majority of compounds in this volume are benzoquinones, naphthoquinones, anthraquinones, acenaphthoquinones, and derivatives thereof. Following the IUPAC recommendations from 1993, the names benzoquinone, naphthoquinone, anthraquinone, acenaphthoquinone, and substituted derivatives thereof are used both as general names in the text and as specific names in the titles of experimental procedures. For all other compounds, quinone is used as a general name in the text, but in titles of experimental procedures its systematic name is used, i.e. as the dione or with the principal functional group. **Table 3** demonstrates the general and specific names of nonheterocyclic quinones including benzoquinones, naphthoquinones, anthraquinones, acenaphthoquinone, phenanthrene-9,10-diones, stilbenequinones, diphenoquinones, and related ring assemblies.

Table 3 General and Specific Names of Nonheterocyclic Quinones

Structure	General Name	Specific Name
	—	benzo-1,4-quinone
	—	naphtho-1,4-quinone
	—	anthra-9,10-quinone
	—	acenaphthoquinone
	—	phenanthrene-9,10-dione

	4,4 -diphenoquinone or <i>p</i> -diphenoquinone	bicyclohexa-2,5-dienylidene-4,4 -dione
	1,1 -binaphthyl-4,4 -quinone	4 <i>H</i> ,4 - <i>H</i> -1,1 -binaphthyl-4,4 -dione
	2,2 -diphenoquinone or <i>o</i> -diphenoquinone	3,3 -dimethoxy-4,4 ,5,5 -tetramethylbicyclohexa-2,4-dienylidene-6,6 -dione
	2,4 -diphenoquinone	3,3 ,5,5 -tetra- <i>tert</i> -butylbicyclohexane-1(1)2 ,3,5,5 -pentadiene-2,4 -dione
	stilbenequinone	4,4 -ethane-1,2-diylidenebiscyclohexa-2,5-dien-1-one
	, -diacetoxystilbenequinone	4,4 -(1,2-diacetoxyethane-1,2-diyl)bis(2,6-di- <i>tert</i> -butylcyclohexa-2,5-dien-1-one)

Heterocyclic quinones are named systematically unless an acceptable trivial name is available for quinones from a natural source. **Table 4** demonstrates some general and specific names of heterocyclic quinones.

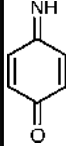

Table 4 General and Specific Names of Heterocyclic Quinones

Structure	General Name	Specific Name
	carbazole-1,4-quinone	1 <i>H</i> -carbazole-1,4(9 <i>H</i>)-dione
	benzimidazole-4,7-quinone	1 <i>H</i> -benzimidazole-4,7-dione
	—	benzo[1,2- <i>d</i> :4,5- <i>d'</i>]diimidazole-4,8(1 <i>H</i> ,5 <i>H</i>)-dione

	—	benzo[1,2- <i>d</i> :4,5- <i>d'</i>]diisoxazole-4,8-dione
	benzo[<i>g</i>]quinoline-5,10-quinone	benzo[<i>g</i>]quinoline-5,10-dione
	—	benzo[<i>b</i>]thiophene-4,7-dione
	—	2-methylbenzothiazole-4,7-dione

Quinones from which one or more quinoid oxygen atoms have been replaced by an imino group are named by following the name of the quinone with the word imine or diimine; substituents on nitrogen are named as prefixes. The terms quinone monoimine or quinone diimine are used in the text as general names but in titles of experimental procedures compounds are named systematically using imino prefixes and imine suffixes as appropriate. **Table 5** demonstrates some general and specific names of benzoquinone and naphthoquinone imines and diimines

Table 5 General and Specific Names of Quinone Imines and Diimines

Structure	General Name	Specific Name
	benzo-1,4-quinone imine	4-iminocyclohexa-2,5-dienone
	naphtho-1,4-quinone imine	4-iminonaphthalen-1(4 <i>H</i>)-one
	benzo-1,4-quinone diimine	cyclohexa-2,5-diene-1,4-diimine

The class name quinone diazide is used in the older literature for quinones in which one quinoid oxygen atom has been replaced by a diazo group. The name quinone diazide is ambiguous (because it implies the presence of an azide group) and the term is now discouraged. Compounds are named as diazocyclohexadienones or the diazo derivative of the appropriate cyclic ketone. Some examples of specific names of diazocyclohexadienones are shown in **Table 6**. Another class name, diazooxide, is also avoided.

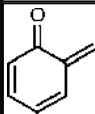
Table 6 Specific Names of Diazocyclohexadienones

Structure	Specific Name

	6-diazo-2,3,4,5-tetrafluorocyclohexa-2,4-dienone
	4-diazo-2,6-dinitrocyclohexa-2,5-dienone
	1-diazonaphthalen-2(1 <i>H</i>)-one

Quinomethanes are methylenecyclohexadienones and are formally derived from quinones by replacement of one of the quinoid oxygen atoms with a methylene group. Quinomethane is used as a general term in the text, but in titles of experimental procedures compounds are named systematically ([Table 7](#)).

Table 7 Specific Names of *o*- and *p*-Quinomethanes

Structure	Specific Name
	6-methylenecyclohexa-2,4-dienone
	2,6-dimethyl-4-prop-2-enylidenecyclohexa-2,5-dien-1-one

Among many substrate-specific synthetic methods, there are several general routes to quinones and heteroatom analogues of quinones, which are briefly described in this introduction. Many more examples as well as experimental procedures can be found in the individual sections of this volume.

Oxidative methods are exceedingly important for the synthesis of a multitude of quinone targets from hydroxylated, amino-substituted, alkylated, or the simple unactivated aromatic precursors. Classical metal-based oxidants include silver(I) oxide, iron(III) chloride, iron(III) chloride immobilized on silica gel, permanganates and manganese(IV) oxide, ammonium cerium(IV) nitrate, ammonium cerium(IV) nitrate immobilized on silica gel, vanadium –oxo complexes, dichromates, chromium(VI) oxide and pyridinium chlorochromate (and supported pyridinium chlorochromate), lead(IV) oxide or lead(IV) acetate, and tungstates. Non-metal-based oxidants include Fremy's salt (potassium nitrosodisulfonate), sodium peroxodisulfate, (diacetoxyiodo)benzene [or the corresponding bis(trifluoroacetate) compound], Dess –Martin periodinane, and sodium hypochlorite. Oxygen-transfer reagents include hydrogen peroxide, singlet oxygen, and dioxirane. Quinones can also serve as oxidants themselves, e.g. 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone^[5] or *p*-chloranil (2,3,5,6-tetrachlorobenzo-1,4-quinone), and oxidize phenols, catechols, and hydroquinones to the corresponding quinones. The unique oxidizing power of Fremy's salt allows the conversion of readily available phenols into the corresponding quinones; depending on the substituent pattern, *o*- as well as *p*-quinones are accessible ([Scheme 1](#)).^[6,7]

Scheme 1 Synthesis *o*- and *p*-Quinones by Fremy's Salt Oxidation^[6,7]

The reaction of metal –carbene complexes with alkynes is a powerful tool for benzannulation (D ötz reaction) under neutral conditions.^[8,9] Among many other examples in natural product synthesis, construction of the anthracycline antitumor agent daunomycin involves the benzannulation of chromium –carbene complexes and acetylenes.^[10] Complex polyannulated quinones are available by the D ötz reaction, e.g. the chrysene-6,12-quinone **2** is available from the alkyne-functionalized Fischer carbene complex **1** (**Scheme 2**).^[11]

Scheme 2 Fischer Carbene Benzannulation Reaction^[11]

Versatile starting materials for the synthesis of many quinone targets include squaric acid and the corresponding dialkyl squarates. Addition of metalated alkynes results in 4-hydroxycyclobutenones, which undergo thermal ring opening to give benzo-1,4-quinones (**Scheme 3**).^[12] When the analogous vinylated 4-hydroxycyclobutenones are ring opened, an additional oxidation step [often using ammonium cerium(IV) nitrate, air, or other reagents] is necessary. Analogously, benzocyclobutenediones can be used as starting materials for the synthesis of naphtho- and anthraquinones. Hetarene-fused quinones are available via addition of metalated heterocycles to cyclobutenediones and subsequent ring expansion.

Scheme 3 Ring Expansion of a 4-Hydroxycyclobutenone^[12]

The Friedel –Crafts reaction plays a major role in the synthesis of naphtho-1,4-quinones and anthra-9,10-quinones, in particular in industrial production. The preparation of the naphthazarin core (5,8-dihydroxynaphtho-1,4-quinone) by double Friedel –Crafts acylation of either hydroquinone or 1,4-dimethoxybenzene derivatives with maleic anhydride in fused aluminum trichloride/sodium chloride dates back to 1928. Many more applications, e.g.

in the synthesis of hetarene-fused quinones, have been reported and can be found in the respective sections of this volume. An elegant version of a sequential inter –intramolecular Friedel –Crafts acylation of α -oxo esters using oxalyl chloride as the bisacylating reagent takes advantage of the Lewis acid as a coordinating species, which generates reactive α -hydroxy enone chelates (**Scheme 4**).^[13]

Scheme 4 Friedel –Crafts Acylation of a α -Oxo Ester^[13]

A major part of modern anthraquinone syntheses relies on the Diels –Alder reaction, which gives access to virtually all possible substitution patterns under comparatively mild reaction conditions. Partial dehydrogenation may occur and often mixtures of tetrahydro, dihydro, and fully aromatized products are isolated. Naphtho-1,4-quinones were among the first classes of compounds derived via a [4 + 2]-cycloaddition reaction. Because quinones are relatively reactive dienophiles, the reaction usually takes place upon heating in nonpolar solvents (e.g., benzene, toluene, xylenes). As an example, the Diels –Alder reaction of 2,3-dichloro-5-hydroxynaphtho-1,4-quinone with Danishefsky's diene **3** to afford the alizarin-type anthra-9,10-quinone **4** is shown in **Scheme 5**.^[14]

Scheme 5 Diels –Alder Cycloaddition of a 2,3-Dichloronaphtho-1,4-quinone^[14]

In the presence of nucleophiles, *o*- and *p*-quinones behave as typical Michael acceptors. Upon oxidation of the Michael adduct, the original quinone system is restored resulting in a net hydrogen substitution process. Depending on the redox potential of the quinone and the reaction conditions, the oxidation often takes place spontaneously during the reaction initiated by the excess quinone, from air during workup, or by an additional oxidant used either after completion or during the addition reaction. In the last case the yield is often improved because oxidation of the intermediate hydroquinone/catechol derivative eliminates the possibility of a retro-Michael reaction. Neutral compounds, electron-rich hetarenes (e.g., the furan derivative **5** shown in **Scheme 6**),^[15] or anionic species such as enolates can be applied as nucleophiles.

Scheme 6 Transformation of a Naphtho-1,4-quinone by Michael Addition and Reoxidation^[15]

A common strategy to obtain substituted naphthoquinones in a regioselective way is the displacement of a leaving group by a nucleophilic reagent via Michael addition followed by elimination of the leaving group. In general, the second step takes place instantaneously during the addition reaction to afford the quinone skeleton. Thus, benzo- or naphthoquinones substituted by halogen, hydroxy, or alkoxy groups at the enone double bond behave like vinylogous acid halides or esters. Chloro- or bromo-substituted quinones, which are readily available, are often used as precursors for nucleophilic substitution. **Scheme 7** shows the displacement of a chloride in 2,3-dichloronaphtho-1,4-quinone by a carbamate group in two steps.^[16]

Scheme 7 Transformation of 2,3-Dichloronaphtho-1,4-quinone by Nucleophilic Substitution^[16]

Palladium-catalyzed cross-coupling reactions (e.g., Heck, Stille, Suzuki) are versatile methods for the synthesis of aryl-, vinyl-, or propargyl-substituted quinones. As an illustrative example, the Suzuki coupling of boronates with aryl bromides is used for the synthesis of aryl-substituted, furan-fused benzo-1,4-quinones. The boronate substituted, furan-fused benzo-1,4-quinone **6** is available via Dötz annulation of a (2-furyl)methoxycarbonyl complex with alk-1-ynylboronates, and subsequent palladium-catalyzed coupling with bromobenzene results in the phenyl-substituted, furan-fused benzo-1,4-quinone **7** in excellent yield (**Scheme 8**).^[17]

Scheme 8 Transformation of a Quinone by Palladium-Catalyzed Cross Coupling^[17]

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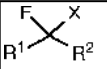
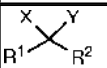
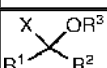
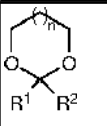
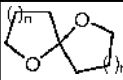
Compounds with Two Carbon–Heteroatom Bonds

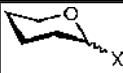
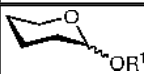
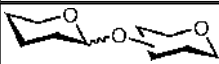
29

Volume 29:**Acetals: Hal/X and O/O, S, Se, Te**Warriner, S. L., in *Science of Synthesis*, **29** (2007), p.1

Volumes 29 and 30 of *Science of Synthesis* are jointly concerned with the synthesis of a class of functional groups that are characterized by the presence of exactly two heteroatoms singly bonded to a carbon atom, the classic feature of the acetal. Volume 29 deals primarily with acetals containing at least one oxygen or halogen atom while *Science of Synthesis*, Vol. 30 (Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues), deals with acetals of sulfur, nitrogen, and phosphorus (including O/N and O/P acetals). The product classes considered in Volume 29 are summarized in [Table 1](#).

Table 1 Classes of Acetals Covered in Volume 29

Product Class	Structure	Section
F/Hal acetals	 $\begin{array}{c} \text{F} \quad \text{X} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{R}^1 \quad \text{R}^2 \end{array}$ <p>X = F, Cl, Br, I</p>	29.1
Hal/Hal acetals (Hal = F)	 $\begin{array}{c} \text{X} \quad \text{Y} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{R}^1 \quad \text{R}^2 \end{array}$ <p>X = Y = Cl, Br, I</p>	29.2
Hal/O acetals	 $\begin{array}{c} \text{X} \quad \text{OR}^3 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{R}^1 \quad \text{R}^2 \end{array}$ <p>X = F, Cl, Br, I</p>	29.3
Hal/S, Hal/Se, and Hal/Te acetals		29.4
Hal/N and Hal/P acetals		29.5
O/O acetals: acyclic and semicyclic		29.6
O/O acetals: 1,3-dioxetanes and 1,3-dioxolanes		29.7
O/O acetals: 1,3-dioxanes, 1,3-dioxepanes and larger rings	 $\begin{array}{c} \text{O} \quad \text{O} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{R}^1 \quad \text{R}^2 \end{array}$ <p>n ≥ 1</p>	29.8
O/O acetals: spiroketals		29.9
O/O acetals: with functionalization attached to the acetal carbon		29.10

OR ¹ /OX acetals		29.11
O/S, O/Se, and O/Te acetals		29.12
glycosylX (X = Hal)	 X = F, Cl, Br, I	29.13
glycosylX (X = S, Se, Te)		29.14
glycosylO (not di- and oligosaccharides)		29.15
glycosylO (di- and oligosaccharides)		29.16

The content of this volume hence spans a huge range of science ranging from the halogen-containing acetals, generally reactive building blocks that are employed in synthesis, through the common acyclic and cyclic acetal protecting groups to finally reach the complex molecular architectures of spiroacetals and carbohydrate chemistry. This volume treats carbohydrate-derived acetals as a separate set of product classes, as frequently the chemistry involved in the synthesis of glycosyl functions requires special methods that do not sit easily with the themes running through traditional acetal chemistry.

The first part of the volume (Sections [29.1](#) –29.5) is concerned with halogen-containing acetals. Along with synthetic procedures that prepare the target halo acetals directly, a number of routes can also be linked with other transformations. For example, oxidative fragmentation of 2-halo glycosides provides access to a wide range of mixed halo acetals,^[1] while atom transfer radical cyclization provides an interesting route to Cl/Cl acetals with concomitant ring formation^[2] ([Scheme 1](#)).

Scheme 1 Oxidative Fragmentation of Anomeric Alkoxy Radicals and Atom Transfer Radical Cyclization^[1,2]

Hal/S, Hal/Se, Hal/Te, Hal/N, and Hal/P acetals are characterized by the presence of a reactive halogen linked to an electron-donating atom; as such, the reactivity of these classes of compounds, considered in Sections [29.4](#) and [29.5](#), is dominated by the loss of the halide leaving group and the modification of the acetal

carbon. These product classes are reactive and are often precursors to the more stable acetal functionalities described later in the volume and also in *Science of Synthesis*, Vol. 30 (Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues). Stereoselective syntheses of halo acetals are relatively rare but in the case of sulfoxides the stereogenic sulfur can be used to induce selective chlorination.^[3] The resulting enantiomerically enriched α -halo sulfoxides can be transformed into the α -halo Grignard reagents, which are configurationally stable (**Scheme 2**).^[3] The synthesis of fluorophosphonate **1** is a rare example of catalytic asymmetric synthesis of a halo acetal.^[4]

Scheme 2 Asymmetric Synthesis of Halo Acetals^[3,4]

The reactivity of the Hal/O acetals makes this compound class an ideal precursor to O/O acetals, and they are the most common starting point for the preparation of the open-chain acetal class of protecting group such as methoxymethyl ethers. Hal/O acetals are also excellent precursors of α -metalated ethers. Samarium(II) iodide mediated reaction of benzyl chloromethyl ether with ketones gives the selectively protected diol (**Scheme 3**).^[5]

Scheme 3 Samarium(II) Iodide Mediated Synthesis of a Monoprotected Diol^[5]

O/O Acetals are the most widely investigated class of acetal and are considered in Sections 29.6–29.11. Section 29.6 discusses the preparations of acyclic and semicyclic acetals (acetals in which the acetal carbon and only one of the oxygens are part of a cyclic structure). These product classes are most commonly found in acetal protecting groups such as methoxymethyl and tetrahydropyranyl ethers along with an array of other molecules that are valuable building blocks in organic synthesis. The asymmetric synthesis of substituted benzaldehyde acetal **2** is an elegant example of the relay of stereochemical information from a chiral axis to

the newly formed stereogenic center. In semicyclic acetal synthesis, hetero-Diels –Alder reactions provide a highly controlled route to the stereoselective synthesis of densely functionalized dihydropyranyl ethers (**Scheme 4**).^[7]

Scheme 4 Asymmetric Synthesis of Acyclic and Semicyclic Acetals^[6,7]

Sections **29.7** and **29.8** deal with the main classes of cyclic acetals, acetals in which both the acetal carbon and both acetal oxygens are contained within the same ring. Both these product classes rest at the heart of modern chemistry as a consequence of their importance as protecting groups. Unlike many protection reactions, in which selectivity is determined by kinetic reactivity, the selectivity in the protection of polyols as cyclic acetals is often determined by the thermodynamic stability of the acetal product. The result can be exquisite control in which correct choice of cyclic acetal group determines the pattern of protection. The complementary protection of the 1,2-diol in butane-1,2,4-triol by acetone^[8] and the 2,4-diol pair by benzaldehyde^[9] is the archetypal demonstration. (**Scheme 5**)

Scheme 5 Selective Protection of Butane-1,2,4-triol^[8,9]

The synthesis of spiroketals, a feature of many of the most elegant natural products, is discussed in Section **29.9**. In many of the syntheses, formation of the spirocyclic acetal function is spontaneous and the authors have concentrated on discussing the differing strategies that can be employed to prepare the precyclization precursors. The section hence provides a definitive discussion of the current state of the art for the preparation of these molecules, which range from simple insect pheromones to the core of natural products such as okadaic acid (**3**), which contains three separate spiroketal motifs (**Scheme 6**).

Scheme 6 A Spiroketal-Containing Natural Product

Sections **29.10** and **29.11** deal with special classes of O/O acetal that have additional functionalization present on the carbon or oxygen atom of the acetal moiety, respectively. OR¹/OX Acetals (X = N, S, O, or metal) include structures formed in the cycloadditions of vinyl ethers, such as tricyclic compound **4**,^[11] and also the peroxyacetals formed during ozonolysis and also found in the remarkable antimalarial natural product artemisinin (**5**) (**Scheme 7**).

Scheme 7 OR¹/OX Acetals^[11]

Although the vast majority of syntheses of acetals employ the conversion of carbonyl equivalents into the acetal function, neighboring functionality sometimes offers different synthetic opportunities and these specialist areas are the subject of Section **29.10**. For example, 2-halo-functionalized acetals can often be easily prepared through haloetherification reactions of enol ethers. The haloetherification of dihydrofuran with isomenthol gives two diastereomers that are easily separated. Cobalt-catalyzed arylation and removal of the auxiliary provides an efficient route to enantiomerically pure 3-aryltetrahydrofurans (**Scheme 8**).^[12]

Scheme 8 2-Halo Acetals via Haloetherification^[12]

The vast array of O/S and O/Se acetals is the focus of Section **29.12**, which includes the synthesis of both open-chain and cyclic examples of these functional groups. Sulfonyl acetals are useful intermediates in organic synthesis as the sulfonyl group can be used to stabilize anions at the acetal center and then be transformed in a variety of ways. Sulfonyloxiranes such as **6** also fall under the general class of O/S acetals (**Scheme 9**).^[13,14]

Scheme 9 Synthesis and Reactivity of Sulfonyloxiranes^[13]

Sections **29.13** –29.16 are concerned specifically with the preparation of carbohydrate-derived acetals. Within this volume, the trivial names of carbohydrates are used; an extensive discussion of the rules for nomenclature of carbohydrates is available.^[15] Different representations of the structures of common monosaccharides are shown in Schemes 10 –12. Within the volume, the 5-membered furanose form is often represented as a Haworth projection and these are also shown in **Scheme 10**. Similarly, the six-membered pyranoside form of saccharides is frequently represented in its chair conformation. The ⁴C₁ chair conformers of the common pyranose sugars are also shown in **Scheme 11**, although it is known that highly axial-substituted sugars, particularly idose and altrose also adopt alternative ring-flipped ¹C₄ and skew-boat conformers.^[16] The pyranoside forms of some other common sugars are shown in **Scheme 12**

Scheme 10 -Furanose Forms of Five-Carbon Sugars

Scheme 11 -Pyranose Forms of Hexoses

Scheme 12 Pyranose Forms of Some Other Common Sugars

In summary, the name of a monosaccharide comprises three key stereochemical descriptors. The name of the sugar (gluco-, manno-, etc.) defines the relative stereochemistry of all of the stereogenic centers except that of the acetal carbon, while the prefix D- or L- defines the absolute stereochemistry of the highest-numbered asymmetric center. Hence, from the combination of D or L and the name of the sugar it is possible to determine the absolute configuration of all of the centers within the molecule with the exception of the acetal position. The configuration of the acetal center within the cyclic form is defined by the prefix α or β and shows the relationship between the configurational reference atom (which is the highest numbered asymmetric carbon for sugars with up to six carbons) and the acetal center. In the α -anomer the stereochemistry of the exocyclic oxygen at the acetal is formally *cis* to the oxygen at the anomeric reference center in a Fischer projection. Fortunately, for the common hexoses in their six-membered cyclic pyranose forms, this formal definition boils down to a *trans* relationship between the exocyclic oxygen at the acetal and the group at C5 corresponding to an α -relationship. For the common pyranoses (glucose, galactose,

mannose), which predominately exist in a C_1 conformation, the β -isomer can also be identified by the axial orientation of the exocyclic oxygen. The formalities of the nomenclature system bring about some peculiarities, which are illustrated in **Scheme 13**. D-Galactose (**7**) and L-arabinose (**8**) have the same absolute stereochemistry at C2, C3, and C4 but have different absolute stereochemical descriptors, as for galactose the determining center is at C5 whereas in arabinose it is at C4 as C5 is no longer stereogenic. The change in determining atom also reverses the α and β definitions at the anomeric center. Thus, despite having virtually identical structures, the descriptors of **7** and **8** are different. The case of *N*-acetylneuraminic acid (sialic acid, formal name 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulopyranosonate) is yet more complicated, with the definition of stereochemistry and anomeric configuration being determined by stereogenic centers within the side chain. The formal definitions result in the naturally occurring molecule having the configurations shown in **Scheme 13** in which, importantly, the β -isomer has an equatorial disposition of the exocyclic oxygen.

Scheme 13 Some Peculiarities of Carbohydrate Nomenclature

The carbohydrate sections of Volume 29 start with consideration of the synthesis of halo glycosides (Section **29.13**). An interesting example of halide formation occurs during the treatment of glycoside **9** with *N,N*-diethylaminosulfur trifluoride (**Scheme 14**). Formation of the glycosyl fluoride occurs with concomitant rearrangement providing access to a range of modified glycosyl donors that are stereospecifically modified at C2.^[17]

Scheme 14 Synthesis of Glycosyl Fluorides with Migration^[17]

Although the main route of exploitation of thio-, seleno-, and telluroglycosides (Section **29.14**) occurs in their use as glycosyl donors, the orthogonality of sulfur chemistry also presents other opportunities. Glycosyl thiosulfonates such as **10** enable the attachment of carbohydrates to cysteine side chains in proteins (**Scheme 15**).^[18]

Scheme 15 Functionalization of Proteins Using Glycosyl Thiosulfonates

The synthesis of O-glycosides is broken down into two sections: the preparation of compounds with non-carbohydrate derived aglycones is considered in Section 29.15 whilst disaccharides and oligosaccharides are considered in the final section of the volume, Section 29.16. The synthesis of complex carbohydrates is an enormous field and the authors present an excellent guide to both the main reactions currently employed to synthesize the glycosidic bond, and the strategies that can be employed to link these reactions together for the efficient assembly of complex carbohydrate architectures. The enzymatic synthesis of tetrasaccharide 11 [19] (Scheme 16) is a fitting final example for Volume 29 showing how the chemistry of the acetal group stretches from the synthesis of simple functionalized building blocks to the frontiers of chemistry and biology.

Scheme 16 Enzymatic Synthesis of Oligosaccharides Using a Mutated Enzyme^[19]

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Compounds with Two Carbon–Heteroatom Bonds

30

Volume 30:

Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues

Otera, J., in *Science of Synthesis*, **30** (2006), p.1

General Introduction

This volume is concerned with the synthesis of acetal-type compounds involving two carbon —heteroatom bonds at the geminal position, mainly focusing on heteroatoms heavier than oxygen. The combinations of heteroatoms covered in this volume are diverse, including O/N, O/P, S/P, S/S, S/N, S/Se, S/Te, Se/Se, Se/Te, Se/N, Se/P, Te/Te, Te/N, Te/P, N/N, N/P, and P/P. These are summarized in [Table 1](#) together with the sections in which they appear.

Table 1 Classes of Acetals Covered in Volume 30

Product Class	Subclass	Section
O,N-acetals		30.1
	acyclic	30.1.1
	cyclic	30.1.2
	carbohydrate derivatives (including nucleosides)	30.1.3
O,P- and S,P-acetals		30.2
S,S-acetals		30.3
	acyclic S,S-acetals	30.3.1
	1,3-dithietanes	30.3.2
	1,3-dithiolanes	30.3.3
	1,3-dithianes	30.3.4
	1,3-dithiepanes	30.3.5
	S,S-acetal S-oxides and S,S-dioxides	30.3.6
	deprotection of S,S-acetals	30.3.7
S,N-acetals		30.4
Se- and Te-containing acetals		30.5
N,N-acetals		30.6
N,P- and P,P-acetals		30.7

Among them, the S,S-acetals play the most important roles because of both availability as protecting groups and versatility as acyl anion equivalents to effect facile C —C bond formation. They have been employed extensively in organic synthesis and thus Section [30.3](#), which deals with this subject, occupies more than half of this volume. In this context, special introductory comments have been included in Section [30.3](#) so that this important class of compounds can be specifically summarized. As a result, this introduction will outline the other product classes.

Section [30.1](#) deals with O,N-acetals, in which an sp³-carbon is bonded to nitrogen and oxygen. The simplest form is derived from combination of amino and alkoxy groups leading to O,N-acetals [1](#). In sharp contrast to O,O-acetals, the hemiacetals of which are usually very unstable, the oxygen function can be a hydroxy group to give aminals [2](#). The cyclic derivatives are also available in three forms: [3](#), [4](#), and [5](#) ([Scheme 1](#)). Essentially

the same methods are employed for synthesis of both acyclic and cyclic compounds. Addition of amines to carbonyl compounds is the most common way,^[1] while hydride addition to amides is also useful.

Transacetalization between *O,O*-acetals with amines is feasible. In particular, this method is employable for the synthesis of cyclic *O,N*-acetals. For this class of compounds, direct acetalization of carbonyls with chiral amino alcohols is also of great use to provide various building blocks for asymmetric synthesis.

Scheme 1 Structures of Acyclic and Cyclic *O,N*-Acetals

Aminals or *O,N*-acetals undergo facile C—O bond cleavage to give rise to subsequent C—C bond formation on the acetal carbon. The reaction is induced by Lewis acids and proceeds via a carbocation, which is stabilized by the contribution of an iminium structure (**Scheme 2**).^[1–3] C—C bond formation is also catalyzed by some transition-metal catalysts.

Scheme 2 Lewis Acid Promoted C—C Bond Formation of *O,N*-Acetals^[1–3]

The synthetic utility of *O,N*-acetals is highlighted for carbohydrate derivatives with particular emphasis on nucleosides and *N*-glycoproteins in Section **30.1.3**

The synthesis of *O,P*- and *S,P*-acetals is described in Section **30.2**. One of the characteristic features of this class of compounds is facile formation by addition of a P—H bond to carbonyl groups (**Scheme 3**).^[4] A variety of phosphorus-containing acetals are available using this strategy, irrespective of the use of phosphorus(III) or phosphorus(V). The reaction is utilized successfully for the synthesis of phosphorus-containing carbohydrates.^[5] Another versatile method is to use addition of phosphorus anions to carbonyl compounds.^[6,7] Again, this protocol is applicable for both phosphorus(III) and phosphorus(V). The *S,P*-acetals are obtained basically by the same methodology.

Scheme 3 Addition of a P—H Bond to a Carbonyl Group^[4]

Combination of S- and N-functions is the subject of Section **30.4**. *S,N*-Acetals, of general structures **6** and **7**, are not only useful building blocks in organic synthesis but also include sulfur-containing bicyclic β -lactams **8** and **9** (**Scheme 4**).

Scheme 4 S,N-Acetals and Sulfur-Containing Bicyclic β -Lactams

In addition to the orthodox S,N-acetalization method of carbonyl compounds, these compounds can be obtained by various specific reactions based on strong nucleophilicity or reactivity of the sulfur functions. Upon exposure to Grignard or organolithium reagents, the C—S bond is cleaved preferentially to the C—N bond, affording a variety of alkylamines (**Scheme 5**).^[8,9]

Scheme 5 Reaction of *N*-Aryl-*N*-[(phenylsulfanyl)methyl]methylamine with Grignard and Organolithium Reagents^[8,9]

When the nitrogen is bonded to aromatic or electron-withdrawing groups, normal deprotonation occurs at the acetal carbon with butyllithium (**Scheme 6**).^[10]

Scheme 6 Lithiation at the Acetal Carbon Followed by Alkylation^[10]

The heaviest acetals containing selenium and tellurium functions are described in Section **30.5**, including S,Se-, S,Te-, Se,Se-, Se,Te-, Te,Te-, Se,*N*-, Se,*P*-, Te,*N*-, and Te,*P*-acetals. Because both elements are heavier members of the same group as sulfur in the periodic table, essentially the same methods used to prepare sulfur-containing acetals can be employed for the selenium and tellurium analogues. As expected, these acetals behave similarly to their oxygen and sulfur analogues in some cases. For example, Se,Se-acetals can be readily metalated by treatment with metal amides, and the resulting β -metallo Se,Se-acetals are useful precursors to substituted Se,Se-acetals.^[11–14] they are also found to be valuable acyl anion equivalents. On the other hand, these heavier derivatives also exhibit characteristic reactivities different from the sulfur-containing acetals, thus occupying a unique position in organic synthesis. The C—Se and C—Te bonds of the acetals are easily cleaved homolytically or heterolytically and useful intermediates such as β -organoselanyl carbanions, β -selanylcarbenium ions, and β -selanyl- or non-selanyl carbon radicals are feasible. β -(Organoselanyl)alkyllithiums bearing alkyl and aryl groups can be generated by selenium–lithium exchange of Se,Se-acetals or triselenoortho esters with butyllithium in tetrahydrofuran/hexane, accompanied by loss of a butyl selenide (**Scheme 7**).^[11] In particular, the reactions of selenium-stabilized carbanions with electrophiles such as allylic alcohols, epoxides, alkenes, and ketones can provide a wide variety of

organoselanyl or non-selanyl compounds.

Scheme 7 Generation of α -(Organoselanyl)alkyllithiums Followed by Reaction with an Electrophile^[11]

The Se,Se-acetals can provide α -selanyl carbocations, which are good electrophiles in Lewis acid mediated C—C bond formation (**Scheme 8**). Applications of this technology to cationic intramolecular cyclization lead to various carbocycles^[15,16] or heterocycles.^[17,18]

Scheme 8 Generation of α -Organoselanyl Carbocations Followed by Reaction with a Nucleophile^[15–18]

The final active species are the carbon-centered radicals produced by the homolytic cleavage of the C—Se bond with tributyltin hydride/triethylborane or 2,2'-azobisisobutyronitrile (**Scheme 9**).^[19] Such versatilities exemplify the synthetic potential of the Se- and Te-containing acetals.

Scheme 9 Homolytic Cleavage of C—Se Bonds^[19]

In Section 30.6, *N,N*-acetals are described. These compounds serve as good protecting groups for carbonyls because they are relatively stable but readily cleaved under acidic conditions. The compounds are most conveniently prepared by *N,N*-acetalization of aldehydes with amines (**Scheme 10**).^[20–23] Synthetic utilization of this class of compounds is limited, but a few examples are given in this section.

Scheme 10 *N,N*-Acetalization of Aldehydes with Amines^[20–23]

The final subjects, *N,P*- and *P,P*-acetals, are described in Section 30.7. The methods employed for the synthesis of these compounds are somewhat similar to those for the *O,P*- and *S,P*-acetals in Section 30.2. Addition of a P—H bond to a carbonyl group in the presence of amine is effective, and direct addition to imines is also useful. Reaction of phosphorus anions with (α -haloalkyl)amines is also available. Essentially similar methods can be employed for the synthesis of *P,P*-acetals. All of these protocols are applicable to both phosphorus(III) and phosphorus(V) reagents.

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Compounds with Two Carbon–Heteroatom Bonds

31

Volume 31:

Arene—X (X = Hal, O, S, Se, Te, N, P)

Ramsden, C. A., in *Science of Synthesis*, **31** (2007), p.1

General Introduction

This volume describes the preparation and important reactions of arene derivatives [$\text{Ar}^1\text{—X}$, where X is a functional group in which the atom bonded to the arene ring is either fluorine, chlorine, bromine, iodine, oxygen, sulfur, selenium, or tellurium (Volume 31a), or nitrogen or phosphorus (Volume 31b)]. These elements give rise to a large number of discrete functional groups, as illustrated in [Tables 1](#) and [2](#), where R^1 is a typical alkyl or aryl substituent, and L is an electronegative ligand/substituent. For each element bonded to the arene ring the number of stable functional groups increases as the valency increases, and also as the electronegativity () decreases, since the strength of hypervalent bonds increases as the electronegativity difference between the element and the ligand increases. Thus, iodine, being the least electronegative of the halogens (= 2.5), forms a number of useful and stable hypervalent derivatives in addition to simple iodides, and nitrogen (= 3.0) and phosphorus (= 2.1) require a whole volume to cover their diverse functional groups.

Table 1 Structures of the Parent Systems Covered in Volume 31a

Compound	Structural Formula	Section
fluoroarenes	Ar^1F	31.1
chloroarenes	Ar^1Cl	31.2
bromoarenes	Ar^1Br	31.3
hypervalent iodoarenes and arylodonium salts		31.4.1
iodoarenes	Ar^1I	31.4.2
phenols and phenolates		31.5
diaryl ethers	Ar^1OAr^2	31.6.1
alkyl aryl ethers	Ar^1OR^1	31.6.2
aryl hypohalites, aryl peroxides, and aryloxy sulfur derivatives	Ar^1OX $\text{Ar}^1\text{—O—OR}^1$ $\text{Ar}^1\text{—O—SY}$	31.7
cyclic aryl ethers		31.8
arenesulfonic acids	$\text{Ar}^1\text{SO}_3\text{H}$, $\text{Ar}^1\text{SO}_3\text{M}$	31.9.1
arylsulfur pentahalides	Ar^1SX_5	31.9.2.1.1
arenesulfonyl halides	$\text{Ar}^1\text{SO}_2\text{X}$	31.9.2.1.2
arenesulfonates, arenesulfonic anhydrides, and arenesulfonyl peroxides		31.9.2.1.3
arenesulfonamides, <i>N</i> -haloarenesulfonamides, <i>N</i> -hydroxyarenesulfonamides, and <i>N</i> -oxoarenesulfonamides		31.9.2.1.4
arenesulfonylhydrazides, <i>N</i> -nitrosoarenesulfonamides, and <i>N</i> -		31.9.2.1.5


nitroarenesulfonamides		
arenesulfonyl azides		31.9.2.1.6
aryl sulfones and N-derivatives		31.10
arenesulfinic acids and derivatives		31.11
aryl sulfoxides and N-derivatives		31.12
arenethiols and arenethiolates	Ar¹SH, Ar¹SM	31.13
aryl sulfides	Ar¹SAr¹, Ar¹SR¹	31.14
arylsulfonium salts		31.15
arenesulfenic acids and derivatives		31.16
aryl di- and polysulfides		31.17
cyclic aryl sulfides		31.18
aryl selenium compounds		31.19
aryl tellurium compounds		31.20

Table 2 Structures of the Parent Systems Covered in Volume 31b

Compound	Structural Formula	Section
nitroarenes	Ar¹NO ₂	31.21

nitrosoarenes	Ar NO	31.22
arenediazonium salts	$\text{Ar}^1\text{N}_2^+ \text{X}^-$	31.23
azoxyarenes	$\text{Ar}^1\text{N}=\text{NOR}^1$	31.24
azoarenes	$\text{Ar}^1\text{N}=\text{NR}^1$	31.25
aryliminophosphines and aryliminophosphoranes	$\text{Ar}^1\text{N}=\text{PR}^1$, $\text{Ar}^1\text{N}=\text{PR}^1_3$	31.26
arylamine oxides and aryl nitroxyl radicals		31.27
arylamines	Ar^1NR^1_2	31.28
arylammonium salts	$\text{Ar}^1\text{NR}^1_3^+ \text{X}^-$	31.29
<i>N</i> -silylarylamines	$\text{Ar}^1-\text{N}(\text{R}^1)-\text{SiR}^2_3$	31.30
<i>N</i> -borylarylamines	$\text{Ar}^1-\text{N}(\text{R}^1)-\text{BR}^2_2$	31.31
<i>N</i> -haloarylamines	$\text{Ar}^1-\text{N}(\text{R}^1)-\text{X}$	31.32
<i>N</i> -arylhydroxylamines	$\text{Ar}^1-\text{N}(\text{R}^1)-\text{OR}^2$	31.33
arylhydrazines	$\text{Ar}^1-\text{N}(\text{R}^1)-\text{NR}^2_2$	31.34
aryl azides	Ar^1N_3	31.35
aryltriazenes, aryltetrazenes, and related compounds		31.36
<i>N</i> -phosphinoarylamines		31.37
cyclic arylamines		31.38
arylphosphonic acids and derivatives	$\text{Ar}^1\text{PO}(\text{OR}^1)_2$	31.39
arylphosphinic acids and derivatives	$\text{Ar}^1\text{R}^1\text{PO}(\text{OR}^2)$	31.40
arylphosphine oxides	$\text{Ar}^1(\text{R}^1)_2\text{P}=\text{O}$	31.41
arylphosphines and derivatives	Ar^1PR^1_2	31.42
arylphosphonium salts and derivatives	$\text{Ar}^1\text{PR}^1_3^+ \text{X}^-$	31.43
P-heteroatom-functionalized arylphosphines		31.44

In addition to benzene and substituted benzene derivatives, the scope of this volume also includes polycyclic derivatives (e.g., naphthalene derivatives), rings having cyclic unsaturation (e.g., cyclobutadiene and cyclooctatetraene derivatives), and heteroarenes (e.g., pyridine derivatives). In general, nonbenzenoid and heterocyclic examples are included to demonstrate the scope of a method, or if the nonbenzenoid derivatives have

special importance. A comprehensive coverage of nonbenzenoid derivatives would, however, be beyond the scope of this work.

Experimental procedures for the preparation of each product subclass are included; however, the coverage of preparative methods is not necessarily comprehensive. Priority has been given to methods that are of general applicability, or are routes to important compounds. Since the primary objective of this volume is to describe useful methods of preparation, reaction mechanisms are not routinely included, and the physical properties and applications of compounds are discussed only briefly. The discussion of each subclass generally adheres to a hierarchical format, where methods are discussed in the order: substitution, elimination, addition, rearrangement, and retention of the functional group. However, because of the wide variety of chemistry employed to prepare substituted arenes, some variation in presentation does occur. For example, substitution includes both electrophilic substitution on an arene ring (replacement of an atom or substituent) and nucleophilic substitution on a functional group (modification of a substituent). Furthermore, the relative importance of these different substitution reactions can vary widely between product subclasses. Oxidation and reduction are sometimes referred to as addition and elimination processes. For example, the oxidation of sulfides to sulfoxides can be regarded as an addition of oxygen, whereas oxidation of a benzene-1,2-diol to a benzo-1,2-quinone may be regarded as an elimination of hydrogen. Where oxidation and reduction are the common descriptions of these processes, the terms have been retained to describe the method. Where applicable, references to relevant material in *Houben –Weyl* have been included. In addition, many of the product classes included in this volume are also described in other reference works.^[1,2]

A superficial analysis might suggest that the chemistry of arenes, especially benzene derivatives, is an exhausted field. This is far from the truth. New arene methodology continues to be at the forefront of synthetic research, as exemplified by palladium-catalyzed substitution, vicarious nucleophilic substitution, and activation by transition-metal-complex formation. These innovations are driven by the important contribution that arene derivatives make to industrial products, including pharmaceuticals and agrochemicals, and there can be few synthetic laboratories that do not routinely prepare arene derivatives as either intermediates or final products.

It is certainly true that the chemistry of arene derivatives ($\text{Ar}^1\text{—X}$) is probably the oldest branch of organic chemistry. Serious interest in "aromatic chemistry" was probably triggered by the foundation of the gas industry in the middle of the nineteenth century, and the subsequent availability of coal tar as a byproduct of this industry. Perkin's discovery of the first coal-tar dye, mauveine, in 1856, and Lister's use of carbolic acid (phenol) as a surgical disinfectant in 1865, added impetus to the search for new and useful aromatic compounds in pure form. Coal tar is rich in benzene and other arenes, and was therefore an economical source of the aromatic amines that were required to make the newly discovered synthetic dyes. The work of Perkin and others led to the formation of the synthetic dye industry, resulting in a huge growth in interest in benzene derivatives, which, in turn, led to the discovery of the antibacterial sulfonamides via the red dye Prontosil. The discovery of the sulfonamides by the infant pharmaceutical industry in the early 1930s led to another massive wave of interest in arene derivatives that continues to the present day.

Michael Faraday discovered benzene (**1**) in 1825 as a component of an illuminating gas made from whale oil. In fact, he was probably the first person to nitrate benzene having, on May 24th, 1825, treated it with nitric acid to give a substance "smelling like almonds", although the nature of this product remained unrecognized. Subsequently, nitrobenzene (**3**) was prepared and characterized in 1834 by Mitscherlich, who also achieved the first synthesis of benzene (**1**) by decarboxylation of benzoic acid in 1833 and assigned the correct molecular formula (**Scheme 1**).^[3,4] These nitrations must have been among the earliest in vitro electrophilic substitution reactions of arenes, and since the 19th century electrophilic substitution methodology for the preparation of arene derivatives has been constantly developed and refined.

Scheme 1 Electrophilic Aromatic Nitration^[3,4]

Electrophilic aromatic substitution (S_EAr), as exemplified by the nitration of benzene (**1**) via an arenium cation **2** (**Scheme 1**), is probably the most important synthetic route to arene derivatives (Ar^1-X) or their precursors. Important chemical developments continue in this field, including the introduction of commercial fluorinating reagents such as Selectfluor (**4**) (**Scheme 2**).^[5–7]

Scheme 2 Electrophilic Fluorination Using Selectfluor^[7]

Technological changes have also aided development, such as with the development of continuous-flow microreactors for safe and convenient fluorination using elemental fluorine gas diluted with nitrogen (**Scheme 3**).^[8]

Scheme 3 Fluorination Using Elemental Fluorine in a Microreactor^[8]

Interest in the synthesis of dyes soon led to another class of arene reaction, namely nucleophilic aromatic substitution (S_NAr). In 1858, Griess was the first person to isolate a diazonium salt **5**, by treating picramic acid with nitrogen trioxide in cold ethanol, and he recognized it as a member of a new class of compound. This led not only to the azo dyes, but also to versatile methods of converting anilines into a wide variety of aromatic derivatives. These methods include the Balz –Schiemann reaction for the preparation of fluoroarenes,^[9] which occurs via a reactive arene cation **6**, and the well-known copper(I)-catalyzed Sandmeyer reaction, which occurs via an aryl radical **7** (**Scheme 4**).^[10,11] These reactions are often described as proceeding by a unimolecular mechanism (S_NAr1).

Scheme 4 Thermal and Copper-Catalyzed Substitution of Arenediazonium Salts^[9,12]

Later, bimolecular nucleophilic procedures (S_NAr2), proceeding via the substituent-stabilized anionic intermediates known as Meisenheimer complexes, e.g., anion **8** ($R^1 = NO_2$), were recognized (**Scheme 5**). Nucleophilic substitution by both of these mechanisms (S_NAr1 and S_NAr2) continues to be important in both aromatic and heteroaromatic synthesis.^[12,13]

The early studies and applications of aromatic substitution are remarkable when it is appreciated how much of this chemistry was developed before Kekulé suggested that benzene is composed of a ring of carbon atoms (1865), and before Ladenburg and Wroblewsky demonstrated the equivalence of all the carbon atoms in benzene (1874). Understanding the mechanism of nucleophilic substitution came much later, when the electronic theory of organic chemistry had been developed by Ingold, Lapworth, Robinson, and others.^[14] In 1953 the involvement of benzyne intermediates **9** in some aromatic substitution reactions that employ a very strong base was demonstrated by Roberts, and this mechanism has become known as the aryne mechanism (**Scheme 5**).^[15,16]

Scheme 5 The Bimolecular Nucleophilic Aromatic Substitution and Aryne Mechanisms^[12,15]

In a more recent development, nucleophilic substitution may be facilitated by the formation of a transition metal ⁶-complex with the aromatic ring. For example, formation of a tricarbonylchromium complex with electron-rich fluoroarenes activates the ring, enabling nucleophilic substitution by amines, alkoxides, and thiolates (**Scheme 6**).^[17] The electronic effect of the chromium metal is similar to that of a 2- or 4-nitro substituent in a Meisenheimer complex, e.g. **8** ($R^1 = NO_2$).

Scheme 6 Nucleophilic Substitution Activated by Chromium Complexation^[17]

In 1970, Bunnett and Kim observed results using iodoarenes that could not be explained by an existing mechanism. This led to the discovery of a pathway involving initial formation of a radical anion, followed by loss of iodide and reaction of the resulting aryl radical with a nucleophile [usually amide anion (NH_2^-)]. This mechanism is known as unimolecular radical nucleophilic substitution, ($S_{RN}Ar1$),^[18] and the process is summarized in **Scheme 7**.

Scheme 7 Unimolecular Radical Nucleophilic Substitution

Although both the aryne and unimolecular radical nucleophilic substitution mechanisms are useful additions to the aromatic substitution repertoire, they are not as versatile and generally useful as the unimolecular and bimolecular nucleophilic aromatic substitution methods (S_NAr1 and S_NAr2). It is interesting to note, therefore, that a more recent development is of both mechanistic interest and broad potential value as a synthetic method. This method is vicarious nucleophilic substitution (VNS), which has been developed since the 1980s by M. Kosza as a new approach to substitution of hydrogen by nucleophiles. The essential features of vicarious nucleophilic substitution are shown in **Scheme 8**.^[19]

Scheme 8 Vicarious Nucleophilic Substitution^[19]

This approach differs from bimolecular nucleophilic aromatic substitution (S_NAr2) in that the leaving group (X) is on the nucleophile ($X-Nu^-$) rather than on the aromatic ring. Thus, initial nucleophilic attack, at the 2- or 4-position relative to the nitro group, converts nitrobenzenes **10** into anions **11**. Elimination of the leaving group (as HX) gives anion **12**, which rearomatizes under acidic conditions to give the desired product **13**, in which a ring hydrogen has been substituted by carbon, nitrogen, or oxygen. Specific examples illustrating preparation of phenol and aniline derivatives are given in **Scheme 9**.^[20,21] The method is also widely applicable to heteroarenes.

Scheme 9 Phenol and Aniline Formation by Vicarious Nucleophilic Substitution^[20,21]

During the last two decades of the 20th century there were a number of important advances in the development of synthetically useful substitution reactions proceeding via free-radical mechanisms. The main thrust of these studies involved alkyl radicals and C—C bond formation, but the work also embraced aryl radicals and the formation of aryl—heteroatom bonds. Reactions involving intermediate arene radicals have been known for a long time. In 1934 Hey made the controversial assessment that, in order to account for the lack of influence of the substituent on isomer distribution, phenyl radicals must be involved in the Gomberg phenylation reaction (**Scheme 10**).^[22]

Scheme 10 The Gomberg Phenylation Reaction^[22]

As noted in **Scheme 4**, the copper(I)-catalyzed Sandmeyer reaction proceeds via an aryl radical **7**. Important developments later in the century were concerned with the generation of radicals under controlled conditions to give synthetically useful products: radicals that Sir Derek Barton, a leader in the field, often referred to as "disciplined radicals".^[23–25] An important modern route to aryl radicals is the treatment of bromo- or iodoarenes with tributyltin hydride, usually in the presence of a radical initiator such as 2,2'-azobisisobutyronitrile (AIBN). The driving force for these reactions is the formation of a strong tin—halogen bond by reaction between the haloarene and a tributylstannyl radical in what is formally a bimolecular homolytic substitution reaction (S_H2). A nice illustration of this approach is a reaction described by Beckwith and Boate in which the cyclic sulfide **15** is formed by treatment of the bromide **14** with tributyltin deuteride in a solution of hot benzene (**Scheme 11**).^[26]

Scheme 11 Intramolecular Bimolecular Homolytic Substitution^[26]

Other functional groups have been found to be convenient precursors of aryl radicals (so-called "radical triggers") including thiohydroxamic esters such as **17**. This ester is readily prepared from the corresponding carboxylic acid **16**. Heating the ester **17** in the presence of excess bromotrichloromethane, together with a small amount of 2,2'-azobisisobutyronitrile as an initiator, gives the bromoarene **18** in 62% yield as shown in **Scheme 12**.^[27]

Scheme 12 Radical Decarboxylative Bromination Using a Thiohydroxamic Ester^[27]

Another area of arene chemistry that has a history extending over a century, but with many significant developments in recent decades, is the use of organometallic reagents. Grignard reagents were discovered in 1900 and the Ullmann reaction, which employs copper catalysis, was first described in 1904. Like aryl radical chemistry, arene organometallic methodology has been primarily directed to the formation of aryl —carbon bonds; however, several important applications also embrace formation of aryl —heteroatom and hetaryl —heteroatom bonds.

One important development occurred in 1934 when Gilman demonstrated directed *ortho*-lithiation of arenes, in which a suitable substituent facilitates lithiation exclusively at the *ortho* position and then stabilizes the resulting aryllithium reagent.^[28] Early work focused on methoxy substituents but subsequently many other metalation-directing groups have been employed (**Scheme 13**). Further information can be found in *Science of Synthesis*, Vol. 8a [Compounds of Group 1 (Li . . . Cs) (Section 8.1.14)]. Advantages of directed *ortho*-metalation include (a) the replacement of hydrogen by a variety of substituents via the nucleophilic aryllithium and (b) exclusive formation of the *ortho*-product, rather than a mixture of *ortho*- and *para*-isomers, which is often a serious disadvantage of direct bimolecular electrophilic substitution ($\text{Ar}_\text{E}2$).

Scheme 13 Directed *ortho*-Lithiation^[28]

Directed *ortho*-lithiation methodology is exemplified by the formation of unsymmetrical diaryl sulfides and fluoroarenes using a disulfide and *N*-fluorobenzenesulfonimide as the electrophile, respectively (**Scheme 14**).
[29,30]

Scheme 14 Diaryl Sulfide and Fluoroarene Formation via *ortho*-Lithiation [29,30]

The use of δ -complexes to facilitate nucleophilic substitution is illustrated in **Scheme 6**. A disadvantage of this methodology, and of *ortho*-metalation, is the requirement for a stoichiometric amount of the metal. A major development in recent years has been the discovery of novel substitution reactions using catalytic amounts of palladium(0) and nickel(0) complexes.

The use of transition metals to catalyze the formation of aryl—carbon bonds ($\text{Ar}^1\text{—C}$) is well established. In 1996–1997, both Buchwald and Hartwig, working independently, laid the foundations for transition-metal-catalyzed aryl—heteroatom bond ($\text{Ar}^1\text{—X}$) formation, and this has led to the synthetic routes to amines, ethers, phenols, and sulfides that are known as Buchwald–Hartwig reactions.^[31,32] These reactions are catalyzed by palladium(0)–phosphine complexes and a generalized catalytic cycle is shown in **Scheme 15**. Oxidative addition of the palladium(0) catalyst **19** to the aryl—heteroatom bond ($\text{Ar}^1\text{—X}$, $\text{X} = \text{Cl, Br, I, OTf}$) gives the palladium(II) complex **20**. Base-mediated displacement of the ligand (X) by an amine, alcohol, or thiol ($\text{R}^1\text{—YH}$, $\text{Y} = \text{N, O, S}$) leads to the alternative palladium(II) complex **21**. Reductive elimination then gives the substitution product ($\text{Ar}^1\text{—YR}^1$) and the regenerated catalyst **19**.

Scheme 15 Generalized Catalytic Cycle for Buchwald–Hartwig Reactions^[31,32]

The Buchwald –Hartwig reactions are an important contribution to arene methodology and **Scheme 16** illustrates the application of this approach to the preparation of amines,^[33,34] ethers,^[35] and sulfides.^[36] Notable advances have also been made using copper-mediated methodology that uses milder conditions than the classical Ullmann reaction.^[37]

Scheme 16 Palladium(0)-Catalyzed Formation of Amines, Ethers, and Sulfides^[33,35,36]

Rearrangement reactions should not be overlooked as methods for forming aryl —heteroatom bonds. Arene 1,2-rearrangements are often a useful method of forming aryl —nitrogen and aryl —oxygen bonds. For example, the Hofmann (1882) and Curtius (1894) rearrangements continue to be useful approaches to amines and their derivatives.^[38] This is illustrated by the Curtius rearrangement of azides derived from furoic acids, and is particularly convenient in this case as furoic acids are readily available, and the free aminofurans are extremely unstable. Using diphenyl azidophosphate, the acid is converted to the azide under mild conditions. Rapid rearrangement and trapping of the isocyanate then occurs in situ to give the product (**Scheme 17**).^[39]

Scheme 17 Curtius Rearrangement of 5-Methyl-2-furoic Acid^[39]

One last general approach to aryl—heteroatom derivatives that should not be neglected is the formation of the aromatic ring from acyclic precursors. This method provides an alternative to aromatic substitution, and can be a convenient and economical alternative strategy. For example, the diaryl ether **23** may most easily be obtained by reacting the (aryloxy)acetone **22** with the sodium salt of nitromalonaldehyde (**Scheme 18**).^[40]

Scheme 18 Nitrophenols from Acyclic Precursors^[40]

Having formed a suitable aryl—heteroatom bond by substitution, rearrangement, or ring closure, much of the chemistry in Volume 31 is concerned with the transformation of one functional group into another with retention of the aryl—heteroatom bond. The chemistry of arene functional group transformations is extensive, including oxidation, reduction, substitution, and elimination, and there is little value in attempting a generalization in this overview. It is more interesting to ask why chemists are interested in introducing particular functional groups into an aromatic ring. In many cases it is because they are valuable synthetic intermediates en route to specific synthetic target, or because they are versatile reagents for use in a variety of applications. In other cases it is the intrinsic physical properties of the functional group that endow a molecule with desirable features, and for these purposes it is useful to be able to quantitatively forecast the influence of arene substituents on molecular properties.

An important landmark in the development of quantitative structure–property relationships occurred in 1935 when Hammett proposed an equation to describe the electronic influence of substituents on the equilibrium constants (K) for the ionization of benzoic acids. This relationship is now known as the Hammett equation, and subsequent research has shown that it can be widely applied to reaction rates and equilibria (**Scheme 19**).^[41,42]

Scheme 19 The Hammett Equation^[41,42]

$$\log K_{\text{Ar}-\text{X}} = \rho \cdot \sigma + \log K_{\text{Ar}-\text{H}}$$

The Hammett constant (σ) is characteristic of the electronic influence of the functional group (X) and different values are used for *meta*- (σ_m) and *para*-substituents (σ_p). Hammett constants for many functional groups have been determined, and a compilation of values for many of the substituents included in Volume 31 is shown in **Table 3**. Powerful electron-withdrawing groups have large positive Hammett constants (e.g., $\sigma_p = 0.78$ for NO₂) and electron-donating groups have negative Hammett constants (e.g., $\sigma_p = -0.27$ for OMe). The other constant (ρ) is determined by the sensitivity of the property under investigation to the electronic effect of the substituents. In Hammett's original work on the ionization of benzoic acids, this constant has a value of one by definition. Later work resolved substituent electronic effects into inductive (polar) and resonance components, and these are characterized by the Swain and Lupton field (F) and resonance (R) parameters (where it may be assumed that $\sigma = F + R$). Values for these substituent constants are also included in **Table 3**.

Quantification of substituent steric effects is more difficult. In 1952, Taft derived a steric constant (E_s), which was

based on the rate of acid hydrolysis of a series of esters (**Scheme 20**). Limited values of E_s (corrected to $E_s = 0$ when $X = H$) are shown in **Table 3**. The representation of a three-dimensional substituent by a single parameter is inevitably problematic, and more sophisticated computer-aided steric parameters, including the Verloop – Hoogenstraaten multidimensional steric parameters, have subsequently been introduced.^[43]

Scheme 20 Definition of Taft's Steric Constant^[43]

$$\log K_{Ar-X} = E_s + \log K_{Ar-H}$$

A substituent property that is of limited interest to synthetic chemists, but of great importance at the interface between chemistry and biology, is hydrophobicity. In 1964, using biphasic octanol/water as a model for biological systems, Hansch defined the hydrophobic substituent constant π , where P is the octanol/water partition coefficient (**Scheme 21**).

Scheme 21 Definition of the Hydrophobic Substituent Constant^[44]

Hydrophobic substituents have a positive hydrophobicity constant and favor a hydrophobic environment relative to hydrogen (e.g., $\pi = 0.71$ for Cl). Hydrophilic substituents have a negative hydrophobicity constant and favor a hydrophilic environment relative to hydrogen (e.g., $\pi = -1.82$ for $SONH_2$). The substituent influences not only the local hydrophobicity of a molecule, but also the overall hydrophobicity. Therefore, it can influence both the partitioning of a molecule through a biological system (drug transport) and the local binding of the molecule at its active site (molecular recognition). A quantitative knowledge of the hydrophobic character of substituents is therefore important. A compilation of hydrophobicity constants for a selection of substituents relevant to Volume 31 is listed in **Table 3**. An authoritative account of substituent constants and a comprehensive compilation of their values has also been published.^[44]

Table 3 Arene Substituent Constants^[44]

Substituent	π_p	π_m	π_o	π_{H}	E_s	σ	Ref
H	0.00	0.00	0.00	0.00	0.00	0.00	[44]
F	0.06	0.34	0.43	-0.34	-0.46	0.14	[44]
Cl	0.23	0.37	0.41	-0.15	-0.97	0.71	[44]
Br	0.23	0.39	0.44	-0.17	-1.16	0.86	[44]
I	0.18	0.35	0.40	-0.19	-1.40	1.12	[44]
IF ₂	0.83	0.85	—	—	—	—	[44]
ICl ₂	1.11	1.10	—	—	—	—	[44]
I(OAc) ₂	0.88	0.85	—	—	—	—	[44]
IO	-3.74	—	—	—	—	—	[44]
IO ₂	0.78	0.68	0.63	0.20	—	-3.46	[44]
OH	-0.37	0.12	0.29	-0.64	-0.55	-0.67	[44]
OMe	-0.27	0.12	0.26	-0.51	-0.55	-0.02	[44]
OCF ₃	0.35	0.38	0.38	0.0	—	1.04	[44]
OMs	0.36	0.39	0.39	0.00	—	-0.88	[44]
SH	0.15	0.25	0.28	-0.11	-1.07	0.39	[44]
SMe	0.00	0.15	0.20	-0.18	-1.07	0.61	[44]
SCF ₃	0.50	0.40	0.35	0.18	—	1.44	[44]
SOMe	0.49	0.52	0.52	0.01	—	-1.58	[44]
SO ₂ Me	0.72	0.60	0.54	0.22	—	-1.63	[44]
SO ₂ Ph	0.70	0.61	0.56	0.18	—	0.27	[44]

SO ₂ CF ₃	0.93	0.79	0.73	0.26	–	0.55	[44]
SCN	0.52	0.41	0.36	0.19	–	0.41	[44]
SO ₂ NH ₂	0.57	0.46	0.41	0.19	–	–1.82	[44]
SO ₂ F	0.91	0.80	0.75	0.22	–	0.05	[44]
SO ₃ H	–	0.55	–	–	–	–	[44]
SF ₅	0.68	0.61	0.57	0.15	–	1.23	[44]
SeMe	0.00	0.10	0.13	–0.12	–	0.74	[44]
SeCF ₃	0.38	0.32	0.29	0.12	–	–	[44]
NH ₂	–0.66	–0.16	0.02	–0.68	–0.61	–1.23	[44]
NHMe	–0.84	–0.30	–0.11	–0.74	–	–0.47	[44]
NHPh	–0.40	–0.12	–0.02	–0.38	–	1.37	[44]
NMe ₂	–0.83	–0.15	0.10	–0.92	–	0.18	[44]
NPh ₂	–0.22	0.00	0.07	–0.29	–	3.61	[44]
NHNH ₂	–0.55	–0.02	0.17	–0.71	–	–0.88	[44]
NHOH	–0.34	–0.04	0.06	–0.40	–	–1.34	[44]
NHCHO	0.00	0.19	0.25	–0.23	–	–0.98	[44]
NHAc	0.00	0.21	0.28	–0.26	–	–0.97	[44]
NHCONH ₂	–0.24	–0.03	0.04	–0.28	–	–1.30	[44]
NHCN	0.06	0.21	0.26	–0.18	–	–0.26	[44]
N ₃	0.15	0.27	0.30	–0.13	–	0.46	[44]
N=NPh	0.39	0.32	0.28	0.13	–	1.69	[44]
NO ₂	0.78	0.71	0.67	0.16	–2.52	–0.28	[44]
NO	0.91	0.62	0.50	0.45	–	1.20	[44]
PH ₂	0.24	0.05	–0.03	0.27	–	–	[44]
PMe ₂	0.31	0.03	–0.08	0.39	–	0.44	[44]
PO(OMe) ₂	0.53	0.42	0.37	0.19	–	–1.18	[44]
POPh ₂	0.53	0.38	0.31	0.24	–	0.70	[44]

Quantifying substituent properties has enabled the development of empirical correlations (linear free-energy relationships) between molecular structure and chemical and biological properties, and this approach has been pioneered at the interface of chemistry and biology by Hansch.^[45] One of the earliest correlations was derived for the plant growth activity of the aryl ethers **24**.^[46] A significant relationship was observed between the Hammett constant (σ), the hydrophobicity constant (π) and the biological activity (**Scheme 22**), where C is the concentration (in M) of **24** causing 10% elongation in 24 hours, n is the number of compounds used to derive the relationship, r is the correlation coefficient, and s is the standard deviation.

Scheme 22 The Relationship between Substituent Constants and Plant Growth Activity^[46]

It is interesting to note that in his original publication, Hansch drew attention to the then recently discovered pentafluoro- σ -sulfanyl group (SF₅). This substituent is both hydrophobic (π = 1.23) and electron withdrawing (σ = 0.68), which is a combination that is associated with very few substituents, and not even the trifluoromethyl group (CF₃; π = 0.88; σ = 0.54) is as hydrophobic or electron withdrawing. For this reason Hansch suggested in 1963 that this substituent was worthy of further attention;^[46] however, after almost 50 years the pentafluoro- σ -sulfanyl substituent is still relatively neglected despite its stability and apparent lack of toxicity.^[47] In recent years,

Dolbier has developed effective new routes to pentafluoro-*o*-sulfanyl-substituted arenes and hetarenes, including the preparation of phenylsulfur pentafluoride (pentafluoro-*o*-sulfanylbenzene, **25**) (**Scheme 23**).

Scheme 23 Synthesis of Phenylsulfur Pentafluoride^[49]

Hopefully, this will lead to further exploitation of this substituent, as stable substituents with special combinations of properties are potentially too valuable to be neglected. Like the synthetically versatile aryl bromides, and the therapeutically useful aryl sulfonamides, the relatively unexplored arylsulfur pentafluorides may one day find a significant role in chemistry and biology.

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Compounds with Two Carbon–Heteroatom Bonds

32

Volume 32:

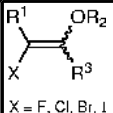
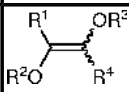
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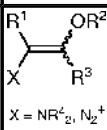
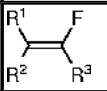
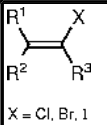
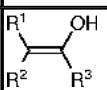
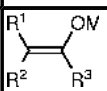
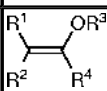
Mulzer, J., in *Science of Synthesis*, **32** (2008), p.1

General Introduction

This volume is concerned with the synthesis of allenes and alkenes with one or two heteroatom substituents. In the allene series, monofunctionalized or 1,3-disubstituted allenes, and the corresponding higher cumulenes, are covered. For the alkenes, monosubstituted (with halogen or oxygen substituents) and 1,2-disubstituted derivatives are described. The synthesis of 1,1-bis(heteroatom-substituted) allenes and alkenes is covered in *Science of Synthesis*, Vol. 24 (Three Carbon —Heteroatom Bonds: Ketene Acetals and Yne —X Compounds), whereas the preparation of sulfur-, nitrogen-, and phosphorus-monofunctionalized alkenes can be found in *Science of Synthesis*, Vol. 33 [Ene —X Compounds (X = S, Se, Te, N, P)]. The contents of Volume 32 are summarized in **Table 1** together with the relevant section numbers.

Table 1 Classes of Compounds Covered in Volume 32

Product Class/Subclass	Structural Formula	Section
1,3-bis(heteroatom-substituted) allenes and analogous higher cumulenes		32.1
monofunctionalized allenes and higher cumulenes		32.2
1,2-dihaloalkenes		32.3.1
1-halo-2-(organooxy)alkenes	 X = F, Cl, Br, I	32.3.2
1-halo-2-(organochalcogeno)alkenes		32.3.3
1-nitrogen-functionalized 2-haloalkenes		32.3.4
1-phosphorus-functionalized 2-haloalkenes		32.3.5
1,2-bis(organooxy)alkenes		32.3.6
1-(organochalcogeno)-2-(organooxy)alkenes		32.3.7

1-nitrogen-functionalized 2-(organooxy)alkenes	 $X = \text{NR}_2^+, \text{N}_2^+$	32.3.8
1-phosphorus-functionalized 2-(organooxy)alkenes		32.3.9
1,2-bis(sulfur-functionalized) alkenes		32.3.10
1-sulfur-functionalized 2-(organochalcogeno)alkenes		32.3.11
1-sulfur-functionalized 2-nitrogen-functionalized alkenes		32.3.12
1-sulfur-functionalized 2-phosphorus-functionalized alkenes		32.3.13
1,2-bis(nitrogen-functionalized) alkenes		32.3.14
1-nitrogen-functionalized 2-phosphorus-functionalized alkenes		32.3.15
1,2-bis(phosphorus-functionalized) alkenes		32.3.16
fluoroalkenes		32.4.1
chloro-, bromo-, and iodoalkenes	 $X = \text{Cl, Br, I}$	32.4.2
enols		32.5.1
enolates		32.5.2
enol ethers		32.5.3
ene —OX compounds (X = O, S, Se, Te)		32.5.4

ene —ON compounds		32.5.5
ene —OP compounds		32.5.6

Among these product classes, monohaloalkenes, in particular the bromo and iodo derivatives, play an important role in transition-metal-catalyzed carbon –carbon cross couplings. Similarly, enols and enolates are central in aldol-type additions, while enol ethers have widespread application in [2 + 2] cycloadditions.

Sections [32.1](#) and [32.2](#) deal with the synthesis of heteroatom-substituted allenes. Among these, the monosubstituted allenes are the most important ones and in a number of cases they serve as nonisolable reactive intermediates in cycloaddition reactions ([Scheme 1](#)).^[1]

Scheme 1 In Situ Formation of an Alkoxyallene^[1]

Section [32.3.1](#) is devoted to the synthesis and application of 1,2-dihaloalkenes, for instance 1,2-diiodo- and 1,2-dibromoalkenes. These important compounds are generally made by addition reactions ([Scheme 2](#)), which can be directed to the *E*- or the *Z*-derivative by the proper choice of conditions.^[2]

Scheme 2 Addition of Iodine to Alkynes^[2]

Most noteworthy, the 1,2-dibromoalkenes may be used for protecting an alkyne moiety ([Scheme 3](#)).^[3]

Scheme 3 Vicinal Dibromoalkenes as Alkyne "Protecting Groups"^[3]

Sections [32.3.2](#) –32.3.5 describe the synthesis of 1-heteroatom-substituted 2-haloalkenes, which are frequently made by nucleophilic or electrophilic substitution reactions at the double bond, as shown in [Schemes 4](#)^[4] and [5](#).^[5] In the case of vinylphosphonates, intramolecular addition within an allene precursor also works ([Scheme 6](#)).^[6]

Scheme 4 Synthesis of 4-Alkoxyated or 4-Aryloxyated 3-Fluorofuran-2(5*H*)-ones^[4]

Scheme 5 Synthesis of *N*-(2-Iodovinyl)-4-toluenesulfonamides by Silicon –Iodine Exchange

Scheme 6 Cyclization of Phosphonoallenes Induced by Halogenation^[6]

1,2-Dialkoxyalkenes may be obtained via numerous transformations, which are discussed in Section **32.3.6**. Quite interesting is the 1,3-dipolar cycloaddition of an oxocarbene intermediate across a carbonyl group (**Scheme 7**).^[7]

Scheme 7 Synthesis of 4-Acyl-5-methyl-1,3-dioxoles^[7]

In Sections [32.3.7](#) –[32.3.16](#) various 1,2-bis(heteroatom-substituted) alkenes are described. For instance, in an example taken from Section [32.3.7](#) for the synthesis of 1-(organochalcogeno)-2-(organooxy)alkenes, 2-alkoxyvinyl sulfones can be made from alkynylselenonium salts by successive addition of a sulfinic acid and an alcohol (**Scheme 8**).^[8]

Scheme 8 Synthesis of 2-Alkoxyvinyl Sulfones from Alkynylselenonium Salts^[8]

As an example of the preparation of a 1-nitrogen-functionalized 2-(organooxy)alkene (Section [32.3.8](#)) the following rearrangement is quite remarkable (**Scheme 9**).^[9]

Scheme 9 Synthesis of a 1,4-Oxazepine by Rearrangement^[9]

An unusual 1,2-rearrangement leads to a vicinal disulfone (**Scheme 10**; see Section [32.3.10](#)).^[10]

Scheme 10 Rearrangement of 1,1-Bis(arylsulfonyl)ethenes^[10]

1-Sulfur-functionalized 2-nitrogen-functionalized alkenes are generated by a variety of methods (see Section [32.3.12](#)), for instance by ring opening of 2*H*-azirines (**Scheme 11**).^[11,12]

Scheme 11 Ring Opening of 2*H*-Azirines

Sections **32.3.14**–32.3.16 deal with various combinations of vicinal nitrogen- and phosphorus-substituted alkenes. Thus, 1,2-dinitroalkenes are prepared from alkynes and dinitrogen tetroxide (**Scheme 12**).^[13–16]

Scheme 12 Synthesis of 1,2-Dinitroalkenes by Addition of Dinitrogen Tetroxide to Acetylenes^[13–16]

Interestingly, alkene-1,2-diamines can be made most easily from alkane-1,2-diols (**Scheme 13**).^[17]

Scheme 13 Synthesis of an Alkene-1,2-diamine from a 1,2-Diol^[17]

Vinyl halides have various applications in organic chemistry. For example, vinyl fluorides are of interest in pharmaceutical chemistry, as the substitution of hydrogen for fluorine results in characteristic changes of the biological properties. The synthesis of vinyl fluorides can be achieved in a variety of ways (Section **32.4.1**), for instance via fluorodestannylation using xenon difluoride with retention of configuration (**Scheme 14**).^[18]

Scheme 14 Fluorodestannylation Using Xenon Difluoride^[18]

Vinyl chlorides, bromides, and iodides (Section **32.4.2**) are of central importance in organic synthesis, mainly due to their ability to undergo a wide variety of transition-metal-mediated carbon–carbon, –nitrogen, or –oxygen coupling reactions. A standard method for the preparation of these vinyl halides is metal–halogen exchange, for instance halodesilylation, which proceeds with inversion of configuration (**Scheme 15**).^[19,20]

Scheme 15 Halodesilylation of Vinylsilanes Using either Bromine or Chlorine^[19,20]

Enols (Section [32.5.1](#)) are mechanistically interesting intermediates, though of limited synthetic value. By contrast, enolates (Section [32.5.2](#)), like vinyl halides, are of foremost importance in carbon –carbon coupling reactions, such as alkylations and aldol additions. Enolates are normally prepared as transient intermediates, mainly by deprotonation of carbonyl compounds. There are, however, interesting alternatives such as the rearrangement of epoxides (**Scheme 16**).^[21]

Scheme 16 Base-Induced Rearrangement of an Epoxide^[21]

The synthesis of vinyl ethers is reviewed extensively in Section [32.5.3](#). Vinyl ethers can be made, inter alia, by alkylation of enolates, Brønsted or Lewis acid catalyzed exchange of the alcohol component, or addition of an alcohol to alkynes. Relatively unusual is the elimination of alkoxide from unsaturated acetals (**Scheme 17**)^[22–24] or sulfinate from α -alkoxy sulfones (**Scheme 18**).^[25]

Scheme 17 Lithiation of Unsaturated Acetals^[22–24]

Scheme 18 Thermal Elimination of Phenyl Sulfoxides^[25]

Sections [32.5.4](#)–[32.5.6](#) deal with OX-monosubstituted alkenes, where X = O, S, Se, Te, N, or P. Thus, in Section

32.5.4, syntheses of enol toluenesulfonates or enol trifluoromethanesulfonates are described; these are normally made by sulfonation of the corresponding enolates. ON- and OP-substituted alkenes are less common, although they can be readily prepared by well-established procedures, for instance 1,3-dipolar cycloaddition (**Scheme 19**)^[26] or O-phosphorylation of enolates (**Scheme 20**).^[27]

Scheme 19 Preparation of Ethyl 2-Benzyl-4-methyl-3-phenyl-2,3-dihydroisoxazole-5-carboxylate^[26]

Scheme 20 Preparation of 3-Butylcyclohex-1-enyl Diphenyl Phosphate^[27]

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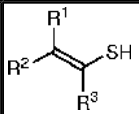
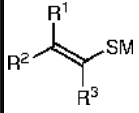
Compounds with Two Carbon–Heteroatom Bonds
Volume 33:
Ene—X Compounds (X = S, Se, Te, N, P)


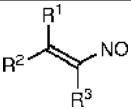
Molander, G. A., in *Science of Synthesis*, **33** (2006), p.1

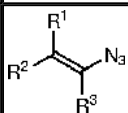



General Introduction

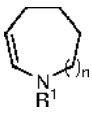


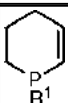
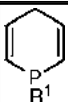
Volume 33 of *Science of Synthesis* outlines the synthesis of ene —X compounds (X = S, Se, Te, N, P). As can be imagined, the various classes of compounds included in this volume constitute a wide range of functionality with diverse properties, unique reactivities, and important synthetic applications. **Table 1** displays the classes of ene —X compounds covered in this volume.

Table 1 Classes of Ene —X Compounds Included in Volume 33

Compound	Structural Formula	Section
alk-1-enyl sulfur compounds		33.1
alk-1-enesulfonic acids and derivatives		33.1.1
alk-1-enyl sulfones		33.1.2
S-alk-1-enylsulfoximides		33.1.3
alk-1-enesulfinic acids and derivatives		33.1.4
alk-1-enyl sulfoxides, sulfimides, and related compounds		33.1.5
alk-1-enethiols		33.1.6
metal alk-1-enethiolates		33.1.7
alk-1-enyl sulfides		33.1.8
alk-1-enylsulfonium salts		33.1.9

alk-1-enesulfenic acids and derivatives		33.1.10
alk-1-enyl disulfides		33.1.11
thietes and derivatives		33.1.12
2,3-dihydrothiophenes and derivatives		33.1.13
3,4-dihydro-2 <i>H</i> -thiopyrans and derivatives		33.1.14
2,3,4,5-tetrahydrothiepins, larger rings, and derivatives		33.1.15
alk-1-enyl selenium compounds		33.2
alk-1-enyl tellurium compounds		33.3
alk-1-enyl nitrogen compounds		33.4
1-nitroalkenes		33.4.1
1-nitrosoalkenes		33.4.2
<i>N</i> -alk-1-enyliminosulfur compounds		33.4.3
alk-1-enediazonium salts, alkeneazoxy compounds, and		33.4.4

alkeneazo compounds		
<i>N</i> -alk-1-enyliminophosphorus compounds		33.4.5
enamines		33.4.6
enammonium salts		33.4.7
<i>N</i> -silylenamines		33.4.8
<i>N</i> -borylenamines		33.4.9
<i>N</i> -haloenamines		33.4.10
<i>N</i> -alk-1-enylhydroxylamines		33.4.11
<i>N</i> -alk-1-enylaminosulfur compounds		33.4.12
alk-1-enylhydrazines		33.4.13
alk-1-enyl azides		33.4.14
<i>N</i> -alk-1-enylaminophosphorus compounds		33.4.15
1,2-dihydroazetes and derivatives		33.4.16
2,3-dihydro-1 <i>H</i> -pyrroles and derivatives		33.4.17
1,2-dihydropyridines, 1,4-dihydropyridines, and derivatives		33.4.18
1,2,3,4-tetrahydropyridines and derivatives		33.4.19
2,3,4,5-tetrahydro-1 <i>H</i> -azepines, larger rings, and derivatives		33.4.20

		
alk-1-enyl phosphorus compounds		33.5
alk-1-enylphosphonic acids and derivatives		33.5.1
alk-1-enylphosphinic acids and derivatives		33.5.2
alk-1-enylphosphine oxides and derivatives		33.5.3
alk-1-enylphosphines		33.5.4
alk-1-enylphosphonium salts		33.5.5
<i>P</i> -heteroatom-substituted alk-1-enylphosphines		33.5.6
1,2-dihydrophosphetes and derivatives		33.5.7
2,3-dihydro-1 <i>H</i> -phospholes and derivatives		33.5.8
1,2,3,4-tetrahydrophosphinines and derivatives		33.5.9
1,4-dihydrophosphinines and derivatives		33.5.10

As is the tradition in *Science of Synthesis*, the compounds are listed in prioritized, hierarchically ordered sections. At the outset of each section, a brief introduction to the targeted class of compounds is presented. Subsequently, the most important and useful synthetic approaches to the functional groups incorporated within each class are outlined. Representative experimental procedures are provided, along with safety precautions when warranted. As synthesis has evolved over time, so have experimental procedures. In light of this, there may be several variations to the general synthetic methods described, each variation representing improved reagents or techniques of interest.

The goal of this effort has been to limit the discussion to only the most important and widely applicable approaches for each class of molecules, and to report only those procedures for which materials have been isolated and fully characterized to insure reliability. Extensive tables are utilized to indicate the scope of various processes, and the authors have given detailed representative experimental procedures for specific examples of particular importance.

The first ene —X molecules considered in this volume are the alk-1-enesulfonic acids and derivatives, which

are described in Section [33.1.1](#). These materials are less readily accessible than the related arenesulfonic acid derivatives, which are available by sulfonation chemistry. However, the emerging biological significance of sulfonamides and the use of the alk-1-enesulfonic acid derivatives in Michael addition and Diels –Alder reactions, as well as in the polymer industry, have placed a premium on new synthetic approaches to this group of compounds.

Alk-1-enyl sulfones, which are presented in Section [33.1.2](#), have traditionally played a much more prominent role in organic chemistry. They serve as electrophiles in Michael-type addition reactions, as acceptors in radical addition reactions, and as excellent 2^o-electron partners in a variety of cycloaddition reactions. Upon processing the alk-1-enyl sulfones, the sulfonyl group can be readily transformed further via reduction, elimination, or α -alkylation. As a consequence of the versatility of the alk-1-enyl sulfones and the sulfone group itself, diverse methods for the stereoselective synthesis of this functional unit have been developed, and these are outlined in this section. The importance of alk-1-enyl sulfones in organic synthesis has evoked reviews outlining their utility.^[1]

Section [33.1.3](#) details important syntheses of S-alk-1-enylsulfoximides. Although in many ways the chemistry of these materials is analogous to that of the corresponding sulfones, the nitrogen atom affixed to the sulfur renders that atom stereogenic, thus making S-alk-1-enylsulfoximides very appealing substrates for asymmetric synthesis. In addition to creating stereogenicity within the molecules, substituents on the nitrogen afford the added advantage of being able to fine tune the reactivity of these species, making them highly useful chiral synthons for organic synthesis.^[2]

The alk-1-enesulfinic acids and their derivatives are much less widely utilized than the alkenyl sulfones and alkenylsulfoximides described above as substrates in organic synthesis. However, stable nonracemic sulfinates and sulfinamides serve as highly valuable precursors to chiral, nonracemic alk-1-enyl sulfoxides. In this context, their importance is increasing. Although historically a limited number of synthetic methods were available to access these materials, in Section [33.1.4](#) recently reported efforts to provide practical, general approaches to these compounds are described.

Alk-1-enyl sulfoxides are among the most widely studied and useful ene —X compounds falling within the bailiwick of Volume 33, and these compounds, along with the related sulfimides, form the basis of discussion in Section [33.1.5](#). The attraction of the alkenyl sulfoxides in particular resides in their ability to be produced and exist as configurationally stable enantiomers with well-defined chiral space about the sulfur atom. As a result of their growing importance in organic synthesis, a variety of general methods for the selective synthesis of these materials have been developed, and these are summarized in Section [33.1.5](#)

Synthetic methods directed toward alk-1-enethiols form the basis for Section [33.1.6](#). Alkenethiols are interesting materials because they are simply tautomeric forms of thiocarbonyls. Unlike their oxygen-based cousins, however, the thiol tautomer is often the predominant form in the equilibrium, thus highlighting an important difference in the chemistry of carbonyl compounds versus that of thiocarbonyl compounds. As indicated in this section, most syntheses of alk-1-enethiols are of academic interest only, and difficulties associated with isolation of pure alkenethiols are well documented.

There are not many general methods for the synthesis of metal alk-1-enethiolates, but these compounds do serve as valuable intermediates in the synthesis of alk-1-enyl sulfides and related derivatives. The few reliable routes that have been described for the construction of alk-1-enethiolates are described in Section [33.1.7](#)

By contrast, there exists a variety of diverse routes to alk-1-enyl sulfides, and twelve of the most important of these are delineated in Section [33.1.8](#). Alkylation of alkenethiolates, transformations of 1-haloalkenes,

syntheses from alkyl sulfides, reduction of alk-1-enyl sulfoxides, syntheses from alkynyl sulfides, and addition of thiols to alkynes comprise the more important processes discussed.

The more useful routes to alk-1-enylsulfonium salts are discussed in Section [33.1.9](#). These include the historically important dehydrohalogenation of 2-(haloalkyl)sulfonium salts, S-alkylation of alkenyl sulfides (the most widely reported method), as well as routes from dithioacetals and alkenes.

Very few alk-1-enesulfenic acids or their derivatives have been isolated and fully characterized, in part owing to instabilities associated with anhydride formation. Nevertheless, a few procedures for the acid chlorides and amides are reported in Section [33.1.10](#), along with a single method for the sulfenic acids themselves.

The sulfenylation of alkenethiolate anions and the addition of nucleophiles to sulfines constitute two approaches to alk-1-enyl disulfides outlined in Section [33.1.11](#), which are the last group of acyclic alkenyl sulfur compounds discussed in this volume.

The synthesis of thietes and their derivatives are considered in Section [33.1.12](#). Although the synthesis and chemistry of this important functional group has been reviewed occasionally over the past two decades,^[3,4] the current contribution provides an important update and consolidation of the most important approaches to this ring system.

The synthesis and chemistry of 2,3-dihydrothiophenes and their oxidized derivatives have also been reviewed,^[5] with the contribution in Section [33.1.13](#) focusing on the best methods of synthesis for these fascinating molecules. One of the more interesting applications of the 2,3-dihydrothiophenes is their use in the formation of various thiasugars, and sulfur analogues of carbohydrates and nucleotides.

Thiopyrans^[6–10] serve as useful starting materials for diverse sulfur-containing structures, including chiral ylides that can be utilized for the Corey –Chaykovsky synthesis of enantiomerically enriched oxiranes. Owing to their importance in these and other areas of synthetic organic chemistry, numerous unique approaches to the construction of these species have been developed. The most significant of these are detailed in Section [33.1.14](#)

Rounding out the discussion of alkenyl sulfur compounds is an outline of synthetic approaches to 2,3,4,5-tetrahydrothiepins, larger rings, and their derivatives^[11–13] in Section [33.1.15](#). Ring-closing methods, ring transformation, elimination reactions, and substituent modification reactions dominate approaches to this class of molecules.

Section [33.2](#) outlines synthetic approaches to alk-1-enyl selenium compounds.^[14] The increasing use of alkenyl selenium compounds in synthetic organic chemistry has increased awareness in their selective synthesis. Alkenyl selenium(II) compounds are the most abundant and well-described materials. Alkenyl selenium(IV) and -(VI) compounds are much more rare, and are generally derived from the lower oxidation state materials.

Access to the related alk-1-enyl tellurium compounds is the subject of Section [33.3](#).^[15] In analogy with the aforementioned alk-1-enyl selenium compounds, the alkenyl tellurium(II) species are the most abundantly described and utilized compounds in this class. Higher oxidation state alkenyl tellurium(IV) and -(VI) species are much less abundant, as is the case for the analogous alkenyl seleniums.

The largest, and arguably the most important, class of compounds covered in Volume 33 is the alkenyl nitrogen compounds. This portion of the contribution begins with 1-nitroalkenes^[16,17] in Section [33.4.1](#). As is

the case with the alk-1-enyl sulfones, 1-nitroalkenes serve as extraordinarily potent electrophiles in both radical and ionic Michael-type reactions, and as dienophiles or heterodienes in Diels –Alder reactions. Following these transformations, the nitro group can also be transformed into a variety of functional groups, making the nitroalkenes highly versatile synthons for selective organic synthesis.

1-Nitrosoalkenes are also quite useful intermediates in organic synthesis, but most often these compounds are generated and utilized in situ. In this regard, their most useful application is in the role of highly reactive heterodienes in Diels –Alder reactions. Some of the more reliable methods for the construction and isolation of nitrosoalkenes are discussed in Section 33.4.2

By contrast, the *N*-alk-1-enyliminosulfur compounds described in Section 33.4.3 are much less well developed, even though members of this subclass appear to be more stable than the nitrosoalkenes mentioned above.

It was intended that Section 33.4.4 would cover the synthesis of alkeneazo compounds, alkeneazoxy compounds, and alk-1-enediazonium salts. Here, however, the reader is directed to the comprehensive reviews found in *Houben –Weyl*, Vol. E 15, pp 909, 1090, and 1101, respectively, with an update of this chemistry to follow in a future edition of *Science of Synthesis*. The *N*-alk-1-enyliminophosphorus compounds described in Section 33.4.5 are quite readily available, and have become useful building blocks in organic synthesis. In particular, they may be employed as starting materials in aza-Wittig reactions, which in turn lead to a diverse array of nitrogen-based heterocycles.

The chemistry of enamines remains strong and indeed ever-expanding, now many years after Stork's work in the 1950s on their use as enolate equivalents in reactions with a broad assortment of electrophiles.^[18] As a consequence, milder and more selective methods for the construction of enamines are appearing in order to keep apace of these developments. Section 33.4.6 covers the most important synthetic routes to enamines, from the classical methods to procedures that permit installation of this functionality into densely functionalized precursors.

Arguably the most important subclass of enammonium ions are the allyl(alk-1-enyl)ammonium ions, which serve as useful intermediates in the charge-accelerated aza-Cope rearrangement. Synthetically viable approaches to these materials are described in Section 33.4.7

N-Silylenamines are the nitrogen analogues of *O*-silyl enol ethers, and share much of the same fundamental reactivity patterns, although they are much less commonly utilized than the enol silanes. The synthesis of both *N*-silylenamines and *N,N*-disilylenamines are covered in Section 33.4.8. The latter are more stable, but less reactive, than the former.

There are many parallels between the chemistry of *N*-silylenamines and *N*-borylenamines, the latter of which are the subject of Section 33.4.9. The *N*-borylenamines are encountered rarely, undoubtedly owing to their instability to air and moisture. The most common application of *N*-borylenamines appears to be the construction of N —B —N heterocycles, although examples of their use in aldol reactions have also been reported.

Even more rare than the *N*-borylenamines are the *N*-haloenamines described in Section 33.4.10, wherein only a handful of compounds have been described. Methods to access these materials include the halogenation of enamides and direct halogenation of *N*-halopyridinones.

The most predominant class of *N*-alk-1-enylhydroxylamines are those bearing a carbonyl group at the -

position (**Scheme 1**).

Scheme 1 *N*-(Alk-1-enyl)hydroxylamines Bearing a Carbonyl Group at the α -Position

These vinylogous hydroxamic acids can be used for the construction of isoxazoles, and some members of this class of compounds have been determined to be pharmacologically active as well. Their synthesis is the focus of Section **33.4.11**

The synthesis of *N*-alk-1-enylaminosulfur compounds forms the basis of discussion in Section **33.4.12**. The majority of the material discussed concerns the synthesis of *N*-sulfonylenamines (or vinylsulfonamides), with minor contributions concerning *N*-sulfanylenamines and *N*-sulfinylenamines. Highly elaborated *N*-sulfonylenamines have been utilized as precursors in the synthesis of a variety of alkaloid natural products.

The literature concerning the synthesis and reactions of alkenylhydrazines is quite extensive. Alkenylhydrazines are key intermediates in the Fischer indole synthesis and in approaches to a variety of other heterocycles. Chiral alkenylhydrazines have also been exploited in asymmetric versions of the Hantzsch dihydropyridine synthesis and in asymmetric Carroll rearrangements. Some of the most important synthetic approaches to alkenylhydrazines are discussed in Section **33.4.13**

Another functional unit of broad application and utility are the alk-1-enyl azides. Extensive use of alkenyl azides has been made for the construction of an amazingly diverse set of nitrogen heterocycles, and a legion of heterocyclic natural products have been constructed utilizing alkenyl azides as key synthetic intermediates. The most important methods by which to synthesize the alk-1-enyl azides are outlined in Section **33.4.14**

The synthesis of *N*-alk-1-enylaminophosphorus compounds is outlined in Section **33.4.15**. As described, these materials can be prepared from imines or enamines by reactions with phosphorus electrophiles, from the reaction of phosphamides with aldehydes via condensation reactions, or from *N*-allylphosphoric triamides or nitriles.

The discussion of approaches to cyclic alkenyl nitrogen compounds begins with 1,2-dihydroazetes and their derivatives in Section **33.4.16**. These materials are highly unstable to a 4 π -electrocyclic ring opening. This transformation has been employed to allow the 1,2-dihydroazetes to serve as masked dienes in hetero-Diels–Alder reactions.

2,3-Dihydro-1*H*-pyrroles and their derivatives play a much more central role in organic chemistry, and numerous approaches to their synthesis have been described. Some of the more general methods are outlined in Section **33.4.17**

The structural analogy between 1,4-dihydropyridines and nicotinamide adenine dinucleotide (NADH) makes the former a widely studied entity among nitrogen heterocycles. The 1,4-dihydropyridine substructure is also present in many pharmacologically active agents. Major synthetic pathways to this subunit and the isomeric 1,2-dihydropyridines are described in Section **33.4.18**

The synthesis of 1,2,3,4-tetrahydropyridines represents a challenge for synthetic organic chemists due to their

inherent instability. Thus, conversion to the corresponding iminium ions is relatively facile. On the other hand, this class of molecules constitutes a potentially important one for the synthesis of piperidines, and therefore in Section [33.4.19](#) several proven methods for the construction of these compounds are covered.

Section [33.4.20](#) covers the most important synthetic routes to 2,3,4,5-tetrahydro-1*H*-azepines, larger ring structural analogues, and their derivatives. In general these systems are more difficult to access than the smaller cyclic enamines, but several general methods are available and described herein.

The transition to alkenyl phosphorus compounds begins with a description of methods for the construction of alk-1-enylphosphonic acids and their derivatives in Section [33.5.1](#)^[19,20] In analogy to the alkenyl sulfones and nitroalkenes discussed above, the alkenylphosphonates participate in a variety of important synthetic transformations including Diels –Alder reactions, Michael additions, and cross-coupling reactions. As a consequence of their role as important synthetic intermediates, a variety of selective methods for their synthesis are outlined.

Although alk-1-enylphosphinic acids and their ester derivatives have found important applications in the pharmaceutical industry, fewer general methods of synthesis are available than for the analogous phosphonate derivatives. Some general approaches are shared between the two classes of compounds, and the most important means to access these materials are outlined in Section [33.5.2](#)

The chemistry of alk-1-enylphosphine oxides in some ways mimics that of the corresponding phosphonates, in that the alkene subunit is activated by the electron-withdrawing, phosphorus-based functional group. What differentiates the phosphine oxides is their ability to exist in nonracemic form, which provides opportunities for asymmetric synthesis. Methods for the construction of the alkenylphosphine oxides can be found in Section [33.5.3](#)

The synthesis of alk-1-enylphosphines is described in Section [33.5.4](#) of this contribution. Alkenylphosphines are valuable starting points for the construction of polyphosphines and phosphine ligands for catalytic transformations. Synthetic entries to alkenylphosphines are quite diverse, and the most important are included in this section.

Alk-1-enylphosphonium salts are more stable than the analogous alkenylphosphines, and are often utilized to characterize the latter. In addition to alkylation and alkenylation reactions of phosphines, elimination reactions and alterations of phosphonium salts provide synthetic entries to these species as outlined in Section [33.5.5](#)

Approaches to the synthesis of *P*-heteroatom-substituted alk-1-enylphosphines form the basis for Section [33.5.6](#). Included are routes to alk-1-enyl(amino)phosphines and alk-1-enyl(halo)phosphines; the latter are relatively unstable, being sensitive to both air and moisture. Consequently, they are most often generated and utilized in situ for further transformations. The alk-1-enyl(amino)phosphines, on the other hand, exhibit enhanced stability and can be employed as precursors for the construction of a variety of other organophosphorus compounds.

Syntheses of 1,2-dihydrophosphetes and their derivatives (phosphines, phosphine oxides, and iminophosphines) are outlined in Section [33.5.7](#). As it transpires, these molecules are relatively stable, but most of the approaches date only from the 1980s.

2,3-Dihydro-1*H*-phospholes, on the other hand, have been known for quite some time, and are among the most well known group of phosphorus heterocycles. Diverse routes to these materials and their derivatives are the subject of Section [33.5.8](#)

In Section **33.5.9**, various ring-closure reactions, addition/eliminations, and selective reductions are outlined as a means to construct 1,2,3,4-tetrahydrophosphinines and their derivatives. As in Section **33.5.8**, derivatives such as phosphines, phosphine oxides, phosphinates, and phosphonium salts are all covered.

To close out Volume 33, Section **33.5.10** describes the synthesis of 1,4-dihydrophosphinines and various functionalized derivatives. Both standard methods as well as techniques specifically targeting dimeric 1,4-dihydrophosphinine oxides are discussed.

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



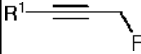

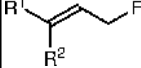
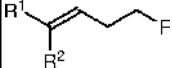
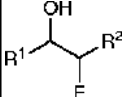
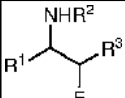
Compounds with One Carbon–Heteroatom Bond
Volume 34:
Fluorine

Percy, J. M., in *Science of Synthesis*, **34** (2005), p.1

General Introduction

This volume covers the synthesis of compounds containing a single fluorine atom bonded to an sp^3 carbon, excluding α -fluorocarbonyl compounds {aldehydes, ketones, and acids and their derivatives (covered in *Science of Synthesis*, Volumes 25, 26, and 20, respectively) and 1,1-dihalides [including geminal difluorides (Volume 29)]}. The volume content is organized firstly according to the different classes of fluorinated molecule, and then by the methods of synthesis. The distribution of content is shown in **Table 1**, along with the appropriate section number.

Table 1 Classes of Compounds Covered in Volume 34

Product Class and Method	Structural Formula	Section
fluoroalkanes		
by substitution of hydrogen		34.1.1
by substitution of metals		34.1.2
by substitution of carbon functionalities		34.1.3
by substitution of a halogen		34.1.4.1
by substitution of hydroxy groups in alcohols		34.1.4.2
by substitution of oxygen and sulfur functionalities		34.1.4.3
by addition reactions to alkenes		34.1.5
by retention of the functional group		34.1.6
fluorocyclopropanes		34.2
(fluoromethyl)cyclopropanes		34.3
fluorocyclobutanes		34.4
propargylic fluorides		34.5
benzylic fluorides		34.6
allylic fluorides		34.7
homoallylic fluorides		34.8
-fluoro alcohols		34.9
-fluoroamines		34.10

References to reviews on the different classes of compounds are given wherever possible, but much of the literature upon which this volume is based deals with methodology rather than type of target molecule. The organofluorine literature contains relatively few comparisons between methods, which can make route selection rather difficult. Where the literature is sufficiently extensive, individual contributors have been encouraged to compare and contrast the scope and effectiveness of the available methodologies. Selected compound data (^{19}F NMR chemical shifts) and experimental details have been reported as fully as possible. In some cases, the original reports of important methodologies contain minimal detail. The material covered in the volume is selective in some chapters and more exhaustive in others, reflecting the fact that there are very few ways of making some of the subclasses of molecule described.

This introduction gives an outline of the individual product classes, together with highlighted synthetic methods. The synthetic chemistry described in this volume achieves the exchange of many of the most common functional groups for a single C—F bond. A significant number of challenges must be met in order to achieve accurate and efficient formation of a C—F bond to an sp^3 carbon. Some of the reagents required are relatively hazardous and require careful handling. Electron demand may be high in some of the reactions, and relatively basic reagents may be required in others, so the chemistry often occurs close to, or at, the $\text{E1/S}_{\text{N}}1$ and $\text{E2/S}_{\text{N}}2$ borderlines. Despite these difficulties, considerable progress has been made and there are many effective and ingenious methods for use in target synthesis. However, there is little real physical organic understanding of any of the transformations described in this volume; predictability of outcome may therefore be lacking.

The costs of the reagents used vary widely, from intrinsically inexpensive species such as hydrofluoric acid or elemental fluorine, which are used on an industrial scale,^[1] to the considerably more costly and exotic xenon difluoride, which is a laboratory reagent for demanding and specialized applications only. A number of commercial electrophilic fluorinating agents are becoming widely used but these are moderately costly, with clear potential for use in the synthesis of pharmaceutical agents, but perhaps beyond the acceptable cost constraints of the synthesis of agrochemicals.

The volumes of *Houben –Weyl* which cover organofluorine chemistry (Volumes E 10a –c) and a number of other reviews, organize their extensive material by type of fluorinating agent rather than by class of product or transformation. This introduction will take the latter approach and attempt to show how synthetic strategy is served by the various types of fluorinating agent, or indeed, fluorinated building blocks.

The most atom-direct method for the synthesis of simple fluoroalkanes, which involves the exchange of sp^3 C—H bonds for their C—F counterparts, is described in Section 34.1.1. The reaction has been achieved with both elemental fluorine and Selectfluor, suggesting strong parallels between the way in which these reagents react (although there are some significant differences between outcomes with the two reagents). Fluorination of C—H bonds occurs most easily at more substituted sites; selective fluorination of *trans*-Decalin occurs (Scheme 1) with elemental fluorine.^[2]

Scheme 1 Selective Fluorination of *trans*-Decalin with Elemental Fluorine^[2]

This pattern of reactivity would be consistent with either carbenium ion or free-radical chemistry. The chemistry is believed to be electrophilic in character and displays a selectivity related to carbenium ion

stability. The reactions with elemental fluorine represent an extremely cost-effective solution in cases where the locus for fluorination is a tertiary site. Electron-withdrawing substituents, if close to the fluorination site, will lower reaction rates strongly. However, fluorination has been shown to occur smoothly at more remote sites. Of course, one of those additional functional groups may serve as a locus for the efficient introduction of fluorine via different methodology so the direct fluorination may complement other methods. Elemental fluorine is not the only reagent capable of carrying out this type of transformation: Selectfluor, xenon difluoride, trifluoromethyl hypofluorite, and cesium fluoroxysulfate may also be used for direct replacement of C—H bonds by C—F bonds.

The reaction of electrophilic fluorinating agents with simple σ -organometallic reagents (Grignard, organolithium species) remains an area where there are relatively few useful reactions (Section 34.1.2). Elemental fluorine and perchloryl fluoride have been used as sources of electrophilic fluorine for a very limited range of organometallic nucleophiles. Perchloryl fluoride is available commercially, but is very reactive, and impurities present in some samples of the reagent can lead to violent reactions. The C—F bond can be relatively vulnerable in the presence of highly reactive (and basic) organometallic reagents. The risk of elimination and alkene formation accompanies the exposure of any alkyl halide to basic organometallic reagents. However, upon exposure to Selectfluor (2), organosilanes (and allylsilanes in particular, formed using ruthenium complex 1) undergo smooth fluorination with loss of silicon to afford allylic fluorides (Scheme 2).^[3]

Scheme 2 Efficient Combination of Fluorodesilylation of Allylsilanes with Alkene Cross-Metathesis^[3]

The procedures are simple and high yielding in many cases, and represent the only really general and effective reactions of electrophilic fluorinating agents with organometallic reagents. The ease of synthesis of substituted allylsilanes via alkene cross-metathesis chemistry makes this approach a particularly valuable one (see Section 34.7 for other approaches to allylic fluorides). Alkene reduction without defluorination delivers the fluoroalkanes. The latter approach to fluoroalkane synthesis, in which other functionalities are removed from the vicinity of a C—F bond, is reviewed in Section 34.1.6.

In a rather limited number of cases, fluorination can be triggered by decarboxylation in a Hunsdiecker-type reaction (Section 34.1.3), or by the removal of other types of carbon-based functional group. The reagents used for this type of transformation include elemental fluorine, xenon difluoride,^[4] and bromine trifluoride; this type of transformation is shown in Scheme 3.

Scheme 3 Fluorination Triggered by Decarboxylation^[4]

Substitution reactions that exchange carbon —heteroatom bonds for C —F bonds (Section 34.1.4) are significantly more common, and make up the bulk of our synthetic capability. The direct displacement of other halogens can be carried out with a wide range of fluoride sources. These are very simple reactions in principle (Section 34.1.4.1); however, they raise a number of issues. There are many sources of fluoride ion, ranging from the ubiquitous to the exotic (and extremely costly). Many of the simple metal fluorides have high lattice energies and low solubility in organic solvents. Species such as ethylene glycol or diglyme, or dipolar aprotic solvents, are often used as solvents for reactions with potassium fluoride and related salts. Considerable effort has been expended in developing soluble and anhydrous fluoride ion sources which can be used in lower boiling solvents under milder conditions. Some species such as tetrabutylammonium fluoride are extremely well-known as reagents for C —F bond formation (in addition to their use for the removal of trialkylsilyl protecting groups). Several forms of tetrabutylammonium fluoride are commercially available including a trihydrate (TBAF •3H₂O) and an "anhydrous" reagent which is supplied as a solution in tetrahydrofuran. Tetrabutylammonium fluoride is extremely hygroscopic, and the water content of the "anhydrous" reagent may be significant. Drying of the reagent must be undertaken with considerable care; exposure to a combination of reduced pressure and even very modest temperatures (>40 °C)^[5] results in elimination of hydrogen fluoride and modification of the chemistry. It has been shown that small amounts of water in tetrabutylammonium fluoride solutions may help the reagent to carry out nucleophilic transformations more effectively.^[6] Tetramethylammonium fluoride is reported to be easier to obtain in an anhydrous state; it is hygroscopic but can be dried effectively.^[7]

All the tetraalkylammonium fluorides are basic as well as nucleophilic so alkene formation (to varying extents) usually accompanies the nucleophilic introduction of fluorine (E2/S_N2 competition). The crystalline nonhygroscopic silicate reagents developed by DeShong^[8] normally yield lower proportions of E2 products than reagents such as tetrabutylammonium fluoride, but they are less reactive and must be used in excess if good conversions are to be secured. Scheme 4 shows a transformation using a DeShong reagent, which is typical of the reactions described in Section 3.1.4.1.

Scheme 4 Efficient Fluorodebromination Using a Nonhygroscopic Silicate Reagent^[8]

Similar concerns apply to the displacements of alkanesulfonates (Section 34.1.4.3) and a very limited number of sulfur functionalities. The highly expensive and moisture-sensitive reagent tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) is often considered to be the least basic and most nucleophilic fluoride source available. Scheme 5 shows a typical application in which a valuable sugar is efficiently transformed to a fluoride 3, along with the formation of a significant quantity of elimination product 4.^[9]

Scheme 5 Substitution of a Trifluoromethanesulfonate with Tris(dimethylamino)sulfur (Trimethylsilyl)difluoride^[9]

The investigator must assess the ease of separation of the alkene from the fluoride (and the haloalkane in the case of procedures which do not run to complete conversion) and undertake cost/benefit analysis before selecting an appropriate fluoride source.

The direct fluorodehydroxylation of alcohols remains a reaction of great strategic importance (Section 34.1.4.2) because the hydroxy group serves not only as a locus for fluorine introduction but also as a site for fragment assembly through C—C bond formation. Many reagents can carry out the exchange of C—OH for C—F in one pot, although they differ widely in terms of ease of handling. Hydrofluoric acid can bring about the conversion when the alcohol is highly substituted (and can lead to a highly stabilized carbenium ion), but *N,N*-diethylaminosulfur trifluoride (DAST) and related reagents^[10] may be required for less substituted alcohols. The original reagent introduced for this conversion (SF₄, which is a gas and must be used in an autoclave) has been largely superseded, and *N,N*-diethylaminosulfur trifluoride is unpopular for scale-up, because of the highly exothermic decomposition which it undergoes at relatively modest temperatures. More recent derivatives such as Deoxo-Fluor [*N,N*-bis(2-methoxyethyl)aminosulfur trifluoride, BAST]^[11] retain the mode of operation of *N,N*-diethylaminosulfur trifluoride, while improving on the thermal properties.

Unfortunately, some chemical reactivity was lost when the structure was optimized for thermal properties.

Scheme 6 shows the structures of some of the most widely used fluorodehydroxylation reagents: *N,N*-diethylaminosulfur trifluoride (**5**, R¹ = Et), *N,N*-bis(2-methoxyethyl)aminosulfur trifluoride [**5**, R¹ = (CH₂)₂OMe], Ishikawa's reagent (**6**, R¹ = CF₃), Yarovenko reagent (**6**, R¹ = Cl), 2,2-difluoro-1,3-dimethylimidazolidine (DFI, **7**), and *N,N*-diethyldifluoro(3-tolyl)methylamine (DFMBA, **8**).

Scheme 6 Fluorodehydroxylation Reagents in General Use

The mechanism of action of these and related reagents remains a subject of contention, in the absence of any quantitative mechanistic work. While there are hundreds of reaction yields reported in the literature, there seem to be no measured reaction rates, and this hinders the prediction of reaction outcomes. The *N,N*-dialkylaminosulfur trifluorides show a very wide tolerance of substrate reactivities but their reactions often involve the development of significant partial positive charge (carbenium ion character). This can lead to the activation of pathways involving group shifts, elimination, and neighboring-group participation, and the formation of unexpected or undesired products.

The reagents pioneered by Ishikawa and Yarovenko show good thermal properties, although their use is considerably less common. They can be made relatively easily from amines and perhaloalkenes and can be supplied commercially at scale. The byproducts of their reactions are carboxylic amides, which can sometimes be separated from reaction products by distillation (of the product from the amide in simple cases) but must often be removed by chromatography. They appear to be generally less reactive than *N,N*-

diethylaminosulfur trifluoride and congeners.

Later developments include the geminally difluorinated imidazolidine reagent **7** (DFI)^[12] and the difluorinated *N,N*-dialkylbenzylamine **8** (DFMBA). The former shows a very useful reactivity profile and has the distinct advantage that it is generated using an inorganic fluoride rather than being derived from sulfur tetrafluoride. The byproduct from the reagent is the solvent 1,3-dimethylimidazolidin-2-one (DMI). *N,N*-Diethyl[*o*-(difluoro(3-tolyl)methyl)amine (**8**) has been developed into a useful fluorinating agent that can be used to achieve rapid and efficient fluorination under microwave conditions.^[13]

Halofluorination, as well as nitrofluorination, fluorosufanylation, and fluoroselanyl ation of alkenes provide extremely valuable routes to a wide range of monofluoro compounds (Section **34.1.5**). Although the simplest route to fluoroalkanes from alkenes would appear to involve hydrofluorination, halofluorination, nitrofluorination, fluorosufanylation, and fluoroselanylation usually permit the efficient conversion of an alkene into a fluoroalkane more readily than does the addition of hydrogen fluoride. These reagents can be generated in situ from readily available electrophiles (e.g., *N*-bromosuccinimide) and convenient hydrogen fluoride equivalents^[14] (e.g., triethylamine trihydrofluoride); they react with a very wide range of alkenes, often very efficiently. An example is shown in **Scheme 7**.^[15]

Scheme 7 Bromofluorination of a Terminal Alkene^[15]

Alkenes deactivated by π -acceptor groups often undergo addition reactions of this type. The regiochemistry of all the transformations of this type is usually highly predictable: the X^+ atom or group adds in such a way that the least destabilized carbenium ion is generated (and subsequently trapped by fluoride anion). Bridged (bromonium, episulfonium) ions are formed and intercepted by fluoride ion. The chalcogenide electrophiles allow a valuable strategic connection with allylic fluorides through thermal sulfoxide or selenoxide elimination (Section **34.7**).

Dehalogenation can be carried out to C—F bonds without loss of the fluorine atom (Section **34.1.6**). These reactions pass through free-radical intermediates; the high homolytic strength of the C—F bond ensures its integrity throughout processes of this type. The addition of XF to an alkene, followed by reductive C—X bond cleavage is a useful but relatively underexplored strategy for fluoroalkane synthesis. Other transformations which convert an already monofluorinated molecule containing other functional groups into a fluoroalkane are discussed in Section **34.1.6**. The reductive cleavage of derivatives of α -fluoro alcohols (via Barton–McCombie reactions) is probably the most commonly used reaction of this type, particularly for the synthesis of fluorinated nucleosides. **Scheme 8** shows a typical example of this type of transformation.^[16]

Scheme 8 Free-Radical Deoxygenation of a Fluorinated Nucleoside^[16]

A number of other methods can be used to achieve cleavage of C—X bonds which are to C—F bonds without loss of the fluorine atom.

Fluorocyclopropanes have a much less well developed chemistry than their difluorinated congeners, with fewer applications and methods for synthesis. Section 34.2 describes this class and the available synthetic routes, which rely upon halomethane starting materials. One of the major challenges in this area of chemistry is sustainability; the fluorinated methanes are under considerable pressure as known or potential stratospheric ozone depleters.^[17] Traditional methods of synthesis involve the preparation of fluorohalocyclopropanes and then cleavage of the carbon—halogen bond leaving the C—F bond intact, although the formation of fluorocyclopropane directly from diiodofluoromethane has also been achieved. There are also methods based on carbene additions to fluoroalkenes and electrophilic fluorinations of certain methylenecyclopropane carboxylates.

(Fluoromethyl)cyclopropanes (Section 34.3) have a very limited chemistry, as do fluorocyclobutanes (Section 34.4); these two classes are related to each other (and to the homoallylic fluorides of Section 34.8) by a set of carbenium ion interconversions. The electronic properties of substituents exert a major influence over the way in which the three reactive intermediates of Scheme 9 partition; therefore, each of these classes of compound may be approached from a number of different directions.^[18]

Scheme 9 The Cyclopropylmethyl Carbocation Triad^[18]

Given the enormous synthetic utility of propargyl species in general, it is perhaps surprising that there are relatively few methods for synthesizing propargylic fluorides (Section 34.5). The direct conversion of propargylic alcohols with *N,N*-diethylaminosulfur trifluoride represents probably the only general method of synthesis; it has been applied very successfully to the stereochemically accurate fluorination, with inversion, of highly enantiomerically enriched secondary propargylic alcohols, as shown in Scheme 10.^[19]

Scheme 10 Fluorination with Inversion of Highly Enantiomerically Enriched Secondary Propargylic Alcohols
[19]

Benzylic fluorides can be synthesized using the methods described in Sections 34.1.4.1 –34.1.4.3, but there are also more specialized methods which are discussed in Section 34.6, including the fluorination shown in **Scheme 11**, which is catalyzed by chiral cationic ruthenium complex **9**.^[20]

Scheme 11 Transition-Metal-Catalyzed Fluorination of a Benzylic Halide^[20]

These results, along with others, may introduce strategically novel methods for controlling absolute configuration at fluorinated benzylic centers.

Allylic fluorides are described in Section **34.7**; fluorodehydroxylation with *N,N*-diethylaminosulfur trifluoride is less effective for substrates of this type because allylic rearrangements occur readily when electron demand is high. Other nucleophilic fluorinations are possible; the reader is also referred to Section **34.1.2** if a nonterminal allylic fluoride is sought.

Sections **34.9** and **34.10** deal with the valuable α -fluoro alcohol and α -fluoroamine targets, for which the synthesis by ring opening of epoxides and aziridines, respectively, with amine–hydrogen fluoride adducts is described extensively (for the former at least). The chemistry in Section **34.9** links with Section **34.1.6** through free-radical and related deoxygenation methodologies.

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Compounds with One Carbon–Heteroatom Bond

35

Volume 35:
Chlorine, Bromine, and IodineSchaumann, E., in *Science of Synthesis*, **35** (2006), p.1

General Introduction

The focus of this volume is on single-bond formation between an sp^3 -hybridized carbon atom and a chlorine, bromine, or iodine substituent. The synthesis of each type of haloalkane is treated separately and is subdivided in each case by a general treatise of the synthesis of the haloalkane (including halocycloalkanes) in question, followed by additional sections on special types of haloalkanes for which special synthetic methods are available or where special care must be taken to secure the synthetic success. Finally, the synthesis of compounds is discussed where the introduction of the halogen in question occurs simultaneously with the generation of another heterofunctionality in a vicinal arrangement or with larger distance between the two functionalities (**Table 1**).

Table 1 Classes of Halo(cyclo)alkanes Covered in Volume 35


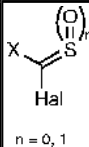

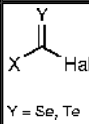
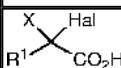
Product Subclass or Method	Structural Formula	Section		
		Hal = Cl	Hal = Br	Hal = I
haloalkanes		35.1.1	35.2.1	35.3.1
by substitution of hydrogen		35.1.1.1	35.2.1.1	35.3.1.1
by substitution of metals		35.1.1.2	35.2.1.2	35.3.1.2
by substitution of carbon functionalities		35.1.1.3	35.2.1.3	35.3.1.3
by substitution of other halogens		35.1.1.4	35.2.1.4	35.3.1.4
by substitution of oxygen functionalities		35.1.1.5	35.2.1.5	35.3.1.5
by substitution of sulfur, selenium, or tellurium functionalities		35.1.1.6	35.2.1.6	35.3.1.6
by substitution of nitrogen functionalities		35.1.1.7	35.2.1.7	35.3.1.7
by addition to π -type C—C bonds		35.1.1.8	35.2.1.8	35.3.1.8
from other halo compounds		35.1.1.9	35.2.1.9	35.3.1.9
propargylic halides		35.1.2	35.2.2	35.3.2
benzylic halides		35.1.3	35.2.3	35.3.3
allylic halides		35.1.4	35.2.4	35.3.4
1-halo-n-heteroatom-functionalized alkanes (n ≥ 2)		35.1.5	35.2.5	35.3.5

The organization of Volume 35 as shown in **Table 1** implies that reactions leading to bond formation between a halogen and an sp^2 - or sp -hybridized carbon atom are excluded; however, because of the hierarchy of functional groups within *Science of Synthesis*, carbon—halogen bond formation next to another functional group of higher priority is covered in other volumes. Thus, although arguably the most important aspects of

organochloro, -bromo, or -iodo chemistry are discussed in this volume, many other types of functional groups with a carbon—halogen unit are not covered, but are dealt with elsewhere within *Science of Synthesis*. **Table 2** gives an overview on where to find the various types of organohalogen compounds within published volumes of *Science of Synthesis*. In addition, syntheses of haloarenes and (1-haloalkyl)arenes are covered in the volumes of Category 2 (Vols. 9–17), typically under the "Synthesis by Substituent Modification" headings. The following volumes of *Science of Synthesis* will also discuss synthesis of halogen-containing compounds: Vol. 29 [Acetals: Hal/X and O/O, S, Se, Te] will include n-halo-n-heteroatom-functionalized alkanes. Vol. 31a [Arene—X (X = Hal, O, S, Se, Te)] will include haloarenes. Various sections of Vol. 32 [X—Ene—X (X = F, Cl, Br, I, O, S, Se, Te, N, P)] will include haloallenes, halocumulenes, 1,2-dihaloalkenes, 1-halo-2-heteroatom-functionalized alkenes, haloalkenes, and (halooxy)alkenes. Finally, Vol. 38 [Peroxides, Inorganic Esters (RO—X, X = Hal, S, Se, Te, N)] will include discussion of organic hypohalites, chlorites, chlorates, and perchlorates.

It should be noted that, irrespective of the rigid basic system, reactions in this volume may lead to product mixtures including compounds that would be a topic of another volume, and sometimes reactions of other volumes are discussed in the present volume for comparison. Thus, to get the full information, a substructure search in the *Science of Synthesis* database is advised.

Table 2 Location of Halogen-Containing Structural Units within Published Volumes of *Science of Synthesis*

Name	Structural Unit ^a	Vol.	Section
trialomethyl lithium compounds	Hal ₃ CLi	8a [Compounds of Group 1 (Li Cs)]	8.1.24.2
cyanogen halides	HalCN	18 (Four Carbon—Heteroatom Bonds: X—C X, X=C=X, X ₂ C=X, CX ₄)	18.1.1
carbonic acid halides			18.3
thiocarbonyl dihalides	 n = 0, 1		18.10.1.1, 18.10.1.2
halothioformate esters			18.10.3, 18.10.4
haloselenoformate and halotelluroformate esters	 Y = Se, Te		18.11
tetrahalomethanes	CHal ₄		18.15.1
alkoxytrialomethanes and trihalomethyl hypohalites	CHal _{4-n} (OR ¹) _n , CHal _{4-n} (OHal) _n		18.15.2
trialomethanethiols and trihalomethyl sulfides	CHal _{4-n} (SR ¹) _n		18.15.3
trialomethaneselenols and trihalomethyl selenides	CHal _{4-n} (SeR ¹) _n		18.15.4
trialomethyl tellurides	CHal _{4-n} (TeR ¹) _n		18.15.5
(trialomethyl)amines	CHal _{4-n} (NR ¹) ₂		18.15.6
(trialomethyl)phosphines	CHal _{4-n} (PR ¹) ₂		18.15.7
acyl halides	R ¹ C(=O)Hal	20a (Three Carbon—Heteroatom Bonds: Acid Halides; Carboxylic Acids and Acid Salts)	20.1
2-halo-2-heteroatom-functionalized alkanolic acids			20.2.6

2-heteroatom-functionalized alkanolic acids			20.2.8.1.1
3-heteroatom-functionalized alkanolic acids			20.2.13.1.1
2-halo-2-heteroatom-functionalized alkanolic acid esters		20b [Three Carbon —Heteroatom Bonds: Esters and Lactones; Peroxy Acids and R(CO)OX Compounds; R(CO)X, X = S, Se, Te]	20.5.9.1
2-heteroatom-functionalized alkanolic acid esters			20.5.11.1.1
3-halo-3-heteroatom-functionalized alkanolic acid esters			20.5.15.1.2
3-heteroatom-functionalized alkanolic acid esters			20.5.16.1.1
N-(-haloalkyl)alkanamides		21 (Three Carbon —Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams)	21.3.1
-haloalkanamides			21.5.1.1
-haloalkanamides			21.7.1.1
N-haloamides			21.13.8
halosulfonium ylides and halosulfoxonium ylides		22 (Three Carbon —Heteroatom Bonds: Thio-, Seleno-, and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives)	22.1.1.2
thioacyl halides	$R^1C(=S)Hal$		22.1.2
C-chloronitriles and n-chloro-n-nitrosoalkanes	$R^1HalC=N(O)R^2$		22.4.2.1.1
imidoyl halides	$R^1C(=NR^2)Hal$		22.4.3
N-haloamidines	$R^1C(=NHal)NR^2R^3$		22.4.9.1.4.1
halophosphaalkenes			22.5.1
haloarsaalkenes			22.6.1
trihalomethyl compounds	R^1CHal_3		22.7.1
, -dihalo ethers and -halo acetals			22.7.2.1.1
thioortho ester halides			22.7.3.1.1
selenoortho ester halides			22.7.4.1
telluroortho ester halides			22.7.5.1
haloketenes		23 (Three Carbon —Heteroatom Bonds: Ketenes and Derivatives)	23.3
1,1-dihaloallenes		24 (Three Carbon —Heteroatom Bonds:	24.1.1

		Ketene Acetals and Yne-X Compounds)	
1-halo-1-heteroatom-functionalized allenes			24.1.2 – 24.1.5
1,1-dihaloalkenes			24.2.1
1-halo-1-heteroatom-functionalized alkenes			24.2.2 – 24.2.5
dihaloacetylenes			24.3.1
1-halo-2-heteroatom-functionalized acetylenes			24.3.2
1-haloalk-1-ynes			24.4.1
2,2-dihalo-substituted aldehydes		25 (Aldehydes)	25.3
2-halo-substituted aldehydes			25.4
3-halo-substituted aldehydes			25.9.4
2,2-dihalo-substituted ketones		26 (Ketones)	26.5
2-halo-substituted ketones			26.6
3- (or higher) halo-substituted ketones			26.11.1
N-haloimines		27 (Heteroatom Analogues of Aldehydes and Ketones)	27.12
halogen-substituted benzo-1,4-quinones		28 (Quinones and Heteroatom Analogues)	28.1.2
dihalogen-substituted benzo-1,4-quinones			28.1.6.1
(1-haloalkyl)-substituted benzo-1,4-quinones			28.1.7.1
fluoro(cyclo)alkanes		34 (Fluorine)	34.1 –34.10
chloro-, bromo-, iodo(cyclo)alkanes	 Hal = Cl, Br, I	35 (Chlorine, Bromine, and Iodine)	_b

^a X = heterofunctionality; Hal = Cl, Br, or I.

^b See [Table 1](#).

The halogen elements (including the radioactive astatine) form group 17 (formerly VIIb) of the periodic table. Consequently, there is a gradual change in physical and, to some extent, in chemical properties on passing from one element to another.^[1] The main common feature is that the atoms are only one electron short of the perfect electron configuration of a noble gas. This makes the halogens typical nonmetals with high electron affinities (**Table 3**).^[2–5] As usual, the biggest difference is in the step between the first two elements, i.e. here the transition from fluorine to chlorine. This justifies the separate treatment of fluoroalkane synthesis in *Science of Synthesis*, Vol. 34 (Fluorine). However, within the remaining three elements chlorine, bromine, and iodine there is a close resemblance (**Table 3**).

Gradual changes are also seen for the covalent radii of the four common halogens (**Table 3**). When compared with the value for carbon (77.2 pm)^[4] the best-matched bond-forming orbital interaction is obviously with fluorine. This is reflected in the high stability of the C—F bond, as shown by the carbon—halogen bond dissociation energies, whereas the other halogens form much weaker bonds with carbon (**Table 3**).

Table 3 Physical Properties of the Halogens^[3–5]

Physical Feature	F	Cl	Br	I	Ref
Electron Affinity for Hal ₂ (eV)	3.08	2.38	2.51	2.58	^[3]
Covalent Radius (pm)	68.1	99.4	114.2	133.3	^[4]
H ₃ C—Hal Bond Dissociation Energy (kJ · mol ^{−1})	452	351	293	234	^[5]

The electronegativity of an element correlates electron affinities, ionization energies, and bond energies. Even though the values differ depending on the method of calculation used, again the special role of fluorine is obvious, and all halogens are more electronegative than carbon (**Table 4**). In the Sanderson scale of electronegativities, the polarizability of an element is emphasized.^[4] Thus, fluorine must be considered as a "hard" atom, while iodine as a particularly "soft" atom marks the other extreme. This is also demonstrated in the polarizability values for fluoride (1.04×10^{-24} mL), chloride (3.86×10^{-24} mL), bromide (4.77×10^{-24} mL), and iodide (7.1×10^{-24} mL).^[6] In addition, the contribution of d-orbitals in the heavy elements should be seen as polarization functions rather than as coordination sites for hypervalent interactions.^[7]

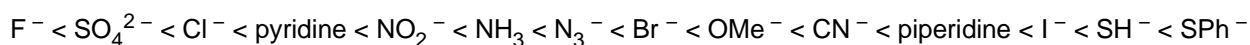
Table 4 Electronegativities of Fluorine, Chlorine, Bromine, Iodine, and, for Comparison, Carbon on Different Scales^[2,4]

Method of Calculation	C	F	Cl	Br	I	Ref
Allred and Rochow	2.50	4.10	2.83	2.74	2.21	^[2]
Pauling	2.50	3.98	3.16	2.96	2.66	^[2]
Mulliken	2.63	3.91	3.00	2.76	2.56	^[2]
Sanderson	2.746	4.000	3.475	3.217	2.778	^[4]

Houben –Weyl, Vols. 5/3 and 5/4 provide a comprehensive review of the synthesis and of synthetic applications of chloro-, bromo-, and iodoalkanes, respectively, up to around 1960. Subsequently, haloalkane chemistry was reviewed in *Comprehensive Organic Chemistry*^[8] and in the more specialized offsprings *Comprehensive Organic Synthesis*^[9] and *Comprehensive Organic Functional Group Transformations*;^[10] the latter series was updated in 2005.^[11] In the *The Chemistry of Functional Groups* series an updated volume of *The Chemistry of the Carbon—Halogen Bond* is available, which includes a chapter on synthesis.^[12] In addition, *Rodd's Chemistry of Carbon Compounds* gives detailed information on many aspects of haloalkane chemistry.^[13] Many of the methods that were reported in the *Houben –Weyl* volumes are still in use and are therefore covered in this volume, including experimental procedures. However, there has been a slow but constant development of improved or novel synthetic methods, which are also included here. Although *Science of Synthesis* does not

claim to be comprehensive in the coverage of methods, the authors have carefully selected the important and reliable methods of haloalkane synthesis.

Quite often, haloalkanes are used as synthetic intermediates. This relies mainly on the high polarizability (**Table 4**) making chloride, bromide, and iodide good nucleophiles as well as good leaving groups. This is also the reason why haloalkanes played an important role in the development of the mechanistic concepts of nucleophilic displacement reactions.^[14] Based on the polarizability, the nucleophilicity increases in the series chlorine < bromine < iodine. The following is a more comprehensive series that shows the position of the halogens within a selection of the common nucleophiles, the order based on the reaction of the nucleophile with iodomethane:^[15]



It should be noted that the order of nucleophilicities of the halogens is inverse to that of the basicities. The latter may also be crucial under special conditions, e.g. if dimethylformamide is used as solvent in displacement reactions.^[16] Another external influence on relative reactions rates of the halogens may be the catalyst. Thus, in the boron trifluoride catalyzed Friedel–Crafts alkylation of arenes by chloro-, bromo-, or iodoalkyl fluorides, the C—F bond is cleaved to give an aryl(halo)alkane (**Scheme 1**).^[17] To account for this unusual selectivity, the high polarity of the C—F bond (cf. **Table 3**) as well as the high bond energy of the B—F bond to be formed by the interaction with the Lewis acid catalyst, together with an obviously small steric hindrance, are invoked to account for the high reactivity of the C—F bond.

Scheme 1 Friedel–Crafts Alkylation Using Chloro-, Bromo-, or Iodoalkyl Fluorides^[17]

There are ample technical uses of haloalkanes, with 15000 chlorinated compounds in commerce in the United States (1994).^[18] In the high-polymer field, poly(tetrafluoroethylene) (PTFE, Teflon), polychloroprene, and poly(vinyl chloride) (PVC) are organic materials that are familiar to almost everybody. Polychloroprene has a chloroalkane structure if the compound polymerizes via the chlorine-free C=C bond. However, this is only a minor polymerization pathway (cf. *Houben–Weyl*, Vol. 14/1, p 736; **Scheme 2**). Poly(vinyl chloride) is within the scope of this volume (cf. Section **35.1.1.9**).

Scheme 2 Polymerization of Chloroprene^[19]

Mixtures of chlorinated alkanes with a chlorine-content of 15 –70% are used as flame-retarding agents. Standard uses of halogenated compounds are as solvents for reactions, extractions, dry cleaning, or solvent dyeing.

Many drugs contain chlorine, though mostly bound to an sp^2 -hybridized carbon atom. It appears, however, that the biological activity is not related to the presence of the halogen substituent; the halogen rather seems to assist in resorption or to direct metabolism. Examples where the chlorine is on an sp^3 -hybridized carbon atom include the chiral anesthetics enflurane (1), isoflurane (2), and halothane (3), the bactericides chloramphenicol (4) and clindamycin (7-chlorolincomycin, 5), the anticonvulsive clomethiazole (6), and the analgesic chlorthenoxazine (7). Then, there is a group of chlorine-containing compounds with cytostatic activity that are derived from N-lost (8); in **Scheme 3** the derivatives melphalan (9), cyclophosphamide (10), trofosfamide (11), ifosfamide (12), carmustine (13), lomustine (14), nimustine (15), and chlorambucile (16) are shown.^[21]

Pharmacological applications of organoiodine compounds are mainly in the area of X-ray contrast media, but it appears that here iodine is always bound to an aromatic ring system.

Scheme 3 Haloalkanes with Pharmacological Activity^[21]

In the field of pesticides, there are several examples of haloalkanes, again mainly chloro derivatives, such as the insecticide DDT (**17**), the insecti- and nematocide cloethocarb (**18**), and, from the family of biologically active thiophosphates, chlormephos (**19**) (**Scheme 4**). Moreover, the insecticidal cycloaliphatics chlordane (**20**), aldrin (**21**), dieldrin (**22**), chlorodecone (Kepone, **23**), and the hexachlorocyclohexanes [e.g., lindane (**24**)] should be mentioned. One of the few examples of a bromine-containing fungicide is bromuconazole (**25**).

Scheme 4 Halogen-Containing Pesticides

Chloroalkanes^[22] as well as most of the compounds in **Scheme 4** have been widely criticized as being harmful for the environment as, due to their high lipophilicity, they are readily taken up by tissue in man and animals where they are only slowly metabolized with half-lives of weeks or months.^[23,24] There is special concern about the possibility of causing liver cancer;^[18,23] adverse effects on wildlife have been proven.^[18,25] In response, there have been calls for a phase-out of chlorinated organics, culminating in chlorine's labeling as "the devil's element".^[26] There is an ongoing debate, where one side emphasizes the health risks, particularly of dioxins and polychlorinated biphenyls, and the opponents demand to differentiate between different classes of chloroorganic compounds and point out the advantages of chlorine and chloroorganics for hygiene, organic

materials, and organic synthesis. A crucial test of industrial production with "responsible care" can be seen in chlorine chemistry.

The scientific and public interest in the fate of chloralkanes in the environment has led to the development of sophisticated analytical methods that now allow high-quality trace analysis.^[13,28]

Not only when working with chloroalkanes, but also with bromo- or iodoalkanes, special care should be taken to protect staff and the environment against any adverse effects. In principle, haloalkanes are alkylating agents and therefore possible carcinogens. This is particularly important with highly volatile haloalkanes. For the frequently used representatives, a vast body of biological tests and epidemiological studies have led to compound-specific risk assessment. On this basis, regulations have been issued which should be obeyed scrupulously. **Table 5** shows the assessment of risks from the German perspective.^[29]

Table 5 Health Risks of Industrially Used Haloalkanes^[29]

Haloalkane	Vapor Pressure (kPa) at 20 °C	Maximum Workplace Concentration	Carcinogenic Effect ^a	Resorption or Sensitization Properties ^b	Ref
bromoethane	50.7	–	2	SR	^[29]
bromomethane	–	12 ppm	3B	–	^[29]
chlordane (20)	–	0.5 mg · m ^{–3}	3B	SR	^[29]
chlordecone (23)	–	–	3B	–	^[29]
1-chloro-2,3-epoxypropane (epichlorohydrin)	–	–	2	SR, SS	^[29]
chloroethane	–	–	3B	SR	^[29]
2-chloroethanol	–	1 ppm; 3.3 mg · m ^{–3}	–	–	^[29]
chloromethane	–	50 ppm; 100 mg · m ^{–3}	3B	SR	^[29]
chloroalkanes	–	–	3B	–	^[29]
3-chloroprop-1-ene	–	–	3B	SR	^[29]
benzyl chloride	–	–	3B	–	^[29]
bis(2-chloroethyl) ether	–	10 ppm; 59 mg · m ^{–3}	–	SR	^[29]
bis(2-chloroethyl) sulfide	–	–	1	SR	^[29]
1,2-dibromoethane	1.5	–	2	SR	^[29]
1,4-dichlorobut-2-ene	–	–	2	–	^[29]
1,2-dichloroethane	–	100 ppm; 410 mg · m ^{–3}	–	–	^[29]
1,2-dichloropropane	5.1	–	3B	–	^[29]
1,3-dichloropropan-2-ol	–	–	2	SR	^[29]
dieldrin (22)	–	0.25 mg · m ^{–3}	–	SR	^[29]
1,2,3,4,5,6-hexachlorocyclohexane (diastereomeric mixture)	–	0.5 mg · m ^{–3}	–	SR	^[29]
iodomethane	43.8	–	2	SR	^[29]
1,2,3-trichloropropane	0.45	–	2	–	^[29]

^a Category 1: positive evidence based on epidemiological studies; category 2: positive experimental evidence from animal tests; category 3B: animal tests indicate a possible positive effect; more evidence is required.

^b SR = skin resorption; SS = skin sensitization.

In the debate on environmental effects of chloroorganics, one issue has been the question of whether there are

chlorine-containing natural products. Here, there has been a dramatic development. In 1973 it was stated that only "a few dozen really natural organic halogen compounds are known".^[28] However, in a 2006 count, some 4500 halogenated natural products were identified, many with promising medicinal properties, especially from marine origins, and with exciting structural features.^[30] **Scheme 5** displays a number of examples, including halomon,^[31,32] prefuroplocamioid,^[33] -synderol,^[34] aplysiaterpenoid A,^[35] laurencin,^[36] 12-chloroillifunone C,^[37] phoyoside II,^[38] and chloroscoparin.^[39] Most of the compounds are terpenes, but astin^[40] is an example of a cyclic peptide with the unusual amino acid 4-chloro-3-hydroxyproline^[35] showing antitumor activity. 1-Chloro-3-methylbut-2-ene has been identified in the compound mix of a bat pheromone.^[41] It now appears that nature often turns to halogenation to fine-tune a natural product's biological properties. This has a parallel in that halogenation has always been and will continue to be a popular tool for tweaking a drug candidate's biological properties in the pharmaceutical industry.

Scheme 5 Examples of Natural Haloalkanes^[31–41]

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


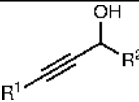

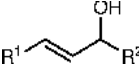
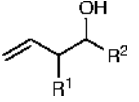
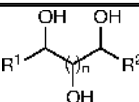
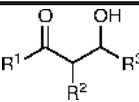
Compounds with One Carbon–Heteroatom Bond

36

Volume 36:
AlcoholsClayden, J., in *Science of Synthesis*, **36** (2007), p.1

Volume 36 of *Science of Synthesis* is concerned with the synthesis of alcohols, including diols and polyols. The volume is organized by structural class, as shown in **Table 1**. Sections **36.2**–36.10 address the synthesis of alcohols with various defining structural characteristics, such as cycloalkanols (Section **36.2**), benzylic alcohols (Section **36.4**), and diols (Section **36.7**).

Table 1 Structural Classes of Alcohols Covered in Volume 36

Product Class or Subclass	Typical Structure	Section Number
alkanols	R^1OH (R^1 = alkyl)	36.1
cycloalkanols		36.2
cyclopropanols		36.2.1
cyclobutanols		36.2.2
cyclopentanols and larger rings		36.2.3
propargylic alcohols		36.3
benzylic alcohols		36.4
allylic alcohols		36.5
homoallylic alcohols		36.6
1,n-diols ($n > 1$)		36.7
polyols		36.8
-hydroxy carbonyl compounds (aldol products)		36.9
n-heteroatom-functionalized alkanols ($n \geq 2$)		36.10

Some hydroxy-bearing compounds are excluded because they appear elsewhere in *Science of Synthesis*. For example, -heteroatom-substituted alcohols, such as -hydroxy carbonyl compounds, are not covered here because they contain an additional functional group of higher priority than the hydroxy group under the *Science of Synthesis* classification system. Coverage of these compounds can be found in the relevant volume that deals with

the higher-priority group in question.

Section **36.1** is more general, dealing with the synthesis of alcohols of any structural class (including simple alkanols) and is organized according to synthetic method, as shown in **Table 2**. Thus, a method might appear in Section **36.1** if it is suitable for the synthesis of alcohols in general, but methods described in Sections **36.2**–**36.10** will be applicable primarily to a more restricted class of alcohols. In a similar vein, Section **36.11** addresses the deprotection of protected alcohols.

Table 2 Methods for the Synthesis of Alkanols Covered in Volume 36

Method	Typical Reaction	Section Number
oxidation (metal and enzyme catalyzed)		36.1.1
reduction		36.1.2
substitution		36.1.3
addition to alkynes and alkenes		36.1.4
carbonylation reactions		36.1.5
addition of organometallics to carbon dioxide, carboxylic acids, and derivatives		36.1.6
addition of organometallics to aldehydes and ketones		36.1.7
resolution or inversion		36.1.8
synthesis from other alcohols		36.1.9
deprotection		36.11

Finally, Section **36.12** covers metal alcoholates: compounds related to alcohols by replacement of the hydroxy hydrogen by a metal.

The most conceptually simple synthesis of an alcohol imaginable would start with an alkane and introduce a hydroxy group. This is a simple idea, the realization of which is an ongoing challenge to chemists, and this is where the chemistry of this volume begins, with the use of oxygen in the presence of transition-metal catalysts to oxidize simple alkanes to alcohols. A 1 mol% quantity of iron catalyzes the conversion of adamantane (**1**) into adamantan-1-ol (**2**) using just oxygen in the presence of an aldehyde (**Scheme 1**).^[1]

Scheme 1 Alcohol Formation by Metal-Catalyzed Hydroxylation^[1]

Oxidation of unactivated C—H bonds can be achieved in biological systems, giving biocatalytic methods the edge when it comes to the regio- and chemoselective introduction of hydroxy groups in this way. Biological methods may be limited in generality, but protective modification of the substrate to suit a specific organism can be used to promote otherwise challenging oxidations. For example, cyclopentanecarboxylic acid can be oxidized regio- and stereospecifically to yield alcohol **4** when protected as its benzoxazole derivative **3** (**Scheme 2**).^[2–5]

Scheme 2 Biocatalytic Hydroxylation Using Biocompatible Protection^[2–5]

Selective oxidation methods allow the use of C—Si, C—B, and carbon—metal bonds as precursors to C—O bonds, and Section **36.1.1** covers the important synthetic strategy of using silanes, and in particular phenyldimethylsilanes, as masked alcohols. Thus, alcohol **6** is formed stereospecifically from silane **5** (**Scheme 3**).^[6] Directed metalation chemistry permits the regioselective introduction of metals, which may then be transformed into hydroxy groups simply with atmospheric oxygen (**Scheme 4**).^[7]

Scheme 3 Silanes as a Masked Hydroxy Group^[6]

Scheme 4 Directed Metalation as a Means of Hydroxylation^[7]

The remainder of Section **36.1** deals with the formation of alcohols from other functional groups by oxidation, reduction, substitution, or addition reactions. Reduction of carbonyl compounds to yield primary alcohols (Section **36.1.2**) is an area where chemoselective methods offer the possibility of reducing selectively one type of carboxylic acid derivative in the presence of another. For example, borane–tetrahydrofuran complex reduces carboxylic acids in the presence of esters,^[8] zinc(II) borohydride reduces aliphatic esters in the presence of aromatic ones,^[9] and lithium triethylborohydride produces alcohols (e.g., **8**) rather than amines from amides (e.g., **7**) (**Scheme 5**).^[10]

Scheme 5 Chemoselective Synthesis of Alcohols by Reduction of Carboxylic Acid Derivatives^[8–10]

Several reagents reduce aldehydes in the presence of ketones (**Scheme 6**),^[11] while chlorodiisopinocampheylborane exhibits remarkable selectivity for the reduction of aldehydes or ketones in the presence of acid chlorides, for example giving alcohol **10** from aldehyde **9**.^[12] Temporary acetal protection in the presence of lanthanide salts provides a powerful way of reducing ketones in the presence of aldehydes (**Scheme 6**).^[13]

Scheme 6 Chemoselective Reduction of Aldehydes or Ketones^[11–13]

Stereoselectivity also features highly in Section **36.1.2** because ketone reductions allow chiral secondary alcohols to be produced in enantiomerically enriched form. The importance of catalytic methods for making chiral secondary alcohols on a large scale has led to some superbly tuned catalysts, such as Noyori's family of ruthenium–diamine–diphosphine complexes. The reduction shown in **Scheme 7** generates essentially enantiomerically pure alcohol **12** in quantitative yield from ketone **11** using sodium formate as the source of hydrogen.^[14]

Scheme 7 Catalytic Asymmetric Reduction of a Ketone^[14]

Substitution reactions (Section 36.1.3) allow alcohols to be formed by displacement of leaving groups with oxygen nucleophiles, but also of course by displacement of an alcohol leaving group with other nucleophiles, as in this alkylative substitution of acetal 13 by an aluminum reagent.^[15]

Scheme 8 Alcohol Synthesis by Alkylative Substitution of an Acetal^[15]

Sections 36.1.4 –36.1.7 describe the synthesis of alcohols by addition to C —C and C —O multiple bonds (excluding methods which proceed via hydroboration and oxidation, which are discussed in Section 36.1.1.3). Hydration or ozonolysis of alkenes and alkynes form the bulk of Section 36.1.4, but also covered are connective hydroxyalkylations of unactivated alkenes, such as the example shown in **Scheme 9**, using a chiral zirconocene catalyst 15. Methylation by trimethylaluminum and air oxidation yields alcohol 16 in 74% ee from alkene 14.^[16]

Scheme 9 Asymmetric Hydroxymethylation of an Alkene^[16]

Carbon monoxide (Section 36.1.5) and carbon dioxide (Section 36.1.6) provide the source of a C —OH unit in the underutilized synthesis of alcohols by carbonylation and carboxylation reactions. For example, hindered tertiary alcohols are formed in a convergent manner by hydroboration of alkenes followed by carbonylation (**Scheme 10**).

The formation of tertiary alcohols by multiple additions to carboxylic acid derivatives is also described in this section.

Scheme 10 Connective Synthesis of an Alcohol by Carbonylation of a Borane^[17]

One of the most common C—C bond-forming reactions used in synthesis is the addition of a carbon nucleophile to an aldehyde or a ketone, and Section 36.1.7 deals with a series of organometallic reagents in such reactions (aldol chemistry is reserved for Section 36.9). As with ketone reduction, stereoselectivity features highly, whether diastereoselectivity, for example in the addition of alkyllithium reagents to chiral aldehydes such as 17^[18] or in the attack on cyclic ketone 18^[19] (**Scheme 11**), or enantioselectivity, for example in the amino alcohol promoted addition of dialkylzinc reagents (**Scheme 12**).^[20]

Scheme 11 Synthesis of Alcohols by Diastereoselective Addition to Carbonyl Compounds^[18,19]

Scheme 12 Enantioselective Addition of Diethylzinc to an Aldehyde^[20]

The challenge of distinguishing the enantiotopic faces of a prochiral ketone makes tertiary alcohols particularly difficult to prepare stereoselectively. Among the most effective methods available is the addition to thioacetals, e.g. 19, which can subsequently be deprotected to reveal hydroxyaldehydes (**Scheme 13**).^[21]

Scheme 13 Synthesis of a Chiral Tertiary Alcohol Using a Thioacetal Auxiliary^[21]

In many cases, asymmetric synthesis is neither practical nor economical, and chiral alcohols are instead obtained

by resolution. Section 36.1.8 describes resolution methods and also methods that invert the stereochemistry at a hydroxy-bearing center. Classical resolution techniques are less suitable for alcohols than for acids or amines, and many of the methods described are kinetic resolutions for which a number of lipases and other enzymes work extremely well. For example, at 51% conversion, *Candida antarctica* lipase converts the alcohol *rac*-20 into its ester 21 in 97% ee, leaving behind unreacted alcohol (*S*)-20 with even higher enantiomeric purity (Scheme 14).^[22]

Scheme 14 Enzymatic Kinetic Resolution of a Chiral Alcohol by Acylation^[22]

The organism *Corynosporium cassiicola* carries out an even more spectacular resolution of *trans*-indane-1,2-diol (*rac*-22) in which the *R,R*-enantiomer is simply converted, by inversion at both stereogenic centers, into the *S,S*-enantiomer in 82% yield from the racemate (Scheme 15).^[23]

Scheme 15 Enantiomeric Enrichment of a Diol by *Corynosporium cassiicola*^[23]

The hydroxy group itself provides alcohols with reactivity and allows their further functionalization to generate new alcohols, usually via another intermediate functionality. The wide variety of these transformations is explored in Section 36.1.9. Acylations and hydroxyalkylations to a hydroxy group can be achieved, for example, by deprotonation of an intermediate acetal 23 (Scheme 16)^[24] or carbamate 25 (Scheme 17).^[25] Both processes generate enantiomerically enriched products: the former leads to alcohol 24 by making use of a sugar-derived auxiliary, and the latter gives alcohol 26 by employing (–)-sparteine as a chiral additive.

Scheme 16 Asymmetric α -Functionalization of an Alcohol via a Lithiated Acetal^[24]

Scheme 17 Asymmetric α -Functionalization of an Alcohol via a Lithiated Carbamate^[25]

Many of the methods discussed for the synthesis of alkanols in Section **36.1** are applicable to the other classes of alcohols described in Sections **36.2**–36.10. However, some have particular significance for certain classes, or exhibit features which are relevant only in certain contexts. The cycloalkanols for example, whose synthesis is described in Section **36.2**, can all be made by simple reduction of ketones. However, cyclization methods, many applicable primarily to a specific ring size, come into their own here. Thus, the Kulinkovich reaction is perfectly suited to cyclopropanol synthesis (**Scheme 18**),^[26] while samarium ketyl cyclization yields cyclobutanols (**Scheme 19**).^[27,28] A much wider range of intramolecular addition reactions, such as the intramolecular Prins reaction shown in **Scheme 20**, yield five- and six-membered and larger rings.^[29]

Scheme 18 Synthesis of a Cyclopropanol by the Kulinkovich Reaction^[26]

Scheme 19 Synthesis of a Cyclobutanol via Samarium-Mediated Ketyl Cyclization^[27,28]

Scheme 20 Synthesis of a Cycloalkanol via Prins Cyclization^[29]

The subsequent synthetic utility of the unsaturated systems makes propargylic, allylic, and homoallylic alcohols particularly valuable intermediates, and routes to these subclasses are dealt with in Sections **36.3**, **36.5**, and **36.6**, respectively. Mild, catalytic methods for C—C bond formation are of particular importance here, and many of the most important methods for synthesizing these classes involve addition of an unsaturated alkynyl, vinyl, or allyl unit to an aldehyde or ketone, often with control of stereochemistry. For example, the zinc-promoted addition of alkynes to aldehydes in the presence of a chiral catalyst derived from amino alcohol **28** is one of the most simple and effective ways of making propargylic alcohols, and with active ketones such as **27** the reaction yields tertiary alcohols enantioselectively (**Scheme 21**).^[30]

Scheme 21 Preparation of a Tertiary Propargylic Alcohol by Alkyne Addition to a Ketone^[30]

Allylic alcohols combine two of the most versatile functional groups in chemistry, and can be prepared by one of the broadest sets of reactions imaginable, including oxidation, reduction, rearrangement, and C—C bond-forming reactions. The latter type includes such unusual processes as the reductive alkylation of lithiated epoxides, which can be enantioselective in the presence of (–)-sparteine as a chiral ligand.^[31–33] Epoxide **29** is metalated and then couples with isopropyllithium to yield the alkylated allylic alcohol **30** (**Scheme 22**). Allylic alcohols are themselves substrates for many important transformations to other subclasses of alcohols, and feature highly in Section **36.1.9**

Scheme 22 Allylic Alcohol by Desymmetrizing Reductive Alkylation of an Epoxide

Homoallylic alcohols, covered in Section 36.6, derive primarily from the allylation of aldehydes or ketones, and their utility lies in the fact that the double bond can itself be considered a masked carbonyl group for subsequent reactions, which leads to 1,3-diols and hence polyketide structures. Chiral allylboron, -tin, -silicon, and -chromium (and other metal) derivatives have been used for their synthesis, while variants which use achiral allylating agents in the presence of chiral Lewis acids are particularly effective (**Scheme 23**).^[34]

Scheme 23 Preparation of Homoallylic Alcohols by Asymmetric Allylation Using a Chiral Lewis Acid^[34]

Homoallylic alcohols are also generated by the [2,3]-Wittig rearrangement, as in the synthetic route to the viridifungins shown in **Scheme 24**.^[35]

Scheme 24 Preparation of a Homoallylic Alcohol by a [2,3]-Wittig Rearrangement^[35]

Benzylic alcohols find greater interest as final targets in a synthetic sequence, and their synthesis, described in Section 36.4, may involve some reactions unique to this structural class, for example enantioselective oxidations of benzylic C—H bonds (**Scheme 25**)^[36] and enantioselective 1,2-Wittig rearrangements (**Scheme 26**).^[37]

Scheme 25 Asymmetric Benzylic Oxidation^[36]

Scheme 26 Synthesis of a Benzylic Alcohol by [1,2]-Wittig Rearrangement^[37]

Compounds with more than one hydroxy group pose a particular challenge in synthesis, but also offer opportunities to the extent that diols are frequently used as precursors to alcohols because of the power of asymmetric dihydroxylation reactions. While the Sharpless asymmetric dihydroxylation (**Scheme 27**)^[38] is by far the most widely used enantioselective method for making 1,2-diols, intriguing alternatives such as the diboration – oxidation reaction shown in **Scheme 28**^[39] are also surveyed in this section.

Scheme 27 Sharpless Asymmetric Dihydroxylation Applied to a Trisubstituted Alkene^[38]**Scheme 28** Diboration –Oxidation as a Means of Dihydroxylation^[39]

Diols with 1,3- and more-remotely related hydroxy groups can be formed by reductions in which one hydroxy-bearing center governs the stereoselective formation of another. Even 1,5-diols can be formed diastereoselectively, via tricarbonyliron complexes (**Scheme 29**).^[40] For example, reduction of complexes **31**, followed by decomplexation and hydrogenation, yields 1,5-diols **32** in up to 96% de.

Scheme 29 Diastereoselective Formation of 1,5-Diols^[40]

Polyols are widespread in nature, particularly in the form of carbohydrates, polyketides, and their derivatives, and Section **36.8** covers methods for polyol synthesis. For example, inositols and inositol derivatives may be prepared by successive dihydroxylations of cyclohexa-3,5-diene-1,2-diols such as **33**,^[41] a product of bromobenzene metabolism by *Pseudomonas putida* (**Scheme 30**). A remarkable culmination of this type of strategy is the synthesis of the inositol hexaacetate **34** by photochemical osmylation of benzene (**Scheme 31**).^[42]

Scheme 30 Synthesis of a Tetrol by Diastereoselective Dihydroxylation of a Diol^[41]

Scheme 31 Synthesis of a Polyol from Benzene

-Hydroxy ketones are covered in two places in *Science of Synthesis* (see also *Science of Synthesis*, Vol. 26 [Ketones (Section 26.11.2)]), but the most important method for their synthesis, the aldol reaction, appears in this volume. Chapter 36.9 highlights, in particular, modern, catalytic methods for aldol additions. Numerous methods exploiting metals bearing chiral ligands are covered, along with the spectacular selectivities possible using simple organic catalysts such as (S)-proline (**Scheme 32**).^[43]

Scheme 32 Application of Proline in an Organocatalytic Aldol Reaction^[43]

The synthesis of other classes of n-heterofunctionalized alcohols (where $n \geq 2$, and the heteroatom is not a halogen) is described in Section **36.10**. Many approaches involve the use of electrophilic, oxygen-containing reagents, and epoxide opening is perhaps the single most important way of making α -functionalized alcohols. However, reactions such as asymmetric aminohydroxylation offer single step methods for making functionalized alcohols directly from alkenes. The example shown in **Scheme 33** generates protected amino alcohol **35**, with higher regioselectivity than most other methods.^[44]

Scheme 33 Asymmetric Aminohydroxylation of an Alkene^[44]

The synthetic utility of the hydroxy group is, in a way, compromised by its relatively acidic proton, and protection – deprotection methods for hydroxy groups are central to the use of alcohols in synthesis. Section **36.11** describes methods for the deprotection of alcohols and diols using the full range of reactivities that can be incorporated into a protecting group. For example, the 2-(benzylsulfanyl)ethyl (BTE) ether protecting group of **36** is stable to the range of reagents typically used in oligosaccharide chemistry, but can be deprotected by oxidation and elimination (**Scheme 34**).^[45]

Scheme 34 Deprotection of a 2-(Benzylsulfanyl)ethyl Ether^[45]

The volume finishes with coverage of a family of compounds closely related to alcohols, the metal alcoholates (Section **36.12**), with the focus on those metal alcoholates that have not been covered in detail elsewhere in *Science of Synthesis*. By far the most widespread method for making these compounds is by deprotonation, but reactions such as the aldehyde addition shown in **Scheme 35** allow a lithium alcoholate to act as a metalation-directing group in the synthesis of **37**.^[46]

Scheme 35 Formation of a Metalation-Directing Lithium Alkoxide by Nucleophilic Addition^[46]

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Compounds with One Carbon–Heteroatom Bond

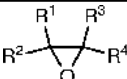


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Volume 37:
EthersForsyth, C. J., in *Science of Synthesis*, **37** (2008), p.1

General Introduction

Ethers, both acyclic and cyclic, are widely represented throughout organic chemistry as prolific synthetic intermediates and targets. This volume provides a comprehensive yet critical review of methods for the synthesis of ethers comprised of $C(sp^3) - O - C(sp^3)$ functionality with no additional heteroatom or metal at the α -carbon. Ethers are categorized into eight product classes, as illustrated in **Table 1**. Section **37.1** includes some general methods of ether synthesis that apply not only to dialkyl ethers but also to examples containing functionality or that could fit into other product classes within this volume.

Table 1 Product Classes within Volume 37

Product Class	Structure	Section
dialkyl ethers	R^1-O-R^2	37.1
epoxides (oxiranes)		37.2
oxetanes		37.3
five-membered and larger-ring oxacycloalk-3-enes	 $n \geq 1$	37.4
five-membered and larger-ring oxacycloalkanes	 $n \geq 1$	37.5
oxonium salts	$R^1-O^+-R^2 \quad R^3 \quad X^-$	37.6
oligo- and monosaccharide ethers		37.7
ethers as protecting groups	R^1-O-R^2 $R^2 = \text{removable group}$	37.8

The preparations of certain types of $C - O$ functionalities are not covered in this volume, but are treated elsewhere in *Science of Synthesis*. These include aryl ethers {see *Science of Synthesis*, Vol. 31a [Arene $-X$ ($X = \text{Hal, O, S, Se, Te}$) (Section 31.6)]}, vinyl ethers {see Vol. 32 [$X - \text{Ene} - X$ ($X = \text{F, Cl, Br, I, O, S, Se, Te, N, P}$), $\text{Ene} - \text{Hal}$, and $\text{Ene} - O$ Compounds]}], α -halo ethers [Vol. 35 (Chlorine, Bromine, and Iodine) (Sections 35.1.5, 35.2.5, and 35.3.5)], and α -heterosubstituted ethers {see Vol. 29 [Acetals: Hal/X and $O/O, S, Se, Te$ (Sections 29.3, 29.6, 29.11 and 29.12)] and Vol. 30 [Acetals: $O/N, S/S, S/N$, and N/N and Higher Heteroatom Analogues (Sections 30.1 and 30.2)]}. α -Alkoxy carbonyl compounds formed by Michael addition are also not covered here, but are covered in the respective carbonyl volumes {see, for example, *Science of Synthesis*, Vol. 25 [Aldehydes (Section 25.9.5)]}.

Sections [37.1](#), [37.2](#), and [37.4](#) are further subdivided according to the synthetic strategy employed, as shown in [Table 2](#).

Table 2 Methods for the Synthesis of Ethers Covered in Volume 37

Product Class or Method	Typical Reaction	Section
dialkyl ethers		37.1
synthesis from esters, aldehydes, ketones, and acetals		37.1.1
synthesis by substitution	$R^1X \longrightarrow R^1-O-R^2$	37.1.2
synthesis by addition to alkenes	$= \longrightarrow X-CH_2-CH_2-OR^1$	37.1.3
synthesis from other ethers	$R^1-O-R^2 \longrightarrow R^1-O-R^3$	37.1.4
epoxides (oxiranes)		37.2
synthesis from alkenes by metal-mediated oxidation		37.2.1
synthesis from alkenes using organic oxidants	$= \xrightarrow{\text{organic oxidant}} \triangle$	37.2.2
synthesis by carbonyl epoxidation		37.2.3
synthesis by ring closure	$X-CH_2-CH_2-OR^1 \longrightarrow \triangle$	37.2.4
five-membered and larger-ring oxacycloalk-3-enes		37.4
synthesis by ring closure		37.4.1
synthesis by ring-closing metathesis		37.4.2
synthesis from other cyclic ethers		37.4.3

The synthesis of acyclic ethers is described initially from functional groups at higher oxidation states of carbon, including from carbonyl and acetal functional groups (Section [37.1.1](#)). Classical substitution methods (Section [37.1.2](#)), additions to alkenes (Section [37.1.3](#)), and elaboration of existing ethers (Section [37.1.4](#)) follow. The synthesis of cyclic ethers is covered systematically and in depth to reflect their synthetic importance and widespread occurrence. The synthetically most versatile ethers are epoxides (Section [37.2](#)), and methods for epoxide preparation are organized into four categories: alkene epoxidation mediated by metals (Section [37.2.1](#)), alkene epoxidation induced by organic oxidants (Section [37.2.2](#)), carbonyl epoxidation (Section [37.2.3](#)), and ring closure of vicinally substituted oxygen-containing species (Section [37.2.4](#)). Oxetanes are discussed thoroughly as a single section (Section [37.3](#)), as are larger oxacycloalkanes (Section [37.5](#)). The diverse methods for the preparation of five-membered and larger-ring oxacycloalk-3-enes (Section [37.4](#)) are subdivided into ring-closing methods (Section [37.4.1](#)), metathesis-based ring closures (Section [37.4.2](#)), and synthesis from other oxacycloalkenes ([37.4.3](#)). Oxonium salts (Section [37.6](#)) are then described, followed by focused coverage of oligo- and monosaccharide ethers (Section [37.7](#)), and a concluding chapter on the widespread use of ethers as protecting groups in organic synthesis (Section [37.8](#)).

When combined, the expert authors contributing to this volume have provided a comprehensive coverage of

ethers, among the most common of functional groups in organic chemistry. A wide range of synthetic techniques are covered in Volume 37. Acyclic ethers are classically obtained through substitution, by the reaction of metal alkoxides with alkyl halides (the Williamson ether synthesis). However, other methods are available, such as Homma's hydrosilylation –reduction of carbonyl groups^[1] and palladium-catalyzed addition to alkenes (**Scheme 1**).^[2]

Scheme 1 Synthesis of Acyclic Ethers from Various Precursors^[1,2]

Well-known procedures for the synthesis of epoxides include the titanium-mediated Sharpless reaction for allylic alcohols (**Scheme 2**).^[3,4]

Scheme 2 Sharpless Asymmetric Epoxidation^[3,4]

Another widely used procedure is the manganese-mediated Jacobsen epoxidation, as exemplified in the synthesis of a precursor to the HIV-protease inhibitor indinavir (**Scheme 3**).^[5,6]

Scheme 3 Jacobsen Asymmetric Epoxidation^[5,6]

Non-metal-mediated procedures also feature for the synthesis of epoxides. For example, Shi's fructose-derived ketone epoxidizes alkenes in excellent yields, and with excellent selectivity, via formation of a dioxirane upon oxidation with Oxone (**Scheme 4**).^[7]

Scheme 4 Dioxirane-Mediated Epoxidation Using Shi's Fructose-Derived Ketone^[7]

Cyclic ethers are classically obtained by cyclization of diols. In some cases this chemistry is amenable to transfer to the solid phase. For example, 3,3-bis[(*tert*-butyldimethylsiloxy)methyl]oxetane can be obtained from the corresponding diol precursor via an intermediate arenesulfonic acid ester (**Scheme 5**).^[8] Larger-ring cyclic ethers may be obtained in a similar fashion, by dehydration of diols using a solid superacidic perfluorinated resin sulfonic acid catalyst (Nafion-H) (**Scheme 5**).^[9]

Scheme 5 Synthesis of Cyclic Ethers from Diols^[8,9]

Modern methods for the synthesis of functionalized cycloalkane ethers include metal-mediated intramolecular oxidative cyclizations of hydroxyalkenes. Two examples are the Kennedy cyclization, employing rhenium(VI) oxide complexes,^[10–13] and the Mukaiyama cobalt-induced etherification process (**Scheme 6**).^[14–16]

Scheme 6 Synthesis of Cyclic Ethers from Hydroxy Alkenes^[10–16]

Oxacycloalk-3-enes can be obtained by various methods. The double bond in the oxacycloalk-3-ene may be formed by metathesis using Grubbs' second-generation catalyst, as illustrated in Mioskowski's triple ring-closing reaction shown in **Scheme 7**.^[17] The archetypal oxacyclohex-3-ene synthesis via a hetero-Diels –Alder reaction process is also noteworthy. An example in the context of the assembly of the C11 –C15 moiety of the natural product phorboxazole A is given in **Scheme 7**.^[18]

Scheme 7 Syntheses of Polycyclic Oxacycloalk-3-enes^[17,18]

Non-metathesis approaches are also possible, such as the gold-catalyzed rearrangement –cyclization of a butynediol monoester (**Scheme 8**).^[19] Oxacycloalk-3-enes have also been obtained by double-bond migration, in a Ferrier-type process, where an allylsilane is added to an oxacycloalk-2-ene. This process contributes to a synthesis of hemibrevetoxin B (**Scheme 8**).^[20]

Scheme 8 Non-Metathesis Routes to Oxacycloalk-3-enes^[19,20]

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Compounds with One Carbon–Heteroatom Bond

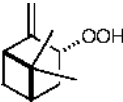
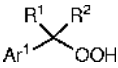
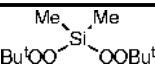
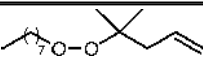
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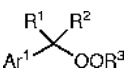

Volume 38:
PeroxidesBerkessel, A., in *Science of Synthesis*, **38** (2008), p.1

This volume is devoted to the synthesis of organic compounds containing the peroxide (O —O) functional group and **Table 1** summarizes the classes of products found within.^[1] It does not describe the synthesis of peroxy acids and derivatives, which are discussed in *Science of Synthesis*, Vol. 20b [Three Carbon —Heteroatom Bonds: Esters and Lactones; Peroxy Acids and R(CO)X, X = S, Se, Te (Section **20.7**)]. The synthesis of peroxidic compounds in general has been previously covered in *Houben –Weyl*, Vol. E 13 and also in Vol. 8, pp 1–74.

Organo hydroperoxides contain the OOH functional group, bonded to just one organic residue. These compounds are covered in Sections **38.1**–**38.4**, depending on whether the organic residue is saturated (Section **38.1**), or of the allylic (Section **38.2**) or benzylic type (Section **38.3**). A separate section deals with salts of hydroperoxides (Section **38.4**). Note that this section also includes ?covalent? metal –peroxide compounds.

Table 1 Classes of Peroxidic Compounds Covered in Science of Synthesis Volume 38

Product Class	General Structure(s)	Examples	Section
alkyl and cycloalkyl hydroperoxides	R^1OOH	<i>t</i> -BuOOH	38.1
allylic hydroperoxides			38.2
benzylic hydroperoxides			38.3
salts of hydroperoxides	R^1OOM	<i>t</i> -BuOONa	38.4
			
alkyl and cycloalkyl peroxides	R^1OOR^2		38.5
			

allylic peroxides			38.6
benzylic peroxides			38.7
monocyclic peroxides			38.8
larger-ring peroxides and endoperoxides			38.9

For compounds containing the peroxide functional group (R^1O-OR^2), a distinction is made between those in which the peroxide moiety is part of a ring (cyclic peroxides) or not (acyclic peroxides). The latter compounds are covered in Sections **38.5**–**38.7**, again categorized according to whether the organic residue is saturated (Section **38.5**), or of the allylic (Section **38.6**) or benzylic type (Section **38.7**). Sections **38.8** and **38.9** are devoted to cyclic peroxides: Section **38.8** deals with monocyclic peroxides and is subdivided into Sections **38.8.1**–**38.8.7**, depending on the size of the peroxidic ring, and on the presence/absence of further oxygen atoms in the ring. Endoperoxides, cyclic by definition, along with monocyclic peroxides containing more than seven atoms in the peroxidic ring, are covered in Section **38.9**.

Within the individual Sections **38.1**–**38.9**, further categorization is made based either on the presence or absence of structural elements and/or on the general approach used for the introduction of the peroxide functionality. For example, in Section **38.1**, -unfunctionalized alkyl hydroperoxides are treated first (**38.1.1**), followed by those which carry halogen (**38.1.2**), oxygen (**38.1.3**), sulfur (**38.1.4**), or nitrogen (**38.1.5**) atoms in the -position. A similar approach is taken throughout Section **38.8**, in which a distinction is made based on the ring sizes and the presence or absence of further oxygen atoms in the ring. In comparison, Sections **38.2** (allylic hydroperoxides)

and 38.3 (benzylic hydroperoxides) are structured according to the substrate to be oxygenated (e.g., alkenes, arenes, haloalkanes, sulfonates, endoperoxides), followed by the reagent (e.g., triplet oxygen, singlet oxygen, hydrogen peroxide). Following these schemes, the type of compound for which synthetic methods are sought, and the general methodology, is rapidly identified. Note that chiral, enantiopure allylic and benzylic hydroperoxides have been prepared by kinetic resolution, based mostly on enzymatic catalysis. Section 38.4 deals with salts of hydroperoxides. This term includes, on the one hand, typical salts such as the lithium alkyl peroxides, and on the other, and to a larger extent, covalent peroxidic compounds such as zinc peroxides, and probably more important in terms of application, silyl and stannyl peroxides. One subsection (Section 38.4.6) deals with transition metal salts of hydroperoxides, which are starting points and intermediates in a number of transition-metal-catalyzed oxidations. Additional discussion of silyl peroxides is also to be found in *Science of Synthesis*, Vol. 4 [Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds (Section 4.4.18)]. Peroxyboranes are further covered in *Science of Synthesis*, Vol. 6 [Boron Compounds (Section 6.1.13)].

Section 38.5 makes the transition from hydroperoxides to peroxides (R^1O-OR^2). Clearly, most of the synthetic approaches to this class of compounds rely on the formation of a second C—O bond starting from hydroperoxides. Many types of carbon electrophile are suitable for this purpose and these include alkyl halides, carbonyl compounds, α,β -unsaturated carbonyl compounds, epoxides, and various others. Section 38.6 deals with allylic peroxides, which are, in most cases, synthesized by one of the following ways: allylation of hydrogen peroxide and derivatives with allyl electrophiles, or (mostly metal-catalyzed) allylic peroxidation of alkenes, dienes, or trienes. For the latter, both oxygen and hydroperoxides have been employed. Section 38.7 is of a similar structure. In many instances, the benzylic peroxides are prepared by radical or ionic substitution of the benzylic position with oxygen, hydrogen peroxide, or hydroperoxides. As mentioned previously, Section 38.8 covers the class of monocyclic peroxides and is substructured according to ring size (three to six) and the presence/absence of further oxygen atoms. Consequently, this product class comprises compounds such as dioxiranes (38.8.1). Only a few isolated examples of this class of peroxides are known. However, they have become most important as oxidants themselves. As a consequence, most of Section 38.8.1 deals (unlike all the other sections) with the application of dioxiranes in synthesis. Note, however, that the epoxidation of alkenes is covered in *Science of Synthesis*, Vol. 37 [Ethers (Section 37.2.2.3)]. Section 38.8.4 covers synthesis of 1,2,4-trioxolanes, but further information on preparation of these cyclic peroxyacetals can be found in *Science of Synthesis*, Vol. 29 [Acetals: Hal/X and O/O, S, Se, Te (Section 29.11.7)]. Section 38.9 covers ring sizes larger than six, as well as bi- and oligocyclic peroxidic structures, the so-called endoperoxides.

In summary, the vast majority of peroxide syntheses involve the formation of the peroxidic C—O bond as the final step. Nevertheless, a number of examples are described throughout the various sections where functional group manipulations are performed on intact peroxides to access the desired target compounds. A typical example is the alkenation of peroxidic carbonyl compounds for the synthesis of unsaturated (hydro)peroxides.

Peroxidic compounds are of great importance in many ways. We are surrounded by a sea of (triplet) oxygen, and the catalyzed and noncatalyzed (autoxidative) dioxygenation of organic compounds leads to hydroperoxides and peroxides. Transformations of this type take place with naturally occurring compounds as substrates, for example in oxidative transformations of unsaturated lipids. Living systems selectively utilize such dioxygenation mechanisms. A key example is the so-called arachidonic acid (**1**) cascade for the generation of the endoperoxide intermediate PGG₂ (**2**), and subsequent transformations to biologically highly active compound classes such as the prostaglandins, prostacyclins, or thromboxanes (Scheme 1).^[2,3]

Scheme 1 Arachidonic Acid and Its Bis-dioxygenation Product, the ?Endoperoxide Intermediate? PGG₂^[2,3]

Another highlight of biology-related peroxide chemistry is artemisinin (**3**), a potent antimalarial drug (**Scheme 2**). The biological activity of compounds such as **2** and **3** has triggered a number of synthetic approaches aiming at these peroxidic target compounds, and they have contributed to the further development of synthetic methodology. For artemisinin (**3**), it was soon realized that the antimalarial activity hinges on the peroxidic character of its 1,2,4-trioxane substructure.^[4,5] A number of analogues have been synthesized and investigated for their biological activity. Probably the simplest active analogue is the 1,2,4,5-tetroxane **4** (**Scheme 2**).^[6] Tetroxanes of this type are readily available from ketones and hydrogen peroxide.

Scheme 2 The Antimalarial Peroxide Artemisinin and a Simple but Still Biologically Active 1,2,4,5-Tetroxane Analogue^[4-6]

In the laboratory, besides triplet dioxygen, two other forms of oxygen are of high importance for the introduction of peroxide or hydroperoxide functional groups: ozone and singlet oxygen, the latter obtained both from photochemical and thermal sources. 1,2,3-Trioxolanes **5**, carbonyl oxides **6**, and 1,2,4-trioxolanes **7** have been described by Criegee as intermediates and products in the ozonolysis of C=C bonds (**Scheme 3**).^[7] A number of synthetically highly useful procedures have been developed, including methods for the selective synthesis of the latter five-membered ring peroxides.

Scheme 3 Peroxidic Compounds Derived from the Reaction of Alkenes with Ozone^[7]

Singlet oxygen is a versatile reagent. It allows the synthesis of cyclic (endo)peroxides **8** by [4 + 2] cycloaddition with dienes and the preparation of allylic hydroperoxides **9** by an ene reaction,^[8] and even gives direct access to

four-membered ring peroxides (1,2-dioxetanes, **10**) if the two other modes of reaction are not accessible (**Scheme 4**).^[9]

Scheme 4 Reaction of Alkenes with Singlet Oxygen^[10]

Reduced forms of oxygen, in particular hydrogen peroxide, form a second group of very important reagents for the synthesis of peroxidic organic compounds. In this case, single or double alkylation with a variety of electrophiles are the typical transformations that lead first to hydroperoxides, and in a second C—O bond formation to organic peroxides. Besides hydrogen peroxide itself, its bis(trimethylsilyl) derivative is of importance in this context. The latter allows the safe handling of what might be called a 'surrogate for anhydrous hydrogen peroxide'. Superoxide^[11-13] is used as the source of the O—O fragment as well, but clearly hydrogen peroxide (and TMSOOTMS) are of dominant importance. Finally, tin derivatives of hydrogen peroxide/hydroperoxides, which have gained some importance as reagents for establishing O—O—C bonds, need to be mentioned.

When a chemist hears the word 'peroxide', probably the most immediate reflex is, 'Careful! Peroxides are explosive!' This is a correct (and healthy!) reflex in the sense that the O—O bond is energy rich. Typical decomposition pathways are homolytic (induced by heat or light) or heterolytic (induced by protonation, Lewis acids, or reaction with redox-active partners such as metal ions) fission. However, it is possible to handle basically all peroxides safely. As indicated throughout this volume, appropriate safety measures are essential for all work involving the synthesis and further transformation of peroxides. Particularly treacherous are polymeric peroxides, which may form during a reaction and are typically filtered off in the course of product isolation: touching these residues with a spatula may be enough to set off a violent explosion. On the other hand, the high energy content of peroxides makes them very attractive in a number of ways. For example, upon thermal cleavage of the four-membered rings of 1,2-dioxetanes (**10**) and 1,2-dioxetanones (**11**), the energy stored in these peroxides is in part released in the form of light (**Scheme 5**).

Scheme 5 Luminescence of 1,2-Dioxetanes

Once again, nature makes use of this phenomenon: light emission by fireflies is based on the enzymatic oxidation of luciferin to the γ -peroxylactone **12**, which is decarboxylated with emission of light (**Scheme 6**).^[14] Similar processes underlie the chemical generation of "cold light" by light sticks:^[15] when activated, hydrogen peroxide and oxalic acid derivatives react with one another to form dioxetanone derivatives, which fragment with emission of light (in practice, the color of the emitted light is a function of an additional fluorescer). Not surprisingly, conjugates of biomolecules and dioxetanes such as the peptide derivative **13** have been synthesized and used as luminescent biological probes.^[16]

Scheme 6 Luciferin-Derived Peroxylactone as the Source of Bioluminescence, and Dioxetanes as Biological Probes^[15,16]

In both the research laboratory and in industrial production processes, hydroperoxides play an important role as sources of a (formal) oxygen atom in metal-catalyzed oxidative transformations, such as the epoxidation of alkenes. Well-known examples are *tert*-butyl hydroperoxide (**14**) and cumene hydroperoxide (**15**) (**Scheme 7**). Oxygen transfer of this type involves heterolytic fission of the peroxidic O—O bond. In contrast, the propensity of peroxides to form radicals by homolytic O—O bond cleavage is the basis for their use as radical initiators. All these transformations rely on the high energy content and the specific reaction modes of the peroxide bond. By the same token, dioxiranes have gained enormous importance as oxygenation agents. Dimethyldioxirane (DMDO, **16**) is ideally suited for the epoxidation of alkenes {see *Science of Synthesis*, Vol. 37 [Ethers (Section 37.2.2.3)]}, including sensitive substrates such as enol ethers (e.g., sugar glycals). The chiral dioxirane derived from the so-called Shi catalyst **17** allows highly enantioselective epoxidations for a broad spectrum of substrate alkenes.^[15,16]

Scheme 7 Hydroperoxides and Dioxiranes as Oxygen-Transfer Agents

In a number of instances, the peroxide functional group serves as the starting point for subsequent transformations to other compound classes. Probably the best-known example is the ionic Hock rearrangement. Treatment of cumene hydroperoxide (**15**) with strong acid affords acetone and phenol; this is the most prominent pathway for contemporary phenol production (**Scheme 8**).^[19]

Scheme 8 Phenol Production via Cumene Hydroperoxide^[19]

Another acid-induced rearrangement is the formation of lactones from cyclic peroxides such as 1,2,4,5-tetroxane **18** (**Scheme 9**).^[19]

Scheme 9 Synthesis of a Lactone from a 1,2,4,5-Tetroxane^[20]

Radical reactions of cyclic peroxides induced by thermolysis or photolysis have been exploited for the synthesis of macrocycles by the Story reaction (**Scheme 10**).^[21] The radical decomposition of peroxides has classically been exploited for the initiation of radical chain reactions (peroxidic ?radical starters?).

Scheme 10 Synthesis of Macrocycles via the Story Reaction^[21]

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Compounds with One Carbon–Heteroatom Bond

39

Volume 39:**Sulfur, Selenium, and Tellurium**Kambe, N., in *Science of Synthesis*, **39** (2007), p.1

This volume of *Science of Synthesis* covers the syntheses of organosulfur, -selenium, and -tellurium compounds of all oxidation states, having at least one sp^3 -carbon —chalcogen bond, where the carbon may form part of an alkyl, allyl, or benzyl group, but does not include compounds with sp^2 - or sp -carbon units directly bonded to the chalcogen. Sulfur, selenium, and tellurium compounds carrying unsaturated carbon substituents on the elements can be found in *Science of Synthesis*, Vol. 24 (Three Carbon —Heteroatom Bonds: Ketene Acetals and Yne —X Compounds), Vol. 31a [Arene —X (X = Hal, O, S, Se, Te)], and Vol. 33 [Ene —X Compounds (X = S, Se, Te, N, P)]. Furthermore, the following two families of compounds are not dealt with here: heteroacetals involving sulfur, selenium, or tellurium [see *Science of Synthesis*, Vol. 29 (Acetals: Hal/X and O/O, S, Se, Te) and Vol. 30 (Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues)], and carbonyl compounds having a sulfur, selenium, or tellurium functional group at the α -carbon [see in particular *Science of Synthesis*, Vol. 20b [Three Carbon —Heteroatom Bonds: Esters and Lactones; Peroxy Acids and R(CO)OX Compounds; R(CO)OX, X = S, Se, Te] and Vol. 26 (Ketones)]. As an exception, however, aryl-substituted seleniranium salts are mentioned in Section [39.24.2.1](#) since this group of compounds is not covered in other volumes.

Since the structures of compounds covered in the present volume have extremely wide variations, not all the possible groups of compounds are covered, but, in general, only those that are stable, versatile, and synthetically important. Some unstable compounds are dealt with where they play important roles as the active intermediates in synthetic reactions and frequently appear in the literature. These include, for example, alkanesulfenic acids, seleniranes and seleniranium salts, and alkanetellurols and their metal salts, which are difficult or impractical to isolate in pure form but can be generated efficiently in solution.

The major focus of this volume is on reviewing the synthetic procedures of each class or subclass of compounds, but selected applications to synthetic reactions are also included in some cases after their preparative methods. In terms of the synthetic application of organosulfur, -selenium, and -tellurium compounds, however, aromatic compounds rather than aliphatic ones are usually more frequently employed. This is reasonable because aromatic compounds generally have higher stability and, when the central element has two or more alkyl substituents, it becomes difficult to distinguish one substituent from another in a stereoselective reaction or in a site-selective chemical transformation of a substituent.

Table 1 lists selected properties of sulfur, selenium, and tellurium. Heavier elements have smaller electronegativity values and lower ionization potentials. This may explain the instability of dialkyl tellurides in air and/or toward light, and that heavier elements more easily form hypervalent compounds with either three-center, four-electron bonds for closed shells or three-center, three-electron bonds for open shells. For example, tellurium tetrachloride is thermally stable to at least 400 °C, whereas sulfur tetrachloride decomposes above –30 °C. As suggested by the sizes of the elements, softness of the element increases in the order of sulfur < selenium < tellurium. Thus it is expected that the heavier elements have higher affinity toward soft nucleophiles such as carbanions. In contrast to ethers, the structures of divalent sulfur, selenium, and tellurium compounds are rectangular, as shown by their bond angles. The bond energies of HX —H decrease in the order sulfur > selenium > tellurium. This can be explained by less-favorable hybridization of $s - p$ orbitals of these chalcogen elements. Indeed, tellurols cannot usually be isolated even under inert conditions and selenols are readily oxidized in air. In addition, there is a trend that heavier elements disfavor forming multiple bonds, due to inefficient $p - p$ overlap. For example, little is known about tellurones and they tend to dimerize or polymerize. Furthermore, alkaneselenonic and alkanetelluronic acids and their derivatives are unavailable or not well identified. Consequently organosulfur

compounds are more stable and well defined in comparison to the corresponding selenium or tellurium analogues.

Table 1 Some Properties of Sulfur, Selenium, and Tellurium^[1–4]


	S	Se	Te	Ref
Allred and Rochow Electronegativity	2.44	2.48	2.01	[3,4]
Pauling Electronegativity	2.58	2.55	2.1	[4]
Covalent Radius ^a (Å)	1.04	1.17	1.37	[1,4]
van der Waals Radius (Å)	1.85	2.00	2.20	[4]
First Ionization Potential (eV)	10.360	9.752	9.009	[4]
HX —H Bond Length (Å)	1.346	1.46	1.70	[4]
H —X —H Bond Angle (°)	92.1	91.0	89.5	[1]
HX —H Bond Energy (kJ ·mol ^{−1})	381	334	277	[2]

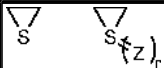
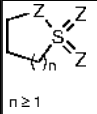
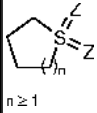
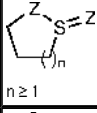
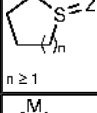
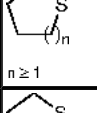
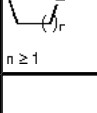
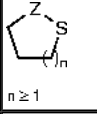
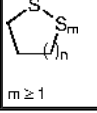
^a Half value of S —S, Se —Se, and Te —Te bond lengths.

There are large differences in the occurrence of organosulfur, organoselenium, and organotellurium compounds in biological systems. Sulfur is involved in amino acids such as cysteine, homocysteine, methionine, and glutathione, as alkanethiol, dialkyl sulfide, or alkanesulfonic acid groups. A number of bioactive organosulfur compounds are known and have been synthesized, including medicines, pesticides, sweeteners, and supplements. In addition to the significance of organosulfur compounds from a biological point of view, many synthetic functional materials for electronic and optical devices involving sulfur have been developed, although many are aromatic compounds. Therefore, the synthesis of organosulfur compounds is an industrially important field of research, not only as synthetic intermediates but also as final products. Selenium is an essential trace element for animals and occurs as selenocysteine. Because of this biological interest, various organoselenium compounds containing aminoalkyl substituents at various oxidation states, such as selenols, diselenides, and seleninic and selenonic acids, have been synthesized and examined. Tellurium is not an essential element but attention is also paid to organotellurium compounds as mimics of biologically active organosulfur and -selenium analogues. However, a major interest in organoselenium and -tellurium compounds is also due to their reactivities as useful intermediates in synthetic transformations, rather than as the final target compounds. Selenium powder is not considered harmful via oral administration (LD₅₀ >5 g ·kg^{−1} in rats).^[5] A review of the toxicology and pharmacology of organoselenium and organotellurium compounds is available.^[6]

The compounds in this volume of *Science of Synthesis* have been organized into product classes and subclasses that are sorted by molecular skeleton (acyclic or cyclic), the heteroatom (S, Se, Te), the oxidation state of the heteroatom, and the number and the type of the substituents. **Table 2** shows the names and general structures of the organosulfur compounds covered and the section numbers where they can be found, along with the section numbers of the corresponding selenium and tellurium analogues.

Table 2 Organosulfur Compounds Described in this Volume, and Their Selenium and Tellurium Analogues

Sulfur Compounds	General Structure ^a	Section Number		
		Sulfur Compounds	Selenium Analogues	Tellurium Analogues
Alkanesulfonic Acids and Acyclic Derivatives		39.1	39.14	39.27
Acyclic Dialkyl Sulfones and Derivatives		39.2	39.15	39.28
Alkanesulfinic Acids and Acyclic Derivatives	R^1SX_3 	39.3	39.16	39.29
Acyclic Dialkyl Sulfoxides and Derivatives		39.4	39.17	39.30

Alkanethiols	R^1SH	39.5	39.18	39.31
Acyclic Alkanethiolates	R^1SM	39.6	39.19	39.32
Acyclic Dialkyl Sulfides	R^1SR^2	39.7	39.20	39.33
Acyclic Trialkyloxosulfonium and Trialkylsulfonium Salts and Derivatives		39.8	39.21	39.34
Alkanesulfenic Acids and Acyclic Derivatives	R^1SX	39.9	39.22	39.35
Acyclic Di- and Polysulfides	$R^1(S)_nR^2$ $n \geq 2$	39.10	39.23	39.36
Thiiranes and Derivatives		39.11	39.24	39.37
Thietanes, 1,2-Oxathietanes, and Derivatives		39.12	39.25	39.38
Cyclic Alkanesulfonic Acid Derivatives	 $n \geq 1$	39.13.1	39.26.1	39.39.1
Cyclic Dialkyl Sulfones and Derivatives	 $n \geq 1$	39.13.2	39.26.2	39.39.2
Cyclic Alkanesulfinic Acid Derivatives	 $n \geq 1$	39.13.3	39.26.3	39.39.3
Cyclic Dialkyl Sulfoxides and Derivatives	 $n \geq 1$	39.13.4	39.26.4	39.39.4
Cyclic Alkanethiolates	 $n \geq 1$	39.13.5 , 39.13.6	39.26.5 , 39.26.6	39.39.5 , 39.39.6
Cyclic Dialkyl Sulfides	 $n \geq 1$	39.13.7	39.26.7	39.39.7
Cyclic Trialkyloxosulfonium and Trialkylsulfonium Salts and Derivatives		39.13.8	39.26.8	39.39.8
Cyclic Alkanesulfenic Acid Derivatives	 $n \geq 1$	39.13.9	39.26.9	39.39.9
Cyclic Dialkyl Di- and Polysulfides	 $m \geq 1$	39.13.10	39.26.10	39.39.10

^a Z = O, NR¹, PR¹; X = Hal, OH, NR¹₂, PR¹₂, SR¹; M = metal.

Organosulfur, -selenium, and -tellurium compounds of the highest oxidation state possessing only one sp³-carbon substituent constitute the families of alkanesulfonic acids (Section [39.1](#)), alkaneselenonic acids (Section [39.14](#)), and alkanetelluronic acids (Section [39.27](#)) having general structures [1](#) and [2](#) where Y = S, Se, and Te, respectively, as the first product class of each element. Here X is a univalent heteroatom moiety such as a halo, hydroxy, alkoxy, sulfanyl, or amino substituent, and Z is a divalent oxygen or nitrogen moiety ([Scheme 1](#)). The corresponding cyclic compounds are described in Sections [39.12](#), [39.25](#), and [39.38](#) for 4-membered sulfur, selenium, and tellurium analogues, respectively, as well as in the first subclasses of larger-ring products (Sections

[39.13](#), [39.26](#), and [39.39](#)). The chemistries of selenium and tellurium analogues of these families are not well developed due mainly to problems with structure identification and instability; however, many derivatives of alkanesulfonic acids are available, and Section [39.1](#) is subdivided into 14 further subsections, each reviewing a different subclass of these compounds.

Scheme 1 Alkanesulfonic, Alkaneselenonic, and Alkanetelluronic Acids, and Their Derivatives

The most synthetically well-used compounds in this product class may be sulfonyl halides [3](#), which can be converted into a variety of other sulfonyl derivatives. Among a number of methods that have been developed for the preparation of sulfonyl halides, oxidation or oxidative halogenation of lower-oxidation-state sulfur compounds constitutes a major route (**Scheme 2**). Sulfonyl halides have been widely employed not only for protection of alcohols but also for activating hydroxy functions as leaving groups, via alkanesulfonates [4](#), with inversion of stereochemistry by a sulfonylation –substitution sequence in a Mitsunobu-type reaction. Among alkanesulfonyl halides, methanesulfonyl chloride (MsCl) and trifluoromethanesulfonyl fluoride or chloride (TfF, TfCl) are most commonly used for this purpose, with triethylamine or pyridine in dichloromethane or toluene. Alkyl alkanesulfonates are good alkylating agents toward a variety of compounds, for example in the transformation of alcohols to ethers, and even amines, nitriles, ethers, sulfides, and selenides to the corresponding onium salts. Methyl trifluoromethanesulfonate (MeOTf) in particular is frequently employed as one of the most powerful methylating reagents. Similarly, alkanethiosulfonates, easily prepared by reaction of sulfonyl chlorides with thiols by selective oxidation of disulfides, or by some other means, are more reactive and efficient sulfonylation reagents than disulfides.

Scheme 2 Synthesis and Reactions of Sulfonyl Halides

The parent compounds, alkanesulfonic acids [5](#), can be used as acid catalysts, but for this purpose arenesulfonic acids are more useful. Alkanesulfonic acids are often synthesized by substitution reactions of alkyl halides or sulfonates with sulfite salts, reaction of alkyl organometallic compounds with sulfur trioxide, or oxidation of thiols, disulfides, and thio acetates, as well as sulfinic acid derivatives (**Scheme 3**).

Scheme 3 Synthesis of Sulfonic Acids

Sulfonamides **2** ($Y = S$; $Z = O$; $X = NR^1_2$; see Section **39.1.8**) are biologically important compounds, and find use as antibiotics, diuretics, hypoglycemic agents, anticancer agents, anti-HIV compounds, enzyme inhibitor and acceptor antagonists, herbicides, and sweeteners. Chiral chelates for asymmetric catalytic transformations can be an interesting application of sulfonamides.

Formal replacement of the hydroxy group of alkanesulfonic acids, alkeneselenonic acids, and alkenetelluronic acids with a second alkyl group leads to dialkyl sulfones (Section **39.2**), selenones (Section **39.15**), and tellurones (Section **39.28**), respectively (**Scheme 4**). Dialkyl sulfones **6** ($Y = S$) and their imino derivatives, sulfoximides **7** ($Y = S$) and sulfonediimines **8** ($Y = S$), are all stable and employed frequently in synthetic reactions. In large contrast to this rich sulfur chemistry, the analogous selenium and tellurium compounds are not well studied, due also to their instability and difficulties in identification of their structures. Several selenones **6** ($Y = Se$) have been synthesized by oxidation of selenides or selenoxides, but only two tellurones **6** ($Y = Te$; $R^1 = R^2 = Me, Bu$) are known. The sulfur, selenium, and tellurium compounds corresponding to structure **9** are all known but of little synthetic importance. Accordingly, the focus of this volume lies mainly on the sections covering the sulfur compounds.

Scheme 4 Sulfones, Selenones, and Tellurones, and Their Derivatives

Several general synthetic routes to dialkyl sulfones **10** are depicted in **Scheme 5**; they are obtained by alkylation of sulfinate anions or oxidation of sulfides or sulfoxides. Sulfonyl halides can also be useful precursors of sulfones by substitution with alkylmetals or addition to alkenes. Rearrangement of sulfinates also affords sulfones. Imine derivatives **11** and **12** are obtained by imidation of sulfoxides and sulfimides, respectively. Sulfoximides **11** are also synthesized efficiently by oxidation of sulfimides.

Scheme 5 Synthesis of Sulfones and Derivatives

The sulfonyl group stabilizes an α -anion and this allows a variety of transformations based on carbanion chemistry. For example, dialkyl sulfone **13** provides a conjugated tetraene by intramolecular coupling triggered by a base (**Scheme 6**).^[7] Chiral sulfoximides have been widely used in modern synthetic chemistry as important chiral auxiliaries and ligands.^[8] A successful example of asymmetric C—C bond formation is shown in **Scheme 6**.^[9]

Scheme 6 Application of Sulfones and Sulfoximines in Synthetic Reactions^[7,9]

Organosulfur, -selenium, and -tellurium compounds of oxidation state +4 with only one alkyl substituent are sulfinic acids (Section **39.3**), seleninic acids (Section **39.16**), and tellurinic acids (Section **39.29**), and structures of their representative derivatives are shown in **Scheme 7**.

Scheme 7 Sulfinic Acids, Seleninic Acids, and Tellurinic Acids, and Their Derivatives

In contrast to sulfonic acids and sulfones, the parent compounds, sulfinic acids **14** (X = OH; Y = S), are kinetically unstable and easily disproportionate into sulfonic acids and thiosulfonates. For example, methanesulfinic acid decomposes within 48 hours at room temperature under nitrogen. Alkanethiosulfinate esters **14** (X = SR²; Y = S) are also unstable and should be stored in the dark at temperatures of $-20\text{ }^{\circ}\text{C}$ or below. Only a few alkanetellurinic acids **14** (X = OH; Y = Te) have been prepared and characterized. Interestingly,

seleninic acids **14** ($X = OH$; $Y = Se$) represent the most stable class of oxyselenium acids and are more stable than the corresponding sulfinic acids. Seleninic acids, like their sulfur analogues, have an asymmetric, pyramidal structure with a formally chiral selenium atom, but undergo fast racemization in solution. Sulfinic and seleninic acids can be prepared by oxidation of thiols, sulfinyl acid derivatives, and disulfides and diselenides, respectively. Sulfonic acids and their derivatives are also suitable precursors of sulfinic acids. Among various procedures for the preparation of sulfinic acids, base-induced reductive S—C bond cleavage of sulfones, such as 3-(alkanesulfonyl) propanoates **16**, phthalimidomethyl sulfones **17**, and 2-sulfonylpyridine 1-oxides **18**, is a useful, general, and reliable procedure (**Scheme 8**). Sulfinylphthalimides **19** are useful precursors of sulfinyl esters by alcoholysis. Optically active sulfinyl esters are the main source of optically active sulfoxides.

Scheme 8 Useful Precursors of Sulfinic Acids and Esters

Alkanesulfinamides **14** ($X = NR^2R^3$; $Y = S$) are easily obtained by the reaction of sulfinyl chlorides with amines. Substitution at the sulfur atom of sulfinates proceeds stereospecifically with inversion of stereochemistry. An interesting chiral amine synthesis via sulfinamide **20** is shown in **Scheme 9**.^[10,11]

Allylic oxidation is possible by use of a catalytic amount of octaneseleninic acid.^[12] This reaction, with the recovery of reusable diselenide **21**, makes an attractive alternative to the use of selenium dioxide.

Scheme 9 Synthetic Applications of a Chiral Sulfoximide and a Seleninic Acid^[10–12]

Four-coordinated trihalides **15** ($Y = S, Se, Te$) are synthesized by halogenation of thiols or disulfides or their selenium and tellurium analogues. These are all isolable but easily hydrolyzed, so special care should be taken with fluoride derivatives in order to avoid hydrogen fluoride generation. Alkyltellurium trihalides are more stable than the corresponding selenium compounds, and the stability increases from trichlorides through triiodides.

Formal replacement of the hydroxy group of sulfinic acids, seleninic acids, and tellurinic acids with an alkyl group provides the families of chalcogen compounds: sulfoxides (Section **39.4**), selenoxides (Section **39.17**), and telluroxides (Section **39.30**) (**Scheme 10**).

Scheme 10 Sulfoxides, Selenoxides, and Telluroxides, and Their Derivatives

Unlike the sulfinic acids, both sulfoxides **22** ($Y = S$) and sulfimides **23** ($Y = S$) are stable and isolable, although some sulfoxides undergo β -elimination to form alkenes and sulfenic acids, or [2,3]-sigmatropic rearrangement when an allylic substituent is present (**Scheme 11**). The β -elimination of selenoxides and telluroxides proceeds much faster than that of sulfoxides. Furthermore, selenoxides and telluroxides are hygroscopic and tend to form dihydroxides. Consequently, only a limited number of dialkyl selenoxides have been synthesized, and few of the corresponding tellurium compounds are known. All three of these elements form dihalides **24**, but the sulfur compounds are less stable than the selenium and tellurium analogues.

Scheme 11 Degradation of Sulfoxides, Selenoxides, and Telluroxides

A major synthetic route to sulfoxides is oxidation of sulfides, and this can be applied to the synthesis of optically active sulfoxides. When the substituent of sulfur is chiral, asymmetric oxidation can be done using achiral oxidizing reagents such as hydrogen peroxide, hydroperoxides, 3-chloroperoxybenzoic acid, sodium periodate, and others by diastereoselection. A more interesting reaction is the asymmetric oxidation of achiral sulfides using chiral catalysts or enzymes. Nucleophilic substitution at the sulfur atom of optically active $S=O$ compounds is a classic but still very reliable route to chiral sulfoxides when suitable precursors are available. This substitution proceeds with inversion of configuration at sulfur and the precursors include sulfinic acid esters, sulfinamides, and even sulfoxides.

Sulfimides are usually synthesized by oxidative amination of sulfides or by amination of sulfoxides via oxysulfonium salt intermediates (**Scheme 12**). Chiral sulfimides are obtained by use of chiral auxiliary groups.

Scheme 12 Synthesis of Sulfimides

Both dialkyl sulfoxides and sulfimides can form stable carbanions at the α -carbon, but such chemistry is mostly

studied using aryl-substituted compounds. Dialkyl sulfoxides are used as mild oxidizing reagents as exemplified by Swern oxidation^[13] using dimethyl sulfoxides (**Scheme 13**). Dialkyl sulfimides are used for the synthesis of N-containing products including sulfoximides. Very large bodies of chemistry based on asymmetric synthesis using aryl-substituted chiral sulfoxides and sulfimides and alkene synthesis by β -elimination of alkyl aryl selenoxides are available, but these are not within the scope of this volume. Asymmetric synthesis using chiral cyclic sulfoxides would be a new addition of dialkyl sulfoxides to such important transformations.

Scheme 13 Oxidation of Alcohols to Carbonyl Compounds by Dimethyl Sulfoxide and Oxalyl Chloride^[13]

Alkanethiols **26** (Y = S) (Section **39.5**), -selenols **26** (Y = Se) (Section **39.18**), and -tellurols **26** (Y = Te) (Section **39.31**) are the analogues of alcohols and the simplest compounds having only one alkyl fragment on the chalcogen atom. Alkanethiols are stable, whereas alkaneselenols are oxidized in air, rapidly under basic conditions, to form diselenides. Alkanetellurols are extremely unstable and their presence is suggested only in solution. All these compounds have an acrid odor and should be handled in a well-ventilated hood. Thiols, selenols, and tellurols are readily prepared by acid hydrolysis or alcoholysis of their metal salts **25**, where group 1, 2, and 13 metal salts and silylated compounds are frequently employed as direct precursors. Several other methods involving C—S bond cleavages have been developed for the synthesis of alkanethiols.

The simplest three preparative methods of metal salts **25** are shown in **Scheme 14**. The lithium or magnesium metal salts are highly nucleophilic reagents and are frequently used for introducing alkanethiolate, -selenolate, and tellurolate units into organic molecules by the reaction with carbon electrophiles such as alkyl halides. They are also employed for the synthesis of other metal salts by transmetalation with various metal halides.

Scheme 14 Synthesis of Alkanethiols, Alkaneselenols, and Alkanetellurols, and Their Metal Salts

Transition metal salts of alkanethiols (Section **39.6.2**), -selenols (Section **39.19.2**), and -tellurols (Section **39.32.2**) have extremely wide diversity in the kind and the number of metal centers and ligands, and in coordination modes. In this volume, they are classified by the number of metal atoms bonding to a chalcogen atom (**Scheme 15**).

Scheme 15 Alkanethiolate, Alkaneselenolate, and Alkanetellurolate Complexes of Group 3–12 Metals

Typical synthetic procedures involve the following types of reactions: (1) transmetalation of a transition metal complex with a main-group metal alkanechalcogenolate, (2) alkylation of a bridging chalcogen atom with an alkyl halide or with a nucleophile, or (3) oxidative addition of a dichalcogenide (R^1YYR^1) or chalcogenol (R^1YH) to a transition metal complex. Some transition metal complexes having chalcogen ligands show unique catalytic activities and bring about useful transformations; an interesting example is shown in **Scheme 16**^[14,15] along with another application to asymmetric alkylation with organozinc reagents.^[16]

Scheme 16 Synthetic Applications of Alkaneselenolate and Alkanethiolates as Ligands^[14–16]

Dialkyl sulfides (Section **39.7**) and selenides (Section **39.20**) are thermally stable and can be isolated in pure form, whereas dialkyl tellurides (Section **39.33**) are somewhat unstable in air and/or toward light and should be stored under inert gas even at room temperature. In particular, attempts to purify allyl or benzyl tellurides often fail. Among a variety of synthetic methods available for this class of compounds, alkylation of thiolate, selenolate, and tellurolate anions and reduction of dihalides and oxides are the major synthetic routes (**Scheme 17**), although selenoxides and telluroxides are not commonly used due to their instability. As the alkylating reagents, alkyl halides, sulfonates, ammonium salts, esters, cyclic ethers, and even enones can be employed. In addition to these procedures for acyclic compounds, Diels–Alder reaction of thio-, seleno-, and tellurocarbonyl compounds provides a useful route to cyclic compounds, especially for synthesis of bicyclic structures using cyclic dienes such as cyclopenta-1,3-dienes.

Scheme 17 Synthesis of Dialkyl Sulfides, Selenides, and Tellurides

Sulfides, selenides, and tellurides are easily converted into the corresponding oxides by use of various oxidizing

reagents, but this reaction is of little synthetic importance for the dialkyl compounds dealt with in this volume. An interesting and potent synthetic application of this class of compounds is the use of cyclic chalcogenides as organocatalysts, as exemplified by asymmetric oxirane synthesis in **Scheme 18**.^[17] Dialkyl tellurides and selenides readily react with organolithium reagents to undergo tellurium –lithium and selenium –lithium exchange (**Scheme 18**). This provides a useful synthesis of allylic and benzylic lithium (or magnesium) compounds in one pot from the corresponding halides.^[18] By use of this method, a variety of heteroatom-substituted methyllithiums can be generated.^[19] Selenium –metal exchange is less efficient than the corresponding reaction of tellurium compounds, but still useful for the generation of thermodynamically stable organolithiums.^[20]

Scheme 18 Synthetic Applications of a Selenide and a Telluride^[17–19]

Trialkylsulfonium (Section **39.8**), trialkylselenonium (Section **39.21**), and trialkyltelluronium (Section **39.34**) salts **27** (Y = S, Se, Te) are stable and can usually be isolated in pure form by recrystallization. The simplest and most general synthetic method for preparation of these onium salts is alkylation of sulfides, selenides, and tellurides with various carbon electrophiles, such as alkyl halides or cyclopropanes, or heterocyclic compounds. Addition of onium salts having a halogen substituent to alkenes and that of electrophiles to ylides can also be employed. These onium salts are transformed to ylides by treatment with base; the other two possible reaction courses of salts **27** are substitution with nucleophiles and base-induced elimination to form alkenes (**Scheme 19**).

The oxosulfonium salts **28** can similarly be prepared by alkylation of sulfoxides, or by oxidation of the corresponding sulfonium salts with hydrogen peroxide, sodium perbenzoate, or 3-chloroperoxybenzoic acid (**Scheme 19**). When hard alkylating reagents are employed O-alkylation predominates, so soft reagents such as alkyl iodides should be selected. Little is known about selenium and tellurium analogues of **28**.

Scheme 19 Synthesis and Reactions of Trialkylsulfonium, Trialkylselenonium, and Trialkyltelluronium Salts and Synthesis of Trialkyloxosulfonium Salts

Oxyacids of chalcogen compounds at the lowest oxidation state are sulfenic acids (Section 39.9), selenenic acids (Section 39.22), and tellurenic acids (Section 39.35). Sulfenic acids are considered to exist as an equilibrium mixture of two tautomers, 29 and 30 (Scheme 20). Sulfenic acids are formed by oxidation of thiols or diselenides, *syn*-elimination from alkyl sulfoxides, or substitution of sulfenyl halides or amides. Addition to alkenes gives alkyl sulfoxides. Alkaneselenenic acids are unstable and assumed to be generated by selenoxide *syn* elimination or oxidation of diselenides; however, they disproportionate rapidly into the corresponding diselenides and alkaneseleninic acids (Scheme 20). Alkanetellurenic acids are not known.

Scheme 20 Alkanesulfenic Acids and Alkaneselenenic Acids

The most synthetically useful compounds of these product classes may be sulfenyl, selenenyl, and tellurenyl halides, which can formally transfer the sulfenyl, selenenyl, or tellurenyl function in reactions with nucleophiles. These compounds can conveniently be synthesized by halogenation of the corresponding disulfides, diselenides, and ditellurides; addition of sulfur dichloride to alkenes also affords alkanesulfenyl halides. Alkaneselenenyl chlorides and bromides are known, but the fluorides and iodides have not been reported. Alkanetellurenyl chlorides, bromides, and iodides are known. For synthetic purposes, however, areneselenenyl halides, as well as their sulfur and tellurium analogues, are much more frequently employed.

Alkyl substituted di- and polysulfides (Sections 39.10 and 39.13.10), -selenides (Sections 39.23 and 39.26.10), and -tellurides (Sections 39.36 and 39.39.10) are useful starting materials for a variety of chalcogen compounds. Disulfides, diselenides, and ditellurides are all isolated in pure form; however, ditellurides are oxidized gradually in air and so should be kept under inert conditions. These dialkyl dichalcogenides can be prepared by oxidation of the corresponding thiols, selenols, or tellurols, or their metal salts.

Efficient methods for the synthesis of alkyl hydrodisulfides 31 have been developed based on the combination of nucleophilic sulfur and electrophilic sulfur (Scheme 21). As the electrophilic sulfur reagents, disulfur dichloride and S-alkyl alkanethiosulfonates are frequently employed. Using similar procedures, dialkyl trisulfides 32 have been synthesized. As a unique example, cyclic heptasulfide 33 has also been prepared.^[21] In contrast to these sulfur compounds, polyselenides and polytellurides are unstable. A single example of a polyselenide, the cyclic triselenide 1,2,3-triselenolane, is prepared in poor yield by alkaline hydrolysis of ethane-1,2-diyl bis (selenocyanate).^[22] Polytellurides have not been isolated.

Scheme 21 Syntheses of Di- and Polysulfides^[21]

Thiiranes (Section 39.11) and seleniranes (Section 39.24) are, respectively, the sulfur and selenium analogues of epoxides. Thiiranes have a strained three-membered ring but are still stable enough for isolation. Although a variety of synthetic reactions leading to thiiranes are available, these methods can be classified into two types of reaction patterns as shown in Scheme 22. One is the direct addition of sulfur to C=C bonds or addition of carbenes to C=S bonds (route A). The other is nucleophilic intramolecular cyclization (route B) (Scheme 22). Thiirane 1,1-dioxides and thiirane 1-oxides can be obtained by oxidation of thiiranes; thiirane 1,1-dioxides are also synthesized by methods similar to those depicted in Scheme 22.

Scheme 22 Synthetic Routes to Thiiranes

Seleniranes are thermally unstable and decompose to the corresponding alkenes, and only a few stable examples are known. However seleniranes occasionally appear in the literature as intermediates for alkene synthesis by elimination of selenium. Seleniranium salts having only alkyl groups are not known, but 1-arylseleniranium salts are dealt with in Section 39.24 since these are useful, although unstable, intermediates for functionalization of alkenes via electrophilic activation of the double bonds by selenenyl cations. No examples of telluriranes are known.

Thietanes, thietane 1-oxides, and thietane 1,1-dioxides are four-membered cyclic sulfides, sulfoxides, and sulfones, respectively, and are all dealt with in Section 39.12.1. 1,2-Oxathietanes and their oxidized derivatives, i.e. four-membered cyclic sulfenic, sulfinic, and sulfonic acid esters, are covered in Section 39.12.2. Other derivatives, such as 1,2-dithietanes, 1,2-thiazetidines, and 1,2-thiaphosphetanes are discussed in Section 39.12.3. The corresponding selenium and tellurium analogues are reviewed in Section 39.25 and Section 39.38, respectively, although four-membered cyclic tellurium compounds are extremely rare.

Theoretical calculations indicate that the strain energy of thietane is larger than that of thiirane (22.2 and 19.1 kcal·mol⁻¹, respectively)^[23] suggesting that thietanes can serve as reactive reagents for organic synthesis.

Representative procedures for the synthesis of thietanes include nucleophilic and electrophilic ring-closing reactions (route A) and photoinduced [2 + 2] cycloaddition of thiocarbonyls and alkenes (route B) (**Scheme 23**); nucleophilic and electrophilic ring-closing methods can also be applied to selenetane synthesis (Section **39.25**). Sulfene ($\text{H}_2\text{C}=\text{SO}_2$) adds to $\text{C}=\text{C}$ bonds to give thietane 1,1-dioxides. 1,2-Oxathietane 2-oxides and 2,2-dioxides are formed by direct reaction of alkenes with sulfur dioxide or trioxide, respectively (**Scheme 23**).

Scheme 23 Synthesis of Thietanes and 1,2-Oxathietanes

Finally, it may be helpful to briefly refer here to peralkylated derivatives of chalcogen compounds with oxidation state of +4 or +6 (represented by R^1_4Y or R^1_6Y , $\text{Y} = \text{S}, \text{Se}, \text{Te}$). Such hypervalent structures are more common with heavier elements. For example, neither tetramethyl-⁴-sulfane (Me_4S) nor hexamethyl-⁶-sulfane (Me_6S) is known, but tetrakis(benzoylmethyl)-⁴-selenane [$(\text{BzCH}_2)_4\text{Se}$] was synthesized in 1972.^[24] In 1989, tetramethyl-⁴-tellane (Me_4Te) was isolated in 77% yield by careful vacuum distillation from the reaction of tellurium tetrachloride with 4.2 equivalents of methyllithium in diethyl ether (**Scheme 24**).^[25]

Scheme 24 Preparation of Tetramethyl-⁴-tellane^[25]

Tetramethyl-⁴-tellane is a malodorous yellow-orange pyrophoric liquid that is stable in the dark under an argon atmosphere at 25 °C. It decomposes above 100 °C to give dimethyl telluride, methane, and ethane and sometimes explodes when combined with oxygen. Tetrakis[(trimethylsilyl)methyl]-⁴-tellane has also been synthesized, by the reaction of tellurium tetrachloride with [(trimethylsilyl)methyl]magnesium bromide, and isolated as a yellow solid in 76% yield.^[26] Tetraethyl-⁴-tellane has been characterized by NMR but not isolated, due to instability toward oxygen and light.

The first synthesis of hexamethyl-⁶-tellane (Me_6Te) was achieved in 68% yield by the reaction of *cis*-tetramethyltellurium difluoride with 1.5 equivalents of dimethylzinc(II) in diethyl ether at 0 °C for 2 hours.^[27] Hexamethyl-⁶-tellane is much more thermally stable than tetramethyl-⁴-tellane, and a sample consisting of 10% hexamethyl-⁶-tellane in benzene- d_6 was unchanged after heating at 140 °C for 4.5 hours.

Tetraalkyl-⁴-tellanes react with terminal acetylenes to afford alkylation products. The alkylation proceeds preferentially in net *trans* fashion to give a *cis*-1,2-disubstituted alkene as the major product.^[28]

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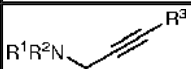
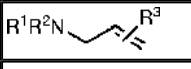
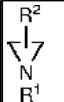

Compounds with One Carbon–Heteroatom Bond**Volume 40:****Amines, Ammonium Salts, Amine N-Oxides, Haloamines, Hydroxylamines and Sulfur Analogues, and Hydrazines**

Schaumann, E., in *Science of Synthesis*, **40** (2008), p.1

General Introduction

This volume of *Science of Synthesis* covers the syntheses of compounds having a single bond between an sp^3 -hybridized carbon atom and a formally sp^3 -hybridized nitrogen substituent. As an aid to organization it has been split into two parts which are, respectively, *Science of Synthesis*, Volume 40a (Amines and Ammonium Salts) and *Science of Synthesis*, Volume 40b (Amine N-Oxides, Haloamines, Hydroxylamines and Sulfur Analogues, and Hydrazines). Among the product classes featured, one of the most prominent representatives is the aliphatic amines (Section [40.1](#)); however, separate sections are devoted to propargylic (Section [40.1.2](#)) and allylic amines (Section [40.1.3](#)) for which special synthetic methods are available, or where special care must be taken to secure synthetic success. Similarly, compounds with more than one amino group or an additional phosphorus functionality are treated separately (Section [40.1.4](#)), as are the obviously special small-ring amine derivatives aziridines (Section [40.1.5](#)) and azetidines (Section [40.1.6](#)). Furthermore, the amino group may be modified in the form of ammonium compounds or of N-ylides ("ammonioalkanides"; Section [40.1.7](#)). There is also a wide range of functionalities where a parent amine structure is combined with one heteroatom. This type of compound is seen in nitroxyl radicals (nitroxides; Section [40.2](#)), amine N-oxides (Section [40.3](#)), N-haloamines (Section [40.4](#)), hydroxylamines ("N-hydroxyamines") in acyclic (Section [40.5](#)) or in cyclic form (Section [40.6](#)), and hydrazines, again in acyclic (Section [40.7](#)) or in cyclic form (Section [40.8](#)), as well as extended hydrazines (Section [40.9](#)). Finally, amido derivatives of sulfur-derived acids, specifically of sulfanediol (Section [40.10](#)), of sulfurous acid (Section [40.11](#)), and of sulfuric acid (Section [40.12](#)) are covered. Ammonium sulfonates, thiohydroxylamines, and aminosulfonium salts are also featured (Section [40.13](#)). For a ready overview, these structures are compiled in [Table 1](#).

Table 1 Classes of Amines and Amine Derivatives Covered in Volume 40

Product Class or Subclass	Structure(s)	Section
amino compounds		40.1
alkyl and cycloalkylamines		40.1.1
propargylic amines		40.1.2
allylic amines		40.1.3
n-nitrogen- or n-phosphorus-functionalized alkylamines (n ≥ 2)		40.1.4
aziridines		40.1.5
azetidines		40.1.6

ammonium compounds	$\begin{array}{c} R^1 \\ \\ R^2 - N^+ - R^+ X \\ \\ R^3 \end{array}$	40.1.7.1.1 – 40.1.7.1.4
nitrogen ylides	$\begin{array}{c} R^1 & R^4 \\ & // \\ R^2 - N^+ & - C \\ & \\ & R^3 & R^5 \end{array}$	40.1.7.1.5
nitroxyl radicals (nitroxides)	$\begin{array}{c} R^1 \\ \\ R^2 - N - O^\bullet \end{array}$	40.2
amine <i>N</i> -oxides	$\begin{array}{c} R^1 \\ \\ R^2 - N^+ - O^- \\ \\ R^3 \end{array}$	40.3
<i>N</i> -haloamines	$\begin{array}{c} R^1 \\ \\ R^2 - N - X \end{array}$ <small>X = halogen</small>	40.4
hydroxylamines		40.5
1-oxa-2-azacycloalkanes	$\begin{array}{c} R^2 \\ \\ [C]_n \\ \\ O - NR^1 \end{array}$	40.6
hydrazines and hydrazinium salts		40.7
1,2-diazacycloalkanes	$\begin{array}{c} R^3 \\ \\ [C]_n \\ \\ R^1N - NR^2 \end{array}$	40.8
triazanes and tetrazanes		40.9
amido derivatives of sulfanediol	$\begin{array}{c} R^1 \\ \\ R^2 - N - S - X \end{array}$	40.10
amido derivatives of sulfurous acid	$\begin{array}{c} O \\ \\ R^1R^2N - S - X \end{array}$	40.11.1 –40.11.3
<i>N</i> -(thio)sulfinylamines	$R^1 - N = S = X$ <small>X = O, S</small>	40.11.4, 40.11.5
<i>N,N</i> -dialkylsulfur diimides	$R^1N = S = NR^2$	40.11.6
<i>N</i> -alkylsulfamic acids and derivatives	$\begin{array}{c} O & O \\ // & / \\ R^1R^2N - S - X \end{array}$	40.12
ammoniumsulfonates, thiohydroxylamines, and aminosulfonium salts		40.13

For a product class to be included in Volume 40, the hierarchy of *Science of Synthesis* requires that the carbon in the C—N bond is sp³ hybridized. The chemistry of ynamines **1** (X = CR³) is covered in *Science of Synthesis*, Vol. 24 [Three Carbon—Heteroatom Bonds: Ketene Acetals and Yne—X Compounds (Section **24.4.4.1**)] and the chemistry of cyanamides **1** (X = N), where an sp-hybridized carbon is bonded to the nitrogen, is described in Vol. 18 [Four Carbon—Heteroatom Bonds: X—C X, X=C=X, X₂C=X, CX₄ (Section 18.1.4)]. If the carbon is sp² hybridized, as in general structure **2**, the products can be enamines **2** (X = CR⁴R⁵) {see *Science of Synthesis*, Vol. 33 [Ene—X Compounds (X = S, Se, Te, N, P) (Section 33.4.6)]} or amide-type derivatives **2** (X = O or heteroanalogues), covered as carbonic acid derivatives in *Science of Synthesis*, Vol. 18 (Four Carbon—Heteroatom Bonds: X—C X, X=C=X, X₂C=X, CX₄), and as carboxylic acid amides in Vol. 21 (Three Carbon—Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams), and as their heteroanalogues in Vol. 22 (Three Carbon—Heteroatom Bonds: Thio-, Seleno-, and Tellurocarboxylic

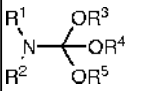
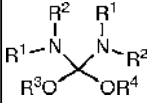
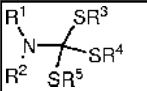
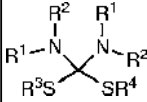
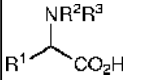
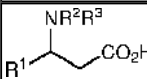
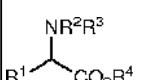
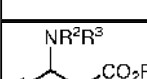
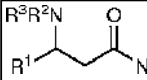
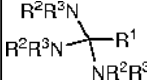
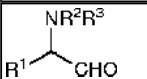
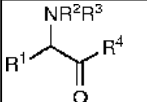
Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives). Compounds **3** with an NR unit as a member of a heteroaromatic ring (n = 1) are the subject of Category 2 (Hetarenes and Related Ring Systems; Vols. 9 –17).

Aliphatic nitrogen compounds **4** with a double bond to another heteroatom are the subject of *Science of Synthesis*, Vol. 41 (Nitro, Nitroso, Azo, Azoxy, and Diazonium Compounds, Azides, Triazenes, and Tetrazenes) as are nitrogen functionalities with two other heteroatoms on the nitrogen as in **5** and **6**. Compounds **6** ("nitroso acetals") formally encompass derivatives **7** (X = Y = NR¹₂). However, from another point of view, compounds **7** are extended hydrazines ("triazanes" when n = 1, "tetrazanes" when n = 2) and therefore are described here in Section **40.9**

Based on the priority rules of *Science of Synthesis*, sp³ hybridization of the carbon in the C—N bond is not a sufficient criterion for inclusion in the present volume; in addition, no other heteroatom on the substituted carbon is allowed. Similarly, if another functional group of higher priority is present on the neighboring carbon, the synthesis is covered at the location of that group. Finally, compounds with nitrogen—metal bonds are covered in Category 1 (Organometallics; Vols. 1 –8). An overview of the location of the different types of formal amino derivatives is given in **Table 2**. In any case, to get the full information that is available in *Science of Synthesis* on amino derivatives, a substructure search in the electronic version is recommended.

Table 2 Amino Group Containing Structural Units Covered Elsewhere in *Science of Synthesis*

Name	Structure(s)	Volume	Section
aminoboranes, borane –amine complexes	$R^1_2N-BR^2_2$ $R^1_3N^+-BR^2_3$	6 (Boron Compounds)	6.1.15
N-(dialkylboryl)amides			6.1.29.3
amine –aluminate complexes	$LiAlH_{4-n}(NR^1R^2)_n$, $LiAlH_4 \cdot NR^1R^2R^3$	7 [Compounds of Groups 13 and 2 (Al, Ga, In, Tl, Be ...Ba)]	7.1.2.19
alkylaluminium amides			7.1.7
magnesium amides	$(R^1R^2N)_2Mg$		7.6.14
lithium amides	R^1R^2NLi	8a [Compounds of Group 1 (Li ... Cs)]	8.1.6
-lithioamines			8.1.21

potassium amides	R^1R^2NK	8b [Compounds of Group 1 (Li ... Cs)]	8.3.2.3.2 , 8.3.6
orthocarbamic acid triesters		18 (Four Carbon —Heteroatom Bonds: X —C X, X=C=X, X ₂ C=X, CX ₄)	18.16.3
orthocarbonic acid diester diamides			18.16.6
alkoxytriaminomethanes			18.16.9
trithioorthocarbamic triesters			18.16.11
dithioorthocarbonic acid diester diamides			18.16.13
organosulfanyl-, and organoselanyltriaminomethanes			18.16.15
orthocarbonic acid tetraamides			18.16.17
2-aminoalkanoic acids		20a (Three Carbon —Heteroatom Bonds: Acid Halides; Carboxylic Acids and Acid Salts)	20.2.7
3-aminoalkanoic acids			20.2.13.1.3
2-aminoalkanoic acid esters		20b [Three Carbon —Heteroatom Bonds: Esters and Lactones; Peroxy Acids and R(CO)OX Compounds; R(CO)X, X = S, Se, Te]	20.5.10
3-aminoalkanoic acid esters			20.5.16.1.3
,N-substituted alkanamides		21 (Three Carbon —Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams)	21.5.3
,N-substituted alkanamides			21.7.5
ortho amides		22 (Three Carbon —Heteroatom Bonds: Thio-, Seleno, and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives)	22.7.6
2-aminoaldehydes		25 (Aldehydes)	25.4.3
-amino ketones		26 (Ketones)	26.6.8
N/X-acetals		30 (Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues)	30.1.1 , 30.1.2 , 30.4 , 30.5.4 , 30.5.5 , 30.6 , 30.7.1

diaryl(aza)sulfonium salts		31a [Arene —X (X = Hal, O, S, Se, Te)]	31.15.4.1.3
alkyl(aryl)(aza)sulfonium salts			31.15.4.1.6
diaza(aryl)sulfonium salts			31.15.4.1.9
arylamines		31b [Arene —X (X = N, P)]	31.28
arylammonium salts			31.29
<i>N</i> -haloarylamines			31.32
<i>N</i> -arylhydroxylamines			31.33
arylhydrazines			31.34
cyclic arylamines			31.38
-fluoroamines		34 (Fluorine)	34.10
-chloro-, -bromo-, and -iodoamines		35 (Chlorine, Bromine, and Iodine)	35.1.5.1.10 , 35.1.5.4 , 35.2.5.1.6 , 35.2.5.4 , 35.3.5.1.4 , 35.3.5.4
-amino alcohols		36 (Alcohols)	36.10.1.1.3 , 36.10.1.1.6 , 36.10.1.1.8 , 36.10.1.1.14
-amino alcohols			36.10.2.1.2 – 36.10.2.1.5
-amino thiols		39 (Sulfur, Selenium, and Tellurium)	39.5.1.7.1 , 39.5.1.8

Compounds with One Carbon–Heteroatom Bond

41

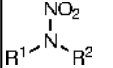
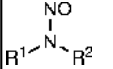
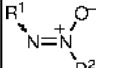
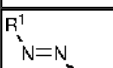
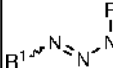
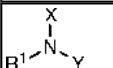
Volume 41:

Nitro, Nitroso, Azo, Azoxy, and Diazonium Compounds; Azides, Triazenes, and Tetrazenes

Banert, K., in *Science of Synthesis*, **41** (2009), p.1

This volume covers the synthesis of compounds containing a nitrogen functionality bonded to sp^3 -hybridized carbon atoms, as shown in **Table 1**. However, only in the cases of nitroalkanes, nitrosoalkanes, azides, and *N,N*-dihaloamines are the substituents R^1 and R^2 strictly limited to alkyl groups. Aliphatic diazonium compounds are divided into the subclasses of short-lived alkanediazonium compounds (Section **41.7.1**) and the less labile alkenediazonium compounds (Section **41.7.2**). Section **41.5** includes 1,2-dialkyldiazene 1-oxides and azoxy compounds carrying a vinyl group at one of the two different nitrogen atoms. In the cases of azo compounds (Section **41.6**) and tetrazenes (Section **41.10**), derivatives bearing aryl, vinyl, or acyl substituents at the nitrogen functionality are described along with such compounds having only alkyl groups. A few examples of rare tetraz-2-enes with lower symmetry than that shown in **Table 1** are summarized in Section **41.10.2.1.5**. The section on alkyltriazenes (Section **41.9**) also includes derivatives with aryl or acyl groups at the nitrogen atom, while *N*-nitroamines bearing aryl or vinyl groups in addition to alkyl groups are discussed in Section **41.3**. In the case of both of these nitrogen functionalities, hydrogen at the sp^3 -hybridized nitrogen ($R^2 = H$) is also possible. This is in contrast to *N*-nitrosoamines (Section **41.4**), which are exclusively derived from secondary dialkyl- or alkyl(aryl) amines, or the corresponding acyl derivatives. *N*-Nitrosoamines originating from primary amines ($R^2 = H$) are unstable and lead to diazonium compounds (see Section **41.7**).

Table 1 Classes of Compounds Covered in Volume 41

Product Class	Structural Formula	Substituents	Section
nitroalkanes	R^1NO_2	$R^1 = \text{alkyl}$	41.1
nitrosoalkanes ^a	R^1NO	$R^1 = \text{alkyl}$	41.2
<i>N</i> -nitroamines		$R^1 = \text{alkyl, aryl, vinyl}; R^2 = H, \text{alkyl}$	41.3
<i>N</i> -nitrosoamines		$R^1 = \text{alkyl, aryl, acyl}; R^2 = \text{alkyl, aryl}$	41.4
aliphatic azoxy compounds (diazene oxides)		$R^1 = \text{alkyl, vinyl}; R^2 = \text{alkyl, vinyl}$	41.5
aliphatic azo compounds (1,2-diazenes)		$R^1 = \text{alkyl, aryl, acyl, vinyl}; R^2 = \text{alkyl, acyl}$	41.6
aliphatic diazonium compounds	$R^1-N^+ \equiv N \ X^-$	$R^1 = \text{alkyl, vinyl}$	41.7
azidoalkanes	$R^1-N-N^+ \equiv N$	$R^1 = \text{alkyl}$	41.8
alkyltriazenes		$R^1 = \text{alkyl, aryl}; R^2 = H, \text{alkyl, aryl, acyl}; R^3 = \text{alkyl, aryl}$	41.9
alkyltetrazenes (tetraz-2-enes) ^b		$R^1 = \text{alkyl}; R^2 = \text{alkyl, aryl, acyl, vinyl}$	41.10
<i>N,N</i> -dihaloamines		$R^1 = \text{alkyl}; X = F, Cl, Br, I; Y = F, Cl, Br, I$	41.11

^a This section also includes *N,N*-dialkoxyamines [nitroso acetals, $R^1N(OR^2)_2$; see Section **41.2.1.11**].

^b A few examples of rare tetraz-1-enes are also described (see Section **41.10.1**).

N-Nitrosoamines are well known to be highly toxic and carcinogenic agents. However, some other compounds bearing other nitrogen functionalities, for example aliphatic azo or azoxy compounds, are also powerful carcinogens. Before handling such substances, the safety advice at the beginning of the corresponding sections and the corresponding references should be noted. The same holds true for the explosive properties of several product classes discussed here. Whereas azides and diazonium compounds with a high proportion of nitrogen are known to be highly energetic materials, and several nitroalkanes and *N*-nitroamines are utilized as commercial explosives, similar properties of other product classes, such as azo compounds, alkyltriazenes, alkyltetrazenes, and *N,N*-dihaloamines, should also be taken into consideration. Synthesis, handling, and reactions of nitrosoalkanes are inseparably linked with the special behavior of these compounds (Section 41.2), which are often in equilibrium with their dimers, the azo dioxides (1,2-diazene 1,2-dioxides). Furthermore, the less stable nitrosoalkanes bearing at least one α -hydrogen atom are able to equilibrate with tautomeric oximes (isonitroso compounds), which are thermodynamically more stable in most cases. Not only azo dioxides, but also aliphatic azo and azoxy compounds (Sections 41.6 and 41.5, respectively) can form *E*- and *Z*-configured stereoisomers of different stability. Thus, the configuration of these diastereomers is important for the synthesis and subsequent reactions of the corresponding substances.

The representatives of the product classes described in this volume are useful intermediates in organic synthesis and have found a variety of applications. In the case of nitrosoalkanes (Section 41.2.2, including nitroso acetals), alkenediazonium compounds (Section 41.7.2.2), azidoalkanes (Section 41.8.2), alkyltriazenes (Section 41.9.2), and *N,N*-dihaloamines (Sections 41.11.1, 41.11.2, 41.11.3, 41.11.4, 41.11.5, 41.11.6, and 41.11.7), applications in organic synthesis are summarized in special subsections. Moreover, a very great number of reactions starting with the compounds shown in Table 1 are described in other volumes of *Science of Synthesis* because these reactions serve as methods to prepare a variety of other functional groups. In several cases, however, representatives of one of the product classes described in Sections 41.1 –41.11 are transformed into compounds that belong to a different product class within Volume 41. Thus, the methods of synthesis of the products shown in Table 2 are, simultaneously, applications of the corresponding starting materials in organic synthesis.

Table 2 Transformations of Representatives of a Product Class Leading to Compounds of Another Product Class of Volume 41

Starting Material	Product	Method	Section(s)
nitroalkanes (Section 41.1)	nitrosoalkanes	reduction	41.2.1.5
		[2,3]-sigmatropic rearrangement	41.2.1.7
nitrosoalkanes (Section 41.2)	nitroalkanes	oxidation	41.1.1.2.10 – 41.1.1.2.18, 41.2.2.1
	azoxy compounds	treatment with <i>N,N</i> -dihaloamines	41.2.2.4.2, 41.5.1.2.2
		treatment with azides	41.2.2.4.2
		reduction of dimers	41.5.1.1.4
		condensation with hydroxylamines	41.5.1.2.1
	azo compounds	condensation with amine derivatives	41.2.2.4.3, 41.6.1.2
<i>N</i> -nitrosoamines (Section 41.4)	<i>N</i> -nitroamines	exchange	41.3.4.1.5
	diazonium compounds	cleavage	41.7.1.1.1, 41.7.1.1.3
	alkyltetrazenes	reductive dimerization	41.10.2.1.2
aliphatic azoxy compounds (Section 41.5)	azo compounds	reduction	41.6.2.3
azo compounds (Section 41.6)	nitroalkanes	treatment with nitrogen dioxide	41.1.1.1.32
	azoxy compounds	oxidation	41.5.1.1.1
	diazonium		

	compounds	cleavage	41.7.2.1.4.4
aliphatic diazonium compounds (Section 41.7)	azo compounds	treatment with arenes	41.7.1
	alkyltriazenes	treatment with amines	41.7.1
azidoalkanes (Section 41.8)	nitroalkanes	oxidation	41.1.1.2.6 , 41.1.1.2.7
		treatment with nitroalkyl anions	41.1.1.5.7
	alkyltriazenes	treatment with organometallic reagents	41.9.1.1
alkyltriazenes (Section 41.9)	diazonium compounds	acid-induced cleavage	41.7.1.1.2 , 41.7.2.1.4.3
<i>N,N</i> -dihaloamines (Section 41.11)	<i>N</i> -nitroamines	substitution	41.3.1.1.4

Synthetic methods are not restricted to the transformation of functional groups. Formation of new C—C bonds and thus construction of molecules with extended scaffolds are also important. In some cases, introduction of a novel functionality and generation of new C—C bonds are performed in one step.

The acidity of primary and secondary nitroalkanes of type **1** facilitates deprotonation to give the anion **2**, which can be treated with carbon electrophiles **3** to yield the product **4** with formation of a new C—C bond (**Scheme 1**). Thus, alkylation of **2** using haloalkanes **3** ($R^3 = \text{alkyl}$) or similar compounds is possible (see Sections [41.1.1.5.1](#)–[41.1.1.5.8](#) and [41.1.1.5.11](#)), and acylation of **2** utilizing acid halides **3** ($R^3 = \text{acyl}$) or other carboxylic and carbonic acid derivatives is also successful (see Section [41.1.1.5.14](#)). Moreover, vinylation (Section [41.1.1.5.9](#)) and arylation (Section [41.1.1.5.10](#)) of **2** have also been reported. Treatment of anions **2** with aldehydes or ketones **5** is called the Henry reaction, and leads to α -nitro alcohols **6** (Section [41.1.1.5.12](#)). Michael addition of **2** at the electron-deficient alkenes **7** gives rise to the products **8**. If the electron-withdrawing group is itself a nitro group ($\text{EWG} = \text{NO}_2$), product **8** includes this unit twice (see Sections [41.1.1.5.66](#)–[41.1.1.5.68](#)). It should be noted that the Michael additions of **2** to unsaturated carbonyl compounds or nitriles are not described in this volume, but are discussed with the synthesis of ketones, esters, and nitriles in other volumes of *Science of Synthesis* [see, for example, Vol. 19 [Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives (Section [19.5.14.8.4](#))]]. Alkylations analogous to the reaction of nitro anion **2** with electrophiles **3** ($R^3 = \text{alkyl}$) to give products **4** have been reported for the anions derived from nitrosoalkanes (Section [41.2.1.9](#)) and *N*-nitrosoamines (Section [41.4.1.2.1](#)). Furthermore, *N*-nitrosoamines deprotonated at the α -position can undergo nucleophilic addition at aldehydes or ketones similar to the Henry reaction (see Section [41.4.1.2.1](#)).

Scheme 1 Formation of C—C Bonds in the Synthesis of Products with a Nitro Group Bound to an sp^3 -Hybridized Carbon

A variety of CH-acidic compounds of type **10**, but also organometallic compounds or other carbon nucleophiles, react with nitroalkenes **9** to afford the Michael products **11** or similar products (see Sections **41.1.1.5.46** – **41.1.1.5.80**). The electron-deficient nature of nitroalkenes enables several cycloaddition reactions (Sections **41.1.1.5.82** – **41.1.1.5.84**). For example, Diels –Alder reaction of **9** and the diene **12** leads to the [4 + 2] cycloadduct **13** (**Scheme 2**).

The transformation of the nitroalkene **14** to the bicyclic *N,N*-dialkoxyamine (nitroso acetal) **18** includes the formation of two new C —C bonds (Section **41.2.1.11**). Thus, nitroalkene **14** and the electron-rich alkene **15** undergo a [4 + 2]-cycloaddition reaction with inverse electron demand, and the resulting intermediate **16** is combined with the electron-poor reaction partner **17** by 1,3-dipolar cycloaddition (**Scheme 3**).

Scheme 2 C —C Bond-Forming Reactions of Nitroalkenes

Substitution of the halogen in α -halonitroalkanes by carbon nucleophiles such as CH-acidic compounds of type **10** or organometallic compounds is strongly influenced by the nitro group (see Sections **41.1.1.5.17** – **41.1.1.5.34**). However, formation of new C —C bonds is certainly not restricted to nitro compounds. For example, the chlorine atom of 2-chloroalkenediazonium compounds can be substituted by electron-rich arenes (Section **41.7.2.1.6**). Deprotonation of the hydrazones **19** leads to the anionic species **20**, which yield the azo compounds **22** by C-alkylation or C-acylation using the electrophilic halides **21**, whereas treatment with the acceptor-substituted alkenes **23** furnishes the Michael products **24** (Section **41.6.2.5**). Carboazidations typically proceed via a radical mechanism starting with an α -functionalized acetic acid ester **25** and a radical initiator (**Scheme 3**). The terminal alkene **26** and an arenesulfonyl azide as the azide source are necessary to get the product **27** (Section **41.8.1.10.4**). Radical processes are also involved in the formation of C —C bonds and the generation of a new nitrogen functionality during photochemical transformation of unsaturated alkyl nitrites into hydroxy-substituted nitrosoalkanes (**41.2.1.6**).

Scheme 3 Formation of C —C Bonds in the Synthesis of Aliphatic Azo Compounds and Azides

Several of the reactions shown in Schemes 1 –3 can be performed enantioselectively. When the Henry reaction of **2** and **5** is conducted in the presence of an enantiopure organocatalyst, the product **6** is isolated with high diastereoselectivity and enantioselectivity (Section 41.1.1.5.12). The same is true for the Michael addition of **10** or other carbon nucleophiles, such as silyl enol ethers or organometallic compounds, at the nitroalkene **9** (Sections 41.1.1.5.49, 41.1.1.5.50, 41.1.1.5.56, 41.1.1.5.57, 41.1.1.5.62, and 41.1.1.5.75.3; for enantioselectivity alone, see Sections 41.1.1.5.54, 41.1.1.5.55, and 41.1.1.5.77.1). Enantioselective hydrogenation of nitroalkenes **9** has also been reported (Sections 41.1.1.5.44 and 41.1.1.5.45).

The synthesis of enantiopure azidoalkanes often starts with enantiopure halides, esters, or alcohols utilizing the clean inversion (S_N2) of the nucleophilic substitution (Sections 41.8.1.4.2, 41.8.1.6.2) and the Mitsunobu reaction (Section 41.8.1.6.2). The same is true for azides prepared by ring opening of optically active γ -lactones (Section 41.8.1.5.2) or epoxides and aziridines (Section 41.8.1.8). In the case of *meso*-epoxides **28** and *meso*-aziridines **30**, desymmetrization and formation of the products **29** and **31**, respectively, can be performed with good enantioselectivity when the ring cleavage is performed in the presence of enantiopure Lewis acids, as shown in **Scheme 4** (see Section 41.8.1.8.2). Kinetic resolution of a racemic epoxide by asymmetric ring opening using azidotrimethylsilane and an enantiopure catalyst has also been reported (Section 41.8.1.8.2). Electrophilic azidation of amides **32**, bearing the Evans auxiliary, successfully gives the azidoalkanes **33** with good to excellent diastereoselectivity (Section 41.8.1.9). Hydroazidation of the electron-deficient alkenes **34** leads enantioselectively to the product **35** if an appropriate catalyst is utilized (Section 41.8.1.10.1). Finally, diastereoselective bromoazidation is also possible when the substituent R^2 is an enantiopure amine or sultam auxiliary. Thus, the addition product **36** is available, and on careful hydrolysis affords the carboxylic acid **37** without epimerization (Section 41.8.1.10.5).

Scheme 4 Asymmetric Synthesis of Enantiopure Azidoalkanes

Science of Synthesis Version 3.10
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Compounds with One Carbon–Heteroatom Bond
Volume 42:
Organophosphorus Compounds (incl. RO—P and RN—P)

Mathey, F., in *Science of Synthesis*, **42** (2008), p.1

General Introduction

With two oxidation states and six coordination numbers, the chemistry of phosphorus is highly elaborate. Many organophosphorus derivatives are sensitive to either hydrolysis or oxidation. With such a background, it is not surprising that organophosphorus chemistry needed a powerful and specific analytical tool to undergo its full development. This tool was provided by ^{31}P NMR spectroscopy, developed at the end of the 1950s; the result was an explosive growth of the domain starting in the 1960s.

For some time, organophosphorus chemists had been obsessed by the vertical analogy with nitrogen. In many cases, this parallel led to dead ends. The pyramidal inversion barrier of tricoordinate phosphorus (ca. 30–35 kcal·mol⁻¹) is much higher than that of nitrogen, while the electronegativity of phosphorus (2.1) is much lower than that of nitrogen (3.0). In fact, it has been realized recently that there is a highly significant and operational diagonal analogy between carbon and phosphorus in their low coordination states^[1] and some horizontal analogy between phosphorus and silicon in their high coordination states. This "chameleon" behavior of phosphorus is another fascinating aspect of its chemistry.

The structure of *Science of Synthesis* means that several classes of organophosphorus compounds are not covered in this volume. Hetarenes with one or more phosphorus atoms in the ring are covered in *Science of Synthesis*, Vols. 9–17. For example, phosphirenes and phospholes are found in *Science of Synthesis*, Vol. 9 [Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom (Sections 9.6 and 9.14, respectively)]; benzophospholes are discussed in *Science of Synthesis*, Vol. 10 [Fused Five-Membered Hetarenes with One Heteroatom (Sections 10.17–10.19)]; and phosphinines are covered in *Science of Synthesis*, Vol. 15 [Six-Membered Hetarenes with One Nitrogen or Phosphorus Atom (Sections 15.13–15.15)]. Compounds with phosphorus bound to an sp¹ or sp² carbon atom can be found in various sections in *Science of Synthesis*, Vol. 24 (Three Carbon—Heteroatom Bonds: Ketene Acetals and Yne—X Compounds), Vol. 31b [Arene—X (X = N, P)], and Vol. 33 [Ene—X Compounds (X = S, Se, Te, N, P)]. Compounds with phosphorus and another heteroatom bound to the same carbon are treated in *Science of Synthesis*, Vol. 30 [Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues (Sections 30.2 and 30.7)]. Compounds with phosphorus functionalities to a carbonyl group can be found in the volume of the respective carbonyl compound. In this introduction, an attempt is made to mention most of the major developments of organophosphorus chemistry, whether they are discussed in the following chapters or not.

Almost all of the important derivatives of phosphorus are manufactured in industry from white phosphorus (P₄). In these processes, the P₄ cage is completely destroyed and yields monophosphorus compounds. However, it has been shown to be possible to control the degradation of the cage and to get some well-defined polyphosphorus compounds. A striking example is provided by the reaction of lithium diazo(trimethylsilyl)methanide with white phosphorus (**Scheme 1**).^[2]

Scheme 1 Synthesis of a 1,2,3,4-Diazadiphosphole^[2]

White phosphorus behaves as a dimer of diphosphyne ($\text{P} \equiv \text{P}$) and undergoes a formal $[2 + 3]$ cycloaddition with the dipolar diazomethanide reagent, the reaction being driven by the aromaticity of the diazadiphospholide product. It is quite fascinating that, some time later, Cummins was able to build a genuine precursor of diphosphyne in the coordination sphere of niobium (**Scheme 2**).^[3] The transient diphosphyne was trapped by cyclohexa-1,3-diene to give a double $[4 + 2]$ adduct.

Scheme 2 Synthesis of a Precursor of Diphosphyne^[3]

Even more recently, Bertrand discovered that a stable nucleophilic carbene is able to open the phosphorus cage to give a P_4 unsaturated chain (**Scheme 3**).^[4] The $\text{P}=\text{P}$ bond can be trapped by 2,3-dimethylbuta-1,3-diene to give a $[4 + 2]$ adduct.

Scheme 3 Activation of White Phosphorus by Bulky Carbenes^[4]

In the same vein, it has been found that Arduengo's carbenes stabilize diphosphyne as L_2P_2 adducts with a $\text{P} - \text{P}$ bond length of ca. 2.20 Å.^[5]

Some time earlier, Baudler discovered that the reaction of white phosphorus with sodium leads, inter alia, to the pentaphospholide anion. This anion is now better prepared from red phosphorus (**Scheme 4**).^[6]

Scheme 4 Synthesis of the Pentaphospholide Anion^[6]

This ion is the first fully inorganic analogue of the aromatic cyclopentadienide anion. As with the cyclopentadienide anion, it gives stable η^5 -complexes with transition metals. 1,2,3,4,5-Pentaphosphaferrocene **1**

and the decaphosphatitanocene dianion **2** are two representative and striking examples of this class of complexes. The synthesis of titanocene **2** is depicted in **Scheme 5**.

Scheme 5 A 1,2,3,4,5-Pentaphosphaferrocene and the Synthesis of Decaphosphatitanocene^[7,8]

As mentioned at the beginning of this introduction, phosphorus displays six coordination states. A coordination number of one is represented by phosphinidenes (R^1-P) and phosphalkynes ($R^1C \equiv P$). Phosphinidenes (Section **42.1**) are fleeting intermediates whose ground state is normally a triplet. Mesitylphosphinidene (MesP), generated by photolysis of 1-mesitylphosphirane, has been characterized by EPR, UV, and IR spectroscopy in a methylcyclohexane matrix at 77 K.^[9,10] A singlet phosphinophosphinidene ($t-Bu_2P-P$) has been trapped by cyclohexene and 2,3-dimethylbuta-1,3-diene to give the expected phosphiranes.^[11,12] Until 1982, however, no versatile carbene-like chemistry was developed with these species. The genuine breakthrough came when it was recognized that upon complexation to a pentacarbonylmetal [$M(CO)_5$ ($M = Cr, Mo, W$)], phosphinidenes are stabilized as singlets and display a diverse carbene-like chemistry (**Scheme 6**).^[13,14] The reaction with alkenes takes place with retention of stereochemistry. The reaction with alkynes led to the discovery of phosphirenes, which are stable in spite of their internal angle of 42° . Several precursors **3–6**^[15–18] of phosphinidenes and several decomplexation techniques are available (**Scheme 7**). This chemistry has been reviewed.^[19–22] In a striking analogy with carbene complexes, terminal phosphinidene complexes also exist as a nucleophilic variety whose chemistry is discussed below.

Scheme 6 The Carbene-Like Chemistry of Electrophilic Phosphinidene Complexes^[13,14]

Scheme 7 Phosphinidene Precursors

Phosphaalkynes ($\text{R}^1\text{C}\equiv\text{P}$; see *Science of Synthesis*, Vol. 19 [Three Carbon–Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives (Section 19.6)]) are the other species representative of a coordination number of one. As early as 1961, Gier reported the synthesis of phosphaacetylene ($\text{HC}\equiv\text{P}$) from phosphine in an electric arc between carbon electrodes.^[23] This discovery was so far in advance of its time that it had no immediate consequences. The real starting point of phosphaalkyne chemistry was the preparation of the stable *tert*-butylphosphaacetylene by Becker in 1981 (**Scheme 8**).^[24] In this species, the HOMO corresponds to the triple bond, and the lone pair at phosphorus is much lower in energy.^[25] As a consequence, most of the chemistry of phosphaalkynes takes place at the P–C bond and resembles the chemistry of alkynes. Numerous cycloaddition reactions have been described.^[26,27] Some spectacular compounds such as the cage compound **7**^[28] and the triphoshabenzene **8**^[29] have also been made by controlled oligomerization (**Scheme 9**).

Scheme 8 Synthesis of *tert*-Butylphosphaacetylene^[24]**Scheme 9** A Cage Structure and a Triphoshabenzene Prepared from Phosphaalkynes^[28,29]

A coordination number of two is represented by phosphaalkenes ($\text{R}^1_2\text{C}=\text{PR}^2$; see *Science of Synthesis*, Vol. 27 [Heteroatom Analogues of Aldehydes and Ketones (Section 27.22)]), iminophosphines ($\text{R}^1\text{N}=\text{PR}^2$; Section 42.2.3), diphosphenes ($\text{R}^1\text{P}=\text{PR}^2$; Section 42.2.4), and phosphonium ions [$(\text{R}^1_2\text{P})^+$; Section 42.3]. Becker discovered the first stable phosphaalkenes while studying the chemistry of acylphosphines (**Scheme 10**).^[30] The π -bond and the lone pair of phosphaalkenes are very close in energy.^[31] As a consequence, the chemistry of phosphaalkenes is a combination of the chemistry of alkenes and the chemistry of the phosphorus lone pair. They act as powerful dienophiles. In some cases, an equilibrium exists between π - and σ -complexes.^[32] The normal polarity of the P=C bond (P^+-C^-) can be inverted with appropriate substituents.^[33]

Scheme 10 First Synthesis of Phosphaalkenes^[30]

The discovery of phosphalkenes was preceded by the synthesis of the first iminophosphine by Niecke (**Scheme 11**).^[34] A striking property of iminophosphines is their ability to behave as carbenes in [1 + 2]-cycloaddition reactions with alkynes to produce phosphiren-1-imines.^[35]

Scheme 11 Synthesis of the First Iminophosphine^[34]

Some time later, diphosphenes were discovered by Yoshifuji (**Scheme 12**).^[36] These diphosphenes are characterized by a ³¹P NMR shift at very low fields and behave as powerful dienophiles. They undergo an *E*-to-*Z* photoisomerization under UV irradiation.^[37]

Scheme 12 Synthesis of the First Diphosphene^[36]

Finally, phosphonium cations **9** and **10** (**Scheme 13**) were characterized in 1972.^[38,39] As for their isoelectronic silicon counterparts,^[40] they need amino substituents to attain stability. They react with alkynes to give phosphirenium salts^[41] and with conjugated dienes to give 2,5-dihydro-1*H*-phospholium salts.^[42,43]

Scheme 13 Phosphenium Cations^[38,39]

With a coordination number of three, the core of classical organophosphorus chemistry is reached (Sections **42.4**–**42.11**). The major recent development in the field is, undoubtedly, the discovery that optically active phosphines are efficient ligands for transition-metal-catalyzed enantioselective reactions (Section **42.10.2**). The testing ground was the asymmetric hydrogenation of prochiral alkenes, and the corresponding work led to the Nobel Prize for Knowles and Noyori in 2001. Several other useful reactions (asymmetric isomerization, hydroformylation, etc.) have also been developed. The four phosphines **11**–**14** illustrate this development (**Scheme 14**).

Scheme 14 Examples of Phosphine Ligands for Enantioselective Reactions^[44–47]

The DIPAMP ligand (**11**), developed by Knowles, possesses two stereogenic phosphorus centers.^[44] It has been applied in a synthesis of L-DOPA.^[48] The Diop ligand (**12**) of Kagan displays two asymmetric carbon centers and is derived from a low-cost starting material, tartaric acid.^[45] Noyori's BINAP ligand (**13**) exists as two atropisomers resulting from the blocked rotation around the binaphthyl bridge.^[46] It has served to devise an industrial synthesis of (–)-menthol. The DuPhos ligands (**14**) of Burk show how the incorporation of phosphorus into a rigid cyclic structure can improve the enantioselectivity of transition-metal-catalyzed reactions.^[47]

For a long time, phosphorus heterocyclic chemistry was ridiculously underdeveloped in comparison to its nitrogen, oxygen, and sulfur counterparts. This is, without any doubt, due to the fact that phosphorus heterocycles are not normally present in nature. From a structural standpoint, however, there is no compelling reason why this domain could not reach a state of development comparable to that of nitrogen heterocyclic chemistry. The real starting point of phosphorus heterocyclic chemistry was the discovery of the McCormack reaction (**Scheme 15**; see also Section **42.6.4.1.4**).^[49]

Scheme 15 The McCormack Reaction^[49]

The next significant step was the discovery of the three-membered phosphiranes (Section **42.6.1**) by Wagner (**Scheme 16**).^[50] With a C—P—C intracyclic angle of 47°, the existence of these species was initially treated with some skepticism. These cycles display a characteristic ³¹P NMR resonance at very high fields and undergo numerous ring-opening and ring-expansion reactions. This area of chemistry was augmented by the discovery of phosphirenes in 1982.^[13]

Scheme 16 Synthesis of Phosphiranes^[50]

Besides cyclic strain, the other specific feature of heterocyclic chemistry is aromaticity. The discovery of phosphinines by M ärkl in 1966 was a milestone of phosphorus chemistry (**Scheme 17**).^[51] The cycle is

rigorously planar with equal-length C —C bonds and short P —C bonds (ca. 1.73 Å). The aromaticity of phosphinines is ca. 88% of that of benzene. The in-plane lone pair is only the third highest occupied level and the LUMO is highly localized at phosphorus. Thus, the heteroatom is not nucleophilic as in pyridines, but electrophilic.

Scheme 17 Synthesis of Phosphinines^[51]

The two other fundamental aromatic systems in phosphorus heterocyclic chemistry are the phospholide ion (isoelectronic with thiophene) (**15**)^[52] and phosphoferrocene (**16**) (**Scheme 18**).^[53] Contrary to phosphinines and phospholides, phosphoferrocenes can be functionalized by electrophilic aromatic substitution. A large series of aromatic heterophospholes is also known.^[54]

Scheme 18 Phospholide Anion and Phosphoferrocene^[52,53]

A coordination number of four is by far the major coordination state of phosphorus chemistry. It includes phosphonium salts (Section **42.12**), phosphine oxides (Section **42.13**), phosphinates (Section **42.14**), phosphonates (Section **42.15**), and phosphates (Section **42.16**). Numerous important small biological molecules contain phosphate groups such as adenosine 5'-triphosphate (ATP), nucleic acids, and oligonucleotides. Novel phosphorylation methods have been developed with the emphasis on regioselectivity, stereochemistry, and purification method. Thio and phosphonate analogues of nucleotides have been synthesized. Some significant references are listed hereafter.^[55–63]

From a synthetic standpoint, the major advance in the field is, undoubtedly, the Wittig reaction (**Scheme 19**).^[64] Wittig was awarded the Nobel Prize in 1979 for this discovery. A definitive book covers all the aspects of this fundamental carbonyl alkenation reaction.^[65] In fact, the first ylides were prepared by Staudinger as early as 1919 but their use as carbonyl alkenation reagents was pioneered by Wittig. Horner was the first to recognize that the phosphorus ylides could be replaced by phosphonate carbanions in this transformation.^[66] It is interesting to note that the first phosphonate carbanion was prepared by Arbuzov as early as 1927.^[67] It is also interesting to note that the so-called aza-Wittig reaction, in which an iminophosphorane reacts with a carbonyl derivative to give an imine, was discovered by Staudinger in 1921.^[68]

Scheme 19 The First Wittig Reaction^[64]

The most recent extension of this reaction is the so-called phospho-Wittig reaction in which a

phosphoranylidene phosphine reacts with a carbonyl derivative to give a phosphalkene. Four versions of this reaction have been reported (**Scheme 20**). The first discovered version was route c.^[69] It has a broad generality because the P=C bond is stabilized by complexation. Route b is less general because the ylide reagent is inert toward ketones.^[70] Route a is the strict analogue of the Wittig reaction, but requires bulky substituents for stability.^[71] Route d makes use of stable nucleophilic phosphinidene complexes derived from high-valent electropositive metals such as tantalum(V) or zirconium(IV).^[72] These nucleophilic phosphinidene complexes are related to the transient electrophilic phosphinidene complexes of **Scheme 6** in a similar way as Schrock carbene complexes are related to Fischer carbene complexes. A review describes the various aspects of the phosphawittig reaction.^[73]

Scheme 20 Four Versions of the Phospha-Wittig Reaction^[69–72]

Section **42.17** is on phosphazenes. Significant discoveries that are discussed there include the syntheses of Schwesinger bases, e.g. the P₄-phosphazene base **17** (**Scheme 21**),^[74] and proazaphosphatranes sulfides and oxides, and their applications in a variety of important organic transformations. Improved syntheses of the phosphazene polymer precursors hexachlorocyclotriphosphazene, and poly(dichlorophosphazenes) are also included in this section.

Scheme 21 Synthesis of a P₄-Phosphazene Base^[74]

The history of phosphorus compounds with a coordination number of five (Section [42.18](#)) was marked by the discovery of pentaphenylphosphorane ([18](#)) by Wittig in 1949 ([Scheme 22](#)).^[75] Pentaalkylphosphoranes are normally unstable and tend to decompose to give a variety of products, including the corresponding ylides. A simple pentaalkylphosphorane [19](#) was prepared by Schmidbaur in 1977.^[76] It is apparently stabilized by its bicyclic structure.

Scheme 22 Examples of Pentaalkylphosphoranes^[75,76]

The most fascinating development in the chemistry of phosphorus with a coordination number of six (Section [42.19](#)) took place when Lacour was able to prepare enantiopure helical hexaorganophosphate anions and use them to separate the enantiomers of chiral cations via ion pairing.^[77] A representative example of such an optically active anion is [20](#) ([Scheme 23](#)).

Scheme 23 Example of an Optically Active Hexaorganophosphate Anion^[77]

After this survey of some of the advances in the various coordination states of phosphorus, one question remains to be asked: what are the trends of the current research in the field? They can be summarized by two words: complexity and applications. Today, it is quite clear that all of the foundations of organophosphorus chemistry are firmly established. The logical further developments consist of building complex structures for specific applications. A first illustration of this trend is provided by the phosphorus dendrimers of the group of Majoral.^[78] Numerous biological and catalytic applications are proposed for this family of molecules. The second illustration is provided by the synthesis of the first phosphaporphyrin [21](#) by Matano ([Scheme 24](#)).^[79]

Scheme 24 The First Phosphaporphyrin^[79]

Aside from the classical applications of organophosphorus chemistry, such as pesticide science, inorganic polymers (polyphosphazenes), and homogeneous catalysis, several unconventional applications are emerging in the domain of organic materials. The availability of strained rings and low-coordinate species has led to the discovery of new types of organophosphorus polymers. The living polymerization of phosphaaalkenes has been uncovered (**Scheme 25**).^[80]

Scheme 25 Living Polymerization of Phosphaalkenes^[80]

In the same vein, the anionic polymerization of phosphirenes has been reported (**Scheme 26**).^[81]

Scheme 26 Anionic Polymerization of Phosphirenes^[81]

Several optoelectronic devices have been prepared from mixed phosphole –thiophene oligomers {e.g., **22** [I_{max} 557 nm (red emission); maximum brightness: $3613 \text{ cd} \cdot \text{m}^{-2}$] (**Scheme 27**).^[82] Reviews have summarized the advances in this field.^[83,84]

Scheme 27 Phosphole –Thiophene Oligomers^[82]

This introduction shall be closed by mentioning a new technique for activating hydrogen that does not involve the

help of transition metals. Stephan has shown that a bulky phosphorus base and a bulky boron Lewis acid are unable to react together as a result of steric hindrance. This mixture is able to perform the push–pull activation of hydrogen at room temperature (**Scheme 28**).^[85]

Scheme 28 The Push–Pull Activation of Hydrogen Using a Phosphorus Base and a Boron Lewis Acid^[85]

If the basic and acidic centers are combined in the same molecule, the system becomes able to reversibly store hydrogen (**Scheme 29**).^[86]

Scheme 29 Reversible Storage of Hydrogen^[86]

As can be seen, organophosphorus chemistry has undergone a complete revolution within the last decades. It is not an adventurous bet to predict that much more is yet to come, especially in the field of applications.

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Compounds with All-Carbon Functions
Volume 43:
Polyynes, Arynes, Enynes, and Alkynes

Hopf, H., in *Science of Synthesis*, **43** (2008), p.1

General Introduction

Alkynes have interested chemists since at least the second half of the 19th century: the first total synthesis of benzene, involving the thermal trimerization of acetylene, was accomplished by Berthelot in 1867,^[1] Adolf von Bayer studied diynes in connection with his ground-breaking indigo work,^[2] and the Glaser coupling, the oxidative dimerization of terminal alkynes in the presence of copper salts (see Section 43.1.1.1.1) was carried out by Glaser in 1869,^[3] to name just three examples. The industrial importance of acetylene reached its zenith shortly before and during World War II with the investigations of Walter Reppe:^[4] a Reppe "acetylene tree" showing how numerous important industrial compounds, such as prop-2-yn-1-ol, but-2-yne-1,4-diol, butane-1,4-diol, tetrahydrofuran, and but-1-en-3-yne, could be prepared from the parent hydrocarbon acetylene was shown in every textbook of organic chemistry at the time. Later, acetylene and its derivatives became of importance in the preparation of special chemicals such as cyclooctatetraene, the retinoids, carotenoids, and many other nonnatural and natural products. Still, the universal importance of the alkynes, and in particular acetylene itself, waned from the 1950s on since other carbon sources became available for industrial syntheses: ethene, propene, and other petroleum-derived hydrocarbons. Oil had replaced coal as the most important industrial starting material.

Although acetylene has not recovered from these developments as a substrate for industrial production, alkynes have experienced a remarkable comeback in research and fine chemicals since the 1980s.^[5] The reasons for this renaissance are manifold, and found both in the reactivity of the C—C bond as well as its special geometry. Of course, there is no ideal functional group; but with organic chemistry being the science of carbon compounds, a group consisting only of "naked" (unsaturated) carbon atoms certainly comes close to it. Since a triple bond "encloses" a double bond, everything that can be done with the latter can in principle be accomplished with the former. The most important reactions of alkynes are additions and isomerizations, and these processes occur under a plethora of conditions involving numerous different mechanisms. Note that since their atom economy is high, it is these two reactions that are of particular importance in any type of sustainable chemistry. Because of its high acidity (pK_a ca. 25), the ethynyl group can be readily converted into an acetylide anion, which in turn provides all kinds of functionalized alkynes on trapping with different electrophiles (see Section 43.8.3.1).



With the discovery of fullerenes and other novel forms of carbon, alkynes have come into focus as carbon-rich compounds and it is in this area where there have been the most stunning structural developments recently concerning the design and construction of novel, highly unsaturated systems.^[6] The (terminal) C—C bond is extremely well suited as a molecular building block because of the linear geometry, because it is small ("sleek"), and because it avoids the stereochemical problems that might arise when double rather than triple bonds are used in organic synthesis. In addition, the cylindrically arranged π -electrons are ideally suited for the transmission of electronic effects and, most importantly, with the numerous coupling reactions now available there is no longer a restriction on the type of carbon hybridization that can be connected to an acetylenic carbon atom. Thus, the coupling partner can be another triple bond, an alkenic, aromatic, or heteroaromatic unit, or a saturated carbon atom, as shown by the numerous examples in this volume. Furthermore, the triple bond is not so rigid as suggested by molecular models; numerous cycloalkynes have been described as displaying a clear deviation from the 180° C—C—C angle suggested by classical models.^[7] Obviously, when several triple bonds are connected to each other the resulting molecular rod resembles more a whip than a stiff stick.

Because of the long and rich history of triple-bond systems, alkyne chemistry has been reviewed numerous times

and is also covered in *Houben –Weyl*, Vol. 5/1d, pp 609 –696 and Vol. 5/2a. It is hence unnecessary to present the synthetic developments that predate the early 1980s in any detail in a volume such as the present one. Of course, alkynes are still often prepared by base-induced β -eliminations (see Section 43.8.1) or from the parent hydrocarbon acetylene by carbon –carbon coupling and substitution reactions (see Section 43.8.3) as in the old days, but many new approaches to C –C bonds have become available since the 1980s.

This volume is concerned with the synthesis of alkynes, grouped into the product classes that are summarized in Table 1.

Table 1 Classes of Alkynes Covered in Volume 43

Product Class/Subclass	Representative/Typical Structure	Section
linear conjugated diynes, oligoynes, and polyyne	$R^1 - \text{C}\equiv\text{C} - (\text{C}\equiv\text{C})_n - R^2$	43.1
cyclic conjugated diynes, triynes, tetraynes, and polyyne		43.2
arynes		43.3
linear enynes		43.4
cyclic enynes		43.5
acyclic arylalkynes	$Ar^1 - \text{C}\equiv\text{C} - R^1$	43.6
cyclic arylalkynes		43.7
linear alkynes	$R^1 - \text{C}\equiv\text{C} - R^2$	43.8
synthesis by elimination	–	43.8.1
synthesis by rearrangement	–	43.8.2
synthesis from other alkynes	–	43.8.3
cycloalkynes		43.9

Section 43.1 deals with the preparation of linear conjugated di-, oligo-, and polyyne, an interesting class of very highly unsaturated compounds that not only occurs in nature, both on Earth^[14] and in interstellar space,^[6,19] but is also very useful for the preparation of numerous other compounds, as demonstrated by the synthesis of heteroaromatic compounds from diynes.^[15] In principle this product class can be prepared by three fundamentally different approaches.

Scheme 1 shows in the most general form the stepwise oxidative coupling of acetylene (1), via buta-1,3-diyne (2) and hexa-1,3,5-triyne (3), all the way to "carbon rods" such as the hypothetical polymer "carbyne" (4). Whereas oligo- and polyyne with an even number of triple bonds can be prepared in principle by homodimerization of the corresponding precursors, the construction of derivatives with an odd number of acetylene moieties requires the combination of two unequal "acetylene bricks". Regardless of the number of triple bonds, it is further obvious that it is preparatively more difficult to prepare this group of compounds when the substituents in the α - and β -positions are different than when they are equal. Altogether, coupling reactions of alkynes are by far the synthetically most

useful route to their higher polyynes analogues.

Scheme 1 Preparation of Polyynes by Stepwise Oxidative Coupling

In the second approach both the number of carbon atoms and their connectivity are identical in substrate and product, i.e. in a linear arrangement (**Scheme 2**). In these cases one does not need to necessarily start with a saturated system (e.g., using compound **5** where the complete π -system is present) but a certain degree of unsaturation may be present in the starting material already, and can be very useful. However, particularly for higher polyynes, the approach becomes increasingly difficult, since the required polyfunctionalized starting materials are often not readily available.

Scheme 2 Preparation of Diynes by Elimination

Occasionally the π -bonds of the target molecules are initially not in linear order. In these cases a rearrangement (see Section **43.8.2**) has to take place and in this category the most famous (and the most often used, even for the preparation of natural products containing a series of conjugated triple bonds^[14]) is the Fritsch –Buttenberg –Wiechell rearrangement (**Scheme 3**) involving carbenes/carbenoids such as **6** to give diynes **7** (Section **43.8.2.1.5**).

Scheme 3 Fritsch –Buttenberg –Wiechell Rearrangement To Give Diynes

Finally, the number of carbon atoms in the starting materials may exceed those found in the product. In these routes fragmentation or cleavage reactions must take place as demonstrated by the decarboxylation of alkynoic acids **8** to diynes **9** (**Scheme 4**). The preparative significance (scope and yields) of these decompositions is rather low, but it should be mentioned that fragmentation processes of "hidden" alkynes such as cyclopropenones or various Diels –Alder adducts play a role for the preparation of cyclic analogues of the linear polyynes, especially in the case of cyclocarbons (see below and Section **43.2.4**).

Scheme 4 Preparation of Diynes by Decarboxylation

The same is true for a set of miscellaneous processes which are probably better called modes of formation than deliberately planned syntheses: the production of polyynes by laser ablation of carbon particles, by electric arcing, or by other high-energy transformations (**Scheme 5**; Section **43.1.3**).

Scheme 5 Synthesis of Polyynes by High-Energy Transformations

Most of the methods leading to symmetrical conjugated 1,3-diynes go back to the classical (1869) Glaser coupling of copper(I) phenylacetylide (**11**), prepared readily from the corresponding terminal alkyne, phenylacetylene (**10**) (**Scheme 6**).^[3] The dimerization step to give 1,4-diphenylbuta-1,3-diyne (**12**) involves air as the oxidant. Although this method is still used successfully, allowing the synthesis of a countless number of diynes^[15] with substituents ranging from alkyl and aryl groups to functional groups (e.g., amines, nitriles, and alcohols) and complex organometallic (e.g., metallocenes), the process has been optimized and extended many times during its nearly 150-year history.

Scheme 6 Classical Glaser Coupling of Phenylacetylene^[3]

The so-called Eglinton variant is a method in which a copper(II)-mediated oxidation is carried out in methanolic pyridine,^[20] a reaction on which most of the annulene work by Sondheimer and co-workers is based (Sections **43.2.1.1.1.1.1** and **43.2.1.2.6**).^[21] The variability of the substituents in this modification is even higher than in the original Glaser method.

A further refinement was introduced by Hay in 1962. In this approach the homocoupling to the 1,3-diyne system is accomplished by passing oxygen through a solution of the alkyne in pyridine in the presence of copper(I) chloride and the bidentate ligand *N,N,N',N'*-tetramethylethylenediamine.^[22] By this protocol (Hay coupling) a still further extension of the scope of the dimerization is accomplished, allowing the preparation of diynes carrying all types of highly functionalized substituents. Under certain conditions even unsymmetrically substituted buta-1,3-diynes are available.

Oxidative dimerizations such as these always lead to mixtures of up to three coupling products when applied to two differently substituted alkynes simultaneously. Hence, to develop a truly general 1,3-diyne synthesis a new approach (heterocoupling) was necessary. The first solution of this problem was provided by Chodkiewicz and Cadot in 1957 by coupling terminal alkynes **13** with 1-bromoalk-1-ynes **14** in the presence of catalytic amounts of copper salts and a suitable amine (**Scheme 7**).^[23]

Scheme 7 Cadot –Chodkiewicz Coupling^[23]

Not only have numerous variations of the Cadiot –Chodkiewicz coupling reaction appeared since the mid-20th century, such as polymer-supported variants or routes in which the activity of the catalyst is enhanced by the addition of cocatalysts, but the leaving group has also been varied over a large range, as have the solvent and the metal or metal salts employed. A sizeable number of these modern variations have also been employed for the homocoupling process, sometimes replacing the traditional Glaser route.

A particularly effective route to symmetrically and unsymmetrically substituted diynes employs various palladium catalysts. Compared to the classical protocols (e.g., Glaser, Cadiot –Chodkiewicz, and variations) the palladium-mediated transformations often take place under milder conditions, are more efficient, and of higher chemoselectivity. A typical case is provided by the two carbohydrate-substituted alkynes **15** and **16**, which are heterocoupled in good yield to give the "acetylenosaccharide" **17** (**Scheme 8**).^[24] Comparable palladium-couplings have also been applied to the synthesis of nonnatural products such as three-dimensional polyynes precursors for fullerenes, as discussed in Section [43.1.1.1.12.2](#)

Scheme 8 Synthesis of an "Acetylenosaccharide" by Palladium-Mediated Heterocoupling^[24]

Compared to the above homo- and heterocoupling processes, elimination reactions have been used far less often to prepare conjugated 1,3-diynes, but they often constitute a valuable alternative provided the starting materials are readily available. Two of the most often employed substrates in this category are 1,4-dihalobut-2-yne **18** and 1-halobut-1-en-3-yne **20** (**Scheme 9**). Whereas in the former case the diyne is obtained directly by double dehydrohalogenation, in the latter, base treatment furnishes the acetylide **21**, which after transmetalation with a zinc(II) halide can be coupled with a second electrophile (R^2I). The starting enynes **20** are easily obtained by Sonogashira coupling of the monoalkynes **19** with (*Z*)-1,2-dichloroethene. The halogen substituent may also be bonded to other positions than the 1-position, as discussed in Section [43.1.1.1.16.2](#)

Scheme 9 Preparation of 1,3-Diynes by Elimination

A typical Fritsch –Buttenberg –Wiechell rearrangement scenario to give 1,3-diynes is illustrated in **Scheme 10**. By an Appel reaction, the acetylenic ketone **22** is converted into the 1,1-dibromoalkene **23**, which on treatment with butyllithium is debrominated, providing a carbene that isomerizes to the desired diyne **24**. If substrates contain the dibromoalkyne unit more than once, products are obtained which carry several 1,3-diyne groups. Contrathermodynamic base-catalyzed propargyl rearrangements leading to terminal diynes have also been described (zipper reaction; see Sections **43.1.1.1.19** and **43.8.2.3.3**).

Scheme 10 Typical Fritsch –Buttenberg –Wiechell Rearrangement

Among the fragmentation routes, the flash-vacuum pyrolyses of (alkynoylmethylene)triphenylphosphoranes stand out (Section **43.1.1.1.18.2**). A case in point is provided by the alkynoyl ylides **27** (**Scheme 11**).^[25] The phosphorane is accessible by treatment of the acid chloride **25** with the ylide **26** and furnishes a diyne on flash-vacuum pyrolysis at 750 °C and pressures between 10^{-3} and 10^{-1} Torr.

Scheme 11 Alka-1,3-diynes by Flash-Vacuum Pyrolysis of Alkynoyl Phosphonium Ylides^[25]

To prepare the longer tri-, oligo-, and polyynes basically the same methods are employed as for the diynes described above, i.e. classical routes such as the Glaser coupling or more recent ones, such as the Hay protocol for homocoupling or the Cadiot –Chodkiewicz heterocoupling approach to obtain unsymmetrically substituted oligoynes. Even more recently, various palladium-catalyzed pathways or β -eliminations,^[26] as well as rearrangements (e.g., the Fritsch –Buttenberg –Wiechell process) have been employed.

One of the highlights in this area is the preparation of the triethylsilyl-end-capped hexadecayne **31** by a series of Hay couplings from **28** via the intermediate extended systems **29** and **30**, as illustrated in **Scheme 12**.^[27] The terminal substitution/protection in these reactions is absolutely mandatory, since the corresponding "free" hydrocarbons are extremely unstable molecules that polymerize quickly to products of unknown composition and structure. In recent years the traditional end groups have been replaced by metal-containing substituents (e.g.,

platinum) giving access to interesting molecular wires with adjustable oxidation states at their termini.

Scheme 12 Stepwise Synthesis of Triethylsilyl-Protected Polyyne^[27]

In Section 43.2 the structural elements discussed in Section 43.1 are incorporated into cyclic and polycyclic systems. Not surprisingly, most of the methods successful for the preparation of acyclic diynes, oligoyne, and polyyne are successful for the synthesis of the cyclic variants as well.

In principle, an acyclic terminal diyne 32 may be oxidatively cyclized either in an intramolecular manner providing the cyclic conjugated diyne 33 or intermolecularly furnishing the cyclic tetrayne 34 (Scheme 13). Many different molecular combinations have been applied as the spacer element, ranging from simple polymethylene chains, complex structures such as a carbohydrate, and many different rings systems, with a small selection represented in Scheme 13. Obviously, there is no limit to the complexity of the spacer element in 32. The ratio of the two pathways depends on various factors, notably the exact reaction conditions and the strain in the products 33 and 34 eventually produced by the respective process.

Scheme 13 Intra- and Intermolecular Cyclization of Terminal Diynes

One of the most famous cyclooligomerizations reported involves hexa-1,5-diyne, which was cyclotrimerized by Sondheimer and his students to the cyclic hexayne 35 (Scheme 14).^[29,30] On base-catalyzed isomerization (see Section 43.8.2.3) this hydrocarbon provides the fully conjugated dehydro[18]annulene 36, the precursor for [18]annulene itself.

Scheme 14 Cyclotrimerization of Hexa-1,5-diyne

In a structurally more complex, three-dimensional case the acyclic hexayne **37** (mixture of isomers) is first dimerized to an isomeric mixture including the "square" dimer **38**, which, after removal of the triisopropylsilyl groups by tetrabutylammonium fluoride treatment, yields a polyyne that can be subjected to a second Hay-coupling step to furnish the expanded cubane **39** (**Scheme 15**).^[31]

Scheme 15 Synthesis of an Expanded Cubane under Hay Conditions^[31]

The diyne moiety does not necessarily need to be generated by a coupling step as in the examples discussed so far, but it can already be present from the very beginning. For example, the disodium salts of buta-1,3-diyne [**40** ($n = 2$)] and hexa-1,3,5-triyne [**40** ($n = 3$)] can be bridged in an intermolecular cyclization (nucleophilic substitution) by reacting them with various ω,ω' -dibromoalkanes **41** (**Scheme 16**).^[32] The yields of the cyclic products are, however, extremely low.

Scheme 16 Intermolecular Cyclization by Nucleophilic Substitution^[32]

As a newer method to prepare medium and large polyynes, the generation of reactive intermediates by

dehalogenation of appropriate precursors has been developed. **Scheme 17** illustrates this approach for the preparation of cyclododeca-1,3,7,9-tetrayne (**43**) from 1,6-dibromohexa-2,4-diyne (**42**) via a cumulene.^[26,33] Cyclic conjugated tetraynes are a poorly investigated class of highly unsaturated hydrocarbons. The preparation of the monocyclic tetraynes **45** ($n = 1-4$) by a double Fritsch –Buttenberg –Wiechell rearrangement of the tetrabromide **44** being one the few examples (**Scheme 17**).^[34]

Scheme 17 Synthesis of Cyclic Polyynes by Dehalogenation^[26,33,34]

Finally, cyclo[n]carbons, e.g. **47**, n-membered monocyclic rings consisting of sp-carbon atoms only and extremely reactive under normal laboratory conditions, have been generated as reactive intermediates by fragmentation (e.g., photodecarbonylation, retro-Diels –Alder, and retro-[2 + 2] reactions) from appropriate precursors, e.g. **46** (**Scheme 18**).^[35]

Scheme 18 Synthesis of Cyclo[n]carbons^[35]

The arynes, dealt with in Section **43.3**, are a well-established class of cyclic alkynes. Not only has the structure of the highly reactive, and for a long time elusive, parent compound 1,2-didehydrobenzene (**48**, benzyne) (**Scheme 19**) been determined by spectroscopic methods (see Section **43.3**), but this compound has been employed countless times as a trappable intermediate in preparative applications. More recently, the aryne concept has been extended to hetarynes such as 3,4-didehydropyridine (**49**),^[36] and many derivatives or exotic representatives, such as **50** where the aryne moiety is incorporated into a [2.2]paracyclophane framework,^[37] or corannulyne (**51**), a nonplanar aryne that has been intercepted with various dienes and nucleophiles.^[38] The field has received a

further strong impulse by extending the dehydrobenzene concept to isomers of **48**. Although these species are not arynes anymore, i.e. they are lacking formal C–C bonds, they are clearly dehydroaromatics. The most famous among these are the parent systems 1,3-didehydrobenzene (**52**, *m*-benzyne) and 1,4-didehydrobenzene (**53**, *p*-benzyne), the latter being the reaction intermediate in the Bergman cyclization (see Section **43.3.3.1.3**).^[39] Both species have been generated and characterized in matrixes at low temperatures.^[40]

Scheme 19 Examples of Arynes and Other Didehydrobenzenes

1,2-Didehydrobenzenes are prepared from two classes of substrates: simple benzene derivatives **54** and benzannulated heteroaromatics **55** (**Scheme 20**). In the former case β -elimination reactions are performed, whereas in the latter case fragmentations, sometimes structurally and mechanistically quite complex, take place. Section **43.3** summarizes these approaches beginning with simple dehydrohalogenations (**54**, X = H; Y = halo) and ending with such examples as the thermal decomposition of phthalic anhydride (**56**) (Section **43.3.1.1.8.2**) or the oxidation of 1*H*-1,2,3-benzotriazol-1-amine (**57**) (Section **43.3.1.1.16**). As far as the β -eliminations are concerned, there is hardly a functional group or substituent which has not been removed from the aromatic core, thus enabling the preparative use of aryne **48** under vastly different reaction conditions.

Scheme 20 Methods for the Generation of 1,2-Didehydrobenzene

Compared to the applications of 1,2-didehydrobenzene (**48**) in synthetic organic chemistry, the use of

didehydrobenzenes **52** and **53** is presently very limited. Most studies concerning these isomers have so far concentrated on their generation, structure proof, and mechanistic behavior (Sections **43.3.2** and **43.3.3**). The ring-opened form of **53**, hexa-3-en-1,5-diyne, is dealt with extensively in Sections **43.4** and **43.5**

Section **43.4** describes the preparation of conjugated acyclic enynes, e.g. **58**, and compounds that contain this moiety as a subunit. Of particular importance in this context are the enediynes, e.g. **59**, and the tetraethynylethenes, e.g. **60** (**Scheme 21**). To include these compounds is not only reasonable because of their structural relationship to **58** but also because the synthetic procedures leading to them are very similar to those for the simplest enyne.

Scheme 21 Examples of Enyne Structures

For the preparation of enynes numerous methods have been developed, most of which can be represented by the general considerations shown in **Scheme 22**. The C_4 unit can be assembled from smaller building blocks as shown by the two $C_2 + C_2$ routes or a $C_3 + C_1$ protocol. Alternatively, the four carbon atoms eventually required may already be connected in the starting material as shown by additions to 1,3-diynes (see Section **43.1.1**), the metathesis of already available enynes, and β -eliminations of suitable acetylenic substrates. In rearrangement processes (Section **43.8.3**) the final connectivity may already be present from the very beginning of the reaction, or not.

Scheme 22 General Routes to Enynes

Numerous name reactions have been applied to the preparation of enynes, and among these the metal-mediated coupling processes predominate. A widely used route to differently substituted enynes **63** is the Sonogashira

cross-coupling reaction of vinyl halides **61** with terminal acetylenes **62**, using different palladium-based catalyst systems in the presence of amines (**Scheme 23**).

Scheme 23 Synthesis of Enynes^[41,42]

This route has also been successfully employed to synthesize various hexenediynes from (*E*)- and (*Z*)-1,2-dichloroethene.^[43] The substituents in the alkene and alkyne coupling partners can be varied over a very broad range. If the coupling is performed between a vinyl halide and an acetylenic organoboron compound it is called the Suzuki–Miyaura cross coupling (Section 43.4.1.1.2), and when the corresponding acetylenic Grignard reagent is employed one speaks of a Kumada–Corriu cross coupling (Section 43.4.1.1.3). Other popular name reactions that have been employed very successfully for the preparation of enynes include the Stille coupling (vinyl halides with organotin compounds; Section 43.4.1.1.4), the Negishi reaction (vinyl halides with alkynylzinc compounds; Section 43.4.1.1.5), and various copper-mediated processes such as the Stephens–Castro process (vinyl halides with copper acetylides; Section 43.4.1.2.4).

Among the alkyne dimerizations (formal nucleophilic 1,2-additions of an acetylide anion to a second alkyne), the dimerization of phenylacetylene to give the enyne **64** under the influence of potassium amide might be cited as an example (**Scheme 23**; Section 43.4.1.9.1).^[41] The same reaction also takes place when phenylacetylene and other terminal alkynes are subjected to the influence of various ruthenium catalysts (Section 43.4.1.9.2; for cyclic variants see Section 43.5.5.1.3).

For the $C_3 + C_1$ approach, the alkenation of acetylenic aldehydes and ketones by the classical processes (e.g., Knoevenagel, Wittig, Wittig–Horner, Corey–Fuchs, and Peterson alkenations) have been applied countless times (Section 43.4.1.4.4). As an example, the preparation of the functionalized enyne **65** from 3-phenylprop-2-ynal and a phosphonate by a Wittig–Horner transformation is shown in **Scheme 23**.^[42]

Among the addition reactions, the reduction of diynes with complex aluminum and boron hydrides predominate (Section 43.4.1.6). However, hydrosilylation, hydrostannylation, and hydroamination have also been reported. Many of these reactions are preparatively useful since they allow the introduction of functional groups into these enyne systems (e.g., amines, ethers, and amides).

The application of the metathesis reaction in this area has so far been largely restricted to exchange of the alkene moiety of an existing enyne. **Scheme 24** illustrates the preparation of the ester **68** by reaction of the allyl ether **66** with the diacetate **67** under the influence of a second-generation Grubbs catalyst.^[44]

Scheme 24 Preparation of an Enyne by Metathesis^[44]

Not surprisingly elimination reactions have often been used to prepare enynes (Section 43.4.1.4). As starting materials, homopropargylic (as shown in Scheme 22) or propargylic substrates (alcohols, halides, toluenesulfonates) are most often used. The former are readily available, for example from the reaction of acetylenic Grignard reagents with oxiranes, the latter from carbonyl compounds and metalated alk-1-ynes. Occasionally, the alkynes are first converted into hexacarbonyldicobalt complexes, which often undergo the elimination reactions under milder conditions than the uncomplexed alkynes (Nicholas reaction).^[45]

Other alkene forming processes such as the Corey –Winter fragmentation^[46] or the Ramberg –Bäcklund reaction, for example in the transformation of a dipropargyl sulfone into the enediyne 69 (Scheme 25),^[47] have also been employed.

Scheme 25 Ramberg –Bäcklund Reaction To Form an Enyne^[47]

Although rearrangement reactions leading to enynes are known in which the –framework of substrate and product are identical (e.g., base-catalyzed isomerizations of alkynes;^[48] see also Section 43.8.2.3), more often deep-seated rearrangement processes connect starting materials and products. This is demonstrated for example by the propargyl allyl alcohol derivative 70, which is enolized by base treatment to give an intermediate that subsequently undergoes a Claisen rearrangement. After esterification with diazomethane, the unnatural amino acid derivative 71 is obtained (Scheme 26).^[49]

Scheme 26 Claisen Rearrangement of a Propargyl Allyl Alcohol Derivative^[49]

Section 43.5 deals with cyclic enynes. Although in a strict sense this might only apply to compounds in which the enyne moiety is part of a monocyclic ring system (e.g., enynes 72), or cyclic molecules where this combination occurs several times such as the cyclic enediynes 73 or the tridehydro[12]annulene 74, compounds such as 75 in which the double bond is arranged in a semicyclic fashion are also included (Scheme 27). Likewise, the section includes bicyclic frameworks such as 76 or 77, the latter type and variations thereof being found as core structures of various cytotoxic natural products (Section 43.5.2).

Scheme 27 Examples of Cyclic Enyne Structures

In principle there are two general strategies to prepare cyclic enynes: one either starts from a cyclic ring system and introduces the triple or the double bond subsequently, or one begins with acyclic precursors and produces the ring by a cyclization reaction at the end. In the latter case the carbon atoms of the intended cyclic enyne may all be present from the very beginning (intramolecular cyclization) or the ring is assembled by an intermolecular process from smaller building blocks.

The first strategy is illustrated by the preparation of one of the simplest known cyclic enynes, cyclooct-1-en-3-yne (**78**), by base-induced fragmentation of a 1,2,3-selenadiazole (**Scheme 28**).^[50]

Scheme 28 Synthesis of a Cyclic Enyne by Base-Induced Fragmentation of a 1,2,3-Selenadiazole^[50]

For the introduction of double bonds into preexisting cycloalkyne derivatives, the usual C=C bond-forming reactions have been employed such as the Corey –Winter fragmentation, e.g. to give **79**,^[51] or even traditional methods such as a simple dehydrobromination in the preparation of enyne **80** (**Scheme 29**).^[52]

Scheme 29 Synthesis of Cyclic Enynes by Corey –Winter Fragmentation or Dehydrobromination^[51,52]

Among the cyclization routes, many of the methods described above for the preparation of acyclic enynes are encountered again (e.g., Glaser, Eglinton, Hay, Stille, Sonogashira, and Suzuki couplings in numerous variations, intramolecular Grignard reactions, and ruthenium-catalyzed cyclization of α,ω -diynes) starting from the appropriately α,ω -difunctionalized precursors. However, approaches have also been used that are hardly employed in acyclic enyne synthesis. Of these routes, pinacolizations or McMurry-type coupling reactions should be mentioned (see Section 43.5.3.1.3), as shown by the preparation of the cyclodecenyne **81** from an α,ω -oxoaldehyde (Scheme 30).^[53] A further interesting approach is provided by the intramolecular Diels–Alder addition of enyne **82**, which produces the adduct **83** with a cycloundecenylene framework in good yield when heated.^[54]

Scheme 30 Preparation of Cyclic Enynes by a Pinacol Cyclization and an Intramolecular Diels–Alder Addition
^[53,54]

As far as cyclic precursors are concerned it may sometimes be advantageous to prepare the target molecule from a substrate with a larger ring size. For cyclic enynes, ring contraction by sulfur dioxide extrusion (Ramberg–Bäcklund reaction) has been particularly valuable, for example in the synthesis of cyclododeca-3-ene-1,5-diyne from the sulfone **84** (Scheme 31).^[55]

Scheme 31 Ramberg–Bäcklund Reaction To Form a Cyclic Enyne^[55]

Acyclic arylalkynes, dealt with in Section 43.6, are a long-known class of compounds, which have, however, attracted a lot of recent interest. The main reason for this growing attention originates from the use of these compounds as building blocks for more complex oligomeric or polymeric systems. These can be two-dimensional networks such as graphyne or graphdiyne^[56] or partial structures thereof (see Section 43.7.1.1.4.5), or extended linear structures such as poly(*para*-phenyleneethynylene)s,^[57] which are of interest because of their optoelectronic properties.

Acyclic arylalkynes can principally be synthesized by three general approaches (**Scheme 32**): (1) coupling a functionalized alkyne with a functionalized aromatic precursor; (2) by introduction of unsaturation into a substrate which possesses already the complete π -framework; and (3) by preparation of the triple bond starting with a functionalized aromatic precursor and connecting it with a reagent that ultimately provides the terminal sp -hybridized carbon atom.

Scheme 32 General Routes to Acyclic Arylalkynes

For the first route, two alternatives are conceivable. These are coupling of a metalated arene with, for example, a haloalkyne, or the "umpoled" situation: combining an aryl halide with a metal acetylide. Although the first strategy has been used occasionally, by far the majority of arylalkynes are synthesized by the second route. In most cases these reactions are palladium-catalyzed, and again we encounter the usual name reactions discussed above for the synthesis of enynes including the Stille and the Negishi protocols (e.g., in the synthesis of arylalkynes **85** from alkynylzinc derivatives; **Scheme 33**),^[58] the Stephens –Castro route (palladium-catalyzed cross coupling of aryl halides with copper alkynides),^[59] the Suzuki coupling (aryl halides coupled with organoboron compounds),^[60] and many other variations.

Scheme 33 Syntheses of Acyclic Arylalkynes^[58,61]

Again, the Sonogashira coupling [cross coupling of aryl halides (usually the more reactive iodides) and terminal alkynes in the presence of a copper/palladium-catalyst system; see Section **43.4.1.12**] is of special value for the preparation of this class of compounds. Not only has the influence of specially designed ligands for the palladium catalyst been investigated to allow the coupling of the less reactive aryl bromides and even chlorides, but the process has also been investigated under a plethora of reaction conditions, a clear sign of its high overall usefulness. These variations include microwave heating (Section **43.6.1.3.4.2**), use of phase-transfer conditions (Section **43.6.1.3.4.3**), and copper-free conditions (Section **43.6.1.3.5**). An important (and very simple) variation involves a domino process where the starting aromatic bromide or chloride is first subjected to a halogen exchange to the iodide, which subsequently couples with the alkyne component. The conversion of 4-chlorobenzonitrile into the diarylalkyne **86** serving as an example (**Scheme 33**).^[61]

In metathesis reactions, arylalkynes already serve as the starting material for the process. The reaction can be used if one wishes to generate a new substitution pattern, as illustrated in **Scheme 34** for the conversion of 3-phenylprop-1-yne into diphenylacetylene (**87**).^[62]

Scheme 34 Synthesis of Diphenylacetylene by Metathesis^[62]

Elimination routes to arylalkynes can either start from fully saturated precursors such as vicinal or geminal dihalides or from a vinyl halide; normally alkoxides are used as bases. If the substrate has the appropriate structure, for example a 1-bromo-2-phenylethene derivative, then the elimination can also be accompanied by a Fritsch –Buttenberg –Wiechell rearrangement (Section **43.8.2.1.5**).

For chain-extending syntheses several protocols have been developed. Classical ones start from an aromatic aldehyde and first convert it into a haloalkene by Wittig or Wittig –Wadsworth –Emmons alkenation routes. The resulting functionalized styrenes are then converted into the corresponding alkynes by β - or γ -elimination. In the very popular Corey –Fuchs modification (see Section **43.6.1.4.5.2**), aromatic aldehydes are first converted into 1,1-dibromoalkenes **88**, which on treatment with alkyllithium reagents yield the arylacetylenes **89** as elimination/rearrangement products (**Scheme 35**).^[63]

Scheme 35 Corey –Fuchs Alkynylation of Aromatic Aldehydes^[63]

Two other one-carbon extensions of aromatic aldehydes and ketones to alkynes that have become popular are the Seyferth –Gilbert^[64] and the Bestmann –Ohira^[65] methods, both involving diazo compounds. In the latter case (see also Section **43.8.2.1.4**) the Bestmann –Ohira reagent dimethyl (1-diazo-2-oxopropyl)phosphonate (**90**) is first deacylated by base to give the Seyferth –Gilbert reagent **91**, the anion **92** of which attacks the aromatic aldehyde in a Wittig –Horner-type process to produce the diazo intermediate **93** (**Scheme 36**).^[66,67] This loses nitrogen and the generated vinylidene carbene rearranges to give the arylalkyne. A further simplification is possible when a mixture of the Bestmann –Ohira reagent and manganese(IV) oxide is applied simultaneously to benzyl alcohols. Now, the alkyne is produced in a two-step, one-pot process without the need to isolate the intermediately produced aromatic aldehyde.^[67]

Scheme 36 Bestmann –Ohira Alkynylation of Aromatic Aldehydes^[65–67]

The product class cyclic arylalkynes, dealt with in Section 43.7, has also been known for a long time, but has recently experienced a rapid growth of interest. Responsible for this development is on the one hand the use of these systems as molecular scaffolds in supramolecular chemistry, and on the other hand their possible application in material science, particularly because of their optoelectronic properties.

As expected, most of the coupling reactions described in earlier sections of this volume (e.g., Sections 43.4 and 43.6) are also employed for the preparation of this class of compounds. In fact, a lot of work in this area is dominated by structural investigations, with not so much on the development of new synthetic routes.

For example, transition-metal-catalyzed cross-coupling reactions are very often used to synthesize cyclic arylalkynes, as demonstrated by the preparation of the cyclic 1,3-phenyleneethynylene hexamer 95 from 1-ethynyl-3-iodobenzene by a Stephens –Castro reaction, with the copper(I) acetylide 94 as an intermediate (Scheme 37).^[68]

Scheme 37 Preparation of a Phenyleneethynylene Hexamer by a Stephens –Castro Reaction^[68]

Two other examples, demonstrating the power of the Sonogashira –Hagihara reaction in this area, are collected in **Scheme 38**. The coupling of the double enyne **96** with the dibromide **97** furnishes the unsaturated [6.6] paracyclophane **98**.^[69] The graphyne substructure **100** can be obtained by intramolecular cyclization from the precursor **99** after the dialkyltriazenyl/trimethylsilyl masking groups are replaced by iodine and hydrogen, respectively.^[70]

Scheme 38 Preparation of Cyclic Arylalkynes by Sonogashira –Hagihara Reactions^[69,70]

The Glaser, Hay, and Eglinton routes (see Section **43.1.1.1.1**) and modern variants thereof such as the Breslow variant of the Eglinton route (see Section **43.7.1.1.5.3**) have also been widely applied for the preparation of cyclic arylalkynes of varying complexity (see Section **43.7.1.1.5**). One example is the cyclooligomerization of 1,2-diethynylbenzene and several of its derivatives **101** (**Scheme 39**).^[71] The yields of the cyclooligomers **102** depend on the substituents R¹ and the exact reaction conditions.

It seems safe to predict that alkyne metathesis will be applied in this area in the future much more often than is presently the case, especially since new catalyst systems are developed continuously. The success of this route to cyclic arylalkynes is demonstrated by the near quantitative conversion of **103** into the cyclic trimer **104** (**Scheme 39**).^[72]

Scheme 39 Preparation of Cyclic Arylalkynes by Cyclooligomerization of 1,2-Diethynylbenzenes and Alkyne Metathesis^[71,72]

Although some routes leading to cyclic arylalkynes may involve "old chemistry", the products obtained are often excitingly new. A case in point is provided by the preparation of conjugated arylalkynes by elimination reactions (see also Section 43.8.1). Dehydrobromination of the product formed by bromine addition to the hexaene 105, certainly one of the oldest routes to alkynes, by treatment with potassium *tert*-butoxide leads in excellent yield to the "bracelet" hydrocarbon 106, a *para*-isomer of the *ortho*-hydrocarbon 95 (Scheme 40).^[73,74]

Scheme 40 Synthesis of a Conjugated Cyclic Arylacetylene by Elimination^[73,74]

Another elimination process leading to a cyclic arylalkyne **109**, which on first sight looks like a Wurtz coupling, is shown in **Scheme 41**.^[26] it uses a different acyclic arylalkyne, the dibromide **107**, as a precursor. Actually the debromination/dimerization is thought to involve the highly reactive cumulene **108** as an intermediate.

Scheme 41 Preparation of a Paracyclophanetetrayne by Cycloaddition of Cumulenic Quinodimethanes^[26]

In practically all examples described in this product class, the benzene ring is a structural element present from the very beginning of a synthesis and carried through all steps of the sequence until its end. That it may sometimes be advantageous to have all structural elements in place except the benzene ring is demonstrated in **Scheme 42** for the preparation of the ortho,paracyclophane **111**, a highly strained arylacetylene because of its bent benzene rings.^[75] This unusual compound can be prepared by exploiting the roof-like structure of the two Dewar benzene moieties that are part of the precursor molecule **110**, and presumably makes it less strained than its valence isomer **111**. Indeed, on irradiation the hoped-for ring opening takes place smoothly and in good yield.^[75]

Scheme 42 Preparation of a Strained Paracyclophane

The voluminous Section **43.8** is composed of three subsections, covering the preparation of linear alkynes by eliminations (Section **43.8.1**), by rearrangements (Section **43.8.2**), and from other alkynes (Section **43.8.3**). Since all of these approaches have been used extensively in the past, and hence been reviewed many times,^[4–19] Sections **43.8.1**–**43.8.3** may be regarded as an update of older procedures. Although several of the routes presented here go back to the very early days of alkyne chemistry, the sections illustrate that these transformations are still widely used in modern alkyne chemistry.

Concerning elimination reactions, one of the formally easiest ways to produce an alkyne from an alkene is by dehydrogenation. Although its reverse is often used in chemistry (Lindlar hydrogenation of alkynes to alkenes), the oxidation process has also been described several times. The conversion of the alkenic hydrocarbons **112** into the corresponding alkynes **113** can serve as an example (**Scheme 43**).^[76]

Scheme 43 Preparation of Alkynes by Dehydrogenation of Alkenes^[76]

The standard situation, however, involves the removal of functionality from the substrate. And in this area there have been many novel developments, based on the classical routes of dehydrohalogenation, dehalogenation, and thermal or photochemical fragmentations, etc. For example, terminal aromatic alkynes **115** can be prepared in nearly quantitative yield from 3-aryl-2,3-dibromopropanoic acids under the influence of microwave irradiation in the presence of a base (**Scheme 43**).^[77] If required, the process can be stopped at the vinyl bromide stage **114**.

A countless number of alkenation reactions leading to alkynes have been performed with heteroatom-substituted vinyl derivatives. A practically useful pathway that starts from methyl ketones and avoids the classical, often preparatively unsatisfactory, route of converting these first into geminal dichlorides by phosphorus pentachloride treatment, converts a ketone, e.g. **116**, into a vinyl phosphate **117**. On lithium diisopropylamide treatment this undergoes β -elimination to give the desired alkynes, e.g. **118**, in excellent yield (**Scheme 44**).^[78]

Scheme 44 1,2-Elimination of a Vinyl Phosphate Derivative

Although 1,2-eliminations dominate this area, 1,1-eliminations have also often been employed. The Corey –Fuchs process (see Section 43.6.1.4.5.2) again serves as one example. In a modern variant applying 1,8-diazabicyclo [5.4.0]undec-7-ene as a base to vinylic geminal dibromides, the Corey –Fuchs process has been diverted to produce 1-bromoalkynes, useful coupling partners for the Cadiot –Chodkiewicz cross coupling (see Section 43.1.1.2.1). An example demonstrating that this transformation can be applied to prepare functionalized alkynes such as 119 is shown in Scheme 45.^[79]

Scheme 45 Modified Corey –Fuchs Reaction for the Synthesis of 1-Bromoalkynes^[79]

Other classical elimination routes [Fritsch –Buttenberg –Wiechell rearrangement (Section 43.8.2.1.5); Ramberg –Bäcklund reaction (Section 43.5.3.1.5.1); thermolytic and photolytic fragmentations, etc.] have also been applied to prepare simple alkynes very often. A general method for the preparation of numerous hydrocarbon alkynes 121 consists of the flash-vacuum pyrolysis of α -oxo ylides 120, precursors that are readily available by treatment of phosphonium salts with acid chlorides in the presence of excess butyllithium (Scheme 46).^[80]

Scheme 46 Preparation of Alkynes by Thermolysis of α -Oxo Ylides^[80]

Chain extension by condensation or alkenation (e.g., Wittig, Bestmann –Ohira, or Peterson reactions) of carbonyl compounds usually involves elimination reactions and can hence be dealt with in this section as well. An elimination (deoxygenation) that goes back to the days of Curtius (1889) involves the oxidation of bis(hydrazones) of 1,2-diketones using various oxidants [e.g., CuCl, O₂; Pb(OAc)₄; HgO]. It has been employed, for example, for

the preparation of the unstable cycloocta-1,3-dien-6-yne (**123**) from the precursor **122** as illustrated in **Scheme 47**.^[81]

Scheme 47 Synthesis of Cycloocta-1,3-dien-6-yne by Elimination^[81]

Rearrangement reactions leading to alkynes occur by numerous different mechanisms: as anionic, cationic, or radical processes; concertedly; in the presence of metals, metal catalysts, and enzymes; and thermally or photochemically induced. Section **43.8.2** provides examples of all of these reaction types. Still, the preparative use of these reactions is now much less widespread than in the early days of alkyne chemistry, when it was often the goal to investigate reactive behavior or simply to have access to a certain target molecule, rather than find a specific and economical route for its preparation. In the case of hydrocarbons, isomerization reactions often furnish complex mixtures of reaction products, requiring sometimes rather involved separation techniques. However, to learn about the finer mechanistic aspects of the reactions of highly unsaturated organic compounds, rearrangement processes of alkynes remain of high interest.

As far as specificity is concerned, concerted reactions leading to alkynes often remain unsurpassed. This is exemplified by the sequence given in **Scheme 48**. Simple hydrocarbons such as 4-methylpent-3-en-1-yne (**124**) can, after epoxidation, be transformed into the linear acetylenic ketone **125** by a protocol combining a 1,5-hydrogen shift and a [3,3]-sigmatropic rearrangement (Claisen rearrangement).^[82] The process does not only introduce new functional groups into the substrate **124** but also connects its carbon atoms in a different order. In another pericyclic process, 1,2-dehydrobenzene (**48**; see Section **43.3**) is connected to the allenes **126** by an ene reaction furnishing aromatic alkynes (**Scheme 48**).^[83]

Scheme 48 Rearrangements To Give Alkynes^[82,83]

Some rearrangement reactions involving alkylidene carbenes, such as the Fritsch –Buttenberg –Wiechell rearrangement, are discussed in earlier sections. They are dealt with in greater depth in Section **43.8.2.1.5**, especially since they can also be carried out under conditions other than the usual base-induced method (photo-Fritsch –Buttenberg –Wiechell: Section **43.8.2.1.5.2**; electrochemical-Fritsch –Buttenberg –Wiechell: Section **43.8.2.1.5.3**; variation of metal counterion: Section **43.8.2.1.5.4**).

Base-catalyzed isomerizations of (usually terminal) alkynes into other, internal alkynes have been described already by Favorskii in 1888,^[84] processes now known to involve allenic intermediates. Although often under these conditions isomeric mixtures are produced, in certain cases this transformation is preparatively useful. For example, many terminal alkynes are converted into their thermodynamically more stable alk-2-yne isomers **127** in excellent yield when treated with alkoxide bases in protic solvents (**Scheme 49**).^[85] On the other hand, the contrathermodynamic base-catalyzed rearrangement of internal to terminal alkynes has also been achieved. The most often used base/solvent system for this process, which derives its driving force from salt (acetylide) formation, is potassium 3-aminopropylamide (KAPA) in propane-1,3-diamine. This so-called "acetylene zipper", which has also been performed with alkynes carrying functional groups, furnishes the terminal alkyne isomers **128** in good to excellent yield (**Scheme 49**).^[86]

Scheme 49 Base-Induced Conversion of Alk-1-yne into Alk-2-yne and the Acetylene Zipper Reaction^[85,86]

Although not a rearrangement in the sense discussed so far, a comprehensive discussion of alkyne metathesis is nevertheless included in Section **43.8.2.5.1**, since formally this process rearranges (shuffles) substituents from one triple-bond system to another one as illustrated in very general form in **Scheme 50**.

Scheme 50 Alkyne Metathesis

As a special class of concerted reactions, the so-called coarctate rearrangements have steadily gained importance. In these reactions two bonds are broken and two bonds are formed simultaneously at one atom.^[87] This type of process is encountered in the fragmentation of cyclopropenylcarbenes **129** into two alkynes, as shown in general form in **Scheme 51**.^[87] A specific example of a coarctate rearrangement of a cyclopropylcarbene into an enyne is given for the thermal decomposition of the tosylhydrazone salt **130** to the , -difunctionalized acetylenic ester **131**.^[88]

Scheme 51 Coarctate Rearrangements of Cyclopropenes and Cyclopropanes To Give Alkynes^[87,88]

Another preparatively very valuable fragmentation of this type is the Eschenmoser –Tanabe fragmentation of epoxy ketones (**Scheme 52**; Section **43.8.2.6.4**).^[89] In the first step of this decomposition process, α,β -unsaturated ketones **132** are epoxidized to the corresponding epoxy ketones, which are subsequently derivatized to their tosylhydrazones **133**. Under acidic or basic conditions at room temperature or below these decompose to give the alkynes **134** (**Scheme 52**). The process is applicable to a wide range of mono- und polycyclic substrates, including numerous steroid derivatives, with the alkyne and the carbonyl product being connected by a spacer element of varying complexity in these latter cases.

Scheme 52 Eschenmoser –Tanabe Fragmentation of Epoxy Ketones^[89]

In Section **43.8.3** the synthesis of alkynes from other alkynes is covered. Although the alkyne-to-alkyne conversion also dates back to the early period of alkyne chemistry, and has hence has been reviewed many times,^[4–18] it is applied very often today because of its simplicity and scope. The process is based on the relatively high acidity of the acetylenic hydrogen atom and on the ready availability of the starting materials, in many cases acetylene itself. In the first step, a terminal acetylene is converted by treatment with a strong base (MX) into the acetylide ion **135**, which is trapped by an electrophilic reagent (E^+) (**Scheme 53**). In principle, there exists a very broad range of electrophilic reagents: taking only carbon-centered electrophiles, all elements with a greater electronegativity than carbon can induce a partial positive charge at the carbon atom carrying this element. However, since many of the products derived from reactions of **135** and an electrophile (alcohols, ketones, acids, etc.) are treated in other volumes of *Science of Synthesis* they are not dealt with here. The majority of the electrophilic reagents used in this chapter are alkyl halides, which, however, may in selected cases carry other functional groups (oxygen functions, alkenes, amines, etc.) in their alkyl side chains. Also included are reactions in which alkyl halide equivalents, such as dialkyl sulfates, toluenesulfonates, and trifluoromethanesulfonates, are employed.

Scheme 53 Synthesis of Alkynes from Other Alkynes

Traditionally, the sodium cation serves as the counterion M^+ in **135**, and the required alkynylsodium has usually been prepared by the reaction of the alkyne with sodium amide, often in liquid ammonia. Later, this was replaced by lithium when lithium amide and especially butyllithium became readily available.

Not surprisingly, however, many other metals can and have been employed numerous times including Grignard reagents, potassium, and transition metals. As far as the reactivity in the halide electrophile series is concerned, it drops in the usual sequence from iodine to chlorine. Bromides are employed most often in routine synthetic work. If acetylene serves as the alkyne substrate, the two hydrogen atoms can be removed successively, to form **136**, or totally to give diacetylide **137**, allowing the preparation of mono- and dialkylated derivatives, respectively. To avoid working with gaseous acetylene (acetylene cylinders) the commercially available, solid lithium acetylide – ethylenediamine complex **138** can be used in these reactions.

Substrates possessing more than one alkyne function such as octa-1,7-diyne, can be reacted with difunctional electrophiles such as 1-bromo-4-chlorobutane to generate the less reactive chloride **139** first (**Scheme 54**).^[90] After its activation by halogen exchange, the nucleophilic substitution can be performed a second time providing the cyclic diyne **140** (see Section **43.9**). The introduction of a reactivity difference in the alkylating reagent prevents the formation of intermolecular S_N2 products. The addition of amines such as *N,N,N,N*-tetramethylethylenediamine and various urea derivatives increases the rates of the alkylation reactions, as does the use of Lewis acids (e.g., aluminum trichloride) as additives in certain cases. The application of dimethyl sulfate as the alkylating reagent for a more complex substrate is illustrated by the conversion of **141** into **142**.^[91]

Scheme 54 Formation of a Cyclic Diyne and Alkylation of a Diyne Using Dimethyl Sulfate^[90,91]

In the reaction of Grignard reagents with alkyl halides the addition of a catalyst, often a copper salt, is usually required, whether chloride or iodide is the leaving group and whether the alkyl group is saturated or activated by unsaturation (e.g., allyl, propargyl). The preparation of the "skipped" hydroxydiyne **143** from a homopropargylic alcohol and a protected propargyl iodide is typical (**Scheme 55**).^[92] Palladium-catalyzed alkynylations of alkyl halides, especially bromides and iodides, have also been reported.^[93]

Scheme 55 Preparation of a Hydroxydiyne Using a Grignard Reagent^[92]

The range of variability of both the alkyne and the alkylation component is demonstrated by the attack of alkynylaluminum compounds on the α -position of propiolactone, which leads to alk-4-ynoic acids **144** in good yield (**Scheme 56**).^[94]

Scheme 56 Reactions of Alkynylaluminum Compounds with Propiolactone^[94]

Although formally involving the reverse of the usual polarization of a $C-C-X$ bond, 1-haloalkynes can be coupled with organometallic reagents in the presence of various metal catalysts. For example, 1-bromo-2-phenylacetylene (**145**) reacts with Grignard reagents in the presence of cobalt(II) chloride to give the 1-phenylalk-1-ynes **146** (**Scheme 57**).^[95] Other metals, such as zinc, aluminum, and zirconium, can replace magnesium.

Scheme 57 Cobalt-Catalyzed Reaction of 1-Bromo-2-phenylacetylene with Grignard Reagents^[95]

Although there is a certain degree of overlap with Section **43.2** on cyclic diynes and polyynes, it is justified to dedicate a separate chapter to cycloalkyne preparation (Section **43.9**). In Section **43.2** the emphasis is on cyclic polyynes in which at least two conjugated triple bonds are present, whereas in Section **43.9** any distance between the alkyne moieties is allowed and there may be either carbon atoms or heteroatoms separating them.

As in the case of the other cyclic compounds discussed in this volume, two fundamentally different strategies may be applied to prepare cycloalkynes: either these compounds are formed by cyclization reactions or by generating the triple bond in a substrate that possesses the desired ring system already. In the first case, intramolecular cyclization of a starting material already having all eventually needed carbon atoms can be performed, or the ring

system can be assembled by putting two (or more) appropriately functionalized fragments intermolecularly together. Of course, ring enlargements or contractions can also be employed, but these approaches are so far not very popular.

To illustrate the building-block approach, the nonconjugated cyclic oligoynes **148** can be synthesized by reaction of bis-metalated ω,ω' -diynes, for example the dilithium salts **147**, with ω,ω' -diiodides (**Scheme 58**).^[96] The yields depend on the lengths of the spacer units and can be as high as 85%.

Scheme 58 Stepwise Approach to Symmetrical and Asymmetrical Cycloalkadiynes^[96]

As an example of the intramolecular cyclization of a substrate with all necessary carbon atoms present, as well as carrying additional useful functional groups, the base-induced cyclization of the diyne **149** can be cited. Besides the intended cyclization product **150**, the cyclized dimer **151** is produced here as well (**Scheme 59**). The yields and ratios of **150** and **151** depend inter alia on the length of the polymethylene spacer.^[97]

Scheme 59 Preparation of Cyclic Diynes and Tetraynes^[97]

Heteroatoms can be introduced into the ring by various protocols. Thus, reaction of 1,4-dichlorobut-2-yne with dichlorodimethylsilane provides 1,1,6,6-tetramethyl-1,6-disiladeca-3,8-diyne (**152**) (**Scheme 60**).^[98] Likewise, the thiadiynes **154** are obtained when the ω,ω' -dibromides **153** are treated with sodium sulfide nonahydrate (**Scheme 60**).^[55] As expected, the yields depend on the length of the polymethylene chain. The basically same reactions with selenium or nitrogen nucleophiles lead to the corresponding seleno- and azacycloalkadiynes.

Scheme 60 Preparation of Heteroatom-Containing Cycloalkynes^[55,98]

In the case of ammonia as the nucleophilic reagent and 1,6-dibromohex-3-yne as the alkylation partner, not only the doubly alkylated product **155** is formed but also the bicyclic bis(tertiary amine) **156** (**Scheme 61**).^[99] The yield of this interesting three-dimensional triyne **156** can be increased when diyne **155** is treated with dibromide **154** under basic conditions.

Scheme 61 Preparation of a Nitrogen-Containing Cycloalkadiyne and Cycloalkatriyne^[99]

Alkyne metathesis has also conquered this area quickly. This route is not only of interest for the preparation of the parent hydrocarbon systems, but has also proven its worth many times for the synthesis of functionalized cycloalkynes, illustrating the great tolerance this method displays for functional groups (see Section **43.8.2.5.1**). For example the cyclization of diyne **157** to cycloalkyne **158** in the presence of a molybdenum catalyst takes place in near quantitative yield (**Scheme 62**).^[100]

Scheme 62 Preparation of a Cycloalkyne by Ring-Closing Metathesis^[100]

Numerous routes to cycloalkynes have been described starting from cyclic precursors and applying the standard triple-bond-forming methods. The β -elimination of 1,5-dibromocycloocta-1,5-diene to give the angle-strained cycloocta-1,5-diyne (**159**) is one example (**Scheme 63**).^[101] Another example is the extrusion of 2 equivalents of carbon monoxide from the bis-cyclopropanone **160** to generate the 14-membered hydrocarbon **161**.^[102]

Scheme 63 Synthesis of Cycloalkynes from Cyclic Precursors^[101,102]

The base-induced or thermal fragmentation of selenadiazoles has already been referred to in the context of preparing cyclic enynes (see Section 43.5.1). This pathway, the so-called Lalezari –Meier fragmentation, is also very useful for the preparation of many nonconjugated cyclic alkadiynes. The preparation of numerous cycloalkynones is best accomplished by the Eschenmoser –Tanabe process, as already stated above (see Section 43.8.2.6.4).

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The challenge in synthesizing allenes and higher cumulenes is twofold: the high energy of these unsaturated systems (enthalpy of formation for $\text{H}_2\text{C}=\text{C}=\text{CH}_2$: ca. $190 \text{ kJ} \cdot \text{mol}^{-1}$)^[1] has to be provided by using suitable energy-rich substrates and/or reagents, and the stereochemistry of the cumulated double-bond system, which can give rise to enantiomers or *E/Z* diastereomers, has to be controlled. Alkynes have a similar energy content to allenes^[1,2] and are therefore ideal precursors. All the classical reaction types of organic chemistry (addition, elimination, substitution, rearrangement) are applicable to the synthesis of (cyclic or acyclic) allenes and higher cumulenes, and the formation of allenes from other allenes is also well developed. Stereoselective variations have been described for many of these transformations, often taking advantage of center-to-axis chirality transfer. The allenes and cumulenes thus formed are highly interesting in their own right, but are also frequently converted into other target molecules, e.g. by (cyclo)addition, cyclization, and rearrangement. Ideally, the chirality of allenes is utilized in these transformations for the controlled formation of stereogenic centers by axis-to-center chirality transfer.

One of the most frequently used methods for the synthesis of allenes is the $\text{S}_{\text{N}}2$ substitution of propargyl electrophiles with organometallic reagents.^[3] Organocopper compounds are the nucleophiles of choice for these transformations, and alk-1-ynyl oxiranes are among the most useful electrophiles, not only because the substitution usually takes place with high $\text{S}_{\text{N}}2$ regioselectivity and *anti* stereoselectivity, but also because the α -hydroxyallenes formed are highly suitable for subsequent modifications, e.g. by cyclization (**Scheme 1**; see also Section 44.2.1.1.4).^[4] Direct substitution reactions of allenic electrophiles are also known, but are used less frequently.

Scheme 1 *anti*-Stereoselective $\text{S}_{\text{N}}2$ Substitution of an Alk-1-ynyl oxirane with Lithium Dimethylcuprate and Subsequent Cycloisomerization of the α -Hydroxyallene Formed^[4]

Besides acyclic allenes, cyclic allenes^[5] and higher cumulenes^[6] can also be prepared by this method. A useful alternative is the application of palladium catalysis, which allows the $\text{S}_{\text{N}}2$ substitution of propargyl electrophiles to be carried out with Grignard reagents, organozinc compounds, and many other carbon nucleophiles. Due to the sometimes-limited configurational stability of the intermediate allenyl/propargylpalladium species, however, application of the method to the stereoselective synthesis of allenes can be problematic. The corresponding $\text{S}_{\text{N}}2$ reduction of certain propargyl electrophiles is possible with lithium aluminum hydride or diisobutylaluminum

hydride as the hydride source (more recently, catalytic amounts of N-heterocyclic carbene stabilized copper hydrides have also be used for this purpose).^[7] For example, reaction of the alk-1-ynoxirane **1** with diisobutylaluminum hydride affords the allene **2** by *syn*-selective hydride delivery, and the latter is converted into the allenic carotenoid mimulaxanthin (**3**) (**Scheme 2**; see also Section 44.2.1.2.6).^[8] The *syn*-stereoselectivity is probably due to precoordination of the hydride source to the epoxide oxygen atom.

Scheme 2 *syn*-Stereoselective S_N2 Reduction of an Alk-1-ynoxirane with Diisobutylaluminum Hydride as a Key Step in the Total Synthesis of Mimulaxanthin^[8]

Syntheses of allenes by addition reactions also take advantage of the high reactivity of acetylenic substrates toward organometallic reagents.^[3] The 1,4-addition of organolithium compounds to conjugated enynes proceeds regioselectively with formation of allenyllithium species, which can be trapped with carbonyl compounds and other electrophiles (**Scheme 3**; see also Section 44.2.3.6).^[9] The introduction of functionality from the nucleophile into the allene is possible by palladium-catalyzed 1,4-addition of carbon pronucleophiles to conjugated enynes (**Scheme 3**; see also Section 44.2.3.7).^[10] The reverse polarity is used in the well-established allene synthesis by addition of allenyl-/propargylmetal nucleophiles to carbonyl compounds.^[11]

Scheme 3 1,4-Addition of Organolithium Compounds and Carbon Pronucleophiles to Conjugated Enynes^[9,10]

If the conjugated enyne bears an acceptor substituent at the double bond, organocopper compounds react in a 1,6-addition to form allenyl enolates, which can be trapped regioselectively with many electrophiles to afford functionalized allenes (**Scheme 4**; see also Section 44.2.3.5.1).^[12] An enantioselective version of this reaction using a rhodium-catalyzed addition of aryltitanium nucleophiles has been developed.^[13] It is also possible to extend the enyne system by introduction of further double bonds; these Michael acceptors undergo regioselective 1,8-, 1,10-, or 1,12-additions of organocuprates to afford conjugated enallenes, dienallenes, or trienallenes, respectively.^[12]

Scheme 4 Allene Synthesis by 1,6-Addition of Organocuprates to Conjugated Enynes and Regioselective Enolate Trapping^[12]

Elimination reactions have found widespread use for the synthesis of both allenes and higher cumulenes. For example, treatment of 2,5-dichloro-2,5-dimethylhex-3-yne with methylmagnesium bromide affords 2,5-dimethylhexa-2,3,4-triene in ca. 90% yield (**Scheme 5**; see also Section 44.1.4.1.2.5.1).^[14] Variations of this method include the use of other halogens and organolithium reagents or zinc metal as reductant. The allene synthesis by elimination can take place stereoselectively with center-to-axis chirality transfer; for example, treatment of the stannylated allylic acetate **4** with tetrabutylammonium fluoride provides allene **5** with 94% ee (**Scheme 5**; see also Section 44.2.2.1.8).^[15]

Scheme 5 Synthesis of an Allene and a Cumulene by Elimination^[14,15]

Elimination reactions of vinyl halides and related substrates have also been utilized frequently for the synthesis of endocyclic^[16] and exocyclic allenes. This applies also to the well-known Doering –Moore –Skattebøl (DMS) synthesis of allenes from the corresponding alkenes by addition of dichloro- or dibromocarbene and subsequent treatment of the dihalocyclopropane with an organolithium reagent.^[17] A typical example is the reaction of the cyclopropanaphthalene derivative **6** with butyllithium; due to its ring strain, the allene **7** cannot be isolated, but dimerizes spontaneously to the dibenzotricyclotetradecadiene derivative **8** (**Scheme 6**; see also Section 44.3.4.1.1.1).^[18] It is interesting to note that application of the DMS procedure to allenes affords butatrienes when 1 equivalent of dihalocarbene is used;^[19] in contrast to this, double cyclopropanation of 2,4-dimethylpenta-2,3-diene and treatment with methyllithium furnishes 2,6-dimethylhepta-2,3,4,5-tetraene.^[20]

Scheme 6 Synthesis of an Allene by Doering –Moore –Skattebøl Synthesis^[18]

The Wittig reaction and related carbonyl alkenations undoubtedly belong to the most important methods for the formation of C=C bonds. Thus, it is not surprising that they have also been utilized for the preparation of allenes and higher cumulenes, usually with ketenes as the carbonyl component. In order to avoid manipulation of these unstable substrates, acid chlorides or other ketene precursors are treated with a base in the presence of the alkenation reagent, directly affording the allene with high yield.^[21] An enantioselective version of this method uses the chiral Horner –Wadsworth –Emmons reagent **10** for the transformation of ester **9** into the allene **11**, which is formed with 89% ee (**Scheme 7**; see also Section 44.2.2.2.2.2).^[22] An intriguing example of the application of carbonyl alkenation to the synthesis of cumulenes is the formation of the bicyclic butatriene **13** from precursor **12** (**Scheme 7**; see also Section 44.1.4.1.2.11.3).^[23]

Scheme 7 Synthesis of an Allene and a Bicyclic Cumulene by Carbonyl Alkenation^[22,23]

The rearrangement of suitable alkynes opens up another important pathway to allenes. Besides the prototropic rearrangement in the presence of base, e.g. of methyl prop-2-ynyl ether to methoxyallene, this class of reactions includes [2,3]- and [3,3]-sigmatropic rearrangements of propargyl derivatives. For example, the α -allenic ester **16** is formed by thermal Claisen rearrangement of the ketene acetal **15**, which is obtained in situ by treating propargyl alcohol **14** with triethyl orthopropanoate (**Scheme 8**; see also Section [44.2.4.3.2](#)).^[24]

Scheme 8 Synthesis of an Allene by Claisen Rearrangement of a Ketene Propargyl Acetal^[24]

The manipulation of functional groups next to an allene moiety by oxidation, reduction, addition, elimination, or rearrangement is often possible without affecting the allenic system. Another method for obtaining structurally complex allenes from simpler allenic precursors takes advantage of the acidity of allenic protons, which is comparable to that of terminal alkynes. For example, treatment of methoxyallene with butyllithium affords 1-lithio-1-methoxyallene with high regioselectivity; this can be trapped with numerous electrophiles (**Scheme 9**; see also Section [44.2.5.1.3](#)).^[25]

Scheme 9 Reaction of Lithiated Methoxyallene with Electrophiles^[25]

Metalated allenes are also accessible from bromoallenes by halogen –metal exchange. The latter can also be employed in palladium-catalyzed cross-coupling reactions, for example in the Stille-type coupling with alkynylstannanes (**Scheme 10**; see also Section 44.2.5.2.3).^[26]

Scheme 10 Stille-Type Coupling of a Bromoallene with Alkynylstannanes^[26]

Applications of allenes in the synthesis of non-allenic target molecules take advantage of the high reactivity of allenes in various reaction types (cycloaddition, cyclization, rearrangement, etc.) and the possibility of transferring the axial chirality of the allene to a new stereogenic center formed in the reaction. For example, an intramolecular cascade of an allenic Diels –Alder reaction and a retro-Diels –Alder reaction has been used for the assembly of the tricyclic carbon skeleton of trikentrin (**Scheme 11**; see also Section 44.2.6.1.3).^[27] Silylallenes participate in the titanium-mediated [3 + 2] cycloaddition to electrophilic alkenes, giving rise to the stereoselective formation of richly functionalized cyclopentenes (**Scheme 11**; see also Section 44.2.6.5).^[28]

Scheme 11 Application of Allenes in [4 + 2] and [3 + 2] Cycloadditions^[27,28]

The axis-to-center chirality transfer is demonstrated nicely in the intramolecular Pauson –Khand reaction of the chiral, enantiomerically enriched ynallene **17** that leads to the bicyclic cyclopentenone **18A** as the major product in 71% yield and 95% ee together with its isomer **18B** (**Scheme 12**; see also Section 44.2.6.4).^[29] An application in natural product synthesis takes advantage of the gold-catalyzed cycloisomerization of the allenic diol **19** that affords the 2,5-dihydrofuran **20** with excellent yield, regio- and stereoselectivity (**Scheme 12**).^[30] This is the key building block of the β -carboline alkaloids (–)-isocyclocapitelline and (–)-isochrysotricine.

Scheme 12 Axis-to-Center Chirality Transfer in a Pauson –Khand Reaction and a Gold-Catalyzed Cycloisomerization^[29,30]

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Volume 45:**Arenes, Quasiarenes, Annulenes, and Polyenes**

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The synthesis of aromatic compounds has an illustrious past dating back to an independent discovery by Faraday (1825)^[1] and a synthetic transformation by Mitscherlich (1833).^[2] Already in 1835,^[3] Berzelius commented on Mitscherlich's 1833 report of an oil he called benzene, which came from distilling the calcium salt of benzoic acid, prepared from gum benzoin and lime. It was soon recognized that this synthetic oil was the same substance reported by Faraday as bicarburet of hydrogen in 1825. By 1836, Charles Mansfield produced benzene directly from coal tar and used this process to found a chemical industry based on benzene. Today, commodity aromatic chemical production is a multibillion-dollar industry, with worldwide production of benzene alone estimated to be 37 million tons per year (2007).^[4]

In addition to benzene, Mitscherlich reported substitution on benzene effected by harsh reagents such as nitric and sulfuric acid as well as elemental chlorine. He also made preliminary investigations of the reactions of these products under reducing conditions. In this manner, by 1834, he had already achieved the first syntheses of nitrobenzene,^[5] benzenesulfonic acid, and azobenzene. Nitrobenzene as a technical product (artificial oil of bitter almond) was introduced by Collas, and its commercial manufacture was disclosed in an 1847 patent by Mansfeld.^[6] Reduction of nitrobenzene with iron filings led to the production of aniline, from which Perkin developed mauve, and the dyestuff industry sprang forth.^[7,8] Aniline is still an important feedstock for dyes, pharmaceuticals, and materials chemistry.^[9] Indeed, it is estimated that in 1985 over 1.4 million tons of aniline were being produced yearly worldwide.^[10]

Classical Friedel –Crafts chemistry entered as a synthetic method only in 1877,^[11–14] long after the industry of aromatic synthesis was well established. Until then, toluene and xylenes were products of the distillation of coal tars. Modern zeolites provide the catalytic power for the formation of xylenes, ethylbenzene,^[15] cumene, and various alkylbenzenes. Through oxidation chemistry of xylene and cumene come terephthalic acid and phenol, respectively. Dehydrogenation of ethylbenzene yields styrene, the polymerization of which leads to a multibillion dollar industry in polystyrene and Styrofoam (Dow alone reported US\$33 billion in sales of Styrofoam in 2005).^[16] All of these alkylbenzene products are commodity feedstocks for industries producing films, coatings, fibers, and composite materials.^[10]

Beyond benzene, condensed-ring aromatic compounds such as naphthalene, anthracene, and pyrene provide the scaffolding for many of the molecules the average person comes into contact with in daily life. The ready availability of polynuclear aromatic feedstocks has placed them center stage for the development of commercial chemicals such as dyestuffs, pharmaceuticals, and plastics. From aspirin to Zoloft, aromatic chemistry is the core of biological action. Fragrances, such as musks, found in commercial care products rely on the stability of the aromatic core to withstand harsh conditions such as those found in the use of laundry detergent in combination with bleach.^[17]

Benzenoids fuel the creative spirit of many synthetic chemists focused on nonnatural products and designer molecules. Cyclophanes^[18–21] and nonbenzenoid aromatics^[22,23] have played an enormous role in the development of chemical structure theory. Acenes, circulenes, phenylenes, and fullerenes form the basis for modern organic materials and nanochemistry,^[24] from organic light-emitting diodes (OLEDs)^[25] to porous organic architectures and metal –organic frameworks (MOFs).^[26] Building molecules with aromatic fragments is one of the best ways to obtain high-molecular-weight, nonpolymeric substances as well as shape-persistent macromolecules. Even molecular gears, rotors, and machines of the current state of the art incorporate ipitycyl,


stilbyl, and trityl fragments.


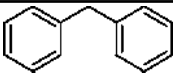
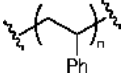
The ability to prepare aromatic molecules efficiently and in diverse structural types is an essential component of the chemical enterprise. Warren's classical text on organic synthesis begins with aromatic compounds as the basis to the subject,^[27] the duality worth highlighting is the comparison of methods to derivatize an existing aromatic nucleus versus the synthesis of the nucleus de novo. Such a parallel view of aromatic synthesis focuses on "aromatic" more as a molecular feature than a functional group feature. Indeed, aromatic synthesis is influenced by changes in retrosynthetic strategy as well as in method development. For example, the oligomerization of alkynes started out as a method for the synthesis of members in the class of annulenes, but developed to be applied as a synthetic strategy toward the classes of cyclophanes or phenylenes.

Various types of aromatic synthesis are presented in this volume but the emphasis is on the formation of aromatic nuclei and bonds directly to an aromatic nucleus. It is not within our purview to survey methods for modifying aromatic compounds at sites remote from the aromatic core. Thus, for example, photobromination of toluene to give benzyl bromide or oxidation of benzoin to benzil, despite the clear aromatic character of the product molecules, are treated in *Science of Synthesis*, Vol. 35 (Chlorine, Bromine, and Iodine) for the synthesis of halides and Vol. 26 (Ketones) for the synthesis of diones, respectively.

The organization of Volumes 45a (Monocyclic Arenes, Quasiarenes, and Annulenes; Sections 45.1 –45.12) and 45b (Aromatic Ring Assemblies, Polycyclic Aromatic Hydrocarbons, and Conjugated Polyenes; Sections 45.13 –45.31) (see [Table 1](#)) follows a rough taxonomic hierarchy based on graphical complexity and size. Following a classical taxonomy parallel, one can view the place of a specific compound as in the following example: aromatic (class), ring assembly (order), polyaryl (family), biaryl (genus), biphenyl (species).

Table 1 Classes of Arenes, Quasiarenes, Annulenes, and Polyenes Included in Volume 45

Product Class	Core or Example Structure(s)	Section
cyclopropenium salts, cyclopropenones and heteroatom analogues, and cyclopropenyl radicals and anions		45.1
cyclobutadienes, cyclobutenediones, and squaric acids		45.2
cyclopentadienyl anions, cyclopentadienones, and heteroatom analogues		45.3
benzene and alkylbenzenes		45.4
styrenes, stilbenes, and other alk-1-enylbenzenes		45.5
annulated benzenes (1 <i>H</i> -cyclopropabenzenes, 1,2-dihydrocyclobutabenzenes, indanes, and indenenes)		45.6
cycloheptatrienylium (tropylium) salts, tropones, tropolones and heteroatom analogues		45.7

cyclooctatetraenes		45.8
nine-membered and higher annulenes and related ions		45.9
fulvenes		45.10
dimethylenecyclobutenes and quinodimethanes		45.11
radialenes	 $n = 1-4$	45.12
biaryls		45.13
arylalkanes		45.14
poly(phenylenes)		45.15
poly(<i>p</i> -phenylenevinylenes)		45.16
poly(xylylenes)		45.17
polystyrenes	 Ph	45.18
naphthalenes, anthracenes, 9 <i>H</i> -fluorene, and other acenes		45.19
cyclobutabenzene, biphenylenes, and [N]phenylenes		45.20

phenanthrenes, helicenes, and other angular acenes		45.21
pyrenes, circulenes, and other condensed acenes		45.22
annulated polycyclic aromatic hydrocarbons		45.23
pentalenes, s-indacenes, as-indacenes, azulenes, heptalenes, and their benzo derivatives		45.24
extended polycyclic aromatic hydrocarbons (graphite, fullerene, and carbon nanotube substructures)		45.25
triphenylenes, tetraphenylenes, and related compounds		45.26
calixarenes and related compounds		45.27

mononuclear cyclophanes		45.28
polynuclear cyclophanes		45.29
conjugated polyenes, including cyclic polyenes that are not fully conjugated		45.30
macromolecular conjugated polyenes		45.31

Using the idea of vertex replacement in a graph, one can consider a single aromatic ring as a vertex element.^[28] Benzene, an archetypal annulene, becomes a trivial point graph, the simplest graph. The size of the annulene dictates its position in the volume, with three-membered rings to nine-membered and higher covered in Sections [45.1](#) –45.9. Cross-coupling reactions play a very important role in the synthesis of substituted benzenes, and [Scheme 1](#) shows one example from Section [45.5](#)

[Scheme 1](#) One-Pot Diazotization –Alkene Arylation^[29,30]

The orientation of the double bonds in an annulene is tangential to the curvature of the ring and they are

connected together with *E* or *Z* stereochemistry via vicinal positions; however, one can imagine rings constructed from double bonds oriented radially to the ring and connected via the geminal positions. Fulvenes, heptafulvalenes, and radialenes are examples of such structures, the aromatic character of which has been debated extensively. Sections 45.10–45.12 survey methods to synthesize these structures and **Scheme 2** shows syntheses of a fulvalene via phenylcarbene (see Section 45.10).

Scheme 2 Preparation of Heptafulvalene by Rearrangement of Phenylcarbene^[31–33]

For systems containing multiple aromatic nuclei, the molecular graph develops beyond the trivial dot. Two points connected by a line represents biphenyl or naphthalene, the weighting of the connection determining the difference. As more nuclei are added to the construct, the possibility of distinction between linear and branched becomes important, analogous to linear and branched alkanes. Thus, 1,3,5-triphenylbenzene and isobutane share a similar graph form; the former having benzene rings as the vertex element in place of the latter's methyl groups. Polyaryls, acenes, and phenylenes all belong to this broader ring-assembly order. Based on ring-connection type, Sections 45.13–45.18 detail simple bonded chains of rings, whereas Sections 45.19–45.21 and 45.24 deal with fused-ring constructs. **Scheme 3** depicts a synthesis of poly(*p*-phenylenevinylene) via ring-opening metathesis polymerization of a paracyclophane (see Section 45.16).

Scheme 3 Synthesis of Poly(*p*-phenylenevinylene) by Living Ring-Opening Metathesis Polymerization of a Paracyclophane Monomer^[34]

A consequence of ring fusion is a conformational and mechanical stability to the linkage. As a result, angular members of this family can define arc shapes, which for steric reasons adopt rigid helical structures on the laboratory time scale. These helicenes are chiral and add a component of stereochemical control to the strategy in aromatic synthesis.^[35–37] The analogous simple chain aromatic systems also show some conformational preference but tend to be in dynamic equilibrium among a variety of forms. The study of these compounds as "foldamers"^[38,39] has stimulated a branch of physical organic and polymer chemistry such that new synthetic methods to designer structures are constantly being sought.

Ring assemblies that themselves form rings make a higher order of aromatic molecular graphs. These can again form by simple connections among the aromatic ring elements or by ring fusions. The latter (see Sections [45.22](#) and [45.23](#)) constitute the condensed polynuclear aromatic hydrocarbons of which circulenes ([Scheme 4](#)) form a special family.

Scheme 4 Synthesis of [7.7]Circulene^[40]

Especially complex graphs come from structures such as graphenes, fullerenes, and carbon nanotube structures (Section [45.25](#)). Issues of directed-versus assembly-based syntheses come to the fore. Ring assemblies built up from simple connections among the aromatic rings comprise the families of calixarenes^[41] and cyclophanes,^[42,43] each having important implications for supramolecular and materials chemistry. Sections [45.27](#)–[45.29](#) reveal the syntheses of a number of key examples within these families.

Also included in this volume but not directly part of aromatic chemistry or the graphical taxonomy proposed are sections on the synthesis of linear and cyclic polyenes. Carotenoids and macrocyclic polyenes belong to this family, and [Scheme 5](#) shows an efficient synthesis of the carotenoid lycopene. Sections [45.30](#) and [45.31](#) discuss the synthesis of these compounds and thereby round out Volume 45.

Scheme 5 Synthesis of Lycopene by Double Elimination^[44]

Overall, the expanse of Volume 45 is enormous, as is the field of aromatic chemistry. The various authors who have devoted their precious time to this adventure are to be heartily thanked. Without their dedication to this project it would not have been possible for us to bring this to fruition. We hope that the information in the following pages provides a good foundation in real-life, reliable methods for the preparation and derivatization of aromatic compounds.

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Compounds with All-Carbon Functions

46

**Volume 46:
1,3-Dienes**

Rawal, V. H.; Kozmin, S. A., in *Science of Synthesis*, **46** (2009), p.1

Volume 46 of *Science of Synthesis* describes the assembly of a variety of cyclic and acyclic 1,3-diene-containing compounds, excluding those that contain direct heteroatom substitution of the diene moiety. The volume is organized by the classes of synthetic methods that are used for preparation of the 1,3-dienes and is intended to provide a comprehensive discussion of all classical and modern transformations that are employed for efficient assembly of this widely utilized class of organic compounds.

The volume begins with a discussion of alkenation methods (see Section **46.1**), including the Wittig, the Horner – Wittig, the Horner –Wadsworth –Emmons, the Peterson, and the Julia reactions. (Note that, for consistency with the rest of *Science of Synthesis*, in this volume the term alkenation, rather than olefination, is used to describe reactions that involve formation of a C=C bond; the term alkenylation is used to describe coupling reactions involving a preformed C=C moiety.) Such methods rely on the general concepts outlined in **Scheme 1**, where heteroatom-stabilized reagents **2** or **6** are generated, typically by the action of a base on compounds **1** or **5**, and then added to the carbonyl compounds **3** or **7**, respectively. The addition step is followed by elimination (either in the same flask or in a separate step) to afford the desired 1,3-diene **4**. Either the carbonyl compound **3** or the ylide **6** must contain an existing alkene moiety in order to yield the conjugated diene system present in **4**.

Scheme 1 Synthesis of 1,3-Dienes by Carbonyl Alkenation

Schemes 2 –5 depict several representative examples of applications of such methods in the context of complex molecule synthesis. The first case, shown in **Scheme 2** (see also Section **46.1.1.2**), represents the Wittig reaction of phosphonium salt **9** with aldehyde **8** to yield an advanced synthetic fragment **10** en route to the natural product callistatin A.^[1] This example highlights the high efficiency of the assembly process, as well as the compatibility of

the reaction with the lactone functionality.

Scheme 2 Application of an Allylic Phosphorus Ylide to the Synthesis of (–)-Callystatin A^[1]

The example in **Scheme 3** (see also Section 46.1.3.1) illustrates the assembly of the 1,3-diene fragment of the natural product mniopetal E. In this case, the Horner–Wadsworth–Emmons reaction of aldehyde **11** with the anion generated upon treatment of ethyl (diethoxyphosphoryl)acetate with sodium hydride affords the desired 1,3-diene **12** with excellent efficiency and superb diastereoselectivity.^[2]

Scheme 3 Horner–Wadsworth–Emmons Reaction of an Enal in the Synthesis of Mniopetal E^[2]

The Peterson reaction represents another efficient entry into 1,3-dienes. The most noteworthy feature of this method is reagent-based control of the diastereoselectivity of the final elimination step. **Scheme 4** provides a representative example. Deprotonation of allyltriphenylsilane (**13**) with butyllithium, transmetalation with titanium (IV) isopropoxide, and finally addition of an aldehyde affords the desired α -hydroxy- β -vinylsilane **14**, which undergoes stereospecific Peterson elimination reactions with acid or base to afford the corresponding *E*- or *Z*-diene, respectively (see also Section 46.1.4.2).^[3]

Scheme 4 Synthesis of a 1,3-Diene by Peterson Reaction^[3]

The Julia reaction provides access to 1,3-dienes from α,β -unsaturated carbonyl compounds and alkyl sulfones under relatively mild conditions. A one-pot variant of this process is shown in **Scheme 5**. Deprotonation of sulfone **15** with sodium hexamethyldisilazide, followed by addition of unsaturated aldehyde **16** affords the advanced synthetic fragment **17**, which is used subsequently for the synthesis of marine natural product phorboxazole B (see also Section 46.1.5.1).^[4]

Scheme 5 Synthesis of the *E,E*-1,3-Diene Moiety of Phorboxazole B

The alkylidenation of α,β -unsaturated carbonyl compounds (see Section 46.2) is a highly effective strategy for the synthesis of 1,3-dienes. Alkylidene complexes of transition metals can be employed to enable such transformations. One of the unique features of these methods is the ability to alkylidenate enolizable ketones or carboxylic acid derivatives, which can be quite challenging to conventional alkenation (olefination) methods. The general concept for assembly of 1,3-dienes using metal alkylidenes is shown in **Scheme 6**. The majority of such transformations entail methylenation or alkylidenation of unsaturated carbonyl compounds **19** with metal carbenes **18**. Alternatively, the 1,3-dienes **20** can be assembled using unsaturated carbene complexes **21**, especially those that are derived from titanium.

Scheme 6 Synthesis of 1,3-Dienes by Metal-Based Alkylidenation Methods

The Tebbe reagent [(μ -chloro)bis(η -5-cyclopentadienyl)(dimethylaluminum)(μ -methyl ene)titanium(IV), (AlMe₂)₂Ti(Cp)₂](μ -CH₂)(μ -Cl)] is the classic reagent to enable efficient methylenation of a wide range of carbonyl compounds. The Tebbe reagent is prepared by the reaction of 2 equivalents of trimethylaluminum with dichlorobis(η -5-cyclopentadienyl)titanium(IV). A representative example of the application of this reagent for the synthesis of 1,3-diene **22** is shown in **Scheme 7** (see also Section 46.2.1.1.1).^[5]

Scheme 7 Transformation of an Unsaturated Aldehyde into a 1,3-Diene by Treatment with the Tebbe Reagent^[5]

Diiodo(μ -methylene)dizinc(II) represents another useful reagent for the alkenation of aldehydes and ketones. Generally, Lewis acid activation is required for efficient use of this reagent. However, ketones that contain α -heteroatom substitution can be methylenated in the absence of a Lewis acid. A representative example is provided in **Scheme 8** (see also Section 46.2.1.2), which illustrates the efficient transformation of enone **23** into diene **24**.^[6]

Scheme 8 Transformation of an Enone into a 1,3-Diene by Methylenation with Diiodo(μ -methylene)dizinc(II)^[6]

Treatment of α -substituted α -chloroallyl sulfide **25** with bis(η -5-cyclopentadienyl)bis(triethyl phosphite)titanium(II) generates the intermediate alkenylcarbene complex **26** (**Scheme 9**; see also Section 46.2.3.1). Subsequent addition of 1,5-diphenylpentan-3-one affords trisubstituted diene **27** in 64% yield.^[7] The efficiency of this process, however, is generally dependent on the substitution of the starting α -chloroallyl sulfide.

Scheme 9 Synthesis of a 1,3-Diene by Bis(η -5-cyclopentadienyl)titanium(II)-Promoted Reaction of a Ketone with a α -Chloroallyl Sulfide^[7]

Section 46.3 covers two main alkene metathesis approaches to conjugated diene synthesis (Scheme 10). The first process involves treatment of an alkene 28 with a stoichiometric amount of alkyne 29 in the presence of an appropriate metal alkylidene metathesis catalyst to give a 1,3-diene 30. This process is termed "ene-yne" or "enyne" metathesis. The second transformation entails the metathesis between a conjugated diene 32 and an alkene 31 to give increased substitution on the resulting conjugated diene 30. The latter approach has been employed less frequently due to the difficulty in differentiating between the two C=C bonds present in diene 32, with the less substituted alkene moiety typically being less reactive.

Scheme 10 Synthesis of 1,3-Dienes by Alkene Metathesis

Two representative examples of enyne metathesis are shown in Scheme 11, which correspond to intramolecular and intermolecular applications of this powerful reaction. Ring-closing metathesis of enyne 33 using ruthenium catalyst 34 gives bicyclic diene 35 and represents a key step in the synthesis of the *Stemona* alkaloid stemoamide (see also Section 46.3.1.1).^[8] Successful intermolecular metathesis of alkyne 36 with terminal alkene 37 in the presence of first-generation Grubbs carbene complex 38 is also shown in Scheme 11 (see also Section 46.3.3.2).^[9] Generally, simple monosubstituted alkenes represent the best substrates for the enyne cross-metathesis reaction.

Scheme 11 Intramolecular and Intermolecular Enyne Metathesis for the Synthesis of 1,3-Dienes^[8,9]

Two examples of alkene –diene metathesis for the synthesis of 1,3-dienes are shown in **Scheme 12**. Macrocyclization of tetraene **39** in the presence of the first-generation Grubbs catalyst **38** gives macrocyclic 1,3-diene **40** en route to the natural product amphidinolide E (see Section **46.3.2**).^[10] The other transformation shown in this scheme corresponds to the cross alkene –diene metathesis between diene **41** and internal alkene **42**, in the presence of a more reactive catalyst **43**, to give diene product **44** in 72% yield (see Section **46.3.4**).^[11] The less substituted C=C bond of diene **41** is generally more reactive toward the catalyst, enabling chemoselective transformation to the desired product.

Scheme 12 Intramolecular and Intermolecular Alkene –Diene Metathesis for the Synthesis of 1,3-Dienes^[10,11]

The general aldol reaction produces β -hydroxy carbonyl compounds by the addition of a carbon-based nucleophile (typically an enolate or enol) to a carbonyl compound. Subsequent dehydration to form an α,β -unsaturated carbonyl compound can be achieved in the same flask or as a separate step. This transformation can offer a simple and efficient method for the assembly of a range of 1,3-diene structures (see Section 46.4). Three main reaction topologies are generally observed (Scheme 13). Diene 48 can be produced by reaction of an enolate 45 with an unsaturated carbonyl compound 46, followed by dehydration of the initially produced aldol adduct 47. Alternatively, diene 48 can be accessed from a vinylogous enolate 49 and carbonyl compound 50 via the intermediacy of alcohol 51, which readily dehydrates to give the 1,3-diene product. Since enolate 49 can exist in equilibrium with the tautomeric form 52, the aldol condensation with 50 can deliver the alternative product 53, which upon dehydration would give 2-acyl-substituted 1,3-diene 54.

Scheme 13 General Approaches to 1,3-Diene Synthesis Using the Aldol Reaction

An interesting example of the use of aldol condensations in the synthesis of an annulene is shown in **Scheme 14** (see also Section 46.4.1.1.1). Two sequential aldol condensations afford the requisite macrocyclization precursor **55**, which contains triene and diene units; subsequent oxidative alkyne coupling affords annulene **56**.^[12]

Scheme 14 Aldol Condensation Reactions in the Preparation of an Annulene^[12]

Scheme 15 depicts two additional examples highlighting the use of aldol condensation for assembly of 1,3-dienes. The α -functionalization of α,β -unsaturated carbonyl compounds represents an efficient entry into 1,3-dienes containing an electron-withdrawing group at the C1 position. This method is exemplified by the preparation of dienoic acid **57**. The assembly of the 1,3-diene is followed by subsequent hydrolysis of the ester group under acidic conditions (see Section **46.4.1.2.1**).^[13] Alternatively, α,β -unsaturated carbonyl compounds can be deprotonated with lithium diisopropylamide and condensed cleanly at the α -position with aldehydes to form α -hydroxy carbonyl compounds such as **59**.^[14] The use of hexamethylphosphoric triamide is generally required to enable regioselective functionalization at the α -position of enoate **58**. Subsequent elimination of the initially produced aldol adduct **59** is achieved by converting the alcohol into the corresponding methanesulfonate, followed by base-promoted elimination to give diene **60** (see Section **46.4.2.1.2**).

Scheme 15 Representative Syntheses of 1,3-Dienes by Aldol Condensations^[13,14]

Sections [46.5](#) and [46.6](#) are devoted to 1,3-diene synthesis using transition-metal catalysis. Such methods play an increasingly significant role in organic synthesis as they are highly chemoselective and are compatible with a variety of functional groups present in 1,3-diene precursors. Section [46.5](#) describes metal-catalyzed C—C bond forming reactions leading to 1,3-dienes starting from alkynes, diynes, or enynes. [Scheme 16](#) summarizes some of the main reaction types covered in this section, which include condensation of two alkynes [61](#) and [62](#) to give dienes [63](#) or [64](#), cycloisomerizations of enynes [65](#) or [66](#), or allenynes [67](#), to afford a range of substituted 1,3-dienes, and additions of 1,3-enynes [68](#) to electrophiles, such as aldehydes, to typically give 1,3-disubstituted dienes [69](#).

Scheme 16 Synthesis of 1,3-Dienes by Metal-Catalyzed C—C Bond Forming Reactions of Alkynes, Diynes, and Enynes

Several representative examples of such reactions are illustrated in **Scheme 17**. The first transformation shows the coupling of two molecules of alkyne **70**, promoted by zirconocene **71**, to give zirconacyclopentadiene **72**. This organometallic intermediate undergoes double nucleophilic substitution with dichloride **73** to afford cyclohexadiene **74** (see Section 46.5.2.1).^[15] The next example illustrates the use of platinum(II) catalysis to enable efficient cycloisomerization of enyne **75** to assemble cyclohexadiene **76** (see Section 46.5.2.3).^[16] An interesting migration of the terminal alkynyl substituent is observed during this process. Alternatively, treatment of allenyne **77** with a catalytic amount of dicarbonylchlororhodium(I) dimer results in facile cycloisomerization to give cross-conjugated triene **78** in 74% yield (see Section 46.5.4.2.3).^[17] The last example shown in **Scheme 17** illustrates the use of nickel-based catalysis, in the presence of chiral phosphine **80**, to enable efficient and chemoselective coupling of 1,3-enyne **79** with benzaldehyde to give 1,3-diene **81** as a result of an intramolecular C—C bond formation (see Section 46.5.1.1.2).^[18]

Scheme 17 Representative Metal-Catalyzed C—C Bond Forming Reactions^[15–18]

Section **46.6** is devoted to a large class of metal-catalyzed cross-coupling reactions. The main focus of the section is on palladium(0)-catalyzed processes for the assembly of a variety of synthetically useful 1,3-dienes structures. Several general reaction pathways covered in this part of the volume are shown in **Scheme 18**. Typically, the catalytic transformations begin with oxidative addition of an appropriate palladium(0) complex to an alkenyl halide **82**. The resulting palladium(II) complex **83** can undergo a variety of subsequent reactions, including transmetalation with **84**, followed by reductive elimination to give 1,3-diene **85**. Alternatively, palladium (II) intermediate **83** can undergo alkene or alkyne insertion, followed by reductive elimination or trapping with an electrophile to give 1,3-dienes **86** or **87**. A particularly powerful feature of palladium-catalyzed reactions is a wide functional group tolerance, which translates into high chemoselectivity of 1,3-diene synthesis in the presence of a variety of other functional moieties. Indeed, such methods have been employed widely in the area of complex molecule synthesis.

Scheme 18 Metal-Catalyzed Cross-Coupling Reactions for the Synthesis of 1,3-Dienes

Trisubstituted 1,3-diene units are found in a large number of natural products of biological and medicinal significance, including terpenoids, carotenoids, retinoids, and various other types of antibiotics and anticancer agents. **Scheme 19** shows a representative example of the use of palladium(0)-catalyzed cross coupling during the synthesis of reveromycin B (**91**).^[19] This process enables efficient union of the two complex synthetic fragments **88** and **89** to give the required diene **90** under mild reaction conditions and with high efficiency and complete diastereoselectivity (see Section **46.6.3.3**).

Scheme 19 Synthesis of a 1,2,4-Trisubstituted 1,3-Diene via Palladium-Catalyzed Alkenyl –Alkenyl Coupling in the Synthesis of Reveromycin B^[19]

The most commonly observed pericyclic reaction pathways leading to 1,3-dienes are depicted in **Scheme 20**. Such transformations are covered in detail in Section **46.7**. They include thermal electrocyclic ring opening of cyclobutenes **92**, thermal or photochemical electrocyclizations of hexatrienes **93**, tandem electrocyclic closures of octatetraenes **94** to the corresponding bicyclic dienes **95**, and [4 + 6] cycloadditions of dienes (e.g., **96**) with trienes (e.g., **97**) to give cyclic dienes (e.g., **98**). The diastereoselectivity of such reactions is governed by the rules of conservation of orbital symmetry, as well as the rotational preference (torquoselectivity).

Scheme 20 Synthesis of 1,3-Dienes by Electrocyclic or Cycloaddition Reactions

Bicyclo[4.2.0]oct-1(6)-ene **99** can be thermally ring opened to afford the corresponding 1,2-dimethylenecyclohexane **100** as the major product (**Scheme 21**). The stereochemistry of the product is determined by the torquoselectivity induced by the substituents on the cyclobutene moiety (see Section **46.7.1.5**).^[20] Heating heptatriene **101** to 60 °C promotes an efficient 6 π -electrocyclization into the corresponding cyclohexadiene **102** (see Section **46.7.3.1**).^[21] The thermal, conrotatory 8 π -electrocyclizations of decatetraenes **103** deliver cyclooctatrienes **104**. Subsequent disrotatory 6 π -electrocyclization affords bicyclic diene **105** (see Section **46.7.5**).^[22] A representative example of a [6 + 4] cycloaddition is also shown in **Scheme 21**, where the reaction between tropone and 2,5-dimethyl-3,4-diphenylcyclopentadienone provides the corresponding tricyclic cycloadduct **106** (see also Section **46.7.6.1**).^[23]

Scheme 21 Representative Pericyclic Reactions Leading to 1,3-Dienes^[20–23]

While electrocyclization and cycloaddition reactions provide important strategies for 1,3-diene synthesis, the reverse process, retrocycloaddition or cycloreversion, is equally valuable. Furthermore, such methods enable unique access to 1,3-dienes that would be difficult to obtain using other methods. Generally, the diene formation is accompanied by the cheletropic extrusion of a small molecule, with ethene, carbon monoxide, carbon dioxide, sulfur dioxide, or nitrogen being the most common. The four most commonly observed reaction pathways covered in Section 46.8 are shown in **Scheme 22**. They include extrusion of fragment X from either five-membered cyclic alkenes **107** or alkenes **109**, bearing a strained three-membered ring, to give dienes **108**. Alternatively, 1,3-dienes **111** can be assembled by extrusion of the X=Y moiety **112** from either the six-membered alkene **110** or the four-membered substrate **113**.

Scheme 22 General Reaction Pathways Leading to 1,3-Dienes by Extrusion

Two representative applications of such methods for efficient 1,3-diene synthesis are shown in **Scheme 23**. Thermolysis of 2,5-dihydrothiophene 1,1-dioxides efficiently affords 1,3-dienes. The use of microwaves is the most effective method for effecting the cheletropic extrusion of sulfur dioxide from 2,5-dihydrothiophene 1,1-

dioxide **114**, providing dienone **115** in 74% yield (see also Section **46.8.4.1.3**). Extrusion of maleic anhydride from adduct **116** affords the steroidal diene **117** (see also Section **46.8.1.3**).^[25]

Scheme 23 Synthesis of 1,3-Dienes by Extrusion of Sulfur Dioxide and Maleic Anhydride^[24,25]

The vast majority of methods used to prepare 1,3-dienes by elimination reactions fall into two basic categories shown in **Scheme 24**. The first group of transformations entails removal of one molecule of HX from the appropriate substrates **118**–**120** via a 1,2- or 1,4-elimination. Such transformations are generally promoted by the action of a base or an appropriate palladium(0) source in the presence of a base. The second category of reactions can be referred to as 1,2,3,4-eliminations as they entail the removal of two molecules of HX (or HY) from substrates **121** or **122**. Each of the two subclasses contains a broad variety of useful methods to afford 1,3-dienes, which are covered in detail in Section **46.9**

Scheme 24 General Elimination Pathways Leading to 1,3-Dienes

Three main reaction pathways that result in the formation of a 1,3-diene moiety by reduction of an appropriate unsaturated precursor are shown in **Scheme 25**. The first two methods are based on partial hydrogenation of an alkyne fragment in either enyne **123** or diyne **125** to give the corresponding dienes **124** and **126**, respectively. The partial hydrogenation (or semihydrogenation) of an alkyne to the corresponding alkene derivative is a challenging task, as overhydrogenation can easily occur, reducing the alkene moiety to the corresponding alkane. There are several catalysts available to perform this transformation, which is covered in detail in Section **46.10**. In addition to alkyne hydrogenation, partial reduction of aromatic hydrocarbons **127** can represent another practical approach for rapid assembly of the corresponding cyclic dienes **128**.

Scheme 25 Synthesis of 1,3-Dienes by Reduction: Three Main Pathways

Three examples of representative reductive protocols for the synthesis of 1,3-dienes are shown in **Scheme 26**. Despite its high catalytic activity, palladium on charcoal has been successfully used as the catalyst for hydrogenation of enynes to give the corresponding dienes. For example, the reduction of enyne **129** affords tetraene **130** (see also Section **46.10.1.1.4**) in 97% yield.^[26] Sequential hydroboration, followed by protonolysis of the resulting bis(alkenylborane) can serve as a useful alternative to hydrogenation of enynes. Indeed, treatment of diynes **131** with 2 equivalents of dicyclohexylborane, followed by addition of acetic acid gives the expected dienes **132** (see Section **46.10.2.2**).^[27,28] Finally, the Birch reduction of suitably functionalized arenes, followed by alkene isomerization is another valuable strategy to cyclohexa-1,3-dienes. For example, the Birch reduction of 4-butylbenzoic acid (**133**) affords cyclohexadiene **134** with excellent efficiency (see Section **46.10.3.1**).^[29]

Scheme 26 Representative Examples of 1,3-Diene Synthesis Using Reduction Methods^[26–29]

Section **46.11** is devoted to the isomerization of unconjugated dienes, alkynes, allenes, methylenecyclopropanes, and polyenes to the corresponding 1,3-dienes. Such transformations can be performed under basic, acidic, metallic, thermal, and photochemical conditions. The four main reaction topologies are shown in **Scheme 27**. Isomerization of unconjugated dienes **135** and **136** represents the most common way of accessing the corresponding 1,3-diene structures. Such transformations can be promoted by the action of appropriate base, acid, halogen, or metal catalyst. Allenes **137** represent another class of possible precursors to 1,3-dienes **138**. Alkynes **139** can also be efficiently isomerized to the corresponding dienes **140**. Most commonly, a range of transition-metal catalysts can be employed to accomplish this transformation. Methylenecyclopropanes **141** can also be efficiently converted into 1,3-dienes. Typically, the use of catalytic palladium in acetic acid produces 1-substituted or 1,1-disubstituted 1,3-dienes **142** as the sole products from the corresponding methylenecyclopropanes **141**. Unsymmetrical methylenecyclopropanes rearrange to the corresponding *E*-1,3-dienes with complete stereochemical control.

Scheme 27 Selected Isomerization Pathways Leading to 1,3-Dienes

Arenes and polyenes are direct precursors to 1,3-dienes, which can be obtained by functionalization of a single

double bond of the fully conjugated system. This apparently simple transformation, however, must proceed with high chemo-, regio-, and stereoselectivity. Section 46.12 describes known methods for conversion of a variety of arenes and polyenes into 1,3-dienes. Such reactions can be classified into the four basic classes shown in **Scheme 28**. The first series of transformations are based on dearomatization of arenes 143 via nucleophilic addition, followed by electrophilic trapping. Typically, an electron-withdrawing group must be present in the starting arene 143 in order for this reaction to proceed to give dienes 144. The second, large class of dearomatization methods is based on oxidation of substituted phenols 145 and subsequent trapping of the cationic intermediate with a nucleophile to produce dienones 146. In many cases, such dienones are highly reactive and must be intercepted with the next reagent in the same reaction flask. Another important area is enzymatic dihydroxylation of arenes 147 to produce the corresponding diols 148 containing a cyclohexa-1,3-diene fragment. Finally, linear trienes and longer polyenes can also serve as 1,3-diene precursors if one of the alkenes can be chemoselectively functionalized to deliver the desired product 149.

Scheme 28 Synthesis of 1,3-Dienes from Arenes and Polyenes

Two selected applications of arene-dearomatization protocols are shown in **Scheme 29**. Mild, hypervalent iodine (III) reagents such as (diacetoxyiodo)benzene are generally used for oxidation of a phenol substrate (e.g., 150). Bromination at the *para* position of the phenol ensures selective functionalization of the *ortho* position by trapping with a large excess of alcohol 151. The initially produced diene 152 undergoes a [4 + 2] cycloaddition upon heating to give tricyclic product 153 with good overall efficiency (see Section 46.12.7.2).^[30] Dihydroxylation of arenes can be efficiently performed by microbial cells. This remarkable transformation employs dioxygenases capable of using oxygen to generate a strong oxidizing agent linked to a mononuclear iron center, surrounded by

a chiral environment. This biocatalytic tool can incorporate both activated oxygen atoms onto the arene ring of benzoic acid to give dihydroxycyclohexadiene **154** with high diastereo- and enantioselectivity (see Section **46.12.19**).^[31]

Scheme 29 Selected Examples of Arene Dearomatization for 1,3-Diene Synthesis^[30,31]

The final section of the volume, Section **46.13**, is devoted to preparative methods for synthesis of 1,3-dienes that are based on functionalization of 1,3-diene–metal complexes. Indeed, metal complexation of dienes or polyenes drastically changes the reactivity of such unsaturated fragments enabling a range of new synthetic transformations; subsequent demetalation reveals a newly functionalized 1,3-diene moiety. The two main strategies are shown in **Scheme 30**. The first approach is based on transformations of tricarbonyl(1,3-diene)iron complexes **155**. A range of different reactions can be employed for functionalization of such compounds under both electrophilic and nucleophilic conditions. Demetalation of iron complexes **156** to give the free diene **157** can be readily accomplished under mild, oxidative conditions. The second strategy represents the double nucleophilic addition to (6-arene)manganese complexes **158**. The first nucleophilic addition provides a tricarbonyl(5-cyclohexadienyl)manganese complex (not shown). Following ligand exchange of carbonyl with nitrosyl, the addition of a second nucleophile readily occurs to give a stable (4-diene)manganese complex **159**, which can be demetalated using trimethylamine *N*-oxide or iron(III) chloride to generate *cis*-5,6-disubstituted cyclohexa-1,3-dienes **160**.

Scheme 30 Synthesis of 1,3-Dienes Using Metal-Diene Complexes

While many conceptually and preparatively diverse methods for the synthesis of 1,3-dienes have been developed

in the past, we anticipate that the arsenal of reactions for the assembly of conjugated dienes will continue to expand in the years to come due to the central importance of this class of compounds in organic synthesis and organometallic chemistry.

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Compounds with All-Carbon Functions

47

**Volume 47:
Alkenes**

de Meijere, A., in *Science of Synthesis*, **47** (2009), p.1

Alkenes are endowed with a C=C bond, and this constitutes the simplest, yet one of the most versatile functional groups in organic molecules. In terms of worldwide annual production by the petrochemical industry, the simple alkenes, namely ethene, propene, and the isomeric butenes, play the dominant role, and are building blocks for a vast number of chemical intermediates and final consumer products. In this volume of *Science of Synthesis* (consisting of two subvolumes, 47a and 47b), the various methods for the preparation of alkenes are discussed and evaluated. The focus is on purely hydrocarbon alkenes and cycloalkenes without any functional groups directly attached to the C=C bond; such functionalized compounds constitute other product classes that are covered in other volumes of *Science of Synthesis*, according to the organizational system employed in the series. However, some of the established methods that need to be covered here, at least briefly for systematic reasons, have mostly or even solely been used to prepare such functionally substituted examples, while alkenes with remote functional groups are also included here, with cross-references to other volumes of *Science of Synthesis* whenever necessary. Previously published reviews, book chapters, and books on any of the presented methods are referred to wherever applicable.

There is a stunningly great variety of methods to access alkenes from appropriately functionalized alkanes (see [Table 1](#) for a schematic listing). The first sections of this volume are devoted to the various carbonyl alkenation (olefination) reactions such as the Wittig reaction and related phosphorus-based alkenations (Section [47.1.1.1](#)), the Peterson alkenation (Section [47.1.1.2](#)), and the Julia and Julia –Kocienski alkenations as well as further related sulfur-based alkenations (Section [47.1.1.3](#)), which all have some mechanistic similarities. The more recently developed alkenations of carbonyl compounds with metal carbenes such as the Tebbe and Petasis reagents, as well as with *gem*-dimetallic species, are also in the same group of transformations (Section [47.1.1.4](#)), and so is the so-called McMurry coupling of (preferably) two identical carbonyl compounds (Section [47.1.1.5](#)). All of these methods have found a wide range of applications in the synthetic laboratory, and some have even been employed in industrial scale production. Alkene metathesis (Section [47.1.1.6](#)), on the other hand, had been used in the petrochemical industry for the conversion of simple alkenes into higher alkenes long before this methodology became applicable to more complex organic molecules with the advent of new classes of catalysts with wide functional-group tolerances. This development was initiated mainly by Grubbs and by Schrock and their coworkers, for which these two scientists shared the Nobel Prize in 2005. Other groups have joined in and made important contributions from the 1990s onwards.

The various transition-metal-catalyzed cross couplings (Section [47.1.2](#)) including the Mizoroki –Heck reaction, the S_N allylations of organometallic compounds, and -allyl substitutions, all of which were discovered in the 1960s and 1970s, some initially as stoichiometric reactions, now find a wide range of applications in research laboratories, and some have made their way into the production processes for fine chemicals in industry. The metal-catalyzed oligomerization of alkenes to higher alkenes, discussed in Section [47.1.2.4](#), has its importance only on the industrial scale.

Table 1 Schematic View of the Synthetic Routes to Alkenes Including Cycloalkenes, and the Corresponding Section in Volume 47

Method	Representative Reaction(s)	Section
Wittig and related phosphorus-based alkenations		47.1.1.1
Peterson alkenation		47.1.1.2
Julia, Julia –Kocienski, and related sulfur-based alkenations		47.1.1.3
alkenation with metal carbenes and related reactions		47.1.1.4
McMurry coupling and related reductive dimerization reactions		47.1.1.5
alkene metathesis		47.1.1.6
cross coupling and Heck reactions		47.1.2.1
S _N allylation of organometallic compounds		47.1.2.2
-allyl substitution		47.1.2.3
oligomerization of alkenes to higher alkenes		47.1.2.4
Diels –Alder reactions ([4 + 2] cycloadditions)		47.1.3.1
ene reactions		47.1.3.2
4 -electrocyclic reactions		47.1.3.3.1
Cope rearrangement		47.1.3.3.3

oxidative decarboxylation and decarbonylative elimination		47.1.4.1
oxidative decarboxylation of dicarboxylic acid derivatives		47.1.4.2
base- and otherwise catalyzed elimination from alkyl halides, methanesulfonates, toluenesulfonates, ethers, sulfides, ammonium salts, and sulfonium salts		47.1.4.3
acid-catalyzed dehydration of alcohols		47.1.4.4
pyrolytic elimination from esters, xanthates, phosphates, thiophosphates, sulfamates, amine <i>N</i> -oxides, ammonium hydroxides, phosphonium salts, and others		47.1.4.5

reductive elimination from α -halohydrins and their esters or ethers		47.1.4.6
reductive elimination from <i>gem</i> -dihalides		47.1.4.7
reductive extrusion from three- to six-membered heterocycles		47.1.4.8
reactions of (arylsulfonyl)hydrazones with strong bases (Bamford –Stevens and Shapiro reactions)		47.1.4.9
dehydrogenation of $\text{CH}_2\text{—CH}_2$ fragments		47.1.4.10
[2 + 2]-cycloaddition reactions		47.1.5.1

hydrogenation reactions (catalytic hydrogenation and chemical reduction)		47.1.5.2
elementometalation (including hydrometalation) and subsequent cross-coupling reactions		47.1.5.3
carbometalation and subsequent cross-coupling reactions		47.1.5.4
dissolving-metal (Birch-type) reduction of arenes		47.1.6.1
catalytic hydrogenation and chemical reduction of allenes		47.1.6.2
catalytic hydrogenation and chemical reduction (e.g., dissolving-metal reduction, hydrocarbonation by organometallic reagents, diimide reduction) of 1,3- and higher dienes		47.1.6.3,
		47.1.6.4
isomerization of alkenes		47.1.7
synthesis from other alkenes without isomerization (electrophilic and nucleophilic substitution)		47.1.8
syntheses of cyclopropenes		47.2.1

syntheses of nonconjugated di-, tri-, and oligoenes		47.3.1

^a Possible stereoisomers and/or regioisomers in products are not shown.

The classical Diels –Alder reaction, including its modern catalyzed versions, along with the so-called ene reactions and electrocyclic reactions make up Sections 47.1.3.1 –47.1.3.3. Among these, the Diels –Alder reaction has by far the widest application, as it is the simplest and most atom-economical way to prepare cyclohexene derivatives of any sort. Ene reactions have only a rather limited range of applicability, but the modern "metallo-ene" reactions {see, for example, *Science of Synthesis*, Vol. 36 [Alcohols (Section 36.2.3.1.4.5)]} are among the most versatile methods for the elegant construction of cyclic and oligocyclic skeletons.

Of course, elimination reactions constitute the largest arsenal of methods for the preparation of alkenes (Section 47.1.4). They range from eliminations of carbonyl or carboxy groups, the latter either without or along with the elimination of a second carboxy or a hydroxy group, via base- or acid-catalyzed or pyrolytic eliminations of HX (in which X can be any leaving group), to the reductive elimination of two vicinal or geminal leaving groups. Such eliminations can proceed regioselectively and some of them are even stereoselective. In particular, the reductive extrusions of oxygen, sulfur, and sulfur dioxide from oxiranes, thiiranes, and thiirane 1,1-dioxides (including in situ formed thiirane 1,1-dioxides in the so-called Ramberg –Bäcklund reaction), respectively, occur stereoselectively. This also holds for the reductive extrusion of sulfur and carbon dioxide or sulfur and carbon disulfide from dioxolane- and dithiolane-2-thiones, respectively. The mechanistically interesting Bamford –Stevens and Shapiro reactions, which occur upon treatment of ketone (arylsulfonyl) hydrazones with 1 and 2 equivalents, respectively, of an organometallic reagent (usually butyl- or methyllithium), complement the vast range of elimination reactions. The latter have most frequently been employed for the preparation of cyclic and oligocyclic alkenes.

Alkynes in general are more precious than alkenes, and they are frequently prepared from the latter. However, they also serve as valuable starting materials for alkenes by various addition reactions (Section 47.1.5). While [2 + 2]-cycloaddition reactions to furnish cyclobutenes have a rather limited range of applications, reductions by stereospecific catalytic hydrogenation and by chemical reduction are frequently employed to transform oligofunctional alkynes, which are more easily assembled than the correspondingly substituted alkenes, into the latter target compounds. Modern transition-metal-catalyzed elementometalations [including hydrometalation (Section 47.1.5.3) and carbometalation (Section 47.1.5.4)] especially, with or without subsequent cross coupling, have gained enormous importance since the 1980s for the access to a wide range of functionalized and nonfunctionalized alkenes, as well as conjugated and nonconjugated di-, tri-, and oligoenes.

Partial reductive removal of double bonds from cumulated and conjugated dienes, trienes, and arenes can also serve as an access to simpler alkenes and cycloalkenes (Section 47.1.6). Thus, the so-called Birch

reduction, i.e. the treatment of arenes with lithium metal in liquid ammonia (or the Benkeser version using lithium in a primary amine), provides convenient access to substituted cyclohexa-1,4-dienes and cyclohexenes. Catalytic hydrogenation as well as Birch-type reduction of allenes (1,2-dienes) occurs selectively at the least-substituted double bond, and 1,3-dienes formally undergo 1,4-addition of hydrogen under Birch reduction conditions; this can be performed in the presence of an additional nonconjugated double bond in the same molecule.

Isomerizations of alkenes (Section [47.1.7](#)) are only of industrial importance, with the exception of the isomerization of vinylcyclopropanes to cyclopentenes, which has gained ever increasing attention since its discovery around 1960 as a method to access five-membered carbocycles. Certain alkenes are most easily accessible by electrophilic or nucleophilic substitutions of appropriately activated (i.e., usually functionally substituted in the case of nucleophilic substitutions) alkenes without isomerizations (Section [47.1.8](#)).

Methods for the syntheses of cyclopropenes (Section [47.2](#)) and of nonconjugated di-, tri-, and oligoenes (Section [47.3](#)) are discussed in two separate sections, although most of the employed methods are basically the same as those discussed in various preceding sections.