



# **Comprehensive Organic Functional Group Transformations**



PERGAMON

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# Preface

Some years ago the three of us met in a London club reviewing an ongoing publishing venture in Organic Synthesis. The conversation drifted to a consideration of volumes on the synthesis of key functional groups. No doubt the good wine helped since we actually broached the idea of a work on the synthesis of *all* functional groups. Would it be useful? Definitely. Would it be feasible? How would it be organized? Where do you start? We recognized that functionality was based on the coordination and heteroatom attachment of a carbon atom. But putting together a complete framework seemed particularly daunting. Two of us became very interested in the fascinating bouquet of the Muscat de Beaumes de Venise.

At our next dinner together Alan announced that he had solved the problems posed last time—problems that Charles and I hoped he had forgotten! He brought out a remarkable matrix analysis of *all* functional groups, analysed rigorously and logically. Even unknown functions were covered. Although we were all very impressed, the practicalities of the idea still seemed daunting. Those who know Alan's terrier instincts will appreciate that he would not give up such a challenge so easily. Our twice yearly club get-togethers, occasionally with friends from Pergamon, refined our thinking. Alan's cosmic vision was tempered by Charles's intuitive realism and fully supported by the publishers.

Another major problem remained: how to reduce our thinking into a practical handbook for authors—a daunting task for three busy chemists. We settled on a seven-volume work and the indomitable ARK produced a rough breakdown to fit such a format. Putting flesh on these bones became feasible during a fortuitous three-month break between jobs by myself, and the largest handbook ever assembled by Pergamon (120 pages) was written and page allocations agreed—even for little or unknown functional groups. Sample chapters were commissioned and finally proved very encouraging, despite our first chosen topic uncovering virtually no known examples!

Contracts were defined and agreed, volume editors approached, and potential authors considered during a pleasant preconference stay in Grasmere. Following the sale of Pergamon to Elsevier Science Ltd there was a lull in the project but soon *Comprehensive Organic Functional Group Transformations* was back on track, and everyone adhered to a very businesslike timetable.

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# Contents of All Volumes

## Volume 1 Synthesis: Carbon with No Attached Heteroatoms

### (Part I Tetracoordinated Carbon with No Attached Heteroatoms)

- 1.01 One or More CH Bond(s) Formed by Substitution: Reduction of C–Halogen and C–Chalcogen Bonds
- 1.02 One or More CH Bond(s) Formed by Substitution: Reduction of Carbon–Nitrogen, –Phosphorus, –Arsenic, –Antimony, –Bismuth, –Carbon, –Boron, and –Metal Bonds
- 1.03 Two or More CH Bond(s) Formed by Addition to CC Multiple Bonds
- 1.04 One or More CC Bond(s) Formed by Substitution: Substitution of Halogen
- 1.05 One or More CC Bond(s) Formed by Substitution: Substitution of Chalcogen
- 1.06 One or More CC Bond(s) Formed by Substitution: Substitution of Carbon–Nitrogen, –Phosphorus, –Arsenic, –Antimony, –Boron, –Silicon, –Germanium, and –Metal Functions
- 1.07 One or More CC Bond(s) Formed by Addition: Addition of Carbon Electrophiles and Nucleophiles to CC Multiple Bonds
- 1.08 One or More CC Bond(s) Formed by Addition: Addition of Carbon Radicals and Electrocyclic Additions to CC Multiple Bonds
- 1.09 One or More CH and/or CC Bond(s) Formed by Rearrangement

### (Part II Tricoordinated Carbon with No Attached Heteroatoms)

- 1.10 One or More =CH Bond(s) Formed by Substitution or Addition
- 1.11 One or More =CC Bond(s) Formed by Substitution or Addition
- 1.12 One or More C=C Bond(s) Formed by Addition
- 1.13 One or More C=C Bond(s) by Elimination of Hydrogen, Carbon, Halogen, or Oxygen Functions
- 1.14 One or More C=C Bond(s) by Elimination of S, Se, Te, N, P, As, Sb, Bi, Si, Ge, B, or Metal Functions
- 1.15 One or More C=C Bond(s) Formed by Condensation: Condensation of Nonheteroatom Linked Functions, Halides, Chalcogen, or Nitrogen Functions
- 1.16 One or More C=C Bond(s) Formed by Condensation: Condensation of P, As, Sb, Bi, Si, Ge, B, or Metal Functions
- 1.17 One or More C=C Bond(s) by Pericyclic Processes
- 1.18 One or More =CH, =CC and/or C=C Bond(s) Formed by Rearrangement
- 1.19 Tricoordinate Anions, Cations, and Radicals

### (Part III Dicoordinate and Monocoordinate Carbon with No Attached Heteroatoms)

- 1.20 Allenes and Cumulenes
- 1.21 Alkynes
- 1.22 Ions, Radicals, Carbenes and Other Monocoordinated Systems

## Volume 2 Synthesis: Carbon with One Heteroatom Attached by a Single Bond

### (Part I Functions Linked by a Single Bond to an $sp^3$ Carbon Atom)

- 2.01 Alkyl Halides
- 2.02 Alkyl Chalcogenides: Oxygen-based Functional Groups
- 2.03 Alkyl Chalcogenides: Sulfur-based Functional Groups
- 2.04 Alkyl Chalcogenides: Selenium- and Tellurium-based Functional Groups
- 2.05 Alkylnitrogen Compounds: Amines and Their Salts
- 2.06 Alkylnitrogen Compounds: Compounds with N–Halogen, N–O, N–S, N–Se, and N–Te Functional Groups
- 2.07 Alkylnitrogen Compounds: Compounds with N–N, N–P, N–As, N–Sb, N–Bi, N–Si, N–Ge, N–B, and N–Metal Functional Groups

- 2.08 Alkylphosphorus Compounds
- 2.09 Alkylarsenic, -antimony, and -bismuth Compounds
- 2.10 Alkylboron and -silicon Compounds
- 2.11 Alkyl Metals

(Part II Functions Linked by a Single Bond to an  $sp^2$  Carbon Atom)

- 2.12 Vinyl and Aryl Halides
- 2.13 Alkenyl and Aryl Chalcogenides: Oxygen-based Functional Groups
- 2.14 Vinyl and Aryl Chalcogenides: Sulfur-, Selenium-, and Tellurium-based Functional Groups
- 2.15 Vinyl- and Arylnitrogen Compounds
- 2.16 Vinyl- and Arylphosphorus Derivatives
- 2.17 Vinyl- and Alkylarsenic, -antimony, and -bismuth Compounds
- 2.18 Vinyl- and Arylsilicon, -germanium, and boron Compounds
- 2.19 Vinyl- and Arylmetals
- 2.20 Stabilized Substituted Ions and Radicals Bearing One Heteroatom ( $R^1R^2C^+X$ ,  $R^1R^2C^-X$ ,  $R^1R^2C\cdot X$ )

(Part III Functions Linked by a Single Bond to an  $sp$  Carbon Atom)

- 2.21 Alkynyl Halides and Chalcogenides
- 2.22 Alkynylnitrogen and -phosphorus Compounds
- 2.23 Alkynylarsenic, -antimony, -bismuth, -boron, -silicon, -germanium, and -metal Compounds

**Volume 3 Synthesis: Carbon with One Heteroatom Attached by a Multiple Bond**

(Part I Tricoordinated Carbon Functions,  $R_2C=Y$ )

- 3.01 Aldehydes: Alkyl Aldehydes
- 3.02 Aldehydes:  $\alpha,\beta$ -Unsaturated Aldehydes
- 3.03 Aldehydes: Aryl and Heteroaryl Aldehydes
- 3.04 Ketones: Dialkyl Ketones
- 3.05 Ketones:  $\alpha,\beta$ -Unsaturated Ketones
- 3.06 Ketones Bearing an  $\alpha,\beta$ -Aryl or -Heteroaryl Substituent
- 3.07 Aldehyde and Ketone Functions Further Substituted on Oxygen
- 3.08 Thioaldehydes and Thioketones
- 3.09 Seleno- and Telluroaldehydes and -ketones
- 3.10 Imines and Their  $N$ -Substituted Derivatives:  $NH$ ,  $NR$ , and  $N$ -Haloimines
- 3.11 Imines and Their  $N$ -Substituted Derivatives: Oximes and Their  $O$ - $R$  Substituted Analogues
- 3.12 Imines and Their  $N$ -Substituted Derivatives: Hydrazones and Other  $=NN$  Derivatives Including Diazo Compounds
- 3.13 Synthesis of P, As, Sb and Bi Ylides ( $R_3P=CR_2$ , etc.)
- 3.14 Doubly Bonded Metalloid Functions (Si, Ge, B)
- 3.15 Doubly Bonded Metal Functions

(Part II Dicoordinated Carbon Functions,  $R_2C=C=Y$ )

- 3.16 Ketenes, Their Cumulene Analogues and Their S, Se, and Te Analogues
- 3.17 Ketenimines and Their P, As, Sb and Bi Analogues

(Part III Dicoordinated Carbon Functions,  $R-C\equiv Z$ )

- 3.18 Nitriles: General Methods and Aliphatic Nitriles
- 3.19  $\alpha,\beta$ -Unsaturated and Aryl Nitriles
- 3.20  $N$ -Substituted Nitriles and Other Heteroanalogues of Nitriles of the Type  $RCZ$

(Part IV Monocoordinated Carbon Functions)

- 3.21 Isocyanides and Their Heteroanalogues ( $RZC$ )

**Volume 4 Synthesis: Carbon with Two Heteroatoms, Each Attached by a Single Bond**

(Part I Tetracoordinated Carbon Functions Bearing Two Heteroatoms,  $R_2CXX'$ )

- 4.01 Dihalo Alkanes,  $R^1_2C(Hal)_2$
- 4.02 Functions Incorporating a Halogen and a Chalcogen
- 4.03 Functions Incorporating a Halogen and Another Heteroatom Group Other than a Chalcogen
- 4.04 Functions Bearing Two Oxygens,  $R^1_2C(OR^2)_2$



- 4.05 Functions Incorporating Oxygen and Another Chalcogen
- 4.06 Functions Incorporating Two Chalcogens Other than Oxygen
- 4.07 Functions Incorporating a Chalcogen and a Group 15 Element
- 4.08 Functions Incorporating a Chalcogen and a Silicon, Germanium, Boron, or Metal
- 4.09 Functions Bearing Two Nitrogens
- 4.10 Functions Incorporating a Nitrogen and Another Group 15 Element
- 4.11 Functions Incorporating a Nitrogen and a Silicon, Germanium, Boron, or a Metal
- 4.12 Functions Containing One Phosphorus and Either Another Phosphorus or As, Sb, Bi, Si, Ge, B, or a Metal
- 4.13 Functions Containing at Least One As, Sb, or Bi with or without a Metalloid (Si or Ge) or a Metal
- 4.14 Functions Containing at Least One Metalloid (Si, Ge, or B) Together with Another Metalloid or Metal
- 4.15 Functions Containing Two Atoms of the Same Metallic Element
- 4.16 Functions Containing Two Atoms of Different Metallic Elements

(Part II Tricoordinated Carbon Functions Bearing Two Heteroatoms,  $R_2C=CXX'$ )

- 4.17 Functions Incorporating Two Halogens or a Halogen and a Chalcogen
- 4.18 Functions Incorporating a Halogen or Another Group Other than a Halogen or a Chalcogen
- 4.19 Functions Bearing Two Chalcogens
- 4.20 Functions Containing a Chalcogen and Any Group Other than a Halogen or a Chalcogen
- 4.21 Functions Containing at Least One Nitrogen and No Halogen or Chalcogen
- 4.22 Functions Containing at Least One Phosphorus, Arsenic, Antimony or Bismuth and No Halogen, Chalcogen or Nitrogen
- 4.23 Functions Containing at Least One Metalloid (Si, Ge, or B) and No Halogen, Chalcogen or Group 15 Element; Also Functions Containing Two Metals

(Part III)

- 4.24 Tri- and Dicoordinated Ions, Radicals and Carbenes Bearing Two Heteroatoms ( $RC^+X^1X^2$ ,  $RC^-X^1X^2$ ,  $RC^{\cdot}X^1X^2$ ,  $:CX^1X^2$ )

**Volume 5 Synthesis: Carbon with Two Attached Heteroatoms with at Least One Carbon-to-Heteroatom Multiple Link**

(Part I Tricoordinate Carbon Functions with One Doubly Bonded and One Singly Bonded Heteroatom,  $RC=YX$ )

- 5.01 Acyl Halides
- 5.02 Carboxylic Acids
- 5.03 Carboxylic Esters and Lactones
- 5.04 Other Acyloxy Compounds
- 5.05 Acylsulfur, -selenium, or -tellurium Functions
- 5.06 Amides
- 5.07 *N*-Heterosubstituted Amides
- 5.08 Acylphosphorus, -arsenic, -antimony, or -bismuth Functions
- 5.09 Acylsilicon, -germanium, or -boron Functions
- 5.10 Acyl Metal Functions
- 5.11 Thio-, Seleno-, and Telluroacyl Halides
- 5.12 Thio, Seleno, and Telluro Acyloxy Functions,  $R^1C(S)OR^2$ ,  $R^1C(Se)OR^2$ ,  $R^1C(Te)OR^2$ , etc
- 5.13 Functions with Two Chalcogens Other Than Oxygen
- 5.14 Thionoamides and Their Se and Te Analogues
- 5.15 *N*-Substituted Thionoamides and Their Se and Te Analogues
- 5.16 Thioacyl Functions linked to a Metalloid (Si, Ge, or B) or Metal; and Their Seleno and Telluro Analogues
- 5.17 Iminoacyl Halides and Oxy Functions
- 5.18 Iminoacyl Functions Linked to Chalcogens Other Than Oxygen
- 5.19 Amidines and *N*-Substituted Amidines
- 5.20 Iminoacyl Functions Linked to Any Heteroatom Other Than Halogen, Chalcogen or Nitrogen
- 5.21 *N*-Heterosubstituted Iminoacyl Functions
- 5.22 Diazo Functions with an  $\alpha$ -Heteroatom ( $RC(X)N_2$ )

- 5.23 Phosphoacyl Functions and Their As, Sb, and Bi Analogues
- 5.24 Doubly Bonded Metalloid Functions,  $R^1C(X)=SiR^2_2$ ,  $R^1C(X)=BR^2$ ,  $R^1C(X)=GeR^2_2$
- 5.25 Functions Doubly Bonded to a Metal

(Part II Dicoordinate Carbon Functions with Two Doubly Bonded Heteroatoms,  $Y=C=Y'$ )

- 5.26 Functions with at Least One Oxygen,  $Y=C=O$
- 5.27 Functions with at Least One Chalcogen Other Than Oxygen
- 5.28 Functions with at Least One Nitrogen and No Chalcogens
- 5.29 Functions with Heteroatoms Other Than Chalcogen or Nitrogen ( $Y=C=Y'$ )

(Part III Dicoordinate Carbon Functions with One Singly Bonded and One Triply Bonded Heteroatom,  $X-C\equiv Z$ )

- 5.30 Nitriles with a Heteroatom Attached to the Cyanocarbon
- 5.31 Triply Bonded Heteroatom Derivatives Other Than Nitriles with Another Heteroatom Attached to the *sp*-Carbon Atom

## Volume 6 Synthesis: Carbon with Three or Four Attached Heteroatoms

(Part I Tetracoordinated Carbon with Three Attached Heteroatoms,  $RCXX'X''$ )

- 6.01 Trihalides
- 6.02 Functions Containing Halogens and Any Other Elements
- 6.03 Functions Containing Three Chalcogens (and No Halogens)
- 6.04 Functions Containing a Chalcogen and Any Other Heteroatoms Other Than a Halogen
- 6.05 Functions Containing at Least One Group 15 Element (and No Halogen or Chalcogen)
- 6.06 Functions Containing at Least One Metalloid (Si, Ge, or B) and No Halogen, Chalcogen, or Group 15 Element; Also Functions Containing Three Metals

(Part II Tetracoordinated Carbon with Four Attached Heteroatoms,  $CXX'X''X'''$ )

- 6.07 Functions Containing Four Halogens or Three Halogens and One Other Heteroatom Substituent
- 6.08 Functions Containing Two Halogens and Two Other Heteroatom Substituents
- 6.09 Functions Containing One Halogen and Three Other Heteroatom Substituents
- 6.10 Functions Containing Four or Three Chalcogens (and No Halogens)
- 6.11 Functions Containing Two or One Chalcogens (and No Halogens)
- 6.12 Functions Containing at Least One Group 15 Element (and No Halogen or Chalcogen)
- 6.13 Functions Containing at Least One Metalloid (Si, Ge, or B) and No Halogen, Chalcogen, or Group 15 Element; Also Functions Containing Four Metals

(Part III Tricoordinated Carbon with Three Attached Heteroatoms,  $Y=CXX'$ )

- 6.14 Functions Containing a Carbonyl Group and at Least One Halogen
- 6.15 Functions Containing a Carbonyl Group and at Least One Chalcogen (but No Halogen)
- 6.16 Functions Containing a Carbonyl Group and Two Heteroatoms Other Than a Halogen or Chalcogen
- 6.17 Functions Containing a Thiocarbonyl Group and at Least One Halogen; Also at Least One Chalcogen and No Halogen
- 6.18 Functions Containing a Thiocarbonyl Group Bearing Two Heteroatoms Other Than a Halogen or Chalcogen
- 6.19 Functions Containing a Selenocarbonyl or Tellurocarbonyl Group— $Se(X)X'$  and  $TeC(X)X'$
- 6.20 Functions Containing an Iminocarbonyl Group and at Least One Halogen; Also One Chalcogen and No Halogen
- 6.21 Functions Containing an Iminocarbonyl Group and Any Elements Other Than a Halogen or Chalcogen
- 6.22 Functions Containing Doubly Bonded P, As, Sb, Bi, Si, Ge, B, or a Metal

(Part IV)

- 6.23 Tricoordinated Stabilized Cations and Radicals,  $^+CXYZ$  and  $\cdot CXYZ$

## Volume 7 Indexes

Author Index  
Cumulative Subject Index

In addition to the general principles, Volume 1 is further organized as follows:

1. By the type of bond formed (i.e. C—H before C—C).
2. By the type of reaction involved (i.e. substitution, then addition, then rearrangement). With C=C bond formation the order is addition, elimination, condensation, then electrocyclic and other methods. One rearrangement chapter only is devoted to each of the Parts I and II.
3. In Parts II and III the treatment of formation of ions, radicals, and carbenes is added at the end of the section dealing solely with those species with a significant rather than a transient lifetime.

In Volume 1, the heteroatom sequence is a secondary feature since only remote heteroatom functions are involved in the products; but the standard order pertains in reactants that contain heteroatoms (see, e.g. Chapters 1.01 and 1.02).

All the major structural influences that are treated throughout this work apply equally (or perhaps more importantly) in Volume 1. Thus the effects of conjugation, remote substituents, rings, stereochemistry, strain, kinetic or thermodynamic factors, solvation, primary, secondary and tertiary nature, etc., are mentioned whenever relevant.

## VOLUME 2 SYNTHESIS: CARBON WITH ONE HETEROATOM ATTACHED BY A SINGLE BOND

Volume 2 is arranged in three parts: I, II and III, dealing respectively with  $sp^3$ ,  $sp^2$ , and  $sp$  carbon linked to the heteroatom. In each chapter we have endeavored to explain important effects due to such features as the primary, secondary, tertiary nature, ring effects, strain activation, effect of beta, gamma, and more remote functionality, stereochemical effects, and so on. Methods that are common to a larger group are dealt with at their first appearance and suitably cross-referenced.

Volumes 2–6 all deal with the synthesis of functions involving at least one heteroatom. To avoid major overlap we have applied the Latest Placement Principle; that is, the chemistry is discussed at the last possible position based on the prioritization of the carbon attached to the heteroatom. Thus the compound  $\text{CH}_3\text{ONH}_2$  is treated under "Alkyl Chalcogenides" in the subsection "Functions Based on the RON-Unit" (i.e. 2.02.6). However,  $\text{CH}_3\text{ONHCH}_3$  appears under "Alkyl Nitrogen Compounds" (2.06.2.3) since the Latest Placement Principle prevails. Also, dialkyl ethers appear in Part I of Volume 2 (Functions Linked by a Single Bond to an  $sp^3$  Carbon Atom), while alkyl aryl ethers appear in Part II of Volume 2 (Functions Linked by a Single Bond to an  $sp^2$  Carbon Atom). Exceptions to the rule are:

- (a) When a fully unsaturated heterocyclic substituent (e.g. thienyl, pyridyl, etc.) is used as an example of an aryl group, the ring heteroatom(s) is (are) not taken into account (e.g. 2-methoxypyridine should strictly appear in Volume 6, but is covered in Volume 2 along with 3- and 4-methoxypyridine).
- (b) Carbon-based metal ligands that are incidental to the synthesis under discussion (e.g. carbonyls, cyclopentadienyls, etc.) are not taken into consideration.

## VOLUME 3 SYNTHESIS: CARBON WITH ONE HETEROATOM ATTACHED BY A MULTIPLE BOND

Volume 3 follows the logical development indicated in Volume 2. Thus, according to the Last Placement Principle, the imines,  $\text{RCH}=\text{N}-\text{R}$ , appear in Volume 3 rather than in Volume 2 (where functions singly bonded to carbon are treated). Furthermore, acetophenone,  $\text{PhCOCH}_3$ , is treated under  $\alpha,\beta$ -unsaturated ketones (3.05) rather than saturated ketones (3.04). Chloronitroacrylonitriles would appear under the section " $\alpha,\beta$ -Vinyl Nitriles with Nitrogen-based Substituents" (3.19.2.7), not under the related earlier section dealing with halo-substituents (3.19.2.3).

## VOLUME 4 SYNTHESIS: CARBON WITH TWO HETEROATOMS, EACH ATTACHED BY A SINGLE BOND

Volume 4 is in three parts. Part I deals with tetracoordinated carbon bearing two heteroatoms, Part II with tricoordinated carbon bearing two heteroatoms, and Part III (a brief chapter) with stabilized radicals, ions, and the like bearing two heteroatoms. The material is arranged according

to the Latest Placement Principle: thus, the synthesis of  $\text{CHBr}_2\text{CHI}_2$  would appear in the section dealing with diiodo, not dibromo functions (i.e. in 4.01.5, not 4.01.4), and the synthesis of  $\text{CF}_3\text{CHBrCl}$  is discussed in Volume 6 (carbons bearing three heteroatoms), rather than in Volume 4.

## VOLUME 5 SYNTHESIS: CARBON WITH TWO ATTACHED HETEROATOMS WITH AT LEAST ONE CARBON-TO-HETEROATOM MULTIPLE BOND

Volume 5 is in three parts. Part I deals with functions with one doubly bonded and one singly bonded heteroatom, Part II with functions containing two doubly bonded heteroatoms and Part III with one triply bonded and one singly bonded heteroatom. Part I constitutes the bulk of Volume 5.

The arrangement of the chemistry in each part follows the same logical sequence. The multiply bonded heteroatom is focused on first and then the other heteroatom in a secondary classification, both following the priority rules already described. Each section excludes the coverage of the previous sections. Thus, all carbonyl derivatives will appear in Chapters 5.01–5.10 but not in Chapters 5.11, *et seq.*

According to the Latest Placement Principle structure  $\text{RC(O)OC(S)R}$  is discussed in the chapter dealing with carbons bearing a doubly bonded sulfur and singly bonded oxygen (5.12.3), *not* in that dealing with doubly and singly bonded oxygen (5.04.1). Another effect of the Latest Placement Principle is that the amides  $\text{RCONMePh}$  are discussed under *N*-arylalkanoamides (5.06.2.4), rather than *N*-alkylalkanoamides (5.06.2.2). Again, exceptions are made to the latest placement rules for: (a) hetaryl rings used as examples of aryl substituents which are not viewed as functional groups. Thus, 2-methylimidazole is not considered as an example of an amidine function and 2-methoxypyridine is not an example of a doubly bonded nitrogen, singly bonded oxygen function; (b) metal ligands that are incidental to the organic chemistry under discussion are not viewed as functions in priority considerations.

## VOLUME 6 SYNTHESIS: CARBON WITH THREE OR FOUR ATTACHED HETEROATOMS

Volume 6 is in four parts. Part I deals with tetracoordinate carbons bearing three heteroatoms. Part II covers tetracoordinate compounds bearing four heteroatoms, i.e. substituted methanes, and Part III deals with tricoordinate systems bearing three heteroatoms, i.e. where one heteroatom is attached by a double bond. Part IV is brief and deals with stabilized radicals and ions. Not surprisingly, the coverage of Volume 6 is very large—and also shows that many gaps in the development of organic chemistry still exist.

The organization within the three sections not only follows the same broad logic developed in the previous volumes, but also has a structure unique to the multiheteroatom volume. According to the Latest Placement Principle  $\text{CF}_3\text{C}(\text{NR}_2)_3$  appears in the section dealing with carbons bearing three nitrogens (6.05.1.1), not that dealing with carbons bearing three halogens (6.01.2), while  $(\text{CF}_3\text{CH}_2\text{O})_2\text{CO}$  appears in Part III, not in Part I.

In the chapter dealing with iminocarbonyl functions in Part III, the substituents on nitrogen are discussed in each appropriate subsection in the order outlined above. Thus, the  $\text{RN}=\text{}$  group would be first considered with  $\text{R} = \text{H}$ , then alkyl, alkenyl, aryl and hetaryl, alkynyl and then heteroatom substituents in the usual order.

In each relevant section, we have endeavored to explain the influence of important secondary effects on the synthesis such as structure (primary, secondary, etc.), ring effects, strain, activation, stereochemistry, remote substituent effects, etc.

The arrangement of the chemistry in each of Parts I–III follows a similar pattern. Thus, each section commences with functions containing at least one halogen. This section deals with all combinations of halogen with other heteroatoms in the described order. The next section deals with functions containing at least one chalcogen in combination with any other heteroatoms except halogens. Subsequent sections each exclude the previous title heteroatom functions.

## VOLUME 7 INDEXES

Subject Indexes are included in each of Volumes 1–6 and Cumulative Subject and Author Indexes appear in Volume 7. Most entries in the Subject Index consist of two or three lines: the first line is the entry itself (e.g. Lactones) and the second line is descriptive of that entry (e.g. reduction); in many cases more detail is given (e.g. with 9-BBN).

## REFERENCES

The references are handled by the system previously used successfully in *Comprehensive Heterocyclic Chemistry*. In this system reference numbers appear neither in the text, nor as footnotes, nor at the end of chapters. Instead, each time a reference is cited in the text there appears (in parentheses) a two-letter code assigned to the journal being cited, which is preceded by the year (tens and units only for twentieth-century references) and followed by the page number. For example: "It was shown <80TL1327> that . . .". In this phrase, "80" refers to 1980, "TL" to *Tetrahedron Letters*, and "1327" to the page number. For those journals which are published in parts, or which have more than one volume number per year, the appropriate part of the volume is indicated, e.g. as in <73JCS(P2)1594> or <78JOM(162)611>, where the first example refers to *J. Chem. Soc., Perkin Trans 2*, 1973, page 1594, and the second to *J. Organomet. Chem.*, 1978, volume 162, page 611.

This reference system is adopted because it is far more useful to the reader than the conventional "superscript number" system. It enables readers to go directly to the literature reference cited, without first having to consult the bibliography at the end of each chapter.

References to the last century quote the year in full. Books have a prefix "B-" and if they are commonly quoted (e.g. *Organic Reactions*) they will have a code. Otherwise, as with uncommon journals, they are given a miscellaneous code (MI) and numbered arbitrarily *abb1*, *abb2*, etc., where *abb* refers to the volume and chapter number and 1, 2, etc., are assigned sequentially. Patents are assigned appropriate three-letter codes.

The references are given in full at the end of each volume. They include *Chemical Abstract* references when these are likely to help; in particular, they are given for all patents, and for less accessible sources such as journals in languages other than English, French, or German, company reports, obscure books, and theses.

# Contents

Preface	vii
Contributors to Volume 1	ix
Contents of All Volumes	xi
Introduction	xv
1.01 One or More CH Bond(s) Formed by Substitution: Reduction of C–Halogen and C–Chalcogen Bonds	1
A. G. SUTHERLAND, <i>University of North London, UK</i>	
1.02 One or More CH Bond(s) Formed by Substitution: Reduction of Carbon–Nitrogen, –Phosphorus, –Arsenic, –Antimony, –Bismuth, –Carbon, –Silicon, –Germanium, –Boron and –Metal Bonds	27
J. HOWARTH, <i>Dublin City University, Republic of Ireland</i>	
1.03 Two or More CH Bond(s) Formed by Addition to CC Multiple Bonds	71
K. JONES, <i>King's College, London, UK</i>	
1.04 One or More CC Bond(s) Formed by Substitution: Substitution of Halogen	105
G. L. EDWARDS, <i>The University of New South Wales, Sydney, NSW, Australia</i>	
1.05 One or More CC Bond(s) Formed by Substitution: Substitution of Chalcogen	171
T. N. BIRKINSHAW, <i>Astra Charnwood, Loughborough, UK</i>	
1.06 One or More CC Bond(s) Formed by Substitution: Substitution of Carbon–Nitrogen, –Phosphorus, –Arsenic, –Antimony, –Boron, –Silicon, –Germanium and –Metal Functions	249
P. C. B. PAGE, H. L. MCFARLAND and A. P. MILLAR, <i>University of Liverpool, UK</i>	
1.07 One or More CC Bond(s) Formed by Addition: Addition of Carbon Electrophiles and Nucleophiles to CC Multiple Bonds	293
A. ARMSTRONG, <i>University of Bath, UK</i>	
1.08 One or More CC Bond(s) Formed by Addition: Addition of Carbon Radicals and Electrocyclic Additions to CC Multiple Bonds	319
A. J. CLARK and P. C. TAYLOR, <i>University of Warwick, Coventry, UK</i>	
1.09 One or More CH and/or CC Bond(s) Formed by Rearrangement	377
I. COLDHAM, <i>University of Exeter, UK</i>	
1.10 One or More =CH Bond(s) Formed by Substitution or Addition	425
M. A. HAYES, <i>Xenova Group, Slough, UK</i>	
1.11 One or More =CC Bond(s) Formed by Substitution or Addition	461
P. G. STEEL, <i>University of Durham, UK</i>	
1.12 One or More C=C Bond(s) Formed by Addition	501
A. C. REGAN, <i>University of Manchester, UK</i>	
1.13 One or More C=C Bond(s) by Elimination of Hydrogen, Carbon, Halogen or Oxygen Functions	553
J. M. PERCY, <i>University of Birmingham, UK</i>	
1.14 One or More C=C Bond(s) by Elimination of S, Se, Te, N, P, As, Sb, Bi, Si, Ge, B or Metal Functions	589
A. R. MAGUIRE, <i>University College Cork, Republic of Ireland</i>	
1.15 One or More C=C Bond(s) Formed by Condensation: Condensation of Non-heteroatom Linked Functions, Halides, Chalcogen or Nitrogen Functions	673
C. M. RAYNER, <i>University of Leeds, UK</i>	

1.16	One or More C=C Bond(s) Formed by Condensation: Condensation of P, As, Sb, Bi, Si, or Metal Functions I. GOSNEY, <i>University of Edinburgh, UK</i> , and D. LLOYD, <i>University of St. Andrews, UK</i>	719
1.17	One or More C=C Bond(s) by Pericyclic Processes H. MCNABB, <i>University of Edinburgh, UK</i>	771
1.18	One or More =CH, =CC and /or C=C Bond(s) Formed by Rearrangement P. J. MURPHY, <i>University of North Wales, Bangor, UK</i>	793
1.19	Tricoordinate Anions, Cations and Radicals J. O. WILLIAMS, <i>University of Exeter and White Knight Chemicals Ltd., Paignton, UK</i> , and M. J. KELLY, <i>University of Exeter, UK</i>	843
1.20	Allenes and Cumulenes C. BRUNEAU and P. H. DIXNEUF, <i>Université de Rennes 1, France</i>	953
1.21	Alkynes M. FURBER, <i>Astra Charnwood, Loughborough, UK</i>	997
1.22	Ions, Radicals, Carbenes and Other Monocoordinated Systems J. M. DICKINSON, <i>Manchester Metropolitan University, UK</i>	1087
	References	1147
	Subject Index	1317

# 1.01

## One or More CH Bond(s) Formed by Substitution: Reduction of C—Halogen and C—Chalcogen Bonds

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1.01.1	REDUCTION OF C—HALOGEN BONDS TO CH	1
1.01.1.1	<i>General Methods</i>	1
1.01.1.2	<i>Reduction of Fluoroalkanes</i>	6
1.01.1.3	<i>Reduction of Chloroalkanes</i>	6
1.01.1.4	<i>Reduction of Bromoalkanes</i>	8
1.01.1.5	<i>Reduction of Iodoalkanes</i>	10
1.01.1.6	<i>Reduction of Hypervalent Haloalkanes</i>	11
1.01.2	REDUCTION OF C—OXYGEN BONDS TO CH	11
1.01.2.1	<i>General Methods</i>	11
1.01.2.2	<i>Reduction of C—OX Bonds</i>	12
1.01.2.2.1	<i>Reduction of C—OH bonds</i>	12
1.01.2.2.2	<i>Reduction of C—O—C bonds</i>	13
1.01.2.2.3	<i>Reduction of C—O—heteroatom bonds</i>	17
1.01.2.3	<i>Reduction of C=O Bonds to CH<sub>2</sub></i>	18
1.01.2.3.1	<i>Reduction of aldehydes</i>	18
1.01.2.3.2	<i>Reduction of ketones</i>	18
1.01.2.4	<i>Reduction of (C=O)X to CH<sub>3</sub></i>	20
1.01.2.5	<i>Reduction of C(OX)<sub>n</sub> Systems</i>	21
1.01.3	REDUCTION OF C—SULFUR, C—SELENIUM AND C—TELLURIUM BONDS TO CH	21
1.01.3.1	<i>General Methods</i>	21
1.01.3.2	<i>Reduction of C—SX Bonds</i>	21
1.01.3.3	<i>Reduction of C=S to CH<sub>2</sub></i>	24
1.01.3.4	<i>Reduction of C(=S)X to CH<sub>3</sub></i>	24
1.01.3.5	<i>Reduction of C(SX)<sub>n</sub> Systems</i>	24
1.01.3.6	<i>Reduction of C—Se Systems</i>	25
1.01.3.7	<i>Reduction of C—Te Systems</i>	25

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### 1.01.1 REDUCTION OF C—HALOGEN BONDS TO CH

#### 1.01.1.1 General Methods

A large majority of the methods available for the reduction of alkyl halides to the corresponding alkanes, often referred to as the process of hydrogenolysis in earlier works, can be loosely grouped



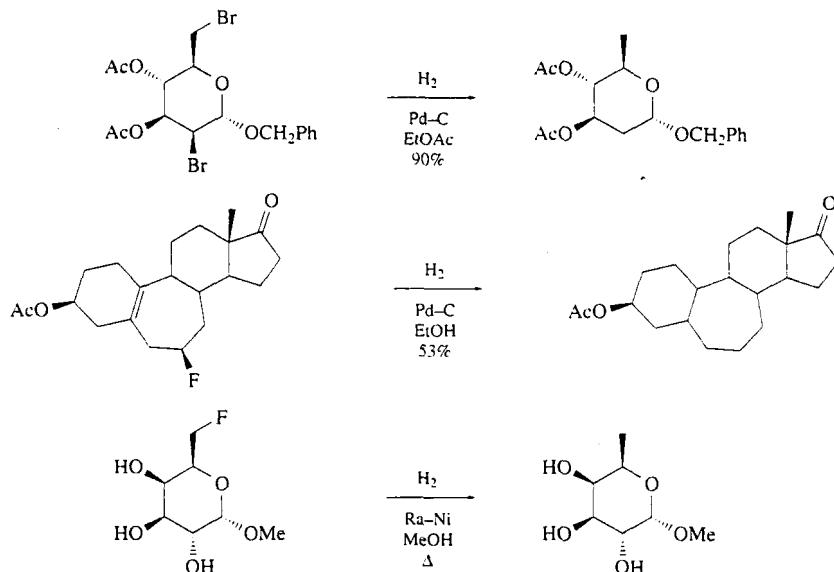
into four categories: catalytic hydrogenation, low-valent metal reduction, metal hydride nucleophilic displacement and radical substitution.

Generally, the observed reactivity is in the order  $I > Br > Cl > > F$  for all four categories, matching the order of bond strengths ( $C-I$  53 kcal mol<sup>-1</sup>,  $C-Br$  67 kcal mol<sup>-1</sup>,  $C-Cl$  81 kcal mol<sup>-1</sup>,  $C-F$  109 kcal mol<sup>-1</sup>). Benzylic and, to a lesser extent, allylic halides also tend to be more reactive than similar alkyl halides. The order of reactivity between primary, secondary and tertiary alkyl halides tends to be dependent on the reagent in use.  $\alpha$ -Halo carbonyl compounds are particularly prone to reduction by these methods, especially in the case of low-valent metal reductions <83OR163>, although competing carbonyl group reductions may occur with some procedures.

Until the late-1970s the first three categories appeared more commonly, as reflected in a contemporary review <80S425>, but radical reduction procedures have dominated since.

Catalytic hydrogenation methods have been reviewed <B-85MI 101-01>. Practical difficulties can be encountered in utilising these procedures, owing to catalyst poisoning by the hydrogen halide evolved, particularly in the reduction of alkyl fluorides <80S425>.

Palladium-on-carbon is employed most regularly as the catalyst in these reductions. Early reports <46JA261> suggested that only activated systems such as ethyl bromoacetate or benzyl chloride could be reduced while, for example, primary alkyl bromides were inert, even under high hydrogen pressure. However, many examples have been reported since which demonstrate a wider reactivity, concomitant with high chemoselectivity (Scheme 1) <79T885, 84CAR(130)125>. Isolated examples of reductions of benzylic fluorides <63JA1609> and even a secondary alkyl fluoride (Scheme 1) <71LA(748)123> have been reported.



Scheme 1

$\alpha$ -Haloketones are readily dehalogenated with no competing carbonyl reduction <58JOC1938, 78JA1786>, while the possibility of utilising transfer hydrogenation has also been highlighted <85JOC3408>.

Raney-nickel has been shown to catalyse the reduction of a series of alkyl bromides and iodides in addition to tertiary and benzylic chlorides <59CB1700>, while the range can be extended to primary alkyl fluorides under more forcing conditions (Scheme 1) <60JCS298>. Platinum oxide has been reported to catalyse the reduction of a benzylic fluoride under relatively mild conditions <65CJC1689>.

As indicated above, low-valent metal-based procedures appear to be the method of choice for the reduction of  $\alpha$ -halocarbonyl compounds <83OR163>. The metal employed most commonly in this context is zinc, although the use of iron pentacarbonyl <79JOC641> and of samarium(II) iodide <86JOC1135> has been exemplified.

The zinc reductions are generally performed in the presence of a proton source, typically acetic acid <72JOC2363> or ammonium chloride <78BCJ2745, 78JA1765>, and give high yields for chloro- <79JA4003, 85JOC3957>, bromo- <78JA1786> and iodo compounds (Scheme 2) <65LA(681)196>. The