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JAN WIELIAM SIMEK

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About the Authors

L. G. "Skip" Wade decided to become a chemistry major during his sophomore year at Rice University, while taking organic chemistry from Professor Ronald M. Magid. After receiving his B.A. from Rice in 1969, Wade went on to Harvard University, where he did research with Professor James D. White. While at Harvard, he served as the Head Teaching Fellow for the organic laboratories and was strongly influenced by the teaching methods of two master educators, Professors Leonard K. Nash and Frank H. Westheimer.

After completing his Ph.D. at Harvard in 1974, Dr. Wade joined the chemistry faculty at Colorado State University. Over the course of fifteen years at Colorado State, Dr. Wade taught organic chemistry to thousands of students working toward careers in all areas of biology, chemistry, human medicine, veterinary medicine, and environmental studies. He also authored research papers in organic synthesis and in chemical education, as well as eleven books reviewing current research in organic synthesis. In 1989, Dr. Wade joined the chemistry faculty at Whitman College, where he continued to teach organic chemistry and pursue research interests in organic synthesis and forensic chemistry. Dr. Wade received the A. E. Lange Award for Distinguished Science Teaching at Whitman in 1993.

Dr. Wade's interest in forensic science has led him to testify as an expert witness in court cases involving drugs and firearms, and he has worked as a police firearms instructor, drug consultant, and boating safety officer. He also enjoys repairing and restoring old violins and bows, which he has done professionally for many years.

Jan Simek was born to humble, coal-mining parents who taught him to appreciate the importance of carbon at a very early age. At age 14, he was inspired to pursue a career teaching chemistry by his high school chemistry teacher, Joe Plaskas. Under the guidance of Professor Kurt Kaufman at Kalamazoo College, Dr. Simek began lab work in synthesis of natural products that turned into research in hop extracts for the Kalamazoo Spice Extraction Company. After receiving a master's degree from Stanford University, Dr. Simek worked in the pharmaceutical industry, synthesizing compounds designed to control diabetes and atherosclerosis, and assisted in the isolation of anti-cancer antibiotics from natural sources. Returning to Stanford University, Dr. Simek completed his Ph.D. with the legendary Professor Carl Djerassi, who developed the first synthesis of steroidal oral contraceptives.

Dr. Simek's 35-year teaching career was spent primarily at California Polytechnic State University, San Luis Obispo, where he received the university's Distinguished Teaching Award. Other teaching experiences include Albion College, the University of Colorado at Boulder, Kalamazoo College, and the University of California at Berkeley. In addition to his pharmaceutical research, he has industrial experience investigating dyes, surfactants, and liquid crystals, and he continues to consult for the biotechnology industry.

Although his outside interests include free climbing in Yosemite, performing in a reggae band, and parasailing over the Pacific, as close as he gets to any of those is tending his backyard garden with his wife Judy.





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New to This Edition

- 1 NEW! Expanded coverage of Acid/Base Chemistry in chapter 2 and separation of the chapter on Substitution and Elimination into two distinct chapters allow students to build upon their existing knowledge and move through their first mechanisms with greater clarity and with more opportunities to test and apply their understanding without getting overwhelmed by organic chemistry. New problem-solving strategy spreads have been added to both corresponding chapters for additional support.
- 2 NEW! Reaction Starbursts/Reaction Maps appear before the end of every 'reaction-based' chapter to help students better understand and mentally organize reactive similarities and distinctions.
- **3** NEW! Visual Guides to Organic Reactions place the reactions covered in each chapter within the overall context of the reactions covered in the course.
- 4 NEW! Problem Solving Strategies have been added and explicitly highlighted in several chapters, including new strategies for resonance, acid-base equilibria, and multistep synthesis.
- 5 NEW! Over 100 New Problems include more synthesis problems and problems based on recent literature.
- 6 **NEW! Green Chemistry** is emphasized with presentation of less toxic, environmentally friendly reagents in many situations, such as oxidation of alcohols with bleach rather than with chromium reagents.
- **7 NEW! Chapter Openers** focus on organic applications, with introductions and images for a more enticing, contemporary presentation.



- 8 20 Key Mechanism Boxes highlight the fundamental mechanistic principles that recur throughout the course and are the basis for some of the longer, more complex mechanisms. Each describes the steps of the reaction in detail with a specific example to reinforce the mechanism and a concluding problem to help students absorb these essential reactions.
- 9 NEW! Explanations and Annotations to Mechanisms help students better understand how each mechanism works.

Brief Chapter-by-Chapter Changes

Global Changes

Every chapter begins with a new chapter-opening photograph showing an interesting, real-world application of the material in that chapter. New Problem-Solving Hints and new Applications have been added to each chapter, and all of the chapters have gone through a careful revision process. All of the structures have been updated to the new IUPAC recommendations for showing stereochemistry. Green curved arrows are used to show the imaginary flow of electrons in resonance forms, in contrast to the red curved arrows used to show the actual flow in reactions.

Chapter 1 Structure and Bonding

• The material on structure, bonding, and molecular geometry has been consolidated into one chapter. A revised discussion of resonance includes a Problem-Solving Strategy, a Problem-Solving Hint on the types of arrows used in organic chemistry, and several new problems.

Chapter 2 Acids and Bases; Functional Groups

• The presentation of acids and bases has been moved from the previous Chapter 1 and greatly enhanced to become the main subject in the new Chapter 2. The new material includes sections on inductive, hybridization, resonance, and solvent effects on acidity and basicity; a section and Problem-Solving Strategy on predicting acid-base equilibrium positions; new Problem-Solving Hints; new figures; new applications; and 18 new problems.

Chapter 4 The Study of Chemical Reactions

• The values of bond dissociation enthalpies have been updated to the most recent experimental results throughout the chapter. A revised discussion of Hammond's postulate includes a figure that has been revised for clarity.

Chapter 5 Stereochemistry

• This chapter includes a revised summary of types of isomers, with revised figures for clarity. There are new Problem-Solving Hints on stereocenters, Fischer projections, and relative versus absolute configurations.

Chapter 6 Alkyl Halides; Nucleophilic Substitution

• The sections on E1 and E2 eliminations have been moved to Chapter 7. A new graphic showing the strengths of common nucleophiles has been added, and the summary of nucleophilic substitution conditions has been expanded. Several Problem-Solving Hints have been added on nucleophiles and bases, acid-base strength in the S_N1 reaction, and carbocation rearrangements.

Chapter 7 Structure and Synthesis of Alkenes; Elimination

• This chapter now contains expanded sections on E1 and E2 eliminations. Several Problem-Solving Hints have been added, as well as graphics on the competition between substitutions and eliminations. Several new problems have been added, including two solved problems.

Chapter 8 Reactions of Alkenes

• Several diagrams, applications, problems, and starburst summaries of reactions have been added. The new visual *Guide to Organic Reactions* is introduced in Chapter 8, and further updated in Chapters 11, 17, 18, 21, and 22.

Chapter 9 Alkynes

• New examples and a new starburst summary have been added. A new Problem-Solving Hint summarizes oxidative cleavages of alkynes.

Chapter 10 Structure and Synthesis of Alcohols

• The material on lithium dialkylcuprates has been expanded into a new section. New Problem-Solving Hints on Grignard reactions and organometallic reactions have also been added. A new starburst reaction summary has been added.

Chapter 11 Reactions of Alcohols

• A newly revised discussion of oxidizing agents emphasizes "green" reactions with sodium hypochlorite and acetic acid, or TEMPO, rather than toxic chromium reagents. A new interim summary compares alcohol oxidations with and without chromium reagents, and a new Problem-Solving Hint discusses ring-size changes and rearrangements. Two new starburst reaction summaries have been added.

Chapter 14 Ethers, Epoxides, and Thioethers

• New material and a new graphic have been added to clarify the regiochemistry of the opening of substituted epoxides. Several new problems have been added.

Chapter 15 Conjugated Systems, Orbital Symmetry, and Ultraviolet Spectroscopy

• Several figures have been revised for clarity, and new applications have been added.

Chapter 16 Aromatic Compounds

• New to this chapter are a Problem-Solving Hint on drawing energy diagrams for the MOs of cyclic systems, plus new applications and problems. A new starburst reaction summary has also been added.

Chapter 17 Reactions of Aromatic Compounds

• A new Problem-Solving Strategy has been added to explain multistep synthesis using electrophilic aromatic substitutions. The discussion of the Suzuki reaction has been expanded, including its mechanism. New applications, two new starburst reaction summaries, and several problems have also been added.

Chapter 18 Ketones and Aldehydes

• The discussion of syntheses of ketones and aldehydes has been revised to emphasize oxidations that use less toxic reagents such as bleach and TEMPO. Several new applications have been added, as well as a starburst reaction summary and several new problems.

Chapter 19 Amines

• A Problem-Solving Hint on p*K*_a of amines has been added, plus new applications and several new problems.

Chapter 20 Carboxylic Acids

• New problems and applications have been added as well as a starburst reaction summary.

Chapter 21 Carboxylic Acid Derivatives

• Several new problems and applications have been added, as well as a starburst reaction summary.

Chapter 22 Condensations and Alpha Substitutions of Carbonyl Compounds

• A new Problem-Solving Hint on ketone and ester carbonyl groups has been added, plus a new starburst reaction summary. Several applications and problems have been added as well.

Chapter 23 Carbohydrates and Nucleic Acids

• This chapter has been updated with a new application on glycoproteins. Some of the obsolete older reactions have been dropped.

Chapter 24 Amino Acids, Peptides, and Proteins

• The material on solid-phase peptide synthesis has been updated to use current techniques, and some of the obsolete, older methods have been deleted.

Chapter 26 Synthetic Polymers

• The organization of the chapter has been revised to emphasize chain-growth versus step-growth polymers, rather than addition versus condensation polymers. A new section has been added on the recycling of plastics, plus applications on 3D printing and PEX pipes.

Preface

To the Student

As you begin your study of organic chemistry, you might feel overwhelmed by the number of compounds, names, reactions, and mechanisms that confront you. You might even wonder whether you can learn all this material in a single year. The most important function of a textbook is to organize the material to show that most of organic chemistry consists of a few basic principles and many extensions and applications of these principles. Relatively little memorization is required if you grasp the major concepts and develop flexibility in applying those concepts. Frankly, I have a poor memory, and I hate memorizing lists of information. I don't remember the specifics of most of the reactions and mechanisms in this book, but I can work them out by remembering a few basic principles, such as "alcohol dehydrations usually go by E1 mechanisms."

Still, you'll have to learn some facts and fundamental principles to serve as the working "vocabulary" of each chapter. As a student, I learned this the hard way when I made a D on my second organic chemistry exam. I thought organic would be like general chemistry, where I could memorize a couple of equations and fake my way through the exams. For example, in the ideal gas chapter, I would memorize PV = nRT, and I was good to go. When I tried the same approach in organic, I got a D. We learn by making mistakes, and I learned a lot in organic chemistry.

In writing this book, I've tried to point out a small number of important facts and principles that should be learned to prepare for solving problems. For example, of the hundreds of reaction mechanisms shown in this book, about 20 are the fundamental mechanistic steps that combine into the longer, more complicated mechanisms. I've highlighted these fundamental mechanisms in *Key Mechanism* boxes to alert you to their importance. Similarly, the *Guide to Organic Reactions* appears in six chapters that contain large numbers of new reactions. This guide outlines the kinds of reactions we cover and shows how the reactions just covered fit into the overall organization. Spectroscopy is another area in which a student might feel pressured to memorize hundreds of facts, such as NMR chemical shifts and infrared vibration frequencies. I couldn't do that, so I've always gotten by with knowing about a dozen NMR chemical shifts and about a dozen IR vibration frequencies, and knowing how they are affected by other influences. I've listed those important infrared frequencies in Table 12-2 and the important NMR chemical shifts in Table 13-3.

Don't try to memorize your way through this course. It doesn't work; you have to know what's going on so you can apply the material. Also, don't think (like I did) that you can get by without memorizing *anything*. Read the chapter, listen carefully to the lectures, and *work the problems*. The problems will tell you whether or not you know the material. If you can do the problems, you should do well on the exams. If you can't do the problems, you probably won't be able to do the exams, either. If you keep having to look up an item to do the problems, that item is a good one to learn.

Here are some hints I give my students at the beginning of the course:

- 1. Read the material in the book before the lecture (expect 13–15 pages per lecture). Knowing what to expect and what is in the book, you can take fewer notes and spend more time listening and understanding the lecture.
- 2. After the lecture, review your notes and the book, and do the in-chapter problems. Also, read the material for the next lecture.
- 3. If you are confused about something, visit your instructor during office hours immediately, before you fall behind. Bring your attempted solutions to problems with you to show the instructor where you are having trouble.

4. To study for an exam, begin by reviewing each chapter and your notes, and reviewing any reaction summaries to make sure you can recognize and use those reactions. The "starburst" summaries are most useful for developing syntheses, since you can quickly glance at them and see the most useful conversions for that functional group. Then concentrate on the end-of-chapter problems. In each chapter, the Essential Problem-Solving Skills (EPSS) outline reviews the important concepts in the chapter and shows which problems can be used to review each concept. Also use old exams, if available, for practice. Many students find that working in a study group and posing problems for each other is particularly helpful.

Remember the two "golden rules" of organic chemistry.

- 1. Don't Get Behind! The course moves too fast, and it's hard to catch up.
- 2. *Work Lots of Problems.* Everyone needs the practice, and the problems show where you need more work.

I am always interested to hear from students using this book. If you have any suggestions about how the book might be improved, or if you've found an error, please let me know (L. G. Wade, Whitman College, Walla Walla, WA 99362: E-mail wadelg@whitman. edu). I take students' suggestions seriously, and hundreds of them now appear in this book. For example, Whitman student Brian Lian suggested Figure 21-9, and University of Minnesota student (and race-car driver) Jim Coleman gave me the facts on the fuels used at Indianapolis.

Good luck with your study of organic chemistry. I'm certain you will enjoy this course, especially if you let yourself relax and develop an interest in how organic compounds influence our lives. My goal in writing this book has been to make the process a little easier: to build the concepts logically on top of each other, so they flow naturally from one to the next. The hints and suggestions for problem solving have helped my students in the past, and I hope some of them will help you to learn and use the material. Even if your memory is worse than mine (highly unlikely), you should be able to do well in organic chemistry. I hope this will be a good learning experience for all of us.

To the Instructor

In writing the first edition of this text, my goal was to produce a modern, readable text that uses the most effective techniques of presentation and review. I wanted a book that presents organic chemistry at the level needed for chemistry and biochemistry majors, but one that presents and explains the material in ways that facilitate success for all the many different kinds of students who take the course. Subsequent editions have extended and refined these goals, with substantial rewriting and reorganizing and with many new features. This ninth edition adds several new features to help students organize types of reactions and mechanisms for easier learning and better understanding, as well as for reference.

New to This Edition

To help students organize functional group reactions, new **Starburst Summaries** have been added that provide visual links between synthetically related functional groups. This new feature is particularly useful when students are developing multistep syntheses, when the visual links help them to see the possible reactions moving forward from a reactant or synthetic intermediate. The new **Guides to Organic Reactions** will help students to organize mentally the many new reactions they are learning, and where those reactions fit within the overall scheme of the types of reactions we use in organic chemistry. **Chapter-opening photographs**, with captions that explain how the photograph relates to the chemistry presented in that chapter, have been added to all of the chapters. We have tried to select photos that are remarkable in some way or another and that grab the viewer's attention. All of the features of the earlier editions have been retained in this ninth edition. In many cases, those that were introduced in earlier editions have been expanded and refined. Many **updated applications** have been added, including those relating to medicine, green chemistry, biochemistry, and other contemporary areas of interest. **Green chemistry** is emphasized in many areas, most notably in the use of methods that avoid chromium reagents, which are known to be toxic and carcinogenic. The older, more toxic reagents are mentioned, but they are no longer given as the first choice for a reagent. Mechanisms have been provided for the newest reactions, such as the Suzuki coupling, when they are relevant to the material and studied well enough to be confident they are correct.

Key Features

Expanded Coverage of Acids and Bases: After reviewing the basics of bonding, hybridization, and molecular structure in Chapter 1, Chapter 2 is centered around acids and bases and how these concepts apply to organic compounds. The Arrhenius, Brønsted-Lowry, and Lewis definitions are introduced and explained. The uses of pK_a and pK_b are described, followed by a discussion and a Problem-Solving Strategy feature on predicting the position of an acid-base equilibrium reaction. Factors that affect acid-ity and basicity are explained, including solvent effects, size, electronegativity, inductive effects, hybridization effects, and resonance effects. Lewis acid-base reactions are discussed, with a careful discussion of the correct use of the curved-arrow formalism.

Separation of Substitution and Elimination Reactions: The crucial chapters on substitution and elimination have been revised, with substitutions covered in Chapter 6 and eliminations in Chapter 7. This organization allows students to become more comfortable with the differences between S_N1 and S_N2 substitutions before the possible reaction pathways are expanded to include eliminations. Chapter 7 presents complete coverage of the competition between substitutions and eliminations, and how one can predict what mechanisms and products are most likely.

Organic Synthesis: Many new synthetic problems have been added, some of them coming from the recent literature. The material on organic synthesis and retrosynthetic analysis has been supplemented, with particular attention to multistep aromatic syntheses.

Nomenclature: We have tried to stay as current as possible with the constantly changing IUPAC nomenclature, and this edition reflects some of the most recent changes. Beginning with the eighth edition, we have used the 1993 IUPAC positioning of the locants in names (e.g., but-1-ene), while also showing the names using the older positions of the locants (e.g., 1-butene). We have also carefully defined stereochemical terms (such as *stereocenter* and *chiral center*) correctly and precisely, and we have endeavored to use the most precise term in each case.

In this edition, we have adopted three of the newest changes in the IUPAC rules:

- 1. In showing stereochemistry, IUPAC now recommends the "reverse perspective" (closer end is smaller) version of wedged dashed bonds. Wedged solid bonds are still drawn with normal perspective, with their closer end larger.
- 2. IUPAC now defines *hydroxyl* as referring only to the radical, not the functional group. The functional group is the *hydroxy group*. We have changed these terms where needed to conform to this rule.
- 3. At one time, the IUPAC banished the term *ketal*. It has now been reinstated as a subclass of acetals, and we have resumed using it.

This ninth edition also includes a new Nomenclature Appendix, which serves as a compact reference to the rules of naming organic compounds. This feature should make it easier for students to name compounds without always having to find the discussion pertaining to that particular functional group.

The Keys to Organic Chemistry

Wade & Simek's ninth edition of *Organic Chemistry* presents key principles of organic chemistry in the context of fundamental reasoning and problem solving. Written to reflect how today's students use textbooks, this text serves as a primary guide to organic chemistry, as well as a comprehensive study resource when working problems and preparing for exams.

PROBLEM-SOLVING STRATEGY Predicting Substitutions and Eliminations



Given a set of reagents and solvents, how can you predict what products will result and which mechanisms will be involved? Should you memorize all this theory about substitutions and eliminations? Students sometimes feel overwhelmed at this point.

Memorizing is not the best way to approach this material because the answers are not absolute and too many factors are involved. Besides, the real world with its real reagents and solvents is not as clean as our equations on paper. Most nucleophiles are also basic, and many solvents can solvate ions or react as nucleophiles or bases.

The first principle you must understand is that you cannot always predict one unique product or one unique mechanism. Often, the best you can do is to eliminate some of the possibilities and make some accurate predictions. Remembering this limitation, here are some general guidelines:

- 1. The strength of the base or nucleophile determines the order of the reaction. If a strong nucleophile (or base) is present, it will force second-order kinetics, either S_N^2 or E2. If no strong base or nucleophile is present, you should consider first-order reactions, both S_N^1 and E1. Addition of silver salts to the reaction can force some difficult ionizations.
- 2. Primary halides usually undergo the S_N2 reaction, occasionally the E2 reaction. Primary halides rarely undergo first-order reactions, unless the carbocation is resonancestabilized. With good nucleophiles, S_N2 substitution is usually observed. With a strong base, E2 elimination may occasionally be observed.

SOLVED PROBLEM 7-7

(a) Propose a mechanism for the sulfuric acid-catalyzed dehydration of *tert*-butyl alcohol. **SOLUTION**

The first step is protonation of the hydroxy group, which converts it to a good leaving group.

The second step is ionization of the protonated alcohol to give a carbocation.

$$\begin{array}{cccc} CH_3 & H \\ CH_3 - C \stackrel{C}{\longrightarrow} O \stackrel{H}{\longrightarrow} & CH_3 - C \stackrel{CH_3}{\longleftarrow} & H \\ \vdots & H & CH_3 - C \stackrel{CH_3}{\longleftarrow} & H \\ CH_3 & H & CH_3 - C \stackrel{H}{\longleftarrow} & CH_3 \\ \end{array}$$

Abstraction of a proton completes the mechanism.

$$H_{2}\ddot{O}: H \stackrel{H}{\longrightarrow} C^{+} CH_{3} \xrightarrow{H} C = C \stackrel{CH_{3}}{\longleftarrow} H \stackrel{H_{3}\ddot{O}}{\longleftarrow} H \stackrel{CH_{3}}{\longrightarrow} H \stackrel{H_{3}\ddot{O}}{\longleftarrow} H \stackrel{CH_{3}}{\longrightarrow} H \stackrel{CH_{3}}{\longrightarrow}$$

(b) Predict the products and propose a mechanism for the acid-catalyzed dehydration of 1-cyclohexylethanol.

PARTIAL SOLUTION:

Protonation of the hydroxy group, followed by loss of water, forms a carbocation.



The carbocation can lose a proton, or it can rearrange to a more stable carbocation.



The resources in this book include Problem-Solving Strategies throughout, plus Partially Solved Problems, Reaction Summaries, new Starburst Summaries, and new Reaction Guides. Through a careful, refined presentation and step-by-step guidance, this ninth edition gives students a contemporary overview of organic chemistry with tools for organizing and understanding reaction mechanisms and synthetic organic chemistry.

PROBLEM-SOLVING HINT Alcohol dehydrations usually go

through E1 elimination of the

protonated alcohol. Reactivity is: $3^{\circ} > 2^{\circ} >> 1^{\circ}$ Rearrangements are common. Protonated primary alcohols dehydrate at elevated temperatures with rearrangement (E1), or the adjacent carbon may lose a proton to a weak base at the same time water leaves (E2).

Principles, Preparation, and Problem Solving

SUMMARY Electrophilic Additions to Alkenes

Methylcyclopentene is an alkene that displays orientation and stereochemistry of addition reactions. New atoms are shown in color. When reactions create chiral products from achiral reactants, racemic mixtures are produced. *N/A* means "Not Applicable to this reaction."



NEW! Starburst Reaction Summaries appear before the end-of-chapter material of "reaction-based" chapters to help students mentally organize the reactions and recognize their similarities and differences.

GUIDE TO ORGANIC REACTIONS IN CHAPTER 11 Reactions covered in Chapter 11 are shown in red covered in earlier chapters are shown in blue Substitution Additior Elimination Oxidation/Reduction Nucleophilic Nucleophilic Basic conditions (E2) Oxidation at *sp*³ C (S_N1, S_N2 Ch 6, 10, 14, 22 t C = O (Nuc. Addn.) Ch 9, 10, 18, 22 E2 de Ch 8, 10, 14 Ch 7. at C = C (conjugate addn.) Ch 22 at sp² C (Nuc. Arom. Subst.) Ch 17, 19 tosylate elimination Ch 11 oxidative cleavage Ch 8, 9, 11, 17, 22 at C = O (Nuc. Acyl Subst.) Hofmann elimination oxygen functional groups Electrophilic Ch 10, 11, 20, 21, 22 Ch 19 Ch 11 18 19 20 at C = C (Elect. Addn.) Ch 8, 9, 10 Electrophilic Acidic conditions (E1) Reduction at sp² C (Elect. Arom. Subst.) Ch 17, 19 at C = C (Carbene Addn.) E1 dehydroha hydride reduction Ch 8, 10, 11, 17, 18, 19, 20, 21 Ch 8 Ch dehydration of alcohols Radical Radical Ch 11 Ch 8, 9, 17, 18, 19 at sp³ C (alkane halogenation Ch 4, 6, 16, 17 at C = C (HBr + ROOR) Pericyclic (Cope elimination) Ch 9, 17, 18, 19 Ch at sp² C (Sandmeyer rxn) Ch 19 Ch 19 Pericyclic cycloaddition (Diels-Alder) Ch 15 Organometallic Gilman Ch 10, 17 Oxidation Suzuki Ch 17 Heck Ch 17 epoxidation Ch 8, 10, 14 Reduction

Ch 8, 9, 17, 18, 19

NEW! Visual **Guides to Organic Reactions** place the reactions covered in each chapter within the overall context of the reactions covered in the course.