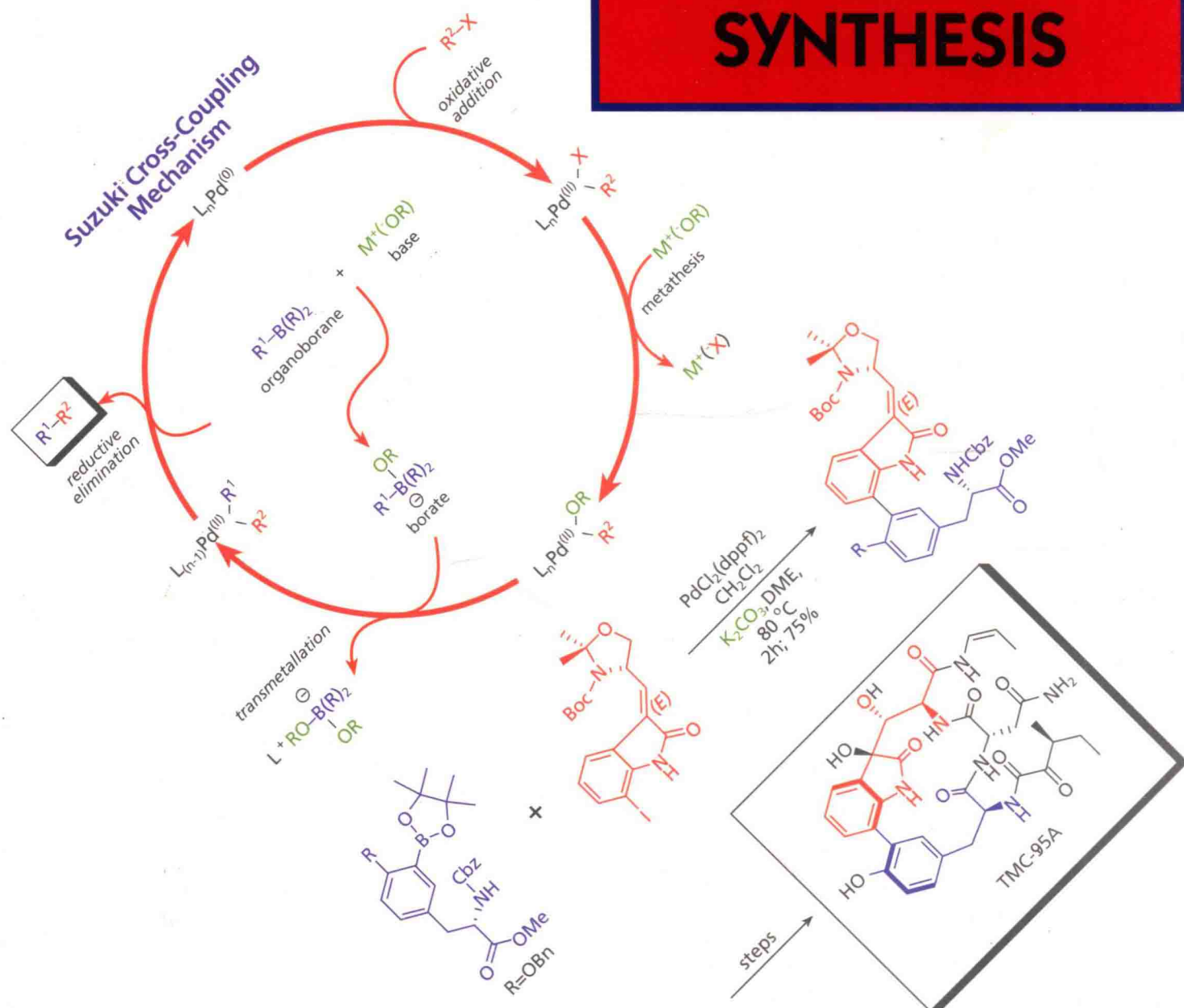


László Kürti  
Barbara Czako

Foreword by E. J. Corey

Introduction by K. C. Nicolaou

# STRATEGIC APPLICATIONS of NAMED REACTIONS in ORGANIC SYNTHESIS



Background and Detailed Mechanisms

# Strategic Applications of Named Reactions in Organic Synthesis

Background and  
Detailed Mechanisms

by  
**László Kürti and Barbara Czakó**

UNIVERSITY OF PENNSYLVANIA

250 Named Reactions



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# **Strategic Applications of Named Reactions in Organic Synthesis**

This book is dedicated to  
**Professor Madeleine M. Joullié**  
for her lifelong commitment  
to mentoring graduate students



## ABOUT THE AUTHORS



**Barbara Czako** was born and raised in Hungary. She received her Diploma from Lajos Kossuth University in Debrecen, Hungary (now University of Debrecen) where she conducted research in the laboratory of Dr. Sándor Berényi. She obtained her Master of Science degree at University of Missouri-Columbia working for Professor Shon R. Pulley. Currently she is pursuing her Ph.D. degree in synthetic organic chemistry under the supervision of Professor Gary A. Molander at the University of Pennsylvania. She will join the research group of Professor E.J. Corey at Harvard University as a postdoctoral fellow in 2006.

**László Kürti** was born and raised in Hungary. He received his Diploma from Lajos Kossuth University in Debrecen, Hungary (now University of Debrecen) where he conducted research in the laboratory of Professor Sándor Antus. He obtained his Master of Science degree at University of Missouri-Columbia working for Professor Michael Harmata. Currently he is pursuing his Ph.D. degree in synthetic organic chemistry under the supervision of Professor Amos B. Smith III at the University of Pennsylvania. He will join the research group of Professor E.J. Corey at Harvard University as a postdoctoral fellow in 2006.



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When we completed half of the manuscript in early 2004, **Professor Amos B. Smith III** was teaching his synthesis class "Strategies and Tactics in Organic Synthesis" and adopted the manuscript. We would like to thank him for his support and encouragement. We also thank the students in his class for their useful observations that aided the design of a number of difficult schemes.

Our thanks also go to **Professor Gary A. Molander** for his valuable remarks regarding the organometallic reactions. He had several excellent suggestions on which named reactions to include.

Earlier this year our publisher, Academic Press/Elsevier Science, sent the manuscript to a number of research groups in the US as well as in the UK. The thorough review conducted by the professors and in some cases also by volunteer graduate students is greatly appreciated. They are (in alphabetical order):

**Professor Donald H. Aue** (University of California Santa Barbara)

**Professor Ian Fleming** (University of Cambridge, UK)

**Professor Rainer Glaser** (University of Missouri-Columbia)

**Professor Michael Harmata** (University of Missouri-Columbia)

**Professor Robert A. W. Johnstone** (University of Liverpool, UK)

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**Professor P. A. Wender** (Stanford University) and two of his graduate students **Cindy Kan** and **John Kowalski**

**Professor Peter Wipf** (University of Pittsburgh)

We would like to express our gratitude to the following friends/colleagues who have carefully read multiple versions of the manuscript and we thank them for the excellent remarks and helpful discussions. They were instrumental in making the manuscript as accurate and error free as possible:

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**Dr. Mehmet Kahraman** (Kalypsys, Inc.)

**Justin Ragains** (University of Pennsylvania)

**Thomas Razler** (University of Pennsylvania)

There were several other friends/colleagues who reviewed certain parts of the manuscript or earlier versions and gave us valuable feedback on the content as well as in the design of the schemes.

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**Prof. Cheon-Gyu Cho** (Hanyang University, Korea/University of Pennsylvania)

**Dr. Shane Foister** (University of Pennsylvania)

**Dr. Eugen Mesáros** (University of Pennsylvania)

**Dr. Emmanuel Meyer** (University of Pennsylvania)

**David J. St. Jean, Jr.** (University of Pennsylvania)

**Dr. Kirsten Zeitler** (University of Regensburg, Germany)

Finally, we would like to thank our editor at Elsevier, **Jeremy Hayhurst**, who gave us the chance to make a contribution to the education of graduate students in the field of organic chemistry. He generously approved all of our requests for technical support thus helping us tremendously to finish the writing in a record amount of time. Our special thanks are extended to editorial assistants **Desirée Marr** and previously, **Nora Donaghy**, who helped conduct the reviews and made sure that we did not get lost in a maze of documents.

## FOREWORD

This book on "Strategic Applications of Named Reactions in Organic Synthesis" is destined to become unusually useful, valuable, and influential for advanced students and researchers in the field. It breaks new ground in many ways and sets an admirable standard for the next generation of texts and reference works. Its virtues are so numerous there is a problem in deciding where to begin. My first impression upon opening the book was that the appearance of its pages is uniformly elegant and pleasing – from the formula graphics, to the print, to the layout, and to the logical organization and format. The authors employ four-color graphics in a thoughtful and effective way. All the chemical formulas are exquisitely drawn.

The book covers many varied and useful reactions for the synthesis of complex molecules, and in a remarkably clear, authoritative and balanced way, considering that only two pages are allocated for each. This is done with unusual rigor and attention to detail. Packed within each two-page section are historical background, a concise exposition of reaction mechanism and salient and/or recent applications. The context of each example is made crystal clear by the inclusion of the structure of the final synthetic target. The referencing is eclectic but extensive and up to date; important reviews are included.

The amount of information that is important for chemists working at the frontiers of synthesis to know is truly enormous, and also constantly growing. For a young chemist in this field, there is so much to learn that the subject is at the very least daunting. It would be well nigh impossible were it not for the efforts of countless authors of textbooks and reviews. This book represents a very efficient and attractive way forward and a model for future authors. If I were a student of synthetic chemistry, I would read this volume section by section and keep it close at hand for reference and further study.

I extend congratulations to László Kürti and Barbara Czako for a truly fine accomplishment and a massive amount of work that made it possible. The scholarship and care that they brought to this task will be widely appreciated because they leap out of each page. I hope that this wonderful team will consider extending their joint venture to other regions of synthetic chemical space. Job well done!

**E. J. Corey**

*January, 2005*



# INTRODUCTION

The field of chemical synthesis continues to amaze with its growing and impressive power to construct increasingly complex and diverse molecular architectures. Being the precise science that it is, this discipline often extends not only into the realms of technology, but also into the domains of the fine arts, for it engenders unparalleled potential for creativity and imagination in its practice. Enterprises in chemical synthesis encompass both the discovery and development of powerful reactions and the invention of synthetic strategies for the construction of defined target molecules, natural or designed, more or less complex. While studies in the former area –synthetic methodology– fuel and enable studies in the latter –target synthesis– the latter field offers a testing ground for the former. Blending the two areas provides for an exciting endeavor to contemplate, experience, and watch. The enduring art of total synthesis, in particular, affords the most stringent test of chemical reactions, old and new, named and unnamed, while its overall reach and efficiency provides a measure of its condition at any given time. The interplay of total synthesis and its tools, the chemical reactions, is a fascinating subject whether it is written, read, or practiced.

This superb volume by László Kürti and Barbara Czakó demonstrates clearly the power and beauty of this blend of science and art. The authors have developed a standard two-page format for discussing each of their 250 selections whereby each named reaction is concisely introduced, mechanistically explained, and appropriately exemplified with highlights of constructions of natural products, key intermediates and other important molecules. These literature highlights are a real treasure trove of information and a joy to read, bringing each named reaction to life and conveying a strong sense of its utility and dynamism. The inclusion of an up-to-date reference listing offers a complete overview of each reaction at one's fingertips.

The vast wealth of information so effectively compiled in this colorful text will not only prove to be extraordinarily useful to students and practitioners of the art of chemical synthesis, but will also help facilitate the shaping of its future as it moves forward into ever higher levels of complexity, diversity and efficiency. The vitality of the enduring field of total synthesis exudes from this book, captivating the attention of the reader throughout. The authors are to be congratulated for the rich and lively style they developed and which they so effectively employed in their didactic and aesthetically pleasing presentations. The essence of the art and science of synthesis comes alive from the pages of this wonderful text, which should earn its rightful place in the synthetic chemist's library and serve as an inspiration to today's students to discover, invent and apply their own future named reactions. Our thanks are certainly due to László Kürti and Barbara Czakó for a splendid contribution to our science.

***K.C. Nicolaou***

*January, 2005*

## PREFACE

Today's organic chemist is faced with the challenge of navigating his or her way through the vast body of literature generated daily. Papers and review articles are full of scientific jargon involving the description of methods, reactions and processes defined by the names of the inventors or by a well-accepted phrase. The use of so-called "named reactions" plays an important role in organic chemistry. Recognizing these named reactions and understanding their scientific content is essential for graduate students and practicing organic chemists.

This book includes some of the most frequently used named reactions in organic synthesis. The reactions were chosen on the basis of importance and utility in synthetic organic chemistry. Our goal is to provide the reader with an introduction that includes a detailed mechanism to a given reaction, and to present its use in recent synthetic examples. This manuscript is not a textbook in the classical sense: it does not include exercises or chapter summaries. However, by describing 250 named organic reactions and methods with an extensive list of leading references, the book is well-suited for independent or classroom study. On one hand, the compiled information for these indispensable reactions can be used for finding important articles or reviews on a given subject. On the other hand, it can also serve as supplementary material for the study of organic reaction mechanisms and synthesis.

This book places great emphasis on the presentation of the material. Drawings are presented accurately and with uniformity. Reactions are listed alphabetically and each named reaction is presented in a convenient two-page layout. On the first page, a brief introduction summarizes the use and importance of the reaction, including references to original literature and to all major reviews published after the primary reference. When applicable, leading references to modifications and theoretical studies are also given. The introduction is followed by a general scheme of the reaction and by a detailed mechanism drawn using a four-color code (red, blue, green and black) to ensure easy understanding. The mechanisms always reflect the latest evidence available for the given reaction. If the mechanism is unknown or debatable, references to the relevant studies are included. The second page contains 3 or 4 recent synthetic examples utilizing the pertinent named reaction. In most cases the examples are taken from a synthetic sequence leading to the total synthesis of an important molecule or a natural product. Some examples are taken from articles describing novel methodologies. The synthetic sequences are drawn using the four-color code, and the procedures are described briefly in 2-3 sentences. If a particular named reaction involves a complex rearrangement or the formation of a polycyclic ring system, numbering of the carbon-skeleton is included in addition to the four-color code. In the depicted examples, the reaction conditions as well as the ratio of observed isomers (if any) and the reported yields are shown. The target of

the particular synthetic effort is also illustrated with colors indicating where the intermediates reside in the final product.

The approach used in this book is also unique in that it emphasizes the clever use of many reactions that might otherwise have been overlooked.

The almost 10,000 references are indexed at the end of the book and include the title of the cited book, book section, chapter, journal or review article. The titles of seminal papers written in a foreign language were translated to English. The name of the author of a specific synthetic example was chosen as the one having an asterisk in the reference.

In order to make the book as user-friendly as possible, we have included a comprehensive list of abbreviations used in the text or drawings along with the structure of the protecting groups and reagents. Also in an appendix, the named organic reactions are grouped on the basis of their use in contemporary synthesis. Thus the reader can readily ascertain which named organic reactions effect the same synthetic transformations or which functional groups are affected by the use of a particular named reaction. Finally, an index is provided to allow rapid access to desired information based on keywords found in the text or the drawings.

**László Kürti & Barbara Czako**

University of Pennsylvania

Philadelphia, PA

*January 2005*



## IV. EXPLANATION OF THE USE OF COLORS IN THE SCHEMES AND TEXT

The book uses four colors (black, red, blue, and green) to depict the synthetic and mechanistic schemes and highlight certain parts of the text. In the “**Introduction**” and “**Mechanism**” sections of the text, the title named reaction/process is highlighted in blue and typed in italics:

“The preparation of ketones *via* the C-alkylation of esters of 3-oxobutanoic acid (acetoacetic esters) is called the *acetoacetic ester synthesis*. Acetoacetic esters can be deprotonated at either the C2 or at both the C2 and C4 carbons, depending on the amount of base used.”

All other named reactions/processes that are mentioned are typed in italics:

“Dilute acid hydrolyzes the ester group, and the resulting  $\beta$ -keto acid undergoes decarboxylation to give a ketone (mono- or disubstituted acetone derivative), while aqueous base induces a *retro-Claisen reaction* to afford acids after protonation.”

In the “**Synthetic Applications**” section, the name of the target molecule is highlighted in blue:

“During the highly stereoselective total synthesis of *epothilone B* by J.D. White and co-workers, the stereochemistry of the alcohol portion of the macrolactone was established by applying *Davis’s oxaziridine oxidation* of a sodium enolate.”

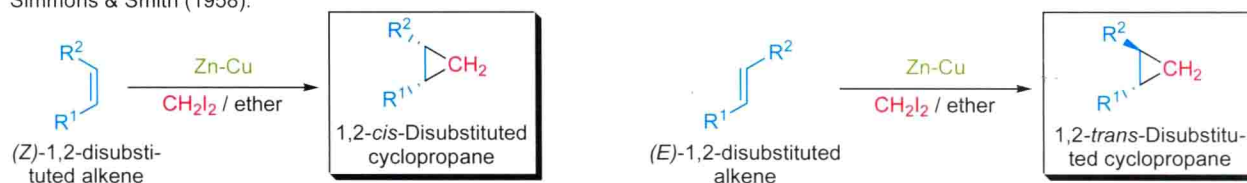
In the schemes, colors are applied to highlight the changes in a given molecule or intermediate (formation and breaking of bonds). It is important to note that due to the immense diversity of reactions, it is impossible to implement a strictly unified use of colors. Therefore, **each scheme has a unique use of colors specifically addressing the given transformation**. By utilizing four different colors the authors’ goal is to facilitate understanding. The authors hope that the readers will look up the cited articles and examine the details of a given synthesis. The following sample schemes should help the readers to understand how colors are used in this book.

- In most (but not all) schemes the starting molecule is colored blue, while the reagent or the reaction partner may be of any of the remaining two colors (red and green). **The newly formed bonds are always black.**

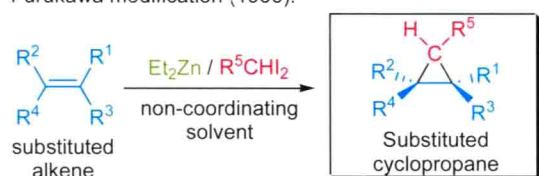


- The general schemes follow the same principle of coloring, and where applicable the same type of key reagents are depicted using the same color. (In this example the two different metal-derived reagents are colored green.)

Simmons & Smith (1958):



Furukawa modification (1966):



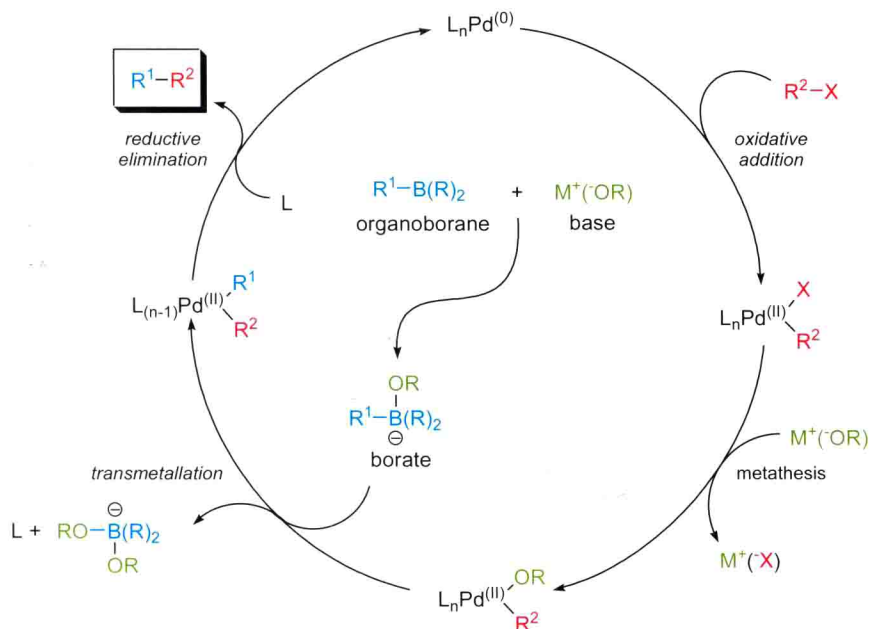
Charette asymmetric modification (1994):



$\text{R}^{1-4} = \text{H}$ , substituted alkyl and aryl;  $\text{R}^5 = \text{H}$ , Me, phenyl;  $\text{R}^6 = \text{CONMe}_2$ ; non-coordinating solvent: toluene, benzene, DCM, DCE



- The mechanistic schemes benefit the most from the use of four colors. These schemes also include extensive arrow-pushing. The following two schemes demonstrate this point very well.
- The catalytic cycle for the *Suzuki cross-coupling*:

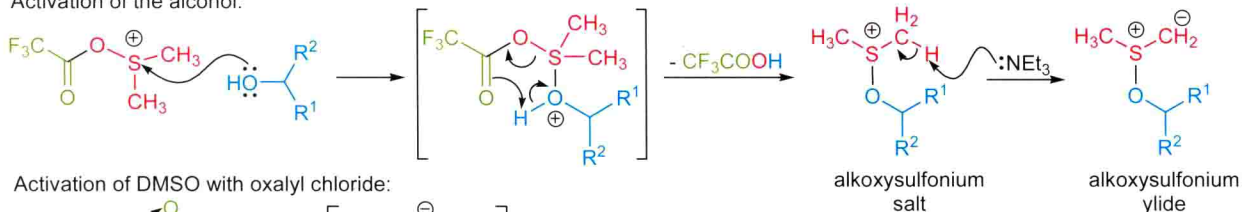


- The mechanism of the *Swern oxidation*:

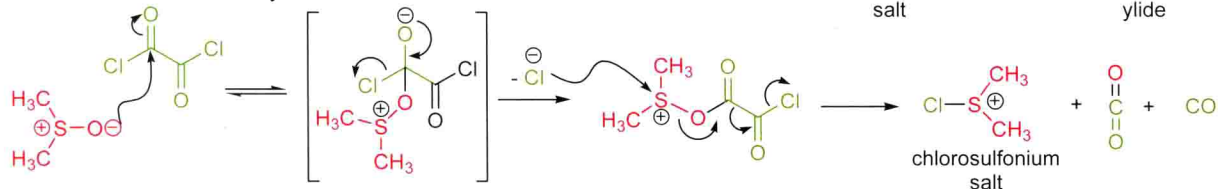
Activation of DMSO with TFAA:



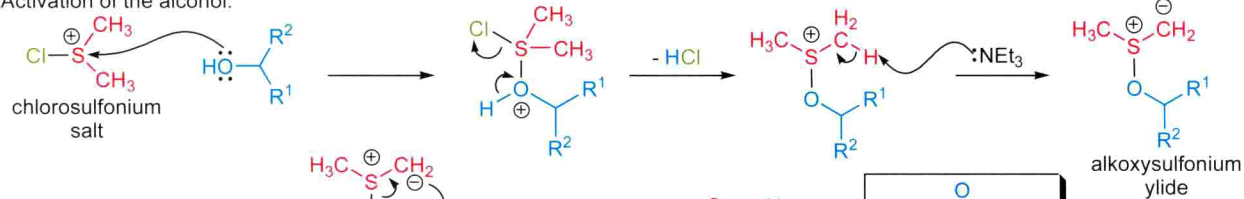
Activation of the alcohol:



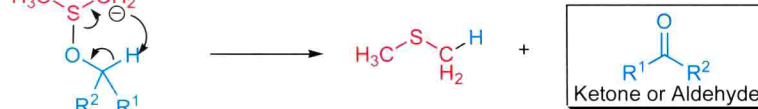
Activation of DMSO with oxalyl chloride:



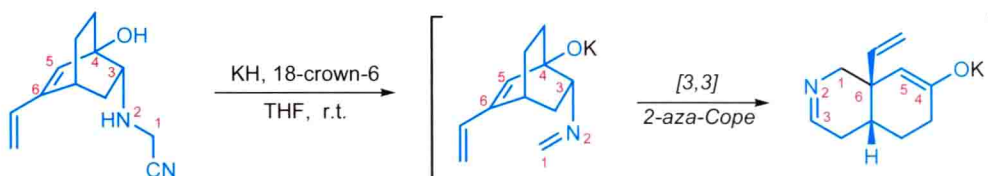
Activation of the alcohol:



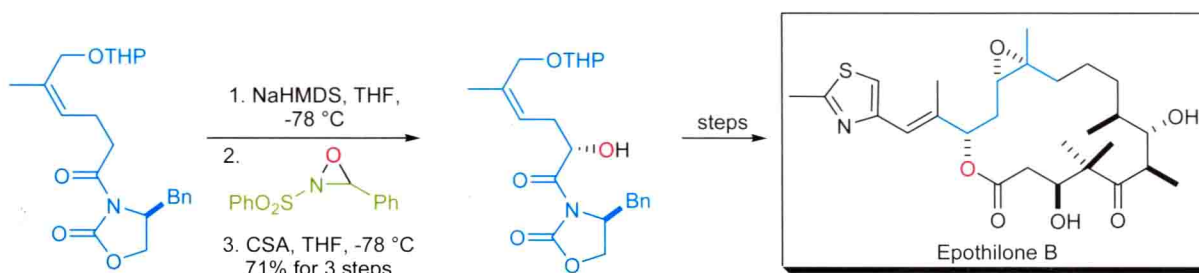
Formation of the product:



- In the case of complex rearrangements, numbering of the initial carbon skeleton has been applied in addition to the colors to facilitate understanding. Again, the newly formed bonds are black.



- In most instances, the product of a given named reaction/process will be part of a larger structure (e.g., natural product) at the end of the described synthetic effort. For pedagogical reasons, the authors decided to indicate where the building block appears in the target structure. It is the authors' hope that the reader will be able to put the named reaction/process in context and the provided synthetic example will not be just an abstract one.



- The references at the end of the book are listed in alphabetical order, and the named reaction for which the references are listed is typed in blue and with boldface (see *Dakin oxidation*). **Important: the references are listed in chronological order when they appear as superscript numbers in the text** (e.g., reference 10 is a more recent paper than reference 12, but it received a smaller reference number because it was cited in the text earlier).

#### **Mechanism:**<sup>12,10,15-17</sup>

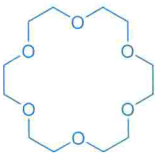

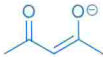

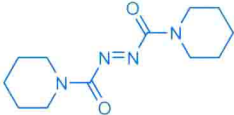
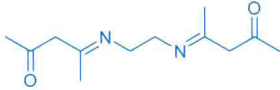
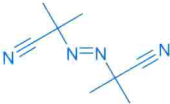


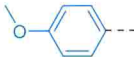
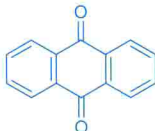
The mechanism of the *Dakin oxidation* is very similar to the mechanism of the *Baeyer-Villiger oxidation*.

- For the *Dakin oxidation* example, the references at the end of the book will be printed in the order they have been cited, but within a group of references (e.g., 15-17) they appear in chronological order.

#### **Dakin oxidation**

- Hocking, M. B. Dakin oxidation of o-hydroxyacetophenone and some benzophenones. Rate enhancement and mechanistic aspects. *Can. J. Chem.* **1973**, 51, 2384-2392.
- Matsumoto, M., Kobayashi, K., Hotta, Y. Acid-catalyzed oxidation of benzaldehydes to phenols by hydrogen peroxide. *J. Org. Chem.* **1984**, 49, 4740-4741.
- Ogata, Y., Sawaki, Y. Kinetics of the Baeyer-Villiger reaction of benzaldehydes with perbenzoic acid in aquo-organic solvents. *J. Org. Chem.* **1969**, 34, 3985-3991.
- Boeseken, J., Coden, W. D., Kip, C. J. The synthesis of sesamol and of its  $\beta$ -glucoside. The Baudouin reaction. *Rec. trav. chim.* **1936**, 55, 815-820.
- Kabalka, G. W., Reddy, N. K., Narayana, C. Sodium percarbonate: a convenient reagent for the Dakin reaction. *Tetrahedron Lett.* **1992**, 33, 865-866.
- Hocking, M. B., Ong, J. H. Kinetic studies of Dakin oxidation of o- and p-hydroxyacetophenones. *Can. J. Chem.* **1977**, 55, 102-110.
- Hocking, M. B., Ko, M., Smyth, T. A. Detection of intermediates and isolation of hydroquinone monoacetate in the Dakin oxidation of p-hydroxyacetophenone. *Can. J. Chem.* **1978**, 56, 2646-2649.
- Hocking, M. B., Bhandari, K., Shell, B., Smyth, T. A. Steric and pH effects on the rate of Dakin oxidation of acylphenols. *J. Org. Chem.* **1982**, 47, 4208-4215.

## V. LIST OF ABBREVIATIONS

Abbreviation	Chemical Name	Chemical Structure
18-Cr-6	18-crown-6	
Ac	acetyl	
acac	acetylacetonyl	
AA	asymmetric aminohydroxylation	NA
AD	asymmetric dihydroxylation	NA
ad	adamantyl	
ADDP	1,1'-(azodicarbonyl)dipiperidine	
ADMET	acyclic diene metathesis polymerization	NA
acaen	<i>N,N'</i> -bis(1-methyl-3-oxobutylidene)ethylenediamine	
AIBN	2,2'-azo bisisobutyronitrile	
Alloc	allyloxycarbonyl	
Am	amyl ( <i>n</i> -pentyl)	
An	<i>p</i> -anisyl	
ANRORC	anionic ring-opening ring-closing	NA
aq	aqueous	NA
AQN	anthraquinone	
Ar	aryl (substituted aromatic ring)	NA

Abbreviation	Chemical Name	Chemical Structure
ATD	aluminum tris(2,6- <i>di-tert</i> -butyl-4-methylphenoxide)	
atm	1 atmosphere = 10 <sup>5</sup> Pa (pressure)	NA
ATPH	aluminum tris(2,6-diphenylphenoxide)	
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)	
	9-borabicyclo[3.3.1]nonyl	
BCME	<i>bis</i> (chloromethyl)ether	
BCN	<i>N</i> -benzyloxycarbonyloxy-5-norbornene-2,3-dicarboximide	
BDPP	(2 <i>R</i> , 4 <i>R</i> ) or (2 <i>S</i> , 4 <i>S</i> ) <i>bis</i> (diphenylphosphino)pentane	
BER	borohydride exchange resin	NA
BHT	2,6- <i>di-t</i> -butyl- <i>p</i> -cresol (butylated hydroxytoluene)	
BICP	2( <i>R</i> )-2'( <i>R</i> )- <i>bis</i> (diphenylphosphino)-1( <i>R</i> ),1'( <i>R</i> )-dicyclopentane	
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl lithium aluminum hydride	
BINAP	2,2'- <i>bis</i> (diphenylphosphino)-1,1'-binaphthyl	



Abbreviation	Chemical Name	Chemical Structure
<b>BINOL</b>	1,1'-bi-2,2'-naphthol	
<b>Bip</b>	biphenyl-4-sulfonyl	
<b>bipy</b>	2,2'-bipyridyl	
<b>BLA</b>	Brönsted acid assisted chiral Lewis acid	NA
<b>bmin</b>	1-butyl-3-methylimidazolium cation	
<b>BMS</b>	Borane-dimethyl sulfide complex	$\text{H}_3\text{B} \cdot \text{SMe}_2$
<b>Bn</b>	benzyl	
<b>BNAH</b>	1-benzyl-1,4-dihydronicotinamide	
<b>BOB</b>	4-benzyloxybutyryl	
<b>Boc</b>	<i>t</i> -butoxycarbonyl	
<b>BOM</b>	benzyloxymethyl	
<b>BOP-Cl</b>	<i>bis</i> (2-oxo-3-oxazolidinyl)phosphinic chloride	
<b>bp</b>	boiling point	NA
<b>BPD</b>	<i>bis</i> (pinacolato)diboron	
<b>BPO</b>	benzoyl peroxide	
<b>BPS (TBDPS)</b>	<i>t</i> -butyldiphenylsilyl	