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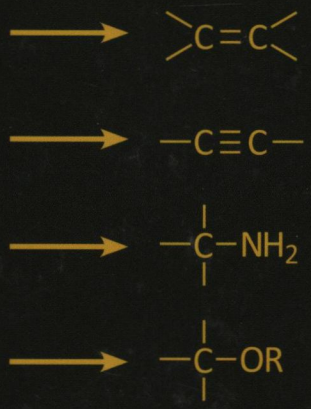
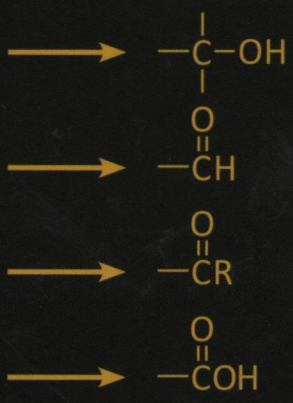


Third Edition

Comprehensive Organic Transformations

A Guide to Functional Group Preparations



Edited by
Richard C. Larock

WILEY

COMPREHENSIVE ORGANIC TRANSFORMATIONS

A Guide to Functional Group Preparations

Third Edition

Edited by
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WILEY

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COMPREHENSIVE ORGANIC TRANSFORMATIONS

DEDICATION

To all those students, postdoctoral fellows, and co-workers with whom
I had the pleasure of developing new synthetic organic chemistry, particularly
those courageous enough to undertake the preparation of this third edition with me,
and especially Professor Charles E. Russell, who passed away unexpectedly
while working on this project.

Richard C. Larock

PREFACE

Organic synthesis is one of the most rapidly developing areas in all of chemistry. Every day useful new reagents and reactions are reported worldwide in the chemical literature and beyond. It is increasingly difficult for the organic chemist to keep up with the latest in synthetic organic methodology without spending an inordinate amount of time reading a wide variety of journals, including many whose focus is not strictly synthetic organic chemistry. Useful new synthetic methodology can now often be found in areas as diverse as biology, medicinal chemistry, and material science, as evidenced by the 73 new journals covered in this third edition of *Comprehensive Organic Transformations*.

In recent years, a variety of reviews, books, and multivolume treatises have appeared to aid the organic chemist interested in synthetic organic methodology, but many of these are inaccessible, limited in scope, inappropriately focused, prohibitively expensive for personal or limited use, and/or inappropriate for those just entering the field. The intent of the present volume is to provide a comprehensive, highly condensed, systematic collection of useful synthetic methodology that both the beginning student and the long-time practitioner of organic synthesis will find useful. With the availability of increasingly sophisticated computer searches, the utility of books for such purposes is often questioned, but computer searches are not always available to everyone, can be expensive, only provide data reflecting the search capabilities of the programmer, and often provide overwhelming amounts of data of limited use. Printed matter also allows the browsing of related processes that might not surface in specific computer searches.

This book began in 1973 as a series of graduate course handouts at Iowa State University on the most important methodology for the synthesis of the major organic functional groups. Like the aforementioned publications, these materials grew rapidly over the years to a major treatise covering a vast amount of synthetic organic chemistry. In the mid-1980s, it was felt that the synthetic organic community might benefit from this compilation, so a serious effort was made to thoroughly update and organize the material for publication and fill in obvious gaps, such as useful processes involving more than one functional group, such as the Diels–Alder reaction. The result was the first edition of *Comprehensive Organic Transformations*, which appeared in late 1989, and covered the literature through 1987. That first edition covered some 160 or more primary chemical journals and a large number of books and reviews.

With the success of that first edition and the growing need for a single, comprehensive, relatively inexpensive compilation on synthetic organic methodology, the author was encouraged to attempt a second edition, which appeared in 1999. That update was generated by carefully scanning every page of the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Tetrahedron Letters*, and *Synlett* for the years 1988 through 1995, and checking references therein for additional materials. Unfortunately, with my full-time obligations as a researcher and teacher, there simply was not enough time available for the author to review the other major, synthetic organic chemistry journals, as thoroughly. However, 39 new journals and

numerous additional reviews and books were covered in the second edition, which more than doubled in size from the first edition.

With retirement in 2011, the author decided to attempt a third edition of *Comprehensive Organic Transformations*. However, with the explosive growth of the synthetic literature since the publication of the second edition and the author's devotion to research and teaching in those intervening years, it was obvious that it would take a team of co-workers to catch up on the literature. Thus, a team of 13 experienced researchers, practically all of them former students or collaborators of mine, was put together and the project was divided into two phases. Fifty-four major organic journals were chosen for coverage and each contributor was assigned several journals to be covered from 1996 through 2011. Some additional reviews and leading references since 2011 have been added, but the literature coverage since is far from complete. During this phase, which lasted until approximately June 2012, nearly 53,000 pdfs were gathered in dropbox.com, two collaborators dropped out for various reasons, and one, Professor Charlie Russell, died unexpectedly.

In phase two of this project, book chapter assignments were made, two new collaborators, Professor Anton Dubrovskiy (who assisted greatly with electronic issues and Dropbox) and Dr. Nataliya Markina, were added to the team, and the work of one early collaborator was reassigned to several others. During this phase, the new team on board sorted the pdfs for their assignment, read the corresponding literature, entered the new data into a crude electronic version of the second edition of *Comprehensive Organic Transformations* supplied by the publisher John Wiley, and prepared any new chemdraw equations that were required. I personally took over a major expansion of the Diels–Alder section in the alkenes chapter. As the Editor-in-Chief, I started to check all new data and quickly decided that it would be necessary for me to check every new reference and all new data and equations for consistency and accuracy, which unfortunately has delayed publication, but has hopefully resulted in a far better product. The final contributors are noted at the start of each section they were responsible for. My co-authors were responsible for the detailed proofreading of the final text and the addition of cross-referencing, although I rechecked all pages for spacing and any other obvious errors.

As in previous editions, the various co-authors take full responsibility for the reactions, reagents, and references covered. In choosing material for the text, the following general guidelines have been observed. All reactions covered are either very general in scope or else so unique that the methodology will find real synthetic utility. Yields are generally at least 50%. The reagents should be readily available or easily prepared and handled in the laboratory. As much as possible, similar transformations appear together in as concise a format as possible. Significant limitations in methodology are noted. No effort has been made to cover the use of protecting groups, since excellent reviews and books on this subject are already available. Likewise, heterocyclic chemistry has been omitted, except where heterocycles have proven useful to effect useful simple functional group manipulations. Synthetically useful, multiple functional group transformations have been covered and cross-referenced in appropriate sections, although they present certain organizational problems. When more than one functional group is produced, the transformation has usually been covered under the functional group appearing later in the book. For example, the considerable new material added on the synthesis of vinylic ethers has been included in the chapter on ethers, not the alkenes chapter. The transition metal-catalyzed coupling of main group organometallics also presents certain organizational problems, but has usually been covered under the stoichiometric metal involved, except where confusion and fragmented coverage might occur. To those chemists whose contributions to synthetic methodology may have been slighted or altogether ignored, I apologize. It would be appreciated if major errors or omissions are brought to the Editor-in-Chief's attention, so that future printings and any subsequent editions may be corrected.

As in the previous editions, all reactions have been systematically organized according to the functional groups. Within each chapter, the methodology is further subdivided into major processes, such as oxidation, reduction, and alkylation. It is hoped that the reader will find the desired transformation by simply skimming the detailed Table of Contents and scanning the appropriate section. Because of the large amount of space the previous transformation index took up (587 pages), the amount of time it would have taken to prepare another,

and the difficulty some readers were having with the necessary organic chemistry nomenclature, the transformation index has been omitted in this third edition (much to my relief!).

Obscure journals not readily available to most synthetic organic chemists have been avoided. The names of authors have been omitted to save space. Original publications describing a new transformation have usually been cited, but they have on occasion been omitted if they do not necessarily describe the best reaction conditions for running the reaction or purvey little of the scope of the reaction. References containing full experimental procedures, although they may be buried in an experimental section, have been favored over communications lacking such detail. An attempt has been made to highlight reviews and significant publications. The immediate problem one encounters is in deciding where to draw the line on references. Initial reports of a useful, new reaction have received complete coverage. However, the time soon comes when a truly significant reaction, such as the use of ester enolates in synthesis, appears routinely in publication after publication and no reviews have appeared. In such situations, the author has tended to include most of the new material and has not had the time to omit the more inconsequential earlier references.

It is hoped that the reader finds the latest effort worthwhile and will not hesitate to make suggestions on ways this material may be improved. Corrections, important additions or deletions, and organizational suggestions would be deeply appreciated.

Richard C. Larock
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ABOUT THE AUTHORS

Editor-in-Chief

Richard C. Larock is Distinguished Professor and University Professor Emeritus at Iowa State University where he taught from 1972 to 2011. Professor Larock received his B.S. degree summa cum laude in Chemistry in 1967 from the University of California at Davis and his Ph.D. from Purdue University in 1972, under the direction of Professor Herbert C. Brown, the 1979 Nobel Laureate in Chemistry. In 1971, he was an NSF Postdoctoral Fellow at Harvard University under Professor E. J. Corey, the 1990 Nobel Laureate in Chemistry. He is a pioneer in the use of palladium catalysts in organic synthesis, particularly in the synthesis of carbocycles and heterocycles, and contributed also to the synthesis and characterization of biopolymers and biocomposites. Professor Larock has given over 460 research presentations and published about 450 articles, 32 patents, and 4 books including two editions of the bestselling classic *Comprehensive Organic Transformations* (1989 and 1999). Professor Larock has been recognized by a number of major awards, including an Alfred P. Sloan Foundation Fellow, a DuPont Young Faculty Scholar Award, two Merck Academic Development Awards, the Iowa Regent's Award for Faculty Excellence, the Edward Leete Award of the American Chemical Society, the Paul Rylander Award of the Organic Reactions Catalysis Society, an American Chemical Society Arthur C. Cope Senior Scholar Award, and the American Chemical Society 2009 Midwest Award.

Contributors

Anton V. Dubrovskiy received his Specialist (B.S./M.S.) degree from the Higher Chemical College of the Russian Academy of Sciences in Moscow, Russia in 2007. He received his Ph.D. from Iowa State University in 2012 under the guidance of Professor Richard C. Larock. His research primarily focused on the development of aryne-mediated synthetic methodologies. Following postdoctoral work at the California Institute of Technology with Professor Sarah Reisman in the area of total synthesis, Dr. Dubrovskiy joined the chemistry faculty of the University of Houston-Clear Lake in 2014.

Tanay Kesharwani is an Assistant Professor at the University of West Florida, Pensacola, FL. He received an integrated B.S./M.S. degree in Chemistry from the Indian Institute of Technology, Bombay, in 2002. He earned a Ph.D. from Iowa State University under the supervision of Professor Richard C. Larock in 2008. His dissertation examined various aspects of electrophilic cyclization, palladium migration, and cationic polymerization. His postdoctoral experience included work at the Department of Drug Development, NewLink Genetics and the Department of Chemistry, Northwestern University. Prior to his current position, he held a visiting assistant professor position at Bard College, NY. His research interests

embrace diverse areas of organic chemistry, including the development of Pd-catalyzed C—H activation reactions, methodology development and the synthesis of biologically interesting heterocycles, and the design and synthesis of porous materials for gas storage and catalysis applications.

Nataliya A. Markina received her Specialist (B.S./M.S.) degree from the Higher Chemical College of the Russian Academy of Sciences in Moscow, Russia, in 2008. She then joined Professor Richard C. Larock's research group at Iowa State University where she received her Ph.D. degree in 2012. Her graduate research focused on NIH-funded heterocyclic library synthesis, multicomponent transition metal-catalyzed processes, and the chemistry of arynes.

María Teresa Molina was born in Madrid, Spain and studied Chemistry (Honors) at the Universidad Complutense de Madrid. She received her Ph.D. degree in 1985 (Institute of Organic Chemistry, CSIC) under the supervision of Professor Francisco Fariña. She was a Postdoctoral Fellow at CSIC (1985–1986) and a Fulbright-MEC Fellow (1986–1988) in the United States, working in the Department of Chemistry (Iowa State University) with Professor George Kraus (1985–1987), and at the University of Kansas (Department of Medicinal Chemistry) with Professors Lester Mitscher and Angelo Vedani (1987–1988). In 1987, she was appointed as Tenured Scientist at the Institute of Medicinal Chemistry (CSIC) in Spain. Her research interests are the synthesis of quinones and heterocyclic systems with biological activity (mainly antitumor and antiparasitic diseases) and the development of new synthetic methods.

Alexandre A. Pletnev is a native of Russia. He received his B.S./M.S. degree from the Higher Chemical College in Moscow in 1995 and his Ph.D., under the guidance of Professor Richard C. Larock, from Iowa State University in 2002. Following postdoctoral work on the synthesis of myrmicarin alkaloids at the University of California, Riverside, Dr. Pletnev joined Materia, Inc., working on the development of olefin metathesis catalysts. In 2007, he moved to Dartmouth College, where he now works as a Research Scientist.

Cristiano Raminelli was born in Brazil. He received his B.S. degree in Chemistry from the State University of Londrina in 1998. Studying at the University of São Paulo, he received his M.S. degree in Organic Chemistry with Professor Antonia T. Amaral in 2001 and his Ph.D. in Organometallic Chemistry with Professor João V. Comasseto in 2005. He was a postdoctoral fellow at Iowa State University working with Professor Richard C. Larock from 2005 to 2006. Returning to Brazil, he was a postdoctoral fellow at the University of São Paulo, working with João V. Comasseto from 2007 to 2008. In 2008, he joined the chemistry faculty of the Federal University of Grande Dourados. In 2011, he moved to the Federal University of São Paulo, where he is presently an adjunct professor. His research interests include the development of new methodologies involving benzyne chemistry and the stereoselective total synthesis of natural products.

Roman Rozhkov is currently a Technology and Innovation Leader at Thermofisher Scientific Corporation, specializing in areas of chemistry, nanoscience, and biotechnology. Dr. Rozhkov earned his M.S. degree in Chemistry in 1996 from the Mendeleev University of Chemical Technology of Russia and his Ph.D. from Iowa State University in 2004, under the direction of Professor Richard C. Larock. From 2004 to 2008, he was a Postdoctoral Fellow at the Department of Medicinal Chemistry and Molecular Pharmacology of Purdue University, working in the areas of nanotechnology and surface chemistry for genomic applications. Dr. Rozhkov has given about 50 research presentations and published over 30 articles and patents. During his industrial career, he has contributed to commercial products for genomics and clinical diagnostics and enabled the successful launch of SOLiD and Ion Torrent DNA sequencing platforms. Dr. Rozhkov is a recognized leader in areas of chemical methodology, surface chemistry, biotechnology, and DNA sequencing.

Charles E. Russell earned his Bachelor's degree from Wesleyan University, and his Ph.D. in organic chemistry from Colorado State University. After graduation, he worked as a research assistant at the University de Paris Sud in Orsay, France, followed by postdoctoral work in Paris at the University de Paris VI. After a postdoctoral appointment at Iowa State University with Professor Larock, and teaching for 2 years at Kansas State University, he joined the chemistry faculty at Muhlenberg College in Allentown, PA, in 1988. He remained a committed teacher, scholar, and mentor to his students until his untimely death in 2012.

Akhilesh K. Verma was born in Lucknow (U.P.), India. He received his M.Sc. in 1992 from B.U., Jhansi and his Ph.D. (2000) from the Department of Chemistry, University of Delhi, India. He was a Postdoctoral Fellow for 2 years with Professor Alan R. Katritzky at the University of Florida and with Professor Richard C. Larock at Iowa State University of Science and Technology, Ames, IA, from June 2007 to August 2008. He joined the University of Delhi in February 1998 and currently is a full Professor in the Department of Chemistry. He has guided 18 Ph.D. students, published more than 75 research papers, and given presentations in various countries. His research interests include copper/palladium-catalyzed coupling reactions, synthetic methodologies, and heterocyclic synthesis using alkynes.

Shilpa A. Worlikar was born in Mumbai, India. She received her B.Sc. and M.Sc. degrees in chemistry from Ruia College, University of Mumbai. She obtained her Ph.D. in 2008 from Iowa State University working with Professor Richard Larock on palladium-catalyzed and electrophilic cyclization reactions. Her postdoctoral work included research on the use of ligands in asymmetric synthesis at Texas A&M, College Station and surface functionalization of nanomaterials and intercalation of graphite at Rice University. She has also worked on anti-cancer therapeutics at the University of Maryland, Baltimore. She later joined eSionic, an energy storage start-up in the San Francisco bay area, where she has worked on lithium-ion battery additives. Her work has led to 18 publications and presentations and 8 patents with over 450 citations. In 2016, she joined Capacitor Sciences as Director of Materials Characterization, where she currently oversees scale-up as the Director of Materials Production.

Tuanli Yao is a Professor at Shaanxi University of Science & Technology. He received his B.S. and M.S. degrees in chemistry from Peking University in China. He then joined the group of Professor Richard C. Larock at Iowa State University, where he received his Ph.D. in 2005. He has since worked as a Postdoctoral Fellow at the University of California, Berkeley in Professor Richmond Sarpong's group, a Senior Scientist at Deciphera Pharmaceuticals, and an Associate Researcher at the University of Kansas, before beginning his academic career. His research interests include aryne chemistry, electrophilic cyclization, and palladium catalysis.

Gilson Zeni was born in Irai, Brazil. He received his M.S. degree from the Federal University of Santa Maria-RS (south Brazil) in 1996, working under the direction of Professor A. L. Braga, and his Ph.D. from the University of São Paulo in 1999, under the direction of Professor J. V. Comasseto. He then moved to the Federal University of Santa Maria, where he is now a professor. In 2003, he received a Brazilian Postdoctoral Fellowship to work with Professor Richard C. Larock at Iowa State University. His current research interests center around the synthesis and reactivity of organochalcogen compounds, the development of new synthetic methods and applications of organochalcogen substrates in electrophilic cyclization reactions, and novel iron catalysts for cross-coupling reactions of organochalcogens.

Li Zhang received his undergraduate degree in chemistry from Nanjing University in China in 1994. After completing his M.Sc. in organic chemistry at Iowa State University with Professor Richard C. Larock in 1999, he joined Chemical Development at Boehringer Ingelheim Pharmaceuticals, Inc. In 2017, he joined Process Chemistry in Pharmaron, Inc., where he is currently a senior director. He is the co-author of more than 30 papers and patents in synthetic organic chemistry and the pharmaceutical industry.

Xiaoxia Zhang received her B.Sc. degree in chemistry from Tsinghua University, China. She obtained her Ph.D. from Iowa State University, Ames, IA, under the supervision of Professor Richard C. Larock. There her research focused on the development of new synthetic methodologies for the synthesis of dienes, polyenes, and halogen-containing heterocycles. After receiving her Ph.D. in 2005, she joined Professor Dirk Trauner's group at the University of California, Berkeley as a postdoctoral research fellow and worked on the total synthesis of natural products. From 2008 to 2010, she worked for NewLink Genetics as a medicinal chemist on the synthesis of small-molecule inhibitors for biological targets. She is currently living in California.

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The preparation of a treatise of this magnitude requires the assistance of a large number of people. The Editor-in-Chief of this third edition, Distinguished Professor and University Professor Emeritus Richard Larock, is indebted to Iowa State University for providing the time and secretarial assistance over many years necessary for the preparation of the first two editions of this book, including a faculty improvement leave in 1994 to get the second edition underway.

The Department of Chemistry at the University of Hawaii at Manoa is gratefully acknowledged for having provided a visiting professorship to Professor Larock in 1985, which allowed the first edition to be brought to fruition, and for providing an office during the 1994 faculty improvement leave, although it is very hard to convince people that you are going to Hawaii to work.

To all those around Professor Larock, who have had to put up with the three editions of this book over more than 30 years, your encouragement, emotional support, patience, and perseverance are deeply appreciated. Professor John Maves deserves particular recognition for his encouragement, support, and putting up with the many personal impositions created by this endeavor over some 40 years. Although students were seldom asked to directly assist with the first two editions of the book, their willingness to take a back seat to this effort over the years is hereby acknowledged.

In this third edition, the contributing co-authors are indebted to Dr. M. Teresa Molina, Professor Akhilesh Verma, and Dr. Charles E. Russell for their participation in phase 1 of the project, the collection of thousands of pdfs covering the new synthetic literature that has been added to the third edition. Unfortunately, for personal reasons Drs. Molina and Verma were unable to complete the second phase of the project, the actual preparation of the new manuscript, and Dr. Russell unexpectedly passed away at that same stage. A number of former students and collaborators of Professor Larock's have played a major role in the development of this third edition by not only collecting the data, but also organizing it, generating the necessary new chemdraw equations, revising and correcting the text, and proofreading the sections for which they were responsible. Their contributions are deeply appreciated, especially when one considers the minimum financial reward for the overall time and effort put forth. Their names are highlighted at the start of the various sections of the book for which they were responsible. The entire team is also indebted to Professor Anton Dubrovskiy, who assisted in various ways, and set up and maintained the Dropbox account that was necessary to handle the large amount of data collected and processed during the project.

A core of highly professional and dedicated secretaries were responsible for the continual updating of the classroom materials that eventually became the basis of the three editions of this book. Particularly noteworthy contributions to the first two editions were made by Mrs. Helen Eggleston, Denise Junod, and Nancy Qvale. In more recent years, Mrs. Patti Boone contributed immensely to the updating of the synthetic organic graduate

course notes and provided help well beyond the call of duty, which freed up time for Professor Larock to consider the third edition.

Finally, the many co-workers of Professor Larock on this third edition are particularly indebted to their family and friends for supporting them and maintaining their sanity through endless corrections and frequent deadlines. As noted in previous editions, Professor Larock is indebted to his parents Hazel and Ralph Larock for having provided the encouragement and opportunities to achieve his academic goals and for having passed on genes with the perseverance and perfectionism necessary to carry the three editions of this project through to completion, when it seemed at times that the project would never end.