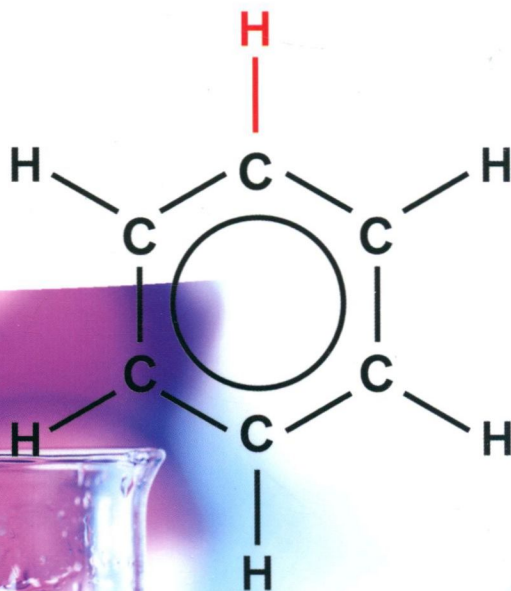


Edited by Lutz Ackermann, T. Brent Gunnoe
and Laurel Goj Habgood

Catalytic Hydroarylation of Carbon-Carbon Multiple Bonds



Filling a gap in the literature, this book comprehensively reviews catalytic C-H addition reactions of (hetero)aromatic hydrocarbons across carbon-carbon multiple bonds. In so doing, it summarizes both the scope as well as the limitations of different catalyst systems and building blocks, while highlighting their application to the synthesis of pharmaceuticals as well as commodity chemicals. Focusing on the latest developments, the team of authors comprising leaders in the field covers such topics as the hydroarylation of olefins, alkyne hydroarylation in the presence of transition metal catalysts, reaction of alkynes with arylboronic acids, and allene hydroarylation, as well as the synthesis of functionalized arenes and heteroarenes. A must-have for synthetic chemists in academia and industry dealing with catalysis, organometallic chemistry, the synthesis of natural products, fine chemicals, pharmaceuticals, products of the chemical industry and organic materials.



Lutz Ackermann is Professor of Chemistry at Georg-August-University Göttingen, Germany. He obtained his PhD under the supervision of Prof. Dr. A. Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr, Germany, in 2001. He then was a postdoctoral fellow with Prof. R.G. Bergman at the University of California (Berkeley, USA), before initiating his independent career in 2003 at Ludwig-Maximilians-University in Munich, Germany. In 2007, he was promoted to full professor at the Georg August-University Göttingen. His research is focused on the development of novel concepts for sustainable catalysis, with a topical focus on C-H activations. He was awarded, among others, the Gottfried-Wilhelm-Leibniz-Prize (2017), an ERC Grant (2012), the BASF Lecture at UC Berkeley (2014), and held visiting professorships in Milano, Perugia, Pavia (Italy), Wisconsin, Madison (USA), and Osaka (Japan). He is the editor of the book „Modern Arylation Methods“ (Wiley-VCH) and has co-authored more than 8 book chapters and 240 referred journal publications.



T. Brent Gunnoe is the Commonwealth Professor of Chemistry at the University of Virginia, USA, since 2008. He received his PhD from the University of North Carolina (USA) in 1997 under the director of Prof. J. Templeton and did postdoctoral work at the University of Virginia from 1997 to 1999. He began his independent career as an assistant professor at North Carolina State University in 1999. He was the recipient of a NSF CAREER Award, an Alfred P. Sloan Research Fellowship and the LeRoy and Elva Martin Award for Teaching Excellence. He currently serves as associate editor for ACS Catalysis. From 2009 until 2015 he was the Director of the Center for Catalytic Hydrocarbon Functionalization (CCHF), which was an Energy Frontier Research Center funded by the United States Department of Energy. He is co-inventor on three patents, co-author of four book chapters and 135 referred journal publications, and he has delivered over 100 invited lectures that are focused on fundamental aspects of catalyst technologies applied to the development of new energy resources as well as improved processes for the petrochemical industry and fine chemical synthesis.



Laurel Goj Habgood is an Associate Professor of Chemistry at Rollins College (USA). She obtained her PhD from Duke University (USA) under the direction of Prof. R. Widenhoefer in 2004. She completed postdoctoral research in the group of Prof. T. B. Gunnoe at North Carolina University (USA) from 2004 to 2006 and a sabbatical project with the group at the University of Virginia (USA) in 2012. In 2006 she started her independent career at Rollins College. Her research with undergraduates utilizes metal-NHC complexes as catalysts for organic transformations. She was awarded the endowed D.J. and J.M. Cram Chair of Chemistry in 2014 and currently serves as chair of the Department of Chemistry at Rollins College.

**Ackermann • Guimnoe
Habgood (Eds.)**

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Edited by

Lutz Ackermann

T. Brent Gunnoe

Laurel Goj Habgood

WILEY-VCH

The Editors

Prof. Lutz Ackermann

Georg-August-Universität
Institut für Organische Chemie
Tammannstr. 2
37077 Göttingen
Germany

Prof. T. Brent Gunnoe

University of Virginia
Department of Chemistry
McCormick Road
PO Box 400319
Charlottesville, VA
United States

Prof. Laurel Goj Habgood

Rollins College
Department of Chemistry
1000 Holt Avenue
Box 2743
Winter Park, FL
United States

Cover

fotolia_@zolnierrek

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Introduction and Preface

Laurel G. Habgood¹, Lutz Ackermann² and T. Brent Gunnoe³

¹Rollins College, Department of Chemistry, 1000 Holt Avenue, Winter Park, FL 32789-4499, USA

²Georg-August-Universität, Institut für Organische und Biomolekulare Chemie, Tammannstrasse 2, 37077, Göttingen, Germany

³Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904-4319, USA

Whether the target is a biologically active compound or a chemical feedstock, the ability to selectively install alkyl or alkenyl groups at a position of an aromatic or heteroaromatic compound is of central importance to synthetic chemistry. Friedel–Crafts catalysis and transition metal-catalyzed carbon–carbon bond coupling using aryl halides and organometallic reagents (e.g., Suzuki, Stille, and Sonogashira reactions) have been developed over time to install C–C bonds into aromatic substrates. These reactions are powerful tools for synthetic chemists, yet they are often hampered by one or more issues including harsh reaction conditions, lack of regioselectivity and/or stereoselectivity, use of toxic organometallic reagents, and the use of halogenated substrates. The direct addition of aromatic C–H bonds to unsaturated substrates (e.g., olefins or alkynes) provides an atom-economical strategy that is complementary to Friedel–Crafts and traditional C–C coupling reactions. Thus, it is not surprising that after the first published reports of hydroarylation of olefins and alkynes, the number of groups interested in the synthetic and mechanistic aspects of transition metal-mediated addition of C–H bonds across C–C double and triple bonds has steadily grown.

To our knowledge, the first review article to include olefin or alkyne hydroarylation chemistry was published in 1990 [1], the first focused review appeared in 2002 [2], and the first book was published in 2009 [3]. The extensive advancements in catalytic addition of C–H bonds across C–C multiple bonds and their rising impact on the methods used in synthetic organic chemistry warrants a comprehensive textbook that can be a single source providing a broad overview of the state of the art in the field. Skilled chemists may look to utilize the chemistry in synthetic applications while graduate students and novices to the field may discover fundamentally interesting chemistry. The authors of each chapter have presented a detailed review of their topic supplementing areas not covered with references for the interested reader, including both experimental and theoretical data. The book provides an overview of what has been accomplished, and also includes commentary on existing challenges and opportunities.

In Chapter 1, Villuendas, Ruiz, and Urriolabeitia detail the use of group 9 and 10 catalysts to functionalize heteroarenes. Hydroarylation reactions with aryl halides or arylboronic acids are not covered as emphasis is placed on the cleavage of heteroaryl C—H bonds. The synthetic utility and versatility of these reactions is conveyed by organizing the sections by type of heterocycle (thiophene, furan, indoles, etc.) rather than by type of catalyst. Future challenges and directions in the field are discussed in the summary.

Chapter 2 includes the alkylation of functionalized arene and heteroaromatic substrates utilizing ruthenium catalysts as detailed by Burns, Kozhushkov, and Ackermann. Electrophilic alkyl halides are omitted as chelation-assisted *ortho*-C—H activation is the focus. The sections of the chapter are organized based on the mechanistic modes of C—H cyclometalation via C—H bond cleavage, C—H oxidative addition, and carboxylate-assisted C—H activation. The summary highlights the broad applicability of the reactivity for a variety of chemical industries while identifying the need for further improvements to develop milder reaction conditions and asymmetric C—H bond functionalizations.

Chapters 3 and 4 examine olefin hydroarylation as organized by catalyst identity. In Chapter 3, McKeown, Habgood, Cundari, and Gunnoe examine d^6 transition metal catalysts for the alkylation of arenes without chelation assistance while in Chapter 4 Suslick and Tilley detail the use of d^8 transition metal catalysts. The industrial relevance of the reactions is emphasized as alkyl benzenes are precursors to large-scale chemicals such as polymer precursors and surfactants. The synergistic use of experimental and theoretical experiments for mechanistic information to further catalyst development is highlighted.

Nakao focuses on nickel-catalyzed hydroarylation of carbon–carbon multiple bonds in Chapter 5, which is an area that has experienced dramatic advancement in recent years. The characteristic features of nickel catalysis that are highlighted include reactivity with electron-deficient arenes including heteroarenes. This chapter is organized by reactions of alkenes and alkynes with fluorobenzenes, five-membered heteroarenes, and azines.

While ruthenium, rhodium, and iridium complexes are the most prevalent for directing group-assisted hydroarylation reactions, there is a growing body of work demonstrating the utility of catalysts from the first row transition metals. In Chapter 6, Yoshikai builds on the nickel catalysis discussed in Chapter 5 by examining the hydroarylation of alkynes and alkenes catalyzed by first row transition metals in groups 7–9. The majority of the chapter consists of hydroarylation reactions of alkynes and alkenes utilizing both high- and low-valent cobalt catalysts. Examples of iron complexes for the hydroarylation of alkenes and alkynes, as well as the use of a Lewis acidic iron salt for the hydroarylation of alkenes, are included. Notable at the end is a discussion on low-valent manganese complexes for the hydroarylation of alkynes.

In Chapter 7 Kirillova, Miloserdov, and Echavarren review copper, silver, and gold catalysts utilized for alkyne hydroarylation. The content is organized by the reactivity, selectivity, and mechanistic aspects of intra- and intermolecular reactions with emphasis on electron-rich heteroarenes and unactivated arenes. Alkyne hydroarylation using arylboron, aryl halide, and related congeners are

reviewed by Yamamoto in Chapter 8. The organization of the sections is first by substrate, and then by catalyst identity. Alkyne hydroarylations as both singular reactions and as part of sequential processes are discussed. Both Chapters 7 and 8 feature the inclusion of synthetic applications to biologically active compounds.

In the final chapter, Chapter 9, Widenhoefer reviews the hydroarylation of allenes. In comparison with the hydroarylations of alkenes and alkynes, which often involve directed C—H bond activation, allenes undergo a π -activation followed by an arene outer-sphere addition. Organized by nucleophile with emphasis on electron-rich arenes and heteroaromatics, both intramolecular and intermolecular reactions are presented with discussion on the mechanistic details related to the modes of ring closure.

Whether read in its entirety or as a specific chapter, the reader is provided with the historical development of catalytic olefin and alkyne hydroarylation chemistry including scope, mechanistic details, and areas for future development. Examples of industrial relevance and synthetic targets are included where appropriate. It is our hope that the readers find the information useful for their endeavors in the laboratory.

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