PREFACE TO VOLUME 117

> *Art is born of the observation and investigation of nature.*
>
> Marcus Tullius Cicero

Organic synthesis is both a science and an art form in which chemists apply their tools to build the desired target molecule efficiently and artfully. The true art of organic chemistry can only be achieved through an understanding of the underlying mechanisms of chemical reactions. Through this *observation and investigation of nature*, chemists have been able to exert precise control over the assembly of molecules. The three chapters in this volume exemplify the ability of chemists to build complex structures with exquisite control through a keen understanding of the fundamental nature of organic reactivity. The first chapter reviews the Catellani reaction in which norbornene shuttles palladium between two positions on an aromatic ring allowing the sequential and chemoselective formation of two bonds on neighboring carbons. The second chapter describes the use of asymmetric catalysts for the atroposelective formation of axially chiral biaryl molecules. In the third chapter on the Nazarov cyclization, an understanding of pericyclic reactions allows the synthesis of new rings often with high stereoselectivity. In each of these transformations, chemists have applied a detailed understanding of reaction mechanisms to develop synthetic methods to efficiently and selectively construct complex structures. *Organic Reactions* chapters are designed to provide a critical and thorough discussion of reaction mechanisms coupled with a demonstration of the breadth of structures that can be generated through this mechanistic understanding. These chapters allow us to appreciate both the art and science of these reactions and their applications.

Chapter 1 by Meichen Xu and Juntao Ye describes the development and application of Catellani-type reactions. Palladium-catalyzed functionalization of C-X and C-H bonds is indispensable in modern organic synthesis, but these reactions are typically limited to functionalization at the initial reaction site only. The Catellani reaction allows functionalization at both the *ipso*- and *ortho*-positions, resulting in the formation of two new bonds in one catalytic process. Catellani's key observation was that norbornene insertion allows palladium to be shuttled between two neighboring positions on an aromatic ring, forming a new bond at each position. These reactions provide ready access to 1,2,3-trisubstituted arenes that are challenging to make by other methods with complete control of chemoselectivity.

The Mechanism and Stereochemistry section illustrates the intricate mechanism by which norbornene transfers palladium between the two reaction sites. Key steps of the mechanism include initial palladation of the arene, carbopalladation of norbornene, and then intramolecular C-H activation at the *ortho*-position to give a palladacyclic intermediate. Reaction of the palladacycle with an electrophile results in the first bond formation at the *ortho*-position. After reductive elimination, extrusion of norbornene by β-carbon elimination places palladium back at the initial palladation site (*ipso*-carbon). A second palladium-mediated bond formation occurs with an orthogonal coupling partner. This section also discusses efforts to develop enantioselective Catellani-type reactions leading to axially chiral products, which provides a connection to Chapter 2 of this volume.

The Scope and Limitations section describes the *ortho*-functionalization of aryl (pseudo)halides through carbon-carbon and carbon-heteroatom bond formation using palladium(0) catalysts. The scope of palladium(II)-catalyzed Catellani-type reactions in which the palladation occurs on electron-rich heterocycles or by directed C-H activation of arenes is also shown. The Applications to Synthesis section highlights the application of Catellani-type reactions to generate densely functionalized arenes in natural products and drugs. The Comparison with Other Methods section compares the Catellani-type reaction with several well-known palladium-catalyzed *ipso*-functionalization processes. This section also compares applications of the Catellani-type reaction with traditional multi-step syntheses to achieve complex molecules. The Tables are organized in the same manner as the Scope and Limitations section, first focusing on Catellani reactions for the *ortho*-functionalization of (pseudo)haloarenes, followed by examples of Catellani reactions where the initial palladium-aryl bond is formed by C-H activation or transfer from an organoboron compound. This is an excellent chapter that highlights a relatively new reaction that has rapidly grown in importance.

Chapter 2 of this volume is authored by Philip H. Gilmartin, William C. Neuhaus, Marisa Kozlowski and Bo Qu and reviews the synthesis of axially chiral biaryl compounds by atroposelective aryl-aryl coupling. Atropisomers are a special class of enantiomers that are chiral due to a restricted rotation about a single bond. Biaryls with three or four *ortho*-substituents are common examples of these axially chiral molecules. Although less common than tetrahedral stereocenters, axial chirality is found in several natural products and in important classes of chiral ligands, such as those based on the 1,1′-binaphthyl structure. This chapter provides an authoritative account of the development of atroposelective routes to biaryl molecules and their applications.

The Mechanisms and Stereochemistry section summarizes the mechanisms for the three main approaches to the synthesis of axially chiral biaryl compounds: transition metal-catalyzed cross-coupling, oxidative coupling of phenols and naphthols, and coupling of oxidized arenes with arene nucleophiles. The mechanisms for enantiocontrol are delineated for each of these methods. The Scope and Limitation demonstrates the applications of each of these methods for atroposelective synthesis of biaryls. Transition-metal-catalyzed couplings using organoboron (Suzuki), Grignard (Kumada), and organozinc (Negishi) nucleophiles are most commonly used for atroposelective biaryl synthesis. Other less-commonly used routes for metal-catalyzed biaryl coupling are also highlighted. Oxidative homo- and cross-coupling of phenols and naphthols to give chiral biphenol or binaphthol products are discussed. Finally, examples where oxidized arenes, such as quinones or naphthalenyldiazenes are coupled with nucleophilic arenes, such as indoles or naphthols, are presented.

The Applications to Synthesis section describes the application of atroposelective syntheses to forming biaryl linkages in several natural products. Applications of these methods to the synthesis of axially chiral ligands, such as 2,2′-binaphthols and 2-binaphthylphosphines are also highlighted. There are few alternate routes to the atroposelective synthesis of axially chiral biaryls making this chemistry particularly valuable. The Comparison with other Methods section highlights examples in which non-aromatic chiral substrates are coupled in diastereoselective fashion, followed by aromatization, prochiral biaryl compounds are functionalized enantioselectively. The tables for this chapter are organized first by the nature of the aryl groups being coupled, including phenyl-phenyl, phenyl-naphthyl, naphthyl-naphthyl, coupling of higher-order arenes, and finally heteroarenes. The tables are further organized by whether the biaryl formation is a homo- or a cross-coupling reaction. This chapter is an excellent overview of the control of axial chirality, a less-common, but important aspect of enantioselective catalysis.

Chapter 3 by Tina N. Grant, Yonghoon Kwon, and F. G. West summarizes developments in the Nazarov cyclization over the past thirty years, updating the chapter on the Nazarov cyclization published in *Organic Reactions* in 1994. The Nazarov cyclization involves the electrocyclization of an oxygen-substituted pentadienyl cation, which is typically generated by Brønsted- or Lewis-acid activation of a 1,4-pentadien-3-one substrate. Electrocyclization affords a 2-oxycyclopentenyl cation that typically undergoes proton transfer to afford a cyclopentenone. Cyclopentenones are common structures in natural products and drugs that are also useful synthetic intermediates, making the Nazarov cyclization a highly useful synthetic method that continues to be further developed and applied in synthesis.

The Mechanism and Stereochemistry section describes the mechanism of the classic Nazarov cyclization and newer variants that generate the oxygen-substituted pentadienyl cation from a variety of precursors. The electrocyclization occurs stereospecifically under orbital symmetry control. The relative stereochemistry at the newly formed bond is often lost in the elimination step that terminates the reaction, however. The 2-oxycyclopentenyl cation can also be captured by nucleophiles in interrupted Nazarov cyclizations to afford more-highly-functionalized products that retain the stereocenters generated in the electrocyclization.

The Scope and Limitation section presents methods to prepare substrates for the Nazarov cyclization and the common activation methods for both traditional and non-traditional substrates. The scope of the Nazarov cyclization for the traditional 1,4-dien-3-one substrates as well other classes of precursors that lead the oxy-substituted pentadienyl cation needed for the Nazarov cyclization is reviewed. Finally, examples of interrupted Nazarov reactions in which the 2-oxycyclopentenyl cation is trapped by a nucleophile are described. The Application to Synthesis section highlights the use of Nazarov cyclizations in the preparation of complex polycyclic natural products, showing the utility of this transformation. The Comparison with Other Methods section briefly covers other common routes to cyclopentenone structures, including enolate cyclizations, radical cyclizations, vinylcyclopropane rearrangements, the Pauson-Khand reaction, [4+1] annulations, and intramolecular Friedel-Crafts reactions. The Tables follow the Scope and Limitation organization.

The initial tables focus on Nazarov cyclizations terminating with an elimination reaction and are organized by the structure of the starting material. The later tables focus on interrupted Nazarov cyclizations where nucleophilic or electrophilic additions occur after the electrocyclization step to give products with additional complexity. These tables are organized by the nature of the trapping event. This chapter does an outstanding job of highlighting the advances in the Nazarov cyclization over the past three decades.

I would like to take this opportunity to acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering these chapters through the various stages of the editorial process. I would particularly like to thank Dr. Rebecca Grange, Prof. Jeffrey Johnston, and Prof. Dennis Hall who served as Responsible Editors for the chapters in this volume and who worked closely with authors to ensure that these chapters came to fruition. I am also deeply indebted to Dr. Danielle Soenen for her continuous efforts as the Editorial Coordinator. Her knowledge of *Organic Reactions* is critical to maintaining the quality and consistency of the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the contributions of the authors, editors, and publisher. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the meticulous efforts of Prof. Steven Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to thank Dr. Michael Evans and Dr. Joseph Ward for maintaining our web presence (organicreactions.org). Thank you to Prof. Barry Snider (Secretary) for keeping everyone on task and Prof. Robert Maleczka (Treasurer) for ensuring *Organic Reactions* continues to remain fiscally viable.

Finally, I want to take this opportunity to recognize Dr. Jeffrey Press for his long and distinguished service to *Organic Reactions*. Jeff's association with *Organic Reactions* began in 1983 when he became secretary. In 1997, he took over as our treasurer as well. In this role he has ensured that *Organic Reactions* remained on sound financial footing through economic ups and downs and shifts in the publishing landscape. Jeff stepped down as treasurer earlier this year, but he remains a member of our Board of Directors. Thank you, Jeff, for your long and dedicated service to *Organic Reactions*.

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