PREFACE TO VOLUME 115

Einstein: "What I most admire about your art is its universality. You do not say a word, yet the world understands you."

Chaplin: "It's true. But your fame is even greater. The world admires you, when no one understands you."

This exchange highlights a profound truth that resonates within the world of synthetic organic chemistry, in which creativity and complexity are evident even when underlying processes are not fully understood. The preparation and identification of functional molecules remain ongoing challenges. Despite the intricate and often unclear mechanisms of the reactions involved, the creativity and innovation they embody are universally appreciated. The *Organic Reactions* series epitomizes the intuitive elegance and scientific rigor essential for new reaction development. Just as Chaplin's silent films communicated universally without words, the outcomes of these reactions speak volumes through their applications to challenging synthetic problems, even if the mechanistic nuances are unclear, much like Einstein's groundbreaking theories. Organic chemistry combines creativity with complexity, like the arts and sciences appreciated by Chaplin and Einstein. This dual nature allows the appreciation of sophisticated transformations and a deeper understanding of the reaction mechanisms, making the field accessible and admirable to a diverse audience. Studying cycloadditions and rearrangements captures the essence of this synergy. While detailed mechanisms may be challenging to grasp fully, the elegant transformations they enable are universally appreciated, reflecting the harmonious blend of scientific rigor and innovative thinking in organic chemistry.

The *Organic Reactions* series is unique in its meticulous curation of information on specific transformations, offering an unparalleled method for the proverbial "finding a needle in a haystack." When Roger Adams founded the series over eighty years ago, he identified a critical issue: while much of the relevant information and expertise existed, it was scattered and challenging to access uniformly across the chemical research landscape at that time. Adams foresaw the immense value of chemical informatics by consistently organizing this data in a database. The series addresses this need by systematically tabulating important examples of each transformation, thereby permitting researchers to evaluate the feasibility of a proposed process on

a specific substrate. Consequently, despite the advent of countless electronic platforms, *Organic Reactions* remains an invaluable resource that can readily identify specific tactics and thereby accelerate "Eureka" moments because of how it presents the information. Each chapter compiles comprehensive data and delves into the mechanistic and experimental details essential for practicing synthetic organic chemists. This detailed documentation facilitates the development of new adaptations, broadening the scope and defining the limitations of various reactions. The two chapters in this *Organic Reactions* volume describe higher-order cycloadditions and rearrangement reactions of allylic cations and propargylic alcohols, respectively.

The first chapter by Michael Harmata, Jianzhou Tu, and Madison M. Clark provides an excellent treatise on the (4+3) cycloadditions of allylic and related cations, updating an earlier chapter by James H. Rigby and F. Christopher Pigge (Vol. 51, Ch. 3, p 351), which covered the literature up to 1997. Hoffmann, Föhlisch, and Noyori independently pioneered the reaction, which is the formal combination of a neutral 1,3-diene with an allyl-type cation, most commonly an oxyallyl cation, to provide an intermediary cycloheptenyl cation that collapses to afford functionalized cycloheptenones. The process is symmetry-allowed and analogous to the Diels–Alder reaction, and as such, it can be envisioned as a [4π (4 atoms) + 2π (3 atoms)] cycloaddition reaction, wherein the allyl cation provides a 2π dienophile. Notably, there are relatively few general methods for the stereoselective synthesis of seven-membered rings.

The Mechanism and Stereochemistry section outlines the intricate pathways involved in allylic cation chemistry, addressing the debate as to whether these reactions proceed via concerted or stepwise mechanisms. Supported by computational and experimental studies, the discussion extends to understanding the regioselectivity observed with unsymmetrical dienes and dienophiles, shedding light on how specific substitution patterns influence reaction outcomes. The section also explores simple and induced diastereoselectivities, documenting how subtle changes in reaction conditions or substrate structure can impact the level of stereocontrol. Although the formation of mixtures of diastereoisomers is often problematic, it can be advantageous in fields like drug discovery, where different stereoisomers provide insight into the origin of biological activity.

The Scope and Limitations section is meticulously organized by the type of allylic cation and the nature of the reaction—inter- or intramolecular. For acyclic allylic cations, both unsubstituted and carbon-substituted species are examined. The discussion on intermolecular reactions highlights the versatility of these cations, particularly those derived from α-halo ketones, strained-

ring precursors, allylic alcohols, and propargylic esters. Each substrate class provides unique reactivity profiles that can be exploited in synthetic applications. In contrast, intramolecular reactions of allylic cations derived from the same precursors, including allenes and alkylidenecyclopropanes, emphasize their utility in constructing complex polycyclic structures. The discussion extends to heteroatom-substituted allylic cations in both inter- and intramolecular contexts. Halogen-, nitrogen-, oxygen-, and sulfur-substituted allylic cations showcase the breadth of functional-group compatibility and the potential for incorporating diverse heteroatoms into target molecules. These transformations are particularly valuable for accessing heterocyclic compounds prevalent in unnatural and natural products. Cyclic allylic cations, both unsubstituted and carbon-substituted, are also discussed in the context of inter- and intramolecular reactions. The section on intermolecular reactions covers allylic cations derived from cyclic α-pseudohalo- and α-halo ketones and the Nazarov cyclization, highlighting the importance of ring strain and electronic effects in these processes. In contrast, the intramolecular reactions include allylic cations derived from allylic alcohols and sulfones to facilitate the synthesis of polycyclic frameworks, which is crucial for natural-product synthesis. Heteroatom-substituted cyclic allylic cations, including those derived from dihalo ketones and oxidopyridinium ions, are also discussed, showcasing their unique reactivities. A section on benzylic and related cations delves into both inter- and intramolecular reactions of heterobenzylic cations derived from pyrroles, indoles, furans, benzofurans, thiophenes, and benzothiophenes. These reactions are instrumental in constructing complex, polycyclic structures and incorporating heteroatoms into aromatic systems.

The Applications to Synthesis section provides selected examples of how this type of cycloaddition has been utilized to prepare an array of challenging and important natural products. These case studies illustrate the practical utility of allylic cation cycloaddition chemistry in complex-molecule synthesis and will likely inspire future developments in this area. The Comparison with Other Methods section compares allylic cation strategies with alternative synthetic approaches, such as cycloadditions of vinyl diazo compounds, the Claisen rearrangement, (5+2) cycloadditions of vinyl cyclopropanes, and ring-closing alkene metathesis. Each method offers unique advantages and limitations, underscoring the versatility and robustness of allylic cation chemistry in the broader context of synthetic organic chemistry. The Tabular Survey mirrors the Scope and Limitations section, wherein the tables are differentiated by inter- and intramolecular reactions, the substitution on the dienophile, and whether it is cyclic or acyclic

to permit the identification of a specific reaction combination of interest. This is an outstanding chapter on an important cycloaddition reaction that will be a valuable resource to the synthetic community, particularly given its utility for target-directed synthesis.

The second chapter by Giovanni Vidari, Debora Chiodi, Alessio Porta, and Giuseppe Zanon describes the Meyer-Schuster rearrangement, which involves the formal conversion of secondary and tertiary propargylic alcohols to an array of α,β-unsaturated carbonyl compounds. The original process was discovered in the early 1920s by Meyer and Schuster, who discovered that propargylic carbinols rearrange using simple Brønsted acids. Although the direct conversion of the propargylic alcohol to the α,β-unsaturated carbonyl compound is atom-economical, the strongly acidic and harsh reaction conditions commonly employed in early versions of the Meyer–Schuster reaction are incompatible with many acid-labile substrates. Hence, relatively few examples that afford acid-labile products were reported in the first 70 years following its discovery. Moreover, the reaction frequently produces a mixture of (*E*)- and (*Z*)-stereoisomers in addition to several competing side reactions, the most notable of which is the Rupe rearrangement, which yields a different constitutional isomer for tertiary alcohol substrates. Nevertheless, this reaction is a conceptually simple and practical method for generating α,β-unsaturated carbonyl groups present in many important intermediates and bioactive molecules. Therefore, the search for milder and more selective methods has been the focus of ongoing developments in this area, which are nicely captured in this chapter.

The Mechanism and Stereochemistry section explores the array of mechanistic pathways available for effecting the Meyer–Schuster rearrangement, focusing on how various conditions and catalysts influence the reaction mechanism. For instance, the classic acid-promoted Meyer–Schuster rearrangement of propargylic alcohols follows an ionic mechanism. In contrast, the rearrangement under basic conditions is relatively rare and is thought to involve a prototropic rearrangement. The discussion also covers the rearrangement of propargylic alcohols activated as oxo complexes of transition metals, emphasizing the role of metal coordination in facilitating these transformations. In addition, this section also describes the rearrangement of propargylic esters and alcohols using gold and other transition metals, including cases involving C-H bond activation of terminal propargylic alcohols via transition-metal insertion. These variations in the mechanism highlight the complex interplay between substrate, catalyst, and reaction conditions.

The Scope and Limitations section provides a comprehensive overview of substrate preparation and the diversity in reaction conditions that facilitate the Meyer–Schuster rearrangement. Both catalyzed and uncatalyzed rearrangements are discussed for propargylic alcohols, with particular attention to those promoted by Brønsted and Lewis acids. The use of oxo complexes of transition metals and transient carbonate intermediates is described, highlighting their influence on reaction efficiency and selectivity. Gold and other transition-metal-based catalysts play a crucial role in these transformations, often leading to enhanced reactivity and selectivity. The Meyer–Schuster rearrangement of propargylic esters and ethers highlights the versatility of this transformation, including the rearrangement of α-allenols, propargylic hemiaminals, and sulfides. The aza-Meyer–Schuster rearrangement offers a pathway for rearranging propargylic amines, hydrazine derivatives, γ-amino ynamides, and propargylic hydroxylamines. The versatility of the Meyer–Schuster rearrangement is further showcased in tandem and consecutive reactions that involve a Meyer–Schuster rearrangement in conjunction with a carbon–carbon bond-forming reactions such as aldol-type condensation, Michael addition, Friedel–Crafts, and Diels–Alder reactions. The utility of these rearrangements is demonstrated in the formation of an array of important heterocyclic scaffolds. These transformations can also readily access aliphatic oxa- and azacyclic derivatives.

The section on the electrophilic and nucleophilic interception of Meyer–Schuster rearrangement intermediates delineates a series of methods that diversify the products. Consecutive reactions involving the interception of an allenyl carbocation or an allenol intermediate are explored, in which the latter are further subdivided into propargylic alcohol and ester precursors, with examples including α-halogenation, α,α-dihalogenation, electrophilic α-arylation, α-trifluoromethylation, aldol-type and Mannich-type addition reactions, and α-allylation. Alternatively, the interception processes from propargylic esters permit the synthesis of diverse structures, such as tetrahydrofurans, tetrahydropyrans, and halo-Meyer–Schuster rearrangement products. In contrast, the dehydrogenative Meyer–Schuster rearrangement produces alkynyl ketones, while the alkylative variant leads to alkyl-α,β-unsaturated ketones. Knoevenagel-type derivatives permit the preparation of α-ylidene-1,3- diones and α-ylidene β-keto esters, broadening the scope of accessible products. Intramolecular Michael addition reactions, Myers–Saito cyclizations, and cycloisomerization reactions further demonstrate the versatility of these pathways. The section culminates with a discussion on intermolecular α-alkylation and α-

allylation reactions, emphasizing the interception of Meyer–Schuster rearrangement intermediates involving allenol intermediates with reversed reactivity, further illustrating the broad applicability and innovative potential of these rearrangements in modern organic synthesis.

The Applications to Synthesis section describes selected applications for preparing several bioactive natural and unnatural products. For example, this process has featured in the synthesis of alkaloids, carotenoids, prostaglandins, sesquiterpenes, etc., in addition to an array of other bioactive agents, each highlighting a unique aspect of the transformation. The Comparison with Other Methods section evaluates other approaches, including elimination, olefination, cross-coupling, alkyne-carbonyl metathesis, cycloadditions, and carbocyclizations reactions that afford α,β-unsaturated carbonyl compounds. The Tabular Survey delineates selected examples, making this the first example of using the condensed tables, which are organized by starting material for the classical reactions and by the product for the tandem and intercepted reactions to permit the identification of a specific reaction combination of interest. The chapter is meticulously crafted to provide both the seasoned chemist and the novice with a thorough understanding of this reaction's potential and place within the broader context of organic synthesis.

As I pen my final preface as the Editor-in-Chief of *Organic Reactions*, I reflect on the remarkable journey over 15 volumes. During my tenure, we have implemented numerous changes to ensure that *Organic Reactions* remains a leading reference text in organic chemistry. We launched a new, user-friendly website, expanded our visibility by being abstracted in SciFinder, and cultivated a robust social-media presence on Twitter and LinkedIn. Additionally, we championed diversity, significantly enhancing the representation on our Boards of Directors and Editors. Recognizing the need for sustainable leadership, we created the role of Executive Editor held by Steven M. Weinreb and divided the President/Editor-in-Chief position to ease its demands. While I will continue to serve as President, I am confident that under Kevin Shaughnessy's capable leadership as Editor-in-Chief, *Organic Reactions* is well-positioned for continued success and excellence in organic chemistry.

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for guiding this volume through the editorial process and their collective efforts throughout my tenure as Editor-in-Chief. I extend my gratitude to Dr. Al Padwa (Chapters 1 and 2) and Dr. Steven M.Weinreb (Chapter 1), who served as the Responsible Editors for marshaling the chapters through the various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her

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I am also indebted to past and present members of the Board of Editors and Directors for ensuring the enduring quality of *Organic Reactions*. The specific format of the chapters, in conjunction with the collated tables of examples, makes this series of reviews not just unique but exceptionally valuable to the practicing synthetic organic chemist, a testament to their collective expertise and dedication.

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