ORGANIC REACTIONS

Volume 115

Organic Reactions

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Organic Reactions

VOLUME 115

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INTRODUCTION TO THE SERIES BY ROGER ADAMS, 1942

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses*, they have not been subjected to careful testing in two or more laboratories. Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required. Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

INTRODUCTION TO THE SERIES
BY SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and abstracting services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject. However, *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of this avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to important experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that, at the dawn of the 21st century, the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

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, Jianzhuo 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 its 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 continued and ongoing contributions to the success of *Organic Reactions* as the Editorial Coordinator: her knowledge is critical to maintaining consistency in the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the contributions of the authors, editors, and publishers. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the efforts of Dr. Steven M. Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to acknowledge Dr. Barry B. Snider (Secretary) for keeping everyone on task and Dr. Jeffery Press (Treasurer) for ensuring we remain fiscally solvent!

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.

P. Andrew Evans
Kingston
Ontario, Canada

John Edwin Baldwin

1937–2024

John Edwin Baldwin was born in Berwyn, Illinois on September 10, 1937 and grew up in Oak Park. He excelled in sports and was valedictorian of his high school graduating class. Baldwin did his undergraduate studies at Dartmouth College, graduating as valedictorian in 1959. He then pursued his doctoral studies in chemistry and physics under Jack Roberts at California Institute of Technology, earning his PhD in 1963.

After five years on the faculty of the University of Illinois he moved in 1968 to the University of Oregon as a professor. During his sixteen-year tenure there, he also served five years as Dean of Arts and Sciences. John moved in 1984 to Syracuse University where he spent his final decades of teaching and research. He co-led the eight-year creation of the 230,000 square foot Life Sciences Complex and chaired the Department of Chemistry with immense distinction. He invested in mentoring other scholars and academic leaders; his colleagues and students are making an impact throughout the world. He was the William Rand Kenan Jr. Professor of Science and was named one of the few Distinguished Professors at Syracuse, also earning a Chancellor's Citation for Excellence. His research was supported by the NSF and by awards, such as those from the John Simon Guggenheim and the Alexander von Humboldt Foundations. Baldwin served on national boards and scientific advisory committees, including the President's Science Advisory Committee; the NIH Medicinal Chemistry Study Section; the NSF's Chemistry Division Standing Review Panel; the executive committee of the ACS Division of Organic Chemistry; and the Advisory Board of the ACS Petroleum Research Fund. He served on the Board of Editors of *Organic Reactions* from Volume 20 (1973) to Volume 25 (1978).

Deeply interested in physical organic chemistry and dedicated to the universities where he worked, as well as to his broader scholarly community, Baldwin developed a reputation as a gifted and meticulous scholar, researcher, collaborator, and legendary teacher and mentor. John's research contributions were diverse and highly influential

and his complex experiments were considered ambitious, elegant, and insightful: one mark of that work was his receipt of the American Chemical Society's James Flack Norris Award in Physical Organic Chemistry in 2010. The citation highlights his original mathematical approaches and ingenious isotopic labeling to solve the most challenging problems.

He was one of the first to use density-functional theory and other emerging quantum calculations to gain insights into chemical bonding and reaction mechanisms. He published over 150 articles and continued to publish important works up until his retirement in 2014 focused on mechanistic studies of structural isomerizations and stereomutations, including those in cyclopropanes and vinylcyclopropanes. Small molecules, especially those in the gas phase, were always of particular interest, since the energy levels of these molecules could be calculated using the programs and computational capabilities of the time. He summarized this work and its history and development in a 2003 *Chemical Reviews* article.

John had a passion for learning that extended beyond his primary professional field. He read broadly, especially in history and philosophy, and studied many foreign languages, including Russian, Swedish, and German. He embraced the professional and personal opportunities to travel and held visiting professor appointments at Heidelberg, Munich and Hamburg, Germany; Krakow, Poland; Stockholm and Göteborg, Sweden; and at his alma mater Cal Tech. His friends and colleagues treasured his intense interest in their work, no matter how far afield it was from his. He loved music and enjoyed being on the board of the Chamber Music Society and supporting the work of the Society for New Music in Syracuse. John and Anne held concerts of those societies in their home and frequently hosted visiting musicians. He was an athlete on the football, lacrosse, track, and ski teams at Dartmouth. He remained an avid runner and took pleasure in running with friends.

John died on May 26, 2024 and is survived by his wife, Anne, three children, and eight grandchildren.

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ORGANIC REACTIONS

CHAPTER 1

(4+3) CYCLOADDITIONS OF ALLYLIC AND RELATED CATIONS

MICHAEL HARMATA, JIANZHUO TU, AND MADISON M. CLARK

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Edited by ALBERT PADWA AND STEVEN WEINREB

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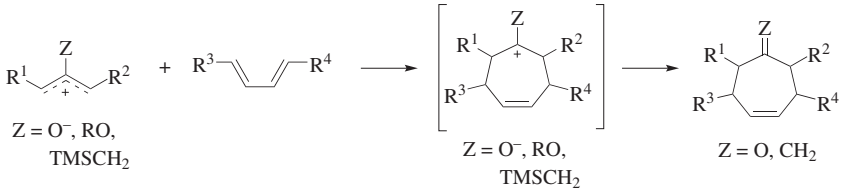
INTRODUCTION

The (4+3) cycloaddition is defined as the reaction between a diene and a cation that is stabilized by a π system. The initial adduct is formally a cycloheptenyl cation, and the process generally terminates by electron donation from a substituent (Z) on the 2-position of the starting allylic cation (Scheme 1). Several interesting variations on this theme are emerging. This review is a continuation of where the previous *Organic Reactions* chapter in this area ended in 1997,[1] and thus covers papers published through June 2018. A supplemental list of references is provided at the end of the bibliography, with papers published in the period of 2018–2023. Also note that any ratios of isomers missing in schemes reflect their omission in the primary literature.



Scheme 1

The foundations of this reaction were first laid by Hoffmann, Föhlisch, and Noyori, whose contributions have been summarized in a number of reviews[2–8] and the previous *Organic Reactions* chapter on this subject.[1] It is worth noting that IUPAC rules

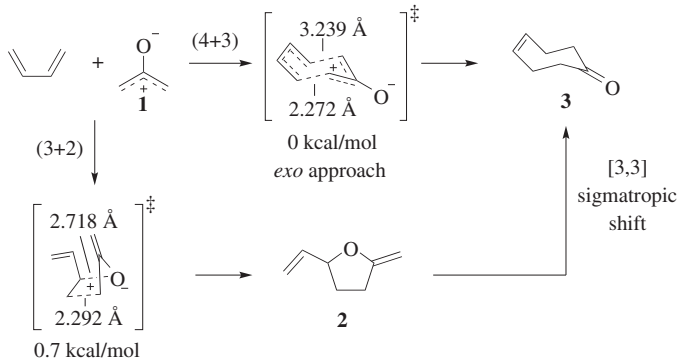
recommend the use of brackets and parentheses in the description of cycloaddition reactions.[9] The former descriptor refers to the *number of electrons* involved in each unit in the bond formation process. Therefore, the reactions described herein would be characterized as [4+2] cycloadditions, as the allylic cation has only 2 π electrons, just as a "normal" dienophile in a Diels–Alder reaction. Parentheses refer to the *number of atoms* involved in each of the components of the cycloaddition. In this case, the processes described herein are referred to as (4+3) cycloadditions.

MECHANISM AND STEREOCHEMISTRY

Concerted or Stepwise? Computational and Experimental Studies

There are two possible mechanistic extremes for the (4+3) cycloaddition: stepwise and concerted. Computational examination of certain (4+3) cycloadditions indicates that both pathways are feasible. Stepwise reactions tend to be favored when the dienophile is more reactive (i.e., electrophilic) and the diene is more electron-rich or nucleophilic.

Calculations involving the reaction of the "parent" oxyallylic cation and its protonated congener, the 2-hydroxyallylic cation, with selected dienes provide some insight into the fundamental reactivity and mechanistic issues in (4+3) cycloaddition chemistry. For example, the parent, unsubstituted oxyallylic cation **1** preferentially reacts in silico with *s-cis*-1,3-butadiene via an *exo* concerted, but asynchronous, transition state. Only slightly higher in energy is a competing, concerted (3+2) cycloaddition leading to dihydrofuran **2**, which then undergoes a [3,3] sigmatropic (Claisen) rearrangement with a barrier of 7.6 kcal/mol to produce the formal (4+3) cycloaddition product **3** (Scheme 2).[10]

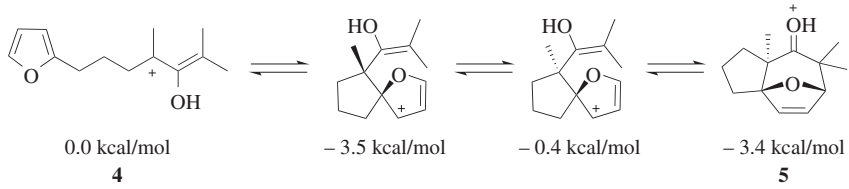


Scheme 2

Cycloadditions of various congeners of the parent oxyallylic cation having a metal cation or a proton associated with the formally negatively charged oxygen were calculated to proceed along paths that are generally experimentally observable. Increasing the electrophilicity of the dienophile by decreasing the formal charge on oxygen leads to either stepwise reactions or concerted (3+2) cycloaddition reactions that could

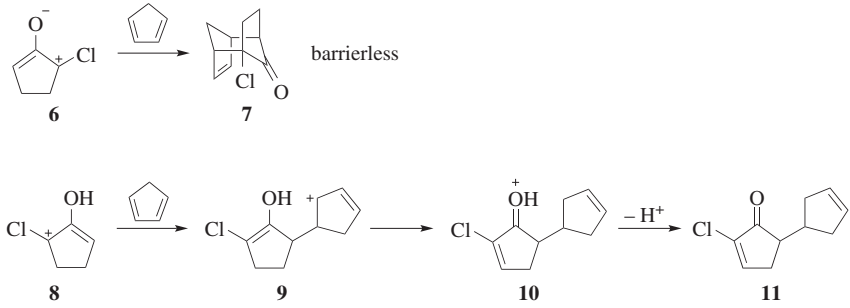
be followed by a Claisen rearrangement to afford (4+3) cycloadducts. Similarly, as the nucleophilicity of the diene increases, stepwise reaction paths are favored.[11] In the most extreme case examined, the reaction of the 2-hydroxyallylic cation with pyrrole gives a σ-complex intermediate, for which any mode of further cyclization is unfavorable. Proton loss from such an intermediate affords the product from a net electrophilic aromatic substitution, which is a common side reaction in this type of chemistry.

In the same vein, calculations indicate that the intramolecular cyclization of oxyallylic cation **4** to tricycle **5** proceeds by a barrierless, stepwise process (Scheme 3).[12] Moreover, the same calculations suggest that the formation of product **5** is reversible, albeit this has apparently not yet been experimentally verified.



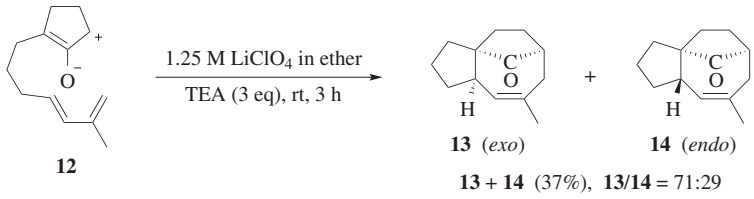
Scheme 3

The idea that divergent reactivity is to be expected based on the electrophilicity of the dienophile is supported by the calculated reaction paths of the cyclic oxyallylic cation **6** and its protonated counterpart **8**. Although the former is predicted to afford the *endo* (4+3) cycloadduct **7** from a barrierless reaction with cyclopentadiene, the latter is calculated to proceed to a cationic intermediate **9** that undergoes an intramolecular hydride transfer to produce **10**, followed by the loss of a proton to form **11** (Scheme 4).[13] Experimental evidence supports the hydride transfer pathway; however, it still is not clear whether **6** and **8** uniquely form **7** and **11**, respectively.



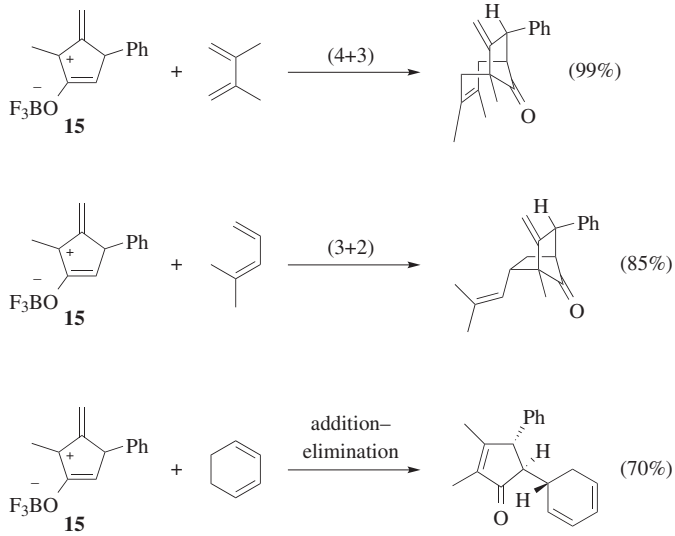
Scheme 4

In a related analysis, the oxyallylic cation **12** is calculated to afford *exo* and *endo* intramolecular (4+3) cycloaddition products **13** and **14** via concerted, asynchronous transition states, in which a nonpolar medium favors the *endo* adduct and a polar environment favors the *exo* adduct. Notably, the computational predictions were substantiated by experimental studies (Scheme 5).[14]



Scheme 5

In a study of cyclic allylic cations like **15**, formed as the result of Nazarov cyclizations of vinyl allenyl ketones, computations suggest that, generally, a subsequent (4+3) cycloaddition should occur with an *exo* preference in a concerted, asynchronous fashion.[15] Dienes that are more electron-rich or sterically hindered kinetically favor stepwise processes that result in either (3+2) cycloaddition or addition/elimination pathways. These calculations were validated by experimental results (Scheme 6).[16] Related studies on the behavior of cations obtained from the Nazarov cyclization of divinyl ketones revealed that pyrrole and furan dienes prefer electrophilic aromatic substitution versus cycloaddition with such dienophiles.[17]

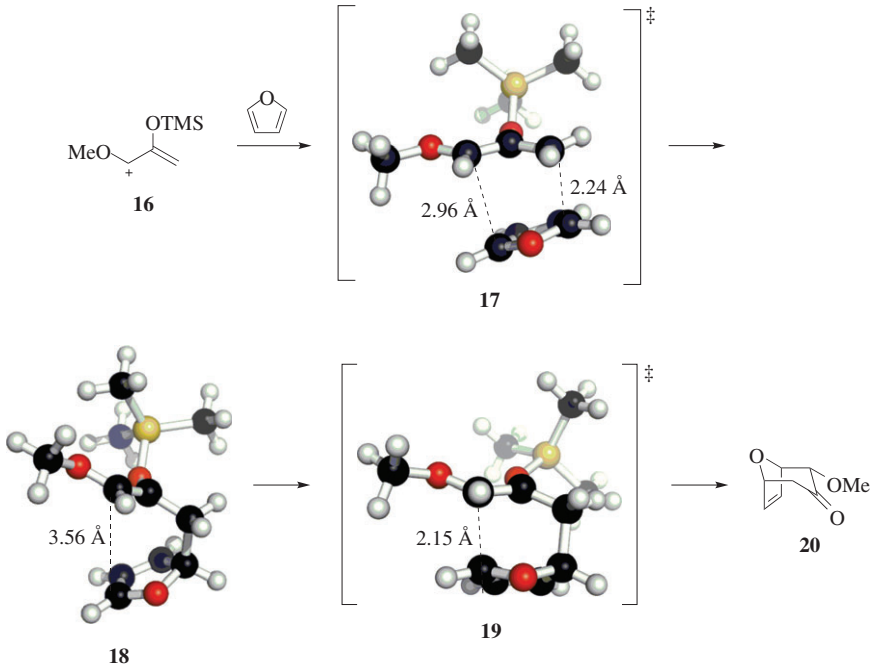


Scheme 6

A relatively recent development in (4+3) cycloaddition chemistry has been the the ability to employ allylic cations as dienophiles that are further stabilized by virtue of a resonance interaction with a heteroatom, such as nitrogen, oxygen, or sulfur. The success of this approach has prompted both experimental and computational mechanistic investigations of the chemistry.

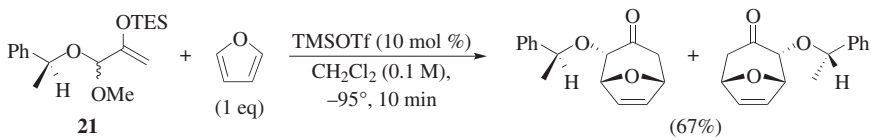
For instance, the (4+3) cycloaddition reaction of the methoxy-stabilized allylic cation **16** with furan was evaluated computationally. The stepwise reaction proceeds

through a reactant complex consistent with *endo* transition structure **17**, wherein the initial formation of intermediate **18** affords cycloadduct **20** via transition structure **19**. The results of gas-phase and solution-phase calculations were similar, wherein the shape of the potential energy surface is the same for both sets of conditions (Scheme 7).[18]



Scheme 7

The same analysis applied to a chiral oxocarbenium ion revealed a contrasteric preference for the approach of the diene to the dienophile. For example, the reaction of **21** with furan in the presence of trimethylsilyl triflate results in the formation of two diastereomeric cycloadducts in 67% yield with modest selectivity (dr 88:12, Scheme 8).[19] A subsequent computational investigation of this cycloaddition supported the structure shown in Figure 1 as the lowest-energy transition state for the process (TMS replacing TES for computational simplicity).[18] A CH–π interaction is rationalized to stabilize the transition structure instead of the steric repulsion that might be anticipated. Importantly, the calculations correctly predict the major stereoisomer formed in the experimental studies.



Scheme 8

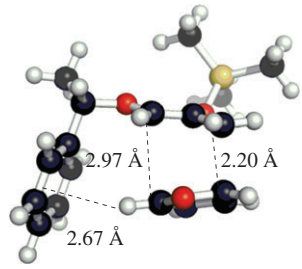
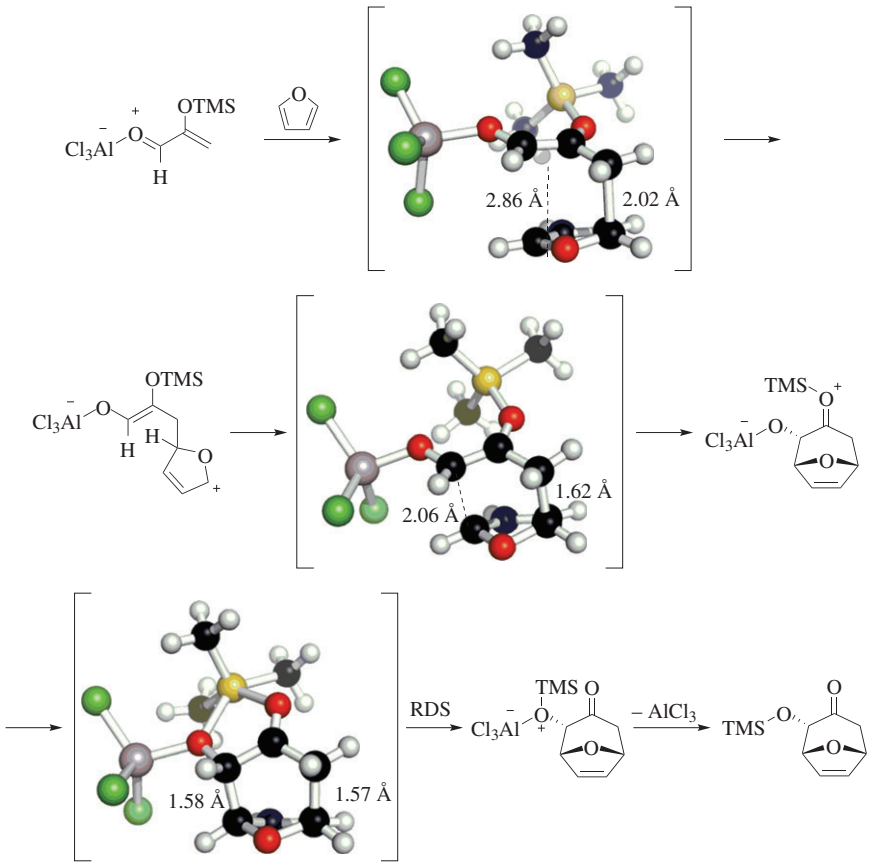


Figure 1. The transition structure for the reaction in Scheme 8.

α,β-Unsaturated carbonyl compounds coordinated to a Lewis acid can be viewed as oxygen-stabilized allylic cations. For example, a complex of 2-trimethylsilyloxyacrolein and aluminum trichloride was calculated to react with furan in a multistep process that involves 1,4-addition of the furan, ring closure to complete the formal (4+3) cycloaddition process, and, finally, rate-determining silyl group migration to afford the final product (Scheme 9).[20,21] Although



Scheme 9

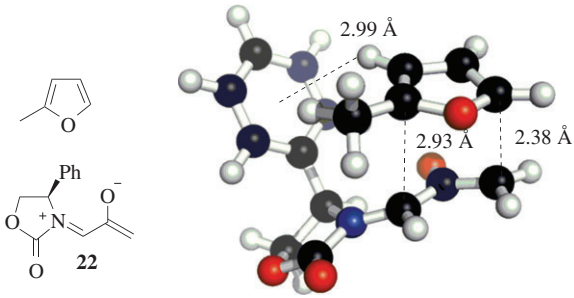


Figure 2. The transition structure for the reaction of allylic cation **22** with 2-methylfuran.

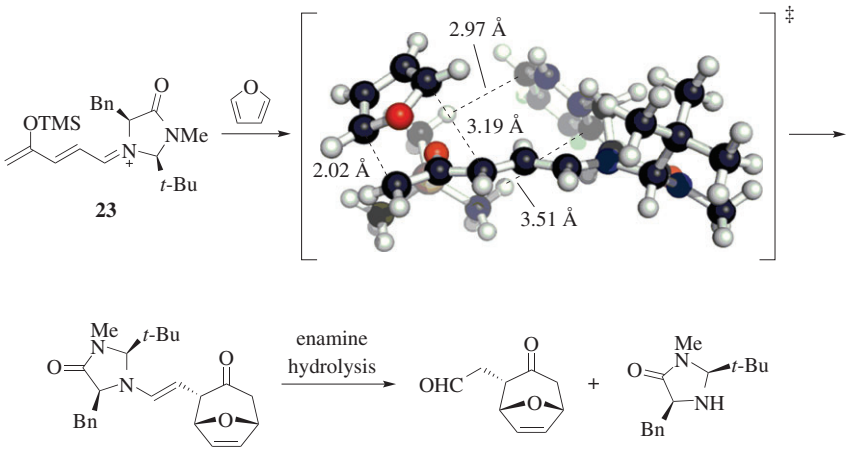
simple, α,β-unsaturated aldehydes with only a proton or carbon substituent at the 2-position react with cyclopentadiene to afford (4+3) cycloadducts, calculations suggest this process begins with a Diels–Alder reaction that is followed by ring expansion and a hydride shift.[22,23]

Computational studies on the (4+3) cycloaddition reactions of unsaturated iminium ions have revealed a steric attractor effect similar to that shown in Figure 1 (for vinyl oxocarbenium ions) when chiral oxazolidinones like **22** (Figure 2) and related allylic cationic species are used as dienophiles.[24] The calculations indicate that this class of vinyl iminium ions is best characterized as ambiphilic—rather than strongly electrophilic—dienophiles that undergo concerted, although asynchronous, cycloadditions. The iminium ions are predicted to react regioselectively with 2-substituted furans with *syn* selectivity, regardless of the electronic nature of the substituent on the furan, and this postulate has been experimentally verified.[25–27]

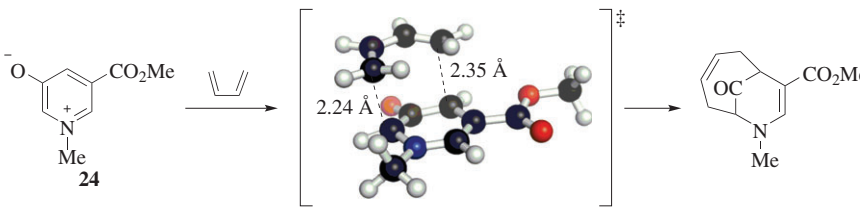
The case of dienyl iminium ions is even more interesting. The cycloaddition of **23** with furan is calculated to be a stepwise process. Facial selectivity is determined by the motion of the OTMS group as it moves away from the incoming diene. This process leaves the OTMS group residing in a position that allows the diene to approach on the same face as the benzyl group of the chiral auxiliary. The methyl groups on the TMS fragment are further stabilized by a CH–π interaction with the aromatic ring of the benzyl group in the catalyst (Scheme 10).[28]

A special case of nitrogen stabilization of an allylic cation is found in certain oxidopyridinium ions. Species such as **24** readily undergo (4+3) cycloaddition reactions with dienes. Calculations support a concerted cycloaddition with dienes, but not with extensive asynchronicity, as demonstrated by the *endo* transition structure in the reaction of **24** with butadiene (Scheme 11).[29]

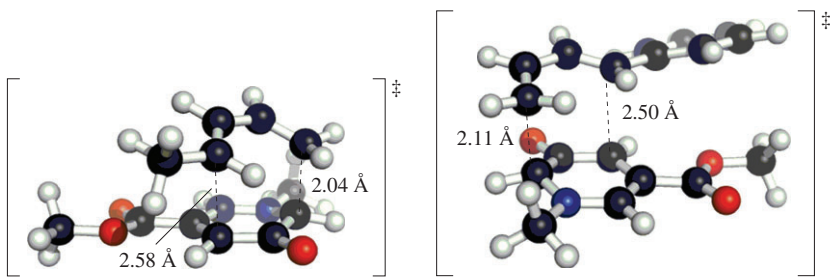
However, with 1-substituted butadienes, calculations indicated greater asynchronicity in cycloadditions with **24**, which is evident from the difference in the lengths of incipient bonds, low *endo*/*exo* selectivity, but high regioselectivity, with the latter two outcomes being supported by experiment (Figure 3).[29]



Scheme 10



Scheme 11



lowest energy transition structure
24 + (*E*)-1,3-pentadiene (*exo*)

lowest energy transition structure
24 + (*E*)-1-phenylbutadiene (*endo*)

Figure 3. The transition structures for the reaction of **24** with two substituted dienes.

A special subclass of (4+3) cycloadditions makes use of cations that are heterobenzylic, derived from, for example, furyl- or indole-substituted alcohols.[30–32] A representative sample of species on which computational work has been performed is shown in Figure 4. All reported studies suggest that reactions of these dienophiles with dienes occur in a stepwise fashion, and that the final step of the cycloaddition process is an electrophilic aromatic substitution reaction.

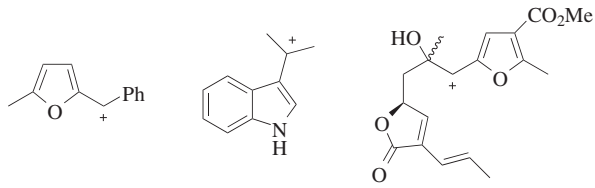
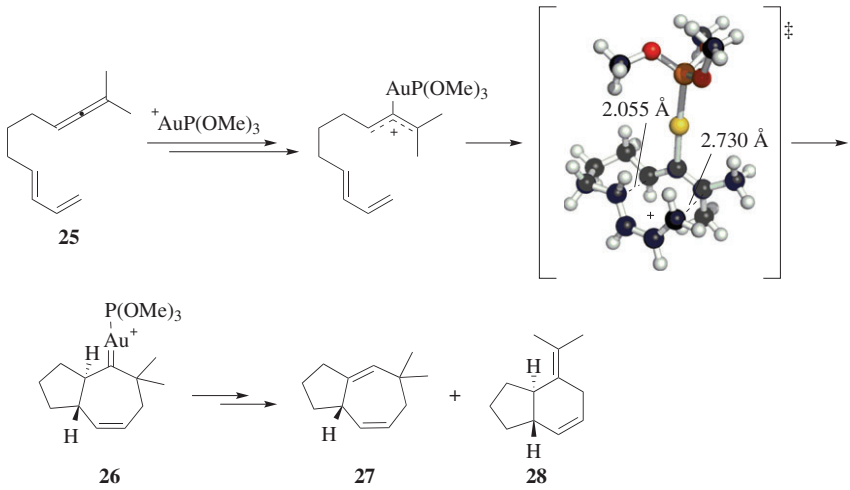


Figure 4. Heterobenzylic cations that engage in (4+3) cycloadditions.

Other classes of (4+3) cycloadditions that have been analyzed computationally are those promoted by metal catalysts. For instance, simple allenes react with coinage metals (e.g., Pd, Au, Pt) to generate a carbon–metal bond at the central carbon of the allene with concomitant formation of an allylic cation, which can undergo a (4+3) cycloaddition reaction in the presence of a 1,3-diene (Scheme 12).[33,34] To date, reactions of this type have only been realized in an intramolecular sense.



Scheme 12

Calculations suggested that when the allenyl diene **25** is activated by a gold–phosphite catalyst, an *exo* (4+3) cycloaddition ensues, in which the transition state is concerted and moderately asynchronous. This process is proposed to proceed via a gold carbene cycloadduct **26** that could evolve to either a (4+3) cycloadduct **27** (by a hydride shift) or a Diels–Alder adduct **28** via a ring-contraction (Scheme 12).[33]

This mechanistic scenario is also reproduced for metal catalysts based on platinum and palladium, which is supported by experimental results.[34–36] For example, substrate **29** reacts with an electron-rich gold catalyst to form a mixture of (4+3) and (4+2) cycloadducts, **30** and **31**, respectively, in a 75:25 ratio in 66% overall yield (Scheme 13).[33] However, when the gold is stabilized by an electron-poor phosphite