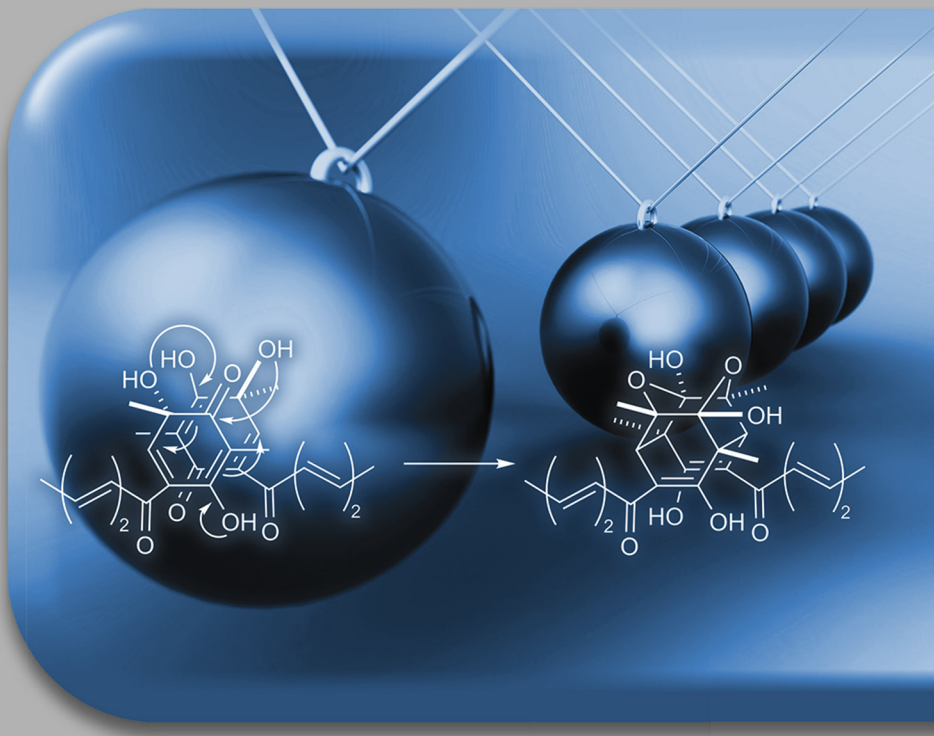
Science of Synthesis

Applications of Domino Transformations in Organic Synthesis 1

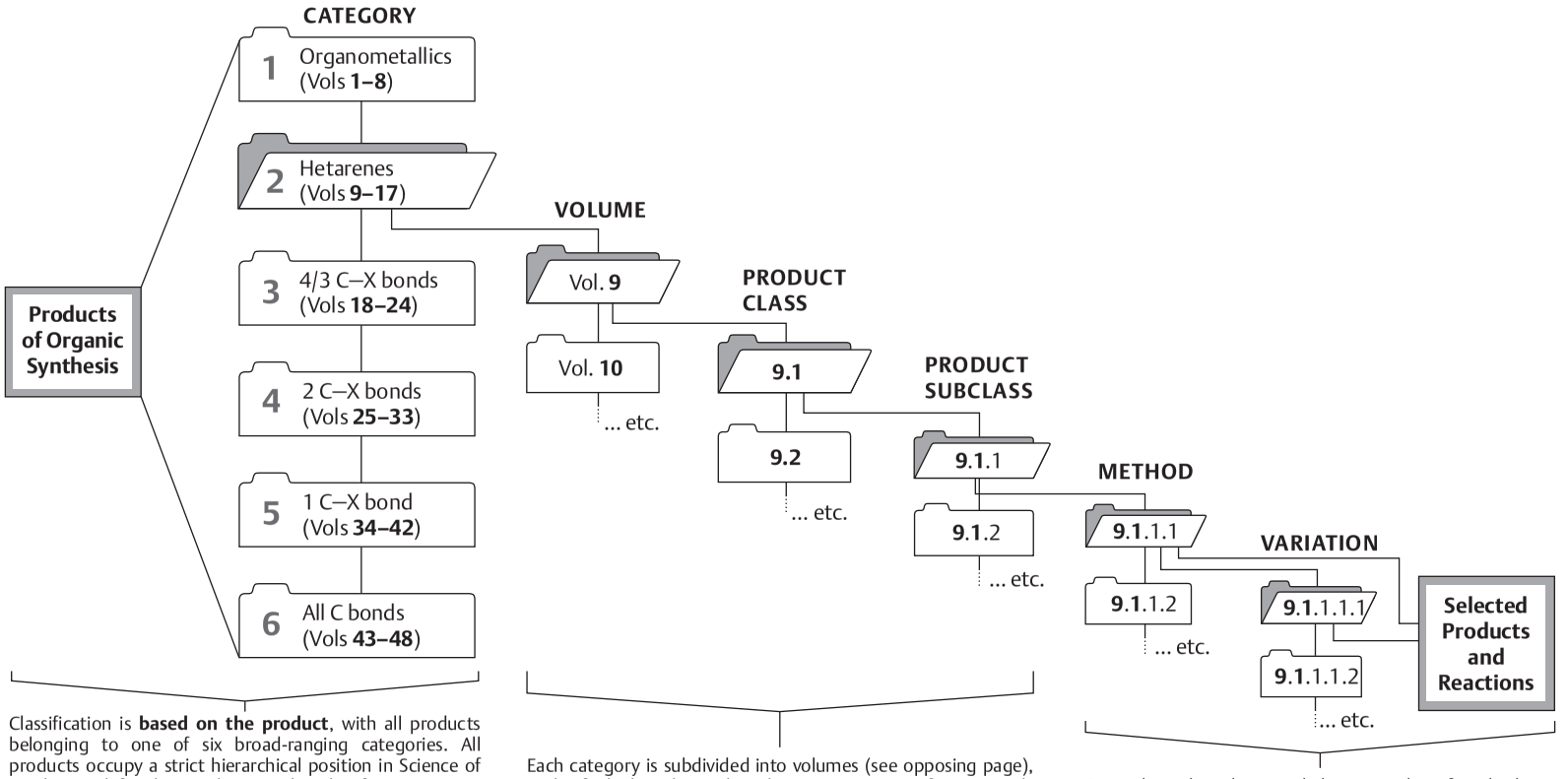
Volume Editor
Scott A. Snyder



Thieme

Organizational Structure of Science of Synthesis*

* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.

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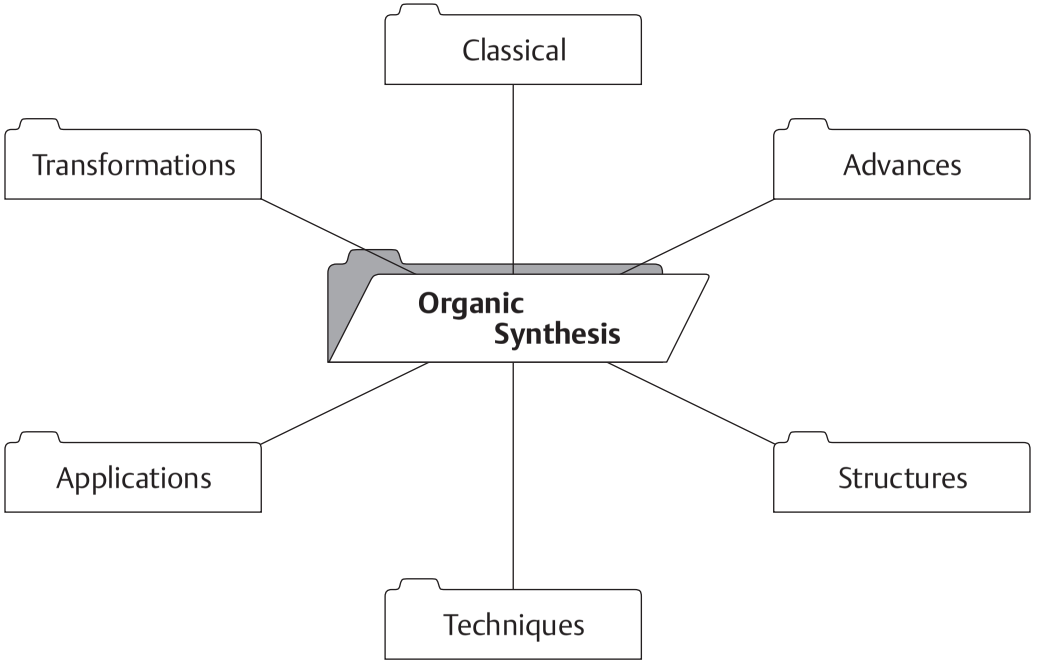
The **Science of Synthesis Reference Library** comprises volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Volumes in the **Science of Synthesis Reference Library** focus on subjects of particular current interest with content that is evaluated by experts in their field. **Science of Synthesis**, including the **Knowledge Updates** and the **Reference Library**, is the complete information source for the modern synthetic chemist.



Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Responsible Member of the Editorial Board **E. Schaumann**

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

The Editorial Board July 2010

Science of Synthesis Reference Library

Applications of Domino Transformations in Organic Synthesis (2 Vols.)
Catalytic Transformations via C—H Activation (2 Vols.)
Biocatalysis in Organic Synthesis (3 Vols.)
C-1 Building Blocks in Organic Synthesis (2 Vols.)
Multicomponent Reactions (2 Vols.)
Cross Coupling and Heck-Type Reactions (3 Vols.)
Water in Organic Synthesis
Asymmetric Organocatalysis (2 Vols.)
Stereoselective Synthesis (3 Vols.)

Volume Editor's Preface

Domino reactions have been a mainstay of synthetic chemistry for much of its history. Domino chemistry's roots trace to achievements such as the one-pot synthesis of tropinone in 1917 by Robinson and the generation of steroidal frameworks through polyene cyclizations, as originally predicted by the Stork–Eschenmoser hypothesis. In the ensuing decades, chemists have used these, and other inspiring precedents, to develop even more complicated domino sequences that rapidly and efficiently build molecular complexity, whether in the form of natural products, novel pharmaceuticals, or materials such as buckminsterfullerene.

Despite this body of achievements, however, the development of such processes remains a deeply challenging endeavor. Indeed, effective domino chemistry at the highest levels requires not only creativity and mechanistic acumen, but also careful planning at all stages of a typical experiment, from substrate design, to reagent and solvent choice, to timing of additions, and even the quench. Thus, if the frontiers are to be pushed even further, there is certainly much to master.

It was with these parameters in mind that the Editorial Board of **Science of Synthesis** decided to focus one of its Reference Library works on domino chemistry, covering the myriad ways that these sequences can be achieved with the full array of reactivity available, whether in the form of pericyclic reactions, radical transformations, anionic and cationic chemistry, metal-based cross couplings, and combinations thereof. In an effort to provide a unique approach in organizing and presenting such transformations relative to other texts and reviews on the subject, the sections within this book have been organized principally by the type of reaction that initiates the sequence. Importantly, only key and representative examples have been provided to highlight the best practices and procedures that have broad applicability. The hope is that this structure will afford a clear sense of current capabilities as well as highlight areas for future development and research.

A work on such a vibrant area of science would not have been possible, first and foremost, without a talented and distinguished author team. Each is mentioned in the introductory chapter, and I wish to thank all of them for their professionalism, dedication, and expertise. I am also grateful to all of the coaching, advice, and assistance provided by Ernst Schaumann, member of the Editorial Board of **Science of Synthesis**. Deep thanks also go, of course, to the entire editorial team at Thieme, particularly to Robin Padilla and Karen Muirhead-Hofmann who served as the scientific editors in charge of coordinating this reference work; Robin started the project, and Karen saw it through to the end. Their attention to detail and passion to produce an excellent final product made this project a true pleasure. Last, but not least, I also wish to thank my wife Cathy and my son Sebastian for their support of this project over the past two years.

Finally, I wish to dedicate this work, on behalf of the chapter authors and myself, to our scientific mentors. It was through their training that we learned how to better understand reactivity, propose novel chemistry, and identify the means to actually bring those ideas to fruition. Hopefully this text will serve the same role to those who study its contents, with even greater wisdom achieved as a result.

Scott A. Snyder

Chicago, October 2015

Abstracts

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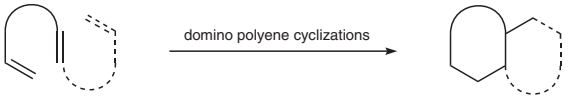
1.1 Polyene Cyclizations

R. A. Shenvi and K. K. Wan

A domino transformation consists of a first chemical reaction enabling a second reaction, which can then effect a third reaction, and so on, all under the same reaction conditions. A polyene cyclization is defined as a reaction between two or more double bonds contained within the same molecule to form one or more rings via one or more C—C bond-forming events. Herein, domino polyene cyclizations are discussed, with an emphasis on operationally simple methods of broad utility. From the perspective of synthesis theory, polyene cyclizations are a powerful approach for the efficient generation of both complexity and diversity, with the potential for a single synthetic route to generate a series of both constitutional and stereochemical isomers. However, with some noteworthy exceptions, the ability to controllably cyclize a linear chain to multiple products with high selectivity still generally eludes synthetic chemists and represents a significant chemical frontier for further development.



Keywords: polyenes · cyclization · carbocations · radicals · polycycles

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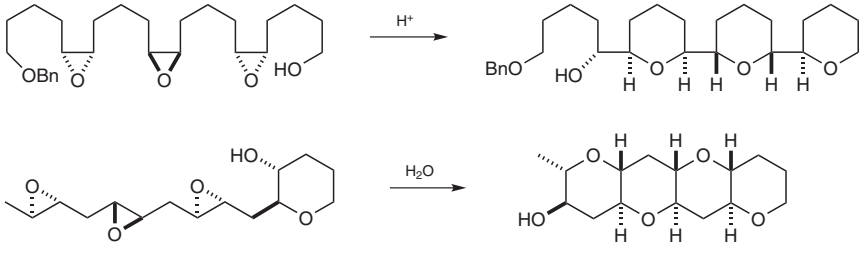
1.2 Cation–π Cyclizations of Epoxides and Polyepoxides

K. W. Armbrust, T. Halkina, E. H. Kelley, S. Sittihan, and T. F. Jamison

This chapter describes the formation of complex polycyclic fragments from linear epoxide and polyepoxide precursors via domino reactions. Depending on the reaction conditions employed, either *exo* or *endo* epoxide opening can be selectively achieved. Applications of these domino reactions toward the synthesis of complex natural products are discussed.



Keywords: oxiranes · cascades · natural products · marine ladder polyethers · ionophores · ethers · oxygen heterocycles · tetrahydrofurans · tetrahydropyrans · oxepanes

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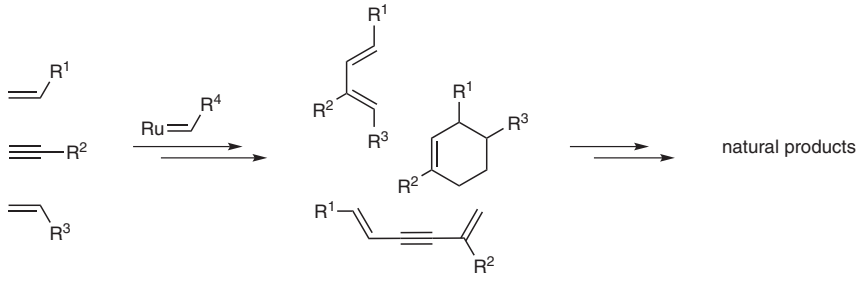
1.3.1 Enyne-Metathesis-Based Domino Reactions in Natural Product Synthesis

D. Lee and M. O'Connor

Enyne-metathesis-based domino processes are highlighted in the context of natural product synthesis; these include domino double ring-closing metathesis, enyne metathesis/metallotropic [1,3]-shifts, enyne metathesis/Diels–Alder reaction, and other variations of their domino combinations. Issues regarding selectivity and mechanism are also discussed.



Keywords: enyne metathesis · π-bond exchange · domino transformations · natural products · total synthesis

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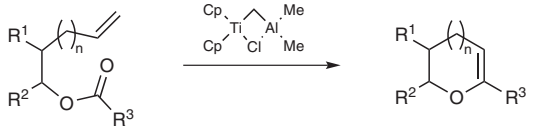
1.3.2 Domino Metathesis Reactions Involving Carbonyls

H. Renata and K. M. Engle

This review describes different methods to perform net carbonyl–alkene metathesis. Reactions of this type generally involve domino transformations employing organometallic reagents. Different conditions and procedures are surveyed and strategic applications of carbonyl–alkene metathesis in the synthesis of natural products are highlighted.



Keywords: metathesis · alkenylation · carbonyl compounds · alkenes · ring closure · transition metals · titanium complexes · organometallic reagents · organocatalysts

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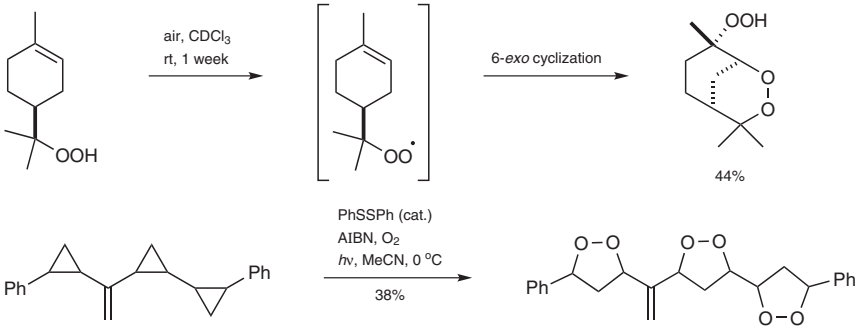
1.4.1 Peroxy Radical Additions

X. Hu and T. J. Maimone

In this chapter, radical addition reactions involving peroxy radical intermediates are reviewed. These transformations typically generate a carbon radical intermediate which then reacts with molecular oxygen forming a peroxy radical species. Following peroxy radical cyclization, various endoperoxide rings are constructed. Two major classes of reactions are discussed: (1) radical additions to alkenes and quenching with molecular oxygen, and (2) radical formation from the opening of cyclopropanes and incorporation of molecular oxygen. Various methods for radical initiation that are compatible with the presence of molecular oxygen are described.



Keywords: peroxide synthesis · endoperoxides · cyclic peroxides · radical addition · peroxy radicals · thiyl radicals · hydroperoxidation · cyclopropane cleavage · 1,2-dioxolanes · 1,2-dioxanes · 1,2-dioxepanes

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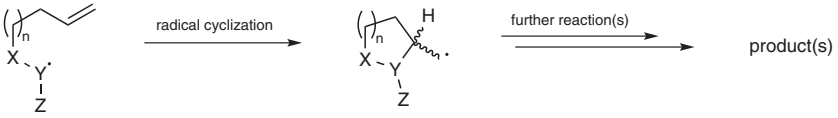
1.4.2 Radical Cyclizations

J. J. Devery, III, J. J. Douglas, and C. R. J. Stephenson

This chapter details recent examples of domino radical reactions that are initiated via an intramolecular radical cyclization.



Keywords: radicals · domino reactions · cyclization · tin · samarium · organo-SOMO · ammonium cerium(IV) nitrate (CAN) · visible light

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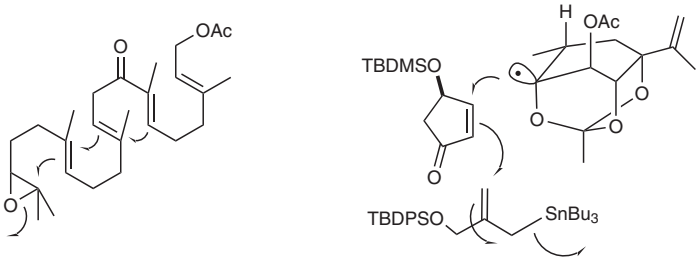
1.4.3 Tandem Radical Processes

K. A. Parker

This review presents selected examples of regio- and stereospecific domino radical reactions developed in the context of total synthesis studies. The underlying strategies demonstrate the variety of connectivity patterns that can be generated by cascades of intra- and intermolecular bond-forming steps.



Keywords: tandem radical cyclization · radical domino cyclization · radical cascade cyclization · intermolecular reactions · radical trapping · manganese(III) acetate · titanocene dichloride · tris(trimethylsilyl)silane · triethylborane · tri-*sec*-butylborane · TEMPO · 1,1,3,3-tetramethylguanidine · samarium(II) iodide · cobaloxime

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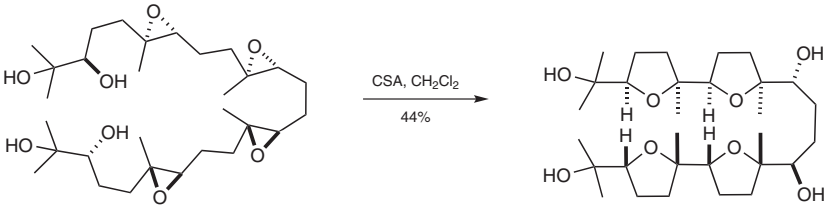
1.5.1 Protic Acid/Base Induced Reactions

D. Adu-Ampratwum and C. J. Forsyth

This chapter covers synthetic domino processes that are induced by protic acid or base. They are broadly classified into those that capitalize upon the release of oxirane ring strain under acidic or basic conditions, and carbocyclic ring expansions and contractions under protic acid or basic conditions. The focus here is upon single substrate, monocomponent domino processes, rather than multicomponent variants.



Keywords: carbocyclic compounds · cyclization · epoxy compounds · ethers · Favorskii rearrangement · intramolecular reactions · Nazarov cyclization · pinacol rearrangement · ring contraction · ring expansion · tandem reactions · Wagner–Meerwein rearrangement

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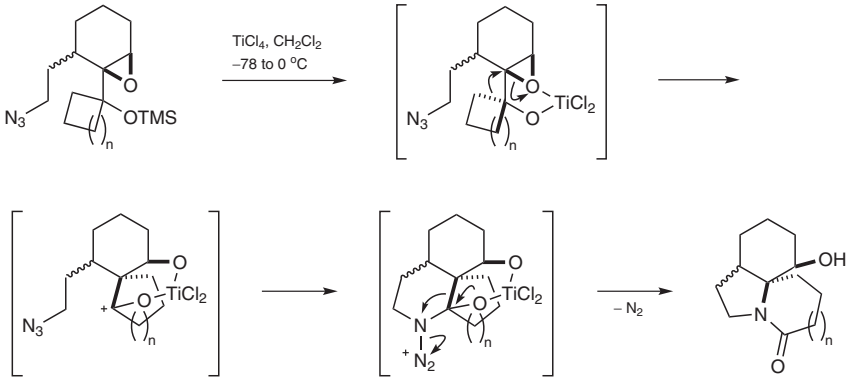
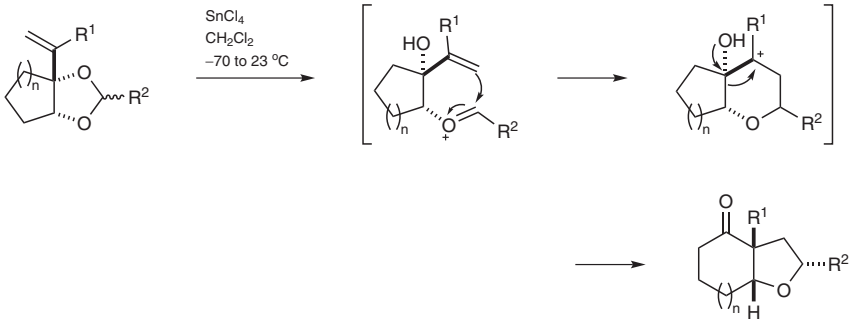
1.5.2 Lewis Acid/Base Induced Reactions

S.-H. Wang, Y.-Q. Tu, and M. Tang

The efficient construction of complex molecular skeletons is always a hot topic in organic synthesis, especially in the field of natural product synthesis, where many cyclic structural motifs can be found. Under the assiduous efforts of synthetic chemists, more and more methodologies are being developed to achieve the construction of cyclic skeletons. In particular, the beauty and high efficiency of organic synthesis are expressed vividly among those transformations realized through a domino strategy. Based on these important methodologies, selected Lewis acid/base induced domino reactions leading to ring expansions, contractions, and closures are presented in this chapter.





Keywords: tandem reactions · Lewis acid · Lewis base · ring expansion · ring contraction · ring closure

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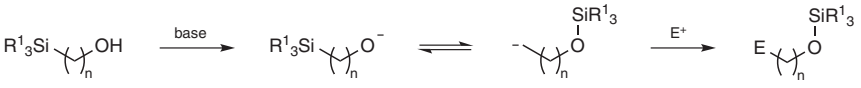
1.5.3 Brook Rearrangement as the Key Step in Domino Reactions

A. Kirschning, F. Gille, and M. Wolling

The Brook rearrangement has lost its Cinderella status over the past twenty years since being embedded into cascade reaction sequences. The powerful formation of carbanions through silyl migration has been exploited for the development of many new methodologies and has been used as a key transformation in complex natural product syntheses. Now, the Brook rearrangement belongs to the common repertoire of synthetic organic chemists.



Keywords: Brook rearrangement · domino reactions · migration · organosilicon chemistry · total synthesis

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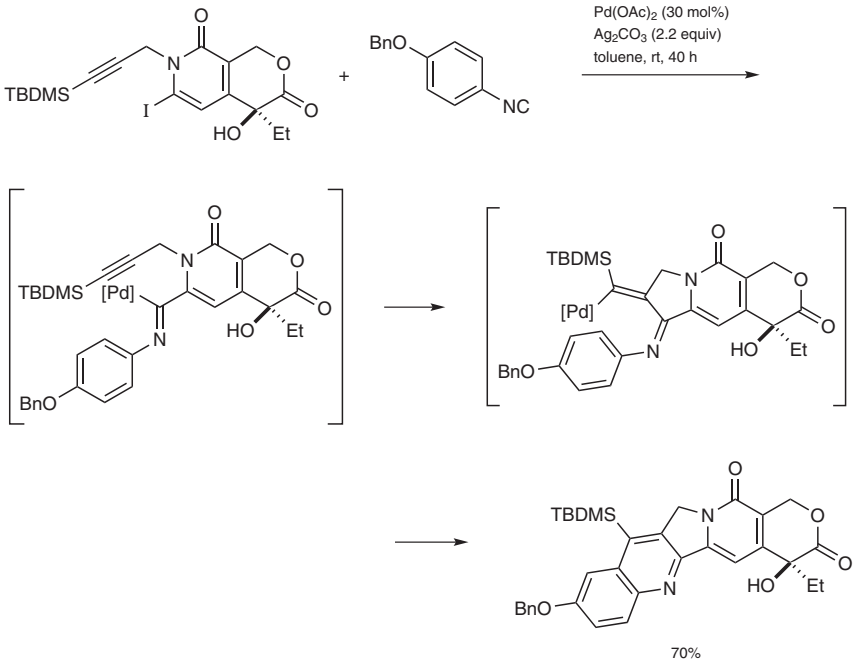
1.6.1 Palladium-Mediated Domino Reactions

E. A. Anderson

Palladium catalysis offers excellent opportunities to engineer domino reactions, due to the ability of this transition metal to engage with a variety of electrophiles and to effect stereocontrolled bond formations in complex settings. This review covers palladium-catalyzed domino processes, categorized according to the initiating species (alkenyl-, aryl-, allyl-, allenyl-, or alkylpalladium complexes), with a particular focus on applications in natural product synthesis that exemplify more general methodology.



Keywords: palladium · domino · cascade · total synthesis

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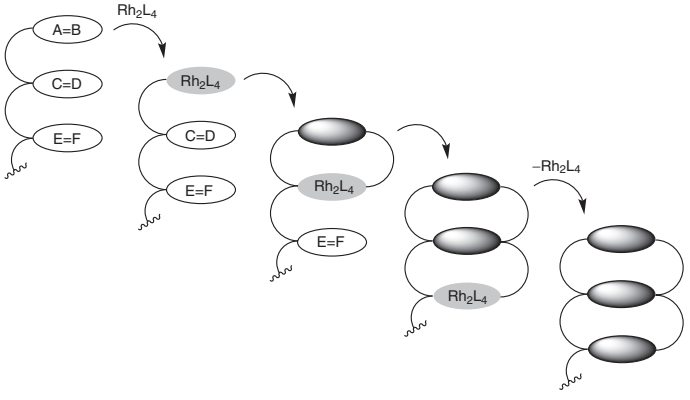
1.6.2 **Dirhodium-Catalyzed Domino Reactions**

X. Xu, P. Truong, and M. P. Doyle

With dirhodium carbenes generated from diazocarbonyl compounds, 1-sulfonyl-1,2,3-triazoles, or cyclopropenes, a subsequent intramolecular cyclization forms a reactive intermediate that undergoes a further transformation that usually terminates the reaction process. Commonly, the electrophilic dirhodium carbene adds intramolecularly to a C≡C bond to provide a second rhodium carbene. Catalytically generated dirhodium-bound nitrenes initiate domino reactions analogously, and recent examples (nitrene to carbene to product) have also been documented.



Keywords: α-carbonyl carbenes · (azavinyl)carbenes · cyclopropenes · [3 + 2] annulation · cyclopropenation · carbene/alkyne metathesis · carbonyl ylide reactions · Claisen/Cope rearrangement · C—H insertion · oxonium ylides · dipolar cycloaddition · aromatic substitution

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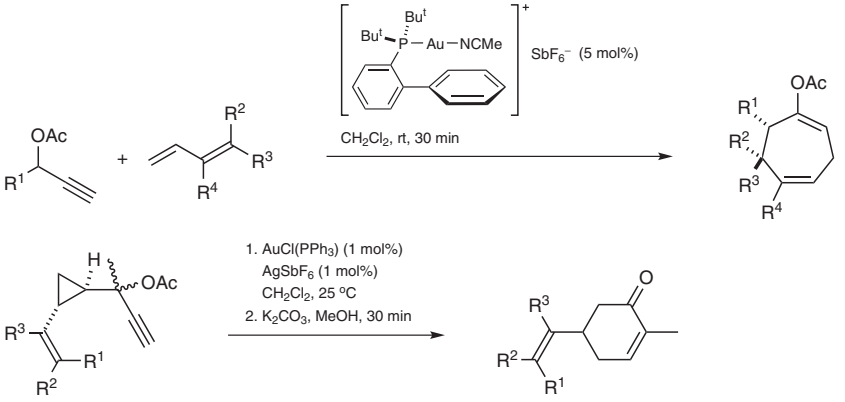
1.6.3 Gold-Mediated Reactions

E. Merino, A. Salvador, and C. Nevado

In this review, a selection of the most relevant examples featuring gold-catalyzed domino transformations are presented. Processes catalyzed by both gold(I) and gold(III) complexes are described, including multicomponent reactions, annulations, cycloisomerizations, and cycloadditions. The scope, limitations, and mechanistic rationalization of these transformations are also provided.



Keywords: domino transformations · multicomponent reactions · cycloisomerizations · cycloadditions · rearrangements · gold

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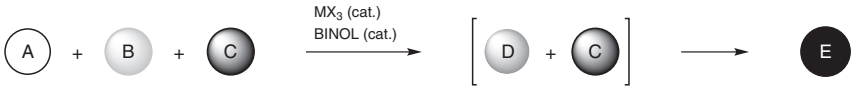
1.6.4 Rare Earth Metal Mediated Domino Reactions

T. Ohshima

Rare earth metals, comprising 17 chemical elements in the periodic table, are relatively abundant in the Earth's crust despite their name. In the series of lanthanides, a systematic contraction of the ionic radii is observed when going from lanthanum to lutetium (often referred to as the lanthanide contraction), but this variation is so smooth and limited, with ca. 1% contraction between two successive lanthanides, that it is possible to fine-tune the ionic radii, Lewis acidity, and Brønsted basicity of rare earth complexes. As a result of the large size of the lanthanide ions compared to other metal ions, lanthanide ions have high coordination numbers, varying from 6 to 12. Due to the strong oxophilicity of rare earth elements, their metal ions have a hard Lewis acidic nature. Most particularly, rare earth metal trifluoromethanesulfonates [M(OTf)$_3$] have been regarded as new types of Lewis acids and are stable and active in the presence of many Lewis bases. Another important type of rare earth metal species, the rare earth metal alkoxides [M(OR)$_3$], exhibit both Lewis acidity and Brønsted basicity. These collated characteristic features of rare earth based complexes, such as high coordination numbers, a hard Lewis acidic nature, high compatibility with various functional groups, ease of fine-tuning, and multifunctionality, have led to the development of a variety of domino reactions catalyzed largely by rare earth metal trifluoromethanesulfonates and alkoxides.



M = rare earth metal; X = OTf, OR^1

Keywords: lanthanide contraction · rare earth metal trifluoromethanesulfonates · rare earth metal alkoxides · Lewis acidity · Brønsted basicity · high coordination numbers · multifunctionality

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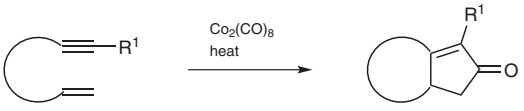
1.6.5 **Cobalt and Other Metal Mediated Domino Reactions: The Pauson–Khand Reaction and Its Use in Natural Product Total Synthesis**

L. Shi and Z. Yang

The Pauson–Khand reaction constitutes one of the most formidable additions to the repertoire of synthetically useful reactions. It rapidly affords a cyclopentenone skeleton from an alkene, an alkyne, and carbon monoxide, based on a domino sequence of bond constructions. In this chapter, the prowess of the Pauson–Khand reaction is illustrated by judicious selection of complex target molecules, the total syntheses of which are cleverly orchestrated by the key Pauson–Khand reaction sequence. Emphasis is placed on cobalt-mediated processes to exemplify the applicability of this classical reaction.



Keywords: Pauson–Khand reaction · alkenes · carbon monoxide · alkynes · cyclopentenones · natural product synthesis · octacarbonyldicobalt · thioureas · allenic alkynes · asymmetric synthesis

Applications of Domino Transformations in Organic Synthesis 1

Table of Contents

Introduction

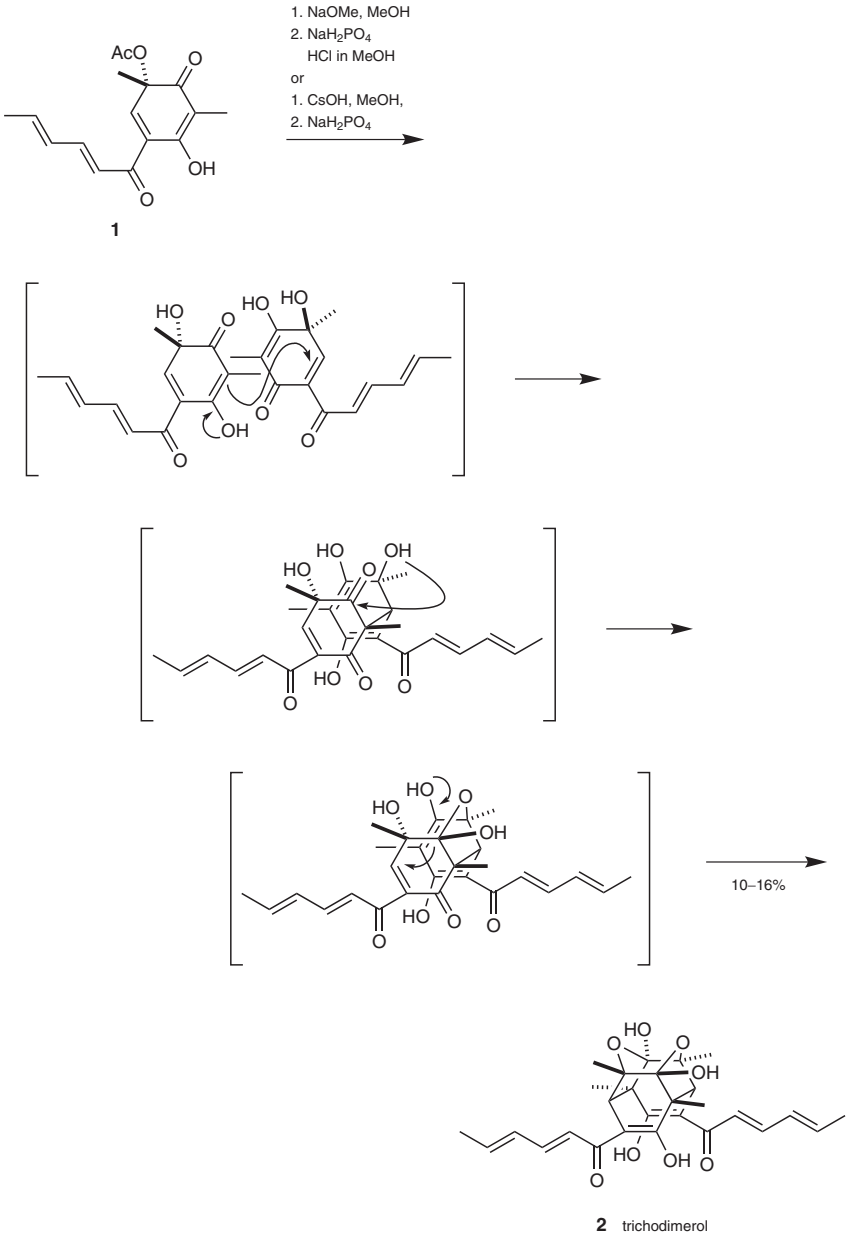
S. A. Snyder

There is something inherently satisfying about setting up a number of dominoes in series, pushing one down at the end of the chain, and watching the rest tumble as if in slow motion until all have been knocked over; I remember spending hours doing this as a child, once my father showed me the principle and I had enough dexterity to not knock anything down before the right moment. I felt the same way about playing with a Newton's cradle, where, although the movement does not cease in the same way as a domino chain, the idea of setting something into motion and causing a series of subsequent reactions was certainly pleasing and mesmerizing to watch.

My first experience with a "domino", or "cascade", sequence in the chemistry world came right at the start of my graduate career in K. C. Nicolaou's laboratory at The Scripps Research Institute, in the summer of 1999. For weeks I watched my talented neighbors in the lab strive to achieve a biomimetic synthesis of trichodimerol (**2**) (Scheme 1) from protected forms of the natural product sorbicillin, e.g. **1**. Although they registered a number of successes in merging **1** with itself to create other members of the bisorbicillinoid family upon exposure to different reaction conditions, trichodimerol itself seemed elusive.[1] Each day, several different products were generated from individual experiments, and I remember my colleagues picking out which ones they would try and characterize, and then thinking about what conditions to change in the hope of achieving success based on the structures they deduced that they had produced. Ultimately, in near-concomitant reports, E. J. Corey (my future postdoctoral supervisor)[2] and the Nicolaou team[3] determined that low water content in the presence of a soluble base was the key to the domino series of Michael reactions and ketalizations needed to form the unique caged structure of **2**; this sequence of events was impressive, even though only relatively modest yields could be achieved.

for references see p 11

Scheme 1 Domino Construction of Trichodimerol through Sequential Michael Reactions and Ketalizations[2,3]



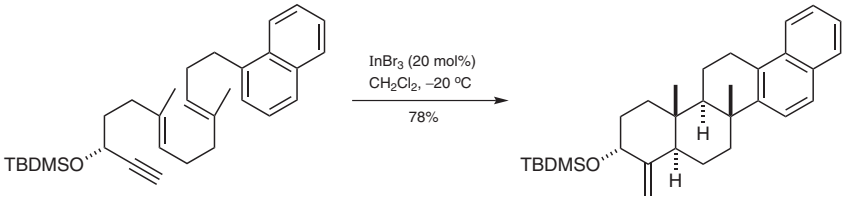
Watching this experience was transformative for me as a chemist. First, it immediately highlighted the artistry, skill, and talent needed by a practicing synthetic chemist to achieve success. Indeed, although individual reaction parameters certainly have a dramatic effect on the outcome, it is deep thinking based on first principles coupled with proper technique that can change those outcomes, ultimately putting everything into place so that the domino process can properly orchestrate itself. Second, it opened up that same joy I felt as a child with my toy dominoes, indicating that I would want to devote a significant portion of my research career into pursuing strategies, reactions, and tactics that could similarly bring molecules together and forge bonds with ballet-like efficiency and

precision. Finally, it made me realize how much I still needed to learn and master if I was ever to reach that goal.

The objective of these two volumes for the *Science of Synthesis Reference Library* is to communicate that same sense of inherent pleasure in the power, artistry, and challenge of domino chemistry, highlighting the current state of the art by teaching the skills and providing the tools needed for success, while also demarcating frontiers for future developments. With the efforts of a spectacular group of world-class authors who have contributed their time and talent to this work, I am confident that this goal has been achieved. Unlike other excellent reviews and monographs that exist on the subject (and there are many, for which no attempt at referencing will be made here; the leading and influential works are cited in the subsequent individual chapters), a different organization framework for domino chemistry has been sought for these volumes based on the reaction type that initiates the sequence. In some cases, this is a specific process such as the Diels–Alder reaction, while in other chapters it is a slightly broader presentation, for example reaction sequences initiated by gold. What has resulted is an effective way to compare and contrast approaches. In addition, because the contributors have provided only the most representative examples along with experimental procedures for processes that have high generality, rather than attempt to be comprehensive, key lessons can be imparted effectively for developing even more powerful approaches.

The first volume opens with polyene cyclizations, a classic domino sequence dating back over half a century to the pioneering ideas inherent in the Stork–Eschenmoser hypothesis, which have been explored non-stop in the ensuing decades. In a welcome contribution by Shenvi and Wan (Section 1.1), not only is a clear sense of the history of the reaction provided with several classic transformations, but the vitality of research in this arena is also evident by the inclusion of newer advances, such as the Corey group's use of indium(III) bromide to activate terminal alkynes for highly efficient domino bond constructions, as shown in the conversion of **3** into **4** (Scheme 2).[4]

Scheme 2 Indium(III) Bromide Catalyzed Polyene Cyclization Involving an Alkyne[4]

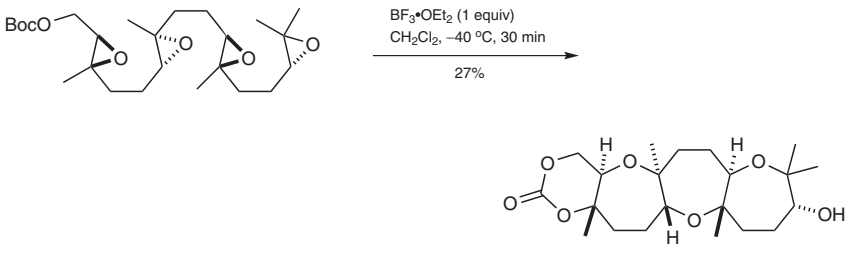


3 **4**

In the very next chapter, an excellent contribution by Jamison, Halkina, Kelley, Sittihan, and Armbrust (Section 1.2) shows how after those polyenes are converted into polyepoxides, appropriate activation can afford polyether natural products along the lines of the original Nakanishi hypothesis for the formation of brevetoxins and related targets. One example of such a powerful sequence is shown in Scheme 3.[5] Specific reaction conditions, careful substrate design, and knowledge of key physical organic principles prove essential to the successful examples that have been achieved to date, as this chapter effectively illustrates.

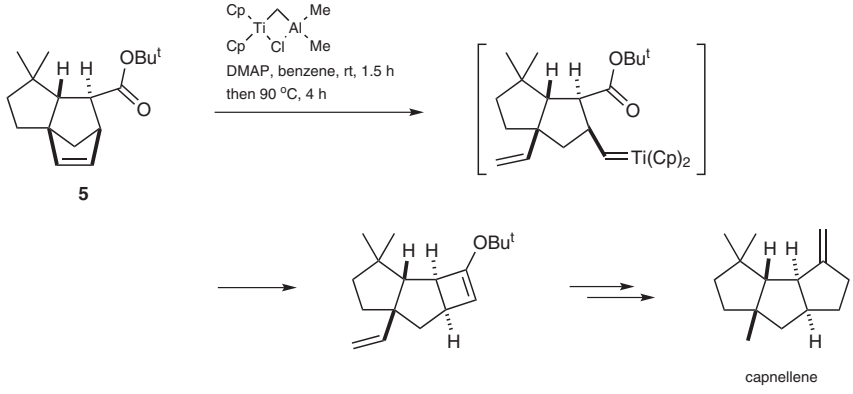
for references see p 11

Scheme 3 An Epoxide-Opening Domino Sequence To Form an Oxepane[5]



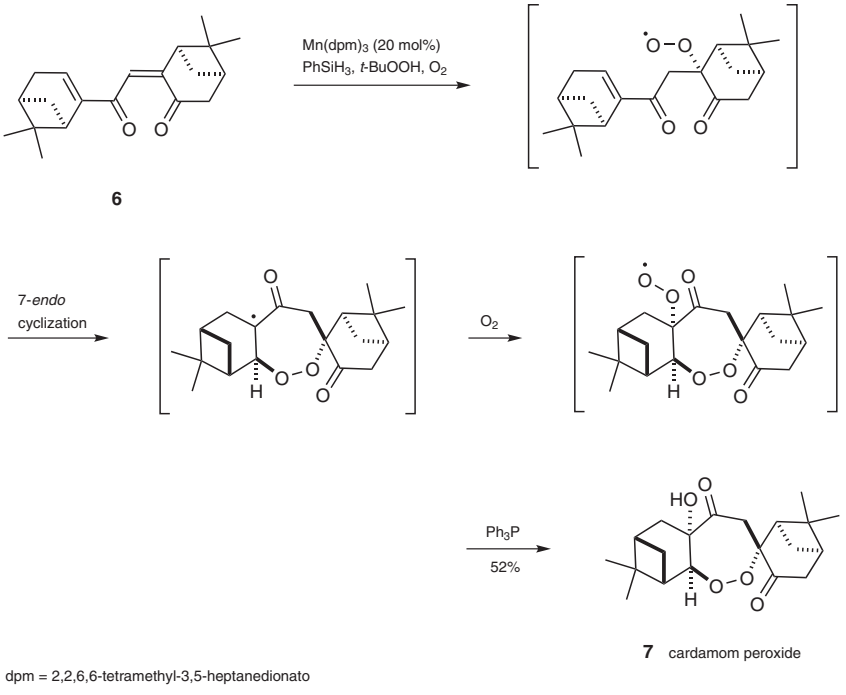
Next, transformations initiated by metathesis events are presented, with an excellent chapter by Lee and O'Connor highlighting various ways that alkenes and alkynes can be manipulated to forge a variety of complex materials, particularly natural products (Section 1.3.1). Their coverage includes detailed mechanistic analyses of several examples, emphasizing both current knowledge and areas where further studies are needed to advance such domino sequences. In the following contribution by Engle and Renata (Section 1.3.2), the extension of metathesis processes to carbonyl substrates highlights some additional directions for the prosecution of domino sequences. One particularly instructive and classic example using the Tebbe reagent is highlighted in Scheme 4.[6] Here, ring-opening metathesis of a strained alkene within bicycle **5** sets the stage for cyclization onto a neighboring carbonyl that affords a highly strained, four-membered ring en route to capnellene.

Scheme 4 A Domino Ring-Opening Metathesis/Carbonyl Cyclization Reaction[6]



We then move on to domino events that begin with a radical reaction. An insightful chapter from Maimone and Hu (Section 1.4.1) opens this section of the volume by focusing on peroxide-initiated additions to functionalized molecules. Given their recent elegant synthesis of cardamom peroxide (Scheme 5) through a key step that features two such additions catalyzed by manganese (i.e., from **6** to **7**),[7] they are able to provide an excellent sense of the state of the art in this important area.

Scheme 5 Domino Hydroperoxidation Reactions Catalyzed by Manganese[7]

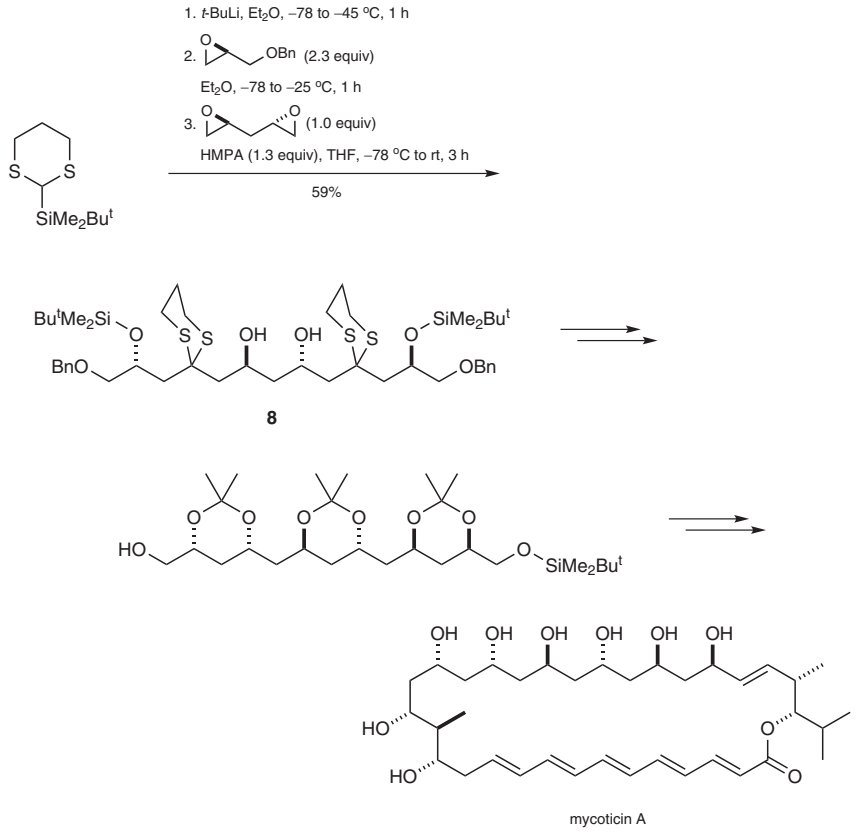


Two chapters on more traditional radical chemistry (particularly involving carbon-centered radicals) follow, with the first from Stephenson, Devery, and Douglas (Section 1.4.2) and the second from Parker (Section 1.4.3). These contributions collectively cover historical cases as well as more modern applications such as photoredox-based radical sequences. They also cover the full gamut of initiators and quenching sources one might wish to consider for both inter- and intramolecular variants of radical-based domino chemistry, whether the goal is cyclizations, rearrangements, and/or fragmentations.

Volume 1 then continues with the presentation of some other, non-radical-based, domino transformations, starting with skeletal rearrangements. Such processes comprise a panoply of chemical reactions, be they the result of ring contractions, ring expansions, ring closures, or fragmentations, noting that all of these can, of course, be effected by many different reagents. Here, Forsyth and Adu-Ampratwum beautifully open the discussions of this body of domino chemistry by focusing on events initiated by protic acids and bases (Section 1.5.1). The following chapter by Tu, Wang, and Tang (Section 1.5.2) then outlines occasions when Lewis acids and bases can provide complementary and/or unique opportunities for related chemistry. The range of reactions covered in these two chapters is quite impressive, and the selections found within should hopefully inspire a number of future studies, be it in the area of transformations such as semipinacol rearrangements or Favorskii chemistry, or the myriad other processes that are touched upon for these types of processes. A final and comprehensive contribution from Kirschning, Gille, and Wolling (Section 1.5.3) then affords a sense of the power of silicon to induce such chemistry, particularly under Brook-rearrangement-type manifolds. One example from their chapter, part of the Smith total synthesis of mycoticin A,[8] is shown in Scheme 6. Here, carefully orchestrated 1,4-Brook rearrangements (i.e., anion relay chemistry) prove capable, in short order, of setting the key chiral centers in structure **8** that constitutes the upper half of the target molecule.

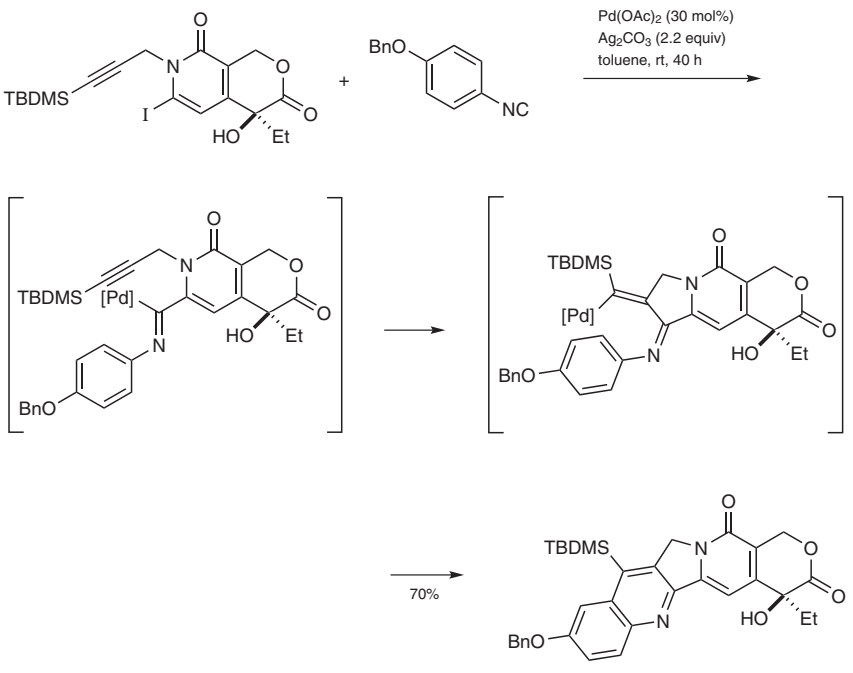
for references see p 11

Scheme 6 1,4-Brook Rearrangements in a Total Synthesis of Mycoticin A[8]



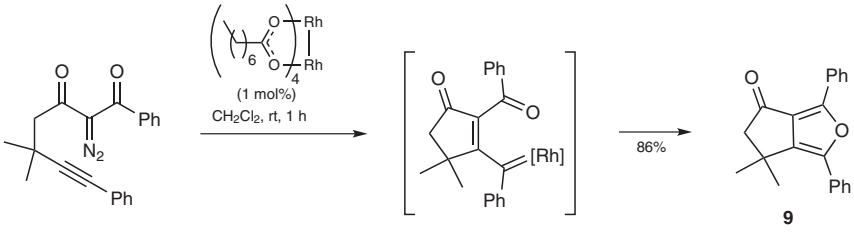
Volume 1 then concludes with five chapters devoted to metal-mediated domino reactions (excluding those cases where the metals are behaving simply as Lewis acids, as those cases are covered earlier in the volume, as already mentioned). Here, the reader is treated to a world-class series of presentations from leading practitioners. We open with palladium-initiated chemistry, where Anderson has provided an excellent collection of domino processes that are possible with the right tools and properly designed substrates (Section 1.6.1). One example found in his chapter is shown in Scheme 7;[9] this work, from the Curran group, highlights beautifully the range of bonds, rings, and materials that are accessible when everything is carefully set up to be orchestrated into greater complexity.

Scheme 7 Palladium-Initiated Domino Sequence En Route to DB-67[9]



Next is a chapter by Doyle, Truong, and Xu on rhodium-mediated domino sequences (Section 1.6.2). A transformation from one of their own reports is presented here in Scheme 8,[10] which highlights, in particular, the value of rhodium in forming reactive carbenes that can effect a range of reactions, in this case the synthesis of fully substituted furan **9**. Well-written, thorough, and interesting chapters then follow on gold chemistry (Nevado, Merino, and Salvador; Section 1.6.3), rare earth metal chemistry (Ohshima; Section 1.6.4), and cobalt chemistry (Yang and Shi; Section 1.6.5). These contributions collectively highlight how diverse and important processes such as Conia-ene reactions and Pauson–Khand chemistry can be effectively orchestrated by many different metals to rapidly build molecular complexity in highly challenging settings.

Scheme 8 Rhodium-Initiated Domino Sequence Involving Carbene/Alkyne Metathesis and Carbonyl Ylide Formation[10]

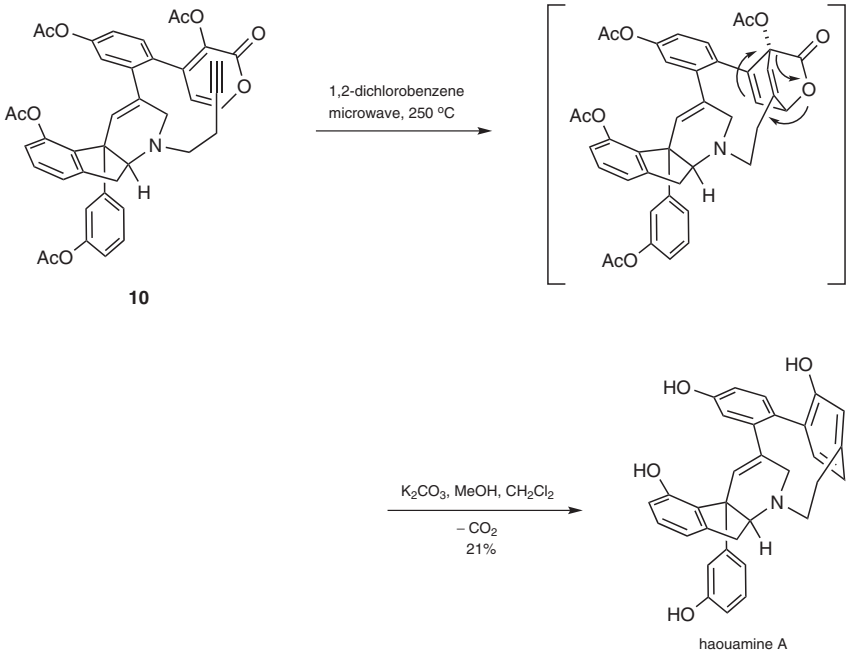


Volume 2 begins with coverage of domino processes that are started by pericyclic reactions. Of the possible ways to achieve domino sequences, pericyclic reactions in all their forms, be it Diels–Alder reactions, Cope rearrangements, electrocyclizations, ene reactions, etc., have perhaps provided some of the most fertile ground for creative approaches to rapidly build molecular complexity; often these domino sequences may well be biomi-

for references see p 11

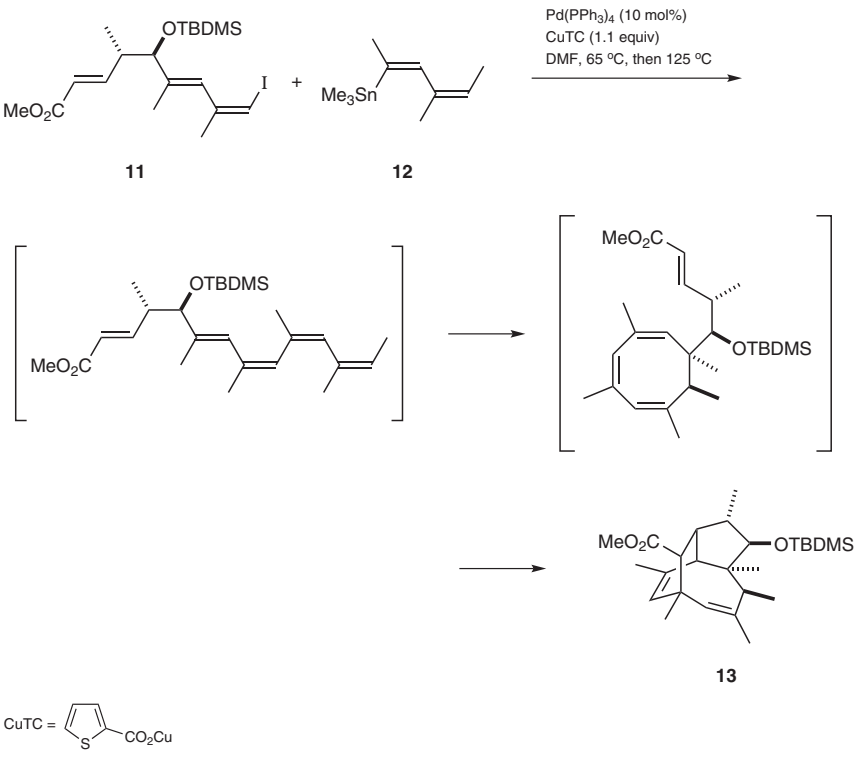
metic bond constructions. The five chapters in this section are, like those in Volume 1, arranged based on the initiating event, with the opening contribution by Sorensen and West (Section 2.1.1) describing domino events that commence with the Diels–Alder reaction. One example from their scholarly presentation is shown below in Scheme 9,[11] highlighting how a tandem Diels–Alder reaction/retro-Diels–Alder sequence involving an alkyne dienophile and a pyrone diene in the form of **10** could lead to the "bent" aromatic ring needed to complete a total synthesis of haouamine A.

Scheme 9 Diels–Alder/Retro-Diels–Alder Domino Sequence for Haouamine A[11]



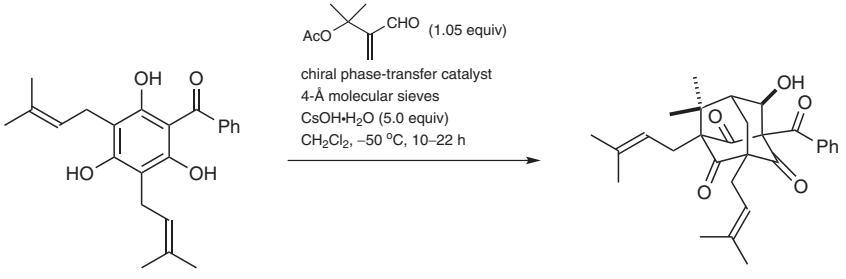
The subsequent chapter from Coldham and Sheikh (Section 2.1.2) beautifully illustrates the power of domino constructions started through [2+2], [3+2], and [5+2] cycloadditions, and other related manifolds that are not of a Diels–Alder-type. We then move onto electrocyclic ring constructions and ring openings in a well-fleshed-out chapter from Suffert, Gulea, Blond, and Donnard (Section 2.1.3). One example discussed there, a tandem 8π-electrocyclization/Diels–Alder sequence that follows a Stille coupling between **11** and **12**, is shown in Scheme 10;[12] this event produces the fused-ring system of **13** via a process that might be similar to Nature's construction of the target PF-1018; it is notable that only a single diastereomer results from this laboratory domino sequence. This example could easily have been put into the palladium chapter, but the centrality of the electrocyclization process in light of other examples in the chapter suggested this as the best location from a didactic perspective. Finally, well-framed and thoroughly presented chapters from Zakarian and Novikov on sigmatropic shifts and ene reactions (Section 2.1.4), and from Guerrero on [3,3]-rearrangements (i.e., Cope and Claisen chemistry; Section 2.1.5) round out this impressive collection of domino chemistry examples.

Scheme 10 Stille Coupling/Electrocyclization/Diels–Alder Domino Sequence toward (–)-PF-1018[12]



The next chapter comes from Porco and Boyce (Section 2.2) and covers attempts to use dearomatization events as part of domino sequences, an area in which the lead author's group has long been engaged. An example of their work is shown in Scheme 11, with a series of alkylative processes effecting subsequent dearomatizations leading to a functionalized cage structure (**14**) in short order if the right conditions are used. Thorough tables in this chapter help the reader identify optimal conditions for each desired transformation.

Scheme 11 Alkylative Dearomatization via a Domino Sequence[13]

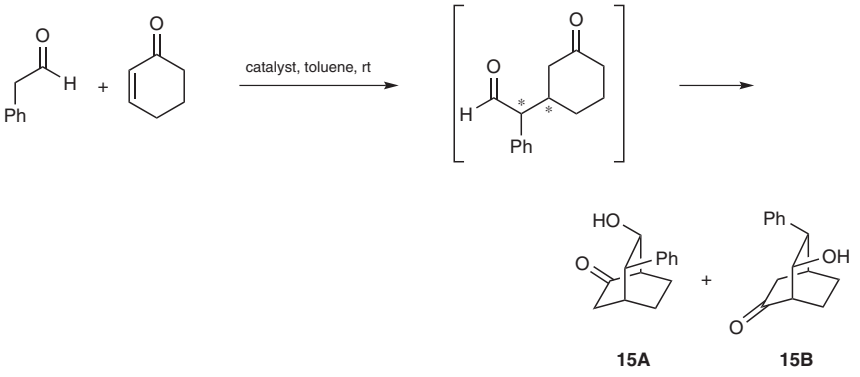


Finally, the volume rounds out with domino sequences that commence with various addition reactions. Yeung and Yu begin these presentations with additions to nonactivated alkenes (Section 2.3.1), covering hydroaminations, hydroetherifications, haloetherifications, and halocyclizations in particular, drawing in many cases on their own expertise

for references see p 11

and scholarship in the area. The following chapter, by Bella, Moliterno, Renzi, and Salvio (Section 2.3.2), focuses on additions to activated double bonds, such as Michael reactions, enamine chemistry, and the reactions of enol ethers to achieve domino transformations. Much of the discussion here focuses on the use of organic catalysts to effect such processes, with a particularly informative and timely discussion on the large-scale industrial synthesis of molecules such as **15A** and/or **15B** (Scheme 12), which can subsequently be converted into chiral diene ligands.[14–16] Other high-value targets discussed at some length through varied approaches include (−)-oseltamivir (Tamiflu).

Scheme 12 A Michael/Aldol Domino Sequence[14]



The next chapter, by Wang and Song, on additions to carbonyls (Section 2.3.3) includes continued discussion of the importance of small molecule organic catalysts, for example to achieve aldol reactions, among other types of additions such as Grignard chemistry. The final chapter, from Dömling, Zarganes Tzitzikas, Neochoritis, and Kroon (Section 2.3.4), moves on to additions to carbon–nitrogen bonds in the form of imines, nitriles, and related functional groups. These final two chapters certainly highlight that there are many diverse targets that can be made through appropriate substrate design coupled with mechanistic creativity and high experimental acumen.

In conclusion, I hope you will find these volumes to be as informative and instructive as I have while editing their pages. They definitely provide a tool-box that can hopefully propel domino chemistry to the next stages of complexity generation and enhanced synthetic efficiency, and I hope you will find inspiration within their pages, whether your goal is new synthetic methodology, target construction, or the development of commercially viable routes to high-value materials. The team of authors has certainly set up several dominoes in place; it is for you, the reader, to add to them (whether at the front or the back of the chain) and/or rearrange them to make even more intricate designs and impressive combinations.

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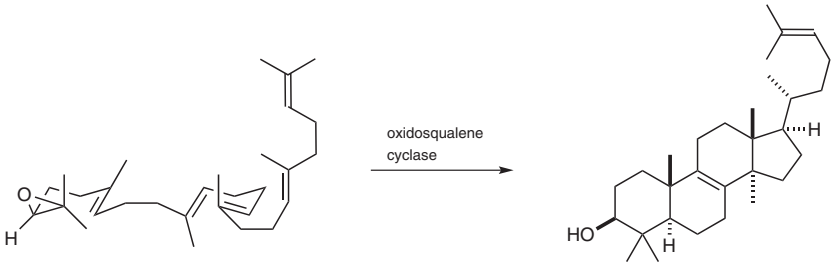
1.1 Polyene Cyclizations

R. A. Shenvi and K. K. Wan

General Introduction

Saturated and partially unsaturated (nonaromatic) carbocycles find broad distribution across the planet as endogenous compounds in all organisms and also as products of the chemical industry. Their isolation from natural sources, in combination with their laboratory chemical synthesis, enables large-scale access to these carbocycles for human use as fragrances, flavors, pharmaceuticals, and polymers.[1] Dissection of any given carbocycle into one or more alkenes benefits from a decrease in complexity, sometimes dramatically, to simple unsaturated building blocks.[2] Steroid biosynthesis is a classic illustration of this abstract principle, whereby (*S*)-2,3-oxidosqualene (**1**) is converted in one step into lanosterol (**2**) (Scheme 1).[3]

Scheme 1 Biosynthesis of Lanosterol from Oxidosqualene in One Step[3]



1 **2**

The Diels–Alder reaction is a more familiar example, and generates two C—C bonds, one or more rings, and as many as four stereocenters. In this chapter, however, the Diels–Alder reaction (Section 2.1.1) and other pericyclic ring-forming reactions (Section 2.1) will not be discussed because these are cycloadditions not cyclizations, and because each pericyclic reaction could constitute its own chapter given the diversity of application {e.g., see *Science of Synthesis*, Vol. 47 [Alkenes (Section 47.1.3.1)]}. Instead, the focus will be on domino (cascade) polyene cyclizations, with an emphasis on those processes with practicality and broad utility rather than idiosyncratic examples with narrower applications. To begin, some terms must be defined.

Domino transformation: A first reaction sets the stage for a second reaction, which can then effect a third reaction, and so on.

Polyene cyclization: A reaction between two or more double bonds contained within the same molecule (a polyene) to form one or more rings via one or more C—C bond-forming events.

In this chapter, we spend very little time on the discussion of intramolecular Michael reactions. Although these reactions fulfill the criteria presented above, the actual building blocks are not alkenes, but rather carbonyls, which are converted into nucleophilic enols, enolates, or enol ethers. Therefore, we will discuss only the most dramatic examples of successful anionic polycyclizations using carbonyl chemistry; more rigorous dis-

for references see p 39

cussions can be found in chapters devoted to domino Michael reactions [see Section 2.3.2 and *Science of Synthesis: Asymmetric Organocatalysis*, Vol. 1 (Section 1.1.4.2.5)]. Our focus here will be primarily on electron-neutral alkenes, which for reasons discussed below, must be evaluated using very different criteria.

Polyene cyclizations can be organized according to substrate structure and/or the mechanism of cyclization. This chapter will be organized according to reaction mechanism. It is important to point out that the substrate scope of polyene cyclizations is, in general, rather narrow and has mostly been restricted to naturally occurring polyisoprenoids and their derivatives. The reasons for this restriction are primarily two-fold: (1) the inexpensive, large-scale availability of geometrically pure geranyl, neryl, and farnesyl derivatives, and (2) the biological utility of cyclized polyisoprenoids, including steroids. It should also be noted that the cationic cyclizations of polyisoprenoids to cyclic terpenes are predictable and reliable, meaning that the all-Markovnikov patterning of cyclization sites in all-head-to-tail isoprenyls predispose the reactions to succeed. In contrast, it is challenging to design polyene cyclizations outside this class that proceed in general, or with high degrees of stereocontrol through appropriate transition states, so cyclizations of other polyene systems are infrequent and occasionally idiosyncratic. Some examples will be provided in this chapter, but it is worth noting at the outset that these events are currently hard to generalize.

From the perspective of synthesis theory, polyene cyclizations are a powerful approach for the efficient generation of both complexity and diversity, because each prochiral alkene within the substrate can generate two new stereocenters in the product. A notable feature of polyene cyclizations is the potential for a single synthetic route to a single target structure to be explosively elaborated to a series of both constitutional and stereochemical isomers. However, the general ability to controllably cyclize linear chains to multiple products, each with high selectivity, is unknown outside of enzymatic mediation. There are some noteworthy exceptions in the synthesis literature (see Section 1.1.3.2.3), but the control exerted by enzymes still generally eludes synthetic chemistry and represents a significant chemical frontier for further development.

1.1.1 Cationic Polyene Cyclizations Mediated by Brønsted or Lewis Acids

The steroid biosynthesis depicted in Scheme 1 is one fragment of an immense area of study in chemistry that can be collectively referred to as cationic polyene (or polyolefin) cyclization (or polycyclization), and also as cation–π cyclizations.[4,5] Formation of carbocations that are unstabilized by conjugation or attached heteroatoms has attracted immense interest over the last 90 years[6] due to the extremely high energy of these electron-deficient species.[7,8] The instability of these unstabilized carbocations can be observed in their short lifetimes, estimated to be between 100 femtoseconds to 1 picosecond[9] in water (close to the time required for a single bond vibration, i.e. 10^{-13} s),[10] and the consequent low activation energies associated with their reactions. The free energy difference between a carbocation and the transition state of its electrophilic reaction with an alkene is nearly "barrier-less".[11,12] Therefore, the ability of cyclase enzymes arrayed with multiple Lewis basic sites to stabilize and direct the reactions of cationic isoprenoids is nothing short of astonishing. It is not surprising that translating the enzyme-mediated reactions into bulk solvent for large-scale chemical preparation meets with numerous obstacles, some of which will be mentioned later in this chapter. However, despite these inherent challenges, polyisoprenyl chains undergo predictable, stereoselective, and occasionally high-yielding cyclizations (head-to-tail) to form multiple rings in bulk organic solvent. Methods to effect this transformation vary in the initiation and termination step, but propagation is generally carried through a single or repeating isoprenyl unit. The benefit of this conserved propagation, and the reason it has seen little variation, is that (1) many common natural product scaffolds can be accessed from these poly-

decalin motifs, (2) installation of functionality within the linear precursors is challenging and has unpredictable consequences,[13] and (3) the polyisoprenyl chains can be easily derived from stereochemically pure, commercial materials. The cationic polycyclization methods discussed in this chapter vary primarily according to initiation step, but constraints on the type of termination possible will also be considered.

1.1.1.1 Most Used Cationic Polyene Cyclization Methods

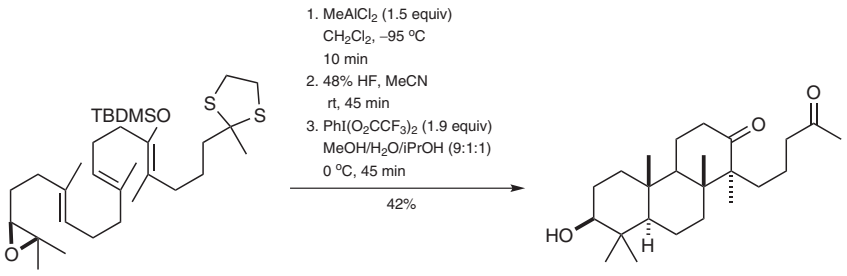
1.1.1.1.1 Polyene Cyclization via Biomimetic Heterolytic Opening of Epoxides by Alkylaluminum Lewis Acids

Early work on the reactions of alkenes with Brønsted acid mediation originally did not recognize the intermediacy of carbocations (or carbenium ions) because the theoretical instability of such structures appeared to preclude their existence.[14] However, once stabilized[15–17] and unstabilized carbocations[6] had been established as viable intermediates, it was not long before they were recognized as possible intermediates in sesquiterpene biosynthesis[18,19] and in steroid biosynthesis.[20,21] Extensive work proved both the possibility and strategic benefit of utilizing cationic polyene cyclization in the synthesis of steroids and other molecules,[22] as well as many rules for carrying out the reactions in bulk solvent, all of which has been reviewed previously.[4,23,24]

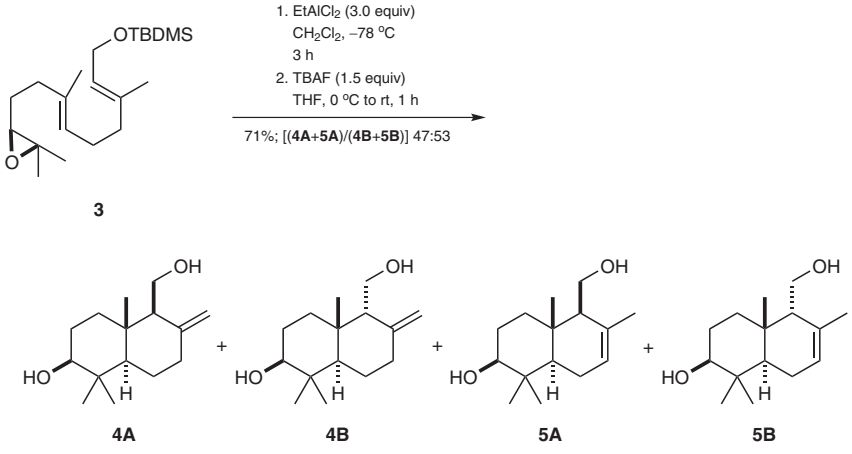
The most consistently utilized method for carrying out polyene cyclization in solution relies on the biomimetic heterolytic opening of epoxides[25–27] by alkylaluminum Lewis acids.[28] There are several advantages to this strategy. First, the strain of the oxirane ring allows reactions at low temperature, which is important for the highly organized transition states of cyclizations because it minimizes the contribution of the entropic term to the transition state free energy (Scheme 2 und Scheme 3).[29,30] Second, alkylaluminum Lewis acids are "self-quenching", so any strong acid generated by adventitious water contamination will react with the strongly basic C—Al bond. Third, the Lewis acids are completely soluble in nonbasic aprotic solvents such as dichloromethane, which does not itself cause the elimination of carbocations (H_0 ~ −17, Hammett acidity), whereas basic solvents such as tetrahydrofuran (pK_a −2.05) or diethyl ether (pK_a −3.05) are problematic. Finally, several methods exist for the enantioselective synthesis of epoxyisoprenoids with high levels of absolute stereocontrol.[31–35] Another benefit of this method has been proposed to be a ligand exchange that can occur between oxirane-ligated and unligated molecules of the alkylaluminum Lewis acids,[28] because similar exchange is observed with pyridine[36] or carbonyl ligands,[37] but whether this exchange is kinetically relevant on the time scale of polycyclization is unknown. It should also be noted that the first ring formation in Brønsted acid mediated epoxide–alkene cyclizations is concerted with epoxide scission rather than a stepwise process,[38] and some evidence suggests that subsequent cyclizations may also be concerted with the initial ionization,[39] but the relevance of this latter data to the methods discussed herein is unclear. An example of a polyene cyclization mediated by ethylaluminum dichloride is shown in Scheme 3 for the formation of decalins **4** and **5** from diene epoxide **3**.

for references see p 39

Scheme 2 Corey's Cationic Polyene Cyclization[29]



Scheme 3 Corey's Cationic Polyene Cyclization with Ethylaluminum Dichloride as Lewis Acid[30]



Decalins 4 and 5; Typical Procedure:[30]

CAUTION: *Ethylaluminum dichloride is highly pyrophoric and corrosive, and is known to ignite spontaneously at room temperature when exposed to air. Extreme caution should be taken during its synthesis, storage, and handling in an effort to avoid exposure to air.*

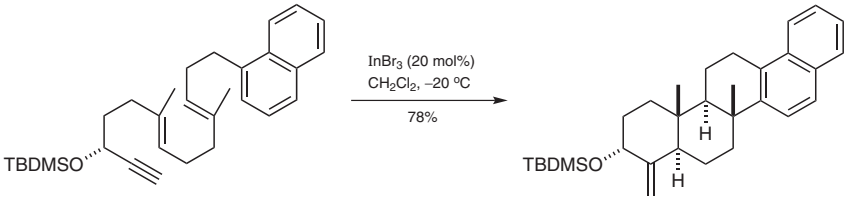
Polyene epoxide **3** (50 mg, 0.142 mmol, 1.0 equiv) was dried azeotropically with toluene (2 × 0.5 mL) under high vacuum for 30 min. The vacuum was then filled with dry N_2 and the flask was fitted with a septum and an argon balloon. Anhyd CH_2Cl_2 (14 mL) was then added and the resulting soln was cooled to −78 °C. A 1 M soln of $EtAlCl_2$ (425 μL, 0.425 mmol, 3.0 equiv) diluted with anhyd CH_2Cl_2 (4.5 mL) was then added down the inner wall of the reaction flask (so it can cool before hitting the reaction mixture) via a 5-mL glass syringe (which was well greased and oven dried) over the course of 3 h while the mixture was stirred rapidly at −78 °C. After the addition was complete, the bright yellow mixture was stirred for an additional 30 min at −78 °C. Et_3N (425 μL, 3.05 mmol, 21.5 equiv) was added slowly over 1 min down the inner wall of the reaction flask. The flask was then taken out of the cooling bath and the septum was removed. Sat. aq potassium sodium tartrate (3 mL) was added while the mixture was stirred rapidly. The mixture was then allowed to warm to ambient temperature, and the volatile components were removed under reduced pressure at 30 °C on a rotary evaporator. The residue was then extracted with EtOAc (3 × 20 mL), and the combined organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude mixture was taken up in EtOAc/hexanes (1:1) and filtered through silica gel to remove any residual amine to afford the crude cyclized product,

which was reacted further without characterization. To a 0.5 M soln of the intermediate in anhyd THF (0.3 mL) at 0 °C was added a 1.0 M soln of TBAF in THF (213 μL, 0.21 mmol, 1.5 equiv). The mixture was then warmed to ambient temperature and TLC analysis indicated complete consumption of the starting materials after 1 h. The mixture was treated with sat. aq $NaHCO_3$ (1 mL) and diluted with EtOAc (10 mL). The organic layer was removed and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 65:35) to give a mixture of the products **4** and **5**; yield: 24 mg (71%); ratio [(**4A+5A**)/(**4B+5B**)] 47:53.

1.1.1.1.2 Polyene Cyclization Mediated by Carbophilic Lewis Acids

A disadvantage of the method described in Section 1.1.1.1.1 is the intolerance of Lewis basic functional groups, which compete with the epoxide for coordination to the aluminum-based Lewis acid. Whereas silyl ethers are generally tolerated due to only weak coordination ability,[30] alcohols, ethers, esters, and carbonates inhibit the initiation step. However, carbophilic Lewis acids such as indium(III) bromide will initiate polycyclization[40] via selective coordination to an appropriately placed alkyne [cationic gold(I) behaves similarly; see Section 1.1.1.3.3]. Notably, free phenols, phenyl ethers, and carbonates are tolerated and serve as efficient terminators via carbocation capture. Furthermore, the ability to initiate the reaction from a chiral nonracemic propargylic ether or alcohol relays this absolute stereochemistry into the rest of the polycyclic core (Scheme 4).

Scheme 4 Indium(III) Bromide Catalyzed Polyene Cyclization[40]

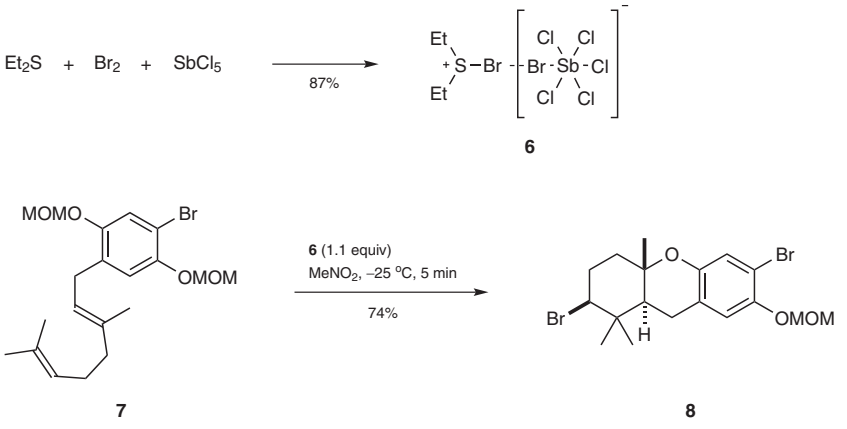


1.1.1.2 Recent Advances in Cationic Polycyclization: Halonium-Initiated Polycyclization

As noted above, the pK_a of protons adjacent to carbocations is extremely low,[8] and preemptive termination of cyclizations through E1 elimination is a general problem. The Snyder group therefore initiated a program[41] to improve the efficiency of halonium-initiated polyene cyclizations[42,43] leading to marine-derived haloterpenes,[44,45] a route which in the past suffered from generally poor yields. Key to the improvement in efficiency of these reactions is the development of electrophilic halogen sources that generate nonbasic anions upon reaction with nucleophiles, in contrast to widely used halosuccinimide or dihalogen reagents. Thus, the Snyder group developed a suite of chloronium, bromonium (e.g., **6**), and iodonium reagents that generate nonbasic, nonnucleophilic antimonate anions and thereby promote polyene cyclizations in good yield and generally excellent diastereoselectivity. A notable advantage of these reagents is that Lewis basic substituents and terminating groups are tolerated, whereas such groups are generally problematic for the aforementioned aluminum Lewis acid reagents, which are competitively coordinated and deactivated. As an example, Scheme 5 shows the conversion of 1,5-diene **7** into tricycle **8** using bromodiethylsulfonium bromopentachloroantimonate(V) (**6**).[42]

for references see p 39

Scheme 5 Bromonium-Initiated Cation–π Cyclization En Route to 4-Isocymobarbatol[42]



Bromodiethylsulfonium Bromopentachloroantimonate(V) (6); Typical Procedure:[42]

CAUTION: *Bromine, diethyl sulfide, and antimony(V) chloride solution are highly toxic, caustic liquids that may be fatal if inhaled, swallowed, or absorbed through skin. All manipulations should be carefully carried out in a well-ventilated fume hood.*

Diethyl sulfide (2.97 mL, 27.5 mmol, 1.1 equiv) and a 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (30.0 mL, 30.0 mmol, 1.2 equiv) were added slowly and sequentially to a soln of Br_2 (1.28 mL, 25.0 mmol, 1.0 equiv) in 1,2-dichloroethane (60 mL) at −30 °C. The dark red heterogeneous mixture was stirred at −30 °C for 20 min, then warmed slowly using a water bath until the soln became homogeneous (~30 °C). At this time, the reaction flask was allowed to cool slowly to 0 °C (4 h), then to −20 °C (12 h), and large orange plates crystallized from the soln. The solvent was decanted and the crystals were rinsed with cold CH_2Cl_2 (2 × 5 mL), then dried under reduced pressure; yield: 11.9 g (87%); mp 104 °C (with decomposition). A checked procedure can be found in *Organic Syntheses*.[46]

(2*R,4a*R**,9a*R**)-2,6-Dibromo-7-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (8); Typical Procedure:**[42]

CAUTION: *Nitromethane is flammable, a shock- and heat-sensitive explosive, and an eye, skin, and respiratory tract irritant.*

A soln of bromodiethylsulfonium bromopentachloroantimonate(V) (**6**; 55 mg, 0.100 mmol, 1.0 equiv) in $MeNO_2$ (0.5 mL) was added quickly via syringe to a soln of 1,5-diene **7** (0.100 mmol, 1.0 equiv) in $MeNO_2$ (1.5 mL) at −25 °C. After the mixture had been stirred at that temperature for 5 min, the reaction was quenched with 5% aq $NaHCO_3$/5% aq Na_2SO_3 (1:1; 5 mL). The mixture was stirred for 15 min, poured into H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel); yield: 74%.

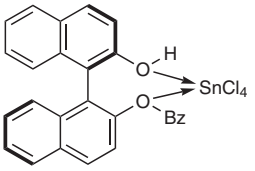
1.1.1.3 Other Common Cationic Polyene Cyclization Methods

1.1.1.3.1 Catalytic, Enantioselective, Protonative Polycyclization

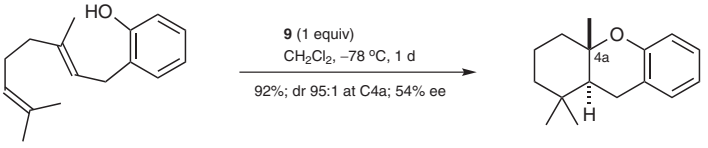
1.1.1.3.1.1 Chiral Transfer from a Brønsted Acid

Enzymes can initiate polyene cyclization through direct protonation of polyisoprenoids to give single enantiomers of a polycycle,[3] a process which is challenging to replicate in bulk solvent because the corresponding unfolded, solvated isoprenyl carbocations are achiral. Therefore, the catalytic, enantioselective protonative polycyclization is truly remarkable in its transmission of chiral information from a Brønsted acid to a carbocationic intermediate in bulk solvent and onto a polycyclic scaffold that possesses multiple points of asymmetry.[47] The difficulty of the reaction is compounded by the facile reversibility of alkene protonation by E1 elimination. However, the Yamamoto group has shown that coordination of 1,1′-bi-2-naphthol derivatives with a strong Lewis acid ($SnCl_4$), e.g. to give **9**, sufficiently lowers the pK_a of these phenols to promote alkene protonation. This initial reaction is highly site-selective for the terminal alkene and provides a sufficiently long-lived cation to allow cyclization (or the cyclization is concerted) and a remarkable induction of asymmetry (Scheme 6).

Scheme 6 Combined Lewis Acid and Chiral Brønsted Acid Catalyzed Cyclization[47]



9

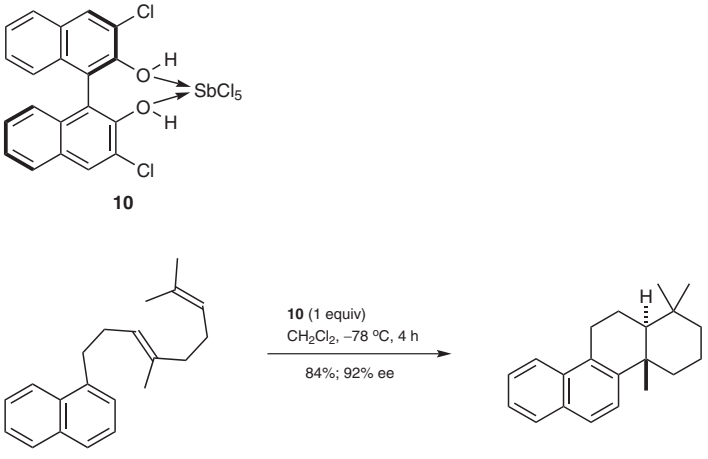


1.1.1.3.1.2 Chiral Transfer from (*R*)-2,2′-Dichloro-1,1′-bi-2-naphthol–Antimony(V) Chloride Complex

An additional, and arguably more convenient, method for site-selective and enantioselective protonation/polyene cyclization developed recently by the Corey group uses simple 2,2′-dichloro-1,1′-bi-2-naphthol complexes with a strong antimony Lewis acid ($SbCl_5$) such as **10**, and causes sufficient alkene protonation at −78 °C and transmission of absolute stereochemistry at 89% enantiomeric excess, on average (Scheme 7).[48] The efficiency of the reaction is attributed to both the electronegativity of the *ortho* chlorides and the increased Lewis acidity of antimony(V) chloride over tin(IV) chloride, rendering the phenols more acidic and the reaction therefore more rapid. The steric bulk of the antimonate complex is proposed to provide enhanced stereoselection, given the only modest steric size of the *ortho* chlorides.

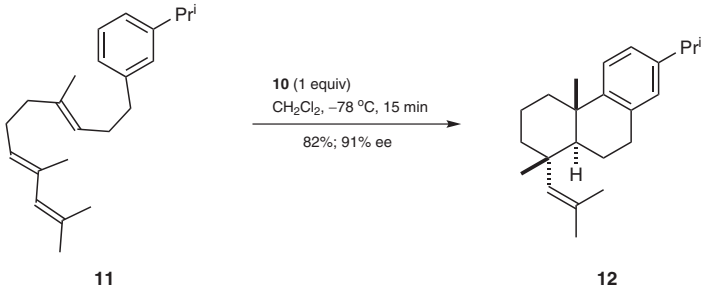
for references see p 39

Scheme 7 Polycyclization with (*R*)-2,2′-Dichloro-1,1′-bi-2-naphthol–Antimony(V) Chloride Complex[48]



Remarkably, this reactivity is generalizable and can be extended beyond the standard polyisoprenyl substrates to more unusual systems such as triene **11**, which cyclizes to enantiomerically enriched tricycle **12**. It is hard to imagine other methods to synthesize **12** easily as a single enantiomer (Scheme 8).[49]

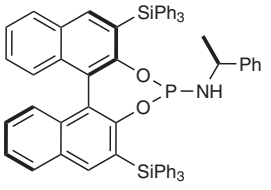
Scheme 8 Polycyclization En Route to Dehydroabietic Acid[49]



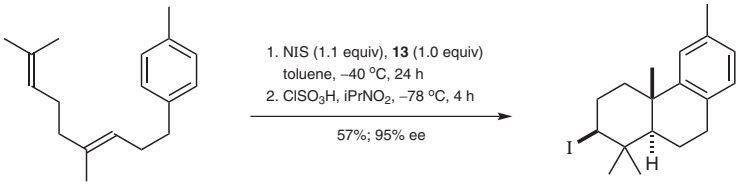
1.1.1.3.1.3 Chiral Transfer via Nucleophilic Phosphoramidites

Introduction of asymmetry into cationic polyene cyclization is most easily accomplished by introduction of a chiral non-alkene initiating group into the precursor polyene. The methods of the groups of Yamamoto and Corey are significant in the direct introduction of asymmetry concomitant with polycyclization, akin to the protonative initiation of isoprenes by cyclase enzymes. In a similar vein, the Ishihara group demonstrated that stoichiometric 1,1′-bi-2-naphthol-based phosphoramidites (e.g., **13**) can mediate the enantioselective transfer of iodonium to a terminal alkene to initiate polyene cyclization as long as electron-rich alkenes and terminating groups are used (Scheme 9).[50]

Scheme 9 Enantioselective Halocyclization Induced by Nucleophilic Phosphoramidites[50]



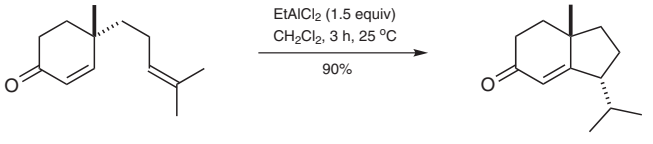
13



1.1.1.3.2 Polyene Cyclization Initiated by Unsaturated Ketones and Mediated by Aluminum Lewis Acids

High energy carbocations have a tendency to undergo Wagner–Meerwein shifts of adjacent hydrogen and carbon atoms to produce rearranged structures.[6] Within cyclase enzymes, these reactions are not restricted to the energy surface of the carbon skeleton itself, but instead are highly controlled by the entire cyclase–substrate complex,[3] although promiscuity abounds in some cases.[51] In bulk solvent, carbocations slip across a very high energy landscape[52] and therefore the ability to mimic and direct the postcyclization rearrangements found in terpene biosynthesis has evaded chemists for decades. The Snider group has developed aluminum Lewis acid mediated reactions that predictably lead to rearranged products (e.g., **15**) in certain substrates by using unsaturated ketones (e.g., **14**) as the initiating moiety (Scheme 10).[53] The intermediate enolate acts as a cation sink, i.e. bond migration places the cationic charge allylic to the enolate as a highly stabilized vinylogous oxonium. The predictability of these Wagner–Meerwein shifts make this method a very useful tool for relaying oxidation state and stereochemistry.

Scheme 10 Lewis Acid Induced Conjugate Addition[53]



14 **15**

(3*R*,7a*S*)-3-Isopropyl-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (15); Typical Procedure:[53]

CAUTION: *Ethylaluminum dichloride is highly pyrophoric and corrosive, is known to ignite spontaneously at room temperature when exposed to air. Extreme caution should be taken during its synthesis, storage, and handling in order to avoid exposure to air.*

A soln of (*S*)-4-methyl-4-(4-methylpent-3-enyl)cyclohex-2-en-1-one (**14**; 200 mg, 1.05 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was treated with a 1.57 M soln of $EtAlCl_2$ in heptane (1.00 mL, 1.57 mmol, 1.5 equiv). After the mixture had been stirred at 25 °C for 3 h, sat. aq NH_4Cl

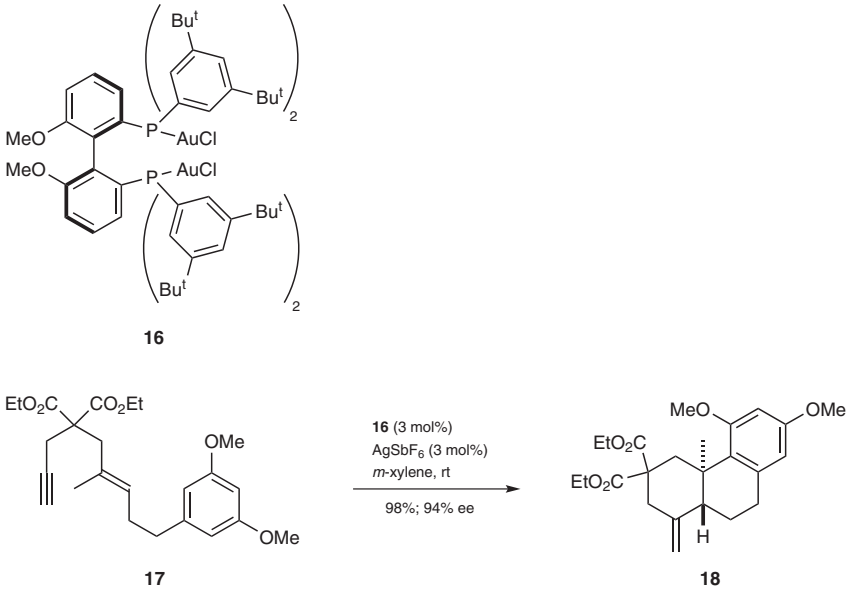
for references see p 39

(10 mL) was slowly added followed by just enough 10% aq HCl to dissolve the precipitated alumina. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were dried ($MgSO_4$) and concentrated to give 200 mg of the cyclized product which was >95% pure. The resulting crude material was purified by flash chromatography (silica gel, EtOAc/hexanes 1:2) to give the pure product; yield: 180 mg (90%).

1.1.1.3.3 Gold-Mediated Enantioselective Polycyclization

Gold(I) catalysts supported by a strong, neutral ligand but unbound by a strong anionic ligand (referred to as "cationic gold") exhibit strong carbophilicity/π-Lewis acidity, weak oxophilicity, and will activate alkynes toward nucleophilic attack. The groups of Fürstner, Kozmin, and others have illustrated the cationic nature of intermediates in gold-catalyzed ene–yne cyclizations[54] by trapping the nascent carbocations[55] with pendent nucleophiles such as sulfonamides[56] and carboxylic acids. Although this early work focused on ene–yne cyclizations, it laid the mechanistic groundwork to prompt investigations into polyisoprenoid cyclizations. A major challenge to π-Lewis acidic gold catalysis is the induction of enantioselectivity, because the alkyne–gold(I)–ligand dihedral angle is nearly linear[57] and therefore the chiral environment of most ligands is difficult to transmit. The Toste group identified[58] extremely sterically encumbered 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl derivatives capable of initiating asymmetric polyene cyclization via coordination and electrophilic activation of an initiating alkyne.[59] Due to the high carbophilicity of gold(I), multiple Lewis basic sites such as esters, phenols, phenyl ethers, and sulfonamides are tolerated in the reaction process. An example of this enantioselective polycyclization is shown in Scheme 11 for the synthesis of tricycle **18** from enyne **17** catalyzed by the digold(I) chloride complex **16**.[60]

Scheme 11 Gold-Catalyzed Enantioselective Polycyclization Reaction[60]



Diethyl (4a*R*,10a*R*)-5,7-Dimethoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2*H*)-dicarboxylate (18); Typical Procedure:[60]

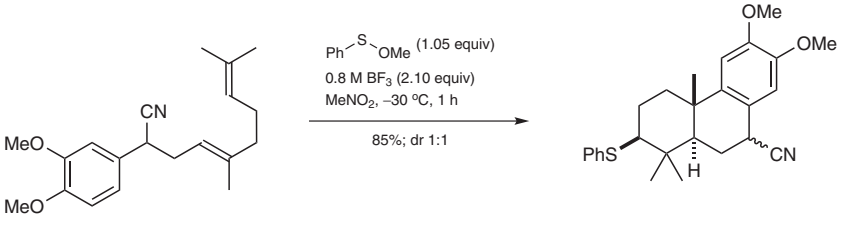
A mixture of $AgSbF_6$ (0.8 mg, 2.2 μmol, 0.05 equiv) and the bisphosphine digold(I) chloride complex **16** (3.32 mg, 2.22 μmol, 0.05 equiv) was suspended in *m*-xylene (300 μL) in a

sealed vial, and sonicated or stirred magnetically at rt for 15 min. The resulting suspension was filtered through a glass microfiber plug directly into a soln of diethyl (*E*)-2-[5-(3,5-dimethoxyphenyl)-2-methylpent-2-enyl]-2-(prop-2-ynyl)malonate (**17**; 18 mg, 0.044 mmol, 1 equiv) in *m*-xylene (600 μL). Thorough mixing was ensured and the resulting homogenous soln was allowed to stand until the substrate had been fully consumed as judged by TLC or ^{1}H NMR analysis. Upon consumption of the starting material, the mixture was concentrated to a volume of ca. 100 μL, which was then eluted through a short silica gel column to obtain the pure cyclized product; yield: 98%; 94% ee.

1.1.1.3.4 Polycyclization Initiated by an Episulfonium Ion

Whereas enzymes utilize a litany of electrophilic agents to initiate polycyclization, electrophilic sulfur, which is present in many biological systems, has not been observed in a cyclase catalytic active site. In contrast, the Livinghouse group demonstrated that combining sulfenic esters and amides with strong Lewis acids will initiate polyene cyclizations that can be terminated with arenes and vinyl esters to provide versatile sulfurated polycycles in good yield (Scheme 12).[61]

Scheme 12 Episulfonium Ion Initiated Polyene Cyclization[61]

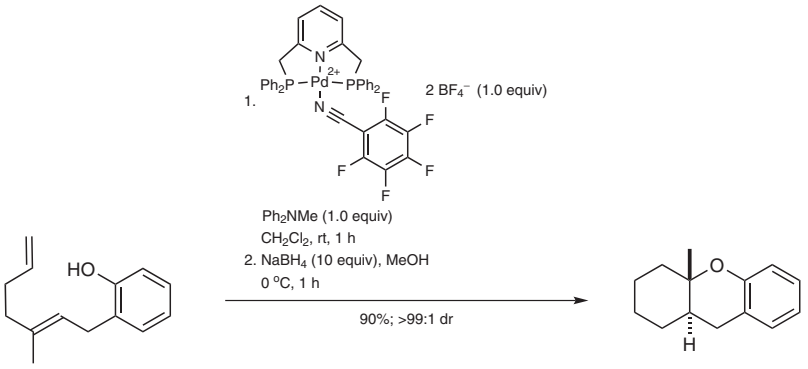


1.1.1.3.5 Polycyclization Initiated by a π-Lewis Acidic Metal

Cyclase enzymes catalyze the polyene cyclization of oxidosqualene and other epoxyisoprenoids using alkali metal co-factors (such as Mg^{2+}) that serve as Lewis acids to initiate heterolytic C—O bond cleavage.[3] To circumvent the intermediacy of an epoxide initiating group, a π-Lewis acidic metal is an ideal candidate to coordinate and polarize the precursor alkene. Because numerous chiral ligands are available for screening, the possibility of obtaining enantioselectivity in the reaction is very good. Unlike Yamamoto's method for asymmetric protonative initiation (see Section 1.1.1.3.1.1), an initiation by a metal–alkene complex does not require multiply substituted alkenes as substrates, and in fact current methods require minimal steric encumbrance on the initiating alkene, as demonstrated by the Gagné group (Scheme 13).[62,63] A disadvantage of this method is that naturally occurring substrates, such as geranyl or farnesyl chains, are not directly amenable to these reactions; an advantage is orthogonality in substrate requirements as compared to other methods. It is noteworthy that bulky chiral bidentate phosphine ligands induce enantioselectivity even using 10 mol% platinum loading, although the selectivity between enantiomers only reaches 79% enantiomeric excess.

for references see p 39

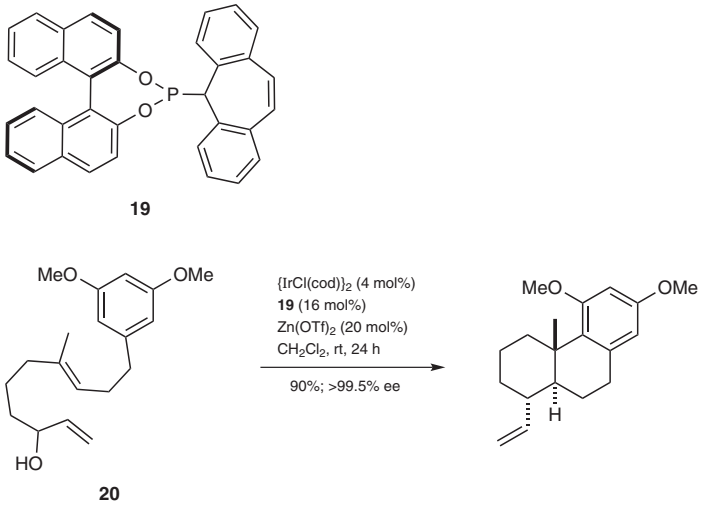
Scheme 13 Palladium-Mediated Polycyclization[62]



1.1.1.3.6 Enantioselective Polyene Cyclization Mediated by Chiral Scalemic Iridium Complexes

Occasionally, use of an unnatural initiating group holds strategic advantages for solving problems in cationic polyene cyclization. Whereas allylic alcohols are not normally electrophilic substrates for head-to-tail polycyclization, the Carreira group has utilized these initiators to good effect in devising a highly enantioselective cascade reaction (>99% ee) that is also high yielding and experimentally simple (Scheme 14).[64] The reaction relies on the ability of chiral iridium complexes, for example with dioxaphosphepin ligand **19**, to intercept racemic allylic alcohols (e.g., **20**) in the presence of an additional Lewis acid and initiate highly enantioselective C—C bond formation. This procedure can lead to short, enantioselective syntheses of challenging terpenes such as asperolide C.[65]

Scheme 14 Iridium-Catalyzed Polyene Cyclization[64]

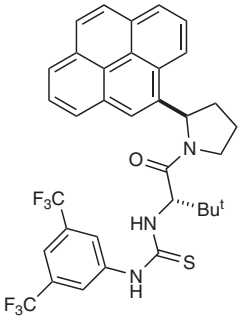


1.1.1.3.7 Acyliminium-Initiated Polyene Cyclization Mediated by Thioureas

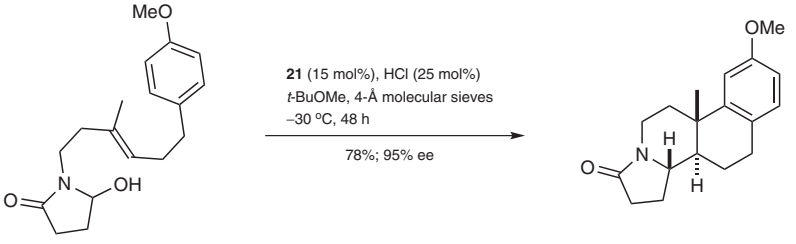
It is believed that aromatic amino acid residues embedded in cyclase active sites undergo stabilizing cation–π interactions with their terpenoid substrates to direct product formation in cationic polyene cyclizations and Wagner–Meerwein rearrangements.[3,66–69] Appli-

cation of these ideas to biomimicry in bulk solvent has been limited by the difficulty of designing systems that capitalize on these interactions. However, Jacobsen, Lin, and Knowles determined that the arene surface area can be correlated to yield and absolute stereoselectivity in an acyliminium-initiated polyene cyclization mediated by a thiourea catalyst (e.g., **21**) (Scheme 15).[70] The authors hypothesize that the cation–π interaction leads to a lower energy pathway than the uncatalyzed, unorganized background reaction. Although the system is idiosyncratic in its initiation and therefore unlikely to see widespread use, the observation of productive and synthetically relevant carbocation–π interactions may lead to widespread redesign of catalysts to control cationic reaction pathways in other manifolds.

Scheme 15 Enantioselective Thiourea-Catalyzed Polycyclizations[70]



21

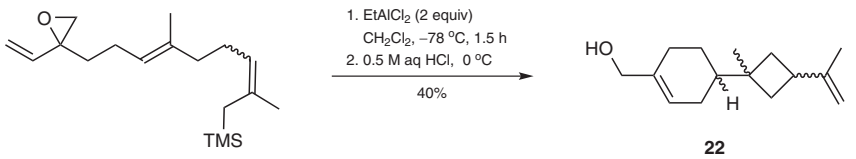


1.1.1.3.8 Tail-to-Head Polycyclization

The examples of biomimicry discussed above primarily explore cationic polyene cyclization initiated at the head terminus of a polyisoprenyl chain, as often occurs in nature. An additional, major branch of terpene biosynthesis instead relies on initiation at the tail terminus (tail-to-head polycyclization). This mode of polyene cyclization has seen relatively little exploration, because multiple ring formations are not kinetically competent to outcompete early termination through elimination, unlike the head-to-tail cyclizations discussed above. The Shenvi group demonstrated that a key obstacle to these cascades is the position of the counteranion relative to the carbocation.[71] If the counteranion is allowed to travel with the carbocation, then elimination occurs due to the highly acidic nature of protons adjacent to carbocations. If instead the counteranion is bound distal to the carbocation, then Wagner–Meerwein shifts become kinetically competent and polycyclic products (e.g., **22**) can be formed (Scheme 16). A major barrier to the broad application of this strategy is the lack of stereocontrol encountered in these cascades, which stands in stark contrast to the head-to-tail cascades covered in Sections 1.1.1.1.1–1.1.1.3.7.

for references see p 39

Scheme 16 Tail-to-Head Polycyclization[71]



22

1.1.2 Radical Polyene Cyclizations

The inherent high energy of carbocations and the difficulty in controlling their behavior has led to the exploration of alternative modes for effecting polycyclization, especially through carbon-centered radicals. Radicals are no panacea for polyene reactions, but there are different pros and cons associated with their use. Whereas carbon radicals are more stable than carbocations due to their lower relative free energy, they are not necessarily more persistent.[72] Persistence, or lifetime, depends on the reaction environment, and carbocations can be rendered remarkably persistent in stabilizing solvent and when the counteranion is the conjugate base of a superacid.[7] Radicals are generally more persistent, but must be formed at low concentrations to prevent homocoupling and in the absence of radicalophiles, especially triplet oxygen, to prevent preemptive capture. However, many C—C bond-forming reactions can use radical intermediates to unique effect due to their geometry, predictability, ease of generation, and the efficiency of intramolecular reactions, especially with alkenes. In the sections that follow, we document the most efficient methods for effecting polyene cyclizations via radical intermediates, some of which can mimic the reaction outcomes of biosynthetic cationic cascades.

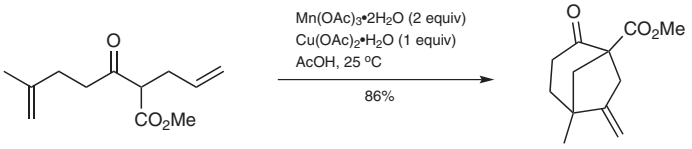
1.1.2.1 Most Used Radical Polycyclization Methods

Manganese(III) acetate has been recognized for several decades as a useful reagent to mediate the single-electron oxidation of carbonyls to their α-radical equivalents. Initially, manganese(III) acetate was used for the addition[73,74] and annulation[75] of carboxylic acids to alkenes. However, it has since been recognized as one of the most powerful reagents for initiating radical polyene cyclization.

1.1.2.1.1 Cyclization of Mono-and Polyunsaturated β-Oxo Esters Mediated by Manganese(III) Acetate

The Snider group has extensively studied the initiation, propagation, and termination of the cyclization of mono- and polyunsaturated β-oxo esters as mediated by manganese(III) acetate. This strategy has several advantages: (1) ease of preparation of substrate, because the polyene can be alkylated efficiently onto the initiating β-oxo ester under mild conditions; (2) the initiating group possesses very different reactivity to the polyene, and therefore chemoselectivity of initiation is not a problem; and (3) the β-oxo ester is retained in the product and can be further functionalized to many different moieties. The biggest disadvantages are (1) early cascade termination, which depends on the relative rate of cyclization versus oxidation to the carbocation/elimination and can only be determined empirically; and (2) that the reaction must be run in acetic acid (only a minor drawback). As long as the relative rates of radical alkene cyclizations are understood, the products are simple to predict and therefore the domino reactions in this manifold are easy to design. A typical example of a manganese(III) acetate mediated cyclization is the reaction of methyl 2-allyl-6-methyl-3-oxohept-6-enoate (**23**) to give **24** (Scheme 17).[76]

Scheme 17 Manganese-Based Oxidative Cyclization[76]



23 24

Methyl 5-Methyl-6-methylene-2-oxobicyclo[3.2.1]octane-1-carboxylate (24); Typical Procedure:[76]

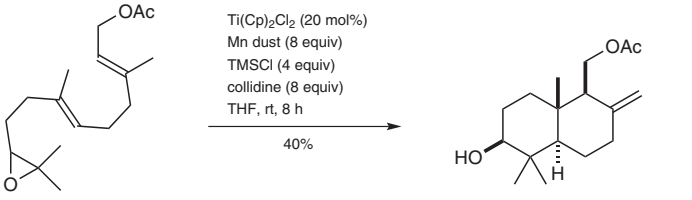
CAUTION: *Glacial acetic acid is a caustic liquid that may be an irritant if inhaled, swallowed, or absorbed through skin. All manipulations should be carefully carried out in a well-ventilated fume hood.*

To a stirred soln of $Mn(OAc)_3•2H_2O$ (0.804 g, 3.0 mmol, 2.0 equiv) and $Cu(OAc)_2•H_2O$ (0.300 g, 1.5 mmol, 1.0 equiv) in glacial AcOH (13.5 mL) was added methyl 2-allyl-6-methyl-3-oxohept-6-enoate (**23**; 0.307 g, 1.5 mmol, 1.0 equiv) in glacial AcOH (4 mL). The mixture was stirred at rt for 26 h. After H_2O (100 mL) had been added, 10% aq $NaHSO_3$ was added dropwise to the mixture to decompose any residual $Mn(OAc)_3$. The resulting soln was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a yellow solid, which was recrystallized (pentane) to give the pure product; yield: 270 mg (86%).

1.1.2.1.2 Titanocene-Catalyzed Polycyclization

A major benefit of using epoxyisoprenyl substrates in polyene cyclizations is that they map onto numerous bioactive terpene scaffolds. As discussed above, Lewis acids mediate cationic polyene cyclization of these substrates, but there are numerous challenges to this approach, especially early termination of the cascade and incompatibility with strong Lewis bases in the substrate. In the 1980s, RajanBabu and Nugent pioneered the use of low-valent titanium complexes to reductively cleave epoxides via carbon-centered radicals, which could also intercept alkenes intramolecularly.[77,78] This reaction was subsequently rendered catalytic.[79] The Barrero group explored the application of this reactivity to the polycyclization of epoxyisoprenyls in the anticipation that radical intermediates may offer a strategic advantage over carbocations (Scheme 18).[80] In general, these reactions are easy to carry out, and do allow the inclusion of Lewis basic groups such as acetates, ketals, and alcohols within the substrates (e.g., **25**). However, the yields of the products (e.g., **26**) are not appreciably better than the ones for the best cationic polyene cyclizations achieved to date. The most important feature of this reaction is the ability to terminate the cascade with an enone function, which is resistant to further radical cyclization and instead forms a stable metalloenolate.[81]

Scheme 18 Titanocene-Catalyzed Polyene Cyclization[80]



25 26

for references see p 39

[(1*R,4a*S**,6*R**,8a*R**)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl]methyl Acetate (26); Typical Procedure:**[80]

Strictly deoxygenated THF (20 mL) was added to a mixture of $Ti(Cp)_2Cl_2$ (0.5 mmol, 0.2 equiv) and Mn dust (20 mmol, 8.0 equiv) under argon and the suspension was stirred at rt until it turned lime green (after about 15 min). Then, a soln of epoxide **25** (2.5 mmol, 1.0 equiv) and 2,4,6-collidine (20 mmol, 8.0 equiv) in THF (2 mL) and TMSCl (10 mmol, 4 equiv) were added and the soln was stirred for 8 h. The reaction was then quenched with 2 M aq HCl and the mixture was extracted with *t*-BuOMe. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in THF (20 mL) and stirred with TBAF (10 mmol, 4.0 equiv) for 2 h. The mixture was then diluted with *t*-BuOMe, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, hexanes/*t*-BuOMe); yield: 40%.

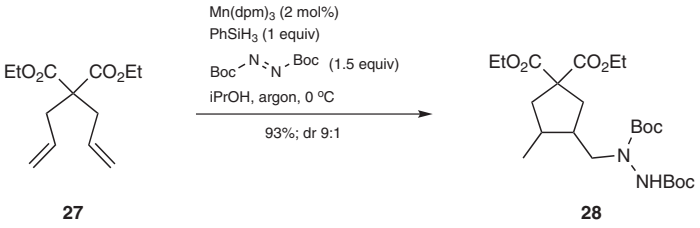
1.1.2.2 Recent Advances in Radical Polycyclization

1.1.2.2.1 Manganese- and Cobalt-Catalyzed Cyclization

Almost thirty years ago, Mukaiyama introduced an array of manganese, iron, and cobalt catalysts that promote the Markovnikov hydrofunctionalization of alkenes via carbon-centered radical intermediates.[82] Hydration and hydroperoxidation of electron-neutral alkenes were demonstrated by Mukaiyama, as was hydronitrosation of electron-deficient alkenes (unsaturated amides and esters). The detailed mechanisms of these reactions have not been elucidated, but they were proposed by the Shenvi group[83] to result from metal hydride hydrogen-atom transfer, in analogy to the reactions studied by the groups of Halpern,[84,85] Bullock,[86,87] Norton,[88–90] and Eisenberg.[91] This proposal contrasts with the hydrometalation mechanisms proposed extensively in the hydrofunctionalization literature originating with Mukaiyama. These mechanisms instead invoke metal hydride addition[92] across the alkene[93] to form an alkylcobalt species,[82,94] similar to hydroboration but with reversed polarity preferences. However, the regioselectivity (Markovnikov) is opposite to that normally observed for hydrometalation, and the porphyrin–metal complexes that can catalyze these reactions[95,96] do not possess a binding site adjacent to the hydride to allow this concerted addition to occur.[97] Additional related reactions in this area were reported by the Magnus group who demonstrated enone reduction[98] and hydration,[99] the Krische group who demonstrated an enone [2+2] cycloaddition from a low-valent cobalt catalyst,[100] and the Carreira group who greatly expanded this area by contributing hydrazidation,[93,101] hydrohydrazidation,[102–105] hydrocyanation,[106] hydrochlorination,[107,108] and hydrooximation.[109] More recent contributions have been made by the Boger group using a combination of iron salts and borohydrides, which can achieve, notably, Markovnikov hydrofluorination[110] in addition to many other transformations,[111] by the Baran group, who have demonstrated conjugate addition to enones,[112,113] and by the Shenvi group, who demonstrated hydrogenation of electron-neutral alkenes with thermodynamic stereocontrol and alkene isomerization.[83] A related reduction of haloalkenes with a cobalt catalyst was reported subsequently by the Herzon group,[114] who also proposed hydrogen-atom transfer to be operative in these reactions.

A significant benefit of this reactivity is that it allows for direct generation of a carbon-centered radical from any alkene, whether electron-neutral, electron-rich, or electron-deficient. There is excellent proof of principle for initiating radical polyene cyclizations using these methods, although there has been no rigorous study of the breadth of this strategy. For example, the Carreira group has used their hydrazidation reaction to initiate five-membered ring cyclization/azidation of diene **27** to give cyclopentane **28** catalyzed by tris(dipivaloylmethanato)manganese(III) [tris(2,2,6,6-tetramethylheptane-3,5-dionato)manganese(III)] (Scheme 19).[93]

Scheme 19 Tris(dipivaloylmethanato)manganese(III)-Catalyzed Hydrazidation of Alkenes[93]



27 **28**

dpm = 2,2,6,6-tetramethylheptane-3,5-dionato

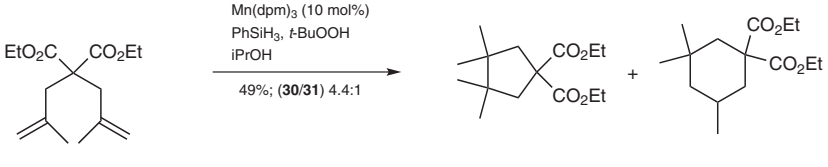
Diethyl 3-[*N*,*N*′-Di-(*tert*-butoxycarbonyl)hydrazinomethyl]-4-methylcyclopentane-1,1-dicarboxylate (28); Typical Procedure:[93]

$Mn(dpm)_3$ (6 mg, 0.01 mmol, 0.02 equiv) was dissolved in iPrOH (2.5 mL) at 23 °C under argon and the dark brown-green soln was cooled to 0 °C. Diethyl 2,2-diallylmalonate (**27**; 121 mg, 0.50 mmol, 1.0 equiv) and $PhSiH_3$ (65 μL, 0.52 mmol, 1.0 equiv) were added, followed by di-*tert*-butyl azodicarboxylate (0.17 g, 0.75 mmol, 1.5 equiv) in one portion. The resulting suspension was stirred at 0 °C and the reaction was monitored by TLC (EtOAc/hexane 1:5). After 4 h (color change to yellow), the reaction was quenched with H_2O (1 mL). Brine (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (silica gel, EtOAc/hexanes 1:10 to 1:5); yield: 221 mg (93%); dr 9:1.

1.1.2.2.2 Manganese-Catalyzed Hydrogenative Polycyclization

If the introduction of further functionality is unnecessary, a simple hydrogenative cyclization procedure is available. It is noteworthy that radical alkene cyclizations usually possess very early transition states and therefore tolerate severe steric clash in the product. Unlike the hydrogenative hydrogen-atom transfer cyclizations previously reported,[89,115] these reactions work well on electron-neutral alkenes. Furthermore, compared to most other metal-mediated cyclizations of polyunsaturated carbon chains, this reaction does not require one more alkyne in the substrate for initial metal coordination, substituted alkenes are tolerated, and the catalysts are based on abundant, non-precious metals with low-cost ligands. As an example, Scheme 20 shows the formation of cyclic diesters **30** and **31** from diene **29** catalyzed by tris(dipivaloylmethanato)manganese(III) [tris(2,2,6,6-tetramethylheptane-3,5-dionato)manganese(III)].[83]

Scheme 20 Reductive Manganese-Catalyzed Radical Cyclization[83]



29 **30** **31**

dpm = 2,2,6,6-tetramethylheptane-3,5-dionato

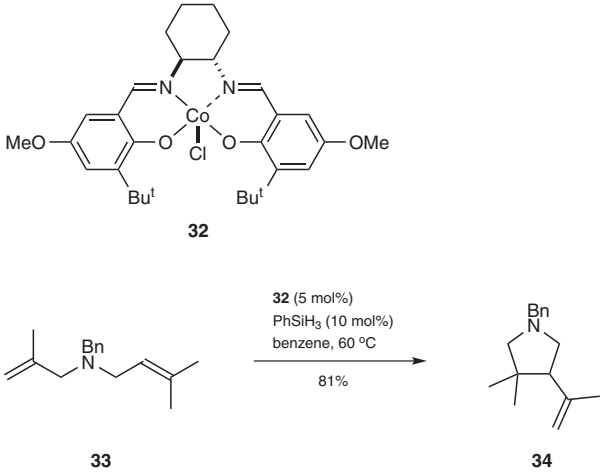
for references see p 39

Diethyl 3,3,4,4-Tetramethylcyclopentane-1,1-dicarboxylate (30**) and Diethyl 3,3,5-Trimethylcyclohexane-1,1-dicarboxylate (**31**); Typical Procedure:**[83]
Diethyl 2,2-bis(2-methylallyl)malonate (**29**; 53.6 mg, 0.20 mmol, 1.0 equiv) was dissolved in anhyd iPrOH (1.0 mL, 0.2 M) under argon. To the stirred soln were added $PhSiH_3$ (24.4 μL, 0.20 mmol, 1.0 equiv) and an 8.0 M soln of *t*-BuOOH in hexanes (37.5 μL, 0.30 mmol, 1.5 equiv) and the resulting mixture was degassed by bubbling argon through the soln for 10 min. $Mn(dpm)_3$ (12 mg, 0.02 mmol, 10 mol%) was added in one portion and the mixture was degassed for an additional 30 s. After the reaction was complete (GC/MS), iPrOH was evaporated and the crude mixture [yield: 85%; ratio (**30**/**31**) 2.4:1.0] was subjected to flash chromatography (silica gel, Et_2O/hexanes 1:99) to obtain an enriched mixture of the products **30** and **31**; yield: 27 mg (49%); ratio (**30**/**31**) 4.4:1.

1.1.2.2.3 Radical Isomerization, Cycloisomerization, and Retrocycloisomerization with a Cobalt–salen Catalyst

Within the mechanistic framework of hydrogen-atom transfer proposed by the Shenvi group[83] to be operative within Mukaiyama hydrofunctionalizations, a broadly applicable radical cycloisomerization of linear polyenes was developed by the Shenvi group,[116] based on observations in related systems by the Norton group.[117] The initiating alkene must be terminal due to the steric constraints of the catalyst, but this allows the cycloisomerization to terminate without further isomerization and loss of stereochemistry. This chemoselective and controlled reorganization of simple alkenes has potential for general use in complex molecule synthesis. In addition to cycloisomerization, the linear isomerization and retrocycloisomerization (formal retro-ene reaction) of terminal alkenes can be effected with the same chemistry. Because carbon radical formation does not require reaction with a Lewis acidic metal, strongly Lewis basic functional groups such as tertiary amines are tolerated. As an example, Scheme 21 shows the formation of 1-benzyl-3,3-dimethyl-4-(prop-1-en-2-yl)pyrrolidine (**34**) from diene **33** catalyzed by cobalt–salen complex **32**.[116]

Scheme 21 Cobalt-Catalyzed Radical Retrocycloisomerization[116]



1-Benzyl-3,3-dimethyl-4-(prop-1-en-2-yl)pyrrolidine (34**); Typical Procedure:**[116]
Cobalt catalyst **32** (4 mg, 7 μmol, 0.03 equiv) was added to a flame-dried small vial under argon, then dissolved in benzene (previously degassed with argon; 2.2 mL) (**CAUTION:** *carcinogen*). This dark green soln was then added to a flame-dried flask containing *N*-ben-

zyl-3-methyl-*N*-(2-methylallyl)but-2-en-1-amine (**33**; 50 mg, 0.22 mmol, 1.0 equiv) under argon. $PhSiH_3$ (1.6 μL, 0.01 mmol, 0.06 equiv) was then added to the stirred soln and the resulting red-orange soln was heated at 60 °C. The reaction was monitored by GC/MS, and after the mixture had been stirred for 12 h, more cobalt catalyst **32** (4 mg, 7 μmol, 0.03 equiv) and phenylsilane (1.6 μL, 0.01 mmol, 0.06 equiv) were added. The mixture was heated at 60 °C until the reaction was complete and concentrated directly under reduced pressure. The residue was purified by flash chromatography (silica gel, Et_2O/hexanes 5:95) to obtain the product as a clear yellow oil; yield: 41 mg (81%).

1.1.2.3 Other Examples of Radical Polycyclization

There are numerous other reports of radical polyene cyclizations, but many utilize unique/nongeneralized initiating groups, engineered propagating groups, or reagents that are inconvenient due to instability or toxicity. Three examples worth mentioning that have not been extensively applied, but showcase important methods for carrying out radical polyene cyclizations are shown in Sections 1.1.2.3.1–1.1.2.3.3.

1.1.2.3.1 Radical Polycyclization via Photoinduced Electron Transfer

Although radical anions and radical cations derived from electron-neutral alkenes are higher in energy than the corresponding neutral carbon-centered radicals, their formation can occasionally be realized with some efficiency. Demuth and co-workers have demonstrated[118] that photoinduced electron transfer from 1,4-dicyano-2,3,5,6-tetramethylbenzene/biphenyl will oxidize the terminal head unit of a polyisoprenyl chain with surprising site selectivity and, after capture with water, radical polyene cyclization ensues. Although this method for polyene cyclization has not been applied extensively outside the Demuth laboratory, the orthogonality of its reactivity compared to most methods make it an enticing prospect for further exploration.

1.1.2.3.2 Polycyclization via Organo-SOMO Catalysis

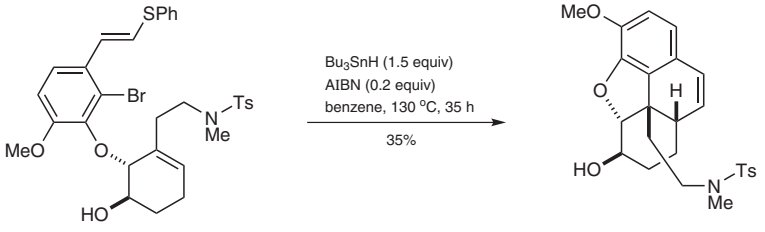
The most closely related reaction to parallel Demuth's method is a recent report of polyene cyclization initiated by single-electron oxidation of a catalytically generated enamine (see also Section 1.4.2.3.1). A great benefit of this strategy is the ability to induce chirality catalytically using a chiral amine and along a radical reaction pathway, which means that electron-poor arenes can be efficiently utilized as terminating groups. A deficiency of this reaction is that electron-deficient alkenes must be used to propagate the cascade beyond an initial bicyclization. However, as a general route to some specific terpene skeletons in asymmetric fashion, the method is excellent.[119]

1.1.2.3.3 Polyene Radical Cascades in Complex Molecule Synthesis

There are numerous, arguably esoteric, examples of radical polyene cyclization in synthesis, and so it is challenging to select the "best" example. However, certainly some of the best benefits of using a polyene radical cascade to construct a complex molecule (e.g., **36** from polyene **35**) are encapsulated by the Parker group in the synthesis of morphine using simple building blocks (Scheme 22).[120] First, carbon-centered radicals are not sensitive to acidic hydrogens, unlike their organometallic equivalents, so unprotected functional groups (e.g., hydroxy groups) can be used. Second, quaternary centers can be formed efficiently. Third, termination need not arise from hydrogen-atom abstraction from initiator or solvent, but rather can occur by elimination of, in this case, a thiol radical.

for references see p 39

Scheme 22 A Radical Cyclization Cascade En Route to Morphine[120]



35 **36**

***N*-[2-{(3*R*,3a*R*,3a^1*S*,9a*S*)-3-Hydroxy-5-methoxy-1,3,3a,9a-tetrahydrophenanthro[4,5-*bcd*]furan-3a^1(2*H*)-yl}ethyl]-*N*,4-dimethylbenzenesulfonamide (36); Typical Procedure:**[120]
A soln of alcohol **35** (120 mg, 0.187 mmol, 1.0 equiv), Bu_3SnH (75 μL, 0.280 mmol, 1.5 equiv), and a catalytic amount of AIBN (0.1–0.2 equiv) in benzene (8 mL) (**CAUTION:** *carcinogen*) was heated in a sealed tube at 130 °C. A small amount of AIBN was added every 8 h to maintain the radical chain. After 35 h, the mixture was concentrated, and the residue was dissolved in Et_2O and then stirred vigorously with 10% aq KF for 2 h. The ether phase was separated, washed with brine, dried (Na_2SO_4), and concentrated. Purification by preparative TLC (silica gel, EtOAc/hexanes/acetone 1:3:1) afforded the pure product; yield: 30 mg (35%).

1.1.3 Polyene Cyclization via Reductive Elimination from a Metal Center or Metathesis

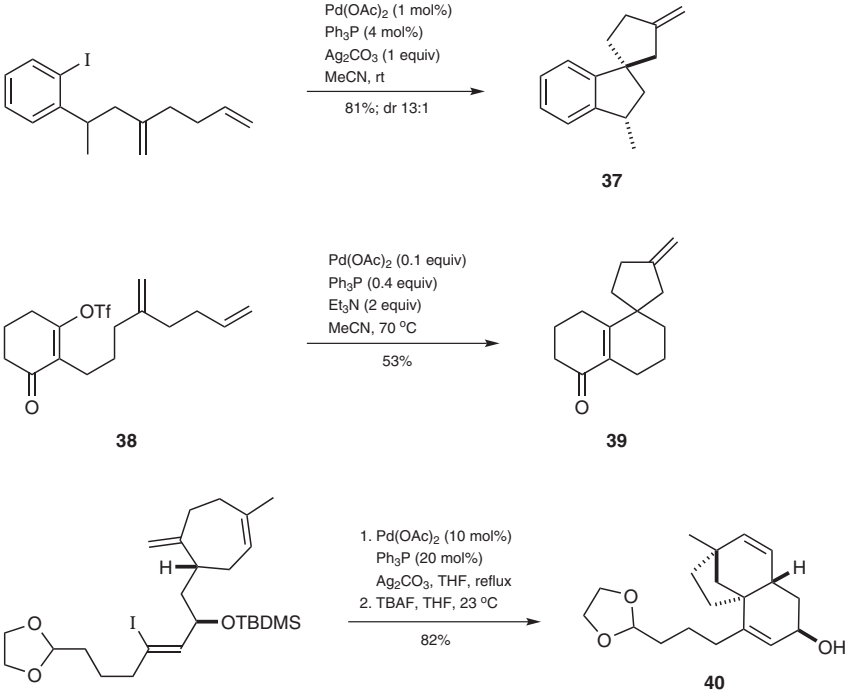
The advent of organometallic chemistry, and especially metal catalysis, in complex organic molecule synthesis over the past four decades has opened many avenues to explore in polyene cyclization. In some sense, these reactions are intramolecular variants of metal-catalyzed polymerization reactions.

1.1.3.1 Most Used Polycyclization Methods via Reductive Elimination

1.1.3.1.1 Palladium Zipper Cyclization Cascades

Unlike cationic and radical methods for polyene cyclization, where reactive intermediates are centered at the more-substituted position of an alkene, reactions that proceed via the intermediacy of carbon—metal bonds tend to propagate at the less substituted position. The groups of Overman,[121–123] Trost,[124] Oppolzer,[125] and Negishi[126,127] were among the first to recognize the power of palladium catalysts to mediate polyene cyclization along these less accessible reaction pathways. In particular, the Overman group demonstrated that quaternary centers (e.g., in compounds **37**, **39**, and **40**, Scheme 23) are easily accessible via intramolecular Heck polyene cyclizations, and that these reactions can be rendered asymmetric using chiral ligands on palladium.[121–123] From the perspective of retrosynthetic analysis, the ability to initiate the cascades using insertion into enol trifluoromethanesulfonates (e.g., **38**) is a powerful asset, because substrates are then easily accessible from functionalized ketones, and in turn from simple unfunctionalized ketones.

Scheme 23 Palladium-Catalyzed Heck Polyene Cyclizations[121–123]



3-Methylene-2′,3′,4′,6′,7′,8′-hexahydro-5′*H*-spiro[cyclopentane-1,1′-naphthalen]-5′-one (39); Typical Procedure:[122]

Et_3N (0.31 mL, 2.2 mmol, 2.0 equiv), Ph_3P (60 mg, 0.23 mmol, 0.2 equiv), and $Pd(OAc)_2$ (13 mg, 0.057 mmol, 0.05 equiv) were sequentially added to a soln of vinyl trifluoromethanesulfonate **38** (407 mg, 1.11 mmol, 1.0 equiv) in anhyd MeCN (37 mL). The resulting green soln was heated to 70 °C. After 22 h, the reaction was ~30% complete. Additional Ph_3P (60 mg, 0.23 mmol, 0.2 equiv) and $Pd(OAc)_2$ (13 mg, 0.057 mmol. 0.05 equiv) were added and heating was continued for an additional 19 h, at which time GLC analysis showed complete consumption of the starting material. The mixture was adsorbed onto Florisil (with a rotary evaporator) and the Florisil was extracted by filtration with Et_2O (ca. 20 mL). Concentration and chromatography of the residue (silica gel, hexanes/EtOAc 20:1 to 10:1) gave the pure product; yield: 0.13 g (53%).

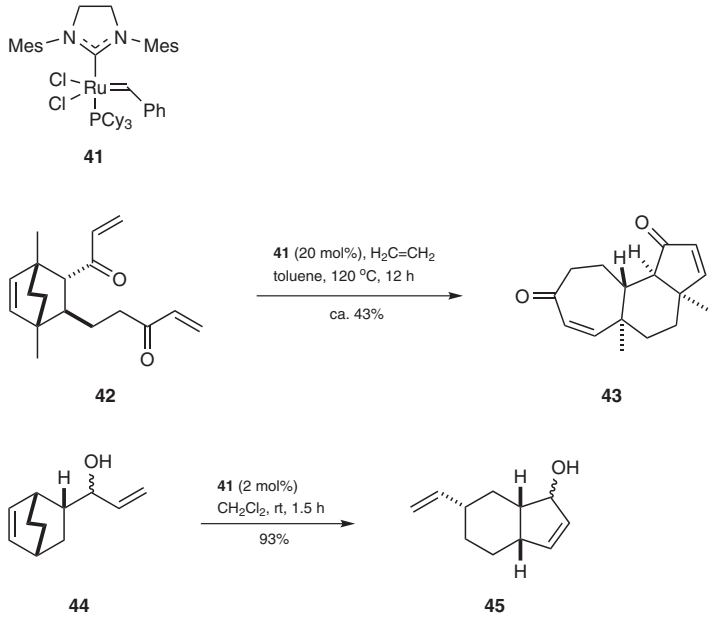
1.1.3.1.2 Polycyclization Cascades via Metathesis

The polyene cyclizations discussed in prior sections differ from those covered in this section in that C—C bonds are only formed, not broken. However, implicit in alkene metathesis based approaches to complex molecule synthesis[128] is the fact that a carbon must be lost, if only temporarily, for the reaction to occur. This loss can involve the fragmentation of a single methylene in the case of a terminal vinyl group, the fragmentation of a longer chain, or, in some cases, the fragmentation of a ring. Although counterintuitive, ring fragmentation can be used to advantage if gross structure assembly of the cycle is facile and strategically important for generating overall complexity more quickly.[2] In this vein, the approach of the Phillips group to the cyanthiwigins is instructive. The polyene cyclization precursor can be synthesized in short order via a chiral auxiliary controlled Diels–Alder reaction followed by some functional group interconversions. Subjection of intermediate **42** to Grubbs' second-generation initiator **41** fragments the cyclohexene ring and engages

for references see p 39

the proximal enones in two ring-closing metathesis reactions to yield the cyanthiwigin core **43** (Scheme 24).[129] So, although one element of complexity – the bridging cyclohexene – is sacrificed, its destruction leads to a rapid assembly of the more challenging 7/6/5 core. In addition, indenol **45** can also be formed with the same strategy from dienol **44**.[130] In a general sense, this is an important maneuver to remember in synthesis, the equivalent of baseball's sacrifice fly.[2]

Scheme 24 Metathesis Cyclization[129,130]



(3a*S*,6*S*,7a*S*)-6-Vinyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-ol (45); Typical Procedure:[130] Grubbs' catalyst **41** (4.8 mg, 5.8 μmol, 2 mol%) was dissolved in CH_2Cl_2 (2 mL) and added by syringe to a soln of dienol **44** (48 mg, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 (28 mL, 0.01 M). This soln was then sparged with ethene three times over a 30-min period for 60 s each time. At 30 min, the remaining ethene was purged from the soln with N_2 and the mixture was stirred at rt under N_2 for 1 h. The solvent was then removed by rotary evaporation and the residue was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1); yield: 45 mg (93%).

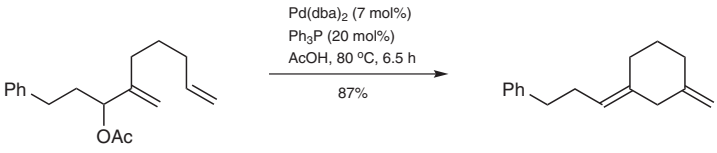
1.1.3.2 Other Polycyclization Methods via Reductive Elimination

1.1.3.2.1 Cyclization via π-Allylpalladium Complexes

Palladium catalysis is a powerful approach to polyene cyclization because of the myriad of C—C bond-forming reactions available to this privileged metal. Of the numerous reaction "silos" that categorize palladium chemistry,[131] among the largest are Heck reactivity (see Section 1.1.3.1.1) and π-allylpalladium reactivity.[132,133] Polyene cyclizations using this latter reaction manifold are difficult to achieve because alkenes are not usually strong enough nucleophiles to engage in outer-sphere attack of the electrophilic η^2 π-allylpalladium complex. However, given the correct geometry, the palladium complex can engage in an alternative mode of reactivity and instead react with proximal alkenes through a metallo-ene reaction. These reactions were described by the Oppolzer group to form

rings with high levels of stereocontrol for point chirality and alkene geometry (Scheme 25).[125,134]

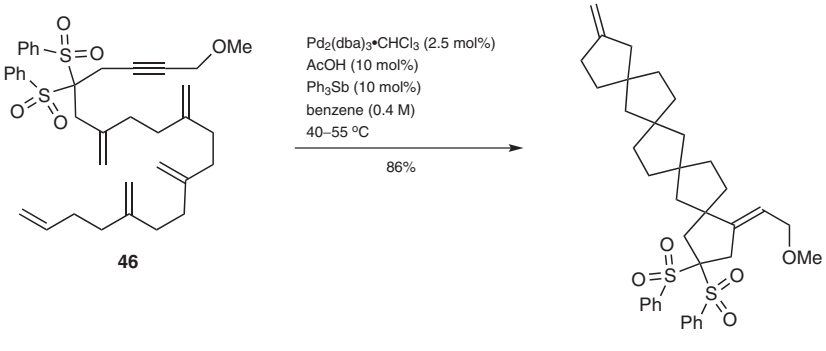
Scheme 25 Palladium-Catalyzed Cyclization[125,134]



1.1.3.2.2 Palladium-Catalyzed Ene–Yne Cycloisomerization

Cycloisomerization is a powerful subset of ring-forming cascade reactions that, as the name suggests, generate cyclic molecules that are isomeric with their acyclic precursors [for an extended discussion see *Science of Synthesis: Stereoselective Synthesis*, Vol. 3 (Section 3.5)]. The discovery of palladium-catalyzed ene–yne cycloisomerizations by Trost opened new vistas of reactivity available to these simple and readily accessed unsaturated hydrocarbon chains. Importantly, these metal-catalyzed reactions extended cycloisomerization chemistry from a high-temperature and little-applied niche reaction into the synthesis mainstream by virtue of their predictability, ease of execution, and interface with the broad field of palladium catalysis. Most early examples of these reactions require enyne substrates, because electron-neutral alkenes are poor ligands for carbophilic metals relative to alkynes and allenes. However, Trost demonstrated that alkynes could initiate a cascade that would be propagated by a polyene chain and terminated by β-hydride elimination. In a dramatic example of this cascade, the polycyclization of pentaenyne **46** can be initiated with catalytic palladium(0) and a Brønsted acid via alkyne hydropalladation, followed by iterative alkene insertions, and hydride elimination termination. Although the reaction yields a mixture of two diastereomers, the reaction mechanism and substrate design constitutes an important proof of principle for designing related cascades (Scheme 26).[124]

Scheme 26 Palladium-Catalyzed Zipper Reaction[124]



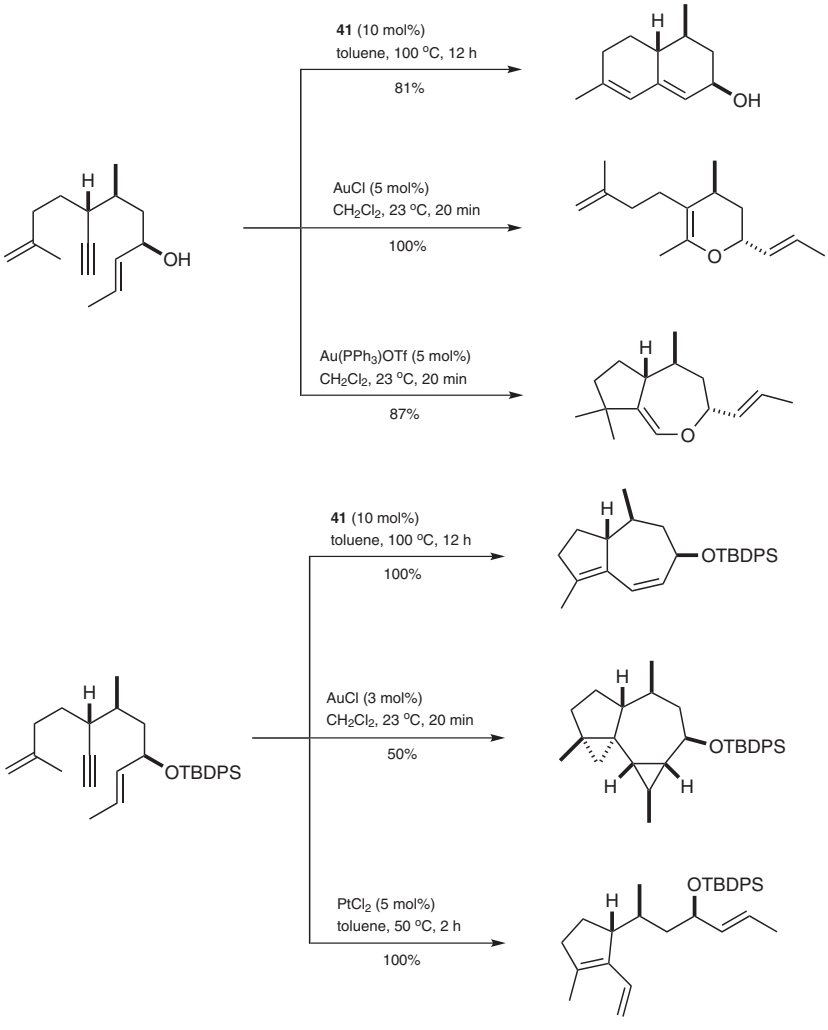
1.1.3.2.3 Cycloisomerization in Complex Molecule Synthesis

The value of cycloisomerization to the synthesis of complex carbocycles is nicely illustrated by work from the Winssinger group, who took inspiration from the polyisoprene polyene cyclization utilized by cells to rapidly build molecular complexity (Scheme 27).[135] Sesquiterpenes in particular display a dazzling array of diversity of carbon skeletons,[136] but their divergent syntheses from farnesyl pyrophosphate is challenging to reproduce

for references see p 39

in the laboratory.[71] However, metal-catalyzed polyene cycloisomerization reactions can circumvent this biomimicry and yield divergent routes to known terpene skeletons. A benefit of this approach is relatively short access to different structural motifs from a single, keystone intermediate. The sole deficits are that this intermediate is not as inexpensive or as easily obtained as farnesol, and that the diversity available still does not match that found in nature, both of which are extraordinarily high benchmarks to reach. This work by the Winssinger group does, however, allow numerous scaffolds to be obtained selectively and in good yield using the now vast arsenal of cycloisomerizations available from transition metals.

Scheme 27 Metal-Mediated Cyclizations[135]



1.1.4 Anionic Polyene Cyclizations

There are two problems with anionic polyene cyclizations. First, there is a problem of definition, because most "carbanions" actually exist as metal-bound organometallics instead of free ionic species and most species involved in polyene cyclization are not carbanions per se, but rather resonance-stabilized anionic functional groups such as enolates, which are similarly metal bound, not free ions. Thus, this section will discuss polyene cycliza-

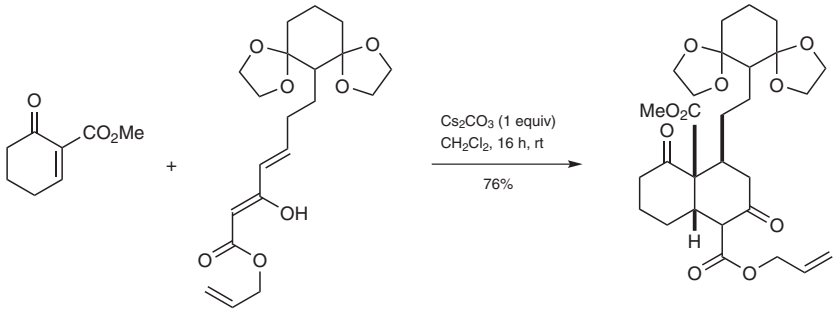
tions that are initiated by a deprotonation event – a relatively weak definition. Second, there are few examples of polyene cyclizations using electron-neutral alkenes. Instead, the two examples shown below involve Michael reaction cascades of enolates and alkenes conjugated to carbonyls. The obvious consequence is that functionality must be installed and/or excised to achieve reactivity, which can lead to inefficient syntheses. On the other hand, if the required functionality is present in the targeted molecule, it can be used not only to effect polycyclization, but also to efficiently construct the substrate polyene using its inherent reactivity.

1.1.4.1 Examples of Anionic Polyene Cyclizations

1.1.4.1.1 Stereoselective Polycyclization via Intramolecular Diels–Alder Cycloaddition Followed by Aldol Condensation

The first example demonstrates a powerful transformation; a stereocontrolled anionic polycyclization reaction that establishes a steroid core with six contiguous chiral centers in a single step. Deslongchamps and Lavallée first reported this transformation in 1988.[137] The intermediate cesium enolate, formed by the deprotonation of the cyclohexenone substrate by cesium carbonate, undergoes an intramolecular Diels–Alder cycloaddition to set the first three stereocenters. This event is followed by a highly stereoselective aldol reaction, which traps the resulting enolate in situ with one of the carbonyl groups of the cyclopentadione to form the remaining three stereocenters of the product in one pot. In 2002, Deslongchamps and Rouillard applied this reaction to the synthesis of a pentacyclic lactone via decalin **49**, formed from methyl 6-oxocyclohex-1-ene-1-carboxylate (**47**) and diketal **48** (Scheme 28).[138]

Scheme 28 Anionic Polycyclization[137,138]



47 48 49

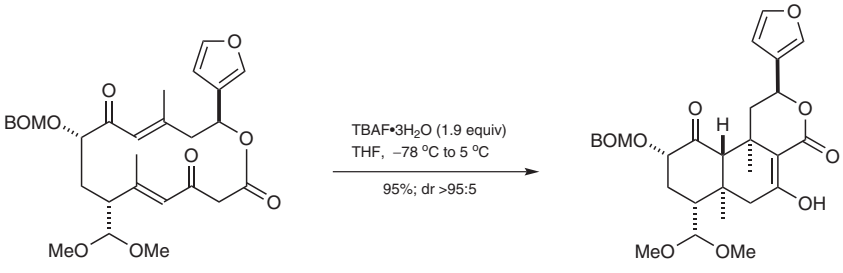
1-Allyl 4a-Methyl (4*S*,4a*S*,8a*S*)-4-{2-(1,4,8,11-Tetraoxadispiro[4.1.4^7.3^5]tetradecan-6-yl)ethyl}-2,5-dioxooctahydronaphthalene-1,4a(2*H*)-dicarboxylate (49); Typical Procedure:[138]
A freshly prepared soln of methyl 6-oxocyclohex-1-ene-1-carboxylate (**47**; 1.36 g, 8.85 mmol, 1.5 equiv) in CH_2Cl_2 (160 mL) was added to a soln of diketal **48** (2.34 g, 5.90 mmol) and Cs_2CO_3 (2.89 g, 8.85 mmol) in CH_2Cl_2 (320 mL). The mixture was stirred for 16 h, filtered through silica gel, and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/Et_2O 1:3) to give the pure product; yield: 2.36 g (76%).

for references see p 39

1.1.4.1.2 Transannular Double Michael Cyclization Cascades

The second example features a transannular double Michael reaction cascade of a bisenone macrocycle to form three stereocenters in one step. The Evans group reported this transformation as part of their synthesis of salvinorin A (Scheme 29).[139] Treatment of the β-oxo lactone **50** with tetrabutylammonium fluoride induces a transannular reaction cascade to give the tricycle **51** as a single diastereomer. While it is assumed that the reaction proceeds via a stepwise process, the authors note that a concerted *exo*-selective Diels–Alder cycloaddition is also possible via the enolate of the β-oxo lactone **50** instead.

Scheme 29 Anionic Polycyclization En Route to Salvinorin A[139]



50 **51**

(2*S*,6a*S*,7*R*,9*S*,10a*S*,10b*R*)-9-[(Benzyloxy)methoxy]-7-(dimethoxymethyl)-2-(furan-3-yl)-5-hydroxy-6a,10b-dimethyl-1,2,6a,7,8,9,10a,10b-octahydronaphtho[2,1-*c*]pyran-4,10(2*H*)-dione (51**); Typical Procedure:**[139]

To a freshly prepared soln of TBAF•$3H_2O$ (172 mg, 0.578 mmol, 1.9 equiv) in THF (13 mL) at −78 °C was added a soln of dioxo macrocycle **50** (162 mg, 0.300 mmol, 1.0 equiv) in THF (10 mL) via cannula over 5 min. The cannula wire was rinsed with DMF (2 × 10 mL). The reaction vessel was transferred to a cold water bath at 5 °C. The mixture was stirred for 2 h, diluted with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with half-sat. brine (2 × 75 mL), dried (Na_2SO_4), and concentrated; yield: 160 mg (95%).