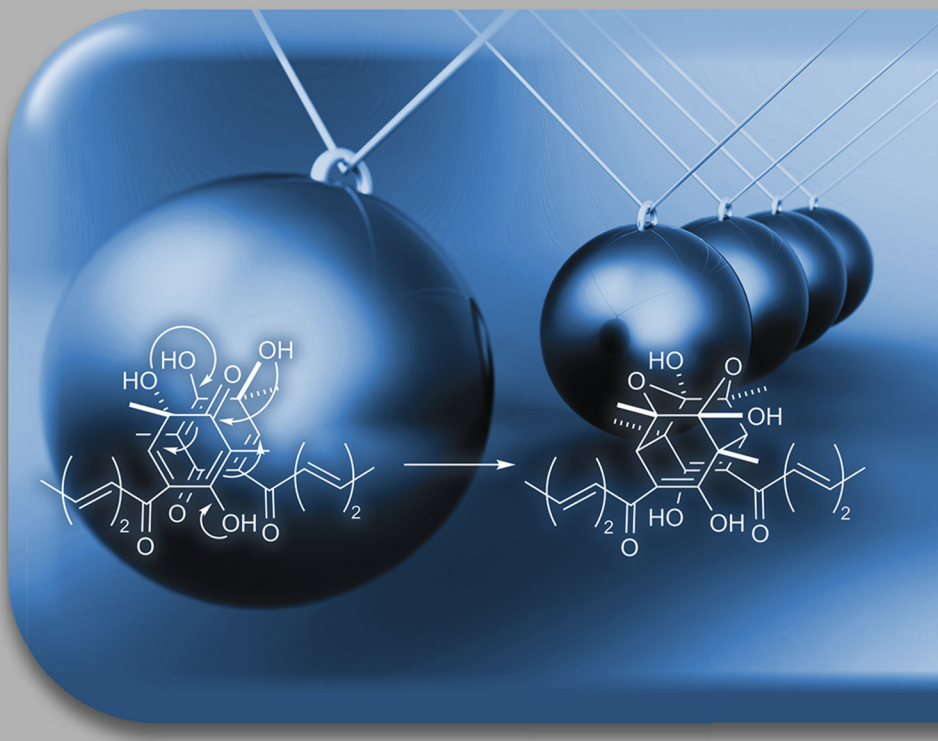
Science of Synthesis

Applications of Domino Transformations in Organic Synthesis 2

Volume Editor
Scott A. Snyder



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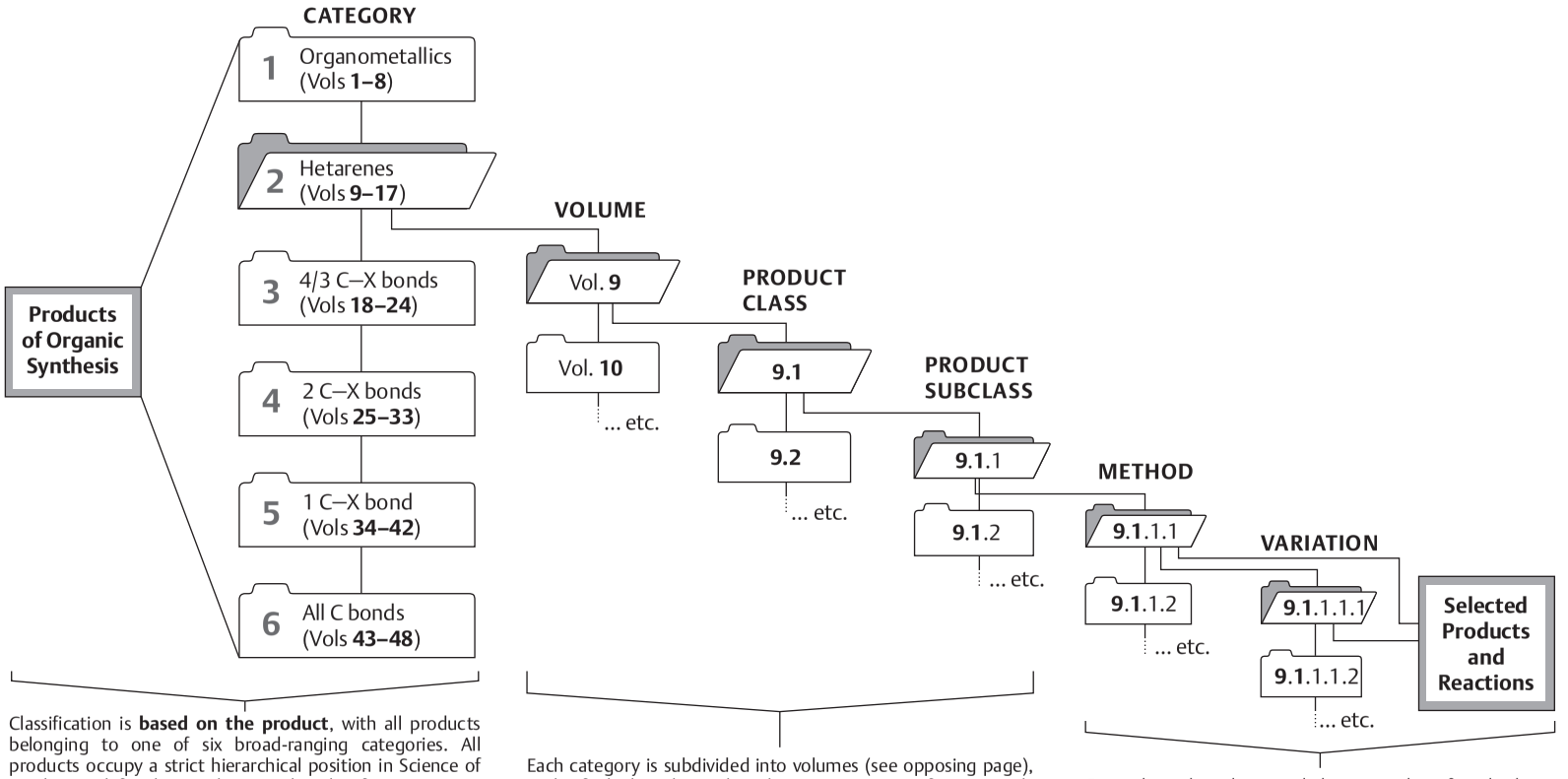

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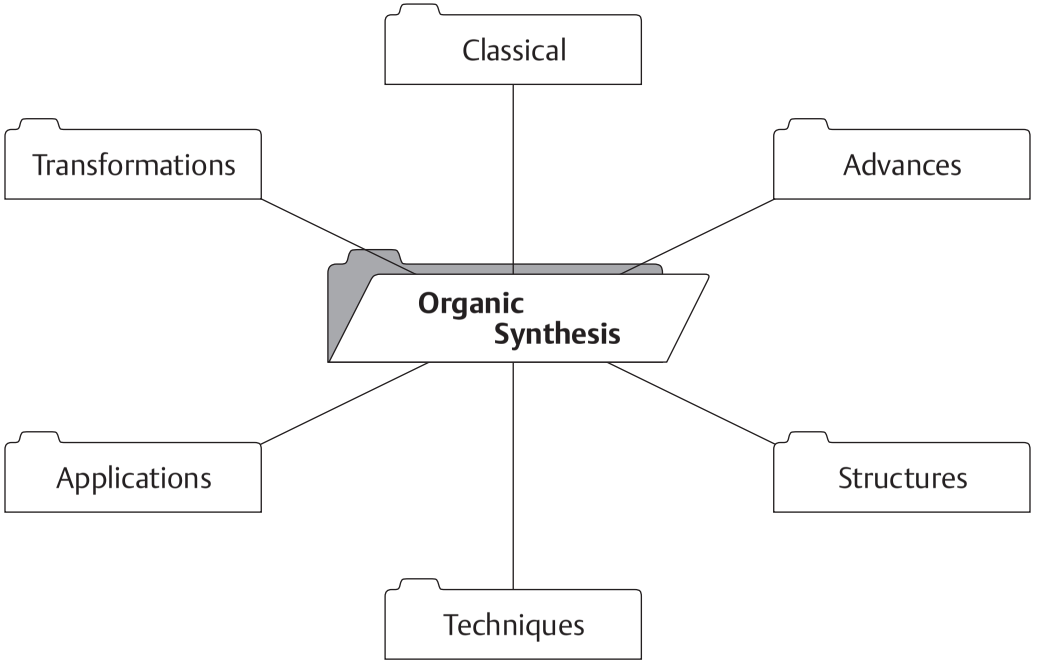

Science of Synthesis

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

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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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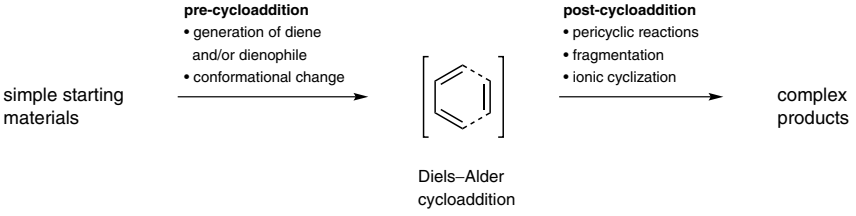
2.1.1 The Diels–Alder Cycloaddition Reaction in the Context of Domino Processes

J. G. West and E. J. Sorensen

The Diels–Alder cycloaddition has been a key component in innumerable, creative domino transformations in organic synthesis. This chapter provides examples of how this [4+2] cycloaddition has been incorporated into the said cascades, with particular attention to its interplay with the other reactions in the sequence. We hope that this review will assist the interested reader to approach the design of novel cascades involving the Diels–Alder reaction.



Keywords: Diels–Alder · cascade · domino reactions · pericyclic · [4+2] cycloaddition

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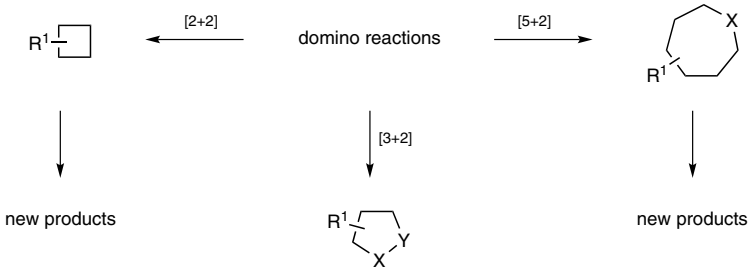
2.1.2 Domino Reactions Including [2+2], [3+2], or [5+2] Cycloadditions

I. Coldham and N. S. Sheikh

This chapter covers examples of domino reactions that include a [2+2]-, [3+2]-, or [5+2]-cycloaddition reaction. The focus is on concerted reactions that occur in a tandem sequence in one pot, rather than overall "formal cycloadditions" or multicomponent couplings. The cycloaddition step typically involves an alkene or alkyne as one of the components in the ring-forming reaction. In addition to the key cycloaddition step, another bond-forming reaction will be involved that can precede or follow the cycloaddition. This other reaction is often an alkylation that generates the substrate for the cycloaddition, or is a ring-opening or rearrangement reaction that occurs after the cycloaddition. As the chemistry involves sequential reactions including at least one ring-forming reaction, unusual molecular structures or compounds that can be difficult to prepare by other means can be obtained. As a result, this strategy has been used for the regio- and stereoselective preparation of a vast array of polycyclic, complex compounds of interest to diverse scientific communities.



Keywords: alkylation · [2+2] cycloaddition · [3+2] cycloaddition · [5+2] cycloaddition · dipolar cycloaddition · domino reactions · Nazarov cyclization · ring formation · [3,3]-sigmatropic rearrangement · tandem reactions

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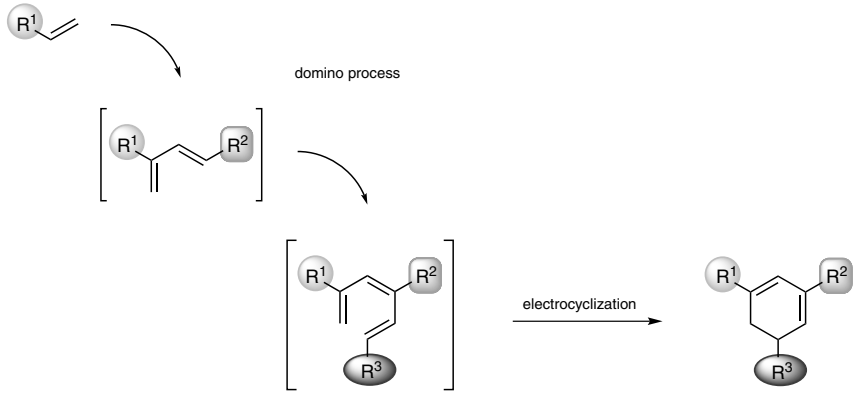
2.1.3 Domino Transformations Involving an Electrocyclization Reaction

J. Suffert, M. Gulea, G. Blond, and M. Donnard

Electrocyclization processes represent a powerful and efficient way to produce carbo- or heterocycles stereoselectively. Moreover, when electrocyclizations are involved in domino processes, the overall transformation becomes highly atom and step economic, enabling access to structurally complex molecules. This chapter is devoted to significant contributions published in the last 15 years, focusing on synthetic methodologies using electrocyclization as a key step in a domino process.



Keywords: electrocyclization · hetero-electrocyclization · domino reactions · cascade reactions

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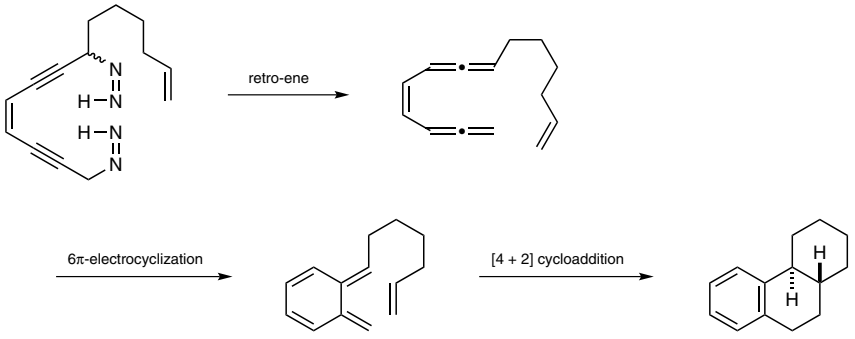
2.1.4 Sigmatropic Shifts and Ene Reactions (Excluding [3,3])

A. V. Novikov and A. Zakarian

This chapter features a review and discussion of the domino transformations initiated by ene reactions and sigmatropic rearrangements, particularly focusing on [2,3]-sigmatropic shifts, such as Mislow–Evans and Wittig rearrangements, and [1,n] hydrogen shifts. A variety of examples of these domino processes are reviewed, featuring such follow-up processes to the initial reaction as additional ene reactions or sigmatropic shifts, Diels–Alder cycloaddition, [3+2] cycloaddition, electrocyclization, condensation, and radical cyclization. General practical considerations and specific features in the examples of the reported cascade transformation are highlighted. To complete the discussion, uses of these cascade processes in the synthesis of natural products are discussed, demonstrating the rapid assembly of structural complexity that is characteristic of domino processes. Overall, the domino transformations initiated by ene reactions and sigmatropic shifts represent an important subset of domino processes, the study of which is highly valuable for understanding key aspects of chemical reactivity and development of efficient synthetic methods.



Keywords: ene reaction · sigmatropic shift · domino reactions · cascade reactions · hydrogen shift · [1,3]-shift · [1,5]-shift · [1,7]-shift · [2,3]-shift · [3,3]-shift · Mislow–Evans rearrangement · Wittig rearrangement · Diels–Alder cycloaddition · Claisen rearrangement · oxy-Cope rearrangement · electrocyclization · chloropupukeanolide D · isocedrene · steroids · mesembrine · joubertinamine · pinnatoxins · sterpurene · arteannuin M · pseudomonic acid A

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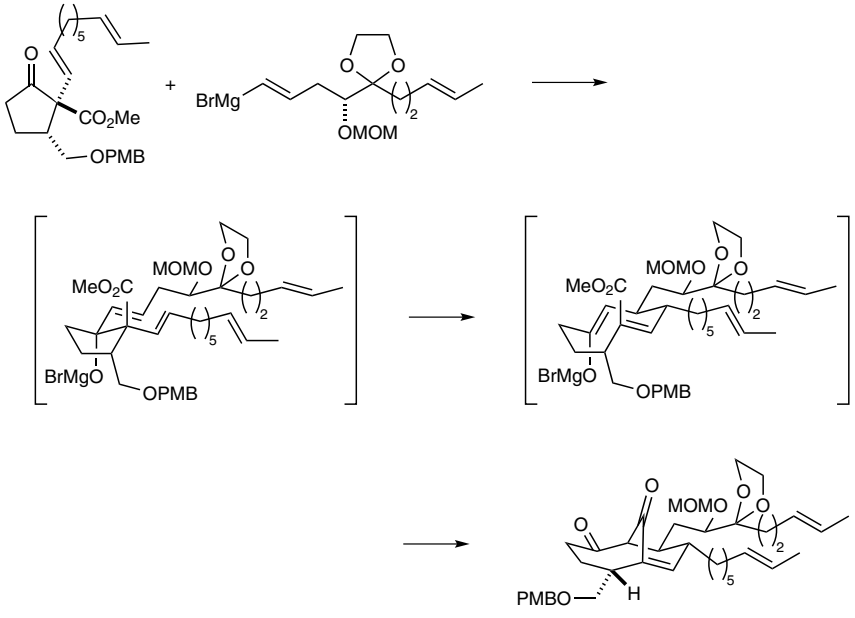
2.1.5 Domino Transformations Initiated by or Proceeding Through [3,3]-Sigmatropic Rearrangements

C. A. Guerrero

This chapter concerns itself with domino transformations (i.e., cascade sequences and/or tandem reactions) that are either initiated by or proceed through at least one [3,3]-sigmatropic rearrangement. Excluded from this discussion are domino transformations that end with sigmatropy. The reactions included contain diverse forms of [3,3]-sigmatropic rearrangements and are followed by both polar chemistry or further concerted rearrangement.



Keywords: rearrangement · sigmatropic · Bellus–Claisen · Cope · Overman · concerted · stereoselective · stereospecific · ene · trichloroacetimidate · Diels–Alder

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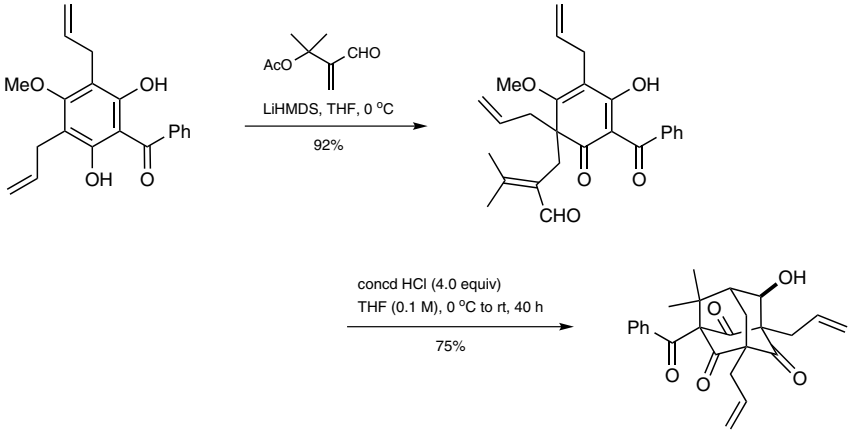
2.2 Intermolecular Alkylative Dearomatizations of Phenolic Derivatives in Organic Synthesis

J. A. Porco, Jr., and J. Boyce

Intermolecular alkylative dearomatization products have shown promise as synthetic intermediates with diverse capabilities. This chapter describes the available methods for constructing these dearomatized molecules and demonstrates their value as synthetic intermediates for efficient total syntheses.



Keywords: alkylative dearomatization · dearomative alkylation · dearomative substitution · domino transformations · domino sequences · dearomative domino transformations · cationic cyclization · radical cyclization · alkylative dearomatization/annulation

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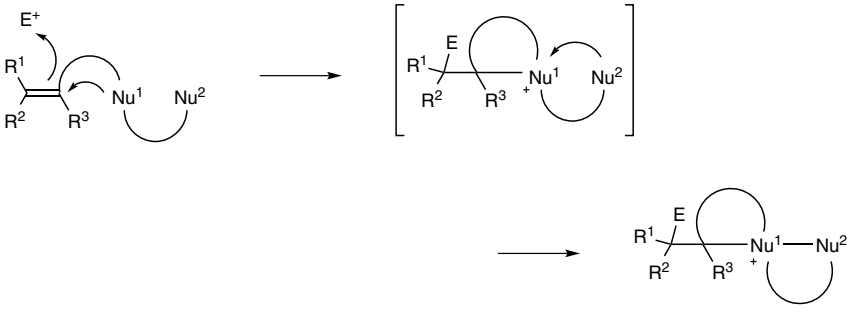
2.3.1 Additions to Nonactivated C=C Bonds

Z. W. Yu and Y.-Y. Yeung

Electrophilic additions to nonactivated C=C bonds are one of the well-known classical reactions utilized by synthetic chemists as a starting point to construct useful complex organic molecules. This chapter covers a collection of electrophile-initiated domino transformations involving alkenes as the first reaction, followed by reaction with suitable nucleophiles in the succession and termination reactions under identical conditions. The discussion focuses on recent advances in catalysis, strategically designed alkenes, and new electrophilic reagents employed to improve reactivity and control of stereochemistry in the sequence of bond-forming steps.



Keywords: nonactivated alkenes · addition · domino reactions · amination · etherification · carbonylation · polyenes · protons · halogens · transition metals · chalcogens

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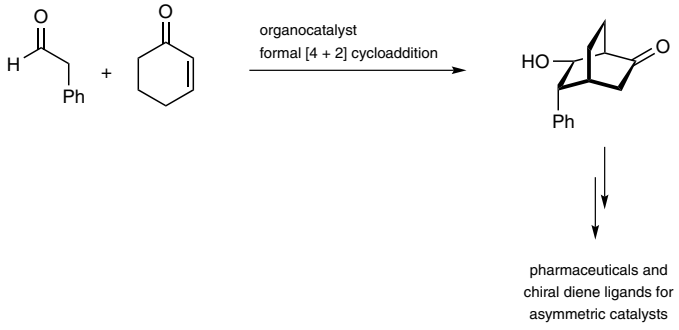
2.3.2 Organocatalyzed Addition to Activated C=C Bonds

P. Renzi, M. Moliterno, R. Salvio, and M. Bella

In this chapter, several examples of organocatalyzed additions to C=C bonds carried out through a domino approach are reviewed, from the early examples to recent applications of these strategies in industry.



Keywords: organocatalysis · domino reactions · iminium ions · enamines · Michael/aldol reactions · nucleophilic/electrophilic addition · α,β-unsaturated carbonyl compounds · spirocyclic oxindoles · cinchona alkaloid derivatives · chiral secondary amines · Knoevenagel condensation · methyleneindolinones

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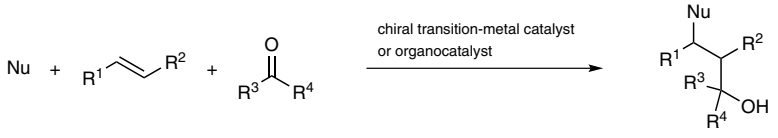
2.3.3 Addition to Monofunctional C=O Bonds

A. Song and W. Wang

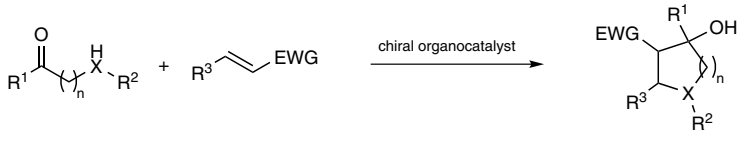
Catalytic asymmetric domino addition to monofunctional C=O bonds is a powerful group of methods for the rapid construction of valuable chiral building blocks from readily available substances. Impressive progress has been made on transition-metal-catalyzed and organocatalytic systems that promote such addition processes through reductive aldol, Michael/aldol, or Michael/Henry sequences. In addition, Lewis acid catalysis has also been developed in this area for the synthesis of optically active chiral molecules. This chapter covers the most impressive examples of these recent developments in domino chemistry.

Asymmetric Michael/Intermolecular Aldol or Henry Reaction

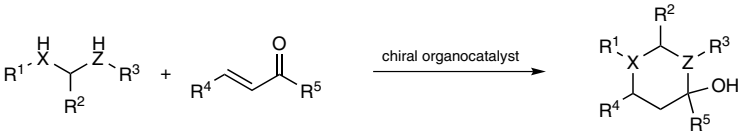


$R^1 = R^2 = R^3 = H$, alkyl, aryl; $R^2 = CO_2R^5$, NO_2

Asymmetric Michael/Intramolecular Aldol or Henry Reaction



n = 1, 2; EWG = electron-withdrawing group



R^5 = H, CO_2R^6

Keywords: aldol reactions · carbonyl ylides · chiral amine catalysis · domino reactions · epoxy alcohols · Lewis acid catalysis · Michael addition · organocatalysis · phosphoric acid catalysis · thiourea catalysis

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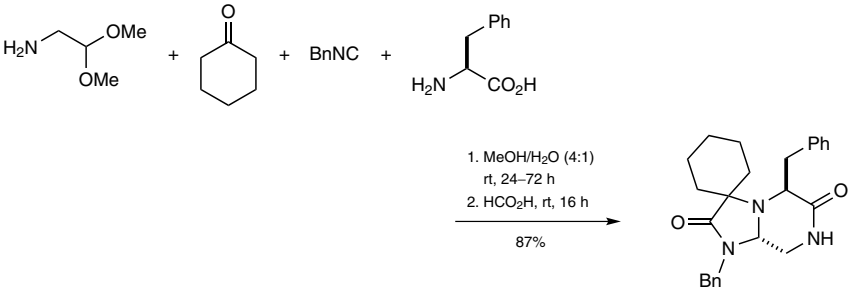
2.3.4 Additions to C=N Bonds and Nitriles

E. Kroon, T. Zarganes Tzitzikas, C. G. Neochoritis, and A. Dömling

This chapter describes additions to imines and nitriles and their post-modifications within the context of domino reactions and multicomponent reaction chemistry.



Keywords: multicomponent reactions · domino reactions · isocyanides · Ugi reaction · Pictet–Spengler reaction · Gewald reaction · isoindoles · benzodiazepines · cyanoacetamides · thiophenes

Applications of Domino Transformations in Organic Synthesis 2

Table of Contents

2.1 Pericyclic Reactions

2.1.1 The Diels–Alder Cycloaddition Reaction in the Context of Domino Processes

J. G. West and E. J. Sorensen

General Introduction

The title that Otto Diels and Kurt Alder chose for their 1928 publication, "Syntheses in the Hydroaromatic Series", in *Annalen*[1] did not signal the revolution that their new insights would bring to the field of organic chemistry. Their pioneering paper described cycloadditions of 4π-electron systems (dienes) with 2π-electron systems (dienophiles), and captured the significance that [4+2] cycloadditions would hold for the field of organic chemical synthesis: "Thus, it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect." The very next sentence, "We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems", is even more colorful, but, in reality, nearly a quarter of a century would pass before the power of the "Diels–Alder" reaction was demonstrated in the context of natural product synthesis. In the year following the awarding of the 1950 Nobel Prize in Chemistry to Diels and Alder "for their discovery and development of the diene synthesis", R. B. Woodward and co-workers described their non-obvious use of a Diels–Alder construction to contend with the *trans*-fused C–D ring junction in cortisone,[2] and Gilbert Stork and his co-workers reported their stereospecific synthesis of cantharidin featuring a creative twofold Diels–Alder strategy.[3] Woodward's landmark 1956 synthesis of reserpine[4] and Eschenmoser's synthesis of colchicine by way of pericyclic reactions[5] provided further, powerful, demonstrations of the value of the Diels–Alder reaction as a structure-building process. On the foundation of these early achievements, the Diels–Alder reaction took its place beside the most reliable bond- and ring-forming methods in organic chemistry.

Today, nearly 90 years after that pioneering report by Diels and Alder, the cycloaddition reaction bearing their names has not lost its vitality. Indeed, few processes have captured the imagination of the practicing synthetic organic chemist as the Diels–Alder cycloaddition has. The ubiquity of six-membered rings in molecules of interest, from natural products to commodity chemicals, has brought this reaction to prominence not only as a singular operation, but also as a component in domino reaction sequences. This last capacity in particular has enabled highly original and powerful cascades to be designed and executed, leveraging the considerable risk inherent in such schemes into breathtaking advances for the field.

Due to the richness of precedent for cascade sequences featuring the Diels–Alder reaction, it is unavoidable that many inspiring examples will be omitted; the interested reader is encouraged to use this chapter and other reference materials[6–21] as a jumping-off point for entry into this fascinating body of literature. A similarly impressive collection of cascades involving formal Diels–Alder reactions permeates the chemical literature; however, these reactions are beyond the scope of this chapter and have been omit-

for references see p 44

ted. The examples in this work have been curated with the goal of presenting a broad survey of how Diels–Alder domino sequences can be used, with particular attention to how the aforementioned reaction is involved in the sequence.

It is the hope of the authors that students of organic chemistry will gain some appreciation for the myriad opportunities to advance a synthesis through the strategic application of Diels–Alder cascade processes and, in so doing, be able to advance not only their own project but, also, the field as a whole.

2.1.1.1 Cascades Not Initiated by Diels–Alder Reaction

A logical division one could imagine making in the presentation of this vast body of literature is whether the Diels–Alder reaction occurs at the beginning of the cascade or not. If the Diels–Alder is not the first step, it follows to consider three cases where it can be invoked: through the in situ generation of the diene or dienophile, or through the union of two pre-existing components promoted by earlier transformations. Each of these strategies presents certain advantages that may prove of high value in a target-oriented campaign.

2.1.1.1.1 Cascades Generating a Diene

The 4π component of the Diels–Alder reaction has been the target of extensive investigation for in situ generation. Presenting significant unsaturation, one can run into issues of chemoselectivity in a synthesis if one wishes to carry a diene through multiple operations. Numerous innovative methods to access dienes have thus been developed, of which many can be described as ionic, pericyclic, or radical in nature.

2.1.1.1.1.1 Ionic Generation of a Diene

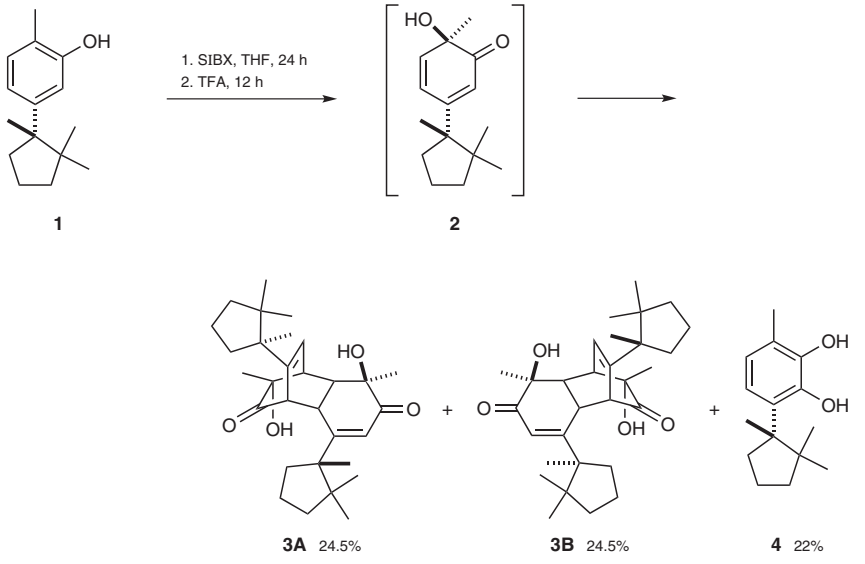
The Diels–Alder reaction, a pericyclic process, proceeds through a mechanism that can be considered orthogonal to ionic reactivity modes. This exclusivity makes the Diels–Alder reaction inherently compatible with many two-electron processes, allowing for ionic components in domino reaction sequences. One area that has benefitted from significant exploration has been the in situ generation of dienes using ionic reactivity.

2.1.1.1.1.1.1 Through Wessely Oxidation of Phenols

The pioneering work of Wessely[22] revealed that electron-rich aromatic compounds can function as masked dienes when treated with a strong oxidant. Originally a two-step protocol, Liao and co-workers[23] showed that phenols could be oxidized in the presence of dienophiles to access Diels–Alder adducts in a cascade process. The use of arenes as diene surrogates provides several advantages in a synthetic design, most notably the relative stability imparted by the aromaticity of the arene. Indeed, it can improve the durability of the eventual diene in prior chemical steps and lead to heightened reactivity of the oxidatively generated diene in comparison to other classes.

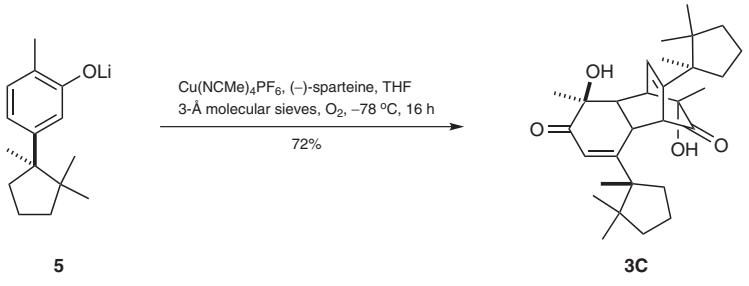
This high utility is exemplified by the propensity of many Wessely oxidation products to undergo self-dimerization via a Diels–Alder reaction, a process that appears to have relevance in a biosynthetic sense. An example of this importance is provided by retrosynthetic analysis of the structure of the bis-sesquiterpene aquaticol by the lab of Quideau,[24] suggesting that its congested architecture might be accessible by Diels–Alder dimerization of orthoquinol **2**. Subjecting enantiopure phenol **1** to stabilized 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide [SIBX; a mixture of IBX (49%), benzoic acid (22%), and isophthalic acid (29%)] results in a 1:1 mixture of Diels–Alder adducts **3A** [(−)-aquaticol] and the closely related **3B**, in addition to catechol oxidation side product **4** (Scheme 1).

Scheme 1 Synthesis of Aquaticol through the Oxidative Dimerization of a Phenol[24]



Subsequent studies by Porco and co-workers[25] found that an enantioselective oxidation/dimerization cascade of the lithium phenoxide **5** of phenol *ent*-**1** can be effected using a copper/sparteine catalyst with oxygen serving as the terminal oxidant, furnishing (+)-aquaticol (**3C**) as a single diastereomer (Scheme 2).

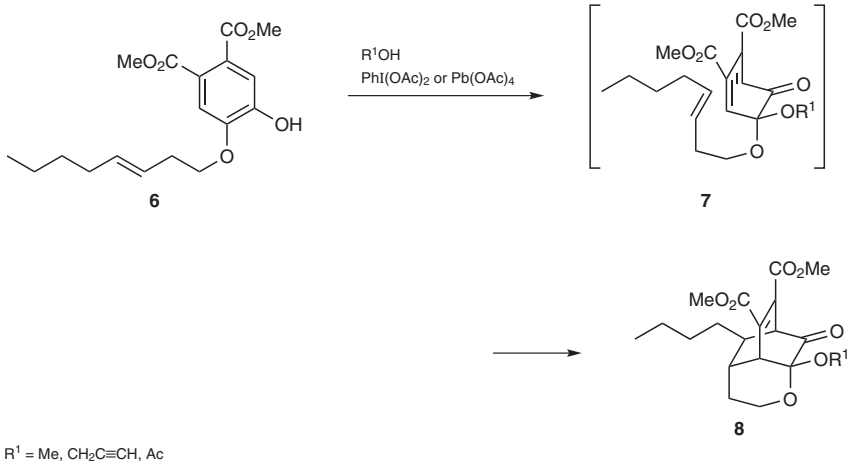
Scheme 2 Asymmetric Oxidation/Dimerization Procedure Developed by Porco[25]



The group of Wood[26] found that an oxidation/intramolecular Diels–Alder cascade could be realized with the dienophilic partner already appended to the aromatic nucleus as a phenolic ether. Here, oxidation of compound **6** with (diacetoxyiodo)benzene in the presence of a variety of alcohols smoothly furnishes polycyclic products **8**, which serve as a convenient entry to the CP-263,114 architecture (Scheme 3). This method provides an added advantage as the alcohol present is incorporated into the final structure through the necessity of an *ortho*-quinone acetal intermediate **7**, allowing for this group to be widely varied through a simple change of solvent.

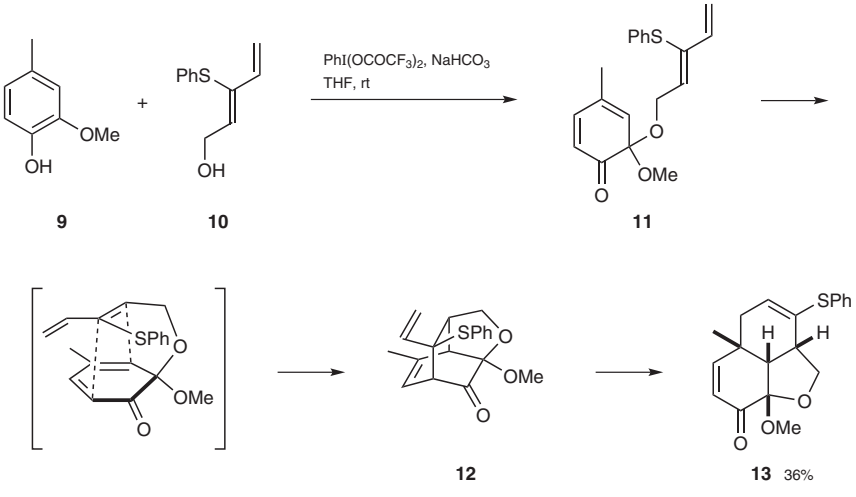
for references see p 44

Scheme 3 Access to the CP-263,114 Core Architecture through the Use of an Oxidation/Intramolecular Diels–Alder Cascade Sequence[26]



A variation on the strategy of Wood is found in the course of Rodrigo's synthesis of halenaquinone,[27] where oxidation of phenol **9** in the presence of alcohol-appended dienophile **10** produces masked *ortho*-quinone **11**. This intermediate smoothly undergoes a proximity-induced Diels–Alder reaction to furnish a key annulated bicyclo[2.2.2]octane product **12**. This diene substrate then undergoes a Cope rearrangement to form naphthofuranone product **13**, which has the core connectivity of halenaquinone (Scheme 4). This strategy is notable as it not only presents a union of both the nascent diene and dienophile, but also remodels the Diels–Alder cycloaddition product in a highly productive fashion.

Scheme 4 Wessely Oxidation in the Presence of an Unsaturated Alcohol Followed by Intramolecular Diels–Alder Reaction[27]



(1*S*,4*S*,8*R*,10*R*)-8,10-Dihydroxy-8,10-dimethyl-3,5-bis[(*S*)-1,2,2-trimethylcyclopentyl]-4,4a,8,8a-tetrahydro-1,4-ethanonaphthalene-7,9(1*H*)-dione (3A):[24]

To a soln of (*S*)-2-methyl-5-(1,2,2-trimethylcyclopentyl)phenol [(–)-**1**; 85 mg, 0.39 mmol, 1 equiv] in THF (4 mL) was added stabilized IBX [a mixture of IBX (49%), benzoic acid (22%), and isophthalic acid (29%); 365 mg, 0.58 mmol, 1.5 equiv] as a solid in one portion.

The resulting suspension was stirred at rt for 24 h, after which time TFA (30 μL, 0.394 mmol, 1 equiv) was added, and the mixture was stirred for a further 12 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). 1 M aq NaOH (5 mL) was added dropwise (until pH 8). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with 1 M aq NaOH (15 mL) and brine (2 × 15 mL), and then shaken vigorously with sat. aq $Na_2S_2O_4$ (40 mL), washed again with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated at rt to give a crude pale-brown oily residue (95 mg). This residue was purified by flash chromatography (silica gel, CH_2Cl_2 then CH_2Cl_2/MeOH 100:1) to give two residues, which were again purified separately by flash chromatography (silica gel, hexanes/acetone 6:1), to furnish, respectively, (*S*)-benzene-1,2-diol (–)-**4** (20 mg; 22% yield) and a 1:1 mixture of (1*S*,4*S*,8*R*,10*R*)-product **3A** and the all-*S* dimer (–)-**3B** as white powders; yield: 45 mg (49%). The diastereomeric mixture of **3A** and **3B** was separated by semi-preparative reverse-phase HPLC [Thermo Spectra system; Deltapak C-18 column (7.8 × 300 mm, 15 μm); gradient elution; flow rate: 3 mL·min^{-1}; mobile phases: solvent A (H_2O/TFA 99:1) and solvent B (MeCN/TFA 99:1); 0–55 min: solvent (A/B) 70:30 to 0:100].

(1*R*,4*R*,8*S*,10*S*)-8,10-Dihydroxy-8,10-dimethyl-3,5-bis[(*R*)-1,2,2-trimethylcyclopentyl]-4,4a,8,8a-tetrahydro-1,4-ethanonaphthalene-7,9(1*H*)-dione [3C; (+)-Aquaticol]:[25]
A soln of Li phenolate **5** {derived from (*R*)-2-methyl-5-(1,2,2-trimethylcyclopentyl)phenol [(+)-**1**; 35.0 mg, 0.16 mmol, 1 equiv]} in anhyd THF (160 μL) was added to the Cu complex [prepared from $Cu(NCMe)_4PF_6$ (131.0 mg, 0.35 mmol, 2.2 equiv) and (–)-sparteine (84.8 μL, 0.37 mmol, 2.3 equiv) in anhyd THF (2.0 mL)] under an O_2 atmosphere at −78 °C. The mixture was stirred at −78 °C for 16 h and then the reaction was quenched with 5% aq H_2SO_4 (1.6 mL) at −78 °C. The mixture was extracted with EtOAc (3 ×), and the combined extracts were washed with 5% aq H_2SO_4, H_2O, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford (+)-aquaticol (**3C**) as a light yellow solid; yield: 27.1 mg (72%).

Dimethyl 9-Butyl-8a-methoxy-8-oxo-3,4,4a,7,8,8a-hexahydro-2*H*-4,7-methanobenzopyran-5,6-dicarboxylate (8, R^1 = Me); Typical Procedure:[26]
To a stirred soln of phenol **6** (47 mg, 0.14 mmol, 1 equiv) in MeOH (1.5 mL) was added $PhI(OAc)_2$ (54 mg, 0.17 mmol, 1.2 equiv). Upon addition of $PhI(OAc)_2$, the mixture changed immediately from colorless to clear yellow; upon stirring at rt for 2 h, it became clear again. The mixture was concentrated under reduced pressure and passed through a plug of silica gel to furnish analytically pure **8**; yield: 36 mg (70%).

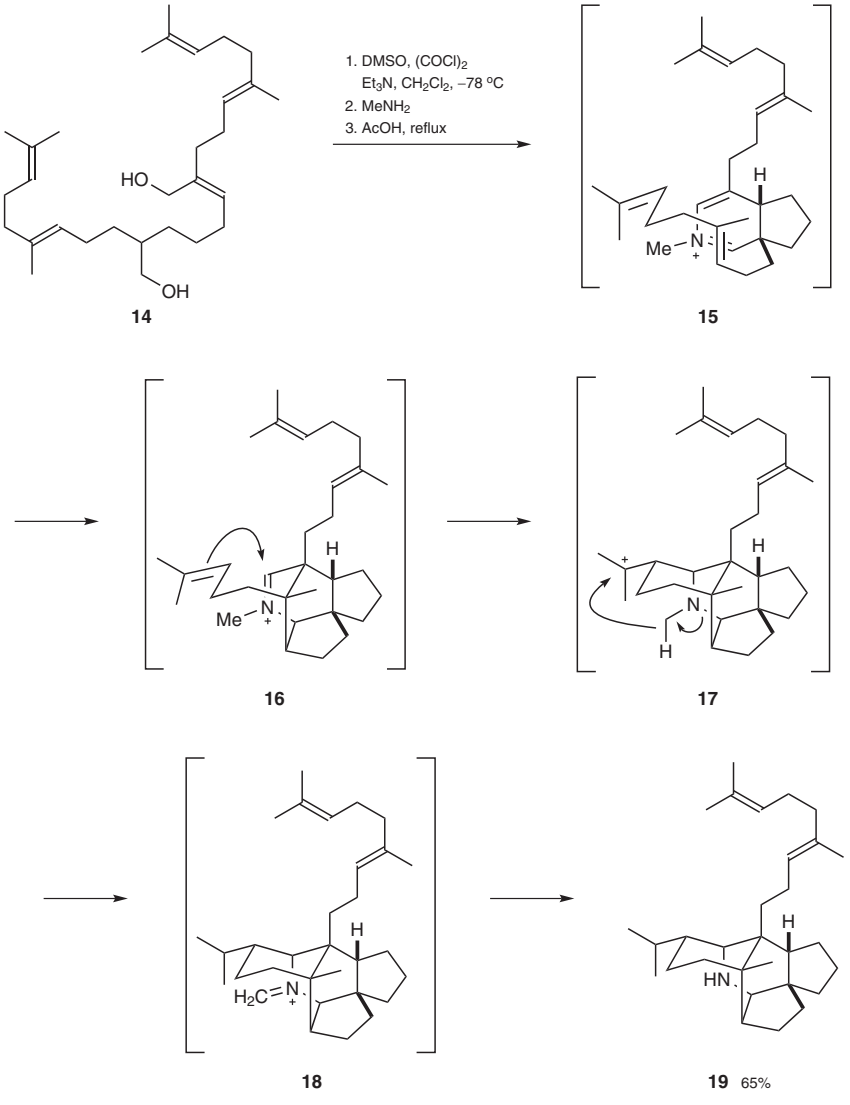
(2a*S*,2a^1*S*,5a*S*,8a*S*)-8a-Methoxy-5a-methyl-3-(phenylsulfanyl)-2,2a,2a^1,5,5a,8a-hexahydro-8*H*-naphtho[1,8-*bc*]furan-8-one (13):[27]
To a soln of 2-methoxy-4-methylphenol (**11**; 100 mg, 0.72 mmol, 1 equiv), 3-(phenylsulfanyl)penta-2,4-dien-1-ol (**12**; 500 mg, 2.60 mmol, 3.6 equiv), and 2,6-di-*tert*-butyl-4-methylphenol (1 crystal; ca. 2 mg) in THF (15 mL) at 0 °C was added [bis(trifluoroacetoxy)iodo]benzene (375 mg, 0.87 mmol, 1.2 equiv). The resulting soln was stirred for 5 min, after which time solid $NaHCO_3$ (150 mg, 1.79 mmol, 2.5 equiv) was added. The mixture was allowed to warm to rt and stirred overnight, and was then partitioned between H_2O and Et_2O. The aqueous phase was extracted twice more with Et_2O, and the combined organic layers were dried ($MgSO_4$) and filtered through a plug of silica gel. After removal of the solvent under reduced pressure, the resulting dark orange oil was dissolved in 1,2,4-trimethylbenzene and refluxed for 2 d. Removal of the solvent under reduced pressure followed by flash chromatography (Et_2O/hexane 3:7) gave a light yellow oil; yield: 86 mg (36%).

for references see p 44

2.1.1.1.1.1.2 Through Ionic Cyclization

Heathcock and co-workers[28] have provided a remarkable example of the utility of the Diels–Alder cycloaddition in polycyclization cascades. Treating a dihydrosqualene dialdehyde, obtained by Swern oxidation of diol **14**, with methylamine leads to the formation of dihydropyridinium species **15** through the conjugate addition/condensation of the methylamine enamine on the enal functionality. This fleeting intermediate can then undergo an intramolecular Diels–Alder reaction to form tetracycle **16**, which can then engage the pendent prenyl alkene in an aza-Prins cyclization to afford carbocation **17**. Next, a proximity-induced hydride transfer from the methyl group of the amine provides iminium species **18**, which, after hydrolysis, completes the preparation of 1,2-dihydro-*proto*-daphniphylline (**19**) in an impressive polycyclization cascade (Scheme 5).

Scheme 5 Synthesis of 1,2-Dihydro-*proto*-daphniphylline via a Cyclization/Diels–Alder/Hydride Transfer Cascade from an Acyclic Precursor[28]



1,2-Dihydro-*proto*-daphniphylline (19**):**[28]
To a soln of DMSO (88 μL, 1.2 mmol, 9 equiv) in CH_2Cl_2 (1 mL) at −78 °C was added a 2.0 M soln of oxalyl chloride in CH_2Cl_2 (276 μL, 0.552 mmol, 4 equiv). After 20 min, diol **14** (61.3 mg, 0.138 mmol, 1 equiv) was added via cannula as a soln in CH_2Cl_2 (1 mL, followed by a 1-mL rinse). The resulting cloudy soln was stirred at −78 °C for 20 min and then treated with Et_3N (0.14 mL, 1.0 mmol). The dry ice bath was removed and the soln was allowed to warm to rt over 50 min. After cooling to 0 °C, a stream of anhyd $MeNH_2$ was then passed over the soln for 3 min. The flask was then sealed tightly and allowed to warm to rt over 5 h. The clear soln was concentrated by passing a stream of dry N_2 over it for 10 min. The resulting white, oily solid was triturated with Et_2O, filtered, and concentrated (high-vacuum pump, 4 h) to provide a clear yellow oil, which was utilized immediately in the next step; yield: 84.0 mg.

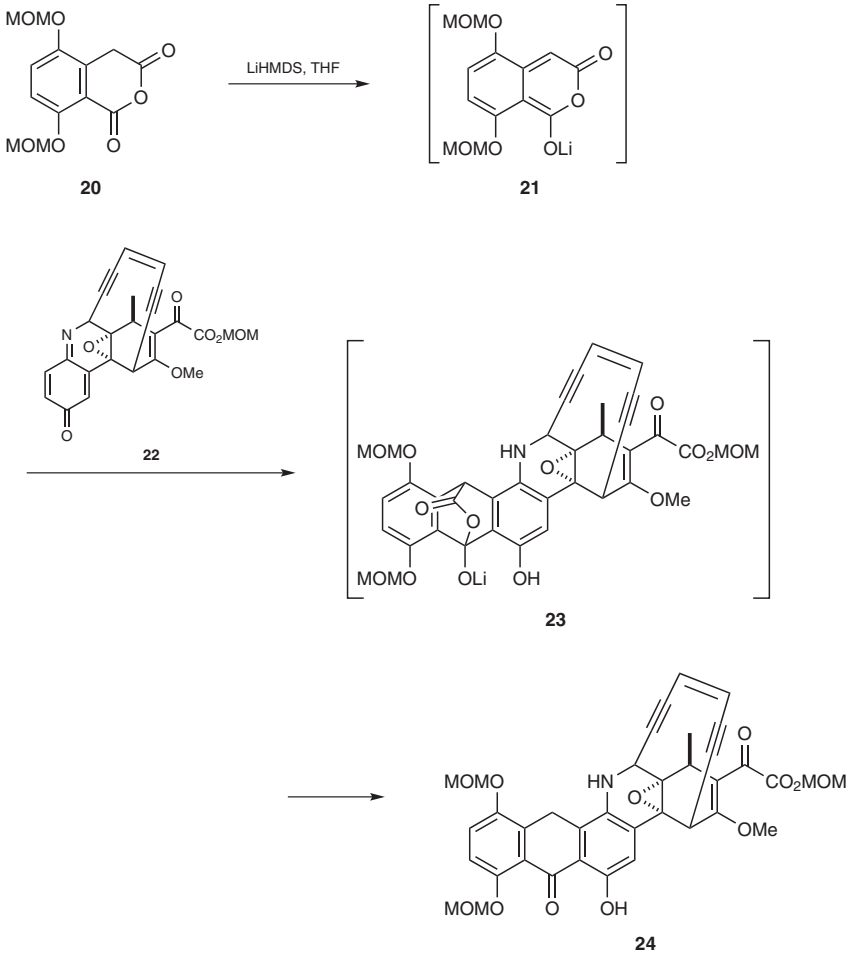
The crude bisimine was taken up in AcOH (1 mL) and placed in an 80 °C oil bath for 11 h. After cooling to 0 °C, the mixture was partitioned between CH_2Cl_2 (5 mL) and 2 M NaOH (5 mL) and stirred vigorously for 15 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic phases were washed with brine and dried ($MgSO_4$). Filtration and concentration provided 68.0 mg of a brown oil, which was purified by flash chromatography (silica gel, gradient elution with 10:1 to 5:1 hexanes/EtOAc) to provide **19** as a clear, pale yellow oil; yield: 38.2 mg (65%).

2.1.1.1.1.1.3 Through Deprotonation of an Alkene

A keen insight from Danishefsky[29] and co-workers has been reported in the construction of the anthraquinone fragment of enediyne antibiotic dynemicin A. Treatment of homophthalic anhydride [1*H*-2-benzopyran-1,3(4*H*)-dione] **20** with lithium hexamethyldisilazanide results in the transient generation of xylylene (quinodimethane) **21** which, in the presence of quinone imine **22**, results in the production of sophisticated anthrone **24** ostensibly through the intermediacy of Diels–Alder adduct **23** followed by the extrusion of carbon dioxide (Scheme 6). The non-isolable intermediate anthrone **24** was immediately oxidized in the next step. The complexity of the fragments in this example illustrates well the ability of Diels–Alder cascades to merge two late-stage intermediates.

for references see p 44

Scheme 6 Participation of a Reactive Xylylene, Generated through Deprotonation, in a Diels–Alder/Retro-Diels–Alder Cascade[29]



Anthrone 24:[29]
1*H*-2-Benzopyran-1,3(4*H*)-dione **20** (49 mg, 0.173 mmol, 6.0 equiv) was dissolved in THF (2.5 mL) and cooled to 0 °C. Then, a 1.0 M soln of LiHMDS (171 μL, 0.171 mmol, 5.9 equiv) was added dropwise, and the soln immediately became bright yellow. After 35 min, the quinone imine **22** (12 mg, 0.029 mmol, 1.0 equiv) was added as a soln in THF (1 mL). The mixture slowly became a dark red-brown color, and, after 35 min, TLC indicated that no starting material remained. The intermediate anthrone **24** was used directly in the next step.

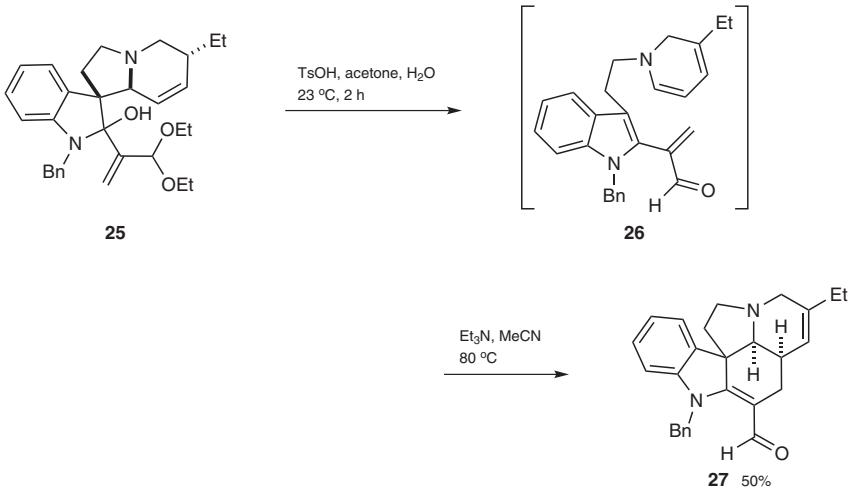
2.1.1.1.1.1.4 Through Elimination Reactions

A classical method by which one could imagine generating unsaturation in a molecule is by elimination processes. An elimination reaction involving an allylic leaving group can be expected to lower the activation energy of the reaction, resulting in the convenient synthesis of a diene. Unsurprisingly, synthesis of a diene by this strategy has been successfully applied in several Diels–Alder cascade sequences.

A particularly striking example of an elimination process forming a diene is provided by the group of Grieco in a concise synthesis of pseudotabersonine.[30] Treatment of amino

alcohol **25** with catalytic 4-toluenesulfonic acid in acetone/water leads to a vinylogous E1 reaction to furnish reactive diene intermediate **26**, which, upon heating, provides Diels–Alder adduct **27** (Scheme 7).

Scheme 7 In Situ Generation of a Diene by a Vinylogous E1 Reaction Prior to an Intramolecular Diels–Alder Reaction[30]



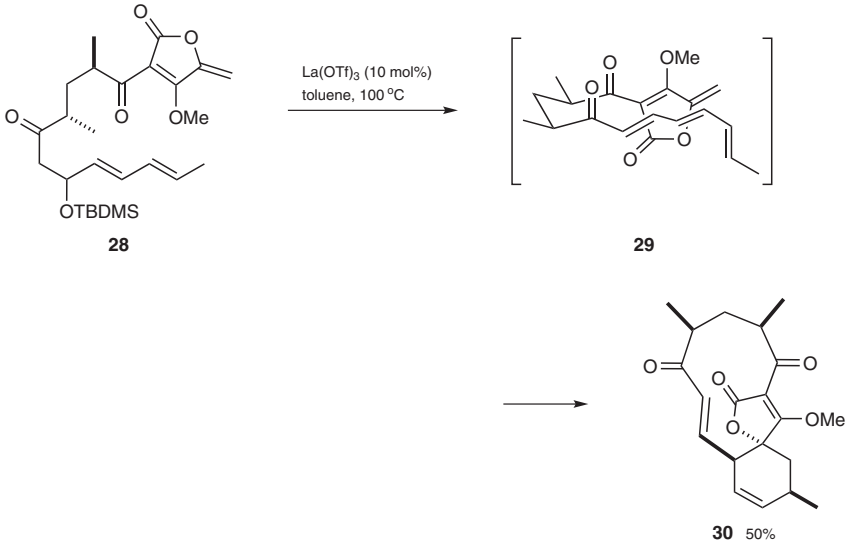
25 **26**

27 50%

A key Diels–Alder macrocyclization was envisioned by Sorensen and co-workers in the course of their synthesis of potent antibiotic abyssomycin C.[31] It was recognized that the requisite trienone diene partner in the desired Diels–Alder reaction would be exceptionally reactive, necessitating a design that introduces it directly prior to the cycloaddition. Treatment of silyl ether **28** with lanthanum(III) trifluoromethanesulfonate in hot toluene leads to the production of the desired trienone **29**. This transient intermediate then undergoes the Diels–Alder macrocyclization to furnish intermediate **30**, a process that is accelerated by heating (Scheme 8).

for references see p 44

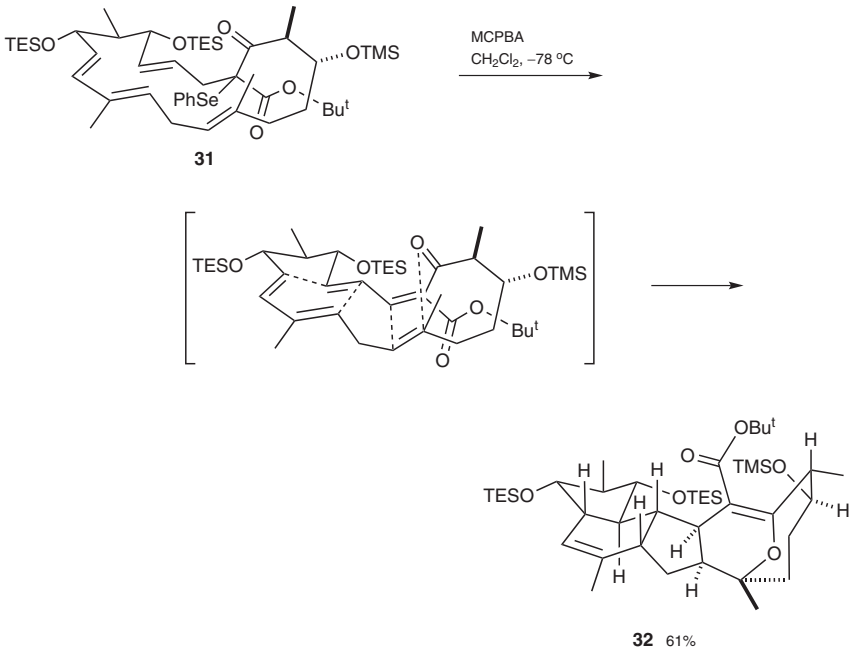
Scheme 8 A Lewis-Acid Catalyzed Elimination Reaction To Unveil a Reactive Trienone That Undergoes an Effective Diels–Alder Macrocyclization[31]



28 **29** **30** 50%

Another strategy that can be described as highly reliant on a Diels–Alder cascade can be found in the Sorensen synthesis of the potent antitumor agent cyclostreptin (also known in early literature as FR182877).[32,33] Seeking to test the viability of a biogenesis involving a twofold transannular intramolecular Diels–Alder transformation, the Sorensen lab targeted macrocycle **31** as a starting material for the cascade. Oxidation of diastereomeric selenide **31** leads to a tandem elimination/double transannular Diels–Alder to furnish a sophisticated product **32** with the connectivity of cyclostreptin (Scheme 9). Evans and Starr completed a nearly contemporaneous, independent synthesis of cyclostreptin using a similar elimination/double Diels–Alder cascade initiated in a slightly different manner.[34]

Scheme 9 A Selenoxide Elimination Reaction To Enable a Bioinspired Diels–Alder/Diels–Alder Cascade[32,33]



(3*E*,5*R*,7*S*,9*E*,10a*S*,13*R*,14a*R*)-15-Methoxy-5,7,13-trimethyl-6,7,13,14-tetrahydro-2*H*-3,14a-(metheno)benzo[*b*][1]oxacyclododecine-2,4,8(5*H*,10a*H*)-trione (30)**:**[31]
To a soln of diene **28** (115 mg, 0.241 mmol, 1 equiv) in degassed toluene (24.1 mL) was added $La(OTf)_3$ (14 mg, 0.024 mmol, 0.1 equiv) and the mixture was stirred at 100 °C for 4 h. The mixture was concentrated under reduced pressure and rinsed through a plug of silica gel (EtOAc/hexanes 1:1) to remove the catalyst. The crude product was purified by column chromatography (EtOAc/hexanes 1:4). The target compound **30** was obtained as a colorless oil [yield: 42 mg (50%)] along with the *Z*-trienone isomer of **29** [yield: 5 mg (5%)]. The trienone was converted into the *E*-isomer and underwent the Diels–Alder macrocyclization in quantitative yield by heating in degassed toluene (0.01 M) in the presence of a single crystal of I_2.

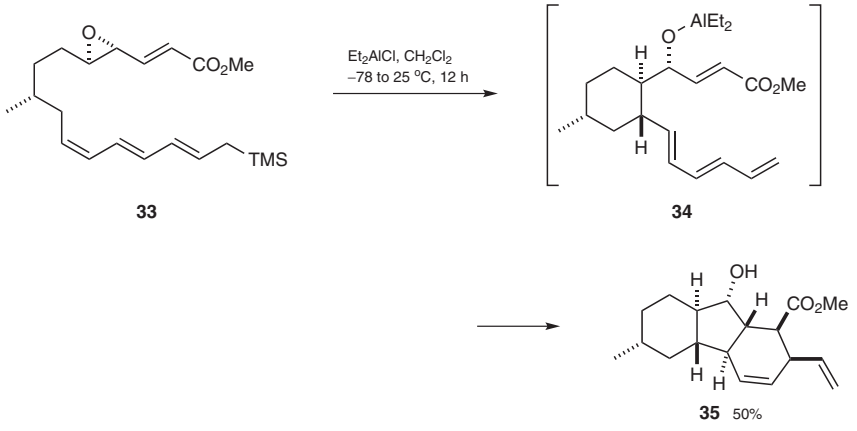
Pentacycle 32**:**[33]
Selenide **31** [diastereomeric mixture (ratio 1:10); 19.0 g, 20.4 mmol, 1 equiv] was dissolved in CH_2Cl_2 (400 mL) at −78 °C, and a soln of MCPBA (70%; 6.04 g, 24.5 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL) was slowly added via cannula. The reaction was complete immediately (determined by TLC analysis) and was quenched at −78 °C by addition of a mixture of sat. aq $Na_2S_2O_3$/sat. aq $NaHCO_3$ (1:1; 300 mL). The mixture was warmed to rt and extracted with hexanes (3 × 300 mL). The combined organic phases were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in $CHCl_3$ (400 mL) and solid $NaHCO_3$ (5 g) was added. The flask was sealed under argon, and the mixture was protected from light and stirred at 45 °C for 4 h. The mixture was filtered through a plug of cotton and concentrated. Purification by chromatography (Et_2O/hexanes 1:99 to >5:95) afforded the desired pentacycle **32** as a clear, colorless, viscous oil; yield: 9.6 g (61%).

for references see p 44

2.1.1.1.1.1.5 Through Allylation

Allylation can be a viable precursor reaction to a Diels–Alder union by virtue of the unsaturation of the resultant product. An inspiring disconnection from the Nicolaou group is provided by their entry into the decahydrofluorenyl core of hirsutellone B.[35] Treatment of acyclic epoxide **33** with diethylaluminum chloride leads to a cascade sequence wherein a doubly vinylogous Sakurai-type alkenation provides dienyl intermediate **34**. Then, through the enhanced proximity provided by the nascent monocycle, this material smoothly undergoes an intramolecular Diels–Alder reaction to provide desired compound **35** (Scheme 10). Overall, this highly productive domino transformation results in the stereoselective formation of three rings in a single operation, allowing for the synthesis to be rapidly advanced.

Scheme 10 Synthesis of the Hirsutellone B Core through an Epoxide-Opening Allylation/Intramolecular Diels–Alder Cascade[35]



33 **34** **35** 50%

Methyl (1*S*,2*S*,4a*S*,4b*S*,6*R*,8a*R*,9*S*,9a*S*)-9-Hydroxy-6-methyl-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1*H*-fluorene-1-carboxylate (35); Typical Procedure:[35]
To a stirred soln of epoxytetraene **33** (100 mg, 0.276 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added a 1.0 M soln of Et_2AlCl in hexanes (2.8 mL, 2.8 mmol, 10.0 equiv) dropwise. The resulting homogeneous soln was allowed to warm to −50 °C for 30 min, and then to rt slowly overnight (12 h). The reaction was then quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes 1:3) provided a white solid; yield: 40 mg (50%).

2.1.1.1.1.2 Pericyclic Generation of a Diene

The product of a pericyclic process, or a change in bonding resulting from the concerted rearrangement of electrons in a cyclic transition state, can sometimes participate in a subsequent pericyclic process, resulting in a so-called pericyclic cascade. The Diels–Alder cycloaddition, itself a pericyclic reaction, is no exception to this trend. The ability to significantly rearrange the bonding framework of molecules in a single chemical step has been recognized as exceptionally valuable for target-oriented synthesis and has resulted in many elegant examples of tandem pericyclic Diels–Alder reaction sequences being reported.

2.1.1.1.1.2.1 Through Electrocyclization

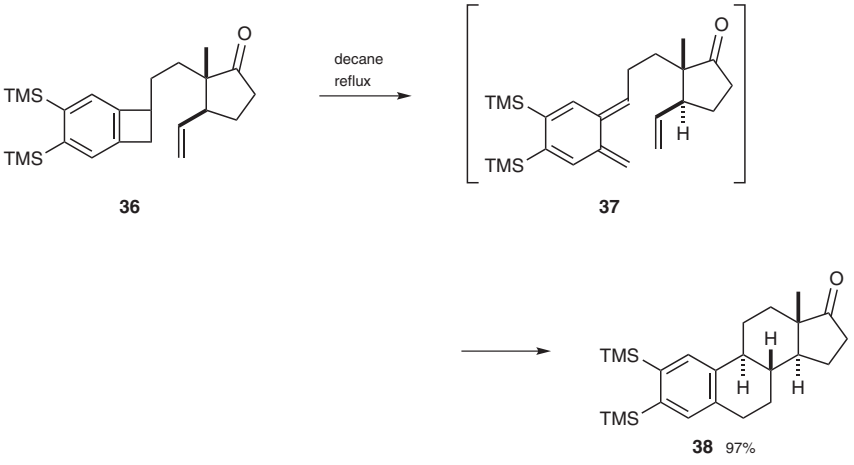
The electrocyclization of polyunsaturated substrates presents the attractive opportunity to alter the number of rings in a starting material. Moreover, one might consider using electrocyclizations to access reactive and otherwise inaccessible Diels–Alder partners from stable precursors.

2.1.1.1.1.2.1.1 Through Benzocyclobutene Ring Opening

ortho-Xylylenes (*ortho*-quinodimethanes) are well known as reactive dienes in Diels–Alder reactions. One method by which one might envision accessing such an intermediate is through the electrocyclic ring opening of a benzocyclobutene. First shown in the context of synthesis by Oppolzer and Keller's preparation of chelidonine,[36] it was soon recognized that many opportunities to streamline routes through this strategy exist in chemical space.

The concurrent development of a cobalt-mediated [2+2+2] cyclotrimerization served as a springboard for the Vollhardt group in their landmark synthesis of estrone. Vollhardt and Funk[37] envisioned forming both the B and C rings of the target through an intramolecular Diels–Alder annulation of a transiently formed *ortho*-xylylene **37** possessing an alkene attached to what is to become the D-ring. Thus, heating the benzocyclobutene intermediate **36** in benzene results in a conrotatory 4π-electrocyclic ring opening to unveil the highly activated *ortho*-dimethylene intermediate **37**, which smoothly engages the pendent alkene in an intramolecular Diels–Alder reaction to furnish intermediate **38** having the connectivity of estrone (Scheme 11). This application of the benzocyclobutene methodology is notable as it rapidly develops the architecture of its target through the simultaneous formation of two rings.

Scheme 11 Synthesis of the B and C Rings of Estrone through an Electrocyclization/Intramolecular Diels–Alder Cascade[37]



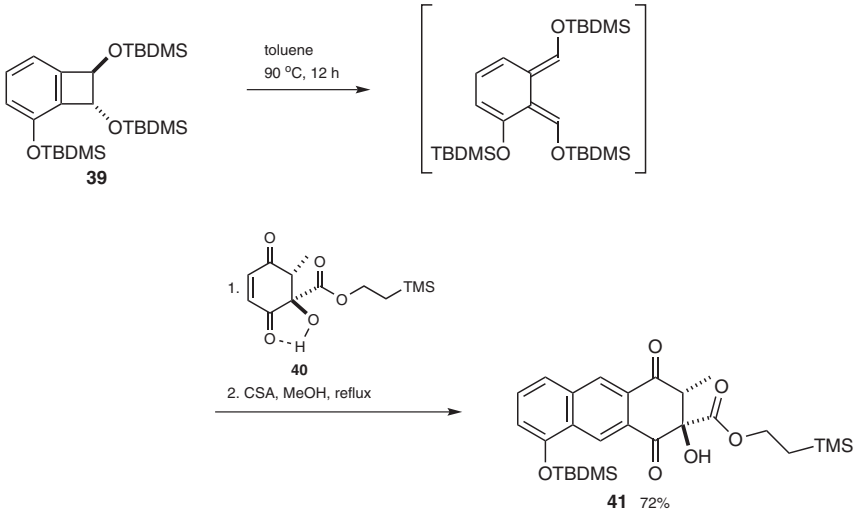
36 **37** **38** 97%

A synthesis of rishirilide B by Danishefsky and co-workers also makes use of the benzocyclobutene diene surrogate to achieve a union of two partners, albeit in an intermolecular fashion.[38] Heating a mixture of benzocyclobutene **39** and enedione **40** in a sealed tube, followed by dehydration, results in the production of the desired tricycle **41** in a regioselective sense (Scheme 12). A notable aspect of this maneuver can be observed in the formulation of its dienophilic component **40**, namely in the hydroxy functionality α to the enone carbonyl. It is proposed that this hydroxy group is able to serve as an internal hy-

for references see p 44

drogen-bond donor, activating the enedione in a mode first recognized by Masamune.[39] This activation not only increases the ease with which the reaction can be effected, but also enhances the regioselectivity of the transformation through differential activation of one ketone. This factor was confirmed through the replacement of the hydroxy group with a silyl ether, resulting in lackluster reactivity with abysmal regioselectivity in the respective cascade.

Scheme 12 Regioselective, Intermolecular Benzocyclobutene/Diels–Alder Cascade Enabled by the Masamune Effect[38]



2,3-Bis(trimethylsilyl)estra-1,3,5(10)-triene-17-one (38**):**[37]
Benzocyclobutene **36** (142 mg, 0.36 mmol) was dissolved in degassed decane (35 mL) and refluxed for 20 h. The solvent was vacuum transferred and the residue was filtered through silica gel and crystallized (petroleum ether); yield: 135 mg (97%).

2-(Trimethylsilyl)ethyl (2*R*,3*R*)-8-(*tert*-Butyldimethylsiloxy)-2-hydroxy-3-methyl-1,4-dioxo-1,2,3,4-tetrahydroanthracene-2-carboxylate (41**):**[38]
Enedione **40** (50 mg, 85 μmol, 1 equiv) and benzocyclobutane **39** (20 mg, 70 μmol, 1 equiv) were dissolved in toluene-d_8 (1 mL) and heated at 90 °C for 12 h in a sealed tube. The solvent was evaporated, the residue was dissolved in MeOH (10 mL), and CSA (16 mg, 70 μmol, 1 equiv) and pyridine (6 μL, 70 μmol, 1 equiv) were added. After heating the mixture at reflux for 4 h, the mixture was concentrated and the residue was purified by column chromatography (silica gel) to afford a colorless oil; yield: 26 mg (72%).

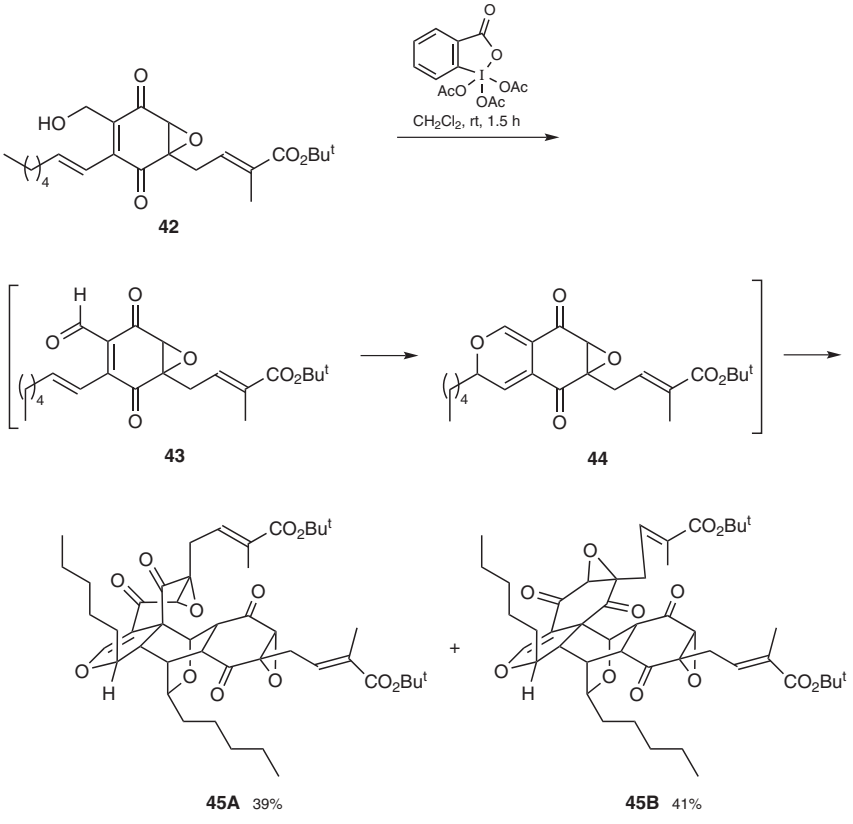
2.1.1.1.1.2.1.2 Through Electrocyclic Ring Closure

Electrocyclic ring closure of arrays with six or more π-electrons generate products with conjugated alkenes, or functionalities able to serve as the diene component of a Diels–Alder cycloaddition. An advantage of producing polyenes via this method is that, by virtue of them being confined to a ring, they must conform to the prerequisite *s-cis* geometry needed for the cycloaddition to occur.

The postulated biosynthesis of torreyanic acid involves the dimerization of dihydropyran monomers through a Diels–Alder process.[40] Taking inspiration from this proposal, Porco and co-workers envisioned accessing the desired cycloaddition partners through oxidation of readily accessible allylic alcohol **42**, which, following aldehyde **43** forma-

tion, should be able to undergo a facile 6π-electrocyclization to provide the desired dihydropyran **44** (Scheme 13).[41] One can then imagine that this intermediate can dimerize via cycloaddition. Treatment of a racemic mixture of **42** with Dess–Martin periodinane at room temperature leads to the desired cascade, culminating in the formation of a 1:1 mixture of the *tert*-butyl esters of torreyanic acid (**45A**) and its close cousin isotorreyanic acid (**45B**).

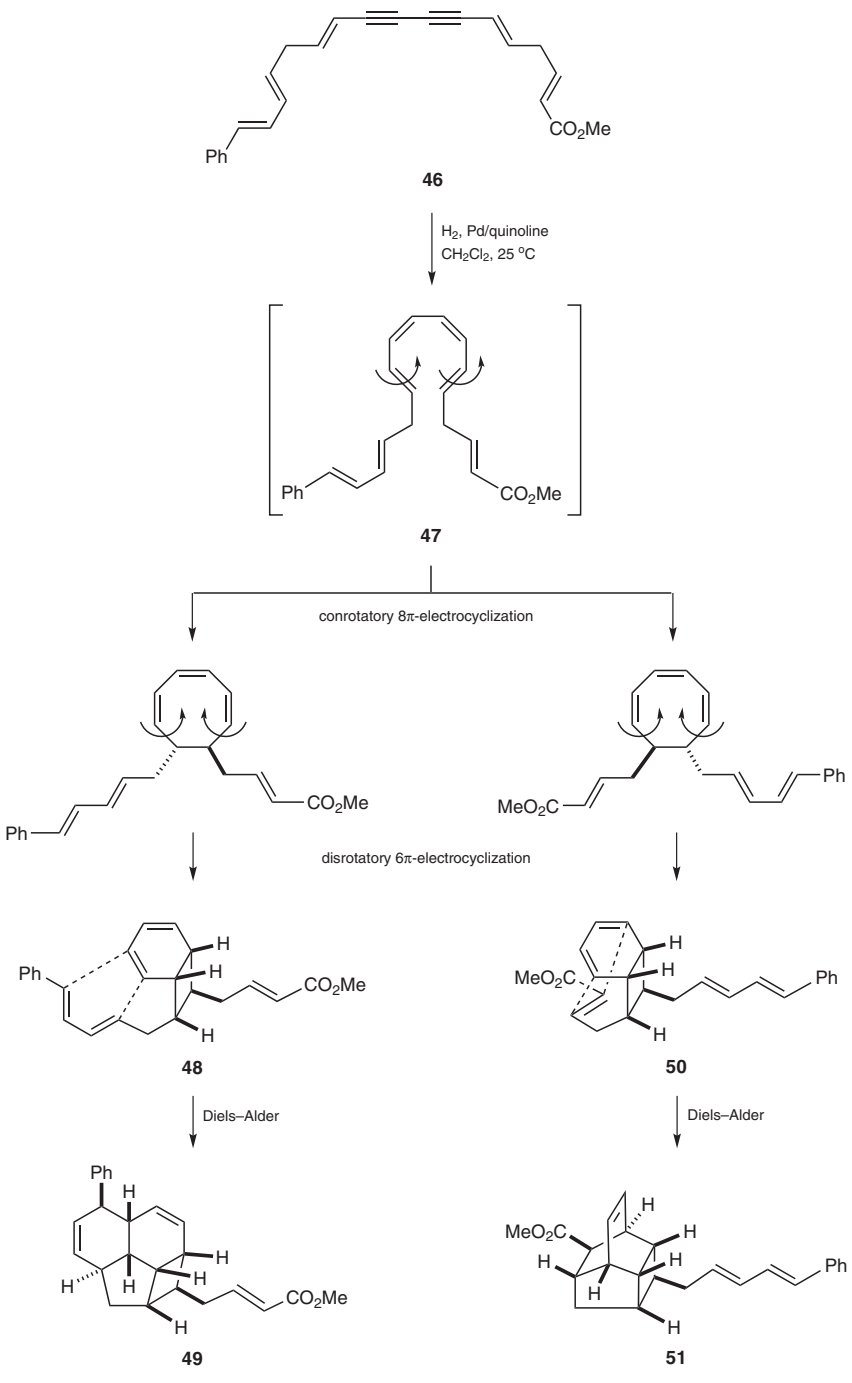
Scheme 13 Oxidation/Electrocyclization/Diels–Alder Cascade in the Synthesis of Torreyanic Acid[41]



There is no restriction on the number of electrocyclizations before the diene partner is formed, a truth that is exemplified by the work of Nicolaou. The daring biosynthetic proposal of Black for the racemic endiandric acids posits that their congested, polycyclic architecture could be achieved by a series of pericyclic reactions starting from a highly unsaturated, linear intermediate.[42] The group of Nicolaou was able to synthesize the methyl ester of this intermediate, compound **47**, through a twofold Lindlar hydrogenation of diyne **46**, and observed that racemic endiandric acid methyl esters B (**49**), C (**51**), F (**48**), and G (**50**) are formed after brief heating of the starting material.[43,44] Esters **49** and **51** are formed through intramolecular Diels–Alder reactions of esters **48** and **50**, themselves products of successive 8π- and 6π-electrocyclizations of linear precursor **47** (Scheme 14).

for references see p 44

Scheme 14 Pericyclic Cascades Interrelating Endiandric Acid Methyl Esters B, C, F, and G with an Acyclic Precursor[44]



Torreyanic Acid *tert*-Butyl Ester (45A**):**[41]
Quinone monoepoxide **42** (10.8 mg, 0.027 mmol, 1 equiv) was dissolved in CH_2Cl_2 (2 mL) and Dess–Martin periodinane (18 mg, 0.042 mmol, 1.6 equiv) was added. After stirring at rt for 1.5 h, the mixture was neutralized with sat. $NaHCO_3/Na_2S_2O_3$ and extracted with Et_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered,

and concentrated under reduced pressure. ^{1}H NMR analysis of the crude product showed *2H*-pyran monomer **44**, dimer **45A**, and dimer **45B** in a 1:1:1 ratio. The mixture was allowed to stand on a silica gel column for 1 h, and then eluted and purified by flash column chromatography to provide *tert*-butyl esters **45A** [yield: 4.3 mg (39%)] and **45B** [yield: 4.5 mg (41%)].

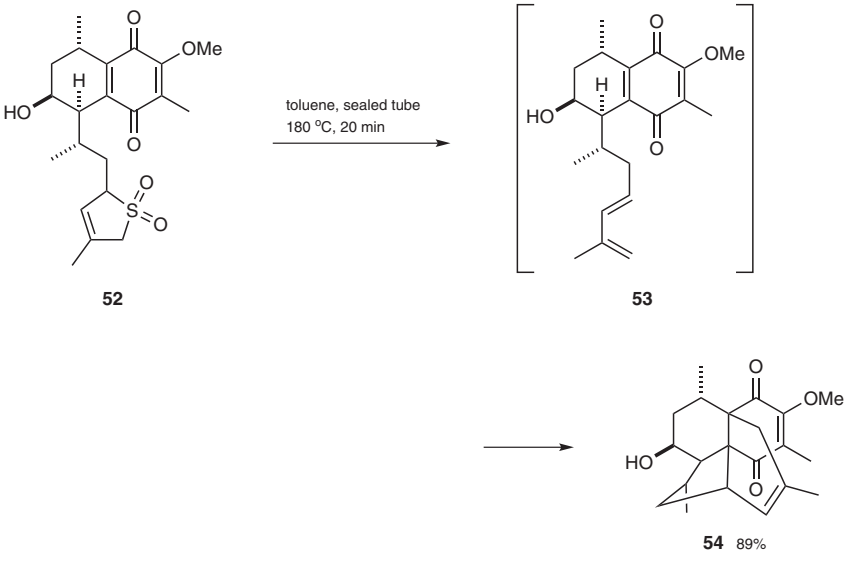
Endiandric Acid Methyl Esters 48–51:[44]
When the acetylenic precursor **46** was mildly hydrogenated (H_2, Lindlar catalyst, quinoline, CH_2Cl_2, 25 °C) followed by brief heating of the resulting mixture at 100 °C (toluene), endiandric acid methyl esters **48–51** were produced and chromatographically isolated.

2.1.1.1.1.2.2 Through Cycloaddition or Retrocycloaddition

The Diels–Alder reaction, itself a reversible cycloaddition, can be expected to have similar activation requirements to other reactions of this class. When combined with the inherent unsaturation of Diels–Alder substrates, it is unsurprising that cascades involving cycloadditions and retrocycloadditions can be implemented productively in synthetic designs.

One advantage of a retrocycloaddition-based approach to the 4π component of the Diels–Alder reaction is the ability to "protect" the unsaturated diene as a cycloadduct, allowing for operations usually incompatible with dienes to be performed with impunity. The synthetic strategy applied toward colombiasin A by the Nicolaou group called for a late-stage intramolecular Diels–Alder between cyclic alkene **53** and its appended diene.[45] In the course of their investigations, it was found that the diene introduced issues of chemoselectivity in the preceding oxidation step. Drawing from the work of Staudinger,[46] it was found that masking the diene as a sulfolene (2,5-dihydrothiophene 1,1-dioxide) group obviated much of this difficulty. Subjecting sulfolene intermediate **52** to heat and pressure unveils the diene **53**, which engages in an intramolecular Diels–Alder to furnish the desired intermediate **54** with the core connectivity of colombiasin A (Scheme 15).

Scheme 15 Use of a Sulfolene as a Diene Masking Group in the Nicolaou Synthesis of Colombiasin A[45]



52 **53** **54** 89%

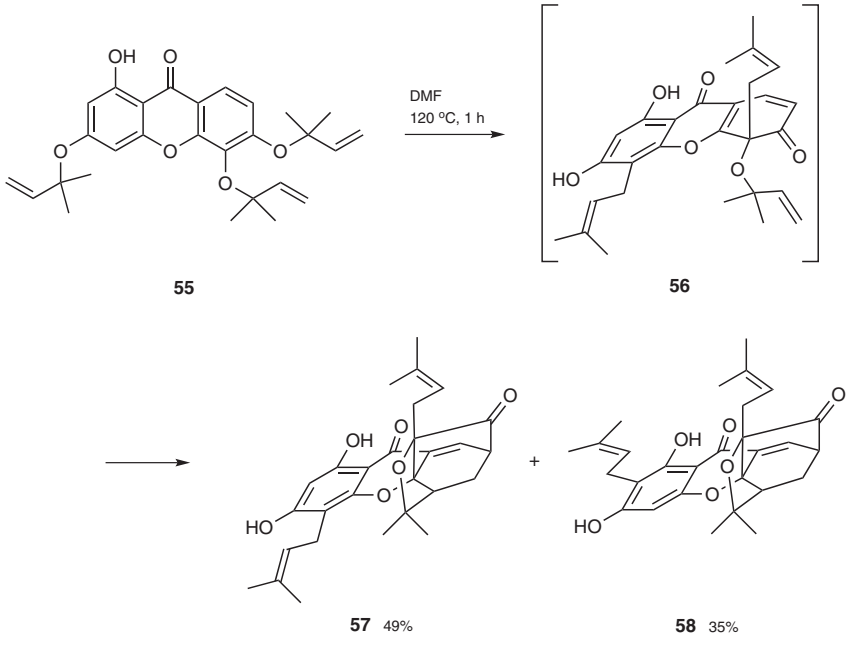
for references see p 44

2.1.1.1.1.2.3 Through Sigmatropic Reactions

The rearrangement of σ-bonds across a π-framework presents an exciting opportunity to radically alter the connectivity of an intermediate in a controlled and predictable fashion. As with other pericyclic reactions, the product of this process can be engaged in a Diels–Alder reaction, allowing for the rapid generation of molecular complexity.

The aromatic Claisen rearrangement, the first reported [3,3]-sigmatropic rearrangement (in 1912),[47] transforms an allyl aryl ether into an allyl dienone. It can be recognized that this fleeting intermediate contains an exceptionally reactive diene that could be engaged in a Diels–Alder cycloaddition, provided that aromatization can be outcompeted. Quillinan and Scheinmann postulated just such a tandem transformation in their proposed biosynthesis of the *Garcinia* natural products.[48] While an elegant study by Nicolaou[49] provided a firm foundation for this hypothesis in his group's route to *O*-methylforbesione, it was not until the work of Theodorakis[50] that a bona fide *Garcinia* compound, forbesione, was synthesized using this strategy. Heating intermediate **55** results in the formation of dienone intermediate **56**, which can then be engaged by a pendent dienophile to provide the caged structure of forbesione (**57**) and isomer **58** through a Diels–Alder event (Scheme 16). Aside from providing validation for the biosynthetic hypothesis, the evolution of the intricate three-dimensional structure of forbesione from the planar starting material **59** represents another powerful demonstration of the Diels–Alder reaction in domino processes.

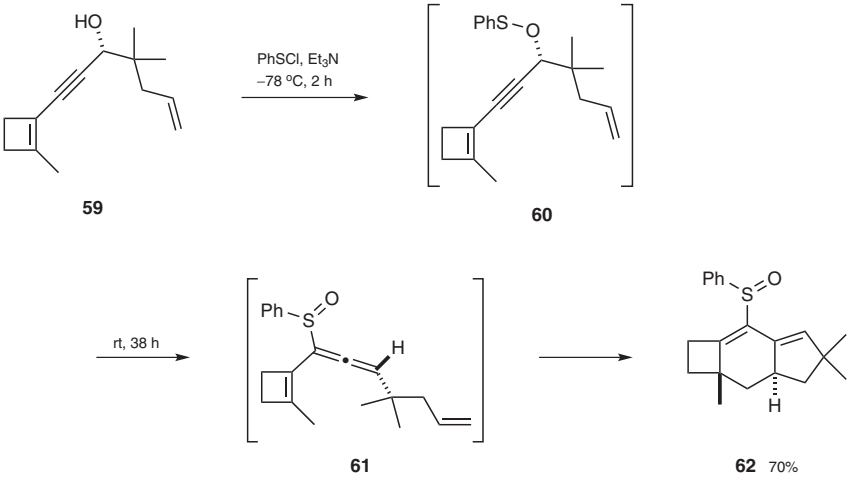
Scheme 16 Rapid Assembly of the Caged Architecture of Forbesione by an Aryl Claisen/Diels–Alder Domino Sequence[50]



Sigmatropic rearrangements provide another strategic factor for the in situ generation of dienes by virtue of the stereospecificity of their highly ordered transition states. Gibbs and Okamura[51,52] realized that asymmetry can be communicated in a pericyclic cascade through the conversion of axial into point chirality via a sigmatropic rearrangement. Sulfenate ester **60**, generated from chiral propargyl alcohol **59**, undergoes efficient [2,3]-rearrangement into transient allenyl sulfoxide **61**, the diene of which is smoothly cap-

tured by the pendent alkene to furnish tricycle **62**, a key intermediate in a synthesis of sterpurene (Scheme 17). This [2,3]-rearrangement/intramolecular Diels–Alder cascade provides a powerful method to translate stereochemical information. Critically, the sterpurene produced from **62** possessed an identical optical rotation to an authentic sample.

Scheme 17 Transfer of Axial to Point Chirality in a [2,3]-Rearrangement/Diels–Alder Cascade[51,52]



(2a*S*,3a*S*)-2a,5,5-Trimethyl-7-(phenylsulfinyl)-2,2a,3,3a,4,5-hexahydro-1*H*-cyclobuta[*f*]indene (62):[52]

A 0.96 M soln of Cl_2 in CCl_4 (1.15 mL, 1.10 mmol) (**CAUTION:** *toxic*) was added to $(PhS)_2$ (240 mg, 1.10 mmol) in a 10-mL flask under N_2 at 0 °C. The resulting mixture was stirred for 10 min and then warmed to rt to give a 1.66 M orange-red soln of PhSCl (3.65 mL, 2.20 mmol).

A freshly prepared 1.66 M soln of PhSCl in CCl_4 (0.40 mL, 0.66 mmol, 1.2 equiv; prepared by the in situ method described above) was added to a stirred mixture of unsaturated alcohol **59** (113 mg, 0.55 mmol, 1 equiv) and Et_3N (0.19 mL, 1.39 mmol, 2.5 equiv; distilled from CaH) in CH_2Cl_2 (11.6 mL; distilled from CaH) under N_2 at −78 °C. After stirring for 2 h, the cooling bath was removed, and the mixture was stirred for 38 h at rt. The mixture was then worked up, and the product was obtained after purification by chromatography; yield: 120 mg (70%).

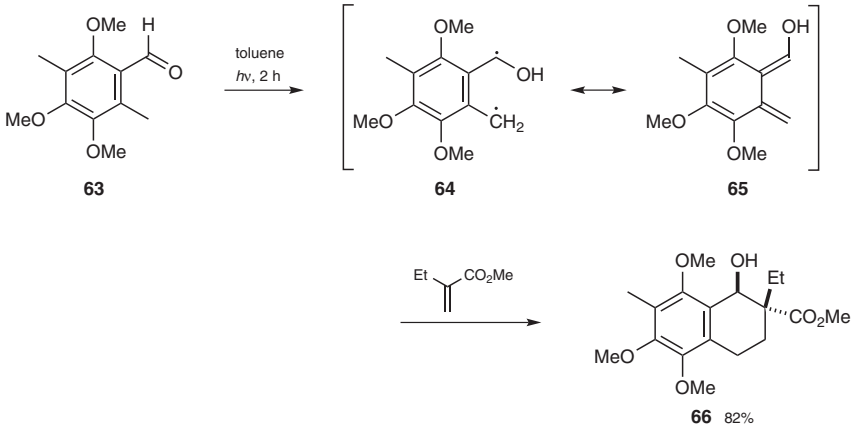
2.1.1.1.1.3 Photochemical Generation of a Diene

An alternative method for generating highly reactive *ortho*-xylylene (*ortho*-quinodimethane) dienes to the electrocyclic ring opening of benzocyclobutenes (see Section 2.1.1.1.1.2.1.1) has been developed by Pfau and co-workers.[53] Seeking a less thermally demanding route, it was found that photoexcitation of an aryl ketone possessing an *ortho* alkyl group could, reasonably, lead to a 1,5-hydrogen abstraction process to furnish an *ortho*-xylyl diradical which, through resonance, can be described as an *ortho*-xylylene. Performing this photolysis in the presence of an external dienophile leads to the smooth formation of the expected Diels–Alder adduct. This method is used to great effect in Nicolaou's[54] synthesis of hybocarpone. Here, 1,5-hydrogen abstraction from the *ortho* methyl group of the highly functionalized benzaldehyde **63** results in the production of ketyl–

for references see p 44

alkyl diradical **64**, a compound which can be described using *ortho*-xylylene resonance form **65**. This intermediate is trapped by a dienophilic acrylate to provide bicycle **66**, a useful building block in the synthesis of hybocarpone (Scheme 18).

Scheme 18 1,5-Hydrogen Abstraction as an Alternative Method To Generate *ortho*-Xylylenes in Nicolaou's Synthesis of Hybocarpone[54]

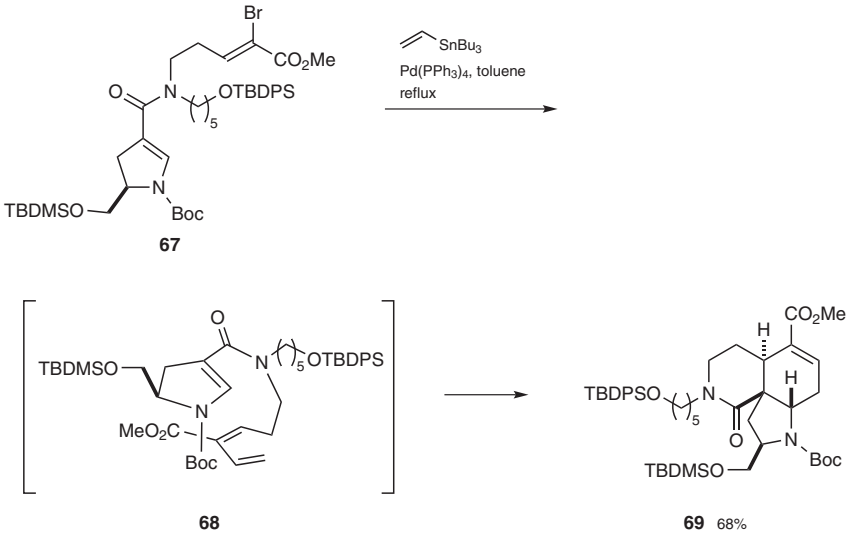


2.1.1.1.4 Metal-Mediated Generation of a Diene

Metal-mediated coupling reactions have taken an increasingly prominent place in the pantheon of useful synthetic transformations, a trend recently recognized by the 2010 Nobel Prize in Chemistry. The reasons for this attention are obvious: few other strategies allow for such versatility in the production of C—C bonds. Both cross coupling and oxidative coupling of fragments have been utilized to form dienes in Diels–Alder-containing domino processes.

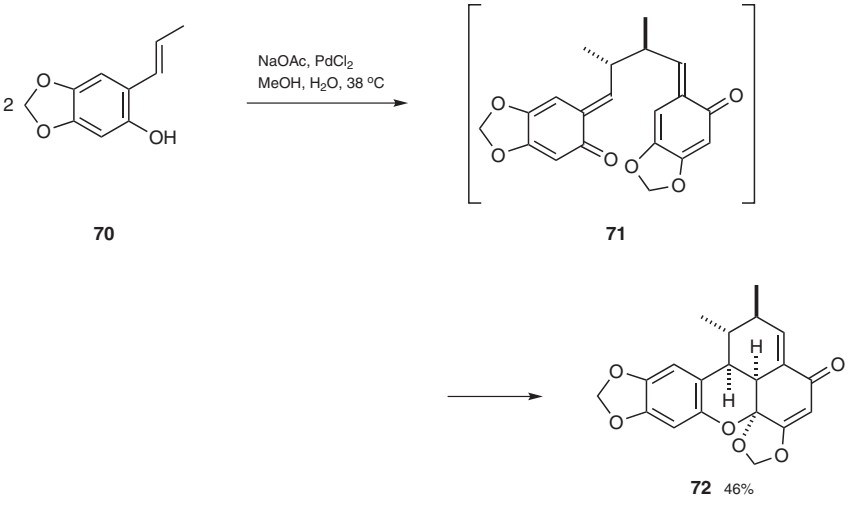
The disconnection strategy utilized by Martin and co-workers in their synthesis of manzamine A involves a key intermolecular Diels–Alder reaction to assemble three of the four rings of the core subunit as intermediate **69**.[55] In the course of optimizing material flow to precursor **68**, it was recognized that the diene could be formed from a Stille cross coupling involving tributyl(vinyl)stannane and vinyl bromide **67**. Heating these two fragments in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) leads to the smooth formation of the desired tricycle **69**, presumably through a Diels–Alder reaction of the in situ generated diene (Scheme 19).

Scheme 19 A Tandem Stille Coupling/Intramolecular Diels–Alder Sequence To Provide a Key Fragment of Manzamine A[55]



Oxidative coupling mediated by metals presents an opportunity to unite two fragments while also generating participants for a Diels–Alder reaction. The Chapman group envisioned accessing the hexacyclic natural product carpanone (**72**) through the oxidative dimerization of prop-1-enyl arene **70**.[56] Palladium-mediated oxidative coupling of two molecules of **70** results in the formation of bis(*ortho*-quinomethane) **71**, a highly reactive intermediate that can readily engage in an intramolecular Diels–Alder reaction to furnish carpanone (**72**) as the major product (Scheme 20).

Scheme 20 Palladium-Mediated Oxidative Dimerization of an Alkenic Phenol in an Exceptionally Direct Synthesis of Carpanone[56]



for references see p 44

8-*tert*-Butyl 5-Methyl (4a*R*,7a*S*,9*R*,10a*S*)-9-[(*tert*-Butyldimethylsiloxy)methyl]-2-[5-(*tert*-butyldiphenylsiloxy)pentyl]-1-oxo-2,3,4,4a,7,7a,9,10-octahydropyrrolo[2,3-*i*]isoquinoline-5,8(1*H*)-dicarboxylate (69):[55]
A mixture of vinyl bromide **67** (27.1 g, 27.2 mmol, 1 equiv), tributyl(vinyl)stannane (9.49 g, 29.9 mmol, 1.1 equiv), and $Pd(PPh_3)_4$ (1.26 g, 1.09 mmol, 4 mol%) in freshly distilled toluene (270 mL; distilled from sodium/benzophenone) was heated under reflux for 30 h. The solvent was removed under reduced pressure at 40 °C and the residue was dissolved in Et_2O (100 mL) containing decolorizing carbon (5 g). The mixture was stirred for 20 min and filtered through Celite to give **69**; yield: 15.1 g (68%).

Carpanone (72):[56]
$PdCl_2$ (0.8 g, 4.5 mmol) was added to a rapidly stirred soln containing substrate **70** (1.6 g, 9.0 mmol) and NaOAc (6.0 g, 73 mmol) in MeOH (150 mL) and H_2O (30 mL). The soln was stirred for 2 h (38 °C) and then left to settle for 1 h at rt. After filtration and dilution with H_2O, the resultant suspension was extracted twice with Et_2O. The ethereal soln was washed with 10% aq NaOH and then H_2O, dried ($MgSO_4$), and then concentrated to give the crude product (1.0 g; 62%). CCl_4 (5 mL) (**CAUTION:** *toxic*) was added, and the product crystallized overnight. The crystals (0.98 g; mp 185 °C) thus obtained contained one molecule of CCl_4 per molecule of product **72** (X-ray crystal structure). Chromatography of the mother liquor gave additional **72**•CCl_4 (0.08 g); total yield of crystalline **72**: 0.733 g (46%).

2.1.1.1.2 Cascades Generating a Dienophile

While the extent to which the development of diene-generating reactions has been pursued is hinted at in the previous sections, it is fair to say that a significant amount of study has been devoted to the generation of their conjugates, dienophiles, in cascade processes. Some major advances in the production of dienophiles have come from exploring the same general strategies as have been applied to the generation of dienes, most notably ionic and pericyclic processes.

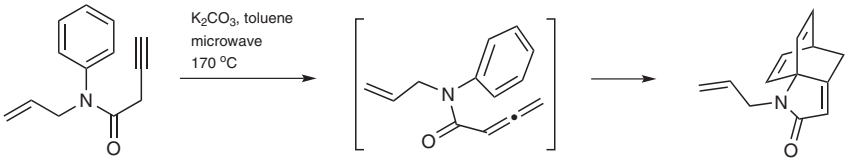
2.1.1.1.2.1 Ionic Generation of a Dienophile

As with the generation of dienes, many two-electron processes have been pursued to generate 2π partners in the Diels–Alder cycloaddition.

2.1.1.1.2.1.1 Through Himbert Cycloadditions

Himbert and Henn provided the first report of a thermal Diels–Alder reaction between anilines and tethered allenes in 1982.[57] This reaction is quite remarkable, as it not only uses a relatively unactivated arene as a diene, but also proceeds with no subsequent rearrangement to prevent reversibility. Despite some uncertainty as to the mechanism of the cycloaddition, recent computational and experimental study[58] has supported that this cyclization proceeds through a concerted [4+2]-Diels–Alder process (as opposed to a stepwise, radical pathway). The group of Vanderwal[59] found that treatment of skipped alkynamide starting materials, e.g. **73**, with base generates a reactive allene dienophile, e.g. **74**, which smoothly engages the pendent arene in the Himbert Diels–Alder cyclization, providing polycyclic lactam products such as **75** in fair to excellent yields (Scheme 21).

Scheme 21 A Complex Lactam Product from a Simple, Skipped Alkyne Precursor via the Himbert Arene/Allene Cycloaddition[59]



73 **74** **75** 74%

1-Allyl-4,5-dihydro-5,7a-ethenoindol-2(1*H*)-one 75; **Typical Procedure:**[59]
To a soln of amide **73** (2.00 g, 10.0 mmol, 1 equiv) in toluene (50 mL) was added K_2CO_3 (0.69 g, 5.00 mmol, 0.50 equiv) and the mixture was heated under microwave irradiation at 170 °C for 8 h. After cooling to rt, the solvent was evaporated. Chromatographic purification (silica gel, hexanes/EtOAc 2:1) of the residue afforded the cycloadduct **75** as a yellow solid; yield: 1.48 g (74%).

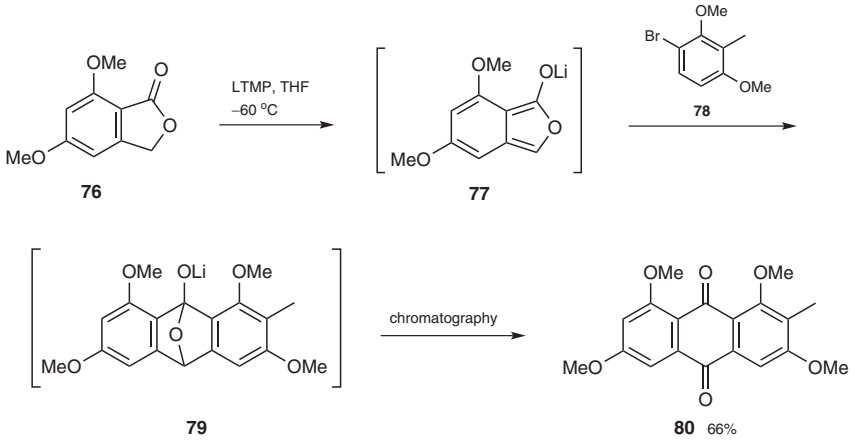
2.1.1.1.2.1.2 Through Benzyne Formation

Since their correct identification by Roberts in 1953,[60] benzynes have enjoyed a privileged position in the execution of concise molecule synthesis. Benzynes can be regarded as exceptionally labile intermediates and, as a result, are almost universally generated in situ, making them well suited to application in domino processes. One quality that has made these reactive intermediates so attractive is their ability to participate in Diels–Alder and/or formal Diels–Alder reactions as the 2π component, although it appears that a stepwise cycloaddition, as opposed to the concerted pericyclic pathway, may be the operative mechanism in some cases. Due to this ambiguity, this strategy will not be extensively treated in this chapter; however, the interested reader is directed to an excellent review on the use of benzynes in synthesis.[61]

An early, ingenious use of the benzyne/Diels–Alder disconnection can be found in the method developed in the Townsend synthesis of the aflatoxin biosynthetic precursor averufin.[62] Treatment of aryl lactone **76** with lithium tetramethylpiperidide at low temperature leads to the formation of the deprotonated species that can be represented as *ortho*-xylylene **77** (Scheme 22). Addition of benzyne precursor **78** to this basic mixture results in the highly regioselective formation of Diels–Alder adduct **79** which, upon workup, provides the desired asymmetrical anthraquinone **80**. This maneuver is particularly notable as Townsend and co-workers not only generate both the diene and dienophile in situ, but also make use of the decomposition of the Diels–Alder adduct to further advance their synthesis.

for references see p 44

Scheme 22 Regioselective Assembly of an Anthraquinone by Union of an In Situ Generated Diene and Dienophile[62]



1,3,6,8-Tetramethoxy-2-methylanthracene-9,10-dione (80**):**[62]
2,2,6,6-Tetramethylpiperidine (135 μL, 113 mg, 0.80 mmol, 3.1 equiv) in THF (0.5 mL) was treated at −60 °C (CH_2Cl_2/dry ice bath) with a 1.4 M soln of BuLi in hexane (600 μL, 0.84 mmol, 3.3 equiv). After being stirred for 10 min, the soln was treated with 5,7-dimethoxybenzo[*c*]furan-1(3*H*)-one (**76**; 50.0 mg, 0.258 mmol, 1 equiv) in dry THF (4.5 mL). After 20 min, the orange soln was warmed to −40 °C (MeCN/dry ice bath) and a soln of 1-bromo-2,4-dimethoxy-3-methylbenzene (**78**; 125.9 mg, 0.545 mmol, 2.1 equiv) in THF (2 mL) was added. After being stirred for 15 min, the mixture was allowed to warm gradually to rt, the color becoming dark red to purple. After 1 h, the mixture was stirred open to the air for at least 4 h. Addition of H_2O (30 mL) and extraction of the resulting mixture with $CHCl_3$ (3 × 8 mL), washing of the combined organic extracts with brine, drying ($MgSO_4$), and removal of the solvents under reduced pressure gave the crude anthraquinone **80**. Purification of the yellow solid by column chromatography [silica gel (3.0 g), EtOAc/hexanes 1:1] gave the product; yield: 60.0 mg (66%).

2.1.1.1.2.1.3 Through Wessely Oxidation

The dimerization of in situ generated quinone acetals through a Diels–Alder process has been a popular area of inquiry. As this topic involves, by definition, the production of both diene and dienophile, it has already been treated in the section for diene generation (see Section 2.1.1.1.1.1.1). There are, however, several examples of the Wessely reaction where a dienophile is the product of the arene oxidation.

An interesting iteration of the tandem aromatic oxidation/Diels–Alder cascade has come from the group of Ciufolini in their efforts toward the polycyclic alkaloid himandrine.[63] It was found that treatment of aryl dienylsulfonamide **81** with (diacetoxyiodo)-benzene provides spirocycle **82** through an oxidative amidation (Scheme 23). Heating this intermediate with the addition of toluene provides a mixture of *cis*- and *trans*-decalone products **83A** and **83B**, presumably through an intramolecular Diels–Alder reaction followed by epimerization of the acidic bridgehead center α to the ketone.