INTRODUCTION TO VOLUME 5: COMBINING C–C Π-BONDS

Olefins and, to a lesser extent, other π-systems are the principal starting point of the chemical value chain as long as mankind relies on crude oil as the major carbon source. It is therefore not surprising that the knowledge about the formation, manipulation, and functionalization of π-bonds in general is overwhelming.

Comprehensive Organic Synthesis II intends to assist the reader in navigating this vast sector of chemical space. In doing so, the present volume covers the immensely important methodologies that allow C–C–π-bonds to be combined; for the sake of coherence, some chemically closely related areas are also dealt with herein.

Even a cursory consideration makes clear that some of the most fundamental and powerful chemical transformations fall onto this thematic map. This refers to a very significant part of cycloaddition chemistry, independent of whether the reactions are photochemically or thermally induced, strain-driven, engendered by stoichiometric metal reagents, or effected with the aid of appropriate catalysts. Furthermore, the present volume has to cover a realm of pericyclic transformations, including electrocyclizations and sigmatropic rearrangements, the entire field of metathesis, hydroarylation and hydrovinylation, as well as the prolific area of reductive coupling chemistry.

This truly Herculean task has only been possible with the help of a panel of expert authors who kindly agreed to share their knowledge with the interested reader. Through their efforts, the 36 chapters of volume 5 capture the crux of the topics mentioned above and provide a highly inspiring source of information. To this end, the individual articles provide only a brief summary of the background, just enough to familiarize a novice reader with the essence of all prior knowledge; rather, they are clearly focused on the methodological advances made during the past two decades. The preparative scope of the presented methodologies is illustrated by a host of specific applications, including many examples of target oriented syntheses of natural products and other biologically active compounds. Great care has been taken that the corresponding schemes and figures allow the essentials of such transformation to be easily grasped.

In line with the general mission of this reference work, the thematic coverage is sufficiently 'comprehensive' in order to demonstrate the progress in a given field and to provide useful information even for a specialist; yet, the flood of material has been filtered by the highly knowledgeable authors to the extent that a less experienced practitioner will not get lost in a morass of details. Although different approaches were taken to reach this goal, I am convinced that the present volume in its entirety provides an invaluable service to all of us.

Arguably, the most important message conveyed by this volume, is the fact that it showcases the truly impressive ability of the chemical community to innovate, even in a field that has already experienced almost two centuries of intense scrutiny in academia and industry alike. A few examples must suffice here to illustrate this notion (**Figure 1**). In the first edition of Comprehensive Organic Synthesis published in 1991, metathesis filled 1 chapter of no more than 13 (!) pages. Two decades and a Noble Prize later, four massive chapters were needed to portray the current state of the art in this timely and exceptionally prolific field of research. During the same period, hydroarylation as well as cycloisomerization chemistry were revolutionized by the advent of carbophilic Lewis acids, notably those based on platinum and gold. But even more 'traditional' areas clearly demonstrate the inexorable force of chemical research: suffice it to mention, *pars pro toto*, the venerable Diels–Alder reaction. Whereas the 1991 edition contained hardly any successful cases of catalytic asymmetric [4+2] cycloadditions, the pertinent chapters in the current

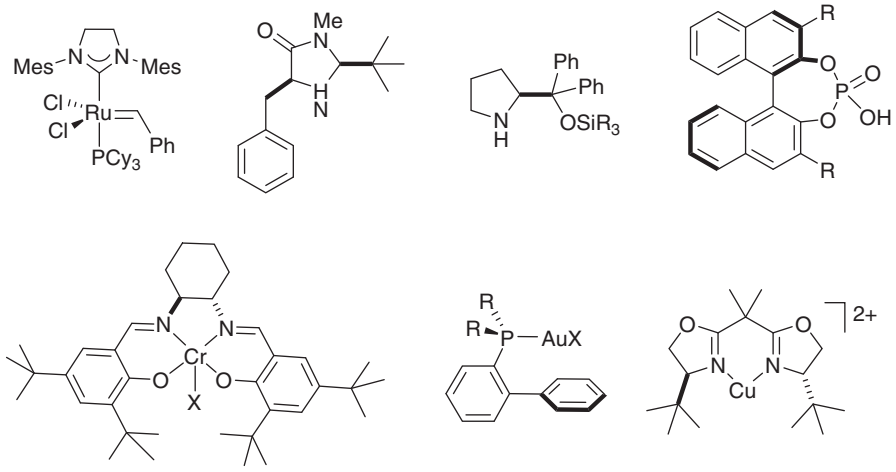


Figure 1 The inexorable power to innovate is exemplified by a small selection of catalysts that were basically unknown at the time when the first edition of Comprehensive Organic Synthesis was published; only two decades later, each of them stands for a prosperous field of research, as witnessed by the many different applications discussed in the present volume.

edition are dominated by this highly enabling methodology. A closer look also makes clear that contemporary asymmetric catalysis does not exclusively rely any longer on cleverly designed new organometallic entities or on the use of enzymes, but also embraces organocatalysis in its broadest sense, which constitutes an entirely new and rapidly growing branch of chemistry that was virtually inexistent two decades ago.

These are perhaps particularly striking examples but definitely not the only illustrations of the fabulous progress that continues to be made. The careful reader will appreciate that basically all chapters contained in this volume bear testimony to the vibrant and unabated development of organic chemistry in general and organic synthesis in particular. Therefore we have every reason to be optimistic about the future of our scientific discipline.

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5.01 Ene Reactions with Carbon Enophiles – Metallo-Ene Reactions

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Glossary

β-H-elimination *syn*-Specific deinsertion of an unsaturated ligand with concomitant transfer of the β-hydrogen to a vacant coordination site of a metal complex.

Concerted reaction A single-step reaction through which reactants are directly transformed into products, i.e., without involvement of any intermediates.

Domino reaction A series of more than two bond forming elementary steps, often proceeding through reactive intermediates, where all reactants and catalysts or activators are present from the very beginning and which occur without isolation of intermediates.

Oxidative addition The insertion of a metal complex into a covalent bond involving formally an overall two-electron loss on one metal or a one-electron loss on each of two metals.

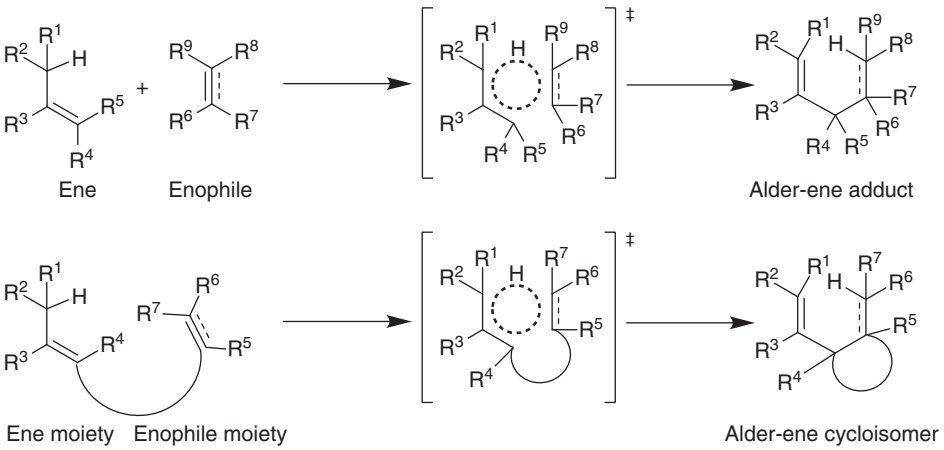
Reductive elimination The reverse of oxidative addition.

Transmetallation An organometallic elementary reaction that involves the transfer of ligands from one metal to another.

5.01.1 Introduction

Ene reactions are very important, versatile, and elegant bond forming reactions, which can be conducted with an enormous variety of substrates that are easily accessible. Therefore, ene reactions have been extensively reviewed in the past.[1] Ene reactions involving alkenes or alkynes as enophiles are called Alder-ene reactions. A special case, where the ene partner results from a population of an enol tautomer and which only proceeds in an intramolecular fashion, is the Conia-ene reaction.[2]

Alder-ene reactions either proceed as intermolecular additions of an ene component and an enophile furnishing an Alder-ene adduct or, intramolecularly, as a cycloisomerization of a substrate containing an ene and an enophile moiety giving rise to the formation of a cycloisomer (**Scheme 1**). If these reactions are pericyclic, they proceed in a concerted fashion via a cyclic transition state involving the rearrangement of six electrons (4π- and 2σ-electrons). Depending on the substitution pattern of both π-systems, Alder-ene reactions can be stereogenic because both combining sp^2-centers become tetrahedral. In addition, the migrating hydrogen from the ene component stereospecifically generates a double bond in the case of alkynyl enophiles or an sp^3-center in the case of alkenyl enophiles. In either case, a double bond is established in the former ene moiety.

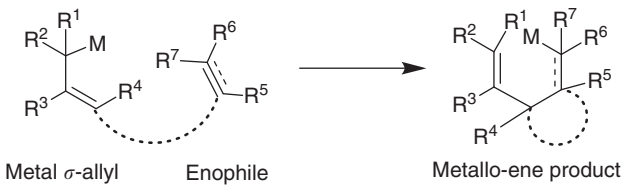


Scheme 1 General mechanistic rationale of concerted Alder-ene reactions.

Mechanistically, uncatalyzed Alder-ene reactions might occur either pericyclically or stepwise. As in the case of Diels–Alder reactions, the favorable electronic combinations implement Alder-ene reactions under normal (electron-rich ene and electron-deficient enophile) or inverse electron demand (electron-deficient ene and electron-rich enophile). Alder-ene reactions can also be catalyzed with Lewis acids in the case where an electron-deficient functionality with Lewis-basic centers is present in either substrate. By lowering the lowest unoccupied molecular orbital (LUMO), asynchronous pericyclic pathways may be still followed.[3] However, combinations of electroneutral enes and enophiles display notoriously sluggish reactivity due to their high activation energy. They have been and still are often reacted under vigorous thermal conditions.

The advent of homogenous transition metal catalysis and the deeper comprehension of the underlying mechanistic principles have considerably enabled the development of formal Alder-ene processes by involvement of carbophilic metal complexes that are capable of coordinating and activating alkenes, alkynes, and allenes as weakly Lewis-basic ligands toward carbon–carbon bond formation via stepwise sequences. Although intramolecular Alder-ene cycloisomerizations have been already known since 25 years, metal catalyzed Alder-ene additions as bimolecular reactions have evolved in the 1990s.

Introduced by Oppolzer the formal replacement of hydrogen by a metal leads to 'metallo-ene' reactions (Scheme 2).[4] Mechanistically, a metal allyl species undergoes a carbometallation of an enophile giving rise to the formation of the metallo-ene adduct, which proceeds via intra- or intermolecular addition or elimination processes. Most interestingly, allyl metal species can be either generated stoichiometrically, or with certain transition metal complexes, in a catalytic fashion by oxidative addition from a suitable precursor.



Scheme 2 General mechanistic concept of metallo-ene reactions.

In this chapter only the developments of ene reactions with carbon enophiles in the past 20 years are considered. Therefore, only the formation of carbon–carbon bonds between ene components and alkenes, alkynes, and allenes are treated. First, new developments in the field of Alder-ene additions and cycloisomerizations are discussed and then metallo-ene reactions are presented. All other ene reactions are discussed in separate chapters.

5.01.2 Alder-Ene Additions

5.01.2.1 Alkenes as Enophiles

Alder-ene reactions, as all pericyclic processes, have been a field of theoretical and mechanistic studies ever since their discovery. More detailed insights in the course of the title reactions have been obtained in the past two decades, not least because of the rapid development and precision of computational methodologies. In particular, the nature of the transition state has been investigated in several remarkable studies.

Mechanistic investigations on model ene reactions by computations, also in comparison,[5,6] have been performed on various levels of theory and important insights on the atomistic pathways have been obtained. Besides predicting stereochemical features by force field models,[7] density functional theory (DFT) and *ab initio* computations have become state-of-the-art tools for studying ene reactions. For instance, an *ab initio* molecular orbital study on the ene reaction of methyl acrylate and propene has revealed a less asynchronous character in the bond reorganization as compared with the parent ene reaction.[8] In addition *exo* and *endo*-transition state structures suggest that the intrinsic *exo*/*endo* selectivity in the ene reactions is not as obvious as in the Diels–Alder reactions. On a similar basis, *ab initio* and DFT computations could support various degrees of asynchronicity. In particular, cyclopropene as an enophile accounts – through its relief of strain energy – for the preference of an *endo*-transition state.[9,10] In a combined experimental and theoretical study on the ene reaction between 1-alkenes and maleimide, an excellent agreement with *ab initio* post-Hartree Fock computations was achieved giving a deeper insight into transition state geometries.[11]

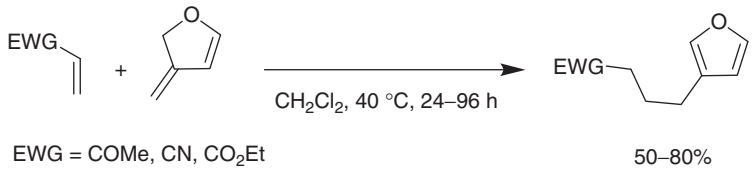
Several mechanistically challenging ene-processes and predictions were tackled by computational studies. For the elusive, highly strained bicyclo[2.1.1]hex-1-ene, the ene reaction with 2-phenyl prop-1-ene as a trapping process was performed experimentally and investigated by high-level DFT computations.[12] Recently, theoretical analyses of ene reactions between propene and several all-carbon or carbon-heteroatom enophiles were performed to quantitatively assign the reactivity on high levels of DFT and *ab initio* theory.[13,14] In addition, a computer-assisted mechanistic evaluation of ene and retro-ene reactions was also successfully carried out to allow predictions of the regioselectivity to be made based on the relative magnitude of frontier orbital coefficients at the interacting termini of the reactants.[15] Furthermore, the influence of geminal bonds of the reactants in pericyclic reactions was theoretically investigated. In a computational study Naruse et al.[16] have elaborated that the interaction between the σ-orbital at the *Z*-configurated position of the double bond of propene as the ene component and the π-orbital of ethylene as the enophile is bonding, whereas the corresponding *Z*-configurated position of the double bond of the ene component should be antibonding. Therefore, according to this theoretical analysis, an increase of the electron donor capability of the *Z*-configurated σ-bond predicts an enhanced reactivity. Finally, based on computationally modeled transition state analogs, Hase et al.[17] have devised and prepared antibodies for catalyzing an ene reaction between maleimide and 1-decene.

Experimental investigations, syntheses as well as kinetic studies, were performed to further scrutinize the concerted nature of these pericyclic processes. A mechanistic issue in concerted, electronically unsymmetrical ene reactions is always the nature of the transition states, i.e., whether either the carbon–carbon bond or the transfer of the allylic hydrogen occurs first. Huisgen and Brückner[18] have employed 2,2-bis(trifluoromethyl)ethylene-1,1-dicarbonitrile (BTF), a highly electrophilic enophile for ene reactions even with unactivated ene partners at room temperature, as a mechanistic probe to permit a classification of alkenes and to allow a prediction of the orientation of their ene reactions. Likewise, tetracyanoethylene (TNCE) was found to undergo a regiospecific ene reaction with γ-alkyl substituted allyltrimethylsilanes.[19] Deuterium as well as ^{13}C labeling in an experimental and computational study on kinetic isotope effects in the ene reaction of allyl benzene as an ene component and maleic anhydride as an enophile support the concerted nature of this process.[20] Finally, Lewis acid catalyzed ene reactions are strongly affected by the solvent polarity and a kinetic study supported the pronounced zwitterionic character of the transition state.[21] In addition, the rates of the model ene reaction between β-pinene and methyl acrylate catalyzed by various Lewis acids led to a linear free energy relationship between the experimentally determined ΔG and the computed LUMO energy as a mechanistic test for the influence of a Lewis acidic catalyst on a chemical reaction.[22]

All these findings, obtained by computational and experimental work, not only have sharpened the mechanistic picture of Alder-ene reactions but also have further paved the way to the rational design of pericyclic key steps in all kinds of synthetic endeavors.

5.01.2.1.1 Electron-deficient alkenes as enophiles

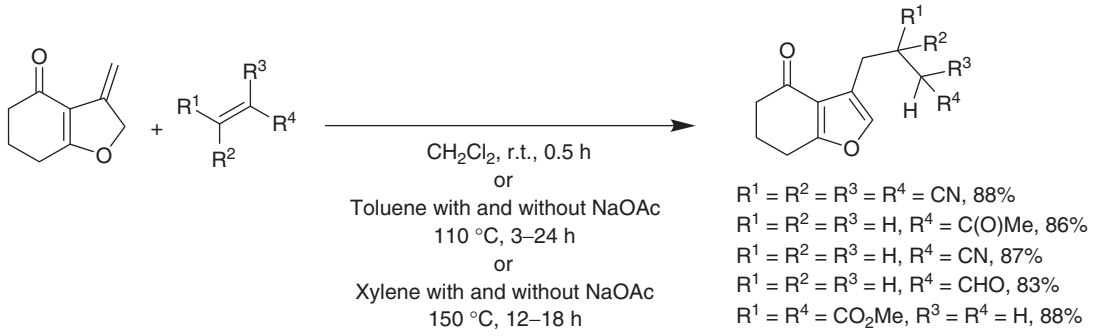
Several electron-deficient alkenes readily react with 3-methylene-2,3-dihydrofuran as the ene component to give the corresponding 3-substituted furans in good yield (Scheme 3).[23] The driving force is definitely the accompanying aromatization, which was also operative when C_{60} was employed as an enophile.[24]



Scheme 3 Ene reaction of electron-deficient alkenes with 3-methylene-2,3-dihydrofuran.

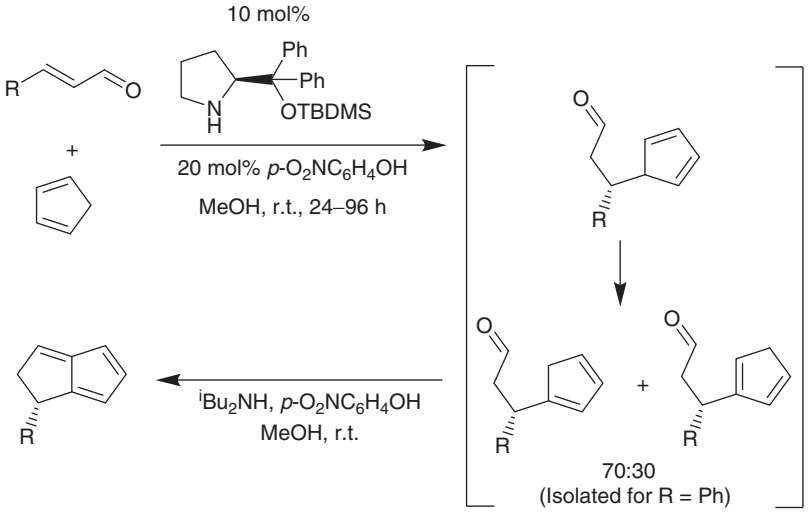
Ojida et al.[25] demonstrated the efficient synthesis of annulated furans with various 3-substituents from various electron-deficient alkenes as enophiles and 3-methylene-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one as ene component (Scheme 4).

Iminium salt formation enhances the electrophilicity of an α,β-unsaturated aldehyde by considerably lowering the LUMO. This circumstance has stimulated organocatalytic approaches in pericyclic methodologies. The iminium salt intermediate formed for cinnamic aldehydes and diphenylprolinol silyl ether allows for an excellent one-pot synthesis of chiral bicyclo[3.3.0]octatrienes



Scheme 4 Ene reaction of electron-deficient alkenes with 3-methylene-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one.

via an organocatalytic ene reaction followed by a base mediated cyclocondensation of the cyclopentadiene intermediate (Scheme 5).[26]



R = Ph, 63% (95% *ee*)
R = 2-naphthyl, 79% (98% *ee*)
R = 1-(3,4-methylenedioxo)phenyl, 67% (99% *ee*)
R = *p*-MeOC$_6$H$_4$, 66% (99% *ee*)
R = *p*-BrC$_6$H$_4$, 70% (99% *ee*)
R = 2-furyl, 51% (97% *ee*)
R = 2-thienyl, 43% (98% *ee*)

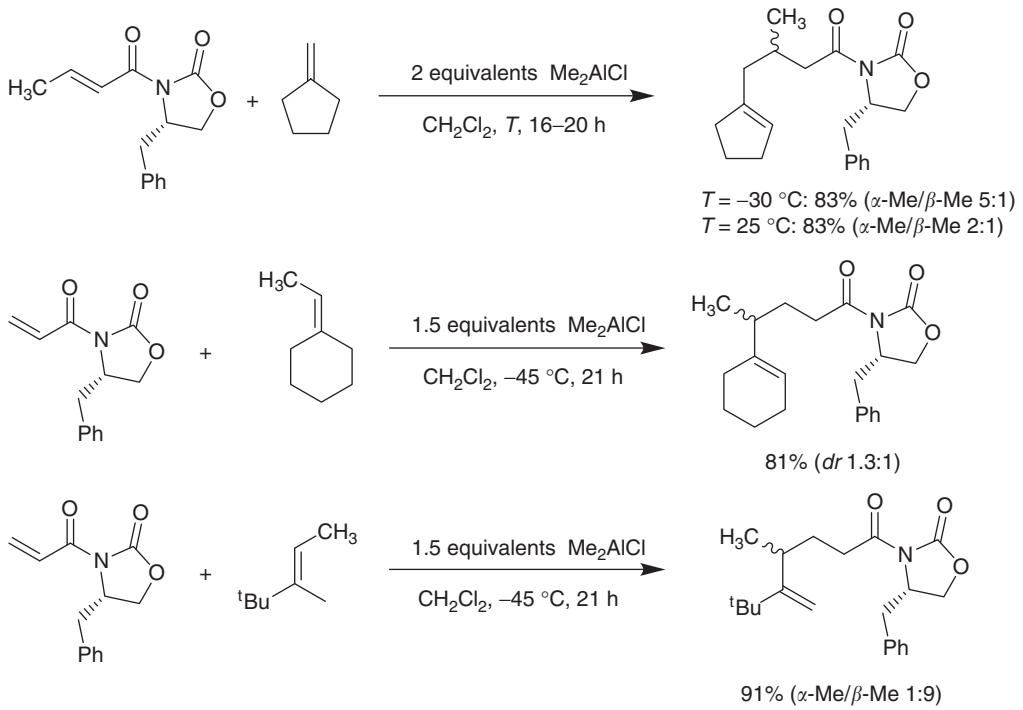
Scheme 5 One-pot synthesis of chiral bicyclo[3.3.0]octatrienes by way of a diphenylprolinol silyl ether-mediated ene-type reaction.

Snider and Zhang[27] showed that chiral α,β-unsaturated *N*-acyloxazolidinones as enophiles react under Lewis acid catalysis with ene components with moderate to excellent asymmetric induction, which depends on the alkene structure and the reaction conditions (Scheme 6).

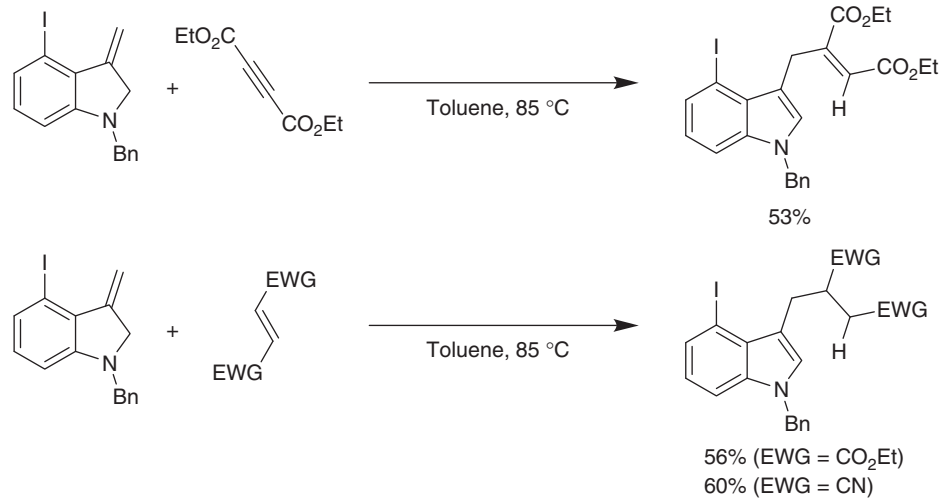
N-Benzyl-4-iodo-3-methyleneindoline, prepared by zirconium-mediated iodo-alkenylation of *ortho*-lithiated *N*-allyl-*N*-benzyl aniline, is an excellent ene partner for intermolecular Alder-ene reactions with activated enophiles, giving rise to the generation of 3,4-disubstituted iodoindole derivatives (Scheme 7).[28]

The advent of domino processes has considerably fertilized the conceptual implementation of pericyclic key steps including the Alder-ene reaction. Just recently, Komeyama et al.[29] have disclosed a domino ene-hydroamination sequence of amino olefins and amino allenes with enophiles using Bi(OTf)$_3$ as a Lewis acid catalyst, which gives rise to functionalized pyrrolidines and piperidines in good yields (Scheme 8).

4-Vinylimidazoles are a peculiar type of electron-rich dienes that readily undergo [4 + 2]-cycloadditions with *N*-phenyl maleimide. The resulting cycloadduct either aromatizes by a formal 1,3-H-shift or via a subsequent ene reaction with excess



Scheme 6 Asymmetric Lewis acid catalyzed ene reactions of α,β-unsaturated *N*-acyloxazolidinones.



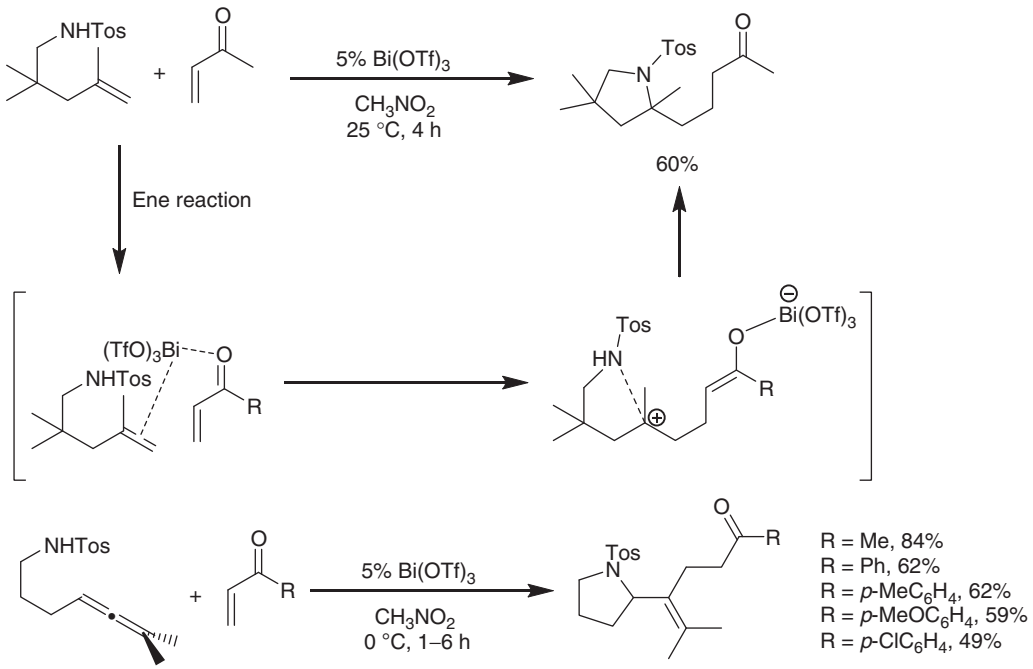
Scheme 7 3,4-Disubstituted indoles via an Alder-ene reaction.

N-phenyl maleimide as enophile (Scheme 9).[30] The product ratios depend on the electronics of the substituent R, the solvent, and the reaction temperature.

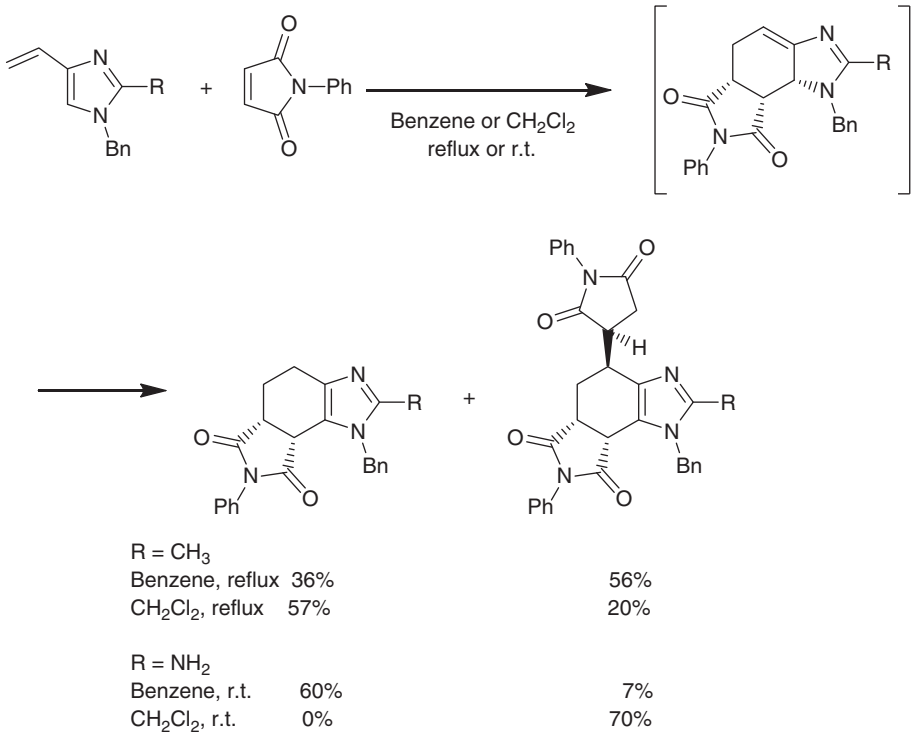
1,4-Bissilylated 1,3-butadienes are densely functionalized building blocks that can undergo pericyclic and organometallic elementary reactions. Li et al.[31] have recently demonstrated the domino-ene-allylation reactivity of these dienes with *N*-ethyl maleimide as an enophile, furnishing complex substituted tricycles (Scheme 10). The same group has elaborated this key steps into domino reactions consisting of ene/allylation/ene and ene/allylation/Diels–Alder sequences (Schemes 11 and 12).[32] In the latter case it was even possible to conclude the domino sequence by a second intramolecular allylation to give a complex polycyclic framework (Scheme 13).

Besides carba-ene partners, hetero-ene components as exemplified in the Conia-ene reaction,[2] have also found considerable interest during the past two decades, in particular, in the development of heterocycle syntheses.

Heterocyclic ketene aminals bearing an electron-withdrawing functionality at the β-position are well-suited to undergo aza-ene reactions with enones, thus opening an efficient entry to imidazo[1,2-*a*]pyridine derivatives (Scheme 14).[33] With methyl vinyl



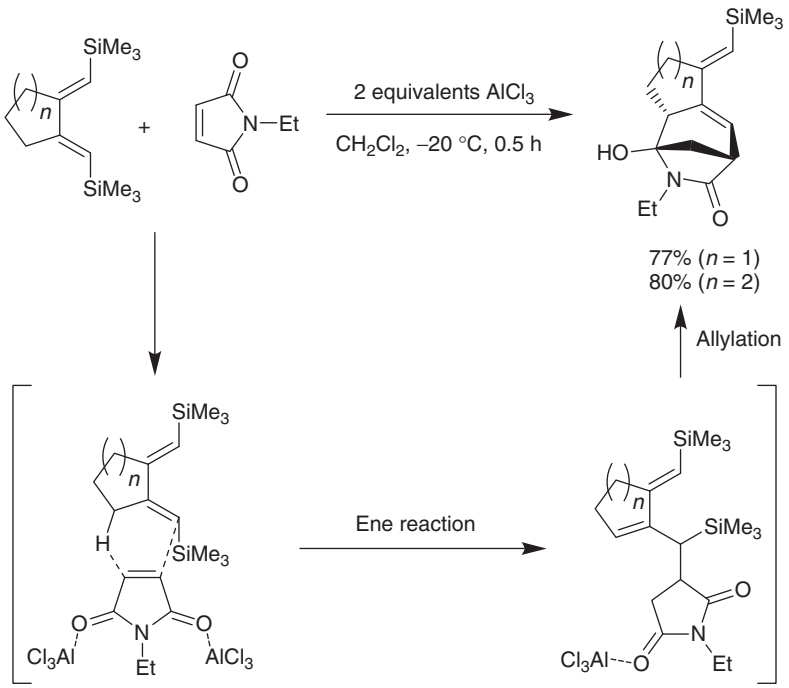
Scheme 8 Domino ene-hydroamination sequence.



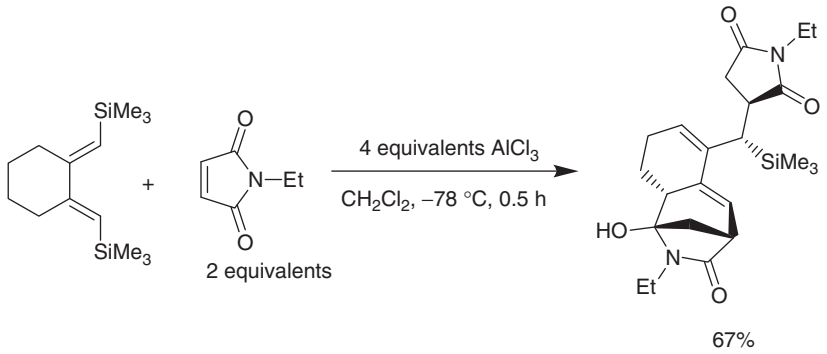
Scheme 9 Domino [4 + 2]/ene reaction sequence starting from 4-vinylimidazoles as dienes.

ketone as the enophile, the aza-ene-cyclization sequence proceeds twice and terminates under acyl cleavage in wet acetonitrile to furnish imidazo[1,2,3-*ij*][1,8]naphthyridinium salts (Scheme 15).

The *in situ* formation of the enophile via Knoevenagel condensation was elaborated by Wen et al.[34] and has opened new avenues to multicomponent syntheses of imidazo[1,2-*a*]pyridines and benzo[*b*]imidazo[1,2,3-*i,j*][1,8]naphthyridines via a domino sequence consisting of an aza-ene-cyclization and subsequent intramolecular nucleophilic aromatic substitution (Scheme 16).



Scheme 10 Domino ene reaction/allylation of 1,4-bissilylated 1,3-butadienes.



Scheme 11 Domino ene/allylation/ene reaction sequence.

5.01.2.1.2 Strained alkenes as enophiles

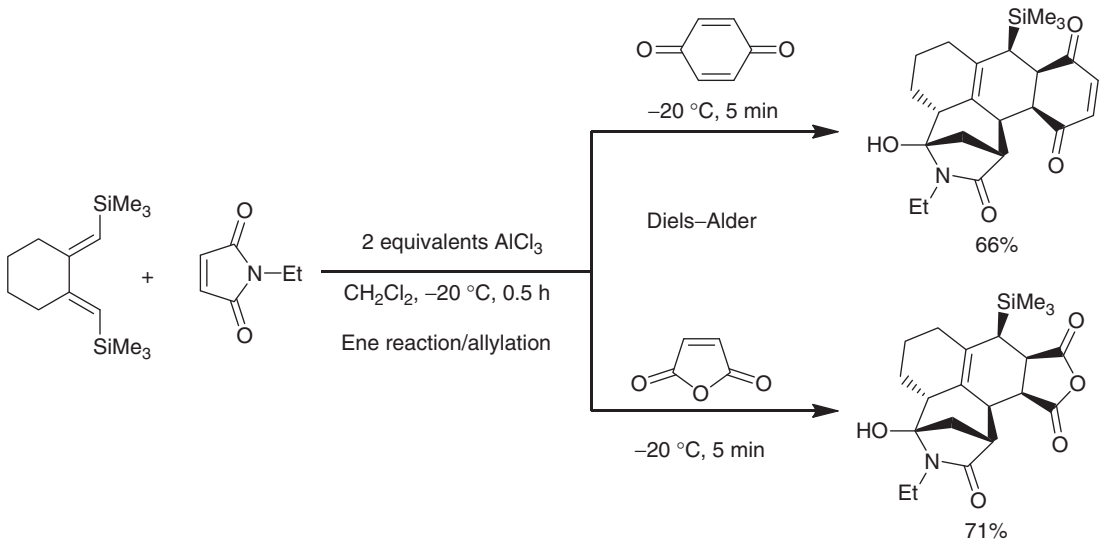
The reactivity of enophiles significantly increases through implemented strain, which directly influences the positioning of the frontier molecular orbitals. Therefore, in the past two decades, strained alkenes have found entry into Alder-ene reactions as enophiles that do not require catalysis in order to reach high rates. In particular, cyclopropenes are well known to readily undergo ene reactions.[35]

Ashirov et al.[36] have impressively demonstrated the use of 3-methylcycloprop-1-ene-3-carbonitrile as a strained enophile that can be favorably applied in prenylations of (–)-*β*-pinene and *R*-(–)-carvone (Scheme 17).

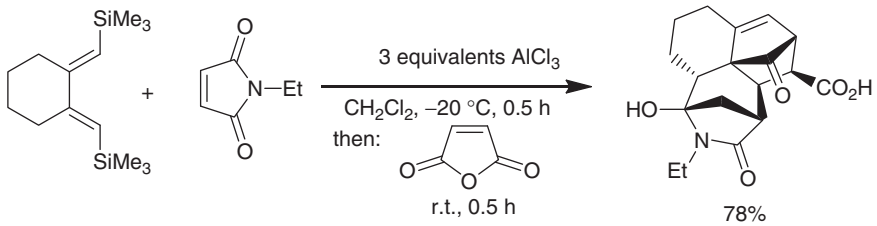
Lodochnikova et al.[37] have discovered a domino sequence where excess 1-methyl-2-cyclopropene-1-carbonitrile was successfully transformed with 1,4-cyclohexandiene or allocimene to give the products of an Alder-ene and a Diels–Alder reaction (Scheme 18). The strained cyclopropene derivative acts first as an enophile and then as a dienophile, giving rise to the formation of the 2:1 adduct as a single diastereomer.

Self-tetramerization of 3-methyl-3-cyanocyclopropene was observed at elevated temperatures. A mechanistic reasoning based on DFT modeling suggests biradical species as intermediates in the course of the process that occurs via cyano migration.[38]

1-Phenylcyclopropene can be readily prepared by bromine–lithium exchange of 1,1,2-tribromo-2-phenylcyclopropane with methyllithium followed by protonation of the trapping cyclopentadiene (Scheme 19).[39] Under these trapping conditions, Lee and Chang also observed that 1-phenylcyclopropene undergoes a dimerization via an *endo*-transition state of an Alder-ene



Scheme 12 Domino ene reaction/allylation/Diels–Alder sequence.



Scheme 13 Domino ene reaction/allylation/Diels–Alder/allylation sequence.

reaction. Without a trapping diene, 1-phenylcyclopropene predominantly trimerizes via the Alder-ene pathway in an *endo-endo*-fashion (Scheme 20). The minor dimer, which was detected under these conditions and identified by subsequent cyclobutane reversion and oxidation, is the product of a formal [2 + 2]-cycloaddition.

1-Trimethylsilyl-3-phenylcyclopropene, which is generated *in situ* from a tribromo phenyl cyclopropane by bromo-lithium exchange and subsequent trapping with trimethylsilyl chloride, readily dimerizes at room temperature to give an Alder-ene product in the absence of another ene partner as a trapping agent (Scheme 21).[40] At temperatures lower than –50 °C, 1-trimethylsilyl-3-phenylcyclopropene is stable toward dimerization; however, the mode of preparation already has a considerable influence on the yield. 1-Trimethylsilyl-3-phenylcyclopropene is the major product from the *trans*-dibromo cyclopropane, whereas the allene or the isomeric alkyne is preferentially formed from the *cis*-diastereomer (Scheme 22).

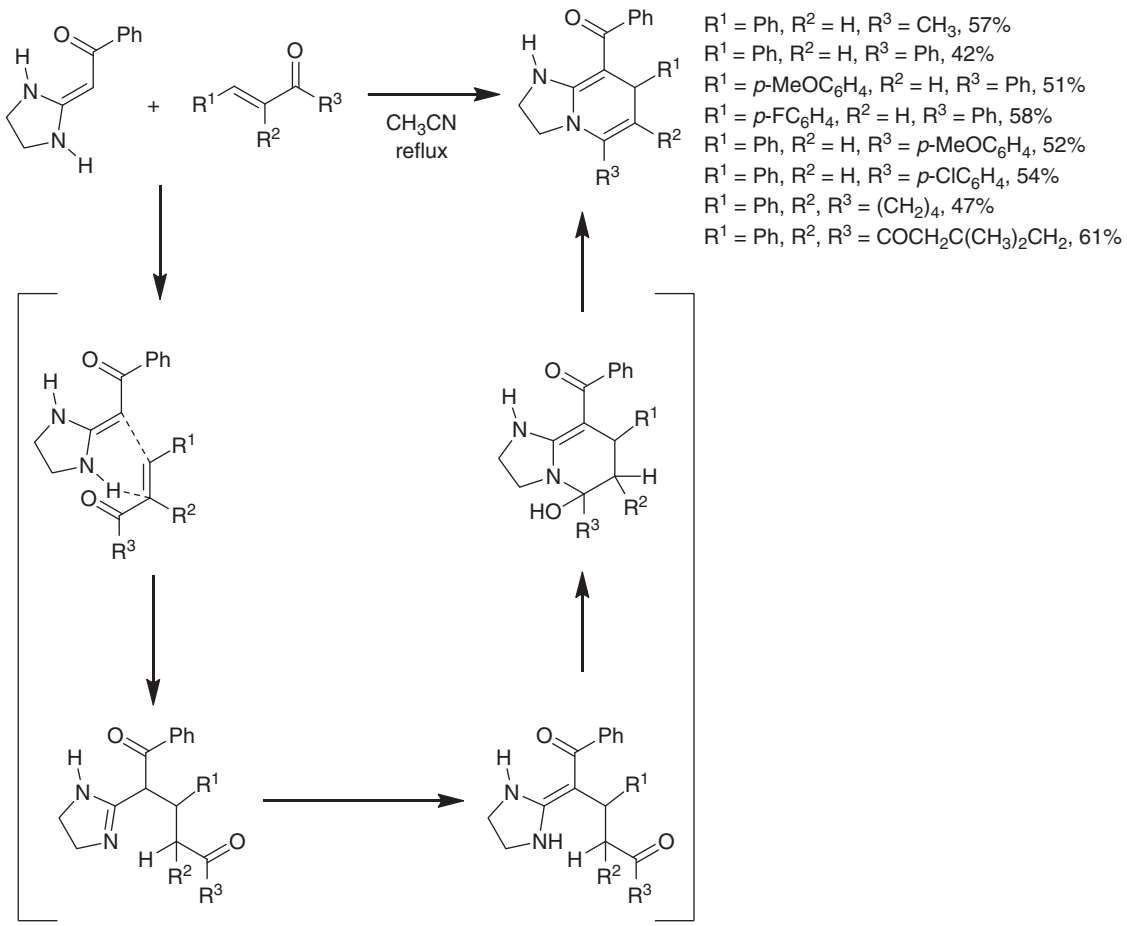
In the absence of a suitable trap, 1-trimethylsilyl-3-phenylcyclopropene reacts in highly stereocontrolled ene reactions to give a dimer and trimers (Scheme 23). The dimer can be trapped by a Diels–Alder reaction with cyclopentadiene.

When embedded in bicyclic and polycyclic frameworks, the reactivity of cyclopropenes is considerably increased. Therefore, characteristic alkene trapping reactions, such as Diels–Alder and ene reactions, can be well applied as an indirect evidence for the presence of highly strained alkenes.

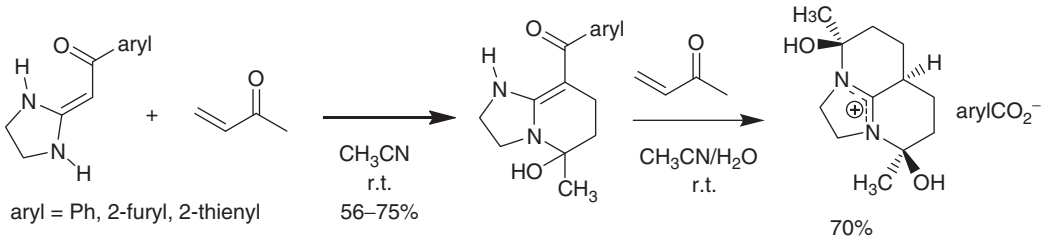
Graf and Szeimies[41] have disclosed several ene trapping reactions. Starting from 1,6-dibromotricyclo[3.1.0.$0^{2,6}$]hexane, bromine–lithium exchange at low temperatures followed by elimination of lithium bromide generated the highly strained tricyclo[3.1.0.$0^{2,6}$]hex-1(6)-ene, which undergoes an instantaneous ene reaction with several allyl derivatives (Scheme 24).

Billups et al.[42] generated bicyclo[4.1.0]hept-1,6-ene by fluoride-induced elimination in the gas phase, which immediately dimerized in an Alder-ene reaction to give two diastereomeric dimers **1** and **2** in a 1:2 ratio (Scheme 25). Likewise, bicyclo-[4.1.0]hept-1,7-ene dimerizes to give only diastereomer **1**.[43] Although the corresponding 7-chlorobicyclo[4.1.0]hept-1,7-ene rather undergoes a cyclopropene-vinyl carbene rearrangement, the homologous 8-chlorobicyclo[6.1.0]oct-1(8)-ene gives rise to the formation of the expected dimer by an Alder-ene reaction.[44] In a similar fashion, bicyclic 1,3-fused 2-(trimethylsilyl)cyclo-prop-1-enes give rise to the formation of dimers in high yields.[45]

Matsuura et al.[46] have isolated cycloprop-2-ene carboxylic acid from the toxic Asian mushroom *Russula subnigricans*. Interestingly, the toxicity, leading to fatal rhabdomyolysis (damage of muscle cells), is caused by this small ring trigger. Most amazingly, on polymerization via Alder-ene reaction, the toxicity is completely lost.



Scheme 14 Aza-ene reaction of ketene aminals with enones.



Scheme 15 Double aza-ene reaction with methyl vinyl ketone and subsequent acyl cleavage.

5.01.2.1.3 Fullerenes as enophiles

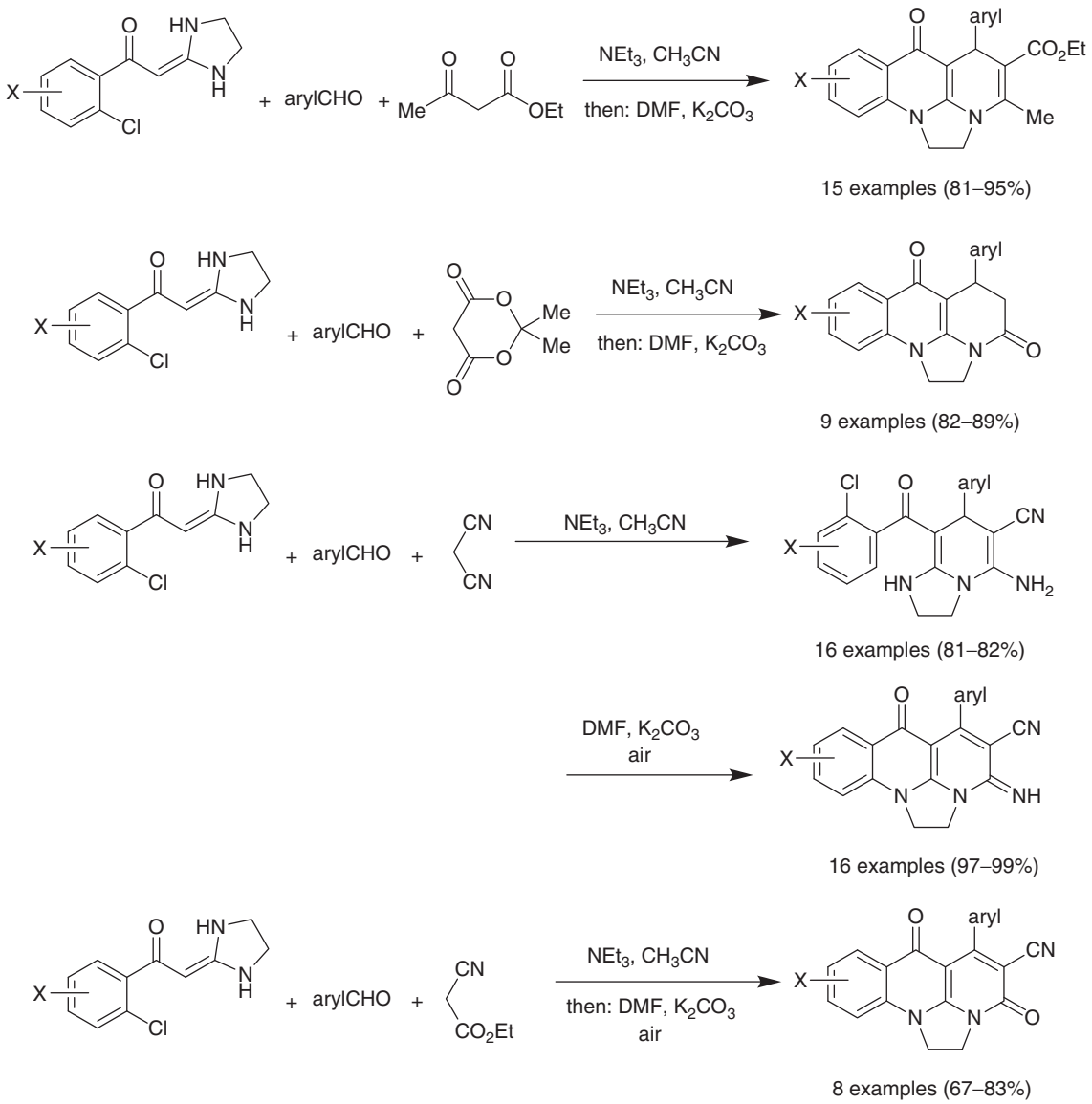
C_{60}-fullerene remarkably combines enhanced enophile reactivity with an unusual globular structural feature. Therefore, after Diels–Alder and [2 + 1] cycloadditions with fullerenes had been developed, it became obvious that ene reactions with fullerenes should also be feasible.

Independently, the groups of Wu[47] and Komatsu[48] reported successful ene reactions with C_{60} as an enophile and allylbenzene derivatives as ene partners at elevated temperatures (Scheme 26). Later, Chronakis and Orfanopoulos[49] determined the C–H breakage as a rate-determining step in the ene reaction of C_{60} with deuterated allyl benzene, hence, making the reversible formation of a charged or dipolar intermediate very likely in this particular case.

5.01.2.2 Alkynes as Enophiles

5.01.2.2.1 Electron-deficient alkynes as enophiles

2-(1-Cyclohexenyl)-1,2-dimethylindole, as well as other 3-vinylindoles,[50] is a favorable substrate for Diels–Alder reactions giving rise to more complex substituted carbazole derivatives. However, dimethylacetylene dicarboxylate (DMAD) not only acts as a



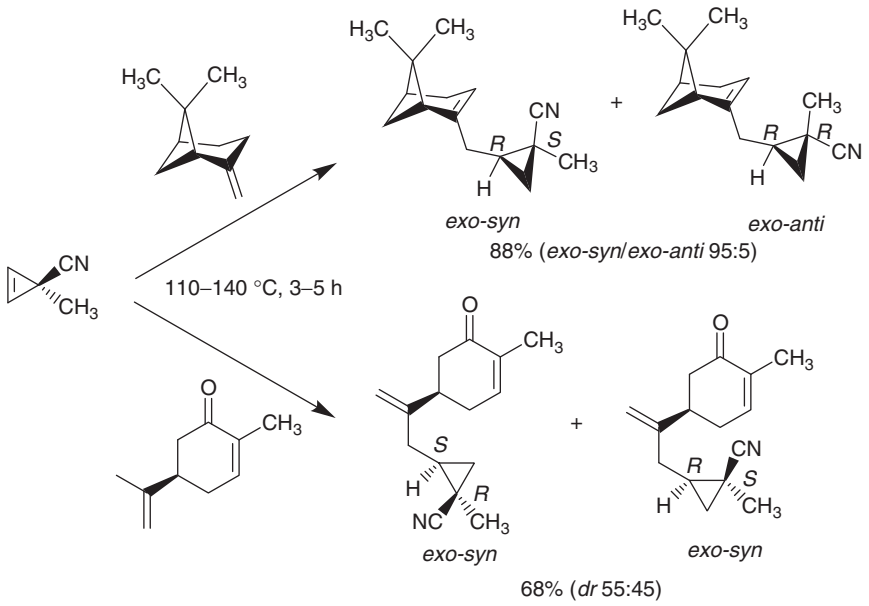
Scheme 16 Multicomponent synthesis of imidazo[1,2-*a*]pyridines and benzo[*b*]imidazo[1,2,3-*i,j*][1,8]naphthyridines.

dienophile furnishing the (4 + 2) adduct in 27% yield, but also as an enophile to give the corresponding ene product in 26% yield as well as a formal Michael type adduct in 10% yield (Scheme 27).[51] A similar dichotomy was also reported for *N*-phenyl maleimide as dienophile/enophile, when 1,2-dimethyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole was applied as a substrate.[52]

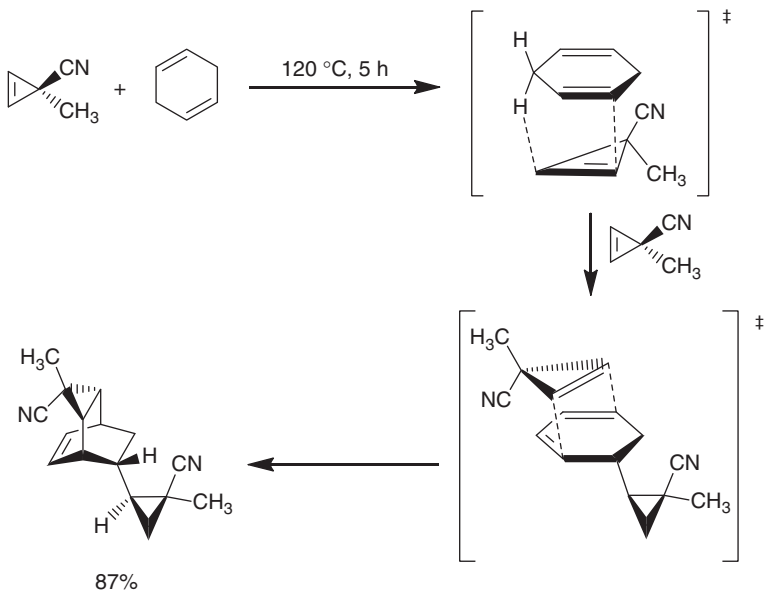
In the course of studies on synthetic transformations of abietic acid methyl ester with dienophiles such as DMAD, Haslinger and Hofner[53] found that DMAD adds to abietic acid methyl ester via an ene reaction to finally give an aromatized product in good yield (Scheme 28).

DMAD is well-suited to act both as a dienophile and as an enophile, a feature that was successfully applied in the formation of polycyclic terpenoid systems.[54] The domino process, where DMAD first reacts as an enophile followed by an intramolecular [4 + 2] cycloaddition of the ene product primarily formed, is known as the Alder–Bong reaction.[55] Giguere et al.[56] have applied this unique sequence, where two regioisomeric ene products are formed, to the stereoselective construction of the methanoazulene framework by acid catalyzed acetal cleavage and rearrangement of the major regioisomer (Scheme 29).

Alkynones behave particularly well as enophiles under Lewis acid catalysis in combination with allyl silanes as ene partners.[57] The group of Thomas has synthesized the C(1)–C(16) fragment of the bryostatins based on this methodology (Scheme 30).[58]



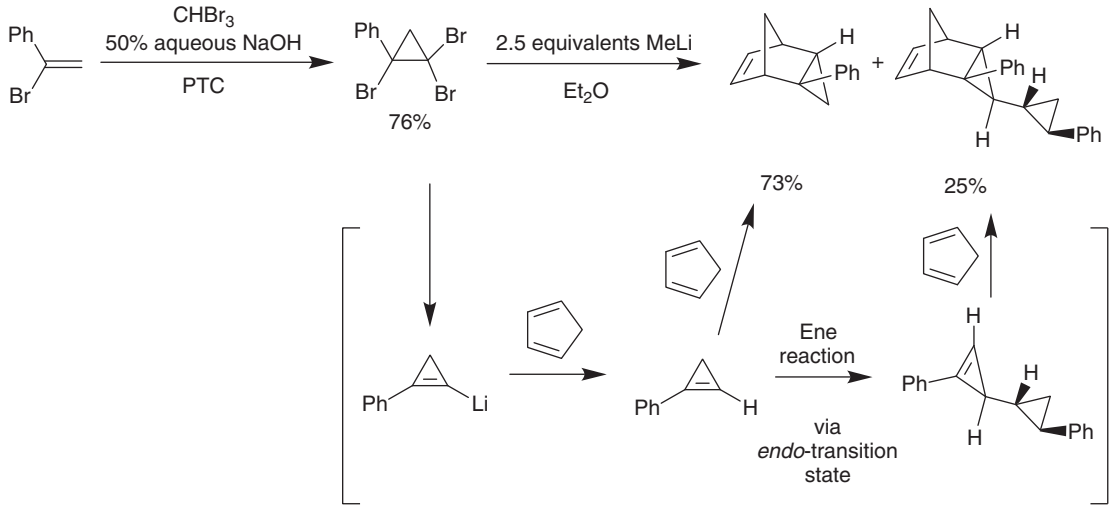
Scheme 17 3-Methyl-3-cyanocyclopropene as a building block for terpene syntheses via Alder-ene reactions.



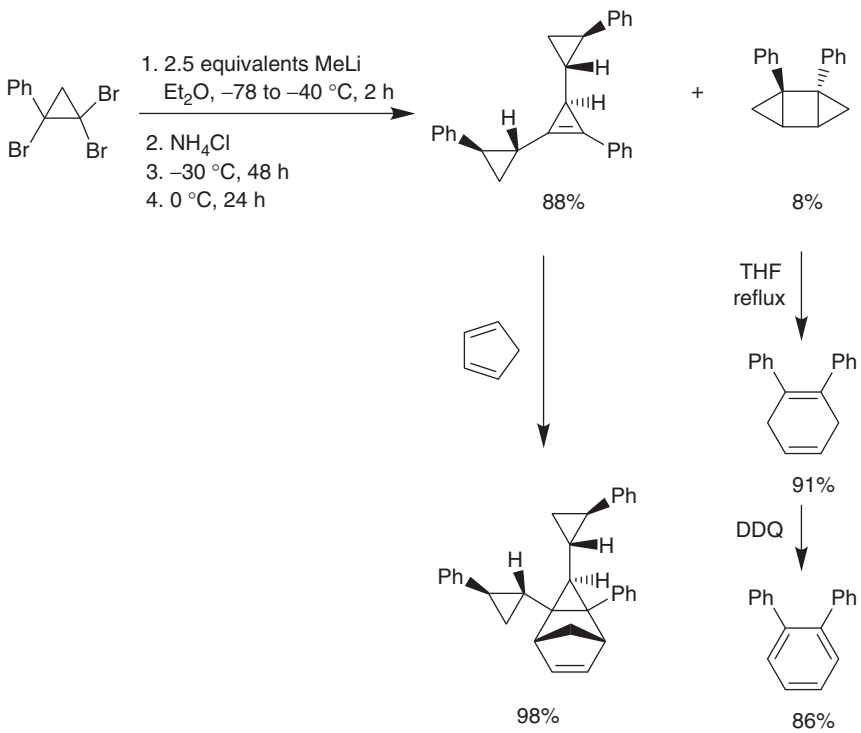
Scheme 18 3-Methyl-3-cyanocyclopropene as an enophile and dienophile in a domino Alder-ene/Diels–Alder sequence.

In a related method, the four step synthesis of (+)-(2*R*,6*R*)-trans-γ-irone was achieved in 68% overall yield starting from (+)-(*R*)-3,4-dimethylcyclohex-2-en-1-one by Monti et al. (Scheme 31).[59] However, in this case the choice of the Lewis acid catalyst is crucial and the allyl silane rather than the vinyl silane becomes the exclusive ene product with Me_2AlCl as catalyst. The synthesis concludes with a regioselective $TiCl_4$-induced protodesilylation.

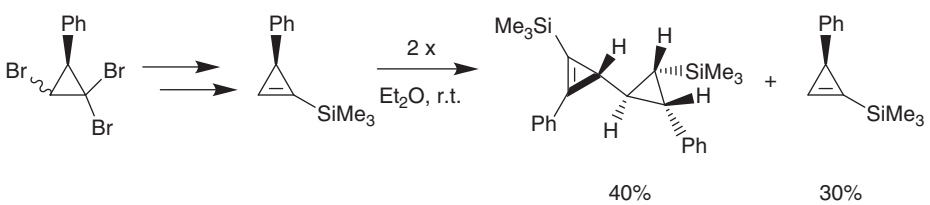
The reactions of heterocyclic ketene aminals with electron-deficient alkenes as enophiles have already been discussed in Chapter 2.1.1. The synthetic potential of reactions with electron-deficient alkynes is comparably broad. Huang and Wang[60] reported on the ene reaction of certain ketene aminals with ethyl propiolate and the subsequent transformation of the ene adducts into annelated heterocyclic systems (Scheme 32, Table 1). Depending on the substrate ratio and on the ring size of the heterocyclic ketene aminal, variable amounts of bisvinylation products can be formed. Later on, the same group scrutinized the substituent effects of this peculiar aza-ene-reaction/δ-lactamization in more detail, also with respect to other electron-withdrawing groups modulating the Michael donor/ene electronics of the aza-ene.[61]



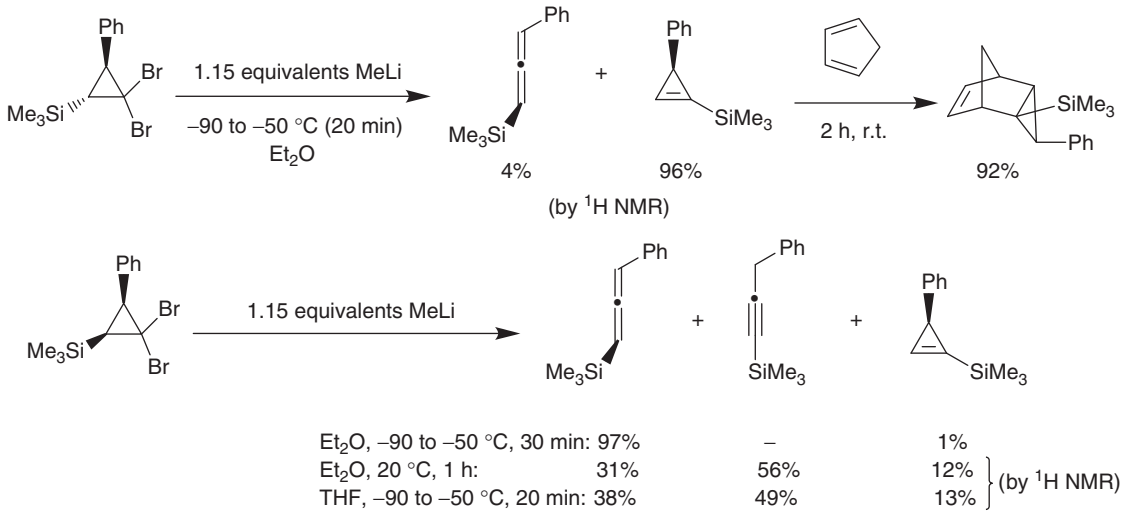
Scheme 19 Formation and trapping reactions of 1-phenylcyclopropene.



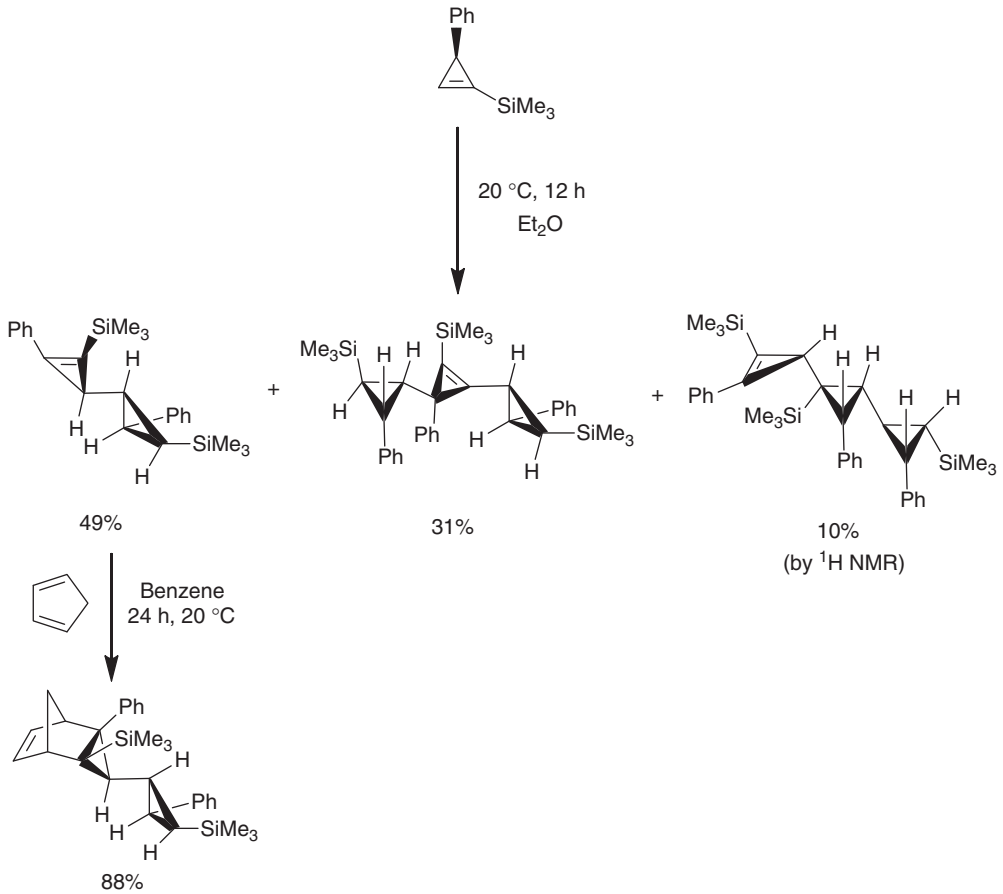
Scheme 20 Alder-ene trimerization of 1-phenylcyclopropene.



Scheme 21 Dimerization of 1-trimethylsilyl-3-phenylcyclopropene via Alder-ene reaction.

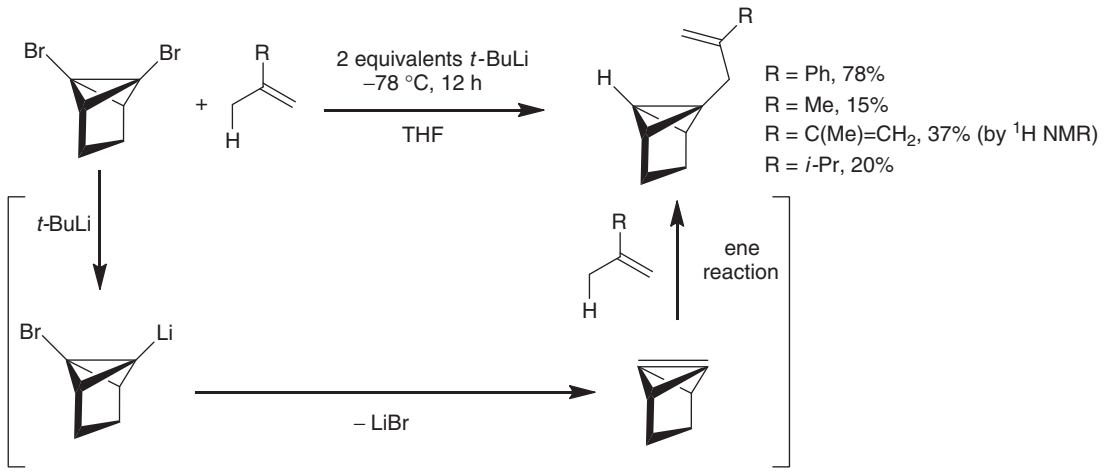


Scheme 22 Formation of 1-trimethylsilyl-3-phenylcyclopropene from 2,2-dibromo-1-trimethylsilyl-3-phenylcyclopropanes.

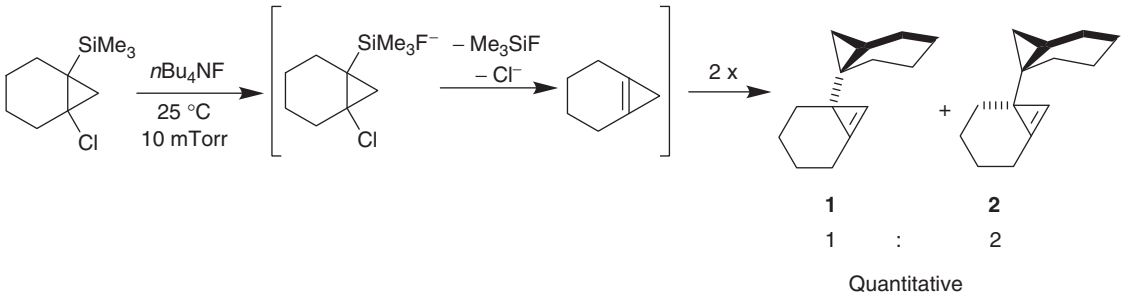


Scheme 23 Di- and trimerization of 1-trimethylsilyl-3-phenylcyclopropene via Alder-ene reaction.

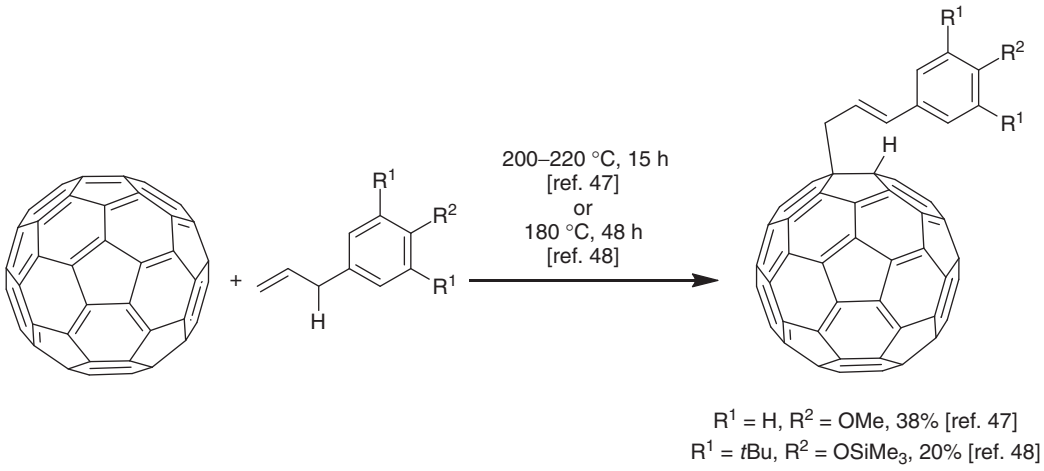
The fairly electron-deficient ethyl 4,4,4-trifluorobut-2-ynoate reacts with cycloheptatriene, a highly versatile dynamic triene (tropylidene-norcaradiene equilibrium), as the ene partner in an intriguing manner. Whereas an electrocyclic ring closure with subsequent Diels–Alder reaction accounts for the formation of the major product, two isomers arising from an initial ene reaction with subsequent intra- and intermolecular pericyclic reactions are formed in constant ratios under thermodynamic and under kinetic control (Scheme 33).[62]



Scheme 24 Generation and *in situ* trapping of tricyclo[3.1.0.0^{2,6}]hex-1(6)-ene by an Alder-ene reaction.



Scheme 25 Generation and dimerization of bicyclo[4.1.0]hept-1,6-ene by Alder-ene reaction.

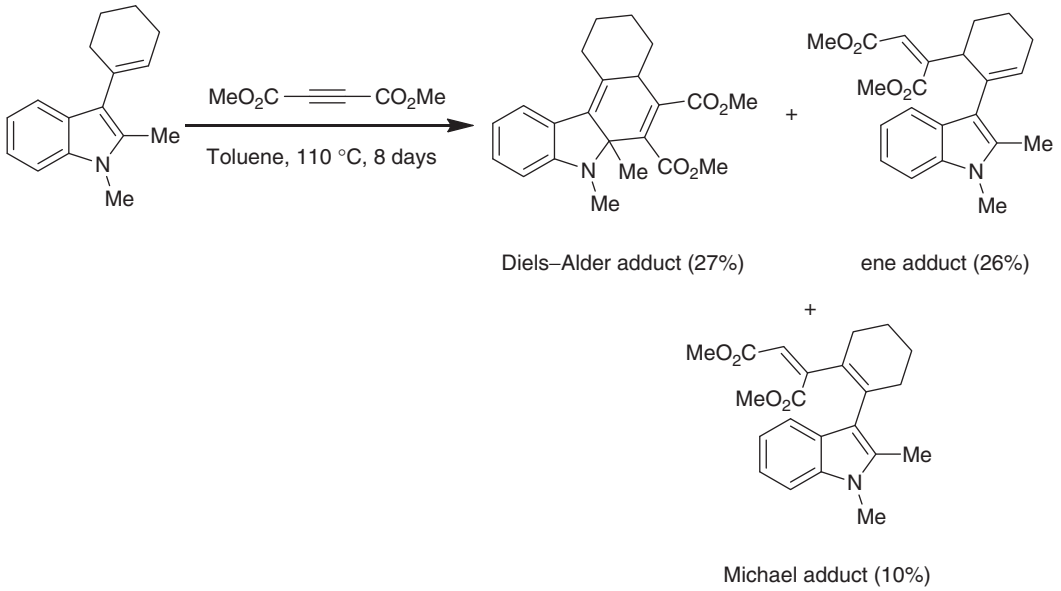


Scheme 26 Alder-ene reactions with C_{60} as an enophile.

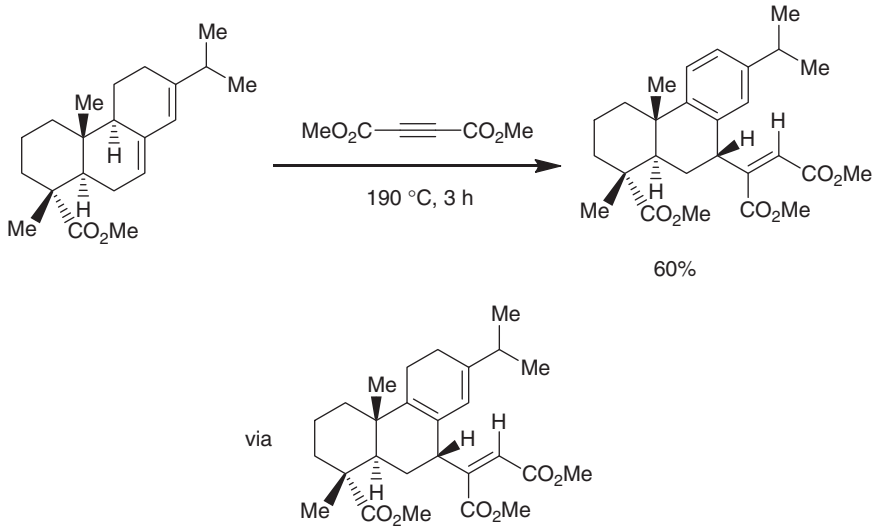
5.01.2.2.2 Electroneutral alkynes as enophiles

As already observed for Diels–Alder reactions, electroneutral alkynes represent relatively unreactive substrates as enophiles within the framework of pericyclic reactivity. This lack of reactivity can be partially compensated by imposing ring strain on the enophile. Protopopova and Galminas[63] have reported the first example of an ene reaction with a strained heterocyclic alkyne as an enophile and cyclopropenecarboxylic acid as an ene partner, which proceeds in good yield (Scheme 34).

However, a major breakthrough in intermolecular Alder-ene-type reactions with unactivated alkynes as enophiles was disclosed by Trost two decades ago, which has opened considerable new avenues toward convergent syntheses of natural and



Scheme 27 Diels–Alder, ene, and Michael dichotomy with DMAD as electron-deficient alkyne.

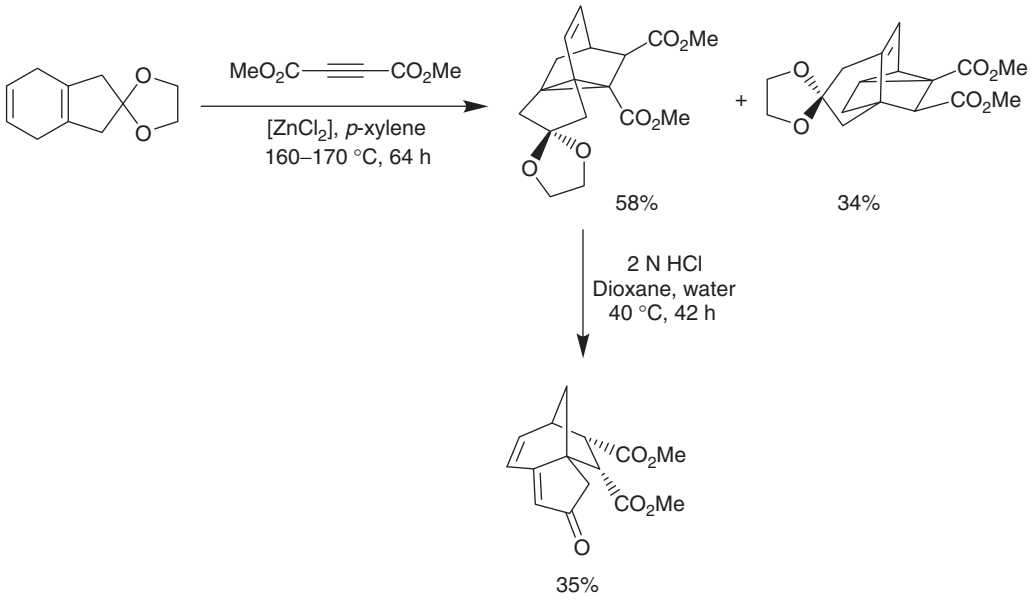


Scheme 28 Ene reaction between abietic acid methyl ester and DMAD as an enophile.

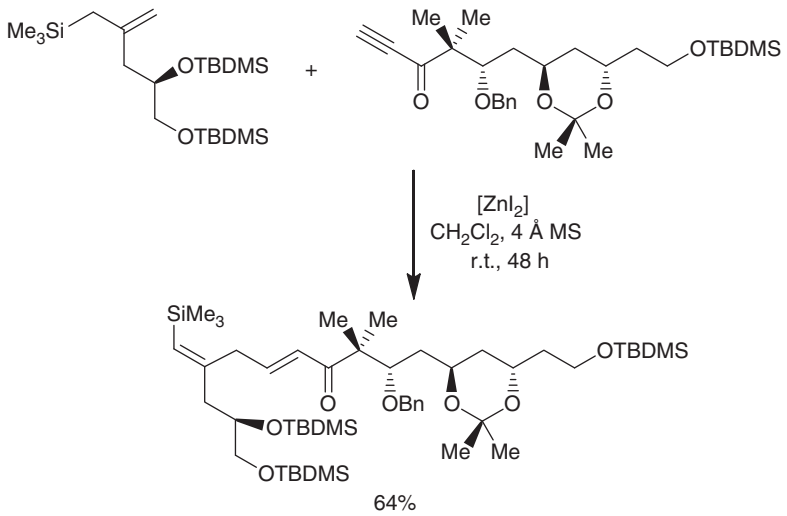
nonnatural targets. This development was based on a conceptual change of mechanism toward transition metal catalysis, in particular enabled by ruthenium catalysts.[64] In this case, a pericyclic one-step mechanism does not apply but rather multiple organometallic elementary steps are very likely involved (coordination, oxidative cyclometallation, β-hydride elimination, and reductive elimination in analogy to other transition metal-mediated processes). Later, other transition metal complexes were also discovered to catalyze the unique combination of unactivated alkyne enophiles and alkenes as ene components.

Trost and Indolese[65] reported first on the Alder-ene-type addition of alkenes to acetylenes catalyzed by CpRu(COD)Cl giving rise to the formation of a branched and a linear adduct in a 5:1 ratio in good yield (**Scheme 35**).

The methodology was soon generally established with terminal and internal alkynes and terminal monosubstituted olefins giving rise to numerous examples of adducts in variable regioisomeric ratios (**Scheme 36**). A broad tolerance of polar functional groups was observed, ranging from aldehydes, esters, ketones, alcohols to internal alkenes and even α,β-unsaturated carbonyl groups.[65,66] Later, Chen and Li[67] have computationally studied the mechanism of Ru-catalyzed Alder-ene-type reaction on the level of DFT, indicating a clear energetic preference of a ruthenacyle arising from an oxidative cyclization of the coordinated alkyne and alkene over Ru-allyl intermediates. However, the clear preference of the ruthenacyle pathway cannot be unambiguously determined for cationic ruthenium species as intermediates.



Scheme 29 Methanoazulene framework formation by Alder–Bong reaction, a domino ene/Diels–Alder reaction sequence with DMAD as an enophile.



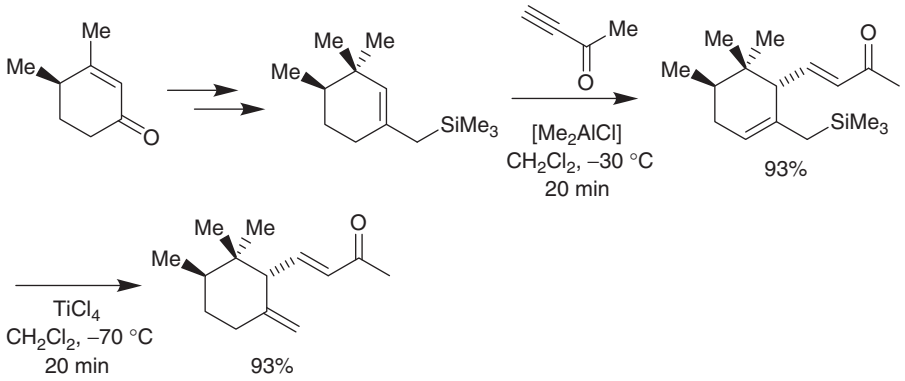
Scheme 30 Allyl silane-ynone ene reaction in the synthesis of the C(1)-C(16) fragment of bryostatins.

Most interestingly, the regioselectivity is largely controlled by steric and coordination effects of the substrates, which become dominant within the coordination sphere of the metal. As a consequence, with propargyl alcohol derivatives such as γ-hydroxy alkynoates, the Alder-ene-type addition even gives rise to the contra-electronic addition of the alkene to the α-position of the ynoate, favoring the formation of α-allylated butenolides **3** over the uncyclized β-allylation product **4** (Scheme 37, Table 2).[68] Likewise γ-amino alkynoates react with monosubstituted alkenes to give the corresponding Alder-ene adducts, which can be subsequently cyclized with a tin catalyst to furnish pyrrolinones.[69]

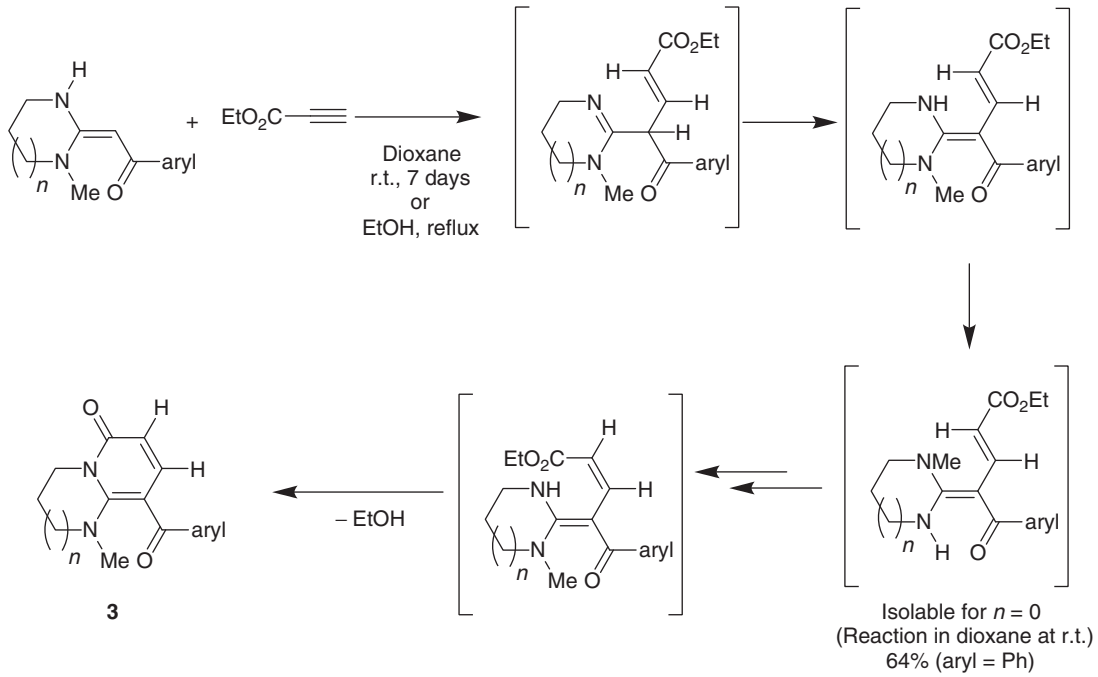
Hartley and Pyne[70] have found that the efficiency of the Ru-catalyzed Alder-ene reaction of hydroxyl substituted alkenes seriously depends on the nature of the O-protecting groups as well as on the number of methylene groups between the hydroxyl and the alkene group (Scheme 38, Table 3).

With the cationic complex $CpRu(MeCN)_3PF_6$, the regioselectivity can be even more enhanced and a broad range of internal alkynes as enophiles can be transformed with moderate to high levels of selectivity, thus opening a stereoselective and versatile access to trisubstituted alkenes.[71,72]

Trost et al.[68–73] and others have impressively demonstrated the utility of this unique reaction as a key step in the total syntheses of the acetogenins (*S*,*S*)-ancepsenolide, and *cis*-solamin,[74] the furanocembranoid (±)-bipinnatin J,[75] the macrolides



Scheme 31 Allyl silane-ynone ene reaction as a key step in the four-step synthesis of (+)-(2*R*,6*R*)-trans-γ-irone.



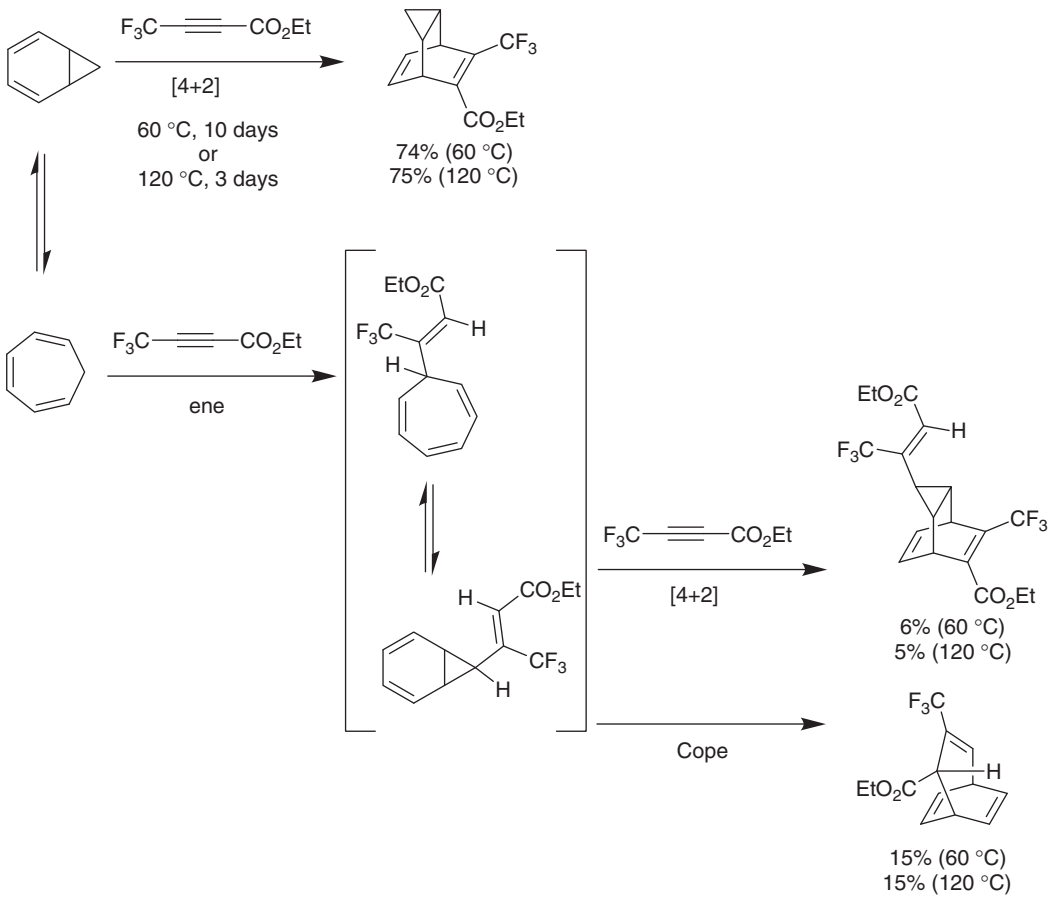
Scheme 32

Table 1 Heterocyclic ketene aminal-ynoate ene reaction as initial step in aza-annulations (**Scheme 32**)

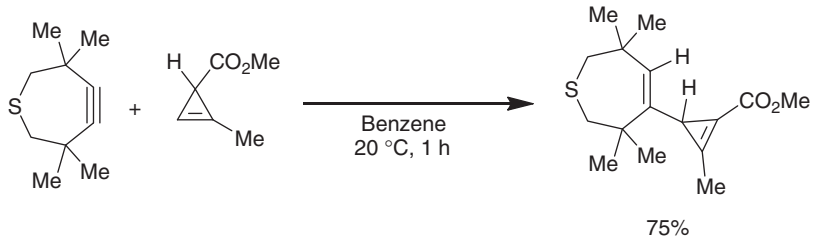
Entry	*n*	*Aryl*	*Yield (%)*
1	0	Ph	78
2	0	*p*-ClC_6H_4	84
3	0	*p*-MeC_6H_4	73
4	0	*p*-$MeOC_6H_4$	76
5	1	Ph	58
6	1	*p*-ClC_6H_4	53
7	1	*p*-MeC_6H_4	35
8	1	*p*-$MeOC_6H_4$	36

deschlorocallipeltoside A,[76] callipeltoside A,[77] and (–)-dactylolide,[78] and in the formal synthesis of the fungal germination inhibitor alternaric acid (Table 4).[79]

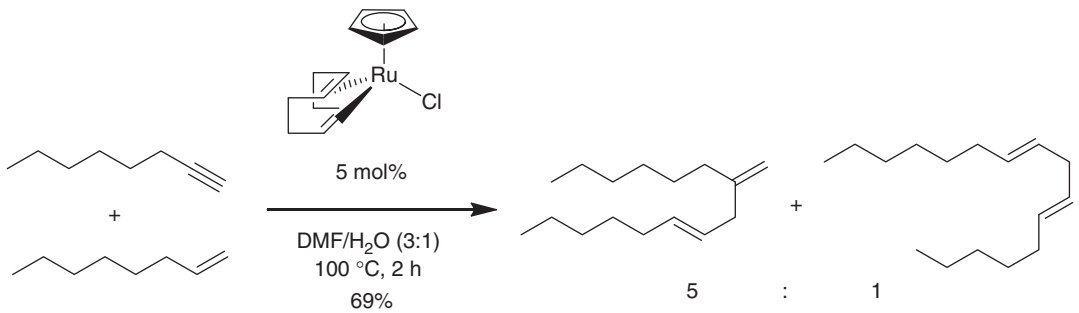
Finally, several further methodological developments have considerably extended the synthetic utility of Ru-catalyzed Alder-ene reactions. Trost et al.[80] could show that vinyl silanes, which are suitable substrates for subsequent Hiyama-type



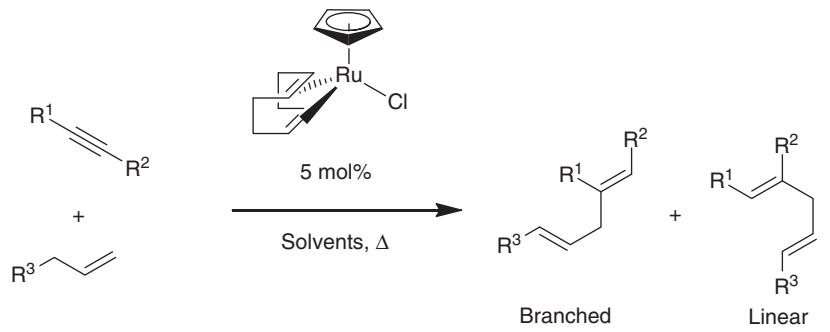
Scheme 33 Ethyl 4,4,4-trifluorobut-2-ynoate as dienophile and as enophile in the reaction with cycloheptatriene.



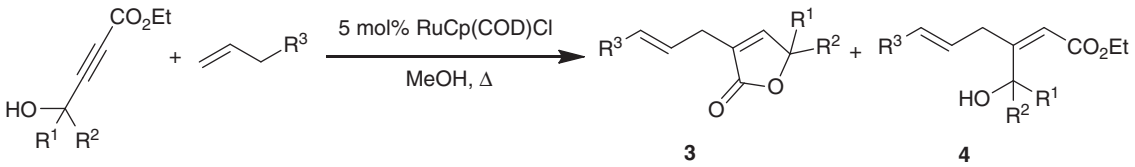
Scheme 34 A strained heterocyclic alkyne as enophile in an ene reaction.



Scheme 35 The first Ru-catalyzed Alder-ene-type addition of 1-octyne and 1-octene.



Scheme 36 The general Ru-catalyzed Alder-ene-type addition of alkynes and 1-alkenes.

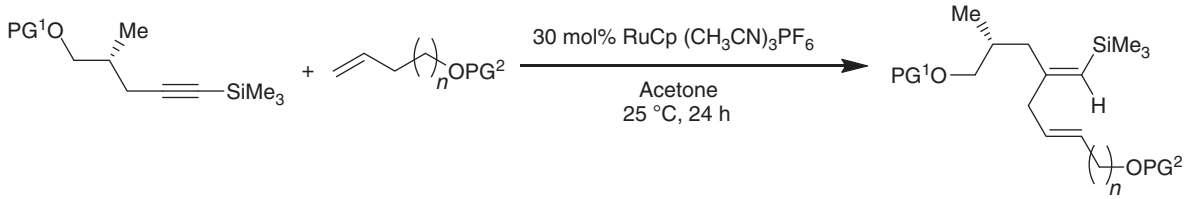


Scheme 37

Table 2 Contra-electronic Ru-catalyzed Alder-ene addition of alkenes to γ-hydroxy alkynoates furnishing α-allylated butenolides (Scheme 37)

Entry	R^1	R^2	R^3	*Yield (%)*	*Ratio **3/4***
1	H	H	*n*Pent	47	2.6:1
2	H	^{i}Pr	*n*Pent	79	4.3:1
3	$(CH_2)_4$	–	*n*Pent	68	6.6:1
4	Me	*t*Bu	*n*Pent	60	100:0
5	H	H	$(CH_2)_7CO_2Me$	51	2.9:1
6	H	^{i}Pr	$(CH_2)_7CO_2Me$	63	4.4:1
7	$(CH_2)_4$	–	$(CH_2)_7CO_2Me$	67	12.2:1
8	$(CH_2)_4$	–	$(CH_2)_7CHO$	80[a]	7.9:1
9	$(CH_2)_4$	–	$(CH_2)_7CH_2OH$	71	100:0

[a]Isolated as dimethylacetal.



Scheme 38

cross-couplings, are very efficiently obtained via Ru-catalyzed Alder-ene reaction from terminal benzyldimethylsilyl-substituted alkynes (Scheme 39).

Lee and his group impressively showed that di- and triynes are enophiles that can be efficiently coupled with terminal alkenes with high regio- and site-selectivity (Scheme 40, Table 5).[81]

Borylated alkynes as enophiles can be transformed with high selectivity into β,β-disubstituted vinyl boronates (Scheme 41),[82,83] which are valuable building blocks for cross-coupling reactions. It is remarkable that these reactions occur with the opposite stereochemistry as compared to reactions of many other types of internal alkynes.

In recent years, Hilt and his group have developed cobalt-catalyzed Alder-ene-type reactions in the course of their methodological and synthetic studies on transformations of alkynes with low-valent cobalt catalysts.[84] Functionalized 1,4-dienes are obtained in good yields and with excellent chemo-, regio-, and stereoselectivity (Scheme 42, Table 6).[85]

Table 3 Effect of hydroxyl protecting groups and functionality on the Ru-catalyzed Alder-ene-type reaction (Scheme 38)

Entry	*PG*^{1}	*PG*^{2}	*n*	*Yield (%)*
1	TBDPS	PNB	1	98
2	TBDPS	PMB	1	14
3	TBDPS	H	1	0
4	TBDPS	PNB	2	96
5	TBDPS	PMB	2	19
6	TBDPS	H	2	96
7	TBDPS	PNB	3	93
8	TBDPS	PMB	3	18
9	TBDPS	H	3	99

Yet, some remarkable differences to the dominant Ru-catalyzed Alder-ene reactions have become apparent. With ynoates as enophiles, the opposite regioselectivity is obtained in comparison to Trost's CpRu-based catalyst systems. Cyclopentene as an ene component furnishes the Alder-ene product **5** if dppe is employed as a ligand on cobalt, whereas dppp gives rise to the formation of the [2 + 2]-cycloadduct **6** (Scheme 43).[86] Mechanistically, this ligand- and substrate-dependent dichotomy is rationalized by the tendency of the cobaltacyclopentene to either undergo reductive elimination (toward cyclobutene anellation) or β-hydride elimination (toward the Alder-ene product).

Alkenyl-silanes and -boronates as ene components can be efficiently employed in cocatalyzed Alder-ene-type reactions furnishing valuable building blocks for silicon and boron mediated C–C bond forming reactions such as Suzuki cross-coupling, Sakurai allylation, or Prins-type cyclization.[87]

5.01.2.3 Benzynes as Enophiles

Benzynes are particularly reactive π-systems, which can only be selectively reacted on *in situ* generation in the presence of suitable trapping agents.[88] With alkenes as traps, benzynes can well behave as enophiles giving rise to the formation of Alder-ene adducts. Mechanistically, this unique type of ene reaction has also been studied by a combination of mass spectrometry and quantum chemical computations.[89]

Drouin and Jacq[90] showed that the *in situ* generation of benzyne from *o*-bromofluorobenzene and magnesium in THF in the presence of β-pinene is well suited for an efficient synthesis of 10-phenyl-α-pinene in the sense of an ene reaction (Scheme 44).

Dolbier et al.[91] have demonstrated the generation of (dehydro)octafluoro[2.2] paracyclophane using the Cadogan method (N-nitrosation of acetanilides followed by thermal elimination of nitrogen and acetic acid) and the *in situ* trapping of the benzyne intermediate with alkenes in the sense of ene reactions (Scheme 45). Likewise, 1,3,5-cycloheptatriene was found to react with the same benzyne derivative via a sequence of an ene reaction, an electrocyclic ring closure (tropylidene–norcardiene equilibrium), and subsequent Diels–Alder reaction with excess aryne.[92]

Arynes can also be prepared under mild conditions (moderate temperatures) from *ortho*-silyl aryltriflates.[93] Jayanth et al.[94] have employed this peculiar *in situ* aryne generation for ene reactions with alkynes possessing a propargylic hydrogen to furnish arylsubstituted allenes in good yields (Scheme 46).

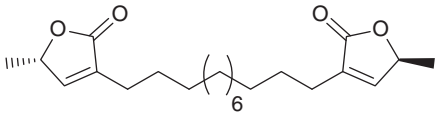
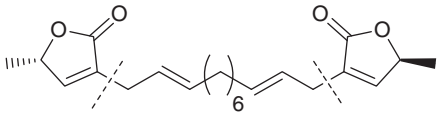
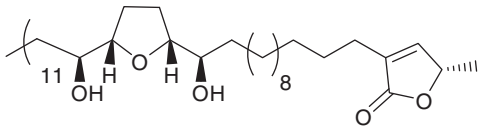
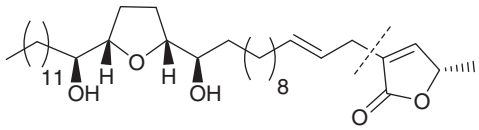
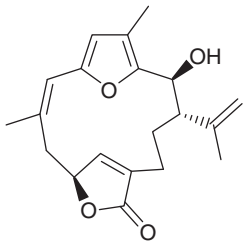
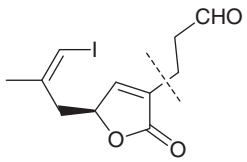
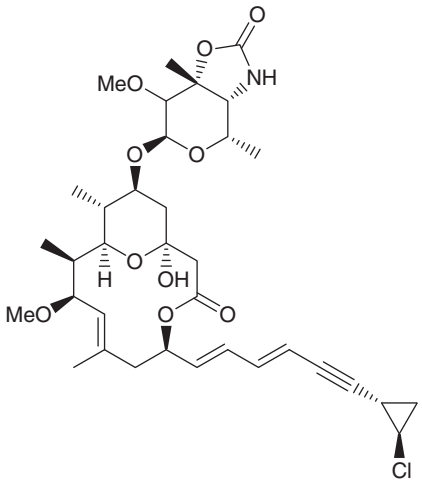
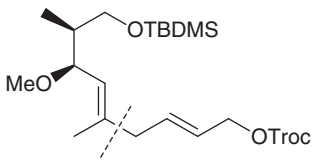
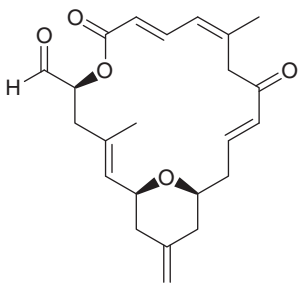
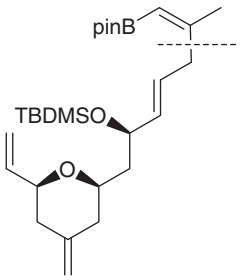
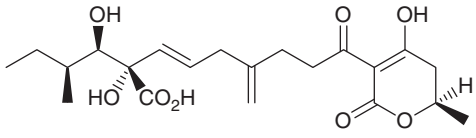
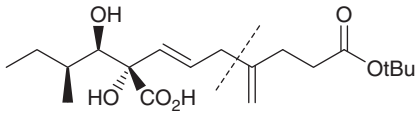
5.01.2.4 Intermolecular Photo-Ene Reactions

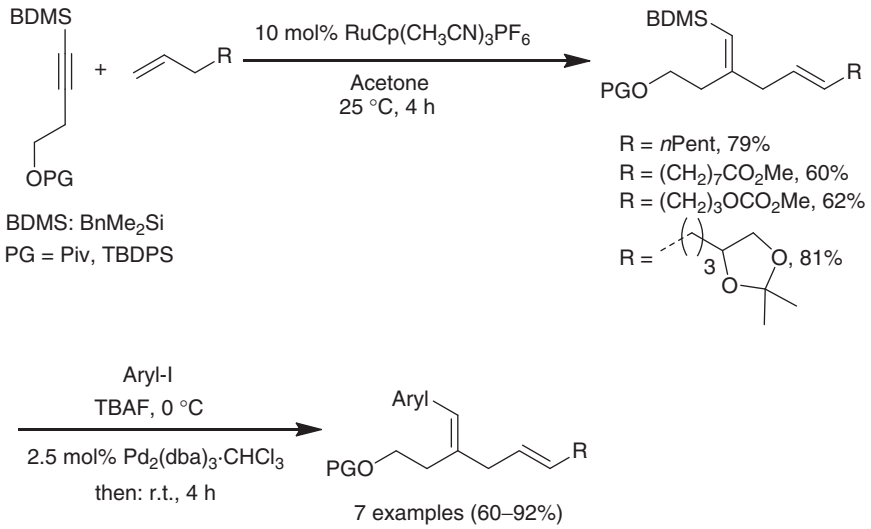
The first photo-ene reactions were observed with methyl-substituted psoralen derivatives, such as 4′-(hydroxymethyl)-4,5′,8-trimethylpsoralen and 4,5′,8-trimethylpsoralen, that preferentially reacted with cyclic olefins in deoxygenated solution via an ene reaction, whereas simple *n*-alkenes rather formed the [2 + 2] cycloadducts.[95] 9-Methylene-9,10-dihydrophenanthrene was found to undergo ene reactions with alkenes as enophiles under irradiation with UV-light, giving rise to the formation of the photo-ene adducts (Scheme 47).[96]

5.01.3 Alder-Ene Cycloisomerizations

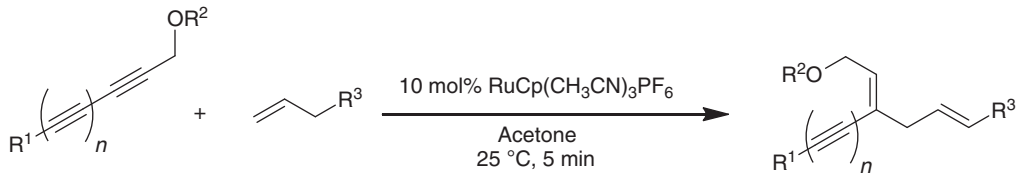
Intramolecular reactions are often entropically favored due to lesser degrees of rotational freedom. As a consequence of unimolecular elementary steps, higher rates are found. In addition, pericyclic reactions always have aroused considerable interest for the rapid construction of complex molecular frameworks. Therefore, many synthetic applications of intramolecular ene reactions have been developed in the past 20 years, additionally enriched by the advent of novel organometallic catalytic methodologies.

Table 4 Targets prepared by applications of the ruthenium-catalyzed Alder-ene-type reaction as a key step

Entry	*Target structure*	*Alder-ene product*
1	 (*S*,*S*)-Ancepsenolide	
2	 *cis*-Solamin	
3	 (±)-Bipinnatin J	 Via enol
4	 Callipeltoside A	
5	 (–)-Dactylolide	
6	 Alternaric acid	



Scheme 39 Vinyl silanes prepared by Ru-catalyzed Alder-ene-type reactions and their Hiyama coupling to arylalkenes.



Scheme 40

Table 5 Ru-catalyzed Alder-ene-type reactions of di- and triynes and alkenes (**Scheme 40**)

Entry	*n*	R^1	R^2	R^3	*Yield (%)*
1	1	$SiEt_3$	H	$(CH_2)_2OH$	81
2	1	$SiEt_3$	H	$(CH_2)_3OH$	73
3	1	$SiEt_3$	H	CH_2OCO_2Et	65
4	1	$SiEt_3$	H	*n*Hept	80
5	1	$SiEt_3$	Ac	*n*Hept	81
6	1	*n*Bu	Boc	CH_2OCO_2Et	65
7	1	$Me_2C(OAc)$	Ac	CH_2OCO_2Et	65[a]
8	1	Bpin	*n*Hex	*n*Hept	65
9	2	$SiEt_3$	H	*n*Hept	60
10	2	$SiEt_3$	Ac	*n*Hept	70

[a]The ratio of regioisomers is 3.5:1.

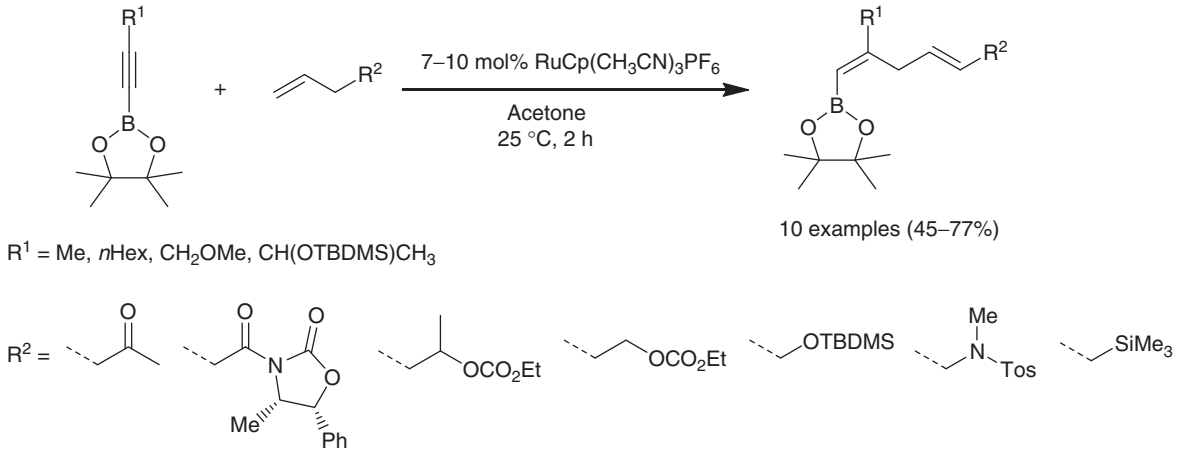
5.01.3.1 Alkenes as Enophile Moiety

5.01.3.1.1 Electron-deficient alkenes as enophile moieties

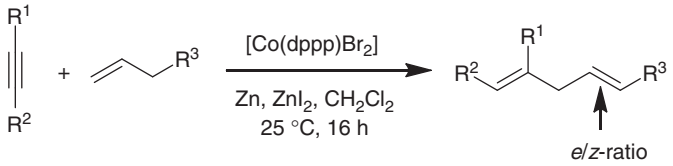
The intramolecular ene reaction with enoates as enophile component and an ene tethered by an alkyl chain opens a general access to substituted cyclopentanes.

Taber et al.[97] have developed a potential route to neuroprostanes and isoprostanes with an intramolecular ene reaction as a key step (**Scheme 48**).

Sarkar et al.[98–100] could show that the Alder-ene cycloisomerization of activated 1,6-dienes allows for a facile access to cyclopentanoid allylsilanes and that the formation of three contiguous stereocenters can be controlled. For illustration, the thermal cycloisomerization at 235 °C found use in the syntheses of two jasmonoid natural products, (±)-methyl cucurbate and



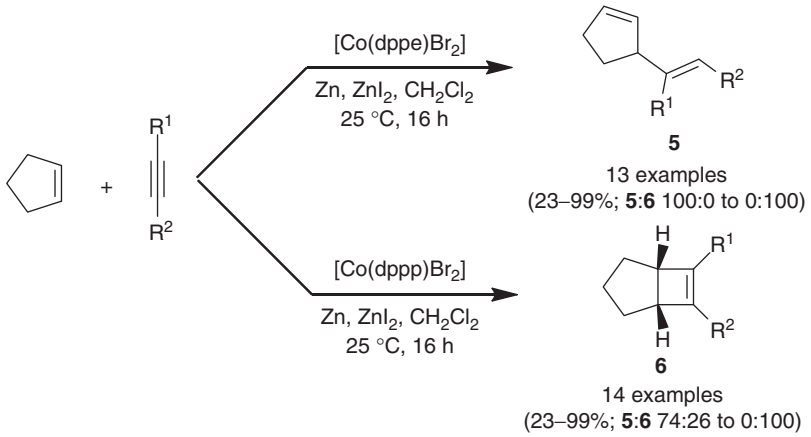
Scheme 41 Synthesis of β,β-disubstituted vinyl boronates via Ru-catalyzed Alder-ene-type reaction of borylated alkynes and alkenes.



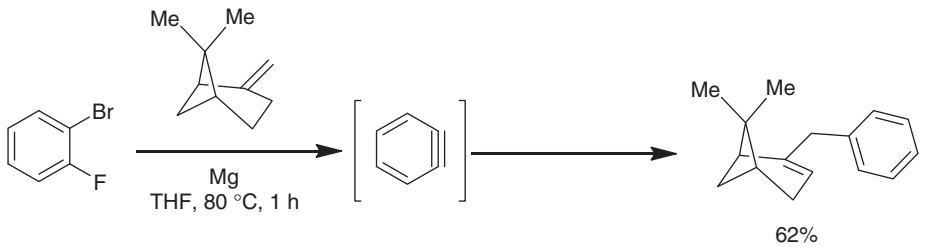
Scheme 42

Table 6 Cocatalyzed Alder-ene-type reactions (**Scheme 42**)

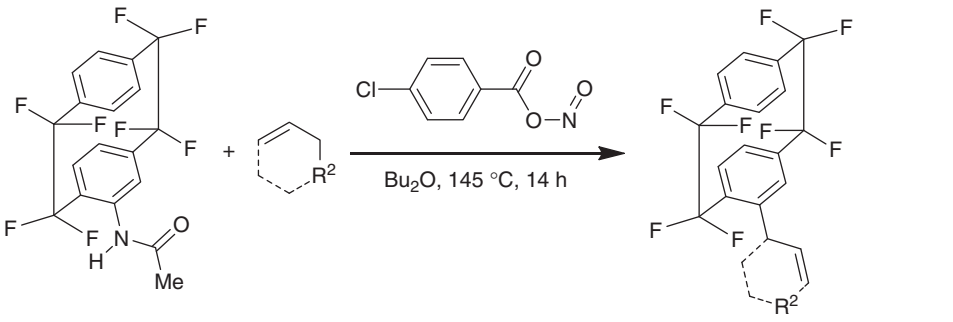
Entry	*R^1*	*R^2*	*R^3*	*Yield (%)*	*Ratio E/Z*
1	Et	Ph	*n*Pr	89	89:11
2	Et	Ph	*n*Pent	84	89:11
3	*n*Bu	Ph	*n*Pr	90	88:12
4	*n*Bu	Ph	*n*Pent	99	88:12
5	*n*Bu	Ph	$SiMe_3$	20	95:5
6	Et	Ph	Ph	85	90:10
7	Et	Ph	2,4-$(MeO)_2C_6H_3$	95	89:11
8	Ph	Ph	*n*Pr	<5	–
9	Me	CO_2Et	*n*Pr	88	90:10
10	Me	CO_2Et	$SiMe_3$	100	>99:1
11	CH_2OMe	CH_2OMe	*n*Pr	74	69:31



Scheme 43 Cocatalyzed Alder-ene-type reaction vs. [2 + 2] cycloaddition.

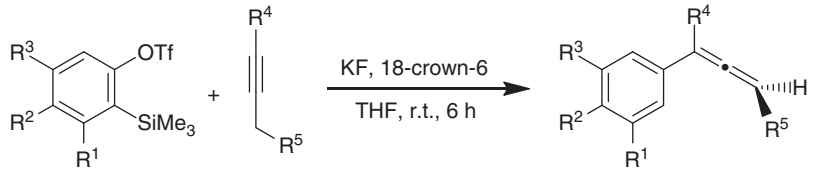


Scheme 44 Synthesis of 10-phenyl-α-pinene via the ene reaction of benzyne and β-pinene.



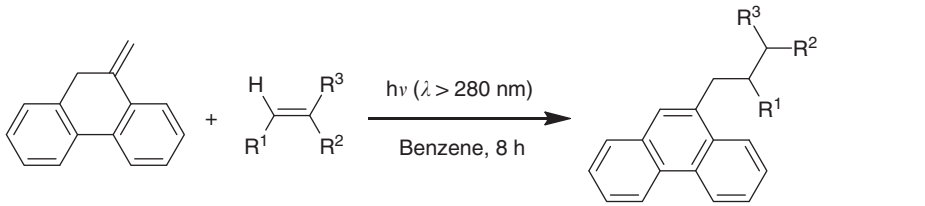
91%, *trans*:*cis* = 2.4:1 (R^2 = *n*Pent)
53%, *dr* = 5.6:1 ($R^2 = (CH_2)_2$)
55%, *dr* = 1:1 ($R^2 = (CH_2)_3$)

Scheme 45 Generation and ene reaction of (dehydro)octafluoro[2.2] paracyclophane.



18 examples (52–73%)

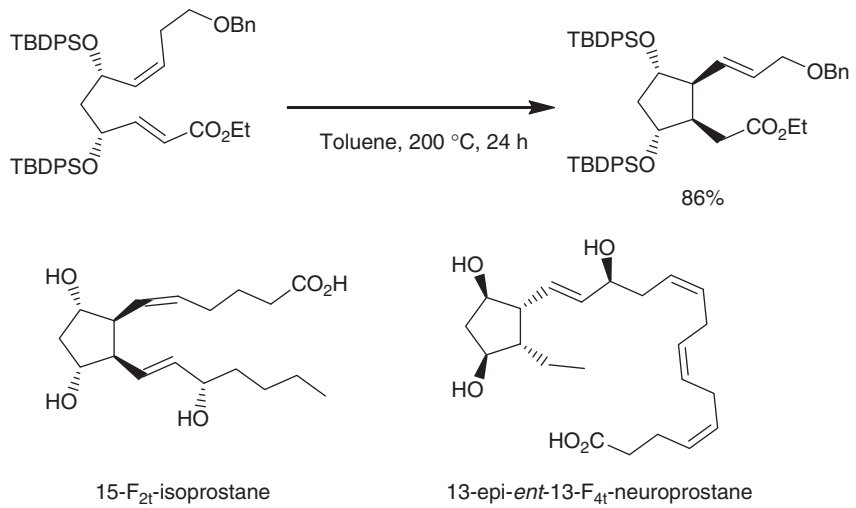
Scheme 46 Ene reaction of arynes as enophiles with alkynes as ene partners.



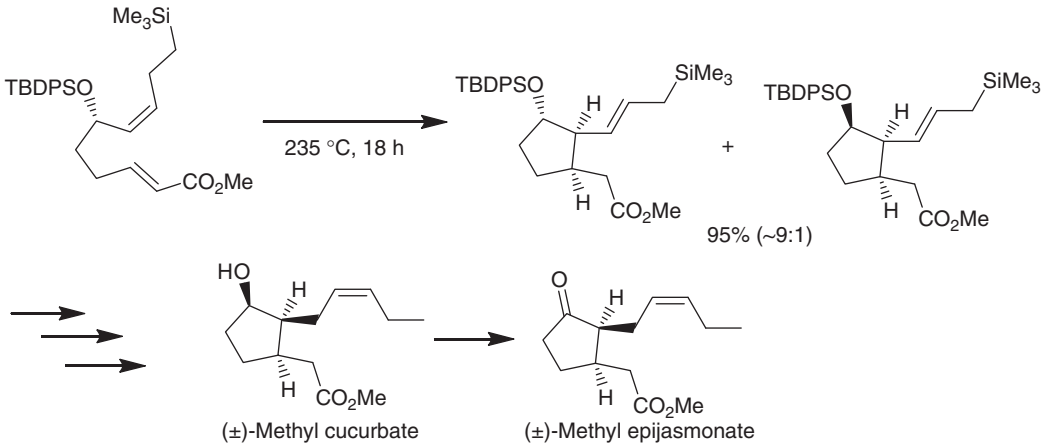
R^1 = H, R^2 = R^3 = Ph, 69%
R^1 = R^3 = H, R^2 = Ph, 62%
R^1 = Me, R^2 = Ph, R^3 = H, 21%
R^1 = R^3 = H, R^2 = CH=CHMe, 15%

Scheme 47 Photo-ene reaction with 9-methylene-9,10-dihydrophenanthrene as ene partners.

(±)-methyl epijasmonate (Scheme 49). Likewise, the same group has applied this methodology to the synthesis of di- and triquinanes and has illustrated the versatility in the synthesis of the fungal metabolite (±)-hirsutene. The use of $LiClO_4$ as a Lewis acid catalyst was demonstrated by Sarkar et al.[101] to cause a dramatic acceleration of the ene reaction, providing a mild and effective methodology for synthetic applications.

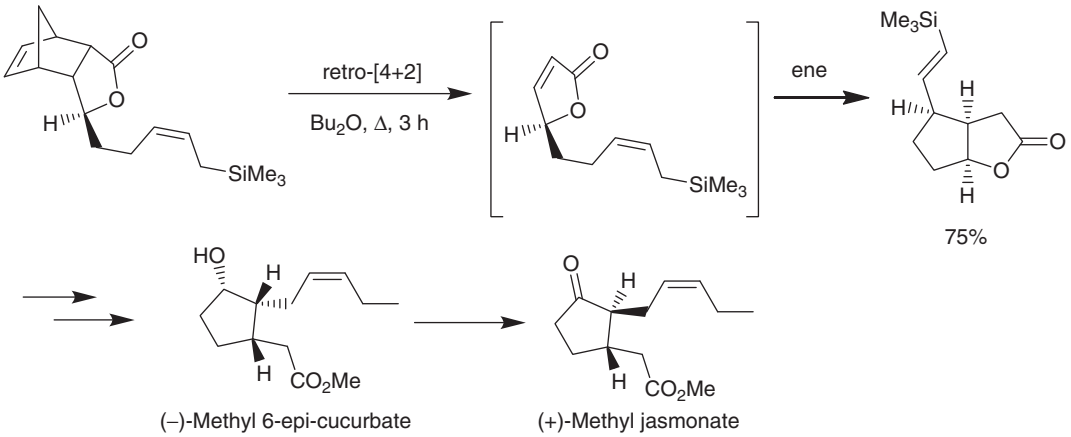


Scheme 48 Thermal intramolecular ene reaction as a key step in the synthesis of isoprostanes and neuroprostanes.



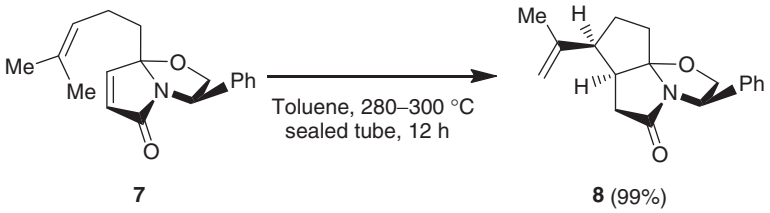
Scheme 49 Ene key step in the synthesis of (±)-methyl cucurbate and (±)-methyl epijasmonate.

In a related fashion, Suzuki et al.[102] successfully used a thermal retro-Diels–Alder/ene domino process, activated by a trimethysilyl substituent, as the key step in an enantiocontrolled synthesis of (–)-methyl 6-epi-cucurbate and (+)-methyl jasmonate (Scheme 50).



Scheme 50 Domino retro-Diels–Alder/ene reaction as a key step in the synthesis of (–)-methyl 6-epi-cucurbate and (+)-methyl jasmonate.

Resek[103] showed that the rigid chiral auxiliary-based bicyclic lactam **7** underwent a thermal ene reaction at 280–300 °C to afford product **8** in excellent yield (Scheme 51).

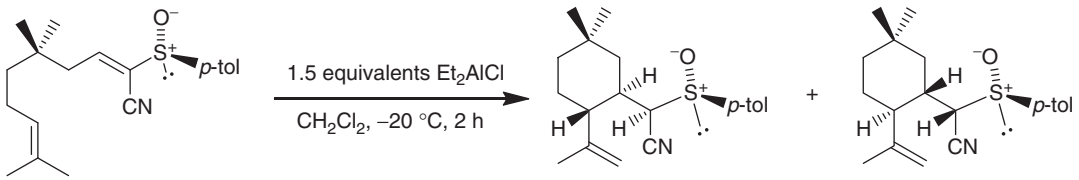


7 **8** (99%)

Scheme 51 Intramolecular ene reaction of a chiral bicyclic lactam.

As Michael systems, vinyl sulfoxides are electronically favorable enophiles, in particular, for ene reactions with normal electron demand. In addition, the inherent chirality of asymmetrically substituted sulfoxides has opened new avenues for applications in asymmetric syntheses.

Hiroi and Umemura[104,105] have disclosed a chiral α-cyanovinyl sulfoxide as an efficient chiral enophile for intramolecular ene reactions with high levels of stereoselectivity, provided that diethylaluminium chloride is employed as a catalyst (Scheme 52). A chiral α-sulfinyl α,β-unsaturated ketone rather furnishes a mixture of Diels–Alder and ene products.[106]



(1*R*,2*R*,α*R*,*Rs*) Major

(1*S*,2*S*,α*S*,*Rs*) Minor

62% (*de* 97.3%)

Scheme 52 A chiral α-cyanovinyl sulfoxide as an efficient chiral enophile for Lewis acid-catalyzed intramolecular ene reactions.

Vinylphosphonates are also well suited as enophile moiety in intramolecular ene reactions. Minami et al.[107] presented a study where vinyl phosphonates, readily generated from citronellal or 2,6-dimethyl-5-heptenal, efficiently underwent an intramolecular Alder-ene reaction (Scheme 53). This key step was successfully applied to the synthesis of cadalane and valerenic acid sesquiterpenoids.

Likewise, heteroatoms in the tether of the enophile and the ene component open accesses to heterocycles via ene reactions. Based on an amide tether incorporated into a chiral aminal auxiliary, Pedrosa et al.[108] have disclosed a thermal intramolecular ene reaction furnishing 3,4-disubstituted pyrrolidinone derivates with excellent levels of diastereoselectivity (Scheme 54).

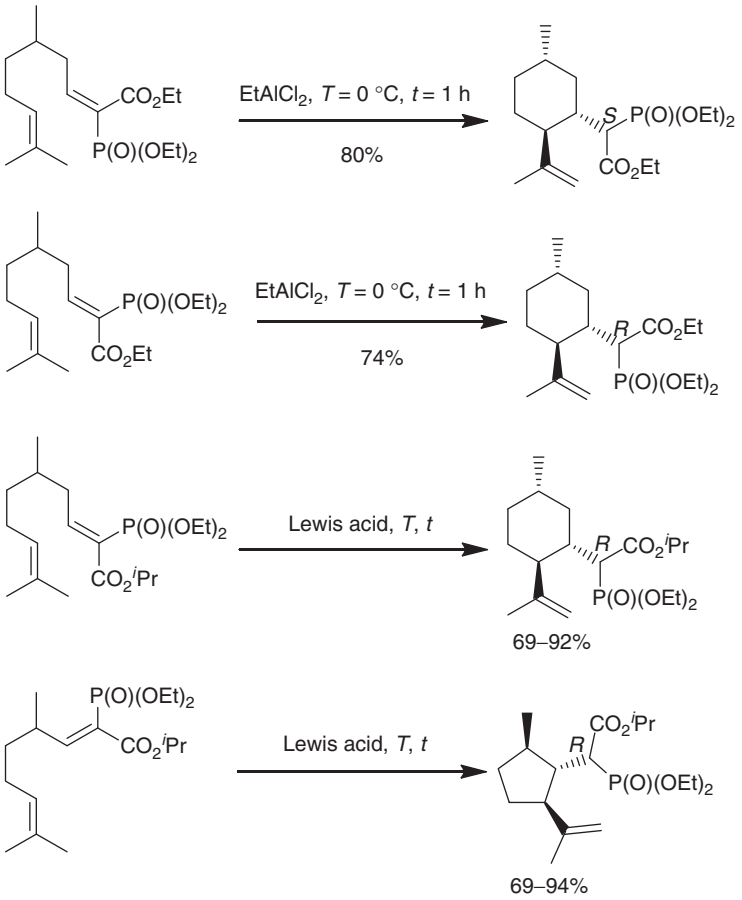
Noguchi et al.[109] found that *N*-allyl or *N*-crotyl substituted 2-amino vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones give annelated azepine derivatives as a consequence of an intramolecular Alder-ene reaction (Scheme 55).

The group of Sammes found that steric buttressing by bulky substituents, such as trityl, on the nitrogen atom of diallyl amine derivatives enables uncatalyzed ene reactions under remarkably mild conditions, which can be even implemented in a domino-Diels–Alder/ene sequence (Scheme 56).[110] *N*-Isoprenyl-*N*-γ-crotonates, i.e., the allyl amines bearing an electron-withdrawing ester group, react under kinetic control to give vinyl pyrrolidines with good levels of diastereoselectivity.[111]

α-Kainic acid is a biologically highly active molecule with a broad pharmaceutical potential, in particular, as it causes neuro-excitatory activity in several neurological disorders.[112] As a consequence, even up to very recently,[113] α-kainic acid and analogs[114] have received considerable attention by the synthetic community. The retrosynthetic analysis suggests an intramolecular ene reaction for the stereoselective formation of the pyrrolidine ring. Several enantioselective syntheses of (–)-α-kainic acid are based on this approach.

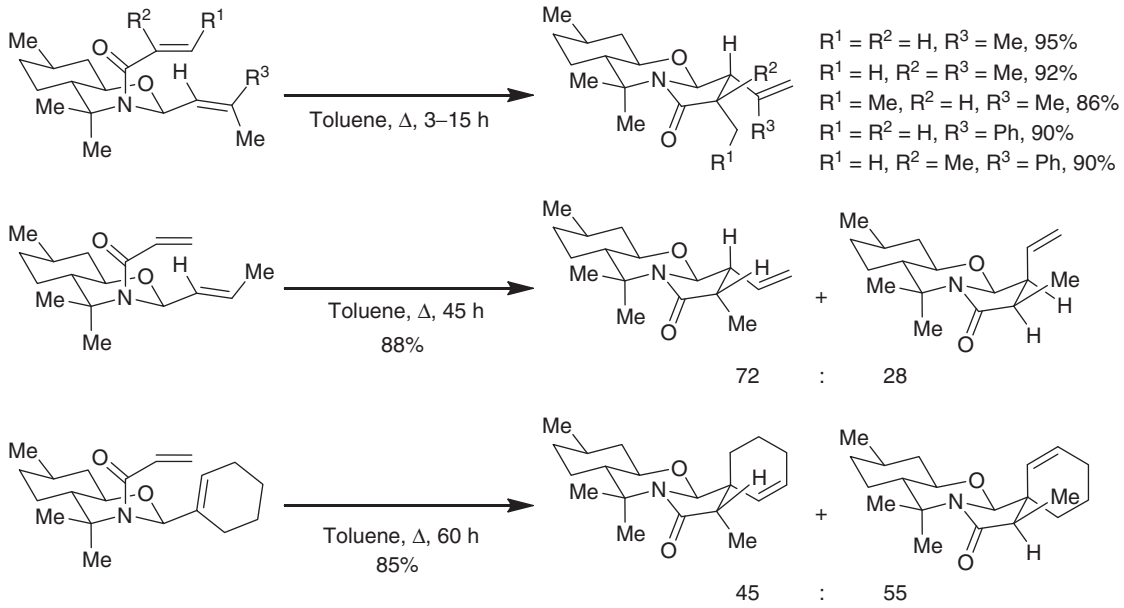
Xia and Ganem[115] reported an elegant application of a Lewis acid mediated enantioselective ene reaction with $Mg(ClO_4)_2$ and a (*R*,*R*)-4,4′-diphenyl bisoxazoline as a chiral ligand on the way to the kainic acid ring system (Scheme 57).

Majik et al.[116] have disclosed very recently the first example of a domino Wittig/intramolecular ene reaction in the synthesis of racemic kainic acid (Scheme 58). In that approach a stabilized phosphorus ylide with a tethered prenyl moiety undergoes a Wittig olefination with glyoxalic acid; the resulting product is subsequently transformed to give the *cis*-fused pyrrolidine skeleton of kainic acid in a one-pot fashion.

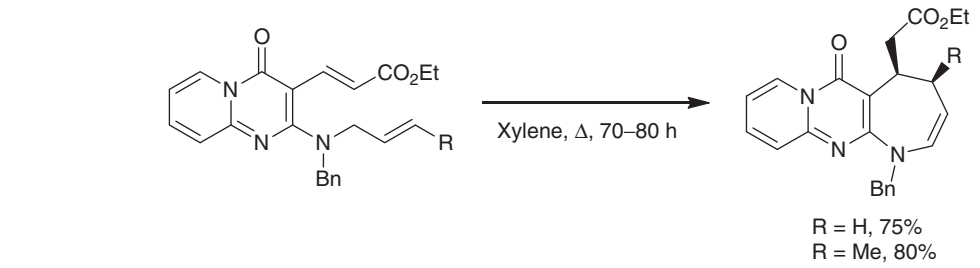


Lewis acid: $EtAlCl_2$, $TiCl_2(O^iPr)_2$, $SnCl_4$, $ZnBr_2$, $TiCl_4$, $FeCl_3$
T: 0 °C, –78 °C, or r.t.; *t*: 0.5–23 h

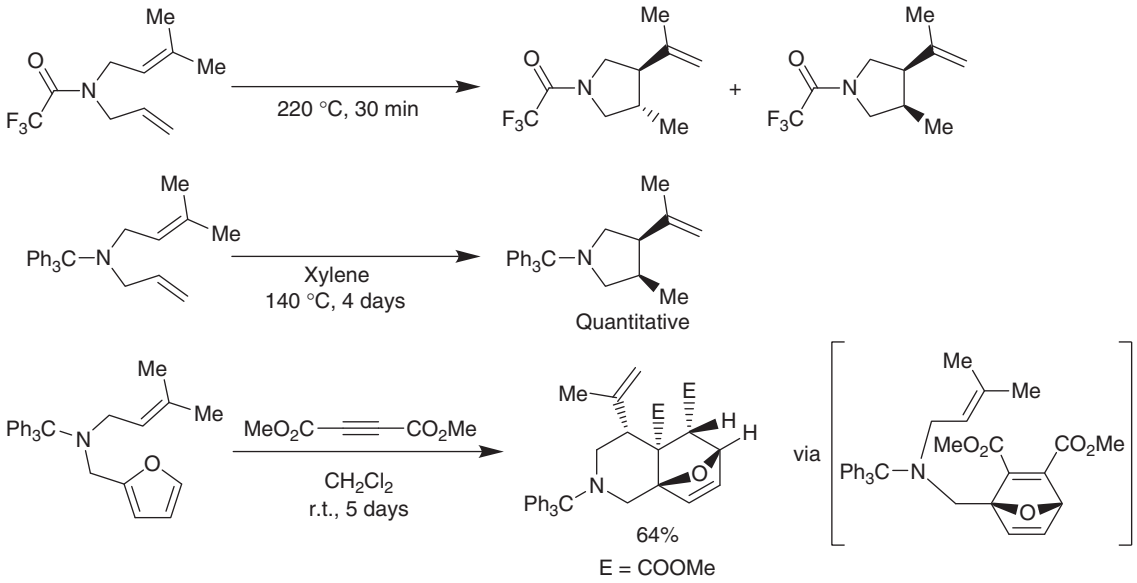
Scheme 53 Intramolecular ene reaction of vinylphosphonates.



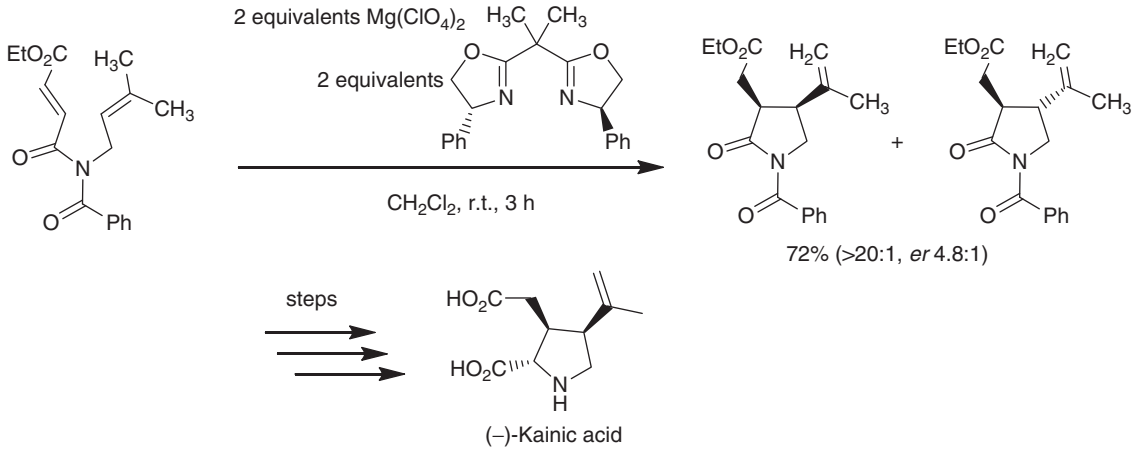
Scheme 54 Chiral auxiliary controlled diastereoselective intramolecular ene reactions.



Scheme 55 Intramolecular ene cycloisomerization with an allyl amine as ene component.



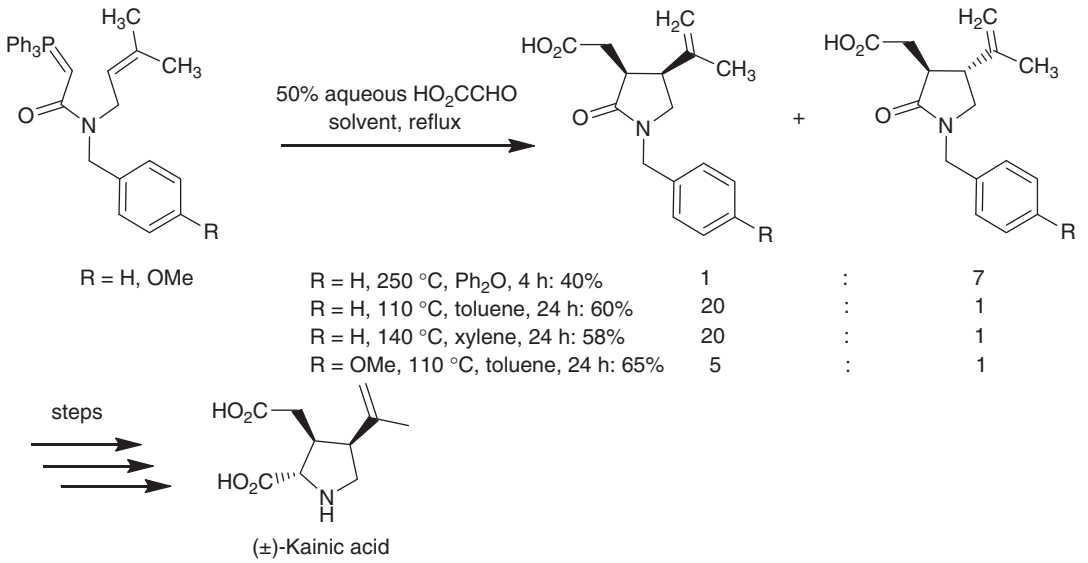
Scheme 56 Trityl steric buttress in intramolecular uncatalyzed ene reactions (for the first entry, no yield is reported).



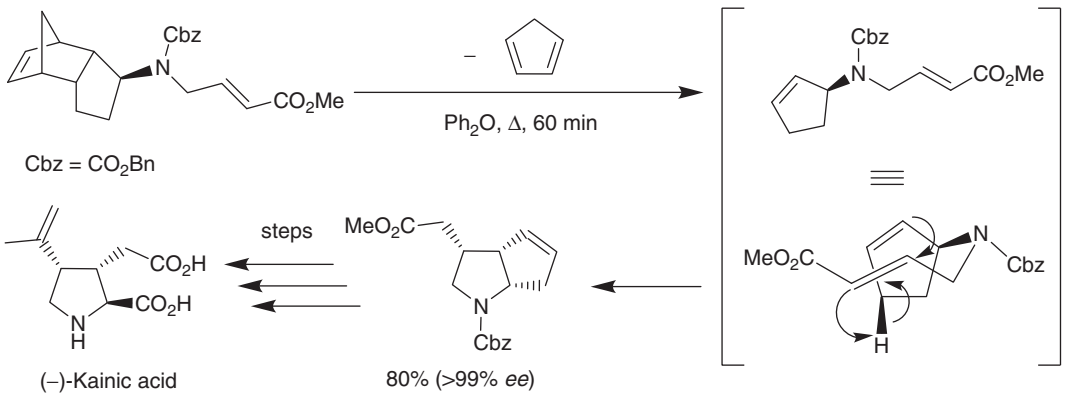
Scheme 57 Lewis acid catalyzed enantioselective ene reaction as a key step in the synthesis of (–)-kainic acid.

Nakada et al.[117] chose a highly enantioconvergent route to (–)-kainic acid by setting the correct stereochemistry of the stereocenter next to the amino group on a tricyclic scaffold (Scheme 59). A retro-Diels–Alder reaction liberates the ene fragment in a very elegant fashion, which undergoes a concomitant intramolecular ene reaction in good yield and with excellent enantioselectivity.

In several systematic contributions the group of Righetti and Desimoni has studied the effect of inorganic cations as Lewis acid catalysts on intramolecular Diels–Alder and ene reactions with several substrates.[118] In these studies α,β-unsaturated enophile



Scheme 58 A domino Wittig/ene reaction as a key step in the synthesis of (±)-kainic acid.



Scheme 59 A retro-Diels–Alder/ene reaction as a key step in the enantioselective synthesis of (–)-kainic acid.

moieties and tethered allyl or crotyl ethers as ene fragments on various aromatic scaffolds were selected. Although under thermal conditions, the formation of hetero-Diels–Alder products is often favored for enone and enoate enophiles,[118a] magnesium perchlorate as a Lewis acid catalyst with bisoxazoline ligands is able to shift the selectivity toward the intramolecular ene reaction; using chiral ligands, good yields and remarkable levels of enantioselectivity were eventually attained (Scheme 60).[118b]

Several applications of intramolecular ene reactions in the past decades have impressively underlined the methodological versatility of this transformation.

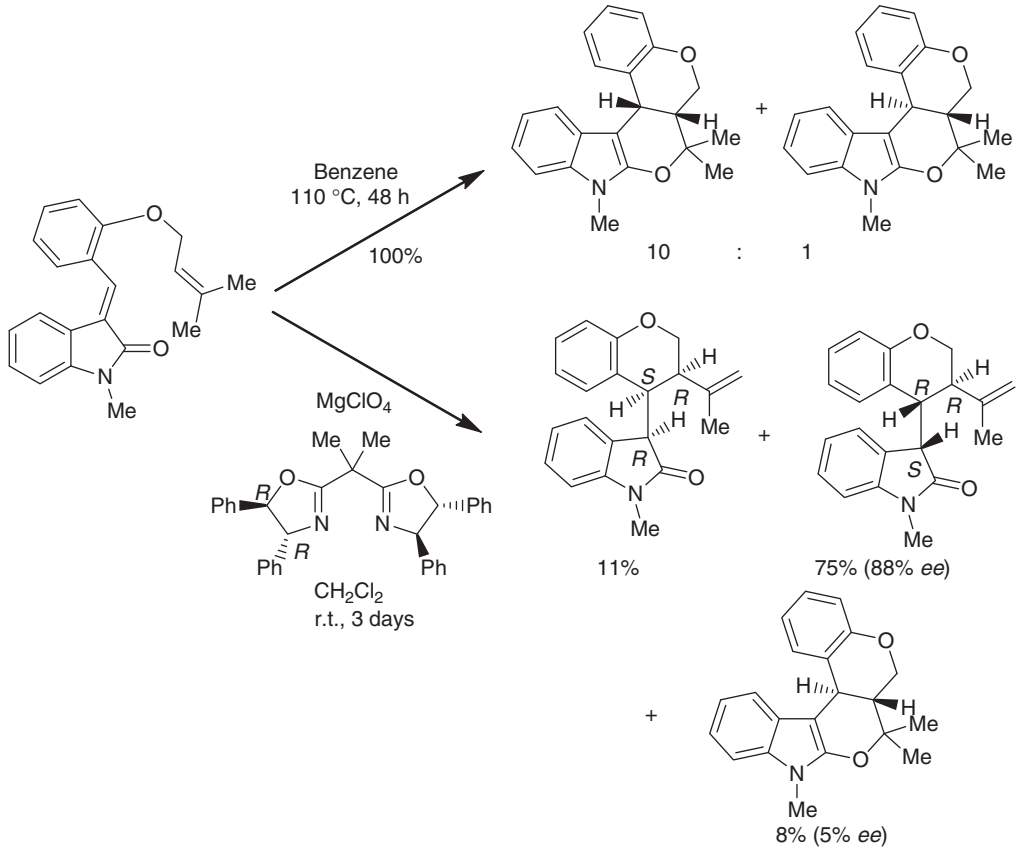
Tietze and Wichmann[119] implemented a sequence comprising a Pictet–Spengler cyclization followed by an intramolecular ene reaction as the diastereoselective key step in the synthesis of derivatives of indole alkaloids of the corynantheine type (Scheme 61).

Difluoroeneamines are peculiar types of enophiles, being neither electron-rich nor electron-deficient. Amii et al.[120] observed that *N*-prenyl difluoroalkenamine undergoes a diastereoselective ene reaction, giving rise to the formation of the pyrrolidine by a 5-*exo* ring closure, obviously through a strained transition state (Scheme 62).

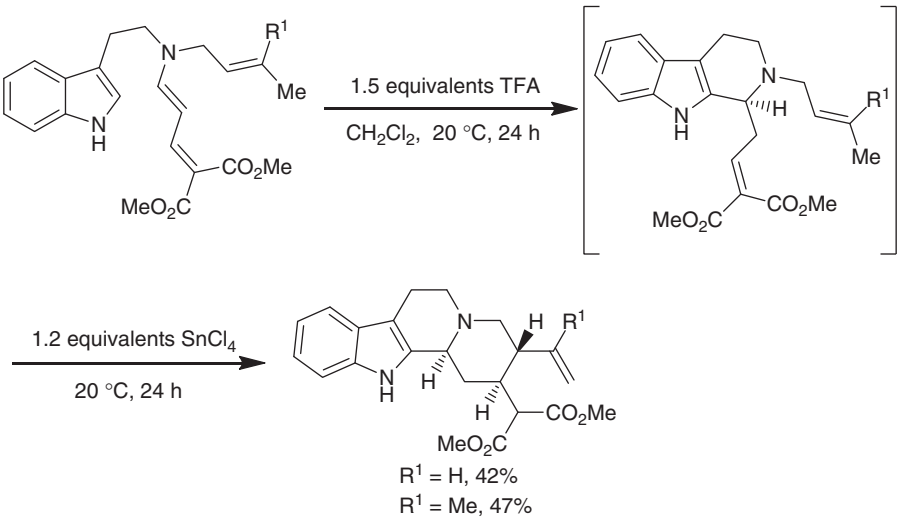
The group of Venkateswaran has reported photolysis experiments with *cis*-tetrahydrobenzopyran-2-ones giving rise to a mixture of the expected [2 + 2]-photoadducts and products of a photo-ene reaction (Scheme 63).[121] Based on the substituent R^2, the product ratio of the cycloadduct **9** and the ene product **10** is apparently correlated to the stability of an intermediate diradical species, which favors the photo-ene reaction.

5.01.3.1.2 Electroneutral alkenes as enophile moieties

Electroneutral alkene fragments as enophile moiety participate relatively sluggishly in ene reactions. Only if bulky substituents, steric strain, or conformational fixation are present in the alkene enophile or if the electronic nature of the ene component allows it, unactivated electroneutral alkene can participate in ene reactions.



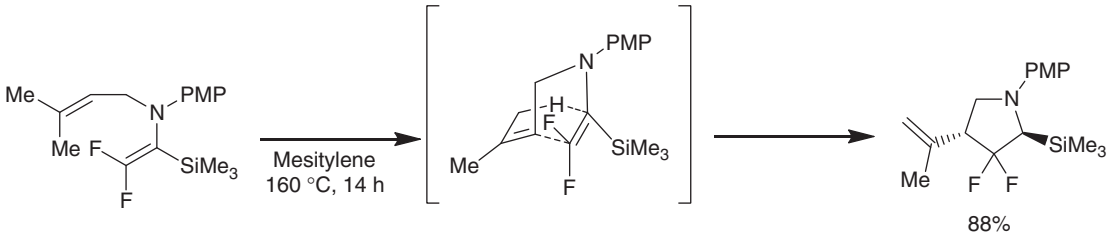
Scheme 60 Thermal hetero-Diels–Alder reaction versus $MgClO_4$-catalyzed ene reaction at room temperature.



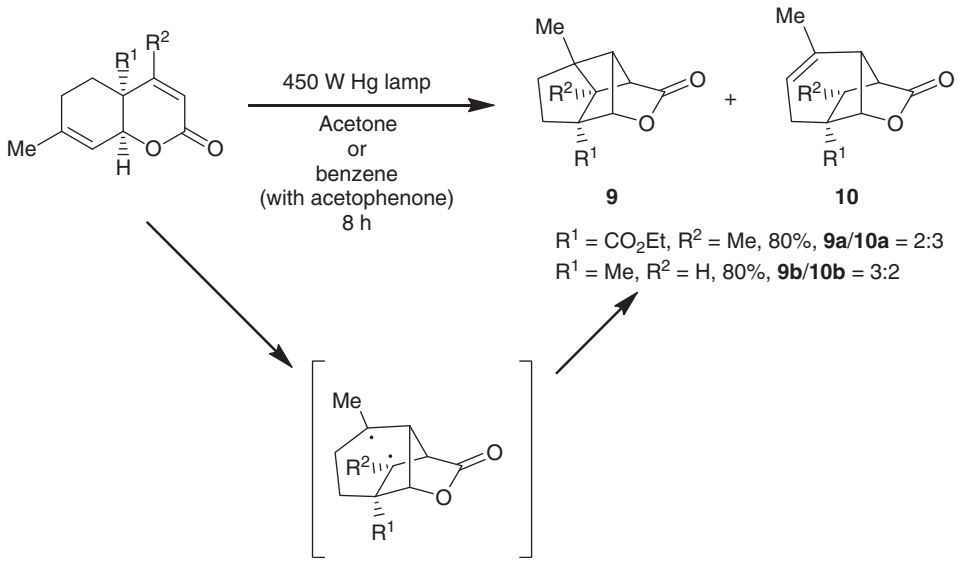
Scheme 61 Pictet–Spengler/ene reaction sequence toward corynantheine alkaloid derivatives.

Hiroi et al.[122] found that the Lewis-acid catalyzed ene reaction of chiral allylic sulfones, obtained by thermal or Pd-catalyzed allylic sulfinate-sulfone rearrangement of optically active allylic sulfinates, gave rise to chiral cyclopentanes with an excellent stereocontrol over three contiguous stereogenic centers (Scheme 64).

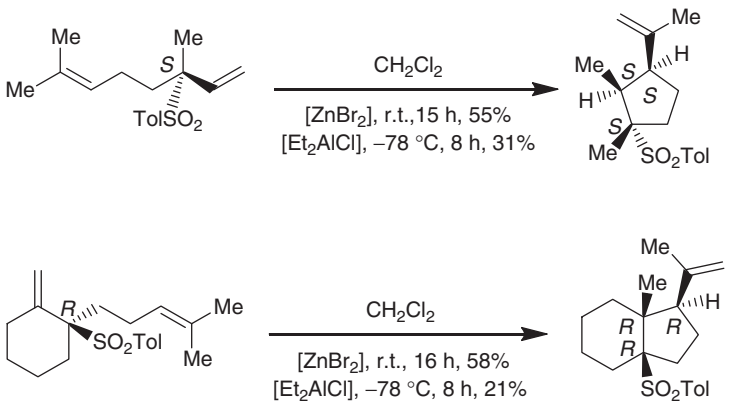
Närhi et al. discovered that enallenes undergo the thermal Alder-ene reaction under fairly mild conditions, whereby the enophile is an electroneutral cycloolefinic fragment and the allenyl moiety acts as the ene component. The reaction gives rise to



Scheme 62 Unusual ene reaction of an *N*-prenyl difluoroalkenamine.



Scheme 63 Intramolecular photo-ene reaction.

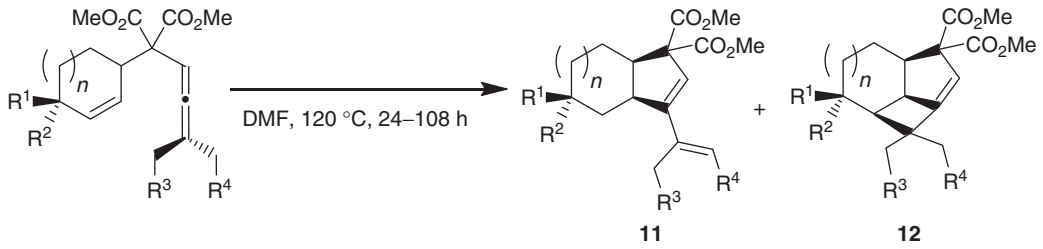


Scheme 64 Asymmetric intramolecular ene reactions of chiral allylic sulfones.

the formation of [n.3.0] bicyclic systems **11** ($n=3$–5) in good yields (Scheme 65, Table 7). The minor byproduct **12** arises from a thermal [2 + 2] cycloaddition.[123]

In a concise total synthesis of (–)-kainic acid starting from enantiopure (+)-*cis*-4-(benzyloxycarbonylamino)-2-cyclopentenol, a Chugaev *syn*-elimination followed by an intramolecular ene reaction via an *exo* transition state were successfully applied as key steps by Nakagawa et al. (Scheme 66).[124]

The same key step was used in a stereocontrolled route to acromelic acids, which are neuroexitatory amino acids isolated from the mushroom *Clitocybe acromelalga*.[125]

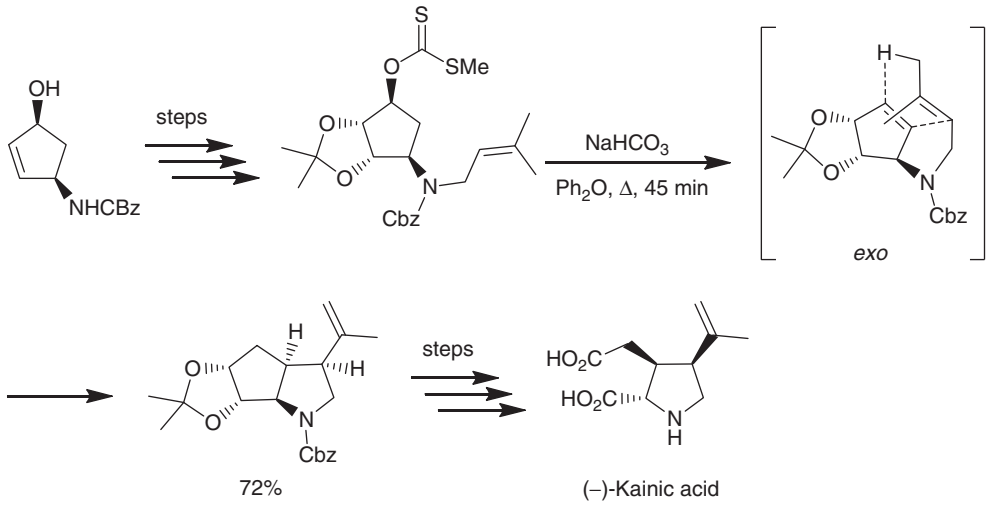


Scheme 65

Table 7 Intramolecular ene reaction of enallenes (**Scheme 65**)

Entry	*n*	R^1	R^2	R^3	R^4	*Yield (%)*	*Ratio **11/12***
1	1	H	H	H	H	84	90:10
2	1	H	H	Me	H	87[a]	80:20
3	1	H	H	$(CH_2)_3$		88	100:0
4	1	Me	Me	H	H	86	95:5
5	1	H	O_2CtBu	H	H	82	90:10
6	1	O_2CPh	H	H	H	72	81:19
7	2	H	H	H	H	81[b]	95:5
8	0	H	H	H	H	77	65:35

[a]The regioisomer ratio of the alkenyl substituent of **11** is 62:38.
[b]The *cis*/*trans* ratio of the alkenyl substituent of **11** is 30:70.



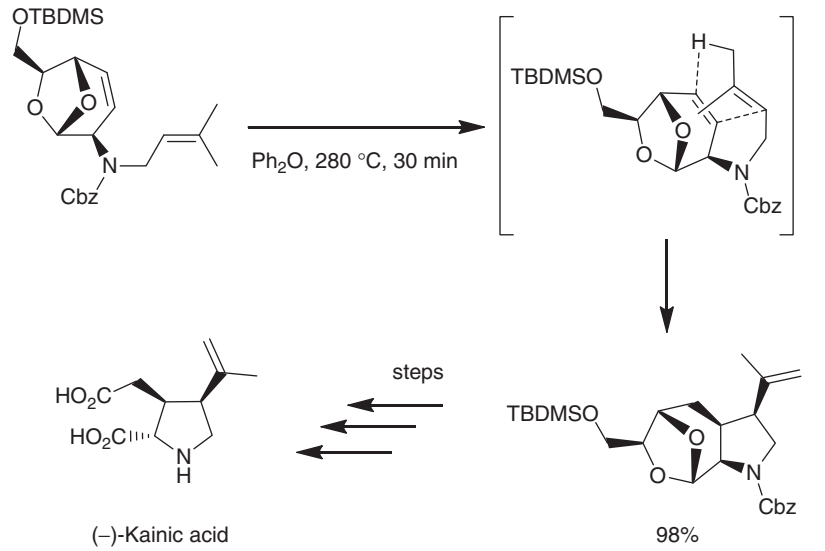
Scheme 66 A retro-Chugaev-ene reaction as a key step in the enantioselective synthesis of (–)-kainic acid.

In the course of yet another enantioselective synthesis of (–)-kainic acid, Hirasawa et al. reported an intramolecular ene reaction of a 1,6-diene embedded and attached on a bicyclo[3.2.1]octane framework, which diastereoselectively formed a tri-substituted pyrrolidine annelated to a pyran ring (**Scheme 67**).[126]

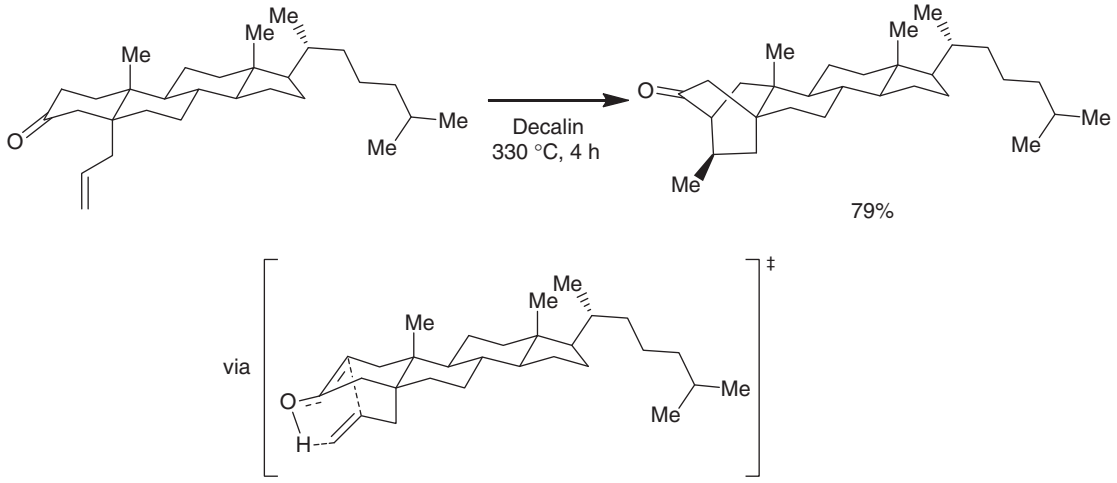
Although electroneutral alkenes remain fairly scarce as enophiles in intermolecular ene processes, they have become increasingly important functionalities in intramolecular ene reactions. This is also correlated to the occurrence of Conia-type ene reactions that proceed via enol tautomers as the hetero-ene components.[2]

Marples and Spilling[127] demonstrated that 5-(prop-2-enyl)-5α-cholestan-3-one, as well as acyloin analogs, smoothly underwent a thermal intramolecular ene reaction via the enol intermediate as an ene moiety to give 2 α,5-(1′-methylethano-5α)-cholestan-3-one in good yield (**Scheme 68**).

Srikrishna et al.[128] discovered an unusual acid-catalyzed rearrangement of γ,δ-unsaturated ketones **13**, which are typical Claisen products. The transformation obviously proceeds via a sequence of an intramolecular ene reaction followed by a retro-ene



Scheme 67 An intramolecular ene reaction on a bicyclo[3.2.1]octane system as a key step in an enantioselective synthesis of (–)-kainic acid.



Scheme 68 Intramolecular ene reaction via an enol as the ene component.

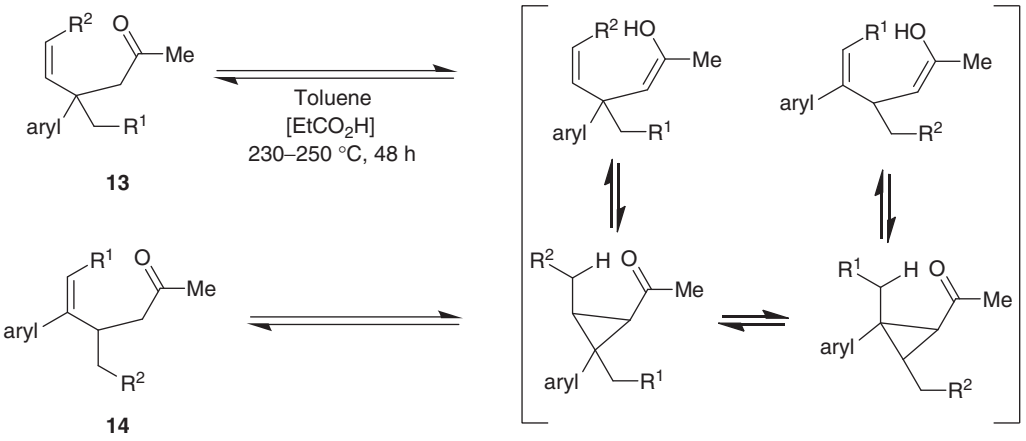
reaction via the intermediacy of an enol, and gives rise to the formation of regioisomeric γ,δ-unsaturated ketones **14** (Scheme 69). The ene intermediates are cyclopropyl methyl ketones, which remain elusive under the reaction conditions.

Enamines are the nitrogen analogs of enols and also well suited for implementation as ene partners into intramolecular ene reactions. This peculiar transformation was developed by Cossy et al.[129] for the synthesis of spirolactams, eventually also in a stereo- and enantioselective fashion. The thermal rearrangement of tertiary and secondary enamino carboxamides with an *N*-allyl substituent as the electroneutral enophile moiety can be successfully involved. The ene reaction furnish enamino or imino spirolactams (Scheme 70) via aza-ene (secondary enamino carboxamides) or carba-ene (tertiary enamino carboxamides) *exo*-transition states, both favoring the formation of *cis*-spirolactams.[129a] The enamino and imino spirolactam diastereomers **15**/**16** and **17**/**18** are separable and can be quantitatively hydrolyzed to the ketone derivatives.

5.01.3.2 Alkynes as Enophile Moieties

5.01.3.2.1 Electron-deficient alkynes as enophile moieties

Mikami et al.[130] found in the studies on the diastereoselectivity of thermal ene cyclizations of propargyl allyl ethers, which contain a methoxycarbonyl group as enophile-activating functionality and an allylic stereocenter, that the cycloisomerization proceeds with excellent yield and very good 1,2-asymmetric induction (Scheme 71, Table 8).

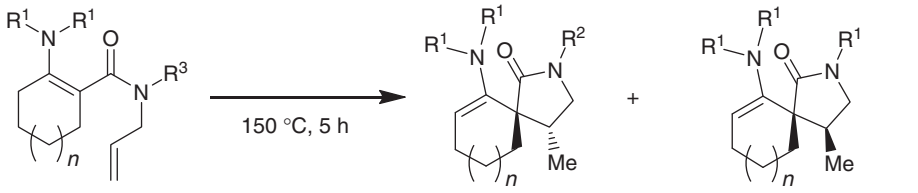


13

14

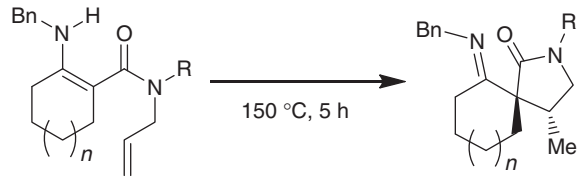
aryl = *p*-tolyl, $R^1 = R^2 = H$, 68% (**14a**/**13a** = 67:33)
aryl = Ph, $R^1 = R^2 = H$, 66% (**14b**/**13b** = 67:33)
aryl = *p*-tolyl, $R^1 = Me$, $R^2 = H$, 66% (**14c**/**13c** = 90:10)
aryl = 2,4-$Me_2C_6H_4$, $R^1 = R^2 = H$, 75% (**14d**/**13d** = 95:5)

Scheme 69 Intramolecular ene/retro-ene rearrangement of γ,δ-unsaturated ketones.

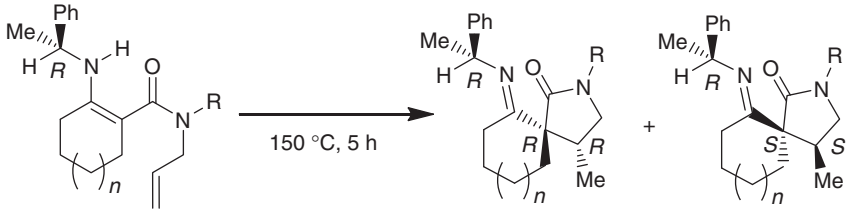


15 **Y**

n = 0, $R^1 = (CH_2)_4$, R^2 = allyl, 85%, **15a**/**16a** = 80:20
n = 0, $R^1 = (CH_2)_4$, R^2 = Me, 76%, **15b**/**16b** = 86:14
n = 1, $R^1 = (CH_2)_4$, R^2 = allyl, 92%, **15c**/**16c** = 87:13
n = 1, $R^1 = (CH_2)_4$, R^2 = Me, 85%, **15d**/**16d** = 90:10
n = 0, $R^1 = (CH_2)_5$, R^2 = allyl, 65%, **15e**/**16e** = 78:22



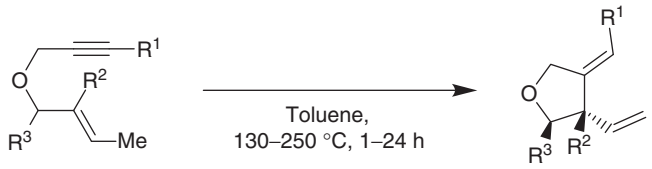
n = 0, R = allyl, 81%
n = 0, R = Me, 76%
n = 1, R = allyl, 95%



17 **18**

n = 0, R = allyl, 90%, (**17a**/**18a** = 77:23)
n = 0, R = Me, 77%, (**17b**/**18b** = 75:25)
n = 1, R = allyl, 95%, (**17c**/**18c** = 76:24)

Scheme 70 Diastereo- and enantioselective synthesis of spirolactams by intramolecular ene reactions.



Scheme 71

Table 8 1,2-Asymmetric induction in intramolecular ene reactions with an alkynyl ester enophile moiety (**Scheme 71**)

Entry	*R^1*	*R^2*	*R^3*	*Yield (%)*	*Ratio* trans/cis[a]
1	H	H	H	95	–
2	CO_2Me	H	H	98	–
3	CO_2Me	H	Me	90	86:14
4	CO_2Me	H	^{i}Pr	90	>95:5
5	CO_2Me	H	Ph	97	93:7
6	CO_2Me	Me	^{i}Pr	93	90:10
7	CO_2Me	Me	Ph	88	92:8

[a]The *trans*/*cis* ratio of the substituents R^2 and R^3.

In an elegant combination with a preceding Claisen rearrangement, this methodology was applied in a domino reaction as a highly convergent key step to the asymmetric synthesis of (+)-9(11)-dehydroestrone methyl ether (**Scheme 72**). The same strategy was reported by Groen–Piotrowska and Groen for the synthesis of the progestagens desogestrel and 3-ketodesogestrel.[131]

5.01.3.2.2 Electroneutral alkynes as enophile moieties

Electroneutral alkyne enophiles are also relatively unreactive substrates in intramolecular ene reactions within the framework of pericyclic reactivity. Alkenes substituted by heteroelements, such as enols, are particularly reactive in cycloisomerizations with the alkyne enophiles. In addition, the change of mechanism from pericyclic to transition metal-catalyzed processes has paved the way for highly efficient intramolecular Alder-ene-type reactions over the past three decades. Besides primordial palladium complexes, many other transition metal complexes have opened a whole new world of transition metal catalyzed Alder-ene-type reactions.

As already discussed in Chapter 3.1.2, enamines are particularly well suited as ene partners in intramolecular ene reactions with unactivated alkene enophiles. This aspect also holds true for unactivated alkynes. Cossy et al.[129] also used a tertiary and a secondary enamino carboxamide with an *N*-propargyl substituent as the electroneutral enophile moiety to obtain the corresponding enamino or imino exomethylene spirolactams in good to excellent yield (**Scheme 73**).

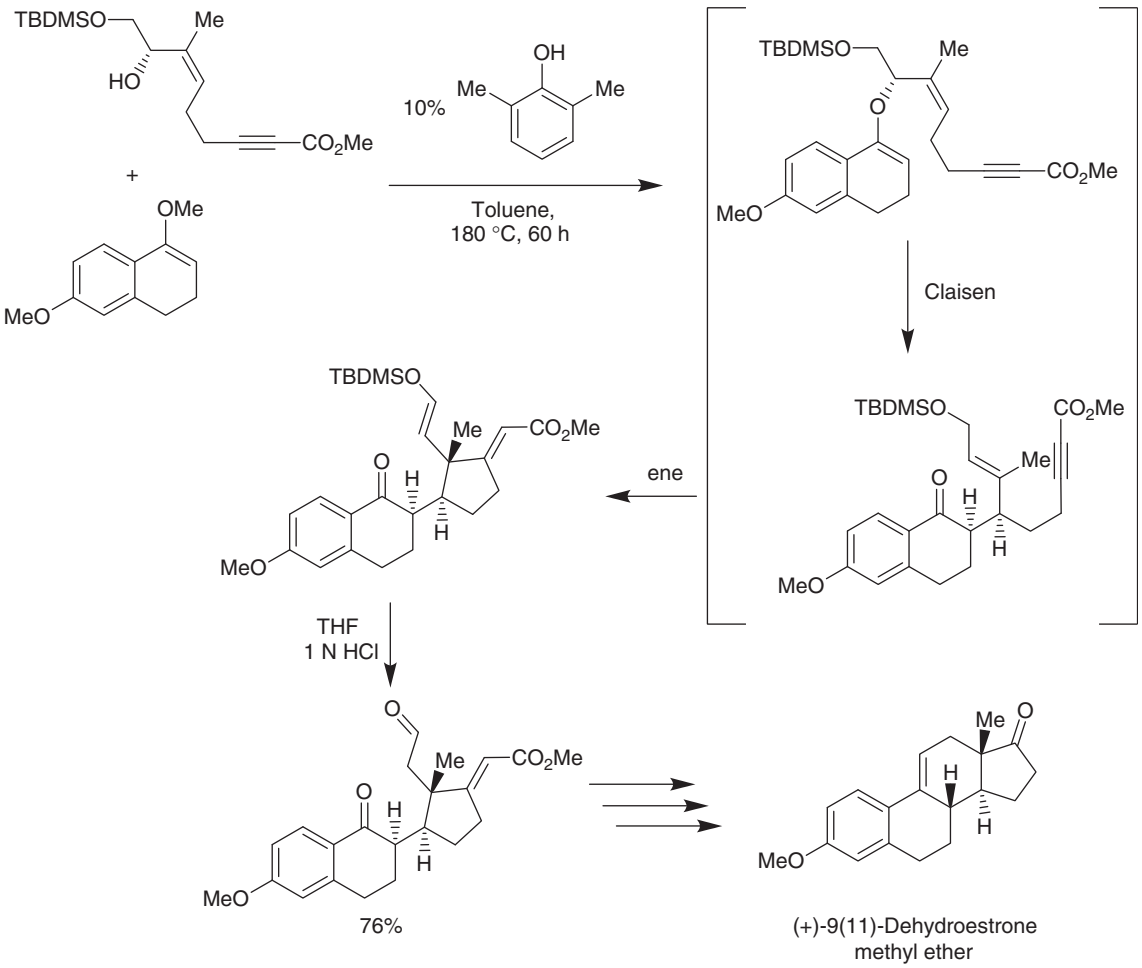
Desai et al.[132] have found an unusual formation of 3,7,7-trimethyl-2,4,7,7a-tetrahydrobenzofuran-4-one starting from 2-formyl-4,4-dimethyl-cyclohexa-2,5-dien-1-one in the sense of a domino Michael/ene/decarbonylation reaction (**Scheme 74**), where the initial Michael addition of propargyl alcohol triggers a subsequent enol-alkyne ene reaction. The fragmentation of the β,γ-enal might occur as a [4 + 1] cheletropic decarbonylation under the given reaction conditions.

Just recently, the groups of Roglans[133] and of Danheiser[134] reported uncatalyzed formal [2 + 2 + 2] cycloadditions of triynes to tricyclic aromatic derivatives, which can be rationalized by a sequence of propargyl ene reaction and subsequent Diels–Alder reaction with concomitant aromatization by hydrogen shift. Macrocyclic triynes and enediynes were found to undergo a thermally induced [2 + 2 + 2] cycloisomerization through the intermediacy of an intramolecular ene reaction with exclusion of diradical intermediates (**Scheme 75**).[133]

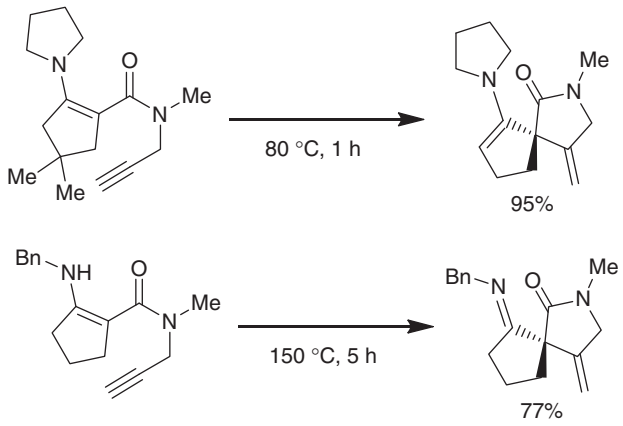
By participation of unactivated cyano groups, several examples of formal intramolecular [2 + 2 + 2] cycloisomerization and cycloadditions via propargylic ene/cyano Diels–Alder reactions were shown (**Scheme 76**).[134a] In addition, this propargylic ene/Diels–Alder reaction was also conducted in an intermolecular fashion with alkene and alkyne dienophiles (**Scheme 77**).[134b]

According to DFT calculations, uncatalyzed [2 + 2 + 2] cycloisomerizations of triynes to tricyclic benzene derivatives bearing a propargyl hydrogen atom proceed through energetically most favorable initial ene transition state.[135] In intramolecular ene reactions, such as Schmittel-ene cyclizations of enyne-allenes, alkyl substituted allenes can well serve as ene components, whereas the alkynyl moiety serves as the electroneutral enophile. As experimentally and computationally demonstrated by Schmittel et al.,[136] these cycloisomerizations rather occur via the intermediacy of very short lived diradical intermediates, as supported by stereochemical evidence and indicated by the lack of cyclopropyl methyl radical ring opening (**Scheme 78**).

Mechanistic investigations based on the determination of kinetic isotope effects as well as theoretical calculations suggest a highly asynchronous transition state, located near the boundary between concerted and stepwise processes.[137] However, in the case of bulky substituents on the alkyne enophile, diradical intermediates have been suggested by computations.[138] Recent isotope-labeling and radical clock experiments could further support the diradical intermediates in enyne-allene



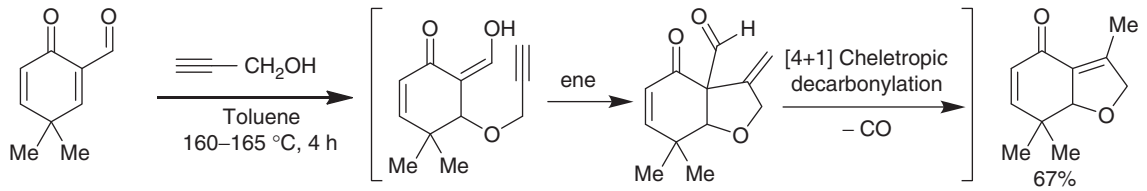
Scheme 72 Domino Claisen/ene reaction sequence as key step in the asymmetric synthesis of (+)-9(11)-dehydroestrone methyl ether.



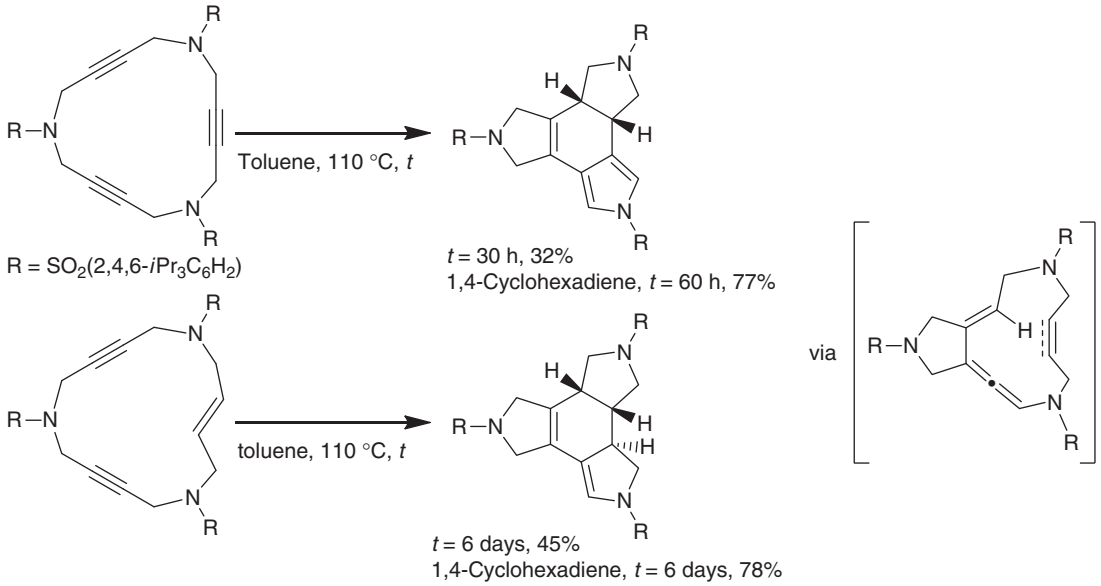
Scheme 73 Synthesis of exomethylene spirolactams by intramolecular ene reactions.

ene-cycloisomerizations.[139] Furthermore, comparable results were obtained under photochemical conditions and spectroscopic evidence of a fulvene triplet diradical intermediate was garnered by laser flash photolysis.[140]

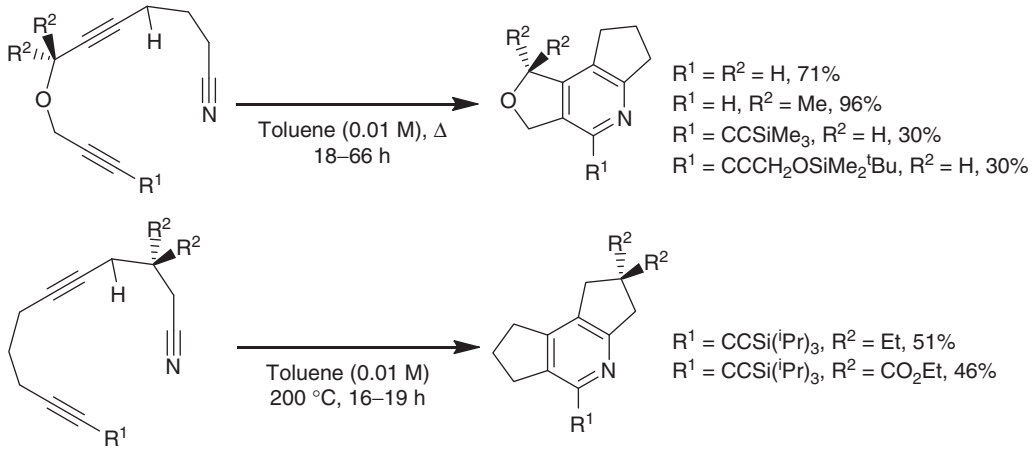
Buisine et al.[141] demonstrated Alder-ene cycloisomerizations of 1,6-allenynes without catalysts in boiling xylenes that provide 6-methylene-1-vinylcyclohexene derivatives in good to excellent yields (Scheme 79, Table 9).



Scheme 74 Domino Michael/ene/decarbonylation sequence for the synthesis of 3,7,7-trimethyl-2,4,7,7a-tetrahydrobenzofuran-4-one.



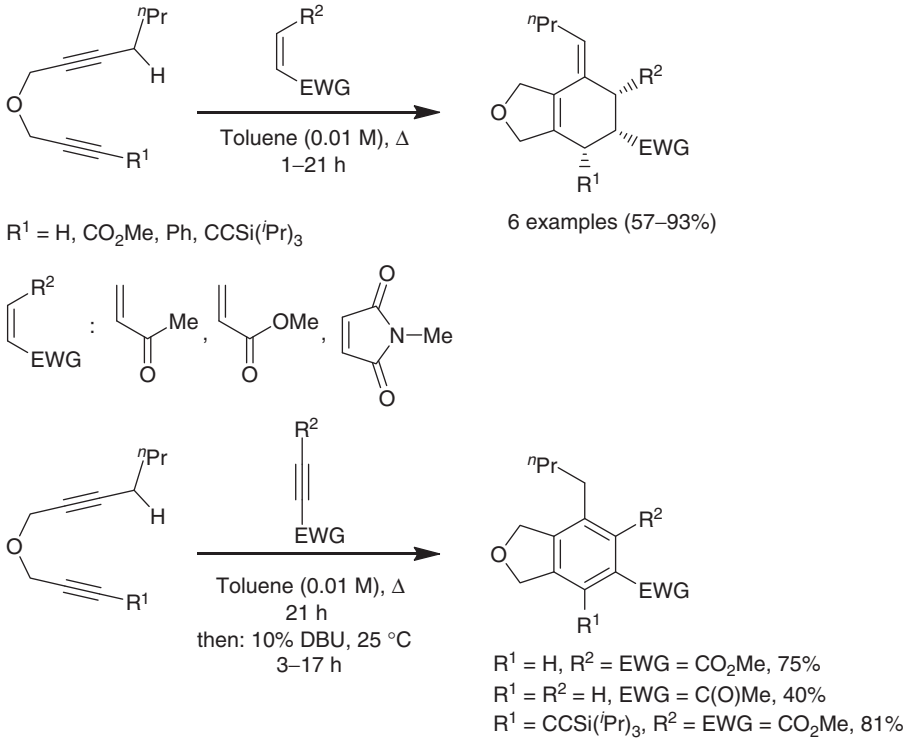
Scheme 75 Thermally induced [2 + 2 + 2] cycloisomerization and cycloadditions of macrocyclic triynes and enediynes.



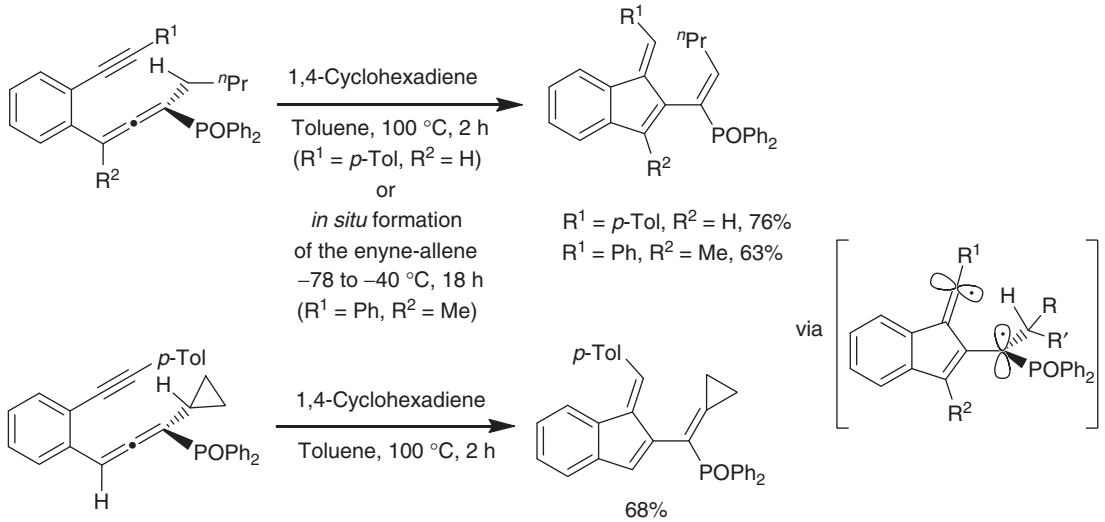
Scheme 76 Formal intramolecular [2 + 2 + 2] cycloadditions via propargylic ene/cyano Diels–Alder reactions.

Intramolecular palladium-catalyzed Alder-ene reactions have been discovered and developed in the 1980s Trost et al.[142] Changing the mechanism from pericyclic to organometallic intermediates has not only contributed a new paradigm, but also enriched the conceptual understanding and realization of the concept of atom economic processes.[143] The cycloisomerization of 1,n-enynes has remained an intensively pursued field of synthetic methodologies ever since.[144] Major advances of enantioselective transition metal catalyzed cycloisomerizations of enynes have also been covered in reviews.[145]

In 1999 Trost et al. disclosed the conditions for the palladium-catalyzed ene cyclizations of 1,6-enynes. Systematic variation of the substitution pattern on the tether and on the enophile and ene termini as well as of the Pd(II)-catalyst system were described



Scheme 77 Formal intermolecular [2 + 2 + 2] cycloadditions via propargylic ene/cyano Diels–Alder reactions with alkene and alkyne dienophiles.

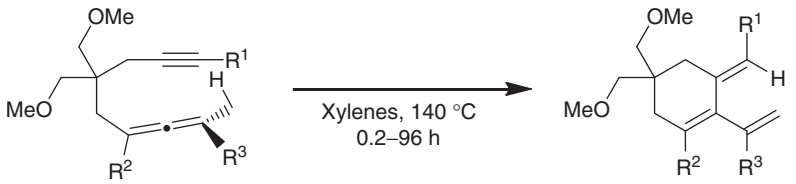


Scheme 78 Formal ene cyclization of enyne-allenes.

(Schemes 80 and 81).[146] The reaction produces both 1,4-dienes **19**/**21** (Alder-ene-type products) (Scheme 80, Table 10) and 1,3-dienes **20**/**22** (Scheme 81, Table 11). Although either the absence of ligands or the use of the diimino ligand *N*,*N*-bis(benzylidene)ethylenediamine (BBEDA) or the soft triphenylarsane ligand favor the 1,4-diene products **19**/**21**, the bulkier tri-*o*-tolylphosphine ligand favors the formation of the 1,3-dienes **20**/**22**.

Most important for the synthesis of polycyclic frameworks, Alder-ene reactions lead to *cis*-annulated ring systems in a stereocontrolled fashion (Scheme 82).

The conditions for the formation of 1,3-dienes, which are excellent substrates for Diels–Alder reactions, were studied in detail by Trost et al.[147] A remote substituent effect of coordinating functionalities additionally enables an asymmetric induction in palladium-catalyzed enyne cycloisomerizations.[148]

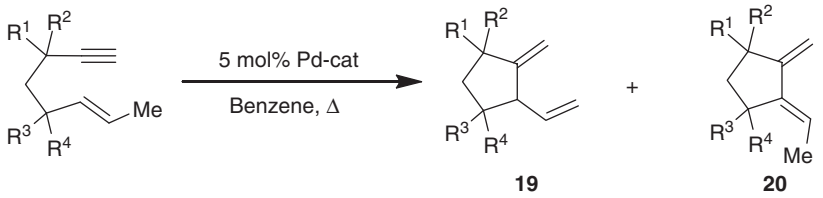


Scheme 79

Table 9 Intramolecular thermal Alder-ene cycloisomerization of 1,6-allenynes (Scheme 79)

Entry	R^1	R^2	R^3	*Yield (%)*
1	H	*t*Bu	H	98
2	$SiMe_3$	*t*Bu	H	98
3	H	*t*Bu	Me	69
4	Ph	*t*Bu	Me	65
5	Ph	Ph	Me	95
6	H	Ph	Me	83
7	H	Me	Me	67[a]

[a]Heating in toluene for 150 h.



Scheme 80

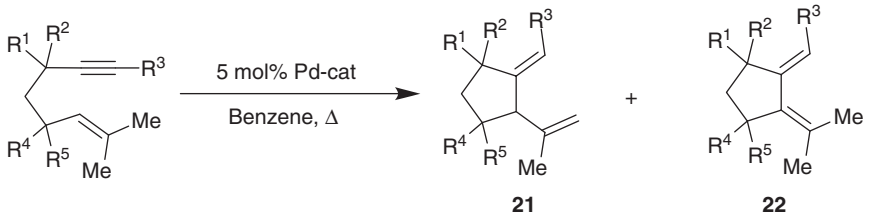
Table 10 Effects of the substitution pattern and the Pd catalysts on ene-type cyclizations of 1,6-enynes (Scheme 80)

Entry	R^1	R^2	R^3	R^4	*Yield (%)*	*Ratio **19/20***	*Diastereomeric ratio of **19***
1[a]	H	H	H	PMBO	42	1:8	1:7.5
2[b]	H	H	H	PMBO	33	4.5:1	8:1
3[c]	H	H	H	PMBO	17	12:1	>99:1
4[a]	PMBO	H	H	H	41	1:1	3.5:1
5[b]	PMBO	H	H	H	33	2:1	1:1
6[c]	PMBO	H	H	H	52	1:2	2:1
7[a]	H	H	Me	TBDMSO	54	1:1	2:1
8[b]	H	H	Me	TBDMSO	64	5:2	1:2
9[c]	H	H	Me	TBDMSO	15	100:0	2:1
10[a]	Me	TBDMSO	H	H	80	3:7	2:1
11[b]	Me	TBDMSO	H	H	86	1:10	3.5:1
12[c]	Me	TBDMSO	H	H	87	2:7	10:7

[a]$Pd(OAc)_2$/*o*Tol_3P as catalyst system.
[b]$Pd(OAc)_2$/BBEDA as catalyst system.
[c]$Pd(OAc)_2$ as catalyst system.

Knierzinger et al.[149] have performed palladium(II)-catalyzed ene-type cyclizations of terpenoid 1,6-enynes with variable alkynyl substitution pattern in good yield (Scheme 83, Table 12). The diastereoselectivity with respect to the 2- and 5-position of the alkylidene-cyclopentane framework depends on the employed substituent.

Trost and Shi have also developed the Alder-ene-type cycloisomerization into domino processes, where, in the absence of *syn*-β-hydrogen atoms, the alkyl-Pd species is forced to continue inserting into another (even up to six additional) alkenyl



Scheme 81

Table 11 Effects of the substitution pattern and the Pd catalysts on ene-type cyclizations of terpenoid 1,6-enynes (**Scheme 81**)

Entry	R^1	R^2	R^3	R^4	R^5	*Yield (%)*	*Ratio **21/22***	*Diastereomeric ratio of **21***
1[a]	H	H	H	TBDMSO	H	10	3.4:1	1:1
2[b]	H	H	H	TBDMSO	H	14	100:0	>99:1
3[c]	H	H	H	TBDMSO	H	14	100:0	>99:1
4[a]	H	H	H	TBDMSO	Me	67	100:0	2.3:1
5[b]	H	H	H	TBDMSO	Me	50	100:0	2:1
6[c]	H	H	H	TBDMSO	Me	42	100:0	3:1
7[a]	PMBO	H	H	H	H	19	6:1	1:2
8[b]	PMBO	H	H	H	H	40	3.5:1	1.2:1
9[d]	PMBO	H	H	H	H	47	4:1	1:1
10[a]	TBDMSO	Me	H	H	H	44	3.5:1	4:1
11[b]	TBDMSO	Me	H	H	H	52	2:1	3:1
12[d]	TBDMSO	Me	H	H	H	43	5:1	1:2
13[a]	OH	Me	H	H	H	18	12:1	4:1
14[e]	OH	Me	H	H	H	49	10:1	4:1
15[b]	PMBO	H	CO_2Me	H	H	77	1.3:1	>99:1
16[d]	PMBO	H	CO_2Me	H	H	49	1:1	>99:1

[a] $Pd(OAc)_2$/*o*Tol_3P as catalyst system.
[b] $Pd(OAc)_2$/BBEDA (BBEDA: *N,N*-bis(benzylidene)ethylenediamine) as catalyst system.
[c] $Pd(OAc)_2$ as catalyst system.
[d] $Pd(OAc)_2$/Ph_3As as catalyst system.
[e] $Pd(OAc)_2$/$P(OCH_2)_3CEt$ as catalyst system.

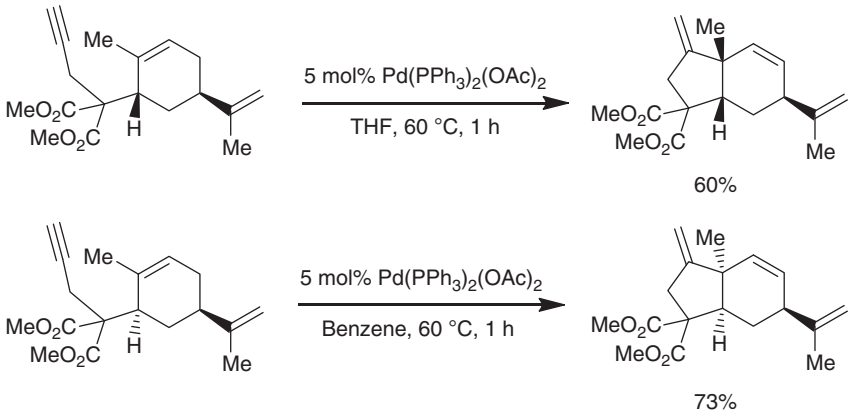
fragment(s).[150] Besides the formation of triquinane frameworks, the Pd(0)-catalyzed Alder-ene reaction could be used for the rapid formation of a polyspirocyclic rope-like molecule in a zipper-fashion (**Scheme 84**).

The groups of Trost and Banwell have contributed some remarkable applications of palladium-catalyzed Alder-ene-type cycloisomerizations to the synthesis of biologically active natural products, such as the antiulcerogenic aglycone (+)-cassiol,[151] the antifungal sesquiterpene (±)-chokol C,[152] the γ-aminobutyric acid antagonist picrotoxanes,[153] the crinine alkaloid (±)-hamayne,[154] and precursors to the *Amaryllidaceae* alkaloid tazettine[155] (**Table 13**).

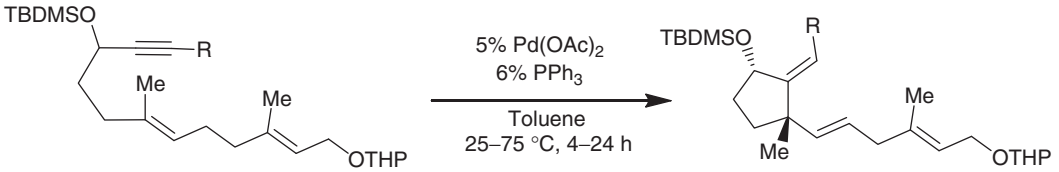
Kressierer and Müller showed in several cases that the palladium(0)-catalyzed Alder-ene reaction of alkynyl allyl alcohols, which furnish cyclic γ,δ-enals as a consequence of the *in situ* enol-aldehyde tautomerism, is excellently suited as an entry into consecutive one-pot transformations (**Scheme 85**).[156] As a consequence, consecutive and sequential cycloisomerization/Wittig,[156] cycloisomerization/reductive amination,[157] and cycloisomerization/Knoevenagel condensation sequences[158] were readily established in a one-pot fashion, giving rise to five-membered carbo- and heterocycles with densely functionalized sidechains (**Scheme 86**).

Strübing et al.[159] illustrated that the enyne products arising from the three-component coupling of aldehydes, amides, and dienophiles are perfectly suited for catalytic postcondensation Alder-ene cyclizations (**Scheme 87**).

The success of the enantioselective rhodium catalyzed hydrogenation has considerably stimulated the development of intramolecular rhodium-catalyzed Alder-ene reactions by taking advantage of a plethora of chiral chelating diphosphane ligands. In 2002, the group of Zhang was the first to report an efficient and highly enantioselective synthesis of functionalized α-methylene-γ-butyrolactones via a rhodium(I)-catalyzed intramolecular Alder-ene reaction (**Schemes 88** and **89**).[160] *S*-2,2′–Bis(diphenylphosphano)–1,1′–binaphthyl) (*S*-BINAP) as a chiral chelating ligand furnishes the *S*-configured butyrolacton (**Table 14**), whereas *R*-BINAP delivers the *R*-enantiomer (**Table 15**). In contrast to palladium-catalyzed cycloisomerizations, the 1,4-diene isomer is formed exclusively. The reaction works equally well with allyl ethers (R^2=OR), allyl acetates (R^2=OAc), and allyl alcohols (R^2=OH). However, in the latter case the elusive enol immediately tautomerizes to give the corresponding aldehyde. An excellent formal synthesis of (+)-pilocarpine was achieved based on this methodology.



Scheme 82 Stereocontrolled *cis*-annulation in Pd-catalyzed Alder-ene cyclizations.



Scheme 83 Palladium(II)-catalyzed ene-type cyclizations of terpenoid 1,6-enynes.

Table 12 Palladium(II)-catalyzed ene-type cyclizations of terpenoid 1,6-enynes (Scheme 83)

Entry	*R*	*Yield (%)*[a]
1[b]	H	60
2[c]	CO_2Et	66
3[c]	$CO_2(CH_2)_8SiMe_2tBu$	69
4[c]	$P(O)(OEt)_2$	68
5[b]	$CONMe_2$	55
6[d]	$CO_2(CH_2)_8CH_3$	81
7[d]	$CO_2(CH_2)_7CH=CH(CH_2)_7CH_3$	36

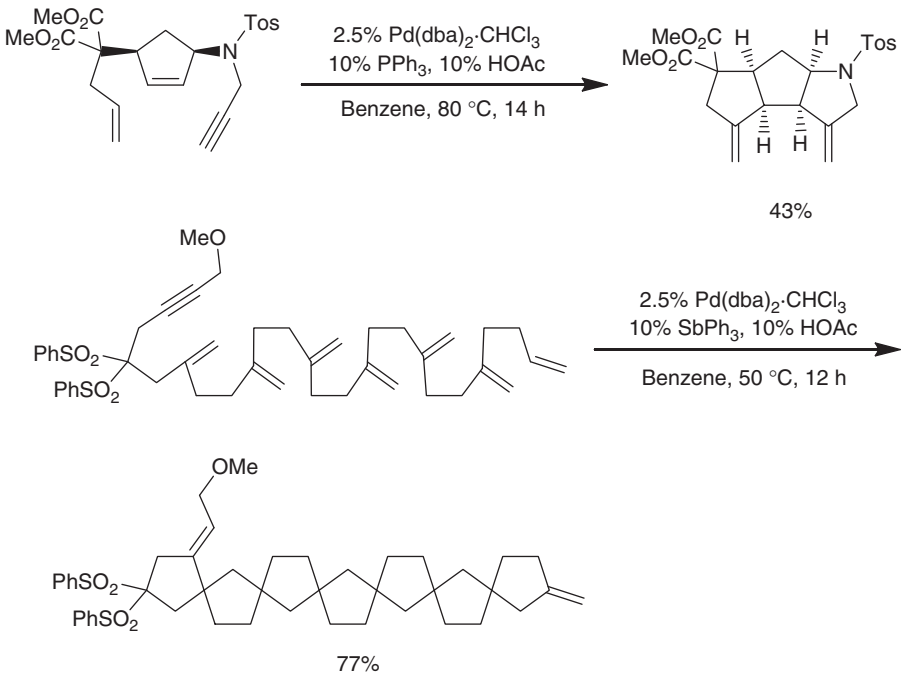
[a]The diastereoselectivity arising from the 2- and 5-substituents was determined after deprotection.
[b]A 1:2 diasteromeric mixture was found.
[c]A single diastereomer was found.
[d]Upon deprotection an anellated furan arising from a cyclocondensation was found.

With the same efficacy and efficiency, chiral α-substituted γ-butyrolactams,[161] tetrahydrofurans,[162] and also 3,4,5-trisubstituted γ-lactones[163] were obtained. In the latter case, the excellent enantioselectivity was applied for kinetic resolutions of racemic substrates and the cyclized enantiomerically enriched γ-lactones were used in formal asymmetric syntheses of (–)-blastmycinolactol and (+)-blastmycinone. Nicolaou et al.[164] have implemented the enantioselective rhodium-catalyzed Alder-ene cycloisomerization of 1,6-enynes as an asymmetric key step into the total synthesis of antibiotic platensimycin, which proceeded with excellent enantiomeric excess.

Based on the Rh-BINAP catalyst system for intramolecular Alder-ene cycloisomerizations sequences were conceived that take advantage of this unique and efficient enantioselective generation of five-membered carbo- and heterocycles. Körber et al.[165] have employed the enantioselective rhodium-catalyzed cycloisomerization of alkyl and (hetero)aryl alkynyl allyl alcohols for the generation of aldehyde-bearing chiral 4-alkyl 3-alkylidene tetrahydrofurans and tetrahydrofuranones, which were converted into α,β-unsaturated carbonyl side chains in a one-pot fashion via a concluding Wittig olefination in good yields (Scheme 90).

Furthermore, based on the initial Alder-ene cycloisomerization of alkyl and (hetero)aryl-substituted alkynyl allyl alcohols, the rhodium(I)-BINAP complex enables a subsequent reduction of the primary products with hydrogen and the transformation into 2,7- dioxabicyclo[3.2.1]octanes in the sense of a sequential rhodium catalyzed process (Scheme 91).[166]

Just recently, Okamoto et al.[167] reported an enantioselective rhodium(I)-BINAP-catalyzed allyl ether isomerization/cycloisomerization domino sequence of phenol- or naphthol-linked 1,7-enynes, giving rise to the formation of dihydrobenzofurans and dihydronaphthofurans (Scheme 92).



Scheme 84 Palladium(0)-catalyzed domino Alder-ene cycloisomerizations.

Also iridium complexes such as $[IrCl(COD)]_2$ have been shown to catalyze the intramolecular Alder-ene reaction of 1,6-enynes to give cyclic 1,4-dienes. Shibata et al.[168] demonstrated the increased efficiency of this catalyst system in an ionic liquid over toluene (Scheme 93). The iridium(I)-catalyzed Alder-ene cycloisomerization of an alkynoyl cyclohexadienyl ester or *N*-tosyl amide have been shown to furnish spirocyclic products (Scheme 94).[169]

Kummeter et al.[170] employed this type of Alder-ene cycloisomerization as an entry into a sequential iridium(I)-catalyzed cycloisomerization/Murahashi reaction sequence in a one-pot fashion, where the intermediate aldehyde arising from the Alder-ene tautomerization step was condensed with cyano acetic esters without addition of acids or bases (Scheme 95).

Fürstner et al.[171] disclosed iron(0)-ate complex catalyzed Alder-ene cycloisomerizations of linear and cycloalkene based enynes in good to excellent yields (Scheme 96).

As the first example of an early transition metal-based catalyst Sturla et al.[172] reported a titanocene catalyzed intramolecular Alder-ene cycloisomerization of enynes and dienynes (Scheme 97).

Cycloisomerizations of enynes with gold and platinum catalysts have received great attention in the past two decades in particular for their rich organometallic chemistry and mechanistic versatility.[173] Muñoz et al.[174] found that platinum and cationic gold complexes are able to catalyze the cycloisomerization of enynes with concomitant methoxylation in the presence of phosphane ligands (Scheme 98). The reactions are thought to proceed via cationic organometallic species and carbenium ion intermediates. Dinuclear gold complexes with BINAP ligands enable enantioselective cycloisomerizations of this type.

The cobalt(I)-catalyzed Conia-ene cycloisomerization of simple cyclic β-ketoester ω-ynes was reported by Renaud to give the corresponding bicyclic products in very good yields (Scheme 99).[175]

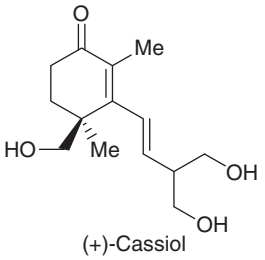
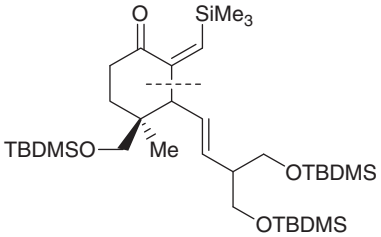
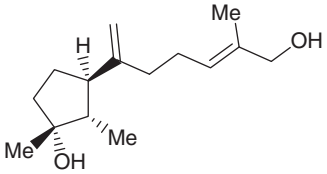
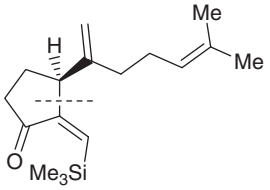
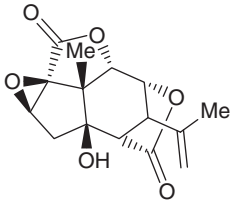
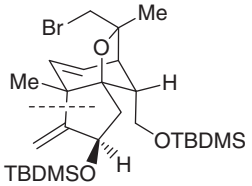
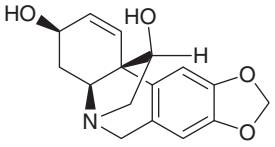
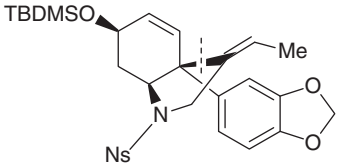
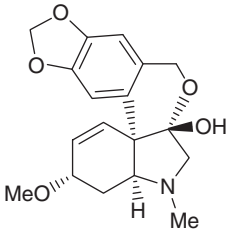
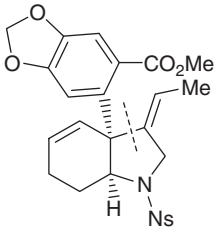
As discussed above, allenynes are suitable substrates for thermal Alder-ene-type cycloisomerizations, where, in the presence of an available hydrogen atom, the allenyl moiety serves as the ene partner and the triple bond adopts the enophile function. These highly unsaturated molecules are excellent ligands for the formation of transition organometallic complexes and, hence, also good substrates for metal-mediated or -catalyzed ene-type reactions.

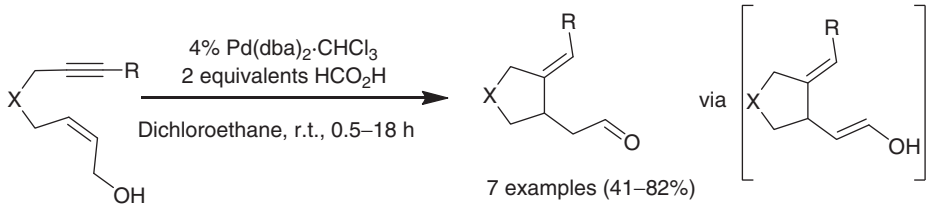
Llerena et al.[176] first reported on cobalt-mediated formal Alder-ene reactions of allenynes on reacting allenynes with a stoichiometric amount of $CpCo(CO)_2$ under irradiation in refluxing xylenes. The reaction furnished 2:3 mixtures of the Alder-ene products **23** and η^4-cyclohexadiene-CpCo complexes **24** (Scheme 100). On their way to the 11-aryl steroid skeleton, the group of Malacria found that *trans*-allenediynes cycloisomerize in the sense of cobalt-mediated $[2+2+2]$ trimerization, whereas the *cis*-allenediyne efficiently undergoes the formal Alder-ene reaction.[177]

Brummond's group[178] and the group of Shibata[179] discovered simultaneously that rhodium(I) complexes are excellent catalysts in the formal Alder-ene cycloisomerization of allenynes to give cross-conjugated trienes under mild conditions and in good yields (Scheme 101).

In the past decade, Brummond and her group have considerably developed and extended this Alder-ene-type cycloisomerization of allenynes. It was expanded to the formation of δ- and ε-lactams,[180] to yne-allenamides as substrates;[181] moreover, it was applied as a key reaction to the synthesis of the angiogenesis inhibitor ovalicin.[182] The obtained cross-conjugated trienes[183] are excellent building blocks for complex molecular frameworks. Therefore, consecutive one-pot transformations initiated by the

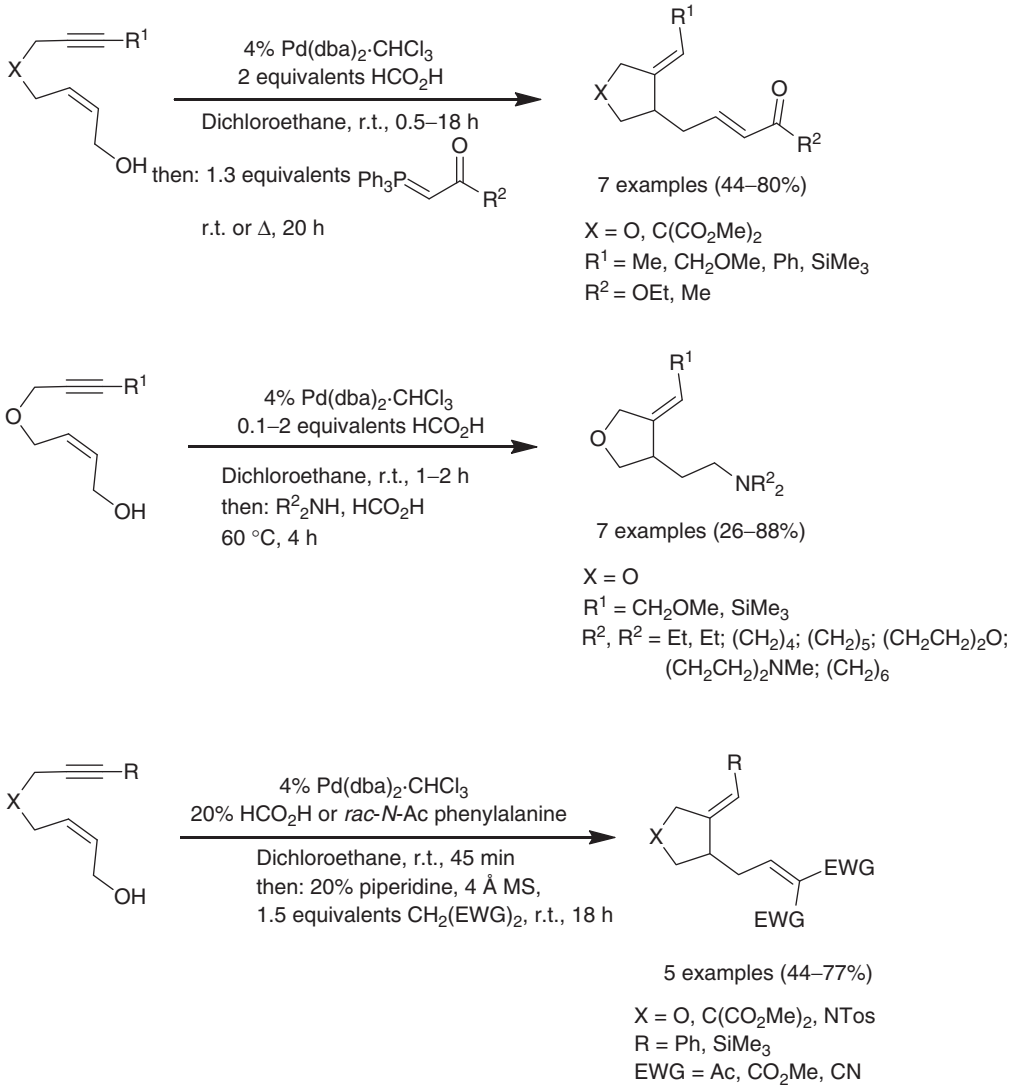
Table 13 Targets formed by application of the palladium-catalyzed Alder-ene-type reaction as a key step

Entry	*Target structure*	*Alder-ene product*
1	 (+)-Cassiol	
2	 (±)-Chokol C	
3	 Picrotoxinin	
4	 (±)-Hamayne	 Ns:*p*-$O_2NC_6H_4$
5	 (±)-Tazettine	

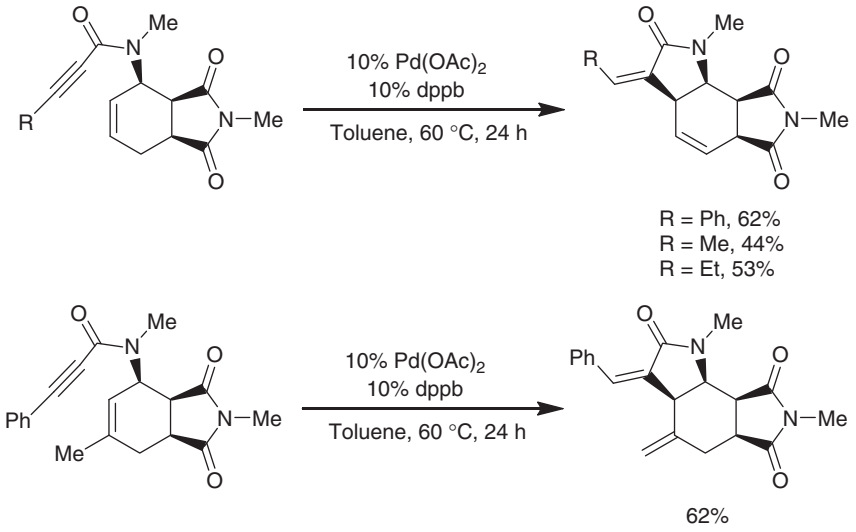


X = O, $C(CO_2Me)_2$
R = Me, CH_2OMe, Ph, $SiMe_3$

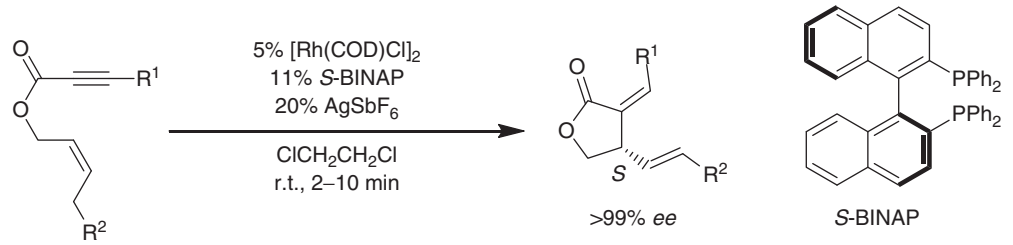
Scheme 85 Palladium(0)-catalyzed Alder-ene cycloisomerization of alkynyl allyl alcohols to give cyclic γ,δ-enals.



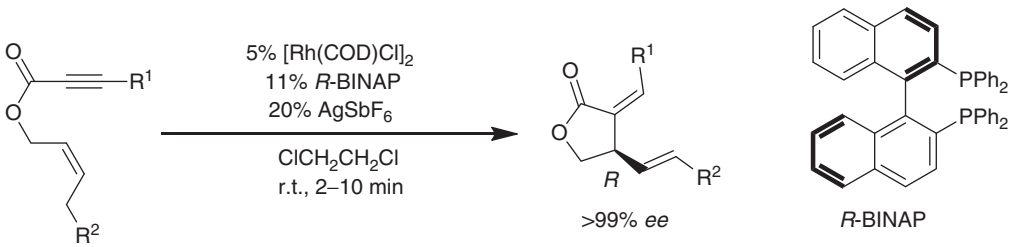
Scheme 86 Consecutive and sequential palladium(0)-catalyzed one-pot sequences with alkynyl allyl alcohols comprising a Alder-ene/cycloisomerization.



Scheme 87 Palladium(0)-catalyzed Alder-ene cycloisomerization of enyne products arising from a three-component coupling of aldehydes, amides, and dienophiles.



Scheme 88



Scheme 89

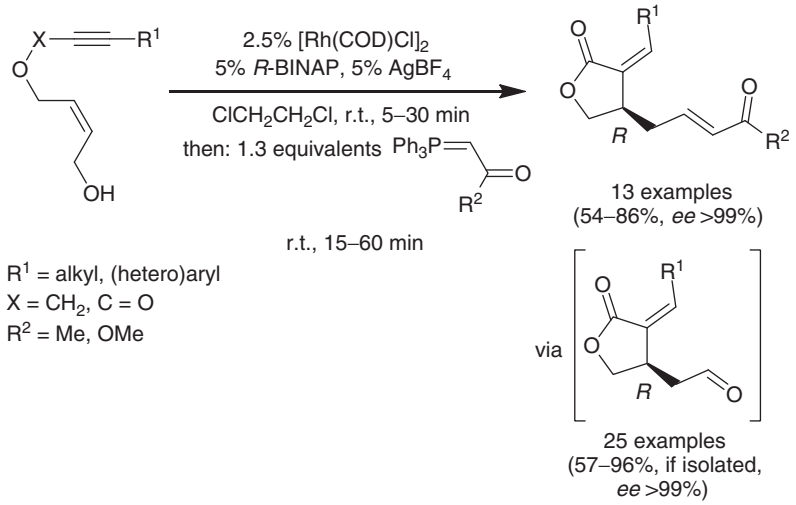
Table 14 Enantioselective synthesis of functionalized (*S*)-α-methylene-γ-butyrolactones via a rhodium(I)-catalyzed intramolecular Alder-ene reaction (**Scheme 88**)

Entry	R^1	R^2	*Yield (%)*
1	Ph	Et	93
2	Ph	Me	93
3	*n*Pent	H	90
4	*n*Pent	Me	95
5	Ph	OMe	96
6	Ph	OBn	92
7	Me	OAc	98
8	Me	OMe	95
9	Me	OBn	91
10	*n*Pent	OAc	97
11	*n*Pent	OMe	96
12	*n*Pent	OBn	92

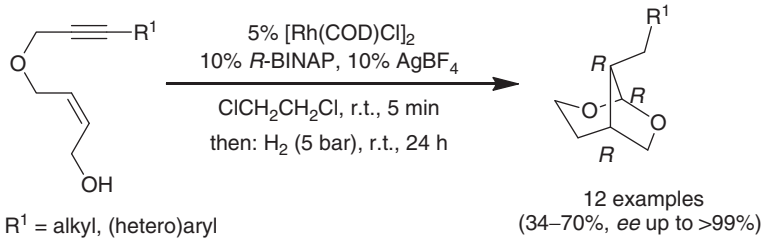
Table 15 Enantioselective synthesis of functionalized (*R*)-α-methylene-γ-butyrolactones via a rhodium(I)-catalyzed intramolecular Alder-ene reaction (**Scheme 89**)

Entry	R^1	R^2	*Yield (%)*
1	Ph	H	94
2	Ph	Me	92
3	Me	H	92
4	Me	Me	98
5	Ph	OAc	96
6	Me	OAc	93
7	*n*Pent	OBn	92

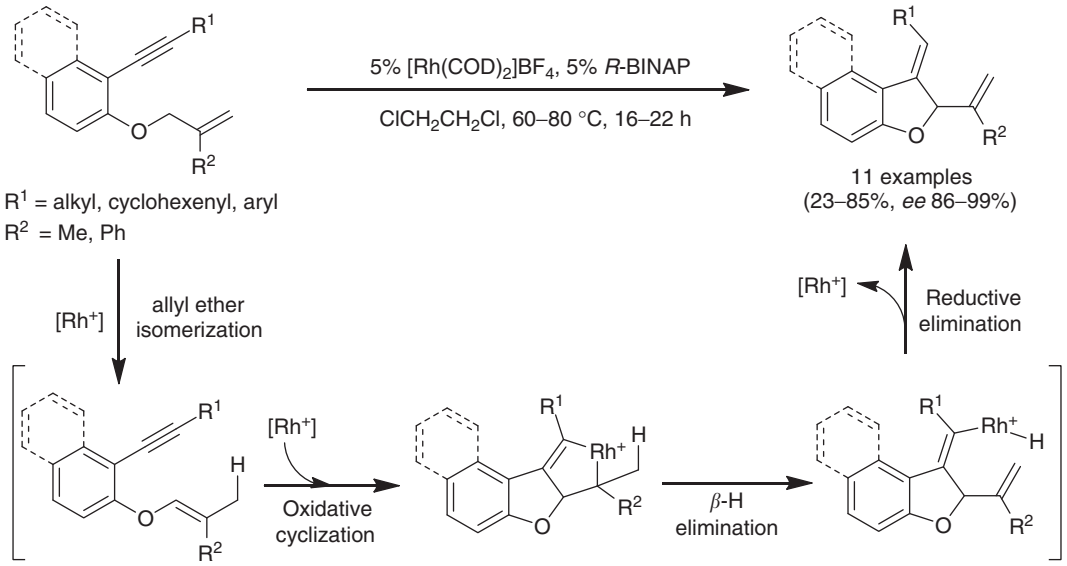
rhodium(I)-catalyzed Alder-ene reactions were devised, such as Alder-ene/Diels–Alder,[184] and Alder-ene/Diels–Alder/Diels–Alder sequences,[185] furnishing complex polycyclic products **25** and **26** (**Scheme 102**). Interestingly, another rhodium(I) complex catalyzes an intramolecular Diels–Alder reaction with the triene moiety to give a diene, ready for an intermolecular [4 + 2] cycloaddition.



Scheme 90 Enantioselective rhodium-catalyzed cycloisomerization/Wittig sequence to enantiomerically pure chiral 4-alkyl 3-alkylidene tetrahydrofurans and tetrahydrofuranones bearing α,β-unsaturated carbonyl side chains.

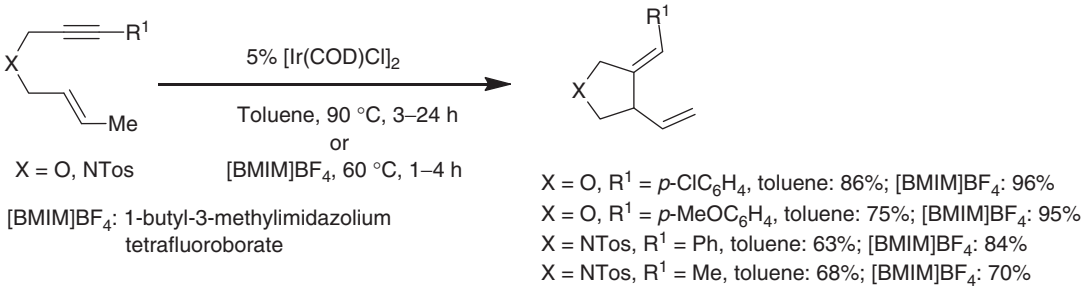


Scheme 91 Enantioselective sequential rhodium(I)-BINAP-catalyzed cycloisomerization/hydrogenation/isomerization/acetalization sequence.

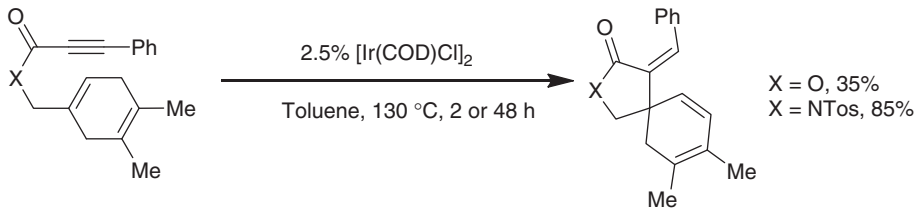


Scheme 92 Enantioselective rhodium(I)-BINAP-catalyzed allyl ether isomerization/cycloisomerization domino sequence.

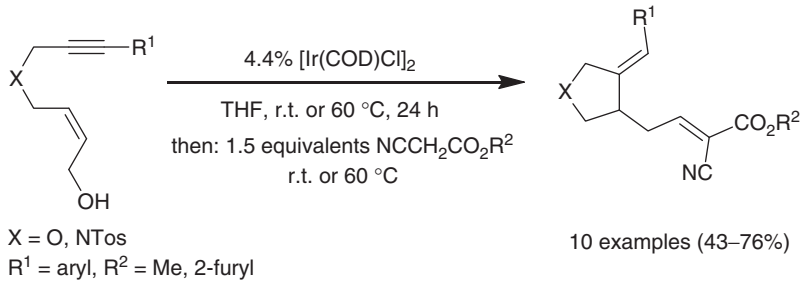
Lemiere et al.[186] found that cationic gold(I) and platinum(II) complexes are able to catalyze the Alder-ene cycloisomerization of allenynes as an optional outcome among other cycloisomerizations. DFT computations with extended basis sets and polarization functionals also supported the bifurcations in the cycloisomerization pathways of platinum(II) complexes.[187] Cheong et al.[188] identified the trinuclear cationic gold complex, $[(Ph_3PAu)_3O]BF_4$ as catalyst for the cycloisomerization of 1,5-allenynes,



Scheme 93 Iridium(I)-catalyzed Alder-ene-type cycloisomerization in an ionic liquid.



Scheme 94 Iridium(I)-catalyzed Alder-ene-type cycloisomerization of an alkynoyl cyclohexadienyl ester and *N*-tosyl amide.



Scheme 95 One-pot iridium(I)-catalyzed Alder-ene/Murahashi reaction sequence.

which lead to the formation of cross-conjugated trienes (Scheme 103, Table 16). Experimental and computational studies revealed that the ene reaction proceeds through a unique nucleophilic addition of the allene double bond to the cationic gold(I) acetylide species, concluded by a 1,5-hydrogen shift.

Zriba et al.[189] discovered that 3-hydroxy-1,5-allenynes are transformed by $PtCl_4$ or $PtCl_2$ as catalysts via an Alder-ene-type cycloisomerization followed by allyl alcohol-enone isomerization into 3-vinylcyclopent-2-enones with remarkable chemoselectivity.

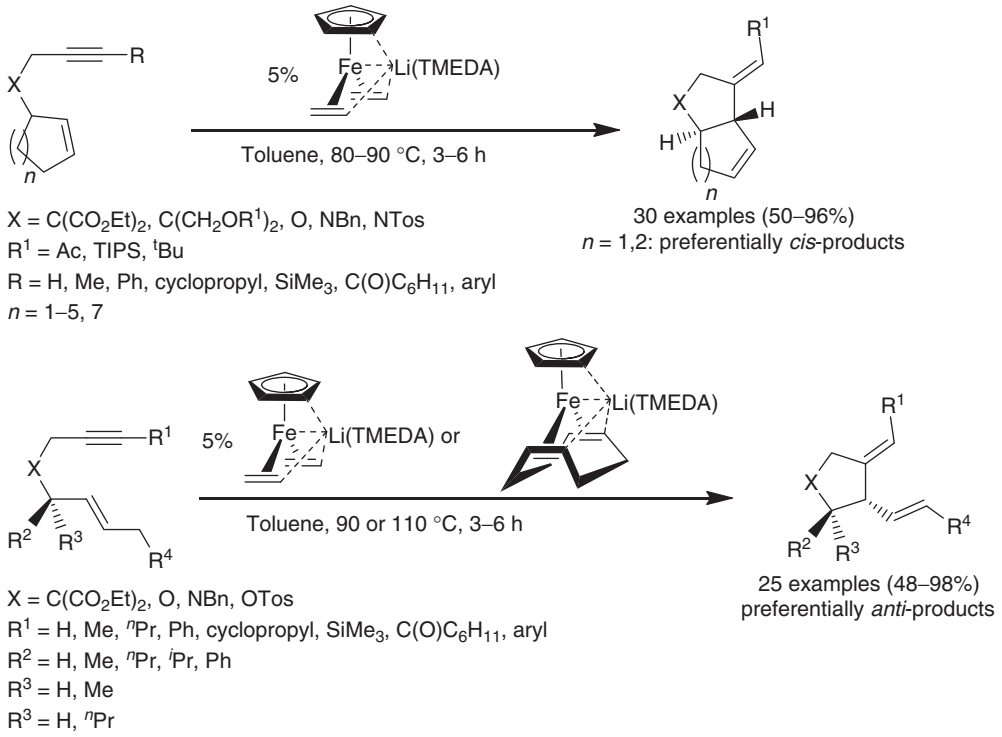
5.01.3.3 Allenes as Enophile Moieties

Allenes can also participate as enophiles in thermal cycloisomerizations. In particular, if the allene bears an electron-deficient substituent, the prerequisites for Alder-ene cycloisomerizations with normal electron demand are fulfilled.

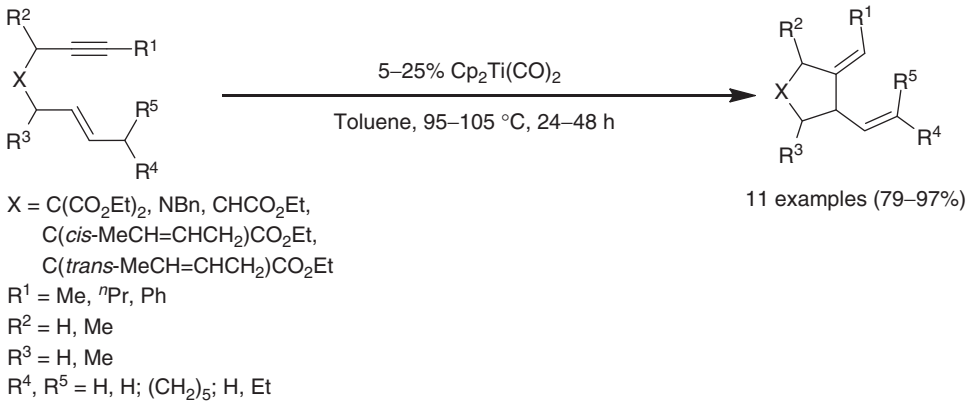
Bintz-Giudicelli and Uguen[190] revealed that, on thermal [2,3]-sigmatropic rearrangement of propargylic toluenesulfinates containing a homoallylic side chain, allenylsulfonyl ene partners are generated, which undergo the Alder-ene cycloisomerization to furnish aryl (cyclopentenyl)methyl sulfones in good yields (Scheme 104). In the case of cycloalkenyl groups as the ene-moieties, the allenyl sulfones give rise to the formation of the spirocycles **27** whereas the propargylic sulfinates form the spirocycles **28**.

Particularly intriguing is an *in situ* generation of alkoxyallenes from propargyl ethers via Müller's coupling/isomerization reaction.[191] Shen et al.[192] reported a domino sequence on the basis of the coupling/isomerization reaction, which concludes the sequence by an intramolecular Alder-ene reaction enabled by the tethered allylether ene moiety (Scheme 105).

Hashmi and Szeimies[193] used the *in situ* generation and subsequent Alder-ene cycloisomerization of an ethano-bridged bis-allenylbicyclo[1.1.0]butane via $Fe(acac)_3$-catalyzed coupling of the corresponding vicinal di-organomagnesium bromides for the first synthesis of a [4.1.1]propella-2,4-diene (Scheme 106).



Scheme 96 Iron(0)-ate complex catalyzed Alder-ene cycloisomerization of enynes.



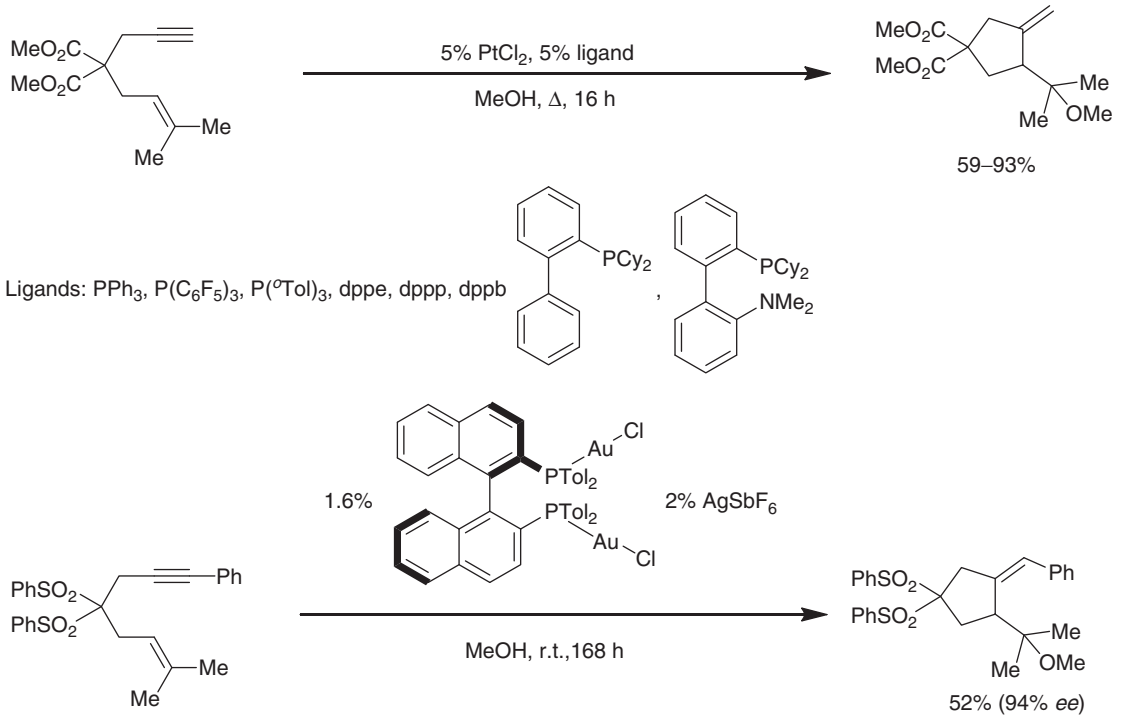
Scheme 97 Titanocene catalyzed Alder-ene cycloisomerization of enynes and dienynes.

Vinylidenecyclopropanes are peculiar allene substrates for transition metal-catalyzed transformations. Li et al.[194] reported that rhodium(I)-catalyzed Alder-ene cycloisomerizations of diarylvinylidenecyclopropanes with a but-3-en-1-yl substituent furnished bicyclo[5.1.0]-octylenes in good to excellent yields (Scheme 107). Mechanistically, the reaction is very likely to proceed through a η^3-allyl-rhodium intermediate.

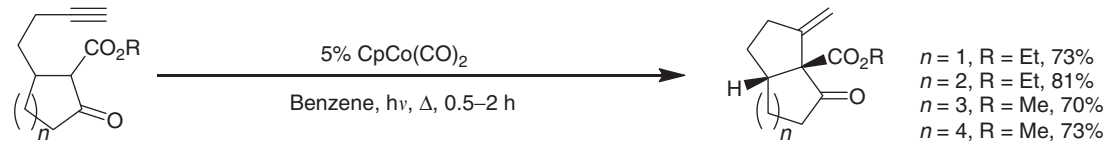
5.01.3.4 Miscellaneous Enophile Moieties in Intramolecular Ene Reactions

Arynes are also well-suited as enophile moieties in intramolecular ene reactions. Just recently, Candito et al.[195] showed in synthetic and mechanistic studies that the intramolecular aryne-ene reaction opens a general, high yielding and selective access to benzo-fused carbo- and heterocycles (Scheme 108, Table 17).

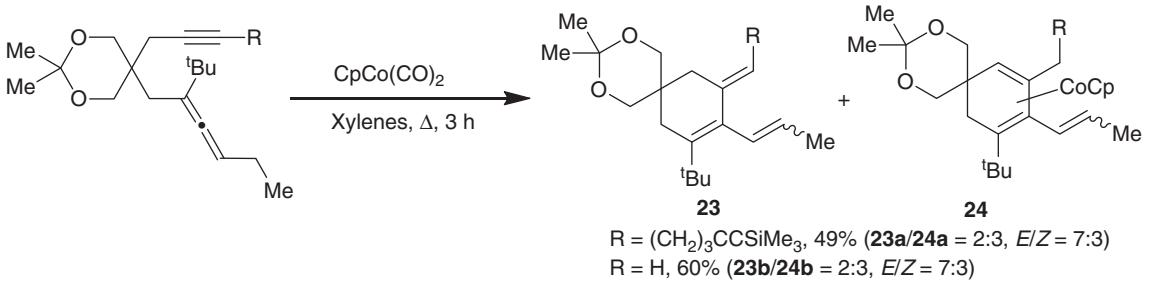
Alkynes bound to fullerenes also represent systems that are able to undergo an Alder-ene-type cycloisomerization, wherein the fullerene serves as an enophile and the alkynyl moiety as the ene component. Altable et al.[196] reported that the thermal reaction of 1,6-fullerenynes bearing an alkyl group on the alkyne terminus furnishes allenes through an intramolecular ene process



Scheme 98 Ligand effects in gold and platinum catalyzed cyclizations of enynes with concomitant methoxylation.



Scheme 99 Cobalt(I)-catalyzed Conia-ene cycloisomerization of cyclic β-ketoester ω-ynes.

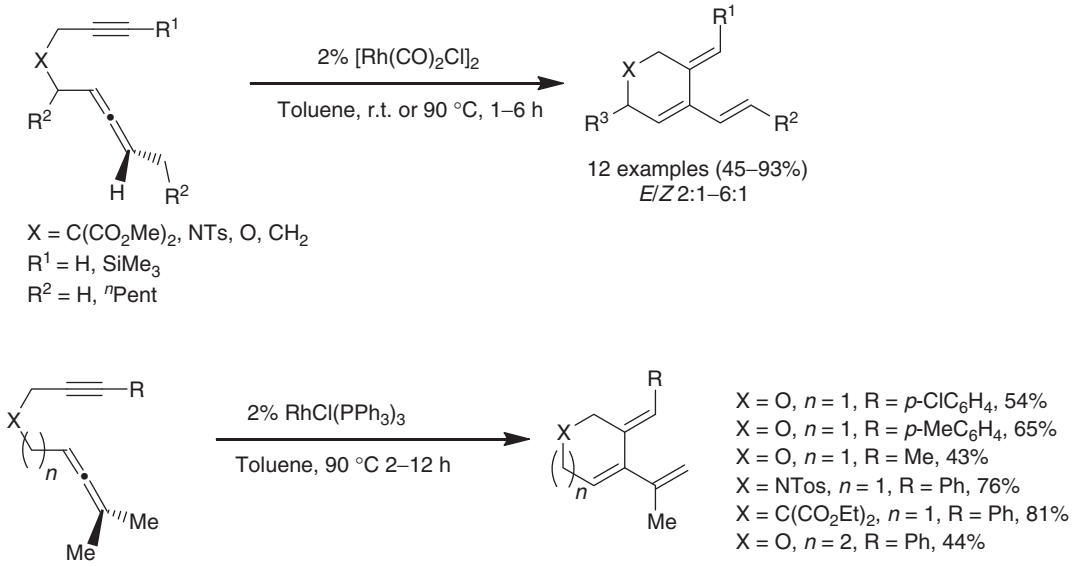


Scheme 100 Cobalt(I)-mediated ene cycloisomerization of allenynes.

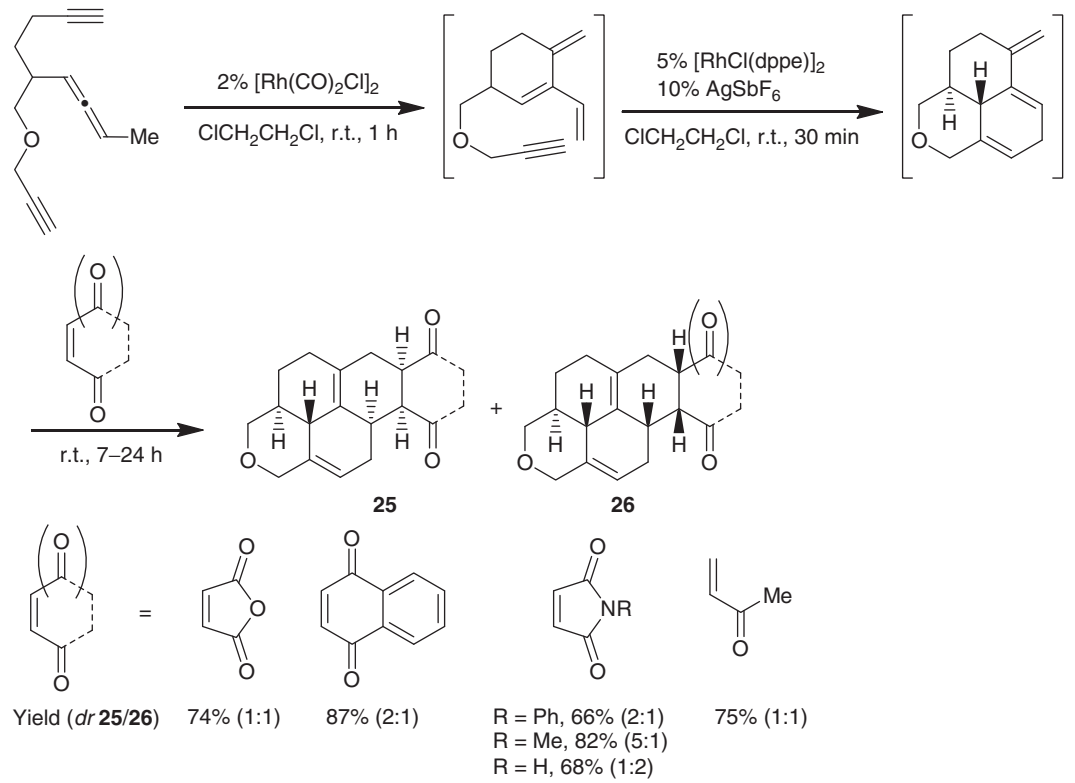
(Scheme 109). Theoretical calculations revealed that the concerted ene reaction is favored over a diradical pathway for methyl terminated 1,6-fullerenynes, which preferentially lead to cyclobutenes in the case of terminal alkynes.[197]

5.01.4 Metallo-Ene Reactions

The concept of metallo-ene reactions, which can be formally considered as substitution of the migrating hydrogen atom by a metal, was introduced by Oppolzer and can be mechanistically understood as a carbometallation of an enophile.[4] As already pointed out in the introduction, the initial stoichiometric version of alkaline and earth alkaline allyl organometallics was

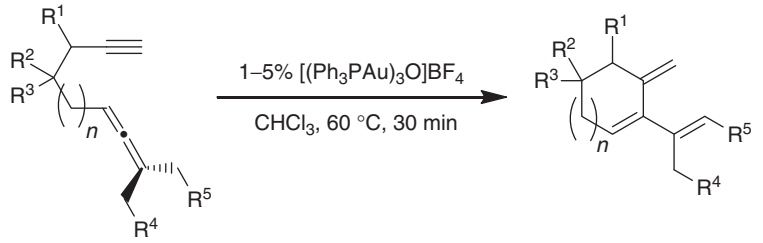


Scheme 101 Rhodium(I)-catalyzed ene cycloisomerization of allenynes.



Scheme 102 One-pot Alder-ene/Diels–Alder/Diels–Alder reactions initiated by rhodium(I)-catalyzed ene cycloisomerization of an allenyne.

transposed in the past two decades to several transition metals. The catalytic generation of allyl metal complexes as intermediates has paved the way to important expansions in the tool set of metallo-ene based reactions. First new contributions to metallo-ene additions, i.e., the intermolecular variation shall be discussed and the chapter shall conclude with intramolecular metallo-ene cycloisomerizations.

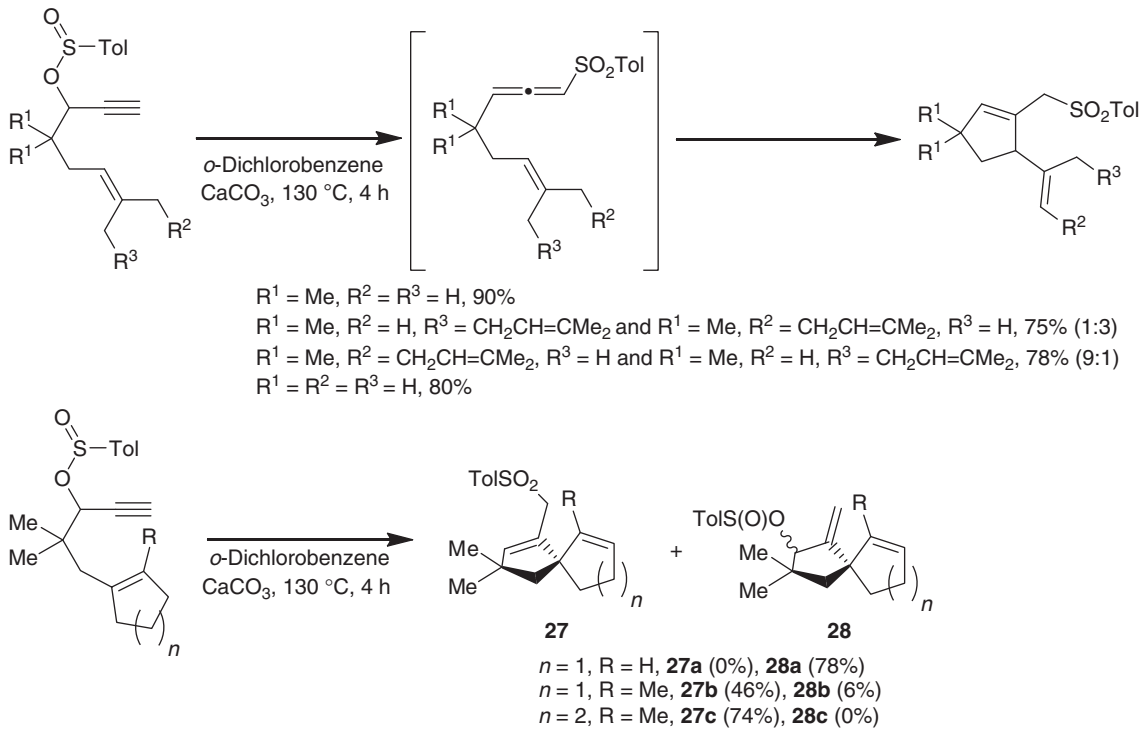


Scheme 103

Table 16 Gold(I)-catalyzed ene cycloisomerization of allenynes (**Scheme 103**)

Entry	*n*	R^1	R^2	R^3	R^4	R^5	*Yield (%)*
1	0	H	H	H	H	H	84
2	0	H	H	Bn	H	H	88
3	0	H	H	Ph	H	H	89
4	0	H	CO_2Me	CO_2Me	H	H	99
5	0	$(CH_2)_4$[a]		H	H	H	78
6	0	$(CH_2)_4$[b]		H	H	H	70
7	0	H	H	H	$(CH_2)_2$		70
8	0	H	H	H	Me	Ph	64[c]
9	1	H	CO_2Me	CO_2Me	H	H	40

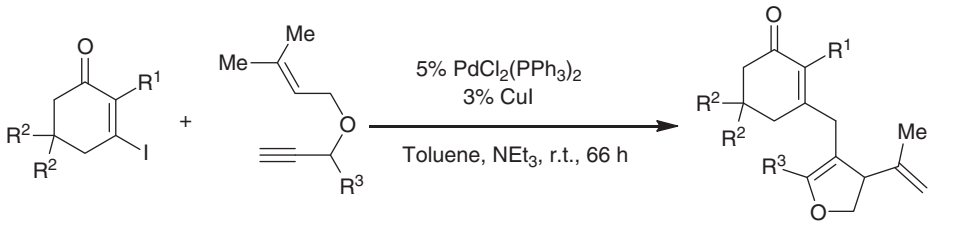
[a] *cis*-1,2-Disubstituted cyclohexane.
[b] *trans*-1,2-Disubstituted cyclohexane.
[c] The regioisomer ratio of the alkenyl substituent is 2.4:1.



Scheme 104 *In situ* generation of allenylsulfonyl enes and Alder-ene cycloisomerization.

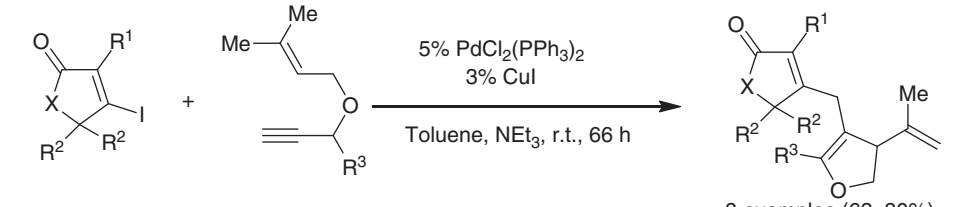
5.01.4.1 Metallo-Ene Additions

The fundamental metallo-ene process was theoretically studied for allyl lithium and allyl sodium with ethylene on the level of *ab initio* calculations, revealing that the reaction proceeds without intermediates, i.e., on a concerted pathway.[198]



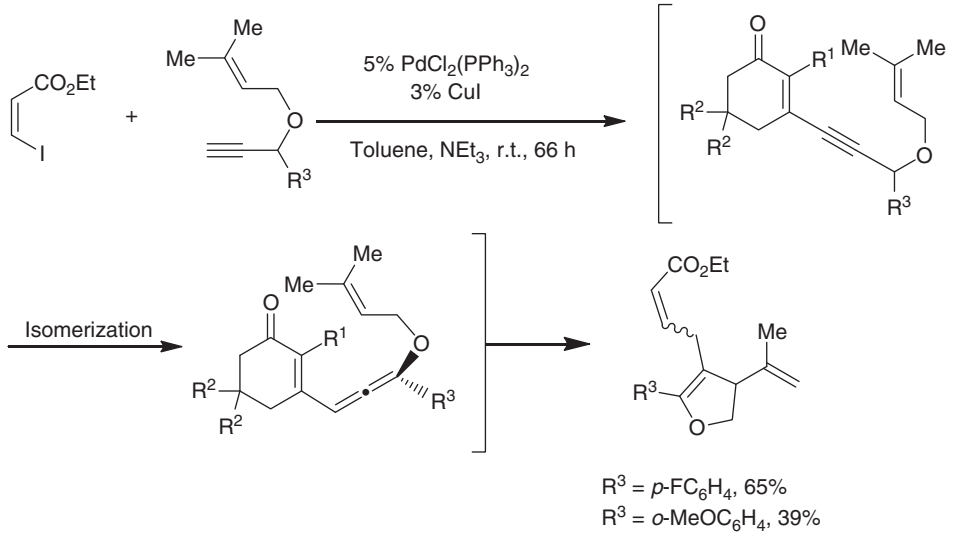
R^1 = H, Me, $CH_2CH{=}CH_2$, 3-methylbut-2-enyl
R^2 = H, Me
R^3 = aryl

11 examples (63–83%)



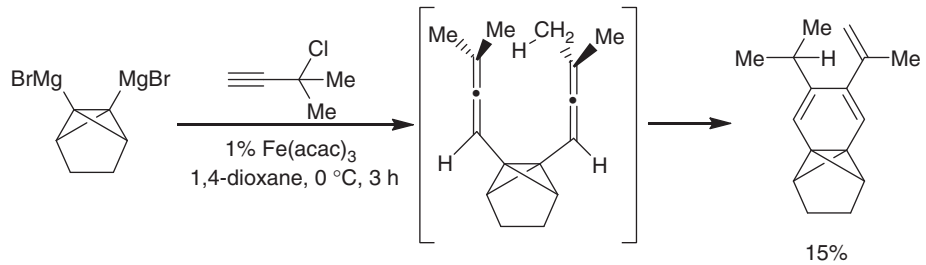
X = CH_2, O
R^1 = H, Me, $CH_2CH{=}CH_2$
R^2 = H, Me; R^2, R^2 = $(CH_2)_5$, H, Et
R^3 = Ph, *p*-ClC_6H_4

8 examples (63–80%)



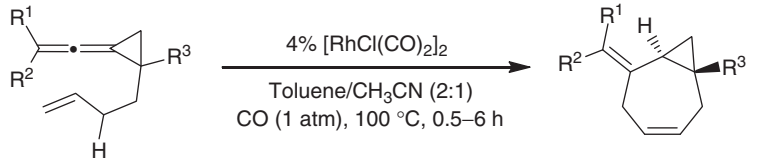
R^3 = *p*-FC_6H_4, 65%
R^3 = *o*-$MeOC_6H_4$, 39%

Scheme 105 *In situ* generation of allenyl allyl ethers via coupling-isomerization reaction and domino Alder-ene cycloisomerization.

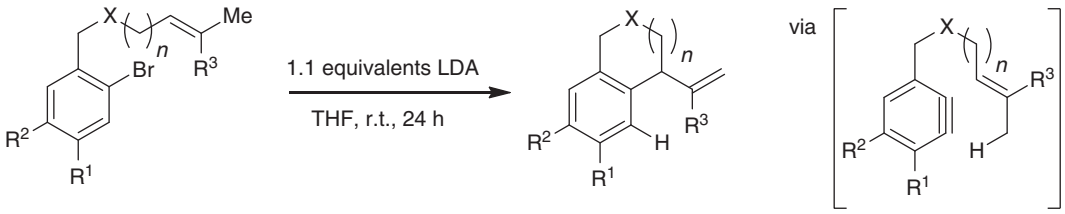


15%

Scheme 106 Synthesis of a [4.1.1]propella-2,4-diene via Alder-ene cycloisomerization.



Scheme 107 Rhodium(I)-catalyzed ene cycloisomerization of diarylvinylidenecyclopropanes.

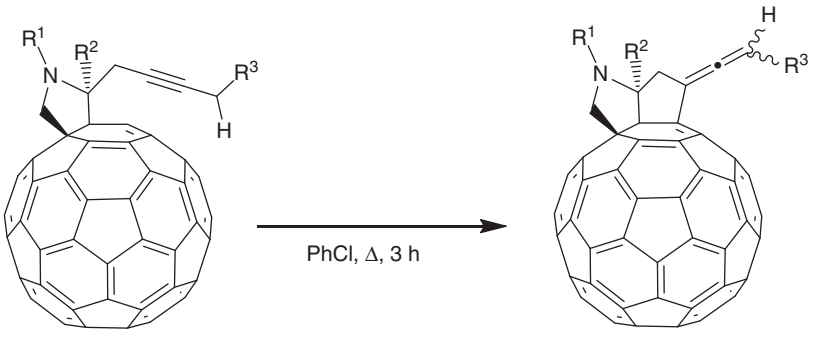


Scheme 108

Table 17 Intramolecular aryne-ene cycloisomerization (Scheme 108)

Entry	*X*	*n*	*R¹*	*R²*	*R³*	*Yield (%)*
1	O	1	OMe	OMe	Me	89
2	NMe	1	OMe	OMe	Me	89
3	O	1	F	H	Me	65
4	O	2	OMe	OMe	Me	95[a]
5	$C(CO_2tBu)_2$	2	OMe	OMe	Me	90
6	O	1	OMe	OMe	Ph	81
7	O	1	OMe	OMe	$(CH_2)_2OTBDMS$	82

[a]Combined yield with the product arising from the addition of iPr_2NH to the aryne (ene product/aryne adduct = 1.7).

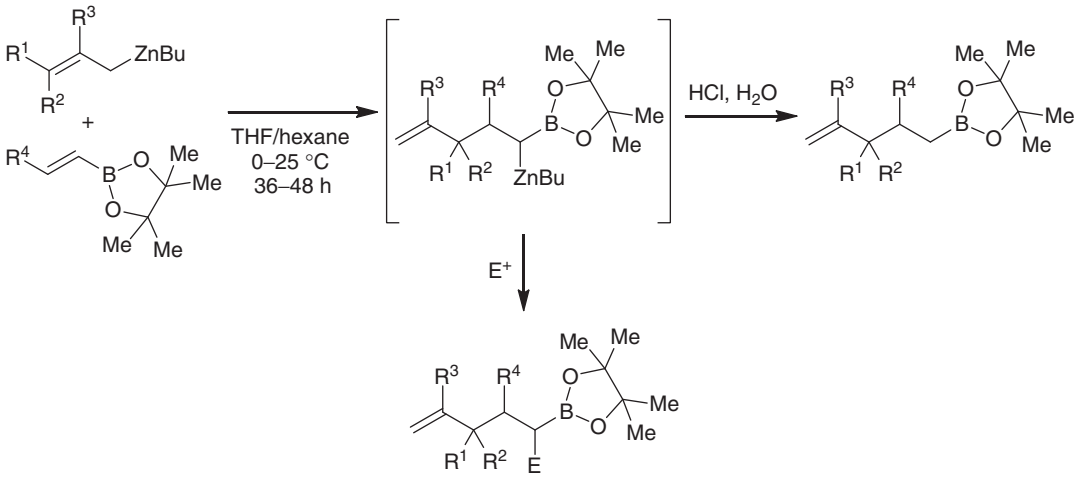


R^1 = H, R^2 = CO_2Et, R^3 = H, 100%
R^1 = H, R^2 = CO_2Et, R^3 = Me, 100%
R^1 = H, R^2 = CH_2CCH, R^3 = H, 100%
R^1 = PhCO, R^2 = CO_2Et, R^3 = H, 100%

Scheme 109 Intramolecular fullerene-ene cycloisomerization.

Computationally, the same results were obtained for metallo-ene reactions with allyl magnesium hydride or allyl magnesium chloride as ene compound and ethylene as enophile.[199]

Experimentally, Nakamura et al.[200] reported a regioselective allylzincation of alkenylboronates furnishing geminal zincio-boryl intermediates, which give rise to the formation of δ,ε-alkenyl boronates on hydrolytic workup (Scheme 110,



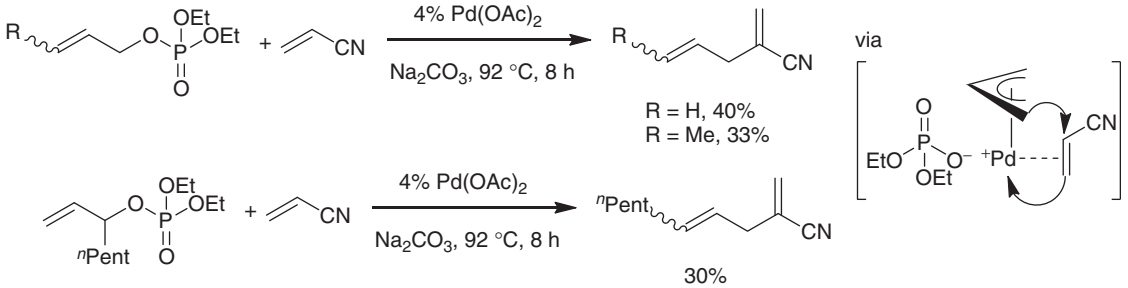
Scheme 110

Table 18). The zincio-boryl intermediates can also be elaborated by trapping with electrophiles or by transmetallation. The mechanistic dichotomy between metallo-ene and Lewis-acid assisted metalla-Claisen reactions was previously studied by DFT calculations for various allyl metal–vinyl metal combinations. Such partners give rise to 1,1-dimetallic organometallic species, indicating that the endothermic key stage of the reaction has both metalla-Claisen and metallo-ene character.[201]

Table 18 Allylzincation of vinylboronates (Scheme 110)

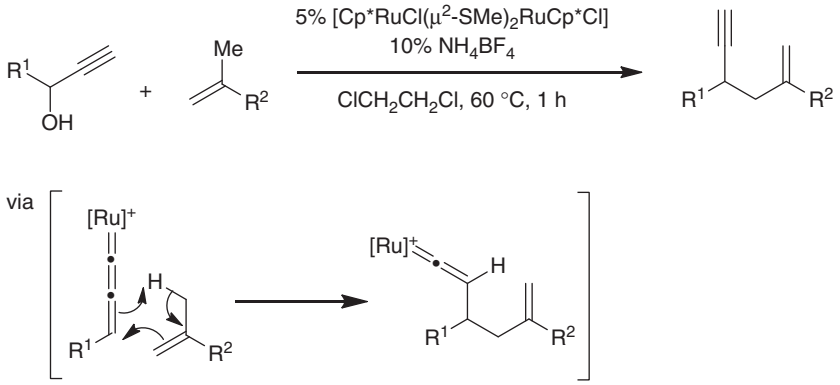
Entry	*R^1*	*R^2*	*R^3*	*R^4*	*Yield (%)*
1	H	H	H	H	82
2	H	H	Me	H	87
3	Me	H	H	H	96
4	*t*Bu	H	H	H	90
5	Ph	H	H	H	69
6	Me	Me	H	H	90
7	Me	H	Me	H	89
8	H	H	Me	Ph	95

Shvo and Arisha[202] found that allyl di-ethyl phosphates and acrylonitrile react in the presence of $Pd(OAc)_2$ as a catalyst via an allyl-Pd species and insertion, i.e., in the sense of a metallo-ene reaction. A subsequent β-hydride elimination furnishes α-allylated acrylonitrile derivatives (Scheme 111).



Scheme 111 Palladium-catalyzed intermolecular metallo-ene reaction of allyl phosphates and acrylonitrile.

Propargylic alcohols and α-methyl styrenes react in a ruthenium-catalyzed allenylidene-ene reaction with formation of 1,5-enynes in moderate to good yield (Scheme 112, Table 19).[203] This transformation is an unusual ene reaction with metal participation, since the ruthenium-allenylidene species serves as an enophile, which is converted into a ruthenium-vinylidene via the classical ene pathway according to mechanistic investigations. An intramolecular version of this specific nonclassical metallo-ene reaction was illustrated by several synthetic examples.



Scheme 112

Table 19 Intermolecular ruthenium-catalyzed allenylidene-ene reaction (**Scheme 112**)

Entry	*R^1*	*R^2*	*Yield (%)*
1	Ph	Ph	46
2	*p*-MeC_6H_4	Ph	56
3	*p*-$MeOC_6H_4$	Ph	13
4	*p*-ClC_6H_4	Ph	27
5	*p*-FC_6H_4	Ph	42
6	Ph	*p*-MeC_6H_4	50
7	*p*-MeC_6H_4	*p*-MeC_6H_4	67
8	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	40
9	*p*-ClC_6H_4	*p*-MeC_6H_4	35
10	*p*-FC_6H_4	*p*-MeC_6H_4	60
11	Ph	*p*-ClC_6H_4	30

5.01.4.2 Metallo-Ene Cyclizations

Metallo-ene cyclizations were pioneered by Oppolzer. As a consequence of higher rates of unimolecular reactions, many aspects of reactivity and selectivity can be more efficiently controlled than in intermolecular processes. Therefore, many examples ranging from stoichiometric to catalytic intramolecular metallo-ene have been disclosed in the past 20 years.

Cheng et al.[204] discovered that the lithium-ene cycloisomerization occurs at significantly lower temperatures than the magnesium analog; however, the initial ene product undergoes intramolecular proton transfer, if feasible, to generate an allyllithium species, which was identified by electrophilic trapping (**Scheme 113**).

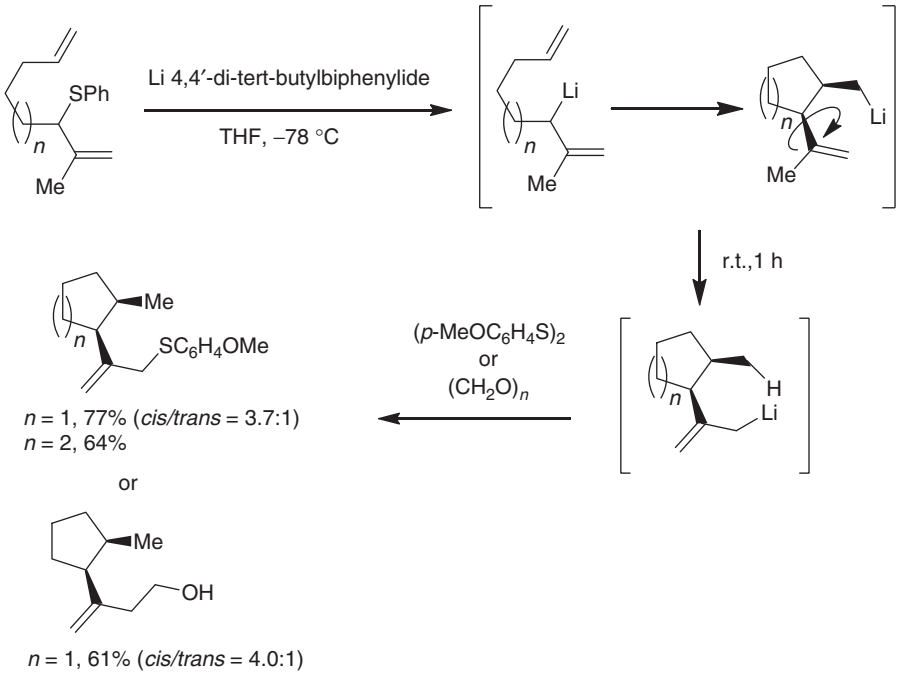
Deiters and Hoppe[205] reported the first asymmetric lithium-ene reaction on the basis of an enantioselective deprotonation induced by (–)-sparteine and butyllithium (**Scheme 114**). This sequence was successfully applied in the synthesis of (+)-(3*R*,4*R*)-1,2-dihydromultifidene.

The 1:2 mixture of $Ti(O^iPr)_4$ and ^{i}PrMgBr forms (η^2-propene)$Ti(O^iPr)_2$,[206] which is an excellent reagent for mediating metallo-ene reactions. Sato and coworkers developed an efficient synthesis of cycloalkanes by titanium(II)-mediated metallo-ene cyclizations of 2,7- and 2,8-bis-unsaturated carbonates and acetate (**Scheme 115**, **Table 20**).[207] The reaction was then extended to the asymmetric cyclizations of chiral ethynyl acetals to optically active polysubstituted cyclopentanes and cyclohexanes.[208] Interestingly, the Ti(II)-mediated metallo-ene reaction works equally well in the intermolecular case.[207]

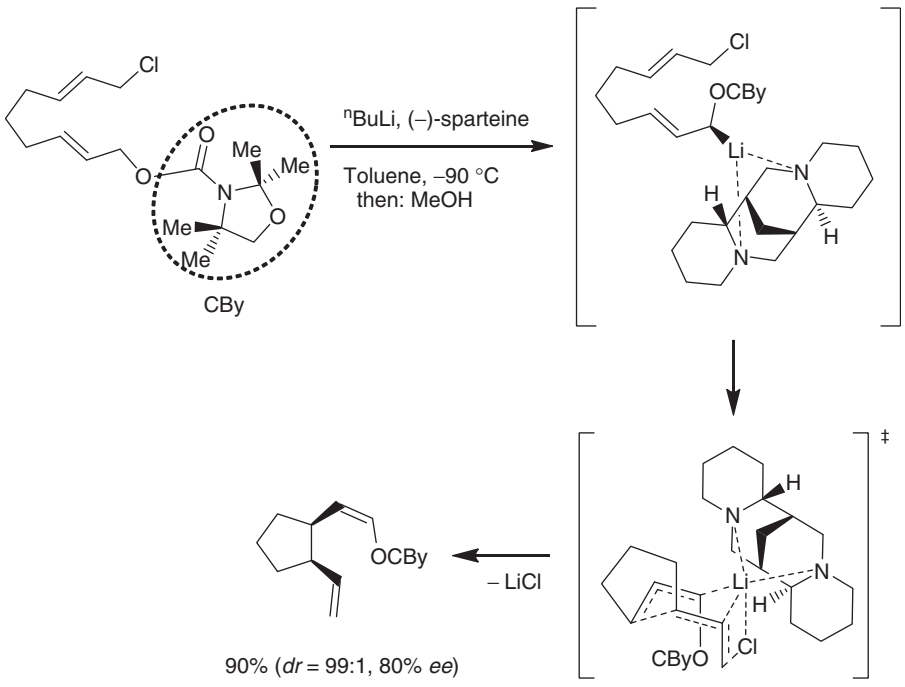
Korotvička et al.[209] reported a zirconocene-mediated metallo-ene reaction followed by trapping with allyl or homoallyl halides to furnish functionalized cyclopentane derivatives for the synthesis of *trans*-fused sesquiterpenoid analogs (**Scheme 116**). Starting from styrene derivatives, Kotora's group applied this zirconoceno-ene/allylation reaction several times to pave an elegant organometallic access to estrone precursors.[210]

Van der Louw et al.[211] found that 3-(alkynyl)-2-(methoxymethyl)-2-propenylzinc bromides are well suited for the preparation of 1,5-annulated 4-methylenecyclopentenes via zinc-ene cycloisomerization and subsequent Pd-catalyzed intramolecular allylic substitution of the zinc intermediates (**Scheme 117**). The products of the intramolecular zinc-ene reaction were unambiguously identified by quenching the reaction mixture with aqueous ammonium chloride solution instead of the addition of the palladium catalyst.

Propargyl/allenyl zinc derivatives with alkenyl or alkynyl substituents can undergo zinc-ene-allene[212] or zinc-yne-allene carbocyclizations[213] to carbocycles in excellent yields. On this basis, Marek's group disclosed new domino reactions that are



Scheme 113 Lithium-ene cyclization with subsequent intermolecular proton transfer.

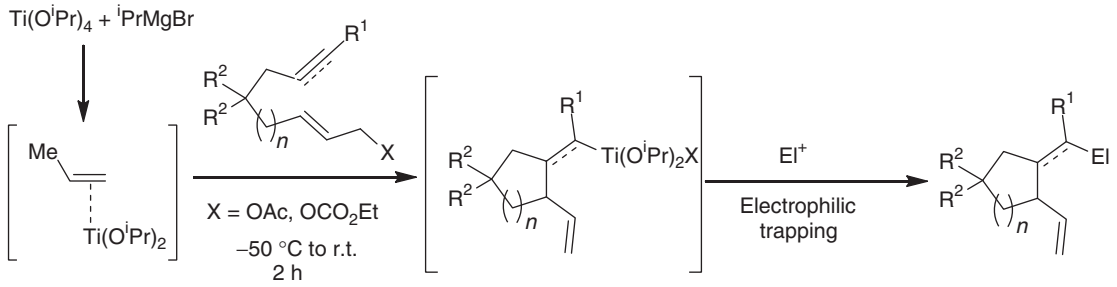


Scheme 114 First asymmetric lithium-ene cyclization.

initiated by zinc-promoted Brook rearrangement followed by instantaneous ene-allene carbocyclization and terminated by addition of electrophiles (Scheme 118).[214]

Starting from enantioenriched propargyl silanols, Marek and coworkers showed that the domino sequences leads to the enantio- and diastereoselective formation of carbocycles in a one-pot operation.[215]

The Oppolzer group discovered that the combination of palladium(0) complexes and alkylzinc compounds enables unique cyclizations of 1-acetoxy-2,7-dienes and 1-acetoxy-2-ene-7-ynes under mild conditions. The workup of the alkyl zinc cyclization

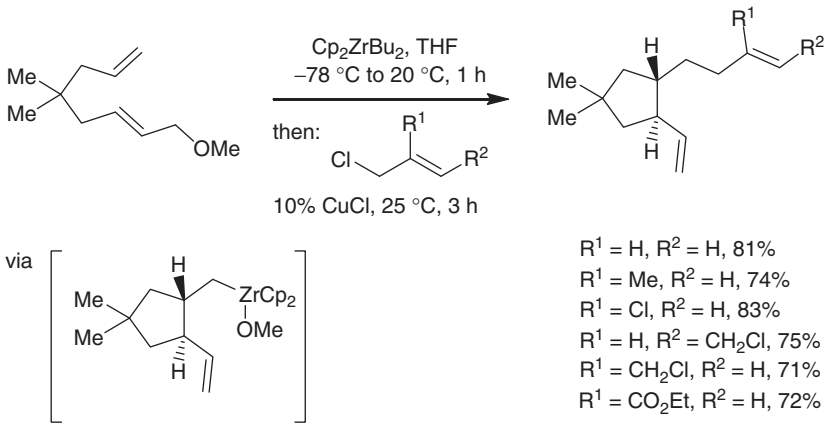


Scheme 115

Table 20 Titanium(II)-mediated metallo-ene cyclizations (Scheme 115)

Entry	*n*	R^1	R^2	*El*	*Yield (%)*	*Diastereomeric ratio*
1[a]	1	H, H	CH_2OBn	H	70	90:10[b]
2[c]	1	$SiMe_3$	H	H	85	–
3[c]	1	$SiMe_3$	H	D	70[d]	–
4[c]	1	$SiMe_3$	H	I	80	–
5[c]	1	$SiMe_3$	H	PhCH(OH)	67	92:8
6[c]	1	Ph	H	H	75	–
7[c]	1	*n*Pent	H	H	77	–
8[c]	1	*n*Pent	H	EtCH(OH)	74	58:42
9[c]	1	*n*Pent	H	*p*-$MeO_2CC_6H_4CH(OH)$	72	55:45
10[c]	1	*n*Pent	H	$Cl(CH_2)_3CH(OH)$	49	53:47
11[c]	2	$SiMe_3$	H	H	82	–

[a] Alkene substrate.
[b] *anti/syn.*
[c] Alkyne substrate.
[d] 97% Deuterium.

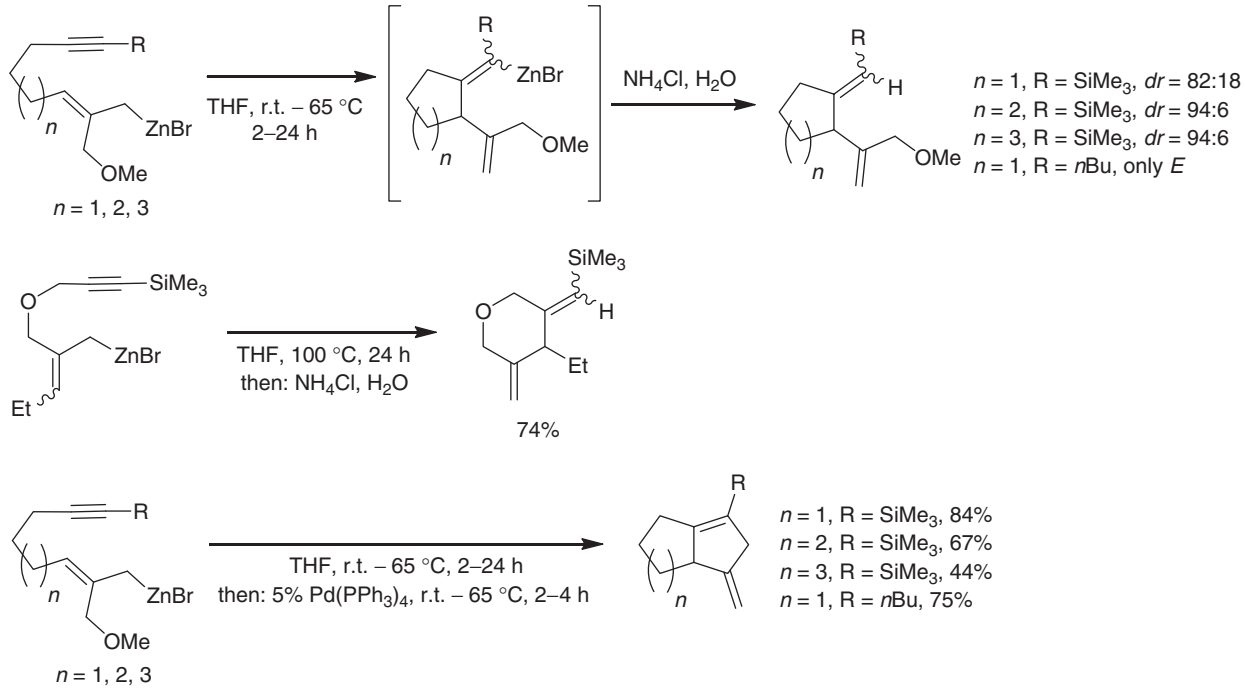


Scheme 116 Zirconocene-mediated metallo-ene cyclizations.

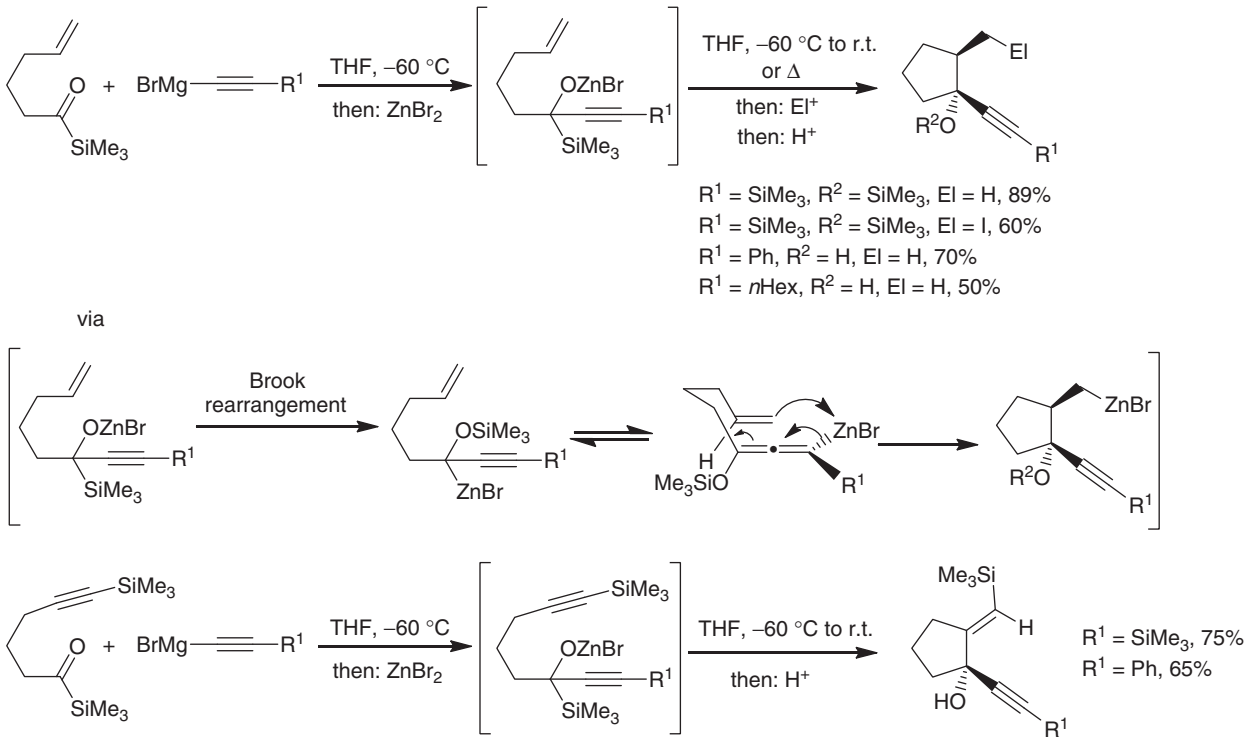
products with electrophiles furnishes *cis*-disubstituted cyclopentanes and pyrrolidines with excellent regio- and stereocontrol (Schemes 119 and 120, Table 21).[216]

Oppolzer and Flachsmann[217] reported a highly diastereoselective synthesis of the marine sesquiterpenoid (–)-erythrodiene applying an intramolecular Pd-catalyzed zinc-ene reaction as the key step. Furthermore, enantioselectivities of up to 47% could be achieved with a chiral C_2-symmetric cyclohexenyl bridged diphosphane ligands.[218]

The cyclization of 1-acetoxy-2,7-dienes[219] to five-membered carbo- and heterocycles was efficiently achieved with several easily prepared catalyst systems, such as $PdCl_2$, $RhCl_2(COD)_2$, $NiCl_2$ $6H_2O$, or $Ni(COD)_2/P(m\text{-}C_6H_4SO_3Na)_3$, and aqueous organic phases (Scheme 121, Table 22).[220]

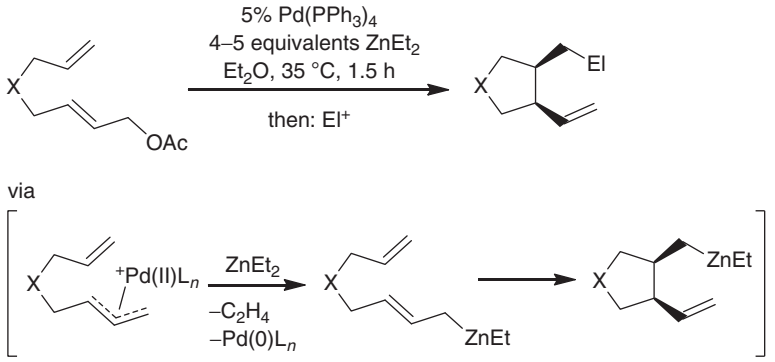


Scheme 117 Intramolecular zinc-ene reaction and intramolecular zinc-ene/allylic substitution sequence.

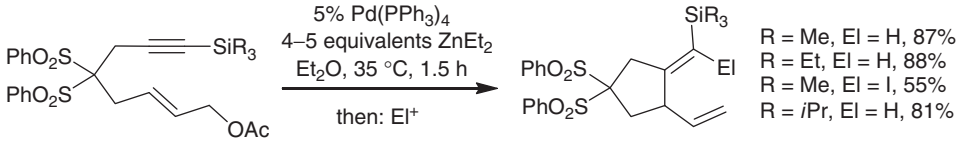


Scheme 118 Domino zinc-promoted Brook rearrangement/ene-allene carbocyclization.

Expectedly, the cyclization concludes with a β-hydride elimination leading to cyclic diene products. Mechanistically, it was corroborated by DFT computations for cationic η^1-allyl palladium(II) complexes that an insertion pathway is strongly favored over a concerted classical metallo-ene pathway.[221]



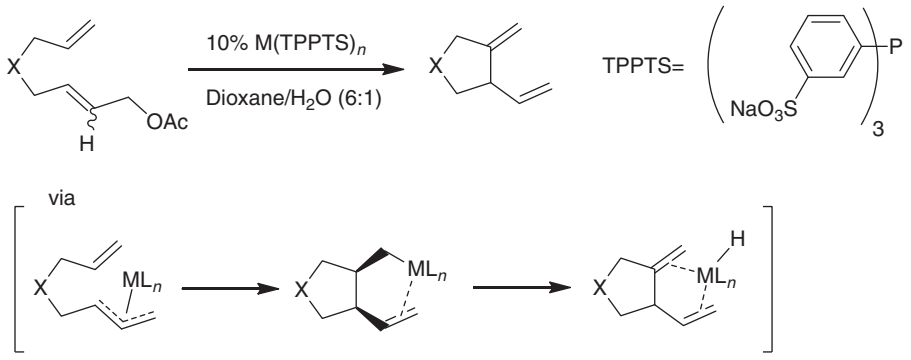
Scheme 119



Scheme 120 Intramolecular palladium-catalyzed zinc-ene reactions of 1-acetoxy-2-ene-7-ynes.

Table 21 Intramolecular palladium-catalyzed zinc-ene reactions of 1-acetoxy-2,7-dienes (**Scheme 119**)

Entry	*X*	*El*	*Yield (%)*	*Ratio cis/trans*
1	$C(SO_2Ph)_2$	H	79	86:14
2	$C(SO_2)_2C_6H_4$	H	45	92:8
3	$NCPh_3$	H	79	98:2
4	N-phenylfluorenyl	H	88	>99.8:0.2
5	NTos	H	44	96:4
6	$C(SO_2Ph)_2$	I	62	83:17
7	$C(SO_2)_2C_6H_4$	I	43	92:8
8	N-phenylfluorenyl	I	87	>98:2
9	NTos	I	51	96:4
10	$C(SO_2Ph)_2$	CN	58	83:17
11	N-phenylfluorenyl	CN	73	>98:2



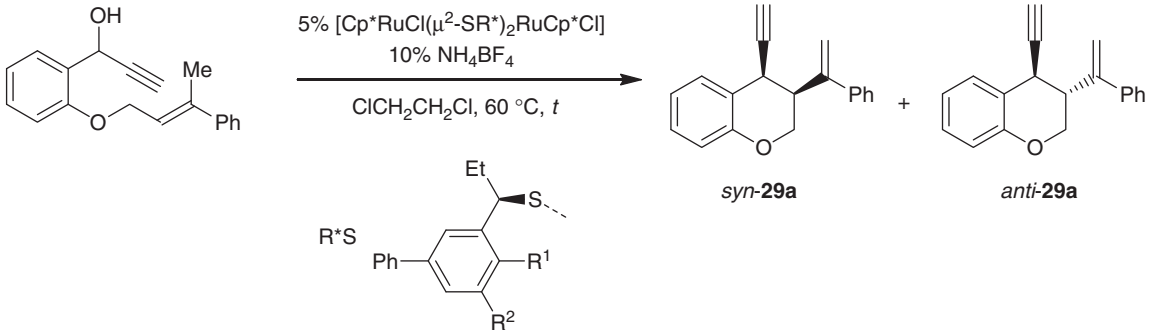
Scheme 121

Hiroi and Hirasawa[222] successfully developed palladium-catalyzed intramolecular metallo-ene reactions of allylic acetates and methyl carbonates bearing allylic sulfones as enophile moiety at appropriate sites. With chiral allylic sulfones derivatives as substrates, obtained by thermal rearrangement of an optically active allylic sulfinate, asymmetric palladium-catalyzed metallo-ene cyclizations were reported to proceed with modest yield but excellent diastereomeric ratios.[223]

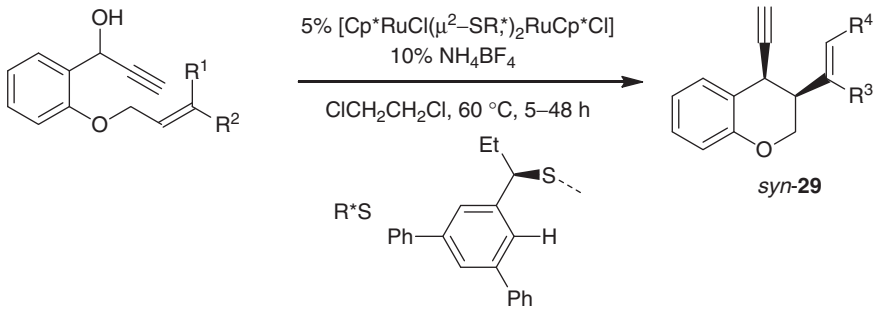
Table 22 Transition metal-catalyzed ene cyclization in aqueous media (**Scheme 121**)

Entry	*X*	*Catalyst system*	*Temperature*	*Time (h)*	*Yield (%)*
1	$C(CO_2Et)_2$	$Rh(TPPTS)_3Cl$	60 °C	6	57
2	NBn	$Rh(TPPTS)_3Cl$	60 °C	24	50
3	NTos	$Rh(TPPTS)_3Cl$	60 °C	3	62
4	$C(CO_2Et)_2$	$Ni(TPPTS)_3$	r.t.	12	99
5	NBn	$Ni(TPPTS)_3$	r.t.	12	<5
6	$C(SO_2Ph)_2$	$Ni(TPPTS)_3$	r.t. to 60 °C	12	0
7	$C(CN)_2$	$Ni(TPPTS)_3$	r.t. to 60 °C	12	0
8	$C(CO_2Me)_2$	$PdCl_2$/TPPTS	60 °C	4	88
9	$C(SO_2Ph)_2$	$PdCl_2$/TPPTS	60 °C	4	80
10	NTos	$PdCl_2$/TPPTS	60 °C	12	56

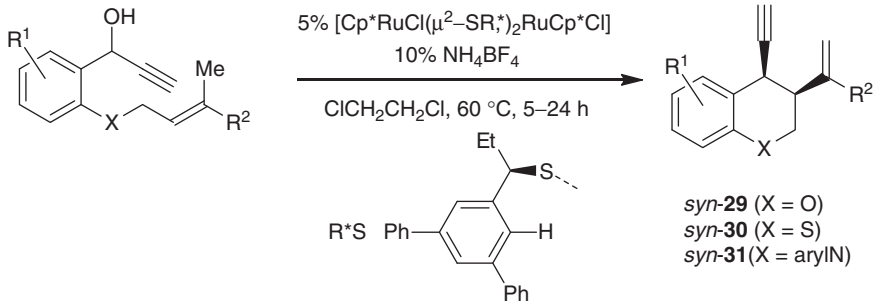
Fukamizu et al.[224] developed an enantioselective intramolecular variation of the ruthenium-catalyzed allenylidene-ene reaction (*see* Chapter 4.1, **Scheme 112**) as an approach to chiral heterocycles, such as chromanes **29**, thiochromanes **30**, and 1,2,3,4-tetrahydroquinolines **31**, in good *syn*-selectivity and with high levels of enantioselectivities (**Schemes 122**, **123**, and **124**, **Tables 23–25**).



Scheme 122



Scheme 123



Scheme 124

Table 23 Ligand screening of the intramolecular ruthenium-catalyzed allenylidene-ene reaction (Scheme 122)

Entry	R^1	R^2	*t*	*Yield (%)*	*syn-**29a**/anti-**29a***	*ee of syn-**29a** (%)*
1	H	Ph	6 h	85	17:1	93
2	H	H	75 h	44	11:1	58
3	Ph	Ph	12 h	31	20:1	90

Table 24 Variation of the allylether in the intramolecular ruthenium-catalyzed allenylidene-ene reaction (Scheme 123)

Entry	R^1	R^2	R^3	R^4	*Yield (%)*	*syn-**29**/anti-**29***	*ee of syn-**29** (%)*
1	Me	Ph	Ph	H	85	17:1	93
2	Me	*t*Bu	*t*Bu	H	76	>99:1	76
3	Me	Me	Me	H	85	10:1	33
4	$(CH_2)_5$		$(CH_2)_4$		87	7:1	47
5	Ph	Me	Ph	H	65	1:2.5	33[a]

[a] *ee* of *anti*-**29e**.

Table 25 Synthesis of chromanes, thiochromanes, and 1,2,3,4-tetrahydroquinolines via intramolecular ruthenium-catalyzed allenylidene-ene reaction (Scheme 124)

Entry	*X*	R^1	R^2	*Yield (%)*	*Ratio syn/anti*	*ee of the syn-diastereomer (%)*
1	O	H	Ph	85	17:1	93
2	O	4-Me	Ph	92	14:1	90
3	O	6-Me	Ph	93	17:1	92
4	O	4-Cl	Ph	85	8:1	90
5	O	H	*p*-MeC_6H_4	78	2.3:1	93
6	S	H	Ph	91	>99:1	89
7	S	H	*p*-MeC_6H_4	87	17:1	88
8	S	H	*p*-ClC_6H_4	90	>99:1	86
9	PhN	H	Ph	65	14:1	98
10	*p*-MeC_6H_4N	H	Ph	45	20:1	94
11	*p*-ClC_6H_4N	H	Ph	80	13:1	95

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5.02 Thermal Cyclobutane Ring Formation

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Glossary

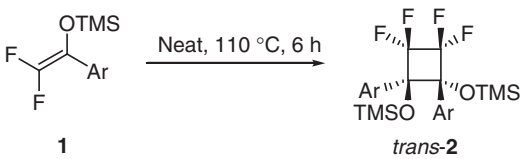
Allenes Hydrocarbons (and by extension, derivatives formed by substitution) having two double bonds from one carbon atom to two others ($R_2C{=}C{=}CR_2$).
Diradical/Biradical Molecular species that have two unpaired electrons, in which at least two different electronic states with different multiplicities (electron-paired (singlet state) or electron-unpaired (triplet state)) can be identified.
Electrocyclization A molecular rearrangement that involves the formation of a σ-bond between the termini of a fully conjugated linear π-electron system (or a linear fragment of a π-electron system) and a decrease by one in the number of π-bonds, or the reverse of that process.
Ketenes The compounds in which a carbonyl group is connected by a double bond to an alkylidene group ($R_2C{=}C{=}O$).
Zwitterion The neutral compounds that have formal unit electrical charges of the opposite sign.

5.02.1 Introduction

The importance of the cyclobutane skeleton originates from its presence in natural products of diverse origin,[1,2] its importance in pharmaceutical and medicinal chemistry,[3] as well as its usefulness as a molecular building block in organic synthesis primarily due to the inherent ring strain.[4–6] The aim of this chapter is to update the current state of the thermal [2 + 2] cyclobutane ring formation since 1991–2011. In contrast to the previous edition,[7] thermal [2 + 2] cycloadditions of other π components such as ketenes and keteniminium salts are included. In addition, due to the increasing use of allenes during recent years, dimerizations and intermolecular and intramolecular [2 + 2] cycloadditions of allenes are also discussed. In some cases, classical papers reported before 1990, not contained in the previous edition, have been included to support the studies published more recently.

5.02.2 Dimerization of Alkenes, Alkynes, and Allenes

The [2 + 2] dimerization of alkenes under thermal conditions is one of the simplest ways to obtain the cyclobutane skeleton. Usually, a biradical intermediate has been proposed. This radical pathway has been proved recently by radical scavenging reactions and electron paramagnetic resonance.[8,9] The same biradical intermediates have also been postulated for the thermal rearrangement of the fused cyclobutane 3,4-dicyanotricyclo[4.2.2.0]decane.[10] In addition, several works have discussed the [2 + 2] cycloreversion of the cyclobutane nucleus with formation of 1,4-butanediyl or tetramethylene radical cation intermediates.[11–14]



1 *trans*-**2** *cis*-**2**

Ar = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$

Ar	*trans*:*cis*	Yield (%)
Ph	53:47	89
p-ClC_6H_4	63:37	63
p-$MeOC_6H_4$	56:44	64

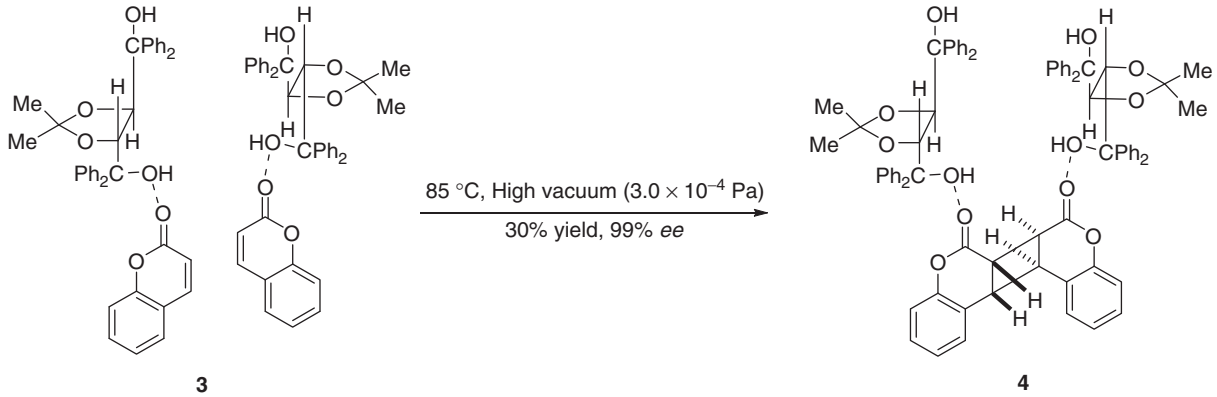
(1)

The thermal [2 + 2] cycloaddition of α,α-difluoro-olefins **1** is one of the well-known methods of obtaining fluorinated cyclobutanes **2** (equation 1). For example, the thermal dimerization of 2,2-difluoro enol silyl ethers gives mixtures of *trans*:*cis* 3,3,4,4-tetrafluorocyclobutanes in a head-to-head fashion.[15] This preference is explained by assuming that the open-chain

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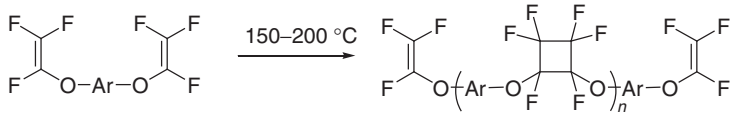
biradical intermediates, generated by radical coupling at the 2-position (head-to-head coupling), are much more stable than those formed by head-to-tail coupling, because of the stabilization of both radical centers by the aromatic and silyloxy groups.

Coumarin and thiocoumarin molecules are usually thermally unreactive for dimerization; however the [2 + 2] dimerization of **3** takes place in crystalline inclusion complexes, under high vacuum conditions (3.0×10^{-4} Pa) at 85 °C, with regio- and enantioselective ionformat of dimer **4** (equation 2).[16] High vacuum may decrease the concentration of O_2 wrapped in the solid and adsorbed on the surface, thus giving the radical intermediate a long enough lifetime for ring closure. The enantioselectivity has been explained by taking the chiral crystal environment and the presence of a rigid pyrone ring into account. Thermal [2 + 2] cycloadditions have also been applied to the dimerization of aryl bis-trifluorovinyl ethers **5** at 150–200 °C to give products of type **6** via a diradical intermediate (equation 3).[17]



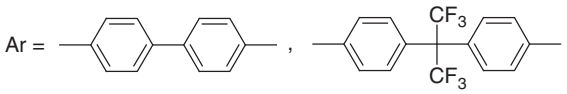
(2)

3 **4**



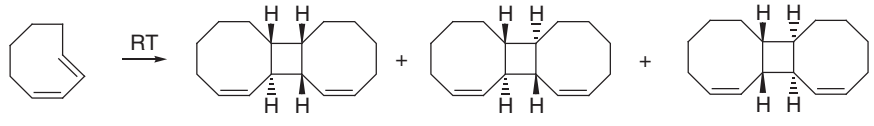
(3)

5 **6**



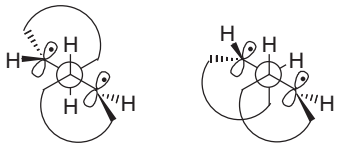
Bridgehead alkenes usually dimerize affording mixtures of different isomers. The thermal dimerization of bicyclo[2.2.0]hex-1(4)-ene has been studied previously[18]; however, its perfluorinated analog was found to be less reactive toward dimerization on prolonged heating, but rather undergoes electrocyclic ring opening.[19] B3LYP calculations have shown that bicyclo[2.2.0]hex-1(4)-ene dimerization is an exothermic process, whereas dimerization of perfluorobicyclo[2.2.0]hex-1(4)-ene is an endothermic process.[20]

The thermal [2 + 2] cyclodimerization of (*E*,*Z*)-cycloocta-1,3-diene **7** has been revisited in the presence of trapping agents for carbon-centered free radicals.[21] Obtention of cyclobutanes **8**, **9**, and **10** has been justified by assuming the formation of the *anti*-configured singlet 1,4-diradicals **11** and **12**, followed by an *anti*-to-*gauche* conformational change of these intermediates (equation 4). The thermal [2 + 2] cycloaddition of a related strained alkene, (5*Z*, 11*E*)-dibenzo[*a*,*e*]cyclooctatetraene, has been carried out in the presence of Ni(0), which facilitates the formation of the corresponding cyclobutane product.[22]



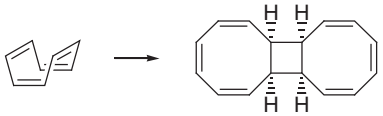
7 **8** **9** **10**

(4)



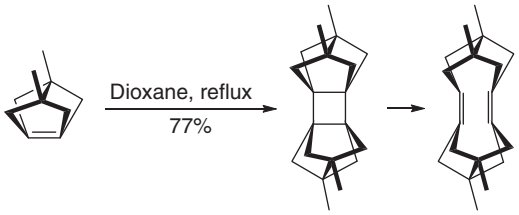
11 **12**

The thermal dimerization of cyclooctatetraene **13** was studied some time ago; however, the structure of the dimer has been discussed controversially.[23] Recently, the *syn* configuration of dimer **14** has been confirmed by X-ray diffraction (equation 5).[24]



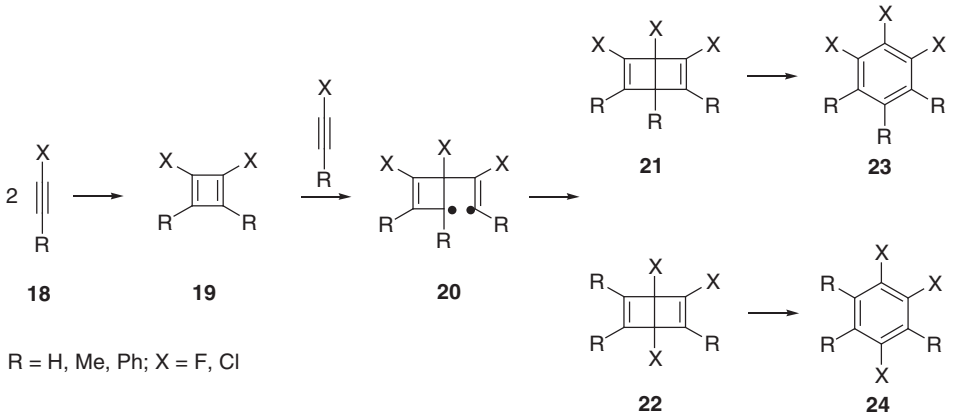
13 **14** (5)

Highly pyramidalized alkenes dimerize through [2 + 2] cycloaddition reactions in the absence of nucleophiles and dienes. 3,7-Dimethyltricyclo[3.3.0.03,7]oct-1(5)-ene **15** dimerizes to the cyclobutane derivative **16**, which undergoes retrocycloaddition to give diene **17** as shown in equation 6.[25] A similar behavior has been observed with other highly pyramidalized alkenes, obtaining the corresponding retrocycloaddition dienes.[26–28] The thermal reversion of the obtained cyclobutanes has been studied by ^{1}H nuclear magnetic resonance (NMR) and ab initio calculations. Strained 7-methylenebicylo[3.2.0]hepta-1,3-diene also affords cyclobutane dimers.[29]



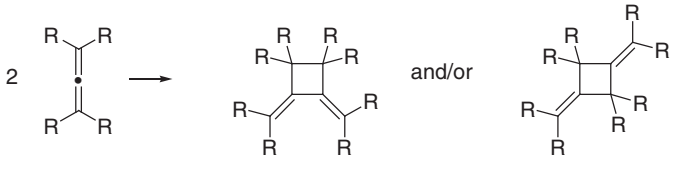
15 **16** **17** (6)

Cyclotrimerization of alkynes to form benzenes via a stepwise mechanism is a very well studied reaction, which first involves the formation of cyclobutadienes through a [2 + 2] cycloaddition.[30] Recently, theoretical studies of the mechanism of the thermal cyclotrimerization of fluoro- and chloroacetylenes **18** have been reported. A third molecule of alkyne would react with cyclobutadiene intermediates of type **19** to form species **21** and **22**, which finally afford benzene derivatives **23** and **24** (**Scheme 1**).[31]

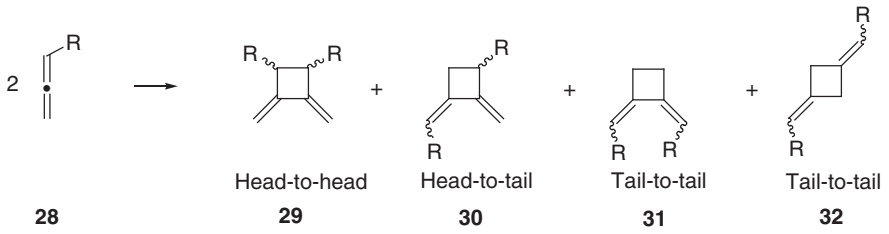


Scheme 1 Reproduced from Yao, Z-K.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*(28), 10864–10877, with permission from American Chemical Society.

Allenes are reactive species with cumulated double bonds, which are widely used as intermediates for organic synthesis.[32] [2 + 2] Homodimerization of allenes has been studied in a large number of systems.[33] However, it is important to consider the substitution of the allene, because it is possible to obtain different regioisomers. Thus, when the allene is symmetrically substituted as in **25**, two regioisomers, **26** and **27**, are obtained (equation 7). However, when the allene substrate is not symmetrically substituted such as **28**, several regioisomers can be isolated: the head-to-head adduct **29**, the head-to-tail adduct **30** and the tail-to-tail adducts **31** and **32**, in the form of the corresponding *cis*-, *trans*-, *Z*-, and *E*-isomers (equation 8).

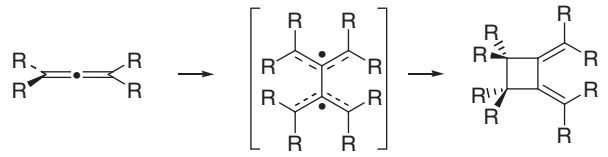


25 **26** **27** (7)

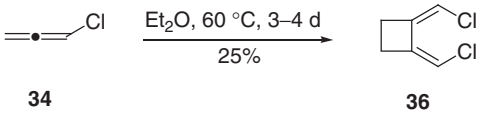


(8)

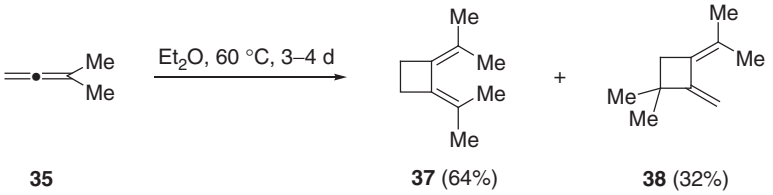
The high stereoselectivity observed in some [2 + 2] cycloadditions has pointed out the possibility that these transformations were concerted reactions. However, other studies have indicated that the [2 + 2] dimerization of allenes is not a synchronous process, and the intermediacy of a 1,1′-bis-allyl diradical intermediate **33** has been proposed to afford the corresponding cyclobutane **26** (equation 9).[34] As an example, chloroallene **34** and 1,1-dimethylallene **35** dimerize mainly in a head-to-head manner to afford the corresponding cyclobutanes **36**, **37**, and **38** respectively (equations 10 and 11).[35,36]



(9)

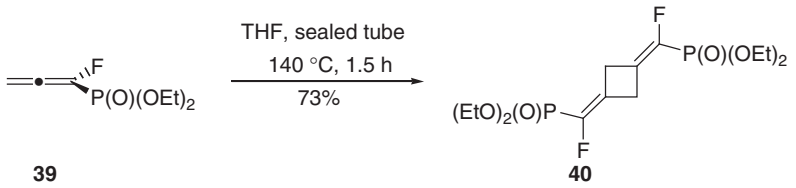


(10)

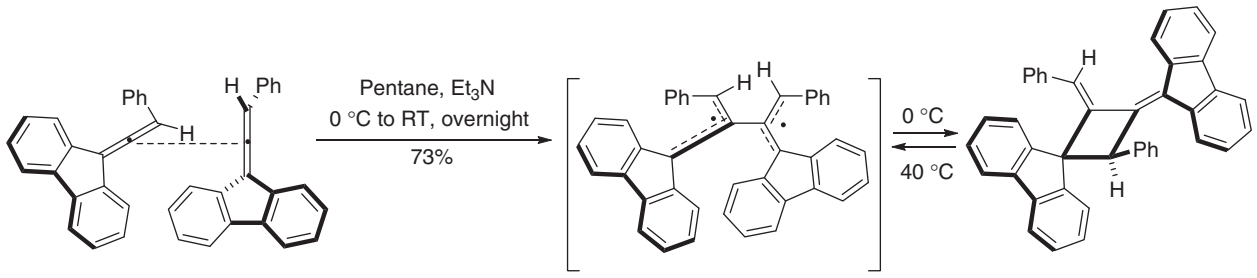


(11)

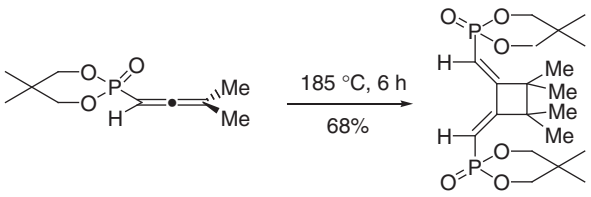
In general, it is important to consider the influence of the nature of the substituents attached to the allene moiety on the regiochemistry of the [2 + 2] cycloaddition. α-Fluoroallenylphosphonate **39** dimerizes under thermal conditions to afford product **40** exclusively as shown in equation 12.[37] This result contrasts with the mechanistic scenario accounting for a concerted [2 + 2] process in the allene dimerization. Probably, the bulky phosphorous substituent on the allene moiety allows rotation in the bis-allyl diradical intermediate yielding the corresponding tail-to-tail dimer **40**. The fluorenylidene-derived allene **41** reacts at room temperature to afford the [2 + 2] head-to-tail dimer **42** (equation 13).[38] Again, a stepwise process involving a diallyl diradical intermediate **43** has been proposed. The orthogonal arrangement of the substituents in allene **41**, together with the preference of large groups to minimize steric hindrance, suggests that the two molecules of **41** approach each other along a C_2-symmetric trajectory. Thus, at the moment of generation, the most favorably oriented *p* orbitals, through which radical coupling can occur, are located on unlike termini, and a least-motion rotation about the central bond suffices to bring these centers close enough for bond formation to occur, which leads to dimer **42**. The entire sequence of intermediates has been elucidated by NMR and X-ray crystallography.[39] In a similar work, ferrocenyl- and fluorenylidenallene dimerizations were studied as well.[40] Dimerization of allene **44** afforded the head-to-head dimer **45** in 68% yield, pointing to a concerted mechanism (equation 14).[41] However, in some cases a mixture of several regioisomers was isolated.[42] A very recent report has studied the dimerization of chlorotriphenylallenes to form rubrene analogs or bis(alkylidene)cyclobutanes depending on the substituents present on the chloroallene.[43]



39 40 (12)



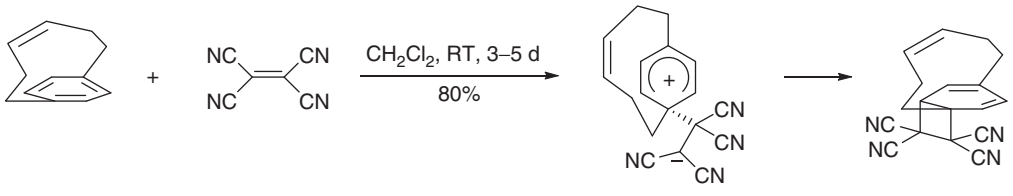
41 43 42 (13)



44 45 (14)

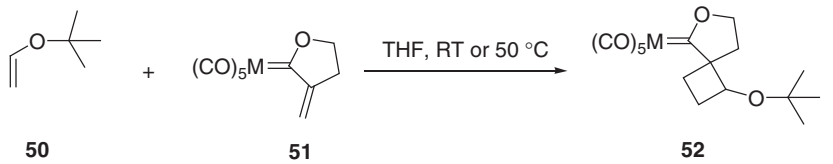
5.02.3 Intermolecular [2 + 2] Cycloadditions

Reaction of (*Z*)-[6]paracycloph-3-ene **46** with tetracyanoethylene **47** gives the [2 + 2] cycloadduct **48** in 80% yield.[44] This thermal cycloaddition has been subject to theoretical studies, assuming the formation of a zwitterion intermediate **49** as shown in equation 15.



46 47 49 48 (15)

The [2 + 2] cycloaddition reaction of enol ethers **50** to *exo*-methylene-2-oxacyclopentylidene complexes of chromium and tungsten **51** provides a novel access to spirocyclobutane skeletons **52** at room temperature or 50 °C (equation 16).[45] Single diastereoisomers were obtained in all cases, consistent with either a concerted mechanism or a two-step process in which ring closure is fast in comparison with rotation around the new C–C bond formed in the first step.

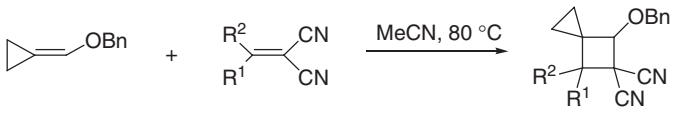


M	Yield (%)
Cr	73
W	71

50 **51** **52**

M = Cr, W (16)

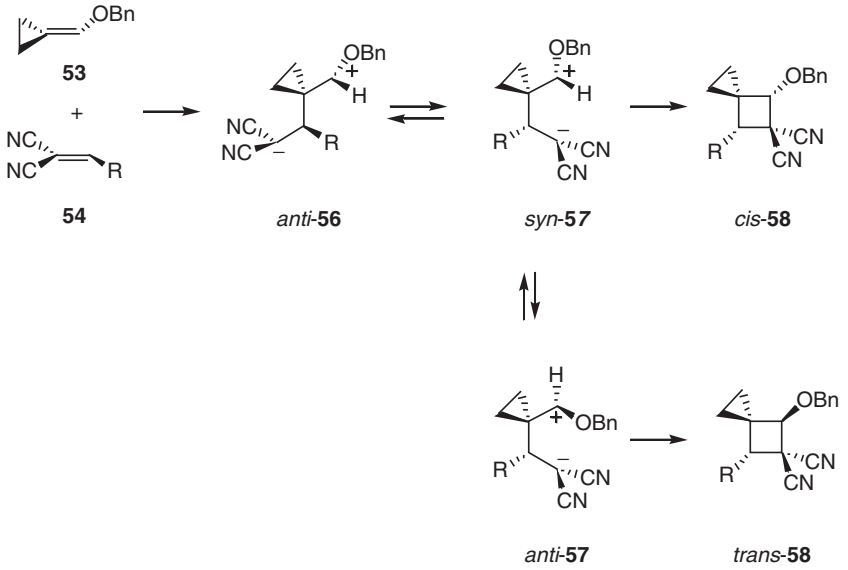
The reaction of (benzyloxymethylene)cyclopropanes **53** with alkylidenemalononitriles **54** at ambient pressure gives the spirocyclopropanated cyclobutane derivatives **55** in good to high yields (equation 17).[46] The formation of compounds **55** has been explained by initial attack of the carbon–carbon double bond in **53** on the β-position of the alkylidenemalononitrile to afford the *anti*-oriented zwitterion *anti*-**56**, which after initial rotation to **57**, cyclizes to the cyclobutanes *trans*-**58** or *cis*-**58** (Scheme 2). The cyclopropyl group adjacent to the cationic center is essential to stabilize the zwitterionic intermediate **57**.



R^1	R^2	*Trans:cis*	Yield (%)
Ph	H	1.5:1	96
Bu^t	H	3.4:1	91
Me	Me	–	54

53 **54** **55**

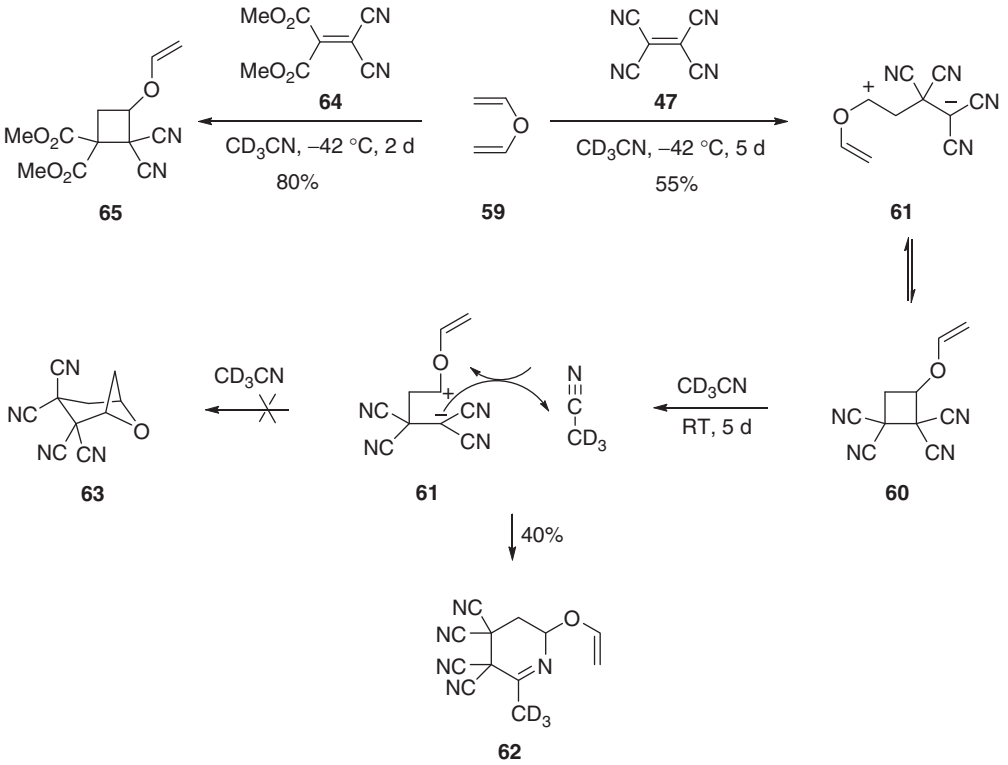
R^1 = Me, Bu^t, Ph; R^2 = H, Me (17)



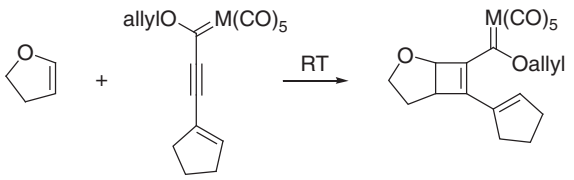
Scheme 2 Reproduced from Nakamura, I.; Nagata, R.; Nemoto, T.; *et al. Eur. J. Org. Chem.* **2007**, *27*, 4479–4482.

The competition between [2 + 2] and [4 + 2] cycloadditions in reactions of electron-rich alkenes with electron poor alkenes is dependent on the energy levels of the participating highest occupied molecular orbital–lowest unoccupied molecular orbitals, and on the chosen reaction conditions. To test the ability of the zwitterionic intermediate to react with an internal double bond, the reaction of electron-rich bifunctional vinyl ethers with electrophilic alkenes has been studied.[47] Thus, reaction of tetracyanoethylene **47** with the divinyl ether **59** afforded the cyclobutane adduct **60**, which, in a polar solvent, is in equilibrium with the zwitterionic intermediate **61** (Scheme 3). This species does not react with the other C–C double bond of the vinyl ether molecule, but does react with the solvent acetonitrile to give compound **62**, instead of an intramolecular reaction to give a [3.1.1]bicyclic adduct **63**. This experiment indicates that under these reaction conditions, the anionic end of the zwitterion **61** reacts faster than the cationic end; and, consequently, that the anionic end is less-stabilized than the cationic one. In contrast, in the reaction of **64** with vinyl ether **59**, only cyclobutane adduct **65** is obtained, because the two ester substituents in the β-positions provide less stabilization to the anionic charge. Thus, the ester moieties stabilize the cyclobutane structure, making it unreactive to tetrahydropyridine formation on prolonged exposure to acetonitrile.

Cyclobutenes **66** containing a 1,3,5-metallahexatriene moiety have been obtained by [2 + 2] cycloaddition of cyclic enol ethers **67** and chromium or tungsten alkynyl carbene complexes **68** at room temperature (equation 18).[48,49]



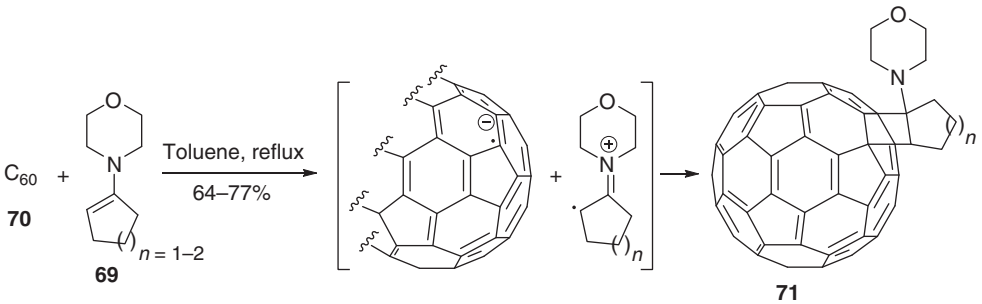
Scheme 3



M	Yield (%)
W	59
Cr	77

(18)

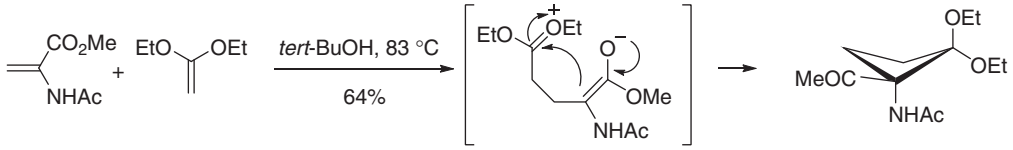
Thermal [2 + 2] cycloadditions of morpholinoenamines **69** have been studied with C_{60} (**70**), yielding the corresponding adducts **71** in high yields (equation 19).[50] This cycloaddition takes place via a single electron transfer, radical coupling, and subsequent ionic cyclization.



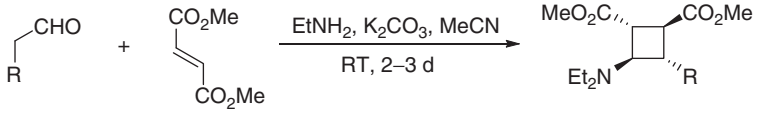
(19)

The highly functionalized cyclobutane serine analog **72** has been obtained in moderate yield by thermal [2 + 2] cycloaddition involving 2-acylaminoacrylate **73** as electron poor acceptor alkene, and ketene diethyl acetal **74** as electron-rich olefin (equation 20).[51–53] The mechanism proposed for the thermal [2 + 2] cycloaddition reaction involves zwitterionic intermediates. The first addition of one molecule of ketene diethyl acetal **74** onto amidoacrylate **73** by Michael reaction leads to zwitterion **75**, which after ring closure gives the cyclobutane core **72**. [2 + 2] Cycloaddition of enamines to electron-deficient alkenes under thermal

conditions has been studied some time ago[54]; however, this reaction has been reevaluated as a multicomponent process of enamines, generated *in situ* from aldehydes **76** and diethylamine, with dimethyl fumarate **77**, which afforded functionalized cyclobutanes **78** with moderate yields (equation 21).[55]



73 **74** **75** **72** (20)

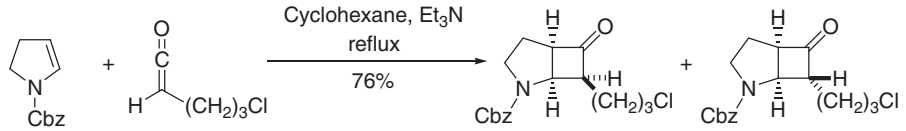


R	Yield (%)
$PMBOCH_2$	65
$MOMOCH_2$	39

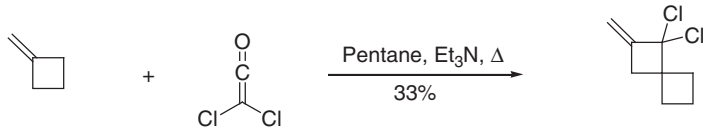
76 **77** **78** (21)

R = $PMBOCH_2$, $MOMOCH_2$

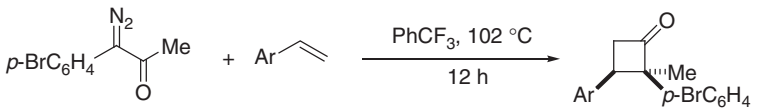
Ketenes are suitable substrates for the [2 + 2] cycloaddition with different π components. The mechanism has been a subject of much interest and controversy. Although a concerted $[_{\pi}2_a + _{\pi}2_s]$ mechanism, as proposed by Woodward and Hoffmann, is widely accepted, an asynchronous $[_{\pi}2_s + (_{\pi}2_s + _{\pi}2_s)]$ pathway involving a dipolar process may operate in certain such reactions. The synthesis of fused cyclobutanes **79** through [2 + 2] cycloaddition of the five-membered endocyclic enecarbamate **80** with ketene **81** is a good example (equation 22).[56] The synthesis of spiranic cyclobutanes **82** has also been reported from olefin **83** and ketene **84** (equation 23).[57,58] In a recent work studying the thermal cyclopropanation of aryldiazoketones **85** and alkenes **86**, cyclobutanones **87** were formed instead. The formation of the four-membered carbocycles **87** may be explained by thermal [2 + 2] cycloaddition of the ketene generated by Wolff rearrangement of the starting aryldiazoketone **85** with alkenes **86** (equation 24).[59] Interestingly, vinyl ketene **88**, formed by thermal [1,5]-H shift of 3-ethoxycarbonyl-2,4-dienal **89**, reacts with butylvinyl ether **90** under thermal conditions to afford the corresponding cyclobutanones **91** (equation 25).[60]



80 **81** **79-*endo*** **79-*exo*** (95:05) (22)

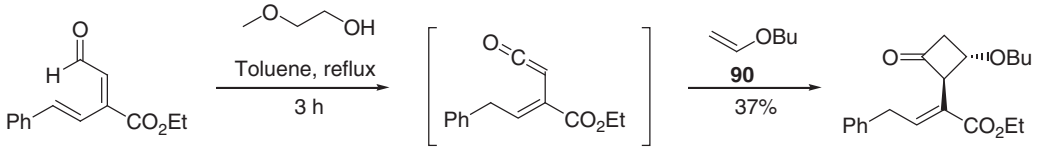


83 **84** **82** (23)



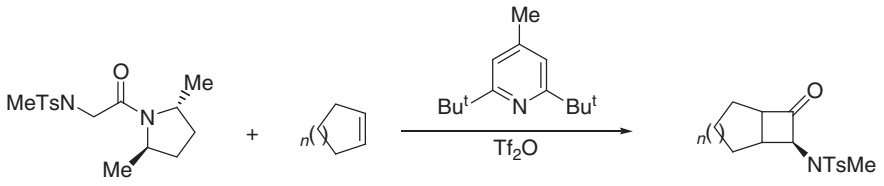
Ar	d.r.	Yield (%)
Ph	91:9	69
p-MeC_6H_4	90:10	91
p-ClC_6H_4	90:10	94

85 **86** **87** (24)



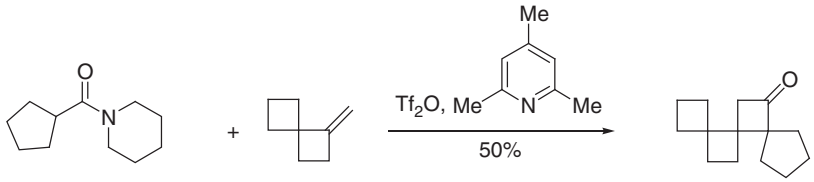
89 **88** **91** (25)

The [2 + 2] cycloaddition of keteniminium salts under thermal conditions was discovered in 1908,[61,62] but its importance was recognized only in the early 1970s.[63,64] Since then, many examples have been reported to prepare the cyclobutane ring.[65] Furthermore, in contrast to alkenes, alkynes, and allenes, keteniminium salts do not dimerize or polymerize. Although in 1972, Marchand-Brynaert and Ghosez proposed a [$\sigma_2^* + \sigma_2^*$] concerted mechanism,[66] Saimoto et al. later showed that this cycloaddition proceeds in a stepwise manner through cationic intermediates.[67] This methodology has been applied to the synthesis of cyclobutanones of type **92** from compound **93** and alkenes **94** (equation 26)[68]; more recently it has been used for the synthesis of the helical hydrocarbon **95** from **96** and **97** (equation 27).[69] However, different reactivity profiles toward dienes have been observed; in most cases [4 + 2] cycloadducts involving the C=N bond as dienophile component are obtained.[70]



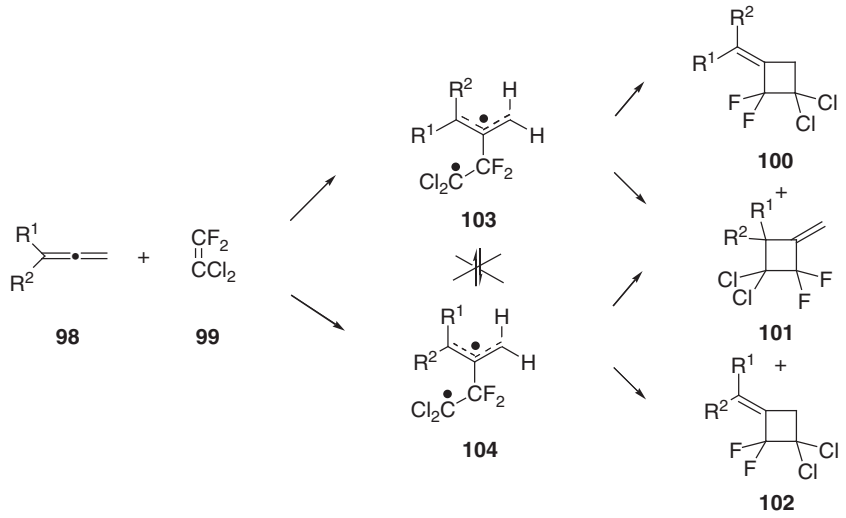
n	Yield (%)
1	75
2	81

93 **94** **92** (26)



96 **97** **95** (27)

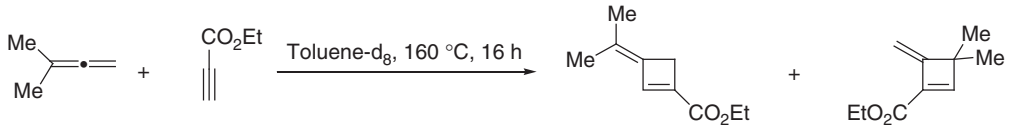
In a series of classic papers, Pasto studied in detail the synthesis of cyclobutanes by intermolecular thermal [2 + 2] cycloaddition of allenes with alkenes or alkynes. A high number of experiments were reported in order to get a better understanding of the mechanism, the stereo- and chemoselectivity, the relative reactivities and kinetic isotope effects.[71–73] For example, mono- and 1,1-disubstituted allenes **98** react with 1,1-dichloro-2,2-difluoroethene **99** to give mixtures of the adducts **100**, **101**, and **102** via the formation of stereoisomeric diradical intermediates **103** and **104** (Scheme 4).[74] In addition, the reversibility of the formation of the biradical intermediates has been investigated as well in the reaction of allenes with diethyl fumarate and maleate.[75] The reactivity of



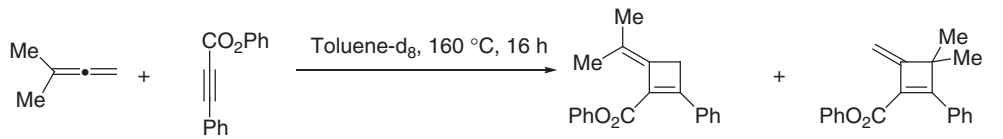
		Ratio		
R^1	R^2	**100 (%)**	**101 (%)**	**102 (%)**
Et	Me	53.4	37.1	6.7
Bu^t	Me	86.0	6.7	7.3
Et	H	50.5	27.3	15.4

Scheme 4 Reproduced from Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*(13), 3670–3676, with permission from American Chemical Society.

(*S*)-(+)-1,3-dimethylallene with acrylonitrile,[76] ethyl acrylate,[76] 1,1-dichloro-2,2-difluoroethene[77] and 1,1-diphenylethene has also been studied.[77] Analogously, Pasto has investigated the stereochemical features of the reaction of 1,1-dimethylallene **105** with different alkynes such as **106**, **107**, and **108**, which normally gave two cyclobutene isomers (equations 28–30).[78]

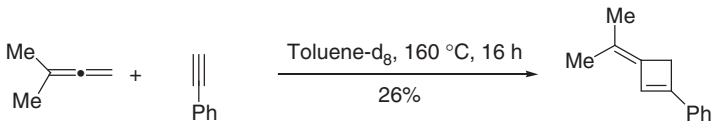


105 **106** **109** (24%) **110** (0%) (28)



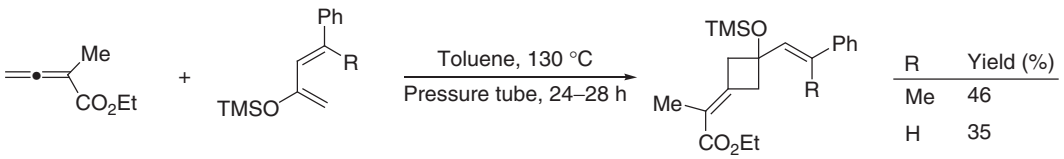
105 **107** **111** **112** (29)

(68:32)



105 **108** **113** (30)

More recently, the reactivity of allene carboxylate **114** with diene **115** to give cyclobutanes **116** (equation 31),[79] and the synthesis of methylene-cyclobutanes **117** and -cyclobutenes **118** by reaction of vinylideneoxazolidin-2-ones **119** with alkenes **120** or alkynes **121** (Scheme 5),[80] respectively, have been described. Formation of cyclobutenes **117** and **118** has been rationalized via a concerted mechanism. However, the [2+2] cycloaddition of C_{60} (fullerene, **70**) with allenamides **122** to afford the cyclobutane annulated fullerene derivatives **123** in moderate yields has been explained via the formation of an iminium intermediate **124** (Scheme 6).[81]



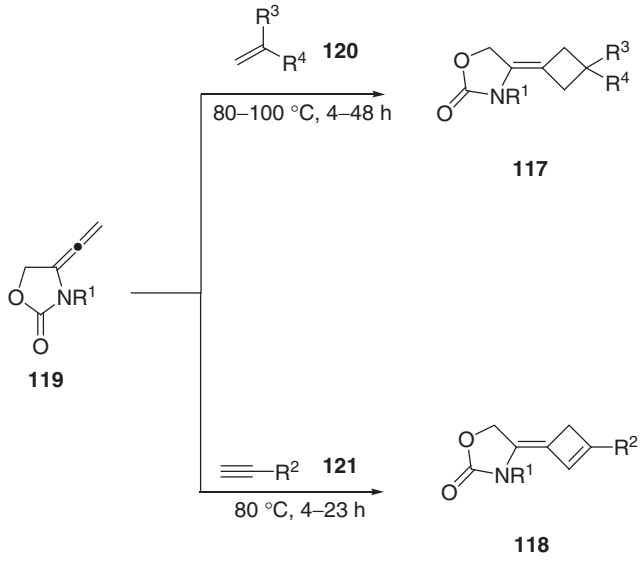
R	Yield (%)
Me	46
H	35

114 **115** **116** (31)

R = H, Me

5.02.4 Intramolecular [2 + 2] Cycloadditions

The intramolecular thermal [2+2] cycloaddition of unsaturated systems is a very useful strategy for the preparation of polycyclic structures in a single step. In addition, some problems found in the intermolecular version have been solved when the reaction was carried out in an intramolecular fashion. For example, stilbene does not give concerted thermal cycloadditions because the required orthogonality is not accessible due to steric hindrance and angle strain.[82] However, recently the intramolecular [2+2] cycloaddition, at room temperature, of 2,5,2′,5′-tetra(4-*N*,*N*-diphenylaminostyryl)biphenyl **125** has been reported; its central biphenyl motif is responsible for the relatively free rotation of the molecule (equation 32).[83] These characteristics allow a swivel-cruciform conformation to be reached in which the biphenyl core places two of the 1,2-disubstituted double bonds in **125** in the orientation required for thermal [2+2] cycloaddition: an orthogonal rearrangement of π orbitals at a short distance. Furthermore, the high electron density of the double bonds in the starting material enhances the reactivity. According to the geometry, the head-to-tail cyclobutane **126** is the product obtained.

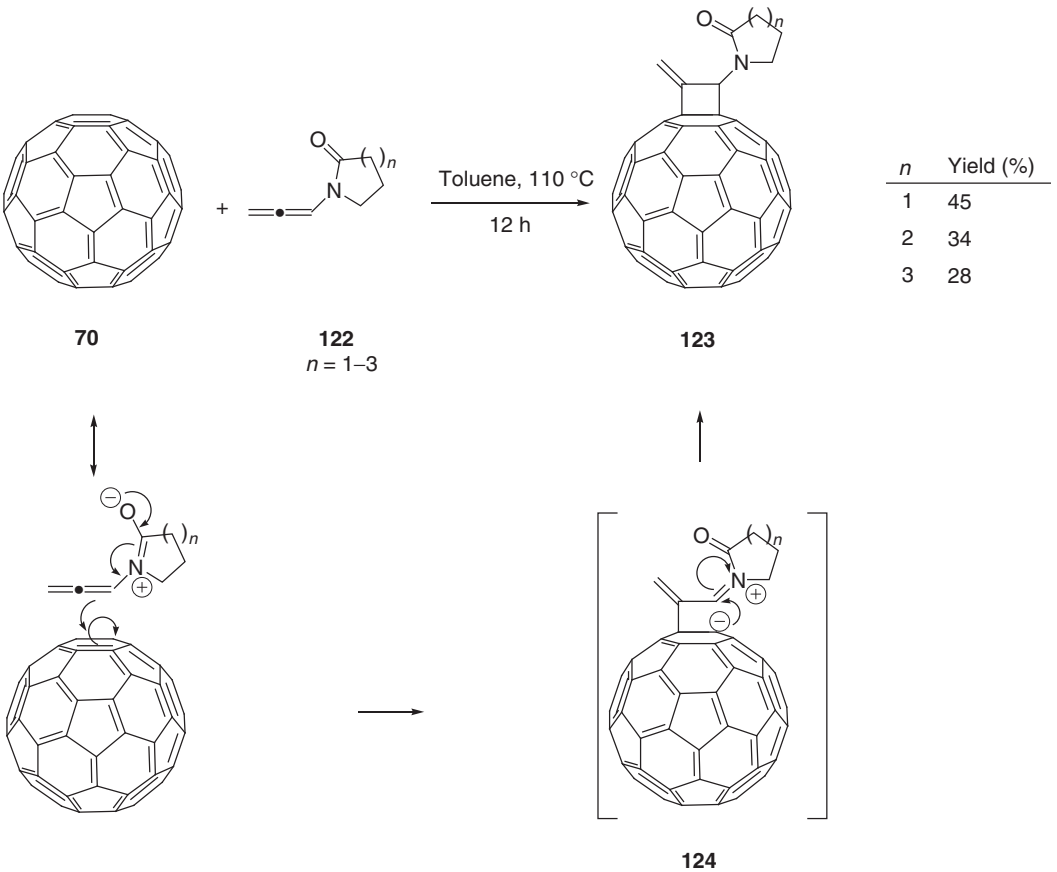


R^1	R^3	R^4	Yield (%)
Ts	H	Ph	73
Ts	H	CO_2Me	73
Bz	H	Ph	70
Bz	H	CO_2Me	71

R^1	R^2	Yield (%)
Ts	CO_2Me	51
Bz	Ph	55

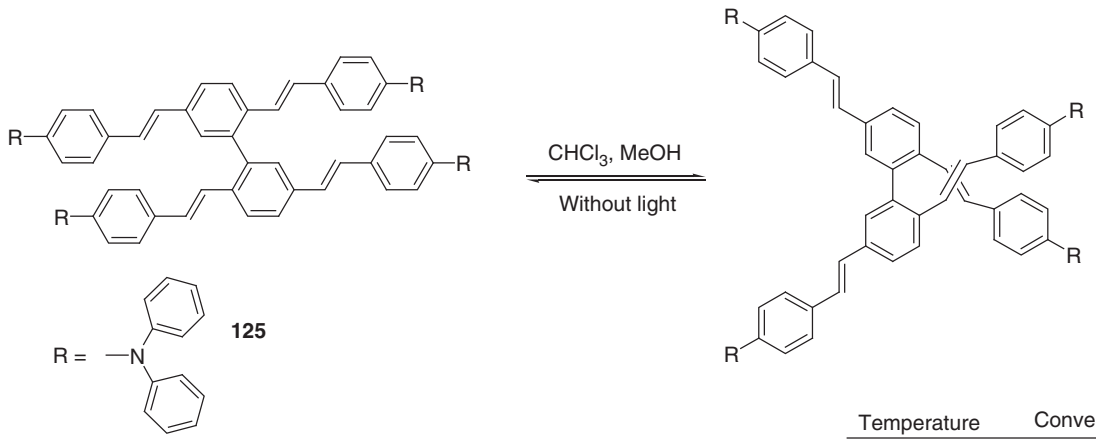
R^1 = Bn, Ts; R^2 = Ph, CO_2Me; R^3 = H, Me; R^4 = Ph, CO_2Me

Scheme 5



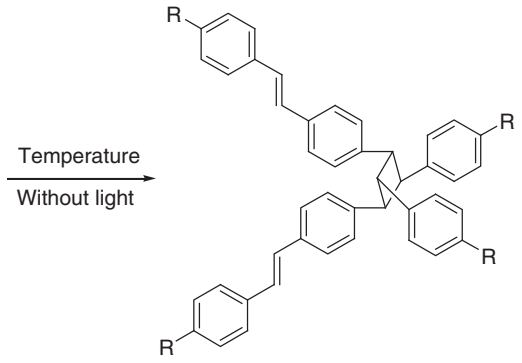
n	Yield (%)
1	45
2	34
3	28

Scheme 6 Reproduced from Nair, V.; Sethumadhavan, D.; Nair, S. M. *Synthesis* **2002**, *12*, 1655–1657.



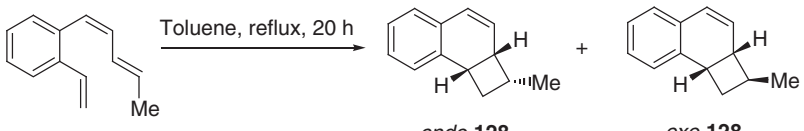
Temperature	Conversion
20 °C	40–50%
30 °C	80%

(32)



126

The reactivity of *cis,trans*-benzooctatetraene **127** has been explored under thermal conditions, and a mixture of two isomeric products, *endo*-**128** and *exo*-**128**, has been obtained (equation 33). Replacement of the terminal methyl group by a furyl or phenyl moiety led to a stereospecific reaction affording the *exo*-adduct exclusively.[84] This transformation involves an $8\pi,6\pi$-electrocyclization cascade.



127

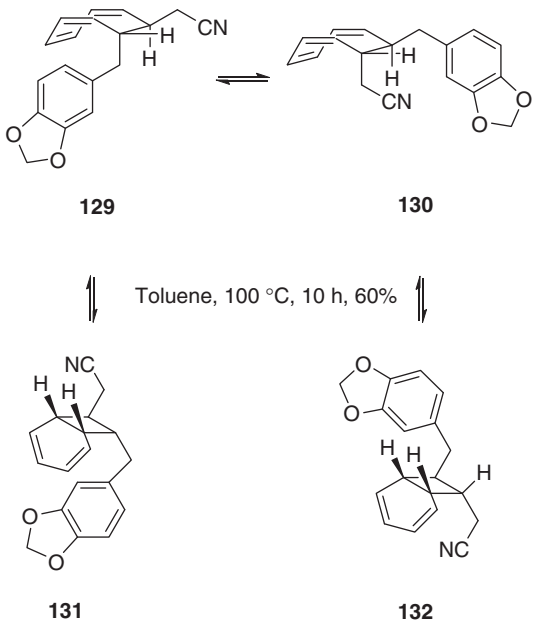
endo-**128** 33%

exo-**128** 11%

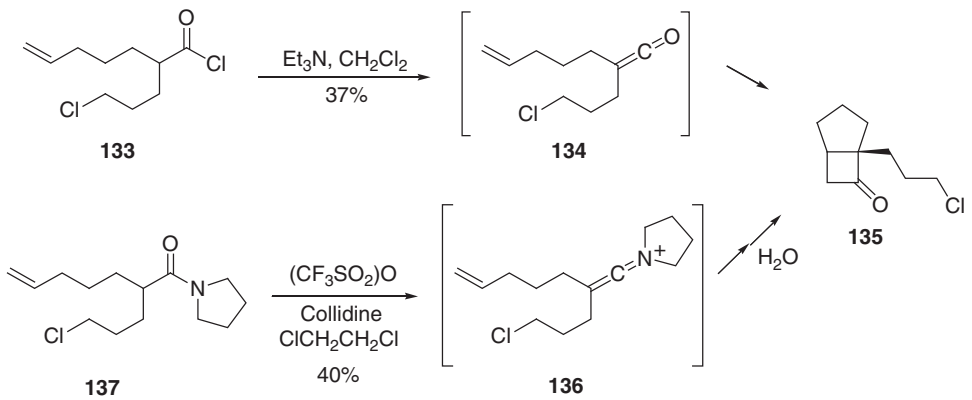
(33)

During the synthesis of the natural product pre-kingianin A, cyclooctatriene conformers **129** and **130** have afforded bicyclooctadienes **131** and **132**, respectively through a rapid 6π-electrocyclization (**Scheme 7**).[85]

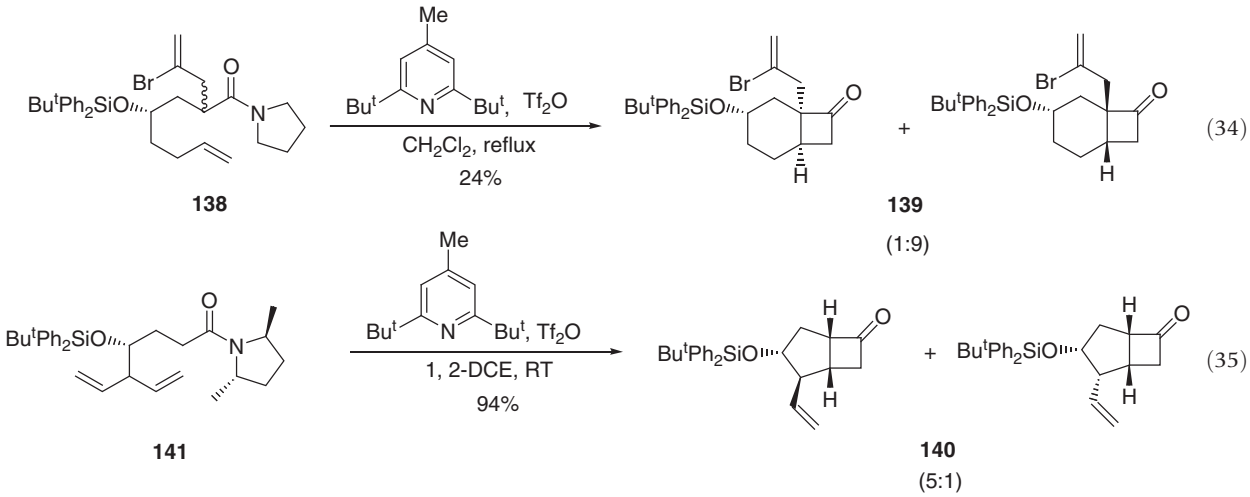
The intramolecular [2 + 2] cycloaddition of alkenes has been studied with ketenes and keteniminium salts as well.[86] Reaction of acid chloride **133** with triethylamine leads to *in situ* formation of the ketene **134**, which then undergoes intramolecular cycloaddition with the olefin to form the fused cyclobutanone **135** (**Scheme 8**). The same skeleton has also been prepared by intramolecular [2 + 2] cycloaddition of alkynyl ketenes.[87] An alternative method for the preparation of cyclobutanones is the hydrolysis of [2 + 2] cycloadducts from keteniminium salts. The keteniminium salt **136** is generated by treatment of an amide **137** with trifluoromethanesulfonic anhydride and 2,4,6-collidine (**Scheme 8**). In general, cycloadditions of keteniminium salts give better yields than the analogous cycloadditions of ketenes. Other examples have been reported in the literature, such as the synthesis of a key intermediate of (+)-gibberellic acid by intramolecular [2 + 2] cycloaddition of **138** to give cyclobutanes **139** (equation 34),[88] and the asymmetric synthesis of the prostanoid scaffolds **140** by employing an asymmetric intramolecular [2 + 2] cycloaddition of keteniminium salts derived from **141** as a key step (equation 35).[89]



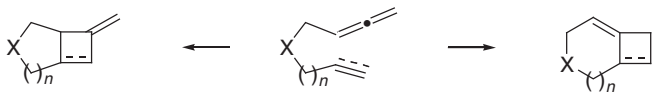
Scheme 7 Reproduced from Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47*(38), 10605–10607, with permission from Royal Society of Chemistry.



Scheme 8 Reproduced from Zhang, W.; Collins, M. R.; Mahmood, K.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*(16), 2729–2732.



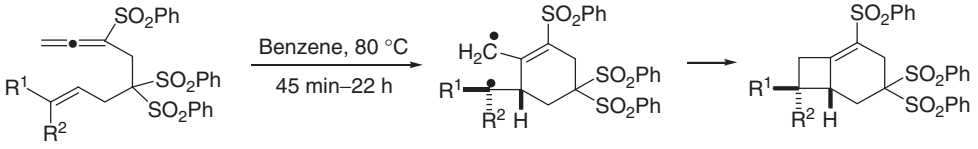
The intramolecular [2 + 2] cycloaddition of allenes is an interesting strategy to prepare polycyclic fused structures. However, it is necessary to consider that two regioisomers can be formed in the reaction of allene-enes and allene-ynes **142**; the proximal cycloadduct **143** is formed by reaction with the internal 2π component, whereas the distal cycloadduct **144** is formed by reaction with the external 2π component of the allene moiety (Scheme 9).



143 **142** **144**

Scheme 9 Reproduced from Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*(2), 783–816, with permission from Royal Society of Chemistry.

Initial works were focused on the study of the regioselectivity depending on the substitution on the alkene moiety. Allene-enes **145** and **146** as starting materials afforded different regioisomers **147** and **148** in excellent yields via biradical intermediates **149** and **150** (equations 36 and 37).[90,91] More recently, an analogous behavior has been observed in β-lactam-based allene-enes **151** and **152**. Once again, the presence of an internal substituent on the alkene moiety controls the regiochemistry of the [2 + 2] cycloaddition, affording cyclobutanes **153** and **154** as single regioisomers with moderate yields.[92,93] In both examples, biradical intermediates have been proposed (equations 38 and 39).

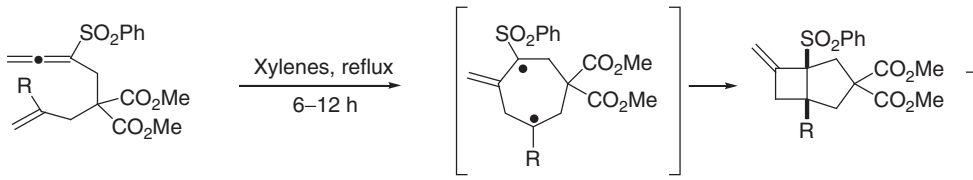


145 **149** **147**

R^1 = H, Me; R^2 = H, Me

R^1	R^2	Yield (%)
H	H	90
M	Me	90
Me	H	80
H	Me	100

(36)

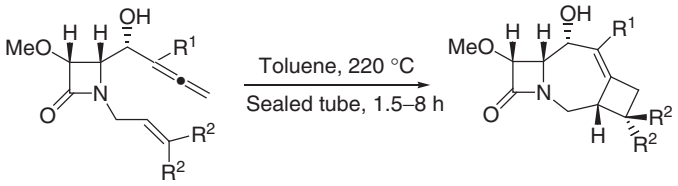


146 **150** **148**

R = Me, Br

R	Yield (%)
Me	77
Br	64

(37)

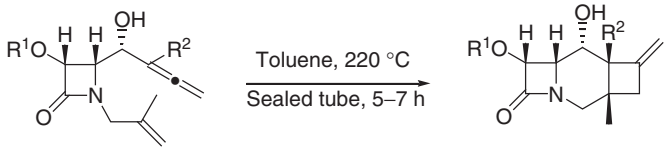


151 **153**

R^1 = H, Me, Ph; R^2 = H, Me

R^1	R^2	d.r.	Yield (%)
H	H	100:0	40
Me	H	100:0	56
Ph	H	100:0	58
Me	Me	100:0	45
Ph	Me	100:0	57

(38)



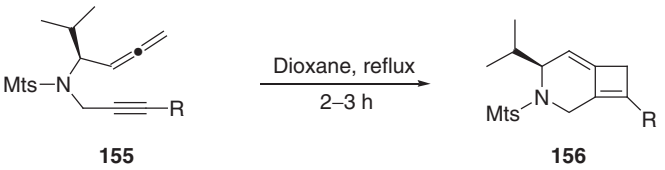
152 **154**

R^1 = Me, Ph; R^2 = Me, Ph

R^1	R^2	d.r.	Yield (%)
Me	Ph	100:0	56
Ph	Me	100:0	52
Ph	Ph	100:0	57

(39)

However, the presence of a nonterminal alkyne moiety is essential for the [2 + 2] cycloaddition of allene-ynes, affording in most of the cases distal adducts with complete regioselectivity. Recently, allene-ynes **155** were shown to give the corresponding cycloadducts **156** in excellent yields (equation 40) under thermal conditions.[94] In addition, this method has been applied to the construction of both bicyclo[6.2.0]deca-1,8-dienes **157** from allene-ynes **158** (equation 41),[95] as well as to the synthesis of 3-oxabicyclo[4.2.0]octa-1(8),5-dien-4-ones **159** via intramolecular [2 + 2] cycloaddition of propargylic 2,3-allenoates **160** under conventional heating conditions (equation 42).[96]

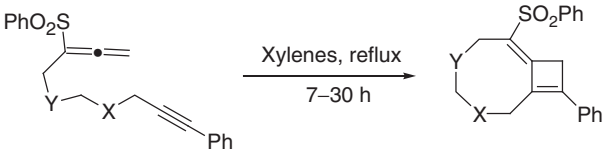


155 **156**

R = Ph, *p*-MeC_6H_4

R	Yield (%)
Ph	92
p-MeC_6H_4	94

(40)

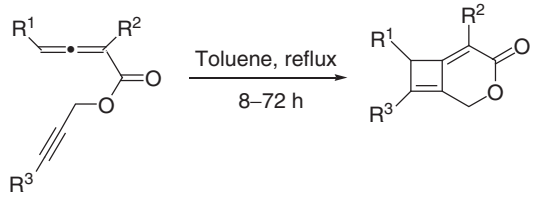


158 **157**

X = O, CH_2, NTs; Y = CH_2, $C(CO_2Me)_2$

X	Y	Yield (%)
O	CH_2	41
NTs	CH_2	74
CH_2	$C(CO_2Me)_2$	60

(41)



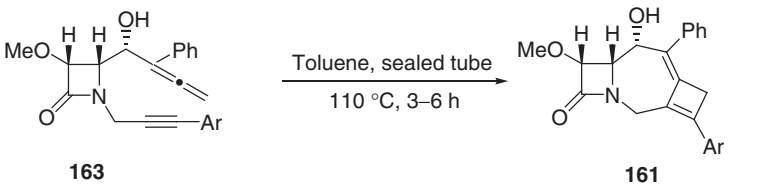
160 **159**

R^1 = Ph, *p*-BrC6H_4; R^2 = Me, Bn, Pr^n, allyl; R^3 = Ph, TMS

R^1	R^2	R^3	Yield (%)
Ph	Me	Ph	82
Ph	Bn	Ph	66
p-BrC_6H_4	Pr^n	TMS	71
Ph	Allyl	TMS	64

(42)

In a very recent work, the mono- and bis(tricyclic) *β*-lactams **161** and **162** containing a cyclobutene ring have been prepared via intramolecular [2 + 2] cycloaddition of the *β*-lactam-derived enynes **163** and **164**, respectively (equations 43 and 44).[97] Similarly, cyclic *α*-amino acid derivatives **165** bearing a fused cyclobutene ring have been synthesized starting from adequately functionalized allene-ynes **166** (equation 45).[98]

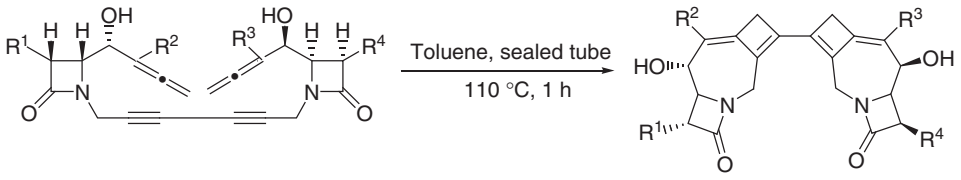


163 **161**

Ar = Ph, *p*-$MeOC_6H_4$, 2-pyridyl, 2-thiophenyl

Ar	Yield (%)
Ph	54
p-$MeOC_6H_4$	55
2-pyridyl	86
2-thiophenyl	53

(43)

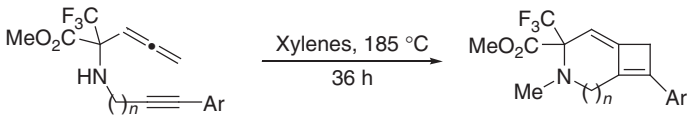


164 **162**

(44)

R^1 = MeO, PhO; R^2 = Me, Ph; R^3 = Me, Ph; R^4 = MeO, PhO

R^1	R^2	R^3	R^4	Yield (%)
MeO	Ph	Ph	MeO	65
PhO	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	PhO	78
PhO	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	MeO	53
PhO	Ph	Ph	MeO	72



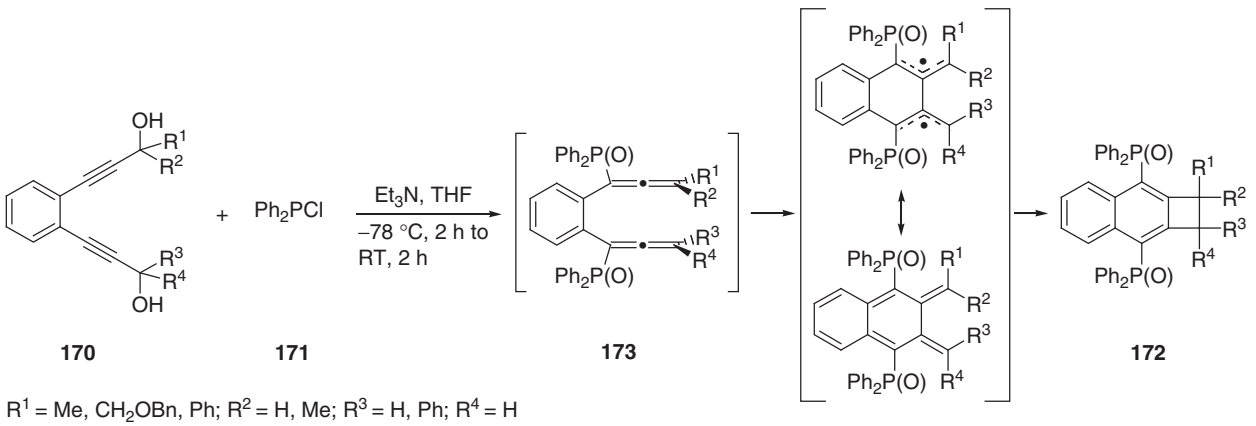
166 **165**

Ar	*n*	Yield (%)
Ph	1	82
p-MeC_6H_4	1	74
o-$NO_2C_6H_4$	2	80

(45)

Ar = Ph, *p*-MeC_6H_4, *o*-$NO_2C_6H_4$; *n* = 1, 2

The thermal [2 + 2] cycloaddition reaction of the cyclic 1,3-bis-(alkylthio)allene **167** gave the fused tricyclic cyclobutane **168** quantitatively via the biradical intermediate **169** as shown in equation 46.[99,100] Bispropargylic alcohols are excellent precursors to bis-allenes. For example, the reaction of bis(propargylic alcohols) **170** with chlorodiphenylphosphine **171** has been reported to afford 3,8-bis(diphenylphosphynyl)naphtho[*b*]cyclobutanes **172** via the corresponding 1,2-bis(α-phosphinylallenyl)benzenes **173**.[101] Formation of compounds **172** has been rationalized via the intermediacy of biradical intermediates **174**. The aromaticity of the final products is probably the driving force to obtain compounds **172** as sole isomers (**Scheme 10**).

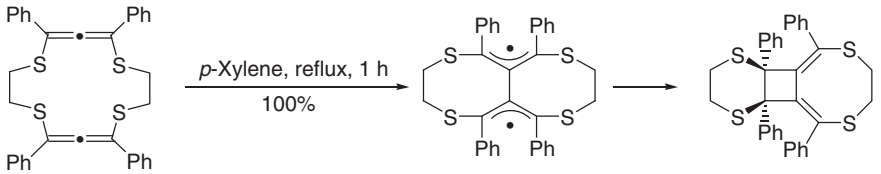


170 **171** **173** **174** **172**

R^1 = Me, CH_2OBn, Ph; R^2 = H, Me; R^3 = H, Ph; R^4 = H

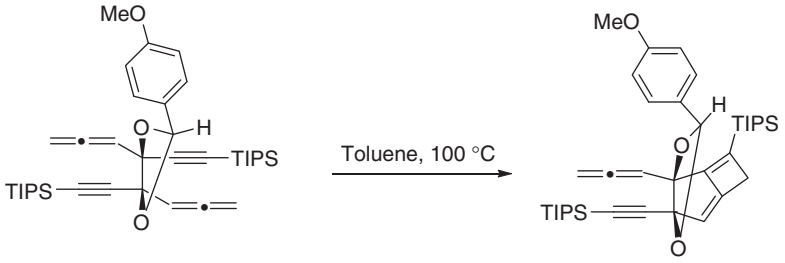
R^1	R^2	R^3	R^4	Yield (%)
Me	H	H	H	84
CH_2OBn	H	H	H	90
Ph	H	Ph	H	87
Me	Me	H	H	86

Scheme 10



167 169 168 (46)

A competitive reaction involving a [2 + 2] cycloaddition of allene-ynes was presented in 2003. During the attempted synthesis of a dicyclopenta[*a*,*e*]pentalene via a Pauson–Khand reaction, the monocyclized [5.4] system **175** was obtained instead on heating the diyne-diallene **176** in toluene at 100 °C (equation 47).[102]



176 175 (47)

5.02.5 Summary

In summary, a high number of different examples have been reported concerning the thermal cyclobutane synthesis, with different π components such as alkenes, alkynes, allenes, ketenes, and iminium salts. In most cases, a biradical intermediate has been proposed to explain the mechanism, although in a few examples zwitterionic intermediates have been postulated. The regiochemistry, which is usually controlled by the nature of the substituents in the starting material, has been discussed in detail for reactions which can lead to several isomers.

A huge amount of work has already been published, but seems to be only the starting point for the preparation of more complex structures, probably focusing on the preparation of biologically active cyclobutane-containing compounds or the synthesis of macrocyclic and polymeric structures with interesting physical properties.

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5.03 Formation of Four-Membered Heterocycles

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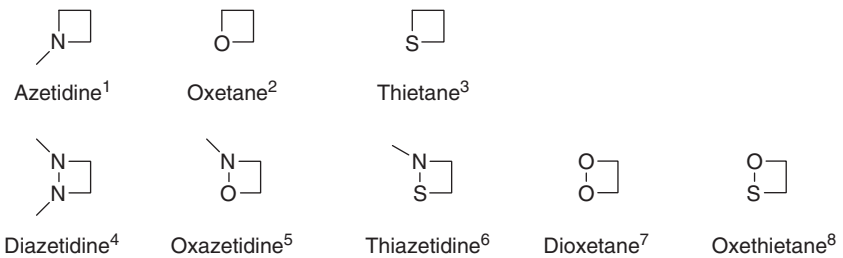
Glossary

Allene Compounds having two double bonds from one atom to two others. It can be a hydrocarbon ($R_2C{=}C{=}CR_2$) or a derivative formed by substitution ($R_2X{=}Y{=}ZR_2$).
Hünig's base *N*,*N*-diisopropylethylamine (DIPEA). It is used as a sterically hindered, hence poorly nucleophilic base in organic chemistry.
Ketene Organic compound in which a carbonyl group is connected by a double bond to an alkylidene group, $R_2C{=}C{=}O$.
β-Lactam A four-membered cyclic amide having a 1-azacyclobutan-2-one (2-azetidinone) structure.
β-Lactone A four-membered cyclic ester having a 1-oxacyclobutan-2-one (oxetan-2-one) structure.
Mukaiyama reagent 2-Chloro-1-methylpyridinium iodide.
Zwitterion Neutral compound having formal unit electrical charges of opposite sign at different locations within that compound, sometimes referred to as inner salts or dipolar anion.

5.03.1 Introduction

This section is devoted to the formation of four-membered cycles containing at least one heteroatom, and obtained by combining π-systems through formal [2 + 2] cycloaddition reactions. Heat-activated and metal-, acid-, or base-catalyzed reactions will be considered here, whereas the photochemical cycloadditions are discussed in Chapter 5.04.

There are several classes of four-membered heterocycles (Scheme 1).[1–8] The considerable attention focused on these heterocycles originates from the discovery of penicillins,[9] cephalosporins,[10] and related antibiotics[11] which feature a β-lactam (azetidin-2-one) ring in their core structures. The β-lactone (oxetan-2-one) ring is also found as an important structural characteristic in several biologically active compounds.



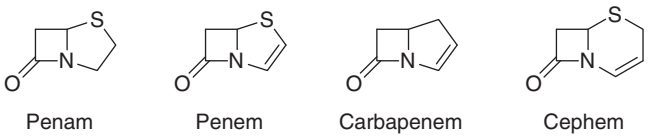
Scheme 1

The functionalities involved in four-membered heterocycles are endowed with increased reactivity resulting from the ring strain. Accordingly, these molecules can be exploited as building blocks in organic synthesis, in particular when regio, stereo, and enantioselectivities have to be controlled.[12–16]

A brief survey of the above mentioned important aspects, lying outside the scope of this section, is presented as Introduction.

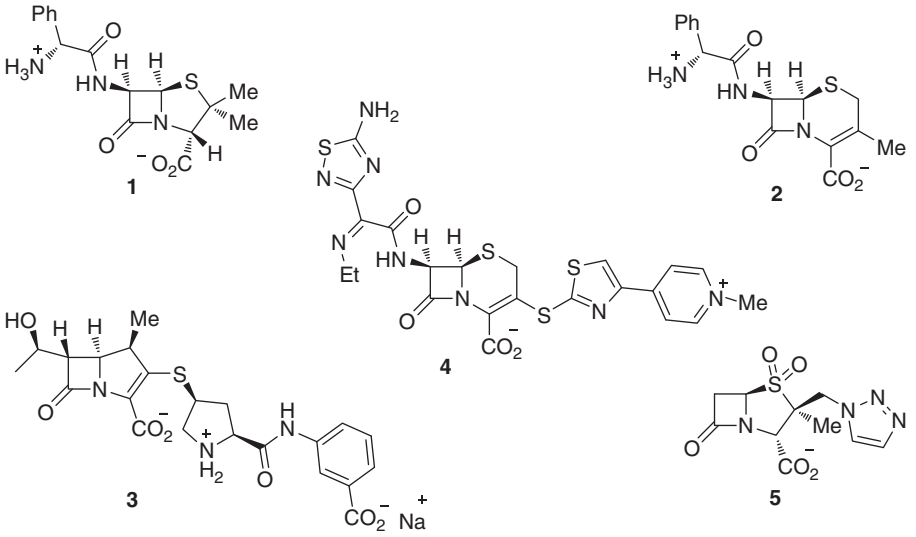
5.03.1.1 Four-Membered Heterocycles as Biologically Active Compounds

The antibiotics belonging to the so-called β-lactam class are still the most prescribed ones against bacterial infections.[17] Several subclasses exist depending on the nature of the fused five- or six-membered rings (Scheme 2).[9–11] Due to the increasing bacterial resistance to early drugs such as ampicillin **1** and cephalexin **2**, increasingly sophisticated derivatives have been developed as illustrated with ertapenam **3**[18] and ceftarolin **4**.[19] These β-lactams are active against methicillin resistant *Staphylococcus aureus* (MRSA) responsible for nosocomial infections in hospitals (Scheme 3). Another way to fight resistant bacteria is the administration of a traditional penicillin (ampicillin for instance) together with an inhibitor of β-lactamases (i.e., bacterial defense enzymes), such as tazobactam **5**.[20]



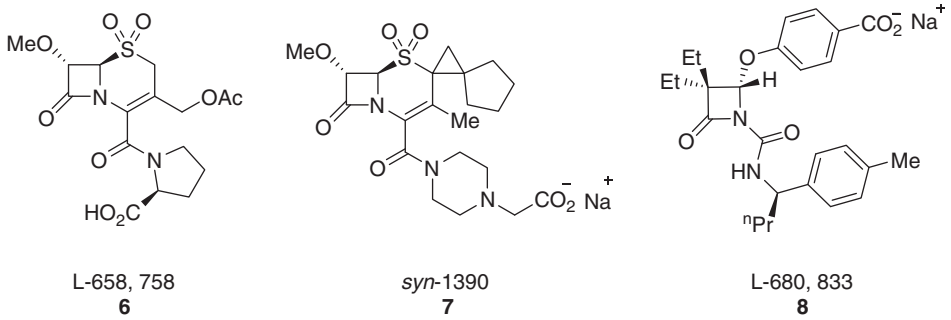
Scheme 2

The mode-of-action of the β-lactam antibiotics as well as the resistance mechanisms have been intensively studied.[17] The structures of several bacterial target enzymes are known at the atomic level, thus allowing the rational design of novel β-lactams



Scheme 3

acting as inhibitors of the so-called penicillin-binding proteins (PBPs).[21,22] Since these enzymes are serine proteases (DD, transpeptidases–carboxypeptidases involved in the bacterial cell-wall biosynthesis), the β-lactam motif was considered by the medicinal chemists as a common pharmacophore for the inhibition of other serine enzymes playing a key role in numerous diseases. For instance, human leukocyte elastase inhibitors L-658758 (**6**)[23] and SYN-1390 (**7**),[24] used in aerosols for the treatment of allergy, are structurally related to the cephem antibiotics (Scheme 4). Orally bioavailable antiinflammatory drugs, such as L-680833 (**8**) are simple monocyclic β-lactams.[25]



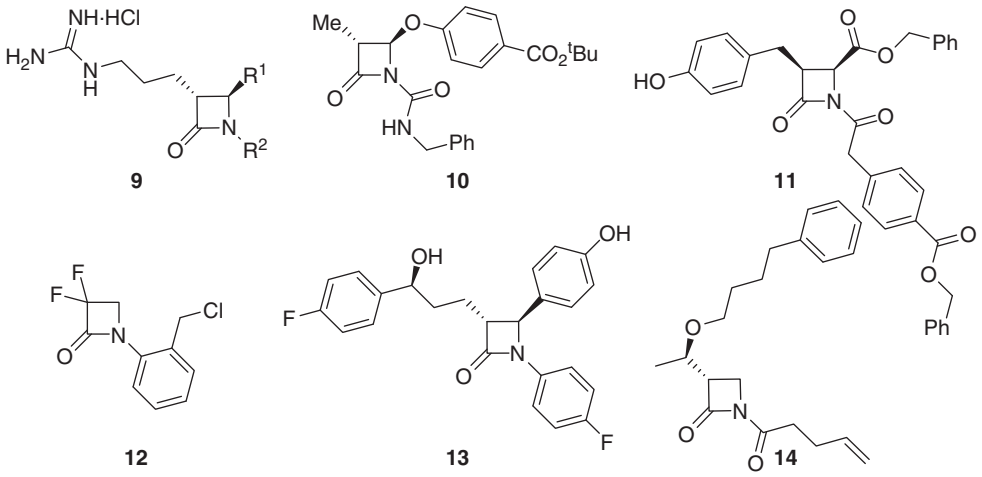
Scheme 4

A lot of monocyclic β-lactams[26–30] have been disclosed for the inhibition of thrombin (e.g, **9**),[31] human cytomegalovirus protease (e.g.,, **10**),[32] prostate specific antigen (e.g., **11**),[33] β-lactamases (e.g., **12**),[34] cholesterol absorption (e.g., **13**),[35] and fatty acid amide hydrolase (e.g., **14**),[36,37] among others (Scheme 5).

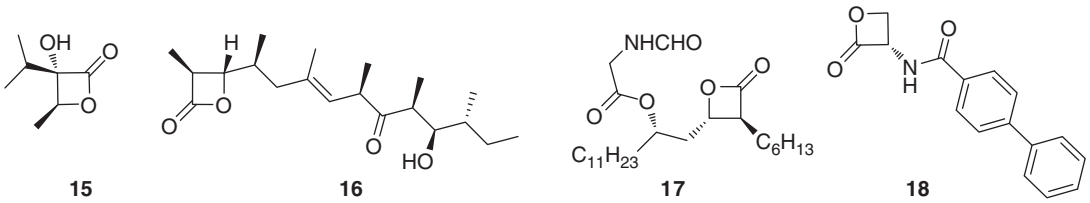
β-Lactones found in nature are pheromones (**15**),[38] esterase inhibitors (**16**),[39] etc. Synthetic derivatives have been designed for the inhibition of pancreatic lipase,[40] monoacylglycerol lipase (MAGL) (**17**),[41] and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) (**18**),[42] as examples (Scheme 6). β-Turn mimics for the construction of Arg–Gly–Asp (RGD) peptidomimetics are based on bicyclic azetines **19**.[43] Antimicrobial (**20**)[44] and anticancer drugs (**21**, paclitaxel)[45] feature an oxetane ring. The synthetic analog with a thietane ring (Taxol-thietane) has also been prepared (Scheme 7).[46]

5.03.1.2 Four-Membered Heterocycles as Reactive Intermediates

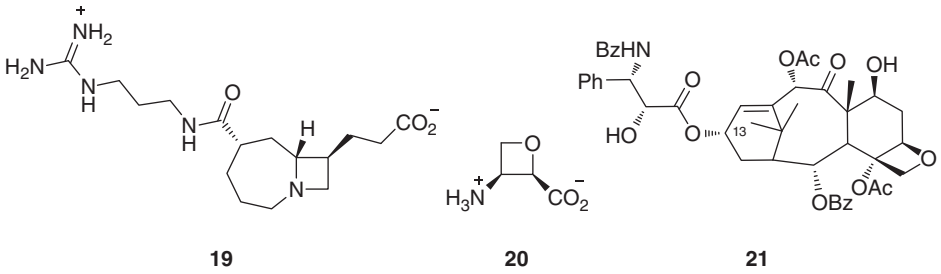
Chiral β-lactams are useful precursors of azetines, amides, and 1,3-aminoalcohols, with preserved chirality, by selective reduction of the C_2 carbonyl, N_1–C_4 bond (R^2 = aryl) and C_2–N_1 bond (R^1 = Boc), respectively (Scheme 8). Nevertheless, the main applications concern the nucleophilic addition on the C_2 carbonyl group accompanied by the C_2–N_1 bond cleavage, leading to chiral β-aminoacid derivatives (Scheme 8).[1,12] The β-lactam function can also be broken by basic or acidic hydrolysis. A general strategy to produce enantiopure, nonproteogenic α,β-diaminoacids makes use of β-lactam precursors.[47]



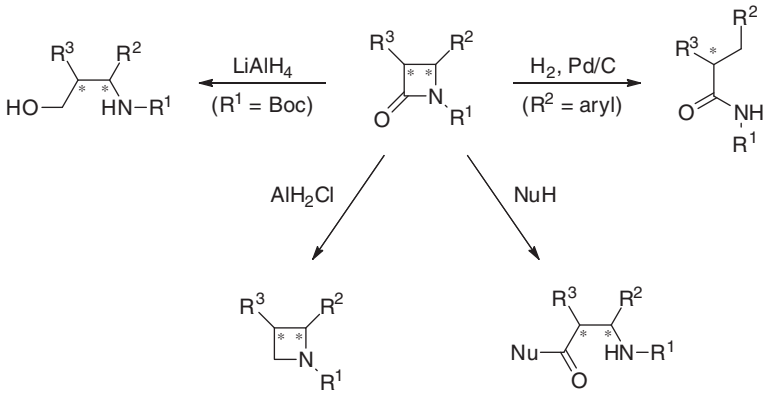
Scheme 5



Scheme 6

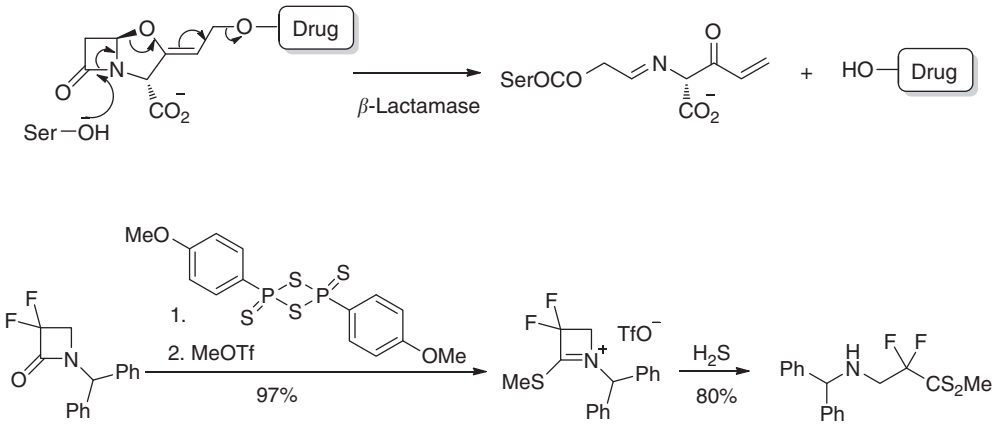


Scheme 7



Scheme 8

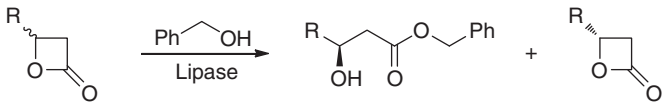
The processing of β-lactams by serine enzymes has been used for the design of pro-drugs. The drug of interest is coupled to a bicyclic β-lactam that is sensitive to β-lactamases; this conjugate is inactive. The enzymatic hydrolysis of the β-lactam core liberates the active drug on the site of infection. Equation 1 illustrates one example of drug delivery based on this strategy.[48,49] β-Lactam ring opening can also proceed via an azetine (or azetinium) intermediate as shown in the synthesis of fluorinated β-amino dithioesters (Scheme 9).[50]



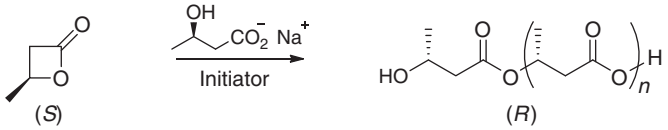
(1)

Scheme 9

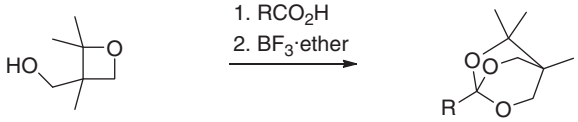
β-Lactones are very sensitive to nucleophilic attack and ring opening. An interesting kinetic resolution has been achieved via a lipase-promoted asymmetric transesterification with benzyl alcohol (O_1–C_2 bond cleavage) (equation 2).[51] Anionic polymerization of β-lactones occurs via the O_1–C_4 bond cleavage. The nucleophilic attack on C_4 (S_N2 reaction) has been established by the inversion of configuration at this center: (*S*)-β-butyrolactone leads to the formation of poly-(*R*)-3-hydroxybutyrate (equation 3).[52] The most commonly used method to synthesize polyethers is the cationic ring-opening polymerization of oxetanes; the living polymerization has been demonstrated.[53] Another example of acid-catalyzed ring opening of oxetanes is given by the synthesis of *ortho*-esters as the protection of carboxylic acids (equation 4).[54,55]



(2)

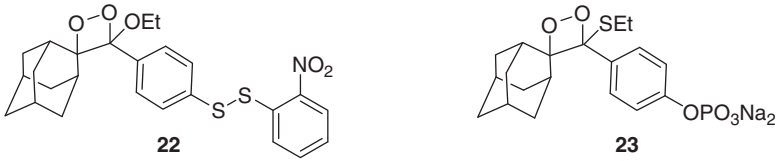


(3)



(4)

Chemiluminescent probes based on the dioxetane moiety are commonly used in molecular biology.[56] The simultaneous O_1–O_2 and C_3–C_4 bond cleavages give carbonyl species at the excited state, the deactivation of which produces light. Scheme 10 depicts the molecules **22** and **23** behind the bioassays for detection of cholin esterase and alkaline phosphatase activities,

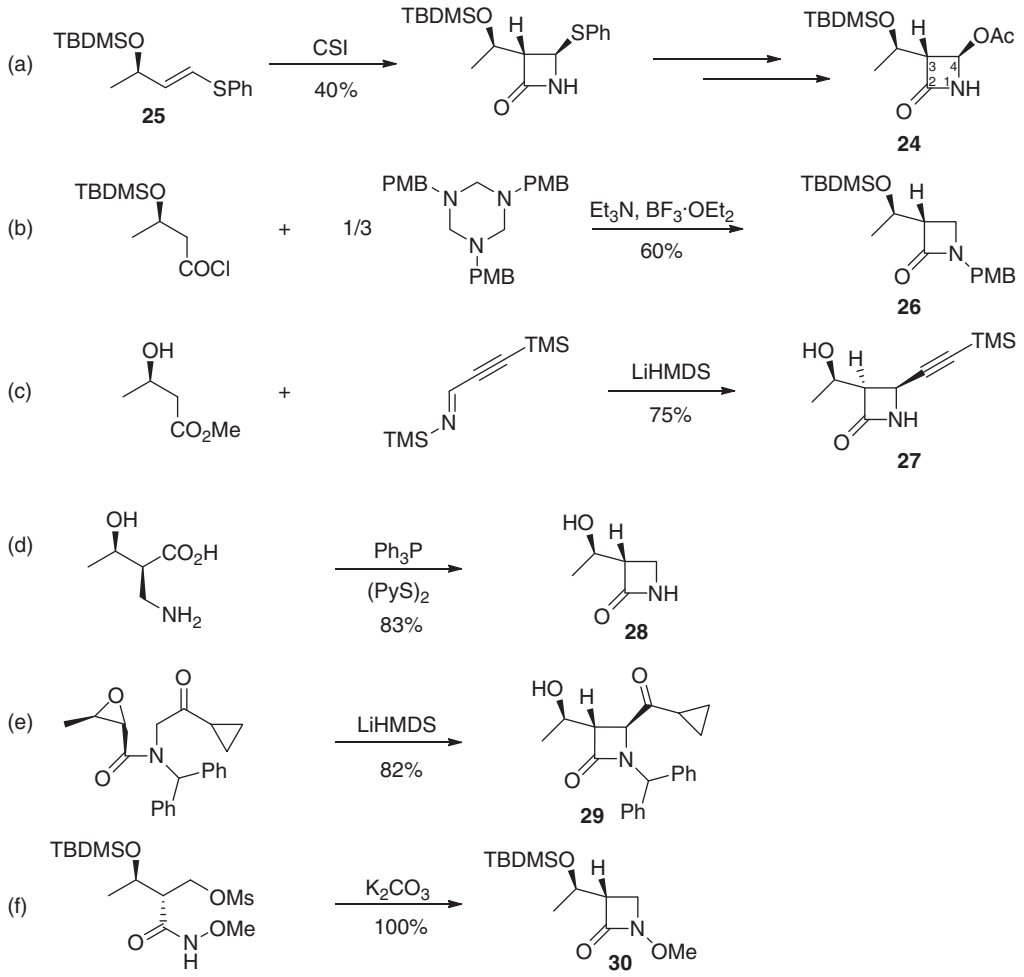


Scheme 10

respectively.[57,58] Bioluminescent assays using a luciferase substrate are based on the *in situ* formation of a dioxetanone, which decomposes into CO_2 and an excited carbonyl species emitting light under decay.[59]

5.03.1.3 Strategies for the Preparation of Four-Membered Heterocycles

The various strategies exploited for the synthesis of four-membered heterocycles are exemplified here with the preparation of acetoxy-azetidinone **24**, the industrial starting material of all the (carba)penem antibiotics (Scheme 11).[60–62] Usually, the chirality is introduced by using enantiomerically pure reagents and controlled reaction mechanisms. A first route (a) is based on the [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) onto the *trans*-phenylthio-alkene **25**,[63] thus forming concomitantly the C_2–C_3 and N_1–C_4 bonds. The [2 + 2] cycloaddition of ketenes or enolates to Schiff bases constitutes other main routes (b)[64] and (c),[65] leading to the simultaneous formation of C_3–C_4 and C_2–N_1 bonds. The cyclization reactions cover the C_2–N_1 bond formation from β-aminoacid precursors[66] (route (d)), the C_3–C_4 bond formation by intramolecular S_N2 reactions[67] (route (e)), and the Miller process for creating the N_1–C_4 bond (route (f)) from hydroxylamide derivatives.[68] All the chiral β-lactams **26** to **30** are precursors of the key building block **24**: the process (a) and (d) have been developed at pharmaceutical production scale.



Scheme 11

Besides these three [2 + 2] cycloaddition strategies and three cyclization appoaches, the carbonylation of aziridines offers a practical access to β-lactams,[69–71] via a ring-expansion reaction. Rearrangement of isoxazolidines (obtained by 1,3-dipolar cycloaddition of nitrones to alkynes, see Section 5.03.7) leads to β-lactams by a ring-contraction known as the Kinugasa reaction.[72,73]

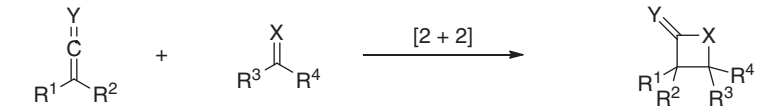
Similarly, β-lactones are prepared by [2 + 2] cycloadditions of aldehydes to ketenes[74,75] or enolates,[76,77] and by lactonization, i.e., O_1–C_2 cyclization from adequately β-substituted carboxylic derivatives,[78,79] as the principal strategies.

5.03.1.4 Aim of the Review

A recent volume of the CHC series (Comprehensive Heterocyclic Chemistry III, 2008) edited by Katritzky covers extensively the chemistry of four-membered heterocycles and all fused systems with a four-membered heterocyclic ring. The synthetic strategies other than the cycloadditions, namely various cyclization methods, ring-expansion, and ring-contraction methods, are discussed in an exhaustive manner for each class of compounds. The present review, which has been written in continuation of the previous one in the first edition of this series (Comprehensive Organic Synthesis 1991, Vol. 5), focuses on new developments in [2 + 2] cycloadditions leading to four-membered heterocycles which appeared in between 1992 and 2012. A special attention is drawn to the mechanistic aspects of the reactions and their consequences on the stereochemical outcome of the cycloaddition processes. Accordingly, the subdivision in sections reflects this point of view: the entries are related to reactions of various reagents (ketenes, enolates, ynolates, isocyanates, etc) with C═X bonds instead of a list of types of heterocycles. New sections have been introduced dealing with cycloaddition of alkenes, allenes, and alkynes with C═N bonds, as well as of alkynes with nitrones and of sulfenes with C═X bonds. The accent is also put on asymmetric catalysis which is of particular interest for the enantioselective synthesis of biologically active compounds or their precursors

5.03.2 Reaction of Ketenes, Ketenimines, and Thioketenes with C═X bonds

Heteroallenes of the type $R_2C{=}C{=}Y$ (Y=O, NR, or S) are reactive intermediates which undergo [2 + 2] cycloaddition with C═X bonds to lead to the corresponding four-membered heterocycles (equation 5).[80–83] Among these reactions, the most important is the [2 + 2] cycloaddition reaction between ketenes and imines, known as the Staudinger cycloaddition (Y=O; X=NR).[84,85] Ketenes are also reported to react with carbonyls and thiocarbonyls, leading to corresponding 2-oxetanones and 2-thietanones.[82]



Y = O, NR, S X = O, NR, S (5)

However, ketenimines and thioketenes (Y=NR and S) have received only little attention.[86–88] In the former case, the reason is the low reactivity of such heteroallenes; for thioketenes, it is their instability and the difficulty to prepare them, which explain the dearth of examples.

Most disubstituted ketenes are stable intermediates which can be isolated. Monosubstituted and heterosubstituted ketenes on the contrary have limited stability (prone to polymerize).[89] Accordingly, ketenes are usually generated *in situ*, from the corresponding acyl chlorides or related derivatives in the presence of a base, by photolysis of metal–carbene complexes, or by rearrangement of α-diazocarbonyl compounds.[90] It is important to note however that the conditions for generating ketenes may have an influence on the mechanism and the stereochemical outcome of the reaction (*vide infra*).

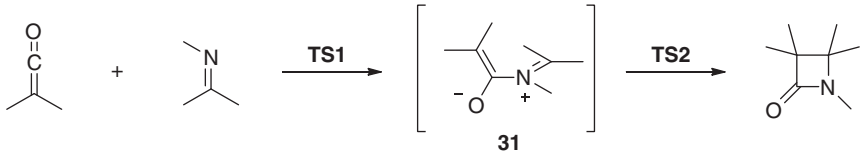
5.03.2.1 Reaction with Imines

The most developed reaction of ketenes is their [2 + 2] cycloaddition with imines, known as the Staudinger cycloaddition.[84,85] This reaction is the most widely used strategy for the preparation of *β*-lactams.[91–94] The relevance of this method is due to its convergent nature and ready access to reagents, and thus a wide range of *β*-lactams are available.

5.03.2.1.1 Mechanism

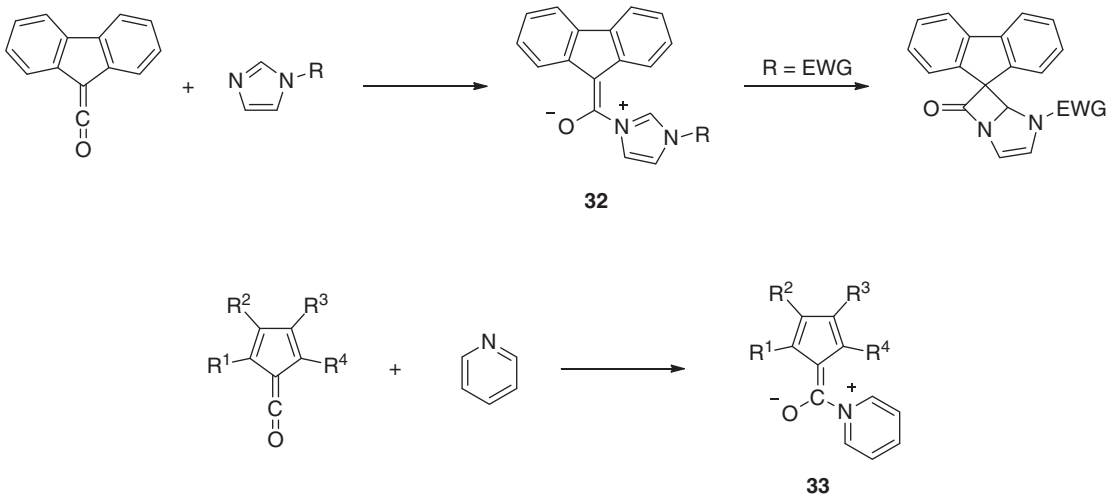
The ketene–imine Staudinger reaction is a [2 + 2] cycloaddition. These cycloadditions are allowed by the Woodward–Hoffmann rules, provided that the approach of the π-systems occurs in a *supra–antara* mode ($[{}_{\pi}2_s + {}_{\pi}2_a]$).[95] There are, however, abundant experimental evidences showing that the mechanism in solution is not concerted but is instead a stepwise process.[93,94]

The accepted mechanism for these reactions involves initial formation of a zwitterionic intermediate (**31**) by addition of the imine nitrogen atom to the central sp-hybridized carbon atom of the ketene (Scheme 12).[91,96] Subsequent conrotatory electrocyclic ring closure ($[{}_{\pi}4_c]$) then leads to the *β*-lactam.

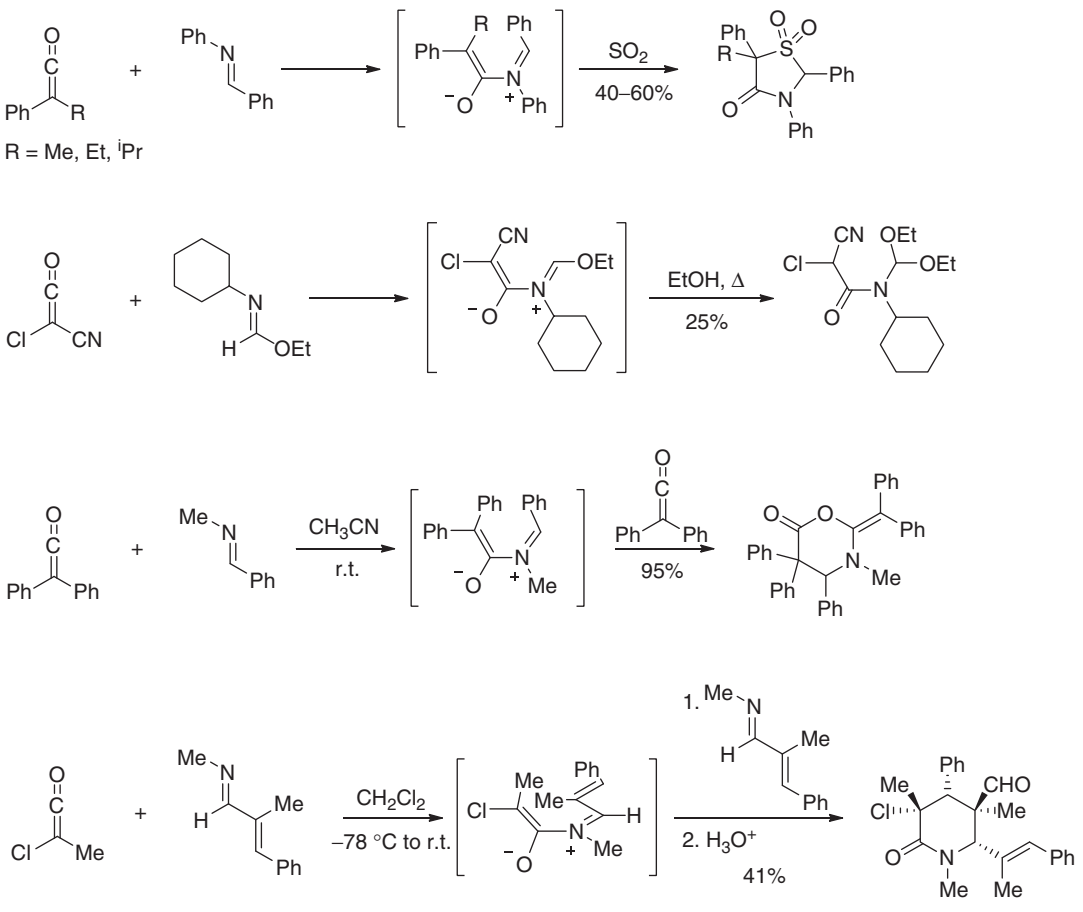


Scheme 12

This mechanism has been confirmed by isolation and characterization of the zwitterionic intermediates of type **32** and **33** in the reaction of stabilized ketenes with imidazoles and pyridine, respectively (Scheme 13).[97,98] In several cases, the zwitterionic intermediate could also be trapped by sulfur dioxide,[99] ethanol,[100] a second equivalent of ketene,[101] or a dienophile[102] (Scheme 14).

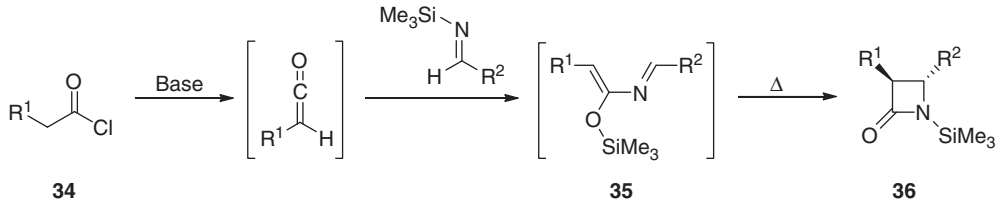


Scheme 13



Scheme 14

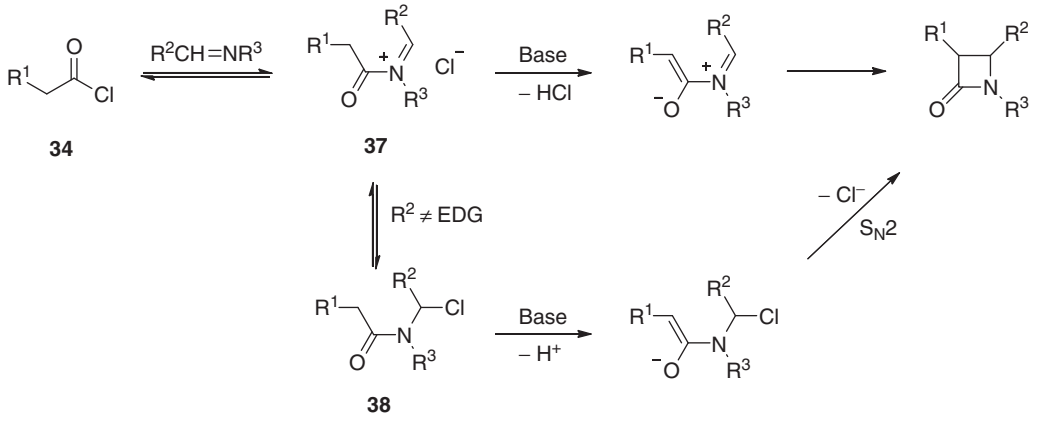
Additionally, in the reaction of monosubstituted ketenes and *N*-silylimines, the unambiguous formation of 3-aza-1,3-dienes **35** has been reported.[103–106] These intermediates were completely characterized and found to yield the corresponding *N*-silyl-*β*-lactams **36** on heating (Scheme 15).



Scheme 15

The two-step mechanism is also supported by computational results. Computational studies on the synthesis of *β*-lactams via [2 + 2] thermal cycloadditions have recently been reviewed by Cossio.[91] It is important to note that inclusion of solvent effects in the calculations of the mechanism was found to be crucial; calculations in the gas phase point to a concerted mechanism. It is also worth mentioning that calculations indicate that addition of the imine onto the ketene is reversible, with electrocyclization being the rate-determining step of the process.[107,108]

Xu et al. have shown that in some cases (when the acyl chloride is used as starting reactant), depending on the mode of addition of reagents, the mechanism may vary.[90,109] Indeed, when the acyl chloride is added to a solution of imine and a base, the ketene is directly formed and the reaction pathway follows the one described in Scheme 12. However, when the base is added to a solution of an imine and an acyl chloride, direct addition of the imine onto the acyl chloride (before ketene formation) produces an acyl iminium chloride **37** (Scheme 16). In most cases, this acyl iminium chloride undergoes a hydrogen abstraction to lead to the zwitterionic intermediate which further produces the *β*-lactam as in the general mechanism. In some specific cases (when the solution of the imine and the acyl chloride is stirred for several hours before the addition of the base, and the imine is not substituted by a strong electron-donating substituent, EDG) addition of chloride has been shown to occur, producing the corresponding chloro amide (**38**). Subsequent deprotonation and intramolecular alkylation (via a S_N2 mechanism) then leads to the *β*-lactam.



Scheme 16

The mechanism thus depends on the substitution of the reactants and on the reaction conditions. This is of particular importance since the nature of the pathway has an impact on the stereochemical outcome of the reaction (*vide infra*).

The reaction can also be catalyzed by Lewis acids (LAs) or nucleophiles (tertiary amines). In the former case, mechanistic studies indicate that activation occurs through complexation of the ketene (see Section 5.03.2.2.3).[110] In nucleophile-catalyzed reactions, the nucleophile adds first to the ketene to form an enolate which then reacts with the imine.[111] The imine-enolate condensation will be discussed in Section 5.03.4.

Reactions of ketenimines and thioketenes have been less studied.[112–117] However, mechanistic studies indicate that the [2 + 2] cycloaddition of these intermediates occurs via the same mechanism as for ketenes.[91]

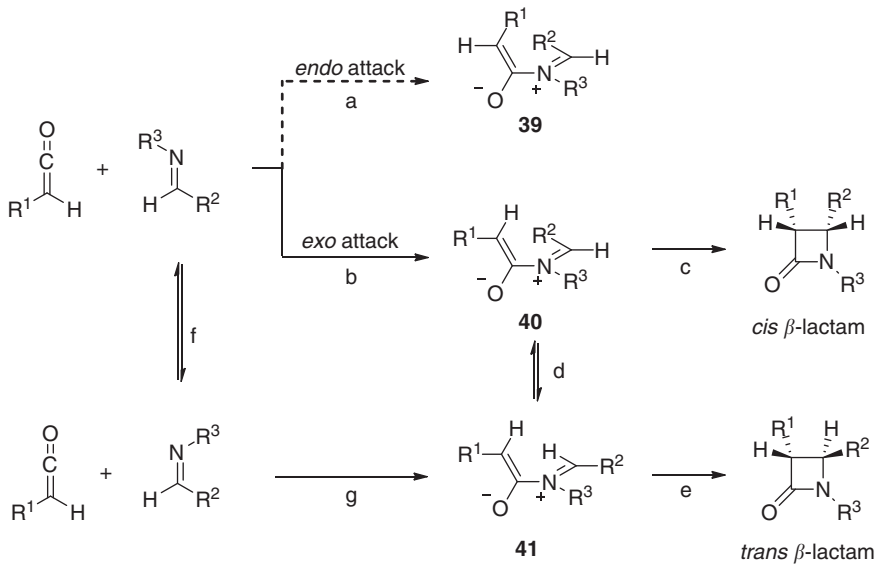
5.03.2.1.2 Cis–trans selectivity

As the four-membered heterocycles formed by [2 + 2] cycloaddition of unsymmetrically substituted ketenes, ketenimines, or thioketenes with imines possess two stereogenic centers, four different stereoisomers can be produced. In order to obtain

selectively one of these isomers, one needs to control both the relative (*cis*/*trans*) and the absolute stereochemistries of these two stereogenic centers.

The relative selectivity has been shown to depend on several factors such as the solvent used, the temperature, and the sequence of addition of the reactants.[91,107,109] Indeed, despite its formal simplicity, the stepwise mechanism of the reaction of ketenes and imines raises a complex stereochemical situation.

First, the initial nucleophilic attack of the nitrogen atom of the imine can occur either via the *endo* or the *exo* side of the ketene, leading to zwitterionic intermediate **39** or **40**, respectively (**Scheme 17**; pathway 'a' or 'b').[118,96,91] Experimental studies showed, however, the exclusive formation of zwitterion **40**, resulting from an *exo* approach. This can be accounted for by steric considerations.[118]



Scheme 17

Next, intermediate **40** can evolve in two ways: it can cyclize directly to form the corresponding β-lactam, or isomerize via rotation around the C=N bond (pathway 'd') before cyclizing to the β-lactam. Ring closure of the zwitterionic intermediate via a stereospecific conrotatory electrocyclization converts the *E*-isomer (**40**) into a *cis*-β-lactam (pathway 'c') whereas the *Z*-isomer (**41**) produces a *trans*-β-lactam (pathway 'e'). Accordingly, variations in the selectivity can be accounted for by the relative rate of cyclization/isomerization of the iminium in the zwitterions (k_c/k_d).[90,118]

In a series of systematic experimental studies, Xu et al. investigated the influence of several factors on the *cis*/*trans* selectivity in the reaction of ketenes with imines.[109,118,119] These results showed that the nature of the substituents of the ketenes and imines (R^1, R^2, and R^3) is the crucial factor that determines the *cis*/*trans* selectivity of this reaction through their influence on the rate of the direct ring closure (k_c). Indeed, electron-donating groups on the ketene (R^1 = EDG) and electron-withdrawing imine substituents (R^2, R^3 = electron-withdrawing group (EWG)) increase the nucleophilicity of the enolate moiety and the electrophilicity of the acyl-iminium group, respectively. This pattern of substitution thus accelerates the direct ring closure (increase k_c), and hence leads to a preference for *cis*-β-lactam formation (**Figure 1**). Conversely, electron-withdrawing ketene substituents and EDGs on the imine lower the rate of the ring closure (decrease k_c), thus allowing isomerization (k_d) to take place before cyclization. In these

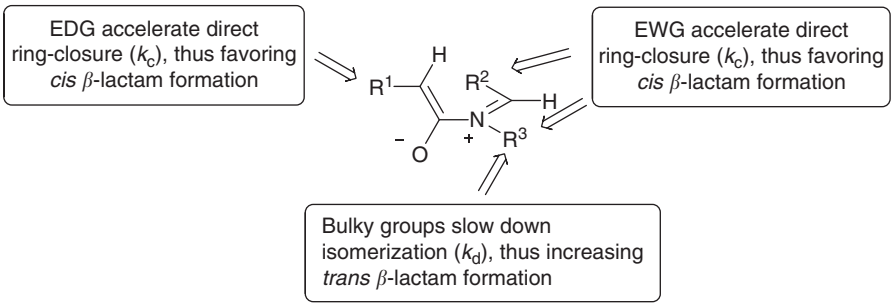


Figure 1 Influence of substitution on the *cis/trans* selectivity in the reaction of ketenes with imines.

cases, formation of the more stable *trans*-β-lactam is therefore observed (via pathway 'e'). The electronic effect of the substituents on the rate of isomarization has been shown to be a minor factor in the stereoselectivity. On the contrary, the presence of a bulky group on the imine nitrogen (R^3) has a significant decelerating effect on the rate of isomerization.

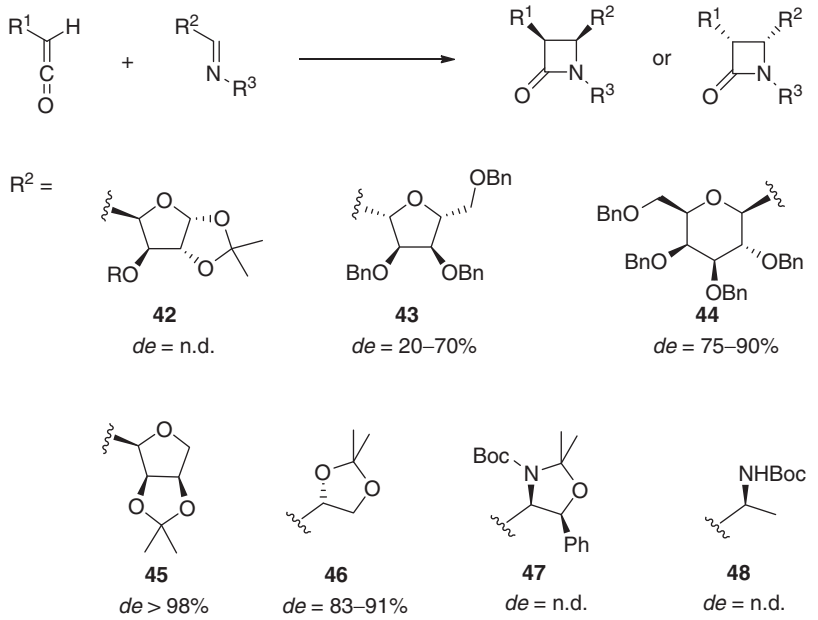
In some specific cases (when R^3 = anthracenyl), calculations have shown that the *E*/*Z* isomerization of the imine (pathway 'f') is faster than the addition ($k_f > k_b$, k_g). In these cases, the observed selective formation of *trans* isomer is thus accounted for by the addition of the more nucleophilic *Z*-imine onto the ketene yielding directly intermediate **41** (pathway *g*).[96,108]

Besides the main factor, which is the nature of the substituents, Xu et al. have shown that the reaction conditions (solvent, temperature, addition order of reagents, base, etc.) could also affect the stereochemical outcome of the Staudinger cycloaddition reaction.[90,109]

5.03.2.1.3 Reaction of chiral imines

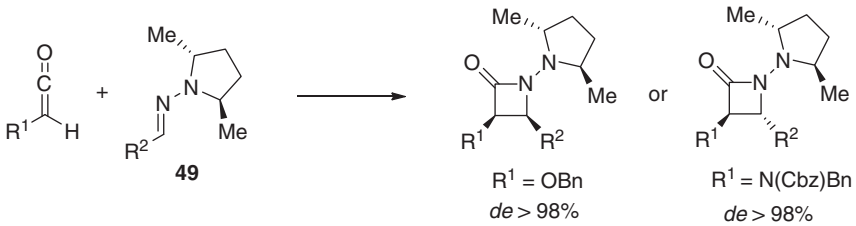
One of the strategies for controlling the absolute stereochemistry of the two chiral centers which are created in the reaction of unsymmetrically substituted ketenes and imines makes use of chiral imines. In this context, the reaction of chiral imines either derived from chiral aldehydes or from chiral amines has been reported.

In the former case, a common approach uses sugar aldehyde-derived imines such as **42**, **43**, and **44** (Scheme 18).[120,121] Other α-oxyimines, **45** and **46**, have also been used successfully.[107,122–124] Similarly, a wide variety of *N*-Boc-α-amino imines (such as **47** and **48**) have been reported to yield the corresponding *cis*-β-lactams with high diastereoselectivity.[94,125,126] The corresponding β-lactams are obtained in most cases as a single *cis* diastereoisomer after purification by column chromatography.



Scheme 18

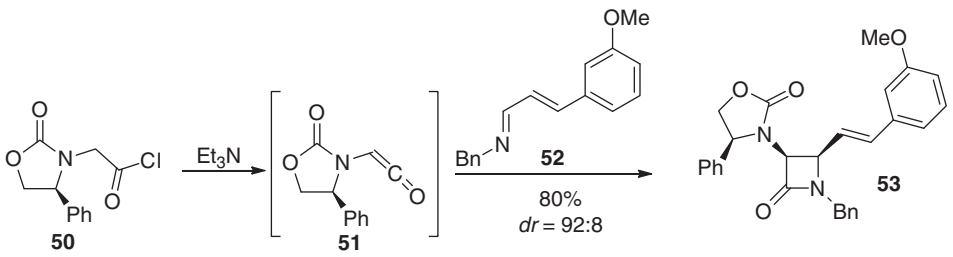
Imines bearing a chiral group on nitrogen have also been used for the asymmetric synthesis of chiral β-lactams (equation 6). Enantiopure *N*,*N*-dialkylhydrazones **49** react with ketenes to yield the corresponding 3,4-disubstituted β-lactams as single diastereoisomers.[127,128] The *cis*/*trans* selectivity depends on the substitution of the ketene: alkoxyketenes lead to *cis* β-lactams with a very high selectivity, whereas cycloaddition of ketenes derived from *N*,*N*-disubstituted glycine occurs *trans*-selectively. Subsequent N–N bond cleavage under oxidative conditions allows the chiral auxiliary to be removed with formation of the corresponding NH β-lactams in high yields.



(6)

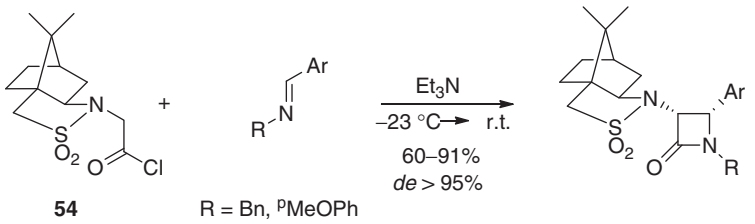
5.03.2.1.4 Reaction of chiral ketenes

Another strategy for the asymmetric synthesis of β-lactams is the [2 + 2] cycloaddition of imines with chiral ketenes.[92,94] The most widely used chiral ketene is 4-phenyloxazolidinylketene (**51**) (Evans–Sjögren ketene), generated from the corresponding oxazolidinylacetyl chloride (**50**) and triethylamine. As an example, the asymmetric synthesis of a carbacephem precursor from chiral ketene **51** and imine **52** has been described by Evans and coworker (Scheme 19).[129,130] After cycloaddition, the oxazolidinone auxiliary of β-lactam **53** can be reductively removed to give the unprotected 3-amino-β-lactam with a high *ee*.



Scheme 19

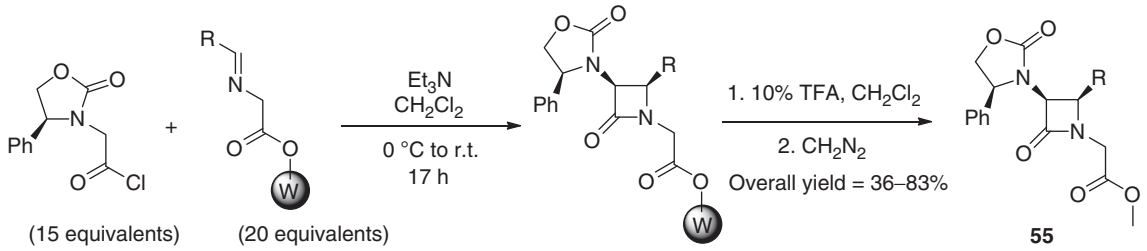
The ketene generated from acid chloride **54** has also been found to allow the formation of β-lactams with excellent diastereoselectivities (equation 7).[131] Nonetheless, all attempts to remove the camphorsultam moiety failed.



(7)

5.03.2.1.5 Applications

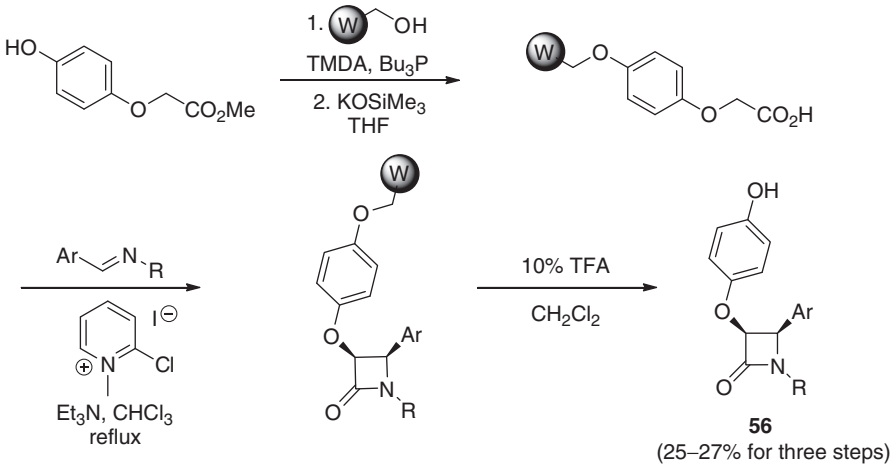
The large-scale production of β-lactams has required the development of solid-phase techniques and polymer-supported synthesis. This has been recently reviewed,[132] with a special topic dedicated to the Staudinger reaction. Most often Wang resins are used and the imine partner is bound to the resin via its *N*-substituent (Scheme 20).[133] Inversely, in few cases, the ketene precursor is linked to the resin (Scheme 21).[134,135] The *cis* (chiral) β-lactams **55** and **56** are precursors of carbapenems and cholesterol absorption inhibitors, respectively.



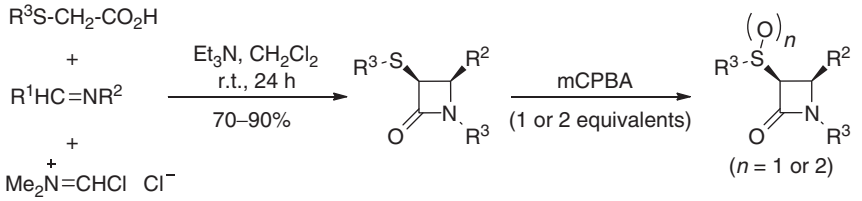
Scheme 20

Methods for the *in situ* activation of carboxylic acids worked efficiently, thus avoiding the isolation of acid chlorides as the ketene precursors. Beside the very popular Mukaiyama reagent (2-chloro-1-methylpyridinium iodide),[136] the Vilsmeier reagent (i.e., (chloromethylene)dimethylammonium chloride) was recently disclosed as a versatile activator of the [2 + 2] cycloaddition, directly from substituted acetic acids and imines.[137,138] 3-Thiolated-2-azetidinones endowed with antibacterial and antifungal activities have been prepared via this one-pot process for the cycloaddition step (Scheme 22).[139]

N-Unsubstituted β-lactams are often desirable as key-intermediates in the synthesis of more elaborated antibiotics. For that purpose, imines bearing *N*-protecting groups are used. The deprotection conditions of *p*-methoxyphenyl and benzhydryl groups are compatible with the β-lactam ring. The former can be cleaved by oxidation with cerium ammonium nitrate on solid phase[140] and the latter by photoactivated bromination followed by smooth aqueous acid treatment.[141] Applications of the above methods

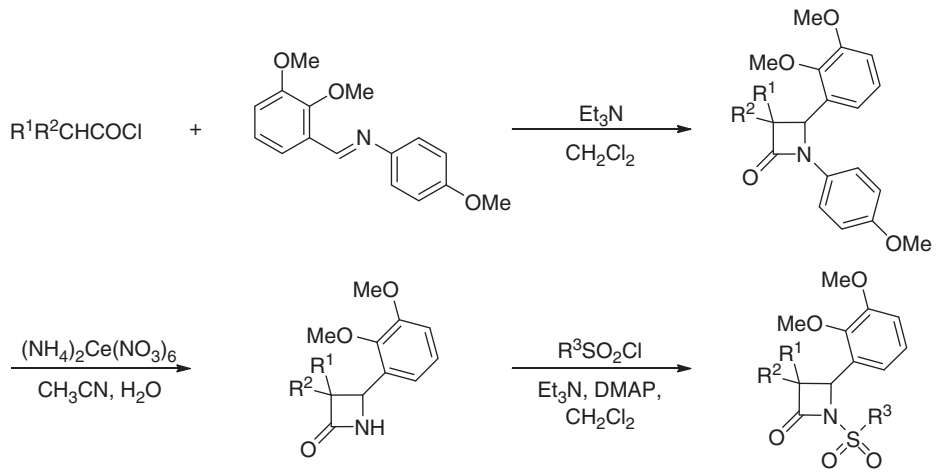


Scheme 21



Scheme 22

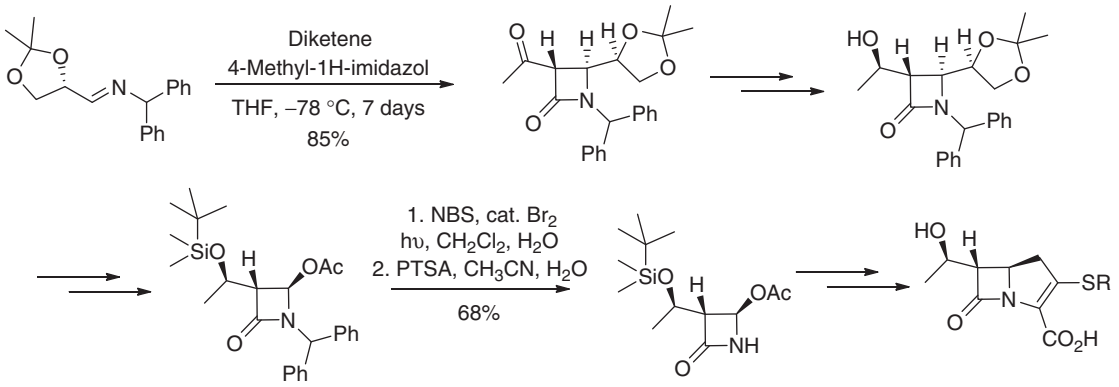
to the synthesis of monobactams (i.e., *N*-sulfonyl monocyclic *β*-lactams)[142] and carbapenems[143] are described in Schemes 23 and 24 respectively.



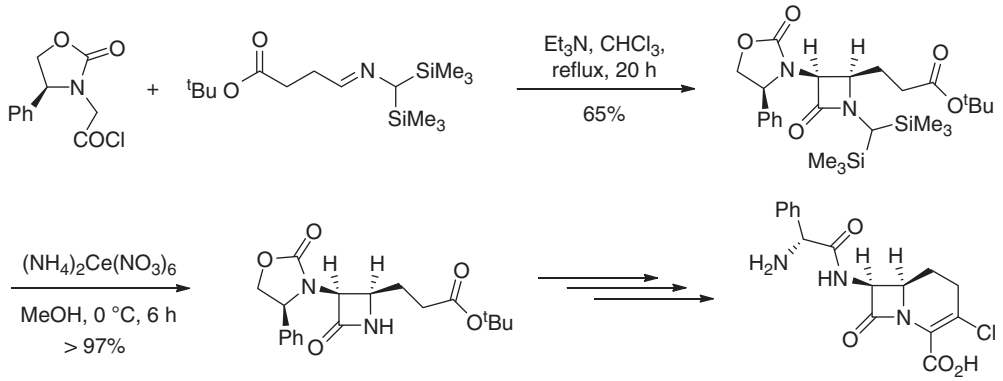
Scheme 23

Virtually all investigations about the Staudinger reaction have dealt with nonenolizable aldimines. Because of the instability of the corresponding imines, 4-alkyl-2-azetidinones were not readily accessible via the [2 + 2] cycloaddition strategy before the work of Palomo et al.[144] who designed α-(trimethylsilyl)methyl imines as stable reagents, due to the ability of the silyl groups to stabilize electron-poor centers in the *β*- or *γ*-position. Deprotection of the *N-bis*(trimethylsilyl)methyl group from the cycloaddition products could be easily performed with cerium ammonium nitrate in methanol. The Loracarbef precursor **57** was prepared according to this strategy as a single enantiomer (Scheme 25).

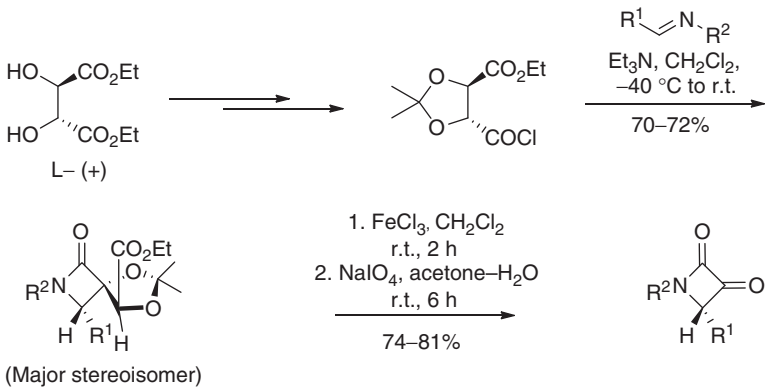
Azetidine 2,3-diones constitute a useful class of synthons. Enantiopure derivatives were obtained by the Staudinger cycloaddition of the ketene derived from L-(+)-diethyl tartrate, giving spiro-*β*-lactams intermediates (Scheme 26).[145]



Scheme 24



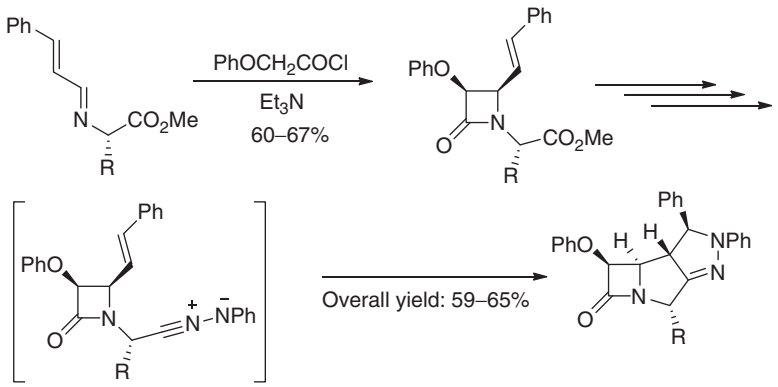
Scheme 25



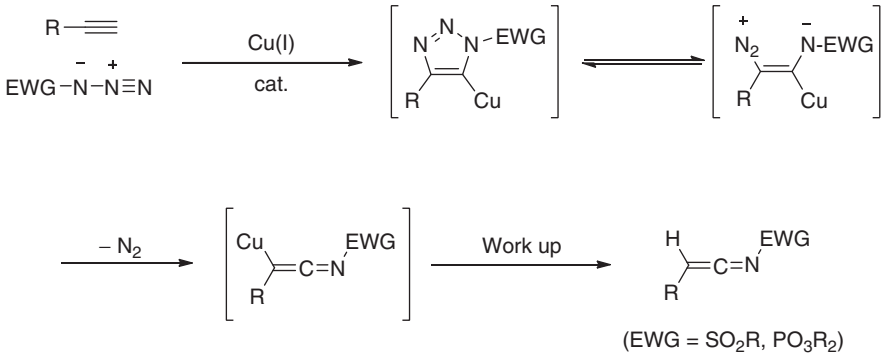
Scheme 26

Numerous polycyclic *β*-lactams of potential interest in medicinal chemistry resulted from reaction sequences including the Staudinger cycloaddition as the first step. Indeed, the *β*-lactam ring could play the role of a scaffold favoring the intramolecular reactions of functionalized chains on its backbone (Scheme 27).[146,147]

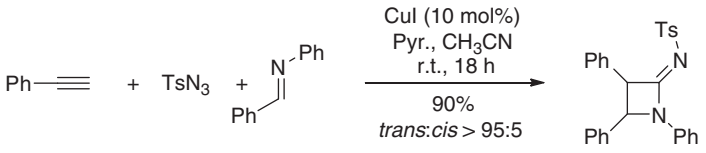
Applications of ketenimine [2 + 2] cycloadditions are less abundant than the ketene analogues. A novel method for *in situ* generation of *N*-sulfonyl- (or *N*-phosphoryl-) ketenimines appears worthy of note because it allowed the development of inter- and intramolecular cycloadditions with imines.[88] The well-known Cu(I)-catalyzed 'click' reaction of aryl- or alkyl-azides with 1-alkynes, affording 1,4-disubstituted triazole adducts, gave a different outcome when using sulfonyl- (or phosphoryl-) azides: a ring-opening rearrangement of the initially formed *N*-sulfonyl- (or phosphoryl-) copper triazole species occurs rapidly (Scheme 28). Thus, *N*-sulfonyl ketenimines could be easily produced and quenched with a range of imines (equation 8),[148,149] enlarging the scope of the initial reaction.[150]



Scheme 27

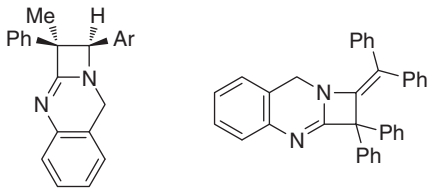


Scheme 28



(8)

Intramolecular ketenimine–imine [2 + 2] cycloadditions led to polycyclic systems such as **58**[151] and **59**.[152]



58

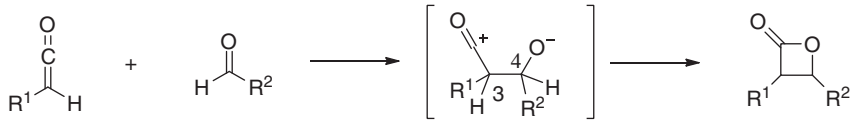
59

5.03.2.2 Reaction with Carbonyl Compounds

The carbonyl π-bond has been found to add also across the alkenic π-bond of ketenes to produce oxetan-2-ones (β-lactones).[83] Unlike in the Staudinger ketene–imine cycloaddition, only highly activated systems (bearing strongly electron-withdrawing substituents) react readily with ketenes in the absence of catalyst (adducts decompose at the high temperatures necessary for their cycloaddition to occur). This lower reactivity can however be compensated by using either a LA or a nucleophile (or both) as catalysts (see Sections 5.03.2.2.3 and 5.03.4.2.2).

5.03.2.2.1 Mechanism

Lecea and Cossio have extensively explored the mechanism of uncatalyzed and LA-catalyzed cycloadditions of ketene onto carbonyl compounds by computational means (*ab initio* and DFT).[153–155] These studies indicate that this cycloaddition occurs in fact via a two-step mechanism (Scheme 29). First, the ketene adds onto the carbonyl double bond, forming the C_3–C_4 bond and leading to a zwitterionic intermediate. Next, this intermediate undergoes cyclization to afford the β-lactones. This mechanism has been supported by kinetic isotope effect measurements.[156]



Scheme 29

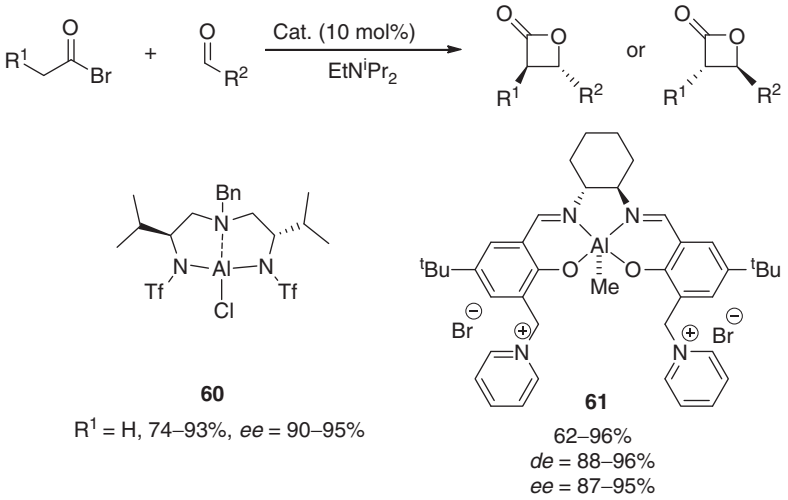
Alternatively, in the presence of a nucleophilic catalyst (an amine or a phosphine), the reaction occurs through formation of an enolate (by addition of the nucleophile onto the ketene) followed by addition of this later onto the carbonyl compound.[111] These reactions will be discussed in Section 5.03.4.

5.03.2.2.2 Cis–trans selectivity

In aldehyde cycloadditions with unsymmetrically substituted ketenes, mixtures of *cis* and *trans* isomers are generally obtained. In most cases, the ratio varies from 1:1 to 2:1.[83] Some LA-catalyzed cycloadditions are however described to afford β-lactones with good diastereoselectivities (see Section 5.03.2.2.3).

5.03.2.2.3 Enantioselectivity with chiral Lewis acids

Nelson and Peters developed the chiral C_2-symmetric aluminum complexes **60** and **61**, respectively, for the cycloaddition of monosubstituted ketenes with aldehydes (Scheme 30).[157,158] The corresponding *trans*-2-azetidinones are obtained with good *ee*'s. The proposed mechanism is based on a contact ion pair-directed Lewis acid catalysis.[156]



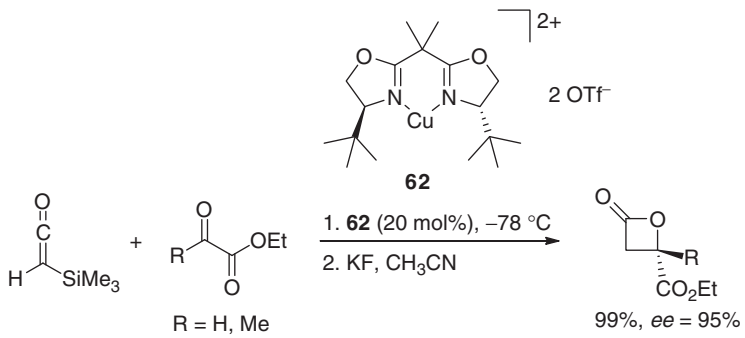
Scheme 30

The asymmetric [2 + 2] cycloaddition of the more stable trimethylsilyl ketene has also been developed using different chiral LA catalysts (Scheme 31).[159–162] The best enantioselectivities have been obtained with the C_2-symmetric copper(II)–bisoxazoline complex **62** of Evans and coworker and glyoxylate derivatives.[163]

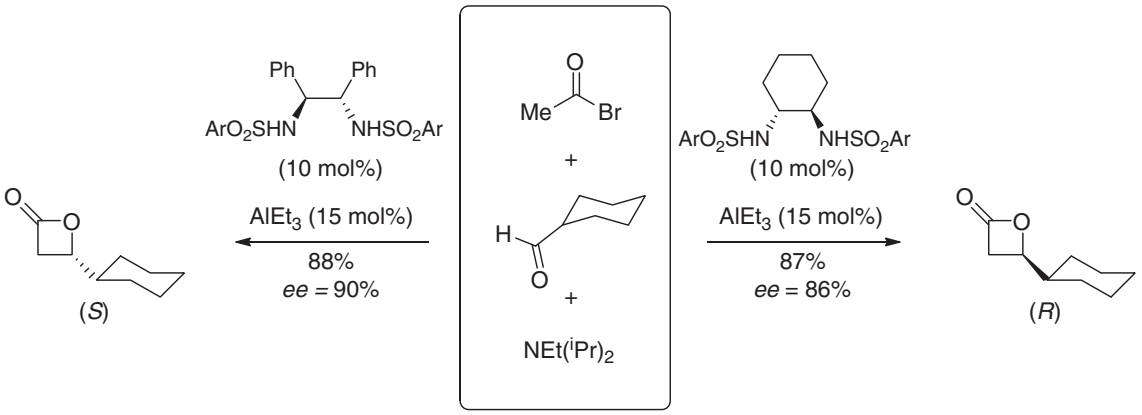
5.03.2.2.4 Applications

Ketene, generated *in situ* from acetyl bromide and Hünig's base, reacts with various α-unbranched and α-branched aliphatic aldehydes to give chiral β-lactones under catalysis by aluminum bis-sulfonamide complexes[164] formed *in situ* from (*R*, *R*)- or (*S*, *S*)-1,2-diamine derivatives and triethylaminium in toluene at $-85\ ^\circ C$ (Scheme 32).

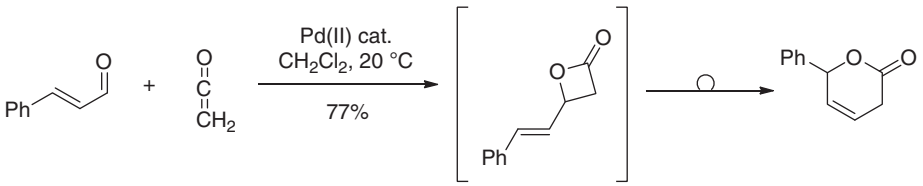
3,6-Dihydro-2*H*-pyran-2-ones are obtained via tandem [2 + 2] cycloaddition-allylic rearrangement of ketene with α,β-unsaturated aldehydes and ketones; both reactions are catalyzed by the cationic palladium (II) complex $[Pd(dppb)(PhCN)_2]BF_4$ (dppb = 1,4-*bis*-(diphenylphosphino)butane) (Scheme 33).[165]



Scheme 31

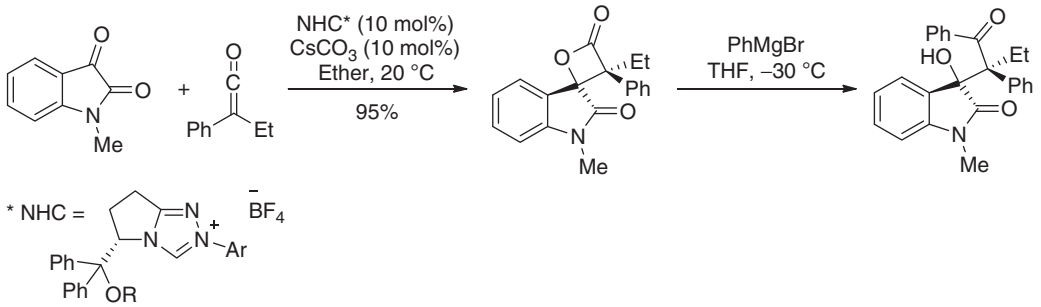


Scheme 32



Scheme 33

Chiral spirocyclic oxindole-β-lactones result from the cycloaddition of ketenes and isatins, catalyzed by *N*-heterocyclic carbenes (NHC).[166] Subsequent ring opening with Grignard reagents leads to 3-hydroxy-oxindoles with high enantionselectivity (Scheme 34).

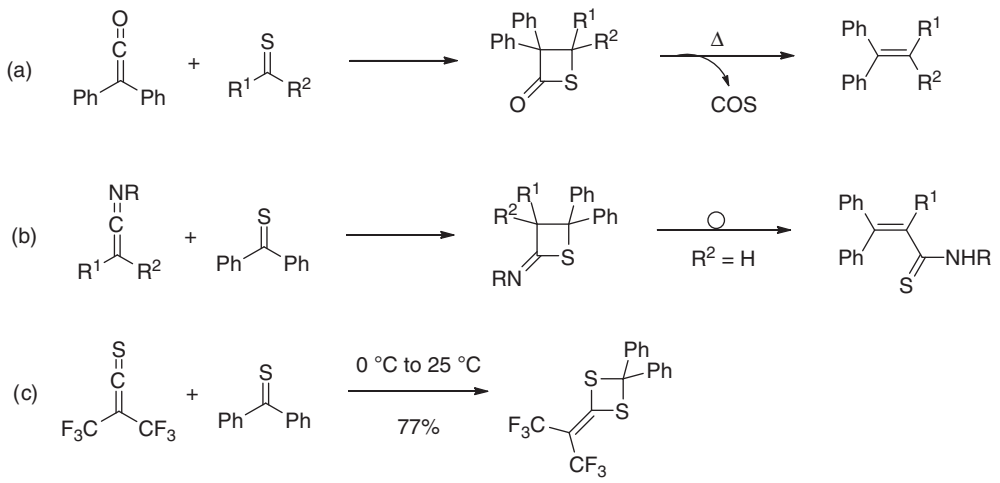


Scheme 34

5.03.2.3 Reaction with Thiocarbonyl Derivatives

Cycloadditions of heteroallenes onto C═S bond are scarcely described, most probably because the corresponding cycloadducts have no real synthetic usefulness and are prone to decompose or rearrange.

Diphenylketene reacts with thiones, thioesters, and thioamides to furnish thietane-2-ones (β-thiolactones), which lead to alkenes on heating (Scheme 35 (a)).[167–169]



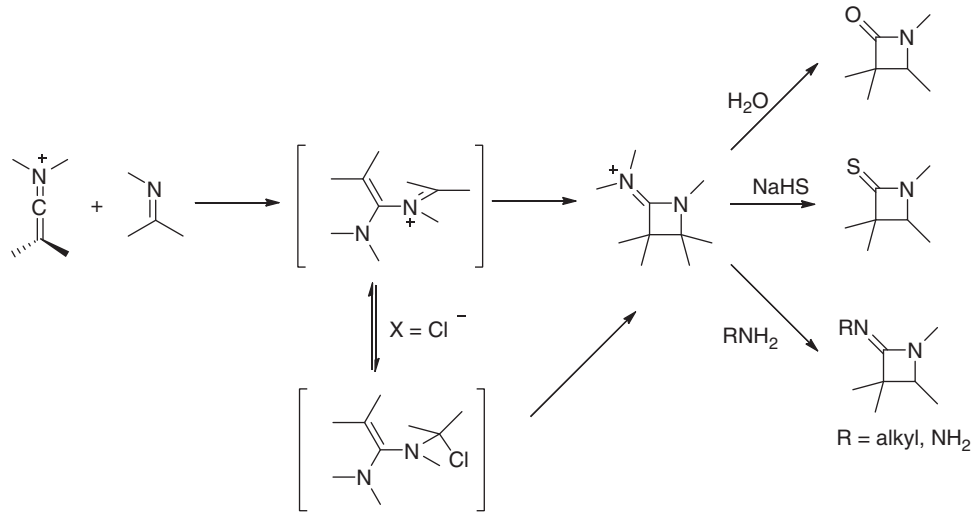
Scheme 35

The reaction of ketenimines with thiobenzophenone leads to thietane-2-imines; enolizable cycloadducts suffer a ring-opening rearrangement into α,β-unsaturated thioamides (Scheme 35(b)).[170,171]

Addition across the C═S bond of bis(trifluoromethyl)thioketene has been observed (Scheme 35(c)) as a curiosity.[172]

5.03.3 Reaction of Keteniminium Salts with C═X Bonds

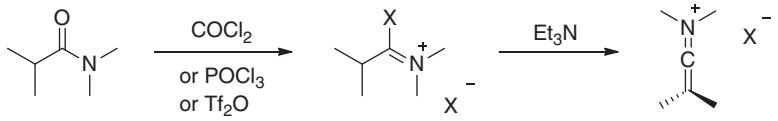
The [2 + 2] cycloaddition reaction of keteniminium salts with imines has been discovered by Ghosez in 1974.[113] It leads to the formation of 2-azetidinium salts which can be easily converted to azetidin-2-ones, -thiones, or -imines (Scheme 36).[114,173,174] No example of cycloaddition of keteniminium salts with (thio)carbonyl compounds can be found in the literature.



Scheme 36

One advantage of keteniminiums salts is that they are highly reactive and can undergo cycloaddition reactions with imines which are unreactive with ketenes.

Due to their high reactivity, keteniminium salts are usually generated *in situ* by treatment of tertiary carboxamides with phosgene or triflic anhydride and a base (Scheme 37).[114]

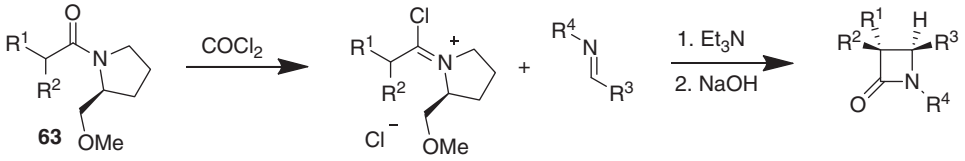


Scheme 37

Similar to the Staudinger reaction, the reaction between keteniminium salts and imines involves a two-step mechanism.[115] First, the imine adds onto the keteniminium to form the N_1–C_2 bond (Scheme 36). Next, this adduct undergoes an electrocyclic ring closure to form the C_3–C_4 bond leading to the 2-azetidinium salts.

The *cis*/*trans* stereoselectivity of the reaction is determined at the second step, when the C_3–C_4 bond is formed. It was found that the stereochemical outcome depends on the nature of the anion, which in turn is related to the method used for generating the keteniminium intermediate. Indeed, the reaction is generally *cis*-selective, but if the anion is nucleophilic, such as chloride, the ring closure preferentially takes place via intramolecular S_N2 reaction (similarly to the mechanism described in Scheme 16 for the Staudinger reaction) and *trans* selectivity is observed.[115]

An important advantage of the reaction of keteniminium salts, as compared with that of ketenes, is that they provide yet another position for the incorporation of chirality. Indeed, starting from the chiral amide **63**, the corresponding chiral *β*-lactams can be obtained after hydrolysis with excellent *ee*'s (Scheme 38).[175] The nature of the keteniminium substituents R^1 and R^2 plays a



R^1	R^2	R^3	R^4	Yield (%)	*cis/trans*	*ee* (%)
Me	Me	Ph	C_3H_5	42	–	98
Me	Me	SPh	CH_2Ph	65	–	99
Ph	Me	Ph	Me	29	0/100	97
Me	H	Ph	Me	30	20/80	40
H	H	Ph	Me	47	–	4

Scheme 38

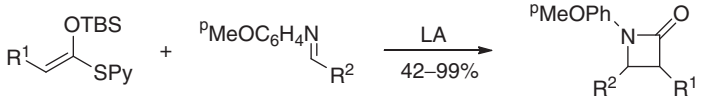
decisive role in determining the stereoselectivity. When R^1 and R^2 are different from hydrogen, the stereoselectivity is very high, but it drops dramatically when R^1 and/or R^2 are hydrogen atoms.[175]

5.03.4 Reaction of Enols and Enolates with C═X Bonds

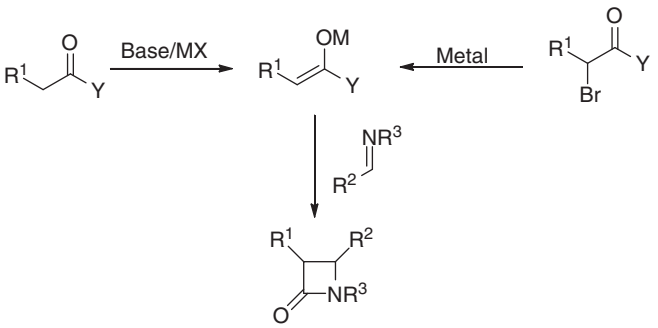
5.03.4.1 Scope and Mechanism

Metal enolates derived from carboxylic acid derivatives have been reported to condense with imines to yield directly *β*-lactams (Scheme 39).[92] In this context, *S*-thioester enolates (Y═SR) serve particularly well.[176] Indeed, thiolates are more readily displaced from the carbonyl carbon than alkoxides. They are also more easily formed because of the enhanced acidity of the CH-α position as compared with that of simple esters. Several metals (MX) have been investigated for these transformations. Best results were obtained with titanium, aluminum, zinc, boron, and tin.[176] Experiments demonstrated however that tin, aluminum, and boron enolates had a more limited application to *β*-lactam synthesis than titanium enolates, and thus their chemistry was less developed.

Although less studied, the reaction of silylketene thioacetals with imines in the presence of a LA has also been reported to yield *β*-lactams (equation 9).[176,177]

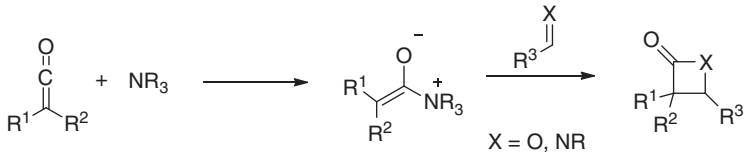


(9)



Scheme 39

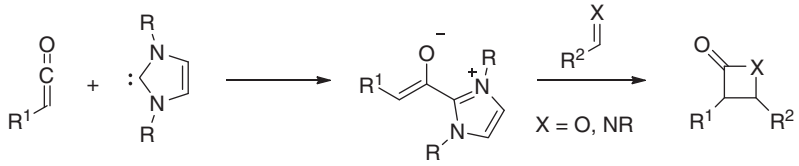
Inspired by early studies on the amine-catalyzed dimerization of ketenes,[178] many groups have worked on the generation of zwitterionic ammonium enolates from ketenes and amines and their reaction with aldehydes and imines to give *β*-lactones and *β*-lactams, respectively (Scheme 40).[81] In the case of imines, the overall process consists of the amine-catalyzed Staudinger reaction.



Scheme 40

Cinchona alkaloids have rapidly emerged as prominent catalysts for these transformations.[111] One drawback associated with this strategy, however, was the need for highly reactive aldehydes or imines, presumably to compete with ketene dimerization. It was shown that the low reactivity of ammonium enolates could be overcome and the scope of the reaction improved by using LA cocatalysts ($In(OTf)_3$, $LiClO_4$).[179–181] Later, Wilson and Fu showed that ammonium enolates derived from planar chiral DMAP derivatives (see Section 5.03.4.2) display increased reactivity as compared with cinchona derivatives.[182] These intermediates react with a large range of aldehydes and imines, allowing for the preparation of highly substituted *β*-lactones and *β*-lactams, respectively.

It was reported that NHCs are also efficient catalysts for the cycloaddition of ketenes with aldehydes and imines (Scheme 41).[183,184]



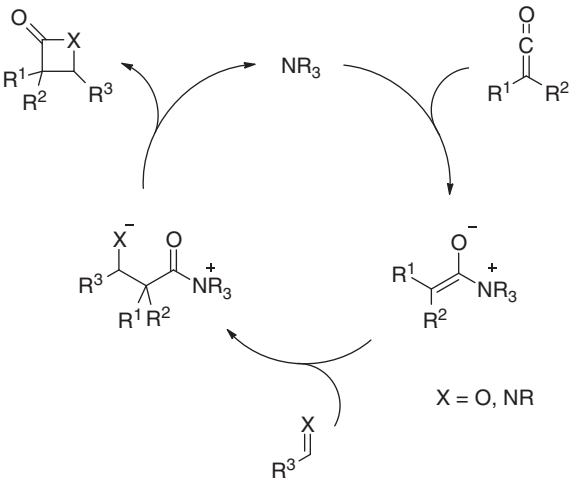
Scheme 41

The mechanism of the [2 + 2] cycloaddition of ketene with aldehydes or imines catalyzed by amines involves three steps: addition of the amine to the ketene to form an ammonium enolate, its addition onto the aldehyde or imine electrophile, followed by cyclization of the newly formed alkoxide or amide onto the acylammonium species (Scheme 42).[81] NHC-catalyzed cycloadditions and metal enolates of (thio)ester reactions have been shown to follow a similar mechanism.[176,184,185]

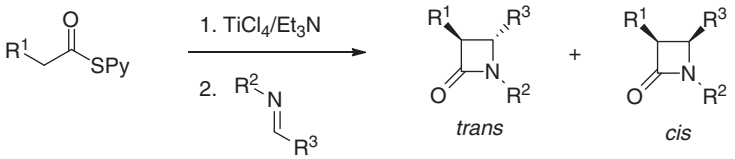
5.03.4.2 Stereoselectivity

5.03.4.2.1 Reaction of metal enolates

Systematic studies on titanium enolates have shown that the *cis*/*trans* selectivity depends highly on the substitution of the two partners (Scheme 43).[176] A few rules can however be drawn from the collected data: (1) large and nonchelating groups at the C_2-position of the *S*-thioester (R^1) and at the imine carbon (R^3) result in the formation of a *trans*-azetidinone; (2) the presence of a chelating substituent at either one of these positions results in a *cis*-selective reaction; and (3) enolizable imines are more prone to produce a *cis*-*β*-lactam than conjugated imines.



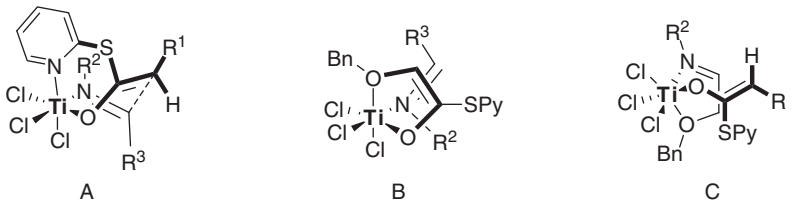
Scheme 42



R^1	R^2	R^3	Yield (%)	*trans*/*cis*
Me	$^{p}MeOC_6H_4$	Ph	99	70/30
Et	$^{p}MeOC_6H_4$	Ph	90	80/20
^{i}Pr	$^{p}MeOC_6H_4$	Ph	91	85/15
Et	Bn	Ph	95	85/15
OBn	Bn	Ph	64	9/91
Me	$^{p}MeOC_6H_4$	PhCH=CH	99	60/40
Me	$^{p}MeOC_6H_4$	Pr	48	37/63
Me	$^{p}MeOC_6H_4$	CH_2OBn	40	23/77

Scheme 43

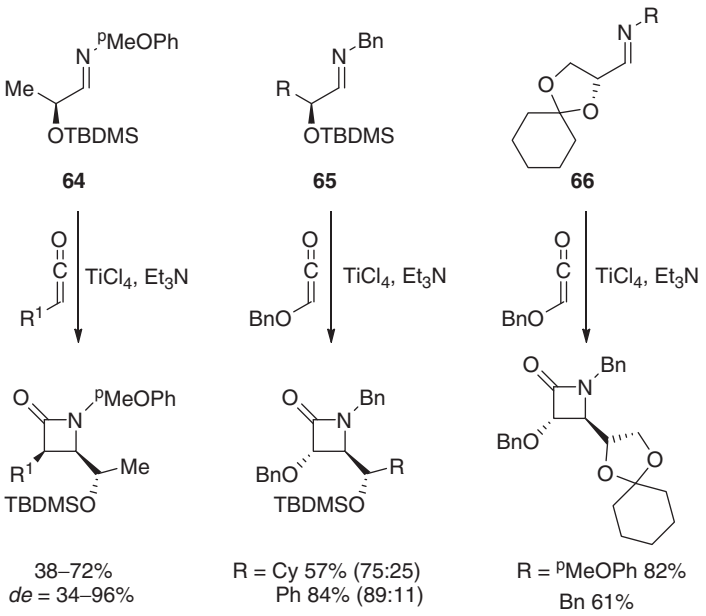
The proposed model to account for the observed *trans* selectivity involves a chair-like six-membered transition state (A) for the addition step in which the steric clash between the bulky R^1 and R^2 groups is minimized (Scheme 44).[176] In the case of small R^1 and R^2 groups, *cis*-*β*-lactams may be formed via similar transition structures involving either an (*E*)-enolate or a (*Z*)-imine. The *E*/*Z* imine equilibrium is also believed to be the origin of the tendency of alkyl-substituted imines to give more *cis*-azetidinones. Indeed, ^{1}H NMR experiments showed that conjugated imines exist predominantly in and are likely to react from their (*E*)-configuration, whereas aliphatic imines consist of almost equal mixtures of (*E*) and (*Z*) isomers.



Scheme 44

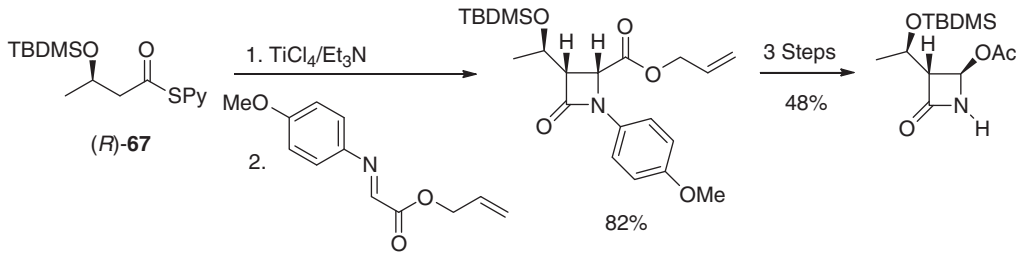
The formation of *cis*-*β*-lactams in the presence of a chelating substituent at either R^1 or R^2 position can be explained by the boat-like transition state models B and C, respectively (Scheme 44).

The absolute stereochemistry of the two chiral centers generated during the [2 + 2] cycloaddition is determined as at the addition step and can be controlled by using either chiral imines or chiral enolates. The first of these strategies has been explored by several groups with α-alkoxy and α,β-dialkoxyimines such as **64**, **65**, and **66** (Scheme 45).[186,187] When these imines were treated with the titanium enolates of 2-pyridyl thioesters, very high levels of stereocontrol were observed in the formation of β-lactams. Several imines bearing a chiral substituent on the nitrogen atom have also been studied but the obtained results were less satisfactory.[176]



Scheme 45

Cozzi investigated the reaction of the chiral 2-pyridyl thioester (*R*)-**67**.[188] Cycloaddition of the derived enolate with imines led to the corresponding β-lactams bearing the (*R*)-1-hydroxyethyl side chain at C_3 present in the penem antibiotics with high diastereoselectivities (Scheme 46).

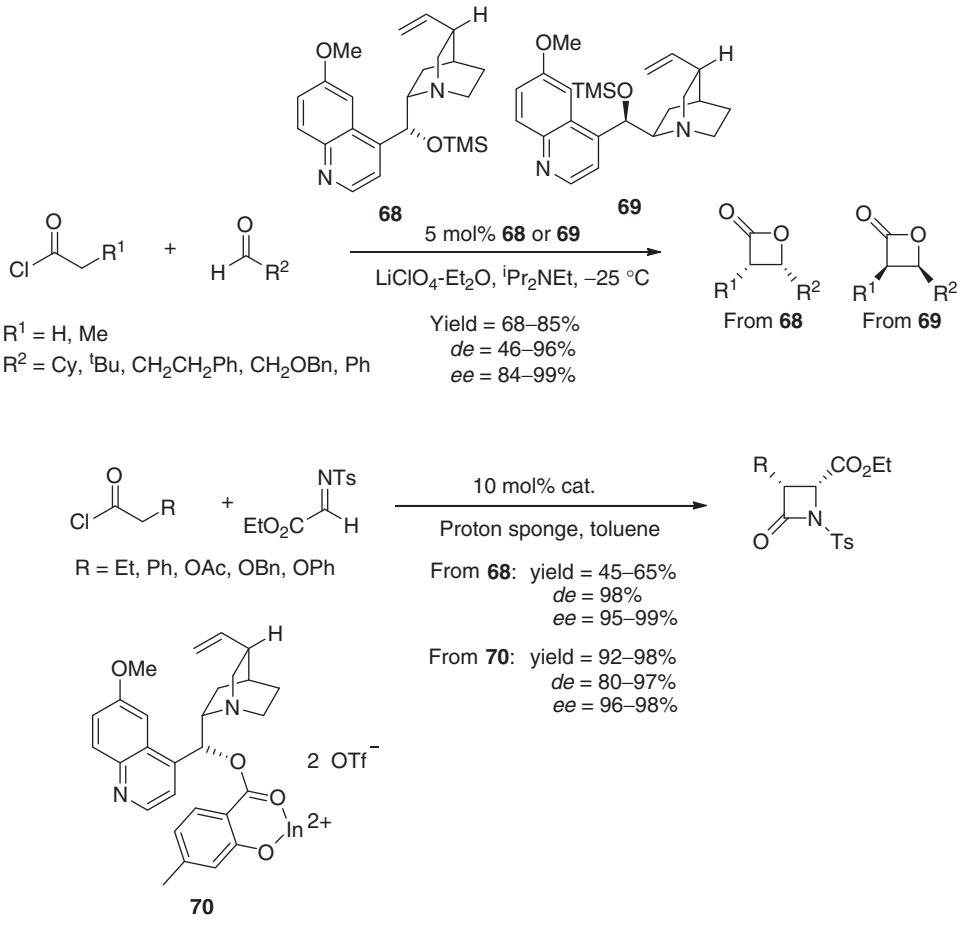


Scheme 46

The possibility of using chiral metal complexes has also been investigated (with boron as metal), but the *ee*'s never exceeded 78%.[189]

5.03.4.2.2 Reaction of ketenes

Both chiral carbene and amine catalysts have been applied to the enantioselective synthesis of β-lactones and β-lactams from ketenes. The first chiral amines to be used in this context were cinchona alkaloids (equation 10).[111] *cis*-β-Lactones and *cis*-β-lactams are obtained in moderate to good yields with excellent diastereo- and enantioselectivity (Scheme 47). Interestingly, by employing the diastereomeric alkaloids quinine (**68**) and quinidine (**69**) as catalysts one can access either enantiomer of a given product.

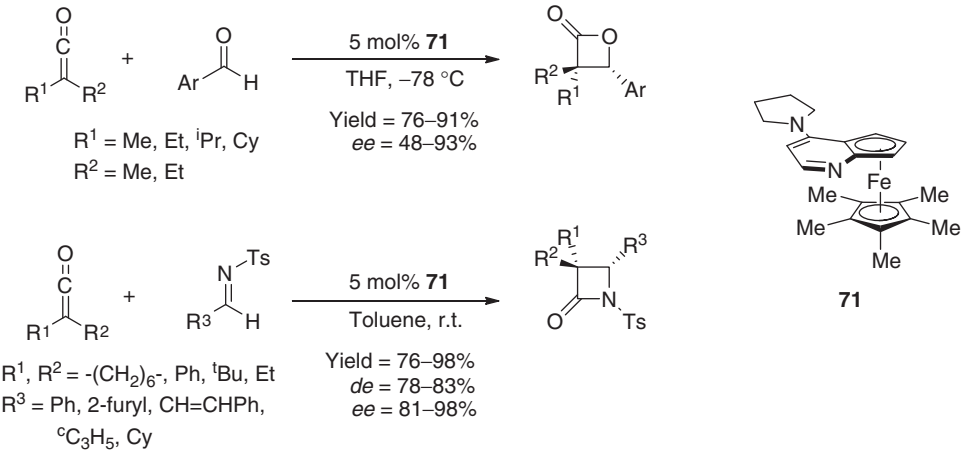


(10)

Scheme 47

Bifunctional catalysts in which the nucleophilic chiral amine is paired with a LA have also been developed (**70**; Scheme 47).[190–194]

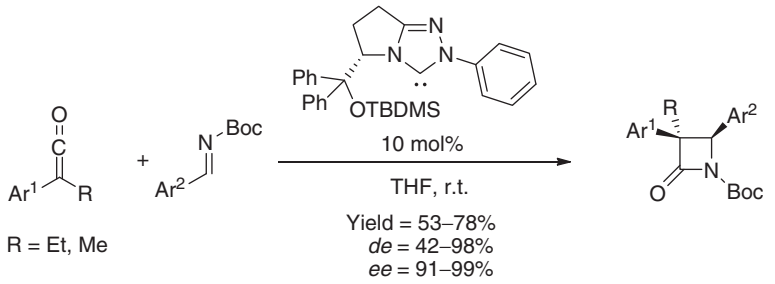
The limited scope of the reaction catalyzed by cinchona alkaloids prompted Fu and Wilson to investigate the application of planar chiral DMAP to these reactions. In the presence of 5 mol% of the chiral catalyst **71**, ketenes react with aldehydes and imines to yield [2 + 2] cycloadducts with excellent yields and stereoselectivities (Scheme 48).[182]



Scheme 48

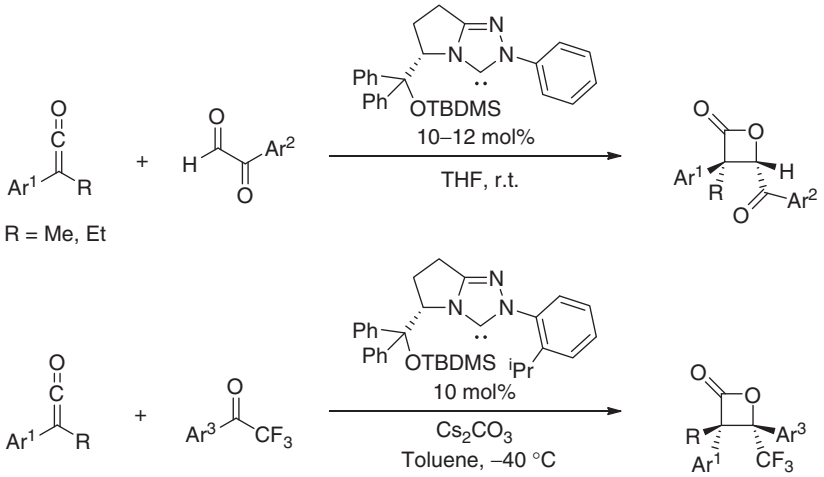
An interesting reversal in diastereoselectivity was observed by employing *N*-Tf-imines instead of *N*-Ts-imines.[132] The switch in selectivity is attributed to a change in mechanism.

More recently, Smith and Ye showed that enantioselective β-lactam formation can also be accomplished by chiral NHC catalysis (Scheme 49).[195,196] The catalytic cycle is similar to the one described for tertiary amine catalysts.[184,185]



Scheme 49

Later, this enantioselective strategy has been applied to the reaction of ketene with carbonyl compounds to form β-lactones bearing two contiguous stereocenters. Indeed, reaction of alkyl(aryl)ketenes with 2-oxoaldehydes or trifluoromethyl ketones leads to the corresponding β-lactones in high yields with good diastereoselectivities and excellent enantioselectivities (Scheme 50).[166,183,197] One drawback of this methodology, however, is the fact that it is limited to activated carbonyl compounds.

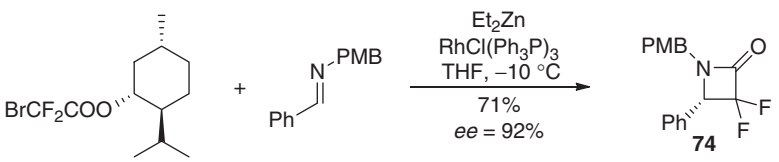


Scheme 50

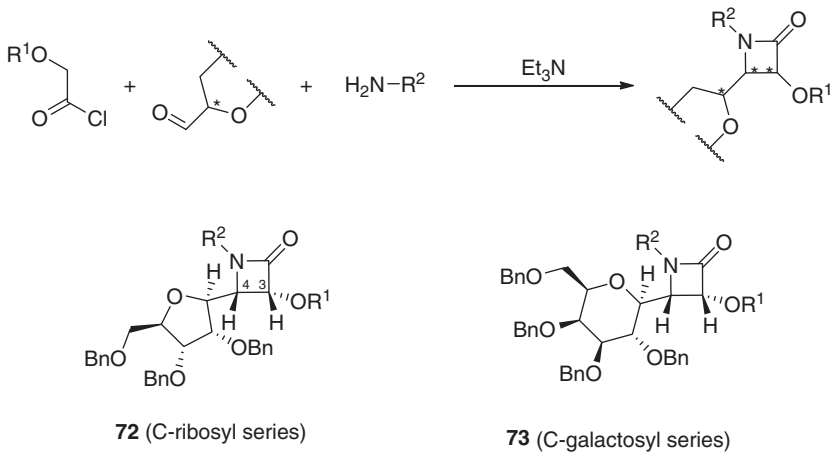
5.03.4.3 Selected Applications

With the aim of simultaneously locking the transglycosidase and transpeptidase domains in PBP2a of resistant bacteria, Dondoni and Massi have synthesized sugar-decorated β-lactams. The C_4-glycoconjugate β-lactams **72** and **73** are obtained by a 3CR-based methodology, i.e., the two-step/one-pot amine-catalyzed Staudinger reaction, combined with the polymer-assisted solution-phase technique (Scheme 51).[121,198]

The Reformatzky-type reaction of imines and α-bromoesters with zinc dust[199,200] is the method of choice for the preparation of 3,3-difluoro-β-lactams,[201] and derivatives thereof such as α,α-difluoro-β-aminoacids. An asymmetric version using (–)-menthyl bromodifluoroacetate has been developed for the preparation of the chiral β-lactam **74** which was further reacted with taxane alcohol to give the 2,2′-difluoro analog of the anticancer drug docetaxel (equation 11).[202]



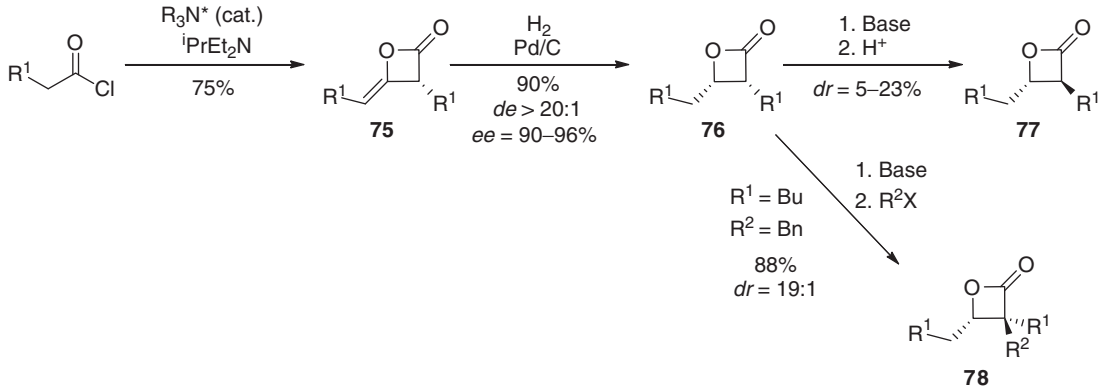
(11)



Scheme 51

3,3-Dichloro β-lactones were obtained from trichloroacetyl chloride, α-oxyaldehydes or α-aminoaldehydes and zinc, and used as precursors of 1,2-diols or 1,2-amino alcohols subunits with predictable stereochemistry.[203]

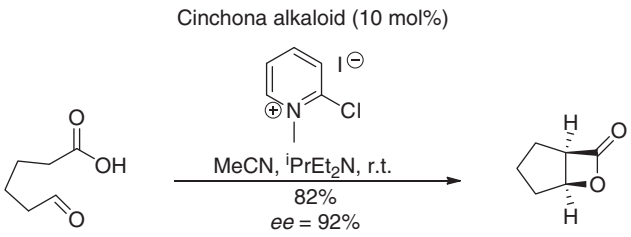
The catalytic asymmetric synthesis of β-lactones via a sequential ketene dimerization/hydrogenation process opens efficient access to inhibitors of the thio-esterase domain of fatty acid synthase (Scheme 52).[204] The facial-selective hydrogenation of the dimer **75** leads to the *cis*-substituted β-lactone **76**. The subsequent epimerization at C_3 under basic treatment gives the *trans* isomer **77** as the major compound. Alkylation of the enolate derived from **76** furnishes the β-lactone **78** with a C_4 quaternary center of controlled configuration.



Scheme 52

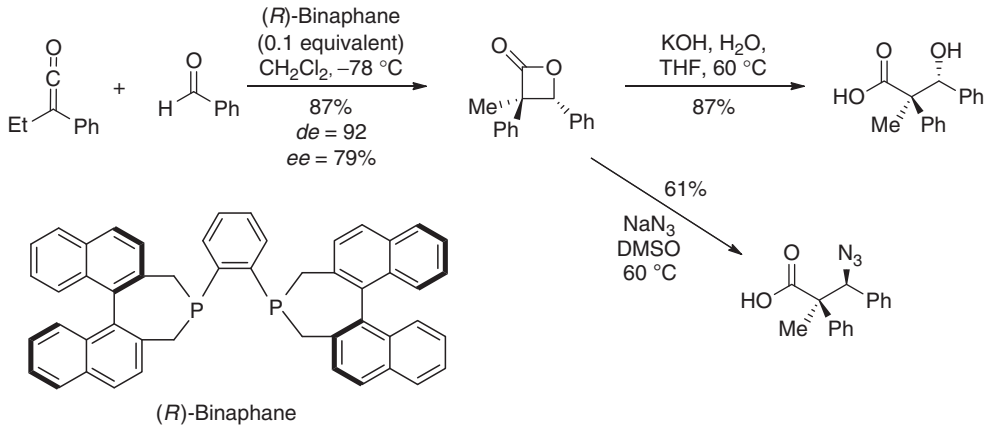
Chiral β-lactones with a C_4 quaternary center can be directly obtained from disubstituted ketenes that cycloadd to aldehydes in the presence of a chiral phosphine catalyst. Further basic hydrolysis and nucleophilic opening of the cycloadducts afford β-hydroxy- and β-amino acid precursors featuring a controlled quaternary asymmetric carbon atom at the α-position (Scheme 53).[205] This reaction sequence illustrates well the use of chiral β-lactones as versatile building blocks.[161]

An intramolecular version of the Wynberg synthesis of β-lactones is proposed by Romo and coworkers (equation 12).[204,206]

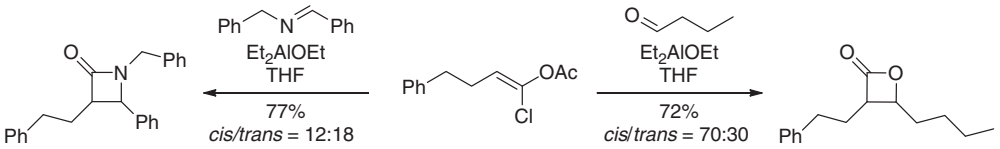


(12)

Mioskowski has disclosed new ketene equivalents, namely α-haloenol acetates, for the practical synthesis of β-lactones and β-lactams. The [2 + 2] cycloaddition occurs readily in the presence of diethylaluminum ethoxide (Scheme 54).[207]



Scheme 53

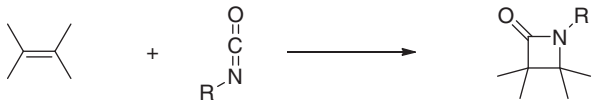


Scheme 54

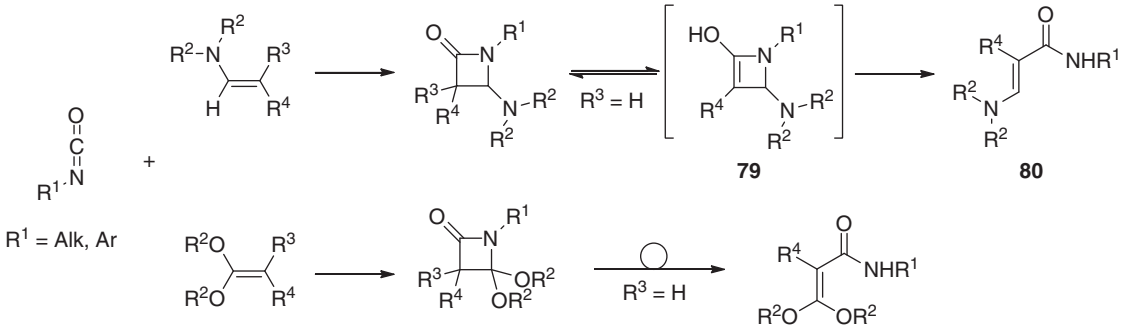
5.03.5 Reaction of Isocyanates with Alkenes

5.03.5.1 Scope

The cycloaddition of alkenes across the C═N bond of an isocyanate is a useful method for synthesizing β-lactams (equation 13).[208] The reaction requires either activation of the alkene by electron-releasing substituents or activation of the isocyanate by EWGs. Nonactivated (alkyl or aryl) isocyanates react with enamines and ketene acetals (Scheme 55). The initial product is a β-lactam. However, when R^3═H, enolization occurs and a fast electrocyclic rearrangement of the enol form (**79**) gives the open-chain isomer (**80**). In both cases, the rearrangement is driven by the release of strain and the presence of an EDG at C_4.



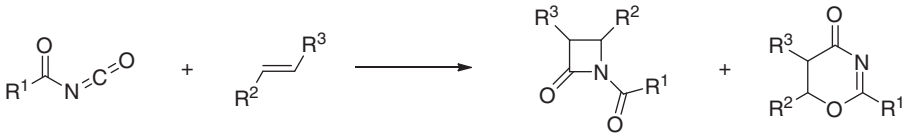
(13)



Scheme 55

Acyl isocyanates are more activated and can react with nonactivated alkenes (equation 14).[209–211] However, the presence of an additional π-bond conjugated to the C═N unit of the isocyanate opens the possibility for [4 + 2] cycloadditions to compete with

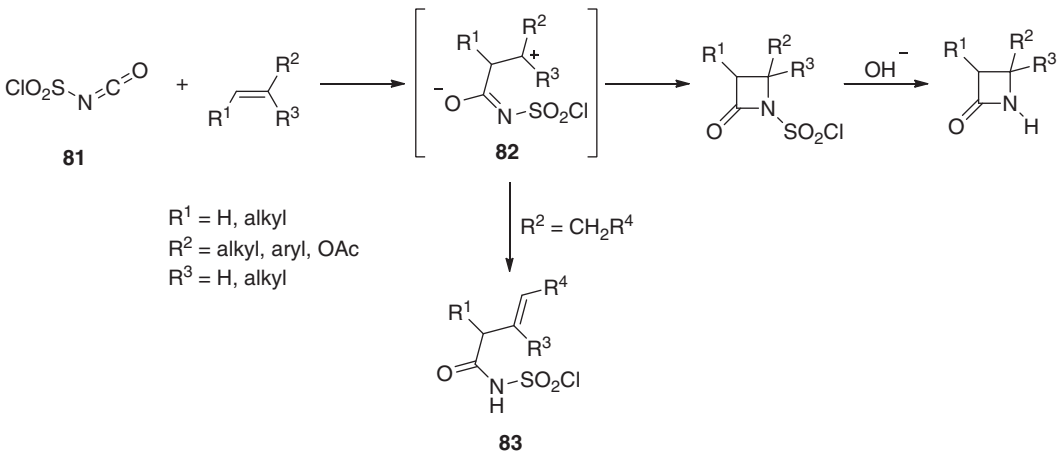
normal [2 + 2] additions. The chemoselectivity varies with subtle changes in the structures of the reactants as well as the experimental conditions.



R^1 = Ph, CCl_3
R^2 = Me, Ph, CH=CH_2
R^3 = H, Me

(14)

A more general and practical approach toward β-lactams from isocyanates uses the cheap chlorosulfonyl isocyante (CSI; **81**; Scheme 56).[212] This derivative, first described by Graf[213] offers several advantages: (1) it has a strong activating effect on the cyanate function; (2) it does not lead to competing [4 + 2] cycloadditions; and (3) it can be smoothly removed by simple basic hydrolysis or reductive treatment. CSI reacts with a wide range of alkenes under mild conditions to produce β-lactams together with variable but usually minor amount of open-chain adducts (**83**).



81

82

83

R^1 = H, alkyl
R^2 = alkyl, aryl, OAc
R^3 = H, alkyl

R^2 = CH_2R^4

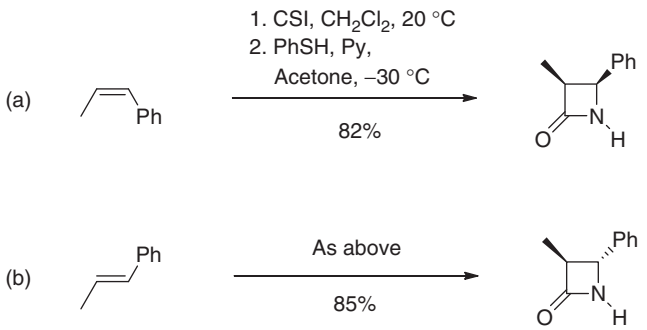
Scheme 56

Based on experimental results and computational studies, a stepwise mechanism via formation of a 1,4-dipolar intermediate (**82**) has been proposed for these reactions (Scheme 56).[214] In some specific cases, however, a concerted mechanism was shown to be preferred.[215] The reaction rates are markedly increased in polar solvents. The cycloadditions of isocyanates to alkenes are always regiospecific, the reaction taking place so as to form the most stable 1,4-dipole.

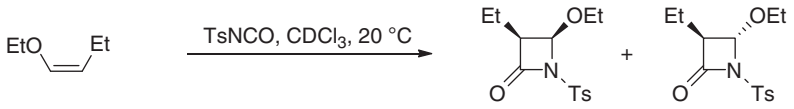
5.03.5.2 Stereochemical Aspects

Reaction of activated isocyanates with alkenes are generally highly stereospecific (Scheme 57).[209,216,217]

In a few cases, it was found that the primary adduct epimerizes under the reaction conditions (Scheme 58).[218]



Scheme 57

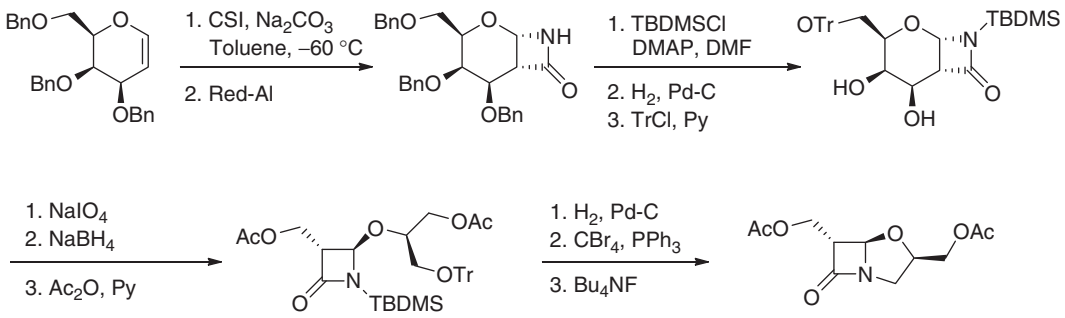


Reaction time	*cis*	*trans*
1 min	> 95%	< 5%
18 min	65	35
24 h	27	73

Scheme 58

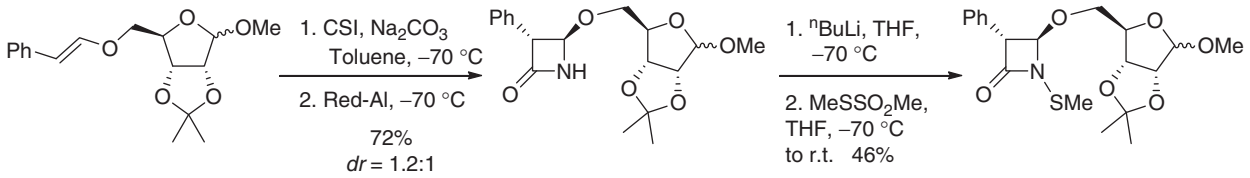
5.03.5.3 Selected Applications

The main applications of the [2 + 2] cycloaddition of isocyanates with alkenes are related to the chemistry of antibiotics. A stereocontrolled synthesis of 1-oxabicyclic β-lactam antibiotics, using the cycloaddition of chlorosulfonyl (or trichloroacetyl) isocyanate to sugar vinyl ethers as the key step, has been developed by Chmielewski et al. (Scheme 59, yields not specified).[219]



Scheme 59

Pyridinyl sulfones bearing carbohydrate moieties at the α-position have been used in the Julia–Lythgoe–Kocienski olefination with aldehydes, in a one-pot protocol affording glycosidic enol ethers with (*E*)-stereoselectivity. Their [2 + 2] cycloaddition reaction with CSI provides glycosylated β-lactams regioselectively and with an exclusive *trans*-stereochemistry (Scheme 60).[220] After conversion into *N*-methylthio derivatives, these β-lactams showed antibacterial activity toward MRSA.

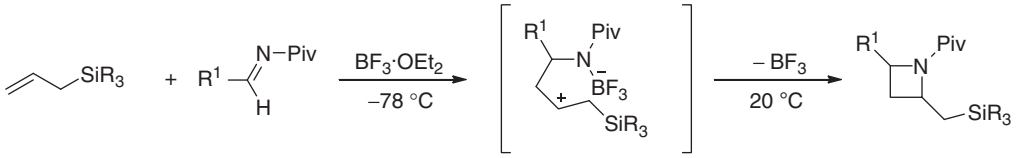


Scheme 60

5.03.6 Reaction of Alkenes, Allenes, and Alkynes with C═N Bonds

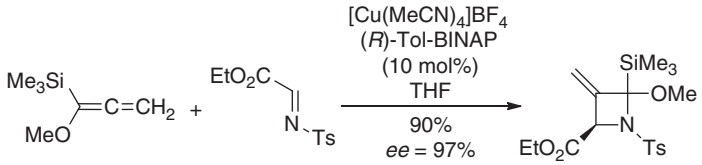
5.03.6.1 Lewis Acid-Catalyzed Reactions

N-Pivaloyl aldimines react with allylsilanes in the presence of boron trifluoride etherate or zinc chloride to give azetidines (Scheme 61). This formal [2 + 2] cycloaddition most probably proceeds in two steps, via a β-silyl cation intermediate.[221]



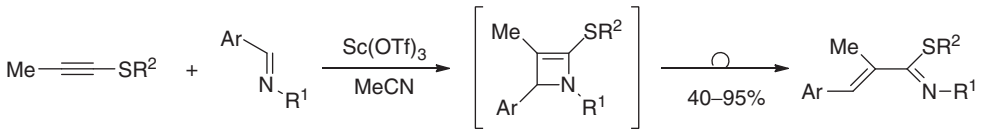
Scheme 61

The reaction of allenylsilanes with *N*-tosyl aldimines has been carried out in the presence of a chiral copper catalyst[222]; 3-*exo*-methylene azetidines were obtained with good *ee*'s (equation 15). An application to allenyl germanes is also described.[222]



(15)

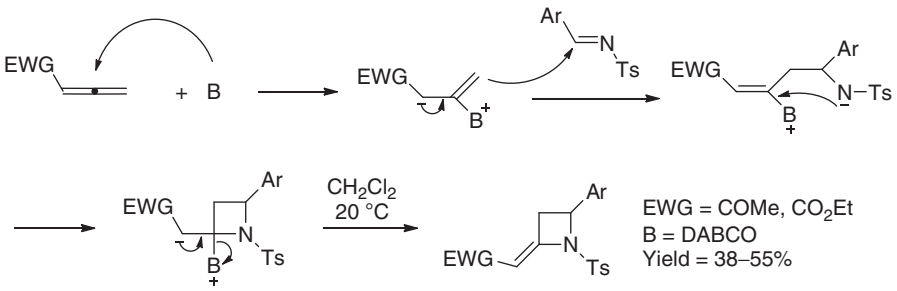
2-Azetine intermediates have been obtained by [2 + 2] cycloaddition of Schiff bases with alkynyl sulfides (or selenides), catalyzed by scandium triflate, ytterbium triflate, or boron trifluoride. The initially formed cycloadducts rearrange rapidly into α,β-unsaturated thioimidates (or selenoimidates) (Scheme 62).[223,224]



Scheme 62

5.03.6.2 Lewis Base-Catalyzed Reactions

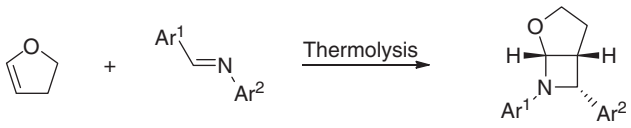
The cycloaddition of allenes substituted with an EWG to *N*-tosyl aldimines is catalyzed by 1,4-diazabicyclo[2.2.2]octane. 2-*Exo*-methylene azetidines are formed via a zwitterionic intermediate undergoing an intramolecular Michael addition (Scheme 63).[225]



Scheme 63

5.03.6.3 Thermic Reactions

On heating under pressure, 2,3-dihydrofuran cycloadds onto (E)-benzylideneanilines to furnish bicyclic azetidines with high stereoselectivity (equation 16).[226]



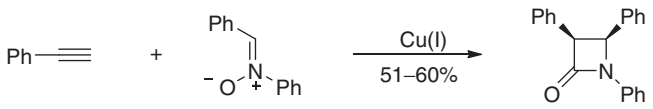
(16)

5.03.7 Reaction of Alkynes with Nitrones

5.03.7.1 The Kinugasa Reaction

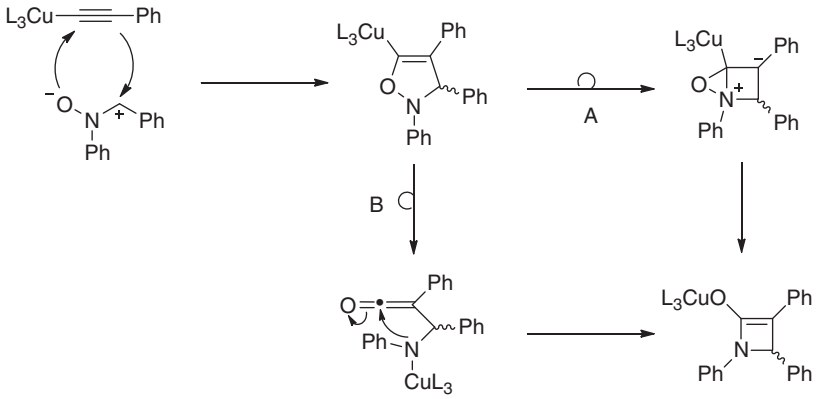
The reaction of C,*N*-diphenylnitrone, phenylacetylene and a stoichiometric amount of a Cu(I) salt in dry pyridine was initially reported in 1972 by Kinugasa and Hashimito (equation 17).[227] Later on, various terminal alkynes and substituted nitrones, both

readily available starting materials, were used for the stereoselective synthesis of *cis*-*β*-lactams.[228] The Kinugasa reaction offers a high functional group tolerance and an atom-economical character since the catalytic version (substoichiometric Cu(I)) could be developed by Miura et al.,[229] and further optimized by Fu and Lo[230] with appropriate metal ligands.



(17)

The proposed mechanism of *β*-lactam formation is outlined in **Scheme 64**: the reactive intermediate is the Cu(I) phenylacetylide which gives a 1,3-dipolar cycloaddition with the nitrone. The five-membered heterocyclic intermediate suffers a rearrangement, via the path A or, most probably, the path B, leading to a *β*-lactam Cu(I) enolate. Protonation of this species occurs from the less shielded side of the skeleton, and consequently the major diastereoisomer displays the relative *cis*-orientation of the *β*-lactam C_3/C_4 protons.[231]

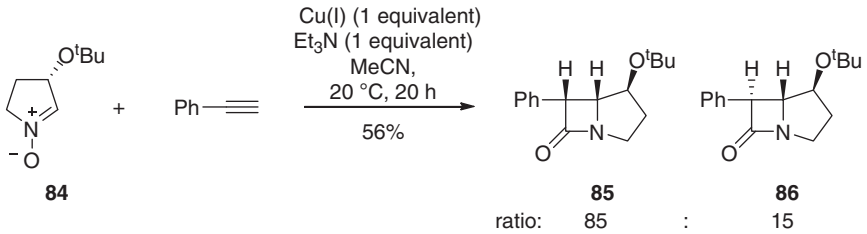


Scheme 64

Recently, Tang et al.[232] found that the Cu(I) salt can be replaced with $Cu(ClO_4)_2 \cdot 6H_2O$ to catalyze the Kinugasa reaction. The advantage of the Cu(II) source is that the reaction does not have to be performed under strictly inert atmosphere and with anhydrous solvents.

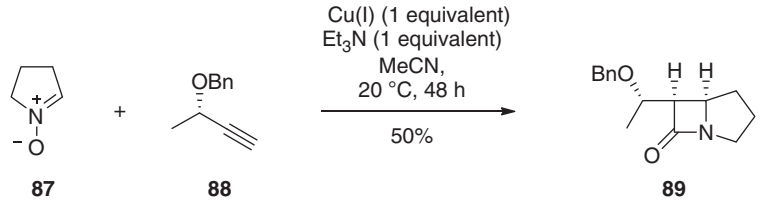
5.03.7.2 Asymmetric Synthesis

The use of chiral nonracemic nitrones as partners of the Kinugasa reaction was explored by Chmielewski et al.[233] For instance, the cyclic nitrone **84** (available from (*S*)-malic acid) reacts with phenylacetylene in the presence of one equivalent of copper iodide and one equivalent of triethylamine to yield a 85:15 mixture of diastereoisomers **85** and **86** (equation 18). The stereochemical outcome is controlled by the initial 1,3-cycloaddition step which determines the configuration of the bridgehead carbon atom. The approach of acetylide to the *Si* face of **84** (i.e., *syn* to the O*t*Bu substituent) is strongly disfavored by steric interactions.



(18)

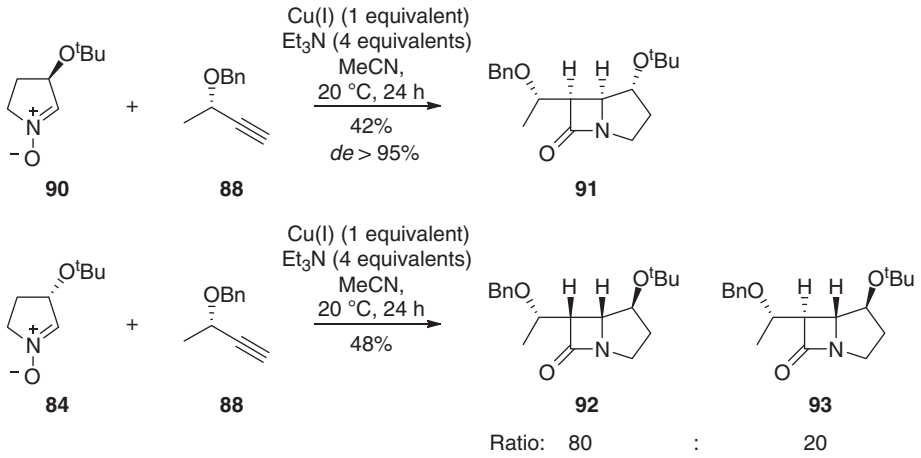
The copper(I)-mediated reaction between nitrones and chiral, nonracemic terminal acetylenes was also studied by Chmielewski et al.[234] As shown in equation 19, the reaction of cyclic nitrone **87** with alkyne **88** proceeds with excellent diastereoselectivity (*de* > 95%), affording the *cis* *β*-lactam **89**.



(19)

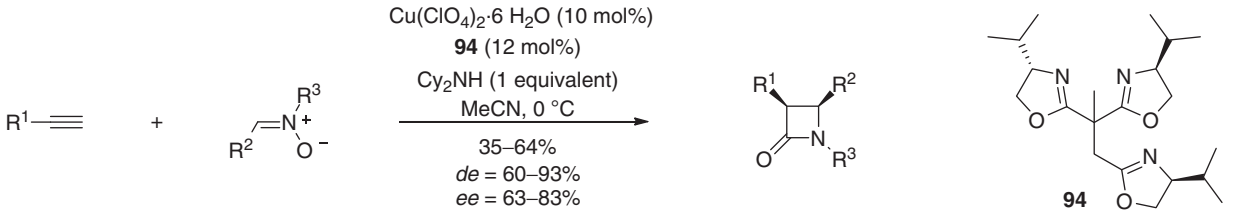
The use of (4*S*)-benzyl-3-propargyl oxazolidinone as acetylenic partner has been reported by Basak et al.[1,3,235]

Using both enantiomerically pure reagents, i.e., nitrone and acetylene, matched and mismatched pairs have been identified (Scheme 65). Specifically, in reactions with acetylene **88**, the nitrone **90** leads to a quasi total diastereoselectivity, whereas its enantiomer **84** gives a 80:20 mixture of diastereoisomers.



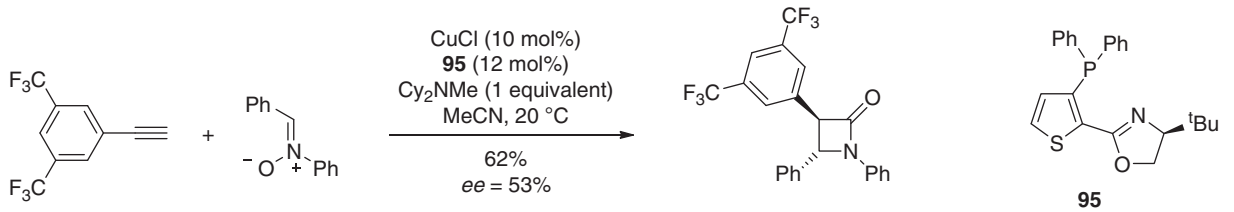
Scheme 65

Pioneering work[229] on the catalytic asymmetric synthesis of *β*-lactams made use of *bis*-oxazolines as chiral ligands. More recently, *bis*-azaferrocenyl ligands allowed the enantioselectivities to be increased from 30% *ee* to approximately 90% *ee*.[230] Tang et al.[73] have designed a pseudo-C_3-symmetric *tris*-oxazoline ligand (**94**) by a 'side-arm approach' and found that the combination of **94**/Cu(II) efficiently catalyzed asymmetric Kinugasa reactions in air (equation 20).[232] The presence of a base was essential to control the dia- and enantio-selectivities; compared with tertiary and primary amines, secondary amines gave the best results.



(20)

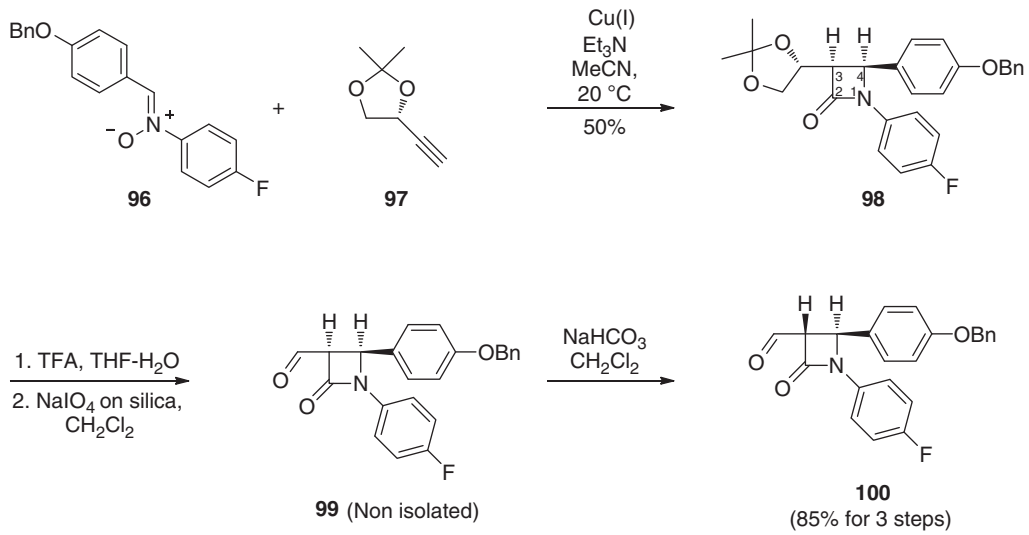
Beside the usual *N*,*N*-ligands, *P*,*N*-ligands, such as **95**, have been applied to the Kinugasa reaction by Guiry et al.[236] High levels of diastereoselectivity are obtained, but with moderate enantioselectivity, approximately 50%. An unexpected reversal of the diastereoselectivity is observed for 3,5-(trifluoromethyl)phenylacetylene (equation 21).



(21)

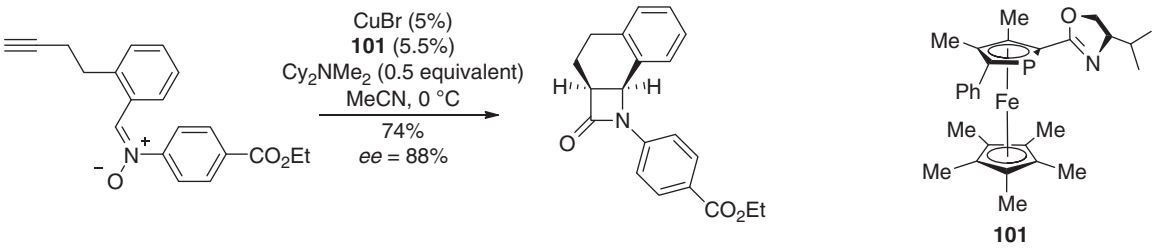
5.03.7.3 Selected Applications

The key-intermediate **100** toward the cholesterol absorption inhibitor Ezetimibe® has been synthesized from the nitrone **96** and the enantiomerically pure acetylene **97** (Scheme 66).[237] Under standard conditions (2 equivalents of **96** with respect to **97**, 1 equivalent of CuI, and 4 equivalents of triethylamine), the Kinugasa reaction provides the desired *cis*-configured *β*-lactam **98** with the (4*S*)-configuration as the major diastereoisomer (separable from the (4*S*)-*trans*, (4*S*)-*cis*, and (4*R*)-*trans* isomers). Acetonide deprotection, followed by oxidation to aldehyde **99** and C_3 epimerization lead to the (4*S*)-*trans* *β*-lactam **100** in 85% overall yield.



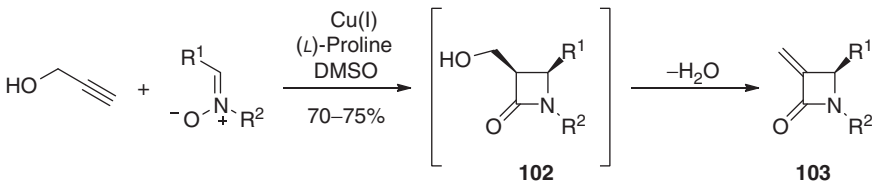
Scheme 66

The intramolecular version of the Kinugasa reaction has been applied to efficiently construct fused tricyclic ring systems with good enantioselectivities when using the chiral ferrocenyl derivative **101** as catalyst (equation 22).[238]



(22)

3-*Exo*-methylene *β*-lactams can be obtained by a one-pot process via Cu(I)-mediated cycloaddition between propargyl alcohol and nitrones in the presence of (L)-proline.[239] In DMSO as solvent (instead of acetonitrile), the intermediate **102** led directly to the dehydration product **103** (equation 23).



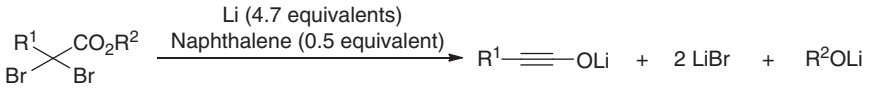
(23)

5.03.8 Reaction of Ynolates with C═X Bonds

5.03.8.1 Synthesis of Ynolates

Contrary to enolates, which are well-established carbanions in synthetic organic chemistry, ynolates have attracted much less attention due to the lack of general and convenient methods[240] for their synthesis, until the work of Shindo et al. was

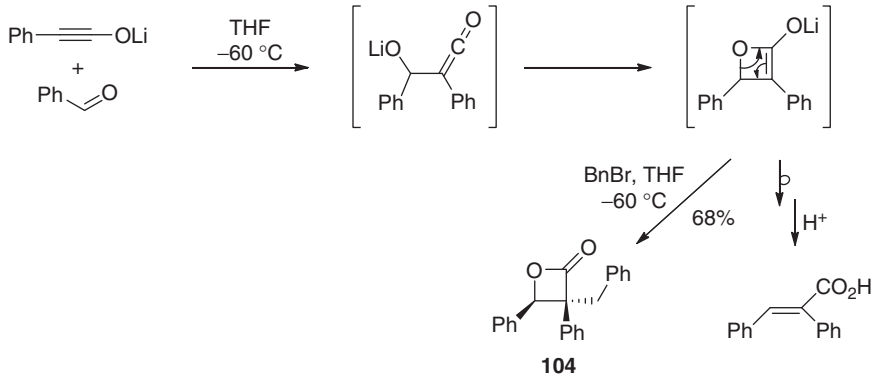
published.[241] They developed a safe and economical preparation of lithium ynolates by reductive lithiation of α,α′-dibromoesters in the presence of naphthalene (equation 24).[242] Ynolates can be stored for a few days at room temperature.



(24)

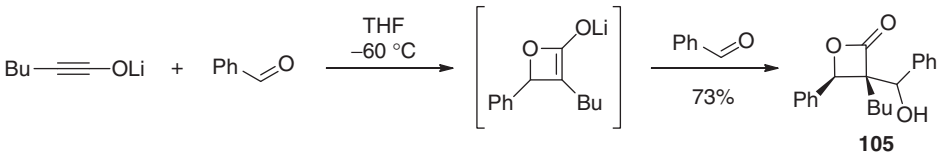
5.03.8.2 Reaction with Aldehydes and Ketones

Lithium phenylynolate reacts with benzaldehyde to give a β-hydroxy lithiated intermediate which cyclizes into a β-lactone enolate; it can be quenched at low temperature with an electrophile such as benzyl bromide to afford the stable β-lactone **104** with high stereocontrol (Scheme 67).[243]



Scheme 67

Lithium butylynolate and 2 equivalents of benzaldehyde yield the β-lactone **105** resulting from the quenching of the enolate intermediate with the aldehyde itself (Scheme 68).[244]



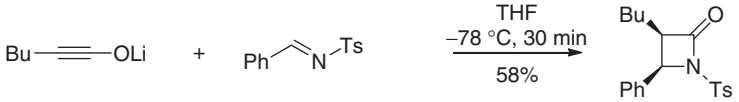
Scheme 68

In the absence of an electrophile, the β-lactone enolate intermediates are transformed on heating into olefins with high stereoselectivity. Tri- and tetrasubstituted alkenes have been prepared; their configuration is controlled by the torquoselectivity of the electrocyclic ring-opening reaction (Scheme 67).[241]

The ynolate chemistry has been successfully applied to the synthesis of furanes, pyrroles, and thiophenes via a cascade of reactions, namely cycloaddition, intramolecular cyclization, decarboxylation, and dehydration.[245]

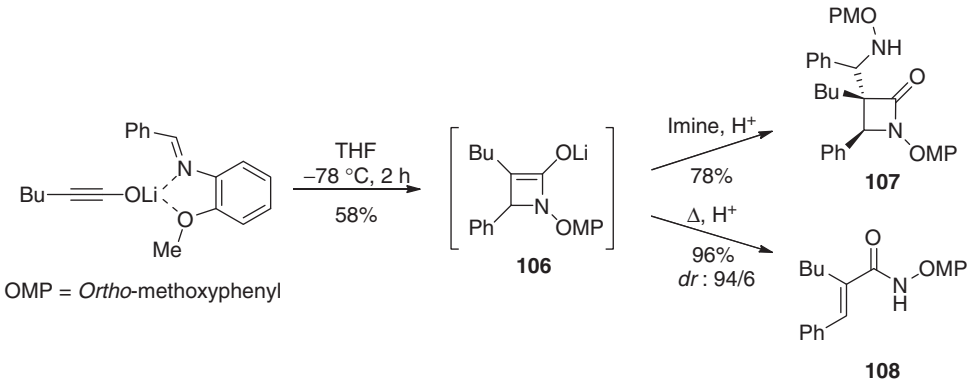
5.03.8.3 Reaction with Imines

Barrett et al.[246] and Murai et al.[240] reported that phenyl- and silylynolates add to aldimines bearing an electron-withdrawing substituent to provide, respectively, β-lactams (2:1 adducts) at low temperature (− 60 °C) and α,β-unsaturated amides at room temperature. Reaction of ynolates with *N*-sulfonyl imines leads to β-lactams (1:1 adducts) at − 78 °C (equation 25).[247]



(25)

Unactivated imines are not reactive, even in the presence of LAs.[248] One exception is worthy of note: *N*-2-methoxyphenyl imine cycloadds to lithium ynolates as shown in Scheme 69. The authors propose an activation of the imino group by double



Scheme 69

chelation of the lithium ynolate. The isolated β-lactam **107** corresponds to the 2:1 adduct, because the nucleophilicity of the enolate intermediate **106** is higher than that of the ynolate. As a matter of fact, 1:1 adducts are obtained with the less nucleophilic *N*-tosyl imines (equation 25). When heated to room temperature before aqueous work-up, the β-lactam enolate **106** suffers a ring-opening reaction leading to the α,β-unsaturated amide **108** with excellent *E*-selectivity.[249]

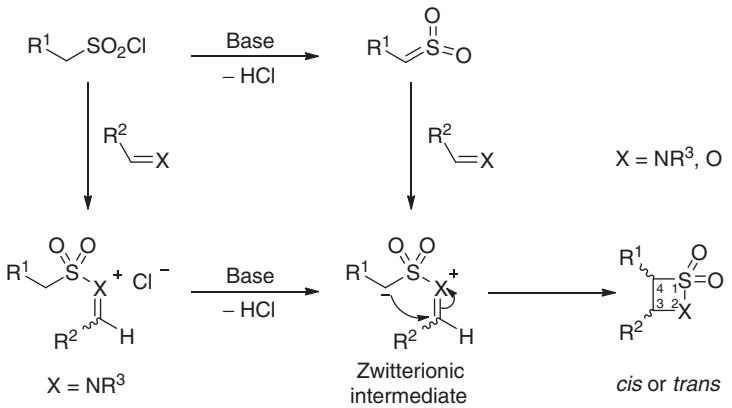
5.03.9 Reaction of Sulfenes with C=X bonds

5.03.9.1 Analogy with the Ketene Chemistry

Similarly to β-lactams and β-lactones, β-sultams (1,2-thiazetidine-1,1-dioxides), and β-sultones (1,2-oxathietane-1,1-dioxides) have been studied for their potential properties in medicinal chemistry[250,251] and synthetic organic chemistry.[252,253]

In particular, β-sultams are exploited for the discovery of active site directed inhibitors of serine enzymes such as elastases,[254] β-lactamases,[255] and D,D-peptidases.[256] However, the high reactivity of β-sultams toward nucleophiles, leading to S–N bond cleavage, opens the route to taurine derivatives.[257]

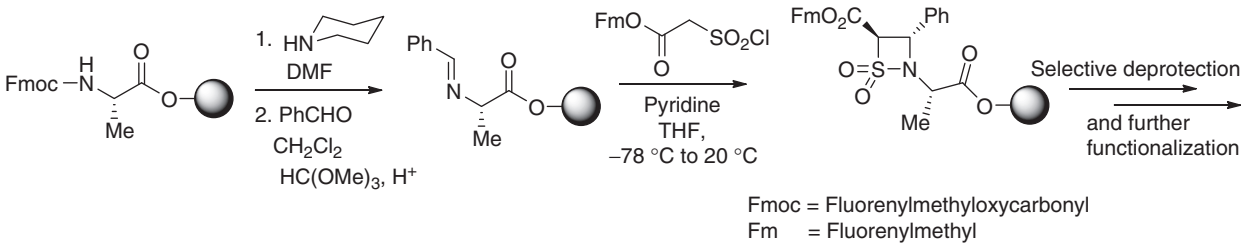
Most often, β-sultams are obtained by cyclization reactions, mainly the formation of the N–S bond[258,259] or the C–C bond.[260] Another general route toward β-sultams is based on the formal [2 + 2] cycloaddition of sulfenes to imines.[250] Sulfenes are formed *in situ* by the dehydrochlorination of alkylsulfonylchlorides with a base at low temperature (**Scheme 70**).[261] Their existence was spectroscopically demonstrated,[262] but in contrast to ketenes, sulfenes cannot be isolated. The reaction with imines (**Scheme 70**, X=NR^3) has been described as a multistep process with a zwitterionic intermediate.[263] Depending on the nature of the R^1, R^2, and R^3 substituents, formation of a zwitterionic intermediate via the initial reaction of the alkylsulfonyl chloride with the imine is also possible.



Scheme 70

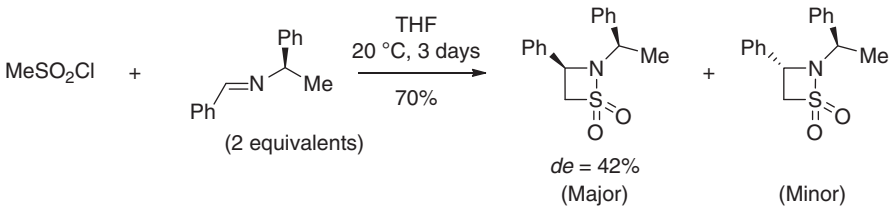
The diastereoselectivity of the reaction is variable and depends mainly on the nature of R^1. Production of *trans* β-sultams has been reported for the reactions of benzoylmethanesulfonyl chloride (R^1=PhCO); [264] mixtures of *cis* and *trans* isomers have been obtained with benzylsulfonyl chloride (R^1=PhCH$_2$).[265] Combinatorial chemistry on solid phase allowed for the synthesis of β-sultams libraries with a broad structural diversity.[250] In this application, the imine partner is produced *in situ* from a TentaGel

resin derivatized with an amino acid; the sulfene partner arises from chlorosulfonyl acetates as exemplified in Scheme 71 with the fluorenylmethyl ester (Fm).



Scheme 71

The 1,3-asymmetric induction in solution phase has been studied using chiral imines derived from (*R*)- or (*S*)-α-methylbenzylamine.[266] The diastereoslectivities are moderate, in favor of the *syn*-stereoisomer, for the [2 + 2] cycloaddition of unsubstituted sulfene produced *in situ* from mesylchloride and 2 equivalents of imine (equation 26).[267]



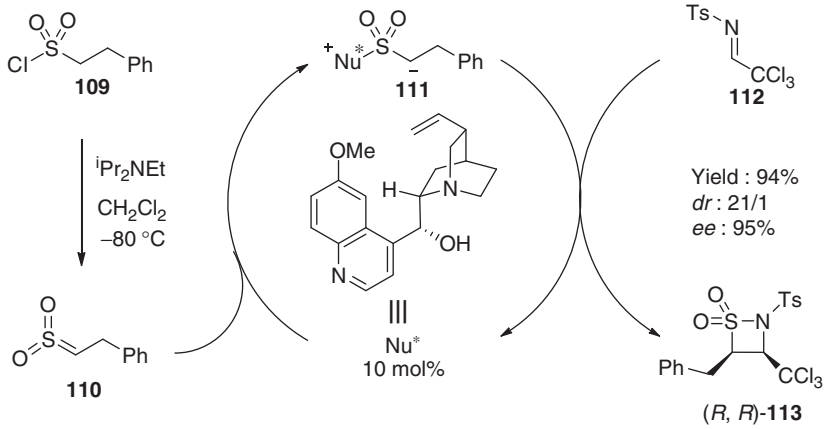
(26)

The number of accessible β-sultones, according to the strategy of Scheme 70 with aldehydes (X=O) as nucleophilic partners of the [2 + 2] cycloaddition, is rather limited because most β-sultones are unstable at room temperature; the occurrence of proton shift, elimination and rearrangement reactions has been reported.[268,269] Derivatives holding an EWG and sterically demanding group at the C_4 atom are the most stable ones (stabilization of the labile C–O bond).[251] For that reason, chloral is the privileged aldehyde for [2 + 2] additions to sulfenes (see Section 5.03.9.2).

5.03.9.2 Catalytic Asymmetric Synthesis of β-Sultams and β-Sultones

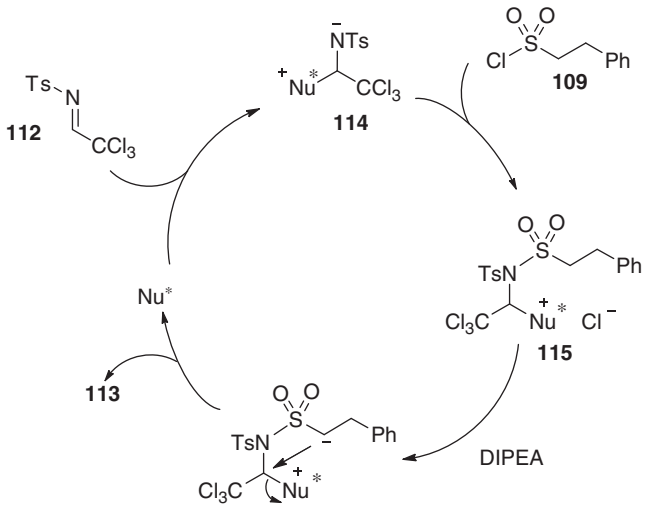
In contrast to ketenes, the use of sulfenes in asymmetric catalysis is scarcely described and the major contribution in this field is from Peters et al.[251,257,270,271] The main problem relies on the instability of sulfenes which have to be produced *in situ* at very low temperature. Nevertheless, reproducible protocols could be validated for the catalytic asymmetric synthesis of β-sultams and β-sultones, using electron-poor imines and aldehydes as highly activated partners of the [2 + 2] cycloadditions, and employing cinchona alkaloid derivatives as nucleophilic organocatalysts.

The sulfene **110**, produced *in situ* by dehydrochlorination of the corresponding sulfonyl chloride **109** by diisopropylethyl amine (DIPEA), reacts with the chiral nucleophilic catalyst (Nu∗) to form the zwitterionic intermediate **111** capable of initiating the asymmetric [2 + 2] cycloaddition with the electron-poor *N*-tosyl imine (**112**) (Scheme 72). Indeed, **112** has to be



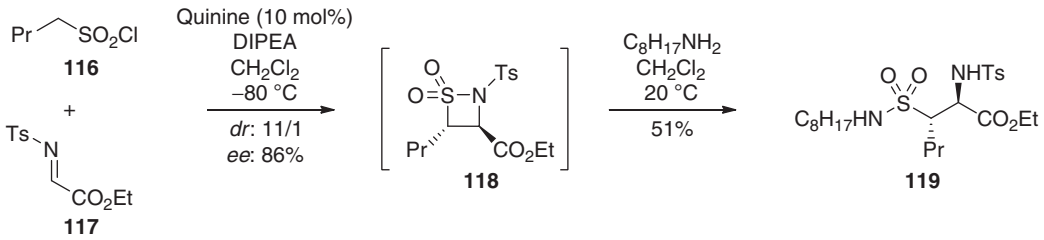
Scheme 72

nonnucleophilic to avoid the noncatalyzed competitive reaction between **112** and **110**. Using the cinchona alkaloid quinine as the catalyst, the *cis* β-sultam **112** was obtained in 94% yield with 95% of *ee*. Depending on the temperature and the order of addition of the reagents, another catalytic cycle has been proposed, involving the intermediate formation of an adduct (**114**) of the catalyst (Nu∗) with the highly electrophilic imine **112**. The negatively charged N-Ts atom of **114** attacks the sulfonyl chloride (without prior formation of a sulfene) to give the intermediate **115** which suffers deprotonation by DIPEA. Lastly, an intramolecular nucleophilic substitution leads to the β-sultam **113** and the release of the catalyst (Scheme 73).



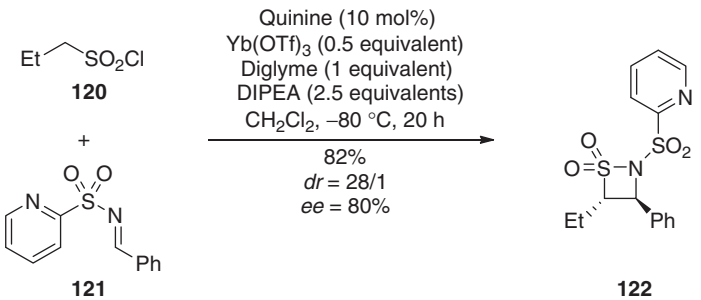
Scheme 73

The methodology has been extended to α-iminoesters. Because these imines are prone to polymerize, the reagent **117** is added very slowly to a solution of catalyst (quinine), DIPEA and sulfonyl chloride **116** at $-80\ ^{\circ}C$ to furnish the *trans*-β-sultam **118** with 86% *ee*. The tandem one-pot cycloaddition/nucleophilic ring-opening sequence with octylamine leads to **119** in 51% yield (Scheme 74).



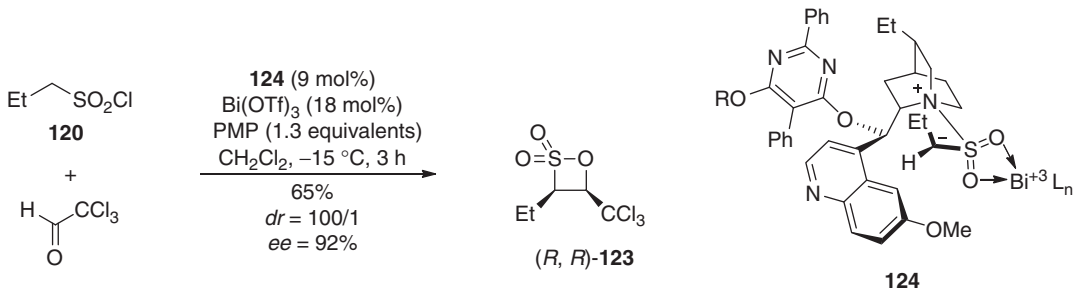
Scheme 74

Arylaldimines are less reactive toward sulfenes and therefore require the replacement of the tosyl group with the 2-pyridylsulfonyl group. Indeed, this moiety offers the possibility of bidentate coordination to a LA cocatalyst, giving an additional activation. For instance, the reaction of sulfonyl chloride **120** with imine **121** in the presence of DIPEA, quinine (10 mol%), ytterbium triflate as cocatalyst and diglyme as additive yielded the *trans*-β-sultam **122** in 82% yield and 80% *ee* (equation 27).



(27)

The catalytic system developed for the asymmetric synthesis of β-sultams (Scheme 73) is not similarly efficient for the preparation of enantiomerically pure β-sultones (replacement of imine **112** with chloral).[251] The addition of a LA cocatalyst is required to enhance the performance. As the result of a large screening of reagents and experimental conditions, the selected catalytic system involves: (1) dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$) as the chiral nucleophilic catalyst; (2) bismuth triflate as the LA cocatalyst; (3) 1,2,2,6,6-pentamethylpiperidine as the stoechiometric nonnucleophilic base; and (4) an excess of chloral (2.75 equivalents) (equation 28). Under these conditions, the cycloaddition of ethyl sulfene to chloral (trichloroacetaldehyde) affords the *cis*-β-sultone **123** with the *R*,*R*-configuration (established by X-ray diffraction analysis).[251] This result can be rationalized by the formation of a sulfene-$(DHQ)_2PYR$ adduct **124** coordinated to the Bi^{3+} salt, which is the reactive species for the addition to chloral. Another role attributed to the bismuth salt was the coordination of the aldehyde; the coordination of both reactants may lead to a highly organized transition state and consequently to high enantioselectivity.

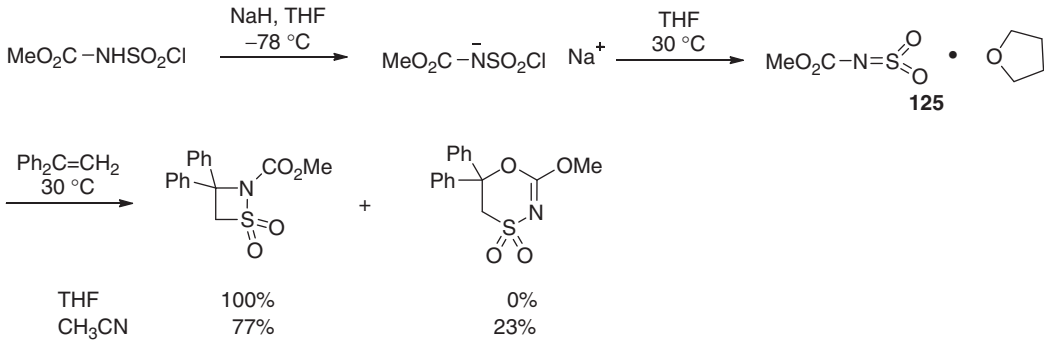


(28)

5.03.10 Miscellaneous

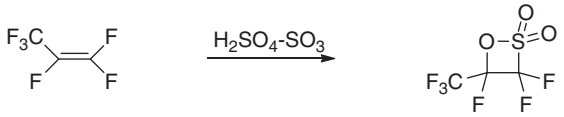
5.03.10.1 Four-Membered Rings Containing One Sulfur Atom (and Another Heteroatom)

N-Sulfonylamines ($RN{=}SO_2$) are able to react with strained or nucleophilic alkenes to furnish β-sultams.[272] Methyl *N*-sulfonylurethan **125** cycloadds to nonactivated alkenes, due to its high electrophilicity (Scheme 75).[273] This species is produced *in situ* from carbomethoxysulfamoyl chloride and is stabilized by complexation with tetrahydrofuran. A solvent dependent competition between [2 + 2] and [4 + 2] cycloadditions has been reported.[273]



Scheme 75

The similar [2 + 2] cycloaddition of sulfur trioxide with alkenes generates β-sultones, a method especially dedicated to the synthesis of perfluorinated derivatives (equation 29). Perfluorinated β-sultones are used for the preparation of hybrid organic–inorganic mesoporous materials featuring terminal sulfonic acid groups; such materials are better catalysts than Nafion-silica® for the esterification of fatty acids.[274,275]

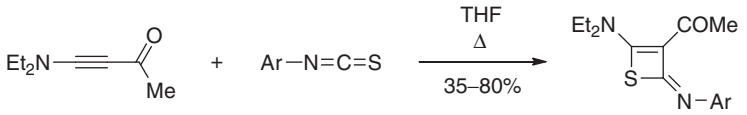


(29)

Oleum (fuming sulphuric acid) can be used as a source of SO_3.[276] Otherwise, the SO_3–pyridine complex is the usual source of SO_3. An alternative way to produce SO_3 *in situ* is based on the reaction of trimethylsilylsulfonyl chloride with iodosobenzene at

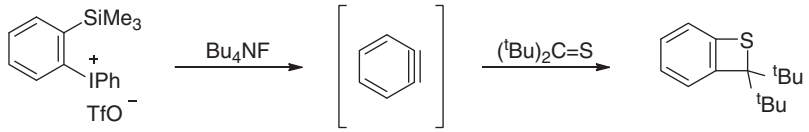
low temperature, performed in the presence of alkenes; this method allows β-sultones to be isolated in moderate to good yields.[277]

The [2 + 2] cycloaddition of 4-diethylamino-3-butyn-2-one (ynamine) with aryl isothiocyanates leads to thietimine derivatives (equation 30).[278]



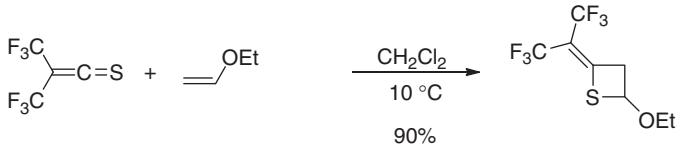
(30)

Fused thietes are obtained by the reaction of benzyne with thioketones (Scheme 76).[279]



Scheme 76

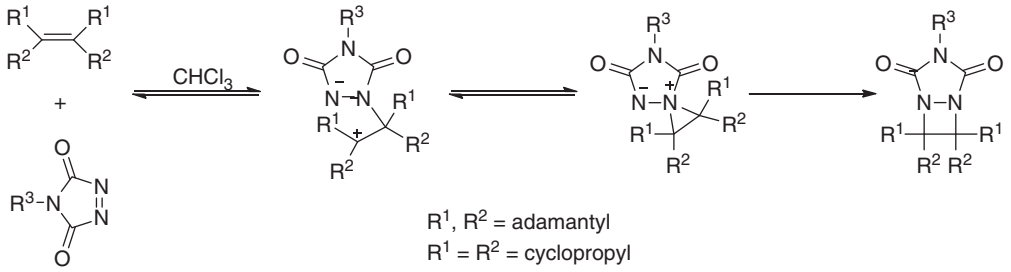
Since thioketenes are usually difficult to prepare, only reactions of bis(trifluoromethyl)thioketene as a stable representative with a range of C=C bonds have been studied. Unlike the other heterocumulenes, [2 + 2] cycloadditions occur across the cumulene C=X bond, leading to 2-*exo*-methylene-thietane derivatives (equation 31).[172]



(31)

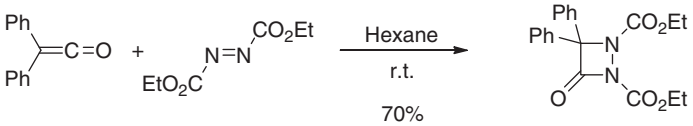
5.03.10.2 Four-Membered Rings Containing Two Nitrogen Atoms

The formation of two C–N bonds by [2 + 2] cycloaddition between alkenes and azo compounds constitutes the general route toward 1,2-diazetidines.[280] Reactions between highly substituted alkenes and 1,2,4-triazoline-3,5-diones lead to bicyclic, N–N fused, diazetidine derivatives, most probably via zwitterionic intermediates (Scheme 77).[281–283]



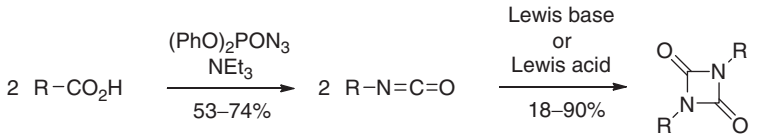
Scheme 77

1,2-Diazetines, accessible from adequately substituted 1,2-diazetidines, behave as excellent dienophiles in [4 + 2] cycloadditions.[284] 1,2-Diazetidin-3-ones are obtained by [2 + 2] cycloaddition of ketenes to azobenzenes. Since only the *cis* stereoisomers are reactive, these reactions require light activation to isomerize the azobenzenes *in situ*.[285] In contrast, azodicarboxylates and azoketones react without irraditation (equation 32).[286,287]



(32)

1,3-Azetidin-2,4-diones are classically obtained by dimerization of isocyanates under either Lewis base or LA catalysis. Non-commercially available isocyanates can be readily obtained from carboxylic acids by the Curtius rearrangement (Scheme 78).[288,289]

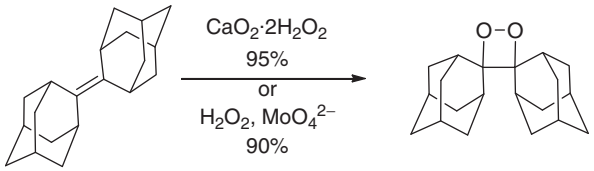


Scheme 78

Carbodiimide dimerization[290] and cross-dimerization between isocyanates and carbodiimides[291] have also been reported.

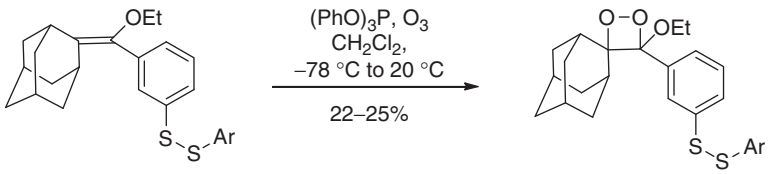
5.03.10.3 Four-Membered Rings Containing Two Oxygen Atoms

In the past, 1,2-dioxetanes were prepared by cyclization methods, from β-halo hydroperoxides or from β-epoxy hydroperoxides. Presently, the cycloaddition of singlet oxygen to electron-rich alkenes is the most useful method, exemplified with a large number of compounds and employing a range of singlet oxygen sensitizers.[292–296] Environmentally friendly sources of singlet oxygen have been described, such as calcium peroxide diperoxohydrate[58,297] and hydrogen peroxide with molybdate ions in a reverse microemulsion (equation 33).[298]



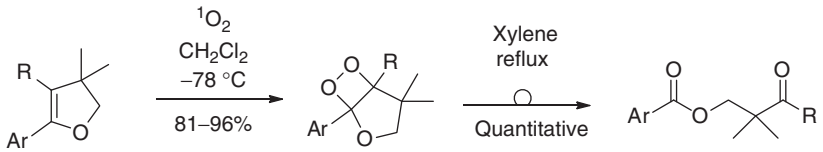
(33)

Beside the above general method, enol ethers could be transformed into 1,2-dioxetanes with triphenylphosphite and ozone (equation 34);[57] this protocol is compatible with the sensitive disulfide function which is not oxidized.



(34)

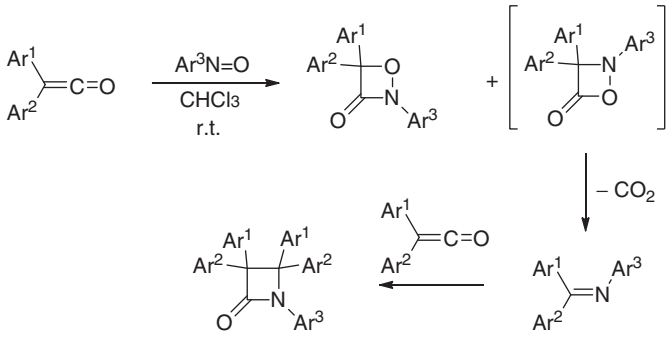
Singlet oxygen oxidation of cyclic enol ethers leads to the fused bicyclic 1,2-dioxetanes prone to rearrange into keto-esters when R=H (Scheme 79).[299]



Scheme 79

5.03.10.4 Four-Membered Rings Containing One Nitrogen and One Oxygen Atom

The cycloaddition of diarylketenes onto arylnitroso derivatives occurs with poor regioselectivity: mixtures of 1,2-oxazetidin-3-ones and 1,2-oxazetidin-4-ones are obtained, the latter being unstable (Scheme 80). Their decomposition leads to imines which are trapped by the ketene reagent to form β-lactams.



Scheme 80

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5.04 Photochemical Cycloadditions

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Glossary

Alkene photocycloaddition Photochemical process leading to the formation of a cyclobutane on addition of an electronically excited alkene to another ground-state alkene, or of an electronically excited α,β-unsaturated carbonyl compound to a ground-state alkene.

Electron transfer Transfer of an electron from one molecular entity to another or between two localized sites in the same molecular entity.

Energy transfer Process by which a molecular entity is excited by absorption of radiation and is deactivated to a lower-lying state by transferring energy to a second molecular entity which is thereby raised to a higher energy state. The excitation may be electronic, vibrational, rotational, or translational.

Intersystem crossing Isoenergetic radiationless transition between two electronic states having different multiplicities.

Photocatalysis Change in the rate of a chemical reaction or its initiation under the action of ultraviolet, visible, or infrared radiation in the presence of a substrate – the photocatalyst – that absorbs light and is involved in the chemical transformation of the reaction partners.

Photocycloaddition Photochemical process leading to carbo- or heterocyclic systems by formation of two new single bonds, either by concerted or multistep processes.

Photosensitization Photochemical or photophysical alteration occurring in one molecular entity as a result of initial absorption of radiation by another molecular entity called a photosensitizer.

Triplet-triplet energy transfer Energy transfer from an electronically excited triplet donor to produce an electronically excited acceptor in its triplet state.

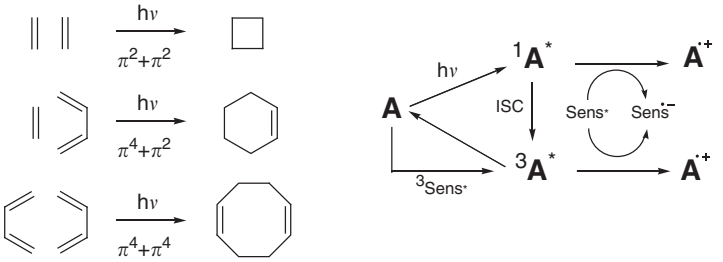
Ultraviolet Region of the electromagnetic spectrum extending from approximately 100 to 400 nm. The region is divided into four subbands as follows: Vacuum ultraviolet (VUV): 100–200 nm; UV-C: 200–280 nm; UV-B: 280–315 nm; UV-A: 315–400 nm.

5.04.1 Introduction

Photocycloadditions are concerted or stepwise photochemical processes that lead to the formation of cyclic products from acyclic or cyclic substrates.[1,2] Stepwise processes often involve 1,*n*-biradicals or radical ion pairs that are formed by photoinduced electron transfer (PET) steps. For initiation of these primary processes, one substrate has to be activated by electronic excitation. There are three major routes that can be used for activation: (a) direct absorption by the substrate in the ultraviolet (UV) or visible region, (b) energy transfer sensitization using appropriate catalysts (sensitizers), and (c) electron transfer sensitization using PET catalysts.

Direct excitation requires appropriate lamp and filter technology to irradiate into the relevant absorption bands of the chromophore in the substrate. These experimental conditions are crucial for selective photochemistry. Before any photochemical experiment, the absorption spectra of substrates as well as that of reagents and the solvents have to be compared in order to

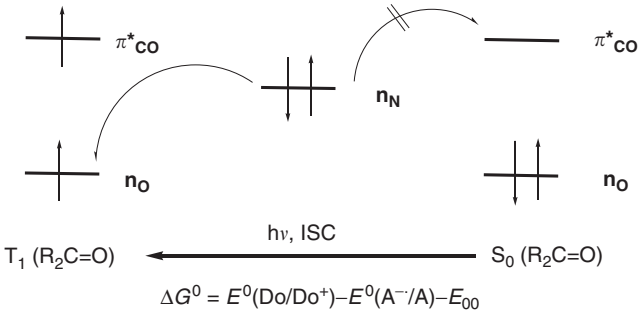
examine and match the irradiation windows. The relevant excited singlet states in organic photochemistry are nπ* and ππ* states of mono- or polyalkenes, alkynes, aromatic substrates, carbonyl, and carbonyl analog groups. The generation of the initial singlet is followed by several deactivation steps that are unproductive with respect to product formation: fluorescence, intersystem-crossing, radiationless decay to the ground state, energy or electron transfer to appropriate acceptor groups either in intra- or intermolecular fashion (Scheme 1). Fluorescence can be measured independently and the singlet lifetimes, determined by time-resolved techniques, are crucial for the application of reagents in intermolecular photoreactions, for example, if reagents can be used in stoichiometric ratios or have to be used in large excess. Efficient intersystem crossing (ISC) generates the excited triplets, which generally have much longer lifetimes but are sensitive against energy transfer to triplet oxygen. From the reaction of excited nπ* and ππ* singlet states, concerted photochemical addition processes can be expected, whereas the corresponding nπ* and ππ* triplets generally react in multistep pathways due to spin restrictions. The electronic spin properties are crucial for the reaction progress, i.e., concerted versus two-step process – influencing regio- and stereoselectivity as well as reaction and quantum yields, respectively.[3]



Scheme 1

As a competing side reaction, singlet excited nπ* and ππ* states can undergo efficient group transfer reactions. Intermolecular hydrogen transfer to excited singlet states can compete with intersystem crossing; however, in many cases this is not synthetically useful because large excess of hydrogen-donor must be used. Addition of nucleophiles to ππ* singlets is an alternative group transfer process. If alcohols are used in excess (e.g., as solvent), efficient ether formation is possible, which is also studied in enantioselective fashion.[4] Triplet excited ππ* and nπ* states can be selectively generated by energy transfer from appropriate energy donors. Prerequisites for triplet energy donors is a proper triplet energy and high intersystem crossing quantum yields as well as low chemical reactivity of singlet and triplet states. Benzophenone is a typical triplet sensitizer for alkene or polyene ππ* triplets, however, with a strong tendency for hydrogen transfer reactions.

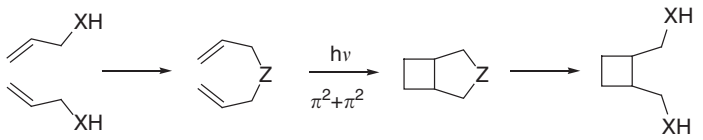
Electronically excited states feature, at the same time, significantly increased reduction and oxidation properties, as compared to ground states. The investigation of PET as a key step in many photochemical reactions was further stimulated by the Nobel Prize awarded work of Marcus[5] and has, in the past few decades, not only led to new synthetic applications,[6] but also to a general paradigm change in photochemistry. As has been described in detail in several reviews,[7] the energetics of light-induced electron transfer can be estimated using a simplified version of the Rehm–Weller equation (Scheme 2; ΔG° = free enthalpy of electron transfer; $E^\circ(\mathrm{Do/Do^+})$ = first oxidation potential of the donor; $E^\circ(\mathrm{A^-/A})$ = first reduction potential of the acceptor; E_{00} = energy difference between ground state and first excited state).[8] Unlike many other physical equations, this relationship immediately shows its chemical relevance: electronically excited states are concurrently much better reductants and oxidants; the actual redox behavior depends on the reaction partner. This concept can be easily explained for the carbonyl–amine system (Scheme 2): the high-lying lone-pair at N and the low-lying antibonding π^*_{CO} render the amine–carbonyl combination suitable for Frontier molecular orbital (FMO)-controlled nucleophile–electrophile ground-state interaction. But only after electronic excitation to the n→π* carbonyl state, an exergonic electron transfer becomes feasible. The same is true for less active electron donors like alkyl carboxylates, unsaturated or strained hydrocarbons, aromatic compounds, and many more.



Scheme 2

To perform an efficient photocycloaddition reaction, the light-absorbing substrate has to be designed carefully: (a) photoexcitation has to be limited to the substrate and neither the product(s) nor potential long-lived reaction intermediates must absorb light in the region applied. This can be achieved by the use of monochromatic light sources or by appropriate filters. Alternatively, triplet sensitizers are advisable that selectively transfer energy to the substrate and absorb in the red-shifted part of the UV–vis region; (b) nondesired electron transfer reactivity of the substrate can be suppressed by introducing electron-withdrawing groups to reduce the donor-capability or electron-donating groups to reduce the acceptor-capability; (c) spin-selectivity has to be investigated for intermolecular photoreactions by variation of the reagent concentration; (d) oxygen sensitivity is often observed for triplet photocyclization reactions where the long-lived substrate donors can transfer energy (or an electron) to triplet oxygen to generate singlet oxygen (or the superoxide radical anion).

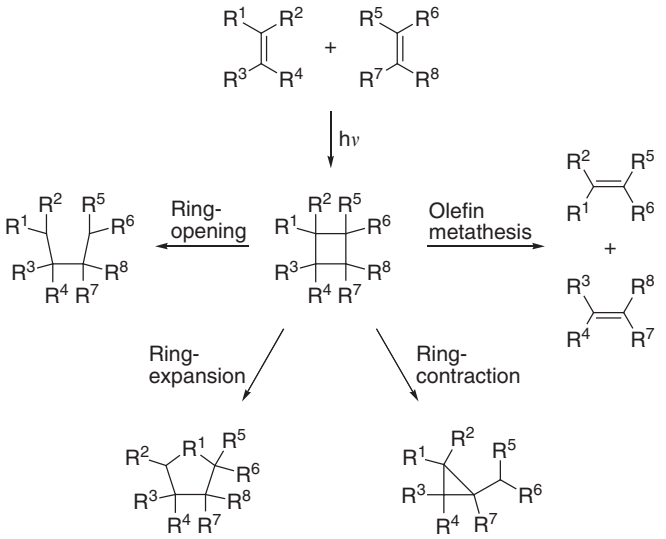
From an orbital symmetry point of view, photocycloadditions of the $\pi^2+\pi^2$- and $\pi^4+\pi^4$-types can be applied for organic synthesis. The $\pi^2+\pi^2$-cycloadditions have been described in recent reviews and can be characterized by the relevant substrates as ene–ene,[9] ene–enone,[10] as well as enone–enone cycloadditions (and carbonyl analogs).[11] The combination of two dienes under photolysis conditions can result in $\pi^2+\pi^2$-(cyclobutanes), $\pi^4+\pi^2$-(cyclohexenes), and $\pi^4+\pi^4$-(cycloocta-1,5-dienes) products.[12] As a special variant of the ene–enone protocol, the photocycloaddition of alkenes to the β-hydroxy enone tautomers of 1,3-dicarbonyl compounds is described as de Mayo reaction. Also, aromatic substrates can be used as ene components, leading to different addition modes which are characterized with respect to the positions involved in the aromatic system as *ortho* (1,2)-, *meta* (1,3)-, and *para* (1,4) aromatic photocycloadditions.[13] Besides direct excitation of the π-chromophore or triplet sensitization, PET is a versatile method for activation of $\pi^n+\pi^m$-substrate combinations. Intermolecular reactions often suffer from the short lifetimes of the excited singlets and the tethering concept has been developed for this purpose. The spatial orientation of two allylic alcohols, for example, by silicon tethering, leads to excellent yields and selectivities in photocycloadditions (**Scheme 3**, $X=SiR_2$). The tether group is most convenient if a nonphotochemical cleavage follows the photocycloaddition.[14]



Scheme 3

5.04.2 [2 + 2]-Photocycloadditions

[2 + 2]-Photocycloadditions are highly useful transformations in modern organic synthesis, since they provide a straight-forward approach to the strained cyclobutane ring system. In addition to that, up to four new stereogenic centers can be formed during the reaction. Various subsequent synthetic manipulations of the resulting cyclobutane give access to a multitude of products, making the [2 + 2]-photocycloaddition a highly versatile tool (**Scheme 4**).[15]



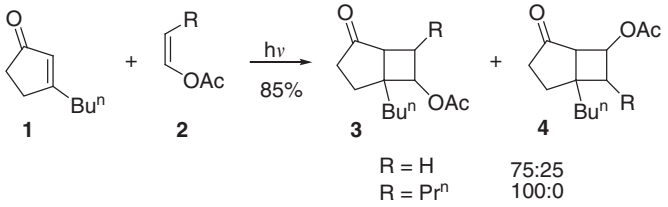
Scheme 4

Several variants of nonheteroatom [2 + 2]-photocycloadditions are known: the addition of one alkene to another (ene–ene), the addition of Michael systems or one Michael system to an alkene (ene–enone, enone–enone), the addition of a carbonyl compound to an alkene (Paternò–Büchi), and the addition of an alkene to an aromatic system (arene–alkene). Concerning [2 + 2]-photocycloadditions, this chapter emphazises ene–enone, ene–ene and enone–enone reactions.

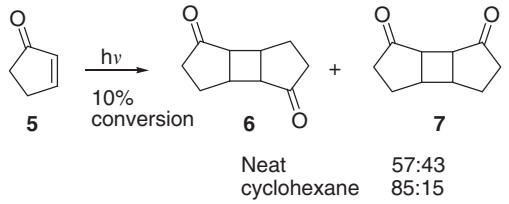
5.04.2.1 Ene–Enone [2 + 2]-Photocycloaddition

5.04.2.1.1 Intermolecular Processes

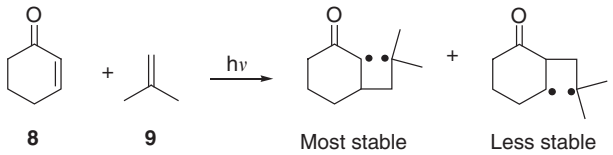
Ene–enone [2 + 2]-cycloadditions are the most widely known type of photocycloaddition forming cyclobutane ring systems. Therefore, extensive research was carried out considering chemo-, regio-, as well as stereoselectivity and application possibilities.[16] It was found that the regioselectivity is affected by steric interactions[17,18] (equation 1), solvent polarity[19,20] (equation 2), and diradical intermediate stability (equation 3).[21]



(1)

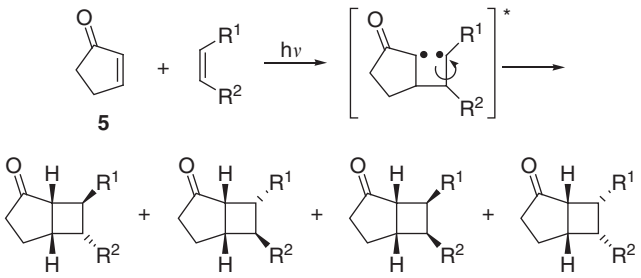


(2)



(3)

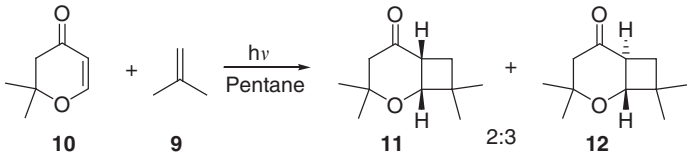
Prediction of the stereochemistry is of equal importance, since up to four new stereogenic centers can be formed of the cycloaddition. In numerous reactions, however, a sufficient control of stereoselectivity has proven to be quite difficult. For instance, the addition of acyclic alkenes to cyclopentenone **5** produces all four possible *cis*-fused bicyclic photoadducts as a result of rotational freedom during the long-lived 1,4-diradicals (equation 4).[22,23]



(4)

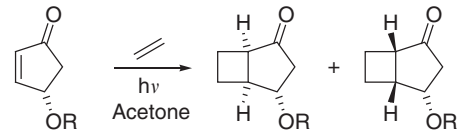
With unsaturated five-membered or smaller ring substrates, *cis-trans* isomerization of this reaction partner is inhibited. Larger rings, however, also show loss of cycloalkene stereochemistry. Cyclic enones with ring sizes of five members or less always retain *cis* configuration at the corresponding stereogenic centers of the resulting cyclobutane[18] (equation 4), whereas cyclohexenones often produce significant amounts of *trans*-fused photoadducts **12** (equation 5, no yield given).[24]

This is due to the fact that cyclohexenone triplets are considerably twisted, thus allowing sequential bond formation on opposite faces of the ring.[25]



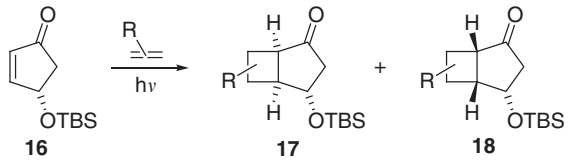
10 **9** **11** **12** (5)

As expected, preexisting stereogenic centers on either the alkene or the enone can also influence the stereochemistry of the resulting products by steric or stereoelectronic interactions. For example, cyclopentenones **13** and **16** bearing a stereogenic center at C4 lead to an excess of the corresponding *anti* products after irradiation (equations 6 and 7).[26]



13 **14** **15** (6)

a R = H	49%	70:30
b R = Ac	43%	63:37
c R = TBS	50%	68:32
d R = *t*BuCO	49%	60:40
e R = MOM	48%	70:30

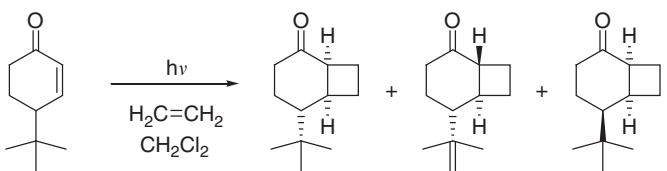


16 **17** **18**

a	45% (60:40)
b	41% (53:47)
c	41% (54:46)
d	40% (73:27)

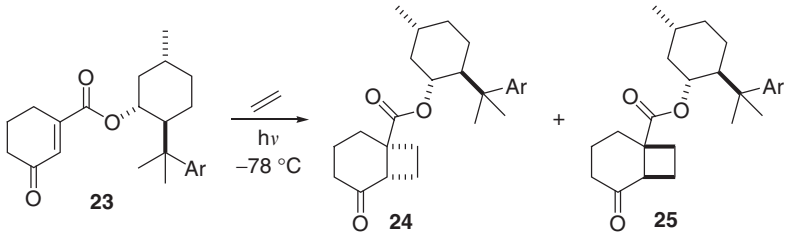
(7)

Chiral cyclohexenone **19** exhibits a similar behavior on irradiation, thus influencing the diastereomeric excess of the corresponding *cis* and *anti* products **20**–**22** (equation 8).[27] The application of stereogenic centers tethered to the cyclohexenone ring (e.g., in **23**) also led to a substantial increase in diastereoselectivity (equation 9).[28]



19 **20** **21** **22** (8)

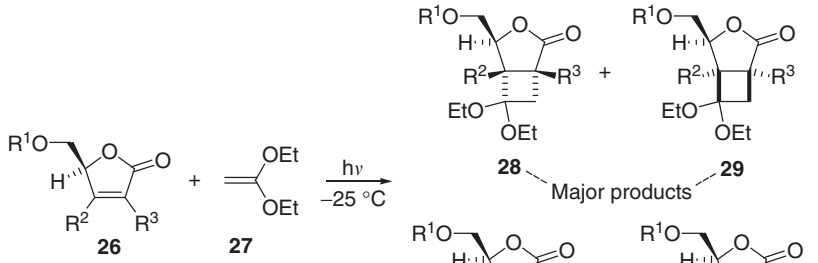
61 : 24 : 15



a Ar = Ph-H 84%, 40% *de*
b Ar = *p*-Ph-*i*Pr 96%, 24% *de*
c Ar = *p*-Ph-OMe 95%, 50% *de*
d Ar = *p*-Ph-NO_2 94%, 88% *de*

(9)

Solvent variation can also influence the stereochemistry of the photoadducts. Heterocyclic enones such as furanone show similar behavior regarding regio- and stereochemistry. Therefore, stereogenic centers at the furanone ring of **26** can be utilized to influence the resulting product distributions (equation 10).[29]

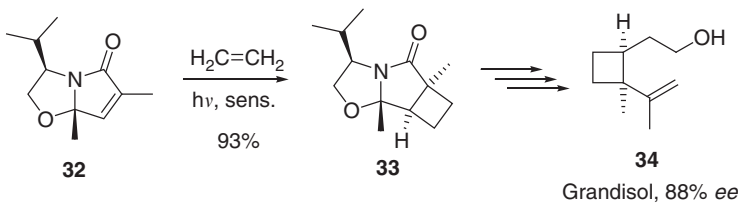


a R^1 = Ac, R^2 = H, R^3 = H; 75%
b R^1 = COAd, R^2 = H, R^3 = H; 77%
c R^1 = CO^{t}Bu, R^2 = H, R^3 = H; 61%
d R^1 = CO^{t}Bu, R^2 = H, R^3 = CH_3; 87%
e R^1 = CO^{t}Bu, R^2 = CH_3, R^3 = H; 85%

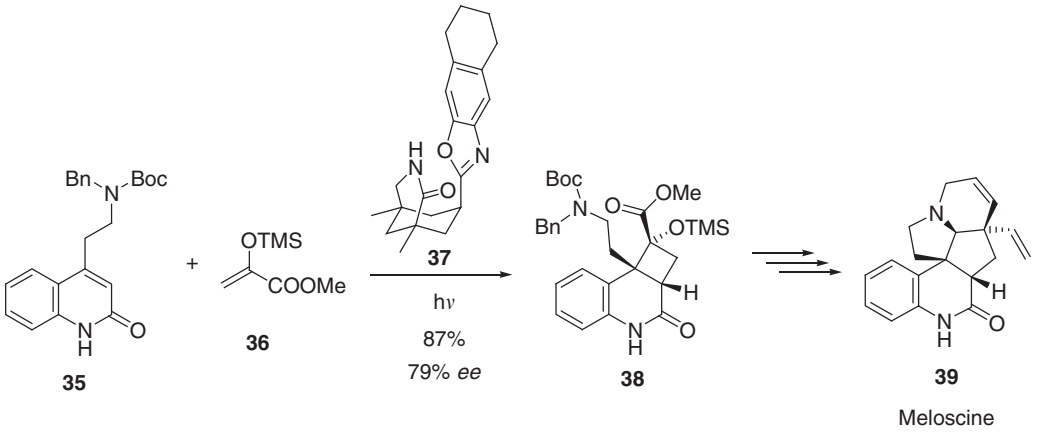
	28	29	30	31
a	47	31	15	7
b	50	21	22	7
c	50	22	21	7
d	60	20	17	3
e	63	31	4	2

(10)

The reaction of 2(*5 H*)-furanone with ethylene was investigated by computational methods, thus developing reaction energy profiles for the corresponding excited states, biradical intermediates, and products.[30] Recently, the addition of pyrimidines to cyclopentene was also the subject of computational research.[31] Although there are various examples of [2 + 2]-photocycloadditions with excellent regio- and (relative) diastereoselectivities, absolute control of stereochemistry still remains difficult despite the advances in the field of asymmetric thermal syntheses. Only few enantioselective ene–enone [2 + 2]-photocycloadditions are known. The synthesis of grandisol (**34**) from a bicyclic lactam **32** (Scheme 5)[32] and the synthesis of meloscine (**39**) from the quinolone **35** (Scheme 6)[33] using a chiral complexing agent **37** are examples of highly selective asymmetric [2 + 2]-photocycloadditions. The first example involves intramolecular chirality transfer using a 'chiral pool' building block derived from valine as auxiliary. The second example utilizes a chiral sensitizer that transfers the excitation energy to the prochiral substrate in an intermediate hydrogen-bonded host–guest complex.

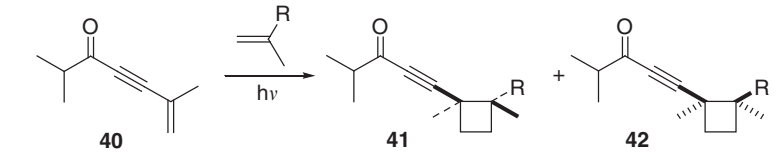


Scheme 5



Scheme 6

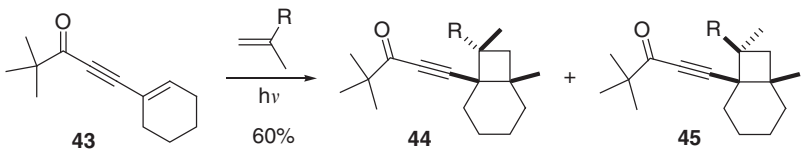
Since [2 + 2] ene–enone photocycloadditions are effective processes with easily available substrates, numerous synthetic applications have been developed for this type of reaction.[34,35] For example, the addition of enynones **40** or **43** to alkenes (equations 11 and 12)[36] proceed with perfect chemoselectivity as the alkyne is completely passive during the cycloaddition. The reaction of a *m*eta di-2-pyrone **46** with ethylene di(methylacrylates) **47** shows sequential inter- and intramolecular cycloadditions, resulting in macrocyclic compounds **48** and **49** with two cyclobutane rings (equation 13)[37] The formation of cyclobutanes was also utilized in the syntheses of natural products like sterpurene (**52**, Scheme 7),[38] bourbonene (**56**, Scheme 8),[39] and alphanamol (**60**, Scheme 9).[40]



a R = —CN 62% (9:1)

b R = 81% (100:0)

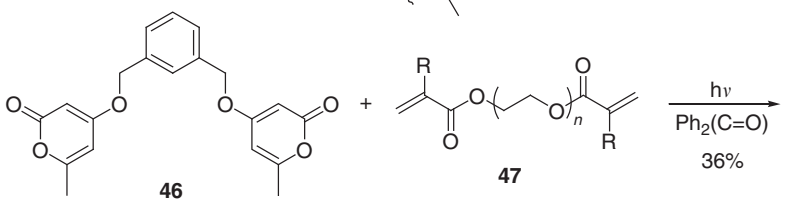
(11)

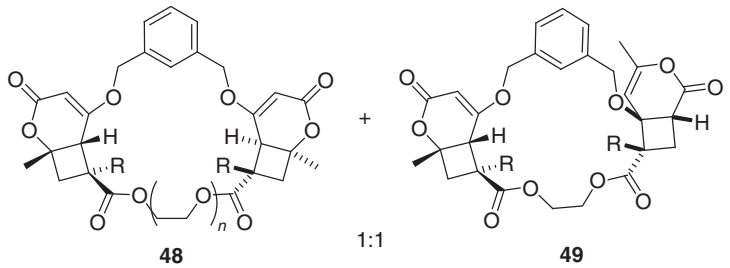


a R = —CN 17:3

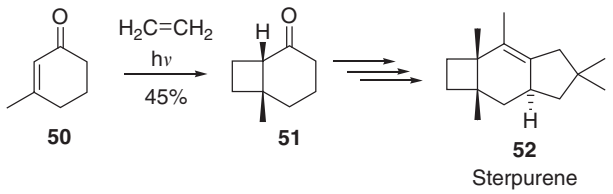
b R = 100:0

(12)

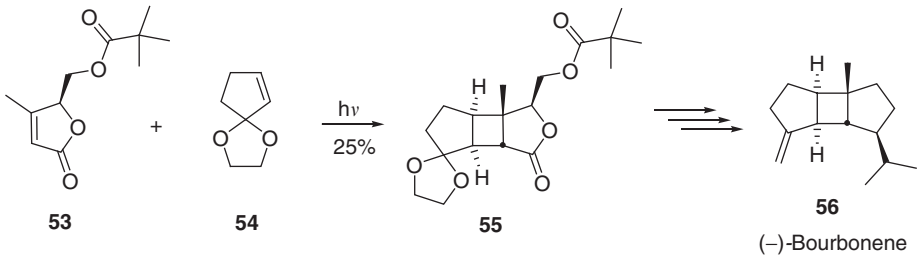




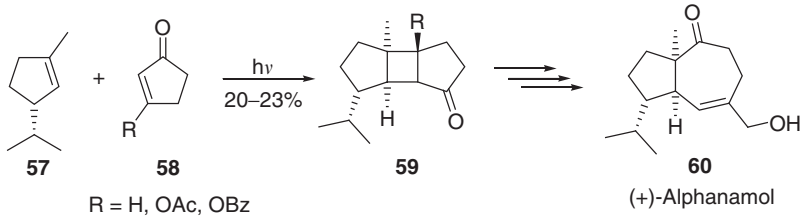
(13)



Scheme 7

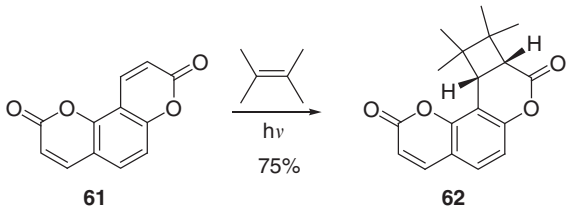


Scheme 8



Scheme 9

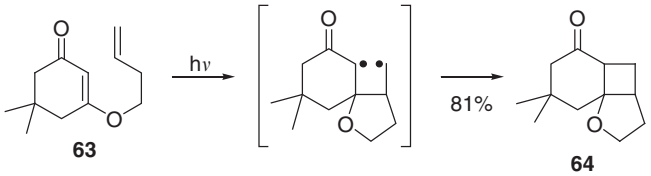
Additionally, synthetic applications can also make use of the locoselective addition of alkenes to one out of two enone groups in the same molecule, for example, the selective addition of 2,3-dimethylbut-2-ene to the benzodipyran **61** (equation 14).[41]



(14)

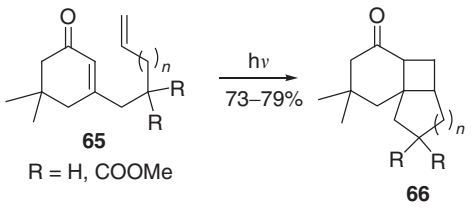
5.04.2.1.2 Intramolecular Processes

Although intermolecular ene–enone [2 + 2]-photocycloadditions are highly useful tools, the low stereoselectivity observed in many reactions limits the possible applications. An easy solution to this problem can be achieved by temporarily incorporating the two reaction sites in the same molecule, often leading to complex polycyclic compounds with high stereoselectivities. The regioselectivity of the intramolecular ene–enone [2 + 2]-photocycloaddition is generally more predictable due to the geometric constraints in the transition states during the ring formation steps. It is apparent that the formation of five-membered rings is favored in the initial attack of the excited-state enone on the ground-state alkene. This observation was termed the 'rule of five.'[42] For example, the cycloaddition of the β-substituted cyclohexenone **63** with a three-atom tether produces exclusively the straight adduct **64** (equation 15).[43]



(15)

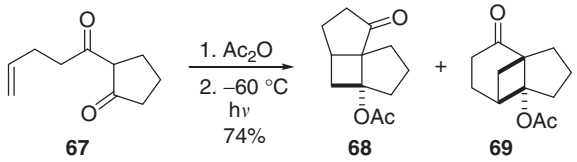
Especially, cyclopentenones and cyclohexenones with linker chains of two or three atoms attached to C-2 or C-3 (**65**) show high regioselectivity. When the reaction sides are tethered with four or more atoms, the straight adducts **66** are formed in most cases albeit with lower regioselectivities (equation 16).[44]



65
R = H, COOMe

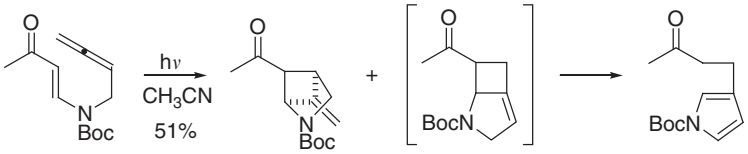
66 (16)

Although a multitude of compounds comply with the 'rule of five' during cycloaddition, there are some exceptions. For example, cyclopentenones with terminal alkene groups (e.g., **67**) sometimes show a mixture of straight (**68**) and crossed adducts (**69**) after irradiation (equation 17).[45] Systems bearing an allene as the alkene component also do not comply with the 'rule of five' (**Schemes 10**, **11** and equation 18).[46–49] The strained products with endocyclic double bond are unstable and rearrange to the heteroaromatic products **72** and **75**, respectively. In some cases, the formation of the straight or the crossed adduct is dependent on the tether length (**Scheme 12**)[50,51] or specific functional groups (**Scheme 13**).[52]



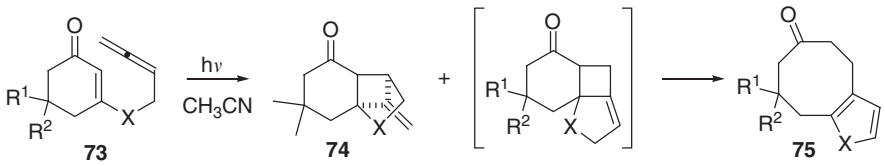
67 **68** **69**

11 : 89 (17)



70 **71** 23:77 **72**

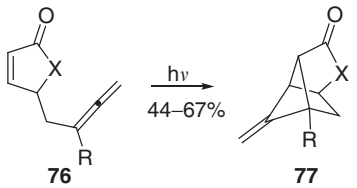
Scheme 10



73 **74** **75**

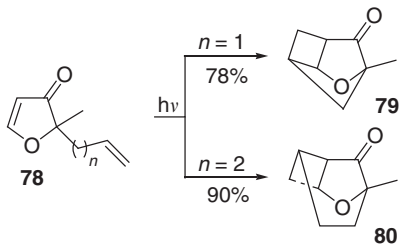
a	$R^1 = R^2 = H$, X = NBoc	87%	20:80
b	$R^1 = R^2 = Me$, X = NBoc	77%	26:74
c	$R^1 = H$, $R^2 = Ph$, X = NBoc	78%	17:83
d	$R^1 = R^2 = Me$, X = O	40%	0:100

Scheme 11

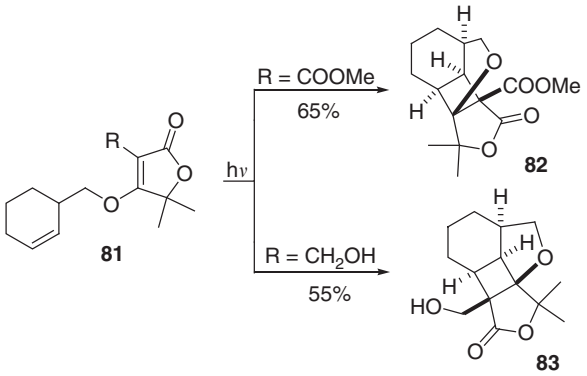


76 **77** (18)

X = NBoc, O
R = H, *n*-Bu

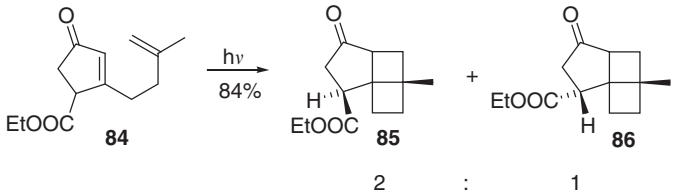


Scheme 12



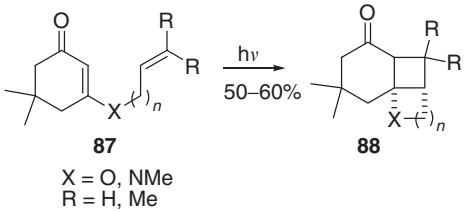
Scheme 13

The preferred formation of five-membered rings in intramolecular cycloadditions is rationalized by the relative orientation of the reaction sites during the initial attack. Unbranched reaction systems usually show 1,5-cyclization, whereas a substituent at C5 can retard the rate of cyclization. However, incorporation of the enone in a five-membered ring reduces the excited triplet twisting, thus altering the cyclization geometry. When both effects are combined as for **84**, 1,6-cyclization becomes predominant (equation 19).[53,54]



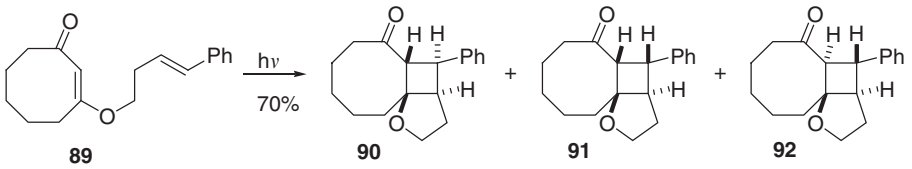
(19)

Similar to that for the regioselectivity, the control of stereochemistry in intramolecular ene–enone [2 + 2]-photocycloaddition is superior compared to intermolecular cycloadditions. The geometric constraints already mentioned before involved in the cyclization often yield to high stereoselectivities. The cyclobutane ring in the photoadducts **88** is *cis*-fused to the linker-chain derived ring in almost all cases (equation 20).[55]

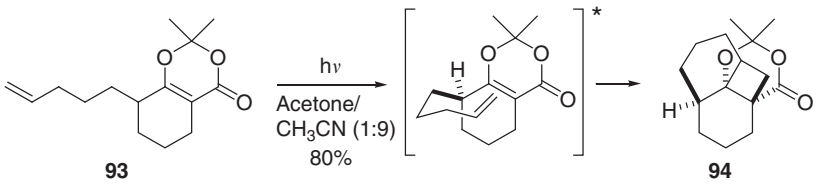


(20)

Exceptions to these trends are rare and result from substrates where either the cycloalkenone is larger than six members (equation 21)[56] or the tethering chain is easily able to stabilize the resulting ring junction (equation 22).[57]

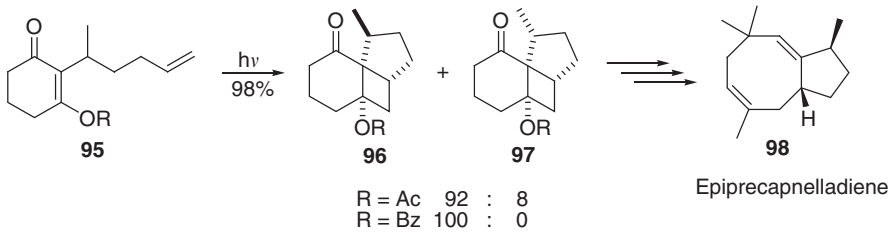


(21)

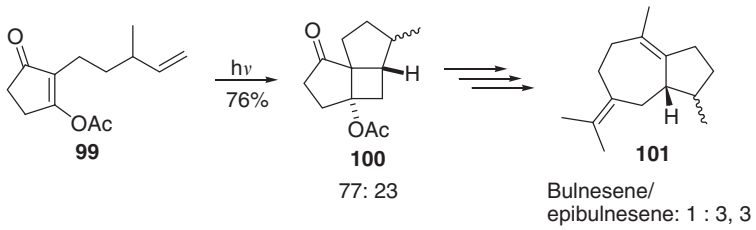


(22)

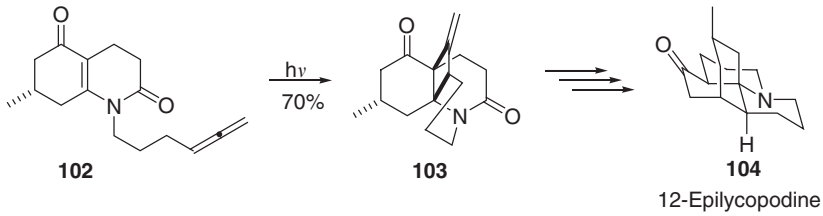
Preexisting stereogenic centers in the starting materials can also influence the stereochemistry in the resulting cycloadducts by steric and stereoelectronic interactions. This was used in the stereoselective synthesis of various natural products like epiprecapnelladiene (**98**, Scheme 14),[58] bulnesene and epibulnesene (**101**, Scheme 15),[59] 12-epilycopodine (**104**, Scheme 16),[60] isocomene (**107**, Scheme 17),[61] punctaporonin C (**111**, Scheme 18),[62] stoechospermol or spatol (**114**, **115**, Scheme 19),[63] and lactiflorin (**118**, Scheme 20).[64]



Scheme 14



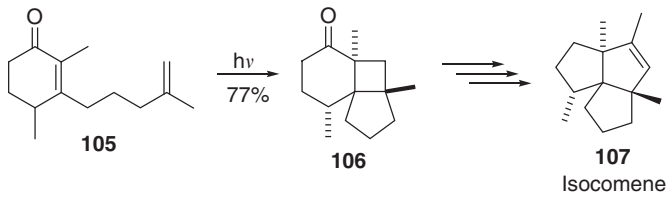
Scheme 15



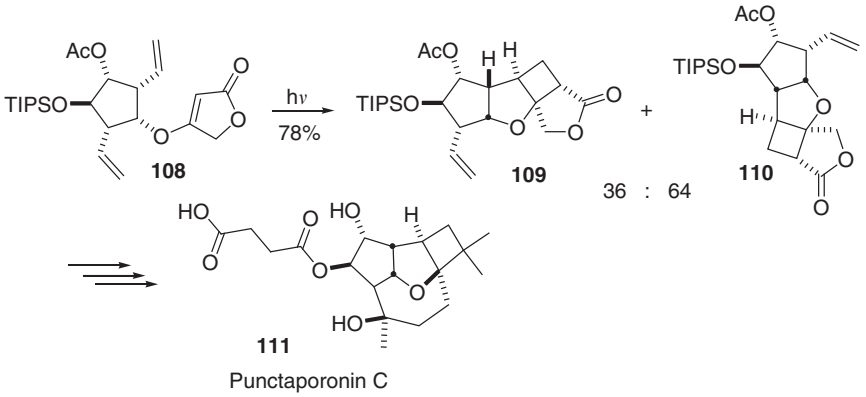
Scheme 16

Chiral substrates have also been used in photocycloadditions for the stereoselective syntheses of hydroxymethylated β-amino acids **121** (Scheme 21)[65] and diterpenoid compounds of the briarellin and asbestinin family **124** (Scheme 22).[52]

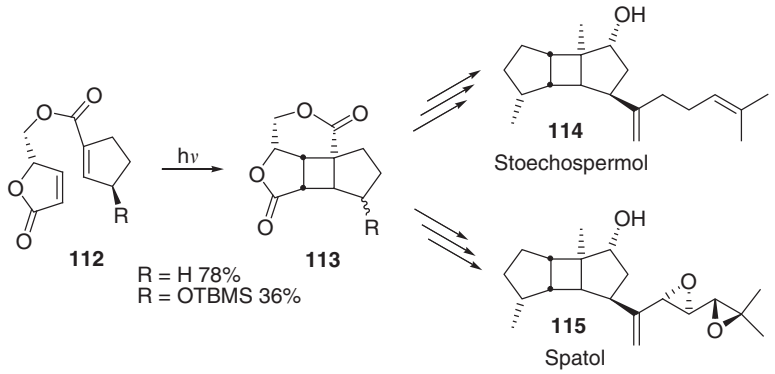
Although various dia- and enantioselective ene–enone cycloadditions have been accomplished with chiral photosubstrates, absolute control of stereochemistry with achiral photosubstrates is still a difficult task to achive. Chiral lactams based on the



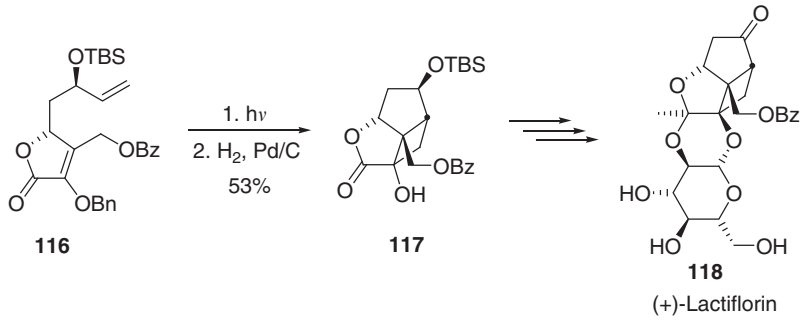
Scheme 17



Scheme 18

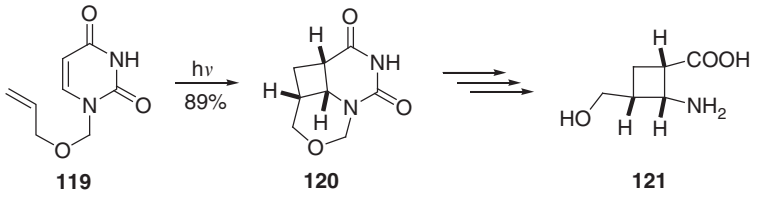


Scheme 19

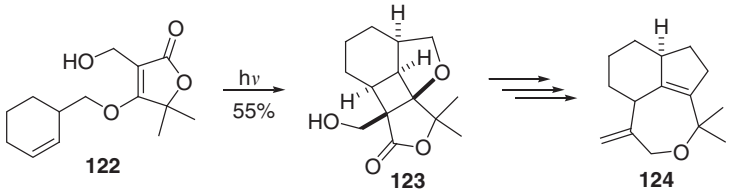


Scheme 20

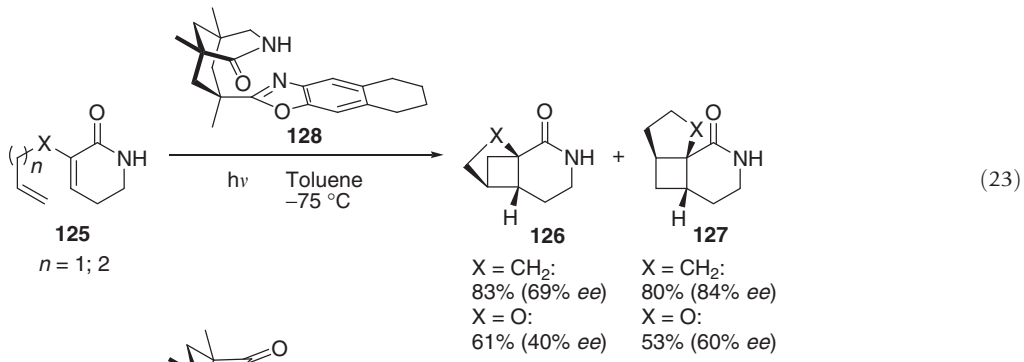
Kemp's triacid as light-absorbing and sensitizing catalysts, which interact with the photosubstrate via hydrogen bonding, have been successfully employed, yielding good to excellent enantiomeric excesses using the constitutional isomers of the catalyst **128** or **129** (equations 23 and 24).[66,67] Chiral Lewis-acids like oxazaborolidines **132** have also yielded moderate enantioselectivities as chiral hosts with catalytic properties (equations 25 and 26).[68]



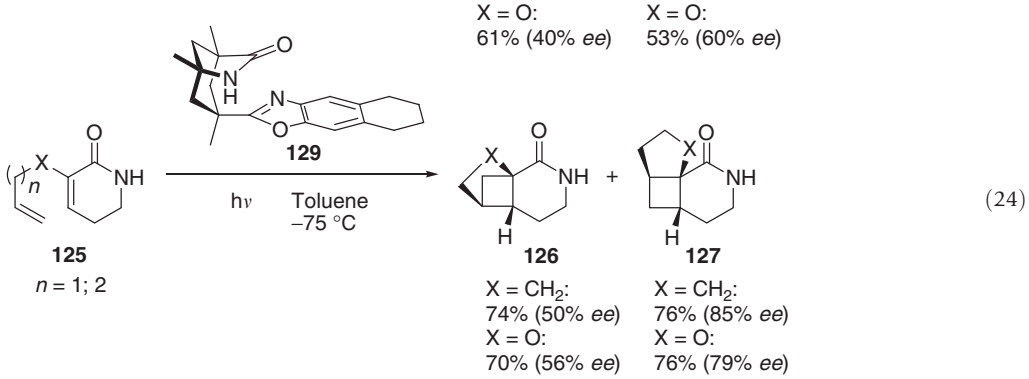
Scheme 21



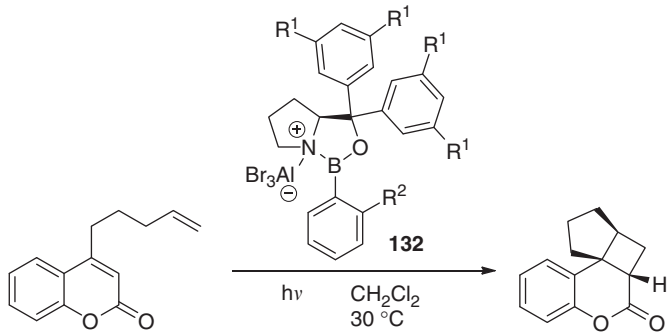
Scheme 22



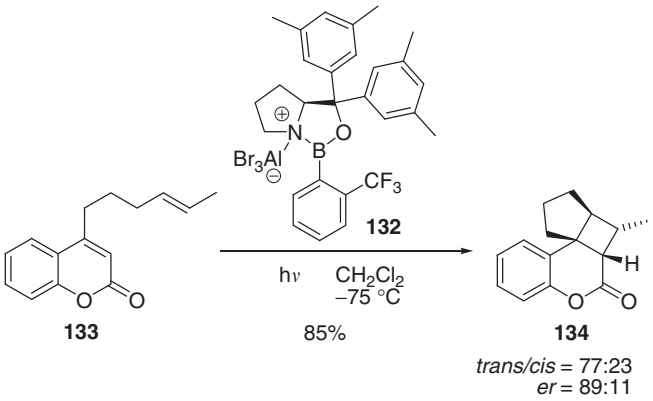
(23)



(24)



(25)

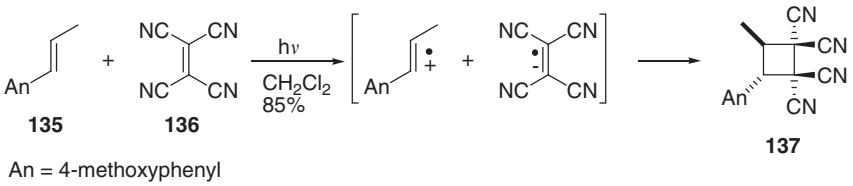


(26)

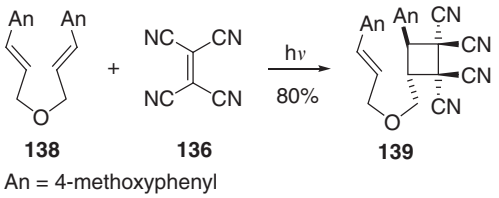
5.04.2.2 Ene–Ene [2 + 2]-Photocycloaddition

5.04.2.2.1 Intermolecular Processes

Compared to ene–enone photocycloadditions, there is a limited number of ene–ene reaction systems which are not tethered or constrained in close proximity. Since the short-lived singlet states[69] are predominant in most excited alkenes, the chance of productive collision is limited. An exception are cycloadditions between electron-rich and -poor alkenes such as methoxyphenyl-substituted alkenes **135** and tetracyanoethylene (**136**), indicating intermediate charge-transfer (equations 27 and 28).[70]

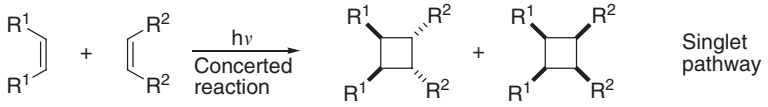


(27)

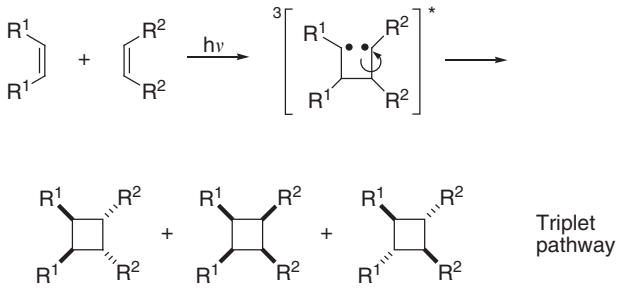


(28)

These matched pairs also benefit from ground state attraction, which leads to a preorientation enhancing the alkene orbital overlap and improving the reaction efficiency. As computational results indicate, photocycloaddition between two propene molecules favors a head-to-tail approach and a concerted reaction pathway via conical intersections.[71] Accordingly, cycloadditions between alkenes with electron-withdrawing groups should favor the formation of the corresponding *trans*-1,3-disubstituted cyclobutane. Although the singlet state is predominant in excited alkene reactions (equation 29), [2 + 2]-photocycloadditons including a triplet alkene excited state are known. Since the lifetime of the 1,4-biradical triplet intermediate formed after the initial attack allows bond rotation, a lower stereoselectivity is expected (equation 30).

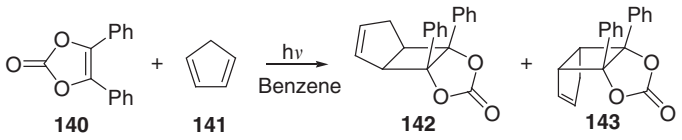


(29)



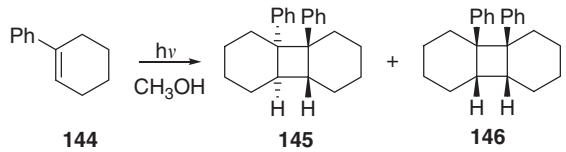
(30)

Therefore, stereochemical analysis of the cycloaddition products can provide direct information on the predominant electronic pathway in the corresponding cycloaddition. Since direct excitation of ene–ene reaction systems often does not lead to effective cycloadditions, triplet sensitizers have been employed in an attempt to facilitate those reactions through triplet sensitization. Although sensitizers like benzil or acetophenone indeed enhanced [2 + 2]-photocycloaddition processes, their application resulted in altered product ratios compared to the direct irradiation (equations 31 and 32, no yields given).[72–75]



Direct excitation	4	:	1
benzil sens.	1	:	9

(31)

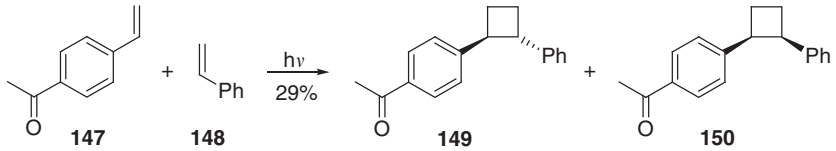


Direct excitation	3	:	1
p-OMe-acetophenone sens.	4	:	1

(32)

As triplet-sensitized photoreactions proceed via triplet pathways and long-lived excited states as well as intermediates, product formation often shows thermodynamic control. Singlet cycloadditions proceed from the transition state featuring the greatest frontier orbital overlap, thus affecting the reaction geometry by kinetic control. The product distributions also indicate that π-stacking plays an important role during the reaction by stabilizing the transition states. In addition to that, the product quantum yields suggest the formation of a loose exciplex in both reaction pathways.

In contrast to the computational results obtained on the dimerization of propene, arylsubstituted alkenes like 1-phenylcyclohexene **144** (equation 32) or styrene **148** (equation 33) preferentially give the corresponding head-to-head products.

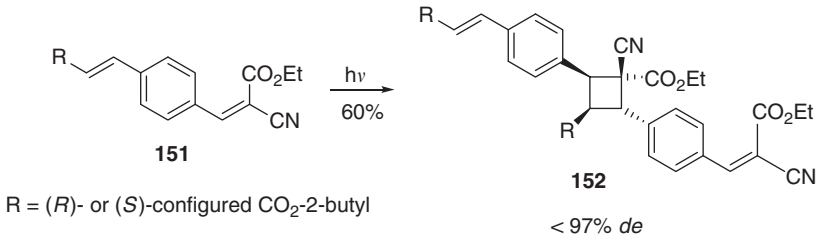


	11	:	1

(33)

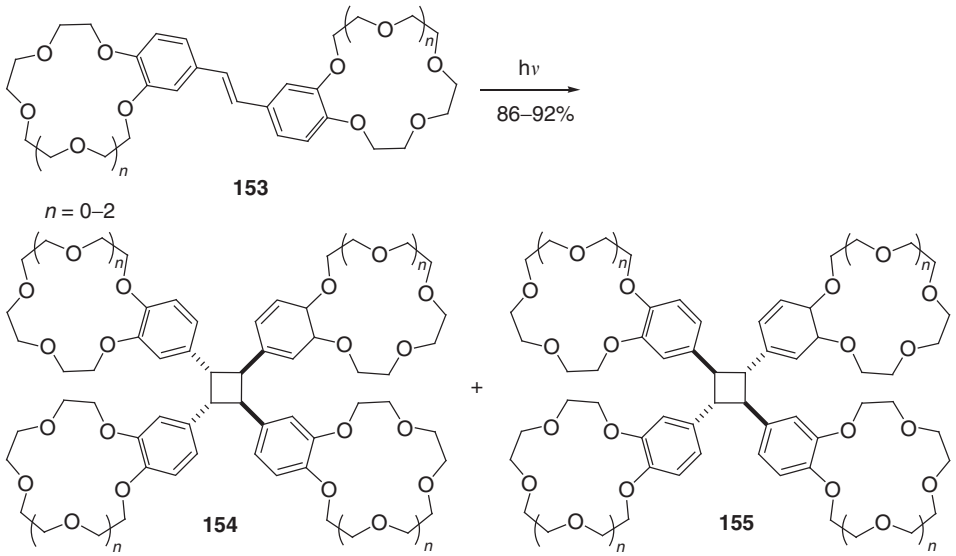
In both cases, preferentially the *trans*-1,2-products are formed. This selectivity can be rationalized for the triplet pathway as a result from steric interactions at the stage of the 1,4-triplet biradical intermediates.

As already discussed for ene–enone reactions, complete control of ene–ene photocycloaddition stereochemistry is a difficult task to achieve. So far, no reports of catalysts or complexing agents which were successfully employed to enhance enantioselectivities are known. Preexisting stereogenic centers on the reaction substrates (e.g., in **151**), however, are well capable of directing the product stereochemistry (equation 34).[76]

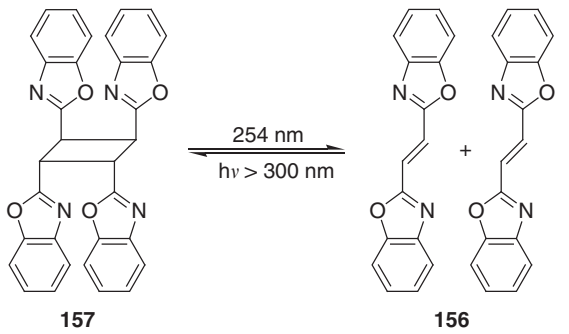


(34)

Useful applications of intermolecular ene–ene photocycloadditions are not as common as for ene–enone reactions, but still exhibit interesting possibilities. One example is the photodimerization of bis(crown)stilbenes **153** to yield unusual bis-sandwich complexes **154** and **155** (equation 35).[77] The reversible dimerization of 1,2-bis-benzoxazol-2-yl-ethene (**156**), forming a rewritable optical data storage material medium **157**, is another interesting example of ene–ene photocycloadditions (equation 36).[78]



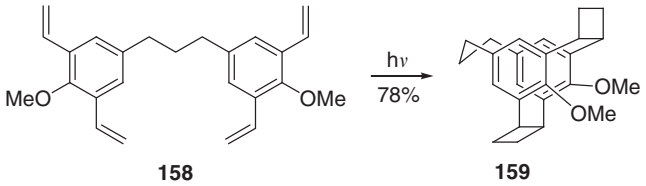
(35)



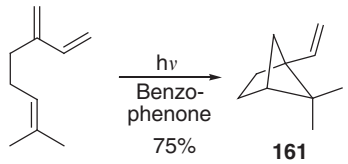
(36)

5.04.2.2.2 Intramolecular Processes

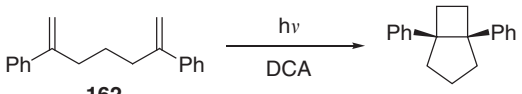
Compared to their intermolecular versions, intramolecular ene–ene photocycloadditions are applied more frequently. Since the two reaction sites are connected by a tether group, simple bond rotation allows productive interactions between the corresponding π-orbitals, thus raising the chance of reaction in the lifetime of the excited states. Also, there is evidence of π-stacking for closely held moieties, therefore improving the orbital interactions between the alkenes.[9] The most prominent examples of the tethering concept are alkyl linked styrenes **158**, which yield cyclophanes **159** on irradiation (equation 37).[79] The application of triplet sensitizers can furthermore enhance the photocycloaddition process (equations 38 and 39).[80,81]



158 159 (37)

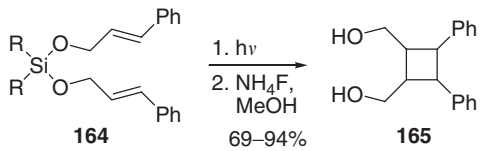


160 161 (38)



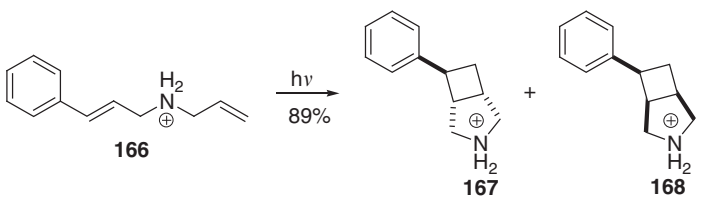
162 163 (39)

Tethered alkenes show significantly higher reactivities and various temporarily usable tethers have been developed in order to facilitate cycloaddition in otherwise ineffective reaction systems. In this regard, the silyloxy tethers in **164** have been proven to be quite useful, giving rise to cyclobutane formation in good to excellent yields (equation 40).[82] Alkyl tethers bearing central amine functionalities have also been employed, yielding cycloadditions with high stereoselectivity (equation 41).[83] This concept was successfully applied for the synthesis of natural products like coerulescine (**171**) and horsfiline (**172**, Scheme 23).[84] Facilitated ene–ene reactions have also been observed for palladium-tethered complexes **173** (equation 42),[85] yielding photochromic systems. Platinum- (**175**, equation 43, no yields given)[86] and iridium- (**177**, equation 44)[87] tethered complexes show intramolecular cycloaddition as well, yielding highly symmetric cyclobutane compounds.



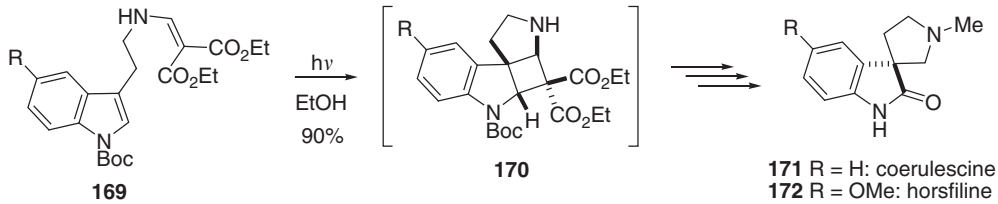
164 **165** (40)

R = Me, Ph, iPr



166 **167** **168** (41)

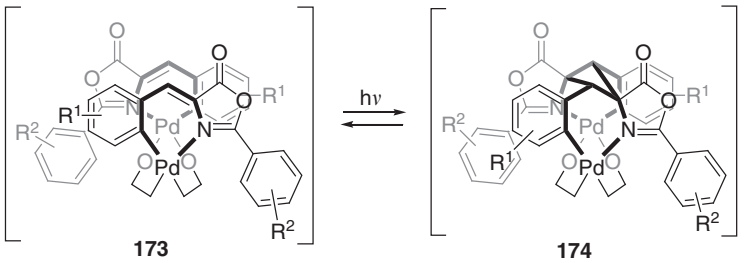
13 : 1



169 **170**

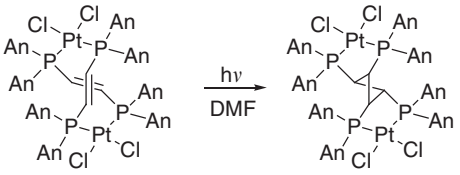
171 R = H: coerulescine
172 R = OMe: horsfiline

Scheme 23



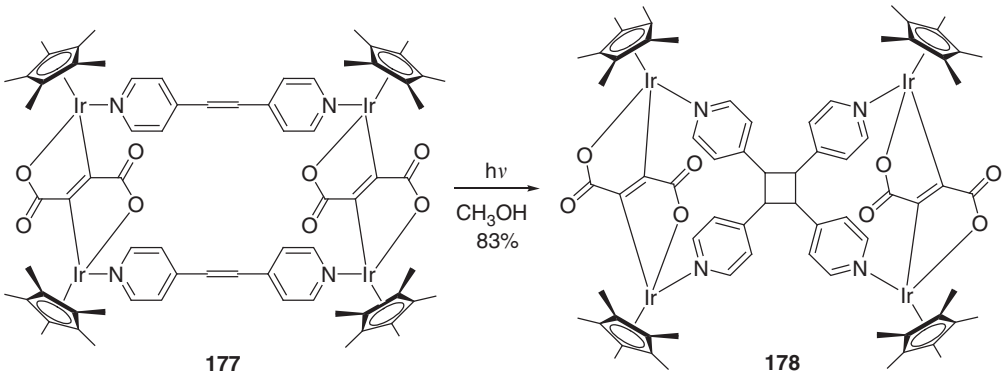
173 **174** (42)

a $R^1 = R^2 = H$
b $R^1 = R^2 = 3\text{-OMe}$
c $R^1 = R^2 = 3,4\text{-(OMe)}_2$
d $R^1 = 4\text{-NO}_2$, $R^2 = 3,4\text{-(OMe)}_2$



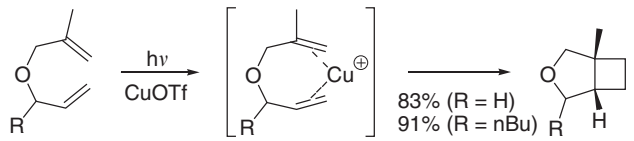
175 **176** (43)

An = 2-methoxyphenyl



177 **178** (44)

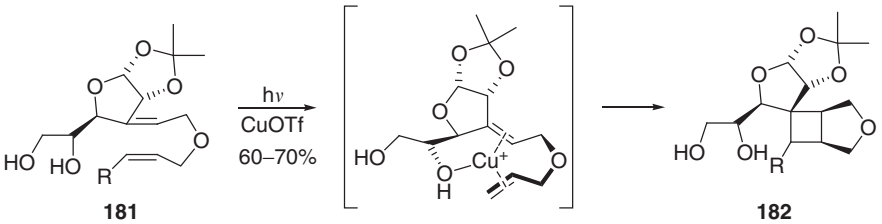
Copper(I)-organic compounds constitute another example for reversible noncovalent tethering reagents. Although there is still some discussion if the copper complex is the chromophore rather than the uncomplexed alkene substrate, copper(I)-compounds are capable of facilitating ene–ene reactions (equation 45).[88]



179 **180** (45)

R = H, n-Bu

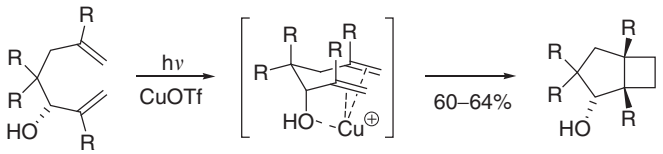
In addition, copper(I)-catalyzed cycloadditions often proceed with high regioselectivity and impressive stereoselectivity due to intramolecular coordination effects (equation 46).[89] The photoreactions of hydroxysubstituted 1,6-heptadienyl compounds are excellent examples regarding these effects (equations 47 and 48),[69,90] providing a synthetic route to grandisol (**34**, Scheme 24) and *β*-panisene (**192**, Scheme 25)[91] among other possible target molecules.



181
R = CH=CHMe, H, Me

182

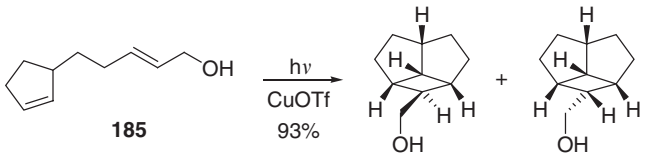
(46)



183
R = H, Me

184

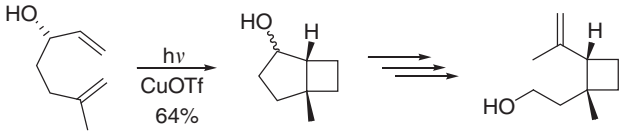
(47)



185

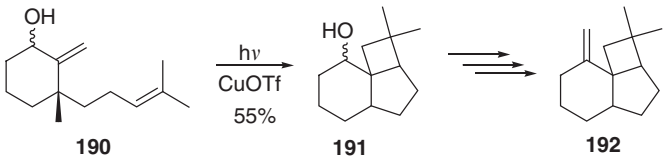
186 : 187
64 : 36

(48)



188 189 34
Grandisol

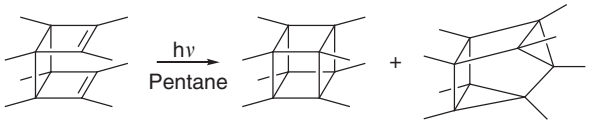
Scheme 24



190 191 192
β-Panisene

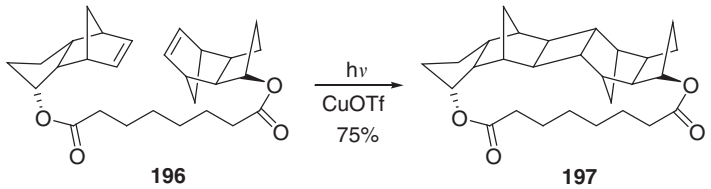
Scheme 25

Since intramolecular ene–ene reactions are capable of forming large multicyclic hydrocarbon cages, they can also be used for assembling structures like methylated cubane **194** (equation 49, no yields given)[92] or norbornene dimer structures **197** (equation 50).[93]



193 194 195
Main product Side product

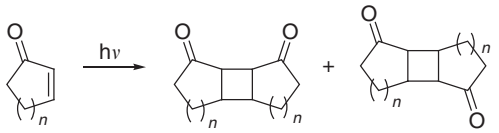
(49)



196 197 (50)

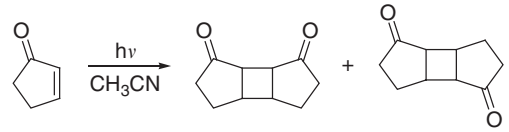
5.04.2.3 Enone–Enone [2 + 2]-Photocycloaddition

In contrast to the variety of examples and synthetic applications of the ene–enone cycloadditions, enone–enone cycloadditions have found little consideration. Until recently, only cyclic enones have shown enone–enone reactions with sufficient efficiency (equation 51).[94,95] Among those reactions, the dimerizations of cyclopentenones and cyclohexenones were intensively investigated.



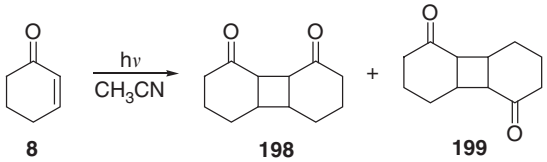
(51)

The regiochemistry of these dimerisations (head to head or head to tail) is strongly affected by solvent polarity (e.g., equation 2) and, in case of nonpolar solvents, also affected by ketone concentrations (equation 52 and 53, product ratios after 10% conversions).[96]



5 6 7 (52)

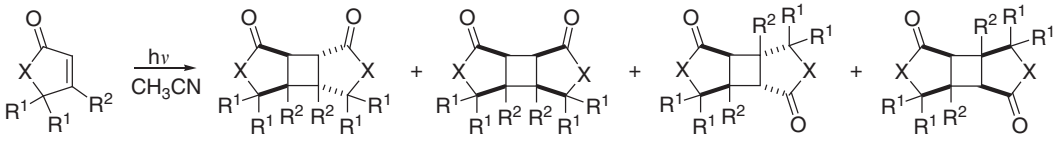
4 : 5



8 198 199 (53)

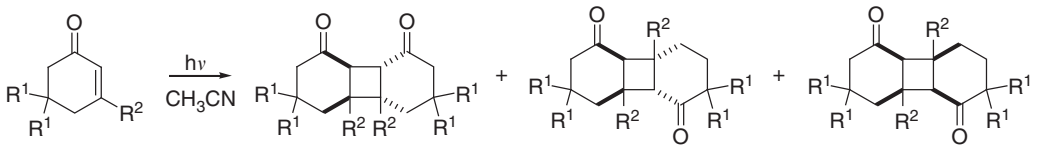
2 : 1

As already described for ene–enone reactions, the stereoselectivity of enone–enone cycloadditions can be influenced by various steric and stereoelectronic interactions between the substrates (equations 54 and 55, no yields reported).[97] Conducting these reactions in zeolites can also alter the ratio between the corresponding photoadducts, which can lead to high diastereomeric excesses.[98,99]



200 201 202 203 204 (54)

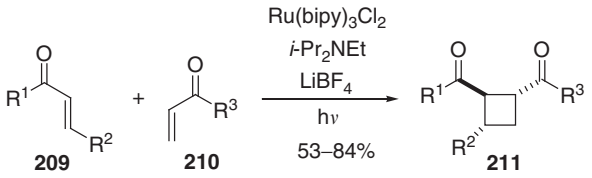
$R^1 = R^2 = H$, X = CH_2	40		60	
$R^1 = H$, $R^2 = Me$, X = CH_2	56	3	31	10
$R^1 = Me$, $R^2 = H$, X = CH_2	20		80	
$R^1 = R^2 = H$, X = O	55		45	
$R^1 = R^2 = Me$, X = O	50		50	



205	206	207	208
$R^1 = R^2 = H$	65	35	
$R^1 = R^2 = Me$	59	23	18
$R^1 = Me, R^2 = H$	45	55	

(55)

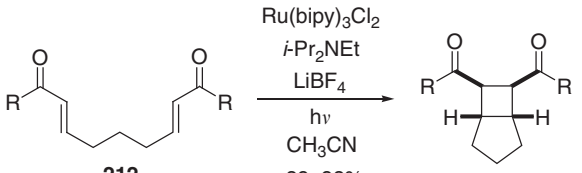
Acyclic enones usually show no enone–enone photocycloaddition reactivity upon direct excitation because of *E*/*Z* isomerization that leads to thermalization of the excitation energy. Recently, however, ruthenium–bispyridin complexes have been successfully employed as photocatalysts in various inter- (equation 56)[100] and intramolecular (equation 57);[101] enone–enone cycloadditions, yielding photoadducts with perfect regio- and high diastereoselectivity via a oxidative quenching cycle (**Scheme 26**).[102]



209 **210** **211**

(56)

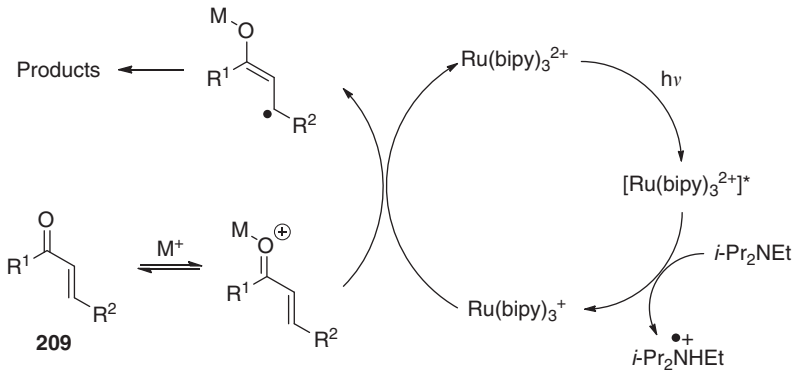
R^1 = Ph, 4-ClPh, 4-MeOPh, 2-furyl, Et
R^2 = Me, *i*-Pr, *t*-Bu, CH_2OBn
R^3 = Me, Et, OMe, SEt



212 **213**

(57)

R = Ph, 4-MeOPh, 4-ClPh, 2-furyl



209

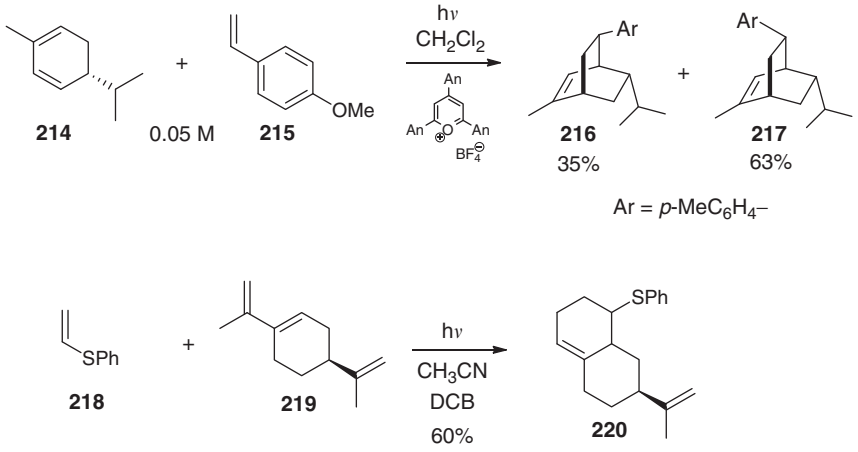
Scheme 26

5.04.3 [4 + 2]-Photocycloaddition

5.04.3.1 Intermolecular Processes

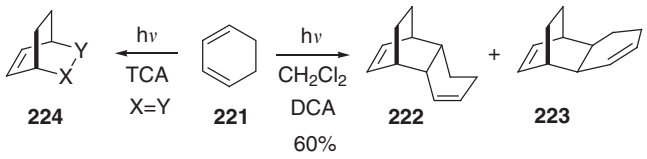
From the viewpoint of orbital symmetry, supra-supra [4 + 2]-cycloadditions (Diels–Alder reactions) are photochemically forbidden and thermally allowed.[103] Thus, the majority of these reactions are conducted either by thermal activation at higher

temperatures or by Broensted/Lewis acid catalysis at room temperature or at lower temperatures.[104] The (thermal) Diels–Alder reactions belong to the most relevant processes for organic synthesis of complex molecules.[105] In general, the majority of these reactions relate to the combination of electron-rich dienes and electron-poor dienophiles. Catalytic variants often increase the acceptor properties of the dienophiles by complexation with Broensted or Lewis acids. An analogous activation mode is the radical cation generation from dienophiles that are converted into superelectrophiles. This has been shown for numerous substrates using thermal one-electron oxidants (e.g., aminium radical cations).[106] Alternatively, PET can be used for generation of radical ions, albeit photochemical processes can also lead to competing [2 + 2]-cycloadditions. A good example for this interplay is the reaction of phellandrene (**214**) and 4-methoxystyrene **215**.[107] The reaction of these substrates in the presence of pyrylium salts as electron transfer catalysts leads to intermolecular [4 + 2] (**216**, **217**) as well as [2 + 2] cycloadducts (Scheme 27). At low substrate concentrations, the formation of the [4 + 2] product prevails with appreciable amounts of homodimers from diene and styrene. At higher concentrations, homodimers and [2 + 2] cycloadducts are formed in larger amounts. The results indicate that in both cases the substrates can be oxidized by the excited sensitizer to the corresponding radical cations.



Scheme 27

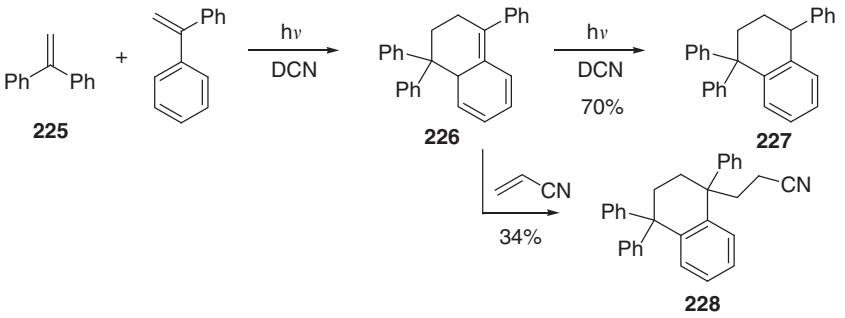
A key step in the synthesis of the natural sesquiterpene substrate *β*-selinene is the phenylvinyl sulfide (**218**) photocycloaddition to the limonene-derivative **219** catalyzed by the photosensitizer 1,4-dicyanobenzene (DCB) in 60% yield.[108] The photodimerization of 1,3-cyclohexadiene (**221**) is another exceedingly well studied process. As a typical photocatalyst, 9,10-dicyanoanthracene (DCA) was used and a 4:1 *endo*/*exo*-mixture of dimers **222**, **223** was isolated in a total yield of 60%.[109] In the presence of electron-rich dienophiles X=Y, the 1,3-cyclohexadiene radical cation can be trapped to give bicyclo[2.2.2]octane derivatives **224**, for example, with styrenes or indene as substrates and 2,6,9,10-tetracyanoanthracene (TCA) as PET-catalysts (Scheme 28).[110]



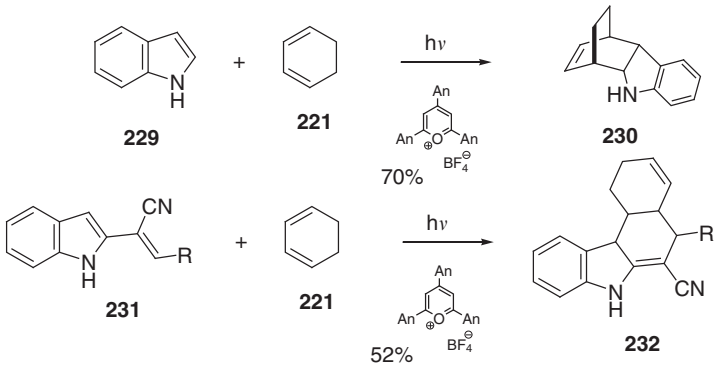
Scheme 28

Better control of chemoselectivity can be achieved by controlled one-electron oxidation of the dienophile. Careful evaluation of the correct sensitizer for rapid PET is thus necessary.[111] Besides organic sensitizers, covering an impressive range of excited state redox potentials, transitions metal complexes have been used for decades and were re-discovered in recent years especially in context with stereoselective photoredox catalysis.[112] Diene and dienophile can also be part of a single substrate molecule and the photochemical Diels–Alder reaction leads a homodimerization. This is analogous to the dimerization of isoprene as the archetypical thermal [4 + 2] homodimerization. 1,1-Diphenylethylene (**225**) is a PET-active substrate and sensitization by 1,4-dicyanonaphthalene (DCN) as PET catalyst leads to a nonaromatic product that isomerized to the tetrahydronaphthalene **227** or is trapped by enophiles, for example, acrylonitrile (Scheme 29).[113]

Using electron-rich dienophiles that can be easily oxidized by PET, the cycloaddition sequence can be reversed, i.e., the dienophile radical cation traps the diene. For indole and 1,3-cyclohexadiene (and other 1,3-dienes), this process leads to a tetracyclic dihydroindole derivative in high yields and with high *endo* selectivity. In this case, pyrylium salts were applied as PET catalysts.[114] When 2-vinylindoles were applied in the presence of 1,3-cyclohexadiene, the role of reagents is inverted and the acceptor diene is trapped by the donor cyclohexadiene (Scheme 30).[115]

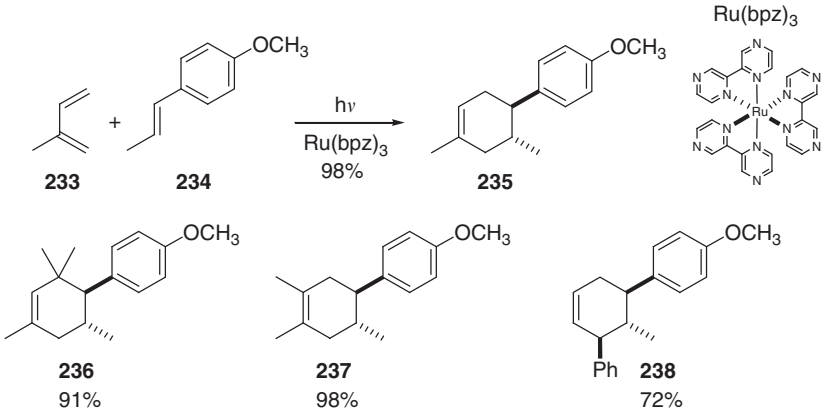


Scheme 29



Scheme 30

Acyclic reaction partners can also be activated for photochemical Diels–Alder reactions by means of PET catalysis. Analogous to the [2 + 2] PET-catalysis,[102] the [4 + 2] cycloaddition of isoprene (**233**) to a styrene derivative **234** is efficiently catalyzed by a ruthenium tris(bipyrazyl) PET sensitizer (equation 58).[116]



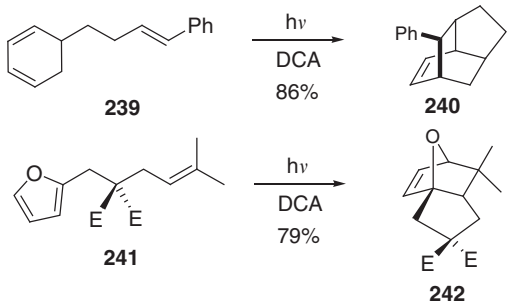
(58)

The reaction was subsequently expanded to radical anion hetero-Diels–Alder reactions[117] and evaluated on a theoretical basis.[118] As a sacrificial electron acceptor, oxygen was used in the optimized version instead of methyl viologen and less than 1 mol% of the PET catalyst was sufficient to convert a number of diene/alkene combinations into Diels–Alder products.

5.04.3.2 Intramolecular Processes

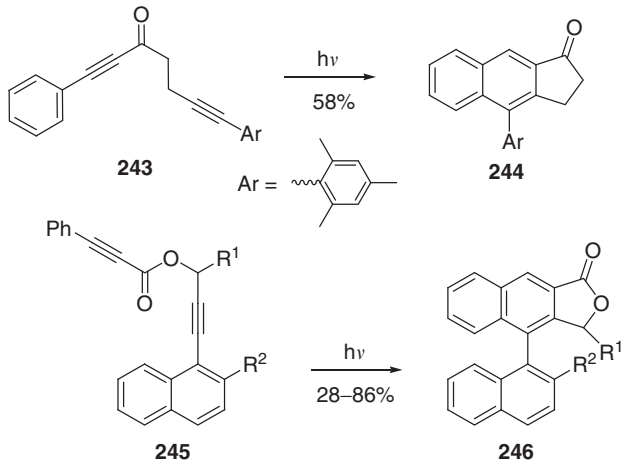
Transformation of the concepts for the intermolecular [4 + 2] photocycloaddition to substrates with tethered dienes and dienophiles leads to intramolecular photochemical Diels–Alder reactions, for example, the PET-DCA sensitized reaction of the cyclohexadiene/styrene pair[119] or the furan/alkene pair (**Scheme 31**).[120]

Intramolecular versions allow also for the generation of highly strained intermediates than can be stabilized by subsequent hydrogen transfer. The intramolecular photo-dehydro Diels–Alder (PDDA) reaction serves as a prominent example



Scheme 31

(Scheme 32).[121] The intramolecular PDDA of propargyl ketone **243** leads to the mesityl-substituted naphthalene **244** after [4 + 2]-photocycloaddition and intramolecular hydrogen transfer.[122] Atropisomeric binaphthyls **246** can also be generated from chiral propargyl esters **245** by direct photolysis.[123]



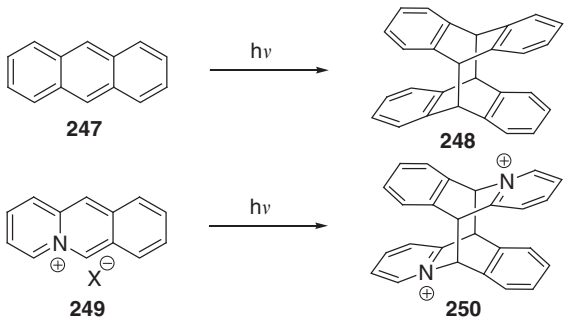
Scheme 32

5.04.4 [4 + 4]-Photocycloadditions

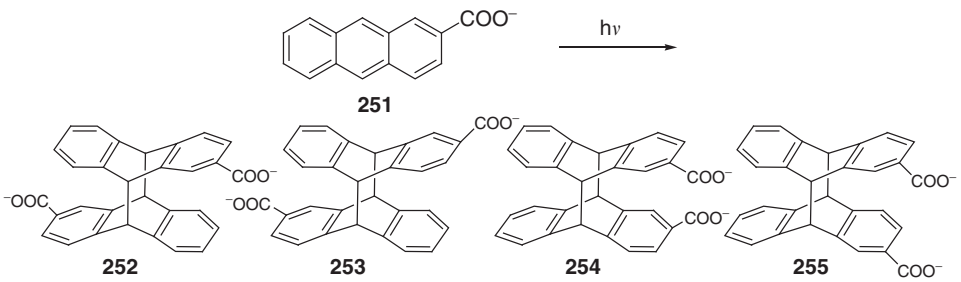
5.04.4.1 Intermolecular Processes

From the viewpoint of orbital symmetry, supra-supra [4 + 4]-cycloadditions are photochemically allowed and thermally forbidden.[103] The archetype of a photochemical [4 + 4]-cycloaddition reaction is the dimerization of anthracene **247**, reported already by J. Fritzsche in 1867.[124] The reaction pathways that originate from the electronic excitation of 1,3-dienes are summarized in numerous reviews.[12] The relevant reactive species in diene photochemistry are the singlet and triplet states (by direct excitation or by triplet sensitization), respectively, as well as radical ions originating from PET steps. After the early experiments that described the formation of a dimer by irradiation of anthracene in solution, this process disappeared from the chemical literature for a considerably long period of time. Only recently, the potential of anthracence photodimerization[125] was rediscovered and several applications of this reversible thermo/photochromic system were developed, for example, for photochemical upconversion[126] or molecular switches.[127] Other useful substrates for photodimerization are acridizinium salts **249** that give rise to the formation of *anti*, *trans*-type adducts (Scheme 33, general processes).[128] The regioselectivity of the reversible photodimerization of substituted acridizinium salts was investigated in solution and under solid-state reaction conditions.[129]

In the context of photochirogenesis, the photocyclodimerization of 2-anthracene carboxylates **251** constitutes highly relevant experiments. Under these conditions, two chiral and two achiral products are formed, the *syn*, *anti* head-to-tail (HT) and *syn*, *anti* head-to-head (HH) diastereoisomers (equation 59). The formation of these compounds is dependent on the reaction conditions, especially under chiral environment conditions; also enantioselectivity for the formation of the chiral photoproducts was obtained, for example, with amino acid derived organocatalysts,[130] in human serum albumin,[131] polysaccharide matrices,[132] with naphthalene-capped cyclodextrins,[133] or in ionic liquids.[134] Recently, also the wavelength dependence of the supramolecular photocyclodimerization in γ-cyclodextrins was observed.[135]

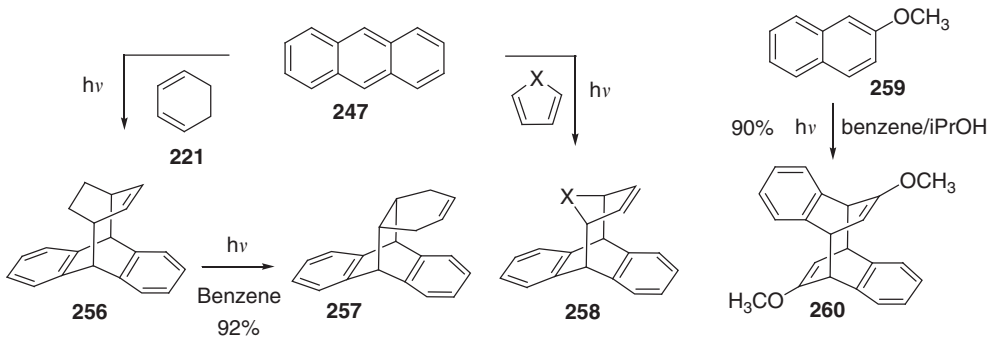


Scheme 33



(59)

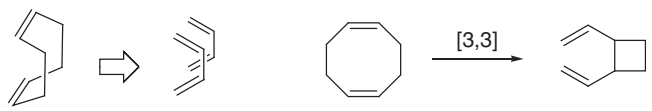
Anthracenes constitute an excellent scaffold for the [4 + 4]-cycloaddition of other dienes such as 1,3-cyclohexadiene or cyclopentadiene.[136] The [4 + 4] cycloadducts of 1,3-cyclohexadiene to anthracene (**256**) or tetracene can be rearranged to the corresponding [4 + 2] cycloadducts **257** by benzene-sensitized photolysis (Scheme 34).[137]



Scheme 34

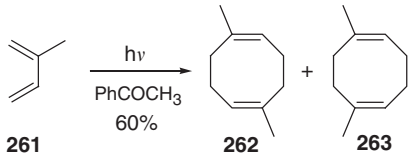
Naphthalene photochemistry is less intensively explored. Irradiation of 2-methoxynaphthalene **259** results in an efficient regioselective photocyclo dimerization.[138] The cycloaddition of naphthalene to other cyclic dienes has also been reported. The corresponding reactions with benzene and benzene derivatives result in very low yields of [4 + 4] products and are synthetically less useful. Benzene derivatives prefer *ortho*- and *meta*-photocycloaddition chemistry. In analogy to substituted anthracences, the enantioselective photocyclodimerization of 3-methoxyl-2-naphthoate in γ-cyclodextrin[139] and other chiral auxiliaries was investigated.[140]

Open-chain and nonaromatic diene compounds are less controllable and more diverse in cycloaddition photochemistry. The photochemistry of the parent diene, 1,3-butadiene, is complex and results in a series of products from unimolecular and bimolecular reactions,[141] among them [2 + 2], [4 + 2], and [4 + 4] photocycloadducts. By use of electron transfer sensitization, the [4 + 4] path can be suppressed.[142] One fascinating property of the [4 + 4]-cycloadducts should be mentioned from the beginning: because the central ring systems is a double Cope system (1,5-cyclooctadiene), Cope-rearrangements can easily be induced either thermally or photochemically to give the formal [2 + 2] cycloadducts (Scheme 35).[143]



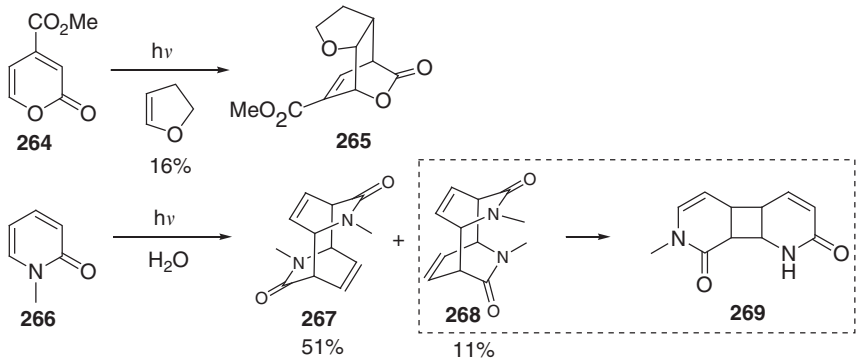
Scheme 35

The simple model nonsymmetric 1,3-diene isoprene **261** gives a mixture of the [2 + 2], [4 + 2], and [4 + 4] cycloadducts (**262**, **263**) in sensitizer-dependent ratios.[144] When acetophenone was used as triplet sensitizer, 60% relative yield of isomeric 1,5-cyclooctadienes were formed (equation 60).



(60)

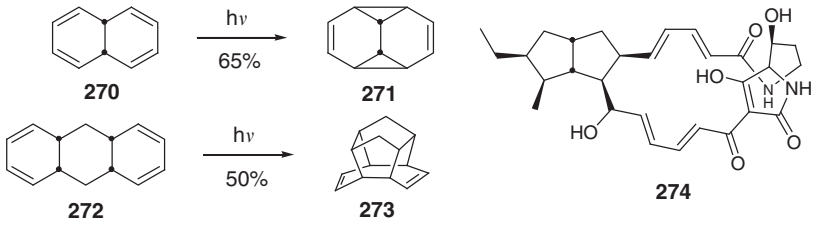
A combination of a conformationally fixed s-*cis* 1,3-diene subunit with activating functional groups, for example, heterocyclic cyclohexadiene analogs, serves as the blueprint for highly active substrates for intermolecular [4 + 4] photocycloadditions. 2-Pyrones are cyclic π^4 components that show [2 + 2] and [4 + 2] photochemical reactivity with alkenes, for example, the reaction of the 2-pyrone-5-carboxylate **264** with 2,3-dihydrofuran yields a mixture of [2 + 2] and the [4 + 2] cycloadduct **265** in 38% and 16% yield, respectively.[144] In contrast to that, 2-pyridones result in efficient formation of the [4 + 4]-cycloaddition products **267** and **268** that can Cope-rearrange to cyclobutanes (e.g., **269**) from the correct stereochemical precursor (**Scheme 36**).[145] 2-Pyridones show [4 + 4] photoreactivity with furan and naphthalene as π^4 reaction partners.[146]



Scheme 36

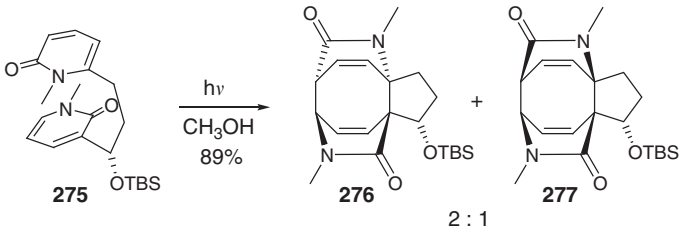
5.04.4.2 Intramolecular Processes

Anthracene can be tethered to other cyclic dienes by alkyl or ethylenglycol chains, for example, in dendrimers with anthracene cores.[147] The photolysis of these dendrimers leads to intramolecular [4 + 4] cycloadduct formation between the π^4 components anthracene and arenes in the side chain, a reaction that is seldomly observed in an intermolecular fashion.[148] A dihydronaphthalene **270** with a saturated central C–C bond constitutes a perfect model compound for the intramolecular $\pi^4 + \pi^4$ interaction and the corresponding tetracyclic product **271** is formed in good yields on irradiation.[149] The analogous hexahydroanthracene **272** results in the cage compound **273** in moderate yields.[150] Another illustrative example was reported for a cyclohexadiene-annulated fullerene.[151] Cyclooctane-based natural products are obvious target molecules for intramolecular [4 + 4] photocycloadditions as shown for alteramide A (**274**) that is quantitatively cyclized by visible light irradiation (**Scheme 37**).[152]



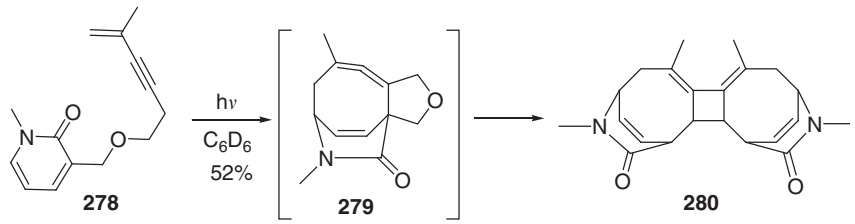
Scheme 37

The intensively studied photochemistry of 2-pyridones is applicable also for intermolecular versions. There are numerous cyclooctene-containing natural compounds that constitute potential targets for [4 + 4]-photocycloadditions. In an approach to the fusicoccin skeleton, a C_3-linked bis-pyridone **275** was used as substrate, leading to cyclopentano-annulated amide-bridged cyclooctadienes **276** and **277**, respectively (equation 61).[153,154]



(61)

The cycloaddition stereochemistry was studied with an additional cyclopentane ring annulated to one of the pyridines,[155] and several other applications in natural product synthesis were reported.[156] Intramolecular enyne/pyridione photocycloadditions lead to highly strained bridged 1,2,5-cyclooctatrienes **279** (cyclic allenes) that are substantially bent and thermal dimerize to give a series of the less strained dimers (e.g., **280**, Scheme 38).[157]



Scheme 38

5.04.5 Conclusions and Outlook

Harvesting solar radiation is one of the central challenges for mankind in the forthcoming decades. Photochemical reactions might be one solution out of many. Shifting the absorption window to the red is therefore crucial. Photochemical redox catalysis is a rediscovered field of activation for many reaction pathways and will probably replace many traditional photochemical routes that produced thermal waste and open new routes to synthetically valuable products of photocycloaddition reactions.

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5.05 The Paternò–Büchi Reaction

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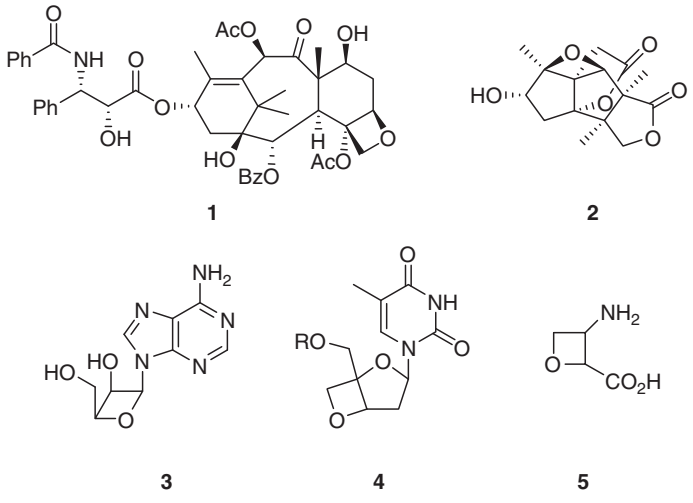
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5.05.1 Introduction

The synthesis of oxetanes can have great importance in the development of compounds with relevant biological properties: an oxetane ring is present in the scaffold of Taxol® (**1**), an important drug used in the treatment of ovarian cancer[1]; merrilactone A (**2**), a sesquiterpene dilactone with neurotrophic activity[2]; and several antiviral oxetanes, such as **3**, **4**, and **5**, have been described in the literature (Scheme 1).[3–5]

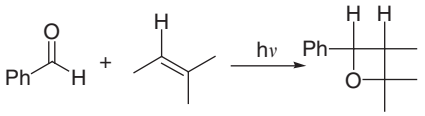


1 **2** **3** **4** **5**

Scheme 1

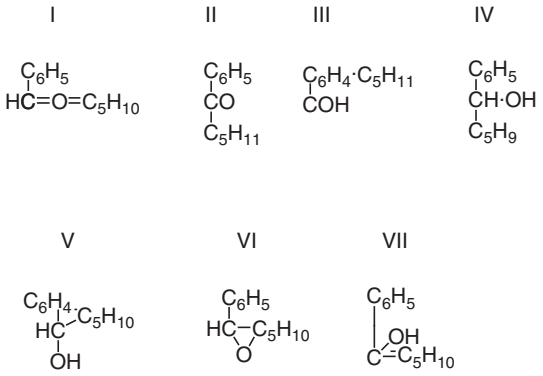
In 1909, Paternò studying the photochemical reaction of benzophenone with amylene showed the formation of the corresponding [2 + 2]cycloadduct (Scheme 2).[6] He started his first article in this field with these words: "In una prima esperienza abbiamo esposto un miscuglio equimolecolare di amilene (gr. 43) e di aldeide benzoica (gr. 67) in un tubo chiuso, dal 5 dicembre 1907 al 20 marzo 1908, cioè per circa tre mesi e mezzo della stagione invernale. Il contenuto del tubo leggermente colorato ed un poco ispessito fu sottoposto alla distillazione frazionata: conteneva ancora dell'amilene e dell'aldeide benzoica inalterata, e distillava da 180° fin sopra 300°, però la porzione maggiore, del peso di gr. 48, passava fra 200° e 250°.[7] (In a first experiment we exposed an equimolecular mixture of amylene (gr. 43) and benzaldehyde (gr. 67) in a sealed tube from 5 December 1907 until 20 March 1908, for almost three months and a half in the winter. The lightly colored and little thickened contents of the tube were fractionally distilled: they still contained amylene and unmodified benzaldehyde and distilled from 180° until over 300°; however, the main fraction, almost gr. 48 in weight, distilled between 200° and 250°)." Some pages later he wrote: "Per spiegare la formazione di un composto di amilene e benzaldeide sei ipotesi sono possibili che conducono a sei diverse

formole di struttura. E cioè: o che amilene bivalente si colleghi all'atomo di ossigeno, formando un composto di ossonio; o che l'amilene unendosi all'idrogeno del gruppo aldeidico formi il radicale amile, o che il radicale amile si formi a spese di un atomo di idrogeno del gruppo fenile al quale resterebbe congiunto, o che l'amilene trasformi l'ossigeno chetonico in ossidrile formando il gruppo amilenico, o che pur formandosi l'ossidrile l'amilene si mette a cavallo fra il carbonio aldeidico ed il fenilico, o ancora che l'ossigeno dell'aldeide si metta a cavallo fra l'amilene ed il benzilidene, o finalmente che l'amilene si unisca per le sue due valenze al carbonio del gruppo aldeidico.

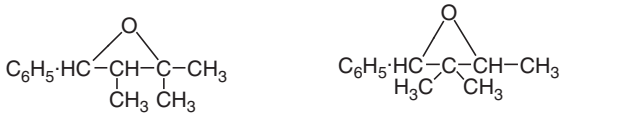


Scheme 2

I composti che ne risultano avrebbero la seguente struttura.



La prima di queste formole non ha alcun carattere di probabilità, avuto riguardo alla formazione ed alle proprietà dell'ossonio, la seconda e la terza dobbono escludersi mancando nel composto le proprietà aldeidiche o chetoniche, la quarta, la quinta e la settima debbono pure escludersi perché non abbiamo potuto riconoscere la presenza di un ossidrile nel composto, cosicché resta come maggiormente probabile la formola sesta. E tenuto presente che il nostro composto si forma dal trimetiletilene esso può corrispondere ad uno dei seguenti schemi:



Ossido di
1. Fenil-2.metil-3,3.dimetil-
trimetilene

Ossido di
1. Fenil-2,2.dimetil-3.metil-
trimetilene

La scelta fra queste due formole è per ora prematura. (To explain the formation of a compound of amylene and benzaldehyde six hypotheses are possible that lead to six different structure formulas. In the order: either the bivalent amylene joins to the oxygen atom to give an oxonium compound; or the amylene, joining to the hydrogen of the aldehydic group, gives the amyl radical, or the amyl radical is obtained at cost of the phenyl group which it is joined to, or the amylene transforms the ketonic oxygen in a hydroxyl giving the amylenic group, or, even if the hydroxyl group is formed, the amylene places itself as a bridge between the aldehydic carbon and phenylic one, or the oxygen atom of the aldehyde places itself as a bridge between the amylene and the benzylidene, or, finally, the amylene joins with its two valences to the carbon atom of the aldehydic group.

The compounds thus obtained should have the following structures.

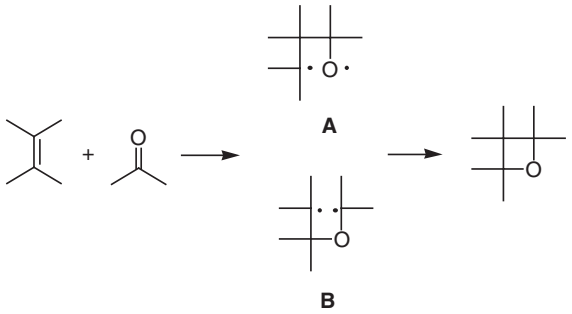
The first of these formulas is not probable, considering the formation and the properties of the oxonium, the second and the third must be excluded considering that the compound has no aldehydic or ketonic properties, the fourth, the fifth, and the seventh formulas must be excluded because we cannot recognize the presence of a hydroxyl group in the compound, then the sixth formula is the most probable one. Furthermore, considering that our compound was obtained from trimethylethylene, it can correspond to one of the following structures.

The choice between these two formulas is not possible now.

Paternò and Chieffi could not distinguish between two possible regioisomers of the oxetane and, obviously, they could not distinguish between all the possible stereoisomers of the product. Only in 1953, Büchi reported the exact identification of the product, showing that this photochemical process could represent an interesting synthetic process.[8]

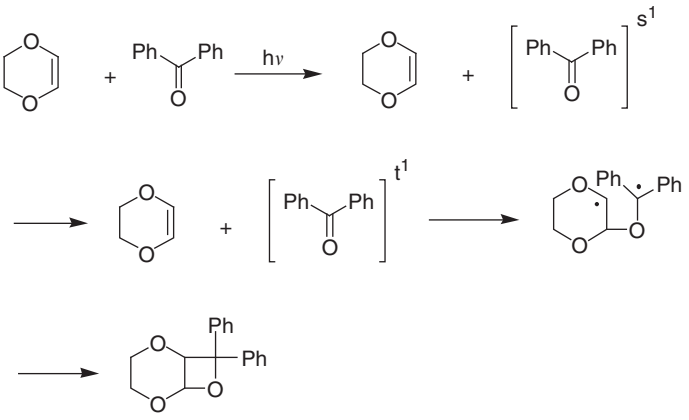
After these pioneering works, several reviews cover all the papers published in this field.[9–24]

The reaction is a photocycloaddition reaction of a carbonyl compound in the excited state with an alkene in the ground state. The carbonyl compound must possess an n,π^* S_1 or T_1 excited states. Frontier orbitals approach has been used to explain the formation of oxetanes. Highest single occupied molecular orbital (HSOMO)–lowest unoccupied molecular orbital (LUMO) interaction is the main process observed where the half-occupied π^* orbital of the carbonyl compound interacts with the unoccupied π^* molecular orbital of an electron deficient alkene: the results of this interaction is the formation of a C,O-biradical (**A** in Scheme 3). If the lowest single occupied molecular orbital (LSOMO)–highest occupied molecular orbital (HOMO) interaction is prevalent (interaction of the half-occupied n orbital of the carbonyl O atom with the π orbital of an electron-rich alkene), the formation of a C,C-biradical (**B** in Scheme 3) is the main process.[25,26]



Scheme 3

The majority of Paternò–Büchi reactions occur from the carbonyl triplet state, which is accessed by an intersystem crossing. The biradicals are the direct consequence of the precursor spin and their lifetimes are connected with the mode of spin inversion processes and the mechanism, thus leading to the formation of closed-shell products. 1,4-Biradicals derived from the addition of a carbonyl compound in its first excited triplet state and an alkene were studied spectroscopically[27–30] and they were trapped by radical quenchers.[31–34] The biradical intermediate in the reaction between benzophenone and an electron-rich alkene has been determined using laser flash photolysis. An absorption with λ_{max} 535 nm has been observed (Scheme 4).[27,29]



Scheme 4

In the reaction between 1,4-dioxene and benzaldehyde, theoretical calculations showed that the only transition able to give the observed transient absorption is that from LSOMO to LUMO (549 nm); the same result was obtained for the reaction between furan and benzaldehyde.[21]

The regioselectivity of the reaction can be explained considering the hard–soft acids and bases theory. This approach gave results in agreement with the experimental results.[35] Another approach able to explain the regiochemistry of the Paternò–Büchi reaction appeared and considered that atoms arrange themselves so that the obtained molecule reaches the minimum electrophilicity.[36]

A theoretical study of the Paternò–Büchi reaction showed that there are two conical intersection points located near the C–C and C–O bonded biradical regions of the ground state. These two conical intersections support a mechanism where the decay

from the excited state is accompanied by a geometric rotation of the terminal group, in the case of C–O attack, and by an orbital rotation at the oxygen center, in the case of C–C attack. Furthermore, for C–O attack, the triplet surface must cross the singlet to reach a diradicaloid minimum. For C–C attack, the triplet biradical minimum is located at the same geometry as the conical intersection between the two singlet states, and the efficiency of the intersystem crossing will be determined by the nature of the spin–orbit coupling (SOC). Thus, for the triplet, the reaction path can be predicted by the most stable biradical rule.[37] A conformational analysis of the biradicals also appeared.[38,39]

A complete active space multiconfiguration self consistent field geometry optimization using triple zeta valence basis set of the intermediate biradicals showed that the diradical region corresponding to the C–C attack lies approximately 10 kcal mol^{-1} lower in energy than the C–O region.[40,41] Unfortunately, this result is not in agreement with the reported experimental results.

The formation of an exciplex is used to explain the reaction behavior of a simple alkene. However, evidence of monoelectron transfer processes is reported for electron-rich alkenes.[42]

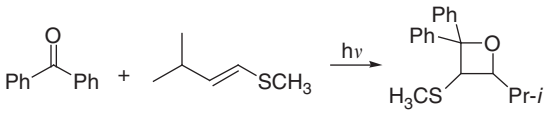
5.05.2 Intermolecular Reactions

5.05.2.1 Reactions with Electron Rich Unsaturated Compounds

5.05.2.1.1 Reactions of carbonyl compounds with enolethers and enolthioethers

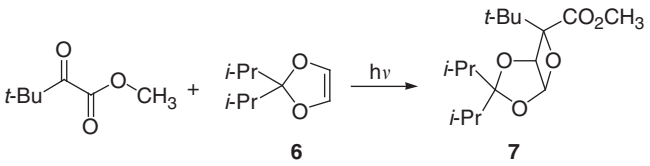
The first oxetane derived from ethyl vinyl ether and benzophenone was described by Paternò.[43] He described the formation of oxetane in the reaction of benzophenone with diethyl ether. He suggested the *in situ* formation of ethyl vinyl ether. The reaction between acetone and ethyl vinyl ether in the presence of ultrasounds gave a different mixture of regioisomers than that obtained without the use of ultrasound.[44]

A high regioselectivity was obtained when ethyl vinyl ether was used as an alkene with benzaldehyde and benzophenone.[45] The reaction of benzophenone with alkenyl sulfide also showed a high regioselectivity (Scheme 5).[46]



Scheme 5

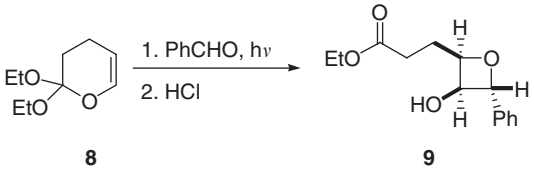
Substituted pyruvates reacted with 1,3-dioxol **6** and this reaction allowed one to obtain the *endo* isomer **7** (Scheme 6).[47–49] The analysis of the conformations of the biradical intermediate was used in order to explain the observed stereochemical behavior.[50]



Scheme 6

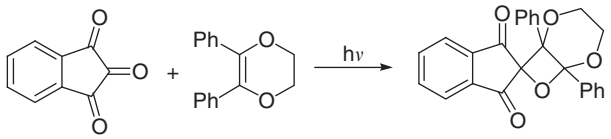
Unsubstituted cyclopropyl enol ethers gave, when reacted with a carbonyl compound, the corresponding oxetane rings. When a substituent is introduced on the cyclopropyl ring, the formation of oxepanes was observed being derived from cyclopropyl ring opening at the level of the biradical intermediate.[51]

When enol ether **8** was irradiated in the presence of benzaldehyde, and the reaction mixture was purified after an acid hydrolysis, oxetane **9** was isolated in good yield with a good diastereoselectivity (Scheme 7).[52]



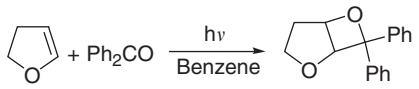
Scheme 7

1,2,3-Indanetrione reacted with 2,3-diphenyl-1,4-dioxene to give the oxetane on the carbonyl in 2 position (Scheme 8).[53] On the contrary, when the less electron rich 2,3-dimethyl-2-butene is used as an alkene, a complex mixture of products is obtained.[54]



Scheme 8

The irradiation of 2,3-dihydrofuran with benzophenone in benzene gave adduct **10** (Scheme 9).[55]



10

Scheme 9

When acetone was used as the carbonyl compound, the adduct was obtained in 52% yield: It was a mixture of two regioisomers in a 200:1 isomeric ratio.[56] Also, the reaction of 5,5-dimethyl-2,3-dihydrofuran with both aromatic and aliphatic aldehydes gave the corresponding oxetanes with high *endo* selectivity.[57] When acetaldehyde was used as the carbonyl compound, the adduct was obtained in 63% yield as a mixture of stereoisomers. The selectivity depended on 2,3-dihydrofuran concentration: This behavior was explained with a switch from a triplet mechanism to a singlet mechanism at higher concentration.[58–62] This behavior can be explained.[63] It can be seen that the best interaction between the frontier orbitals is that from the LSOMO of acetaldehyde and the HOMO of 2,3-dihydrofuran (Figure 1). The atomic coefficients on the olefinic carbon atoms in 2,3-dihydrofuran were –0.26 at C-2 and –0.38 at C-3. The atomic coefficient on the oxygen atom in the LSOMO of singlet excited acetaldehyde was 0.48, whereas the atomic coefficient at the C-1 of acetaldehyde in the HSOMO was 0.49.

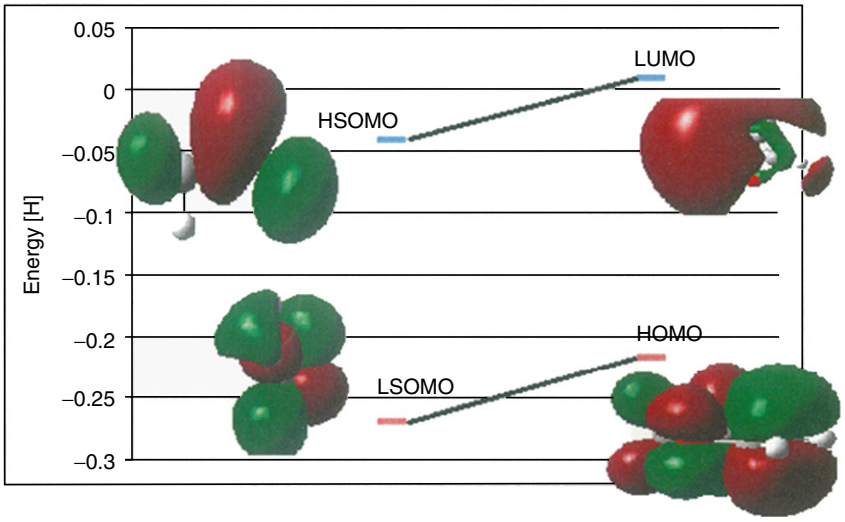
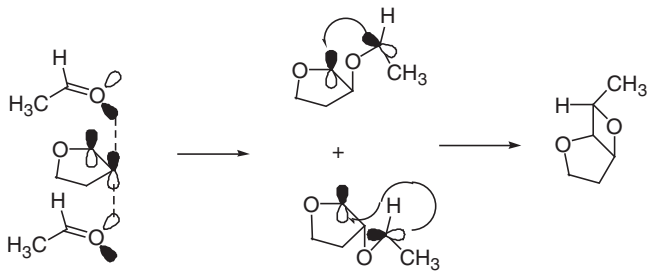


Figure 1 Frontier orbitals interaction in the reaction of 2,3-dihydrofuran with acetaldehyde in its excited singlet state.

The nature of the LUMO of 2,3-dihydrofuran excludes the possibility of a concerted mechanism. The reaction has to provide for the formation of an extremely labile singlet biradical. In this case, the oxygen atom of acetaldehyde has to attack the C-3 carbon atom in 2,3-dihydrofuran in order to give the more stable biradical intermediate. This interaction can occur as described in Scheme 10.

The reaction, in this case, allowed the formation of only the *exo* isomer. This can explain the observed reactivity admitting that, when the reaction is performed in a concentrated solution, the excited singlet state gave the *exo* isomer, whereas the excited triplet state is responsible for the formation of the *endo* isomer. In the triplet state, the interaction between the frontier orbitals is depicted in Figure 2.



Scheme 10

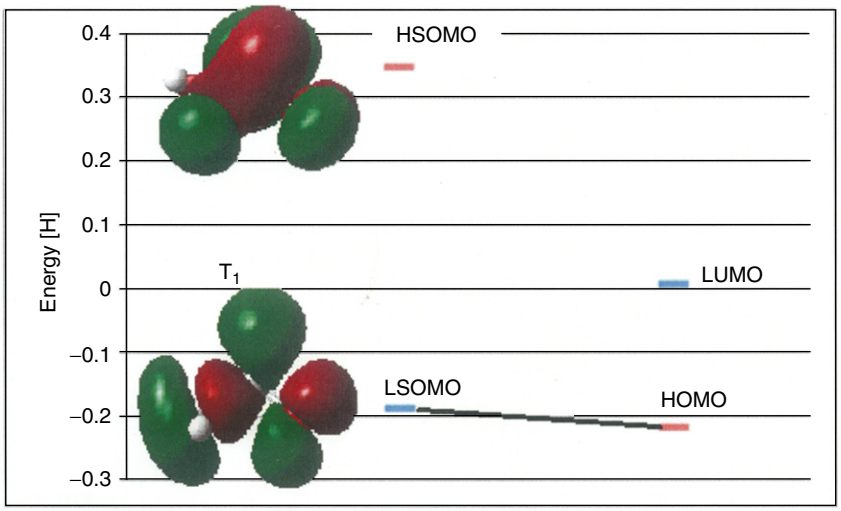
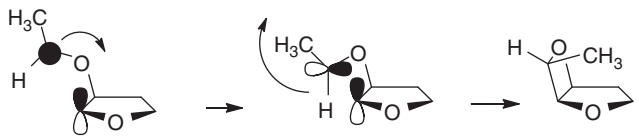


Figure 2 Frontier orbitals interaction in the reaction of 2,3-dihydrofuran with acetaldehyde in its excited triplet state.

The main interaction is that between the LSOMO of the triplet state acetaldehyde and the HOMO of the dihydrofuran. This interaction leads to the formation of the corresponding C–C biradical intermediate (Scheme 11).



Scheme 11

The HSOMO on the biradical intermediate was mainly localized on the aromatic ring and it is extended to the radical carbon. The LSOMO was mainly localized on the dihydrofuran ring (Figure 3). The coupling between the radical carbons in these two orbitals was possible (the atomic orbitals involved can superimpose themselves) only if the *endo* isomer was formed (Scheme 11).

When benzaldehyde was used as carbonyl compound, the reaction showed good regio- and stereoselectivity (Scheme 12).[61,64–66] The adducts were obtained with an overall yield of 98% as a >98:2 regioisomeric mixture; the major isomer is 88:12 *endo–exo* mixture. The stereoselectivity was partially lost when benzaldehyde reacted with a 2,3-dihydrofuran derivative substituted in two positions.[64,67]

A change of regioselectivity was observed when the reaction between 2,3-dihydrofuran and benzaldehyde was performed in a high polar solvent: This result has been interpreted as a proof of an electron-transfer mechanism (Scheme 13).[58,59]

The reaction of dihydrofuran with benzaldehyde is the first example where a spin controlled selectivity is observed.[60,68] In singlet photoreactions, stereoselectivity is often controlled by the optimal geometries for radical–radical combinations. On the contrary, in triplet photoreactions the optimal geometries are those able to favor the intersystem crossing from the triplet excited state to the singlet one. The singlet biradicals should be too short-lived to enable rotation about the endocyclic C–O or C–C bonds, and therefore conformation memory effects on the stereochemistry are expected. The geometries in the triplet state can be quite different from the former ones due to differences of the SOC values. The lifetimes of many triplet biradical intermediates are definitely high enough to enable bond rotations. Therefore, the formation of the thermodynamically favored product can be

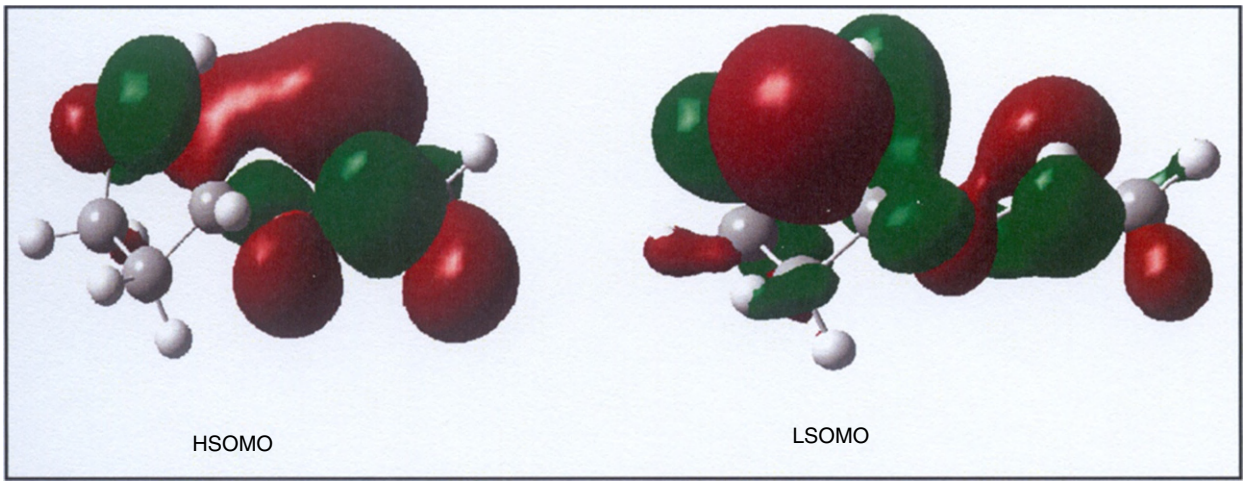
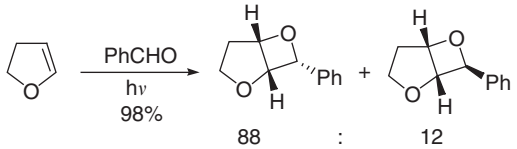
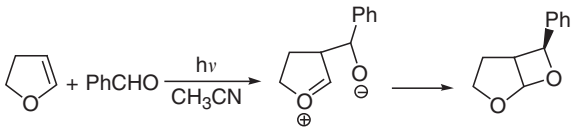


Figure 3 HSOMO and LSOMO of the biradical intermediate in the reaction between acetaldehyde and 2,3-dihydrofuran.



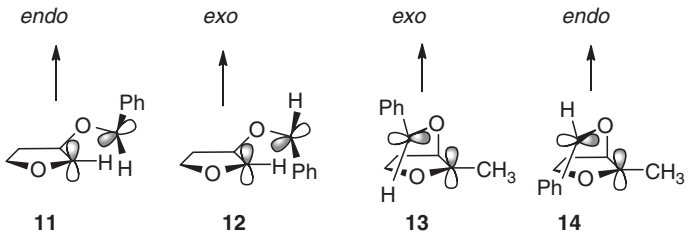
Scheme 12



Scheme 13

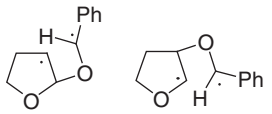
expected because the radical–radical combination step should not be influenced by the approach geometry: 'memory effects' should be erased due to the relatively long lifetimes. After transition from the triplet to the singlet potential energy surface, immediate product formation is expected. Thus, the ISC proceeds in a concerted fashion with the formation of a new bond or the cleavage of the primarily formed single bond. As a consequence, the stereoselectivity of the Paternò–Büchi reaction is the result of a combination of several rate constants for cyclization versus cleavage reactions.

Benzaldehyde reacts in its triplet state. This way, a triplet biradical intermediate is formed. To obtain the products, intersystem crossing into the singlet manifold is necessary. The most important factor influencing an intersystem crossing for flexible triplet biradicals is SOC. The angle between p orbitals at the radical centers is approximately 90° for maximum SOC. For the pronounced *endo* selectivity in the reaction between aromatic aldehydes and 2,3-dihydrofuran, the two biradical conformers **11** and **12** can be considered to be responsible, with the alkyloxy substituent localized in a pseudoequatorial position and **11** being more populated because of fewer steric interactions (Scheme 14).



Scheme 14

When a methyl group is present, the increasing *gauche* interactions with the β-alkyloxy substituent led to a certain concentration of **13** and **14**, again with **13** being preferred because of fewer steric interactions. Another explanation for the regio- and stereochemistry appeared.[69] In fact, theoretical calculations showed that the biradical **15** is more stable than **16** by 1.49 kcal mol^{-1} (Figure 4).



15 **16**

Figure 4 Possible biradical intermediates in the reaction of 2,3-dihydrofuran with benzaldehyde.

Furthermore, the HSOMO was mainly localized on the aromatic ring and it is extended to the radical carbon. The LSOMO was mainly localized on the dihydrofuran ring (Figure 6(a)). The coupling between the radical carbons in these two orbitals was possible (the atomic orbitals involved can superimpose themselves) only if the *endo* isomer was formed (Figure 5).[69]

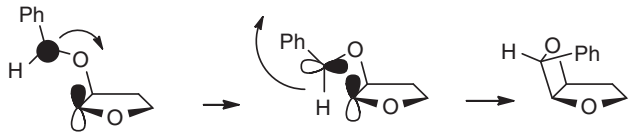
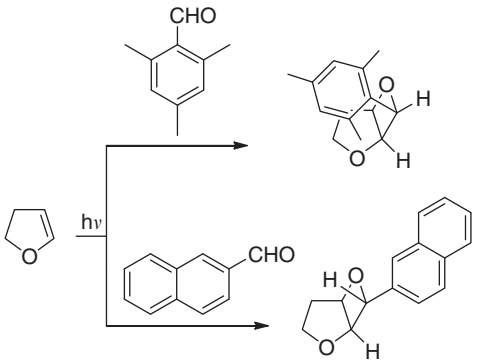


Figure 5 Ring closure reaction in the formation of the *endo* isomer of the adduct between 2,3-dihydrofuran and benzaldehyde.

α- and β-Naphthaldehydes, on the contrary, gave high *exo* selectivity (Scheme 15). The reaction also occurred in the presence of triplet quenchers, whereas fluorescence quenching in the presence of dihydrofuran was observed.



Scheme 15

In this case, the singlet excited state was responsible for the high *exo* selectivity.[61,70] In this case, the coefficients on the HSOMO and LSOMO allowed the coupling of the radical carbons only if the *exo* isomer is obtained (Figures 6 and 7).[71]

When 2,3-dihydrofuran derivatives react with α,β-unsaturated carbonyl compounds, [2 + 2] cycloaddition between the olefins occurs.[72] Benzaldehyde reacts with L-ascorbic acid giving a mixture of regioisomeric compounds with *exo* stereoselectivity.[73]

Irradiation of the oxetane **17** in the presence of 1-methoxynaphthalene and 2,7-dimethoxynaphthalene as sensitizers gave an efficient carbonyl-alkene metathesis of bicyclic oxetanes through an electron transfer process (Scheme 16).[74]

A cycloreversion reaction was supposed also in the photochemical reaction of α,α-diphenyl substituted diazotetrahydrofuranones.[75]

5.05.2.1.2 Reactions with enol esters, enol silyl ethers, and enamines

High regio- and stereoselectivity (*syn* addition) was observed in the reaction of pentafluorobenzaldehyde with enol acetates.[76] The reaction between a 2,3-thiophenone derivative and vinyl acetate gave the corresponding adduct on a ketonic function in low yields.[77]

The reaction between benzaldehyde and a silyl derivative of cinnamyl alcohol gave the corresponding oxetane with high stereoselectivity (Scheme 17).[78]

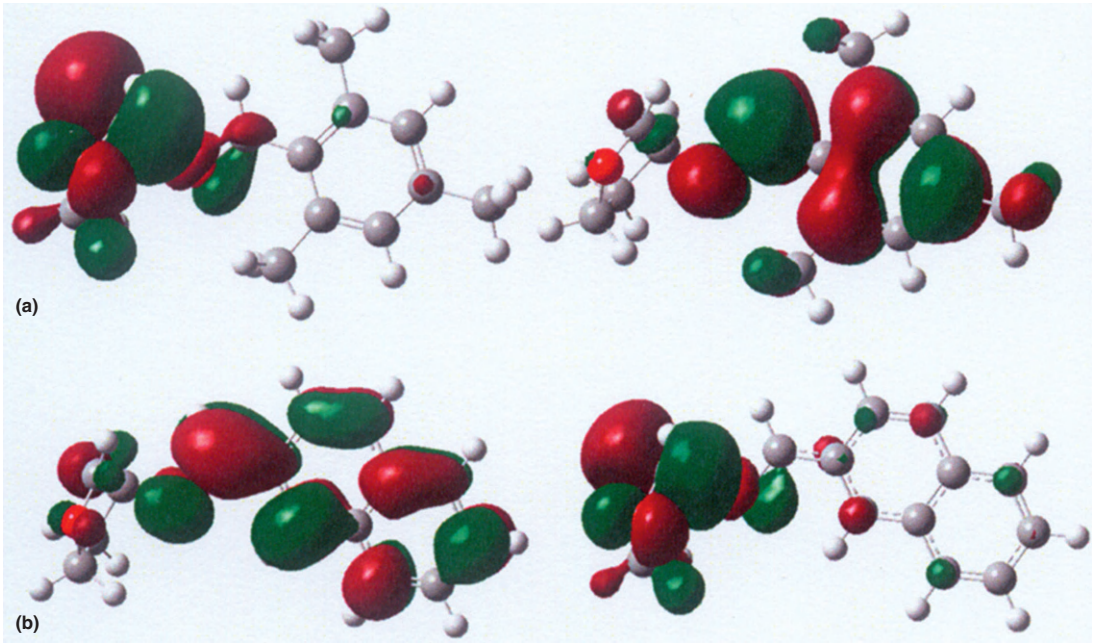


Figure 6 (a) HSOMO (left) and LSOMO (right) of the biradical intermediate in the reaction of trimethylbenzaldehyde with dihydrofuran. (b) HSOMO (left) and LSOMO (right) of the biradical intermediate in the reaction of 2-naphthaldehyde with dihydrofuran. Reproduced from D'Auria, M.; Racioppi, R. *Eur. J. Org. Chem.* **2010**, 3831–3836, with permission of Wiley-VCH.

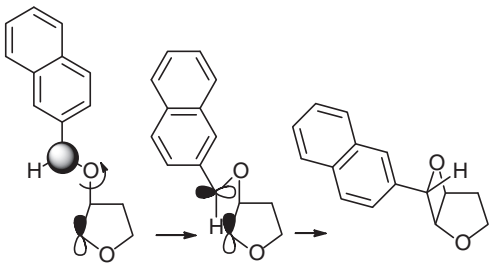
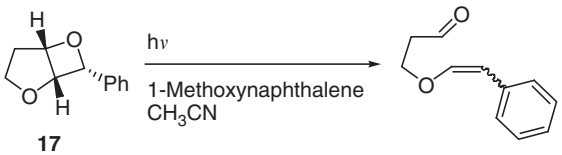
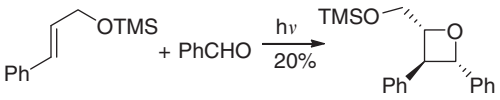


Figure 7 Coupling of the radical centers in the biradical intermediate in the reaction of 2-naphthaldehyde with dihydrofuran.

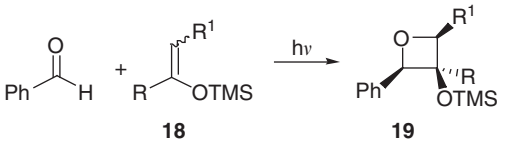


Scheme 16



Scheme 17

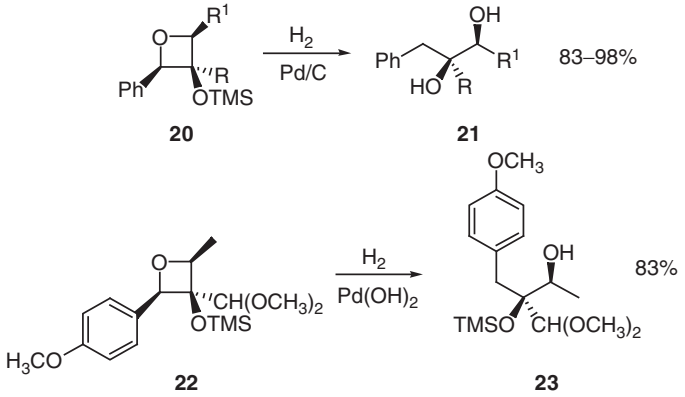
3-(Silyloxy)oxetanes **19** were successfully prepared from silyl enol ethers **18** containing carbon–chlorine, carbon–silicon, or carbon–sulfur bonds (Scheme 18).[79–81] Ether and ester groups were compatible with the reaction. The presence of an alkene moiety was also compatible. When a β-alkyl substituted silyl enol ether was used, a *trans* relationship between α and β susbstituents in the oxetanes was observed. This result did not depend on the (*E*)- or (*Z*)- nature of the alkene. The products were obtained with high simple diastereoselectivity (*ds* 74–95%).[82]



Scheme 18

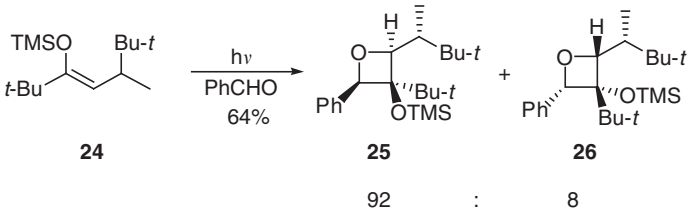
In the triplet biradical, free rotation leads to the highly preferred, sterically least congested conformation. The further reaction pathway of this species includes ISC and an assumed selection step (cleavage versus ring closure) at the singlet 1,4-diradical level which accounts for the high simple diastereoselectivity at C-2/C-3.

The oxetanes **20** can be converted into the corresponding diols **21** using hydrogenolysis under Pd catalysis (Scheme 19). Acid-sensitive substrates can be hydrogenated using $Pd(OH)_2$ as catalyst as reported in the reaction of the acetal **22** (Scheme 19).[83] Also $LiAlH_4$ can be used in order to induce the cleavage of the oxetane ring.[84]



Scheme 19

The presence of a stereogenic center in the *β*-alkyl group (as in **24**) induced a facial diastereoselectivity. In some cases, high diastereoisomeric ratios were observed (Scheme 20).[85]



Scheme 20

The diastereoselectivity was probably due to the presence of a conformational preference represented in Figure 8. This conformation allows the *Si* attack.[84]

In this case, a fluoride-promoted cleavage can be used to open the oxetane ring.[85] When the chiral center is in *α* position, low facial diastereoselectivity was observed.[86] The best results were obtained using both the silyl enol ether **27**, which gave the adducts **28** and **29** with a 67/33 *dr*, and the compound **30**, giving the adducts **31** and **32** in 15/85 *dr* (Scheme 21).[87]

In the reaction of **27** with benzaldehyde, two conformers of the biradical intermediate have been observed. These conformers showed almost the same energy (the conformer **A** is more stable than **B** for 3.11 kcal mol^{-1}): the conformers of the biradical are shown in Figure 9.[70] Considering the biradical conformer **A**, the LSOMO of this biradica was at −0.077 Hartries (H), whereas the HSOMO was at −0.073 H (Figure 10). Considering the reactive sites and the atomic coefficients at these sites, the coupling of the radical carbon atoms can occur only as depicted in Scheme 22.

The conformer **A** can give the major stereoisomer **28** observed in the reaction. The results are in agreement with the experimental results showing that the course of this reaction is strictly frontier orbitals controlled. The other biradical conformer gave the other diastereoisomer. The observed diastereoisomer ratio (67:33) can be explained by the low difference between the energies of the conformers of the biradical intermediate (3.11 kcal mol^{-1}).

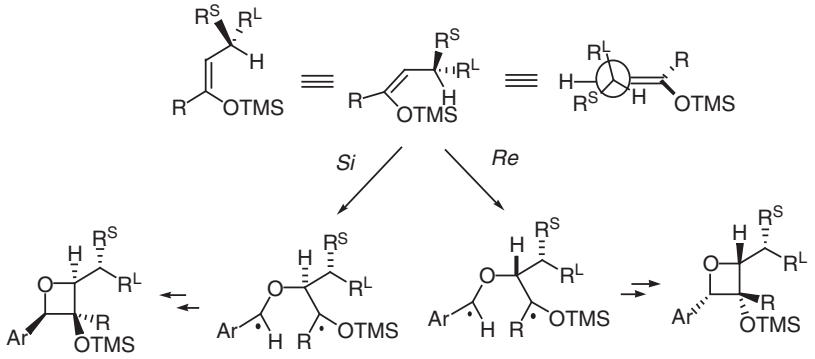
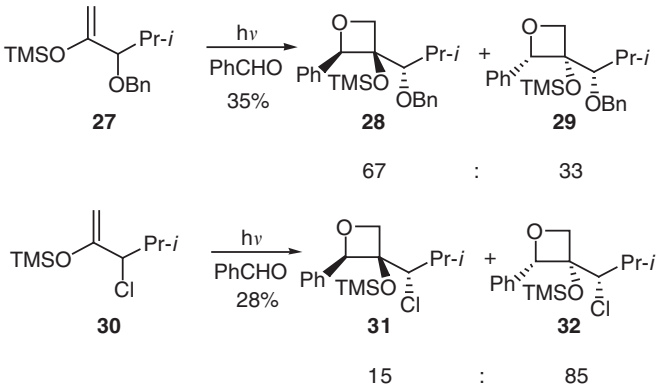


Figure 8 Diastereoselectivity in chiral enol silyl ethers reaction with benzaldehyde.



Scheme 21

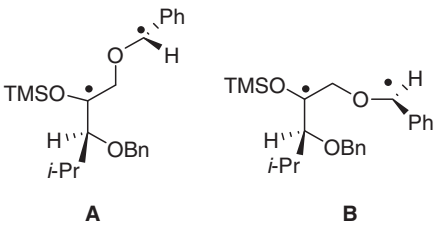


Figure 9 The conformers (**A** and **B**) of the biradical intermediate in the photoreaction between **27** and benzaldehyde.

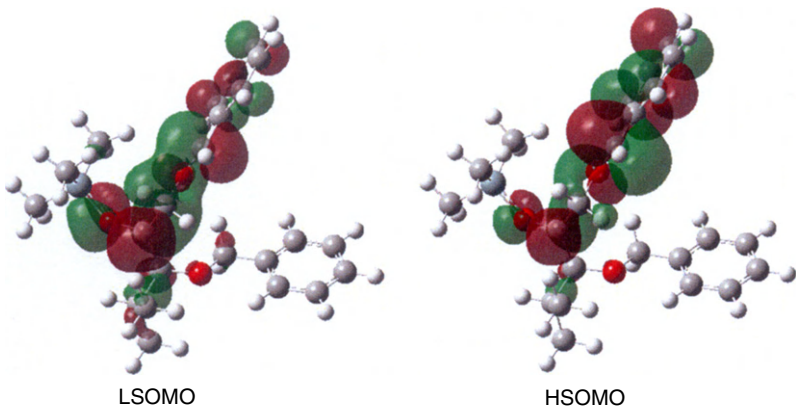
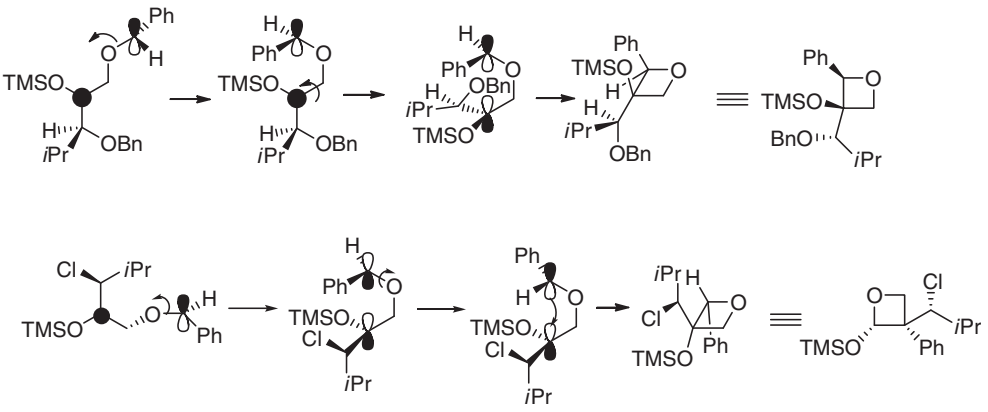


Figure 10 HSOMO and LSOMO of the biradical **A** obtained in the reaction of **27** with benzaldehyde. Reproduced from D'Auria, M.; Emanuele, L.; Racioppi, R. *Lett. Org. Chem.* **2006**, *3*, 244–246, with permission of Wiley-VCH.



Scheme 22

To confirm this result the behavior of **30** has been examined. In this case, the authors observed an inverse diastereoselectivity.[86] Also, in this case, two conformers of the biradical intermediate were possible. The energy difference between these two conformers was 4.6 kcal mol^{-1}. The coupling between the carbon atom considering the atomic coefficients allowed the formation of the observed diastereoisomers (**31** and **32**): the most stable conformer gave compound **32**. The larger diastereoisomeric ratio (85:15) here observed in comparison with that found between **28** and **29** is in agreement with the larger energy difference between the conformers of the biradical intermediate.

The synthetic utility of the oxetanes has been studied considering the presence of a removable protecting group in the side chain of the same oxetane. The possible intramolecular nucleophilic attack on the oxetane ring gave some interesting products (Scheme 23).[87]

1,2-Diketones reacted with trimethylsilyl ketene acetals giving the corresponding oxetanes in low yields.[88] In the reaction of ketene silyl acetals with aromatic carbonyl compounds byproducts have been identified as oxetanes: in some cases they represent the main product.[89] Cyclic ketene silyl acetals **33** reacted with 2-naphthaldehyde to give the corresponding adduct **34**. The treatment of the reaction mixture with water gave the aldol-type product **35** with high stereoselectivity (Scheme 24). The oxetane was obtained with *anti* stereochemistry.[90,91] The effect of both the solvent and the nature of the silyl group has been examined.[92] When silyl O,S-ketene acetals were used as alkene, some interesting results were obtained.[93] In particular when the *E* isomer **36** was used, only the *trans*,*trans*-isomer **37** was obtained (Scheme 24).

The stereochemical behavior was explained by considering the capability of the sulfur atom to coordinate the oxygen atom of the carbonyl compound.[93] The presence of such an atom induced the attack of the carbonyl compound on the side where the sulfur atom is present (Figure 11). The same regio- and stereoselectivity was observed when silyl O,Se-ketene acetals were used.[94]

Oxetanes were obtained in the reaction of *N*-acyl enamines **38** and **41**: these compounds gave the corresponding adducts with high regio- and stereoselectivity (Scheme 25).[95–98] The main product was the thermodynamically more stable isomer.[99]

The optimized structure of the biradical intermediate is shown in Figure 12 with the HSOMO at -0.215 H and the LSOMO at -0.241 H.[70]

The coupling of the radical carbon atoms considering the atomic coefficients on the SOMOs allowed the formation of the *exo* isomer, in agreement with the experimental results (Scheme 26).

Chiral enamines did not give the corresponding adduct with high diastereoselectivity. The only exception was found using the enamine **43**. It gave the corresponding adduct with 62% *de* (Scheme 27).[100,101]

N-Formyl protected oxetanes could be converted into the corresponding *syn*-1,2-amino alcohols through treatment with $LiAlH_4$.[97] Alternatively, the treatment of **44** with TFA gave the oxazolidinone **45**. Furthermore, **45** can be converted into the corresponding *anti*-1,2-amino alcohol **46** (Scheme 28).[97,102]

This approach has been used in the synthesis of both (±)-oxetin (**47**)[103] and (+)-preussin (**48**) (Figure 13).[104,105]

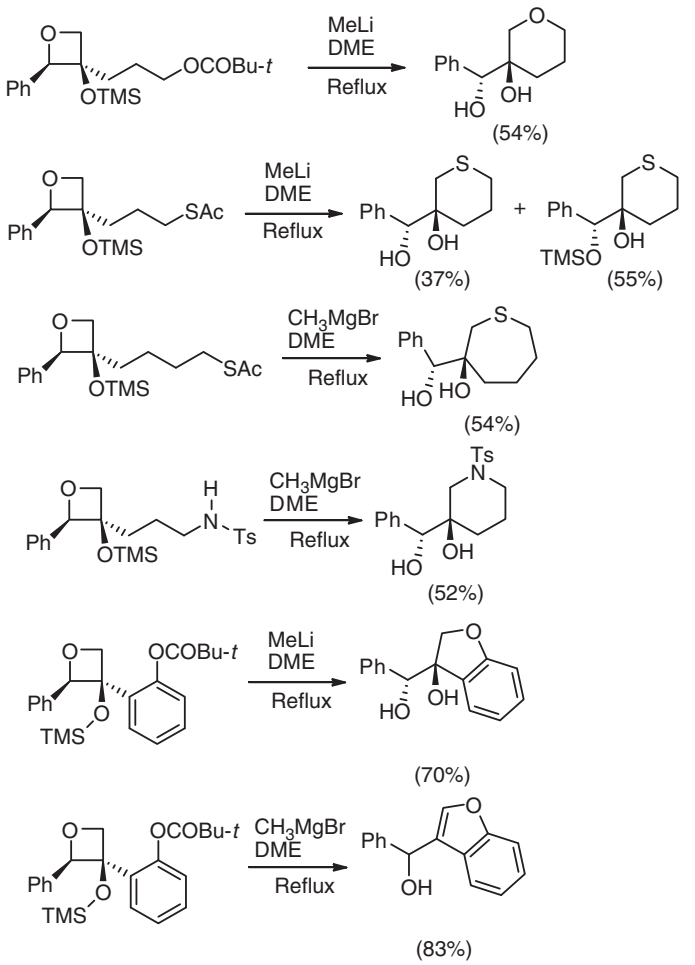
The Paternò–Büchi reaction could be obtained also using alkenes bearing both electron donating groups (nitrogen atoms) and electron withdrawing groups. 2-Morpholinopropenenitrile gave in very low yields a product deriving from a Paternò–Büchi reaction when it reacted with naphthalene-1,4-dicarboxylic acid.[106] The same result was obtained when benzil was used as substrate. On the contrary, when methyl phenylglyoxylate was used as carbonyl compound, the corresponding adduct was isolated in good yields.[107]

When benzil was irradiated in the presence of a 2-aminopropenenitrile derivative, it gave the corresponding adduct in variable yields (Scheme 29).[108] The reaction showed good stereoselectivity. When unsymmetrical benzil derivatives are used, both the isomers were obtained.

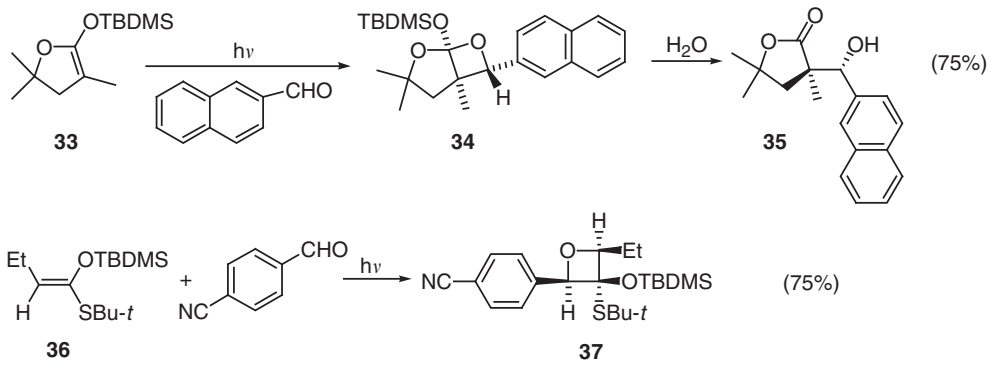
5.05.2.2 Reactions with Heterocyclic Compounds

5.05.2.2.1 Reactions with five-membered heterocycles

The reactivity of pentatomic aromatic heterocycles different from furan toward carbonyl compounds to give the corresponding oxetanes has been the object of other review articles.[109] These compounds showed lower reactivity than furan (see below).



Scheme 23



Scheme 24

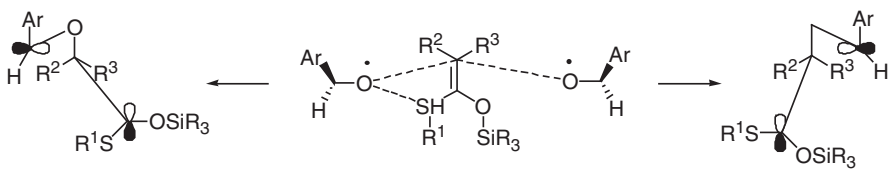
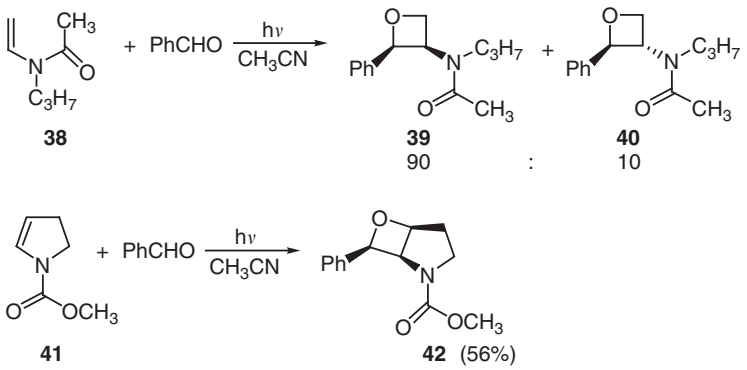


Figure 11 The reaction O,S-ketene acetals with carbonyl compound. A possible explanation of the stereochemical behavior.



Scheme 25

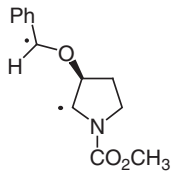
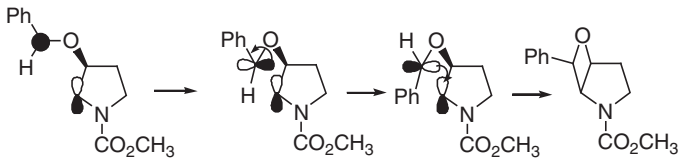
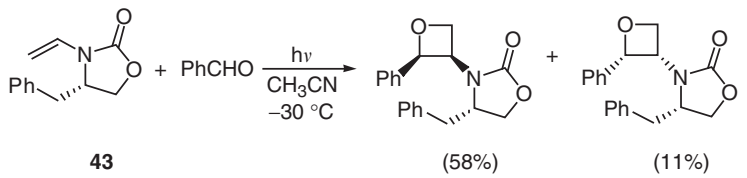


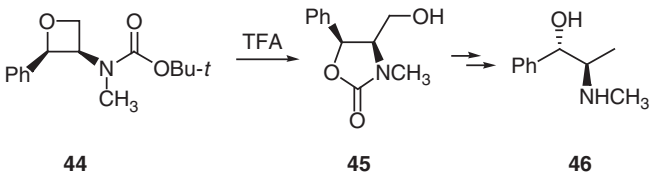
Figure 12 Optimized structure of the biradical intermediate in the reaction **41**→**42**.



Scheme 26



Scheme 27

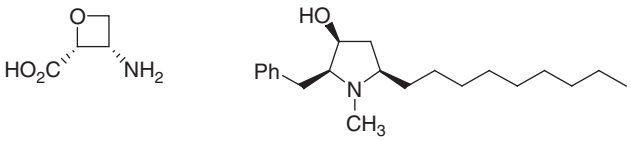


Scheme 28

The reason for this behavior is not clear. It could be related to the different aromaticity of these compounds in comparison with that of furan, or could be due, as reported below, to the quenching properties of the heterocycles.

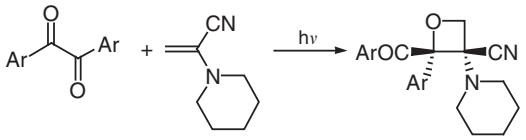
Thiophene did not react with benzophenone. The reaction occurred only if the irradiation is performed in the presence of BF_3 (Scheme 30).[110] Probably, in this reaction BF_3 was able to catalyze the ring opening of the oxetane.

The benzophenone BF_3 complex, excited by light, leads to an exciplex whose excitation energy was lower than the lowest triplet energy level of thiophene, which under the circumstances cannot act as a quencher. On the contrary, 2,5-dimethylthiophene reacted with benzophenone at -10 °C yielding the corresponding cycloadduct in 62% yield (Scheme 31).[111,112]

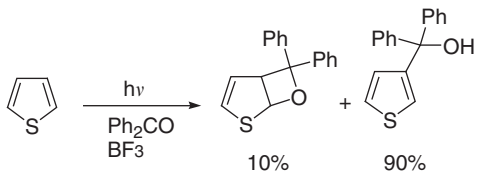


47 **48**

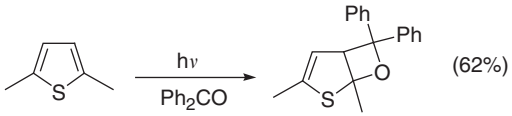
Figure 13 Oxetin (**47**) and preussin (**48**).



Scheme 29



Scheme 30



Scheme 31

The reaction product could be obtained also using 1-naphthaldehyde (50%), 2-, 3-, and 4-benzoylpyridine (62, 58, and 60%, respectively), and 2-benzoylthiophene (50%), whereas 2-naphthaldehyde, benzaldehyde, and acetophenone did not react.[113] 2,3-Dimethylthiophene also gave the corresponding oxetane when irradiated in the presence of benzophenone (60%).[114] On the contrary, 2,3-dimethyl- and 2,3,5-trimethylthiophene did not react.

Pyrrole, such as thiophene, did not react with benzophenone and did not furnish the corresponding oxetane. However, pyrrole reacted with aliphatic aldehydes and ketones giving the corresponding 3-pyrryl carbinols. The alcohols derived from the cleavage of the corresponding oxetanes (Scheme 32).[115] The yields increased when *N*-methylpyrrole was used as substrate, whereas the reactivity was depressed in the presence of substituents on the pyrrole ring.

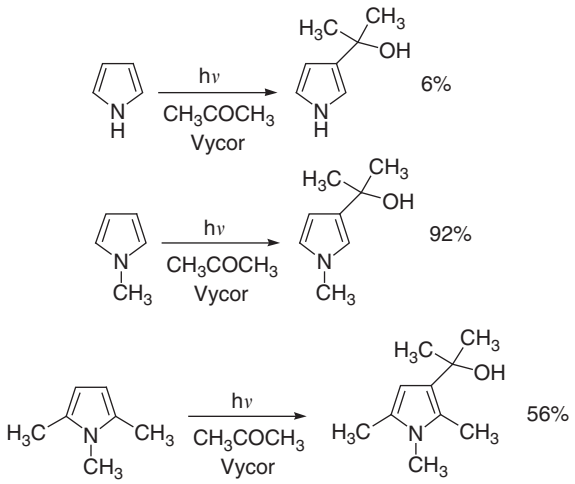
Only when pyrrole, with an electron-withdrawing group such as benzoyl on to the nitrogen atom, was irradiated in the presence of benzophenone, it was able to give the corresponding oxetane (Scheme 33).[116,117] When *N*-phenylpyrrole was used as a substrate, the corresponding 2-pyrryl carbinol was isolated.[116]

Selenophene did not react with benzophenone.[111] On the contrary, the irradiation of 2-methylselenophene gave the corresponding adduct. The reaction occurred on the most hindered side of the molecule (Scheme 34).[118]

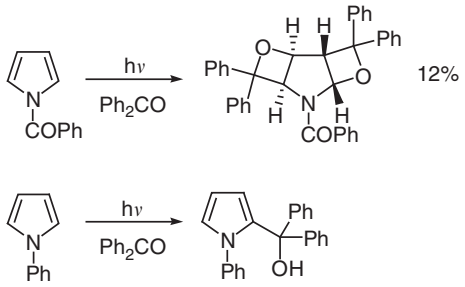
Imidazole, *N*-methylimidazole, and 1,2-dimethylimidazole reacted with aliphatic aldehydes and ketones. In all the cases, the product was the corresponding 4-imidazolyl carbinols (Scheme 35).[114,119] The carbinols were obtained through the cleavage of the corresponding oxetanes. On the contrary, the reaction of imidazole with benzophenone gave only 7.7% yield of the corresponding alcohol,[119] whereas, the same reaction, performed in the presence of acetophenone as carbonyl compound, gave only 1.2% yield of the product.[119]

On the photochemical behavior of *N*-methylimidazole, there was no agreement between the work of Jones[115] and that of Matsuura.[119] Whereas Jones reported that *N*-methylimidazole gave the corresponding imidazolyl carbinol in excellent yields, Matsuura reported that the same substrate gave the corresponding carbinol in 9% yield. They also reported that 2-methylimidazole gave a mixture of two products with an overall yield of 22.5% (Scheme 36).[119]

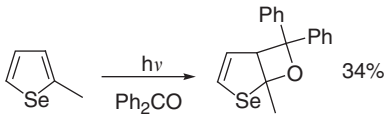
1,2-Dimethylimidazole reacted with benzophenone. However, this compound gave a reaction on the methyl in 2 position in low yield.[120,121] *N*-Benzylimidazole, when irradiated in the presence of benzophenone in *t*-BuOH, gave a reaction on the



Scheme 32



Scheme 33



Scheme 34

methylene group.[120,121] Only the irradiation of *N*-acetylimidazole allowed one to obtain the corresponding oxetane when the reaction was performed in the presence of benzophenone (Scheme 37). The same result was obtained using *N*-benzoylimidazole and *N*,*N*′-carbonyldiimidazole.[120,121]

The oxetane can also be obtained in the reaction of *N*-methyl-2,4,5-triphenylimidazole with aromatic ketones. It is noteworthy that, in this case, the reaction did not work in the presence of acetophenone and benzaldehyde.[122]

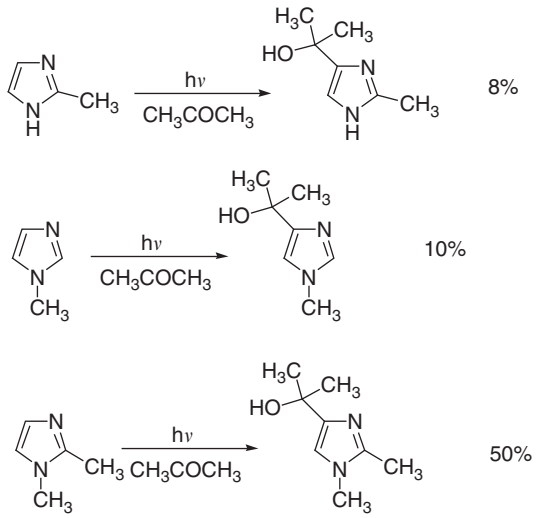
The irradiation in the presence of benzophenone of 2,4-dimethylthiazole gave the corresponding oxetane, whereas the same reaction failed when acetophenone was used as carbonyl compound (Scheme 38).[123] The irradiation in the presence of benzophenone of 3,5- and 4,5-dimethylisoxazole gave the corresponding oxetane in good yields, whereas 4-methylisothiazole gave a reaction on the methyl substituent (Scheme 38).[123]

Recently, the reactivity of isoxazole derivatives has been revisited, showing that some derivatives, such as 3,4,5-trimethylisoxazole, gave the corresponding oxetanes in very good yield (in the case reported in the Scheme 39, almost quantitative yields were obtained) and excellent diastereoselectivity (>99:1).[124]

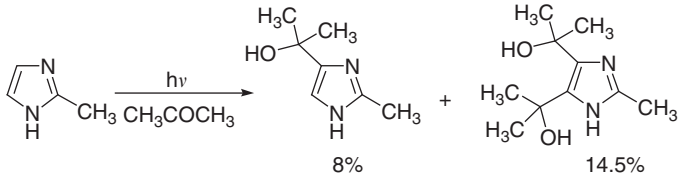
On the contrary, 3-phenyl substituted derivatives did not give the Paternò–Büchi reaction, allowing to obtain only the ring contraction products.[122] In this case, the isoxazole was able to absorb the light giving the corresponding excited state able to give the isomerization reaction.[122–128]

Aliphatic and aromatic carbonyl compounds reacted with oxazole derivatives with good to high *exo* diastereoselectivity, but low facial stereoselectivity. This reaction can be used in the synthesis of *erythro*-α-amino β-hydroxy carboxylic acid derivatives.[129–133]

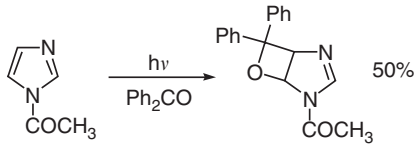
The irradiation of indole with benzophenone did not give the corresponding adduct. On the contrary, a benzoyl derivative of indole reacted with benzophenone, giving the corresponding oxetane (Scheme 40).[134] It did not react with acetophenone,



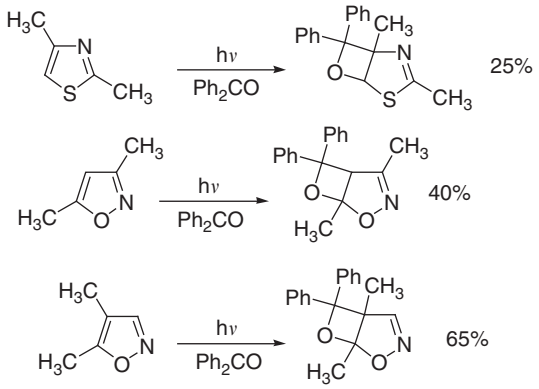
Scheme 35



Scheme 36



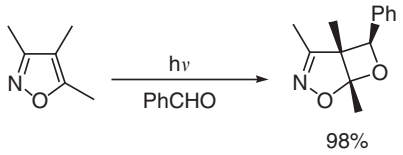
Scheme 37



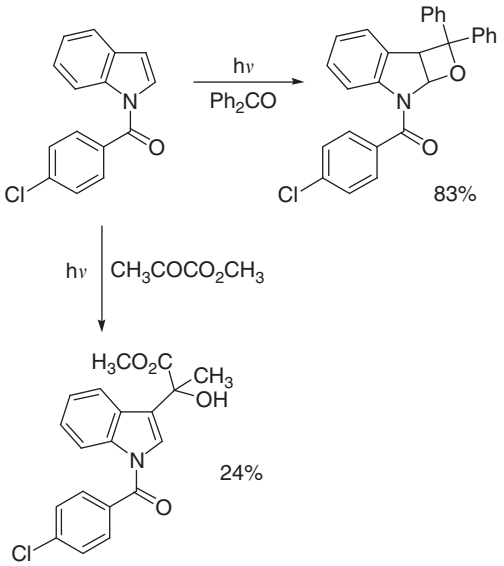
Scheme 38

benzaldehyde, acetone, and propionaldehyde. When methyl pyruvate was used as the carbonyl compound, the corresponding 3-indolyl carbinol was obtained (Scheme 40).[134]

The same reaction has been described on the *N*-acetyl derivative of 7-azaindole. Although the reaction represents a method able to obtain a new class of compounds, the low yields of the product (4%) prevent a synthetic use of this reaction.[134]

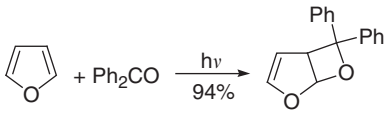


Scheme 39



Scheme 40

Schenck reported that the irradiation of benzophenone in furan gave the corresponding adduct in 94% yield (Scheme 41).[135] The structure was confirmed by Gagnaire et al.[136]



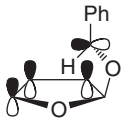
Scheme 41

Furan and 2-methylfuran were found to react with propanal and benzaldehyde.[111,137–142] In this case, the *exo* stereochemistry at C-6 on the dioxabicyclo[3.2.0]heptene skeleton has been assigned.[143] Good regioselectivity was observed using silyl and stannyl furan derivatives: in this case, the reaction occurred on the less hindered side of the molecule.[144] When 2-silyloxyfuran was irradiated in the presence of aliphatic carbonyl compounds or with benzaldehyde, it gave a 1:1 mixture of regioisomeric products. On the contrary, when benzophenone was used, only the product deriving from the attack on the most hindered side of the molecule was recovered. The same result was obtained using acetone in a reaction when a low concentration of furan was used. In all the cases, an *exo* selectivity was observed.[145] On the contrary, 2-furylmethanol and the corresponding silyl ether gave a low regioselectivity.[145,146]

The high *exo* stereoselectivity of the reaction has been extensively studied: the formation of the product occurred on a triplet 1,4-biradical. The triplet biradical was converted into the singlet one to give the product. In order to explain the pronounced *exo* stereoselectivity, a secondary orbital effect can be postulated: an interaction between the rather flexible α-oxy radical center and the allyloxy ring localized radical in **49**, likely plays a major role (Figure 14).[147,148]

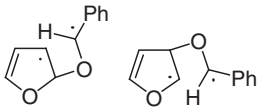
The regioisomeric biradical intermediates **A** and **B** resulting from the head-to-head and head-to-tail addition, respectively, have been examined (Figure 15).[69] The biradical **A** is more stable than **B** by 16.5 kcal mol^{-1}. The biradical **A** exists as two conformers and only that conformer able to give the ring closure was considered.

The HSOMO is mainly localized on the benzaldehyde fragment of the biradical whereas the LSOMO is mainly localized on the furanoid part of the molecule. The HSOMO and LSOMO of the biradical **A** are reported in Figure 16. The coupling between the radical carbons in these two orbitals, considering that the atomic orbitals involved can superimpose themselves, can give only the *exo* isomer, in agreement with the experimental results (Figure 17).



49

Figure 14 Structure of the biradical intermediate in the reaction of furan with benzaldehyde.



A **B**

Figure 15 Possible biradical intermediates in the reaction of furan with benzaldehyde.

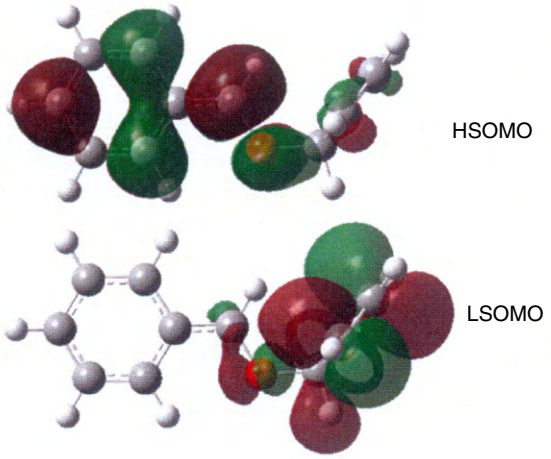


Figure 16 HSOMO and LSOMO of the biradical intermediate **A** (reproduced with permission of Bentham Science Publishers).

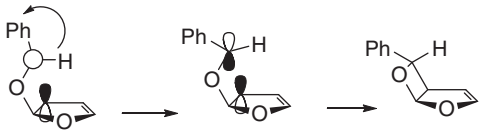


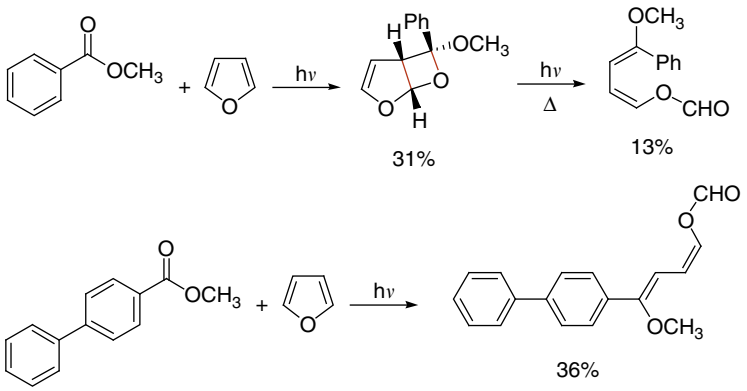
Figure 17 Ring closure reaction in the formation of the *exo* isomer of the adduct between furan and benzaldehyde.

When the reaction was carried out in benzene, dimers can be obtained.[55,149–151] Furan reacted with chloral to give unexpectedly the corresponding 2-furyl carbinols.[152] Furthermore, 2-cyanofuran did not react, whereas 2-furfural diacetate and furfural ethylene acetal showed low reactivity.[152]

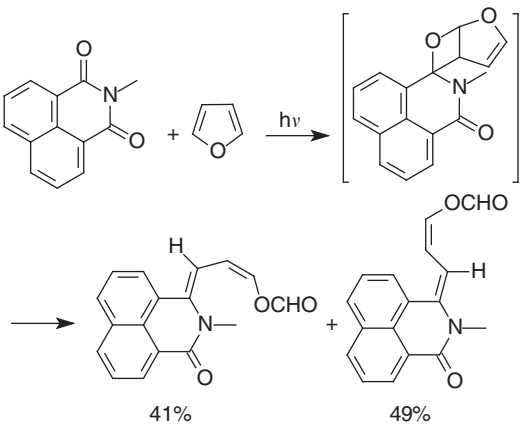
The cycloaddition reaction can be performed on esters. In this case, the adducts can be obtained in a few cases. In most of the examples, they underwent a cycloreversion reaction to give the ring opening products (Scheme 42: the bonds are broken in the cycloreversion reaction are in red).[153] More recently, this result has been questioned and a 95:5 mixture of stereoisomeric adducts was identified as the product.[148] Cycloreversion products were obtained also in the reaction of furan in the presence of furan-2-carboxyaldehyde.[154]

Coupling products can be obtained carrying out the reaction between an amide and furan: also in this case the cycloadduct cannot be isolated, but the subsequent decomposition products can be isolated (Scheme 43).[155] Furan quenches the fluorescence of the substrate, whereas a small new emission at 500 nm appears: this evidence is in agreement with a mechanism involving a reaction in the excited singlet state via the formation of an exciplex.

The reaction of some aromatic carbonyl compounds (benzophenone, benzaldehyde) with benzofuran has also been reported (Scheme 44); when compounds showing high triplet energy were used, dimers of benzofuran were obtained. On the contrary,

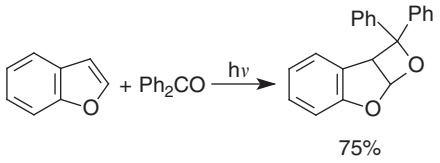


Scheme 42



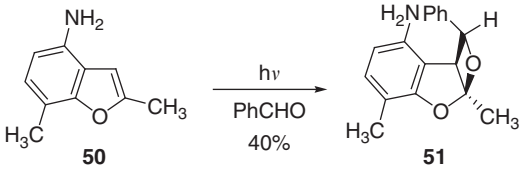
Scheme 43

when carbonyl carbonyl with a low triplet energy were used, oxetanes were the products of the reaction.[156] As in the case of furan, Schenck obtained only one regioisomer. A reinvestigation of the reaction of benzofuran when it was irradiated in the presence of acetophenone or propiophenone, showed that, also in this case, the corresponding oxetanes were the products of the reaction.[157]



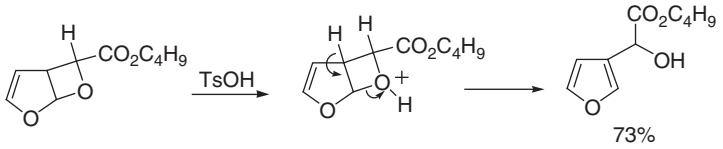
Scheme 44

The irradiation of **50** in the presence of benzaldehyde in benzene gave the corresponding adduct **51** in good yields (Scheme 45).[158] It is interesting to note that the reaction allowed the formation of the *endo* isomer. The reaction between benzo[*b*]furan and benzaldehyde gave an adduct whose stereochemistry has not been described.[156]



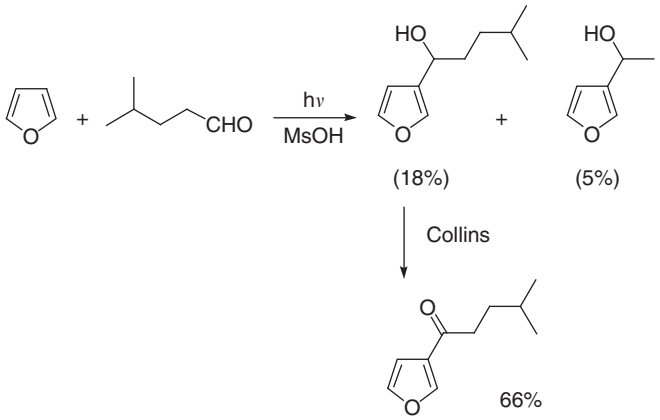
Scheme 45

3-Furylcarbinol derivatives could be obtained through the treatment of the oxetanes with TsOH.[142] The formation of a protonated oxetane is in agreement with the high negative entropy of activation (Scheme 46).[159]



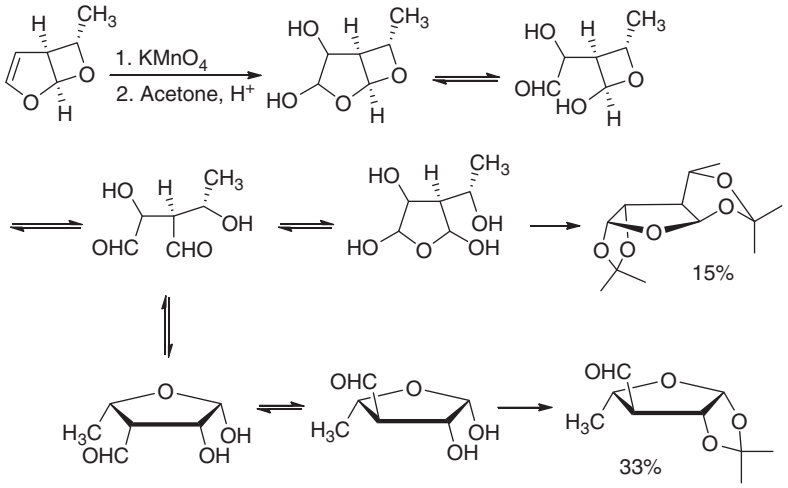
Scheme 46

If the irradiation was performed in the presence of an acid, 3-furylcarbinol can be obtained in a one-step procedure in better yields.[160] This procedure has been used in the synthesis of perillaketone, a naturally occurring 3-substituted furan (Scheme 47).[160] On the contrary, Lewis acids catalyzed a different behavior: the treatment with $BF_3 \cdot Et_2O$ gave only 3-substituted furan in THF and 89% of 2-substituted furan in acetonitrile.[159]



Scheme 47

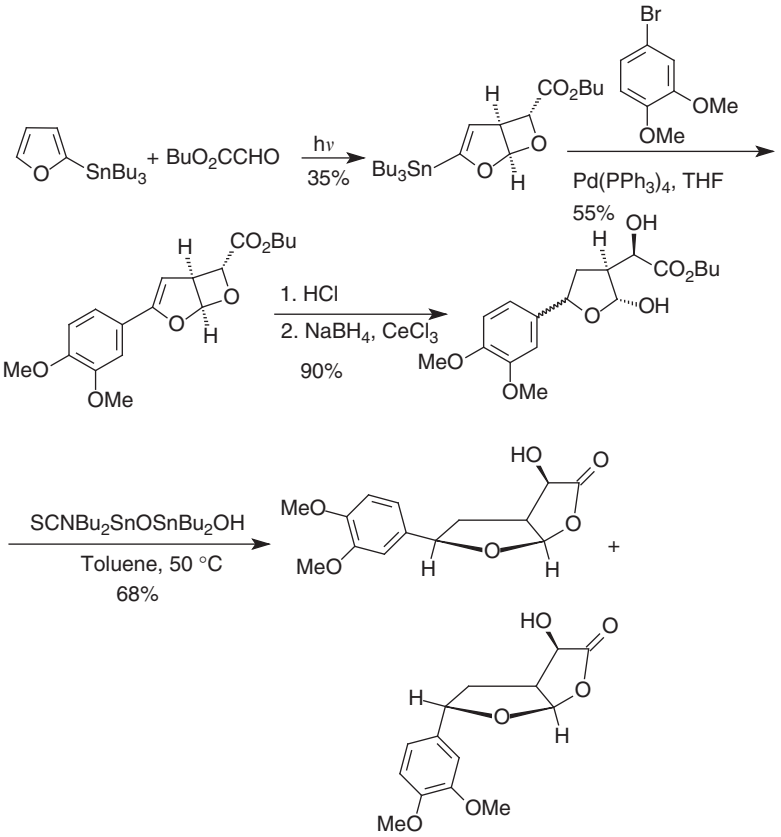
The oxetane derivatives were treated also with $KMnO_4$ and the resulting *cis* diol reacted with acetone in the presence of an acid. This procedure allowed the synthesis of a carbohydrate derivative (Scheme 48).[161]



Scheme 48

An epimerization reaction occurred on the *trans* diol obtained when the oxetane was treated with MCPBA.[161] Schreiber studied the possible chemical modifications on the cycloadduct deriving from the reaction between an aldehyde and a furan.[162]

Hydrolytic ring opening, reductions, hetero Diels–Alder, the reaction with MCPBA, and hydroboration–oxidation were the reactions he studied. The reaction with MCPBA was used by Schreiber and coworkers in the synthesis of Asteltoxin,[163,164] and in that of Avenaciolide, an antifungal metabolite.[165] The reaction of tributylstannylfuran with butyl glyoxylate was used in the synthesis of a ginkgolide B-kadsurenone hybrid of two inhibitors of a platelet activating factor (Scheme 49).[144]



Scheme 49

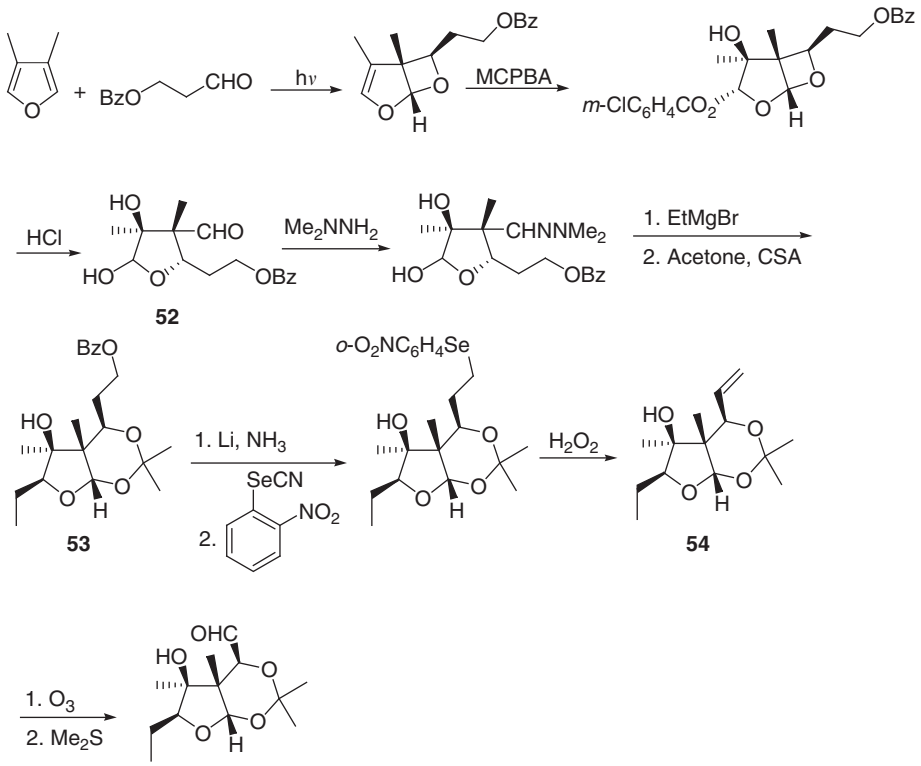
In the synthesis of Asteltoxin, the synthetic sequence implies the photochemical coupling of 3,4-dimethylfuran with a functionalized aldehyde to give the corresponding adduct in 63% yield. The subsequent reaction with MCPBA gave the protected *trans* diol that was converted into **52** through acid hydrolysis. Then, the aldehyde was converted into the corresponding hydrazone and this substrate was treated with EtMgBr to give **53** with complete stereochemical control obtained through chelation. The subsequent conversion of the benzyl ether into a seleno derivative and the elimination of the selenoxide gave **54**. Compound **54** could be treated with ozone to give the corresponding aldehyde that was then converted into Asteltoxin (Scheme 50).

In fact, the aldehydic product could be alkylated with a vinyl anion and the subsequent double [2,3] sigmatropic rearrangement at room temperature furnished **55** as a 3:1 mixture of epimers. Camphorsulfonic acid induced the transposition of the substrate into a bis(tetrahydrofuran) derivative. Pummerer rearrangement and hydrolysis gave aldehyde **56**. Aldol condensation gave **57** and elimination gave Asteltoxin (Scheme 51).

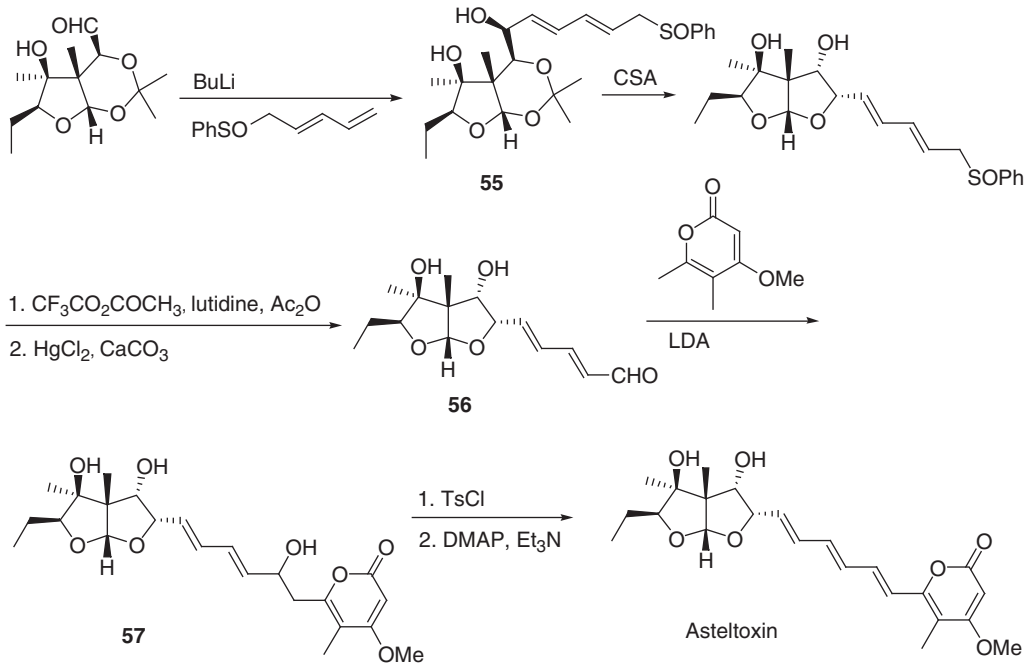
The same research group reported a formal synthesis of Avenaciolide, an antifungal metabolite (Scheme 52). In this case the oxetane (obtained in multigram quantities in high yields and with complete stereochemical control) was treated with hydrogen to give the saturated compound. The key step in this synthetic procedure is a reaction with ozone followed by a base catalysed epimerization with potassium carbonate and cyclization in acidic medium.

Furthermore, the cycloadduct obtained from the reaction between furan and an aldehyde can be treated with an excess of Schlosser's base (BuLi, *t*-BuOK). The reaction gave the corresponding anion which can react with carbonyl compounds or alkyl halides (Scheme 53).[166]

The most important target in this field was oxetanocin (**3**), a nucleoside isolated from *Bacillus megaterium* NK 84-0218 showing anti-HIV activity. An approach to the synthesis of this compound has been reported.[167] The treatment of oxetane **58** with *N*-iodosuccinimmide in the presence of methallyl alcohol gave the corresponding iodoacetals **59** (Scheme 54). The subsequent treatment of **59** with iodonium di-*sym*-collidine perchlorate (IDCP) gave **60** in low yields as a relatively unstable mixture of



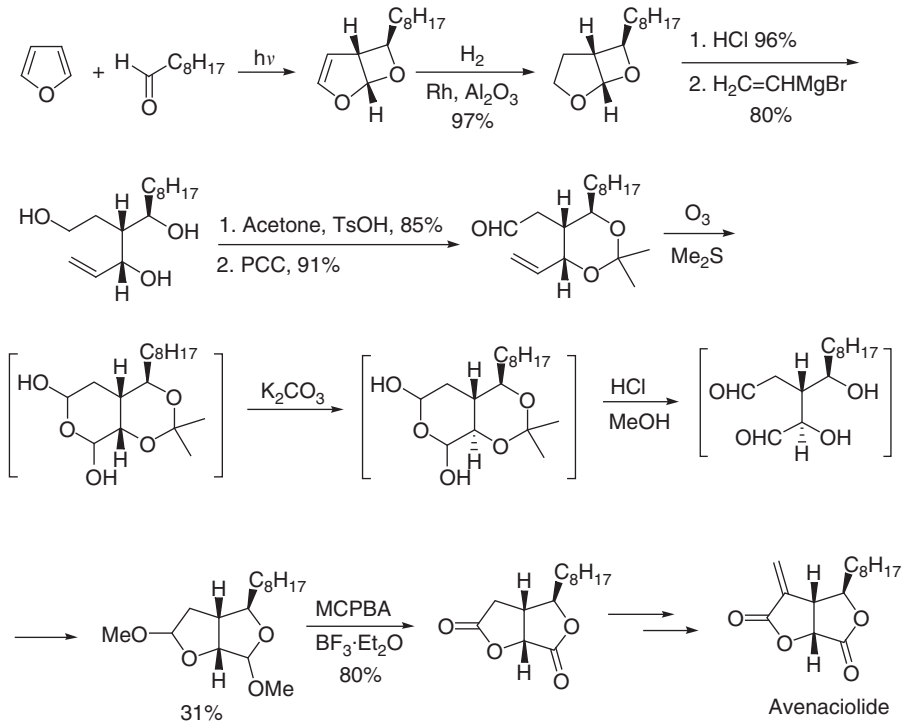
Scheme 50



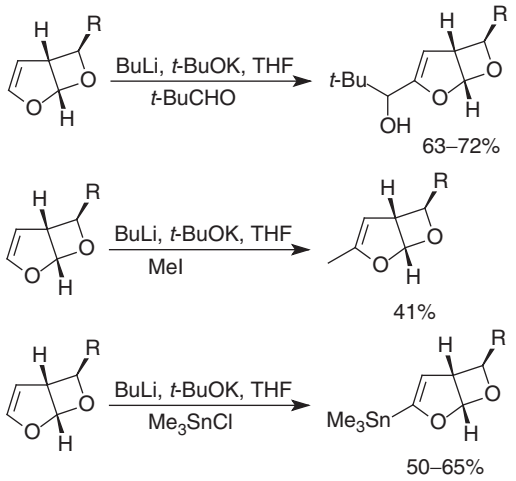
Scheme 51

diastereoisomers. Alternatively, treatment of **61** with dimethyl dioxirane gave the corresponding epoxide and the treatment with methallyl alcohol gave the hydroxy acetal **62**. The treatment of **62** with IDCP gave **63** in moderate yields.

Oxetanocin was also obtained carrying out the reaction between 2-methylfuran and benzoyloxyacetaldehyde.[168] The corresponding adduct was treated with ozone and the product was reduced with $NaBH_4$. The obtained alcohols were protected. Product **64** was treated with *N*-benzoyl-disilyladenine and $SnCl_4$ to give **3** (Scheme 55).



Scheme 52

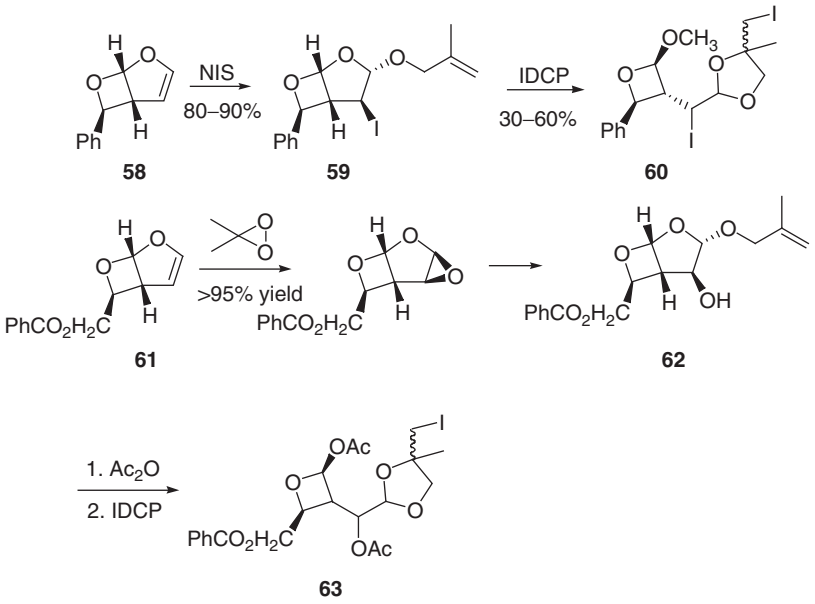


Scheme 53

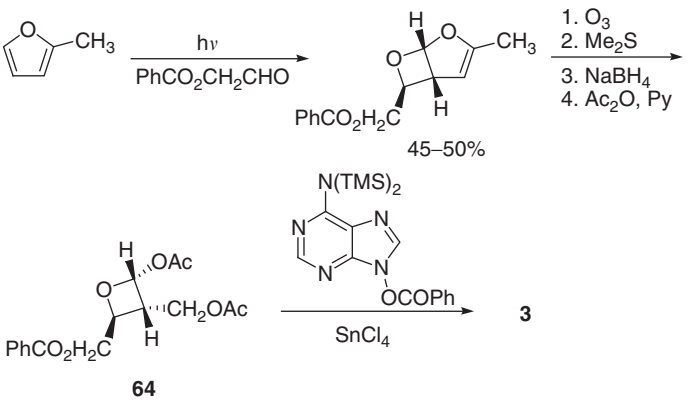
The reaction of glyoxylates with furan can be performed also using chiral glyoxylate. In particular, the use of *R*-(–)-menthol, 2-octanol, and 2,2-dimethyl-3-butanol as chiral auxiliaries gave the corresponding oxetanes in high yields. These compounds can be converted into the corresponding 3-substituted furans. The furans showed low enantiomeric excess (Scheme 56).[169] On the basis of the experimental data the configuration of the oxetane was 1*R*,5*S*,6*S*.

The use of chiral phenylglyoxylate gave better results. The use of chiral alcohols gave diastereoisomeric excess in the range of 4–80% (Scheme 57).[170–172]

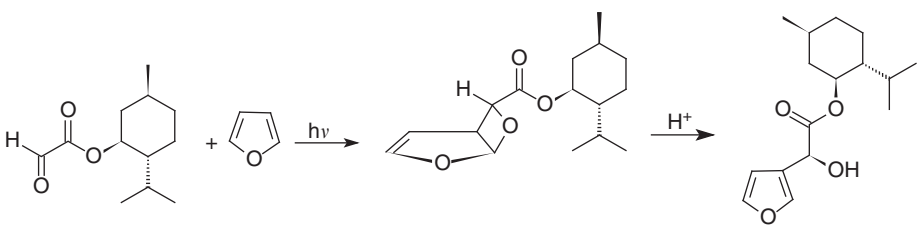
An important variability of the diastereoisomeric excess in function of the temperature has been observed with the presence of an inversion temperature.[173] These results were explained assuming that the diastereoselection was produced on two levels: (1) the preferred formation of the diastereoisomeric 1,4-biradical intermediate **65** and (2) the preferred retrocleavage of the energetically unfavored diastereoisomeric intermediate **66** to the starting materials.[174] The diastereoisomeric excess in the high-temperature region ($T > T_{inv}$) is dominantly controlled by steric effects of the chiral auxiliaries, whereas in the low-temperature



Scheme 54



Scheme 55

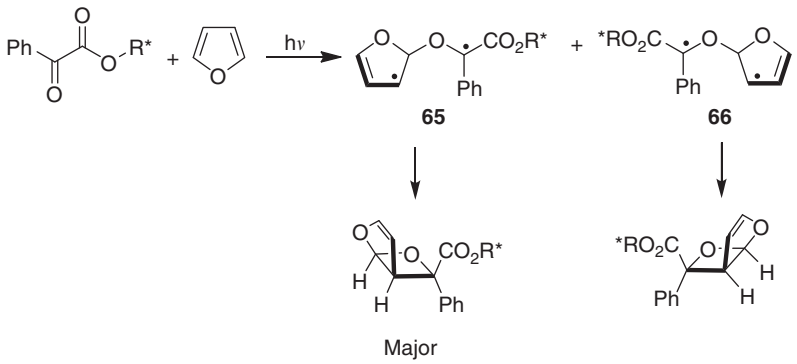


Scheme 56

region ($T<T_{inv}$), the nature of the olefin has a dominating influence. When the reaction is carried out on 2-methylfuran, a 2:1 regioisomeric mixture was obtained with a very high diastereoisomeric excess.[175]

In order to justify the observed stereoselectivity the triplet biradical intermediates in the reaction of some phenylglyoxylate derivatives with furan could be considered.[173] Calculations on these biradical intermediates showed that **67** (the precursor of the observed product) was more stable than **68** by 0.73 kcal mol^{-1} (Figure 18).

Neckers studied the reaction of ethyl phenylglyoxylates with several alkenes showing that it gave the cycloaddition reaction only when electron-rich alkenes were used. Furthermore, the main reaction observed when monosubstituted alkenes were used



Scheme 57

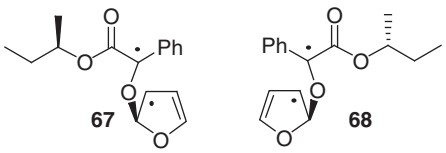
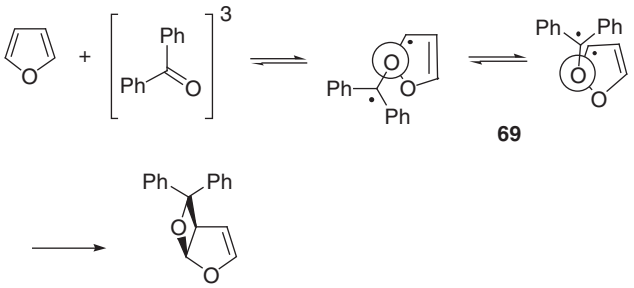


Figure 18 Radical intermediates in the reaction of chiral phenylglyoxylates with furan.

was the Norrish type II reaction and the same behavior was observed reducing the electron richness of the alkenes.[176] Methyl 2-thienylglyoxylate showed a transient absorption at 390 nm and a broad band at approximately 600 nm. This transient band has been assigned to the triplet state. This compound reacted with 2,3-dimethyl-2-butene to give the corresponding adduct.[177]

To improve diastereoselectivity, the reaction was carried out in an organized medium, for example, in the presence of different zeolites.[178] NaY was the best solid zeolite support for this reaction. The origin of this behavior can be explained considering the possible effect of the confinement on the reaction. In the Paternò–Büchi reaction the biradical intermediate **69** can assume two possible conformations.[30,68] One has the radical carbons in almost *anti* conformation, whereas the other one shows a *syn* conformation (Scheme 58).

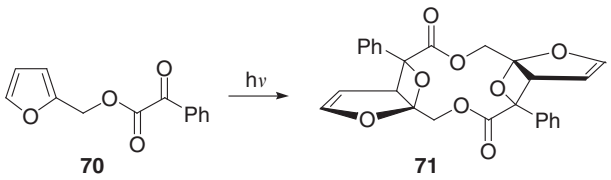


Scheme 58

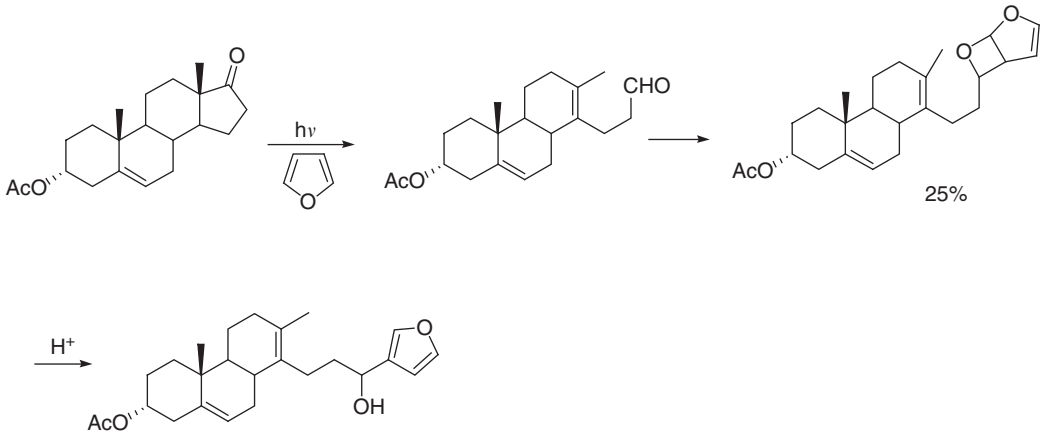
The *syn* conformation can undergo the following cyclization, after the intersystem crossing from the triplet to the singlet state. For the *anti* conformation the most favored process is the retrocleavage to the starting material. The *syn* conformations take up a smaller volume than the *anti* one. The preferential formation of a stereoisomer in the reaction within a zeolite could be explained: the *SS-syn* conformer was obtained preferentially, whereas the *RS* conformer was obtained preferentially in *anti* conformation. The latter conformer has to rotate along the C–O bond to give the *syn* conformation the ability to cyclize. Zeolites could act as agents able to reduce the conformational mobility of the intermediates. They inhibited the rotation of this conformer and, then, favored the formation of the product deriving from the (*S*,*S*)-biradical intermediate.

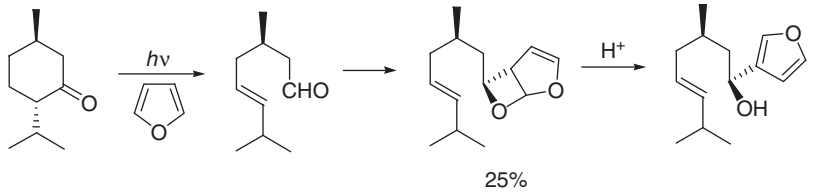
Recently, Abe reported an attempt to obtain an intramolecular version of the Paternò–Büchi reaction between furan and a carbonyl compound. Nevertheless, the irradiation of the phenylglyoxylate derivative **70** allowed only the formation of the product **71**, deriving from an intermolecular reaction. Low yields were obtained (Scheme 59).[179]

The irradiation of furan in the presence of acyl cyanides yielded the corresponding oxetanes but both diastereoisomeric *endo*- and *exo*-oxetanes are formed. Low asymmetric induction was observed when chiral acyl cyanides were used.[180] Furan reacted also with chiral ketones. In this case, before the 2 + 2 cycloaddition, an α-cleavage reaction modified the expected products (Scheme 60). A chiral product was obtained as a 2:1 diastereoisomeric mixture where the most abundant product has 1*R*,3*R*



Scheme 59

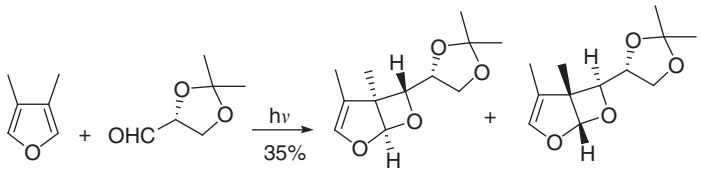




Scheme 60

configuration when (–)-menthone was used as a substrate.[181] If the irradiation was performed on the ketonic functional group in a protected carbohydrate, a complex reaction mixture was obtained.[182,183]

The reaction between 3,4-dimethylfuran and *R*-isopropylidene glyceraldehyde was performed in order to obtain a stereoselective Paternò–Büchi reaction. The coupling products were obtained with an overall yield of 35% as a 1.2:1 mixture of diastereoisomers. Furthermore, the compound **72** was obtained with 54% *ee* (Scheme 61).[184]

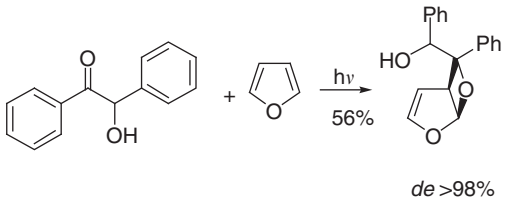


72 12 : 1

Scheme 61

This behavior suggested a mechanism that was insensitive to the substitution pattern of chiral aldehydes. Reaction between an excited aldehyde (singlet or triplet state) and furan proceeds with initial carbon–oxygen bond formation to produce either of the two biradical species. The stereocenter adjacent to the carbonyl is now in a 1,4-relationship to the newly formed stereocenter at the acetal carbon and is expected to exert little influence as a stereocontrol device.[184] This hypothesis is not in agreement with the stereochemical behavior of using phenyl glyoxylate esters where the chiral carbon atom was farther than in *R*-isopropylidene

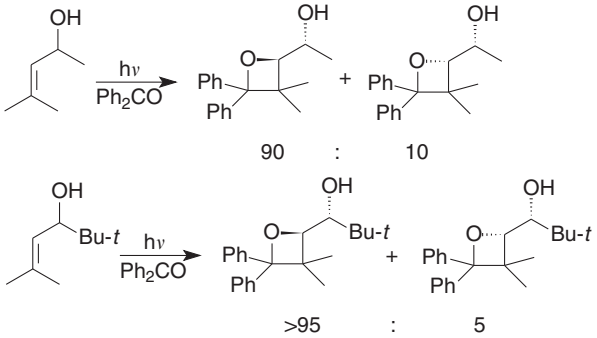
glyceraldehyde. The extensive racemization observed probably reflects the photolability of the aldehydes toward racemization under the conditions of the reaction.[184] Nevertheless, compound **72** can be used in a chiral synthesis of the bicyclic part of asteltoxin confirming the assigned absolute configuration.[184] On the contrary, benzoin reacted with furan to give the corresponding adduct in acceptable yield (56%) and *de* > 98% (Scheme 62).[185]



Scheme 62

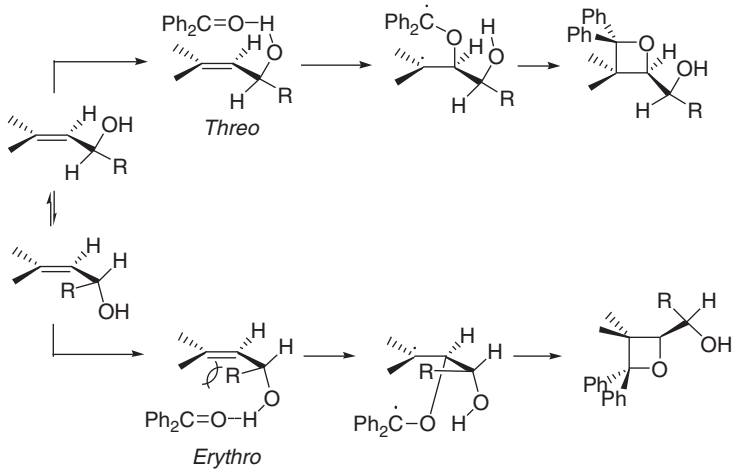
The observed stereoselectivity was explained considering the relative stability of the biradical intermediates. Nevertheless, chiral ketones gave the Norrish Type II reaction as the only observed reaction. In order to avoid Norrish Type II reaction a substrate without γ-hydrogen was used.[186]

In 1990 Griesbeck found that the reaction of benzaldehyde with homoallylic alcohols did not show diastereoselectivity.[61] Nevertheless, Adam showed that allylic alcohols reacted with benzophenone to give the corresponding adducts with high regio- and diastereoselectivity (Scheme 63).[187–190]



Scheme 63

In the presence of protic methanol, the diastereoselectivity dropped drastically, whereas it totally disappeared using the corresponding silyl ethers. These data are in agreement with the presence of a hydroxyl directing effect in the Paternò–Büchi reaction. The formation of a hydrogen bond between triplet excited benzophenone and the substrate in the exciplex favored the formation of the *threo* isomer. On the contrary, the formation of the *erythro* stereoisomer would be less favored due to allylic strain (Scheme 64).



Scheme 64

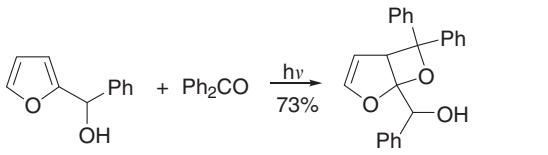
The formation of a hydrogen bond to direct the Paternò–Büchi reaction has been considered by other researchers. Diastereoselective cycloaddition has been obtained using chiral enamide,[191,192] or in the reaction of allylic alcohols with naphthalene rings.[193] When unsymmetrical carbonyl partners such as acetophenone or benzaldehyde were used, the corresponding *cis* isomer was observed with high diastereoselectivity. The regioselectivity was high with acetophenone but lower with benzaldehyde.[188]

Cis diastereoselectivity can be explained using the Griesbeck rule on the possible triplet biradicals formed in the reaction. Steric interactions are minimized when the biradical assumes the optimal conformation and this conformation accounts for the formation of the observed stereoisomer.[190]

When chiral allylic alcohols were used as substrates in the reaction *cis* diastereoisomers were formed. Furthermore, also in this case, a pronounced *threo* diastereoselectivity was observed, in agreement with a less pronounced hydroxyl directing effect when acetophenone and benzaldehyde were used.[188,190] Chiral allyl ether gave the corresponding adduct with high diastereoselectivity.[98] It is to be noted that this result is not in agreement with previous reported data on the reactivity of silyl ethers of allylic alcohols.[187]

The reaction of 2,3-dihydrofuran-3-ol derivatives (a particular type of allylic alcohol) with benzophenone gave the corresponding adducts. In methanol, a *trans* relationship between the oxetane ring and the hydroxyl group was observed, whereas, in benzene, the *cis* isomer prevailed. The Eyring plot showed that the *trans* isomer increased with a nonlinear behavior on decreasing the temperature.[194]

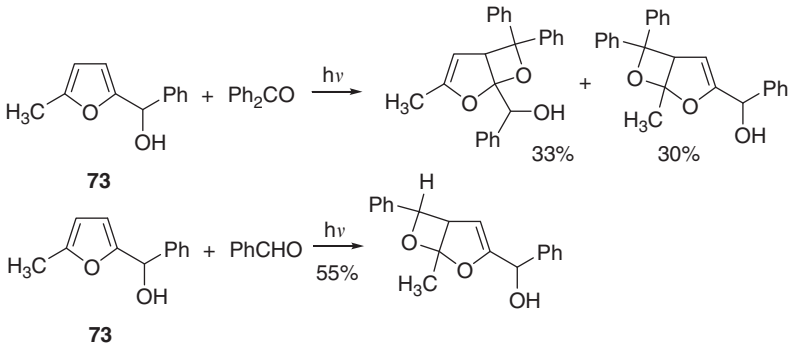
The reaction of allylic alcohols with carbonyl compounds was tested also on 2-furylmethanol derivatives. The presence of large substituents on the carbon bearing the alcoholic function allows a high regioselectivity (Scheme 65).[195]



One diastereoisomer

Scheme 65

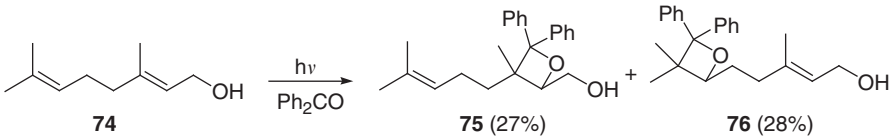
5-Methyl-2-furyl derivatives were used as substrates showing a different regioselectivity. Compound **73** gave a 1:1 mixture of regioisomers, when irradiated in the presence of benzophenone, and a single regioisomer in the presence of benzaldehyde (Scheme 66).[196] In agreement with the results obtained with 2-furyl derivatives, the products deriving from the attack on the side bearing the alcoholic function were obtained as a single diastereoisomer, whereas those deriving from the attack on the side bearing the methyl group were obtained as a mixture of diastereoisomers.



Scheme 66

The above described reactions showed that on furan two possible regioisomers could be obtained. The experimental results showed that, in some cases, the reactions occurred mainly on the side when the hydroxyl group was present, whereas other reactions showed a completely different regioselectivity. The reason of this behavior can be found in kinetic factors depending on the different stability of the biradical intermediates. These considerations are in agreement with the results obtained irradiating geraniol (**74**) in the presence of benzophenone (Scheme 67).[197]

In this case, two different double bonds were present: a double bond able to give a tertiary radical intermediate, and an allylic alcoholic moiety. The authors found that at $-75\ ^{\circ}C$ **76** was obtained in 44% yields whereas **75** was obtained only in 13% yields. Furthermore, at $20\ ^{\circ}C$ the yields were 29% and 15%, respectively. In this case, then, the attack on the terminal double bond was favored.



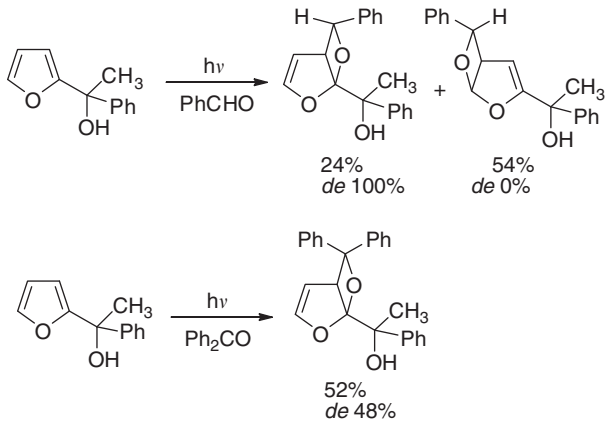
74 **75** (27%) **76** (28%)

Scheme 67

The reaction of 2-furylmethanol derivatives with aliphatic aldehydes and ketones gave the corresponding adducts with high regioselectivity: the reaction occurred on the most hindered side of the substrate. However, no diastereoselectivity was observed.[198] The relative stability of the biradical intermediates was able to explain the regioselectivity of the reaction. A computational study (density functional theory (DFT)) showed that the biradical obtained on the most hindered side of the molecule was more stable than the other one.[196]

The diastereoselectivity of the reaction between 2-furylmethanol derivatives and aromatic carbonyl compounds clearly showed that it increased in relation to the nature of the substituents on the carbon bearing the alcoholic function as described by Adam. However, whereas Adam considered the allylic strain with a methyl group in β-position as the driving force for the diastereoselectivity, in this case, a methyl group on the C-3 of the furan ring was not present.

In order to have more data to explain the observed stereoselectivity the photochemical behavior of tertiary 2-furylcarbinols was studied.[199] The irradiation of 1-methyl-1-phenyl-1-(2-furyl)methanol with benzaldehyde gave a mixture of two regioisomeric products. The regioisomer on the most hindered side of the molecule was obtained in low yield, but it showed a complete diastereoisomeric control. On the contrary, the main product was a mixture of four diastereoisomeric products (Scheme 68). The reaction of the same compound with benzophenone gave only the product deriving from the attack on the most hindered side of molecule. This compound was obtained with 48% diastereoisomeric excess.



Scheme 68

The regioselectivity was explained, as described above, considering the relative stability of the biradical intermediates. In this case, in the reaction of the 1-methyl-1-phenyl-1-(2-furyl)methanol with benzaldehyde the biradical obtained on the less hindered side of the substrate was more stable than the other one by 18.03 kJ mol^{-1}. Recently, some authors reported that no stereoselectivity was observed using cyclic 2-furyl methanol derivatives.[200] However, in another work, the stereoselective behavior of the same substrates was assumed.[201]

On the basis of these results an explanation of the stereochemical behavior was attempted.[199] 1-Methyl-1-phenyl-1-(2-furyl)methanol showed three conformations. All three conformers were in the range of 1.97 kJ mol^{-1} and they did not show a preference. The directing effect exerted by the hydroxyl group is due to the formation of a hydrogen bond between the hydroxyl group and the oxygen of the excited carbonyl compound, or it is due to the formation of a complex. This type of interaction could favor the formation of a preferential conformation in the biradical intermediate where the hydroxyl group and the oxygen of the carbonyl compound are near. These conformations could have different energies for different diastereoisomeric biradicals, giving an explanation of the observed behavior. In the case of 1-methyl-1-phenyl-1-(2-furyl)methanol, if the hydroxyl group drove the attack of the oxygen of the carbonyl group, the conformations of the biradical intermediate represented in Figure 19 were obtained. **B** and **D** were the preferential conformations: calculations on these conformations showed that there was a difference of 13.26 kJ mol^{-1} between the energies of these two conformations. This difference can account for the observed complete diastereoselectivity of the reaction. In the reaction of the same substrate with benzophenone, the corresponding conformers **B** and **D** showed a difference energy of 7.79 kJ mol^{-1}: this difference is in agreement with the observed diastereoselectivity.

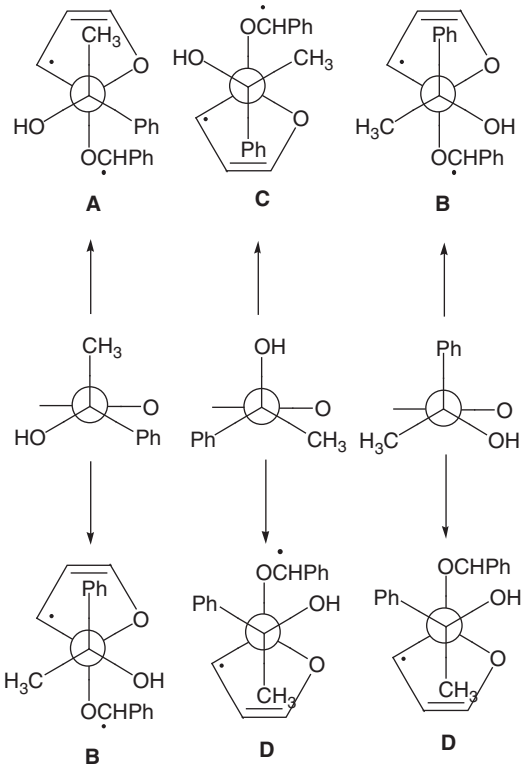
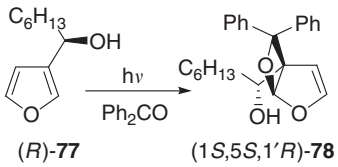


Figure 19 Possible conformations of the biradical intermediate from the reaction of 1-methyl-1-phenyl-1-(2-furyl)methanol with benzaldehyde.

The same approach can be used to justify the stereochemical behavior of the reaction of allylic alcohols with benzophenone.[202] The irradiation of (*R*)-**77** in the presence of benzophenone gave the (1*S*,5*S*,1′*R*)-**78** (Scheme 69).[203]



Scheme 69

The above reported results in this section represent all the available data on the Paternò–Büchi reaction on pentaatomic heterocycles. One can see that, with the exception of furan, there are very few data: in particular, (1) most of the unsubstituted tested compounds different from furan did not react, (2) only a few substituted derivatives showed a significative reactivity toward excited carbonyl compounds.

This behavior may be due to different reasons. First, the different aromaticity of the compounds could play an important role in order to define the reactivity of the compounds. Furan is the lowest aromatic pentaatomic heterocyclic compound known, whereas the other compounds show higher aromaticity. However, this type of explanation cannot justify why thiophene does not react whereas simple dimethylthienyl derivatives react and why some dimethylthienyl derivatives react whereas some others do not show any reactivity.

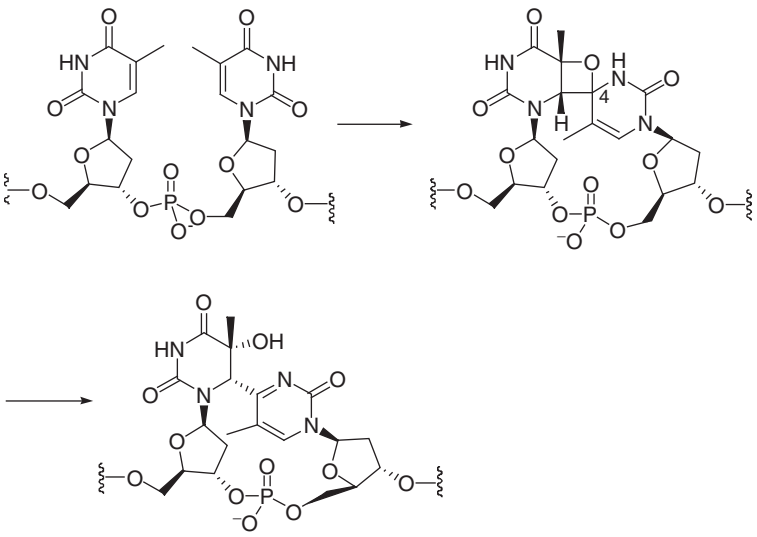
A different explanation was identified in the quenching properties of these heterocycles. Thiophene and monomethyl derivatives are efficient quenchers of triplet benzophenone. The Stern–Volmer plot showed a linear relationship.[204,205] On the contrary, 2,5-dimethylthiophene (a compound able to give the cycloaddition reaction) is not a good quencher of the triplet benzophenone.[206] In this case, the Stern–Volmer plot is not linear. This situation is commonly encountered when the quencher employed quenches two excited states. It seems reasonable that pyrrole acts as quencher of both triplet benzophenone and the exciplex between triplet benzophenone and pyrrole.[206]

On the basis of these investigations, the common five-membered heterocycles may be classified into two categories in regard to their quenching properties: those with electron-donating groups, which give Stern–Volmer plots in the shape of straight lines, and those substituted with halogens and electron-attracting groups, such as *N*-benzoylpyrrole, which give parabola-shaped curves.

Those in the first category give oxetanes when they are bad quenchers. Since these compounds do not presumably form exciplexes, they should go from starting materials to products through a biradical intermediate. However, those in the second category most likely give oxetanes when they are good quenchers, as may be shown for 2,5-dibromothiophene, and furthermore they go from starting materials to products through an exciplex.[207]

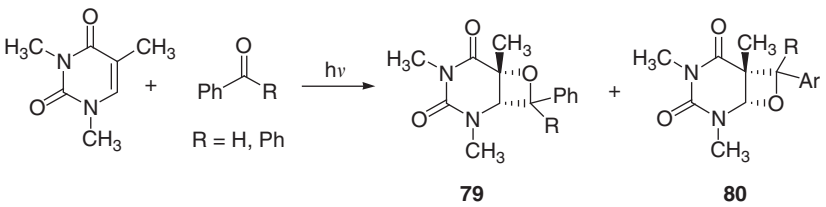
5.05.2.2.2 Reactions of six-membered heterocycles

The (6–4) photoproduct is an adduct of two pyrimidines that occupy adjacent sites on the same DNA strand. It is the second major lesion induced in DNA by UV radiation. Although statistically four times less frequent than CPD lesion, (6–4) photoproducts are believed to be severely mutagenic. Its formation is believed to occur via an initial Paternò–Büchi type cycloaddition to form an oxetane intermediate. Subsequent C4–O bond cleavage gave the observed (6–4) photoproducts (Scheme 70).



Scheme 70

The (6–4) photoproduct is one of the major mutagenic classes of DNA photoproducts and is involved in the etiology of skin cancer. The oxetane **79** was prepared in a triplet reaction and both electron donor and acceptor substituents were found to be able to photosensitize the splitting reaction (Scheme 71).[208–211] Only one regioisomer (**79**) was observed. The other regioisomer **80** was rarely observed.[212]

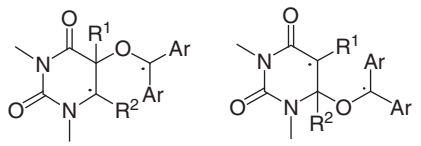


Scheme 71

The temperature can determine the regiochemistry of the reaction. At −38 °C the regioisomer **79** dominates (61:39). However, at 70 °C the regioisomeric behavior of the reaction is inverted.[212,213] A change of the selectivity-determining step has been determined considering a nonlinear Eyring plot. Two different cases can be assumed: the situation where the conformational changes of the triplet intermediates were slower than ISC at low temperature and the case where the conformational changes exceed the ISC process.[213] When the conformational interchange is faster than the ISC process, the population of high potential energy conformations decreases, whereas the population of a lower potential energy conformer increases.

A weak solvent effect was observed on the regioselectivity of the reaction.[214] Substituents on benzophenone modified the regiochemistry of the reaction: when *p*-methoxybenzophenone is used on 1,3-dimethyluracil the isomer **79** is obtained (**79**/**80** > 95:5), whereas, using *p*-cyanobenzophenone, a 32:68 **79**/**80** ratio was observed.[215,216] The benzophenones with electron-withdrawing groups gave more efficient Paternò–Büchi reactions and lower **79**/**80** ratios, whereas benzophenones with

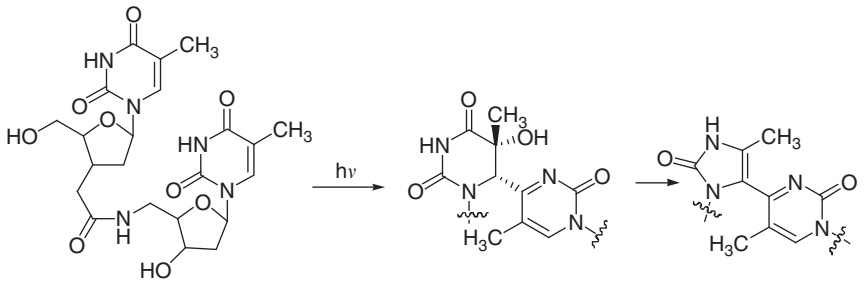
electron donating groups underwent less efficient Paternò–Büchi reactions and had higher **79**/**80** ratios.[217] The quantum yields correlated with the energy gap between SOMO of benzophenone derivatives and the HOMO of the uracil. Recently, a computational approach to this reaction appeared.[218] The authors studied the biradical intermediates **81** and **82** (Figure 20). They found that **82** is more stable than **81**, and that the formation of **81** is faster than **82**. Then, **80** can be considered as a thermodynamic product, whereas **79** a kinetic one.



81 **82**

Figure 20 Biradical intermediate in the reaction of dimethyluracil.

Recently, it has been observed that, due to the energy barriers between the two stable conformers, the equilibrium was more favorable for the formation of the oxetane **80**, rather than oxetane **79** at a higher temperature. Triplet benzophenones with a short lifetime would give rise to a less efficient Paternò–Büchi reaction.[217] The oxetane was obtained also in the reaction between benzophenone and benzophenone-derived drugs and thymidine.[211,219] An enantioselectivity factor for triplet deactivation was found using enantiopure ketoprofen. The use of enantiopure ketoprofen showed that thimidine was able to give an enantioselective quenching of the chiral ketoprofen triplet state. This quenching was related to the formation of the C–O bond, the first step of oxetane formation.[67] An intramolecular reaction between thymidine esterified by ketoprofen has been reported.[220] The irradiation of **83** gave **85** deriving from the (6–4) photoadduct **84** (Scheme 72).[221]



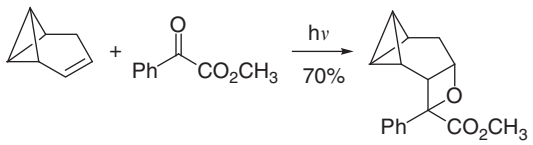
83 **84** **85**

Scheme 72

A reaction between 5-fluoro-1,3-dimethyluracil with 1,5-dimethoxynaphthalene has been reported.[222] The reaction gave product where an aromatic ring of naphthalene is broken. The presence of the intermediate adduct has been proposed.

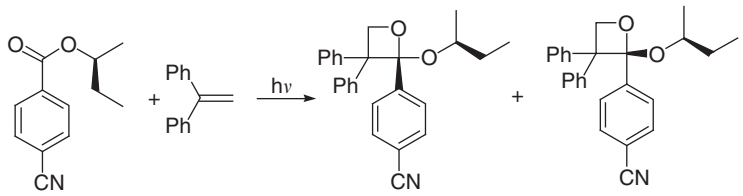
5.05.2.3 Other Intermolecular Reactions

5-Substituted adamantan-2-ones gave the corresponding cycloadducts via the n,π^* excited singlet state. This substrate gave a regiospecific reaction with a low stereoselectivity (the best result was 59:41 ratio in favor of the *anti* isomer).[223–226] Methyleneadamantane reacted with acetone. However, the Paternò–Büchi adduct was obtained in only 5% yield.[223] The reaction of biacetyl with benzvalene gave the corresponding adduct, whereas benzophenone gave, as the only product, benzene.[44] When homobenzvalene was used as the alkene in the reaction with ethyl phenylglyoxylate, the irradiation gave the corresponding adduct in 70% yield with high stereoselectivity (Scheme 73).[227]



Scheme 73

Esters could be used as carbonyl compounds in the reaction with chiral alkyl cyanobenzoate derivatives (Scheme 74).[228,229]



86 **87** (1′*S*,2*R*)-**88** (1′*S*,2*S*)-**89**

Scheme 74

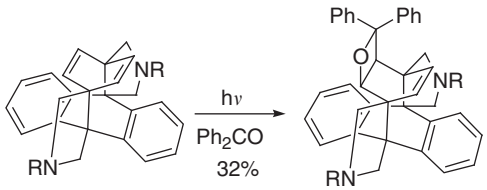
The reaction occurred through the first excited singlet state. The authors showed the presence of a charge transfer band at 300–330 nm. Irradiating at 254–290 nm, a good diastereoselectivity was observed (*de* 77%). The irradiation at 330 nm afforded the formation of an epimeric mixture. The photocyclization was likely to proceed via a short lived 1,4-biradical mechanism. Then, the diastereo-face-differentiating complexation of chiral alkyl cyanobenzoate with the olefin donor is responsible for the observed *de* values. Calculations showed that the conformational population in the charge-transfer complex is almost the same in agreement with the observed lack in diastereoselectivity.

A stereoselective behavior has been described in the reaction between benzophenone and cyclooctene. At $-95\,^{\circ}C$ the *cis* adduct was formed with a very high diastereoselectivity from *cis*-cyclooctene. On the contrary, at $-20\,^{\circ}C$ both diastereoisomers were generated. At higher temperatures, the *trans* adduct dominated. Over a broad temperature range (-80 to $+60\,^{\circ}C$), the more strained *trans*-cyclooctene gave nearly exclusively the *trans* adduct.[93,94] Triplet ketone could attack the double bond to give two biradical intermediates and the authors suggested that temperature-dependent conformational changes of the biradical competed with the cyclization to the oxetane and the retro cleavage to the *cis*-cyclooctene. The activation barrier between two conformers of the biradical intermediate could explain the increase of *trans*-oxetane with the temperature.[94]

1-Acetylisatin reacted with styrene and furan derivatives to give the *endo* adduct with high stereoselectivity.[230,231]

Quinones reaction with stilbene derivatives has been described.[73,232] In this case, a charge-transfer absorption band was observed at 480 nm. Time-resolved (ps) absorption spectrum showed an absorption at 480 nm (chloranil anion radical) and a broad band at approximately 760 nm. After 50 ps, a transient absorption typical for triplet chloranil at 510 nm was observed. The reaction occurred through selective excitation at 480 nm. Quinones reacted with diarylacetylene giving a product deriving from the ring opening of a transient oxetene. Time-resolved (ps) absorption spectrum was in agreement with an electron-transfer mechanism.[233] When 2-chloro-5-methoxybenzoquinone reacted with arylacetylenes, CIDNP experiments suggested a mechanism where the attack of the triplet quinone on the acetylene gives a biradical intermediate.[92] The same behavior has been observed in the reaction between quinone and quadricyclane and norbornadiene.[234,235] The adduct was also found in the reaction between quinones and acenaphthylene.[77]

Benzophenone can react also with a paracyclophane derivative **90** (Scheme 75).[236]



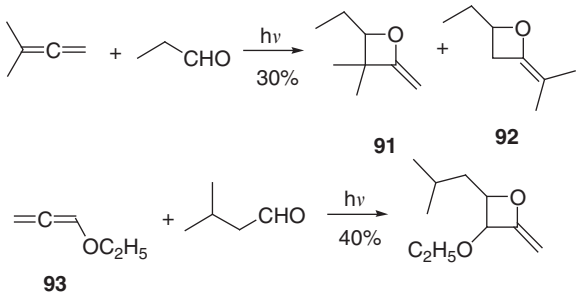
90

Scheme 75

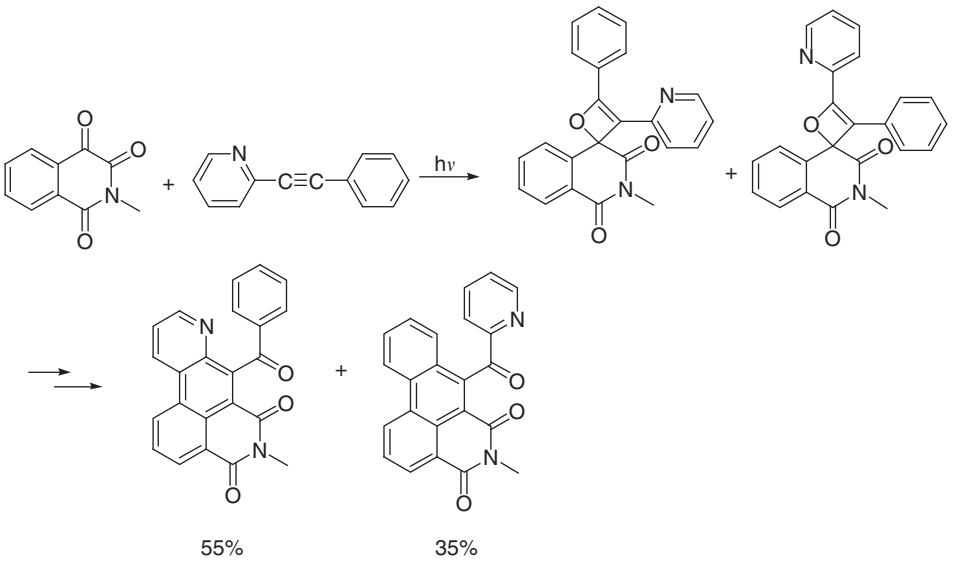
The Paternò–Büchi reaction can also be applied to other unsaturated systems other than alkenes, such as dienes,[10] allenes,[237] acetylenes,[238] and ketenimines.[237] When tetramethylallene reacted with aromatic ketones the main products resulted from bis-addition of the carbonyl compounds to give dioxaspiroheptanes.[239,240] On the contrary, 1,1-dimethylallene gave only the monoaddition 2:1 mixture of **91** and **92** in a reaction with aliphatic aldehydes (Scheme 76).[241] A higher regioselectivity was obtained using the allene **93** (Scheme 76).

The irradiation of isoquinoline-1,3,4-trione with alkynes gave a product deriving from an initial Paternò–Büchi reaction on the carbonyl at C-4 to give the corresponding oxetene (Scheme 77).[242]

DFT calculations on the relative stability of the biradical intermediate showed that the more stable one was the precursor of the main product of the reaction.



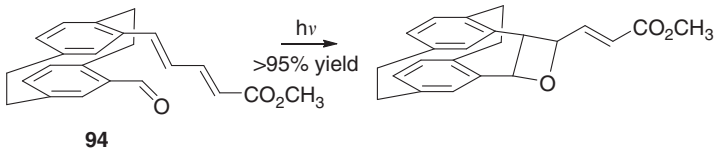
Scheme 76



Scheme 77

5.05.3 Intramolecular Reactions

An intramolecular Paternò–Büchi reaction on a paracyclophane derivative **94** has been reported giving the corresponding adduct in quantitative yield (Scheme 78).[90]

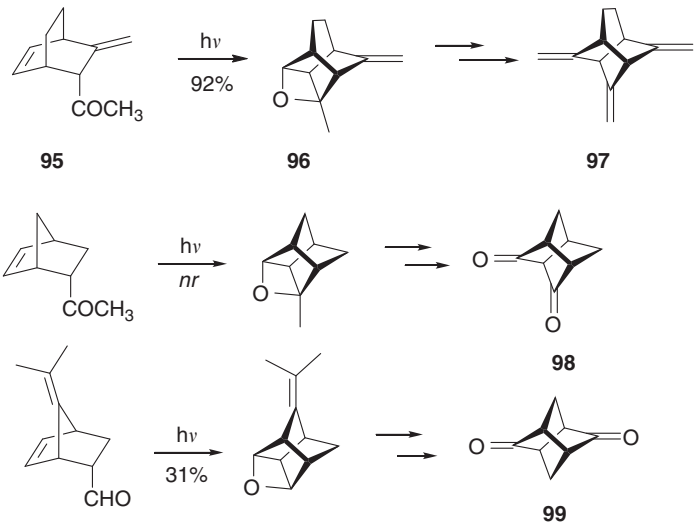


Scheme 78

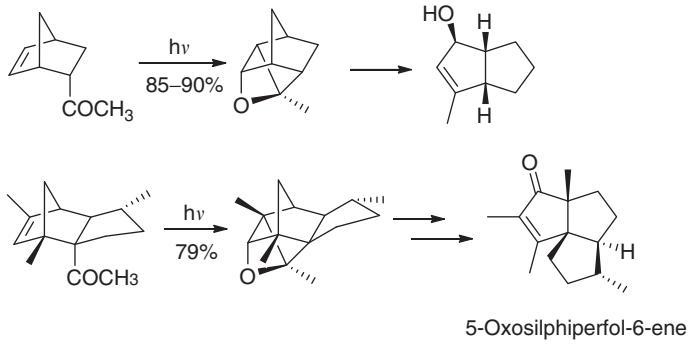
An intramolecular Paternò–Büchi reaction of **95** to give **96** has been used in the synthesis of 2,7,9-trimethylenetricyclo[4.3.0.0^{3,8}]nonane **97** (Scheme 79).[243]

The same synthetic scheme was used in the synthesis of 2,7,9-trimethylenetricyclo[4.3.0.0^{3,8}]non-4-ene.[244] The preparation of some stelladiones such as tricyclo[3.3.0.0^{3,7}]octane-2,4-dione **98** or tricyclo[3.3.0.0^{3,7}]-octane-2,6-dione **99** (Scheme 79).[245] This type of intramolecular reaction was the key step used in the synthesis of diquinanes and triquinanes (Scheme 80).[246–248]

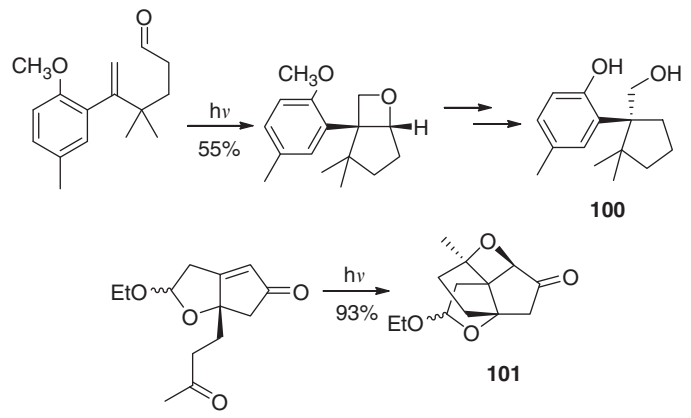
The synthesis of 1,13-herbertenediol **100** was performed using an intramolecular Paternò–Büchi reaction between an aldehydic group and an α-alkyl substituted styrene moiety (Scheme 81).[249] An intramolecular stereoselective Paternò–Büchi reaction was the key step also in the synthesis of some derivatives of *R*-(+)-sclareolide.[250] A synthesis of the scaffold of merrilactone A also involved an intramolecular 2 + 2 cycloaddition to give the adduct **101** (Scheme 81).[251]



Scheme 79



Scheme 80

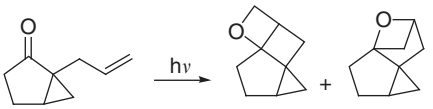


Scheme 81

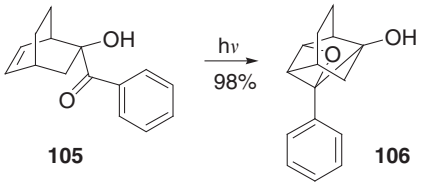
However, a project devoted to obtain tromboxane analogs using an intramolecular reaction of a carbonyl group with an enol ether, failed.[252]

An intramolecular reaction on allyl cyclopentanone derivatives has been reported.[230,253,254] In this case both *straight* **103** and *crossed* **104** oxetanes can be obtained (Scheme 82). Using 2-allylcyclopentanone nearly equal amounts of these isomers were obtained. However, the use of the more rigid starting material **102** allowed the preferential formation the *straight* isomer.

An intramolecular cycloaddition reaction was found in the reaction of **105** to give **106** (Scheme 83).[255]

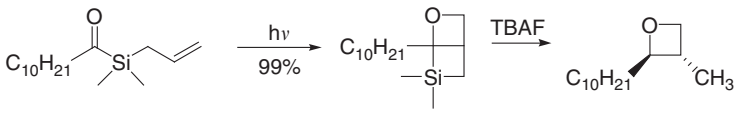


Scheme 82



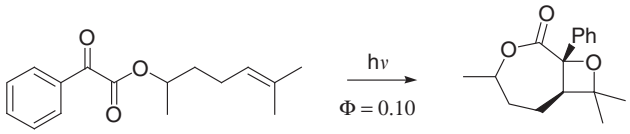
Scheme 83

Compound **107** gave in quantitative yield the oxetane **108** through an intramolecular reaction. The oxetane thus obtained could be converted into **109** via fluoride desilylation (Scheme 84).[256]



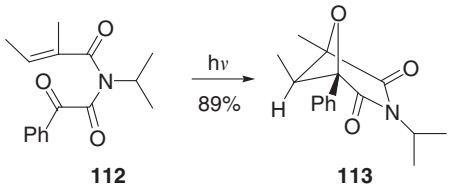
Scheme 84

When alkenyl phenylglyoxylates were used as substrates, Norrish type II is the main reaction in most of the cases, with the exception, for example, of compound **110** able to give the adduct **111** (Scheme 85).[257,258]



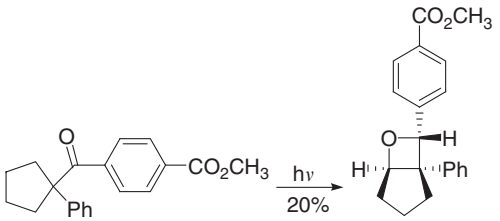
Scheme 85

N-Isopropyl-*N*-tigloylbenzoylformamides gave an intramolecular cycloaddition reaction in high yields (50–99%) to give the *syn* adduct (*syn*/*anti* = 2.1).[259,260] The compound **112**, irradiated in solid state, showed a different behavior: the crystals of **112** are in a chiral group, so **112** gave **113** with a *syn*/*anti* = 6.7 and *syn*-**113** was obtained with a high *ee* value (> 99%) (Scheme 86).[260]



Scheme 86

When the ketone **114** was irradiated in the solid state, the only possible reaction was a Norrish Type I reaction. The reaction gave an alkene and a carbonyl compounds, able to react in an intermolecular reaction giving the corresponding adduct **115** (Scheme 87). The reaction occurred with high stereoselectivity, and, when performed on a chiral salt gave the product with *ee* in the range 42–52%.[237]



114 **115**

Scheme 87

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5.06 Di-π-methane, Oxa-di-π-methane, and Aza-di-π-methane Photoisomerization

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Glossary

Enantiomorphous crystals When they crystallize, molecules can be repetitively arranged in 230 different ways (230 space groups) in a three-dimensional network. Of these, 165 space groups possess inverse elements of symmetry (linked to symmetry operations of the second kind or improper operations), such as planes or centers. These elements of symmetry enable the transformation of an object into its mirror image. Consequently, enantiopure compounds cannot crystallize in these space groups. A total of 65 space groups do not possess inverse elements of symmetry. Only symmetry operations of the first kind or proper operations linked, for instance, to rotation are possible. Enantiopure compounds, therefore, only crystallize in one of these 65 space groups (or more of them in the case of polymorphism) and form enantiomorphous crystals. After the formation of molecules from atoms, crystallization of these molecules constitutes a second step of structure building of material. Chiral objects such as molecules can be formed from achiral objects such as atoms. Consequently, achiral molecules may also form enantiomorphous crystals with chiral morphologies. Generally, the same number of single crystals of each enantiomorphology (handedness) is formed although techniques have been developed to direct the crystallization toward only one enantiomorphology. Chemical transformation in such crystals is applied to absolute asymmetric synthesis. Most frequently, however, achiral molecules and racemic mixtures of chiral molecules prefer crystallizing in achiral space groups.

Mesoporous silica Mesoporous silica possesses tunable pore diameters of 2–30 nm and surface areas $>600\ m^2\ g^{-1}$. Generally, such materials are produced by combination of supramolecular templating and sol-gel chemistry. Surface-modified mesoporous silica is applied to adsorption, catalysis, separation, drug delivery, and sensing.

Photochemical electron transfer Molecules change their chemical properties when they are electronically excited. Thus, the redox-potentials of organic molecules are different at the ground state and at the excited state. In many cases, an electron transfer between two molecules only occurs if one of them is photochemically excited. Using the photochemical electron transfer, the redox chemistry of many organic compounds is considerably enriched.

Photochemical excitation When a molecule absorbs light (UV, visible), an electron is transferred from one orbital to another (electronic excitation). For example, in a carbonyl function, an electron may be transferred from the nonbonding orbital n to the π^* orbital ($n\pi^*$ excitation). The corresponding molecule reaches the lowest excited singlet state S_1. In the same molecule, by absorbing light with a lower wavelength (higher energy), the second excited state S_2 may be reached by transfer of one electron from the π orbital to the π^* orbital ($\pi\pi^*$ excitation). Most organic molecules possess a singlet ground state S_0 in which all electron spins are paired. When such molecules are electronically excited, they may also change their spin multiplicity and the corresponding triplet states T_1 or T_2 are reached by intersystem crossing. Generally, these triplet states possess lower energy and the intersystem crossing is exothermic.

Photochemical sensitization A photochemical reaction may also be induced by sensitization. In this case, not the substrate but another compound (sensitizer) absorbs light and transfers its excitation energy to the substrate. The latter becomes electronically excited and undergoes a

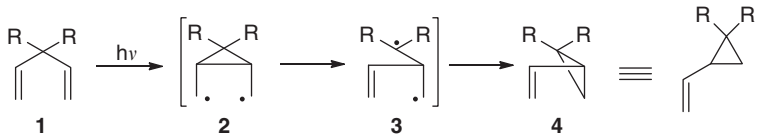
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photochemical reaction. The sensitizer may transfer its singlet energy and the substrate reaches a singlet excited state. The sensitizer may also transfer its triplet energy (triplet sensitizer) to the substrate, which reaches directly a triplet excited state. These two sensitizing processes are frequently applied to organic photochemical reactions.

Zeolite Zeolites are crystalline aluminosilicates containing regularly arranged pores and cavities (ca. 3–15 Å). They are widely used as sorbents, catalysts, or ion exchange materials. Zeolite Y ($M_{56}(AlO_2)_{56}(SiO_2)_{136}$) is a synthetically obtained zeolite possessing faujasite structure.

5.06.1 Introduction

The di-π-methane photoisomerizations belong to those photochemical reactions that impress by their mechanistic complexity and beauty. In many cases, these reactions are well foreseeable and therefore frequently applied to organic synthesis. As in many of such cases, starting from simple substrates, in only one defined and selective step, a complex structure is generated.[1–3] Most commonly, the reaction takes place in molecules possessing two olefinic double bonds or one olefinic and one C=X double bond connected by a sp^3 hybridized carbon atom.[4,5] Generally, the mechanism is presented as a two-step process (Scheme 1). After excitation of the 1,4-diene **1**, the 1,4-biradical **2** is formed. A rearrangement takes place leading to **3**. In the last step, radical combination yields the cyclopropane derivative **4** as the final product. However, mainly in the past but also more recently, a concerted mechanism is discussed.[6–8] Furthermore, a direct transformation of the electronically excited 1,4-diene **1** into the 1,3-biradical **3** via a 1,2-aryl shift was discussed for benzonorbornadiene derivatives.[9] The reaction occurs at the singlet or the triplet state and is induced either by direct light absorption of the substrate or by photochemical sensitization. As can easily be deduced from the general scheme, the reaction may occur in two senses when the double bonds are carrying different substituents. A lot of investigations on this topic have been carried out and this aspect has been frequently reviewed.[5,6,10–13] This chapter focuses on applications of the di-π-methane rearrangement to organic synthesis. In specific cases, aspects of regio- and stereoselectivity will be discussed. Several previous reviews and book chapters also deal with this aspect.[14] Therefore, examples are preferentially chosen from the recent literature.



Scheme 1

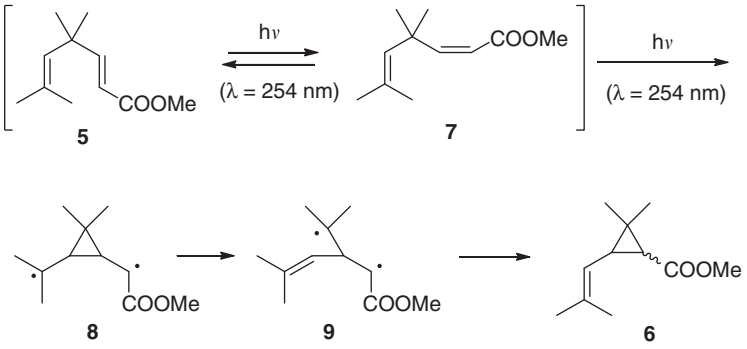
5.06.2 Di-π-methane Photoisomerization

As already briefly mentioned, the di-π-methane photoisomerization may occur at the singlet or at the triplet state. In the case of the all-carbon variant, these are $\pi\pi^*$ states. It was shown that in the case of open chain structures, the isomerization mainly occurs at the singlet state. In this case, the di-π-methane rearrangement is considered as a concerted process and would be described as a formal $[_\sigma 2_a + _\pi 2_a]$ cycloaddition.[15] At the triplet state, however, *cis*/*trans* isomerization is frequently observed as a competing reaction.[14] In contrast to these acyclic substrates, more constrained cyclic and polycyclic compounds readily undergo di-π-methane photoisomerization at the triplet state. Thus, many sensitized processes have been reported.

5.06.2.1 Acyclic Substrates

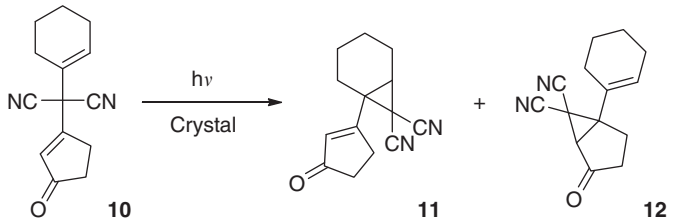
An interesting application of the di-π-methane photoisomerization to synthesis is the transformation of compound **5** by direct irradiation in hexane into methyl chryanthemate **6**, which possesses insecticidal activities. When compound **5** was irradiated at $\lambda = 254$ nm, a mixture of four products was isolated. The starting material was recovered as a *cis*/*trans* mixture (**5**/**7**, 1:1) (80%) and the chrysanthemate **6** formed as a *cis*/*trans* mixture of 1:2 (20%) (Scheme 2).[16] Prolonged irradiation under these conditions let to degradation of the product. When irradiated in the presence of acetophenone as triplet sensitizer, only a mixture of the *cis*/*trans* isomers **5** and **7** was formed. These observations suggest that the di-π-methane rearrangement occurs at the singlet state, whereas the *cis*/*trans* isomerization may occur at the singlet and the triplet state.[17] An extensive mechanistic study was performed with similar compounds carrying a diphenylvinyl moiety.[18] A detailed investigation performed with a large variety of triplet sensitizers revealed that the di-π-methane photoisomerization in acyclic systems may also occur at the triplet state.[19] The outcome of such reactions then highly depends on the structure of the sensitizer. A photostationary equilibrium is established between compounds **5** and **7**. In order to optimize the reaction and to limit degradation at prolonged irradiation, a further investigation may be performed by studying the photostationary equilibrium, as has been previously done for industrial photochemical

transformations such as vitamin D production.[20] More adapted photochemical reactors such as microstructured continuous flow systems[21] may be helpful.



Scheme 2

Asymmetric synthesis was carried out with the di-π-methane rearrangment using absolute chiral induction. Several achiral compounds form crystals with chiral space groups. In such enantiomorphous crystals,[100,101] the substrates are placed in a chiral environment.[22–24] When transformed by solid-state irradiation, the products are generally obtained in high optical purity. Photochemical transformations are particularly suitable because photons easily enter into the crystal. In contrast, transformations at the ground state with chemical reagents only occur at the crystal surface. Crystals of the achiral malodinitrile derivative **10** are enantiomorphous and have the space group $P2_12_12_1$. When such crystals are irradiated, two asymmetric di-π-methane isomerizations take place (Scheme 3, Table 1).[25] The enantioselectivity is induced by the chiral environment in the crystal and depends on the irradiation time, the conversation, and the reaction temperature. The same reaction, but without any chiral induction, was observed in solution. The product ratio **11**:**12** also depends on these reaction parameters. Based on these observations, the mechanism depicted in Scheme 4 was suggested. The $\pi\pi^*$ excited substrate **10** rearranges to the biradical **13** (also compare Scheme 1). The next steps determine the regioselectivity of the isomerization. Either bond a or bond b is broken, leading to the corresponding 1,3-biradical intermediates **14** and **15**. Radical combination yields the final products **11** and **12**. Equilibria between the two radical intermediates **13** and **14** on one hand and between product **12** and intermediate **15** on the other have been discussed. They are determined by the relative stability of the delocalized oxoallyl radicals **13** and **15**. As the conversion in the solid state progresses, the formation of regioisomer **12** is favored over that one of **11**. Attempts to apply this method of chiral induction to slightly varied structures were so far unsuccessful because in such cases crystals with achiral space groups were obtained.[26]



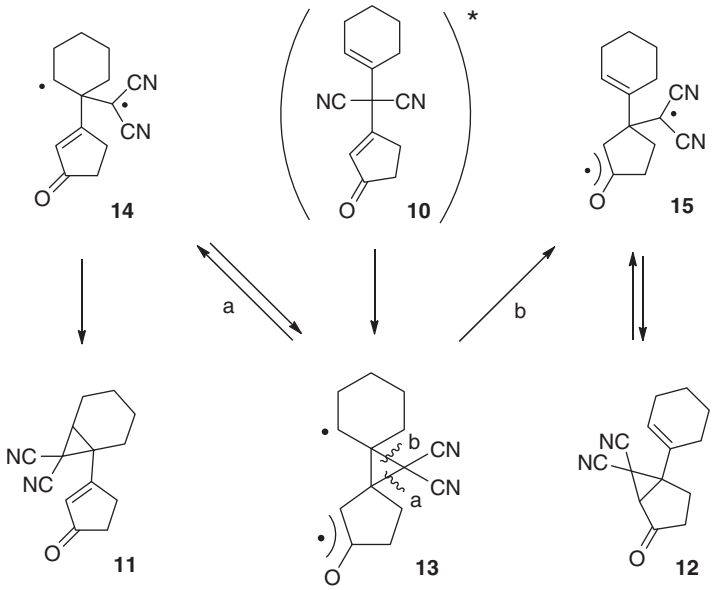
Scheme 3

Table 1 Enantio- and regioselectivity of the reaction of **10** in solution and in the solid state (Scheme 3)

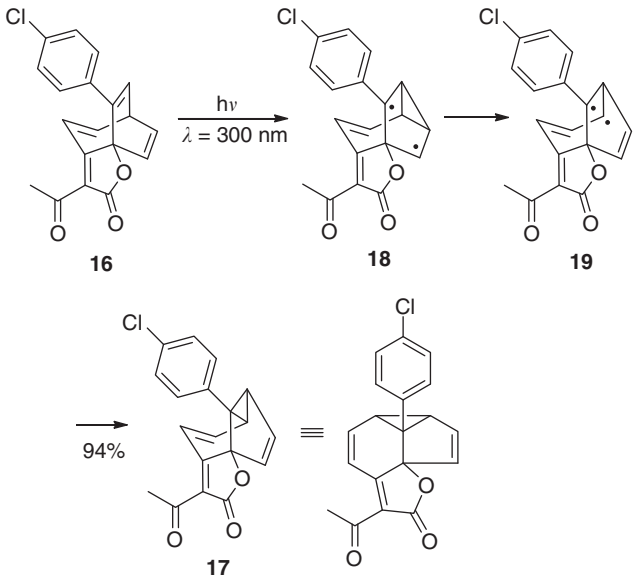
Medium	*Time (h)*	*Conversion (%)*	*Ratio **11**:**12***	*Enantiomeric excess (%)*	
				11	***12***
Solution (MeCN)	22	100	3.2:1	0	0
Neat (crystals)	2–8	9–51	1.2:1–1:1.9	22–44	55–96

5.06.2.2 Cyclic Substrates

The di-π-methane photoisomerization is facilitated when the 1,4-diene moiety is included in a cyclic or polycyclic system. Thus, the polycyclic compound **16** was efficiently transformed into the cyclopropane derivative **17** by direct excitation (Scheme 5).[27]



Scheme 4

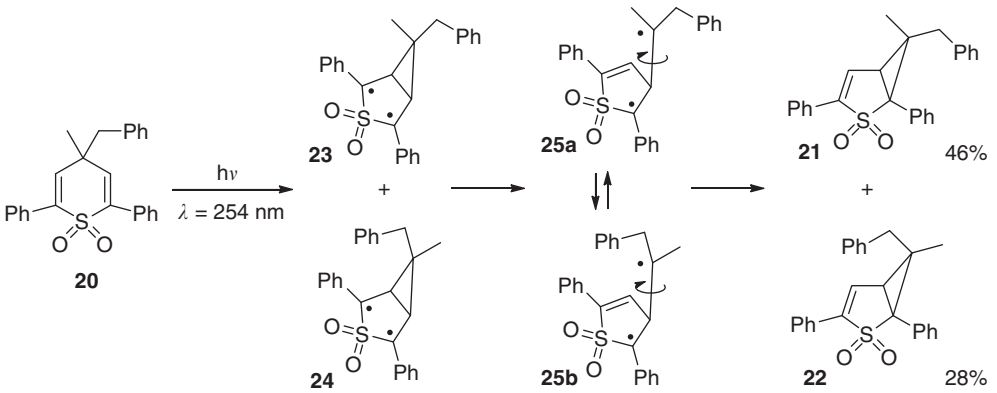


Scheme 5

It must be pointed out that this reaction is stereo- and regio-specific. The selectivity is certainly induced by the favored formation of intermediates **18** and **19** possessing both a benzyl radical center.

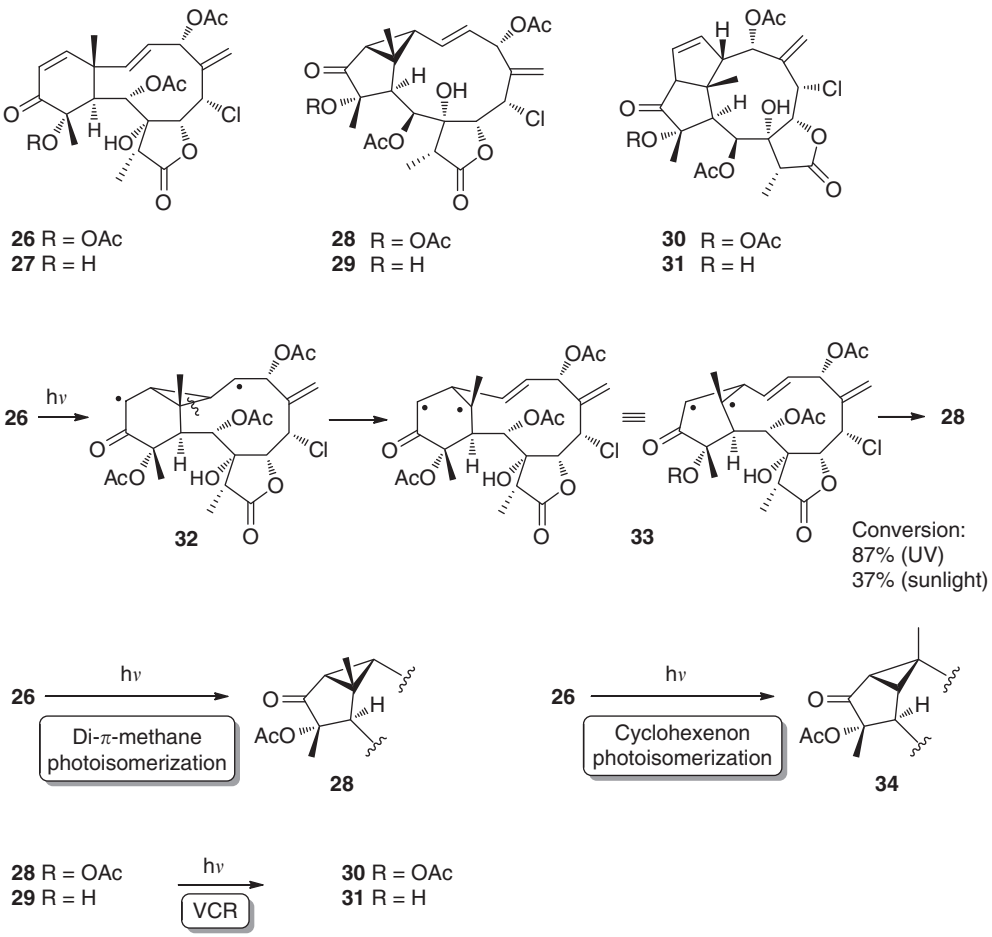
Heterocyclic compounds such as 4-*H*-thiopyran-1,1-dioxides undergo easily di-π-methane photoisomerization.[28] Thus, compound **20** has been transformed into stereoisomers **21** and **22** (Scheme 6).[29] After excitation, the biradical intermediates **23** and **24** are generated. At this stage, a certain diastereoselectivity is induced. Bond breaking at the cyclopropane moiety leads to the 1,3-biradical intermediate **25a,b**. A conformational equilibrium between *syn* (**25b**) and *anti* (**25a**) arrangements also contributes to the stereoselectivity.

The di-π-methane photoisomerization was also observed or discussed in the context of the biosynthesis of natural products. Among other diterpenoids, compounds **26**, **27**, **28**, **29**, **30**, and **31** have been recently isolated from the Caribbean gorgonian coral *Erythropodium caribaeorum* (Scheme 7).[30] It was previously suggested that compounds **28** and **29** result from a di-π-methane rearrangement of **26** and **27**, respectively. In order to prove this hypothesis, compound **26** was separated and irradiated with light under different conditions.[31] In the case of UV irradiation (medium pressure Hg lamp) in benzene, after 3 h, a high conversion of compound **26** was observed. When a 5% solution in methanol was exposed to sunlight, a conversion of 37% was reached after



Scheme 6

8 days. The latter conditions resemble more with those of the biosynthesis. The transformation occurs via the corresoponding 1,4- and 1,3-biradical intermediats **32** and **33**. Compounds **26** and **27** also contain a cyclohexenone substructure. A photochemical cyclohexenone rearrangement also generates a bicyclo[3.1.0] moiety. In this case, however, the methyl group would be placed in a different position on the cyclopropane ring (compare **28** and **34**). As **34** was not contained in the isolated natural product nor generated by photochemical transformation of **26**, it was concluded that the bicyclo[3.1.0] substructure was generated by a di-π-methane photoisomerization. Furthermore, it was suggested that compounds **30** and **31** are generated by a photochemical vinylcyclopropane rearrangement (VCR) of **28** and **29**, respectively.[30]

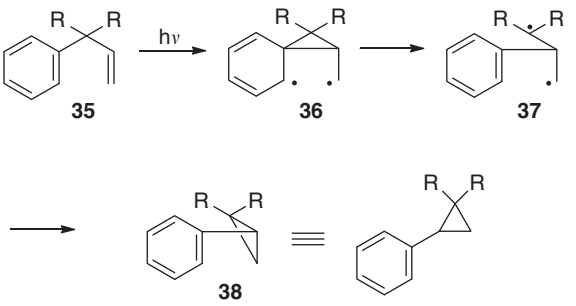


Scheme 7

5.06.2.3 Transformations Involving Aromatics as Unsaturated Moiety

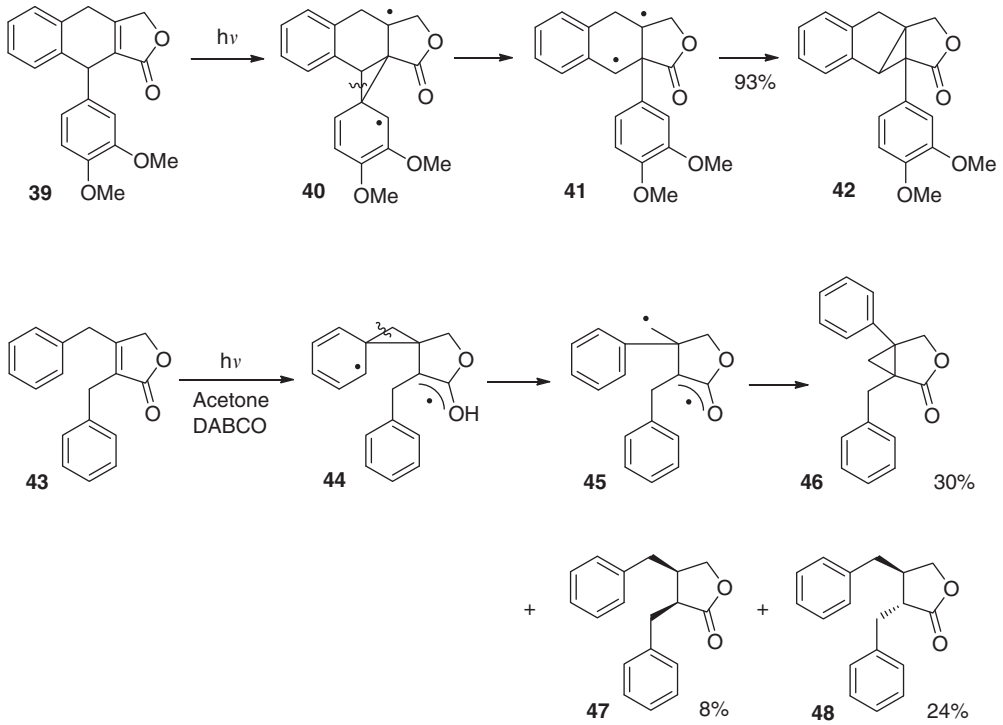
5.06.2.3.1 Reaction centers arranged in an acyclic system

Di-π-methane photoisomerizations have been carried out with substrates in which an aromatic moiety gets involved. In such cases, the aromaticity is temporally suppressed when the 1,4-biradical intermediate **36** is formed from **35** (see general Scheme 8).[32] The rearrangement to the corresponding 1,3-biradical **37** occurs in the way that the aromatic character is regenerated and the final product **38** is formed from **37** by radical combination.



Scheme 8

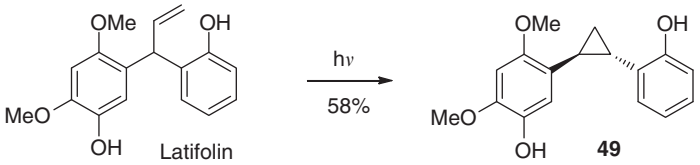
Details of the regioselective di-π-methane rearrangment involving aromatics have been studied with furanone derivatives. These investigations have been carried out in the context of synthetic studies of lignanes.[33] Two examples are depicted in Scheme 9. On direct irradiation, the furanone derivative **39** forms the 1,4-biradical intermediate **40** in which the aromatic character of the 3,4-dimethoxyphenyl moiety is suppressed.[34] The formation of the 1,3-biradical **41** regenerates the aromaticity in this substituent. Radical combination then leads to the final product **42** in high yield. It must be pointed out that the transformation is regiospecific and only the 3,4-dimethoxyphenyl substituent is involved in the rearrangement, whereas the benzene aromatic system of the 1,4-dihydro naphthalene moiety does not react. A corresponding derivative possessing no substituents on the phenyl group is transformed in acetone solution with almost the same efficiency as compound **39**.[35] Under such conditions, acetone also acts as triplet sensitizer. In the case of the transformation of the furanone derivative **43** possessing two benzyl groups, a different regioisomer is formed (Scheme 9).[35,36] The phenyl group of the substituent in the β-position yields first the corresponding 1,4-biradical **44**. This intermediate is additionally stabilized by delocalization of one radical position by the carboxyl function. As in the previous case, C–C bond breaking in the cyclopropane moiety leads to the regeneration of the aromaticity and



Scheme 9

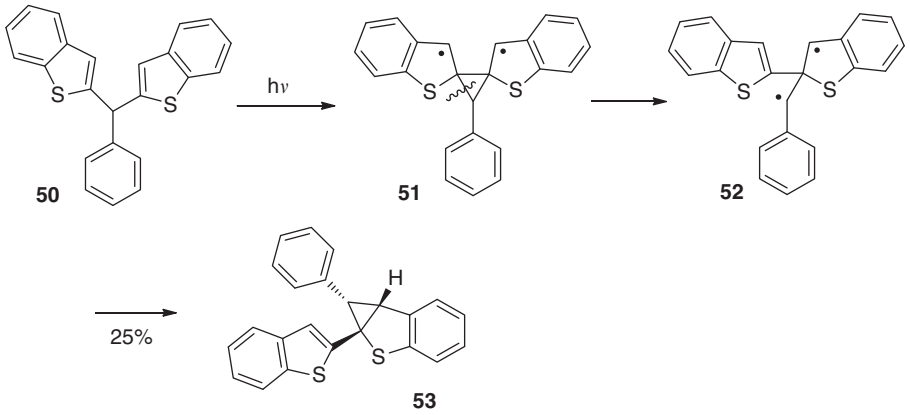
to formation of the 1,3-biradical intermediate **45**. Radical combination finally yields compound **46**. A similar reaction carried out with a furanone derivative carrying only one benzyl substituent in the *β*-position was less efficient.[37] This observation may be explained in part by the conformational flexibility of this system, which enables side reactions. Furthermore, products **47** and **48** resulting from a photoreduction process were obtained. This side reaction occurred because the transformation was carried out in the presence of 1,4-diazabicyclo[2.2.2]octane. Further studies on the chemo-, regio-, and stereoselectivity as well as on the influence of spin multiplicity on the transformation of similar compounds have been carried out.[38]

In a similar reaction, latifolin was transformed (Scheme 10). This important neoflavonoid is isolated from the heartwood of *Dalbergia latifolia*. In this compound, two benzene substituents and one vinyl group are linked to the sp^3 hybridized carbon atom. On irradiation in benzene solution and in the absence of a sensitizer, latifolin readily yields the cyclopropane derivative **49**. In this case, only the *trans* isomer was isolated,[39] whereas the irradiation of similar compounds under the same reaction conditions yielded mixtures of *cis*/*trans* isomers of the corresponding cyclopropane derivatives.



Scheme 10

Di-π-methane photoisomerizations have also been carried out with heterocycles. In Scheme 11 such an example is depicted.[40] On direct excitation, the dibenzothiophene derivative **50** forms the typical biradical intermediates **51** and **52**. The final product **53** is obtained in moderate yield by radical combination of intermediate **52**. In such transformations, the products of the di-π-methane rearrangement often undergo further photochemical rearrangements.[40,41] Compounds such as **50** possessing three π-bonds capable of being involved in photochemical rearrangements may also undergo a tri-π-methane photoisomerization.[41,42]

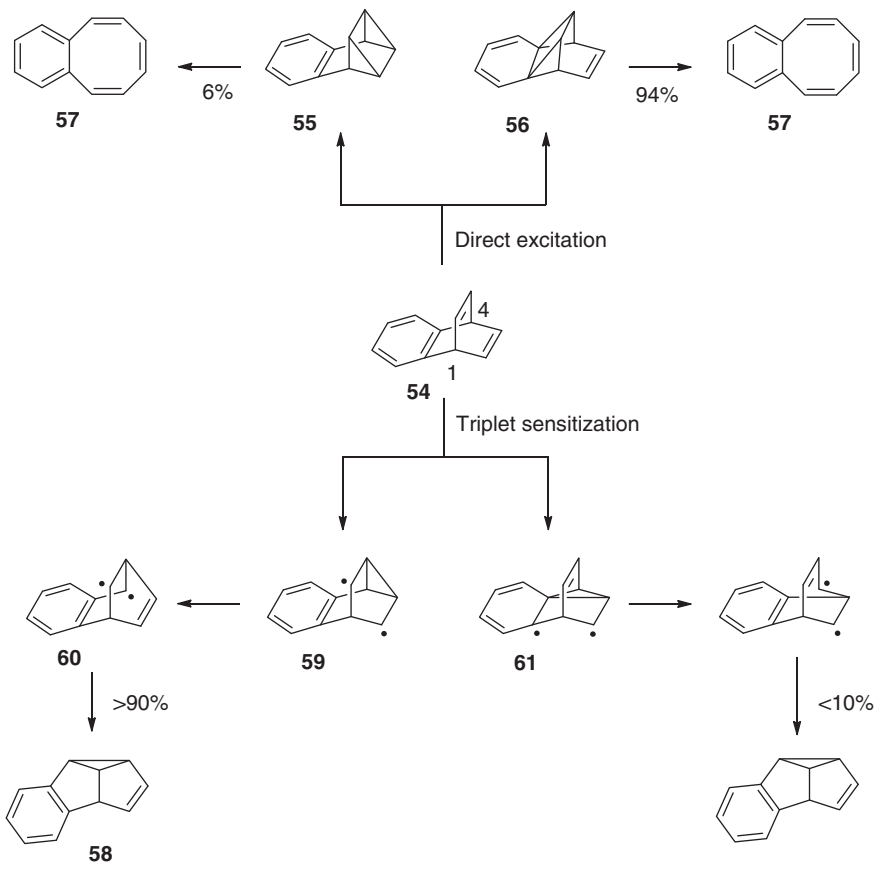


Scheme 11

5.06.2.3.2 Reaction centers arranged in cyclic systems

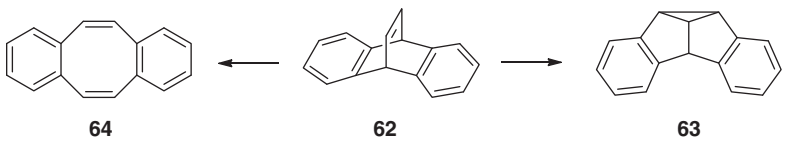
5.06.2.3.2.1 Benzo and dibenzobarrelene derivatives

Many investigations have been carried out with benzo- or dibenzobarrelene derivatives and related compounds.[11,13,14,43,44] In these compounds, two reaction pathways are generally observed depending on whether electronic excitation occurs by direct light absorption (singlet reaction) or by triplet sensitization (Scheme 12). The reaction pathways have been identified and discussed on the basis of the results obtained from the transformation of compound **54**, which was isotopically labeled in positions 1 and 4. In the first case, compounds such as **54** undergo intramolecular [2 + 2] photocycloaddition leading to intermediates **55** and **56**.[45] The formation of **56** is favored although the aromaticity of the benzo-moiety is suppressed. A subsequent rearrangement leads to the final product benzocyclooctatetraene **57**. In the case of triplet sensitization – the reaction is carried out in acetone as solvent – a di-π-methane rearrangement occurs. Once again, two reaction pathways can be distinguished. Only product **58** was obtained indicating that the reactions take place via the intermediates **59** (vinyl-vinyl bridging) and **60**. In contrast to the singlet reaction leading to **57**, in the triplet reaction the suppression of the aromatic character in intermediate **61** via a benzo-vinyl bridging is avoided.



Scheme 12

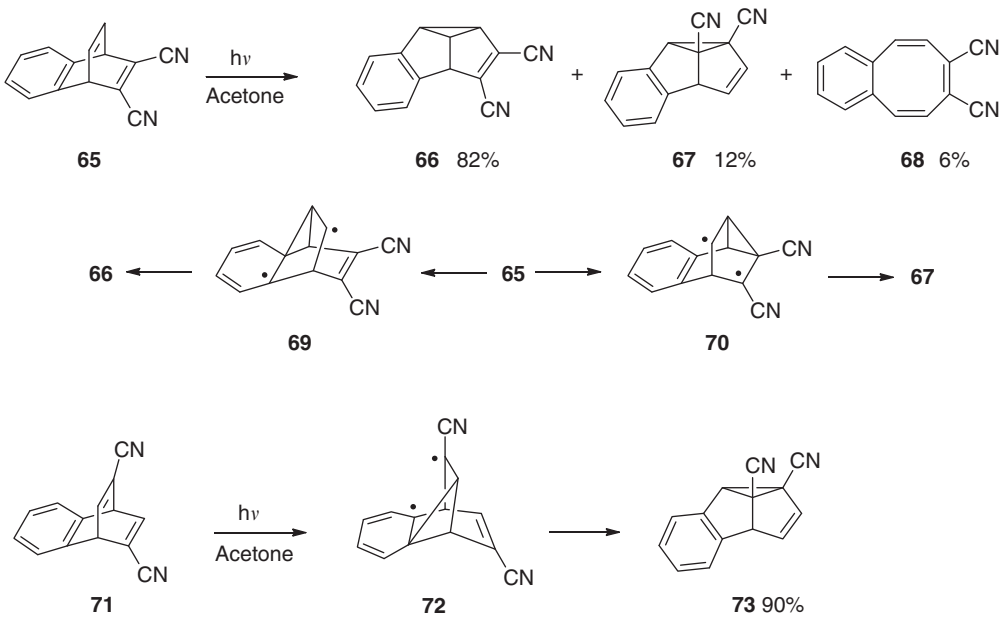
In the case of dibenzobarrelene derivatives such as **62** (Scheme 13), a competition between the formation of di-π-methane isomerization products **63** and dibenzocyclooctatetraene **64** was also observed. The course of the reaction depends on the substitution pattern.[46]



Scheme 13

In the following Schemes, some recent examples of benzobarrylene reactions are depicted. Electron withdrawing substituents such as a cyano group on the benzobarrylene core determine the reaction pathway.[47] A dicyano derivative (**65**) was transformed into the di-π-methane isomerization products **66** and **67** (Scheme 14).[48] The reaction was performed in acetone as solvent and triplet sensitizer. Only minor amounts of the corresponding benzocyclooctatetraene derivative **68** were obtained. The major positional isomer **66** was formed via the intermediate **69** (vinyl-benzo bridging) in which the aromatic character is suppressed. The minor isomer **67** resulted from a rearrangement via intermediate **70** (vinyl-vinyl bridging). As previously discussed, the benzocyclooctatetraene derivative **68** might result from a singlet reaction. The corresponding transformation of the positional isomer **71** was more efficient. Only one product (**73**) was obtained in high yield. In this case intermediate **72** (vinyl-benzo bridging) was generated. Additional information on the reaction mechanism was obtained from the transformation of similar benzobarrylene derivatives under the same conditions.[49]

Aromatic heterocyclic compounds have also efficiently been transformed. Thus, the polycyclic benzopyrazino derivative **74** was obtained from the reaction of the corresponding benzobarrylene substrate **75** (Scheme 15).[50] The product was formed via intermediates from vinyl-vinyl bridging. Although no mechanistic studies have been performed in this case, it was assumed that the reaction took place at the triplet state. The corresponding dibenzoquinoxalino derivative **76** was transformed under the same conditions,[51] but the reaction was less selective. The percentage values shown in Scheme 15 represent the product ratio. The main products **77** and **78** were formed involving intermediates of a vinyl-vinyl bridging. In the case of the minor product **79**,



Scheme 14

intermediates with a vinyl-heteroaryl bridging were generated. Because the C═N bond of the quinoxaline moiety is involved, this reaction was also designed as an aza-di-π-methane isomerization (see Section 5.06.4). The aza-analog reaction was mainly observed in the transformations of compounds **80** and **81**.

The di-π-methane rearrangement of dibenzobarrelene derivatives (compare Scheme 13) was intensively studied and applied to the synthesis of functional products. Thus, the irradiation of the quaternary ammonium derivative **82** in acetone efficiently yielded the isomerization product **83** (Scheme 16).[52] Compound **83** was used as phase transfer catalyst in alkylation reactions. In particular in the alkylation of β-ketoesters, this compound was more efficient than the classical catalyst TBAC (tetrabutylammonium chloride). The high tolerance of functional groups in these reactions was also observed in the transformations of corresponding urea and thiourea derivatives **84**.[53] Crown ether derivatives (**85**) have also been obtained.[54]

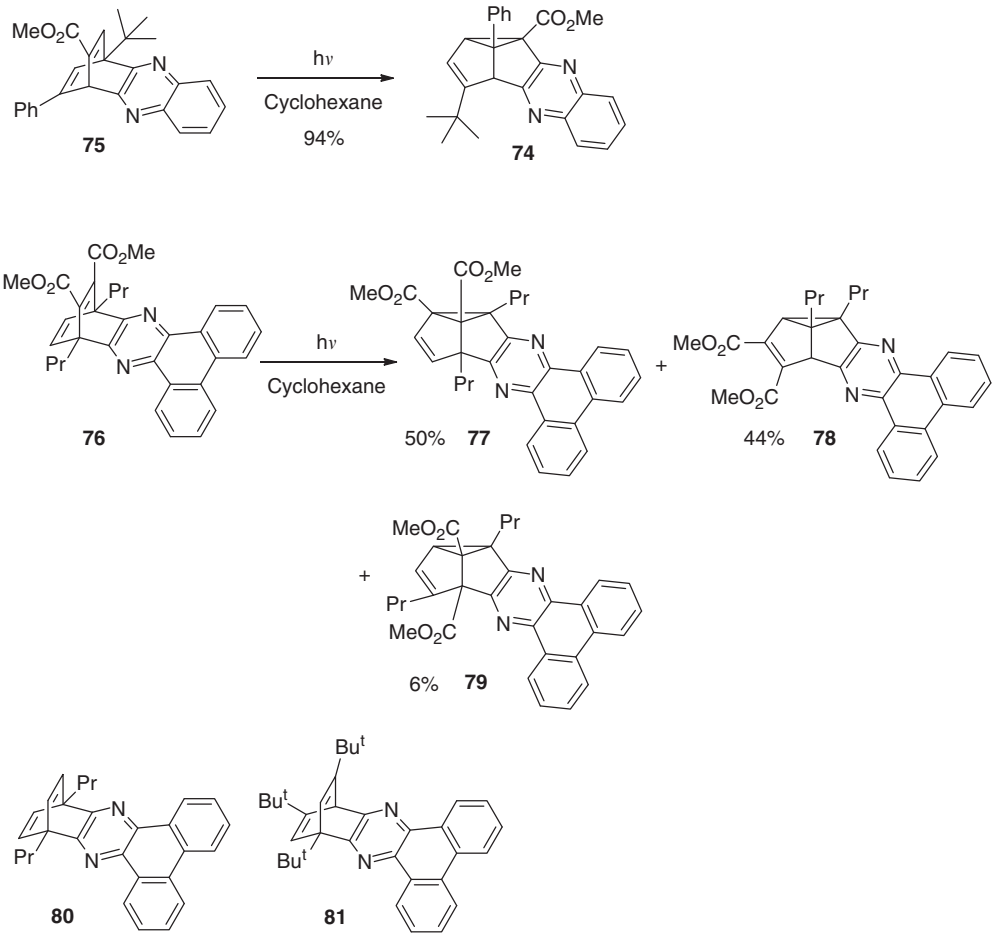
A lot of dibenzobarrelene derivatives have been transformed in the solid phase. As already pointed out above (compare Scheme 3, Table 1), this technique was used for chiral induction.[22–24] Photochemical transformations of solids are particularly easy and thus this method may play a central role in chiral induction in photochemical reactions.[55] Various techniques have been applied in this context. Among them, the crystallization of achiral compounds in chiral space groups leading to enantiomorphous crystals[100,101] is certainly the most attractive one because it allows absolute asymmetric synthesis. The bisphosphinoxid derivative **86** crystallized in the chiral space group $P2_12_12_1$ (Scheme 17).[56] The crystallization is carried out from ethanol solution and crystals contain one ethanol molecule per molecule of **86**. Enantiomorphous crystals are thus obtained in which one enantiomeric conformation of **86** is frozen. This conformation directs the reaction on one enantiomeric pathway and **87** is obtained in high enantiomeric excess. Reduction of the rearranged product leads to the phosphine derivative **88** that is a chiral ligand for transition metal catalyzed asymmetric hydrogenation.

The corresponding carboxylate derivatives have also been transformed. In this case, chiral ammonium ions were used to induce chiral crystallization.[57] Irradiation of chiral salts is an alternative and more general approach to obtain enantiopure compounds via solid-state photochemistry.[58] Cocrystallization with a chiral molecule is another method to induce chirality in the di-π-methane photoisomerization.[59] Recently, the reaction was also carried out in other chiral media such as chiral mesoporous silica[60,102] or ionic liquids.[61] All of these approaches apply the concept of photochemical transformations in confined environments.[62]

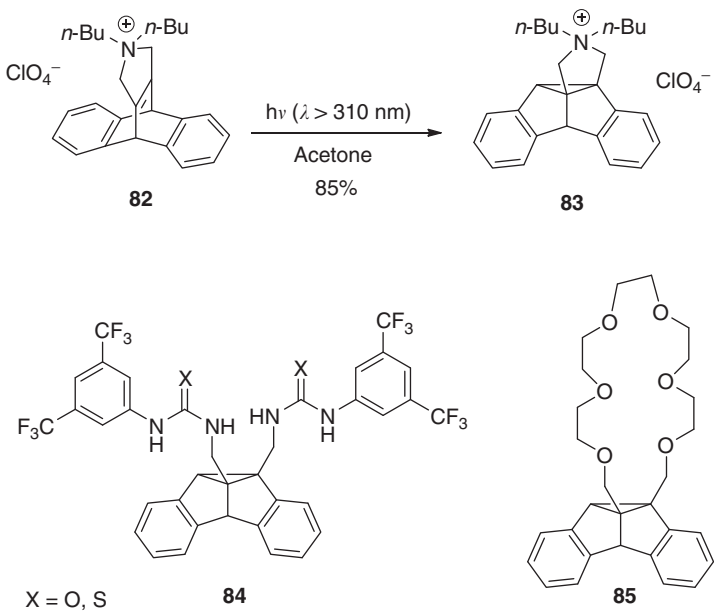
5.06.2.3.2.2 Barrelene related derivatives

Benzonorbornadiene derivatives also undergo di-π-methane photoisomerization (for some early examples see[63]). Thus, compound **89** was efficiently transformed into the polycyclic triazolidine derivative **90** under triplet sensitization conditions (Scheme 18).[64] The di-π-methane rearrangment product **90** was transformed via the intermediate **91** into the benzopinene analog **92**. It must be pointed out that, under the same conditions, the corresponding derivative **93** devoid of the annulated benzene ring undergoes [2 + 2] photocycloaddition leading to **94**.

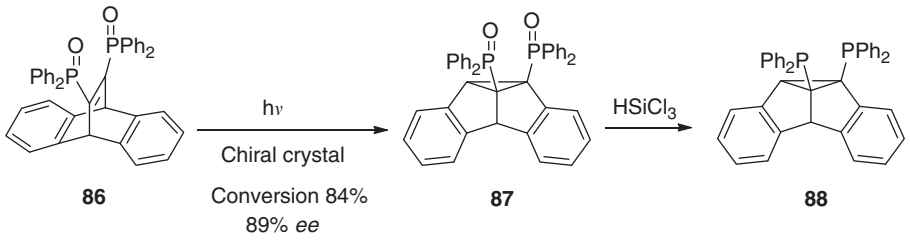
As briefly mentioned in Section 5.06.2.3.2.1, irradiation of salts with at least one optically pure ion may be applied to asymmetric synthesis. Such an efficient transformation was carried out with the salt **95•96** (Scheme 19, Table 2).[65] When performed at low temperature, a high enantioselectivity was detected for product **97**. At room temperature, the stereoselectivity is



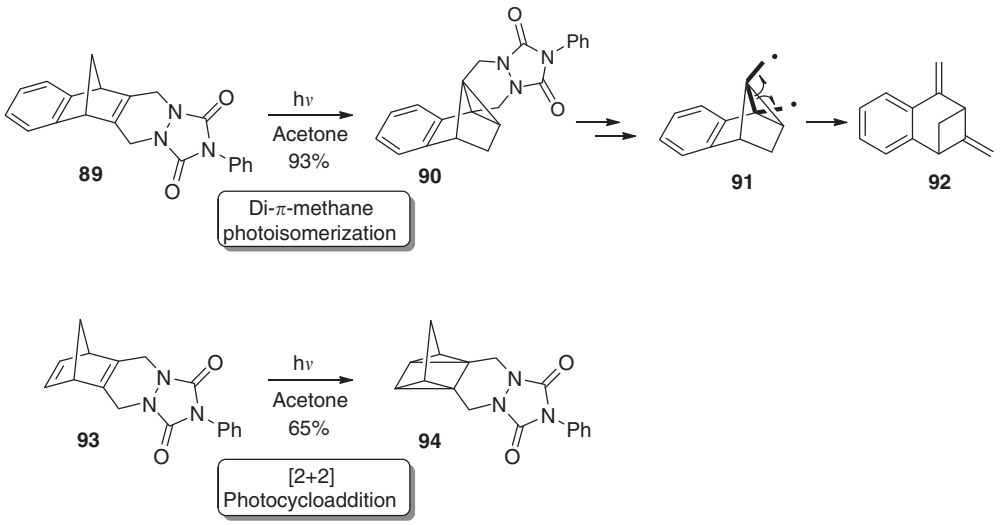
Scheme 15



Scheme 16

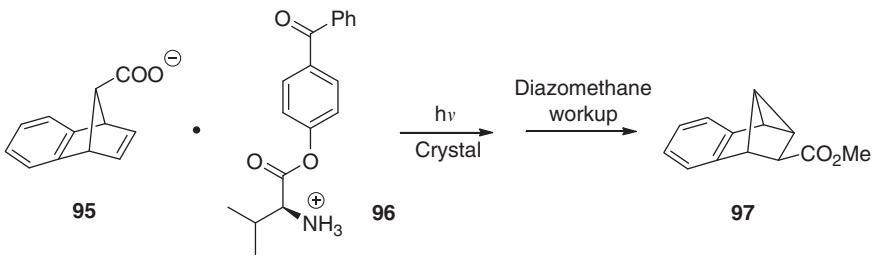


Scheme 17



Scheme 18

somewhat lower but the transformation is significantly faster. The L-valine derivative **96** not only acts as auxiliary to establish a chiral environment in the crystal but it also carries a benzophenone moiety as the triplet sensitizer.



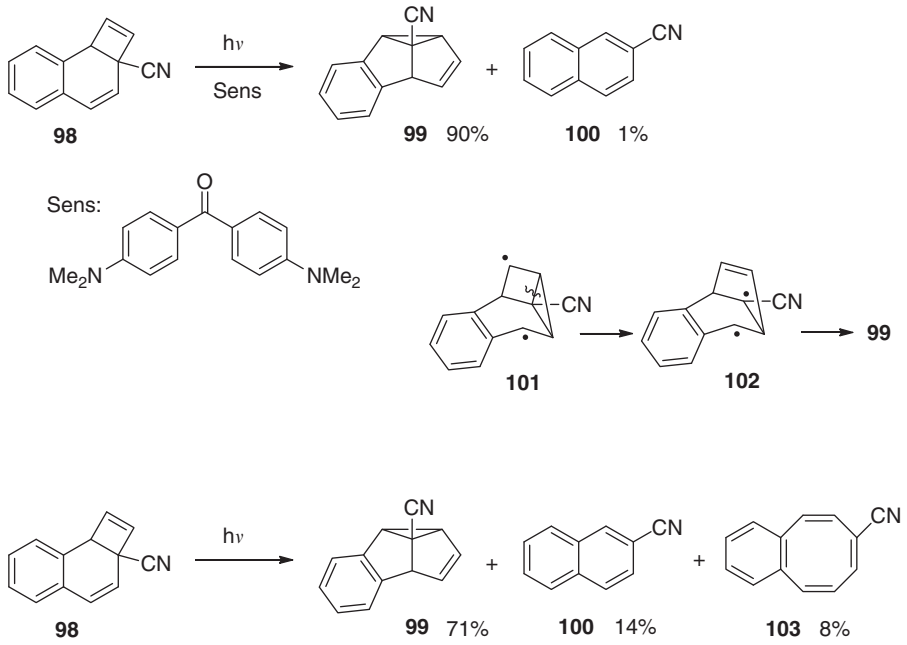
Scheme 19

Table 2 Enantioselectivity of the solid state reaction of the chiral salt **95•96** (Scheme 19)

Time	*Temperature*	*Conversion (%)*	*Enantiomeric excess (%)*
4 h	− 20 °C	100	91
1 min	Room temperature	58	84
5 min	Room temperature	100	82

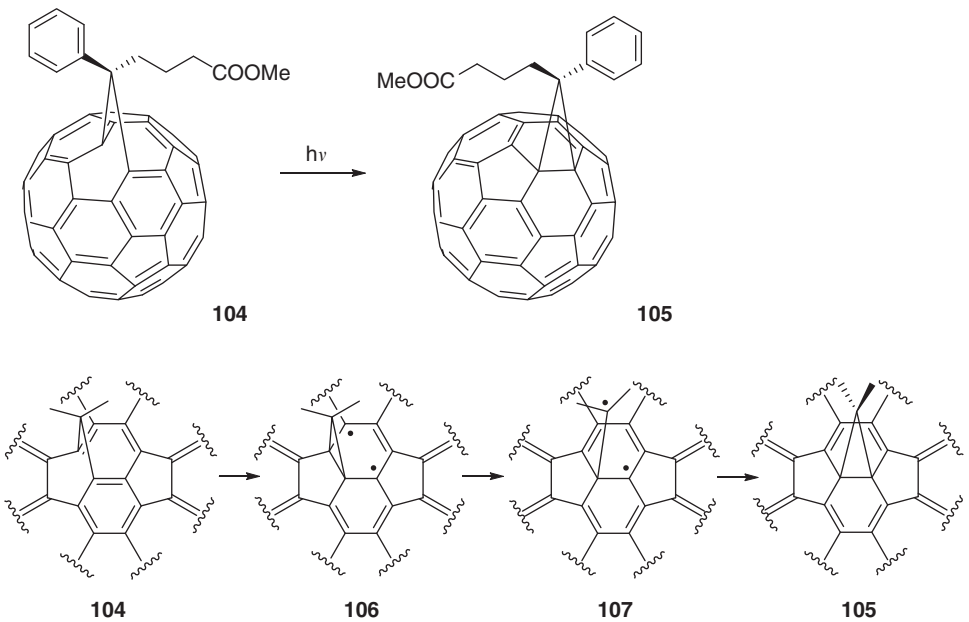
6-Cyano-2,3-benzobicyclo[4.2.0]octa-2,4,7-triene **98** (Scheme 20) may be considered as a regioisomeric structure of the benzobarrelene core. When irradiated in the presence of Michler's ketone as sensitizer, the di-π-methane photoisomerization product **99** was obtained in high yields.[66] Small amounts of 2-cyanonaphthalene **100** were also isolated. Intermediates **101** and **102** are involved in the formation of the major product **99**.[66,67] When the reaction is induced by direct excitation, the yield of

compound **99** diminishes, whereas the amount of **100** increases. Furthermore, the benzocyclooctatetraene derivative **103** is formed, resulting from competitive processes. Its formation dominates in some reactions of cyano-2,3-benzobicyclo[4.2.0]octa-2,4,7-trienes. The complex reaction mechanisms of the photochemical transformations of such cyano substituted tricyclic compounds have been systematically investigated.[67,68] Similar studies have also been performed with the unsubstituted core structure and a methyl derivative.[69]



Scheme 20

A photochemical rearrangement observed with C_{60} fullerene derivatives has been explained by a di-π-methane photoisomerization. On direct excitation, compound **104** was transformed into the cyclopropane derivative **105** (Scheme 21).[70] Starting compounds such as **104** are easily obtained from the reaction of the corresponding diazo compounds with C_{60}.[71] Only one regioismer is formed in which the phenyl ring is orientated *syn* with respect to a former five-membered ring of the fullerene



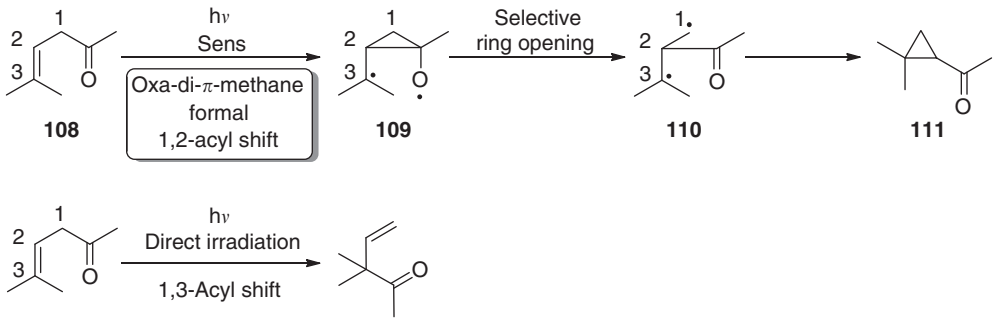
Scheme 21

moiety. Compounds such as **105** are only isolated in minor amounts from this latter transformation. In the first step of the di-π-methane rearrangement, a C–C sigma bond is formed in the fullerene moiety. The resulting species **106** may be compared with the 1,4-biradical intermediate of a typical di-π-methane isomerization (compare Scheme 1). The cleavage of a C–C bond in the cyclopropane moiety leads to the 1,3-biradical intermediate **107** in which one radical is largely delocalized. The final product **105** is formed by radical combination. In the overall transformation, a bridge between a five-membered and a six-membered ring (5,6 ring junction) move to a bridge between two six-membered rings (6,6 ring junction). More precisely, a bicyclo[4.3.1] system is transformed into a tricyclo[4.4.1.$0^{1,6}$] system. The reaction was quantitative after 1 h of irradiation. The transformation was also carried out under thermal conditions; however, up to 6 h of heating to 180 °C was needed. Several derivatives such as the corresponding *t*-butyl ester could not be transformed under such drastic thermal conditions.[72] Under mild photochemical reaction conditions, the isomerization product was obtained with 96% yield after 0.5 h of irradiation.

5.06.3 Oxa-Di-π-methane Photoisomerization

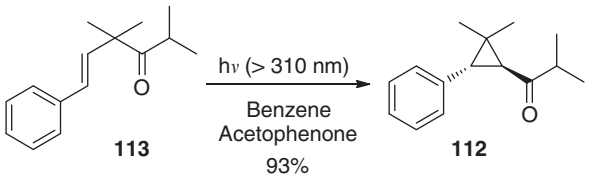
5.06.3.1 Basic Mechanistic Considerations and ODPM Photoisomerization of Acyclic β,γ-Unsaturated Carbonyl

The oxa-di-π-methane photoisomerization (ODPM) occurs by irradiation of a β,γ-unsaturated carbonyl framework **108**.[14] A formal mechanistic overview closely related to the two-step process previously mentioned for di-π-methane photoisomerization is highlighted in Scheme 22. In most cases, ODPM rearrangements are induced by triplet sensitization, whereas direct irradiation leads to a 1,3-acyl shift reaction, which is the major competitive photochemical process. Notably, the biradical intermediate **109** (or in the case of a concerted mechanism, a structurally related minimum along the reaction coordinate) produced in the primary photochemical process always undergoes a selective ring opening to produce the 1,3 biradical **110** leading the cyclopropyl ketone **111**. The overall process corresponds to a 1,2-acyl shift.



Scheme 22

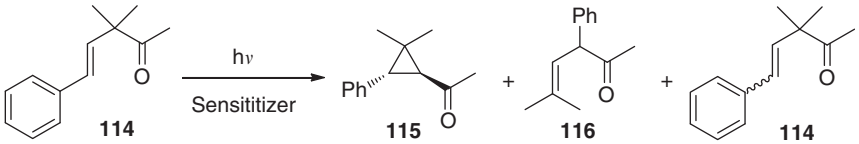
Although an acyclic β,γ-unsaturated carbonyl was chosen in Scheme 22 to illustrate the connectivity of the ODPM reaction, it is actually rarely observed with such substrates. Indeed, as previously mentioned, direct irradiation mainly induces a 1,3-acyl shift occurring at the singlet state S_1 (n,π^*). Moreover, when acyclic β,γ-unsaturated carbonyl are excited to a triplet state (either by direct irradiation followed by intersystem crossing or by triplet sensitization), deactivation by a free rotor effect predominantly leads to *E*/*Z* double bond isomerization. Extensive literature search in the field allows to identify the structural requirement that favors efficient ODPM rearrangement of acyclic β,γ-unsaturated ketones.[14] The ODPM photoisomerization was observed when the central carbon of the β,γ-unsaturated carbonyl was dialkylated, or mono alkylated with a sterically hindered group, and when the carbon–carbon double bond is a part of a conjugated system. For example, the ODPM rearrangement product **112** was obtained in 93% yield on irradiation of compound **113** in the presence of acetophenone as sensitizer (Scheme 23).[73] The presence of the phenyl ring is expected to favor ODPM by stabilization of radical intermediates. Conformational constraints induced by substituentes at the central carbon additionally favor the transformation of these biradicals into cyclopropane rings.



Scheme 23

However, this simple substitution pattern is not sufficient to induce ODPM rearrangements, as illustrated by the absence of the formation of the ODPM photoisomerization product on irradiation of compounds **114** in triplet sensitization conditions with

benzophenone (Scheme 24). Nevertheless, recently a new aspect of the ODPM photoisomerization of acyclic β,γ-unsaturated ketone was reported.[74] The reactivity of compounds **114** and related structural analogs was reinvestigated under triplet sensitization conditions using a broader range of triplet sensitizers. It was found that the ratio between different photoproducts nicely correlates with the triplet energy of the sensitizers (Table 3). As depicted in Scheme 24, on irradiation in the presence of different triplet sensitizers, variable yields of compounds **115**, **116**, and an *E*/*Z* mixture of the starting material **114** were obtained.



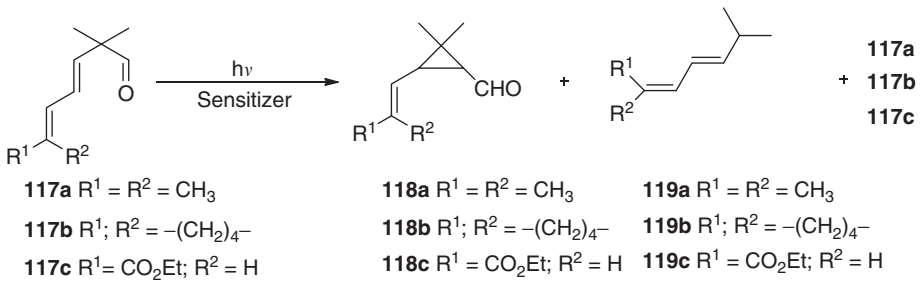
Scheme 24

Table 3 Product distribution depending on the triplet energy of the sensitizer (Scheme 24)

Triplet sensitizer	*Estimated $\Delta E_{D\text{-}A}$ (kcal mol^{-1})*	*Yield (%)*		
		115	***116***	***114***
Acetophenone	12	–	–	91
Thioxanlthone	1	50	–	20
4-Phenylbenzophenone	−1	10	28	35
Chrysene	−5	–	6	56

Based on the results obtained with several acyclic β,γ-unsaturated ketones and different sensitizers, it was concluded that when the triplet energy of the sensitizers is 12 kcal mol^{-1} higher than that of the alkene moiety, the *E*/*Z* isomerization of the olefin is the only observed photochemical process (Table 3). In contrast, when the triplet energy of the sensitizer is slightly higher (1–5 kcal mol^{-1}) than that of the alkenes moieties, the ODPM photoisomerization becomes the major photochemical process, and the corresponding products are obtained in yields higher than 50%. Finally, if the triplet energy of the sensitizer is lower than that one of the alkene groups (1–5 kcal mol^{-1}), the formation of ODPM products is usually observed in lower yields and 1,3-acyl migration to form the corresponding enone becomes a competitive photochemical process.

In another report concerning the fundamental understanding of ODPM photoisomerization, it was demonstrated that, in contrast to previous observations, the excited state S_2 (π,π^*) of the alkene may be involved in some ODPM reactions.[75] The ODPM photoisomerization of β,γ-unsaturated aldehydes was also studied. In this case, decarbonylation becomes an additional competitive photochemical reaction. Nevertheless, some β,γ-unsaturated aldehydes, which possess the favorable structural features described for ketone derivatives, undergo OPDM photoisomerization by triplet sensitization (Scheme 25, Table 4).[76] Moreover, as previously demonstrated for ketone derivatives,[74] high yields of ODPM products are obtained by judicious choice of the triplet sensitizer.[77] For example, when compound **117a** was irradiated in the presence of 3-methoxyacetophenone, the ODPM product **118a** is obtained in 52% yield; when 4-phenylbenzophenone was used as sensitizer under the same reaction conditions, an even higher yield of the ODPM product **118a** is observed.



Scheme 25

As reported in Table 4, this phenomenon seems to be general for this compound family. The high yields obtained using this methodology could provide a useful synthetic route to cyclopropanecarboxylic acids present in pyrethrins and pyrethroids natural products.

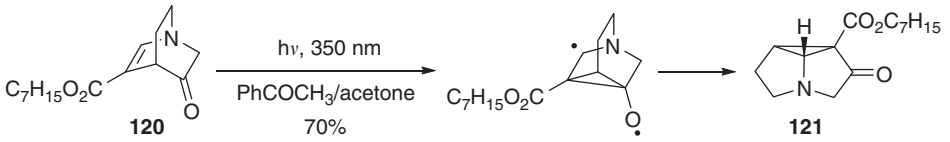
Table 4 Product distribution depending on the sensitizer (Scheme 25)

Substrates	*Sensitizer*	*Yield of **118** (%)*	*Yield of **119** (%)*	*Recovered **117** (%)*
117a	3-Methoxyacetophenone	52	6	30
117a	4-Phenylbenzophenone	94	–	–
117b	3-Methoxyacetophenone	47	6	30
117b	4-Phenylbenzophenone	94	–	–
117c	3-Methoxyacetophenone	22	4	52
117c	4-Phenylbenzophenone	96	–	–

Despite the fundamental interest of these recent advances in the understanding of the ODPM photoisomerization of acyclic β,γ-unsaturated carbonyl compounds, they did not find widespread applications to the synthesis of complex organic molecules yet. The situation is completely different for cyclic β,γ-unsaturated ketones. Indeed, in many cases, the conformational constraints induced by the cyclic structure allow the formation of ODPM photoisomerization products in a high yield and in a predictable way. This behavior is well illustrated by the involvement of ODPM photoisomerization as efficient key step in the synthesis of natural products. In addition, several new synthetic strategies allowing efficient access to complex but unnatural molecular scaffolds and new asymmetric transformation were reported. Some relevant examples reported in the recent literature are described in the following section.

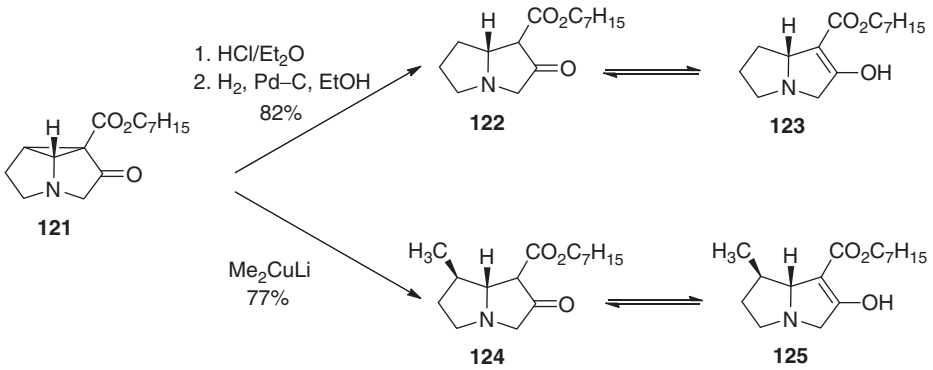
5.06.3.2 Synthetic Application of ODPM Photoisomerization

The pyrrolizidine skeleton is present in numerous biologically active alkaloids.[78] A straightforward access to this skeleton involving ODPM photoisomerization of nitrogen containing bicyclic systems was proposed (Scheme 26).[79] The 1-aza-3-carboalkoxybicyclo[2.2.2]oct-2-en-5-one (quinuclidinone) **120** serving as the photoprecursor was synthesized according to previously described procedures. The photochemical irradiation (using a 450 W medium-pressure lamp) of a solution of compound **120** in acetophenone or 5/95-acetophenone/acetone afforded the ODPM product **121** in 70% yield. Noteworthy, when acetone was used as solvent and sensitizer, a very low conversion (2%) into the ODPM product was observed.



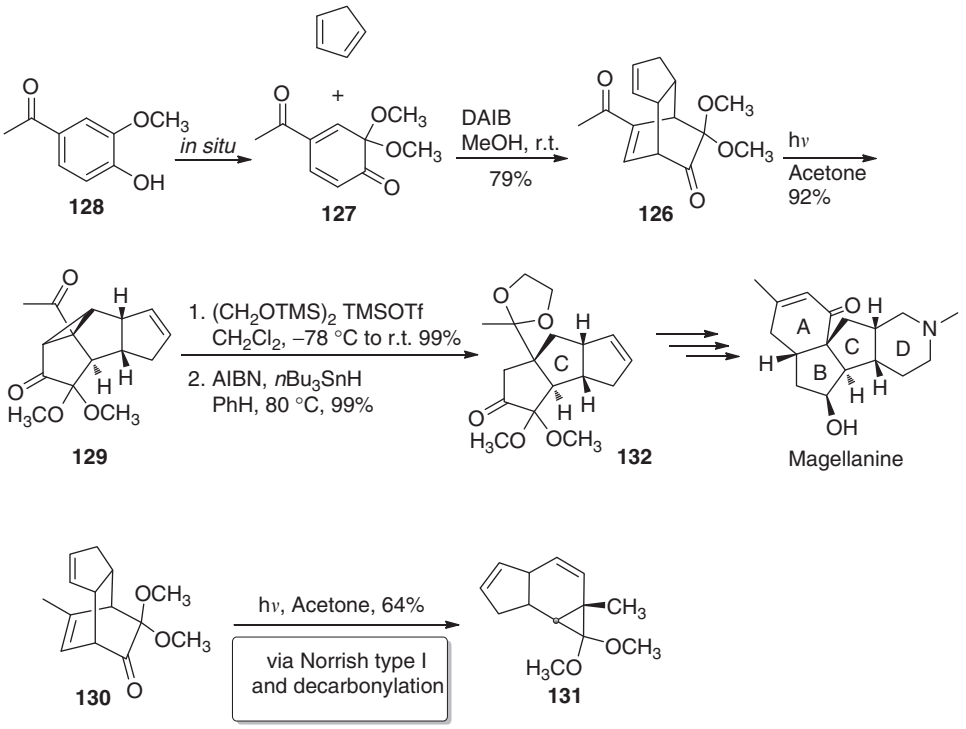
Scheme 26

The pyrrolizidine skeleton was then obtained by reductive cleavage of the cyclopropane ring, affording compound **122** in equilibrium with its keto enol form **123** in 82% yield (Scheme 27). Alternatively, a regioselective cyclopropane ring opening was achieved by the addition of lithium dimethylcuprate affording compound **124** in 77% yield as a single stereoisomer, which is in equilibrium with its keto enol form **125**. The latter transformation is analogous to the 1,4-addition of cuprates to α,β-unsaturated carbonyl compounds.



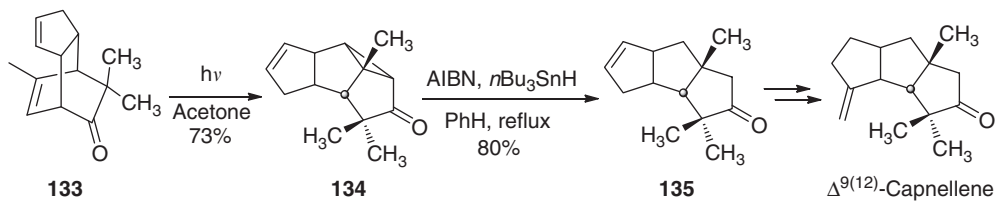
Scheme 27

Two-step sequences involving Diels–Alder reactions and ODPM photoisomerizations were extensively used to build up linear triquinanes scaffolds.[80–83] As an illustrative example, this type of sequence was successfully involved in the total synthesis of the challenging polycyclic alkaloid megellanine (Scheme 28).[84] Compound **126** was easily obtained by a Diels–Alder reaction between cyclopentadiene and the masked *o*-benzoquinone **127**. The latter compound is readily generated *in situ* from acetovanillone **128**. This Diels–Alder reaction is regio- and stereocontrolled and affords compound **126** possessing four contiguous stereocenters in 79% yield. The ODPM rearrangement was achieved by irradiation of compound **126** in acetone, affording the tetracyclic diketone **129** in 92% yield. The presence of the acetyl group is crucial to ensure a high yield in the ODPM photoisomerization, most probably by stabilization of typical radical intermediates involved in this reaction. This fact is nicely illustrated by the photochemical reaction obtained by irradiation of compound **130**, which includes a methyl group instead of the acetyl group, under the same reaction conditions. In this case, a Norrish type I reaction followed by decarbonylation afforded compound **131** in 64% yield.[85] The cyclopropane ring opening of **129** was then achieved in quantitative yield, after protection of the acetyl group, using tributyltin hydride/azobisisobutyronitrile. Starting from the key intermediate **132**, three main tasks were then achieved to complete the total synthesis of megellanine. Several steps were necessary to carry out the functional interconversion of ring B and construction of ring A. Finally, the cyclopentene ring was converted into the piperidine ring D by oxidative cleavage and double reductive amination.



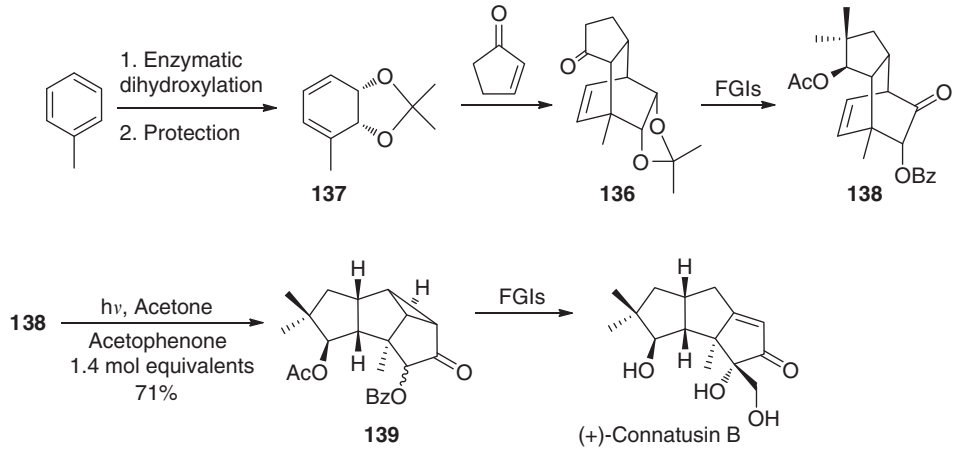
Scheme 28

The same methodology was applied to the total synthesis of Δ-$^{9(12)}$-capnellene, a triquinane sesquiterpene isolated from the soft coral *Capnella imbricate*. The irradiation of compound **133** in acetone afforded the ODPM product **134** in 73% yield (Scheme 29). The advanced intermediate **135** toward the synthesis of Δ-$^{9(12)}$-capnellene was then obtained in 80% yield by reductive ring opening of compound **134**.[85]



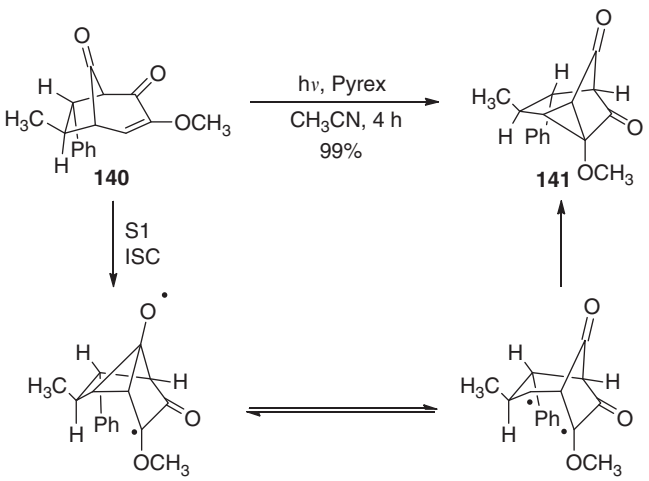
Scheme 29

The enantioselective synthesis of various linear triquinane sesquiterpenoids was also performed using ODPM photoisomerization as a key step. As illustrated by the total synthesis of (+)-cannatusin B,[86] the success of the strategy is based on the synthesis of enantiopure cyclopenta-fused bicyclo[2.2.2]octenone **136** (Scheme 30).[87,88] The scaffold was built up by a Diels–Alder reaction between cyclopentenone and the enantiopure diene **137**, which is obtained by enzymatic dihydroxylation of toluene. Further functional groups interconversions lead to compound **138**, which was subjected to the ODPM rearrangement. Irradiation of compound **138** in the presence of 1.4 mol equivalents of acetophenone afforded the ODPM product **139** in a 71% yield. Suitable functional interconversion including reductive ring opening of the cyclopropane was then achieved to complete the total synthesis of enantiopure (+)-cannatusin B.



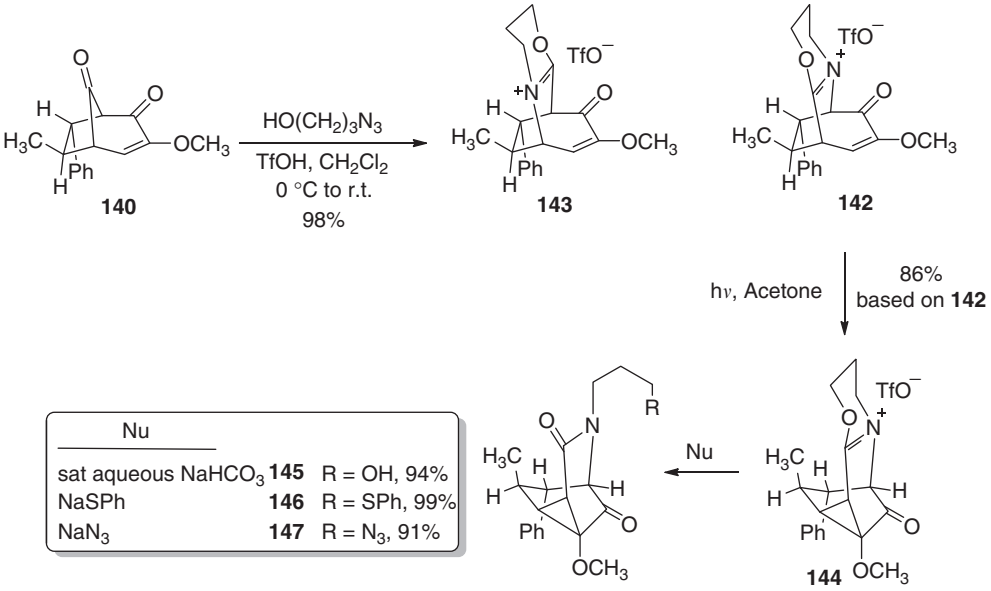
Scheme 30

Photochemical reactions are efficient tools to rapidly accomplish the synthesis of complex pattern as found in natural products. They were also frequently used to synthesize challenging nonnatural molecular architectures like caged hydrocarbons or molecules possessing high strain.[2,89] In related approaches, photochemical reactions have been successfully used in a diversity-oriented synthesis toward underrepresented scaffolds. The high value of this last strategy is illustrated by the photochemical study of bicyclo[3.2.1]octanoid **140** (Scheme 31).[90] The presence of a β,γ-unsaturated ketone moiety in the compound **140** allows the ODPM rearrangement. Remarkably, product **141** is obtained in quantitative yield by irradiation of an acetonitrile or acetone solution of compound **140** using a Pyrex vessel (Scheme 31). Under such reaction conditions, it was suggested that the ODPM rearrangement occurs at a triplet excited state resulting from singlet excitation followed by intersystem crossing. The ODPM reaction tolerates modifications of the substituents on the bicyclo[3.2.1]octanoid moiety even if the presence of an α,β-unsaturated ketone moiety is a prerequisite. The presence of the strained cyclopropane ring in the ODPM product **141** was further exploited for the discovery of new transformations. Indeed, compound **141** was successfully engaged in several reactions such as retro-Dieckmann, Grignard addition, azido-Schmidt or dipolar cycloadditions resulting in a substantially increased scaffold diversity.



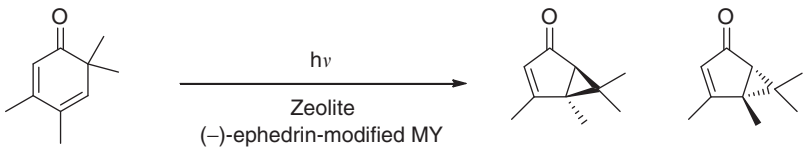
Scheme 31

Another interesting aspect of this work relates to the successful aza-di-π-methane rearrangement (see Section 5.06.4) of the β,γ-unsaturated iminium substrate **142** (Scheme 32). The iminium ions **143** and **142** were readily obtained in 98% yield from the bicyclo[3.2.1]octanoid precursor **140** by an azido-Schmidt reaction.[91] Irradiation of an acetone solution of this mixture of regioisomers leads to the transformation of compound **142** (the only one which possesses the required β,γ-unsaturated iminium pattern) via the aza-di-π-methane rearrangement, affording product **144** in 86% yield. This compound can undergo nucleophilic ring opening to afford cyclopropyl amides **145**, **146**, and **147** in high yields using previously described methodologies.



Scheme 32

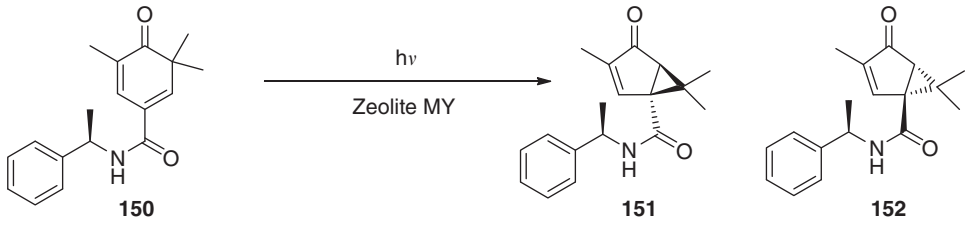
The achievement of asymmetric chemical reactions at the excited state is more challenging than in the ground state and often-required unusual strategies. It was previously demonstrated that in several photochemical reaction the asymmetric induction could be achieved by 'caging' a liquid reactant close to a chiral inductor using a zeolite super cage.[92,103,104] Moreover, the zeolite cavity may also be used to control the nature of the excited state of an enone through cation binding.[93] The photochemistry of 2,4-cyclohexadienones such as compound **148**, was investigated in zeolite medium, based on previous reports describing that the nature of the excited state involved in solution is strongly dependent on the reaction medium (Scheme 33).[94] In a nonpolar solvent such as hexane the formation of a ketene intermediate is observed occurring from the $n\pi^*$ excited state; in contrast, when the transformation is carried out in polar solvents such as trifluoroethanol, the reaction occurs at a $\pi\pi^*$ excited state affording the ODPM rearrangement product in a high yield. As anticipated by the authors, the ODPM rearrangement occurring from the $\pi\pi^*$ excited state is the only photochemical process observed when the reaction is carried out in the cavity of an alkali ion exchanged Y zeolite. Moreover, irradiation of a mixture of compound **148** and (−)-ephedrine as chiral inductor included in zeolite NaY (hexane slurry; 1 molecule of 2,4-cyclohexadienone per 10 supercages and 1 molecule of (−)-ephedrine per 1 cage) afforded compound **149** as the only product with an enantiomeric excess of 32%. Among the wide range of evaluated chiral inductors, the highest *ee* value was obtained using the (−)-ephedrine. The enantiomeric excess was improved using the same chiral inductor, when the reaction was carried out at lower temperature (− 55 °C, *ee* 49%). More interestingly, the nature of the zeolite cation has a strong influence on the enantiomeric excess as revealed by the *ee* obtained using different (−)-ephedrine-modified alkali ion exchanged Y zeolites.



MY	LiY	NaY	KY	RbY	CsY
ee	0%	32%	26%	5%	0%

Scheme 33

A diasteroselective approach was also evaluated by inclusion of chiral 2,4-cyclohexadienone **150** in different alkali ion exchanged Y zeolites (Scheme 34). The irradiation of compound **150** in trifluoroethanol afforded the ODPM products **151** and **152** in a low diastereoisomeric excess (5%). However, when the reaction was carried out in Y zeolites (hexane slurry; 1 molecule of 2,4 cyclohexadienone per 20 supercages) diastereoisomeric excesses up to 59% were obtained.

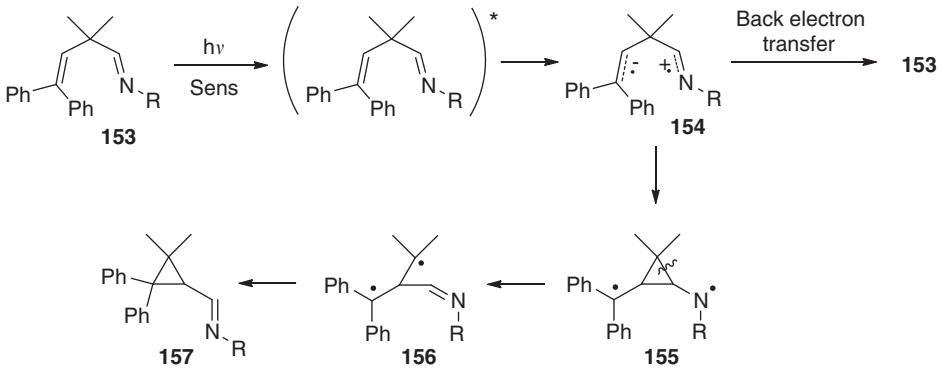


MY	Trifluoroethanol	LiY	NaY	KY	RbY	CsY
de	5%	17%	59%	53%	39%	9%

Scheme 34

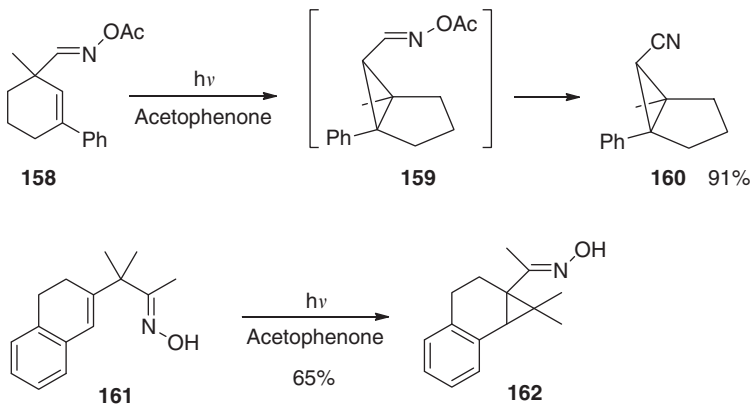
5.06.4 Aza-Di-π-methane Photoisomerization

Similar to the previously presented oxa-di-π-methane photoisomerization, reactions have been carried out with imines of type **153** (Scheme 35). The reactivity depends on the electronic properties of the substituent R.[14,95,96] After photochemical excitation, intramolecular electron transfer may occur leading to the intermediate **154**. Back electron transfer regenerates the starting product **153**, which limits the efficiency of the reaction. In the case of different benzyl substituents for R, a Hammett relationship was observed between a variety of aromatic groups and the product quantum yield.[96] The excellent correlation is based on σ^+ values. This observation indicates that in **154**, a positive charge is localized on the imine function and that this intermediate plays an important role in the proposed mechanism. More recently, the reaction was also induced by photochemical electron transfer sensitization.[97] The zwitterionic intermediate **154** generates the typical 1,4-biradical intermediate of the di-π-methane photoisomerization **155**. A rearrangement of this intermediate leads to the 1,3-biradical **156**; radical combination generates the final product **157**.



Scheme 35

The aza-di-π-methane photoisomerization was successfully performed with a variety of oxime acetates. Two examples are depicted in Scheme 36. On irradiation in the presence of acetophenone as triplet sensitizer, compound **158** was transformed into **159**.[11] During workup, acetic acid was eliminated from the photo product, giving nitrile **160** in high yields. Only the *endo* isomer was isolated. Various examples of nitrile formation in the context of the aza-di-π-methane photoisomerization of oxime derivatives have been published.[98] The same reaction conditions with acetophenone as triplet sensitizer were applied to the transformation of the ketoxime **161** into the rearranged product **162**.[98] It should further be pointed out that the hydroxyl function of the ketoxime group did not need to be acylated. In this case, the reactivity is increased by the conformational rigidity of the substrate. The triplet sensitized aza-di-π-methane photoisomerization of acylated aldoximes was also applied to the synthesis of pyrethroid derivatives.[99] As already mentioned above, such compounds possess insecticidal properties.



Scheme 36

5.06.5 Conclusion

Starting from simple precursors, the di-π-methane photoisomerization and its oxa-di-π-methane and the aza-di-π-methane analogs provide facile access to complex polycyclic products. As in many cases of photochemical reactions, a lot of mechanistic studies have been carried out. Although the reaction is possible at the singlet state, most of the transformations occur at the triplet state. When carried out in solution, the reactions can thus be easily performed via triplet sensitization. Less frequently, electron transfer sensitization was applied. For the purpose of asymmetric synthesis, the di-π-methane rearrangements were studied in confined environments such as in crystals or zeolithes. These isomerizations were also applied to organic synthesis, in particular to the total synthesis of natural or biologically active products. In this context, it must be pointed out that significant molecular complexity is generated in only one step and under mild reaction conditions. Thus syntheses may be considerably facilitated, for example, by diminishing the number of steps.

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5.07 Metal-Mediated and Metal-Catalyzed [2 + 2] Cycloadditions

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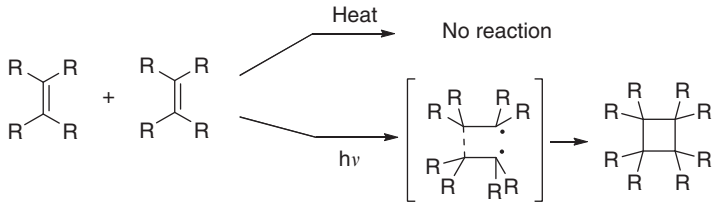
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Glossary

Chiral auxiliary A chiral fragment that is temporarily incorporated into a substrate in order to control the stereochemical outcome of a chemical transformation.
Cycloaddition reaction An addition reaction in which a ring is formed.
Enantiomeric excess (*ee*) The excess of one enantiomer over the other in a mixture of enantiomers.
Endo* and *exo Terms used to identify the stereochemistry of a substituent on a bridged ring system; for a bicyclic compound, the prefix *endo* is reserved for the substituent located *syn* to the longer bridge (more atoms) and the prefix *exo* is for the substituent *syn* to the shorter bridge.
Expressed mathematically Enantiomeric excess = % of major enantiomer − % of minor enantiomer.
Metallacycle A cyclic compound comprising at least one metal center within the ring.
Oxidizing agent (oxidant) In a redox reaction, the reactant that causes the oxidation, and is itself reduced.

5.07.1 Introduction

Cycloaddition reactions, in general, are one of the most powerful and frequently applied methods for the construction of cyclic frameworks.[1] In general, $[m+n]$ cycloadditions can be induced by heat, light, Lewis acids, high pressure, and sonication.[1] The [2 + 2] cycloaddition is a thermally forbidden process as predicted by the Woodward–Hoffmann rules,[2] but it can be achieved photochemically via biradical intermediates (Scheme 1). Many of these reactions require the presence of a polarized functional group in the substrate to facilitate the transformations. Substrates without polar substituents usually show poor reactivity and require extreme reaction conditions. The transition metal-catalyzed reactions provide new opportunities for the cycloadditions of otherwise unactivated substrates and for cycloadditions which are difficult to achieve or theoretically forbidden. Metal-catalyzed cycloadditions have made a great contribution to the preparation of a variety of cyclic compounds.[3] In particular, metal-catalyzed [2 + 2] cycloaddition reactions provide a synthetically important method for the construction of cyclobutanes or cyclobutenes using simple and easily available materials. These four-membered ring products have been applied in many organic transformations owing to the natural ring strain that leads to selective and facile bond cleavage within the ring. These reactions are generally highly atom- and step-economical. The proposed mechanism for the metal-catalyzed [2 + 2] cycloaddition of two different carbon–carbon multiple bonds (alkynes, alkenes, allenes, etc.) generally involves the coordination of these substrates to a low-valence metal center, followed by oxidative cyclometalation to give a metallacyclopentane or metallacyclopentene intermediate as the key steps (Scheme 2).[4] Reductive elimination of **A**, **B**, or **C** affords the cyclobutene or cyclobutane products and regenerates the active metal species for the next catalytic cycle. Many reviews on different metal-catalyzed cycloaddition reactions, including [2 + 2 + 1], [2 + 2 + 2], [3 + 2], and [4 + 2] cycloadditions, are known, but so far, only a small number of short reviews focusing on metal-catalyzed [2 + 2] cycloaddition in organic synthesis have appeared. Moreover, all of these reviews only covered the [2 + 2] chemistry partially.[3] In this chapter, we will cover the metal-mediated and -catalyzed [2 + 2] cycloaddition reactions and related chemistry comprehensively. For convenience and clarity, the [2 + 2] cycloaddition reactions are first classified according to the various types of unsaturated π substrates involved and then according to the type of metal catalysts used. Finally, attention is focused on the reaction mechanism, substrate scope, the limitations of the reaction, and the synthetic applications.

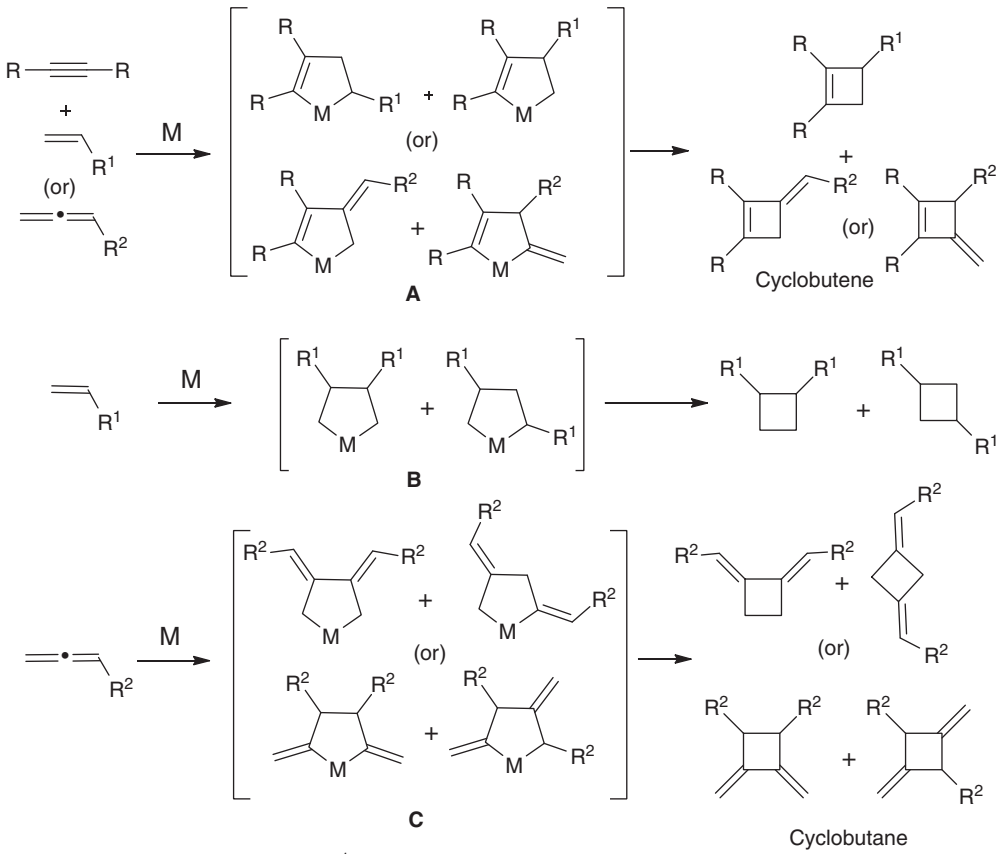


Scheme 1 Traditional method for the [2 + 2] cycloaddition reaction.

5.07.2 Intermolecular Metal-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

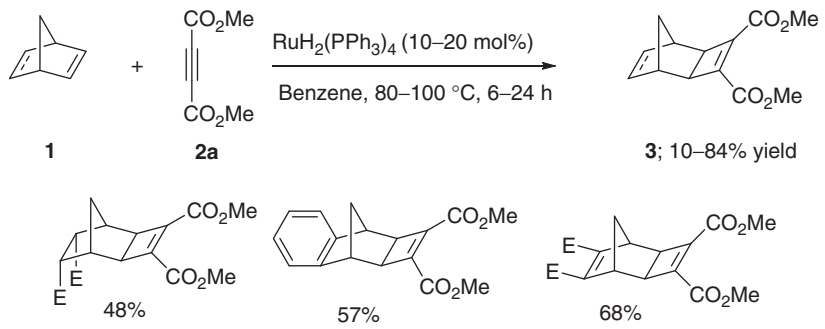
5.07.2.1 Ru-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

The metal-catalyzed [2 + 2] cycloaddition of alkynes with alkenes is a powerful and efficient tool to synthesize cyclobutene derivatives. In this context, ruthenium complexes represent one of the major metal catalysts.[4] The reaction is quite easy and very flexible, giving the user access to a wide range of [2 + 2] cycloaddition products. Initially, Mitsudo et al. used a low-valent ruthenium complex as the catalyst for the [2 + 2] cycloaddition of norbornenes with acetylenes. Thus, the reaction of equimolar amounts of a bicyclic alkene and an alkyne in the presence of a catalytic amount of $RuH_2(PPh_3)_4$ in benzene at 80–100 °C for



Scheme 2 Possible metallacyclopentene and -pentane intermediates for the synthesis of cyclobutenes and cyclobutanes.

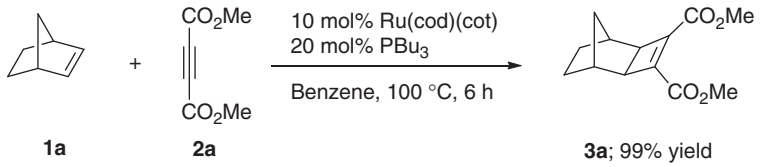
6–24 h gave modest to good yields (10–84%) depending on the type of bicyclic alkene chosen (Scheme 3).[5a] In almost all cases, the cycloadditions were found to be highly stereoselective, forming only the *exo* adducts.[5b]



Scheme 3 Ruthenium-catalyzed [2 + 2] cycloaddition of norbornene with DMAD; E = CO_2Me.

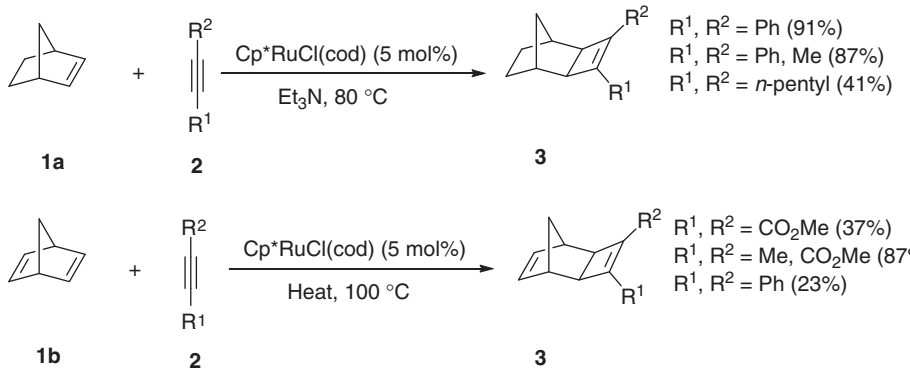
Later, the Mitsudo group also studied other Ru catalysts to increase the yields of cycloadducts. Interestingly, the best result in the [2 + 2] cycloaddition reaction of norbornene **1a** with dimethyl acetylenedicarboxylate (DMAD) (**2a**) was obtained with the combination of [Ru(cyclooctadiene (cod))(cyclooctatetraene (cot))]/PBu_3 as the catalyst, which led to product **3a** in 99% yield (Scheme 4).[6] However, the use of low-valent ruthenium complexes with oxidation states of 0 or II, such as [Ru(cod)(cot)], [$RuH_2(PPh_3)_4$], and [$RuH_2(CO)(PPh_3)_3$], as catalysts had a severe limitation with regard to the alkynes: only alkynes with strongly electron-withdrawing (CO_2R) groups attached could be used for this reaction.

Finally, Mitsudo et al. found that pentamethylcyclopentadienyl(Cp^*)RuCl(cod) was a remarkable catalyst for the [2 + 2] cycloaddition of norbornene derivatives with various alkynes. Both aliphatic and aromatic internal alkynes readily reacted with



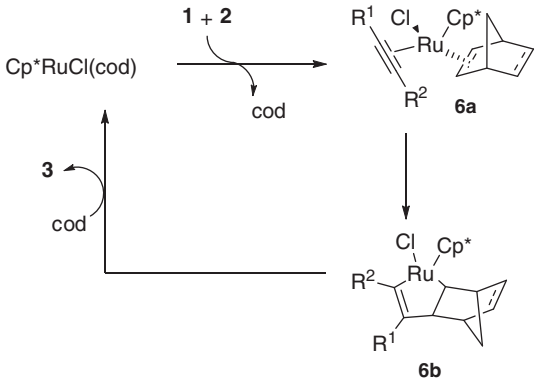
Scheme 4 Ru(0)-catalyzed [2 + 2] cycloaddition of norbornene with DMAD.

norbornene to give the corresponding [2 + 2] cycloadducts in high yields (Scheme 5).[7] However, the reaction of terminal alkynes with norbornadiene (NBD) or norbornene gives cyclobutenes in low yield along with 1,3-disubstituted benzene derivatives. Based on their experiments, the authors proposed that the active species in the catalytic mechanism is predominantly the neutral [Cp*RuCl] moiety and not the cationic $[Cp^*Ru]^+$ species. This mechanism also explains the exclusive formation of the *exo* cycloadducts (Scheme 5).



Scheme 5 [Cp*RuCl]-catalyzed [2 + 2] cycloaddition.

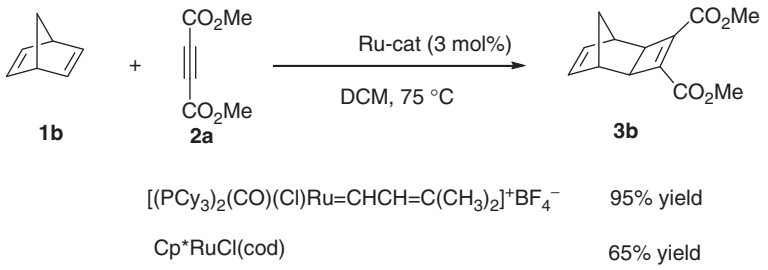
A possible reaction mechanism for the [2 + 2] cycloaddition is shown in Scheme 6. The first step is the dissociation of the labile cod ligand from the Ru-complex to generate the active neutral [Cp*RuCl] species. Highly regioselective *exo* coordination of a bicyclic alkene **1** and alkyne **2** to the Ru center forming π-complex **6a**, followed by oxidative cyclometalation leads to a ruthenacyclopentene **6b**. Density functional theory (DFT) calculations also show that generation of this intermediate is the rate-determining step in the catalytic cycle. Reductive elimination of **6b** results in the formation of the *exo*-[2 + 2] cycloadduct **3** and regenerates the active [Cp*RuCl] species for the next catalytic cycle. The coordination of the bicyclic alkene to the ruthenium occurs on the *exo* face because it is thought to have increased π-electron density over the *endo* face due to hyperconjugative effects.[8]



Scheme 6 [Cp*RuCl]-catalyzed [2 + 2] cycloaddition.

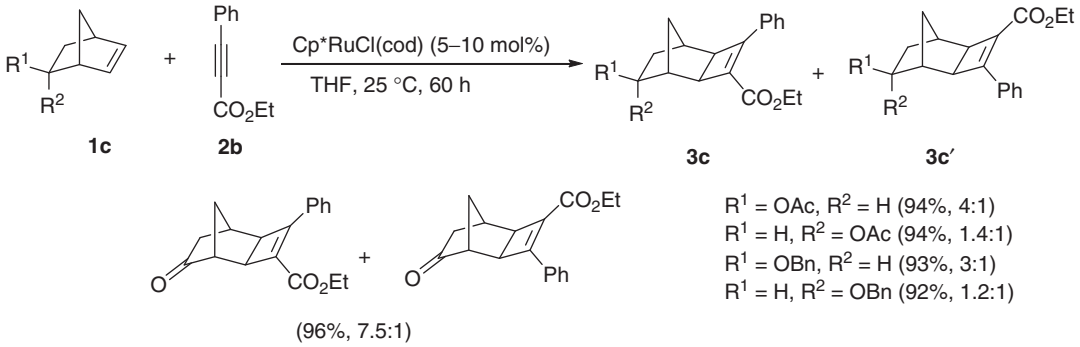
It is noteworthy that there are instances in the literature in which cationic Ru-species predominate. For example, Yi et al. have demonstrated that the [2 + 2] cycloaddition of **2a** with NBD **1b** in the presence of a catalytic amount of $[(PCy_3)_2(CO)(Cl)Ru{=}CHCH{=}C(CH_3)_2]^+BF_4^-$ in dichloromethane (DCM) at 75 °C gives the corresponding [2 + 2] cycloadduct

in 95% gas chromatography (GC) yield,[9] whereas under similar reaction conditions Mitsudo's group obtained only a 65% GC yield using Cp*RuCl(cod) (Scheme 7).



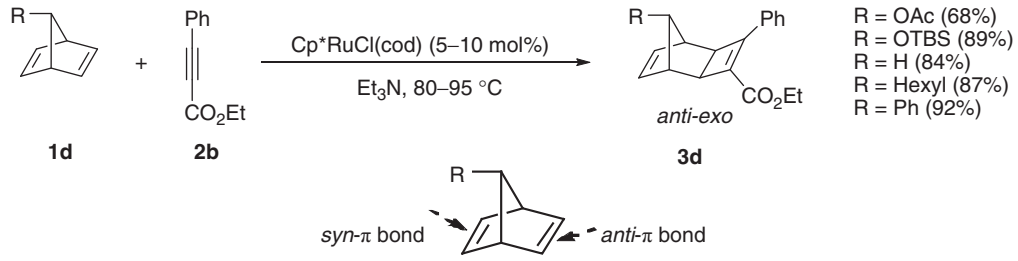
Scheme 7 Cationic Ru-catalyzed [2 + 2] cycloaddition.

Later on, Tam's group revealed a series of Cp*RuCl(cod)-catalyzed [2 + 2] cycloaddition reactions between bicyclic alkenes and alkynes. In 2000, the first example of remote substituent effects on the regioselectivity of ruthenium-catalyzed [2 + 2] cycloaddition of 2-substituted norbornenes with ethyl 3-phenylpropiolate **2b** was reported.[10] This cycloaddition occurred even at room temperature (r.t.), giving the *exo* cycloadducts in excellent yields. Regioselectivities of 1.2:1–7.5:1 were observed with norbornenes **1c** with various substituents on the C2 position (Scheme 8).



Scheme 8 Ruthenium-catalyzed [2 + 2] cycloadditions of 2-substituted norbornene with alkyne **2b**.

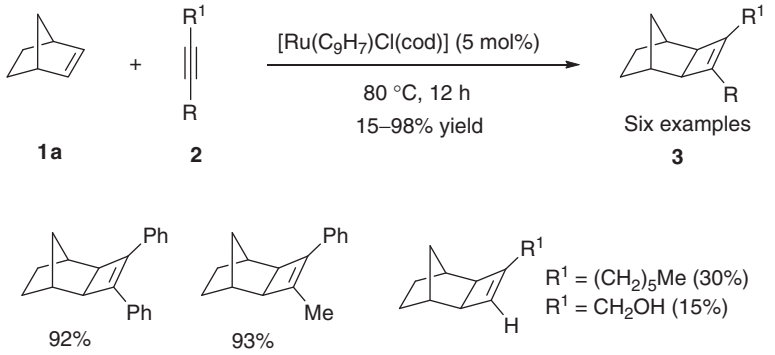
The same research group has developed a ruthenium-catalyzed [2 + 2] cycloaddition of 7-substituted NBDs **1d** with ethyl 3-phenylpropiolate **2b**. The catalytic reaction is completely regio- and stereoselective, giving only the *anti–exo* cycloadducts as single regio- and stereoisomers in good yields (Scheme 9).[11] The results of experimental and theoretical studies on the relative reaction rate of different 7-substituted NBDs showed that electron-deficient alkenes reacted slower than electron-rich alkenes. The authors anticipated that the *exo* face of the *syn*-π bond is sterically shielded by the R substituent, and so the Ru-catalyzed cycloaddition occurred preferentially on the *exo* face of the *anti*-π bond.



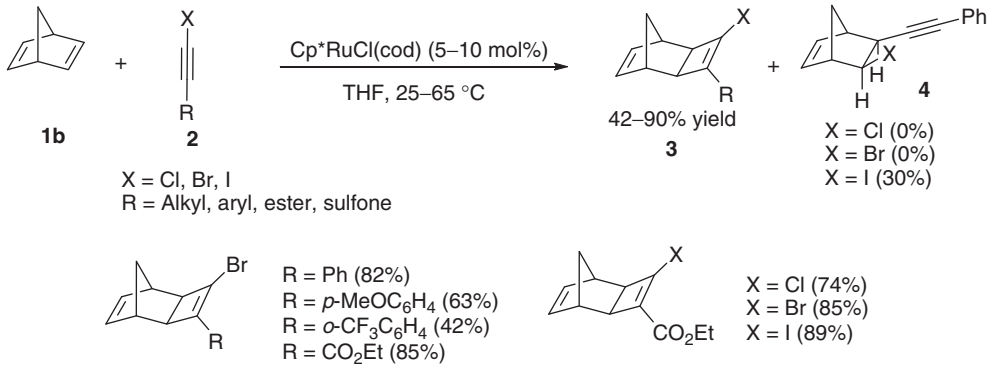
Scheme 9 Ruthenium-catalyzed [2 + 2] cycloadditions of 7-substituted NBDs with alkyne **2b**.

Gimeno and coworkers found that [Ru(η^5-C_9H_7)Cl(cod)] is a highly efficient and selective catalyst for the [2 + 2] cycloaddition of norbornene with internal alkynes, giving *exo* cycloadducts in excellent yields (Scheme 10).[12] However, the cycloadditions of 1-heptyne or propargyl alcohol proceed with lower yield and selectivity. In fact, terminal alkynes drive the reaction toward cyclotrimerization that is more facile than the [2 + 2] cycloaddition.

Tam's group reported a Ru-catalyzed [2 + 2] cycloaddition of NBD with alkynyl halides in moderate to good yields (42–89%).[13] The effects of the different halogens on the alkyne were also investigated (X = Cl, Br, I; Scheme 11). Cycloadditions of



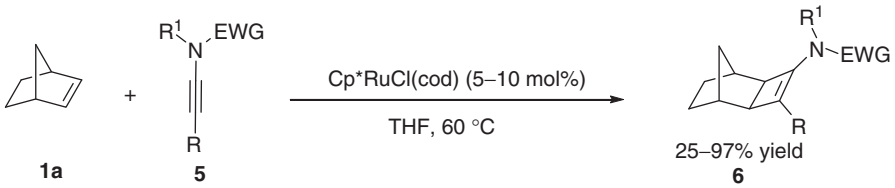
Scheme 10 Ruthenium-catalyzed [2 + 2] cycloadditions of norbornene with alkynes.



Scheme 11 Ruthenium-catalyzed [2 + 2] cycloadditions between NBD and alkynyl halides.

alkynyl chlorides and bromides occurred smoothly at 25 °C, giving the corresponding *exo* cycloadducts in good yields. Interestingly, iodoalkynyl ester reacted well with NBD to give the corresponding cycloadduct **3** in 89% yields, whereas 1-iodo-2-phenylethyne gave the cycloaddition in modest yield along with the corresponding addition product **4**.

Tam then extended the reaction to ynamides that are less reactive than electron-deficient alkynes. The cycloadditions took place slowly at 25–60 °C, requiring reaction times of 72–168 h. Moderate to good yields of the cycloadducts were obtained using various acyclic and cyclic ynamides (Scheme 12).[14]

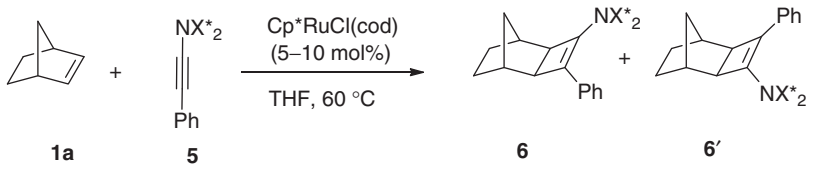


Scheme 12 Ruthenium-catalyzed [2 + 2] cycloaddition of NBD with ynamide.

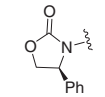
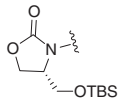
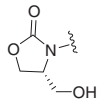
Ru-catalyzed [2 + 2] cycloadditions with chiral cyclic ynamides afforded the cycloadducts in good yields but with low to moderate diastereoselectivity (Scheme 13). The diastereomeric ratios (*dr*) were determined using ^{1}H nuclear magnetic resonance (NMR).

In the examples discussed so far, the cycloaddition of norbornene-type alkenes with alkynes generally afford the corresponding *exo* isomers. Effective asymmetric cycloadditions represent a more daunting task. Tam's group demonstrated an asymmetric induction in ruthenium-catalyzed [2 + 2] cycloadditions between alkenes and alkynes bearing chiral auxiliaries. This method was found to be highly stereo- and regioselective, and excellent levels of asymmetric inductions (up to 98.8% enantiomeric excess (*ee*) after removal of the recoverable chiral auxiliary) were observed (Scheme 14).[15]

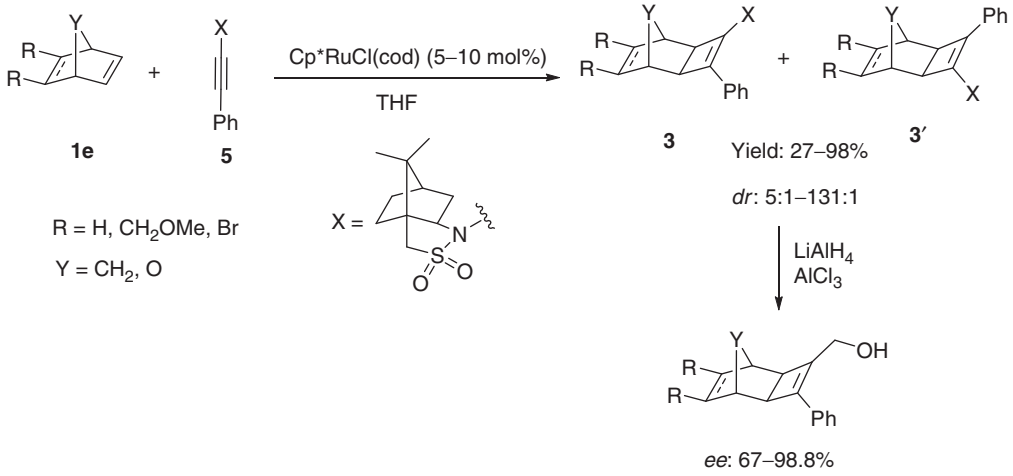
In 2006, Tam described the reaction between bicyclic alkenes with alkynyl sulfides and alkynyl sulfones in the presence of 5–10 mol% of Cp*RuCl(cod) in tetrahydrofuran (THF) in the dark at 90 °C for 72–168 h. The cycloaddition was highly chemo- and stereoselective, affording cyclobutene derivatives as single isomers in moderate to good yields (Scheme 15).[16]



1a **5** **6** **6′**

NX^*_2	Yield (%)	*dr* (%)
	83	72:28
	72	58:42
	81	71:29

Scheme 13 Ruthenium-catalyzed [2 + 2] cycloadditions of NBD with chiral cyclic ynamides.



1e **5** **3** **3′**

R = H, CH_2OMe, Br

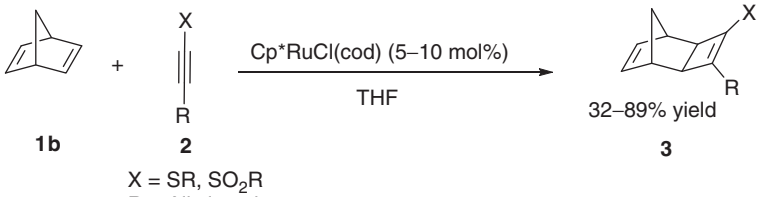
Y = CH_2, O

Yield: 27–98%

dr: 5:1–131:1

ee: 67–98.8%

Scheme 14 Ruthenium-catalyzed asymmetric [2 + 2] cycloadditions between norbornene-type alkenes and an alkyne carrying a chiral auxiliary.

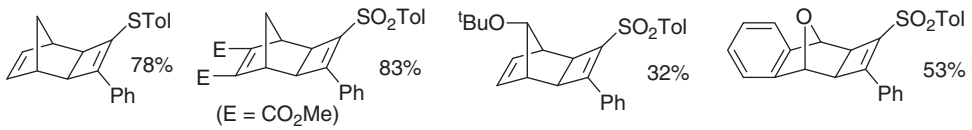


1b **2** **3**

X = SR, SO_2R

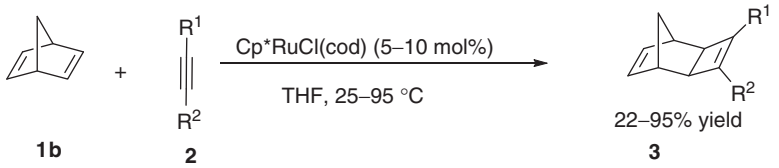
R = Alkyl, aryl, ester

32–89% yield



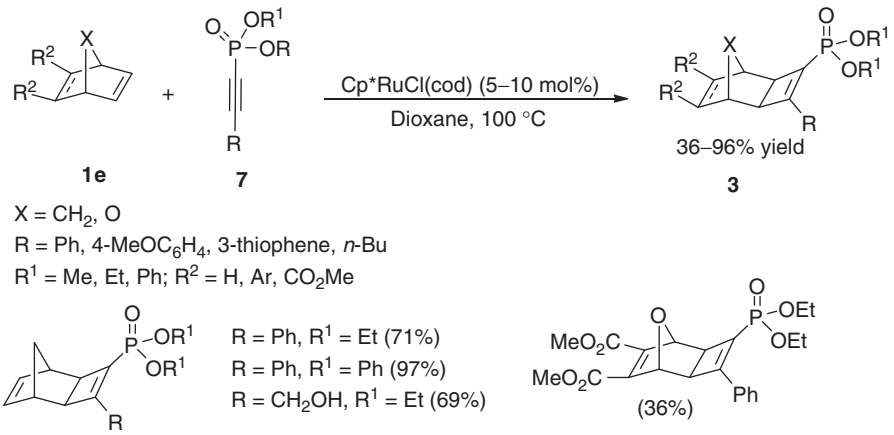
Scheme 15 Ruthenium-catalyzed [2 + 2] cycloaddition of bicyclic alkenes with alkynyl sulfides and sulfones.

In the same year, Tam also studied the reactivity of different types of alkyne substrates in Ru-catalyzed [2 + 2] cycloadditions with a bicyclic alkene.[17] They observed that the electronic effect of the alkyne plays an important role on the rate of the cycloaddition, and the reactivity increases dramatically as the alkyne becomes more electron deficient. They also observed that the steric bulkiness of the substituent on the alkyne decreases the reactivity (Scheme 16).



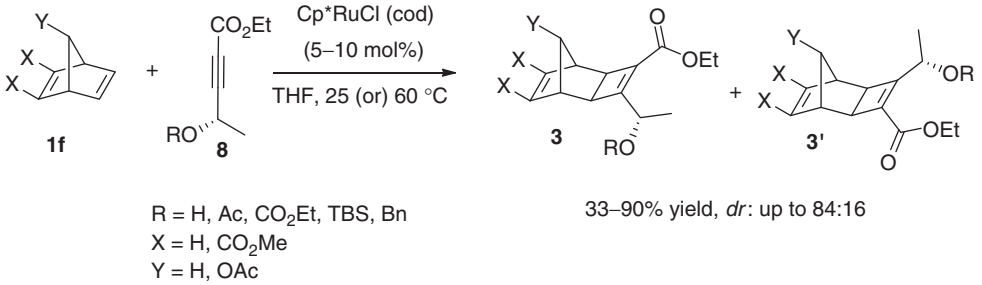
Scheme 16 Relative rate of Ru-catalyzed [2 + 2] cycloadditions of alkynes with NBD.

Similarly, the reaction between bicyclic alkenes and alkynyl phosphonates afforded cyclobutene adducts in moderate to good yields.[18] Various alkynyl phosphonates bearing diethyl, dimethyl, and diphenyl substituents reacted efficiently with bicyclic alkenes in a chemo- and stereoselective manner (Scheme 17).



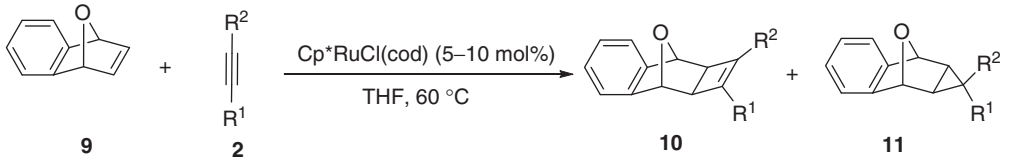
Scheme 17 Ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with alkynyl phosphonates.

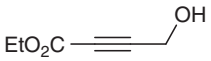
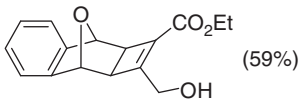
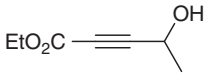
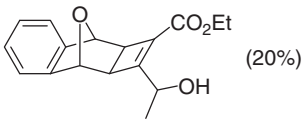
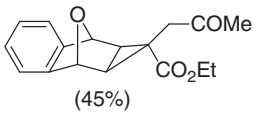
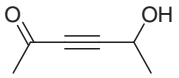
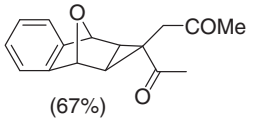
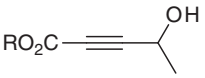
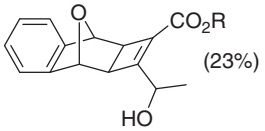
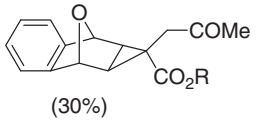
Tam and coworkers investigated a diastereoselective ruthenium-catalyzed [2 + 2] cycloaddition between chiral propargylic alcohols and bicyclic alkenes.[19a] Various bicyclic alkenes underwent the reaction to give cyclobutenes in good yields but with modest to moderate diastereoselectivities (Scheme 18).



Scheme 18 Ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with propargylic alcohols.

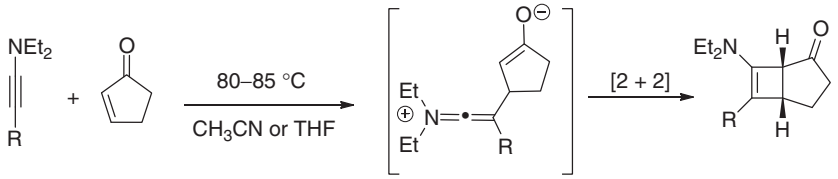
However, when expanding the scope of this reaction to oxabicyclic alkenes, the unexpected cyclopropane **11** was isolated as the major product and cyclobutene as the minor component in some cases (Scheme 19). The formation of the cyclopropane was shown to be highly selective, giving only one stereoisomer.[19b]



Alkynes	Product **10**	Product **11**
		–
		
	–	
 R = 4-NO_2-Ph		

Scheme 19 Ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with propargylic alcohols.

Earlier in 1976, Ficini disclosed a useful method for the synthesis of aminocyclobutenes on reaction of ynamines with cyclic enones via a thermally driven stepwise [2 + 2] cycloaddition (Scheme 20).[20]

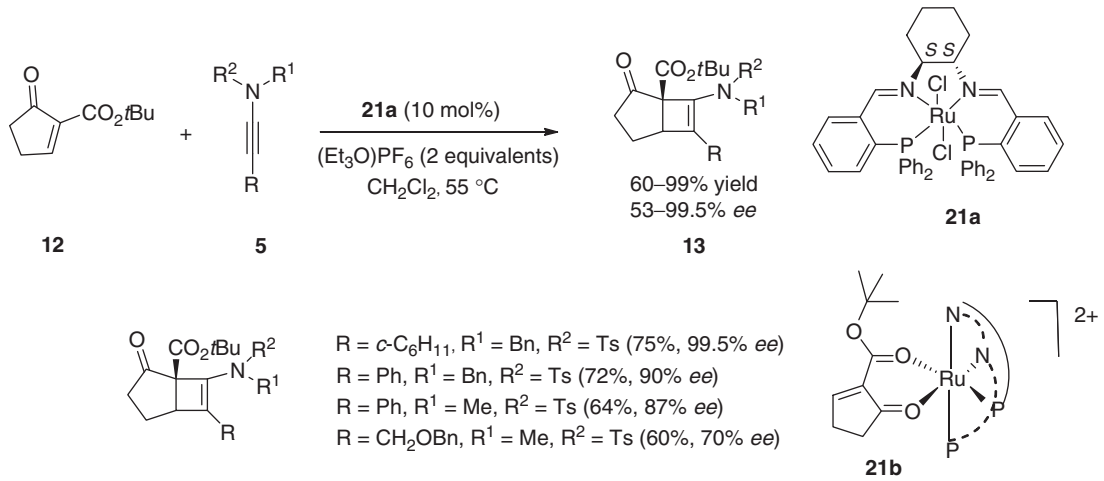


Scheme 20 Ficini's ynamine [2 + 2] cycloaddition.

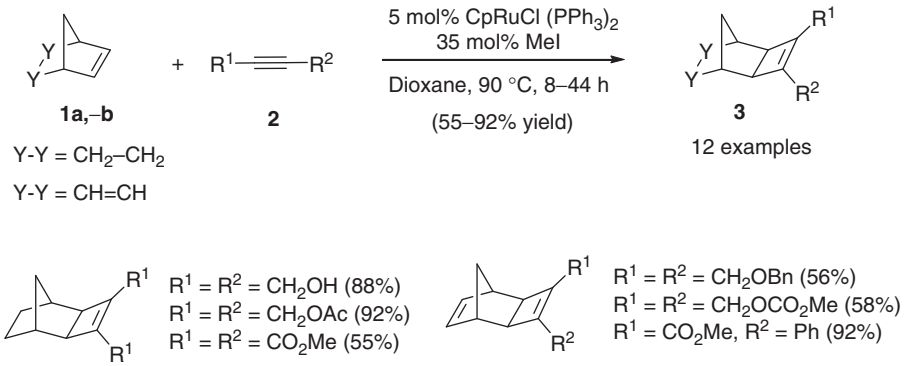
The development of metal-catalyzed processes has become an emerging field over the past decade. The first Ru-catalyzed enantioselective [2 + 2] cycloaddition (Ficini reaction) between ynamides **5** and the cyclic enone **12** was reported by Schotes and Mezzetti in 2011 (Scheme 21).[21] In this process, 10 mol% of a complex formed from ruthenium/(1*S*,2*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine (PNNP) complex and $(Et_3O)PF_6$ (2 equivalents) was found highly efficient in terms of yield and enantioselectivity. Under the reaction conditions, a wide range of ynamide substrates effectively reacted with cyclic enones to give the corresponding amidocyclobutenes **13** with high yield and excellent enantioselectivity. The authors suggested that the dicationic nature of **21b** is the possible key feature to ensure the catalytic activity. The coordination of the unsaturated *β*-keto ester to the chiral, oxophilic ruthenium/PNNP fragment appears to be an efficient strategy for enantioselection.

In 2003, Tenaglia and Giordano noticed that the electron-rich $[RuCl_2(PPh_3)_2$/MeI] system effected an intermolecular [2 + 2] cycloaddition of norbornenes with disubstituted alkynes to afford cyclobutenes in satisfactory to excellent yields (Scheme 22).[22] MeI played an important role for this reaction to proceed; no cycloadduct was observed in its absence. Previously, it was known that haloalkanes are able to coordinate with the metal center of Ru-complexes via *σ*-donation of a halogen lone pair. Another possibility is that methyl iodide might react with PPh_3 to give the corresponding phosphonium salt, thus removing a phosphine ligand to enhance the coordinating ability of the catalysts. These complexes easily undergo ligand substitution with common coordinating solvents.

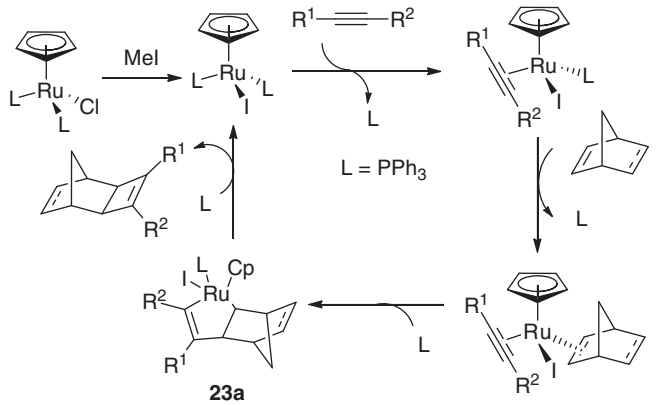
Based on the above observation, the authors proposed a possible reaction mechanism for the [2 + 2] cycloaddition of norbornenes with alkynes as shown in Scheme 23. First, the active precatalyst $CpRuI(PPh_3)_2$ is generated on reaction with MeI. Then, coordination of the alkyne and the alkene to the Ru center followed by oxidative cyclometalation gives the



Scheme 21 Ruthenium-catalyzed enantioselective [2 + 2] cycloadditions of unsaturated cyclic enones with ynamides.



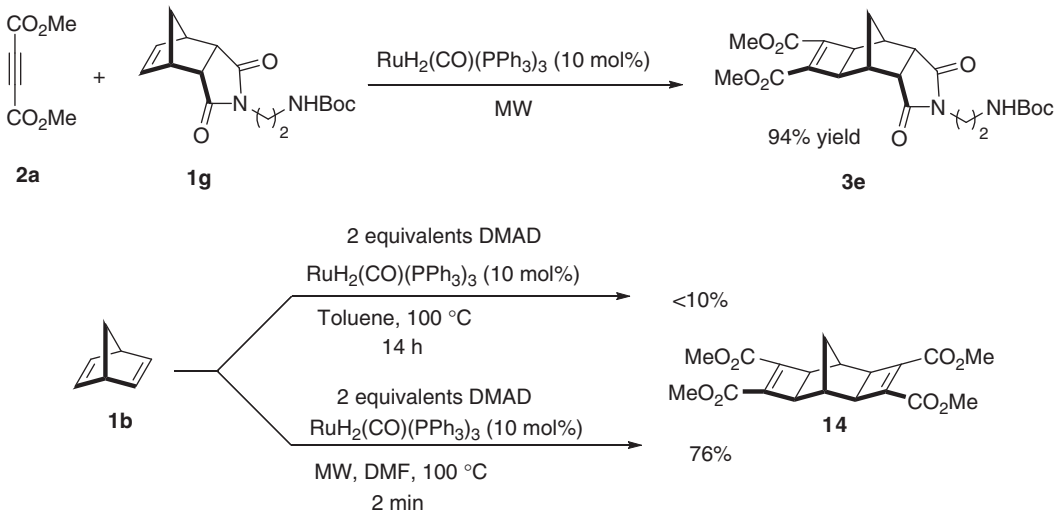
Scheme 22 The $RuCl_2(PPh_3)_2$/MeI system employed for [2 + 2] cycloadditions of norbornenes with alkynes.



Scheme 23 Proposed mechanism for the [2 + 2] cycloaddition of norbornenes with alkynes.

ruthenacyclopentene intermediate **23a**. Subsequent reductive elimination of **23a** affords the cycloaddition product **3** in a highly regio- and stereoselective manner and regenerates the active Ru species.

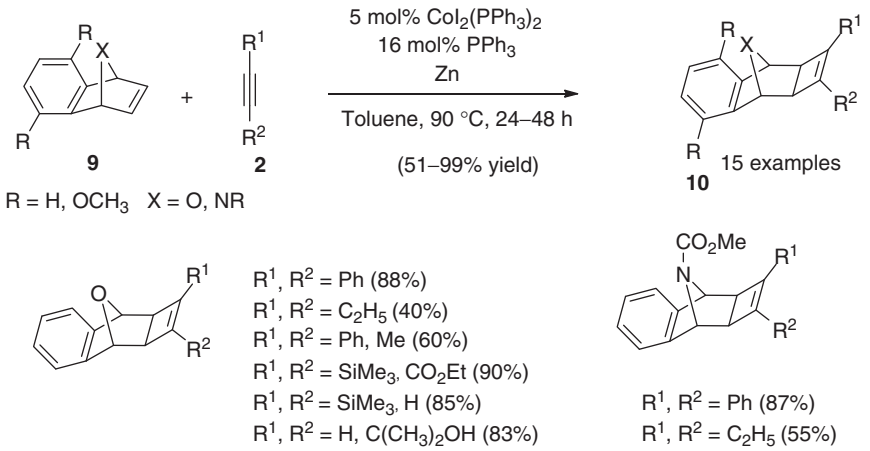
Various cyclobutene diesters were synthesized using a ruthenium-catalyzed, microwave (MW)-assisted [2 + 2] cycloaddition of norbornenes with DMAD (**2a**). High yields of the desired products were realized in only 2 min reaction time. This methodology was successfully applied to the synthesis of dicyclobutene tetraester **14** via twin cycloaddition of norbornenes with DMAD in a single-step manner. It is noteworthy that the conventional heating gave < 10% yield of this product (Scheme 24).[23]



Scheme 24 MW-assisted [2 + 2] cycloadditions of norbornenes with DMAD catalyzed by a Ru-complex.

5.07.2.2 Co-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

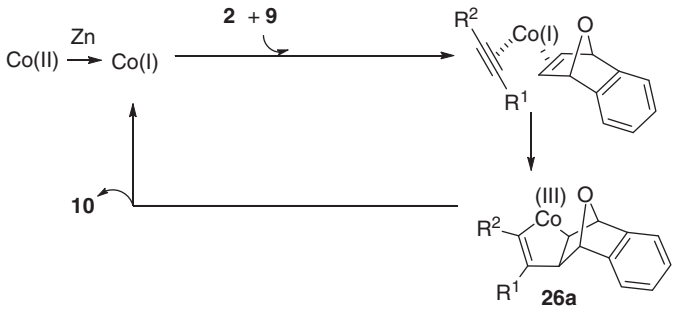
Cobalt catalysis is attractive because of the low cost of the catalysts as well as the unique reactivities or selectivities that are often achieved. Cobalt complexes have also been extensively used as catalysts for Pauson–Khand- and [2 + 2 + 2]-cycloaddition reactions.[24] Because of these observations, few reports on Co-catalyzed [2 + 2] cycloaddition are known. 7-Oxa- and azabicyclic alkenes are a class of activated substrates that show substantial coordinating ability to transition-metal centers due to the large bond-angle strain of the alkenes.[25] In this context, Cheng's group observed a cobalt-catalyzed cross [2 + 2] cycloaddition of bicyclic alkenes with alkynes. Thus, the reaction of 7-oxabenzonorbornadiene (**9**, X = O) with diphenylacetylene (**2**) in the presence of $Co(PPh_3)_2I_2$ (5 mol%), PPh_3 (16 mol%), and zinc powder in toluene at 90 °C for 24 h gave cyclobutene product **10** in excellent yield (Scheme 25).[26] Control reactions indicate that, in the absence of either the cobalt complex or zinc powder, no **10** was formed. This catalytic reaction requires excess PPh_3 in order for the reaction to proceed smoothly. In the absence of extra PPh_3, the cobalt complex decomposed readily under the reaction conditions and no catalytic activity was observed. Addition of PPh_3 to the solution improved the stability of the catalyst and increased the yields of product **10**.



Scheme 25 Cobalt-catalyzed [2 + 2] cycloadditions of bicyclic alkenes and alkynes.

Under similar reaction conditions, various symmetrical, unsymmetrical, and terminal alkynes reacted well with 7-oxabenzonorbornadiene to give the corresponding cyclobutene derivatives in good yields. The structures and yields of the individual products **10** are shown in Scheme 25.

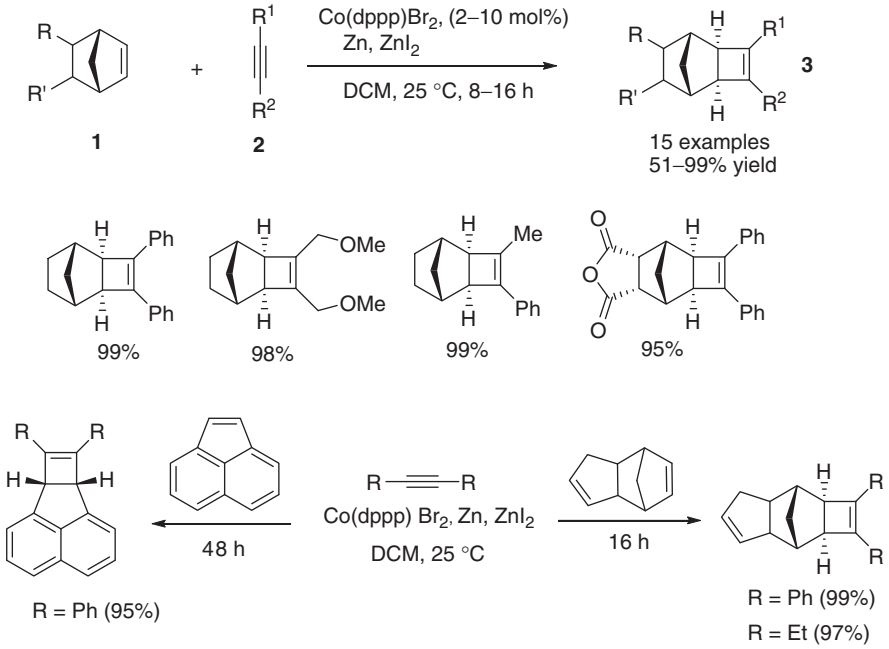
A possible mechanism for the cobalt-catalyzed [2 + 2] cycloaddition of bicyclic alkenes and alkynes is shown in Scheme 26. Reduction of $Co(PPh_3)_2I_2$ to a Co(I) species by zinc metal initiates the catalytic reaction. Coordination of an alkyne and



Scheme 26 Proposed mechanism for the cobalt-catalyzed [2 + 2] cycloaddition of bicyclic alkenes and alkynes.

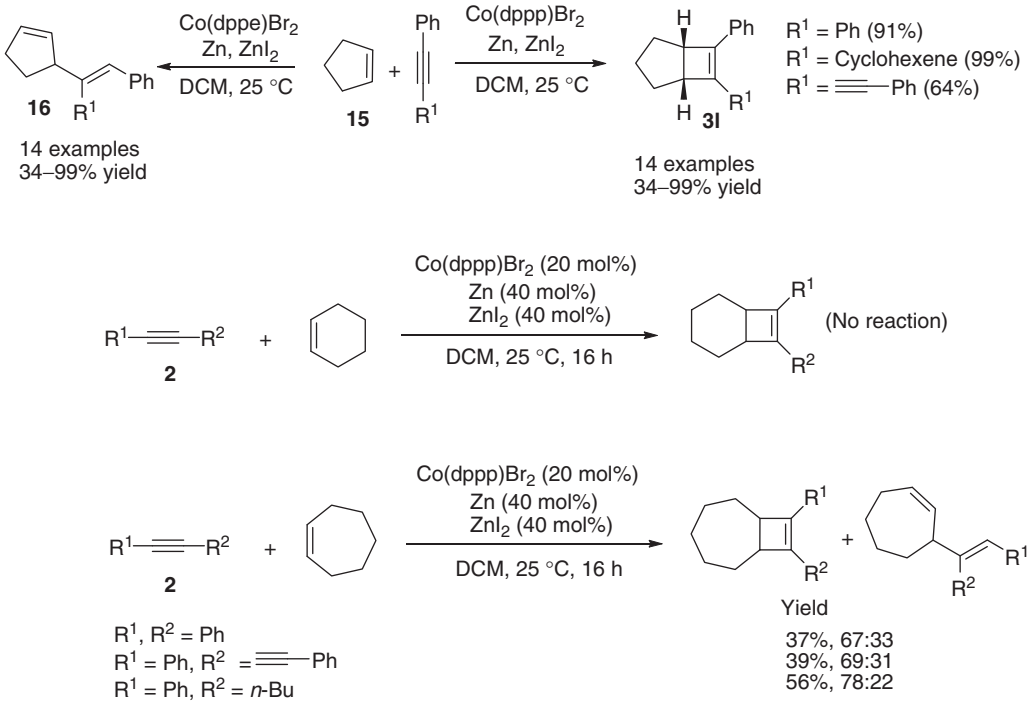
7-oxabenzonorbornadiene (**9**) to the cobalt center followed by oxidative cyclometalation affords the cobaltacyclopentene intermediate **26a**. Subsequent reductive elimination of **26a** gives the cyclobutene product and regenerates the Co(I) species.

On the basis of Cheng's work, Hilt and his group achieved a very similar intermolecular [2 + 2] cycloaddition of alkynes with alkenes. The substrates reacted in the presence of Co(1,3-bis(diphenylphosphino)propane (dppp))Br_2 (2 or 10 mol%), Zn (10 mol%), and ZnI_2 (10 mol%) in DCM at 25 °C to give the expected cycloadducts in good to excellent yield (Scheme 27).[27a] The *exo* relative configuration of the cyclobutene ring was confirmed by two-dimensional NMR spectroscopic analysis. In these reactions, both symmetrical and unsymmetrical alkynes worked equally well. However, when terminal alkynes were used as substrates, only very little of the desired [2 + 2] cycloaddition product was detected using GC-mass spectrometry (MS). With these substrates, [2 + 2 + 2] cyclotrimerization of the terminal alkynes led to the corresponding substituted benzenes. The reaction of cyclopentadiene dimer with internal alkynes led exclusively to products derived from the participation of the strained double bond, in excellent yields of 97–99% (Scheme 27). Interestingly, acenaphthylene reacted with diphenylacetylene to generate the corresponding cyclobutene in 95% isolated yield after a reaction time of 2 days.



Scheme 27 Cobalt-catalyzed [2 + 2] cycloaddition reactions between norbornenes and alkynes.

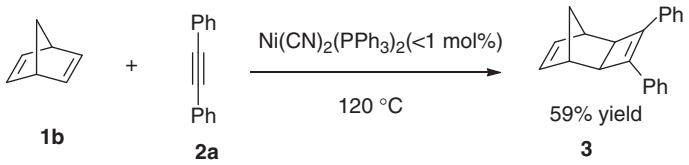
In 2010, the same author published a [2 + 2] cycloaddition of cyclopentene with internal alkynes by using the same cobalt system, which also led to cyclobutene derivatives in good to excellent yield.[27b] Various internal alkynes were compatible with the catalytic reaction. However, alkynes bearing bulky substituents such as 1,2-bis(trimethylsilyl (TMS))acetylene were unreactive under these conditions. It is surprising that cyclohexene did not undergo the [2 + 2] cycloaddition, whereas cycloheptene gave the expected cycloadduct in moderate yield along with the 1,4-diene coupling products. However, the Co(1,3-bis(diphenylphosphino)ethane (dppe))Br_2 complex favored Alder–Ene reactions of alkenes with internal alkynes in the presence of Zn, and ZnI_2 in CH_2Cl_2 to give the 1,4-diene products **16** in good to excellent yields with a high stereoselectivity (Scheme 28).



Scheme 28 Cobalt-catalyzed Alder–Ene reaction or [2 + 2] cycloaddition of cyclopentene with unsymmetrical alkynes.

5.07.2.3 Ni-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

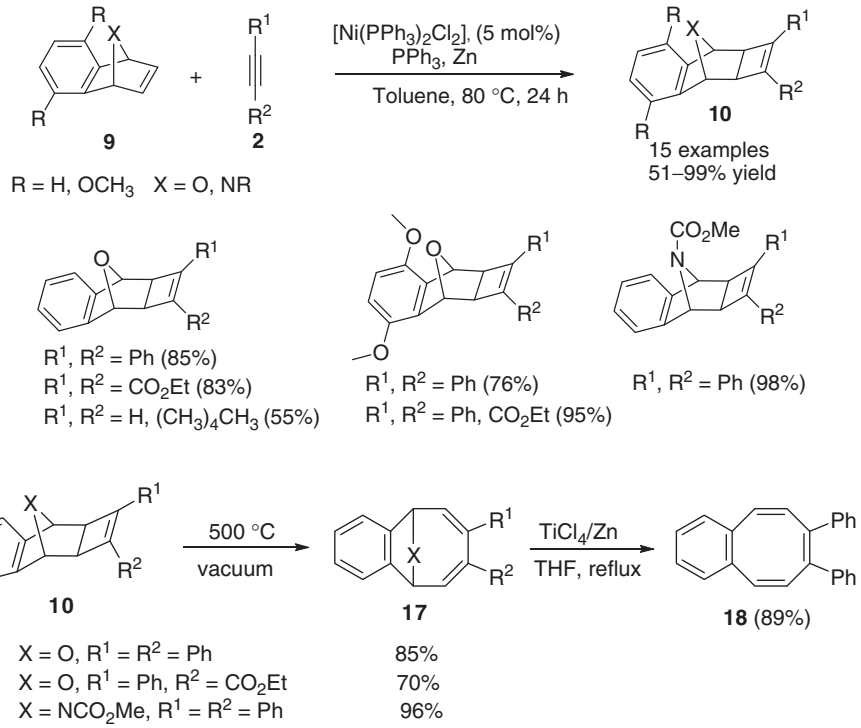
The first nickel-catalyzed [2 + 2] cycloaddition of NBD was reported in 1964 (Scheme 29). However, only very few types of acetylenes, for example, diphenylacetylene, underwent the [2 + 2] cycloaddition with NBD.[28] Instead, most activated acetylenes reacted with NBD to give alternative homo-Diels–Alder reaction products.



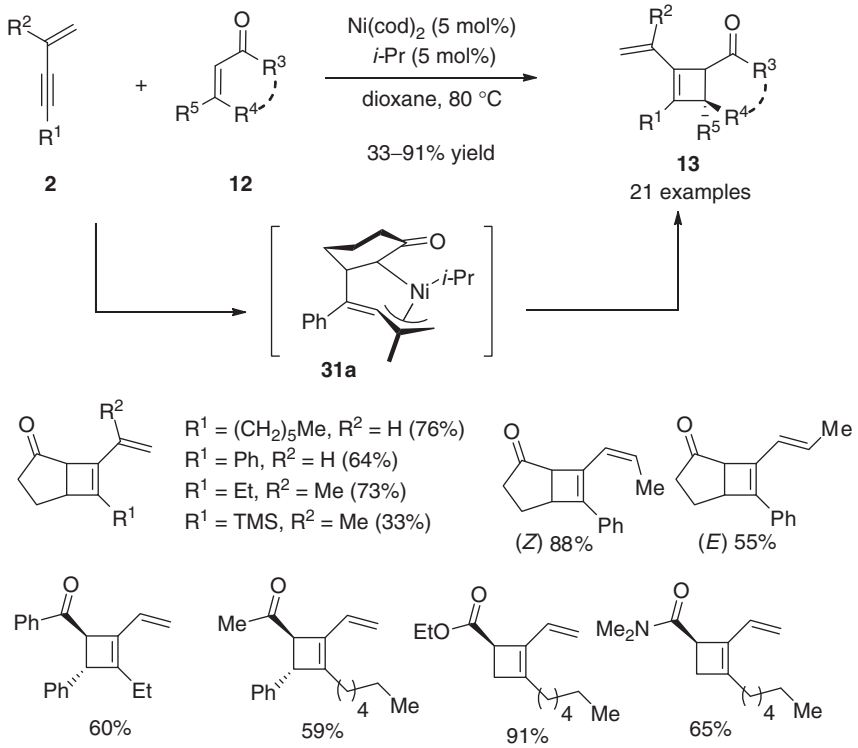
Scheme 29 Ni-catalyzed [2 + 2] cycloaddition of NBD with diphenylacetylene.

Cheng et al. also found that oxa- and azabenzonorbornadiene **9** underwent [2 + 2] cycloaddition with alkynes **2** in the presence of $NiCl_2(PPh_3)_2$, PPh_3, and zinc powder in toluene at 90 °C to give the *exo*-cyclobutene derivatives **10** in high yields (Scheme 30).[29] Other nickel-complexes such as $NiBr_2$/Zn and $Ni(cod)_2$ were also active, giving the cyclobutenes in low yields along with homocycloaddition products of oxabenzonorbornadiene. It is noteworthy that dialkylacetylenes did not undergo such [2 + 2] cycloadditions with bicyclic alkenes. On thermolysis, the cyclobutene derivatives **10** underwent a novel ring expansion, converting the fused four- or six-membered rings into an eight-membered cod moiety in high yields. For example, flash vacuum pyrolysis of **10** at 500 °C readily afforded diene **17** in 85% yield with 99% selectivity. Subsequent deoxygenation of **17** (X = O, $R^1 = R^2 = Ph$) with $TiCl_4$ and Zn gave the cot derivative **18** in 89% yield.

More recently, Ogoshi and coworkers developed a nickel-catalyzed intermolecular [2 + 2] cycloaddition of conjugated enynes with alkenes to provide cyclobutene derivatives in good yields with high chemo- and regioselectivity. Various electron-deficient alkenes as well as the electronically neutral norbornene underwent [2 + 2] cycloaddition with conjugated enynes in the presence of 5 mol% of $Ni(cod)_2$/*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) in dioxane at 80 °C for 5 h to give cyclobutanes in good yields (Scheme 31).[30] Notably, the use of conjugated enynes completely suppressed possible side reactions, such as oligomerizations and cyclotrimerizations or [2 + 2 + 2] cycloadditions. The authors isolated the η^3-butadienyl nickelacycle intermediate (**31a**).



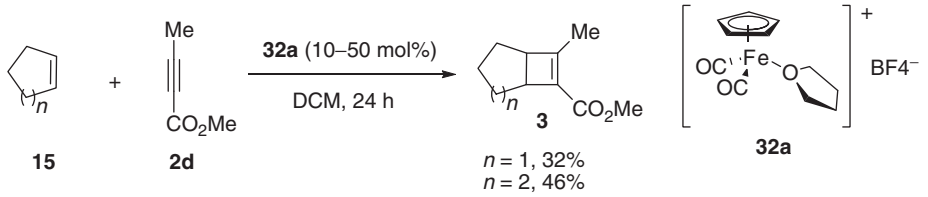
Scheme 30 Ni-catalyzed [2 + 2] cycloadditions of 7-oxa- and 7-azabenzonorbornadienes with alkynes.



Scheme 31 Ni(0)-catalyzed [2 + 2] cycloaddition of conjugated enynes with alkenes.

5.07.2.4 Fe-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

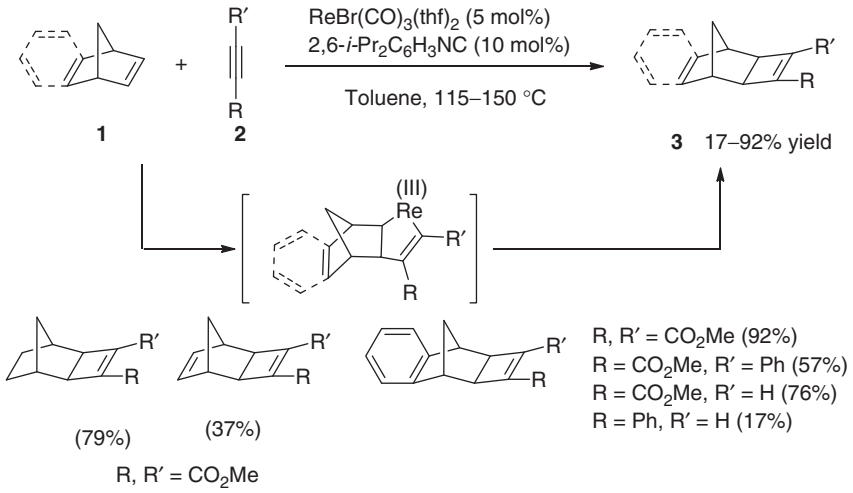
The use of iron catalysts in organic synthesis is attractive because of their abundance, low price, and low toxicity.[31] Previously, cyclopentadienyldicarbonyliron (Fp^+) (= $[CpFe(CO)_2]^+$) was found to function as a unique catalyst for cycloaddition and ene-type reactions involving the co-condensation of acetylenic-esters and olefins. Thus, treatment of methyl propiolate with olefins in the presence of the iron complex **32a** in DCM afforded cyclobutenes in moderate yield (Scheme 32).[32] The course of the reaction is strongly dependent on the structure of the olefin reactant; 1,2-disubstituted cyclic and acyclic alkenes yielded cyclobutenes along with the formation of 1,3-diene products. In addition, some of the olefins also gave lactones, whereas 1,l-disubstituted or trisubstituted alkenes gave only the latter products. Monosubstituted olefins yield principally the corresponding Fp complexes.



Scheme 32 Fe-catalyzed [2 + 2] cycloadditions of 1,2-disubstituted alkenes with methyl propiolate.

5.07.2.5 Re-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

Takai and coworkers reported that treatment of norbornenes and either internal or terminal acetylenes with a catalytic amount of $[ReBr(CO)_3(THF)]_2$ and 2,6-diisopropylphenyl isocyanide as an additive in toluene at 150 °C cleanly afforded the corresponding cyclobutene derivatives in good to excellent yields (Scheme 33).[33] In this reaction the role of the isocyanides was not clear; they may inhibit the polymerization of the acetylenes and improve the product yield. These reactions supposedly proceed via the formation of a rhenacyclopentene intermediate and a subsequent reductive elimination.

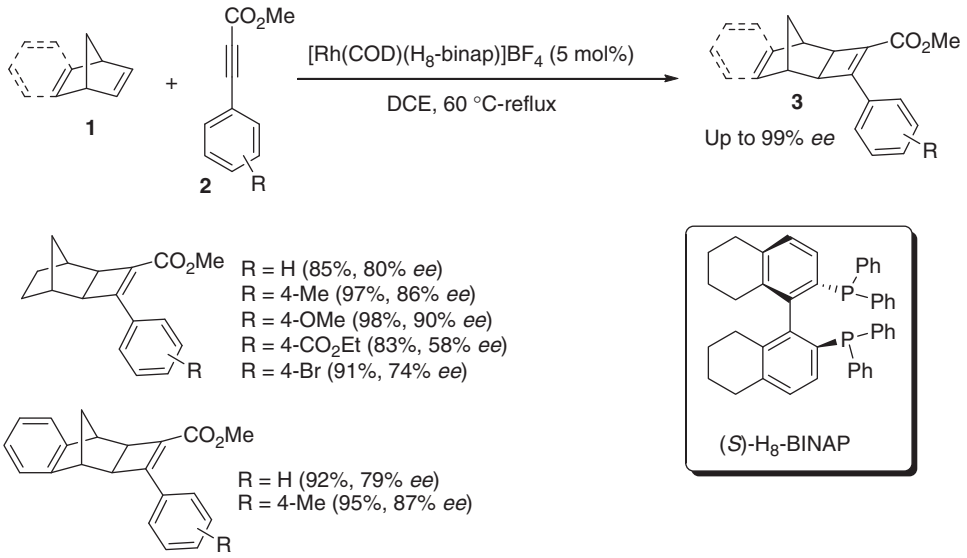


Scheme 33 Re-catalyzed [2 + 2] cycloadditions of norbornenes with alkynes.

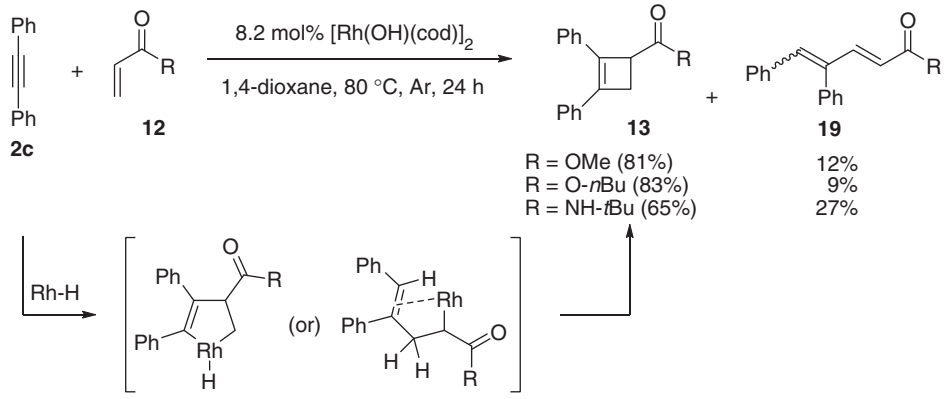
5.07.2.6 Rh-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

The metal-catalyzed asymmetric [2 + 2] cycloaddition is one of the most convergent strategies for the synthesis of chiral cyclobutene products. In this respect, Shibata et al. introduced a Rh-catalyzed enantioselective [2 + 2] cycloaddition of alkynyl esters with norbornene derivatives. The chiral tri- and tetracyclic cyclobutenes were obtained in moderate to high *ee*'s. The electron-withdrawing moiety on an alkyne terminus was important to promote the [2 + 2] cycloaddition and the ester oxygen atom played a key role in the asymmetric induction (Scheme 34).[34]

In 2011, Baba and coworkers discovered a new method for the synthesis of cyclobutenes from alkynes and electron-deficient alkenes. Thus, the reaction of diphenylacetylene **2c** and methyl acrylate (**12**, R = OMe) in the presence of $[Rh(OH)(cod)]_2$ in 1,4-dioxane at 80 °C for 24 h gave cyclobutene **13** in 81% yield along with the corresponding Mizoroki–Heck-type ene–yne coupling product **19** (Scheme 35).[35] Under similar reaction conditions, other olefins such as acrylamide derivatives also worked well for



Scheme 34 Rh-catalyzed enantioselective [2 + 2] cycloadditions of norbornene with alkynyl esters.



Scheme 35 Synthesis of cyclobutenes from diphenylacetylene and electron-deficient olefins catalyzed by a Rh(I) complex.

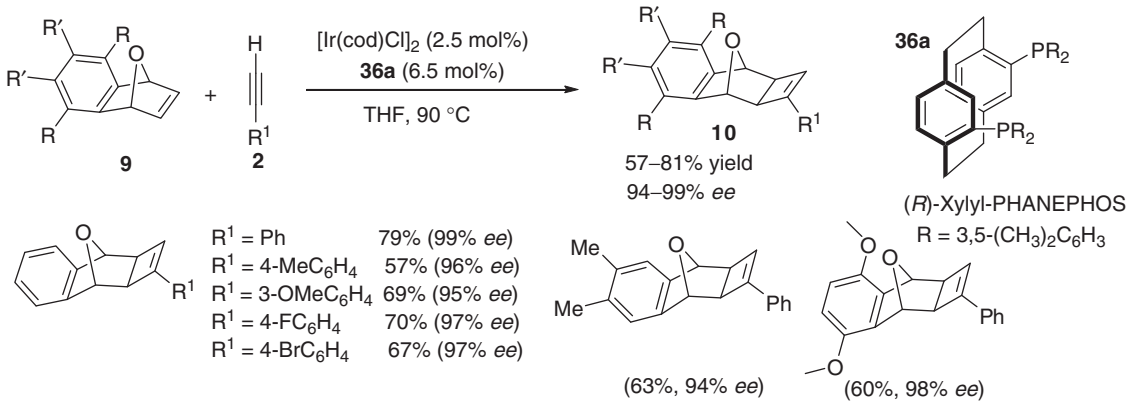
this reaction. The authors speculated about two plausible pathways, including either a metallacyclopentene intermediate or the hydrometalation of the alkyne. The coordinatively unsaturated environment of the Rh-H species seems to be necessary for the reaction pathways. Finally, the authors confirmed that a Rh-H species was generated from $[Rh(OH)(cod)]_2$ by several experimental studies.

5.07.2.7 Ir-Catalyzed [2 + 2] Cycloaddition of Terminal Alkynes and Oxabicyclic Alkenes

Shao and coworkers found a first catalytic asymmetric [2 + 2] cycloaddition of oxabicyclic alkenes and terminal alkynes using $[Ir(cod)Cl]_2$/(*R*)-xylyl-4,12-bis(diphenylphosphino)-[2.2]-paracyclophane (PHANEPHOS) as the catalyst (Scheme 36).[36] This iridium-catalyzed enantioselective [2 + 2] cycloaddition constructs four stereocenters in a single step with excellent enantioselectivity (94–99% *ee*).

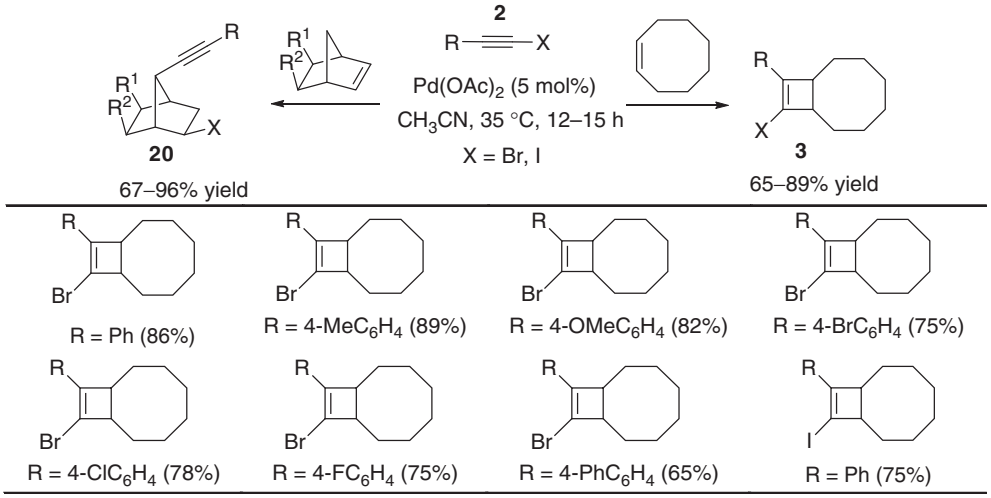
5.07.2.8 Pd-Catalyzed [2 + 2] Cycloaddition of Bromoalkynes and Cyclooctene

Very recently an unprecedented $Pd(OAc)_2$-catalyzed [2 + 2] reaction of bromoalkyne and cyclooctene was reported by Jiang and coworkers. Various aromatic alkynyl bromides carrying electron-withdrawing or donating groups underwent the [2 + 2] cycloaddition with cyclooctene to generate the corresponding cycloaddition products in moderate to good yields.[37] Interestingly, even the highly sensitive phenylethynyl iodide worked well. However, the ring size of the alkenes played a key role in the formation of the product. Other alkenes such as cyclohexene, cyclopentene, and cyclododecene were completely ineffective for the



Scheme 36 Ir-catalyzed asymmetric [2 + 2] cycloadditions of oxabicyclic alkenes with terminal alkynes.

catalytic reaction whereas cycloheptene is less effective. However, the strained alkenes (norbornene derivatives) unexpectedly gave the 7-alkynyl halonorbornane **20** in good yield (Scheme 37).



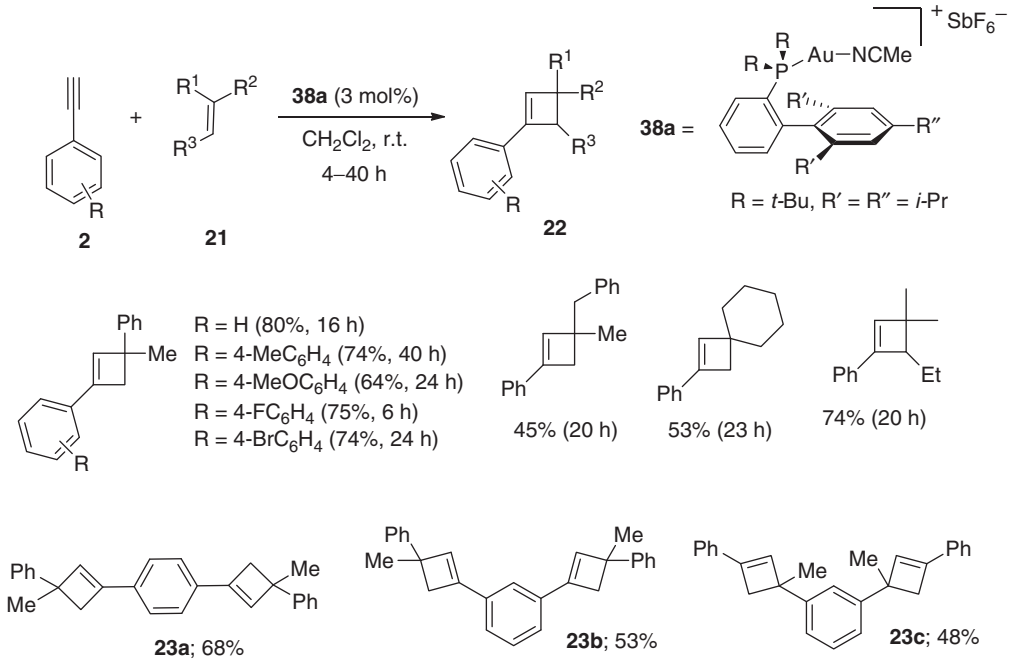
Scheme 37 Pd(II)-catalyzed [2 + 2] cycloadditions of haloalkynes with cyclooctene.

5.07.2.9 Au-Catalyzed [2 + 2] Cycloaddition of Terminal Alkynes and Alkenes

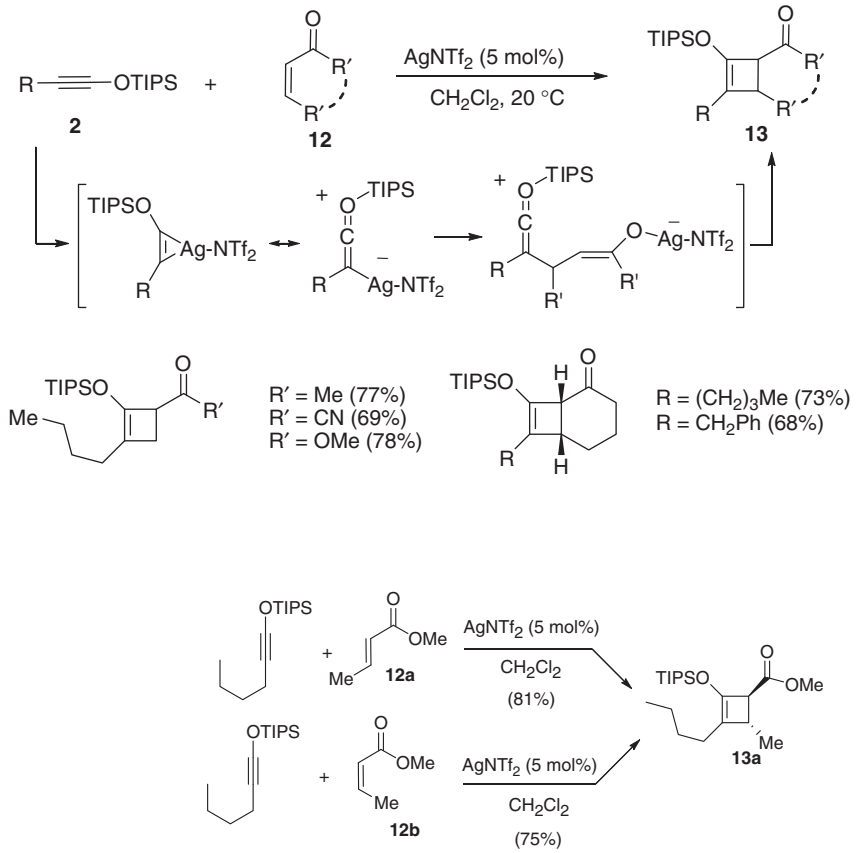
Echavarren and coworkers reported that Au(I)-catalyzed intermolecular [2 + 2] cycloadditions of terminal alkynes with alkenes lead to substituted cyclobutenes in a regioselective manner (Scheme 38).[38] The use of a sterically hindered cationic Au(I) complex (**38a**) as catalyst is key for the success of this reaction. The reaction proceeds satisfactorily with terminal alkynes having either electron-rich or electron-poor substituents. The biscyclobutenes **23a–c** were also obtained from *p*- and *m*-diethynylbenzene, respectively (Scheme 38). The cyclobutene derivatives from terminal alkynes and alkenes are usually difficult to obtain by using transition metal catalysts, due to facile [2 + 2 + 2] alkyne cyclotrimerization reactions. It should be noted that no [2 + 2 + 2] cyclotrimerization products were detected during these gold-catalyzed reactions, showing another advantage of this system.

5.07.2.10 Ag-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

Kozmin et al. reported the first intermolecular silver-catalyzed [2 + 2] cycloadditions of siloxyalkynes with various unsaturated carbonyls to form complex siloxy cyclobutenes (Scheme 39).[39] A wide range of alkenes with electron-withdrawing substituents, including acrylonitrile, methyl acrylate, and cyclohexenone, successfully participated in the reaction. The authors proposed a sequential mechanism that involves the activation of the alkyne by Ag(I), 1,4-addition, subsequent trapping of the ketenium ion intermediate and cyclization to give the final product. An interesting feature of this reaction is that treatment of the *E*- and *Z*-crotonates **12a** and **12b** with siloxy alkyne **2** invariably resulted in the formation of the *trans*-substituted siloxy cyclobutene **13a**.



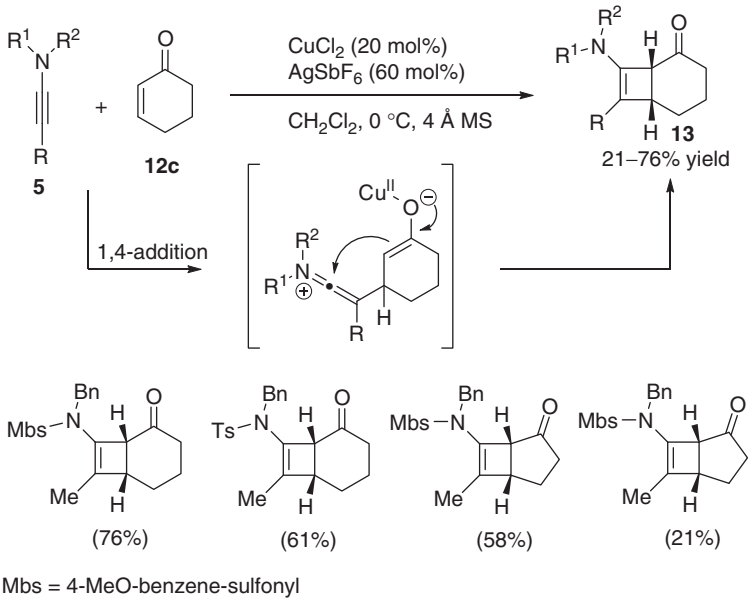
Scheme 38 Au(I)-catalyzed intermolecular [2 + 2] cycloaddition of terminal alkynes with alkenes.



Scheme 39 Silver-catalyzed [2 + 2] cycloadditions of siloxyalkynes with unsaturated carbonyls.

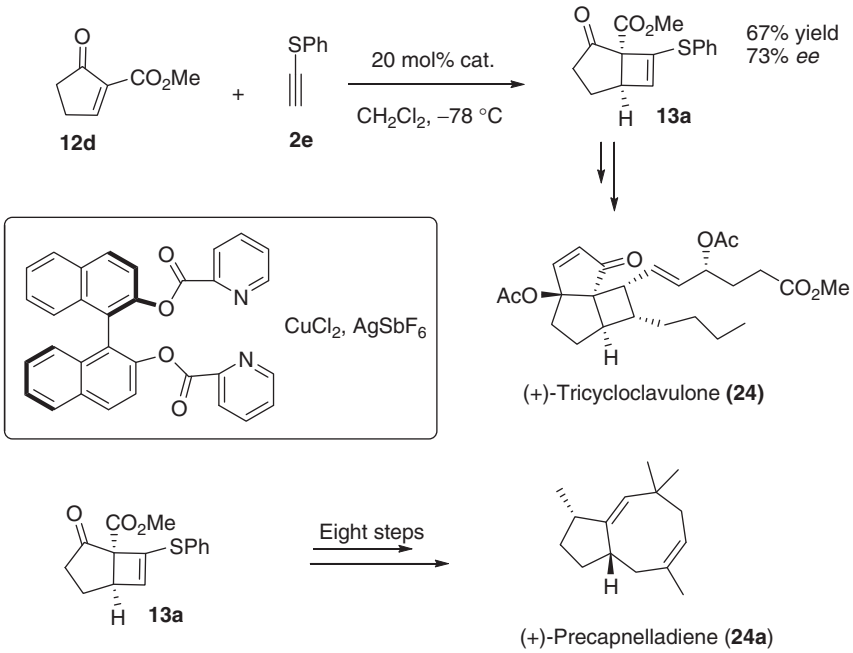
5.07.2.11 Cu-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

Hsung's group reported the first copper-catalyzed Ficini-[2 + 2] cycloaddition of *N*-sulfonyl-substituted ynamides **5** with enones such as **12c**, which provide direct access to cyclobutenamines (Scheme 40).[40] This catalytic reaction proved compatible with a wide variety of *N*-sulfonyl ynamides and cyclic and acyclic enones. The authors proposed a stepwise mechanism with a nucleophilic 1,4-addition by the ynamide onto the enone activated via the cationic Cu(II) catalyst to give a keteniminium intermediate, which subsequently undergoes intramolecular addition to afford the observed cyclobutenamine derivatives.



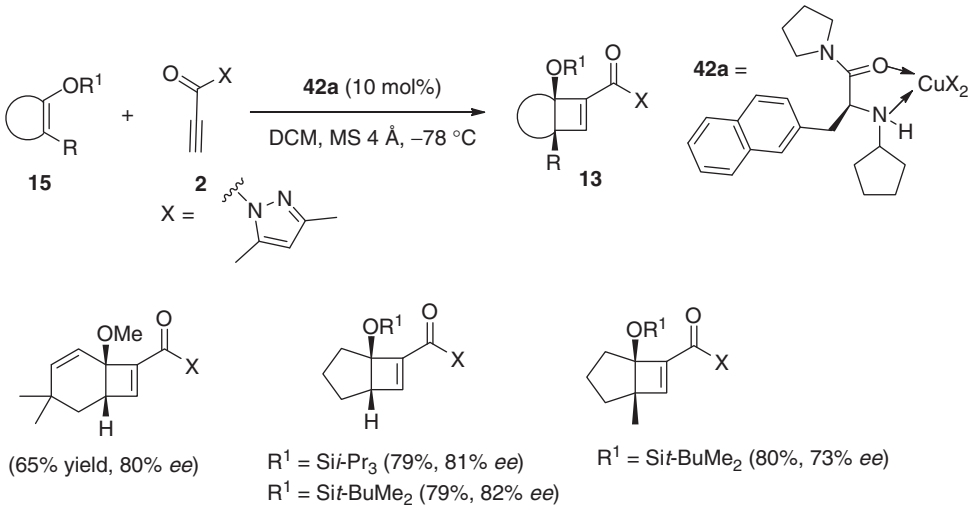
Scheme 40 Copper-catalyzed Ficini-[2 + 2] cycloadditions of *N*-sulfonyl-substituted ynamides with enones.

Ito, Iguchi, and coworkers developed enantioselective [2 + 2] cycloaddition of 2-methoxycarbonyl-2-cyclopenten-1-one **12d** with phenylthioacetylene catalyzed by chiral Lewis acids, which give cyclobutene **13a** in good yield. This protocol has been successfully applied to the enantioselective total synthesis of tricycloclavulone (**24**),[41a,b] as well as to the formal synthesis of (+)-precapnelladiene (**24a**)[41c] by using the [2 + 2] cycloadduct as the key intermediate (Scheme 41).



Scheme 41 Enantioselective [2 + 2]-cycloadditions of a cyclic enone with phenylthioacetylene.

A highly effective copper-catalyzed enantioselective [2 + 2] cycloaddition of enol ether derivatives with propiolamides was developed by Ishihara and Fushimi in 2008. Various substituted alkenes **15** underwent facile cycloaddition with propiolamide **2** to furnish the densely substituted cyclobutenecarboxamides **13** with high *ee*'s (Scheme 42).[42]

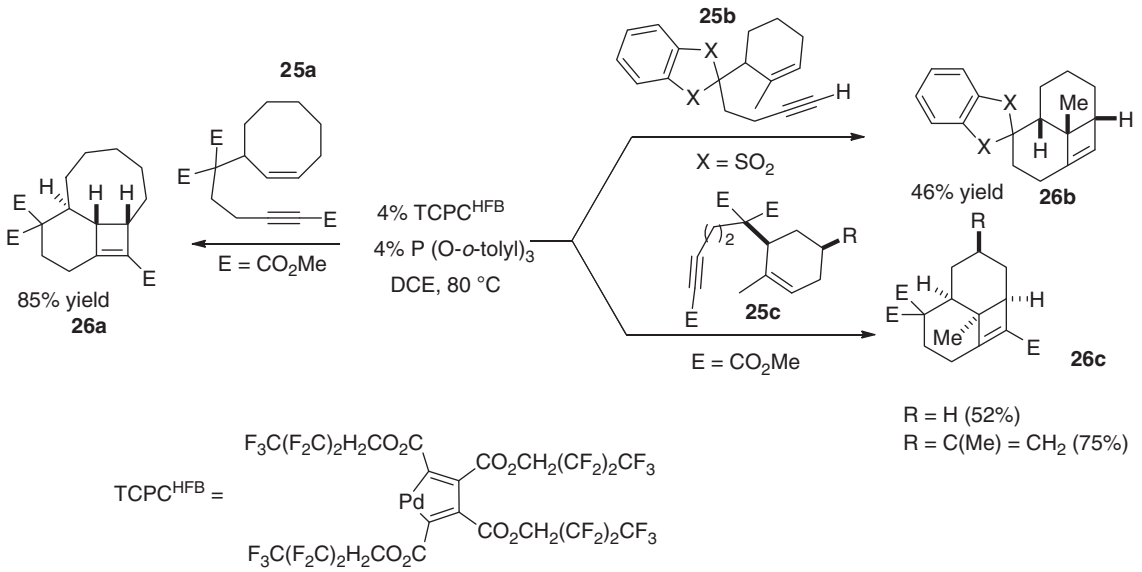


Scheme 42 Copper-catalyzed enantioselective [2 + 2] cycloadditions of enol ether derivatives with propiolamides.

5.07.3 Intramolecular Metal-Catalyzed [2 + 2] Cycloaddition of Alkynes and Alkenes

5.07.3.1 Pd-Catalyzed Intramolecular [2 + 2] Cycloaddition

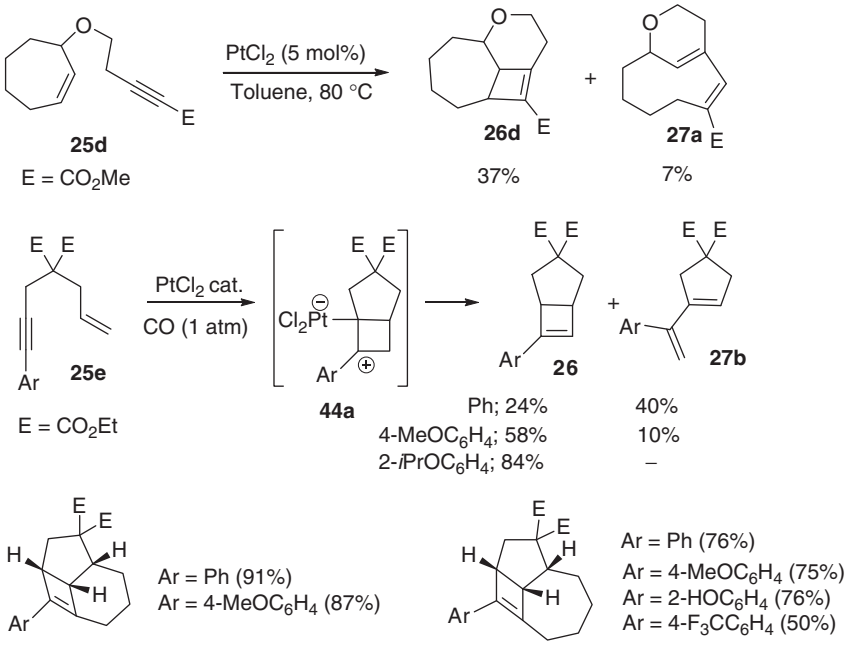
Metal-catalyzed intramolecular [2 + 2] cycloaddition reactions offer a highly efficient and atom-economical synthetic strategy for increasing molecular complexity and diversity in a single step. In this context, Trost et al. have observed that in the presence of a low-valent palladium catalyst ($TCPC^{HFB}$), the 1,7-enyne **25a** undergoes an intramolecular [2 + 2] cycloaddition to give a highly strained cyclobutene ring, which contained an unexpected *trans*-fused 8/6-ring system (Scheme 43).[43] However, 1,7-enynes **25b** and **25c**, which contain cyclohexene rings, gave a *cis–cis* ring fusion.



Scheme 43 Palladium-catalyzed intramolecular [2 + 2] cycloadditions of 1,7-enynes.

5.07.3.2 Pt-Catalyzed Intramolecular [2 + 2] Cycloaddition

In 2001, Fürstner et al. reported a $PtCl_2$-catalyzed formal enyne metathesis reaction leading to 1,3-dienes. For example, treatment of enyne **25d** in the presence of 5 mol% $PtCl_2$ in toluene at 80 °C for 24 h gave the cyclobutene **26d** in 37% yield along with the enyne metathesis product **27a** in 7% yield (Scheme 44).[44a]



Scheme 44 Platinum-catalyzed cyclobutene synthesis.

The authors tried various reaction conditions to improve the yield of the cyclobutenes. Thus, treatment of enyne **25e** in the presence of 5 mol% $PtCl_2$ in toluene under 1 atm of carbon monoxide at 80 °C provided cyclobutene **26d** in 24% yield with the regular metathesis product **27b** in 40% yield. Gratifyingly, enyne **25e**, bearing a *p*-methoxyphenyl ring is able to stabilize a putative benzylic cation of type **44a** more effectively, and therefore clearly favors **26** over **27b**. However, the reaction was fairly slow and required >16 h for completion. Various related enynes with electron-donating and -withdrawing groups cyclized remarkably well to the corresponding cyclobutenes in good yields.[44b]

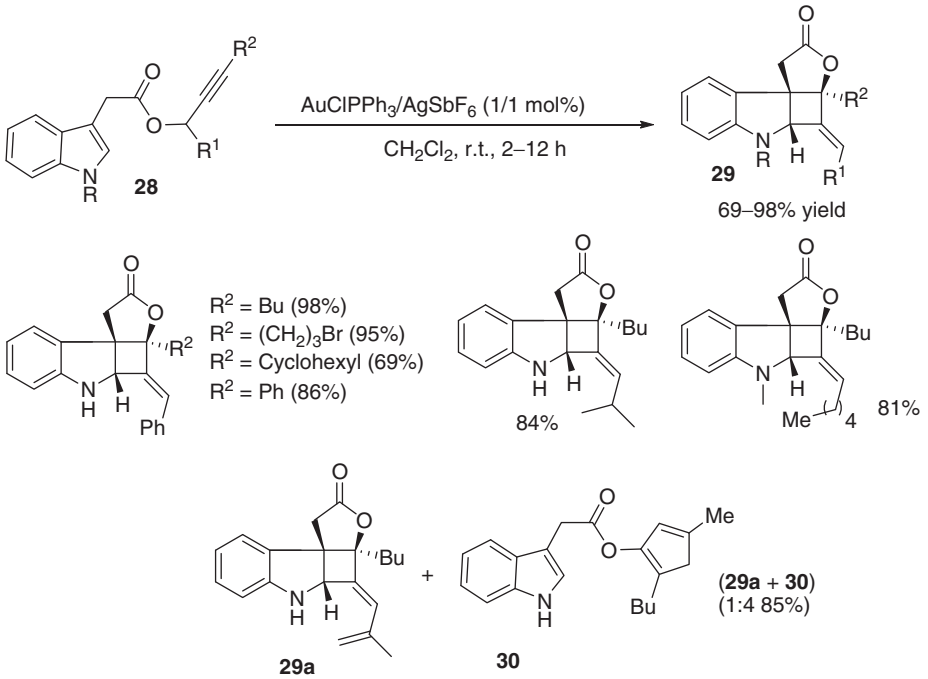
5.07.3.3 Au-Catalyzed Intramolecular [2 + 2] Cycloaddition

The indole ring system is a common heterocycle found in many natural and pharmaceutical compounds.[45] Zhang reported a Au(I)-catalyzed synthesis of highly functionalized 2,3-indoline-fused cyclobutanes via sequential 3,3-rearrangement and [2 + 2] cycloaddition. Various propargylic indole-3-acetates **28** underwent [2 + 2] cycloaddition in the presence of 1 mol% of $AuCl(PPh_3)/AgSbF_6$ in CH_2Cl_2 for 2 h to give cyclobutanes in good yields (Scheme 45).[46] In the tetracyclic product **29**, the cyclobutane is fused to a 2,3-indoline and a γ-lactone; only one geometrical isomer was observed, in which the exocyclic double bond was *E*-configured. It should be noted that the treatment of ester **28a** with a 2-propenyl group at the propargylic position under the same reaction conditions resulted in a 1:4 mixture of the desired cyclobutane **29a** and the cyclopentenone derivative **30**.

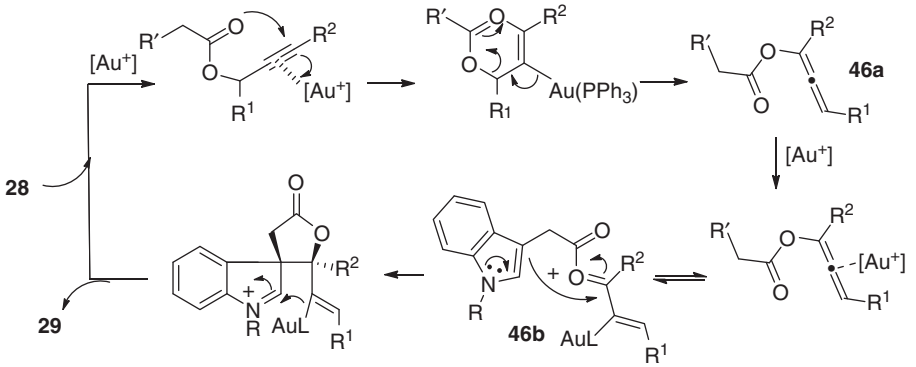
The proposed mechanism involves activation of the C–C triple bond of the propargylic ester **28** by $[Au(PPh_3)]^+$, promoting a 3,3-rearrangement of the indole-3-acetoxy group that leads to the formation of allenylic ester **46a** (Scheme 46). The allene moiety of **46a** is further activated by the cationic Au(I) complex, resulting in the formation of **46b** with the opposite double bond geometry. Cyclobutane **29** with an exocyclic *E*-double bond is formed via cyclization of the oxonium group in **46b** to the 3-position of the indole ring, followed by intramolecular trapping of the resulting iminium species by the alkenyl gold(I) group.

Very recently, Chan et al. developed a very unique method for the preparation of azabicyclo[4.2.0]oct-5-enes that relies on gold(I)-catalyzed tandem 1,3-migration/[2 + 2] cycloaddition of 1,7-enyne benzoates (Scheme 47).[47] Other Au(I) and Au(III) complexes as well as $PtCl_2$ as the catalyst gave similar outcomes. The scope of the reaction was broad. The reaction was shown to tolerate a diverse set of substrates and furnished stereochemically well-defined cyclobutane-fused piperidines in good yields.

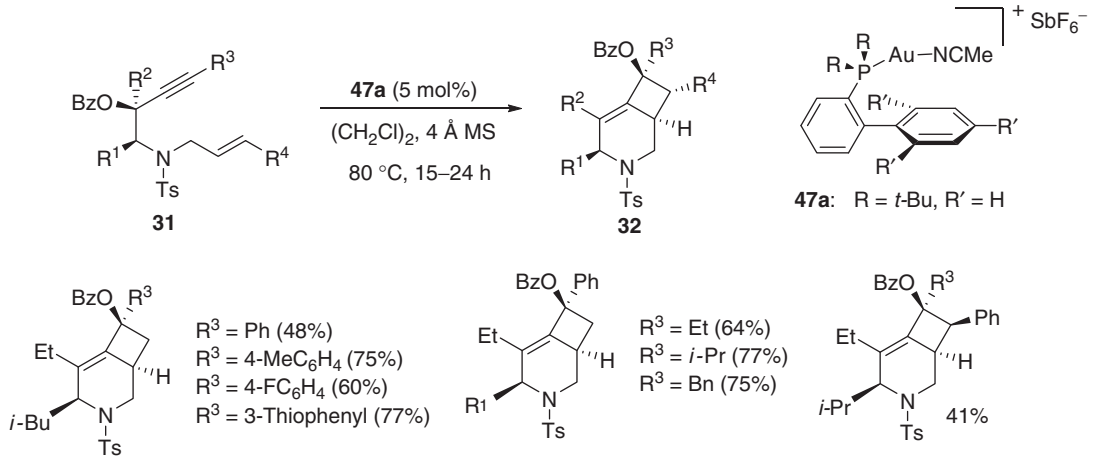
The authors proposed a mechanism that involves initial activation of the alkyne moiety of the 1,7-enyne benzoates by the gold(I) catalyst, resulting in a *syn*-1,3-migration of the carboxylic ester group and formation of allenene **48a** via **I** and **II**. Next, the gold catalyst likely coordinates with the alkene moiety; a subsequent intramolecular cyclization step would then deliver **32** with release of the gold(I) catalyst (Scheme 48).



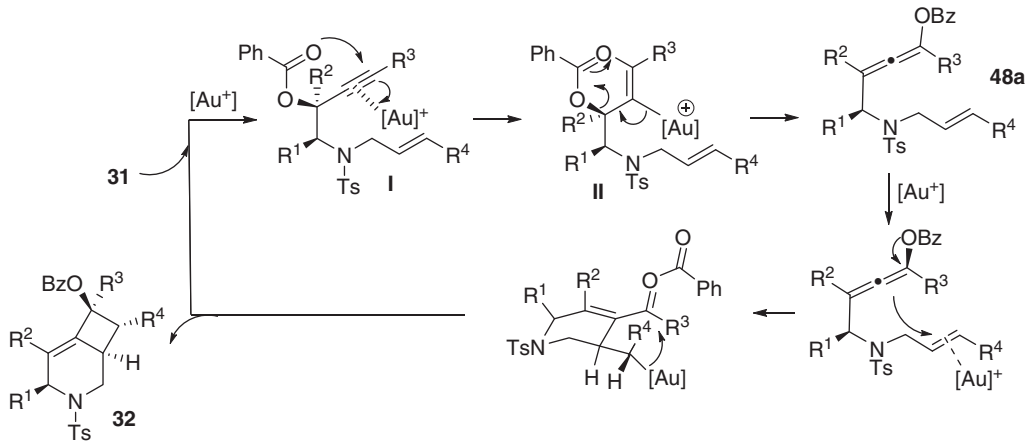
Scheme 45 $AuCl(PPh_3)/AgSbF_6$-catalyzed synthesis of highly functionalized cyclobutenes.



Scheme 46 Proposed mechanism for the formation of cyclobutane.



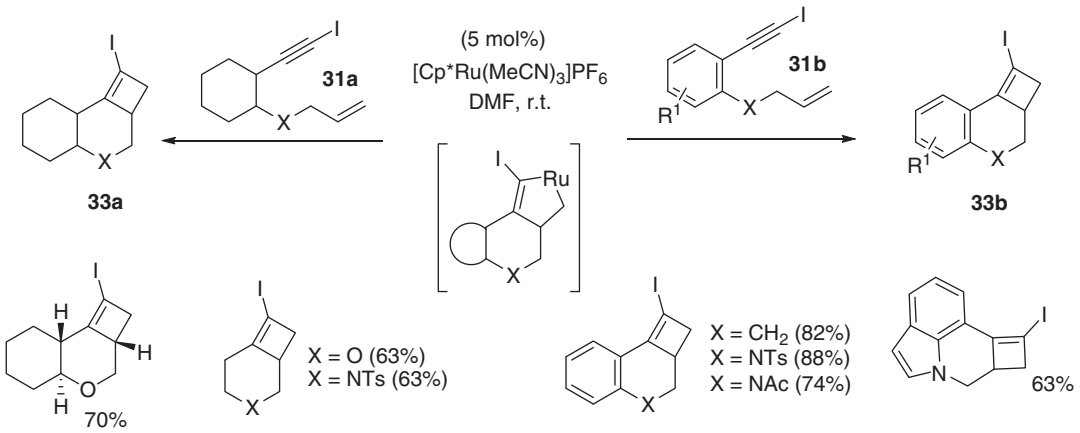
Scheme 47 Gold(I)-catalyzed tandem 1,3-migration/[2 + 2] cycloaddition of 1,7-enyne benzoates.



Scheme 48 Proposed mechanism of the intramolecular [2 + 2]-cycloaddition of 1,7-enyne benzoates.

5.07.3.4 Ru-Catalyzed Intramolecular [2 + 2] Cycloaddition

In 2007, Fürstner's group reported that enynes bearing an iodide at their alkyne terminus reacted in the presence of catalytic amounts of $[Cp^*Ru(MeCN)_3]PF_6$ in dimethylformamide (DMF) to give strained iodocyclobutene derivatives in good to excellent yields (Scheme 49). Various aromatic or aliphatic enynes incorporating ether or amido groups in the tether between the olefin and the iodoalkyne compounds were converted into the corresponding cyclobutenes. It is also important to mention that the substituent on the alkyne plays a major role in the cyclization process. Thus, alkynyl bromides were less reactive than the corresponding iodides and required a higher catalyst loading to reach full conversion. More notably, alkynyl chlorides, terminal and internal alkynes were totally inactive under the same reaction conditions. The authors believed that these reactions proceeded via the formation of a ruthenacyclopentene intermediate and subsequent reductive elimination.[48]

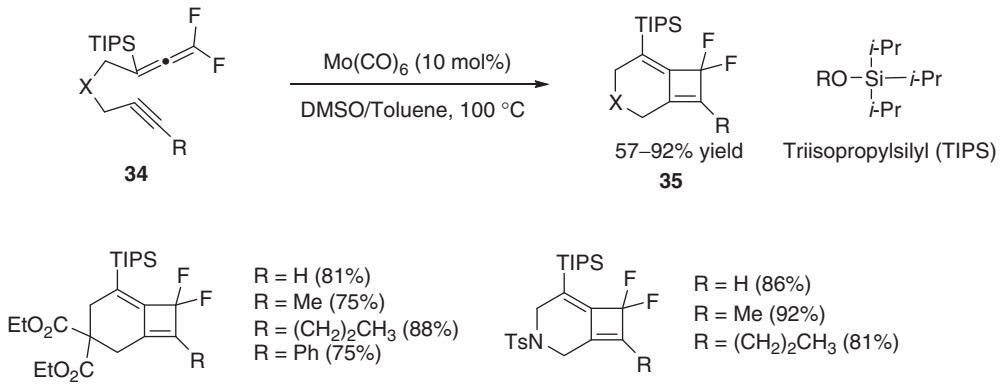


Scheme 49 Formation of iodocyclobutene derivatives and proposed reaction mechanism for this transformation.

5.07.4 Metal-Catalyzed [2 + 2] Cycloaddition of Alkynes and Allenes

5.07.4.1 Molybdenum-Catalyzed Intramolecular *gem*-Difluoroallene-Alkyne [2 + 2]-Cycloaddition

The intramolecular [2 + 2] cycloaddition of an allene and alkyne group via a metallacyclopentene intermediate is also a powerful and promising methodology for the synthesis of cyclobutene products. Mo-, Pd-, and Ru-catalyzed cycloadditions of this type will be described here. Molybdenum is not a very common metal in [2 + 2] cycloadditions and so its applications are rather limited. However, Hammond and Shen reported an unexpected synthesis of bicyclo[4.2.0]octadienes by a novel molybdenum-catalyzed intramolecular *gem*-difluoroallene-alkyne [2 + 2]-cycloaddition (Scheme 50).[49] In all cases, CF_2-fused cyclobutenes were obtained in good to excellent yield. More notably, the intramolecular allene–alkyne cycloaddition showed that the rate of the reductive

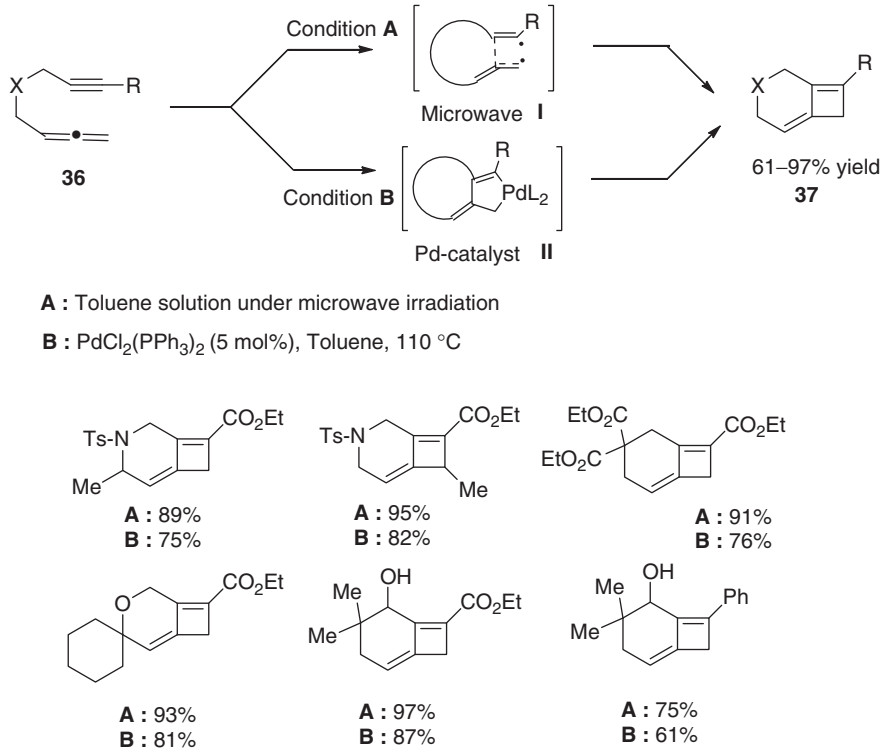


Scheme 50 Molybdenum-catalyzed intramolecular [2 + 2]-cycloadditions of *gem*-difluoroallenes and alkynes.

elimination step was faster than carbonylation, since no Pauson–Khand product was detected even in the presence of 1.5 equivalents of $Mo(CO)_6$.

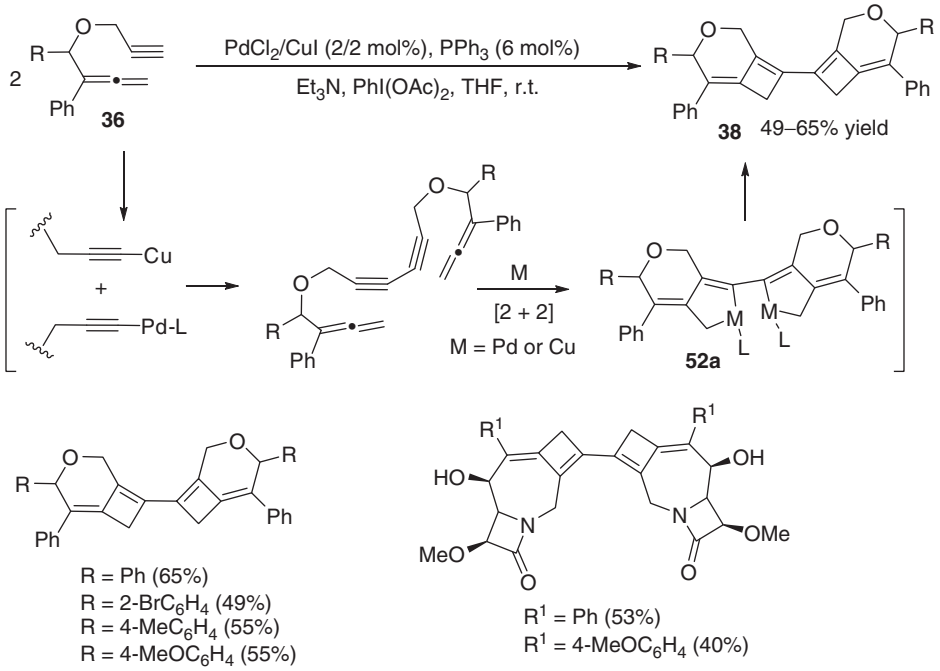
5.07.4.2 Palladium-Catalyzed Intramolecular [2 + 2] Cycloaddition of 1,6- and 1,7-Allenyne

In 2005, Oh et al. developed a palladium-catalyzed or MW-mediated [2 + 2] cycloaddition of 1,6- and 1,7-allenyne carboxylates which led to the formation of fused bicyclo[m,2,0]alkadienes in good yields.[50] Under these reaction conditions, various substituted allenynes were successfully employed to provide [2 + 2] cycloaddition products (Scheme 51). The authors proposed a mechanism involving a MW irradiation of the allenyne to give a biradical intermediate (**I**), which then undergoes rapid cyclization to afford the cyclobutene product. However, for the palladium-catalyzed [2 + 2] cycloaddition, the reaction proceeds likely via a metallacyclopentene (**II**), but the details are not yet known.



Scheme 51 Intramolecular [2 + 2]-cycloaddition of allenynes under conditions **A** and **B**.

In 2009, Alcaide and Almendros reported a bimetallic Pd/Cu-catalyzed domino alkyne homocoupling/double [2 + 2] cycloaddition reaction of allenynes which delivers bis(heterocyclic)-fused cyclobutene rings (Scheme 52).[51] Under the reaction



Scheme 52 Pd-catalyzed or Cu-promoted double [2 + 2] cyclization of bis(allenynes).

conditions, enantiopure bis(tricyclic) *β*-lactams were conveniently prepared in good yields. For the double [2 + 2] allenyne cyclization, it is believed that the metal salt regioselectively forms a *π*-complex with both the triple bond and a double bond of substrates **36**. Such *π*-complexes may undergo migratory C–C coupling to give pallada- or cupra-cycles **52a**. The observed regioselectivity of the reaction could be explained in terms of the regioselective formation of metallacycles **52a**, which are controlled by the stereoelectronic effects of the aryl substituent in the allenynes. Cyclization toward the internal allenic double bonds is probably restricted by the ligands on the metal and the aryl substituent at the putative quaternary stereocenter.

5.07.4.3 Ruthenium-Catalyzed Intramolecular [2 + 2] Cycloaddition of α,ω-Allenynes

Saito et al. disclosed the synthesis of two quite different types of products **37** and **39** from *α,ω*-allenynes in the presence of Cp*RuCl(cod) as the catalyst (Scheme 53).[52] The formation of these two different products greatly depends on the chosen solvent. Treatment of allenyne **36** with Cp*RuCl(cod) as catalyst in the presence of methanol produced only the [2 + 2] cycloaddition product **37** in quantitative yield, whereas the use of toluene as the solvent led to the exclusive formation of the cyclodimerization product **39** in excellent yield. Two types of ruthenacycles (**53a** and **53b**) could be formed from an allenyne and the ruthenium complex as shown in Scheme 53 to account for these outcomes. The authors believed that the [2 + 2] cycloaddition was initiated by a cationic ruthenium complex generated *in situ* from Cp*RuCl(cod) and methanol.

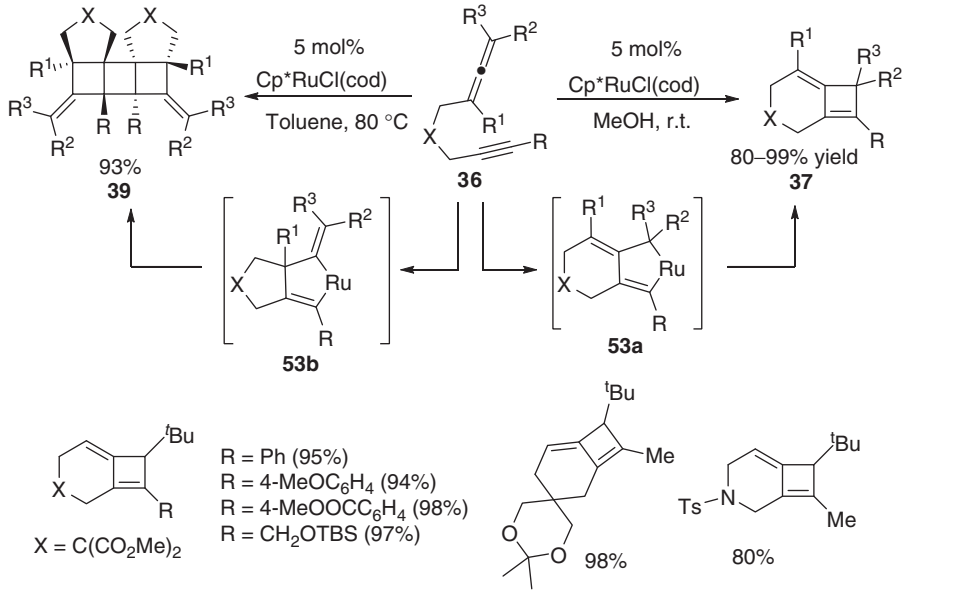
5.07.5 Palladium-Catalyzed [2 + 2] Cycloaddition of Alkynes and Ketones

Very recently, Mikami and coworkers reported an enantioselective synthesis of stable oxetenes via [2 + 2] cycloaddition of alkynes **2** with trifluoropyruvate **40** by using the dicationic (*S*)-BINAP–Pd complex **54a** as the catalyst (Scheme 54).[53] The cycloaddition occurred at low temperature (− 40 °C) with excellent enantioselectivity of up to 99%. Alkynes bearing both electron-donating and -withdrawing substituents on the aromatic ring worked well to give the desired oxetenes in good yields with excellent asymmetric inductions. Notably, the [2 + 2] cycloaddition of alkynes bearing very reactive iodide and pinacolborane groups also proceeded smoothly at − 20 °C to give highly enantioenriched oxetenes.

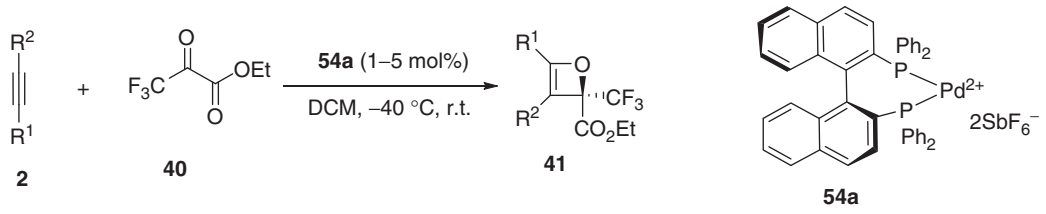
5.07.6 Metal-Catalyzed [2 + 2] Cycloaddition of Alkynes

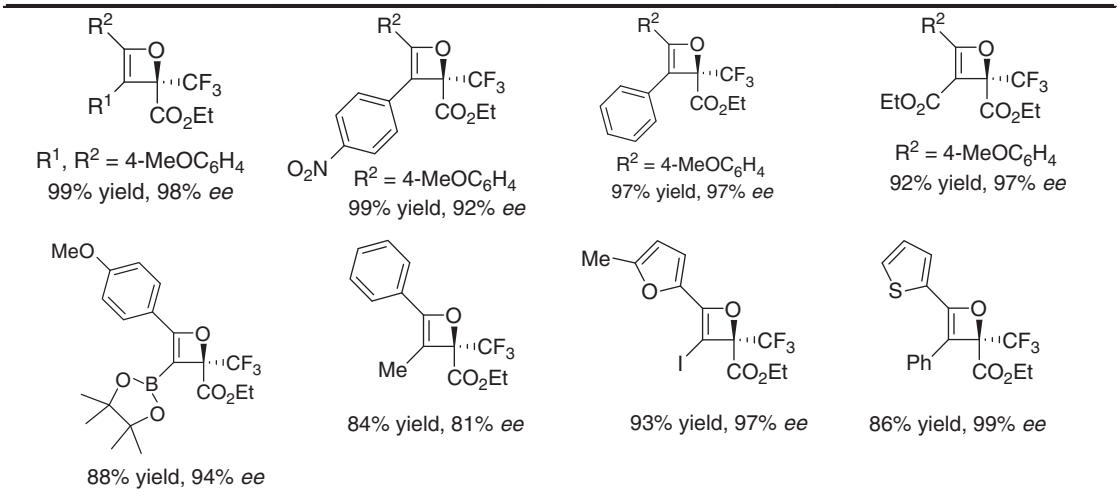
5.07.6.1 Cobalt-Mediated Intramolecular [2 + 2] Cycloaddition of a Vinyl Tetraalkyne

Fossey et al. observed an interesting Co(I)-mediated double [2 + 2] cyclodimerization of the tetraalkyne derivative **42** to afford the stable binuclear cobalt complex **43** in good yield (Scheme 55).[54] Unfortunately, the highly strained fused tetracyclic complex **43′**



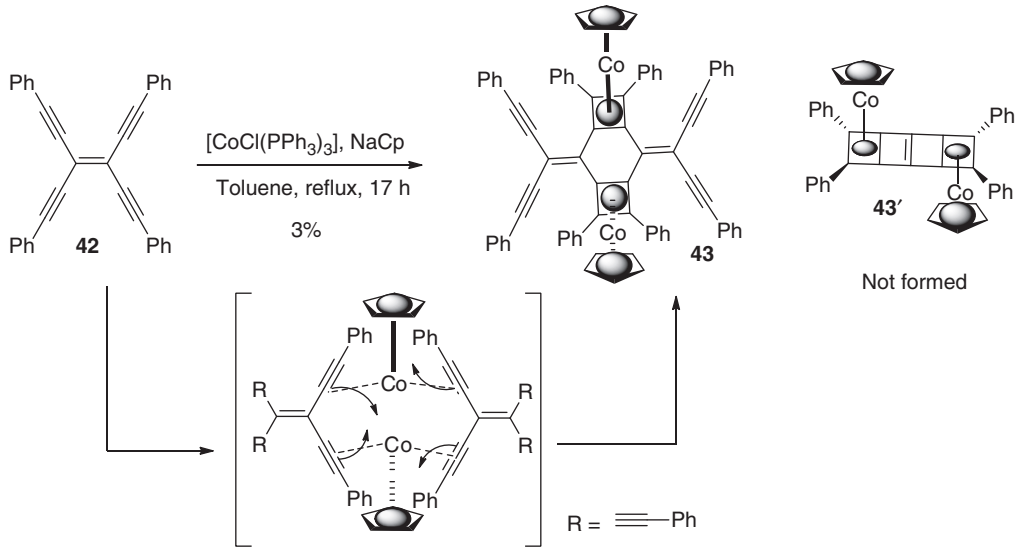
Scheme 53 Ruthenium-catalyzed [2 + 2] cycloadditions and cyclodimerizations of allenynes.





Scheme 54 Catalytic asymmetric [2 + 2] cycloadditions of alkynes with trifluoropyruvate.

did not form. The authors emphasized that the double cycloaddition reaction was carried out under a dry nitrogen atmosphere, but no precautions were taken to protect the crude reaction products from external moisture or oxygen. The double [2 + 2] cyclodimerization product was confirmed using single crystal X-ray analysis. The crystal structure shows that two newly formed cyclobutadiene rings are separated by only 2.378 Å forcing the cobalt η^5-cyclopentadienyl (Cp) units to sit on opposite faces of the planes of the newly formed cyclobutadiene rings.

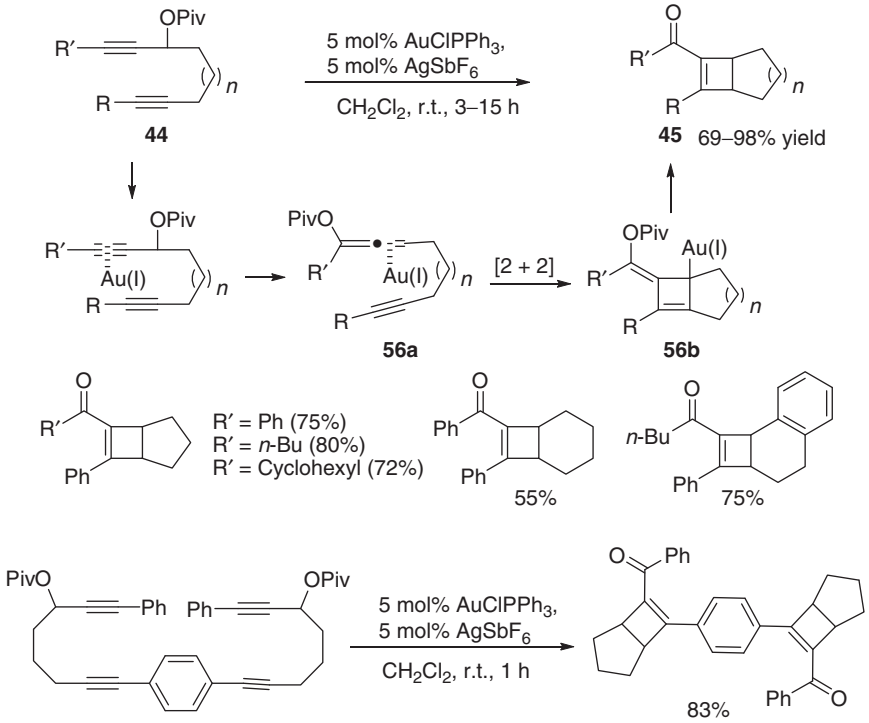


Scheme 55 Synthesis of a binuclear cobalt(I) complex.

5.07.6.2 Au-Catalyzed Intramolecular [2 + 2] Cycloaddition of 1,8-Alkadiynylic Pivaloates

In 2008, Oh and Kim reported the synthesis of fused cyclobutenes **45** via a gold-catalyzed [2 + 2] cycloaddition of 1,8-alkadiynylic pivaloates **44** (Scheme 56).[55] The corresponding cycloadducts were obtained in good yields in all cases. Interestingly, two alkyne-pivaloate molecules linked by a phenyl (Ph) group underwent the [2 + 2] cycloaddition to give the corresponding dimeric bicycles, which are useful building blocks.

A plausible mechanism for the gold-catalyzed cyclization of substrates **44** is shown in Scheme 56. Initial coordination of gold(I) to the propargylic ester induces migration of the pivaloate to give the allene intermediate **56A**, which then undergoes [2 + 2] cycloaddition to give intermediate **56B**, from which the final product **45** is released on protonolysis.

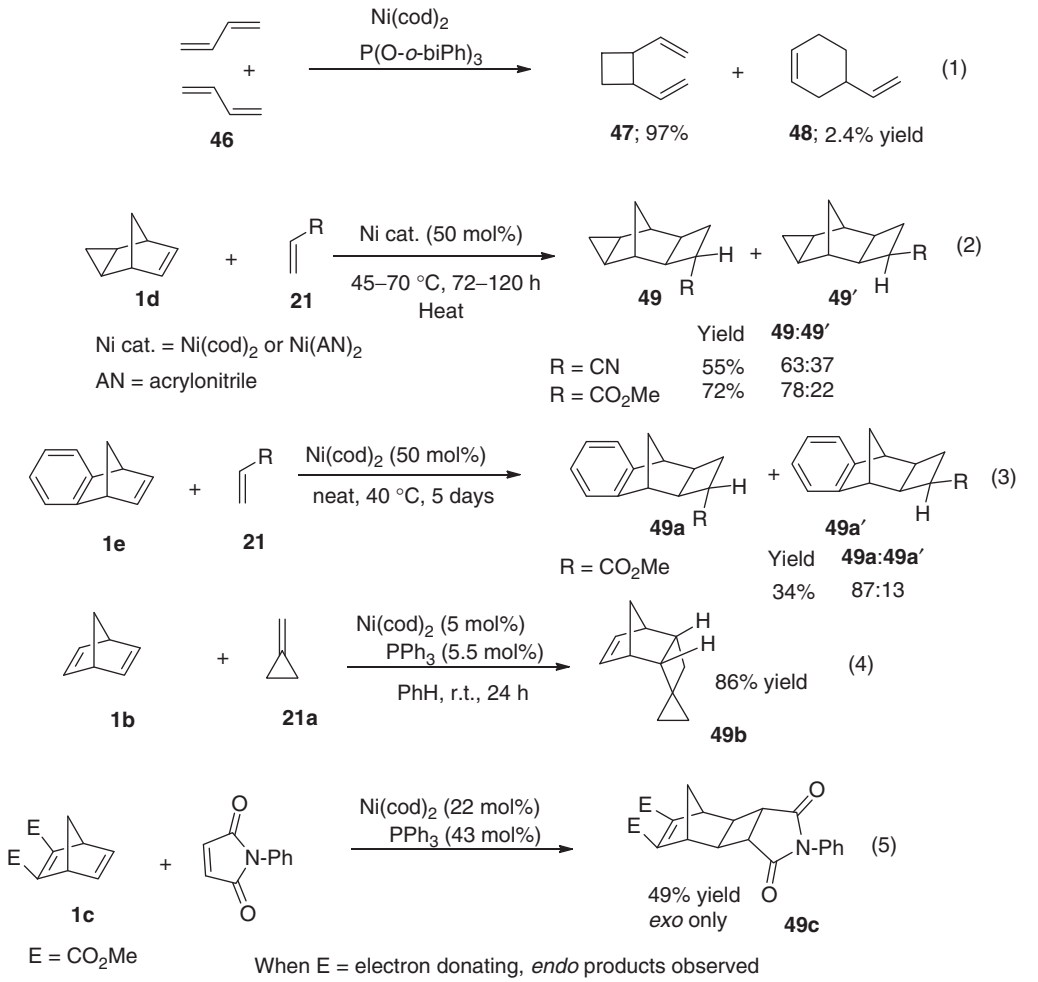


Scheme 56 Gold(I)-catalyzed [2 + 2] cycloaddition of 1,8-alkadiynylic pivaloates.

5.07.7 Metal-Catalyzed [2 + 2] Cycloaddition Between Two Alkenes

5.07.7.1 Nickel-Catalyzed Intermolecular [2 + 2] Cycloaddition of Alkenes

The [2 + 2] cycloaddition between two alkenes is an attractive transformation for the direct construction of strained cyclobutanes. Early examples include Ni(0)-catalyzed [2 + 2] cycloadditions of 1,3-butadiene, or of strained alkenes (cyclopropanated norbornene, benzonorbornadiene, and NBD) with alkenes to give the corresponding cycloadducts in good yields (Scheme 57; equations 1–5).[56]



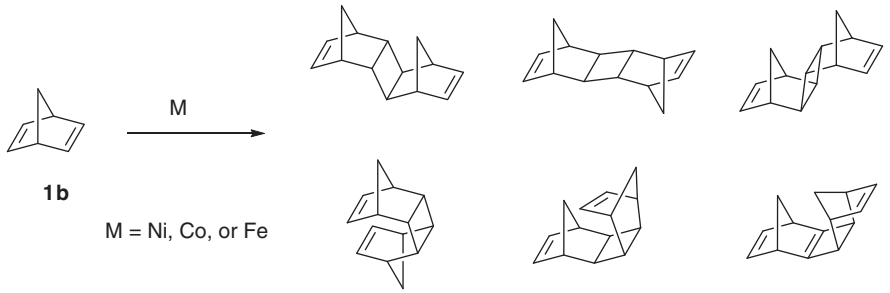
Scheme 57 Early examples of Ni(0)-catalyzed [2 + 2] cycloaddition reactions of alkenes.

The transition metal-catalyzed dimerization of NBD **1b** was reported in 1957.[57] Since then, various dimerization reactions of NBD have been observed with Ni, Co, and Fe complexes as the catalysts, providing a range of dimerization products (Scheme 58).

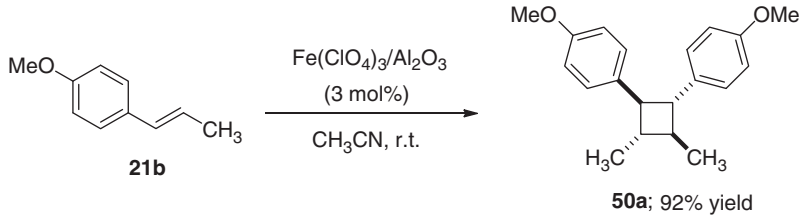
5.07.7.2 Iron-Catalyzed Intermolecular [2 + 2] Cycloaddition

A Fe(III)-catalyzed [2 + 2] cyclodimerization of *trans*-olefin **21b** was described by Nakamura in 2001.[58] Excellent results were obtained with a catalyst supported on aluminum oxide (3 mol%), which afforded exclusively the C_2-symmetric cyclobutane **50a** in 92% yield (Scheme 59). It should be noted that the reaction with chiral catalysts bearing bisoxazoline (BOX) ligands remained unsuccessful ($ee \leq 7\%$).

Chirik's group developed an intermolecular [2 + 2] cycloaddition between butadiene and ethylene to form vinylcyclobutane by using a bis(imino)pyridine iron dinitrogen complex as the catalyst. The reaction of an equimolar mixture of ethylene and butadiene in the presence of 5 mol% of the iron catalyst in benzene-d_6 at 23 °C provided the [2 + 2] cycloaddition product **47** in

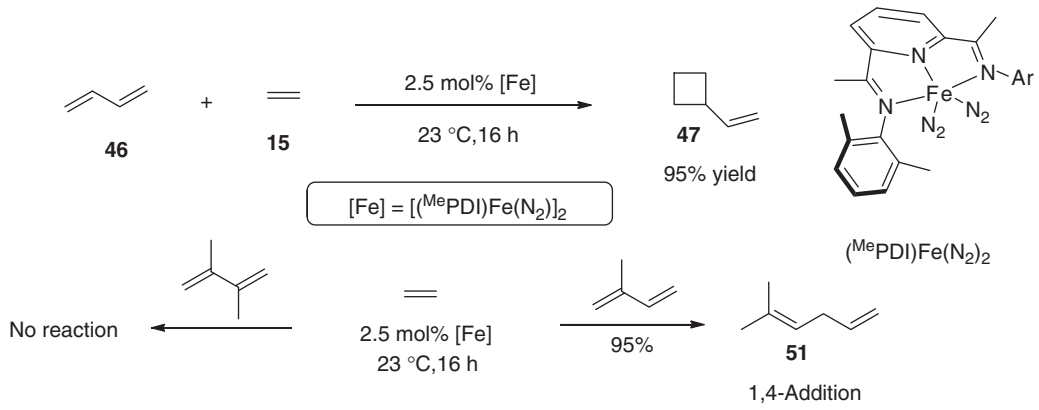


Scheme 58 Overview of Ni, Co, and Fe-catalyzed dimerizations of NBD.



Scheme 59 Fe(III)-catalyzed [2 + 2] cyclodimerization of a *trans*-olefin.

95% yield. Under similar reaction conditions, isoprene reacted with ethylene to give an unexpected 1,4-addition product in high yield rather than the [2 + 2] cycloadduct. It is important to mention that more highly substituted dienes did not react with ethylene under these reaction conditions (Scheme 60).[59]

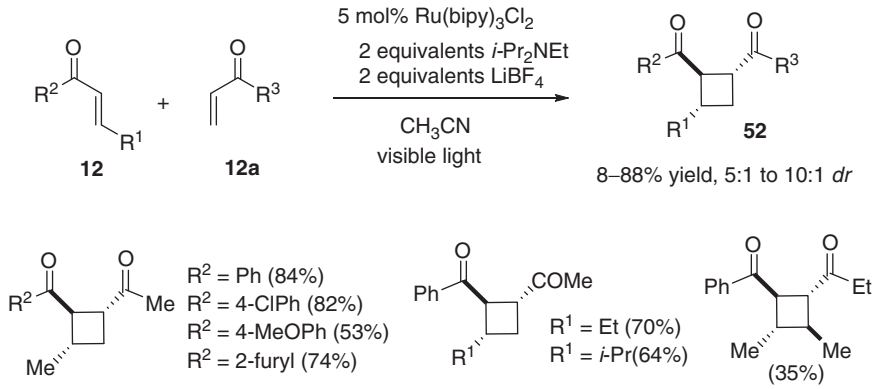


Scheme 60 Iron-catalyzed intermolecular [2 + 2] cycloaddition of ethylene and butadiene.

5.07.7.3 Ruthenium-Catalyzed Intermolecular [2 + 2] Cycloaddition

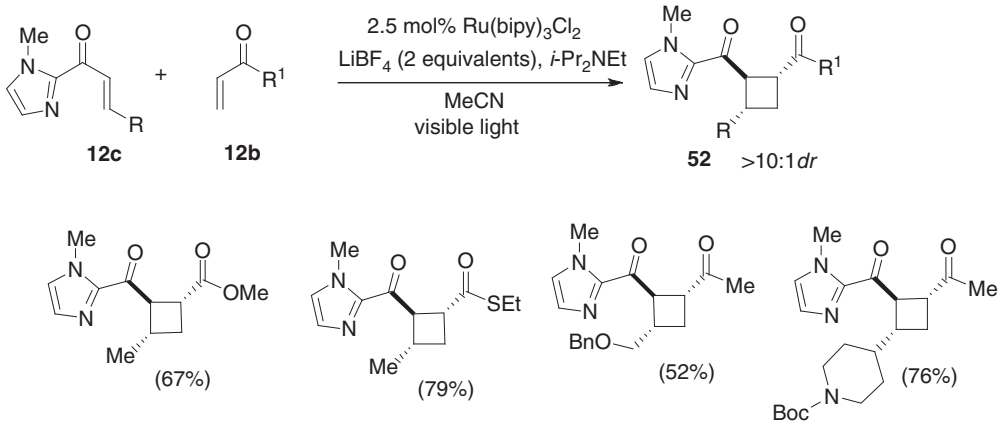
Yoon and coworkers developed an efficient method for the Ru-catalyzed crossed [2 + 2] cycloaddition of acyclic enones promoted by visible light (Scheme 61).[60] The excellent chemo- and stereoselectivity observed in this reaction represents a considerable advance in the construction of strained four-membered rings. Acyclic enones having α- and β-substitutions participate in this highly stereoselective cycloaddition reaction. However, β-substituted enones gave lower yields. The authors speculated that β-substituents sterically reduce the Michael acceptor ability of the enone, causing homodimerization of **12** to be the predominant pathway.

In a similar fashion, Yoon and coworkers have revealed an inter- and intramolecular [2 + 2] cycloaddition of α,β-unsaturated 2-imidazolyl ketones with a variety of Michael acceptors on irradiation with visible light in the presence of Ru(2,2′-bipyridyl(bipy))$_3^{2+}$.[61] In most of the intermolecular reactions, the best yield and highest *dr* were obtained when the aryl enone was added slowly via a syringe pump to the reaction mixture, presumably to minimize the homodimerization. Under these conditions, the concentration of aryl enone is minimized with respect to methyl acrylate, although keeping the ratio of Lewis acid



Scheme 61 Ru-catalyzed crossed [2 + 2] cycloadditions of acyclic enones promoted by visible light.

to substrate high. By using this slow addition protocol, the desired cycloadduct could be isolated in good yield with excellent diastereoselectivity (Scheme 62).



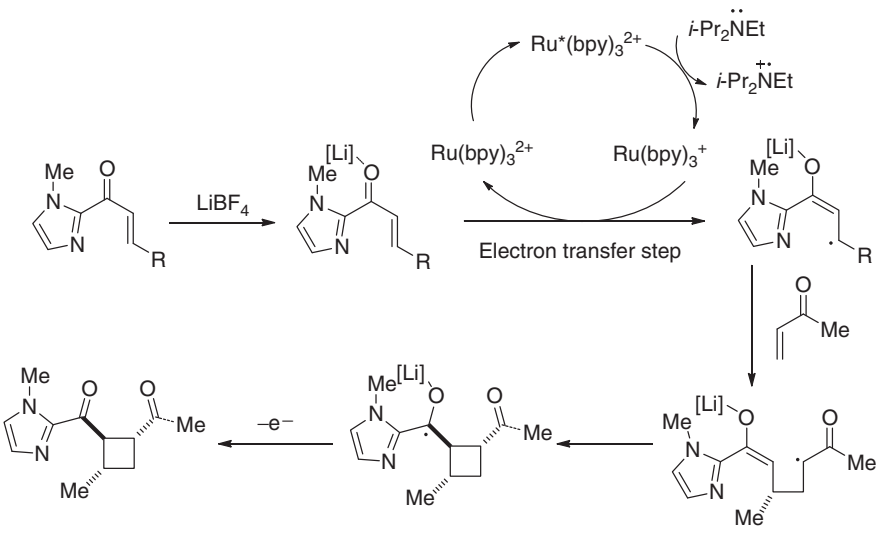
Scheme 62 Crossed intermolecular [2 + 2] cycloadditions of α,β-unsaturated 2-imidazolyl ketones.

The proposed mechanism for these transformations involves photoexcitation of Ru(2,2′-bipyridyl(bpy))$_3^{2+}$ with visible light resulting in a photoexcited state (Ru(bpy)$_3^{2+}$) that can undergo reductive quenching by *i*-Pr$_2$NEt. The resulting Ru(bpy)$_3^{+}$ complex is a powerful reducing agent that can transfer an electron to the enone activated by coordination to a lithium cation, which triggers the [2 + 2] cycloaddition and regenerates the Ru^{2+} photocatalyst (Scheme 63).

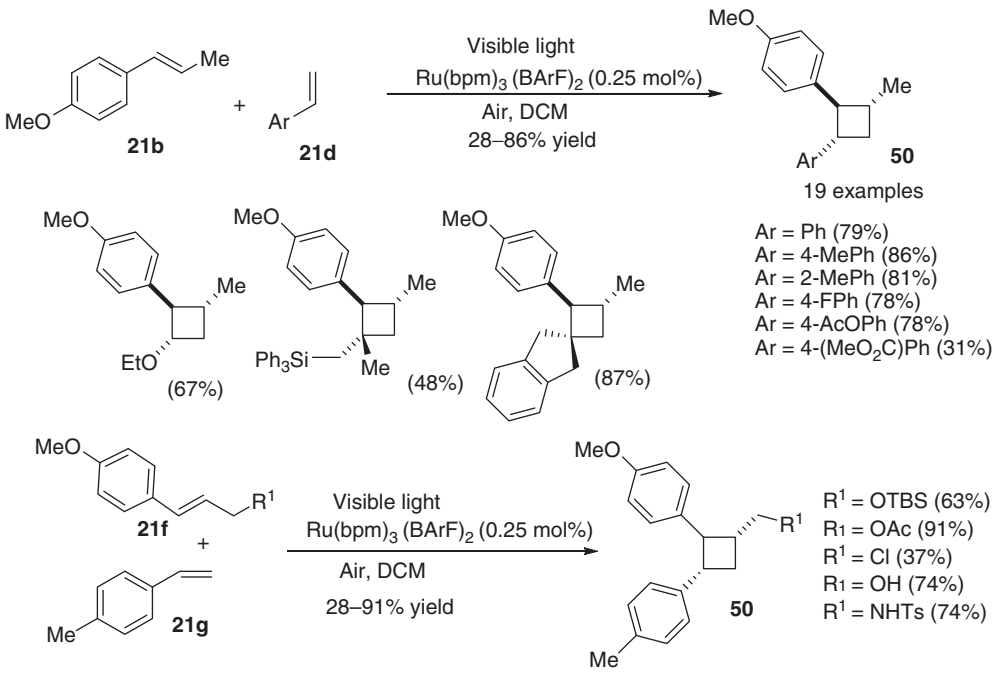
Very recently, the same authors developed a highly efficient method for the chemoselective radical cation-mediated crossed [2 + 2] cycloaddition of styrenes under photocatalytic conditions. Thus, irradiation of a mixture of 1,2-disubstituted alkenes and monosubstituted alkenes in the presence of 0.25 mol% Ru(bpm)$_3^{2+}$ (bpm = 2,2′-bipyrimidine) in DCM at −15 °C gave cross-cycloaddition products **50** in excellent yield (Scheme 64).[62] Control studies confirmed that no reaction occurred in the absence of light or the photocatalyst. Under similar conditions, a wide variety of styrene derivatives were suitable coupling partners in this reaction. Interestingly, α-substituted styrenes reacted in a highly diastereoselective manner, whereas β-substituted styrenes gave homodimerization. The extension of the photocatalytic [2 + 2] cycloaddition reactions to substituted allylic benzene derivatives was also successful, giving the corresponding cyclobutanes in good yields.

Later, Xiao and coworkers have explored the intermolecular [2 + 2] cycloaddition reaction of 3-ylideneoxindoles by visible-light photocatalysis. The irradiation of a DMF solution of a 3-ylideneoxindole in the presence of 2 mol% Ru(bipy)$_3$Cl$_2$.6H$_2$O with a 36 W fluorescent light bulb provided spirocyclobutane **51c** in 93% yield with a *dr* of > 19:1 (Scheme 65).[63] The photocatalysis reaction is highly diastereoselective and regioselective. Various 3-ylideneoxindoles with electron-donating and -withdrawing groups are compatible with the catalytic reaction.

A terminal phosphido complex of ruthenium containing a Ru=PR$_2$ π bond showed high activity in 1,2-addition reactions of polar and nonpolar substrates.[64] In this context, Rosenberg et al. reported a [2 + 2] cycloaddition of a planar phosphido complex with both activated and simple alkenes to yield metallaphosphacyclobutanes.[65] The five-coordinate half-sandwich complex [Ru(η^5-indenyl)(PR$_2$)(PPh$_3$)] (**53**) reacts rapidly with acrylonitrile to give two isomers of the metallacyclic product, **54** and **54′**, in which the nitrile group on the ruthenium-bound α-carbon atom is oriented either *syn* or *anti* with respect to the Ru–indenyl bond (Scheme 66). X-ray crystallography confirmed that *syn* isomer is the major product in the solid state. In solution, these complexes



Scheme 63 Mechanism of the radical anion [2 + 2] cycloaddition.



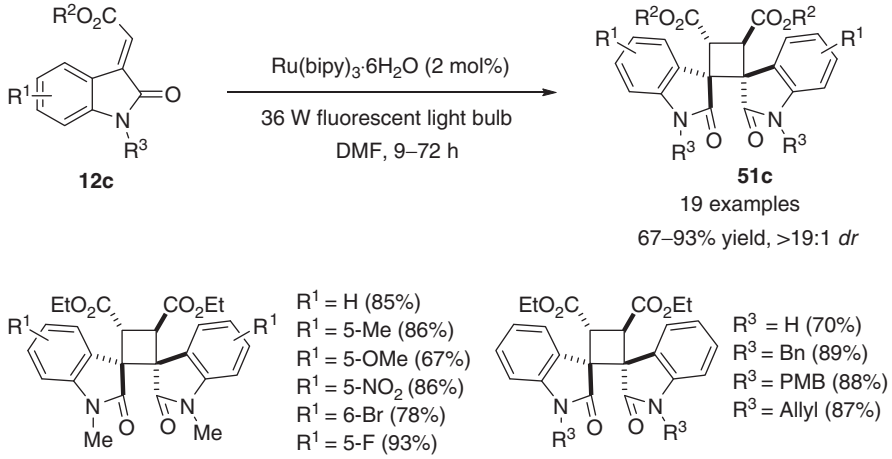
Scheme 64 Chemoselective crossed [2 + 2] cycloadditions of styrenes under photocatalytic conditions.

showed diagnostic upfield $^{31}P\{^{1}H\}$ NMR signals due to the phosphorus atom in the metallacycle (e.g., *syn*-**54**: $\delta = 13.3$ ppm), and upfield $^{13}C\{1H\}$ NMR signals for the α-carbon atom attached to Ru (e.g., *syn*-**54**: $\delta = 28.3$ ppm).

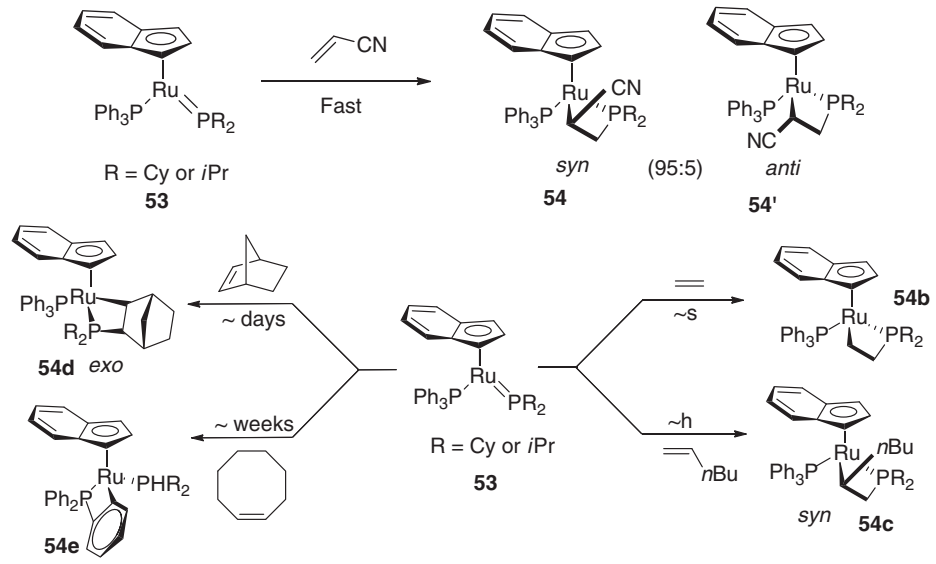
Simple alkenes also undergo [2 + 2] cycloaddition reactions with the Ru=PR_2 bond of **53** (Scheme 66). Solutions of **53** placed under 1 atm of ethylene rapidly and quantitatively transformed into [Ru(η^5-indenyl)(κ^2-$CH_2CH_2PR_2$)(PPh_3)] (**54**) at r.t., as determined by $^{31}P\{1H\}$ NMR analysis. Similar products were obtained from the addition of 1-hexene and the strained internal alkene norbornene; the latter gave exclusive addition to the *exo* face. However, for more sterically demanding substrates long reaction times were required, which resulted in competing decomposition to the orthometalated complex **54e**.

5.07.7.4 Rhodium-Catalyzed Intermolecular [2 + 2] Cycloaddition

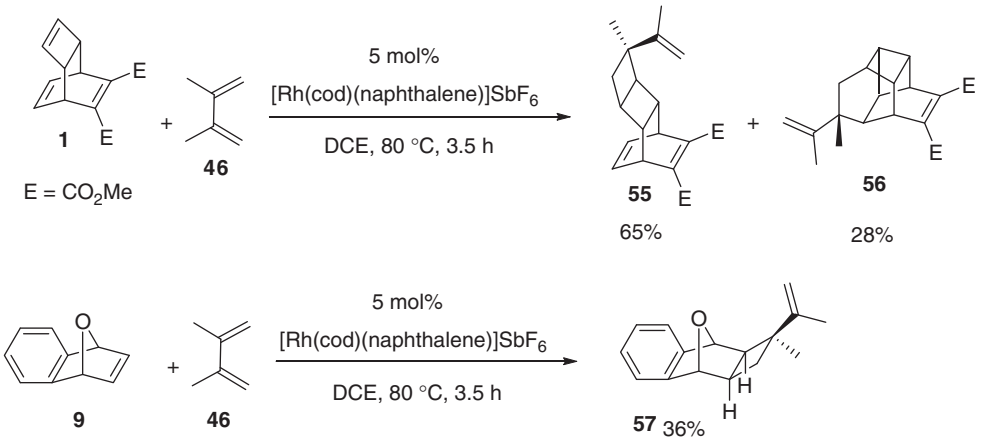
In 2009, Wender et al. reported intermolecular [2 + 2] cycloaddition reactions of a tricyclic substrate with dienes catalyzed by cationic Rh(I)-complexes, which gave the corresponding cyclobutanes in 65% yield (Scheme 67).[66] In all cases, a minor amount



Scheme 65 Intermolecular [2 + 2]-cycloadditions of 3-ylideneoxindoles by visible light photocatalysis.



Scheme 66 [2 + 2] Cycloadditions of a planar phosphido complex with both activated and simple alkenes.



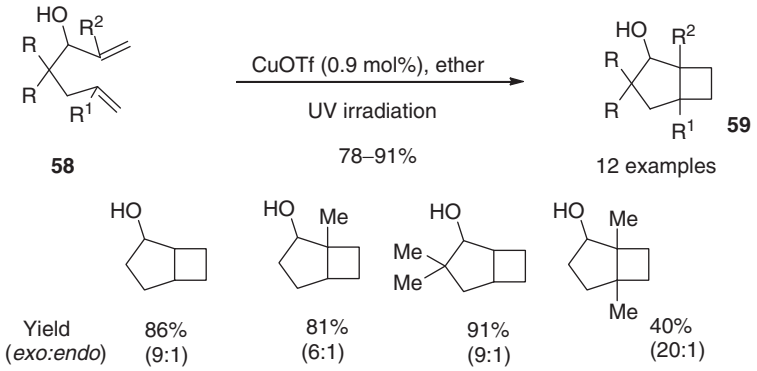
Scheme 67 Cationic Rh(I)-catalyzed intermolecular [2 + 2] cycloaddition reactions with dienes.

of [2 + 2 + 2] cycloaddition products were obtained. Under similar reaction conditions, 1,4-epoxy-1,4-dihydronaphthalene (**9**) reacted with 2,3-dimethyl-1,3-butadiene **46** to give only vinylcyclobutane **57** in 36% yield. The authors proposed a mechanism for the [2 + 2] reaction via rhodium coordination to the *exo* face of the cyclobutene carbon–carbon double bond, although the [2 + 2 + 2] reaction is derived from *endo* face coordination.

5.07.8 Intramolecular [2 + 2] Cycloaddition Between Two Alkene Groups

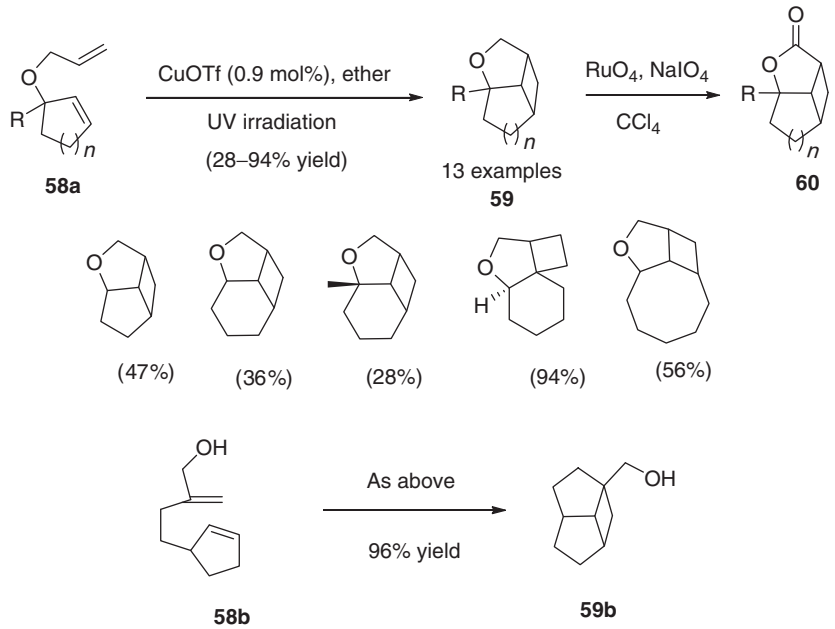
5.07.8.1 Copper-Catalyzed Intramolecular [2 + 2] Cycloaddition of Two Alkenyl Groups

The intramolecular [2 + 2] photocycloaddition of alkenes is an extremely useful synthetic tool for the preparation of strained cyclobutanes. An intramolecular Cu(I)-catalyzed photocycloaddition of functionalized alkenes was reported by Salomon et al.[67] Thus, UV irradiation of 1,6-heptadien-3-ol **58** in the presence of CuOTf in Et_2O cleanly afforded 3-hydroxybicyclo[3.2.0]heptanes **59** in good yields as *endo* and *exo* epimers (Scheme 68).[68a]



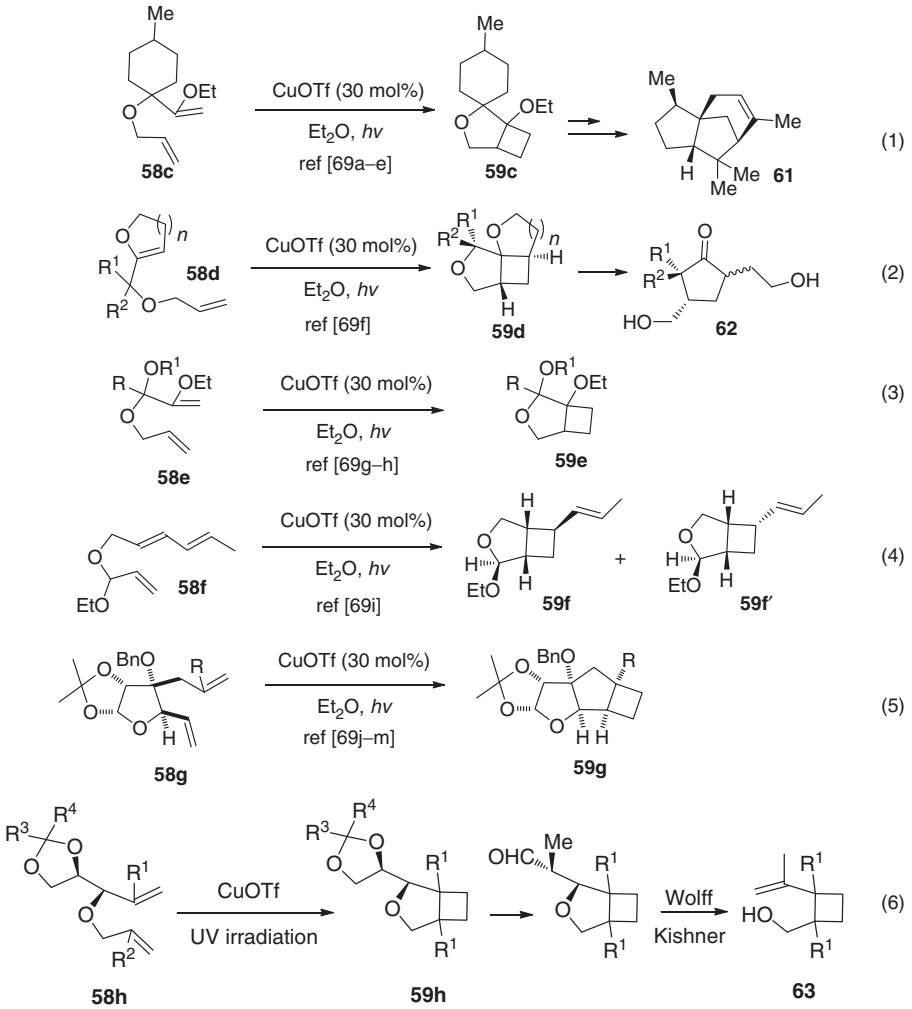
Scheme 68 CuOTf-catalyzed synthesis of 3-hydroxybicyclo[3.2.0]heptanes.

Under similar reaction conditions, various homoallylvinyl or diallyl ethers underwent photocycloaddition to give a variety of polycyclic THFs in reasonable yields. The utility of the reaction was further demonstrated by selective oxidation of the methylene group of the THF photoproducts **59** to butyrolactones (Scheme 69).[68b,c] These photoreactions tolerated hydroxyl, acetoxy, allyl, and vinyl substituents. Subsequently, similar protocols also applied to the formation of polycyclic cyclobutanes.[68d]



Scheme 69 CuOTf-catalyzed photocycloaddition of alkenes.

In addition to Salomon's work, Ghosh's group independently developed an intramolecular photocycloaddition of alkenes (Scheme 70). In 1993, the authors found that treatment of dienes with CuOTf in Et_2O provided a range of cyclobutane derivatives in good yields. The resulting cyclobutane derivatives are key compounds for the synthesis of (+)-α-cedrene and cyclopentanones (equations 1 and 2).[69a–e] The same methodology was successfully applied to the reductive coupling of internal alkynes with conjugated alkenes. Under similar reaction conditions, various functionalized dienes underwent intramolecular [2 + 2] cycloaddition to give fused cyclobutanes in good yield (Scheme 70; equations 3–6).[69f–m]



Scheme 70 CuOTf-catalyzed photocycloadditions of alkenes.

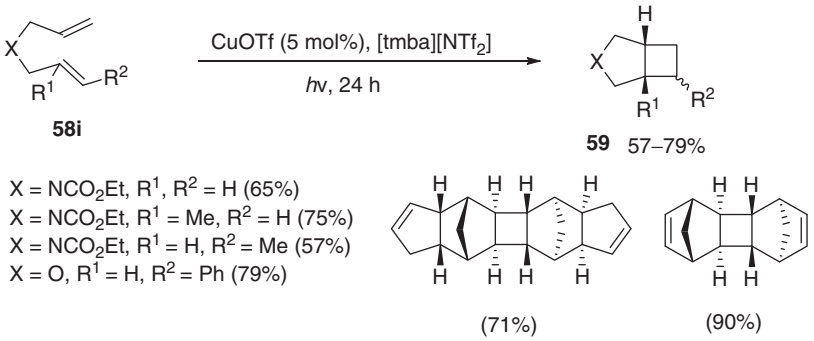
Asymmetric induction in intramolecular Cu(I)-catalyzed [2 + 2] photocycloadditions of alkenes has been investigated by Ghosh et al. in 2004. Their approach involved a cleavage of THF rings present in oxa-bicyclo[3.2.0]heptanes, which resulted in the formation of useful *cis*-1,2-disubstituted cyclobutanes in enantiomerically pure form.[69n]

In a similar manner, Ghosh et al. reported an intra- and intermolecular copper-catalyzed [2 + 2] photocycloaddition of alkenes **58i** in the presence of the ionic liquid [tmba][NTf_2] (tmba = *N*-trimethyl-*N*-butylammonium, NTf_2 = bis(trifluoromethylsulfonyl)-imide) at r.t. The process gave access to azabicyclo[3.2.0]heptanes and oxa-bicyclo[3.2.0] heptanes in good yields (Scheme 71). An intermolecular reaction of dicyclopentadiene and norbornene had also been realized to afford cyclobutene products in high yields.[69]

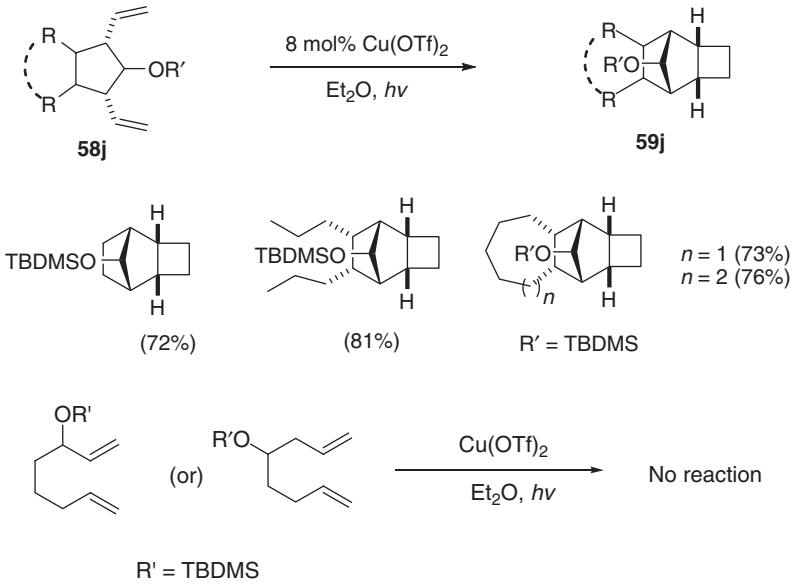
Bach's group developed a Cu-catalyzed photocycloaddition of 1,6-dienes of type **58j**, which gave to enantiomerically pure bicyclo[4.2.0]octanes. The *t*-butyldimethylsilyl (TBDMS)-protected cyclic 1,6-dienes **58j** turned out to be a key factor in the process as no reaction takes place with open-chain 1,7-dienes (Scheme 72).[70]

5.07.8.2 Iron-Catalyzed Intramolecular [2 + 2] Cycloaddition of α,ω-Dienes

In 2006, Chirik and coworkers discovered an efficient method for the synthesis of cyclobutanes via iron-catalyzed intramolecular [2π + 2π] cycloaddition of the corresponding α,ω-dienes (Scheme 73).[71] The key feature of the catalytic cycle is the redox activity of



Scheme 71 Inter- and intramolecular copper-catalyzed [2 + 2] photocycloadditions of alkenes in an ionic liquid.



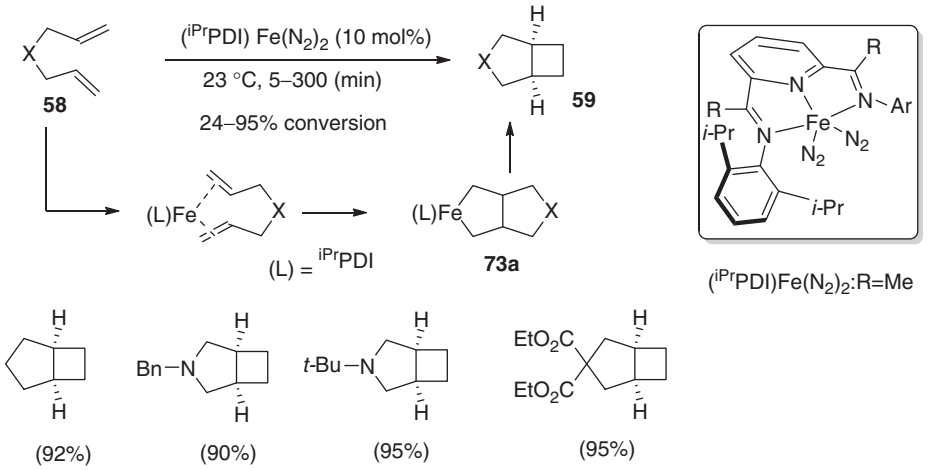
Scheme 72 Copper-catalyzed photocycloaddition of 1,6-dienes.

the supporting bis(imino)-pyridine ligand. The iron catalyst is tolerant of various functional groups and all of the cycloadditions gave *cis* products in good yields. However, some substrates such as **58** ($X=SiMe_2$) and those with internal olefins (allyl-*tert*-butylcrotylamine or *tert*-butyldicrotylamine) were not successfully cyclized even though the reaction is thermodynamically favorable. The authors proposed a mechanism for the formation of the bicyclic cyclobutane. The cycloaddition involves initial substitution of the N_2 ligands by the diene molecule, followed by C–C coupling to form the metallacycle intermediate **73a**. This intermediate undergoes formal reductive elimination to give cyclobutane **59** as the final product and regenerates the iron diene complex.

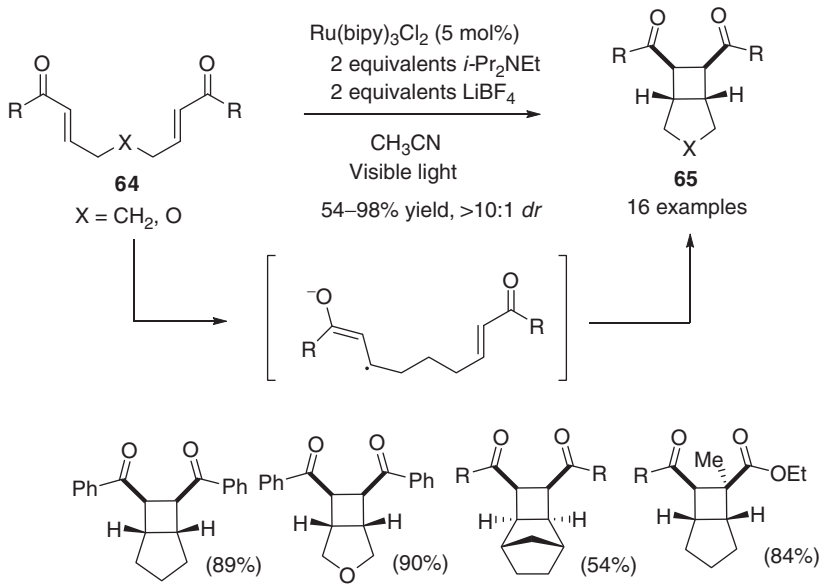
5.07.8.3 Ruthenium-Catalyzed Intramolecular [2 + 2] Cycloaddition of Enones

Yoon and coworkers found that bis(enone) **64** undergoes efficient [2 + 2] cycloaddition on visible light irradiation in the presence of 5 mol% of $Ru(bipy)_3Cl_2$ and $LiBF_4$ and *i*-Pr_2NEt as additives (Scheme 74).[72] The *meso* diastereomer of the cyclobutane-containing bicyclic dione **65** was produced with excellent selectivity. The use of $LiBF_4$ and *i*-Pr_2NEt was crucial for the success of the reaction; no [2 + 2] cycloaddition occurred without these additives. Various bis-enones underwent intramolecular [2 + 2] cycloaddition to give the corresponding cyclobutanes **65** in good yields with excellent diastereomeric selectivity. The authors speculated that a photoreductant generated by irradiation of $Ru(bipy)_3^{2+}$ served as an excellent photocatalyst for the intramolecular anion radical-mediated [2 + 2] enone cycloadditions.

Subsequently, Yoon et al. demonstrated that $Ru(bipy)_3^{2+}$ is a powerful photocatalyst for the [2 + 2] cycloaddition of both electron-rich and electron-deficient olefins, which furnish cyclobutanes in good yield and diastereoselectivity (Scheme 75).[73] The mechanism involves $Ru(bpy)_3^{3+}$ generated on visible light irradiation of $Ru(bpy)_3^{2+}$ in the presence of MV^{2+} (MV^{2+} = methyl viologen hexafluorophosphate ($MV(PF_6)_2$)) as the oxidant to oxidize electron-rich styrenes, affording a key radical cation



Scheme 73 Iron-catalyzed [2 + 2] cycloadditions of α,ω-dienes.



Scheme 74 [2 + 2] Cycloadditions of enones under visible light photocatalysis.

intermediate which then undergoes the [2 + 2] cycloaddition. Interestingly, the cycloaddition reaction could be conveniently carried out on a gram scale by using sunlight to give cyclobutane **65** in excellent yield.

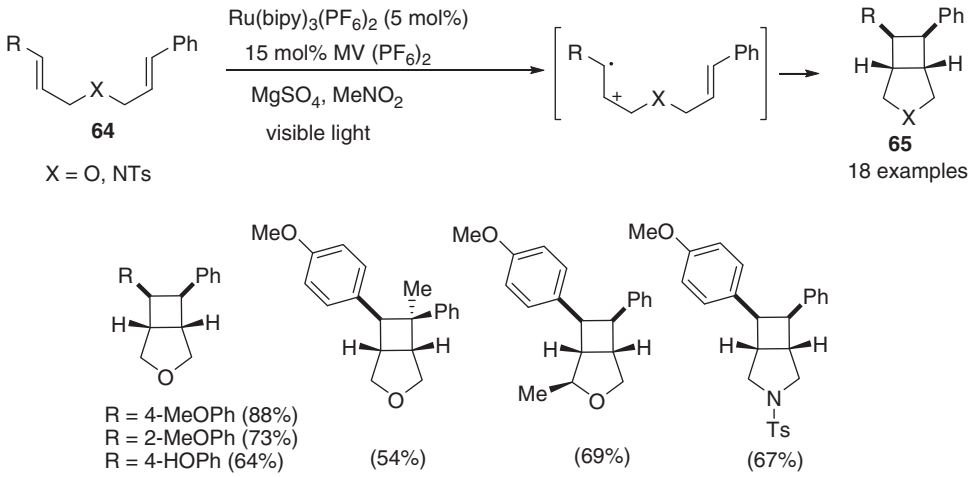
The intramolecular photoreductive [2 + 2] cycloaddition always gives somewhat higher yields in the presence of 0.5 equivalent of $LiBF_4$. Under similar reaction conditions, intramolecular cycloadditions worked well with a variety of acceptor moieties including esters, ketones, and amides[61] (Scheme 76).

Cleavage of the imidazolyl auxiliary from the cycloadducts affords cyclobutane carboxamides, esters, thioesters, and acids in good yield. It is noteworthy that direct cycloaddition of the corresponding unsaturated acid derivatives does not proceed under similar reaction conditions.

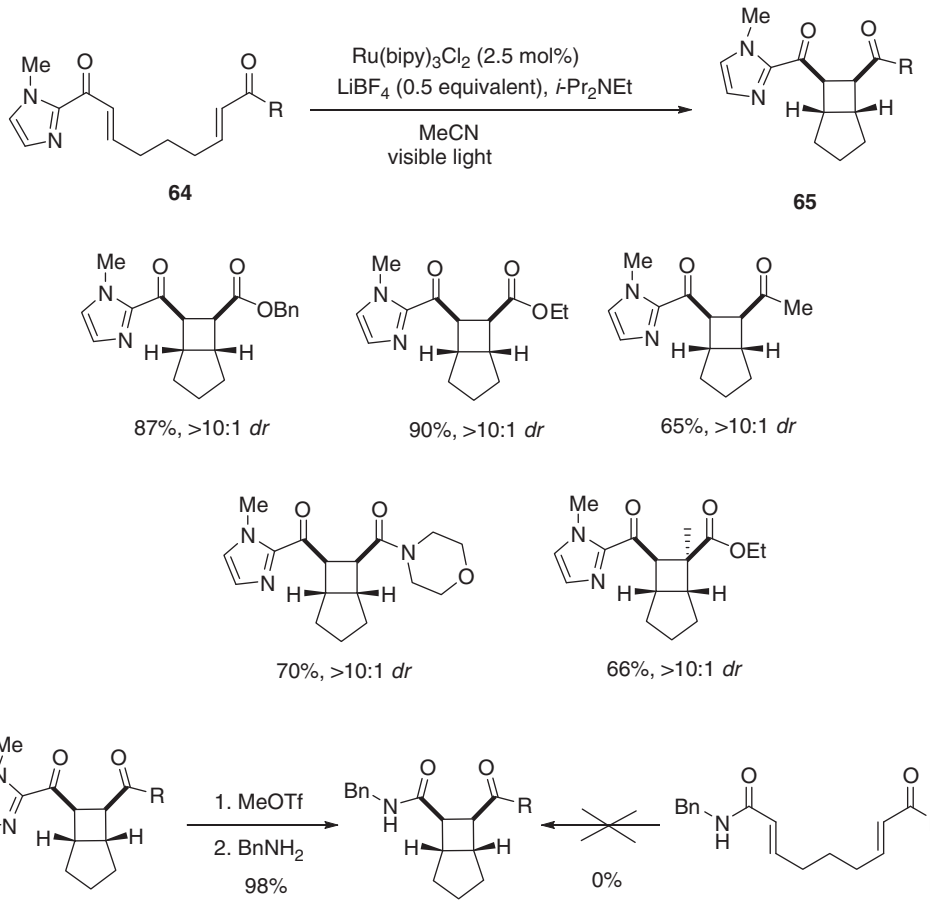
5.07.9 Metal-Catalyzed [2 + 2] Cycloaddition of Two Allenes

5.07.9.1 Nickel-Catalyzed Intermolecular [2 + 2] Cycloaddition of Allenes

Allenes are unique substrates with characteristic reactivity and steric properties, which originate from the cumulated propadienyl structures. Although allenes have gained much attention as synthetic intermediates, their applications in [2 + 2] cycloaddition are still relatively unexplored compared to those of alkenes and alkynes.

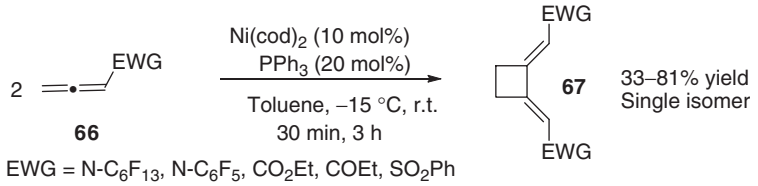


Scheme 75 Photo-oxidative [2 + 2] cycloadditions.



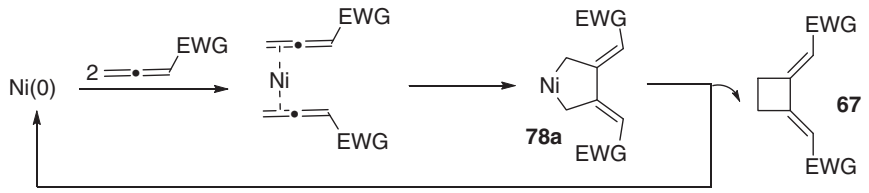
Scheme 76 Intramolecular photoreductive [2 + 2] cycloadditions and cleavage of the imidazolyl group.

In 2000, Saito and Yamamoto described a Ni(0)-catalyzed [2 + 2] annulation of electron-deficient allenes **66** to give bismethylenecyclobutane products under mild conditions.[74] The catalytic reaction is completely regioselective and only head-to-head cyclodimerization was observed. The corresponding cycloadducts **67** were isolated as single isomers in good to fair yields (Scheme 77). However, it is noteworthy that the presence of an electron-withdrawing group (EWG) is crucial for the [2 + 2] cycloaddition to proceed efficiently in a highly regioselective manner. Other allenes resulted in the formation of a complex mixture composed of oligomeric compounds.



Scheme 77 Ni(0)-catalyzed head-to-head cyclodimerization of electron-deficient allenes.

A possible catalytic reaction mechanism for the cyclodimerization of allenes is proposed in Scheme 78. Regioselective coordination of two molecules of the allenes to the Ni(0) center followed by oxidative coupling leads to a nickelacyclopentane intermediate **78a**. Reductive elimination of this intermediate gives the final product **67** and regenerates the Ni(0) species.



Scheme 78 Proposed mechanism for the cyclodimerization of electron-deficient allenes.

5.07.9.2 Ruthenium-Catalyzed Intermolecular [2 + 2] Cycloaddition of Allenes

1,3-Dialkylidenecyclobutanes are key precursors for the formation of non-Kekule hydrocarbon diradicals with a triplet ground state: the 1,3-dialkylidenecyclobutane-2,4-diyls.[75] The previous method for the preparation of 1,3-dimethylenecyclobutanes involves a six-step synthesis from allene and acrylonitrile. Dixneuf and coworkers developed an interesting ruthenium-catalyzed synthesis of 1,3-dimethylenecyclobutanes via head-to-tail [2 + 2] cyclodimerization of allenyl-boronates to give the isomeric products **67a** + **67a′** in moderate yield with a 2:3 ratio (Scheme 79). Importantly, the decomposition of **67a** + **67a′** with concomitant release of pinacol was always observed, which hindered the separation of the two isomers.[76]

Furthermore, the authors found a sequential Ru-catalyzed [2 + 2] cyclodimerization of allenyl boronate **66a** and a palladium-catalyzed Suzuki coupling (Scheme 79). The reaction of allenyl boronate **66a** in the presence of 5 mol% of [Cp*RuCl(cod)] in refluxing dioxane at 100 °C was followed by the addition of an aryl iodide in the presence of a catalytic amount of $Pd(PPh_3)_4$ and base (K_2CO_3); under these conditions, the [2 + 2] cyclodimerization products **67b,c** were formed. Although a mixture of the two Ph-substituted isomers (*E*,*E*) and (*Z*,*Z*) was obtained, recrystallization allowed the major (*E*,*E*)-isomer to be isolated in moderate yields. Total regioselectivity has been achieved during the dimerization of phenylallene **66b** by using the sterically hindered ruthenium catalyst $[Cp^*Ru(PPh_3)(MeCN)_2][PF_6]$. Only the tail-to-tail coupling compound **67d** was isolated in 44% yield (Scheme 79).

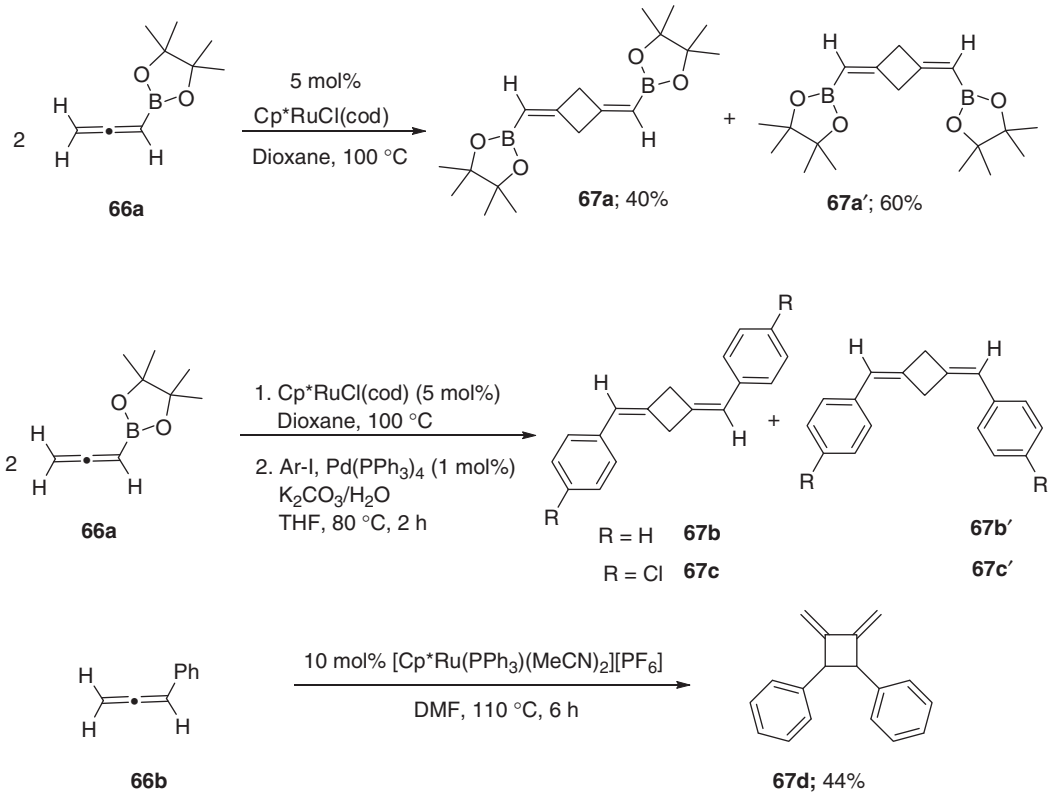
5.07.9.3 Gold-Catalyzed [2 + 2] Cycloaddition of Allenes

Interestingly, a series of alleneamides underwent dimerization in the presence of $AuCl(PPh_3)/AgSbF_6$ in DCM at r.t. Under these reaction conditions, benzyl (Bn)-, Ph-, oxazolidinone, and 2,3-dihydrobenzo[*d*]isothiazole-substituted alleneamides underwent dimerization to give 1,3-dimethylenecyclobutanes in moderate to good yields (Scheme 80).[77]

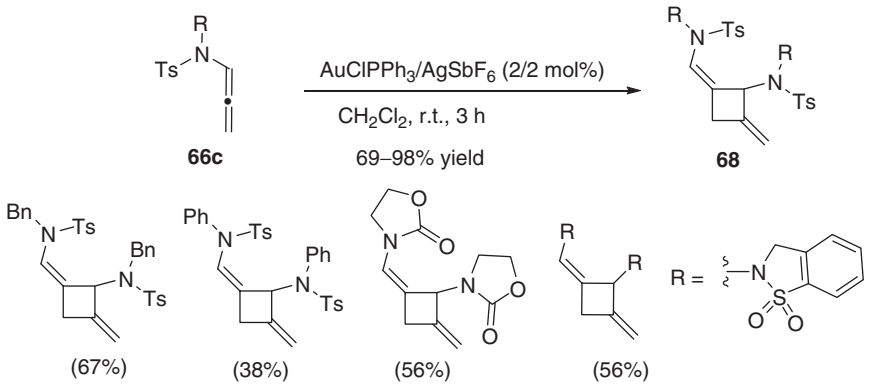
5.07.10 Intramolecular [2 + 2] Cycloaddition of Bisallenes

5.07.10.1 Palladium-Catalyzed Intramolecular [2 + 2] Cycloaddition of 1,5-Bisallenes

Ma's group observed a regiocontrolled synthesis of cyclobutenes via Pd(0)-catalyzed [2 + 2] cycloaddition of 1,5-bisallenes.[78] After several optimization studies, $[Pd(PPh_3)_4]$, K_2CO_3, and nBu_4NI was found to be most effective, furnishing bicyclo[3.2.0] derivatives **70** in moderate to good yields. The catalytic reaction did not proceed in the absence of K_2CO_3 and nBu_4NI. More notably, when X is the chiral L-valine ester, compound **70a** was formed in greater than 99% *ee* (Scheme 81), which indicates that the reaction proceeds without racemization of the α-amino acid ester. To demonstrate the utility of compound **70a** in organic synthesis, the authors carried out the [4 + 2] Diels–Alder cycloaddition of **70a** with *N*-phenyl maleimide to afford the 2-azabicyclo[2.2.2]octane (isoquinuclidine) derivative **71a** in 80% isolated yield (Scheme 81). The palladium system does not effectively catalyze cycloadditions of compounds **69b–d** having substituents on the proximal side, probably for steric reasons.



Scheme 79 Ru-catalyzed [2 + 2] cycloadditions of allenyl-boronates or phenylallene.



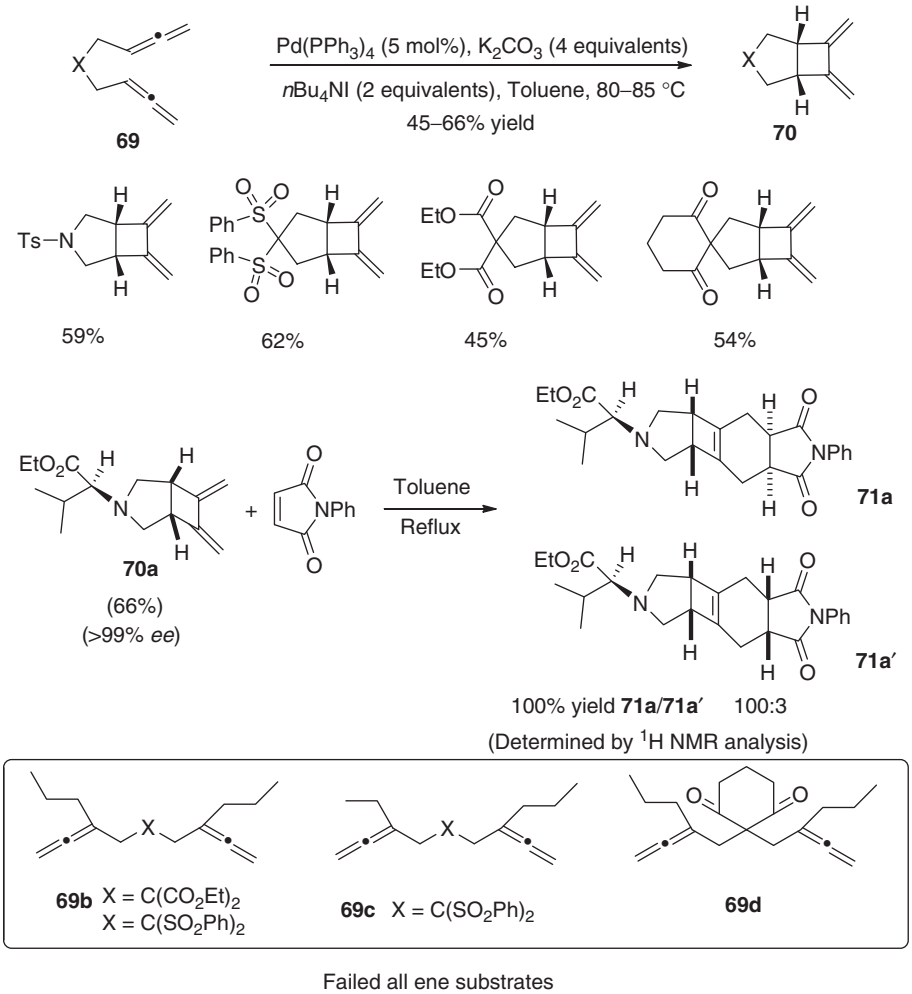
Scheme 80 $AuClPPh_3/AgSbF_6$-catalyzed dimerization of allenamides.

The proposed mechanism is shown in Scheme 82. The first step involves coordination of the 1,5-allene's internal C═C bond to the Pd-center assisted by the electron lone pair on the N atom, leading to the exclusive formation of intermediate **82a**. Subsequent reductive elimination affords the cycloaddition product. In the present catalytic reaction, the role of nBu$_4$NI is not entirely clear, which could act as a ligand facilitating the reductive elimination process.

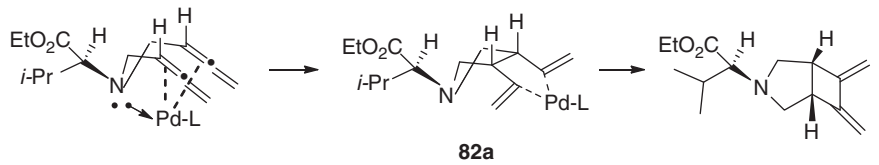
However, the thermal [2 + 2] cyclization of 1,5-bisallenes **69** in refluxing xylene afforded bicyclo[5.2.0] products of type **72** via tail-to-tail [2 + 2] cyclization. Thermal tail-to-tail [2 + 2] cycloadditions represent a facile and versatile access to cyclobutane derivatives in good yield (Scheme 83).[78]

5.07.10.2 Gold-Catalyzed Intramolecular [2 + 2] Cycloaddition of 1,5-Bisallenes

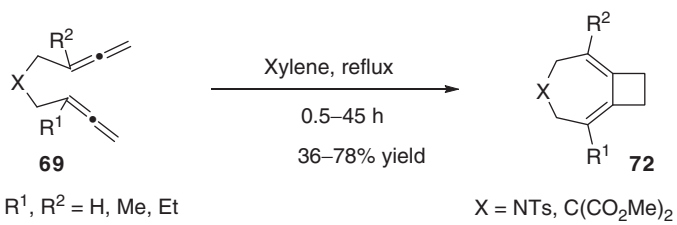
In 2009, Kang and Chung reported an efficient cationic N-heterocyclic carbene (NHC)-gold-catalyzed [2 + 2] cycloaddition of amino-tethered 1,5-bisallenes to produce 6,7-dimethyleneazabicyclo[3.1.1]heptanes (Scheme 84).[79] The formal head-to-head



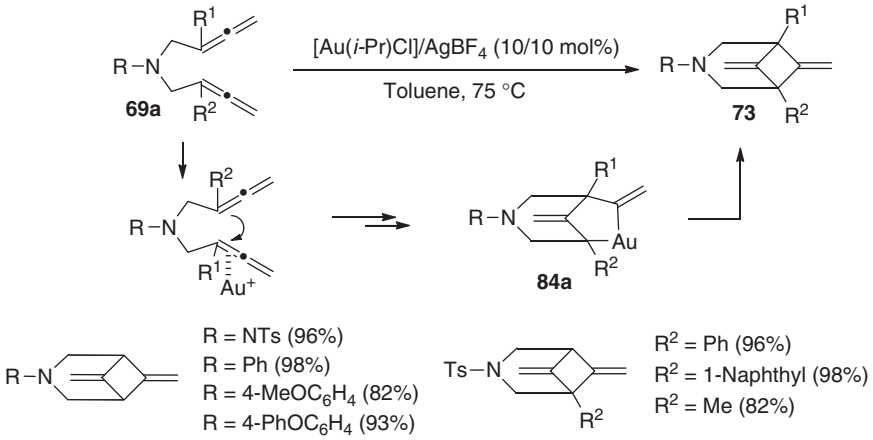
Scheme 81 $Pd(PPh_3)_4$-catalyzed [2 + 2] cycloadditions of 1,5-bisallenes.



Scheme 82 Proposed mechanism for the palladium-catalyzed formation of cyclobutanes from bisallenes.



Scheme 83 Thermal [2 + 2] cycloadditions of bisallenes.

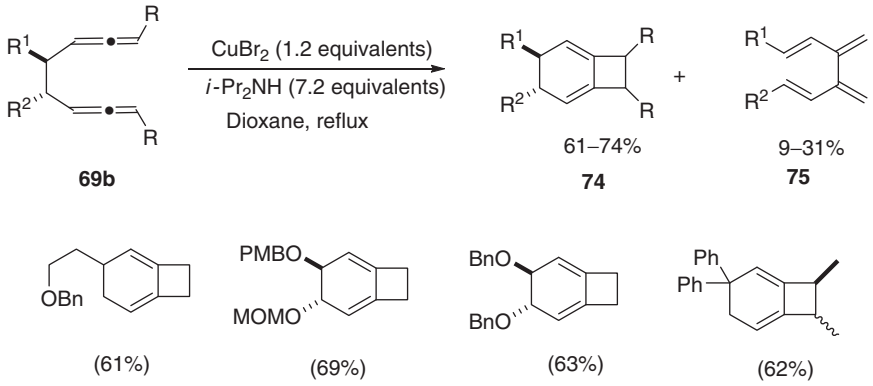


Scheme 84 Cationic NHC-gold catalyzed [2 + 2] cycloadditions of amino-tethered 1,5-bisallenes.

cycloaddition products are observed in good to excellent yields. One allene acts as a nucleophilic reagent attacking another Au^+-coordinated allene group in the 1,5-bisallene molecule to form a C–C single bond. The mechanism of this transformation was studied using DFT calculations. Among the several mechanistic scenarios, the authors envisioned that **84a** is the key intermediate, which forms the final product **73** via reductive elimination.

5.07.10.3 Copper-Mediated Intramolecular [2 + 2] Cycloaddition of 1,4-Bisallenes

It is well known that 1,4-bisallenes easily undergo formal [3,3]-sigmatropic rearrangement to produce tetraenes on heating.[80] Interestingly, in the presence of $CuBr_2$/*i*-Pr_2NH, the 1,4-bisallenes undergo a [2 + 2] cycloaddition to afford highly selective bicyclo[4.2.0]octadienes in good yields (Scheme 85).[81] In this reaction, more than 1 equivalent of the Cu salt is needed to suppress the [3,3]-sigmatropic rearrangement or other side reactions. *i*-Pr_2NH probably plays three roles in the reaction. First, it likely reduces Cu(II) to Cu(I) and assists the coordination of the 1,4-bisallenes to the Cu(I) center. Second, it dissociates the polymeric precatalyst and also stabilizes the active species. Third, it likely makes the oxidative addition more facile.



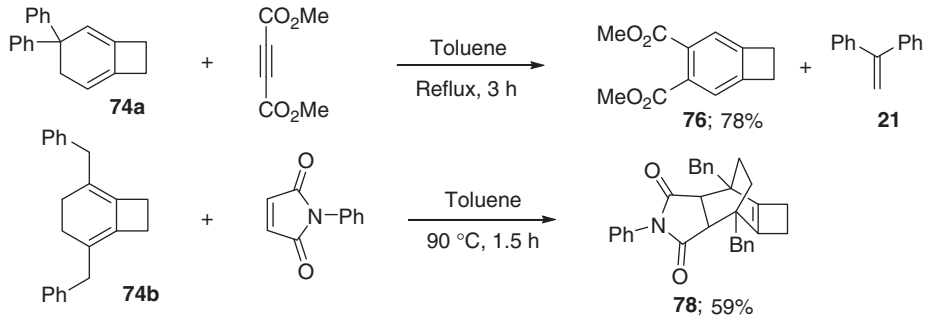
Scheme 85 $CuBr_2$-mediated [2 + 2] cycloadditions of 1,4-bisallenes.

Furthermore, the cycloadduct **74a** undergoes [4 + 2] cycloaddition with DMAD followed by a retro-Diels–Alder reaction of the resulting product to produce benzocyclobutene **76** in 78% yield (Scheme 86). However, **74b** readily reacted with *N*-phenylmaleimide to produce the bridged polycyclic compound **78**.

5.07.11 Metal-Catalyzed [2 + 2] Cycloaddition of Allenes and Alkenes

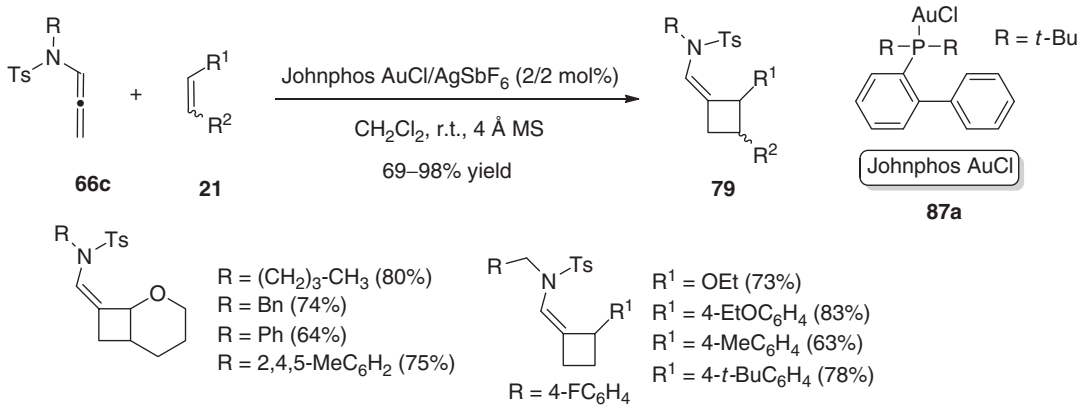
5.07.11.1 Gold-Catalyzed Intermolecular [2 + 2] Cycloaddition of Allenes and Alkenes

An efficient method for the construction of highly functionalized cyclobutane adducts via (Johnphos)AuCl-catalyzed formal intermolecular cycloaddition of alleneamides with electron-rich alkenes has been developed by Chen et al.[77] The reaction provides a practical entry to cyclobutane derivatives **79**, which were obtained in good yields with excellent selectivities



Scheme 86 [4 + 2] Cycloadditions of cyclobutanes **74** with DMAD.

(Scheme 87). The scope of the reaction is broad with respect to both alleneamides and alkenes (vinyl ethers, amides, and electron-rich styrenes).



Scheme 87 Gold-catalyzed formal intermolecular cycloadditions of allenamides with electron-rich alkenes.

5.07.11.2 Ruthenium-Catalyzed Intramolecular [2 + 2] Cycloaddition of Allenes and Alkenes

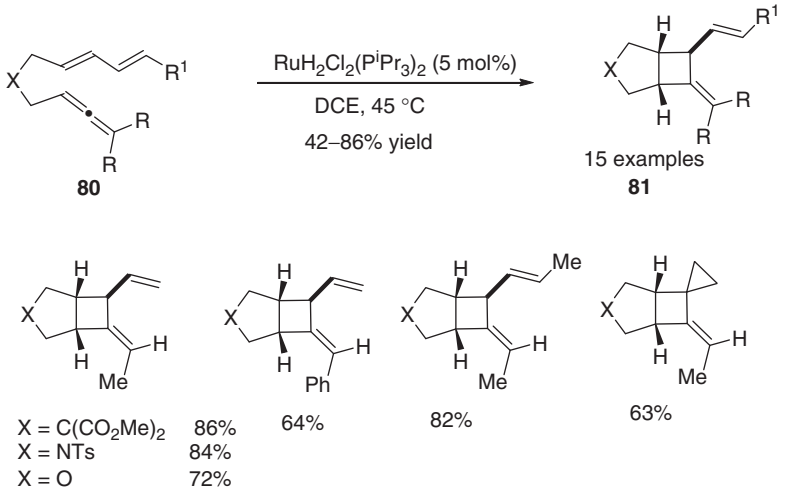
Esteruelas, Mascarenas, and coworkers developed a new type of intramolecular [2 + 2] cycloaddition of allenes and alkenes using $RuH_2Cl_2(P^iPr_3)_2$ as the catalyst.[82] The reaction proceeded under mild conditions and was fully diastereoselective, providing a new practical entry to bicyclic cyclobutanes (Scheme 88). Notably, the internal C═C double bond of the allene moiety participated in the cycloaddition via a possible ruthenabicyclic intermediate.

Based on DFT calculations, the authors suggested that the catalytic cycle is initiated by the unsaturated species $[RuCl_2(P^iPr_3)]$, which comes from the dissociation of molecular hydrogen and one triisopropylphosphine ligand from $RuH_2Cl_2(P^iPr_3)_2$ (Scheme 89). Then, coordination of the conjugated diolefin unit and the internal allenic double bond of the substrate to the Ru center of **89a** generates complex **89b**, which evolves into the ruthenabicycle **89c** by oxidative cyclometalation. Further, σ- to π-allyl rearrangement of **89c** affords **89d**, which enables a subsequent reductive elimination to give the cycloaddition product **81** and regenerates the Ru catalyst.

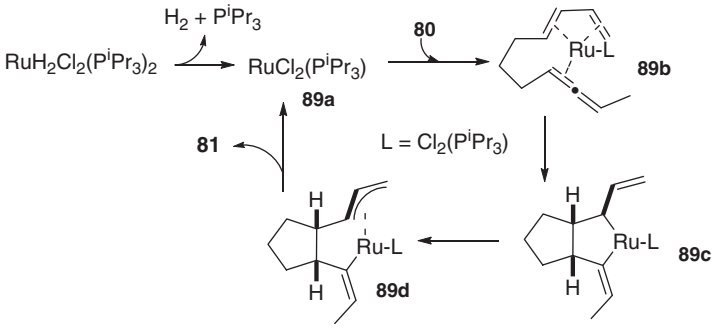
5.07.11.3 Gold-Catalyzed Intramolecular [2 + 2] Cycloaddition of Allenes and Alkenes

Toste et al. demonstrated an intramolecular $AuCl(PPh_3)/AgBF_4$-catalyzed [2 + 2]-cycloaddition reaction of allenes and alkenes affording cyclobutanes in good yield. The reaction proceeds with a high selectivity for the internal C═C bond of the allenene moiety in **80** (Scheme 90).[83a] It is interesting to note that only the internal C═C double bond of the allene moiety participated in the cycloaddition via a possible carbocationic mechanism. Under these conditions, a variety of aryl-substituted alkenes reacted intramolecularly with allenes to furnish cyclobutanes. Interestingly, trisubstituted olefins also participate to give highly substituted cyclobutanes.

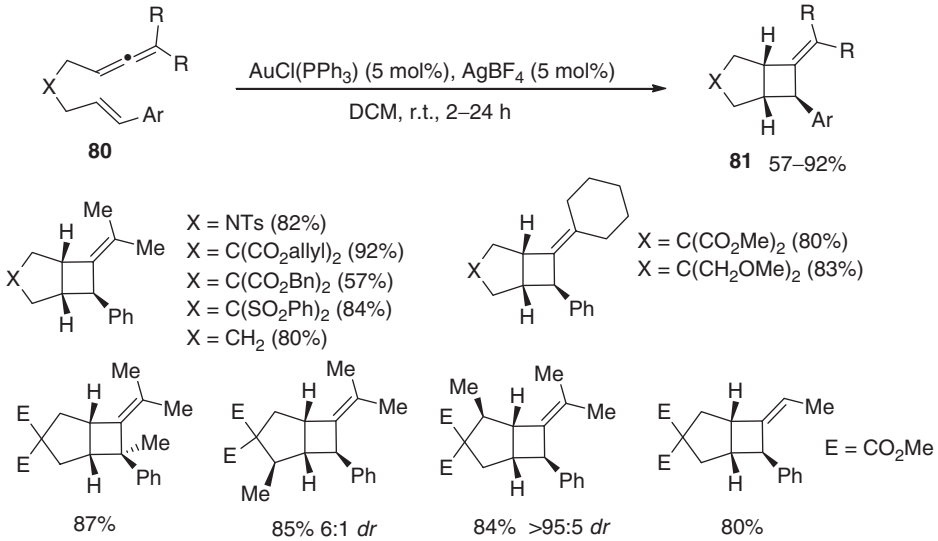
The same group reported an asymmetric [2 + 2] cycloaddition of allene-enes in the presence of (*R*)-(–)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole ((*R*)-DTBM-SEGPHOS)$(AuCl)_2$ (**91a**) and 6 mol% of $AgBF_4$ to



Scheme 88 Intramolecular [2 + 2] cycloadditions of allenes and alkenes.

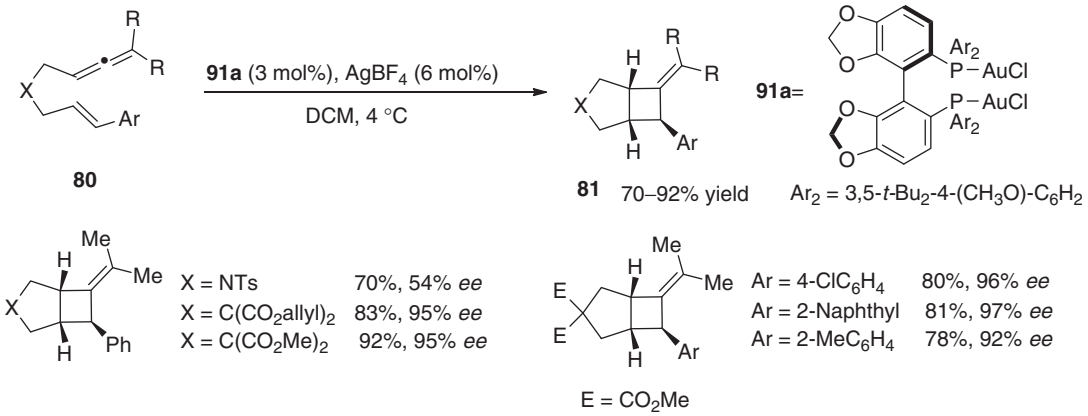


Scheme 89 Proposed mechanism for the formation of the bicyclic cyclobutanes of type **81**.



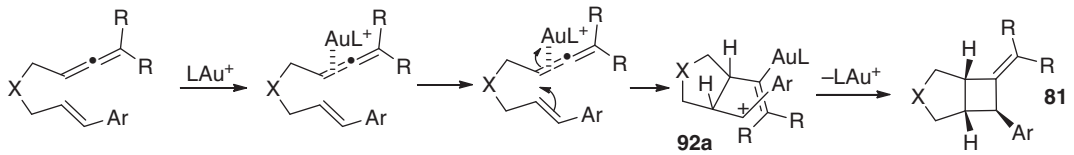
Scheme 90 Gold(I)-catalyzed intramolecular [2 + 2]-cycloaddition reactions of allenes and alkenes.

afford cyclobutanes **81** in 70–92% yields with 54–97% *ee*. A variety of allene-enes containing a styrenyl moiety gave good yields and excellent enantioselectivity (Scheme 91).[83b]



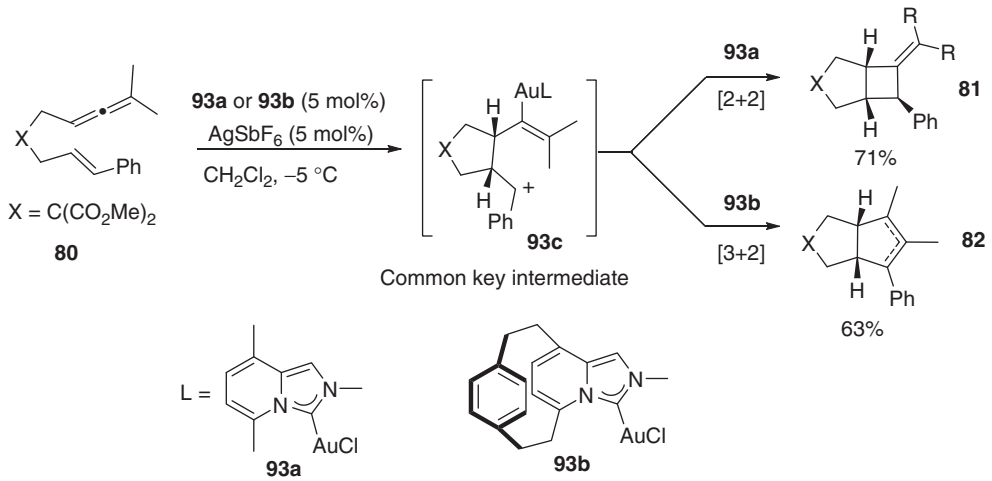
Scheme 91 Gold(I)-catalyzed asymmetric [2 + 2]-cycloadditions.

The proposed mechanism involves the activation of the internal allene double bond by the cationic gold species, which undergoes cyclization to give the benzylic cation **92a** (Scheme 92). A subsequent ring closure through the carbon adjacent to the gold atom provides the final cycloadduct **81**.



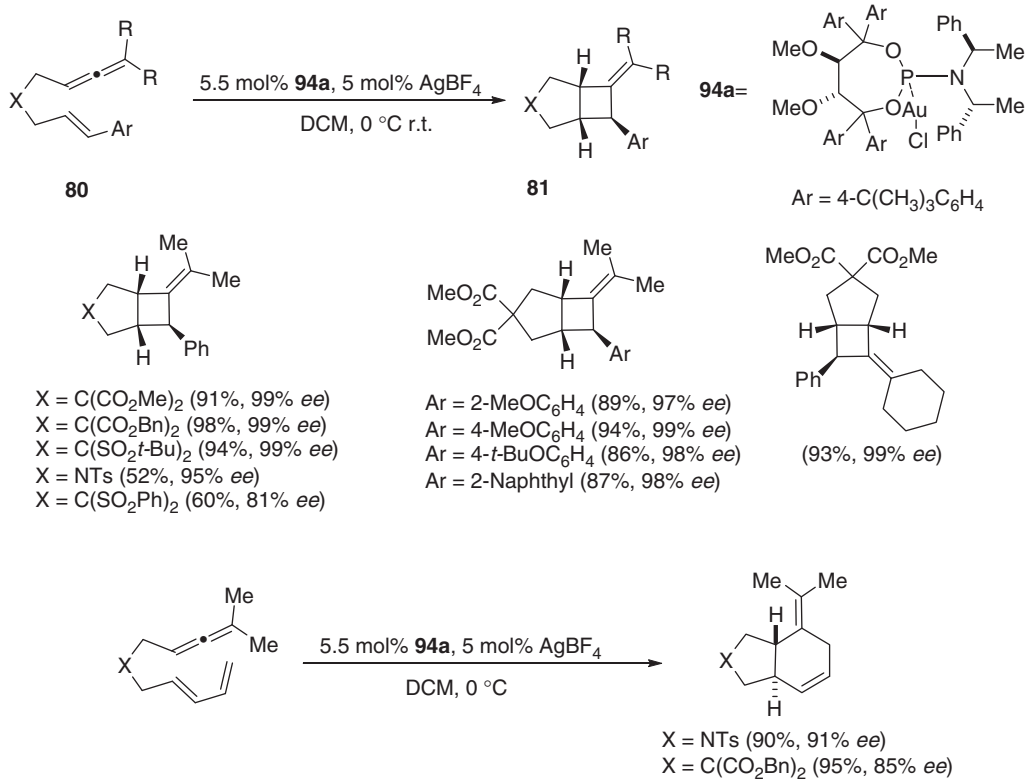
Scheme 92 Proposed mechanism for the intramolecular [2 + 2]-cycloaddition leading to bicycles of type **81**.

More recently, Fürstner et al. observed a remarkable ligand effect on the course of the cycloaddition. For example, an eneallene treated with the more electron-deficient gold catalyst (**93a**) favors the [2 + 2]-cycloaddition product, whereas the electron-rich gold catalyst (**93b**) affords [3 + 2] products.[84] Mechanistically, the reaction proceeds via the formation of a common intermediate **93c** in the presence of gold complex **93a** or **93b** (Scheme 93).



Scheme 93 Ligand effects on the course of gold-catalyzed cycloaddition reactions of ene-allenes.

Very recently, the Fürstner group demonstrated an asymmetric [2 + 2] cycloaddition of ene-allenes in the presence of 5.5 mol% of the phosphoramidite gold complex (**94a**) and 5 mol% of $AgBF_4$ to afford cyclobutanes **81** in good yields with excellent *ee*. The asymmetric cycloadditions occurred at 0 °C to r.t. with outstanding enantioselectivities of up to 99%. The authors studied an effect of remote substituents on the arene part of the TADDOL-type ligand on the enantioselectivity and reaction rate of gold-catalyzed [2 + 2] cycloaddition. Gratifyingly, the *tert*-butyl group has performed well on the enantioselective [2 + 2] cycloaddition and >99% *ee* was obtained. Under similar reaction conditions, a series of ene-allenes containing a substituted styrenyl moiety gave good yields and excellent enantioselectivity (Scheme 94).[85] However, ene-dienes favored asymmetric [4 + 2] cycloadditions in the presence of 5.5 mol% of the phosphoramidite gold complex **94a** and 5 mol% of $AgBF_4$ furnishing the cycloadducts in good to excellent yields with a high enantioselectivity (Scheme 94).[85]



Scheme 94 Gold-catalyzed asymmetric [2 + 2]-cycloadditions of ene-allenes.

5.07.11.4 Indium-Catalyzed Intramolecular [2 + 2] Cycloaddition of Allenes and Alkenes

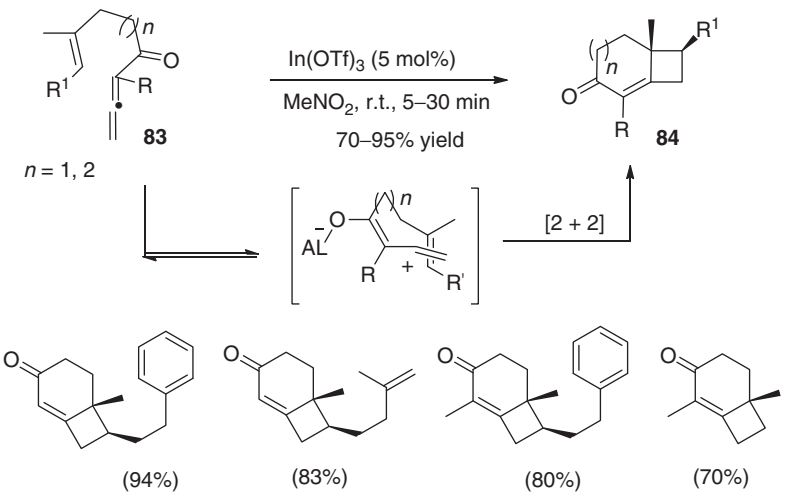
Loh and coworkers have shown that $In(OTf)_3$ is a versatile catalyst for the intramolecular [2 + 2] cycloaddition between a distal allenic double bond and an unactivated alkene. The cycloaddition reactions provide easy access to strained bicyclo[n.2.0] cyclobutenes under very mild reaction conditions with high yields and excellent diastereoselectivities. This reaction probably proceeds via a $[_{\pi}2_s + _{\pi}2_a]$ concerted mechanism, which involves a vinyl-cation resonance structure, as shown in Scheme 95.[86]

To probe the mechanism of this [2 + 2]-cycloaddition, the stereospecificity of the reaction and the steric effects on the alkene motif were examined. Thus, substrates **83a** and **83b** were treated under the standard conditions (Scheme 96). Both **83a** and **83b** with a methylene group on the alkene motif were smoothly transformed to the [2 + 2]-cycloaddition products **84a** and **84b** with excellent yields and diastereoselectivities. Another interesting observation is that the *cis* and *trans* products were obtained almost exclusively from the *Z* and *E* alkenes, respectively, which demonstrated that this is a stereospecific process.

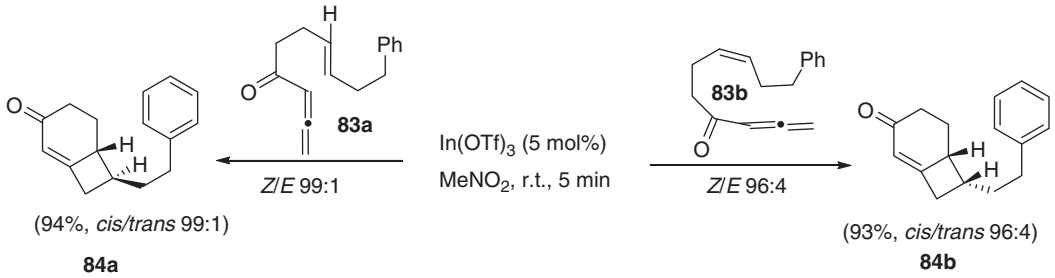
5.07.12 Metal-Catalyzed [2 + 2] Cycloaddition of Imines with Allenes, Alkenes, Allyl Phosphates, and Halides

5.07.12.1 Copper-Catalyzed Intermolecular [2 + 2] Cycloaddition of Imines and Allenes

As described above, alkynes, alkenes, and allenes efficiently participate in the [2 + 2] cycloaddition leading to various four-membered cyclic compounds. However, the cycloaddition of polar unsaturated bonds to give four-membered heterocyclic



Scheme 95 $In(OTf)_3$-catalyzed intramolecular [2 + 2]-cycloadditions between the distal allenic double bond and inactivated alkenes.



Scheme 96 Investigation of stereospecificity and steric effects of indium-catalyzed [2 + 2] cycloadditions.

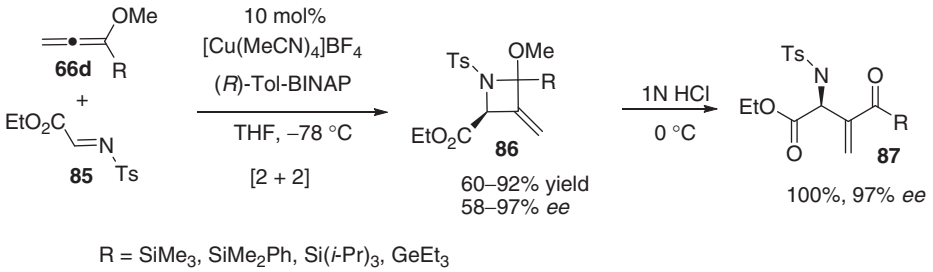
compounds catalyzed by metal complexes are less explored. In this respect, Akiyama et al. reported enantioselective [2 + 2] cycloaddition reactions of 1-methoxyallenylsilanes **66** with α-imino ester **85** in the presence of $[Cu(MeCN)_4]BF_4$/(*R*)-(–)-2,2′-bis(*p*-tolyl-phosphino)-1,1′-binaphthyl ((*R*)-Tol-BINAP) as the catalyst system (Scheme 97).[87] The reaction afforded azetidines **86** in good yields with excellent enantiomeric excess at low temperature. Azetidines **86** were cleanly converted to chiral acylsilanes (**87**) by acid-catalyzed ring opening at 0 °C.

5.07.12.2 Silver-Catalyzed Intermolecular [2 + 2] Cycloaddition of Imines and Alkenes

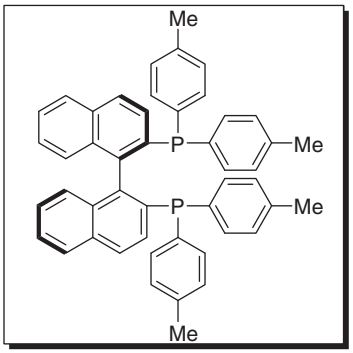
Azetidines are versatile building blocks for a number of naturally occurring products and have attracted much attention due to their unique biological activities.[88] However, the azetidine skeleton has been one of the most difficult amines to synthesize, because of the ring strain. Several methods for the synthesis of azetidines are known. An Ag(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato (fod)) (**98a**) catalyzed [2 + 2] cycloaddition is a simple and efficient method for the synthesis of azetidines from imines with (alkoxymethylene)cyclopropanes (Scheme 98).[89] Various imines performed well. It is important to mention that substrates lacking the *exo*-enol ether group on the cyclopropane ring did not react with the imines under the reaction conditions.

This reaction proceeds through the coordination of the imine nitrogen to the silver catalyst, which certainly enhances the electrophilicity of the imine and hence favors the nucleophilic attack of the carbon–carbon double bond of **21** leading to the *anti*-oriented zwitterion *anti*-**99a**. The latter cyclizes to give azetidine *cis*-**86** or *trans*-**86′** after internal rotation. The *cis* isomer *cis*-**86** is thermodynamically more stable (Scheme 99) and the *trans* isomer can be isomerized to the *cis* product under the reaction conditions.

The utility of the *cis* products was demonstrated by the synthesis of the β-phenylalanine analogue **89**, which is a known biologically active compound.[90] Thus, hydrolysis of *cis*-**86** afforded aldehyde **87** in 86% yield. Subsequent Jones oxidation and removal of the nosyl (Ns) group from **88** gave amino acid **89** (Scheme 100).

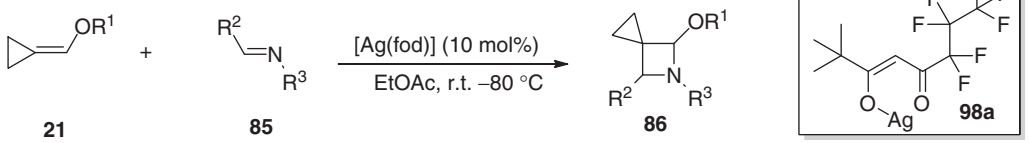


R = $SiMe_3$, $SiMe_2Ph$, $Si(i\text{-}Pr)_3$, $GeEt_3$



(*R*)-Tol-BINAP

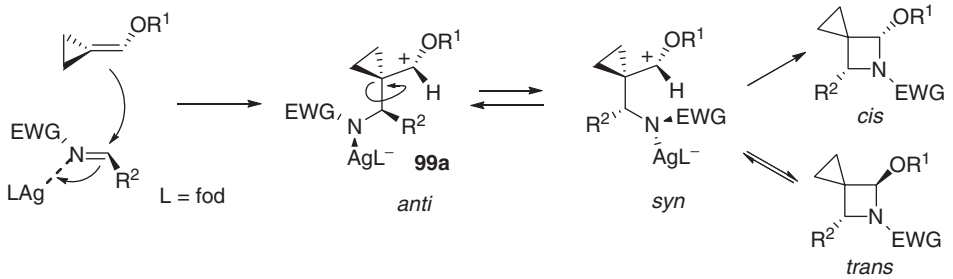
Scheme 97 Enantioselective [2 + 2] cycloaddition reactions of 1-methoxyallenylsilanes with an α-imino ester.



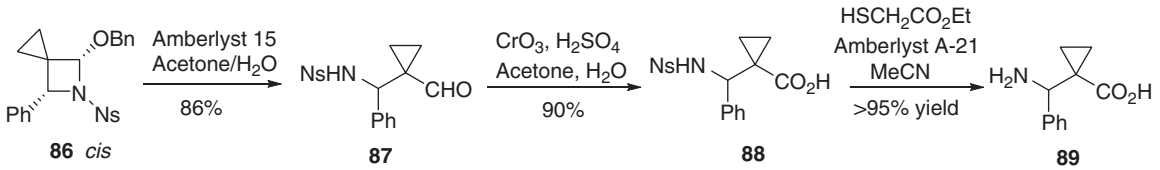
R^1 = Bn, R^2 = Ph, R^3 = Ts (97%, *cis*:*trans* = 51:1)
R^1 = Bn, R^2 = 4-$MeOC_6H_4$, R^3 = Ts (82%, *cis*:*trans* = 24:1)
R^1 = Bn, R^2 = 4-$CF_3C_6H_4$, R^3 = Ts (91%, *cis*:*trans* = 18:1)
R^1 = Bn, R^2 = Ph, R^3 = SO_2Ph (71%, *cis*:*trans* = 28:1)
R^1 = *n*Bn, R^2 = Ph, R^3 = Ts (80%, *cis*:*trans* = 8:1)

(6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyl-3,5-octanedionato)silver

Scheme 98 Silver-catalyzed [2 + 2] cycloadditions of imines with cyclopropanes with an exocyclic enol ether subunit.



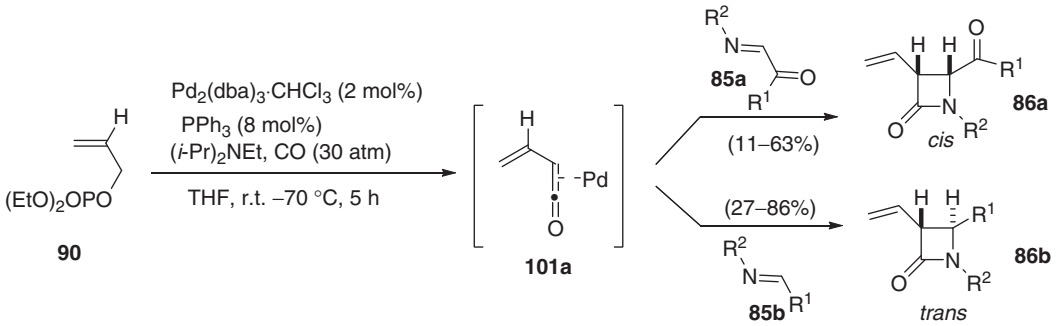
Scheme 99 Proposed mechanism for the formation of azetidines.



Scheme 100 Synthetic application of azetidine **86** to the preparation of a β-phenylalanine analog.

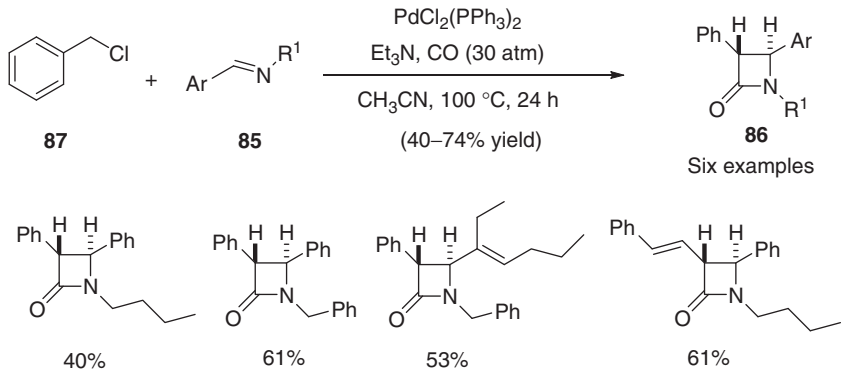
5.07.12.3 Palladium-Catalyzed Carbonylative [2 + 2] Cycloaddition of Imines, Allyl Phosphates, and Halides

Palladium-catalyzed carbonylative [2 + 2] cycloadditions of allyl phosphates with imines under CO pressure lead to either *cis*- or *trans*-β-lactams (**86**) in moderate to high yields.[91] The stereochemical outcome strongly depends on the nature of the imines employed. For example, imines conjugated with a carbonyl such as a ketone or an ester stereoselectively produce *cis*-β-lactams at r.t., whereas imines unconjugated with a carbonyl group exclusively afford *trans*-β-lactams at 70 °C. This reaction was proposed to occur via an enolate of a 3-butenoyl-Pd species **101a** (Scheme 101).



Scheme 101 Pd(0)-catalyzed carbonylative [2 + 2] cycloaddition of allyl phosphates with imines.

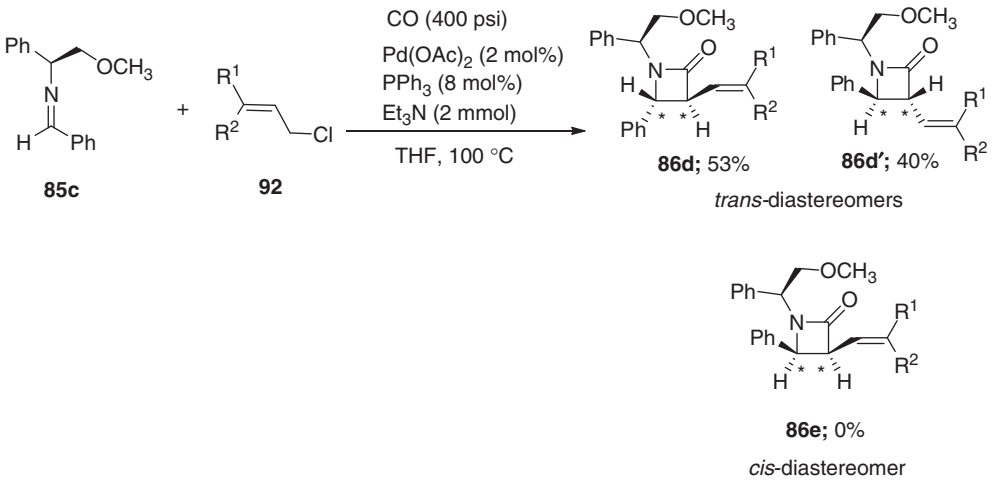
Shim et al. observed that Bn and allyl halides react stereoselectively with imines under CO pressure to give the corresponding β-lactams in good yields when the reaction is catalyzed by $PdCl_2(PPh_3)_2$ (Scheme 102).[92]



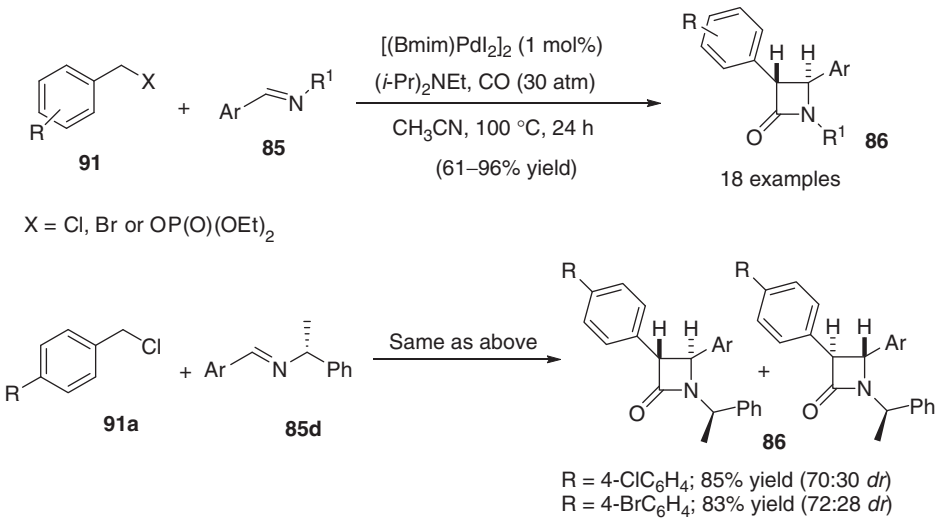
Scheme 102 Pd-catalyzed carbonylative [2 + 2] cycloadditions of benzyl chloride with imines.

The [2 + 2] carbonylative cycloaddition of chiral imines with various allyl halides, under CO pressure, in the presence of a catalyst system comprising $Pd(OAc)_2$, PPh_3, and Et_3N gives chiral alkenyl-β-lactams in good yields with high *trans* diastereoselection (Scheme 103).[93]

Very recently, Huang, Xia, and coworkers reported an efficient synthesis of β-lactams by carbonylative [2 + 2] cycloaddition of Bn chlorides or allyl derivatives with imines catalyzed by a palladium/NHC complex (Scheme 104).[94] The desired β-lactam derivatives were obtained in good to excellent yields (61–96%) with excellent regioselectivity (*trans*/*cis* > 95:5). Under similar reaction conditions, optically active lactams could be obtained in good yields with moderate diastereoselectivity. Bn acetate, carbonate, and sulfonate are not suitable for this carbonylative [2 + 2] cycloaddition.



Scheme 103 Pd-catalyzed carbonylative [2 + 2] cycloadditions of a chiral imine with various allyl halides for the synthesis of β-lactams.



Scheme 104 Synthesis of β-lactams via the carbonylative [2 + 2] cycloadditions of benzyl or allyl chlorides with imines.

5.07.13 Conclusion

In this chapter, we have compiled various metal-mediated, metal-catalyzed, inter- and intramolecular [2 + 2] cycloaddition reactions of alkyne/alkene, alkyne/allene, alkyne/ketone, alkyne/alkyne, alkene/alkene, allene/allene, allene/alkene, and imine/allene pairs, as well as of alkenes, allyl phosphates, and halides. Mechanistically, most of the reactions proceed via metallacyclopentenes or metallacyclopentanes as key intermediates. These reactions are regio- and stereoselective providing an atom- and step-economical method for the synthesis of various highly substituted cyclobutane or cyclobutene rings in good to excellent yields. These reactions are excellent alternatives to the more traditional methods for making four-membered rings. Overall, we believe that this comprehensive chapter will support the synthetic community in further developing the [2 + 2] cycloaddition chemistry and its application to organic synthesis.

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5.08 Thermal and Metal-Induced [3 + 2] Cycloadditions

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Glossary

1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) A representative *N*-heterocyclic carbene.

Distal and proximal bond of methylenecyclopropane The 'distal bond cleavage' means cleavage of C2–C3 bond generating a TMM, whereas the 'proximal bond cleavage' means cleavage of C1–C2 bond.

Trimethylenemethane (TMM) 1,3-Diradical or 1,3-dipole species composed of four carbon atoms containing an *exo*-methylene moiety at the central carbon. TMM and its transition metal complexes have been utilized as a useful three-carbon unit in synthetic chemistry.

Tris(2,2′-bipyrazine)ruthenium(II) ($[Ru(bpz)_3]^{2+}$) A photoredox catalyst that absorbs visible light.

5.08.1 Introduction

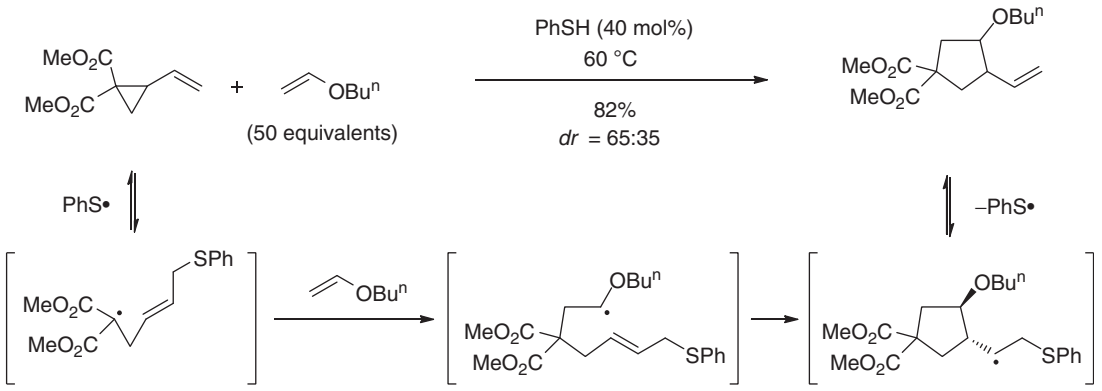
This chapter deals with [3 + 2] cycloaddition and related reactions for the formation of five-membered carbocycles. In contrast to the extensively investigated 1,3-dipolar [3 + 2] cycloaddition reactions for the construction of five-membered heterocyclic compounds, the corresponding all-carbon [3 + 2] cycloadditions were rather limited. In the first edition of this book, thermal and transition metal-catalyzed trimethylenemethane (TMM) cycloaddtions (*see* Chapters 3.1 and 3.2), [3 + 2] cycloadditions of allenylsilanes with electron-deficient alkenes (*see* Chapter 3.2), some cyclopropane-related reactions (*see* Chapter 8.1), and photochemical *meta*-cycloadditions of benzene derivatives (*see* Chapter 5.3) were described.[1] Since then, important developments of these reactions have been made and, more importantly, various new approaches for the [3 + 2] cycloaddition or annulation reactions could be realized based on organo- and transition metal-catalyzed processes. This chapter intends to summarize these new aspects of the all-carbon [3 + 2] cycloaddition reaction, along with recent advances in the chemistry already described in the first edition of this book.

5.08.2 Thermal and Photochemical [3 + 2] Cycloaddition Reactions

5.08.2.1 Radical Reactions

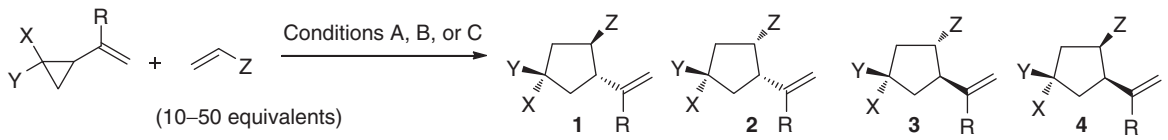
Cyclopropylmethyl radicals are well known to isomerize to homoallyl radicals, which add to alkenes followed by further cyclization onto the alkene moiety generated from the cyclopropane precursors to give cyclopentylmethyl radicals. This reaction can be regarded as a [3 + 2] cycloaddition of a cyclopropane ring with alkenes, but it is necessary to devise a system which enables efficient control over the reactivity of the highly reactive intermediates. Several methods to realize such reactions were reported; one common method is the addition of a thiyl radical to vinylcyclopropanes. In the original studies, the necessary thiyl radical

was generated by photoirradiation of a disulfide in the presence of 2,2′-azodiisobutyronitrile (AIBN) or simply by heating a mixture of the substrates with benzenethiol. Addition of this radical to the olefinic moiety of a vinylcyclopropane generates cyclopropylmethyl radicals, which undergo smooth ring opening to give butenyl radicals. These radicals then undergo addition to the alkenes followed by radical cyclization to give cyclopentylmethyl radicals, which finally eliminate the thiyl radical to give the [3 + 2] cycloadducts (Scheme 1).[2] It is necessary to employ 2-substituted vinylcyclopropanes, such as vinylcyclopropyl ethers or vinylcyclopropanecarboxylates, which generate substituted radicals stabilized by these groups. As a 2π unit, both electron-rich and -deficient alkenes along with electron-deficient alkynes were employed in large excess, although the efficiency of the reaction was dependent on the combination of the electronic nature of the substituents. In general, the diastereoselectivity of the reaction was not very good, but in some cases improvements were observed by adding a Lewis acid (Table 1).[3a,b] By using 2,2-dihalovinylcyclopropanes as the substrates, the diastereoselectivity of the products was improved in favor of the 3,4-*cis* isomer, although the reaction with electron-rich alkenes became less efficient.[3c]



Scheme 1

Table 1 Phenylthio radical-catalyzed [3 + 2] cycloadditions of vinylcyclopropanes and alkenes



X	*Y*	*Z*	*R*	*Conditions*	*Yield (%)*	***1***	:	***2***	:	***3***	:	***4***	*References*
CH_2Ph	H	CO_2Me[a]	H	A	70	2.9		1.9		1.0		3.8	3a
OCH_2Ph	H	OCOMe	H	A	39	2.3		1.9		1.0		3.4	3a
$OSiBu^tMe_2$	H	CO_2Me	H	A	78	3.8		2.3		5.1		1.0	3a
$COOBu^t$	H	OBu^n	H	A	94	6.1		1.4		1.3		1.0	3a
$COOBu^t$	H	OBu^n	H	B	75	14.2		2.0		2.2		1.0	3a
$COOBu^t$	H	$COOBu^t$	H	A	53	4.4		1.2		1.0		1.9	3a
$COOBu^t$	H	OBu^n	Me	A	53	4.2		1.4		1.0		1.1	3a
COOMe	COOMe	$OSIMe_3$	H	C	65			(81:19)[b]					2b
COOMe	COOMe	COOMe	H	C	38			(76:24)[b]					2b
COOMe	COOMe	*n*-C_5H_{11}	H	C	54			(69:31)[b]					2b
Cl	Cl	CO_2Me	H	A	57			(*cis*:*trans* = 7.8:1)					3c
Br	Br	CO_2Me	H	A	74			(*cis*:*trans* = 9:1)					3c

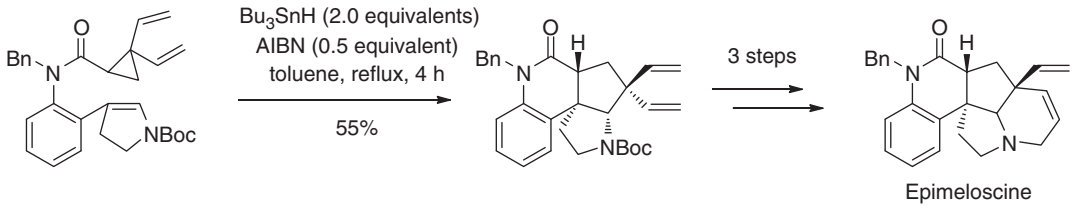
[a]1 equivalent.

[b]Stereochemistry not determined.

Conditions A: 0.05–1 equivalent PhSSPh, 0.01–1 equivalent AIBN, hν, benzene, 80 °C; Conditions B: 1 equivalent PhSSPh, 0.2 equivalent AIBN, 0.8 equivalent Me_3Al, hν, toluene, −25 °C; Conditions C: 40 mol% PhSH, 60 °C.

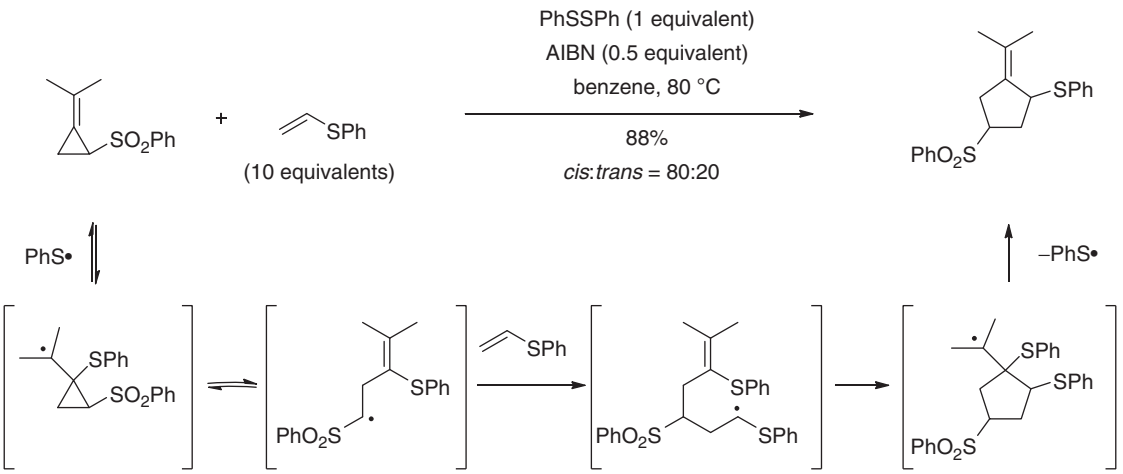
A related tin-mediated intramolecular reaction was applied to the construction of the tetracyclic core of epimeloscine (Scheme 2).[3d]

As another mode of addition of a thiyl radical to generate cyclopropylmethyl radicals, the reaction of 2-(phenylsulfonyl)methylenecyclopropanes or methylenecyclopropanecarboxylates with simple or electron-rich alkenes gave methylenecyclopentenes in



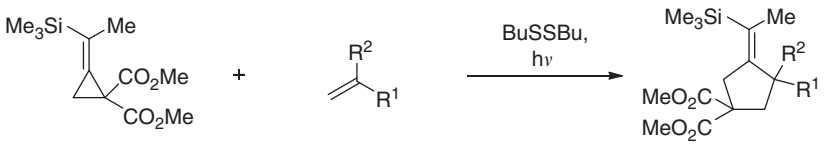
Scheme 2

good yield (Scheme 3).[4–c] The reaction of [(trimethylsilyl)methylene]cyclopropanedicarboxylates with electron-rich alkenes gave functionalized methylenecyclopentanes in good yield (Table 2).



Scheme 3

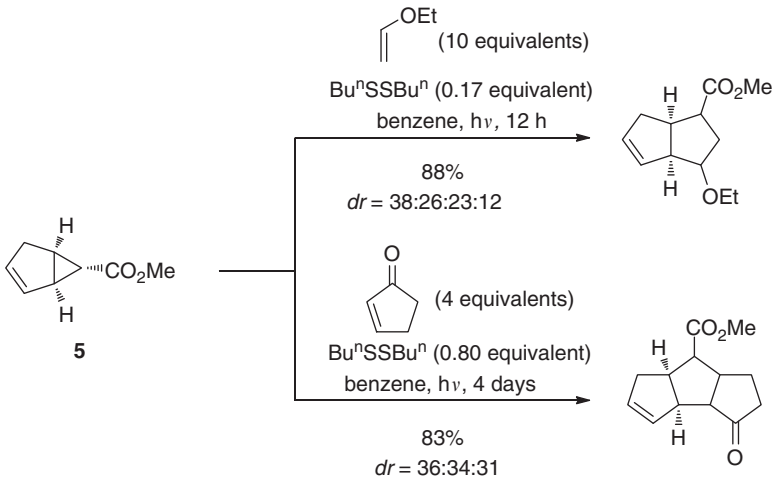
Table 2 [3 + 2] Cycloadditions of electlon-rich alkenes with [(trimethylsilyl)methylene]cyclopropanedicarboxylates



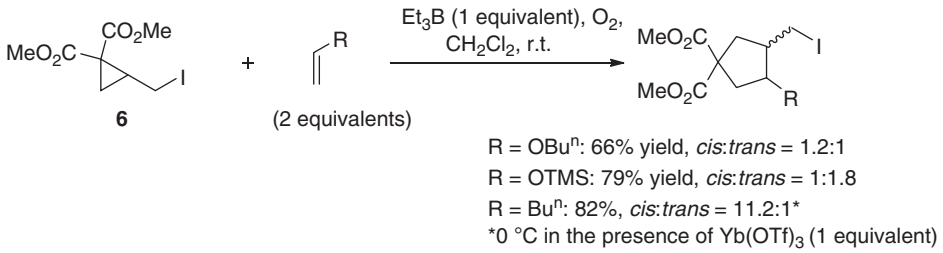
R^1	R^2		*BuSSBu*	*Yield (%) (E:Z)*
$-(CH_2)_5-$		(5.4 equivalents)	0.4 equivalent	81 (95:5)
SPh	H	(3.0 equivalents)	0.2 equivalent	61 (72:28)
$OSiMe_3$	Me	(1.8 equivalents)	0.25 equivalent	64 (single isomer)

By using bicyclo[3.1.0]hex-2-ene-6-carboxylate **5** as the vinylcyclopropane partner, the reaction with various kinds of alkenes in the presence of di(*n*-butyl) disulfide under photoirradiation conditions gave diquinane or triquinane derivatives in good yields (Scheme 4).[5]

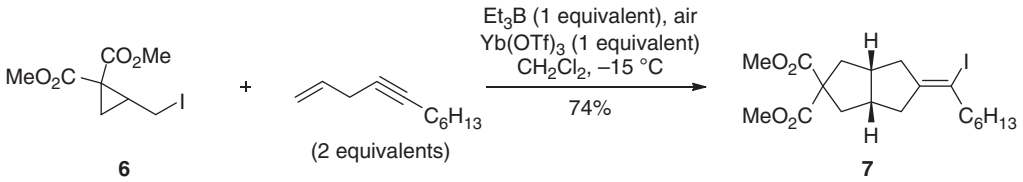
In addition to the thiyl radical addition to vinylcyclopropane derivatives, iodine atom-transfer [3 + 2] cycloadditions were achieved using 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **6** as the precursor of the cyclopropylmethyl radical. The reaction with electron-rich alkenes proceeded smoothly in the presence of Et_3B under O_2 atmosphere, whereas simple alkenes gave good yields of the products in the presence of an equimolar amount of $Yb(OTf)_3$, which was thought to increase the electrophilicity of the generated bis(methoxycarbonyl)methyl radical (equation 1). A one-step construction of bicyclo[3.3.0]octane skeleton **7** could be achieved based on this protocol using dienes or enynes as radical acceptor (equation 2).[6]



Scheme 4



(1)



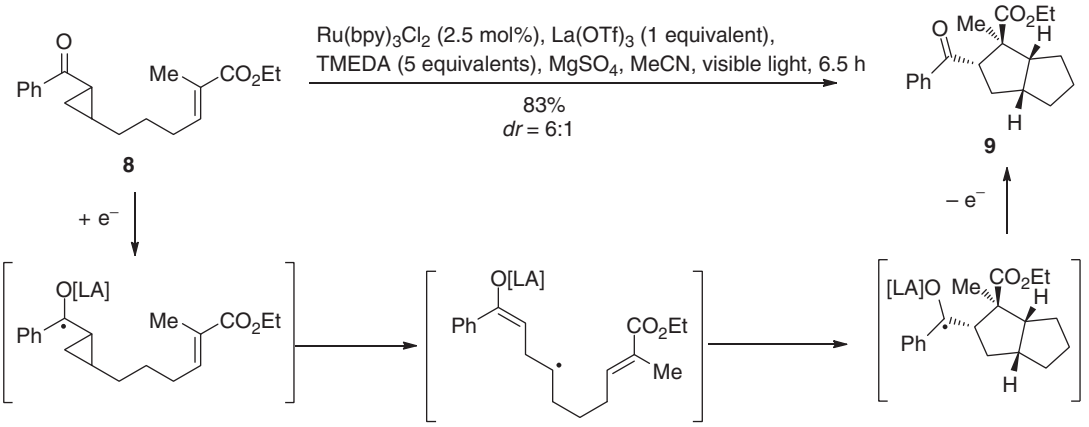
(2)

Recently, two related methods for the generation of cyclopropylmethyl radicals were devised for the intramolecular [3 + 2] cycloaddition reaction.[7] One consists in the one-electron reduction of cyclopropyl aryl ketones **8** to the corresponding radical anions, which was accomplished using a photocatalytic system composed of $Ru(bpy)_3Cl_2$, $La(OTf)_3$, and tetramethylethylenediamine (TMEDA). Radical anions of cyclopropyl aryl ketones **8** were generated by one-electron transfer from the $Ru(bpy)_3^+$ on visible light irradiation, which underwent ring opening followed by sequential intramolecular radical additions to give cyclized ketyl radicals, which, on loss of an electron, gave the formal intramolcular [3 + 2] cycloaddition products **9**. Use of $La(OTf)_3$ for the activation of cyclopropyl ketones was essential for the success of the reaction (Scheme 5).[7a]

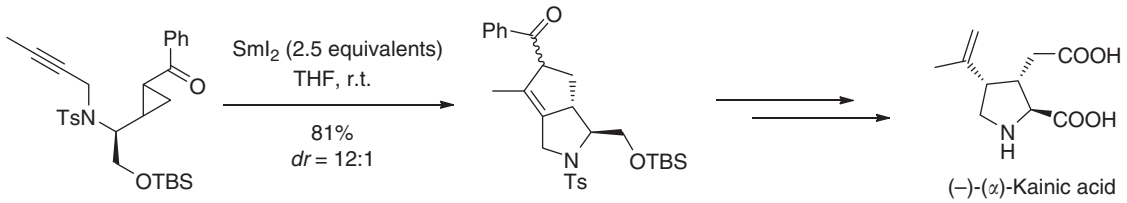
A similar ketyl radical was generated by SmI_2-mediated reduction of cyclopropyl phenyl ketone **10**. A subsequent diastereoselective intramolecular cycloaddition reaction afforded a key intermediate for the synthesis of (–)-(α)-kainic acid (Scheme 6).[7b]

Radical cations of cyclopropylamines also undergo ring opening to give β-imino radicals, which react with alkenes in a [3 + 2] cycloaddition manner to give cyclopentylamine derivatives. Ceric ammonium nitrate (CAN)-mediated one-electron oxidation of tertiary cyclopropylbenzylamines **11** generated γ-imino radicals, which underwent tandem cyclization to give the debenzylated bicyclic amines **12**. The reaction proceeded with either electron-rich or -deficient alkenes in *N*,*N*-dimethylformamide (DMF) at room temperature (Table 3).[8]

A visible light-mediated intermolecular [3 + 2] cycloaddition of *N*-arylcyclopropylamines with alkenes was achieved using $Ru(bpz)_3(PF_6)_2$ as a photocatalyst. Photoirradiation of mono- or bicyclic *N*-arylcyclopropylamines and styrene derivatives or acrylonitrile in the presence of 2 mol% of $Ru(bpz)_3(PF_6)_2$ using a fluorescent light bulb at room temperature gave the corresponding cyclopentylamine derivatives in good yield. The diastereoselectivity of the monocyclic cyclopropylamines was low, but bicyclic derivatives showed moderate selectivity (Scheme 7). The reaction proceeded in a similar manner as in the above photocatalyzed ketyl radical reaction.[9]

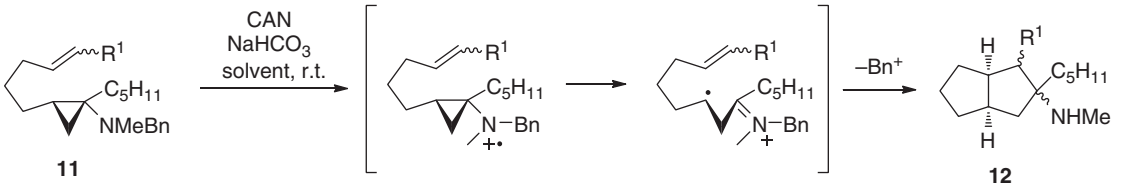


Scheme 5

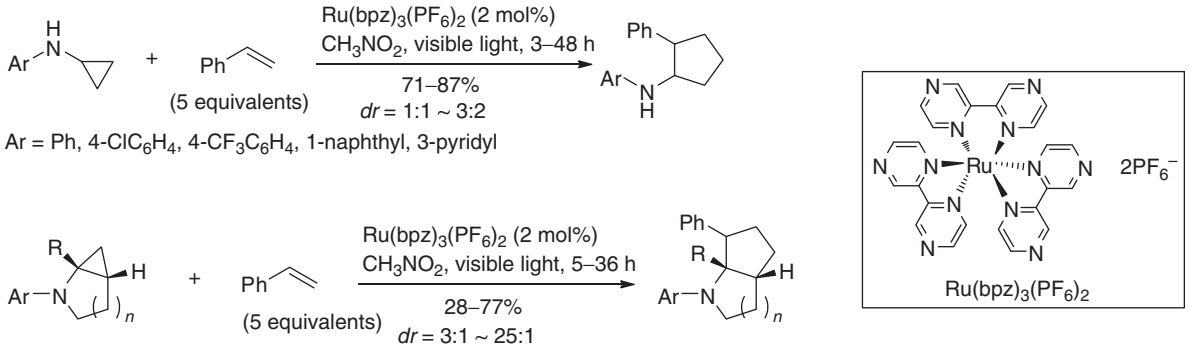


Scheme 6

Table 3 Ceric ammonium nitrate-mediated [3 + 2] cycloaddition of tertiary cyclopropylbenzylamines



R^1	*Solvent*	*Yield (%) (dr)*
OMe	MeOH–THF (5:1)	43 (5.2:2.3:1.3:1)
CO_2Et (*E*-isomer only)	DMF	77 (6:1)

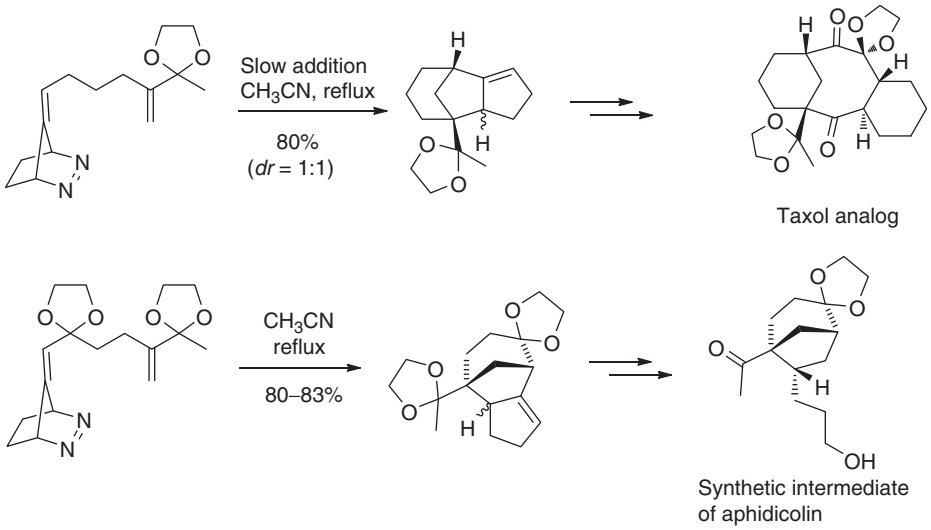


Scheme 7

5.08.2.2 TMM Chemistry

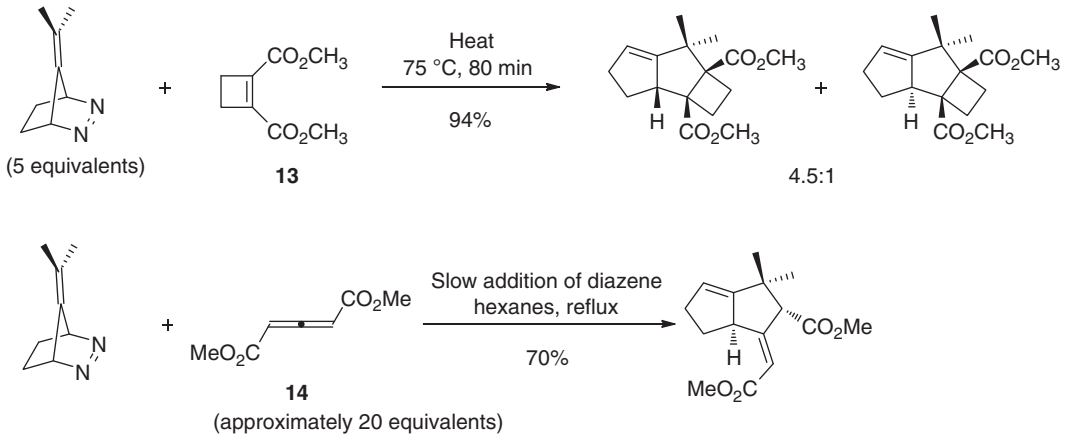
TMM has continued to be a useful three-carbon unit for [3 + 2] cycloaddition reactions. The basic approaches for the generation of TMMs have been categorized mainly into two types, that is, thermal and transition metal (mainly Pd)-catalyzed reactions, each of which is further categorized into several kinds of reactions. This section describes the recent development of thermal reactions since the first edition of this book.[1a,10] The transition metal-catalyzed reactions will be treated in Section 5.08.4.2.1.

Since the first edition of this work, several applications of TMMs, generated from diazenes under thermal conditions, to natural product synthesis, have been reported with an emphasis on the regio- and stereo-selectivity of the reaction. Owing to the competitive dimerization of diyls, most of the examples are intramolecular reactions, which enable the concise construction of synthetically useful polycyclic frameworks. Some representative examples are shown below with the key [3 + 2] cycloaddition step (Scheme 8).[11]



Scheme 8

Intermolecular [3 + 2] cycloadditions were achieved by using highly electron-deficient alkenes **13** or allenes **14**. The former reaction was applied to the preparation of bicyclo[n.3.0] systems by a cycloaddition-fragmentation sequence (Scheme 9).[12] Mechanistic studies suggested that the diyls generated from diazenes have a character of 'dipolar diradical' as they could be trapped either with water or with 1,4-cyclohexadiene.[13]

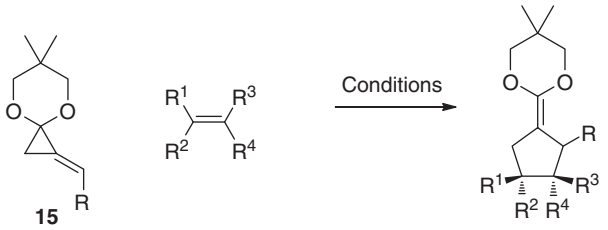


Scheme 9

Another method for the generation of TMM utilizes methylenecyclopropane derivatives as precursors. The character of the generated TMM differs considerably depending on the kind of substituent on the chosen substrate. For example, TMMs generated from simple methylenecyclopropane derivatives show a diradical character like diyls, which are difficult to trap intermolecularly because of insufficient equilibrium concentration and short life time. In contrast, dialkoxy-substituted methylenecyclopropane derivatives generate an electron-rich TMM, which shows zwitterionic character and is sufficiently stable to undergo nucleophilic

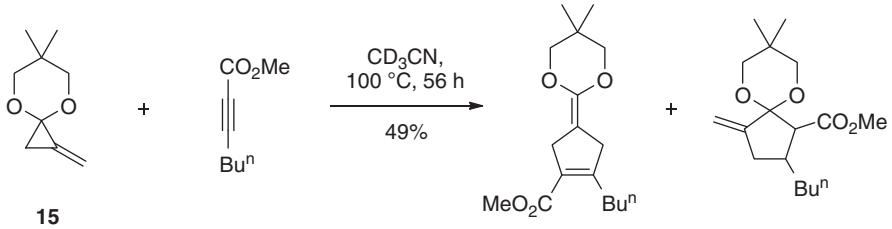
addition or single-electron transfer to electron-deficient alkenes to give [3 + 2] cycloaddition products.[14a] For example, treatment of cyclopropane **15** (R = H), which was prepared from 1,3-dichloro-2-propanone acetal in a few steps and could be stored for a long time, with various electron-deficient alkenes gave the [3 + 2] cycloaddition products by heating the mixture in acetonitrile. A variety of alkenes substituted with a single-electron-withdrawing group (EWG) reacted at 70–80 °C to give ketene acetals of cyclopentanecarboxylates in high yields, in which the geometry of the alkenes was transferred to the stereochemistry of the products, thus suggesting a concerted nature of the reaction.[14b] When a substituted dialkoxymethylenecyclopropane was employed as the substrate, high *endo*-selectivity was attained by carrying out the reaction in nonpolar solvents (Table 4).[14c]

Table 4 Trimethylenemethanes (TMMs) from dialkoxy-substituted methylenecyclopropanes



R	R^1	R^2	R^3	R^4	*Conditions*	*Yield (%)*	*dr*	*References*
H	H	H	Me	COOMe	CH_3CN, 80 °C	91	–	14b
H	Bu^n	H	H	COOMe	CH_3CN, 70 °C	89	–	14b
H	H	Bu^n	H	COOMe	CH_3CN, 70 °C	86	–	14b
Me	H	COOMe	H	COOMe	Octane, 80 °C	77	97:3 (β-R:α-R)	14c
Me	H	COOMe	H	COOMe	CH_3CN, 80 °C	78	80:20(β-R:α-R)	14c
Me	H	H	Me	COOMe	Toluene, 100–120 °C	72	1:1(β-R, alkene regioisomer)	14c
Pr^i	Me	H	H	COOMe	CD_3CN, 100–120 °C	71	96:4(β-R, alkene regioisomer)	14c

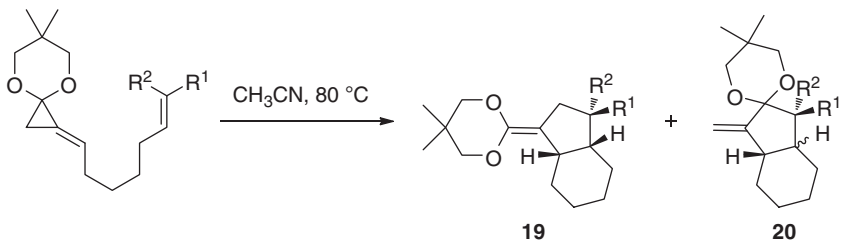
Electron-deficient alkynes also reacted as a 2π unit to give ketene acetals **16** as the major products along with small amounts of methylenecyclopentanes **17**, although alkynes were found less reactive than alkenes and needed higher reaction temperatures (equation 3).[14d]



(3)

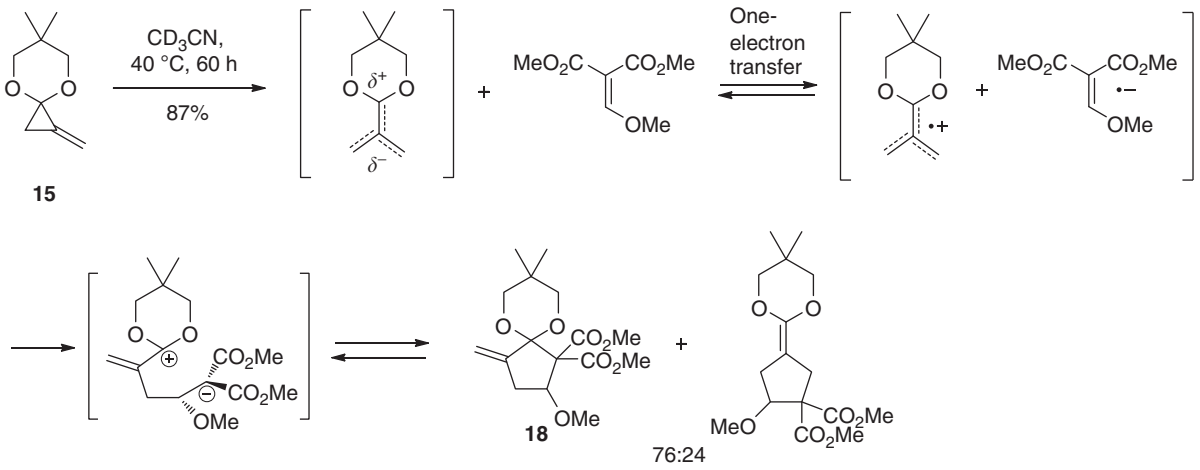
Interestingly, when highly electron-deficient alkenes were employed as substrates, stepwise [3 + 2] cycloadditions occurred to give predominantly the regioisomeric α-alkylidene acetals **18**. The reaction was proposed to proceed through single-electron transfer from the TMM to the electron-deficient alkenes to generate radical ion pairs, which undergo intermolecular radical coupling followed by ring-closure to give the products (Scheme 10).[14e]

The stereochemistry of the intramolecular reaction was shown to be controllable by the choice of the olefinic substituent, owing to the concerted or stepwise nature of the [3 + 2] cycloaddition reaction (equation 4). Monoester derivatives gave ketene acetals **19** selectively as single stereoisomers through a concerted reaction pathway, whereas diesters gave α-alkylidene acetals **20** as a major product as a mixture of stereoisomers.[14f]



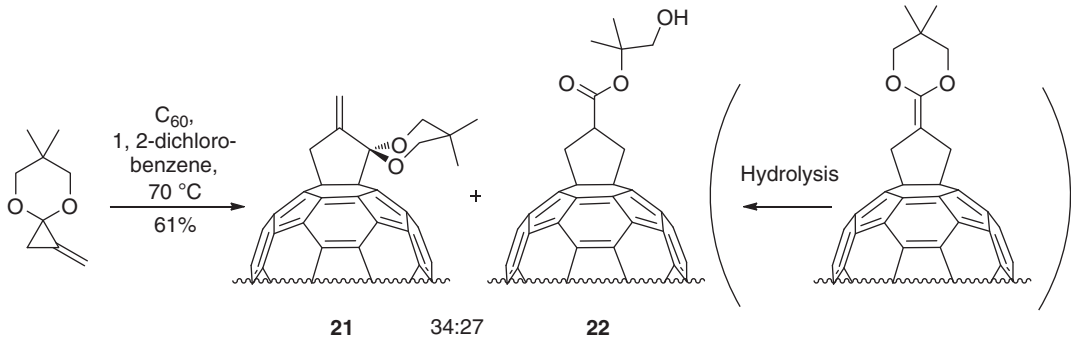
(4)

R^1 = COOMe, R^2 = H: 76% (**19**:**20** = 100:0), **19**: single isomer
R^1 = COOMe, R^2 = COOMe: 81% (**19**:**20** = 36:64), **20**: 17:83



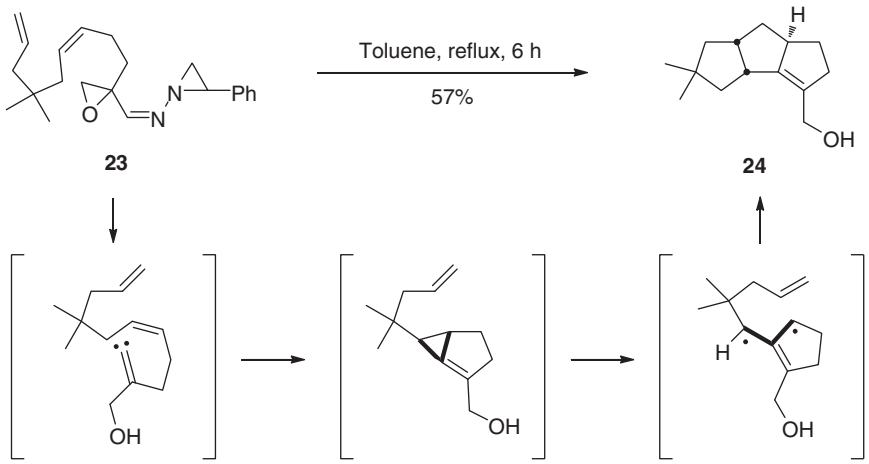
Scheme 10

The [3 + 2] cycloaddition reaction of 1,1-dialkoxymethylenecyclopropane with C_{60} furnished a mixture of the *exo*-methylene product **21** and hydrolyzed ketene acetal **22** in 34 and 27% yield, respectively, after silica gel chromatography. The *exo*-methylene product **21** was isomerized to the ketene acetal by heating at higher temperature (equation 5).[14g,h]



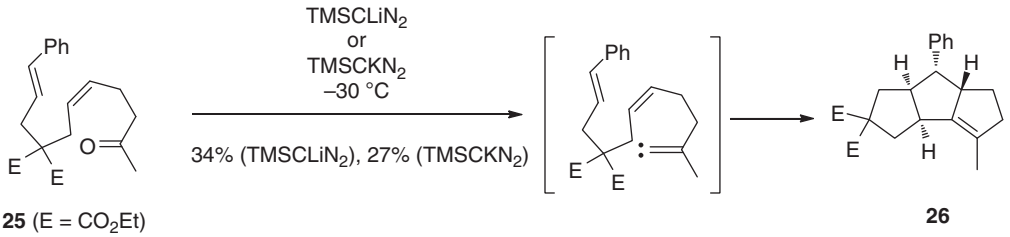
(5)

Several other useful methods for the preparation of methylenecyclopropanes as precursors of TMM have been developed. Most of them utilize intramolecular cyclopropanations of alkenes with vinylidene carbenes, that can be generated by several different methods. For example, the thermal decomposition of epoxyaziridinylimines was utilized to generate vinylidenes, which underwent intramolecular cyclopropanation to give methylenecyclopropanes. On heating in toluene at 110 °C, epoxyaziridinylimine **23** generated TMM diyl to give the intramolecular [3 + 2] cycloaddition product **24** in reasonable yields (**Scheme 11**). Based on this methodology, triquinanes could be prepared in a single operation starting from linear substrates.[15a]



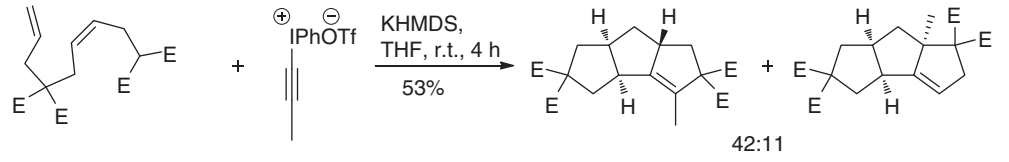
Scheme 11

The reaction of ketones with the anion of trimethylsilyl (TMS)-diazomethane also generated alkylidenes under mild conditions. Treatment of an appropriate dienone, such as **25** with the lithium or potassium enolate of TMS-diazomethane at − 30 °C to room temperature gave the triquinane derivatives **26** in moderate yield through TMM diyl intermediates (equation 6).[15b]

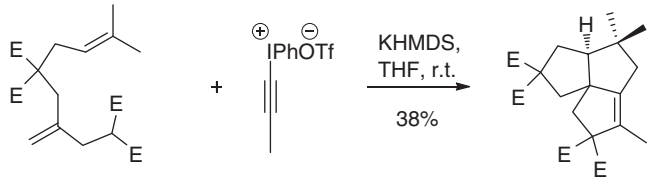


25 (E = CO_2Et) **26** (6)

The addition of nucleophiles to alkynyliodonium compounds is another method for the generation of vinylidenes. Active methylene compounds containing olefinic moieties added to the propynyliodonium salt **27** in tetrahydrofuran (THF) at room temperature gave polycyclic compounds in moderate yields through vinylidene generation, cyclopropanation, TMM diyl generation, and [3 + 2] cycloaddition. All the sequences proceeded at room temperature; either linearly fused or angularly fused triquinanes **28**, **29** were prepared on appropriate choice of the substrates (equations 7 and 8).[15c–f]

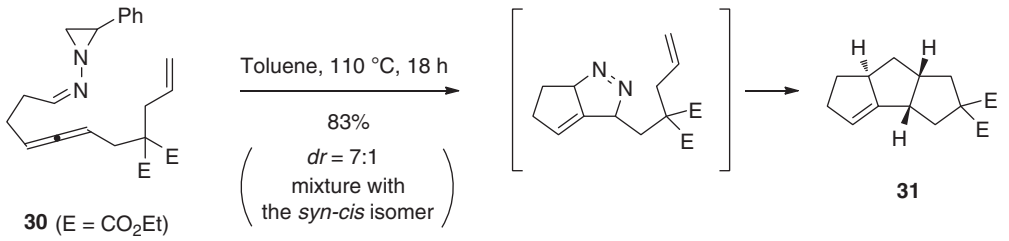


(E = CO_2Et) **27** **28** (7)

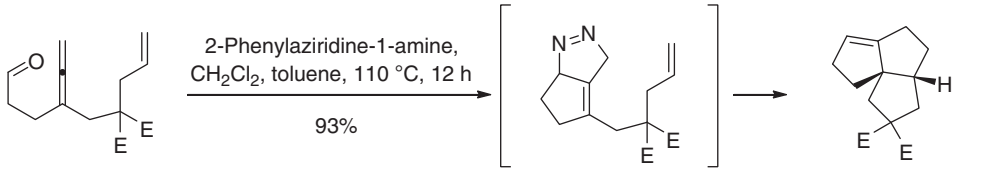


(E = CO_2Et) **27** **29** (8)

The reaction of diazo compounds with allenes can also generate TMM diyls. Thermal reaction of the 1,3-disubstituted allene **30** containing an appropriately arranged diazo precursor gave good yields of the triquinane derivative **31** (equation 9). Treatment of 1,1-disubstituted allenyl carbonyl compounds **32** with 2-phenylaziridin-1-amine or tosylhydrazine in toluene at 110 °C gave angularly fused triquinanes **33** in good yields (equation 10).[15g,h]

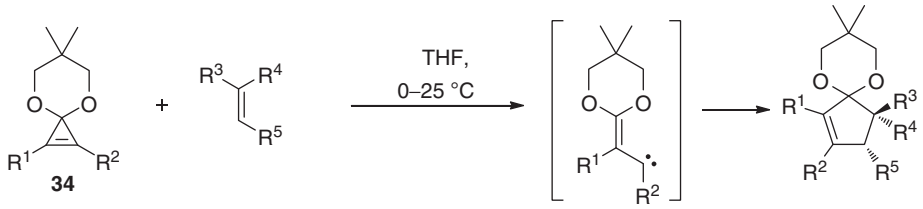


30 (E = CO_2Et) **31** (9)



32 (E = CO_2Et) **33** (10)

A seemingly related [3 + 2] cycloaddition reaction of cyclopropenone acetals with alkenes is briefly described here. The reversible thermal generation of π-delocalized singlet vinylcarbenes from cyclopropenone acetals and subsequent [3 + 2] cycloaddition with electron-deficient alkenes under mild conditions was described in the first edition of this book (*see* Chapter 3.1). Thereafter, the reactivity of various substituted cyclopropenone acetals was examined and the reaction with highly electron-deficient alkenes was found to proceed even below room temperature by using phenylthio- or alkoxycarbonyl-substituted substrates of type **34** (equation 11).[16a]



34 (11)

R^1 = Et, R^2 = SPh, R^3 = R^4 = CN, R^5 = Ph: 64%
R^1 = Ph, R^2 = $COOPr^i$, R^3 = COOMe, R^4 = CN, R^5 = OMe: 78%*
*Stereochemistry of the product was not assigned.

The reaction with C_{60} gave the corresponding [3 + 2] cycloaddition product in moderate yields when 2-ethylcyclopropenone acetal was employed as the substrate. Double cycloaddition was also realized by using a new reagent containing two tethered cyclopropenone acetal units (equation 12).[16b–d]

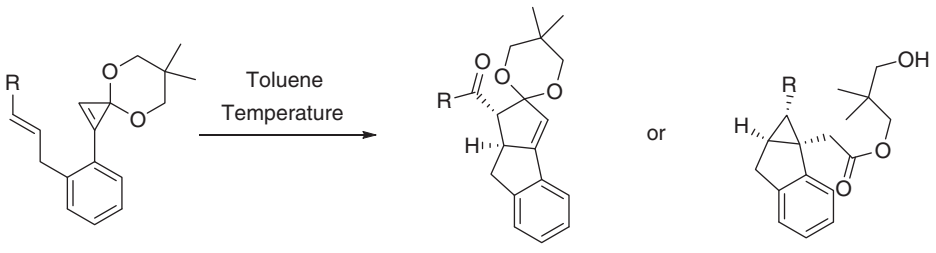


(12)

A, A = 2, 2-dimethylpropane-1,3-diyl acetal

The reaction was further extended to the intramolecular version. Substrates bearing an aldehyde- or ketone-substituted electron-deficient alkene and an aryl-cyclopropenone acetal moiety built into the linking tether gave the desired products in good yield under mild reaction conditions. Less activated substrates bearing an ester- or nitrile-substituted alkene provided the corresponding [2 + 1] cycloadduct of a singlet π-delocalized vinyl-carbene at lower temperature (80–100 °C); the same reaction at higher temperature (170–180 °C) gave the [3 + 2] cycloadducts formed by vinylcyclopropane rearrangement of the intermediate [2 + 1] cycloadducts (**Table 5**).[17]

Table 5 Intramolecular [3 + 2] cycloaddition of cyclopropenone acetals

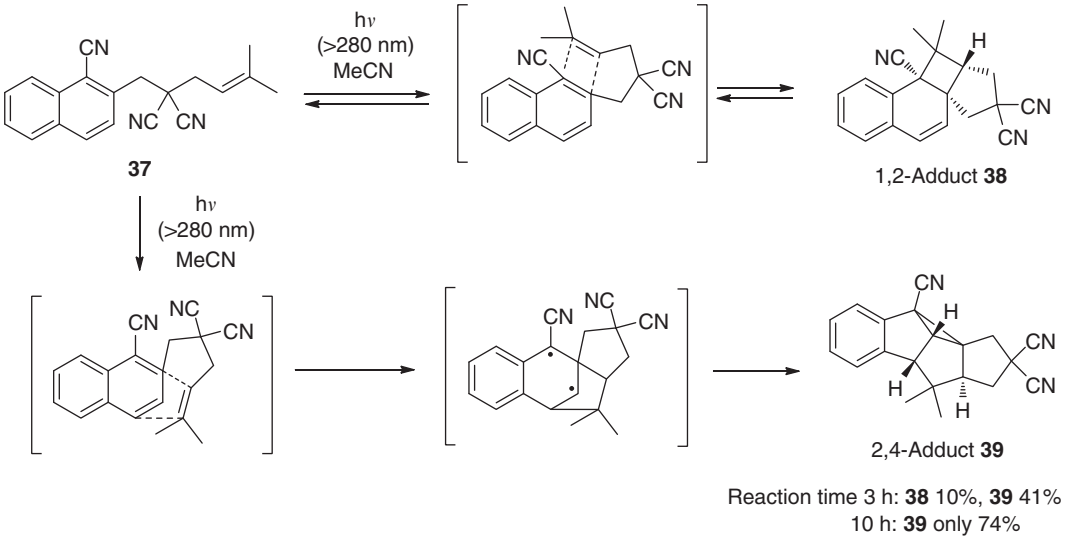


35 **36**

R	*Temperature*	*Yield (%)*
CHO	80 °C (12 h)	**35**:70
COMe	100 °C (8 h)	**35**:77
CN	80 °C (16 h)	**36**:94
CN	170 °C (8 h)	**35**:72 (*dr*=5:2)
CO_2Et	80 °C (16 h)	**36**:95
CO_2Et	170 °C (8 h)	**35**:80 (*dr*=7:1)

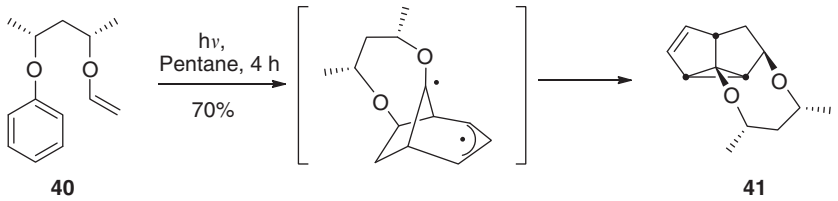
5.08.2.3 Photochemical [3 + 2] Cycloaddition Reactions

Photochemical [3 + 2] cycloaddition reactions of a benzene ring with alkenes (*meta*-cycloaddition) were treated extensively in the first edition of the book.[1c,18] Since then, some advances have been made for this reaction (*see* Chapter 5.15). For example, naphthalene was found to be a good substrate of intramolecular [3 + 2] cycloaddition with alkenes. Irradiation of 1-cyano-2-(4-pentenyl)naphthalene derivatives **37** through a pyrex filter (> 280 nm) afforded the products in good yield. Interestingly, the reaction initially gave [2 + 2] cycloadducts **38**, but prolonged irradiation afforded the [3 + 2] cycloadducts **39** selectively, suggesting that the initial [2 + 2] cycloaddition reaction is reversible (**Scheme 12**).[19]



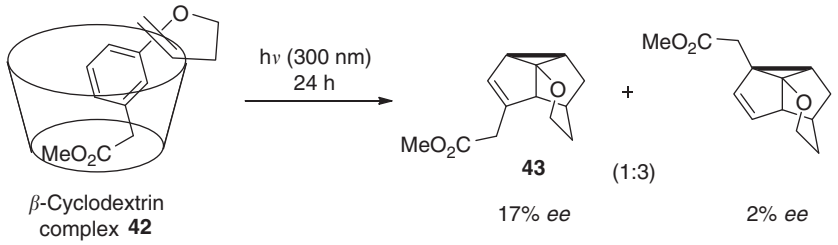
Scheme 12

Photoirradiation of substrate **40** having phenyl and vinyl groups connected by a chiral 2,4-pentanediol tether was found to give the corresponding [3 + 2] cycloadduct with high diastereoselectivity. Removal of the tether afforded an optically active bicyclo[3.2.1]octane derivative (equation 13).[20]



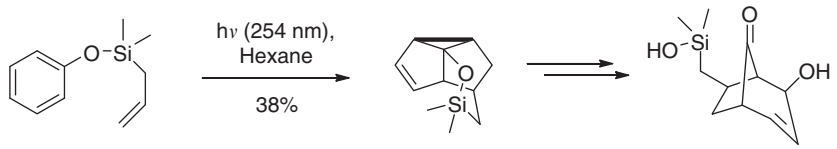
(13)

Asymmetric induction was examined using *β*-cyclodextrin complexes of phenoxyalkenes. Irradiation (300 nm) of the solid cyclodextrin complexes of substituted phenyl butenyl ethers **42** gave the corresponding [3 + 2] cycloadducts **43** in up to 17% *ee* (equation 14). Although the selectivity of the reaction was low, this is a unique example of an enantioselective *meta*-cycloaddition reaction.[21]



(14)

One serious drawback of this transformation is the formation of several isomeric [3 + 2] cycloadducts (*see* Chapter 5.03). Partial control could be achieved by carrying out the reaction intramolecularly as described above. The use of temporary tethers, in particular silicon tether, was studied for this purpose. For example, a silicon-tethered intramolecular *meta*-cycloaddition gave a photoadduct, which was further transformed into a model for the gelsemine skeleton (equation 15).[22]

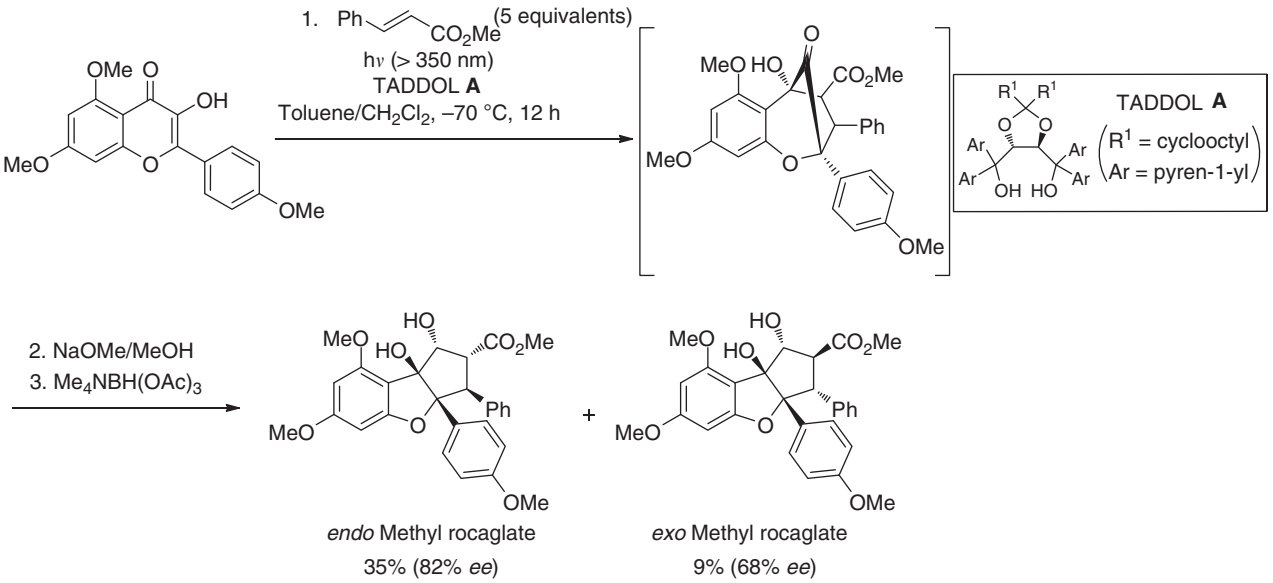


(15)

Some applications of the intramolecular variant to the synthesis of polycyclic natural or unnatural products are shown in Table 6.[23]

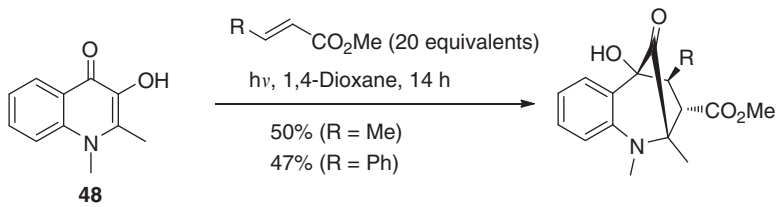
Oxidopyrylium salts usually undergo [5 + 2] cycloaddition with alkenes; however, oxidopyryliums generated photochemically from 3-hydroxyflavones by excited-state intramolecular proton transfer were found to give [3 + 2] cycloadducts with cinnamates as a biomimetic approach toward rocaglamides. Irradiation (> 350 nm) of 3-hydroxyflavone **44** in the presence of cinnamate gave a mixture of the *endo* [3 + 2] cycloadduct **45** and [2 + 2] cycloadduct **46**. Interestingly, an equilibration of these two products was observed during silica gel purification. Another product **47** was also obtained, which derives from the *exo* [3 + 2] cycloadduct by an acyloin rearrangement (Scheme 13).[24a]

An enantioselective version of this reaction was realized using α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL) derivatives as chiral Brønsted acids and was applied to the synthesis of rocaglates and other natural products (equation 16).[24b–g]



(16)

A similar reaction proceeded with 3-hydroxyqunolinones **48** (equation 17).[24h]

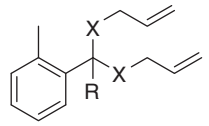
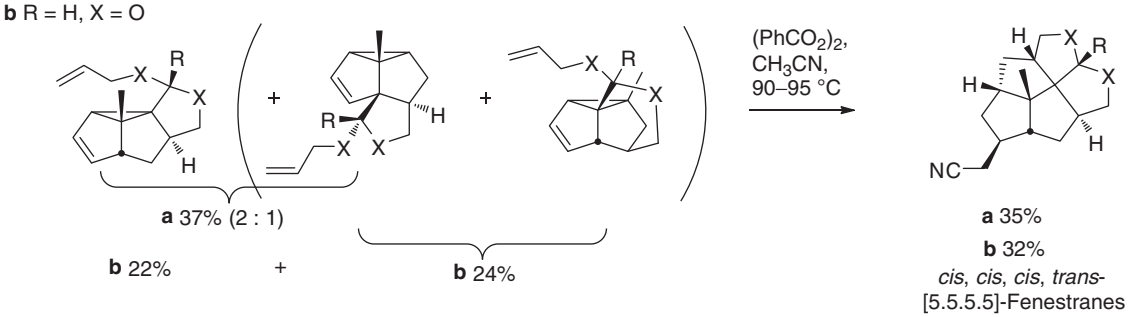
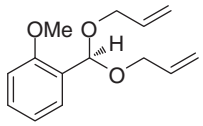
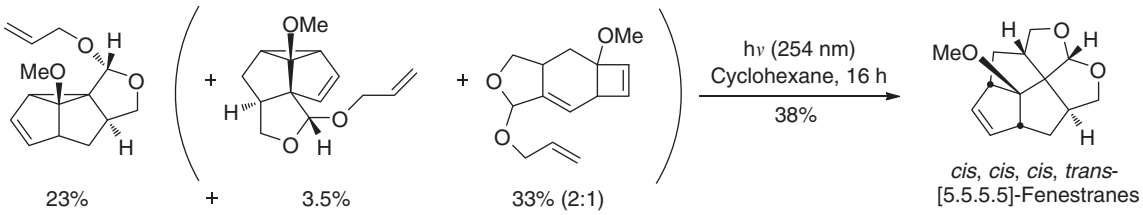
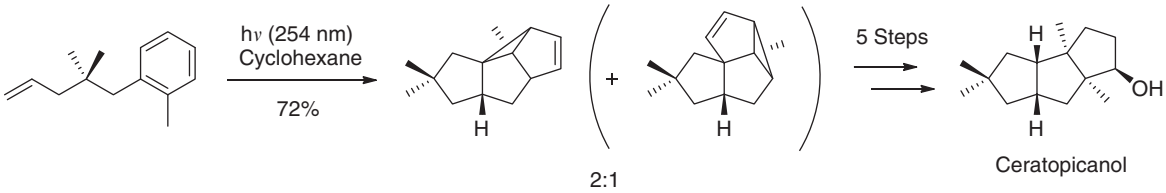
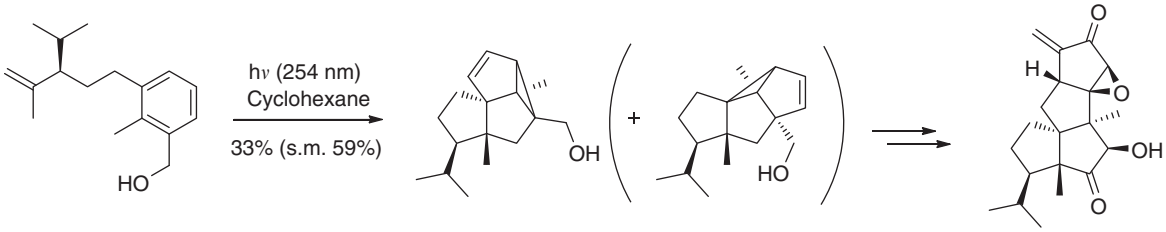
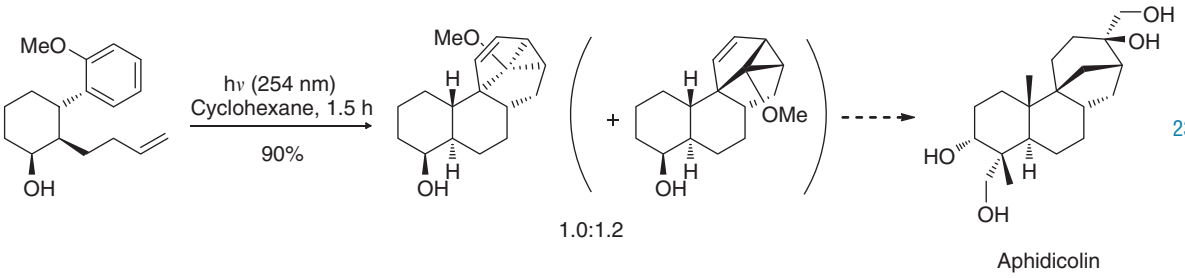


48

(17)

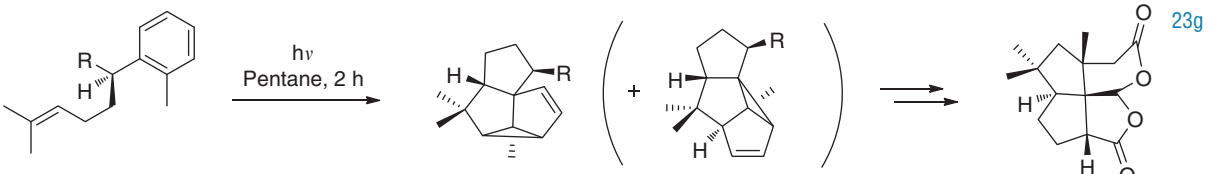
A mechansitically interesting [3 + 2] cycloaddition reaction of 2-(1-alkynyl)cyclohexenones with alkenes was reported to give tricyclic furans in good yield. The reaction was thought to proceed through the photochemically generated diradical intermediate **50**, which undergoes a 5-*exo* cyclization to give the carbene intermediate **51**. Finally, this species undergoes cyclization with the carbonyl group to give the furan derivative **52**. Although the scope of the reaction was quite restricted, a unique transformation was realized (Scheme 14).[25]

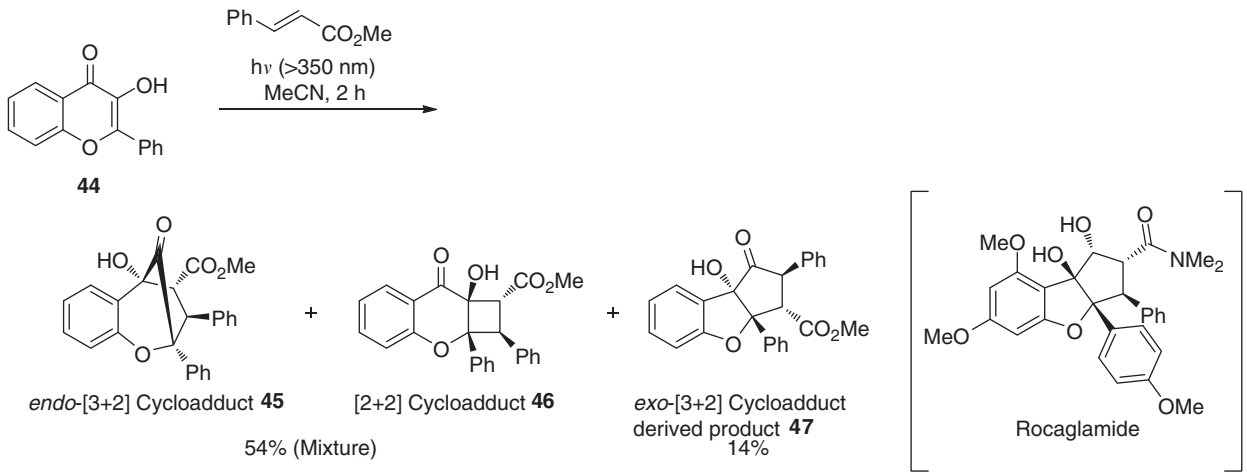
Table 6 Application of photochemical [3 + 2] cycloaddition reactions to the synthesis of natural and unnatural products

Key reaction	*Natural and unnatural products*	*References*
		23a
a R = OH, X = CH_2 **b** R = H, X = O	 **a** 37% (2 : 1) **b** 22% + **b** 24% **a** 35% **b** 32% *cis*, *cis*, *cis*, *trans*-[5.5.5.5]-Fenestranes	
		23b,c
	 23% + 3.5% + 33% (2:1) 38% *cis*, *cis*, *cis*, *trans*-[5.5.5.5]-Fenestranes	
	 2:1 Ceratopicanol	23d
	 Crinipellin B	23e
	 1.0:1.2 Aphidicolin	23f

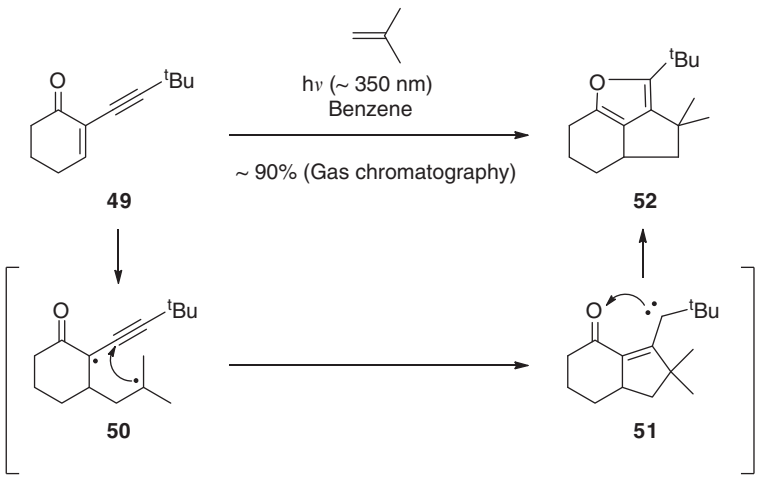
(*Continued*)

Table 6 Continued

Key reaction	*Natural and unnatural products*	*References*
	**a** R = CH_2OH **b** R = CO_2H 70% (55:45) 62% (46:54) Penifulvin A	23g



Scheme 13



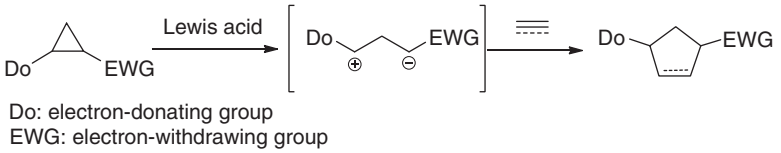
Scheme 14

5.08.3 Lewis Acid or Lewis Base-Catalyzed [3 + 2] Cycloaddition Reactions

5.08.3.1 Donor/Acceptor-Substituted Cyclopropanes

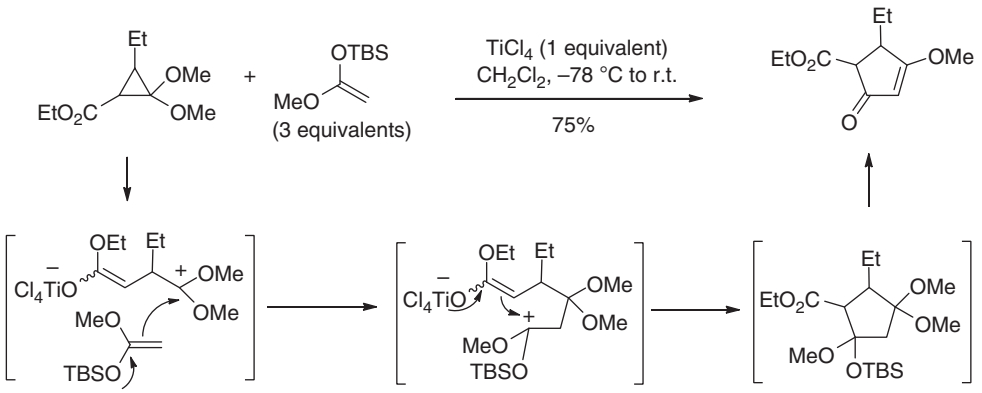
When the first edition of this book was published, Lewis acid-mediated [3 + 2] cycloaddition reactions of cyclopropyl carbonyl compounds without heteroatom substituents on the ring had already been reported.[26] However, the use of cyclopropanes

substituted with both electron-donating and EWGs on neighboring positions, which facilitate the generation of 1,3-dipoles on treatment with Lewis acids, had been limited to rearrangement and ring-opening reactions.[1d] The utilization of donor/acceptor-substituted cyclopropanes as a three-carbon unit in [3 + 2] cycloaddition reactions with electron-rich 2π components has been studied extensively since that time, and representative new results will be described according to the chosen types of substrates (Scheme 15).[27]



Scheme 15

As an early example, the reaction of 2,2-dialkoxycyclopropane carboxylates with ketene silyl acetals was found to proceed smoothly in the presence of a stoichiometric amount of $TiCl_4$ to give cyclopentenone derivatives in good yields. The reaction was sensitive to steric hindrance, and the use of 3,3-disubstituted cyclopropane or disubstituted ketene silyl acetal lowered the yields of the products considerably. The reaction was thought to proceed as follows: Treatment of 2,2-dialkoxycyclopropanecarboxylate with $TiCl_4$ generates a ring-opened zwitterionic intermediate via a retro-aldol type reaction, which was observed by ^1H nuclear magnetic resonance; the ketene silyl acetal then attacks the cationic center, followed by a Dieckmann-type condensation to give a cyclopentanone intermediate. Elimination of alcohol provides the final product (Scheme 16).[28]



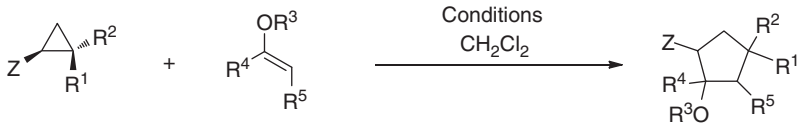
Scheme 16

In a similar manner, the reaction of 2-alkoxycyclopropane carboxylates with silyl enol ethers using a stoichiometric amount of $SnCl_4$ afforded highly functionalized cyclopentanes in good yield as a mixture of stereoisomers. Similar reactions of 2-methoxycyclopropyl methyl ketone with silyl enol ethers proceeded even with 3 mol% of $SnCl_4$.[29a] A higher diastereoselectivity was observed for the reaction of 2-phenylthiocyclopropyl methyl ketone with *t*-butyldiphenylsilyl (TBDPS)-enol ethers in the presence of Me_2AlCl as a Lewis acid.[29b] Triflic imide (Tf_2NH) was found to be an active catalyst for this type of reaction. Even 1–2 mol% of the catalyst was sufficient to promote the reaction of 2-butoxycyclopropanecarboxylate or 2-(*p*-methoxyphenyl)cyclopropyl phenyl ketone with various silyl enol ethers even at $-78\ ^\circ C$ (Table 7).[30]

In the reaction of 2-arylcyclopropane-1,1-dicarboxylates with silyl enol ethers, [3 + 2] cycloadducts or the derived ring-opening products were obtained selectively by choosing appropriate reaction conditions or additives. For example, in the $Cu(SbF_6)_2^-$catalyzed reaction, addition of a bisoxazoline–Zn(II) complex gave the [3 + 2] cycloaddition products selectively with high diastereoselectivity, whereas without this additive, further ring opening occurred to give 1,6-dicarbonyl compounds selectively (Scheme 17).[31]

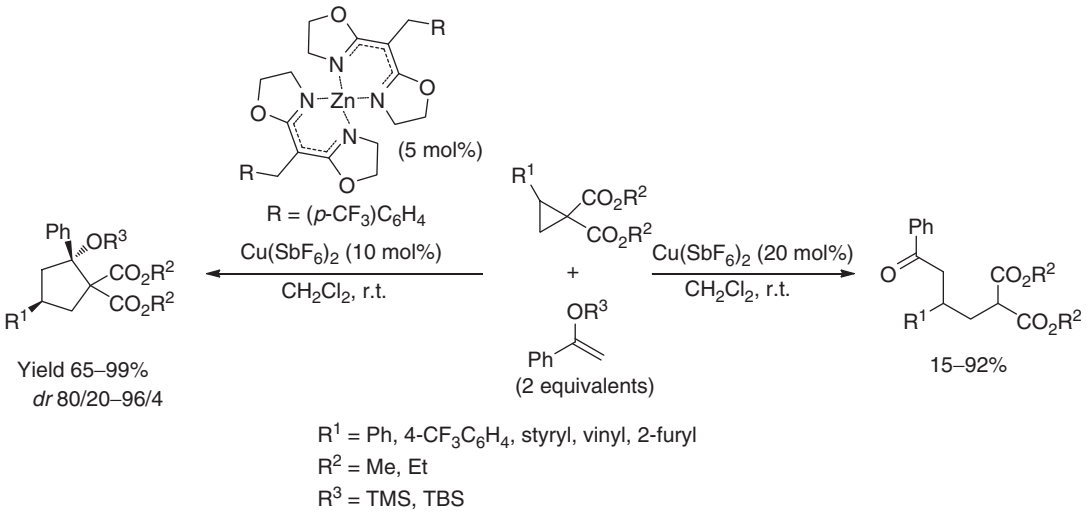
Indoles are also useful partners for this type of reaction as a 2π-component to give synthetically useful cyclopenta[*b*]indoles. $Yb(OTf)_3$-catalyzed reactions of 3-alkylindoles with 1,1-cyclopropane diesters were performed in CH_3CN at room temperature to elevated temperatures or under high pressure, depending on the kind of substituent on the cyclopropane (equation 18).[32a,b] The reaction of 2-arylcyclopropyl ketones and diesters with various indoles in the presence of $BF_3 \cdot OEt_2$ proceeded with perfect diastereoselectivity in most cases to give the products as a single stereoisomer (equation 19).[32c] Highly diastereoselective annulation reaction between indoles and 2-alkoxycyclopropane carboxylates have also been reported using TMSOTf as a Lewis acid. In these cases, a single stereocenter on the cyclopropane allowed the diastereoselective formation of up to four new stereogenic centers to be controlled (equation 20).[32d]

Table 7 [3 + 2] Cycloadditions of donor-acceptor-substituted cyclopropanes with electron-rich alkenes

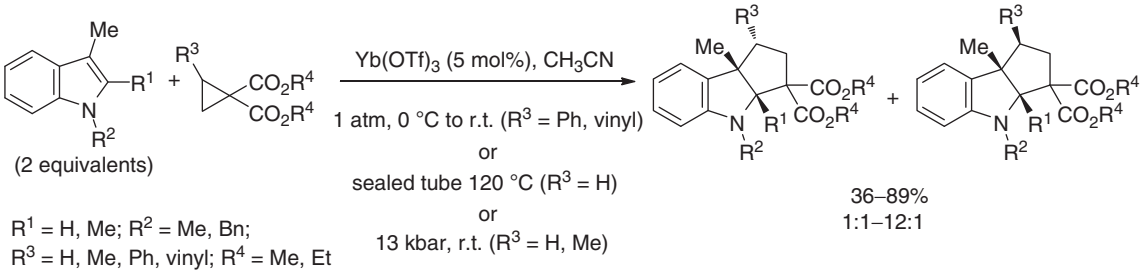


Z	R^1	R^2	OR^3	R^4	R^5	*Conditions*	*Yield (%)*[a]	*References*
COOEt	OBu^n	H	OTBS	Bu^n	H	$SnCl_4$ (1.1 equivalents), −78 °C	69	29a
COOEt	OBu^n	H	OTMS	$-(CH_2)_4-$		$SnCl_4$ (1.1 equivalents), −78 °C	70	29a
COMe	H	OMe	OTMS	Bu^n	H	$SnCl_4$ (3 mol%), −78 °C	60	29a
COMe	H	SPh	OTBDPS	Ph	H	Me_2AlCl (1.1 equivalents), −45 °C	95[b]	29b
COMe	H	SPh	OTIPS	$-(CH_2)_3-$		Me_2AlCl (1.1 equivalents), −45 °C	89[b]	29b
COOEt	H	OBu^n	OTBS	$-CH_2)_4-$		Tf_2NH (1 mol%), −78 °C	69	30
COPh	H	PMP	OTBS	$-(CH_2)_4-$		Tf_2NH (1 mol%), −78 °C	84	30

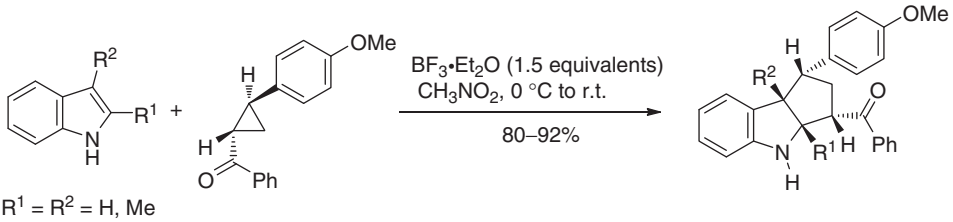
[a]Products were obtained as a mixture of four diastereomers.
[b]Products were obtained as a mixture of two diastereomers.



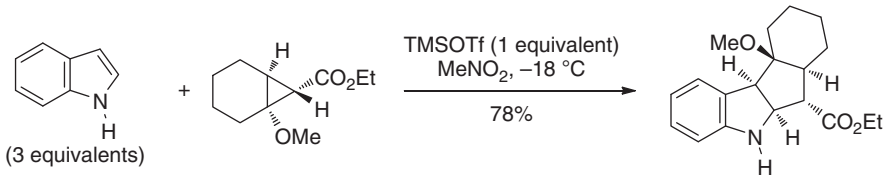
Scheme 17



(18)



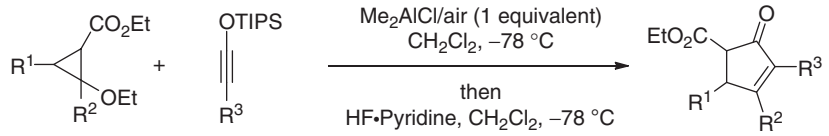
(19)



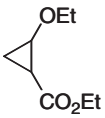
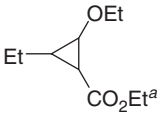
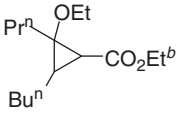
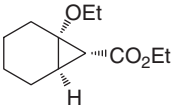
(20)

Silyl ynol ethers were also employable as an electron-rich 2π unit to give cyclopentenone derivatives. Treatment of 2-ethoxycyclopropane carboxylates with silyl ynol ethers in the presence of a stoichiometric amount of Me_2AlCl pretreated with air gave cyclopentenone derivatives in good yield after acid treatment (Table 8). It was postulated that the active catalyst for this reaction was (MeO)AlMeCl, which has sufficient Lewis acidity to promote the reaction but does not decompose the silyl ynol ether.[33a]

Table 8 Synthesis of cyclopentenones from silyl ynol ethers and cyclopropanes

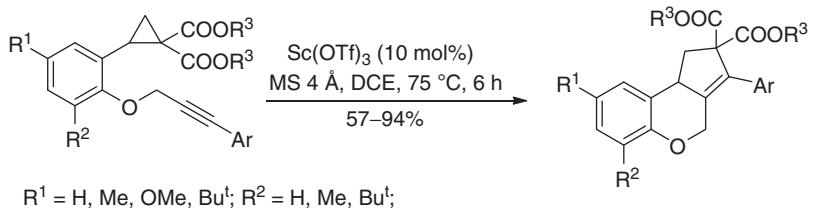


(1.3 equivalents)

Cyclopropane		*Ynol ether* R^3	*Yield (%)*
	*cis-*	Bu^n	77
	trans-	Bu^n	75
	cis-	*Cyclo-Hex*	76
		Bu^n	76
		Bu^n	46[c]
		Bu^n	79[c]

[a]Mixture of diastereomers.
[b]Single unassigned diastereomer.
[c]$dr = > 20{:}1$.

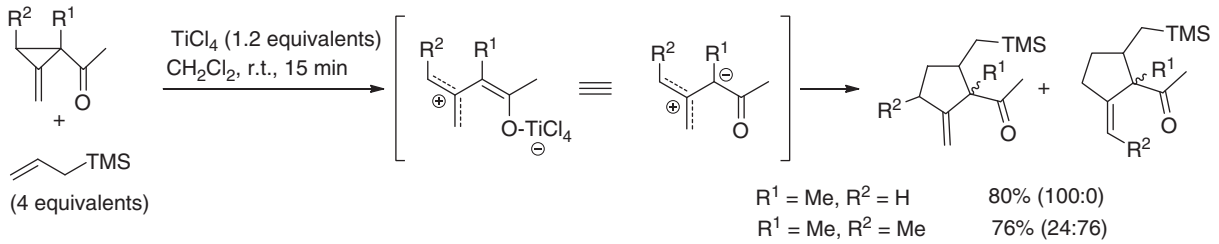
Simple aryl alkynes could also be employed as 2π unit in the intramolecular reaction. Cyclopropane dicarboxylates tethered with aryl alkynes through an aromatic ring underwent intramolecular [3 + 2] cycloadditions in the presence of 10 mol% of $Sc(OTf)_3$ to realize an efficient synthesis of cyclopenta[c]chromene skeletons (equation 21).[33b]



(21)

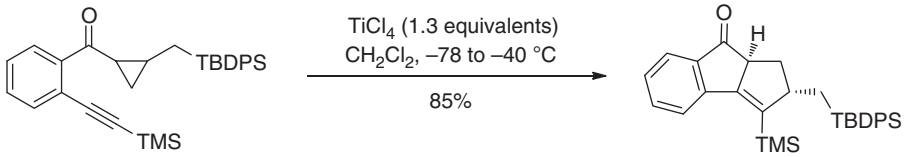
R^1 = H, Me, OMe, Bu^t; R^2 = H, Me, Bu^t;
R^3 = Me, Et; Ar = Ph, 4-$MeOC_6H_4$, 3-MeC_6H_4, 2-$MeOC_6H_4$

Methylenecyclopropyl ketones were also used to generate allylcationic intermediates on treatment with $TiCl_4$. The resulting 1,3-dipoles underwent [3 + 2] cycloaddition with allylsilane as a two-carbon unit to give methylenecyclopentane derivatives. Regioisomeric products were obtained depending on the substituents on the cyclopropane (equation 22).[34]



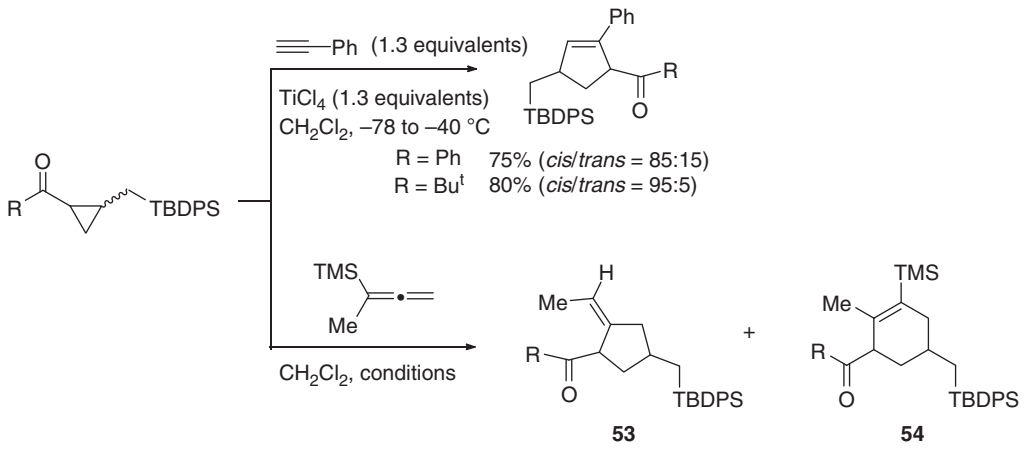
(22)

2-TBDPS-methyl-substituted cyclopropyl ketones were also employed as 1,3-dipole precursors. On treatment with arylacetylenes in the presence of $TiCl_4$, cyclopentenylketones were obtained in good yields as a mixture of *cis* and *trans*-isomers. The intramolecular variant of the reaction also proceeded without problem to give the corresponding products stereoselectively (equation 23).[35a] Allenylsilanes also reacted as a 2π unit in the presence of $TiCl_4$ (− 78 to − 40 °C) or Et_2AlCl (r.t.) to give [3 + 2] or [3 + 3] cycloaddition products, depending on the kind of substrates and the chosen conditions. In most cases, $TiCl_4$ favored methylenecyclopentane formation, whereas Et_2AlCl favored cyclohexene formation (Table 9).[35b]



(23)

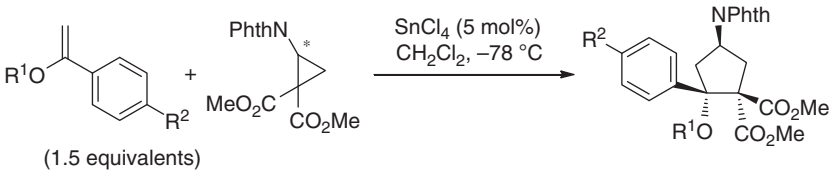
Table 9 [3 + 2] Cycloadditions of acceptor-substituted cyclopropylmethylsilanes to allenylsilanes

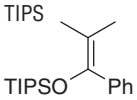


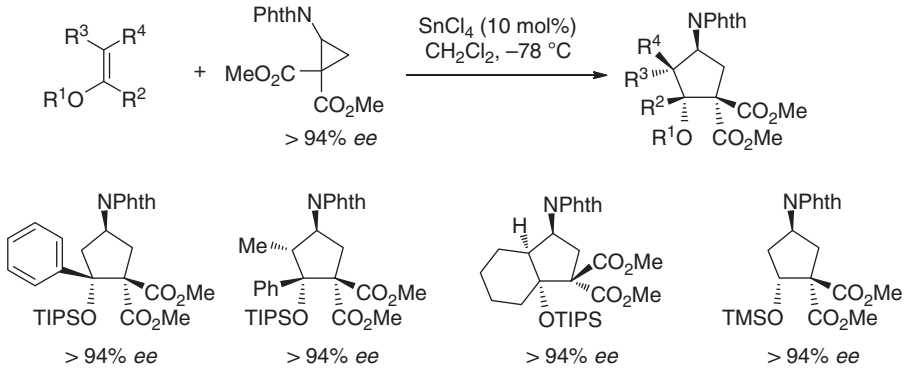
R	*Conditions*	*Yield (%)*		*cis/trans*
		53	***54***	
Ph	$TiCl_4$ (1.3 equivalents, − 78 to − 40 °C)	90		3.2:1
Ph	Et_2AlCl (1.5 equivalents, 25 °C)		65	100:0
Bu^n	$TiCl_4$ (1.3 equivalents, − 78 to − 40 °C)	75		1.9:1
Bu^n	Et_2AlCl (1.5 equivalents, 25 °C)		65	100:0

Recently, cyclopropane dicarboxylates with a phthalimide group at the 2-position of the cyclopropane were found to react with silyl enol ethers or vinyl ethers on treatment with 5 mol% of $SnCl_4$. The choice of the phthalimide group as a nitrogen donor was essential for the success of the reaction. The transformation showed wide generality to give variously substituted cyclopentylamines in good yields with high diastereoselectivity (Table 10). The most unique feature is that the use of optically active cyclopropane dicarboxylates gives substituted cyclopentylamines without loss of optical purity (Scheme 18).[36]

Table 10 [3 + 2] Cycloadditions of aminocyclopropanes



Alkene		*Yield (%)*	*dr*
R^1	*R*^{2}		
TBS	H	98	> 20:1
TIPS	CO_2Me	95	> 20:1
TIPS	OMe	99	> 20:1
		81	4:1
		99	20:1
		99	1.7:1



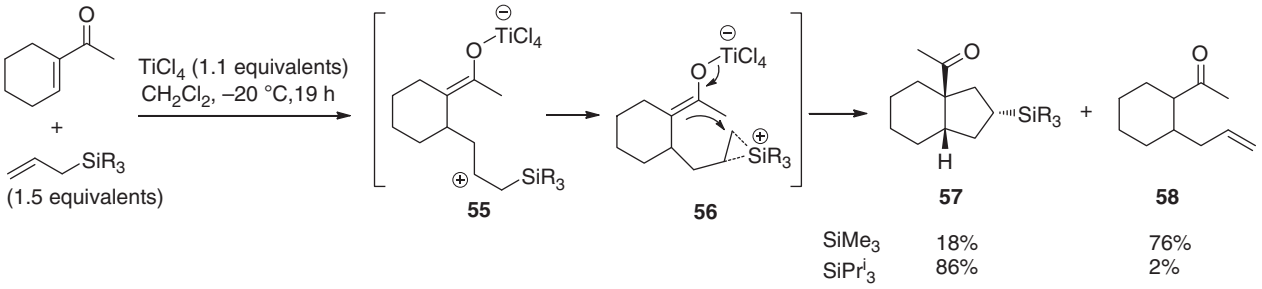
Scheme 18

5.08.3.2 Allylsilanes

The reaction of allyl- or allenylmetallic species with α,β-unsaturated carbonyl compounds with 1,2-migration of the metallic moiety to give cyclopentyl- or cyclopentenyl-metallic derivatives as formal [3 + 2] cycloaddition products had been studied since 1970s and the major investigations were described in the first edition of this book (*see* Chapter 3.2).[1b] Early studies include the reaction of allyliron, allyltungsten, and several other allylmetallic species, but applications had been limited until the Lewis acid-promoted reaction of allenylsilanes with α,β-unsaturated carbonyl compounds was reported.[1b,37] The use of allylsilanes as a three-carbon unit for [3 + 2] cycloadditions was discovered by careful analysis of the side products of the Hosomi–Sakurai reaction, and has been extended since then to a useful cyclopentane annulation process, which is mainly summarized in this section.

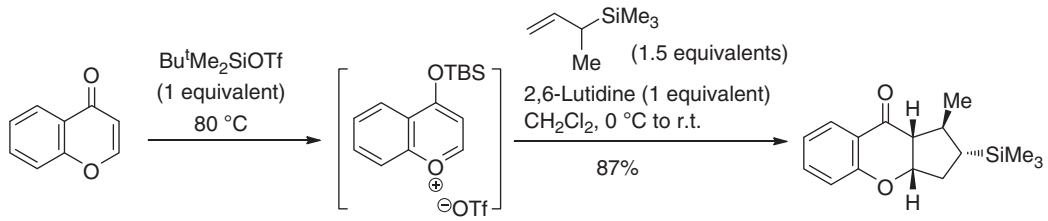
Allylsilanes have been employed as a very useful reagent for the Lewis acid-catalyzed allylation of carbonyl and related compounds (the Hosomi–Sakurai reaction) and extensive investigations have been carried out on this chemistry. During these studies, it was found that (trimethylsilyl)cyclopentanes, formal [3 + 2] cycloadducts, were obtained as side products of the Hosomi–Sakurai reaction when α,β-unsaturated carbonyl compounds were used as the electrophile. Actually the formation of such side products was noted in earlier papers but they were assigned to be cyclobutane derivatives. By careful analysis, the structure was revised to the cyclopentane derivatives. The mechanism of the reaction is as follows: Nucleophilic 1,4-addition of allylsilanes to enones activated by Lewis acid provides zwitterionic intermediate such as **55**, in which the generated carbocation is stabilized by the presence of the silicon atom in the β-position. This cation is in equilibrium with the silacyclopropane intermediate **56** (or 1,2-silicon-migrated carbocation), which is attacked by the enolate so as to make the five-membered ring product.

The ratio of the Hosomi–Sakurai product and the [3 + 2] cycloaddition product strongly depends on the steric hindrance at the silicon atom. For example, the $TiCl_4$-promoted reaction of 1-acetylcyclohexene with allyltrimethylsilane in CH_2Cl_2 at $-20\,^{\circ}C$ gave a simple allylation product **58** and the cyclopentane product **57** in 76 and 18% yield, respectively, whereas the same reaction using allyltriisopropylsilane gave the two products in 2 and 86% yield, respectively (Scheme 19).[38]



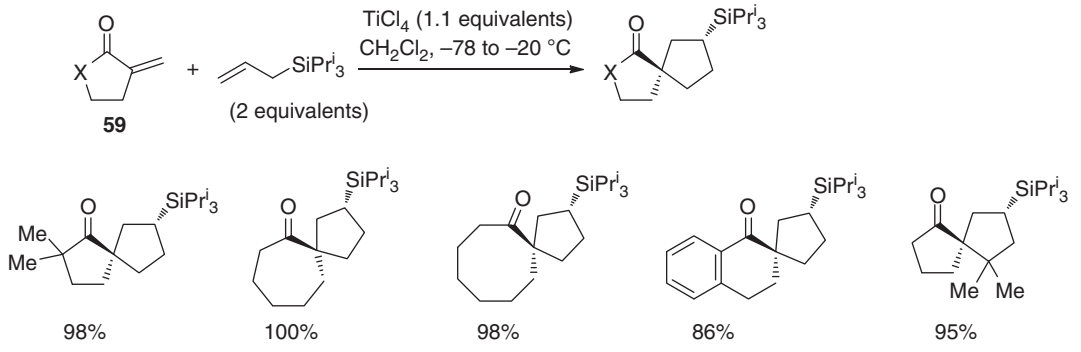
Scheme 19

Nearly at the same time, the reaction of chromone derivatives with 3-butenylsilane was reported to give the corresponding [3 + 2] cycloaddition products stereoselectively (equation 24).[39]

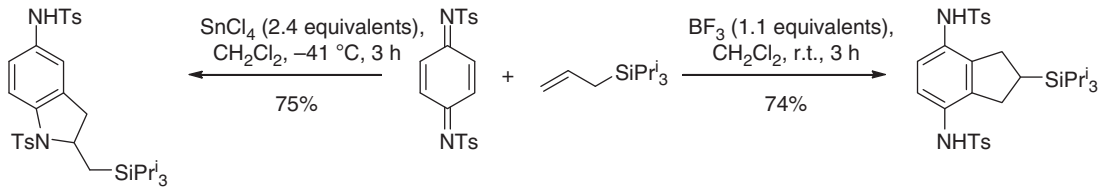


(24)

The reaction showed wide generality, and various kinds of α,β-unsaturated carbonyl compounds can be used. For example, 2-alkylidenecycloalkan-1-ones **59** gave spirocyclic ring compounds in high yields (Scheme 20),[40a] and quinones and quinone diimines gave the corresponding [3 + 2] cycloaddition products by choosing appropriate reaction conditions (Scheme 21).[40b,c] Even simple dienes could be employed as a 2π-component by carrying out the reaction with allyltrimethylsilane using $AlCl_3$ as a promoter in the presence of TMSCl (Table 11).[40d] Cyclic allylsilanes gave bicyclo[n.2.1] systems with high diastereoselectivity (equation 26).[40e]

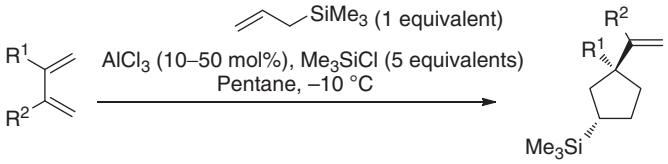


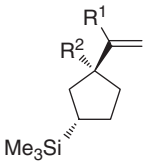
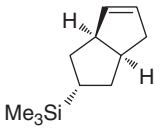
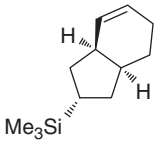
Scheme 20

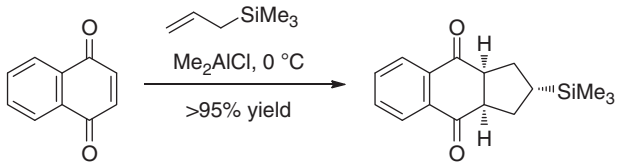


Scheme 21

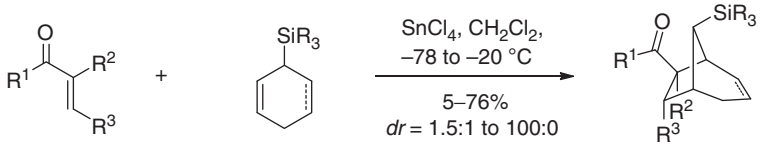
Table 11 [3 + 2] Cycloaddition reactions of allylsilane with dienes



Diene	Product	Diene	Product
			 56%
R^1, R^2 = Me 67% R^1 = H, R^2 = Me 29% R^1, R^2 = H 38%			 72%



(25)



(26)

R^1 = H, Me, OMe, *cyclo*-C_6H_{11}, Ph
R^2, R^3 = H, Me
R_3 = Pr^i_3, Me_2Ph

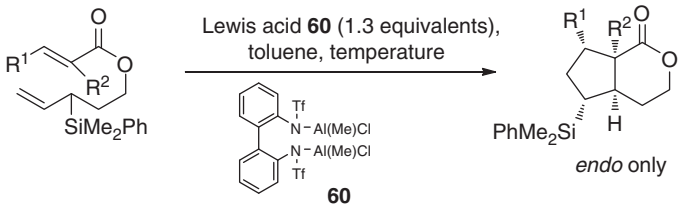
The intramolecular version of the reaction was reported to give bicyclic lactones by using the novel bidentate aluminum Lewis acid **60**. Treatment of 3-(dimethylphenylsilyl)-4-pentenyl alkenoates with a stoichiometric amount of the aluminum reagent prepared from 1.1′-biphenyl-2,2′-di(triflyl)amide (BIPAM) and Me_2AlCl (2 equivalents) in toluene gave the intramolecular [3 + 2] cycloaddition products diastereoselectively in good yields (Table 12).[41]

By using optically active allylsilanes, enantiospecific syntheses of cyclopentane derivatives were achieved. The reactions proceeded with almost perfect chirality transfer to give the corresponding products with high diastereoselectivity (Scheme 22).[42]

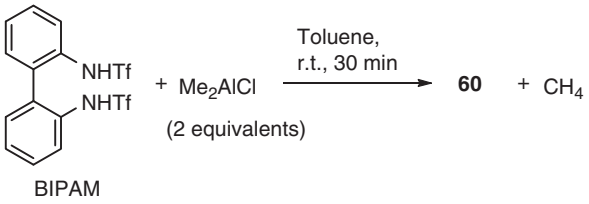
In addition to allylsilanes, propargylsilanes containing an alkyl substituent at the silicon-bearing carbon also participated in the $TiCl_4$-mediated [3 + 2] cycloaddition with electron-deficient alkenes when the reaction was carried out in CH_2Cl_2 at −78 °C. In general, however, the diastereoselectivity of the products was low (Table 13).[43]

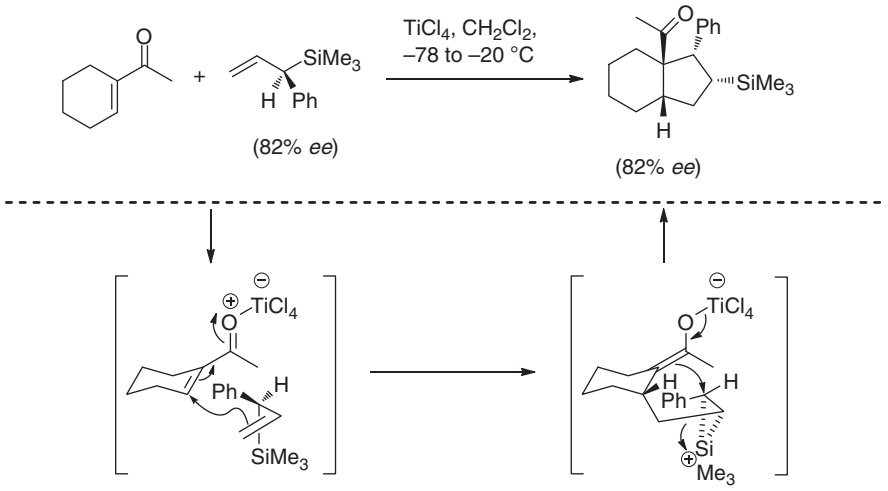
In order to utilize the remaining silicon group on the cyclopentane ring for further functionalization, the reactions of allyldimethyltritylsilane,[44a,b] allyl(*t*-butyl)diphenylsilane,[44c] allyldiisopropylphenylsilane,[44d] and allylbenzhydryldimethylsilane[44e] were developed. These allylsilanes are not only bulky but also easily convertible into the hydroxy group by Tamao oxidation, thus providing synthetically useful cyclopentanol derivatives. One application of such a reagent in the total synthesis of the triquinane sesquiterpene *β*-isocomene is shown in Scheme 23.

Table 12 Intramolecular [3 + 2] cycloaddition reactions catalyzed by a bidentate Lewis acid

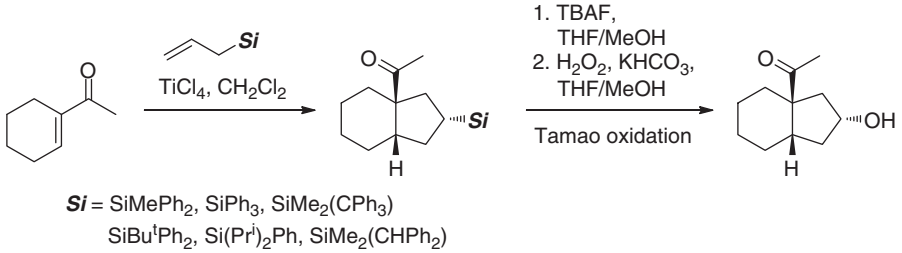


R^1	R^2	*Temperature (°C)*	*Time (h)*	*Yield (%)*
H	H	50	7	73
H	Me	80	5	65
H	CF_3	r.t.	20	76
CO_2Et	H	80	10	72
Me	H	80	40	72



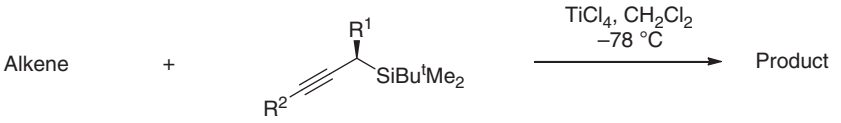


Scheme 22

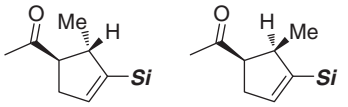
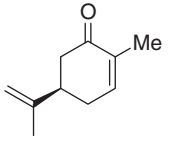
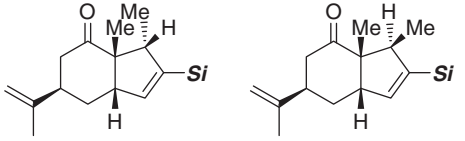
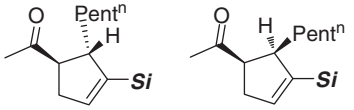
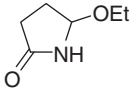
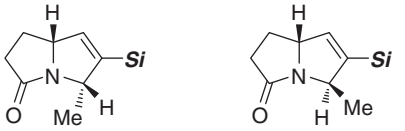
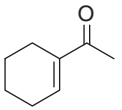
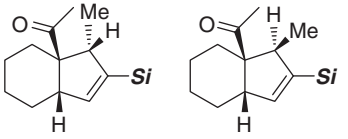
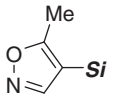
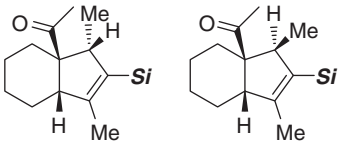
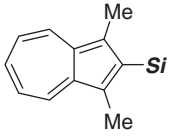


(27)

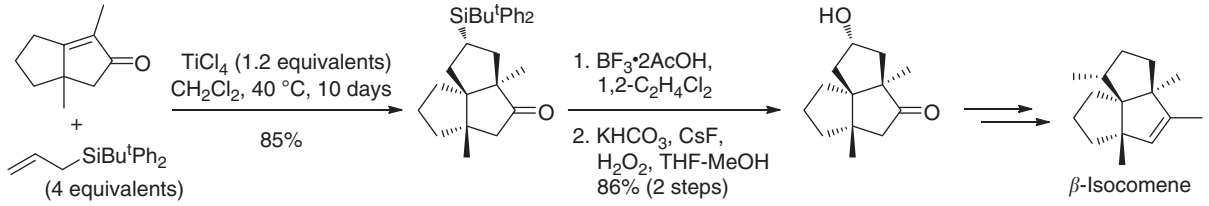
Table 13 [3 + 2] Annulation using propargylsilanes



a R^1 = Me, R^2 = H
b R^1 = $Pent^n$, R^2 = H
c R^1 = Me, R^2 = Me

Alkene	Silane	Product	Alkene	Silane	Product
	**a**	 78% (*dr* = 1:1)	 (*R*)-(–)-Carvone	**a**	 75% (*dr* = 1:1)
	b	 51% (*dr* = 1:1)		**a**	 53% (*dr* = 1:1)
	**a**	 74% (*dr* = 2:1)	$NOBF_4$	**a**	 70%
	c	 74% (*dr* = 2:1)		**c**	 55%

Si = $SiBu^tMe_2$.

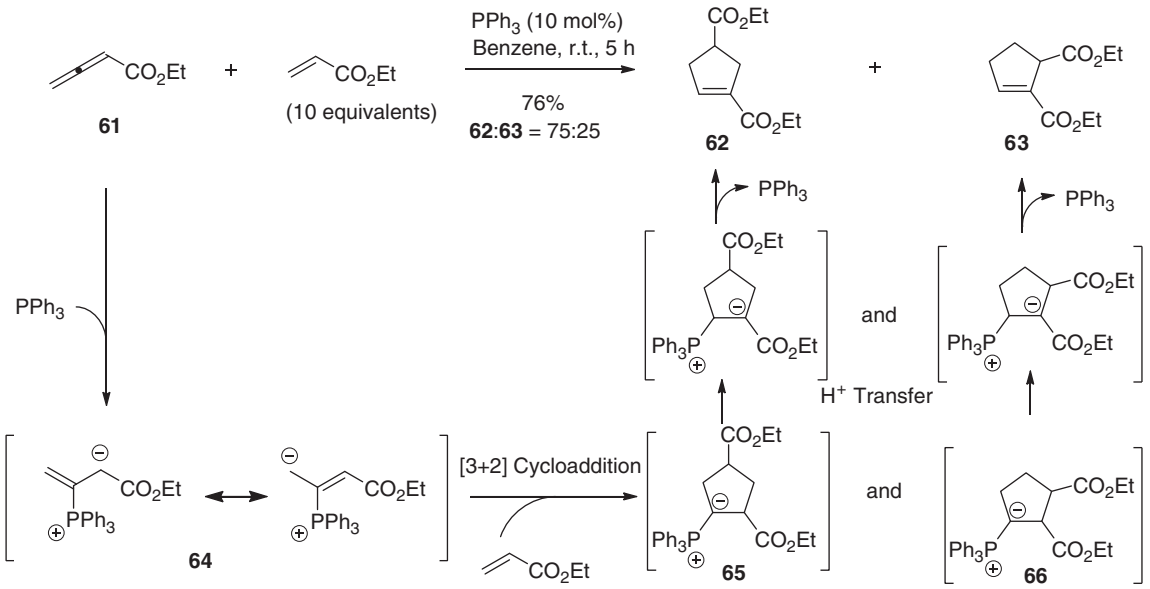


Scheme 23

5.08.3.3 Lu Reaction

In 1995, the first example of a phosphine-promoted reaction of allenoates with electron-deficient alkenes, now known as the Lu reaction, was reported.[45a] This reaction attracted much attention because of its simplicity, the easy availability of the starting materials, and the utility of the products. Not only electron-deficient alkenes but also aldehydes and imines have been utilized as the 2π component. Triphenylphosphine has been employed in most cases, but tributylphophine has also found some applications. In particular, the development of asymmetric versions of this reaction has recently been extensively studied, with the focus on the design of new chiral phosphines as organocatalysts. In this section, these reactions will be summarized with an emphasis on the scope of the reaction and applications to asymmetric catalysis.[46]

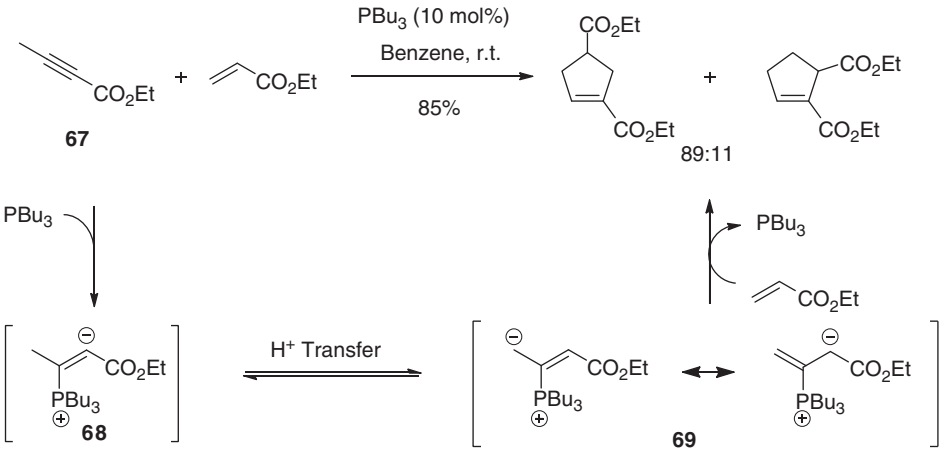
Treatment of ethyl 2,3-butadienoate **61** with ethyl acrylate in the presence of 10 mol% of PPh_3 in benzene at room temperature gave a regioisomeric mixture of the cyclopentenedicarboxylates **62** and **63**, formal [3 + 2] cycloaddition products, in good yield.[45a] The reaction was proposed to proceed as follows: The phosphine attacks the allenoate in a 1,4-manner to generate the zwitterionic enolate intermediate **64**. This species then undergoes a [3 + 2] cycloaddition with the electron-deficient alkene to give cyclopentyl ylides **65** and **66**, which undergo proton transfer followed by elimination of the phosphine to give the products (Scheme 24). The reaction with diethyl fumarate and maleate gave *trans* and *cis* cyclopentenetricarboxylate, respectively, suggesting a concerted nature of the [3 + 2] cycloaddition, although later theoretical analyses by several research groups strongly suggested a stepwise pathway. It should also be noted that the mechanistic analysis suggested that a water molecule plays an important role in this reaction.[47]



Scheme 24

The reaction of 2-butynoate **67** with electron-deficient alkenes catalyzed by tributylphophine also proceeded in a similar manner. The same zwitterionic species **69** was generated by proton transfer from the primary addition intermediate **68** (Scheme 25).[45]

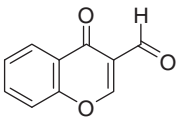
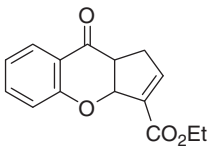
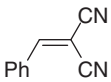
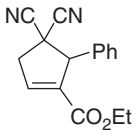
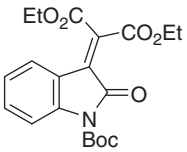
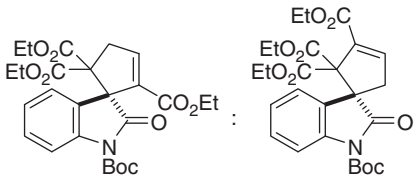
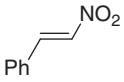
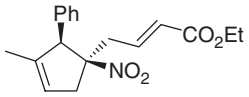
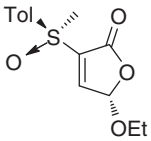
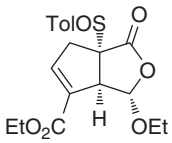
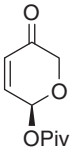
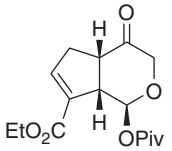
One drawback of the reaction is the regioselectivity concerning the acceptor alkene. Highly electron-deficient alkenes such as 3-formylchromones,[48a] arylidenemalononitriles,[48b] isatine-derived α,β-unsaturated diesters,[48c] nitroalkenes,[48d] and cyclic alkenes[48e,f] gave the corresponding [3 + 2] cycloaddition products regioselectively, whereas β-unsubstituted alkenes such as acrylates and *exo*-methylene ketones often afford mixtures (Table 14).



Scheme 25

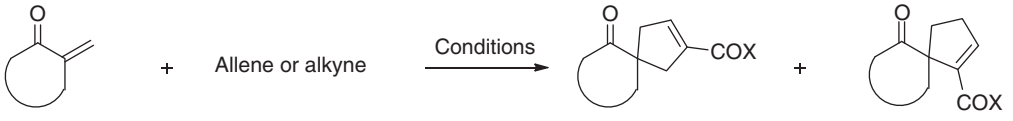
Table 14 Regioselective [3 + 2] cycloadditions of ethyl 2,3-butadienoate with acceptor alkenes



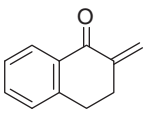
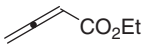
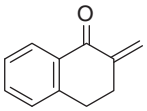
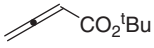
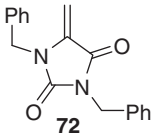
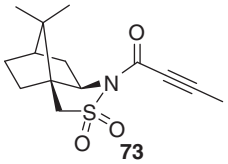
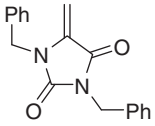
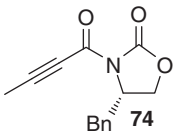
Acceptor alkene	*Conditions*	*Product(s)*	*Yield (%)*	*References*
	PPh_3 (14 mol%) benzene, reflux, 80 h		74	48a
	PPh_3 (9 mol%) toluene, 15 °C		89	48b
	PBu_3 (20 mol%) toluene, r.t., 2 h	 13 : 1	86	48c
	$P(p\text{-}FC_6H_4)_3$ (20 mol%) toluene, 60 °C, 12 h	 *cis/trans* = 3.9 : 1	90	48d
	PPh_3 (30 mol%) benzene, r.t., 3 h		96	48e
	PPh_3 (10 mol%) toluene, 110 °C, 30 min		63	48f

In the reaction with *exo*-methylene ketones, the use of *t*-butyl 2,3-butadienoate instead of the ethyl ester gave higher selectivity in favor of **70**. Furthermore, when *t*-butyl 2-butynoate was used in the tributylphophine-catalyzed reaction, the regioselecitivty was improved in some cases, although the reason is not obvious.[49a,b] Such an influence of the components on the regioselectivity was more pronounced in the reaction of methylenehydantoins **72** with various 2-butynoate derivatives. Camphor sultam **73** gave **70** selectively, whereas the oxazolidinone derivative **74** gave **71** as a major product. The electrostatic interaction was thought to play an important role in determining the regioselectivity (**Table 15**).[49c]

Table 15 Regioselective [3 + 2] cycloadditions with *exo*-methylene carbonyl compounds



70 **71**

Exo-methylenen carbonyl	*Allene or alkyne*	*Conditions*	*Yield (%) (ratio = **70:71**)*	*References*
		PPh_3 (10 mol%) toluene, r.t., 11 h	93 (79:21)	49a
		PPh_3 (10 mol%) benzene, reflux, 18 h	98 (91:9)	49a
 **72**	 **73**	PBu_3 (10 mol%) benzene, r.t.	74 (100:0)	49c
	 **74**	PBu_3 (10 mol%) benzene, r.t.	54 (11:89)	49c

As the electron-deficient allene partners, allenyl ketones,[50a,b] allenylphosphonates,[50c] 3-butynoate,[50d] and allenylsulfones[50e] could also be employed, although the reaction with allenylsulfones was found to proceed through a somewhat different mechanism (**Table 16**).

The intramolecular version of this phosphine-catalyzed reaction of electron-deficient 1,7-enynes was found to proceed efficiently to give bicyclo[3.3.0] ring systems diastereoselectively by heating the substrates with 10 mol% of PBu_3 in ethyl acetate at 110 °C.[51a] This reaction was successfully applied to the total synthesis of hirsutene (**Scheme 26**).[51b] A very efficient synthesis of cyclopentene-fused dihydrocoumarins **77** from cinnamyl allenoates **76**, that are easily prepared from salicylaldehyde derivatives **75**, was also achieved (**Scheme 27**).[51c]

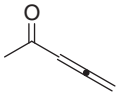
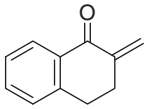
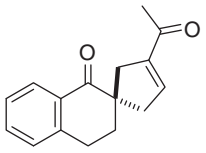
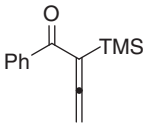
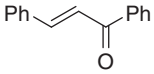
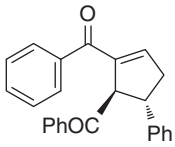
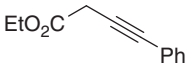
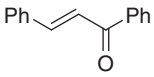
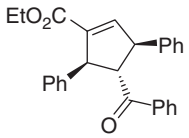
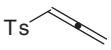
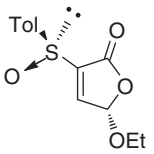
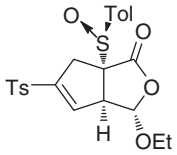
Soon after Lu's original work had been published, the first successful example of the asymmetric version of this reaction was reported. By using the chiral 7-phosphabicyclo[2.2.1]heptane derivatives **78**, which were prepared from 1,4-disubstituted benzenes in a multistep sequence, cyclopentene carboxylate was obtained regioselectively in good yield with up to 93% *ee* on reaction of 2,3-butadienoate with acrylate in the presence of 10 mol% of the phosphine (**Scheme 28**).[52a]

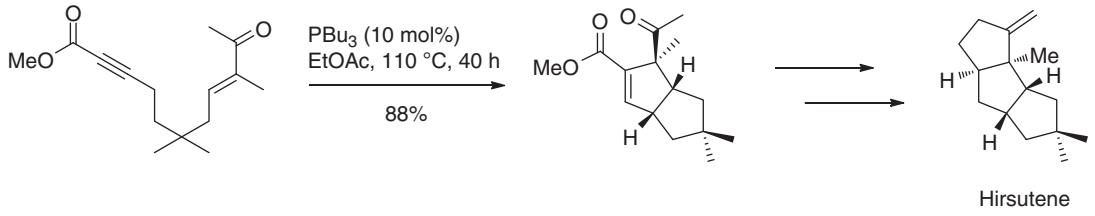
Nearly 10 years passed until the second example of this type of reaction was reported using the binaphthyl type phosphine **79**. By using this phosphine, the reaction of 2,3-butadienoate with chalcone and related α,β-unsaturated ketones proceeded to give functionalized cyclopentene derivatives in nearly 90% *ee*. It should be noted that the regiochemical outcome of this reaction using β-substituted enones was opposite to the reaction with β-unsubstituted α,β-unsaturated carbonyl compounds.[52b] Thereafter, several research groups reported unique chiral phosphine catalysts, which realized good to high enantioselectivity in this reaction. Representative examples are summarized in **Table 17**.[52c–j]

Another type of phosphine-catalyzed formal [3 + 2] cycloaddition reaction of allylic bromides or acetates having an ethoxycarbonyl group at the central carbon with electron-deficient alkenes was reported. The reaction was carried out with 10 mol% PPh_3 and a stoichiometric amount of K_2CO_3 in toluene at 110 °C; slow addition of the reactants to the toluene solution

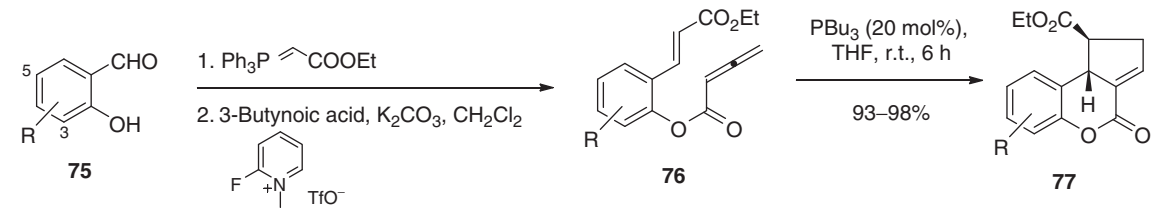
Table 16 Phosphine-catalyzed [3 + 2] cycloaddition with electron-deficient allenes



Allenes	*Alkene*	*Conditions*	*Products*	*Yield (%)*	*References*
		PPh_3 (15 mol%) toluene, r.t., 12 h	 (regioselectivity = 62:38)	75	50a
		PPh_3 (20 mol%) toluene, r.t.		84	50b
		PBu_3 (20 mol%) toluene, r.t.		75	50d
		PPh_3 (40 mol%) THF, r.t., 1.5 h		71	50e



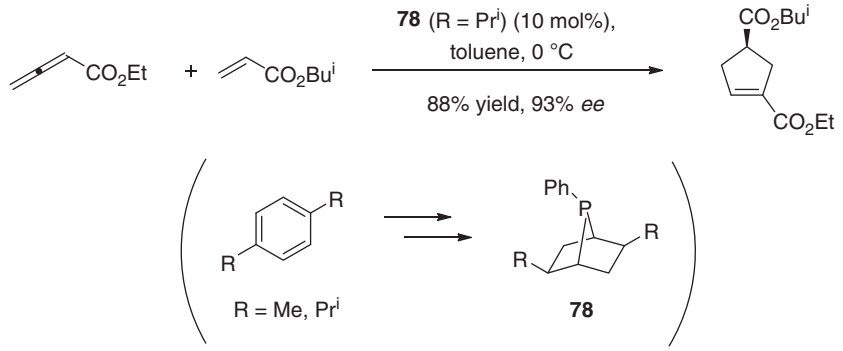
Scheme 26



R = H, 3-Me, 4-MeO, 5-Br

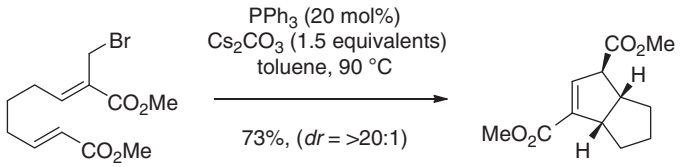
Scheme 27

containing the phophine and K_2CO_3 improved the yield. The reaction was thought to proceed through the phosphonium salts **80** generated by an S_N2 or addition/elimination reaction of PPh_3 to the allylic bromides or acetates. The salts are then deprotonated by the base to afford ylides **81**, which undergo nucleophilic addition to electron-deficient alkenes to yield zwitterionic intermediates **82**. Subsequent cyclization by intramolecular conjugate addition provides betain-like intermediates **83**, which finally undergo elimination of the phosphine to complete the catalytic cycle. By using allylic *t*-butylcarbonate as the substrate, the reaction proceeded without the necessity of adding a base (Scheme 29).[53a]

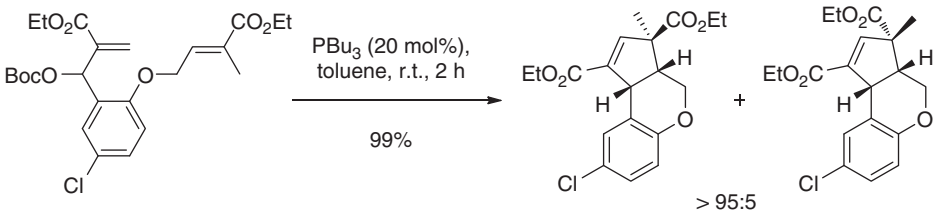


Scheme 28

An intramolecular variant was developed for the diastereoselective synthesis of bicyclo[n.3.0] compounds, and an asymmetric version was also reported using a chiral phosphine catalyst (equations 28 and 29).[53b]



(28)



(29)

The use of easily available Morita–Baylis–Hillman carbonates instead of the corresponding bromides has expanded the utility of this reaction. It is not necessary to add bases, as *t*-butoxide is generated during the reaction. Various applications to the preparation of synthetically useful cyclopentene derivatives, including enantioselective reactions, have been realized (Table 18).[54]

5.08.3.4 Other Acid or Base-Promoted Reactions

This section briefly describes other types of acid or base-promoted reactions of high utility.

3-Acetoxy-1-(methylthio)-2-(triisopropylsiloxy)-1-propene **84** reacts with various electron-rich alkenes such as enol ethers or vinyl sulfides to afford the corresponding cyclopentanones in good yield, when the reaction is performed in the presence of a stoichiometric amount of $EtAlCl_2$. The reaction of 1-acetoxy-3-(methylthio)-2-(triisopropylsiloxy)-2-butene with vinyl sulfides proceeded with high stereoselectivity and was applied to the total synthesis of (–)-coriolin (Table 19, Scheme 30).[55]

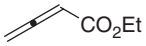
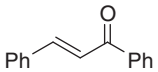
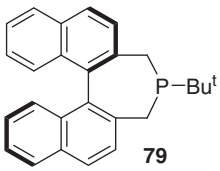
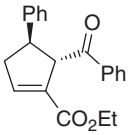
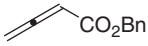
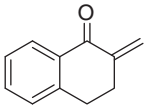
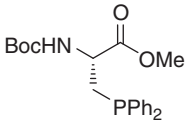
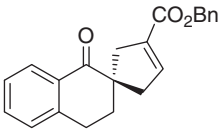
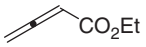
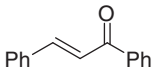
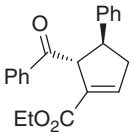
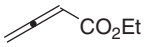
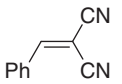
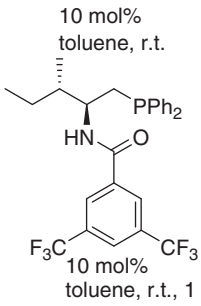
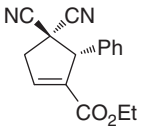
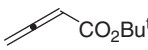
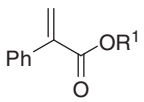
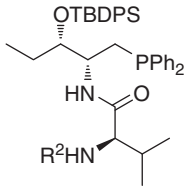
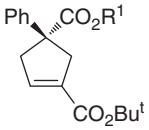
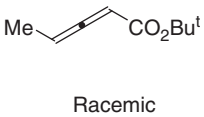
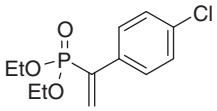
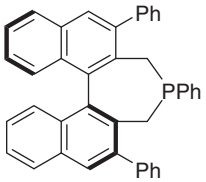
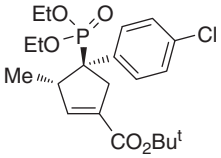
Domino Mukaiyama-aldol reactions of 1,3-bis(trimethylsiloxy)-1,3-dienes **85** with enolizable 1,2-diketones gave substituted cyclopentenones regioselectively. The reaction proceeded smoothly at $-78\ ^{\circ}C$ to room temperature by using 2 equivalents of $TiCl_4$ and showed reasonable generality (Scheme 31).[56]

A unique [3 + 2] cycloaddition of silyl enol ethers with terminal alkynes to give cyclopentenones was realized by using a combination of $SnCl_4$ and Et_3N followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) treatment. It was proposed that $SnCl_4$ and Et_3N promote the addition of silyl enol ethers to the internal carbon of the terminal alkynes to give γ-stannyl α,β-unsaturated ketone intermediates **86**, which undergo intramolecular cyclization by the action of DBU, whereby $SnCl_3$ serves as a leaving group liberating a Sn(II) species (Scheme 32).[57]

Several nucleophilic addition reactions of 1,3-dipole equivalents to electron-deficient alkenes followed by ring-closure were reported. For example, the lithiated 2-(bromomethyl)allyl sulfone **87** reacted with nitroolefins, 2-(phenylsulfonyl)enones, and α,β-unsaturated esters and ketones to give the corresponding methylenecyclopentane derivatives.[58a,b] In particular, the reaction with α,β-unsaturated esters proceeded in good yields with high diastereoselectivity (Table 20).[58c,d]

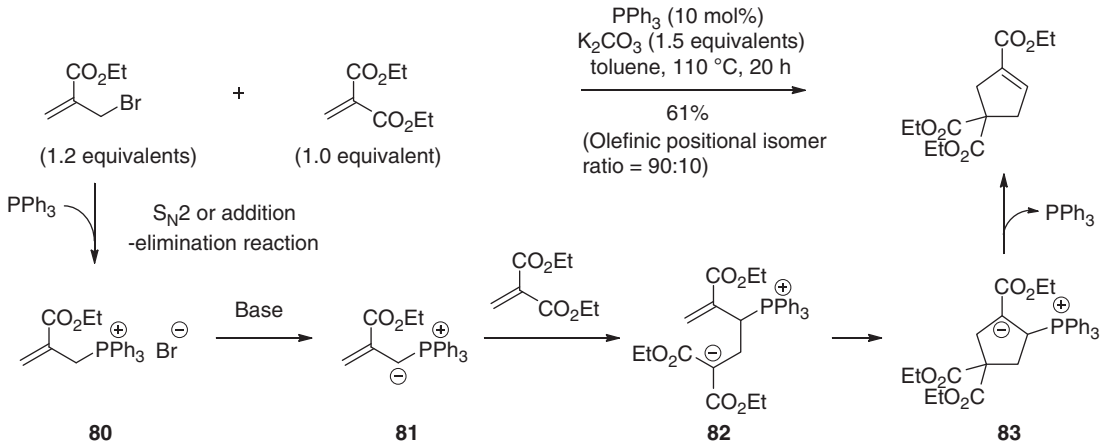
Addition of nucleophiles to an allenylsulfone or 2,3-bis(phenylsulfonyl)-1,3-butadiene generates 1,3-dipole equivalents, which react with electron-deficient alkenes in a 1,4-addition manner followed by intramolecular addition of the generated anionic species to the vinylsulfone moiety. By using malonates containing an electron-deficient alkene, bicyclic products were obtained in

Table 17 Chiral phosphine-catalyzed enantioselective [3 + 2] cycloaddition

Allene	*Alkene*	*Chiral phosphine*	*Product(s)*	*Yield (%), ee (%)*	*References*
		 **79** 10 mol% toluene, r.t.		64, 88	52b
		 10 mol% toluene, –25 °C, 30 h		95, 80	52c
		 10 mol% toluene, r.t.		65, 92	52d,e
		 10 mol% toluene, r.t., 1 h		87, 85	52g
	 R^1 = 9-phenanthryl	 $R^2 = CO_2C(CH_3)_2CCl_3$ 5 mol% toluene, r.t., 0.5 h		95, 91	52h
 Racemic		 10 mol% Pr^i_2O. r.t.		82, 99	52j

good yield. It should be noted that this reaction proceeded stereospecifically concerning the alkene geometry, as observed in examples **c** and **d** shown in Scheme 33.[59]

Several anionic methods have also been reported.[60e] For example, β-heteroatom-substituted α,β-unsaturated acylsilanes reacted with ketone lithium enolates to give functionalized cyclopentenol derivatives. The reaction proceeds through 1,2-addtion of the enolates to the carbonyl group of the acylsilanes, followed by a Brook rearrangement to give allyl anionic species containing a ketone carbonyl, which cyclizes to give the products. The use of β-silyl or β-thio-substituted α,β-unsaturated acylsilanes was



Scheme 29

essential for the success of the reaction, as crotonoyl derivative gave cyclopropanol derivatives instead (Scheme 34). The reaction was applied to the synthesis of some natural products.[60]

5.08.4 Transition Metal Mediated or Catalyzed Reactions

5.08.4.1 Fischer Carbene Chemistry

Use of α,β-unsaturated Fischer carbene complexes of group 6 metals as a three-carbon unit in the reaction with various alkenes or alkynes has been studied, and several different types of [3 + 2] cycloaddition reactions have been developed, most of which include 1-metalla-1,3,5-trienes as intermediates.[61] These reactions employ preformed carbene complexes and thus are stoichiometric. Therefore, although the reactivity of the carbene complexes is unique, applications to synthetic purposes are rather limited. At the end of this section, recently developed new approaches toward the catalytic generation of α,β-unsaturated carbene complexes for [3 + 2] cycloaddition reactions will be described.

The reaction of {[2-(dialkylamino)alkenyl]ethoxycarbene}chromium complexes **88** with alkynes afforded 5-dialkylamino-3-ethoxycyclopentadiene derivatives **89** in good yield, that are a kind of [3 + 2] cycloadducts. When performed in acetonitrile or pyridine as a donor solvent, the reaction was found to be applicable to various (2-aminoalkenyl)carbene complexes. When terminal alkynes were employed, the regioselectivity was approximately 10:1, favoring the isomer containing the alkyne substituent neighboring the amino group. The ethoxycyclopentadiene products were easily hydrolyzed to cyclopentenone derivatives under acidic conditions. The reaction was thought to proceed as follows: In analogy with the Dötz reaction, a metathesis process occurred between the alkyne and the carbene moiety to give a dienylcarbene complex **90**, which undergoes 6π electrocyclization followed by reductive elimination of the cyclopentadiene product. The CO insertion observed in the Dötz reaction was suppressed probably by coordination of the solvent molecule to chromium (Scheme 35).[62a–d]

By applying this methodology, an angular triquinane was synthesized with an overall yield of 22% from (+)-2-carene (Scheme 36).[62e,f]

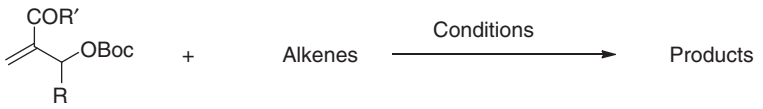
An interesting application concerns the synthesis of indanone derivatives by the reaction of the carbene complexes with 1,5-diene-3-ynes. In this case, dialkenylcyclopentadienes **91** were produced as the initial [3 + 2] cycloaddition products, which further underwent 6π-electrocyclization followed by elimination of the amine to give the products (Scheme 37).[62g,h]

Formal [3 + 2] cycloaddition reactions of alkenylcarbene complexes with ynamines or of alkynylcarbene complexes with enamines have also been developed for the preparation of cyclopentadienes. For example, the reaction of an α,β-unsaturated tungsten carbene complex with an ynamine gave 1-tungsta-1,3,5-hexatriene, which underwent a smooth ring-closure at 20 °C to give a cyclopentadiene product (Scheme 38).[63a,b]

The reaction of alkynylcarbene complexes with enamines was more general and highly regioselective and proceeded at room temperature simply by mixing the two compounds. In both reactions, 1-metalla-1,3,5-hexatrienes are formed as key intermediates, the former through the metathesis reaction via a metallacyclobutene intermediate, and the latter through the 1,4-addition of the enamine to the alkynylcarbene complexes followed by 1,3-proton transfer. Final electrocyclization followed by reductive elimination gives the corresponding cyclopentadiene derivatives (Table 21, Scheme 39).[63c]

A related reaction of α,β-unsaturated tungsten carbene complexes with enamines gave cyclopentenyl ethers in good yield with high diastereoselectivity. The regioselectivity can be reversed depending on the chosen kind of enamines. Enamines derived from ketones afforded 4-amino cyclopentenyl ethers **92**, whereas enamines derived from aldehydes afforded 5-amino derivatives **93** with high regioselectivity. Use of chiral pyrrolidino enamines gave optically active products with high selectivity (Scheme 40).

Table 18 [3 + 2] Cycloaddition with Morita–Baylis–Hillman carbonates



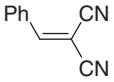
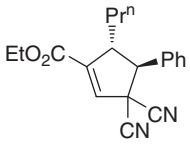
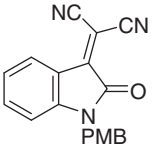
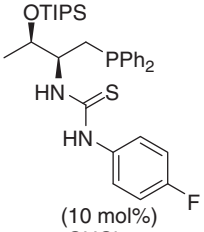
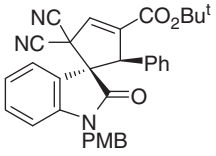
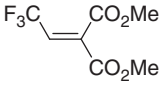
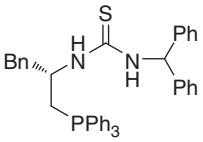
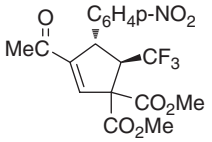
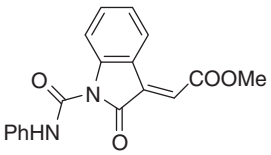
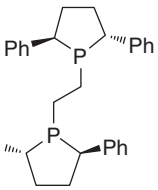
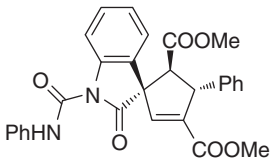
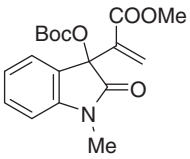
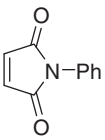
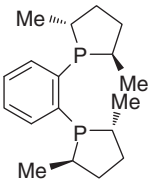
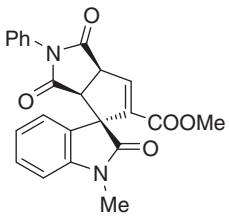
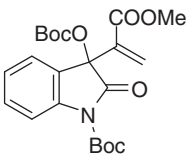
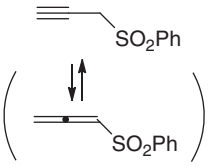
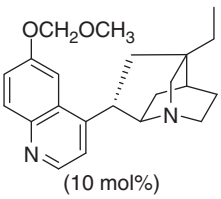
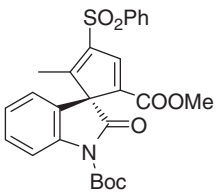
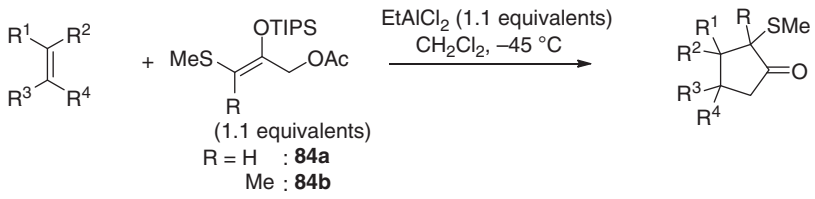
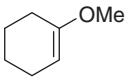
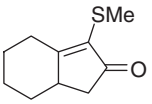
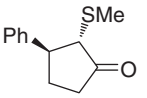
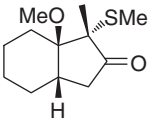
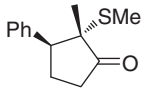
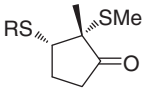
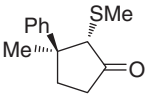
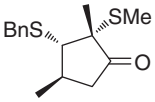
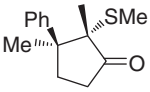
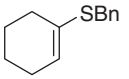
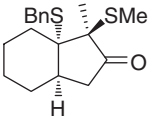
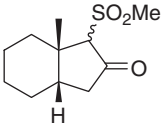
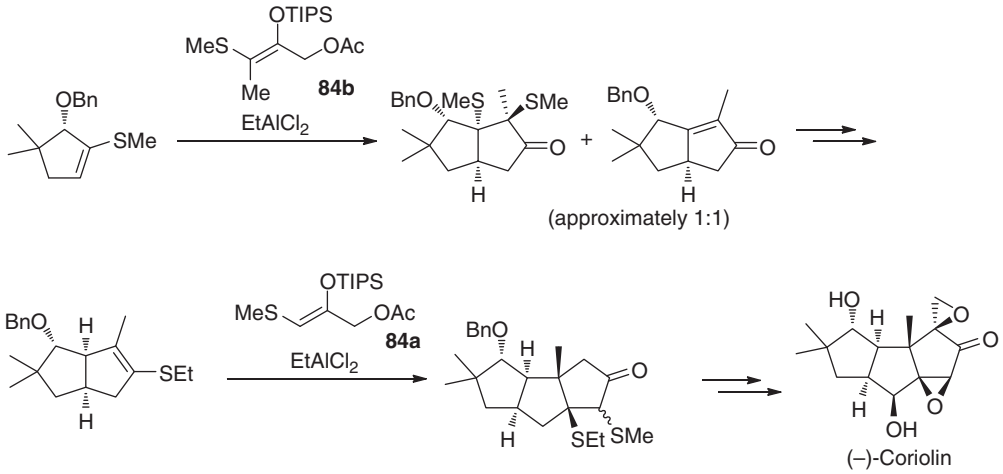
R	*R*[1]	*Alkenes*	*Conditions*	*Products*	*References*
Pr^n	OEt		$EtPh_2P$ (10 mol%) toluene, r.t., 1 h	 90%	54a
Ph	OBu^t		 (10 mol%) $CHCl_3$, r.t., 18 h	 93% (96% *ee*)	54b,c
p-$NO_2C_6H_4$	Me		 (20 mol%) toluene, r.t., 24 h	 99% (91% *ee*)	54d
Ph	OMe		 (10 mol%) CH_2Cl_2, r.t., 2 h	 85% (99% *ee*)	54e
			 (30 mol%) toluene, r.t., 72 h	 62% (93% *ee*)	54f
			 (10 mol%) *m*-xylene, 0 °C, 24 h	 84% (99% *ee*)	54g

Table 19 Annulation reaction with enol ethers, vinyl sulfides, styrenes, and trisubstituted alkenes

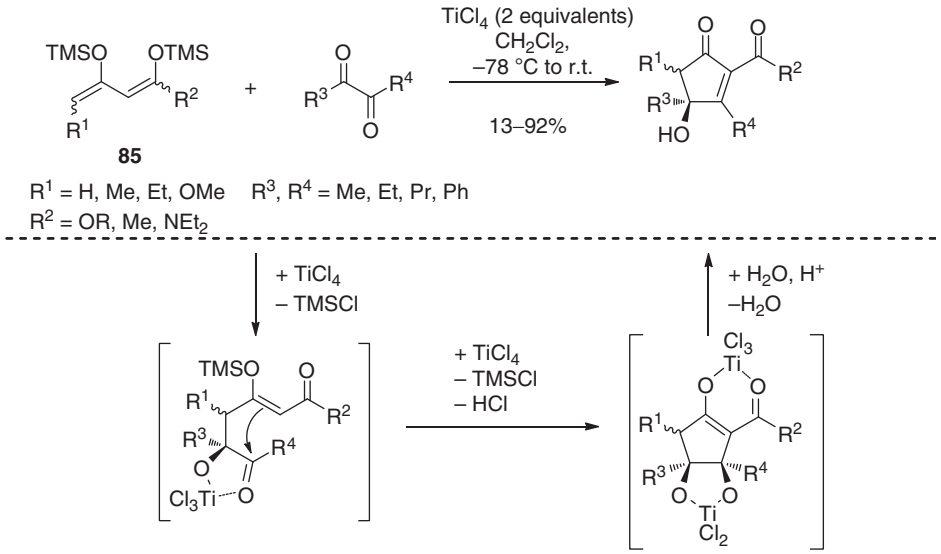


Alkenes	*Enophile*	*Product/Yield*	*Alkenes*	*Enophile*	*Product/Yield*
	**84a**	 86%[a]		**84a**	 66% (50 : 50)
	84b	 95% (> 99: <1)		**84b**	 95% (>99 : <1)
	**84b**	 R = Ph : 82% (>99 : <1) Bn : 86% (>99 : <1)		**84a**	 79% (84 : 16)
	**84b**	 84% (95 : 5)		**84b**	 86% (74 : 26)
	**84b**	 95% (> 99 : <1)		**84a**	 64%[b] (54 : 46)

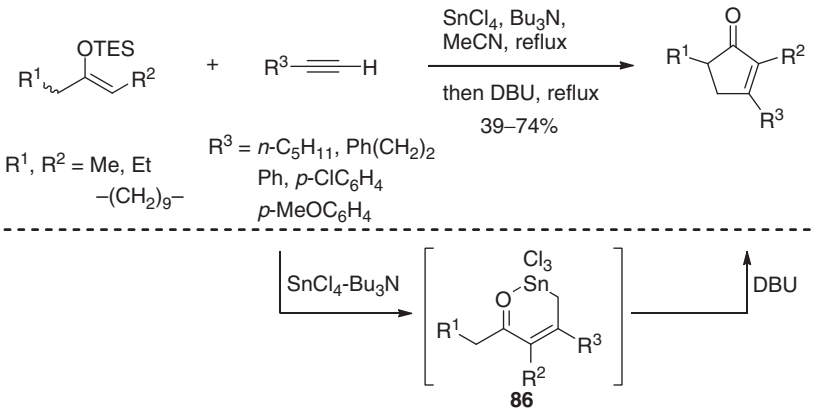
[a]The crude product was treated with DBU to afford the corresponding enone.
[b]The adduct was isolated as the corresponding sulfone after treating the crude product with oxone.



Scheme 30



Scheme 31



Scheme 32

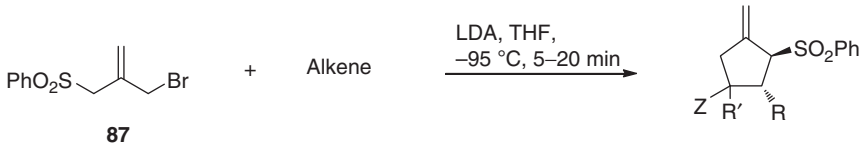
The reaction was proposed to proceed through 1,2-addition (ketone enamines) or 1,4-addition (aldehyde enamines) followed by cyclization with $W(CO)_5$ elimination.[63d]

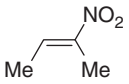
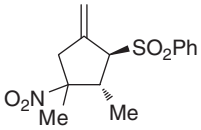
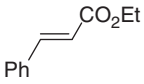
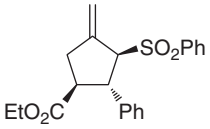
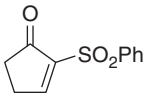
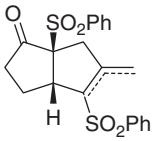
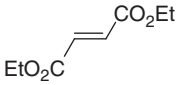
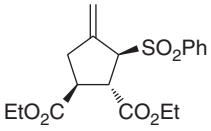
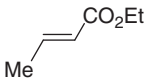
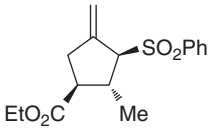
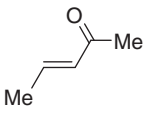
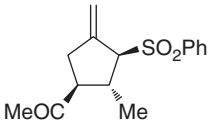
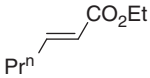
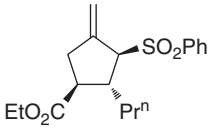
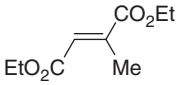
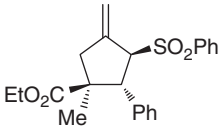
The reaction of α,β-unsaturated carbene complexes with dienes was first realized by using a donor/acceptor-substituted diene in 1,2-dichloroethane (DCE) at 80 °C. It was reported that among several dienes examined, only this diene gave the [3 + 2] cycloaddition product.[64a] Simple dienes were also found to undergo [3 + 2] cycloadditions by choosing appropriate reaction conditions. In these reactions, the choice of the solvent was crucial for the success; by carrying out the reaction in toluene at 80 °C in the presence of 2,6-di-*t*-butyl-4-hydroxytoluene (BHT), cyclopentenyl ethers were obtained in good yield, whereas the reaction in THF at 120 °C in a sealed flask gave [4 + 1] cycloaddition products selectively in moderate yield. Tungsten carbene complex gave higher yields when polysubstituted dienes were employed. An asymmetric version was also presented using menthyloxy carbene complexes. A metalla-Diels–Alder reaction pathway to give metallacyclohexenes followed by reductive elimination was proposed as a possible reaction mechanism (Table 22).[64b]

Reactions of lithium enolates of methyl ketones with α,β-disubstituted alkenyl(methoxy)carbene complexes **96** afforded cyclopentenol derivatives **97** in good yields. Depending on the chosen solvent (Et_2O or THF; or use of pentamethyldiethylenetriamine (PMDTA) as cosolvent), either of two diastereoisomers could be obtained with high selectivity. The reaction proceeded through addition of lithium enolates to the carbene carbon, followed by addition of the generated allyltungsten to the ketone carbonyl with 1,2-$W(CO)_5$ migration. Finally $W(CO)_5$ was eliminated to give the products (Scheme 41).[65]

Additions of alkenyllithiums to alkynyl(methoxy)carbene complexes afforded cyclopentenone derivatives in good yield. The reaction proceeds through 1,4-addition of the alkenyllithiums, followed by protonation to generate $\alpha,\beta,\gamma,\delta$-unsaturated carbene complex intermediates, which undergo cyclization to give cyclopentadienyl ethers. Hydrolysis of the dienyl ethers gave the products. Use of a tungsten carbene complex with a chiral alkoxy group gave optically active products with high selectivity (Scheme 42).[66]

Table 20 Reaction of lithiated 2-(bromomethyl)allyl sulfone with electron-deficient alkenes

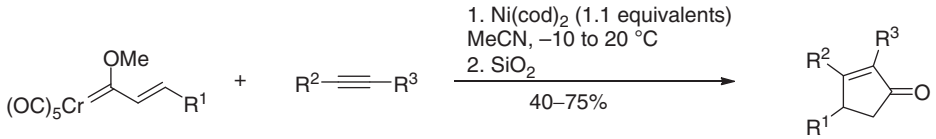


Alkene	*Product/Yield*	*Alkene*	*Product/Yield*
	 51%[a,b]		 92%
	 59%[a,c]		 81%
	 93%		 95%
	 93%		 86%

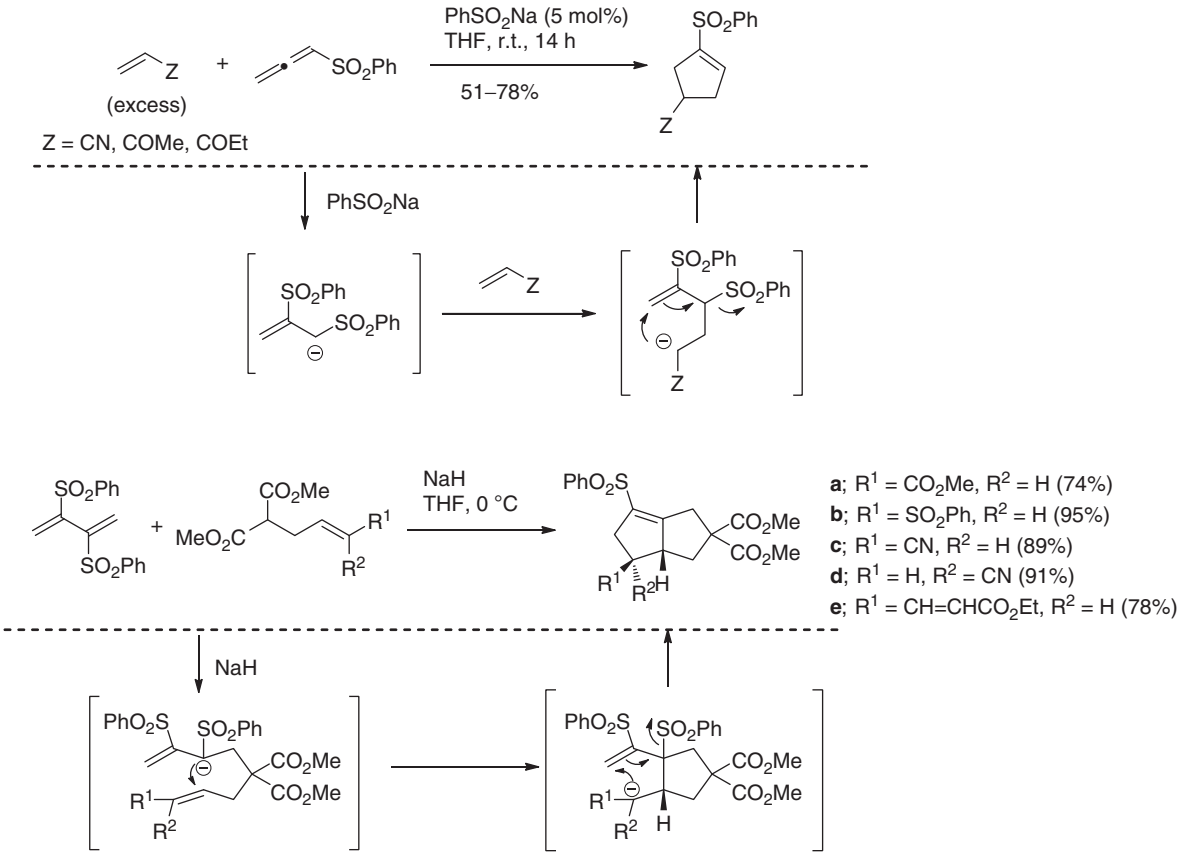
[a]Hexamethylphosphoric triamide was added.
[b]A mixture of *cis*-dimethyl: 40% and *trans*-dimethyl: 11%.
[c]A mixture of diastereo and olefinic positional isomers in a ratio of 9:9:1.

Metal-promoted or -catalyzed reactions of carbene complexes with carbon–carbon double or triple bonds were also reported. A rhodium-catalyzed formal [3 + 2] cycloaddition of α,β-unsaturated chromium carbene complexes with electron-deficient alkynes was developed to give a variety of cyclopentenone derivatives. The reaction was carried out by mixing the chromium carbene complexes and alkynes in the presence of 10 mol% of a cationic Rh(I) complex, and was proposed to proceed through the rhodium carbene complexes generated by transmetallation. The [4 + 2] cycloaddition of the rhodium carbene species with alkynes followed by reductive elimination and hydrolysis gave the cyclopentenone products. The formation of the rhodium carbene complexes was confirmed by X-ray analysis (**Scheme 43**).[67a,b]

Furthermore, the generality of the reaction was greatly expanded by using a stoichiometric amount of $Ni(cod)_2$. In this case, both electron-rich and -deficient alkynes could be employed to give cyclopentenone or cyclopentadiene derivatives in reasonable yield (equation 30).[67c]



R^1 = alkyl, aryl, alkenyl R^2, R^3 = alkyl, aryl, CO_2Me, OEt, $SiMe_3$, Bpin, $SnBu_3$ (30)

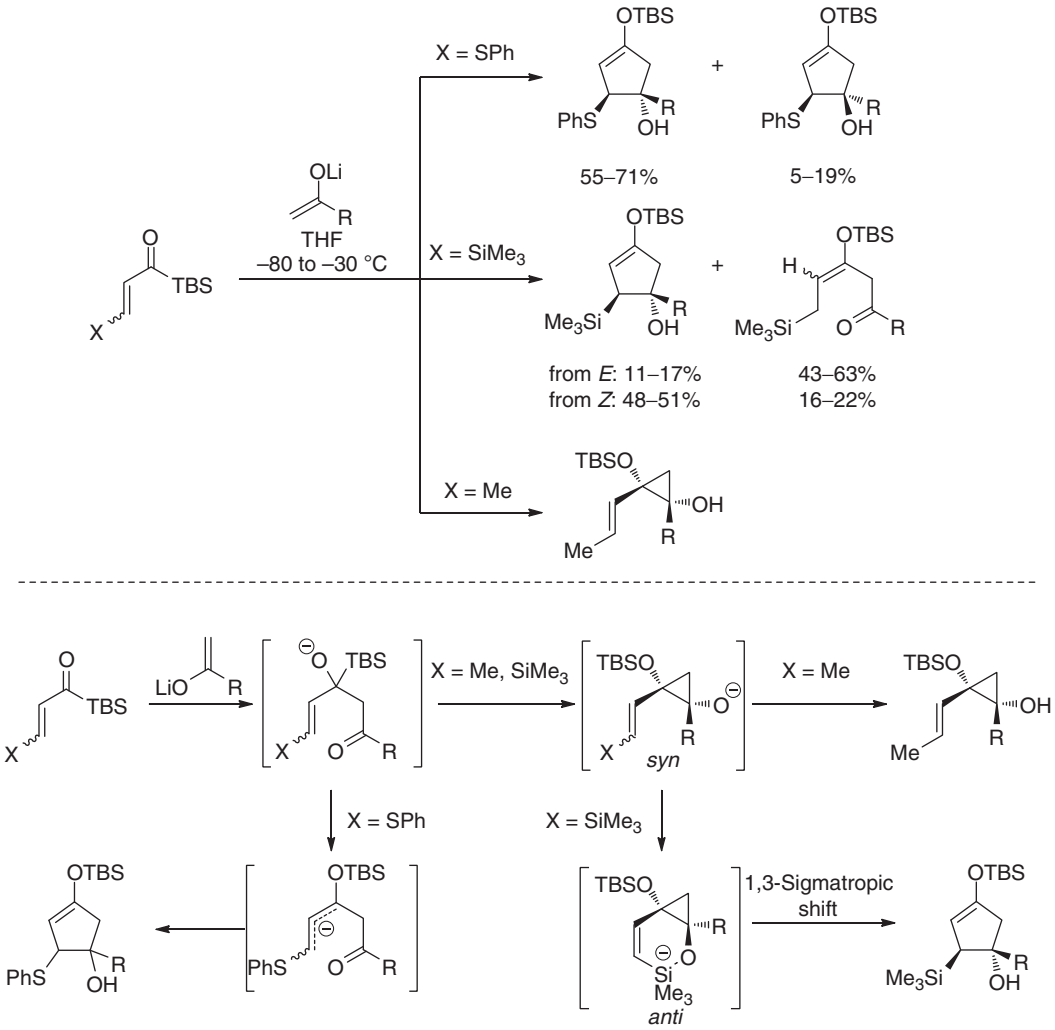


Scheme 33

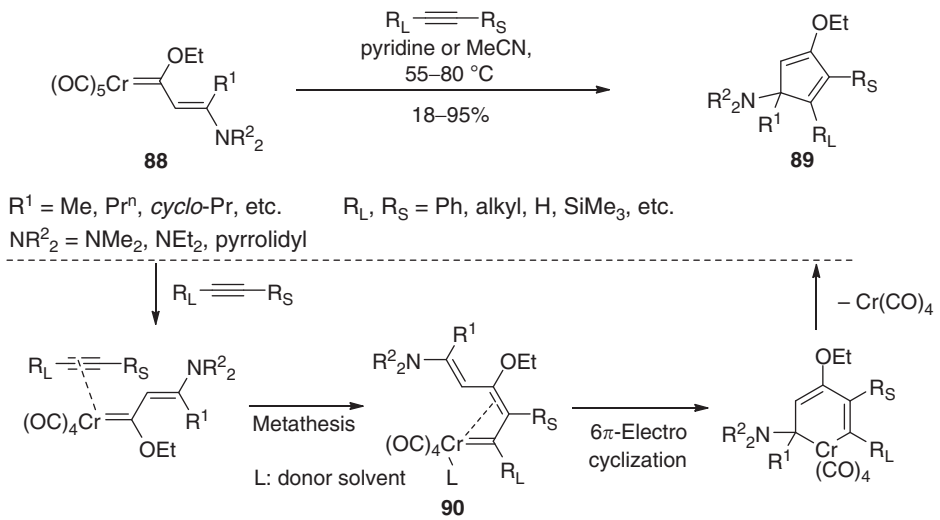
A similar transition metal-promoted reaction of α,β-unsaturated chromium carbene complexes with allenes gave 4-alkylidene-1-methoxycyclopentenes **98** or 1-methoxy-5-methylenecyclopentenes **99** in moderate to high yield depending on the kind of the metal complex employed. Thus, in the presence of an equimolar amount of $Ni(cod)_2$, the reaction gave 4-alkylidene-1-methoxycyclopentenes **98** by the [2 + 2] cycloaddition of the nickel carbene complex with the allene at the less substituted double bond, followed by 1,3-allylic shift of nickel to give the formal [3 + 2] cycloaddition products. However, the Rh(I)-catalyzed reaction initially gave 1-rhoda-1,3-dienes, which undergo a [4 + 2] cycloaddition with the allenes at the more substituted double bond because of the higher degree of stabilization of the transition structure to give 6-methylene-1-rhoda-2-cyclohexenes. Reductive elimination provides 1-methoxy-5-methylenecyclopentenes of type **99**. Allenamides, phenoxyallene, and allenyl esters were applicable to this Rh(I)-catalyzed reaction and gave the corresponding products with complete regio- and stereoselectivity (Scheme 44).[67d,e]

An interesting [3 + 2] cycloaddition reaction of alkynyl tungsten carbene complexes with indoles was reported to give tricyclic indolines **100** in good yield. By using the (–)-8-phenylmenthyl ester, the reaction gave nearly optically pure products in acceptable yield. The reaction was proposed to proceed through 1,4-addition of the indole to the alkynyl carbene complex, followed by ring-closure of the allenyltungsten to the iminium carbon (Scheme 45).[68]

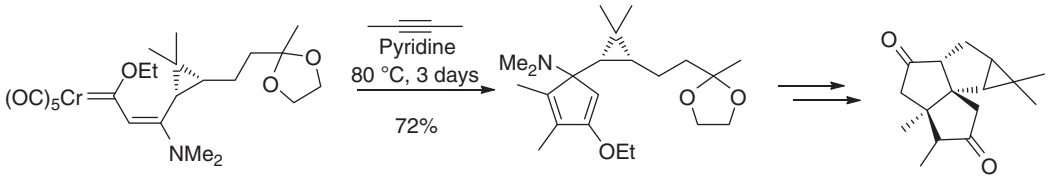
All the examples described so far employ a stoichiometric amount of preformed carbene complexes. As a method to generate α,β-unsaturated carbene complexes catalytically, the Rh(II)-catalyzed reaction of vinyldiazo compounds was developed. Although the Rh(II)-catalyzed reaction of diazoacetate with alkenes is widely employed as a reliable method for the preparation of cyclopropanecarboxylates, it was found that when vinyldiazocarbonyl derivatives were reacted with vinyl ethers in the presence of Rh_2(S-DOSP)$_4$ catalyst, cyclopentenes **101** were obtained as a single diastereomer with high enantioselectivity (equation 31). Although the details of the reaction mechanism were not presented, a direct [3 + 2] cycloaddition pathway or [4 + 2] cycloaddition including the Rh carbenoid moiety followed by reductive elimination was proposed.[69a] Recently, this method was extended to the reaction with indoles instead of vinyl ethers to give cyclopenta[b]indoles **102** in a highly enantioselective manner, in which a stepwise mechanism including nucleophilic addition of the indoles to the Rh carbenoid carbon followed by ring-closure of the intermediate allylrhodiums to the iminium carbon was proposed (equation 32).[69b]



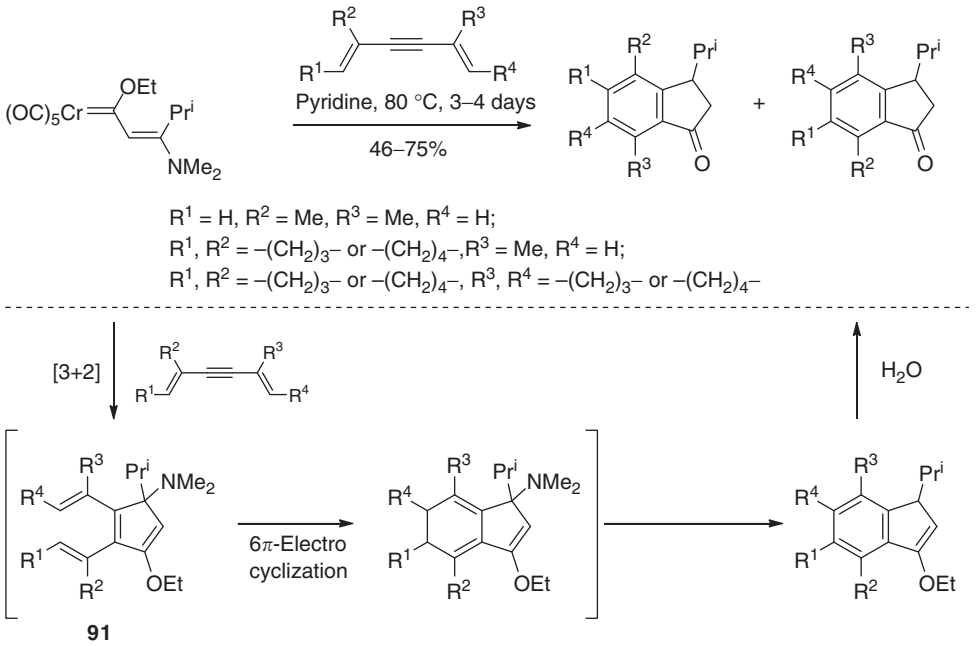
Scheme 34



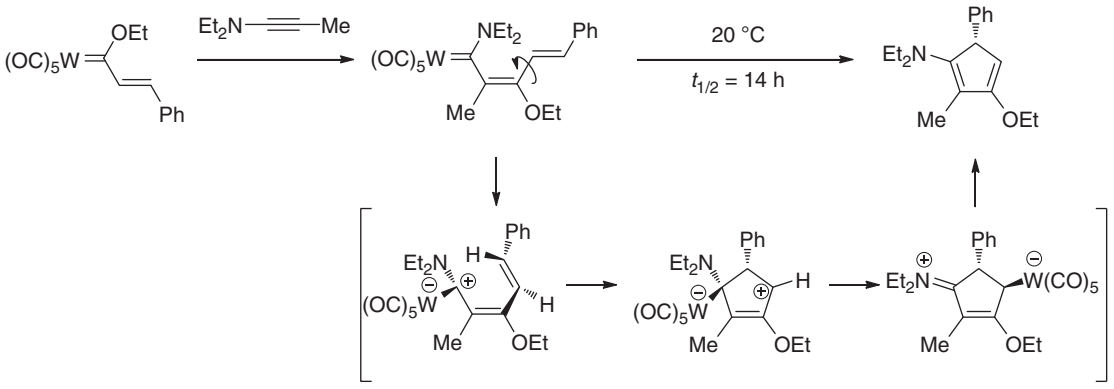
Scheme 35



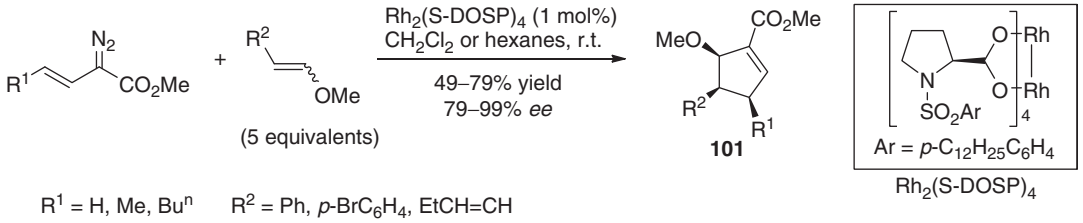
Scheme 36



Scheme 37

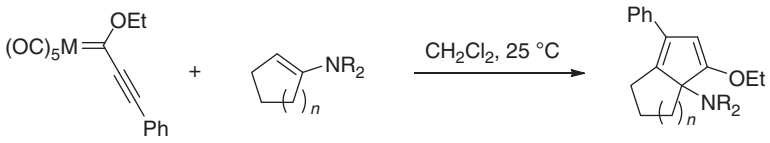


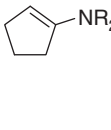
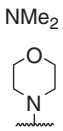
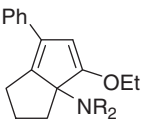
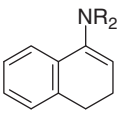
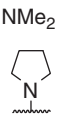
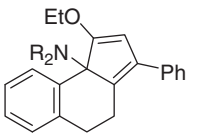
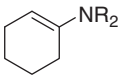
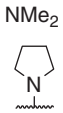
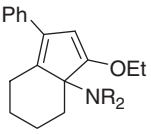
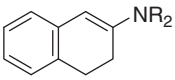
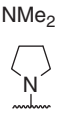
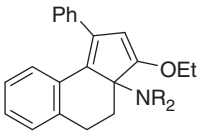
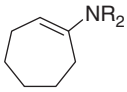
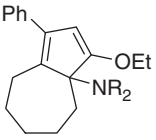
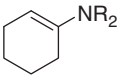
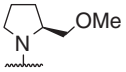
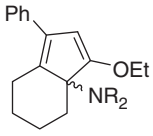
Scheme 38



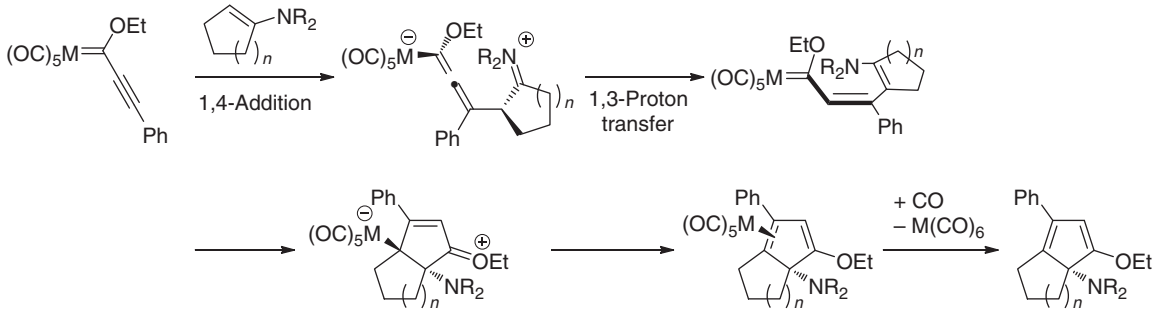
(31)

Table 21 Regioselective cyclopentadiene annulation to 1-aminocycloalkenes

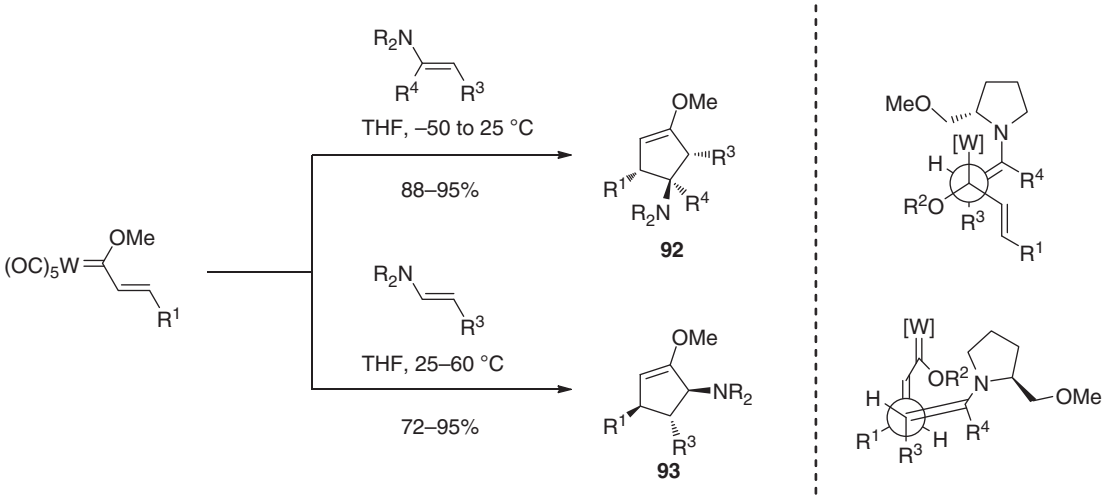


Enamine	*NR_2*	*Product*	*Yield (%)*		*Enamine*	*NR_2*	*Product*	*Yield (%)*	
			M=W	*Cr*				*M=W*	*Cr*
			73 67	– –				80[a] 99[a]	– 94[a]
			94 72	77 87				76 61	56 75
			76[a]	–				85	–

[a]At 50 °C for 1 h.

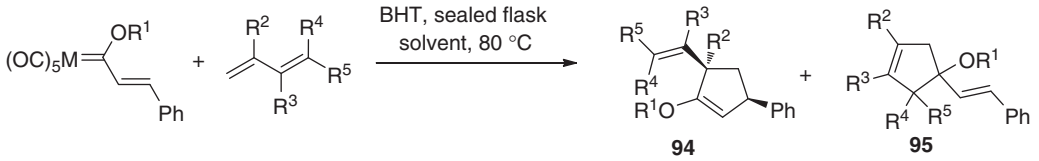


Scheme 39

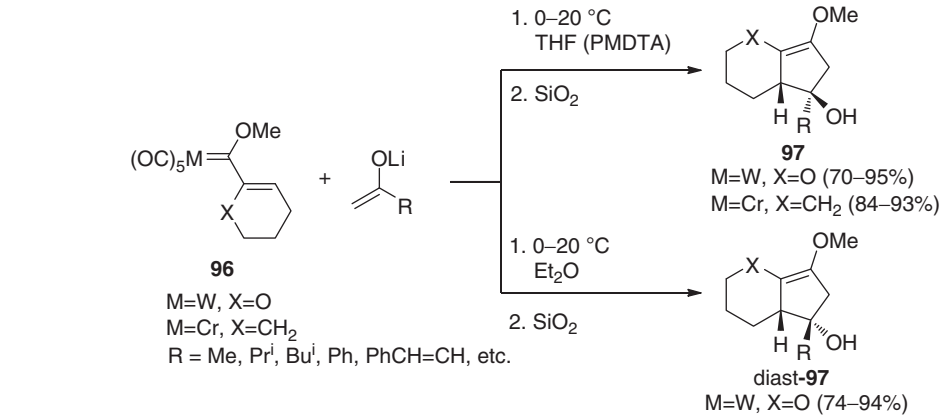


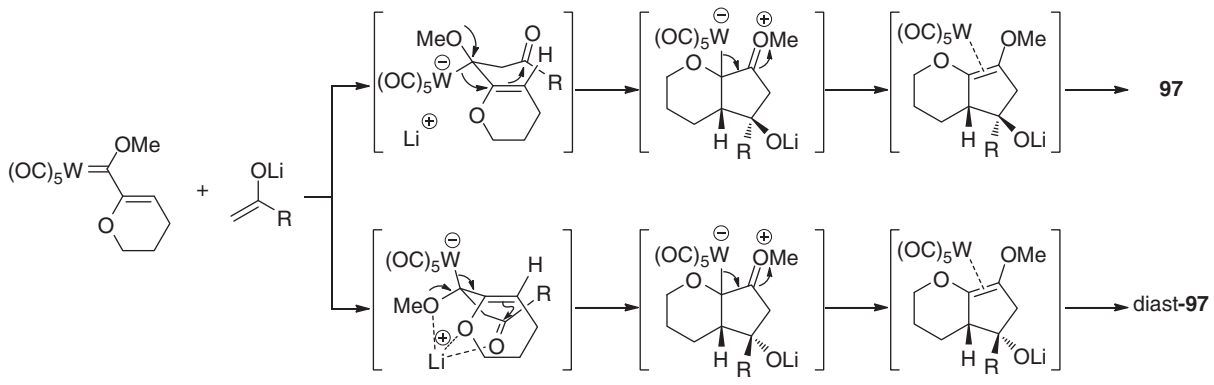
Scheme 40

Table 22 [3 + 2] Cycloaddition of Fischer carbene complexes and dienes

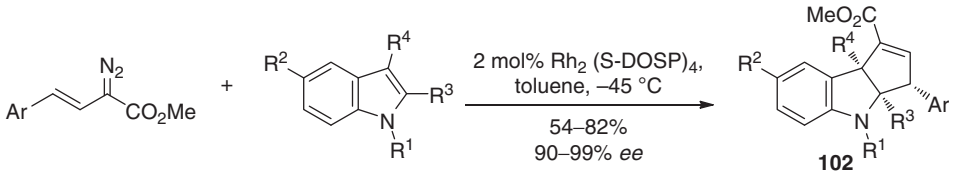


M	R^1	R^2	R^3	R^4	R^5	*Solvent*	*Yield of **94** (%)*	*Yield of **95** (%)*
Cr	Me	OTBS	H	H	COOMe	1,2-Dichloroethane (DCE)	72	0
Cr	Me	Me	H	H	H	THF (120 °C)	0	47
Cr	Me	Me	H	H	H	Toluene	94	0
W	Me	Me	Me	H	H	Toluene	50	0
W	Me	Me	H	Me	Me	Toluene	65	0
W	(–)-8-Phenylmenthyl	Me	Me	H	H	Toluene	73 (*de* 74%)	0
W	(–)-8-Phenylmenthyl	H	H	H	H	Toluene	90 (*de* > 99%)	0



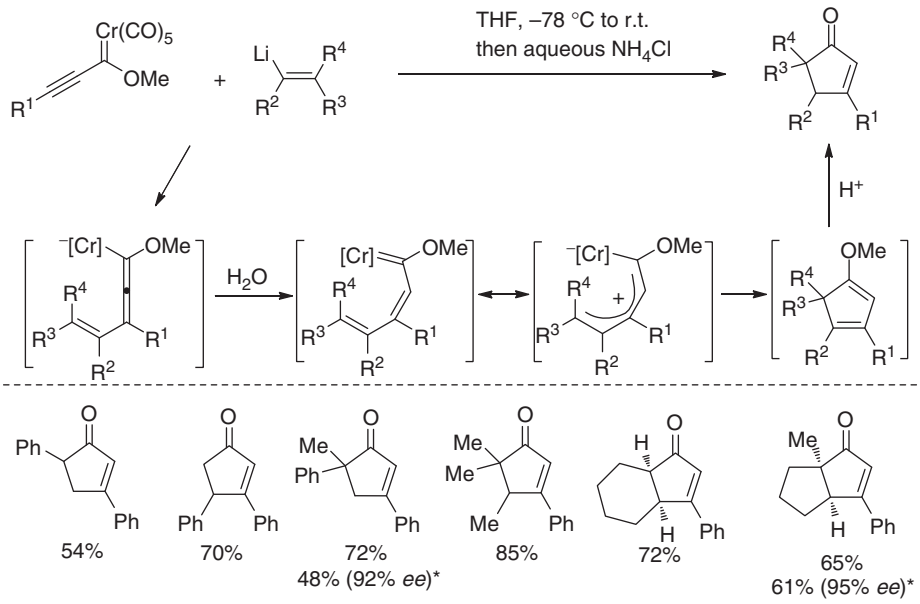


Scheme 41



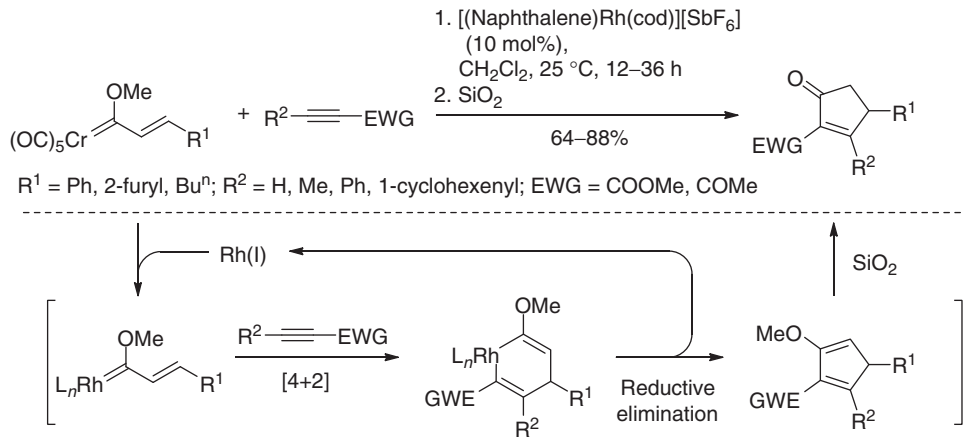
(32)

Ar = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 3-(*N*-Boc-indolyl)
R^1 = Me, Bz; R^2 = H, Me, Br, NO_2, OMe; R^3, R^4 = Me, H or H, Me



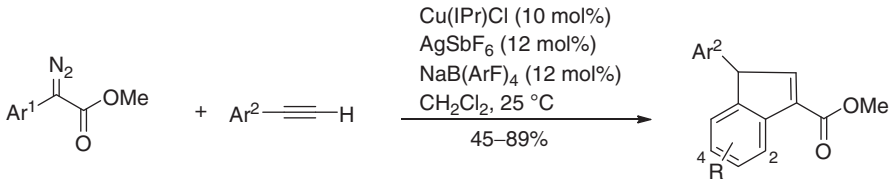
*Corresponding tungsten complex with (–)-8-phenylmenthyloxy group instead of methoxy group.

Scheme 42



Scheme 43

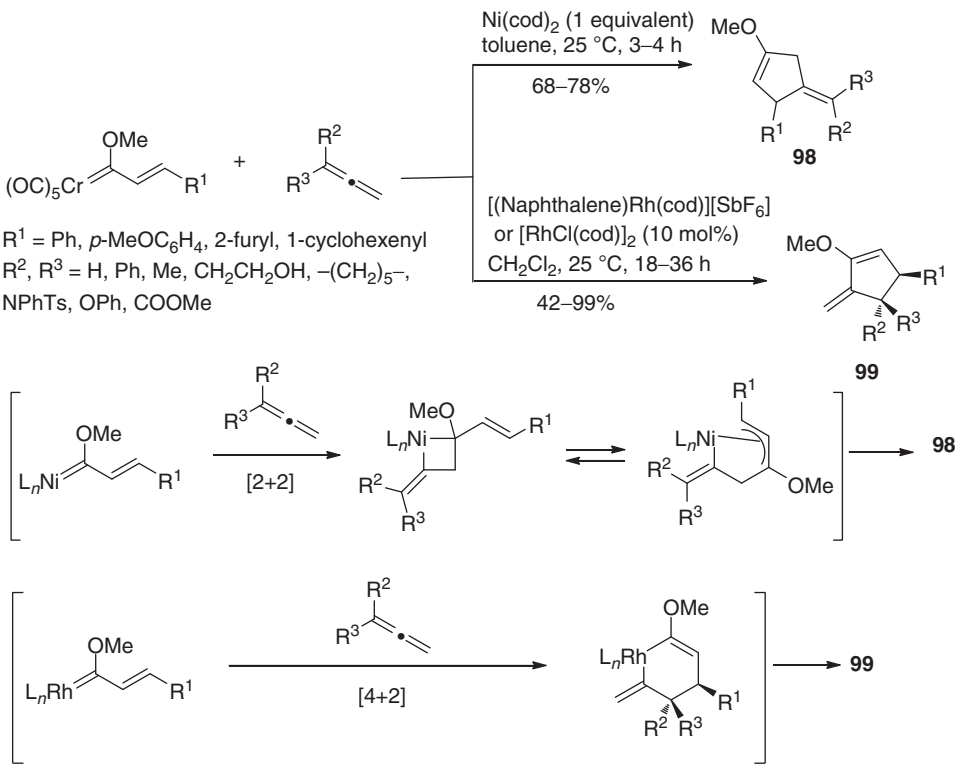
Copper-catalyzed formal [3 + 2] cycloaddition reactions of α-aryldiazoesters with terminal aryl or alkenyl alkynes gave indene derivatives in reasonable yield. Electrophilic addition of the alkyne to the carbene carbon generates zwitterionic intermediates, which cyclize to the corresponding products (equation 33).[70]



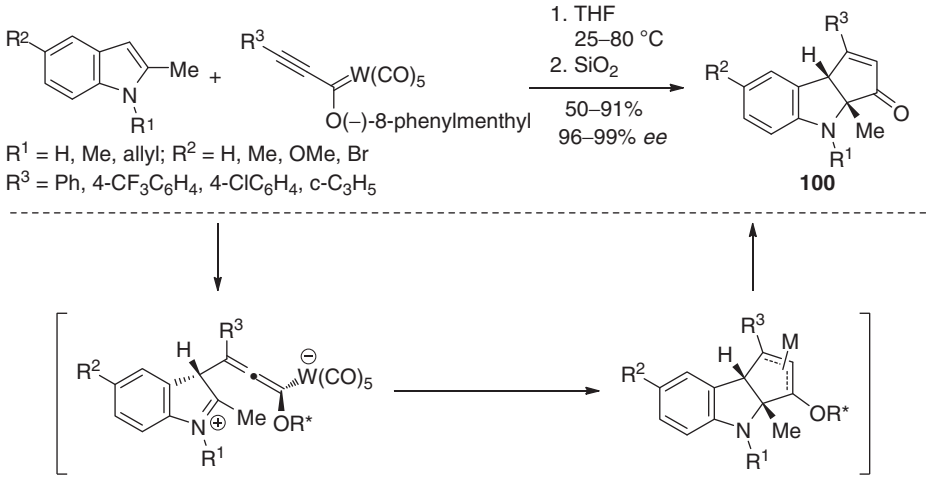
(33)

Ar^1 = Ph, 2-naphthyl, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-BrC_6H_4, 2-MeC_6H_4
Ar^2 = 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-thienyl, 1-cyclohexenyl

As a new method for the catalytic generation of α,β-unsaturated carbene complexes for [3 + 2] cycloadditions, the cationic Rh(I)-catalyzed reaction of propargyl esters with electron-deficient alkynes was developed. The Rh(I) catalyst worked as an electrophilic reagent; specifically, the reaction of the alkoxycarbonyl-substituted propargylic esters with the Rh(I) complex



Scheme 44

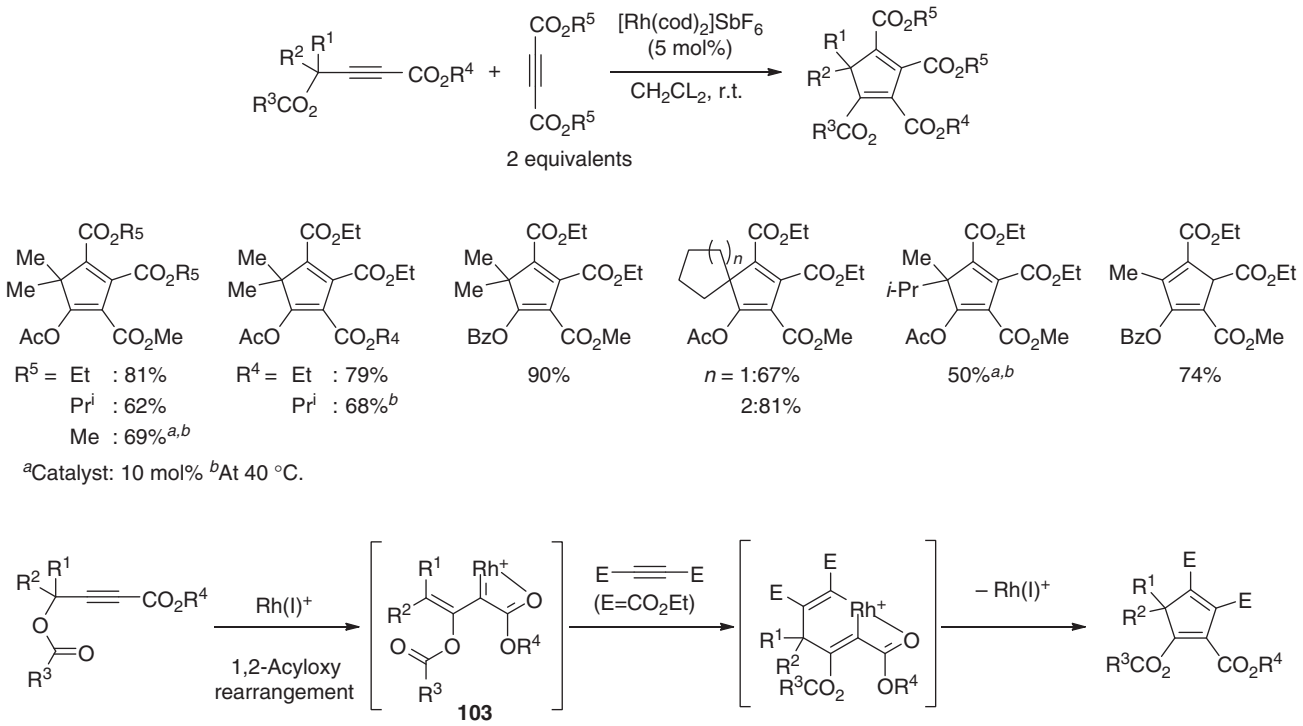


Scheme 45

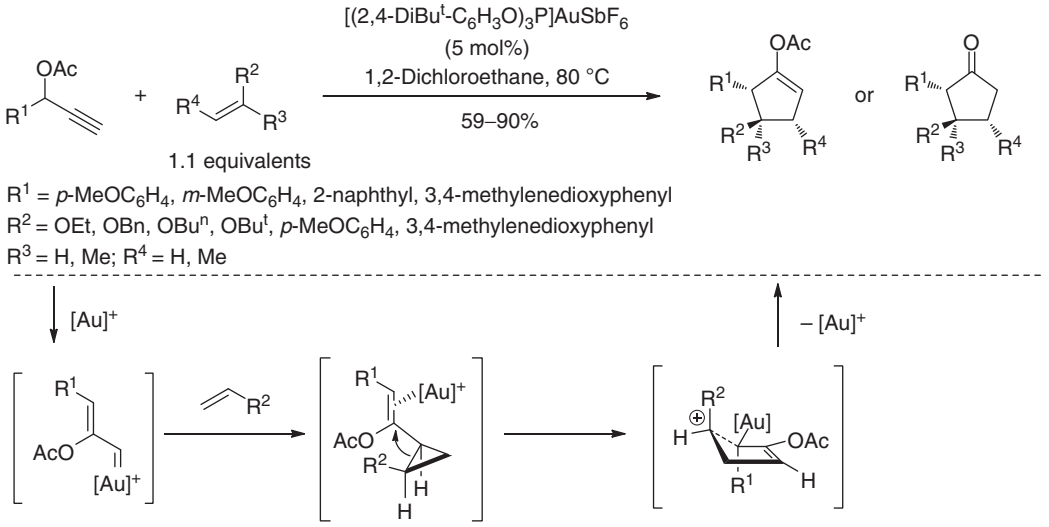
generated an α,β-unsaturated carbene complex intermediate through 1,2-acyloxy rearrangement, which then reacted with acetylenedicarboxylate to give cyclopentadiene derivatives. The essential part of the pathway is the intermolecular [3 + 2] cycloaddition of the α,β-unsaturated Rh(I) carbene complex intermediates **103** with the electron-deficient alkynes. The method showed reasonable generality concerning the propargyl esters, but the use of electron-deficient alkenes gave cyclopropanes instead of cyclopentene derivatives in good yields (Scheme 46).[71]

Although limited to arylpropargyl esters, a similar reaction with electron-rich alkenes was achieved using a cationic Au(I) complex to give cyclopentenyl acetates in good yields. It was proposed that the Au(I)-catalyzed 1,2-acetoxy migration of the propargyl acetates generates α,β-unsaturated carbene complex intermediates, which react with the alkenes to give vinylcyclopropanes. Subsequent opening of the cyclopropane ring was promoted by coordination of the Au(I) to the adjacent alkenyl moiety, followed by cyclization to give the products (Scheme 47).[72]

Another approach realizing a unique 1,3-dipole generation and subsequent [3 + 2] cycloaddition reaction appeared quite recently. Treatment of α-alkynyl-substituted α,β-unsaturated ketones **104** with 3-alkenylindole in the presence of a cationic Au(I)

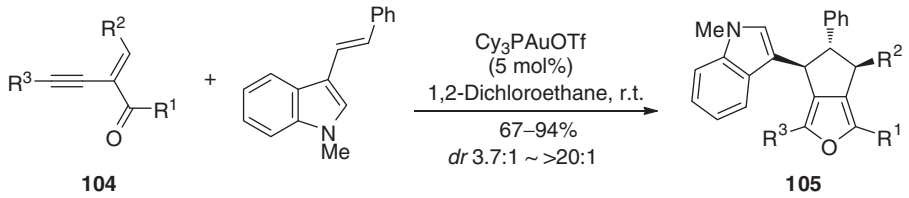

[Rh(cod)2]SbF6
(5 mol%)
CH2CL2, r.t.
2 equivalents
R5 = Et : 81%
Pri : 62%
Me : 69%a,b
R4 = Et : 79%
Pri : 68%b
90%
n = 1:67%
2:81%
50%a,b
74%
aCatalyst: 10 mol% bAt 40 °C.
Rh(I)+
1,2-Acyloxy
rearrangement
103
E=CO2Et
– Rh(I)+

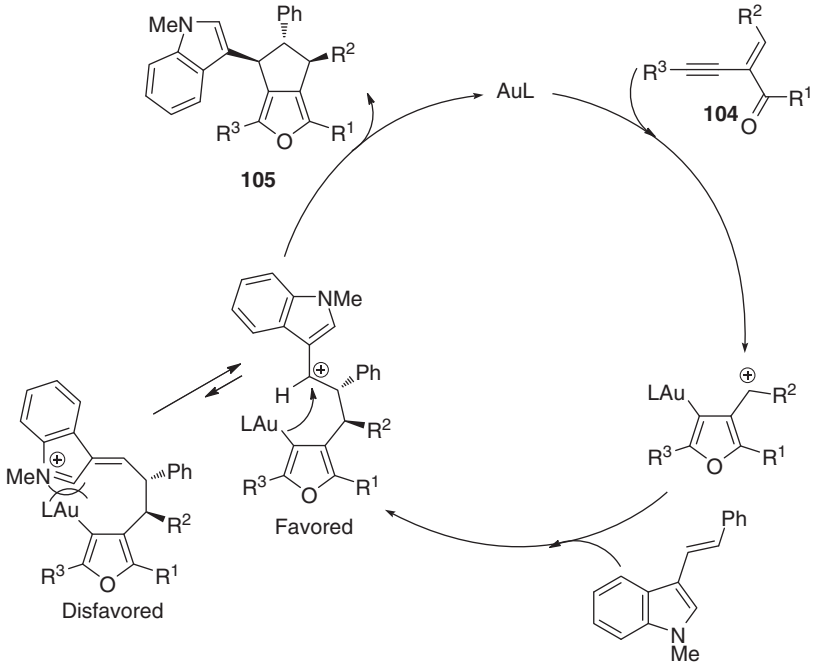
Scheme 46



Scheme 47

complex gave furan-fused cyclopentane derivatives in good yields with high diastereoselectivity. A furan-containing 1,3-dipole equivalent was generated by the intramolecular cyclization of the carbonyl oxygen to the Au(I)-activated alkyne moiety. Then the nucleophilic attack of the olefin moiety at the C3 position of the indole followed by ring-closure of the furylgold(I) to the cation next to the indole gave the [3 + 2] cycloaddition product (Scheme 48).[73]

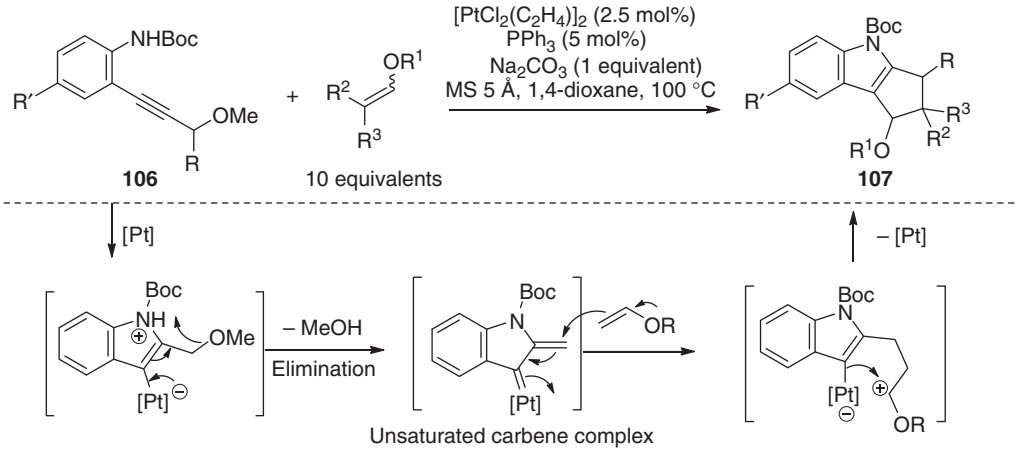




Scheme 48

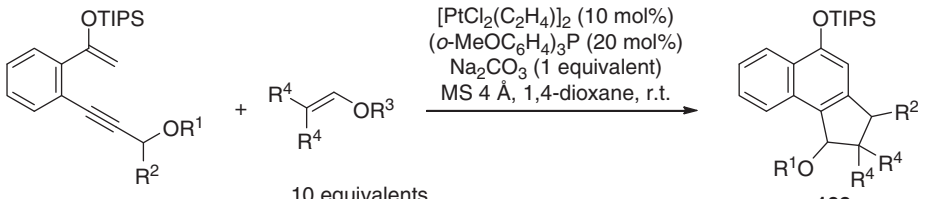
The Pt(II)-catalyzed generation of α,β-unsaturated carbene complex intermediates from various propargyl ether derivatives based on the electrophilic activation of alkynes was employed for [3 + 2] cycloaddition reactions with electron-rich alkenes. Treatment of 2-(3-methoxyprop-1-ynyl)aniline derivatives **106** and vinyl ethers with 2.5 mol% of $[PtCl_2(C_2H_4)]_2$ (5 mol% based on Pt) and 5 mol% of PPh_3 at 100 °C in the presence of Na_2CO_3 as base gave tricyclic indoles in good yield. The reaction was thought to proceed through 5-*endo* nucleophilic attack of the amine nitrogen onto the alkyne, activated electrophilically by Pt(II), to give a zwitterionic intermediate. Then, elimination of the methoxy group triggered by electron-donation from the alkenyl metallic part along with deprotonation from the ammonium nitrogen occurs to give an unsaturated carbene complex. Nucleophilic attack of the vinyl ether to the β-carbon of this α,β-unsaturated carbene moiety generates an alkenyl metallic intermediate, which undergoes intramolecular nucleophilic attack onto the oxonium carbon to afford the final product with regeneration of the catalyst. The efficient formation of indoles, naphthols, and benzofuran fused with a five-membered ring was achieved in high yields based on the same strategy (**Table 23**, equation 34).[74]

Table 23 Platinum-catalyzed [3 + 2] cycloaddition reaction of α,β-unsaturated carbene complex



R	*R′*	*R*^{1}	*R*^{2}	*R*^{3}	*Yield (%)*
H	H	Bu^n	H	H	83
H	H	Bu^t	H	H	79
H	H	*Cyclo*-Hex	H	H	88
H	H	–$(CH_2)_2$Cl	H	H	70
H	H	PMB	H	H	82
H	H	–$(CH_2)_2$–		H	63
H	H	Et	Me	H	70[a]
H	H	Et	Me	Me	73
Me	H	Bu^n	H	H	68[b]
H	MeO	Bu^n	H	H	67
H	F	Bu^n	H	H	80

[a] *dr* = 66:34.
[b] *dr* = 4:1.



(34)

108a (R^1 = Me, R^2 = H)
108b (R^1 = Et, R^2 = OEt)

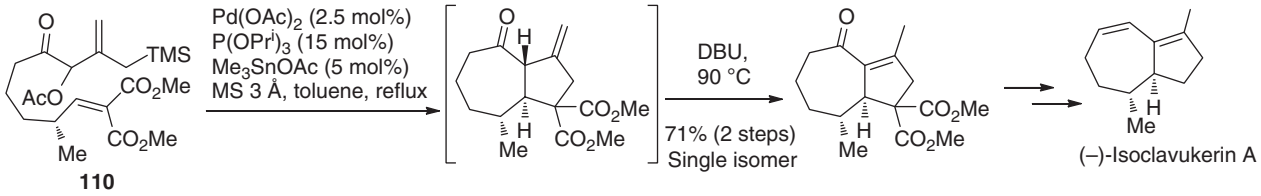
109a (R^2 = H, R^3 = Bu^n, R^4 = H, 82% yield) from **108a**
109b (R^2 = H, R^3 = PMB, R^4 = H, 60% yield) from **108a**
109c (R^2 = H, R^3 = Et, R^4 = Me, 79% yield)[a] from **108a**
109d (R^2 = OEt, R^3 = Bu^n R^4 = H, 62% yield (one isomer))[a] from **108b**
[a] 100 °C, 3 h.

5.08.4.2 Use of Cyclopropane Rings as Three-Carbon Unit in the Transition Metal-Catalyzed Reaction

5.08.4.2.1 Palladium-catalyzed TMM reaction

There are two major approaches for the generation of TMM–transition metal complexes and their further [3 + 2] cycloaddition reactions. The first method employs 2-(trimethylsilylmethyl)-3-acetoxy-1-propenes, whereas the other employs methylenecyclopropanes as precursors. Most of these reactions are catalyzed by palladium complexes, but some other metals such as nickel were also employed. Various aspects of the two methods have been studied, including chemo-, regio- and stereoselectivities, which were already described in the first edition of this book (*see* Chapter 3.2).[1a] Since then, further investigations have been done mainly on the application of this methodology to natural product synthesis and asymmetric catalysis. The recent advances are summarized below.[75]

Concerning the first method of employing 2-(trimethylsilylmethyl)-3-acetoxy-1-propenes as precursor of TMM, applications to natural product synthesis were studied, including intramolecular versions of the reaction. For example, the diastereoselectivity of the intramolecular [3 + 2] cycloaddition of substrate **110** having a stereogenic center adjacent to the acceptor was shown to be very high when doubly activated acceptors were employed. This reaction was applied to the total synthesis of (–)-isoclavukerin A (Scheme 49).[76a]

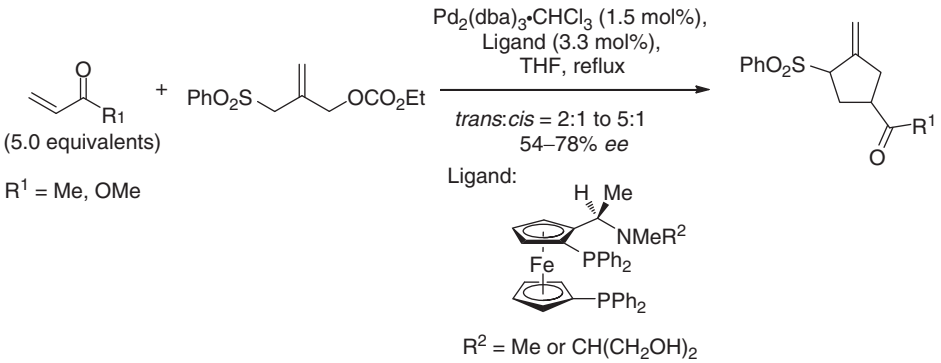


Scheme 49

Various other compounds such as kempane diterpenes,[76b] the basic skeleton of the kaurane diterpenes,[76c] (±)-cephalotzxine,[76d] 11-hydroxyjasionone,[76e] (+)-brefeldin A,[76f,g] pinnaic acid,[76h] and several others[76i] have been synthesized utilizing this methodology. By means of a carboxylative TMM-cycloaddition using the silylated TMM precursor **111**,[76j] a concise total synthesis of (±)-marcfortine B was achieved (Table 24).[76k]

Some additional aspects of this reaction were reported. Several factors were examined in the reaction with α,β-unsaturated ketones. 1,4-Addition reactions occurred as a major pathway when triisopropyl phosphite or tri(*o*-methoxyphenyl)phosphine was employed as ligand, whereas 1,2-addition predominated when the reaction was carried out in the presence of a catalytic amount of $In(acac)_3$ along with PPh_3 as the ligand (Scheme 50).[77]

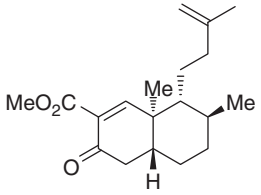
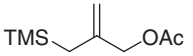
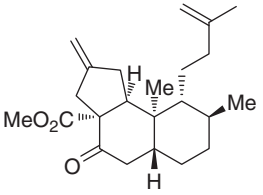
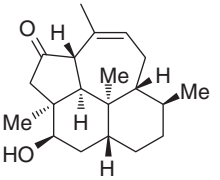
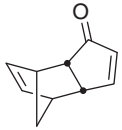
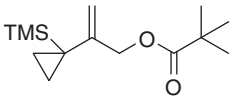
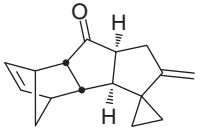
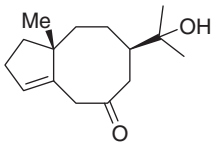
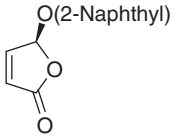
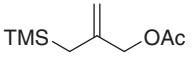
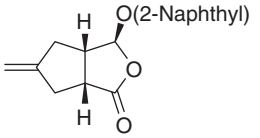
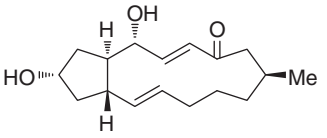
Recently, asymmetric catalytic variants of this reaction have been developed.[78a] The first example of a [3 + 2] cycloaddition of 2-(sulfonylmethyl)-2-propenyl carbonate with methyl acrylate or methyl vinyl ketone catalyzed by a chiral palladium complex was reported to give methylenecyclopentane derivatives in up to 78% *ee* by using a chiral ferrocenylphosphine ligand (equation 35).[78b]



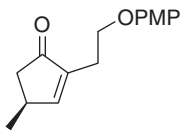
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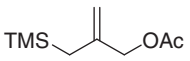
The second example of this type of reaction appeared more than 15 years later using a phosphoramidite-type ligand containing 1,1′-bi-2-naphthol and 2,5-diphenylpyrrolidine, which realized a wider scope of the reaction with reasonably high enantioselecivity.[78c] For example, treatment of 2-(trimethylsilylmethyl)-3-acetoxy-1-propene and an electron-deficient alkene with 5 mol% of $Pd(dba)_2$ and 10 mol% of the phosphoramidite ligand gave methylenecyclopentane derivatives in high yield with high enantioselectivity. As the electron-deficient alkene, α,β-unsaturated ketones, esters, amides, nitriles, and nitroalkenes could be employed without problem; in particular, α,β-unsaturated acyl pyrroles reacted with a substituted TMM precursor to give highly substituted cyclopentane derivatives in very high diastereo- and enantioselectivity.[78d–f] In these reactions, the use of a bulky

Table 24 Representative examples of Pd-catalyzed TMM [3 + 2] cycloaddition reactions

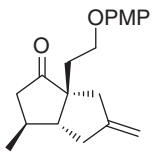
Alkene	*TMM precursor*	*Conditions*	*Product/Yield*	*Target*	*References*
		$Pd(OAc)_2$ (24 mol%), $P(OEt)_3$ (110 mol%), THF, reflux, 20 h	 98%	 Kempane diterpenes	76b
		$Pd(OAc)_2$ (5 mol%), $P(OPr^i)_3$ (50 mol%), dioxane, 150 °C	 50–60%	 11-Hydroxyjasionone	76e
 Enantiopure		$Pd(OAc)_2$ (2.5 mol%), $P(OPr^i)_3$ (20 mol%), toluene, 100 °C,12 h	 93%, >98:2 *dr*	 (+)-Brefeldin A	76f

(*Continued*)

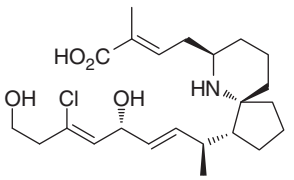




$Pd(OAc)_2$, $P(OPr^i)_3$, THE, reflux

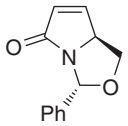


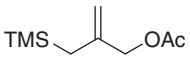
80%



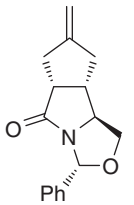
Pinnaic acid

76h

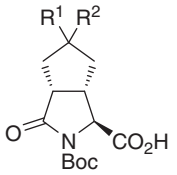




$Pd(OAc)_2$ (20 mol%), $P(OPr^i)_3$ (160 mol%), toluene, reflux

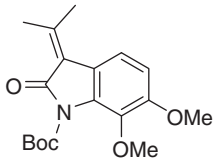


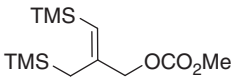
80%



5,5-Fused proline analogs

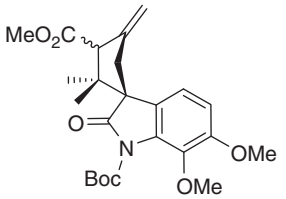
76i



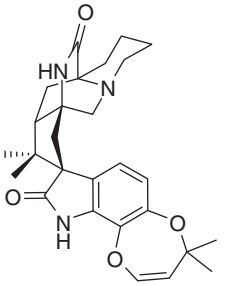


111

$Pd(OAc)_2$ (5 mol%), $P(OPr^i)_3$ (35 mol%), toluene, reflux then Me_2SO_4, K_2CO_3, acetone, reflux

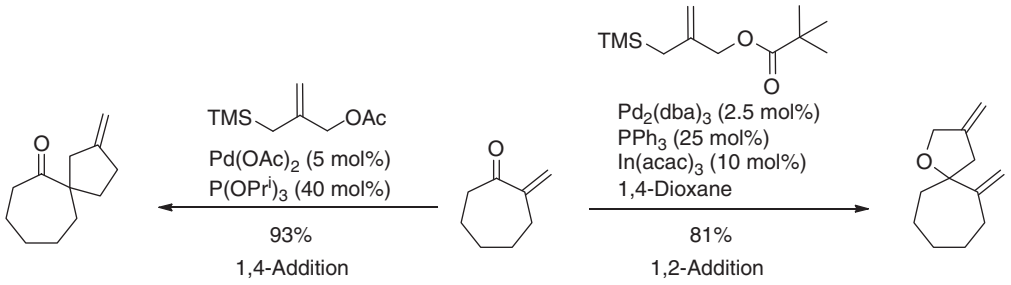


93% (2 steps)



(±)-Marcfortine B

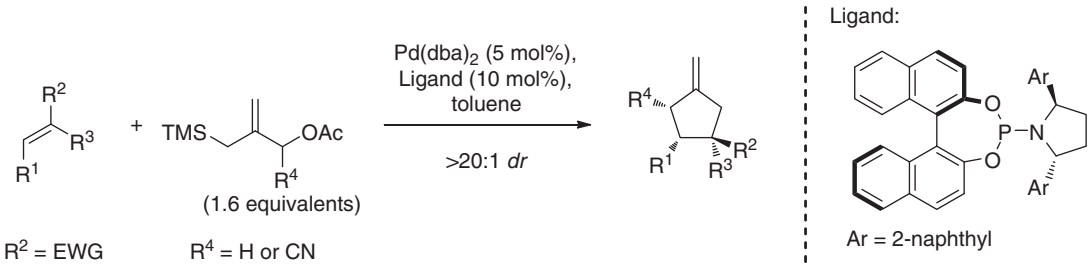
76k

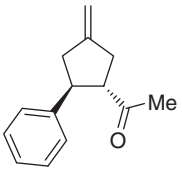
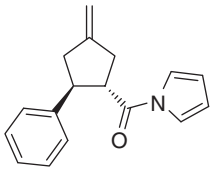
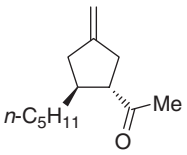
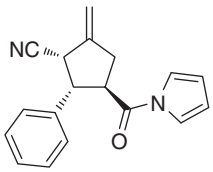
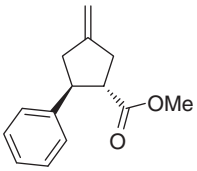
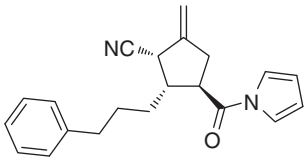
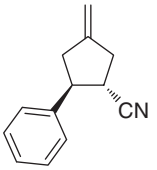
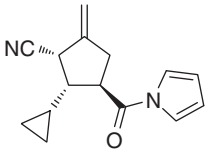
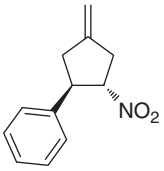
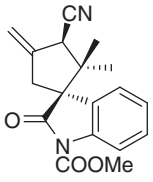


Scheme 50

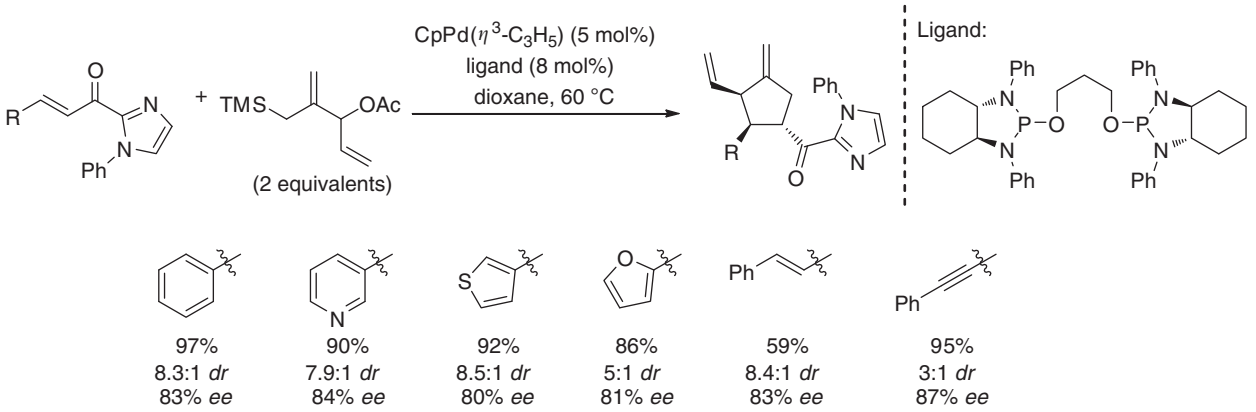
phosphoramidite ligand enabled control of the nucleophilic attack of the zwitterionic intermediates to the alkenes, which occurred distal to the coordinated chiral ligand on the palladium (Table 25).

Table 25 Asymmetric TMM-cycloaddition reaction



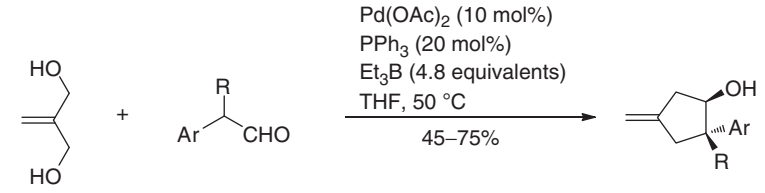
Product	*Temperature (°C)*	*Yield (%)*	*ee (%)*	*Product*	*Temperature (°C)*	*Yield (%)*	*ee (%)*
	23	91	98		45	80	91
	23	80	95		23	87 (>20:1 *dr*)	92
	45	97	90		23	82 (>20:1 *dr*)	94
	45	98	92		23	84 (>20:1 *dr*)	94
	50	93	87		23	97 (6.2:1)	>99

Diamidophosphite ligands derived from chiral *trans*-1,2-cyclohexanediamine and 2,4-pentanediol were employed for the reaction of vinyl-substituted TMMs with α,β-unsaturated acyl imidazoles to give tetra-substituted cyclopentanes bearing three contiguous stereocenters in high yields with good diastereo- and enantioselecitivity (Scheme 51).[78g]



Scheme 51

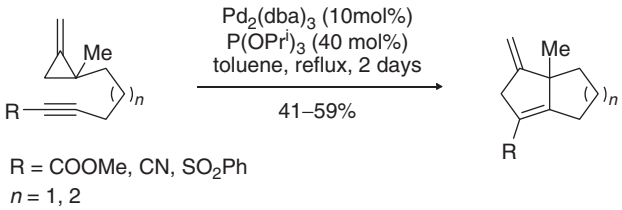
Bis-allylic alcohol could be employed as a 1,3-dipole equivalent in the palladium(0)-catalyzed reaction with α-branched aliphatic aldehydes. Treatment of a mixture of 2-hydroxymethyl-2-propen-1-ol and an aldehyde with 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, and excess of Et_3B gave methylenecyclopentanol derivatives in good yield. In this reaction, a π-allylpalladium intermediate was generated first by the action of palladium(0) and Et_3B. The aldehyde attacks this intermediate at the α-position to give an addition product, from which a new allylpalladium species is generated that then nucleophilically attacks the carbonyl carbon to give the product. In the palladium-catalyzed TMM chemistry, electron-deficient alkenes are usually employed and the reaction proceeds by a sequence of nucleophilic-electrophilic alkylation. However, the present reaction proceeds in the opposite order: Electrophilic-nucleophilic alkylation (equation 36).[79]



(36)

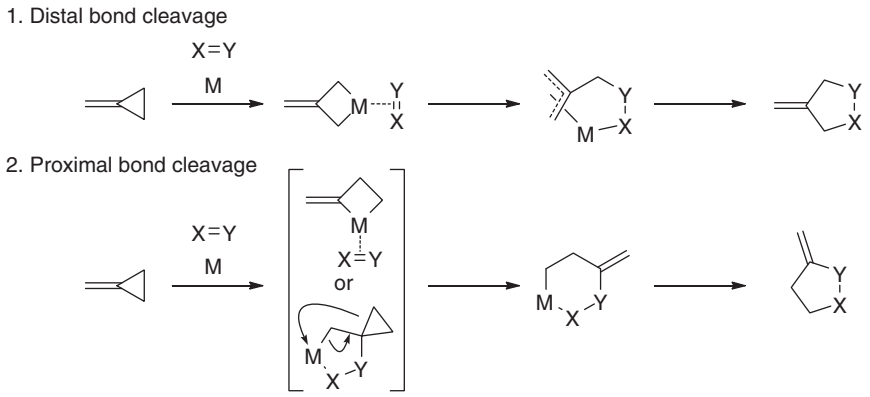
The use of methylenecyclopropanes in transition metal-catalyzed reactions has been extensively studied, initially with nickel and then with palladium catalysts. In almost all cases, the distal ring opening occurred in the palladium-catalyzed reaction, whereas the nickel-catalyzed reaction gave distal or proximal ring opening depending on the substituent on the cyclopropane ring (Scheme 52). Fundamental aspects of these reactions were described in the first edition of this book (*see* Chapter 3.2).[1b,80]

A major advance since the first edition is the intramolecular version of the reaction. Various tether lengths were examined, and substrates with three- or four-carbon tethers and electron-withdrawing substituents at the alkyne terminus gave the products in acceptable yield on heating in the presence of 10 mol% of $Pd(dba)_2$ and 40 mol% of triisopropylphosphite (equation 37).[81a,b]



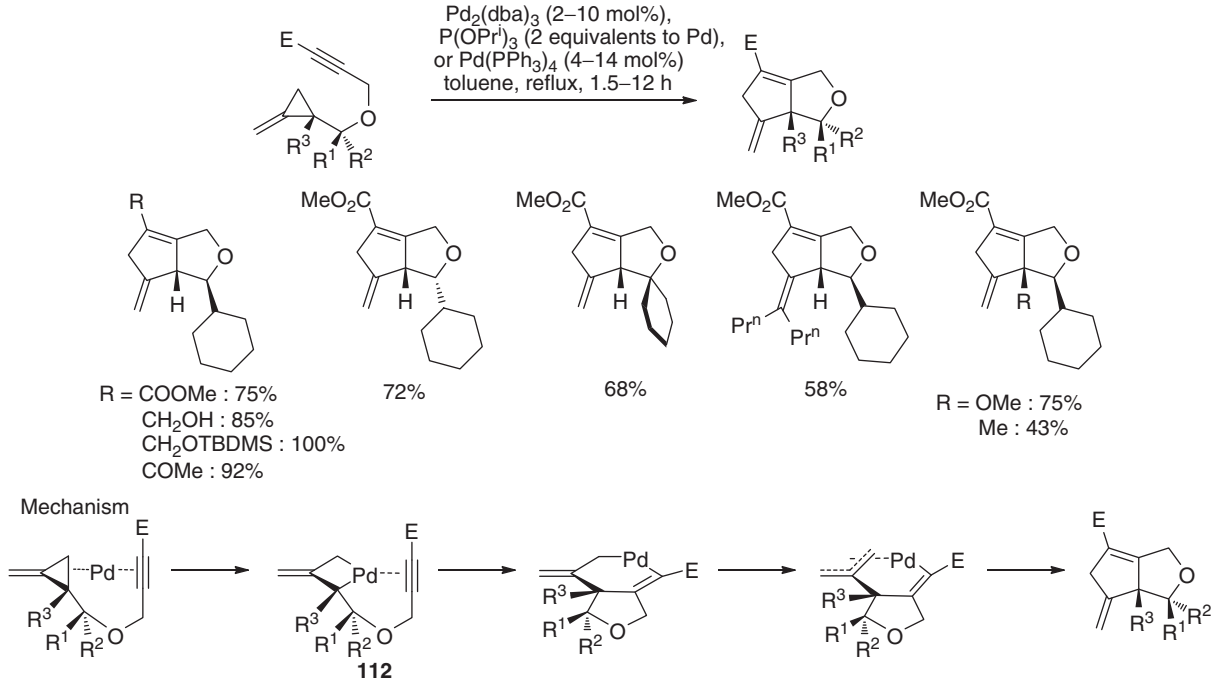
(37)

The reaction proceeded with retention of configuration at the substituted cyclopropane to give the products in good yield using $Pd_2(dba)_3$-P(O*i*-Pr)$_3$ with MS 4 Å or $Pd(PPh_3)_4$ as the catalyst. The reaction was proposed to proceed through a metallacyclobutane



Scheme 52

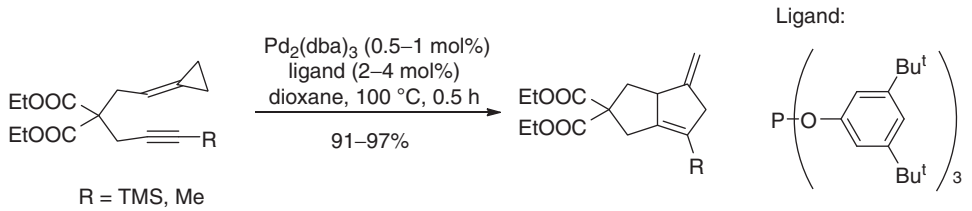
intermediate **112** generated by insertion of palladium(0) into the distal carbon–carbon bond of the cyclopropane, which undergoes carbometallation of the alkyne followed by reductive elimination to give the product stereospecifically (Scheme 53).[81c,d]



Scheme 53

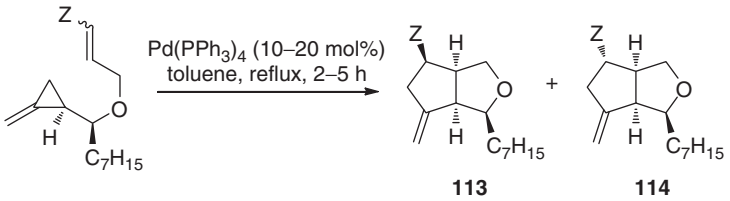
Similar intramolecular reactions using diastereomerically pure methylenecyclopropanes bearing tethers with electron-deficient alkenes proceeded stereospecifically to give the products in good yield, but both geometrical isomers of the alkene moiety gave the same diastereomer, suggesting a stepwise nature of the cycloaddition reaction. The *trans*-bicyclo[3.3.0]octane skeleton was constructed from one of the diastereomeric methylenecyclopropanes (Tables 26 and 27).[81e]

The same type of products was obtained using substrates tethered with alkynes at the *exo*-methylene carbon, which could be synthesized easily from 1-ethenylcyclopropanol. The reaction proceeded under similar conditions. The use of bulky phosphite and phophoramidite ligands was found to accelerate the transformation, such that a lower catalyst loading was sufficient (equation 38).[82a,b]



(38)

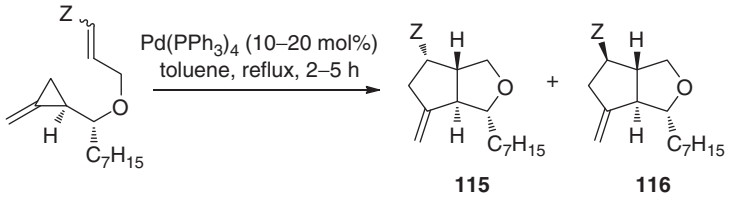
Table 26



113 **114**

Z	*Alkene*	*Product*	*Yield (%)*
CO_2Et	*E*	**113**	78
CO_2Et	*Z*	**113**	75
COMe	*E*	**113**	81
SO_2Ph	*E*	**114**	60
CN	*Z*:*E*=1:2	**113**:**114**=1:1	92

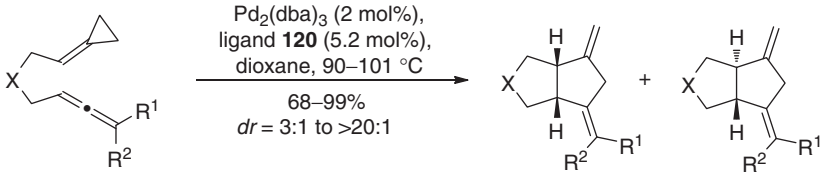
Table 27



115 **116**

Z	*Alkene*	*Product*	*Yield (%)*
CO_2Et	*E*	**115**:**116**=1:1	87
CO_2Et	*Z*	**115**:**116**=1:1	83
SO_2Ph	*E*	**115**:**116**=4:1	86
CN	*Z*:*E*=1:4	**115**:**116**=1:1.5	91

Again, similar reactions with substrates tethered to an alkene (instead of alkyne) occurred smoothly. Even with unactivated alkenes or allenes, the reaction proceeded by using a bulky phosphite ligand. Interestingly the behavior of the geometrical isomers was different when the bulky phosphite **120** was used instead of triisopropyl phosphite (Table 28, equation 39).[82c,d] A mechanistic analysis of the reaction was carried out to reveal that several different pathways are possible for the palladacyclobutane intermediate generated by the oxidative addition of the distal carbon–carbon bond of the cyclopropane to Pd(0) (Scheme 54).[82e,f]



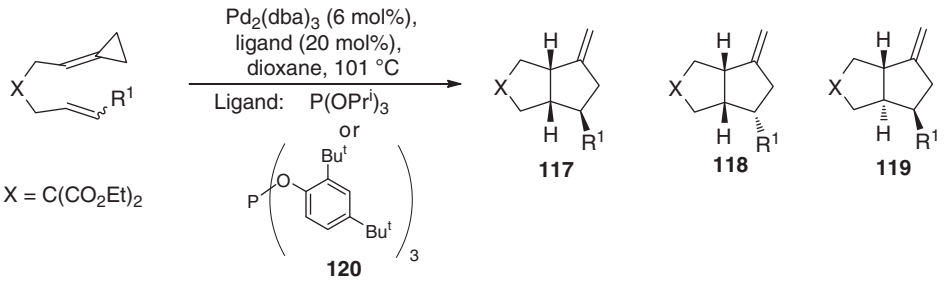
X = $C(CO_2Et)_2$, $NCHPh_2$, O
R^1, R^2 = H, Me

(39)

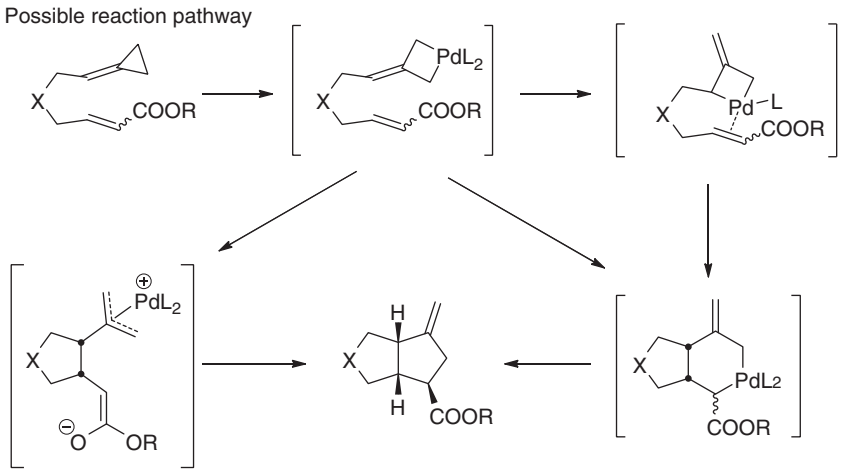
A ruthenium complex was also found to be effective for this reaction. Heating of a toluene solution of the substrate at 110 °C in the presence of 10 mol% of the first-generation Grubbs catalyst **121** gave the [3 + 2] cycloadducts in reasonable yield instead of the enyne metathesis product. The active catalytic species was thought to be a noncarbene ruthenium complex generated under the reaction conditions (Table 29).[83]

There has been much less work on the cleavage of the proximal bond of methylenecyclopropanes. Just one example of a Ni(0)-catalyzed intramolecular reaction is shown here (Scheme 55).[84]

Table 28 Intramolecular [3 + 2] cycloaddition between alkenes and alkylidenecyclopropanes



R[1]	*Ligand*	*Product*	*Yield (%)*
CO_2Et(*E*)	$P(OPr^i)_3$	**117**	74
CO_2Et(*E*)	**120**	**117**	82
CO_2Et(*Z*)	$P(OPr^i)_3$	**117**	72
CO_2Et(*Z*)	**120**	**118** + **119**	87 (5.3:1)
COMe(*Z*)	$P(OPr^i)_3$	**117**	78
CN(*E*/*Z* = ~3.5:1)	**120**	**117** + **119**	96 (3.5:1)
H	**120**	**117** + **119**	83 (1:1.6)
Ph(*E*)	**120**	**117**	70



Scheme 54

5.08.4.2.2 Pd and Rh-catalyzed reactions of vinylcyclopropanes

Use of simple cyclopropanes as a three-carbon unit in transition metal catalyzed [3 + 2] cycloaddition reactions was rather difficult. However, such reactions become possible by introducing a vinyl group, because of the efficient activation of the cyclopropane by the transition metal coordinated to the neighboring olefin.

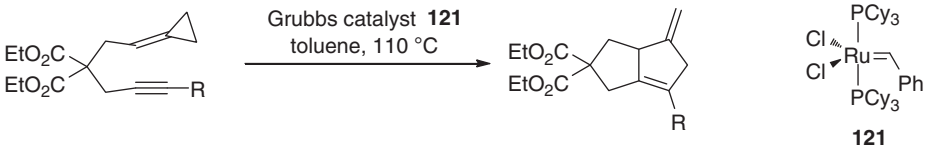
It was found that the reaction of 2-vinylcyclopropanedicarboxylate with Pd(0) generates a zwitterionic intermediate containing π-allylpalladium and malonate anion moieties, which can work as a 1,3-dipole (Scheme 56).[85]

This reaction was extended to the asymmetric synthesis of cyclopentane derivatives. A palladium-catalyzed enantioselective formal [3 + 2] cycloaddition between 2-vinylcyclopropane diesters with alkylidene azlactones was developed using **123** as a ligand. The use of the bis(2,2,2-trifluoroethyl)malonate derivative **124** gave higher yields and selectivities, in particular, when aryl-substituted alkylidene azlactones **125** were employed. This reaction provides a concise access to highly functionalized chiral amino acid derivatives (Table 30).[86a]

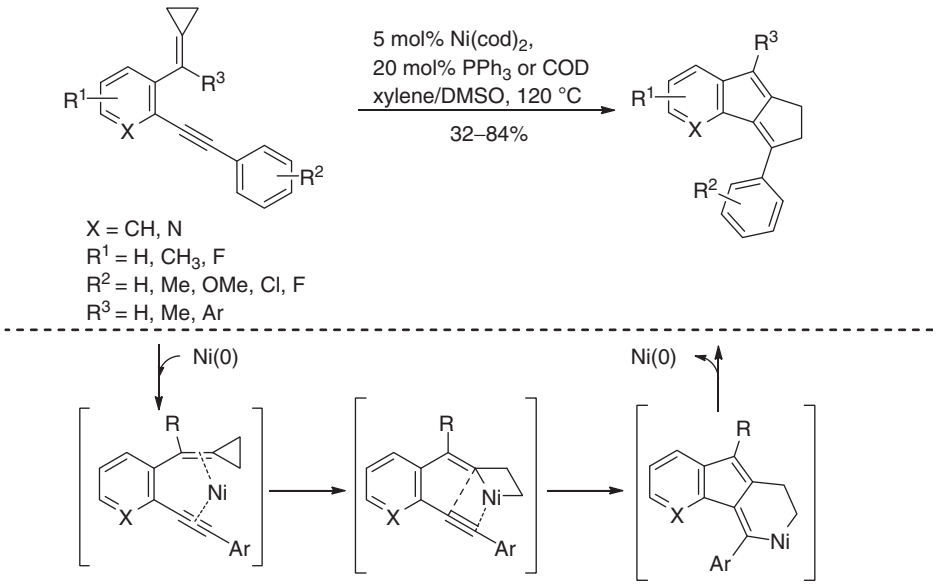
An efficient synthesis of the cyclopentene core of the *Melodinus* alkaloids was achieved utilizing this method (Scheme 57).[86b]

Allenylboronic esters and electron-deficient alkenes react in the presence of a palladium catalyst to give cyclopentene derivatives in good yield. Allenyl boronic esters undergo transmetallation to give propargyl/allenylpalladium species, which insert electron-deficient alkenes to give allenyl intermediates. *Endo*-carbopalladation of the pendant allene and protodepalladation

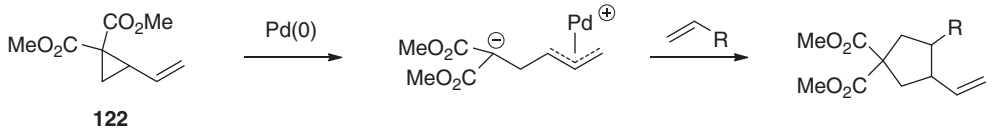
Table 29 Ruthenium-catalyzed intramolecular cycloaddition



R	*Catalyst (mol%)*	*Yield (%)*
Me	10	78
H	10	47
Et	15	73
$Pent^n$	15	67
CH_2OTBS	15	62
CH_2OH	10	26



Scheme 55

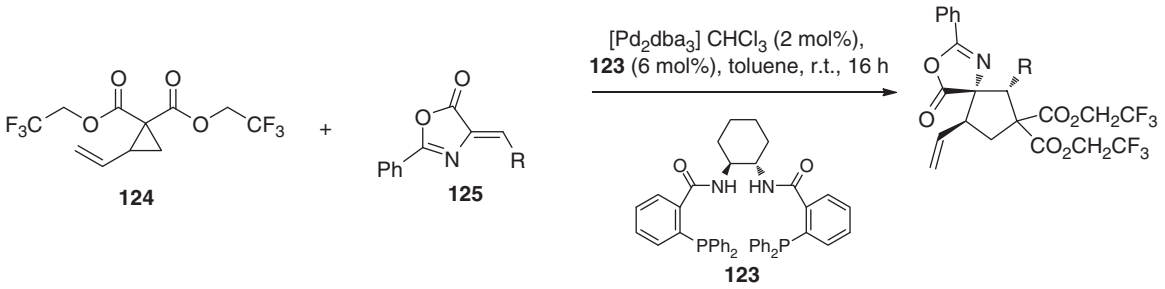


Scheme 56

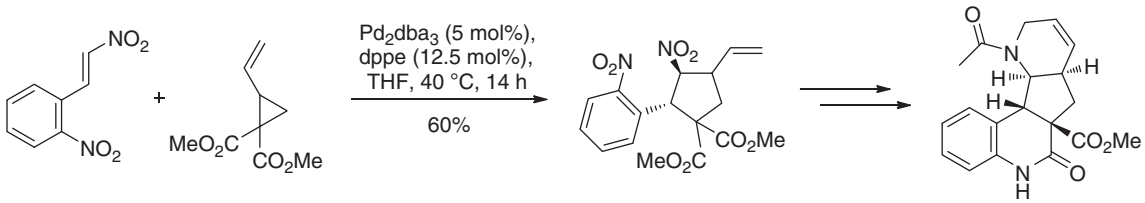
afford the cyclopentene products. By using a phosphoramidite ligand, the reaction proceeded smoothly in the presence of 10 mol% $PdCl_2(PhCN)_2$, 50 mol% NaO^tBu, and 1.1 equivalents ^tBuOH. The reaction showed reasonable generality with benzylidene cyanoesters and malononitriles (Scheme 58).[87]

Vinylcyclopropanes had been utilized as a five-carbon unit in the Rh(I)-catalyzed [5 + 2] cycloaddition reaction, but the position of the 2π unit was found to be crucial. Certain substrates undergo [3 + 2] cycloadditions, in which the vinyl group just remains intact. Thus, when 2-alkenyl-vinylcyclopropanes **126** were treated with 5 mol% of $[Rh(CO)_2Cl]_2$ at 80–110 °C, bicyclo[3.3.0]octane derivatives were obtained in reasonable yield as a single diastereoisomer. Use of a cationic complex generated from $[Rh(CO)_2Cl]_2$ and AgOTf promoted the reaction at lower temperature and sometimes gave the corresponding products in

Table 30 Asymmetric [3 + 2] cycloaddition reactions of vinylcyclopropane carboxylate



R	*Yield (%)*	*dr*	*ee (%)*
p-BrC_6H_4	78	19:1	98
m-ClC_6H_4	70	>19:1	93
m-$MeOC_6H_4$	83	19:1	94
Hex^n	63	8:1	74
OEt	73	10:1	63



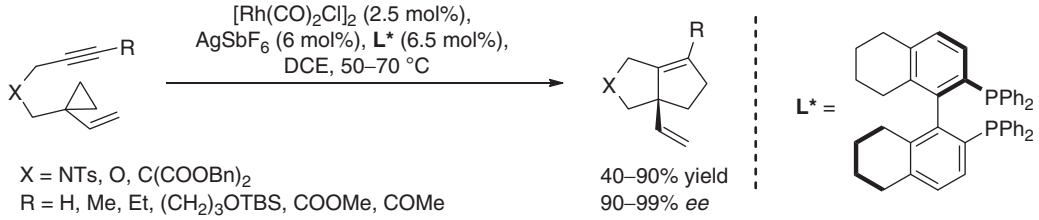
Scheme 57

higher yield. It should be noted that only the *trans*-isomers gave the [3 + 2] cycloadducts, whereas the *cis*-isomers furnished the [5 + 2] cycloadducts exclusively (Scheme 59).[88a]

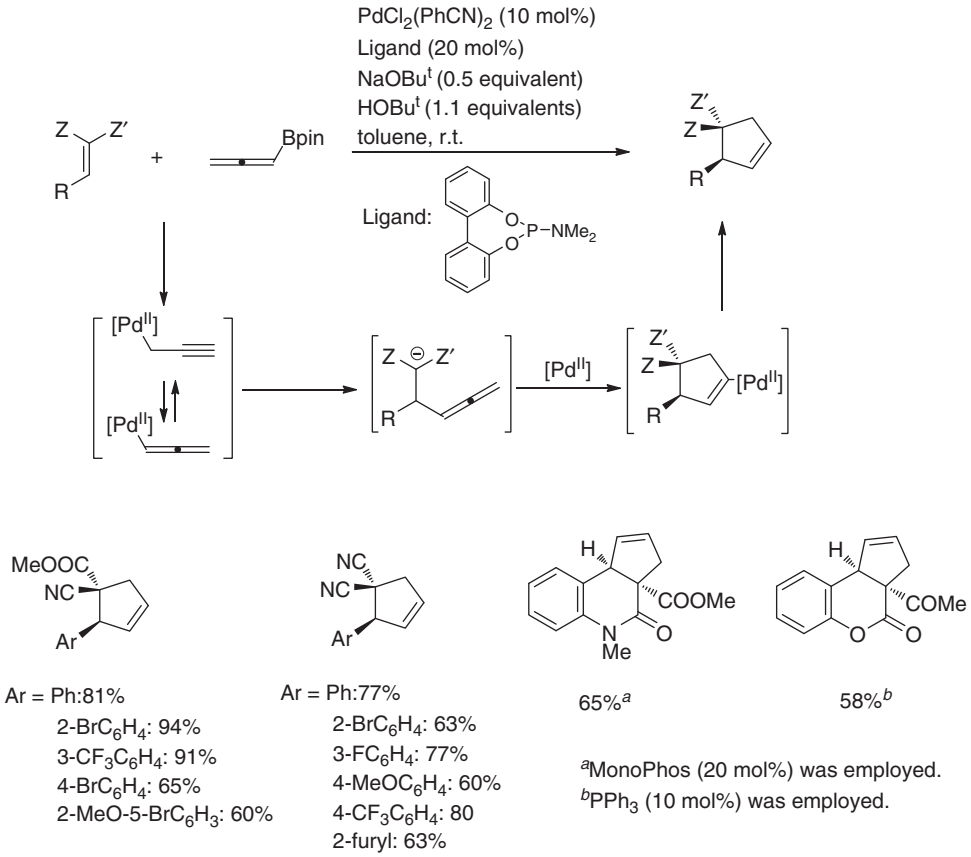
Similar reactions were also achieved with vinylcyclopropanes bearing an alkenyl substituent as 2π component on the vinyl group. In these cases, a cationic Rh(I) complex, [Rh(dppm)]SbF_6, gave good results, and bicyclo[4.3.0]nonane and bicyclo[5.3.0]decane derivatives with an *exo*-methylene group were obtained diastereoselectively. Addition of MS 4 Å improved the yield of the product without accompanying isomerization of the double bond (Scheme 60).[88b]

Furthermore, 1-alkenyl-, 1-alkynyl, and 1-allenyl-vinylcyclopropanes also gave the corresponding [3 + 2] cycloaddition products in good yields by carrying out the reaction in dichloroethane at 80 °C using [Rh(dppm)]SbF_6 as catalyst. A DFT analysis of the reaction supported a catalytic cycle composed of substrate-catalyst complex formation, cyclopropane cleavage, alkene/alkyne insertion, and reductive elimination. The alkene/alkyne insertion step was shown to be the rate-determining step of the reactions (Scheme 61).[88c,d]

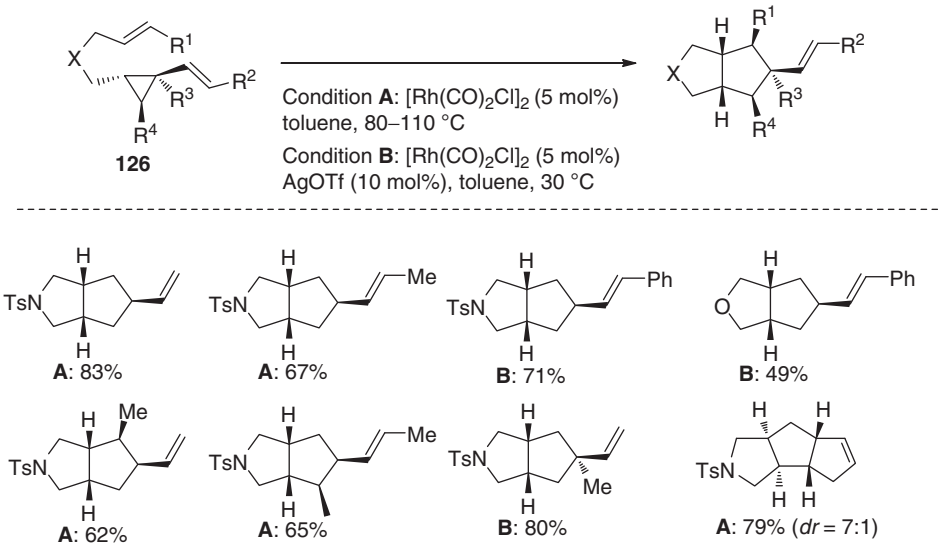
Recently, a highly enantioselective Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 1-alkynyl-vinylcyclopropanes to give bicyclo[3.3.0]octene derivatives was achieved using a cationic Rh(I) complex with (*R*)-H_8-BINAP as ligand (equation 40). The enantioselectivity could be explained considering the two diastereomeric transition states of the alkyne insertion step based on DFT calculations.[89]



(40)

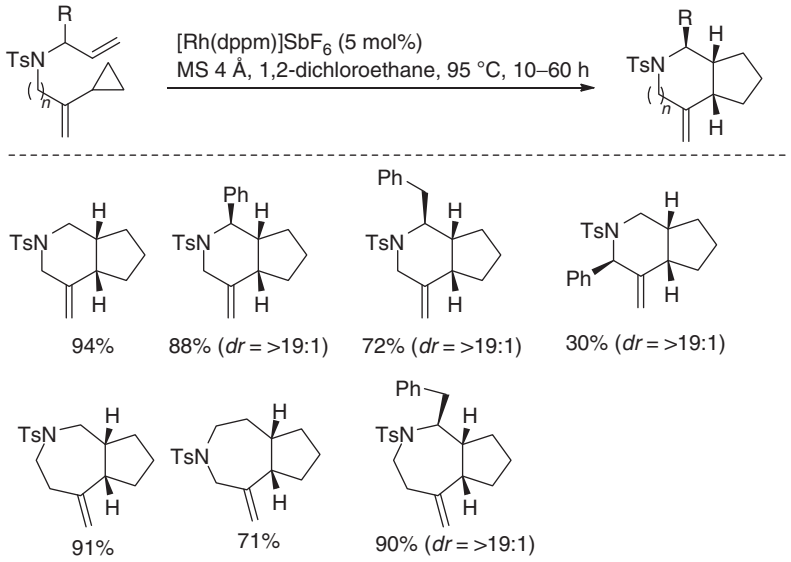


Scheme 58

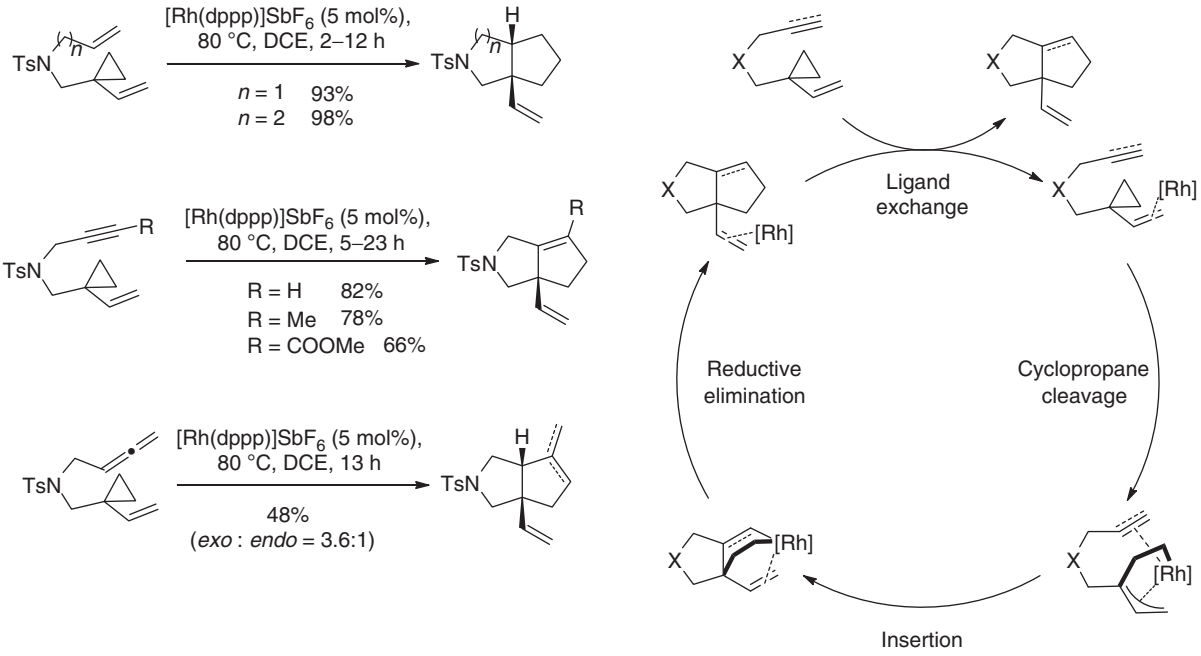


Scheme 59

Another Rh(I)-catalyzed [3 + 2] cycloaddition reaction was achieved using cyclopropenones. Treatment of cyclopropenones and alkynes at 80–110 °C in toluene in the presence of 1 mol% of $[Rh(CO)_2Cl]_2$ gave cyclopentadienones in good yield. The cyclopropenones serve as a three-carbon unit with cleavage of the C1–C2 bond; aryl alkynes selectively afforded products with the aryl substituent neighboring the carbonyl group (Table 31).[90]



Scheme 60

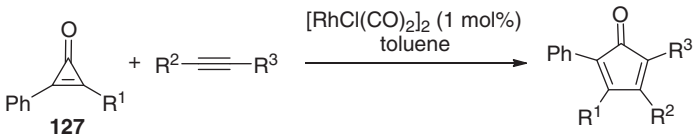


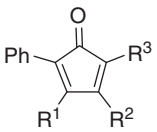
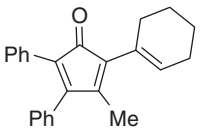
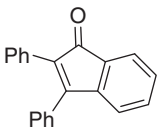
Scheme 61

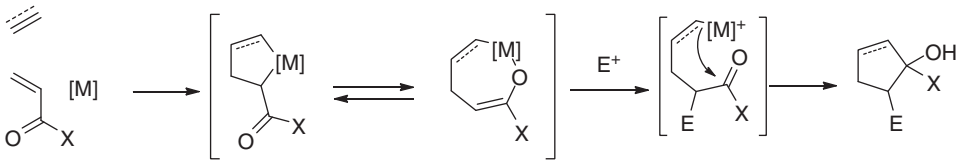
5.08.4.3 Reductive Coupling Using Low-Valent Transition Metal Complexes

After the publication of the first edition of this book, all-carbon [3 + 2] cycloadditions utilizing the reducing ability of transition metal complexes have emerged as a useful method for the construction of functionalized cyclopentane and cyclopentene derivatives. Most of the reactions utilized the reductive coupling of enals, enones, and enoates with alkynes, wherein the α,β-unsaturated carbonyl compounds served as a three-carbon unit. The basic idea is as follows: Reductive coupling of the above two components generates metallacyclopentene intermediates, which, on treatment with an appropriate electrophile, react like enolates at the α-carbon to give alkenylmetal species containing a carbonyl group. Then the alkenylmetals attack the carbonyl carbon to give cyclopentenol derivatives. Thus, the carbon atoms of the alkynes react with the α,β-unsaturated carbonyl compounds in a 1,4- and 1,2-manner, respectively. Initially, stoichiometric reactions were reported based on the use of low-valent titanium-mediated reactions, followed by Ni(0)-promoted transformations; the latter have been developed into catalytic processes by the combination with appropriate reducing agents (Scheme 62).

Table 31 Rh(I)-catalyzed intermolecular[3 + 2] – cycloaddition of cyclopropenones



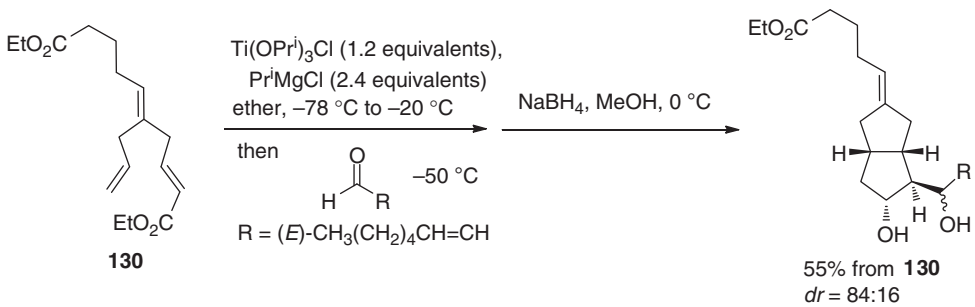
	Product	*Conditions*	*Yield (%)*
	R^1=Ph, R^2=Me, R^3=Ph	80 °C, 2 h	94
	R^1=Ph, R^2=CH_2OMe, R^3=Ph	80 °C, 2 h	97
	R^1=Ph, R^2=$CONH_2$, R^3=Ph	80 °C, 12 h	99
	R^1=Ph, R^2=CHO, R^3=Ph	110 °C, 3 h	42
	R^1=Ph, R^2=Ph, R^3=Ph	110 °C, 17.5 h	57
	R^1=Ph, R^2=C(O)Me, R^3=Ph	110 °C, 5 h	61
		80 °C, 3 h	88
		120 °C, 3.5 h	69



Scheme 62

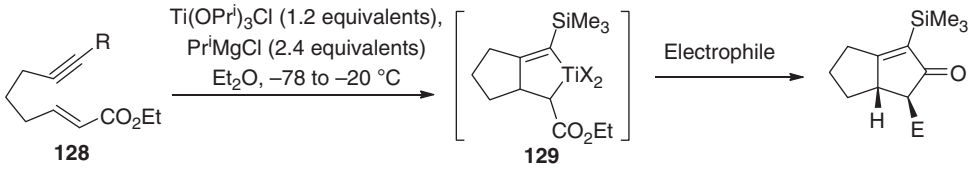
The first example of this type of reaction was achieved using a stoichiometric amount of low-valent titanium complexes. Thus, treatment of a mixture of 8-trimethylsilyl-2-octen-7-ynoate **128** (R=TMS) with (η^2-propene)TiX_2, generated *in situ* from Ti(O-*i*-Pr)$_3$Cl and *i*-PrMgCl in ether, afforded a titanacyclopentene intermediate **129**, which on addition of an equimolar amount of *s*-BuOH gave a bicyclic ketone in good yield. The product was produced by mono-protonation of the titanacyclopentene intermediate at the α-position to the ester functionality, followed by nucleophilic attack of the resulting alkenyltitanium to the ester carbonyl. This reaction can be regarded as a formal [3 + 2] cycloaddition reaction between an alkyne and an α,β-unsaturated ester. More importantly, the electrophile was not limited to protons but carbonyl compounds were also employable, and functionalized cyclopentenones could be obtained by this protocol where the electrophiles had been introduced to the convex face of the bicyclo[3.3.0]octane system with high selectivities. The reaction was applicable to various 2-octen-7-ynoates and 2-nonen-8-ynoate, and the substituent at the allylic position controlled the direction of cyclization to give the product with high selectivity (Table 32).[91a,b]

The reaction was further applicable to 2,7-dienoates having a terminal double bond to give saturated bicyclic ketones, and was applied to an efficient and highly stereocontrolled synthesis of carbacyclin. Treatment of the cyclization precursor **130** with Ti(O-*i*-Pr)$_3$Cl and *i*-PrMgCl, followed by addition of a side-chain aldehyde gave the basic carbon skeleton of carbacyclin with high stereoselectivity in an efficient manner (equation 41).[91c]



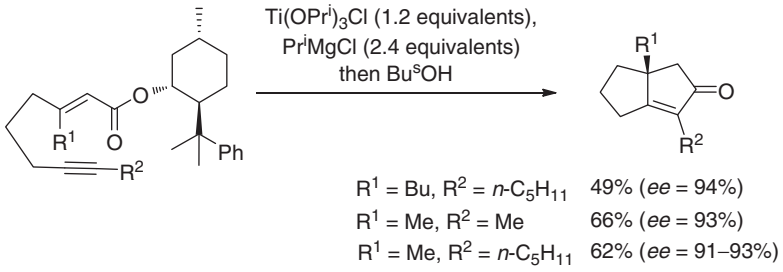
(41)

Table 32 Titanium-mediated reductive coupling



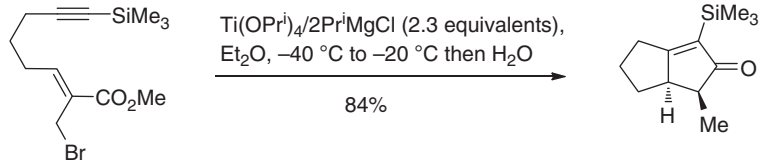
R	*Electrophile*	*E*	*Yield (%)*
TMS	Bu^sOH	H	80
TMS	EtCHO	EtCH(OH)–	78 (*dr* = 63:37)
TMS	Et_2CO	$Et_2C(OH)$–	65
n-C_5H_{11}	Bu^sOH	H	73

This titanium(II)-mediated cyclization was also performed asymmetrically by using 8-phenylmenthyl enynoates as the substrates. Synthetically useful, angularly substituted bicyclic ketones of up to 94% *ee* were obtained by this method (equation 42).[91d]

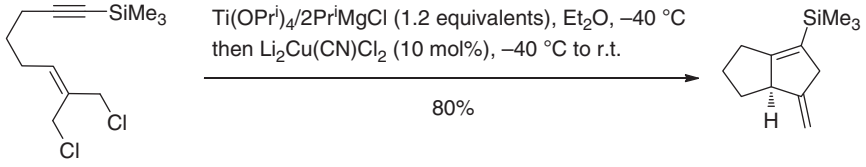


(42)

A further extension of this chemistry was achieved by the reaction of α,β-unsaturated esters containing an allylic chloride or bis(allylic chloride) moiety. Instead of protonation, β-elimination of chloride generated active alkenyltitanium intermediates, which further reacted with the ester or another allylic chloride to give five-membered ring products (equations 43 and 44).[91e]

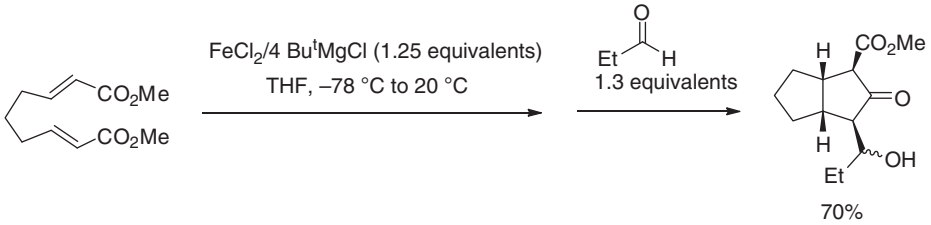


(43)



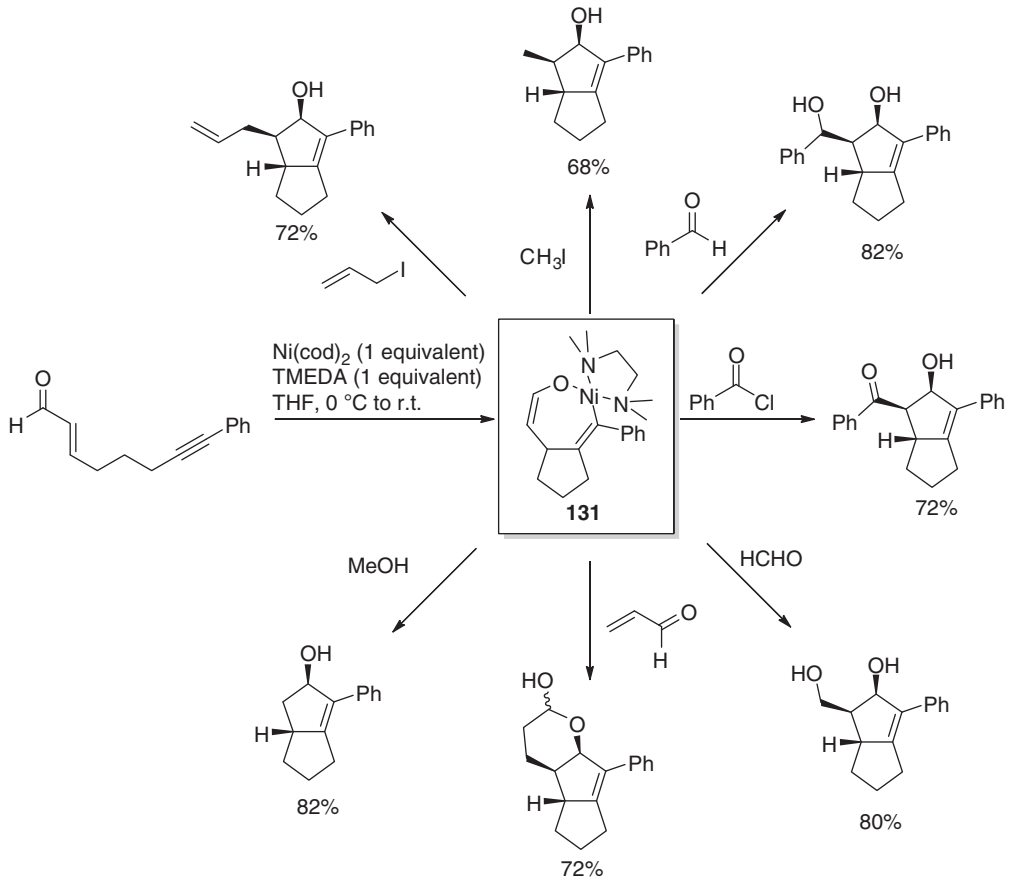
(44)

Recently an iron version of this reaction was also realized. Treatment of 2,7-nonadienedioates with low-valent iron, generated *in situ* from $FeCl_2$ and *t*-BuMgCl in a ratio of 1:4, gave metallacyclic intermediates, which afforded bicyclic keto esters after the addition of *s*-BuOH or carbonyl compounds as electrophiles to trap the iron enolate intermediates (equation 45).[92]



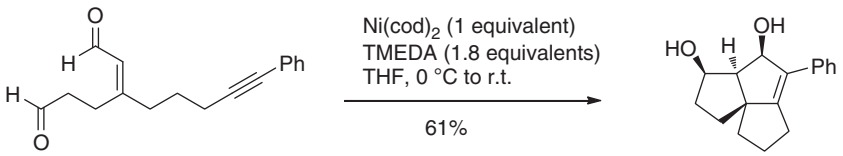
(45)

Nickel-promoted coupling reactions of unsaturated molecules have found abundant application in organic synthesis. Moreover, the combination with appropriate reducing reagents enables such reactions to be performed catalytically, which further expands their utility. Among these reactions is the Ni(0)-catalyzed [3 + 2] cycloaddition of enones or enals with alkynes. Initially, the intramolecular coupling of alkynyl enones and enals was reported using a stoichiometric amount of $Ni(cod)_2$ in the presence of TMEDA to give oxanickellacycloheptadiene intermediates, which afford a variety of synthetically useful compounds by subsequent transformations. Among the reported transformations were the reactions with electrophiles such as water, aldehydes, alkyl and acyl halides, and an α,β-unsaturated aldehyde to give alkenylnickel intermediates containing a carbonyl group, which furnished cyclopentenol derivatives with high stereoselectivity by the addition of the alkenylnickel to the carbonyl group.[93a,b] Concerning the mechanism of the reaction, the key oxanickellacycloheptadiene intermediate **131** was isolated from the reaction of 8-phenylocta-7-yn-2-enal with a stoichiometric amount of $Ni(cod)_2$-TMEDA (1:1) and its structure was determined by X-ray analysis. Further, treatment of this complex with either methanol or dilute aqueous acid actually gave the bicyclo[3.3.0]octene derivative in good yield with high diastereoselectivity. This is the same type of transformation as the Ti(II)-mediated reactions, and the main difference lies in the use of α,β-unsaturated ketones or aldehydes instead of α,β-unsaturated esters as the three-carbon unit (**Scheme 63**).[93c,d]



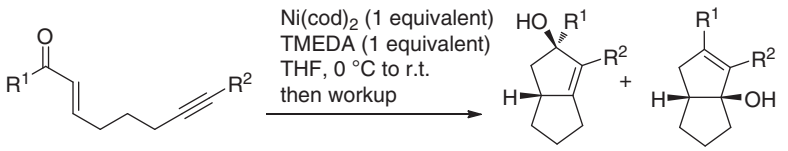
Scheme 63

Concerning the substituent on the alkyne, aromatic, aliphatic, and silyl groups gave good yields of the products, whereas terminal alkynes and alkynoates were poor substrates. In all cases, a single diastereomer was obtained. The reaction was further extended to the synthesis of more elaborate structures and one example is shown in **Table 33** and equation 46.



(46)

Table 33 The intramolecular coupling of alkynyl enones and enals



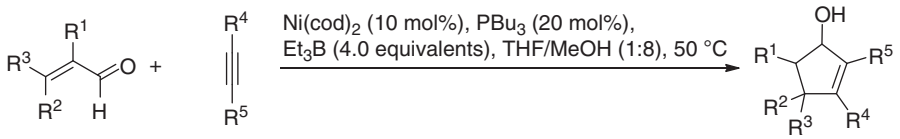
132 **133**

R^1	R^2	*Yield (%)*	
		132	***133***
H	Me	72[a]	
H	TMS	55[b]	
H	$COCH_3$	15[a]	
Ph	Ph	71[b]	
Ph	Ph		53[a]
Ph	Me		52[a]
Ph	TMS	61[b]	

[a]Aqueous workup.
[b]Methanol workup.

This reaction was successfully developed into a catalytic, intermolecular [3 + 2] cycloaddition of enals and alkynes when carried out in the presence of triethylborane as a reductant and MeOH as a proton source. The choice of the reducing agent was crucial: It must be stable under protic conditions and must have a sufficient reducing ability to convert Ni(II) to Ni(0). As such reducing agent, triethylborane has been known to be effective in several related reactions, and it certainly worked well in this system too. Furthermore, the choice of the ligand had a considerable effect on this intermolecular reaction with tributylphosphine giving the best results. Thus, by carrying out the reaction in THF-MeOH (1:8), the formal [3 + 2] cycloaddition reaction of enals and alkynes proceeded in the presence of 10 mol% of $Ni(cod)_2$ and 20 mol% of PBu_3 along with 4 M equivalents of Et_3B to give cyclopentenol derivatives in good yield. As substrate, various enals could be used, and terminal and internal alkynes were applicable. High regioselectivity was achieved when aryl-substituted alkynes were employed (Table 34).[94a,b]

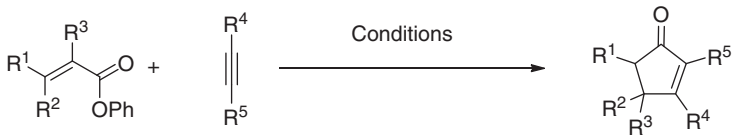
Table 34 Ni(0)-catalyzed intermolecular reductive cycloaddition of enals and alkynes



R^1	R^2	R^3	R^4	R^5	*Yield (%)*	*dr*
H	H	Ph	Me	Ph	56	81:19
H	H	Pr^n	Me	Ph	85	87:13
Me	H	H	Me	Ph	80	90:10
Me	H	Me	Me	Ph	75	71:17:12
Me	H	H	TMS	*p*-$MeOC_6H_4$	69	90:10
H	Me	Me	H	Ph	60	100:0
H	H	Pr^n	Et	Et	64	63:37

The reaction using triethylborane as a reductant was further extended to enoates instead of enals to give cyclopentenone derivatives. Although simple methyl enoates were unreactive, phenyl enoates and α,β-unsaturated acyl oxazolidinones participated in this reaction. PCy_3 and N-heterocyclic carbene (NHC) ligands (IMes) were found to be optimal; in particular, IMes showed the best generality. Although a variety of alkynes reacted smoothly with β-substituted phenyl enoates with high regioselectivity, α-substituted enoates reacted smoothly only with terminal alkynes, whereas internal alkynes mostly gave acyclic reductive coupling products (Table 35).[94b] Essentially the same reaction was found to proceed in isopropyl alcohol without using Et_3B as a reductant. Treatment of α,β-unsaturated phenyl esters and alkynes in *i*-PrOH at 130 °C in the presence of 10 mol% $Ni(cod)_2$,

Table 35 Ni(0)-catalyzed reductive cycloaddition reaction of α,β unsaturated phenyl esters with alkynes

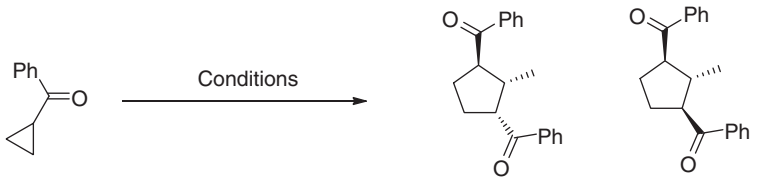


R^1	R^2	R^3	R^4	R^5	*Conditions*[a]	*Yield (%)*	*dr*
Me	H	H	Hex	Hex	a	87	–
H	H	H	Oct	H		67	90:10
Me	H	H	Me	Ph		77	86:14
Ph	H	H	Me	Ph		97	95:5
H	H	Me	Oct	H		63	97:3[b]
Pr	H	H	$(CH_2)_2OH$	Me		68	87:13[b]
Ph	H	H	Me	Me	b	84	–
Ph	H	H	Ph	Ph		64	–
Ph	H	H	Bu^n	H		30	76:24
Me	H	H	Et	Et		86	–
Pr^i	H	H	Et	Et		84	–
H	H	Me	Et	Et		62	–

[a]Conditions a = $Ni(cod)_2$ (10 mol%), IMes • HCl, Bu^tOK (10 mol %), Et_3B (5.0 equivalents), THF/MeOH (50:1), 50 °C. Conditions b = $Ni(cod)_2$ (10 mol%), PCy_3 (20 mol%), zinc powder (4.0 equivalents), Pr^iOH, 130 °C.
[b]PCy_3 (20 mol%) was used as ligand.

20 mol% PCy_3, and 4 equivalents of Zn powder gave the corresponding cyclopentenones in good yield. It was thought that isopropyl alcohol worked as a reductant through β-hydride elimination in this reaction; the addition of Zn powder improved the yield of the products considerably (Table 35).[94c]

As another type of [3 + 2] cycloaddition utilizing the reducing ability of Ni(0), the reaction of cyclopropyl ketones or imines with enones was developed. Initially, it was found that treatment of cyclopropyl aryl ketones with 5–10 mol% $Ni(cod)_2$ in the presence of an NHC or tricyclohexylphosphine ligand gave dimerized cyclopentane derivatives in good yield. Cyclopropyl alkyl ketones were less reactive in this process and the introduction of a substituent on the cyclopropane ring also lowered the yield. A careful study on the mechanism of this reaction was carried out to reveal that the reaction of Ni(0) with cyclopropyl ketones generated six-membered oxanickelacycles **134**, which isomerized to α,β-unsaturated ketones presumably through β-hydride elimination followed by reductive elimination. The remaining oxanickelacycles reacted with the produced enones in a 1,4-addition manner, followed by reductive elimination of the cyclopentane derivatives with regeneration of Ni(0). These key intermediate complexes were isolated and their structures were determined by X-ray analysis (Schemes 64 and 65).[95a–c]

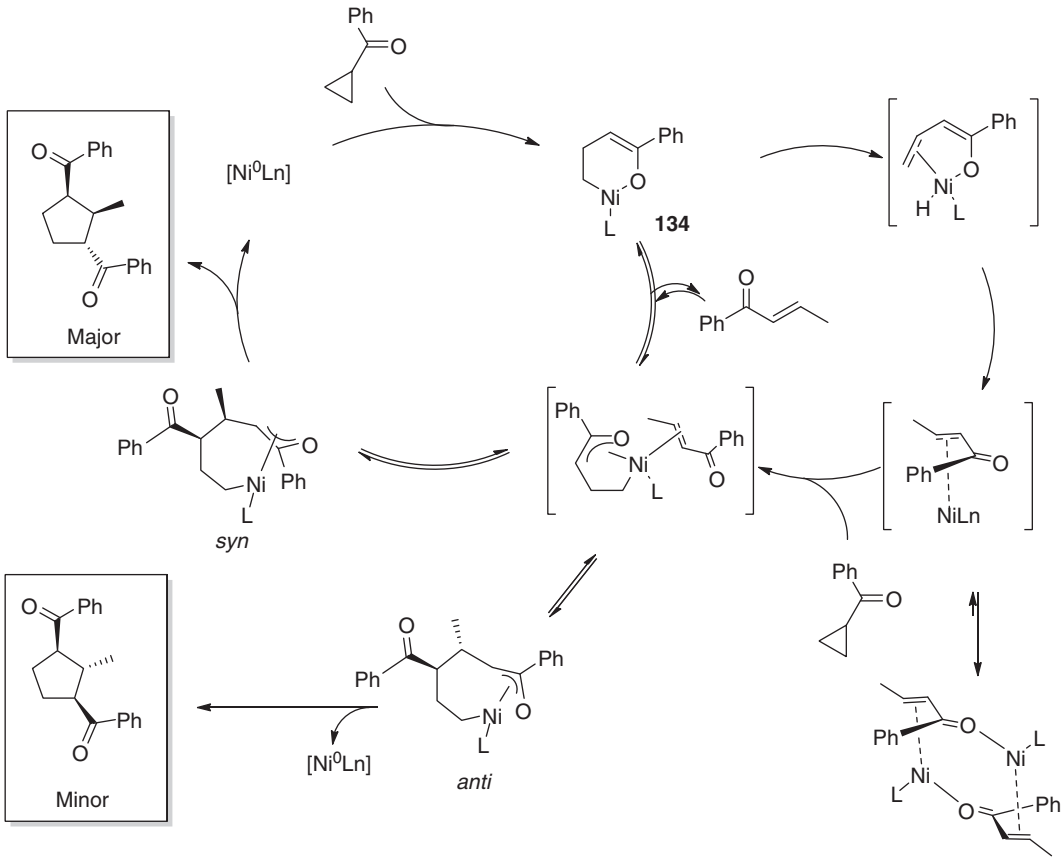


$Ni(cod)_2$ (10 mol%), PCy_3 (20 mol%), toluene-d_8, 100 °C, 1.5 h — 93 (76:17)

$Ni(cod)_2$ (10 mol%), IMes•HCl, Bu^tOK (10 mol%), toluene, 90 °C — 85 (98:2)

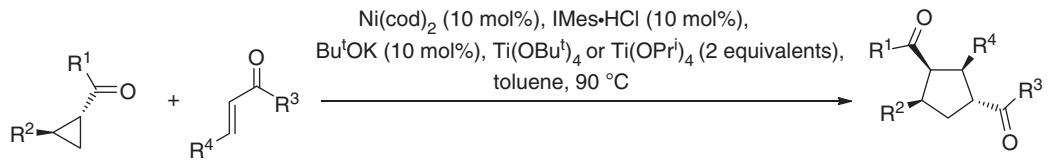
Scheme 64

The crossed reaction of cyclopropyl ketones with α,β-unsaturated ketones was realized by keeping the enone concentration low by syringe-drive addition to suppress the self-dimerization. Addition of Ti(O-*i*-Pr)$_4$ or Ti(O-*t*-Bu)$_4$ improved the yields and increased the reaction rates. The diastereoselectivity was generally good and tri- or tetra-substituted cyclopentane derivatives were obtained with high selectivity. In this reaction, the substrate scope was much improved, and cyclopropyl ketones with a substituent on the ring or cyclopropyl methyl ketone could be employed, whereas α,β-unsaturated ketones seemed to be limited to those having an aryl group on the carbonyl (Table 36).[95d]



Scheme 65

Table 36 Crossed coupling reactions of cyclopropyl ketones and enones

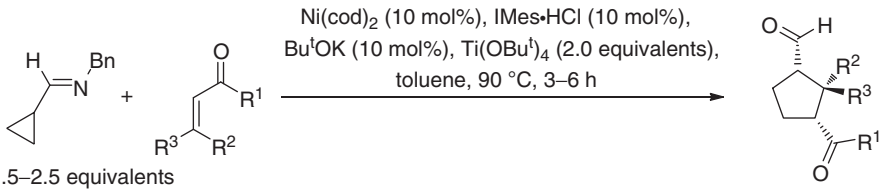


R^1	R^2	R^3	R^4	*Yield (%)*	*dr*
4-FC_6H_4	H	Ph	Me	77	94:6
Thiophen-2-yl	H	Ph	Me	59	97:3
Ph	H	2-Furyl	Me	58	96:4
4-FC_6H_4	H	Ph	C_6H_{13}	66	93:7
Ph	H	Ph	TMS	41	>97:3
Me	H	Ph	Me	47	93:7
Ph	Me	Ph	Me	52	75:25

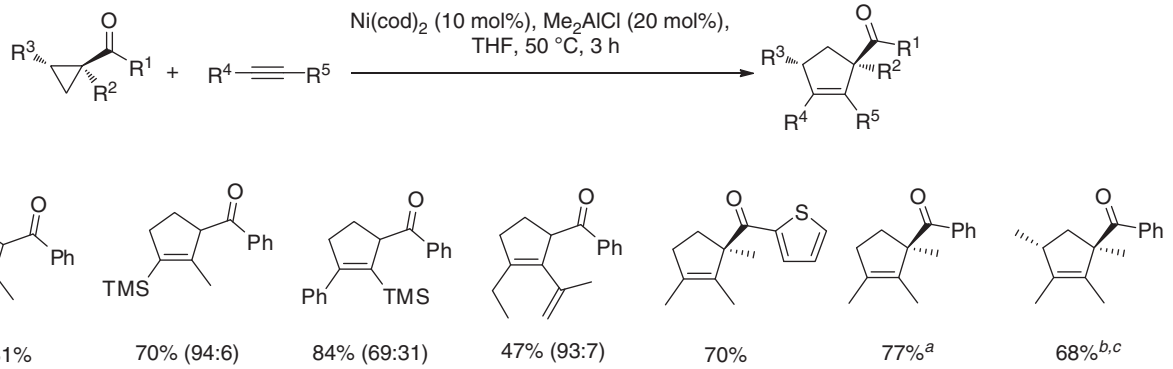
Furthermore, cyclopropyl imines could be applied to give trisubstituted cyclopentanecarbaldehyde in good yield, whereas the corresponding reaction of cyclopropanecarbaldehyde was totally ineffective. The reaction showed wide generality and various synthetically useful functionalized cyclopentanes were obtained by this protocol (Table 37).[95e]

Recently, [3 + 2] cycloadditions of cyclopropyl ketones with alkynes were realized using a combination of nickel and aluminum compounds as catalyst. Thus, treatment of a mixture of a cyclopropyl ketone and an alkyne with 10 mol% of $Ni(cod)_2$ and 20 mol% of Me_2AlCl gave a cyclopentenyl ketone in good yield. Addition of the aluminum reagent was crucial for the reaction to proceed, which is supposed to activate the cyclopropyl ketones and stabilize the nickelacyclobutane intermediate **135** in order to inhibit isomerization to an unreactive oxanickelacycle **136**. Various cyclopropyl ketones and internal alkynes were amenable to this reaction, and high regioselectivity was achieved when aryl or silyl alkynes were employed as substrates (Scheme 66).[95f]

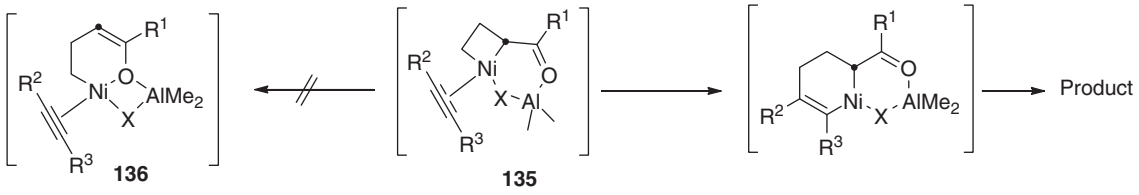
Table 37 Crossed coupling reactions of a cyclopropyl imine and enones



R^1	R^2	R^3	*Yield (%)*	*dr*
Ph	H	Ph	98	92:8
Ph	H	Me	81	72:28
Ph	H	Bu^t	93	>98:2
Ph	Me	Me	87	54:46
Naphthyl	H	Me	87	84:16



[a]100 mol% of Me_2AlCl was used. [b]100 mol% of Me_2AlOAc was used.
[c]1,4-*trans* : 1,4-*cis*:1,5-*trans* (regioisomer) = 62:26:12.

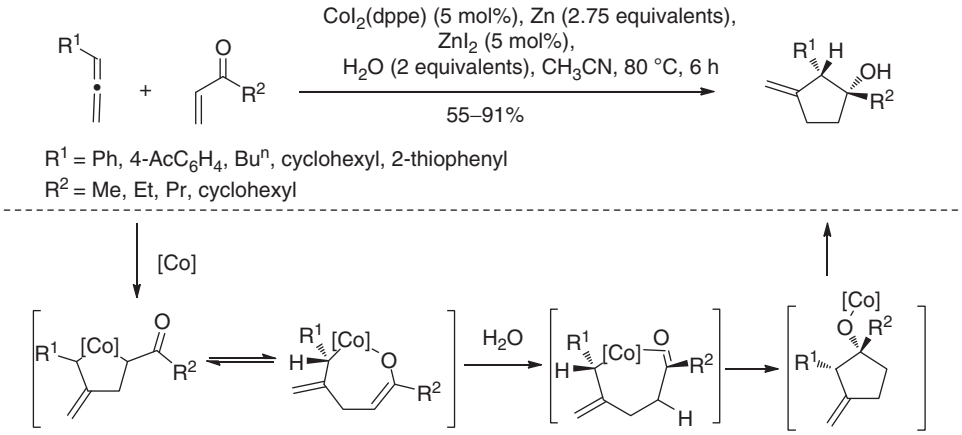


Scheme 66

In a related study, a cobalt-catalyzed reductive [3 + 2] cycloaddition of allenes and enones was realized. In this reaction, the low-valent Co complex, generated from CoI_2 with Zn, gave cobaltametallacycle intermediates from allenes and enones, which on protonation with H_2O, gave allylcobalt species with a ketone moiety. Subsequent intramolecular allylation gave the corresponding methylenecyclopentanols stereoselectively as formal [3 + 2] cycloadducts. The reaction was carried out in the presence of 5 mol% CoI_2(1,2-bis(diphenylphosphino)ethane (dppe)) and stoichiometric amounts of Zn as a reductant and H_2O as a proton source; the addition of a catalytic amount of ZnI_2 was crucial for the success of the reaction (Scheme 67).[96]

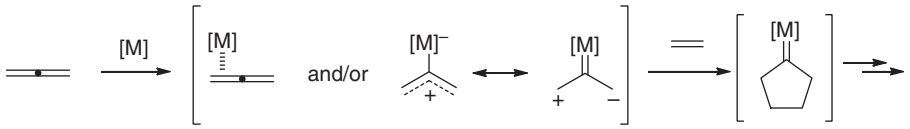
5.08.4.4 Electrophilic Transition Metal Catalyst

The electrophilic activation of alkyne derivatives has attracted tremendous attention of synthetic chemists and a variety of new methodologies has been developed in the last decade. Recently, these investigations have been extended to the activation of allenes. Thus, it was found that the electrophilic activation of allenes can generate all-carbon 1,3-dipoles, which undergo [3 + 2] cycloaddition with an olefinic substrate.[97] The basic concept is as follows: Coordination of the allenes to an electrophilic transition metal complex such as gold(I) or platinum(II) generates a zwitterionic intermediate which can be regarded as an allyl



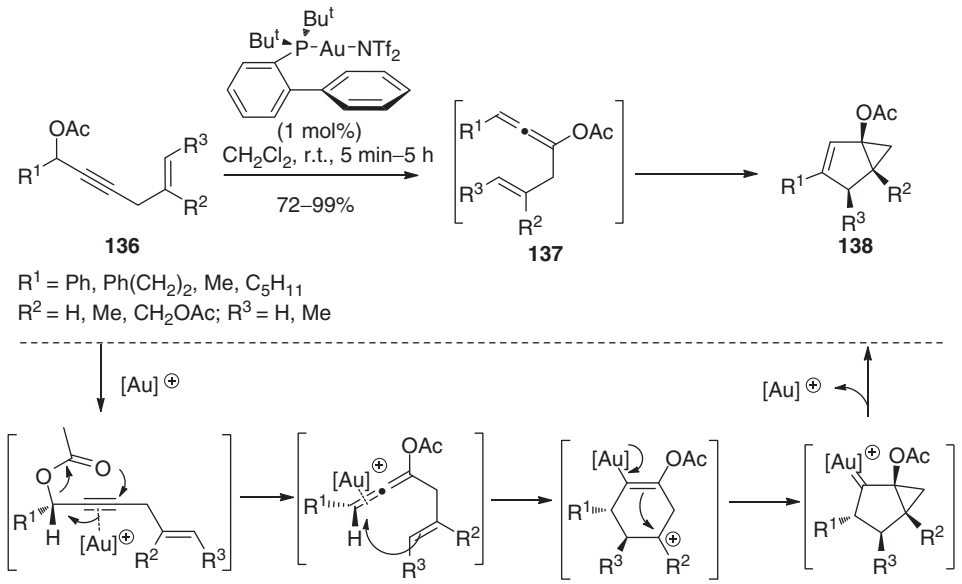
Scheme 67

cation with the anionic (or neutral when the starting complex is cationic) metal attached to the central carbon or, alternatively, as an all-carbon 1,3-dipole with the central carbon coordinated to the metal in a carbene-like fashion. [3 + 2] Cycloaddition reactions with appropriate olefins would give cyclopentylidene carbene complexes, which further undergo typical reactions of metal carbenes such as 1,2-hydrogen migration to give cyclopentene derivatives (Scheme 68).



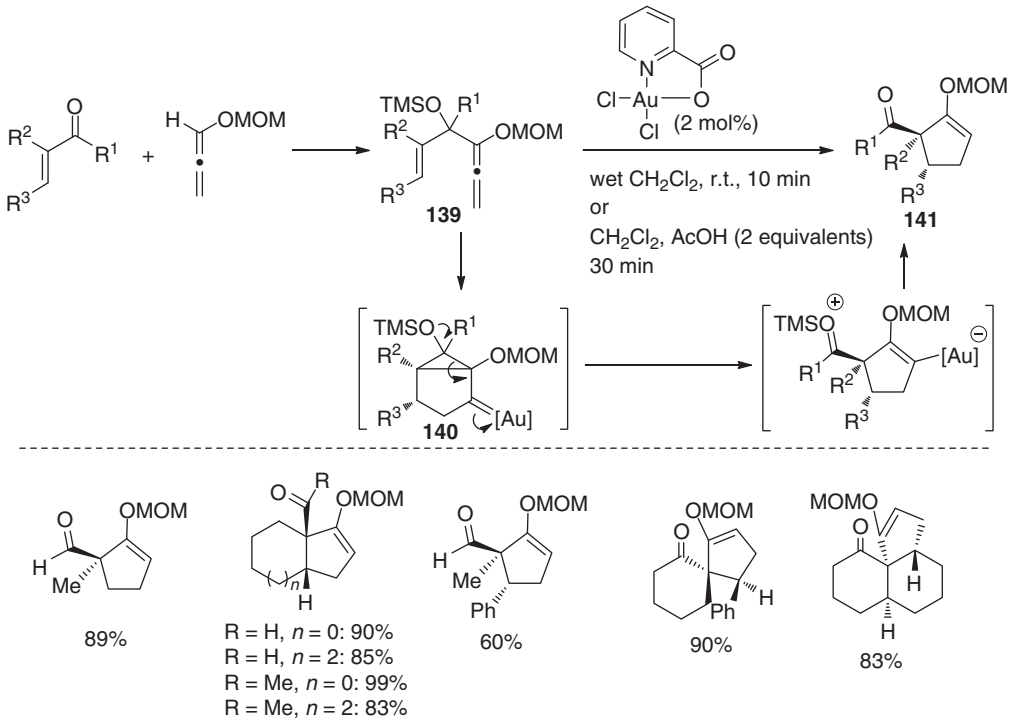
Scheme 68

The first example of this type of reaction was realized as an intramolecular process. Specifically, treatment of 5-en-2-yn-1-yl acetates **136** with 1 mol% of a cationic Au(I) catalyst containing a bulky phosphine ligand gave bicyclo[3.1.0]hexene derivatives **138**. The reaction was proposed to proceed through 3,3-sigmatropic rearrangement of the propargyl acetates to give allenes **137**, which undergo formal intramolecular [3 + 2] cycloaddition with the alkene moiety to give bicyclo[3.1.0]hexylidene carbene intermediates. 1,2-Hydrogen shift furnishes the products and regenerates the cationic Au(I) catalyst. Variously substituted 5-en-2-yn-1-yl acetates reacted smoothly at room temperature to give the corresponding products in good yields (Scheme 69).[98a]



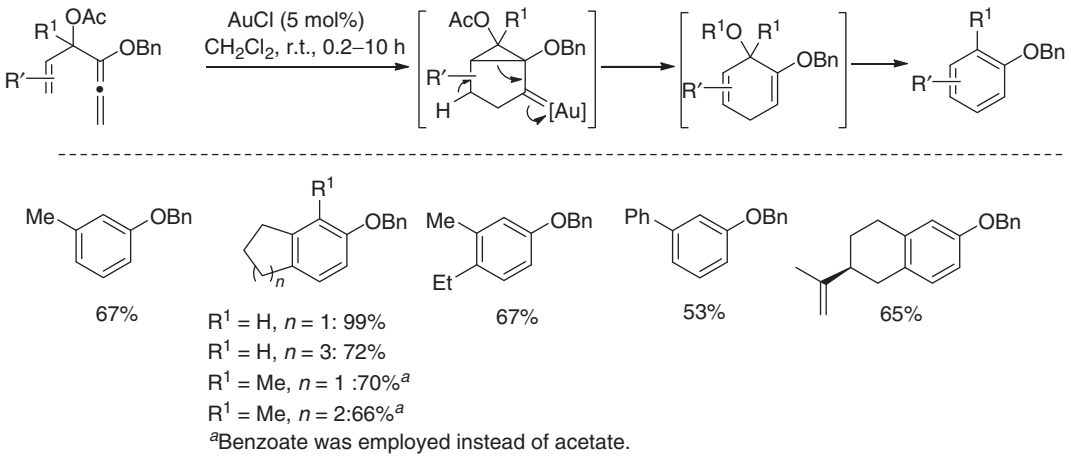
Scheme 69

A related reaction of TMS-protected allenyl carbinols **139** also gave cyclopentene derivatives **141** by using a Au(III) catalyst. The reaction was thought to proceed in a similar manner to first give bicyclo[3.1.0]hexane intermediates **140**, which undergo cyclopropane ring opening instead of 1,2-hydrogen shift to give the cyclopentene derivatives. The reaction showed wide generality concerning the olefinic moiety to produce monocyclic, bicyclic, and spirocyclic products in good yields with high stereoselectivity. The starting allenyl carbinols were prepared by the addition of a lithiated allenyl methoxymethyl (MOM) ether to α,β-unsaturated aldehydes or ketones. This method thus corresponds to a formal intermolecular [3 + 2] cycloaddition reaction of allenyl ethers and α,β-unsaturated carbonyl compounds (Scheme 70).[98b]



Scheme 70

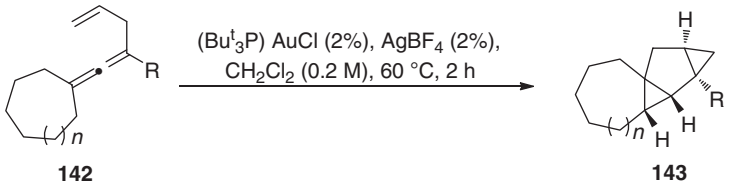
By using acetates or benzoates instead of TMS ethers in the above reaction, the intermediates [3 + 2] cycloadducts underwent another mode of cyclopropane ring opening to give phenol derivatives in good yields. In this case, the use of simple Au(I)Cl gave the best results (Scheme 71).[98c]



Scheme 71

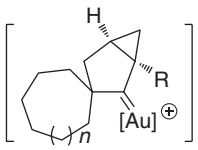
C–H insertion is another typical reaction of carbenoid intermediates. Such a process was exemplified in the Au(I)-catalyzed [3 + 2] cycloaddition of 1,4-enallenes **142**. Treatment of 1,4-enallenes with 2 mol% of a cationic Au(I) catalyst gave bis(cyclopropanes) **143** formed by insertion of the produced Au(I) carbene complex intermediates **144** into a neighboring C–H bond (Table 38).[99]

Table 38 Gold(I)-catalyzed cycloisomerization of 1,4-enallenes



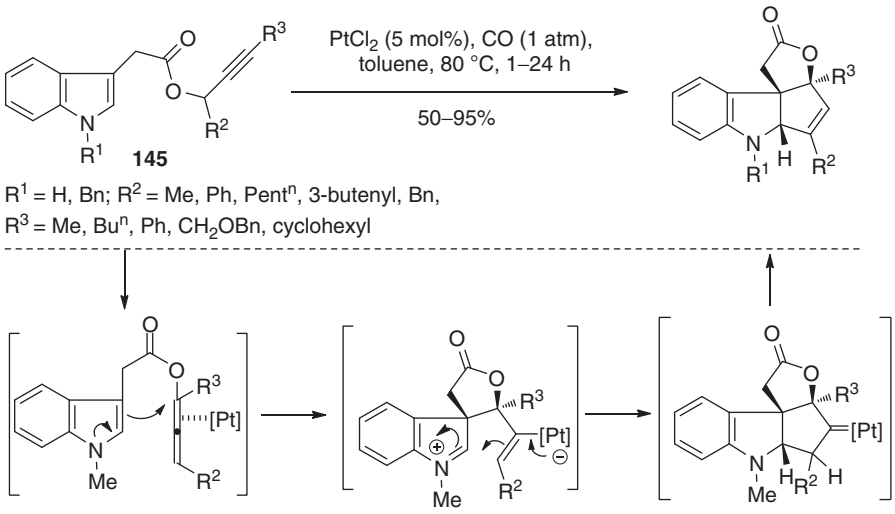
142 **143**

n	R	Yield (%)
1	H	73
1	Bn	83
2	Bn	62
1	Ph	88
2	Ph	85
2	*p*-CF$_3$C$_6$H$_4$	63



144

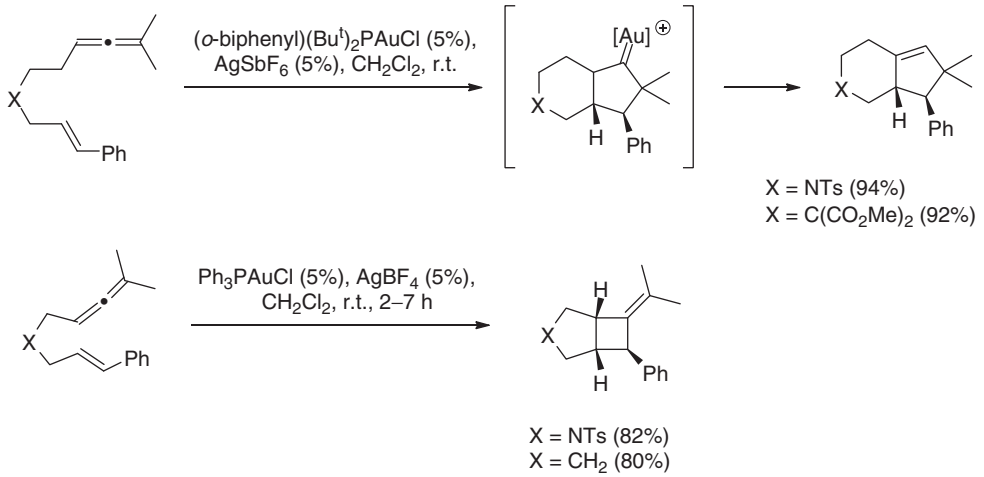
The concept was extended to indole derivatives **145** using a Pt(II) catalyst. In this reaction, allenyl esters were again generated by 3,3-rearrangement of propargyl esters of indole-3-acetic acid and reacted with the C2–C3 double bond of the indole moiety to give polycyclic indoles containing a cyclopentene ring in good yields. It is also noted that the use of the cationic Au(I) complex gave an intramolecular [2 + 2] cycloadduct selectively. Thus, by appropriate choice of the catalyst, either [3 + 2] or [2 + 2] cycloadducts could be obtained selectively (Scheme 72).[100]



145

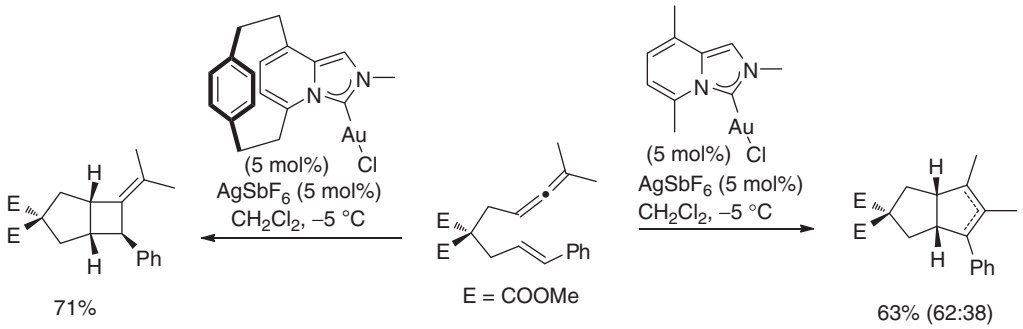
Scheme 72

Simple intramolecular [3 + 2] cycloaddition reactions of 1,2,7-trienes were reported as an extension of Au(I)-catalyzed [4 + 2] and [4 + 3] cycloadditions of allene-dienes. By using a cationic Au(I) catalyst containing a bulky phosphine ligand, 1,2,7-trienes gave bicyclo[4.3.0]nonene derivatives in high yield.[101a] In contrast, the use of a cationic Au(I) complex containing PPh_3 as the ligand gave the [2 + 2] cycloadduct selectively under similar reaction conditions (Scheme 73).[101b]



Scheme 73

A unique ligand effect was observed for the cationic Au(I) complex containing NHC ligands in a similar cyclization of 1,2,7-trienes. An electron-rich NHC–Au(I) complex favored the [3 + 2] pathway, whereas an electron-deficient catalyst delivered the [2 + 2] cycloadduct selectively. The π-acceptor ability of the ligand was thought to play an important role in this reaction (Scheme 74).[101c]

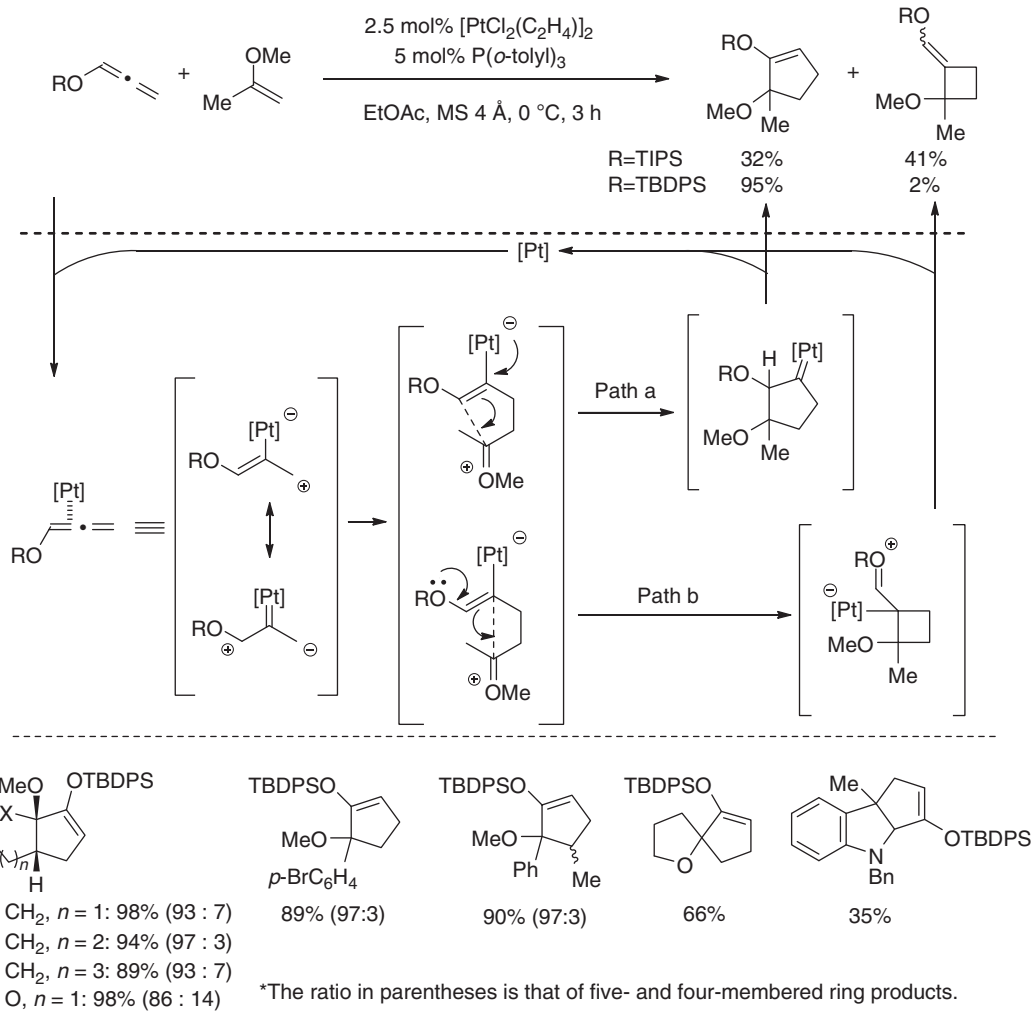


Scheme 74

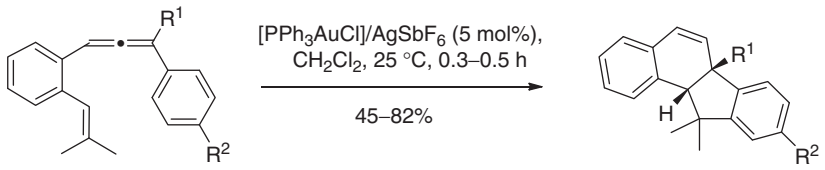
Intermolecular [3 + 2] cycloaddition reactions of silyl propadienyl ethers and alkenyl ethers was achieved by using platinum(II) catalysts. Treatment of a mixture of a TBDPS–propadienyl ether and alkenyl ether with 2.5 mol% of $[PtCl_2(CH_2{=}CH_2)]_2$ (5 mol% based on Pt) and 5 mol% P(o-tol)$_3$ gave synthetically useful oxygenated cyclopentanone derivatives in good yield. When a triisopropylsilyl (TIPS)–allenyl ether was employed instead, the reaction gave a mixture of [2 + 2] and [3 + 2] cycloadducts, whereas cyclopentene derivatives were formed with high selectivity by using TBDPS–allenyl ether as the three-carbon unit. It was postulated that the lower electron-donating ability of the TBDPS group rendered the [2 + 2] cycloaddition reaction less favorable. The method showed wide generality for the electron-rich alkenes and is therefore complementary to the phosphine-catalyzed [3 + 2] cycloaddition of electron-deficient allenes with electrophilic 2π components (Scheme 75).[102]

Intramolecular [3 + 2] cycloadditions of arenyne-yne functionalities was realized based on electrophilic alkyne activation using cationic Au(I) catalysts. Treatment of diyne **146** with 2 mol% of Ph$_3$PAuSbF$_6$ gave the formal [3 + 2] cycloadduct **147**. Various aryl-substituted diynes, endiyne, and alkenyl-substituted diynes were applied to this reaction to give the corresponding products in good yields. The reaction was thought to proceed through the nucleophilic attack of the aromatic ring to the electrophilically activated alkyne at the benzylic position to give the nine-membered alkenylgold intermediate **148**. This intermediate was further protonated at the alkyne moiety to give a cationic intermediate, which undergoes 5-*exo*-*dig* or Nazarov cyclization to give the product (Table 39).[103a]

This reaction was further developed into the intramolecular [3 + 2] cycloaddition of 1-aryl-1-allene-6-enes to give dihydrobenzo[a]fluorene derivatives in good yields using the same cationic Au(I) catalyst under similar conditions (equation 47).[103b]



Scheme 75



(47)

R^1 = Me, Pr^n; R^2 = H, Me, OMe, F, Cl

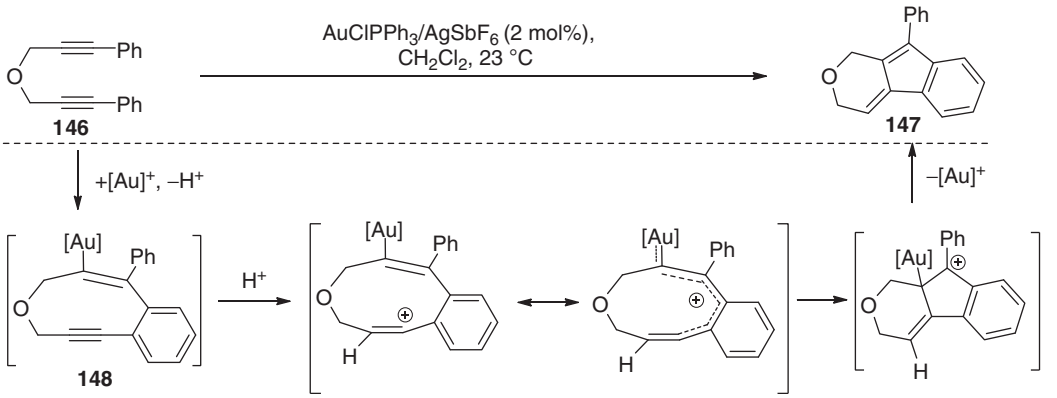
5.08.4.5 Use of Aryl Carbonyl and Related Derivatives as a Three-Carbon Unit

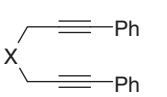
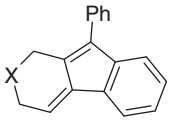
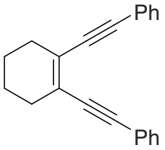
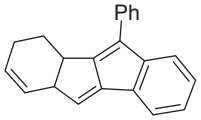
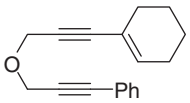
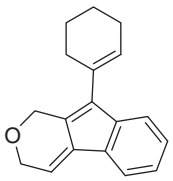
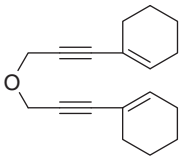
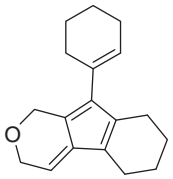
This section summarizes recent progress in the annulation of aryl carbonyl and related compounds as a three-carbon unit via transition metal-catalyzed reactions with alkynes or alkenes.

Initially, transition metal-catalyzed [3 + 2] cycloadditions of *o*-haloarylcarbonyl and related derivatives with alkynes have been developed. *o*-Bromo and *o*-iodobenzaldehyde were employed as substrate for the reaction with alkynes using 5 mol% of $Pd(OAc)_2$, 4 equivalents of Na_2CO_3, and 1 equivalent of n-Bu_4NCl. The reaction worked well with internal alkynes and the regiochemistry was sterically controlled.[104a] The cycloaddition was proposed to proceed through a palladium(IV) intermediate generated by oxidative addition of the aldehyde C–H bond to a primary alkenylpalladium(II) intermediate (Scheme 76).[104b,c]

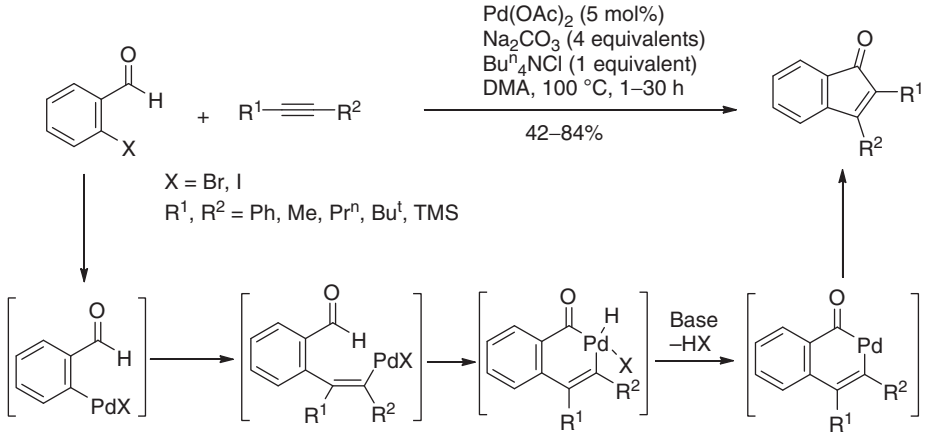
Interestingly, when carried out using 5 mol% $Pd(OAc)_2$ and 2 equivalents KOAc, indenol derivatives were obtained in good yield. In this case, the reaction was thought to proceed via nucleophilic addition of alkenylpalladium intermediates to the aldehyde. This process worked well even with *o*-bromophenyl ketone derivatives (Table 40).[104d,e]

Table 39 Catalytic intermolecular [3 + 2] cycloaddition of arenyne-ynes



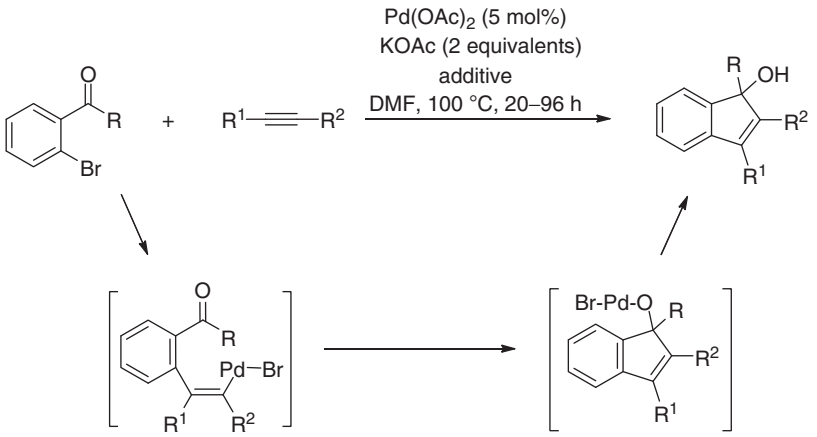
Substrate		*Product*	*Yield (%)*
	X = NTs X = $C(CO_2Me)_2$ X = CH_2		61 90 72
			64[a]
			73
			51[b]

[a] $PtCl_2$ was used at 100 °C.
[b] $AuClPPh_3$-AgOTf was used at 100 °C.



Scheme 76

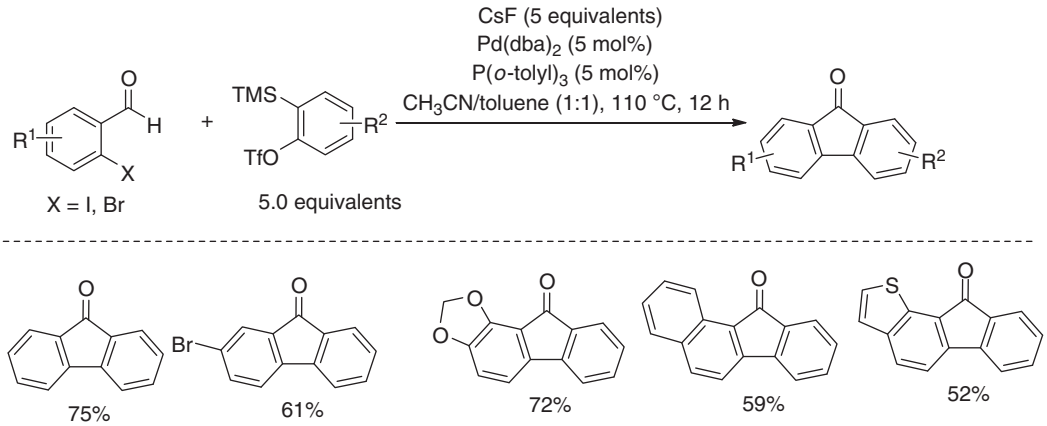
Table 40 Palladium-catalyzed synthesis of indenols



R	R^1	R^1	*Additive*	*Yield (%)*
Me	Pr^n	Pr^n	A	82
Me	Ph	Ph	A	63
Bu^t	Pr^n	Pr^n	C	51
Ph	Pr^n	Pr^n	B	86
Ph	Ph	Ph	B	75
Ph		$-(CH_2)_{10}-$	B	76
Me	Me	Ph	A	68[a]
Me	Bu^n	$C{\equiv}CBu^n$	A	75[b]
H	Pr^n	Pr^n	D	71
H		$-(CH_2)_{10}-$	D	73
H	Me	Bu^t	D	67

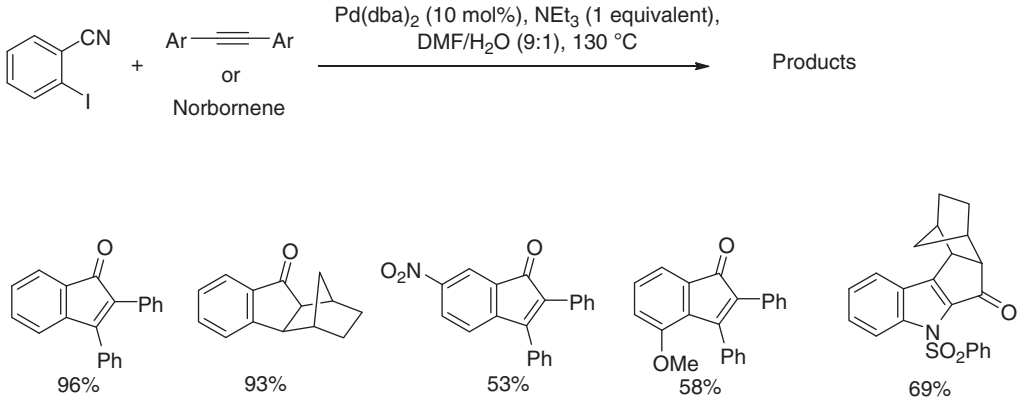
[a]A mixture of regioisomers (48:20).
[b]A mixture of regioisomers (67:33).
Note: A: None, B: PPh_3 (10 mol%), C: PPh_3 (10 mol%), EtOH (equivalent), and D: EtOH (10 equivalents), 60 °C.

Since these early studies, various investigations have been carried out concerning the electrophilic moieties that participate in the reaction, such as ketone carbonyls, cyano-, and imine groups. Various metal catalysts have also been developed; for example, even benzynes, generated *in situ* from 2-(trimethylsilyl)aryl triflate and CsF, could be employed as a two-carbon unit to give fluoren-9-ones (Scheme 77).[105a,b]



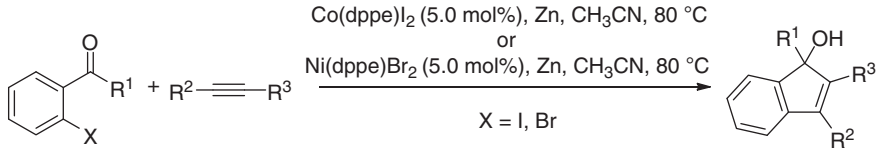
Scheme 77

Similar nucleophilic additions of alkenylpalladium species to nitriles were found to proceed with *o*-iodobenzonitrile and alkynes or alkenes, although the efficiency of the reaction was not necessarily good. Diaryl alkynes and norbornene derivatives gave better results (Scheme 78).[105c,d]



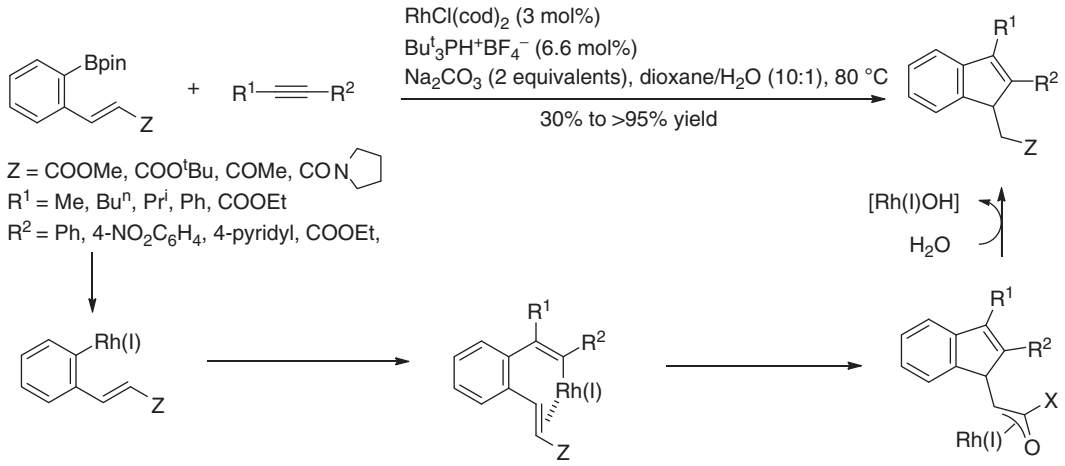
Scheme 78

Furthermore, nickel- and cobalt-catalyzed reactions were also realized (equation 48).[106]



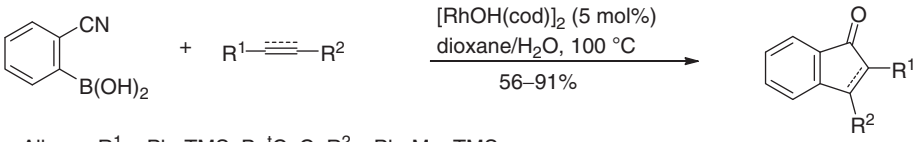
(48)

Phenylboronic acids with an electrophilic *ortho* substituent were also employed for this type of reaction using rhodium(I) or palladium(II) catalysts. In these cases, redox processes are not involved in the catalytic cycle but the reaction proceeds through arylrhodium(I) or arylpalladium(II) species generated by transmetallation. These intermediates insert alkynes or alkenes to give alkenyl- or alkyl-metallic species, which then add to the electron-deficient carbon to give the formal [3 + 2] annulation products. For example, arylboronates bearing a pendant electron-deficient alkene reacted with alkynes to give indene derivatives in good yield using a rhodium(I) catalyst with a bulky, electron-rich phosphine ligand (Scheme 79).[107]



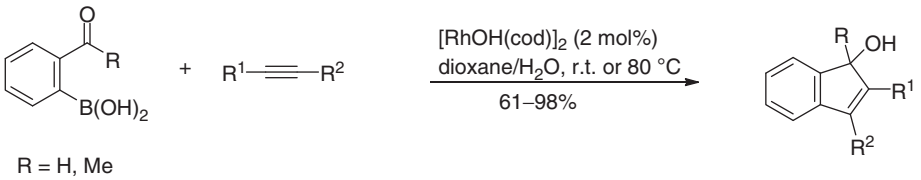
Scheme 79

As for the electrophilic moiety, cyano and formyl functionalities have been utilized in such rhodium-catalyzed reactions. Some representative examples are shown in equations 49 and 50.[107c,d]



(49)

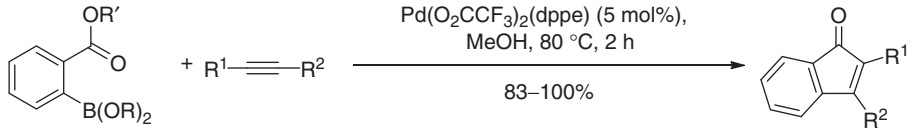
Alkyne: R^1 = Ph, TMS, $Bu^tC{\equiv}C$; R^2 = Ph, Me, TMS
Alkene: norbornene



(50)

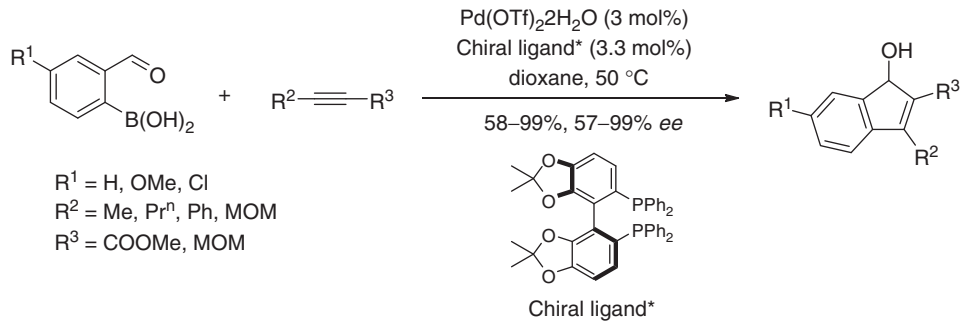
R = H, Me
R^1 = Ph, Et, CH_2OAc, COOEt, COMe
R^2 = Ph, Me, Et, CH_2OAc, TMS

Palladium complexes have also been employed for similar reactions. For example, treatment of a mixture of *o*-alkoxycarbonylphenylboronic acid and an internal alkyne with 5 mol% of $Pd(O_2CCF_3)_2$(dppe) gave indenone derivatives in good yield. Not only aryl alkynes but also dialkyl alkynes were applicable to this reaction (equation 51).[108a] *o*-Formylarylboronic acids furnished indenol derivatives. Cationic palladium complexes were effective catalysts, and optically active products have been prepared by using a chiral palladium complex (equation 52).[108b,c]



(51)

$B(OR)_2$ = $B(OH)_2$ or Bpin; R′ = Me, Et, Pr^i
R^1 = Ph, 4-$MeOC_6H_4$, Pr; R^2 = Ph, 4-$MeOC_6H_4$, Me, Pr

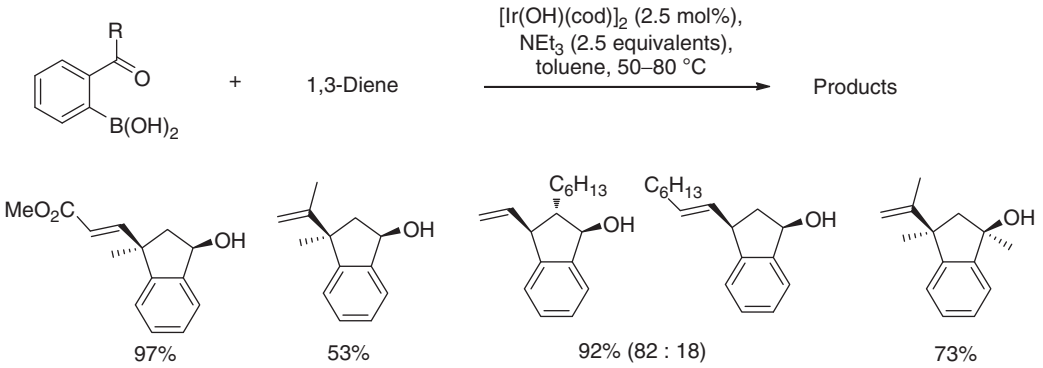


(52)

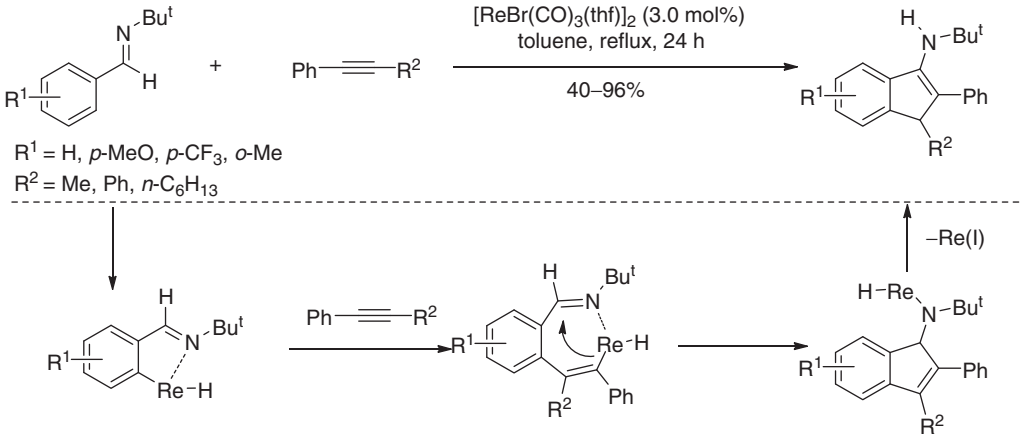
R^1 = H, OMe, Cl
R^2 = Me, Pr^n, Ph, MOM
R^3 = COOMe, MOM

Furthermore, *o*-carbonylated phenylboronic acids reacted with 1,3-dienes to give indanol derivatives in the presence of an iridium(I) catalyst (**Scheme 80**).[109]

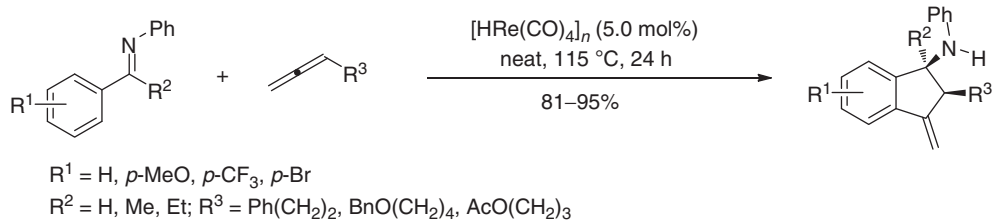
Recently, this type of reaction was combined with C–H activation chemistry. Thus, simple aryl carbonyl derivatives, in particular, arylimines could be employed as a three-carbon unit in reactions with alkenes and alkynes. Treatment of a mixture of benzaldehyde imines and arylalkynes with 3 mol% of $[ReBr(CO)_3(thf)_2]_2$ afforded aminoindene derivatives in good yield. The reaction proceeded with arylalkynes regioselectively, with the aryl substituent getting positioned next to the amino group. Arylrhenium species are generated by C–H activation; insertion of the alkyne followed by nucleophilic addition of the generated alkenylrhenium to the imine moiety and subsequent reductive elimination gave the product with regeneration of the Re(I) catalyst (**Scheme 81**).[110a,b] Allenes could also be employed in a similar process; specifically, aniline-derived ketimines gave the corresponding methylene aminoindane derivatives diastereoselectively on heating with the allenes in the presence of a catalytic amount of $[HRe(CO)_4]_n$ (equation 53).[110c]



Scheme 80

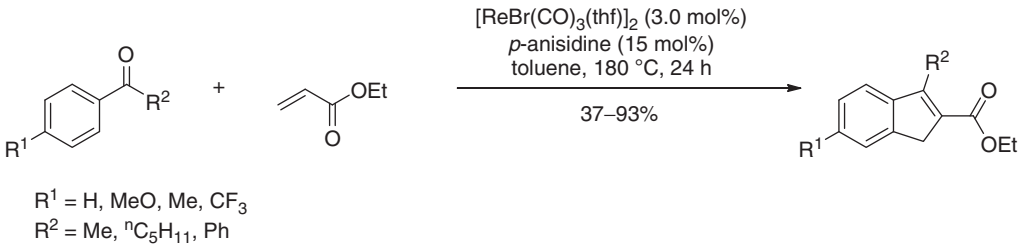


Scheme 81



(53)

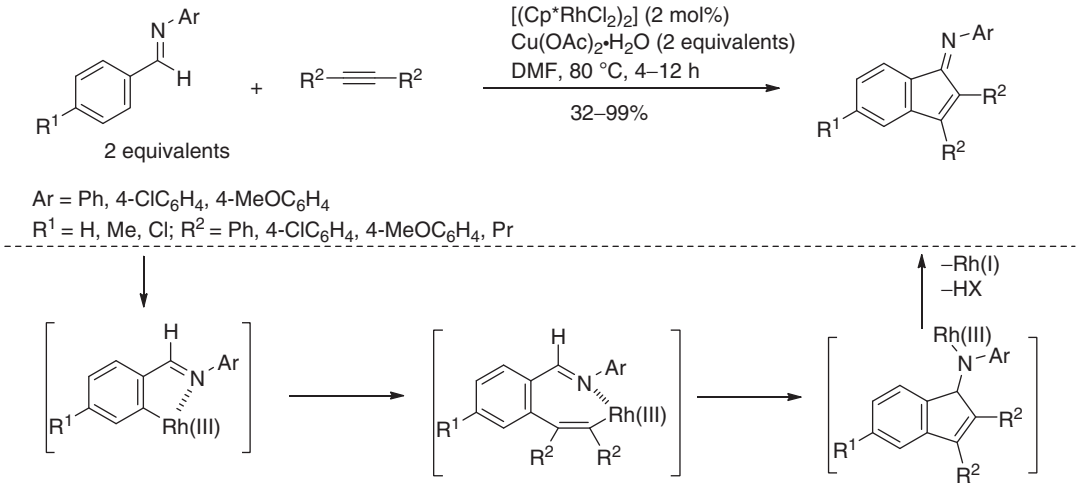
A similar reaction using acrylate instead of alkynes or allenes gave indene derivatives by elimination of aniline from the initial product. A rhenium- and aniline-cocatalyzed annulation of aromatic ketones with acrylate was achieved in good yield (equation 54).[110d]



(54)

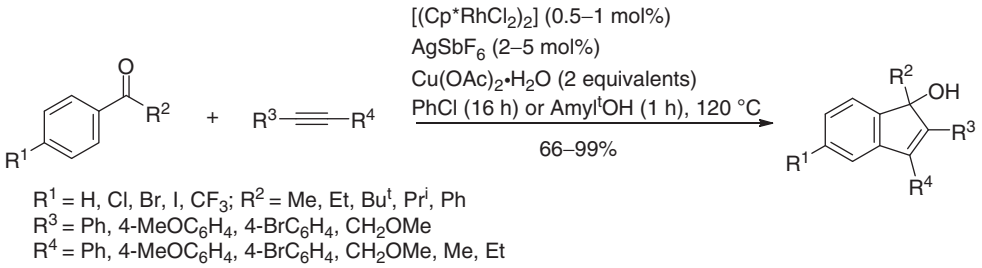
Rhodium-catalyzed reactions have also been accomplished recently, and these are classified into three reaction types, that is, (1) oxidative couplings using a Rh(III) catalyst with a stoichiometric Cu(II) reoxidant, (2) Rh(III)-catalyzed reactions in combination with a stoichiometric Cu(II) reagent, although no obvious reoxidation process is involved, and (3) Rh(I)-catalyzed

reactions based on a redox cycle. The first type of reaction employs $[Cp*RhCl_2]_2$ with $Cu(OAc)_2$ as a reoxidant. The reactions of aromatic aldimines with internal alkynes proceeded at 80 °C in DMF to give the corresponding [3 + 2] coupling products in good yield (Scheme 82).[111]

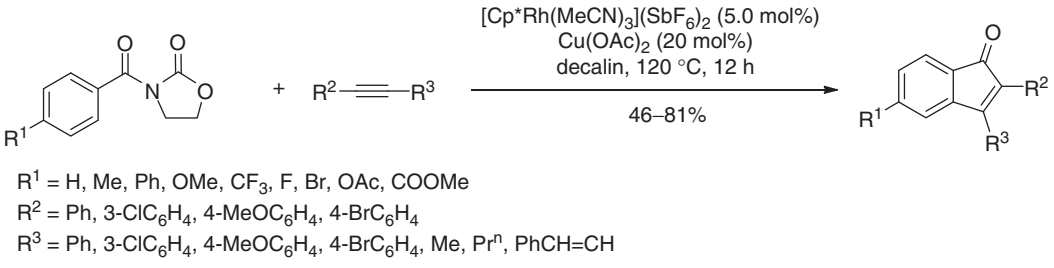


Scheme 82

The second type of reactions employs cationic Rh(III) catalysts in combination with $Cu(OAc)_2$ for the reactions of aromatic ketones or aroyl imides with internal alkynes. Almost all examples employed arylalkynes as substrates. Treatment of the aryl ketones or aroyl imides with aryl alkynes in the presence of cationic Rh(III) catalysts and $Cu(OAc)_2/H_2O$ gave indenol or indenone derivatives. Although the reason is not obvious, the use of $Cu(OAc)_2$ was essential to obtain the products in good yield. Representative examples are shown below (equations 55 and 56).[112]

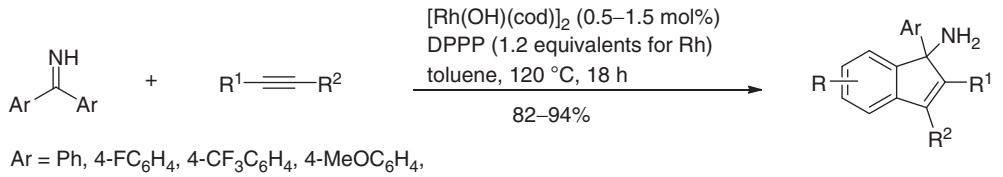


(55)



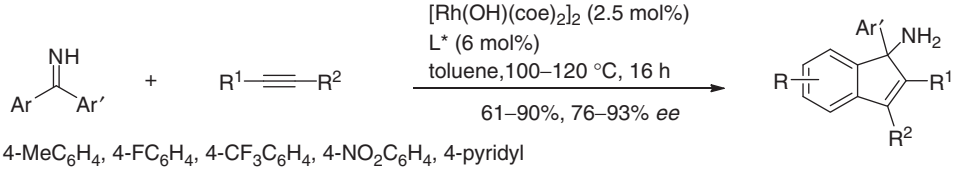
(56)

The third type of reactions employs Rh(I) complexes with phosphine ligands without further additives. For example, in the presence of 0.5–1.5 mol% $[Rh(OH)(cod)]_2$ and dppp, N-unsubstituted diaryl ketimines and internal alkynes were coupled to give tertiary 1*H*-inden-1-amines in good yield. In this reaction, oxidative addition of C–H bonds to Rh(I) and reductive elimination of the products from the Rh(III) metalacycle intermediates are involved.[113a,b] This reaction was extended to an enantioselective version using a chiral phosphine ligand (equations 57 and 58).[113c]



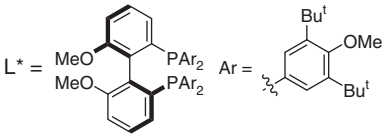
(57)

Ar = Ph, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$,
$R^1 = R^2$ = Ph, Et, Pr^n, $MeOCH_2$
R^1 = Ph, R^2 = Me, Et



(58)

Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-pyridyl
Ar′ = Ph, Ph, 4-MeC_6H_4, 4-FC_6H_4,
$R^1 = R^2 = MeOCH_2$
R^1 = Ph, Me, R^2 = $MeOCH_2$, $AcOCH_2$, $PhthNCH_2$



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5.09 Intermolecular Diels–Alder Reactions

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Glossary

Biomimetic synthesis Biomimetic synthesis is an attempt to assemble natural products using a specific reaction or a sequence of reactions that mimic a proposed biological pathway without recourse to the full enzymatic machinery of nature.

CH–π interaction CH–π interaction is a weak attractive noncovalent interaction between CH groups and π-systems. For example, intramolecular CH–π interaction is used to stabilize the conformation of some proteins.

Cinchona alkaloid Cinchona alkaloids are an important subgroup of the polycyclic β-carboline alkaloids, which include (dihydro)cinchonine, (dihydro)cinchonidine, (dihydro)quinidine, and (dihydro)quinine. These alkaloids are isolated from cinchona, a genus of approximately 38 species in the family Rubiaceae, native to tropical South America.

Endo*, *exo The Diels–Alder reaction of cyclopentadiene with 2-propenal can produce two possible diastereomers, the *endo*- and the *exo*-adducts. The prefix *endo* refers to the isomer with the substituent located closest, or *syn*, to the longest bridge. The prefix *exo* is reserved for the isomer with the substituent located farthest, or *anti*, to the longest bridge. Here 'longest' and 'shortest' refer to the number of atoms that comprise the bridge. *Endo* and *exo* are also used to describe the stereochemistry of transition-state assemblies that lead to the *endo*- and the *exo*-adducts, respectively.

HOMO, LUMO HOMO and LUMO are acronyms for highest occupied molecular orbital and lowest unoccupied molecular orbital, respectively. HOMO and LUMO are sometimes referred to as frontier orbitals. Electron-rich dienes have high-energy HOMOs and interact strongly with the LUMOs of electron-poor dienophiles.

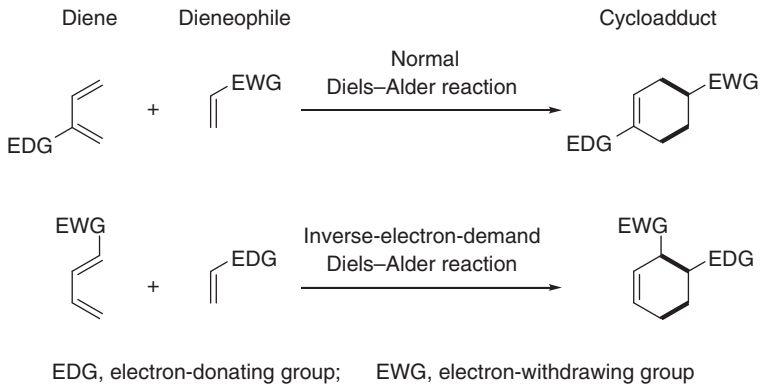
π–π Interaction π–π Interaction refers to attractive, noncovalent interactions between π-systems. In general, electron-rich π-systems (π-electron donor) interact with electron-deficient π-systems (π-electron acceptor) in parallel orientation.

s-cis*, *s-trans The spatial arrangement of two conjugated double bonds about the intervening single bond is described as *s-cis* if synperiplanar and *s-trans* if antiperiplanar. This term should not be applied to other systems such as *N*-alkyl amides (use *E*/*Z* or *sp*/*ap*).

5.09.1 Introduction

The cycloaddition reaction of a diene with a dienophile (alkene or alkyne) generates a cyclohexene derivative. This concerted [4 + 2] cycloaddition is known as the 'Diels–Alder reaction.' The Diels–Alder reaction has significant synthetic utility since it generates two new σ-bonds and a π-bond with the selective construction of multiple stereogenic centers in a single operation. In general, electron-deficient alkenes, such as quinones and α,β-unsaturated aldehydes, are more reactive toward electron-rich dienes

(Scheme 1). However, for the reaction with electron-poor dienes, electron-rich alkenes, such as vinyl ethers, are more reactive. This type of reaction is called an 'inverse-electron-demand' Diels–Alder reaction. An excellent review of intermolecular Diels–Alder reactions was presented in the first edition of Comprehensive of Organic Synthesis in 1991: 'Intermolecular Diels–Alder Reactions' by W. Oppolzer.[1]



Scheme 1 Conceptual Diels–Alder reactions.

Since the discovery of the Diels–Alder reaction, stereoselective versions of the reaction have been widely investigated. In 1960, the Diels–Alder reactions of anthracene with maleic anhydride, benzo-1,4-quinone, or dimethyl fumarate were shown to be markedly accelerated by the presence of aluminum trichloride.[2] This catalytic effect is the result of the coordination of the Lewis acid with the dienophile, which lowers the energy of the lowest unoccupied molecular orbital (LUMO), thereby allowing the Diels–Alder reaction to be conducted under mild conditions with enhanced regio- and diastereoselectivity. Furthermore, enantioselectivity in the reaction can be achieved with the use of chiral Lewis acid catalysts. This chapter focuses on recent advances in the diastereo- and enantioselective Diels–Alder reaction using chiral Lewis acid catalysts or chiral organocatalysts.

5.09.2 Catalysis Using Chiral Boron Compounds

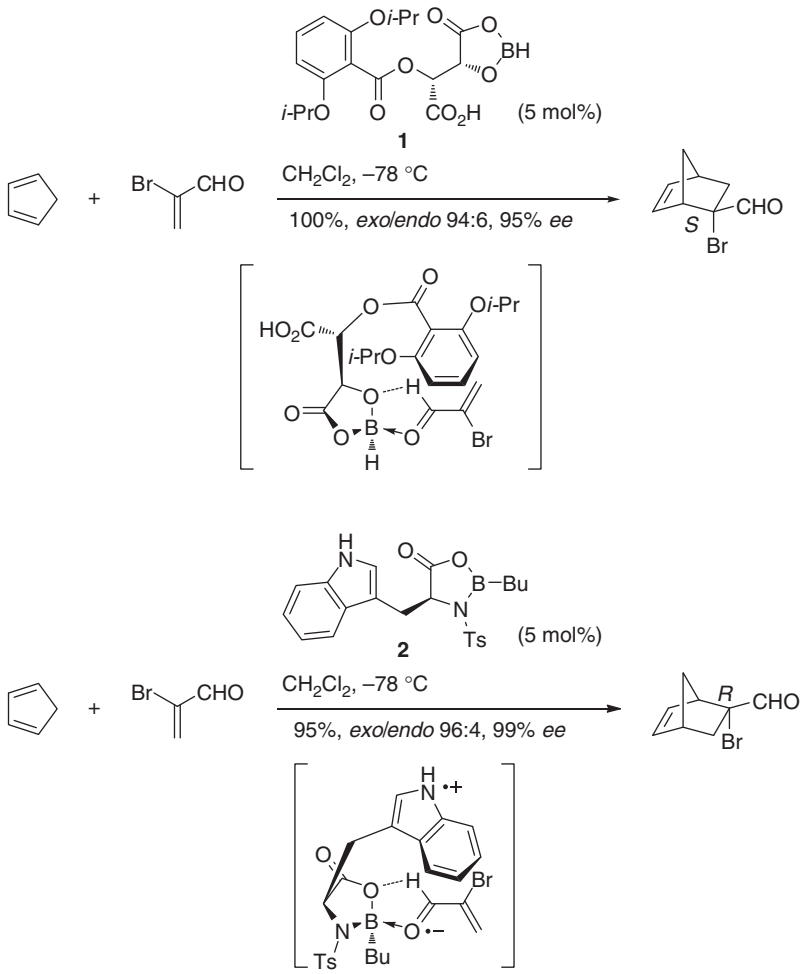
5.09.2.1 Chiral Cationic Oxazaborolidines

Early examples of chiral boron catalysts for the enantioselective Diels–Alder reaction include the chiral acyloxyborane (CAB) catalyst **1** derived from *O*-[2,6-di(isopropoxy)benzoyl]-L-tartaric acid[3–6] and the chiral oxazaborolidine **2** derived from *N*-tosyl-L-tryptophan and butylboronic acid (Scheme 2).[7–9] Catalyst **1** is effective for the Diels–Alder reaction with acrylic acids, α,β-alkenals and α,β-alkynals. Effective shielding of the *Si* face of α,β-alkenal coordinated to **1** arises from π–π stacking between the electron-rich 2,6-diisopropoxybenzene ring and the coordinated aldehyde. The high enantioselectivity in the Diels–Alder reaction of α,β-alkenals catalyzed by **2** is induced by attractive interactions between the π-donor indole ring and the coordinated aldehyde. Based on the bright orange-red color of the complex of **2** with 2-methylpropenal, this attractive interaction may be due to charge-transfer complexation, which is stronger than a π–π attractive interaction.

Activation of oxazaborolidines through coordination with a strong acid on nitrogen generates highly Lewis acidic cationic oxazaborolidines.[10,11] Thus, cationic oxazaborolidines **3**–**7** have been developed as powerful catalysts for the enantioselective Diels–Alder reaction. Oxazaborolidines **3** (X=TfO, Tf_2N) and **4**, derived from an α,α-diphenyl-L-prolinol and tri-2-tolylboroxin, are activated by superacids such as trifluoromethanesulfonic acid (TfOH),[12,13] trifluoromethanesulfonimide (Tf_2NH),[14,15] or strong Lewis acids such as aluminum tribromide.[16] Oxazaborolidines **3** and **4** show excellent catalytic activities for the Diels–Alder reactions of various α,β-alkenals, α,β-unsaturated ketones, and α,β-unsaturated esters (Table 1) (Figure 1).

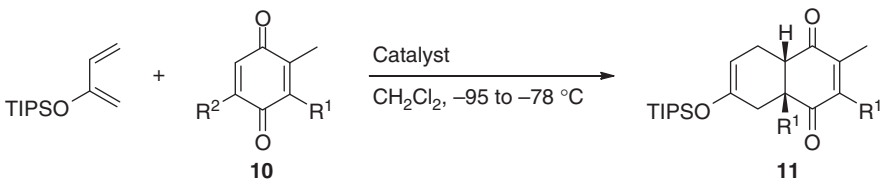
As shown in Table 1, the face selectivities of the enantioselective Diels–Alder reactions of α,β-unsaturated ketones and esters are opposite to those observed for α-substituted propenals. This reversal in face-selectivity can be explained in terms of the pretransition-state complexes **8** and **9** (Figure 2).[13] In pretransition-state complex **8** for α,β-alkenals, the oxygen of the oxazaborolidine catalyst interacts with the formyl CH proton (formyl CH–O interaction), whereas for other α,β-unsaturated carbonyl compounds, the oxygen interacts with the α-CH proton (α-CH–O interaction) in pretransition-state complex **9**. In the Diels–Alder reactions of α,β-unsaturated esters, an alternative mode of coordination that does not involve an α-CH–O interaction has also been proposed on the basis of computational investigations.[17]

In general, quinones are highly reactive dienophiles and the scope of their reactions is broad. The Diels–Alder reaction of quinones is very useful for the synthesis of natural products and other complex molecules. For example, oxazaborolidines **3b** and **4** successfully catalyze the Diels–Alder reaction of quinones **10** to afford the corresponding adducts **11** with high regio- and enantioselectivities (equation 1, Table 2).[15,16] In particular, aluminum tribromide-activated oxazaborolidine **4** shows excellent



Scheme 2 Early examples of chiral boron catalysts for the enantioselective Diels–Alder reaction.

catalytic activity and can promote the reaction of quinones **10** with low catalyst loading (4 mol%). The sense of the enantioselectivity of the Diels–Alder reaction of quinones **10** is consistent with pretransition-state complex **9**.

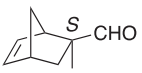
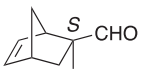
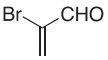
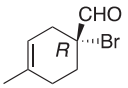
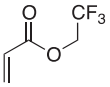
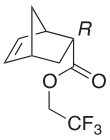
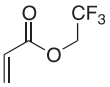
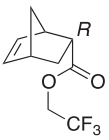
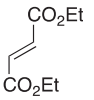
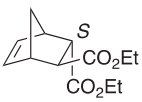
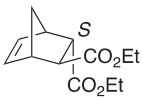
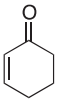
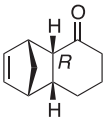
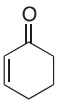
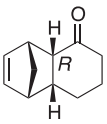


(1)

The following set of selection rules for the Diels–Alder reaction of unsymmetrical 1,3-butadienes with unsymmetrical 1,4-benzoquinones has been proposed.[15]

1. For a quinone carbonyl flanked by Cα–H and Cα–R, the major product will result from catalyst coordination preferentially at the oxygen lone pair on the C–H side rather than the C–R side because the C–H side is sterically more accessible (Figure 3).
2. Catalyst coordination at the more basic of the two 1,4-quinone oxygens will predominate, and this mode will lead to the preferred Diels–Alder adduct (Figure 3).
3. If a double bond of the quinone in a 1,3-diene addition bears two hydrogens, it will be more reactive than that bearing substituent(s), especially one or two π-electron-donating groups.
4. For monosubstituted 1,4-quinones (or *p*-benzoquinone itself), the major product pathway will involve coordination of the catalyst at the C=O *syn* to the HC=CH subunit that undergoes [4 + 2]-cycloaddition (Figure 3).
5. C-1 of 2-triisopropylsilyloxy-1,3-butadiene, the more nucleophilic end of the diene, will attach to the carbon β to the carbonyl group that coordinates with the catalyst, that is, the more electrophilic carbon.

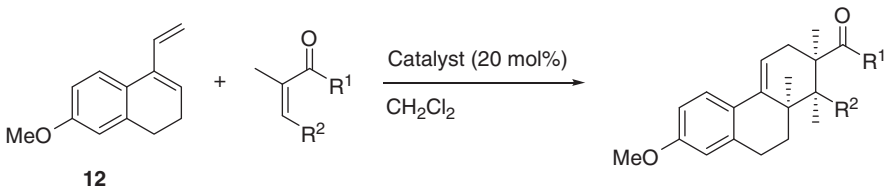
Table 1 Enantioselective Diels–Alder reactions of α,β-unsaturated carbonyl compounds catalyzed by oxazaborolidines **3** and **4**[a]

Reactants		*Catalyst (mol%)*	*Adduct*	*Yield (%)*	*Endo/exo*	*ee (%)*	*References*
Diene	*Dienophile*						
		**3a** (6)		99	9:91	91	12
		**4** (4)		99	8:92	93	16
		**3a** (6)		98	–	97	12
		**3b** (20)		97	98:2	>99	14
		**4** (4)		98	97:3	99	16
		**3b** (20)		99	–	>99	14
		**4** (4)		95	–	98	16
		**3a** (20)		97	91:9	93	13
		**4** (4)		99	94:6	95	16

[a]Conditions: diene (1.1 equivalents), catalyst (4–20 mol%), CH_2Cl_2.

6. The preferred three-dimensional transition state corresponds to the *endo* arrangement of the diene and catalyst-coordinated quinone.

Another type of chiral Lewis acid with an oxazaborolidine core is the *N*-methyloxazaborolidinium salt **5**,[18] which generally affords better results than catalyst **4**. For instance, the *ent*-**5**-catalyzed Diels–Alder reaction of Dane's diene **12** with 2-methylcyclopent-2-enone gives the corresponding *endo*-adduct **13** in 98% yield with 82% *ee* (equation 2, **Table 3**). However, the corresponding reaction with catalyst **4** provides *ent*-**13** in lower yield (50%) with lower enantioselectivity (75%).



(2)

The stereoselective construction of halogenated quaternary stereogenic centers is an important synthetic task because they are important structures in drug candidates and/or their synthetic intermediates. The asymmetric Diels–Alder reaction of halogenated dienophiles is an attractive approach for the stereoselective formation of halogenated quaternary carbons. Lewis acid-activated

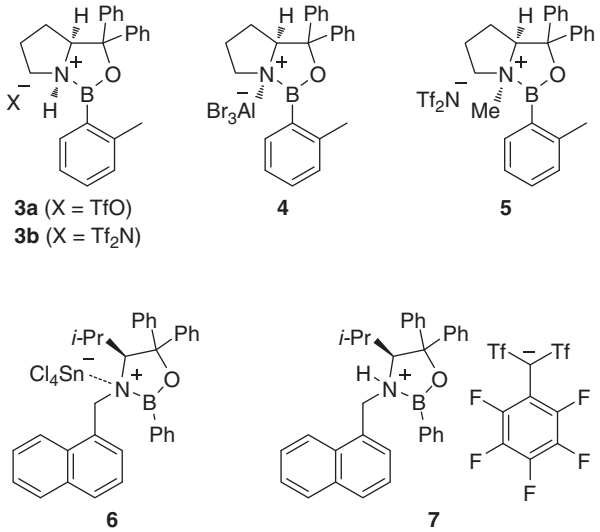


Figure 1 Cationic chiral oxazaborolidine catalysts.

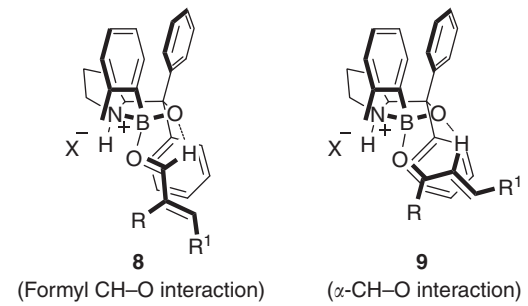


Figure 2 Proposed pretransition-state complexes **7** of oxazaborolidine catalysts and substrates.

Table 2 Enantioselective Diels–Alder reaction of quinones **10** catalyzed by oxazaborolidines (equation 1)

R^1	R^2	*Catalyst (mol%)*	*Yield of **11** (%)*	*ee (%)*	*References*
Me	H	**3b** (20)	98	>99	15
Me	H	**4** (4)	99	99	16
Me	Me	**3b** (20)	98	99	15
I	Me	**3b** (20)	99	>99	15
I	Me	**4** (4)	99	99	16

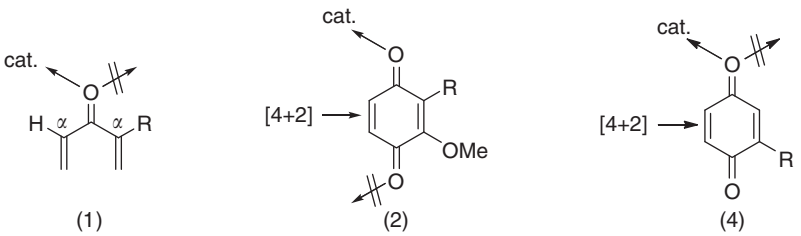
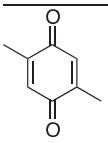
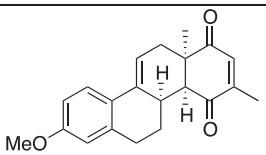
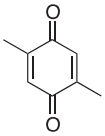
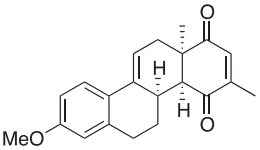
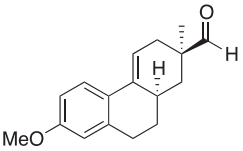
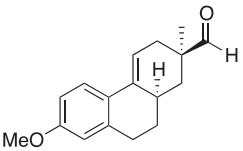
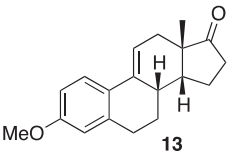
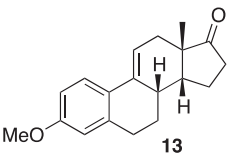


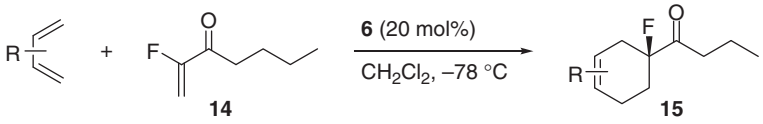
Figure 3 Selection rules for the quinone Diels–Alder reaction.

Table 3 Enantioselective Diels–Alder reaction of **12** catalyzed by chiral *N*-methyloxazaborolidinium Salt **5** (equation 2)

Dienophile	*Catalyst*	*Conditions (°C, h)*	*Adduct*	*Yield (%)*	*ee (%)*	*References*
	**5**	−78, 2.5		87	98	18
	**4**	−78, 2		87	84	18
	**5**	−78, 2.5		90	98	18
	**4**	−78, 0.5		95	98	18
	*ent*-**5**	23, 24	 **13**	98	82	18
	**4**	−20, 48	 **13**	50	75	18

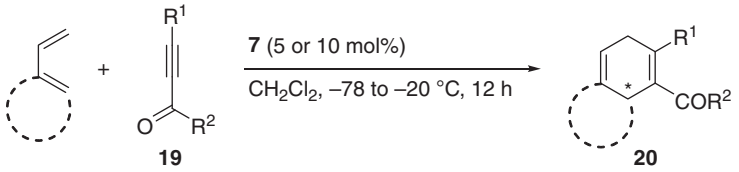
chiral oxazaborolidine **6** is an efficient catalyst for the enantioselective Diels–Alder reaction of 2-fluorohept-1-en-3-one **14** and gives the corresponding adducts **15** with high optical purity (equation 3, Table 4).[19] Notably, the reaction of **14** with cyclopentadienes catalyzed by **6** preferentially gives the *exo*-adducts, whereas the same reaction of ethyl vinyl ketone gives the corresponding nonfluorinated adducts with high *endo* selectivities.

Catalyst **6** can also promote the enantioselective Diels–Alder reaction of 2-halocycloalken-1-ones. For example, the reaction of 2-bromocyclopenten-1-one **16** with diene **12** affords the corresponding *endo*-adduct **17** with high enantioselectivity (Scheme 3). The adduct **17** can be converted to a *trans*-fused CD ring system **18** via a three-step sequence that includes *trans*-selective reductive alkylation as a key step.



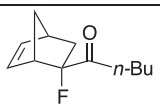
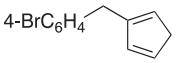
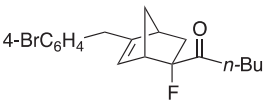
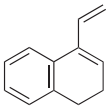
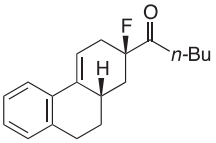
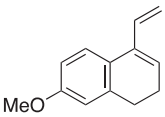
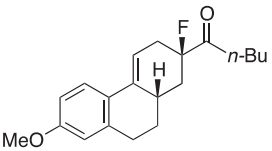
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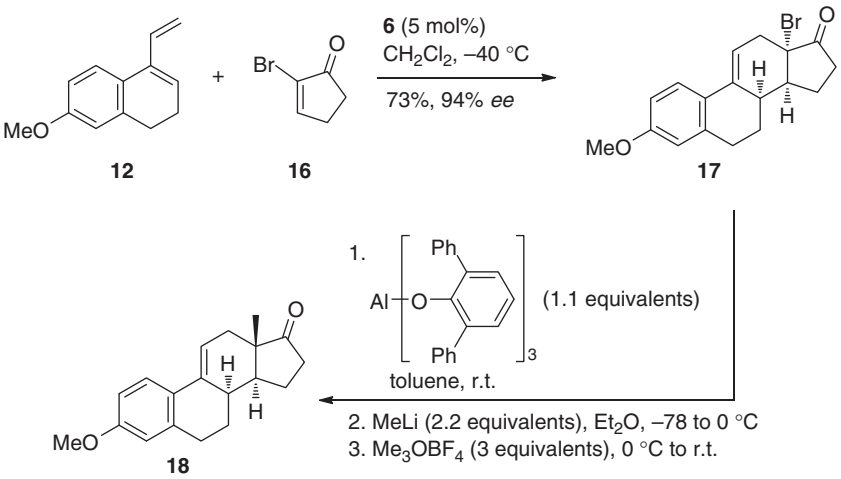
Despite advances in asymmetric catalysis, only a few methods have been reported for the enantioselective Diels–Alder reactions of alkynes. The L-valine-derived cationic oxazaborolidine **7** shows good catalytic activity for regio- and enantioselective Diels–Alder reactions of α,β-ynones **19** (equation 4, Table 5).[20] Both cyclic and acyclic dienes provide the corresponding adducts **20** in high yields with high enantioselectivities. In the reaction with cyclopentadiene, the use of dienophile **19** bearing a *tert*-butyldimethylsilyl (R^1=TBDMS) group improves the enantioselectivity, whereas the reaction of **19** bearing a trimethylsilyl (R^1=TMS) group shows moderate enantioselectivity. Importantly, a high level of asymmetric induction is observed with dienophiles that lack the hydrogen-bonding motif required for cationic oxazaborolidine-catalyzed Diels–Alder reactions.



(4)

Table 4 Enantioselective Diels–Alder reaction of α-fluoroenone **12** catalyzed by Lewis acid-activated chiral oxazaborolidine **6** (equation 3)

Diene	*Adduct*	*Yield (%)*	*dr*	*ee (%)*	*References*
		75	83:17	94	19
		83	95:5	94	19
		83	98:2	89	19
		75	>99:1	94	19

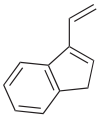
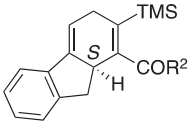
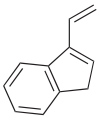
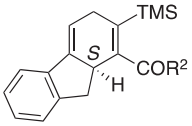
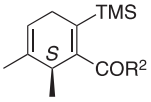
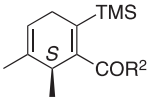
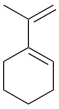
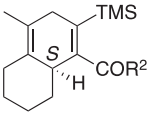
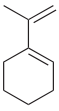
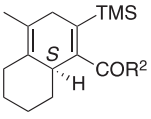
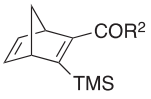
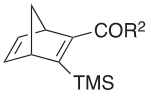
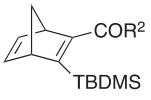
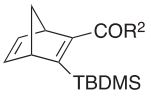


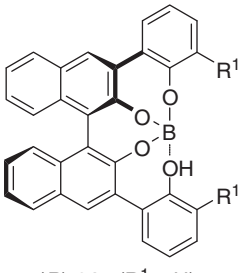
Scheme 3 Enantioselective Diels–Alder reaction of 2-bromocyclopenten-1-one **16**.

5.09.2.2 Boric or Boronic Acid Esters of Chiral 1,1′-bi-2-naphthols (BINOLs)

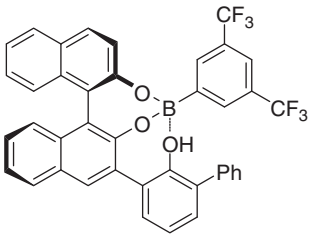
Chiral boric or boronic acid esters of binaphthols, e.g., **21** and **22** (Figure 4), can serve as Brønsted acid-assisted chiral Lewis acid (BLA) catalysts for the enantioselective Diels–Alder reactions of α,β-alkenals.[21–24] For example, in the presence of (*R*)-**21a** (R^1 = H, 10 mol%), the Diels–Alder reaction of 2-substituted propenals **23** ($R^2 \neq H$) with cyclopentadiene gives the corresponding *exo*-adduct **24** with high enantioselectivity, whereas the reaction of 2-unsubstituted propenals **23** (R^2 = H) preferentially gives the *endo*-**24** with moderate enantioselectivity (equation 5, Table 6). For the Diels–Alder reaction of propenal ($R^2 = R^3 = H$), the use of (*R*)-**21b** (R^1 = Ph) improves the enantioselectivity to 92% *ee*.[24] However, the scope of dienophiles that are suitable for use with less-reactive dienes is rather limited.

Table 5 Oxazaborolidine-catalyzed Diels–Alder reaction of α,β-ynones **19** (equation 4)

Diene	*Dienophile*		*Adduct*	*Yield (%)*	*ee (%)*	*References*
	R^1	R^2				
	TMS	Et		96	99	20
	TMS	Ph		85	99	20
	TMS	Et		96	99	20
	TMS	Ph		96	99	20
	TMS	Et		94	99	20
	TMS	Ph		88	99	20
	TMS	Et		88	74	20
	TMS	Ph		90	71	20
	TBDMS	Et		90	95	20
	TBDMS	Ph		98	90	20



(*R*)-**21a** (R^1 = H)
(*R*)-**21b** (R^1 = Ph)



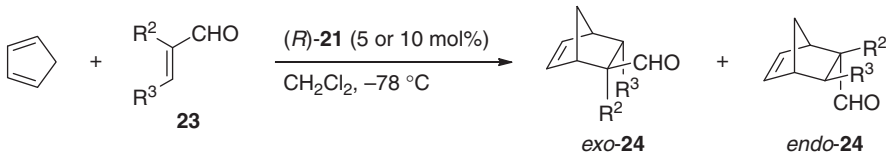
(*R*)-**22**

Figure 4 Brønsted acid-assisted chiral Lewis acid catalysts **21** and **22**.

Table 6 Enantioselective Diels–Alder reaction of α,β-alkenals **23** with cyclopentadiene catalyzed by (*R*)-**21** (equation 5)

R^2	R^3	**21**	Yield (%)	Exo/endo	ee (%) (configuration)	References
Br	H	**21a**	>99	>99:1	99 (*S*)	21,24
Me	H	**21a**	>99	>99:1	99 (*R*)	21,24
Et	H	**21a**	>99	97:3	92	21,24
Me	Me	**21a**	>99	>99:1	98	21,24
$(CH_2)_3$	–	**21a**	>99	98:2	93	21,24
H	H	**21a**	91	9:91	40 (*R*)	24
H	H	**21b**	85	14:86	92 (*R*)	24
H	Me	**21a**	12	11:89	36 (*R*)	24

The asymmetric induction in the (*R*)-**21**-catalyzed Diels–Alder reaction can be understood in terms of the most favorable transition-state complex **25** (Figure 5). It is conceivable that the coordination of a proton of the 2-hydroxyphenyl group with an oxygen of the adjacent B–O bond in complex **25** plays an important role in face selection. Hydrogen bonding through the Brønsted acid presumably causes the Lewis acidity of boron and the π-basicity of the phenoxy moiety to increase, which stabilizes the transition state. In transition state **25**, the hydroxyphenyl group blocks the C*α-Re* face of the carbon–carbon double bond in the 2-substituted propenals, which leaves the *Si* face open to an approach by the diene.



(5)

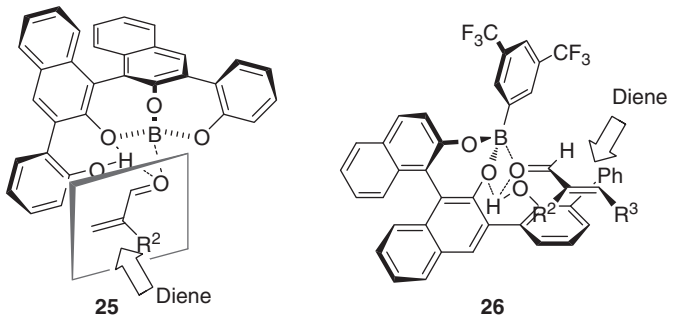


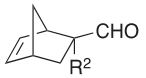
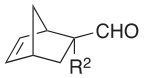
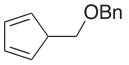
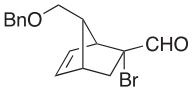
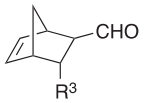
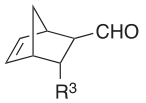
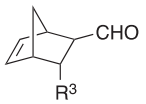
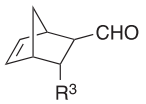
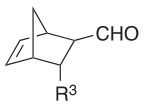
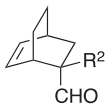
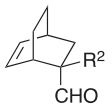
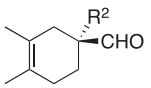
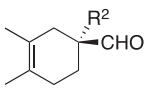
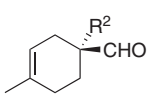
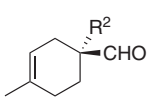
Figure 5 Proposed transition-state complexes **25** and **26**.

The chiral BLA catalyst (*R*)-**22** shows excellent activity for the Diels–Alder reaction of α,β-alkenals **23** with both α-unsubstitution ($R^2 = H$) and α-substitution ($R^2 \neq H$) with a variety of dienes (Table 7).[22,24] The BLA (*R*)-**22** is prepared *in situ* by reaction of the corresponding chiral (*R*)-triol with commercially available 3,5-bis(trifluoromethyl)phenylboronic acid in dichloromethane. In the presence of 5–20 mol% of (*R*)-**22**, the Diels–Alder reaction proceeds smoothly to afford the corresponding adducts with excellent diastereo- and enantioselectivities. The asymmetric induction in the (*R*)-**22**-catalyzed Diels–Alder reaction is opposite that in the reaction catalyzed by (*R*)-**21a**. This means that the presence of the 3,5-bis(trifluoromethyl)phenyl group greatly affects the asymmetric induction of (*R*)-**22**, which can be understood in terms of transition state **26** (Figure 5).

The chiral BLA **21** and **22** are also efficient catalysts for the enantioselective Diels–Alder reaction of acetylenic dienophiles **19** ($R^2 = H$).[23] The reaction of cyclic dienes with acetylenic dienophiles in the presence of (*R*)-**21a** or (*R*)-**22** (10–20 mol%) proceeds smoothly to afford the corresponding cycloadducts with a range of enantioselectivities (Table 8). Interestingly, (*R*)-**21a** generally gives higher enantioselectivity than (*R*)-**22**. As in the reaction with α,β-enals, the absolute configurations of the adducts with (*R*)-**21a** are opposite to those with (*R*)-**22**. The absolute configuration of the products of this reaction can be explained in terms of an *anti-exo* transition-state model **27** (Figure 6), and this view is strongly supported by theoretical studies. The frontier molecular-orbital theory explains *exo* selectivity in terms of the secondary antibonding interaction between the lobes on C-2 of cyclopentadiene and the carbonyl oxygen of propynal in the *endo*-transition state (TS) (Figure 6).

Because the *endo*/*exo* selectivity in the Diels–Alder reaction strongly depends on the substrates, it is quite difficult to control both the enantioselectivity and anomalous *endo*/*exo* selectivity by conventional chiral catalysts, which can only discriminate the enantiofaces of the dienophiles. For example, in the reaction of cyclopentadiene with propenal, an *endo* preference is observed with regard to second-order orbital interactions without significant steric interactions (Scheme 4). In sharp contrast, in the reaction

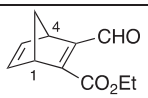
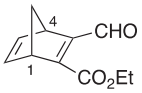
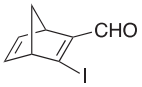
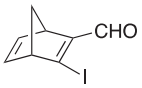
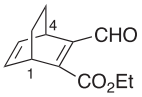
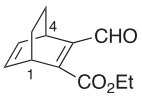
Table 7 Enantioselective Diels–Alder reaction of α,β-alkenals **23** catalyzed by (*R*)-**22**[a]

Diene	*Dienophile*		*Adduct*	*Yield (%)*	*Exo/endo*	*ee (%) (configuration)*	*References*
	R^2	R^3					
	Br	H		>99	90:10	>99 (*R*)	22,24
	Me	Me		90	98:2	96	22,24
	Br	H		>99	89:11	>99 (*R*)	24
	H	H		84	3:97	95 (*S*)	22,24
	H	Me		94	10:90	95 (*S*)	22,24
	H	Et		73	9:91	98	22,24
	H	Ph		94	26:74	80	22,24
	H	CO_2Et		91	2:98	95 (*R*)	22,24
	Br	H		65	10:90	95	22,24
	H	H		>99	0:100	96 (*S*)	22,24
	Br	H		95	–	91	22,24
	H	H		97	–	>99	22,24
	Br	H		95	–	>99 (*R*)	22,24
	H	H		95	–	99	22,24

[a]Conditions: diene (4 equivalents), (*R*)-**22** (5–20 mol%), CH_2Cl_2, –78 °C.

with 2-methylpropenal (R^1 = Me), an *exo* preference is observed with regard to steric interactions between the methylene moiety of cyclopentadiene and the substituent R^1 at the 2-position of the dienophile. In the reaction with 2-unsubstituted propenal, the thermodynamically more stable and enantiomerically enriched *exo*-**28** can be generated by the epimerization of *endo*-**28**. In contrast, enantiomerically enriched *endo*-**29** with a quaternary carbon center cannot be generated by the epimerization of *exo*-**29**. Therefore, the only approach for the synthesis of *endo*-**29** should be the enantioselective, anomalous *endo*-selective Diels–Alder reaction (Scheme 4).

Table 8 Enantioselective Diels–Alder reaction of cyclic dienes with acetylenic aldehydes **19** (R^2 = H) catalyzed by chiral BLA **21a** and **22**[a]

Diene	*R^1*	*Catalyst*	*Adduct*	*Yield (%)*	*ee (%) (configuration)*	*References*
	CO_2Et	(*R*)-**21a**		97	95 ((+)-(1*R*,4*S*))	23
	CO_2Et	(*R*)-**22**		98	63 ((–)-(1*S*,4*R*))	23
	I	(*R*)-**21a**		72	85 ((–)-(1*S*,4*R*))	23
	I	(*R*)-**22**		85	81 ((+)-(1*R*,4*S*))	23
	CO_2Et	(*R*)-**21a**		81	84 ((–))	23
	CO_2Et	(*R*)-**22**		54	34 ((+))	23

[a]Conditions: diene (4 equivalents), (*R*)-**21a** or (*R*)-**22** (10–20 mol%), CH_2Cl_2, –78 °C.

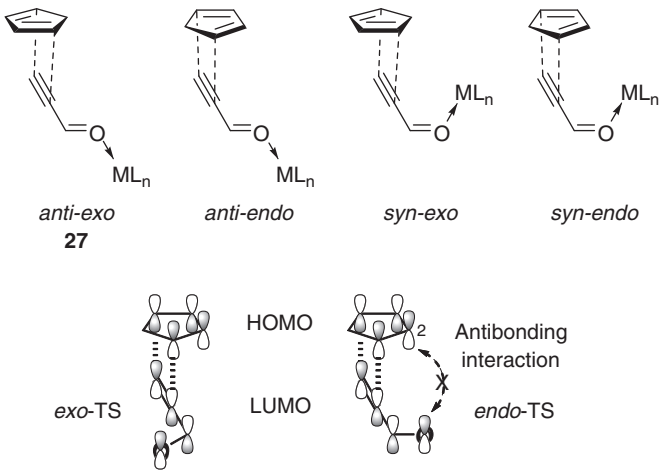
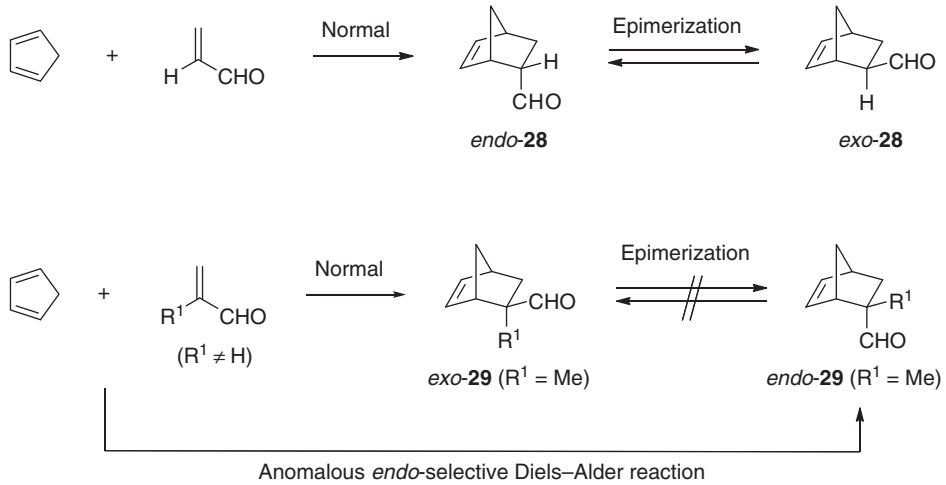
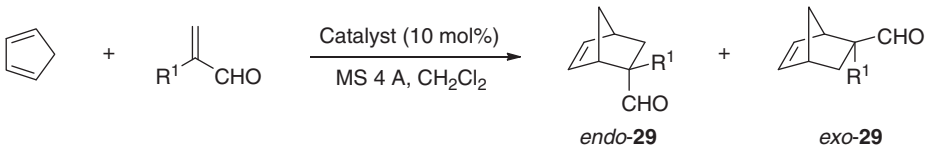


Figure 6 Four possible transition structures, and the secondary antibonding interaction in *endo*-TS. ML_n = Lewis acid.

Chiral supramolecular catalysts **32**–**35** are readily prepared *in situ* from the corresponding chiral diol **30** (10 mol%), an electron-deficient arylboronic acid **31** (10 mol%) and *tris*(pentafluorophenyl)borane (20 mol%) (Scheme 5).[25,26] Intermolecular acid–base coordinative bonds in the two P=O–B$(C_6F_5)_3$ moieties are critical for the design of the conformationally flexible complexes **32**–**35**. *Tris*(pentafluorophenyl)borane acts as a bulky functional group to form a chiral, narrow, and deep cavity around the Lewis acidic boron center. In addition, the strong electron-withdrawing nature of tris(pentafluorophenyl)borane increases the Lewis acidity of the central boron through conjugated bonds. Catalysts **32**–**35** can catalyze the anomalous *endo*-selective, enantioselective Diels–Alder reaction of cyclopentadiene with 2-substituted propenals ($R^1 \neq H$, equation 6). For example, the reaction with 2-methylpropenal (R^1 = Me) catalyzed by the chiral supramolecular catalyst **32** preferentially affords *endo*-(2*S*)-**29** as the major product (99% yield, *endo*/*exo* = 83:17) with 99% *ee* (Table 9). In contrast, the use of 3,5-*bis*(trifluoromethyl)phenylboronic acid **31** ($R^4 = CF_3$) or *tris*(pentafluorophenyl)borane as a catalyst gives the expected *exo*-**29** as the major product (*endo*/*exo* = 6–12:94–88). The chiral supramolecular catalysts **33**–**35** promote the Diels–Alder reaction with 2-bromopropenal, 2-chloropropenal, and 2-fluoropropenal, respectively, to give the corresponding adduct **29** (R^1 = Br, Cl, and F) with anomalous *endo* selectivities (*endo*/*exo* = 93–82:7–18) and excellent enantioselectivities (96–99% *ee*).



Scheme 4 Normal versus anomalous *endo*/*exo* selectivity in Diels–Alder reaction with 2-substituted propenals.



(6)

5.09.3 Catalysis Using Chiral Copper(II) Complexes

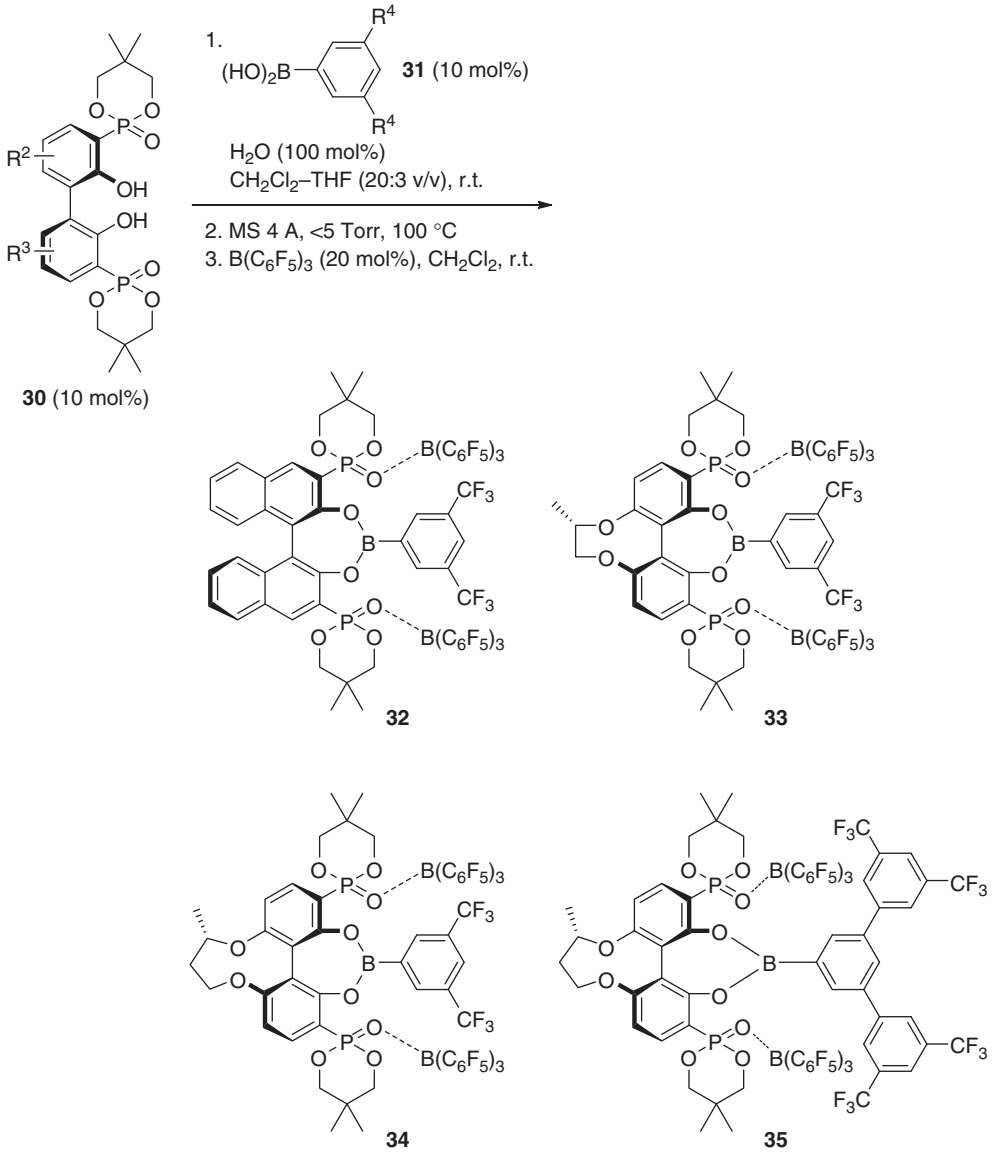
5.09.3.1 Chiral Copper(II)–*Bis*(oxazoline) Complexes

During the course of a synthetic study on prostaglandins, Corey and colleagues discovered that copper(II) tetrafluoroborate catalyzes the Diels–Alder reaction with α-chloroacrylonitrile.[27–29] The use of $Cu(BF_4)_2$ accelerates the Diels–Alder reaction at 0 °C without the isomerization of 5-(methoxymethyl)cyclopentadiene. Since then, various copper(II) salts have been used as Lewis acid catalysts for the Diels–Alder reaction.[30]

Bis(oxazoline) ligands are a major class of chiral ligands for asymmetric catalysis, among which **36** (R^1 = Bu^t, Pr^i, and Ph), **37**, and **38** (R = Bu^t and Ph) are representative examples (Figure 7).[31–33] The copper(II) complexes of these ligands are efficient catalysts for enantioselective Diels–Alder reactions. The C_2-symmetric copper(II) complexes of *bis*(oxazoline) **36a** (R^1 = Bu^t) show high catalytic activity for the enantioselective Diels–Alder reaction of dienes with *N*-alkenoyloxazolidinones **39** (Scheme 6).[34–37] The salts of copper(II) are the most effective among those of the first-row transition metals, since they offer both strong Lewis acid activation and rapid ligand-exchange. Representative results for enantioselective Diels–Alder reactions catalyzed by the copper(II) salt of **36a** are summarized in Table 10. Most acyclic and cyclic dienes afford the corresponding *endo*-adducts **40** in high yields with high enantioselectivities, whereas 2-substituted buta-1,3-dienes, such as isoprene and 2,3-dimethylbuta-1,3-diene, provide moderate enantioselectivities. The absolute configuration of the adducts **40** is consistent with activation through bidentate coordination of the dienophile **39** to a distorted square-planar copper(II) center (Scheme 6). A diene can approach the C*α*-*Re* face of the activated *s-cis* dienophile via an *endo*-transition state to afford the corresponding cycloadduct **40** with excellent enantioselectivity.

In contrast to 2,3-unsubstituted dienes, 3-methylbuta-1,3-dienyl acetate shows a significant *exo* preference (*endo*/*exo* 73:27). This diastereoselectivity could be explained by the steric hindrance of the 3-methyl substituent (R^3 = Me, Figure 8). The steric effect of the 3-methyl substituent could also explain the low enantioselectivity observed in the reaction of isoprene (59% *ee*). Isoprene is presumed to approach the activated dienophile largely via an *exo* transition-state **42**. The disfavored *exo* approach **43** of isoprene to the C*α*-*Si* face of the activated dienophile does not involve substantial steric interaction with the ligand to decrease the enantioselectivity. In contrast, the acetoxy group of 3-methylbuta-1,3-dienyl acetate contracts the ligand substituent in the disfavored *exo* approach **44** to generate high enantioselectivity (Figure 9).

The chiral copper(II) trifluoromethanesulfonimide complex of the *bis*(oxazoline) **37** produces a high degree of enantioselectivity in the Diels–Alder reaction of dienophile **39** with a variety of cyclic and acyclic dienes, including 2-substituted buta-1,3-dienes (Scheme 7, Table 11).[38,39] The reaction of acyclic dienes with *β*-substituted dienophiles, which is one of the most challenging reactions, successfully affords the corresponding adducts with high enantioselectivities. For example, the $Cu(NTf_2)_2$•**37**-catalyzed Diels–Alder reaction of isoprene with dienophile **39** (R^2 = $CH_2OTBDMS$) gives the corresponding *endo*-adduct with 95% *ee*; this product is a key intermediate for synthesis of the decahydrofluorene core of hirsutellones.[40]

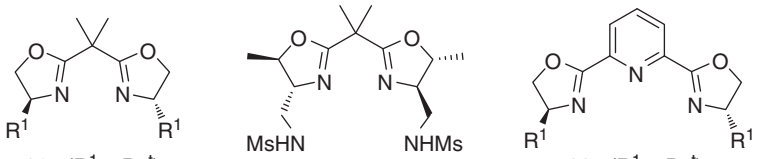


Scheme 5 Preparation of chiral supramolecular catalysts **32–35**.

Table 9 Anomalous *Endo*-selective asymmetric Diels–Alder reaction with 2-substituted propenals (equation 6)

R^1	*Catalyst*	*Conditions (°C, h)*	*Yield (%)*	*Endo/exo*	*ee (%) (configuration)*		*References*
					*endo-**29***	*exo-**29***	
Me	**32**	−78, 3	99	83:17	99 (*S*)	80 (*S*)	25,26
Me	**31** (R^4 = CF_3)	−78, 3	>99	6:94	–	–	25,26
Me	$B(C_6F_5)_3$	−78, 3	93	12:88	–	–	25,26
Br	**33**	−98, 6	94	93:7	>99 (*R*)	76 (*R*)	25,26
Br	$B(C_6F_5)_3$	−98, 6	>99	15:85	–	–	25,26
Cl[a]	**34**	−98, 5	>99	88:12	99 (*R*)	47 (*R*)	25,26
Cl	$B(C_6F_5)_3$	−98, 5	>99	10:90	–	–	25,26
F	**35**	−98, 5	>99	82:18	96 (*R*)	73 (*R*)	25,26
F	$B(C_6F_5)_3$	−98, 5	>99	49:51	–	–	25,26

[a]The reaction is conducted in the presence of hydroquinone (10 mol%).

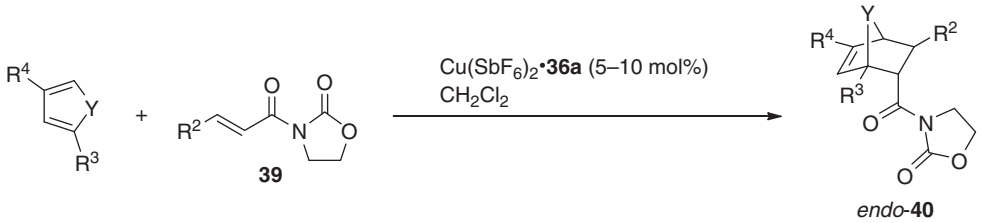


36a (R^1 = Bu^t)
36b (R^1 = Pr^i)
36c (R^1 = Ph)

37

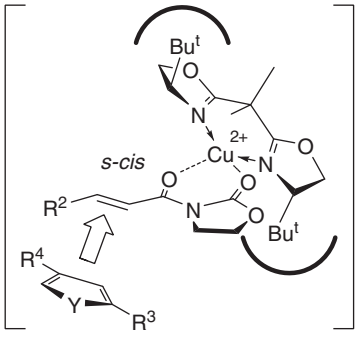
38a (R^1 = Bu^t)
38b (R^1 = Ph)

Figure 7 Representative bis(oxazoline) ligands **36**–**38**.



39

endo-**40**



endo, Cα-*re* face approach

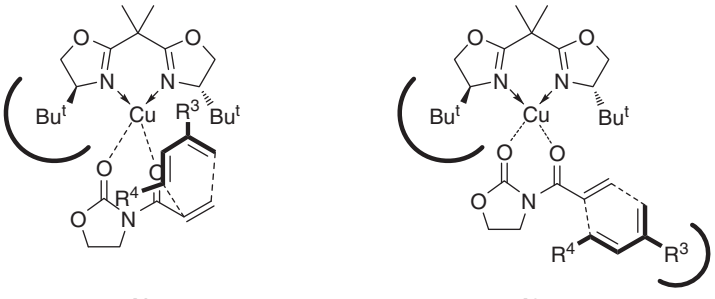
Scheme 6

Table 10 Enantioselective Diels–Alder reaction of *N*-alkenoyloxazolidinones **39** catalyzed by a $Cu(SbF_6)_2$•**36a** (Scheme 6)

R^3	Diene		Dienophile	Conditions (°C, h)	Yield (%)	Endo/exo	ee (%) (configuration)	References
	R^4	Y	R^2					
H	H	CH_2	Me	−15, 20	99	85:15	99 (2*R*)	33
H	H	CH_2	Ph	−10, 48	77	88:12	98 (2*R*)	33
H	H	CH_2	CO_2Et	−55, 20	88	82:18	87 (2*R*)	33
H	H	CH_2	Cl	25, 24	96	87:13	96 (2*R*)	33
H	H	$(CH_2)_2$	H	25, 5	90	95:5	93 (2*S*)	34
H	H	O	H	−78, 42	97	80:20	97 (2*S*)	34
Ph	H	H, H	H	−20, 24	95	85:15	97 (2*S*)	34
OAc	Me	H, H	H	−20, 18	57	73:27	98 (2*S*)	34
H	Me	H, H	H	25, 12	81	96:4	59 (2*S*)	34

A theoretical study suggests that the *n* electrons of the 4,4′-sulfonamide groups interact with the copper(II) cation (*n*–cation interaction), and the counteranions interact with the sulfonamidyl protons (Scheme 7).[38,39] This coordination is thought to be essential for high catalytic activity, because it results in the formation of a cationic but stable catalyst. It is conceivable that dienes predominantly approach the C*α*-*Si* face side of *s*-*cis*-**39**, because a sulfonamide group and a trifluoromethanesulfonimide anion preferentially shield the *Re* face of the acrylimide moiety. The flexible but highly efficient asymmetric environment created by the secondary interactions provides a broad substrate scope and a high level of asymmetric induction.

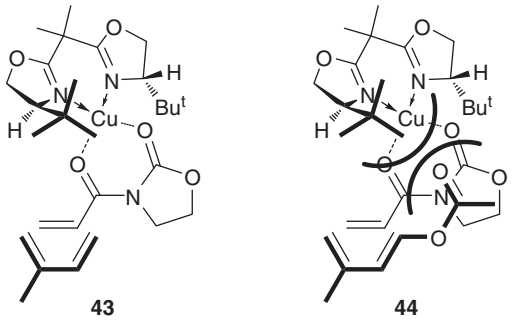
The *n*-cation catalyst also promotes the Diels–Alder reaction of diene **45** with *N*-alkenoyloxazolidinones **39** (R^2 = CO_2Et) to give the corresponding *endo*-adduct **46** in 97% yield with 95% *ee* (Scheme 8).[41] This procedure is scalable with a minimal



41
endo approach (favored for R^3 = H)

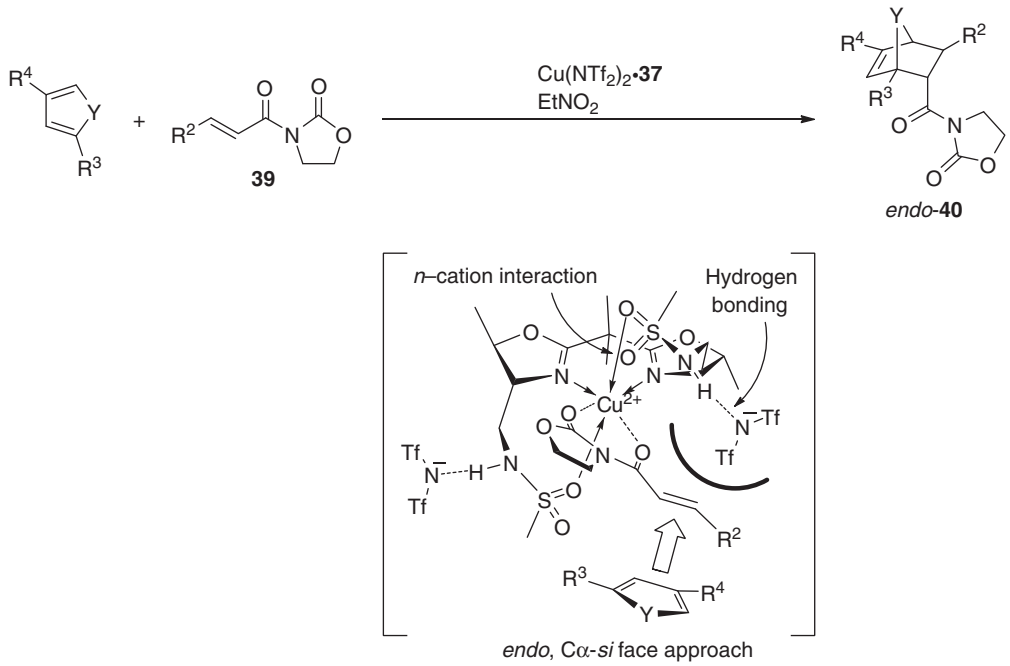
42
exo approach (favored for R^3 = Me)

Figure 8 Proposed transition-state complexes **41** and **42**.



43 **44**

Figure 9 Minor *exo*, Cα-*Si* face approaches of isoprene **43** and 3-methylbuta-1,3-dienyl acetate **44**.

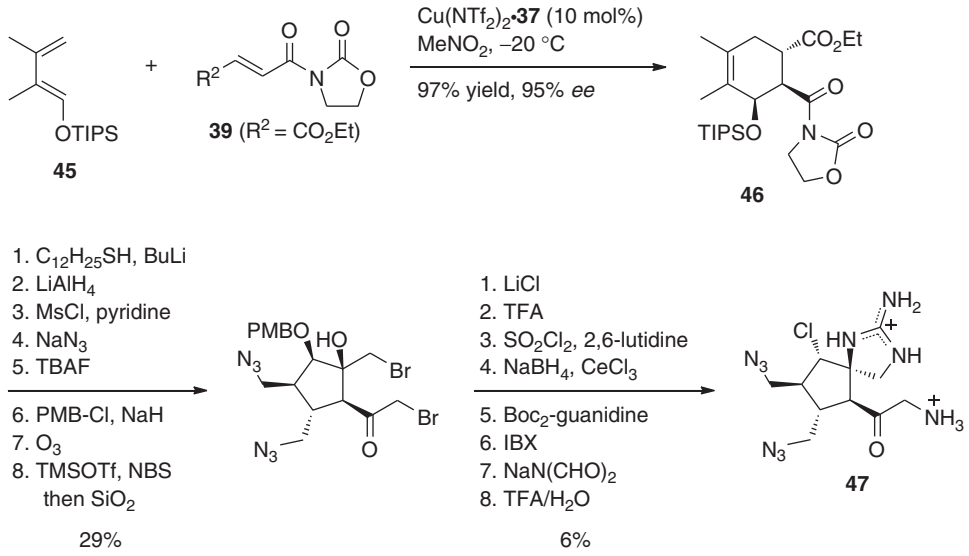


Scheme 7

decrease in yield and enantioselectivity: the reaction of **45** (2.5 equivalents) with **39** (19.2 g) in the presence of $Cu(NTf_2)_2$•**37** (5 mol%) affords 35.3 g of **46** (84% yield, 89% *ee*). The adduct **46** is converted to spiro compound **47**, which is a key common precursor for the synthesis of the pyrrole-imidazole alkaloids (–)-palau'amine, (–)-axinellamines, and (–)-massadines.

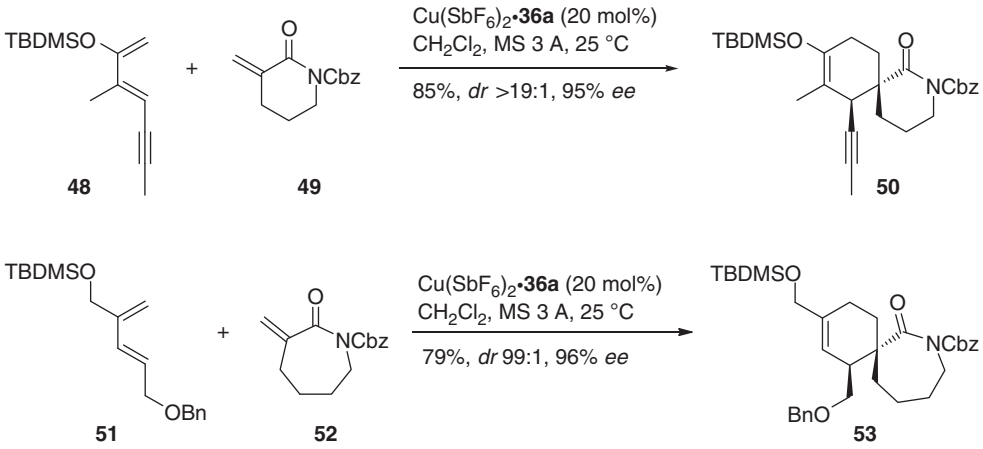
Table 11 Enantioselective Diels–Alder reaction of *N*-alkenoyloxazolidinones **39** catalyzed by $Cu(NTf_2)_2$•**37** (Scheme 7)

R^2	Diene		Dienophile	Conditions (°C, h)	Yield (%)	Endo/exo	ee (%) (configuration)	References
	R^3	Y	R^1					
H	H	CH_2	H	−72, 1	95	99:1	98 (2*R*)	36,37
H	H	$(CH_2)_2$	H	0, 30	95	99:1	92 (2*R*)	36,37
H	H	O	H	−72, 72	92	76:24	98 (2*R*)	36,37
Me	H	H, H	H	0, 72	92	85:15	92 (1*R*,2*S*)	36,37
OAc	Me	H, H	H	−20, 12	96	52:48	99 (1*R*,2*S*)	36,37
H	Me	H, H	H	−20, 24	93	>99:1	99 (1*R*)	36,37
H	Me	H, H	CO_2Et	r.t., 60	87	94:6	90 (1*R*,6*S*)	36,37
H	Me	H, H	$CH_2OTBDMS$	r.t., 66	76	>99:1	95 (1*S*,6*S*)	36,37



Scheme 8 Synthesis of spiro compound **47**, a key common precursor for the synthesis of pyrrole-imidazole alkaloids, (–)-palau'amine, (–)-axinellamines and (–)-massadines.

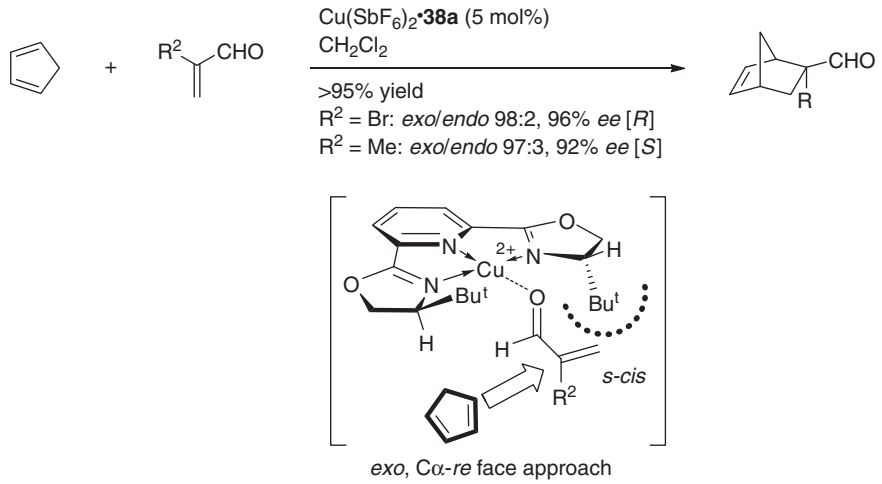
The *N*-Cbz-protected lactams **49** and **52** are also good dienophiles for the Diels–Alder reaction catalyzed by the copper(II) hexafluoroantimonate complex of the *bis*(oxazoline) **36a** (Scheme 9). In this context, the diene **48** reacts with the six-membered lactam **49** via an *exo*-transition state, to afford the spirolactam **50**, which is a key intermediate in the synthesis of the spirocyclic imine core of (–)-gymnodimine.[42] In a related example, the $Cu(SbF_6)_2$•**36a**-catalyzed cycloaddition of the diene **51** with the



Scheme 9 Enantioselective Diels–Alder reaction of *N*-Cbz-protected lactams **49** and **52**.

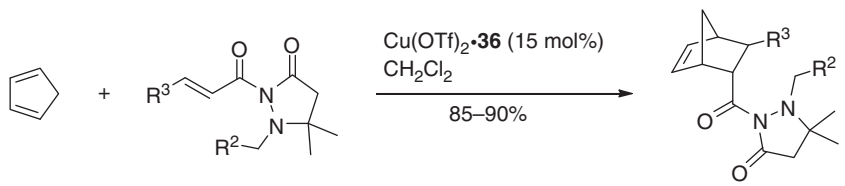
seven-membered lactam **52** gives the spirolactam **53**, which is useful as an intermediate in the synthesis of the azaspiro[5.6]dodec-9-ene system in the marine toxins pinnatoxin A and pteriatoxin A.[43]

For the enantioselective Diels–Alder reaction of α-substituted α,β-alkenals, such as 2-methylpropenal and 2-bromopropenal, the copper(II) complex of a tridentate *bis*(oxazolinyl)pyridine (pybox) **38a** ($R^1 = Bu^t$) is among the most efficient catalysts and gives the corresponding *exo*-adducts with high diastereo- and enantioselectivity (Scheme 10).[36,44] It is presumed that α-substituted α,β-alkenals coordinate to the copper(II) center in a square-planar geometry. Cyclopentadiene predominantly approaches the Cα-*Re* face of the *s-cis*-dienophile via an *exo*-transition state.



Scheme 10 Enantioselective Diels–Alder reaction of α-substituted propenals catalyzed by $Cu(SbF_6)_2$•**38a**.

N-Alkenoylpyrazolidinones **54** can also act as dienophiles in the copper(II)-catalyzed enantioselective Diels–Alder reaction to give the corresponding cycloadducts **55** (equation 7).[45,46] Although the copper(II) complex of *bis*(oxazoline) **36b** ($R^1 = Pr^i$) generally shows poor enantioselectivity for the reaction of cyclopentadiene with *N*-alkenoyloxazolinones **39**,[35] the reaction of **54** (R^2 = 1-naphthyl) provides a high enantioselectivity (Table 12). Interestingly, this dienophile provides higher enantioselectivity when Lewis acids with relatively small chiral ligands are used; this has been attributed to the size of the fluxional group (R^2 = Me < Ph < 1-naphthyl) and the ability of the pyrazolidinone template to relay stereochemical information from the ligand to the reaction center.



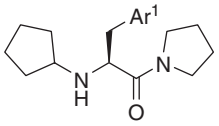
54 **55** (7)

Table 12 Enantioselective Diels–Alder reaction of cyclopentadiene with *N*-alkenoylpyrazolidinones **54** (equation 7)

36 (R^1)	R^2	R^3	*Temperature (°C)*	*Endo/exo*	*ee (%)*	*References*
36a (Bu^t)	Me	Me	r.t.	93:7	77	46
36a (Bu^t)	Ph	Me	r.t.	92:8	97	46
36a (Bu^t)	1-Naphthyl	Me	r.t.	90:10	99	46
36b (Pr^i)	Me	Me	r.t.	96:4	56	45,46
36b (Pr^i)	Ph	Me	r.t.	92:8	84	45,46
36b (Pr^i)	1-Naphthyl	Me	r.t.	93:7	95	45,46
36b (Pr^i)	1-Naphthyl	H	0	93:7	90	46
36b (Pr^i)	1-Naphthyl	CO_2Et	–20	93:7	96	46

5.09.3.2 Chiral Copper(II)–3-Arylalanine Amide Complexes

The enantioselective Diels–Alder reaction of cyclopentadiene with 3-phenyl-1-(2-pyridyl)prop-2-ene-1-one is catalyzed by copper(II) nitrate and the sodium salt of L-abrine (*N*-methyl-L-tryptophan) or *N*-methyl-L-tyrosine in water (equation 8).[47,48] In this reaction, water enhances the enantioselectivity to give a product with up to 74% *ee*. However, the enantioselectivity is reduced to 17–44% *ee* in organic solvents, such as acetonitrile, tetrahydrofuran (THF), ethanol, and chloroform. The asymmetric induction may originate from the intramolecular π–cation interaction between the indole ring of L-abrine and the copper(II) cation. On the basis of such intramolecular π–cation interactions, chiral copper(II)-3-aryl-L-alanine amide complexes CuX_2•**56** have been designed as efficient catalysts for the enantioselective Diels–Alder reaction of 1-alkenoyl-3,5-dimethylpyrazoles **57** (Figure 10).[49,50] In particular, the copper(II) complex of **56a** (Ar^1 = 3,4-$(MeO)_2C_6H_3$) bearing an electron-rich aromatic group shows excellent catalytic activity (Scheme 11). In the presence of 2–10 mol% of the complex of this ligand with copper(II) trifluoromethansulfonimide, cyclic, and acyclic dienes undergo Diels–Alder reactions with various β-substituted dienophiles **57** to afford the corresponding *endo*-adducts **58** with high enantioselectivities (Table 13).



56a (Ar^1 = 3,4-$(MeO)_2C_6H_3$)
56b (Ar^1 = 2-Naphthyl)

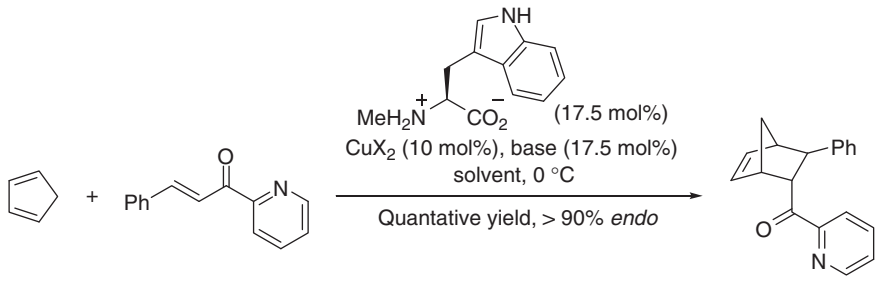
Figure 10 3-Aryl-L-alanine amide ligands **56**.

Table 13 Diels–Alder reaction of acrylamides catalyzed by $Cu(NTf_2)_2$•**56a** (Scheme 11)

Y	R^1	R^2	R^3	*Yield (%)*	*Endo/exo*	*ee (%) (configuration)*	*References*
CH_2	H	H	H	>99	98:2	97 (2*S*)	49,50
CH_2	H	H	Me	95	97:3	97 (2*S*)	49,50
CH_2	H	H	Ph	93	93:7	95	49,50
CH_2	H	H	OBz	89	93:7	90	49,50
CH_2	H	H	Cl	95	>99:1	97	49,50
H, H	Me	H	CO_2Et	83	93:7[a]	87	49,50
H, H	Me	Me	CO_2Et	76	–	93	49,50
H, H	Ph	H	CO_2Et	93	>99:1[a]	91	49,50
H, H	OMe	H	CO_2Et	96	>99:1[a]	97	49,50

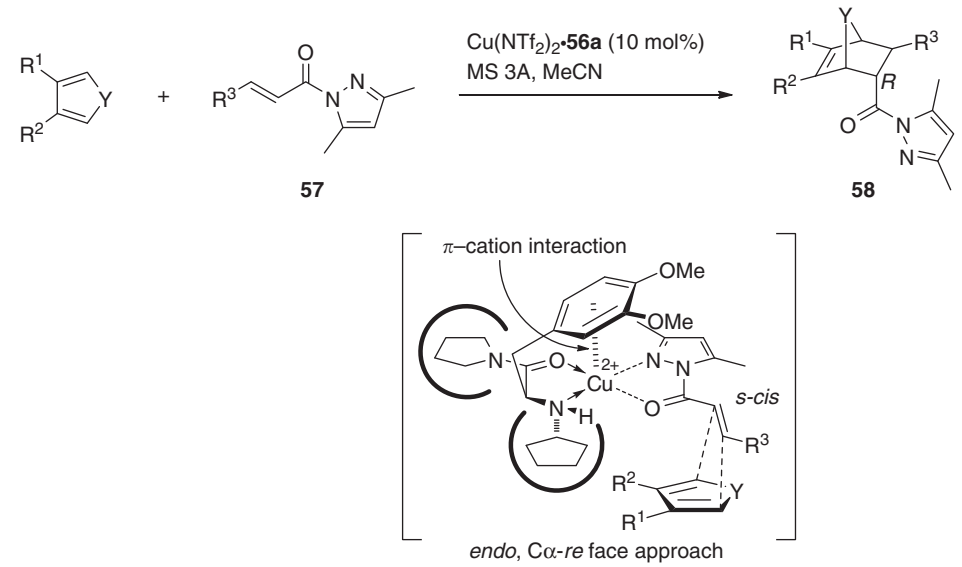
[a]The molar ratio of the 4- and 3-substituted diastereomers is shown.

The stereochemical outcome for the $Cu(NTf_2)_2$•**56a**-catalyzed Diels–Alder reaction can be understood in terms of the *trans*, *s-cis*-transition-state complex (Scheme 11).[49,50] Furthermore, the *N*-cyclopentyl and pyrrolidinyl groups in the ligand **56** sterically assist the π–cation interaction, whereas the 3- and 4-methyl groups on the pyrazole moiety sterically control the coordination environment around the copper(II) complex [*cis* (disfavored) versus *trans* (favored)] and the conformation of **35** [*s-cis* (favored) versus *s-trans* (disfavored)], respectively. Interestingly, the catalytic activity of $Cu(NTf_2)_2$•**56a** is slightly higher than that of $Cu(NTf_2)_2$. The π–cation interaction promotes the release of counteranions from the copper(II) center, thereby increasing the Lewis acidity and catalytic activity.



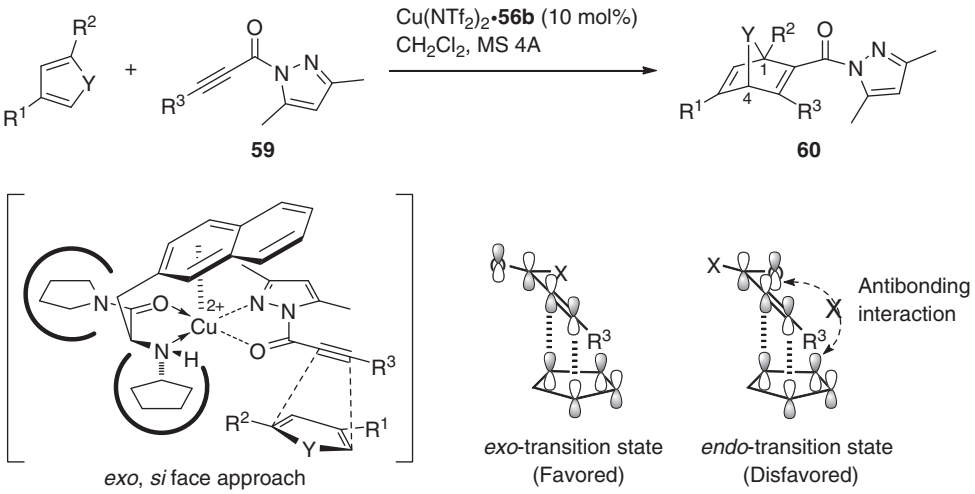
Solvent = H_2O, X = NO_3, base = NaOH: 74% *ee*
Solvent = MeCN, X = TfO, base = Et_3N: 17% *ee*

(8)



Scheme 11

In general, alkynes are less reactive as electron-deficient dienophiles than the corresponding alkenes. Furthermore, alkynes are more challenging substrates for asymmetric induction with a chiral Lewis acid due to the presence of the linear sp–sp bond, which orients the alkynyl moiety away from the metal center and the cylindrical orbital symmetry of the alkyne. However, propiolamides **59** undergo a catalytic and highly enantioselective Diels–Alder reaction with cyclic dienes in the presence of the chiral copper(II) complex $Cu(NTf_2)_2$•**56b** (Ar^1 = 2-naphthyl) (10 mol%) to afford the corresponding cycloadducts **60** (Scheme 12, Table 14).[51] Complex $Cu(NTf_2)_2$•**56b** (Ar^1 = 2-naphthyl) shows higher enantioselectivity than $Cu(NTf_2)_2$•**56a** (Ar^1 = 3,4-$(MeO)_2C_6H_3$) for the Diels–Alder reaction of propiolamides **59**. The expanded asymmetric environment created by π–cation interaction between the copper(II) center and the 2-naphthyl group may be effective for high-level asymmetric induction. The absolute configuration of the cycloadducts **60** can be explained in terms of the *exo*-transition-state complex (Scheme 12). Due to a secondary antibonding interaction between the lobes at the C2-position of cyclopentadiene (HOMO) and the carbonyl oxygen of **59** (LUMO) in the *endo*-transition state, cyclopentadiene predominantly approaches the *Si*-face side of **59** via an *exo*-transition-state. Since the 3-iodo adducts **60** (R^3 = I) can be readily transformed into 3-nonsubstituted and 3-alkyl derivatives by known methods, the propiolamide **59** (R^3 = I) represents the synthetic equivalent of alkyl- or aryl-substituted alkynes.



Scheme 12

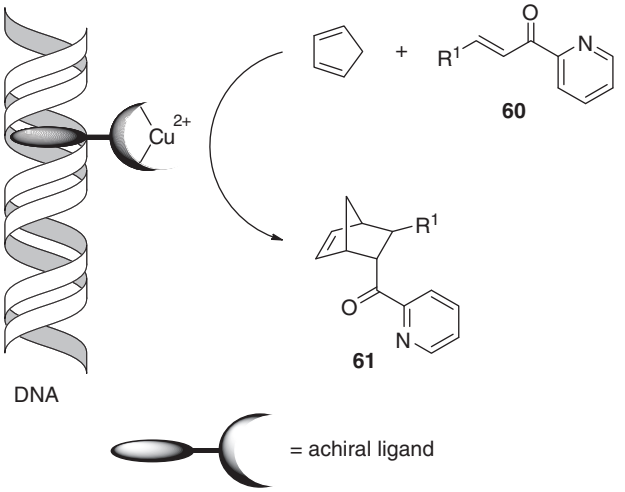
5.09.3.3 Copper(II)–Deoxyribonucleic acid (DNA) Complexes

The chirality of the DNA double helix can be transferred directly to the copper(II)-catalyzed Diels–Alder reaction. DNA from salmon testes (st-DNA) in combination with the achiral copper(II) complex of an achiral ligand catalyzes the enantioselective

Table 14 Enantioselective Diels–Alder reaction of propiolamides **59** catalyzed by $Cu(NTf_2)_2$•**56b** (Scheme 12)

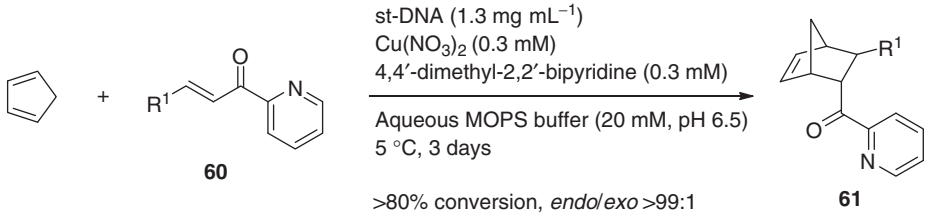
Y	R^1	R^2	R^3	*Yield (%)*	*ee (%) (configuration)*	*References*
CH_2	H	H	H	91	88 (1*R*,4*S*)	51
CH_2	H	H	Me	22	89	51
CH_2	H	H	I	82	89	51
$(CH_2)_2$	H	H	H	68	96 (1*R*,4*S*)	51
$(CH_2)_2$	Ph	H	I	83	95	51
$(CH_2)_2$	Bn	H	I	83	96	51
$(CH_2)_2$	H	OMe	I	84	96	51

Diels–Alder reaction of cyclopentadiene with azachalcones **60**[52,53] and α,β-unsaturated 2-acyl-1-methylimidazoles[54] in water (Scheme 13). Two generations of DNA-based catalysts that differ in the type of ligand used have been reported. In the first design, the achiral ligand **62** is composed of aminomethylpyridine, a metal-binding domain, which is linked through a short spacer to 9-aminoacridine, a DNA intercalator (equation 9).[52] With this design, up to 53% *ee* can be achieved in the Cu(II)-catalyzed Diels–Alder reaction of cyclopentadiene with **60** ($R^1 = C_6H_4$-4-OMe). However, no rate-acceleration is observed in the presence of DNA in this catalytic system.[56]



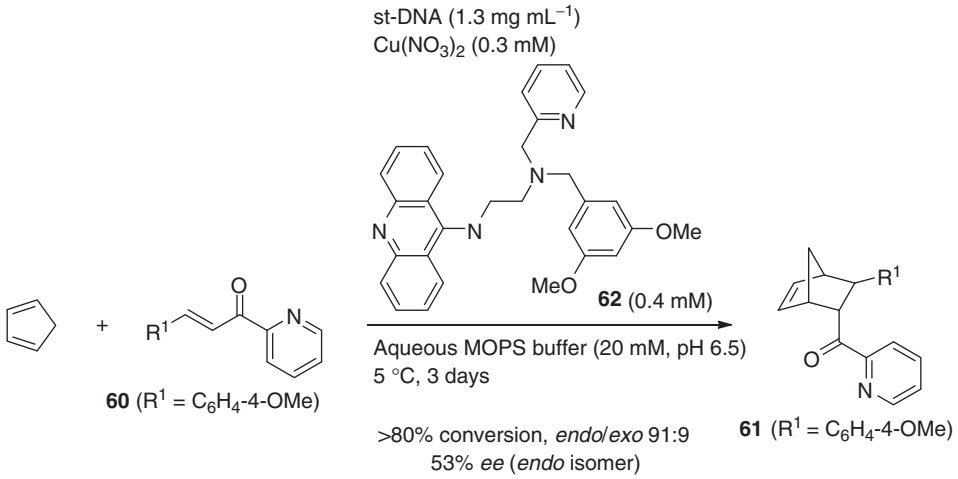
Scheme 13 DNA-based asymmetric catalysis of Diels–Alder reaction.

In the other design, the DNA-binding moiety is integrated into the metal-binding domain without any spacer.[53] DNA in combination with the Cu(II) complex of 4,4′-dimethyl-2,2′-bipyridine shows high enantioselectivity in the Diels–Alder reaction of cyclopentadiene with azachalcones **60** (Scheme 14). In this approach, DNA is more than a chiral scaffold; rate-accelerations of up to two orders of magnitude have been observed in the presence of DNA.[55] In addition, both the enantioselectivity and the rate-enhancement are dependent on the DNA sequence.



R^1	*ee*
Ph	99%
C_6H_4-4-OMe	99%
Bu^t	97%

Scheme 14 DNA-based asymmetric catalysis of Diels–Alder reaction.



(9)

5.09.4 Catalysis Using Other Chiral Lewis Acids

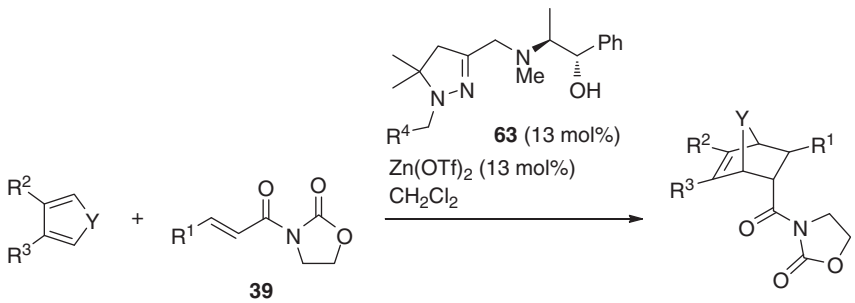
Several other chiral Lewis acid catalysts, including compounds of chromium(III), magnesium(II), aluminum(III), scandium(III), titanium(IV), zinc(II), and the lanthanides, have also been used in enantioselective Diels–Alder reactions.

Zinc(II) complexes of the chiral ligands **63** (equation 10) catalyze the enantioselective Diels–Alder reaction.[57] For example, the chiral complex derived from zinc(II) trifluoromethanesulfonate and a chiral ligand **63** (13 mol%) catalyzes the Diels–Alder reaction of *N*-alkenoyloxazolidinones **39** to afford the corresponding *endo*-(*S*)-adducts with high enantioselectivity (Table 15). The copper(II) complex of **63** also catalyzes the Diels–Alder reaction of **39** and shows high enantioselectivity, which is similar to that of the zinc(II) complex. The level of selectivity depends on the size of the fluxional group (R^4 = Me < Ph < 1-naphthyl), where a larger group provides higher selectivity for both the *endo*- and *exo*-isomers. Based on the requirement of a hydroxy group in the chiral ligand for achieving high selectivity, an octahedral environment around the metal center is proposed, in which the naphthyl group shields the *Re* face of **39**.

Table 15 Diels–Alder reaction using Zn(II) complexes of fluxional ligands **63** (equation 10)

Y	R^2	R^3	R^1	R^4	*Yield (%)*	*Endo/exo*	*ee (%)*	*References*
CH_2	H	H	H	Me	95	80:20	54	57
CH_2	H	H	H	Ph	85	77:23	89	57
CH_2	H	H	H	1-Naphthyl	83	79:21	96	57
CH_2	H	H	H	1-Naphthyl[a]	90	71:29	92	57
CH_2	H	H	Ph	1-Naphthyl	94	60:40	94	57
CH_2	H	H	CO_2Et	1-Naphthyl	90	57:43	96	57
H, H	Me	H	H	1-Naphthyl	69	–	95	57
H, H	Me	Me	H	1-Naphthyl	67	–	90	57

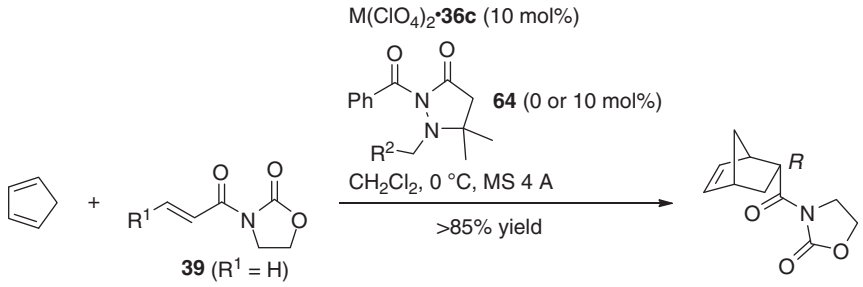
[a]$Cu(OTf)_2$ is used instead of $Zn(OTf)_2$.



(10)

In the same context, additive **64** bearing a benzyl group as a fluxional substituent improves the enantioselectivity of the chiral Lewis acid-catalyzed Diels–Alder reaction of cyclopentadiene with **39** (R^1 = H) (equation 11).[58] In the presence of 10 mol% of **64**, high

enantioselectivity is achieved in the Diels–Alder reaction catalyzed by Lewis acid complexes with chiral *bis*(oxazoline) **36c** (R^1 = Ph), whereas the same reaction in the absence of **64** shows moderate enantioselectivity (Table 16). The level of selectivity depends on the size of the fluxional group in **64** (R^2 = Me < Ph < naphthyl). The fluxional additive may aid in the formation of a well-defined octahedral complex in which the ligand phenyl group is compressed closer to the substrate, which results in enhanced face shielding.

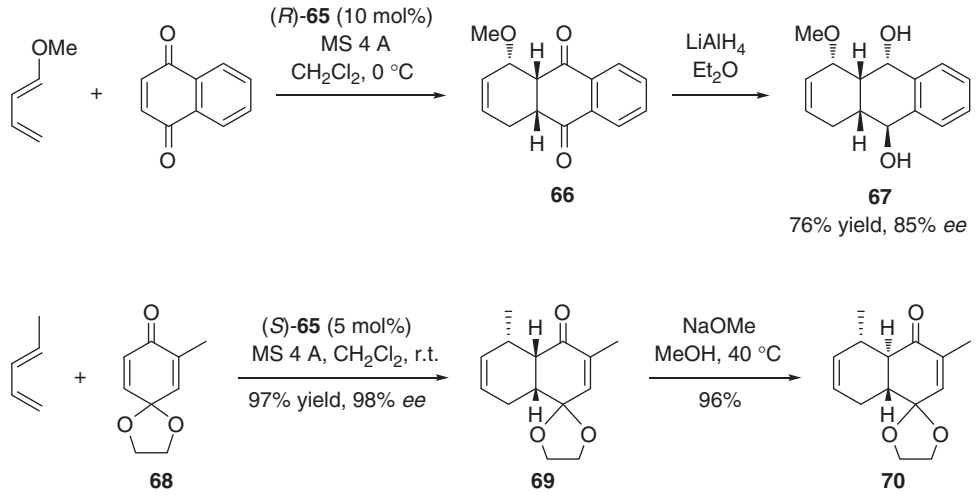


(11)

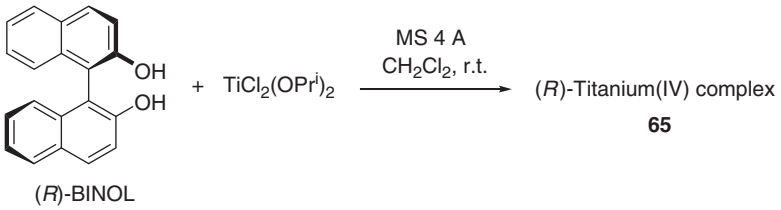
Table 16 Diels–Alder reaction catalyzed by chiral Lewis acid complexes and fluxional additives **64** (equation 11)

M	*Fluxional additive*	*Endo/exo*	*ee (%)*	*References*
Mg	–	83:17	56	58
Mg	**64** (R^2 = Me)	88:12	75	58
Mg	**64** (R^2 = Ph)	88:12	84	58
Mg	**64** (R^2 = 1-Naphthyl)	90:10	86	58
Mg	**64** (R^2 = 2-Naphthyl)	90:10	89	58
Ni	–	83:17	66	58
Ni	**64** (R^2 = Ph)	93:7	92	58

A chiral titanium(IV) complex **65**, prepared *in situ* from the reaction of (*R*)-BINOL and $TiCl_2(OPr^i)_2$ in the presence of molecular sieves 4 Å and H_2O, also acts as a Lewis acid catalyst for enantioselective Diels–Alder reactions (equation 12).[59,60] Although the structure of **65** is not entirely clear, it appears to be chloride-free and to involve μ-oxo bridges between at least two Ti units. The (*R*)-titanium(IV) complex **65** catalyzes the reaction of naphthoquinone with 1-methoxybuta-1,3-diene to give the corresponding *endo*-adduct **66** (Scheme 15). Because the 1,4-quinone adducts are readily aromatized and difficult to handle, the adduct **66** is stereoselectively converted to the more stable derivative **67** in 76% yield (two steps from naphthoquinone) with 85% *ee*. The enantioselective Diels–Alder reaction of 1,4-quinone monoketal **68** is also catalyzed by (*S*)-**65** to give stable *endo*-adduct **69** in 97% yield with 98% *ee* (Scheme 15).[61] Methoxide-catalyzed epimerization of **69** gives the corresponding *cis*-fused ketone **70** without the complication of aromatization.

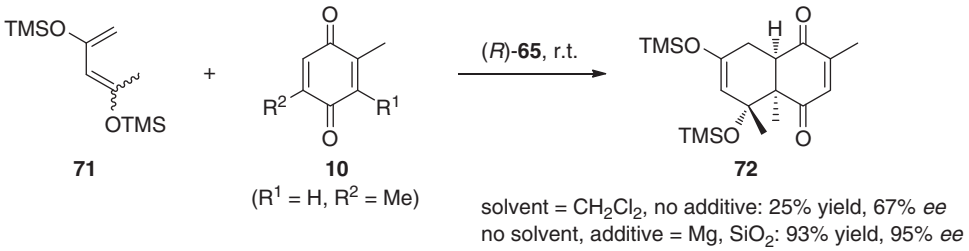


Scheme 15 Enantioselective Diels–Alder reaction of 1,4-quinones catalyzed by chiral titanium(IV) complex **65**.



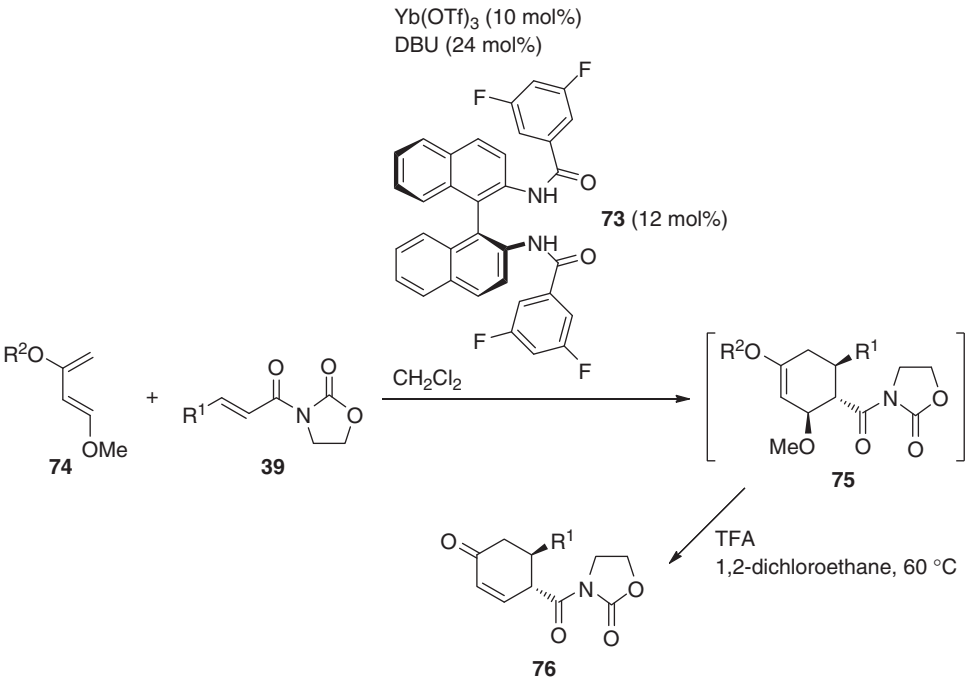
(12)

Although several methods are available for the enantioselective hetero-Diels–Alder reactions of Danishefsky-type dienes, only a limited number are known for the carbo-Diels–Alder reaction, presumably due to their sensitivity to Lewis acids. For example, the reaction of Danishefsky-type diene **71** (Scheme 16) with quinone **10** (R^1 = H and R^2 = Me) catalyzed by cationic oxazaborolidine **2b** (20 mol%) gives no Diels–Alder adduct because of the decomposition of diene **71**. For the enantioselective Diels–Alder reaction of Danishefsky-type diene **71** with quinone **10** (R^1 = H, R^2 = Me), the chiral titanium(IV) complex (*R*)-**65** efficiently gives the corresponding adduct **72** with good enantioselectivity (Scheme 16).[62] Importantly, the addition of Mg powder and silica gel increases the stability of **71** and improves the yield and enantioselectivity of **72**. Cycloadduct **72** is a key intermediate for the synthesis of cyathin A_3, a bioactive natural product.



Scheme 16 Enantioselective Diels–Alder reaction of Danishefsky-type diene **71** catalyzed by chiral titanium(IV) complex **65**.

Ytterbium(III) complexes of chiral 1,1′-(2,2′-bisacylamino)binaphthalene (**73**, BINAMIDE) catalyze the highly enantioselective Diels–Alder reaction of Danishefsky-type dienes with *N*-alkenoyloxazolidinones **39** (Scheme 17, Table 17).[63] In the presence of the ytterbium(III)–BINAMIDE complex prepared from ytterbium(III) trifluoromethanesulfonate, BINAMIDE (**73**), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Danishefsky-type dienes **74** undergo cycloaddition with **39** to afford the corresponding



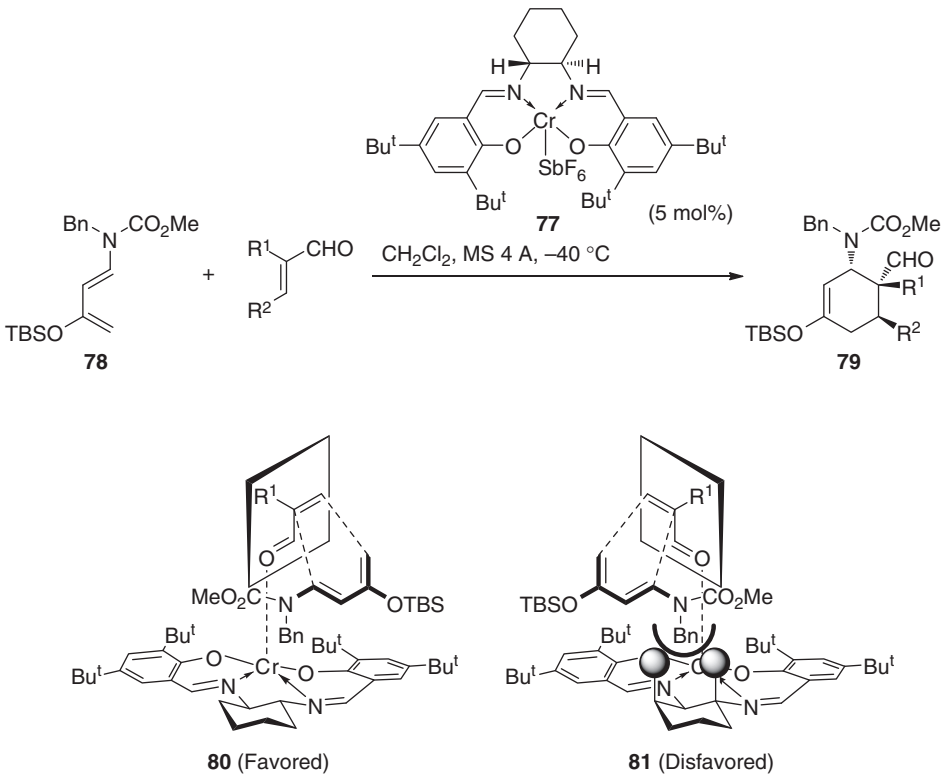
Scheme 17

Table 17 Diels–Alder reactions of Danishefsky-type dienes **74** catalyzed by ytterbium(III)–BINAMIDE complexes (**Scheme 17**)

R^1	R^2	*Conditions (°C, h)*	*Yield (%) of* ***76***	*ee (%) of* ***76***	*References*
H	TIPS	−20, 3	93	71	63
Me	TBDMS	0, 5	94	94	63
Bu^i	TMS	r.t., 8	88	87	63
CH_2Cl	TBDMS	0, 24	79	88	63
$(CH_2)_2Ph$	TBDMS	r.t., 4	96	94	63
CH_2OBn	TBDMS	0, 24	97	89	63
CO_2Me	TMS	0, 2	93	92	63

exo-adducts **75**. Acid treatment of adducts **75** gives the corresponding cyclohexenones **76** quantitatively with high enantioselectivity. In the reaction of **39** (R^1 = H), the diene bearing a sterically hindered triisopropylsilyl group (R^2 = triisopropylsilyl (TIPS)) provides the optimal enantioselectivity (71% *ee*). In contrast, when the substituent on **39** is larger ($R^1 = Bu^i$), the diene bearing a sterically less-hindered trimethylsilyl group (R^2 = trimethylsilyl (TMS)) provides the optimal enantioselectivity (87% *ee*). Apparent (+)-nonlinear effects between asymmetric induction and the enantiomeric composition of **73** suggest the possible formation of a reservoir of nonreactive aggregates.

In addition to the Danishefsky-type dienes, 1-amino-3-siloxy-1,3-butadienes are also multiply heteroatom-substituted acyclic dienes, which are useful for Diels–Alder reactions. The enantioselective catalysis of 1-amino-3-siloxybutadienes in Diels–Alder reactions is promising, because uncatalyzed cycloadditions with 2-substituted propenals are known to proceed with excellent regio- and diastereoselectivities. Thus, a chiral catalyst must select between two enantiomeric *endo* adducts. Chiral chromium(III)–salen complex **77** catalyzes the enantioselective Diels–Alder reaction of 1-amino-3-siloxybutadiene **78** with 2-substituted propenals to give the corresponding *endo*-adducts **79** with high enantioselectivity (**Scheme 18**, **Table 18**).[64] The benzyl substituent on the nitrogen of **78** is crucial for obtaining high enantioselectivity. A consideration of the stereochemical outcome and a careful analysis of the salen scaffold suggest transition-state assemblies **80** and **81**. The diene **78** can approach the dienophile from the more open surface on the scaffold, which is believed to be over the imine linkages, away from bulky *tert*-butyl groups. Transition state **80** seems to be more favorable than **81**, which suffers from steric interaction between the benzyl group and the axial hydrogens (**Scheme 18**).

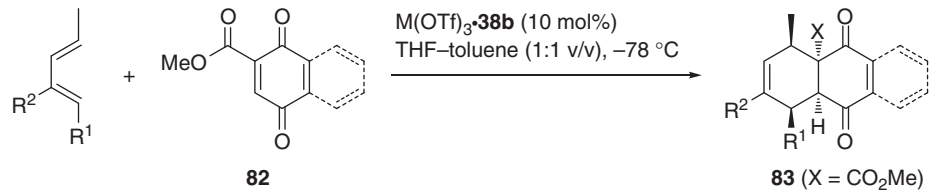


Scheme 18

Table 18 Diels–Alder reaction of 1-amino-3-siloxybutadiene **78** catalyzed by chromium(III)-salen complex **77** (Scheme 18)

R^1	R^2	Temperature (°C)	Time (days)	Yield (%)	ee (%)	References
Me	H	−40	2	93	97	64
Et	H	−40	2	91	97	64
Pr^i	H	−40	5	92	>97	64
$(CH_2)_2OTBDMS$	H	−40	2	93	95	64
OTBDMS	H	−40	2	86	>97	64
$(CH_2)_3$		−40 to r.t.	5	76	96	64

The enantioselective formation of all-carbon quaternary centers is an area of intense research in which Diels–Alder reactions play a major role. For this purpose, 2-methoxycarbonylated quinones **82** are highly active as dienophiles.[65] Chiral Lewis acid complexes derived from the pybox ligand **38b** (R = Ph) with lanthanide(III) triflates are effective catalysts in the enantioselective Diels–Alder reaction of quinones **82**. In the presence of 10 mol% of the samarium(III) and gadolinium(III) trifluoromethanesulfonate complexes with **38b**, the cycloaddition of various acyclic dienes with quinones **82** in THF–toluene (1:1 v/v) gives the corresponding *endo*-adducts **83** with high enantioselectivity (equation 13, Table 19). The reaction between **82** and dienes possessing different alkyl substituents in the 1- and 4-positions is regioselective. For example, the reactions with *trans*-2,4-heptadiene (R^1 = Et and R^2 = H) and *trans*-2,4-octadiene (R^1 = Pr and R^2 = H) give 5:1 and 15:1 mixtures, respectively, of regioisomers with 98% *ee*.



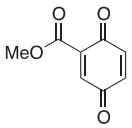
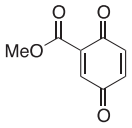
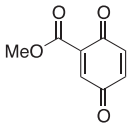
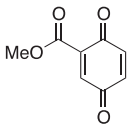
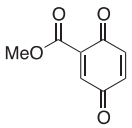
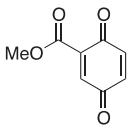
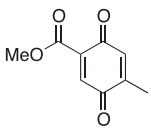
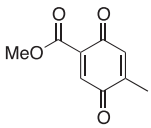
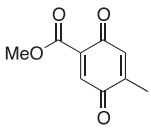
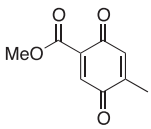
82 **83** (X = CO_2Me) (13)

For the enantioselective construction of all-carbon quaternary centers, α-methylene β-ketoesters are possible alternatives as dienophiles. However, bulkier unsaturated β-ketoesters, such as cyclic carboxypentenones, are much less reactive due to their tendency to undergo polymerization and keto–enol tautomerization. A dicationic ruthenium(II) catalyst, prepared *in situ* from the chiral ruthenium(II) complex **84** and 2 equivalents of $(Et_3O)PF_6$ in dichloromethane, efficiently promotes the enantioselective Diels–Alder reaction of α-methylene β-ketoesters **85** with Dane's diene **12** to give the corresponding (8*R*,13*S*,14*S*)-adducts **86** with high enantioselectivity (Scheme 19).[66] Because the use of a *tert*-butyl ester improves the *exo*/*endo* ratio and enantioselectivity, the *tert*-butyl ester moiety on **85** is pivotal for achieving excellent diastereo- and enantioselectivity. Enantiomerically pure adduct **86** (R = Bu^t) is obtained in 85% yield after recrystallization from 2-propanol, and the *exo*/*endo* ratio is improved to 145:1.

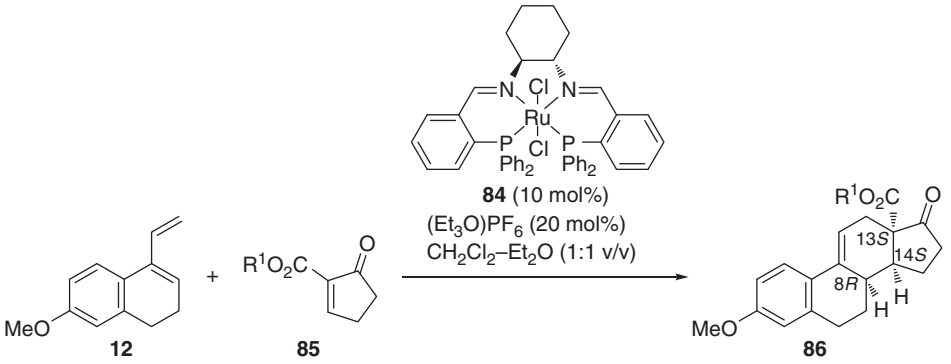
The inverse-electron demand Diels–Alder reaction of tropones provides direct access to bicyclo[3.2.2] ring structures, which can be further developed into more complex molecular architectures through selective manipulation of their preexisting functional groups. The chiral dinuclear BINOL–aluminum complex **87**, a Lewis acid-assisted Lewis acid catalyst prepared from the *tris*(*m*-xylyl)silyl-substituted BINOL ligand and two equivalents of diisobutylaluminum hydride at ambient temperature in dichloromethane, catalyzes the Diels–Alder reaction of 2-substituted tropones **88** with ketene diethyl acetal (Scheme 20).[67] The reaction exclusively gives the corresponding Diels–Alder adducts **89** without other types of cycloadducts, such as [8 + 2] adducts. Although the reaction of unsubstituted tropone shows modest enantioselectivity (46% *ee*), 2-substituted tropones **88** (X ≠ H) generally give high enantioselectivity.

Although several Lewis acid-catalyzed asymmetric Diels–Alder reactions have been reported to date, including those using ketone-derived siloxy dienes such as Danishefsky's diene, none of them use 1-siloxybutadiene **91** because of the lability of **91** under acidic conditions. However, the acid-sensitive diene **91** can be activated by barium alkoxides, which are prepared *in situ* from barium isopropoxide and a chiral diol, through the transmetalation or formation of a hypervalent silicate (HOMO-raising mechanism). Under these conditions, **91** reacts with dimethyl fumarate to give the corresponding Diels–Alder adduct **92** (equation 14).[68] The use of chiral diol **90** as a ligand gives the best results in terms of diastereoselectivity and enantioselectivity (Table 20). The addition of cesium fluoride significantly improves the reactivity and the reaction is complete within 30 min. It is conceivable that the silicon transfer step is accelerated by the formation of a pentavalent silicate with the fluoride ion. In addition, the enantioselectivity also increases to 96% *ee*. This reaction is practical, and the catalyst loading is reduced to 2.5 mol% under more concentrated conditions. On a 58-g scale, both the enantiomeric excess and the diastereomeric ratio are constant, though the reaction is slower. The resulting Diels–Alder adduct **92** is an important chiral building block for the synthesis of (−)-oseltamivir (Tamiflu).[68]

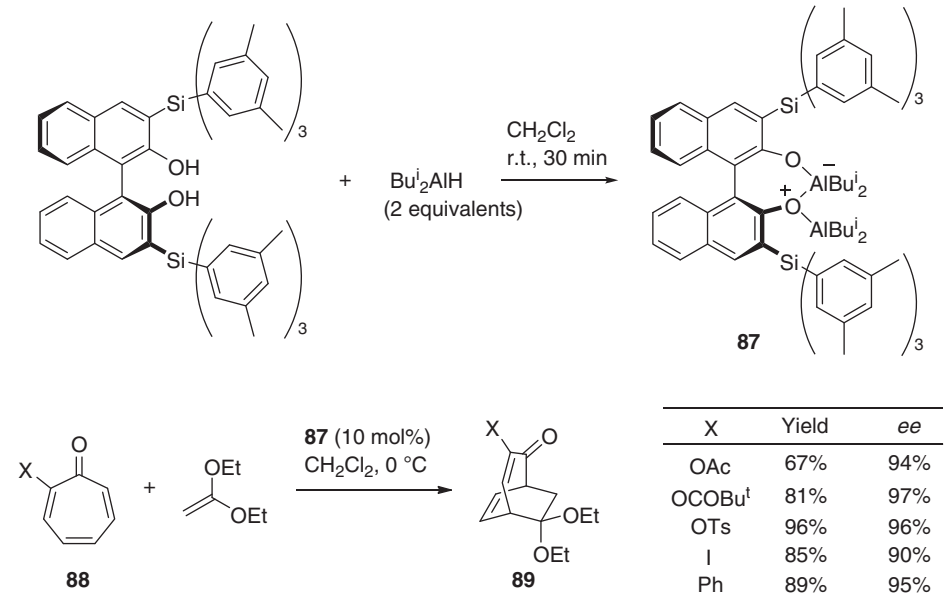
Table 19 Diels–Alder reaction of quinones **43** catalyzed by chiral lanthanide complexes (equation 13)

Diene		*Quinone* ***43***	*M*	*Yield (%)*	*ee (%)*	*References*
R^1	R^2					
Me	H		Sm	87	97	65
Me	H		Gd	99	98	65
H	Me		Sm	97	91	65
H	Me		Gd	99	97	65
Et	H		Gd	99 (5:1)[a]	98	65
Pr	H		Gd	96 (15:1)[a]	98	65
Me	H		Gd	91	>99	65
H	H		Gd	88	95	65
Me	H		Gd	>99	91	65
H	H		Gd	91	91	65

[a]Ratio of regioisomer.

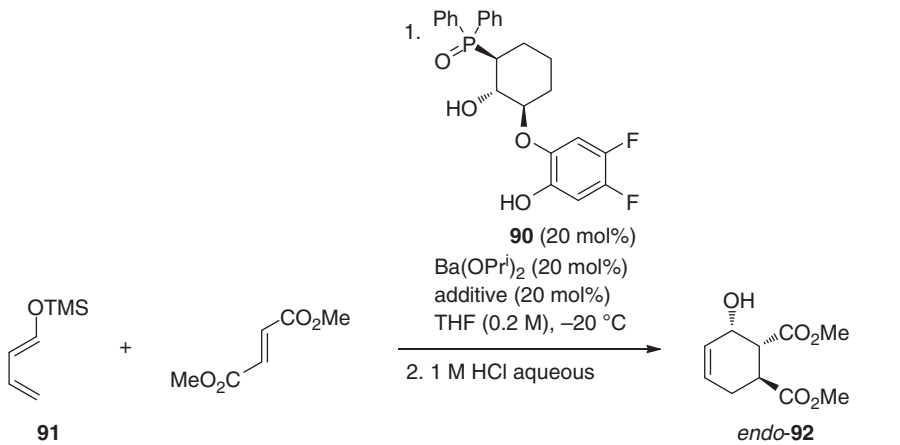


Scheme 19 Enantioselective Diels–Alder reaction of α-methylene β-ketoesters **85** with Dane's diene **12** using a dicationic ruthenium(II) catalyst.



X	Yield	*ee*
OAc	67%	94%
$OCOBu^t$	81%	97%
OTs	96%	96%
I	85%	90%
Ph	89%	95%

Scheme 20 Inverse-electron demand Diels–Alder reaction of tropones **88** catalyzed by chiral dinucleus BINOL–aluminum complex **87**.



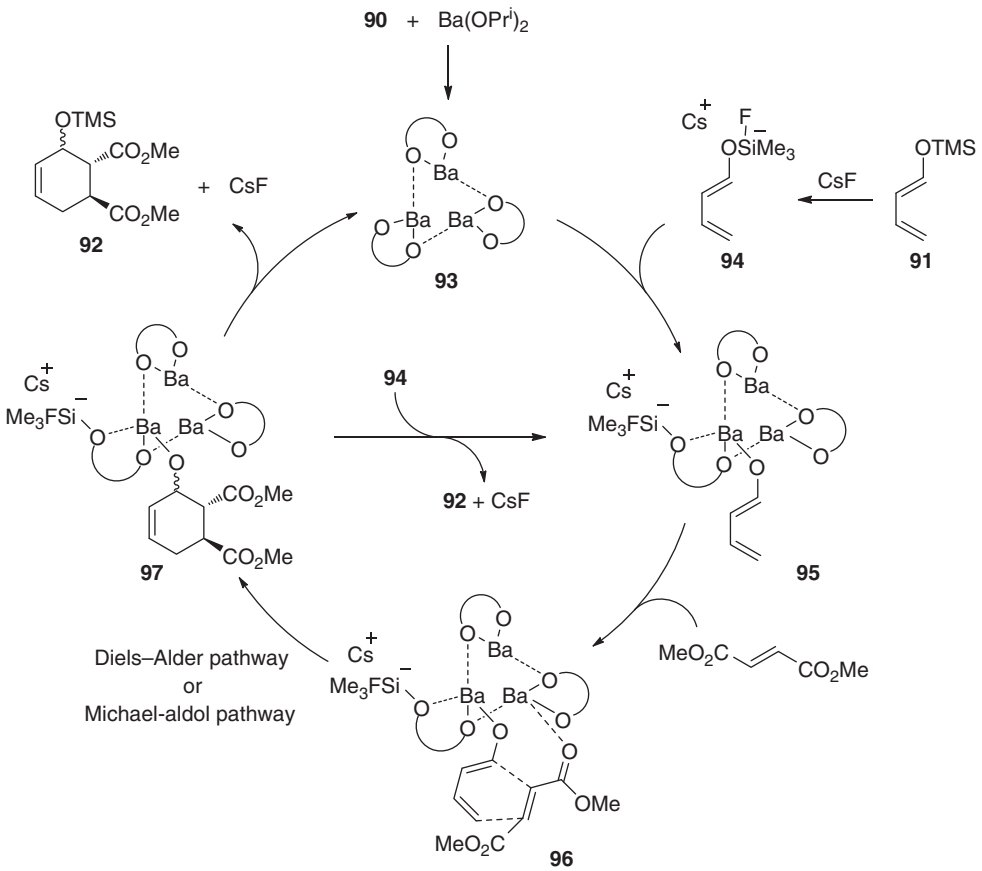
(14)

Table 20 Diels–Alder reaction of 1-siloxybutadiene **91** with dimethyl fumarate catalyzed by barium(II) complex of **90** (equation 14)

Additive	*Time (h)*	*Yield (%)*	*Endo/exo*	*ee (%) of endo-**92***	*References*
–	23	64	75:25	88	65
CsF	0.5	>99	67:33	96	65
CsF[a]	36	91	80:20	97	65
CsF[a,b]	96	91	83:17	95	65

[a]$Ba(OPr^i)_2$ (2.5 mol%), **90** (2.5 mol%), 0.67 M of dimethyl fumarate.
[b]58-g scale.

The following reaction mechanism is proposed for the Diels–Alder reaction of **91** with dimethyl fumarate catalyzed by barium(II)-**90** complex (**Scheme 21**).[68] Based on electrospray ionization mass spectrometry studies, the active catalyst is considered to be the 3:3 complex **93**. Chiral barium dienolate **95** is generated through transmetalation between catalyst **93** and siloxydiene **91**. Cesium fluoride may facilitate the generation of **95** through the formation of pentavalent silicate **94**. The cyclization of the barium dienolate **95** with dimethyl fumarate occurs in either a concerted manner (Diels–Alder pathway) or a stepwise manner (Michael-aldol pathway). It is possible that the catalyst promotes the reaction through an intramolecular transfer of the barium dienolate to an activated dienophile by a Lewis acidic barium center, as shown in **96**. Finally, the product barium alkoxide in **97** attacks the trimethylsilyl group attached to the ligand, and catalyst **93** is regenerated, whereas the silylated product **92** is liberated from the catalytic cycle. Alternatively, **97** reacts with another molecule of siloxy diene **94**, liberating product **92** whereas regenerating the active barium dienolate **95**.



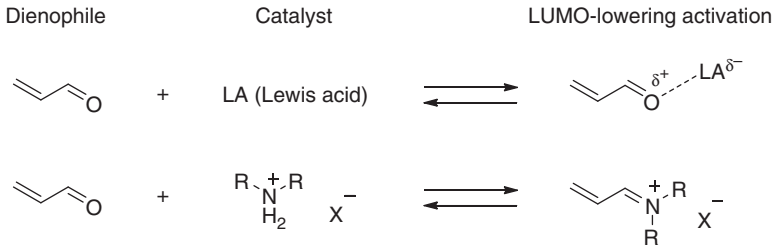
Scheme 21 Proposed catalytic cycle of barium(II)-**90** complex-promoted Diels–Alder reaction.

5.09.5 Chiral Organocatalysis

5.09.5.1 LUMO-Activation Using Organoammonium Salts

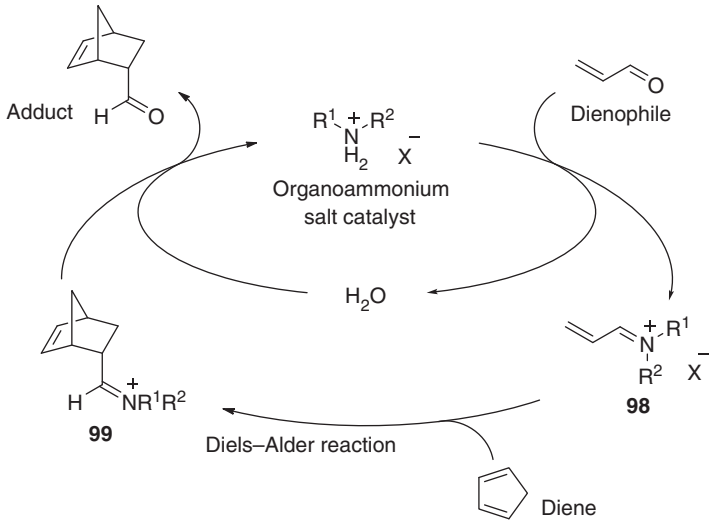
5.09.5.1.1 Secondary ammonium salt catalysts

As shown in the above sections, the catalytic effect of Lewis acids (LA) in the Diels–Alder reactions is the result of coordination with α,β-unsaturated carbonyl compounds (dienophile), which lowers the LUMO energy, thereby allowing Diels–Alder reactions to be conducted under mild conditions with enhanced regio-, diastereo-, and enantioselectivity (Scheme 22).



Scheme 22 LUMO-lowering activation of α,β-unsaturated carbonyl compounds.

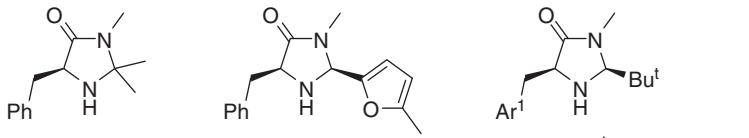
Organocatalysts have been successfully used as alternatives to Lewis acid catalysts in enantioselective Diels–Alder reactions.[69–71] The first highly enantioselective organocatalytic Diels–Alder reaction was developed by MacMillan and colleagues, who used secondary organoammonium salts of α-amino acid-derived imidazolidinones as catalysts.[72–74] They also described the concept of iminium catalysis by using the term 'LUMO-lowering activation' (Scheme 22). The principle of the reaction mechanism for the organoammonium salt-catalyzed Diels–Alder reaction is shown in Scheme 23. This concept is based on the hypothesis that the reversible formation of iminium cations **98** from α,β-unsaturated aldehydes and chiral ammonium salts might emulate the equilibrium dynamics and π-orbital electronics that are found in Lewis acid catalysis.



Scheme 23

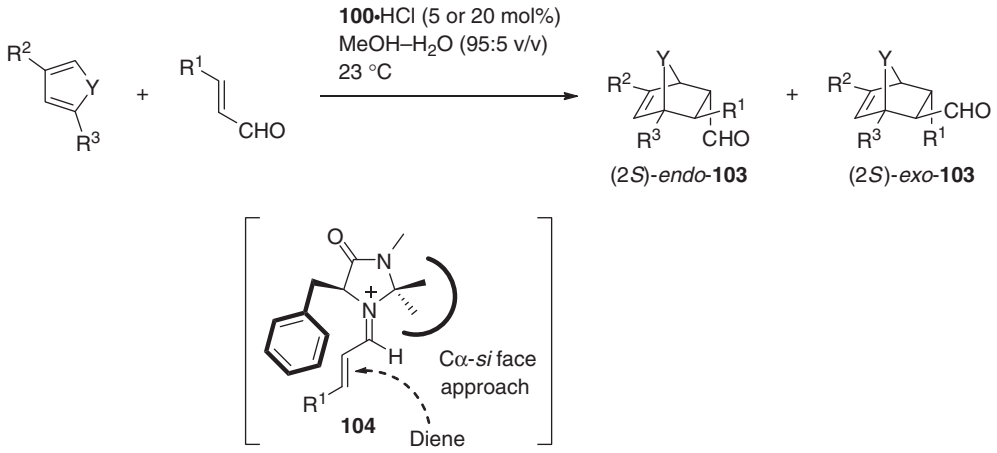
The ammonium salts of chiral imidazolidinones such as **100**–**102** (Figure 11) are efficient organocatalysts for enantioselective Diels–Alder reactions, including those of β-substituted propenals.[72–74] In the presence of imidazolidinone salt **100**•HCl (5 mol%), the reaction of cyclopentadiene with various β-substituted propenals is conducted in MeOH–H_2O (95:5) to give an approximately 1:1 diastereomeric mixture of the corresponding (2*S*)-*exo*- and (2*S*)-*endo*-adducts **103** with high enantioselectivity (Scheme 24, Table 21). A range of α,β-unsaturated aldehydes are exposed to a variety of dienes using the organoammonium salt catalysts **100**•HCl to give the corresponding *endo*-adducts **103** with high enantioselectivity, although the diastereoselectivity is low. Remarkably, the presence of water has beneficial effects on both the reaction rates and selectivities by facilitating the hydrolysis of iminium ion **99** in the catalytic cycle.

A mechanism has been proposed for the asymmetric induction observed in the **100**•HCl-catalyzed Diels–Alder reaction of β-substituted propenals (Scheme 24).[72,74] The sense of asymmetric induction observed in all cases is consistent with the



100 **101** **102a** (Ar^1 = Ph) **102b** (Ar^1 = 1-Naphthyl)

Figure 11 Chiral imidazolidinones **100–102**.



(2*S*)-*endo*-**103** (2*S*)-*exo*-**103**

104

Scheme 24

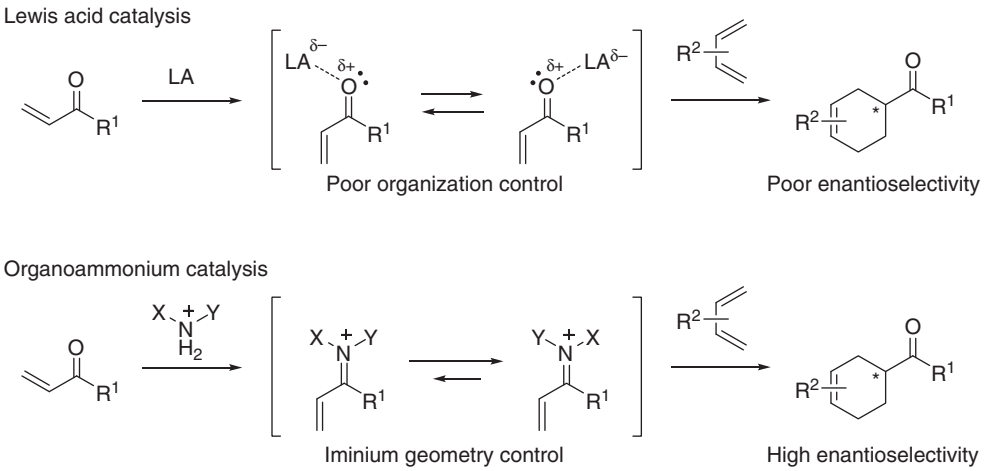
Table 21 Diels–Alder reaction with β-substituted propenals catalyzed by **100**•HCl (Scheme 24)

R^1	Y	R^2	R^3	Catalyst loading (mol%)	Yield (%)	Endo/exo	ee (%) of endo-**103**	References
Me	CH_2	H	H	5	75	1:1	90	72,74
Pr^i	CH_2	H	H	5	81	1:1	93	72,74
Ph	CH_2	H	H	5	99	1:1.3	93	72,74
2-Furyl	CH_2	H	H	5	89	1:1	93	72,74
H	$(CH_2)_2$	H	H	5	82	14:1	94	72,74
H	H, H	Ph	H	20	90	–	83	72,74
Me	H, H	Ph	H	20	75	–	90	72,74
H	H, H	Me	Me	20	75	5:1	90	72,74
H	H, H	H	OAc	20	72	11:1	85	72,74

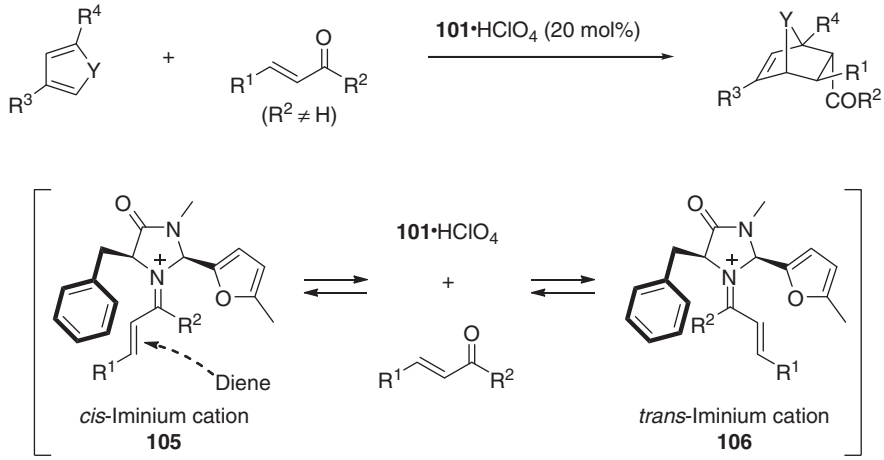
intermediacy of iminium cation **104**. This mechanism includes two salient stereocontrol elements: (1) the selective formation of the (*E*)-iminium isomer to avoid nonbonding interactions between the substrate olefin and the geminal methyl substituents on the catalyst framework and (2) effective shielding of the *Re*-face of the olefinic π-system of the iminium cation by the benzyl group on the catalyst. Dienes can then preferentially approach the Cα-*Si* face of *s-trans*-iminium cation **104**.

The ability to use simple α,β-unsaturated ketones as dienophiles in the Diels–Alder reaction remains a challenge in the field of asymmetric catalysis. The coordination of LA to ketone dienophiles is normally a nonselective process because the participating lone pairs are positioned in similar steric and electronic environments (Scheme 25). The diastereomeric activation pathway in this case often leads to poor levels of enantiocontrol and ultimately has almost completely precluded the use of simple ketone dienophiles in the catalytic asymmetric Diels–Alder reaction. In contrast, organoammonium catalysts might enable simple ketone dienophiles to function as useful substrates for enantioselective Diels–Alder reactions. In this case, the capacity to perform substrate activation through specific lone-pair coordination is replaced by the requirement for selective π-bond formation (Scheme 25).[73]

An organoammonium salt of imidazolidinone **101** catalyzes the Diels–Alder reaction of simple α,β-unsaturated ketones (Scheme 26, Table 22),[73] whereas the organoammonium salts of **100** and **102** give the adduct in racemic form. Importantly, whereas methyl ketones are usually poor substrates, higher homologs (ethyl, butyl, and isoamyl ketones) give good levels of



Scheme 25 Activation of α,β-unsaturated ketones.



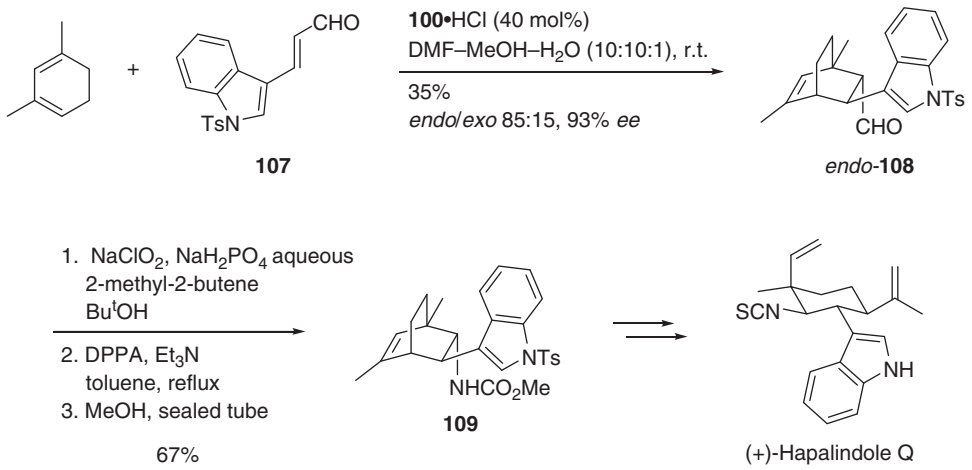
Scheme 26

Table 22 Enantioselective Diels–Alder reaction with vinyl ketones catalyzed by **101**•$HClO_4$ (Scheme 26)

R^1	R^2	Y	R^3	R^4	Solvent	Temperature (°C)	Yield (%)	Endo/exo	ee (%)	References
Me	Et	CH_2	H	H	H_2O	0	89	25:1	61	73
Me	Bu	CH_2	H	H	–	0	83	22:1	92	73
Me	Am^i	CH_2	H	H	H_2O	0	86	20:1	92	73
Pr	Et	CH_2	H	H	H_2O	0	84	15:1	92	73
Pr^i	Et	CH_2	H	H	H_2O	0	78	6:1	90	73
H	Et	H, H	H	OMe	EtOH	–30	88	>200:1	96	73
H	Et	H, H	H	NHCbz	EtOH	–30	91	>100:1	98	73
H	Et	H, H	Me	Me	EtOH	–30	90	>200:1	90	73
H	Et	H, H	H	Me	–	–30	79	>200:1	85	73

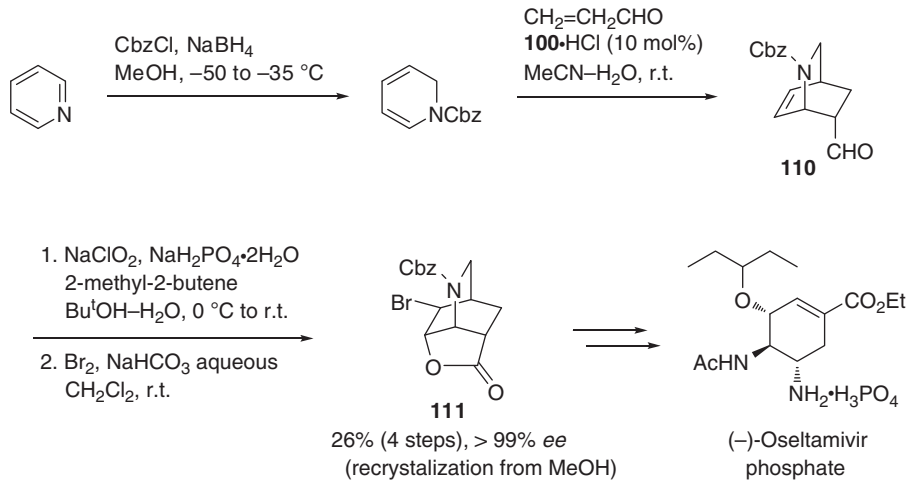
enantiocontrol and high *endo*-selectivities. The present Diels–Alder reaction is also quite general with respect to the diene structure, and thus allows enantioselective access to a range of alkyl-, aryl-, alkoxy-, and amino-substituted cyclohexyl ketones as single diastereomers ($dr > 100{:}1$). The sense of asymmetric induction observed in all cases is consistent with selective engagement of the diene substrate with the *Si*-face of the *cis*-iminium cation intermediate **105**, in which the olefin *Re*-face in the iminium intermediate is shielded by the benzyl group in **101**. The computational models provide supporting evidence that the *trans*-iminium isomer **106** is energetically disfavored based on nonbonding interactions between the benzyl and R^2 substituents.

The Diels–Alder reaction catalyzed by secondary organoammonium salts has been used for the synthesis of key intermediates in the total synthesis of bioactive natural compounds. For example, the **100**•HCl-catalyzed Diels–Alder reaction of 1,3-dimethylcyclohexadiene with α,β-enal **107** is conducted in DMF–MeOH (1:1 v/v) containing 5% water to give *endo*-adduct **108**, which is a key intermediate for the synthesis of (+)-hapalindole Q, in 35% yield with 93% *ee* (Scheme 27).[75] Pinnick oxidation of **108** gives the corresponding carboxylic acid, which undergoes Curtius rearrangement with diphenylphosphoryl azide (DPPA) to give carbamate **109**, which can be converted to (+)-hapalindole Q in six steps.



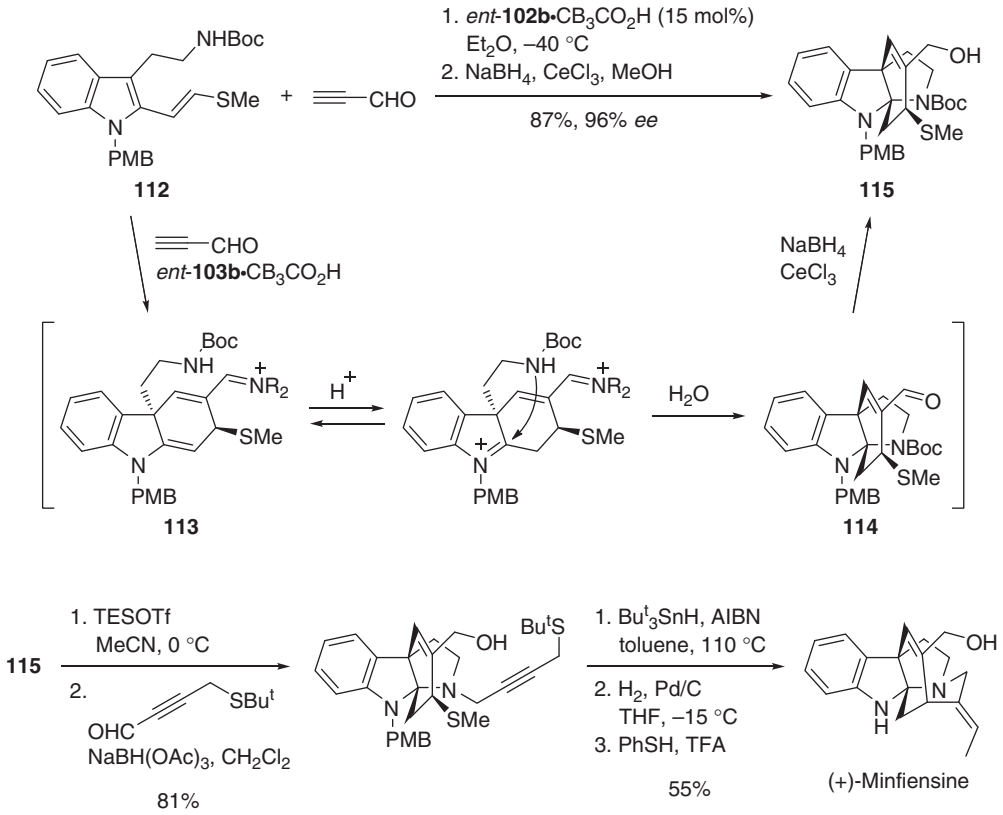
Scheme 27 Synthesis of (+)-hapalindole Q.

In a practical synthesis of (–)-oseltamivir, the **100**•HCl-catalyzed Diels–Alder reaction of a dihydropyridine derivative with propenal gives azabicyclo[2.2.2]compound **110** as a key intermediate (Scheme 28).[76] Subsequent oxidation of the aldehyde, followed by bromolactonization produces bromolactone **111** in 26% yield (four steps) with >99% *ee*. Importantly, neither tedious chromatographic separations nor expensive reagents are needed in this synthetic sequence. Oseltamivir phosphate can be synthesized in 22% yield (11 steps) from the bromolactone **111**.



Scheme 28 Synthesis of (–)-oseltamivir.

In a related study, an organoammonium salt of 1-naphthylmethyl-substituted *ent*-**102b** with tribromoacetic acid is used to construct the central tetracyclic pyrroloindoline framework of (+)-minfiensine through an elegant organocascade sequence starting with the Diels–Alder reaction between **112** and propynal (Scheme 29).[77] In the presence of *ent*-**102b**•CBr_3CO_2H (15 mol%), the Diels–Alder reaction regioselectively gives the corresponding adduct **113** via the *endo*-transition state. Simultaneous protonation of the enamine moiety of **113**, followed by a 5-*exo* amine heterocyclization affords the tetracyclic pyrroloindoline **114**. Subsequent reduction of **114** with $NaBH_4$ and $CeCl_3$ produces allylic alcohol **115** in 87% yield with 96% *ee*. In general, acetylene derivatives with a linear sp–sp bond make asymmetric induction with a chiral catalyst difficult because the alkynyl moiety is far from the chiral center of the catalyst. The extended chiral environment created by the naphthyl group in **102b** might be crucial for the high



Scheme 29 Synthesis of (+)-minfiensine.

level of asymmetric induction. Actually, the use of **102a** bearing a phenyl group decreases the enantioselectivity (88% *ee*). The allylic alcohol **115** can be converted into (+)-minfiensine in five steps (nine overall steps, 21% overall yield).

Several types of chiral secondary ammonium salt catalysts are available for use in the enantioselective Diels–Alder reactions of *β*-substituted propenals. Representative chiral secondary amines **116** (R^1 = H and Me), **117**, **118**, and **119** (R^1 = TMS and TES) are shown in Figure 12.

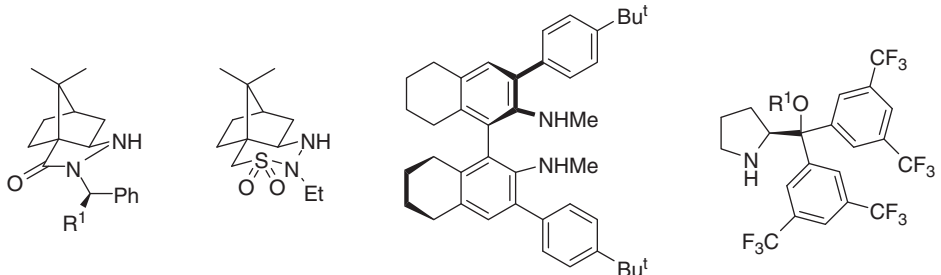
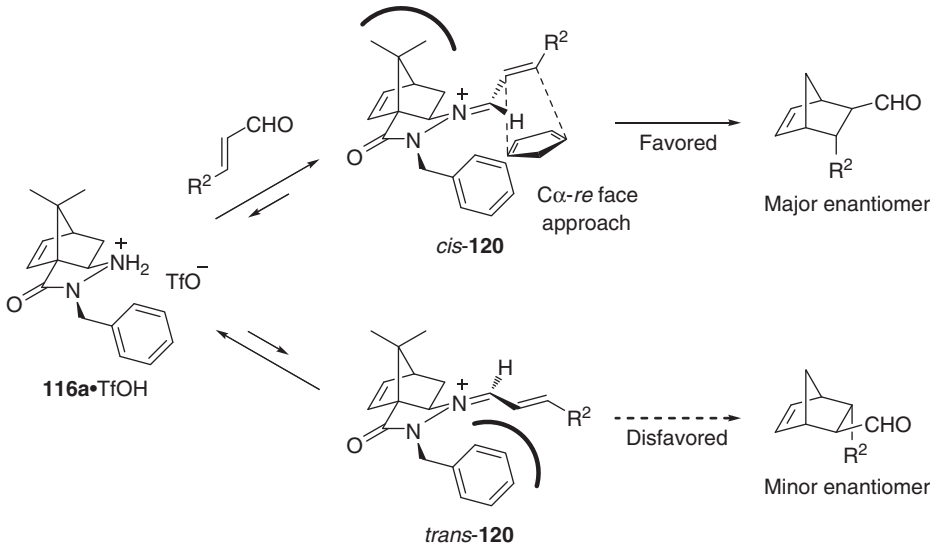


Figure 12 Representative chiral secondary amines **116**–**119**.

Organoammonium salts of chiral secondary amine **116** with trifluoromethanesulfonic acid are efficient catalysts for the Diels–Alder reaction of cyclopentadiene with *β*-substituted propenals (equation 15, Table 23).[78–80] The secondary ammonium salt catalysts **116**•TfOH function best in water. The reaction catalyzed by **116**•TfOH (20 mol%) in water gives the corresponding adducts with high enantioselectivities, although the diastereoselectivities are low. Mechanistic studies indicate that the cycloaddition step of an iminium cation intermediate with a diene is rate-limiting in the hydrazide-catalyzed Diels–Alder reaction.[79] Iminium formation is extremely rapid and the equilibrium heavily favors the iminium cation intermediate, thus maximizing the effective concentration of the reactive dienophile. Based on the sense of asymmetric induction, the **116**•TfOH-catalyzed Diels–Alder reaction proceeds via the C*α*-*Re* face approach of a diene to *cis*-iminium cation intermediate **120** (Scheme 30). The phenyl

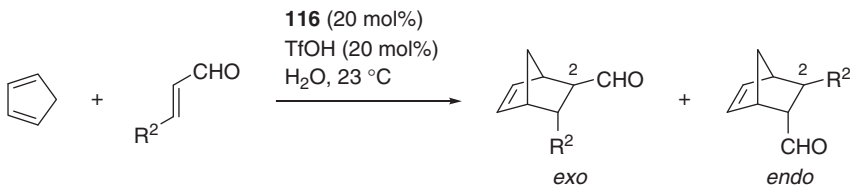
Table 23 Enantioselective Diels–Alder reaction catalyzed by organoammonium salts of chiral hydrazides **116** (equation 15)

116 *(R^1)*	*R^2*	*Yield (%)*	*Exo/endo*	*ee (%) of exo*	*ee (%) of endo*	*References*
116a (H)	Me	74	1.1:1	68 (2*S*)	72	80
116b (Me)	Me	78	1.8:1	82 (2*S*)	80	80
116a (H)	Ph	96	1.9:1	90 (2*R*)	88	80
116b (Me)	Ph	94	2.8:1	95 (2*R*)	93	80
116b (Me)	C_6H_4-4-NO_2	90	4:1	96 (2*R*)	93	80



Scheme 30

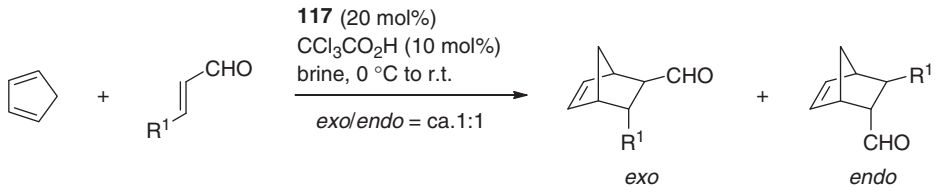
group of **116** interferes with the formation of an undesired *trans*-iminium cation intermediate. Hydrazine **116b** yields better diastereo- and enantioselectivities than **116a**.[80] The introduction of a methyl group makes the phenyl group properly positioned to interfere with the formation of the *cis*-iminium cation intermediate **120** to improve both the diastereo- and the enantioselectivity.



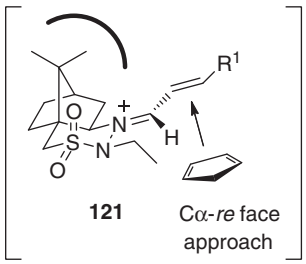
(15)

A related study showed that an organoammonium salt of chiral camphor sulfonyl hydrazine **117** could catalyze the enantioselective Diels–Alder reaction of cyclopentadiene with β-substituted propenals (Scheme 31).[81] The use of less acidic trichloroacetic acid (CCl_3CO_2H, 0.5 equivalent/**117**) improves the enantioselectivity of the *endo*-adducts. Both the reactivity and enantioselectivity are higher in brine than in water. The reaction is proposed to proceed via iminium ion intermediate **121**. As in the case of *cis*-**120**, the top face of **121** is blocked by the dimethyl groups of the camphor scaffold. Cyclopentadiene approaches from the bottom face.

In general, the Diels–Alder reactions with β-substituted propenals yield the corresponding *endo*-adducts as major products. In contrast, the opposite *exo*-selectivity, particularly in the catalyst-controlled *exo*-selective Diels–Alder reaction, is not readily attainable. However, a highly *exo*-selective, enantioselective Diels–Alder reaction with β-substituted propenals occurs in the presence of the ammonium salt of binaphthyl-substituted secondary diamine **118** (10 mol%) when the reaction is conducted in (trifluoromethyl)benzene ($PhCF_3$) (equation 16, Table 24).[82,83] The reaction gives the corresponding *exo*-adducts with up to >20:1 diastereoselectivity. The presence of two methylamino groups in **118** is essential for rate-acceleration. One methylamino group promotes the reaction of the other methylamino group with an α,β-unsaturated aldehyde to give the iminium cation intermediate **122** and the protonated aminal **123** (Scheme 32). The more reactive iminium cation intermediate **122** reacts with cyclopentadiene to yield the *exo*-adduct under the influence of the sterically hindered octahydrobinaphthyl moiety. The observed



R^1	*ee* (*exo*)	*ee* (*endo*)
Pr	66%	90%
Ph	78%	93%
C_6H_4-4-Br	86%	96%



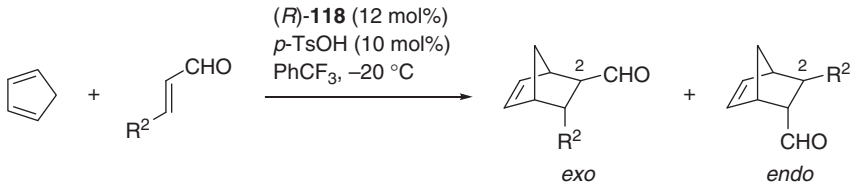
Scheme 31 Enantioselective Diels–Alder reaction catalyzed by the salt of **117**.

Table 24 *Exo*-selective Diels–Alder reaction catalyzed by organoammonium salts of chiral diamine **118** (equation 16)

R^2	*Yield (%)*	*Exo/endo*	*ee (%) of exo*	*ee (%) of endo*	*References*
H	93	1.9:1	86	68	83
Me	72	>20:1	88 (2*S*)	–	82
CO_2Et[a]	90	5.5:1	83	56	82
Ph	80	13:1	92 (2*R*)	91 (2*R*)	82
C_6H_4-4-NO_2	99	7.4:1	95	98	83

[a]The reaction is conducted at −60 °C.

sense of asymmetric induction can be explained by two possible transition-state models, **124a** and **124b**. In both cases, the Cα-*Si* face of the iminium cation moiety is blocked by a 4-*tert*-butylphenyl substituent and the Cα-*Re* face is open for the approach of cyclopentadiene, in accordance with the experimental results.



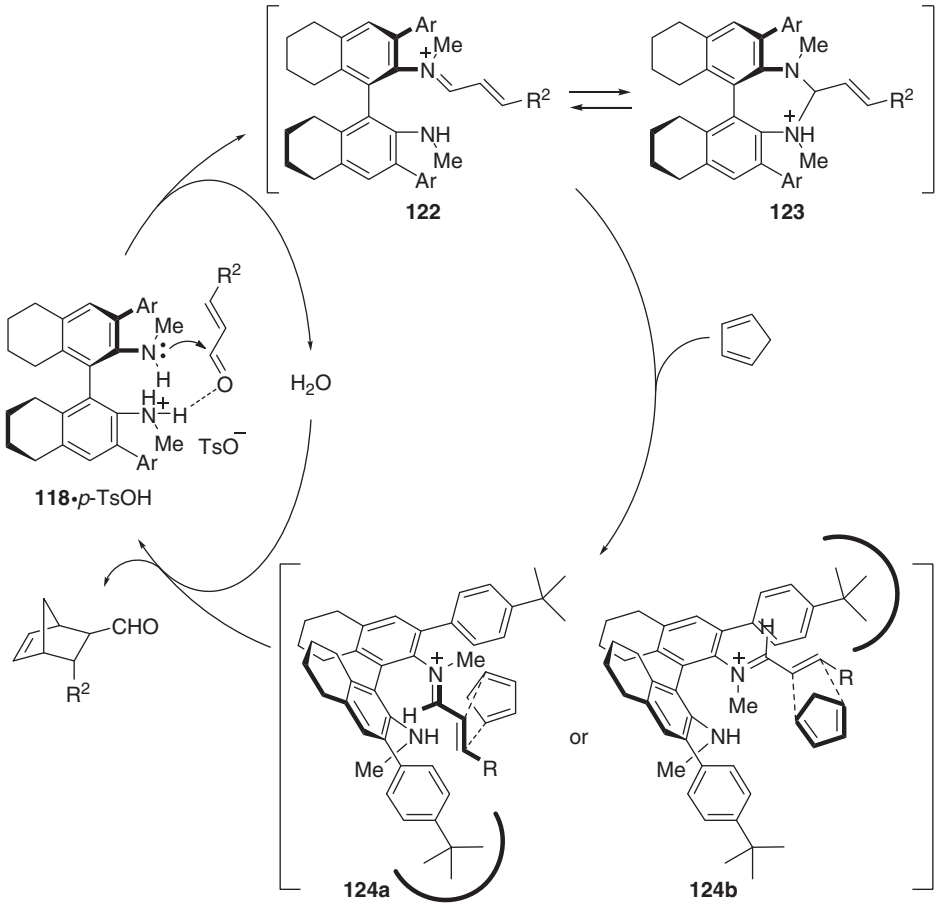
(16)

Another *exo*-selective, enantioselective Diels–Alder reaction uses diarylprolinol silyl ether **119** (Table 25).[84,85] For example, the hydroperchlorate salt **119a**•$HClO_4$ (5 mol%) catalyzes the Diels–Alder reaction with β-substituted propenals in water to give the corresponding *exo*-adducts (*exo*/*endo* 2:1 to 6:1) with excellent enantioselectivities. The use of water as a solvent accelerates the reaction and increases the enantioselectivity. Ammonium salts of **119** can catalyze the enantioselective Diels–Alder reaction of not only cyclic dienes but also acyclic dienes such as isoprene. Although butadiene is a useful diene component in the Diels–Alder reaction, its reaction is rather limited as a result of its low reactivity. The present method can provide the cycloadduct of butadiene with propenal with high enantioselectivity. The multigram-scale preparation of the Diels–Alder adduct of cyclopentadiene with cinnamaldehyde can be conducted under completely organic solvent-free conditions, including the purification step.

5.09.5.1.2 Primary ammonium salt catalysts

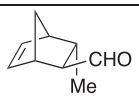
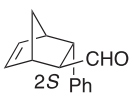
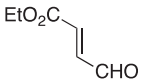
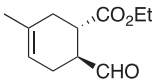
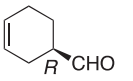
Although secondary ammonium salt catalysts can promote the Diels–Alder reactions with α-unsubstituted propenals, it is difficult to activate α-substituted propenals with these sterically hindered secondary ammonium salts, presumably because of the problems associated with the generation of the corresponding iminium cation intermediates. The greater bulkiness of the secondary amines is thought to be unfavorable for generating an iminium cation intermediate with an α-substituted propenal. In this context, chiral primary ammonium salt catalysts[86,87] have been developed for the Diels–Alder reaction with α-substituted propenals. Representative chiral primary amines **125**–**129** for the enantioselective Diels–Alder reaction are shown in Figure 13.

The primary ammonium salt of a dipeptide-derived triamine **125** and that of 1,1′-binaphthyl-2,2′-diamine **126** are efficient catalysts for the enantioselective Diels–Alder reaction with 2-(acyloxy)propenals **130**.[88–91] 2-(Acyloxy)propenals **130**[92] are among



Scheme 32 Proposed catalytic cycle of **118•***p*-TsOH-catalyzed Diels–Alder reaction.

Table 25 Enantioselective Diels–Alder reaction catalyzed by organoammonium salts of diarylprolinol silyl ether **119a**[a]

Diene	*Dienophile*	*Adduct*	*Yield (%)*	*Exo/endo*	*ee (%) of exo*	*References*
			73	72:28	99	84
			93	80:20	97 (2*S*)	84
			93	–	94	84
			41	–	87 (*R*)	84

[a]Conditions: **119a**•$HClO_4$ (5–10 mol%), H_2O, 4 °C to r.t.

the most promising alternatives to 2-halopropenals,[7,8] which are outstanding dienophiles in catalytic Diels–Alder processes because of the high reactivity and the exceptional synthetic versatility of the resultant adducts. However, 2-halopropenals are irritants and are unstable at ambient temperature. In contrast, 2-(acyloxy)propenals **130** are relatively stable and their reactivity can be controlled by switching the acyloxy group. The ammonium salt (10–20 mol%) of triamine **125** with pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$) can catalyze the reactions of various acyclic dienes and cyclopentadienes with **130a** ($R^1 = C_6H_4$-4-OMe) with excellent enantioselectivity to give the corresponding (2*S*)-adducts (equation 17, Table 26).[88] The reaction of 5-(benzyloxymethyl)cyclopentadiene with **130a** in THF gives the corresponding (2*S*)-*exo*-adduct with 83% *ee*. The adduct of 5-(benzyloxymethyl)cyclopentadiene is an important intermediate for the enantioselective synthesis of prostaglandins.

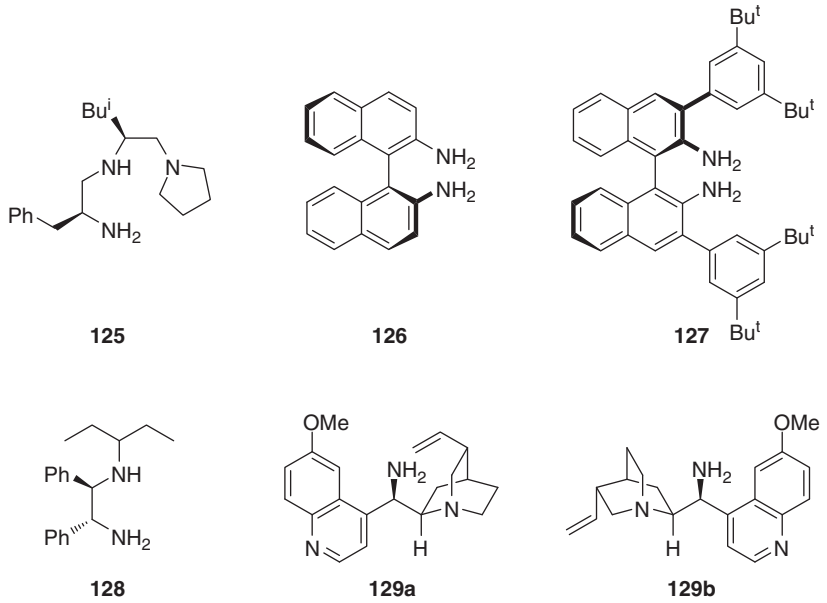
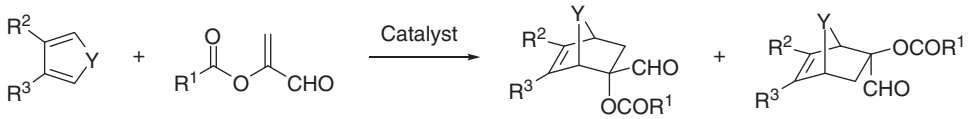


Figure 13 Representative chiral primary amines **125**–**129**.

Table 26 Diels–Alder reaction with 2-(*p*-methoxybenzoyloxy)propenal **130a** ($R^1 = C_6H_4$-4-OMe) catalyzed by **125**•2.75$C_6F_5SO_3H$ (equation 17)[a]

Y	R^2	R^3	*Solvent*	*Temperature (°C)*	*Yield (%)*	*Exo/endo*	*ee (%)*	*References*
CH_2	H	H	THF	−20	99	87:13	83	88
$CHCH_2OBn$	H	H	THF	−20	81	88:12	83	88
$(CH_2)_2$	H	H	$EtNO_2$	0	84	7:93	91	88
H, H	Me	Me	$EtNO_2$	0	92	–	92	88
H, H	Me	H	$EtNO_2$	0	90	99:1[b]	88	88

[a]Conditions: **125**•2.75$C_6F_5SO_3H$ (10–20 mol%), −20 to 0 °C.
[b]The molar ratio of 4-methyl and 3-methyl isomers.



130a ($R^1 = C_6H_4$-4-OMe)
130b (R^1 = cyclohexyl)
130c ($R^1 = C_6H_4$-4-OTIPS)

exo-(2*S*) *endo*-(2*S*) (17)

Although the enantioselectivity in the **125**•2.75 $C_6F_5SO_3H$-catalyzed Diels–Alder reaction of cyclopentadiene is slightly low (83% *ee*), the ammonium salt of **126** with trifluoromethanesulfonimide (Tf_2NH) shows higher catalytic activity than the ammonium salt of **125** (94% *ee*, Table 27).[89,90] Both enantiomers of **126** are commercially available, and the ammonium salt catalysts can be easily prepared *in situ* by mixing **126** and Tf_2NH. Since **126** is an aromatic diamine, the catalytic activity of the ammonium salt of **126** is greater than that of **125,** and the reaction can be conducted at a lower reaction temperature (−75 °C) with a lower catalyst loading (5–10 mol%). 2-(Acyloxy)propenal **130c** ($R = C_6H_4$-4-OTIPS) is suitable as a dienophile for the **126**•1.9 Tf_2NH-catalyzed Diels–Alder reaction, due to the electron-donating nature of the acyloxy group and good solubility under the reaction conditions. The adducts of cyclopentadiene and cyclohexadiene with 2-(acyloxy)propenals **130** can be readily converted into bicyclo[2.2.1]hept-5-en-2-one and bicyclo[2.2.2]oct-5-en-2-one, which are promising synthetic intermediates for the total synthesis of several bioactive natural compounds.

A possible mechanism that accounts for the observed absolute stereochemistry of the adducts is shown in Figure 14. Because **125**•2 $C_6F_5SO_3H$ is much less active than **125**•2.75 $C_6F_5SO_3H$ as a catalyst for the Diels–Alder reaction with **130**, it is conceivable that **125**•3 $C_6F_5SO_3H$ is the actual active catalyst, which activates **130** as (*Z*)-iminium salt **131** with **125**•3 $C_6F_5SO_3H$.

Table 27 Diels–Alder reaction with 2-(acyloxyl)propenal **130** catalyzed by **126**•1.9 Tf_2NH (equation 17)[a]

Y	R^2	R^3	***130***	*Solvent*	*Yield (%)*	*Exo/endo*	*ee (%)*	*References*
CH_2	H	H	**130a**	EtCN	48	93:7	94	89
CH_2	H	H	**130b**	EtCN	88	92:8	91	89
CH_2	H	H	**130c**	EtCN	76	93:7	94	90
$(CH_2)_2$	H	H	**130b**	$EtNO_2$	90	1:>99	91	89
H, H	Me	Me	**130b**	$EtNO_2$	88	–	70	89
H, H	Me	Me	**130c**	$EtNO_2$	85	–	85	90
H, H	Me	H	**130b**	$EtNO_2$	67	>99:1[b]	71	89
H, H	Me	H	**130c**	$EtNO_2$	85	>99:1[b]	82	90
H, H	H	H	**130b**	$EtNO_2$	65	–	68	89
H, H	H	H	**130c**	$EtNO_2$	77	–	82	90

[a]Conditions: **21**•1.9Tf_2NH (5–10 mol%), −75 °C.
[b]The molar ratio of 4-methyl and 3-methyl isomers.

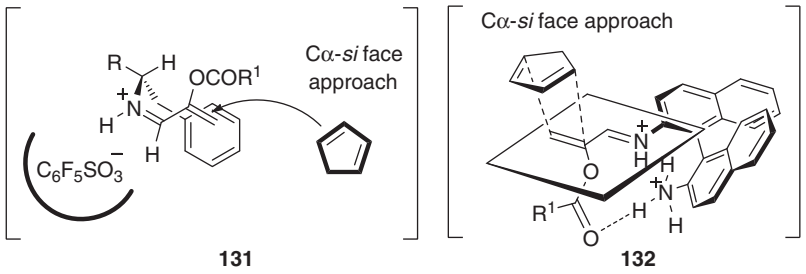
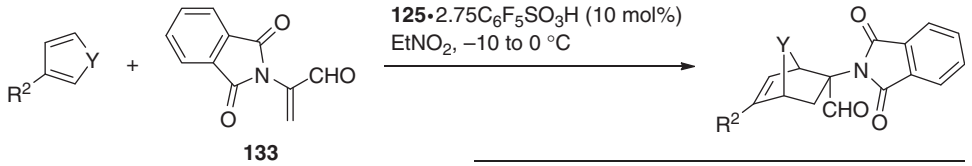


Figure 14 Proposed transition-state assemblies.

The Diels–Alder reaction may proceed via the (*Z*)-iminium intermediate **131**, where the phenyl group of **125** shields the Cα-*Re* face of the α,β-unsaturated iminium moiety.[88,91,93] However, the mechanism for asymmetric induction for the reaction catalyzed by **125**•2.75 $C_6F_5SO_3H$ is still unclear.[93] Based on the result that the use of the ammonium salt of **126** (5 mol%) and Tf_2NH (5 mol%) as a catalyst produces a lower yield and enantioselectivity, **126**•2 Tf_2NH should be the actual active catalyst for the reaction catalyzed by **126**•1.9 Tf_2NH. The reaction may proceed via an (*E*)-iminium intermediate **132**, in which the acyloxy group interacts with the other ammonium group through hydrogen bonding.[89,90] The electron-donating nature of the 4-(triisopropylsilyloxy)benzoyloxy group presumably enhances the hydrogen bonding between the acyl group and the ammonium proton to stabilize the conformation of the (*E*)-iminium intermediate **132**. In both cases, dienes should approach the Cα-*Si* face of an electron-deficient alkene enantioselectively.

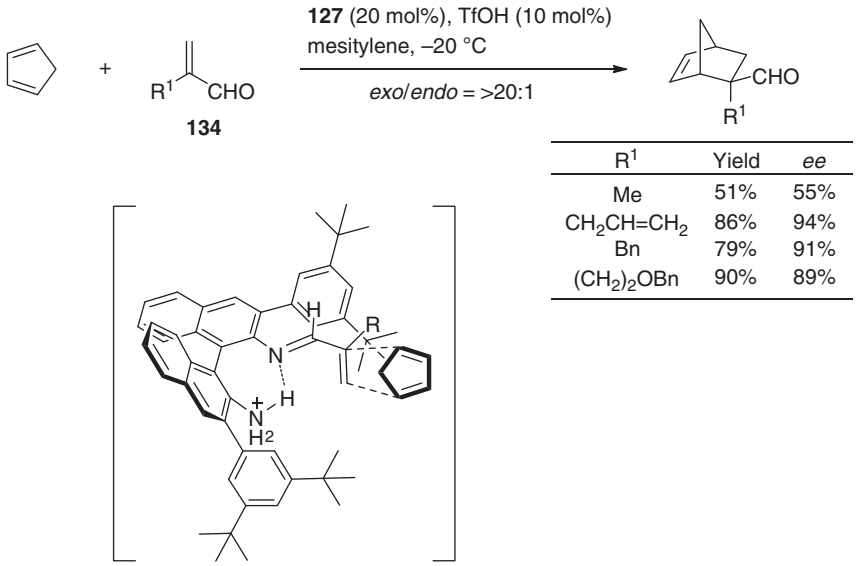
The ammonium salt of chiral triamine **125** can also be used for the Diels–Alder reaction with 2-(phthalimido)propenal **133** to give cyclic α-quaternary α-amino acid precursors.[93] In the presence of **125**•2.75 $C_6F_5SO_3H$ (2.5–10 mol%), the cycloaddition reaction of cyclic and acyclic dienes with **133** is conducted in $EtNO_2$ to give the corresponding *endo*-adducts with high enantioselectivities. For example, cyclopentadiene, isoprene, 2-phenylbutadiene, and myrcene react smoothly with **133** to give the desired 4-alkylsubstituted cyclohex-3-enecarboxaldehydes with 88–94% *ee* (**Scheme 33**). In contrast, another candidate **126**•1.9 Tf_2NH as a catalyst does not catalyze the Diels–Alder reaction with **133** because **126** irreversibly reacts with **133** even at –78 °C in the presence of Tf_2NH.



Y	R^2	Yield	*Endo/exo*	*ee*
CH_2	H	73%	72:28	90%
H, H	Me	82%	—	94%
H, H	Ph	79%	—	88%
H, H	$(CH_2)_2CH{=}CMe_2$	73%	—	94%

Scheme 33 Enantioselective Diels–Alder reaction with 2-(phthalimido)propenal **133** catalyzed by the ammonium salt of chiral triamine **125**.

All-carbon quaternary stereocenters, that is, carbon atoms bearing four different carbon substituents, pose a particular challenge in organic synthesis. At present, few methods have been reported for the catalytic enantioselective construction of all-carbon quaternary stereocenters. The Diels–Alder reaction with α-alkyl-substituted propenals **134** is a promising candidate for the preparation of compounds with one all-carbon quaternary stereocenter. For example, the salt of the binaphthyl-based primary diamine **127** with TfOH is an efficient catalyst for the enantioselective Diels–Alder reaction of cyclopentadiene with **134** (Scheme 34).[94] The enantioselectivity of the reaction with **134** highly depends on the reaction solvent and the acid cocatalyst. The reactions in mesitylene and toluene give good results, whereas the use of other solvents significantly decreases the enantioselectivity. In addition, the use of TfOH as an acid cocatalyst is crucial for obtaining high reactivity and enantioselectivity. Although the reaction of 2-methypropenal gives the corresponding adduct (R^1 = Me) with moderate enantioselectivity (55% *ee*), the introduction of longer alkyl substituents at the α-carbon of the propenal significantly improves the level of asymmetric induction.[94]



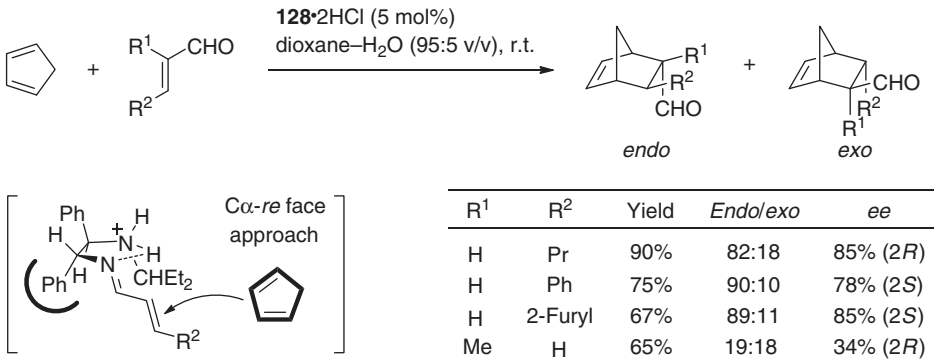
R^1	Yield	*ee*
Me	51%	55%
$CH_2CH{=}CH_2$	86%	94%
Bn	79%	91%
$(CH_2)_2OBn$	90%	89%

Scheme 34 Enantioselective Diels–Alder reaction with α-alkyl-substituted propenals **134** catalyzed by the salt of binaphthyl-based primary diamine **127**.

The observed stereochemistry in the asymmetric reaction catalyzed by the salt of **127** can be explained by the possible transition-state model shown in Scheme 34.[94] In this model, the aldimine moiety is activated by internal hydrogen bonding with the ammonium proton. A 3,5-di-*tert*-butylphenyl group of **127** effectively blocks one face of *s-cis*-aldimine, while leaving the other face open for the approach of cyclopentadiene. In the case of 2-methylpropenal, due to the small size of the methyl group, it may be difficult to discriminate between *s-cis*- and *s-trans*-aldimine with the 3,5-di-*tert*-butylphenyl group, and this induces moderate enantioselectivity.

An ammonium salt of primary diamine **128** is also an effective organocatalyst for the enantioselective Diels–Alder reaction.[95] The **128**•2HCl-catalyzed reaction with 2-unsubstituted propenals yields the corresponding *endo*-adducts with high enantioselectivities (Scheme 35). Although **128** is a chiral primary amine, the ammonium salt of **128** shows poor catalytic activity and enantioselectivity for the Diels–Alder reaction with 2-substituted propenals.

Cinchona alkaloids have been widely used in asymmetric organocatalysis.[96,97] They are abundant natural products that exist as *pseudo*-enantiomeric pairs, as exemplified by quinine and quinidine. They are readily accessible amine catalysts that can be used to generate either enantiomer of a chiral product of interest. Accordingly, numerous efforts have been devoted to the development of cinchona alkaloid-catalyzed enantioselective reactions. For example, ammonium salts of cinchona alkaloid-derived primary amines **129** with trifluoroacetic acid (TFA) are efficient catalysts for the enantioselective Diels–Alder reaction of 2-hydroxy-2-pyrones **135** with simple α,β-unsaturated ketones.[98] In the presence of **129a**•4 TFA (5 mol%), the reaction of **135** with α,β-unsaturated ketones gives the corresponding *exo*-adduct **136** with excellent enantioselectivities (equation 18, Table 28). However, the same reaction catalyzed by *pseudo*-enantiomeric **129b**•4 TFA preferentially affords *ent*-**136**. The present method catalyzed by **129a**•4 TFA can be applied to various β-aryl, β-alkyl, and β-unsubstituted α,β-unsaturated ketones. Catalyst **129**•4 TFA also tolerates substituted 2-pyrones. The primary amine functionality in **129** is critical to its activity, which is abolished when the amine is replaced with a thiourea group. The presence of TFA is essential for the selectivity of **129**, although TFA itself does not promote the Diels–Alder reaction. Moreover, electron-rich dienes that do not bear either a hydrogen-bonding acceptor or donor such as cyclopentadiene and cyclohexadiene are inactive for the present Diels–Alder reaction in the presence of **129** and TFA. These results indicate that the activation of **135** by **129**•4 TfOH is also required for the Diels–Alder reaction to occur.

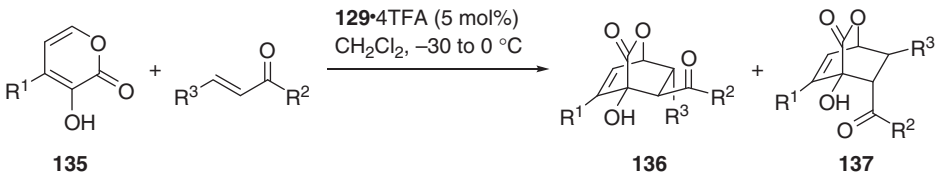


R^1	R^2	Yield	*Endo*/*exo*	*ee*
H	Pr	90%	82:18	85% (2*R*)
H	Ph	75%	90:10	78% (2*S*)
H	2-Furyl	67%	89:11	85% (2*S*)
Me	H	65%	19:18	34% (2*R*)

Scheme 35 Enantioselective Diels–Alder reaction catalyzed by the salt of primary diamine **128**.

Table 28 Diels–Alder reaction of 2-hydroxy-2-pyrones **135** with α,β-unsaturated ketones (equation 18)

R^1	R^2	R^3	***129***	*Yield (%)*	***136/137***	*ee (%) of* ***136***	*References*
H	Me	Ph	**129a**	99	80:20	98	98
H	Me	Ph	**129b**	95	83:17	–97	98
H	Me	2-Thienyl	**129a**	85	80:20	99	98
H	Me	Me	**129a**	92	84:16	99	98
H	Me	$(CH_2)_3OBn$	**129a**	92	76:24	99	98
H	Et	H	**129a**	99	97:3	99	98
Ph	Me	Ph	**129a**	83	83:17	96	98
Me	Me	Ph	**129a**	60	80:20	96	98
Cl	Me	C_6H_4-4-Br	**129a**	63	67:33	90	98



(18)

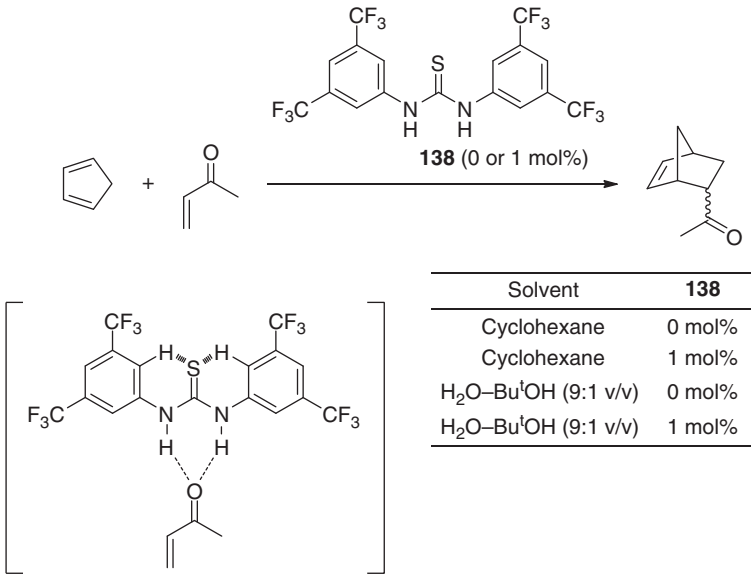
5.09.5.2 Hydrogen-Bonding Catalysis

Some small organic molecules capable of forming hydrogen-bonding interactions can catalyze the Diels–Alder reaction.[99–102] Rate-acceleration by these hydrogen-bonding donors results from the decrease in energy of the electron-deficient dienophile's LUMO, as in Lewis acid activation. For example, electron-deficient diaryl thiourea **138** can promote the Diels–Alder reaction of but-3-en-2-one with cyclopentadiene via the simultaneous donation of two hydrogen bondings.[103] The electron-withdrawing substituents at the *meta*-positions aid in reducing the flexibility of the catalyst, thereby minimizing the decrease in entropy on complexation with carbonyl compounds. The hydrogen atoms at the *ortho*-positions are more positively polarized. The hydrogen-bonding donor ability of these C–H bonds leads to internal interactions between the Lewis basic sulfur and the *ortho*-hydrogen atoms, which prevent rotation of the phenyl groups (Scheme 36).

Some chiral hydrogen-bonding donors are useful tools as catalysts for the asymmetric Diels–Alder reaction. Representative chiral Brønsted acid catalysts **139**–**141** for the enantioselective Diels–Alder reaction are illustrated in Figure 15.

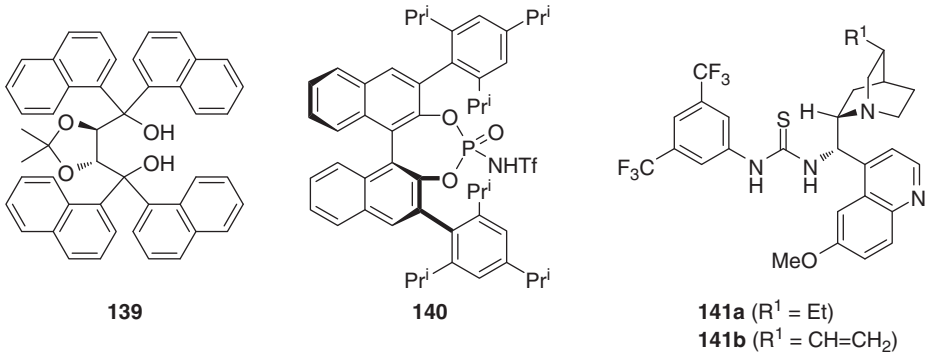
The commercially available chiral diol **139**, α,α.α′,α′-tetraaryl-1,3-dioxylane-4,5-dimethanol (TADDOL, aryl = 1-naphthyl) considerably accelerates the reaction of electron-rich aminosiloxydiene **143** with α-substituted propenals to give the intermediate *endo*-adducts **144** (Scheme 37).[104,105] Treatment of **144** with excess HF in acetonitrile produces aldehydes **145** in yields of 77–85% (Table 29). Alternatively, reduction of **144** with an excess of $LiAlH_4$ followed by acidic hydrolysis gives alcohols **146** with high enantioselectivities of up to 92% *ee*. Interestingly, the enantioselective Diels–Alder reaction with propenal itself is less enantioselective than the analogous reaction with α-substituted propenals, probably due to the greater conformational flexibility of propenal.

As the temperature of the reaction is decreased from ambient temperature to –80 °C, the enantiopurity of the cycloadduct increases steadily. This is attributed to the formation of more persistent hydrogen bonding and a better-organized TADDOL–substrate hydrogen bond complex as the available thermal energy is decreased. TADDOL **139** is expected to exist in a



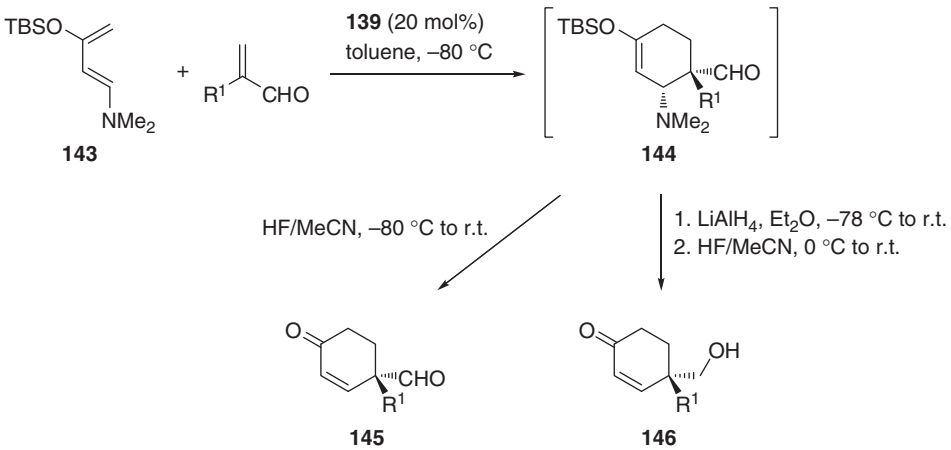
Solvent	138	Yield
Cyclohexane	0 mol%	18%
Cyclohexane	1 mol%	42%
H_2O–Bu^{t}OH (9:1 v/v)	0 mol%	74%
H_2O–Bu^{t}OH (9:1 v/v)	1 mol%	85%

Scheme 36 Rate-acceleration by hydrogen-bonding donors.



139 **140** **141a** (R^1 = Et) **141b** (R^1 = CH=CH_2)

Figure 15 Representative chiral Brønsted acid catalysts **139**–**141**.



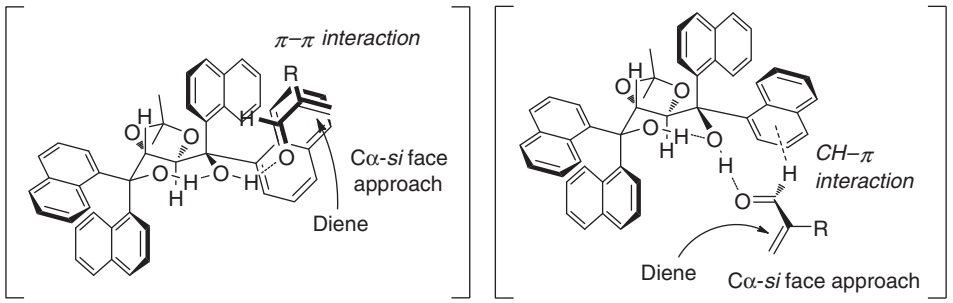
143 **144** **145** **146**

Scheme 37

Table 29 TADDOL-catalyzed enantioselective Diels–Alder reaction of aminosiloxydiene **143** (Scheme 37)

R^1	Yield of **145** (%)	Yield of **146** (%)	ee of **146** (%)	References
H	–	77	73	104
Me	85	83	91	104
Et	80	83	88	104
Pr^i	77	81	92	104
Bn	84	82	89	104
$(CH_2)_2OTBS$	80	80	86	104

well-defined, internally hydrogen-bonded arrangement **147** in the reaction mixture at –80 °C (Figure 16).[104] An α-substituted acrolein may interact with **139** through hydrogen bonding with the free hydroxyl group and π–π interaction with the proximal equatorial 1-naphthyl group, which selectively shields the Cα-*Re* face of the dienophile. However, a theoretical study for the **139**-catalyzed hetero-Diels–Alder reaction of diene **143** with benzaldehyde showed that the complex of **139** and benzaldehyde is stabilized by CH–π interaction between the aldehyde CH and the pseudoequatorial naphthalene ring of **139** instead of π–π interaction.[106] The present **139**-catalyzed Diels–Alder reaction of α-substituted acroleins may also proceed via transition-state **148** with a CH–π interaction.



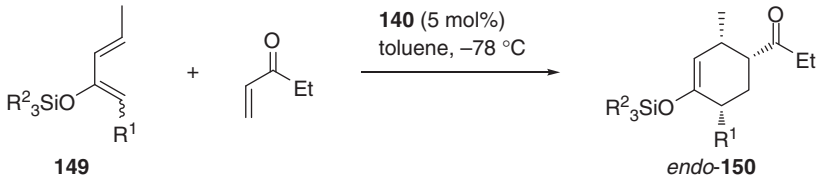
147 **148**

Figure 16 Proposed transition-state assemblies **147** and **148**.

Binaphthyl-based axially chiral phosphoric acids have become an important class of chiral Brønsted acid catalysts,[107–109] especially for the activation of relatively Brønsted-basic imine substrates. However, the relatively low acidity of phosphoric acid makes this excellent catalyst of rather limited use in future applications. For example, it is difficult to apply chiral phosphoric acids to the Diels–Alder reaction of simple α,β-unsaturated ketones. The binaphthyl-based *N*-(trifluoromethanesulfonyl)phosphoramide **140**, which is more acidic than phosphoric acids, can catalyze the Diels–Alder reaction of 1-substituted 2-siloxybutadienes **149** with α,β-unsaturated ketones, for example, pent-1-en-3-one, to give the corresponding *endo*-adducts **150** with high enantioselectivities (equation 19, Table 30).[110] An aromatic solvent, such as toluene, is suitable for the **140**-catalyzed enantioselective Diels–Alder reaction of **149** with pent-1-en-3-one, whereas the use of dichloromethane as a solvent significantly decreases the yield, probably due to the dimerization of diene. Although the bulkiness of the silyl group (SiR_3^2) in **149** does not affect the enantioselectivity, the yields of the reactions are quite sensitive to the stability of siloxydienes due to the protonation of the diene and the deactivation (silylation) of the catalyst. For the same reason, α-unsubstituted **149** ($R^1 = H$) produces a relatively low yield. The acid-sensitive TBS ether is tolerated in this reaction. The Lewis basic benzoyl group does not affect either the reactivity or the enantioselectivity.

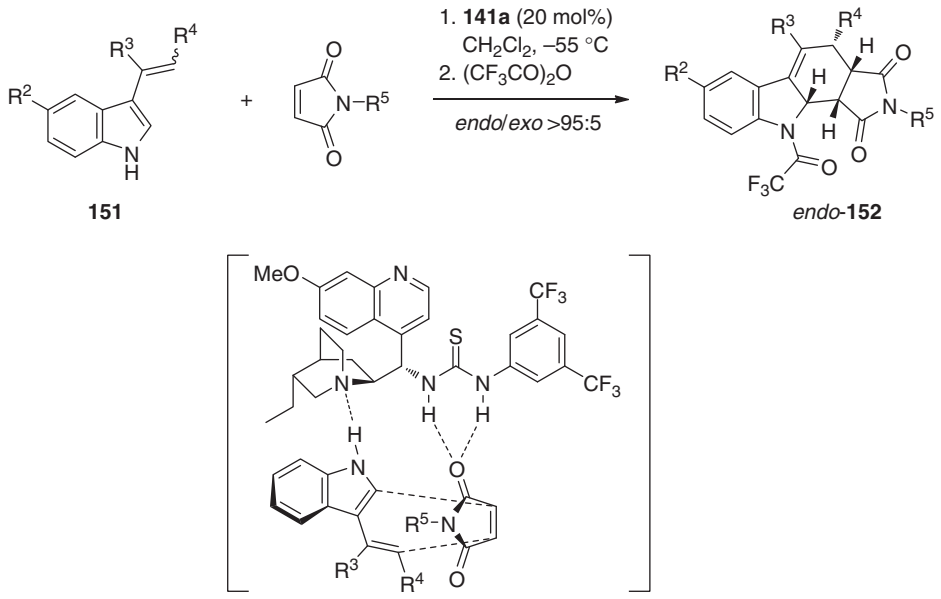
Table 30 Diels–Alder reaction of pent-1-en-3-one catalyzed by *N*-(trifluoromethanesulfonyl)phosphoramide **140** (equation 19)

R^1	SiR_3^2	Yield (%)	ee (%)	References
Me	TBS	43	92	110
Me	TIPS	95	92	110
H	TIPS	43	88	110
Bn	TIPS	>99	85	110
$CH_2C_6H_4$-4-OTBS	TIPS	>99	92	110
$(CH_2)_2OBz$	TIPS	>99	91	110



(19)

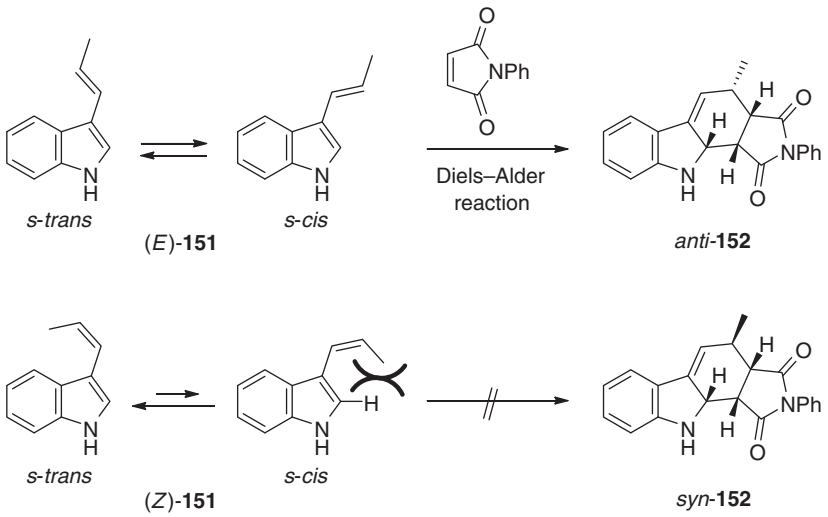
The cinchona alkaloid-derived bifunctional organocatalyst **141a** promotes the enantioselective Diels–Alder reaction of 3-vinylindoles **151** (Scheme 38, Table 31).[111] In the presence of **141a** (20 mol%), the reaction of **151** with *N*-substituted maleimides in CH_2Cl_2, followed by treatment with trifluoroacetic anhydride, produces the *endo*-adducts **152** in good yields with excellent enantioselectivities. The bifunctional catalyst **141a** can simultaneously activate **151** with the tertiary amine moiety and *N*-substituted maleimides with a thiourea moiety through hydrogen bonding. The fact that 1-tosyl and 1-*tert*-butoxycarbonyl derivatives of **151** give the corresponding **152** in racemic form supports the proposed double activation through hydrogen bondings. The rather low enantioselectivity in the reaction with *N*-unsubstituted maleimide can be attributed to possible interference by the hydrogen-bonding interaction between the catalyst and the imide hydrogen. When 3-vinylindole **151** (R^2, R^3 = H, and R^4 = Me) bearing a methyl group on the exocyclic vinyl substituent is used as a 1:1 *E*/*Z* mixture, the *E*-isomer exclusively undergoes the Diels–Alder reaction to give the corresponding *anti*-adduct **152** with 92% *ee* as a single diastereomer. The preferential reactivity of the *E*-isomer relative to the *Z*-isomer can be explained by the easier accessibility to the *s-cis*-conformation, which is the key structural feature for the Diels–Alder reaction to occur (Scheme 39). *Endo*-**152** (R^2, R^3, and R^4 = H and R^5 = Ph) is successfully converted into the known intermediate **153** of a synthesis of a Strychnos alkaloid, tubifolidine[112] (Scheme 40). Benzoquinone and naphthoquinone, another well-known class of dienophiles for Diels–Alder reactions, are also used to give the corresponding adducts with high enantioselectivities.



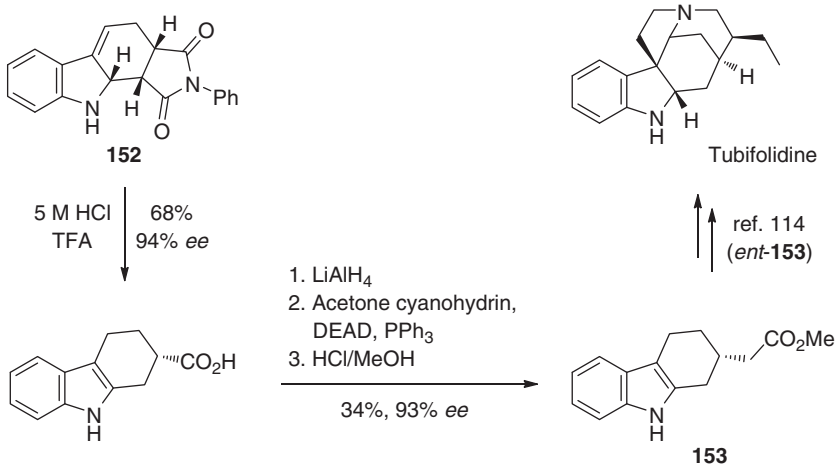
Scheme 38

Table 31 Diels–Alder reaction of 3-vinylindoles **151** catalyzed by cinchona alkaloid-derived bifunctional catalyst **141a** (Scheme 38)

R^2	R^3	R^4	R^5	Yield (%)	ee (%)	References
H	H	H	Ph	91	98	111
Br	H	H	Ph	86	90	111
OMe	H	H	Ph	77	96	111
H	Me	H	Ph	79	96	111
H	H	H	Bn	89	96	111
H	H	H	H	72	52	111
H	H	Me	Ph	58	92	111



Scheme 39



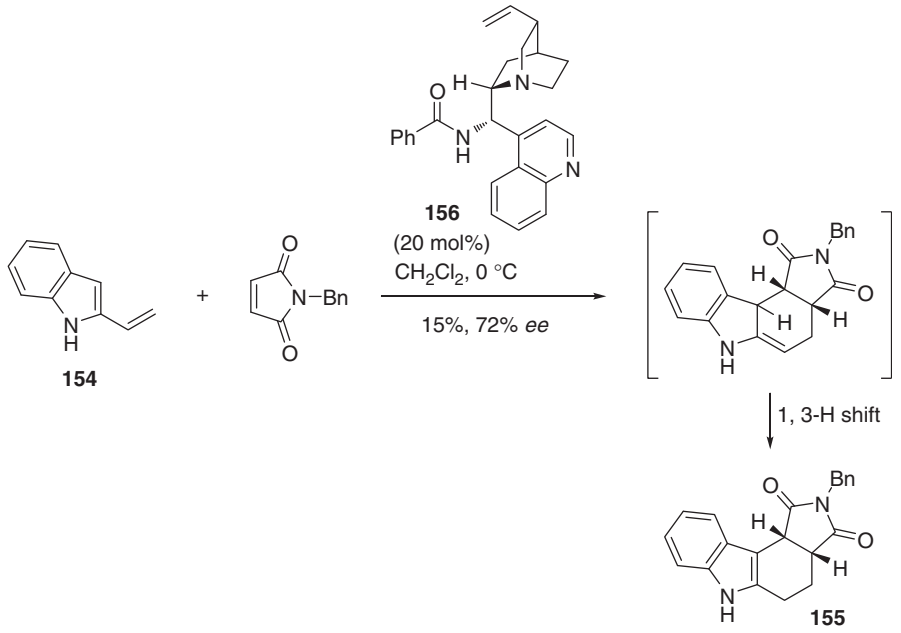
Scheme 40

2-Vinylindole (**154**), the olefin moiety of which is considerably less electron-rich, is less reactive than 3-vinylindoles **151** in the Diels–Alder reaction. When the Diels–Alder reaction of **154** with *N*-benzylmaleimide is conducted in the presence of a cinchona alkaloid-derived catalyst **156** (20 mol%) at 0 °C, tetrahydrocarbazole **155** is obtained via the spontaneous 1,3-hydrogen shift in the cycloadduct (Scheme 41). Although the yield of **155** is low (15%), it was isolated with 72% *ee*.[113]

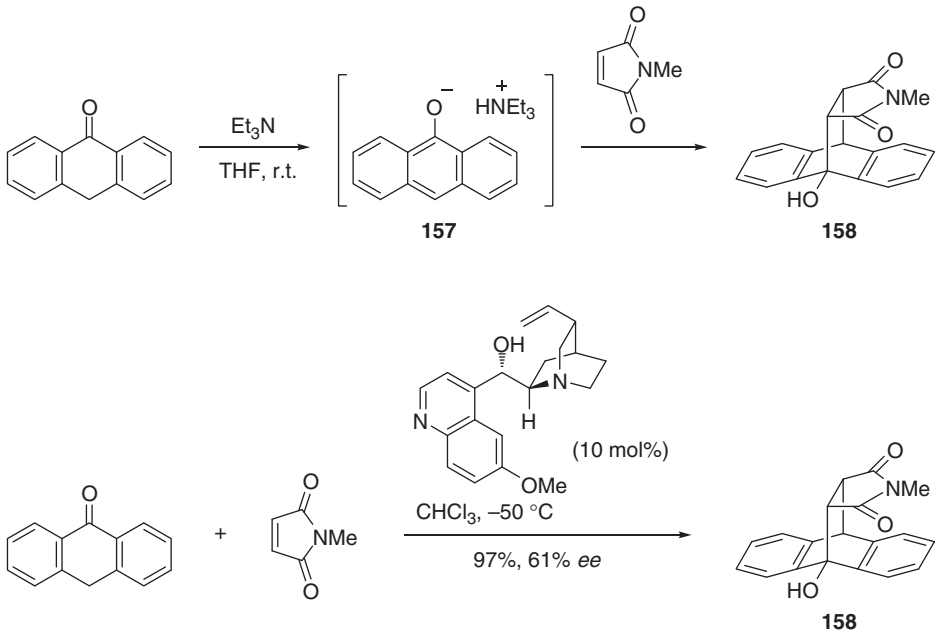
5.09.5.3 HOMO-Activation Using Brønsted Bases

In the presence of a Brønsted base, anthrone functions as a reactive diene. For example, when the reaction of anthrone with *N*-methylmaleimide is conducted in the presence of triethylamine, the corresponding adduct **158** is quantitatively obtained within 15 min (Scheme 42).[114] The reaction proceeds $\geq 10^4$ faster than the reaction in the absence of a Brønsted base. The results of mechanistic investigations are consistent with a concerted [4 + 2] process. A Brønsted base activates anthrone through the formation of an oxyanion intermediate **157**. In contrast to the organoammonium salt catalysis and hydrogen-bonding catalysis (LUMO-lowering activation) described above, the Brønsted base activates anthrone by raising the HOMO energy (HOMO-raising activation), thereby allowing it to react with an electron-deficient dienophile.

This HOMO-raising activation of anthrone can also be used in an asymmetric Diels–Alder reaction using a chiral Brønsted base catalyst. For example, a catalytic amount of quinidine can catalyze the enantioselective Diels–Alder reaction of anthrone with *N*-methylmaleimide to give **158** in 97% yield with 61% *ee* (Scheme 42).[115,116] The free hydroxy group in quinidine is essential for achieving a high optical yield. When quinidine is replaced by dihydroquinidine *O*-*p*-chlorobenzoate, the adduct **158** is obtained



Scheme 41 Enantioselective Diels–Alder reaction of 2-vinylindole (**154**).



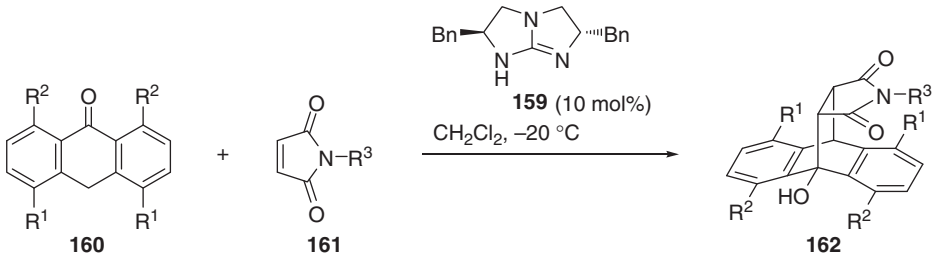
Scheme 42 HOMO-raising activation of anthrone.

in racemic form. A lower reaction temperature and the use of a less polar solvent are also important for achieving high enantioselectivity.

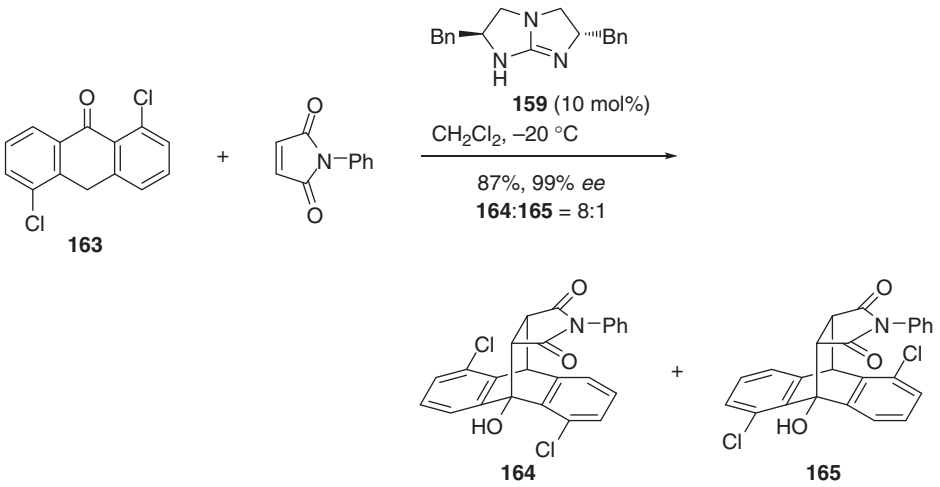
The enantioselectivities of the anthrone Diels–Alder reaction are improved with the bicyclic guanidine catalyst **159** (equation 20, Table 32).[117] The reaction of a series of substituted anthrones **160** and *N*-substituted maleimides **161** is conducted under mild conditions and gives the corresponding adducts **162** in high yields with high enantioselectivities. Excellent regioselectivity is also observed when 1,5-dichloro-9-anthrone **163** is used as the diene. The Diels–Alder reaction of **163** with *N*-phenylmaleimide gives the corresponding adducts **164** in an 8:1 ratio with the regioisomer **165** (equation 21). The guanidine catalyst **159** is proposed to generate the active diene *in situ* through deprotonation.

Table 32 Diels–Alder reaction of substituted anthrones **160** with maleimides **161** catalyzed by chiral bicyclic guanidine **159** (equation 20)

R^1	R^2	R^3	Yield (%)	ee (%)	References
H	H	C_6H_4-2-NO_2	87	98	115
H	H	C_6H_3-2,5-Cl_2	88	95	115
H	Cl	Bn	92	95	115
H	Cl	*c*-Hexyl	88	98	115
Cl	H	Ph	92	99	115
Cl	H	C_6H_3-2,6-F_2	92	99	115
Cl	H	C_6H_4-2-OMe	90	98	115



(20)



(21)

3-Hydroxy-2-pyrones **135** are also reactive dienes that can be activated by a Brønsted base. For example, the enantioselective Diels–Alder reactions of 3-hydroxy-2-pyrones are promoted by the cinchona alkaloid-derived catalysts **166** and **167** (Scheme 43, Table 33).[118] Cinchona alkaloids bearing an active proton can act as acid–base bifunctional catalysts. The tertiary amino group in **166** and **167** acts as a Brønsted base to activate 3-hydroxy-2-pyrones by raising the energy of the HOMO. Simultaneously, the 6′-hydroxyl group acts as a Brønsted acid to activate the dienophiles by lowering the energy of the LUMO. The use of **166** gives the corresponding *exo*-adducts **168** with high diastereo- and enantioselectivities.

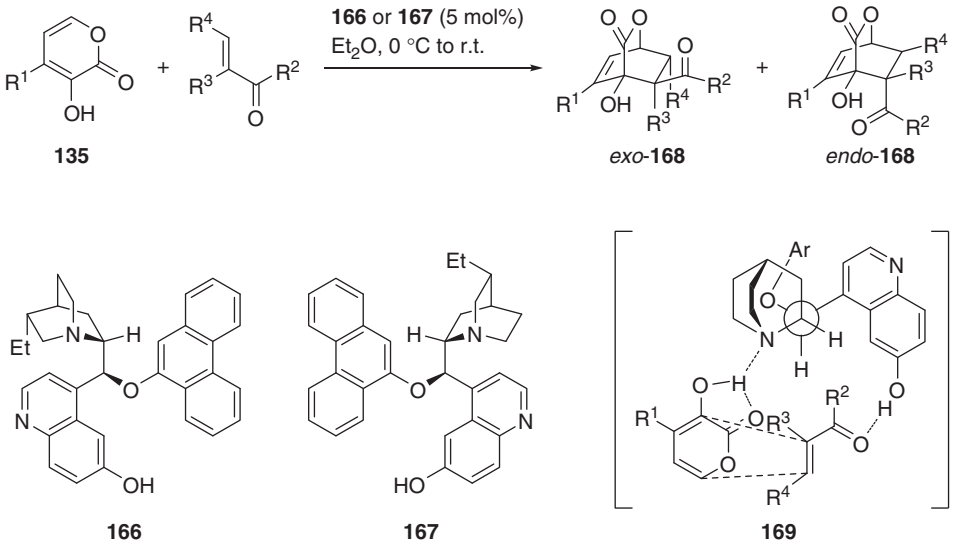
Although catalyst **166** tolerates a significant degree of alterations in both pyrones **135** and dienophiles, catalyst **170** bearing a thiourea group gives low diastereo- and enantioselectivity (73:27 *dr*, 37% *ee*) for the reaction of **135** (R^1 = H) with ethyl 4-oxo-4-phenylbut-2-enoate (R^2 = Ph, R^3 = H, and R^4 = CO_2Et). In contrast, catalyst **166** is ineffective for reactions with fumaronitrile, whereas the use of **170** drastically improves the diastereo- and enantioselectivity (Scheme 44).[118] These reactions are stereospecific with respect to the geometry of the double bond, which is consistent with a concerted cycloaddition mechanism.

Furthermore, the *endo*/*exo*-selectivity can be successfully controlled using cinchona alkaloid-derived bifunctional catalysts (Scheme 45).[118] Thus, in the Diels–Alder reaction of **135** (R^1 = H) with 2-chloroacrylonitrile, the use of **166** selectively gives the *endo*-adduct **172**, whereas the use of **170** affords the *exo*-adduct **173**. Consequently, each of the four possible stereoisomers can be obtained stereoselectively.

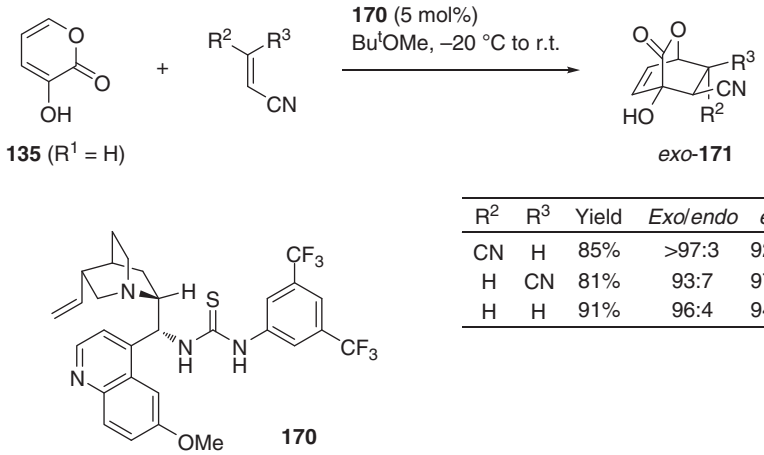
As described in Section 5.09.5.1, organoammonium salts of chiral amines with strong Brønsted acids can activate α,β-unsaturated carbonyl compounds through the generation of iminium intermediates **174** (LUMO-lowering activation) (Scheme 46). However, free amines or organoammonium salts with weak Brønsted acids can activate α,β-unsaturated ketones

Table 33 Diels–Alder reaction of 3-hydroxy-2-pyrones **135** catalyzed by cinchona alkaloid-derived bifunctional catalysts **166** and **167** (Scheme 43)

R^1	R^2	R^3	R^4	Catalyst	Yield (%)	Exo/endo	ee (%)	References
H	Ph	H	CO_2Et	**166**	87	93:7	94	118
H	Ph	H	CO_2Et	**167**	90	94:6	−87	118
H	Ph	H	COPh	**166**	100	93:7	90	118
H	Me	Me	H	**166**	65	24:76	91	118
H	Me	Me	H	**167**	63	26:74	−90	118
Ph	Ph	H	CO_2Et	**166**	84	95:5	85	118
Me	Ph	H	CO_2Et	**166**	87	88:12	82	118
Cl	Ph	H	CO_2Et	**166**	77	86:14	84	118
Br	Ph	H	CO_2Et	**166**	75	85:15	83	118



Scheme 43 Enantioselective Diels–Alder reaction of 3-hydroxy-2-pyrones **135**.

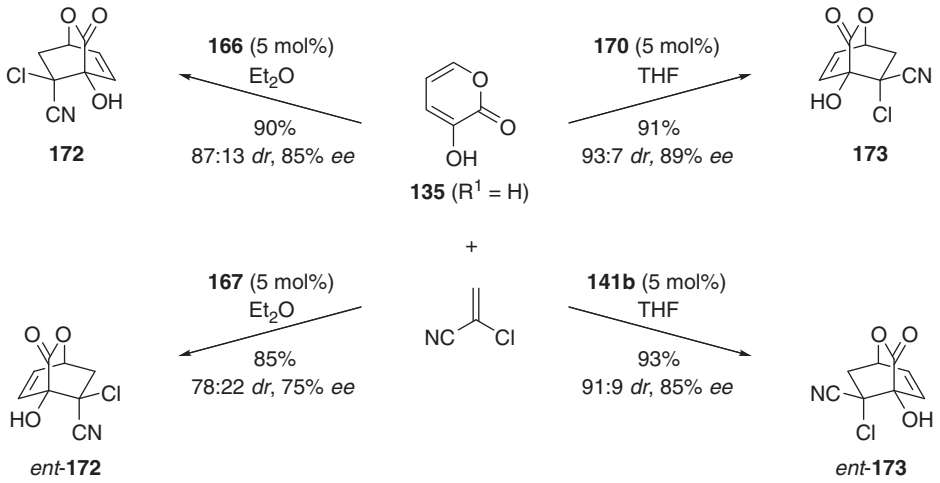


R^2	R^3	Yield	Exo/endo	ee
CN	H	85%	>97:3	92%
H	CN	81%	93:7	97%
H	H	91%	96:4	94%

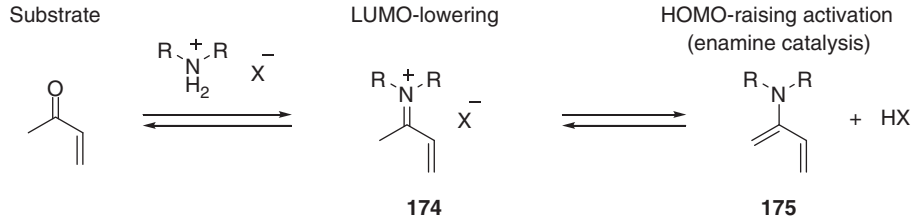
Scheme 44 Enantioselective Diels–Alder reaction with α,β-unsaturated nitriles catalyzed by chiral thiourea **170**.

through the formation of 2-dienamine **175**. This electron-rich diene reacts with electron-deficient alkenes to give the corresponding Diels–Alder adducts.[119,120] This catalytic strategy involving HOMO-raising activation is called enamine catalysis.

Recently, chiral amine-catalyzed enantioselective Diels–Alder reactions involving *in situ* enamine activation have been reported. A chiral secondary amine **176** (20 mol%) catalyzes the enantioselective Diels–Alder reaction of cyclohexadienes with nitroalkenes in the presence of 4-$CF_3C_6H_4CO_2H$ (20 mol%) in seawater or brine to give the corresponding cycloadducts **177** with



Scheme 45 High-level diastereo- and enantiocontrol in Diels–Alder reaction of **135** with 2-chloroacrylonitrile.

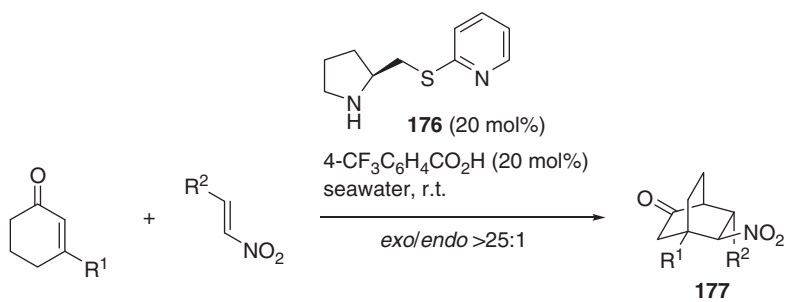


Scheme 46 HOMO-raising activation of α,β-unsaturated carbonyl compounds: Enamine catalysis.

high diastereo- and enantioselectivity (equation 22, Table 34).[121] Although R^2 is limited to aryl groups, the electronic properties and the position of the substituents on the aryl group have little influence on the diastereo- and enantioselectivity of the reaction. Interestingly, the best result is obtained when seawater, taken from the East China Sea, is used as the solvent. The reaction in boiled seawater gives results similar to those in untreated seawater, which suggests that salts, rather than microorganisms, play an important role in the reaction. The concentration of aqueous NaCl evidently affects the performance of the reaction. Due to the good dispersion of the reactants in aqueous salt solutions and the salting-out effect, conversions of approximately 100% and high diastereo- and enantioselectivities are obtained with seawater or a 7.5% NaCl aqueous solution.

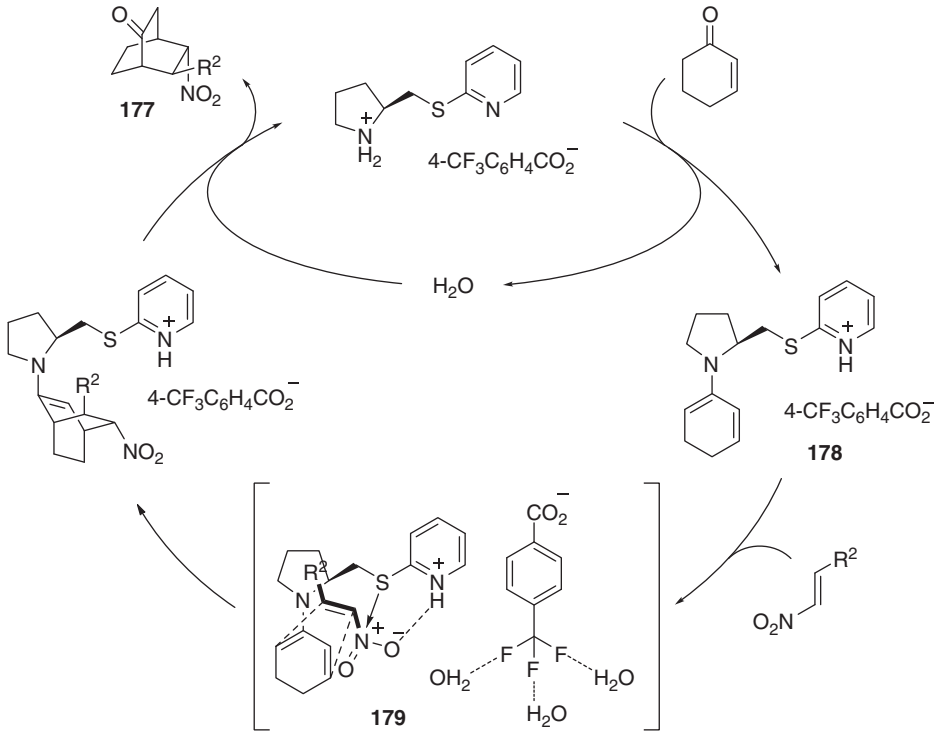
Table 34 Diels–Alder reaction of cyclohexenones with nitroalkenes catalyzed by **176** and 4-(trifluoromethyl)benzoic acid (equation 22)

R^1	R^2	*Yield (%)*	*ee (%)*	*References*
H	Ph	98	95	121
H	C_6H_4-4-OMe	98	93	121
H	C_6H_4-3-Br	55	88	121
H	C_6H_4-4-Br	92	92	121
H	2-Furyl	96	92	121
Me	Ph	95	83	121



(22)

The reaction proceeds via a chiral dienamine intermediate **178**, which is generated from the catalyst **176** and cyclohexenones (Scheme 47).[121] A nitroalkene is activated by the pyridinium proton of dienamine intermediate **178** to approach the *Si* face of **178**. The fact that seawater or brine significantly enhances the catalytic performance of the Diels–Alder reaction suggests that they play other roles in the process besides the salt effect, which may stabilize transition state **179** through a hydrogen-bonding interaction with 4-$CF_3C_6H_4CO_2H$ and favor the hydrolysis step to close the catalytic cycle. Interestingly, the corresponding Michael adducts of cyclohexenones with nitroalkenes are not found during the transformation, which suggests that the cyclization proceeds via the one-step concerted addition pathway rather than a sequential Michael/Michael mechanism in the present catalytic system.



Scheme 47 Catalytic cycle of Diels–Alder reaction of cyclohexenones with nitroalkenes catalyzed by **176**.

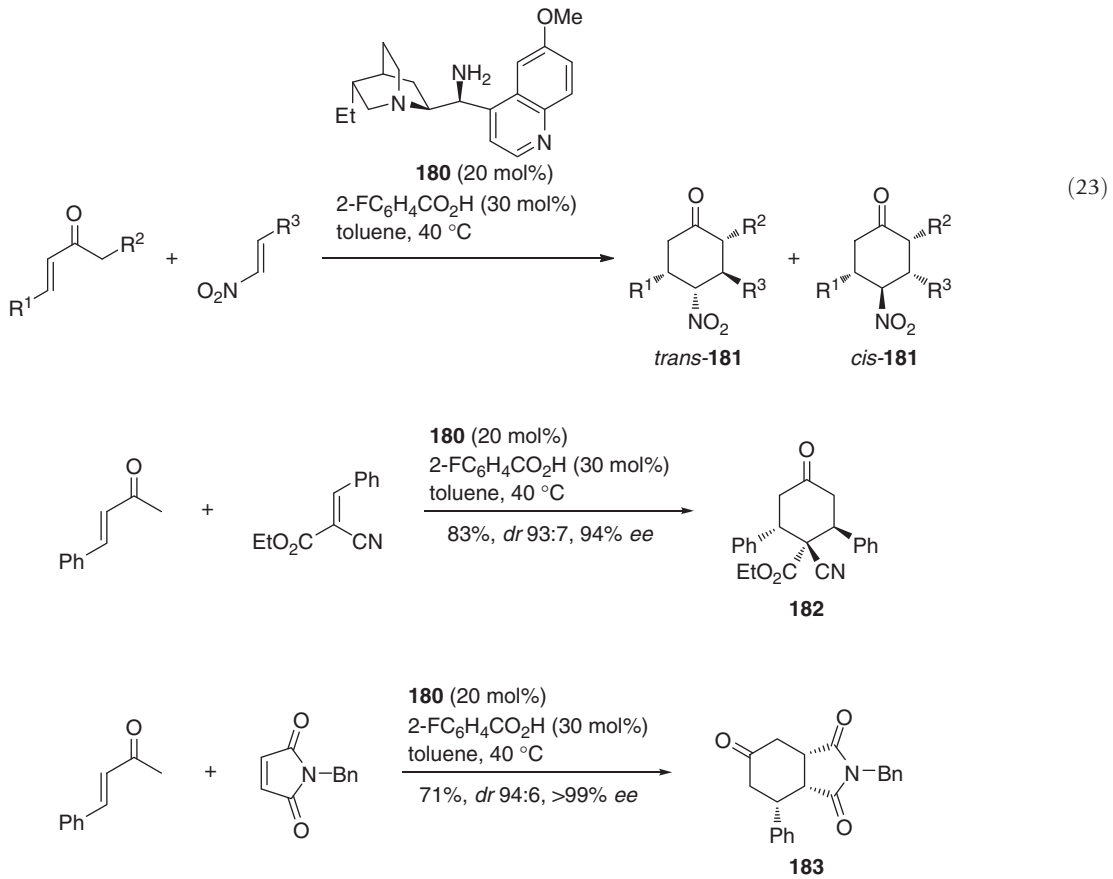
Although chiral secondary amine catalysis has been shown to be efficient in promoting the stereoselective Diels–Alder reactions of cyclic α,β-unsaturated carbonyl compounds via *in situ* dienamine activation, the reaction proceeds with essentially no enantioselectivity. However, a chiral primary amine **180** (20 mol%) catalyzes the formal Diels–Alder reaction of acyclic α,β-unsaturated ketones with nitroalkenes in the presence of 4-$FC_6H_4CO_2H$ (30 mol%) in toluene (equation 23, Table 35).[122] The reaction preferentially gives *endo* products *trans*-**181** with high enantioselectivities. The nature of the acidic cocatalyst strongly influences both the reactivity and the stereochemical outcome of the reaction. For example, the use of salicylic acid (30 mol%) as a cocatalyst improves the diastereoselectivity and the reaction rate, albeit with slightly lower enantioselectivity. The primary amine-catalyzed reaction is proposed to proceed via a stepwise double-Michael sequence. The formal Diels–Alder reaction of acyclic

Table 35 Formal Diels–Alder reaction of acyclic α,β-unsaturated ketones with nitroalkenes catalyzed by chiral primary amine **180** (equation 23)

R^1	R^2	R^3	*Yield (%)*	*Trans/cis*	*ee (%)*	*References*
Ph	H	Ph	78	>95:5	96	122
Ph	H	2,6-$Cl_2C_6H_4$	85	93:7	95	122
4-ClC_6H_4	H	Ph	77[a]	67:33	94	122
4-ClC_6H_4[b]	H	Ph	40	>95:5	90	122
Thiophenyl	H	Ph	50[a]	75:25	96	122
Thiophenyl[b]	H	Ph	53	>95:5	88	122
Ph	Me	Ph	58	94:6	99	122
Thiophenyl	Me	Ph	65	93:7	99	122

[a]Yield refers to the sum of diastereomers.
[b]The reaction was conducted in the presence of salicylic acid (30 mol%) as a cocatalyst.

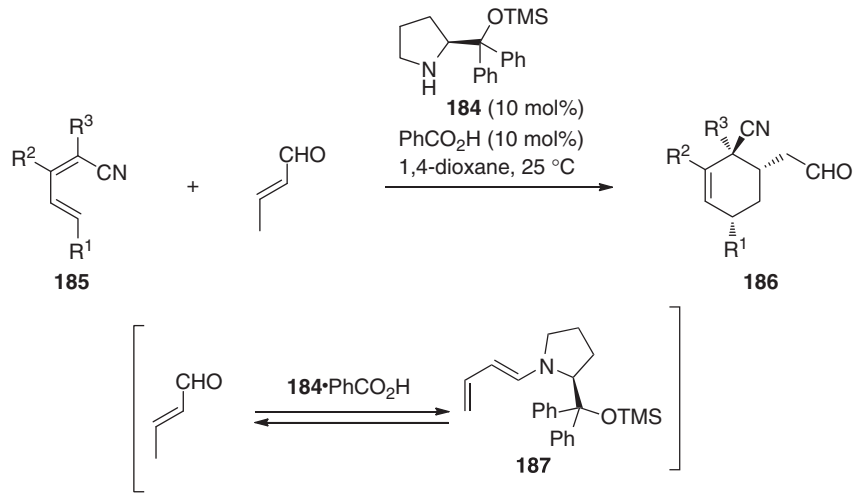
α,β-unsaturated ketones can also be performed with other electrophiles (Scheme 48). For example, the reaction with *trans*-α-cyanocinnamate gives the corresponding cyclohexanone **182** in 83% yield with 94% *ee*. The reaction of *N*-benzylmaleimide affords the bicyclic cyclohexanone **183** in 71% yield with >99% *ee*.



(23)

Scheme 48

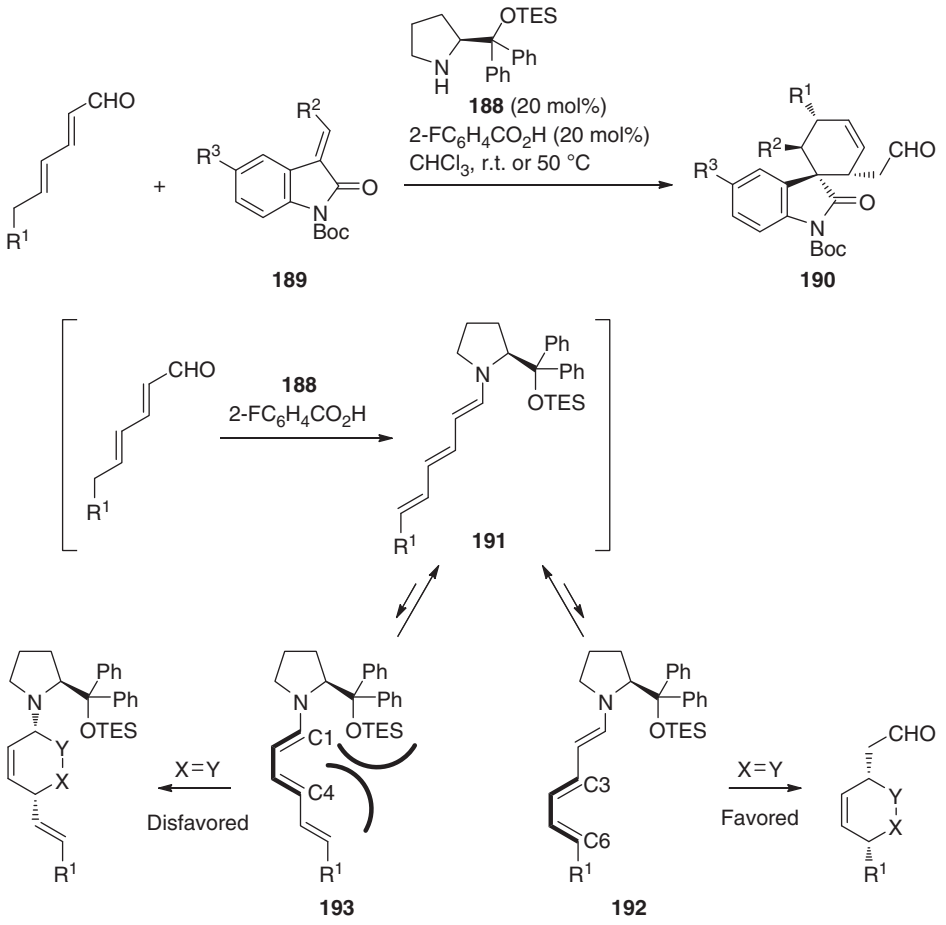
The inverse-electron-demand Diels–Alder reaction of α,β-alkenals with electron-deficient dienes is also promoted by the HOMO-raising activation using chiral amines. When the reaction of (*E*)-2-butenal with electron-deficient dienes **185** is conducted in the presence of the chiral secondary amine **184** (10 mol%) and benzoic acid (10 mol%), the corresponding *endo*-adducts **186**



Scheme 49 HOMO-raising activation of (*E*)-2-butenal using chiral amine **184**.

Table 36 Inverse-electron-demand Diels–Alder reaction with electron-deficient dienes **185** (Scheme 49)

R^1	R^2	R^3	Yield (%)	dr	ee (%)	References
Ph	Et	CN	75	89:11	98	123
2-ClC_6H_4	Et	CN	74	84:16	98	123
4-$(MeO)C_6H_4$	Et	CN	68	90:10	97	123
2-Furyl	Et	CN	75	90:10	99	123
Ph	Bu^i	CN	70	87:13	99	123
Ph	H	CO_2Et	44	94:6	99	123
Me	H	CO_2Et	45	92:8	99	123



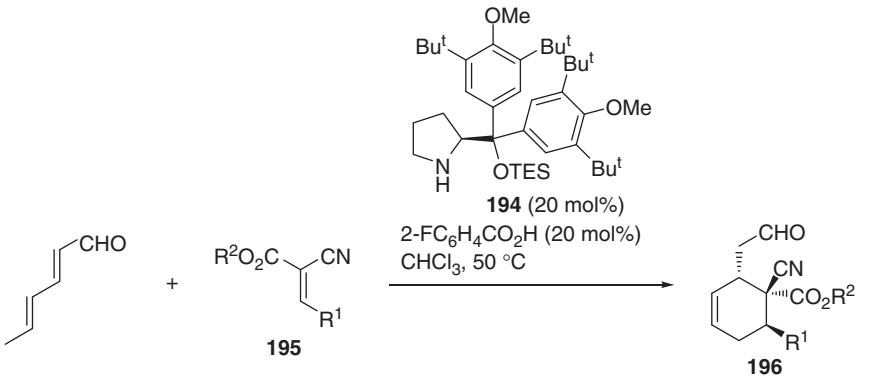
Scheme 50 Inverse-electron-demand Diels–Alder reaction of α,β,γ,δ-dienals based on HOMO-raising activation.

are obtained with high diastereo- and enantioselectivity (Scheme 49, Table 36).[123] Chiral amine **184** activates (*E*)-2-butenal with the aid of benzoic acid through the formation of chiral dienamine **187** (HOMO-raising activation).

The inverse-electron-demand Diels–Alder reaction of α,β,γ,δ-dienals with 3-olefinic oxindoles **189** is catalyzed by chiral secondary amine **188** (20 mol%) and 2-fluorobenzoic acid (20 mol%) to give spirocyclic indoles **190** with high enantioselectivity (Scheme 50, Table 37).[124] It has been shown that the merger of α,β,γ,δ-dienals, **188** and 2-fluorobenzoic acid generates trienamines **191** as active intermediates. In the HOMO-raising activation of **191**, both C3–C6 of **192** and C1–C4 of **193** may act as a diene. However, a computational study suggested that the bond-rotation barrier for the formation of **192** is 1.8 kcal mol^{-1} lower than that of **193**. In addition, the location of the energetically important frontier molecular orbital points to **192** as more reactive intermediate than **193**: the HOMO of **192** is 2.17 eV higher in energy than that of **193**, and the LUMO of **192** is 4.41 eV lower in energy than that of **193**. Thus, both the rotation barrier and the energy of the orbitals suggest that **192** should be the more reactive intermediate for the Diels–Alder reaction with electron-deficient alkenes.

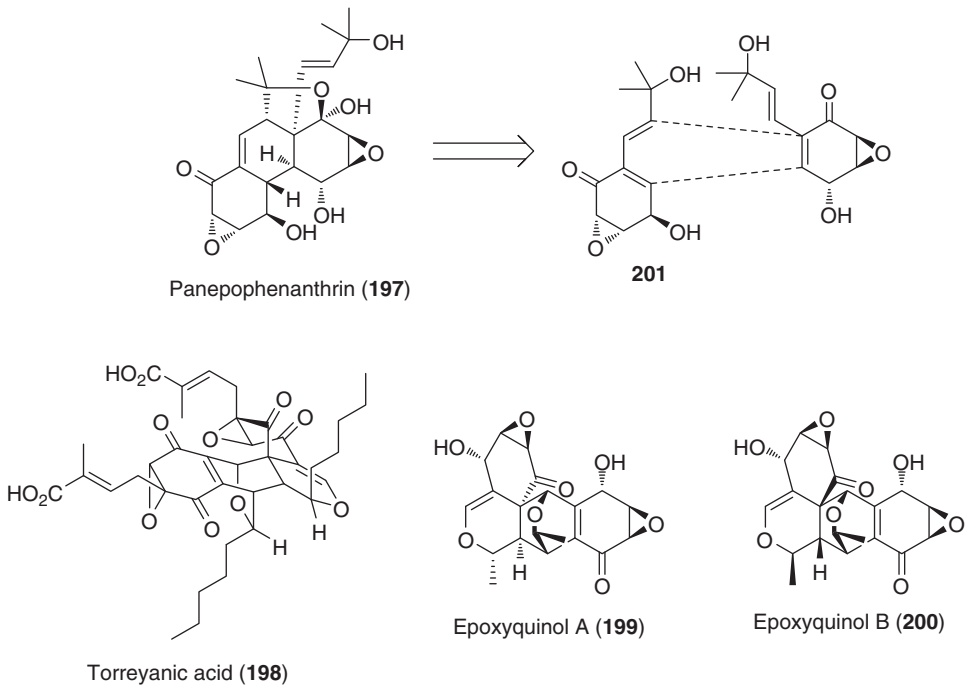
Table 37 Diels–Alder reaction with 3-olefinic oxindoles **189** (Scheme 50)

R^1	R^2	R^3	*Yield (%)*	*dr*	*ee (%)*	*References*
H	CO_2Bu^t	H	98	–	98	123
H	3-Pyridyl	H	96	85:15	97	123
H	Ph	H	67	92:8	97	123
H	Et	H	70	88:12	98	123
H	CO_2Bu^t	OMe	93	–	98	123
Me	COPh	H	94	79:21	94	123
Bu	COPh	H	90	91:9	96	123

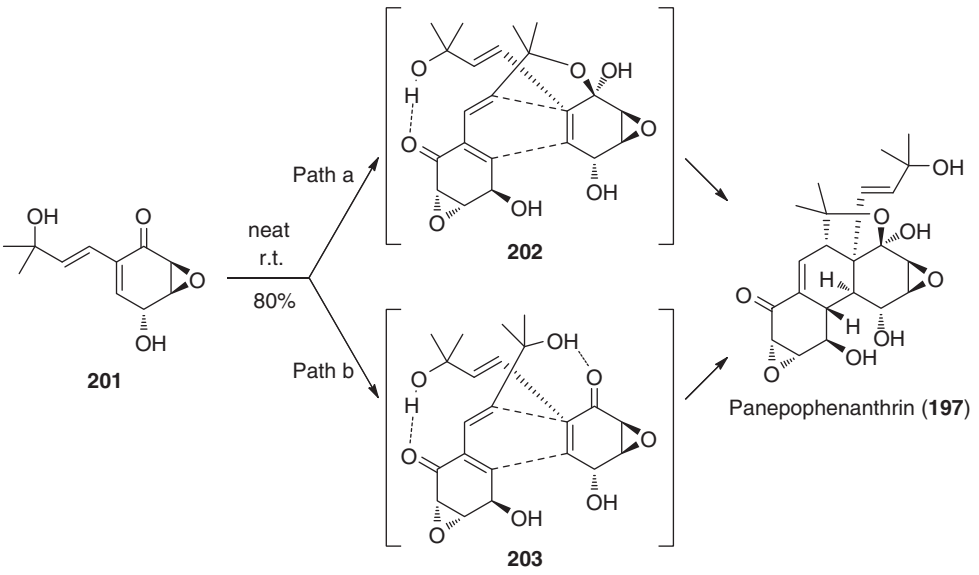


R^1	R^2	Yield	*dr*	*ee*
Ph	Bn	97%	78:22	88%
Ph	Bu^t	71%	90:10	89%
Pr	Bu^t	72%	82:18	86%

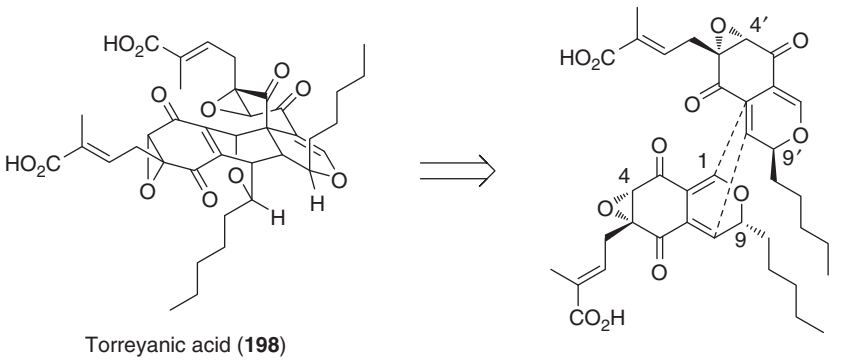
Scheme 51 Trienamine-Diels–Alder reaction with electron-deficient alkenes **195**.



Scheme 52 Dimeric epoxyquinoid natural products.



Scheme 53 Biomimetic Diels–Alder dimerization of epoxyquinol monomer **201**.



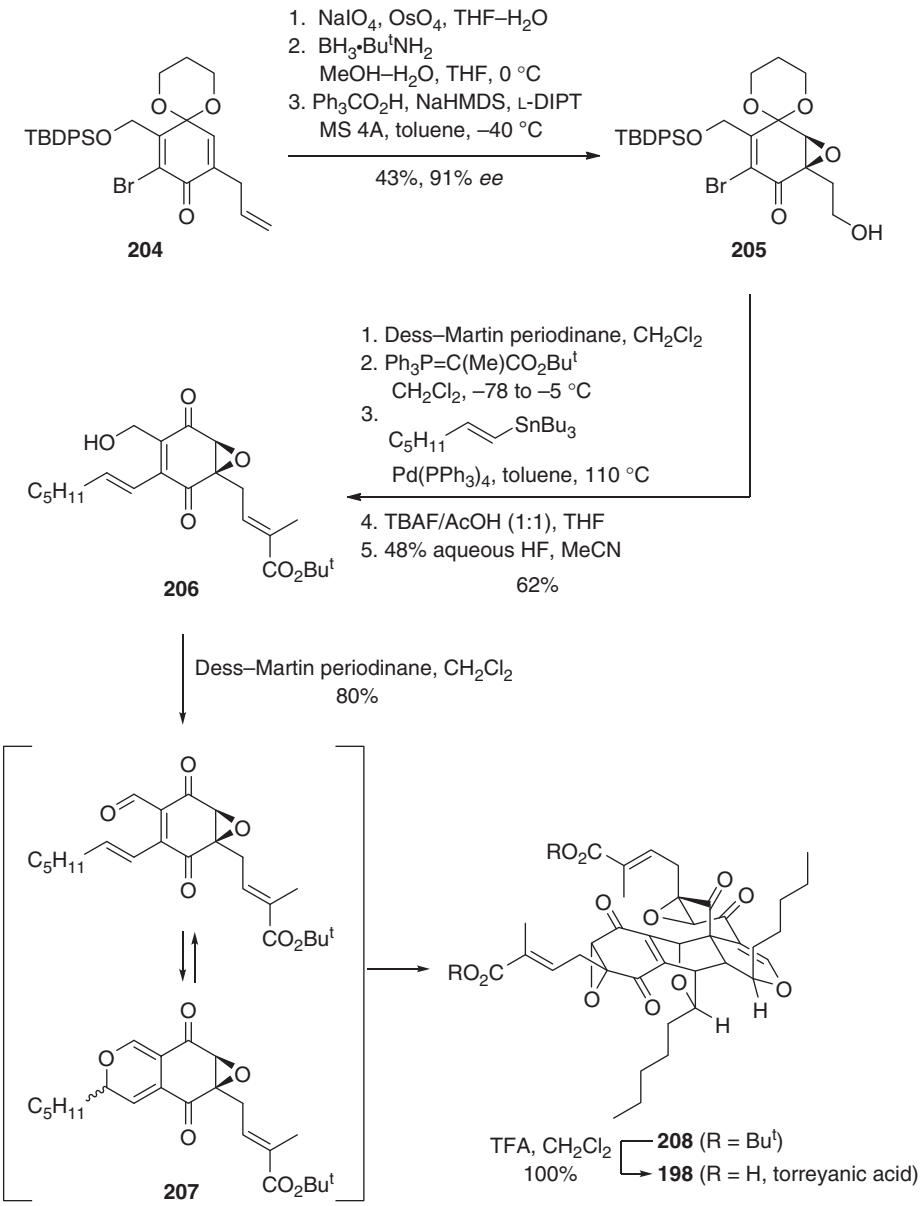
Scheme 54 Torreyanic acid (**198**), a dimeric quinone epoxide.

The trienamine-Diels–Alder reaction can also be used with electron-deficient alkenes **195** (Scheme 51).[124] The sterically more-demanding secondary amine **194** catalyzes the reaction to give the corresponding *endo*-adducts **196** with high diastereo- and enantioselectivity.

5.09.6 Biomimetic Synthesis of Natural Compounds Using Intermolecular Diels–Alder Reactions

Biomimetic chemistry has become an integral part of organic chemistry, especially in the field of natural compound synthesis.[125,126] In many cases, a biomimetic approach can give the stereoselective production of highly complex carbon skeletons from rather simple precursors. This section focuses on the biomimetic synthesis of bioactive natural compounds using intermolecular Diels–Alder reactions.

Epoxyquinones are one of the main classes of polyketide-based metabolites and originate from a variety of natural sources. For example, panepophenanthrin (**197**, Scheme 52) is an inhibitor of the ubiquitin-activating enzyme (E1), which was isolated from the fermented broth of the mushroom strain *Panus rudis* Fr. IFO8994.[127] This molecule falls into a general class of epoxyquinoid natural products produced by Diels–Alder-type dimerization, along with torreyanic acid (**198**)[128] and epoxyquinols A (**199**)[129] and B (**200**).[130] The biomimetic Diels–Alder dimerization of epoxyquinol monomer **201** proceeds under solvent-free conditions at 25 °C to give panepophenanthrin (**197**) in 80% yield (Scheme 53).[131] Two plausible mechanistic pathways can be proposed for the Diels–Alder reaction. In the first pathway (path a), the tertiary hydroxyl group of one monomer adds to the carbonyl group of the second to form a hemiacetal intermediate **202**. An intramolecular, inverse-electron-demand Diels–Alder reaction gives the dimeric structure. In the alternative pathway (path b), a normal 'pseudo-transannular' Diels–Alder reaction takes place through a transition state **203** involving hydrogen-bonding interactions between the monomers.

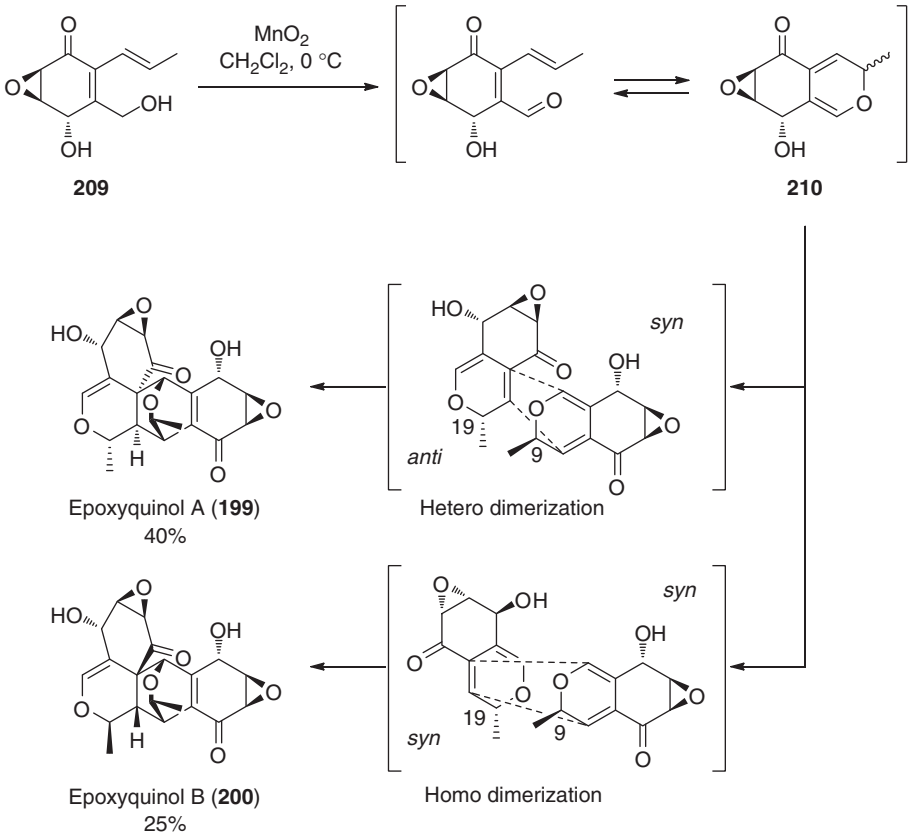


Scheme 55 Biomimetic total synthesis of torreyanic acid (**198**).

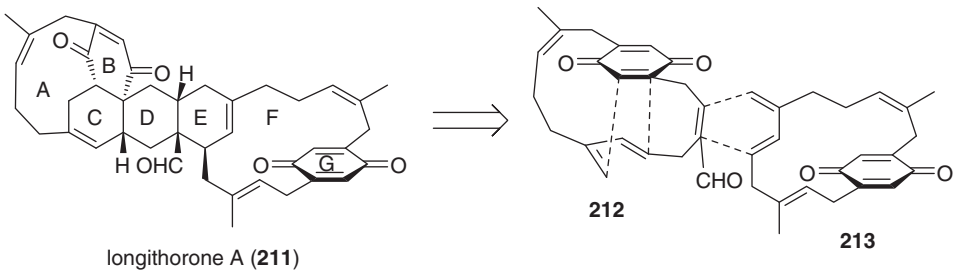
Torreyanic acid (**198**) is a dimeric quinone epoxide that is produced by the endophytic fungus *Pestalotiopsis microspora* associated with the Florida torreya tree.[128] The biosynthesis of torreyanic acid has been proposed to involve the Diels–Alder dimerization of 2*H*-pyrane monomers that are epimeric at C9 (C9′) (Scheme 54). In this *endo*-Diels–Alder reaction, the two pentyl side chains are oriented away from one another in the transition state.

Based on the proposed biosynthetic pathway, torreyanic acid (**198**) was synthesized through the biomimetic Diels–Alder dimerization of diastereomeric 2*H*-pyran monomers **207** (Scheme 55).[132] Oxidative cleavage of monosubstituted alkene of **204** followed by asymmetric nucleophilic epoxidation gives epoxide **205** with high enantioselectivity (91% *ee*). Subsequent transformations of **205**, involving a Wittig and a Stille reaction, give quinone epoxide **206**, which is a precursor of **207**. Dess–Martin oxidation of **206** initiates the tandem oxidation/electrocyclization/Diels–Alder dimerization process to give adduct **208** as a single diastereomer in 80% yield. The stereochemistry is consistent with the biosynthetic pathway. Treatment of **208** with TFA effects the removal of the *tert*-butyl ester to give torreyanic acid (**198**).

The same strategy has been applied to the biomimetic synthesis of epoxyquinols A (**199**) and B (**200**) (Scheme 56).[133,134] The oxidation of quinone epoxide **209** with excess MnO_2 in CH_2Cl_2 gives 2*H*-pyranes **210** as a diastereomeric mixture. The hetero-dimerization of **210** through the *endo*-Diels–Alder reaction gives epoxyquinol A (**199**) in 40% yield. In contrast to the biomimetic synthesis of torreyanic acid (**197**), the homo-dimerization of **210** also proceeds to give epoxyquinol B (**200**) through the



Scheme 56 Biomimetic synthesis of epoxyquinols A (**203**) and B (**204**).

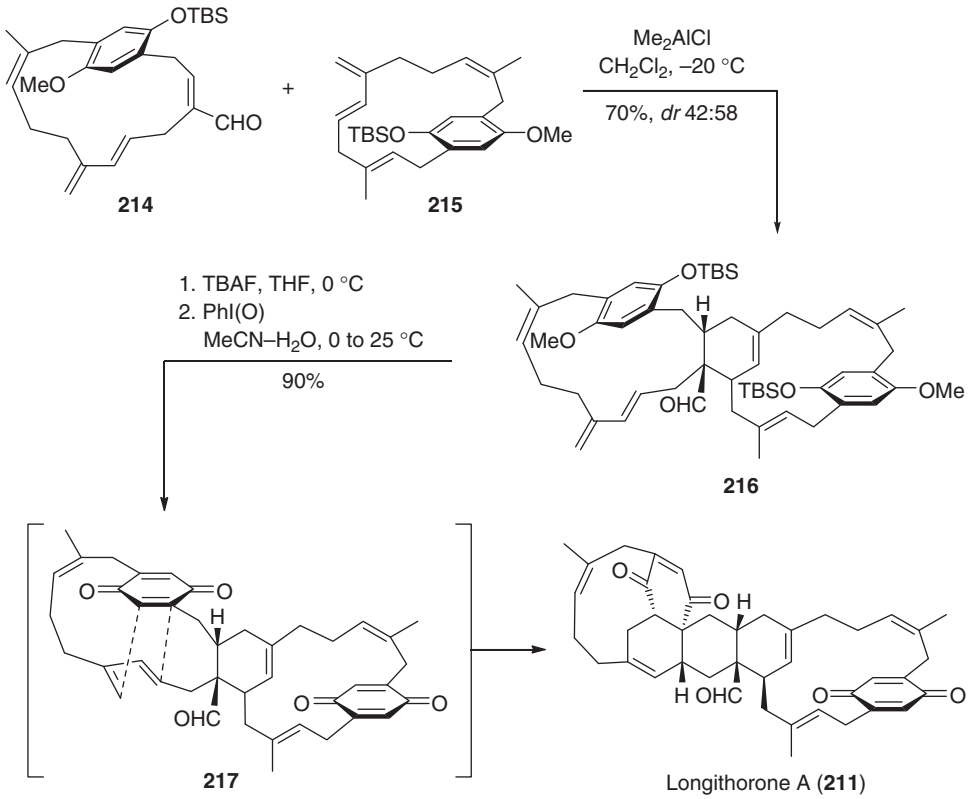


Scheme 57 Proposed biosynthesis of longithorone A (**211**).

exo-Diels–Alder reaction. In the case of the biomimetic dimerization of **201**, steric hindrance by the unsaturated ester moiety may prevent homo-dimerization.

Longithorone A (**211**) is a cytotoxic compound that was isolated from freshly thawed specimens of *Aplydium longithorax* (Monniot) collected in Palau (Scheme 57).[135] This compound has an unusual heptacyclic structure, the biosynthesis of which may involve an intermolecular Diels–Alder reaction between [12]-paracyclophanes **212** and **213** to form the E ring, and a transannular Diels–Alder reaction of **212** to form the A, C, and D rings.

Based on a proposed biosynthesis, longithorone A (**211**) can be synthesized from [12]-paracyclophanes **214** and **215**, which are single atropisomers (Scheme 58).[136,137] An intermolecular Diels–Alder reaction between **214** and **215** proceeds with the aid of Me_2AlCl at -20 °C to give cyclohexene **216** in 70% yield as a 42:58 diastereomeric mixture. Although the present cycloaddition is completely *endo*-selective, the reaction shows only moderate facial selectivity. The lack of substrate-based diastereoselectivity in the cycloaddition suggests that this step is promoted by enzymatic catalysis. Deprotection of **216** followed by oxidation generates bisquinone **217**, which undergoes a transannular Diels–Alder reaction at room temperature to give longithorone A (**211**) in 90% yield.



Scheme 58 Biomimetic total synthesis of longithorone A (**211**).

5.09.7 Conclusion and Outlook

The ultimate goal of organic synthesis is a stereoselective assembly of a given chiral organic compound from readily available starting achiral materials and reagents in the most efficient way. In modern multistep organic synthesis, the word 'efficient' should include high yield and selectivity of each step as well as the reduction of the total number of steps and the improvement of the overall atom economy. In this context, the enantioselective Diels–Alder reaction has been one of the most powerful tools for short-step synthesis of bioactive natural products as described in this chapter. The stereoselective construction of multiple carbon –carbon bonds in a single operation is one of the ideal methods. However, there still is much more to study with respect of the extension of substrate generality, the reagent-control of diastereoselectivity, the decrease of catalyst loading and the determination of mechanistic details. The extension of substrate generality and the reagent-control of diastereoselectivity should allow us to make highly efficient synthetic strategies. The decrease of catalyst loading improves the atom economy. The determination of mechanistic details would result in the development of new catalytic systems that can promote the reaction of less active substrates. Further development of stereoselective Diels–Alder reactions can lead us to achieve 'efficient' synthesis of complex bioactive natural products.

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5.10 Hetero-Diels–Alder Reactions

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Glossary

CH–π Interaction CH–π Interaction is a weak, attractive, noncovalent interaction between CH groups and Q-systems. For example, intramolecular CH–π interaction is used to stabilize the conformation of some proteins.

endo*, *exo The Diels–Alder reaction of cyclopentadiene with 2-propenal can produce two possible diastereomers: *endo*- and *exo*-adducts. The prefix *endo* refers to the isomer with the substituent located closest, or *syn*, to the longest bridge. The prefix *exo* is reserved for the isomer with the substituent located farthest, or *anti*, from the longest bridge. Here, 'longest' and 'shortest' refer to the number of atoms comprising the bridge. *Endo* and *exo* are also used to describe the stereochemistry of transition-state assemblies that lead to the *endo*- and *exo*-adducts, respectively.

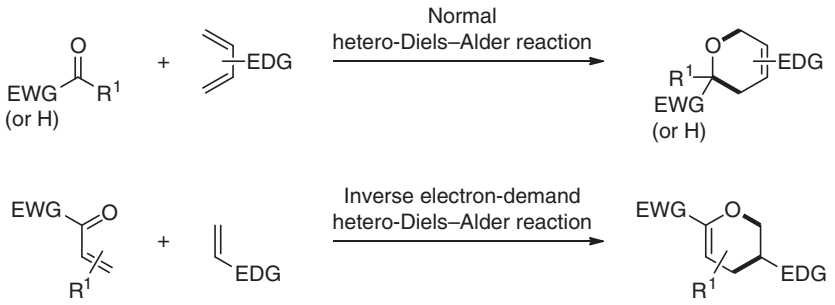
π–π Interaction π–π Interaction refers to attractive, noncovalent interactions between π-systems. In general, electron-rich π-systems (π-electron donor) interact with electron-deficient π-systems (π-electron acceptor) in a parallel orientation.

s-*cis*, s-*trans* The spatial arrangement of two conjugated double bonds about an intervening single bond is described as s-*cis* if they are *syn*periplanar and s-*trans* if they are *anti*periplanar. This term should not be applied to other systems such as *N*-alkyl amides (use *E*/*Z* or *sp*/*ap*).

5.10.1 Introduction

The hetero-Diels–Alder reaction is an important variant of the Diels–Alder reaction in which either the diene or the dienophile contains a heteroatom, most often nitrogen or oxygen. The asymmetric hetero-Diels–Alder reaction of carbonyl compounds is among the most powerful methods for the construction of optically active heterocycles, and has been extensively used in the synthesis of bioactive natural and synthetic compounds.[1–8] The two concepts that underlie the hetero-Diels–Alder reactions of carbonyl compounds are illustrated in **Scheme 1**. In the normal electron-demand reaction, a carbonyl compound reacts with an electron-rich diene. To promote this reaction, an acid catalyst activates the carbonyl compound by lowering its lowest unoccupied molecular orbital (LUMO) energy. In the inverse electron-demand reaction, however, an α,β-unsaturated carbonyl compound reacts with an electron-rich dienophile. This type of reaction can also be promoted by using acid catalysts to lower the LUMO energy of the α,β-unsaturated carbonyl compound. Therefore, the introduction of additional electron-withdrawing groups (EWG) should provide additional activation for both types of hetero-Diels–Alder reaction.

The hetero-Diels–Alder reaction of imines or related compounds (the aza-Diels–Alder reaction) is also a useful method for constructing nitrogen-containing cyclic compounds.[4,6,9–12] Due to the fundamental importance of nitrogen-containing natural compounds, much attention has been given to the development of asymmetric aza-Diels–Alder reactions. In addition to carbonyl



EDG, electron-donating group; EWG, electron-withdrawing group

Scheme 1 Hetero-Diels–Alder reactions of carbonyl compounds.

compounds and imines, various heterodienes and heterodienophiles, which include nitroso compounds, *ortho*-benzoquinones, and so on, also undergo diastereo- and enantioselective Diels–Alder reactions. This chapter focuses on recent advances in diastereo- and enantioselective hetero-Diels–Alder reactions using chiral Lewis acid (LA) catalysts or chiral organocatalysts.

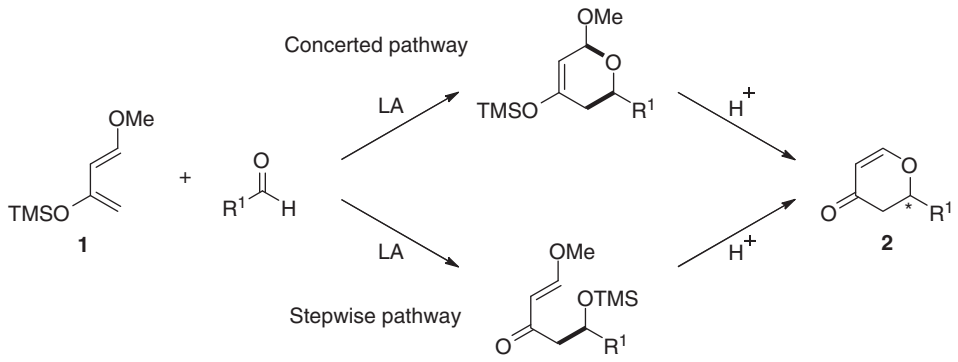
5.10.2 Oxo-Diels–Alder Reactions

5.10.2.1 Reactions of Carbonyl Dienophiles

5.10.2.1.1 Chiral LA catalysts

As described in the Introduction, the normal electron-demand oxo-Diels–Alder reaction is promoted by an LA catalyst through the activation of the carbonyl dienophiles. Several chiral LA catalysts, including compounds of boron(III), chromium(III), titanium(IV), zirconium(IV), rhodium(II or III), or indium(III), have been used in enantioselective hetero-Diels–Alder reactions of carbonyl compounds.

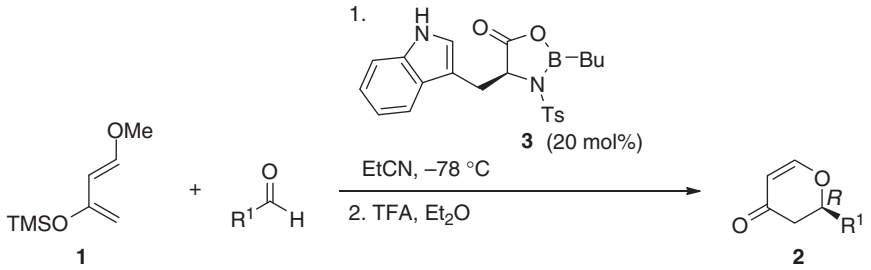
Electron-rich 1-methoxy-[(trimethylsilyl)oxy]-1,3-butadiene (**1**, Danishefsky's diene) is a highly reactive diene for the hetero-Diels–Alder reaction that can react with unactivated aldehydes. Two hetero-substituents of **1** increase the highest occupied molecular orbital (HOMO) energy, which results in a reduction of the energy-difference between the HOMO of **1** and the LUMO of the dienophile. With the aid of LA catalysis, the hetero-Diels–Alder reaction of **1** with aldehydes provides useful access to 2,3-dihydro-4*H*-pyran-4-one derivatives **2**, a class of compounds with extensive utility in organic synthesis. For the hetero-Diels–Alder reaction of **1** with aldehydes, two mechanistic pathways have been considered (Scheme 2): a concerted [4 + 2] cycloaddition pathway and a stepwise pathway (Mukaiyama aldol and cyclization).[13]



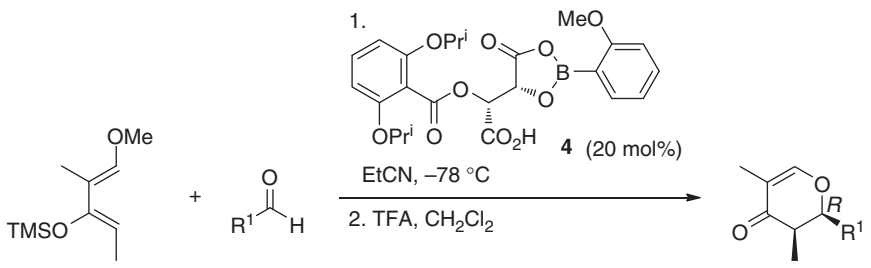
Scheme 2 Two mechanistic pathways for the oxo-Diels–Alder reaction.

Chiral boronic acid derivatives **3** and **4** are efficient catalysts not only for the carbo-Diels–Alder reaction but also for the oxo-Diels–Alder reaction of Danishefsky-type dienes (Scheme 3). Chiral oxazaborolidine **3** derived from *N*-tosyl-L-tryptophan and butylboronic acid catalyzes the Mukaiyama aldol reaction of **1** with aldehydes.[14] Subsequent acid treatment of the Mukaiyama aldol products gives the formal hetero-Diels–Alder adducts **2** with good enantioselectivities. The chiral acyloxyborane (CAB) catalyst **4** derived from *O*-[2,6-di(isopropoxy)benzoyl]-L-tartaric acid and 2-methoxyphenylboronic acid also catalyzes the reaction of Danishefsky-type diene **5** with aldehydes to give the hetero-Diels–Alder adducts **6** with high enantioselectivities.[15]

Chiral chromium(III) complexes, such as **7** (X = BF_4, Cl) and **8** (X = Cl, SbF_6) (Figure 1), are highly efficient catalysts for the hetero-Diels–Alder reactions of Danishefsky-type dienes **9** with unactivated aldehydes.[16–18] The chiral salen–chromium(III)



R^1	Yield	*ee*
Ph	100%	82%
$^cC_6H_{11}$	80%	76%
$(CH_2)_2Ph$	57%	69%



R^1	Yield	*ee*
Ph	95%	97%
(*E*)-CH=CHPh	86%	97%
$CH=CHCH_3$	79%	92%

Scheme 3 Hetero-Diels–Alder reaction of Danishefsky-type dienes **1** and **5** catalyzed by chiral boronic acid derivatives **3** and **4**.

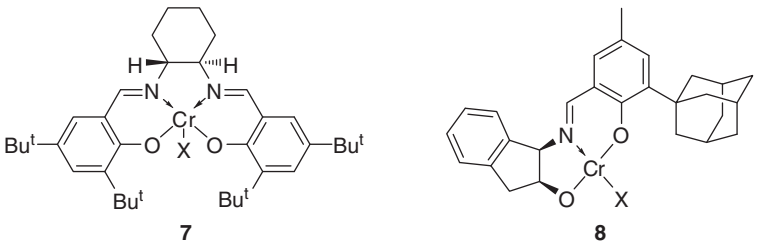
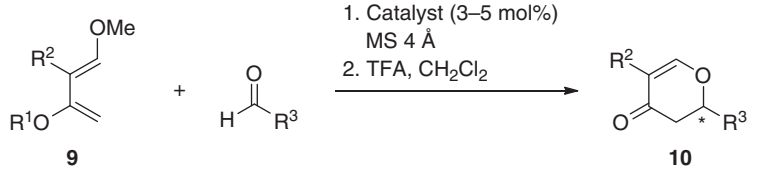


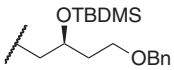
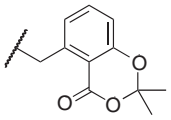
Figure 1 Chiral chromium(III) complexes **7** and **8**.

complex **7** (X = BF_4) catalyzes the hetero-Diels–Alder reaction of **1** with various aldehydes to give the corresponding cyclohexenones with high enantioselectivity (equation 1, Table 1).[16–22] The addition of oven-dried powdered molecular sieves (MSs) 4 Å to the reactions increases the yield and enantioselectivity. The present reaction is proposed to proceed via a concerted [4 + 2] mechanism. The cycloadducts shown in Table 1 are key intermediates for the total synthesis of the polyene macrolide RK-397,[20] the marine ladder toxin gambierol,[21] and the macrocyclic salicylate apicularen A.[22]

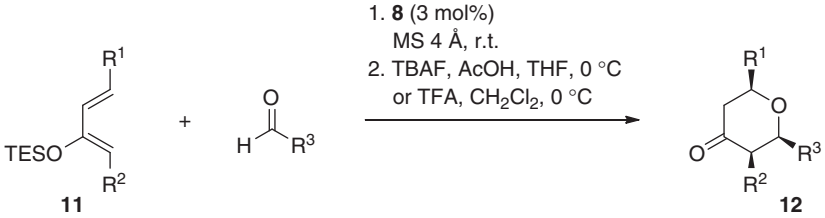


(1)

Table 1 Hetero-Diels–Alder reaction of Danishefsky-type diene **9** catalyzed by chromium(III) complexes **7** and **8** (equation 1)

R^1	R^2	R^3	*Catalyst*	*Solvent*	*Yield (%)*	ee *(%)*	*References*
TMS	H	Ph	**7** (X = BF_4)	Bu^tOMe	85	87 (*R*)	16
TMS	H	$^cC_6H_{11}$	**7** (X = BF_4)	Bu^tOMe	71	93 (*R*)	16
TMS	H	$^nC_5H_{11}$	**7** (X = BF_4)	Bu^tOMe	86	83 (*S*)	16
TMS	H	$(CH_2)_3CO_2Me$	*ent*-**7** (X = BF_4)	Bu^tOMe	71	84 (*R*)	19
TMS	H		**7** (X = Cl)	Bu^tOMe	89	94 (*S*)	20
TMS	Me	$(CH_2)_3OBn$	**8** (X = Cl)	–	90	94 (*S*)	21
TBDMS	H		**8** (X = SbF_6)	Acetone	89	94 (*S*)	22

The chiral tridentate Schiff base chromium(III) complexes **8** are the most efficient catalysts for the reactions of less nucleophilic dienes bearing fewer than two oxygen substituents with unactivated aldehydes.[17,18] This class of asymmetric hetero-Diels–Alder reaction provides a direct route to enantiomerically enriched dihydropyran derivatives from simple achiral starting materials. In the presence of complex **8** (X = Cl, SbF_6) (3 mol%), the reaction of a 2-siloxy-1,3-diene **11** with a nonactivated aldehyde gives the corresponding 2,3-*cis*-adduct **12** with excellent diastereo- and enantioselectivity (equation 2, **Table 2**).[17] The reaction is performed at room temperature and requires the presence of MS for optimal results. Whereas the use of acetone as a solvent is generally beneficial, and is critical in the case of aromatic aldehydes, the use of solvent-free conditions is satisfactory for some substrates.



(2)

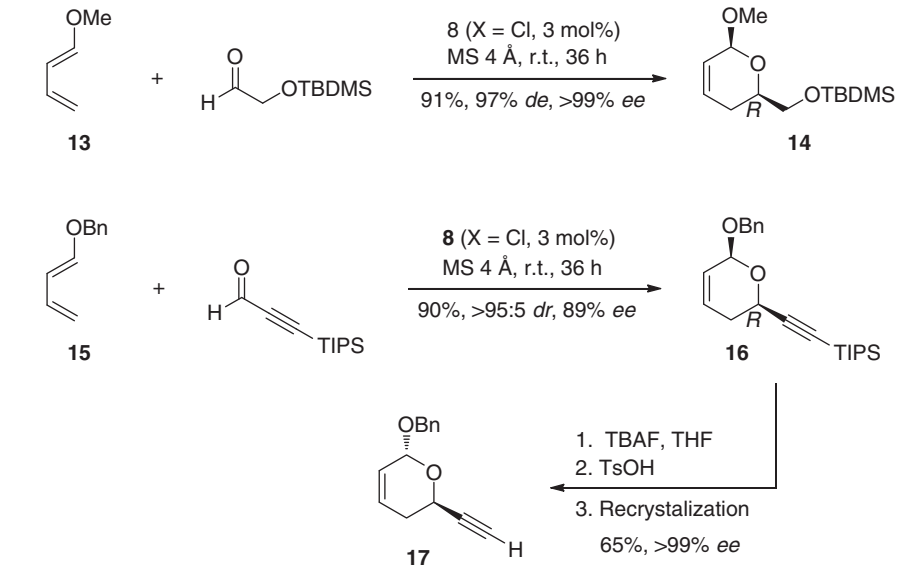
Table 2 Hetero-Diels–Alder reaction of 2-siloxybutadienes **9** catalyzed by chiral chromium(III) complex **8** (equation 2)

R^1	R^2	R^3	*X*	*Solvent*	*Yield (%)*	ee *(%)*	*References*
Me	Me	$CH_2OTBDMS$	Cl	Acetone	90	99	17
Me	H	$CH_2OTBDMS$	Cl	Acetone	78	98	17
H	Me	$CH_2OTBDMS$	Cl	–	50	91	17
Me	Me	Ph	SbF_6	Acetone	72	90	17
Me	Me	$(CH_2)_4CH=CH_2$	SbF_6	–	78	98	17
Me	Me	$(CH_2)_2NHBoc$	SbF_6	Acetone	28	96	17

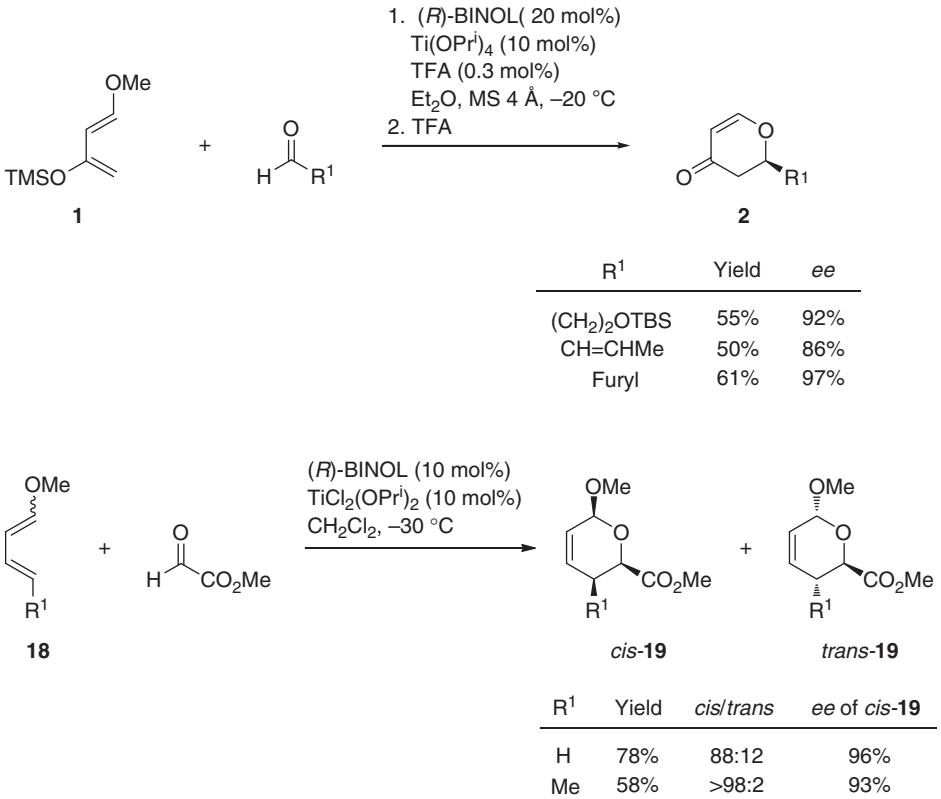
The chromium(III) complex **8** also catalyzes the hetero-Diels–Alder reaction of 1-alkoxydienes **13** and **15** with aldehydes to give the corresponding cyclic acetals **14** and **16** with excellent enantioselectivities; the products can be subjected to hydrolysis and oxidation to afford the corresponding lactones (**Scheme 4**).[17] This method provides highly efficient access to several interesting natural product structures; for example, desilylation of adduct **16** followed by acidic workup and recrystallization gives **17**, a key intermediate in a total synthesis of fostriecin (CI-920), with >99% *ee*.[23]

A titanium(IV) complex of chiral 1,1′-bi-2-naphthol (BINOL) is an efficient catalyst for the hetero-Diels–Alder reaction of carbonyl compounds. The catalytic activity of the Ti(IV)–BINOL complex closely depends on the preparation method. For example, a Ti(IV)–BINOL complex prepared from $Ti(OPr^i)_4$ (10 mol%) and (*R*)-BINOL (20 mol%) in the presence of trifluoroacetic acid (TFA) (0.3 mol%) and MS 4 Å catalyzes the reaction of Danishefsky's diene **1** with unactivated aldehydes to give the adducts **2** with high enantioselectivities (**Scheme 5**).[13] In contrast, a complex prepared from $Ti(OPr^i)_4$ (10 mol%) and (*R*)-BINOL (10 mol%) in the presence of MS 4 Å gives lower enantioselectivity.

A Ti(IV)–BINOL complex prepared from $TiCl_2(OPr^i)_2$ (10 mol%) and (*R*)-BINOL (10 mol%) in the presence of MS 4 Å catalyzes the hetero-Diels–Alder reaction of 1-methoxybutadienes **18** with methyl glyoxylate to give the corresponding adducts *cis*-**19** with high diastereo- and enantioselectivities (**Scheme 5**).[24] Use of the Ti(IV)–BINOL complex under MS-free conditions improves the *cis*-selectivity and enantioselectivity.

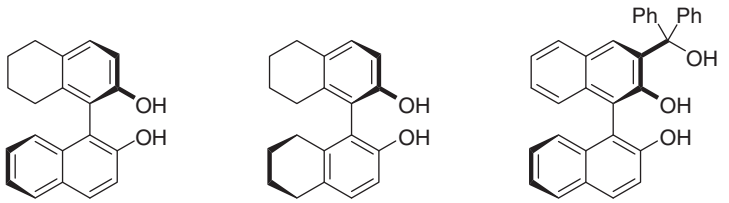


Scheme 4 Hetero-Diels–Alder reaction of 1-alkoxydienes **13** and **15**.



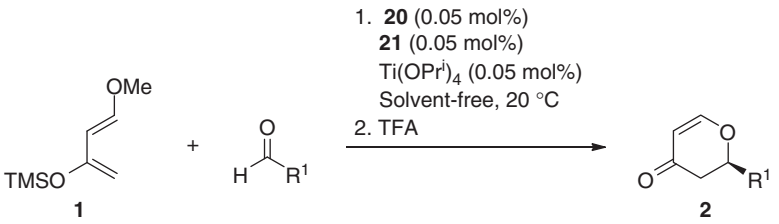
Scheme 5 Hetero-Diels–Alder reactions catalyzed by Ti(IV)–BINOL complexes.

Titanium(IV) complexes of the chiral BINOL derivatives **20**–**22** (Figure 2) are also efficient catalysts for the hetero-Diels–Alder reaction of Danishefsky-type dienes with aldehydes. For example, a chiral Ti(IV) complex prepared from $Ti(OPr^i)_4$, (*R*)-tetrahydro-BINOL **20**, and (*R*)-octahydro-BINOL **21** (1:1:1 ratio) shows high catalytic activity for the reaction of **1** under solvent-free conditions (equation 3, Table 3).[25,26] Catalyst loadings of only 0.1–0.05 mol% are sufficient for obtaining the corresponding adducts **2** in quantitative yields and with high enantioselectivities.



20 **21** **22**

Figure 2 Representative chiral BINOL derivatives **38**–**40** as ligands for Ti(IV) complexes.



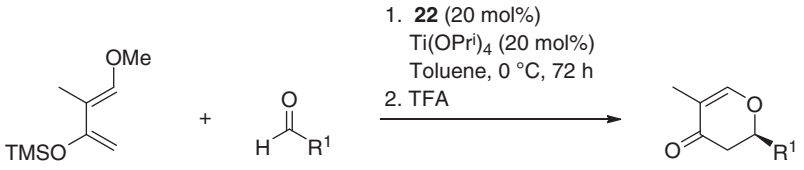
1 **2** (3)

Table 3 Hetero-Diels–Alder reaction of Danishefsky's diene **1** catalyzed by a chiral Ti(IV) complex of BINOL derivatives **20** and **21** (equation 3)

R^1	*Time (h)*	*Yield (%)*	ee *(%)*	*References*
Ph	24	82	99	25,26
C_6H_4–4-Cl	48	>99	99	25,26
C_6H_4–3-Br	48	98	98	25,26
C_6H_4–4-OMe	48	>99	98	25,26
C_6H_4–3-OMe	48	83	>99	25,26
C_6H_4–2-OMe	48	>99	95	25,26
2-Furyl[a]	96	>99	98	25,26
(*E*)-CH=CHPh	96	57	97	25,26
$(CH_2)_2$Ph	96	>99	98	25,26

[a]Catalyst loading is 0.01 mol%.

A 1:1 complex of Ti(IV) and the chiral triol **22** also promotes the hetero-Diels–Alder reaction of the Danishefsky-type diene **23** with aldehydes (Scheme 6).[27] The present reaction can be applied to a variety of aldehydes and the corresponding adducts **24** are obtained in high yields with high enantioselectivities. Triol **22** acts as a tridentate ligand for the titanium(IV) cation, and the 3-diphenylhydroxymethyl group of **22** is critical for increasing the catalytic activity. Since an unusual nonlinear effect is observed in this reaction, a variety of aggregated catalyst species may be involved in the catalytic system. In contrast to the reaction catalyzed by the Ti(IV)–BINOL complex, the present reaction is proposed to proceed via a concerted Diels–Alder pathway.

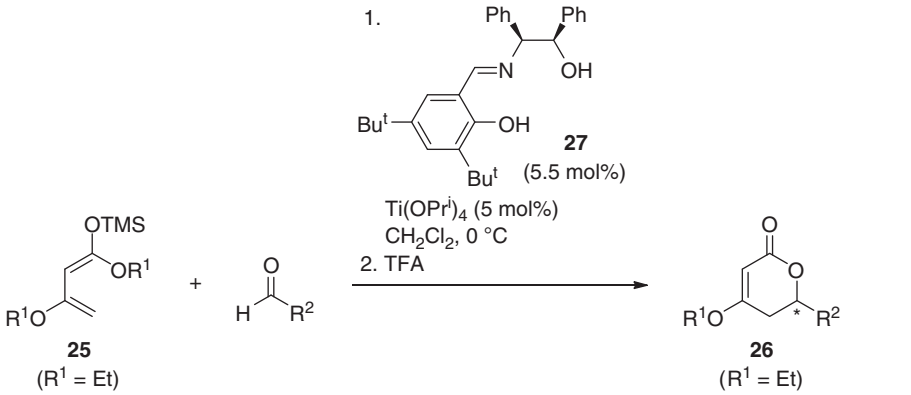


23 **24**

R^1	Yield	*ee*
Ph	98%	94%
C_6H_4-4-Cl	99%	98%
C_6H_4-4-Me	89%	93%
(*E*)-CH=CHMe	86%	91%
$^nC_6H_{13}$	92%	97%

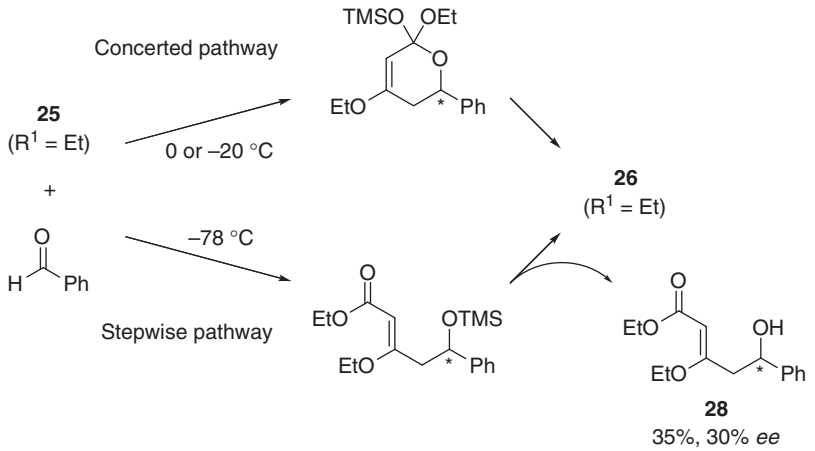
Scheme 6 Hetero-Diels–Alder reaction catalyzed by the Ti(IV) complex of chiral triol **22**.

Brassard's diene **25** is a highly useful substrate for the hetero-Diels–Alder reaction and provides a convenient access to δ-lactones **26**. A chiral titanium(IV) complex of the tridentate Schiff base ligand **27** catalyzes the hetero-Diels–Alder reaction of Brassard diene **25** (R^1 = Et) with aromatic aldehydes to give the corresponding δ-lactones **26** with high enantioselectivities (Scheme 7).[28,29] However, the reaction shows poor enantioselectivity for aliphatic aldehydes. In the present reaction, the temperature influences the reaction pathway (Scheme 8). When conducted at 0 or −20 °C, the reaction proceeds via the concerted pathway, and the silylated intermediate is hydrolyzed by purification through a silica gel column at the end of the reaction to give **26** without TFA treatment. However, when the reaction is conducted at −78 °C by the same procedure, the Mukaiyama aldol product **28** is obtained in 35% yield with 30% *ee*. The reaction mostly follows the Diels–Alder pathway at higher temperature (0 or −20 °C), but the Mukaiyama aldol pathway at lower temperature (−78 °C).



R^2	Yield	*ee*
Ph	71%	93%
C_6H_4-3-OMe	45%	96%
C_6H_4-4-Cl	87%	97%
2-naphthyl	61%	96%
Pr^i	48%	21%

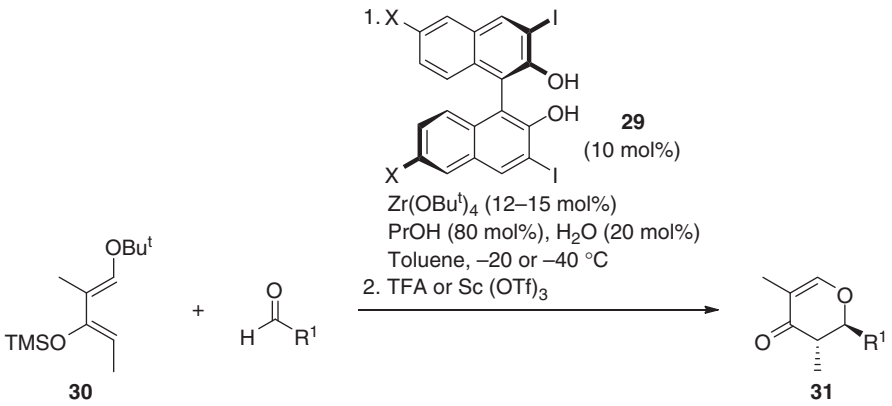
Scheme 7 Hetero-Diels–Alder reaction of Brassard's diene **25** (R^1 = Et) catalyzed by a Ti(IV) complex.



Scheme 8 Proposed mechanism for the hetero-Diels–Alder reaction of Brassard's diene **25** (R^1 = Et).

Chiral zirconium complexes, prepared from zirconium(IV) *tert*-butoxide and the (*R*)-3,3′-disubstituted binaphthol derivatives **29** (X = CF_2CF_3, I) in aqueous propan-1-ol, catalyze the hetero-Diels–Alder reaction of Danishefsky-type dienes with nonactivated aldehydes (equation 4, Table 4).[30] In contrast to the chromium(III)-complex-catalyzed reaction, the zirconium-complex-catalyzed reactions of Danishefsky-type dienes **30** give the corresponding 2,3-*trans*-adducts **31** with high diastereo- and enantioselectivity. The cycloadducts **31** can be used in syntheses of biologically important pyranone-containing natural products. The hetero-Diels–Alder reaction of the 4-oxygenated Danishefsky-type diene **32** is also promoted by the chiral zirconium(IV) complex to give the

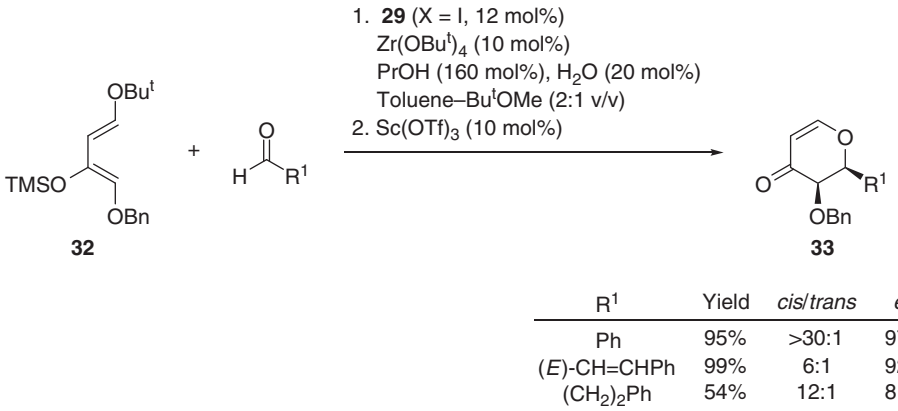
corresponding 3-oxygenated pyranone derivatives **33** with high enantioselectivity (Scheme 9).[30] Interestingly, the present reaction gives the 2,3-*cis* product **33** as the major diastereomer, whereas the reaction of **30** predominantly gives the 2,3-*trans* product **31**.



(4)

Table 4 Zirconium(IV) complex-catalyzed hetero-Diels–Alder reaction of Danishefsky-type diene **30** (equation 4)

R^1	*X*	*Yield (%)*	Trans/cis	ee *(%)*	*References*
Ph	CF_2CF_3	99	24:1	97	30
C_6H_4–4-Me	CF_2CF_3	99	16:1	93	30
C_6H_4–4-Cl	CF_2CF_3	99	24:1	98	30
(*E*)-CH=CHPh	CF_2CF_3	96	9:1	90	30
$(CH_2)_2$Ph	I	97	9:1	90	30
$(CH_2)_4$Me	I	94	10:1	95	30

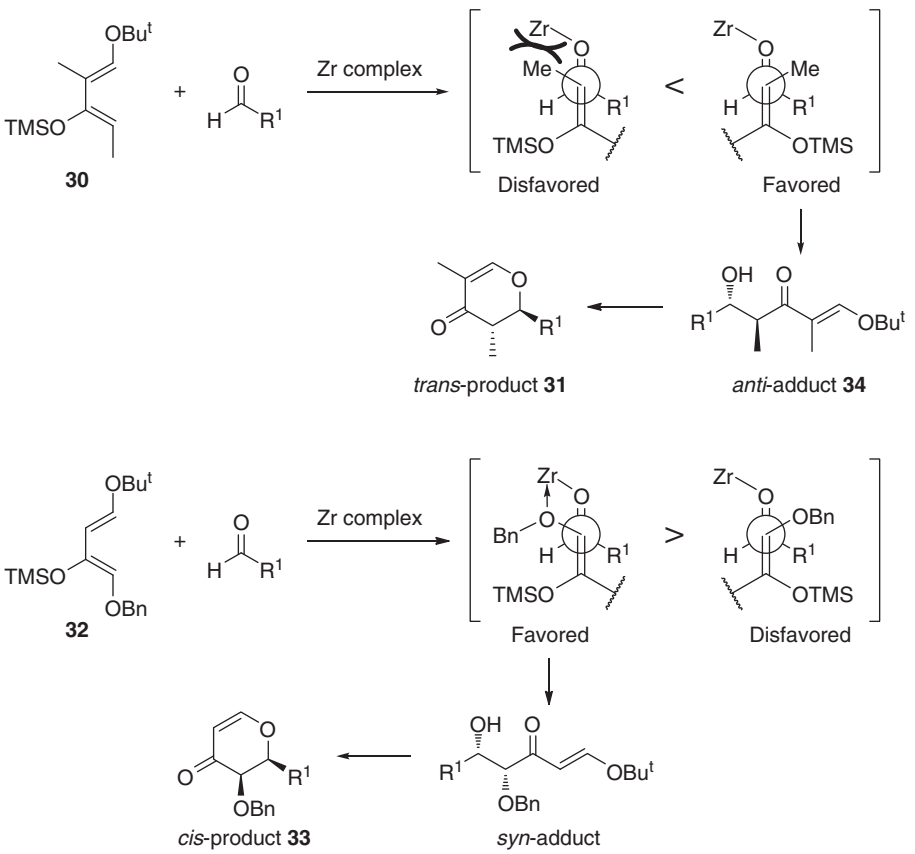


R^1	Yield	*cis*/*trans*	*ee*
Ph	95%	>30:1	97%
(*E*)-CH=CHPh	99%	6:1	92%
$(CH_2)_2$Ph	54%	12:1	81%

Scheme 9 Hetero-Diels–Alder reaction of the 4-oxygenated Danishefsky-type diene **32**.

In general, a favored transition state in the concerted pathway would be the *endo*-type cycloaddition to afford a 2,3-*cis* product. Therefore, the zirconium(IV) complex-catalyzed hetero-Diels–Alder reaction of **30**, which predominantly gives 2,3-*trans* product **31**, is proposed to proceed via a stepwise pathway (Scheme 10).[30] When the reaction of **30** is conducted without treatment with TFA, the *anti*-aldol adduct **34** (*anti*/*syn*=92:8) is obtained. In addition, TFA treatment of **34** gives the *trans*-product **31** (*trans*/*cis*=92:8). These results support the proposal that the reaction proceeds via a stepwise Mukaiyama aldol-cyclization pathway. The anti-preference in the Mukaiyama aldol step is explained by the steric hindrance between the Zr(IV) catalyst and the 4-methyl group, which prevents the formation of a *syn*-aldol adduct.However, the *cis*-selectivity observed in the reaction of **32** is explained by the interaction of the benzyloxy group with the zirconium center of the catalyst.

The chiral dirhodium(II) carboxamidate Rh_2(5*S*-mepy)$_4$ (**35**) (Figure 3) is an efficient catalyst for the hetero-Diels–Alder reaction of Danishefsky's diene **1** (equation 5, Table 5).[31–33] Although **35** has high catalytic activity, the use of the cationic dirhodium(II) carboxamidate [Rh_2(5*S*-mepy)$_4$]BF_4 (**36**), which is prepared by the oxidation of **35** with $NOBF_4$, further improves the catalytic activity and enantioselectivity (Table 5).[34] With **36**, the rate is estimated to increase by at least a factor of 10. In its use



Scheme 10 Proposed origin of *trans*- and *cis*-selectivity.

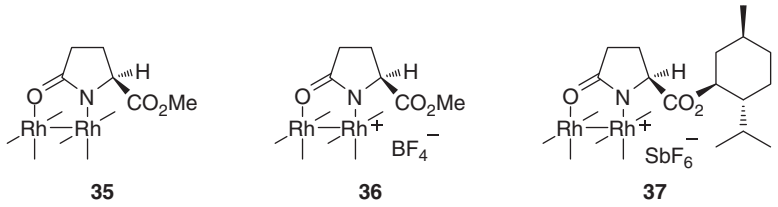
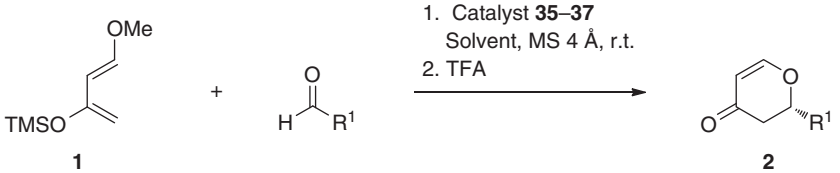


Figure 3 Chiral dirhodium(II) carboxamidate complexes **35–37**.

as an LA catalyst, coordination of the cationic rhodium complex with water is expected to produce a protic acid. To circumvent this problem, this reaction can be performed in the presence of a noncoordinating base such as 2,6-di-*tert*-butylpyridine. The use of a less polar solvent such as toluene further improved the reactivity and enantioselectivity (Table 5).[35] This enhancement is attributed to diminished or absent association of toluene with the catalyst, which lessens the relative importance of the uncatalyzed background reaction.



(5)

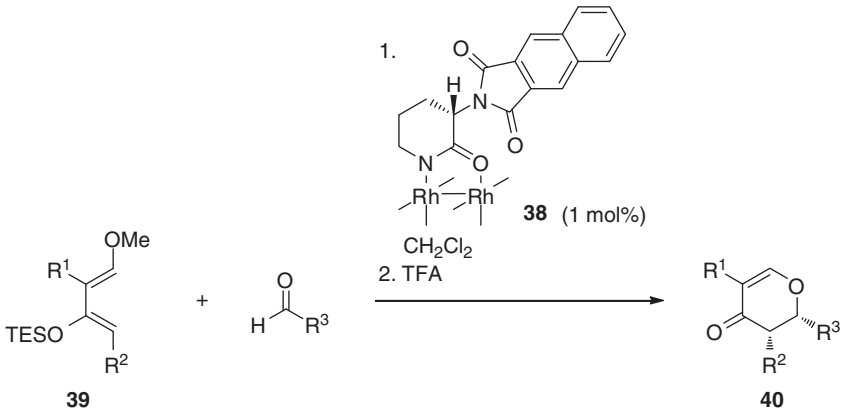
For the enantioselective hetero-Diels–Alder reaction of Danishefsky-type dienes **39**, the dirhodium(II) carboxamidate complex Rh_2(*S*-BPTPI)$_4$ (**38**) shows higher catalytic activity than **35–37** (equation 6, Table 6).[36] Dirhodium(II) catalyst **38** promotes the reaction with a variety of aldehydes to give 2,3-*cis*-dihydropyranones **40** in high yields with high enantioselectivities. Importantly, complex **38** can catalyze the reaction with sterically less-hindered α,β-acetylenic, α,β-olefinic and aliphatic aldehydes with excellent enantioselectivities. The present method can be applied to a large-scale synthesis without compromising the yield or

Table 5 Hetero-Diels–Alder reaction of Danishefsky's diene **1** catalyzed by chiral dirhodium(II) carboxamidates **35–37** (equation 5)

R^1	Catalyst	Solvent	Time (h)	Yield (%)	ee (%)	References
C_6H_4–4-NO_2	**35** (1 mol%)	CH_2Cl_2	24	53	73	31,34
C_6H_4–4-NO_2	**36** (1 mol%)	CH_2Cl_2	24	70	93	34
Ph	**35** (1 mol%)	CH_2Cl_2	24	<5	–	34
Ph	**36** (1 mol%)	CH_2Cl_2	24	40	88	34
C_6H_4–4-NO_2	**37** (5 mol%)[a]	CH_2Cl_2	24	86	91	35
C_6H_4–4-NO_2	**37** (5 mol%)[a]	Toluene	2	97	94	35

[a]The reaction was conducted in the presence of 2,6-di-*tert*-butylpyridine (20 mol%).

enantioselectivity: when the reaction of **39** ($R^1=R^2=H$) with 4-nitrobenzaldehyde (10 mmol) is conducted in the presence of **38** (0.0075 mol%), the corresponding adduct **40** ($R^1=R^2=H$, $R^3=C_6H_4$–4-NO_2) is obtained in 96% yield with 94% *ee*. The **38**-catalyzed hetero-Diels–Alder reaction proceeds though a concerted [4 + 2] cyclization mechanism in an *endo* mode, since the crude reaction mixture obtained without TFA treatment does not include the Mukaiyama aldol adduct, and no detectable cyclization of the Mukaiyama aldol adduct prepared independently is observed under the present reaction conditions.



(6)

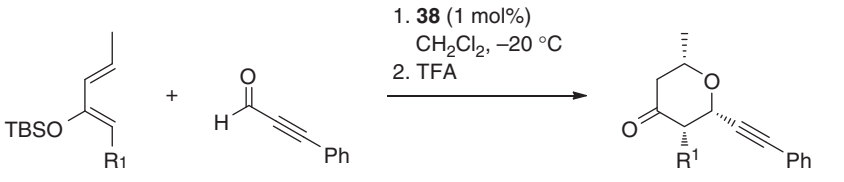
Table 6 Hetero-Diels–Alder reaction of Danishefsky-type dienes **39** catalyzed by the Rh(II) complex **38** (equation 6)

R^1	R^2	R^3	Temperature (°C)	Time (h)	Yield (%)	ee (%)	References
H	H	C_6H_4–4-NO_2	0	48	96[a]	94	36
H	H	C≡CPh	−20	6	91	92	36
H	H	(*E*)-CH=CHPh	23	36	86	96	36
H	H	C_6H_4–4-Me	23	24	97	96	36
H	H	C_6H_4–4-Cl	23	6	95	95	36
H	H	$(CH_2)_2$Ph	23	9	89	94	36
Me	H	CH_2OMOM	−20	18	83	91	36
H	Me	C_6H_4–4-NO_2	23	18	97	96	36
Me	Me	C_6H_4–4-NO_2	23	10	92	97	36

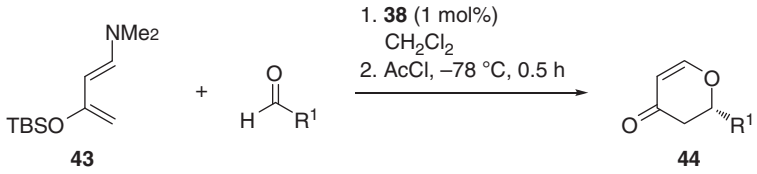
[a]The reaction is conducted on a 10 mmol scale in the presence of 0.0075 mol% of **38**.

The dirhodium(II) catalyst **38** also promotes the reaction of 2-siloxybutadienes **41**, which are less nucleophilic than the Danishefsky-type dienes, to give the corresponding tetrahydropyranones **42** with high diastereo- and enantioselectivity (Scheme 11).[36] Rawal's diene **43** is known to exhibit significantly higher reactivity than Danishefsky dienes in the Diels–Alder reaction under mild conditions. In the presence of the dirhodium(II) complex **38** (1 mol%), Rawal's diene **43** reacts with a variety of aldehydes at quite a low reaction temperature to give dihydropyranone **44** with high enantioselectivities (Scheme 11).[37]

The indium(III) complex of the chiral *N*,*N*-dioxide ligand **45** shows high catalytic activity for the hetero-Diels–Alder reaction of Danishefsky-type dienes **46** (Scheme 12, Table 7).[38] In the presence of the chiral indium(III) complex (5 mol%), a variety of aldehydes, including aromatic, heterocyclic, α,β-olefinic, and aliphatic aldehydes, are converted to the corresponding 2,3-*cis*-dihydropyranones with excellent enantioselectivity. The use of anisole as a solvent is crucial for obtaining high diastereo- and enantioselectivity. Based on a theoretical calculation, it has been proposed that the reaction proceeds through a concerted pathway in an *endo* mode (Scheme 12).[39] In the transition state **48**, a *Si* face approach is preferred over a *Re* face approach, since there is no distinguishable repulsion between the diene and the ligand in this case.

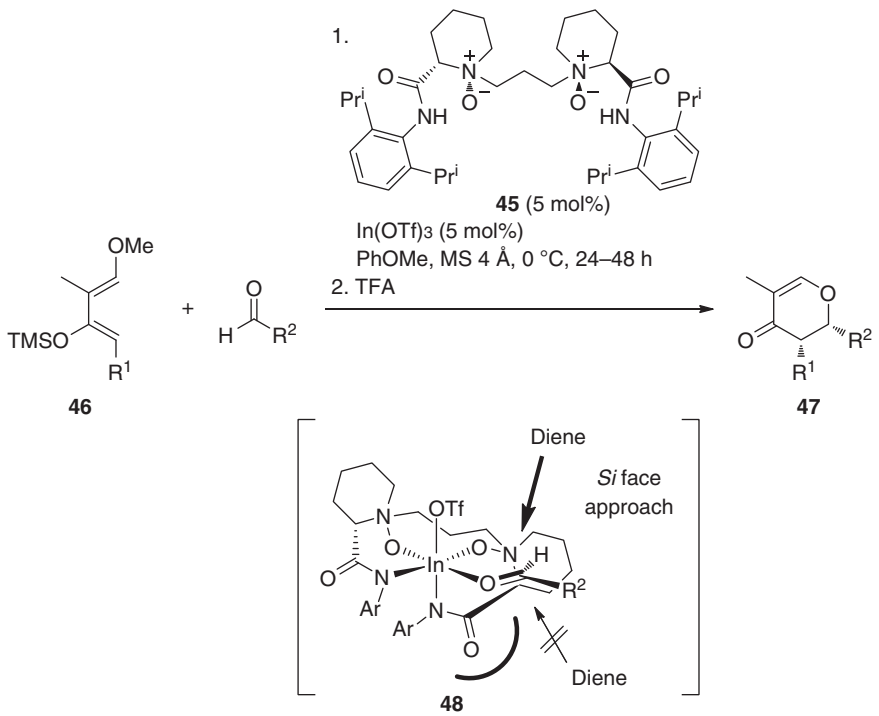


R^1	Yield	*ee*
H	87%	99%
Me	81%	97%



R^1	Conditions	Yield	*ee*
Ph	–40 °C, 6 h	82%	97%
C_6H_4-4-Cl	–60 °C, 2 h	71%	97%
C≡CCH_2OTBDPS	–90 °C, 0.5 h	72%	87%
$(CH_2)_2$OTBDMS	–40 °C, 2 h	74%	98%

Scheme 11 Hetero-Diels–Alder reaction of 2-siloxybutadienes **41** and Rawal's diene **43**.

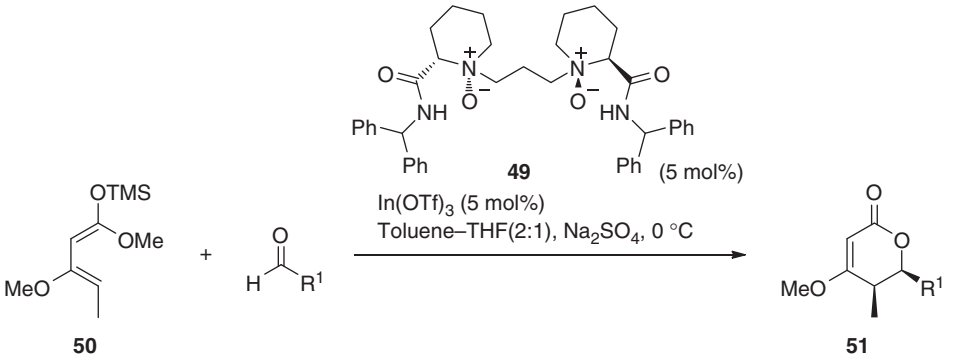


Scheme 12

For the hetero Diels–Alder reaction of the Brassard-type diene **50**, the use of the *N*,*N*-dioxide ligand **49** bearing *N*-diphenylmethyl groups gives better results than **45** (Scheme 13).[40] In the presence of a In(III) complex with **49**, the reaction of **50** with various aliphatic aldehydes gives δ-lactones **51** with high diastereo- and enantioselectivities. The addition of anhydrous Na_2SO_4 to the reaction mixture protects the system from instability caused by the absorption of moisture from air by $In(OTf)_3$.

Table 7 Hetero-Diels–Alder reaction of Danishefsky-type dienes **46** catalyzed by an In(III) complex of **45** (Scheme 12)

R^1	R^2	*Yield (%)*	cis/trans	ee *(%)*	*References*
Me	Ph	96	>20:1	98	38
Me	C_6H_4–4-Cl	89	>20:1	98	38
Me	C_6H_4–2-Cl	80	4:1	78	38
Me	C_6H_4–4-Me	96	>20:1	98	38
Me	Et	70	9:1	98	38
Me	(*E*)-CH=CHPh	92	17:1	98	38
H	Ph	99	–	98	38
H	C_6H_4–2-Cl	97	–	84	38
H	Et	82	–	80	38
H	(*E*)-CH=CHPh	99	–	97	38



R^1	Yield	*cis/trans*	*ee*
Pr^i	84%	85:15	90%
Pr	69%	65:35	72%
Bu^t	86%	97:3	94%
(*E*)-CH=CHCH$_3$	17%	88:12	84%

Scheme 13 Hetero-Diels–Alder reaction of the Brassard-type diene **50** catalyzed by an In(III) complex.

5.10.2.1.2 Chiral organocatalysts

Recent significant advances in organocatalysis have revealed that hydrogen-bonding catalysts can promote the hetero-Diels–Alder reaction of reactive substrates. For example, TADDOL **52** (Figure 4) catalyzed the enantioselective hetero-Diels–Alder reaction of 1-amino-3-siloxybutadiene **43** (Rawal's diene), which is a highly nucleophilic diene (equation 7, Table 8).[41] In the presence of **52** (20 mol%), the reaction with various unactivated aldehydes proceeds smoothly to yield (2*S*)-dihydropyrone **44** with high enantioselectivity after treatment with acetyl chloride. Axially chiral 1,1′-biaryl-2,2′-dimethanols (BAMOL) **53** (Figure 4) are also highly effective catalysts for the hetero-Diels–Alder reaction of **43**.[42] As shown in Table 8, **53** generally gives results superior to those with **52** under the same reaction conditions. Diols **52** and **53** catalyze the hetero-Diels–Alder reaction of both aromatic and

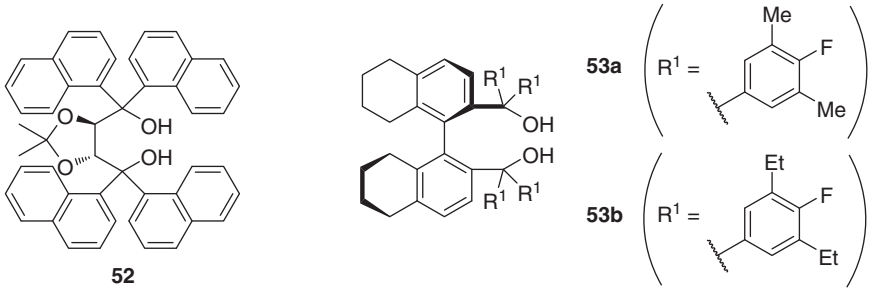
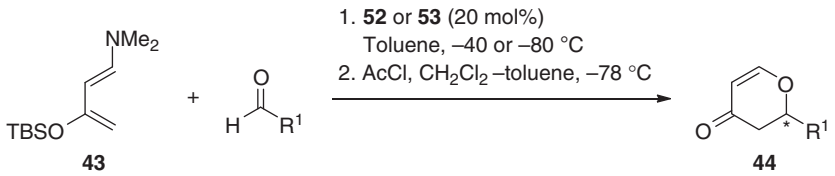


Figure 4 Axially chiral diols **53** and **54**.

aliphatic aldehydes. Aromatic aldehydes and straight-chain aliphatic aldehydes yield the corresponding adducts with excellent enantioselectivity, whereas aliphatic aldehydes with branched chains yield adducts with slightly lower enantioselectivity.



(7)

Table 8 Hetero-Diels–Alder reaction of Rawal's diene **43** catalyzed by chiral diols

R^1	Catalyst	Yield (%)	ee (%)	References
(*E*)-CH=CHPh	**52**	52	94 (*S*)	41
Me	**53b**	75	97	42
$^c C_6H_{11}$	**52**	64	86 (*S*)	41
$^c C_6H_{11}$	**53a**	99	84 (*R*)	42
Ph	**52**	70	>98 (*S*)	41
Ph	**53b**	84	98 (*R*)	42
2-Furyl	**52**	67	92 (*S*)	41
2-Furyl	**53b**	96	>99 (*R*)	42

A theoretical study suggested that benzaldehyde is activated by TADDOL **52** through single-point hydrogen bonding.[43] Figure 5 shows the two lowest energy-transition structures **54** and **55** for *Si* face and *Re* face additions, respectively. Transition-state assembly **54** is stabilized by a CH–π interaction between the aldehyde CH and the pseudoequatorial naphthalene ring of **52**. However, transition-state assembly **55** lacks the CH–π interaction and instead possesses a π–π stacking interaction. The transition-state assembly **54** is more reactive than **55**, since the naphthyl moieties in **55** restrict the approach of the diene to the coordinated aldehyde, whereas transition-state assembly **54** has no steric repulsion of this type. The calculated difference between **54** and **55** ($\Delta E = 1.5$ kcal mol^{-1}) corresponds to an *S*:*R* product ratio of 97:3 at -40 °C, which is in reasonable agreement with the experimentally observed enantiomer ratio of 99:1.

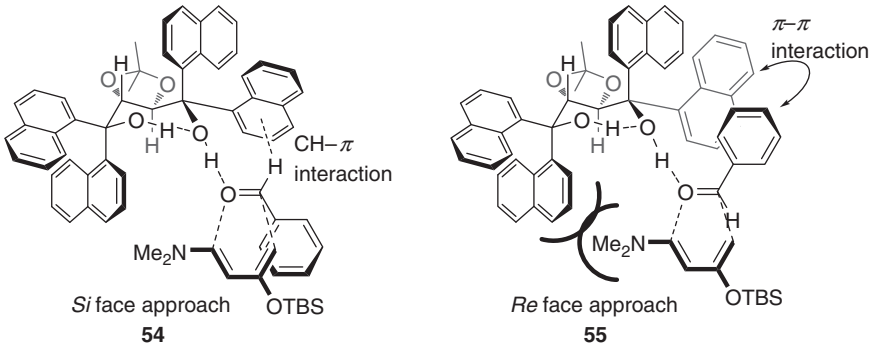
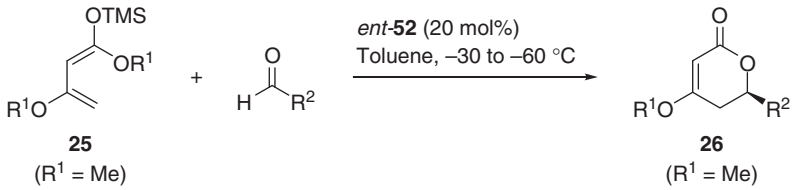


Figure 5 Proposed transition-state assemblies based on a theoretical study.

TADDOL **52** also catalyzes the hetero-Diels–Alder reaction of Bassard's diene **25** (R^1 = Me) with aromatic aldehydes to give the corresponding δ-lactone derivatives **26** in moderate to good yields with high enantioselectivities (Scheme 14).[44] Although the reaction can proceed under solvent-free conditions, a small amount of toluene is used to reduce the viscosity of the reaction mixture at a low reaction temperature.

3,3′-Diphenyl-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**56a**, Figure 6) catalyzed the hetero-Diels–Alder reaction of less nucleophilic dienes, which have less than two oxygen substituents, with the activated aldehyde ethyl glyoxylate.[45] In the presence of **56a** (5 mol%), the reaction of 2-siloxydienes or 1-methoxydienes with ethyl glyoxylate yields the corresponding (2*S*)-*anti*-adducts with high diastereo- and enantioselectivity (Table 9). In contrast, conventional chiral Lewis catalysts yield adducts with high *syn*-diastereoselectivity, probably due to the dominant secondary π-orbital interactions and the steric demand of the chiral LA catalysts. Chiral phosphoric acid catalyst **56b**, which possesses bulkier aryl groups at the 3- and 3′-positions, also yields a *syn*-adduct with low enantioselectivity. For the **56b**-catalyzed reaction, it has been proposed that the *endo*-orientation (*endo*-**57b**) of



R^2	Yield	*ee*
C_6H_4-2-Me	54%	68%
C_6H_4-4-Br	72%	78%
C_6H_4-3-Br	67%	89%
C_6H_4-3-OMe	45%	91%

Scheme 14 Hetero-Diels–Alder reaction of Bassard's diene **25** catalyzed by *ent*-**52**.

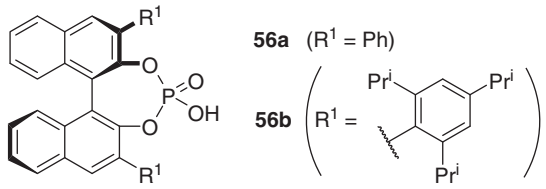
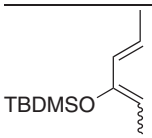
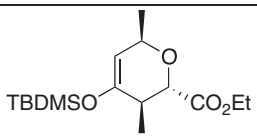
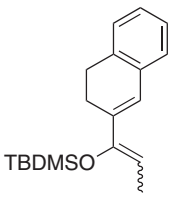
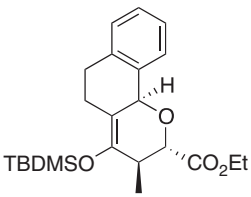
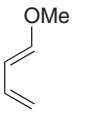
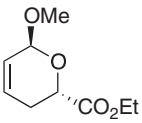
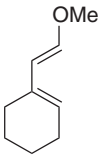
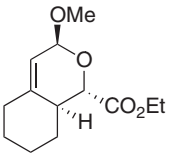


Figure 6 3,3′-Diaryl-1,1′-binaphthyl-2,2′-diyl hydrogenphosphates **56**.

Table 9 *anti*-Diastereoselective hetero-Diels–Alder reaction with ethyl glyoxylate catalyzed by chiral phosphoric acids **56**

Diene	*Adduct*	*Catalyst*	*Yield (%)*	anti/syn	ee *(%)*	*References*
		**56a**	95	>99:1	99	44
		56b	50	1:25	29	44
		**56a**	56	79:21	99	44
		**56a**	84	93:7	98	44
		**56a**	75	95:5	97	44

the diene to aldehyde is preferred over the *exo*-orientation (*exo*-**57b**) because of the steric hindrance between the diene substituents and the bulky aryl groups of **56b** around the activation site (Figure 7). For the **56a**-catalyzed reaction, the much smaller phenyl groups at the 3- and 3′-positions of **56a** allow the diene to occupy an *exo*-orientation (*exo*-**57a**). The *endo*-selectivity (*endo*-**57a**) is not favorable because of the steric repulsion between the diene substituents and ethyl glyoxylate.

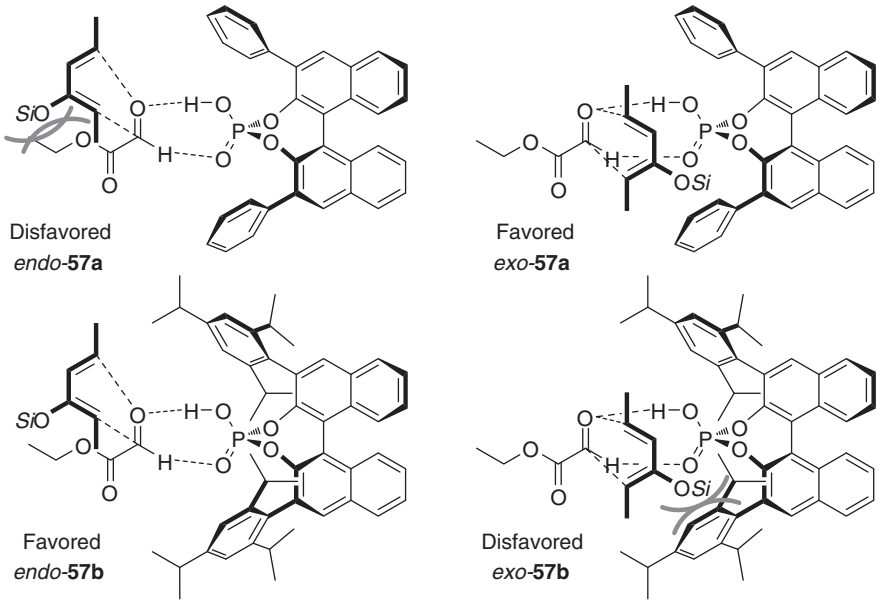
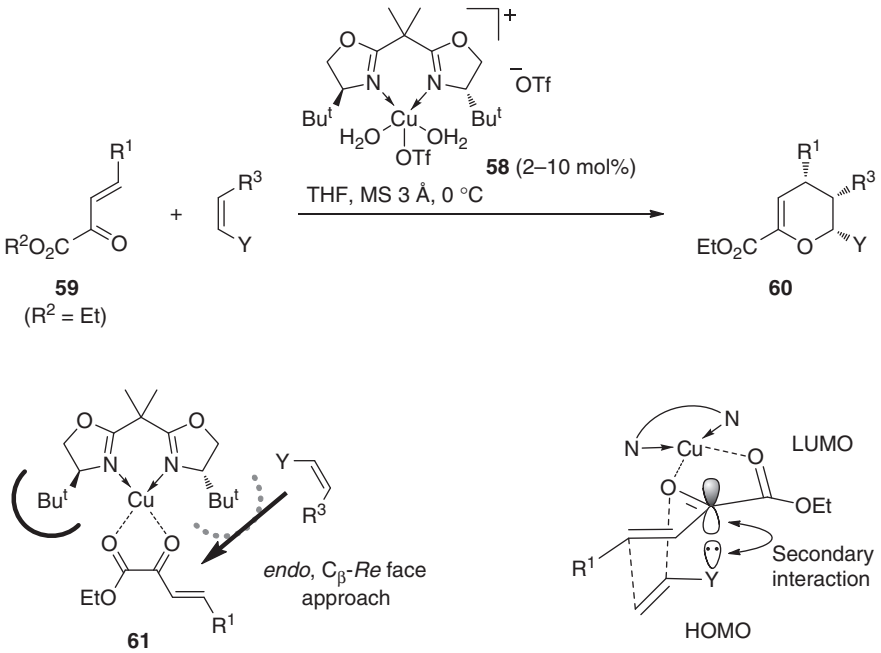


Figure 7 Plausible transition-state assemblies **57** (*Si*=TBDMS).

5.10.2.2 Inverse Reactions of α,β-Unsaturated Aldehydes and α,β-Unsaturated Ketones

5.10.2.2.1 Chiral LA catalysts

Chiral bis(oxazoline)–copper(II) complexes **58** are the catalysts that are most frequently used for inverse electron-demand hetero-Diels–Alder reactions, such as those of β,γ-unsaturated α-keto esters and α,β-unsaturated acyl phosphonates.[46–51] The ester and phosphonate groups activate the heterodienes as the substrate for a hetero-Diels–Alder reaction by lowering the LUMO. In addition, they provide a second 'docking point' for coordination to the chiral copper(II) LA. In the presence of aquo complex **58** (2–10 mol%) and MS 3 Å, β,γ-unsaturated α-keto esters **59** (R^2=Et) react with various vinyl ethers or vinyl thioethers to give the corresponding *endo*-adducts **60** (R^2=Et) with high diastereo- and enantioselectivity (Scheme 15, Table 10).[46,47] Although aquo complex **58** shows poor catalytic activity, MS 3 Å activate **58** *in situ* to give a catalyst which shows high activity and high selectivity. The reaction is presumed to proceed



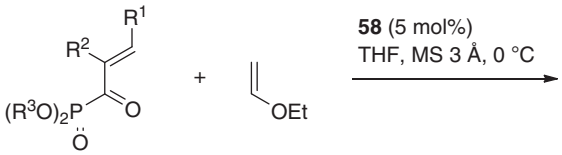
Scheme 15

through a bidentate activated intermediate **61**, and the dienophile should approach the Cβ-*Re* face of the activated heterodiene via an *endo* transition state. The *endo* preference can be explained by a secondary orbital interaction between the oxadiene C-2 (LUMO) and dienophiles Y group (HOMO), which may stabilize the transition-state assembly.

Table 10 Inverse-electron-demand hetero-Diels–Alder reaction of **59** catalyzed by aquo complex **58** (**Scheme 15**)

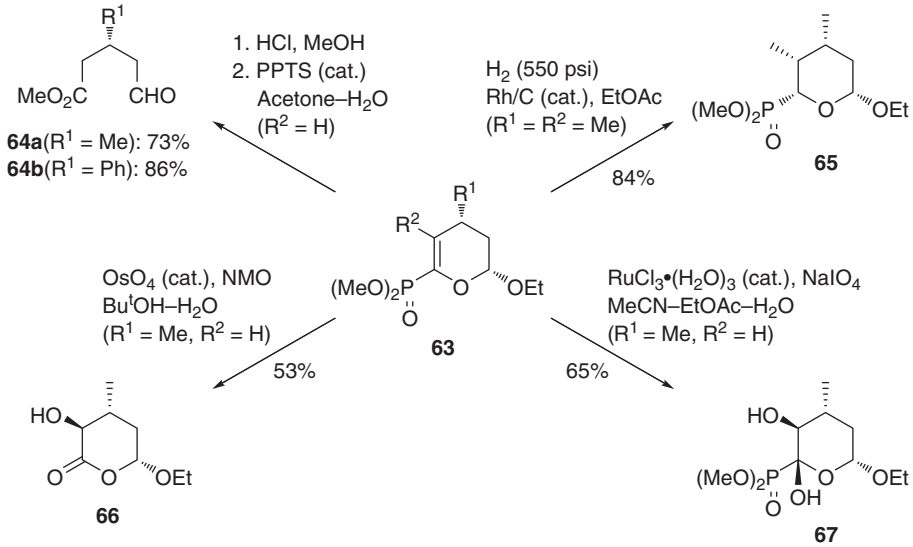
R^1	R^3	Y	*Yield (%)*	Endo/exo	ee *(%)*	*References*
Me	H	OEt	87	96:4	97	46,47
Ph	H	OEt	93	>95:5	97	46,47
OMe	H	OEt	90	98:2	98	46,47
SBn	H	OEt	97	>95:5	99	46,47
Ph	$(CH_2)_2O$		96	94:6	97	46,47
Pr^i	$(CH_2)_2O$		94	94:6	95	46,47
Ph	H	SEt	94	>95:5	97	46
Ph	H	SPh	91	>95:5	99	46

The hetero-Diels–Alder reaction of α,β-unsaturated acyl phosphonates **62** (R^3=Me) is also catalyzed by the aquo complex **58** to give the corresponding cycloadducts **63** in high yields with high enantioselectivities (**Scheme 16**).[46,48] Cycloadducts **63** can be converted to various chiral compounds (**Scheme 17**). For example, treatment of **63** with dry HCl in methanol followed by hydrolysis under mild acidic conditions gives aldehydic esters **64** in yields of 73–86%. Rh/C-catalyzed hydrogenation of the enol



R^1	R^2	Yield	*Endo/exo*	*ee*
Me	H	84%	97:3	93%
Ph	H	95%	96:4	97%
OEt	H	92%	98:2	97%
Me	Me	98%	96:4	>90%

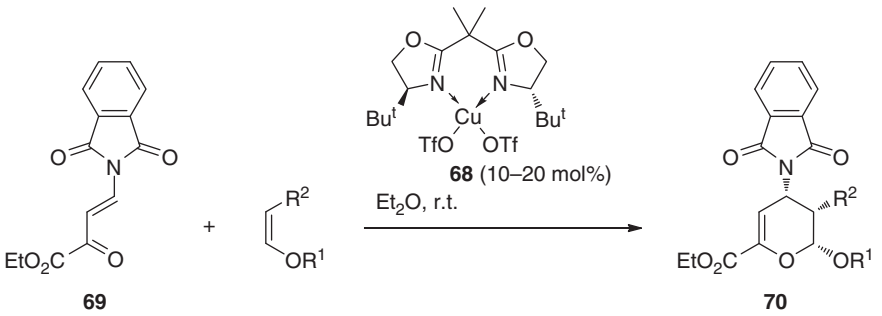
Scheme 16 Inverse electron-demand hetero-Diels–Alder reaction of α,β-unsaturated acyl phosphonates **62**.



Scheme 17 Derivatization of cycloadduct **63**.

double bond in **63** gives **65** with high diastereoselectivity ($dr > 20{:}1$). Under the standard dihydroxylation conditions, α-hydroxy lactone **66** is obtained stereoselectively, presumably via the intermediacy of the α,β-dihydroxy phosphonate **67**. $RuCl_3$-catalyzed oxidation of **63** gives **67** with high diastereoselection. Subjection of **67** to the action of $NaHCO_3$ (MeOH, 25 °C, 5 min) results in the elimination of dimethyl phosphite to give **66**.

The γ-phthalimido-β,γ-unsaturated α-keto ester **69** is a useful heterodiene for the inverse electron-demand hetero-Diels–Alder reaction with vinyl ethers (Scheme 18).[51] The reaction of **69** is catalyzed by the chiral copper(II)–bis(oxazoline) complex **68** to give the corresponding *endo*-adducts **70** with high enantioselectivities. The present approach can be used for the synthesis of a series of different types of protected amino sugars.

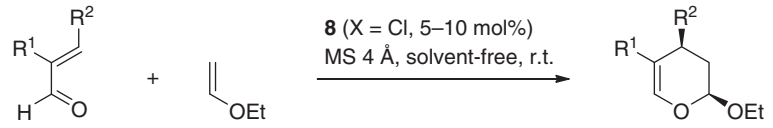


69 **70**

R^1	R^2	Yield	*de*	*ee*
Et	H	98%	88%	98%
Et	OAc	82%	85%	99%
$(CH_2)_2$		95%	57%	96%

Scheme 18 Hetero-Diels–Alder reaction of γ-phthalimido-β,γ-unsaturated α-keto ester **69**.

As described above, copper(II) complexes require EWGs, such as ester or phosphonate groups, in oxadienes to promote the hetero-Diels–Alder reaction. However, the chiral chromium(III) catalysts **8** (Figure 1) can promote the enantioselective inverse electron-demand hetero-Diels–Alder reaction of unactivated α,β-enals, which do not bear EWGs.[52] In the presence of **8** (X=Cl) (5–10 mol%), the reactions of α,β-enals **71** with ethyl vinyl ether take place under solvent-free conditions to give the corresponding dihydropyran derivatives **72** in high yields and excellent enantioselectivities (equation 8, Table 11). The reaction of 3-oxoprop-1-en-1-yl benzoate (**71**, R^1=H, R^2=OBz) provides the corresponding 4-benzoyloxy-substituted dihydropyran derivative, which is a versatile intermediate for an assortment of useful substitution reactions (Scheme 19).[53]

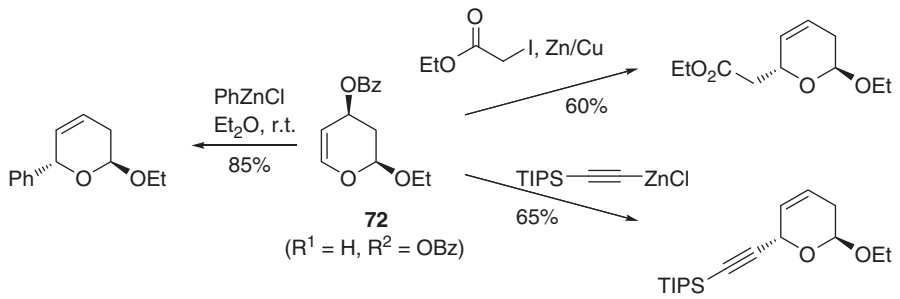


71 **72** (8)

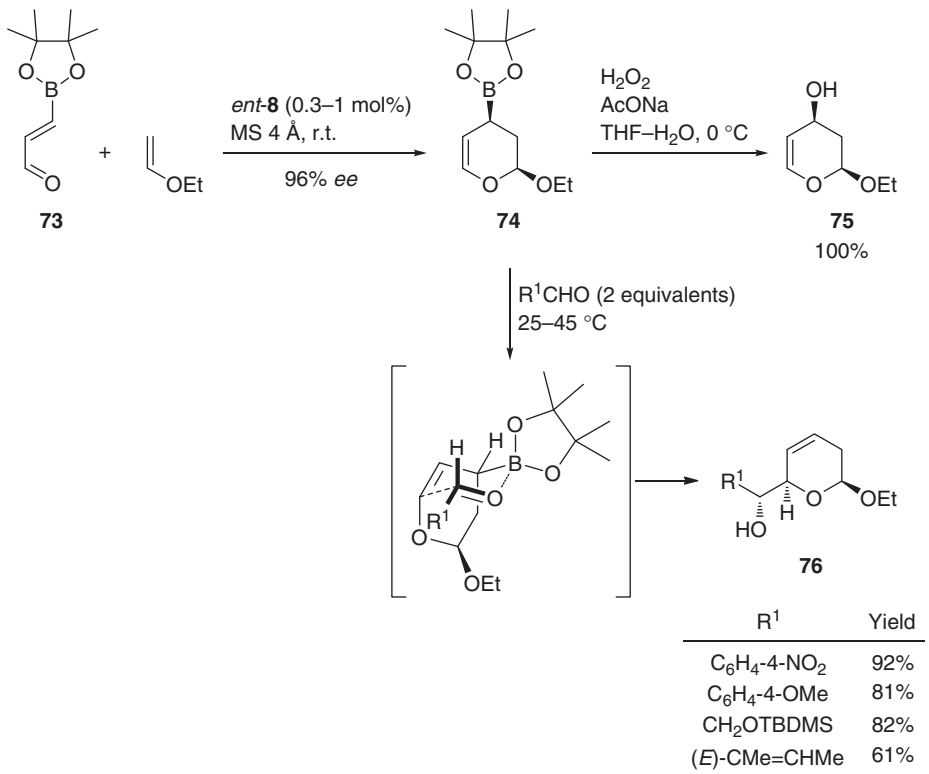
Table 11 Hetero-Diels–Alder reaction of unactivated α,β-enals **71** (equation 8)

R^1	R^2	*Catalyst loading (mol%)*	*Time (h)*	*Yield (%)*	ee *(%)*	*References*
H	Me	5	24	75	94	52
H	Ph	10	48	75	98	52
H	CH_2OBn	5	24	90	95	52
H	OBz	5	48	80	89	52
Br	Ph	5	48	75	98	52
Me	Me	7	96	75	92	52

3-Boronoacrolein pinacolate (**73**) is a useful oxadienophile for the inverse-electron-demand hetero-Diels–Alder reaction. In the presence of *ent*-**8** (X=Cl) (0.3–1 mol%), the hetero-Diels–Alder reaction of enal **73** with ethyl vinyl ether affords the corresponding adduct **74**, subsequent oxidation/hydrolysis of which quantitatively gives the secondary alcohol **75** with 96% enantiomeric excess (Scheme 20).[54–56] The use of distilled **73** is crucial for obtaining high enantioselectivity. The adduct **74** also undergoes a subsequent allylboration reaction with various aldehydes to give the corresponding dihydropyrans **76** in high yields (61–92%) and excellent diastereoselectivities (Scheme 20).[54–56] This methodology has been successfully applied to the synthesis of various natural compounds. For example, the hetero-Diels–Alder/allylboration sequence between enal **73**, enol ether **77**, and



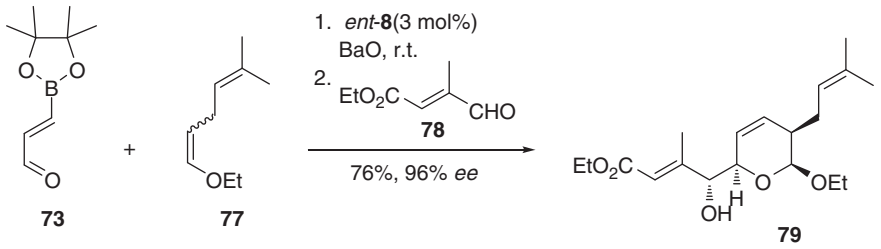
Scheme 19 Substitution reaction of the dihydropyran derivative **72** (R^1 = H, R^2 = OBz).



R^1	Yield
C_6H_4-4-NO_2	92%
C_6H_4-4-OMe	81%
CH_2OTBDMS	82%
(*E*)-CMe=CHMe	61%

Scheme 20 Hetero-Diels–Alder of 3-boronoacrolein pinacolate **73**.

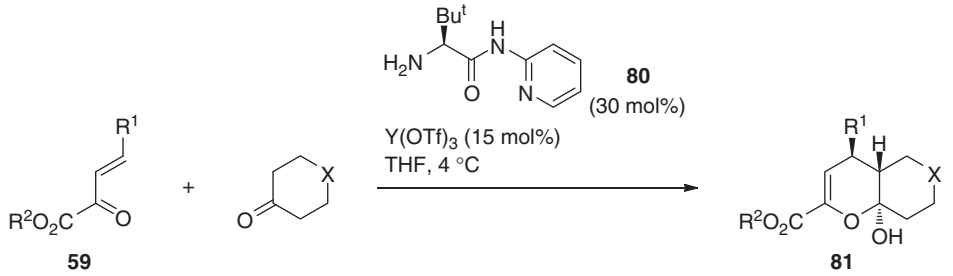
aldehyde **78** gives the dihydropyran **79** in 76% yield and 96% enantiomeric excess (Scheme 21). Although the 2-substituted enol ether **77** is an isomeric mixture, the *Z*-form is more reactive than the *E*-form, and this provides dihydropyran **79** as a single diastereomer. The cycloadduct **79** is a key intermediate for the total synthesis of a potent thiomarinol antibiotic.[57]



Scheme 21 Hetero-Diels–Alder/allyboration sequence as part of the synthesis of a potent thiomarinol antibiotic.

As described above, in most of the inverse-electron-demand hetero-Diels–Alder reactions, enol ethers derived from aldehydes act as electron-rich alkenes (dienophiles). However, a Y(III) complex with chiral ligand **80** bearing a primary amino group can catalyze the enantioselective reaction of β,γ-unsaturated α-keto esters **59** with cyclohexanone derivatives to give the *endo*-adducts

81 in high yields with high enantioselectivity (equation 9, Table 12).[58] Only two *endo*-diastereomers are detected, even though three to four stereogenic centers are generated in the present hetero-Diels–Alder reaction. The reaction of **59** (R^1 = Ph, R^2 = Bn) with 4-methylcyclohexanone gives the corresponding adduct in which four stereogenic centers are stereoselectively created.

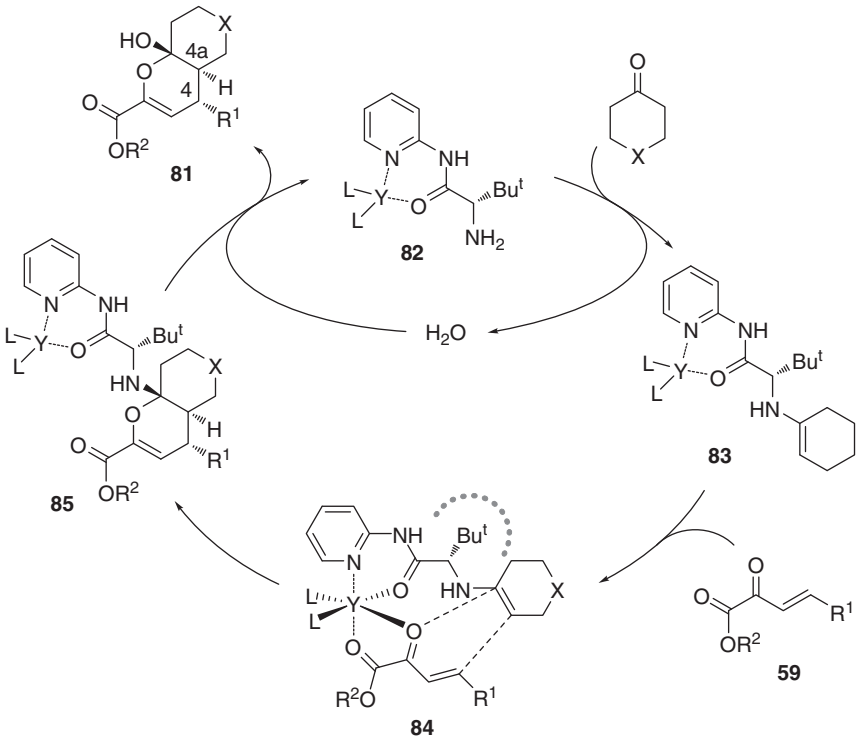


(9)

Table 12 Inverse-electron-demand hetero-Diels–Alder reaction of **59** with cyclohexanone derivatives (equation 9)

R^1	R^2	X	Yield (%)	dr	ee (%)	References
Ph	Me	CH_2	81	90:10	99	58
Ph	Bn	CH_2	75	89:11	99	58
C_6H_4–4-Br	Me	CH_2	85	90:10	93	58
C_6H_4–4-Me	Me	CH_2	80	86:14	96	58
C_6H_4–3-NO_2	Et	CH_2	80	75:25	92	58
C_6H_4–3-NO_2	Et	O	72	80:20	95	58
C_6H_4–3-NO_2	Et	S	63	75:25	94	58
Ph	Bn	(*R*)-CHMe	73	83:17	97	58

The following reaction mechanism is proposed for the inverse-electron-demand hetero-Diels–Alder reaction catalyzed by the Y(III) complex with **80** (Scheme 22).[58] The 1:1 complex **82** is a bifunctional catalyst, the primary amino group of which activates the cyclohexanone derivative via the formation of an enamine intermediate **83** by raising the HOMO energy. In addition, the Y(III) LA moiety of **82** simultaneously activates **59** through chelation. The proposed transition-state assembly **84**, which features an *endo*-selective mode of the reaction, matches well with the relative stereochemistry at C4 and C4a. The sterically hindered *tert*-butyl group shields the *Re* face of the enamine, and thus the activated enone approaches the *Si* face, which accounts for the

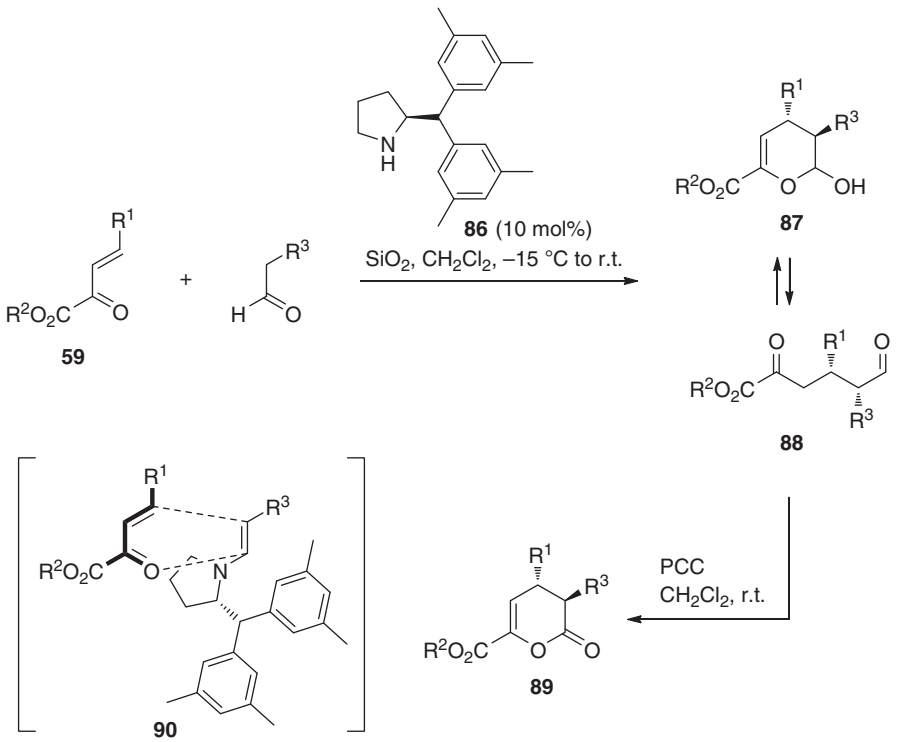


Scheme 22 Proposed catalytic cycle.

absolute configuration of **81**. The water generated *in situ* plays a critical role in the hydrolysis of the aminal intermediate **85**. When MS are included in the reaction, the hetero-Diels–Alder reaction is noticeably slower and the yield decreases significantly.

5.10.2.2.2 Chiral organocatalysts

Chiral secondary amines have emerged as effective catalysts for the enantioselective reactions of aldehydes, which proceed via chiral enamine intermediates. Thus, the inverse electron-demand hetero-Diels–Alder reaction of aldehydes with reactive α,β-unsaturated carbonyl compounds is catalyzed by a chiral secondary amine.[59,60] The *in situ* generation of a chiral *trans*-enamine from the secondary amine catalyst **86** and an unactivated aldehyde, followed by a hetero-Diels–Alder reaction with the β,γ-unsaturated α-keto esters **59**, yields a mixture of two isomers of hemiacetals **87** and aldehydes **88** (Scheme 23, Table 13).[59] Oxidation of this mixture gives lactones **89** as single diastereomers with high enantioselectivity. The presence of silica (50 mg on a 0.5 mmol scale) facilitates the hydrolysis of an aminal intermediate to the acetal **87**. The absolute and relative stereochemistries of the hetero-Diels–Alder adduct are consistent with the proposed transition-state assembly **90**. The 2,2-diarylmethyl substituent on the pyrrolidine ring shields the *Si* face of the enamine to control the addition of the enone to the *Re* face of the alkene moiety.



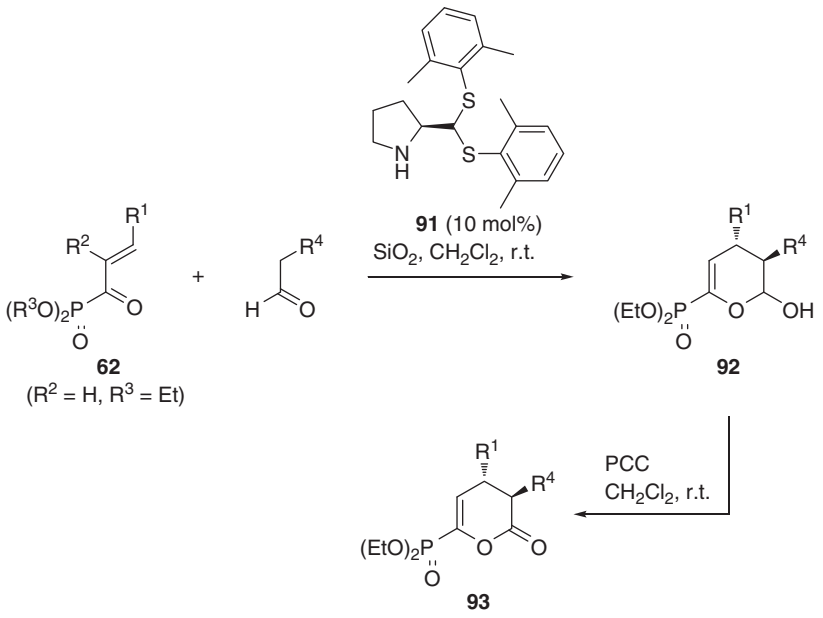
Scheme 23

Table 13 Inverse electron-demand hetero-Diels–Alder reaction of aldehydes with β,γ-unsaturated α-keto esters **59** catalyzed by chiral secondary amine **86** (Scheme 23)

R^1	R^2	R^3	*Yield (%) of* ***87*** *+* ***88***	ee *(%) of* ***89***	*References*
Ph	Me	Et	69	84	59
Ph	Me	Pr^i	93	89	59
Ph	Me	Bn	65	86	59
C_6H_4–4-Cl	Me	Pr^i	70	90	59
Me	Et	Et	81	86	59

Prolinal dithioacetal **91** is an effective catalyst for the inverse-electron-demand hetero-Diels–Alder reaction with α,β-unsaturated acyl phosphonates **62** (R^2 = H, R^3 = Et) (Scheme 24).[60] Pyridinium chlorochromate (PCC) oxidation of the adducts **92** gives the corresponding lactones **93** with high enantioselectivity (up to 94% *ee*).

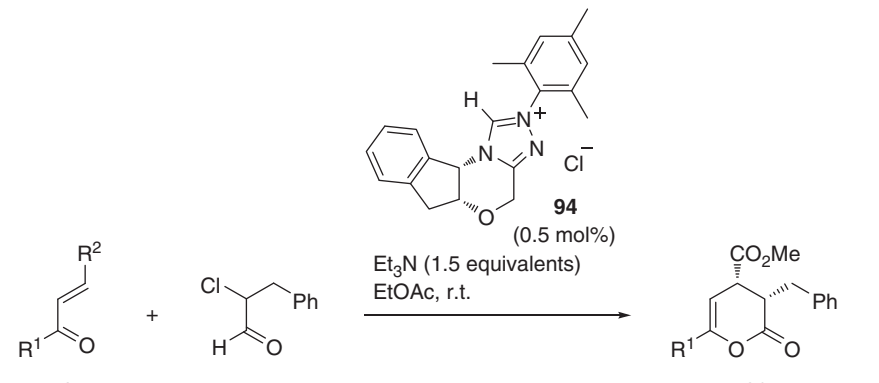
A chiral *N*-heterocyclic carbene prepared from triazolium salt **94** with triethylamine can catalyze the enantioselective hetero-Diels–Alder reaction of α-chloroaldehydes with α,β-unsaturated carbonyl compounds.[61–63] For example, the *N*-heterocyclic carbene-catalyzed hetero-Diels–Alder reaction of 2-chloro-3-phenylpropionaldehyde with α,β-unsaturated ketones **95** (R^2 = CO_2Me)



R^1	R^4	Yield of **92**	*ee* of **93**
Me	Me	79%	87%
Me	Bn	69%	94%
Et	Et	71%	89%

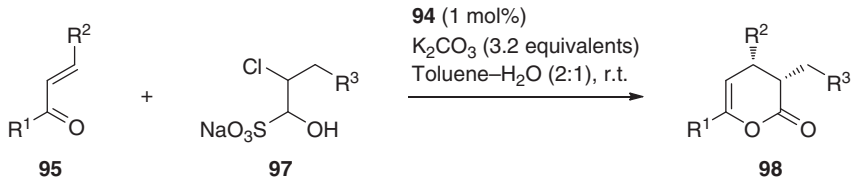
Scheme 24 Inverse electron-demand hetero-Diels–Alder reaction with α,β-unsaturated acyl phosphonates **62** catalyzed by chiral secondary amine **91**.

gives corresponding adducts **96** with high enantioselectivity, albeit the diastereoselectivity is moderate in some cases (Scheme 25).[61] The lower diastereoselectivity appears to result from epimerization of the initially formed *cis*-annulated products. In addition, α-chloroaldehydes are sensitive to moisture and oxygen, and their preparation and storage require precautions. In contrast, α-chloroaldehyde bisulfite adducts **97**, which are bench-stable solids that are readily prepared by the addition of aqueous sodium bisulfite to a solution of the appropriate aldehydes, can be used as precursors of α-chloroaldehydes under aqueous conditions (equation 10, Table 14).[62] The use of an inorganic base, K_2CO_3 (1.0 M aqueous solution), and a less polar solvent, toluene, successfully suppresses the epimerization of the *cis*-annulated products and gives the adduct **98** as single diastereomers with high enantioselectivity.



R^1	Yield	*dr*	*ee*
Me	88%	>20:1	99%
Ph	91%	8:1	99%

Scheme 25 *N*-Heterocyclic carbene-catalyzed hetero-Diels–Alder reaction of 2-chloro-3-phenylpropionaldehyde with α,β-unsaturated ketones **95** ($R^2 = CO_2Me$).

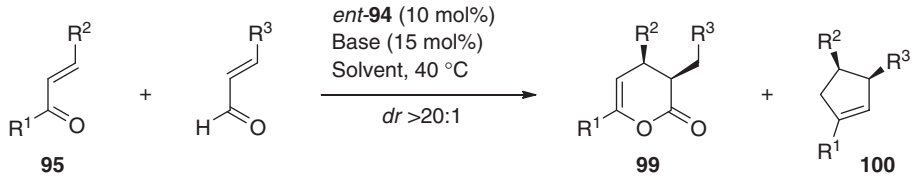


(10)

Table 14 *N*-Heterocyclic carbene-catalyzed hetero-Diels–Alder reaction of α-chloroaldehyde bisulfite adducts **97** (equation 10)

R^1	R^2	R^3	*Yield (%)*	ee *(%)*	*References*
Ph	CO_2Et	H	84	90	62
$^cC_6H_{11}$	CO_2Et	H	52	91	62
Ph	CO_2Et	Ph	98	99	62
$^cC_6H_{11}$	CO_2Et	Ph	70	91	62
Ph	CO_2Et	$^nC_9H_{19}$	74	>99	62
CO_2Et	C_6H_4–4-Me	H	74	99	62
CO_2Et	C_6H_4–4-Me	Ph	73	>99	62
CO_2Et	Pr^n	Ph	78	>99	62

The *N*-heterocyclic carbene prepared from **94** can also activate α,β-unsaturated aldehydes and promote the inverse-electron-demand hetero-Diels–Alder reaction with various α,β-unsaturated ketones **95** to give **99** with high enantioselectivity (equation 11, Table 15).[63] For the selective promotion of the desired hetero-Diels–Alder reaction, following three factors are beneficial: (1) the use of a catalytic amount of weak amine bases such as 4-(dimethylamino)pyridine (DMAP) and *N*-methylmorpholine (NMM) gives the best results; (2) toluene and CH_2Cl_2 are the preferred solvents; and (3) a slightly elevated temperature (40 °C) gives cleaner reactions. Otherwise, the competing formation of cyclopentenes **100** is predominant.[64,65]

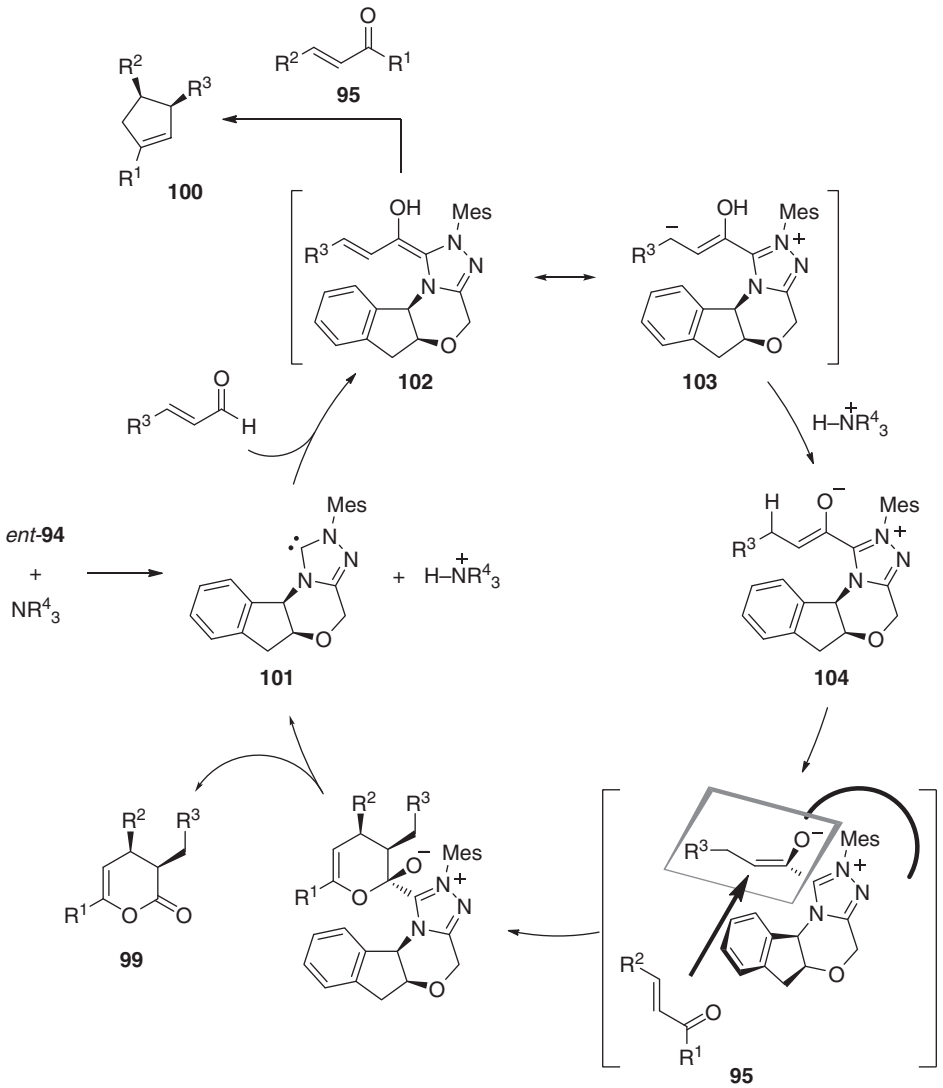


(11)

Table 15 *N*-heterocyclic carbene-catalyzed hetero-Diels–Alder reaction of α,β-enals (equation 11)

R^1	R^2	R^3	*Base*	*Solvent*	*Yield (%)*	ee *(%)*	*References*
C_6H_4–4-OMe	CO_2Me	Ph	NMM	Toluene	62	99	63
C_6H_4–4-OMe	CO_2Me	Pr	NMM	Toluene	60	99	63
Me	CO_2Et	Ph	Pr^i_2NEt	CH_2Cl_2	94	99	63
Me	CO_2Et	C_6H_4–4-Br	Pr^i_2NEt	CH_2Cl_2	88	99	63
Me	CO_2Et	H	Pr^i_2NEt	CH_2Cl_2	63	99	63
Me	CO_2Et	Pr	Pr^i_2NEt	CH_2Cl_2	95	94	63
CO_2Et	Me	Ph	NMM	CH_2Cl_2	85	98	63
CO_2Et	Me	H	NMM	CH_2Cl_2	51	99	63
CO_2Et	$^cC_6H_{11}$	Pr	NMM	CH_2Cl_2	79	98	63
CO_2Et	$^cC_6H_{11}$	H	NMM	CH_2Cl_2	49	99	63

A plausible mechanism for the *N*-heterocyclic carbene-catalyzed hetero-Diels–Alder reaction is shown in Scheme 26.[63] *N*-Heterocyclic carbene **101**, prepared from azolium salt *ent*-**94** with a base NR^4_3, activates α,β-unsaturated aldehydes to form the homoenolate equivalents **102** and **103**. The reaction of the homoenolates **102** and **103** with α,β-unsaturated carbonyl compounds **95** gives cyclopentenes **100**.[64,65] If the conjugate acid of the catalytic base NR^4_3, generated by the deprotonation of *ent*-**94**, is acidic enough to protonate the homoenolate **103** at the β-position, the enolate equivalent **104** is formed. If the α,β-unsaturated carbonyl compound **95** is sufficiently electrophilic, annulation occurs to give the hetero-Diels–Alder adduct **99**. In the transition-state assembly, the mesityl group shields the *Re* face of the enolate to control the addition of the enone **95** to the *Si* face of the alkene moiety.



Scheme 26 Plausible catalytic cycle of the *N*-heterocyclic carbene-catalyzed hetero-Diels–Alder reaction.

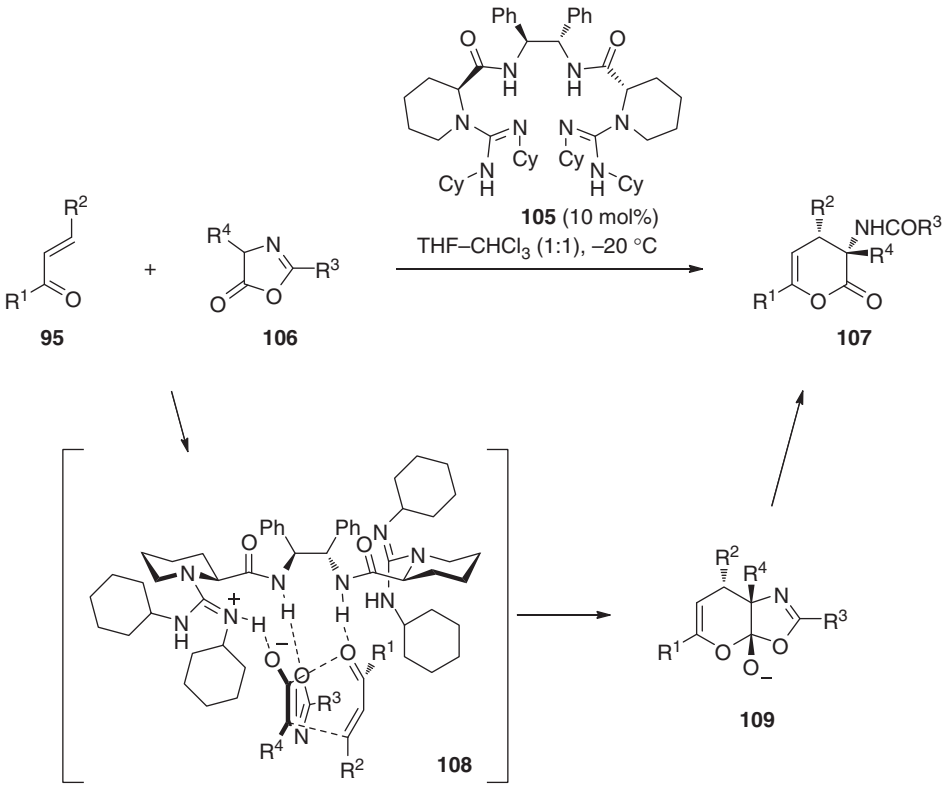
Chiral bisguanidine **105** catalyzes the inverse-electron-demand hetero-Diels–Alder reaction of racemic azlactones **106** with chalcones **95** (R^1, R^2 = aromatic group) to give δ-lactones **107** with high enantioselectivity (Scheme 27, Table 16).[66] Both electron-deficient and electron-rich chalcones show high enantioselectivities. In this reaction, chiral bisguanidine **105** activates azlactones **106** through deprotonation by raising the HOMO energy. Based on the absolute configuration of the product **107**, it is conceivable that the reaction proceeds via the *endo*-transition-state assembly **108**, in which the enolized azlactone approaches the C*β*-*Re* face of **95** to give adduct **109**. The subsequent ring-opening of **109** gives δ-lactones **107**.

5.10.3 Aza-Diels–Alder Reactions

5.10.3.1 Reactions of Imine Dienophiles

5.10.3.1.1 Chiral LA catalysts

As in the case of the hetero-Diels–Alder reactions of carbonyl compounds, in the normal electron-demand reaction, an imine is activated by an acid catalyst through lowering of the LUMO energy to react with an electron-rich diene. Chiral boron compounds **110** and **111** (Figure 8) can promote the aza-Diels–Alder reaction of aldimines **112** with Danishefsky's diene **1** (equation 12, Table 17).[67–69] Although the reaction requires a stoichiometric amount of **110** or **111**, the cycloadducts **113** are obtained with high enantioselectivity. The use of chiral aldimines bearing an *N*-(α-methylbenzyl) group improves the enantioselectivity.



Scheme 27

Table 16 Hetero-Diels–Alder reaction of azlactones **106** catalyzed by bisguanidine **105** (Scheme 27)

R^1	R^2	R^3	R^4	*Yield (%)*	ee *(%)*	*References*
Ph	Ph	Ph	Bn	73	96	66
C_6H_4–4-F	Ph	Ph	Bn	67	92	66
C_6H_4–4-Me	Ph	Ph	Bn	73	96	66
2-Thienyl	Ph	Ph	Bn	65	92	66
Ph	C_6H_4–3-Br	Ph	Bn	88	93	66
Ph	C_6H_4–3-Me	Ph	Bn	65	94	66
Ph	2-Naphthyl	Ph	Bn	70	94	66
Ph	Ph	C_6H_4–2-Cl	Bn	76	95	66
Ph	Ph	C_6H_4–3-OMe	Bn	68	93	66
Ph	Ph	Ph	Me	76	92	66
Ph	Ph	Ph	$(CH_2)_2SMe$	78	90	66

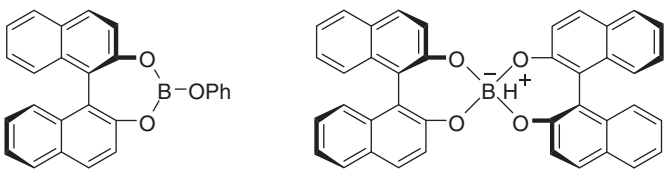
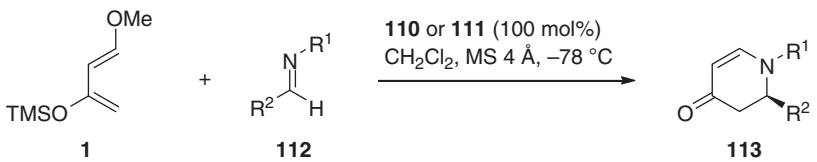


Figure 8 Chiral boron compounds **110** and **111**.

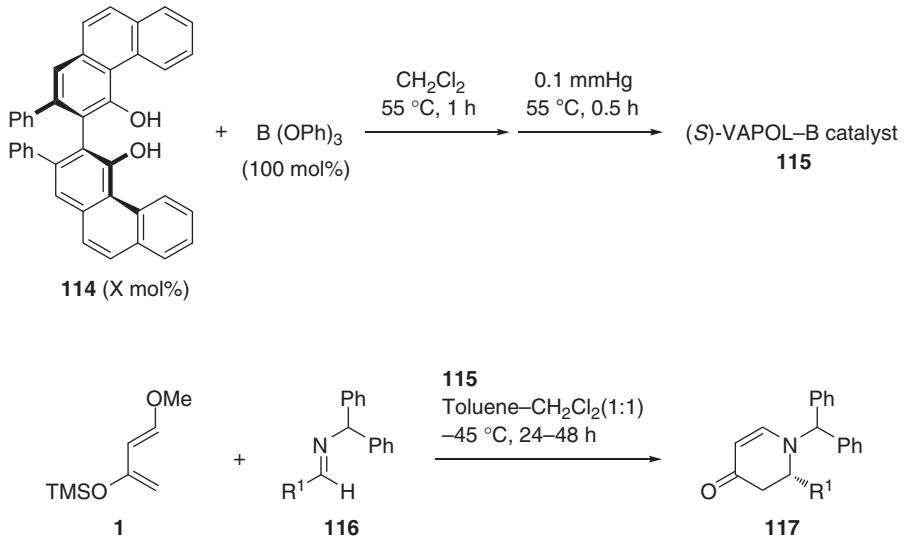


(12)

Table 17 Enantioselective aza-Diels–Alder reaction of aldimines **112** with Danishefsky's diene **1** (equation 12)

R^1	R^2	*Catalyst*	*Yield (%)*	ee *or* de *(%)*	*References*
Bn	Ph	**110**	75	82	67,68
Bn-3,4-$(OMe)_2$	Ph	**110**	73	85	67,68
(*S*)-CHMePh	Ph	**110**	61	98	68
Bn	3-Pyridyl	**110**	71	90	67,68
Bn	C_6H_3–3,5-$(OMe)_2$	**110**	89	74	67,68
Bn	$^cC_6H_{11}$	**110**	45	76	67,68
Bn	Ph	**111**	78	86	69
(*S*)-CHMePh	Ph	**111**	64	99	69

Attempts to catalytically promote the enantioselective aza-Diels–Alder reaction of imines faces the problem that the product is more basic than the starting imine, which leads to a difficulty in turnover. Indeed, when the reaction of **1** and **112** is conducted in the presence of 10 mol% of **110**, **113** is obtained in less than 5% yield. However, both turnover and asymmetric induction can be achieved, when two catalysts are used, one chiral (catalytic) and one nonchiral (excess), and the excess nonchiral additive frees up the chiral catalyst for turnover. For example, the chiral (*S*)-VAPOL–B catalyst **115**, prepared from (*S*)-VAPOL **114** (5–10 mol%) and $B(OPh)_3$ (100 mol%), can promote the enantioselective aza-Diels–Alder reaction of *N*-diphenylmethylaldimine **116** with Danishefsky's diene **1** to give the corresponding adducts **117** with high enantioselectivity (Scheme 28, Table 18).[70] The use of a bulky *N*-diphenylmethyl group is crucial for obtaining high enantioselectivity. The reaction of various aromatic aldimines and α-branched aliphatic aldimines gives adducts with high enantioselectivities, whereas sterically less-hindered aldimines give racemic adducts. These results indicate that the (*S*)-VAPOL–B(OPh) catalyst selectively interacts with aldimines **116** to promote the enantioselective aza-Diels–Alder reaction. A study of the binding constants showed that the (*S*)-VAPOL–B(OPh) catalyst binds to **116** (R^1 = Ph) seven times stronger than $B(OPh)_3$, whereas it binds to **117** (R^1 = Ph) only about twice as strongly.

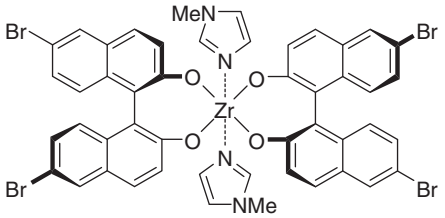


Scheme 28

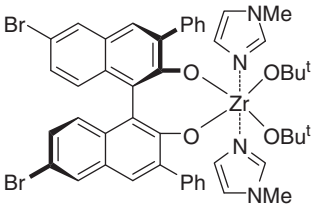
Table 18 Aza-Diels–Alder reaction of aldimines **116** using (*S*)-VAPOL–B catalyst **115** with excess $B(OPh)_3$ (Scheme 28)

R^1	*X (mol%)*	*Yield (%)*	ee *(%)*	*References*
Ph	5	85	90	70
C_6H_4–4-Br	5	84	89	70
C_6H_4–4-OMe	10	71	90	70
1-Naphthyl	10	78	90	70
$^cC_6H_{11}$	10	90	93	70
Pr^i	10	64	90	70
$^nC_7H_{15}$	5	41	0	70

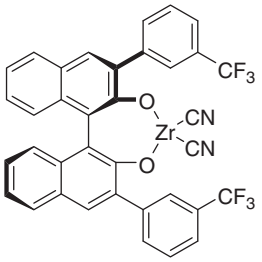
The chiral zirconium(IV) complex **118** (Figure 9) prepared from $Zr(OBu^t)_4$, (*R*)-6,6′-dibromo-1,1′-binaphthol, and *N*-methylimidazole catalyzes the aza-Diels–Alder reaction of aldimine **122** with Danishefsky-type diene **121** to give cycloadducts **123** in high yields with high enantioselectivities (equation 13, Table 19).[71] The use of *N*-methylimidazole as an additional ligand gives the best results. Although various aromatic aldimines are converted to the corresponding adducts with high enantioselectivities, the reaction of cyclohexyl (Cy)-substituted aldimine ($R^2 = {}^cC_6H_{11}$, $R^3 = H$) shows low enantioselectivity. This may be caused by isomerization of the *cis* and *trans* forms of the imine. The introduction of a methyl group to the *N*-phenyl group ($R^3 = Me$) prevents this isomerization to improve the enantioselectivity (86% *ee*).



118

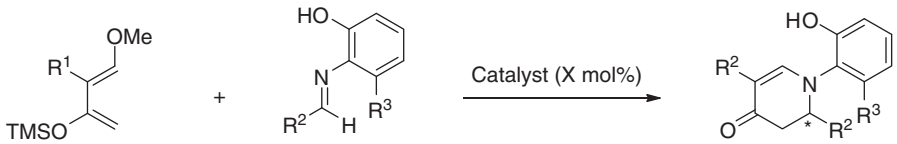


119



120

Figure 9 Chiral zirconium(IV) complexes **118–120**.



121 **122** **123** (13)

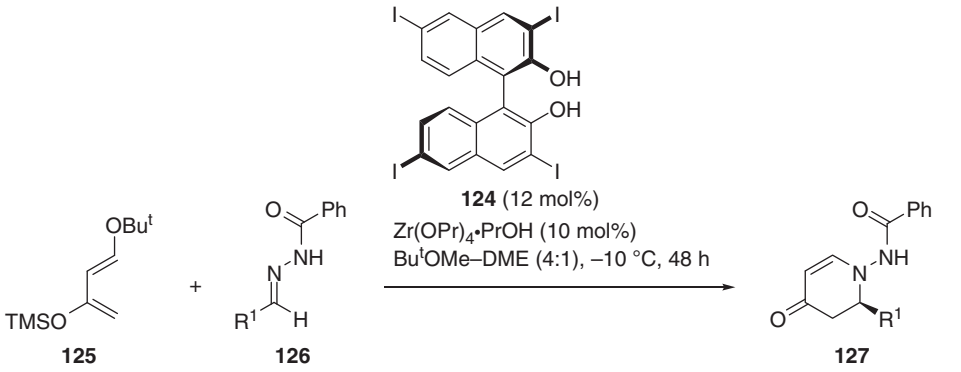
Table 19 Aza-Diels–Alder reaction of aldimine **122** catalyzed by chiral zirconium(IV) complexes **118–120** (equation 13)

R^1	R^2	R^3	*Catalyst (X mol%)*	*Condition*[a]	*Yield (%)*	ee *(%)*	*References*
H	1-Naphthyl	H	**118** (10)	A	86	82 [*S*]	71
Me	1-Naphthyl	H	**118** (20)	A	93	93 [*S*]	71
H	C_6H_4–4-Me	H	**118** (20)	A	83	82 [*S*]	71
Me	C_6H_4–4-Me	H	**118** (20)	A	97	77 [*S*]	71
Me	C_6H_3–2,3-$(OMe)_2$	H	**118** (20)	A	95	74 [*S*]	71
Me	$^cC_6H_{11}$	Me	**118** (20)	A	51	86 [*S*]	71
H	Ph	H	**119** (20)	B	94	82 [*R*]	72
Me	Ph	H	**119** (20)	B	100	80 [*R*]	72
H	1-Naphthyl	H	**119** (20)	B	88	84 [*R*]	72
Me	1-Naphthyl	H	**119** (20)	B	78	80 [*R*]	72
H	$^cC_6H_{11}$	H	**119** (20)	B	64	81 [*R*]	72
Me	$^cC_6H_{11}$	H	**119** (20)	B	67	80 [*R*]	72
H	C_6H_4–4-Me	H	**120** (1)	B	64	83 [*R*]	73
Me	C_6H_4–4-Me	H	**120** (2)	B	72	88 [*R*]	73
H	1-Naphthyl	H	**120** (5)	B	80	92 [*R*]	73
Me	1-Naphthyl	H	**120** (2)	B	71	84 [*R*]	73
H	2-Thienyl	H	**120** (2)	B	61	83 [*R*]	73
Me	$^cC_6H_{11}$	Me	**120** (5)	B	75	84 [*R*]	73

[a]Condition A: in toluene at −45 °C. Condition B: in the presence of MS 3 Å in benzene at r.t.

The chiral zirconium(IV)-3,3′-substituted BINOL complex **119** (Figure 9) prepared from $Zr(OBu^t)_4$ (20 mol%), (*R*)-6,6′-dibromo-3,3′-diphenyl-1,1′-binaphthol (40 mol%), and *N*-methylimidazole (60 mol%) also catalyzes the aza-Diels–Alder reaction of aldimine **122** (R^3 = H) (equation 13, Table 19).[72] The use of MS 3 Å improves the enantioselectivity. Very interestingly, the introduction of phenyl groups at the 3,3′-positions of BINOL reverses the absolute stereochemistry of the adducts: the **118**-catalyzed reaction gives (*S*)-**123**, whereas (*R*)-**123** is obtained by the use of **119** as a catalyst. In the reaction of not only various aromatic aldimines but also aliphatic aldimines, **119** shows high enantioselectivity. Another chiral zirconium(IV)-3,3′-substituted BINOL complex **120** (Figure 9) shows higher catalytic activity than **118** and **119** in the aza-Diels–Alder reaction of aldimines **122** (equation 13, Table 19).[73] Only 1–5 mol% of **120** can catalyze the reaction to give cycloadducts **123** in high yields with high enantioselectivities, whereas catalyst loadings of 10–20 mol% are required in the reactions catalyzed by **118** and **119**.

In a related study, a zirconium(IV) complex derived from 3,3′,6,6′-tetraiodo–BINOL **124** and $Zr(OPr)_4$•PrOH was shown to catalyze the aza-Diels–Alder reaction of *N*-benzoylhydrazones **126** with Danishefsky-type diene **125** to give the corresponding 2,3-dihydro-4-pyridones **127** with high enantioselectivities (Scheme 29).[74] Since the N–N bond of **127** can be easily cleaved by reduction with SmI_2, adducts **127** are highly useful as chiral building blocks for the synthesis of several nitrogen-containing natural products.



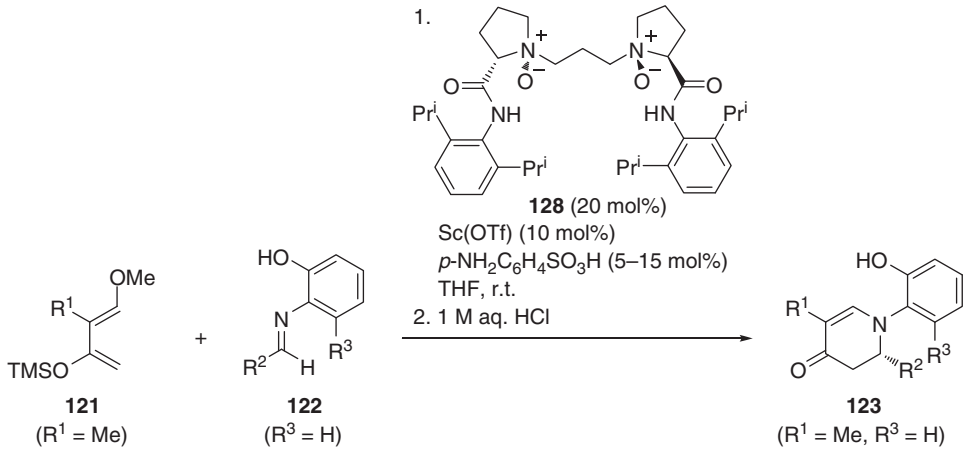
R^1	Yield	*ee*
$(CH_2)_2Ph$	70%	91%
Pr	70%	93%
Bu^i	31%	92%
$^cC_6H_{11}$	44%	89%

Scheme 29 Enantioselective aza-Diels–Alder reactions of *N*-benzoylhydrazones **127**.

A chiral scandium(III) complex with the L-proline-derived *N*,*N*′-dioxide ligand **128** also catalyzes the aza-Diels–Alder reaction of aldimine **122** (R^2 = H) with Danishefsky-type diene **121** (R^1 = Me) (Scheme 30).[75] The addition of 5–15 mol% of sulfanilic acid (4-$NH_2C_6H_4SO_3H$) improves the enantioselectivity. Under the optimized conditions, aromatic, heteroaromatic, conjugated, and aliphatic aldimines are converted into the corresponding 2,5-disubstituted dihydropyridinones **123** (R^1 = Me, R^3 = H) with moderate to good yields and up to 90% *ee*. Based on the NMR study, it is conceivable that a C_2 symmetric scandium-**128** (1:2) complex may be generated as an active catalyst species. Since the reaction shows a strong positive nonlinear effect, the homochiral complex seems to be more active than the heterochiral complex.

A chiral Cu(I) complex with (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl ((*R*)-Tol-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), **129**) is an efficient catalyst for the aza-Diels–Alder reaction of α-imino esters **130** (Scheme 31).[76,77] In the presence of 10 mol% of the Cu(I) complex, the reaction of **130** (R^1 = Ts) with cyclopentadiene and cyclohexadiene gives the corresponding *endo*-adducts **131** with high enantioselectivities. In the reaction with Danishefsky's diene **1**, *N*-*o*-methoxyphenyl glyoxylate imine **130** (R^1 = C_6H_4–2-OMe) and *N*-*p*-methoxyphenyl glyoxylate imine **130** (R^1 = C_6H_4–4-OMe) are converted to the corresponding cycloadducts **132** with high enantioselectivities. Although the reaction of *N*-tosyl glyoxylate imine **130** (R^1 = Ts) shows poor enantioselectivity in dichloromethane, the use of THF as a solvent improves the results.

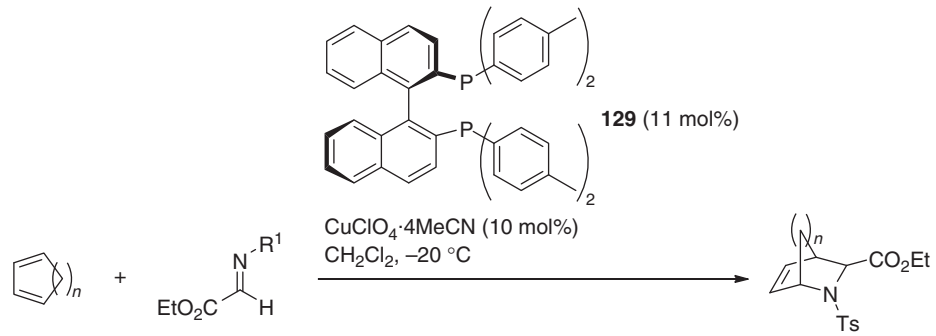
N-Sulfonyl imines are very appealing heterodienophiles because of their low LUMO energy and the high crystallinity of their adducts. The dimeric Cu(I) complex **133** prepared from CuBr and a chiral phosphino sulfenyl ferrocene ligand catalyzes the aza-Diels–Alder reaction of *N*-sulfonyl imines **134** with Danishefsky-type diene **121** (equation 14, Table 20).[78] In the presence of $AgClO_4$ (10 mol%), the reaction successfully proceeds to give the cycloadducts **135** in high yields with high enantioselectivities. An active cationic form of the copper(I) catalyst may be generated *in situ* as a result of the presence of $AgClO_4$, which acts as a halogen scavenger. The presence of an additional substituent at the diene or a change in the nature of the arylsulfonyl group of the heterodienophile provides similar results in terms of both chemical yield and enantioselectivity. Importantly, α,β-unsaturated imines (R^3 = CH = CHPh) act as heterodienophiles in the **133**-catalyzed aza-Diels–Alder reaction.



121 (R^1 = Me) + **122** (R^3 = H) → **123** (R^1 = Me, R^3 = H)

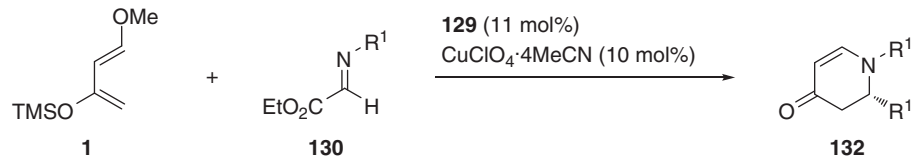
R^2	Yield	*ee*
Ph	74%	81%
C_6H_4-4-CN	84%	90%
1-Naphthyl	80%	87%
(*E*)-CH=CHPh	92%	84%

Scheme 30 Aza-Diels–Alder reaction of aldimine **122** catalyzed by scandium(III) complex with *N,N′*-dioxide ligand **128**.



130 (R^1 = Ts) → **131**

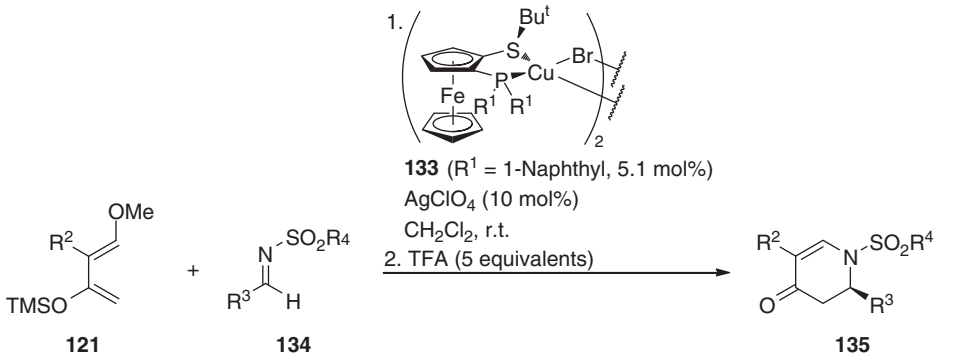
n	Yield	*Exo*/*endo*	*ee*
1	92%	92:8	83%
2	59%	88:12	95%



1 + **130** → **132**

R^1	Solvent	Yield	*ee*
Ts	CH_2Cl_2	89%	26%
Ts	THF	80%	79%
C_6H_4-2-OMe	CH_2Cl_2	78%	91%
C_6H_4-4-OMe	CH_2Cl_2	75%	78%

Scheme 31 Aza-Diels–Alder reaction of α-imino esters **130** catalyzed by a chiral Cu(I) complex with (*R*)-Tol–BINAP **129**.

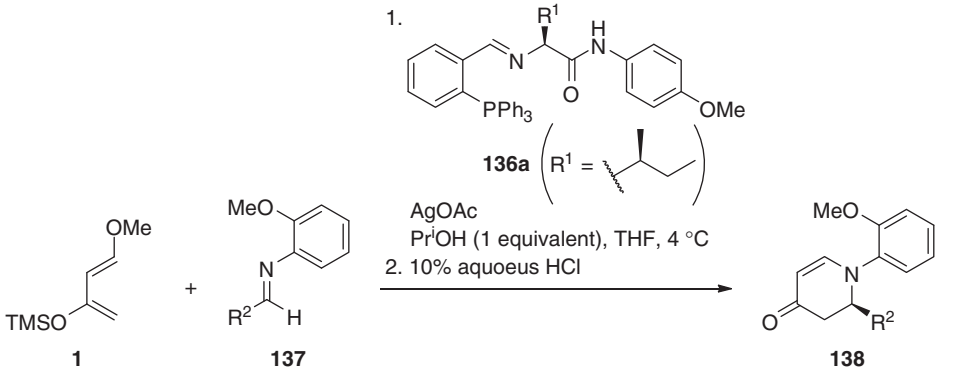


(14)

Table 20 Aza-Diels–Alder reactions of *N*-sulfonylimines **134** catalyzed by a copper(I) complex **133** (equation 14)

R^2	R^3	R^4	*Yield (%)*	ee *(%)*	*References*
H	Ph	C_6H_4–4-Me	90	93	78
Me	Ph	C_6H_4–4-Me	64	87	78
H	C_6H_4–4-F	C_6H_4–4-Me	78	88	78
H	C_6H_4–4-OMe	C_6H_4–4-Me	76	91	78
H	CH=CHPh	C_6H_4–4-Me	66	83	78
Me	CH=CHPh	C_6H_4–4-Me	57	88	78
H	Ph	C_6H_4–4-OMe	61	94	78
H	Ph	C_6H_4–4-NO_2	58	90	78

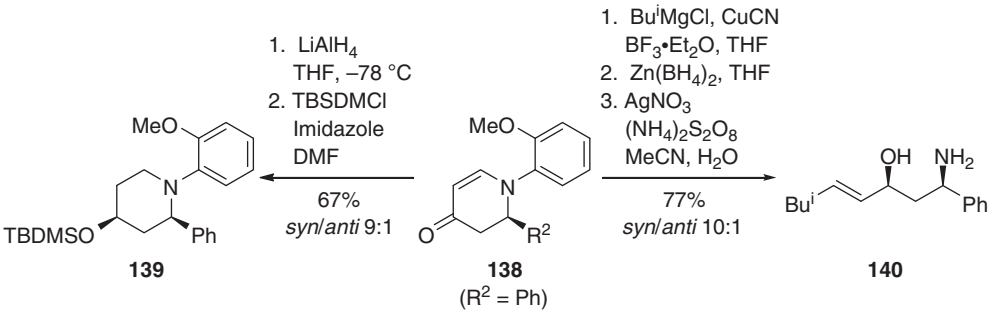
A chiral silver(I) complex prepared from AgOAc and the phosphine ligand **136a** catalyzes the aza-Diels–Alder reaction of relatively inactive imines **137** with Danishefsky diene **1** (equation 15, Table 21).[79] A catalyst loading of only 0.1–1 mol% is required to complete the reaction and give the cycloadducts **138** in high yields with high enantioselectivities. The presence of an *ortho*-methoxy group in the imine substrates is required for high enantioselectivity, but not for reactivity. In addition, the presence of isopropyl alcohol significantly increased both the reactivity and enantioselectivity. Importantly, the present reaction can be carried out in the presence of air with undistilled commercial solvents, or under solvent-free conditions with little change in yield or enantioselectivity. The stereoselective reduction of the adduct **138** (R^2=Ph) with $LiAlH_4$ gives cyclic amine **139** with 9:1 diastereoselectivity (Scheme 32). The treatment of **138** (R^2=Ph) with diisobutylcuprate followed by stereoselective reduction with $Zn(BH_4)_2$ gives the linear 1,3-amino alcohol **140** with 10:1 diastereoselectivity (93% *ee*).



(15)

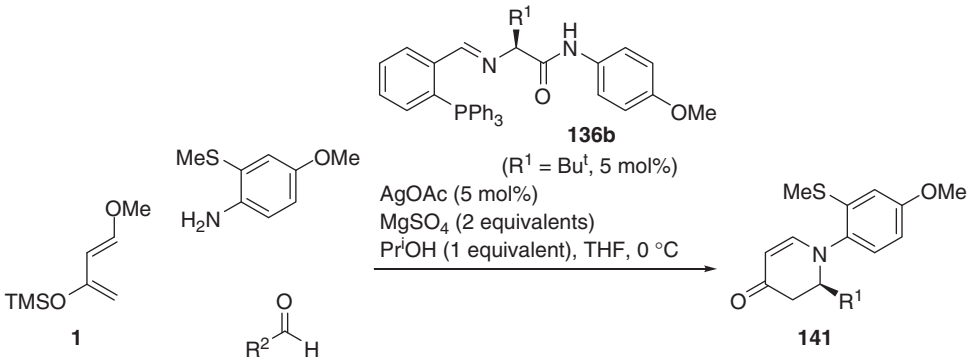
Table 21 Aza-Diels–Alder reactions of imines **137** catalyzed by chiral silver(I) complex with phosphine ligand **136a** (equation 15)

R^2	*Catalyst loading (**136a**, AgOAc) (mol%)*	*Yield (%)*	ee *(%)*	*References*
Ph	0.5	92	92	79
Ph	0.1	78	88	79
2-Naphthyl	0.5	>98	95	79
C_6H_4–4-OMe	1	86	91	79
C_6H_4–2-Br	1	91	89	79
C_6H_4–4-NO_2	1	>98	92	79
2-Furyl	1	89	92	79



Scheme 32

A direct three-component enantioselective aza-Diels–Alder reaction of aliphatic aldehydes, 4-methoxy-2-(methylthio)aniline and Danishefsky diene **1** is catalyzed by a silver(I) complex prepared from AgOAc and the phosphine ligand **136b** (Scheme 33).[80] In the presence of the chiral silver(I) catalyst (5 mol%), the reaction is carried out under an atmosphere of air and in undistilled THF, to give the cycloadducts **141** in up to 88% yield with up to 95% *ee*.



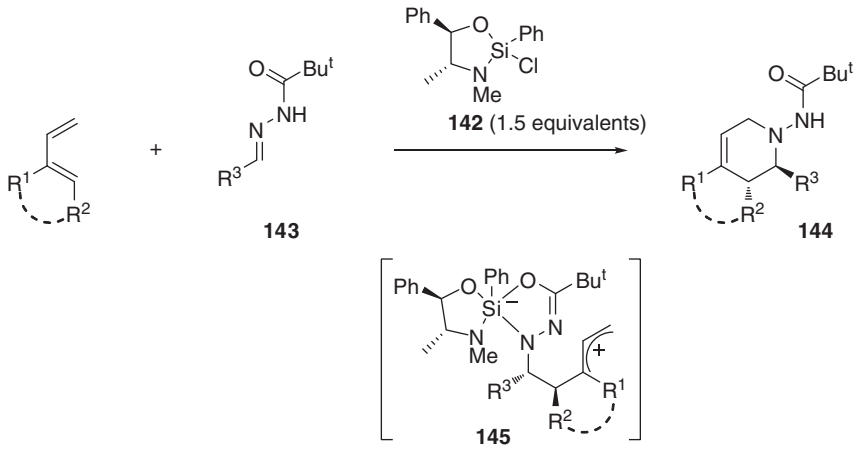
R^2	Yield	*ee*
Bu^i	88%	92%
$(CH_2)_2Ph$	88%	93%
$(CH_2)_2CO_2Me$	53%	90%
CH_2OBn	66%	95%

Scheme 33 Direct three-component enantioselective aza-Diels–Alder reaction catalyzed by a silver(I) complex with phosphine ligand **136b**.

The enantioselective aza-Diels–Alder reactions described above are limited to the use of highly reactive Danishefsky-type dienes, and reactions with non-Danishefsky-type dienes are rare. A stoichiometric amount of chiral silane **142** can promote the aza-Diels–Alder reaction of acyl hydrazones **143** with non-Danishefsky-type dienes (Scheme 34, Table 22).[81,82] The reaction proceeds in a stepwise fashion via allyl cation intermediate **145**. The use of sterically hindered pivaloyl hydrazones **143** selectively gives the aza-Diels–Alder adducts **144**, whereas the [3 + 2] cycloadduct is obtained along with **144** when *o*-methoxybenzoyl hydrazone is used. Both electron-poor hydrazones ($R^3 = CO_2Pr^i$) and less reactive aliphatic aldehyde-derived hydrazones ($R^3 = (CH_2)_2Ph$) are converted to the corresponding adducts **144** with high enantioselectivities. The **142**-promoted reaction with diene **146** gives the corresponding *endo*-adduct **147** with complete regio- and diastereoselectivity and 86% *ee* (Table 22). However, the reaction with diene **148** gives **149** with reversed regioselectivity. The reaction appears to be governed by the minimization of steric interaction during the initial C–C bond formation.

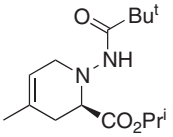
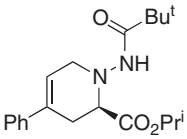
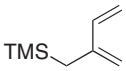
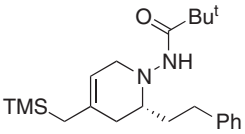
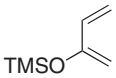
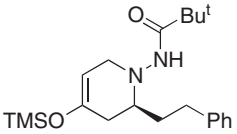
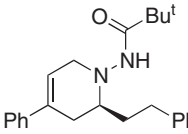
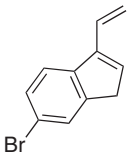
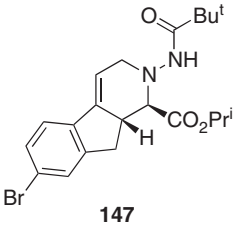
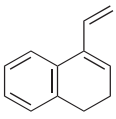
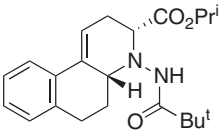
5.10.3.1.2 Chiral organocatalysts

(*S*)-Proline **150a** and its derivatives **150b** and **150c** can catalyze the three-component direct aza-Diels–Alder reaction between aromatic amines, formaldehyde, and α,β-unsaturated ketones **151** in dimethylsulfoxide (DMSO) (equation 16, Table 23).[83]



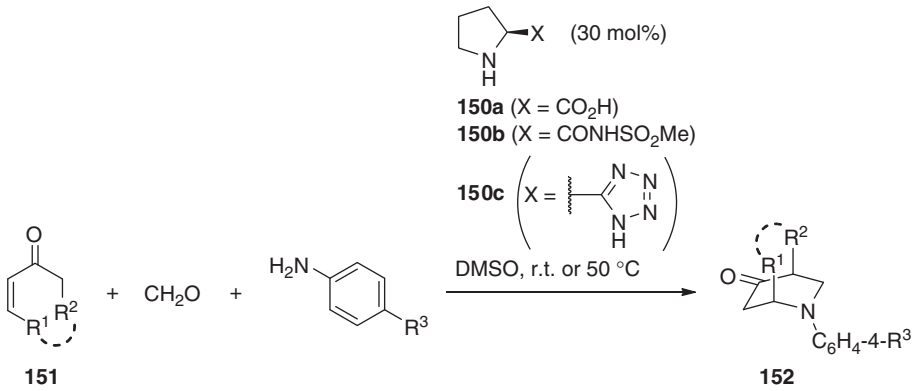
Scheme 34

Table 22 Chiral silane **142**-promoted aza-Diels–Alder reaction of acyl hydrazones **143** with non-Danishefsky-type dienes (**Scheme 34**)

Diene	*R^3*	*Conditions*	*Adduct*	*Yield (%)*	ee *(%)*	*References*
	CO_2Pr^i	$CHCl_3$, 23 °C		96	85	81,82
	CO_2Pr^i	Toluene, 23 °C		66	95	81,82
	$(CH_2)_2Ph$	$CHCl_3$, reflux		99[a]	90	81,82
	$(CH_2)_2Ph$	CH_2Cl_2, reflux		78	87	81,82
	$(CH_2)_2Ph$	$CHCl_3$, reflux		82	84	81,82
 **146**	CO_2Pr^i	CH_2Cl_2, 23 °C	 **147**	66	86	81,82
 **148**	CO_2Pr^i	CH_2Cl_2, 23 °C	 **149**	61[b]	97	81,82

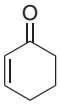
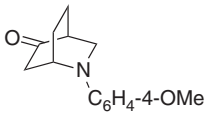
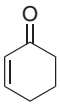
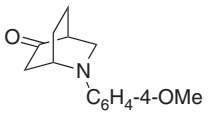
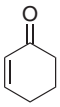
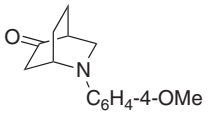
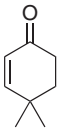
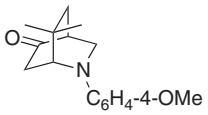
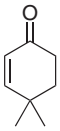
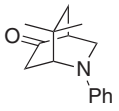
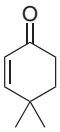
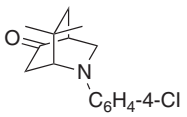
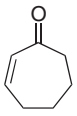
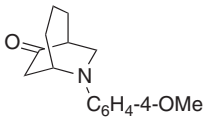
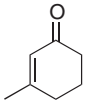
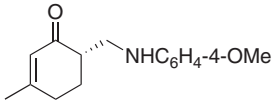
[a] *ent*-**142** was used.
[b] 4:1 Regioselectivity, 4:1 diastereoselectivity.

α,β-Unsaturated cyclohexenones and cyclopentenones are excellent substrates, and the corresponding bicyclic adducts **152** are obtained with high enantioselectivities. For the reaction of α,β-unsaturated cyclopentenones, (*S*)-proline **150a** is the most effective catalyst. However, the reaction of 3-methylcyclohex-2-enone only generates the α,β-unsaturated Mannich adduct in 40% yield with 94% *ee*, and not the aza-Diels–Alder product.



(16)

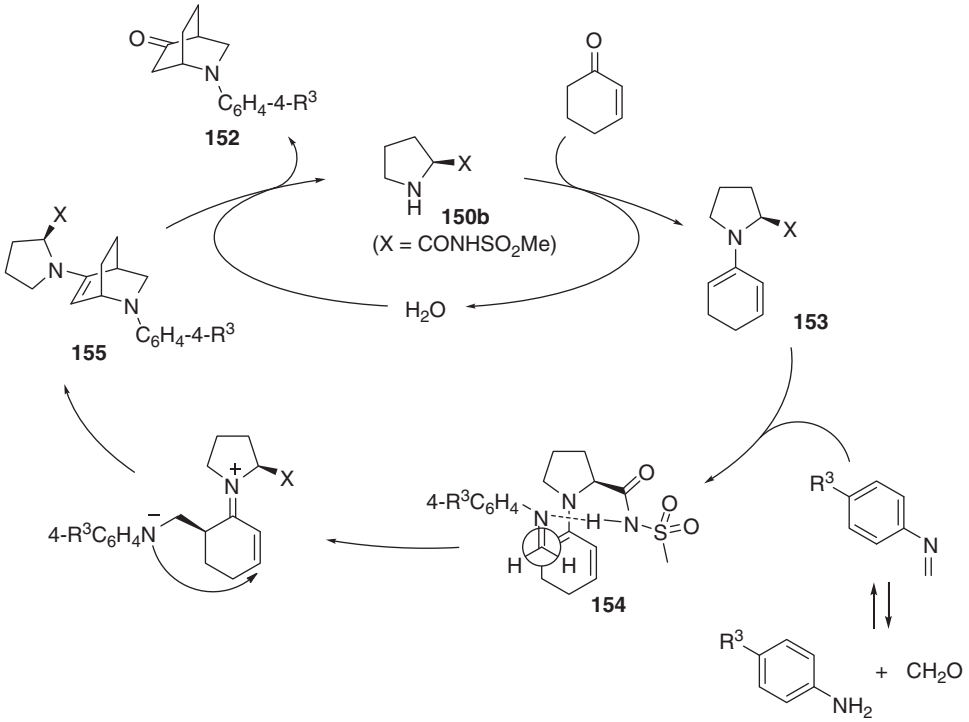
Table 23 Three-component direct aza-Diels–Alder reaction catalyzed by (*S*)-proline and its derivatives **150** (equation 16)

Ketone	*R^3*	*Catalyst*	*Adduct*	*Yield (%)*	ee *(%)*	*References*
	OMe	**150a**		82[a]	99	83
	OMe	**150b**		31	94	83
	OMe	**150c**		61	99	83
	OMe	**150a**		70	>99	83
	H	**150a**		69	98	83
	Cl	**150a**		32	>99	83
	OMe	**150a**		75	98	83
	OMe	**150a**		40	94	83

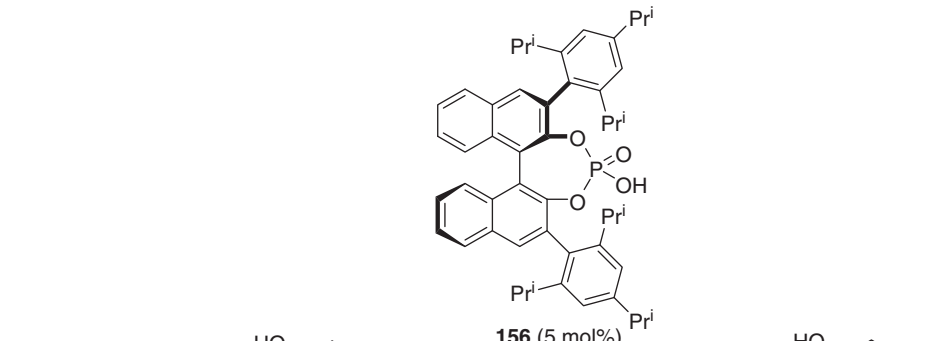
[a]Yield of the corresponding alcohol (a 1:1 *cis*/*trans* mixture) obtained by *in situ* reduction of **152** with $NaBH_4$ after column chromatography on silica gel.

Based on the absolute stereochemistry of the adducts and the generation of the Mannich product, the following reaction mechanism is proposed (Scheme 35). In the first step, the (*S*)-proline derivative **150b** activates an α,β-unsaturated ketone **151**

through the formation of chiral dienamine **153**. Next, the *in situ*-generated imine reacts with **153** via transition state **154**, followed by a selective 6-*endo-trig* cyclization to give the bicyclic compound **155**. In the transition state **154**, the Brønsted acidic site may act as a directing group for the imine to approach the *Si* face of **153**. The final hydrolysis of **155** affords the aza-Diels–Alder adduct **152**, and the (*S*)-proline derivative is regenerated.



Scheme 35 Proposed catalytic cycle.

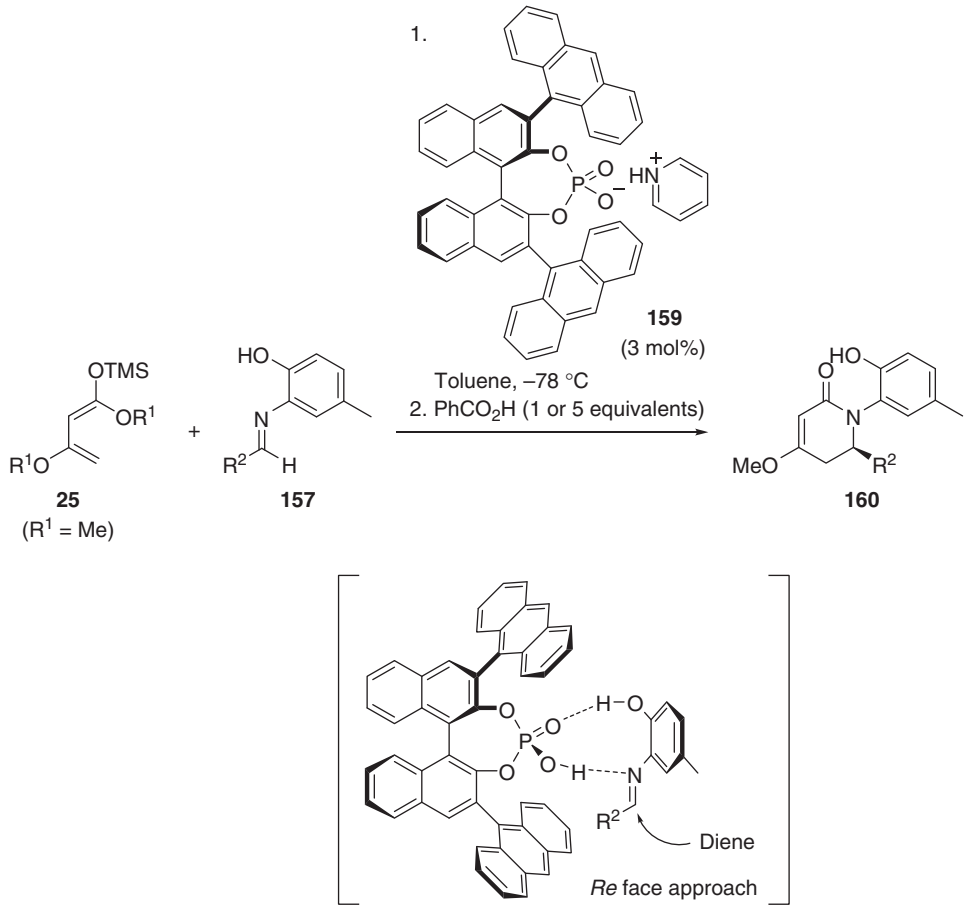


R^1	Yield	*ee*
Ph	99%	80%
C_6H_4-4-Br	100%	84%
C_6H_4-2-Br	96%	80%
1-naphthyl	100%	91%

Scheme 36 Chiral Brønsted acid-catalyzed aza-Diels–Alder reaction with Danishefsky's diene **1**.

Chiral phosphoric acids **156** and **159** derived from (*R*)-BINOL are efficient catalysts for the enantioselective aza-Diels–Alder reaction of aldimines **157** with Danishefsky's diene **1** and Brassard's diene **25**. For the reaction with Danishefsky's diene **1**, the chiral Brønsted acid **156** is highly effective for giving the corresponding cycloadducts **158** with high enantioselectivities (Scheme 36).[84] The addition of a protic additive such as acetic acid (1.2 equivalents) improves the enantioselectivity, although its role is not clear.

Brassard's diene **25** (R^1 = Me) is also a useful diene for the aza-Diels–Alder reaction of aldimines, which affords piperidinone derivatives. In the presence of the pyridinium salt of chiral phosphoric acid **159** (3 mol%), the reaction of aldimine **157** with Brassard's diene **25** is conducted in mesitylene at $-40\ ^\circ C$, and subsequent treatment of the reaction mixture with $PhCO_2H$ (1 equivalent) gives dihydropyridone derivatives **160** with high enantioselectivity (Scheme 37, Table 24).[85] Interestingly, the less acidic pyridinium salt **159** shows greater catalytic activity than the corresponding phosphoric acid. This result may be attributed to the instability of Brassard's diene **25** toward strong Brønsted acids. Indeed, a ^1H NMR study showed that, in the presence of **159**, 75% of **25** was detected after 1 h, whereas only 12% of **25** was detected in the presence of the corresponding phosphoric acid. The presence of the hydroxyl moiety on the *N*-aryl group is essential for attaining high enantioselectivity. These results suggest that the present aza-Diels–Alder reaction proceeds via a nine-membered cyclic transition state, wherein the phosphoryl oxygen atom participates in hydrogen bonding with the hydrogen atom of the imine hydroxyl moiety, with the nucleophile preferentially attacking the *Re* face of the aldimine **157** (Scheme 37). The methoxy group of the product can be transformed into other functionalities via acid hydrolysis, followed by an addition–elimination reaction.

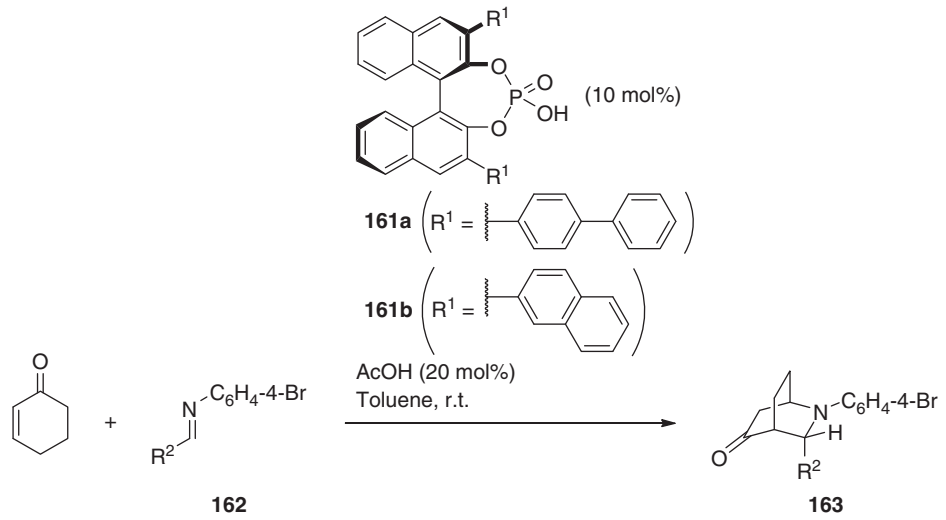


Scheme 37

The simultaneous use of a chiral strong Brønsted acid catalyst and an achiral weak Brønsted acid catalyst can promote the direct aza-Diels–Alder reaction of aldimines **162** with cyclohexenone (equation 17, Table 25).[86] In this reaction, the chiral strong Brønsted acid activates the aldimine **162** through protonation, and the achiral weak Brønsted acid activates cyclohexenone through the formation of cyclohexadienol. Thus, the fundamental requirement for successful promotion of the reaction is that the achiral Brønsted acid is not able to activate the aldimine **162**. Under the optimized conditions, chiral BINOL-phosphoric acids **161** are suitable as a strong chiral Brønsted acid catalyst, and acetic acid works best as an achiral weak Brønsted acid. In the presence of **161** (10 mol%) and acetic acid (20 mol%), the reaction of aldimines **162** with cyclohexenone gives the corresponding isoquinuclidines **163** in good yields with high enantioselectivities.

Table 24 Chiral Brønsted acid-catalyzed aza-Diels–Alder reaction with Brassard's diene **25** (R^1 = Me) (**Scheme 37**)

R^2	*Yield (%)*	ee *(%)*	*References*
Ph	87	94	85
C_6H_4–4-Cl	90	97	85
C_6H_4–4-OMe	84	99	85
1-Naphthyl	79	98	85
2-Furyl	63	97	85
CH=CHPh	76	98	85
$^cC_6H_{11}$	69	99	85



(17)

Table 25 Double-Brønsted acid-catalyzed direct aza-Diels–Alder reaction of aldimines **162** with cyclohexenone (equation 17)

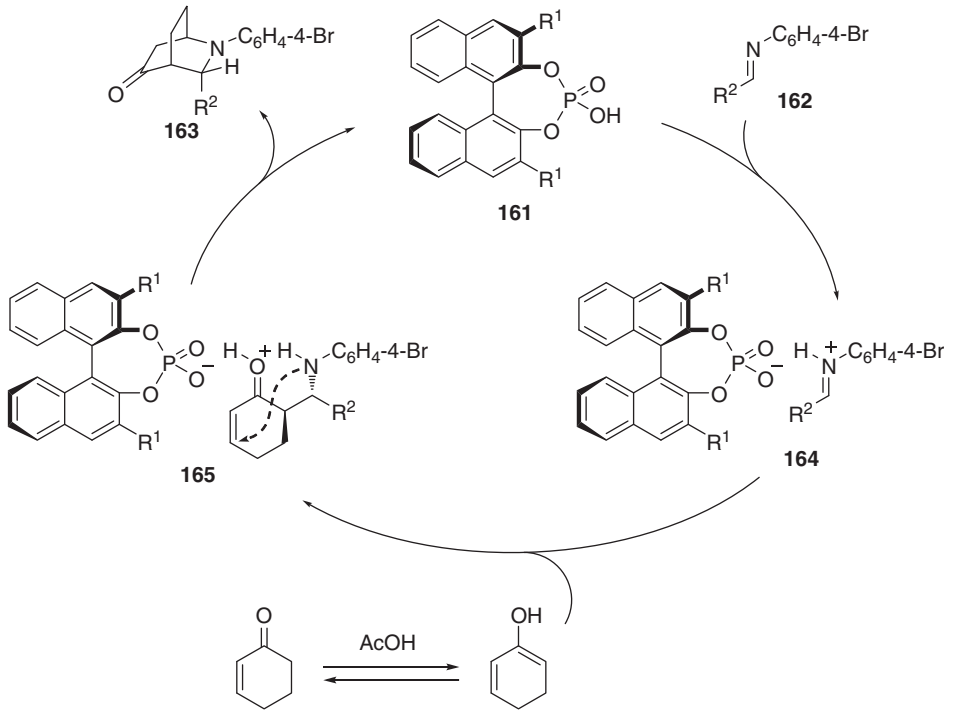
R^2	***161a*** *(R^1 = 4-biphenyl)*			***161b*** *(R^1 = 2-naphthyl)*			*References*
	Yield (%)	Endo/exo	ee *(%)*	*Yield (%)*	Endo/exo	ee *(%)*	
Ph	62	80:20	84	71	80:20	86	86
C_6H_4–4-Cl	57	80:20	86	73	80:20	88	86
C_6H_3–2,3-$(OMe)_2$	76	90:10	86	84	89:11	86	86
9-Pyrene	65	83:17	88	67	80:20	86	86
4-Biphenyl	64	80:20	80	54	80:20	84	86
2-Thienyl	63	80:20	86	70	80:20	88	86

It is conceivable that the reaction proceeds in a stepwise fashion as shown in **Scheme 38**. In the first step, the chiral Brønsted acid **161** activates an aldimine **162** to form a chiral ion pair **164**, whereas cyclohexadienol is formed with the aid of achiral weak Brønsted acid (acetic acid) through a shift of the keto–enol equilibrium. The subsequent intermolecular Mannich reaction provides the adduct **165**, which leads directly to the corresponding chiral isoquinoline **163**. The rate-determining step of the reaction may be the formation of cyclohexadienol, since no significant conversion is observed in the absence of acetic acid.

5.10.3.2 Inverse Reactions of Azabutadienes

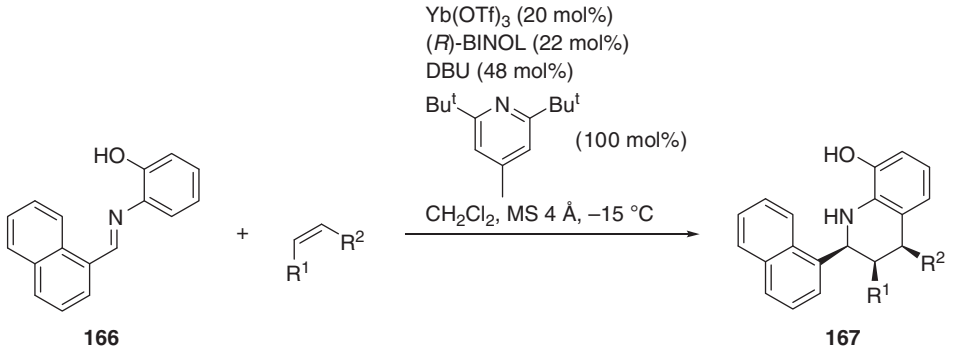
Aza-1,3-butadienes are versatile building blocks for the construction of various nitrogen-containing heterocyclic compounds.[9,12] Due to their electron-deficient nature, aza-1,3-butadienes tend to undergo an inverse electron-demand Diels–Alder reaction with electron-rich dienophiles such as vinyl ethers and enamines.

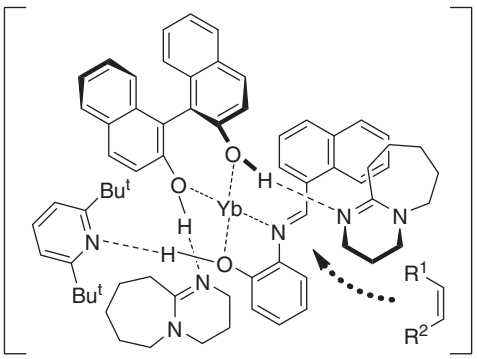
LA catalysts activate an aza-1,3-butadiene by lowering its LUMO energy to promote the inverse electron-demand aza-Diels–Alder reaction with alkenes. For example, aldimine **166** acts as a 2-aza-1,3-butadiene and is activated by a chiral Yb(III) complex prepared from $Yb(OTf)_3$, (*R*)-BINOL, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**Scheme 39**, **Table 26**).[87] In the presence of



Scheme 38 Plausible catalytic cycle.

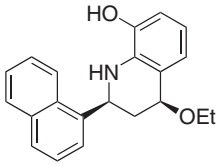
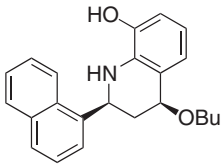
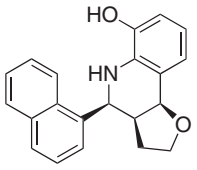
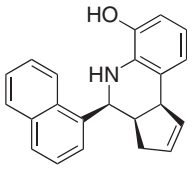
the chiral Yb(III) complex, aldimine **166** reacts with electron-rich alkenes to give the tetrahydroquinolines **167** with good enantioselectivities. The use of 2,6-di-*tert*-butyl-4-methylpyridine as the additive is crucial for preventing the interaction of DBU with the phenolic hydrogen on the aldimine **166** and for improving the selectivity. A proposed transition-state assembly is shown in Scheme 39. $Yb(OTf)_3$, (*R*)-BINOL, and DBU form a complex with two hydrogen bondings, and 2,6-di-*tert*-butyl-4-methylpyridine may interact with the phenolic hydrogen of **166**. Since the top face of the coordinated imine is shielded by DBU, the dienophile approaches the bottom face.



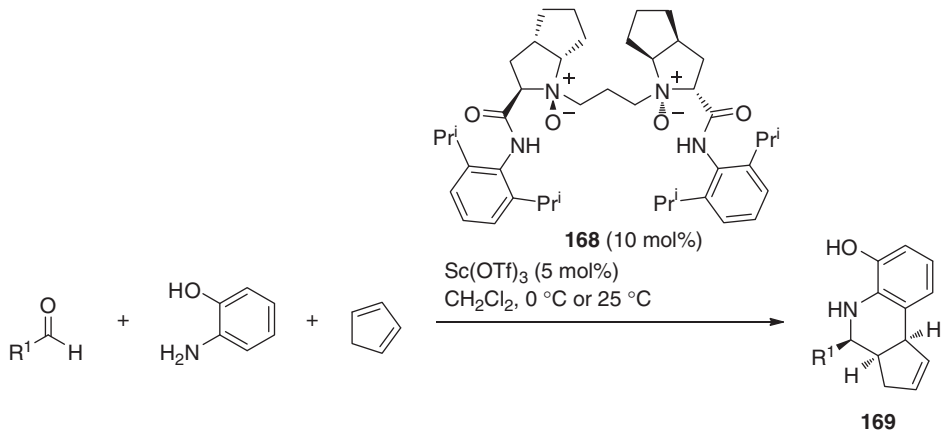


Scheme 39

Table 26 Inverse electron-demand aza-Diels–Alder reaction of aldimine **166** catalyzed by the Yb(III) complex (**Scheme 39**)

Dienophile	*Adduct*	*Yield (%)*	Cis/trans	ee *(%)*	*References*
		74	>99:1	91	87
		80	66:34	70	87
		90	91:9	78	87
		69	>99:1	68	87

As in the case of normal electron-demand aza-Diels–Alder reactions, the three-component direct inverse electron-demand aza-Diels–Alder reaction can be catalyzed by a chiral scandium(III) complex with *N*,*N*′-dioxide ligand **168** (equation 18, **Table 27**).[88] In the presence of the Sc(III) complex (5 mol%), the reaction of aldehydes, 2-aminophenol and cyclopentadiene proceeds to give ring-fused tetrahydroquinolines **169** with three contiguous stereocenters. In this reaction, *in situ*-generated aldimines act as 2-azadienes and cyclopentadiene acts as a dienophile. The present reaction can be applied to a variety of aldehydes to give adducts **169** in high yields with excellent enantioselectivities.

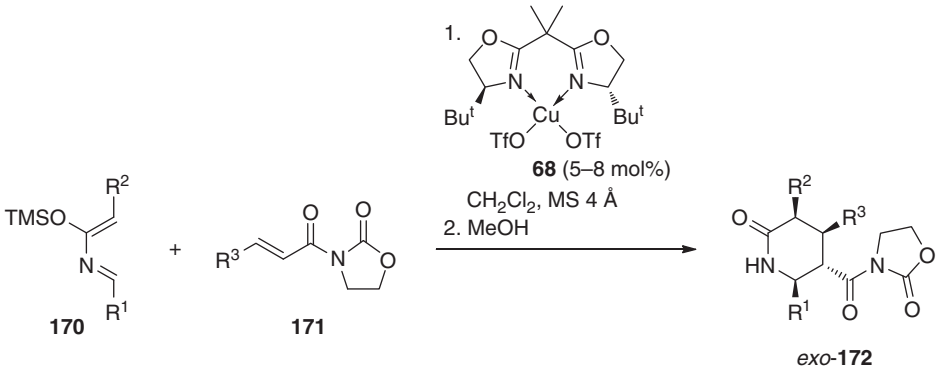


(18)

2-Azadienes **170** are electron-rich dienes and react with *N*-alkenoyloxazolidinones **171**, which are electron-deficient dienophiles, in the presence of an LA catalyst (equation 19, **Table 28**).[89] The copper(II)–bis(oxazoline) complex **110** is an efficient catalyst for the present reaction and subsequent methanolysis gives piperidones **172** in high yields with high diastereo- and enantioselectivities. As in the case of the enantioselective carbo-Diels–Alder reaction with 1,3-dienes, *N*-alkenoyloxazolidinones **171** are activated by the Cu(II) catalyst **110** in a bidentate fashion by lowering of its LUMO energy. Thus, mechanistically, the aza-Diels–Alder reaction of **170** is categorized as a 'normal electron-demand' reaction. The absolute configuration of **172** is consistent with the proposed transition-state assembly for the **68**-catalyzed carbo-Diels–Alder reaction of **171** (*see* Chapter 5.09).[90]

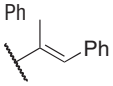
Table 27 Three-component direct inverse electron-demand aza-Diels–Alder reaction catalyzed by a chiral scandium(III) complex with *N,N'*-dioxide ligand **168** (equation 18)

R^1	*Yield (%)*	cis/trans	ee *(%)*	*References*
Ph	90	96:4	97	88
C_6H_4–2-Me	62	92:8	92	88
C_6H_4–4-Cl	99	95:2	96	88
C_6H_4–4-OMe	63	90:10	>99	88
1-Naphthyl	85	96:4	95	88
2-Thienyl	93	96:4	98	88
$^cC_6H_{11}$	99	>99:1	99	88
$CHEt_2$	62	>95:5	94	88

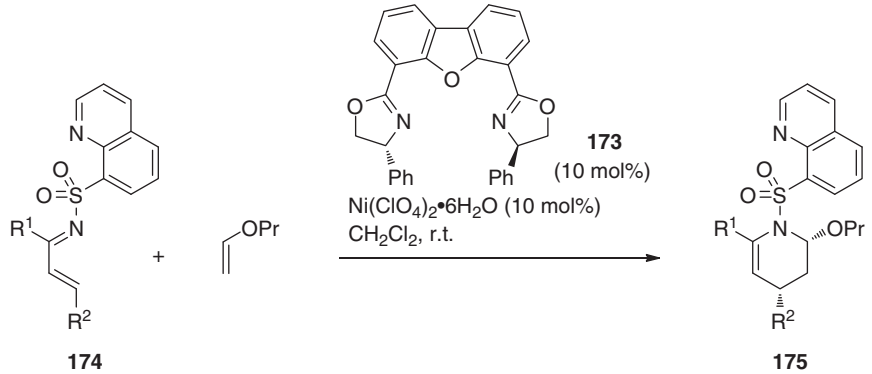


(19)

Table 28 Inverse electron-demand aza-Diels–Alder reaction of 2-azadienes **170** (equation 19)

R^1	R^2	R^3	*Temperature (°C)*	*Yield (%)*	Exo/endo	ee *(%)*	*References*
Ph	Me	Me	r.t.	96	>99:1	94	89
Ph	H	H	−45	83	86:14	98	89
Ph	Me	H	−45	96	>99:1	98	89
Ph	H	Me	r.t.	80	>99:1	93	89
	Me	Me	−45	62	>99:1	95	89

Section 5.10.3.1.1 states that *N*-sulfonylimines **134** including α,β-unsaturated derivatives act as azadienophiles and react with Danishefsky-type dienes **121** with the aid of the chiral Cu(I) complex **133** (equation 14). In contrast, a chiral Ni(II) complex with DBFOX-Ph ligand **173** promotes the inverse electron-demand aza-Diels–Alder reaction of α,β-unsaturated *N*-[(8-quinolyl)sulfonyl]imines **174** with propyl vinyl ether to give the corresponding adducts **175** (equation 20, Table 29).[91] In this reaction, α,β-unsaturated imines **174** act as 1-aza-1,3-butadienes, and the *N*-(8-quinolyl) group is crucial for obtaining high yield and high enantioselectivity. The enantioselectivity strongly depends on the R^2 group of **174**, whereas *para*-substituted aryl groups are compatible, sterically demanding 2-naphthyl group and sterically less-hindered vinyl group significantly reduce the enantioselectivities.



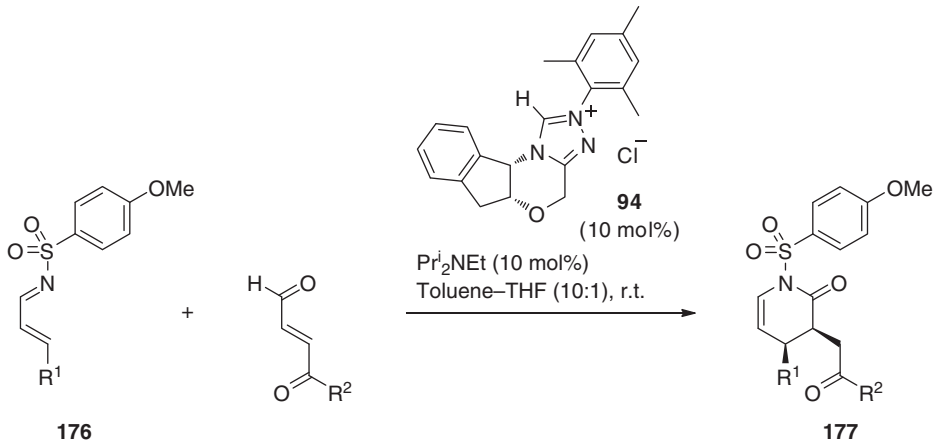
(20)

As described in Section 5.10.2.2.2, the chiral *N*-heterocyclic carbene prepared from triazolium salt **94** catalyzes the *oxo*-Diels–Alder reaction of α,β-unsaturated carbonyl compounds **95** with α,β-enals (equation 11). The chiral *N*-heterocyclic carbene can also

Table 29 Inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated *N*-[(8-quinolyl)sulfonyl]imines **174** (equation 20)

R^1	R^2	*Yield (%)*	Endo/exo	ee *(%)*	*References*
Ph	Ph	66	98:2	91	91
Ph	C_6H_4–4-F	75	98:2	92	91
Ph	2-Furyl	52	97:3	77	91
Ph	Bu^t	61	98:2	84	91
C_6H_4–4-CF_3	Ph	69	97:3	91	91
C_6H_4–4-CN	(*E*)-CH=CHPh	70	98:2	92	91
2-Naphthyl	Ph	67	98:2	6	91
(*E*)-CH=CHPh	Ph	68	90:10	20	91

catalyze the aza-Diels–Alder reaction of α,β-unsaturated *N*-(*p*-methoxybenzenesulfonyl)aldimine **176** (equation 21, **Table 30**).[92] In the presence of **94** (10 mol%) and *N*,*N*-(diisopropyl)ethylamine (10 mol%), the reaction of **176** with α,β-unsaturated aldehydes gives the corresponding dihydropyridinones **177** with excellent diastereo- and enantioselectivities. This process tolerates a full range of unsaturated aldimine substrates including both electron-rich and electron-deficient cinnamaldehyde derivatives as well as heterocyclic and aliphatic examples. As in the *oxo*-Diels–Alder variant, the (*Z*)-enolate **104** is believed to be generated as the active species and react with **176** via an *endo*-transition state (see **Scheme 26**).

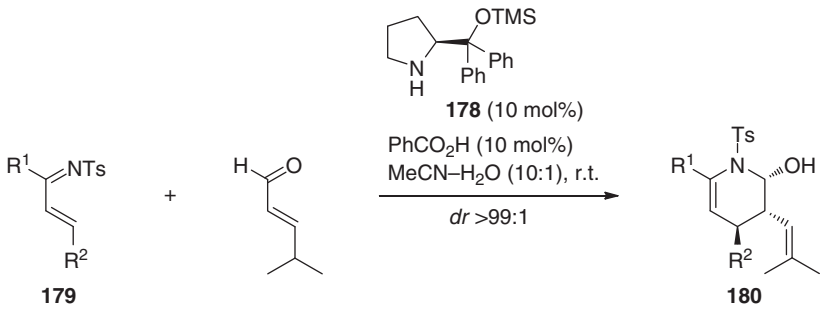


(21)

Table 30 Chiral *N*-heterocyclic carbene-catalyzed aza-Diels–Alder reaction of α,β-unsaturated *N*-sulfonylaldimine **176** with α,β-unsaturated aldehydes (equation 21)

R^1	R^2	*Yield (%)*	ee *(%)*	*References*
Ph	OEt	90	99	92
C_6H_4–4-OMe	OEt	81	99	92
C_6H_4–4-$COCH_3$	OEt	55	99	92
2-Furyl	OEt	71	99	92
Pr	OEt	58	99	92
Ph	OBu^t	70	97	92
Pr	Me	71	98	92
C_6H_4–4-OMe	Ph	52	99	92

The chiral secondary amine **178** (10 mol%) and benzoic acid (10 mol%) can activate α,β-unsaturated aldehydes to promote the aza-Diels–Alder reaction with *N*-tosylaldimines **179** (equation 22, **Table 31**).[93] In contrast to the *N*-heterocyclic carbene-catalyzed reaction, this reaction gives the corresponding hemiaminals **180** bearing a dimethylvinyl group in high yields with excellent diastereo- and enantioselectivities. As in the case of the oxo-Diels–Alder reaction of α,β-unsaturated carbonyl compounds **59** (**Scheme 23**), the reaction proceeds via a chiral enamine as the active species, which is an electron-rich dienophile. The addition of water leads to a dramatic acceleration of the reaction due to facile hydrolysis of the aminal intermediate. The reaction of **179** (R^1=Ph, R^2=CO_2Et) with unbranched α,β-enals **181** followed by PCC oxidation selectively gives the corresponding lactam **182** bearing an (*E*)-alkenyl group with high enantioselectivities (**Scheme 40**). Saturated aldehydes are also activated by the combined use of **178** and acetic acid (10 mol% each), and the reaction with **179** (R^1=Ph) gives the corresponding hemiaminals **183** with high diastereo- and enantioselectivities (**Scheme 41**).[94] The use of acetic acid instead of benzoic acid slightly improves the enantioselectivity. For the reaction with butyraldehyde, a wide range of substituents can be presented at the β-position of **179**.

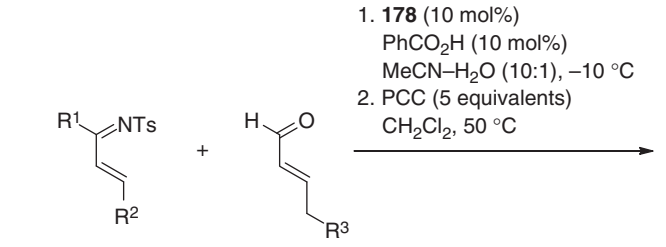


(22)

Table 31 Chiral secondary amine-catalyzed aza-Diels–Alder reaction of *N*-tosylaldimines **179** (equation 22)

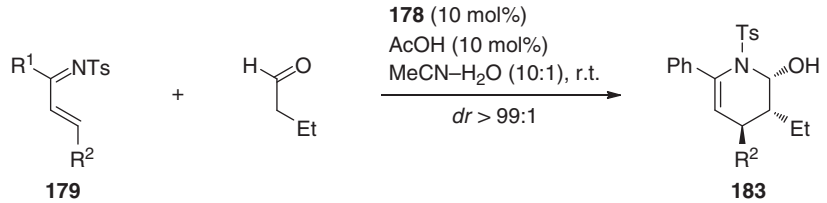
R^1	R^2	*Temperature (°C)*	*Yield (%)*	ee *(%)*	*References*
Ph	CO_2Et	r.t.	95	99	93
2-Thienyl	CO_2Et	r.t.	91	99	93
CO_2Et	Ph	r.t.	95	>99	93
CO_2Et	C_6H_4–2-Br	35	91	>99	93
CO_2Et	C_6H_4–4-OMe	r.t.	96	>99	93
Ph	Ph	35	89	99	93
Ph	Me	35	85	98	93

Bifunctional organocatalysis is a potentially powerful tool for asymmetric transformations that cannot be achieved by the use of either an LA or a base catalyst alone. The chiral primary amine/thiourea **184** (10 mol%), a bifunctional organocatalyst, in combination with acetic acid (20 mol%) promotes the inverse electron-demand aza-Diels–Alder reaction of *N*-tosylazadienes **185** with



R^3	Yield	*E*/*Z*	*ee*
Me	66%	85:15	98%
Et	68%	89:11	99%
Pr	70%	87:13	97%

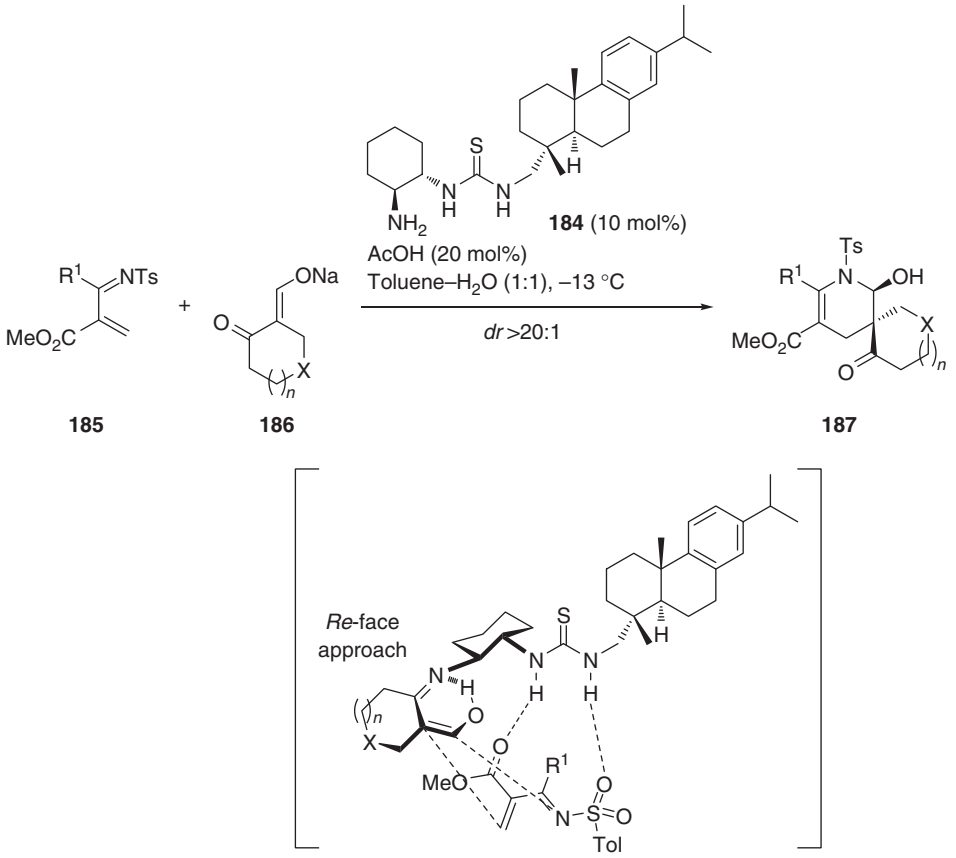
Scheme 40 Chiral secondary amine-catalyzed aza-Diels–Alder reaction with unbranched α,β-enals **181**.



R^2	Yield	*ee*
Ph	88%	97%
C_6H_4-3-Cl	92%	99%
2-Furyl	83%	98%
Me	83%	93%

Scheme 41 Chiral secondary amine-catalyzed aza-Diels–Alder reaction with saturated aldehydes.

cyclic keto/enolate salts **186** (Scheme 42, Table 32).[95] When the reaction is conducted in a biphasic mixture of toluene and water (1:1) at −13 °C, the corresponding azaspirocyclic compounds **187** are obtained with high diastereo- and enantioselectivities. With regard to the absolute stereochemistry of the inverse electron-demand aza-Diels–Alder reaction, it has been proposed that the azadiene **185** is fixed and activated by the two thiourea hydrogen atoms through weak hydrogen bonding (lowering of the LUMO energy), whereas the cyclic keto/enolate salt **186** is activated by the formation of a ketimine (increase in the HOMO energy), as shown in Scheme 42. The activated azadiene **185** should approach the *Re*-face of the activated cyclic keto/enolate salt **186**.

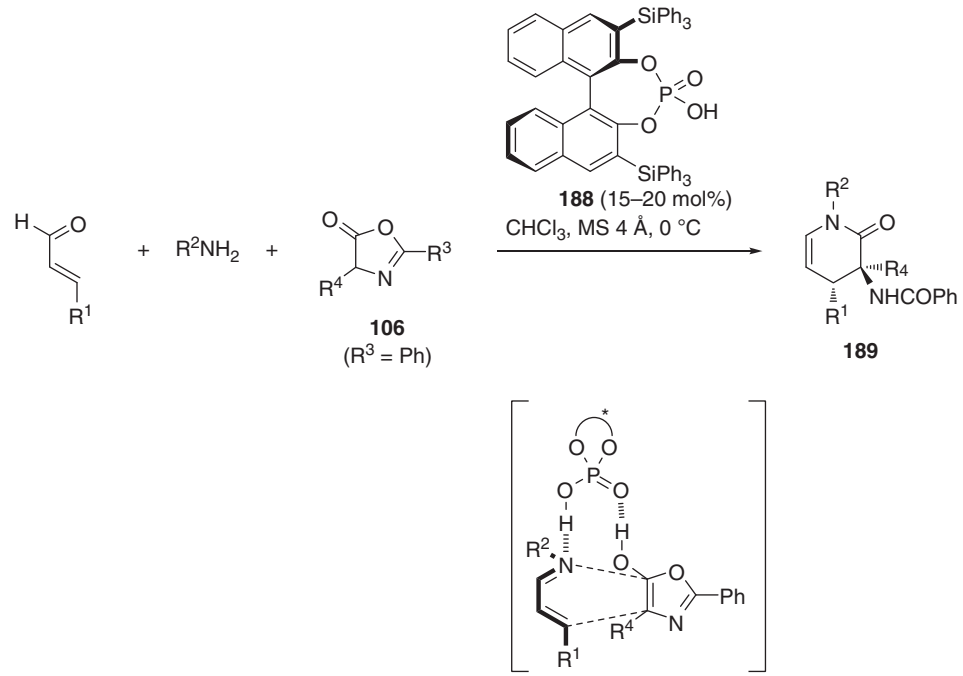


Scheme 42

Table 32 Aza-Diels–Alder reaction of *N*-tosylazadienes 185 with cyclic keto/enolate salts 186 promoted by bifunctional organocatalyst 184 (Scheme 42)

R^1	X	n	Yield (%)	ee (%)	References
Ph	CH_2	0	99	>99	95
C_6H_4–4-OMe	CH_2	0	99	90	95
C_6H_4–4-Cl	CH_2	0	97	91	95
2-Furyl	CH_2	0	99	92	95
2-Thienyl	CH_2	0	98	97	95
C_6H_4–4-OMe	CH_2	1	87	93	95
C_6H_4–4-OMe	O	1	85	>99	95
C_6H_4–4-OMe	S	1	84	>99	95
C_6H_4–4-OMe	CH_2	2	96	88	95

As described in Section 5.10.2.2.2, azlactones **106** are versatile dienophiles for the hetero-Diels–Alder reaction with α,β-unsaturated ketones (Scheme 27). When the reaction of **106** (R^3 = Ph) with α,β-unsaturated aldehydes is conducted in the presence of an electron-rich aniline, δ-lactams **189** are obtained with high enantioselectivities (Scheme 43, Table 33).[96] The use of chiral phosphoric acid **188** gives the best results in terms of yield and stereochemical outcome. It is conceivable that the three-component reaction proceeds through the formation of α,β-unsaturated aldimines. The chiral phosphoric acid simultaneously activates the aldimines and azlactones **188** to promote the aza-Diels–Alder reaction.



Scheme 43

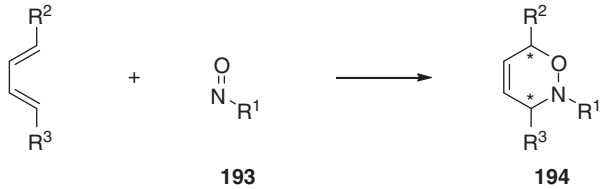
Table 33 Chiral phosphoric acid-catalyzed three-component aza-Diels–Alder reaction of azlactones **106** (Scheme 43)

R^1	R^2	R^4	*Yield (%)*	ee *(%)*	*References*
C_6H_4–2-NO_2	C_6H_4–4-OMe	Me	81	91	96
C_6H_4–2-NO_2	C_6H_4–3-OMe	Me	80	96	96
C_6H_4–4-NO_2	C_6H_4–2-OMe	Me	73	84	96
C_6H_4–2-OMe	C_6H_4–3-OMe	Me	76	62	96
C_6H_4–2,3-Cl_2	C_6H_4–3-OMe	Me	62	96	96
1-Naphthyl	C_6H_4–3-OMe	Me	88	86	96
C_6H_4–2-NO_2	C_6H_4–3-OMe	Et	80	91	96
C_6H_4–2-NO_2	C_6H_4–3-OMe	$(CH_2)_2SMe$	62	80	96

Importantly, substituted 2-arylethylamines are good reaction partners for the **188**-catalyzed three-component reaction. When the reaction of *p*-bromocinnamaldehyde, 2-arylethylamine **190**, and azlactone **106** (R^3 = Ph, R^4 = Me) is conducted under the optimized conditions, the corresponding δ-lactam **191** is obtained (Scheme 44). Treatment of **191** with $BF_3 \cdot OEt_2$ in dichloromethane promotes the Pictet–Spengler-type reaction to give the benzo[*a*]quinolizidine derivative **192** in 75% overall yield with 97% *ee*.

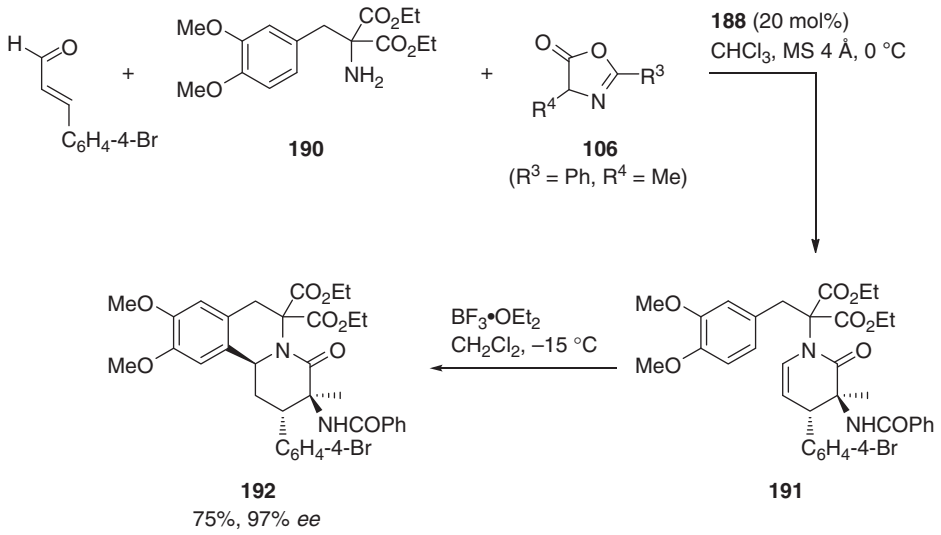
5.10.4 Diels–Alder Reactions of Nitroso Compounds

Nitroso compounds are highly reactive and useful dienophiles for the Diels–Alder reaction.[97–100] The nitroso Diels–Alder reaction between compounds **193** and unactivated dienes gives 3,6-dihydro-1,2-oxazines **194**, which could serve as 1-amino-4-hydroxy-2-ene derivatives, in a single step (equation 23). This section summarizes recent advancements in diastereo- and enantioselective nitroso Diels–Alder reactions.

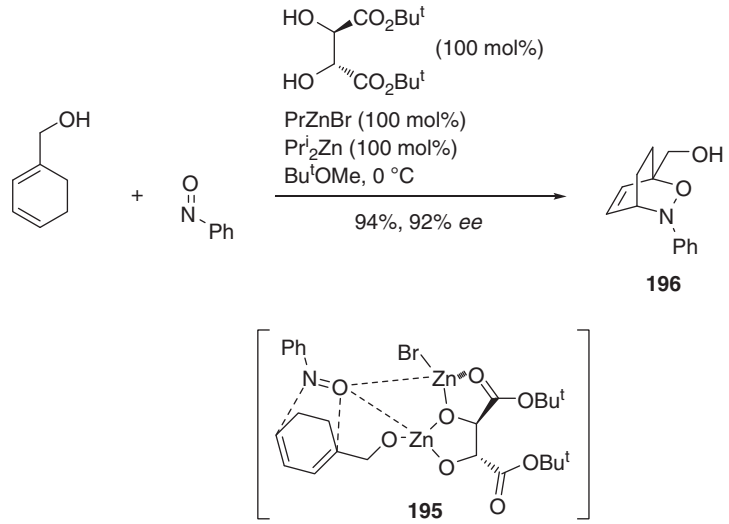


(23)

The first enantioselective nitroso Diels–Alder reaction, which was reported in 2003, uses a stoichiometric amount of a zinc(II)–tartaric acid ester complex (Scheme 45).[101] The dinuclear zinc complex and (cyclohex-1,3-dienyl)methanol forms zinc alkoxide **195**, which reacts with nitrosobenzene to give the corresponding adduct **196** with complete diastereoselectivity in 94% yield with 92% *ee*.



Scheme 44 Synthesis of benzo[*a*]quinolizidine derivative **192**.

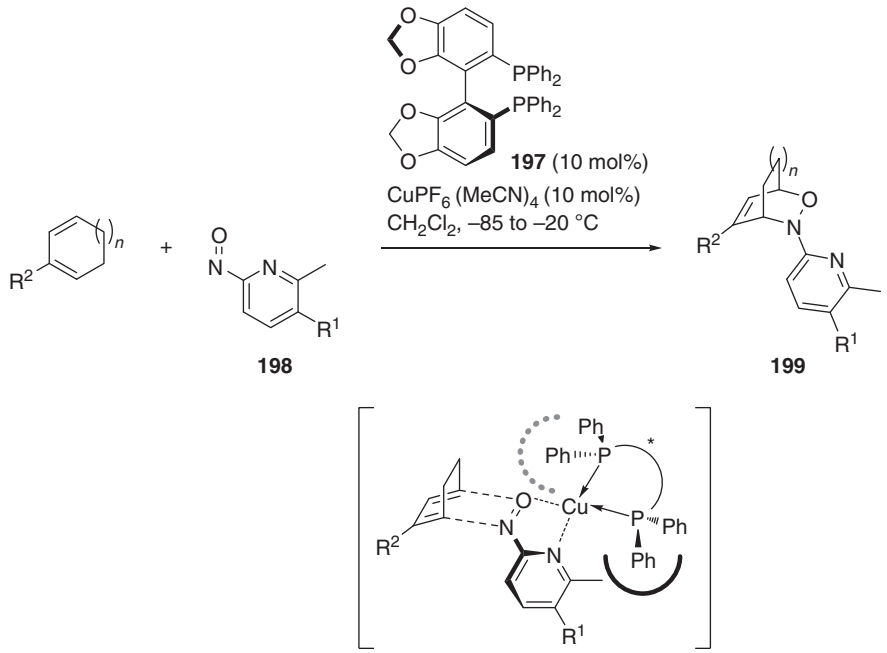


Scheme 45 Enantioselective nitroso Diels–Alder reaction promoted by a zinc(II)–tartaric acid ester complex.

Since nitroso compounds exist in organic solvents as a monomer-azetoxy dimer equilibrium, the generation of chelated monomeric nitroso derivatives with a suitable LA is important for catalytic promotion of the enantioselective nitroso-Diels–Alder reaction. When the reaction of 6-methyl-2-nitrosopyridines **198** with cyclic 1,3-dienes is conducted in the presence of the Cu(I) complex of (*S*)-SEGPHOS (**197**) (10 mol%), the corresponding adducts **199** are obtained in high yields with high enantioselectivities (Scheme 46, Table 34).[102] It is conceivable that the chelation of pyridine and the nitroso oxygen would generate the monomeric nitrosopyridine–catalyst complex (Scheme 46), which would immediately react with dienes.

6-Methyl-2-nitrosopyridine **198** ($R^1 = H$) also reacts with acyclic 2-triisopropylsilyloxy (OTIPS)-1,3-butadienes **201** to give the corresponding adducts **202** with excellent regio- and enantioselectivities (Scheme 47).[103] In this reaction, the use of (*S*)-DIFLUORPHOS (**200**) as the ligand gives better results than (*S*)-SEGPHOS (**197**). The OTIPS dienes **201** show higher reactivity and enantioselectivity than the corresponding trimethylsilyloxy (OTMS) or *tert*-butyldimethylsilyloxy (OTBDMS) dienes. The high reactivity of **201** arises from the bulk of the triisopropylsilyl (TIPS) group, which forces the diene to adopt an *s-cis* conformation in favor of the concerted [4 + 2] cycloaddition reaction.

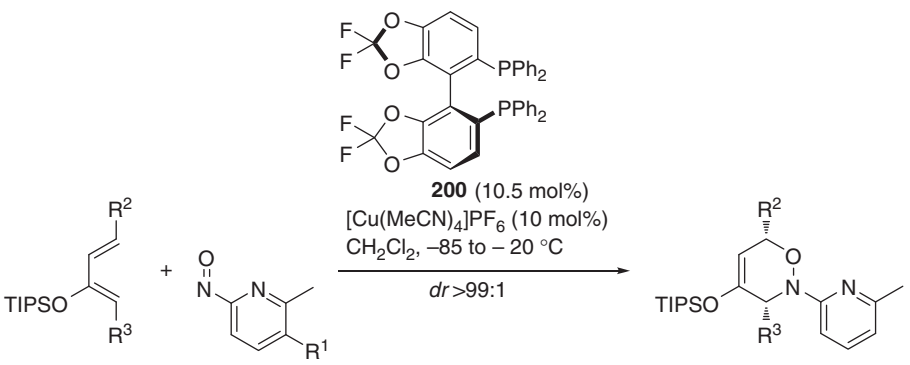
When the Diels–Alder reaction of 2-nitrosopyridine with racemic diene **204** is conducted using the chiral Cu(I) complex of Walphos-CF_3 (**203**), only two of eight possible isomers are generated through kinetic resolution (equation 24, Table 35).[104] The two products, **205** and **206**, are isolated by column chromatography in high combined yields with high enantioselectivity. In particular, the use of a sterically hindered R^1 substituent, such as CMe_2OTMS or aryl groups, completely suppresses the generation of other isomers. The present method has been successfully applied to a total synthesis of (+)-*trans*-dihydronarciclasine (**209**), a potent antitumor and



Scheme 46

Table 34 Enantioselective Diels–Alder reaction of nitrosopyridine **198** catalyzed by cu(I) complex of (*S*)-segphos (**197**) (Scheme 46)

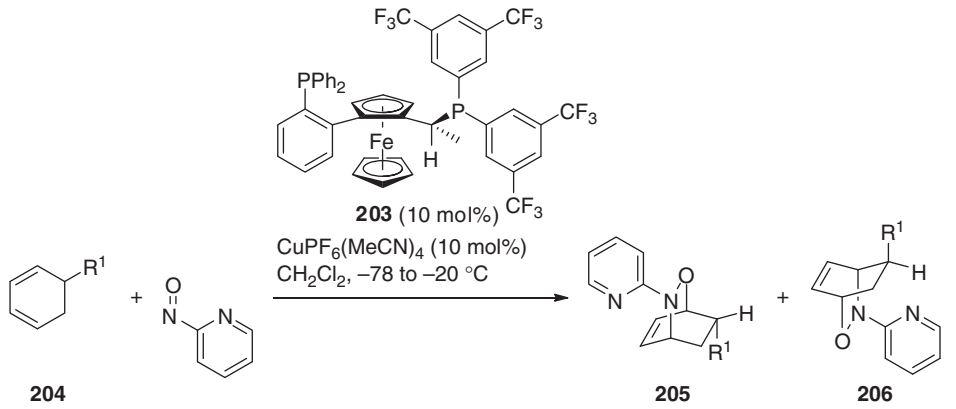
R^1	R^2	n	*Yield (%)*	ee *(%)*	*References*
H	H	0	>99	90	102
H	H	1	>99	92	102
Br	H	1	>99	94	102
H	Ph	1	>99	97	102
H	OTBDMS	1	95	92	102
H	H	2	>99	72	102



R^2	R^3	Yield	*ee*
Me	Me	95%	99%
CH_2OBn	$(CH_2)_3OTBDMS$	86%	95%
Ph	Pr^i	97%	95%

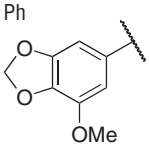
Scheme 47 Enantioselective nitroso Diels–Alder reaction with acyclic 2-OTIPS-1,3-butadienes **201**.

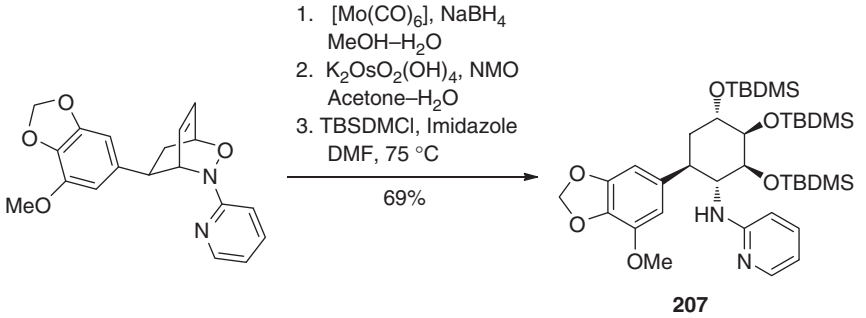
antiviral substance (equation 25).[105] Reductive cleavage of the N–O bond of adduct **206** with $[Mo(CO)_6]$ and $NaBH_4$ followed by diastereoselective dihydroxylation gives **207**. The pyridyl group of **207** is removed by quaternization with methyl triflate and consequent alkaline hydrolysis to give **208**. (+)-*trans*-Dihydronarciclasine (**209**) can be synthesized from **208** via a five-step transformation.



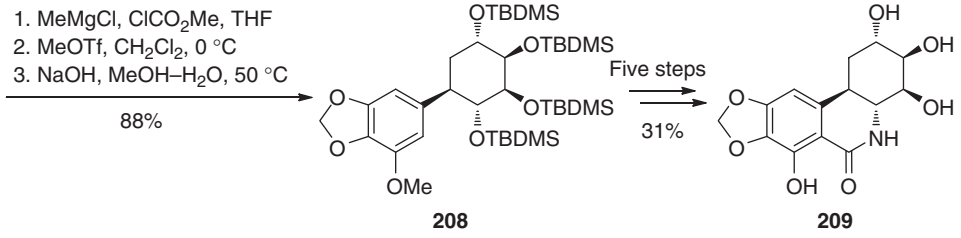
(24)

Table 35 Kinetic resolution of racemic diene **204** through an asymmetric nitroso Diels–Alder reaction (equation 24)

R^1	*Yield (%) of* ***205***	ee *(%) of* ***205***	*Yield (%) of* ***206***	ee *(%) of* ***206***	*References*
CMe_2OTMS	48	95	52	89	104
$CH_2OTBDPS$	42	99	45	88	104
CH_2Ph	40	98	43	84	104
CH_2OAc	39	98	42	82	104
Ph	45	98	54	94	104
	51	92	48	>99	105



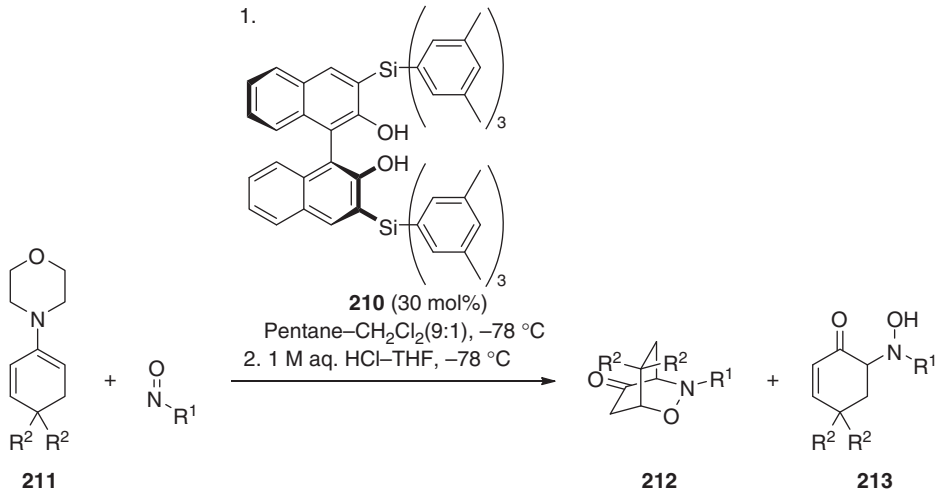
(25)



A completely regioselective and efficient enantioselective nitroso Diels–Alder-type bicycloketone synthesis can be achieved using preformed or *in situ*-generated dienamine. As in the case of the addition reaction of carbon nucleophiles to nitroso compounds (nitroso aldol reaction),[99,106,107] the appropriate amine framework of the enamine and a proper adjusted acidity of the Brønsted acid catalyst contribute to the regioselectivity of the nitroso Diels–Alder-type bicycloketone synthesis.

In the presence of the chiral binaphthol **210** bearing tri(*m*-xylyl)silyl groups at the 3,3′-positions, the reaction of 2-morpholino-4,4-dimethylcyclohexadiene **211** (R^2 = Me) with nitroso compounds yields single-regioisomer 2-oxa-3-aza-bicycloketones **212** (R^2 = Me) with high enantioselectivity (equation 26, Table 36).[108] Importantly, the steric bulkiness of the triarylsilyl group in the catalyst plays an important role in constructing the chiral environment. As the triarylsilyl group becomes sterically bulky, the enantioselectivity increases, and chiral binaphthol **210** bearing tri(*m*-xylyl)silyl groups gives the highest enantioselectivity.

However, the more sterically bulky substituent tri(*o*-tolyl)silyl causes a significant decrease in enantioselectivity. In contrast to the reaction of **211** (R^2 = Me), the reaction of 2-morpholino-4,4-diphenylcyclohexadiene **212** (R^2 = Ph) exclusively produces the corresponding *N*-nitroso aldol adduct **213** (R^2 = Ph) in 37% yield with 61% *ee* (Table 36).

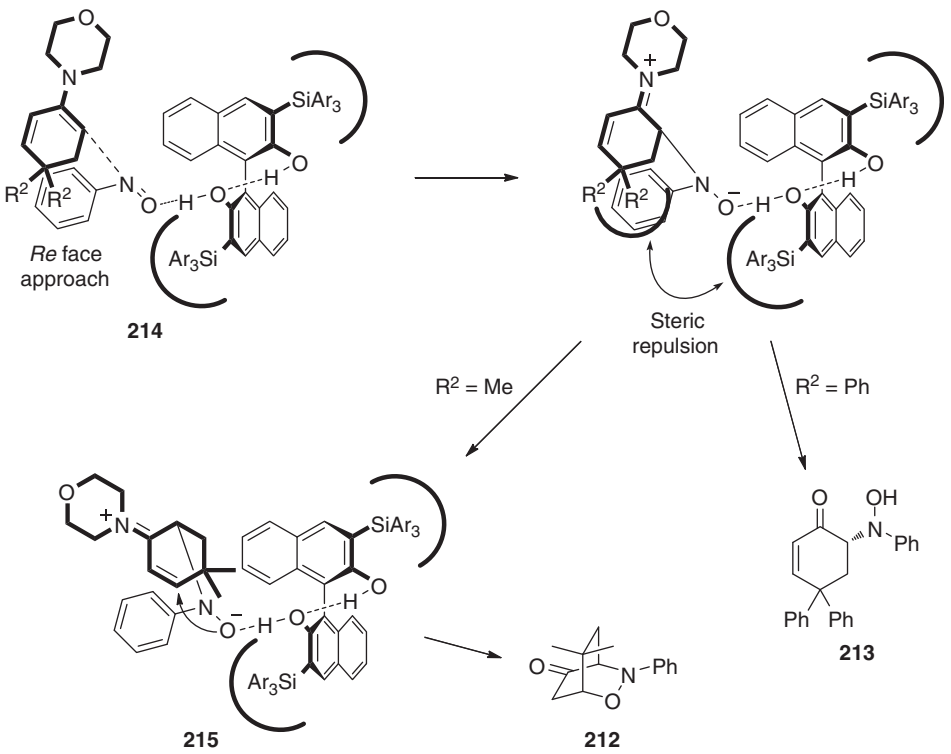


(26)

211 **212** **213**

Table 36 Diastereo- and enantioselective synthesis of nitroso Diels–Alder-type bicycloketones catalyzed by chiral binaphthol **210** (equation 26)

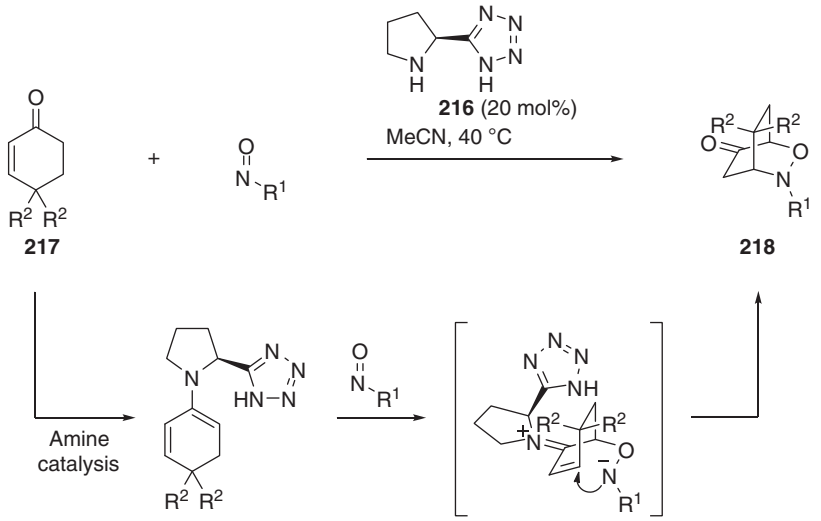
R^1	R^2	Yield (%) of **212**	ee (%) of **212**	Yield (%) of **213**	ee (%) of **213**	References
Ph	Me	90	90	–	–	108
C_6H_4–4-Br	Me	65	87	–	–	108
C_6H_4–4-Ph	Me	78	90	–	–	108
C_6H_4–4-OPh	Me	63	92	–	–	108
C_6H_3–3,5-Me_2	Me	52	80	–	–	108
Ph	Ph	<1	–	37	61	108



Scheme 48 Proposed transition-state assemblies in the **210**-catalyzed nitroso Diels–Alder reaction.

The present reaction may proceed through a sequential *N*-nitroso aldol/Michael reaction. To account for the observed diastereo- and enantioselectivities, the overall hydrogen-bonding network between the two hydroxyls of **210** via the Brønsted acid-assisted Brønsted acid system and the nitroso oxygen may be the dominant factor (Scheme 48).[108] Nucleophilic attack of the dienamine is postulated to occur from the *Re* face (transition state **214**), which gives the *N*-nitroso aldol adduct. A subsequent Michael addition occurs in the case of a dimethyl group via a conformational change that involves a 60° counterclockwise rotation as transition state **215**. In contrast, the sterically more demanding diphenyl group does not allow such a counterclockwise rotation to receive the subsequent Michael attack. Thus, the *N*-nitroso aldol iminium intermediate is hydrolyzed during workup to yield the *N*-nitroso aldol product **213**.

In contrast to the chiral binaphthol **210**, the pyrrolidine-derived tetrazole **216** catalyzes the reaction of α,β-unsaturated ketone **217** to yield 3-oxa-2-aza-bicycloketones **218** with excellent enantioselectivity (Scheme 49, Table 37).[108,109] Pyrrolidinyl tetrazole **216** exhibits higher reactivity than proline and gives the cycloaddition with complete enantioselectivity. These bicycloketone products shown in Tables 36 and 37 are useful precursors of various optically active cyclic amino alcohols.



Scheme 49

Table 37 Diastereo- and enantioselective synthesis of nitroso Diels–Alder-type bicycloketones catalyzed by pyrrolidinyl tetrazole **216** (Scheme 49)

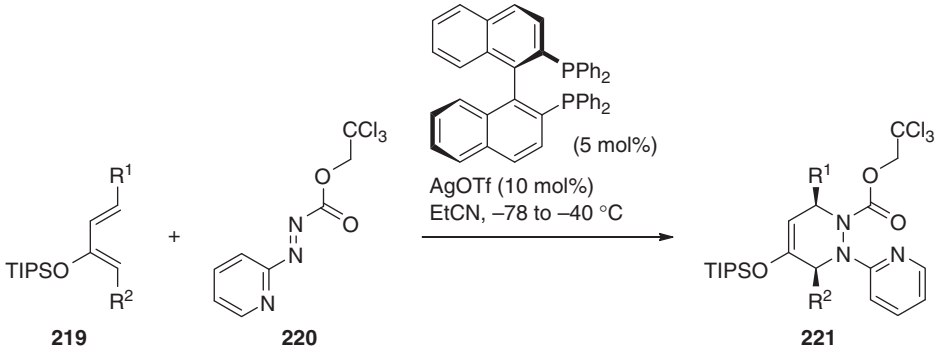
R^1	R^2	*Yield (%)*	ee *(%)*	*References*
Ph	H	34	99	108,109
Ph	Me	64	99	108,109
Ph	Ph	56	99	108,109
C_6H_4–4-Me	Me	47	99	108,109
C_6H_3–3,5-Me_2	Me	52	98	108,109
C_6H_4–4-Br	Me	50	99	108,109

5.10.5 Other Heterodienes and Heterodienophiles

In addition to carbonyl, imine, and nitroso compounds, various heterodienes and heterodienophiles undergo diastereo- and enantioselective Diels–Alder reactions. Such heterodienes and heterodienophiles include azo compounds, benzoquinones, benzoquinone imides, and benzoquinone diimides. This section describes the diastereo- and enantioselective Diels–Alder reactions of these heterodienes and heterodienophiles.

The hetero-Diels–Alder reaction of azo compounds (azo hetero-Diels–Alder reaction) produces 1,4-diamines, which are important structural motifs as building blocks for the synthesis of pharmaceutically important compounds such as human immunodeficiency virus (HIV) protease inhibitors. The 2-azopyridine **220** undergoes an enantioselective hetero-Diels–Alder reaction with 1,4-disubstituted siloxydienes **219** in the presence of a silver(I) complex of (*R*)-BINAP (5 mol%) to give the corresponding cycloadducts **221** in good yields and high enantioselectivities (equation 27, Table 38).[110] The use of a 2:1 complex of Ag(OTf) and (*R*)-BINAP in propionitrile gives the best results. The cycloadducts **221** can be readily converted into the corresponding acyclic 1,4-diamino alcohols by reductive cleavage of the N–N bond with samarium(II)

iodide. This catalytic process is an effective synthetic route to chiral 1,4-diamines, which are pharmaceutically important compounds.

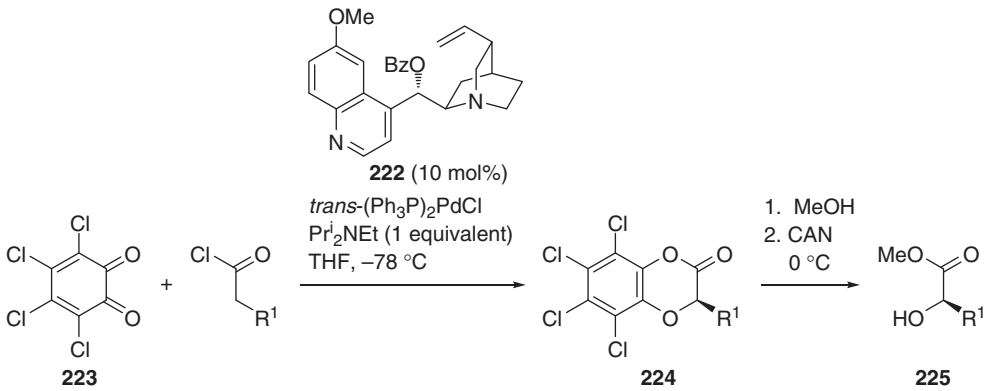


(27)

Table 38 Enantioselective hetero-Diels–Alder reaction of 2-azopyridine **220** (equation 27)

R^1	R^2	*Yield (%)*	ee *(%)*	*References*
$(CH_2)_2Me$	Me	84	95	110
Pr^i	Me	65	84	110
$(CH_2)_3CO_2Me$	Me	74	98	110
2-Furyl	Me	78	92	110
CH_2OBn	$(CH_2)_3OTBDMS$	84	98	110
Bu^i	$(CH_2)_3NNsBoc$	77	98	110

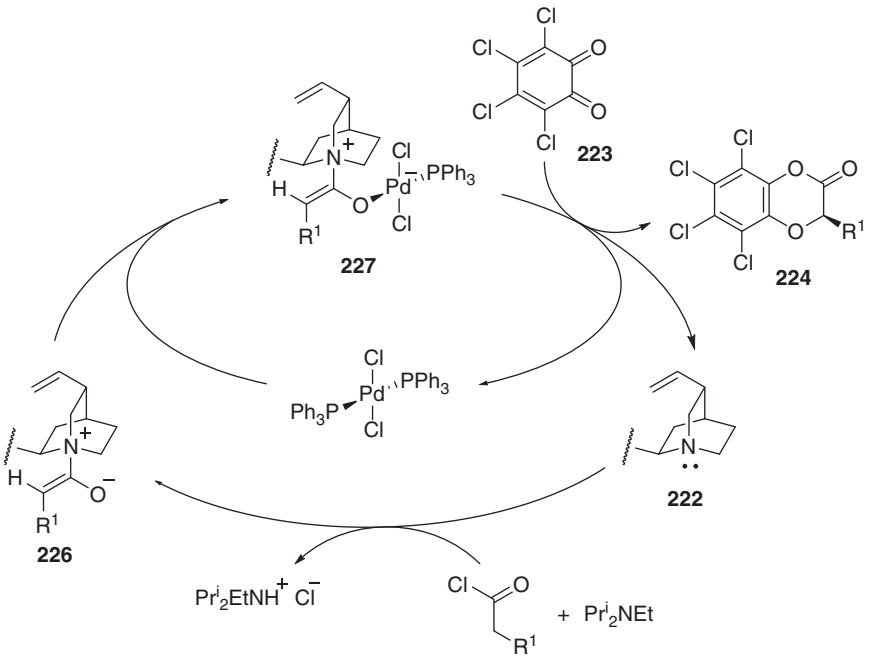
Several *ortho*-quinones undergo hetero-Diels–Alder reactions with ketene enolates generated *in situ* from the corresponding acyl chlorides.[111] In the presence of benzoylquinidine (**222**) (10 mol%) and *N,N*-diisopropylethylamine (1 equivalent), 3,4,5,6-tetrachlorobenzo-1,2-quinone (**223**) reacts with various acyl chlorides to afford the corresponding adducts **224** with high enantioselectivity (Scheme 50). The cycloadducts **224** can be readily converted into chiral α-hydroxy carboxylic acid derivatives



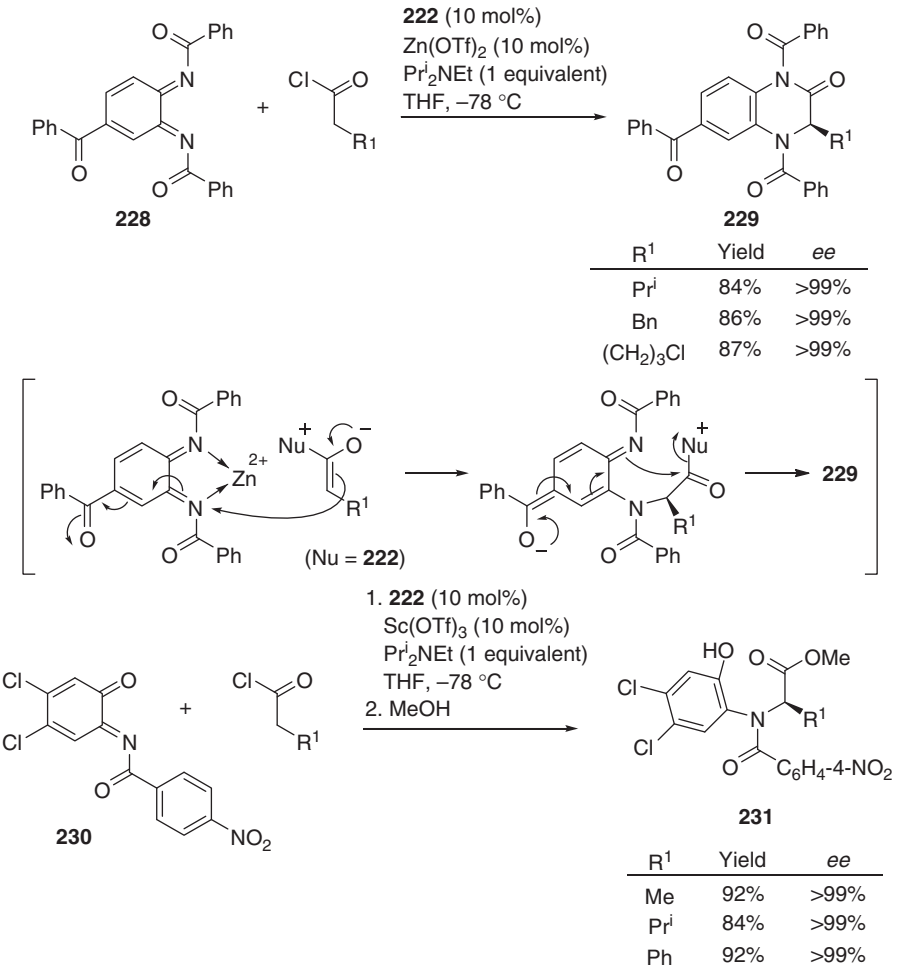
Scheme 50

Table 39 Hetero-Diels–Alder reaction of 3,4,5,6-tetrachlorobenzo-1,2-quinone (**223**) (Scheme 50)

R^1	Trans-$(Ph_3P)_2PdCl_2$ *(mol%)*	*Yield (%) of* ***224***	ee *(%) of* ***225***	*References*
Et	0	78	99	111
Bn	0	63	99	111,112
Pr^i	0	55	93	111,112
Pr^i	10	88	93	111,112
C_6H_4–4-OMe	0	49	99	111,112
C_6H_4–4-OMe	10	77	98	111,112
C_6H_4–4-Me	0	64	93	111,112
C_6H_4–4-Me	10	87	94	111,112

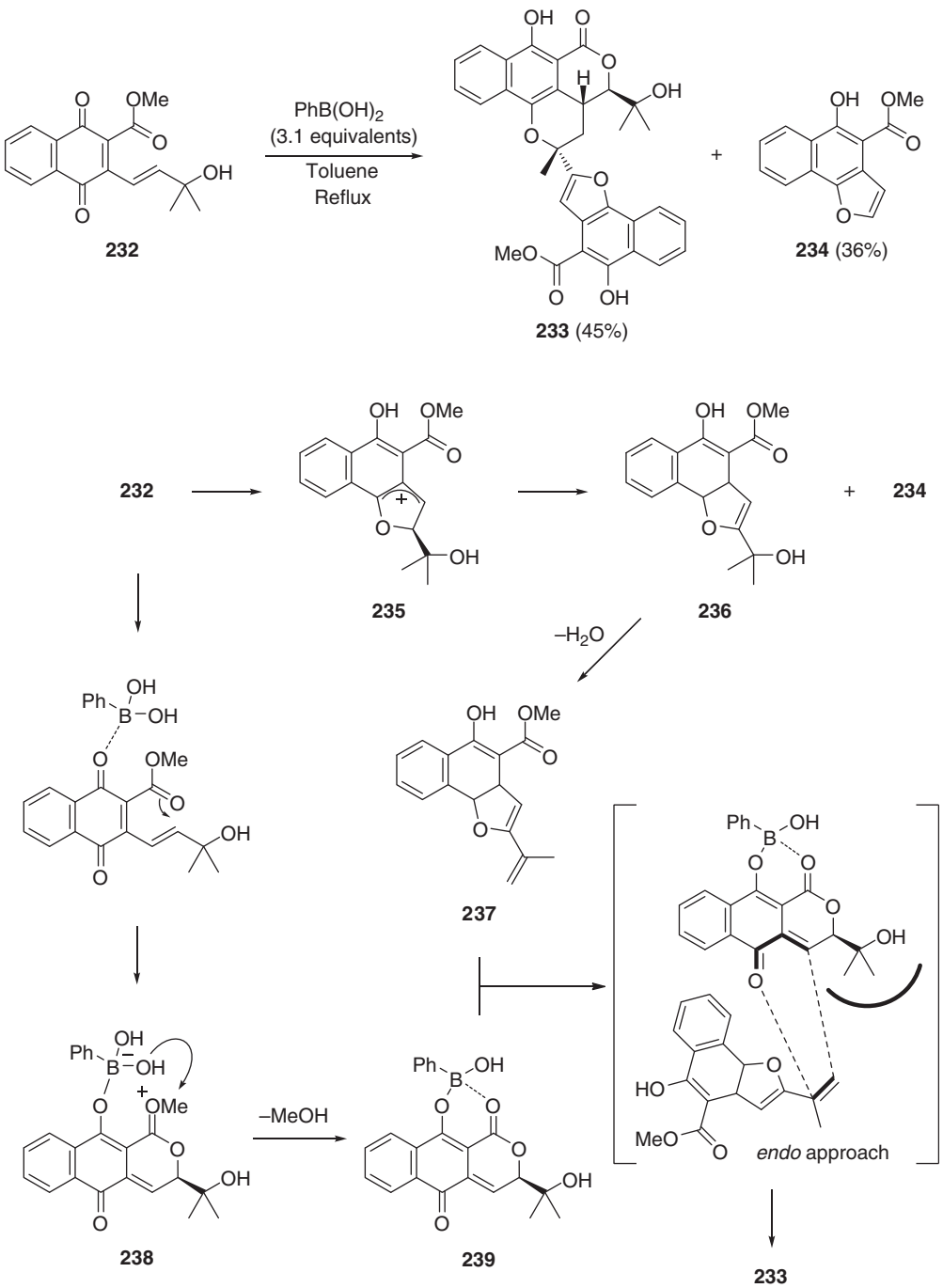


Scheme 51 Proposed bifunctional mechanism for the palladium(II)-cocatalyzed reaction.



Scheme 52 Enantioselective Diels–Alder reaction of *o*-benzoquinone imides **228** and *o*-benzoquinone diimides **230**.

225 via methanolysis followed by oxidation with cerium(IV) ammonium nitrate (CAN). For less reactive acyl chlorides, the reactivity is improved by the addition of a phosphine complex of a transition metal as a cocatalyst without any loss of enantioselectivity.[112] For example, in the presence of *trans*-dichlorobis(triphenylphosphine)palladium(II) (10 mol%), the reaction of quinone **223** with 3-methylbutanoyl chloride ($R^1 = Pr^i$) gives the corresponding adduct in 88% overall yield and 93% *ee* (Table 39). A proposed mechanism for the *trans*-$(Ph_3P)_2PdCl_2$ cocatalyzed reaction is shown in Scheme 51. The acid chloride and benzoylquinidine (**222**), with the aid of Pr^i_2NEt, form a chiral ketene enolate **226**, which is in equilibrium with free ketene. The enolate **226** then binds to the palladium cocatalyst, thus increasing its relative concentration and providing enhanced chemoselectivity toward the quinone **223**. Once this cocatalyst-bound enolate **227** and quinone **223** react, they release both catalysts while forming the [4 + 2] cycloaddition product **224**.



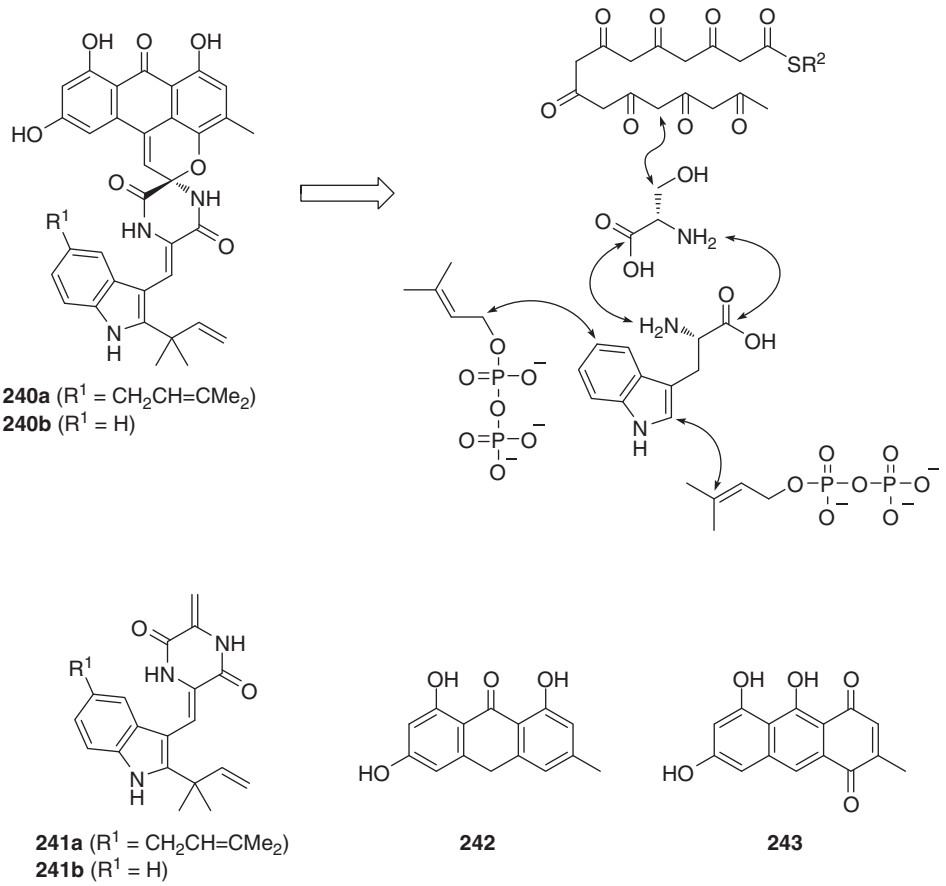
Scheme 53 Biomimetic synthesis of rubicordifolin (**233**).

The same catalytic system can be used in the hetero-Diels–Alder reactions of ketene enolates with *o*-benzoquinone diimides[113,114] or *o*-benzoquinone imides.[113,115,116] In the presence of $Zn(OTf)_2$ (10 mol%) as an LA cocatalyst, the reaction of *ortho*-benzoquinone imide **228** with acyl chlorides gives the corresponding adducts **229** with >99% *ee* (Scheme 52).[114] In contrast to the reaction of quinone **223**, activation of the potentially chelating *ortho*-benzoquinone diimides by an LA cocatalyst may increase the rate of the desired reaction. The observed regioselectivity is explained by the stepwise mechanism shown in Scheme 52, where the reaction is initiated by the nucleophilic attack on the more electrophilic nitrogen. The reaction of *ortho*-benzoquinone imides **230** is also promoted by the combined use of benzoylquinidine (**222**) and an LA cocatalyst, $Sc(OTf)_3$.[116] Subsequent methanolysis of the adducts gives α-amino carboxylic acid derivatives **231** with excellent enantioselectivity. The aryl group of **231** can be removed by oxidative cleavage with CAN.

5.10.6 Biomimetic Synthesis of Natural Compounds Using Hetero-Diels–Alder Reactions

An intriguing aspect of the biosynthetic proposals regarding various secondary metabolites involves the possible enzymatic catalysis of Diels–Alder reactions, which would accommodate the stereochemistry extant in the respective natural products.[117] 'Biomimetic synthesis' is an attempt to assemble natural products using a specific reaction or sequence that mimics a proposed biosynthetic pathway. Biomimetic synthesis has become a powerful tool for the efficient, stereoselective construction of highly complex skeletons of natural products from rather simple precursors.[118,119] This section focuses on the biomimetic synthesis of bioactive natural compounds using hetero-Diels–Alder reactions.

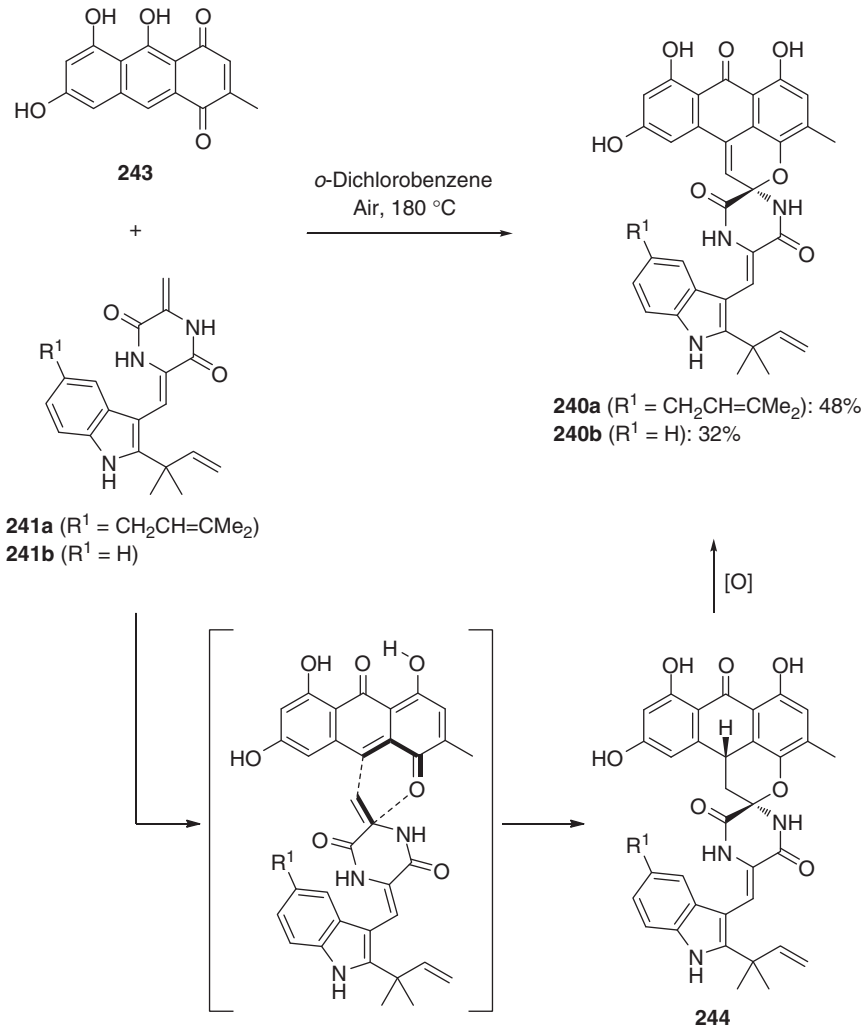
Rubicordifolin (**233**), isolated from the methanolic extract of the dried roots of *Rubia cordifolia*, shows significant cytotoxicity and inhibits the growth of sarcoma ascites in mice at low concentration.[120] It has been proposed that this natural product may be biosynthesized via the Diels–Alder dimerization of vinyl quinone **232**. Thus, in the presence of phenylboronic acid (3.1 equivalents), the biomimetic Diels–Alder dimerization of **232** proceeds in toluene at reflux conditions to give rubicordifolin (**233**) in 45% yield along with furomollugin (**234**) in 36% yield (Scheme 53).[121] The mechanism of this dimerization can be explained as follows. Under thermal conditions, the unstable vinyl quinone **232** is converted into naphthofuran **236** and furomollugin (**234**). For example, 23% yield of **236** and 24% yield of **234** are obtained when **232** is allowed to stand in THF at



Scheme 54 Proposed biosynthesis of variecolortides A (**240a**) and B (**240b**).

ambient temperature for 5 days. This reaction presumably proceeds through cation **235**, which undergoes either deprotonation to give **236** or retro-Friedel–Crafts hydroxyalkylation to give **234**. Dehydration of naphthofuran **236** gives **237**. Simultaneously, the phenylboronic acid-mediated cyclization of **232** gives **238**, intramolecular demethylation of which affords *ortho*-quinone methide **239**. The hetero-Diels–Alder reaction of the electron-deficient α,β-enone **239** with the electron-rich alkene **237**, followed by hydrolysis, gives rubicordifolin (**233**). The stereochemical outcome of this Diels–Alder reaction is compatible with an *endo*-transition state, the diastereoselection of which is governed by the bulky hydroxyisopropyl group.

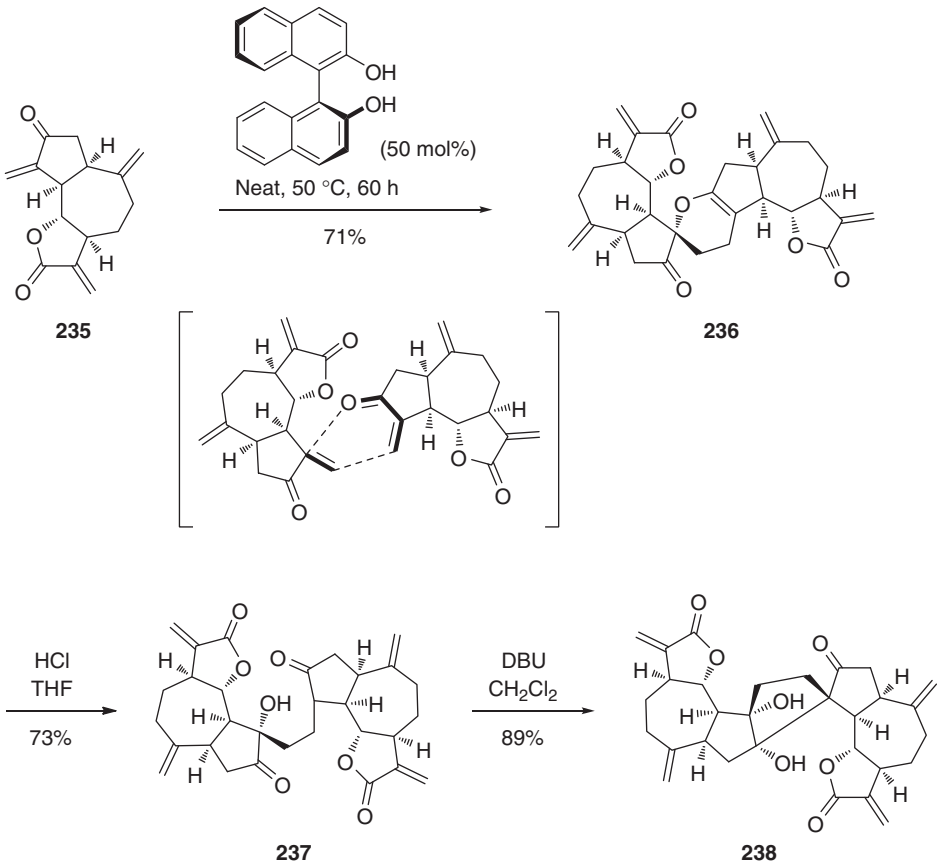
Variecolortides A (**240a**) and B (**240b**) are cytotoxic compounds isolated from a halotolerant strain of the fungus *Aspergillus variecolor* (Scheme 54).[122] The variecolortides **240** appear to be biosynthesized from a C_{16} polyketide, serine, tryptophan, and 1 or 2 equivalents of dimethylallyl pyrophosphate. Since emodin anthrone (**242**) and hydroxyviocristin (**243**) are isolated from *Aspergillus cristatus*[123] and unsaturated diketopiperazine isoechinulin B (**241a**) is isolated from *Aspergillus ruber*,[124] the variecolortides **240** might be biosynthesized through the assembly of these compounds, although compounds **241–243** have not been reported to occur in *Aspergillus variecolor*. In agreement with this consideration, variecolortide A (**240a**) is obtained in 48% yield when diketopiperazine isoechinulin B (**241a**) and hydroxyviocristin (**243**) are heated at 180 °C under aerobic conditions (Scheme 55).[125] Variecolortide B (**240b**) is also generated from **241b** and **243** in 32% yield under the same conditions. It is conceivable that the reactions proceed through the hetero-Diels–Alder reaction of *exo*-methylene diketopiperazines **241** with the quinone methide tautomer of **243**, followed by rapid oxidation of the labile benzylic C–H bond of adduct **244** in the presence of air. Theoretical calculations strongly support the notion that the reaction between **241** and **243** proceeds through a concerted cycloaddition pathway.



Scheme 55 Total synthesis of variecolortides A (**240a**) and B (**240b**).

A sesquiterpene lactone dimer (+)-ainsliadimer A (**238**), which was isolated from *Ainsliaea macrocephala*, has potent inhibitory activity against the production of nitric oxide in RAW264.7 cells stimulated by lipopolysaccharide (Scheme 56).[126] The biosynthesis of **238** appears to involve the hetero-Diels–Alder dimerization of monomeric sesquiterpene lactone dehydrozaluzanin C

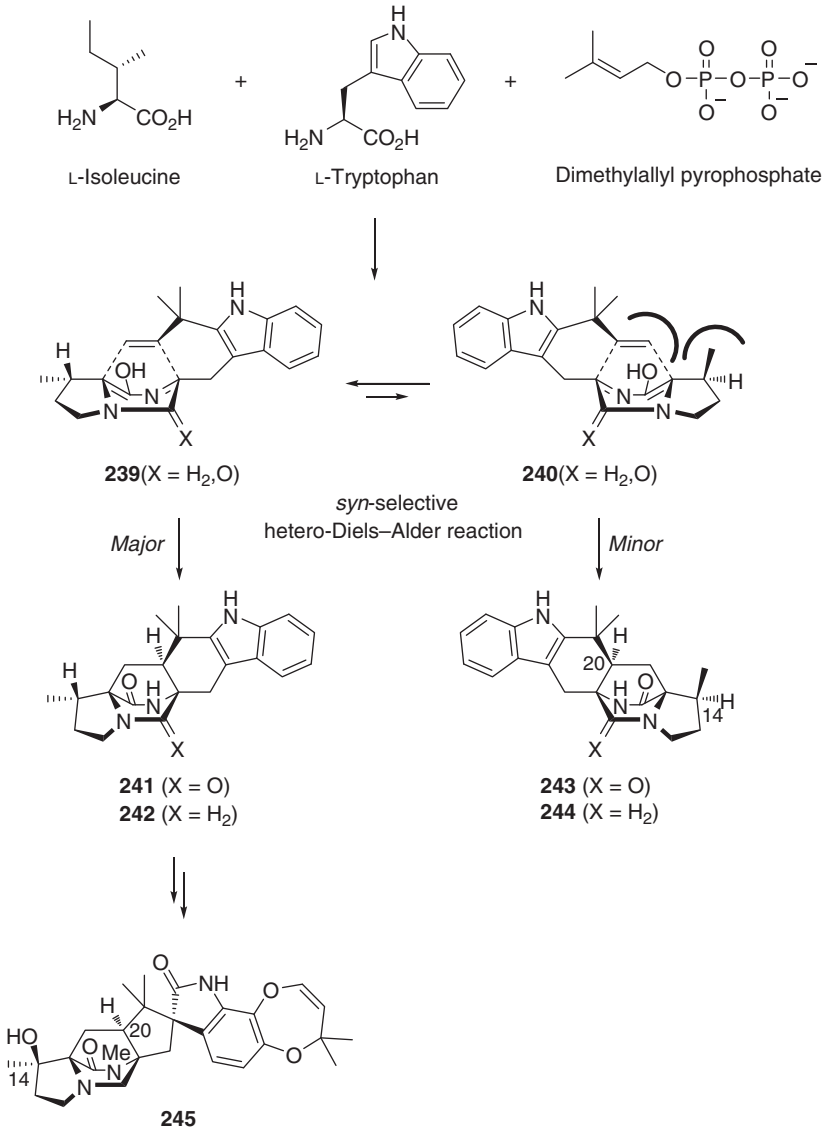
(**235**) as a key reaction. Based on this biosynthetic hypothesis, (+)-ainsliadimer A (**238**) was synthesized from **235**. Although the exposure of **235** to several LA catalysts led to either no reaction or decomposition, the use of (+)-BINOL as a hydrogen bonding catalyst showed good catalytic activity to give the desired dimer **236** in 71% yield (Scheme 56).[127] Interestingly, chiral BINOL showed a slightly higher activating effect than racemic BINOL (64% yield). This result might be explained by the fact that, on the solid state, racemic BINOL could be composed of a centrosymmetric structure characterized by intermolecular hydrogen bonding between a pair of (+)- and (−)-enantiomers, which reduces the hydrogen bonding effect on the substrate **235**. The high facial selectivity can be explained by the fact that the bulky seven-membered ring of dienophile blocks the *β*-face, and as a result, the diene approaches the dienophile from the less-hindered α-face. Acidic hydrolysis of dimer **236** gives compound **237** in 73% yield. The subsequent intramolecular aldol reaction is promoted by a large excess of DBU in dilute CH_2Cl_2 solution (0.0008 M) to give (+)-ainsliadimer A (**238**) in 89% yield.



Scheme 56 Biomimetic synthesis of (+)-ainsliadimer A (**238**).

Paraherquamide A (**245**), which was isolated from *Penicillium paraherquei*, is a potent anthelmintic alkaloid that bears a spirooxindole core (Scheme 57).[128] Other members of this class include VM55599 (**244**), which contains an indole ring instead of an oxindole ring.[129] Interestingly, the relative stereochemistry of C14 and C20 in **244** is opposite that in **245**. These compounds are proposed to be biosynthesized from L-isoleucine, L-tryptophan, and dimethylallyl pyrophosphate via the intramolecular hetero-Diels–Alder reaction between the azadiene and the terminal alkene in **239** or **240** (Scheme 57).[130] When the hetero-Diels–Alder reaction occurs from the more hindered face of the azadiene system (**240**), the corresponding adduct **243** is obtained. The reduction of **243** gives VM55599 (**244**). However, the hetero-Diels–Alder reaction from the other face of the azadiene system (**239**) gives the adduct **241**, which is a biosynthetic precursor of paraherquamide A (**245**).

Based on the proposed biosynthesis, VM55599 (**244**) is synthesized from diketopiperazine **246** and the indole derivative **247**. The base-promoted addition of **246** to aldehyde **247** followed by removal of the methylthiomethyl (MTM) group and acid treatment gives **248** as a precursor of the hetero-Diels–Alder reaction (Scheme 58).[131] The treatment of **248** with acetyl chloride gives a mixture of three diastereomeric cycloadducts: **243** (35%), **251** (10%), and **252** (15%). It has been proposed that the acetylation of **248** gives the *O*-acetyl lactim **249**, which tautomerizes to azadiene **250**, which in turn undergoes an intramolecular hetero-Diels–Alder reaction followed by loss of acetate. Very interestingly, cycloadduct **241**, which contains the relative and absolute stereochemistry of paraherquamide A (**245**), is not obtained from the hetero-Diels–Alder reaction. The cycloaddition reaction shows a proclivity for the formation of adduct **243**, which has the same relative stereochemistry as VM55599. In sharp



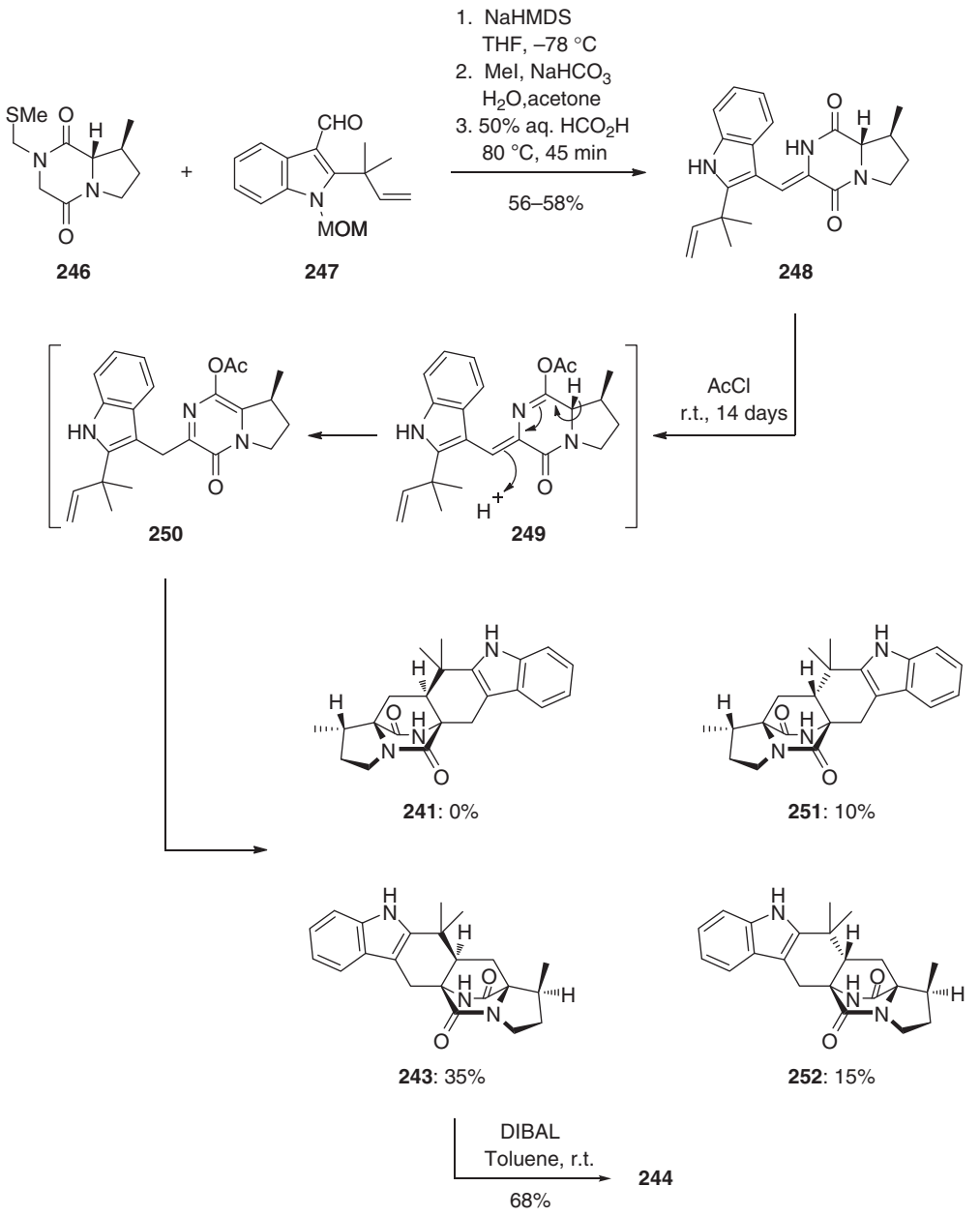
Scheme 57 Proposed biosynthesis of paraherquamide A (**245**) and VM55599 (**244**).

contrast, in the biological system, the diastereochemical distribution is expressed as >600:1 (corresponding to **241** or **242**:**243** or **244**) without the generation of anti-adducts (such as **251** and **252**). The reduction of adduct **243** with an excess of diisobutylaluminium hydride (DIBAL) in toluene gives VM55599 (**244**) in 68% yield.

5.10.7 Conclusion and Outlook

This chapter describes the recent advances in stereoselective hetero-Diels–Alder reactions. The most significant achievement in this field is the development of high-performance catalysts, including chiral LA catalysts and chiral organocatalysts. Based on these significant developments, the hetero-Diels–Alder reaction has become one of the most powerful tools for the efficient synthesis of bioactive natural products.

Catalytic enantioselective promotion of the normal electron-demand hetero-Diels–Alder reaction of unactivated ketones is still a challenge, since ketones are less reactive than aldehydes. The asymmetric inverse electron-demand hetero-Diels–Alder reaction with simple alkenes that do not have an electron-donating group is also an important issue to address for the synthesis of a variety of optically active heterocycles. As described in this chapter, diastereo- and enantioselective hetero-Diels–Alder reactions are currently limited to heterodienes and heterodienophiles, which contain oxygen and/or nitrogen as heteroatoms. The development of catalytic asymmetric hetero-Diels–Alder reactions that include other heteroatoms such as sulfur, phosphorus, and selenium is also a task for chemists in the coming years.



Scheme 58 Biomimetic synthesis of VM55599 (**244**).

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5.11 Intramolecular and Transannular Diels–Alder Reactions

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5.11.1 Introduction

The Diels–Alder (DA) [4 + 2] cycloaddition, first disclosed[1] in 1928, quickly gained respect as an unusually powerful synthetic method because of its stereospecificity, its diastereo- and regioselectivity, and its ability to form up to four contiguous stereocenters in a single step.[2] The intramolecular DA (IMDA) cycloaddition[3] (Figure 1) took longer to become established,[4] but now enjoys a well-deserved reputation as a particularly potent and rapid technique for building up molecular complexity, especially in the field of total synthesis.[5] As depicted in Figure 1, the IMDA cycloaddition can be subdivided into two types, depending on the position of the tether linking the diene and dienophile components. The IMDA process has been the subject of a number of extensive reviews,[3a,5] and it is the purpose of this chapter to highlight some of the major advances in the field since the first edition[6] of *Comprehensive Organic Synthesis*. Transannular DA (TADA) cycloadditions (Figure 1) will also be discussed. For both the IMDA and TADA reactions, emphasis will be placed on the use of such cycloadditions as key transformations in multistep target oriented synthesis, in particular the total synthesis of structurally complex and biologically active natural products and analogs thereof.

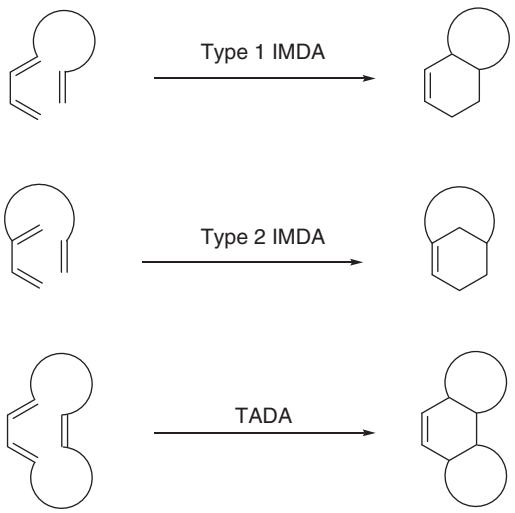


Figure 1 Three different modes of IMDA cycloadditions: Type 1, Type 2, and TADA.

5.11.2 Type 1 IMDA: Effects of the Tether

In its archetypical form, the type 1 IMDA cycloaddition involves a 'permanent' all-carbon tether of an appropriate length that allows access to relatively unstrained transition states, which usually means that the reaction is possible only if the tether contains at least three atoms (Figure 2, top). The IMDA process can be a stereochemically intricate one, the observed stereochemical outcome being dependent on the length and nature of the tether, along with the number, position, and nature of substituents attached to the reacting partners (Figure 2). This can be illustrated by the results of extensive recent studies[7] combining experiment and density functional theory (DFT) calculations; in all cases, good to excellent agreement between experiment and calculation was obtained, highlighting the importance of high-level computational methods as an explanatory/predictive tool which allows detailed analysis of subtle steric and electronic effects in competing transition states. For example, the DFT calculations provided a convincing explanation[7a] for the observed diastereoselectivity and the cooperative effect of the allylic methyl

group and the bromine atom in the IMDA reaction of **3** (X = Br). From a synthetic viewpoint, the vinylic bromine substituent in **3** serves not only as a useful stereocontrol element but can also be regarded as a surrogate C–H bond or used as a convenient 'handle' for introduction of further functionality via cross-coupling or other techniques. The topic of substrate-controlled IMDA cycloaddition in asymmetric synthesis will be discussed further in Section 5.11.7.

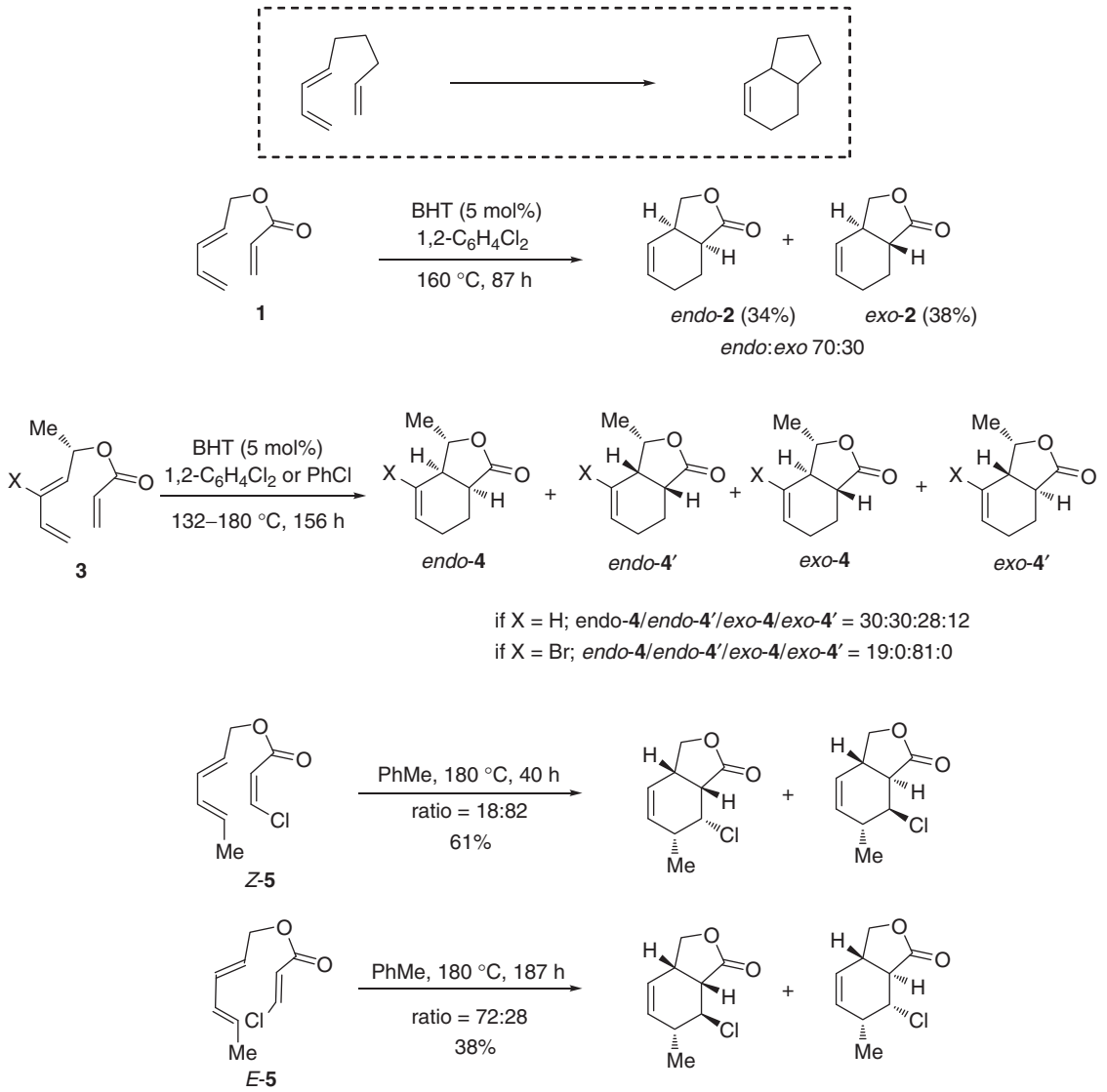


Figure 2 Type 1 IMDA cycloaddition influenced by functional groups and substituents.

The ester tethers shown in Figure 2 illustrate a very useful synthetic tactic, i.e., the use of a 'temporary' (disposable) tether to provide the advantages[8] of an intramolecular process (enhanced regio- and/or stereoselectivity and lower negative entropy of activation), followed by cleavage of the tether, which overall affords the products of a highly regio- and stereoselective intermolecular process (Figure 3, top). Of the linking groups that have been developed, tethers based on silicon[8] have proved to be versatile, and some examples are shown in Figure 3. From the IMDA reaction of **6**, a single (racemic) diastereomer was formed, arising from an *exo* transition state. This remarkable result underscores that, at the high temperature required for the cycloaddition process, the normal preference for the *endo* transition state (because of secondary orbital overlap between the diene and dienophile π-systems), has been overridden by other factors (both steric and stereoelectronic). As well as minimizing nonbonded steric interactions, a key feature of reactive conformer **6** is suggested[9] to be the alignment of the allylic C–O bonds: in the diene component, the acceptor 1,2-σ^* orbital is aligned *syn* to the 3,4 bond (minimum overlap with π-system, maximum nucleophilicity of diene), whereas the acceptor 1′,2′-σ^* has maximum overlap with the dienophile π-system (maximum electrophilicity of dienophile). A more recent variation on the silicon-tether theme is provided by the reaction of siloxacyclopentenes[10] such as **9**, which are expected to react via transition state **10** to yield *trans*-fused cycloadducts such as **11**. The pseudoaxial alignment of the alkoxyl group in **11** is dictated by the constrained nature of the dienophile, and Fleming–Tamao oxidation of the cycloadducts

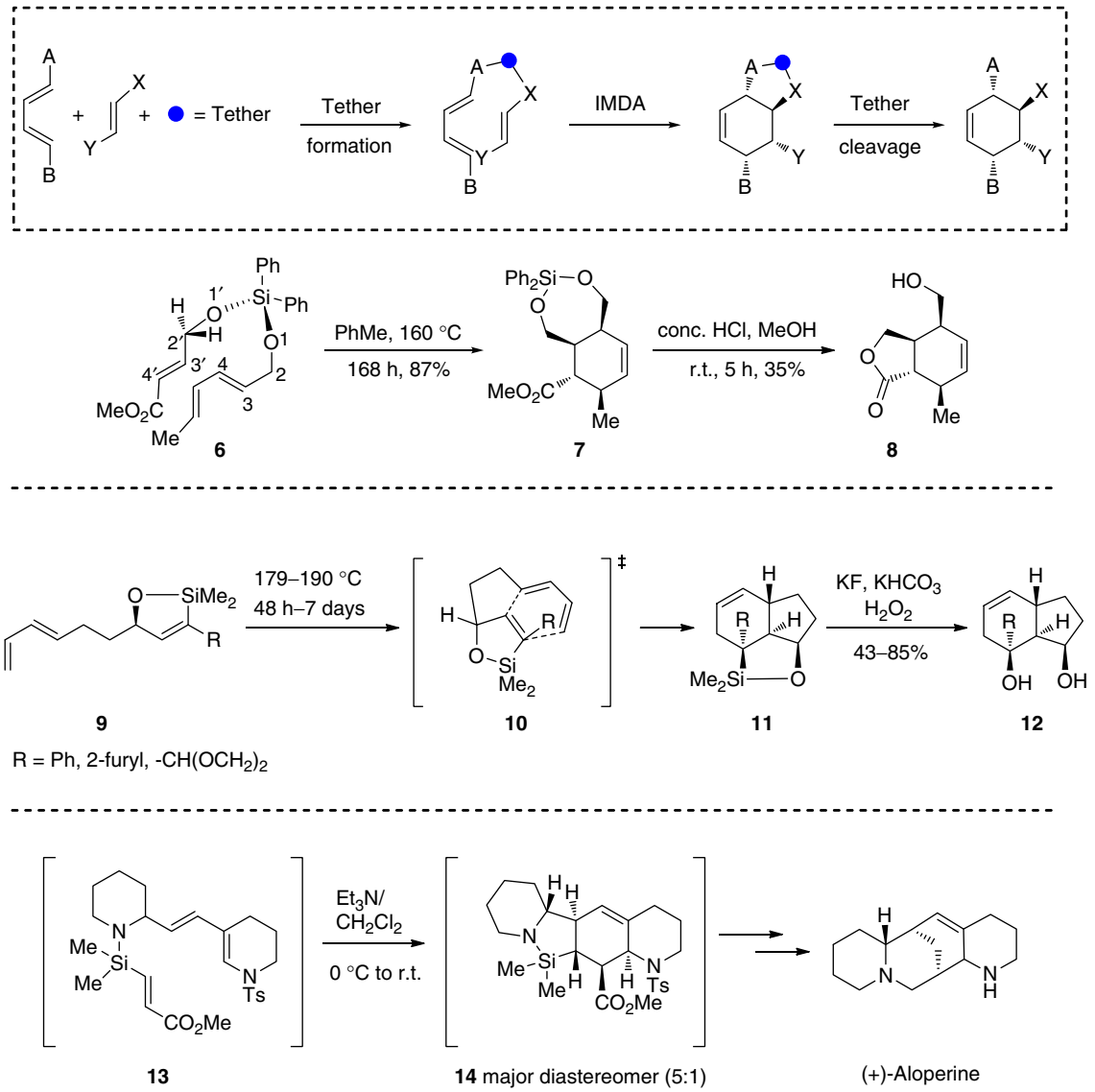


Figure 3 Type 1 IMDA involving silicon tethers.

yields diols **12** containing four stereogenic centers. This IMDA strategy proved to be highly diastereoselective for the expected *trans*-fused products (>20:1 selectivity) and provides convenient access to fused bicyclic motifs found in a wide range of biologically active natural products.[10] The use of an *N*-silyl linkage for IMDA cycloaddition is highlighted[11] in the impressive conversion of **13** to tetracycle **14**, as a key step in a total synthesis of the alkaloid (+)-aloperine. For further examples of the use of IMDA cycloaddition in the complex settings characteristic of natural product target molecules, the reader is referred to Section 5.11.11.

Intramolecular [4 + 2] cycloaddition by means of temporary connection through metal centers[12a] is also possible, and it is instructive to compare the relative rates of reaction for **15** and **16** (Figure 4). In **16**, the 'dienophile' is formally a vinyl carbanion, which indicates that the mechanism of the cycloaddition is a stepwise process[12b] rather than a concerted IMDA reaction, but the intermediacy of species **16′** was inferred from quenching experiments using D_2O. Aluminum and zinc species[12c] can also be used to tether and mediate the intramolecular cycloaddition of otherwise recalcitrant reaction partners. The oxophilicity of boron[13] makes it also a useful tether component for IMDA, and two examples[14,15] are shown in Figure 4. Bicyclic compound **22**, obtained as a single regio- and diastereomer, contains four contiguous stereocenters, attesting to the power of the IMDA process to rapidly build up molecular complexity in a stereocontrolled fashion; this particular example was an important stage in the total synthesis of taxol. The IMDA cycloaddition of intermediate alkenylboronate **25** yields the *endo* adduct **26** with high diastereoselectivity and complete regiocontrol. The method could be extended to give IMDA cycloadducts containing four contiguous stereocenters, with complete diastereoselectivity.

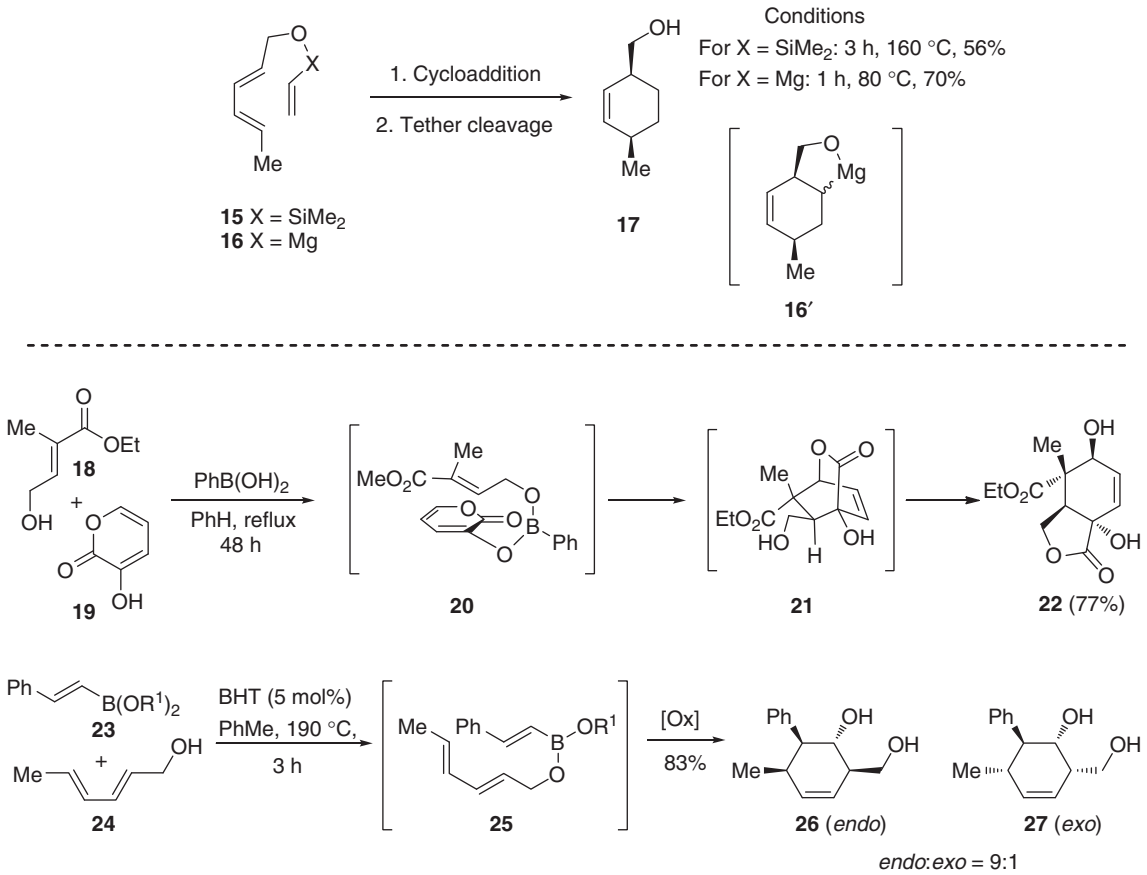


Figure 4 Type 1 IMDA cycloaddition by means of temporary connection through metal centers.

5.11.3 Acceleration of IMDA Cycloadditions

5.11.3.1 Proximity Effects

R. B. Woodward once famously remarked[16] that "enforced propinquity often leads on to greater intimacy" and two examples of this precept in the form of remarkably rapid IMDA reactions, both involving proximity effects highly conducive to bond formation, are presented in Figure 5. IMDA cycloaddition[17] of **28** to **29** occurs under unusually mild conditions, being complete at room temperature within 24 h. This can be compared and contrasted with the corresponding reaction[18] of **30**, which requires a similar reaction time, but at 205 °C (both **29** and **31** were important intermediates for the construction of taxol analogs). In **28**, the acetonide moiety serves as a conformational constraint, providing a low-energy pathway (via an entropic effect) to the required pericyclic transition state; the absence of the geminal dimethyl grouping on the diene (as compared to **30**) is obviously also an important factor (the reactions of **28** and **30** are excellent examples of Type 2 IMDA, further discussion of which is deferred to Section 5.11.5). Both **28** and **30** have the electronically matched DA combination of electron-rich diene (high-energy highest occupied molecular orbital (HOMO)) and electron-deficient dienophile (low-energy lowest unoccupied molecular orbital (LUMO)). In this respect, the ease of the (quantitative) IMDA reaction[19] of **32** is even more remarkable than that of **28**, because in **32** neither diene nor dienophile is electronically activated. This striking observation was made in the course of a total synthesis of the natural product vinigrol.

5.11.3.2 Use of 5 M Lithium Perchlorate in Diethyl Ether

In the early 1990s, the intriguing observation[20] was made that both the rate and diastereofacial selectivity of intermolecular DA reactions can be enhanced when the cycloaddition process is carried out in 5 M lithium perchlorate–diethyl ether. An instructive example, involving the often-troublesome furan as the diene component, is shown in Scheme 1. The conditions are remarkably mild, and the major product (the *exo*-anhydride) possesses the correct stereochemical array for the total synthesis of the natural product cantharidin (which will be discussed in Section 5.11.3.3).

The accelerative effect has been attributed to either high 'internal pressure'[20] (i.e., cycloaddition in this medium is suggested to be akin to cycloaddition in 'normal' solvents under high external pressure – see Section 5.11.3.3) and/or Lewis acid catalysis[21] by

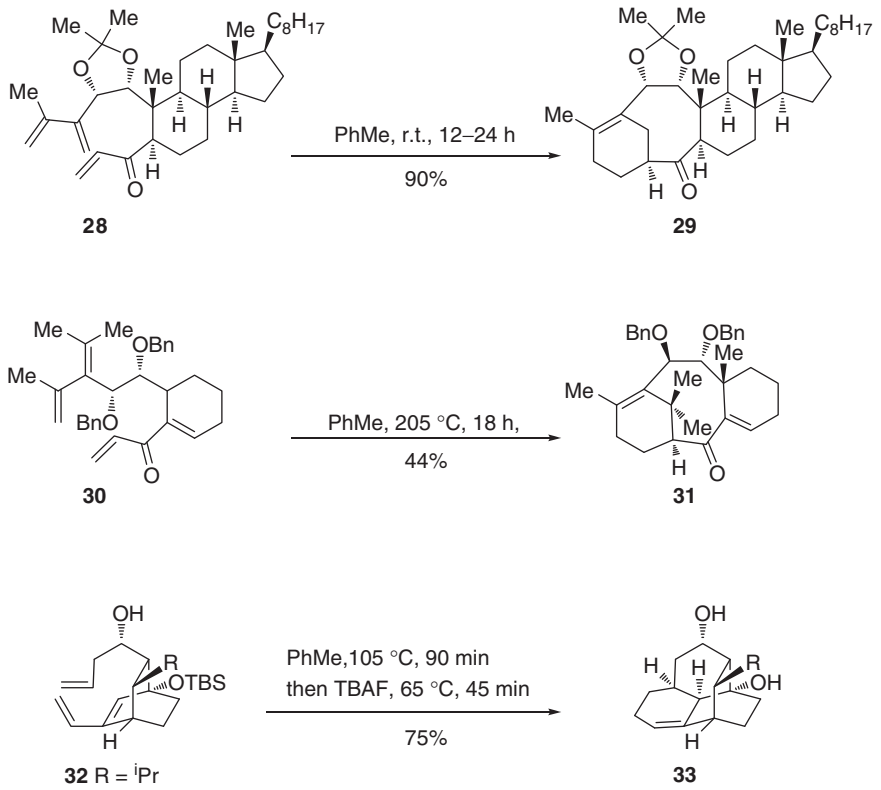
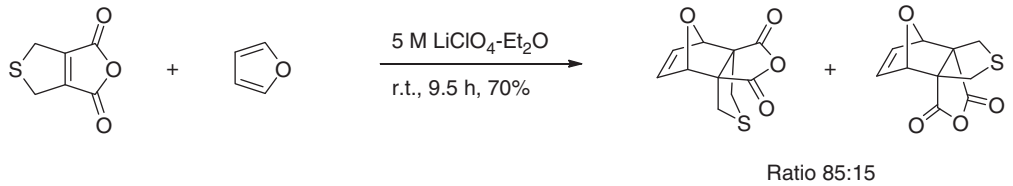


Figure 5 Proximity effects in IMDA cycloadditions.

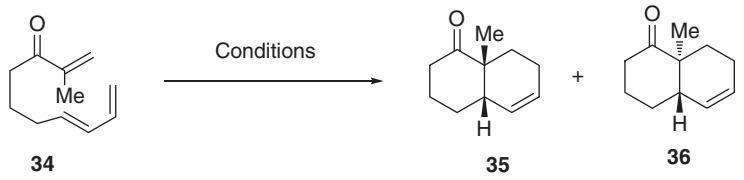


Scheme 1

the lithium ion. The enhancement of both rate and *endo*/*exo* selectivity was also observed[22] for the IMDA process, as shown in Figure 6 (conversion of **34** to **35** and **36**). Furthermore, addition of catalytic amounts of camphorsulfonic acid (CSA) to the lithium perchlorate–diethyl ether medium further increased reaction rate and diastereofacial selectivity. A prime example of the use of this technique as a key step in the total synthesis of the natural product equisitin is also shown; it was suggested[23] that the type 1 IMDA of **37** proceeds via the highly ordered reactive conformation **38** which has a chair-like arrangement with a pseudoequatorial methyl group and an *endo* arrangement of the dienophile, which is further organized by the lithium cation. The diastereomeric ratio of the cycloadducts was >95:5. In this way, the stereochemical bias associated with the single (and remote) stereocenter in **37** is parlayed into four new contiguous centers in **39**, one of which is quaternary. The use of aqueous media for IMDA cycloadditions is discussed further in Sections 5.11.6.2 and 5.11.12.

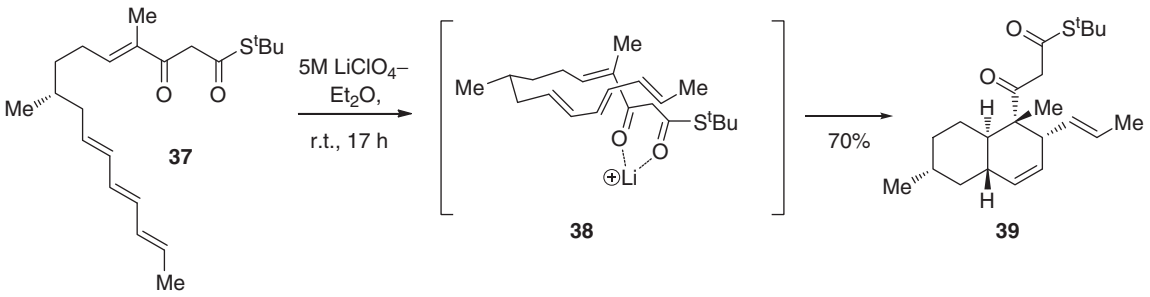
5.11.3.3 Use of High Pressure

It has long been recognized that since the DA cycloaddition has a negative volume of activation (i.e., the transition state is more compact than the reactants), it is a prime candidate for the application of high pressure[24] to promote the reaction. A classical example[24] is the high-pressure intermolecular DA cycloaddition of furan shown in Scheme 2. This formed the basis of a short and efficient synthesis of the natural product cantharidin **40**, a target molecule which had been unsuccessfully pursued, by means of a thermal cycloaddition, by Diels and Alder themselves[25] as early as 1929. The synthesis can also be compared to that shown in Scheme 1, for which 5 M lithium perchlorate–diethyl ether was used to promote the cycloaddition at ambient temperature.



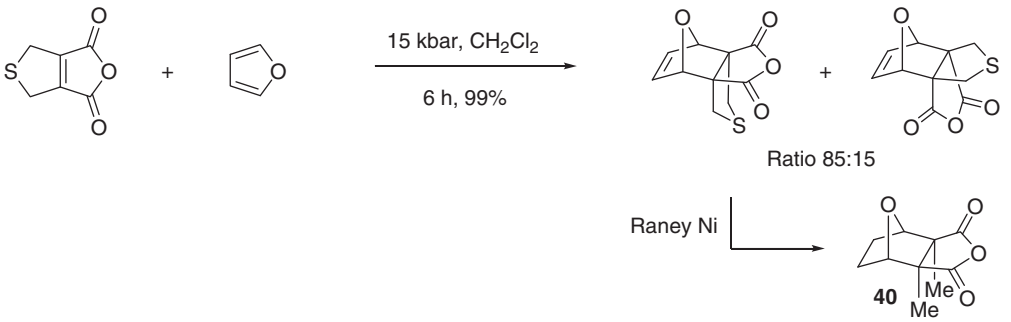
34 35 36

Conditions	Yield (%)	Product distribution **35:36**
C_6H_6, 120 °C, 18 h	72	1.6:1
5 M $LiClO_4$-Et_2O, 25 °C, 24 h	65	3.0:1
5 M $LiClO_4$-Et_2O, 10 mol% CSA, 0.6 h	78	5.0:1



37 38 39

Figure 6 Lithium perchlorate assisted IMDA cycloaddition.

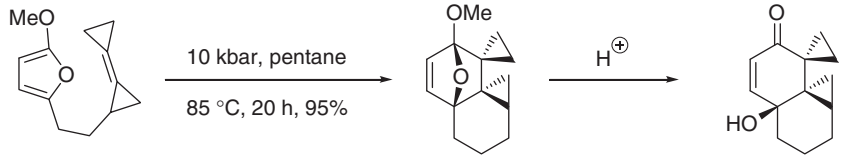


40

Scheme 2

The advantages of these two complementary techniques become apparent as alternatives to the purely thermal DA reaction for cycloadditions with unreactive dienes such as furan derivatives, in cases where thermal cycloreversion is a problem, and for reactions in which the cycloadducts decompose readily at high temperature.

The use of high pressure for IMDA cycloadditions using furan as the diene component (Intramolecular Diels–Alder with furan as diene (IMDAF), see also Section 5.11.6.1) was thoroughly and systematically investigated[26] towards the end of the 1990s (Scheme 3). This kinetics study employed unconventional dienophile components such as **41** which are activated exclusively by

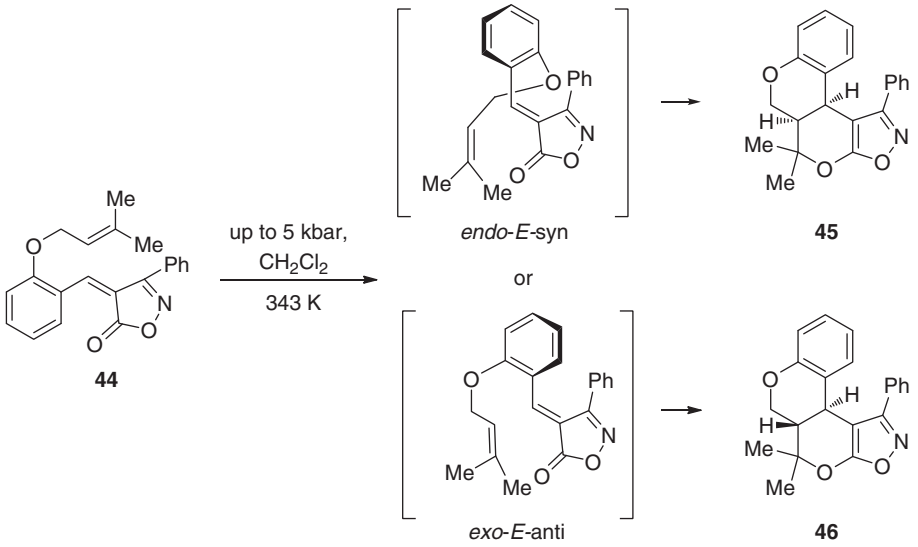


41 42 43

Scheme 3

their strain energy, and give rise to some rather unusual cycloadduct topology, as in **42**. An important conclusion from this work was that IMDA processes do not necessarily have less negative activation volumes than their intermolecular counterparts.

A similarly rigorous physical-organic investigation[27] of an intramolecular hetero-DA (IMHDA) cycloaddition (see also Section 5.11.6.2) was performed to study not only kinetics but also the aspect of pressure-induced diastereoselectivity. The substrate chosen was the benzylidene–isoxazolone **44** (Scheme 4). Before cyclization, **44** isomerizes at the benzylidene moiety, and the two competing transition states for formation of **45** and **46**, respectively, are as shown. This study revealed the first example of an intramolecular transformation for which a pressure-induced shift in diastereoselectivity could be observed, the proportion of **45** increasing steadily with pressure. It can be concluded that the *endo* transition state, leading to **45**, has the more negative activation volume.



Entry	*P* [bar]	Ratio **45**:**46**
1	500	5.48:1
2	1200	5.53:1
3	2000	5.63:1
4	5000	6.75:1

Scheme 4

Returning to the IMDAF cycloaddition, this reaction has been used in 'ultra-high pressure' mode[28] as part of a synthetic study aimed at the phorbol class of natural products (Figure 7). Reaction of **47** under 19 kbar pressure gave a single cycloadduct, the 2-thioether substituent on the diene being crucial for both the cycloaddition and the later cleavage of the oxygen bridge. Unexpectedly, the nature of the thioether moiety was also all-important (compare the performance of **49** and **51**, the latter giving either no reaction or decomposition under a range of high-pressure conditions). A plausible explanation is that the benzylthioether enhances the HOMO energy of the furan unit, whereas the phenylthioether does not.

A high-pressure type 1 IMDA cycloaddition was used in an enantioselective route[29] to chiral hexahydronaphthalene units characteristic of the mevinolin family of natural products (Scheme 5). Interestingly, high pressure was also used in the synthesis of IMDA precursor **54** from **52**, via Weinreb amide **53**. For the IMDA process, the predominant formation of **55** was explained on the basis of steric effects: the 'eclipsed ethanone – *skew* butene' conformational combination being the one of lower energy.

5.11.3.4 Use of Microwave Heating or Ionic Liquids

To test a proposition regarding the biosynthesis of the alkaloid symbioimine,[30] the innocuous-looking *trans*-enone **57** (Figure 8) was heated under conventional IMDA conditions and was also subjected to the action of well-established Lewis acid catalysts, but no cycloadduct formation was observed. Success was finally achieved by the use of microwave heating,[31a] a technique[31b] that has proved to be very useful also for many other reaction types. The role of IMDA cycloaddition in the symbioimine biosynthetic proposal will be further discussed in Sections 5.11.4.1 and 5.11.11.1.2.

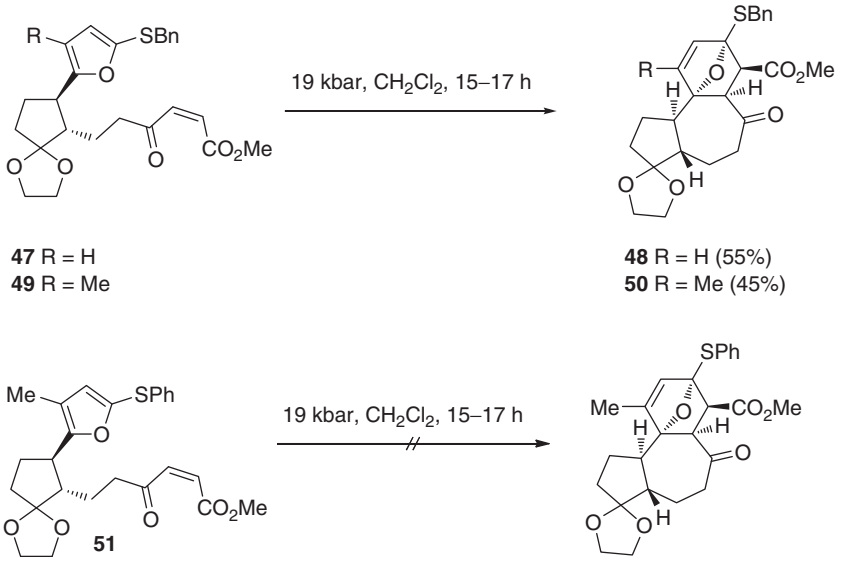
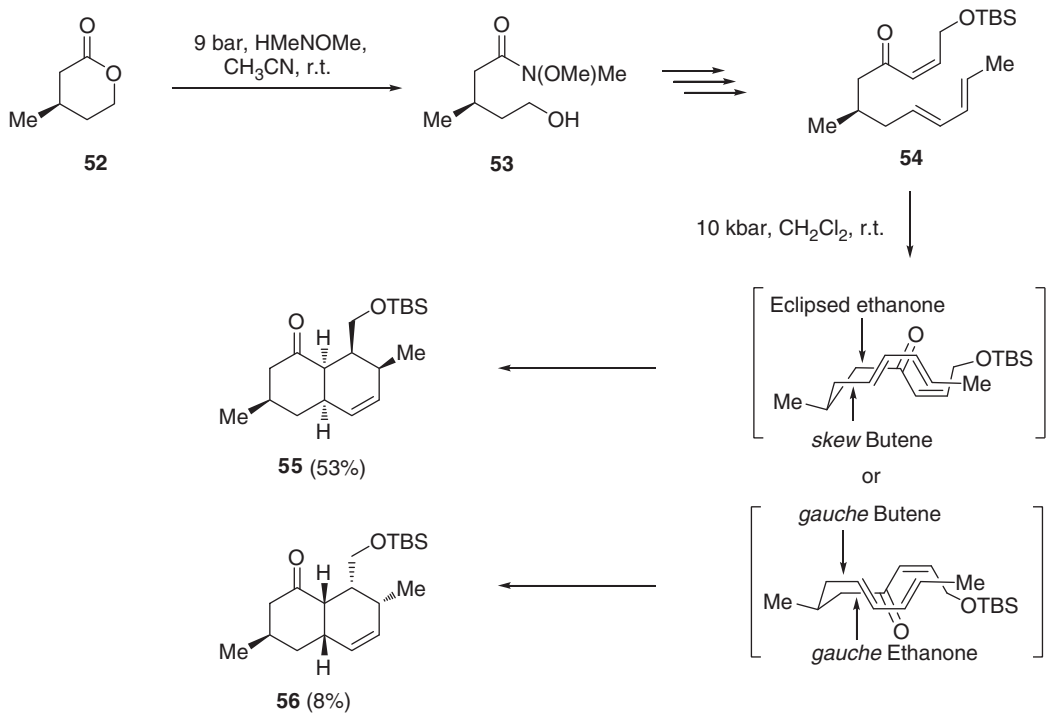
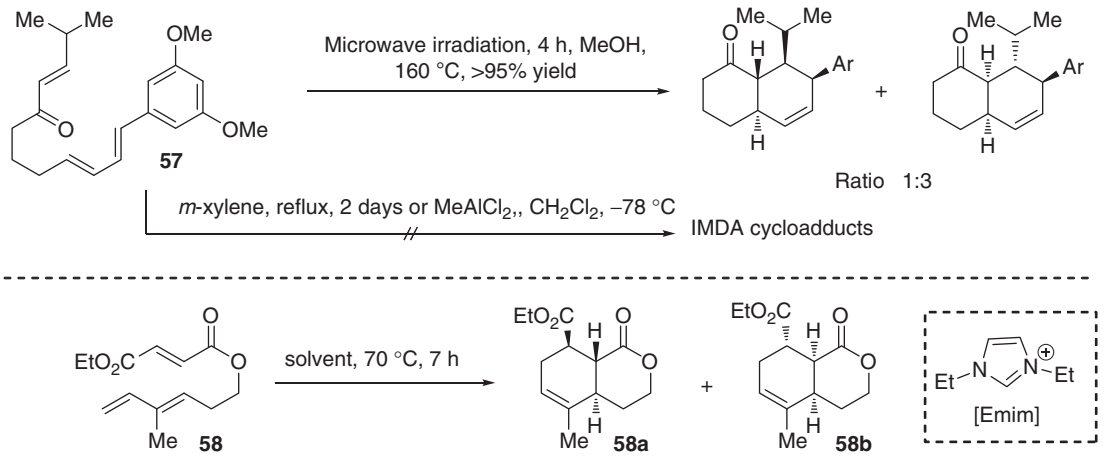


Figure 7 Pressure induced IMDA cycloaddition.



Scheme 5

For the promotion of organic reactions by use of 'green' media, ionic liquids[32] offer the advantages of high thermal stability, negligible vapor pressure, and recyclability. A recent example[33] involving an IMDA cycloaddition in ionic liquid media is shown in Figure 8, and the results can be compared to those obtained when precursor **58** was heated in 'normal' solvents, of either low (xylene) or high (water) polarity. It was suggested that the ionic liquid medium, by virtue of its polarity, helps to negate the repulsive dipole interaction between the two oxygens of the ester in the *cisoid* conformation shown for **58**, thus facilitating the IMDA process. It was also speculated that the microviscosity of the ionic liquid medium assisted the diene component in folding into the correct orientation for the cycloaddition.



Solvent	Yield (%)	Product distribution **58a:58b**
Toluene	14	1:4.6
H_2O	43	1:4.1
[Emim]BF_4	84	1:3.6

Figure 8 IMDA cycloaddition promoted in ionic liquid media.

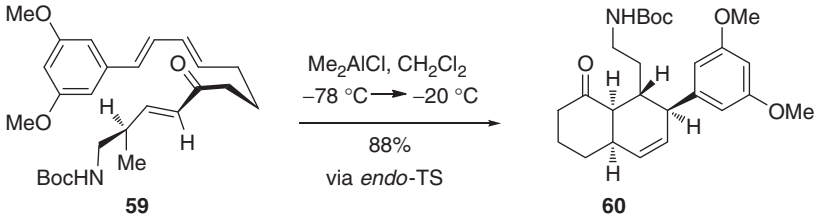
5.11.4 Catalysis of IMDA Cycloaddition

The most cursory of literature searches suffices to ascertain that the literature on the general subject of catalysis of DA cycloadditions is indeed vast. Because the present writing is not intended to provide an encyclopedic collection of data, only a small selection of recent methods (from the period 2000–11) for the catalysis of IMDA reactions is presented in the following subsections.

5.11.4.1 Oxophilic Lewis Acid Catalysis

The use of Lewis acids to facilitate the DA cycloaddition has been known for over 50 years[34] and a plethora of such mediators/catalysts (including chiral species suitable for asymmetric synthesis, see Section 5.11.6) is now available.[35] The role of the Lewis acid is to activate the dienophile component (typically by complexation to a carbonyl or carboxyl oxygen) thus lowering the LUMO energy, and such catalysts/promoters are capable of enhancing not only reaction rate but also regio- and stereoselectivity. The earliest examples[34] of Lewis acid-mediated DA cycloaddition employed stoichiometric amounts of aluminum trichloride in conjunction with robust cycloaddition partners, but it did not take long before catalytic procedures came into use, involving delicate applications to the total synthesis of complex natural products such as the prostaglandins.[36] It should be emphasized, however, that many DA and IMDA reactions described as being 'Lewis acid catalyzed' actually involve stoichiometric or even superstoichiometric amounts of the promoter; nevertheless, for the purpose of comparison with other approaches, it is appropriate to include such processes at this point, because many Lewis acid-mediated DA/IMDA cycloadditions take place under remarkably mild conditions.

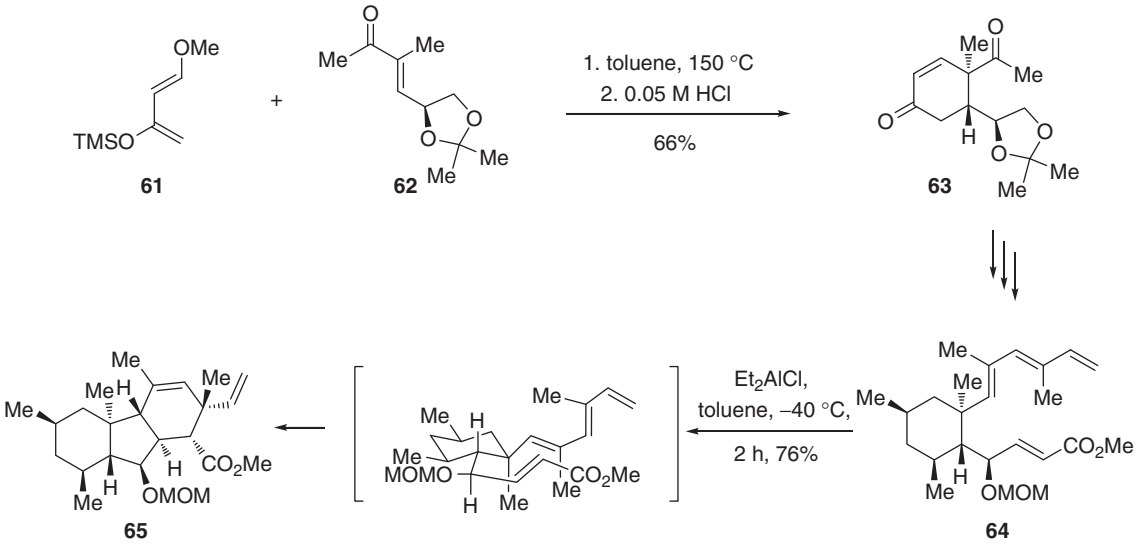
In Section 5.11.3.4 (Figure 8, top) was documented the failure of a Lewis acid ($MeAlCl_2$) to mediate the cycloaddition of precursor **57** in an attempted synthesis of the alkaloid symbioimine, a project that was inspired by a proposal for the biosynthetic generation of the natural product, involving an unusual *exo*-selective IMDA process. A more recent study[37] (Scheme 6) employed the stereochemically more elaborate IMDA precursor **59** that proved amenable to Lewis acid 'catalysis' (by Me_2AlCl) and delivered



Scheme 6

a single diastereomer of the cycloadduct under very mild conditions. The product was apparently formed via the *endo* transition state, which cast doubt on the original biosynthetic proposal (which had duly been modified[38] to include an alternative pathway via the more traditional *endo* mode). This result is also noteworthy in that the single stereogenic center at the allylic position of the dienophile unit of **59** which, in the IMDA transition state, is out with the pericyclic array leading to the product, is capable of exerting a very high level of stereocontrol over the π-facial selectivity of the cycloaddition. A related example of such 'exocyclic' stereocontrol by an allylic substituent in the diene component – in a thermal IMDA cycloaddition – is presented in Section 5.11.7.1.

A total synthesis[39] of the antitumor antibiotic GKK1032 agents (Scheme 7) began with an intermolecular DA using the classical Danishefsky diene **61** that was elaborated to IMDA precursor **64**. After some screening of Lewis acids, Et_2AlCl was found to mediate the IMDA cycloaddition under mild conditions to give **65** as a single diastereomer in 76% yield. The corresponding thermal IMDA reaction (toluene, 120 °C) gave the desired product in only 46% yield, along with 20% of a compound formed via an intramolecular ene reaction (a process which is also subject to Lewis acid catalysis). The preferred *endo* transition state for the IMDA, which minimizes steric repulsion between the cyclohexane ring and the proximal methyl group on the triene side-chain, is indicated in Scheme 7.



Scheme 7

5.11.4.2 Carbophilic Lewis Acid Catalysis

Soft, carbophilic Lewis acids (e.g., salts of Cu, Au, and Pt) can be used to activate alkynes and catalyze a variety of their reactions, including intramolecular [4 + 2] cycloadditions, as outlined in Figure 9. Stereoselective formation[40] of tricycle **67** can be explained by initial coordination of copper to the alkyne, followed by formation of an isobenzopyrylium intermediate that undergoes an intramolecular [4 + 2] cycloaddition and bond rearrangement to give the product, with regeneration of the catalytic species. Au(III) complexes can also catalyze this type of reaction. A total synthesis[41] of the natural product heliophenanthrone **69** relied on either Au(III) or Pt(II) catalysts to form the tricyclic system via cycloaddition and aromatization. The gold catalyst gave only 35% total yield in the key cyclization step, whereas the Pt(II) species gave 71% (mixture of diastereomers). Copper (I) catalysts[42] have been used to promote the IMDA of unactivated dieneynes such as **70** via copper acetylide and vinylcopper intermediates (**71** and **72**, respectively). Evidence for **72** was obtained by quenching the reaction with D_2O, and computational studies indicated that formation of **71** significantly lowers the alkyne LUMO energy, thus facilitating the IMDA cycloaddition. An elegant cascade sequence (see Sections 5.11.5.2 and 5.11.8), initiated by mesitylcopper, was also developed (IMDA followed by intramolecular Michael addition of the vinylcopper intermediate).

5.11.4.3 Brønsted Acid Catalysis

Although Lewis acids can efficiently promote or catalyze DA cycloadditions with carbonyl/carboxyl-substituted dienophiles, often with enhanced stereo- and regioselectivity, attempts at Lewis acid catalysis of the corresponding nitroalkene cycloadditions have met with little success.[43] Recently, however, the Brønsted acid **77** has been reported[44] to catalyze a nitroalkene type 1 IMDA cycloaddition with enhanced stereoselectivity as compared to the thermal process (Scheme 8). For pyridinium catalyst **77**, the

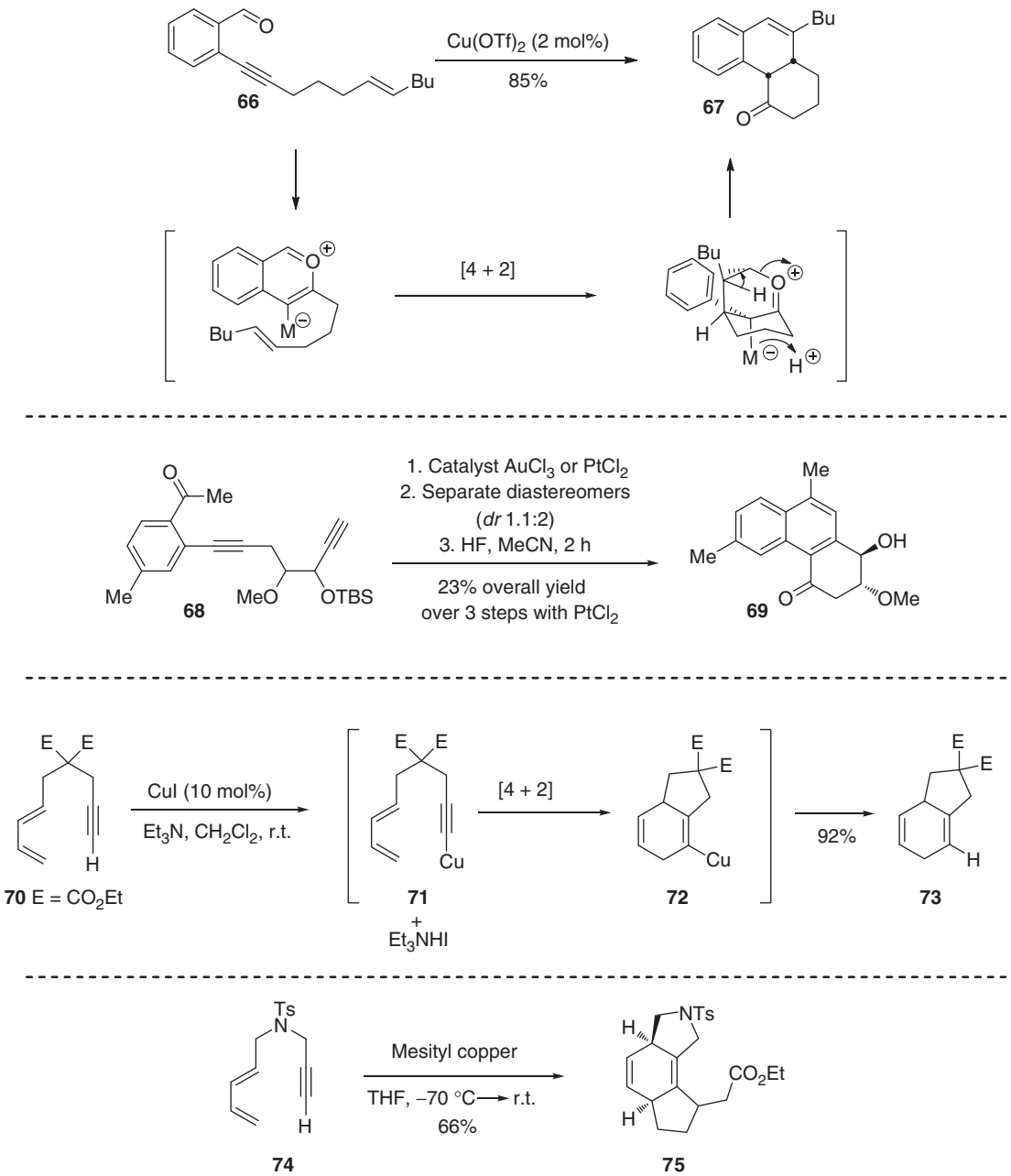
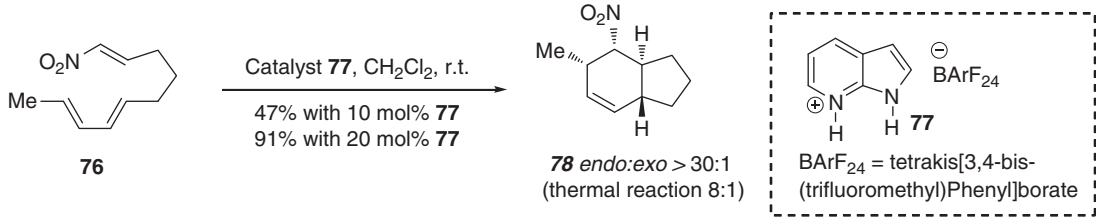


Figure 9 Carbophilic Lewis acid-assisted IMDA cycloadditions.



Scheme 8

yield of the cycloaddition increased with catalyst loading, which was not the case when the corresponding Na salt was used. This is a useful addition to the IMDA armory in view of the versatile chemistry of the nitro group in subsequent transformations.

5.11.4.4 Enzymatic Catalysis – 'Diels–Alderases'?

The fascinating topic of 'Diels–Alderases' has piqued the interest of organic chemists for considerable time.[45] In 1998, the first claimed Diels–Alderase, solanapyrone synthase, was used[46] to catalyze the *exo*-selective IMDA cycloaddition of **79** (the enzyme first oxidizes the alcohol group to the aldehyde **80**, which is the actual IMDA precursor). The natural product (–)-solanapyrone A **81** was obtained in essentially enantiomerically pure form, and the *exo*-selectivity of the IMDA reaction was 6:1 (Figure 10, top). This is in contrast to the nonenzymatic IMDA process, which in a variety of organic solvents and especially in water, gave *endo*-selectivity (up to 20:1). An alternative mode of catalysis for the synthesis of the solanapyrone family is presented in Section 5.11.7.3.3.

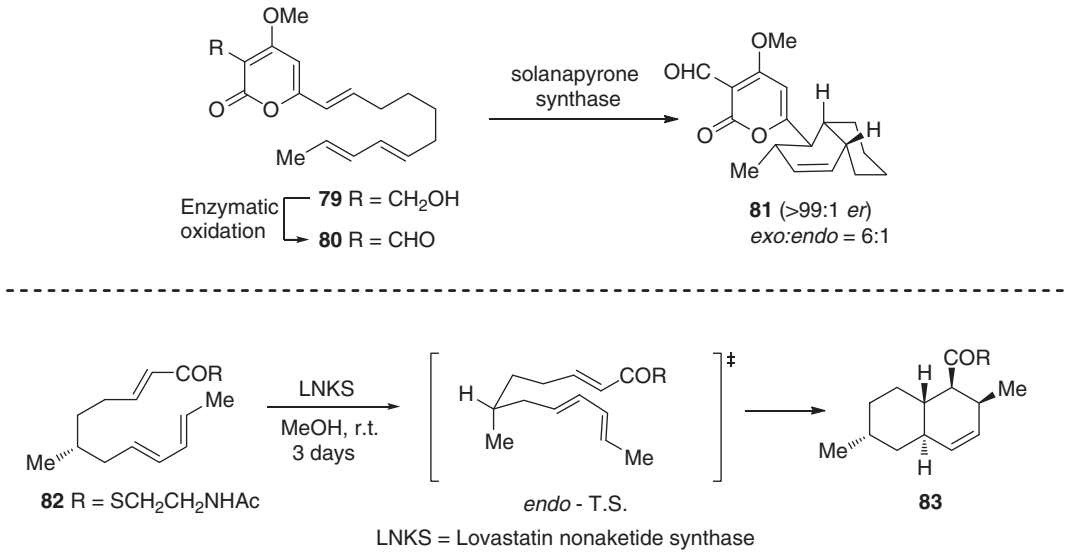


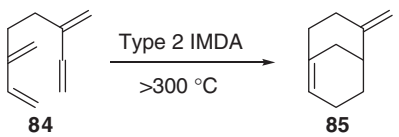
Figure 10 Enzymatic IMDA cycloadditions.

Although the solanapyrone synthesis utilized a crude cell-free preparation of the enzyme, a later study[47] of Diels–Alderases employed the purified enzyme lovastatin nonaketide synthase (LNKS) to catalyze the *endo* IMDA cyclization of **82** to **83** (Figure 10). Again, the course of the enzyme-catalyzed cyclization was markedly different from the nonenzymatic IMDA: cycloadduct **83** (which has the same stereochemistry as intermediates on the biosynthetic pathway to the lovastatin natural products) was observed only in the LNKS reaction, and is formed via a transition state in which the Me group is pseudoaxial. It was proposed that the hydrophobic active site of the protein determines the folding of the substrate as it approaches the transition state, and hydrogen bonding to the carbonyl oxygen is also likely to aid the cyclization by lowering the LUMO energy of the dienophile.

A very interesting recent paper[48] describes the computational design of an enzyme catalyst for a stereoselective bimolecular (i.e., intermolecular) DA cycloaddition, for which naturally occurring enzymes have yet to be found. The topic of biosynthetic IMDA cycloadditions is discussed in Section 5.11.12.

5.11.5 Type 2 IMDA

Fifty years after the original Diels and Alder paper, the first example[49] of a type 2 IMDA cycloaddition was discovered serendipitously (Scheme 9). Tetraene **84** (generated at temperatures >300 °C) yielded the highly strained and reactive *anti*-Bredt alkene **85** which nevertheless could be isolated and characterized. This unexpected result opened up a new area of DA cycloaddition, rich



Scheme 9

in opportunities for physical-organic and synthetic organic chemists alike. The type 2 IMDA was the subject of an excellent and extensive review[50] in 2001 and only selected examples taken from the literature in the period since 2000 will be described in Section 5.11.5.2 below (two examples[17,18] have already been presented in Section 5.11.3.1).

5.11.5.1 Type 2 and Type 1 IMDA Compared

Because the Type 2 IMDA process yields a strained bridgehead alkene and because the transition state is characterized by repulsive nonbonding interactions, the free energy of activation is usually considerably higher than that for the type 1 IMDA counterpart. Experimentally derived activation energies[50] lie in the range 155–172 kJ mol^{-1}, a barrier that originally was overcome by extended heating at elevated temperatures. However, the advantages of Lewis acid catalysis (as described earlier for the type 1 IMDA reaction) soon became apparent[51] (compare the thermal and Lewis acid-promoted reactions of **86** shown in Figure 11). More recently,[52] microwave heating has proved to be a useful activation method, for example, the conventional thermal reaction of **88** (Figure 11) gave yields between 40% and 60%. As for type 1 IMDA (Section 5.11.3.4), the microwave technique is particularly useful for cases when the cycloaddition substrates and/or products are unstable at high temperatures or contain functionality incompatible with Lewis acids. In line with the Type 1 IMDA, the stereospecificity of the type 2 IMDA reaction is consistent with a concerted pericyclic process.

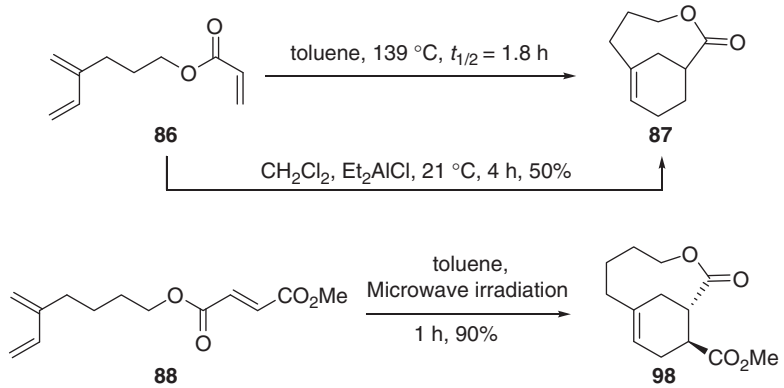


Figure 11 Type 2 IMDA cycloadditions influenced by conventional and microwave heating.

5.11.5.2 Some Recent Examples of Type 2 IMDA

The type 2 IMDA reaction provides a very convenient one-step entry to bridgehead alkenes and constitutes a powerful methodology for the total synthesis of complex molecules, including natural products. Some recent examples are shown in Figure 12. The remarkably smooth conversion of **90** to bridgehead alkene **91** was a key early step in the asymmetric total synthesis of the CP molecules.[53] A dramatic example[54] is provided by the intramolecular [4 + 2] cycloaddition of **92,** which after loss of CO_2, and deacetylation, provided the very unusual natural product haouamine A (**94**), which contains a nonplanar aromatic ring (for further examples of aromatization via IMDA reactions, see Sections 5.11.6.2 and 5.11.6.3). An approach to the welwitindolinone alkaloids[55] utilized a type 2 IMDAF (cf. Sections 5.11.3.3 and 5.11.6.1) with substrate **95** as part of an attractive cascade sequence (see also Sections 5.11.6.2 and 5.11.8). The cycloaddition was completely diastereoselective.

5.11.6 IMDAF, IMHDA and Inverse Electron Demand IMDA Cycloaddition

The following sections will deal with the topics of IMDAF[56] (see also Section 5.11.3.3), IMHDA (see also Section 5.11.3.3), and IMDA reactions with inverse electron demand. Emphasis will be placed on recent applications in complex molecule synthesis.

5.11.6.1 IMDAF Cycloaddition

A large-scale enantioselective synthesis of the tetracycline antibiotics[57] involved an IMDAF reaction with the diastereomeric mixture of alcohols **97** (Figure 13). The reaction was carried out on a 98 g scale, and the chiral allylic amine efficiently directed the diene to a single π-face of the dienophile. Another interesting aspect was that the major cycloadducts from the stereoisomeric alcohols were both *endo* diastereomers; furan-DA cycloadditions tend otherwise to be *exo*-selective, because of reversibility, and in the present case, the 3-methoxy substituent on the furan is the key factor.[58] The IMDAF reaction of **98** proceeded efficiently under

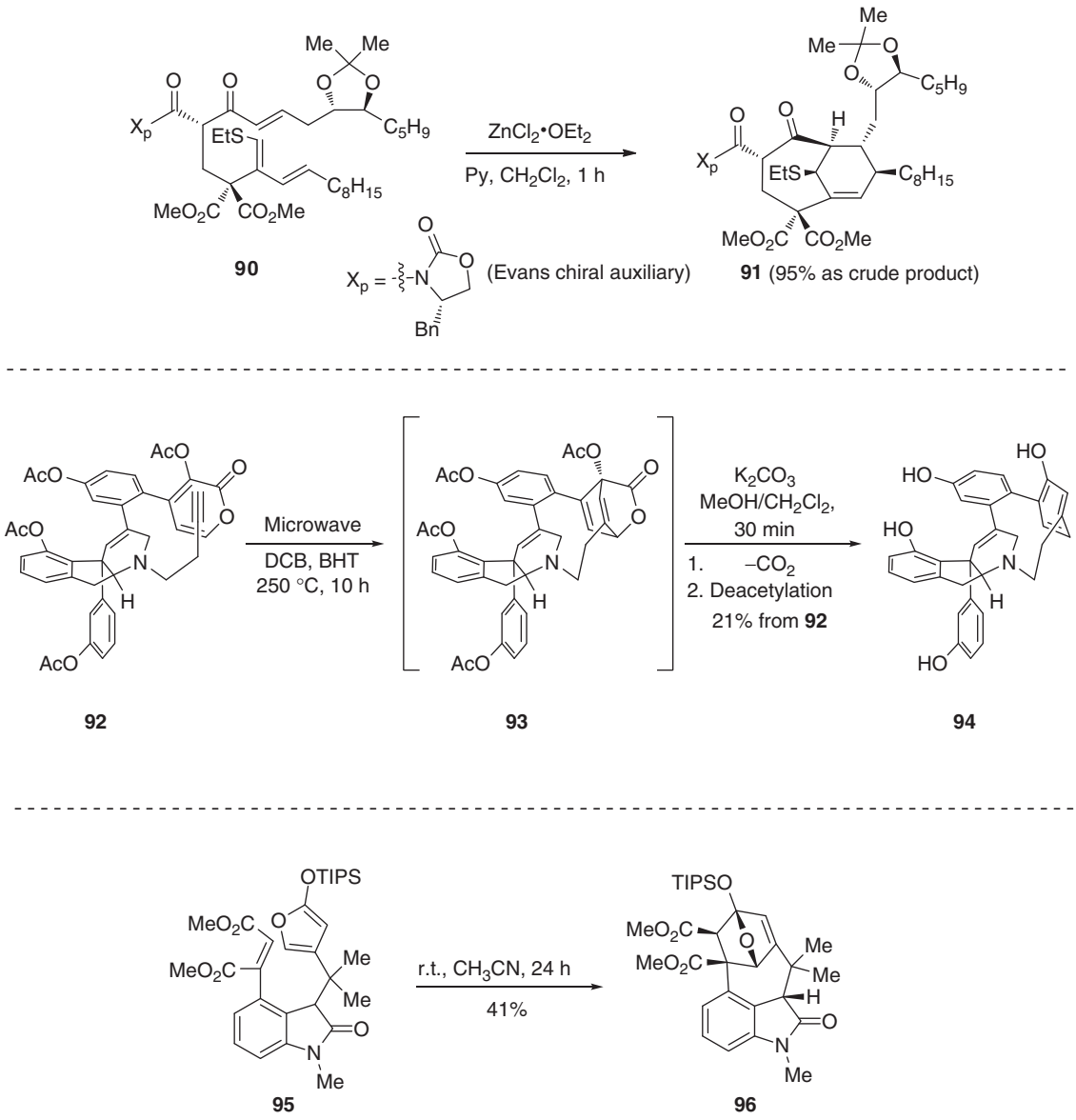


Figure 12 Examples of type 2 IMDA cycloadditions.

thermolytic conditions, the initially formed cycloadduct being subject to a nitrogen-assisted ring opening to yield **100**, an intermediate for the projected total synthesis of the lycopodium alkaloid fawcettidine.[59] In Section 5.11.3.3, the use of high pressure to enable IMDAF reactions is described. The cycloaddition of furans **101** with unactivated alkynes employed a very different form of acceleration, in the form of a Grignard addition reaction.[60] The formation of a chelated magnesium species was suggested to be important for the rate acceleration, by raising the HOMO energy of the furan diene component. The Grignard-accelerated reactions were also more stereoselective than the corresponding purely thermal processes. Oxanorbornadienes such as **102** are versatile building blocks for further synthesis.

5.11.6.2 IMHDA Cycloaddition

Incorporation of heteroatoms (in particular, N, O, and S) into the pericyclic array of a DA cycloaddition allows for the synthesis of heterocycles, and an impressive array of examples can be found.[61] Not surprisingly, much effort has been concentrated on *N*-heterocyclic systems, and some recent examples of type 1 IMHDA reactions are shown in **Figure 14**. In pursuit of the total synthesis of the marine natural products fasicularin and lepadiformine, an IMHDA cycloaddition using an acylnitroso grouping as the dienophile was developed.[62] Periodate oxidation of **103** generated the substrate **104** for the cycloaddition, which gave best yield and stereoselectivity when carried out in aqueous media (taking advantage of the 'hydrophobic effect').[63] The major cycloadduct **105** was suggested to be formed via the then-unprecedented *anti*-facial transition state **107**, with the tether equatorially disposed.

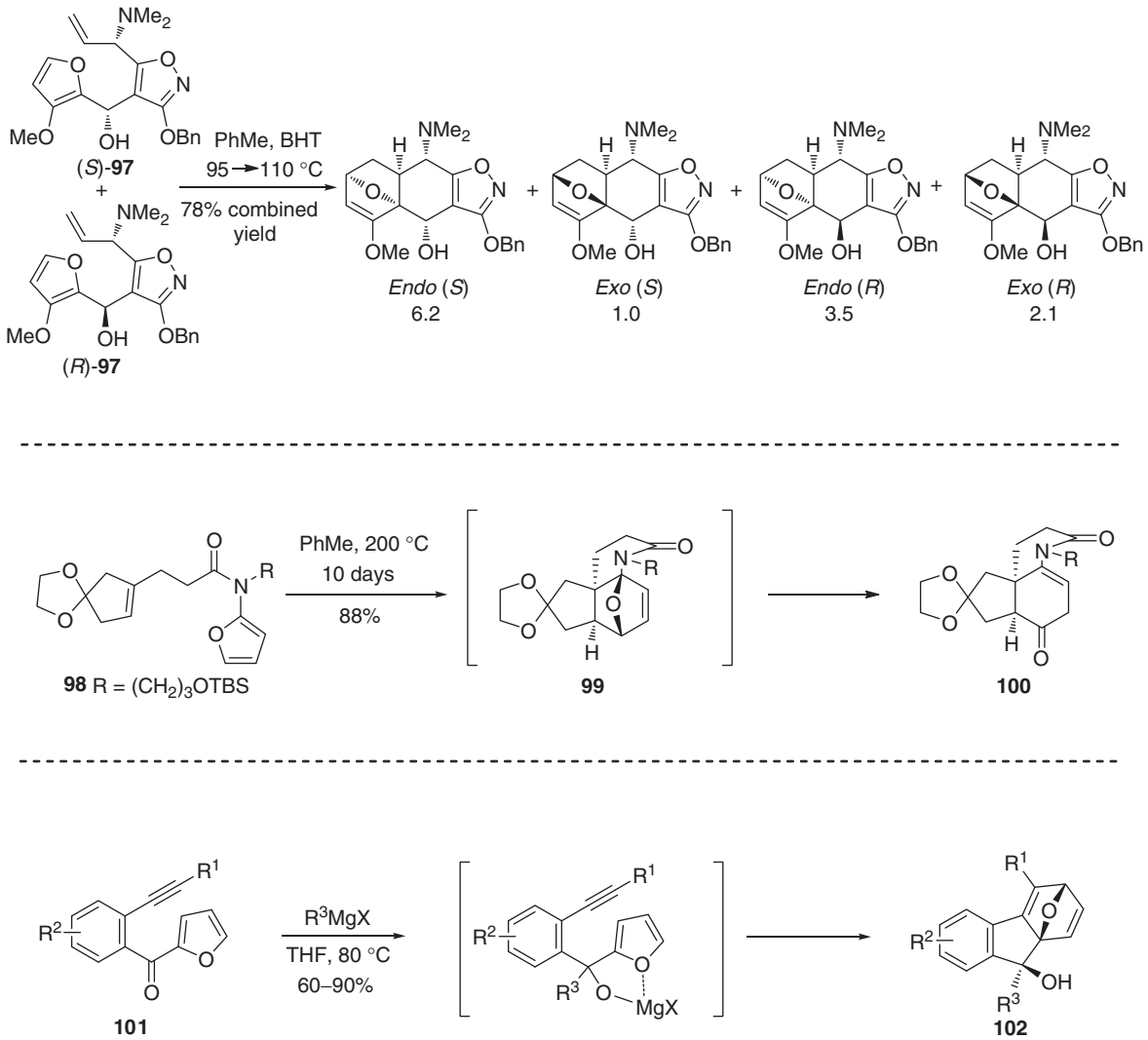


Figure 13 Examples of IMDAF cycloadditions.

This meant that the least hindered approach of the dienophile was to the face of the diene opposite to the anchor position of the tether. Interestingly, the facial selectivity of this IMHDA process could be reversed by the simple expedient of placing a bromine atom in the 2-position of the diene, to take advantage of 1,3-allylic strain effects[64] (this is similar to one of the IMDA substrates shown in Figure 2). Iminoacetonitriles such as **108** were introduced[65] as azadienophiles in 2003 and provide simple access to bicyclic α-amino nitriles **109** via a stereoconvergent process (both isomers of the iminoacetonitriles give the product with the axial cyano group, via equilibration). It is important to note that the α-amino nitrile grouping present in **109** is a latent iminium ion, ripe for unmasking by the action of mild protic or Lewis acids, thereby providing a convenient handle for further stereoselective introduction of functionality. An intriguing IMHDA involving an indole as dienophile and an aza-*ortho*-xylene (see **110**) was developed[66] for the total synthesis of a pentacyclic substructure of communesin B. The highly reactive azadiene component was generated *in situ* from an aziridine under mild conditions, and the desired cycloaddct **111** was obtained in excellent yield.

A convenient route to substituted pyridines[67] is provided by a high-pressure IMHDA reaction of oximino malonate dienophiles such as **112**, followed by aromatization under mild conditions to give **114** (Scheme 10). Further examples of IMDA followed by aromatization are presented in Section 5.11.6.3.

Figure 15 summarizes progress[68] in the use of type 2 IMHDA cycloadditions that allow convenient access to a range of *N*-heterocycles suitable for further synthetic manipulation. In particular, the studies of the *N*-acylazo substrates **116** revealed improved protocols for oxidation of the hydrazide precursors **115**, and allowed an evaluation of Lewis acid catalysis for the IMHDA process. It was found that oxidation of **115** with *N*-bromosuccinimide[69] allowed for the isolation of **116**, which in the presence of 10 mol% $ZnCl_2$ smoothly provided the cycloadduct **117** under mild conditions. This is a rare example[70] of Lewis acid-catalyzed DA reactions of azo compounds. The bridgehead alkene, the lactam grouping, and the N–N bond of **117** provide excellent opportunities for subsequent synthetic elaboration.

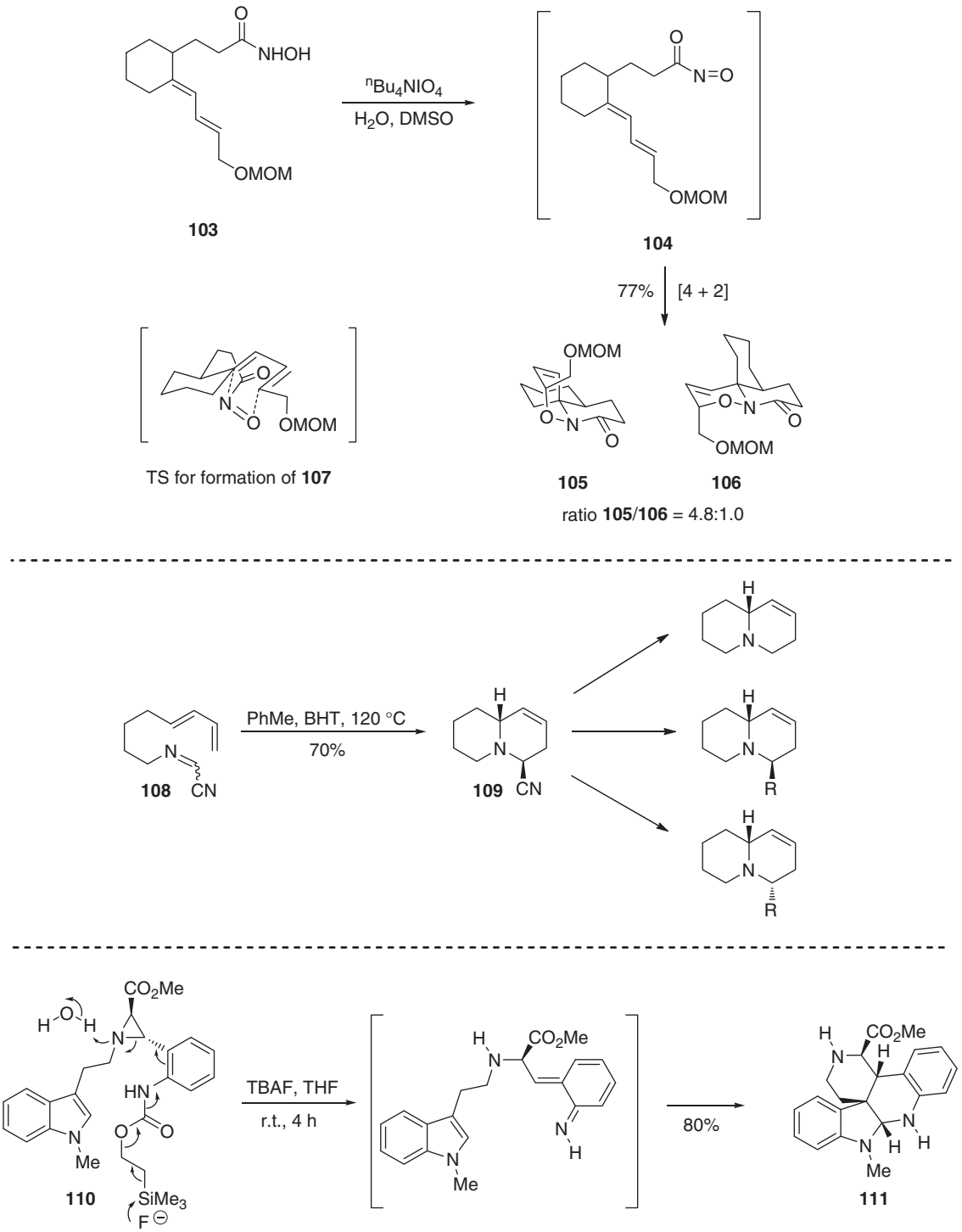
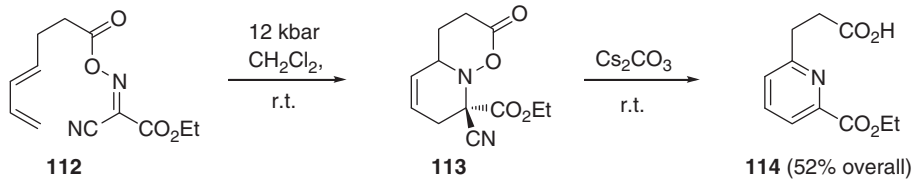


Figure 14 Examples of IMHDA cycloadditions.

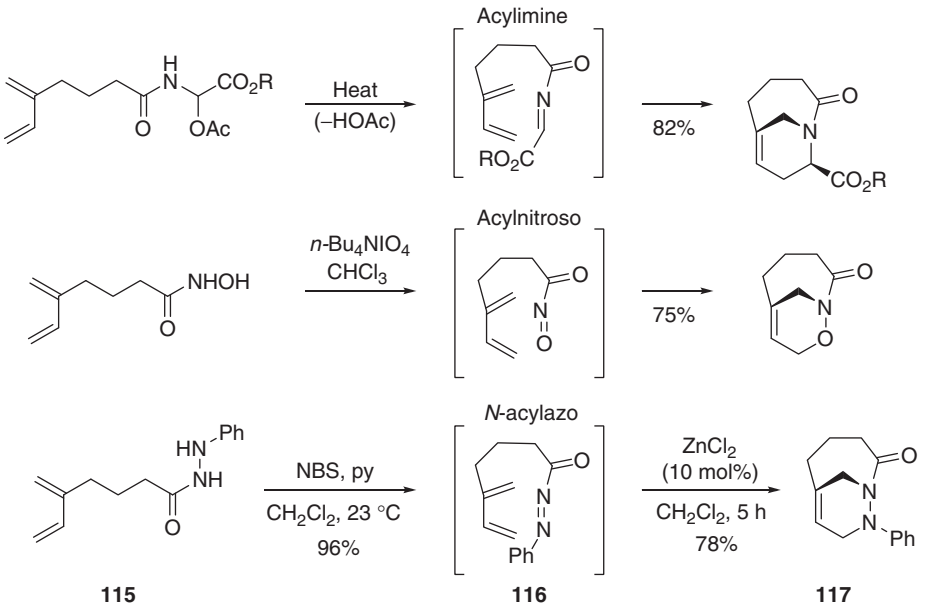
5.11.6.3 IMDA and IMHDA Cycloadditions with Inverse Electron Demand

'Normal' DA, IMDA, and IMHDA cycloadditions are controlled by the ($HOMO_{diene}$–$LUMO_{dienophile}$) combination of frontier molecular orbitals.[71] However, with the correct choice of substituents on the pericyclic array, the electronic situation can be inverted to allow smooth cycloaddition between an electron-deficient diene and an electron-rich dienophile. Figure 16 exemplifies some applications of inverse electron demand IMDA/IMHDA reactions to the synthesis of biologically significant natural products. Vinyl quinone **119** underwent[72] a slow and relatively inefficient thermal IMDA, and addition of Lewis acids (to further lower the diene LUMO) did little to improve the yield. Success was realized by application of high pressure (Section 5.11.3.3)



112 **113** **114** (52% overall)

Scheme 10



115 **116** **117**

Figure 15 Type 2 IMHDA cycloadditions.

which provided the aromatized product **121** in excellent yield, via cycloadduct **120**. Because **120** could not be isolated, the simple diastereoselectivity of the IMDA reaction (*exo*/*endo*) could not be estimated directly, but DFT calculations provided insight on this matter. Sequential IMHDA reactions were used[73] for the total synthesis of pentacyclic *Amaryllidaceae* alkaloids, the first cycloaddition with subsequent loss of N_2 taking place at ambient temperature to give **125** in near-quantitative yield. The second cycloaddition required elevated temperature, but was also very high-yielding, and provided access to advanced intermediate **127** (after loss of N_2 and aromatization by elimination of methanol).

5.11.7 Asymmetric Synthesis via IMDA Cycloaddition

As noted in section 5.11.1, the stereospecificity and regio- and diastereoselectivity of the DA cycloaddition allows – in a single operation – control over up to four contiguous stereocenters, which can be augmented to six by manipulation of the newly formed endocyclic double bond. These features make the DA reaction (in both inter- and intramolecular modes) a uniquely powerful method for stereochemical control in either a relative or absolute sense. The IMDA cycloaddition of **119** (Figure 16) is an excellent example of substrate-controlled asymmetric synthesis, in which a 'permanently resident' stereocenter efficiently steers formation of one or more new stereocenters via a diastereoselective reaction with a highly-ordered transition state. Numerous other examples of substrate control in the IMDA reaction can be found throughout the preceding discussion (starting with the cycloaddition of **3** depicted in Figure 2), and this section will focus on some of the important strategic and tactical developments within the field of asymmetric IMDA cycloadditions. Strategically, the general arena of asymmetric synthesis offers four possibilities: (1) substrate control, (2) the use of chiral auxiliaries, (3) reagent control, and (4) the use of chiral catalysts. This quartet can certainly be regarded as a hierarchy of increasing difficulty, sophistication, and efficiency – with enantioselective catalysis at the pinnacle – but, given the present state of the art, it is still appropriate to consider these approaches as complementary solutions to the very challenging problem of absolute stereocontrol.[74a]

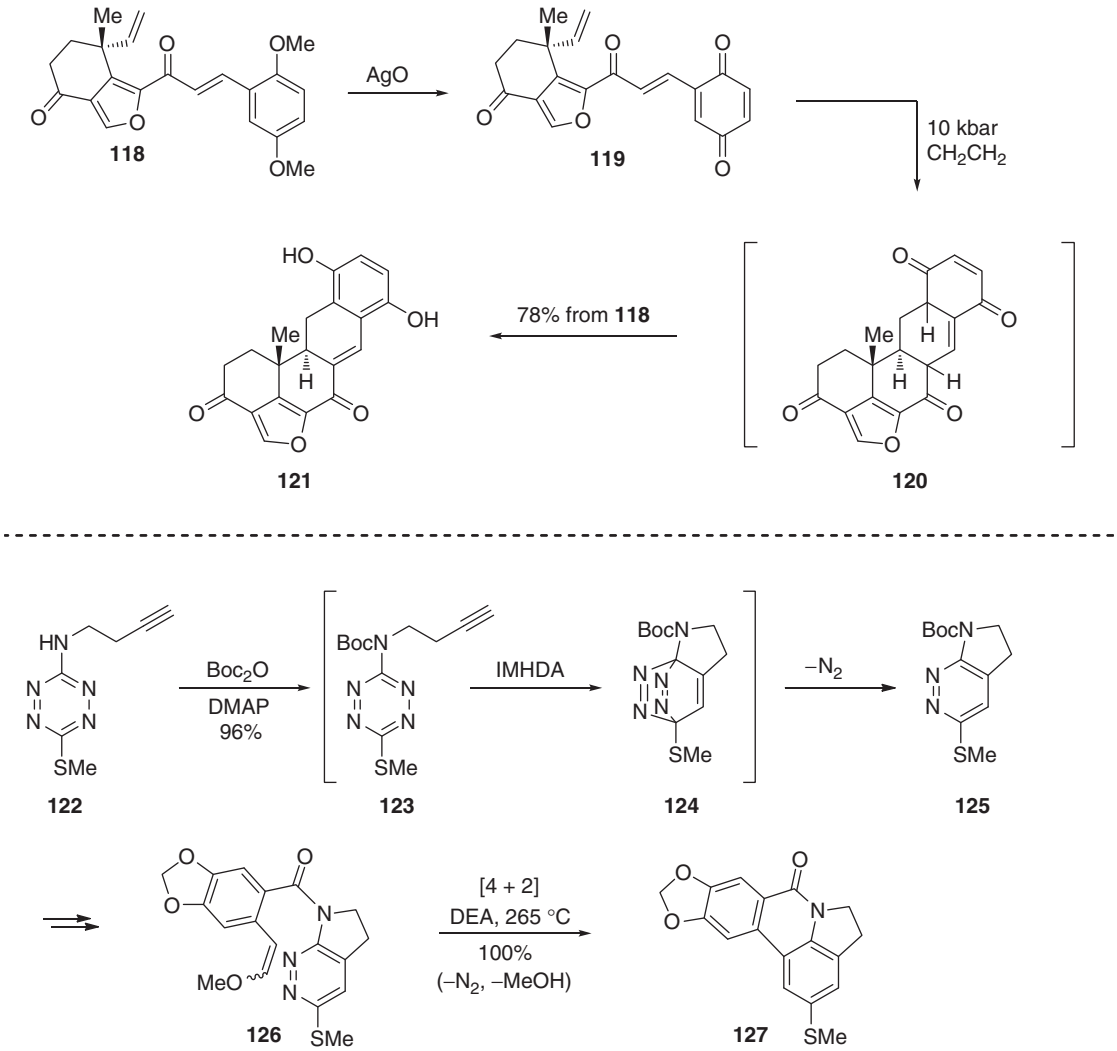


Figure 16 IMDA and IMHDA with inverse electron demand.

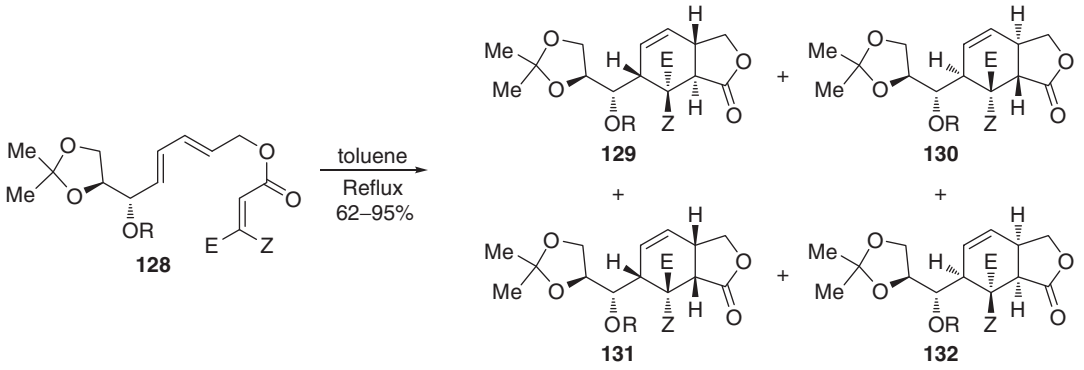
5.11.7.1 Substrate Control of IMDA Cycloaddition

In Section 5.11.2 (Figure 2) the (limited) ability of an allylic stereocenter in the tether of the Type 1 IMDA substrate **3** (X=H) to exert a bias on both the *endo*/*exo* and the π-facial selectivity of the cycloaddition was described.[7] A later study,[74b] also involving a combination of experimental and computational methods, explored the scope and limitations of stereocontrol by a stereogenic center at the terminus of an acyclic diene (Figure 17). Enantiomerically pure substrates were used in all cases. The nature and steric bulk of the group R was found to have a major impact on the diastereoselectivity of the cycloaddition, with bulky silyl groups (triisopropylsilyl (TIPS)) providing the highest levels of stereocontrol. The influence of the homoallylic stereocenter was probed using substrates **133**, which gave considerably lower π-facial selectivities.

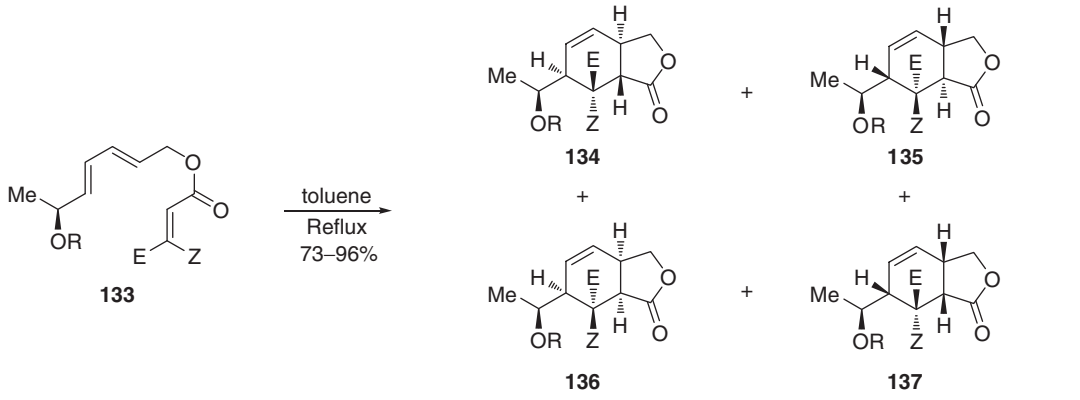
As in the previous investigation[7] DFT calculations were used to probe the stereochemical intricacies of the transition states, in particular how the allylic conformational preferences influenced the π-facial selectivity. For substrates such as **133** the reactive conformer was suggested to be that shown in Figure 18, in which the C–OSi bond eclipses the double bond, with a stabilizing electrostatic interaction between the C–OSi and the C2–H bonds. This array is similar to that suggested earlier for silylacetal-tethered IMDA reactions[9] (cf. the reaction of **6** shown in Figure 3). In **133**, it is thus a combination of the stereoelectronic preference of the silyloxy group and the steric properties of the allylic Me group which determines the π-facial selectivity.

5.11.7.2 Use of Chiral Auxiliaries

Of the multitude of chiral auxiliaries that have been developed,[75] the readily available Evans oxazolidinones[76a] and Oppolzer camphorsultams[76b] probably take pride of place, due to their versatility. The use of the former in a type 2 IMDA has actually



R / *E* / *Z*	Yield (%)	**129** : **130** : **131** : **132**
H / H / CO_2Me	86	56 : 32 : 8 : 4
TIPS / H / CO_2Me	68	92 : 7 : 1 : 0



R / *E* / *Z*	Yield (%)	**134** : **135** : **136** : **137**
H / H / CO_2Me	88	41 : 36 : 5 : 18
TIPS / H / CO_2Me	85	63 : 26 : 5 : 6

Figure 17 Substrated controlled IMDA cycloaddition.

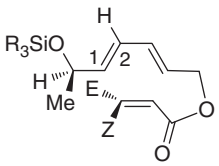


Figure 18 Reactive conformer for the substrate 133.

already been alluded to in Figure 12 (cycloaddition[53] of **90**) but a more detailed discussion is presented below, for the type 2 IMDA[77] of **138** and **140** (Figure 19). These reactions are mediated by a Lewis acid, Me_2AlCl, which forms a chelate with the 1,3-dicarbonyl unit of the dienophile, locking the enone substrate into the s-*cis* conformation that avoids repulsive nonbonded interactions with the oxazolidinone substituent. The molecule then folds into an *endo* transition state with the diene approaching the less hindered face of the dienophile. The diphenylmethyl substituent R provided the highest levels of diastereoselectivity, and a single crystallization gave the pure compound (minor diastereomer not detectable by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy). The Evans oxazolidinones possess all the qualities desirable in a chiral auxiliary: ease of availability, introduction and removal, high levels of diastereoselection, and ease of diastereomer separation.

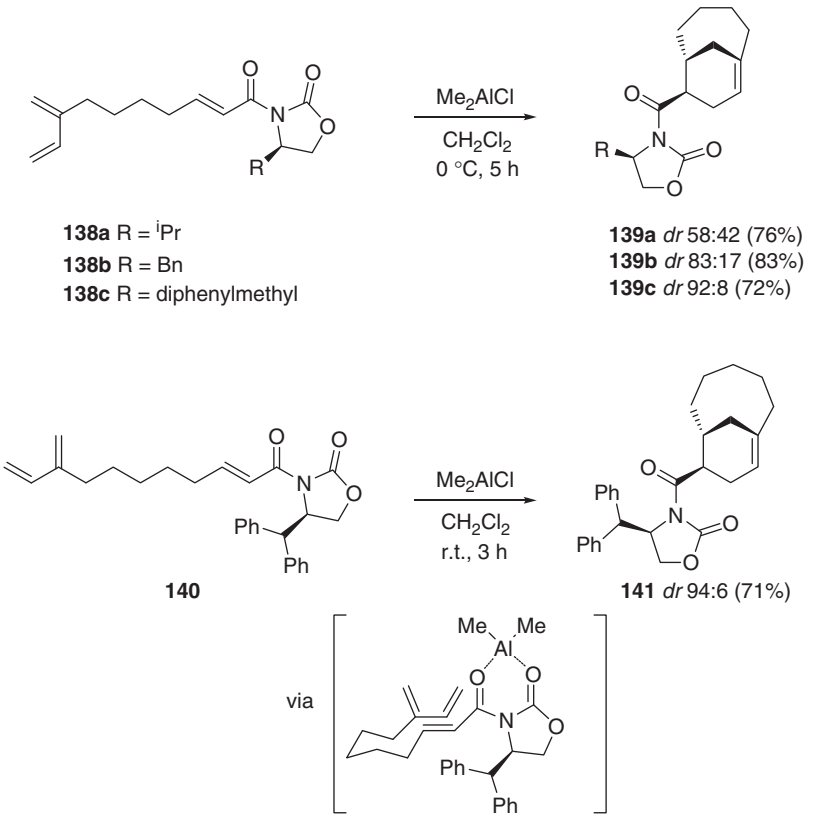


Figure 19 Diastereoselective type 2 IMDA mediated by a chiral auxiliary and a Lewis acid.

5.11.7.3 Use of Chiral Catalysts

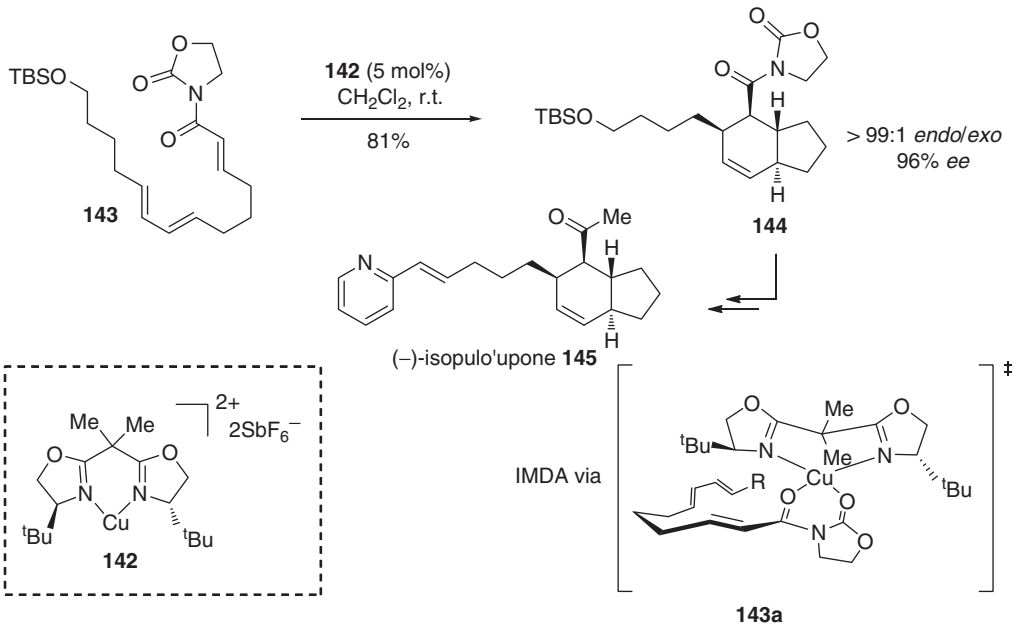
The following sections highlight the use of enantioselective catalysis[78] in IMDA cycloadditions, with emphasis on applications to total synthesis.

5.11.7.3.1 Chiral metal complexes for enantioselective catalysis

In the 1990s, a major breakthrough in catalytic enantioselective IMDA cycloadditions was provided by chiral C_2-symmetric Cu(II) complexes[79] such as **142** (Scheme 11). The example shown was part of an asymmetric synthesis[80] of the marine natural product (–)-isopulo'upone **145**. The (achiral) oxazolidinone moiety in IMDA precursor **143** is proposed to form a four-coordinate square planar Cu(II)–chiral ligand complex that mediates reaction via essentially a single *endo*-transition state (>99:1 *endo*/*exo*, 98:2 *er*), involving approach of the diene to the Si-face of the dienophile (see assembly **143a** in Scheme 11). The C_2 symmetry of the ligand reduces the number of possible diastereomeric transition states. This IMDA reaction required only 5 mol% of the catalyst and provided **144** in 81% yield under mild conditions. Other noteworthy features are that the reaction could be run at high concentration (1 M in substrate) and that both reactivity and enantioselectivity are dependent on the nature of the counterion, with SbF_6^- being superior to triflate. The chelating ability of the oxazolidinone is reminiscent of its role in the auxiliary-mediated asymmetric synthesis shown in Figure 19.

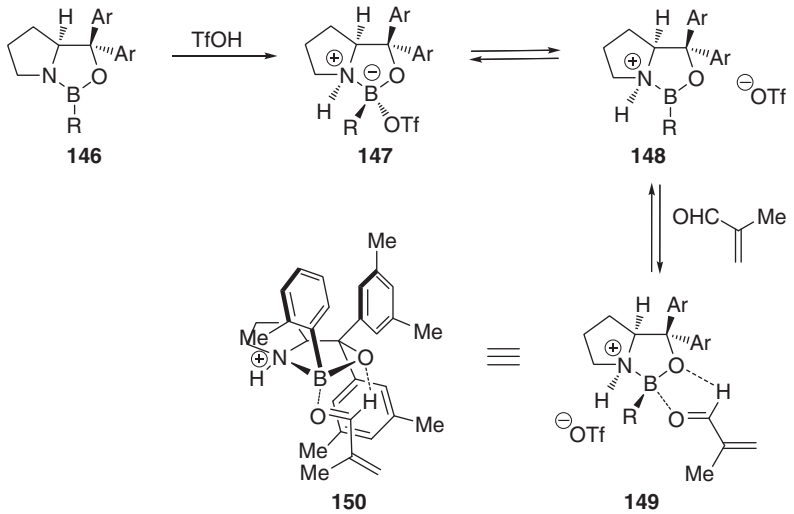
5.11.7.3.2 Use of chiral oxazaborolidine catalysts

Chiral oxazaborolidine complexes were originally developed[81] to catalyze the enantioselective reduction of ketones, a process which inspired their application to intermolecular DA cycloaddition[2b,82] followed by catalysis of the IMDA reaction.[83] Before discussing the IMDA reaction, the rationale[82] behind the use of chiral oxazaborolidine complexes for enantioselective catalysis will be presented. Precatalyst **146** (Scheme 12) is easily derived from proline, and when subjected to reaction with a strong protic acid such as TfOH forms **147**, which is in equilibrium with **148** (a process which can be monitored by NMR spectroscopy at low temperature). The cationic character of **148** makes it a powerful Lewis acid, well-suited to coordination with carbonyl groups, with the added bonuses of a hydrogen bond to the formyl hydrogen of an aldehyde, as shown for the methacrolein complex **149**, and an attractive π–π interaction between the enal and the proximal aryl group on the oxazaborolidine ring. This exquisite pre-organization should be ideal for enantioselective DA cycloaddition, via assembly **150**. For the intermolecular DA cycloaddition, the optimal R substituent was found to be *o*-tolyl, whereas the best geminal Ar moiety was 3,5-dimethylphenyl: this combination



Scheme 11

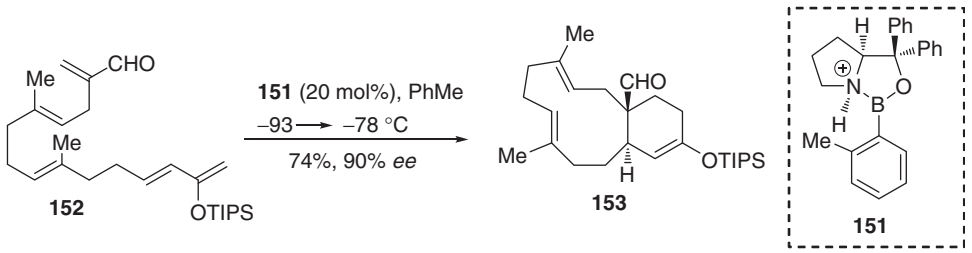
catalyzed the DA cycloaddition between methacrolein and cyclopentadiene with 96% *ee* (89:11 *exo/endo* selectivity). One of the 3,5-dimethylphenyl groups effectively blocks one of the π-faces of the dienophile, which controls the approach of the diene.



Scheme 12

This methodology was applied, in stunning fashion,[83] to the IMDA cycloaddition shown in Scheme 13, which formed part of a program aimed at the enantioselective total synthesis of the dolabellane-type marine natural products. The catalyst used in this case was **151**, which proved to be unique in promoting the IMDA cyclization (standard Lewis acids such as Me_2AlCl or application of heat did not lead to the desired product). The transition state for the IMDA cycloaddition is presumed to resemble that proposed for the bimolecular DA reaction shown in Scheme 12, and involves the Si-face of the dienophile. The impressive transformation of **152** to **153** is both a catalytic enantioselective IMDA reaction and a macrobicyclization, and provides a common key intermediate for the asymmetric total synthesis of a variety of natural products.

More recently, computational investigations[84] of similar DA reactions have revealed an alternative transition state assembly that does not involve CH–O hydrogen bonding, and which is probably involved in the [4 + 2] cycloaddition of certain ester-activated dienophiles. The topic of enantioselective catalysis will be returned to in Section 5.11.13, which deals with TADA cycloadditions.



Scheme 13

5.11.7.3.3 Organocatalysis

In recent years, few areas of organic synthesis have burgeoned like organocatalysis, i.e., the use of small organic molecules to catalyze organic transformations.[85] The role of the organocatalyst is to activate one or more of the reactant partners and thereby facilitate the reaction by lowering the energy barrier. Several modes of activation are now available,[85] including transient formation of an iminium species (to lower the LUMO of a carbonyl or α,β-unsaturated carbonyl species) or via enamine formation (to raise the HOMO of an alkene or diene). Both these approaches have recently been applied to catalysis of the IMDA process, and are presented in Figure 20. The imidazolidinone[86a] organocatalyst **155** (as its triflic acid salt) enables the highly diastereo- and enantioselective type 1 IMDA cycloaddition[86b] of **154** via iminium species **156**. In this pretransition state array, the *E*-iminium ion is favored in the orientation shown for steric reasons (minimize clash with ^{t}Bu) whereas the benzyl group effectively shields one of the faces of the dienophile. The diene then folds into the reactive conformation for a π-facial selective *endo*-IMDA reaction. This transformation sets four contiguous centers in a single operation, and provided a short route to the natural product solanapyrone D. This chemistry can be compared with the enzyme-catalyzed IMDA route[46] to the related molecule solanapyrone A shown in Scheme 10. Organocatalyst **155** was also used for the first example of a catalytic enantioselective type 2 IMDA cycloaddition[86b] involving conversion of **159** to **160** with superb levels of diastereo- and enantioselectivity. Proline derivatives **161** can be used as organocatalysts[87] for intramolecular [4 + 2] cycloadditions by electronically activating the diene HOMO via formation of enamines **163** (formed via the corresponding iminium species). The substituent on the stereogenic center of **163** dictates the orientation and π-facial selectivity of the diene in what is formally an *endo*-selective IMDA cycloaddition (formation of **164** can also be described in terms of a stereoselective Michael–Mannich sequence.) Elimination from **164** yields the bicyclic product **165** and regenerates the organocatalyst. An example of the use of organocatalysis in connection with a tandem sequence involving an IMDA cycloaddition is given in Section 5.11.8.1.

5.11.8 Tandem Reaction Sequences involving IMDA Cycloaddition

Tandem reaction sequences are those in which the product of one reaction is the substrate for a subsequent one, allowing two or more transformations to be carried out in a one-pot operation (the terms 'domino reactions'[88a,b] and 'cascade reactions'[88c] are also used). Examples have been mentioned briefly in Sections 5.11.4.2 and 5.11.5.2 (see Figures 9 and 12, respectively) and this section will seek to further illustrate the variety of reaction types that can be harnessed to the IMDA cycloaddition reaction.

5.11.8.1 Tandem Sequences for Polycyclic Carbon Frameworks

Section 5.11.7.3.3 was a showpiece for the area of organocatalysis, and this section will start by continuing on that theme, with an excellent example of the use of organocatalysis for an efficient asymmetric domino sequence,[89] in tandem with a Lewis acid-catalyzed IMDA as the final step.[90] As shown by the retrosynthetic analysis in Figure 21, this elegant Michael/Michael/aldol/IMDA strategy should allow for the one-pot construction of three rings, five carbon–carbon bonds and eight stereocenters. The proline-derived organocatalyst **161** (20 mol%) mediated the first three steps of the cascade involving **166**, **167**, and **168** to yield IMDA precursor **169**, which in the same pot was treated with the Lewis acid Me_2AlCl to promote the cycloaddition. The tricyclic cycloadduct **170** was obtained in 49% yield, 10:1 *dr*, and >99% *ee*, and the sterically most favored *endo* transition state is indicated in Figure 21. These functionalized carbocycles are excellent starting points for the total synthesis of natural products.[90]

Tandem sequences based on a combination of enzyme-catalyzed kinetic resolution (KR) of a racemate, metal-catalyzed racemization of the slow-reaction enantiomer, and IMDA have also been applied[91] to the asymmetric synthesis of tricyclic carbon frameworks (Scheme 14). The combination of the enzyme and the ruthenium catalyst provides an efficient dynamic KR (DKR) of the racemic allylic alcohol **171** in a transesterification reaction yielding the IMDA precursor **172** that reacts via an *exo* transition state to **173**. Compounds such as **173** are useful for the synthesis of important natural products such as forskolin.[91]

Ruthenium catalysts are also well known in alkene/alkyne metathesis chemistry,[92] and this too can be combined with an IMDA cycloaddition, as shown in Figure 22. Baylis–Hillman product **174** was subjected to a one-pot Ru-catalyzed enyne cross-metathesis and Dess–Martin oxidation to give **175**, which spontaneously underwent the IMDA cycloaddition to give **176** in good overall yield. Both *E*- and *Z*-**175** converged to the *cis*-fused cycloadduct via *exo* and *endo* transition states, respectively.[93] A tandem

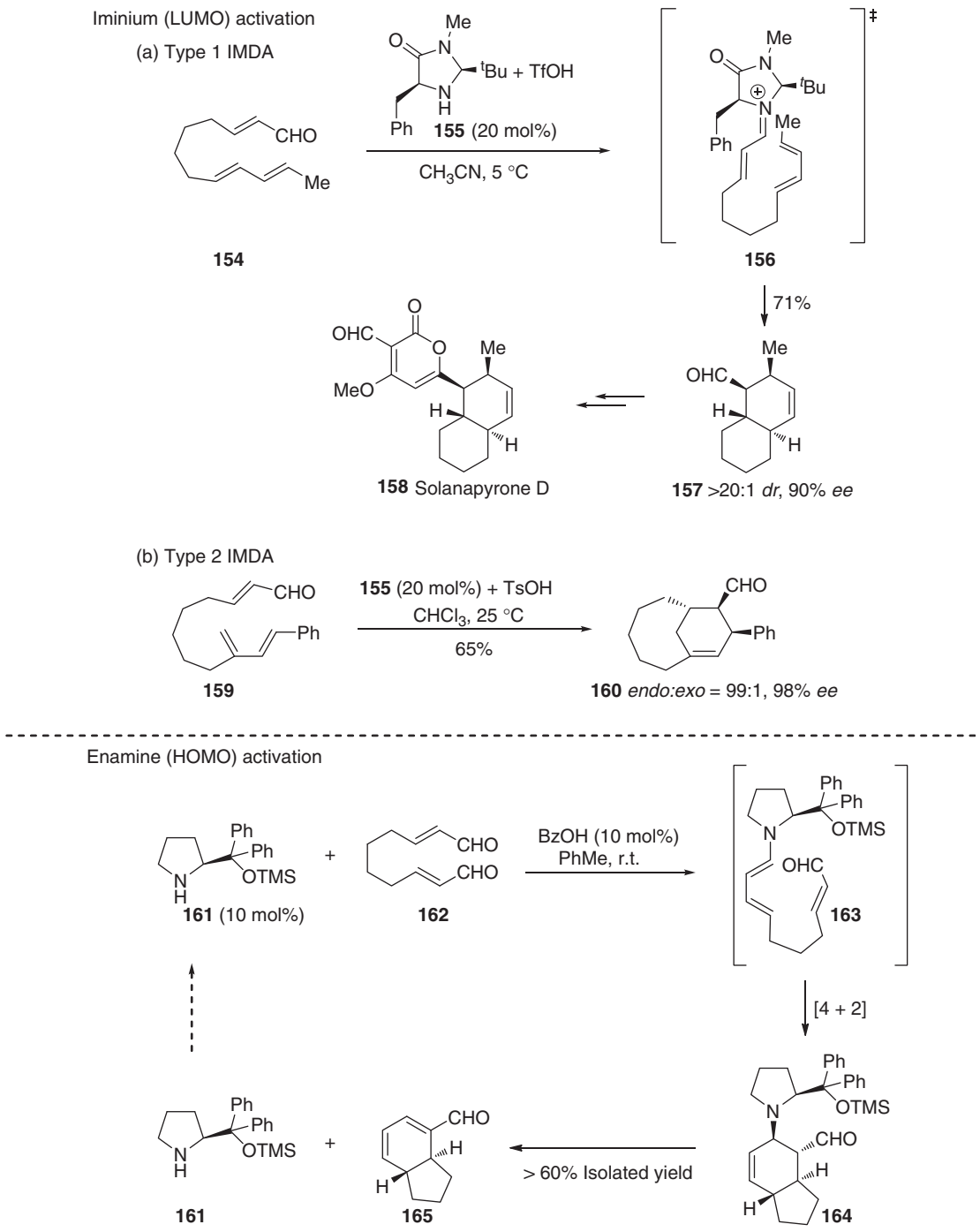


Figure 20 Organocatalyzed IMDA cycloadditions.

sequence[94] to linear triquinanes characteristic of sesquiterpene natural products is also described in Figure 22. In this sequence, the IMDA cycloaddition of **177** was the first step, and was carried out under conditions of microwave heating[31a] (see also Section 5.11.3.4). The Grubbs II ruthenium catalyst was then added to the solution containing **178**, to mediate a fascinating sequence of ring-closing–ring-opening–cross-metathesis (RCM–ROM–CM) which yielded the linear triquinane **179**.

A projected asymmetric total synthesis of the natural product salvinorin A employed an IMDA cycloaddition in harness with a substrate-controlled Tsuji–Trost allylation (Scheme 15) to set up a *trans* decalin system **182** with control over three contiguous stereocenters, two of which are quaternary.[95] Although this is not strictly a tandem, i.e., one-pot, sequence (the IMDA was unfortunately nonstereoselective, and the diastereomeric cycloadducts had to be separated by recrystallization before the Tsuji–Trost reaction), it is nevertheless a very good example of the strategic use of the IMDA process: the cycloaddition of

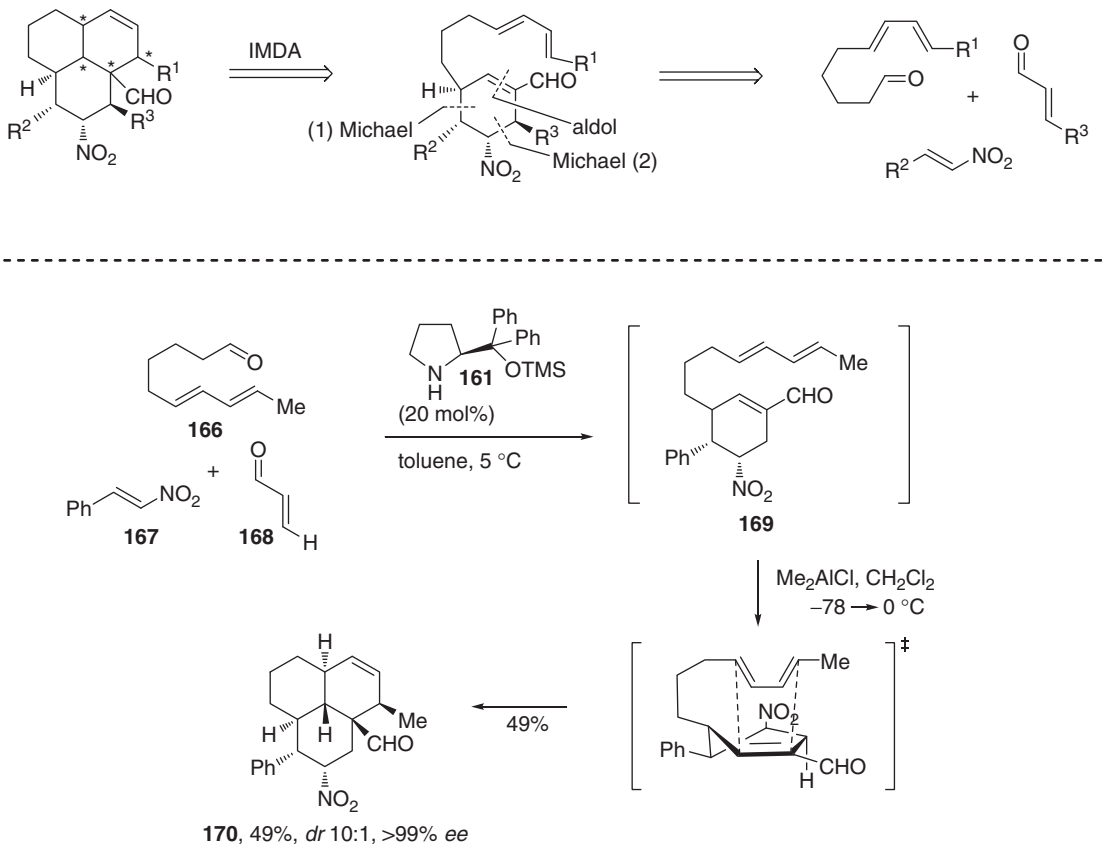
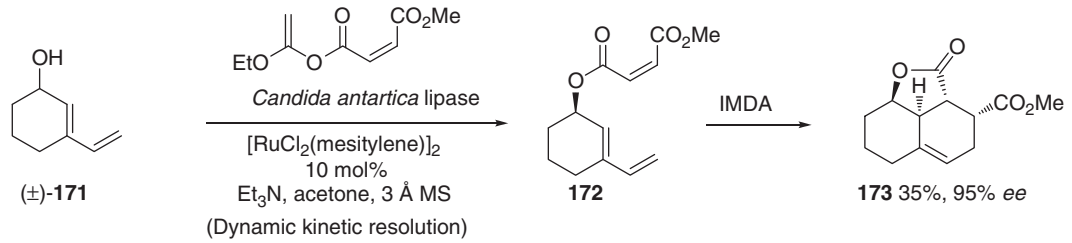


Figure 21 Organocatalysis in tandem with a Lewis acid-catalyzed IMDA cycloaddition.



Scheme 14

enantiopure **180** (derived from tartaric acid) regioselectively provides an enolate equivalent in **181**, with the allyl group required for the Tsuji–Trost reaction cleverly incorporated. The stereochemical course of the allylation is controlled by the angular methyl group in **181**, leading to **182** via net equatorial addition to the enolate species.

A tandem sequence consisting of two pericyclic reactions (Ireland–Claisen and IMDA) was used as a key step in a very short total synthesis[96] of the structurally intriguing basiliolide/transtaganolide natural products (Scheme 16). Ester **183** was sigmatropically rearranged to **184** via the Ireland–Claisen technique, followed directly by a thermal IMDA cycloaddition with the pyrone diene component. The ratio of diastereomers in the (racemic) product was 2:1 with respect to C8 in **185**, both being formed via *endo* transition states. In this case, there is obviously no low-energy pathway for loss of CO_2 from the cycloadduct (cf. Section 5.11.5.2).

5.11.8.2 Tandem Sequences for *N*-Heterocyclic Frameworks

This section will concentrate on some recent applications of IMDA cycloaddition to tandem sequences for the total synthesis of *N*-heterocyclic systems, particularly biologically significant alkaloids. The discussion of a particularly elegant and efficient cascade sequence for the total synthesis of certain pentacyclic alkaloids is deferred until Section 5.11.12.

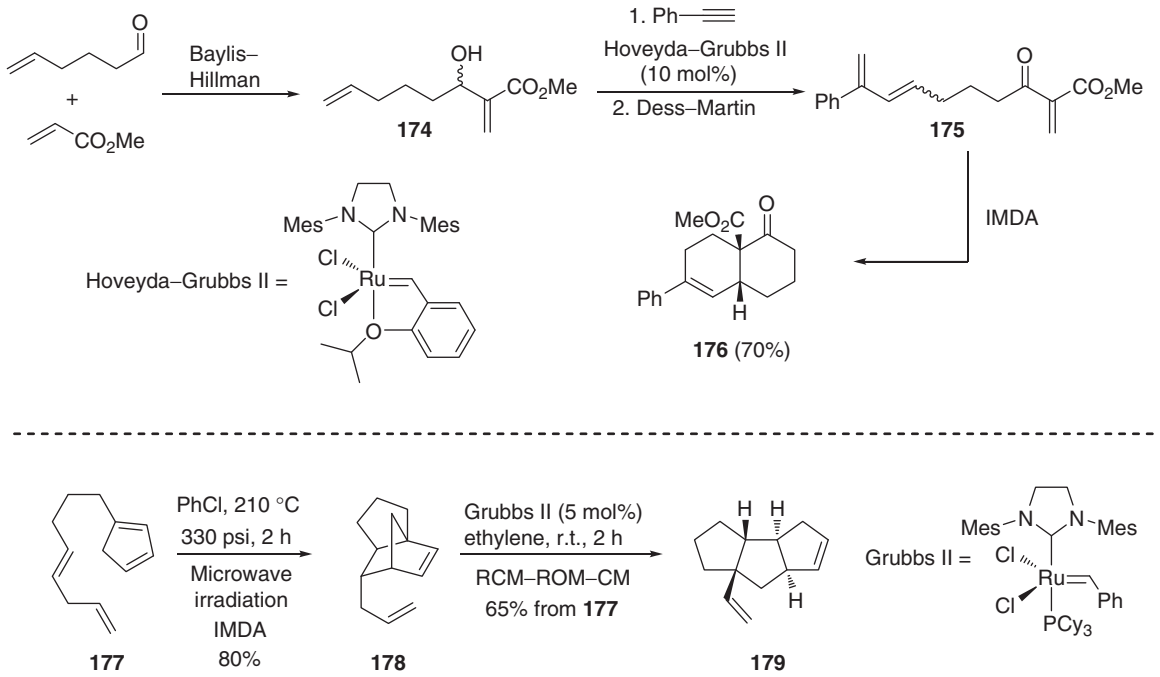
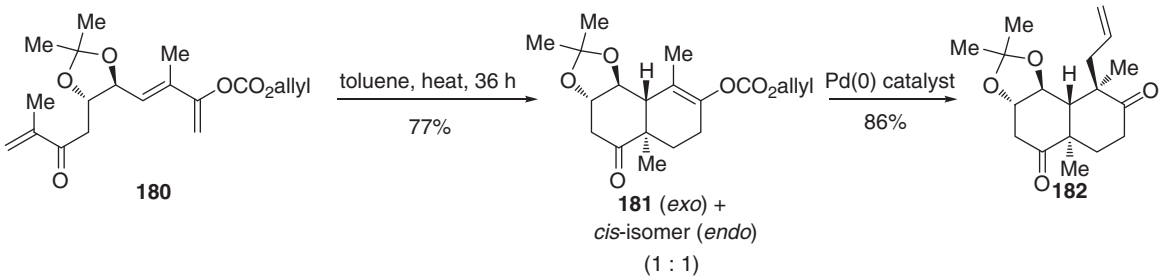
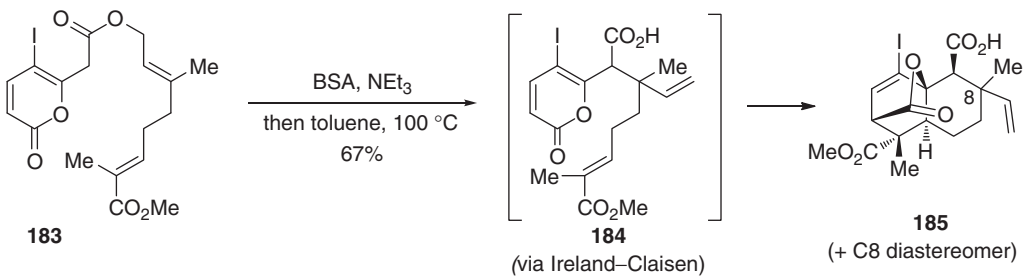


Figure 22 Tandem Ru-catalyzed metathesis/IMDA cycloaddition sequence.

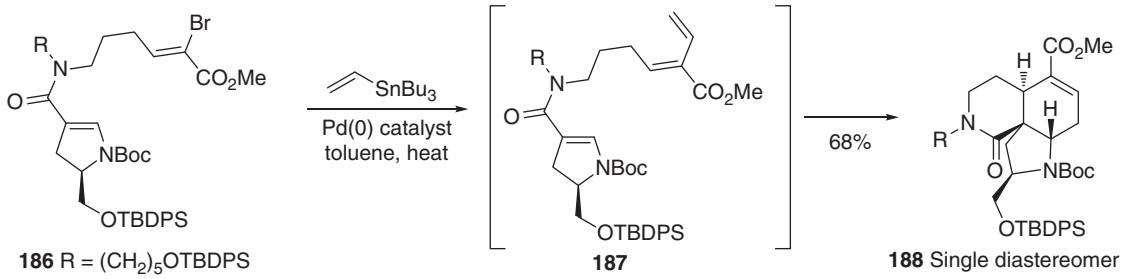


Scheme 15



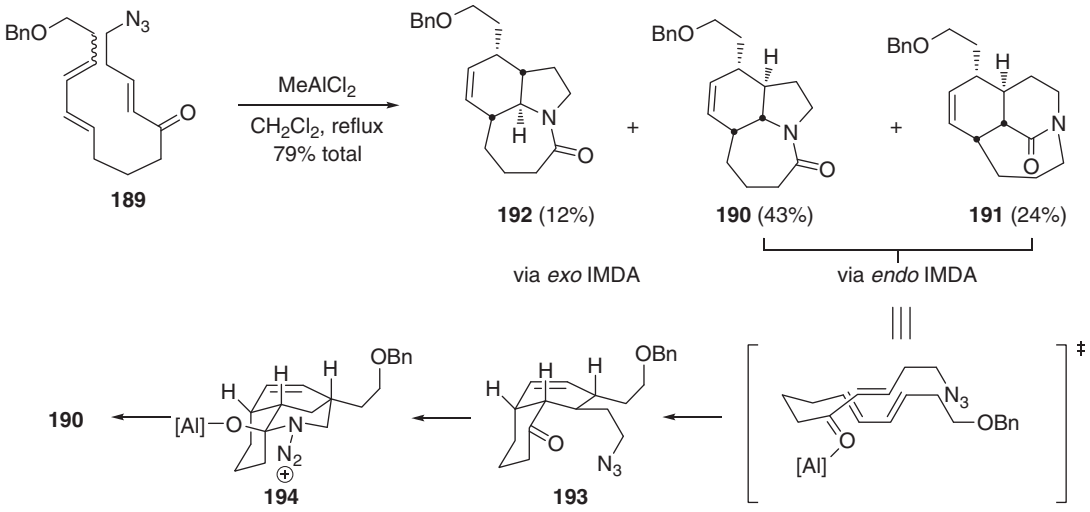
Scheme 16

An enantioselective total synthesis[97] of the marine alkaloid manzamine A took advantage of a tandem Stille cross-coupling–IMDA cycloaddition for preparation of advanced tricyclic intermediate **188**. The Stille reaction was used to fashion the diene component of **187** via stereospecific cross coupling of vinyl bromide **186**. Continued heating of the solution containing **187** smoothly furnished **188** as a single diastereomer in 68% yield. The IMDA cycloaddition is substrate-controlled, the diene approaching the less hindered face of the dienophile (Scheme 17). The biosynthetic origin of the manzamine family of natural products is further discussed in Section 5.11.12.



Scheme 17

Scheme 18 shows a tandem sequence with azidotriene **189** in which both steps were Lewis acid-catalyzed: a type 1 IMDA was immediately followed by an intramolecular Schmidt reaction.[98] Of the three diastereomers formed, the major one **190** had the correct stereochemistry for use in a total synthesis of the racemic form of the alkaloid stenine. Diastereomers **190** and **191** both emanated from the *endo* IMDA cycloadduct **193** (boat-like arrangement of the forming cyclohexanone ring),[99] which then followed two regioisomeric pathways in the Schmidt reaction; the Schmidt intermediate leading to the major product is **194**, with an equatorially disposed N_2^+ group, (C–to–N) migration occurring in the stereoelectronically favorable antiperiplanar fashion. Compound **192** was produced via the *exo* IMDA–Schmidt tandem route.



Scheme 18

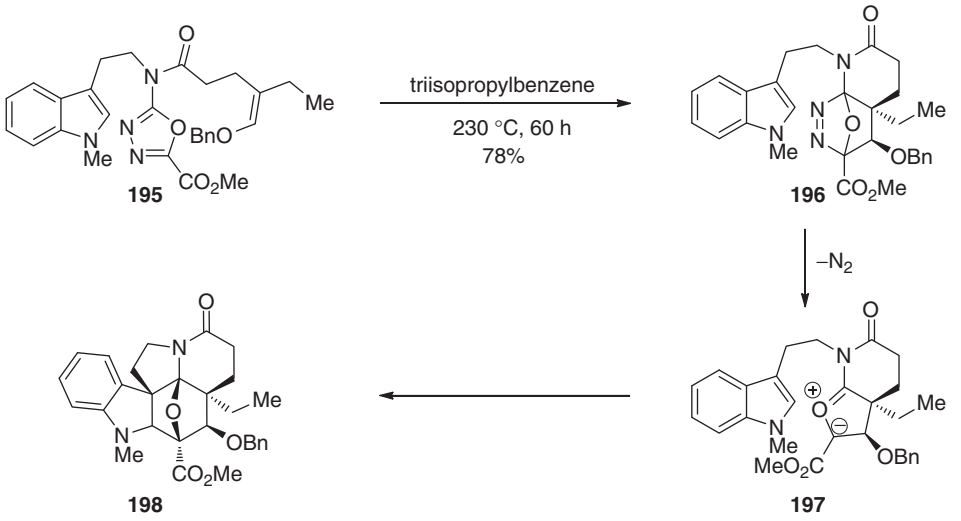
An admirably concise route to the pentacyclic alkaloid vindorosine employed a tandem sequence of IMDA cycloaddition and 1,3-dipolar cycloaddition to set up the pentacyclic system with formation of four new C–C bonds, three rings, and six stereocenters in a single operation (Scheme 19).[100] Prolonged heating of **195** promoted the IMDA reaction with inverse electron demand (Section 5.11.6.3) followed by loss of N_2 from **196** to give 1,3-dipole **197** that completed the intramolecular sequence by reaction with the indole. Product **198** was obtained as a single diastereomer in yields up to 78%, provided the reaction was carried out in dilute solution to disfavor competing bimolecular reactions.

N-tethered allenamides such as **199** were subjected to a stereoselective isomerization to give 1-amidodienes **200** that underwent *endo* selective IMDA cyclization to **201** on heating.[101] A range of bi-, tri- and tetracyclic heterocycles, including quinoline derivatives, could be accessed by this elegant method in good to moderate yields and with diastereoselectivities up to 10:1 (Scheme 20).

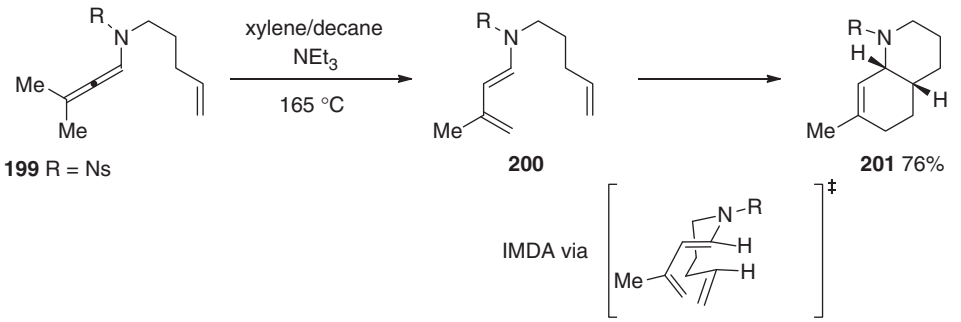
5.11.9 Photochemically Generated Reactive Intermediates for IMDA Cycloaddition

5.11.9.1 Photochemical Generation of Reactive Dienophiles

In the 1960s it was reported[102] that ultraviolet irradiation (>300 nm) of *Z*-cycloheptenone and *Z*-cyclooctenone caused isomerization to the corresponding highly strained *E*-isomers that were excellent dienophiles for the intermolecular DA reaction.



Scheme 19



Scheme 20

Surprisingly, more than 30 years were to pass before this technique was applied[103] to the IMDA cycloaddition, some examples being shown in Figure 23. The photoisomerization of 4-substituted cycloheptenones **202** complicates the stereochemical analysis, in that the 4-substituted *E*-enones are planar chiral in addition to having a stereogenic center. Two diastereomers are thus possible, each of which can react via an *endo* or *exo* transition state, for a total of four possible diastereomeric cycloadducts. In the event, irradiation of **203** using a uranium glass filter gave an 88% yield of three cycloadducts **204–206**, the major product being derived from the transition state with three chair-like conformations. The stereospecificity of the DA reaction ensures that the *trans* ring junction is formed exclusively in all cases. The diastereoselectivity of the reaction of **203** could be enhanced significantly (10:1) by running the reaction at low temperature (ca. -75 °C). This also attests to the high reactivity of the *E*-enone: refluxing in xylene is required[103] to promote the thermal IMDA reaction of *Z*-**203**. The effect of the length of the tether was also examined, and an interesting difference was found between the 'regular' IMDA and the IMDAF (Section 5.11.6.1) substrates with a two-carbon tether (compare the reactions of **207** and **209**). For **207**, the IMDA reaction is completely out-competed by the photochemically allowed [2 + 2] cycloaddition.

5.11.9.2 Photochemical Generation of Reactive Dienes

Hydroxy-*o*-quinodimethanes such as **213** are excellent candidates for both bimolecular DA reactions and IMDA cycloadditions, and can be generated[104a] by photochemical enolization of benzaldehyde derivatives **212** (Figure 24). Cycloadducts **214** are densely functionalized polycycles adorned with stereogenic centers (including quaternary) and are useful building blocks for total synthesis. An application to the total synthesis of the hamigeran family of natural products[104b] made use of cycloadduct **216** that was formed very rapidly at ambient temperature via the transient hydroxy-*o*-quinodimethane. The single stereocenter in **215** efficiently controls the way the IMDA substrate folds into the transition state, setting up the crucial *trans* relationship between the angular Me and the ^{i}Pr groups in **216**. Use of a related, enantiomerically pure substrate gave the cycloadduct in >99% enantiomeric purity on a multigram scale.[104b]

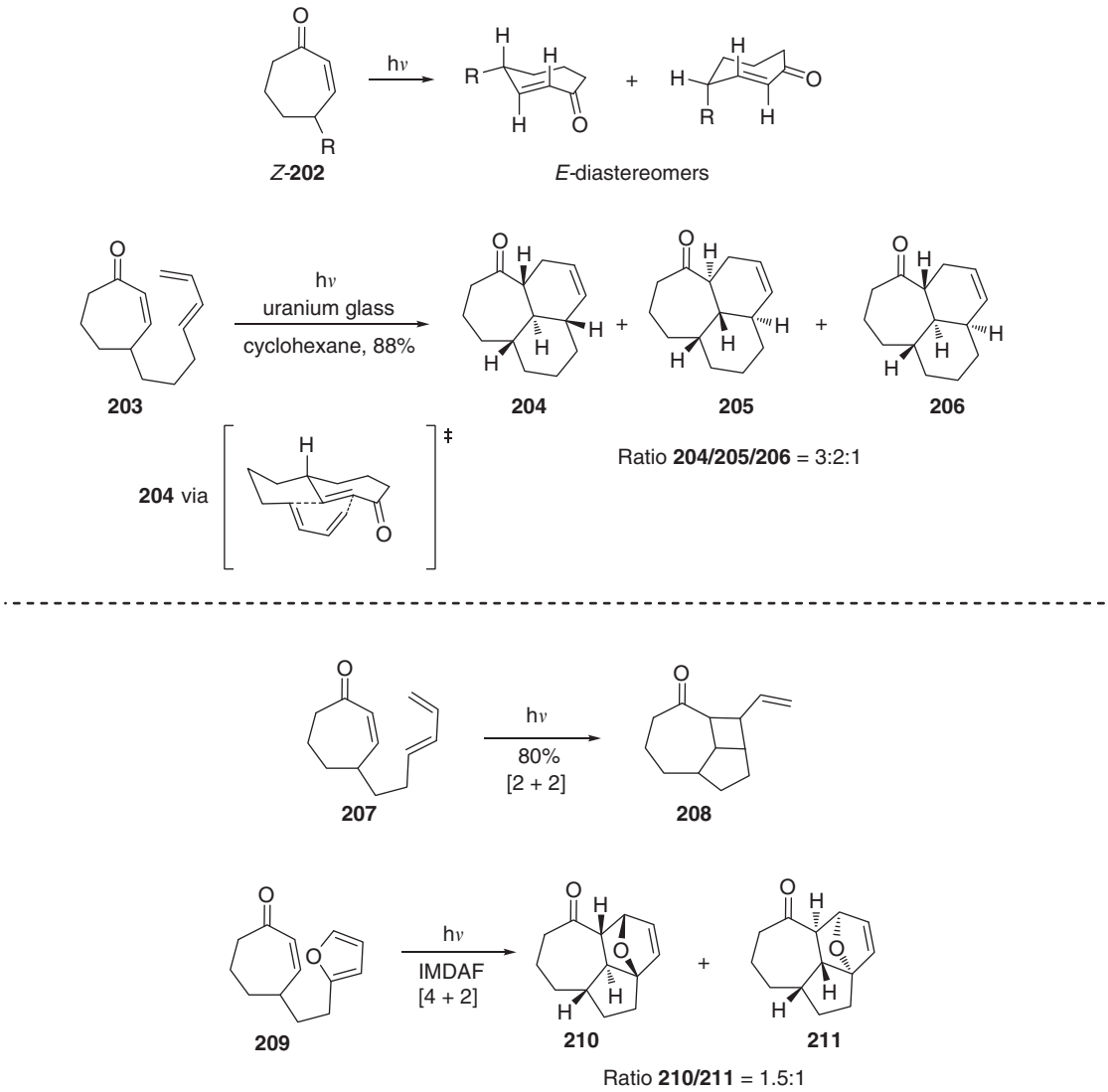


Figure 23 Photochemically induced IMDA cycloadditions.

5.11.10 *Exo* Selectivity Regardless: IMDA Reactions of Cyclopropenone Ketals

Cyclopropenone ketals are chemically surprisingly robust moieties[105] that are nevertheless characterized by high ring strain energy (ca. 100 kJ mol^{-1}). A [4 + 2] cycloaddition with the cyclopropenone acetal as the dienophile would considerably relieve the ring strain, making these species attractive substrates for both DA and IMDA reactions. Reactivity and stereoselectivity in the IMDA mode were studied[105] using the substrates **217** shown in Scheme 21. The substituents R in **217** were chosen to ring the changes in the electronic properties of the diene (from electron-deficient, through aryl-conjugated and unactivated, to electron-rich). In all cases, the *exo* products were the only detectable ones, the fastest reacting dienes being **217a** and **217d**, for which the cycloaddition was complete at 25 °C. The ease of reaction of the unactivated diene **217c** (12 h at 45 °C) is remarkable, and under these mild conditions the IMDA reaction is considerably more facile than potential competitors such as [1 + 2], [3 + 2], and [3 + 4] cycloadditions[105] via singlet vinylcarbenes.

5.11.11 Recent Applications of IMDA Cycloadditions to Total Synthesis

Given the extraordinary power and versatility of the IMDA cycloaddition, it is hardly surprising that this methodology has been utilized time and again in impressive multistep total syntheses, some of which have been referred to in the previous sections. An excellent far-reaching review of applications of IMDA reactions to the stereoselective total synthesis of complex and biologically active natural products appeared[3a] in 2005, followed by a shorter version[3b] in 2009, so in this section only a selection of examples

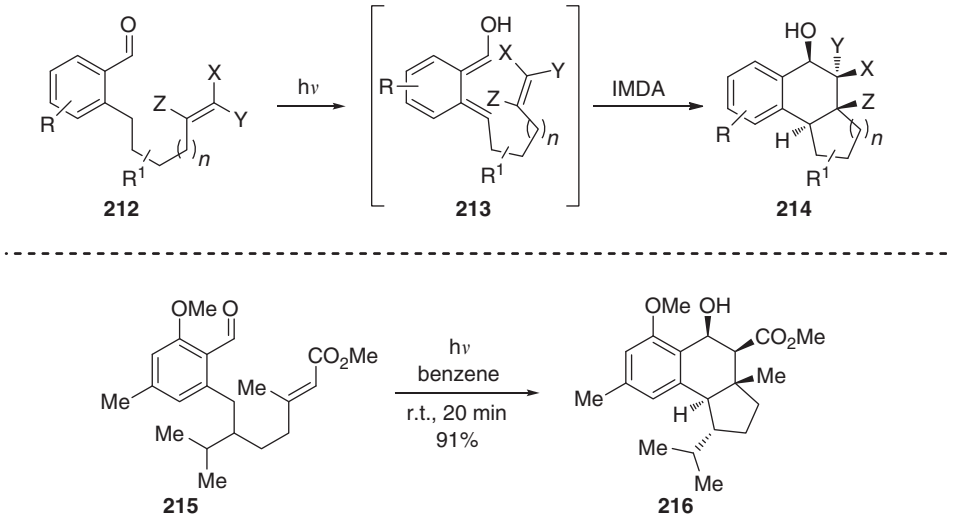
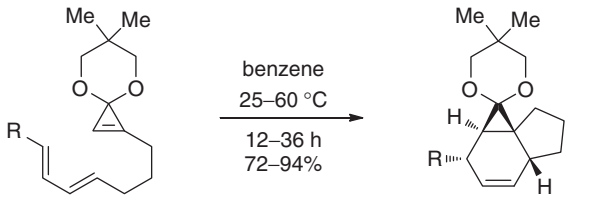


Figure 24 Photochemically induced enolization leading to IMDA cycloaddition.



217a (R = CN)
217b (R = Ph)
217c (R = H)
217d (R = OBn)

218a 86% (25 °C, 36 h)
218b 94% (60 °C, 20 h)
218c 72% (45 °C, 12 h)
218d 85% (25 °C, 16 h)

Scheme 21

will be presented. A variety of natural product types (following the convention of reference[3a]) is considered, and only completed total syntheses are discussed. Each synthesis is laid forth in retrosynthetic form, to highlight the strategic importance of the IMDA transformation, without much detailed discussion of the steps before, or following, the cycloaddition event.

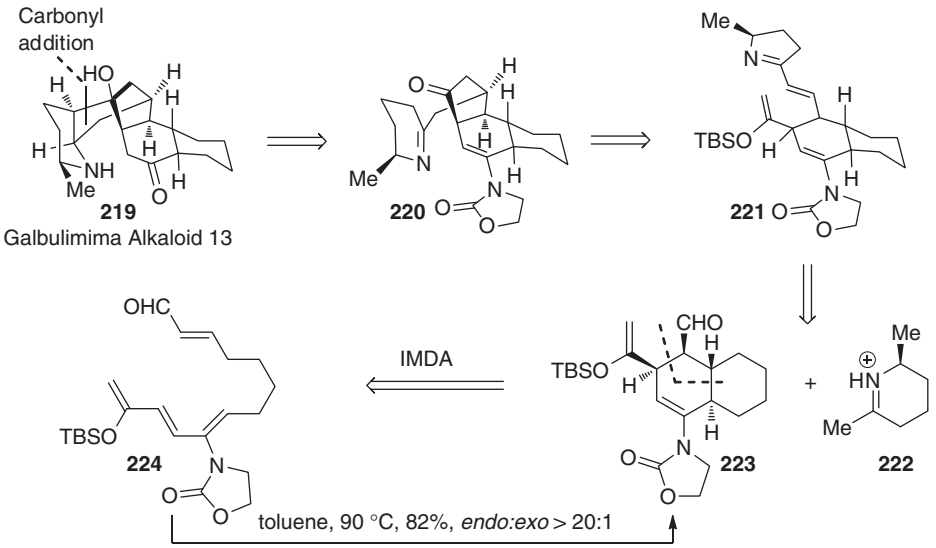
5.11.11.1 Alkaloids

5.11.11.1.1 Total synthesis of (–)-galbulimima alkaloid 13

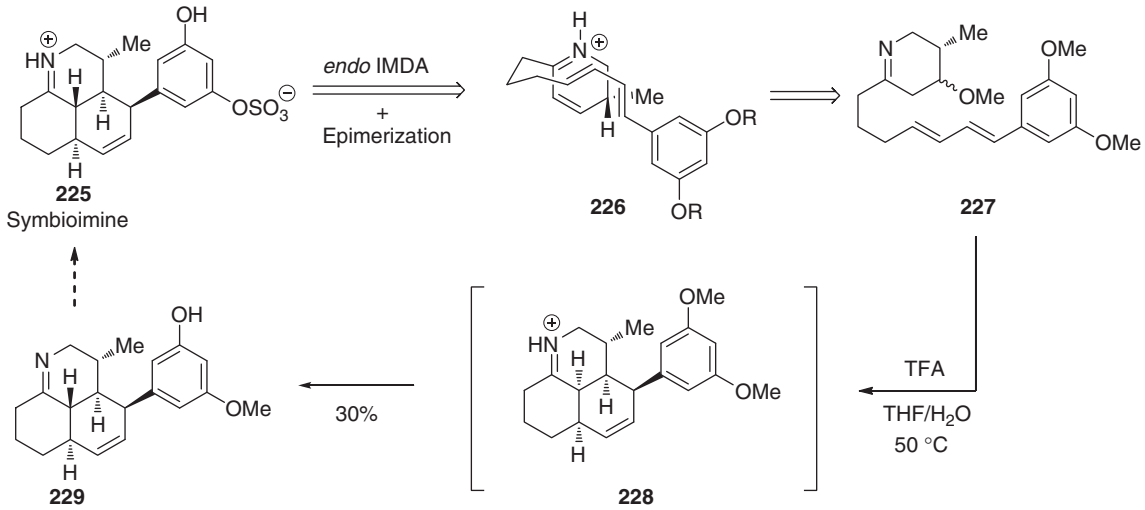
The galbulimima alkaloids such as galbulimima alkaloid 13 (**219**, Scheme 22) present a major challenge to synthetic planning and execution.[106] Careful consideration of possible biosynthetic pathways led to the strategic bond disconnection shown for **219**, which simplified the target to tetracyclic intermediate **220**. Further retrosynthetic simplification revealed **221**, which in turn was traced back to two relatively simple building blocks **222** and **223**, the latter containing the IMDA retron (the oxazolidinone moiety serves as a masked ketone). It was decided to prepare **223** in racemic form and couple it with the enantiomerically pure reagent derived from regioselective lithiation of **222**, followed by separation of the diastereomeric products. The IMDA precursor **224**, prepared via a short convergent route, was heated in toluene to give key intermediate **223** in 82% yield and with excellent diastereoselectivity (>20:1, *endo*:*exo*). The successful completion of the total synthesis allowed a revision of the absolute stereochemistry of the natural product, highlighting the important role which synthesis still has to play in structural elucidation and assignment.[107]

5.11.11.1.2 Total synthesis of (+)-symbioimine

The marine natural product symbioimine (**225**, Scheme 23) has been alluded to in Sections 5.11.3.4 and 5.11.4.1, and was of interest for both its biological properties (possible treatment of osteoporosis) and its mode of biosynthesis (originally proposed[30] to occur via an unusual *exo*-selective IMDA reaction). As shown in Scheme 23, an alternative route[108] is available via the more common *endo*-selective IMDA cycloaddition of **226** followed by epimerization to the thermodynamically more stable product containing all-*trans* ring junctions. The IMDA precursor **226** is a chiral cyclic iminium ion, expected to induce high levels of



Scheme 22



Scheme 23

diastereoselectivity in the cycloaddition reaction, and was generated by acid treatment of readily available **227**. Under the conditions for the cycloaddition, the initially formed **228** epimerized to **229** that was isolated as a single diastereomer, albeit in modest yield (ca. 30%). The poor yield notwithstanding, this brief route provided evidence to support the modified biosynthetic pathway.

5.11.11.1.3 Total synthesis of (+)-yohimbine

The indole alkaloid yohimbine **230** is a classical target for total synthesis, and an interesting recent approach[109] is shown in Figure 25. The synthesis was projected to rely on two key features: enantioselective synthesis of **233** and *endo*-selective IMDA cycloaddition of **232** or **231**. The first problem was readily solved via a highly enantioselective (94% ee) catalytic asymmetric acyl-Pictet–Spengler reaction of **234**. Based on literature precedent, the IMDA *endo* selectivity of **231** and/or **232** was a greater cause for concern, and DFT calculations on model substrates were used to guide the synthetic efforts. The calculations actually predicted poor *endo* diastereoselectivity for **231**, but this option was nevertheless pursued. It was reasoned that a chiral catalyst for the IMDA reaction could be brought into play should the substrate-controlled route fail. The substrate for the crucial IMDA reaction was **235** that under mild conditions of (achiral) Lewis acid catalysis delivered the desired cycloadduct **236** in high yield and as a single diastereomer. The very high *endo* diastereoselectivity was not predicted by the original calculations (which involved an unprotected indole nitrogen), and was found to be dependent on the indole protecting group. Further modeling of the transition states

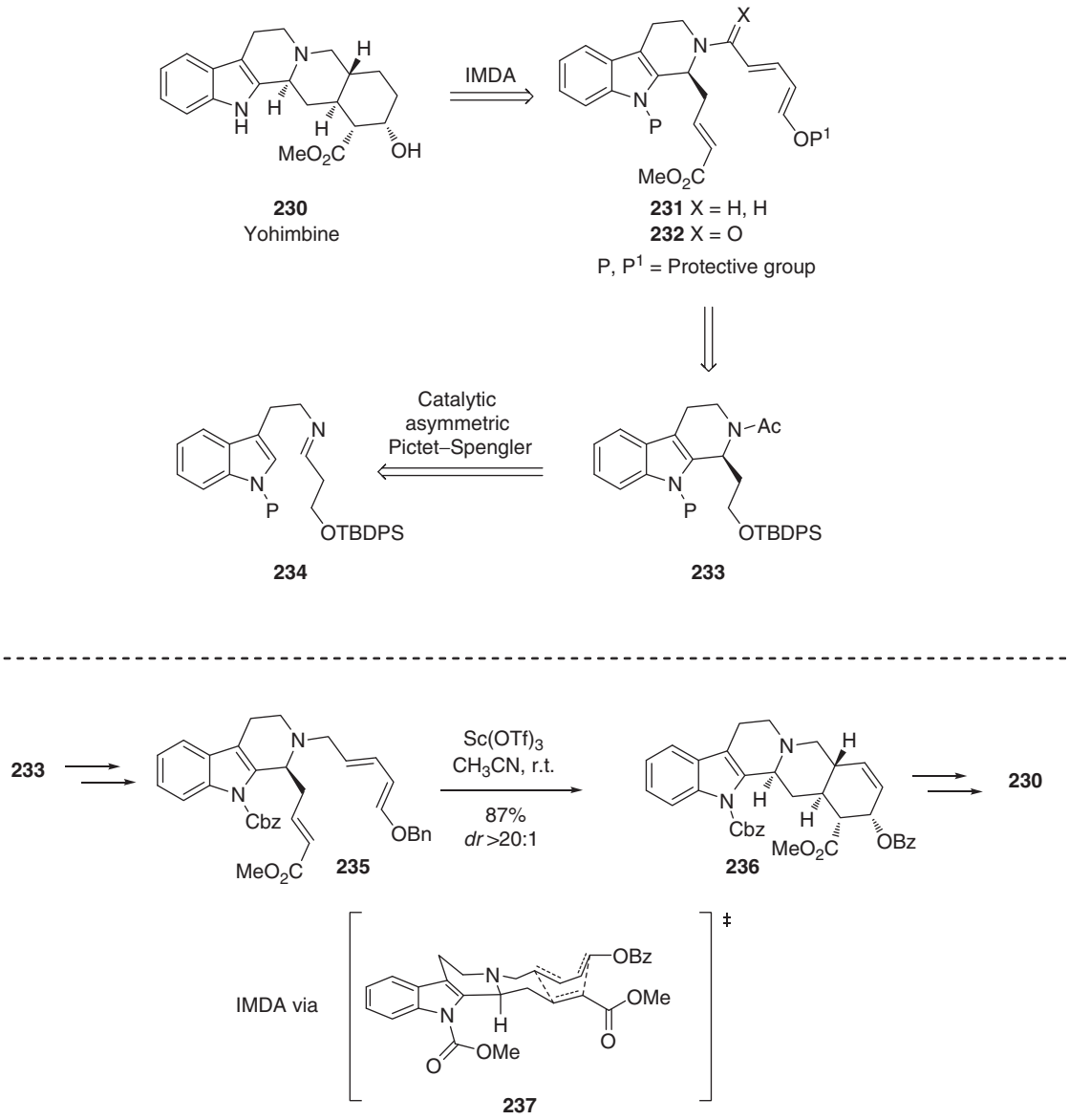


Figure 25 IMDA cycloaddition as a key step in the total synthesis of Yohimbine.

revealed the *endo* array **237** to be the one of lowest energy, dictated in part by the strong preference of the carbamate group to be coplanar with the indole ring.

5.11.11.1.4 Total synthesis of the zoanthamine alkaloids

The zoanthamine alkaloids[110] (e.g. norzoanthamine, **238**, Figure 26) are truly daunting synthetic targets, but the IMDA cycloaddition has on two occasions risen admirably to this task. In the first approach,[111] the bis-*N*,*O*-acetal was disconnected first followed by retrosynthetic manipulation of **239** to reveal the IMDA retron in **240**. IMDA substrate **241** was projected to be available via photosensitized oxidation of the trisubstituted furan moiety in **242**. This demanding IMDA, if successful, would set up two quaternary all-carbon stereocenters in a single operation. Not surprisingly, high temperature was required for the cycloaddition, which proceeded in near-quantitative total yield with a 72:28 ratio in favor of the desired *exo* adduct. Key intermediate **244** was isolated as a crystalline solid in 51% overall yield. The pretransition state conformation for the *exo*-selective cyloaddition is shown in Figure 26, and is the arrangement that minimizes steric interactions between the two methyl groups on the perimeter of the pericyclic array. This crucial transformation that enabled completion of a benchmark total synthesis required 43 steps, with an overall yield of 2.2% (an average of 92% per step).

A complementary route[112] to norzoanthamine, relying on a similar endgame involving the heterocyclic moieties, was devised on the basis of an alternative IMDA cycloaddition (Figure 27). Tetracycle **245** was envisioned to arise from **246** via an IMDA reaction and a Saegusa oxidation. Retrosynthetically, **246** could in turn be traced back to the enantiomerically pure Hajos–Parrish

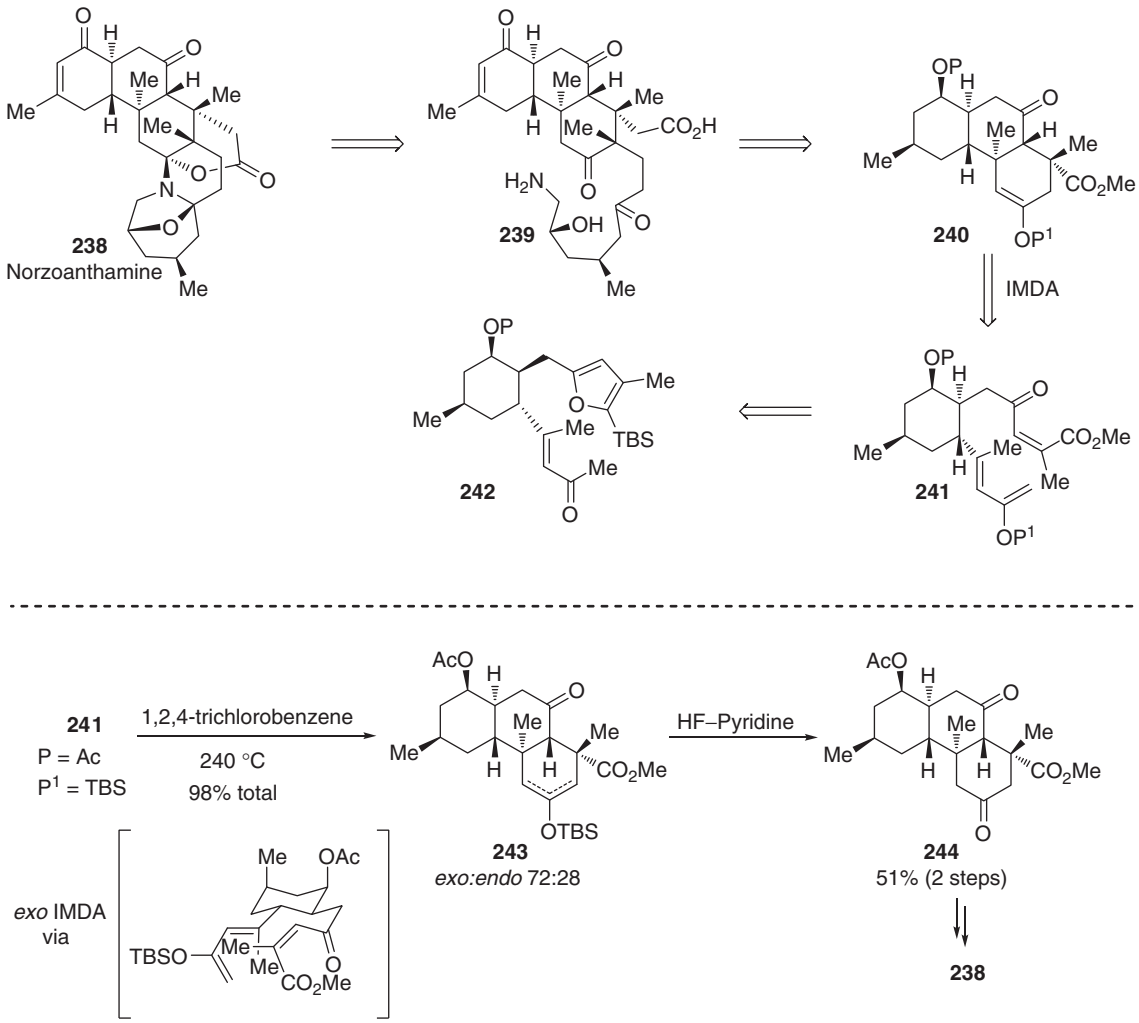


Figure 26 IMDA cycloaddition as a key step in the total synthesis of Norzoanthamine.

ketone **247**. In practice, it proved impossible to obtain **246** (R=Me) in useful yields, so the key IMDA was carried out on the simpler diene with R=H. After Saegusa oxidation of cycloadduct **248**, tetracycle **249** was obtained as a single diastereomer. The 'missing' methyl group could then be introduced via a Saegusa oxidation–Michael addition sequence. The conformation of **246** which leads to the IMDA transition state is proposed to have a chair-like array with the *O-tert*-butyldimethylsilyl (OTBS) pseudoequatorial, a key feature in determining the excellent diastereoselectivity observed.

5.11.11.1.5 Total synthesis of strychnine

For the organic chemist, few natural products have captured the imagination like strychnine[113] (**250**, Figure 28) and the IMDA cycloaddition has played a prominent role in the total synthesis of this intriguing target molecule.[114a,114b] To date, the shortest synthesis[114c] of strychnine (in racemic form) proceeds via a longest linear sequence of only six steps. The key transformation was a formal IMDA cycloaddition involving a Zincke aldehyde and an indole as the diene and dienophile components, respectively (see structure **254**). Intermediate **254** was itself to be assembled easily from three very simple starting materials. In practice, **254** was replaced by **255** which underwent base-promoted cycloaddition and conjugation to yield **256** in 64% yield. Conversion to **253** (M=$SiMe_3$ and R=H) was also efficient, but the otherwise impressive progression toward the target almost foundered completely on the transformation of **253** to the Wieland–Gumlich aldehyde **252** (an operation requiring a Brook rearrangement and a conjugate addition that proceeded in a meager 5–10% yield, despite very extensive experimentation).

5.11.11.2 Polyketides

5.11.11.2.1 Total synthesis of dynemicin A

Dynemicin A **257** (Scheme 24) is a member of one of the most unusual class of natural products, the enediyne antibiotics. After insightful retrosynthetic analysis, a total synthesis[115] of racemic dynemicin A was devised that relied on an early-stage Lewis

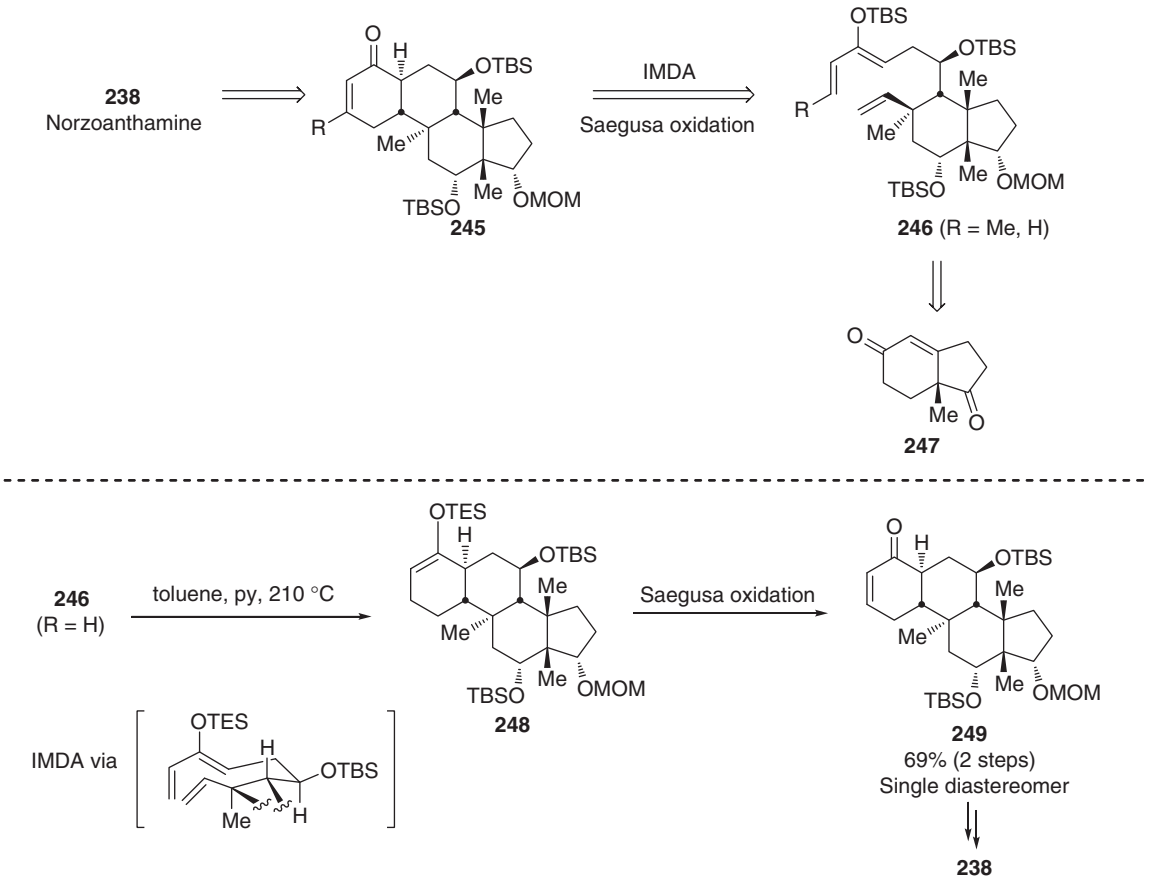


Figure 27 An alternative IMDA route to Norzoanthamine.

acid-catalyzed IMDA to cleverly set up two stereocenters of key intermediate **259** via **260** and **261** (compare the asterisked carbons in the latter two structures). The IMDA cycloaddition of **262** was completely *endo*-selective provided a Lewis acid was used (the diastereoselectivity of the purely thermal process was only 3: 1). As can be imagined from the extraordinary (and sensitive) structure of the target molecule, the rest of the dynemicin A adventure involved the solution of many challenging synthetic problems at both the strategic and tactical levels, a discussion of which is beyond the scope of this writing. Suffice it to say that one of the late-stage key steps involved a (formal) intermolecular DA cycloaddition with **259** as dienophile and the anion of **258** as diene.

5.11.11.2.2 Total synthesis of (–)-chlorothricolide

Chlorothricolide (**263**, Figure 29), the aglycon of the antibiotic chlorothricin, is a target molecule that virtually impels the application[116] of cycloaddition methodology, given the presence of two DA retrons. As shown in Figure 29, the synthesis was planned to proceed via a tandem (Section 5.11.8) inter- and intramolecular DA sequence, defining **264** and **265** as the key building blocks. Consideration of all the feasible DA/IMDA stereo- and regiochemical combinations reveals 96 possible products from the proposed tandem sequence. Fortunately, the desired mode of reaction is expected to be one of the lowest energy: for example, for the IMDA process the C2–C3 bond is the most reactive dienophile (lowest LUMO) and will react fastest with the C8–C11 diene. For the bimolecular process, previous studies[116] had indicated that the C18–C21 portion of the conjugated triene subunit would react fastest with **265**. The synthesis was thus approached with confidence, and the results of the tandem cycloaddition are summarized in Figure 29. Heating **264** and **265** in toluene yielded initially a mixture of **266** (ca. 40%) and **267** (ca. 30%) as the major components, the latter being resubjected to the action of **265** to provide the desired **266** in 55–59% yield overall (the C20–C21 double bond isomerizes under the conditions of the cycloaddition, and only the *Z* isomer undergoes the DA reaction). The key elements of stereocontrol are the high diastereofacial and *exo* selectivity of **265** for the bimolecular DA, and the steric directing effect of the bulky C9-trimethylsilyl group for the IMDA (see Figure 29, bottom). The preferred IMDA transition state is the one in which destabilizing nonbonded interactions are minimized, and the trimethylsilyl group is a surrogate for the C9–H bond of the target molecule.

5.11.11.2.3 Total synthesis of (+)-cochleamycin A

A biosynthetic proposal for (+)-cochleamycin (**268**, Scheme 25) involves an IMDA reaction of a polyketide-derived intermediate. A total synthesis[117] of **268** via key intermediate **269** employed a Lewis acid-catalyzed IMDA reaction to set up the tetrasubstituted

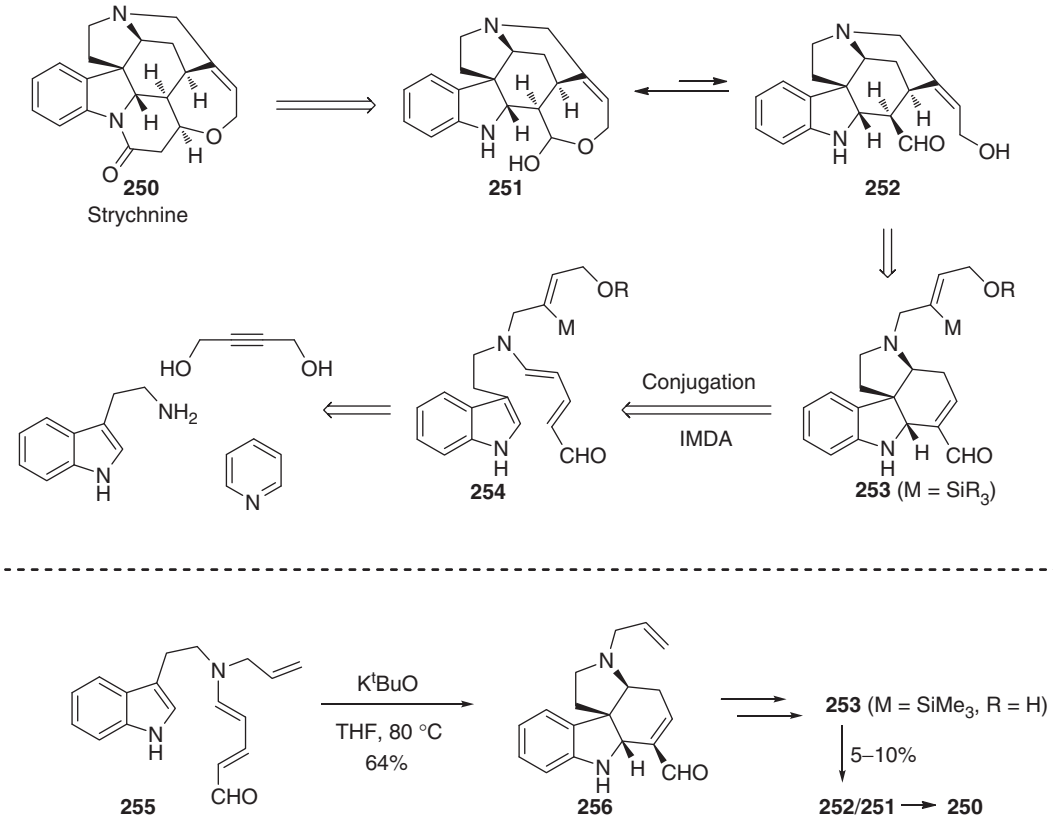
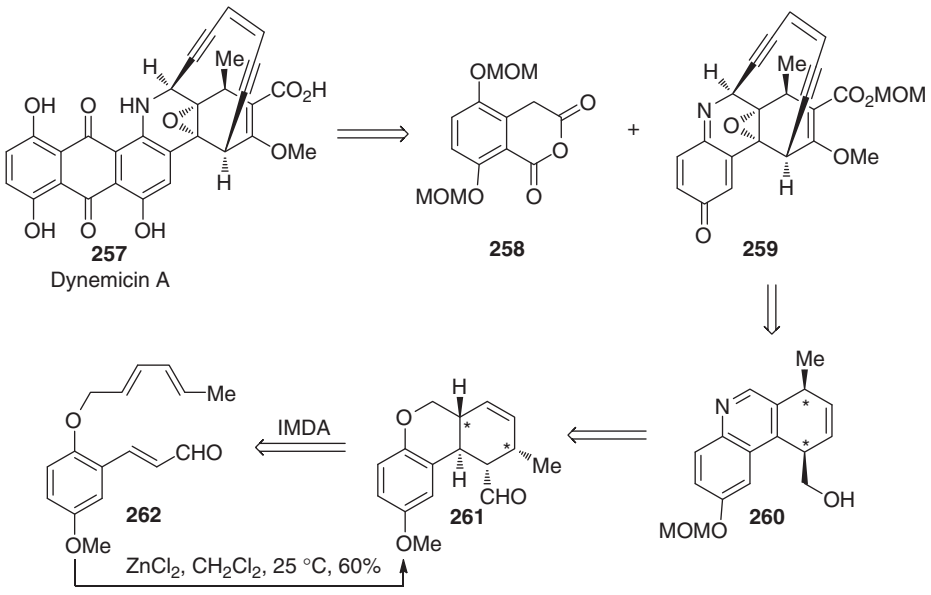


Figure 28 IMDA cycloaddition as a key step in the total synthesis of Strychnine.



Scheme 24

tetrahydroindan unit of **270** from the (*E,Z,E*)-triene **271**. The required *Z* configuration at the C6–C7 bond (which controls the *cis* fusion geometry in the cycloadduct) was secured by controlled reduction of the corresponding alkyne, formed by a Sonogashira cross-coupling reaction (C7–C8). A possible *endo* transition state leading to **270** is depicted as a Newman projection about the C4–C5 bond of **271** (Scheme 25). These studies provide yet another example of the use of total synthesis for the determination of absolute configuration.

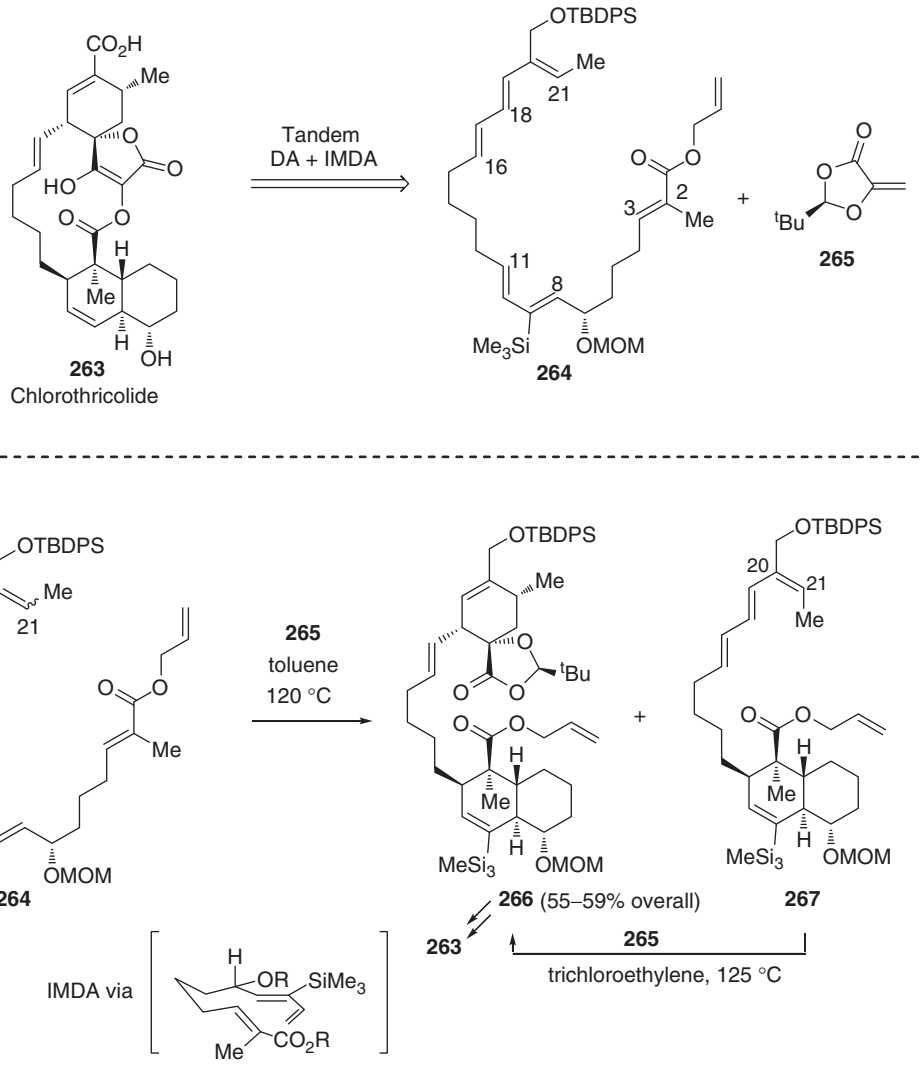
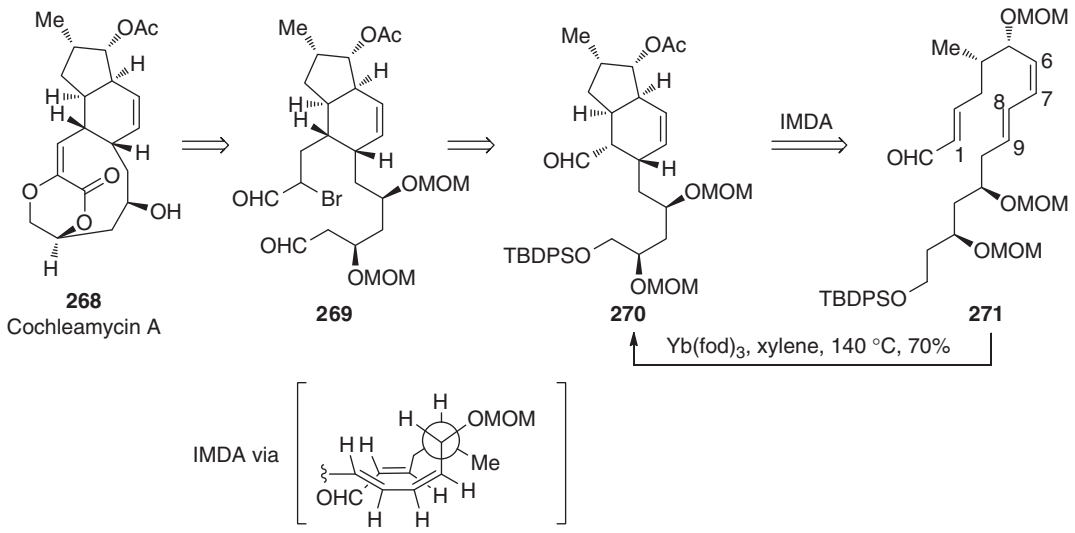


Figure 29 IMDA cycloaddition as a key step in the total synthesis of Chlorothricolide.



Scheme 25

5.11.11.2.4 Total synthesis of 8-deshydroxyajudazol B

At first sight, 8-deshydroxyajudazol B (**272**, Figure 30, top) is not a prime candidate for an IMDA disconnection, but closer analysis does in fact reveal an IMDA strategy[118] for construction of the isochromanone unit. This is based on retrosynthetic Br→O exchange and an aromatization process, defining **276** as the precursor for the synthesis of **275**. The IMDA-aromatization sequence was performed in tandem, with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone being used to oxidize the cyclic 1,4-diene produced by the cycloaddition. This technique was based on an earlier formal total synthesis[119] of the natural product (–)-apicularen A in which an elegant IMDA-aromatization sequence with **277** was used to simultaneously create a 10-membered ring (Figure 30, bottom).

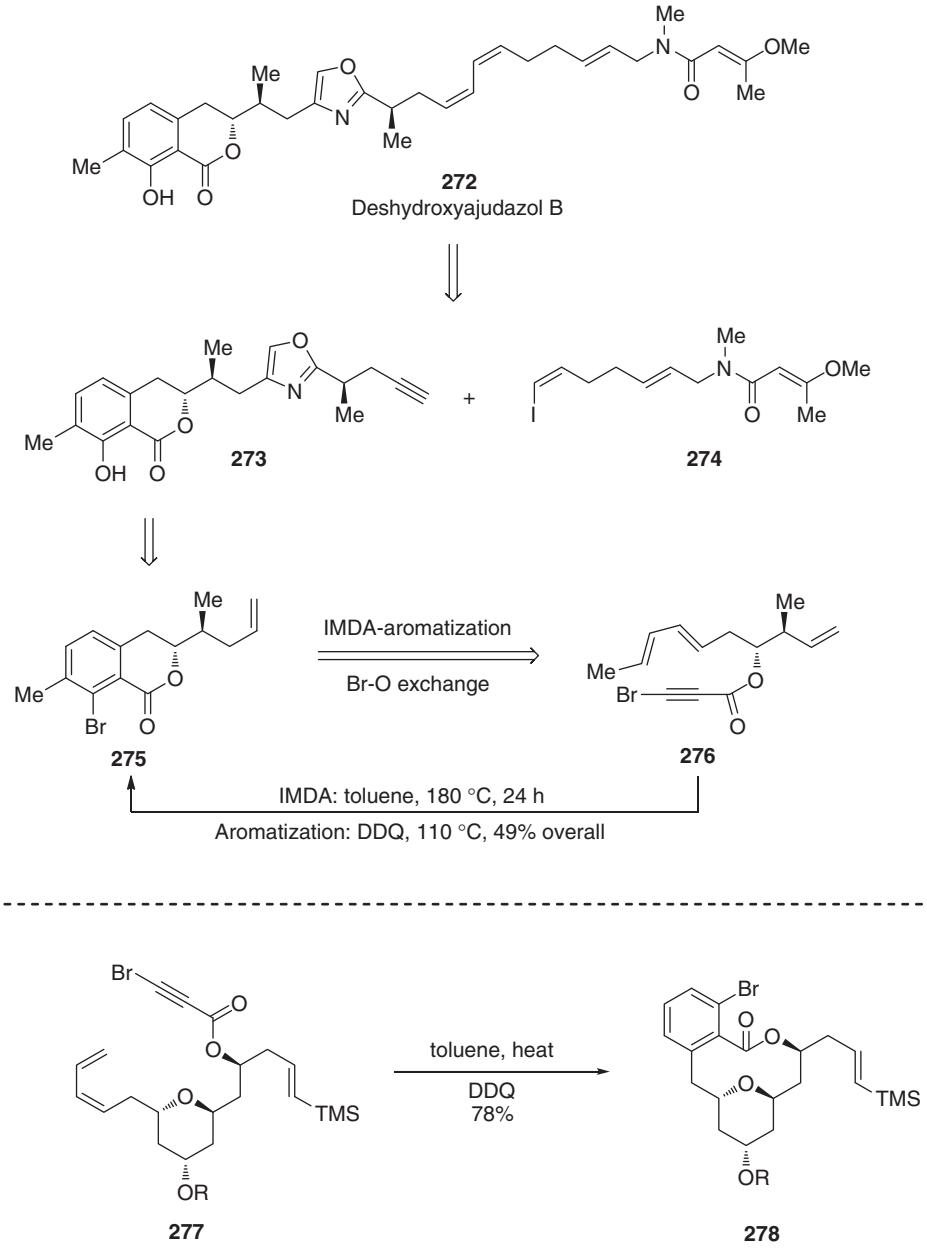
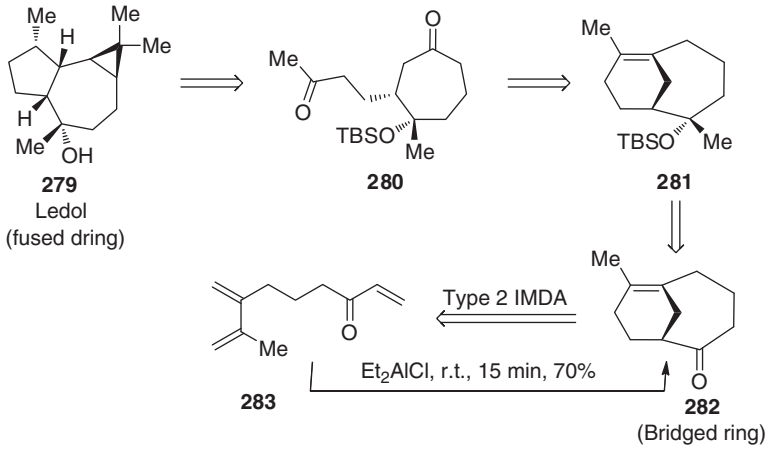


Figure 30 IMDA cycloaddition as a key step in the total synthesis of Deshydroxyajudazol B.

5.11.11.3 Terpenoids

5.11.11.3.1 Total synthesis of ledol

The total synthesis of ledol (**279**, Scheme 26) illustrates a 'bridged-to-fused ring interchange' strategy[120a] and also highlights the use of a type 2 IMDA cycloaddition for formation of medium rings[120b] in target molecules that themselves bear little resemblance

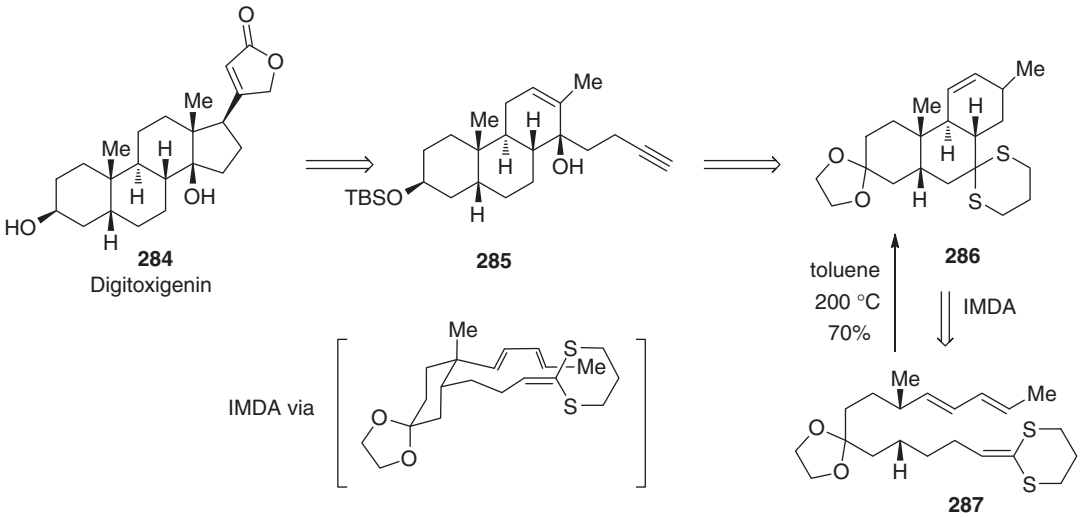


Scheme 26

to DA cycloadducts. Disconnective simplification of the target molecule to **280**, followed by retrosynthetic reconnection of the carbonyl groups reveals **281** and thus type 2 IMDA cycloadduct **282**. The cycloaddition of **283**, which proceeded under exceptionally mild conditions, not only formed the seven-membered ring of the target molecule but also provided a conformationally strongly biased system for diastereoselective nucleophilic attack on the carbonyl. The bridged ring system could then be dismantled and eventually transformed into the fused ring system of **279**.

5.11.11.3.2 Total synthesis of (+)-digitoxigenin

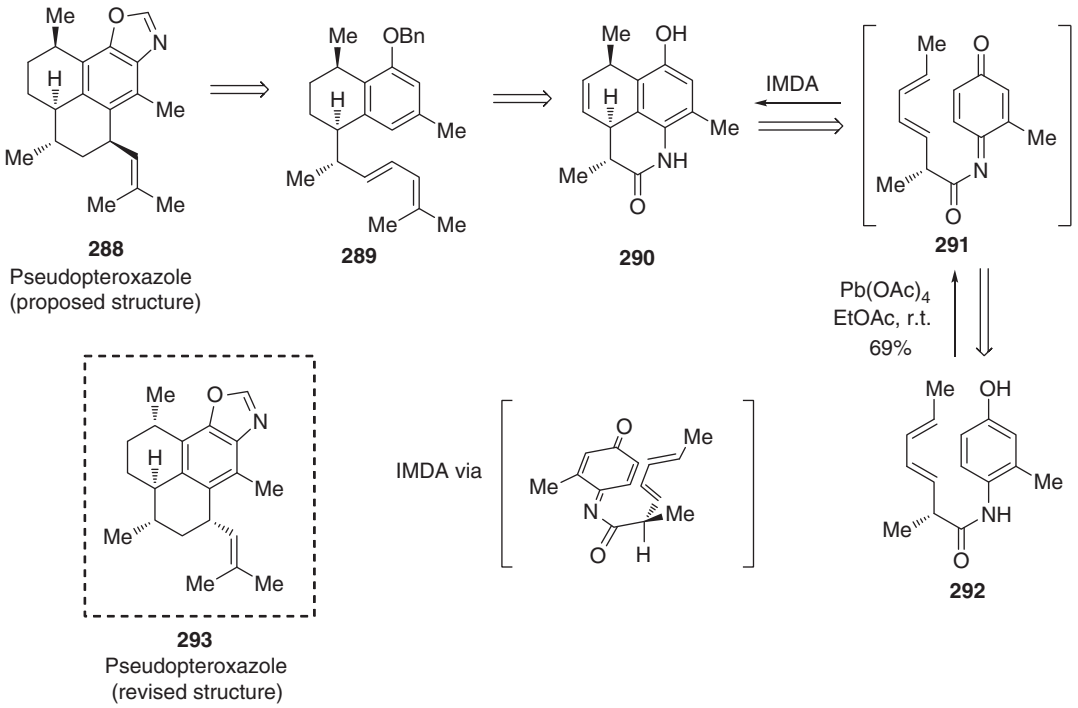
The cardenolide steroid (+)-digitoxigenin (**284**, Scheme 27) was assembled[121] via intermediate **285** that derived in turn from IMDA cycloadduct **286**. Thermal cycloaddition of **287** was completely diastereoselective, proceeding presumably via the *endo*-type conformation shown in Scheme 27. The use of the dithiane moiety as a masked carbonyl was important, because none of the other usual *endo*-selective substituents on the dienophile (e.g., CN or NO_2) could later be transformed into the carbonyl group which was necessary for stereoselective introduction of the butynyl side-chain in **285**.



Scheme 27

5.11.11.3.3 Total synthesis of 'pseudopteroxazole' (proposed structure)

As pointed out in Sections 5.11.11.1.1 and 5.11.11.2.3, total synthesis is still an important tool (in some cases the only available one) for the correct assignment of structure and/or configuration. Another example[122] is given in Scheme 28, in the form of an asymmetric synthesis of the proposed structure of the biologically active marine natural product pseudopteroxazole **288**. As shown by the retrosynthetic analysis, the nitrogen tether in **292** ensures a regio- and diastereoselective substrate-controlled IMDA cycloaddition via transient formation of **291** by mild oxidation. The nitrogen also serves as a removable group to allow formation



Scheme 28

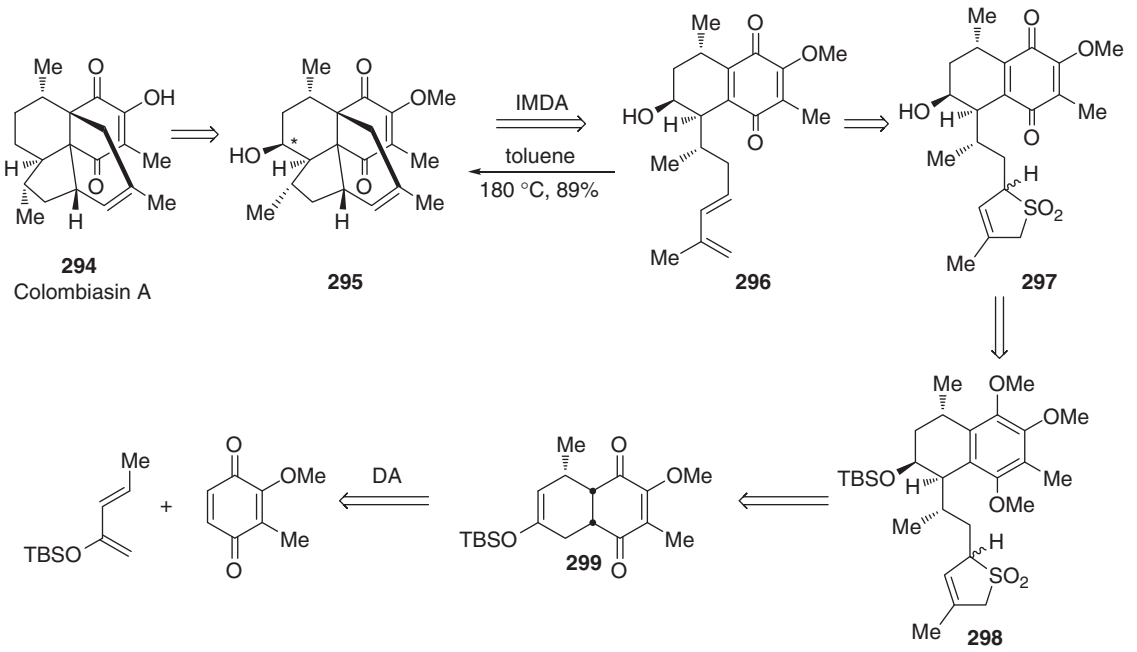
of key intermediate **289** from cycloadduct **290**. The final product was not identical with the natural isolate, necessitating a stereochemical revision; the probable structure[122] of pseudopteroxazole is **293**.

5.11.11.3.4 Total synthesis of colombiasin A

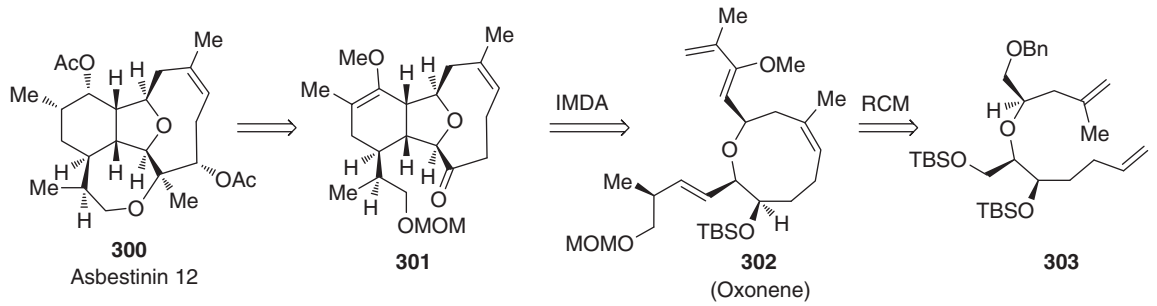
The diterpene colombiasin (**294**, Scheme 29) has a compact cage-like structure featuring six stereogenic centers, including two adjacent quarternary carbons. A total synthesis[123] of colombiasin was based on two key DA cycloadditions, one intermolecular, and one IMDA (the latter being used to install the two adjacent quaternary centers in one step). The synthesis proceeded via late-stage key intermediate **295** (Scheme 29), the extraneous oxygen at the asterisked carbon being necessary for correct introduction of the tethered diene in **296**. IMDA substrate **296** was generated transiently by cheletropic removal of SO_2 from **297**, a tactic made necessary by the incompatibility of the diene itself with reagents used for the oxidation of **298**. To complete the retrosynthetic analysis, **298** was traced back to **299**, which is the product of a regio- and stereoselective bimolecular DA cycloaddition. The IMDA reaction involving **296** was carried out in the dark to suppress competing photochemical [2 + 2] cycloadditions between the less-substituted portion of the diene and the quinone, and under these conditions an excellent 89% yield of **295** was obtained. Finally, use of a chiral Lewis acid catalyst (cf. Section 5.11.7.3.1) for the initial bimolecular DA cycloaddition provided enantiomerically enriched **299** that was used to assign the absolute configuration of the natural product.[123]

5.11.11.3.5 Total synthesis of asbestinins

An intriguing general strategy[124] for the total synthesis of the asbestinins (e.g., asbestinin 12, **300**, Figure 31) was based on the use of an oxonene template **302** to induce high stereoselectivity in an IMDA reaction, forming a tricyclic precursor **301** to the tetracyclic target molecule. Oxonene **302** was projected to be formed by RCM[92] of **303**. It was found that the exocyclic alkene in IMDA substrates such as **302** was not sufficiently dienophilic to participate in the desired IMDA cycloaddition, so the synthetic plan was modified to incorporate an electron-withdrawing group, as in **304**. This proved to be highly successful, the IMDA cycloadduct **305** being produced as a single diastereomer in 80% yield. The selectivity of the IMDA reaction rests on the conformational bias of the oxonene ring, as well as the steric bulk of the ether substituent and the configuration at C3 in **304**, which is responsible for the desired *exo*-selective cycloaddition (see partial structures **306**, Figure 31). For the IMDA to occur, both side-chains must adopt pseudoaxial positions and this means that in the *endo* conformation there is a steric clash between the OR group on C3 and one of the vinyl protons of the dienophile. This destabilizing nonbonded interaction is relieved in the *exo* conformation and, in line with this model, use of a sterically less demanding OR group (OPMB) at C3 gave lower diastereoselectivity (4:1 in favor of *exo*).



Scheme 29



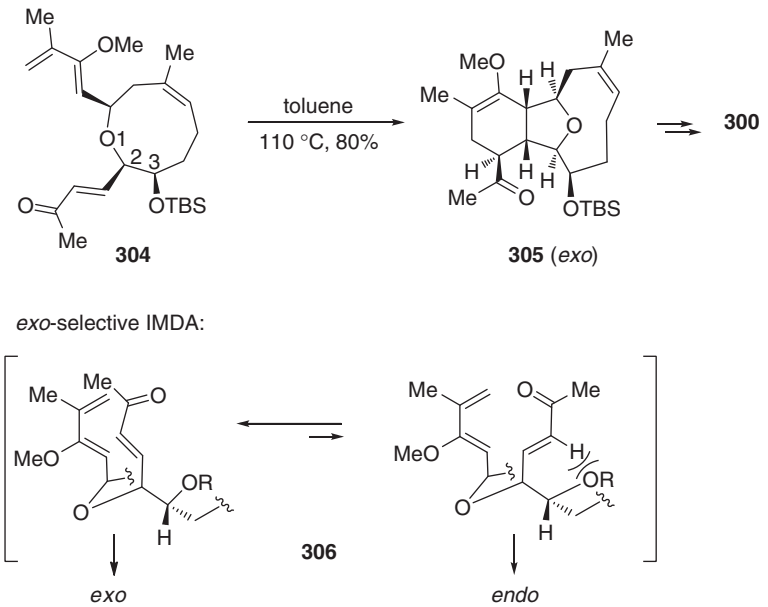
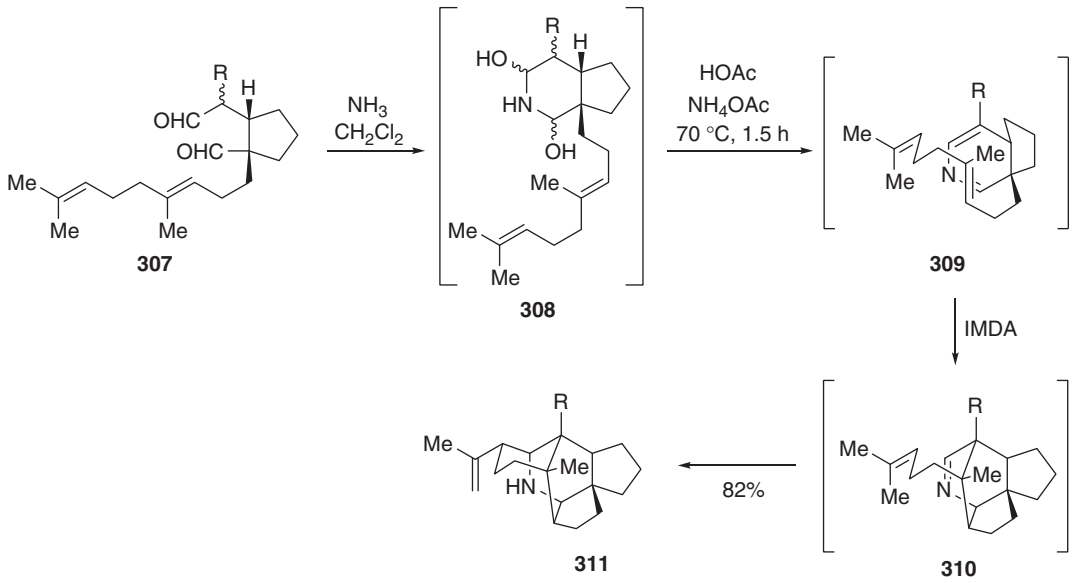


Figure 31 IMDA cycloaddition as a key step in the total synthesis of Asbestinin 12.

5.11.12 Biomimetic versus Bio-inspired IMDA Cycloadditions

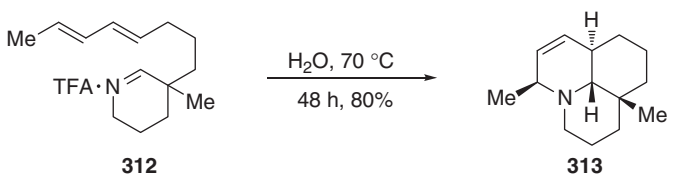
In Section 5.11.4.4 the intriguing but contentious topic of Diels–Alderases was mentioned, and there is now a multitude of natural products[125] for which DA and/or IMDA reactions have been proposed as key steps on the biosynthetic pathway. Indeed, many of the total synthesis efforts described or referred to in previous sections have been motivated by consideration of possible biosynthetic [4 + 2] cycloadditions and, understandably, interest in this topic continues unabated.[126] At this point, it seems reasonable to make a distinction between the terms 'biomimetic' (which is meant here as reactions occurring in aqueous media at, or close to, ambient temperature) and 'bio-inspired' (which refers here to reactions designed on the basis of an established or putative biosynthetic step, but carried out under abiotic conditions vastly different from those pertaining to enzymatic processes).[127] Thus, to paraphrase (without denigrating) some of the extant experimental protocols, an IMDA cycloaddition which proceeds only on prolonged heating in a sealed vessel at temperatures well above the boiling point of the aromatic hydrocarbon solvent of choice, in the presence of (super-)stoichiometric amounts of a powerful 'man-made' Lewis acid, may well be bio-inspired but is not biomimetic.

A classic example of a bio-inspired IMDA cycloaddition (as part of a cascade sequence, cf. Section 5.11.8.2) is the general approach[128] to the *Daphniphyllum* alkaloids summarized in Scheme 30. In a consummate combination of aesthetics and efficiency, a readily accessible dialdehyde such as **307** is treated sequentially with ammonia, acetic acid, and ammonium acetate to form IMDA precursor **309**. The acetic acid solution of the cycloadduct **310** is then heated to induce an aza-Prins cyclization which delivers pentacyclic amine **311**. At one fell swoop, this superbly designed and executed sequence elegantly forms three carbon–carbon and two carbon–nitrogen bonds, forges five rings, and establishes six stereocenters.



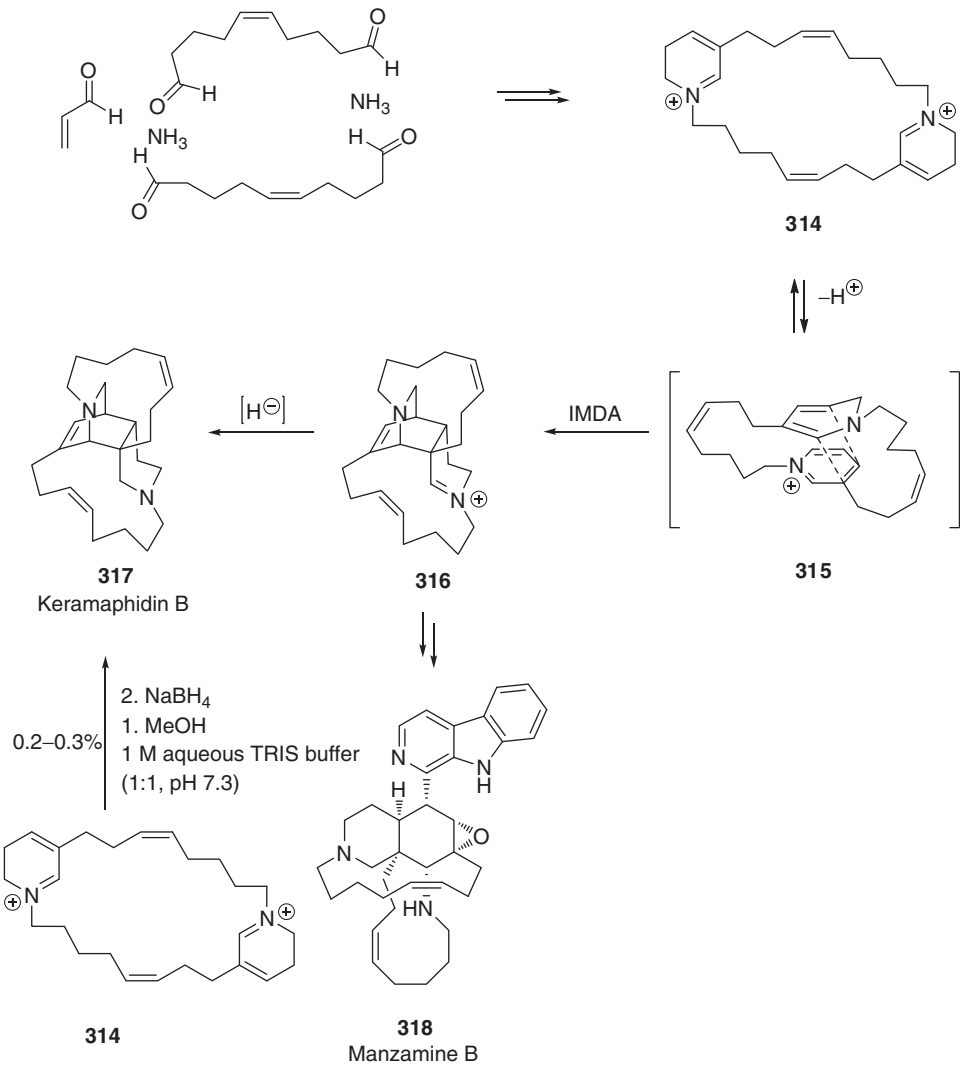
Scheme 30

As far as biomimetic reaction conditions are concerned, the use of aqueous media for the DA cycloaddition has been known since the work[129] of Diels and Alder themselves in 1931, but it was not until the 1980s that interest in this technique was rekindled in earnest.[130, 131] On occasion, water proved to be the medium of choice as shown for the IMHDA reaction[132] in Scheme 31. Cycloadduct **313** was obtained as a single diastereomer and, in this case, water easily outperformed other polar media such as 5.0 M lithium perchlorate–diethyl ether (Section 5.11.3.2) in which the reaction gave only 13% yield. Another fine example of the use of aqueous media to promote an IMHDA reaction[62] can be found in Section 5.11.6.2.



Scheme 31

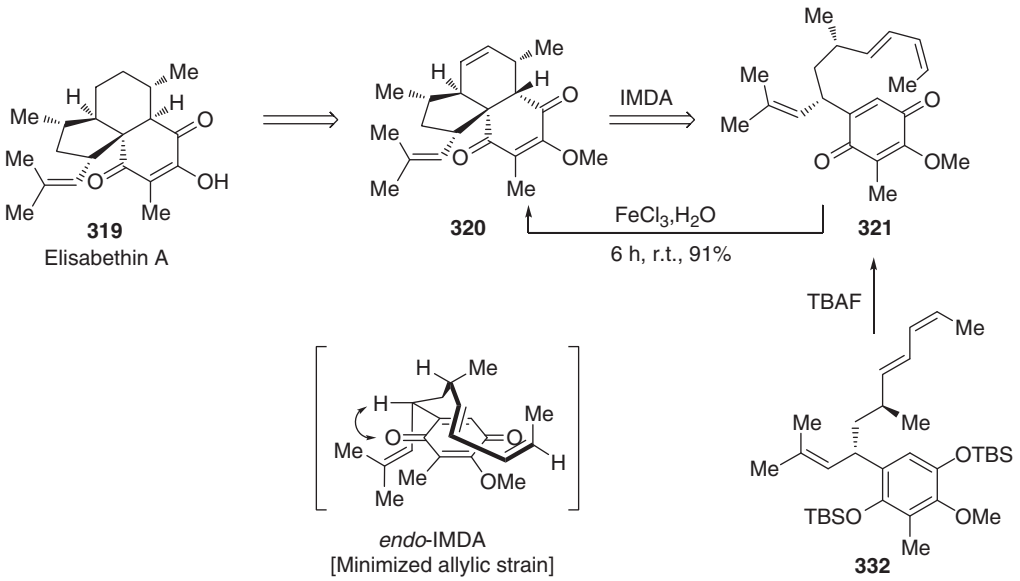
In the early 1990s, an appealing biogenetic hypothesis was presented[133] to explain the unprecedented structure of the manzamine alkaloids (Scheme 32). An alkaloid related to the manzamines, keramaphidin B **317**, was later isolated[134] and it was proposed that the biosynthetic pathway from simple precursors to the intricate natural products involved an *endo*-selective IMDA cycloaddition[135] of bisdihydropyridine **315**, the product of which, **316**, would diverge to keramaphidin B and the manzamines (e.g. manzamine B **318**, the aromatic moiety of which comes from tryptamine). In practice, trace amounts of **317** could indeed be isolated from the reaction of **314** in aqueous medium, the major pathway being disproportionation of intermediate **315**. It was suggested that a putative Diels–Alderase could decrease or even exclude the disproportionation reaction and also have a favorable entropic effect on the IMDA cycloaddition by limiting the conformational freedom of the substrate.



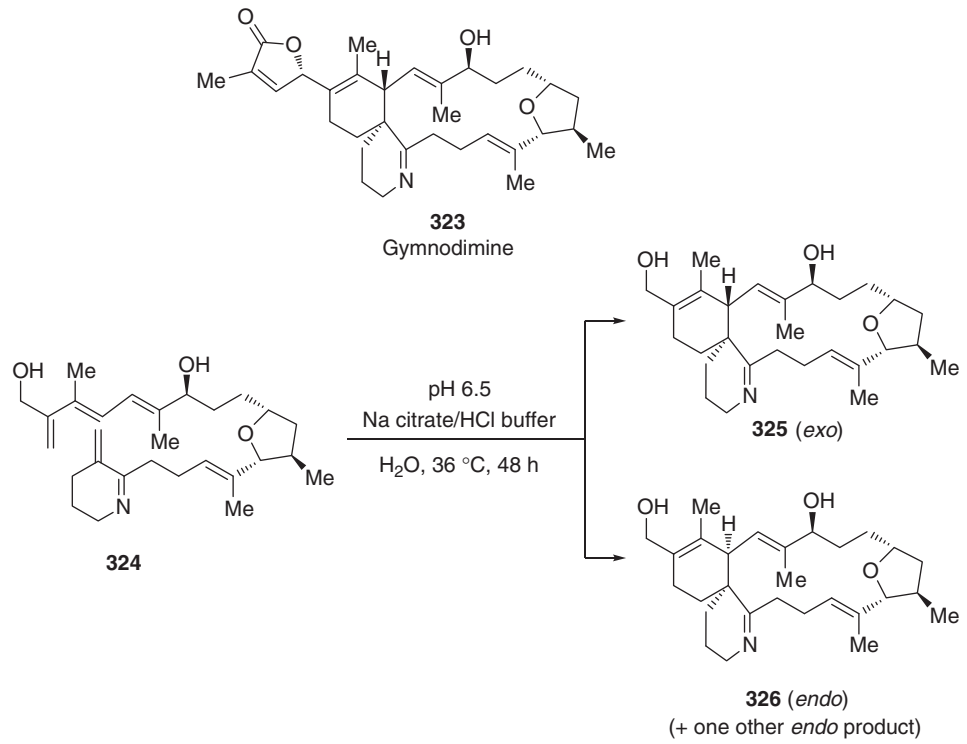
Scheme 32

A plausible biosynthetic precursor to the natural product colombiasin **294** (Scheme 29) is elisabethin A (**319**, Scheme 33). Retrosynthetically,[136] **319** can be derived from **320** (requiring epimerization, demethylation, and reduction) that in turn leads back to IMDA precursor **321**, generated by oxidation of the corresponding hydroquinoid derivative **322**. The choice of the TBS protective groups was crucial to allow deprotection under mild conditions, and the IMDA reaction is noteworthy for the 'virtually biomimetic'[136] conditions, the very high yield and essentially complete diastereoselectivity, and the fact that this was apparently the first successful IMDA involving a terminal *Z*-alkene in the diene unit. The *endo* transition state shown in Scheme 33 is the one which minimizes allylic strain involving the quinoid carbonyl moiety. This admirable total synthesis also served to assign the absolute configuration of the natural product.

In Scheme 13, the use of an IMDA reaction for a macrobicyclization was presented, and this type of process also characterizes the synthesis of the core unit **325** of the natural product gymnodimine[137] **323** shown in Scheme 34. The α,β-unsaturated imine



Scheme 33



Scheme 34

324 (and also simpler congeners) was found to be remarkably stable in water at acidic and neutral pH, and underwent an IMDA cycloaddition at moderate temperatures and pH 6.5 to yield **325** (*exo*) and **326** (*endo*) as the major products. The *exo* cycloadduct remained unchanged in aqueous solution, whereas the *endo* species were prone to hydrolysis to keto-amines. These experimental results were taken as an indication that a biosynthetic IMDA leading to **323** could well occur without recourse to enzymatic catalysis.

Another intriguing set of experiments[138] is related to the question of possible enzymatic catalysis of an IMDA cycloaddition in the biosynthesis of UCS1025A (**327**, Figure 32), the putative IMDA precursor being triene **328**. The racemic form of **330** was dissolved in a phosphate buffer (pH 7.2, D_2O) at RT and was observed to immediately ring-open to **331** followed by rapid IMDA cycloaddition (with a $t_{1/2}$ of only 10 min) to give a 1:1 mixture of **332** and tetra-*epi*-**332** which on acidification yielded **327** and

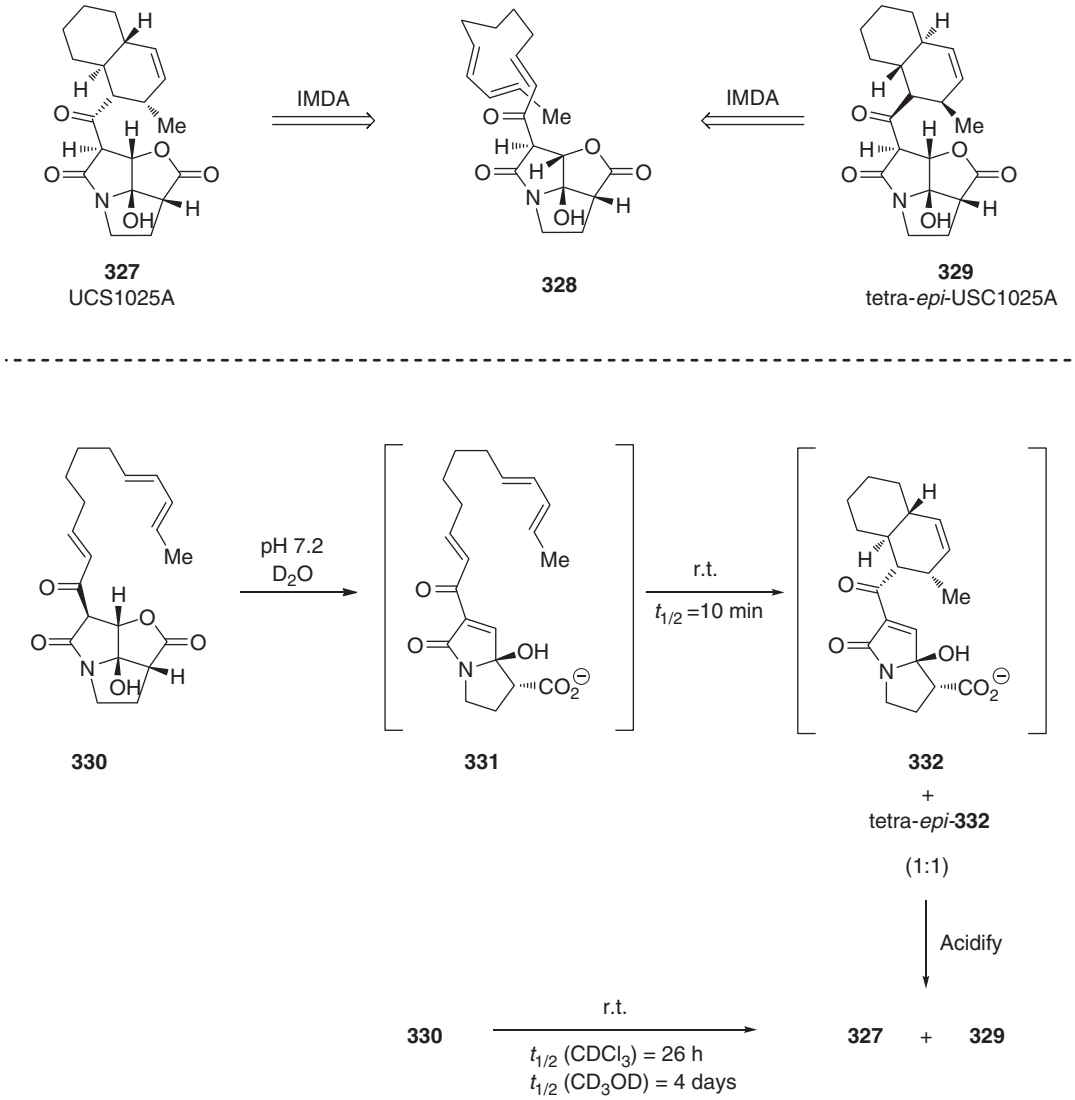


Figure 32 Experiments related to possible enzymatic catalysis of an IMDA cycloaddition.

329, respectively. The aqueous medium obviously plays a major role in determining the rate of the cycloaddition (cf. the results obtained for $CDCl_3$ and CD_3OD solutions). The IMDA process is highly *endo*-selective, but essentially no diastereoselectivity was observed. Thus, although the rate of cycloaddition of **331** is fast enough to be the natural event, the lack of substrate-controlled diastereoselectivity means that some external stereocontrol element must be operative in the biosynthetic pathway leading to the natural diastereomer of **327**. Whether or not such control is provided by enzymatic catalysis is still a moot point.

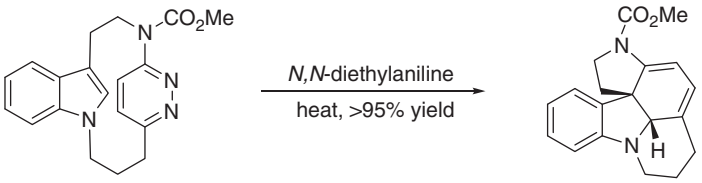
5.11.13 TADA Cycloadditions

Transannulation reactions[139] can provide an appealing and efficient strategy for the synthesis of polycyclic molecular frameworks. The general approach requires initial construction of a medium or large ring appropriately functionalized to provide for the formation of one (or more) bond(s) across the perimeter, with the simultaneous formation of two or more smaller rings. If the smaller rings in the products are 'normal-sized' (5-, 6- or 7-membered) an obvious potential stumbling block is the generation of the 'awkward' ring sizes required in the substrates. Provided that the precursor can be accessed without too much difficulty, the overall success of the transannular strategy will then rest on the conformational and electronic preferences of the medium-sized or macrocyclic ring as the molecule approaches the transition state; it seems reasonable to assume that such steric and/or stereoelectronic bias can be induced by careful choice of the substituents on the ring perimeter. Since DA and IMDA reactions represent

extraordinarily efficient stereospecific methods for the rapid generation of molecular complexity, with often exquisite levels of regio- and stereoselectivity, dictated by a highly-ordered transition state, the TADA mode of cycloaddition would appear be a very powerful synthetic tool. It is of course not surprising that the evolution of the TADA reaction has gone hand in hand with methodological advances in the synthesis of medium and large rings. The historical development and deployment of the TADA cycloaddition strategy have been reviewed at length and in depth,[140] and this section will concentrate on a selection of recent examples, with the emphasis on applications to the total synthesis of natural products.

5.11.13.1 Cyclophanes as TADA Precursors

Scheme 35 shows an approach[141] to the total synthesis of strychnine which involves a highly efficient inverse electron demand TADA reaction of cyclophane **333**. It was claimed that **334**, formed via the TADA reaction and subsequent loss of N_2, could be transformed into a known key intermediate for the total synthesis, but this was later shown to be in error.[142]



333 **334**

Scheme 35

The enantioselective total synthesis[143] of (–)-longithorone A (**339**, Scheme 36) utilized first an intermolecular DA cycloaddition of the atropisomerically pure cyclophanes **335** and **336** followed by oxidation and a TADA reaction of transient bisquinone intermediate **338**. This total synthesis was inspired by a biosynthetic proposal, and is noteworthy for a very clever use of chirality transfer to dictate enantioselectivity via an elegant interplay of stereogenic centers and atropisomerism. The lack of stereocontrol in the bimolecular DA reaction (the desired product was the minor diastereomer) could be taken as evidence for the intervention of a Diels–Alderase in the biosynthetic pathway.

5.11.13.2 Tandem TADA Cycloadditions

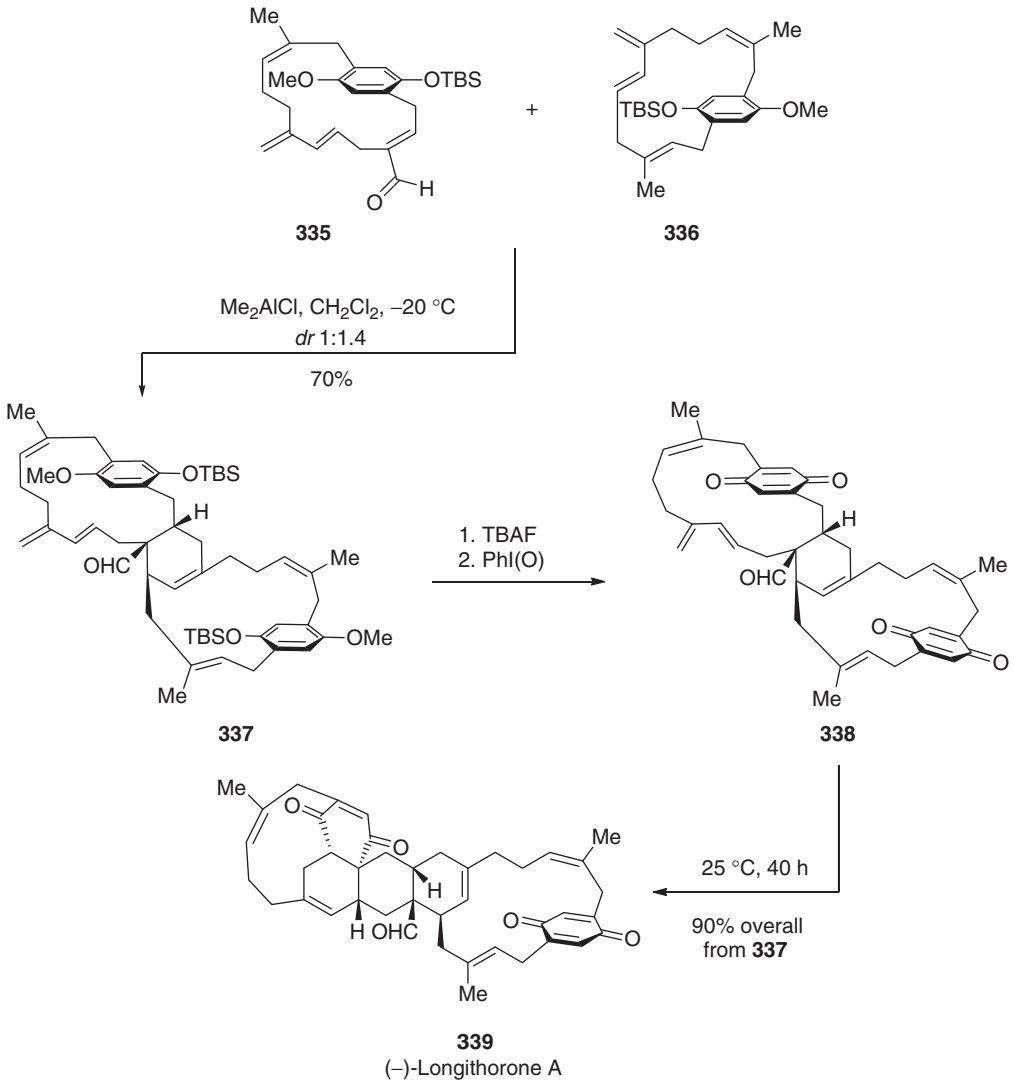
An impressive tandem sequence involving a pair of TADA cycloadditions formed the basis of two very similar, independent and concomitant total syntheses[144] of the hexacyclic natural product FR182877 (**344**, Scheme 37). The second TADA reaction is of the hetero-Diels–Alder type, and the TADA precursors **340** differ only in the nature of the protective groups and the R^4 substituent. Both sequences delivered the pentacyclic intermediates **343** in respectable yields, in a truly spectacular demonstration of the power of the DA reaction to rapidly build up molecular complexity: five rings, three C–C bonds, one C–O bond and seven stereocenters are formed in a single operation. Interestingly, the same target molecule was later accessed[145] from key intermediate **345** by a tandem sequence of IMDA–IMHDA cycloadditions which provided the advanced building block **346**, albeit in modest yield (Scheme 38). A further comparison of IMDA and TADA approaches to a common target molecule is provided in Section 5.11.13.5.

5.11.13.3 Total Synthesis of (+)-Macquarimicin A

Related to FR182877 is the tetracyclic compound macquarimicin A (**350**, Scheme 39) which was synthesized enantioselectively[146] via **349** by means of a TADA reaction of **348**. As indicated in Scheme 39, it is the (*Z*,*E*) geometry of the diene unit that determines the *endo* selectivity, whereas diastereofacial selectivity is controlled by the lactone moiety. This total synthesis also allowed for a structural reassignment of the natural isolate (the alkene exocyclic to the lactone ring in **350** is *Z*, rather than the *E* configuration which was originally proposed).

5.11.13.4 A TADA Approach to the Mangicols

Scheme 40 shows a TADA-based approach[147] to the total synthesis of the mangicol family of natural products (e.g., mangicol A, **353**). The 12-membered macrocycle **351** gave a quantitative yield of TADA cycloadduct **352** as a single diastereomer. Unexpectedly, the outcome of the TADA reaction was found to be dependent on the configuration at the C3 allylic alcohol: the C3-epimer of **351**



Scheme 36

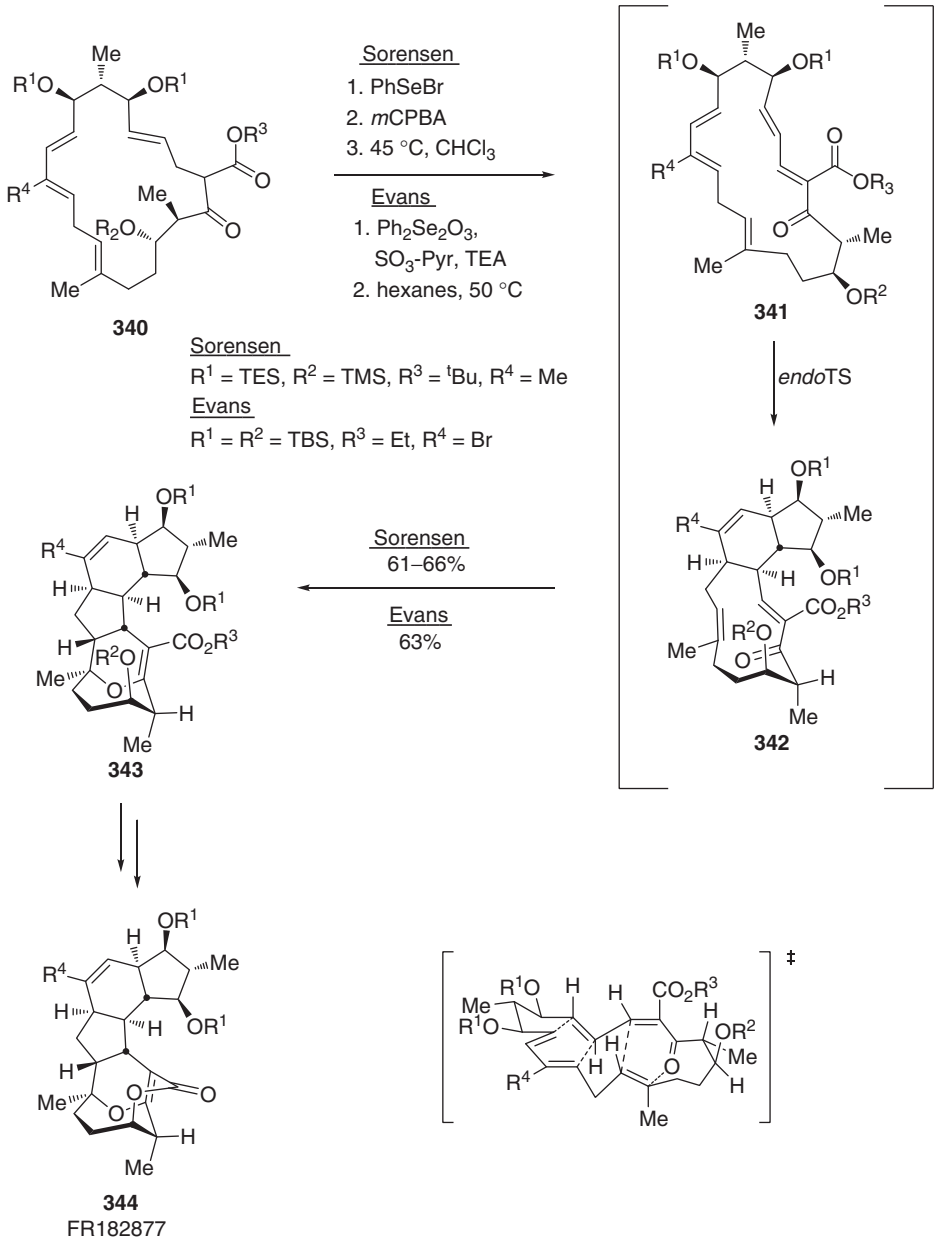
gave a 1:1 mixture of diastereomers under the same conditions as for **351** itself. It was suggested that the lower-energy transition state for the TADA reaction of **351** was that in which destabilizing transannular nonbonded interactions are minimized.

5.11.13.5 *Endo*-IMDA versus *Exo*-TADA

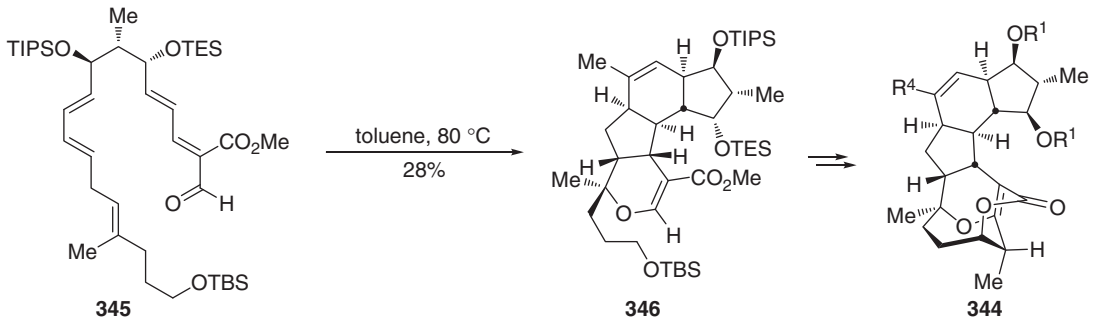
A projected synthesis[148] of the antibiotic branimycin (**354**, Figure 33) was envisioned to proceed either via an IMDA cycloaddition of **356** (*endo* transition state) or a TADA reaction of **358** (*exo* transition state). In the event, all attempts (heating, Lewis acid-catalysis, and high pressure) to access **355** by the IMDA reaction failed, whereas TADA precursor **358** smoothly delivered **357** in excellent yield and as a single diastereomer.

5.11.13.6 Catalytic Asymmetric TADA Cycloaddition

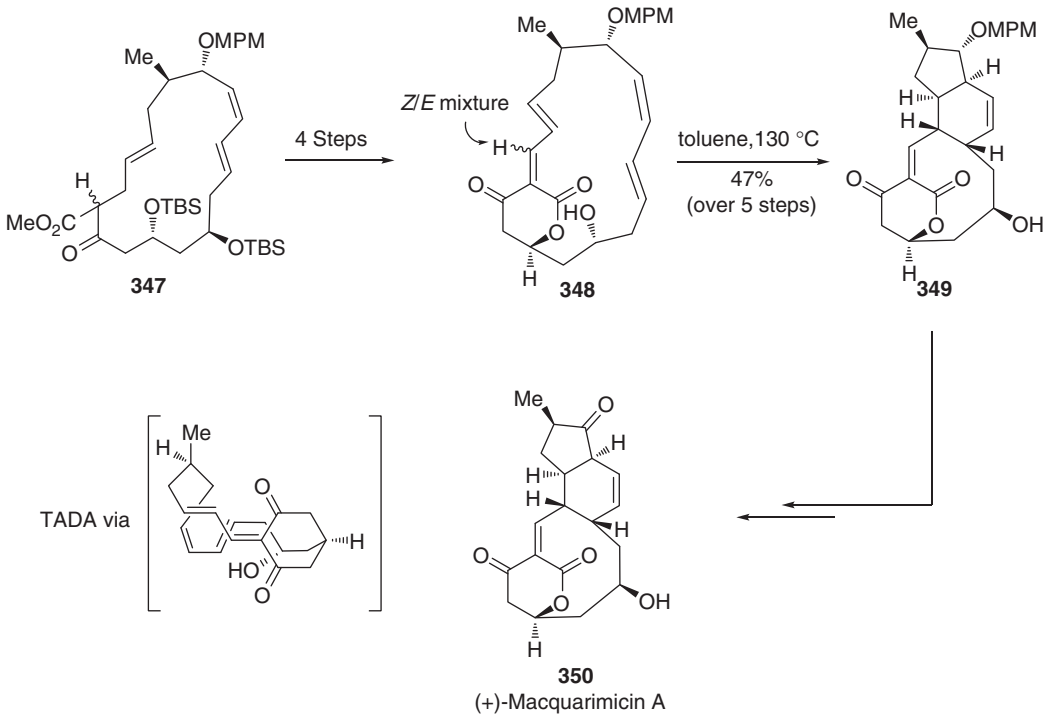
The enantioselective total synthesis[149] of the sesquiterpene 11,12-diacetoxydrimane **362** shown in Scheme 41 illustrates the powerful and elegant combination of a temporary silicon tether (cf. Section 5.11.2) and enantioselective catalysis via chiral oxazaborolidines (Section 5.11.7.3.2) for TADA cycloadditions. It was found that when the silicon-tethered macrocyclic TADA precursor **359** was subjected to the Corey catalyst **360**,[83] complete conversion of the *E,E*-isomer occurred to give **361** with >20:1 diastereoselectivity and 83% *ee*. Importantly, it was also found that the oxazaborolidine catalyst was capable of overriding any inherent diastereofacial bias in TADA substrates containing stereogenic centers, thus opening up a general synthetic route to many polycyclic terpene natural products.



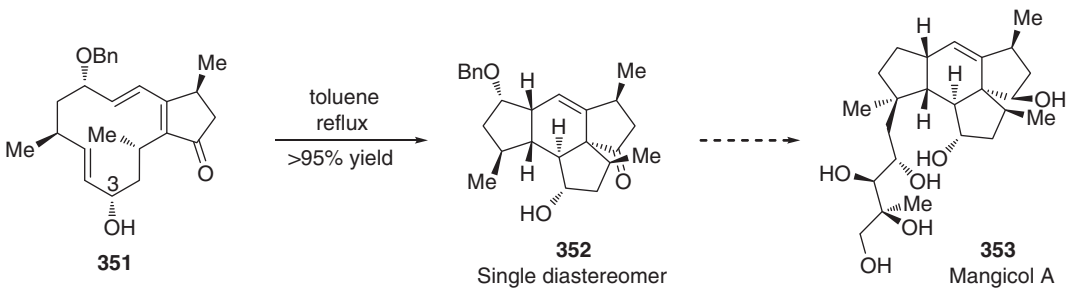
Scheme 37



Scheme 38



Scheme 39



Scheme 40

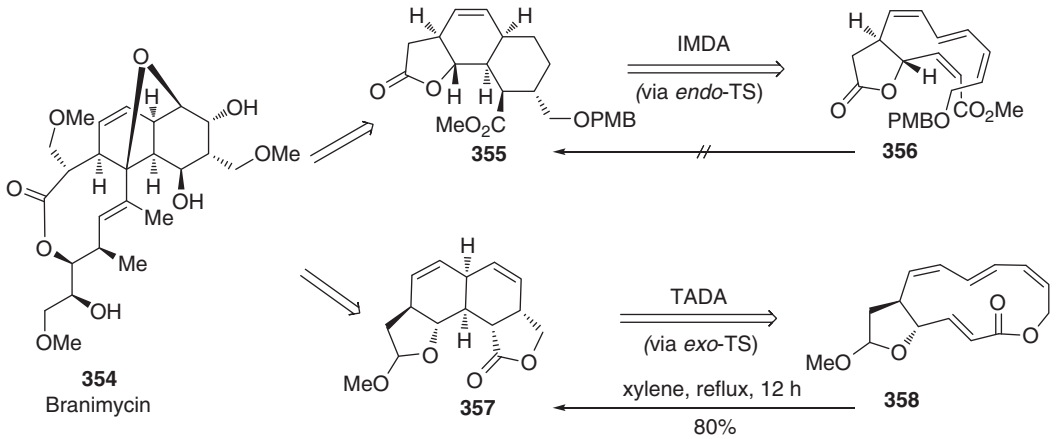
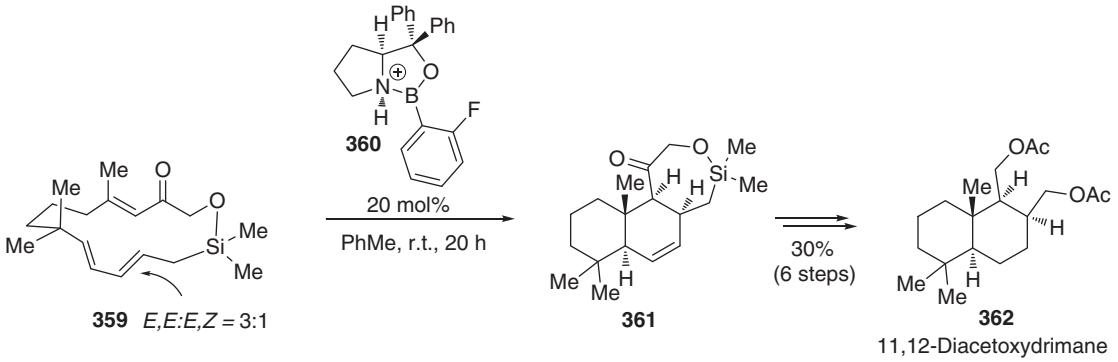


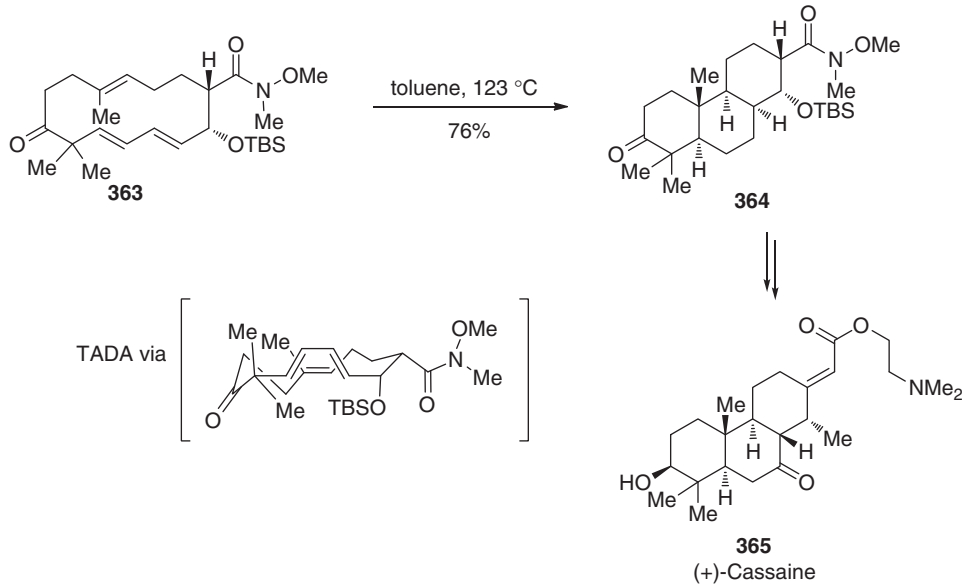
Figure 33 TADA cycloaddition approach to Branimycin.



Scheme 41

5.11.13.7 Total Synthesis of (+)-Cassaine

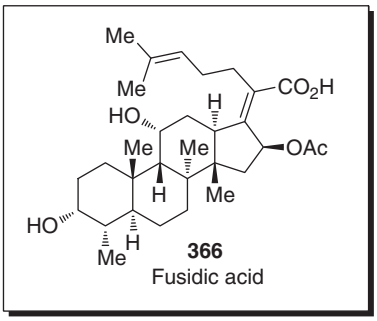
An efficient substrate-controlled TADA reaction was used[150] as a key step in the asymmetric total synthesis of (+)-cassaine (**365**, Scheme 42). The diastereoselective TADA cycloaddition of **363** (see the pretransition state conformation in Scheme 42) efficiently set up the tricyclic system of **364**, with control over four new contiguous stereocenters (one of which was later epimerized). The TADA strategy also allowed for the use of an electronically unactivated dienophile.



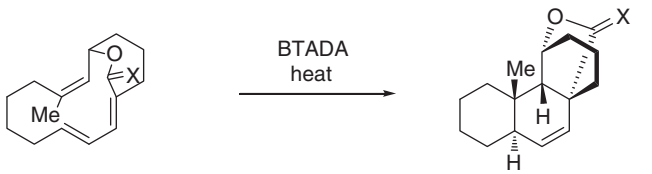
Scheme 42

5.11.13.8 Bicyclic Transannular Diels–Alder (BTADA) Cycloaddition

The BTADA approach was considered[151] for the total synthesis of natural products such as fusidic acid **366**, and model studies revealed some very interesting patterns of reactivity (Scheme 43). Lactone **367** failed completely to undergo the desired cycloaddition, whereas ether **369** smoothly delivered tetracycle **370** in quantitative yield. DFT calculations revealed the reason for the lack of reactivity of **367**: there is a prohibitively high barrier (ca. 215 kJ mol^{-1}) for conversion of the lactone from its lowest energy conformation to the one in which the diene and dienophile components are correctly aligned to undergo the BTADA cycloaddition. The high barrier to interconversion is because of increased trannsannular strain and to loss of conjugation in the diene as the molecule changes conformation. Calculations also guided the choice of the ether **369**, for which the corresponding energy barrier is only 63 kJ mol^{-1} (the energy barriers for the BTADA reaction itself were calculated to be 100 and 110 kJ mol^{-1} for **367** and **369**, respectively).



366
Fusidic acid



367 X = O
369 X = H_2

368 X = O (0%)
370 X = H_2 (100%)

Scheme 43

5.11.14 Conclusions and Outlook

Since 1928, the DA cycloaddition has been one of the most powerful tools available for the rapid generation of molecular complexity, particularly in the field of total synthesis. The extension of this peerless reaction to the IMDA and TADA modes described above now allows impressively brief and highly stereoselective routes to target molecules of daunting complexity. It is expected that these already powerful synthetic transformations (perhaps in harness with new modes of catalysis) will continue to thrive and to provide uniquely efficient and elegant solutions to challenging problems in synthesis.

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5.12 Retro Diels–Alder Reactions

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Glossary

[4 + 2] Cycloaddition Reaction of a conjugated diene with a dienophile to give an adduct.

***Exo–endo* isomerization** The *endo* adduct is thermodynamically less stable than the *exo* adduct and isomerizations can occur by a sequence of DA/rDA reactions.

Retro Diels–Alder (rDA) fragmentation Decomposition of an adduct, which requires high temperature or sometimes flash vacuum pyrolysis; promoted rDA fragmentation: dienes and dienophiles formed are stable, volatile or easily removable.

Retro Diels–Alder (rDA) reaction A reverse process of a Diels–Alder reaction.

Retrodiene methods Retrodiene methods provide new approach for preparation of heterocycles synthetic application can be used in the chemistry of oligomers and polymers. New strategy involves synthetic application to fullerens and graphenes and suitable to build up natural products with complicated structures.

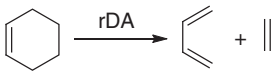
5.12.1 Introduction

The Diels–Alder (DA) reaction comprises a reversible [4 + 2] cycloaddition between a conjugated diene and a substituted alkene, commonly termed dienophile. The reverse process is generally named as a retro DA (rDA) reaction. The thermally allowed cycloreversion [$_{\pi}4 + _{\pi}2_{s}$] of an organic compound containing a double bond in a six-membered ring leads to the formation of a diene and a dienophile. Even though the DA cycloaddition is thermodynamically reversible, the DA products are fairly stable, and their spontaneous cleavage generally does not occur. Besides the normal thermolysis of DA adducts, a wide range of conditions and other methods to facilitate the rDA process have been reported.

The rDA fragmentation usually requires high temperatures (simple heating of neat compounds or of solutions of the compounds in an inert solvent) in order to surmount the high activation barrier of the cycloreversion, but in some cases extreme conditions such as flash vacuum pyrolysis (FVP, at 600–900 °C) are required. It should be mentioned that the thermal rDA reaction of anthracene cycloadducts can be accelerated by electron-donating groups. Photochemical irradiation, sonication, and the application of high pressure or acid- and base-mediated processes also promote cycloreversion. The incorporation of an oxide into an anionic substituent strongly accelerates the rDA process too.[1,2]

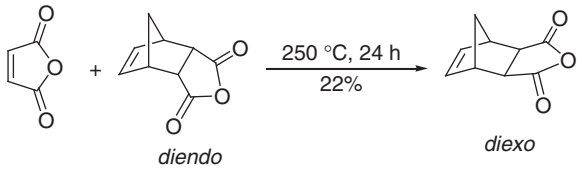
Promoted rDA fragmentation readily occurs when the dienes and/or dienophiles formed are particularly stable (e.g., an aromatic ring) or when volatile or easily removable molecules (e.g., nitrogen, carbon dioxide, acetylene, or ethylene) are formed. The rDA fragmentations, which often take place on analysis of organic compounds by mass spectrometry, are not of preparative importance and therefore not covered herein.

A fundamental and simple example of a thermal rDA process is the reaction of cyclohexene to 1,3-butadiene and ethylene (equation 1). With an appropriate driving force, the DA reaction may proceed in the reverse direction, providing the separable diene and dienophile from the starting cyclohexene.



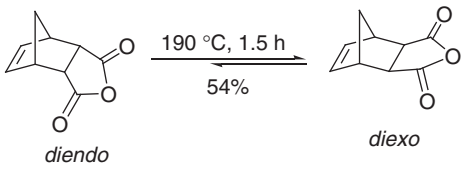
(1)

In 1929, this process was described for the first time and applied to the detection of 1,4-bridged cyclohexadiene derivatives, from which ethylene and aromatic compounds were released through an rDA process.[3] Since then, a large number of substrates have been subjected to rDA reactions and a variety of dienes and dienophiles have been formed. When the rDA process is conducted in the presence of a scavenging diene or dienophile, numerous transient reactive species can be captured.[4] Likewise, the observation of *endo–exo* isomerization of DA adducts serves as evidence for an intervening rDA reaction.[5,6] It has been postulated that at high temperatures the kinetic *endo* adducts undergo isomerization to the thermodynamically more stable *exo* products via an rDA/DA sequence (equation 2).



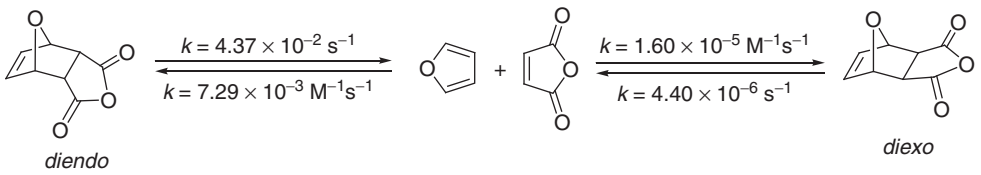
(2)

The DA reaction of cyclopentadiene with maleic anhydride (MA) occurs at room temperature, with kinetically favored formation of the *diendo* isomer. The cycloaddition is exothermic by ~25 kcal mol^{-1}.[6] The reaction of many substrates that undergo dissociative rDA processes proceed through similar cycloadducts that are not always easily detected. Interconversion to the *diexo* isomer at reasonable rates requires temperatures of approximately 150 °C, but best yields of the *diexo* isomer were isolated by heating of the *diendo* isomer at a higher temperature (equation 3).[7]



(3)

Another system that has been fully characterized and kinetically studied is the DA formation of *diexo*-7-oxabicyclo[2.2.1]-heptene-2,3-dicarboxylic anhydride (equation 4). Rate constants for both the DA and the rDA reaction were measured in MeCN at 40 °C.[8] The *diendo* isomer was formed much faster than the *diexo* adduct but was less stable especially in a diluted solution.



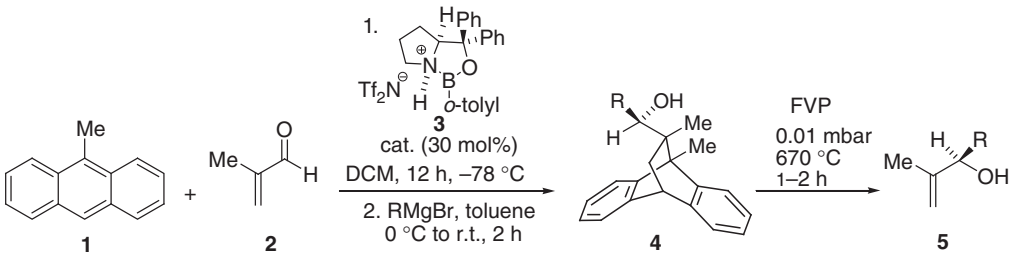
(4)

A number of comprehensive valuable review articles and books have been written related to rDA processes earlier, which surveyed this important reaction theoretically and/or practically.[9–18] The rDA reactions have become an important field of organic chemistry with regard to the mechanistic features and the wide-ranging preparative applications.

5.12.2 Preparation of Substituted Alkenes

5.12.2.1 α,β-Unsaturated Alcohols

Allylic alcohols have been prepared enantioselectively by oxazaborolidinium ion-catalyzed DA/rDA reactions. The procedure is based on anthracene templates with chiral substituents for the generation of small-molecule building blocks with high enantioselectivity. The catalytic DA cycloaddition of 9-methylanthracene **1** to methacrolein **2** using Corey's cationic oxazaborolidine **3** resulted in the regioselective formation of the aldehyde–adduct intermediate (ratio 92:8). Reaction of the major cycloadduct with various Grignard reagents (Scheme 1) led to alcohols **4** in yields of 59–87%. As the diastereoselectivity of this reaction could not be fully controlled, compounds **4** needed purification by column chromatography or recrystallization. The final diastereomeric ratio (*dr*) was high (from 84:16 to 98:2). FVP of the cycloadducts furnished the secondary allylic alcohols **5** in excellent yields and high *ee* (Table 1).[19]



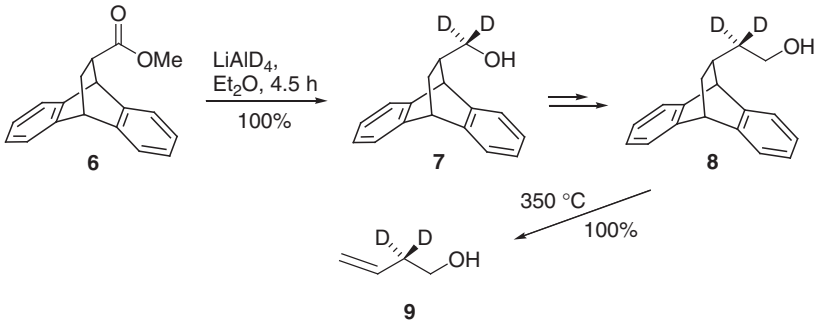
Scheme 1

Table 1 Cycloreversion of adduct **4** by FVP (Scheme 1)

No.	*R*	*Yield (%)*	ee
1	Me	93	82
2	Et	94	76
3	Ph	99	86
4	CH_2=CH	94	63
5	CH≡C	94	82

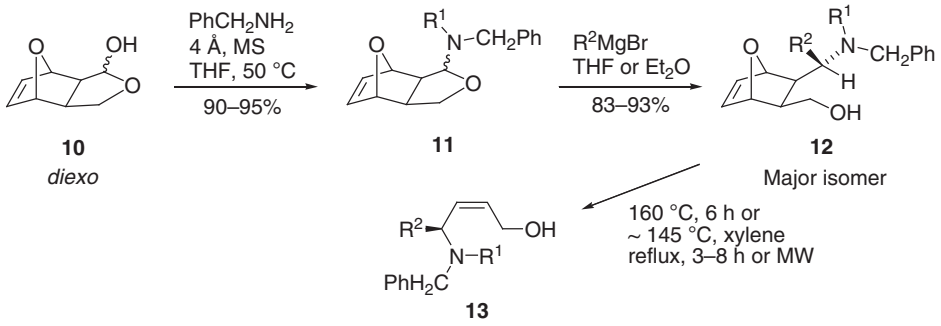
By application of the anthracene template, labeled 3,3-dideuterobut-1-en-4-ol **9** was prepared from the anthracene–methylacrylate DA adduct **6**. Lithium aluminum deuteride reduction of **6** yielded the hydroxymethyl derivative **7**, which was converted to the bromide and then to the Grignard reagent, which was reacted with methyl chloroformate. Reduction of the ester

gave the hydroxymethyl derivative **8** quantitatively, which was cleaved by FVP to yield the labeled unsaturated primary alcohol **9** Scheme 2.[20]



Scheme 2

The additions of organomagnesium bromides to the C=N bond of masked chiral imines were found to be highly diastereoselective, and this allowed the preparation of unsaturated amino alcohols. The reactions of lactols **10** with an excess of benzyl- or dibenzylamine afforded hemiaminals **11**, which reacted with the Grignard reagents to give oxabicyclic amino alcohols **12** after hydrolysis with excellent stereoselectivity (Scheme 3). Simple rDA reactions of **12** afforded substituted unsaturated amino alcohols **13** on heating of the neat compound or refluxing of a solution in xylene.[21] The microwave (MW)-assisted thermolysis of 7-oxabicyclo[2.2.1]hept-2-en-1,4-amino alcohols **12** resulted quantitatively in the desired unsaturated derivatives **13** within a very short time (10–15 min) and at relatively low temperature s (120–140 °C) (Table 2). Conventional heating at similar temperatures required longer reaction times (3–10 h). Thus, MW activation at 300 W under solvent-free conditions proved best for the rDA reaction. For monobenzylated amino alcohols, this was the only method that proceeded fast and cleanly. All products exhibited similarities in their hydrogen-1 nuclear magnetic resonance spectroscopy (^{1}H-NMR) spectra; the values of the coupling constants between the vicinal ethylenic protons were characteristic of *Z*-olefins.[22]

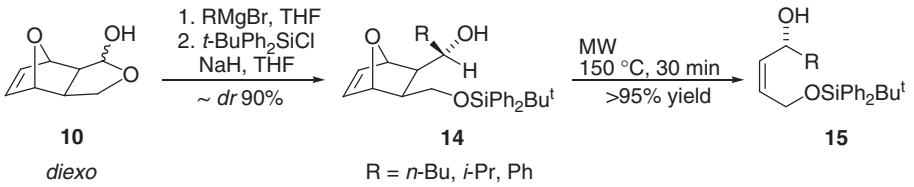


Scheme 3

Table 2 Preparation of unsaturated amino alcohols **13** by cycloreversion (Scheme 3)

No.	R^1	R^2	*rDA conditions*	*Yield of* ***13*** *(%)*
1	H	*n*-Bu	Neat, 160 °C, 6 h	74
2	H	CH_2=CH	Neat, 160 °C, 6 h	80
3	$PhCH_2$	*n*-Bu	Xylene, 145 °C, 8 h	85
4	$PhCH_2$	CH_2=CH	Xylene, 145 °C, 2.5 h	95
5	$PhCH_2$	Me	Xylene, 145 °C, 4 h	85
6	H	*n*-Bu	MW, 120 °C, 15 min	≥98
7	$PhCH_2$	*n*-Bu	MW, 140 °C, 10 min	≥98

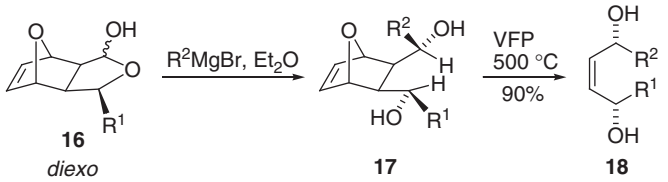
Starting from racemic lactol **10**, the efficient syntheses and rearrangements of (*Z*)-allylic trichloroacetimidates have been reported. Treatment of *diexo* **10** with different Grignard reagents and protection of the resulting primary hydroxy group with *t*-butyldiphenylchlorosilane, followed by MW-assisted rDA, led to the monoprotected allylic diols **15** (Scheme 4).[23]



Scheme 4

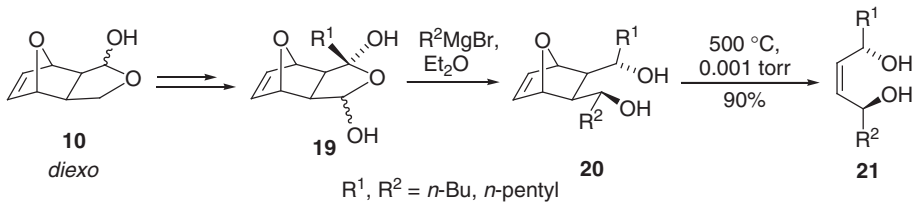
5.12.2.2 Unsaturated 1,4-Diols

Nucleophilic Grignard addition to the tricyclic lactol **16** or its diastereoisomer led to allylic diols **18** with very high selectivity via reductive ring opening and then pyrolysis (Scheme 5). From scalemic lactol **16**, three of the four possible diastereoisomeric *syn* or *anti* 1,4-diols were obtained. This example of remote asymmetric induction is evident from the synthesis of optically pure (2*R*,5*R*)-2,5-hexanediol and (3*S*,6*R*)-4-decene-3,6-diol **18** (R^1, R^2 = Et, *n*-Bu).[24]



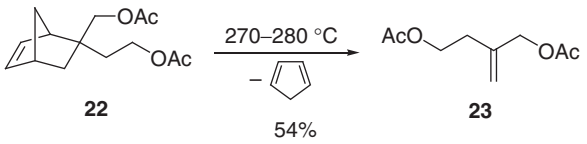
Scheme 5

Bicyclic 1,4-diols **20** were prepared from lactol **10** through Grignard reactions followed by oxidation, recyclization to the lactols and repeated Grignard processes (Scheme 6). Addition of alkylmagnesium bromides to lactol **10** led to bicyclic monoalkylated diols; oxidation of the primary alcohol with tetrapropylammonium perruthenate as selective and mild oxidizing agent in the presence of 4-methylmorpholine *N*-oxide gave lactols **19**, which reacted with another Grignard reagent to afford dihydroxyalkyl-7-oxabicyclo[2.2.1]hept-5-enes **20** with good diastereoselectivity. Under FVP conditions, chiral (*Z*)-alkene-1,4-diols **21** were obtained from these substrates.[25]



Scheme 6

One of the key reactions of a recent synthesis of alternaric acid[26,27] was the Julia olefination of a tertiary aldehyde and a phenylsulfone containing an *exo*-methylene motif. The diester precursor **23** required for the preparation of the latter synthon was indirectly obtained by rDA reaction from 2-norbornenyl-1,4-butanediol-1,4-diacetate **22** (equation 5).



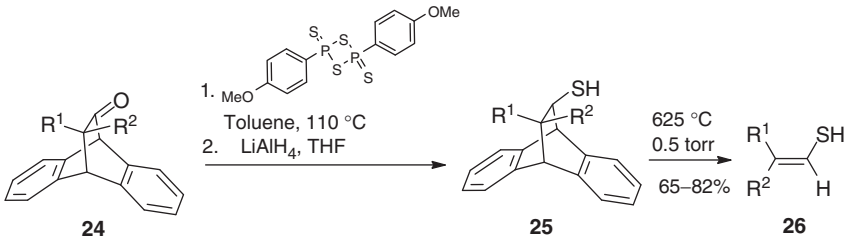
(5)

From suitable 9,10-dihydro-9,10-ethanoanthracene-*cis*-11,12-diols, a number of (*Z*)-1,2-disubstituted ethenes, including derivatives with two different substituents, have been prepared by rDA reactions. However, attempts to prepare 1,3,2-dioxasiloles bearing substituents only on the Si atom failed and resulted in dimers containing the ten-membered ring system (*Z*,*Z*)-2,2,7,7-tetraalkyl-1,3,6,8-tetraoxa-2,7-disilacyclodeca-4,9-diene. These compounds were formed diastereoselectively with regard to the double bonds.[28]

Five (*Z*)-2-alkoxyvinyl (isopropyl, butyl, hexyl, decyl, and 10-undecenyl) acetates were prepared by application of an rDA technique. Through the use of cyclopentadiene instead of anthracene in DA reactions, the synthesis of these typical detergents with long alkyl residues could be markedly improved. Amphiphilic polymers were obtained by cationic homopolymerization of these long-chain derivatives.[29]

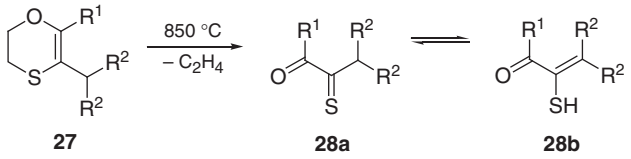
5.12.2.3 α,β-Enethiols

On treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulfide], 11-oxo-9,10-dihydro-9,10-ethanoanthracenes **24** resulted in thioxo derivatives, which were reduced to thiols **25** using $LiAlH_4$. Compounds **25** underwent cycloreversion to give enethiols **26** on application of an FVP technique (Scheme 7).[30]



Scheme 7

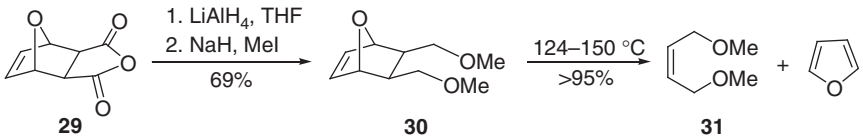
Retroene reactions of 2,3-dihydro-1,4-oxathiins **27** or FVP of α-allylthio-carbonyl compounds have been used to synthetize enethiolizable α-oxothiones at high temperatures (equation 6) by the extrusion of ethylene. In the course of the cleavage, α-thioxo-β-oxo alkanes **28a** are formed, which are in equilibrium with the enethiol forms **28b**.[31]



(6)

5.12.2.4 Unsaturated Mono- and Polyethers

In experimental and theoretical studies of rDA reactions, 5,6-disubstituted-7-oxabicyclo[2.2.1]hept-2-ene derivatives have recently been applied.[32] The corresponding cyclic anhydride, methoxy ether or cyclic ether were submitted to thermal analysis to measure the kinetics of cycloreversion at different temperatures. The classical DA *diexo*-anhydride adduct **29** was methylated in two steps using an excess (2.5 equivalents) of MeI after reduction (Scheme 8). Thermogravimetric analysis (TGA) under a nitrogen atmosphere revealed rapid and complete decomposition, and thermolysis of **30** furnished the expected (*Z*)- *cis*-1,4-dimethoxy-2-butene **31**.



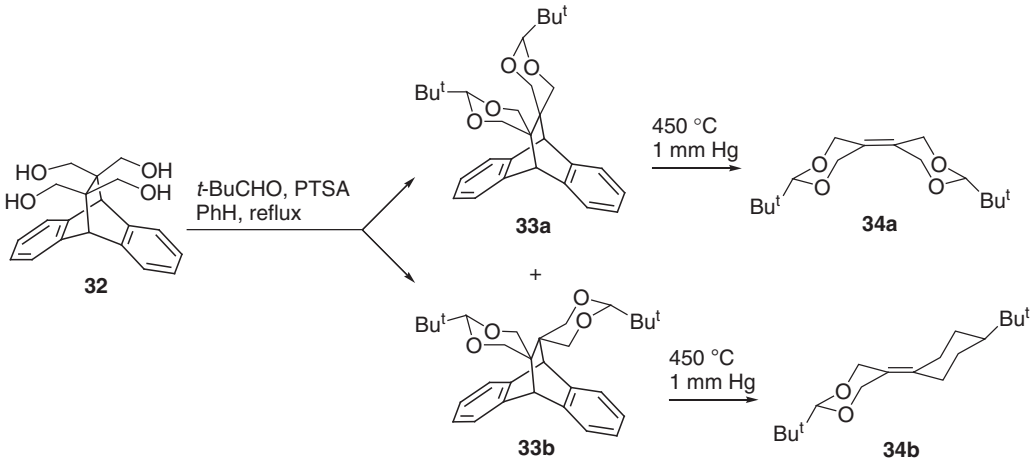
Scheme 8

5.12.2.5 Alkenediol Acetals

The stereofacial selectivity of addition reactions to the C=C bond of methylenecyclohexanes and methylenedioxanes is influenced by a substituent in a conformation fixed with respect to the double bond. Hence, 5-methylene-1,3-dioxanes containing a conformationally locked Ph or *t*-Bu group have been applied in theoretical and experimental studies.[33] One of these model compounds, anthracene-protected tetrole **32**, was condensed with pivalaldehyde by acid catalysis to give a mixture of two separable isomeric compounds. Sublimation of the bisacetals **33a,b** thus obtained afforded the stereoisomerically pure unsaturated *cis*- and *trans*-acetals **34a,b** (Scheme 9).

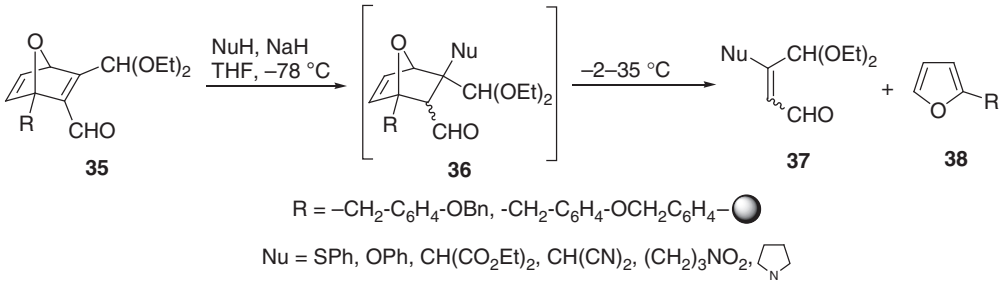
5.12.2.6 α,β-Unsaturated Aldehydes and Ketones

2- and 3-Benzylated soluble furans have been subjected to a sequence involving a DA reaction with an α,β-acetylenic carbonyl compound and a Michael addition, followed by an rDA process to yield a small library of α,β-unsaturated aldehydes.[34,35] Application of a resin with a dienic moiety immobilezed the unsaturated compounds by DA; after transformation of the



Scheme 9

cycloadduct, rDA cleavage released the modified unsaturated carbonyl products with regeneration of the starting resin under mild conditions. Functionalzation of α,β-ethylenic aldehydes **35** was attained through Michael additions with thiophenol, phenol, pyrrolidine, diethyl malonate, etc. An excess of the nucleophile and a catalytic amount (0.3 equivalent) of NaH were used (Scheme 10, Table 3). At room temperature, the reaction resulted in furans **38** and aldehydes **37** in variable ratios of the *E* and *Z* isomers. When a 2-furyl resin was used in a solid-supported procedure, only one regioisomer was obtained in the DA reaction, and a higher diastereoselectivity was observed both in the Michael addition and in the yields of the olefinic products.



Scheme 10

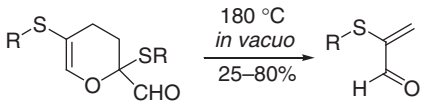
Table 3 Reactions of **35** with Michael donors and subsequent rDA conditions (Scheme 10)

No.	*Nucleophile (NuH) (3 equivalents)*	*Temperature of rDA*	*Product **37** Z/E ratio*	*Yield (%)*
1	PhSH	– 2–20 °C	75/25	88
2	PhOH	20 °C	35/65	31
3		35 °C	0/100	40[a]
4	$CH_2(CO_2Et)_2$	0–35 °C	38/62	25[b]
5	$CH_2(CN)_2$	20 °C	–	–
6		35 °C	100/0	51[c]

[a]With polymer-bound DA adduct.
[b]On heating at 55 °C, the *Z*/*E* ratio was 41/59.
[c]Instead of NaH, benzyltrimethylammoniumhydroxide (Triton® B) was used.

Retrodiene decomposition of 2,5-dialkylthio-3,4-dihydro-2*H*-pyran-2-carbaldehydes **39** as cyclodimers resulted in α-alkylthioacrolein monomers **40** by thermal cleavage[36] (equation 7). On heating to 175–200 °C, the diethylacetal derivative of **39** underwent the rDA reaction and gave 2-butylsulfanylprop-2-enal (R=*n*-Bu) and the corresponding acetal. Similar partial

decomposition was observed during the gas chromatography–mass spectrometry analysis (injector temperature 250 °C and oven temperature 280 °C), when the diethylacetal of **39** was formed.[37]

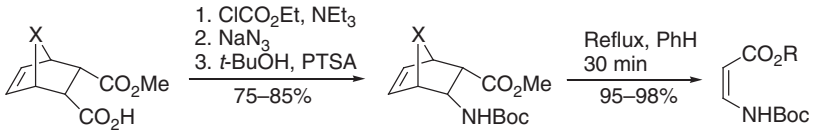


39 **40** (7)

R = Et, *n*-Pr, *n*-Bu, *c*-hexyl

5.12.2.7 α,β-Unsaturated Esters and β-Aminoesters

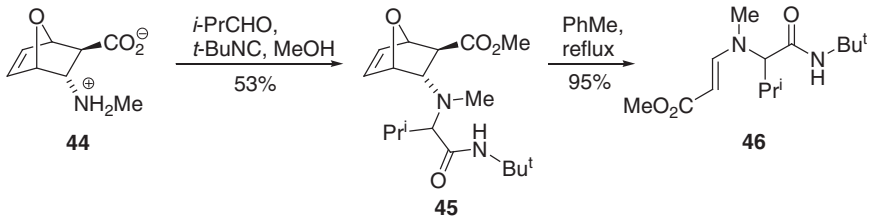
β-Aminoacrolein itself is unstable, whereas its *N*-substituted derivatives and esters are stable. β-Aminoacrolein cannot be prepared directly from *diendo* or *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids in an rDA reaction. The thermolysis of *N*-protected oxa- or methylene-bridged bicyclic β-amino acids was developed by Akssira et al.[38] Starting from dicarboxylic monoesters **41,** through the protected aminoacid esters **42**, *N*-*t*-butyloxycarbonyl β-aminoacids **43** were prepared via the Curtius rearrangement followed by cycloreversion. Saponification of the aminoacid ester **43** (R=Me) and acidification gave the free unsaturated acid (R=H) (Scheme 11).



41 *diendo, diexo* **42** **43**

Scheme 11

By modification of a known procedure, a multicomponent reaction was devised that involved conversion of the unsaturated bicyclic *trans*-β-amino acid **44** to the sole diastereoisomer **45**, which was subjected to an rDA process to furnish compound **46** (Scheme 12). This method was successfully applied with chiral auxiliaries and the reverse DA reactions proceeded under very mild conditions.[39]



44 **45** **46**

Scheme 12

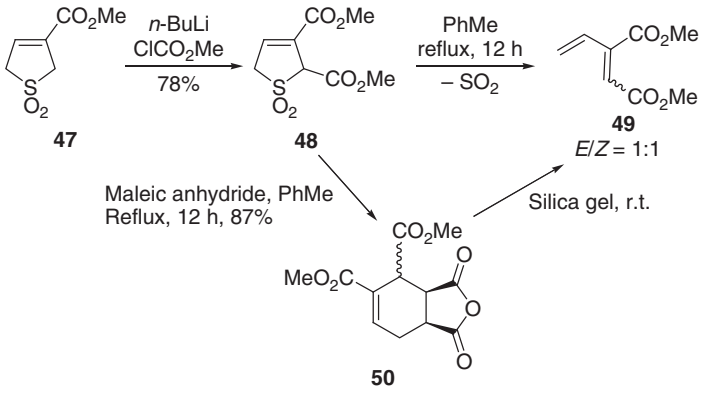
5.12.3 Preparation of Polysaturated Hydrocarbons and Arenes

5.12.3.1 Acyclic 1,3-Dienes

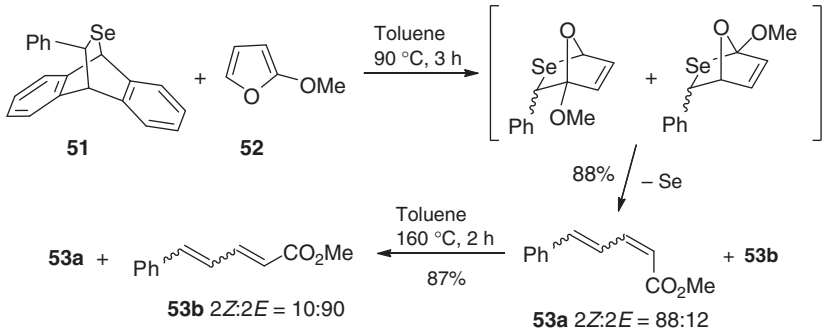
Treatment of sulfolene monoester **47** with 2 equivalents of *n*-BuLi led to the dianion, which was acylated with methyl chloroformate to yield diester **48**. On heating, a sigmatropic elimination of SO_2 occurred to afford stable but volatile 1,3-dienes **49** as a mixture of *E* and *Z* isomers. When **48** was refluxed with MA, two isomeric cycloadducts **50** were formed in a ratio of approximately 1:1 (Scheme 13). By chromatographic purification on a silica gel column, anhydride **50** underwent rDA cleavage, which gave back the MA and resulted in dimethylpenta-2,4-dienoate **49**.[40]

The selenoaldehydes regenerated in thermal rDA reactions of anthracene cycloadducts under neutral conditions reacted with 2-methoxyfuran **52** to give methyl penta-2,4-dienoates.[41] Thus, the reaction of compound **51** and 2-methoxyfuran **52** led to methyl 5-phenylpenta-2,4-dienoate **53a** (as a mixture of four geometrical isomers) and Se (Scheme 14).

An increase in the temperature influenced the ratio of the 2*Z* and 2*E* isomers of the resulting dienes, whereas the substituents on the aromatic ring did not affect the isomer ratio. A sulfur analog was subjected to a similar reaction: when the

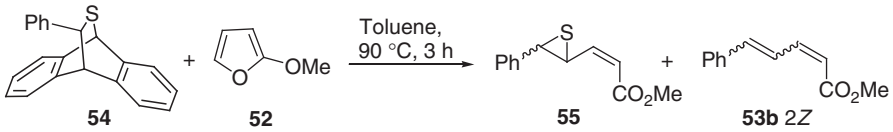


Scheme 13



Scheme 14

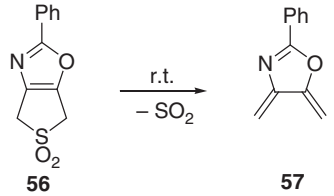
thioaldehyde–anthracene-[4 + 2] cycloadduct **54** was heated with 2-methoxyfuran, the thiirane derivative **55** was formed and isolated as a mixture of *cis* and *trans* isomers together with 2*Z*-penta-2,4-dienoate **53b** (equation 8).



(8)

5.12.3.2 Exo- and Endocyclic 1,3-Dienes

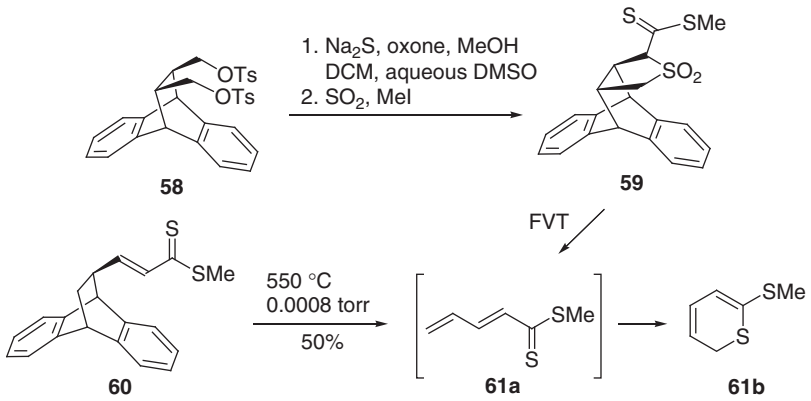
The thermal reactivity was studied and theoretical considerations were taken into account in the process by which 2-phenyloxazolo-3-sulfolene **56** afforded the exocyclic 1,3-diene 4,5-dimethylidene-2-phenyl-4,5-dihydro-1,3-oxazole **57** by extrusion of sulfur dioxide (equation 9).[42]



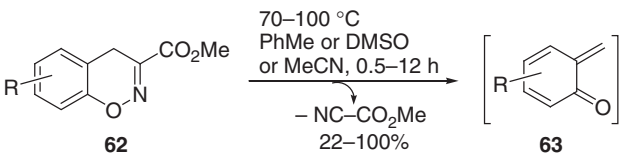
(9)

Methyl penta-2,4-dienedithioate **61a** was generated by flash vacuum thermolysis of the ethanoanthracene precursors **59** or **60** via different routes (Scheme 15). One of the key intermediates, sulfolene **59**, was obtained from the 1,4-diol ditosylate **58** in a multistep procedure. However, the acyclic 1,3-diene **61a** proved to be unstable and underwent spontaneous transformation to the much more stable endocyclic diene **61b**.[43]

When heated at different temperatures, 4*H*-1,2-benzoxazines **62** with various substituents on the benzo-ring afforded *o*-quinone methides through an rDA process (equation 10). The *o*-quinone methides **63** formed are highly reactive short-lived intermediates and underwent immediate DA reactions with dienophiles *in situ* to yield phenol and chromane derivatives.[44]



Scheme 15

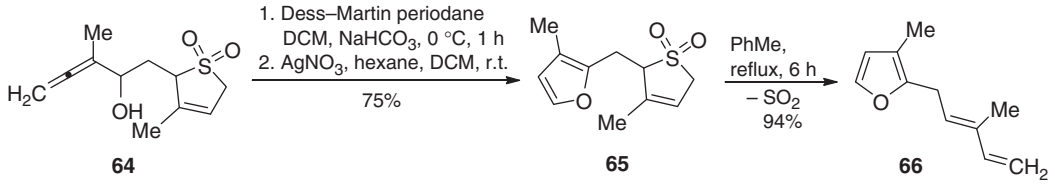


(10)

R = H, Me, F, Cl, Br, CF_3, CN, NO_2

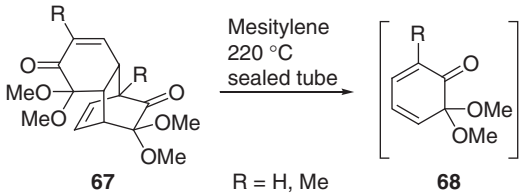
In an analogous process, 3-methyl 4*H*-1,2-benzoxazine **62** (R = H) underwent thermolysis when boiled in $CHCl_3$ and gave the tetracyclic 12a-methyl-7*H*,12a*H*,13*H*-[1,3]benzoxazino[3,2-*b*][1,2]benzoxazine. Rearrangement to the isomeric 5a-methyl-5a*H*,11*H*,13*H*-[1,3]benzoxazino[2,3-*b*][1,3]benzoxazine took place on prolonged heating (~17 h), and *o*-quinonemethide was also generated by thermolysis; the latter was trapped by ethyl vinyl ether to yield 2-ethoxy dihydrobenzopyran.[45]

A straightforward synthesis of an unusual bis(acyclic–cyclic) 1,3-diene from an allenic alcohol was achieved by Winkler et al.[46] The Dess–Martin oxidation of **64** to the corresponding ketone, followed by furan formation by Ag^+-promoted intramolecular cyclization led to 2-furanylsulfolene **65**. rDA fragmentation of this compound in the presence of $NaHCO_3$ (with the loss of SO_2) gave bisdiene **66** (Scheme 16).



Scheme 16

Dimers **67** were prepared by the self-dimerization of cyclohexa-2,4-dienones through *endo* [4 + 2] cycloaddition. However, this reaction was reversible at higher temperatures leading to the *in-situ* generation of dienes **68** (equation 11). These compounds, which proved to be unstable intermediates, could be masked very successfully with *o*-benzoquinones for further DA reactions with dienophiles.[47]



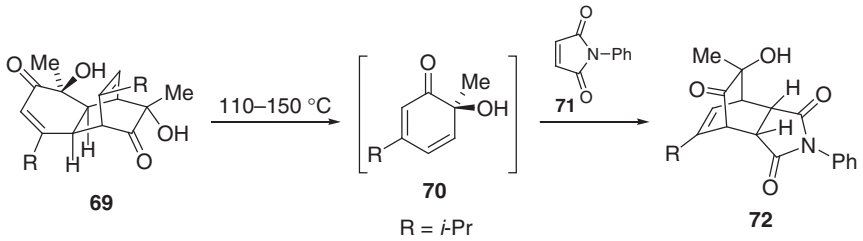
(11)

Tandem rDA/DA reactions of dimers derived from *o*-quinol or masked *o*-benzoquinone proceed well, for example, between the readily accessible dimer (–)-**69** and *N*-phenylmaleimide **71** as dienophile, in a thermolytic process (Table 4). Although the reactions in toluene and chlorobenzene generated the desired cycloadducts **72** in moderate to good conversions after 12 h, the

reactions in mesitylene at 150 °C gave both excellent conversions and yields of the isolated cycloadduct **72** after 1.5 h.[48] A concise total synthesis, which involves an rDA/DA cascade of dimer **69**, was achieved for both enantiomers of chamaecypanone C, a novel microtubule inhibitor.

Table 4 Tandem thermolytic rDA/DA reactions of dimer **69** (Scheme 17)

No.	*Solvent*	*T* (°C)	*Reaction time (h)*	*Conversion (%)*
1	Toluene	110	12	74
2	Chlorobenzene	130	12	92
3	Mesitylene	150	1.5	>99

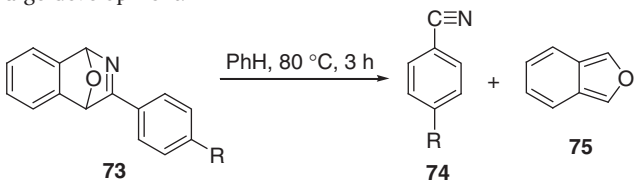


Scheme 17

Various examples have been detailed in the review articles which survey these domino rDA/DA reactions and report alternative preparations of masked *o*-benzoquinones as key synthons.[49–53]

5.12.3.3 Benzene and Other Aromatic Ring Systems

The rDA expulsion of benzonitriles **74** from 1,4-dihydro-1,4-epoxy-3-phenylisoquinolines **73** led to the formation of isobenzofuran **75** when the adducts were heated (equation 12). The sequence proved suitable for the preparation of isobenzofuran, which could be utilized *in situ* or isolated as a solution for subsequent applications. Benzyne cycloadducts have also been prepared from 4-(4-nitrophenyl)- and 4-(4-methoxyphenyl)oxazoles, in order to assess the effects of the remote substituents in rDA reactions. The first-order rate constants were determined at three different temperatures in the range of 40–70 °C. The order of reactivity was found to be *p*-NO_2 > H > *p*-OMe; the substituent effects were small, with a factor of <4 separating the rate for *p*-NO_2 from that for *p*-OMe. All three substrates exhibited small ΔS values. The expulsion of the nitrile was presumed to occur in a concerted reaction with little charge development.[54]



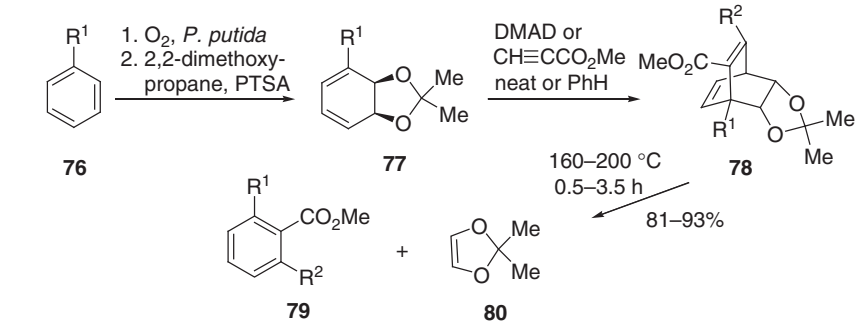
(12)

In a world patent, Williams reported an rDA method for the preparation of polysubstituted benzene derivatives. Starting from cycloadducts of type **78** endowed with either hydroxy or acetal groups, methyl benzoates or dimethyl phthalates were formed with the concomitant elimination of dioxolene species.[55] Adducts **78** can be obtained by DA cycloaddition of an acetylenic dienophile to cyclohexadiene-*cis*-1,2-ketaldiols **77**; the required cyclohexadienes may be prepared from arenes by biological oxidation of *Pseudomonas putida*. The thermolysis of **78** was achieved under mild conditions and gave the substituted arenes **79** (Scheme 18).

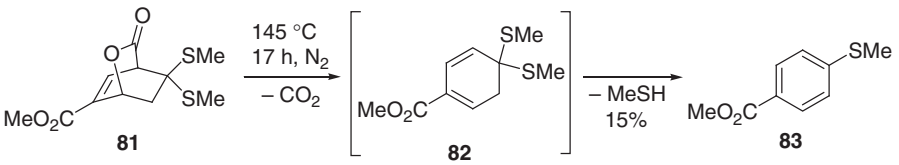
With diethyl acetylenedicarboxylate and ethyl propiolate, similar reactions of substituted 1,3-cyclohexadienes took place within 20 min on MW irradiation or in 1–9.5 h on conventional refluxing in toluene, which resulted in analogous formations of polysubstituted benzenes. The cycloadducts underwent elimination of ethylene and gave benzene derivatives as sole and pure products. MW procedures were found to be more effective and rapid than classical heating for these one-step DA/rDA reactions.[56]

The oxygen-bridged DA adduct **81** was prepared by the reaction of methyl coumalate with bis(methylthio)ethene. On heating, the adduct decomposed as monitored by ^{1}H-NMR. Among the other products, the substituted benzene derivative **83** was formed by the loss of CO_2 and further elimination of methanethiol from the intermediate cyclohexadiene **82** (Scheme 19).[57]

On conventional heating with acetylenic dienophiles **85** under MW-promoted conditions, the irreversible DA cycloaddition of 3-carbomethoxypyrone **84** improved the synthesis of substituted benzoates (Scheme 20).[58] The reaction of **84** with ethyl

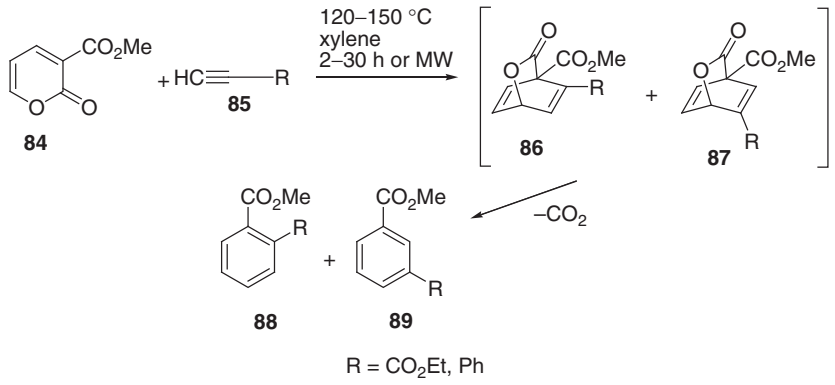


Scheme 18



Scheme 19

propiolate (R = CO_2Et) proceeded with a product ratio **88**/**89** = 65/35 in 50% yield (Table 5). With phenylacetylene (R = Ph) **85** as dienophile, the reaction also gave a mixture with poor selectivity (**88**/**89** = 65/35) on extended heating in toluene at 250 °C (in a closed vessel). Solvent-free MW-assisted conditions were found to be best for the rDA aromatization processes. These reactions were generally irreversible because of the expulsion of CO_2 from the adducts.

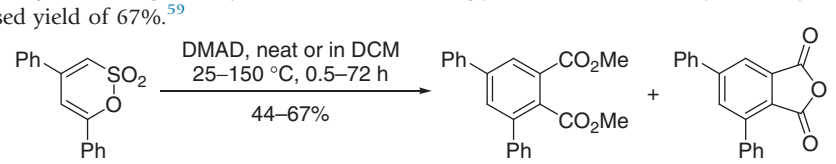


Scheme 20

Table 5 Preparation of methyl benzoates **88** and **89** (Scheme 20)

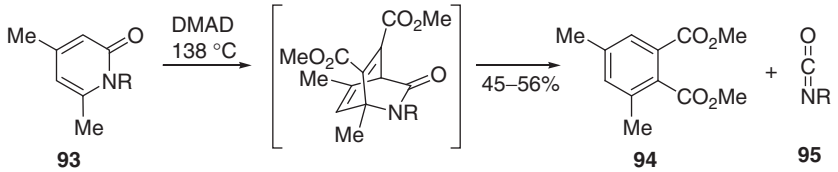
No.	*R*	*Heat*	*Solvent*	*T (°C)*	*Time (h)*	*Yield (%)*	*Ratio **88/89***
1	CO_2Et	Reflux	Xylene	140	30	50	20/80
2	CO_2Et	MW	Xylene	120	2	7	28/72
3	CO_2Et	MW	–	120	2	80	31/69
4	Ph	Reflux	Toluene	250	24	60	65/35
5	Ph	Conventional	–	150	3	19	100/0
6	Ph	MW	–	150	3	64	100/0

When MW irradiation (100 W) was applied with an excess (5 or 8 equivalents) of dimethyl acetylenedicarboxylate (DMAD), the domino DA/rDA reaction of 1,3-dienic δ-sultone **90** resulted in the formation of phthalic diester **91** and the anhydride **92** in a ratio of ~3:1 (equation 13). The use of conventional heating in a solvent-free medium led to a **91**/**92** ratio of 3:2. In DCM at a high pressure (1300 MPa), the analogous DA/rDA reactions surprisingly produced the diphenyl dimethyl phthalate **91** as the sole product in an increased yield of 67%.[59]



90 **91** **92** (13)

The release of isocyanates **95** from the DA adducts of pyridones **93** can be used to generate highly substituted aromatic compounds **94** (Scheme 21). By trapping or isolation, the isocyanates may be separated from the product.[60]

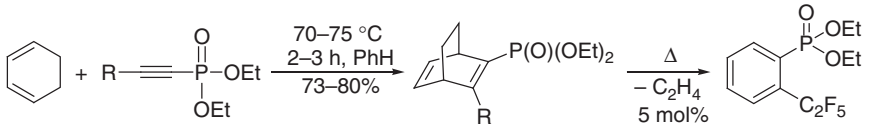


93 **94** **95**

R = Me, Et, *n*-Pr

Scheme 21

The reactions of perfluoroacetylenephosphonates **97** with cyclohexa-1,3-diene **96** on heating furnished the bicyclic adducts **98** as fairly stable fluids in yields of 73–80% (Scheme 22). However, when R = C_2F_5, the product underwent an rDA reaction during distillation, with the splitting-off of ethylene and the formation of the aromatic diethyl 2-(pentafluoroethyl)phenylphosphonate **99** together with traces of isomeric cyclohexa-2,4- and -2,6-dienylperfluoroalkylphosphonates as confirmed by ^{31}P-, ^{19}F-, and ^{1}H-NMR spectroscopy.[61]

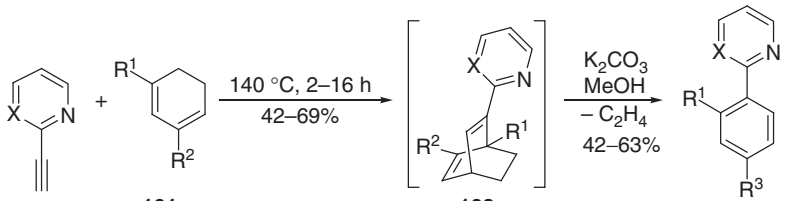


96 **97** **98** **99**

R = CF_3, C_2F_5

Scheme 22

Domino [4 + 2]/retro [4 + 2] cycloadditions of alkynyl-substituted pyridines and pyrimidines **100** with electron-rich dienes **101** afforded pyridyl- and pyrimidyl-substituted benzenes **103**. The reactions proceeded through the formation of bridged cycloadducts **102**, with the subsequent thermal extrusion of ethylene in a pressure tube (Scheme 23).[62]

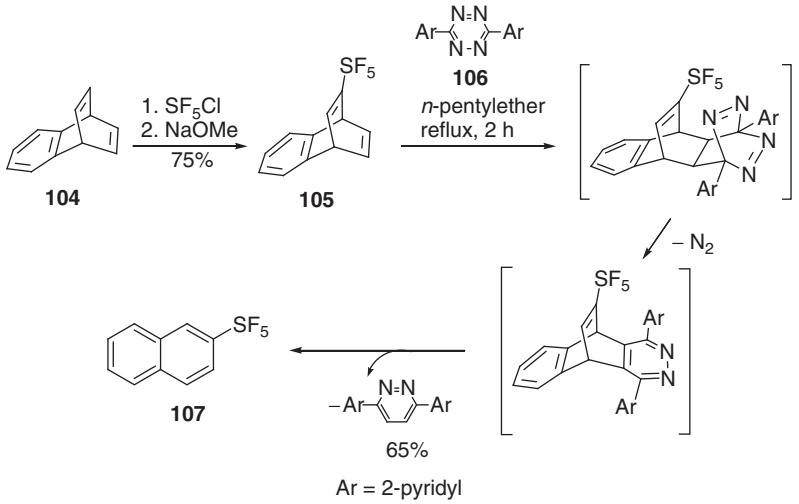


100 **101** **102** **103**

X = CH, N; R^1 = OMe, OEt; R^2 = H, OTMS; R^3 = H, OH

Scheme 23

When 2-pentafluorosulfanylbenzobarralene **105** was heated with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine **106,** the reaction involved elimination of the ethylene bridge, which prevented cycloaddition and retro reaction sequences and yielded 2-pentafluorothionaphthalene **107** (Scheme 24). Cycloadduct **105** was prepared by the addition of SF_5Cl to benzobarralene, followed by the base-promoted elimination of HCl.[63] The direct thermal rDA of the adduct **105** was unsuccessful, because it is sufficiently stable between 250 and 350 °C.

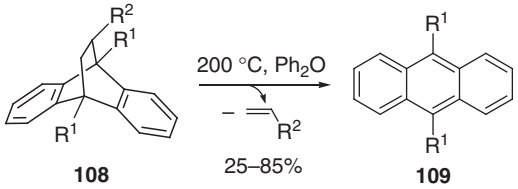


Scheme 24

The application of MW-mediated heating (90–120 W, max. 301–421 °C) of various anthracene DA adducts supported on graphite resulted in the recovery of the starting anthracene and dienophile (MA, fumaric diester, or 1,4-benzoquinone) in 56–80% yields.[64]

The kinetics, rate constants, enthalpies, entropies, and volumes of activation for the rDA reaction of the 9-chloroanthracene–tetracyanoethene cycloadduct were determined in different solvents (e.g., MeCN, DCE, benzene, toluene, or EtOAc). Complete decomposition was reached only in the presence of an appropriate reagent, used for irreversible trapping of the 9-chloroanthracene. It was found that cyclopentadiene combined rapidly and irreversibly with tetracyanoethene and gave more stable adducts.[65]

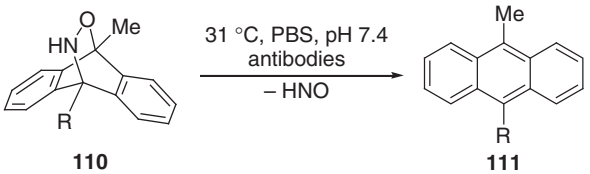
To accelerate the rDA splitting of other anthracene cycloadducts or adducts, compounds containing distal siloxy substituents were studied; the reactions were carried out in Ph_2O (equation 14). A comparison of the rate constants indicated a clean first-order kinetic process. On linear least-squares analyses, a 19-fold rate increase was observed for the siloxy compounds relative to other substituted derivatives.[66]



(14)

R^1 = H, Me, OSiMe; R^2 = CN, CO_2Et

To accelerate the rDA process in aqueous phosphate-buffered saline medium, nitroxyl synthase antibodies (10F11, 9D9, and 27C5), which catalyze the release of nitroxyl (HNO), were gained from the tricyclic prodrugs **110** (equation 15). The reaction led to 9-methyl-10-carboxy derivatives of anthracene **111**. Theoretical and experimental results relating to the catalytic effect of the antibodies were reported by Hugot et al. and Leach et al., who employed programs to calculate the docking modes of molecules into the protein-binding sites.[67,68]



(15)

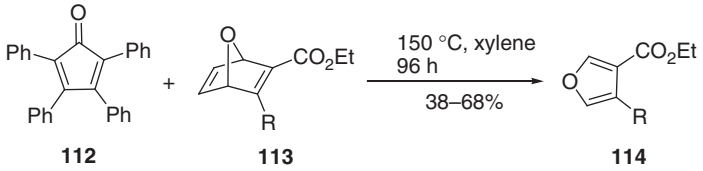
R = H, $(CH_2)_2CO_2H$, $(CH_2)_2CONH(CH_2)_2NH_2$, $CONH(CH_2)_2CO_2H$

Photo rDA reactions of a variety of [4 + 2] anthracene and tetracene cycloadducts have been studied extensively. The experimental results demonstrated that the photoreactivity depends on the electron-donating ability of the diene and the electron-withdrawing ability of the dienophile. The mechanism was investigated by means of fluorescence spectroscopy through trapping

of the reaction intermediate and measurement of the time-resolved absorption. For the photoreactivity (quantum yield), a wavelength of 254 nm was chosen, at which the polyaromatic ring systems absorb efficiently.[69]

5.12.3.4 Furan as a Heteroaromatic 1,3-Diene

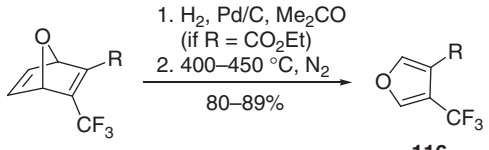
By cycloreversion, 3-perfluoroalkyl-4-ethoxycarbonylfurans **114** were prepared from 2-perfluoroalkyl-3-ethoxycarbonyl-7-oxabicyclo[2.2.1]hepta-2,5-dienes **113** with tetraphenylcyclopentadienone **112** as forceful diene (equation 16). This diene-exchange process was carried out in xylene.[70]



112 **113** **114**

R = CF_3, C_5F_9, C_7F_{15} (16)

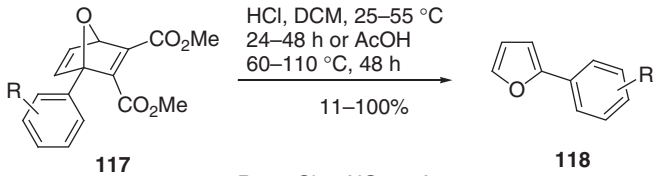
Thermolysis of 2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-dienes **115** yielded 3,4-bis(trifluoromethyl)furans **116** (R=CF_3) through the splitting-off of acetylene.[71] However, when R=CO_2Et, regioselective hydrogenation of adducts **116** was necessary in order to achieve complete pyrolysis at 400 °C (equation 17).[72]



115 **116**

R = CF_3, CO_2Et (17)

On reaction with Lewis acids (e.g., $ZnBr_2$ or ZnI_2), 7-oxabicyclo[2.2.1]heptadienes **117** could be converted easily to phenols or 6-hydroxyfulvenes, which, depending on their nature, reacted with Brønsted acids to give rearranged products. In the presence of gaseous HCl or glacial $MeCO_2H$, unique acid-promoted rDA processes were observed, leading to 2-phenylfurans **118** almost exclusively (equation 18, Table 6).[73]



117 **118**

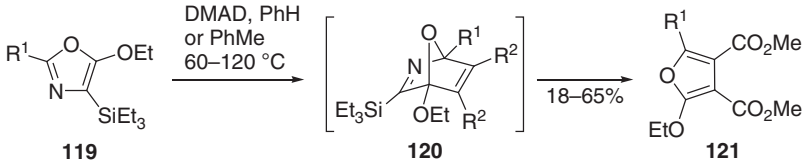
R = 2-Cl, 4-NO_2, 4-Ac (18)

Table 6 Acid-catalyzed rDA transformation of 7-oxanorbornenes **117** (R=2-Cl) (equation 18)

No.	*Acid*	*Solvent*	*T (°C)*	*Time (h)*	*Yield (%)*
1	HCl (g)	DCM	25	48	100
2	HCl (aqueous)	DCM	55	24	50
3	AcOH	–	60	48	60
4	AcOH	–	90	48	75
5	AcOH	–	110	48	82

With electron-poor alkynes (e.g., DMAD), silylated oxazoles **119** underwent intermolecular and intramolecular DA/rDA reactions to generate polysubstituted furans **121** through unstable bicyclic [4 + 2] adducts **120** (Scheme 25). From these, nitriles were eliminated under mild conditions, the process resulting in the formation of furan derivatives **121** (Table 7). Similar reactions with other oxazoles (R^1=2-furanyl, NMe_2) were completely unsuccessful, possibly because of the electron-donating effect of these substituents; the yield of the methyl derivative was also poor, whereas with electron-withdrawing groups (e.g., Ph or CO_2Me) the yield increased. With DMAD, 2-furanyloxazole **119** gave a 1:1 cycloadduct, because the furan ring is more electron-rich than

the oxazole.[74] The highly electron-rich dimethylaminooxazole underwent a rapid reaction to furnish products that could not be isolated.



Scheme 25

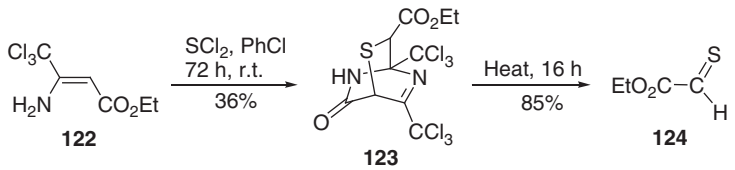
Table 7 Preparation of substituted furans **121** from cycloadducts **120** (Scheme 25)

No.	*R^1*	*T (°C)*	*Solvent*	*Yield (%)*
1	Ph	100	PhMe	65
2	Me	60	PhH	18
3	2-Thiophenyl	120	PhMe	52
4	CO_2Me	120	PhMe	62
5	2-Furanyl	110	PhMe	0

5.12.4 Formation of Small Molecules Containing C=X or X=Y Heteroatom Bonds

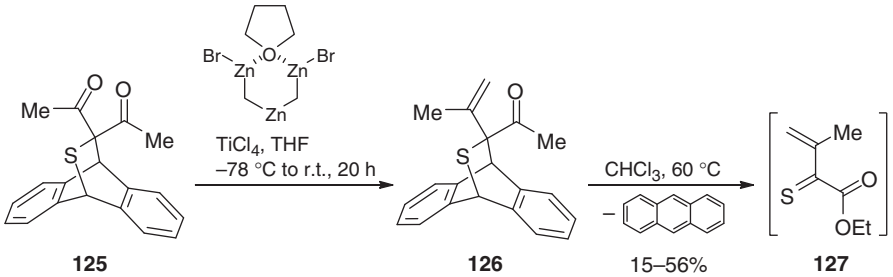
5.12.4.1 Unsaturated Thioaldehydes, Thioketones, and α-Thioxoesters

Lee et al. trapped ethyl thioxoacetate **124**, prepared by rDA fragmentation of the bicyclic precursor **123**, which in turn was obtained by a fascinating reaction of aminocrotonate **122** with SCl_2 (Scheme 26). For the trapping, 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene were used.[75]



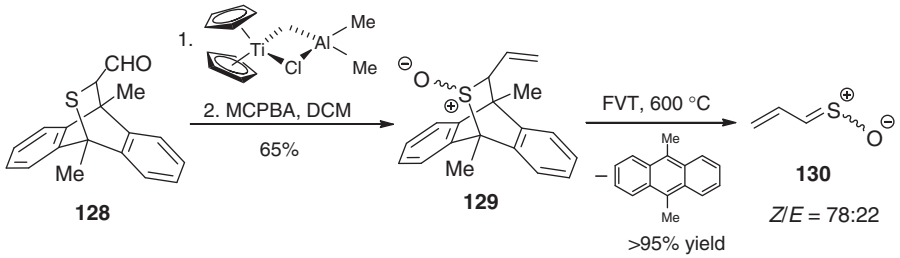
Scheme 26

For the transformation of the oxo group to a methylene, the anthracene–α,α′-dioxothioketone cycloadduct **125** was treated with the Nysted reagent and a Ti compound. The resulting product **126** underwent thermal decomposition via rDA fragmentation to give the unstable α,β-unsaturated-α′-oxo derivative **127** (Scheme 27). This thioketone reacted as heterodiene or heterodienophile to furnish 5,6-dihydro-4 H- or 2 H-thiopyrans, respectively.[76]



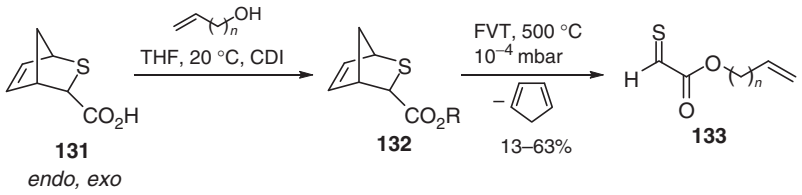
Scheme 27

Through conversion of the formyl group to a methylene unit with the Tebbe reagent, the first synthesis of thioacrolein *S*-oxide **130** was achieved by means of a similar anthracene template. By selective and mild oxidation with *m*-chloroperoxybenzoic acid (MCPBA), **128** afforded sulfoxide **129** as a mixture of two stereoisomers (*Z*/*E* = 70/30 by ^{1}H-NMR). Flash vacuum thermolysis of **129** led to 9,10-dimethylanthracene, which was recovered (Scheme 28). The volatile **130**, trapped at − 196 °C and analyzed by NMR at − 60 °C, consisted of two isomeric sulfines in different *Z*/*E* ratios.[77]



Scheme 28

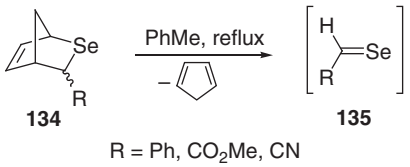
The cycloadduct of cyclopentadiene and thioaldehyde–acetic acid (HO_2C–CHS) **131** was converted to esters **132** on reaction with alkenols. When subjected to FVP, **132** gave alkenyl thioxoacetates **133** (Scheme 29), which then underwent spontaneous intramolecular reaction on silica in MeOH at 20 °C to give thia-alkenolides containing 6- to 11-membered rings.[78,79]



Scheme 29

5.12.4.2 Unsaturated Selenoaldehydes

Bicyclic adducts **134** yielded selenoaldehydes **135** when refluxed in an inert solvent (equation 19). This procedure proved advantageous over other methods for the *in-situ* preparation of selenoaldehydes, which react with suitable Wittig reagents in a regular fashion to give the corresponding alkene products (e.g. cinnamate esters or fumarates). The adducts **134** in turn were prepared by simple mixing of a stabilized ylide and elemental selenium and heating of the mixture in the presence of cyclopentadiene.[80]

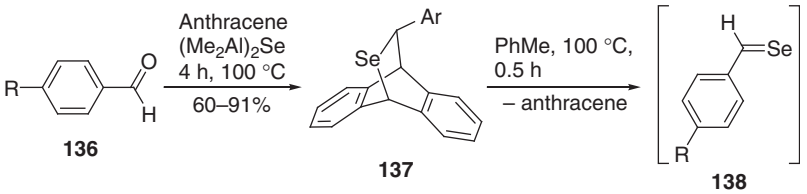


(19)

With bis(dimethylaluminum)selenide in the presence of anthracene, 4-substituted benzaldehydes **136** gave cycloadducts **137**, which could be cleaved to reactive selenoaldehydes **138** in a one-step reaction (Scheme 30). The latter were trapped by 2-silyloxy-1,3-butadiene, 2-methoxyfuran, or 5-ethoxyoxazoles to give the corresponding selenacyclic cycloaddition products.[81]

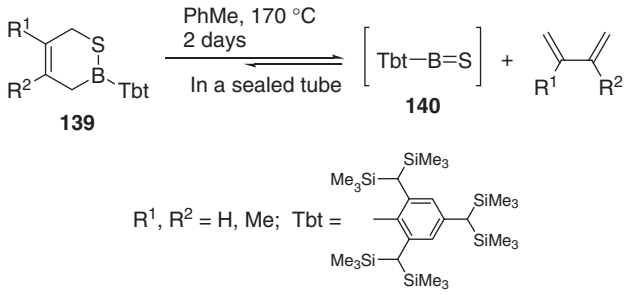
5.12.4.3 Compounds Containing X=Y Heteroatom Bonds

Regioisomeric (2:1) mixtures of adducts 4- and/or 5-methyl-1,2-thiaboracyclohex-4-enes **139** readily underwent [4 + 2] cycloreversion, but the starting compounds were recovered in 59% yield after cooling. ^{1}H-NMR spectroscopic monitoring showed that the initially formed thioxoborane (Tbt-B=S) **140** did not dimerize, but existed as a monomer even at a high temperature (170 °C). It therefore had a sufficient lifetime for a DA reaction with an equimolar amount of diene (isoprene), leading to the regeneration of a (1:1) mixture of the starting cycloadducts.[82]



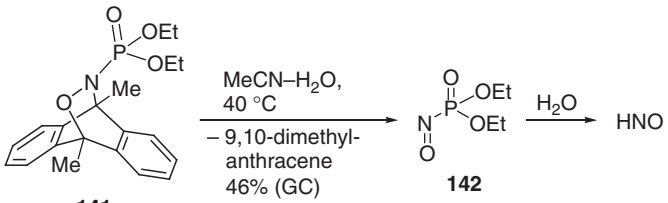
136 **137** **138**

Scheme 30



139 **140** (20)

P-nitrosophosphates reacted as *N*-*O* heterodienophiles with 1,3-dienes to give functionalized cycloadducts, which could be transformed directly to allylic phosphoramidates. With 9,10-dimethylanthracene, the *P*-nitrosophosphate gave rise to cycloadduct **141**, which underwent rDA dissociation to reform **142** (equation 21). In the absence of 1,3-dienes, the mild thermal decomposition of the DA adducts resulted in formation of NO, as evidenced by the presence of HNO. The yield of **142** (46%) was determined by GC. The results identified *P*-nitrosophosphates as the new species that react similarly to acyl nitroso compounds as useful synthetic intermediates and potential HNO delivery agents.[83]



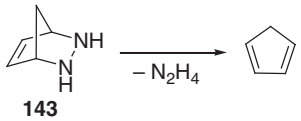
141 **142** (21)

The *N*-acylnitroso analogs were found to be photoinducible HNO-releasing agents, which were also prepared by [4 + 2] cycloaddition of 9,10-dimethylanthracene with nitroarylaminoacylnitroso (NO_2–Ar–NHCON=O) derivatives.[84] The reaction rate proved to be dependent on the intensity of the light source. Some derivatives were thermally stable and not activated by ultraviolet A irradiation. The results indicated that their stability was largely dependent on the steric hindrance of the substituents.

5.12.5 Production of Cycloalkane Derivatives

5.12.5.1 Cyclopentane Derivatives

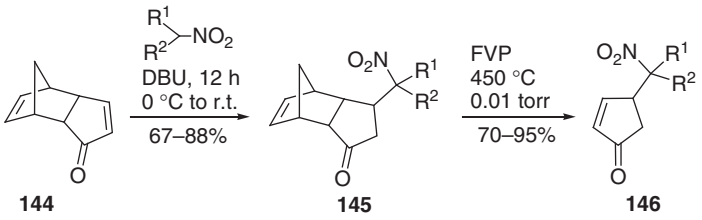
The first synthesis of 2,3-diazabicyclo[2.2.1]hept-5-ene **143** in 1993 was facilitated by the isolation of the biscarboxylates formed by the hydrolysis of biscarbamates. The rDA splitting to diimide and cyclopentadiene under mild conditions was explored (equation 22).[85]



143 (22)

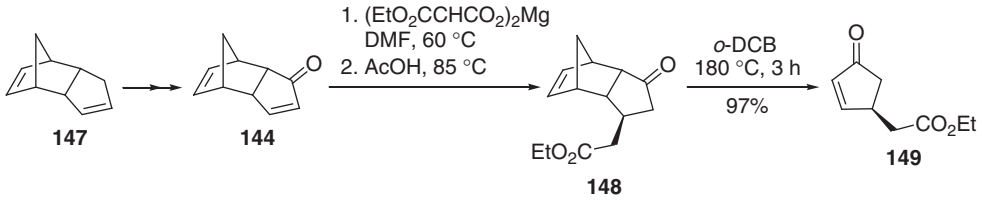
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) catalysis of the Michael addition of nitroalkanes to dicyclopentadienone **144** provided bicyclic nitroketones **145**, which were subjected to FVP to furnish cyclopentenones **146** (Scheme 31). Although organonitro derivatives are usually labile and have explosive properties at high temperatures, **146** proved to be fairly stable. Compounds **145** can be transformed via an Nef reaction to carbonyl derivatives (R^1=H and R^2=H, Me, Et) by the use of MeONa and $TiCl_3$ in aqueous MeOH. FVP of the resulting bicyclic ketones at 350 °C gave the expected 4-acetyl- and propionylcyclopentenones.[86]

A chemoenzymatic multistep synthesis was developed for the preparation of enantiomerically pure oxoester **149**, with rDA fragmentation as the key step. Dicyclopentadiene **147** was transformed to enone **144** in several steps via manganese



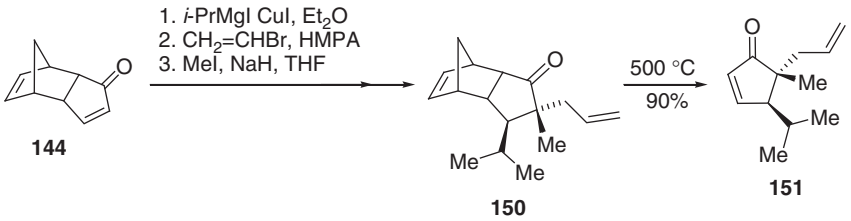
Scheme 31

triacetate-mediated allylic acetoxylation, and the racemic mixture of acetates was then hydrolyzed to the corresponding alcohols. After enzymatic resolution with lipase polystyrene (PS), separation and oxidation with pyridinium chlorochromate afforded the enantiopure cyclic ketone **144**. With magnesium monoethyl malonate, the conjugate addition to **144** resulted in the corresponding Michael adduct as a single diastereomer. Acidic workup gave oxoester **148** through partial decarboxylation (Scheme 32). Refluxing of oxoester **148** in 1,2-dichlorobenzene resulted almost quantitatively in the cyclopentenone derivative **149** by an rDA reaction.[87]



Scheme 32

In studies aimed at the total synthesis of the biologically important natural product guanacastepene A, a new and concise route to a fully functionally endowed hydroazulenic core was devised. The strategy set the requisite stereochemical features on the *endo*-tricyclo[5.2.1.$0^{2,6}$]decane matrix followed by excision of the five-membered ring in an rDA reaction (Scheme 33). Specifically, enone **144** was alkylated and allylated regioselectively in multiple steps. The crowded ketone **150** was pyrolyzed to give product **151**.[88]

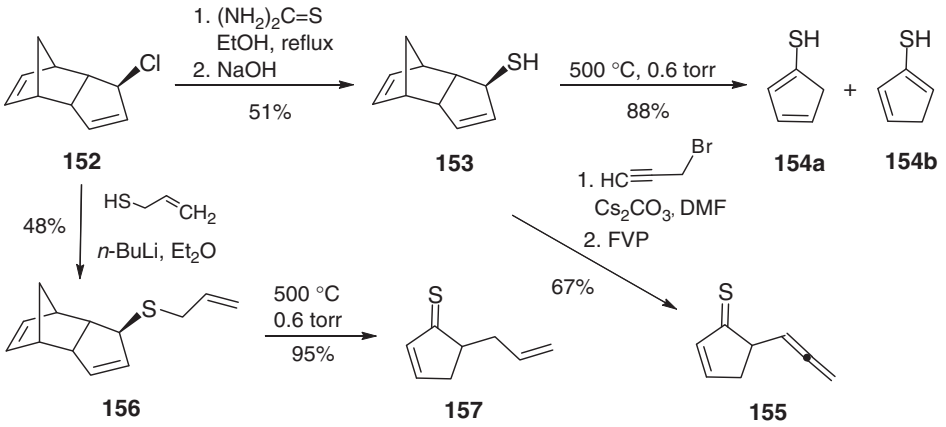


Scheme 33

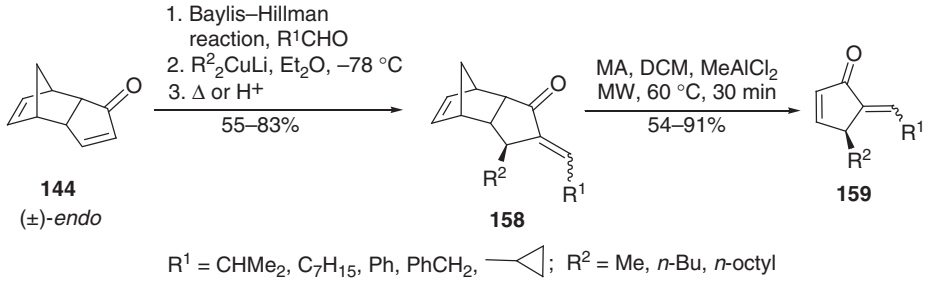
By elimination of cyclopentadiene in an rDA reaction, the FVT of tricyclic allyl- (e.g. **156**) or propargyl-substituted sulfides led to mixtures of isomeric allylthio- or propargylthiocyclopentadienes (e.g. **157**), respectively (Scheme 34). However, the propargyl derivative underwent a thio-Claisen rearrangement, which resulted in the reactive 5-allenylcyclopentene-1-thione **155** (Scheme 34). The corresponding alkenyl- and alkinylthiobicycles were prepared by two different known routes from chlorodicyclopentadiene **152**. Possible retroene reactions involving the elimination of propene or allene from the allylthio or propargylthio moieties were not observed. Under FVT, the tricyclic thiol **153** afforded a mixture of isomeric cyclopentadienethiols **154a** and **154b**, which tautomerize to cyclopentenethione on warming.[89]

From racemic *endo*-dicyclopentadienone **144**, a straightforward and efficient synthesis yielded optically pure alkylidene- and arylidene-disubstituted cyclopentenones **159** via one-pot alkyl cuprate addition/aldol condensation/dehydration followed by an MW-mediated and Lewis acid-catalyzed rDA procedure.[90] An alternative route involved a modified Baylis–Hillman protocol followed by conjugate addition with alkyl cuprates at a low temperature, with the final cycloreversion step in an MW reactor under mild conditions (Scheme 35). For cyclopentadiene trapping, an excess of MA was used. The reactions, followed by means of ^{1}H-NMR spectroscopy, demonstrated exclusive *E* selectivity (>95%).

Similar preparations of cross-conjugated dienone 5-alkylidenecyclopent-2-enones **159** and prostanoids have been described through tandem conjugate addition–Peterson olefination, starting from 2-trimethylsilyltetrahydro-4,7-methanoinden-1-one **162**

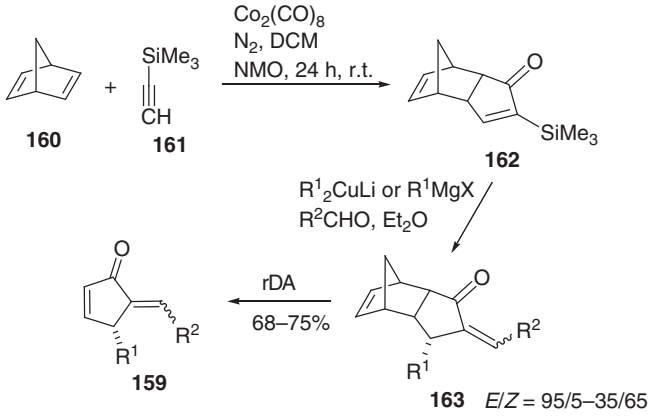


Scheme 34



Scheme 35

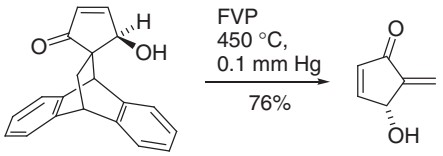
as the reactive intermediate obtained by a Pauson–Khand reaction. Compound **162** was prepared by treating norbornadiene **160** and trimethylsilanylacetylene **161** with $Co_2(CO)_8$, with subsequent addition of 10 equivalents of *N*-methylmorpholine-*N*-oxide (Scheme 36). The selectivity of the exocyclic alkenes was controlled by the use of an organometallic species in the conjugate addition step. Organocuprates led to the formation of *E*-exocyclic alkene adducts **163**, whereas Grignard reagents promoted the formation of the *Z*-alkenyl isomers. When adduct **163** was refluxed in hexane for 3–35 h or subjected to Lewis acid-catalyzed rDA cleavage, enantioenriched disubstituted cyclopentenones **159** were obtained.[91,92]



Scheme 36

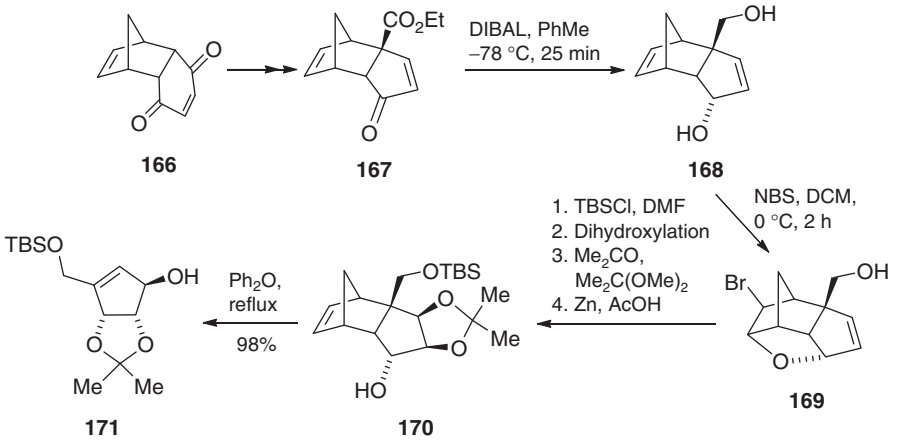
A short and simple chemoenzymatic synthesis of (–)-epipentenomycin I comprised a lipase-catalyzed kinetic resolution of the racemic pentacyclic alcohol followed by FVP of (–)**164**. In this way, enantiomerically pure 4-hydroxy-5-methylene-2-cylopentenone

165 was obtained without racemization or side reactions (equation 23). Epoxidation and hydrolytic ring opening of **165** then gave (–)-epipentenomycin I.[93]



164 **165** (23)

A silylated intermediate, prepared in a multistep and enantioselective procedure, was applied in the synthesis of neplanocin A, which displays a strong antitumor activity. This process started from optically active 2-hydroxymethyl-5-hydroxytricyclodecadiene **168** with rDA reaction as the key step. The readily available dione **166** was treated with aqueous H_2O_2, and the resulting product was warmed with NaOH. The oxoester **167** obtained was reduced with diisobutylaluminum hydride (DIBAL) to the dihydroxy derivative **168**. After bromination, the 9-bromo-5,8-epoxytricyclodecane was regioselectively silylated on the hydroxymethyl group with *tert*-butyldimethylsilyl chloride (TBSCl) and the double bond dihydroxylated. Acid-catalyzed protection with dimethoxypropane in acetone and transformation with active Zn and AcOH resulted in the acetonide derivative **170** (Scheme 37). Derivative **170** was refluxed in Ph_2O solution to give the rDA product **171** as required for the synthesis of neplanocin A.[94]

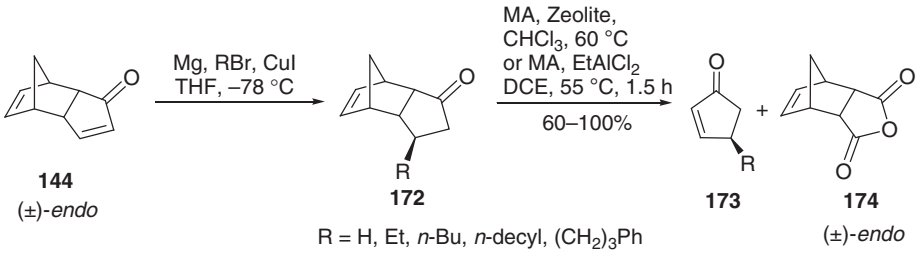


166 **167** **168** **169** **170** **171**

Scheme 37

A similar procedure led to the diastereocontrolled preparation of (+)-tanikolide, a toxic and antifungal marine natural product isolated from *Lyngbya majuscula*.[95]

Zeolite H-Beta catalyzed the rDA reactions of a range of cyclopentadiene cycloadducts in the presence of an active dienophile. A screening of different zeolites suggested that the rDA fragmentation of tricyclodecenones **172** was catalyzed by Brønsted acid, and the high catalytic performance of H-Beta could be ascribed to the optimal balance between the number of acidic sites, their strength, and accessibility.[96] As an alternative to the Lewis acid-catalyzed rDA procedure, the methodology was applied to the synthesis of a series of 4-alkylcyclopentenones **173**, with MA being used to trap the dienophile (Scheme 38).



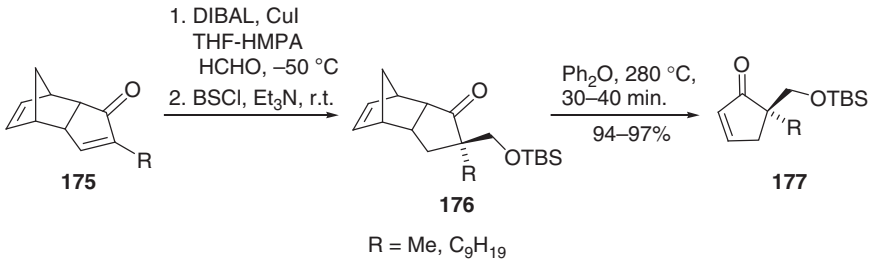
144 (±)-*endo* **172** **173** **174** (±)-*endo*

R = H, Et, *n*-Bu, *n*-decyl, $(CH_2)_3Ph$

Scheme 38

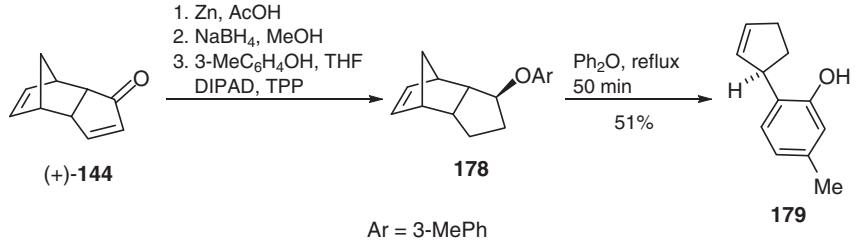
A [4 + 2] cycloreversion was applied as a key step for the synthesis of the pheromone (+)-frontalin and the structurally related marine antibiotic (–)-malyngolide. From 4-methyl- and 4-nonyltricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones **175**, *O*-silylated

hydroxyketones **176** were obtained in a two-step procedure (Scheme 39). An rDA reaction then led to the required intermediate hydroxyketones **177**.[97]



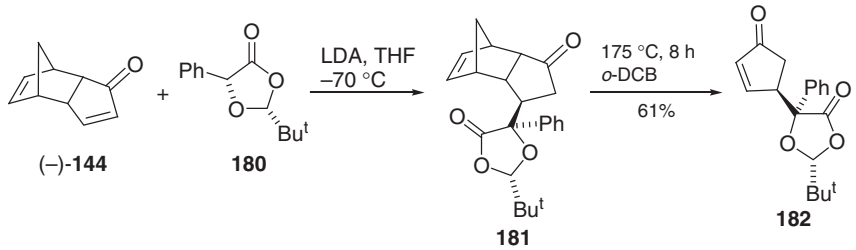
Scheme 39

From the chiral ketone **144**, a new stereocontrolled route was developed to (+)-curcuphenol, a sesquiterpene from a marine sponge. The compound **144** was transformed by chemo- and stereoselective reduction with $NaBH_4$ to the chiral *endo*-tricyclic alcohol. The reaction with 3-methylphenol, diisopropylazodicarboxylate (DIPAD), and triphenylphosphine (TPP) furnished the *exo*-aryl ether **178**. After thermolysis, the chiral 3-arylcyclopentene **179** was obtained (Scheme 40) through a concurrent rDA reaction and Claisen rearrangement.[98] The phenolic compound **179** was used as the key precursor for the total synthesis of (+)-curcuphenol.



Scheme 40

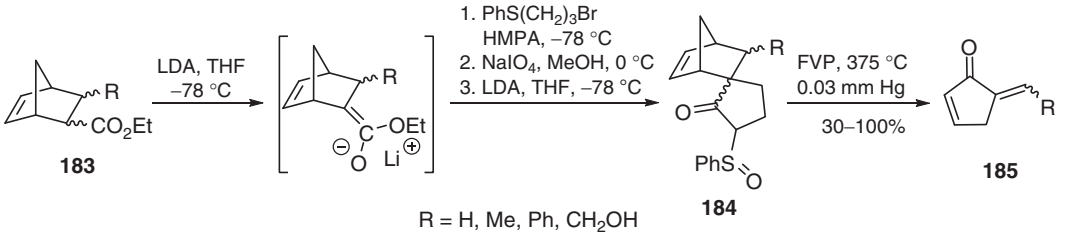
The diastereoselective synthesis of 2-cyclopentyl-2-hydroxy-2-phenylacetic acid, a moiety of a new muscarinic M_3-receptor antagonist, was achieved through the Michael addition of the enolate of chiral dioxolane **180** to dicyclopentadienone **144** in the presence of lithium diisopropylamide (LDA) (Scheme 41). Adduct **181** was submitted to an rDA process by heating in 1,2-dichlorobenzene (*o*-DCB).[99]



Scheme 41

A general method for the preparation of 5-alkylidene-2-cyclopentenones **185** relied on the thermolysis of spiro-cyclopentanones **184**. The FVP step was reported to take place with *E*/*Z* selectivity (Scheme 42), resulting in the quantitative or high yielding release of **185** (>95% yield, R=H) (R=Me, Ph, *E*/*Z* ratio: 100/0–83/15) at 375–450 °C (0.03–0.05 mm Hg). When R was hydroxymethylene, the yield was low (30%), presumably due to decomposition under the pyrolytic conditions; only the *Z* isomer was obtained in this case.[100]

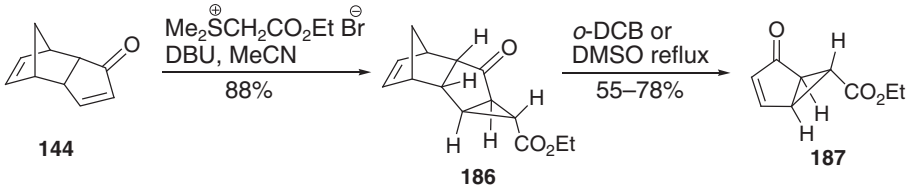
The rDA fragmentation of 1,4-benzoquinone-annelated spirobicyclo[2.2.1]heptenes was studied both experimentally and theoretically. On refluxing in MeCN or toluene, the reactions gave spirocyclopentadienes (spiro[2.4]hepta-4,6-dienes) in 35–87% yields through the decomposition of the cycloadducts during 8–28 h. The results were supported theoretically by computation of the activation barrier (with ΔE^{+}/kcal mol^{-1} calculated for the gas or solution phase at the B3LYP/6–31 G* level of theory).[101]



183 **184** **185**

Scheme 42

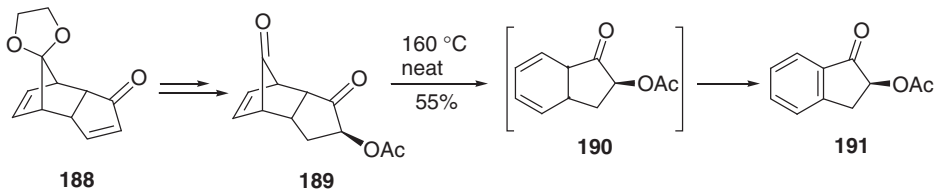
On cyclopropanation of dicyclopentadienone **144**, enantiomerically pure bicyclic cyclopentenone γ-ester **187** was prepared by a modification of Payne's sulfur ylide method. Thus, **144** was reacted with ethyl(dimethylsulfuranylidene)acetate to afford tetracycle **186** as a single diastereomer (Scheme 43). For the cycloreversion, this oxoester was refluxed under a blanket of N_2, which gave rise to **187** in moderate yield (55% after 23 h). The reaction could be carried out more rapidly and efficiently (with a yield of 78%) using dimethyl sulfoxide (DMSO) as the solvent (~189 °C, 8 h).[102]



144 **186** **187**

Scheme 43

Enantiomerically pure aminoindanol has drawn attention as the key component of the human immunodeficiency virus-protease inhibitor Indinavir and through its use in some chiral auxiliaries and catalysts for asymmetric reactions. The important precursor acetoxyindanone **191** was prepared by a multistep procedure. Starting from the protected dienone **188,** acetoxy diketone **189** was obtained as a single isomer in a regio- and stereoselective manner. The thermally induced extrusion of CO from (+)-**189** via rDA fragmentation and aromatization of the unstable diene intermediate **190** led to (2*S*)-acetoxyindan-1-one **191**, which could be readily converted to aminoindanol (Scheme 44).[103]



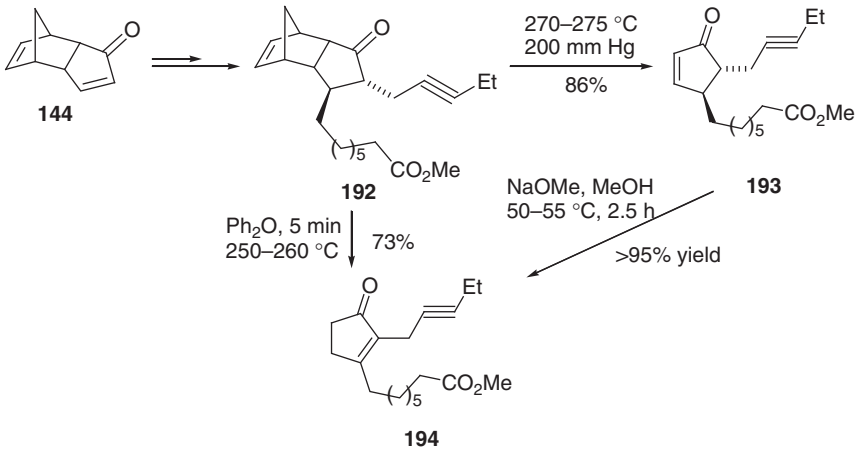
188 **189** **190** **191**

Scheme 44

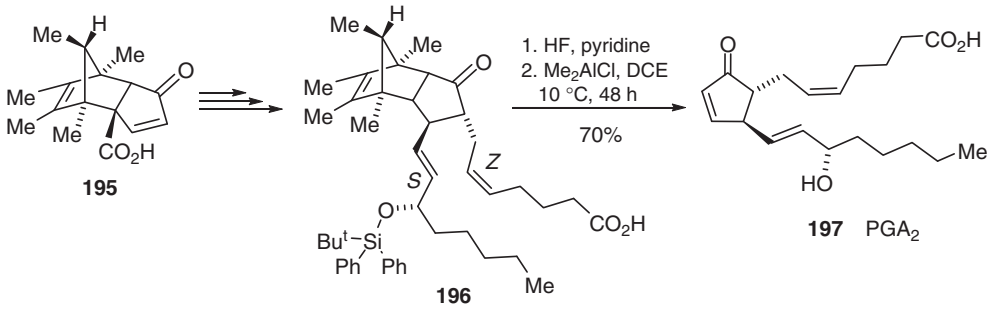
The chromomoric acid family (chromomoric acid B and F methyl esters) as metabolites of linolenic acid, isolated from *Chromolaena morii* and *Chromolaena chasleae* but also found in other species, exhibits antibiotic and antihypertensive activities. A convenient total synthesis of these compounds with a cyclopentenone skeleton has been described starting from enone **144**. This compound was converted to the *trans*-4,5-dialkylated tricyclodecen-3-one **192**, which was subjected to thermolysis *in vacuo* with the splitting-off of cyclopentadiene to afford dehydrochromomoric acid B methyl ester **193** diastereoselectively (Scheme 45). When **192** underwent thermolysis, the rDA step resulted in a 2:1 mixture of **193** and **194**, which readily converged to enone **194** (intermediate to chromomoric acid F methyl ester).[104] Similarly, the total synthesis and structural revision of chromomoric acid D-I methyl ester were reported.[105]

A facile rDA reaction of pentamethyltricyclo[5.2.1.$0^{2,6}$]decenone **196** led to the total synthesis of prostaglandin A_2 (PGA_2) **197**. The incorporation of methyl groups into **196** at positions C(1), C(7), C(8), C(9), and C(10) accelerated the retro process dramatically, which occurred under Lewis acid catalysis with Me_2AlCl. Subsequent deprotection of the hydroxy group (Scheme 46) permitted synthetic access to the natural PGA_2.[106]

Through conjugate addition/Peterson olefination, racemic $\Delta^{12,14}$–15-deoxyprostaglandin-J_1 was readily synthesized from trimethylsilyl ketone **162** in a multistep procedure. One-pot conjugate addition of the silyl-protected Grignard reagent under Cu(I) catalysis followed by addition of *trans*-2-octenal gave a mixture of *cis*/*trans* isomers, which were separated. With the Jones reagent or Dess–Martin periodinane sodium chlorite, oxidation of the primary –OH group to the methyl ester was possible, which yielded the precursor **198** (Scheme 47). Subsequent Lewis acid-mediated rDA fragmentation of adduct **198** in the presence of MA

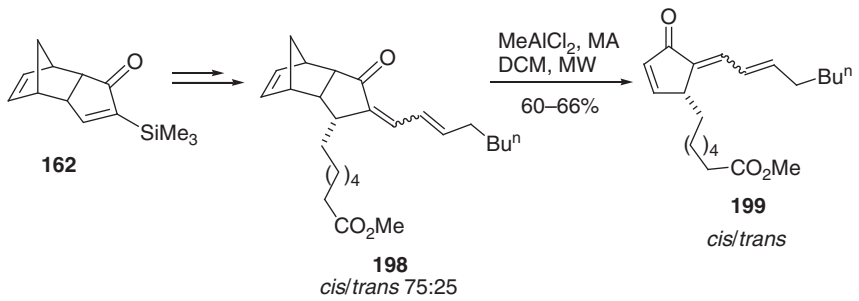


Scheme 45



Scheme 46

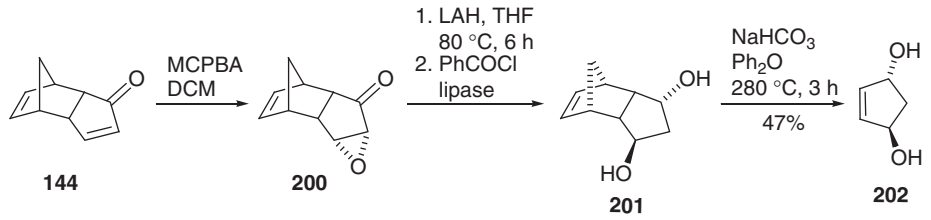
afforded both geometric isomers of cyclopentenone **199**. The thermal cycloreversion was optimized by means of short bursts (~200 s) of MW irradiation at 300 W at 110 °C.[107]



Scheme 47

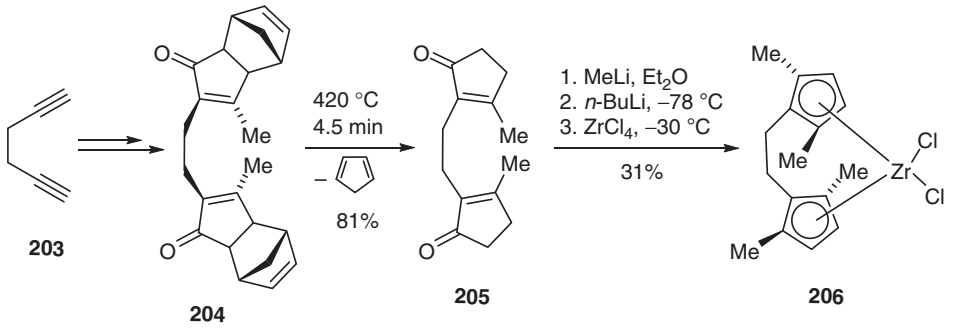
From racemic tetrahydro-4,7-methanoinden-1-one **144**, the optically pure C_2-symmetric 4-cyclopentene-1,3-diol **202** has been prepared in both enantiomeric forms by employing lipase-mediated kinetic resolution. The known (3a*S**,4*R**,7*S**,7a*S**)-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-inden-1-one **144** was transformed to (1′*S**,3′*S**,3′a*R**,4′*S**,7′*R**,7′a*S**)-2′,3′,3′a,4′,7′,7′a-hexahydro-3′-hydroxy-4′,7′-methano-1′*H*-inden-1′-yl benzoate by stereo- and regioselective hydride reduction of epoxyketone **200** and sequential benzoylation, with resolution via transesterification in the presence of lipase. Hydride reduction of the benzoate or acetate gave chiral diol **201** (Scheme 48), which was transformed to both enantiomers of the C_2-symmetric 4-cyclopentene-1,3-diol **202** in an rDA reaction.[108] 4-Cyclopentene-1,3-diols are important intermediates for the synthesis of enantiopure prostaglandins and other natural products.[109–111]

When the symmetrical ethylene-bridged bisdicyclonorbornadienone **204** was heated, a rare double rDA reaction occurred to give ethylene biscyclopentenone **205**, which was transformed to a novel zirconium chloride complex. The ligand was prepared from 1,5-hexadiyne **203** by a Pauson–Khand reaction and rDA fragmentation (Scheme 49). The metallation of compound **205**,



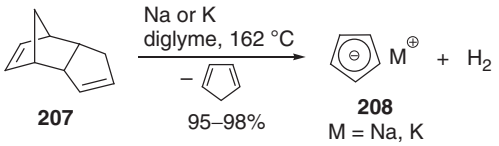
Scheme 48

conducted in a trimethyltin-mediated step through the biscyclopentadiene intermediate, led to the isolation of **206** in a rather low yield (31%). The resulting zirconocene complex **206** was fully characterized by NMR spectroscopy and X-ray crystallography.[112] To obtain a 9-fluorenylmethyl-dicyclopentadienone skeleton, another unsymmetrical zirconocene complex with cyclopentadiene and fluorene moieties was prepared and decomposed by rDA cycloreversion at 300 °C.[113]



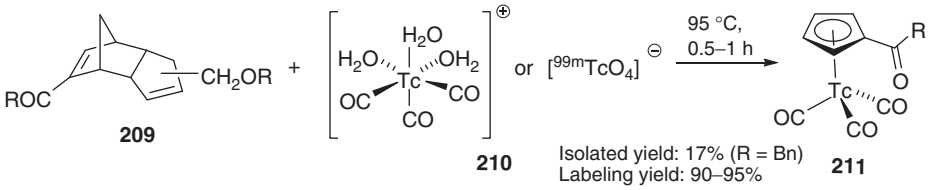
Scheme 49

By the direct reaction of dicyclopentadiene with alkali metals, a novel method for the synthesis of metal cyclopentadienides was developed. Unlike conventional methods, which use dicyclopentadiene **207** to first generate cyclopentadiene in an rDA reaction, the new preparation directly afforded metal cyclopentadienides **208** starting from dicyclopentadiene when the temperature reached the boiling point of the solvent (equation 24). During the addition of cyclopentadiene, the cessation of H_2 evolution indicated the end of the reaction, which furnished sodium or potassium cyclopentadienide adducts.[114]



(24)

The metal-mediated rDA fragmentation of dicyclopentadiene derivatives (Thiele's acid, its ketone or amide) was studied, and their Tc and Re complexes were synthetized. DA dimers **209** are 'protected' cyclopentadienes. Although the thermal cracking of **209** required a high temperature (over 160 °C), the rDA complexes formed from Thiele's acid derivatives **209** in the presence of a group 7 transition metal (Mn, Tc, or Re) decomposed at a low temperature and resulted in the quantitative formation of complexes such as **211** (equation 25). Compound **211** could also be prepared directly from TcO_4^- in the presence of dimers **209** under the same conditions. This was particularly interesting, because they have been used to carry Tc-99 m (half-life 6 h), commonly employed in scanning procedures in nuclear medicine. For similar reactions, 'cold' Re was also applied because it was much more robust than technetium; the rhenium carbonyl complex $[Re(OH_2)_3(CO)_3]^+$ required longer reaction times or higher temperatures with Thiele's acid (R=OH).[115,116]

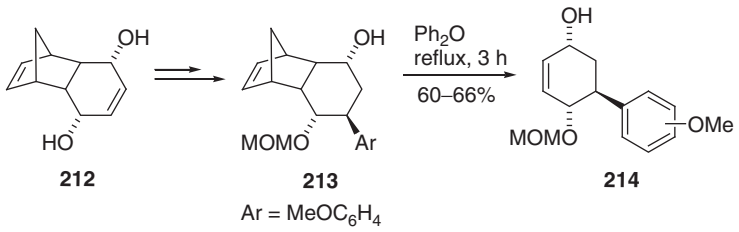


(25)

R = OH, Bn, $BnNH_2$, $NHCH_2CO_2H$

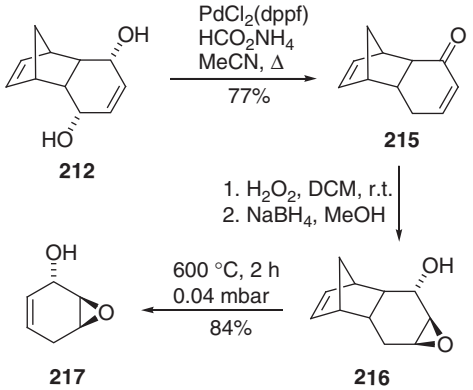
5.12.5.2 Cyclohexane Derivatives

Through the use of the chiral 5-phenylcyclohex-2-ene-1,4-diol, structural analogs of the potent nonopioid analgesic alkaloid epibatidine were prepared via an enantio- and diastereo-controlled route. These diol intermediates were obtained from cycloadduct **212** by rDA cleavage; protection of the methoxymethyl (MOM) ether and subsequent arylation followed by cleavage in refluxing Ph_2O gave **214** (Scheme 50). These 2-, 3- or 4-methoxyphenylcyclohexenols were suitable for further transformations to compounds containing an azabicyclo[2.2.1]heptane skeleton.[117]



Scheme 50

From the readily accessible cyclopentadiene–p-benzoquinone cycloadduct, a synthetic route to 2-deoxystreptamine, a common moiety in many pharmacologically active aminoglycosides, was devised. Reduction under Luche conditions (with $NaBH_4$–$CeCl_3$ in MeOH at ~0 °C) led diastereoselectively to diol **212**, which was converted to enone **215** before being transformed into **216** by nucleophilic epoxidation (Scheme 51). To avoid a Payne rearranged product and other side reactions, the reduction was performed at a low temperature (−78 °C). The desired thermolytic rDA process was achieved by application of FVP, which furnished pure epoxycyclohexenol **217**.[118]



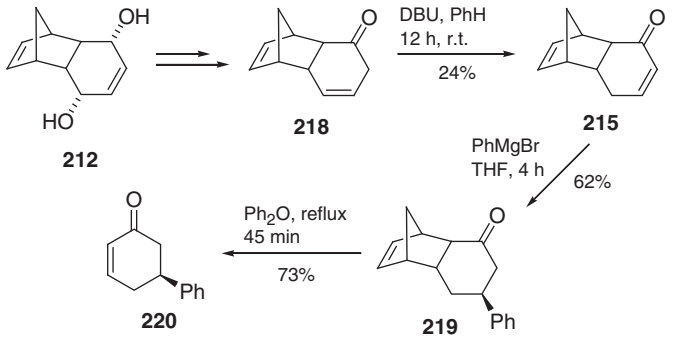
Scheme 51

Norbornene-fused hexanediol **212** has also been used to obtain phenyl- and other aryl-substituted cyclohexenones **220**. By transesterification with a specific ester in the presence of lipase, the crude diol afforded an optically active derivative. Pure **212** was acylated by a conventional method and treated with Zn under ultrasonic waves to give deacyloxylated cyclohexenone **218**, which was isomerized to **215** with DBU. After purification by column chromatography over silica gel, a Grignard reagent was added to obtain the phenyl-substituted ketone **219** (Scheme 52). This tricyclic product readily afforded the rDA fragmented chiral ketone **220** as the target compound.[119]

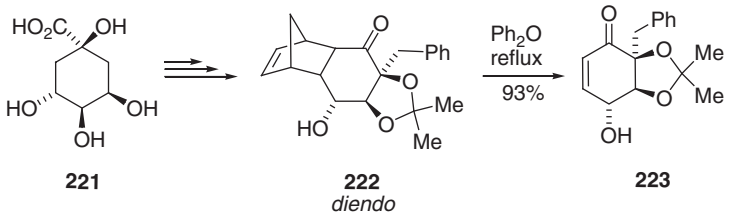
With slight modifications, the discussed methods could be applied widely and successfully in other cases, when oxo, hydroxy, epoxy, or aryl(alkyl) moieties were built onto the cyclohexene skeleton. These usually diastereo- and/or enantioselective procedures furnished fairly good yields when side products were not observed in the course of the rDA fragmentations. The use of norbornene as the carrier part of the cycloadducts proved best, mostly in the rDA cleavage, because cyclopentadiene readily splits off from the molecule on thermolysis at different temperatures.[120–125]

Multifunctional polysubstituted cyclohexene derivatives were synthetized through a similar enantiocontrolled route. 6-Benzyl-4,5-epoxy-6-hydroxy-2-cyclohexenone **223** was studied as the model compound for the epoxycyclohexenone moiety of scyphostatin. The starting material was obtained from the commercially available (–)-quinic acid **221**, which was converted to cycloadduct **222** in a multistep procedure. The thermolytic reverse cycloaddition of the tetracyclic ketone **222** proved to be critical. This finally provided pure acetonide **223** without decomposition or isomerization (Scheme 53).[126]

Through application of a DA/rDA sequence, the first synthesis of the antifungal and plant growth-promoting compound (±)-grass sterile dark ectotrophic fungus (SDEF) 678 was achieved; this compound was isolated earlier from the roots of an Australian

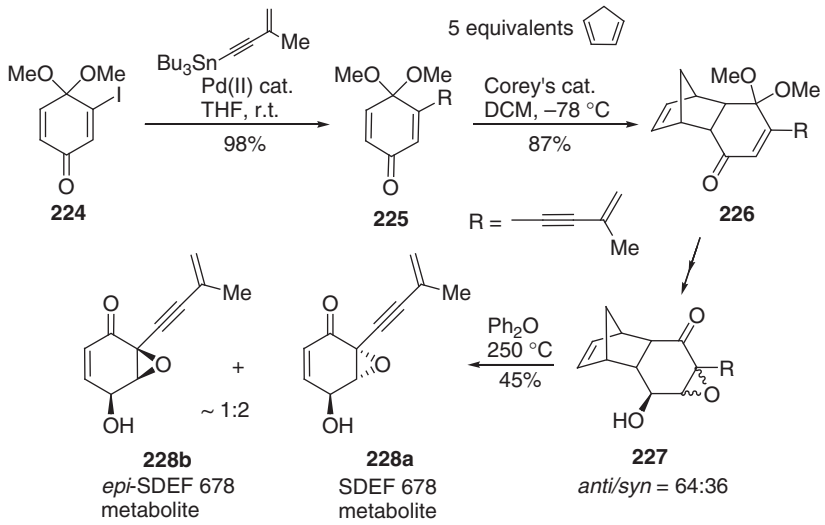


Scheme 52



Scheme 53

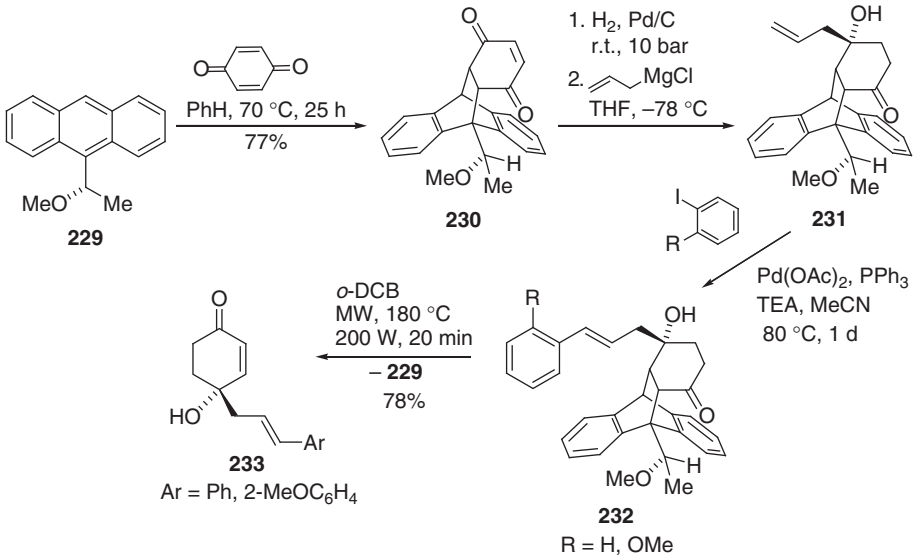
native SDEF.[127] The compound contains a 2-(but-1-en-3-ynyl) sidechain, which made the synthetic strategy somewhat problematic. Via the use of an alkynyl stannane and Stille coupling, iodocyclohexadienone **224** was converted to **225**. Corey's chiral oxazaborolidine in combination with triflic acid served to catalyze the cycloaddition of ketone **225** with cyclopentadiene to furnish norbornene-fused **226**. After reduction, deprotection and selective epoxidation, rDA reaction in boiling Ph_2O led to the metabolite SDEF 678 **228a** and the *epi* derivative **228b** (Scheme 54).[128]



Scheme 54

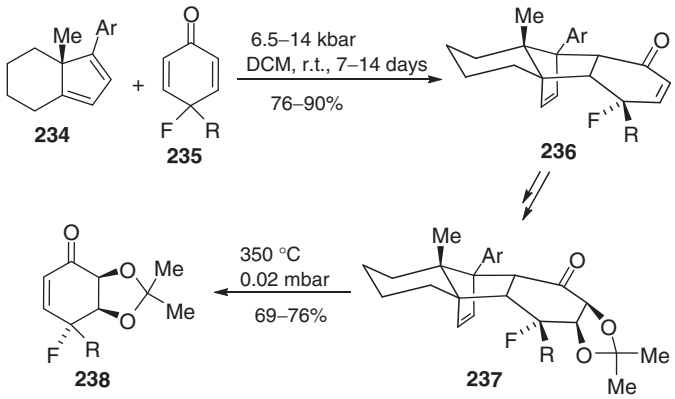
From cycloadducts with furan or anthracene, only a few examples have been reported for the preparation of cyclohexene derivatives. A rare and interesting procedure was reported by Jones et al., who used a chiral anthracene auxiliary and 1,4-benzoquinone for the DA/rDA methodology in the enantioselective synthesis of candenatenins B and C. They applied a highly diastereoselective cycloaddition of the 9-substituted anthracene **229** with 1,4-benzoquinone, which gave the chiral adduct **230**; after catalytic hydrogenation and a Grignard reaction, hydroxycyclohexanone **231** was obtained as the major product. Heck coupling with iodobenzene yielded the aryl ring; no *Z*-alkenes were formed in the reaction (Scheme 55). The cycloreversion of **232** was optimized in various solvents (chlorobenzene, 1,2-dichlorobenzene or DMSO), at different temperatures (75–230 °C)

and under MW irradiation (150–300 W); the catalytic effect of a Lewis acid [$Sc(OTf)_3$] was also studied. Best results were obtained under MW irradiation to give the chiral compounds **233**.[129]



Scheme 55

With the cyclopentadiene enantiomer **234,** a highly face-selective DA reaction took place under high pressure. Thus, 4-fluorocyclohexadienones, prepared in an improved Jacquesy process, underwent cycloaddition with fluoroketone dienes **235** and furnished adducts **236** under forceful conditions. The polycyclic fluoroketones **236** were reacted with $RuCl_3$–$NaIO_4$ through a 'flash-dihydroxylation', and an acid-catalyzed ketal was then formed using 2-methoxypropene or 2,2-dimethoxypropane (Scheme 56). FVP of the acetonide adducts **237** led to protected fluorocyclohexadienones **238**.[130,131]



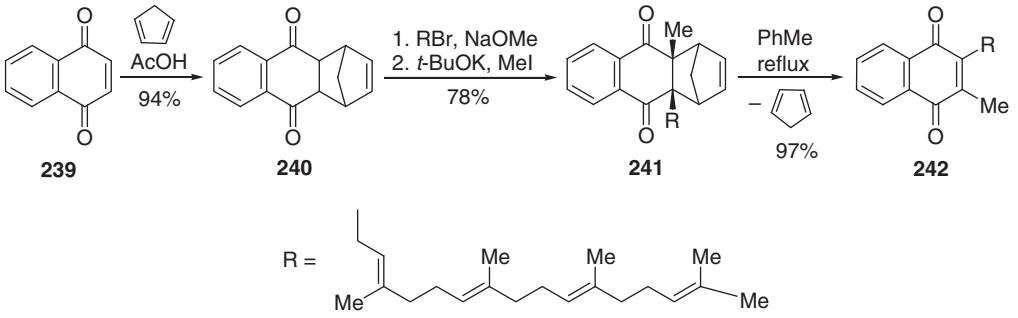
Scheme 56

From optically pure cyclopentadiene **234,** spiroisoxazolines (1-oxa-2-azaspiro[4.5]deca-2,6-dien-8-ones) were prepared in a DA/rDA procedure. These compounds are chromophore subunits of the marine antibiotics agelorin A and B isolated from the sponge *Agelas oroide*.[132,133]

5.12.5.3 Polycondensed Cycloalkanes

With cyclopentadiene, the DA cyclization of 1,4-naphthoquinone **239** afforded 1,4,4a,9a-tetrahydro-1,4-methanoanthraquinone **240**, which was alkylated with 3,7,11,15,-tetramethyl-2(*E*),6(*E*),10(*E*),14-hexadecatetraenyl bromide (RBr). A subsequent methylation gave anthraquinone **241**, refluxing of which in toluene resulted in the formation of vitamin K_2 (menaquinone) **242**

by an rDA process (Scheme 57).[134,135] Analogously, the DA reaction of the methyl anthraquinone followed by alkylation and the retrodiene reaction finally yielded vitamin K_1.[136]

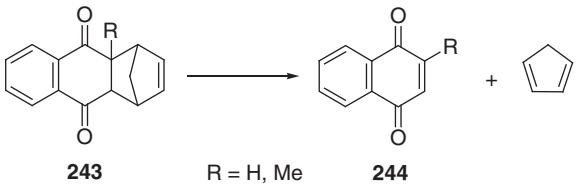


Scheme 57

The effect of the solvent on the rDA reaction of 1,4,4a,9a-tetrahydro-4a-methyl-1,4-methanoanthracene-9,10-dione–cyclopentadiene adduct **243** (R=Me) has been studied kinetically (Table 8). The hyperbolic relationship observed between the kinetic data and the acceptor number of the solvent was strong evidence for the fact that the solvent acts as an electrophile which lowers the activation energy of the reaction. The linearity clearly indicated that the nature of the solvent effect is the same in both the DA and rDA reactions. These relationships and the thermodynamic parameters suggest that the rDA process is a 'late transition state' pericyclic reaction, the solvent effect arising from the specific interaction between the solvent and the product **244**.[137] The rDA process of methanoanthracenedione proceeded considerably faster in aqueous solutions than in organic solvents (equation 26). The addition of organic solvents retarded the reaction. Data correlation demonstrated that the origin of the water-induced acceleration involved primarily the enhanced H-bonding of water to the activated complex for the rDA cleavage of methanoanthracenedione.[138]

Table 8 First-order rate constants and Gibbs energies for activation of the rDA reaction of **243** (R=Me) in different solvents at 40.0 °C (equation 26)

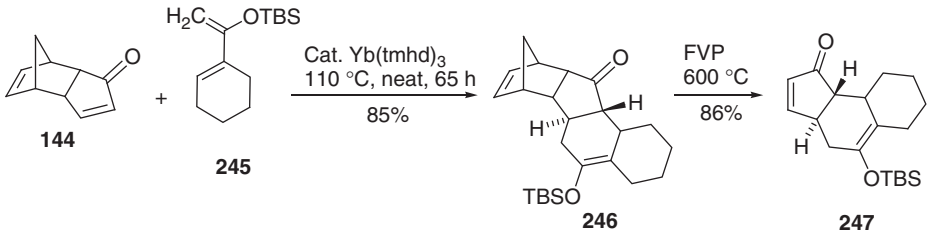
No.	*Solvent*	$10^8 \times k_1$ (s^{-1})	ΔG^0 (kJ mol^{-1})
1	*n*-Hexane	2.6	122.3
2	Benzene	6.6	119.9
3	DMSO	23	116.6
4	*i*-PrOH	27	116.2
5	AcOH	62	114.0
6	Water	359	109.5



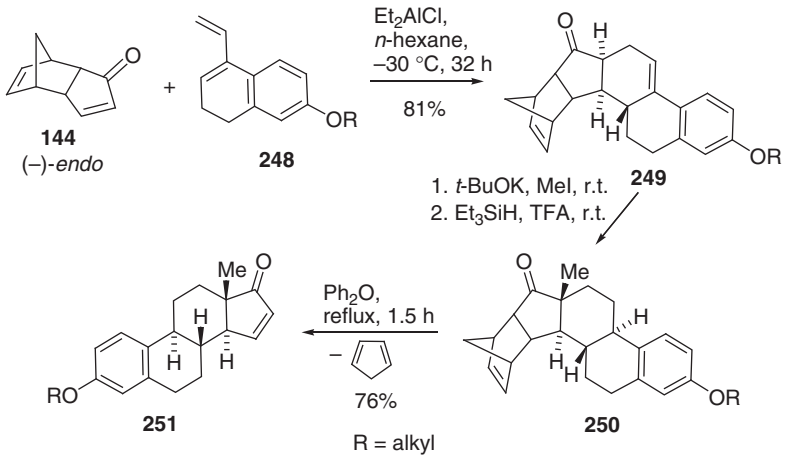
(26)

For the total synthesis of the *Galbulimima* alkaloid (±)-GB 13, a retrosynthetic strategy led to the pentacyclic framework, which, on incorporation of a piperidine moiety, furnished the alkaloid in the racemic form. The use of a rhodium(I)-catalyzed ketone–hydroarylation and a late-stage pyridine reduction afforded the target compound in a multistep procedure.[139] The carbotricylic unit **247** was synthetized from pentadienone **144** and silyloxydiene **245**. The ytterbium-catalyzed DA reaction proceeded via an *endo*-transition state, and epimerization *in situ* resulted in ketone **246**. FVP of adduct **246** afforded the condensed cyclopentenone **247** (Scheme 58), which was applied in further steps to obtain (±)-GB 13.

A novel method was described for the preparation of (+)-estrone derivatives. From dicyclopentadienone **144** and 4-vinyl-7-alkoxy-1,2-dihydronaphthalenes **248** in the presence of Lewis acids, the process led to DA polycylic enantiomeric adducts **249** (Scheme 59). Methylation on the neighboring carbonyl and then chemoselective reduction with a triethylsilane–trifluoroacetic acid (TFA) mixture gave **250**, which underwent rDA cycloreversion to give 3-methyl- or other 3-alkyl-substituted (+)-estrones **251**.[140,141]



Scheme 58



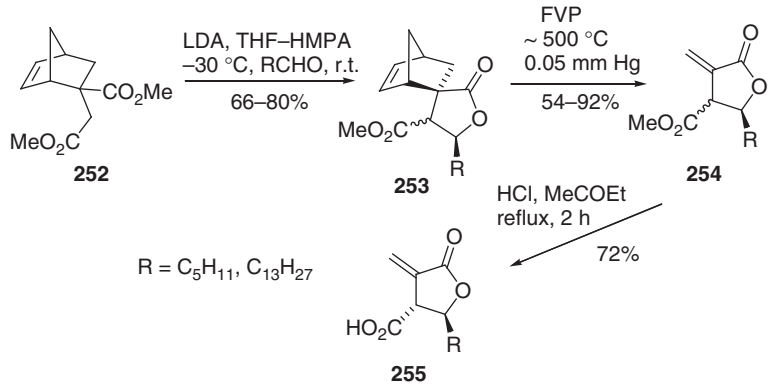
Scheme 59

5.12.6 Syntheses of Unsaturated Heterocycles

5.12.6.1 Heterocycles Containing One Heteroatom

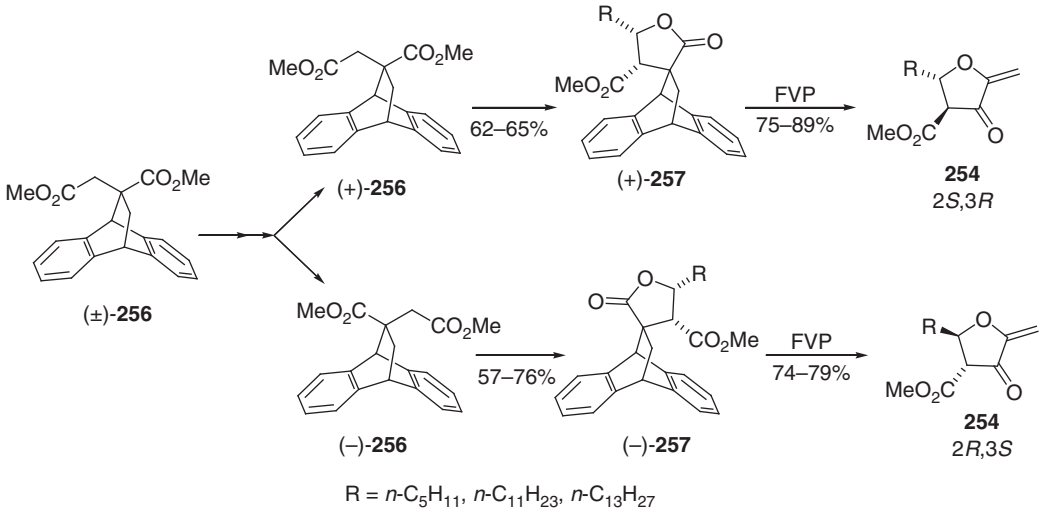
5.12.6.1.1 Oxygen-containing heterocycles

A facile preparation of β-carboxy-α-methylene-γ-lactones made use of an rDA reaction as the key step, leading to the total synthesis of the antibacterial and antitumoral (±)-methylenolactocin (**255**, R=C_5H_{11}) and (±)-protolichesterinic acid (**255**, R=$C_{13}H_{27}$). The preparation of these lactones involved some challenges, relating to the construction of the *exo*-methylene group and the susceptibility of the lactone to ring opening. In the coupling of the lithium ester enolate with the aldehyde, an unseparable mixture of diastereomeric spirolactones **253** was formed. The removal of cyclopentadiene by FVP resulted in a mixture of diastereomeric α-methylene lactones **254** in a smooth rDA process (Scheme 60). On refluxing in *n*-BuOH, the acid-catalyzed hydrolysis of the *exo*-methylenelactones gave rise exclusively to epimerization of the *cis*-acids to *trans*-methylenolactocin and protolichesterinic acid **255**.[142]



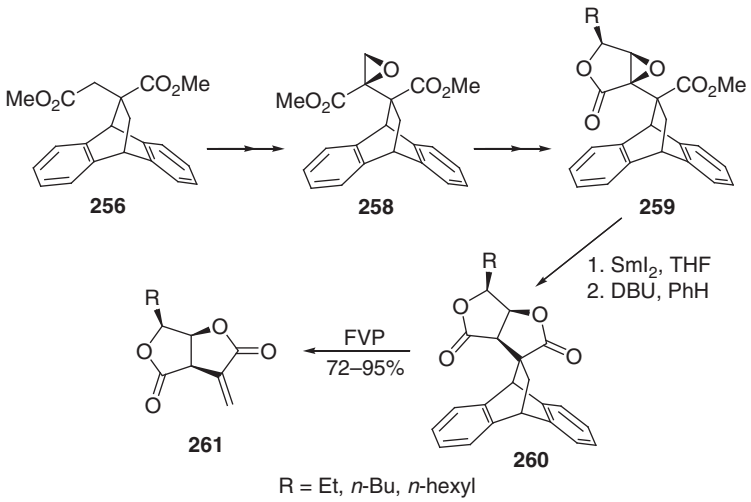
Scheme 60

For the formation of both the enantiomers of methylenolactocin (R=C_5H_{11}), protolichesterinic acid (R=$C_{13}H_{27}$) and nephrosterinic acid (R=$C_{11}H_{23}$) **255**, an alternative cycloreversion was introduced, involving the application of itaconate–anthracene adducts (Scheme 61). Enantiomerically pure (+)- and (–)-**256** were prepared by partial hydrolysis of (±)-esters **256** with KOH in aqueous MeOH, followed by regioselective esterification with enantiopure menthol. Transesterification of the menthyl esters followed by tandem aldol lactonization by the previous method led to the optically active main adducts **257**, which by means of FVP provided enantiomers **254**; subsequent acidic hydrolysis afforded enantiomerically pure **255**.[143]



Scheme 61

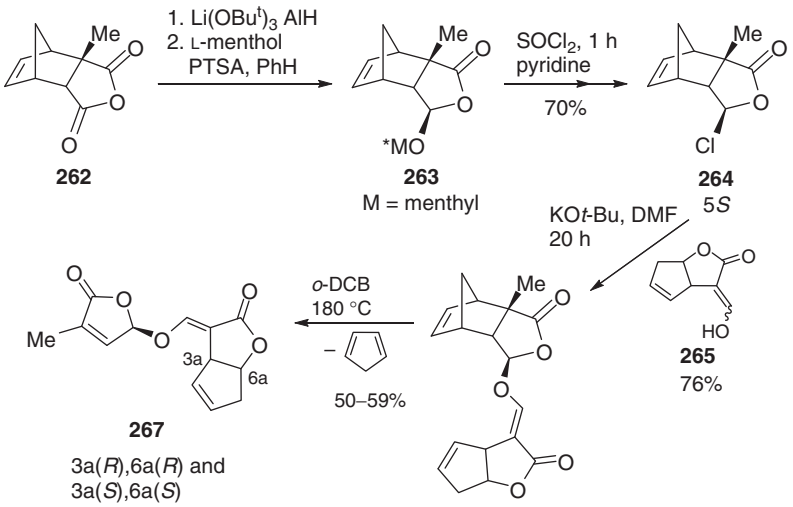
The itaconate–anthracene adduct **256** served as a methylene-carbonyl equivalent in the synthesis of various other natural products. Treatment of adduct **256** with LDA in tetrahydrofuran (THF) at 0 °C or with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −78 °C generated the ester enolate. With various electrophiles such as aldehydes, the enolate anion reacted stereospecifically to afford **258** after epoxidation, which underwent consecutive aldol lactonization to give epoxy lactones **259**. The samarium iodide-catalyzed ring opening of the epoxide, followed by treatment with catalytic DBU resulted in *cis*-fused bislactones **260** via ring reclosure (Scheme 62). The FVP of **260** led smoothly to naturally occurring α-methylene-bis-γ-butyrolactones **261**, such as xylobovide (R=Et), canadensolide (R=*n*-Bu), and sporothriolide (R=*n*-hexyl).[144,145]



Scheme 62

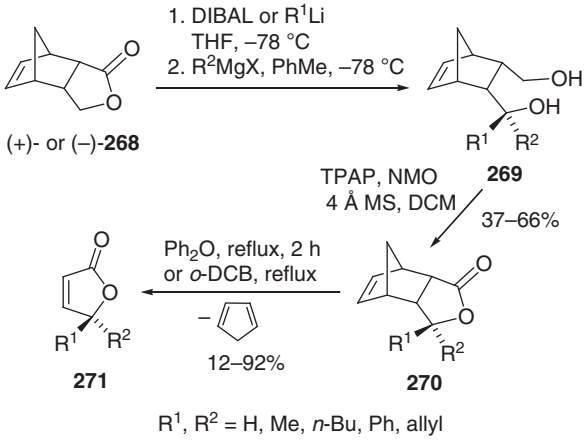
Several natural products, such as (+)-strigol and the related compounds (sorgolactone and alectrol) or their analogs (GR7) contain a butenolide ring and display, for example, a germination-stimulant effect. From cyclopentadiene-'protected' butenolides as reusable DA adducts, asymmetric conversion of the D-ring synthon to strigol derivatives was accomplished. On partial

reduction with alkoxyaluminum hydrides (lithium tributoxyaluminohydride, LTBA), **262** gave the racemic hydroxylactone, which on treatment with L-menthol in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst under azeotropic conditions furnished the separable diastereomers of menthyloxy lactone **263**. Acidic hydrolysis with 80% TFA and subsequent chlorination resulted in enantiopure chlorolactone **264**, which was coupled with racemic hydroxymethylenolactone **265** to give bislactone **266** (Scheme 63). When heated in *o*-DCB for 15 h, the DA adduct **266** underwent cycloreversion to diastereomers **267** (compound GR7) without epimerization.[146,147]



Scheme 63

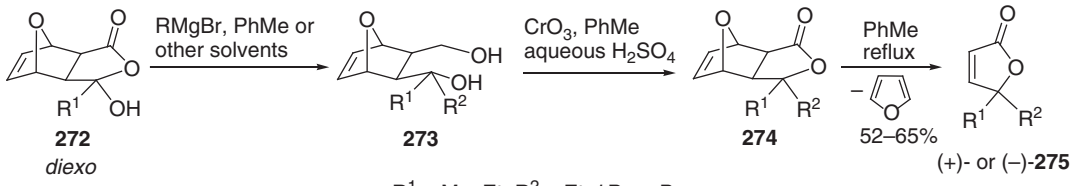
Appropriate norbornene adducts provided butenolides **271** by rDA cleavage. From tricyclic lactone **268**, a concise and enantiodivergent synthesis of (+)- and (–)-*trans*-quercus lactone,[148] γ-substituted butenolides with tertiary and quaternary asymmetric centers,[149] as well as a formal synthesis of (–)-ngaione via asymmetric synthesis of methyl- and allyl-disubstituted butyrolactone **271**[150] were achieved (Scheme 64).



Scheme 64

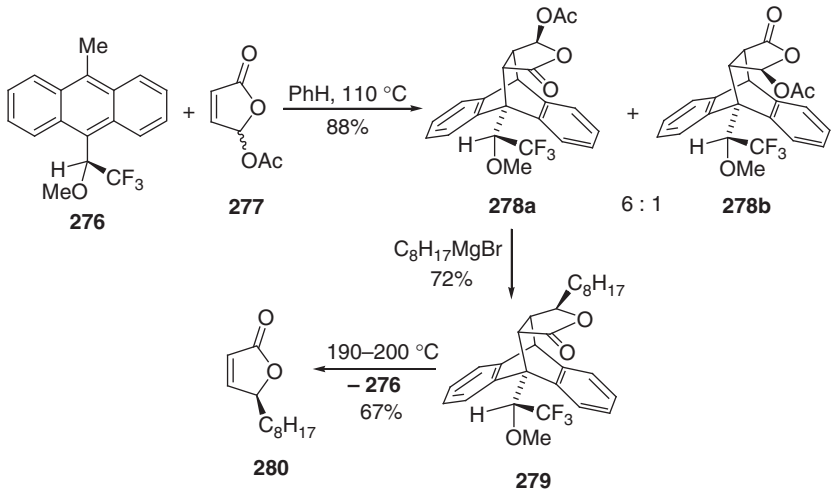
An unusually strong solvent effect on the diastereoselectivity of nucleophilic additions of alkylmagnesium bromides to the oxabicycloheptene-fused lactols **272** allowed the formation of 1,4-diols **273** in diastereoisomerically pure form. From these, γ,γ-disubstituted γ-butyrolactones **275** were obtained after oxidation with chromium(VI) oxide followed by a mild rDA process, without affecting the chiral center at C5 of the furan-2(5*H*)-one moiety (Scheme 65).[151]

A chiral anthracene template, 10-methyl-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene **276**, underwent a highly diastereoselective cycloaddition with MA or 5-acetoxy-2(5*H*)-furanone **277** to give a chiral adduct of value for further transformations, for example, for the preparation of enantioenriched butenolides. The cycloaddition of dienophilic furanone **277** with anthracene **276** in a sealed tube yielded a mixture of the regioisomeric adducts **278a** and **278b**. Because of the difficulty in separation and the



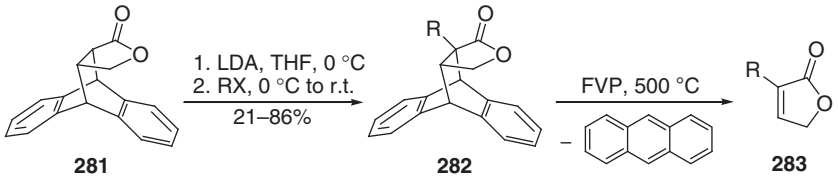
Scheme 65

instability of the adducts, this mixture was used in the subsequent step. Grignard reaction of the mixture of **278a** and **278b** resulted in the enantiopure lactone **279**, which by cycloreversion furnished optically active butenolide **280**, a precursor for the rove beetle pheromone (Scheme 66).[152]



Scheme 66

Deprotonation and electrophilic quenching of lactone **281**, derived from the DA adduct of anthracene and MA by $NaBH_4$ reduction, led to 3-substituted 2(5*H*)-furanones **283** after rDA cleavage of **282** by means of FVP. A low temperature (− 78 °C) precluded enolate formation; 0 °C was found to be the optimal temperature for the deprotonation of **281** with LDA. The addition of excess electrophile (1.5–3 equivalents) afforded *C*-alkylated lactones (Scheme 67), whereas the reaction with tributyltin chloride gave stannane **282** only in low yields (Table 9). On application of FVP, rDA fragmentation generally readily took place; for stannane **282**, however, it failed. This compound survived the MW irradiation, but application of FVP readily led to retrodiene cleavage and furnished the destannylated furanone **283**.[153]



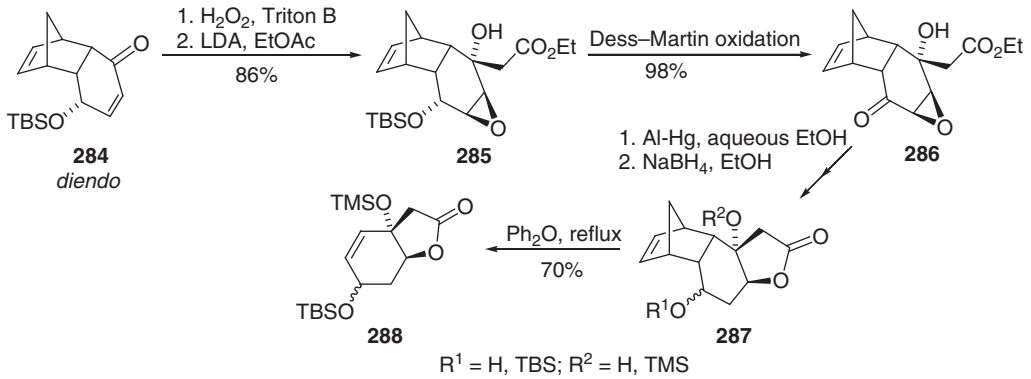
Scheme 67

Some cyclohexane-fused butenolides are natural products (e.g., menisdaurilide and aquilegiolide and its dihydro derivatives), isolated from *Tamarindus indica* L. or *Sinomenium acutum* species. Honzumi and Ogasawara developed a straightforward synthesis, using an rDA method starting from norbornene-fused cyclohexenone. Enantiopure **284** was transformed to the *exo*-epoxide, and the oxo group was then converted to the *β*-hydroxy ester in **285** on reaction with the lithium enolate derived from ethyl acetate. The secondary hydroxy group was selectively oxidized to give **286** under Dess–Martin conditions, and the epoxide ring was cleaved by using aluminum amalgam. Finally, $NaBH_4$-mediated reduction of the oxodiol ester afforded the polycyclic

Table 9 Substitution and cycloreversion of the anthracene–furanone adducts **281** (Scheme 67)

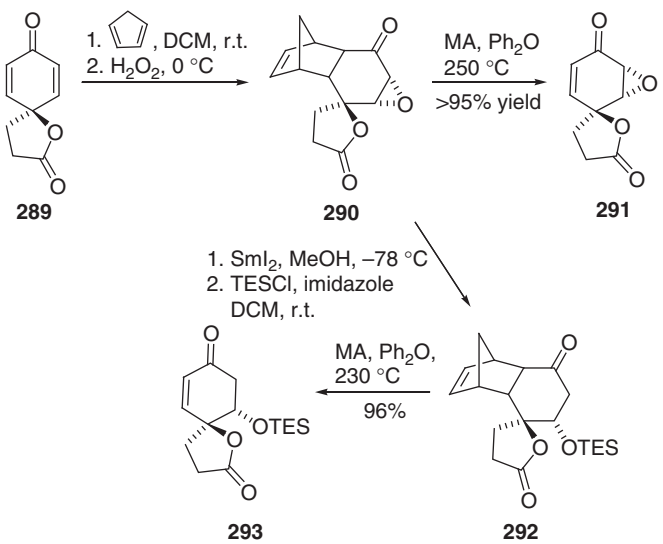
No.	*RX (electrophile)*	*Yield of **282** (%)*	*Yield of **283** (%)*
1	MeI	76	78
2	$CH_2{=}CHCH_2I$	71	83
3	BnBr	78	79
4	*n*-Bu_3SnCl	21	–
5	$(EtO)_2P(O)Cl$	74	67
6	Me_3SiCl	86	82

intramolecular lactone **287**, which, after protection, was refluxed to give cyclohexanenebutenolide **288** by cycloreversion (Scheme 68).[154]



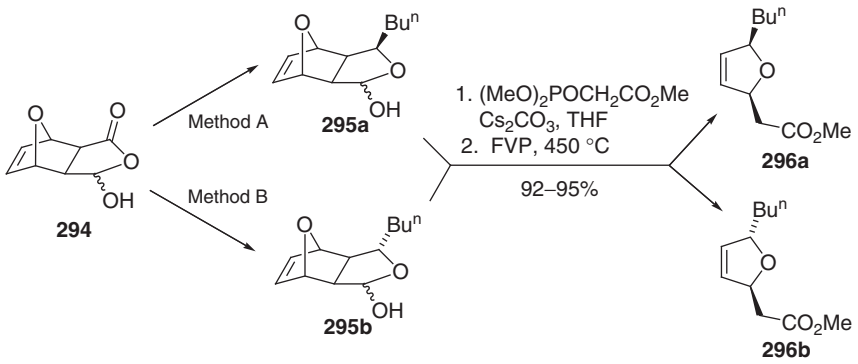
Scheme 68

Scyphostatin was isolated from a mycelial extract of *Dasyscyphus mollissimus* SANK-13892, and numerous enantioselective and highly efficient methods were later developed for its total synthesis. In one retrosynthetic strategy, preparation of the hydrophilic 6-alkyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one moiety was attempted by an rDA process. DA [4 + 2] cycloaddition of spirolactone **289** with cyclopentadiene furnished the adduct with a high π-facial selectivity. The epoxidation of the resulting dienone gave spirolactone **290**. The rDA process was carried out in the presence of MA to give product **291**. Treatment of epoxide **290** with samarium(II) iodide, reductive epoxide ring cleavage, protection with a triethylsilyl group (TES) and an rDA reaction afforded **293** (Scheme 69). This compound was later converted to 4,5-epoxy-2-cyclohexen-1-one bearing a spirolactone, which could be regarded as a Scyphostatin analog.[155,156]



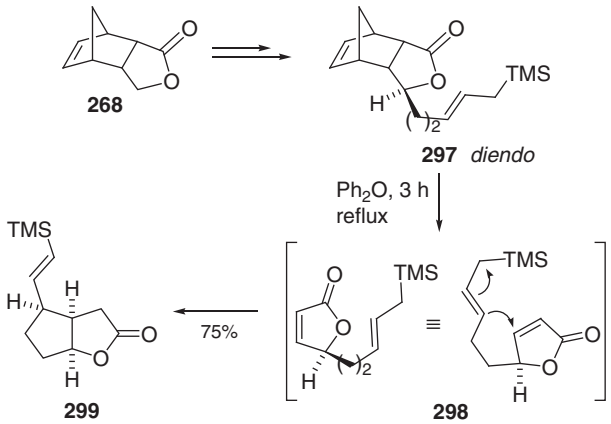
Scheme 69

In a stereocontrolled process, the addition of *n*-BuMgBr to racemic *diexo*-lactol **294** either in Et_2O (method A) or in THF, in the presence of $ZnBr_2$ as additive (method B), resulted in the corresponding butyldiols. With 4-methylmorpholine *N*-oxide and tetrapropylammonium perruthenate, oxidation to the lactones followed by reduction with DIBAL hydride (DIBAL-H) led to lactols **295a** and **295b**. Tandem Wittig–Horner/intramolecular Michael reactions resulted in the methyl esters of the tricyclic ethers, which were heated for a very short time (1 ms) and gave the rDA products *cis*- and *trans*-2,5-disubstituted dihydrofuran **296a,b** in excellent yields (92–95%) (Scheme 70).[157]



Scheme 70

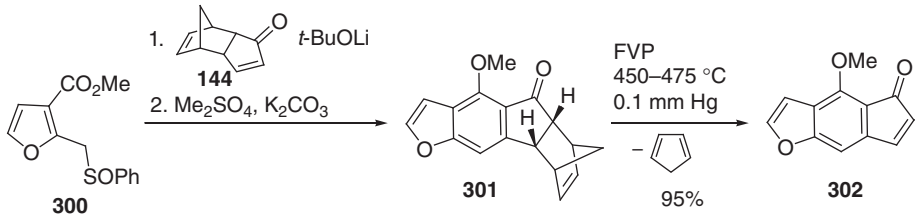
An enantiocontrolled synthesis of (–)-methyl 6-*epi*-cucurbate and (+)-methyl jasmonate proceeded from a chiral tricyclic lactone **268** via a new type of tandem rDA/ene-reaction activated by a trimethysilyl substituent. A solution of lactone **268** in toluene was successively treated with DIBAL at $-78\ ^{\circ}C$ and with the Grignard reagent prepared from 5-bromo-1-(trimethylsilyl)pent-2-ene. The resulting diol was cyclized oxidatively to lactone **297** by a known procedure with *N*-methylmorpholine-*N*-oxide (NMO)/tetrapropylammonium perruthenate (TPAP) at 0 °C. Finally, the rDA method gave intermediate **298** (Scheme 71). However, a tandem ene-type intramolecular cyclization occurred spontaneously in the course of the cycloreversion, which diastereoselectively yielded the cyclopentane-fused γ-lactone **299**.[158] This bicyclic lactone is an important precursor, for example, for the preparation of methyl jasmonate.



Scheme 71

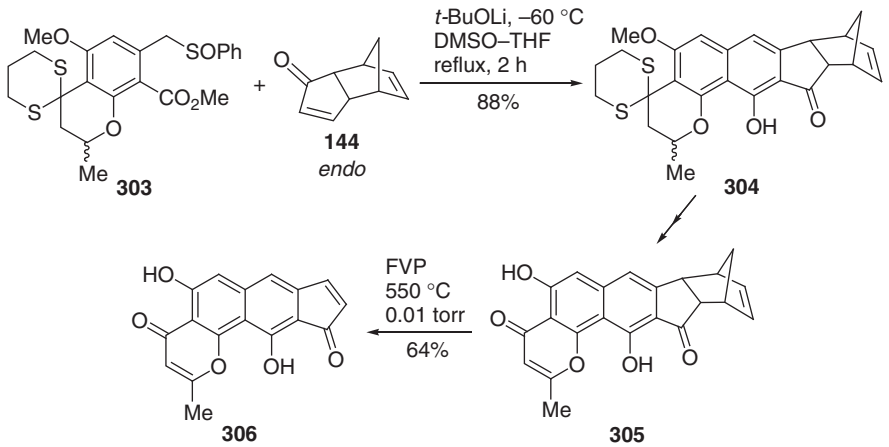
In multistep reactions, similar diastereomeric cyclopentene-condensed γ- and δ-lactones were prepared by using a synthon containing the dicyclopentadiene skeleton for the rDA step. A tricyclic building block, chiral 3-(hydroxymethyl)cyclopenta-2,4-dien-1-ol, served as equivalent for the two iridoids, the (–)-iridolactone and (+)-pedicularis-lactone, which were synthetized in an enantio- and diastereocontrolled manner.[159]

A simple method for the total synthesis of coriandrin and psoralen precursors involved an anion [4 + 2] cycloaddition–rDA strategy, starting from sulfoxide ester **300** and bicyclic enone **144**. Addition and *O*-methylation resulted in the pentacyclic ketone **301** in good yields (>70%). The product underwent rDA fragmentation under FVP conditions to afford 4-methoxy-5*H*-indeno[5,6-*b*]furan-5-one **302** (Scheme 72). Epoxidation with H_2O_2/Et_3N followed by pyrolytic rearrangement led to demethylcoriandrin, an isocoumarin derivative. 8-Methoxypsoralen and its isostere were prepared analogously.[160–162]



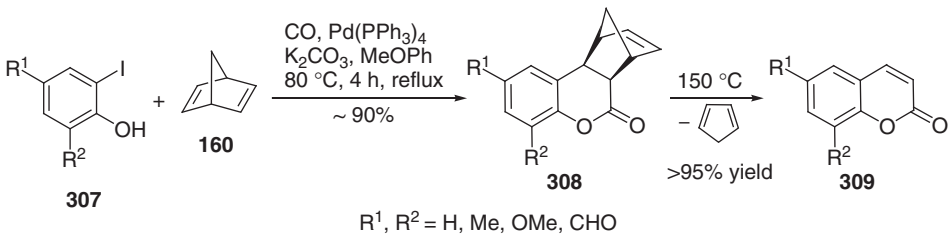
Scheme 72

The first total synthesis of the natural product euplectin, a metabolite isolated from *Flavoparmelia euplecta* lichen which contains a rare chromone (1,4-benzopyrone) ring-condensed indenone structure, comprised 17 steps, including a Hauser sulfoxide-annulation, chromone ring formation, and an rDA process. The preparation of sulfoxide ester **303** from methyl 2-hydroxy-4-methoxy-6-methylbenzoate in a multisequenced procedure proved to be a difficult and crucial task. The modified annulation of sulfoxide **303** with enone **144** yielded the target intermediate **304**, which, after desulfurization, dehydrogenation, and demethylation, afforded polycyclic pyrone **305** (Scheme 73). FVP of this adduct and cleavage of the cyclopentadiene ring led to euplectin **306**.[163]



Scheme 73

A variety of substituted coumarins have been prepared through Pd-catalyzed coupling of *o*-iodophenols **307** with internal alkenes. The reactions of norbornadiene **160** with *o*-iodophenols **307** in the presence of tetrakis(TPP)palladium gave norbornene-fused coumarins **308** with *diendo* selectivity (Scheme 74). On heating, the rDA reactions of adducts **308** readily led to substituted coumarins **309** by the elimination of cyclopentadiene.[164,165]

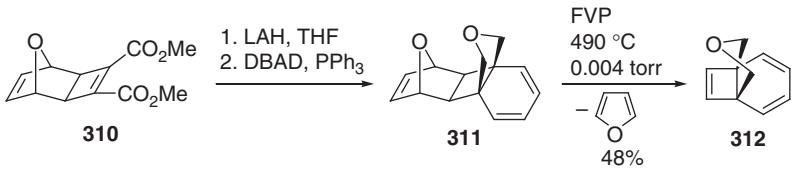


Scheme 74

Oxabicycloheptene-fused cyclobutenedicarboxylic ester **310** was reduced to the diol, which underwent the Mitsunobu reaction with dibenzyl azodicarboxylate (DBAD) and Ph_3P to furnish the pentacyclic tetrahydrofuran **311**. When subjected to FVP *in vacuo*, adduct **311** resulted in the unique oxygen-bridged bicycle[4.2.0]octa-2,4,7-triene **312** (Scheme 75).[166]

5.12.6.1.2 Nitrogen-containing heterocycles

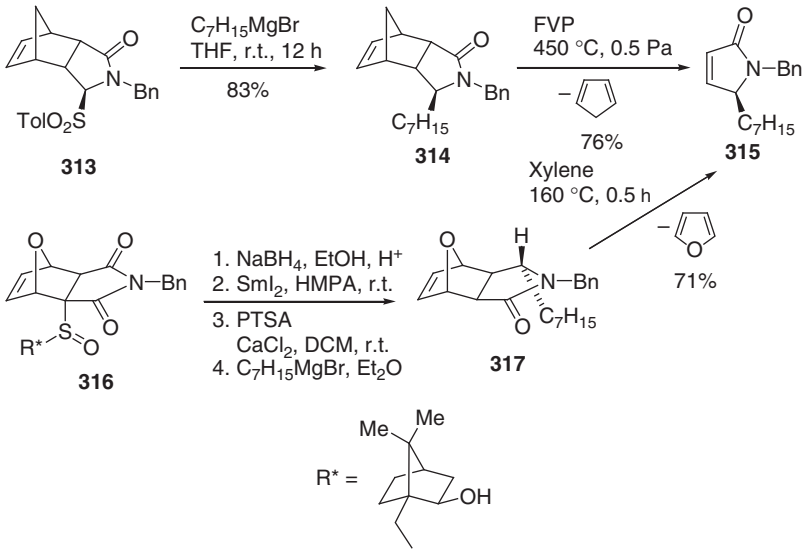
From the bicyclo[2.2.1]heptene- or 7-oxabicyclo[2.2.1]heptene-fused pyrrolidinone **313**, a novel route was developed to furnish the 5-substituted 3-pyrrolin-2-one **315** in high optical purity (Scheme 76). The reaction of lactam **313** with heptylmagnesium bromide in the presence of $ZnBr_2$ gave the (+)-alkylated derivative **314**, FVP of which afforded (+)-5-heptyl-3-pyrrolin-2-one **315**, though the enantiomeric excess was only moderate (*ee* 74%). To increase the enantiopurity of **315**, an alternative method was



310 **311** **312**

Scheme 75

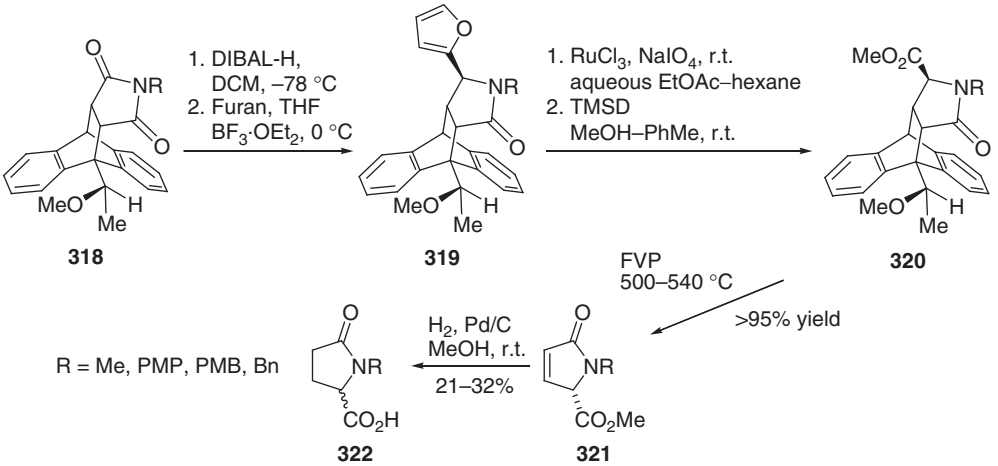
applied, using the enantiomerically pure *N*-substituted α-(2-*exo*-hydroxy-10-bornylsulfinyl)maleimide–furan adduct **316** as the starting compound. After reduction, desulfinylation with SmI_2 and two-step sequenced alkylation, lactam **317** was obtained; in contrast to the bicyclo[2.2.1]heptene, the nucleophile addition took place from the less-hindered *endo* face on the 7-oxabicyclo[2.2.1]heptene. On heating, the (+)-tricyclic lactam **317** gave (+)-**315** via rDA fragmentation in a similar yield (71%) but in high optical purity (*ee* >97%).[167]



313 **314** **315** **316** **317**

Scheme 76

On the basis of an anthracene chiral auxiliary, a new asymmetric synthesis of pyroglutamic acids **322** was reported (Scheme 77). Anthracene adducts **318** were prepared from chiral methoxyanthracene and maleimides. Introduction of the furan ring into these masked carboxylic acid units ensured excellent diastereoselectivity for **319**, and later allowed conversion to ester through oxidative steps and methylation on treatment with $RuCl_3$–$NaIO_4$ followed by trimethylsilyldiazomethane

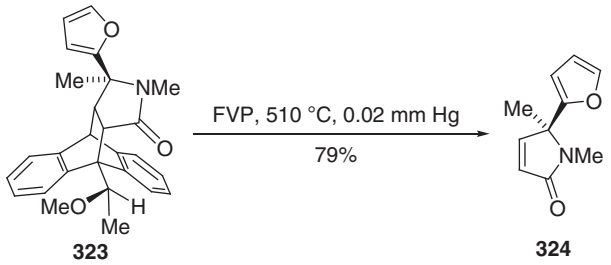


318 **319** **320** **321** **322**

Scheme 77

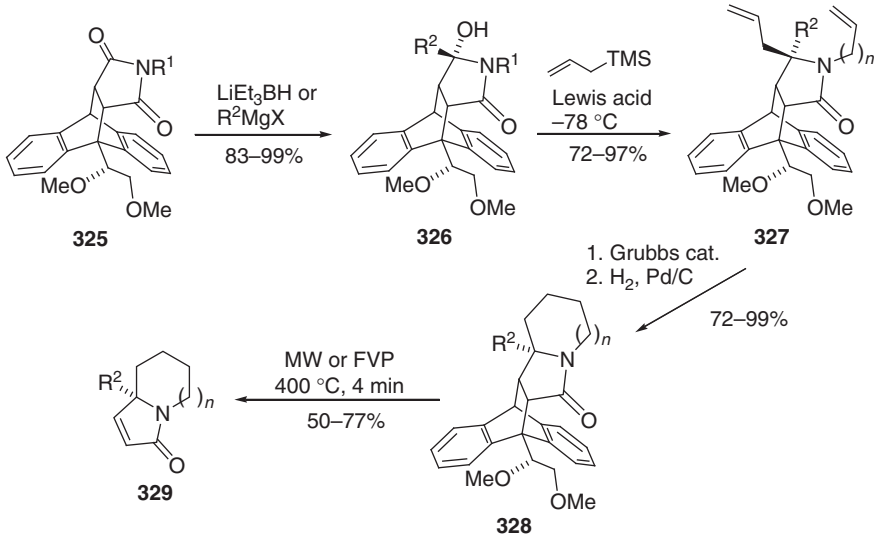
(TMSD). The obtained pyroglutamic ester adducts **320** were subjected to FVP, when rDA cleavage of the chiral anthracene templates occurred to give *N*-substituted 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylates **321** with a conversion of 100%. These products were directly hydrogenated to afford *N*-alkylpyroglutamates **322**, although complete racemization occurred under these conditions.[168]

Starting from the chiral anthracene template, an analogous rDA resulted in arylated or heteroarylated derivatives through the stereoselective intermolecular Friedel–Crafts reaction of the hydroxylactam derivative of **318** (R=Me). Thus, the 5-furanyl-1,5-dimethylpyrrolone enantiomer **324** was obtained by thermolysis of the dimethyl cycloadduct **323** via an rDA process (equation 27).[169]



323 **324** (27)

For the preparation of α,β-unsaturated lactams or bicyclic lactams, 9-(1,2-dimethoxyethyl)anthracene **325** was successfully employed as chiral template in DA/rDA sequences. The cycloadditions took place with complete diastereo- and regioselectivity; moreover, the cycloreversion allowed the use of an FVP method. Superhydride reductions or Grignard reactions of adducts **325** resulted in hydroxylactams **326**. Subsequent allylation furnished dialkenyllactams **327**, which were suitable for ring-closing metathesis in the presence of the Grubbs catalyst. Hydrogenation led to indolizidines **328** ($n=1$) or their seven-membered homologs ($n=2$), and subsequent FVP yielded bicyclic lactams **329** (Scheme 78). By means of cycloaddition, the 3-allyl-5-phenyl-substituted analog of **324** was also prepared from 9-(1,2-dimethoxyethyl)anthracene and *N*-methyl-2-bromomaleimide in several steps. The experimental results demonstrated that 9-(1,2-dimethoxyethyl)anthracene was more reactive (2.8 times) than anthracene itself.[170] Under other conditions (e.g., irradiation, acid catalysts, and a silica gel adsorbent), rDA cleavage with MW-promoted cycloreversion on graphite as a support at 150 °C proceeded with lower yields.[171]



325 **326** **327** **328** **329**

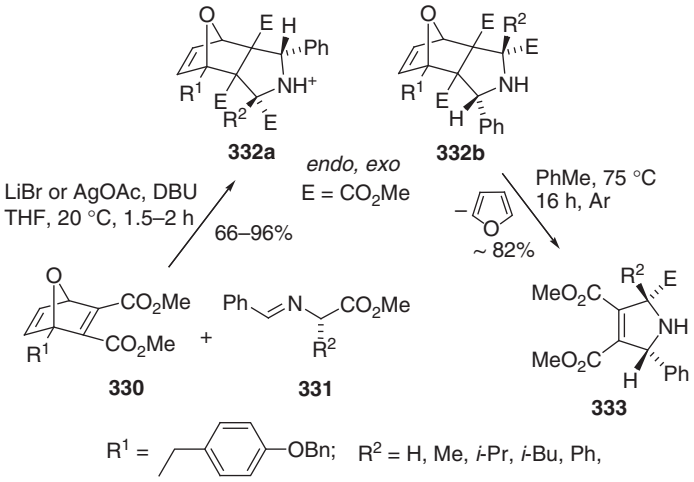
R^1 = Me, vinyl, allyl, $(CH_2)_2CH{=}CH_2$; R^2 = H, Me, Ph; n = 1, 2

Scheme 78

In similar enantioselective syntheses of substituted α,β-unsaturated γ-lactams, 9-(2-phenylethyl)aminoanthracene proved to be a valuable chiral template in DA/rDA reaction sequences in terms of stereo- and regioselectivity.[172]

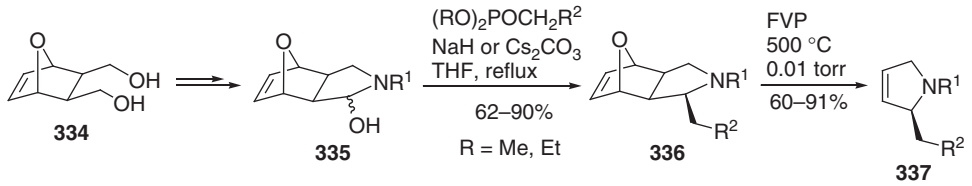
The [3 + 2] cycloaddition of *N*-methylated azomethine ylides derived from α-amino esters with dimethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylates **330** was described for the production of 3-pyrrolines **333**. 1,3-Dipolar cycloaddition to the C=C bond, catalyzed by LiBr or AcOAg in the presence of DBU, afforded mixtures of the stereo- and regioisomeric adducts **332**. The Ag(I)-catalyzed reactions led mainly or exclusively to the *diexo* isomers of **332**. In contrast, the application of LiBr gave

the tricylic products **332a** and **332b** through *diendo* transition states. The cycloreversions were generally carried out under argon in toluene (Scheme 79), which resulted in 5-phenyl-2,5-dihydro-1*H*-pyrrole-2,3,4-tricarboxylates **333**. For R=H, isomerization to 2-phenyl-3,4-dihydro-2*H*-pyrrole-3,4,5-tricarboxylate was observed, probably by a 1,3-hydrogen shift and a C=C double bond migration.[173,174]



Scheme 79

A general synthetic procedure for the preparation of optically active 2-substituted 2,5-dihydropyrroles was based on a highly stereoselective intramolecular Michael reaction, which afforded enantiopure dihydropyrroles after an rDA reaction (Scheme 80). For the key compound **336**, the commercially available *diexo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was reduced with LAH to diol **334**, which was converted by transesterification in the presence of lipase to an optically active intermediate, followed by cyclization to an *N*-acetyl- or other *N*-protected (*tert*-butoxycarbonyl- or *N*-benzyloxycarbonyl) derivative **335**. The tandem Wittig–Horner/intramolecular Michael reaction of hemiaminals **335** with phosphonates in basic medium gave rise to tricyclic pyrrolidines **336** with considerable diastereoselectivity (82–90% *de*), depending on the phosphonate substituent R^2, the base and the *N*-protecting group. On FVP, the tricyclic pyrrolidines **336** underwent cycloreversion and furnished enantioenriched 2-substituted 3-pyrrolines containing an *N*-protecting group **337**.[175]

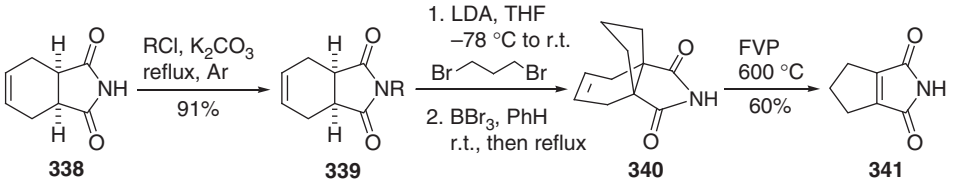


Scheme 80

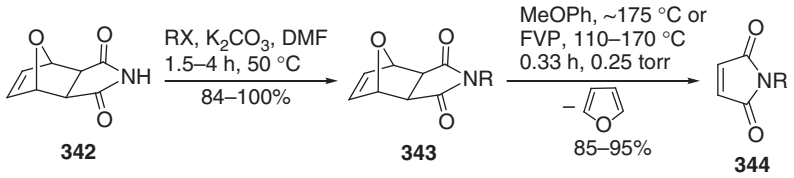
A convenient synthesis of maleimycin, an antibiotic isolated from *Streptomyces showdoensis*, was based on the dianion-mediated reaction of *cis*-1,2,3,6-tetrahydrophthalimide **338**. The maleimycin precursor was constructed in four stages, including protection and deprotection steps. After protection of the imide with benzylchloromethyl ether, compound **339** was alkylated at the annelation sites with 1,3-dibromopropane, resulting in an 'azapropellane-like' propylene-bridged maleimycin moiety. The imide was deprotected under mild conditions with BBr_3 to give 7,9-dioxo-8-azatricyclo[4.3.3.0]dodec-3-ene **340**, which underwent an rDA process on FVP (Scheme 81) to afford the required skeletal framework **341** of the target molecule.[176]

From the *diexo*-7-oxabicycloheptene adduct, *N*-alkylmaleimides **344** were easily prepared via rDA fragmentation on cleavage of furan. After alkylation of imide **342** by heating with alkyl, alkenyl or benzyl halides, the resulting alkylimides **343** were subjected to a thermolytic rDA reaction (Scheme 82) by means of FVP.[177] This method allowed the use of the widely available starting materials and gave maleimides in high purities and yields. It is noteworthy that the products were also of interest for potential thermo- and photo-setting polymerizations. Similar preparations of 2-hydroxyethyl-*N*-maleimide and the related compounds of biological interest were recently patented.[178]

A series of dicyanodihydrofuran (DCDHF) fluorophores containing a thiol-capturing maleimide function were prepared by the above strategy. Alternative and generally useful procedures involved the combination of the Mitsunobu reaction of a



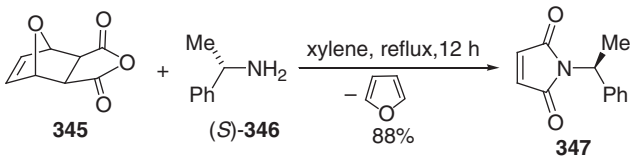
Scheme 81



Scheme 82

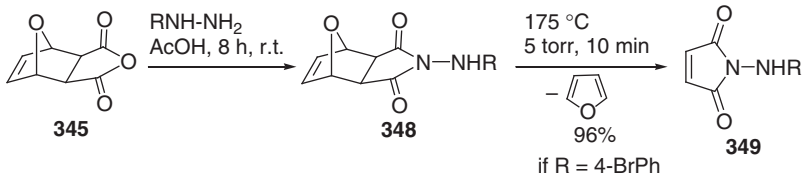
hydroxy-DCDHF with 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic imide **342** and subsequent rDA cycloreversion in refluxing toluene or xylene, leading to maleimide derivatives in high yields.[179]

(1*S*)-*N*-(1-Phenylethyl)maleimide **347** was prepared through π-cationic cyclization. Its reactivity was studied and this compound was applied to the synthesis of the chiral pyrroloisothiochromane and pyrrolobenzo[*d*]thiepine.[180] The key compound was constructed from the commercially available *diexo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **345** via a tandem amine–anhydride cyclodehydration/rDA reaction involving the release of furan in a one-pot procedure (equation 28). Compound **347** was obtained in another three-step reaction from MA, but in a lower overall yield (73%).



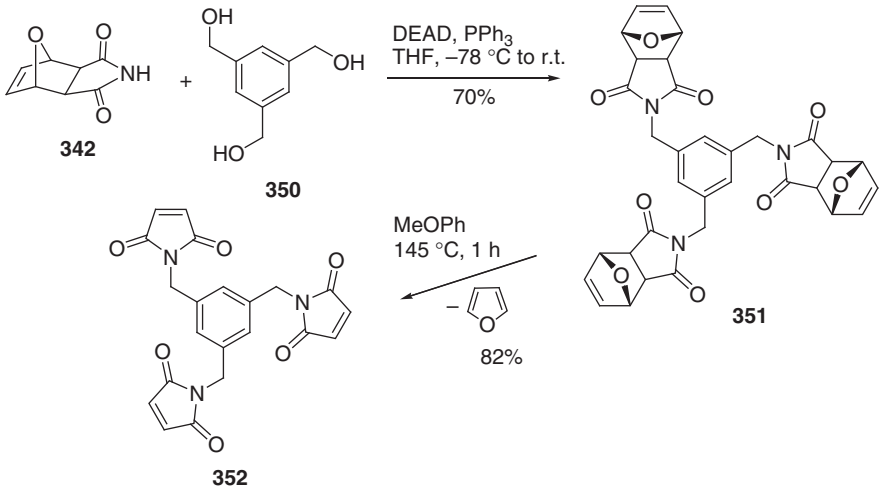
(28)

Thanks to the special behavior of MA, a new synthetic route to *N*-substituted aminomaleimides was devised through condensation of *diexo*-**345** with hydrazine or one of its derivatives. The mixture was stirred under nitrogen to give bicyclic alkyl- or aryl-substituted *N*,*N*′-maleimides **348** (Scheme 83). When the bicylic imide (R = 4-bromophenyl) **348** was heated, rDA decomposition to furan and the aryl-protected aminomaleimides **349** occurred.[181] In other cases, however, the cycloreversion failed.



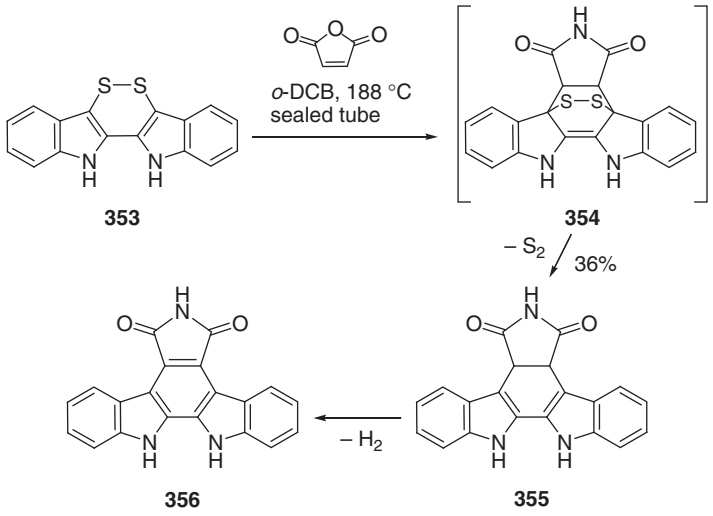
Scheme 83

A novel homotrifunctional conjugation reagent, 1,3,5-tris-(*N*-maleimidomethyl)benzene, was synthetized in pure form and high yield, and its reactivity was examined by the application of L-cysteine as a model nucleophile. Use of the Mitsunobu reaction for the coupling of imide **342** with 1,3,5-tris(hydroxymethyl)benzene **350** under standard conditions (DEAD = diethyl azodicarboxylate) afforded trisubstituted benzene **351,** which underwent an rDA reaction on heating and led to the reactive maleimide **352** on cleavage of furan (Scheme 84). The reactivity of this unsaturated triimide **352** in thiol conjugation was studied using L-cysteine methyl ester hydrochloride as a simple but representative thiol-containing molecule for the demonstration of peptide conjugation.[182]



Scheme 84

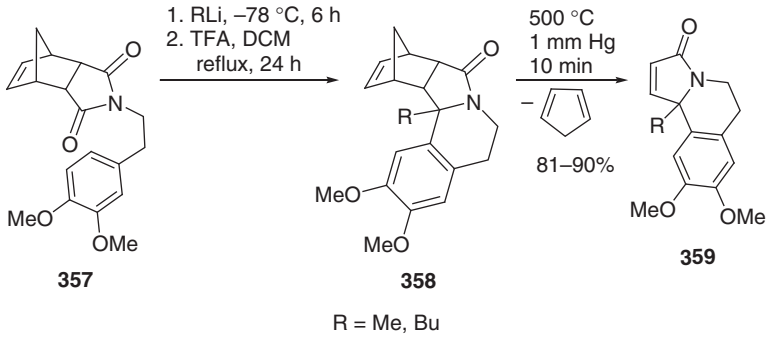
The DA/rDA sequence involving the formation and transformation of maleimide was applied in an approach to the natural product arcyriaflavin-A **356**, a potent inhibitor of CDK4/cyclin D1 (IC_{50} = 59 nM), which also inhibits the human cytomegalovirus in cell cultures (IC_{50} = 200 nM). Heating of the conformationally rigid dithiete **353** with maleimide furnished arcyriaflavin-A (Scheme 85) via [4 + 2] adduct **354**, which underwent an rDA process to yield S_2 and dihydroarcyriaflavin-A **355**. The latter presumably underwent dehydrogenation by dissolved oxygen and/or extruded sulfur to afford the targeted alkaloid **356**.[183]



Scheme 85

The reactions of organolithium compounds with *N*-phenylethylimides proved to be an effective means of accessing functionalized norbornene-fused dihydropyrrolo[2,1-*a*]isoindolones. Thus, imide **357**, prepared by condensation of the phenylethylamine with the bicyclic anhydride, was treated with MeLi or *n*-BuLi to afford α-hydroxylactam intermediates as diastereomeric mixtures in ratios of 88:12 and 85:15, respectively. Intramolecular cyclization with TFA gave methylene-bridged isoindoloisoquinolines **358**, which on heating resulted in the unsaturated pyrroloisoquinolinones **359** through an rDA procedure (Scheme 86).[184]

An enantiodivergent synthesis of 10b-substituted pyrrolo[2,1-*a*]isoquinolines (R = H, Me, *n*-Bu, allyl) **359** was developed from enantiomerically pure *N*-phenethylnorborn-5-ene-*diendo*-2,3-dicarboxyimide **357** with the 2-*exo*-hydroxy-10-bornylsulfinyl group as the chiral auxiliary. The key transformations resulted from the diastereoselective intramolecular cyclization of aryllithiums and α-amidoalkylation, wherein the ethylidene bridge of the norbornene directed the stereochemical outcome in either reaction. Hence, the organolithium addition–intramolecular α-amidoalkylation sequence on imides **359** afforded the *R* configuration stereoselectively, whereas the tandem Parham cyclization–intermolecular α-amidoalkylation on the iodinated imide led to the epimeric compound. Refluxing in *o*-DCB and the subsequent reductive removal of the chiral auxiliary followed by the rDA step afforded (10b*S*)- and (10b*R*)-pyrroloisoquinolines **359** in optical purities (> 99% *ee*).[185,186] This synthetic strategy was also used

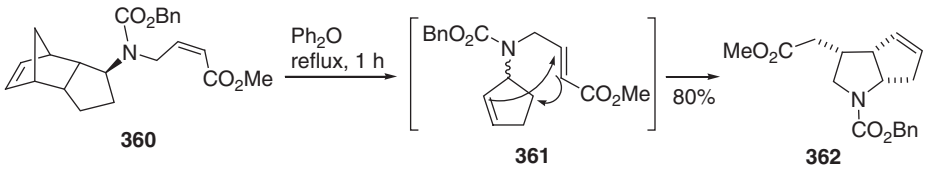


Scheme 86

for the preparation of 10b-functionalized dihydropyrrolo[2,1-*a*]isoquinolines, serving as intermediates for the synthesis of the erythrinane ring systems.[187]

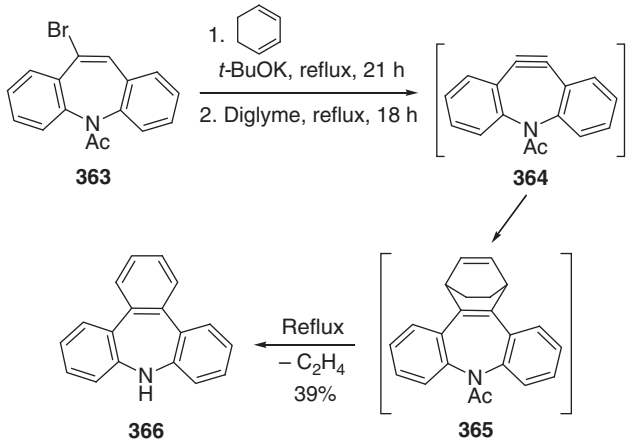
The application of Grignard reagents instead of organolithium compounds led to similar results in addition to carboximide **357**; the expected methyl- and pentenyl-substituted pentacyclic dihydropyrrolo[2,1-*a*]isoindolones were obtained in good yields (75–81%) and with complete diastereocontrol. Cycloreversions by heating in vacuum at 0.25 mm Hg gave the same heterocycles **359** in 65–90% yield.[188]

A stereocontrolled route to (–)-kainic acid, a representative of the kainoid amino acids which exhibit insecticidal, anthelminthic, and neuroexcitatory properties, was devised by enantioconvergent conversion of the *diendo*-bicyclopentadienone **144** to amine starting materials for concurrent rDA fragmentation and intramolecular ene reaction. The thermolysis of the amine diastereomers **360** gave best results in boiling Ph_2O at ~260 °C. However, an intramolecular ene reaction took place with high diastereo- and enantioselectivity (>99% *ee*) to give all-*cis* tetrahydrocyclopenta[*b*]pyrrole carboxylate **362** instead of the expected cyclopentenylamine **361** (Scheme 87). Compound **362** was transformed to a direct precursor of kainic acid in a multistep procedure by cyclopentene ring-opening reactions.[189]



Scheme 87

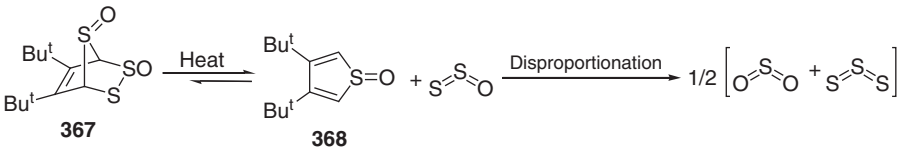
By means of an rDA procedure, a new route to 9*H*-tribenz[*b,d,f*]azepine **366** was developed. As a reactive intermediate, 10,11-didehydro-5-acetyl-5*H*-dibenz[b,f]azepine **364**, prepared *in situ* with *t*-BuOK from 5-acetyl-10-bromo-5*H*-dibenz[*b,f*]azepine **363**, was reacted with 1,3-cyclohexadiene in a DA reaction. The resulting cycloadduct **365** underwent an rDA reaction on refluxing in diglyme (Scheme 88) and a simultaneous hydrolysis resulted in the targeted 9*H*-tribenz[*b,d,f*]azepine **366**.[190]



Scheme 88

5.12.6.1.3 Sulfur-containing heterocycles

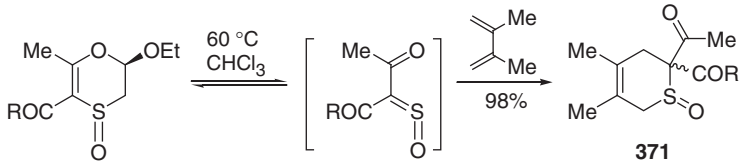
5,6-Di-*t*-butyl-2,3,7-trithiabicyclo[2.2.1]hept-5-ene-7-*endo*-oxide was prepared by the addition of S_2Cl_2 to 3,4-di-*tert*-butylthiophene-1-oxide. Oxidation with dimethyldioxirane gave a 7:1 isomeric mixture of 5,6-di-*t*-butyl-2,3,7-trithiabicyclo[2.2.1]hept-5-ene-2-*endo*-7-*endo*-dioxide **367** and the 2-*exo*-7-*endo*-dioxide. The thermally labile **367** underwent an rDA process, which produced S_2O and *S*-oxide **368** in a reversible way (Scheme 89). By trapping with dienes, S_2O gave 3,6-dihydro-1,2-dithiin-1-oxides. In the absence of dienes, the S_2O disproportionated to SO_2 and S_3, the latter participating in 1,3-dipolar cycloaddition with 3,4-di-*tert*-butylthiophene 1-oxide **368**, on its syn-π-face with respect to the S=O bond, to give a trithiolane derivative on hydrolysis. In the presence of excess norbornene, the 1,3-dipolar cycloadduct was produced. Thus, the rDA cycloreversion of **368** served as a source of S_2O and S_3.[191]



367 **368**

Scheme 89

When oxathiin-*S*-oxides **369** were heated, α,α′-dioxosulfines **370** were generated as unisolable electron-poor dienes by thermal rDA cycloreversion; they were reacted *in situ* with 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene as the dienophile. In direct DA reactions, sulfines were formed as dihydrothiopyran cycloadducts **371**, which could be isolated in almost quantitative yields (Scheme 90). However, a longer reaction time was required for the cycloaddition of α-oxo-α′-carbethoxysulfine (R=OEt) than for the corresponding dioxosulfine (R=Me) cycloreversion intermediate.[192,193]



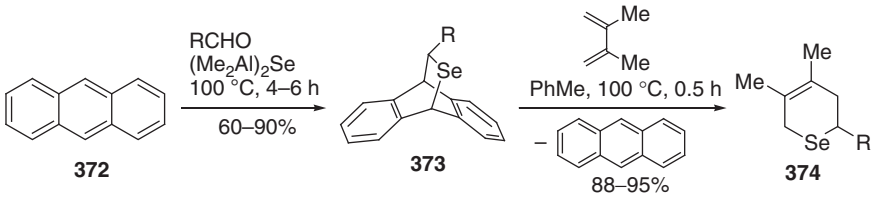
369 **370** **371**

R = Me, OEt

Scheme 90

5.12.6.1.4 Selenium-containing heterocycles

From alkylaldehydes or substituted benzaldehydes, the [4 + 2] cycloadducts **373** of anthracene **372** with selenoaldehydes were prepared using bis(dimethylaluminum)selenide as the reagent. *In-situ* regeneration from the selenoaldehyde adducts through a thermal rDA/DA process in the presence of 2,3-dimethyl-1,3-butadiene as the trapping agent afforded dihydroselenopyranes **374** (Scheme 91).[81]

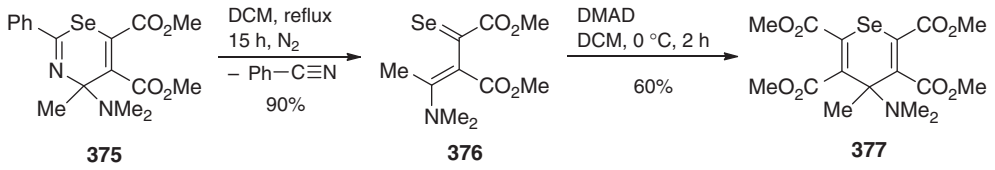


372 **373** **374**

R = *n*-Pr, Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, $(CH_2)_2Ph$

Scheme 91

The reactivities of *N*-selenoacylamidines as 4π heterodienic systems in [4 + 2] cycloadditions with electrophilic dienophiles have been reported. Selenoketone **376** was generated *in situ* from 4*H*-1,3-selenazine **375** through the release of benzonitrile via cycloreversion. When quenched with an excess of DMAD, this stable heterodienic diester **376** afforded 4*H*-selenopyrane **377** (Scheme 92) by [4 + 2] cycloaddition.[194]

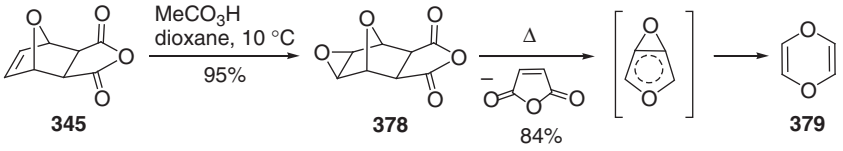


Scheme 92

5.12.6.2 Heterocyclic Ring Systems Containing Two Identical Heteroatoms

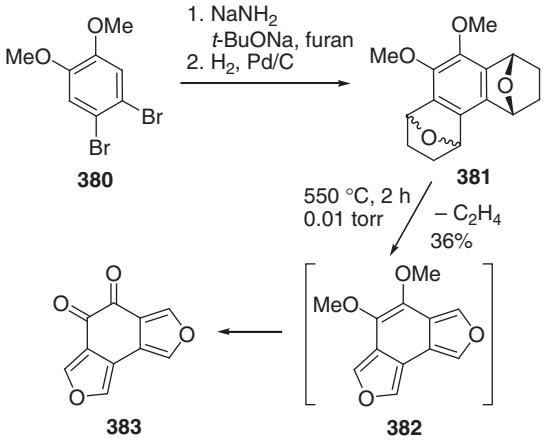
5.12.6.2.1 Heterocycles containing two oxygen atoms

The [4 + 2] cycloaddition of furan to MA opens access to 1,4-dioxin **379**. With peracetic acid, the unsaturated adduct **345** was converted to epoxide **378**, which underwent a thermal rDA reaction to give 1,4-dioxin **379** (Scheme 93) by the regeneration of MA. Compound **379** was then transformed to acrylaldehyde.[195]



Scheme 93

Treatment of dibromide **380** with sodium amide and sodium *t*-butoxide (Caubère's superbase) in the presence of furan gave a mixture of *syn*- and *anti*-9,10-dimethoxydiepoxyphenanthrene, which afforded diepoxytetrahydrophenanthrene **381** in a yield of 97% on hydrogenation over a Pd catalyst. Pyrolysis of **381** led to the angular benzodifuran-4,5-dione **383** directly, though in poor yield. The formation of the *o*-quinone could be rationalized by double rDA extrusion of ethylene from phenanthrene **381** through intermediate **382** (Scheme 94), which underwent homolytic C–O bond cleavage of the methoxy groups.[196]

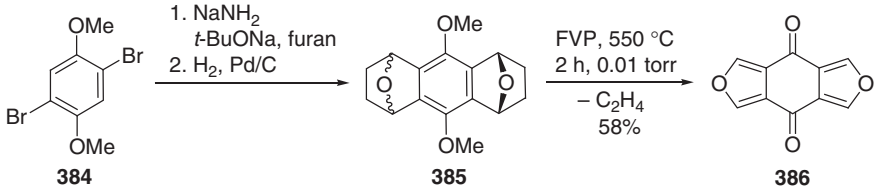


Scheme 94

Through a similar route, linear *p*-quinone analogs were synthetized from 1,4-dibromo-2,5-dimethoxybenzene **384** in a stirred one-pot reaction (Scheme 95) with superbase and dry furan. After workup, the corresponding diepoxyanthracene **385** was obtained from the mixture. Hydrogenation and FVP rDA fragmentation of **385** led to benzodifuran-4,8-dione **386**.

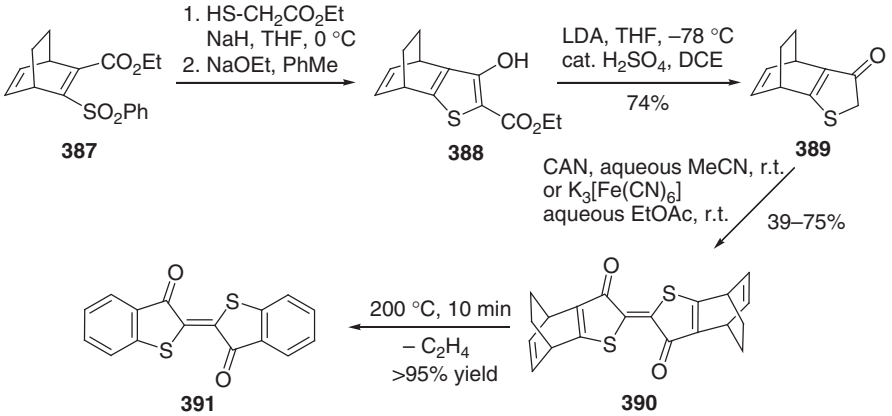
5.12.6.2.2 Heterocycles containing two sulfur atoms

Thioindigo **391**, a unique thio analog of the natural dye indigo, was synthetized by an rDA method from the symmetrical bisthiophenonylidene attached to two bicycle[2.2.2]octadiene (BCOD) units (Scheme 96). From commercially available ethyl propiolate, cycloadduct **390** was prepared in six steps by the construction of the DA adduct **387** with cyclohexadiene. The thiophene ring was formed by Dieckmann condensation followed by an intramolecular reaction, which directly afforded 2*H*-thiophen-3-one **389** after an acidic workup. The subsequent step led to oxidative dimerization to **390**, for which a variety of



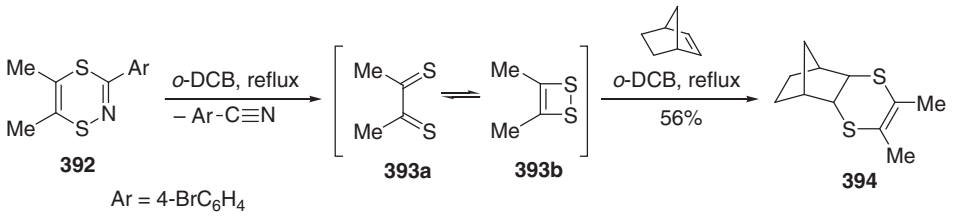
Scheme 95

conditions were studied: two-phase oxidation with potassium ferricyanide was found to be best, though the application of ceric ammonium nitrate (CAN) was also efficient. As the precursor adduct, compound **390** was obtained as a 1:1 mixture of diastereoisomers but as a single *E* isomer with regard to the newly formed C=C bond. Cycloreversion of dimer **390** on heating resulted in pure thioindigo **391**.[197]



Scheme 96

Under forcing conditions (refluxing in 1,2-dichlorobenzene at 180 °C), 5,6-dimethyl-3-*p*-bromophenyl-1,4,2-dithiazine reacted with dienophiles such as DMAD or with less reactive alkenes (e.g., norbornene). The mechanism of this reaction was not proven, but seemed to occur by cycloreversion of dithiazine **392** via the loss of nitrile to the butane-2,3-dithione intermediate **393a** or its ring-closed 3,4-dimethyl-1,2-dithiete tautomer **393b**, which was trapped by norbornene to give the stable and isolable hexahydro-5,8-methano-1,4-benzodithiine **394** (Scheme 97). However, thermolysis of **392** with an electron-rich substituent on the phenyl ring did not result in 1,4-dithiines but in isothiazoles formed by extrusion of elemental sulfur from the ring. Electron-withdrawing subtituents such as bromide on the phenyl group promoted the DA-type [4 + 2] cycloreversion/cycloaddition process at a reasonable temperature.[198]



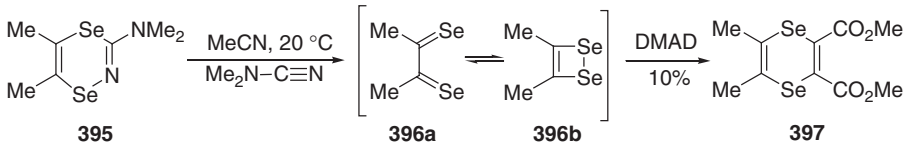
Scheme 97

5.12.6.2.3 Heterocycles containing two selenium atoms

1,3-Diselenolium salts reacted with ammonia and iodine to afford unstable 1,4,2-diselenazine **395**, which, similar to the thio analog, was fragmented under mild rDA conditions to furnish dimethylcyanamide and 1,4-diselenine **397**, presumably via the intermediate 1,2-diselenete **396b**, which is trapped with DMAD to give cycloadduct **397** (Scheme 98).[199]

5.12.6.2.4 Heterocycles containing two phosphorus atoms

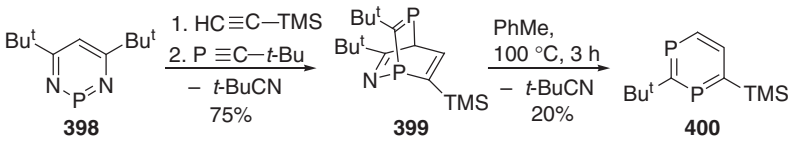
t-Butylphosphaethyne (*t*-Bu–C≡P) in combination with trimethylsilylacetylene underwent a DA reaction with 1,3,2-diazaphosphinine **398** to furnish azadiphosphabarrelene **399** by elimination of one molecule of pivalonitrile (Scheme 99). Through



395 396a 396b 397

Scheme 98

smooth [4 + 2] cycloaddition with other silylated acetylenes (e.g., ferrocenyl), the reaction also gave different azadiphosphabarrelenes in yields of 53–75%. Although the thermolysis of these barrelenes led exclusively to the starting compounds, the pyrolysis of **399** under the same conditions proceeded by [4 + 2] cycloreversion with concomitant elimination of a further molecule of pivalonitrile led to 1,3-diphosphinine **400**, unambiguously identified by an analysis of its tungsten complex.[200]

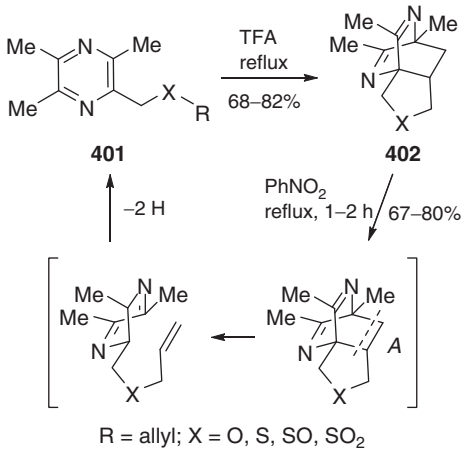


398 399 400

Scheme 99

5.12.6.2.5 Heterocycles containing two nitrogen atoms

On heating in TFA (bp. 72 °C) for 1–8 h, the intramolecular DA cycloaddition of a series of pyrazines **401** with ω-alkenyl sidechains led to 3-oxa- and 3-thia-8,10-diazatricyclic dienes **402**. The cycloadduct **402** was converted into the starting pyrazines **401**, via rDA reaction at a higher temperature (~210 °C). Thus, the unstable DA adduct **402** was thermally cleaved at the site labeled 'A' in Scheme 100 and dehydrogenated by the hydrogen acceptor nitrobenzene (Scheme 100).[201]

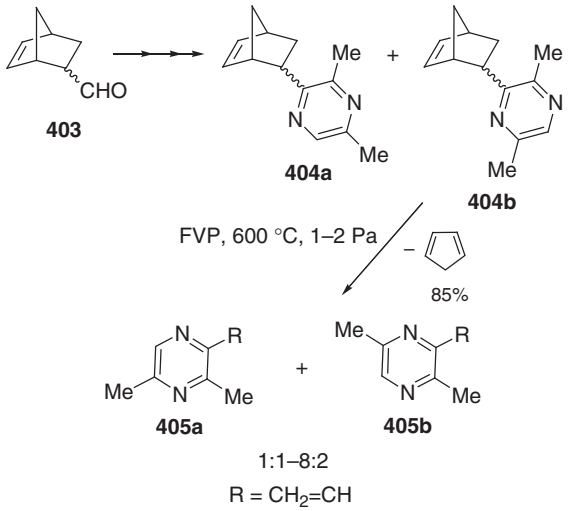


401 402

Scheme 100

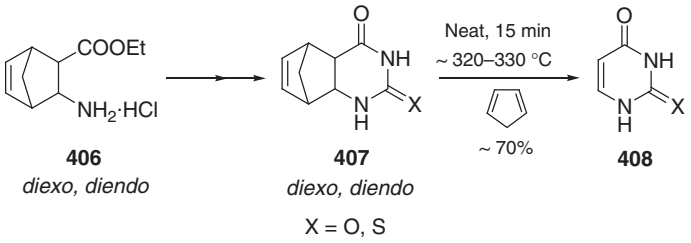
Regioisomeric 2-vinyl-3,5-dimethylpyrazine **405a** and 3-vinyl-2,5-dimethylpyrazine **405b** were obtained via norbornene-substituted derivatives **404a,b** in a multistep procedure (Scheme 101). These pyrazines were identified in ground or freshly roasted coffee beans and in volatile aromatic compounds of roasted peanuts. Earlier attempts at the total synthesis of these compounds were quite unsuccessful or the products were obtained in only very poor yields (1–5%). With the aid of a DA/rDA methodology, however, the dimethylpyrazine moiety was successfully built up from carboxaldehyde **403** by condensation with acetaldehyde, followed by oxidation in ethoxyethanol with Bi_2O_3 to a propanedione derivative. This diketone (a mixture of *exo* and *endo* isomers) was then reacted with 1,2-diaminopropane to yield 5,6-dihydropyrazines, which were subsequently oxidized to pyrazines **404** in the presence of MnO_2. The mixture of regioisomers **404a** and **404b** was pyrolyzed to pyrazines **405a** and **405b** in various ratios (equimolarly from *exo* isomer **404**, and in a ratio of 8:2 from the *endo* compound **404**) in a yield of 85% (and an overall yield of 14% over five steps).[202]

With KOCN, the reaction of 2-aminonorbornenecarboxylate hydrochlorides **406** gave urea ester intermediates, which were cyclized to norbornene-fused 5,6-dihydrouracils **407** (X = O). The *diexo* adduct **407** afforded 2,4-pyrimidine-2,4-dione (uracil) **408**



Scheme 101

(X=O) on heating at around the melting point through the release of cyclopentadiene (Scheme 102).[203] The transformation of the norbornene-condensed *β*-aminoester with thiophosgene resulted in an isothiocyanate, which, on reaction with NH_3 in MeOH and standing overnight at room temperature, cyclized spontaneously to *diendo*- or *diexo*-tricyclic dihydrothiouracils **407** (X=S). When **407** were heated to the melting point, a retrodiene decomposition took place with the cleavage of cyclopentadiene, resulting in pure thiouracil **408** (X=S).[204]



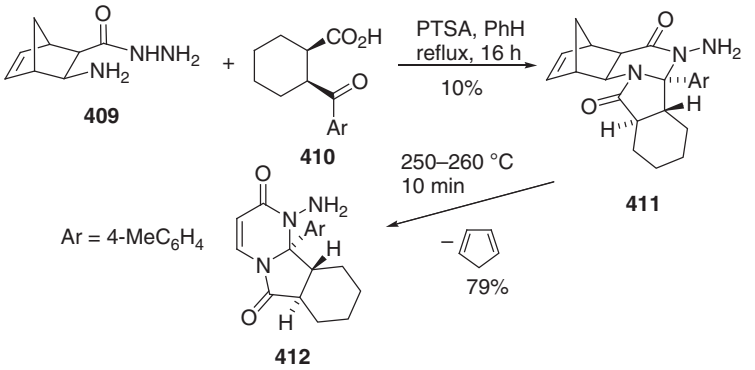
Scheme 102

The reactions of *diexo*-3-amino-2-norbornenecarbohydrazide **409** and *cis*-2-toluoyl-cyclohexanecarboxylic acid **410** or its aromatic analogs involved two unusual transformations (Scheme 103). When **409** and **410** were refluxed in benzene in the presence of a catalytic amount of PTSA,[205] the pentacyclic *N*-aminopyrimido[2,1-*a*]isoindole-2,6-dione **411** was obtained first, in contrast to the expected methylene-bridged decahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one. At the same time, a *cis*→*trans* isomerization took place at the annelation carbons in the isoindolone moiety of **411**, which was followed by fragmentation via an rDA process to give cyclopentadiene and aminopyrimido[2,1-*a*]isoindole-2,6-dione **412** (Scheme 103).

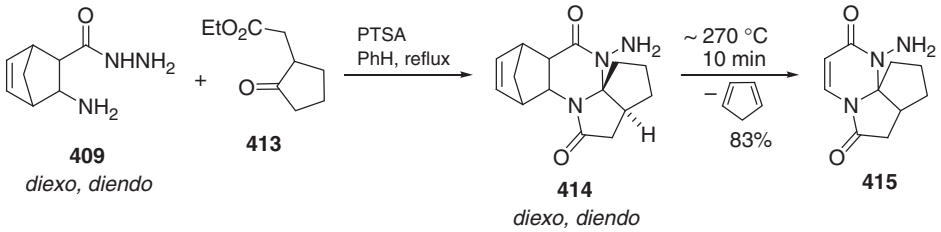
Similar reactions of *diexo*- or *diendo*-3-amino-2-norborneneaminocarbohydrazides **409** with ethyl (2-oxocyclopentyl)-acetate **413** afforded the pentacylic *N*-aminopyrrolo[1,2-*a*]quinazoline-1,5-dione **414**. On heating at temperatures between 270 and 275 °C, this compound gave tetrahydrocyclopenta[2,3]pyrrolo[1,2-*a*]pyrimidine-2,6-dione **415** in an rDA reaction (Scheme 104).[206]

From *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide **416** and levulinic acid or *p*-toluoylpropionic acid **417**, all diastereomers of the tetracyclic pyrrolopyrimidine derivatives **418a** and **418b** were prepared in a three-step domino reaction. When subjected to an MW-mediated rDA reaction, the tetracycles furnished bicyclic pyrrolo[1,2-*a*]pyrimidines **419a** and **419b** by loss of cyclopentadiene (Scheme 105). From enantiomerically pure *diexo*-3-aminobicyclo [2.2.1]hept-5-ene-2-carboxamide, the heterocyclic products were formed with *ee* >99%, demonstrating that the starting compound was an excellent chiral source.[207]

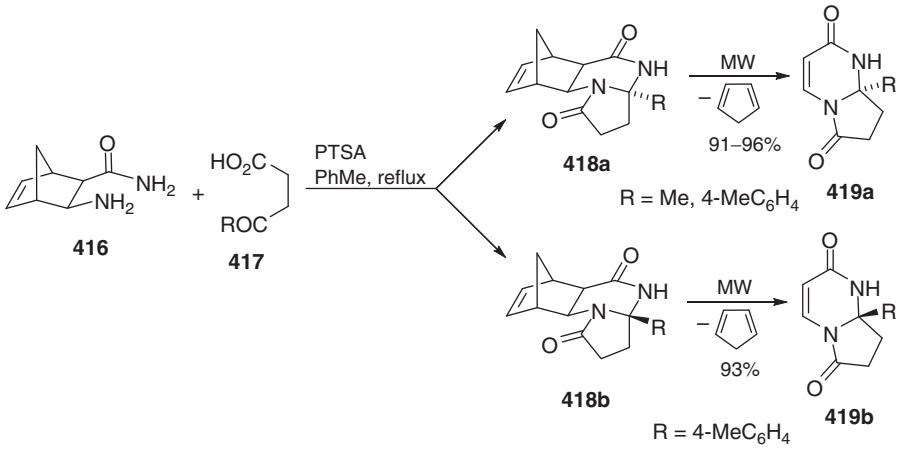
Through cyclization of *diexo*-3-amino-7-oxanorbornene-2-carboxamide **420** with *γ*-oxocarboxylic acids such as levulinic acid or *p*-toluoylpropionic acid **417**, pyrrolo[1,2-*a*]pyrimidinediones **419** were formed directly or indirectly, with the loss of furan by thermolysis (equation 29). When 2-formylbenzoic acid was used, the same sequence of condensation with **420** and cycloreversion led to the corresponding pyrimido[1,2-*a*]isoindoledione.[208]



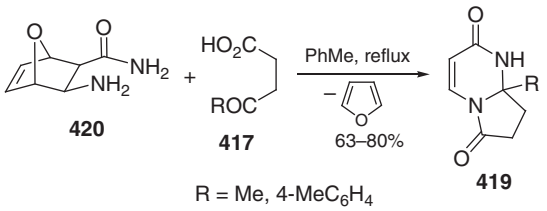
Scheme 103



Scheme 104

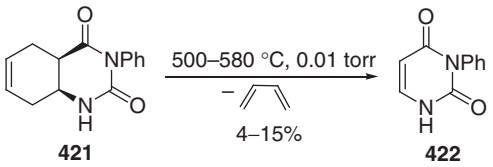


Scheme 105



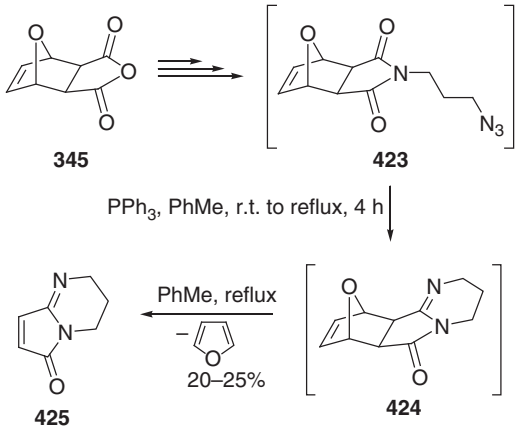
(29)

When *cis*-3-phenyltetrahydroquinazoline-2,4-dione **421** was subjected to FVP during a contact time of ~0.01 s, rDA cycloreversion took place at all the temperatures studied, furnishing uracil **422** as the main product, together with butadiene (equation 30).[209]



(30)

From commercially available 7-oxabicycloheptenedicarboxylic anhydride **345,** the bicyclic amidinium salt of the antibacterial and cytotoxic agent phloeodictine A1 (isolated from the sponge *Phloeodictyon* sp.) was synthetized in a convergent seven-step route, in an overall yield of 8%. The Eguchi-aza-Wittig reaction of **423** furnished the tetracyclic intermediate **424**, which, following an rDA reaction, liberated 3,4-dihydropyrrolo[1,2-*a*]pyrimidin-6(2*H*)-one **425** (Scheme 106). Specifically, with 3-aminopropanol, the furan–MA DA adduct **345** provided a cyclic hydroxypropyl-*N*-imide, which was converted to the mesylate and then azide **423** with NaN_3. When refluxed with polystyrene-supported PPh_3, **423** underwent the intramolecular Eguchi-aza-Wittig cyclization to **424**, spontaneous rDA cycloreversion of which gave **425**.[210]



Scheme 106

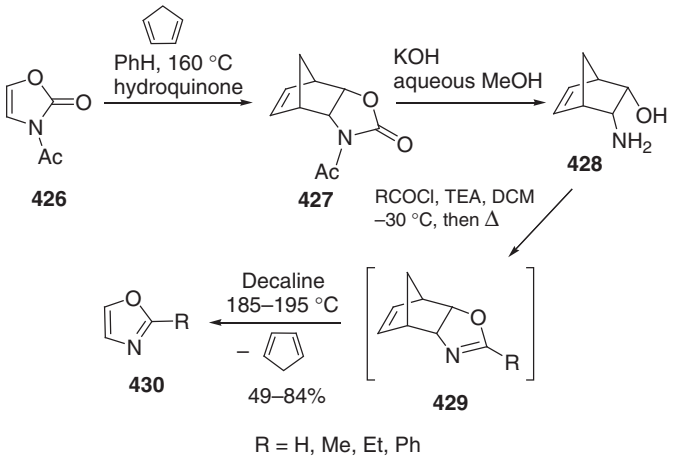
5.12.6.3 Heterocycles Containing Two Different Heteroatoms

5.12.6.3.1 Heterocycles containing nitrogen and oxygen

After earlier attempts to synthetize the oxazole moiety through classical condensation strategies had failed, a facile and mild rDA approach to prepare 2-substituted oxazoles was developed that involved a cycloaddition–cycloreversion method. For the preparation of norbornene-2-aminoalcohol **428,** cyclopentadiene was reacted with 3-acetyl-2(3*H*)-oxazolone **426** and the adduct **427** was hydrolyzed. Acylation and thermal cyclization allowed the simultaneous retrodiene reaction to afford oxazoles **430** (Scheme 107). Attempts at the cyclization of α-amino alcohol **428** to tricyclic oxazoles **429** by other methods, for example, with phosphoryl chloride or thionyl chloride, were ineffective.[211] The above method, however, was successfully applied to the preparation of analogs of disoxaril (Win 51711 and Win 54954), which inhibit the replication of poliviruses types 1 and 2 and display antirhinoviral activity against human rhinovirus type 14 (HRV-14).[212]

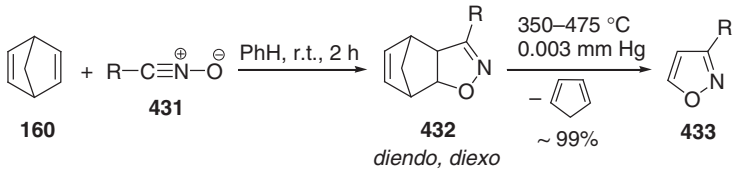
3-Vinyl- and 3-phenylisoxazoles **433** were prepared by a sequence involving the cycloaddition of nitrile oxides to norbornadiene **160**, followed by rDA cycloreversion on FVP (Scheme 108). The 1,3-dipolar addition was achieved *in situ* from acrylonitrile and benzonitrile oxides **431**, with an excess (5 equivalents) of norbornadiene, after which the reaction mixture was purified by column chromatography to afford *diexo* and *diendo* adducts **432** in different ratios (~3:1). Traditional thermal rDA fragmentation of the adducts in mesitylene at 163 °C for 19 h was unsuccessful, whereas FVP at temperatures between 350 and 400 °C (R=Ph) or at 475 °C (R=vinyl) gave complete conversion.[213]

A practical and convergent route to the key precursor (AB enone ring core) for tetracycline antibiotics from simple starting materials was developed using a diastereoselective Michael–Claisen coupling. Specifically, a Michael–Claisen cyclization of the dimethylphenylsilyl-substituted cyclohexenone **434** and the isoxazole ester **435** was effected with sodium hexamethyldisilazide (NaHMDS), and the resulting adduct then treated with potassium hexamethyldisilazide (KHMDS) to ensure rapid deprotonation of the Claisen product. In the preferred sequence, the Michael–Claisen cyclization product **436** was heated to induce the rDA reaction (Scheme 109), which resulted in a mixture of cleaved dimethylphenylsilyl–cyclopentadiene isomers in different ratios and the desired 9-amino-5-hydroxydihydronaphtho[2,3-*d*]isoxazolone derivative **437**. Two other rDA fragmentations of the adduct **436** under different conditions were also studied. Heating in diphenyl ether at 170 °C for 6 min provided tricyclic **437** in



426 **427** **428** **429** **430**

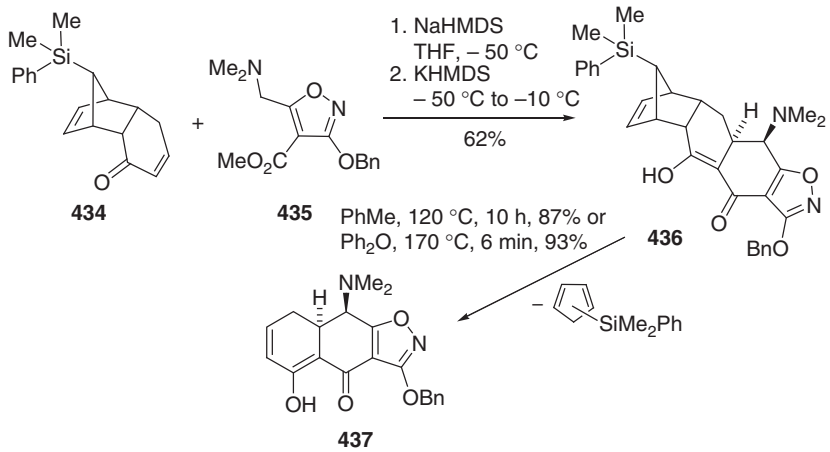
Scheme 107



160 **431** **432** *diendo, diexo* **433**

Scheme 108

93% yield, and heating of the hydrochloride of **436** in hexafluoroisopropanol under reflux (60 °C) for 12 h afforded the same product in 69% yield after the basic workup. However, the rDA process of the analogous nonsilylated cycloadduct **436** occurred only above 200 °C, and partial decomposition (55%) took place in the presence of dimethyl maleate when continuous-flow reaction conditions were applied.[214]

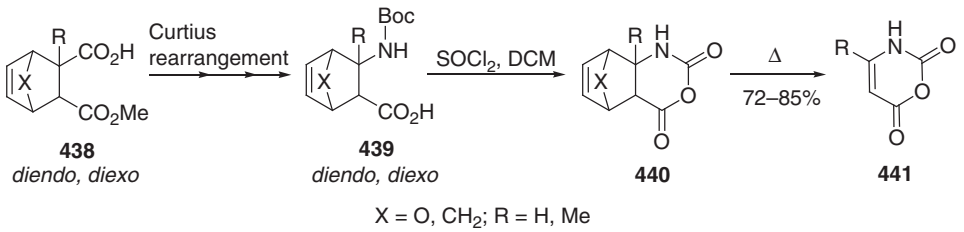


434 **435** **436** **437**

Scheme 109

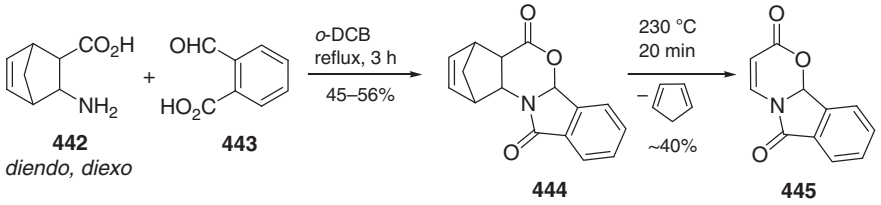
From bicyclic monoesters **438**, methylene- and oxygen-bridged bicyclic *N*-protected *β*-amino acids **439** were prepared diastereo- and regioselectively via Curtius rearrangement. Subsequent cyclization by $SOCl_2$ led to the fused 1,3-oxazinane-2,6-dione adducts **440** (Scheme 110), which provided versatile substrates for the synthesis of dipeptides and could be easily converted to 2*H*-1,3-oxazine-2,6(3*H*)-diones **441** by thermal [4 + 2] cycloreversion.[215] The conditions of the retrodiene reactions differed greatly, depending on the bridge atom: in the presence of a methylene bridge (X=CH_2), more forceful heating was required

(160 °C) than in the case of an oxygen bridge (refluxing in benzene). This proved that furan splits off more readily than cyclopentadiene in the course of the rDA reaction.



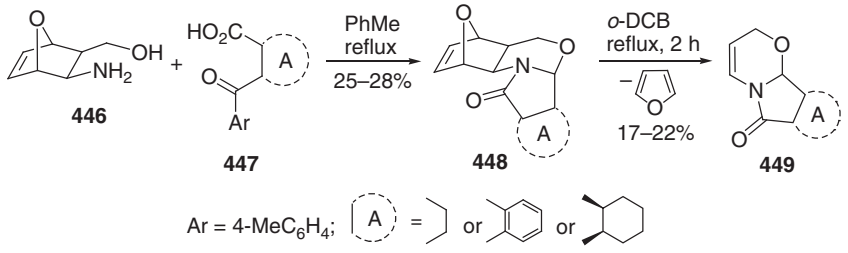
Scheme 110

Methylene-bridged tetrahydroisoindolo[2,1-*a*][3,1]benzoxazine-6,12-diones **444** were isolated from the cyclocondensation of *diendo*- or *diexo*-3-aminobicyclo[2.2.1]heptene-2-carboxylic acid **442** and 2-carboxybenzaldehyde **443** on refluxing in 1,2-dichlorobenzene. Further heating of the pentacyclic isoindolone **444** at an elevated temperature led to 1,3-oxazino[2,3-*a*]isoindole-2,6-dione **445** in a retrodiene reaction (Scheme 111).[216]



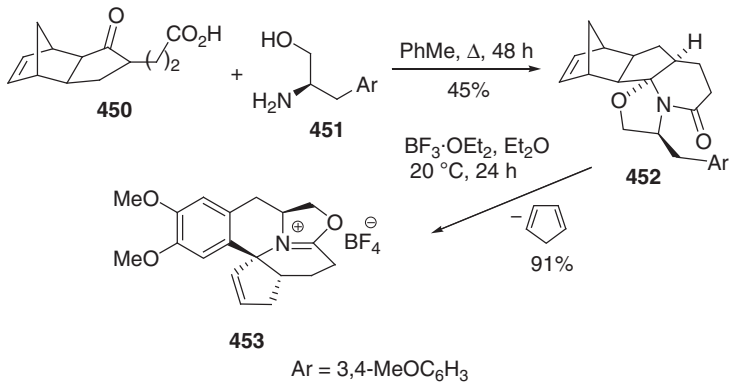
Scheme 111

Through refluxing in toluene in the presence of PTSA as catalyst, the cyclocondensation of *diexo*-7-oxabicyclonorbornene-3-aminopropanol **446** with aliphatic, aromatic, or cyclohexane ring (A)-containing γ-oxocarboxylic acids **447** afforded oxanorbornene-fused pyrrolo[1,3]oxazine or isoindolo[1,3]oxazines **448**, together with the rDA products **449**, which could be separated by column chromatography (Scheme 111). When the same reaction was performed in refluxing *o*-DCB (bp. 180 °C), pyrrolooxazine and oxazinoisoindolones **449** could be obtained directly. On heating in chlorobenzene (bp. 131 °C), furan was released from the polycyclic 1,3-oxazines **448** and products **449** were formed in better yields (e.g., 57% vs. 17%).[217] The MW-assisted [4 + 2] cycloreversion for the direct preparation of **449** from *cis*-2-*p*-tolyl-cyclohexanecarboxylic acid **447** (ring A=cyclohexane) with the bicyclic aminoalcohol was achieved by reaction at 160 °C for 15 min, which afforded hexahydro-1,3-oxazino[2,3-*a*]isoindolone **449** in fairly good (67%) yields and in pure form Scheme 112.[218]



Scheme 112

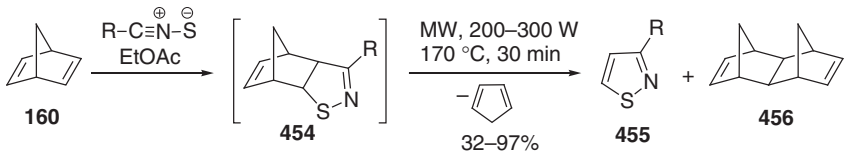
For the preparation of polycyclic benzo[*a*]quinolizidines, a subunit of naturally occurring isoquinoline alkaloids, a facile asymmetric approach has been described. During the construction of functionalized derivatives, the generation of an iminium ether salt intermediate was observed by novel rDA/*N*-acyliminium cyclization cascade reactions (Scheme 113). With chiral β-aminoalcohols **451,** the tricyclic δ-oxocarboxylic acid **450** was cyclized to diastereomerically and enantiomerically pure pentacyclic oxazolidines **452**, from which cyclopentadiene could be split off under unusually mild conditions (at 20 °C) through an rDA process on treatment with BF_3. At the same time, *N*-acyliminium cyclization took place at the phenylethyl moiety, which gave the structural analog **453** of *Erythrina* and the related alkaloids.[219]



Scheme 113

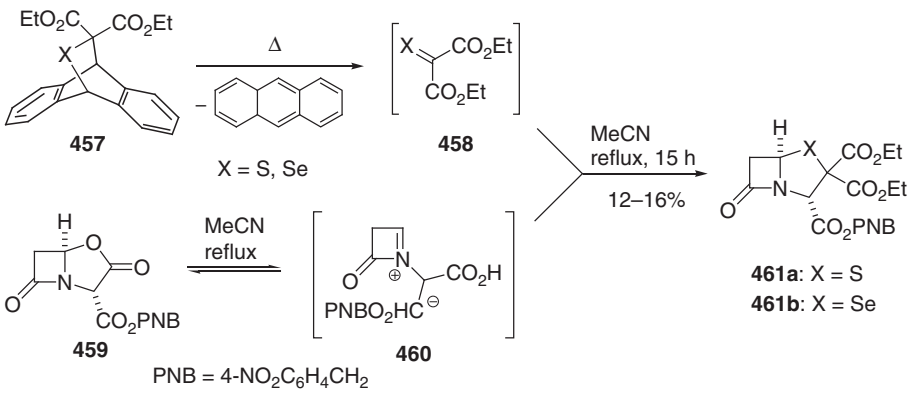
5.12.6.3.2 Heterocycles containing sulfur or selenium and nitrogen

The 1,3-dipolar cycloaddition of nitrile sulfides generated by MW-assisted decarboxylation of 1,3,4-oxathiazol-2-ones has been studied. The reactions of aryl nitrile sulfides with norbornadiene **160** led to 3-arylisothiazoles via the proposed initial cycloadduct **454** (presumably as a mixture of *exo* and *endo* isomers), which on classical heating (e.g., at ~130 °C for 100 h) underwent DA cycloreversion to isothiazoles **455** with the expulsion of cyclopentadiene (Scheme 114). With MW irradiation, the reactions were complete in 30–60 min at 170 °C, with varying yields. The spectroscopic assignments indicated a common byproduct in all of the norbornadiene reactions; tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene **456** was obtained from the DA cycloaddition of norbornadiene, acting as a dienophile with the cyclopentadiene generated in the fragmentation of the fused 4,5-dihydro-1,2-thiazoles **454**.[220]



Scheme 114

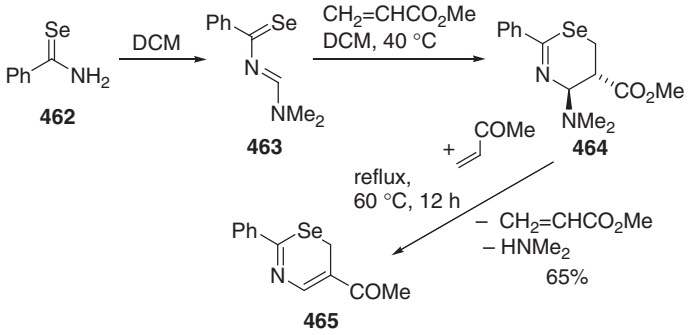
The diethyl thioxomalonate (X=S) or selenoxo (X=Se) analog **458**, both produced by transient rDA reactions from **457**, underwent 1,3-dipolar cycloaddition (Scheme 115) with azomethine ylide **460** as the trapping agent (derived from *β*-lactam oxazolidinone **459**) to furnish *p*-nitrobenzyl (PNB)-protected penam **461a** and 2,2-disubstituted selenapenam **461b,** respectively.[221]



Scheme 115

On reaction with selenobenzamide **462**, *N*,*N*-dimethylformamide dimethylacetal (prepared from thiobenzamide) led to *N*-selenoacylamidine **463** in a yield of 30%, which, as a 4π heterodienic system, took part in [4 + 2] cycloaddition with electrophilic dienophiles. Thus, compound **463**, generated *in situ*, was quenched with an excess of methyl acrylate, which furnished 5,6-dihydro-4*H*-1,3-selenazine **464** in 91% yield in methyl vinyl ketone as the solvent. The thermal cycloreversion of **464** then

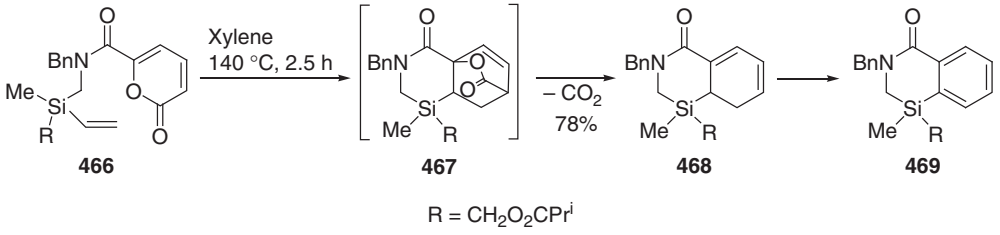
resulted in the release of heterodiene **463** which was trapped by the DA reaction with an excess of methyl vinyl ketone to afford 6*H*-1,3-selenazine **465** through *in-situ* elimination of the dimethylamino group (Scheme 116) from the intermediate cycloadduct.[194]



Scheme 116

5.12.6.3.3 Heterocycles containing silicon and nitrogen

The intramolecular DA reaction of pyran-2-one-6-carboxamide **466** linked to a vinyl dienophile by a chiral Si atom, followed by CO_2 extrusion in an rDA reaction, led diastereoselectively to 4-silatetrahydroisoquinolin-2-one **468** (Scheme 117). Specifically, carboxamide **466** produced 1-methyl-2,3,8,8a-tetrahydrobenzo[*d*][1,3]azasilin-4(1*H*)-one **468** on heating as a mixture of two diastereomers (36% *de*), which could not be separated by silica gel chromatography; no trace of the tricyclic intermediate **467** was observed. When the reaction was performed at 110 °C for 1 day, the yield of **468** decreased to 42% and 2,3-dihydrobenzo[*d*][1,3]azasilin-4(1*H*)-one **469** was isolated in poor yields, presumably as a result of oxidative aromatization in air.[222]

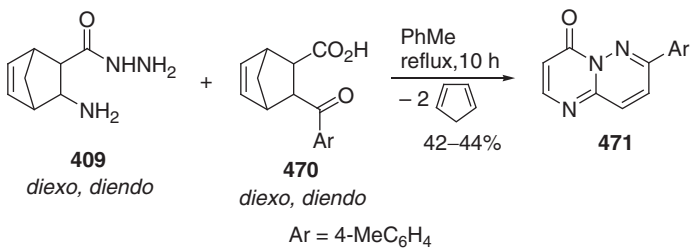


Scheme 117

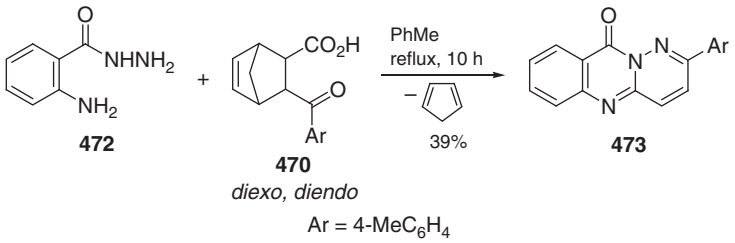
5.12.6.4 Heterocycles Containing Three Heteroatoms

5.12.6.4.1 Heterocycles containing three nitrogen atoms

A facile method was developed for the synthesis of heteroring-fused pyrimidines, by using a rare double cycloreversion. The *diendo*- and *diexo*-2-aminobicyclo[2.2.1]hept-5-enecarbohydrazides **409** were allowed to react with norbornene-2-aroylcarboxylic acids **470** to yield pyrimido[1,2-*b*]pyridazine **471** directly, through the loss of two molecules of cyclopentadiene (equation 31). Analogously, anthranilic acid hydrazide **472** and bicyclic γ-oxocarboxylic acids **470** furnished 2-tolyl-10*H*-pyridazino[6,1-*b*]quinazolin-10-one **473** in a single cycloreversion (equation 32).[223]

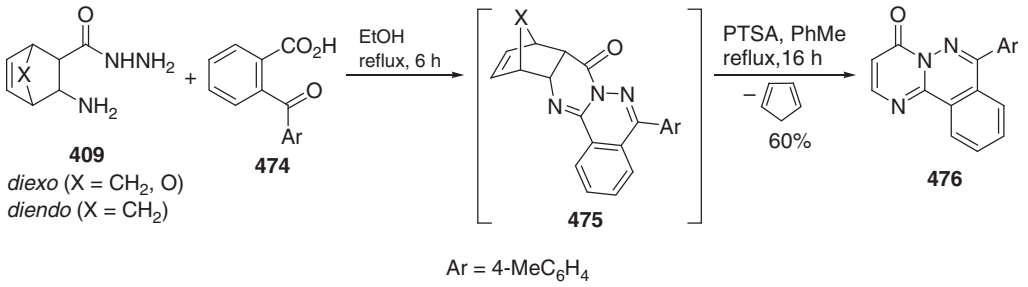


(31)



(32)

Similar reactions of bicyclic *diendo*- or *diexo*-2-aminocarbohydrazides **409** and 2-(4-methylbenzoyl)benzoic acid **474** and its *cis*-hexahydro analogs afforded tri- and pentacyclic ring systems, but rDA fragmentation also occurred, resulting in pyrimido[2,1-*a*]phthalazin-4-one **476**. Specifically, compound **476** was prepared by refluxing a mixture of *diendo*-2-aminocarbohydrazide **409** and oxoacid **474**, first in EtOH and then in toluene for a prolonged time, by cleavage of cyclopentadiene without isolation of the intermediate **475** (Scheme 118).[205]

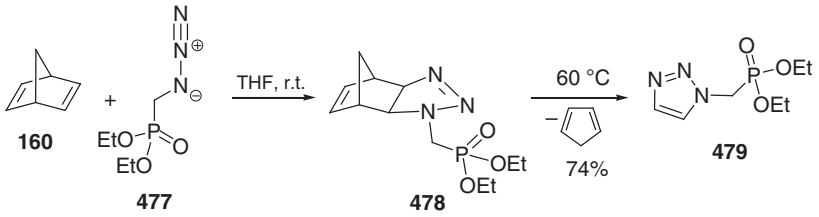


Scheme 118

Compound **476** was also prepared in a moderate yield (42%) from bicyclic 2-aminocarbohydrazides (X=CH_2) or oxacarbohydrazide (X=O) **409** by a similar cyclocondensation/rDA reaction, on heating of the norbornene or 7-oxanorbornane intermediates **475** (X=O) in refluxing toluene.[224]

On reaction with norbornadiene **160,** diethyl azidomethanephosphonate **477** gave triazoline **478** in 86% yield, which decomposed with the elimination of cyclopentadiene on heating to provide triazolylmethanephosphonate **479** (Scheme 119). The formation of this simple product containing a 1,2,3-triazole moiety was explained by a thermolytic reverse DA mechanism.[225]

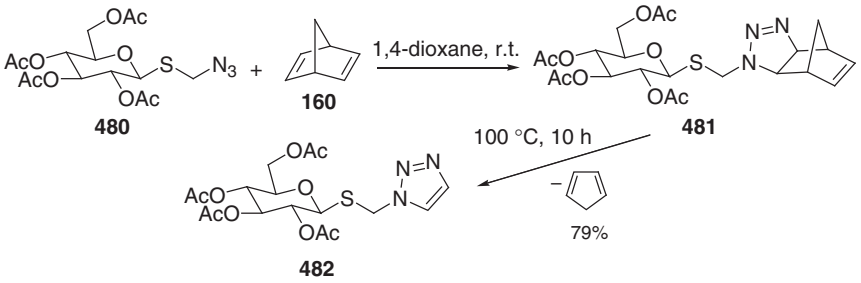
The reaction of *O*-acyl-protected glucosylthiol with dichloromethane readily afforded glucosylthiomethyl chloride, which, on treatment with sodium azide, gave glucosylthiomethyl azide **480**. The reaction with norbornadiene **160** led to a tandem 1,3-dipolar cycloaddition/rDA decomposition, which furnished the parent 1-glycosylthiomethyl-1,2,3-triazole **482**. Specifically, the norbornadiene underwent a 1,3-dipolar cycloaddition with the glucose-derived azide to give *diexo*-triazoline **481**. The following rDA process furnished triazole **482** through the extrusion of cyclopentadiene (Scheme 120).[226]



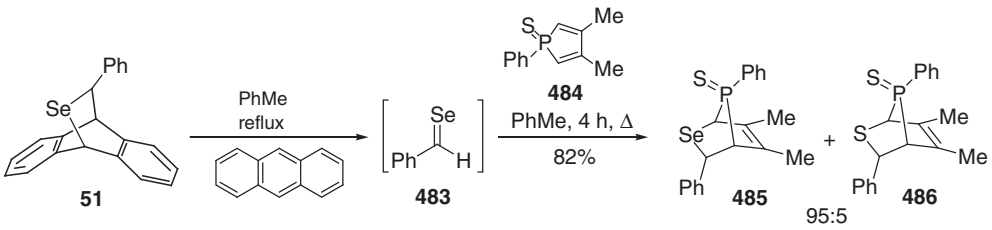
Scheme 119

The stereoselective [4 + 2] hetero DA cycloaddition of selenoaldehyde **483** (generated by thermal cycloreversion of the anthracene adduct **51**) with pentavalent 3,4-dimethylphosphole sulfide **484** at 110 °C afforded the 2-selena-7λ^5-phosphabicyclo[2.2.1]hept-5-ene-7-thione [4 + 2] cycloadduct **485** as a single diastereoisomer (*endo*), accompanied by a small amount of the heteroatom-exchanged thiin **486** as a side product (Scheme 121).[227]

As selenoaldehyde precursors, 16-aryl-15-selenatetracyclic compounds **487** underwent facile decomposition in an rDA reaction. Thus, unstable selenoaldehyde intermediates **488** were reacted with nitrile oxides (obtained *in situ* from the precursor

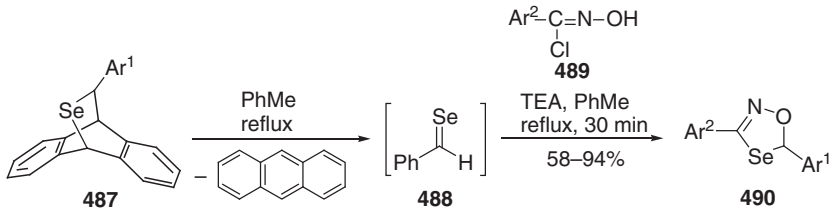


Scheme 120



Scheme 121

chlorides **489** with Et_3N) to give 3,5-diaryl-1,4,2-oxaselenazoles **490** (Scheme 122) in efficient 1,3-dipolar [3 + 2] cycloadditions at 110 °C (Table 10).[228]



Ar^1 = Ph, 4-$CF_3C_6H_4$, 1-naphthyl; Ar^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2,4,6-MeC_6H_2

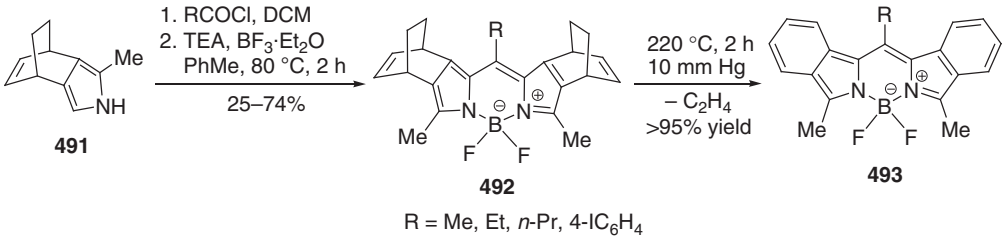
Scheme 122

Table 10 Yields of 3,5-diaryl-1,4,2-oxaselenazoles **490** (Scheme 122)

No.	*Ar^1*	*Ar^2*	*Yield of **490** (%)*
1	Ph	4-$MeOC_6H_4$	67
2	1-Naphthyl	4-$MeOC_6H_4$	67
3	4-$F_3C_6H_4$	4-$MeOC_6H_4$	94
4	4-$F_3CC_6H_4$	Ph	65
5	4-$F_3CC_6H_4$	4-ClC_6H_4	58
6	Ph	4-ClC_6H_4	76
7	Ph	2,4,6-Me C_6H_2	85

A new class of boron dipyrromethene (BDP) dyes with rigid BCOD units were prepared by conversion to benzo-BDP derivatives via rDA fragmentation of the BCOD moiety with the elimination of ethylene. 4,7-Ethanodihydroisoindolecarboxylate was converted to the tricyclic 2-methylpyrrole **491**, which was transformed to stable boron complexes **492** in several steps. On heating, these BCOD-fused complexes (Scheme 123) resulted quantitatively in fused 2,2-difluoro-1 λ^5,3-diaza-2 λ^4-bora-tricyclo[7.3.0.$0^{3,7}$]dodecapentaen-1-ylium derivatives **493**.[229]

In a direct reaction, norbornadiene **160** combined with tributylphosphine and CS_2 to give the stable adduct **494**, which underwent cycloaddition with acetylenic esters and furnished norbornene-fused dihydrotetrathiafulvalenes **495**, even though in

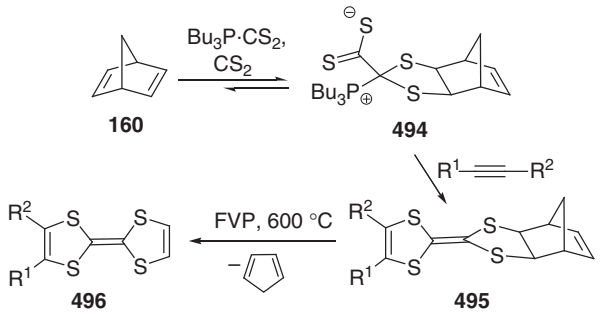


Scheme 123

fairly poor yields (5–21%). On FVP, the compounds decomposed to substituted tetrathiafulvalenes **496** (Table 11) in reverse DA reactions involving the release of cyclopentadiene in good to excellent yields (Scheme 124).[230]

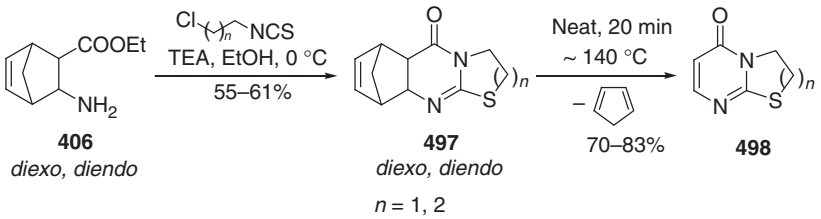
Table 11 Yields of tetrathiafulvalenes **496** (Scheme 124)

No.	R^1	R^2	*Yield of* ***496*** *(%)*
1	CO_2Me	CO_2Me	98
2	CO_2Et	CO_2Et	92
3	CO_2Me	H	97
4	CO_2Et	H	60
5	CO_2Me	Ph	77



Scheme 124

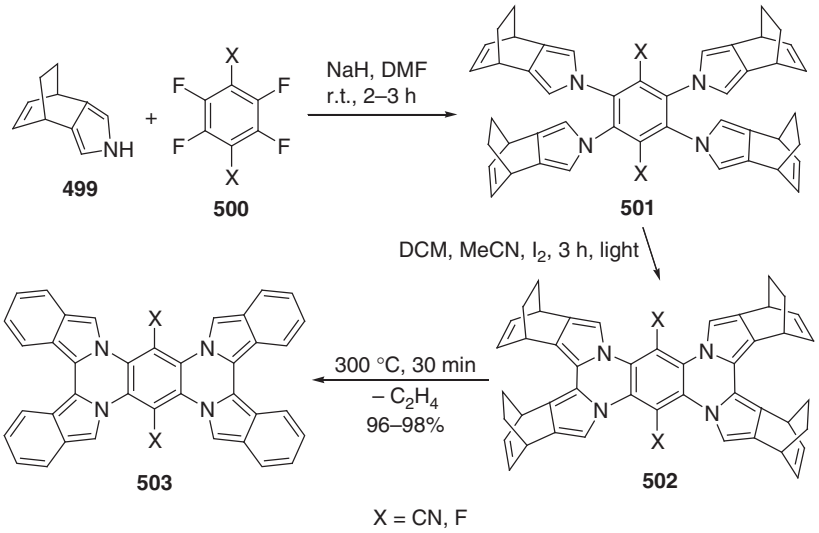
Ethyl 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate **406** and its *diendo* counterpart reacted with ω-chloroalkyl isothiocyanates in the presence of triethylamine on stirring for 24 h to furnish tetracyclic norbornene-fused 6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-5(3*H*)-one ($n=1$) or tetrahydropyrimido[2,1-*b*][1,3]thiazin-6(2*H*)-one ($n=2$) **497**, respectively. On melting, these heterocycles underwent retrodiene fragmentation to give **498** by cleavage of cyclopentadiene (Scheme 125). The annelation mode (*diendo* vs. *diexo*) did not significantly influence the yield of products, but the decomposition of thiazolidine **497** ($n=1$) was faster than that of its homologs.[231]



Scheme 125

Substitution of 4,7-dihydro-4,7-ethano-2*H*-isoindole **499** with tetrafluoro-*p*-phthalonitrile (X=CN) or hexafluorobenzene **500** (X=F) under basic conditions afforded the tetrasubstituted derivatives **501** in good yields. On oxidative coupling with I_2

and irradiation with light, these compounds gave tetrapyrrolotetraazaanthracenes **502**, which were converted to tetraisoindolotetraazaanthracene derivatives **503** by cycloreversion (Scheme 126).[232]

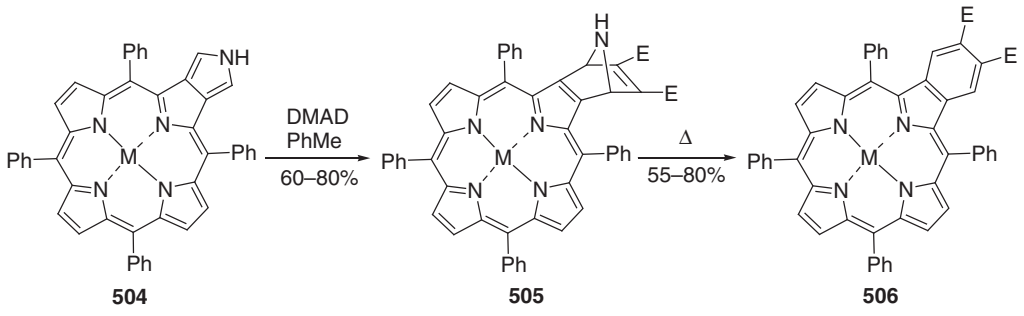


Scheme 126

5.12.6.5 Porphyrins, Phthalocyanins, and Related Compounds

Porphyrins, which occur widely in nature, are composed of four modified pyrrole subunits interconnected at their α-carbons via methano bridges. One of the best known porphyrins is heme, a pigment in red blood cells. Phthalocyanins are structurally related macrocyclic pigments. They are intense blue–green colored compounds that are widely used as dyestuffs. In tetrabenzotetraazaporphyrins the pyrrole rings are coupled by four nitrogen atoms instead of methine bridges.

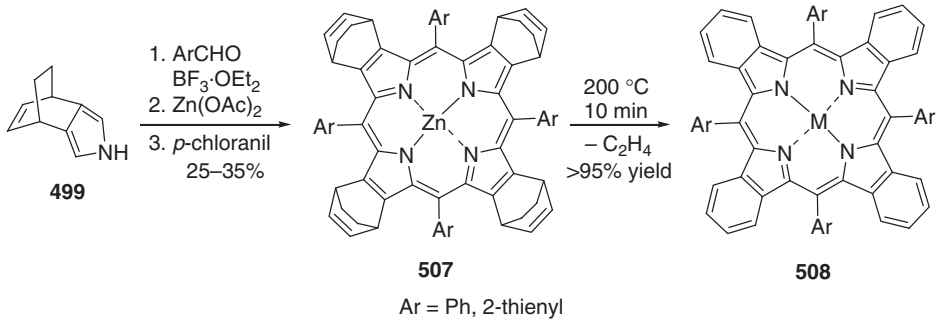
Benzoporphyrins **506** were obtained as the major products from the cycloaddition of fused metallopyrroloporphyrins **504** with DMAD. In the presence of excess dienophile, adduct **505** was obtained, which underwent an rDA reaction to produce **506**. When copper(II) or nickel(II) complexes **504** were refluxed with DMAD, the [4 + 2] cycloadducts **505** were obtained, which could be converted into benzoporphyrins **506** by prolonged reflux (Scheme 127).[233]



Scheme 127

When heated, 4,7-dihydro-4,7-ethano-2*H*-isoindole **499**, a key compound for porphyrin synthesis, underwent an rDA reaction to furnish the reactive and unstable isoindole, essentially in quantitative yield; this was used for the novel synthesis of tetrabenzoporphyrins and monobenzoporphyrins. The reaction of isoindole prepared *in situ* with aromatic aldehydes followed by subsequent oxidation gave *meso*-tetraarylated porphyrins **507** (Scheme 128), which were converted into benzoporphyrins **508** by retrograde thermolysis.[234]

From 4,7-dihydro-4,7-ethano-2*H*-isoindole as a masked isoindole equivalent, facile new syntheses of unsubstituted tetrabenzoporphyrins and their metal complexes, as well as of polysubstituted monobenzo- and dibenzo-fused derivatives were reported via a similar thermal retrodiene route.[235]

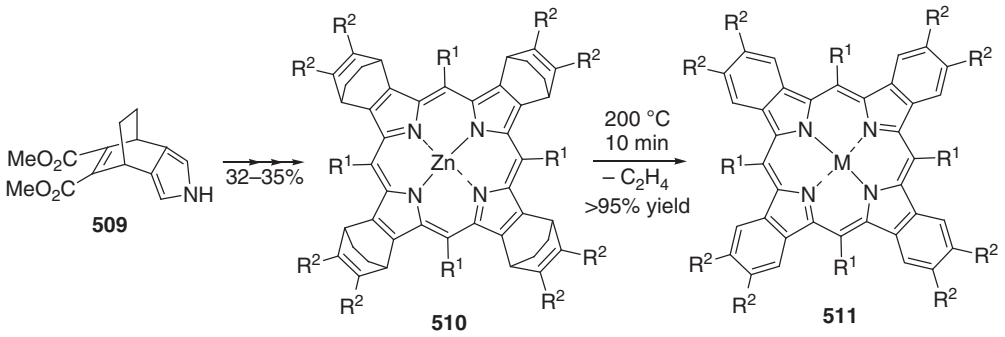


499 507 508

Ar = Ph, 2-thienyl

Scheme 128

From 4,7-dihydro-5,6-dimethoxycarbonyl-4,7-ethano-2*H*-isoindole **509**, benzoporphyrins **510** functionalized with eight ester groups and their water-soluble derivatives **511** were synthetized by a similar cycloreversion method (Scheme 129).[236,237]



509 510 511

R^1 = H, Ph; R^2 = CO_2Me, CO_2H, CO_2Na

Scheme 129

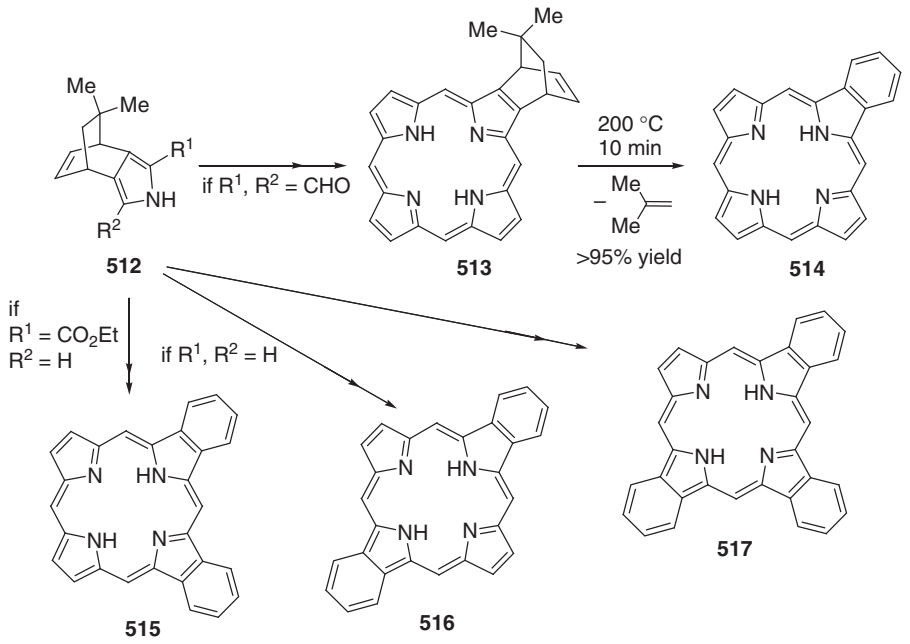
The BF_3-catalyzed Rothemund condensation of phenylpropargylaldehyde with 4,7-dihydro-4,7-ethano-2*H*-isoindole **499**, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and rDA fragmentation of the resulting BCOD-fused porphyrin gave a quantitative yield of tetrakis(phenylethynyl)benzoporphyrin, which has special redox and spectroscopic properties.[238]

Although *β*-alkyl monobenzoporphyrins and *meso*-aryl dibenzoporphyrins were prepared from pyrrole fused with BCOD, the corresponding parent compounds could not be obtained by the usual methods. Only Okujima et al. have reported an appropriate synthesis of the parent mono-, di-, and tribenzoporphyrins **514–517**, from their soluble precursors by an rDA procedure. 4,7-Dihydro-8,8-dimethyl-4,7-ethano-2*H*-isoindole **512**, when treated with methyl orthoformate in TFA, gave the corresponding dialdehyde (R^1, R^2=CHO) in 55% yield. Subsequent condensation and oxidations led to the monoannelated porphyrin **513**, which on heating underwent an rDA reaction to result in monobenzoporphyrin **514** through cleavage of volatile isobutylene. The reactions to di- and tri-BCOD-annelated derivatives were based on analogous methodology. In this way, the bicyclic ester, pyrrole and carboxy ester derivatives were applied in further reactions (Scheme 130). The thermal decomposition was carried out in vacuum in a glass tube oven.[239]

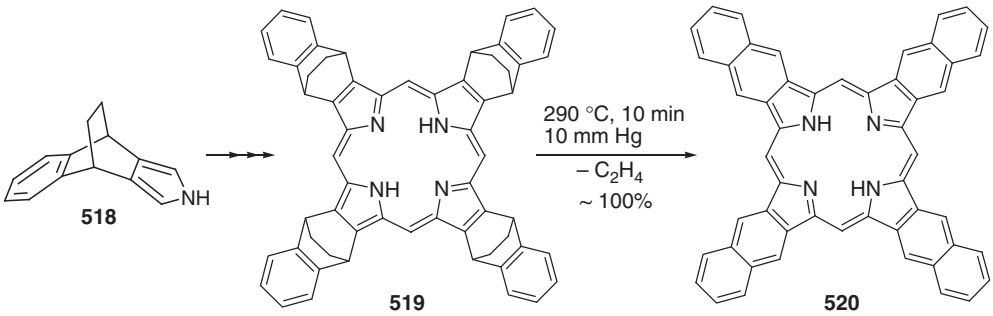
Benzporphyrins fused with acenaphthylene or fluoroanthene rings were prepared by the condensation of BCOD-annelated tripyrans with the appropriate pyrroledialdehydes followed by an rDA reaction.[240]

A method for the synthesis of fused porphyrins was developed starting from 4,9-ethano-2*H*-benz[*f*]isoindole **518**, which gave [2,3]-naphthoporphyrins. In a general multistep procedure, ethylene-bridged porphyrins were obtained through the tetramerization and oxidation of **518**. After the introduction of a Zn(II) ion into the tetrafused porphyrin, both the parent compound **519** and its Zn(II) complex could be converted to pure insoluble tetranaphthoporphyrin **520** in a retrodiene process by heating in vacuum (Scheme 131).[241] The use of MW-assisted heating allowed the reaction time and temperature in the rDA reaction used for the synthesis of the octamethoxy derivative of **520** to be reduced.[242] The benzene homolog of synthon **507** proved suitable for the construction of the linearly *π*-expanded tetraanthrophorphyrin analog of **520** via rDA methodology.[243]

A soluble gable bisporphyrin linked with a BCOD ring **522** was prepared and converted to the insoluble, conjugated, and planar bisporphyrin **523** through thermal cycloreversion. The synthetic strategy was based on the formation of dipyrrole **521** comprising a BCOD core, which was prepared from ethyl 4,7-dihydro-4,7-ethano-2*H*-isoindole-2-carboxylate in four steps as already reported.[244] The bisporphyrin **522** fused to a BCOD core was prepared by the usual procedure on application of a [3+1] approach. For the rDA fragmentation of the zinc(II)bisporphyrin complex, pyrolysis was applied (Scheme 132), which yielded the planar bisporphyrin **523** in pure form.[245]



Scheme 130

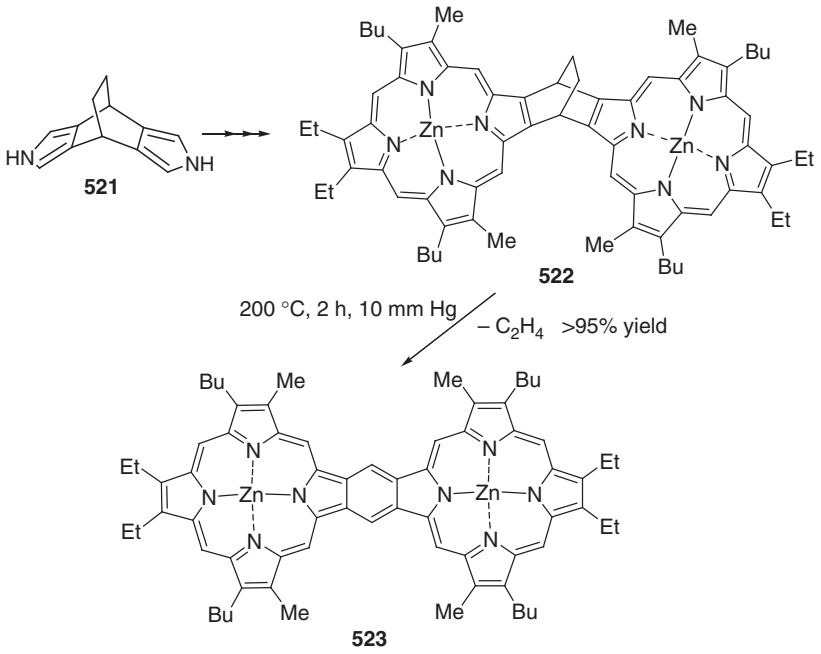


Scheme 131

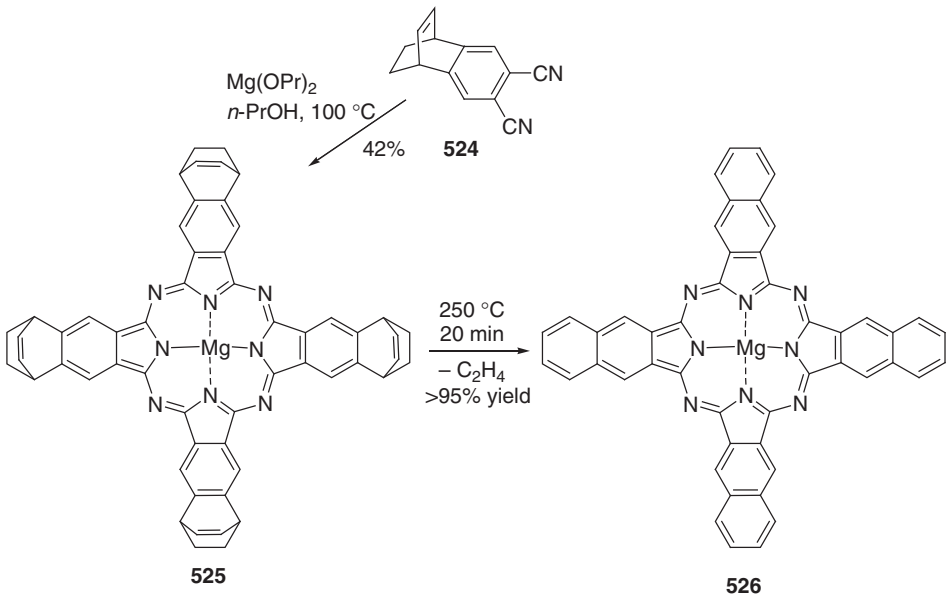
Phthalocyanines are formed on heating of phthalic acid derivatives containing functionalized nitrogen groups, such as the classical precursor phthalonitrile. Relatively few articles have dealt with the application of retrodiene reactions in phthalocyanin chemistry. One of them involved the use of the bicycle[2.2.2]octene-fused phthalonitrile **524** as a synthon for the construction of the tetrakis-bicyclooctene-annelated phthalocyanin **525**, which was obtained by treating derivative **524** with Mg(II) propoxide (Scheme 133). The purified Mg(II) complex **525** was heated in a glass tube under vacuum to give naphthalocyanin **526** with the release of four ethylene units.[246] A soluble precursor of the 2,3-naphthalocyanin derived from phthalonitrile **524** was prepared and converted into an insoluble semiconducting thin film by a similar rDA reaction.[247]

An efficient synthesis of the conjugation-expanded tetrabenzocarbaporphyrin **528** and tribenzoazuliporphyrin **529** was achieved using a BCOD-fused tripyrane as a versatile intermediate, and thermolytic cycloreversion of adduct **527** (Scheme 134). The key compound tripyrrane obtained from 4,7-dihydro-4,7-ethano-2*H*-isoindole **499** and its *t*-butoxycarbonyl derivative were condensed with diformylindene or azulene-1,3-dicarbaldehyde under acidic conditions; subsequent oxidation resulted in carba- and azuliporphyrin homologs, which were fragmented in an rDA process.[248]

The first successful synthesis of cyclo[8]isoindole **532** as a ring-expanded and annelated porphyrinoid was achieved from BCOD-fused 2,2′-bipyrrole **530** by oxidative coupling and rDA cleavage of the cyclo[8] BCOD-pyrrole **531** (Scheme 135) through the extrusion of ethylene molecules. For the preparation of the conjugated (octa)bicyclic system **531,** oxidative homocoupling of bipyrrole **530** was used and the oxidizing agents, acids, and additives were optimized (Table 12).[249]



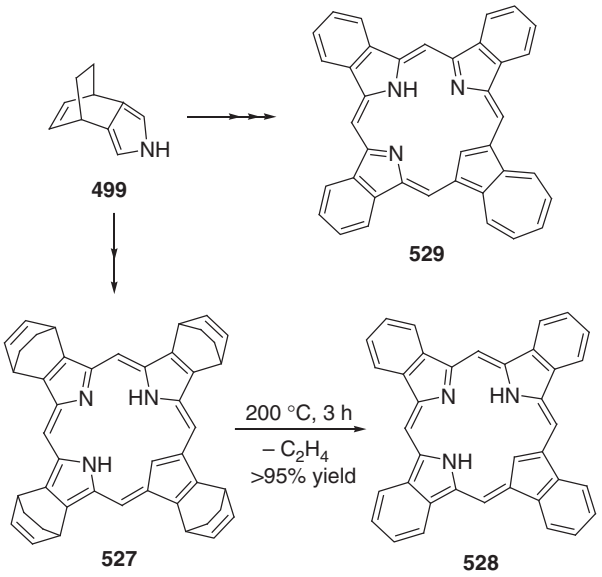
Scheme 132



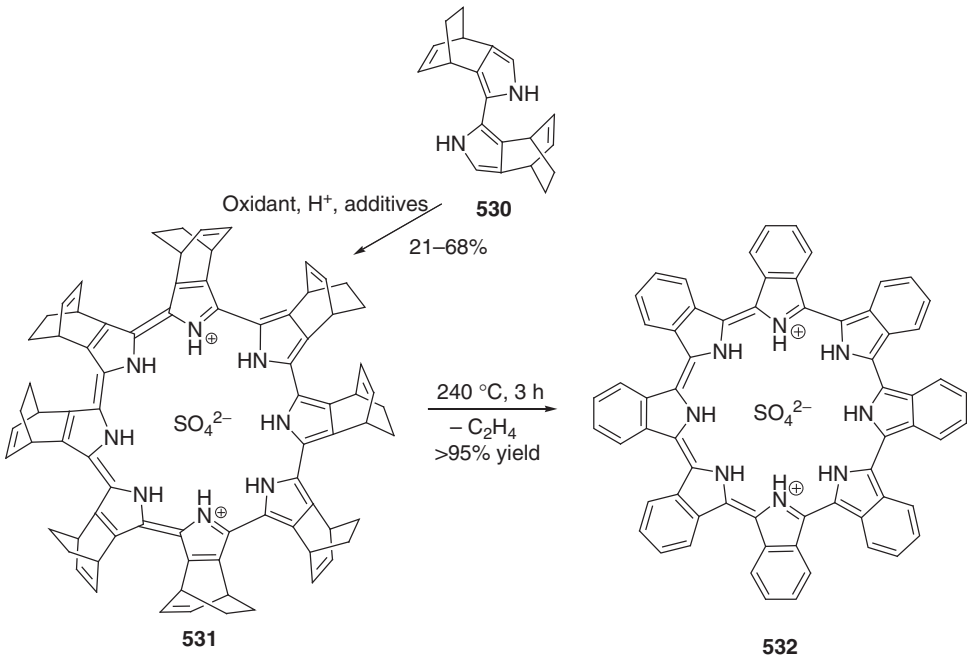
Scheme 133

By means of a cycloreversion strategy starting from 4,7-dihydro-4,7-ethano-2*H*-isoindole **499** as the precursor, five-membered porphyrin-homolog benzosapphyrins have recently been prepared.[250] Similar protocols were adapted for the syntheses of expanded porphyrins (penta-, hexa-, hepta-, and octaporphyrin), when ethanoisoindole **499** was reacted with pentafluorobenzaldehyde in the presence of $BF_3.OEt_2$ as the catalyst, followed by oxidation of the primary product. However, the rDA reaction at 170–200 °C under a reduced pressure (0.1 mm Hg) afforded rather complicated mixtures of multiple fluorine-eliminated products or structurally unusual benzoporphyrins in some cases.[251]

A series of core-modified tetrabenzoporphyrins with interesting optical properties, including thia-, dithia-, and oxathiatetrabenzoporphyrins, were synthetized in a simple procedure. The process for the preparation of BCOD-fused porphyrins **537** and their conversion to core-modified tetrabenzoporphyrins is outlined in Scheme 136. For the formation of different heteroatom-containing conjugated ring systems, the classical [3 + 1] construction was applied. Dipyrrole analog **535** with a central thiophene



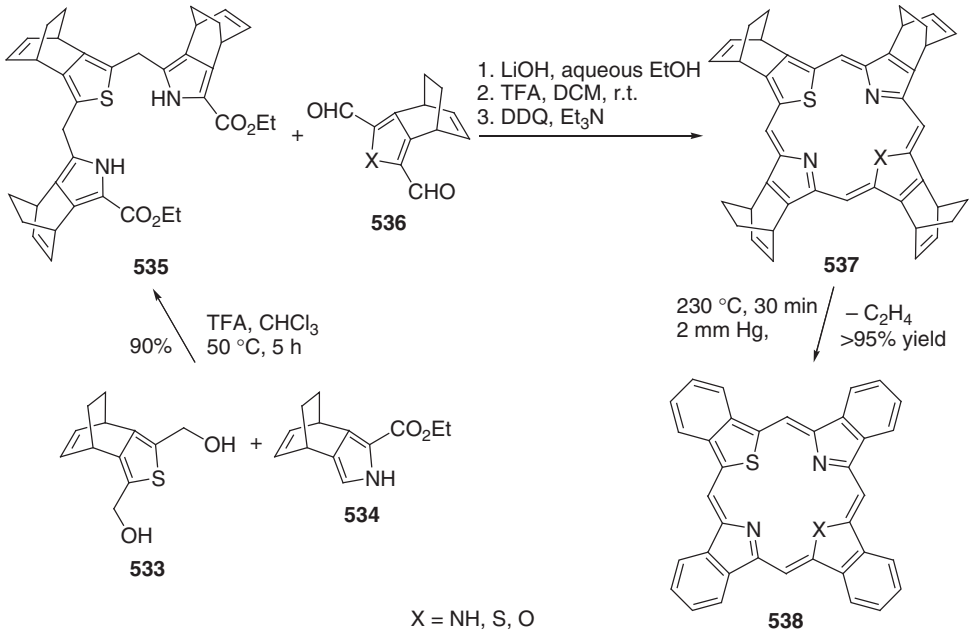
Scheme 134



Scheme 135

Table 12 Oxidative coupling of the 2,2′-bipyrrole derivatives **530** to **531** (Scheme 135)

No.	*Oxidant*	*Acid*	*Additive*	*Yield of **531** (%)*
1	$FeCl_3 \cdot 6H_2O$	1 M H_2SO_4	–	43
2	$NaNO_2$	Concentrated H_2SO_4	–	40
3	CAN	AcOH	Na_2SO_4	28
4	AgO	Concentrated HNO_3	Na_2SO_4	41
5	$Ce(SO_4)_2$	6 M H_2SO_4	Na_2SO_4, $(n\text{-Bu})_4NHSO_4$	68



Scheme 136

ring was prepared by acid-catalyzed condensation of diol **533** with the ethoxycarbonyl derivative **534**. Hydrolysis and cyclization with dialdehydes **536** and subsequent oxidation resulted in macrocycles **537** as diastereomeric mixtures in variable yields (23–42%). When heated, macrocycles **537** furnished the core-modified tetrabenzoporphyrins **538** by rDA reaction involving the cleavage of ethylene.[252,253]

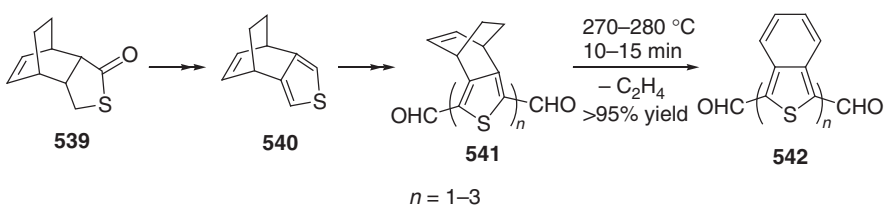
An application of the [3 + 2] condensation strategy was described for the preparation of a BCOD-fused trithiasapphyrin. Following the condensation of BCOD-fused thiatripyrrane and BCOD-fused bithiophene with TFA in dichloromethane at room temperature and neutralization with triethylamin, the mixture was oxidized. The thermal rDA reaction of trithiasapphyrin at different temperatures demonstrated that pyrrolysis at 230 °C for 1 h achieved the total extrusion of all ethylene molecules and led to trithiapentabenzosapphyrin.[254]

5.12.7 Application of rDA Reactions in the Chemistry of Oligomers and Polymers

5.12.7.1 Synthetic Applications Involving Oligomers

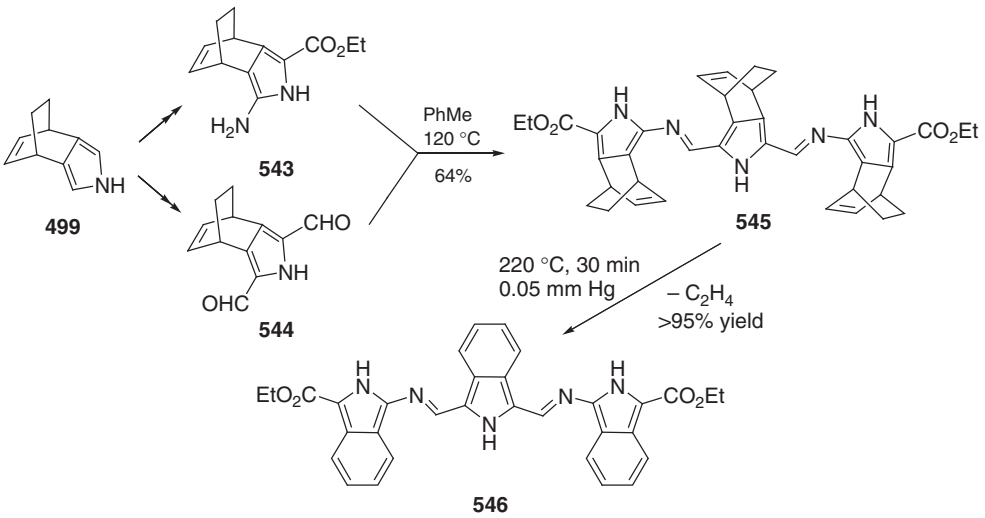
Oligomer molecules consist of a relatively small number of monomer units, in contrast to polymers, which, at least in principle, contain an unlimited number of monomers joined by repetitive covalent linkages. The units may involve one or more than one species, so that the oligomers can be dimers, trimers, or tetramers, etc.

A convenient synthesis of isothianaphthene oligomers **542** was presented and their electrochemical behavior was studied by Ono and coworkers, who used the rDA process as an important step in the decomposition of oligothiophens **541** annelated with BCOD rings. The method was based on the preparation of the stable tricyclic thiophene **540** from *endo*-4-thiatricycloundecenone, which was obtained simply by the DA reaction of 2-hydroxythiophene with 1,3-cyclohexadiene. Compound **540** was readily functionalized in the 1,3-positions and then oligomerized to the dimer and trimer ($n = 2$, 3) by various coupling methods. The rDA fragmentation of dialdehydes **541** proceeded very slowly, even at 200 °C for 3 h, and the cycloreversion conditions were therefore optimized. The procedure proved successful in a shorter time in vacuum (2 mm Hg), when the retrodiene process took place smoothly (Scheme 137) and the products **542** were sufficiently pure.[255]



Scheme 137

In the coupling of aminopyrrole ester **543** with 1,3-dicarbaldehyde **544** (both compounds derived from dihydro-4,7-ethanoisoindole **499** in several steps), the BCOD trimer-fused bisimino pyrrole derivative **545** was obtained. Bulk conversion of BCOD-fused pyrrole was successfully performed under a reduced pressure, when trisisoindole **546** linked with methylideneamino units were obtained on extrusion of ethylene (Scheme 138). Thermogravimetric data indicated that the extrusion of ethylene from the BCOD-fused moiety was hardly affected by substituents on the pyrrole ring; the starting temperature of elimination was invariably at approximately 170 °C.[256]



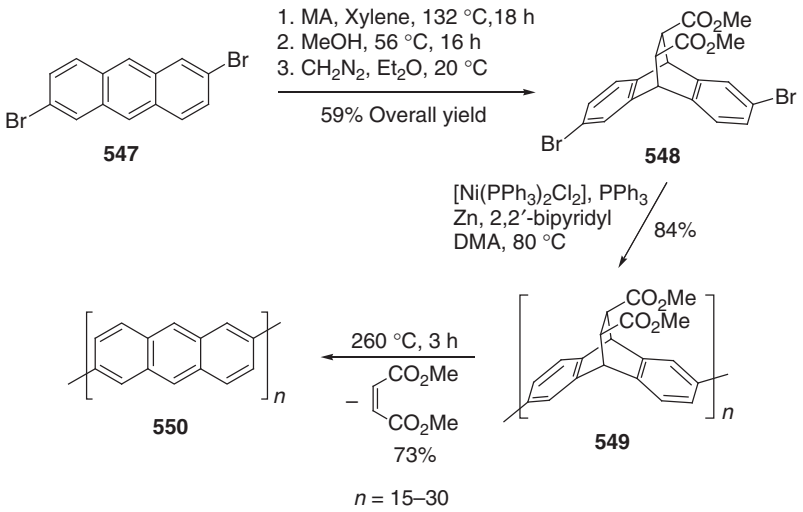
Scheme 138

5.12.7.2 Synthetic Applications Involving Polymers

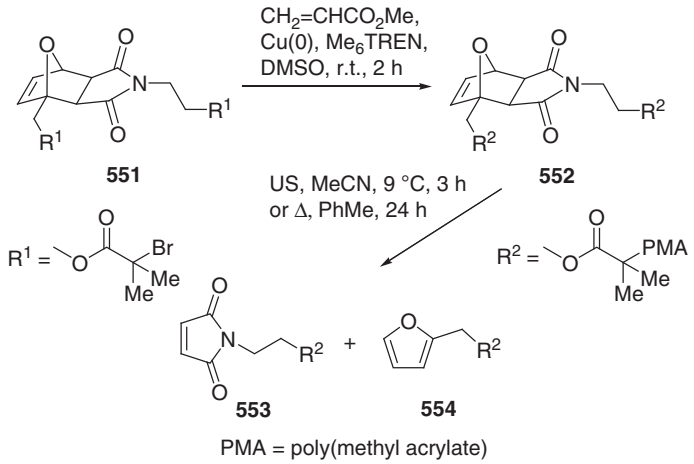
Polymers are large molecules (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Although the term polymer is sometimes taken to refer to plastics, it actually encompasses a large class comprising both natural and synthetic materials with a wide variety of properties. Many commercially important polymers are synthetized by chemical modification of naturally occurring polymers. The identity of the monomer residues (repeat units) making up a polymer is its first and most important attribute. Polymer nomenclature is generally based on the type of monomer residues comprising the polymer. Polymers that contain only a single type of repeat unit are known as homopolymers, whereas polymers containing a mixture of repeat units are known as copolymers. An important microstructural feature determining polymer properties is the polymer architecture. The simplest polymer architecture is a linear chain, that is, a single backbone with no branches. A related unbranched architecture is a ring polymer. A branched polymer molecule is composed of a main chain with one or more substituent sidechains or branches. Special types of branched polymers include star polymers, comb polymers, brush polymers, dendronized polymers, ladders, and dendrimers.

Many anthracene compounds are photoluminescent, and the polymers containing these units as part of larger π-electron systems are also likely to be electroluminescent. Synthesis of such copolymers occurs via precursor polymers **549** or their *p*-phenylene-substituted homologs of poly(anthracene-2,6-diyl) **550**. The procedure exploited the rDA reaction. DA adduct **548** was conveniently obtained from 2,6-dibromoanthracene **547** by treatment with an excess of MA in xylene, followed by a two-step esterification to the corresponding dimethyl ester **548**. In a nickel(0)-mediated organometallic coupling in *N*,*N*-dimethylacetamide (DMA) as the solvent, adduct **548** resulted in precursor polymers **549** in 86% yield (Scheme 139). Conversion of **549** to the target polymers **550** was achieved in a thermal rDA process on heating at 260 °C for 3 h, which led to the elimination of dimethyl maleate to give the desired poly(anthracene-2,6-diyl)s.[257]

Poly(methyl acrylate)s (PMAs) with different molecular weights were grown from a DA adduct of maleimide with furan **551** containing two polymerization-initiating moieties. The initial efforts were directed toward polymerizing methyl acrylate from the oxanorbornane-based, difunctional brominated initiator derivative **551**, using a copper(0)-mediated single-electron transfer radical polymerization in DMSO in the presence of tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as a very active ligand at room temperature (Scheme 140). At an initial monomer to initiator ratio of ~800:1, polymer **552** with a number average molecular weight (M_n) of 69 kDa was obtained. When the corresponding PMA (>30 kDa) chain was subjected to ultrasound (US), reverse [4 + 2] cycloaddition occurred, as observed by gel permeation chromatography (GPC) and labeling of the liberated maleimide **553** and furan **554** moieties. This is a rare example of mechanically induced retro [4 + 2] cycloaddition. The preliminary experiments with thermally activated rDA also led to a reduction in the molecular weight. After removal



Scheme 139



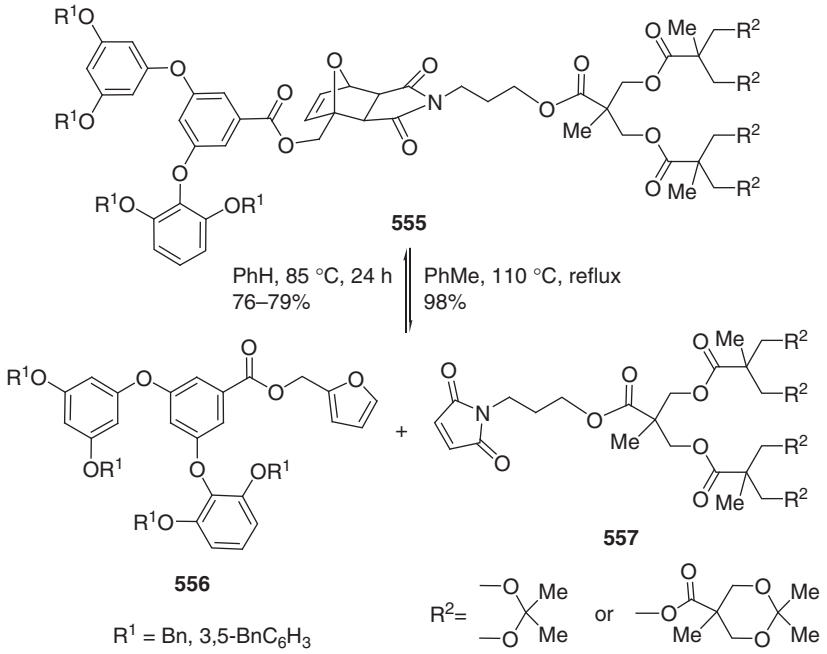
Scheme 140

of the solvent, the resulting material was determined by GPC to have $M_n = 35$ kDa, similar to that of the postsonification polymer.[258]

Another interesting application of the rDA process in polymer chemistry is the formation of thermally reversible networks. The use of [4 + 2] cycloadditions to polymers bearing furan moieties with either a monomaleimide or a bismaleimide has been reported. Spectroscopic evidence, supported by data from model compounds, indicated that the resulting linear and cross-linked products contained extensive percentages of adduct structures formed from the furan moieties. Both types of materials were heated in solvent containing a large excess of 2-methylfuran, in order to induce retrodiene reactions involving the furan rings contained in some styrene copolymers.[259]

Poly(ethylene terephthalate) (PET) copolymers containing 2,6-anthracenedicarboxylate structural units were also prepared and modified by DA reactions with maleimides. This DA cross-linking reaction was thermally reversible, but at the required temperature (250 °C) the reverse reaction was slow and the PET–anthracene copolymer was therefore prone to thermal decomposition.[260]

Segment block dendrimers **555** consisting of polyester and polyaryl ether dendrons were synthetized through reagent-free DA cycloaddition by heating. Three generations of furan-functionalized polyaryl ether dendrons were reacted with maleimide-functionalized polyester dendrons of the same generation to obtain segment block dendrimers. The thermoreversible nature of macromolecules **555** was investigated by heating them at elevated temperatures to afford the corresponding furan **556** and maleimide derivatives **557** through an rDA process, in the absence or presence of anthracene as a scavenger diene (equation 33).[261]



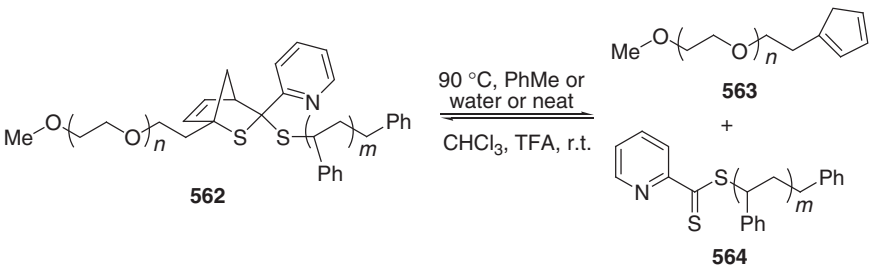
(33)

An invention for the synthesis and use of copolymers with furan and maleimide moieties in oilfield applications has been described, which involved rDA fragmentation to form a gel. Under appropriate conditions, the cycloreversion resulted in a decreased viscosity of this polymeric gel.[262]

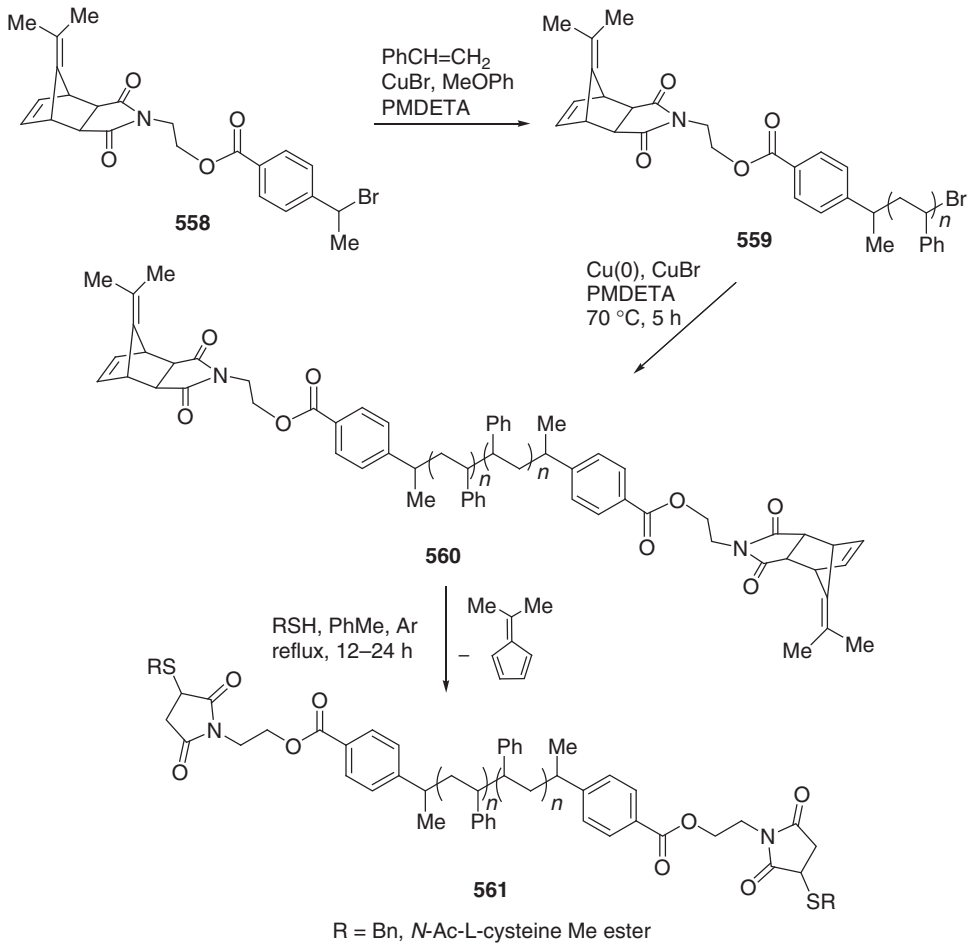
A straightforward synthesis of the thiol-capturing telechelic polystyrene and conjugation of cysteine was achieved via the formation of dimethylfulvene-protected maleimide-functionalized atom transfer radical (ATR) polymerization initiator **559** in the presence of CuBr and pentamethyldiethylenetriamine (PMDETA) in anisole; the thermostability was compared with that of an analogous furan-protected initiator. Polystyrene with an M_n of 2530 Da was then prepared and subjected to ATR coupling with nanocopper(0) to form the bis-functionalized polymer **560** (**Scheme 141**). The reactivity of the polymer was demonstrated by *in-situ* rDA cleavage involving the elimination of dimethylfulvene and the formation of thioether adduct **561** with benzylmercaptan and *N*-acetyl-L-cysteine methyl ester.[263]

DA cycloaddition proved suitable as a convenient route for the formation of carbon–carbon bonds through a facile reaction under undemanding conditions that fulfilled the requirements of a click reaction. Moreover, such DA reactions are thermoreversible and this feature was exploited in the synthesis of self-healing polymers carrying functionalities, either as a polymer chain-end or among the repeating units. Hence, the preparation of novel well defined linear and star methyl methylacrylate polymers bearing DA adducts was devised from *N*-hydroxyethyl maleimide and furfuryl alcohol or 9-anthracenemethanol, and a preliminary evaluation was made of their thermolability. Refluxing of the polymers based on an oxabicyclonorbornene-skeleton in toluene led to cleaved copolymers through a retrodiene process. Heating of the anthracene–maleimide linker by refluxing in DMSO was unsuccessful, due to its high thermal stability.[264]

In a reversible DA/rDA process, poly(styrene)–block–poly(ethylene oxide) (PS–*b*–PEO) copolymers **562** were synthetized by a combination of reversible chain transfer (RAFT) polymerization and hetero DA cycloaddition. The resulting products could be cleaved on heating in the solid state or in solution by hetero rDA fragmentation to give nanoporous films. Cyclopentadienyl-functionalized poly(ethylene oxides) **563** were prepared by tosylation of monomethylated PEO, followed by conversion into the cyclopentadienyl derivative. Benzylpyridin-2-yldithioformate was used as a controlling agent to prepare poly(styrene) **564** by RAFT polymerization. A RAFT-hetero DA cycloaddition was carried out as outlined in equation 34. The successful formation of PS–*b*–PEO **562** was consistent with the estimated M_n. With regard to the thermal cleavage of the block copolymer in the solid state or in the solvent (toluene), the rDA reaction was essentially quantitative.[265]



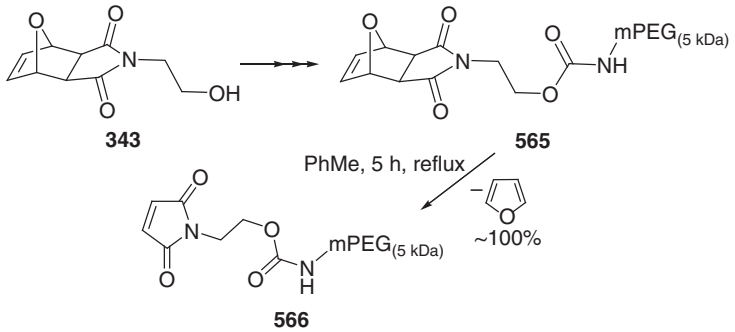
(34)



Scheme 141

The DA click reactions illustrated above are many-faceted methods for preparations and applications in polymer material science. The main [4 + 2] cycloaddition routes utilized in click chemistry take advantage of the thermal reversibility of DA/rDA reactions. Some DA reactions readily satisfy the requirements of click chemistry. The advantage of these reactions is clear: no metal catalyst is necessary. The results of the application of click reactions in polymer chemistry have been reviewed.[259–269]

A simple method for the construction of maleimide-functionalized polymers includes an rDA step. The thermally unstable oxanorbornene unit is used and a cycloalkyl group (e.g., a *trans*-1,4-cyclohexyl chain) is incorporated. The compound containing polyethylene glycol (PEG) spacers and a terminal amino group was reacted with the commercially available tricyclic oxabicycloheptenedicarboxylic anhydride in several steps to form the polymer intermediate **565**, which was heated in toluene to furnish the maleimide-functionalized polymer **566** and furan through a retrodiene reaction (Scheme 142).[270]

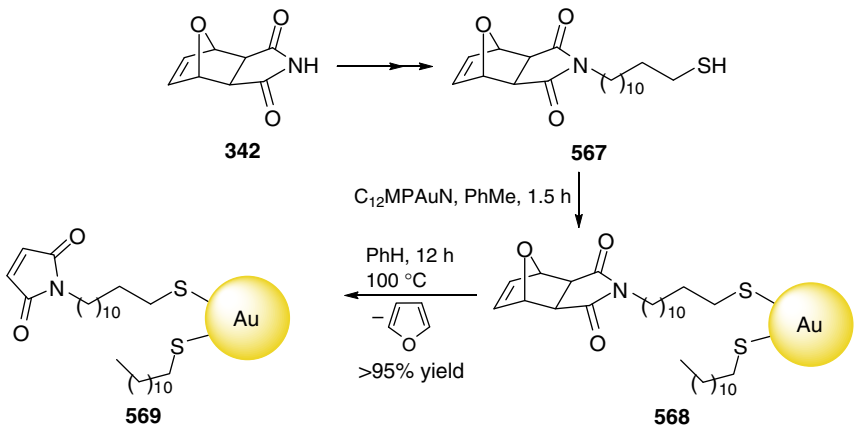


Scheme 142

From *diexo*-*N*-hydroxyethylmaleimide **343**, a similar synthetic strategy was developed for the preparation of α-functional maleimide polymethacrylates (M_n = 4.1–35.4 kDa) via Cu-catalyzed living radical polymerization (LRP). The synthetic pathway involved an initiator containing a maleimide unit protected as a DA adduct. After polymerization, the maleimide functionality was released by application of an rDA reaction. These maleimido-terminated poly(methoxy)$PEG_{(475)}$, methacrylates and poly(-glycerol)methacrylates differed in behavior, size, and solubility in water. Such polymers can be ideal candidates for the synthesis of new polymer/(poly)peptide conjugate biomaterials.[271]

The 7-oxabicycloheptene moiety can serve as a convenient linker for solid-phase organic syntheses, and has been utilized in the preparation of a maleimide-functionalized neuropeptide Leu-enkephalin by standard peptide coupling techniques. Relatively mild conditions (≥150 °C for 8 h) were necessary for the rDA cleavage, which afforded the appropriate maleimide-tagged pentapeptide and a separable furfuryl resin.[272]

From furan–maleimide adduct **342,** maleimide-modified monolayer-protected Au nanoparticles (MPAuN) **569** were prepared by thermally reversible DA reactions under mild conditions (refluxing in benzene), with the release of a molecule of furan. Adduct **568** was prepared in a multistep procedure from the simple *diexo*-7-oxabicycloheptene-fused imide **342** through *N*-ω-bromo-alkylation with an excess of 1,12-dibromododecane in DMF. The resulting bromide was converted to thiol **567**, which was then incorporated into the dodecanethiolate-modified C_{12}MPAuN to afford **568** (Scheme 143) using the Brust–Schiffrin method starting from dodecanethiol and hydrogen tetrachloroaurate under reducing conditions. These maleimide-MPAuNs served as a general platform that allowed DA reactions with furan-modified MPAuN to reversibly provide larger 3D networks.[273]

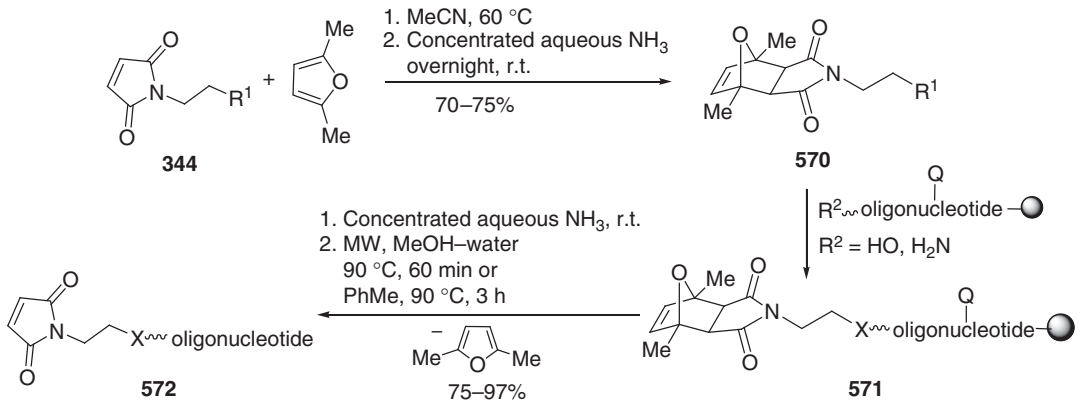


Scheme 143

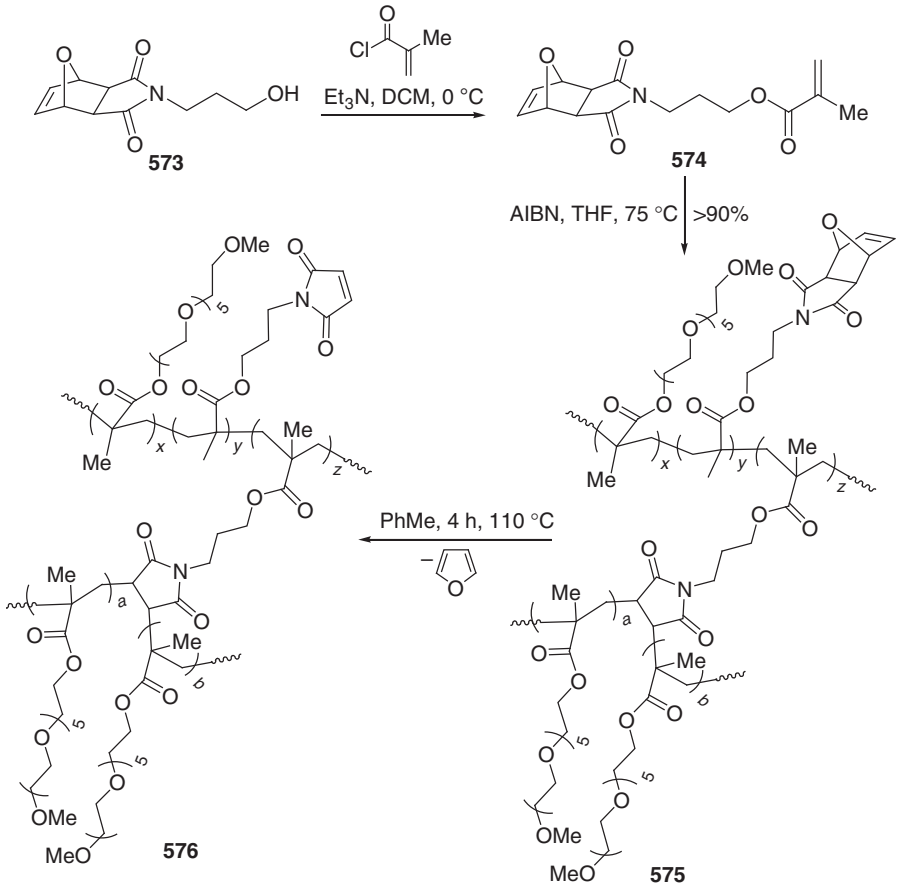
Maleimide-containing compounds **344** reacted with 2,5-dimethylfuran to give mixtures of *exo* and *endo* isomers in different ratios, from which the *diexo* cycloadduct could be easily isolated due to its stability in concentrated aqueous ammonia. The bifunctional dimethylfuran-protected maleimide (*exo* adducts) were attached to resin-linked oligonucleotide chains as in **571**. Removal of the protecting groups from the masked oligonucleotide functionalities followed by (MW-assisted or thermal) unmasking of the maleimide by rDA afforded maleimido-oligonucleotides **572** (Scheme 144) suitable for conjugation, as assessed by reactions with different thiols, lipophilic compounds such as thiocholesterol or water-soluble peptides (glutathione and other cysteine peptides).[274]

A novel DA cycloaddition/cycloreversion-based strategy allowed for the synthesis of poly(ethyleneglycol) methacrylate-based hydrogels containing thiol-capturing maleimide functional groups. Masked maleimide groups were directly incorporated into the hydrogel matrix during the gelation process by utilization of the furan-protected maleimide-containing methacrylate monomer **574**. During polymerization of this latent-reactive monomer **574** derived from *N*-hydroxypropylimide **573**, thermal deprotection of the maleimide groups led to compound **575** (AIBN = azobisisobutyronitrile). After gelation, the protected maleimide groups could be activated to their reactive gel forms **576** through thermal cycloreversion by the cleavage of furan (Scheme 145). The efficacy of gel formation, maleimide incorporation, functionalization, and bioconjugation of the hydrogel was investigated. These reactive hydrogels containing embedded maleimide groups could be readily derivatized with thiol-containing molecules such as fluorescent dyes. Likewise, thiolated biotin derivatives were covalently attached to these hydrogels under mild conditions.[275]

Thermally reversible polyethylene was synthetized by DA and rDA reactions from the furan–maleimide [4 + 2] cycloadduct as a cross-linking agent. The relative ease of adduct formation and rDA cleavage of furan–maleimide moieties permitted modulation of the properties of the grafted polymers. Various temperatures were applied in the solid or molten state to study the thermal reactivity by measuring the Fourier transform infrared spectroscopy absorption frequency at 700 cm^{-1} as the characteristic spectroscopic signature of the =C–H bond in maleimide. An original method was applied to graft the two molecules onto Lotader® poly(ethylene-co-glycidyl methacrylate) in a one-step procedure; the cycle of DA and rDA reactions was reproducible without significant polymer degradation.[276]



Scheme 144



Scheme 145

A smart poly(ethylene oxide) (PEO) polymer containing two thermally reversible groups located at the chain center (bisfuran–PEO) was prepared by a maleimide–furan [4 + 2] cycloaddition (DA) between one bis[(furan-2-yl)methyl]terephthalate and two maleimide-terminated poly(ethylene glycol) methyl ethers. These maleimide–furan adducts underwent rDA decomposition at high temperatures, with simultaneous maleimide–anthracene DA addition. Thus, when bisfuran–PEO and bis[(anthracen-10-yl]methyl) succinate were refluxed in toluene, the bisfuran–PEO cores were replaced by maleimide–anthracene adducts, which gave new polymers *in situ*. Moreover, when bisfuran–PEOs were mixed with molecules containing four anthracene units, cycloreversion of the maleimide–furan adducts and maleimide–anthracene addition took place in parallel, to generate a four-arm star arrangement of PEOs.[277]

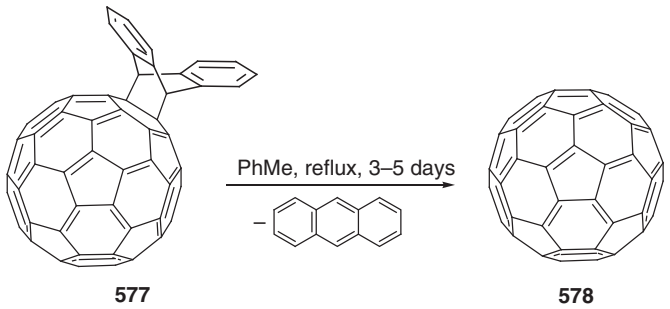
Polymers have a limited lifetime and this can lead to the degradation of materials by cracking or breaking. Mending at a microscopic level may be done with adhesives, which, through a reversible polymerization process, can restore the original properties of the polymers, even repeatedly. The DA-based polymers (e.g., of furan–maleimide or anthracene–maleimide type) with important reversibility (DA/rDA) properties may solve this problem, and these polymers were named mendable polymers by Wudl et al.[278]

5.12.8 Fullerenes and Graphenes – New Perspectives

5.12.8.1 Synthetic Applications of rDA Involving Fullerenes and Carbon Nanotubes

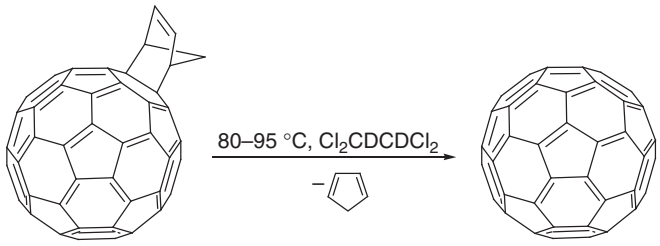
Cycloadditions are the most important amongst the reactions that allow the preparation of functionalized fullerenes, including [1 + 2], [2 + 2], [3 + 2], [4 + 2], [6 + 2], and [8 + 2] cycloadditions. However, only the reverse [4 + 2] reactions and DA adducts of fullerenes are discussed in this section.

Some [4 + 2] cycloadditions of C_{60} (**578**) and the related fullerenes and the reversibility of these reactions have been studied. Because the rDA reaction of the C_{60}–anthracene adduct **577** took place very easily, the resulting cycloadduct is relatively unstable. The preparation, purification, and characterization of the 1:1 adduct of C_{60} and anthracene were reported. The increased solubility of this adduct (in comparison with the parent C_{60} molecule) in common organic solvents facilitated crystallization with organic donors, creating a new class of charge-transfer salts with novel electronic and magnetic properties. Cycloadduct **577** was prepared by the reaction of a high excess (10 equivalents) of anthracene with 1 equivalent of C_{60} when the mixture was refluxed in toluene for 3 days. If a different excess of anthracene was used, the equilibrium shifted toward the starting materials, which caused low product yields. The 1:1 adduct remained stable for some weeks when stored in a freezer (at −10 °C). However, refluxing of purified **577** in toluene for several days resulted in degradation with the formation of neutral C_{60} (**578**) and anthracene by an rDA reaction (equation 35).[279]



577 **578** (35)

The kinetic thermal stability of the C_{60}–cyclopentadiene DA adduct **579** was studied via the rate of cycloreversion in the temperature range of 80–95 °C (equation 36). At 80 °C and at 95 °C, half-lifetimes of 97 min and 18 min, respectively, were measured.[280]



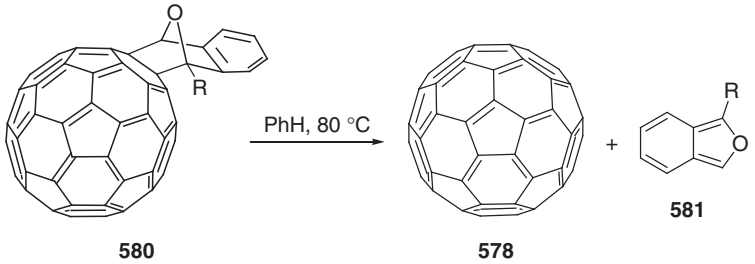
579 **578** (36)

Fullerene adducts with perfluoroalkylated 1,3-cyclopentadiene were also synthetized and studied. The perfluorinated substrates were less reactive toward C_{60} than cyclopentadiene itself, likely because of the electron-withdrawing effect of their side-chain. For the same reason, the rDA reactions of the fluorinated adducts required a lower temperature (70 °C) than that for the cyclopentadiene adducts with C_{60} (95 °C).[281]

Similar DA adducts of C_{60} with anthracene derivatives readily underwent cycloreversion to the component molecules on heating. The thermal dissociation of the DA adducts of C_{60} with amphiphilic anthracenes bearing a carboxylic acid group was utilized to prepare Langmuir–Blodgett films. Furthermore, 9-substituted anthracenes and bis(9-anthranylmethyl)adipate were studied as model compounds to evaluate the DA reactions with fullerene (C_{60}) and the thermostability of the cycloadducts formed.[282] Reversible DA reactions of anthracenes bearing a dendritic substituent with C_{60} were observed as new examples of the

chemistry of poly(amidoamine) dendrimers grafted to fullerene, a novel class of photosensitive water-soluble fullererenes.[283] A racemic mixture of trisdi(ethoxycarbonyl)methanofullerenes Bingel trisadducts[60] was prepared by malonate addition and a subsequent rDA reaction starting from a C_{60}-tris-*e,e,e* adduct of anthracene as precursor. Because the anthracene protecting groups directed the orientation of new additions, specific and particular geometrical polyadducts were obtained. In the event, the DA cycloaddition of fullerene and anthracene led to a trisadduct, which was cyclopropanated in a Bingel reaction to form a hexaadduct. Finally, cycloreversion was applied to remove the anthracene.[284] The reactions of anthracene malonates with C_{60} in a 1:1 M ratio in toluene resulted in mono DA adducts. However, when the purified cycloadduct was refluxed in toluene for several hours, C_{60}–anthracene malonate and anthracene malonate were formed through rDA cycloreversion.[285]

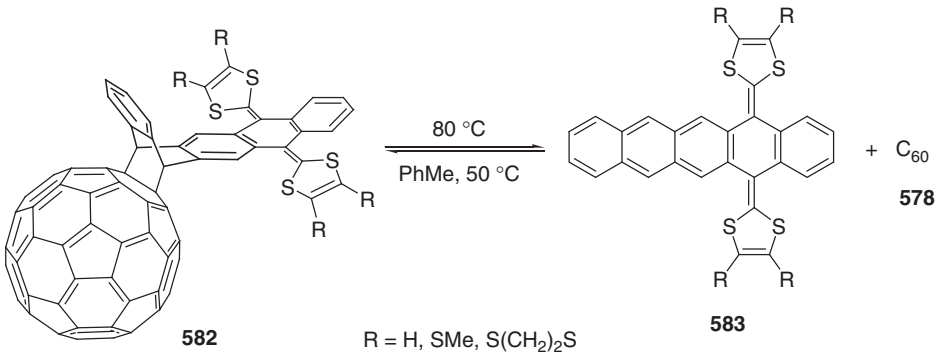
With fullerene C_{60}, the reactions and kinetic stability of 1,3-disubstituted isobenzofurans were examined. A variety of substituted isobenzofurans **581**, generated by the reactions of 1,4-substituted 1,4-epoxynaphthalenes with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine or 1,2,4,5-tetrazine, underwent addition to C_{60} to afford DA adducts **580**. The thermal stability of these adducts *vis-a-vis* rDA fragmentation in solution and the solid state differed greatly. In solution, the relatively facile rDA fragmentation of monoadducts **580** gave C_{60} and isobenzofurans **581** (equation 37) with rate constants (and activation barriers) of $k = 9.29 \times 10^{-5}\ s^{-1}$ at 70 °C ($E_a = 32.6$ kcal mol^{-1}) and $k = 1.36 \times 10^{-4}\ s^{-1}$ at 40 °C ($E_a = 33.7$ kcal mol^{-1}), indicating that the addition of isobenzofurans to C_{60} was readily reversible at these temperatures. However, the TGA of adduct **580** (R=H) in the solid state indicated that its decomposition occurred only within the temperature range of 220–300 °C. Thus, **580** in the solid state can be stored at room temperature for some weeks without significant decomposition, but it must be handled within only a few hours in solution.[286]



580 **578** **581**

R = H, CO_2Me (37)

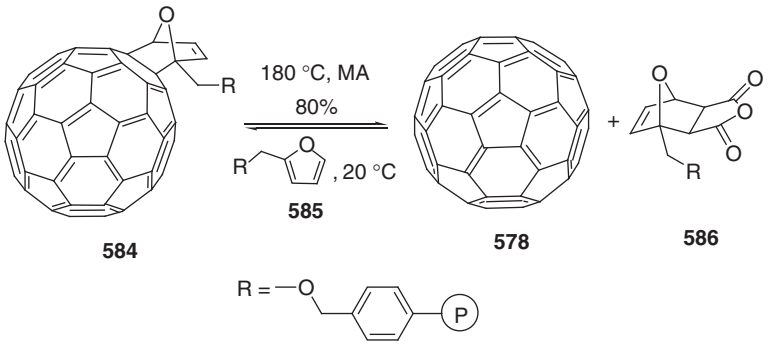
The DA cycloadducts of C_{60} and anthracene derivatives bearing fused π-extended tetrathiafulvalenes (TTF) behaved as thermally reversible donor–acceptor materials (dyads), which functioned as molecular fluorescence on/off switches. Dyads **582** could be obtained in poor yields (10–12%) from the [4 + 2] cycloaddition of equimolecular amounts of fullerene C_{60} and 5,14-bis(1,3-dithiol-2-ylidene)-5,14-dihydropentacenes **583**, with purification by column chromatography. The rDA decomposition of dyads **582** was studied at different temperatures by means of ^{1}H-NMR. The rDA process started at approximately 50 °C and continued up to 80 °C, when the decomposition of adducts **582** to TTF derivatives **583** and fullerene **578** was almost quantitative (equation 38). Increase of the temperature in 10 °C intervals from room temperature to 80 °C led to a gradual reactivation of the fluorescence-excited state.[287]



582 **583** **578**

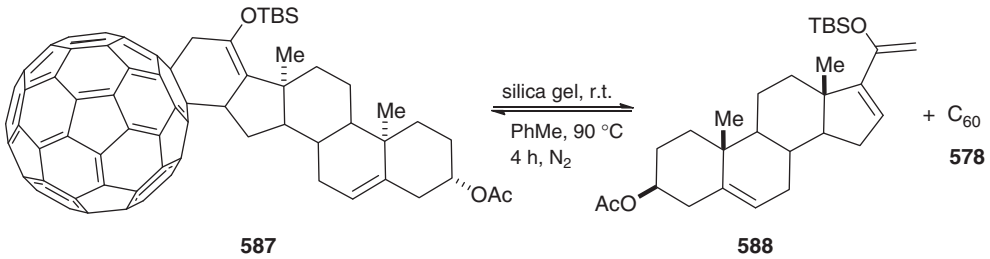
R = H, SMe, $S(CH_2)_2S$ (38)

The furan-functionalized polymer resin **585** reacted rapidly with C_{60} at room temperature, furnishing fullerene-substituted polymer **584** in a reversible DA covalent coupling reaction. This resin proved to be twice as efficient as the previously reported cyclopentadiene-substituted resin. Moreover, polymer **584** exhibited better reversibility on heating in the presence of the MA dienophile as the trapping agent (equation 39).[288]



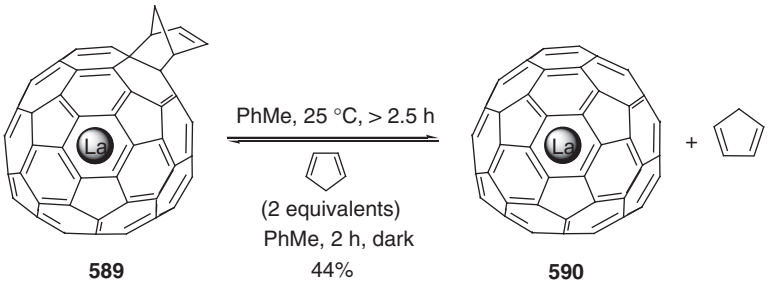
(39)

Certain novel fullerene–steroid adducts displayed activity on sarcoplasmic reticulum Ca^{2+}-ATPase. From commercially available 3β-acetoxypregna-5,16-dien-20-one, the corresponding *tert*-butyldimethylsilyl ether **588** was prepared and used as a diene. Its [4 + 2] cycloaddition with C_{60} was carried out in toluene. During attempted purification through chromatography on a silica gel column, adduct **587** unexpectedly suffered an rDA reaction (equation 40) under mild conditions.[289]



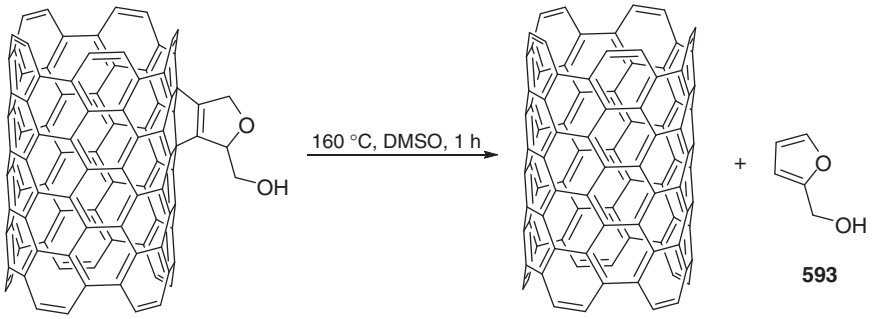
(40)

Endohedral fullerenes are a new and special class of carbon clusters which contain one or more atoms inside the hollow fullerene cage. This type of metallofullerenes has useful and unique electronic properties, such as low oxidation and reduction potentials which permit valuable applications. Reversible DA cycloaddition is therefore a useful method for the separation or protection of endohedral metallofullerenes. Kinetic analysis revealed that the rDA decomposition of cycloadduct **589** to La@C_{82} endohedral metallofullerene **590** and cyclopentadiene took place even in toluene (equation 41). The cleavage was much faster than that of the parent C_{60}–cyclopentadiene adduct (half-lifetime $\tau \sim 1.8$ h for **589** and $\tau \sim 1.8 \times 10^3$ h for **579**).[290]



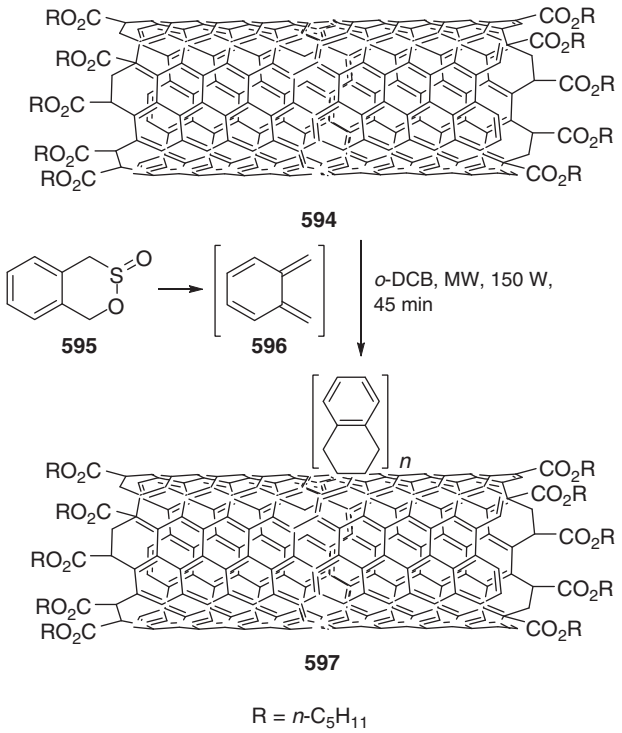
(41)

Carbon nanotubes (CNTs) are well known members of the fullerene structural family, which also includes the spherical buckyballs; the ends of a nanotube may be capped with a hemisphere with a buckyball substructure. They are categorized as single-walled nanotubes (SWNTs) or multiwalled nanotubes (MWNTs). The chemical bonding of nanotubes involves only sp^2 bonds, similar to those in graphite. These bonds, which are stronger than the sp^3 bonds in alkanes, provide nanotubes with their unique strength. Because of their unique properties, the functionalization of CNs through DA reactions offers a new perspective in the search for new and special materials. As compared with fullerenes, the CNTs are less reactive in direct cycloadditions, but the reactivity of SWNTs toward dienes in DA reactions can be promoted with transition metal catalysts under high pressure, by fluorination, by the use of reactive dienes (e.g., furan) or dienophile (maleimide) agents, among others. Studies of the functionalization of MWNTs demonstrated that these CNTs can serve either as dienophiles or as dienes. Further, the adducts can undergo a reverse DA reaction on heating. Thus, MWCNT–furfuryl alcohol adduct **591** formed CNTs **592,** which were collected by filtration in pure form (equation 42). The cycloreversion of the MWCNT–*N*-(4-hydroxyphenyl)maleimide adduct was carried out similarly.[291]



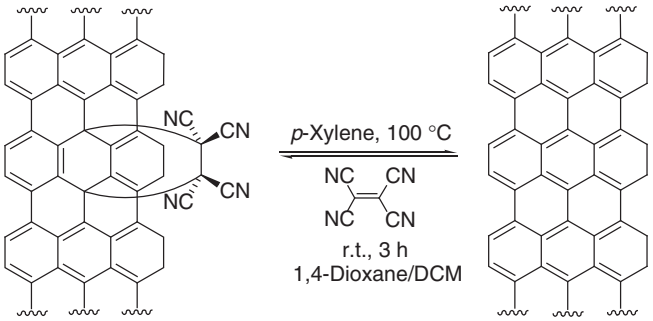
591 **592** **593** (42)

MW-assisted sidewall functionalization was first performed through an rDA/DA sequence involving cycloaddition of *o*-quinodimethane to SWNT ester **594**. Diene **596** was generated *in situ* from 4,5-benzo-1,2-oxathiin-2-oxide (sultine) **595** in an rDA reaction under MW irradiation. Repeated cycloaddition was achieved when a mixture of sultine **595** and ester-functionalized SWNT **594** was irradiated in a focused MW reactor. On workup, the reaction mixture gave the modified nanotube **597** (equation 43), opening up an access to a new family of modified SWNTs.[292]



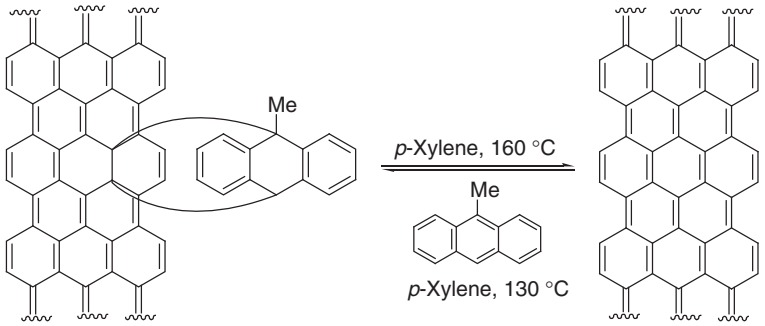
(43)

Graphene, a carbon allotrope, consists of one-atom-thick planar sheets of sp^2-bonded carbon atoms densely packed in a honeycomb crystal lattice. Graphene is a basic structural element of certain forms of carbon, including graphite, charcoal, CNTs, and fullerenes. It can also be regarded as an indefinitely large aromatic molecule, the limiting case in the family of flat polycyclic aromatic hydrocarbons. Furthermore, graphene as an electronic material is of great potential thanks to its excellent transport properties, stemming from the unique Fermi surface and ballistic conductance. The zero-band-gap electronic structure of graphenes enables them to act either as diene or as dienophile in DA reactions and related reversible modification processes. Haddon et al. made a detailed study of the DA and rDA chemistry of graphite and graphene. When the tetracyanoethylene dienophile was reacted with graphene, a DA reaction occurred on addition of a few drops of 1,4-dioxane at room temperature. The cycloaddition was reversible when adduct **598** was heated at 100 °C in xylene, and starting graphene **599** was recovered after the rDA reaction (equation 44). The similar formation of graphene adducts with MA proved to be sensitive to the nature of the graphene sample and the reaction temperature (80–120 °C), but at ~150 °C the rDA reaction was complete.



598 **599** (44)

Investigations were also made into the use of graphite and graphene as dienophiles in DA cycloadditions involving 9-methylanthracene and 2,3-dimethoxy-1,3-butadiene, and the reversibility of the reaction was also examined. After optimization, the 9-methylanthracene–graphene cycloadduct **600** could be obtained in high yields. However, when the temperature was increased to 160 °C, the reverse DA reaction took place to regenerate graphene **601** and 9-methylanthracene (equation 45). The wide-ranging scope of DA/rDA chemistry and the dual nature of the reactivity of graphene with various dienophiles and dienes led to modifiable chemical functions and ready reversibility of the cycloadducts. The covalent functionalization of graphene by DA and/or rDA procedures is therefore a simple and valuable approach for optical and electronic applications.[293]



600 **601** (45)

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5.13 (4 + 3) Cycloadditions

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Glossary

Aldol condensation A reaction in which an enol or enolate ion react with a carbonyl compound to form a β-hydroxyaldehyde or β-hydroxyketone, followed by a dehydration to give a conjugated enone.

Asymmetric transformation The conversion of a racemate into a pure enantiomer or a mixture in which one enantiomer is present in excess, or of a diastereoisomeric mixture into a single diastereoisomer or into a mixture in which one diastereoisomer predominates.

Diels–Alder A cycloaddittion reaction between a conjugated diene and substituted alkene, commonly termed the dienophile, to form a substituted cyclohexene system. The reaction can proceed even if some of the atoms in the

newly formed ring are not carbon (hetero-Diels–Alder reaction). The cycloaddition reaction is allowed by the Woodward–Hoffman rules.

Endo, exo *Endo* and *exo* are descriptors of the relative orientation of groups attached to nonbridgehead atoms in a bicyclo[x.y.z]alkane ($x \geq y > z > 0$). If the group is orientated towards the highest numbered bridge (z bridge, e.g., C-7 in example below) it is given the description *exo*; if it is orientated away from the highest numbered bridge it is given the description *endo*.

Favorskii rearrangement The Favorskii rearrangement is mainly a rearrangement of cyclopropanones and α-halo ketones which leads to carboxylic acid derivatives. In the case of cyclic α-halo ketones, the Favorskii rearrangement involves a ring contraction.

Friedel–Crafts The Friedel–Crafts reactions are a set of reactions developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring. There are two main types: alkylation and acylation reactions, both proceeding by an electrophilic aromatic substitution pathway.

Nazarov electrocyclization The Nazarov cyclization reaction is a chemical reaction used for the synthesis of cyclopentenones. It was originally discovered by Ivan Nikolaevich Nazarov (1906–57) in 1949 while studying the rearrangements of allyl vinyl ketones. As originally described, it involves the activation of a divinyl ketone using a stoichiometric Lewis acid or protic acid promoter. The key step of the reaction mechanism involves a cationic 4π-electrocyclic ring closure which forms the cyclopentenone. Variants involving substrates other than divinyl ketones and catalytic promoters or others than Lewis acids have also been reported under the same name due to a similar mechanistic pathway.

Oxyallyl cation It refers to allylic cations substituted at the 2-position with an oxygen substituent. This type of 2π components participate in cycloadditions with dienes (4π) yielding cycloheptenones as adducts.

Transition state The transition state of a reaction is defined as the state corresponding to the highest potential energy along its reaction coordinate. It is often marked with the double dagger ‡ symbol.

Trialkylsilylenol ethers A type of enol ether in which the oxygen atom is linked to a trialkylsilyl group.

Vinyl oxocarbenium A type of oxocarbenium ion (canonical form of a carbocation, real or hypothetical, which places a formal positive charge on an oxygen atom) that incorporates a vinyl group attached to one of their atoms.

5.13.1 Introduction

Seven-membered rings are present in the structural core of many biologically relevant natural products and, in general, are more difficult to construct than the five- and six-membered congeners. Indeed, syntheses of products featuring seven-membered rings as key skeletal elements are much scarcer than those leading to cyclic products bearing smaller rings.

From the practical point of view, one of the best ways to construct seven-membered rings consists of the use of cycloaddition reactions owing to the intrinsic increase in complexity that can be achieved in just one step, from simple acyclic precursors. Among the different cycloaddition alternatives,[1] the more common are based on (5 + 2) and (4 + 3) assembling strategies. (It should be noted that in this chapter the authors use the (4 + 3) rather than the more frequent [4 + 3] notation. The designation (m + n) is used here in accordance with Woodward–Hoffmann/IUPAC conventions for describing cycloadditions based on the number of atoms, as opposed to the bracketed [m + n] designation, which indicates the number of electrons involved.) (5 + 2) Cycloadditions usually make use of alkynes or alkenes as two-carbon partners and vinylcyclopropanes, cyclopropyl imines, pyrones, pyranulose acetates, betaines, and quinones as five-atom components.[2] However, (4 + 3) cycloadditions are mainly based on the use of highly accessible conjugated dienes as four-carbon components, and different types of three-atom precursors.

In many cases (4 + 3) annulation strategies rely on the reaction between allyl cation precursors and dienes, because the overall reaction involves a thermally allowed 4π + 2π cyclic rearrangement, homologous to that occurring in Diels–Alder cycloadditions. Nevertheless, in recent years other very interesting alternatives for this type of cycloadditions have been developed. Herein, the authors try to collect classical as well as more recent (4 + 3) cycloaddition approaches so that the reader can easily assess the evolution and current potential of this constructive strategy. They have tried to avoid excessive discussions on reactions that are already collected in previous reviews and, in particular, those already included in the first edition of Comprehensive Organic Synthesis. To facilitate reading and understanding, the different cycloaddition strategies are organized into sections according to common mechanistic features and/or related hypothetical intermediates. Thus, the (4 + 3) cycloaddition of allyl cations (e.g., oxyallyl, aminoallyl, metal-allyl, etc.), donor–acceptor strained cycles, metallacyclic intermediates, or Pd-trimethylenemethane (TMM) species, are collected in different sections. A final section on (4 + 3) cycloaddition strategies leading to seven-membered rings that involve sequential processes have also been included, occurring via well established and even isolable organic intermediates.

Finally, a number of synthetic applications have been collected in specific sections so that the reader can learn, at a glance, the potential of the technology to make biologically relevant cyclic targets.

5.13.2 (4 + 3) Cycloadditions Between Dienes and Allyl Cation Precursors

5.13.2.1 Introduction

Considering that cycloadditions involving 4π + 2π electron rearrangements are allowed by the orbital symmetry rules, it is not surprising that allyl cations can react with dienes to make seven-membered rings. It also makes sense that the transformation

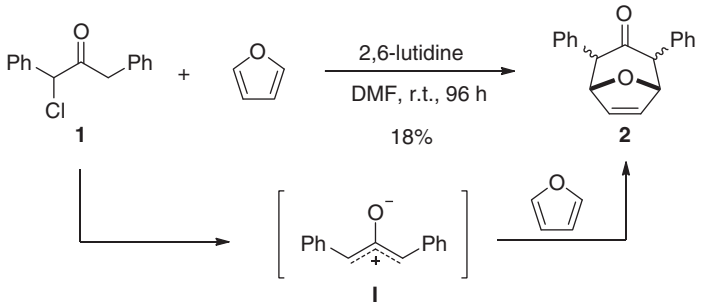
should be favored by substituents in the 3C precursor that favor the formation of the allyl cation intermediate and stabilize the resulting carbocation of the cycloheptenic ring.

In the following sections the authors will discuss the most relevant methodologies thus far described to generate cycloaddition-active allyl cations. Each section discusses the chemistry of allyl cation intermediates bearing a specific type of substituent at the central carbon atom. The first section, devoted to oxyallyl cations, is organized based on the type of precursors used for their generation and, therefore, complements other very recent reviews that use a different organization.[3]

5.13.2.2 Reactions Involving Oxyallyl Cation Intermediates

5.13.2.2.1 Introduction

The success of a (4 + 3) cycloaddition strategy mainly depends on the facility for generating suitable three-carbon species capable of undergoing a cyclocondensation with a 1,3-diene (four-carbon partner). Among the different types of three-carbon allyl cations, those substituted at the central position with an oxygen substituent, termed 'oxyallyls', are the most common.[3] In 1951, Anston and Newkirk proposed for the first time the formation of oxyallyl cations as transient intermediates in the Favorskii rearrangement.[4] However, it was not until 1962 when Fort provided the first example of a (4 + 3) cycloaddition involving an oxyallyl cation intermediate (**I**) (equation 1). The reaction was accomplished by treatment of chloroketone **1** with 2,6-lutidine (4 equivalents) in the presence of excess furan (2.5 equivalents), and gave the oxacyclic products **2** in a modest 18% yield (equation 1).[5]



(1)

Since the discovery of Fort, many other (4 + 3) cycloadditions, which have been proposed to involve oxyallyl cation intermediates, have been reported. Although these key intermediates can be generated in different ways, there are some basic rules for the (4 + 3) cycloaddition of oxyallyl cations, which are applicable in most of the cases, and useful to understand, and even predict, the outcome of the reaction.

The (4 + 3) cycloaddition of dienes to oxyallyl cations, analogous to the Diels–Alder reaction, can be viewed as a [4π + 2π] process between a diene and a dienophile (Figure 1). However, in these cycloadditions, the dienophile works as a three- rather than as a two-carbon component as is the case of Diels–Alder reactions. Like for (4 + 2) cycloadditions, the (4 + 3) annulation can be explained in terms of the interaction between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile (oxyallyl cation). Whereas in Diels–Alder reactions the energy level of the LUMO is lowered by electron-withdrawing groups (EWGs) in the alkene or alkyne partners, the LUMO orbital of an oxyallyl cation is of lower energy when the O–M bond features a higher covalent character. Therefore, the electrophilicity of oxyallyl cationic intermediates decreases along the series M = alkyl or H > iron > silyl > zinc ≥ lithium > sodium > cyclopropanone ('oxidoallyl') (Figure 1).[3b,f]

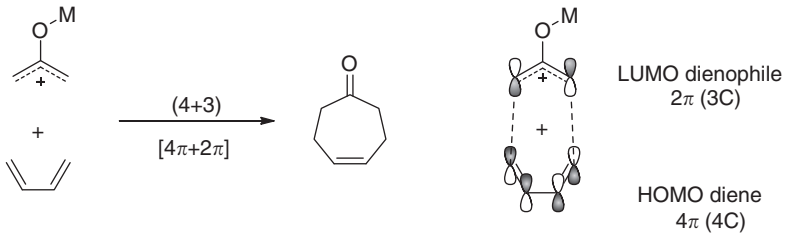


Figure 1 [4π + 2π] Cycloaddition between an oxyallyl cation and a conjugated diene.

The regioselectivity of the cycloaddition is controlled by the coefficient of the frontier molecular orbitals at the edge carbons of the oxyallyl moiety, which, in many cases, tend to be quite similar.

Substituted oxyallyl cations can, in principle, adopt different geometries, but we can consider that there are three basic structures: U-, sickle-, and W-shaped (Figure 2). The W form is usually proposed for acyclic substrates because it represents the conformation of lowest energy; the U-shaped conformation is the only one possible in case of cyclic structures (although the

'sickle' form could be an alternative for large rings). With regard to the dienes, the most reactive and commonly used are furan and its derivatives, as well as cyclopentadiene, owing to their enforced *s-cis* conformation. Other cyclic dienes such as pyrroles, cyclohexadienes, anthracenes, or fulvenes have also been used; however, they usually give rise to less efficient and selective reactions. Acyclic dienes can also work as four-carbon partners, albeit they generally provide modest cycloaddition yields, probably because of the low concentration of the reactive *s-cis* conformers.

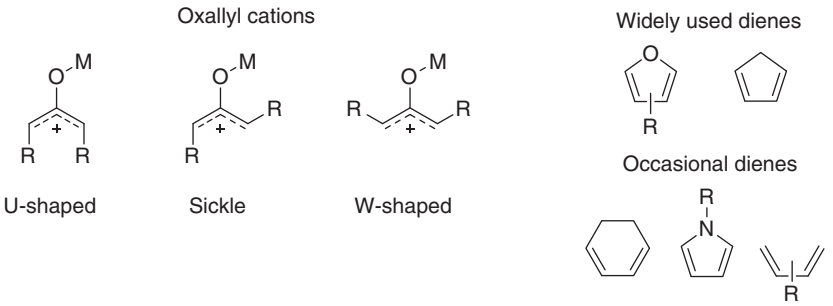


Figure 2 Oxyallyl cations and their diene counterparts.

Although from the above discussion it could be inferred that the (4 + 3) cycloaddition between oxyallyl cations and dienes is a concerted pericyclic process, this is not always the case, and in many instances it has been reported to take place in a stepwise manner. The mechanism depends on the reaction conditions, with stepwise processes being more favored for electron-rich dienes such as pyrrole and furan derivatives, because of the higher stability of cationic intermediates of type **II** (Figure 3). The stepwise mechanism is also more favored in the case of electrophilic oxyallyl cations featuring more covalent O–M bonds. Cramer and coworkers have recently investigated the mechanism of the (4 + 3) cycloaddition using computational methods, and agree that it depends on the electrophilicity of the oxyallyl cation and the nucleophilicity of the diene. These authors also suggest that in some cases the reaction may involve a (3 + 2) cycloaddition followed by Claisen rearrangement of intermediates like **III**.[6]

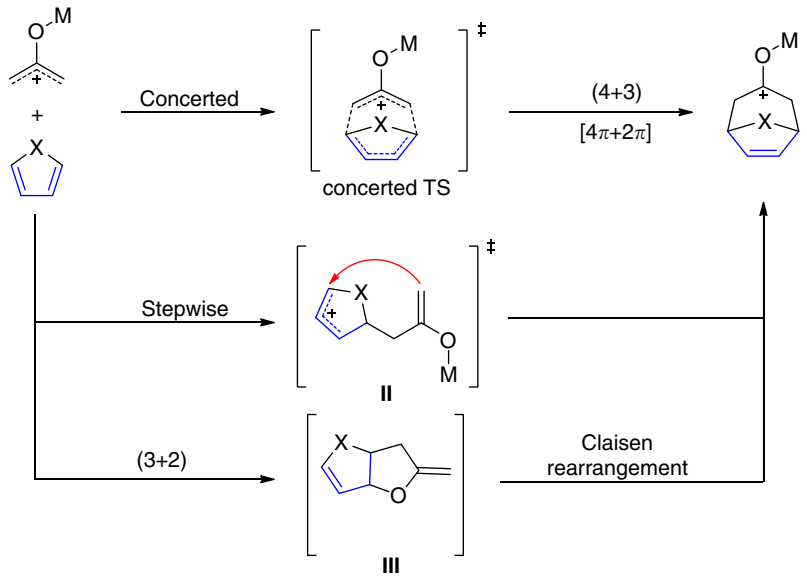


Figure 3 Mechanistic possibilities for the (4 + 3) cycloaddition of oxyallyl cations and dienes.

With regard to the stereochemistry, the cycloaddition can proceed for concerted processes through two topologically distinct transition states, called 'compact' or 'extended'. The 'compact' transition state (**TS-I**) is 'boat-like' and is related to the *endo* transition state of the Diels–Alder processes. The alternative is an 'extended' transition state (**TS-II**), which is 'chair-like' and is related to the *exo* transition state. In the case of substituted acyclic oxyallyl cations with a preferred 'W-shaped' conformation, reactions through compact transition states lead to diequatorial type of products (Figure 4), whereas those proceeding through extended transition states give products with the substituents R in a diaxial orientation. The formation of axial-equatorial products could be explained in terms of stepwise mechanisms, at least in those cases where the oxyallyl cation adopts a 'W-shaped' conformation (Figure 4). In general, oxyallyl cycloadditions are less stereoselective than Diels–Alder reactions, although in some cases impressive selectivities can be achieved.

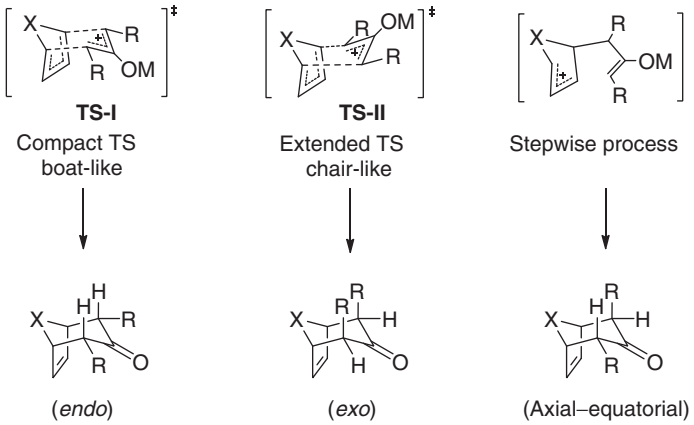


Figure 4 Stereochemical possibilities in the cycloaddition of acyclic oxyallyl cations with W-shape conformation.

In the following subsections, the authors present different examples of (4 + 3) cycloadditions mediated by oxyallyl cations which, as commented above, have been organized according to the type of precursors employed to generate the reactive allylic species. Given the large literature body on this topic and the previous review of 1991 in Comprehensive Organic Synthesis, the authors will mainly cover work published after 1990.

5.13.2.2.2 α-Haloketones

5.13.2.2.2.1 Acyclic precursors

The first example of an oxyallyl-diene cycloaddition, reported by Forth in 1962, was based on the generation of the allyl cationic intermediate by treatment of an α-chloroketone with a base (see equation 1). The method represents a rather attractive approach to generate oxyallyl cations because of the mild conditions and the relative simplicity of the starting materials. Although the efficiency of these preliminary transformations was limited, subsequent improvements on reactions conditions by Föhlisch and coworkers, based on the use of ethereal lithium perchlorate or fluorinated solvents like trifluoroethanol (TFE), or 2,2,3,3-tetrafluoropropanol (TFP) brought an important enhancement of the efficiency and scope of the methodology.[3a]

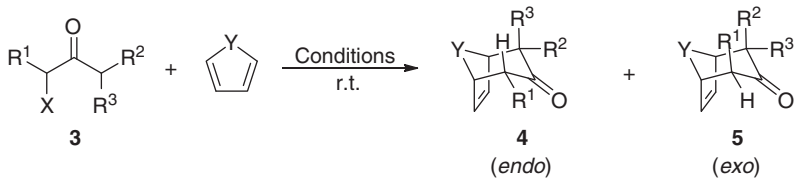
Most of the work on this type of (4 + 3) cycloadditions of acyclic haloketones and dienes was developed in the 1970s and 1980s and is detailed in the first edition of Comprehensive Organic Synthesis.[3e] However, some representative examples are included in Table 1. Simple 1-chlorobutan-2-one (**3a**) only reacts with furan in a testimonial 5% yield. However, reaction of 2-bromopentan-3-one (**3b**) or 2-chloropentan-3-one (**3c**) with furan led to the corresponding oxabicycles in good yields and good selectivities in favor of the *endo* cycloadducts (**4**). Interestingly, the cycloaddition of 2-chloropentan-3-one (**3c**) with furan or cyclopentadiene could be performed even in water, using triethylamine as the base (conditions C, entries 4 and 9) and only require a smaller amount of diene (2 equivalents). A further increase in the substitution of the starting haloketone (**3e**) led to fully stereoselective processes (entry 6).[7d] In general, when the diene is furan (Y=O), good yields and selectivities can be achieved under different conditions. However, with cyclopentadiene, although the overall yield is good, the *endo*:*exo* selectivity drops (entries 3 vs. 8 and 4 vs. 9).

5.13.2.2.2.2 Cyclic precursors

Cyclic α-chloro- or α-bromoketones also participate in (4 + 3) cycloadditions with dienes under 'basic conditions,' providing interesting carbon-bridged bicyclic structures. Inspired by the work of Föhlisch with α-bromocyclohexanones (**6a**) and α-bromocyclopentanones (**6b**),[7a,d] Cha and coworkers reported in 1995 that treatment of substituted α-chlorocyclohexanones **6c–f** with cyclic dienes (2–4 equivalents) and Et_3N (2 equivalents) leads to the expected tricyclic cycloadducts (Table 2).[8] Although yields are from moderate-to-good, selectivities are generally very good, favoring the formation of *endo* products of type **7** even with cyclopentadiene (entries 4 and 7). In these cases, the reaction involves the formation and subsequent cycloaddition of 'U-shaped' cyclic oxyallyl intermediates like **IV**. The stereoselection observed in these intermolecular cycloadditions of cyclic oxyallyl cations with furans has been rationalized in terms of secondary orbital interactions and steric effects.

The same group reported an interesting asymmetric version of the transformation based on the use of cyclohexanone substrates **8**, bearing a chiral center in an adjacent position. These allyl cation precursors were prepared by chlorination (SO_2Cl_2) of ketones which, in turn, were ensembled by aldol condensation of cyclohexanone with an appropriate aldehyde and subsequent silylation. The cycloaddition reaction is proposed to proceed through a compact transition state which favors formation of the *endo* product resulting from the approach of the diene to the oxyallyl cation from its less-hindered face, opposite to the bulky alkoxy group, thus leading to the exclusive formation of cycloadduct **9** (equation 2). Interestingly, running the same reaction with the unprotected precursor **10** leads to products of complementary stereochemistry (**11**). This result is explained in terms of an internal hydrogen bonding, which favors a complementary facial approach to that observed in case of **8** (equation 3).[9]

Table 1 (4 + 3) Cycloaddition of acyclic haloketones with cyclic dienes under basic conditions

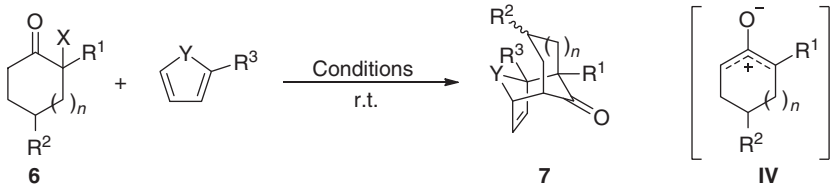


3 **4** (*endo*) **5** (*exo*)

Numbers	***3***					*Diene*	*Conditions*[a]	*Yield (%)*[b]	***4:5***	*References*
		X	*R*[1]	*R*[2]	*R*[3]	*(Y)*				
1	**3a**	Cl	H	Me	H	O	A	5	55:45	7a
2	**3b**	Br	Me	Me	H	O	A	75	82:18	7a
3	**3b**	Br	Me	Me	H	O	B	78	93:7	7b
4	**3c**	Cl	Me	Me	H	O	C	88	90:10	7c
5	**3d**	Cl	H	Me	Me	O	A	66	–[c]	7a
6	**3e**	Cl	Me	Me	Me	O	D	68	100:0	7d
7	**3f**	Br	^{i}Pr	^{i}Pr	H	O	A	47	82:18	7a
8	**3b**	Br	Me	Me	H	CH_2	B	71	65:35	7b
9	**3c**	Cl	Me	Me	H	CH_2	C	76	70:30	7c

[a]Conditions A: Furan-Et_2O (6:4 v/v), $LiClO_4$ (2 equivalents), Et_3N (2 equivalents); conditions B: Diene (15 equivalents), 1 M solution of NaTFP in TFP; conditions C: Diene (2 equivalents), Et_3N (1 equivalent) H_2O; and conditions D: Furan-TFE(1:1 v/v), Et_3N (2 equivalents).
[b]Combined yield of **4** and **5**.
[c]Only one isomer is possible.

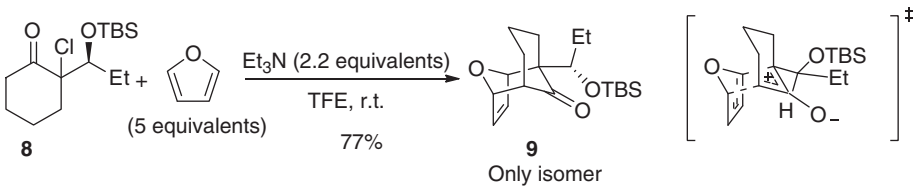
Table 2 (4 + 3) Cycloadditions of cyclic oxyallyl cations with cyclic dienes



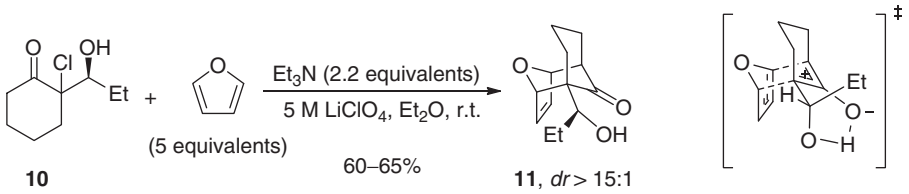
6 **7** **IV**

Numbers	***6***					*Diene*		*Conditions*[a]	***7*****, *Yield (%)***	*References*
		n	*X*	*R*[1]	*R*[2]	*Y*	*R*[3]			
1	**6a**	1	Br	H	H	O	H	A	84	7d
2	**6b**	0	Br	H	H	O	H	B	63	7a
3	**6c**	1	Cl	H	H	O	H	C	70	8
4	**6c**	1	Cl	H	H	CH_2	H	D	65	8
5	**6c**	1	Cl	H	H	O	Me	C	66	8
6	**6d**	1	Cl	Me	H	O	H	C	56	8
7	**6d**	1	Cl	Me	H	CH_2	H	D	43	8
8	**6e**	1	Cl	H	OTIPS	O	H	C	41[b]	8
9	**6f**	1	Cl	H	Me	O	H	C	49[c]	8

[a]Conditions A: Furan-TFE (1:1 v/v), Et_3N (2 equivalents); conditions B: Furan-Et_2O (6:4 v/v), $LiClO_4$ (2 equivalents), Et_3N (2 equivalents); conditions C: Furan (2–4 equivalents), Et_3N (2 equivalents), TFE; and conditions D: Diene (2–4 equivalents), Et_3N (2 equivalents), TFP.
[b]*dr* = 1.9:1.
[c]*dr* = 2.7:1.



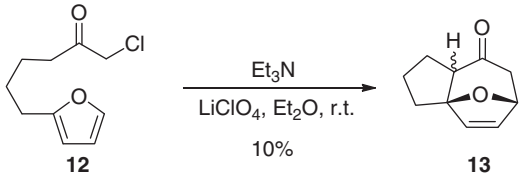
8 **9** Only isomer (2)



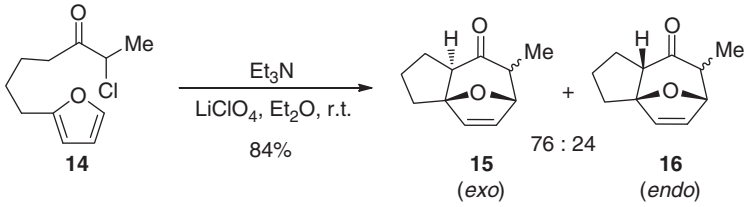
(3)

5.13.2.2.2.3 Intramolecular cycloadditions

As expected, this type of base-induced cycloadditions can also be implemented in an intramolecular manner. Therefore, treatment of the furan-tethered chloroketone **12** with Et_3N induces the formation of the expected carbobicyclic product **13**, but the reaction takes place in very low yield (equation 4). Remarkably, a simple incorporation of a methyl substituent at the ketone α-position, such as in **14**, increases the stability of the putative allyl cation intermediate, thus leading to a clear improvement in the yield (equation 5).[10] Nevertheless, the products are formed as a mixture of up to four diastereoisomers, and an *exo* (**15**) : *endo* (**16**) selectivity of 76:24 (equation 5).

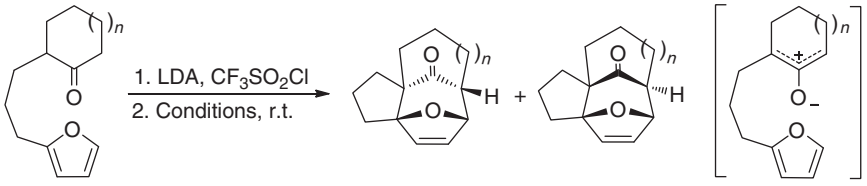


(4)



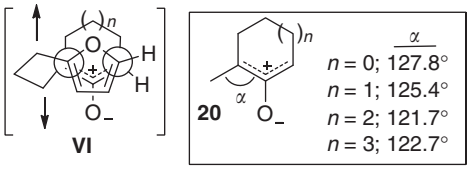
(5)

In the mid-1990s, Harmata et al. reported a detailed study on the intramolecular cycloaddition of furan-tethered cyclic α-chloroketones prepared by *in situ* chlorination of **17** under standard conditions (equation 6).[11] Although the yields are moderate, the reaction offers substantially better selectivities compared with the intramolecular cycloaddition of acyclic precursors mentioned earlier (equations 4 and 5). The reaction was proposed to take place through U-shaped oxyallyl cations (**V**), which react preferentially via extended transition states (thus leading to *exo* products), except in the case of cyclopentenyl oxyallyl cations, which prefer to approach the diene in a compact mode (that leads to the *endo* product). The authors explained this result on the basis of the induced strain on the endo transition state (VI) when the angle α increases.



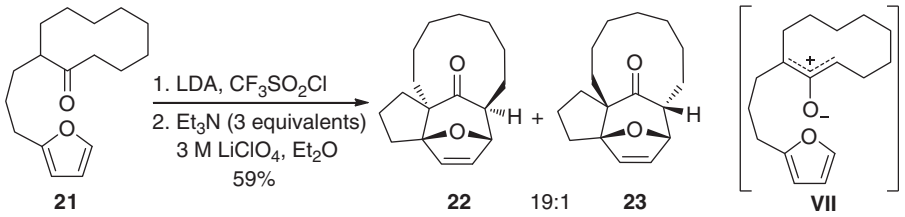
n	Conditions[a]	Yield (%)	**18** : **19**
0	A	55	15 : 1
1	A	54	1 : 2.5
2	A	56	1 : 7.3
3	B	61	1 : 10.1

[a]Conditions A: Et_3N (3 equivalents), 3M $LiClO_4$ in Et_2O; conditions B: NaTFE (5 equivalents), TFE.



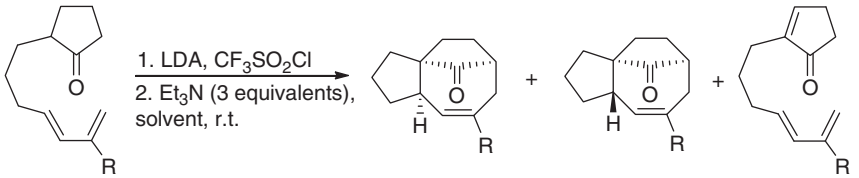
(6)

In the case of substrate **21**, the formation of cycloadducts **22** and **23** can be better explained assuming that the intermediate cyclic oxyallyl cation adopts a sickle-shaped conformation of type **VII**.[11]



21 **22** **23** **VII** (7)

Precursors featuring less nucleophilic acyclic dienes instead of furans are less prone to participate in this type of cycloaddition. Therefore, substrate **24a** did not give the expected cycloadducts, but mainly cyclopentenone **27a** (equation 8). It is, however, possible to promote the cycloaddition, although in modest yield and with poor *endo–exo* selectivity, by increasing the substitution of the diene, like in **24b**. In this case, such substitution probably favors a *s-cis* conformation. The yield can be improved using TFE as the solvent, but the selectivity is negligible.[12] It is interesting to note that, although this transformation is a (4 + 3) cycloaddition, it can alternatively be viewed as a [4C + 4C] annulation and therefore allows one to construct very interesting carbon-bridged cyclooctane systems.



24 **25** (*exo*) **26** (*endo*) **27** (8)

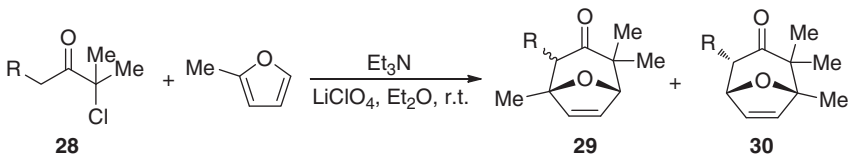
R	**24**	solvent	**25** : **26**	**25**+**26**, Yield (%)	**27**, Yield (%)
H	**24a**	$LiClO_4$, Et_2O	–	–	42
Me	**24b**	$LiClO_4$, Et_2O	71 : 29	37	38
Me	**24b**	TFE	52 : 48	53	2

5.13.2.2.3 Polyhaloketones

Although *polyhaloketones* are generally more expensive and difficult to make than monohaloketones; these oxyallyl cation precursors (di-, tri-, tetra-, and pentahaloketones) were shown to be excellent cycloaddition partners in a broad range of intermolecular oxyallyl cation (4 + 3) cycloadditions. They often provide advantages in terms of reactivity and selectivity compared with the much simpler monohaloketones.[3]

5.13.2.2.3.1 α,α- and α,α′-Dichloroketones

Both α,α- and α,α′-dichloroketones are useful three-carbon partners in (4 + 3) intermolecular cycloadditions with furans.[13] Apparently, the presence of extra chlorides in the α-position of the carbonyl groups is beneficial for their reactivity as oxyallyl cation precursors. Thus, although treatment of a monochloroketone **28a** with methylfuran under 'basic conditions' leads to a 1:1 mixture of regioisomeric cycloadducts **29a** and **30a** in modest yields, α,α′-dichloroketone **28b** reacts under the same conditions to generate oxyallyl cations such as **VIII**, which reacts with methylfuran to mainly produce regioisomer **29b** with good *endo*:*exo* selectivity (13:1) (equation 9). Similar results were achieved in the cycloaddition of α,α-dichloroketone **31** (equation 10). The regiocontrol seems to be grounded in both steric and electronic effects.

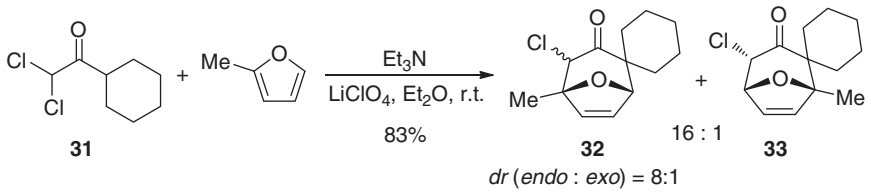


28 **29** **30** (9)

VIII

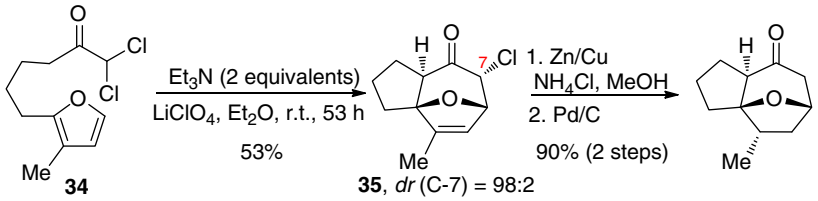
R **28**	Yield (%)	**29** : **30**	**29**, *dr*[a]
H **28a**	49	1 : 1	–
Cl **28b**	68	9 : 1	13 : 1

[a] *endo* : *exo* ratio.

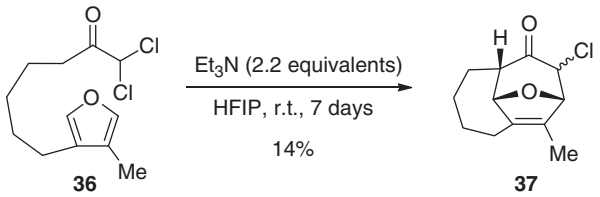


(10)

Similarly, beneficial effects of additional chloride atoms in the oxyallyl precursors were observed in the case of intramolecular processes. Although the cycloaddition of monochloride **12** (see equation 4, Section 5.13.2.2.2.3) is low yielding, dichloroketone **34** undergoes an efficient reaction to give the tricyclic product **35** in good yield and almost complete diastereoselectivity (equation 11).[14] Interestingly, it is even possible to accomplish the topologically difficult cycloaddition of substrates like **36**, which yields interesting bridged carbobicyclic products **37**, although in low yields (equation 12).[15]



(11)



(12)

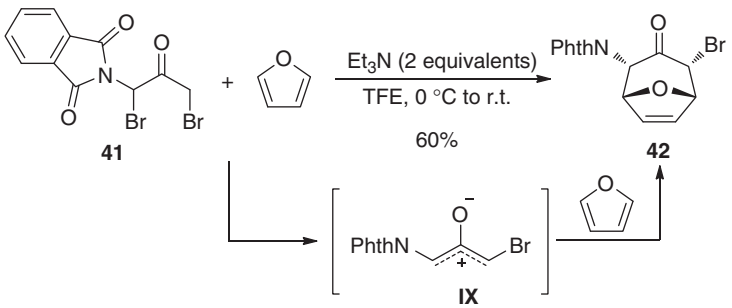
5.13.2.2.3.2 Polychloroketones

Trichloroacetone derivatives can also be used as precursors of oxyallyl cation intermediates with good results (e.g., the formal synthesis of Phorbol, Scheme 14, Section 5.13.2.6). Similarly Föhlisch and coworkers demonstrated that 1,1,1,3,3-pentachloro-2-propanone **38** (pentachloroacetone (PCA)) also participates in a variety of (4 + 3) cycloadditions with dienes to produce tetrachlorobicyclic adducts **39**.[16] These cycloadditions of PCA are advantageous over other related processes owing to the symmetry of the intermediate oxyallyl cations, and hence only one type of oxabicyclic products can be formed. The cycloaddition provides good yields for a variety of substituted furans (Table 3, entries 1–6). The polyhalogenated products can be readily converted to halogen-free, synthetically appealing oxabicycles **40** on treatment with zinc or zinc–copper, according to the standard procedures.[16a] It is also possible to perform the cycloaddition of PCA with acyclic-substituted dienes (entries 7–9), although in these cases the yields are moderate and the dehalogenation of the resulting products under standard conditions is inefficient.[16b]

5.13.2.2.3.3 α,α′-Dibromoketones

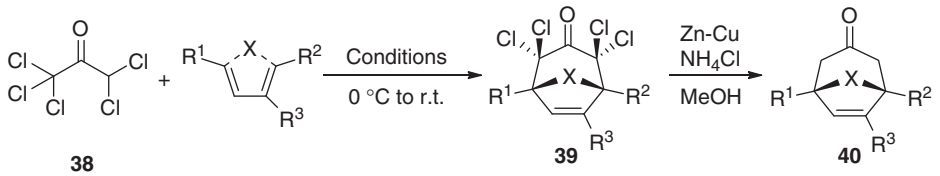
Similar to dichloroketones, α,α′-dibromoketones can also be used as precursors for oxyallyl cations. However, their use has been rather limited due to their frequent instability and lachrymatory properties. Some examples of the use of cyclic α,α′-dibromoketones in the synthesis of natural products can be found in Section 5.13.2.6 (Schemes 15 and 16).

In 1995, Walters and coworkers demonstrated that the readily available α,α′-phthalimidoyldibromide **41** reacts with furan on treatment with Et_3N in either TFE or $LiClO_4/Et_2O$, to give the expected seven-membered cycloadduct *endo*-**42** in 60% yield.[17] The reaction must involve the intermediacy of an *N*-substituted oxyallyl cation **IX** that prefers to react in a W-conformation (equation 13). Substituted furans and cyclopentadiene are also accepted; however they lead to mixtures of isomers with poor selectivity. A related strategy to generate *N*-stabilized oxyallyl cations from allene-amides will be discussed in Section 5.13.2.2.9.



(13)

Table 3 (4 + 3) Cycloaddition of 1,1,1,3,3-pentachloro-2-propanone (**38**) with dienes



Numbers	*X*	*R*^{1}	*R*^{2}	*R*^{3}	*Conditions*[a]	***39**, Yield (%)*	***40**, Yield (%)*	*References*
1	O	H	H	H	A	57	97	16a
2	O	Me	H	H	A	66	65	16a
3	O	Me	Me	H	A	81	87	16a
4	O	H	H	Me	A	86	87	16a
5	O	$H_2C=CH$	H	H	A	83	71	16a
6	O	$H_2C=CH$	Me	H	A	84	60	16a
7	H,H[b]	H	H	H	B	5	–[c]	16b
8	H,H[b]	H	H	Me	C	42	–[c]	16b
9	H,H[b]	H	H	^{i}Pr	C	65	–[c]	16b

[a]Conditions A: PCA (**38**) (1.1 equivalents), furan (1 equivalent), 2 M solution NaTFE in TFE; conditions B: Butadiene:TFE (1:1 v/v), 0.5 M solution of NaTFE in TFE; and conditions C: PCA (0.63–1 equivalent), diene (1 equivalent), 1 M solution NaTFE in TFE.

[b]Diene: 1,3-butadiene and derivatives (i.e., R^3-substituted).

[c]Only small amounts were obtained.

Although this example by Walters made use of basic conditions to generate the reactive cationic intermediate, it is pertinent to comment that the generation of oxyallyl intermediates from α,α′-dibromoketones is most often achieved using reductive, rather than basic conditions. These reductive conditions involve the treatment of α,α′-dihaloketones (or polyhaloketones) with metal-based reducing agents to give metal enolates, which evolve by loss of the second halide to generate metal-bound oxyallyl cations (Figure 5). Therefore, and in contrast to the base-promoted cycloaddition of dibromoketones, these reductive methods produce bromide-free cycloadducts. Some typical reaction conditions involve the use of copper/sodium iodide in acetonitrile, zinc dust/triethyl borate in THF, zinc–copper couple in DME or [$Fe_2(CO)_9$] in benzene.[3b]

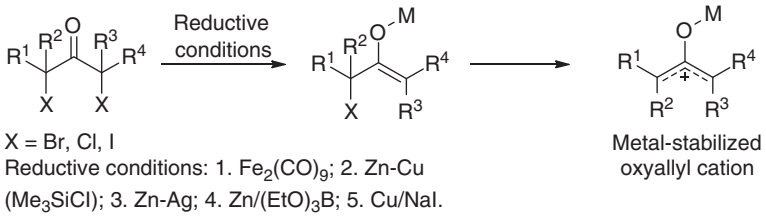


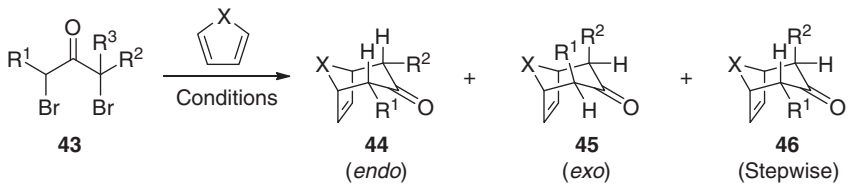
Figure 5 Oxyallyl cation generation from α,α′-dihaloketones under reductive conditions.

As shown in Table 4,[18] treatment of 2,4-dibromopentan-3-one (**43a**) with furan (2.5 equivalents) in the presence of Cu/NaI gives preferentially the *endo* cycloadduct **44a**, arising from a compact transition state (Table 4, entry 1). When the same reaction is carried out with Zn/Cu, the *endo*/*exo* selectivity drops, and some amount of epimer **46a** is isolated, probably arising from a stepwise pathway (entry 2). Finally, using an excess of $Fe_2(CO)_9$ as well as of the diene (solvent or in large amounts), the reaction produces a mixture of cycloadducts **44a** and **46a** in good yield (entry 3). The different stereochemical results can be explained in terms of an increasing electrophilic character of the oxyallyl cation when moving from Cu/NaI to $Fe_2(CO)_9$, owing to a greater covalent character of the O–M bond. Polybromoketone **43b** and the diphenyl derivative **43c** gave similar results (entries 4 and 5). Cyclopentadiene and *N*-methylpyrrole can also efficiently participate in the cycloaddition, although the resulting *endo*/*exo* selectivities were moderate (entries 6 and 7). The case of the pyrrole is interesting because this substrate tends to give products of electrophilic substitution instead of cycloadditions when other methods are used.

Acyclic dienes do also participate in this type of (4 + 3) cycloadditions. Indeed, the first examples reported by Noyori[18c] as early as 1978 showed that symmetrical α,α-dibromoketones of type **43** react with butadiene, isoprene or 2,3-dimethylbutadiene in the presence of stoichiometric amounts of $Fe_2(CO)_9$ to give the corresponding cycloheptenones **47**, although the yields were generally low (Table 5).

It was later shown that better overall yields can be obtained, even with the simplest dienes, if they were precoordinated to the metal and hence locked in the *s-cis* arrangement required for the cycloaddition (equation 14).

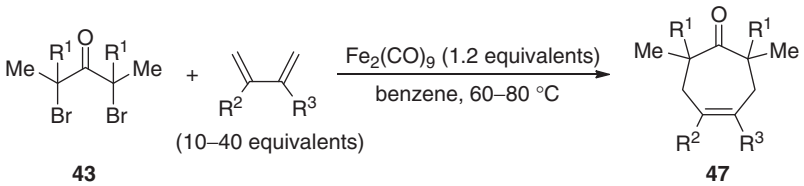
Table 4 (4 + 3) Cycloaddition of α,α′-dibromoketones with cyclic dienes under reductive conditions



Numbers	43			Diene	Conditions[a]	Yield (%)[b]	44:45:46	References
		R^1	R^2	X				
1	**43a**	Me	Me	O	A	53	91:9:0	18a
2	**43a**	Me	Me	O	B	85	81:10:9	18b
3	**43a**	Me	Me	O	C	90	44:0:56	18c
4	**43b**	Br	Br	O	C	63	90:0:10	18c
5	**43c**	Ph	Ph	O	C	90	50:0:50	18c
6	**43a**	Me	Me	CH_2	A	91	86:14:0	18d
7	**43a**	Me	Me	NMe	A	89	85:15:0	18e

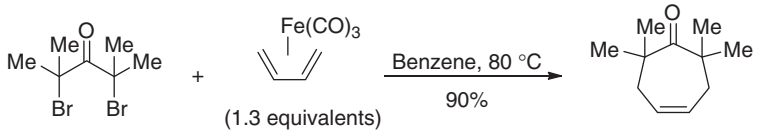
[a]Standard conditions A: Cu (4 equivalents), NaI (3 equivalents), diene (1–2.5 equivalents), MeCN, 45–60 °C; conditions B: Zn/Cu (~3 equivalents), diene (4–10 equivalents), DME, −10 °C; and conditions C: $Fe_2(CO)_9$ (1–1.5 equivalents), diene (solvent), 40 °C or reflux.
[b]Combined yields of **44**–**46**.

Table 5 (4 + 3) Cycloadditions of α,α′-dibromoketones and acyclic dienes



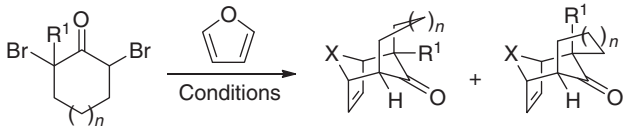
Numbers	43		Diene		47, Yield (%)
		R^1	R^2	R^3	
1	**43a**	H	H	H	30[a]
2	**43a**	H	Me	H	36[a]
3	**43f**	Me	H	H	33
4	**43f**	Me	H	Me	47
5	**43f**	Me	Me	Me	71

[a]Stereochemistry of the product not provided.



(14)

Cyclic α,α′-dibromoketones also participate in (4 + 3) cycloadditions with cyclic dienes, but the yields are lower than those obtained by the alternative methodologies described above based on α-haloketones (see Section 5.13.2.2.2.2, Table 2, entries 1 and 6). Interestingly, in the case of oxyallyl cation precursors embedded in large rings ($n=7$), the formation of cycloadducts **50** arising from a sickle-shaped allyl cation conformation is preferentially observed (equation 15).[18c,f]



48 **49** **50**

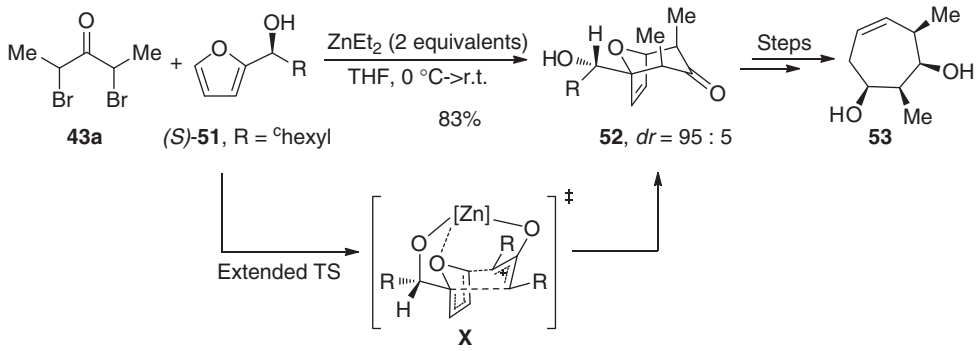
n	R^1	Conditions[a]	Yield (%)[b]	**49** : **50**	Ref
1	H	A	35	100 : 0	18c
1	Me	B	25	100 : 0	18f
2	H	A	54	100 : 0	18c
7	H	A	52	13 : 87	18c

[a]Conditions A: $Fe_2(CO)_9$, furan (solvent), reflux; conditions B: Cu, NaI, MeCN, r.t.

[b]Combined yield of **49** and **50**.

(15)

In 1996, Lautens and coworkers reported an interesting asymmetric version of this type of (4 + 3) cycloadditions.[19] Thus, treatment of 3 equivalents of the enantiopure furan derivative (*S*)-**51** with diethylzinc (2 equivalents) in the presence of 2,4-dibromopentan-3-one (**43a**, 2 equivalents) produces the oxabicycle **52** in good yields and with excellent diastereocontrol. The formation of the product can be explained in terms of a chelation-controlled extended transition state **X**, which justifies both the facial and the *exo* diastereoselectivities (Scheme 1).



43a (*S*)-**51**, R = ^{c}hexyl **52**, *dr* = 95 : 5 **53** **X**

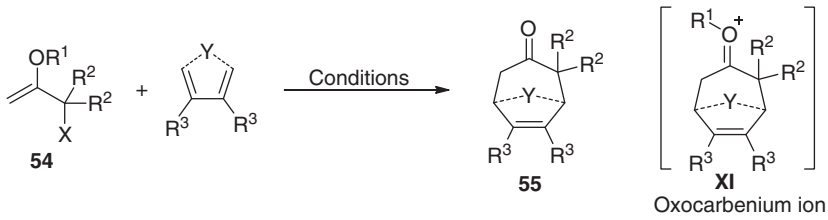
Scheme 1

5.13.2.2.4 2-Alkoxy- and 2-silyloxyallyl halides and related compounds

As might be envisioned, 2-alkoxyallyl halides and related 2-silyloxyallyl halides of type **54** participate in (4 + 3) cycloaddition reactions with dienes when treated with suitable Lewis acid promoters. Some examples are shown in Table 6. The transformation was investigated by several groups in the 1970s and 1980s, most notably those of Hoffmann,[20] Hosomi,[21] or Shimizu,[22] and has been proposed to involve the formation of oxyallyl cationic intermediates. From the practical point of view, the methodology is not the most appealing because making and handling of the required precursors is not so trivial and the cycloaddition yields are quite variable depending on the specific substitutions of the substrates. Initial results reported by Hoffmann with simple enol ethers (Table 6, entries 1–2) led to poor yields in the reactions with furan. Most probably the reactions produce oxocarbenium intermediates of type **XI**. Later, Hosomi and Shimizu reported that good yields and selectivities could be achieved when the oxyallyl intermediates are generated from crowded silyl enol ethers using $ZnCl_2$ (Hosomi) or $AgClO_4$ (Shimizu) as promoters (entries 3–6). Under these conditions acyclic dienes also can participate in the cycloaddition with moderate efficiency (entries 7–8).

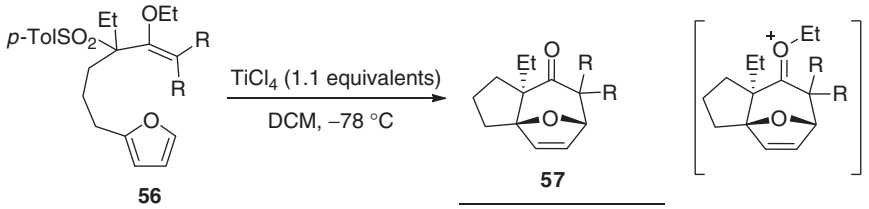
Harmata and coworkers have extensively studied a variant in this type of chemistry based on the use of sulfones instead of halides as leaving groups. The method was mainly explored in intramolecular processes.[23] The required 2-alkoxyallyl sulfones can be prepared in a relatively simple manner from sulfonylallenic precursors. As an example, treatment of precursors **56a** or **56b** with stoichiometric amounts of $TiCl_4$ promotes their intramolecular cycloaddition to give the expected cycloadducts of type **57** in good yields and excellent diastereoselectivity (equation 16).

Table 6 (4 + 3) Cycloaddition of alkoxyallyl halides under solvolytic conditions



Numbers	*X*	*R*[1]	*R*[2]	*Y*	*R*[3]	*Conditions*[a]	***55**, Yield (%)*	*References*
1	Br	Me	H	O	H	A	15	20
2	Br	Me	H	CH_2	H	A	17	20
3	Br	TMS	Me	O	H	B	97	21
4	Cl	TMS	Me	O	H	C	85	22
5	Br	TMS	Me	CH_2	H	B	54	21
6	Cl	TMS	Me	CH_2	H	C	91	22
7	Br	TMS	Me	H,H[b]	H	B	26	21
8	Br	TMS	Me	H,H[b]	Me	B	60	21

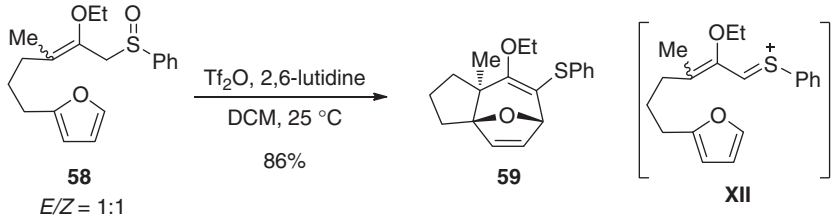
[a]Conditions A: AgO_2CCF_3 (1 equivalent), diene (10–15 equivalents), Na_2CO_3, benzene, isopentane, r.t.; conditions B: $ZnCl_2$, diene (2–7 equivalents) DCM, −60 or −78 °C; and conditions C: $AgClO_4$ (2 equivalents), $CaCO_3$, diene (5 equivalents), Et_2O–THF, 0 °C.
[b]Diene: 1,3-butadiene (R^3 = H) or 2,3-dimethylbutadiene (R^3 = Me).



	R	Yield (%)
a	Me	74
b	$-(CH_2)_5-$	66

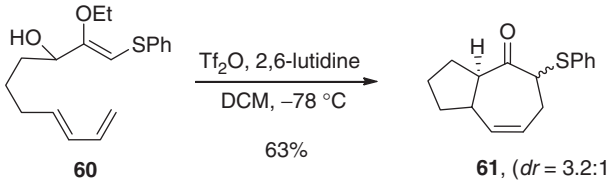
(16)

Unfortunately, the method fails for substrates with less substituted allyl cation precursors. To circumvent this problem, Harmata et al. designed precursors with a terminal sulfur-based substituent that could stabilize the incipient positive charge of the allyl cation through the formation of vinylthionium intermediates.[24] These authors showed that treatment of compound **58** (1:1 mixture *E*/*Z* isomers) with triflic anhydride and 2,6-lutidine affords the expected cycloadduct **59** as a single stereoisomer in good yield. In this case, the vinylthionium ions are generated by means of a Pummerer rearrangement (equation 17, intermediate **XII**).



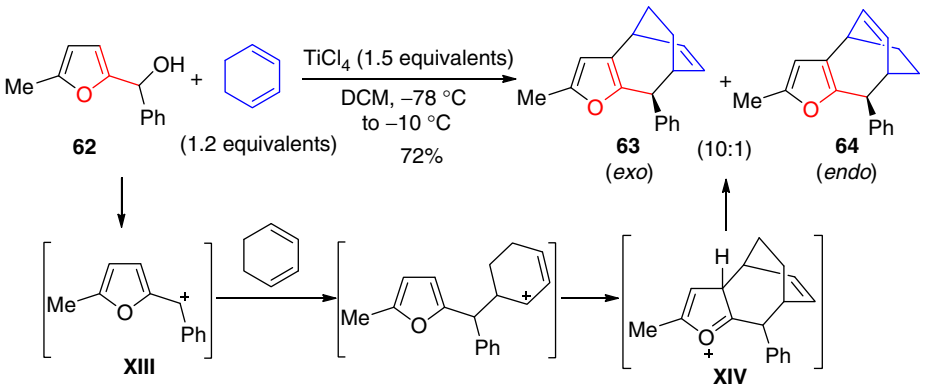
(17)

Hydroxy groups can also work as leaving groups in the generation of allyl cations, which are further stabilized by the presence of sulfur substituents. Thus, vinylsufide **60** reacts intramolecularly with simple dienes to form bicyclic products such as **61** as a mixture of diastereoisomers (equation 18).[25]



(18)

Equation 19 shows another example of a cycloaddition involving a hydroxyl function as the leaving group to generate stable carbocations. Furfuryl alcohol **62** reacts with dienes in a (4 + 3) manner when activated with Lewis acids to give the interesting bicyclic adducts **63** (major) and **64** (minor).[26] The presence of a Lewis acid most probably generates a furfuryl cation intermediate **XIII** that can be viewed as an oxyallyl or oxocarbenium ion. DFT calculations suggested that the reaction then takes place through a stepwise process involving an initial electrophilic addition to the furfuryl cation followed by a 7-*endo*-trig cyclization to yield **XIV**. A final deprotonation leads to the observed products (equation 19). Although this is the most probable mechanism, a concerted [6π + 4π] combination between the furfuryl cation and the diene to form the intermediate **XIV** cannot be fully discarded.

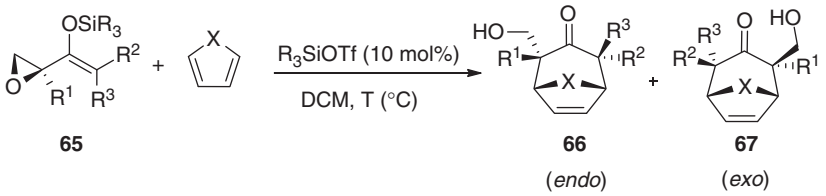


(19)

5.13.2.2.5 Epoxyenol silanes

Epoxides can also work as leaving groups in the generation of reactive oxyallyl carbocations. Indeed, Eguchi and coworkers demonstrated in 1990 that epoxy enol silanes of type **65** engage in intermolecular (4 + 3) cycloaddition reactions with dienes such as furan or cyclopentadiene when treated with Lewis acids, albeit the cycloadducts are produced in low yields and with low diastereoselectivities (Table 7, entries 1 and 2).[27] Importantly, the reaction can be carried out using catalytic amounts of a Lewis

Table 7 Cycloadditions of epoxy enol silanes[a]



Numbers	Epoxy enol silane **65**					Diene	Temperature (°C)	**66**:**67**	Yield (%)[b]	References
		$OSiR_3$	R^1	R^2	R^3	X				
1	**65a**	$OSiMe_3$	H	H	H	O	−50	60:40	12	27
2[c]	**65a**	$OSiMe_3$	H	H	H	CH_2	−50	60:40	47	27
3[d]	**65b**	$OSiEt_3$	H	H	H	O	−50	–[e]	56	28a
4[d]	**65b**	$OSiEt_3$	H	H	H	O	−94	55:45	75	28b
5[d]	**65b**	$OSiEt_3$	H	H	H	CH_2	−91	55:45	76	28b
6[d,f]	**65c**	OSi^tBuPh_2	H	H	H	$C(CH_2)_2$	−78	100:0	46	28b
7[d]	**65d**	$OSiEt_3$	Me	H	H	O	−91	72:28	57	28b
8[d]	**65d**	$OSiEt_3$	Me	H	H	CH_2	−91	45:55	56	28b
9[d]	(*Z*)-**65e**	$OSiEt_3$	H	Me	H	CH_2	−91	50:50	57	28b
10[d]	(*Z*)-**65f**	$OSiEt_3$	H	Ph	H	CH_2	−91	45:55	97	28b
11[d]	(*E*)-**65f**	$OSiEt_3$	H	H	Ph	CH_2	−91	72:28	60	28b

[a]5 equivalents of diene were used. R_3SiOTf = TMSOTf for entries 1–2 and TESOTf for entries 3–11.
[b]Isolated combined yields.
[c]2 equivalents of cyclopentadiene were used.
[d]Reaction was quenched by addition of triethylamine hydrofluoride to exclusively obtain desilylated cycloadducts **66** and **67**.
[e]Poor diastereoselectivity, but ratio not provided.
[f]20 mol% of TESOTf was used.

acid, with trimethylsilyl triflate (10 mol%) being the most effective. Almost 20 years later, Chiu and coworkers demonstrated that the yield of this type of intermolecular (4 + 3) cycloadditions could be dramatically increased by appropriate selection of the epoxy enol silane and the reaction conditions.[28] In particular, using a triethylsilyl enol ether in combination with triethylsilyl triflate as catalyst (10 mol%), and performing the reaction at a significantly lower temperature (− 94 °C), the cycloadducts are obtained in good yields (entries 3–5). Although the diastereoselectivity is generally low, it is possible to obtain better results by using epoxy enol silanes bearing silyl groups with higher steric demand. Thus, the cycloaddition of TBDPS-substituted enol ether **65c** with spirocyclopentadiene provided the corresponding *endo*-cycloadduct **66** which was isolated in a 46% yield (entry 6).[28b] The reaction can be extended to other alkene-substituted vinyl epoxides as can be deduced from entries 9–11. In all cases, only one pair of diastereoisosomes (**66** and **67**) was detected, suggesting that the reactions are stereospecific.

From a mechanistic point of view, it has been suggested that the transition state of the cycloaddition is reactant-like, with a significant epoxide and alkene character; therefore there is no generation of a neat allyl cation. Accordingly, the activated epoxide adopts a conformation resembling **XV** (Figure 6), which is approached by the diene from the less sterically demanding face, *anti* with respect to the epoxide, in both the *exo* and *endo* cycloaddition modes. As in other reactions with oxyallyl cation intermediates, the cycloadditions to furan are proposed to be quite asynchronous.

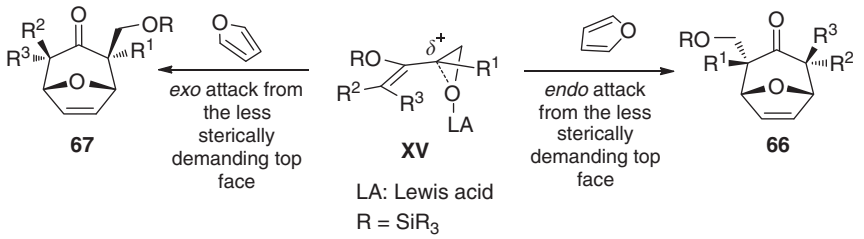
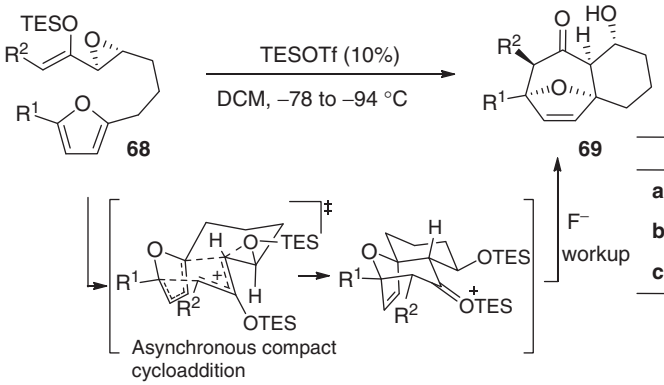


Figure 6 Mechanistic proposal for the epoxy enol silane cycloadditions with furans.

In contrast to the general lack of *endo*/*exo* diastereoselectivity in the intermolecular processes, the related intramolecular cycloadditions between furans and epoxy enol silanes **68** afford good yields of the corresponding cycloadducts **69**, which are obtained as single diastereoisomers and in a sterospecific manner with respect to the epoxy enol silane. Therefore, using a single enantiomer of the epoxy enol silyl ether **68a** provides optically pure cycloadduct **69a** (equation 20).[28a] The high diastereoselectivity of the intramolecular process could be explained on the basis of a compact transition state, in which the tether adopts a chair-like conformation and the silyloxylallyl cation adopts a W-type configuration (equation 20). This strategy has been recently used as key step in a concise and asymmetric synthesis of the pentacyclic framework of steroidal alkaloid Cortistatins (see Section 5.13.2.6, Scheme 20).[29]

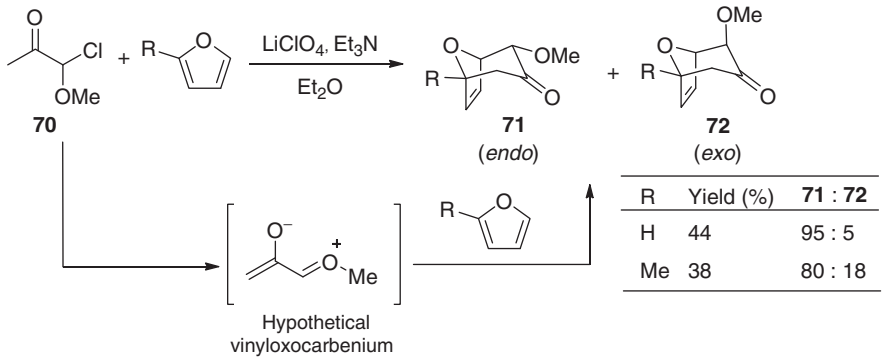


	R^1	R^2	Yield (%)
a	H	H	**69a**, 83
b	Me	H	**69b**, 76
c	H	Me	**69c**, 70

(20)

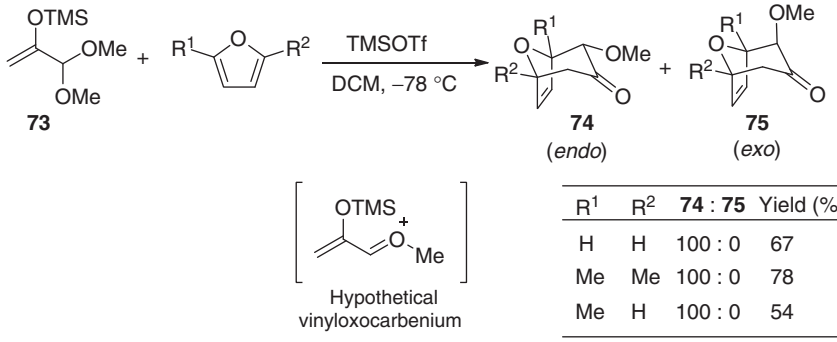
5.13.2.2.6 α,α-Dialkoxy trialkylsilylenol ethers and related

In 1988, Föhlisch and coworkers demonstrated that α-chloro-α-alkoxy ketones of type **70** serve as satisfactory oxyallyl cation precursors in base-promoted (4 + 3) cycloadditions.[30] In this case, the oxyallyl cation is stabilized by the alkoxy group which generates a vinyloxocarbenium resonance form (equation 21). Shortly after this report, the group of Albizati reported that α,α-dialkoxy trialkylsilylenol ethers such as **73** are very good three-carbon cycloaddition partners in a Lewis acid-induced (4 + 3) reaction with furan derivatives.[31] Although several Lewis acids successfully promoted the reaction in a stoichiometric fashion (e.g., $SnBr_4$, $SnCl_4$, $TiCl_4$, BCl_3, etc.), TMSOTf is effective in substoichiometric amounts, typically 40 mol%. Most probably the reaction involves the generation of vinyloxocarbenium ion intermediates as shown in equation 22. Despite the similarities between this method and that of Föhlisch,[30] different diastereoselectivities and regiochemical outcomes were sometimes observed (equations 21 and 22), suggesting that slightly different mechanistic scenarios might be operative.



R	Yield (%)	**71** : **72**
H	44	95 : 5
Me	38	80 : 18

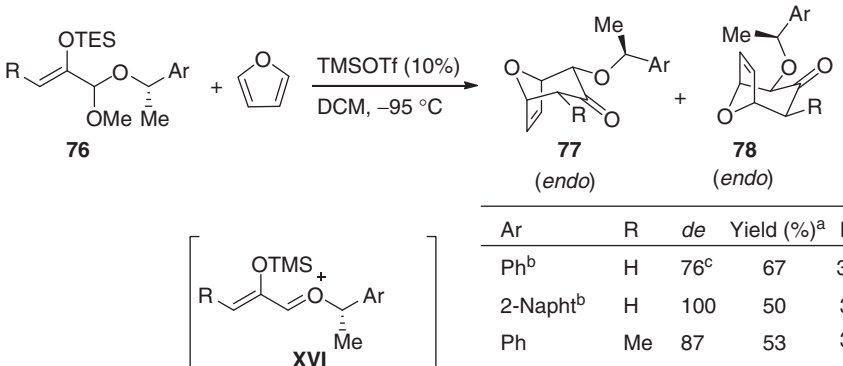
(21)



R^1	R^2	**74** : **75**	Yield (%)
H	H	100 : 0	67
Me	Me	100 : 0	78
Me	H	100 : 0	54

(22)

A few years later, the groups of Hoffmann and Harmata extended this type of chemistry to more elaborated allyl acetals equipped with additional substituents at the alkene and/or at the acetal group.[32] Additionally, in 1998 Hoffmann and coworkers developed an interesting asymmetric variant of these cycloadditions, based on the use of mixed chiral allyl acetals derived from α-methyl benzylic alcohols (equation 23).[33] In this case, treatment of **76** with the Lewis acid promoter generates a chiral oxyallyl cation **XVI**, which preferentially reacts with furan through an *endo* transition state providing good or even complete levels of diastereoselectivity depending on the solvent, temperature and the choice of aryl group at the acetal stereogenic center. In the case of a 2-naphthyl group, the (4 + 3) cycloadduct was formed as a single diastereoisomer, when the reaction was carried out in CH_2Cl_2 at $-95\ ^{\circ}C$.[34] The reaction is also possible with furans containing bromine, silicon, tin, or sulfur substituents at their 3-position; however 2,5-disubstituted furans react with poor diastereoselectivities.[35]



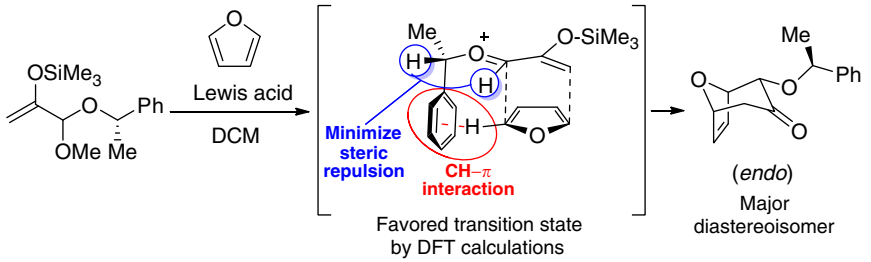
Ar	R	*de*	Yield (%)[a]	Ref
Ph[b]	H	76[c]	67	33a
2-Napht[b]	H	100	50	34
Ph	Me	87	53	34
2-Napht	Me	82	91	34

[a]Combined yield of **77** and **78**. [b]Experiments were carried out with (*R*)-1-(2-naphthyl)ethanol and (*S*)-1-(2-phenyl)ethanol as chiral auxiliaries, therefore providing opposite absolute configurations. Stereochemistry exemplified for Ar = Ph. [c] **77**:**78** ratio = 7.5 : 1.

(23)

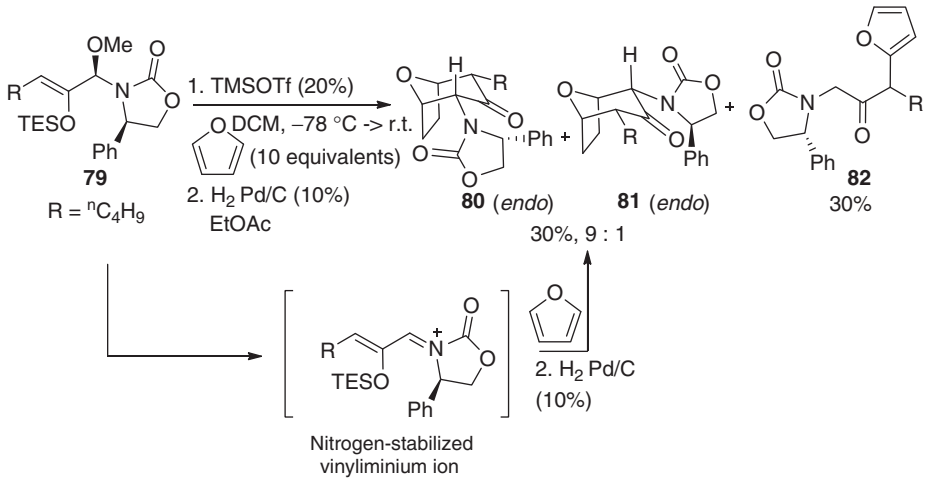
The stereochemical outcome of these asymmetric reactions with furans was originally rationalized by Hoffmann by assuming a silicon–oxygen chelation in the allyl cation. However, a more recent theoretical study by Houk and Harmata[36] suggests that it can be better explained by an *endo* cycloaddition pathway, which is a stepwise process, in which the approach of the reaction components is governed by two main factors: the minimization of repulsive interactions between the allyl cation and the methyl group of the chiral auxiliary, which fixes a preferred conformation for the dienophile, and the presence of an attractive edge-to-face

CH–π interaction between the aryl ring of the chiral auxiliary and the hydrogens of the furan moiety. The calculations based on this model also predict the increase in selectivity observed when going from a phenyl to a 2-naphthyl group in the chiral auxiliary, as well as the low diastereoselectivity observed with 2,5-dimethylfuran, which cannot establish stabilizing CH–π interactions at the C-2 or C-5 positions of the furan (equation 24).



(24)

Related asymmetric cycloadditions were developed in 2002 by Hsung and coworkers, who demonstrated that enol silyl ethers such as **79**, incorporating a chiral aminal instead of an acetal, could also be used in asymmetric (4 + 3) cycloaddition reactions with dienes. Thus, the activation of **79** with TMSOTf (20 mol%) in CH_2Cl_2 produces a chiral nitrogen-stabilized vinyliminium ion, which can be trapped by furan in a (4 + 3) way.[37] Although the reaction was fully *endo* selective and the diastereofacial selectivity was also high (**80**:**81** = 9:1), the yield of the (4 + 3) adducts was moderate (30%, equation 25), mainly because of the formation of a nondesired acyclic byproduct **82**. The generation of related chiral amido-stabilized oxyallyl cations from allenamides and their subsequent (4 + 3) cycloaddition reactions with dienes was extensively developed by the same authors and it is discussed in Section 5.13.2.2.9.



(25)

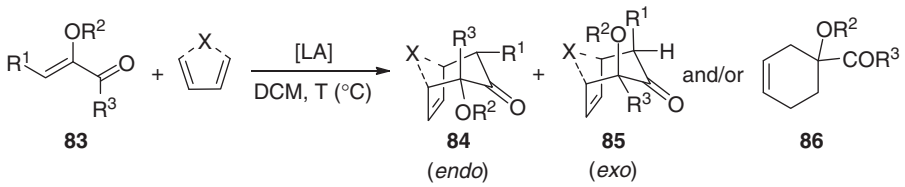
Finally, it is worth mentioning that the formation of vinyloxocarbenium ions from allyl acetals and their subsequent use in (4 + 3) cycloadditions was successfully exploited in natural product synthesis by several authors. Particularly noteworthy is the work of Cha and coworkers on the total synthesis (–)-colchicine, imerubrine, and grandirubrine,[38] Hoffmann and coworkers in the synthesis of functionalized scopolines,[39] and more recently by the Watanabe group in a stereoselective synthesis of (±)-urechitol A.[40] The methodology has also been applied to the synthesis of carbohydrates and chiral ketones.[41] For more details on these synthetic applications see Section 5.13.2.6.

5.13.2.2.7 α-Silyloxy-α,β-unsaturated carbonyls and vinylogous congeners

Vinyloxocarbonium species related to those proposed above should be, in principle, also accessible from α-silyloxy-α,β-unsaturated carbonyls. Indeed, in the early 1980s, Sasaki and Childs independently reported that 2-(trimethylsilyloxy)propenal **83a** and 3-(trimethylsilyloxy)-but-3-en-2-one (**83b**) react with dienes such as furan, cyclopentadiene, or 1,3-butadiene in a (4 + 3) manner in the presence of stoichiometric amounts of Lewis acid promoters (Table 8, entries 1–4).[42] Although the reactions were not particularly efficient and in general provided mixtures of the *endo* and *exo* (4 + 3) adducts **84** and **85**, and/or (4 + 2) adducts like **86**, these results set the basis for further developments in the area. In 2000, Harmata demonstrated that 2-(triisopropylsilyloxy) propenal **83c** reacts with selected dienes in the presence of catalytic amounts of scandium(III) triflate to afford the (4 + 3) cycloadducts **84** and/or **85** in good-to-excellent yields (Table 8, entries 5–7).[43]

The required dienophile precursor **83c** can be easily prepared by reaction of triisopropylsilyl triflate and 2-methoxy-2-methyl-[1,3]dioxan-5-one (**87**) in the presence of triethylamine (equation 26). Nearly contemporaneously, Funk and coworkers

Table 8 (4 + 3) Cycloadditions of α-silyloxy-α,β-unsaturated carbonyls

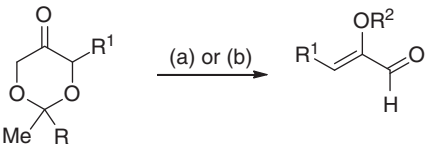


83 **84** (*endo*) **85** (*exo*) **86**

Numbers	***83***				*Diene*	*[LA] (equivalents)*	*Temperature (°C)*	*Yield (%)*	***84:85***	*References*
		R^1	*R^2*	*R^3*	*X (equivalents)*					
1	**83a**	H	TMS	H	CH_2 (1.5)	$SnCl_4$ (1)	−78	72[a]	73:27	42a
2	**83a**	H	TMS	H	O (1.5)	$SnCl_4$ (1)	−78	43[a]	0:100	42a
3	**83a**	H	TMS	H	H,H[b] (1.5)	$SnCl_4$ (1)	−78	32[a]	–[c]	42a
4	**83b**	H	TMS	Me	H,H[b] (1.1)	$TiCl_4$ (1)	−78	24[d]	52:48[c,e]	42b
5	**83c**	H	TIPS	H	CH_2 (2.5)	$Sc(OTf)_3$, (0.1)	0 to > r.t.	72	75:25	43
6	**83c**	H	TIPS	H	O (2.5)	$Sc(OTf)_3$, (0.1)	0 to > r.t.	90	100:0	43
7	**83c**	H	TIPS	H	H,H[b] (2.5)	$Sc(OTf)_3$, (0.1)	0 to > r.t.	67 (**86**)[f]	–	43
8	**83d**	^{n}Bu	TBS	H	CH_2 (5)	Me_2AlCl, (1)	−78	100	100:0	44
9	**83d**	^{n}Bu	TBS	H	O (5)	Me_2AlCl, (1)	−78	76	77:23	44
10	**83e**	Bn	TBS	H	H,H[b] (5)	$EtAlCl_2$, (1)	−78	65	–[c]	44

[a]Combined yields of the corresponding hydrolyzed TMS ethers (R^2 = H) after aqueous workup.
[b]Diene: 1,3-butadiene.
[c]In this case **84** and **85** are the same product.
[d]Global yield of the (4 + 3) and (4 + 2) cycloadducts **84**, **85**, and **86**.
[e]Ratio of **84**,**85**:**86**.
[f]The reaction exclusively provided the (4 + 2) adduct **86**.

demonstrated that 2-(trialkylsilyloxy)-2-enals of type **83** could also be generated with high stereoselectivity by retrocycloaddition reactions of substituted 4*H*-1,3-dioxins (**88**, equation 26).[44] The higher stability of dioxins of type **88**, compared with dioxanones **87**, allows for their more facile functionalization and eventually for a more ready access to 3-substituted silyloxyalkenals such as **83d** ($R^1 \neq H$, Table 8), thereby, increasing the potential and the scope of the resulting (4 + 3) cycloaddition processes.



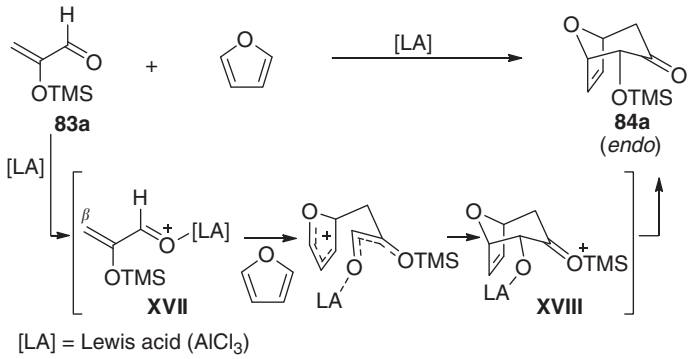
(26)

87, R = OMe, R^1 = H
88, R = Me, R^1 = H or alkyl

(a) R^2OTf, Et_3N, benzene (R^2 = TIPS, TES, TBS);
(b) i, R^2Cl, NaHDMS; ii, toluene, 110 °C (R^2 = TIPS, TES, TBS)

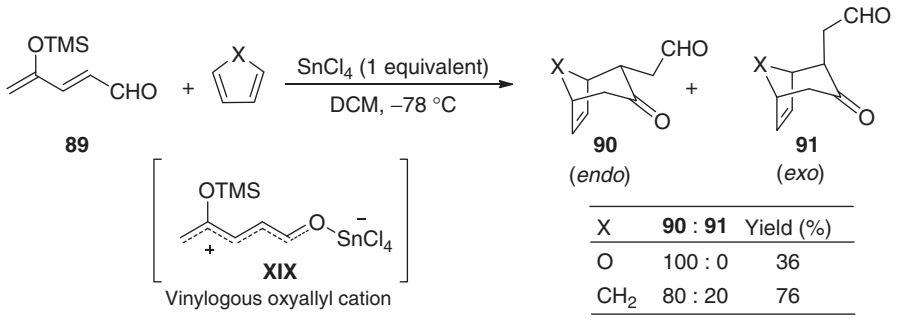
More recently, Harmata and coworkers expanded the versatility of the methodology, by showing that silyloxydioxins of type **88** undergo direct (4 + 3) cycloadditions with furan on treatment with catalytic amounts of $AuCl_3/AgSbF_6$.[45] The potential of the cycloaddition chemistry of α-silyl-α,β-unsaturated carbonyl derivatives was recently demonstrated by Funk et al. in the total synthesis of (±)-cortistatin J (see Section 5.13.2.6).[46]

With regard to the mechanism of these cycloadditions, recent theoretical calculations by Domingo et al.[47] suggest that the reaction is indeed initiated by coordination of the Lewis acid to the carbonyl group to generate an oxonium-stabilized form of a silyloxyallyl cation (**XVII**). In the case of furan, the cycloaddition begins by the attack to the dienophile's β position to give a zwitterionic intermediate, which evolves to the *endo* oxabicycle (**XVIII**). Finally, a silyl migration affords the experimentally observed (4 + 3) *endo* product of type **84**, which is favored over the *exo* one (equation 27).



(27)

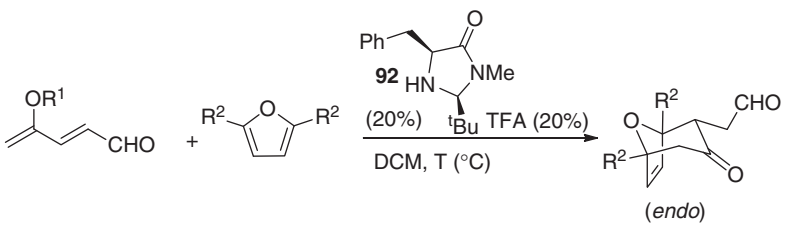
4-(Trimethylsilyloxy)-2,4-pentadienal (**89**), which can be viewed as a vinylogous congener of enal **83a**, does also work as a precursor of oxyallyl cations. Thus, the addition of $SnCl_4$ (1 equivalent) to **89** in CH_2Cl_2 at $-78\ ^\circ C$, in the presence of an excess of furan or cyclopentadiene, provides the cycloheptenyl adducts of types **90** and **91**.[27] The reaction is suggested to involve the formation of an oxyallyl cationic intermediate such as **XIX** (equation 28).

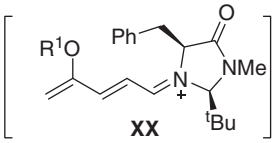


X	**90** : **91**	Yield (%)
O	100 : 0	36
CH_2	80 : 20	76

(28)

Quite recently, Harmata and coworkers developed an elegant enantioselective version of these (4 + 3) cycloadditions of silyloxy pentadienals, based on the use a chiral amine organocatalyst **92**, previously developed by MacMillan for enantioselective Diels–Alder and Friedel–Craft reactions. Although the yield and enantioselectivity of the (4 + 3) cycloadditions of silyloxy pentadienals with furan were quite low, the analogous reactions with 2,5-disustituted furans provided the corresponding adducts with moderate or good yields and good enantioselectivities (typically 80–90% *ee*) (equation 29).[48] Also importantly, most reactions were completely diastereoselective, leading to the exclusive formation of *endo* adducts. Mechanistically, the authors proposed that the organocatalyst initially reacts with the aldehyde to generate a chiral unsaturated iminum ion (**XX**) which subsequently participates in an asymmetric (4 + 3) cycloaddition reaction with the furan derivative. The isolation of acyclic secondary products in the cycloadditions of C-2 monosubstituted furans suggests that these (4 + 3) annulations might occur by stepwise mechanisms (equation 29).



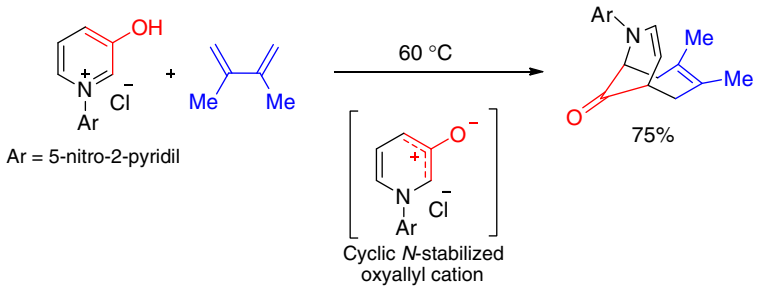


R^1	R^2	T (°C)	Yield (%)	*ee* (%)
TMS	H	0	8	50
TMS	Me	–78	64	89
TES	Me	–60	51	81
TBS	Me	–60	44	80
TMS	Et	–60	55	81
TES	^{n}Pr	–65	74	85

(29)

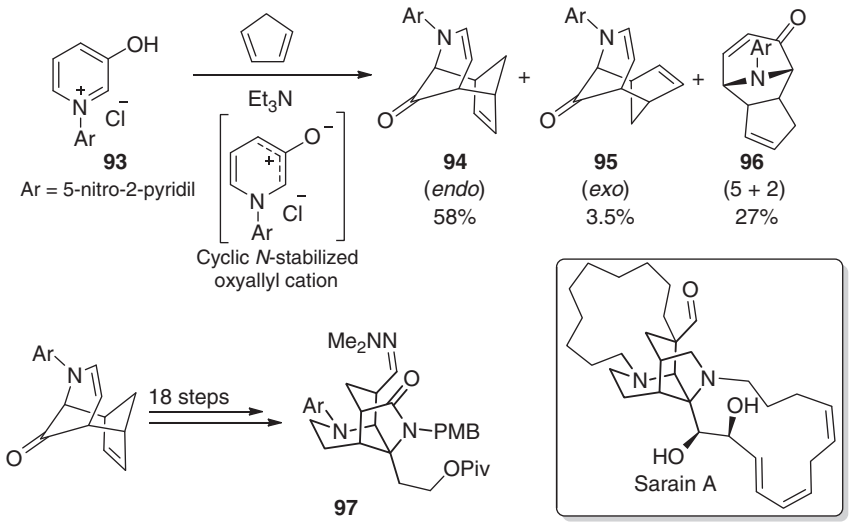
5.13.2.2.8 3-Oxidopyridinium betaines

During the 1970s and 1980s, the cycloaddition chemistry of 3-oxidopyridinium ions was extensively studied.[49] Although this type of heteroaromatic betaines usually participate in dipolar (5 + 2) cycloadditions with carbon–carbon double bonds, the groups of Nye and Katritzky independently demonstrated that they could also participate in formal (4 + 3) cycloadditions with dienes such as cyclopentadiene or 2,3-dimethyl butadiene.[50] Indeed, although oxidopyridinium ions are cyclic aromatic species, they can be alternatively viewed as cyclic *N*-stabilized oxyallyl cations capable of undergoing [3C(2π) + 4C(4π)] cycloadditions (equation 30).



(30)

Interestingly, in 1999, Cha and coworkers applied this relatively unexplored (4 + 3) cycloaddition reaction as the key step for the synthesis of the tricyclic core of Sarain A, an alkaloid present in the marine sponge *Reniera sarai*.[51] In particular, a slight modification of Katritzky's cycloaddition, consisting of a slow addition of Et_3N into a mixture of pyridinium salt **93** and cyclopentadiene at room temperature, provided the *endo* and *exo* (4 + 3) adducts **94** and **95** in 58% and 3.5% yields, respectively, together with the (5 + 2) adduct **96** (27% yield, **Scheme 2**). Importantly, the reaction was robust enough to be performed on large scale, so that the *endo*-cycloadduct **94** could be further manipulated in a sequence of 18 steps to afford compound **97**, which incorporates the tricyclic core of Sarain A.

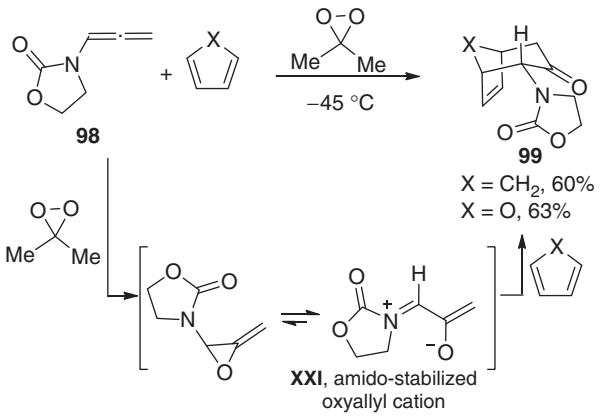


Scheme 2

5.13.2.2.9 Allenamides

5.13.2.2.9.1 Intermolecular examples

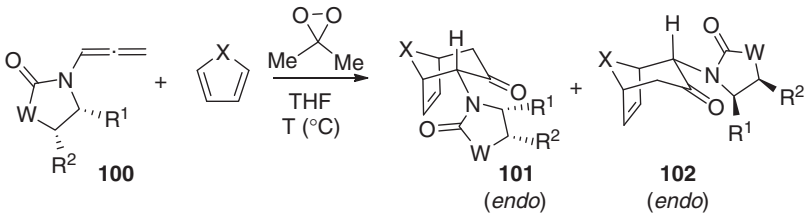
As shown above, nitrogen-stabilized oxyallyl cations have been shown to work as effective partners in (4 + 3) cycloadditions to dienes (see Sections 5.13.2.2.3.3 and 5.13.2.2.6).[17,37,52] In 2001, Hsung and coworkers demonstrated that treatment of oxazolidinone-substituted allenamides such as **98** with dimethyldioxirane (DMDO) provides an allene oxide, which subsequently opens to give the nitrogen-stabilized oxyallyl cation **XXI**. This oxyallyl cationic species could be trapped by cyclic dienes such as furan or cyclopentadiene in a standard (4 + 3) annulation (equation 31).[53] This cycloaddition chemistry has been extensively studied and optimized by Hsung during the past decade, and can be considered among the most versatile, selective, and efficient (4 + 3) cycloaddition methodologies relying on allyl cation intermediates.[54]



(31)

In their original report,[53] the authors demonstrated that by incorporating chiral oxazolidinones in the allene moiety, the (4 + 3) cycloaddition with dienes can take place with good-to-high levels of diastereoselectivity, depending on the chiral oxazolidinone used (Table 9). The reactions were completely *endo* selective and the best results (*dr* up to 96:4) were obtained with allenamides that incorporate a phenyl group at the nitrogen α-position, using $ZnCl_2$ (2.0 equivalents) as additive. Notably, these intermolecular cycloadditions can also be carried out in good yields and selectivities using *N*-protected pyrroles as diene counterparts, providing an efficient and direct entry to tropinone alkaloids.[55] The potential of the methodology has been demonstrated by its application to the synthesis of the tricyclic core of parvineostemonine (see Section 5.13.2.6).

Table 9 (4 + 3) Cycloadditions of allenamides with dienes



Numbers	Allenamide (**100**)				Diene	Temperature (°C)	Yield (%)[a]	**101**:**102**	References
		W	R^1	R^2	*X*				
1	**100a**	O	Ph	H	CH_2	−40 to > −50	40	≥95:5	53
2	**100b**	*N*-Me	Ph	Me	O	−40 to > −50	60	≥95:5	53
3	**100b**	*N*-Me	Ph	Me	CH_2	−40 to > −50	83	≥95:5	53
4[b]	**100a**	O	Ph	H	*N*-Boc	−45	76	82:18	55
5[b]	**100a**	O	Ph	H	*N*-Bz	−45	86	83:17	55

[a]Conditions: DMDO (2.0–3.0 equivalents), $ZnCl_2$ (2.0 equivalents) and diene (10 equivalents) in THF at the corresponding temperature unless otherwise noted.
[b]Reactions carried out with DMDO (6 equivalents) and diene (4–6 equivalents) in DCM with 4 Å MS.

Based on experimental data and DFT-theoretical calculations, Houk and Hsung have recently proposed a mechanistic model that accounts for the regio- and stereoselectivities of these cycloadditions.[56] The authors analyzed the different possible conformations of the amido-stabilized oxyallyl cation **XXII** derived from the oxidation of the allenamide. Contrary to the original hypothesis,[53] these studies revealed that the most stable allylic intermediate presents an (*E*)-configuration, in which the oxazolidinone carbonyl (C=O) and the oxyallyl oxygen are *anti* to each other in order to minimize electronic repulsions ((*E*)-**XXII**, Figure 7). Similarly, the calculations revealed that this conformation is maintained in the transition state of the (4 + 3) cycloaddition. The incorporation of a Lewis acid, such as $ZnCl_2$, decreases the activation barrier of the cycloaddition but does not change the conformation of the (*E*)-oxyallyl cation (*E*)-**XXII′** to a (*Z*)-chelate structure (*Z*)-**XXII′**, as had been initially hypothesized (Figure 7).[53]

The (4 + 3) cycloadditions between these oxyallyl cations and dienes were found to be *endo*-type concerted processes, in which the bond development at the transition state is most advanced at the most electron-rich CH_2 terminus of the oxyallyl cation.[56a] With regard to the diastereoselectivity, when chiral oxazolidinones incorporate a phenyl group at carbon atom adjacent to the nitrogen (**100a**), the calculations predict that there is an important stabilizing C–H–π interaction between the phenyl ring of **100a** and the hydrogen atom located at the C-3 position of the furan moiety. This interaction is strong enough to favor the cycloaddition through the more crowded face of the oxyallyl cation. On the contrary, with chiral oxazolidinones lacking aromatic groups

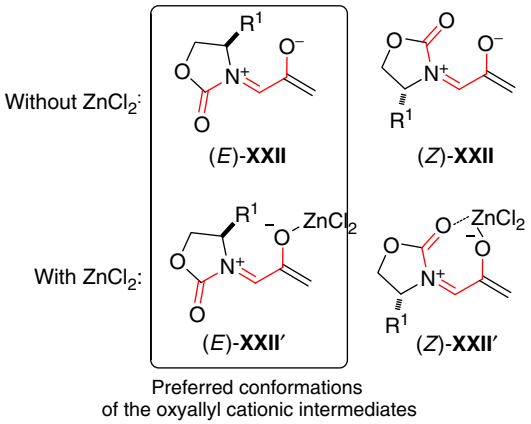


Figure 7 Preferred conformations of the *N*-stabilized oxyallyl species.

at this position, the stabilizing C–H–π interaction is not viable, so that the stereoselectivity is strictly controlled by steric factors, favoring an approach through the opposite, less crowded face of the oxyallyl cation (Figure 8).

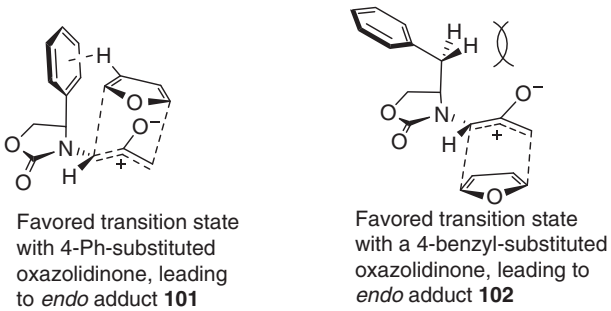
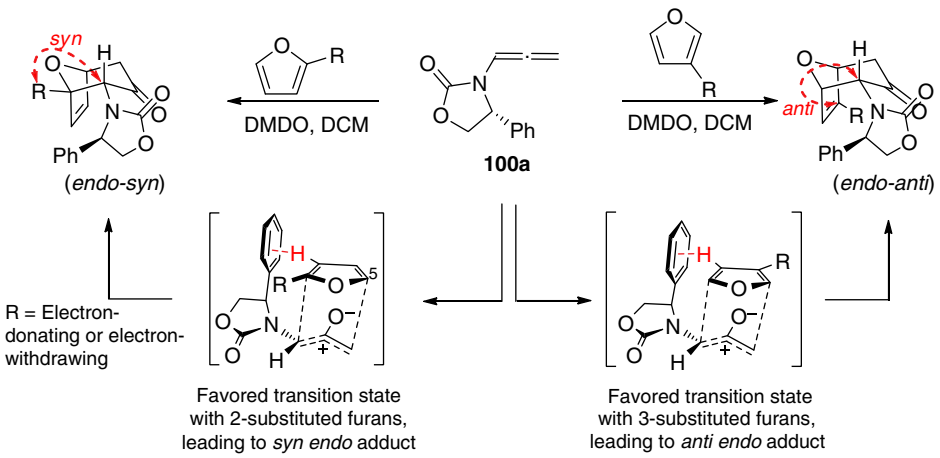


Figure 8 Favored transition states for the formation of products of types **101** and **102**.

The existence of C–H–π interactions also helps one to understand the regioselectivities of these cycloadditions.[56a] Reactions of **100a** with 2-substituted furans gave *syn* cycloadducts selectively, with the oxazolidinone and furan substituents at the same face of the adduct (Scheme 3). On the contrary, cycloadditions with 3-substituted furans gave selectively *anti* cycloadducts, in which the oxazolidinone and furan substituents are on the opposite sides of the cycloadduct. In both cases, the major diastereoisomer is derived from the addition of the furan to the more crowded face of the oxyallyl, favored by stabilizing C–H–π interactions. When a substituent at the 2-position of the furan is present, the preferred orientation that determines the regiochemistry is that which leads to bond formation between the more nucleophilic CH_2 terminus of the oxyallyl intermediate and the less-substituted carbon (C-5) of the furan (Scheme 3).

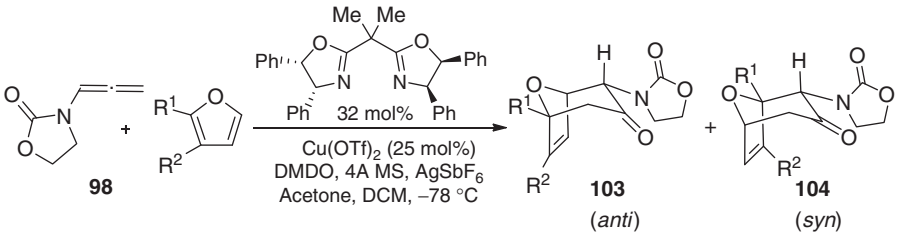


Scheme 3

DFT calculations also explained the good regioselectivities observed when achiral oxazolidinones (e.g., **98**) were used, both with 3- and 2-substituted furans.[56c] Like in the asymmetric cases, as a general trend, reactions of allenamide **98** with 3-substituted furans gave predominantly *endo-anti* products, whereas 2-substituted furans, such as 2-methyl furan or 2-furoate, predominantly provided the opposite *endo-syn* cycloadducts.

In an important advance, the same authors have recently disclosed a catalytic and highly enantioselective version of this intermolecular cycloaddition using a chiral Lewis acid derived from $Cu(OTf)_2$ and a chiral C_2 symmetric bisoxazoline ligand (Table 10).[57] This is one of the few reports on catalytic and asymmetric (4 + 3) cycloadditions between allyl cations and dienes (see Sections 5.13.2.2.7 and 5.13.2.5 for other examples).

Table 10 Enantioselective (4 + 3) cycloadditions of allenamide **98** and furans

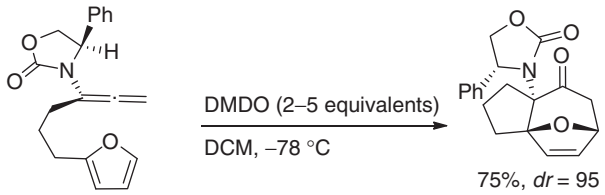


Numbers[a]	R^1	R^2	***103*:*104***	*Yield (%)*[b]	ee *(%)*[c]
1	H	H	–	91	99
2	Me	H	1:20	88	71
3	CO_2Me	H	0:1	61	67
4	H	Me	1:0	91	99
5	H	Br	14:1	58	84
6	H	CH_2OTBS	2.3:1	66	92

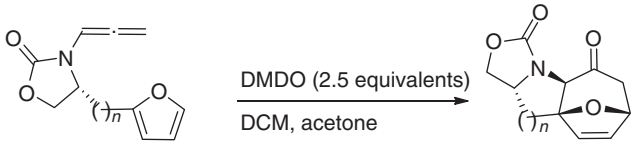
[a]Conditions: Diene (9 equivalents). DMDO was added via syringe pump.
[b]Isolated combined yields.
[c]*ee* of the major regioisomer.

5.13.2.2.9.2 Intramolecular examples

The group of Hsung has also studied and developed efficient intramolecular versions of these (4 + 3) cycloadditions, which provide synthetically appealing polycyclic systems incorporating seven-membered carbocycles.[58] The authors developed four different strategies depending on the way the carbon chain that holds the diene unit is linked to the allene moiety: (1) to its proximal position (equation 32), (2) to its terminal position, (3) to the oxazolidinone backbone (equation 33), or (4) to the nitrogen atom of the allenamide (equation 34). As can be observed in the corresponding equations, these strategies provided excellent yields and good or very good diastereoselectivities in many cases.

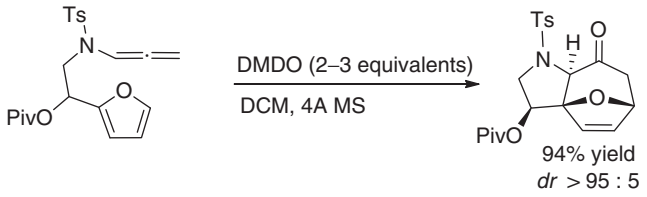


(32)



(33)

n	T (°C)	**106**, Yield (%)	*dr*
1	–45	82	> 96 : 4
2	–45	75	> 96 : 4
3	r.t.	70	83 : 17



(34)

5.13.2.2.10 Cyclopropanone derivatives

Parent oxyallyl cations like **XXIII** might hypothetically exist in equilibrium with a closed oxidoallene or cyclopropanone form (Figure 9).[59] Therefore, cyclopropanones can be envisioned as potential oxyallyl cation precursors. However, cyclopropanones are not easy to prepare and handle, and therefore have almost not been used as three-carbon precursors for (4 + 3) cycloadditions.[3b]

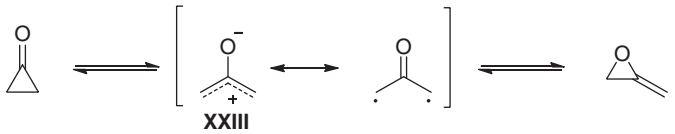
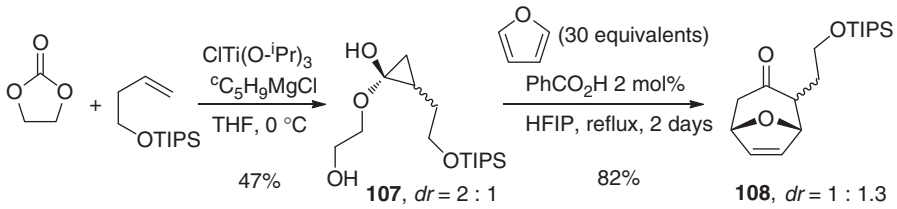


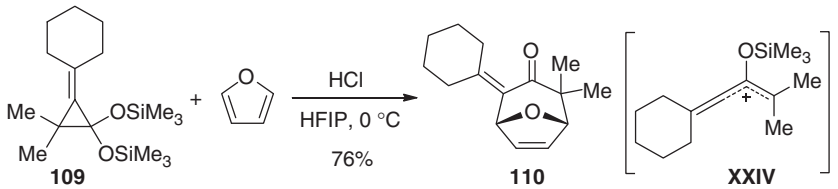
Figure 9 Oxyallyl forms of cyclopropanone.

However, some stable derivatives of cyclopropanones, such as their hemiacetals, can be used as oxyallyl cation precursors. For instance, Cha and coworkers reported that hemiacetals of type **107** react with furan (30 equivalents) when treated with a catalytic amount of benzoic acid to give (4 + 3) adducts of type **108** (Scheme 4).[60] The reaction most probably takes place through the *in situ* generation of an oxyallyl cation species. The required hemiacetals (**107**) are synthesized in one step from the corresponding alkenes using a Kulinkovich cyclopropanation.



Scheme 4

The group of Fujita has shown that alkylidenecyclopropanone acetals such as **109** react with furan under acidic conditions, to give interesting oxabridged cycloheptenes **110** in good yields.[61] It is quite probable that the reaction involves a silyloxyallyl cation intermediate **XXIV** (equation 35).

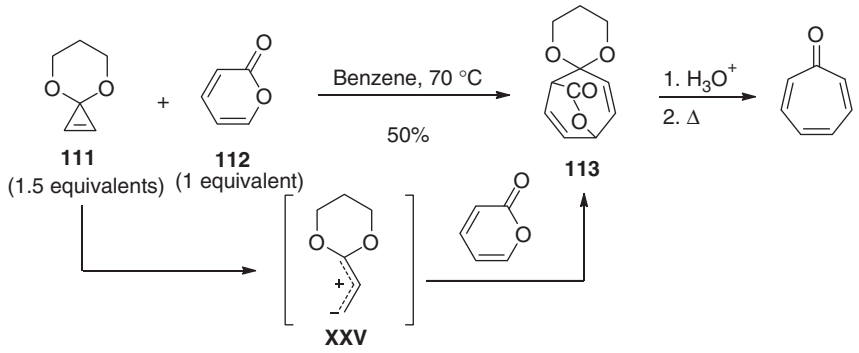


(35)

Finally, it is interesting to note here that cyclopropene acetals like **111** also participate in (4 + 3) cycloaddition with dienes such as **112** to form cycloheptadienes **113**.[62] However, the reaction does not involve the generation of a standard oxyallyl cation, but probably a delocalized singlet vinylcarbene such as **XXV** (Scheme 5).

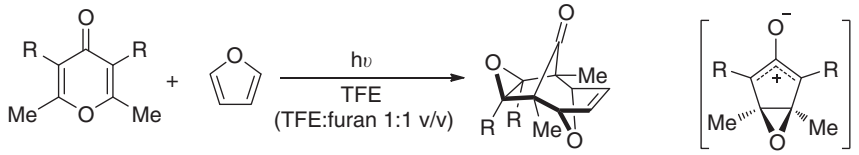
5.13.2.2.11 4-Pyrones

Oxyallyl cation intermediates can also be generated from less obvious precursors, such as 4-pyrones, using photochemical techniques. For instance, Barltrop demonstrated that pyrones **114a** react photochemically with excess furan to provide cyclic cyclooctanoids **115a** with moderate efficiency, which formally results from a (4 + 3) cycloaddition (equation 36).[63] West and coworkers found similar results with tetrasubstituted pyrone **114b**.[64] These results can be explained by assuming the formation of the cyclic oxyallyl cation **XXVI** on irradiation of the pyrone. Unfortunately, the efficiency and scope of the transformation is rather

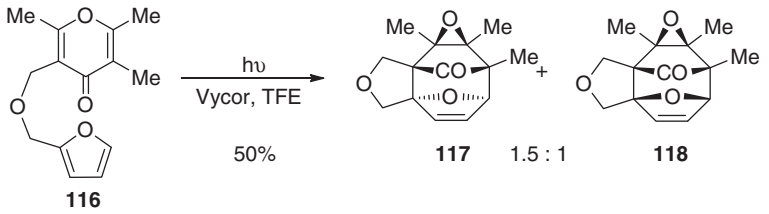


Scheme 5

limited. A related intramolecular version allowed highly functionalized cyclooctanoids (**117** and **118**) to be constructed, although with poor *endo*/*exo* selectivity (1.5:1) and moderate yield (50%) (equation 37).[64]



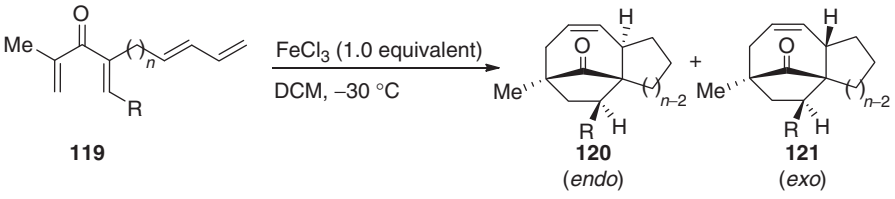
(36)

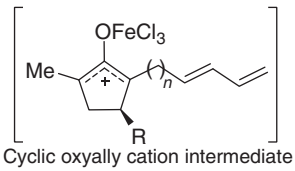


(37)

5.13.2.2.12 Conjugated dienones

Other nonobvious oxyallyl precursors are cross-conjugated dienones such as **119**, because they can undergo a Nazarov electrocyclization when treated with appropriate Lewis acid activators. The resulting cyclic allyl cations, similar to those previously discussed in Sections 5.13.2.2.2.2 and 5.13.2.2.2.3, can be intramolecularly intercepted by a conjugated diene linked to the α-position of the dienone.[65] Interestingly, the stereocenter generated during the electrocyclization controls the facial selectivity of the subsequent (4 + 3) cycloaddition, with a preferred approach of the diene from the less hindered face of the cyclic oxyallyl cation. The process is efficiently promoted at low temperatures by Lewis acids such as $FeCl_3$, providing keto-bridged cyclooctene derivatives **120** and **121** with moderate-to-high *endo*–*exo* selectivities, depending on the length of the connecting chain (equation 38). Importantly, the authors also demonstrated, in a specific case, that the loading of $FeCl_3$ can be reduced to 0.2 equivalent without affecting the yield or selectivity of the process. Overall, the reaction converts achiral acyclic reactants into tricyclic products by concomitant formation of three new carbon bonds and four stereocenters.



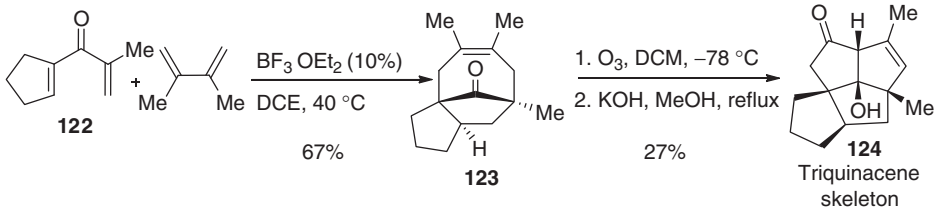


R	*n*	**120** : **121**	yield (%)[a]
Me	3	1.3 : 1	65
Ph	3	1.3 : 1	72[b]
Me	4	0 : 1	67
Ph	4	0 : 1	75

[a]Combined isolated yield. [b]An identical result was obtained using 0.2 equivalent of $FeCl_3$.

(38)

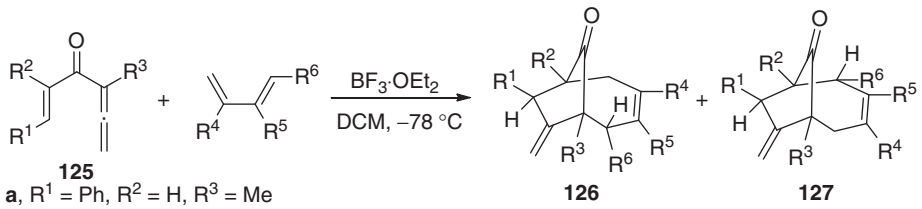
The analogous intermolecular (4 + 3) cycloaddition is also effective with a variety of simple dienones and cyclic or acyclic 1,3-dienes.[66] In these cases, optimal conditions consisted of the use of 2 equivalents of diene and 1 equivalent of $BF_3 \cdot OEt_2$. In some particular cases, however, such as the one shown in Scheme 6, the cycloaddition could be carried out under catalytic conditions, using 0.1 equivalent of $BF_3 \cdot OEt_2$, to give the corresponding cycloadduct in a good 67% yield as a single diastereoisomer. The skeletal and functional richness of this type of bicyclic adducts facilitates their straight transformation into relevant targets such as centro-substituted triquinacene skeletons of type **124** (Scheme 6).[67] The cycloadditions could also be carried out with unsymmetrical 1,3-dienes such as isoprene; however, in these cases, regioisomeric mixtures of products were obtained with a selectivity up to 5:1.



Scheme 6

Quite recently, Burnell and coworkers demonstrated that certain allenyl vinyl ketones of type **125** are also suitable precursors for these Nazarov-interrupted (4 + 3) cycloadditions.[68] In particular, allenyl vinyl ketones **125a–c**, with alkyl substituents at the ketone α position on either the allene or the alkene, react efficiently with 1,3-dienes in the presence of $BF_3 \cdot OEt_2$ to provide the expected (4 + 3) adducts (**126** and/or **127**) with moderate-to-good yields. The best results were achieved with acyclic dienes such as isoprene, *trans*-piperylene, and 2,3-dimethylbutadiene (Table 11). The reactions proceeded with excellent diastereofacial selectivity, complete *exo* selectivity (Table 11, entries 2, 5, and 8) and, in general, with very good regioselectivity. Curiously, electron-rich cyclic dienes such as furan did not provide the expected (4 + 3) adducts, but addition products arising from trapping of the cyclic oxyallyl cation by electrophilic substitution.[68a]

Table 11 Nazarov-interrupted (4 + 3) cycloadditions of allenyl vinyl ketones



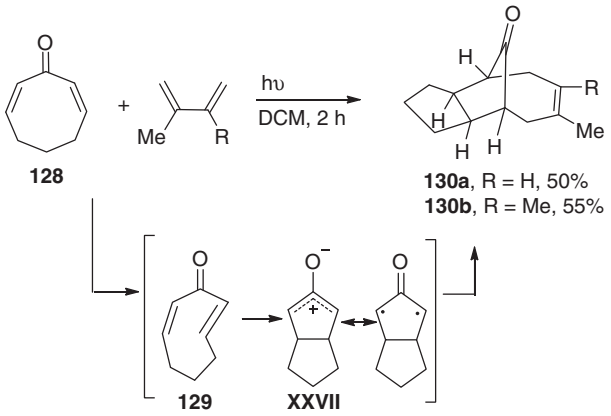
a, R^1 = Ph, R^2 = H, R^3 = Me
b, R^1 = Ph, R^2 = Me, R^3 = H
c, R^1, R^2 = $(CH_2)_4$, R^3 = H

Numbers	***125***		*Diene*			***126*:127**	*Yield (%)*[a]	*References*
		$BF_3 \cdot OEt_2$ (equivalent)	*R^4*	*R^5*	*R^6*			
1	**125a**	0.3	Me	H	H	2.8:1	56	68a
2	**125a**	0.3	H	H	Me	100:0	14[c]	68a
3	**125a**	0.3	Me	Me	H	–[b]	99	68a
4	**125b**	1.1	Me	H	H	4:1	73	68b
5	**125b**	1.1	H	H	Me	100:0	50	68b
6	**125b**	1.1	Me	Me	H	–[b]	79	68b
7	**125c**	1.1	Me	H	H	1.3:1	65	68b
8	**125c**	1.1	H	H	Me	100:0	48	68b
9	**125c**	1.1	Me	Me	H	–[b]	74	68b

[a]Combined isolated yields of **126** and **127**.
[b]In this case **126** and **127** are the same product.
[c]An additional (3 + 2) cycloadduct was also isolated in 37% yield.

In 1999, Matlin and coworkers described an interesting cycloaddition example also based on a photochemically promoted Nazarov cyclization.[69] Relying on previous work, which had shown that irradiation of *cis,cis*-2,7-cyclooctadienone **128** results in

its isomerization to (*Z*,*E*)-2,7,cycloactadienone **129**,[70] these authors demonstrated that this intermediate, which is only stable at temperatures below −70 °C, readily undergoes a conrotatory Nazarov cyclization above −30 °C to give the cyclic cyclopentyl cation **XXVII**. This oxyallyl intermediate – which might be better described as a polarized single diradical according to the author's DFT calculations – reacts *in situ* in a concerted cycloaddition to simple acyclic dienes to give bicyclic products of type **130**. Only two isolated examples of this (4 + 3) cycloaddition were reported (equation 39).



(39)

5.13.2.2.13 α-Halo benzyloxyamides

In this section the authors show the only example so far reported dealing with the generation and (4 + 3) cycloaddition reaction of an aza-oxyallyl cation, a nitrogen analog of standard all-carbon oxyallyl cations. Thus, in 2011, Jeffrey et al. reported the development of an aza-(4 + 3) cycloaddition reaction between cyclic dienes and aza-oxyallyl cations, *in situ* generated from α-haloamides.[71] In this report, the authors demonstrate that, similarly to the base-mediated dehydrohalogenation of α-haloketones (see Section 5.13.2.2.2), the dehydrohalogenation of an *N*-alkoxyhaloamide like **131** affords *aza*-oxyallyl cations (**XXVIII**) which can participate as three-atom components in (4 + 3) cycloadditions with appropriate dienes (i.e., furan or cyclopentadiene). The corresponding (4 + 3) lactam cycloadducts **132** could be isolated in moderate-to-good yields (Table 12). Interestingly, related α-haloamides with alkyl, instead of alkoxy groups at nitrogen, did not afford the desired (4 + 3) adducts, suggesting that the electron-donating group at nitrogen (OBn) is essential for the cycloaddition.

Experimental data and DFT calculations carried out by the same authors support a mechanism consisting of dehydrohalogenation of the α-haloamide to generate the reactive *aza*-oxyallyl cationic intermediate. The requirement of an OR group at nitrogen is also reproduced by the calculations, because it stabilizes the proposed aza-oxyallyl cationic species. Further developments on this approach, including intramolecular versions and asymmetric variants are expected.

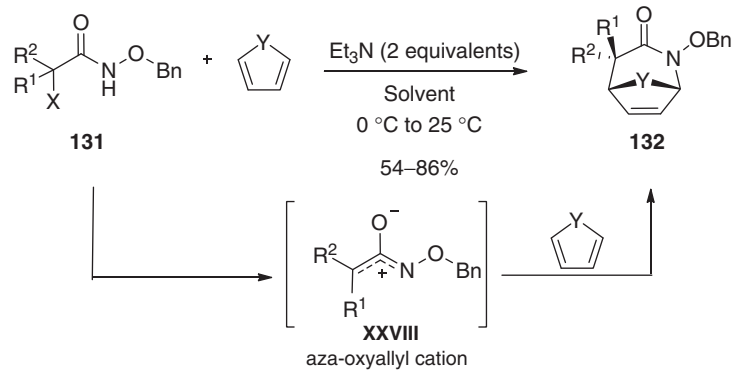
5.13.2.3 Reactions Involving 2-Aminoallyl Cation Intermediates

2-Amino-stabilized allyl cations are less common that their oxyallyl counterparts, perhaps because of the difficulties for their generation. In a pioneering work, Schmid demonstrated that cyclic enamines **133** derived from cyclohexanone reacted very efficiently with furan or cyclopentadiene with complete *endo* selectivity, leading to the formation of the cyclic cycloheptanones after hydrolysis (Scheme 7).[72] More recently Cha expanded the scope of this reaction and demonstrated that this methodology is particularly efficient when the cyclohexenyl ring is substituted with alkyl or silyloxy groups, and when *N*-Boc-pyrrole or spirocyclopentadiene are used as diene partners.[8]

α-Haloimines can also work as precursors of amino-allyl cations. In 1997, Kende et al. took advantage of the presence of a chiral center in the α-position of an imine to develop the first asymmetric cycloaddition of 2-aminoallyl cations.[73] Unfortunately, the efficiency and the asymmetric induction achieved with this method were modest (Scheme 8). The authors suggest that the diastereoselectivity could be explained by assuming a preferred reactive conformation of the allyl cation due to the existence of cation/π-interactions with the phenyl ring, forcing the dienes to preferentially attack the less hindered *Re* face.

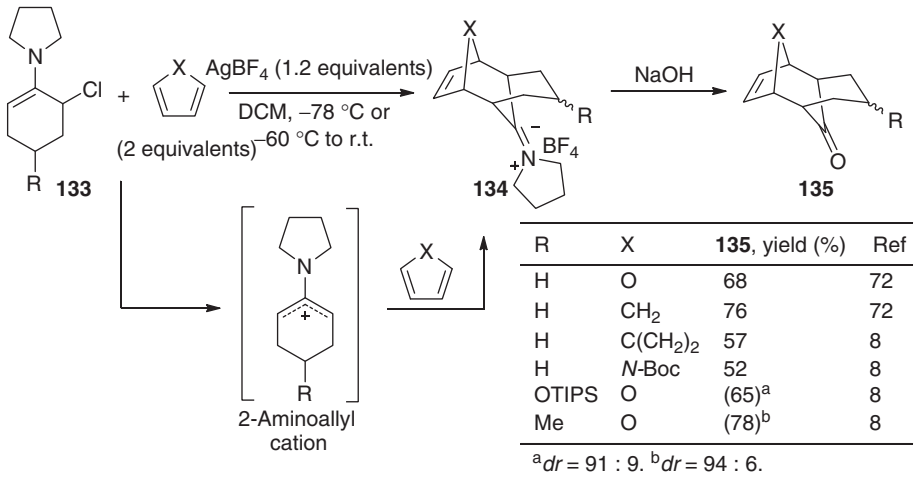
As might be expected from related reactions with oxidoallenes hypothetically formed in the oxidation of allenamides (see Section 5.13.2.2.9), Lewis acid promoted ring opening of strained alkylideneaziridines generate 2-aminoallyl cations capable of undergoing a standard (4 + 3) cycloaddition with dienes.[74] The authors propose that the intramolecular cycloaddition of substrates **138**, which feature a three-carbon tether, proceed via a compact transition state with the tethering arm orientating itself *anti* to the bulky Lewis acid (U-form of the allyl cation). An extended transition state may prevail in the case of precursor **140**, which has a longer linking tether (Scheme 9). In any case, the authors did not fully rule out other explanations based on mechanistic alternatives.

Table 12 (4 + 3) Cycloadditions of aza-oxyallyl cations and dienes



Numbers[a]	131				Diene	Solvent	endo:exo	Yield (%)[b]
		R^1	R^2	X	Y			
1	**131a**	H	H	Br	O	TFE	–[c]	0
2	**131b**	H	Me	Br	O	TFE	>19:1[d]	67
3	**131c**	H	^{t}Bu	Br	O	TFE	>19:1[d]	54
4	**131d**	H	Me	Cl	O	TFE	>19:1[d]	78
5	**131e**	H	Cl	Cl	O	TFE	2:1	73
6	**131f**	H	*p*-Cl-C_6H_4	Cl	O	TFE	>19:1[d]	52
7	**131g**	Me	Me	Br	O	HFIP	–[c]	78
8	**131h**	H	Et	Br	CH_2	TFE	3:1	85

[a]Conditions: furan or cyclopentadiene is used as cosolvent (1:1 v/v, 0.25 M).
[b]Global isolated yield.
[c]*endo* and *exo* **132** are the same adduct.
[d]The minor diastereoisomer was not detected (NMR).



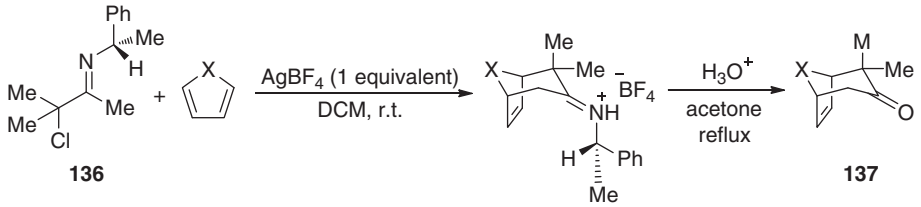
R	X	**135**, yield (%)	Ref
H	O	68	72
H	CH_2	76	72
H	$C(CH_2)_2$	57	8
H	*N*-Boc	52	8
OTIPS	O	(65)[a]	8
Me	O	(78)[b]	8

[a]*dr* = 91 : 9. [b]*dr* = 94 : 6.

Scheme 7

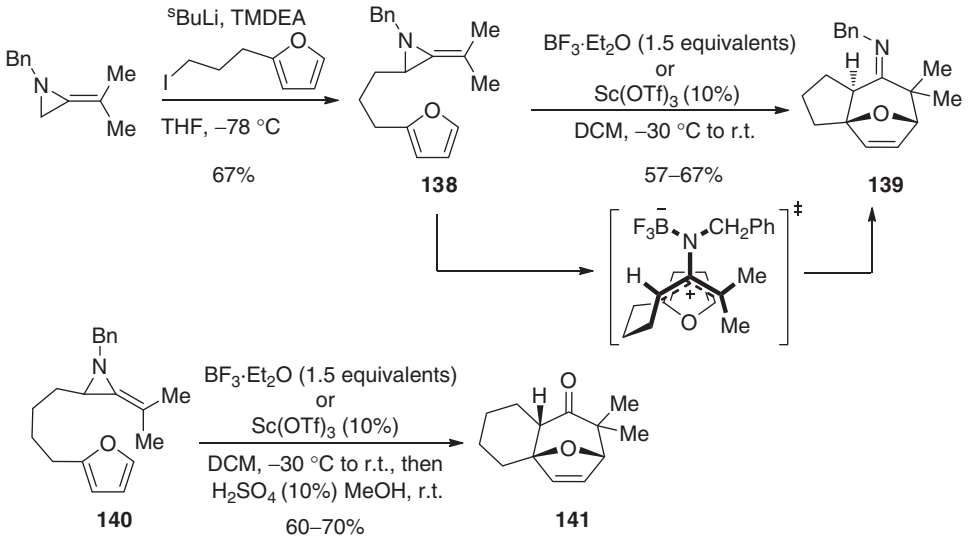
5.13.2.4 Reactions Involving (Trimethylsilyl)methyl Allyl Cation Intermediates

Although allyl cations, which feature oxygen or nitrogen groups at the C-2 position (oxyallyl and aminoallyl cations, see Sections 5.13.2.2 and 5.13.2.3), are the most common three-carbon reactants in thermal (4 + 3) cycloadditions, there are other interesting alternatives that do not incorporate a heteroatom at the central position of the allylic system. In particular, a variety of cycloaddition strategies relying on the generation of 2-(trimethylsilyl)methyl allyl cationic intermediates have been developed (Scheme 10).[75] Importantly, the seven-membered carbocycles resulting from these (4 + 3) cycloadditions contain an *exo* methylene carbon substituent, which is an attractive functionality for further synthetic manipulations.

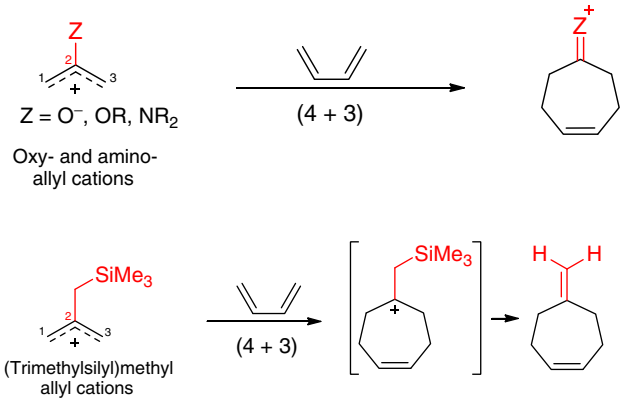


X	**137**, Yield (%)	*ee* (%)
O	37	60
N-Boc	23	41

Scheme 8



Scheme 9

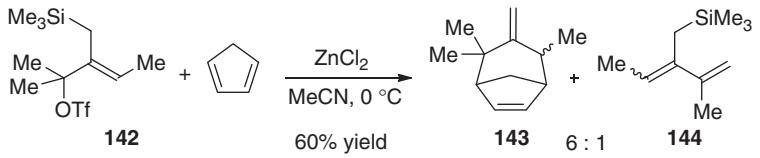


Scheme 10

5.13.2.4.1 (Trimethylsilyl)methyl allyl alcohols and acetates

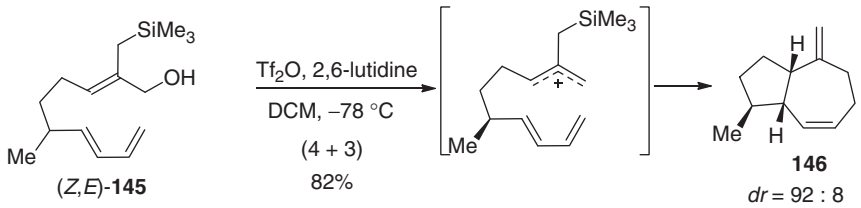
At the beginning of the 1980s, Hoffmann and coworkers reported pioneering examples of inter- and intramolecular (4 + 3) cycloadditions of (trimethylsilyl)methyl allyl trifluoroacetates such as **142** with dienes (i.e., cyclopentadiene or furan). It is proposed that these precursors are readily converted to the reactive (trimethylsilyl)methyl allyl cations on treatment with an

appropriate ionization promoter ($ZnCl_2$ or $TiCl_4$/PhNHMe, equation 40).[76] Despite the novelty of the approach, its versatility and efficiency were not that good.

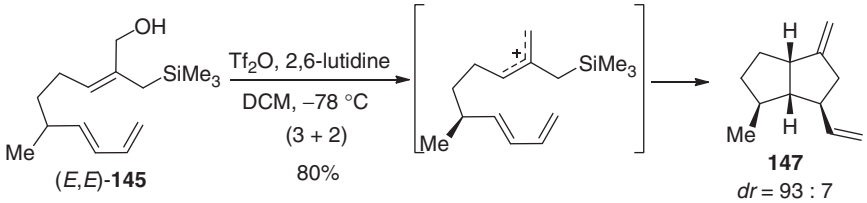


(40)

A few years later, Giguere and coworkers made an additional seminal contribution to this area by establishing more effective conditions to promote direct intramolecular cycloadditions between (trimethylsilyl)methyl allyl alcohols (the triflate is formed *in situ*) and acyclic dienes (equation 41).[77] Moreover, these authors established a relationship between the configuration of the allyl cation precursor and the chemoselectivity of the process. Thus, the reaction of alcohol (*Z*,*E*)-**145**, in the presence of triflic anhydride and 2,6-lutidine at -78 °C afforded the (4 + 3) cycloadduct **146** in 82% yield in a regio- and stereoselective manner. On the contrary, reaction of the configurational isomer (*E*,*E*)-**145** under the same conditions provided the (3 + 2) cyclopentyl adduct **147** in 80% yield (equations 41 and 42). These results suggest that the configuration of the allyl cation played an essential role in the selectivity of the process, and that the relative rate of seven-membered ring closure versus allyl silane rotation determines which cycloadduct is obtained.

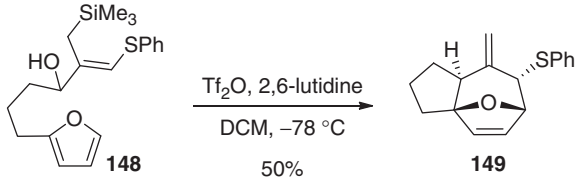


(41)

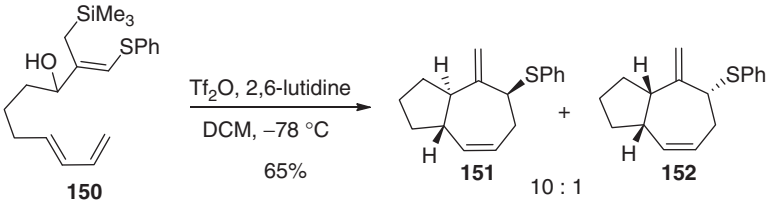


(42)

More recently, in 2001, Harmata and coworkers studied the reactions of (trimethylsilyl)methyl-substituted vinylthionium ions, which are generated *in situ* from appropriately substituted allyl alcohols.[78] Thus, treatment of **148** with Tf_2O and 2,6-lutidine at -78 °C afforded the corresponding cycloadduct **149** in 50% yield as a single diastereoisomer. The related cycloaddition of **150**, which incorporates an acyclic diene instead of the furan, afforded a 10:1 mixture of the diastereoisomers **151** and **152** in a combined 65% yield (equations 43 and 44).



(43)



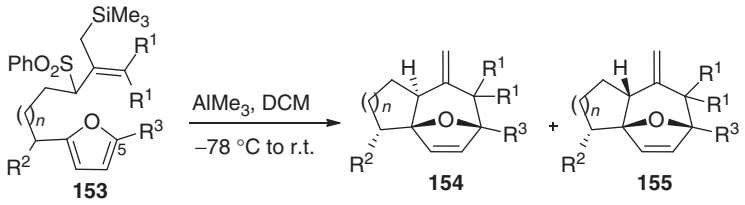
(44)

5.13.2.4.2 (Trimethylsilyl)methyl allyl sulfones

In consonance with the work carried out using alkoxyallyl sulfones (see Section 5.13.2.2.4), Harmata and coworkers also studied the use of the trimethylsilylmethyl group instead of the alkoxy substituent as terminator of the (4 + 3) cycloaddition.

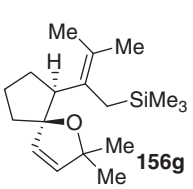
Cycloaddition precursors such as **153** can be prepared from readily accessible sulfonyl allenes in a few steps. Importantly, the cycloaddition of **153a** proceeded efficiently on treatment with $AlMe_3$ in CH_2Cl_2 at room temperature to give a 1.7:1 mixture of the (4 + 3) cycloadducts **154a** and **155a** in a combined 71% yield (Table 13, entry 1). Therefore, there is a substantial improvement with respect to the same reaction from secondary alkoxyallyl sulfones which afforded poorer results.[75] As can be seen in Table 13, the method worked well for a broad range of substrates and, in some cases, high diastereoselectivities could be obtained.[79] Also relevant, a high degree of relative facial stereocontrol could be achieved with substrates such as **153e** equipped with stereocenters in the tether, although the *endo*/*exo* selectivity is low (Table 13, entry 5). This might arise by coordination of trimethyl aluminum to the furan; which forces the methyl group away from the oxygen to avoid steric repulsions. This induced-conformational bias has no effect on the *endo*/*exo* selectivity. Limitations of the methodology are the requirement of a cyclic diene as four-carbon partner (simple butadienes do not trap the allylic intermediate). Moreover, furans incorporating substituents at their C-5 position ($R^3 \neq H$) cannot be used. In these cases, alternative cyclization products derived from a stepwise interception of the allyl cation were detected (**156g** and **157h**) (Table 13, entries 7 and 8).

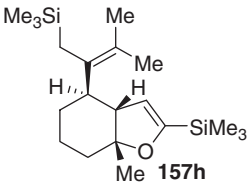
Table 13 Intramolecular cycloadditions of (trimethylsilyl)methyl allyl sulfones to furans[a]



Numbers	153	R^1	R^2	R^3	n	154:155	Yield (%)[b]	References
1	**153a**	Me	H	H	1	1.7:1	71	79a
2	**153b**	$-(CH_2)_5$	H	H	1	1.7:1	71	79a
3	**153c**	Me	H	H	2	1:93	39[c]	79a
4	**153d**	$-(CH_2)_5$	H	H	2	1:13	50[c]	79a
5	**153e**	Me	Me	H	1	1.2:1	40	79b
6	**153f**	$-(CH_2)_5$	Me	H	1	2:1	48	79b
7	**153g**	Me	H	Me	1	–	0[d]	79b
8	**153h**	Me	H	$SiMe_3$	1	–	0[e]	79b

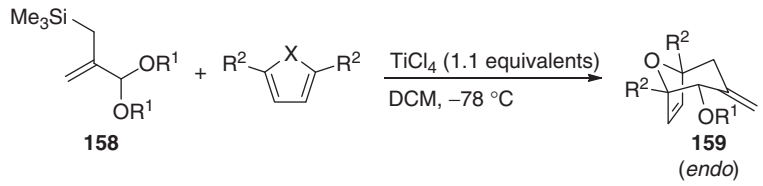
[a] $AlMe_3$ (1–2 equivalents), DCM at −78 °C and slow warming to r.t.
[b] Isolated combined yields unless otherwise noted.
[c] Yield of the major diastereoisomer.
[d] Compound **156g** was formed in 27% yield.
[e] Compound **157h** was obtained in 74% yield.

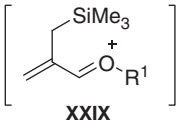




5.13.2.4.3 (Trimethylsilyl)methyl allyl acetals

The group of Harmata has also studied the use of 2-trimethylsilylmethyl substituted allyl acetals as precursors of active allyl cations. In 1997, these authors demonstrated that allyl acetals **158** could undergo intermolecular (4 + 3) cycloadditions with furan or cyclopentadiene in moderate-to-good yields when treated with suitable Lewis acids.[33b] Among the different promoters studied, $TiCl_4$, in CH_2Cl_2 at −78 °C, provided the best results (equation 45). The reactions exhibit high diastereoselectivity to give products arising from a preferred *endo* approach of the diene to the putative oxocarbenium ion intermediate.



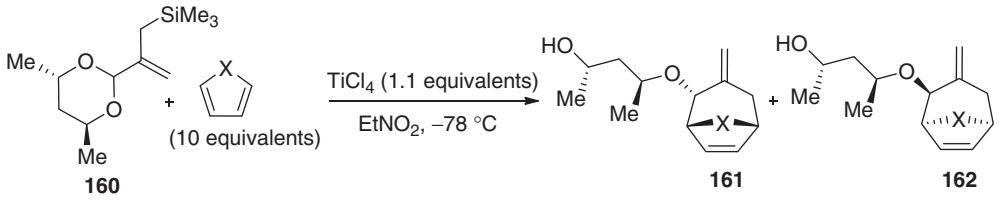


XXIX
Vinyloxocarbenium intermediate

X	R^1	R^2	Yield (%)
O	Et	H	99
CH_2	Et	H	62
O	Et	Me	47
O	Me	H	62

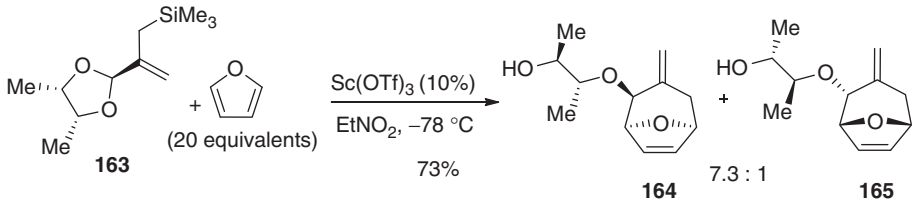
(45)

Importantly, the use of chiral allyl acetals enabled the development of asymmetric transformations. As an example, the reaction of allylic acetal **160** with furan in nitroethane, in the presence of stoichiometric amounts of $TiCl_4$, gave rise to the (4 + 3) cycloadducts **161** and **162** in good yield and with excellent diastereoselectivity (**161**:**162** = 17.3:1). When cyclopentadiene was used as diene, the diastereoselectivity dropped significantly (equation 46).[80] Importantly, the reaction of chiral dioxolanes such as **163** can also be induced using catalytic amounts of the Lewis acid, affording good yields of cycloadducts **164** and **165** and high diastereoselectivities[81] (equation 47).



X	**161** : **162**	Yield (%)
O	17.3 : 1	71
CH_2	1.7 : 1	73

(46)



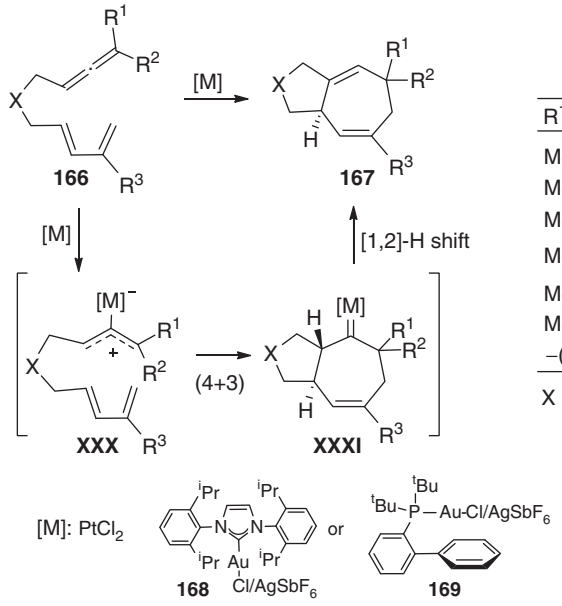
(47)

5.13.2.5 Reactions Involving Metal-allyl Cation Intermediates

In recent years, platinum and, particularly, gold complexes have emerged as excellent catalysts for promoting novel types of cycloaddition reactions, usually involving nonactivated C–C unsaturated systems (e.g., alkynes, allenes, alkenes, or 1,3-dienes).[82] The excellent reactivity of these group 11 catalysts can in part be explained in terms of relativistic effects,[83] which confer singular characteristics, like a high carbophilicity (affinity for C–C π-unsaturated systems) and a low propensity to participate in typical redox processes characteristic of other transition metal catalytic cycles. In this context, several research groups have demonstrated that some of the metal intermediates arising from the activation of designed unsaturated compounds can participate in cycloaddition reactions. In this section, metal-catalyzed (4 + 3) cycloadditions suggested to involve metal-allyl cation intermediates are discussed.

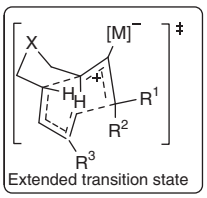
Based on several reports demonstrating the ability of gold(I) and platinum(II) catalysts to induce reactions of allenes through allyl cationic intermediates, Mascareñas and coworkers investigated the possibility of using allenes as allyl cation surrogates, so that they could participate in [4C(4π)–3C(2π)] cycloadditions with conjugated dienes. Initially, it was found that $PtCl_2$ was an excellent catalyst for promoting these intramolecular (4 + 3) cycloadditions of allenedienes **166** (equation 48).[84] DFT calculations as well as experimental data agreed with a mechanistic pathway based on the metal activation of the allene to afford a metal-allyl cation intermediate of type **XXX**, which subsequently undergoes a concerted (4 + 3) cycloaddition reaction with the diene moiety.

Finally, the resulting metal carbene species (**XXXI**) evolves through a 1,2-hydrogen shift, leading to seven-membered carbocycles of type **167** and regenerating the catalyst ($PtCl_2$). DFT calculations also suggested that gold catalysts should equally work and be even more active than $PtCl_2$. Accordingly, the use of a cationic Au^I catalyst containing a σ-donating *N*-heterocyclic carbene ligand (**168**/$AgSbF_6$, equation 48) allowed these reactions to be performed at lower temperatures than with $PtCl_2$, which increased the scope and synthetic utility of the process.[85] As in other cases of intramolecular allyl cation/diene cycloadditions, the reactions are completely *exo*-selective. The groups of Toste and Gung also demonstrated that other gold(I) complexes, for example, complexes containing a highly donating biaryl di-*tert*-butylphosphine ligand (**169**), are also effective for these cycloadditions.[86] In general, the reactions tolerate a wide variety of substituents in the allene and the diene, providing the corresponding bicyclo[5.3.0]decane systems in good yields (equation 48).



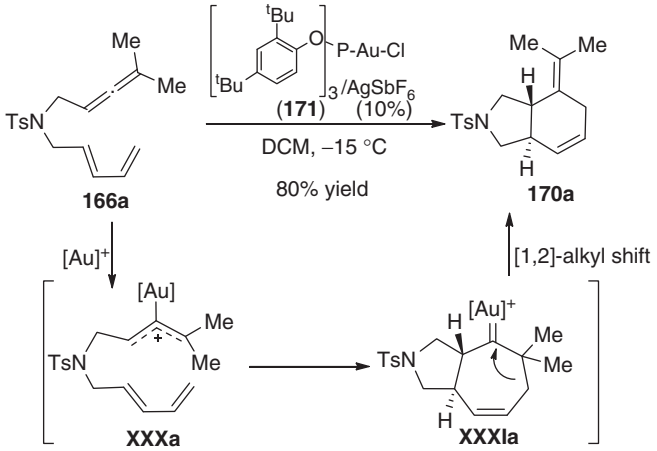
R^1	R^2	R^3	[M]	T (°C)	Yield (%)	Ref
Me	Me	H	$PtCl_2$	110	92	85
Me	Me	H	**168**	r.t.	91	86
Me	Me	H	**169**	r.t.	85	87a
Me	Me	Me	$PtCl_2$	110	72	85
Me	Me	Me	**168**	r.t.	84	86
Me	Me	Me	**169**	r.t.	81	87a
$-(CH_2)_5-$		H	**169**	r.t.	81	87a

X = $C(CO_2R)_2$



(48)

Curiously, allenediene, when disubstituted at the distal position of the allene as in **166a**, on treatment with a gold(I) catalyst bearing a π-acceptor ligand such as a triarylphosphite, give rise to (4 + 2) cycloaddition products **170a** instead of the (4 + 3) adducts (equation 49).[85,86a,87] Several experimental data as well as theoretical calculations suggest that the observed cyclohexene cycloadducts **170** are indeed the result of a ring contraction event (1,2-alkyl shift) in the initially formed cycloheptenyl gold carbene intermediate **XXXIa**, that results from the (4 + 3) cycloaddition pathway (equation 49). Thus, the ligand at gold determines the fate of this carbenoid intermediate to give either the (4 + 3) or the (4 + 2) adducts.



(49)

Mascareñas and López have also discovered that it is possible to achieve these allene–diene cycloadditions in a highly enantioselective manner using gold complexes with chiral phosphoramidite ligands, in particular **172**, bearing anthracenyl substituents at the 3- and 3′-positions of the binaphthol moiety (Figure 10). The (4 + 3) or (4 + 2) fate of the reactions is mainly determined by the substitution pattern of the allene (Table 14), and hence in some cases it is possible to obtain the

bicyclo[5.3.0]decane systems with very high *ee*'s (Table 14, entries 2–6).[87,88] The groups of Toste and of Fürstner independently reported related phosphoramidite–gold complexes, as well as the chiral phosphite gold catalyst **175**, which are also capable of inducing excellent enantioselectivities in intramolecular (4 + 2) allene diene cycloadditions (Table 14, entries 7–9).[89]

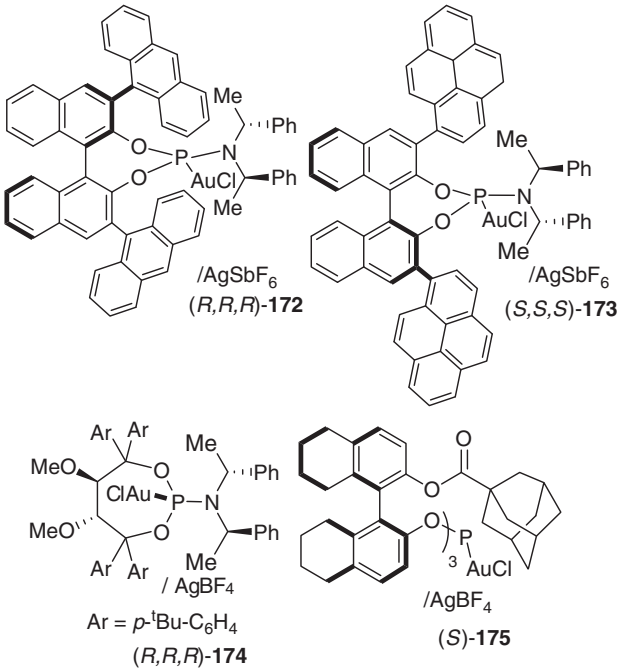
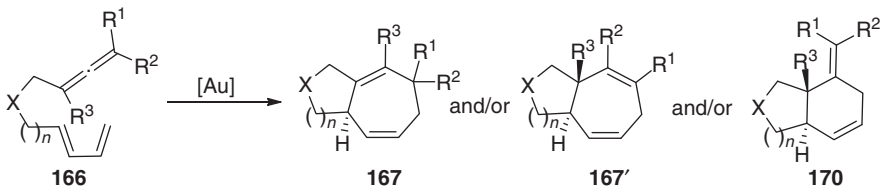


Figure 10 Chiral gold catalysts.

Table 14 Enantioselective Au-catalyzed allene–diene cycloadditions

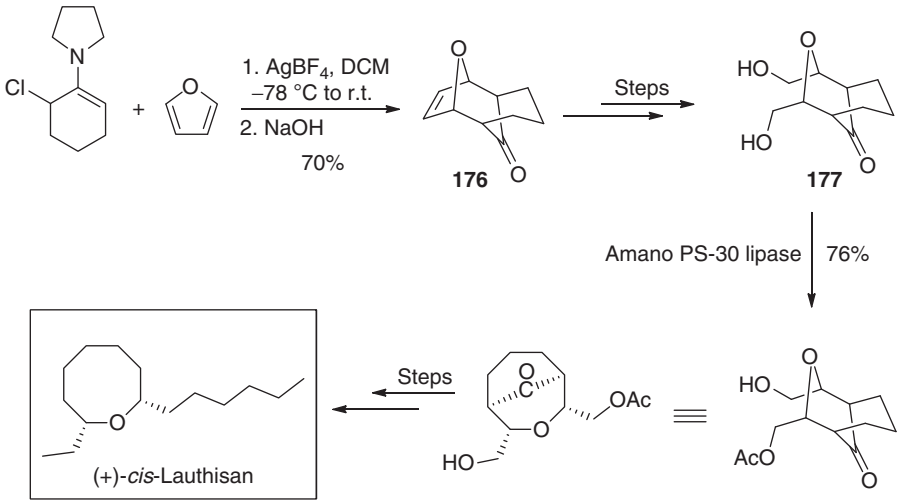


Numbers	*[Au] (5%)*	*n*	*X*	*R^1*	*R^2*	*R^3*	*Product*	*Yield (%)*	ee	*References*
1[a]	(*R*,*R*,*R*)-**172**[b]	1	NTs	Me	Me	H	**170**	93	92	87
2[c]	(*R*,*R*,*R*)-**172**	1	NTs	Ph	H	H	**167**	74	95	88
3[c]	(*R*,*R*,*R*)-**172**	1	$C(CO_2Me)_2$	Ph	H	H	**167** + **167′**[d]	64	87	88
4[c]	(*R*,*R*,*R*)-**172**	1	NTs	*o*-$OMeC_6H_4$	H	H	**167′**	80	98	88
5[c]	(*R*,*R*,*R*)-**172**	1	NTs	Me	H	Me	**167′**	78	95	88
6[c]	(*R*,*R*,*R*)-**172**	2	NTs	Me	H	Me	**167′**	95	98	88
7[a,e]	(*S*,*S*,*S*)-**173**	1	NTs	Me	Me	H	**170**	83	99	89a
8[f]	(*R*,*R*,*R*)-**174**	1	NTs	Me	Me	H	**170**	90	91	89b
9[e,g]	(*S*)-**175**	1	$C(CO_2Me)_2$	Me	Me	H	**170**	87	92	89a

[a]Reaction at −15 °C.
[b]2 mol% used.
[c]Reaction at −15 °C to 0 °C.
[d]Ratio of **167**:**167′** = 9:1.
[e]Opposite enantiomer of **170** is obtained.
[f]Reaction at 0 °C.
[g]Reaction at r.t.

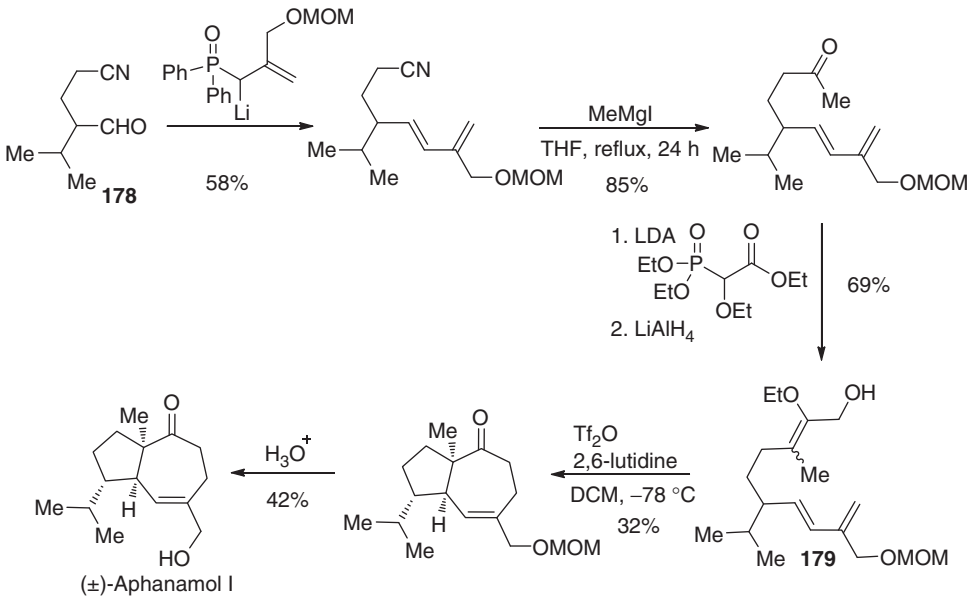
5.13.2.6 Synthetic Applications of (4 + 3) Cycloadditions of Allyl Cations

Some of the (4 + 3) cycloaddition approaches described above have been successfully applied to the total synthesis of cyclic natural products featuring cycloheptane rings, and in other cases to the partial assembly of their basic cyclic cores. In 1995, Cha and coworkers published the enantioselective synthesis of (+)-*cis*-lauthisan from oxabicycle **176**.[90] This compound was prepared using a (4 + 3) cycloaddition of 2-chlorocyclohexanone and furan under Föhlisch conditions as the key step. The same compound could also be efficiently prepared from a Schmid (4 + 3) cycloaddition of the 3-chloro-2-pyrrolidinocyclohexene and furan. The enantioselectivity was introduced using an enzyme-catalyzed acetylation of the *meso* intermediate **177** (Scheme 11).



Scheme 11

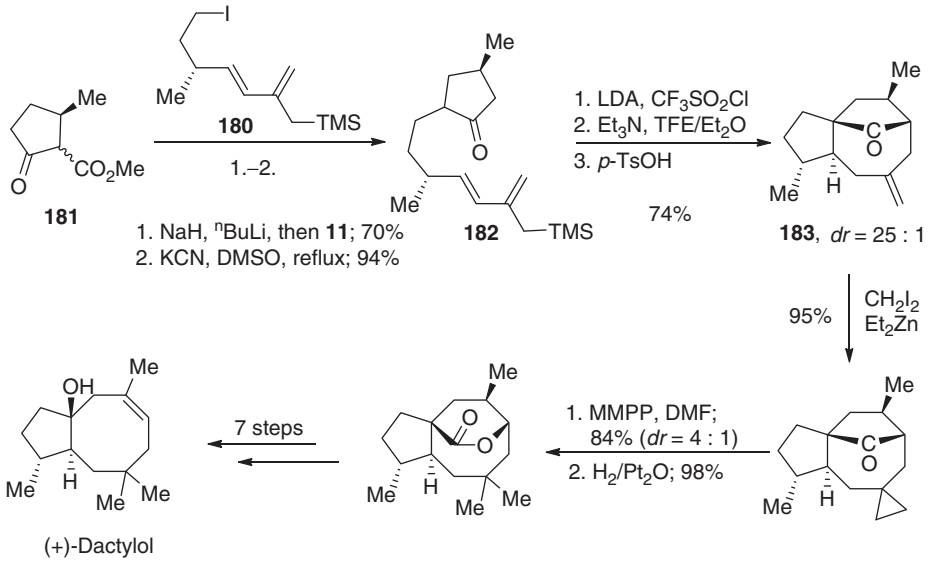
In 1997, Harmata et al. described the total synthesis of racemic aphanamol I, using as the key step an intramolecular (4 + 3) cycloaddition of the 2-ethoxyallyl alcohol precursor **179**, which was synthetized from readily available aldehyde **178** relying on phosphorous chemistry to construct the double bonds. Although the cycloaddition reaction is low yielding, it establishes the core of the molecule in a single step, and therefore allows for a short synthetic approach (Scheme 12).[91]



Scheme 12

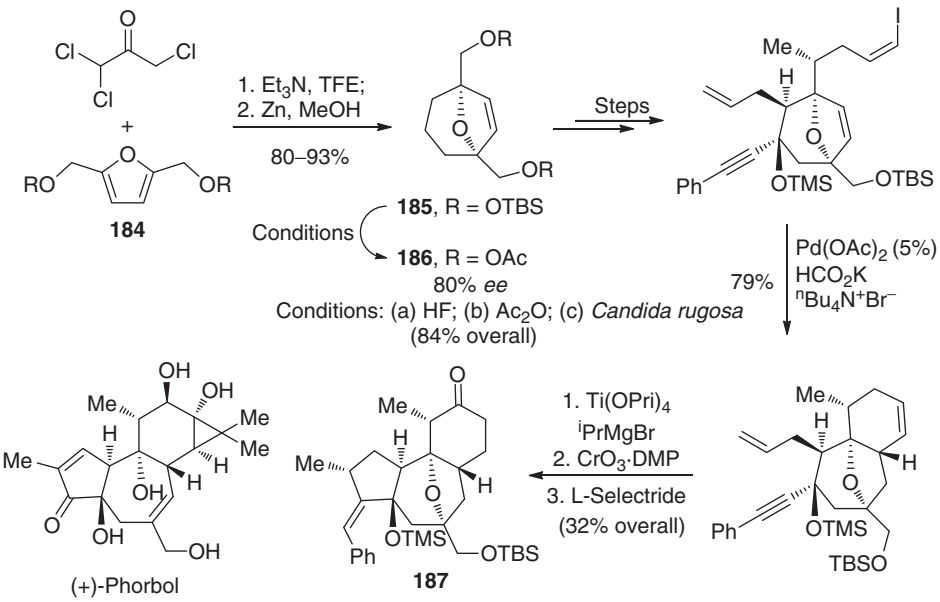
In 2000, the group of Harmata reported another interesting example of a synthetic application of a (4 + 3) intramolecular cycloaddition via allyl cation intermediates in the synthesis of (+)-dactylol.[92] In this case the reactive oxyallyl cation is embedded

in a cyclopentane ring, so that the cycloaddition is indirectly producing a cyclooctanic system. The process started by alkylation of the dianion of the ketoester **181**, prepared in a straightforward fashion from (*R*)-pulegone, with iododiene **180**, followed by decarboxylation using the Krapcho procedure (Scheme 13). Chlorination of **182**, followed by treatment of the resulting chloroketone with triethylamine and work up with *p*-TsOH afforded the tricyclic cycloadduct **183** with excellent diastereocontrol and 74% yield. Simmons–Smith cyclopropanation reaction followed by a Baeyer–Villiger oxidation with magnesium bis(monoperoxyphthalate (MMPP) afforded a 4:1 mixture of two regioisomeric compounds, the major isomer being that which resulted from migration of the less substituted carbon atom. Hydrogenative cleavage of the cyclopropyl ring to establish the required skeleton followed by several functional group transformations yielded enantiomerically pure (+)-dactylol (Scheme 13).



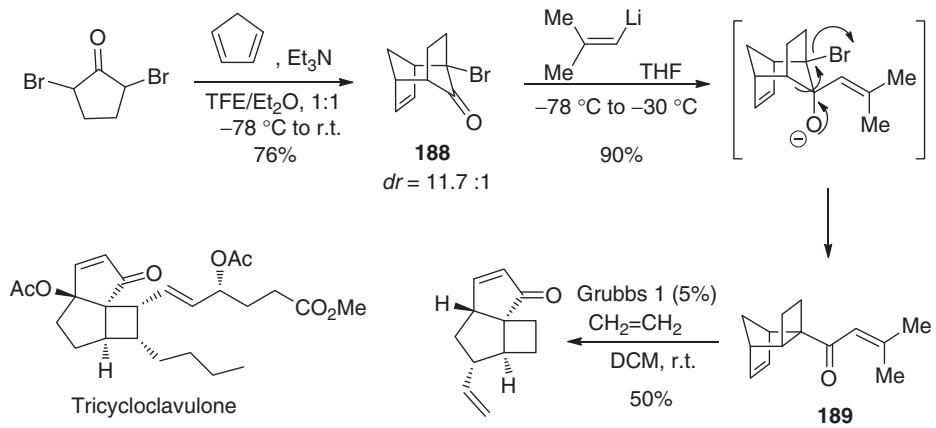
Scheme 13

In 1999, Cha and coworkers demonstrated that the intermolecular (4 + 3) cycloaddition of 1,1,3-trichloropropan-2-one to the symmetrical furan **184**, followed by dehalogenation, generates the oxabicycle **185**, which constitutes the central seven-membered ring of (+)-phorbol.[93] The other two rings were installed in consecutive reactions through a palladium-catalyzed intramolecular Heck reaction and a $Ti(OPr^i)_4$-promoted cyclization (Scheme 14). Straightforward manipulations then led to the formation of compound **187**, a known intermediate in the synthesis of (+)-phorbol previously reported by Wender.

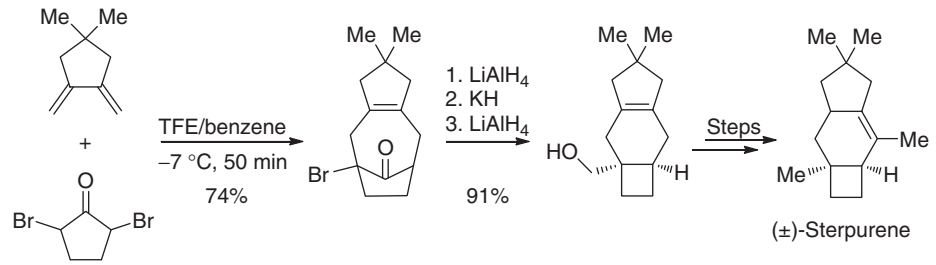


Scheme 14

An interesting protocol based on a (4 + 3) cycloaddition of cyclic oxyallyl cations precursors followed by a Favorskii rearrangement has been successfully used by Harmata for the synthesis of target-relevant fused cyclobutanic derivatives. Thus the (4 + 3) cycloaddition of 2,5-dibromocyclopentanone and cyclopentadiene gives the cycloadduct **188** in 76% yield and with high diastereoselectivity.[94] Addition of (2-methylprop-1-en-1-yl)lithium generates an alkoxide which undergoes a quasiFavorskii rearrangement to give the cyclobutane product **189**. Subsequent ring closing metathesis generates the basic tricyclic core of tricycloclavulone (Scheme 15). The same strategy of a tandem cycloaddition–quasiFavorskii rearrangement was used to synthesize the tricyclic natural product (±)-sterpurene (Scheme 16).[95]



Scheme 15



Scheme 16

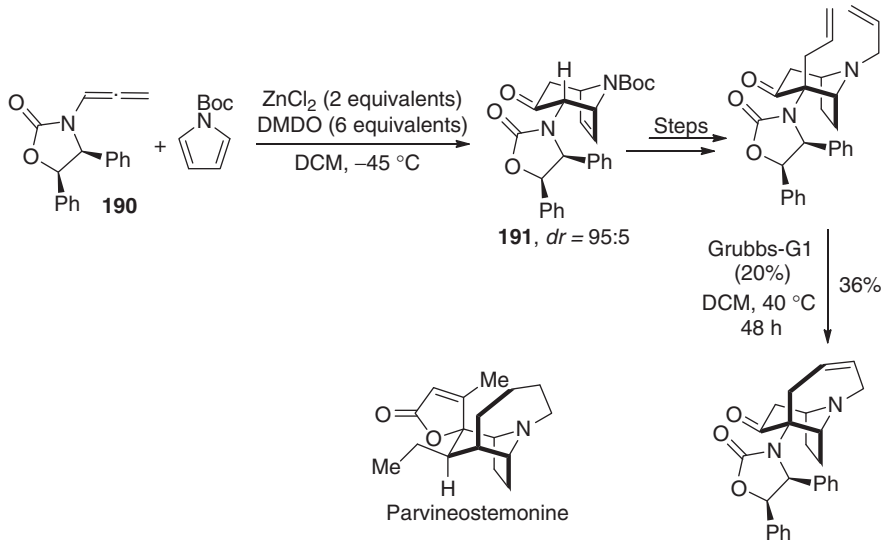
Hsung and coworkers have successfully used their allenamide (4 + 3) cycloaddition methodology in the synthesis of the sketetal core of parvineostemonine. The key step of the process is a (4 + 3) annulation between the allenamide **190** and a *N*-Boc-protected pyrrole, which takes place with good yields and excellent diastereoselectivity. The other ring of the natural product was installed by means of a ring closing metathesis with the first generation Grubbs catalyst (Scheme 17).[55]

Another interesting synthetic application of (4 + 3) cycloadditions involving oxyallyl cations was reported by Cha in the context of a total synthesis of alkaloids such as colchicine.[38] In this case the four-carbon cycloaddition component is a furan embedded into a tricyclic system (**193**), which itself is prepared by thermolysis of compound **192**, whereas 3,3-((dimethoxyprop-1-en-2-yl)oxy)trimethylsilane was used as the oxyallyl precursor. The diastereoselectivity derives from the dienophile approaching from the less hindered face of the furan in a 'compact' mode. Double elimination to the tropone **194** and final Boc deprotection and acetylation generated (–)-colchichine with ~90% *ee* (Scheme 18).[38a] A related methodology has been used by the same group for the synthesis of the isoquinoline alkaloids imerubrine, grandirubrine, and isoimerubrine.[38b]

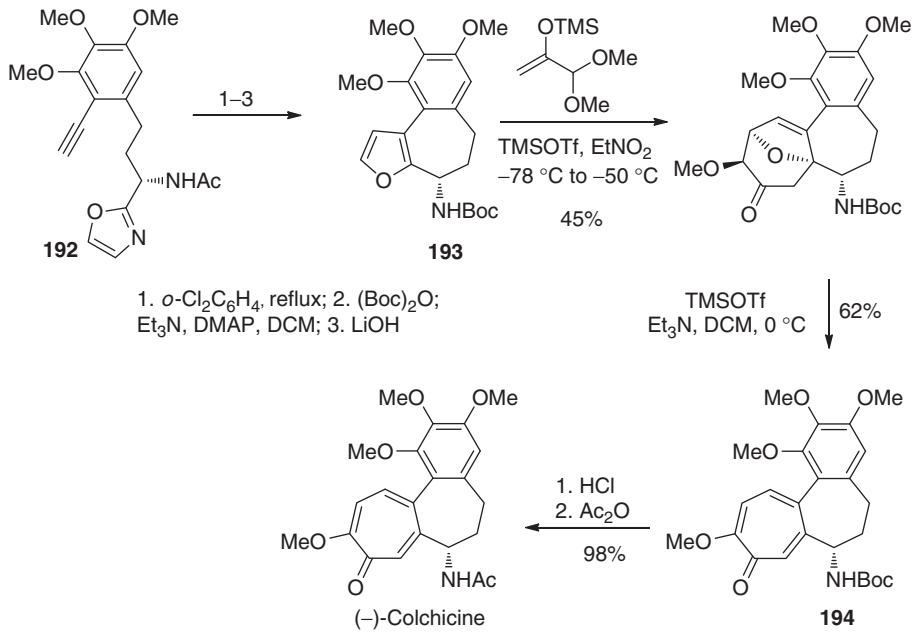
A Lewis acid-promoted cycloaddition of the oxyallyl cation precursor **196** and furan **195** was used by Watanabe et al. to synthetize the oxabridged cycloheptane derivative (±)-urechitol A in racemic form (Scheme 19).[40] The oxafunctionalization of the cycloheptane adduct resulting from the cycloaddition is well poised to ensemble the required cycloheptyl system of urechitol in just two steps, consisting of a Sharpless epoxidation and a methanol-assisted intramolecular epoxide opening. The product **198** was converted to the natural product in nine steps (Scheme 19). Thus the synthesis of racemic urechitol A was eventually achieved in 12 steps with an overall yield of 2.3%

Recently, several allyl cation-based approaches have been reported to streamline the synthesis of the antitumoral polycyclic products of the cortistatin family. Chiu and coworkers accomplished an asymmetric synthesis of the pentacyclic core of this molecule (**202**) using a highly efficient and diastereoselective intramolecular (4 + 3) cycloaddition of the enantiopure epoxy enol silane **200** as the key step (see Section 5.13.2.2.5), which was prepared in seven steps from cyclopentadienone **199** (Scheme 20).[29]

Finally, very recently Funk et al. reported a 20-step total synthesis of (±)-cortistatin J involving an intramolecular (4 + 3) cycloaddition between a disubstituted furan and a (*Z*)-2-(trialkylsilyloxy)-2-enal as the key transformation. The reaction takes



Scheme 17

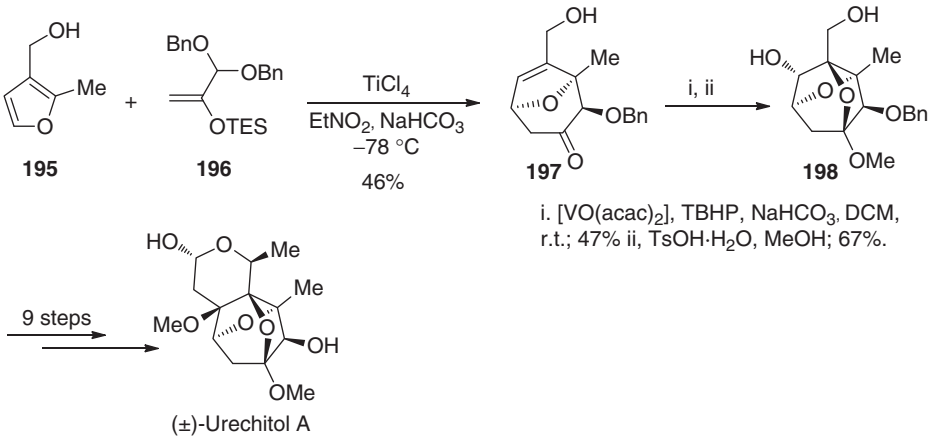


Scheme 18

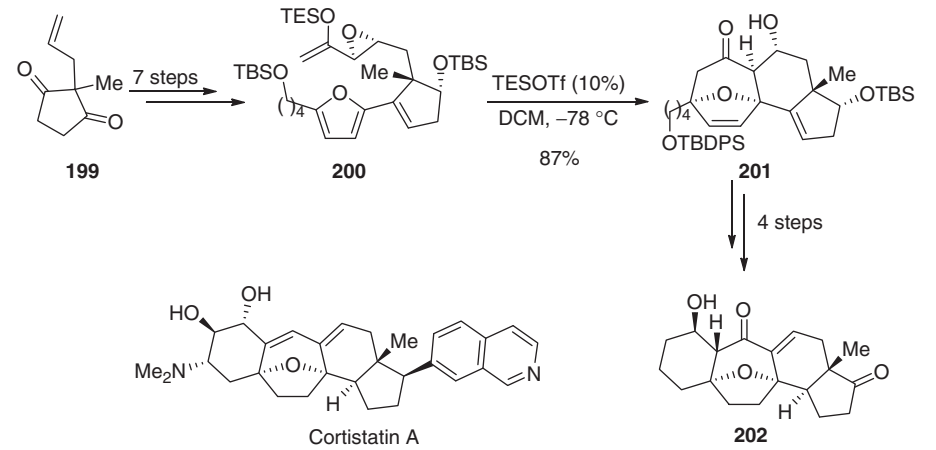
place in good yield and with total diastereoselectivity, forming four new stereocenters of the tetracyclic compound **204**, which is very similar to the compound **201** prepared by Chiu (Scheme 20) in racemic form (Scheme 21).[46]

5.13.3 (4 + 3) Cycloadditions of Donor–Acceptor Strained Cycles

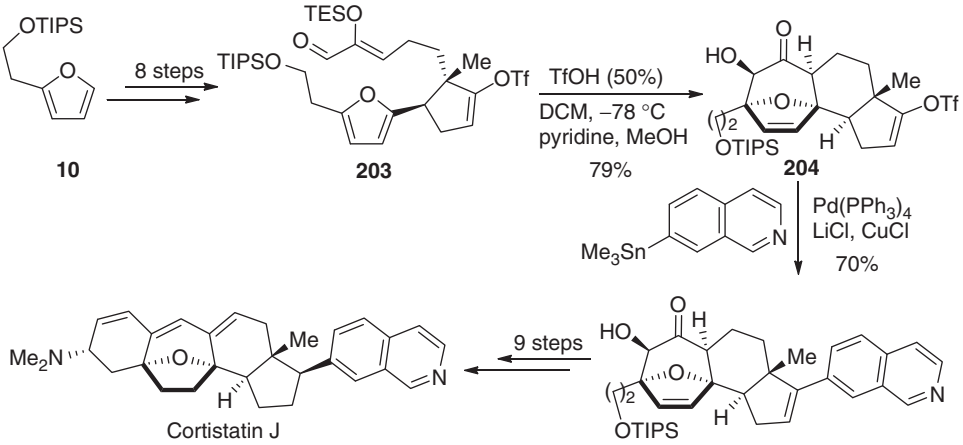
The presence of both electron-donating and electron-withdrawing substituents on a cyclopropanic ring favors ring opening to generate 1,3-carbon dipoles capable of engaging in cycloaddition reactions. In this context, Ivanova et al. have shown that 2-aryl-1,1-cyclopropanic diesters such as **205** react, on simple thermolysis, with specific dienes such as 1,3-diphenylisobenzofuran **206** to give oxabridged cycloheptanes **207** and **208** derived from a formal (4 + 3) cycloaddition.[96] This reaction provides good yields of the corresponding products, but poor *endo*:*exo* selectivities, and is restricted to cyclopropanes bearing appropriate functionalities that stabilizes the putative dipole intermediate (Table 15).



Scheme 19



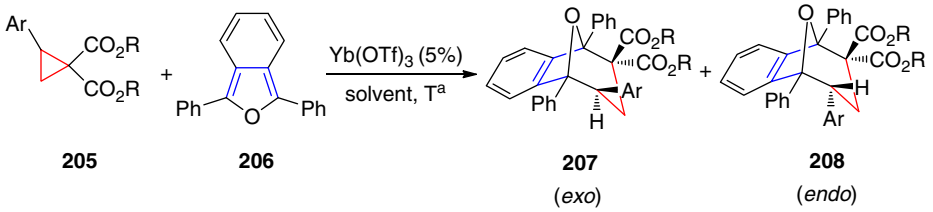
Scheme 20



Scheme 21

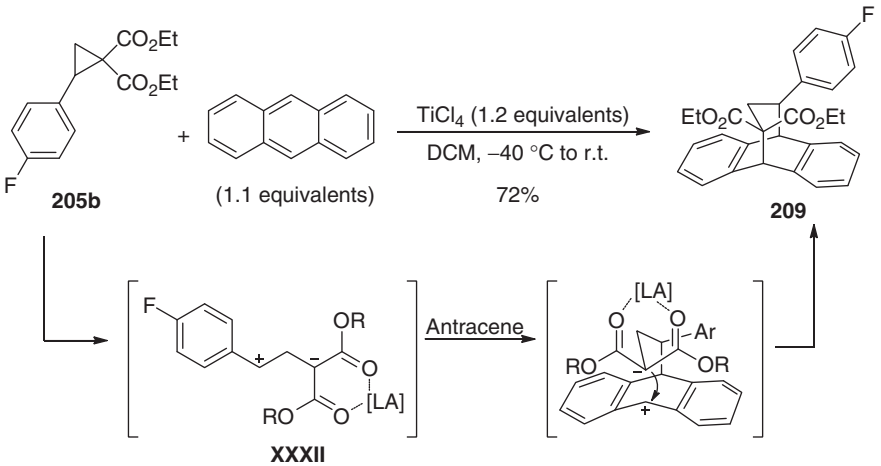
This type of 2-aryl-1,1-cyclopropane diesters also react with anthracene on treatment with a Lewis acid catalyst to give (4 + 3) adducts **209**.[97] In this case it is proposed that the reaction proceeds in a stepwise manner, consisting of initial ring opening of the cyclopropane to form a 1,3-zwitterionic species **XXXII**, followed by nucleophilic attack of the anthracene and ring closure (equation 50).

Table 15 (4 + 3) Cycloadditions of donor–acceptor cyclopropanes



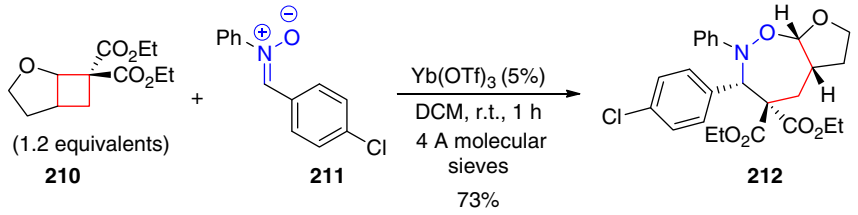
Numbers	***205***	*Ar*	*R*	*Temperature (°C)*	*Solvent*	*Yield (%)*[a]	***207:208***
1	**205a**	Ph	Et	Reflux	DCM	85	56:44
2	**205a**	Ph	Et	80	PhCl	50[b]	<1:19
3	**205b**	4-FC_6H_4	Et	Reflux	DCM	90	53:47
4	**205c**	4-$MeOC_6H_4$	Et	r.t.	DCM	86	86:14
5	**205d**	3,4,5-$(MeO)_3C_6H_2$	Me	r.t.	DCM	89	77:23
6	**205e**	2-Thienyl	Et	r.t.	DCM	92	74:26
7	**205f**	2-Furyl	Et	r.t.	DCM	84	64:36

[a]Combined isolated yield.
[b]44% of side product was also isolated.



(50)

Donor–acceptor (DA) cyclobutanes share with cyclopropanes also a high degree of strain and can therefore undergo ring-opening processes to give 1,4-carbon dipolar type of synthons. In this context, Pagenkopf demonstrated that DA-cyclobutanes like **210** participate as four-carbon components in (4 + 3) cycloadditions to nitrones (**211**), when treated with $Yb(OTf)_3$.[98] The reaction allowed structurally unique oxazepines (**212**) to be assembled in moderate-to-high yield, tolerating a wide range of nitrones. An example is shown in equation 51.

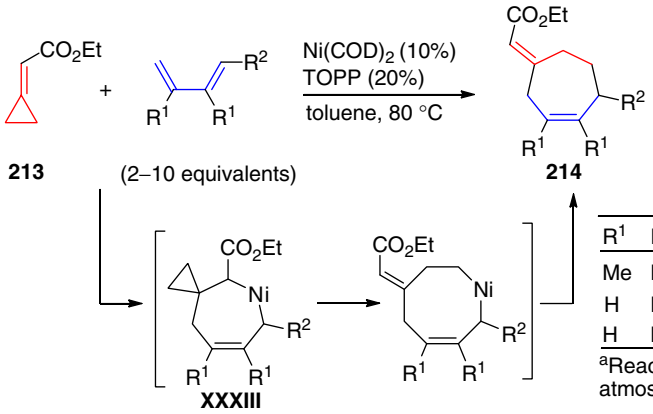


(51)

5.13.4 (4 + 3) Cycloadditions Involving Metallacyclic Intermediates

The standard mechanism of many metal-catalyzed cycloadditions of unsaturated substrates involves the formation of metallacyclic intermediates that evolve to the final cycloadduct by reductive elimination of the metal catalyst. One can envision a similar type of mechanism for achieving (4 + 3) annulations, provided suitable three-atom reaction partners are found.

Alkylidenecyclopropanes, owing to the simultaneous presence of a metal coordinating position (the double bond) and a strained ring, have been shown to work as three-carbon synthons in different types of metal-promoted (3 + 2) intermolecular and intramolecular cycloadditions to alkenes and alkynes.[99] In 2007, Saito et al. demonstrated that ethyl cyclopropylideneacetate is able to react with 1,3-dienes in presence of catalytic amounts of $Ni(COD)_2$ and tri-*o*-biphenylyl phosphate (TOPP) to give formal (4 + 3) cycloaddition products.[100] The reaction provides moderate yields of the resulting adducts and requires a controlled slow addition of both substrates to the reaction medium. The proposed mechanism involves the initial formation of a Ni–butadiene complex, followed by insertion of **213** to generate a seven-membered nickelacycle **XXXIII**. A cyclopropylmethyl-butenyl rearrangement of this intermediate followed by reductive elimination generates the observed cycloheptenyl products **214** (equation 52).



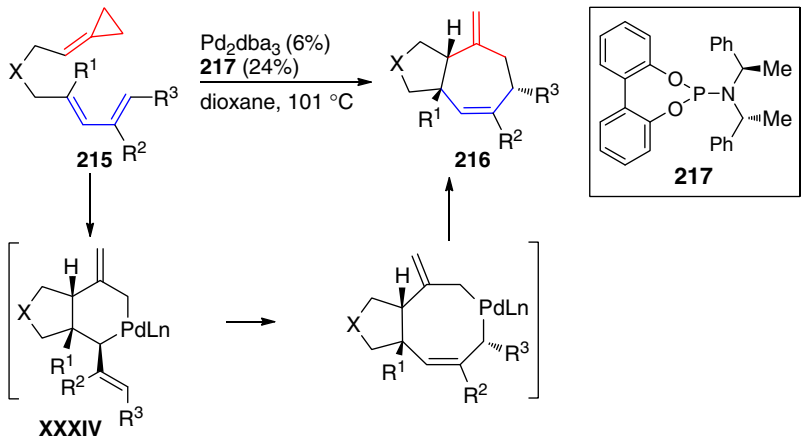
R^1	R^2	yield (%)
Me	H	70
H	H	38[a]
H	Me	45

[a]Reaction carried under atmosphere of butadiene.

(52)

Alkylidenecyclopropanes can also engage in intramolecular cycloadditions to dienes in the presence of Pd catalysts, as demonstrated by Mascareñas and coworkers.[101] The cycloaddition of substrates **215** provides better results with dienes bearing EWGs at their terminal position (R^3 = EWG, **Table 16**). In some cases, the formation of small proportions of five-membered adducts, resulting from a competitive (3 + 2) cycloaddition between the alkylidenecyclopropane and the internal double bond of

Table 16 (4 + 3) Intramolecular Cycloaddition between Alkylidenecyclopropanes and Dienes



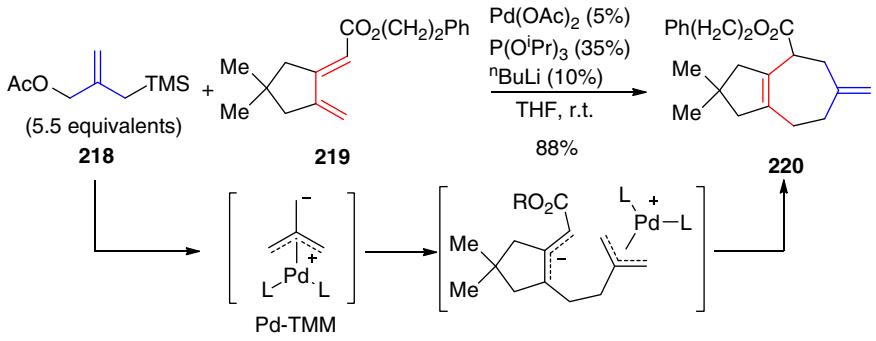
Numbers	***215***	*X*	R^1	R^2	R^3	*(4 + 3):(3 + 2)*[a]	***216**, Yield (%)*	ee *(%)*
1	**215a**	$C(CO_2Et)_2$	H	H	CO_2Et	10:1	73	47
2	**215b**	O	H	H	CO_2Et	10:1	74	45
3	**215c**	$C(CO_2Et)_2$	H	H	H	15:1	58	–[b]
4	**215d**	$C(CO_2Et)_2$	Me	H	CO_2Et	3.5:1	59	64
5	**215e**	O	H	H	Ph	>8:1	40	–[b]
6	**215f**	NBn	H	H	H	4:1	60	–[b]
7	**215g**	$C(CO_2Et)_2$	H	Me	CO_2Et	4:1	61[c]	–[b]

[a]Ratio between the (4 + 3) product **216** and the (3 + 2) derivative.
[b]Asymmetric example not reported.
[c]This yield refers to the mixture of the (4 + 3) and (3 + 2) cycloadducts.

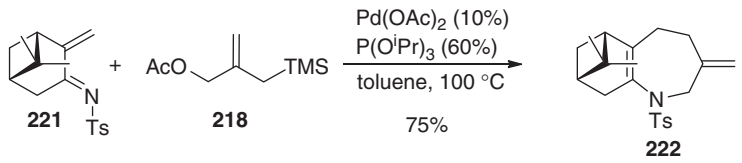
the diene, is also observed (Table 16). Preliminary studies on the development of an asymmetric version of this reaction using chiral phosphoramidite ligand **217** led to the isolation of the (4 + 3) adducts in 45–64% *ee*. Mechanistically, it has been proposed that the reaction might proceed by initial formation of palladacycles **XXXIV**, which undergo a σ–π rearrangement to palladacyclooctenes followed by reductive elimination. Reductive elimination from **XXXIV** would explain the formation of the (3 + 2)-cyclopentanic side products.[102]

5.13.5 (4 + 3) Cycloadditions via Pd–TMM and Related Species

Pd–TMM complexes have been proposed as intermediates in a variety of (3 + 2) cycloaddition reactions leading to five-membered rings.[103] Examples on the utilization of Pd–TMM complexes in (4 + 3) cycloaddition reactions with dienes are much scarcer, and restricted to dienes blocked in a *cisoid* conformation and featuring electron-withdrawing substitutents.[103] In particular, Trost et al. have shown that treatment of 3-acetoxy-2-trimethylsilylmethyl-1-propene (**218**) with a Pd(0) catalyst in the presence of excess diene **219** generates the cycloadduct **220** in good yield. Formation of five-membered ring products in addition to the seven-membered adducts is taken as evidence for a stepwise process, as outlined in equation 53.[104] Similarly, conjugated imines (**221**) also participate in the (4 + 3) cycloaddition to give the corresponding azepines (**222**), although this reaction is only efficient when the competitive (3 + 2) cycloaddition to the alkene is clearly disfavored (equation 54).[105]



(53)



(54)

Recently it has been shown that γ-methylidene-δ-valerolactones (**223**) react with Pd(0)-complexes to generate zwitterionic species related to the Pd–TMM, but with one additional carbon atom (Figure 11).

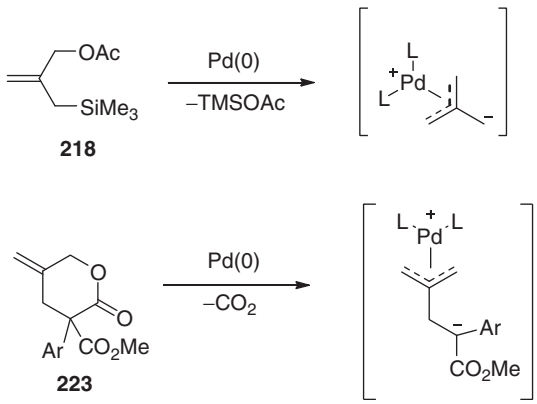
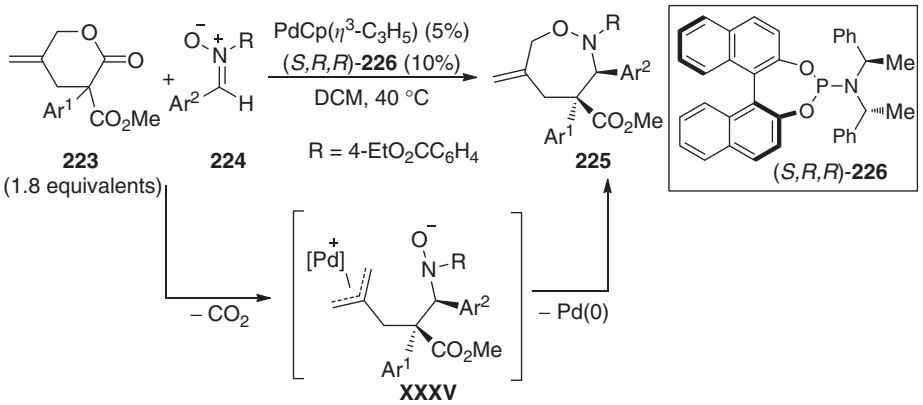


Figure 11 Zwitterionic species related to Pd–TMM from γ-methylidene-δ-valerolactones.

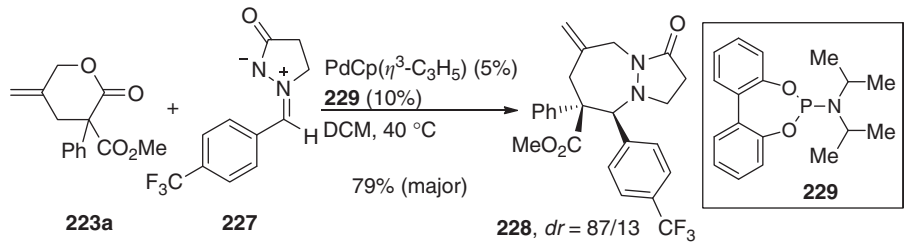
Interestingly, Hayashi and Shintani demonstrated that these precursors can behave as four-carbon components in palladium-catalyzed (4 + 3) cycloaddition with aromatic nitrones of type **224**. The reactions produce 1,2-oxazepines such as **225** in

good-to-excellent yields and with moderate-to-good diastereoselectivities. Moreover, good-to-excellent enantioselectivities could be obtained with the chiral phosphoramidite ligand (*S,R,R*)-**226**. Electron-deficient, heteroaromatic, and naphthyl valerolactones are tolerated as well as different types of aryl-substituted nitrones (Table 17). The reaction was suggested to proceed in a stepwise fashion through intermediate **XXXV**. The same palladium-catalyzed decarboxylative (4 + 3) cycloaddition was also achieved in good yield and moderate selectivity using azomethine imines such as **227** as coupling partners instead of nitrones (equation 55).[106]

Table 17 (4 + 3) Cycloadditions of γ-methylidene-δ-valerolactones with nitrones

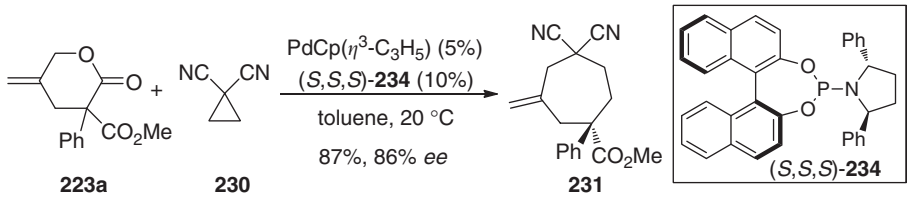


Numbers	***223***	*Ar*^{1}	*Ar*^{2}	*Yield (%)*	dr	ee *(%)*
1	**223a**	Ph	4-$CF_3C_6H_4$	98	81:19	83
2	**223b**	1-Napthtyl	4-$CF_3C_6H_4$	98	80:20	96
3	**223b**	1-Napthtyl	4-MeC_6H_4	99	70:30	89

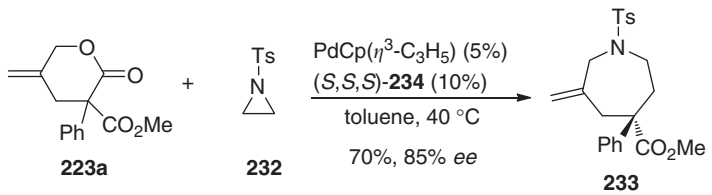


(55)

This type of γ-methylidene-δ-valerolactones **223** can also react with 1,1-dicyanocyclopropane (**230**) or *N*-tosyl aziridines (**232**) to give seven-membered ring products resulting from (4 + 3) cycloadditions. The use of a chiral phosphoramidite ligand such as (*S,S,S*)-**234**, in combination with a Pd(0) source, allowed reasonably good enantioselectivities to be obtained in these processes (equations 56 and 57).[107]



(56)



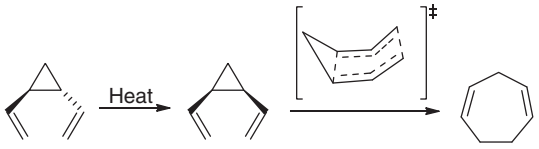
(57)

5.13.6 'Formal' (4 + 3) Cycloadditions Involving Sequential Processes

In the previous sections different types of pericylic and 'formal' (4 + 3) cycloadditions that take place in one or several steps, and involve the temporary formation of highly reactive intermediates are discussed. Now alternative annulation methodologies that rely on the formation of well-defined and relatively stable organic intermediates that can further evolve under the reaction conditions are described. Overall, these sequential transformations allow acyclic components to be converted into seven-membered cycles in a 'formal' (4 + 3) manner. Most of the examples described are based on a cyclopropanation/rearrangement sequence, but some other methods relying on the expansion of smaller rings are also discussed.

5.13.6.1 Sequential Cyclopropanation/Cope Rearrangements

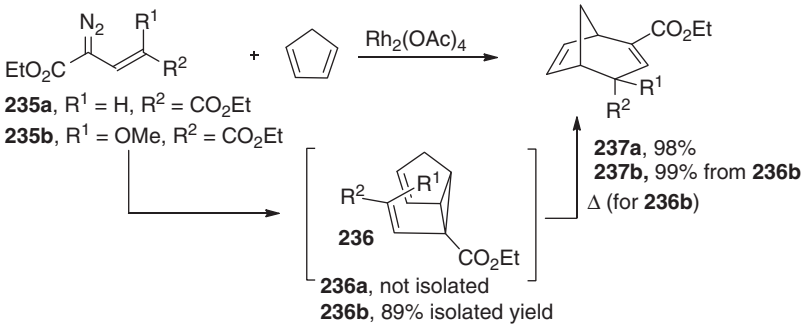
The Cope rearrangement of *cis*-divinylcyclopropanes is a well-established manner of assembling seven-membered rings.[108] The first examples of the transformation go back to the early 1960s, when Vogel discovered that 1,2-divinylcyclopropane can thermally rearrange to cycloheptan-1,4-diene (equation 58).[109] Ensuing mechanistic studies suggested that the rearrangement requires a *cis*-disposition of the cyclopropane vinyl substituents, which allows the rearrangement to proceed through a boat-like transition state. *Trans*-divinylcyclopropanes can also undergo the reaction but, in general, at much higher temperatures, most probably required to induce epimerization to the reactive *cis*-configuration (equation 58). The fact that the reaction proceeds through a well-defined transition state has important consequences in terms of predictable stereoselectivity of the process, which allows the installation of up to three stereogenic centers in the resulting cycloheptadiene.



(58)

One of first synthetic uses of the strategy was published in the late 1970s by Wender and coworkers as part of their effort to develop efficient synthesis of terpenoid skeletons.[110] In this as well as in other applications, the required divinylcyclopropane precursors were usually assembled by reacting cyclopropylmetal derivatives with appropriate acceptors. A more practical way to obtain the required substrates consists of the cyclopropanations of dienes using vinylcarbenes. Although achieving this transformation with good control of reactivity and selectivity is not trivial, Davies et al. has extensively demonstrated that vinylcarbenoids equipped with adjacent EWGs promote highly stereoselective cyclopropanation of dienes. The approach allows for a great variety of 'formal' (4 + 3) annulations between dienes (four-carbon components) and vinylcarbenes (three-carbon partners).[111]

Key to the success of this chemistry is the use of alkenyldiazoalkanes containing EWGs as sources of relatively stable carbene moieties, and rhodium(II) carboxylates as catalysts responsible of inducing the decomposition of the diazo compounds. Early results demonstrated that rhodium(II) acetate catalyzes the decomposition of the vinyldiazomethane **235a** in the presence of cyclopentadiene to give the bicyclo[3.2.1]octane system **237a** in 98% yield under mild conditions. The exclusive formation of the *endo* product is consistent with a mechanism involving a stereoselective cyclopropanation following Cope rearrangement. The mechanism could be confirmed by isolation of the *cis*-divinylcyclopropane **236b**. This derivative rearranges to **237b** more slowly than **236a** (i.e., it requires heating in toluene) because of the steric interference of the methoxy substituent (equation 59).[112]



(59)

The high degree of stereoselectivity of the cyclopropanation, which only gives the *cis*-divinylcyclopropane derivative, is not so unusual in the carbenoid area. Although there is no definitive explanation, the outcome can be interpreted in terms of a nonsynchronous mechanism with charge-buildup in the transition state. The diene approaches the carbene 'side-on' from the side of the EWG group and avoiding steric collisions with the catalyst; the EWG substituent of the carbene contributes to favor a preferred orientation to give *cis*-dialkenylcyclopropane products.[113] The model also explains the lower reactivity of *trans*-alkenes because they have a substituent which unavoidably points directly toward the rhodium catalyst surface (**Figure 12**).

The nonsynchronous nature of the reaction appears also to be consistent with other observations, such as the higher diastereoselectivities of the cyclopropanation reactions in the case of electron-rich alkenes. Apparently, in carbenoid systems lacking the combination of donor (i.e., alkene) and acceptor (i.e., EWG) functionalities, the trajectory for the alkene approach is less rigorously defined, leading to a lower overall diastereoselectivity.

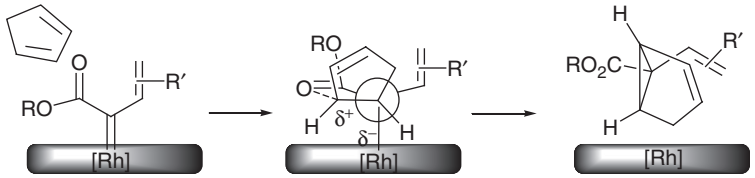
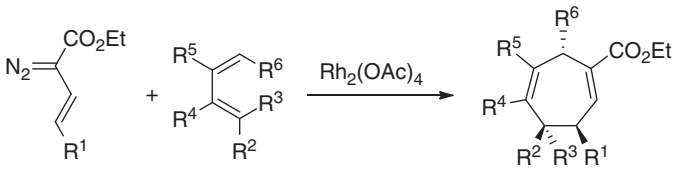


Figure 12 Mechanistic view of the tandem Rh-catalyzed cyclopropanation/Cope rearrangement.

Nonsymmetric acyclic dienes are also effective partners in the formal cycloaddition to α-ester alkenyldiazo compounds of type **235**; however, in some cases the efficiency of the reaction is lower than with cyclopentadiene because of the formation of a higher proportion of unproductive *trans*-cyclopropane intermediates. In any case, a wide range of dienes participate in the process to give an interesting variety of substituted cycloheptadienes **238** (Table 18). The regioselectivity of the reaction is very good, because of the preferred cyclopropanation of the less-substituted double bond of the diene.[113b]

Table 18 Formal (4 + 3) cycloaddition of vinylcarbene **235** and dienes[a]



235 **238**

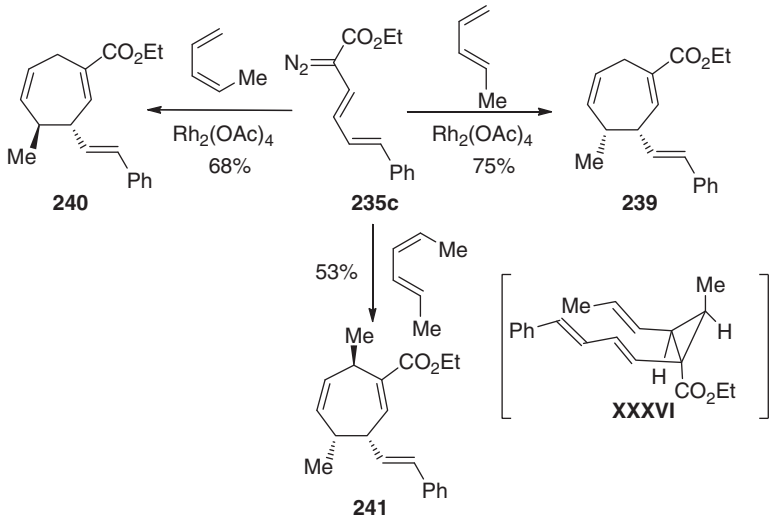
Numbers	***235***		*Diene*					*Yield (%)*
		R^1	R^2	R^3	R^4	R^5	R^6	
1	**235a**	CO_2Et	Me	Me	H	H	H	58[b]
2	**235a**	CO_2Et	Me	Me	H	Me	H	63[b]
3	**235a**	CO_2Et	H	H	Me	Me	H	49[b]
4	**235c**	CH=CHPh	Me	Me	H	H	H	80
5	**235c**	CH=CHPh	Me	Me	H	Me	H	59

[a] $Rh_2(OAc)_4$ (1–5%), refluxing DCM.
[b] The formation of 13–14% of the *trans*-cyclopropane is also observed.

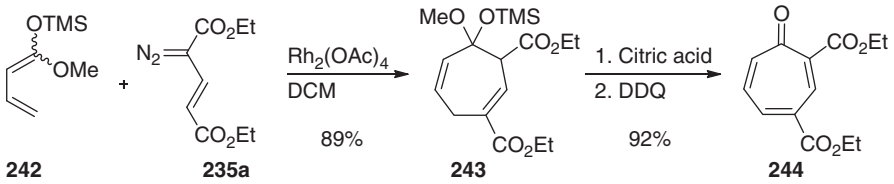
The performance of the diazoderivative **235c** with a series of sterically defined dienes provided a great deal of information on the regioselectivity and stereoselectivity of this type of vinylcarbenoid reactions (Scheme 22). In the case of (*E*)- and (*Z*)-1,3-pentadiene, the transformation provides cycloheptadienes **239** and **240**, respectively, resulting from the cyclopropanation of the most accessible double bond of the diene and a stereospecific Cope rearrangement. As already commented, cyclopropanation with vinylcarbenes is sensitive to steric hindrance in the alkene, and (*E*)-alkenes are less effective to capture the carbene than the related (*Z*)-counterparts. Therefore, reaction of **235c** with (*E*,*E*)-2,4-hexadiene failed to generate a cycloheptadiene product, whereas the reaction with (*E*,*Z*)-2,4-hexadiene proceeded smoothly to generate the cycloheptadiene **241**, the stereochemistry of which is consistent with exclusive cyclopropanation of the *cis* double bond to give intermediate **XXXVI**.[113b]

Oxygenated dienes are also excellent partners in the (4 + 3) cycloaddition with vinyldiazoacetates, because their initial cyclopropanation is more stereoselective than that of alkyl-substituted dienes. The use of highly oxygenated dienes like **242** offers a direct approach to tropones and tropolones. The cycloadduct **243** is formed in a very good 89% yield,[114] and can be readily transformed into the tropone **244** by hydrolysis with citric acid followed by DDQ oxidation (92% overall yield, Scheme 23).

Particularly interesting from the constructive point of view is the (4 + 3) cycloaddition chemistry of cyclic dienes like furans or pyrroles with alkenyldiazo derivatives. The annulation provides highly functionalized oxa- or azabicyclic systems, which are of considerable synthetic and biological interest. In the case of the cycloaddition of furans, care must be taken for the competitive formation of triene products such as **247**, arising from ring opening of a zwitterionic-like intermediate **XXXVII**. This side reaction

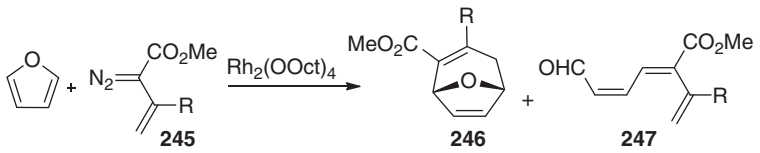


Scheme 22



Scheme 23

depends on the furan substituents, but can be avoided to some degree with the vinylcarbenoid **245b**, which is equipped with a *β*-silyloxy group that favors the ring closure to **246b** (equation 60).[115]



245	R	246[a]	247[a]
a	H	51	15
b	OTBS	90	0

[a]Isolated yields.

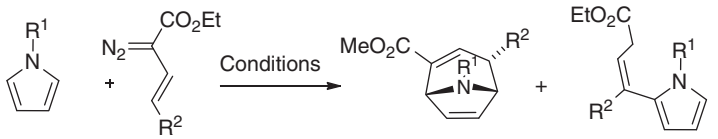
(60)

In the case of pyrroles it is important to note that the direct reaction of vinyldiazomethane with pyrrole leads to addition (i.e., **249**) rather than the cycloaddition products **248**. However, acylation of the nitrogen to decrease the electron richness of the pyrrole unit allows for efficient (4 + 3) cycloadditions (Table 19, entries 1–4).[116] The products are formed as *endo* isomers, consistent with the stereochemistry expected for a tandem cyclopropanation/rearrangement sequence. In the case of vinyldiazomethanes in which R^2 = H, the reaction gives a mixture of the cycloaddition and addition products (entry 4), but the use of slightly different reaction conditions (rhodium hexanoate/hexane) increases the proportion of the tropanic products (entry 5).[117]

Davies et al. has also extensively studied different approaches to induce asymmetry in the above (4 + 3) cycloadditions. The presence of an ester group in the vinyldiazoacetates can serve as a linking position for introducing chiral auxiliaries such as lactate or pantolactone. The strategy has allowed the annulation of silyloxy-substituted vinyldiazomethanes **250** with different furans, with very high diastereoisomeric excesses (Table 20).[115c]

The asymmetric induction can be rationalized by assuming that the carbonyl group of the auxiliary (e.g., (*R*)-pantolactone) interacts with the carbenoid as shown in Figure 13. This array allows efficient transfer of chiral influence to the carbenoid position, because one of the faces of the carbene is blocked and the furan will approach the carbene from the other, more accessible face.

Table 19 Formal (4 + 3) cycloaddition of pyrroles and vinylcarbenes

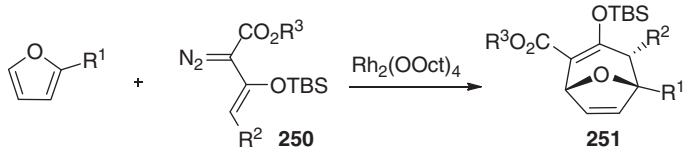


235 **248** **249**

Numbers	*R*[1]	*R*[2]	*Conditions*[a]	***248**, Yield (%)*	***249**, Yield (%)*
1	H	CO_2Et	A	0	71
2	CO_2Me	CO_2Et	A	62	0
3	CO_2Me	Ph	A	53	0
4	CO_2Me	H	A	35	30
5	CO_2Me	H	B	75	3

[a]Conditions A: pyrrole (5 equivalents) $Rh_2(OAc)_4$ (1%), DCM, reflux and conditions B: pyrrole (5 equivalents), $Rh_2(OHex)_4$ (1%), hexane, reflux.

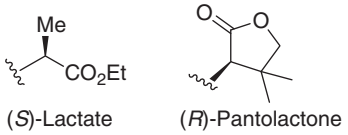
Table 20 Diastereoselective formal (4 + 3) cycloadditions[a]



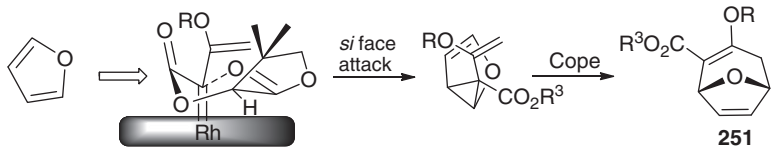
250 **251**

Numbers	*R*[1]	*R*[2]	*R*[3]	de *(%)*	*Yield (%)*
1	H	H	(*S*)-Lactate	79	72
2	H	H	(*R*)-Pantolactone	94	82
3	H	Me	(*S*)-Lactate	90	62
4	H	Me	(*R*)-Pantolactone	95	75
5	Me	H	(*S*)-Lactate	75	81

[a]Conditions: **250** is added over 1 h to a refluxing solution of furan (10 equivalents) and $Rh_2(OOct)_4$ (1%) in hexane.



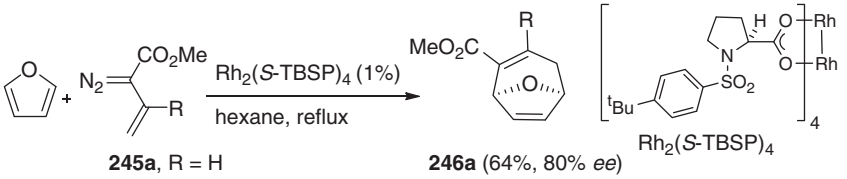
(*S*)-Lactate (*R*)-Pantolactone



R = TBS R^3 = (*R*)-pantolactone

Figure 13 Mechanistic rationale for the asymmetric induction.

Even more relevant is the possibility of inducing asymmetry in the (4 + 3) cycloaddition of achiral diazoderivatives, by using chiral rhodium catalysts. Initially, the best reaction yields with the chiral Rh(II) catalyst Rh_2(*S*-TBSP)$_4$ were obtained with *β*-silyloxy-diazovinylderivatives (**245b**), but the enantioselectivity of the reaction was modest (46% *ee*) (equation 61).[115c]



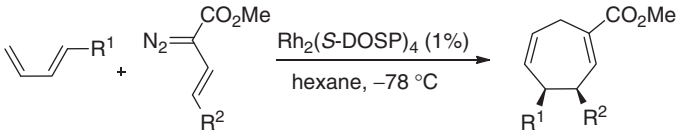
245a, R = H
245b, R = OTBS

246a (64%, 80% *ee*)
246b (94%, 46% *ee*)

(61)

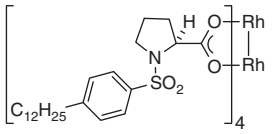
Subsequent research showed that the related rhodium(II) (*N*-dodecylbenzenesulfonyl)prolinate [Rh_2(*S*-DOSP)$_4$] is able to catalyze a highly enantioselective (4 + 3) cycloaddition of alkenyldiazoacetates with a variety of acyclic dienes. Some examples of this synthetic technology are included in Table 21.[118]

Table 21 Highly enantioselective (4 + 3) cycloadditions of alkenyldiazoacetates and acyclic dienes[a]



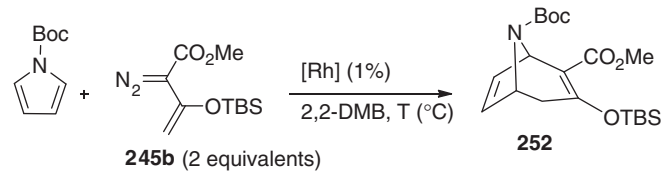
Numbers	*R*^{1}	*R*^{2}	*Yield (%)*	ee *(%)*
1	Ph	Me	87	98
2	Ph	Ph	83	98
3	Ph	H	41	73
4	Me	Ph	51	98
5	Me	CH=CHPh	82	95

[a]Conditions: vinyldiazoacetate added (0.5–2 h) over diene (5–16 equivalents) and Rh complex (1%) at −78 °C.

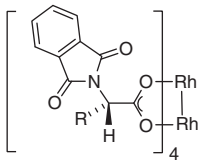


Rh_2(*S*-DOSP)$_4$

These types of catalysts are also effective in promoting the enantioselective cycloaddition of hetereodienes such as 1,2-dihydropyridines,[119] and importantly, of *N*-Boc-pyrroles,[120] which provides a straightforward enantioselective entry to the 8-azabicyclo[3.2.1]octane framework of tropanes. In this case, the best results were obtained with the catalyst Rh_2(*S*-PTAD)$_4$, and using smooth heating to improve the conversions. Importantly, the reaction can be conducted with the pyrrole as a limiting agent, which provides the opportunity to use more complex pyrroles. Indeed, 2-, 2,3-, and 2,5-substituted pyrroles do also participate in the cycloaddition, leading to good yields of the adducts **252** and excellent levels of enantioselectivity (equation 62). Later on, this same catalyst was found to be also very efficient for the cycloaddition of acyclic dienes.[121]



245b (2 equivalents) **252**



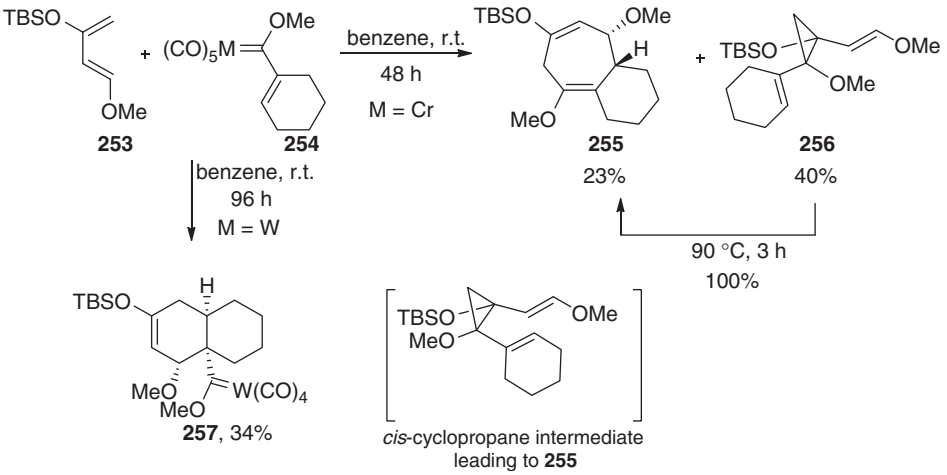
Rh_2(*S*-PTTL)$_4$: R = Ad
Rh_2(*S*-PTAD)$_4$: R = ^{t}Bu

[Rh]	T (°C)	yield (%)	*ee* (%)
Rh_2(*S*-DOSP)$_4$	23	31	29
Rh_2(*S*-PTTL)$_4$	23	34	88
Rh_2(*S*-PTAD)$_4$	23	38	91
Rh_2(*S*-PTAD)$_4$	50	86	92

2,2-DMB: 2,2-dimethylbutane

(62)

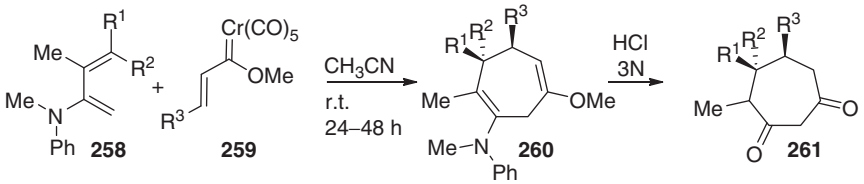
As might be expected, isolable metal vinylcarbenes can also participate in formal stoichiometric cycloadditions with dienes. Therefore, Wulff et al. demonstrated that Fischer chromium vinylcarbene **254** reacts with 1-methoxy-3-(dimethyl-*tert*-butylsilyloxy)-1,3-butadiene **253** to give the (4 + 3) adduct **255** (23%) together with the *trans*-cyclopropane derivative **256**, which can quantitatively evolve to the cycloadduct **255** on heating at 90 °C. Curiously, although the chromium carbene yields these seven-membered adduct **255**, the analogous tungsten complex leads to the Diels–Alder product **257**. Therefore, the nature of the metal has a dramatic influence on the product distribution, with the chromium derivative preferring to react as a carbene instead of as a Diels–Alder dienophile (Scheme 24).[122]



Scheme 24

Barluenga and coworkers have extended this chemistry to 2-amino-1,3-butadienes **258**, a particularly useful and readily available diene unit. Hydrolysis of the initially formed enamine cycloadduct generates cyclohepta-1,3-diones **261** with total regio- and stereoselectivity in a one-pot process (Table 22).[123] When the amino group is part of a prolinol derivative, the corresponding cyclic diketones are obtained with very high enantiomeric excesses.[123b] The same group demonstrated that 2-azadienes can also participate in the reaction, which is particularly relevant given that the strategy provides access to azepinones.[124]

Table 22 1,3-Cycloheptadiones from 2-amino-1,3-butadienes and Fischer-type carbenes[a,b]



Numbers	*R^1*	*R^2*	*R^3*	*Yield (%)*
1	CH_2OMe	H	2-Furyl	82
2	CH_2OMe	H	Ph	71
3	CH_2OBn	H	2-Furyl	78
4	CH_2OBn	H	Ph	76
5	H	CH_2OMe	2-Furyl	62

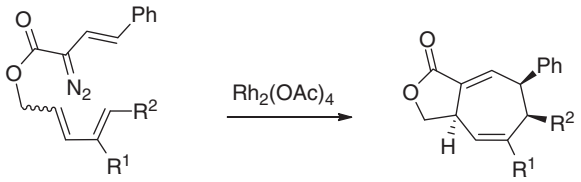
[a]Yield of isolated **261**.
[b]Equimolar amounts of **258** and **259** are used.

Obviously, the above formal cycloadditions can also be performed in an intramolecular manner. Tethering the vinylcarbene and the diene ensures highly stereoselective cyclopropanations and hence very efficient cycloadditions. In contrast to the intermolecular cases, the cyclopropanation of the internal *trans*-double bond can now take place effectively.[115b] The stereoselectivity of the cyclopropanation is controlled by the alkene geometry: *trans*-dienes **262a–c** (Table 23, entries 1–3) give the seven-membered products **263** in good yield, whereas *cis*-stereoisomers such as (*Z*)-**262c** provide stable *trans*-cyclopropanes **264c**, which do not evolve to the seven-membered adduct (e.g., entry 4).

In an interesting tandem version of this transformation, Barluenga et al. has shown that acylchromates **265** react with *β*,*γ*-*δ*,*ε*-unsaturated acyl chlorides to directly give cycloheptadiene derivatives (**268**) in good yields. The reaction takes place by initial formation of *cis*-divinyl cyclopropanes **267**, which are obtained with complete selectivity and can even be isolated in some specific cases (Scheme 25).[125]

A rather interesting alternative to generate the vinylcarbenes required for the cyclopropanation reactions relies on a metathesis reaction between alkynes and Fischer carbenes. In this context, Harvey et al. demonstrated that alkyl methoxy molybdenum carbene complexes react with alkynes to generate vinylcarbenes which can be trapped by electron-poor olefins to produce vinylcyclopropanes.[126] On this basis, the group developed a quite appealing approach to 5,7-bicarbocyclic systems from

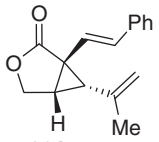
Table 23 Intramolecular formal (4 + 3) cycloadditions



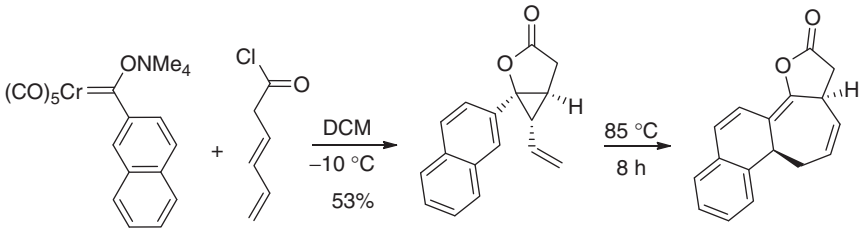
262 **263**

Numbers	***262***	R^1	R^2	***263**, yield (%)*
1	(*E*)-**262a**	H	H	68
2	(*E*,*E*)-**262b**	H	Me	76
3	(*E*)-**262c**	Me	H	60
4	(*Z*)-**262c**	Me	H	0[a]

[a] *trans*-divinylcyclopropane **264c** was formed in 94% yield.



264c

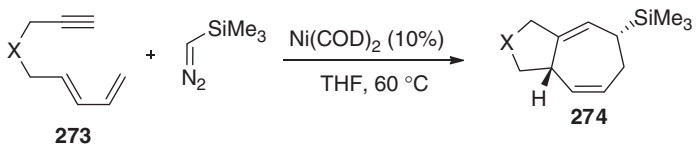


265 **266** **267** **268**

Scheme 25

1,5-dien-8-ynes (**269**) and molybdenum carbene complexes (**270**). Formally, instead of (4 + 3) annulations, the reactions could be considered as (4 + 2 + 1) processes (Table 24).[127] Interestingly, although the use of molybdenum carbenes produces the seven-membered systems **271** and **272** via the corresponding divinylcyclopropanes, chromium carbenes lead to the preferred formation of products arising from insertion of CO into intermediate **XXXVIII**.

Relying on a similar strategy, Montgomery et al. developed a very interesting catalytic version of the annulation process. In this case, the initiator is a nickel carbene species generated from trimethylsilyldiazomethane. These authors demonstrated that treatment of dienynes like **273** with trimethylsilyldiazomethane in THF with 10% of $Ni(COD)_2$ at 60 °C produces the corresponding carbocyclic or heterocyclic bicycles in good yields and excellent diasteroselectivities. Mechanistic studies suggested that the reaction proceeds by the formation of *cis*-dialkenylcyclopropanes and subsequent sigmatropic Cope rearrangement. An example is shown in equation 63.[128]

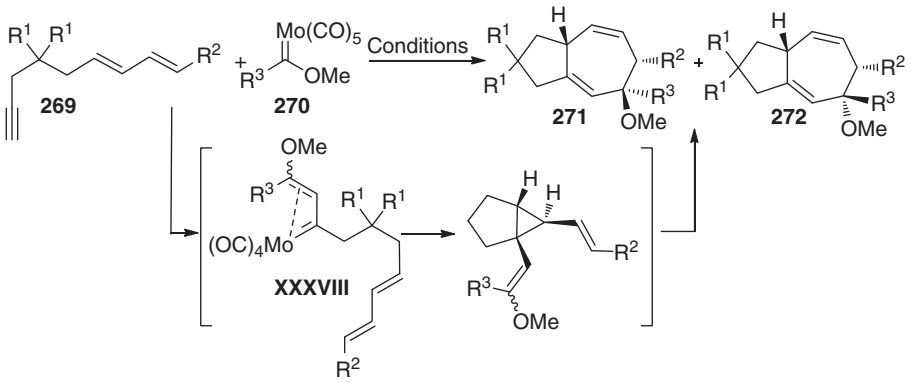


273 **274**

X	yield (%)	*dr*
$C(CO_2Me)_2$	76	13 : 1
NTs	68	95 : 5
O	65	10 : 1

(63)

Table 24 (4 + 3) Cycloadditions of *in-situ* generated vinylcarbenes



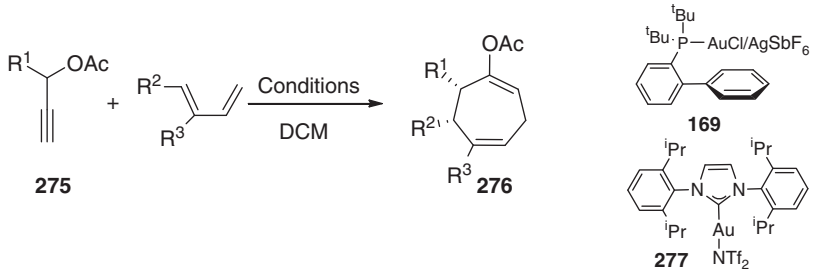
Numbers	*R*[1]	*R*[2]	*R*[3]	*Conditions*[a]	***271:272***	*Yield (%)*[b]
1	H	CO_2Et	^nBu	A	1:4.8	87
2	H	H	^nBu	A	–	0
3	CO_2Me	CO_2Me	^nBu	B	1:1.3	91
4	CO_2Me	H	^nBu	C	1:1	42
5	H	$CH=CHCO_2Et$	^nBu	A	0:1	66
6	H	$CH=CHCO_2Et$	Ph	B	1:2	50
7	H	$CH=CHCO_2Et$	2-Furyl	D	1:0	42

[a]Conditions A: Benzene, 60–70 °C, 50 min; conditions B: THF, 60 °C, 60 min; conditions C: toluene 110 °C, 40 min; and conditions D: THF, 100 °C (sealed tube).
[b]Combined yield of **271** and **272**.

Before ending this section, it must be noted that some isolated examples of related (4 + 3) annulations involving alternative ways of generating the required *cis*-1,2 alkenylcyclopropanes have been reported. Cha and coworkers used a Kulinkovich reaction to install the cyclopropane system,[129] whereas Yoshii's group published a (4 + 3) annulation based on the reaction of lithium enolates of unsaturated methyl ketones with (*β*-(trimethylsilyl)acryloyl)silanes.[130] However, this chemistry has not been further pursued.

More recently, the magic of gold catalysis has also touched this type of (4 + 3) annulations. This is a consequence of the well-known ability of gold complexes to convert unsaturated units, mainly alkynes and propargylic systems, into vinylgold carbenes.[82] Thus, Nevado's group has shown that propargyl acetates **275** react with 1,3-dienes in the presence of gold catalysts to give good yields of cycloheptadiene products **276** resulting from a formal (4 + 3) annulation (Table 25).[131]

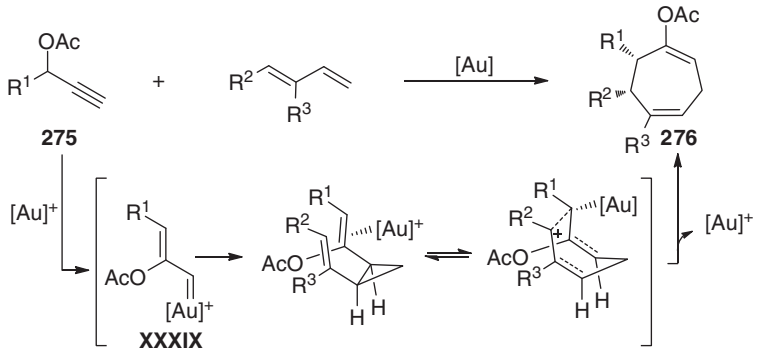
Table 25 Gold-catalyzed formal (4 + 3) cycloadditions



Numbers	*R*[1]	*R*[2]	*R*[3]	*Conditions*[a]	*Yield (%)*
1	*p*-$OMeC_6H_4$	Ph	Me	A	85
2	*p*-$OMeC_6H_4$	Ph	H	B	92
3	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	H	B	77
4	Ph	Ph	H	B	80
	Me, Me	Ph	H	A[b]	52

[a]Conditions A: **169** (5%), DCM, 30 min and conditions B: **277** (2.5%), DCM, 10 min, then $(PhO)_3PAuSbF_6$ (2.5%), 30 min.
[b]Reaction carried out at 120 °C and the product is isolated as ketone after hydrolysis of the vinylacetate with K_2CO_3/MeOH.

A possible mechanism for these transformations might consist of a gold-mediated 1,2-acyloxy migration of the propargyl ester to generate a gold carbenoid species (**XXXIX**), which reacts with the olefinic reactant to form a *cis*-cyclopropane intermediate. Subsequent gold-catalyzed Cope rearrangement through a boat-like transition state delivers the *cis*-2,3-disubstituted cycloheptenyl acetates of type **276** (equation 64).

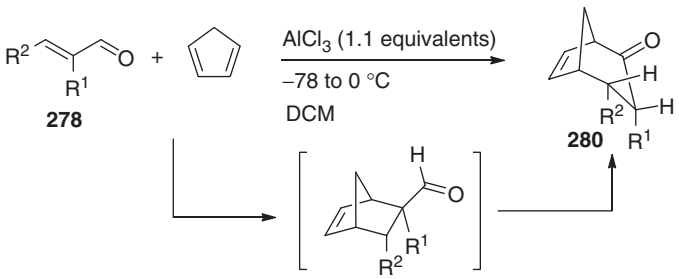


(64)

5.13.6.2 Cycloaddition/Ring Expansion Processes

As shown in Section 5.13.2.2.7, α-silyloxy-α,β-unsaturated carbonyls can participate as three-carbon partners in (4 + 3) cycloadditions with furans when treated with Lewis acid promoters. Such reactions can be classified as belonging to the group of oxyallyl cation/diene annulations.[43,44] In 2004, Davies and Dai reported that analogous α-alkyl-α,β-unsaturated aldehydes such as **278** also undergo efficient (4 + 3) cycloadditions to cyclopentadiene in presence of one equivalent of $AlCl_3$, to yield the *endo* diastereoisomers **280** with excellent stereocontrol (Table 26). The presence of an alkyl substituent in the unsaturated system (R^1 = alkyl) as well as the use of a strained diene like cyclopentadiene seems to be required. Curiously, if the temperature is kept low (−78 °C), the reaction gives (4 + 2) cycloadducts **279** instead of the seven-membered products, which on heating to 0 °C rearrange to the (4 + 3) cycloadducts. On this basis, the authors suggested that the formal (4 + 3) annulation indeed takes place in two consecutive steps, namely by a Diels–Alder (4 + 2) process followed by a ring expansion (Table 26). The most likely mechanism for the ring expansion consists of a 1,2-alkyl shift to form a tertiary cation **XL** with the alkoxide at the *endo* position. A suprafacial 1,2-hydride migration would then generate the observed *endo* (4 + 3) cycloadduct (Scheme 26).[132] This hypothesis was supported by control experiments which demonstrated that with an enantioenriched (4 + 2) adduct of type **279**, the ring-expanded seven-membered product **280**, obtained after treatment with $AlCl_3$, retains the optical purity.

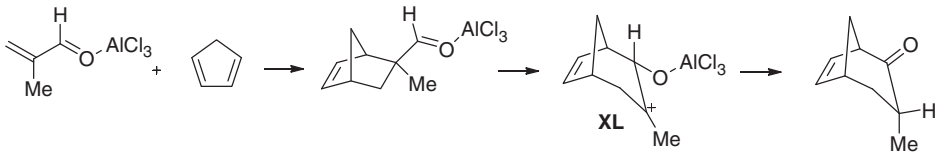
Table 26 Formal (4 + 3) Cycloaddition of α-alkyl-α,β-unsaturated aldehydes and cyclopentadiene[a]



Numbers	*R^1*	*R^2*	de[b]	*Yield (%)*[c]
1	Me	H	98	90
2	Et	H	98	80
3	$-(CH_2)_4-$		98	21
4	$-(CH_2)_3-$		98	86

[a]Conditions: diene (2.5 equivalents), $AlCl_3$ (1.1 equivalents), −78 to 0 °C, DCM, 2 h.
[b]*de* determined by ^{1}H-NMR of the crude mixtures.
[c]Isolated yield of **280**.

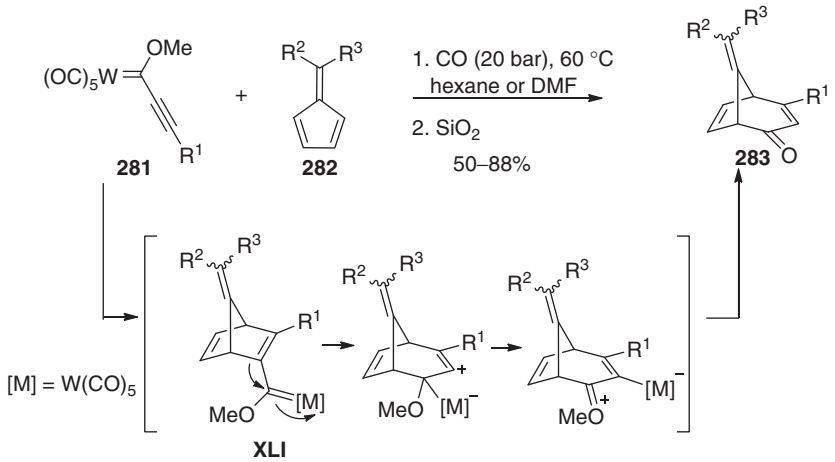
Moreover, the mechanism was further confirmed by theoretical calculations carried out by Domingo and coworkers, who analyzed the role of the Lewis acid in the competitive formation of the formal (4 + 2) and (4 + 3) cycloadducts of 2-methylacroleins with cyclopentadiene (Scheme 26).[133]



Scheme 26

Barluenga et al. found an interesting related cycloaddition/ring expansion sequence using alkynyl tungsten carbenes **281** and fulvenes **282** as cycloaddition partners (Table 27).[134] The reaction was tentatively explained in terms of an initial Diels–Alder cycloaddition to give species **XLI**, followed by a two-step ring expansion. This intermediate is stable under the reaction conditions and affords cycloadduct **283** after treatment with silica gel.

Table 27 Formal (4 + 3) cycloaddition of Fischer carbenes and Fulvenes



Numbers	*R*[1]	*R*[2]	*R*[3]	*Solvent*	E/Z *ratio*[a]	*Yield (%)*[b]
1	Ph	^{t}Bu	H	Hexane	3:1	65
2	Ph	AcO	H	Hexane	2:1	70
3	Ph	Me	Me	DMF	–	88
4	Ph	Et	Et	DMF	–	84
5	1-Cyclohexenyl	Me	Me	DMF	–	50

[a]*E/Z* ratio determined by ^{1}H-NMR of the crude mixtures.
[b]Isolated yield of **283**.

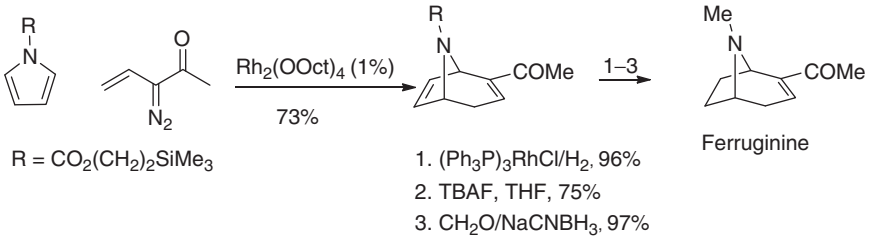
5.13.6.3 Synthetic Applications of 'Formal' (4 + 3) Cycloadditions

The relative simplicity of the above-mentioned annulation methodologies has led to the development of a variety of rather rapid and efficient synthetic approaches to different types of natural products featuring seven-membered rings. In particular, the cyclopropanation/Cope rearrangement sequence using metal-catalyzed decomposition of alkenyldiazo compounds has found important applications, most of them developed by Davies and coworkers.[135]

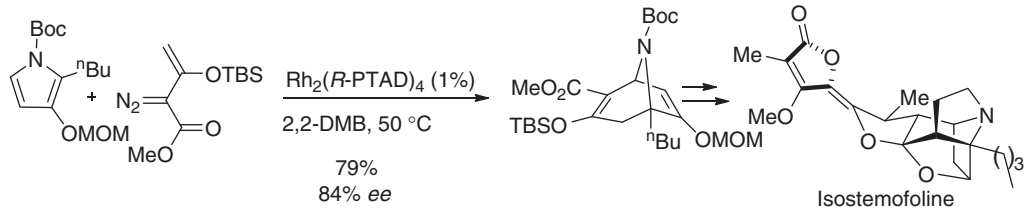
An early example of the use of this chemistry is the total synthesis of ferruginine, first in a racemic (Scheme 27) and later in an enantioselective version.[117]

More elaborated starting pyrroles can be readily converted into highly functionalized azabicyclic intermediates that have been used for the first total synthesis of complex polycyclic products such as Isostemofoline,[136] even in an enantioenriched form (Scheme 28).[120]

Aside from the construction of tropanes, more remarkable examples on the use of this annulation chemistry concern the synthesis of sequiterpenes like tremulenolide and tremulenediol (Scheme 29). The key step is a rhodium-catalyzed reaction of

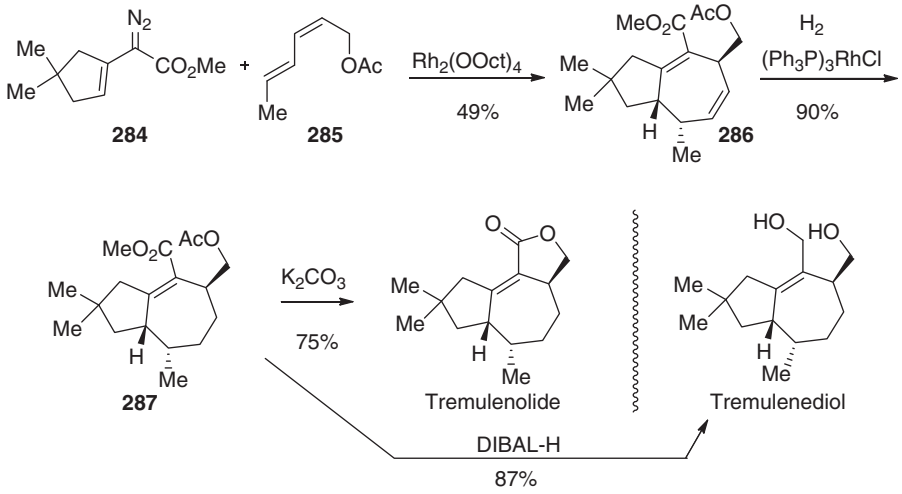


Scheme 27



Scheme 28

vinyldiazoacetate **284** with the (*E*,*Z*)-diene **285**, which generates the cycloheptadiene **286** as a single regioisomer and diastereomer in 49% yield. As previously commented, donor/acceptor carbenes such as **284** are very sensitive to steric influences during cyclopropanation. Therefore, a selective cyclopropanation of the (*Z*) double bond to generate the corresponding *cis*-divinylcyclopropane was observed in this case (see Section 5.13.6.1). The Cope rearrangement of this intermediate proceeds through a boat-like transition state to generate **286** as a single diastereomer.

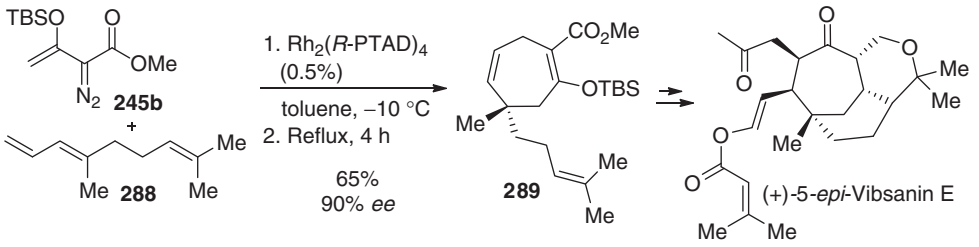


Scheme 29

The *cis*-olefin in cycloheptadiene **286** was selectively hydrogenated by Wilkinson's catalyst to form cycloheptene **287** in 90% yield. Hydrolysis of the acetyl group with aqueous potassium carbonate followed by *in situ* lactonization completes the synthesis of (±)-tremulenolide A. Alternatively, DIBAL-H reduction of the two ester groups in cycloheptene **287** resulted in the synthesis of (±)-tremulenediol A (Scheme 29).[137]

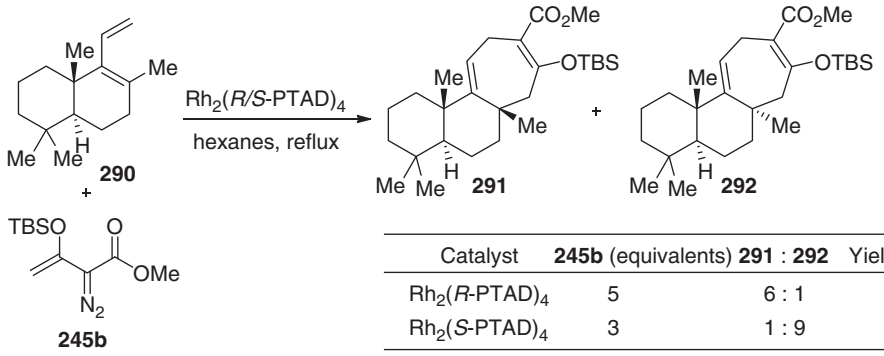
An enantioselective (4 + 3) cycloaddition was a crucial step for the first total synthesis of a single enantiomer of the diterpene 5-*epi*-vibsanin E (Scheme 30).[121] In this case the authors demonstrated that vinyldiazoacetate **245b** reacts with triene **288** in the presence of 0.5 mol% of chiral catalyst Rh_2(*R*-PTAD)$_4$ to produce the cycloheptadiene **289** in 65% yield and 90% *ee*. Therefore, this cycloaddition, which can be carried out on a 10-g scale, allows the quaternary center of the natural product to be established. Transformation of this intermediate into the product involves a 10-step process, with key steps being an intramolecular hetero-Diels–Alder reaction to establish the oxacyclic ring of 5-*epi*-vibsanin E and a conjugated addition/alkylation process.

In collaboration with the Sarpong group, Davies et al. have further demonstrated the great synthetic potential of the cycloaddition technology by developing several total syntheses of complex diterpenes of the cyanthane and barekol family. During



Scheme 30

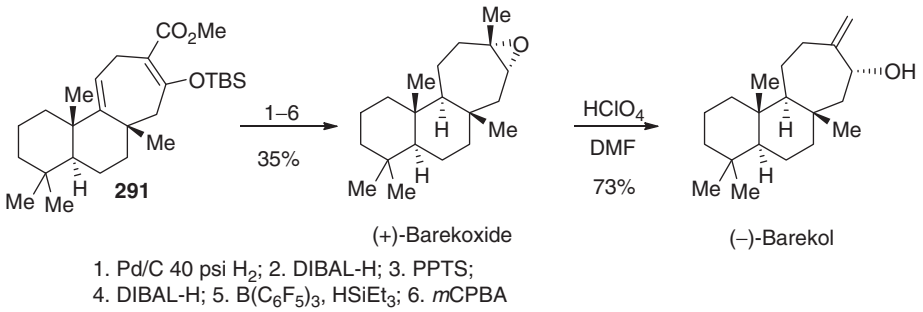
this research, the authors found that the use of chiral catalysis in the (4 + 3) cycloaddition can overwhelm the inherent directing nature of a chiral substrate. Therefore, although the reaction of diene **290** with diazoester **245b** in presence of the Rh_2(*R*-PTAD)$_4$ gave **291** as the major diastereoisomer, the use of the enantiomeric catalyst Rh_2 (*S*-PTAD)$_4$) led to the diasterosimer **292** as the major product (Scheme 31). Tricycle **291** could be readily converted to (+)-barekoxide and (–)-barekol following the sequence of steps indicated in Scheme 32.[138]



Catalyst	**245b** (equivalents)	**291** : **292**	Yield (%)[a]
Rh_2(*R*-PTAD)$_4$	5	6 : 1	65
Rh_2(*S*-PTAD)$_4$	3	1 : 9	63

[a]Combined isolated yield of **291** and **292.**

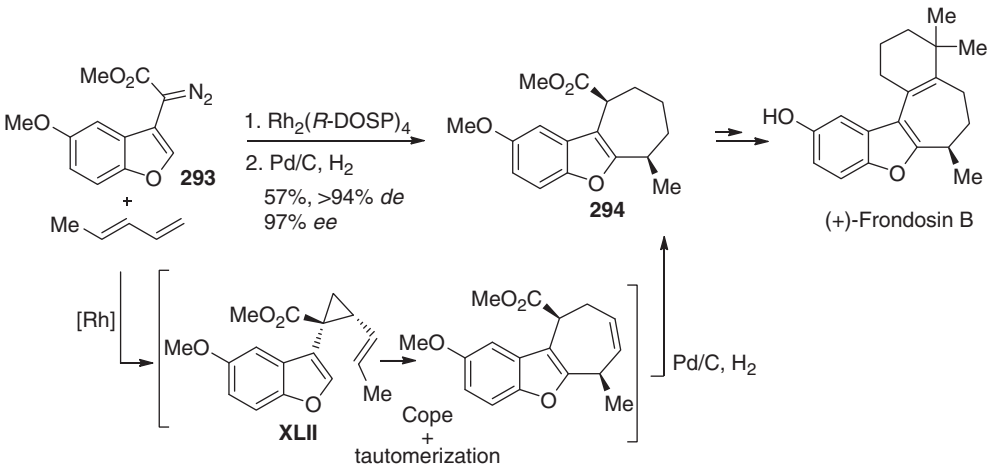
Scheme 31



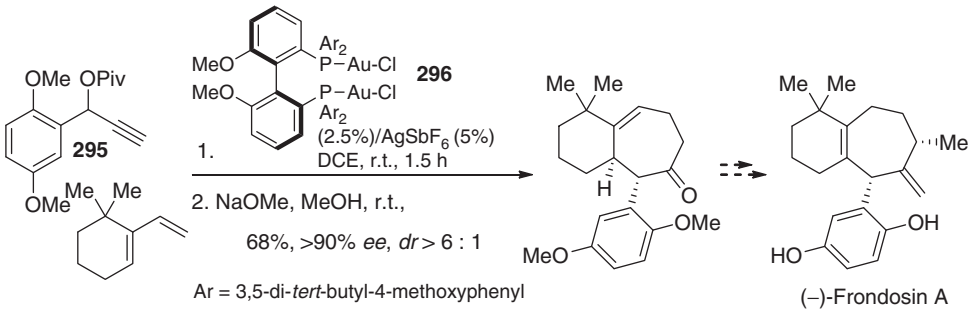
Scheme 32

The (4 + 3) cycloaddition strategy can also be accomplished with heteroaryldiazoacetates as illustrated by the formal synthesis of (+)-frondosin B (Scheme 33).[139] Reaction of heteroaryldiazoacetate **293** with *trans*-piperylene in the presence of Rh_2(*R*-DOSP)$_4$ followed by immediate hydrogenation of the product generated the reduced (4 + 3) cycloadduct **294** in 57% yield over the two steps, with excellent diastereoselectivity and enantioselectivity (97% *ee*). In this case the *cis*-divinylcyclopropane **XLII** undergoes the Cope rearrangement followed by a tautomerization to generate the aromatic benzofuran ring. Tricycle **294** was then further advanced to an intermediate used in Danishefsky's synthesis of (+)-frondosin B.[140]

Nevado and coworkers have recently described an alternative and straightforward synthetic route to (+)-frondosin A relying on a gold-catalyzed (4 + 3) annulation between propargylic acetates and dienes (see above).[131a] The authors demonstrated that treatment of pivaloate **295** with 6,6-dimethyl-1-vinyl cyclohexene in the presence of (*S*)-OMe-DTBM-BIPHEP–gold(I) complex (**296**), followed by *in situ* hydrolysis, allows the basic bicarbocycle of frondosin to be installed in an enantioselective manner. Since this bicyclic enone was recently elaborated into frondosins A and B, the approach represented a streamlined formal enantioselective synthesis of both molecules (Scheme 34).[141]



Scheme 33

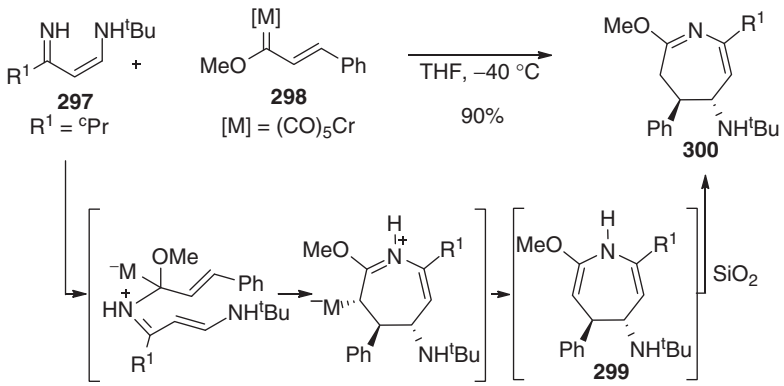


Scheme 34

5.13.7 Miscellaneous

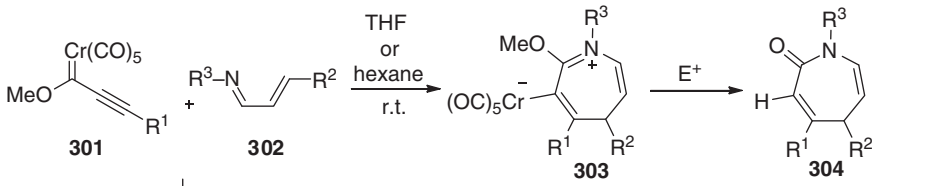
In the previous sections, the authors have discussed the most common (4 + 3) assembly strategies to make seven-membered rings organized according to mechanistic scenarios. However, there are isolated examples of other (4 + 3) annulations that take place by alternative, less common mechanisms.

As previously shown, vinylcarbenes are powerful three-carbon components in cycloaddition reaction with a broad range of dienes. In 1994, Barluenga et al. found that 4-amino-1-azadienes **297** react with alkenylcarbene complexes **298** under unusually mild conditions to give 4,5-dihydroazepines **299**.[142] Although the reaction was initially considered to proceed through a cyclopropanation/rearrangement sequence, later NMR identification of several intermediates in the reaction with tungsten vinylcarbenes[142b] led the authors propose an alternative mechanistic pathway. This route consists of an initial attack of the imine nitrogen to the carbene carbon, followed by cyclization induced by the [1,2] migration of the metal fragment, and a final thermal demetalation and decomplexation to give the observed azepines **299**. Treatment of the resulting mixture with SiO_2 allows the azepines of type **300** to be isolated in excellent yields (equation 65).



(65)

The same group also reported that simple 1-azadienes add to alkynyl carbene complexes in a similar way as shown in equation 66.[143] The reaction again must involve the initial formation of an intermediate such as **XLIII**, which evolves to the σ-complex azepine **303** by [1,2]-metallotrophic shift and cyclization. Although these complexes are air-stable, the carbon–metal σ-bond is sufficiently labile to provide, under thermal, hydrolytic, or electrophilic conditions, azepinones of type **304**. The authors were able to obtain an X-ray crystal structure of a complex **303** with R^1 = Ph, R^2 = Pr, and R^3 = Ph, which reinforced the mechanistic hypothesis.



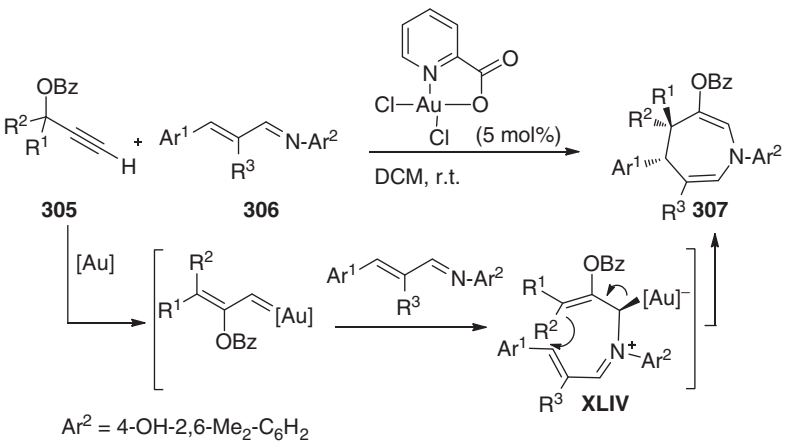
R^1	R^2	R^3	Yield **303**, **304**[a] (%)
Ph	Pr	Ph	90, 93
Ph	Bn	Ph	80, 87
Me	^{n}Pr	TMS	60, 85

[a]**304** obtained after heating **303** at 50 °C.

(66)

In the context of this chemistry, Toste and coworkers have recently reported a related approach to azepines such as **307** based on a gold-catalyzed reaction between propargylic esters **305** and α,β-unsaturated arylimines **306** (Table 28).[144] According to the authors, the reaction must involve the initial generation of a vinylgold carbene from the rearrangement of the propargylic ester. Subsequent addition of the imine nitrogen to the carbene, as in the case of the previous reactions of Barluenga, generates the allylgold intermediate **XLIV**, which undergoes an intramolecular nucleophilic addition onto the pendant α,β-unsaturated imine electrophile. The mechanism is supported by different observations, such as a rate enhancement when the Ar group in the nitrogen is more electron rich.

Table 28 Synthesis of Azepines by a gold-catalyzed intermolecular (4 + 3)-annulation[a]

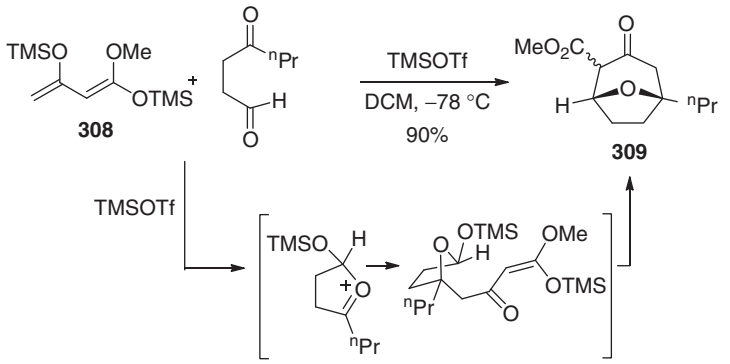


Numbers	*R^1*	*R^2*	*R^3*	*Ar^1*	*Yield (%)*	dr
1	Me	Me	Me	C_6H_5	87	–
2	Me	Me	Me	4-MeO-C_6H_4	80	–
3	4-MeO-C_6H_4	H	Br	C_6H_5	73	>20:1
4	^{i}Bu	Me	Me	C_6H_5	83	1.4:1[b]
5	Ph	Me	Me	C_6H_5	73	3.3:1[b]

[a]Propargyl ester (1.3 equivalents), catalyst (5%), DCM, r.t.
[b]Relative stereochemistry of the diastereoisomers not determined.

Finally, it should also be mentioned that Molander et al. have developed different types of annulative strategies to construct medium-sized rings which involve the condensation of a three-carbon 1,3-dinucleophile and a dicarbonyl electrophile. When the

carbonyls are in a 1,4-disposition, the strategy can be considered as a formal (4 + 3) cycloaddition, and allows interesting oxabicyclic products to be made in a rapid and practical manner.[145] Key aspects of the strategy are the use of bis(trimethylsilyl) enol ethers **308** as synthetic equivalents of β-dicarbonyl dianions and TMSOTf as Lewis acid promoter. This Lewis acid activates the less hindered carbonyl group of a 1,4-dicarbonyl compound, which then undergoes an intramolecular addition of the other carbonyl oxygen to give an oxocarbenium intermediate. Nucleophilic attack of the terminal carbon of the dinucleophilic synthon at this electrophilic center followed by cyclization generates the observed product. The reaction is quite efficient with keto-aldehydes, although a number of good yielding annulations of diketo-substrates has also been described. An example is shown in equation 67.



(67)

5.13.8 Conclusion

The (4 + 3) cycloaddition of dienes and oxyallyl cations is a classical and powerful method to assemble seven-membered rings. The past century has witnessed many developments in the area, particularly in the implementation of different types of oxyallyl cation precursors. However, in more recent years, there have been many other developments that greatly expanded the potential of the methodology from many points of view, namely, the availability of the precursors, the scope and efficiency, the implementation of substoichiometric variants, and the development of asymmetric processes. Furthermore, other alternatives to generate cycloaddition-active allyl cations have been developed, with special emphasis on metal-catalyzed processes. However, there have also been substantial advances in the discovery of different classes of (4 + 3) annulations that are not necessarily mediated by allyl cations.

Despite all these advances, truly catalytic versions of inter- and intramolecular versions of (4 + 3) annulations relying on readily accessible starting materials are still very scarce. Even rarer are the enantioselective versions of these transformations. However, the versatility of many of the processes, in particular with regard to the diene component, is not as good as one might wish. Therefore, there are still many challenges in this area, and new, and important advances are expected in the coming years. For related chapters in this Comprehensive, you can refer to Chapters 1.16, 2.07, 2.08, 2.09, 2.10, 3.17, 5.09, 5.11, 5.18, 5.19, 5.22, 5.29, 6.17, and 7.15.

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5.14 Higher Order Cycloadditions

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Glossary

Cycloaddition A reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. Cycloadditions may be pericyclic reactions or (nonconcerted) stepwise reactions.

Dynamic kinetic resolution A reaction in which one enantiomer of a racemic compound reacts selectively, with the unreacted enantiomer undergoing facile epimerization.

Exo*/*Endo These terms refer to the location of a specific motif. *Exo* (outside) and *endo* (inside) originate from the Greek language.

Kinetic resolution A reaction in which only one enantiomer of a racemic compound reacts selectively.

Structure–activity relationship The relationship between the chemical properties of a molecule and its biological activity. Comparison of chemical and biological properties can provide information on the mechanism of a particular molecule/functional group.

Synthon A motif that represents a synthetic equivalent. A synthon can either be described as an actual compound or as cation/anion equivalents. This terminology is often utilized when describing retrosynthesis.

5.14.1 Introduction

Over the past 60 years, higher-order cycloadditions have become extremely useful tools in organic chemistry because these reactions generate complex molecular architectures from readily accessible building blocks with predictable regio-, diastereo- and enantioselectivity.[1] Additionally, the combination of simple precursors in multicomponent transformations has the potential for broad substrate scope and high atom efficiency. Hence, it is unsurprising that there are many applications in medicinal, agrochemical and materials chemistry, which attests to their continued importance in the construction of complex cyclic systems. This chapter focuses on seminal examples of higher-order cycloadditions within the past 20 years and provides a comprehensive overview of a variety of approaches to small- and medium-sized carbo- and heterocycles.

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The chapter commences with [‘$m+n$’] cycloadditions using the size of the synthon to categorize the various reactions. For example, [‘$3+n$’] will be followed by [‘$4+n$’], which will precede [‘$5+n$’], and so on. The sections on [‘$m+n+o$’] and [‘$m+n+o+p$’] are also categorized in an analogous manner.

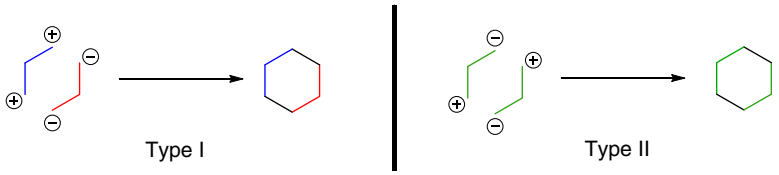
5.14.2 [‘$m+n$’] Cycloadditions

The first section of the chapter outlines various [‘$m+n$’] cycloaddition reactions ($m=3$–8, $n=2$–8), however, [‘$m+1$’] (*see* Chapter 5.24), [‘$2+2$’] (*see* Chapters 5.04 and 5.07), [‘$3+2$’] (*see* Chapters 4.21, 4.22, and 5.08), [‘$4+2$’] (*see* Chapters 5.09, 5.10, and 5.11) and [‘$4+3$’] cycloadditions (*see* Chapter 5.13) are not described, in addition to all photochemical cycloadditions, including arene–ene [‘$5+2$’] reactions (*see* Chapter 5.04). The nomenclature used to describe intra- and intermolecular reactions follows the recently described nomenclature for categorizing these types of reactions.[1q,2] For example, intermolecular reactions are denoted by $[m+n+o]$, whereas intramolecular are represented by $[(m+n+o)]$. Finally, the three-component semi-intermolecular cycloadditions are represented by $[(m+n)+o]$ and generic cycloadditions by [‘$m+n+o$’].

5.14.2.1 [‘3 + 3’] Cycloadditions

The [‘$3+3$’] cycloaddition represents one of the most studied reaction of this class and has provided an attractive alternative to the classical [‘$4+2$’] cycloaddition. Pioneering work by Link, Prelog, Stork and Seebach provided the basis for the development of this field over the past 20 years, with the introduction of a plethora of three-atom synthons.[3] These synthons can generally be classified on the basis of an anion/cation equivalent, which can have a profound effect on the outcome of a given [‘$3+3$’] cycloaddition reaction. Type I describes the coupling of donor–donor and acceptor–acceptor synthons, which afford six-membered adducts. The alternative reaction (Type II) relies on the implementation of two 1,3-dipoles, which combine to generate six-membered rings.

The following section focuses on various three-atom synthons that are capable of promoting [‘$3+3$’] cycloaddition reactions. As depicted in Scheme 1, acceptor–acceptor synthons are only permitted to react with donor–donor synthons, whereas donor–acceptors combine with an additional donor–acceptor to generate the cycloadduct. Several advantages and disadvantages exist for each type of system, for example, Type I dianions and dications are relatively unstable compared to the corresponding Type II processes involving 1,3-dipoles, however, the latter have to rely on orthogonal reactivity of each component to minimize homodimerization and polymerization. Figure 1 highlights various synthons that participate in Type I and II [‘$3+3$’] cycloadditions and the following sections focus on reactions using these types of reactive intermediates. Furthermore, because there are a significant number of combinations, some examples will be covered in other sections of the chapter.



Scheme 1 Potential classes of [3 + 3] cycloadditions.

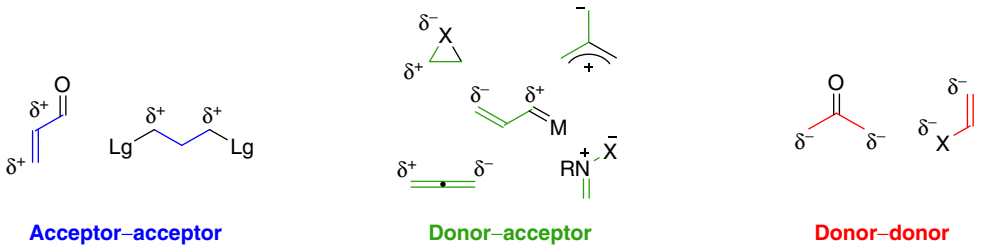
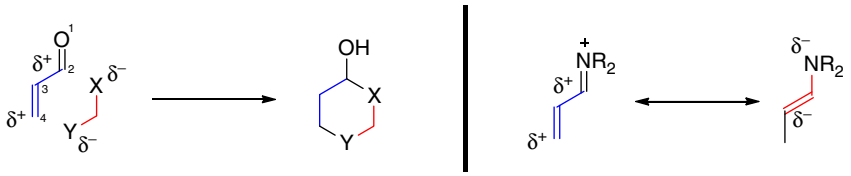


Figure 1 Various three-atom synthons utilized in [‘$3+3$’] cycloadditions.

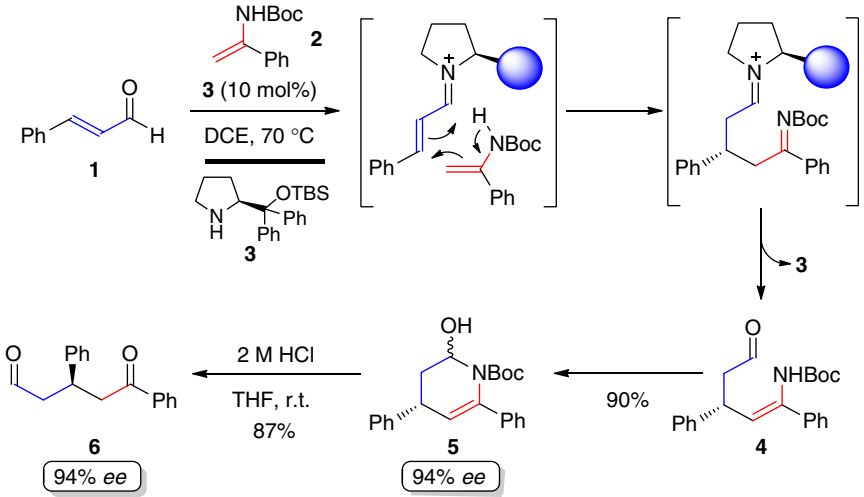
5.14.2.1.1 Michael addition-promoted reactions

Many cycloadditions take advantage of the inherent electron deficiency at the 2- and 4-positions of α,β-unsaturated carbonyl compounds. Hence, the ability for these intermediates to react with 1,3-dianions provides an opportunity for a Type I [‘$3+3$’] cycloaddition, in which the enantioselective variants utilize iminium ion catalysis. A key component with this approach is that imines, derived from α,β-unsaturated carbonyl compounds, display antipodean behavior through their ability to tautomerize to the corresponding enamines (Scheme 2).



Scheme 2 General mechanism of the Michael addition-promoted ['3 + 3'] cycloaddition.

Hayashi and Wang independently reported the catalytic enantioselective aza-[3 + 3] cycloadditions in 2008.[4] Hayashi and coworkers serendipitously discovered this process while investigating the use of enamines as enolate equivalents in the conjugate addition reaction with enals (Scheme 3). The unexpected cyclization occurred via the rapid ring closure of **4** to generate piperidine **5**, rather than the expected hydrolysis of the enamine in **4** to provide *δ*-keto aldehyde **6**. Iminium ion activation of the *α*,*β*-unsaturated aldehyde **1** by the secondary amine catalyst **3** results in a lowering of the lowest unoccupied molecular orbital (LUMO) coefficient of the *π*-system and initiates nucleophilic attack at the 4-position to provide the iminium ion. Hydrolysis of the iminium ion with the water generated in the iminium ion activation step provided **4**, which spontaneously cyclized to afford **5**, albeit as an inconsequential 1:2 mixture of *α*/*β*-anomers, in 90% yield and with 94% enantiomeric excess. The expected hydrolysis product **6** could, however, be obtained via the addition of either a Brønsted or Lewis acid.

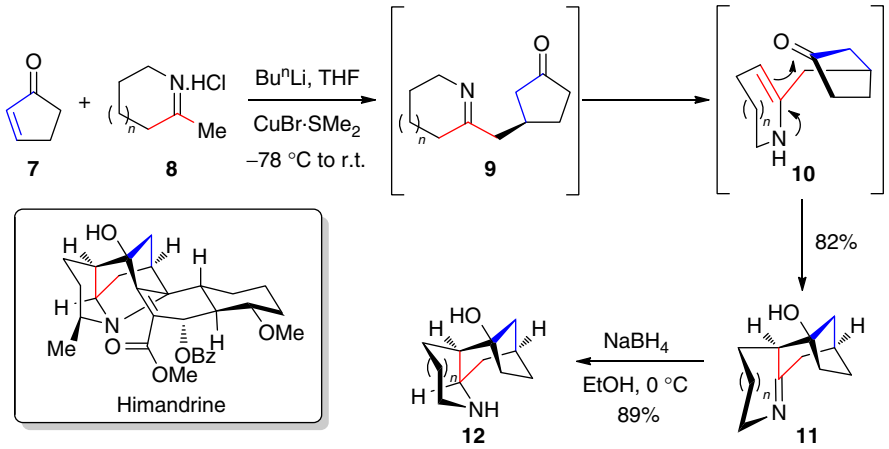


Scheme 3 Iminium ion-activated Michael addition.

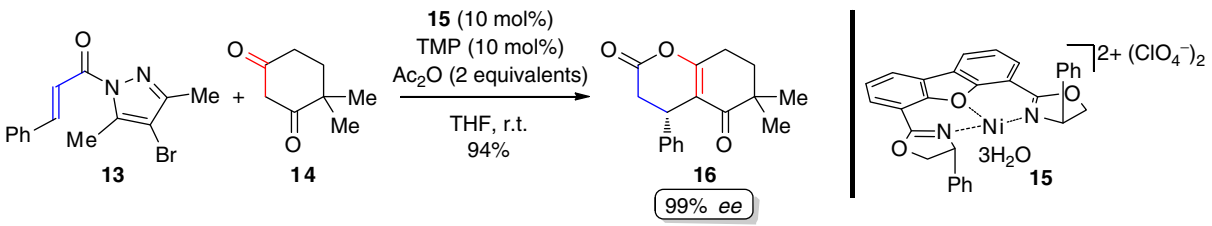
In a related transformation, the dimerization of crotonaldehyde proved successful through the ability of *α*,*β*-unsaturated carbonyls to provide 1,3-dication and dianion equivalents, respectively, in the presence of organocatalysts (Scheme 2).[5] Moreover, the high enantioselectivity, which is governed by chiral proline derivatives, afforded functionalized cyclohexene products that provide important intermediates for the expeditious construction of a number of monoterpene natural products. Despite the growing number of organocatalyzed cycloaddition reactions, this represents the first example of dual enamine/iminium activation in a [3 + 3] cycloaddition.

In this context, the potential of enamines as three-atom synthons was highlighted in an elegant approach to the densely functionalized core of himandrine (Scheme 4).[6] Initial conditions probed the addition of the *in situ*-generated cuprate, derived from **8** ($n = 1$), to the cyclopentenone **7** to afford the imine **9**. Tautomerization of the imine to the enamine **10**, followed by the intramolecular addition to the carbonyl and concomitant reduction of the imine afforded tricycle **12** ($n = 1$). Although the first step in the synthesis relies on the 1,4-addition of an organocuprate to generate imine **9**, the process is also amenable to iminium ion catalysis with a chiral organocatalyst. For example, L-proline catalyzed the initial reaction between **7** and **8** ($n = 0$) to afford the cyclopentanone **9**; however, it did not undergo spontaneous tautomerization/ketone addition in a similar manner to the analogous cuprate conditions and the enantioselectivity was modest (52% *ee*).

Enamines, in the form of vinylogous amides, have also been used in conjunction with the 1,2-/1,4-acceptor, acryloyl chloride, for the construction of six-membered lactams.[7a] The formation of nonracemic lactams was successful by employing chiral directing groups in a diastereoselective reaction. Vinylogous esters can also be used to generate lactones, and vinylogous ester equivalents, namely **14**, can provide enol lactones via a nickel-catalyzed process (equation 1).[7b] The chiral nickel(II) catalyst acts as a Lewis acid by activating both the carbonyl of **13** and enol form of **14**.

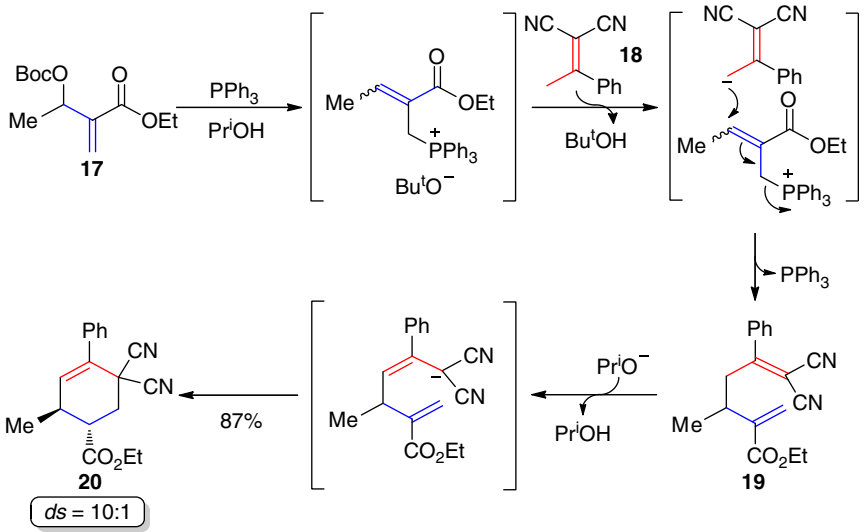


Scheme 4 Total synthesis of himandrine via [3 + 3] cycloaddition.



(1)

Phosphines have recently attracted significant interest as nucleophilic catalysts for the synthesis of functionalized cycloadducts. The aptitude of the Lewis basic phosphine to act as a good nucleophile, while also enabling facile elimination, provided the basis for these interesting developments. For example, the triphenylphosphine-catalyzed reaction of allylic carbonate **17** with alkylidenemalonitriles provides the requisite cyclohexene **20** (Scheme 5).[8] The reaction is thought to proceed via a series of 1,4-additions, with the leaving group in **17** being vital to the success of the reaction, since the resultant alkoxide must be sufficiently basic to deprotonate **18**.

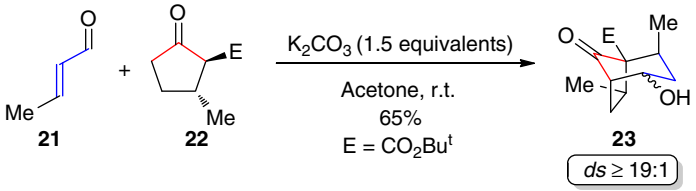


Scheme 5 Phosphine-catalyzed [3 + 3] cycloaddition.

5.14.2.1.2 α,α′-Carbonyl 1,3-dianions

Dianion equivalents, derived from sequential deprotonation of the α- and α′-positions of carbonyl compounds have long been used as three-carbon synthons in organic chemistry. The combination of these systems with additional three-atom synthons has emerged as a convenient protocol to prepare densely functionalized six-membered polycycles. In 1995, Rodriguez and coworkers

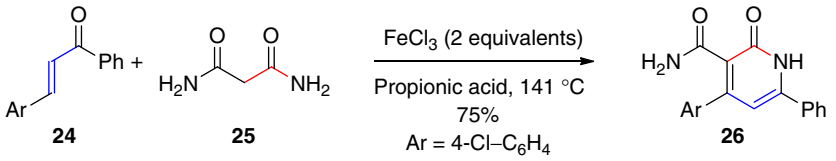
described the sequential base-promoted Michael addition/aldolization for the synthesis of optically active bicyclo[3.2.1]octane systems.[9] The thermodynamic enolate reacts selectively at the 4-position of the enal followed by reenolization and intramolecular aldol cyclization with the pendant aldehyde (equation 2). The reaction displays good to excellent diastereoselectivity for a variety of examples, because the enal is attacked from the least hindered face of the cyclic enolate, albeit the secondary alcohol is generated as a 2.8:1 mixture of equatorial and axial epimers, respectively.



(2)

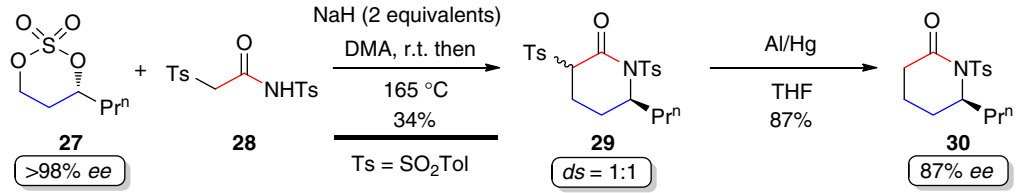
This principle has been extended to α,β-unsaturated ketones as dication equivalents in an organocatalyzed [3 + 3] annulation for the formation of [3.3.1] cycloadducts under mild conditions. The reaction is quite general with broad substrate scope affording excellent yields and enantioselectivities.[10]

Pyridones are of considerable synthetic interest, largely due to the plethora of pharmaceuticals that contain substituted 2-pyridones. The formation of these systems via a formal [3 + 3] cycloaddition is desirable from a structure–activity relationship (SAR) standpoint because it provides the desired motif at a late stage, which permits analogs to be readily prepared. Recently, the iron-mediated synthesis of trisubstituted 2-pyridones was reported by Wang (equation 3).[11] In this context, the metal-mediated combination of **24** and **25** affords 2-pyridone **26** via a Michael addition and dehydration, followed by aromatization of the 3,4-dihydro-2-pyridone intermediate, which occurs in the absence of additional oxidants or leaving groups.



(3)

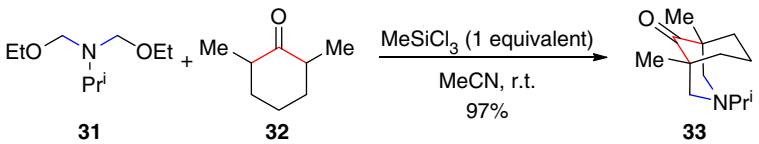
Stabilized dianions have also found application in the formation of enantiomerically enriched lactams. In 2000, Gallagher and Eskici reported the alkylation of such anions with C(sp^3) 1,3-electrophiles, which provided an opportunity to develop a stereospecific protocol using chiral C(sp^3) stereogenic centers (**Scheme 6**).[12]



Scheme 6 Cyclic lactams from [3 + 3] cycloaddition.

The reaction spontaneously occurs between the more electrophilic primary C(sp^3) and the nucleophilic carbanion at room temperature in the presence of sodium hydride. The second S_N2 reaction is considerably more challenging and requires extensive heating to provide the [3 + 3] adduct. Although the lactam was isolated as a mixture of diastereoisomers, removal of the sulfone provided **30** in 87% yield and with 87% enantiomeric excess, which indicates some stereochemical leakage in the alkylation. Hence, this strategy provides enantiomerically enriched lactams in a facile manner and has the capacity for extension to more complex [3 + *n*] cycloaddition reactions because the two electrophilic sites are independent of each other and do not form part of a larger motif, as is the case with α,β-unsaturated carbonyl derivatives.

In an effort to generate bicyclo[3.3.1]octane derivatives via a [3 + 3] cycloaddition, several groups have probed the double Mannich annulation of cyclic ketones.[13] The products of this transformation have great synthetic utility because they represent a pharmacophore present in biologically important molecules and have demonstrated important biological activity as antagonists for nicotinic receptors. For instance, the Lewis acid-mediated double Mannich condensation of the ketone **32** with the bis-imine equivalent **31** affords the cycloadduct **33** in excellent yield (equation 4). Additionally, replacing the isopropyl group on the amine with a chiral α-methylbenzyl functional group provided enantiomerically enriched intermediates, albeit as a mixture of diastereoisomers.

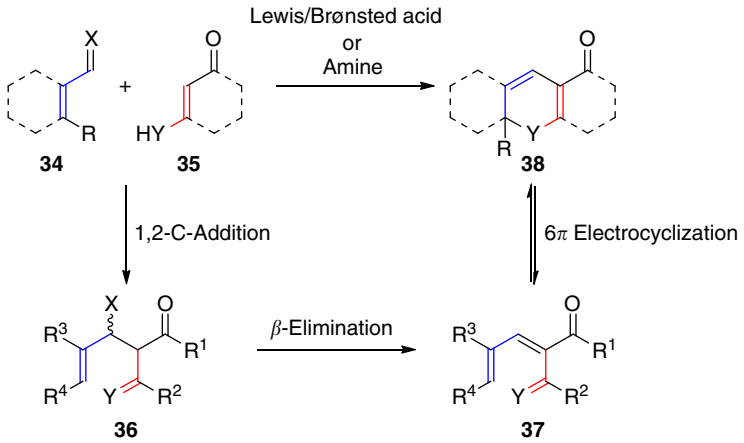


(4)

A major disadvantage with 1,3-dianions as three-carbon synthons is their propensity to undergo polymerization, which has led to the preparation of 1,3-dianion equivalents that provide a slow release of the desired nucleophile. This approach was initially developed by Chan et al. for the synthesis of methyl salicylates and has recently found favor in a number of α,α′-carbonyl dianion [3 + 3] cycloadditions.[14a] Later developments by Langer and coworkers, who have dominated this particular area of [3 + 3] cycloadditions, provided a new approach to spiroannulated hydroxycyclohexenones using 1,3-bis(silyl enol ethers) as mild three-carbon synthons,[14b] which is the subject of a recent comprehensive review.[1n]

5.14.2.1.3 Sequential Knoevenagel/6π electrocyclization reactions

Similarly to the Michael addition-mediated [3 + 3] cycloaddition reaction of α,β-unsaturated carbonyls with 1,3-diketo equivalents, which each provide three-atom synthons, there is an alternative reaction pathway for this cycloaddition. In this context, the sequential Knoevenagel condensation/6π electrocyclization reaction has become a well-studied class of [3 + 3] cycloaddition reactions. A general scheme for this reaction is highlighted in Scheme 7, which proceeds via the initial 1,2-C-addition of **35** to α,β-unsaturated **34**. Subsequent β-elimination of **36** provides the Knoevenagel condensation product **37**, which undergoes rapid 6π electrocyclization to afford the formal [3 + 3] cycloadduct **38**. It is noteworthy that the stereochemically defining step for the formation of the stereocenter adjacent to the heteroatom occurs during the 6π electrocyclization, and as such has proven challenging for the development of asymmetric versions of this transformation.

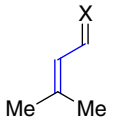
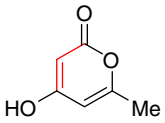
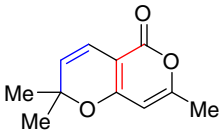
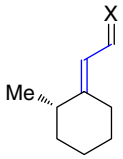
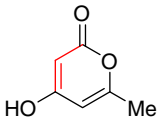
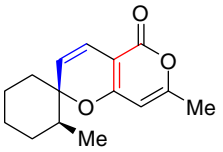
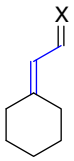
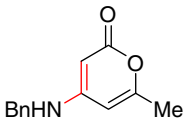
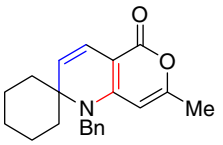
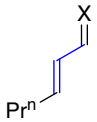
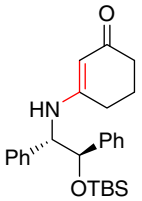
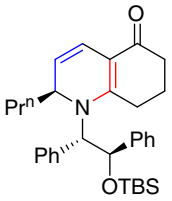
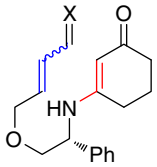
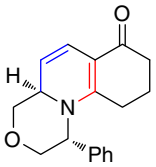


Scheme 7 Mechanism of the Knoevenagel condensation/6π electrocyclization reaction.

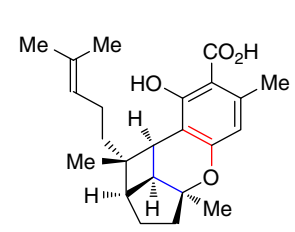
The reaction was first reported in 1944 by Link, and then further developed by Moreno–Mañas. However, its synthetic utility remained problematic because of the formation of several isomers from competing reaction pathways. The side reactions primarily result from initial 1,4-C- and Y-addition (X/Y = O), with the desired [3 + 3] adduct constituting less than 10% of the reaction mixture. In an effort to overcome this limitation, Jonassohn and Hua independently reported the use of cyclic enals, which favor the 1,2-C-addition. More recently, Hsung has expanded the scope of this transformation by employing iminium salts (X = piperidine acetate) for the construction of six-membered heterocycles using both cyclic and acyclic systems.[15] Table 1 outlines several examples that highlight this process. A key and striking feature with the substrate scope is that oxygen and nitrogen substitution can be tolerated at the vinylogous position and that quaternary stereogenic centers can be readily prepared adjacent to this heteroatom, which includes spirocyclic centers (entries 2–3). Although high diastereocontrol was not achieved when **34b** was employed, **38d** and **38e** were formed with excellent stereocontrol using chiral *N*-directing groups. The mechanism of this transformation has been the subject of extensive investigation[16] and supported by the isolation of the triene intermediate **37**. For example, the 1-azatriene derived from **34c** and **35c** was isolated and found to undergo thermal 6π electrocyclization at 150 °C, affording the corresponding [3 + 3] adduct **38c** in quantitative yield. Additional experiments provided evidence for a reversible cyclization process between **37** and **38**, which results in thermodynamic control in the formation of **38**. For example, subjecting the minor diastereoisomer of **38d** to thermal conditions at 150 °C provided the major isomer **38d** with ≥19:1 selectivity. More recently, catalytic Lewis and Brønsted acids have been demonstrated to promote these cycloadditions under mild conditions with excellent efficiency without the requirement of iminium ion activation.[17]

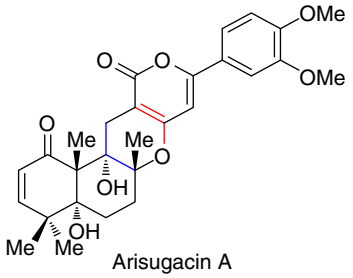
Interestingly, although the intramolecular version of this reaction also provides the corresponding [(3 + 3)] cycloadduct **38e** in modest yield as a single diastereoisomer, it was proposed to occur via an alternative pathway. The isolation of a reactive intermediate again provided additional support for this hypothesis, which suggested that initial 1,4-N-addition followed by 1,2-C-addition prevails. The low yield for the intramolecular reaction is presumably a result of a challenging β-elimination of the amine, albeit there are advantages for this transformation compared to the intermolecular version. The stereochemically defining step in this process is the initial 1,4-N-addition and chiral iminium ion catalysis activation provides some asymmetric induction, although the enantioselectivities are generally modest (≤50% *ee*). The major highlight of this type of cycloaddition has been the successful implementation in complex total syntheses, which have been extensively reviewed by Hsung and coworkers (Figure 2).[1k]

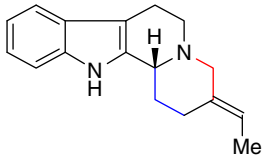
Table 1 Knoevenagel condensation/6π electrocyclization of α,β-unsaturated imines

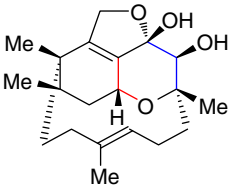
Entry	34[a]	35	38		ds	Yield (%)	References
1				**a**	–	72	15c
2				**b**	2:1	72	15a
3				**c**	–	60	15b
4				**d**	≥19:1	77	15b
5				**e**	≥19:1	55	15b

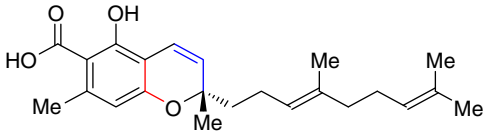
[a]X = piperidine acetate.


Rhododaurichromanic acid A


Arisugacin A


Deplancheine


Phomactin A


Daurichromenic acid

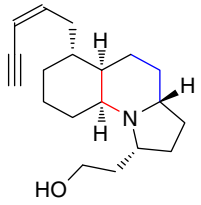

Gephyrotoxin

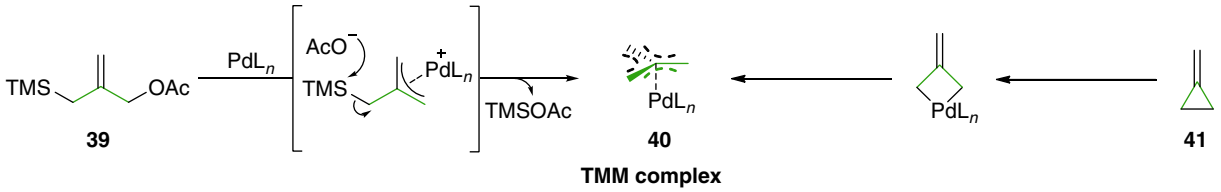
Figure 2 Natural products synthesized via Knoevenagel condensation/6π electrocyclization cycloadditions.

5.14.2.1.4 Trimethylenemethane-promoted reactions

Cyclopropanes provide important three-carbon synthons because of their ability to release ring strain and provide important reactive intermediates that facilitate useful synthetic transformations, particularly in the presence of transition metals. For

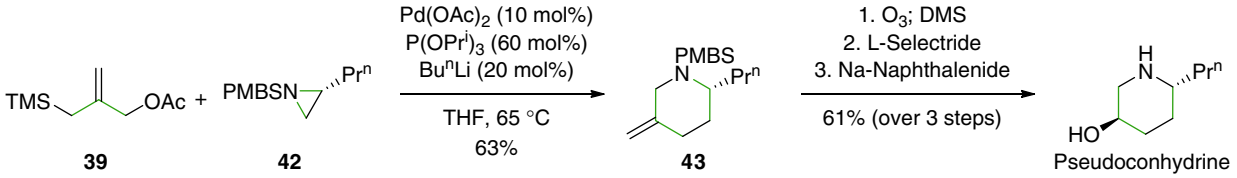
example, the cyclopropane ring has a calculated strain energy of 27.5 kcal mol^{-1} higher than the acyclic counterpart. Moreover, when one of the carbon atoms contained within the cyclopropane ring becomes sp^2-hybridized, as in the methylenecyclopropane (MCP) **41**, the strain energy increases further to 40.9 kcal mol^{-1}. Hence, it is unsurprising that cyclopropanes bearing a C(sp^2) have become extremely popular in synthetic organic chemistry.

Noyori, Binger, and Trost pioneered the studies on cycloadditions of trimethylenemethane (TMM) complexes (**40**) in the 1970s and 1980s, in which they demonstrated their propensity to provide novel 1,3-dipoles for cycloaddition reactions.[18] Although the reactive intermediate can be derived either from the MCP (**41**) or from the 2-[(acetoxymethyl)-3-allyl]trimethyl silane (**39**) with a nickel or palladium complex, the two systems have contrasting modes of reactivity despite their similarities. In this context, countless examples of [3 + 2] cycloadditions involving **40** have been reported, whereas only a few [3 + 3] cycloadditions have proven successful, all of which have been promoted using **39** with a palladium catalyst (Scheme 8). The following examples will highlight the potential of Type II cycloadditions utilizing palladium-bound TMM complexes.



Scheme 8 Formation of palladium–TMM complexes.

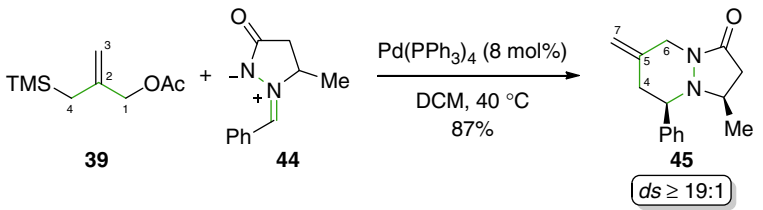
The most studied [3 + 3] cycloaddition involving TMM complexes involves the ring-opening of aziridines. The reaction is highly regioselective for the nucleophilic addition to the aziridine at the less substituted carbon, and as a result permits the formation of piperidines with α-nitrogen stereogenic centers. Although the early reports did not probe the effect of enantiomerically enriched aziridines, Harrity and coworkers have developed the enantiospecific reaction, which proceeds without appreciable loss in enantiomeric purity (Scheme 9). The facile preparation of enantiomerically enriched aziridines, coupled with their reactivity toward TMM complexes, provides a very convenient approach to optically active piperidine alkaloids such as pseudoconhydrine.[19]



Scheme 9 [3 + 3] Cycloaddition of TMM complexes and aziridines.

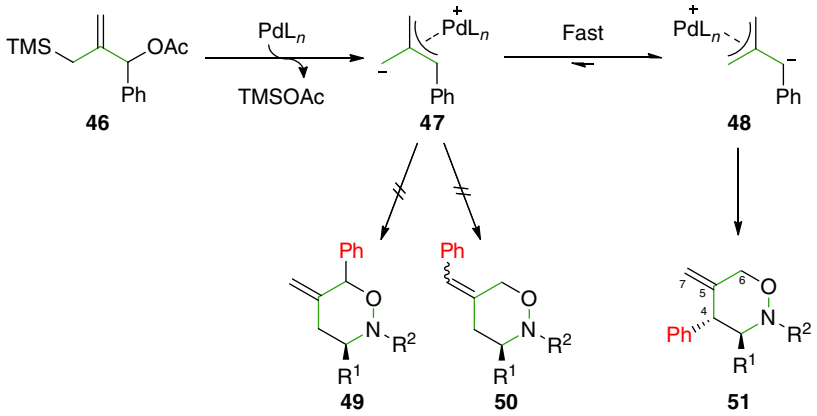
The most plausible reaction pathway invokes the initial formation of a TMM complex followed by nucleophilic attack of the strained methylene of **42**. The catalytic cycle culminates with *N*-nucleophilic attack of the π-allyl-palladium intermediate to generate the six-membered heterocycle. Interestingly, only electron-rich sulfonamides on nitrogen are tolerated and byproducts resulting from nucleophilic addition of acetate to the methylene of the aziridine are often detected in more complex systems.

Despite the plethora of asymmetric palladium-catalyzed [3 + 2] cycloadditions of TMM complexes, the corresponding asymmetric [3 + 3] cycloaddition is limited to a single example. In 2006, Hayashi and Shintani provided the basis for the asymmetric approach with the development of a novel [3 + 3] cycloaddition of TMM complexes with azomethine imines.[20] Azomethine imines were reported in 1968 to be stable 1,3-dipoles, however, they had not previously been coupled with three-atom synthons in the context of a [3 + 3] cycloaddition. Nevertheless, the palladium-catalyzed reaction of the ylide **44** with **39** furnished the aza-bicycle **45** in excellent yield and diastereoselectivity (equation 5).



(5)

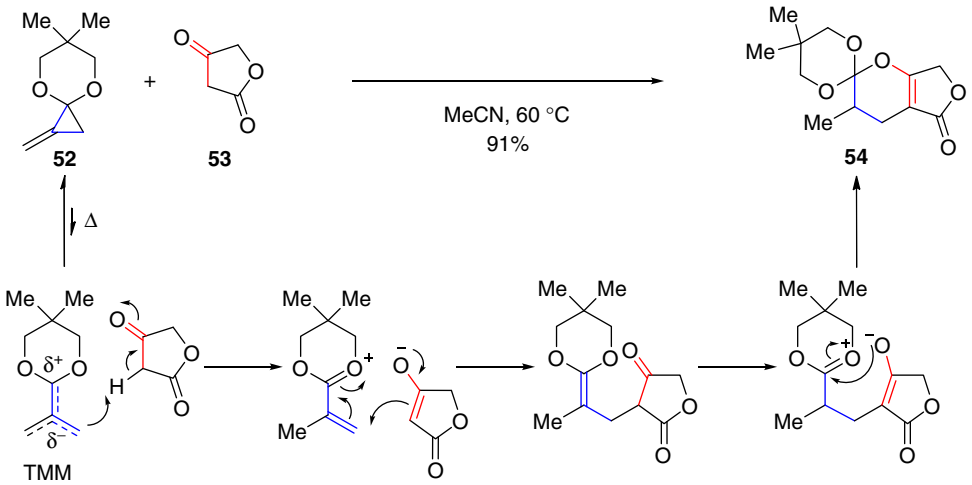
Interestingly, the C1-substituted derivative of **39** (C1 = Me) provides three products in the cycloaddition, which correspond to the cycloadduct having a methyl group at C4, C6, and C7 (3:20:77). Hence, this implies that the TMM intermediate is both highly fluxional and lacks chemoselectivity. However, in a related reaction involving nitrones as 1,3-dipoles, aryl TMM substitution leads to a highly stereoselective reaction with the aryl group proving critical to the stabilization of the TMM intermediate (**Scheme 10**). For example, the initial TMM complex **47**, generated from **46** with palladium(0), undergoes rapid isomerization to the more stable benzylic anion **48**, which affords **51** as the exclusive constitutional isomer (cf. **49** and **50**) with good diastero- (up to 8:1) and excellent enantioselectivity (up to 93% *ee*) with a chiral phosphoramidite.



Scheme 10 Chemoselectivity for aryl substituted TMM complexes in the [3 + 3] cycloaddition.

A number of similar cycloadditions, which do not proceed through a TMM intermediate, afford [3 + 3] cycloadducts in a sequential palladium-catalyzed allylic alkylation/allylic etherification with *β*-diketones and *β*-ketoesters. Although the reaction affords related cycloadducts, this process is regarded as a Type I cycloaddition because it represents a donor–donor synthon reacting with an acceptor–acceptor synthon.[21]

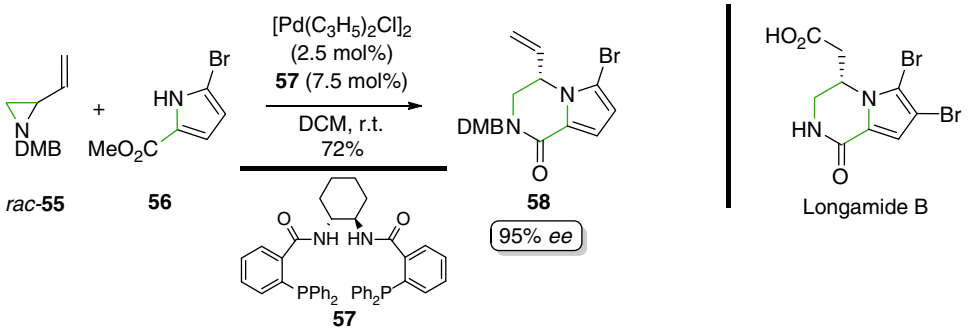
TMM derivatives can also be prepared in the absence of transition metals via the formation of a thermally promoted 1,3-dipole, which exists in rapid equilibrium with its neutral counterpart **52** (**Scheme 11**). These intermediates have also been utilized in [3 + 3] cycloadditions, however, a vital requirement is a strained MCP in conjunction with heteroatom stabilization.[22] The major drawback with the reaction is the formation of [3 + 2] cycloadducts as a result of the competitive cycloaddition of **52** with the carbonyl of the *β*-diketone/*β*-ketoester counterpart. The extent of the side reaction is primarily controlled by the ease of tautomerization of the *β*-diketone/*β*-ketoester to its enol form. Employing 3-methylpent-2,4-dione elegantly supported the intermediate ketene acetal, which has only one available proton for deprotonation. This prevents the *β*-diketone from tautomerizing to an enol, and subsequently prohibits the final cyclization step. It is noteworthy that this type of TMM is not a donor–acceptor synthon, as described for palladium TMM complexes, rather an acceptor–acceptor *α*,*β*-unsaturated carbonyl is developed *in situ*, making this a Type I process.[22]



Scheme 11 Thermally promoted formation of TMM.

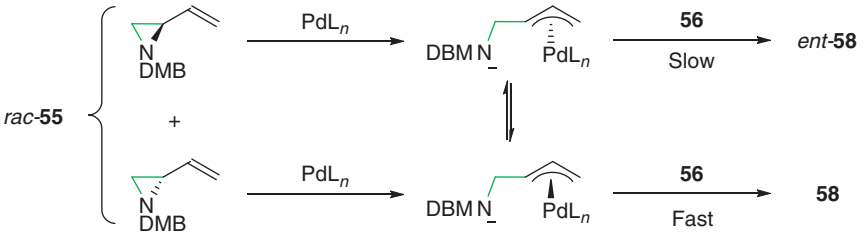
5.14.2.1.5 1,3-Dipoles from three-membered rings

The asymmetric allylic alkylation reaction is an extremely useful reaction for the synthesis of a diverse range of structural motifs and has been the subject of intensive investigation. In this context, a variety of transition metals are able to ring-open vinyl oxiranes and aziridines with concomitant formation of a metal–allyl species, which can be formally envisioned as a 1,3-dipole. Hence, in the presence of an additional donor–acceptor, such as pyrrole **56**, the reaction has the potential to generate [3 + 3] cycloadducts in a highly controlled manner. This strategy was elegantly demonstrated by Trost and Dong in the concise enantioselective synthesis of longamide B (equation 6).[23]



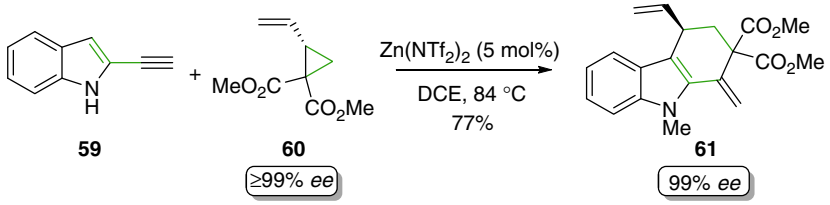
(6)

The enantioselective construction of the pyrrolopiperazinone pharmacophore in this manner is particularly noteworthy given that the vinyl aziridine **55** is racemic (Scheme 12). Hence, the reaction involves a dynamic kinetic resolution, which relies on the rate of equilibration of the π-allyl-palladium intermediates via π–σ–π isomerization relative to the rate of nucleophilic attack leading to **58** and *ent*-**58**. This strategy allows a racemic aziridine to be directly employed, without the necessity for separation of the unreacted starting material, which is typically required in a classical kinetic resolution reaction.



Scheme 12 Dynamic kinetic asymmetric allylic alkylation.

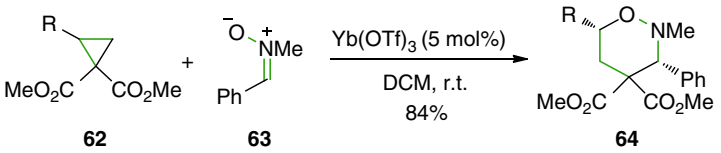
A number of [3 + 3] cycloadditions involve cyclopropane ring-opening as a precursor to 1,3-dipoles. To this end, one of the most common methods for ensuring the dipole lifetime is to utilize 1,1-cyclopropane diesters with Lewis acid catalysts to stabilize the developing anion in conjunction with a vicinal π-donor to assist the ring-opening. For example, vinyl and phenyl stabilizing groups provide a highly regioselective and efficient reaction, whereas less stabilizing groups lead to low regioselectivity because of competing steric and electronic factors. This type of three-carbon synthon behaves in a manner reminiscent of an α,β-unsaturated carbonyl compound, which undergoes Michael addition followed by enolate alkylation. In this regard, cyclopropane diesters have been widely developed by Johnson for [3 + 2] cycloaddition reactions,[24] and Kerr first utilized this concept in combination with three-carbon synthons in [3 + 3] cycloaddition reactions. Subsequent sections of this chapter will highlight cycloadditions between cyclopropanes and aza-ylides; however, in the context of other donor–acceptor groups, 2-alkynyl indoles have been utilized as three-carbon synthons and react via ring-opening of the cyclopropane followed by a Conia-ene cyclization of the malonate on to the alkyne.[25] The mechanism is thought to proceed in a stepwise manner with initial alkylation at the 3-position of the indole with the electron-deficient carbon of the cyclopropane followed by the coordination of the Lewis acid to the alkyne and subsequent Conia-ene cyclization. A critical component of the process is the ability for the metal complex to act as a Lewis acid for both the malonate and alkyne components. In this regard, $Zn(NTf_2)_2$ provides the optimal catalyst for this particular transformation (equation 7).



(7)

5.14.2.1.6 Y=N$^+$–X$^-$ 1,3-dipoles

Cyclopropanes also react with nitrones to generate a range of heterocycles with a nitrogen–oxygen bond. For instance, Kerr and Young reported the first example of this type of cycloaddition for the synthesis of tetrahydro-1,2-oxazines.[26] Although the exact reaction mechanism has not been determined, it is thought to be a concerted process, wherein the Lewis acid activates the cyclopropane for ring-opening by coordination to the malonate moiety. The mechanistic rationale is based on the fact that conventional stepwise S_N2 ring-opening followed by malonate addition to the iminium ion is more likely to provide lower diastereoselectivity with substituted cyclopropanes, albeit this cannot be ruled out. In these cases the formation of the tetrahydro-1,2-oxazine with α-oxy substitution is highly selective, favoring the formation of the *syn*-isomer **64** (R=Ph), which is the kinetic product (equation 8).

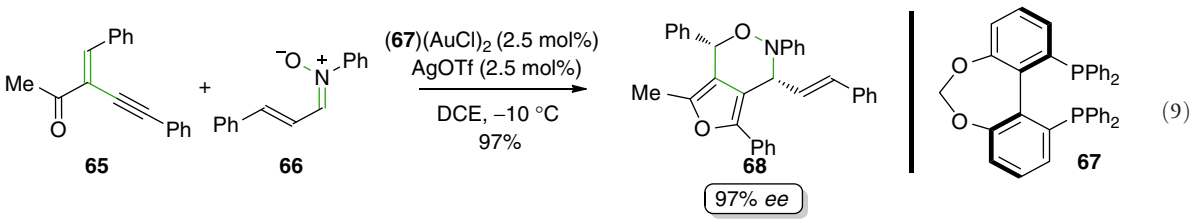


(8)

The rapid assembly of tetrahydro-1,2-oxazines is particularly attractive for medicinal chemistry, since this motif is present in a small class of antitumor and antibiotic natural products that provide challenging targets for conventional organic chemistry. Cleavage of the weak nitrogen–oxygen bond in tetrahydro-1,2-oxazines, by either hydrogenation or single-electron transfer reagents, provides a range 1,4-hydroxylamines. Moreover, *O*-mesylation of the resultant hydroxyamine promotes intramolecular amination to facilitate a stereocontrolled synthesis of substituted *anti*-2,5-pyrrolidines. This strategy was recently utilized in the total synthesis of nakadomarin A.[26b]

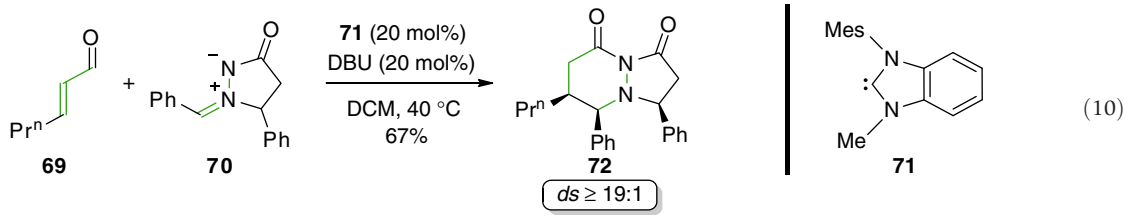
Asymmetric variants of this strategy have also been reported using chiral PyBox-derived nickel catalysts, which furnish the enantioenriched tetrahydro-1,2-oxazines with excellent selectivity.[27] For example, **64** (R=H) was generated under mild reaction conditions (DCM, r.t.) in 99% yield and with 92% enantiomeric excess. Although the reaction was initially limited to unsubstituted 1,1-cyclopropane diesters because the substituted systems provide poor diastereocontrol, Tang and coworkers improved the selectivity using a pseudo-C_3-symmetric triazoline ligand.[28] The diminished selectivity in the former case was attributed to a switch from a concerted to a stepwise process, which presumably allows the intermediate anion to freely rotate and thereby provide a mixture of stereoisomers.

2-(1-Alkynyl)-2-alken-1-ones have a rich history in the synthesis of furans and their small, but intrinsic complexity make them ideal candidates for elaboration into a range of functionalized polycycles. Many of these syntheses have relied on gold catalysts with nucleophiles to promote an intermolecular cyclization to afford a furanogold species, which concludes with the protonation of the carbon–gold bond. A recent [3+3] cycloaddition took advantage of this mechanism by employing nitrones, which initially provide a nucleophilic source in the formation of the furanogold species, and promotes addition onto the resultant iminium ion to generate the cycloadduct.[29] This transformation provided spectacular levels of enantioselectivity in excellent yield when the bisphosphine (*R*)-C_1-tunephos ligand **67** was employed; however, the level of selectivity is reliant on the number of aryl groups present in **65** and **66** (equation 9).



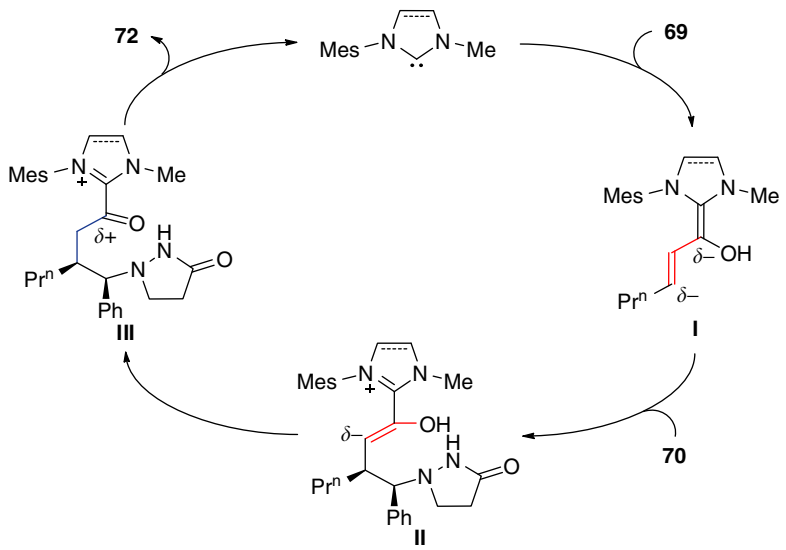
(9)

The advantages of organocatalysts in Michael addition-promoted Type I cycloadditions were outlined earlier; however, there are relatively few examples in the context of Type II [3+3] cycloaddition reactions. For example, the only 1,3-dipole system (Y=N$^+$–X$^-$) to utilize an organocatalyst was for the synthesis of pyridazinones, which relied on the capacity of *N*-heterocyclic carbenes (NHCs) to provide umpolung reactivity in the presence of α,β-unsaturated carbonyl compounds, albeit the reaction requires high catalyst loadings (equation 10).[30]



(10)

The mechanism of this transformation is intriguing, with the initial attack of the NHC onto the formally acceptor–acceptor α,β-unsaturated aldehyde **69** to afford the Breslow intermediate **I**, which switches the polarization (Scheme 13). Hence, the system becomes a donor–donor species, which as a consequence promotes nucleophilic attack onto the azomethine imine **70**. Proton transfer results in an acceptor at the same position, which leads to the desired pyridazinone **72** on elimination of the catalyst via nucleophilic acyl substitution. The ambiphilic nature of the α,β-unsaturated aldehyde functionality makes this transformation feasible, however, it can formally be represented as a donor–acceptor group.

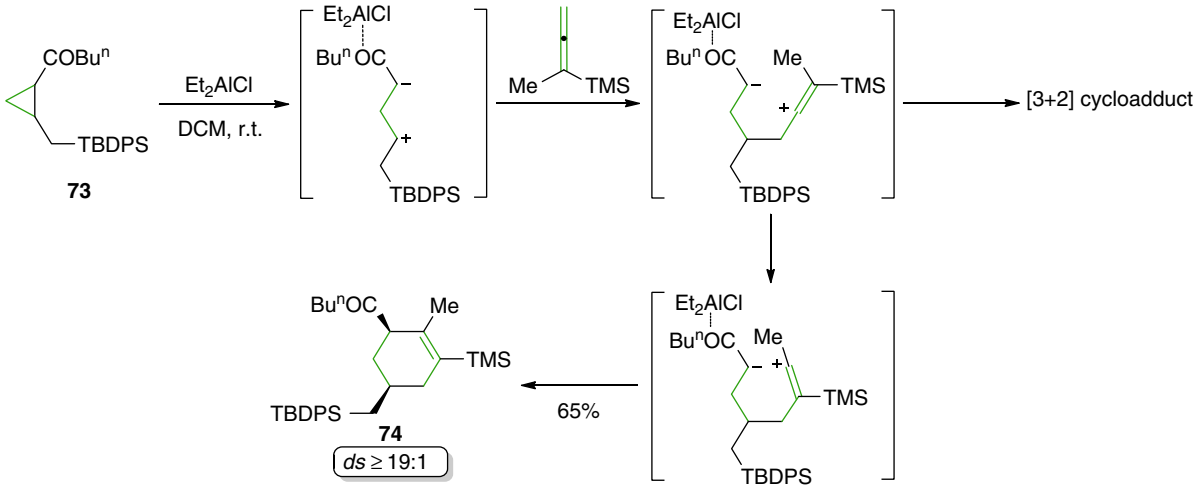


Scheme 13 Catalytic cycle for the NHC-catalyzed [3 + 3] cycloaddition reaction.

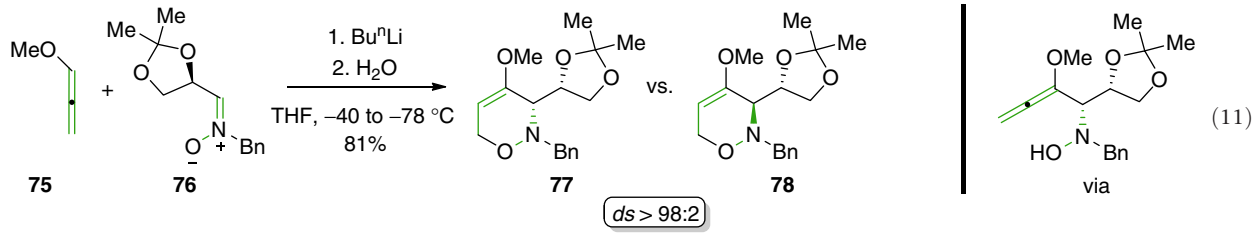
5.14.2.1.7 Allene/metal–carbene-promoted reactions

Allenes represent interesting intermediates in cycloaddition reactions because they display varied reactivity depending on a number of factors, which include allene substitution and the metal. Furthermore, because allenes can provide two- and three-carbon synthons, the ability to predict the outcome of a given transformation is often challenging. This is amply demonstrated with silylallenes and activated cyclopropanes where the silicon stabilizes the developing β-carbocations in both components. For example, cyclopropane **73**, which bears only one electron-withdrawing group, generates the acyclic dipolar intermediate in the presence of a Lewis acid, which is additionally stabilized by the silicon group *beta* to the newly formed carbocation. Nucleophilic addition of the allene generates a vinyl cation, which in some examples led to 1,2-silyl migration, followed by nucleophilic attack of the enolate to afford the [3 + 3] cycloadduct **74** (Scheme 14).[31] The reaction affords highly complex cyclohexene products with excellent diastereoselectivity; however, the inability to control the formation of [3 + 2] cycloadducts significantly detracts from the generality of this important transformation. The propensity for allenes to provide multiple synthetic equivalents has also reduced the synthetic utility of a number of recent phosphine-catalyzed [3 + 3] cycloadditions. These reactions, which employ azomethine imines with allenic esters, provide products resulting from the allene behaving as a two-, three-, and four-carbon synthon in [3 + 2], [3 + 3], [4 + 3] and [3 + 3 + 2] cycloaddition reactions, respectively.[32] Interestingly, the [3 + 3 + 2] cycloaddition represents the first example of this type and utilizes two equivalents of the allene ethyl buta-2,3-dienoate as a two- and three-carbon synthon.

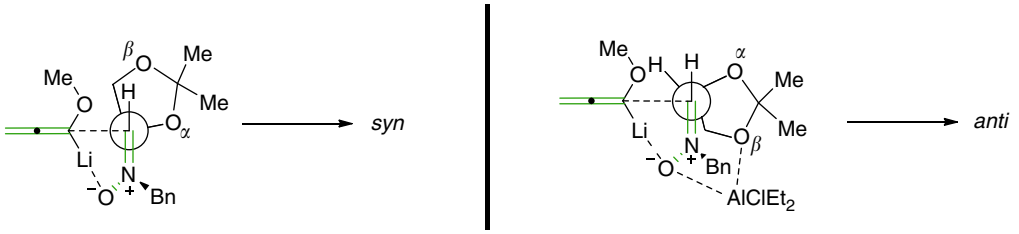
In 2005, Reißig and coworkers reported the stereodivergent synthesis of 1,2-oxazines from simple nitrones with lithiated allenes. Treatment of the methoxy-substituted allene **75** with *n*-butyllithium affords the metallated species that reacts with the nitrone to afford an acyclic allenyl hydroxylamine intermediate. This then undergoes a spontaneous and highly selective *O*-6-*endo* trig cyclization over the competing *N*-5-*endo* trig cyclization, to afford the 1,2-oxazine **77** in 81% yield with excellent diastereocontrol favoring the *syn*-product (equation 11).[33]



Scheme 14 [3 + 3] Cycloaddition reaction of allenes with cyclopropanes.



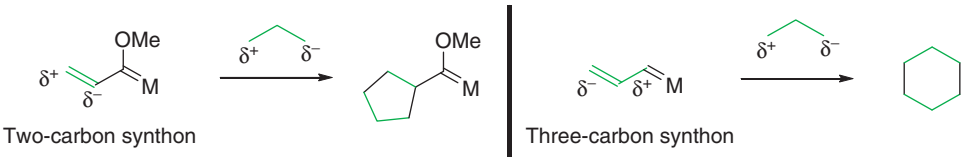
Scheme 15 outlines the origin of the excellent diasterocontrol in the addition, which utilizes the Felkin–Anh model for nucleophilic additions to C=X bonds. In a similar manner to related reactions, the Lewis acid promotes the formation of the *anti*-product via a chelate controlled addition. For example, precomplexation of Et_2AlCl to the nitrone, followed by addition of the allenyl lithium afforded the *anti*-diastereoisomer **78** in 77% yield with >98:2 diastereoselectivity.



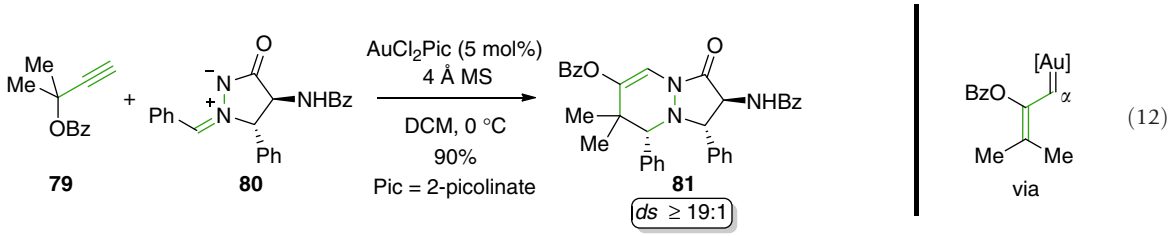
Scheme 15 Rationalization for the observed stereocontrol for nucleophilic addition.

Alkenyl Fischer carbenes provide useful two-carbon synthons for the formation of metal containing [3 + 2] cycloadducts. The metal facilitates the transformation by polarizing the alkene component, in which the alkene terminus is inherently electrophilic and the internal portion is nucleophilic (Scheme 16). Toste et al. recently reported the extension of this concept to vinyl metal-alkylidenes, which provide three-carbon synthons in what are formally stable vinyl carbene equivalents.[34] A critical limitation with this process is the necessity to generate the vinyl metal-alkylidenes from the decomposition of the requisite diazo compound. Since diazo species, particularly alkyldiazo compounds, are notoriously explosive, they generally require additional stabilization from α-carbonyl compounds.

In contrast, the gold(III)-catalyzed process provides the required vinyl metal-alkylidene from propargylic esters, which not only eliminate the necessity for a diazo precursor but also provide the reactive intermediate with high atom economy. The propargylic ester **79** reacts with the azomethine imine **80** to furnish the six-membered adduct **81** in excellent yield and diastereoselectivity (equation 12). The reaction proceeds in a stepwise manner with initial formation of the carbene via rearrangement of the propargylic ester **79**, followed by nucleophilic attack at the α-position by the azomethine imine **80** to generate a allylgold species, which on cyclization eliminates the gold catalyst to afford the pyrazolidinone **81**. Although the α-nitrogen stereogenic center primarily controls the selectivity, the level of distereocontrol was optimal for disubstituted azomethine imines, as exemplified by **80**.

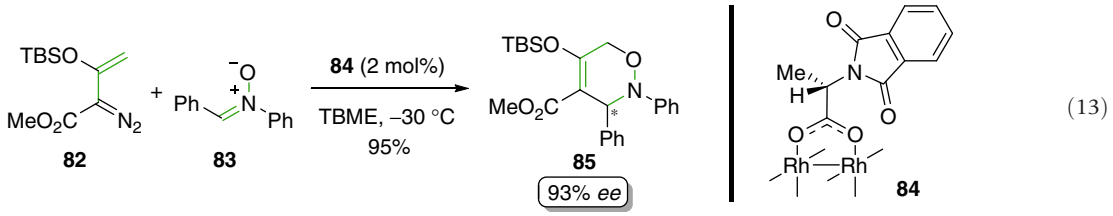


Scheme 16 Synthetic equivalents of vinyl carbenoids.



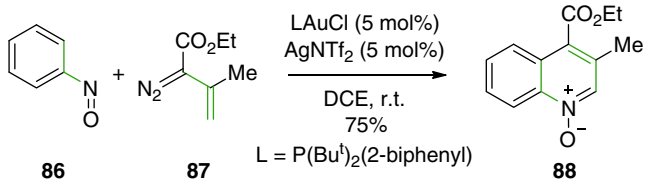
(12)

The asymmetric rhodium-catalyzed reaction, which employs the corresponding diazo precursors, generates the requisite cycloadducts with excellent enantioselectivity. For example, treatment of the diazo ester **82** with the nitrone **83** using the chiral dirhodium carboxylate catalyst **84**, furnished the 1,2-oxazine **85** in 95% yield and with 93% enantiomeric excess (equation 13).[35]



(13)

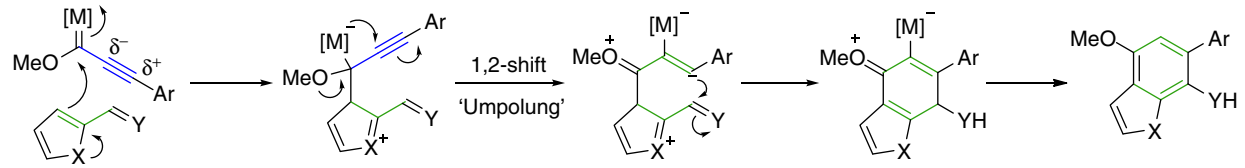
Despite the aforementioned advantages of employing propargylic esters as vinyl gold-alkylidene equivalents, they often lead to unwanted metathesis/[4 + 2] cascade byproducts rather than the anticipated [3 + 3] cycloaddition. For example, when Liu and coworkers explored the reaction of **79** with nitrobenzene **86** in the presence of a gold(I) catalyst (cf. equation 12), none of the desired cycloadduct was obtained. Nevertheless, the corresponding alkenyldiazoacetate **87** in the presence of rhodium(II), copper(I) or gold(I) promotes the desired [3 + 3] cycloaddition to afford **88**, in which the gold(I) catalyst proved optimal (equation 14).[36] The mechanism is proposed to proceed via initial carbene formation followed by *N*-attack on the terminal alkene of the carbene with concomitant 6π-electrocyclization to provide, on protodemetallation, the quinoline *N*-oxide **88**.



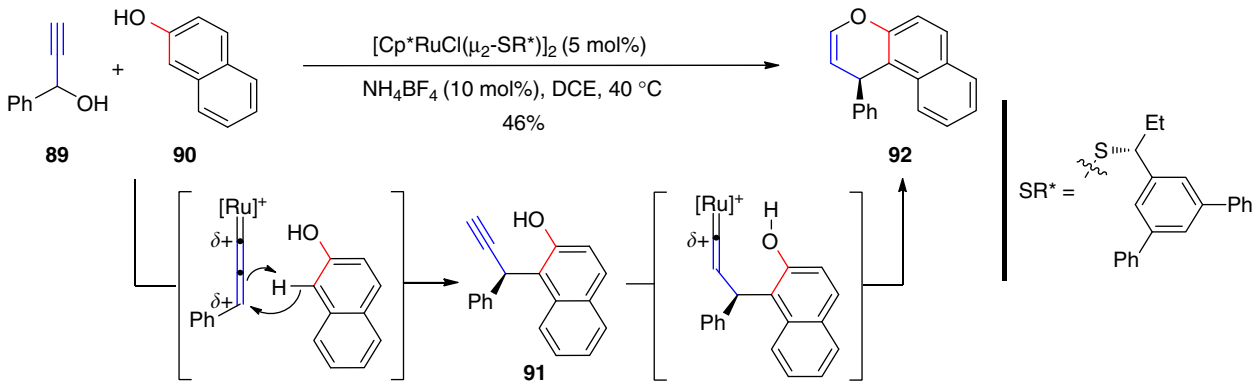
(14)

Notwithstanding the numerous examples of alkenyl and alkynyl Fischer carbenes behaving as two-carbon synthons in cycloaddition reactions (Scheme 16), an unusual 1,2-shift of an intermediate carbene provided a new approach to [3 + 3] cycloaddition reactions, thus permitting Fischer carbenes to provide three-carbon synthons (Scheme 17). The neutral coupling partner attacks the α-position of the carbene to generate a charged metal intermediate, which promotes the 1,2-migration to furnish a nucleophilic vinyl carbanion.[37] The intermediary carbanion undergoes a 6-*exo* cyclization to afford the six-membered zwitterion, which is followed by proton transfer, reductive elimination and tautomerization to furnish the aromatic product. Although the products of these reactions are purely organic cycloadducts, it requires a stoichiometric transition metal, which negatively impacts its synthetic utility for preparing these types of systems.

In a related manner to the gold cyclization of propargylic esters, propargylic alcohols undergo rearrangement in the presence of a chiral ruthenium complex to afford a ruthenium–allenylidene intermediate (Scheme 18).[38] This three-carbon acceptor–acceptor species, derived from **89**, undergoes dynamic kinetic resolution in the alkylation with 2-naphthol to afford the enantiomerically enriched acyclic intermediate **91**, which is an isolable intermediate. Cyclization of the propargylated adduct **91** via the ruthenium–vinylidene provides the enantioenriched cycloadduct **92** in 46% yield and with 72% enantiomeric excess. The reaction affords modest enantioselectivity in most cases; however, the yields are generally poor because of **91** failing to generate the ruthenium–vinylidene species.



Scheme 17 Fischer carbenes as three-carbon synthons via a 1,2-shift.



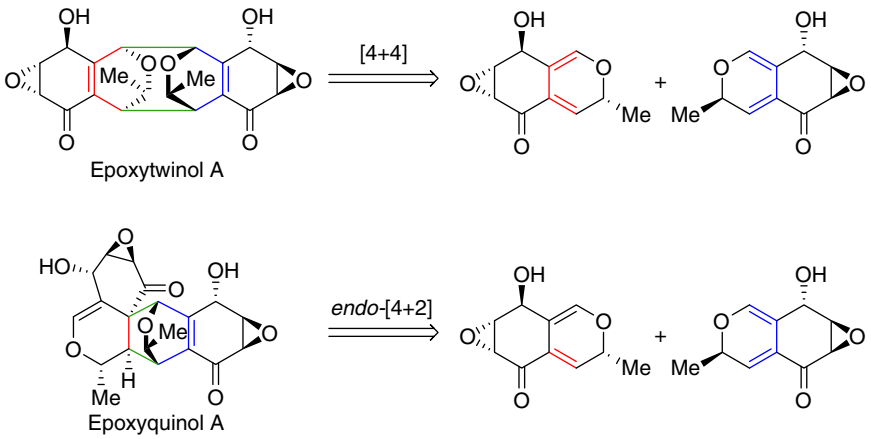
Scheme 18 Sequential ruthenium allenylidene and vinylidene cyclizations.

5.14.2.2 ['4 + 4'] Cycloadditions

The construction of eight-membered rings using ['4 + 4'] cycloadditions provides an important strategy, which has prompted the development of an array of synthetic methodology. Furthermore, the ability to affect a transannular cyclization of aliphatic cyclooctanes to provide bicyclo[3.3.0]octane adducts in a stereoselective manner provides an additional incentive for the development of this cycloaddition reaction. This section describes recent advances in thermal and metal-catalyzed ['4 + 4'] cycloaddition reactions; however, light-promoted photochemical cycloaddition reactions are discussed in Chapters 5.04 and 5.15.[1a,39] The color employed in this section provides clarity in distinguishing between the two four-carbon synthons and is not an indication on the electronic parameters of each fragment.

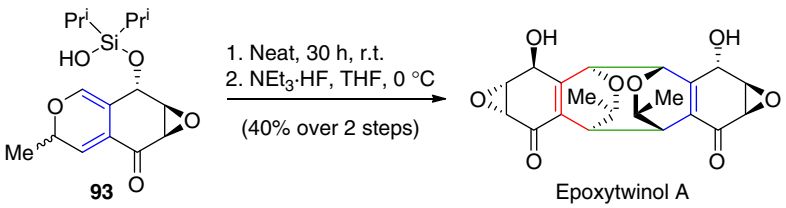
5.14.2.2.1 Thermal-promoted reactions

The thermal [4 + 4] cycloaddition reaction is relatively unexplored, which is presumably because of the fact that these cycloadditions are disfavored according to the Woodward–Hoffmann rules. In this context, a significant portion of the developments in this area have focused on the total synthesis of epoxytwinol A, because a formal [4 + 4] dimerization is the proposed biosynthetic pathway (Scheme 19).[40] Indeed, this represents the only natural product prepared in Nature via a [4 + 4] cycloaddition pathway, which coexists in the same fungus with [4 + 2] dimers, namely epoxyquinol A–C. Although structurally intriguing from a biosynthetic standpoint, epoxytwinol A is also an important biological agent since it exhibits potent antiangiogenic activity.



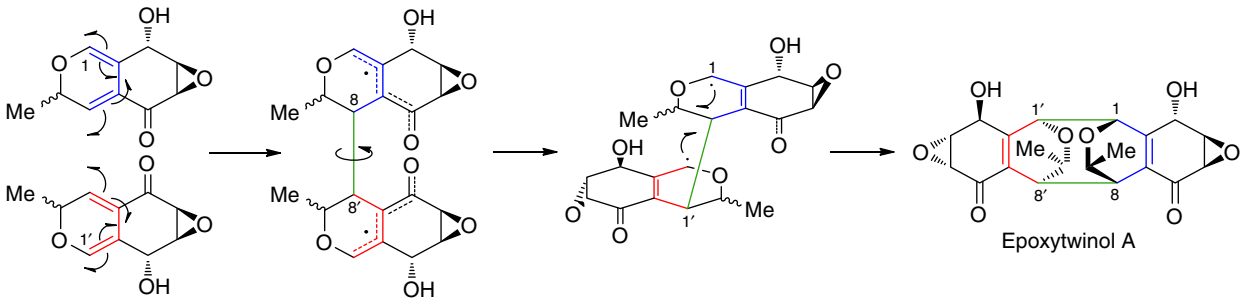
Scheme 19 Proposed retro-biosynthesis of epoxytwinol A and epoxyquinol A.

Despite extensive effort to optimize this process, the dimerization of the monomeric species is inefficient because of the competing [4 + 2] pathway and as a result the [4 + 4] adduct was obtained in only 8% yield.[40] Porco and Li recently improved the overall efficiency of this process, through a subtle modification to the monomer to disfavor the [4 + 2] pathway and thus promote the formation of epoxytwinol A.[41] In this context, they discovered that although protected hydroxyl groups, such as *tert*-butyldimethylsilyl ethers, are resistant to thermal [4 + 2] and [4 + 4] cyclizations, the unprotected monomer dimerizes during purification on silica gel (hexane/ethyl acetate). This prompted the utilization of diorganosilanol protecting groups, which favor the formation of the [4 + 4] cycloadduct in an improved 40% yield after removal of the protecting groups (equation 15).



(15)

The facile rearrangement of epoxytwinol A to the epoxyquinols, in the absence of light, provides an additional challenge for the isolation. In addition, computational studies indicate that the dimerization is a stepwise process, which occurs through a biradical intermediate that is formed from the homolytic cleavage at C1 and C1′ (Scheme 20).[42] Subsequent rotation around C8–C8′ and recombination of the diradical furnishes epoxytwinol A. Hence, the total synthesis using the silanol protecting groups to promote free rotation between C8–C8′ eliminates the competing [4 + 2] pathways and supports the theoretical analysis. The thermodynamic formation of the epoxyquinols via rearrangement of epoxytwinol A was also supported computationally, which indicates that the [4 + 4] adduct is 6.0 kcal mol^{-1} higher in energy.



Scheme 20 Stepwise biradical mechanism for the synthesis of epoxytwinol A.

5.14.2.2.2 Metal-catalyzed reactions

Transition metal-catalyzed cycloaddition reactions continue to play an important role in the formation of polycyclic systems. In contrast to thermally promoted [4 + 4] reactions, the metal-catalyzed variants are not classified as pericyclic reactions and thereby are not rationalized by the aforementioned Woodward–Hoffmann rules as being disfavored. It is therefore unsurprising that the majority of work on ['4 + 4'] cycloaddition reactions have involved transition-metal catalysis. Inspired by the nickel-catalyzed oligomerization of dienes, Wender and coworkers explored the effect of intramolecularity to suppress the former process and promote the intramolecular [(4 + 4)] reactions of bis-dienes. In this context, intramolecularity provides the ability to control diene concentration and thereby promote a highly controlled process with an array of functionality that would otherwise not be possible in the intermolecular variant. Figure 3 depicts different types of intramolecular [(4 + 4)] cycloaddition reactions, which afford bicyclo[6.*m*.0] and [5.*m*.1] systems that are present in a number of biologically important natural products.

In a continued effort toward the synthesis of eight-membered polycycles, Wender has reported both types of [(4 + 4)] cycloadditions. For example, the Type I cyclization of the bis-diene **94** affords **95**/**96** in 68% yield with modest selectivity, where the C5 group dictates the facial selectivity of the reaction (equation 16).[43] Although the conversion of **95** to ophiobolin F was unsuccessful, the rapid formation of **94** and its expeditious conversion to the highly functionalized core of the natural product is noteworthy. In addition, efforts to improve the yield and selectivity, by exploring the effect of alkene geometry indicates that each isomer of the bis-diene affords a similar outcome.

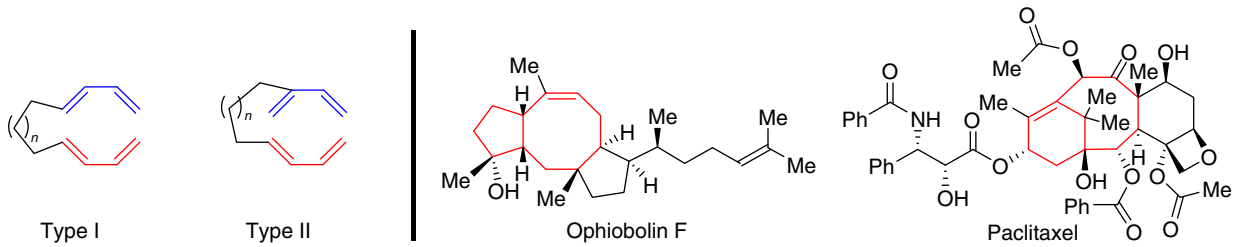
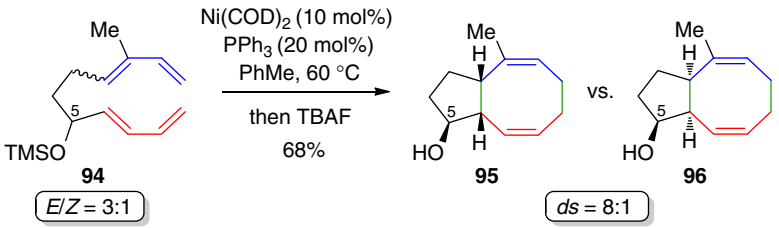
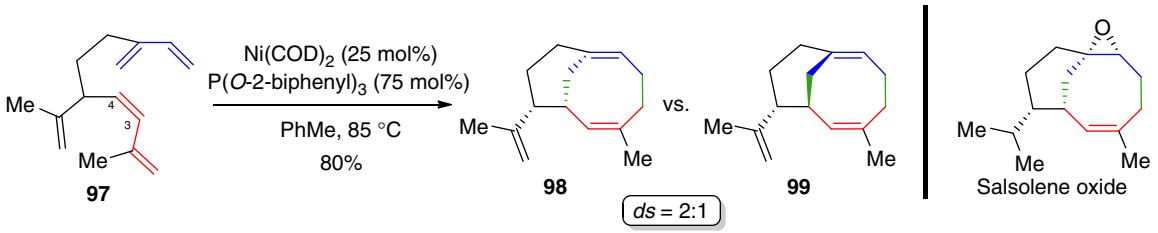


Figure 3 Various types of bis-diene [(4 + 4)] cycloaddition reactions and representative natural products that could be synthesized via these processes.



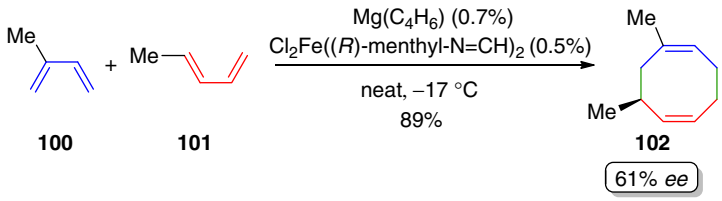
(16)

In contrast, the Type II cyclization is dependent on alkene geometry as exemplified in the concise total synthesis of salsolene oxide (equation 17).[44] For instance, the cyclization of bis-diene **97**, which has a *Z*-olefin at C3/C4, affords the bicyclo[5.3.1]undecanes **98**/**99** in excellent yield albeit with poor diastereocontrol, whereas the corresponding *E*-isomer afforded none of the desired cycloadducts. Despite the lack of reactivity of the *E*-isomer, it readily undergoes photoequilibration to a mixture of *E*/*Z*-isomers, which permits the recycling of the unreactive isomer.



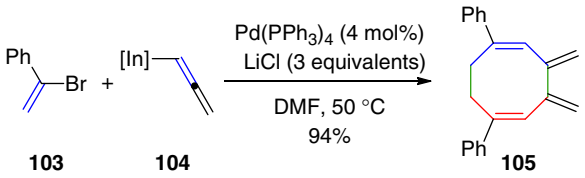
(17)

Notwithstanding the success of the intramolecular nickel-catalyzed [(4 + 4)] cycloaddition, the corresponding intermolecular reaction has received significantly less attention. Moreover, the intramolecular reaction is generally limited to diastereoselective reactions, which utilize preformed stereogenic centers to communicate stereochemical information. In contrast, the intermolecular iron-catalyzed [4 + 4] cycloaddition of **100** and **101**, using a chiral iron-complex, affords 1,5-cyclooctadiene **102** with moderate enantioselectivity (equation 18).[45] The reaction is highly selective for the formation of **102** despite the possibility of constitutional isomers and potential dimerization products. Although the reaction proceeds efficiently with a low catalyst loading using a cheap and nontoxic transition metal, it has not been further developed.



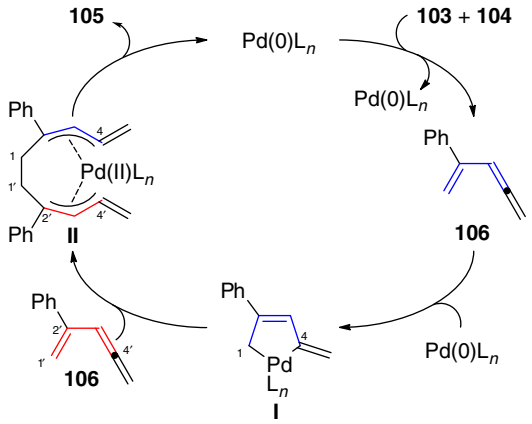
(18)

Vinyl allenes also provide four-carbon synthons for palladium-catalyzed [4 + 4] cycloadditions.[46] For instance, Lee and coworkers demonstrated that vinyl allenes can be generated *in situ* through a palladium-catalyzed cross-coupling of α-bromo styrene and allenyl indium (equation 19).[47] The one-pot sequential coupling/[4 + 4] cycloaddition generates the eight-membered adduct **105** in excellent yield favoring the head-to-head rather than the head-to-tail cycloadduct, in addition to providing competing [4 + 2] cycloadducts that are generated from sterically encumbered allenes (not depicted for clarity).



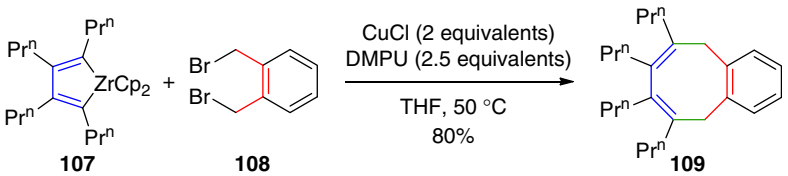
(19)

Scheme 21 highlights the proposed catalytic cycle for this process. Initial cross-coupling of **103** and **104**, via oxidative addition of palladium into the α-bromo styrene followed by transmetallation and reductive elimination, affords the vinyl allene **106** and regenerates the active palladium(0) catalyst. Oxidative addition of the metal into **106** affords palladacyclopentene **I** in a similar fashion to the corresponding isolable rhodium and platinum intermediates.[48] Subsequent chemo- and regioselective insertion at the internal double bond of a second allene into the generally less favorable alkyl–palladium bond (C1–Pd) furnishes the bis-allyl palladium complex **II** which undergoes reductive elimination between C4 and C4′ to provide the [4 + 4] adduct **105**. The existence of intermediate **II** also rationalizes the formation of the [4 + 2] cycloadduct, which arises via reductive elimination between C4 and C2′. Despite efforts to increase the synthetic potential of this multicomponent reaction, including manipulation of the exocyclic olefins in a sequential Diels–Alder reaction, the products are limited to aryl and silyl groups at C2 (and C2′).[47]



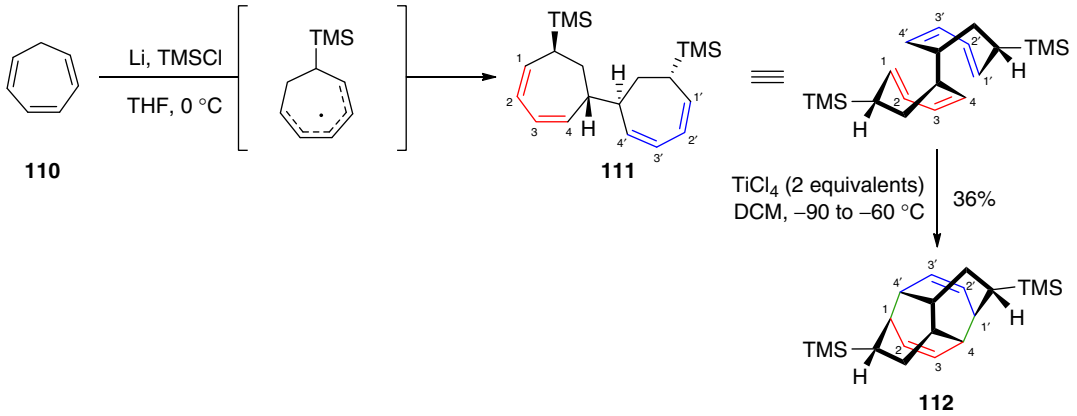
Scheme 21 Catalytic cycle for the palladium-catalyzed [4 + 4] dimerization of vinyl allenes.

The combination of bis-electrophiles with bis-nucleophiles also provides a convenient approach to eight-membered cycloadducts. Moreover, this process provides almost unlimited versatility given that the number of atoms linking each component defines the type of cycloaddition. For example, nucleophile **107** and electrophile **108** behave as four-carbon synthons and provide the desired [4 + 4] product in 80% yield (equation 20), whereas 1,8-bis(bromomethyl)naphthalene provides a five-carbon electrophile for the [5 + 4] cycloaddition with **107**.[49] The reaction proceeds via a sequential transmetallation/nucleophilic substitution reaction of the zirconium species with copper(I) chloride, in which catalytic copper can be utilized in the absence of *N*,*N*′-dimethyl-*N*,*N*′-trimethyleneurea (DMPU), albeit extended reaction times and a reduction in yield is usually observed.



(20)

Santelli et al. recently reported the titanium-mediated intramolecular [(4 + 4)] cycloaddition of 1,3-cycloheptadienes to generate the highly intriguing cage structure **112** from bis-cycloheptadiene **111**, which in turn can be constructed from the dimerization of the radical anion derived from cycloheptatriene (**110**) (Scheme 22).[50] The structure of the cycloadduct **112** was confirmed by X-ray diffraction, which provided additional physical information on the nature of the cage structure. Interestingly, the longest carbon–carbon bonds in the molecule were the newly formed C1–C4′ and C1′–C4, which highlights the inherent strain and rigidity within the molecule. Although the role of stoichiometric titanium is unclear but vital for this process, it is proposed to most likely serve as a one-electron oxidant.



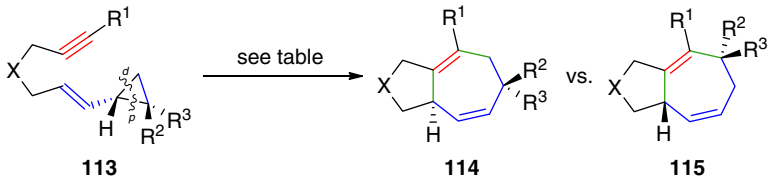
Scheme 22 Formation of cage structures via a [(4 + 4)] cycloaddition.

5.14.2.3 ['5 + 2'] Cycloadditions

The ['5 + 2'] cycloaddition has been widely utilized in the synthesis of seven-membered rings. The following section will mainly focus on the transition metal-catalyzed [5 + 2] cycloaddition of vinylcyclopropanes (VCPs), which act as five-carbon synthons. Several photochemical cycloadditions of this nature, including arene/alkene cycloadditions, are described in Chapters 5.04 and 5.15. In addition, the thermal rearrangement of VCPs is outlined in Chapter 5.22.

Since the discovery of the transition metal-catalyzed [(5 + 2)] reaction by Wender and coworkers in 1995,[51] this process has been the focal point of extensive investigation. The transition metal-catalyzed process circumvents many of the limitations associated with the thermal rearrangement of VCPs by reducing the activation barriers. The exponential growth of this reaction has led to the introduction of several transition metals to catalyze the formation of seven-membered rings, which include rhodium, ruthenium, iron and nickel. Despite the extensive research on rhodium as the catalytic species, ruthenium and iron provide important alternatives, albeit in most cases less general and certainly less well explored relative to rhodium.[52]

The intramolecular [(5 + 2)] reaction of VCP **113** bearing a tethered alkyne provides entry to highly functionalized bicyclo[5.3.0] adducts **114**/**115** in an atom-economical transformation (equation 21). Preliminary reaction conditions provided proof-of-concept for this challenging cycloaddition and required cationic Wilkinson's catalyst in toluene at 110 °C (**Table 2**, entries 1–3). In addition, the cycloadditions tolerate several substituents at R^1 to provide the corresponding cycloadducts in excellent yield.



(21)

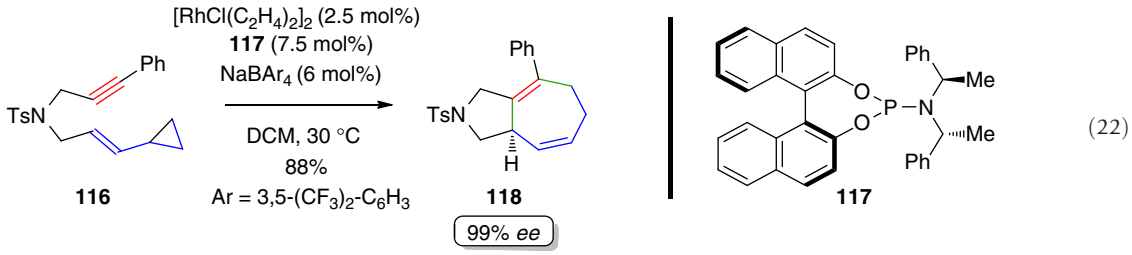
Table 2 Transition metal-catalyzed [(5 + 2)] cycloaddition of alkynyl-tethered VCPs (equation 21)

Entry	***113***	*Conditions*	***114/115***		*Yield (%)*	*Reference*
1	X = O, R^1 = Me, and R^2/R^3 = H	$RhCl(PPh_3)_3$ (10 mol%) and PhMe, 100 °C	–	**a**	88	51
2	X = O, R^1 = TMS, and R^2/R^3 = H	$RhCl(PPh_3)_3$ (10 mol%) and PhMe, 100 °C	–	**b**	83	51
3	X = O, R^1 = CO_2Me, and R^2/R^3 = H	$RhCl(PPh_3)_3$ (10 mol%) and PhMe, 100 °C	–	**c**	74	51
4	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = CH_2OH, and R^3 = H	$RhCl(PPh_3)_3$/AgOTf (10 mol%) and PhMe, 110 °C	>99:1	**d**	96	53
5	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = CH_2OH, and R^3 = H	$[Rh(CO)_2Cl]_2$ (10 mol%) and PhMe, 110 °C	2:1	**d**	86	53
6	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = CO_2H, and R^3 = H	$[Rh(CO)_2Cl]_2$ (10 mol%) and PhMe, 110 °C	1:22	**e**	73	53
7	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = CO_2H, and R^3 = H	$[(Cp)Ru(MeCN)_3]PF_6$ (10 mol%) and acetone, RT	1:3	**e**	78	54
8	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = H, and R^3 = CO_2Me	$[(Cp)Ru(MeCN)_3]PF_6$ (10 mol%) and acetone, RT	>19:1	**f**	87	54
9	X = $C(CO_2Me)_2$, R^1 = Me, R^2 = H, and R^3 = CO_2Me	$RhCl(PPh_3)_3$/AgOTf (10 mol%) and PhMe, 110 °C	6:1	**f**	95	53

Employing substituted cyclopropane derivatives is particularly challenging for these systems because the breaking of the cyclopropane ring can occur distal or proximal to the substituent (R^2/R^3). Although mechanistically more demanding, these systems provide additional functionality in the cycloadducts and stereodefined enantioenriched cyclopropanes have the potential to generate optically active products with high diastereoselectivity. In this regard, the original cationic rhodium conditions proved fruitful for this system with *anti*-substituted cyclopropanes. For example, **113** ($X=C(CO_2Me)_2$, $R^1=Me$, $R^2=CH_2OH$, $R^3=H$) furnished **114** as a single diastereoisomer in which the configuration of the cyclopropane is translated to the cycloadduct via the breaking of the distal bond (entry 4).[53] In contrast, the corresponding neutral complex, $[Rh(CO)_2Cl]_2$, because of the inner-sphere chloride counterion, furnished the same cycloadducts with poor selectivity (entry 5). Nevertheless, this system does provide advantages over the cationic complex. For instance, when R^2 is electron-withdrawing, as in **113e** (entry 6), the cycloadduct is generated via the breaking of the proximal bond. A possible explanation for the reversal in bond breaking may be attributed to the stabilization of negative charge by the electron-withdrawing group in a similar manner to 1,3-dipoles (cf. Scheme 14). Moreover, this system is far superior to others, including a ruthenium-based catalytic system, which provides poor selectivity for this cycloadduct (entry 7).[54] However, the ruthenium system is highly dependent on the stereochemistry of the cyclopropane, in which the corresponding *syn*-substituted cyclopropane afforded **114** as a single isomer in excellent yield (entry 8), whereas rhodium afforded modest diastereocontrol (entry 9). It is also noteworthy that the ruthenium catalytic system permits the reaction at room temperature.

The discovery of a more effective rhodium catalyst improves the synthetic potential of this class of reactions by facilitating these transformations under milder conditions in an analogous manner to the aforementioned ruthenium catalyst. In addition, this enables the more challenging applications, namely, cycloadditions of more demanding alkene- and allene-tethered VCPs (*vide infra*). In 2002, Wender and Williams isolated the cationic rhodium complex $[(Np)Rh(COD)]SbF_6$ (Np = naphthyl), which furnished the cycloadducts with superior results relative to other rhodium systems and has considerable stability to air and moisture.[55] For example, **113c** was converted to the desired cycloadduct in 96% yield in about 16 minutes at room temperature using only 2 mol% of this catalyst (cf. entry 3).

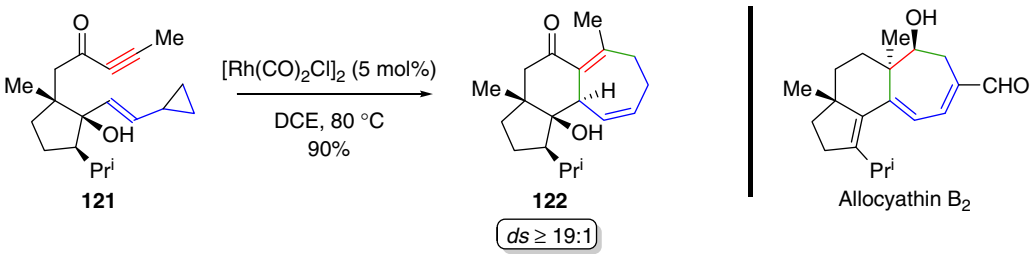
In 2004, Evans and coworkers reported the first metal-catalyzed ['$m+n+o$'] cycloaddition (*vide infra*) using a rhodium–NHC-catalyst.[56] Interestingly, this catalyst was applied to the [(5 + 2)] cycloaddition and provided analogous results to Wender's catalyst.[57] Despite several efforts to develop an asymmetric version, the only general catalytic system to afford high levels of asymmetric induction utilizes rhodium–phosphoramidite complexes (equation 22).[58] For example, the cycloadduct **118** was generated in high yield and with excellent enantioselectivity using the chiral ligand **117**, in which the combination of the chirality in the binaphthyl and amine components are crucial for asymmetric induction.



(22)

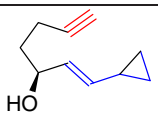
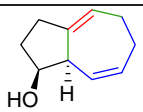
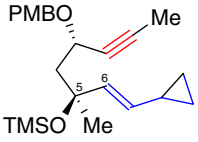
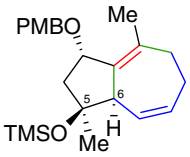
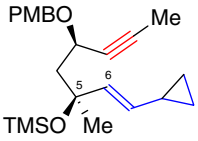
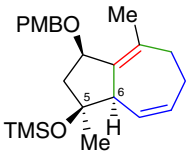
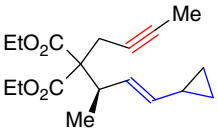
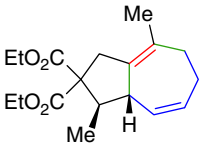
Although Wender and Trost have independently examined substituted cyclopropanes in diastereoselective [5 + 2] reactions, substituted 1,6-enynes have received significantly less attention. In this regard, ruthenium complexes are excellent catalysts, providing excellent diastereocontrol with a series of secondary and ternary allylic alcohols (Table 3).

The stereoinduction for the unprotected and trimethylsilyl-protected hydroxyls is remarkable, particularly the tertiary derivatives, because the ability to distinguish between a methyl and hydroxyl group is very challenging. In addition, the diastereoselectivity is controlled solely by the allylic stereochemistry (vs. proparglic), for example, **119b** and **119c** furnish **120b** and **120c**, respectively, which have the same relative configuration at C5/C6. Moreover, the stereoselectivity cannot be rationalized by invoking a steric repulsion model for the approaching metal, which prompted the authors to propose an 'inside alkoxy' model to provide a plausible rationale for the stereoinduction, in which the σ^*_{CO} orbital is aligned orthogonal to the alkene to minimize overlap with the alkene π-orbital.[54b] In contrast, the rhodium-catalyzed cycloaddition of **121**, in which the 1,6-enyne component is tethered via a fused five-membered ring, provides the cycloadduct **122** with the opposite stereochemistry (equation 23). The stereoselective synthesis of **122** provided a key step in the asymmetric synthesis of the tricyclic core of (+)-allocyathin B_2.[59]



(23)

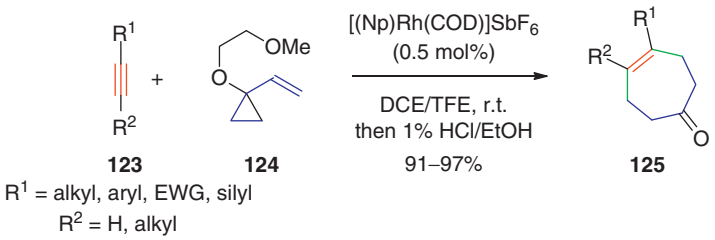
Table 3 Diastereoselective [5 + 2] cycloadditions of VCPs and alkynes

Entry	*VCP/alkyne **119***	*Conditions*	*Cycloadduct **120***		*ds*	*Yield (%)*	*Reference*
1		$[(Cp)Ru(MeCN)_3]PF_6$ (10 mol%) and acetone, RT		**a**	≥19:1	86	54b
2		$[(Cp)Ru(MeCN)_3]PF_6$ (10 mol%) and acetone, RT		**b**	≥19:1	70[a]	54b
3		$[(Cp)Ru(MeCN)_3]PF_6$ (10 mol%) and acetone, RT		**c**	≥19:1	72[a]	54b
4		$(Cp)Fe(C_2H_4)_2 \cdot$ LiTMEDA (20 mol%) and PhMe, 90 °C		**d**	9:1	92	60

[a]Combined yield of cycloadduct and desilylated cycloadduct.

Interestingly, iron also catalyzes this type of transformation, which provides great advantages over ruthenium and rhodium catalysts, because iron is cheap, nontoxic, and abundant compared to the others. The iron-catalyzed [5 + 2] reaction was reported in 2008 by Fürstner and coworkers and affords good levels of stereoselectivity in excellent yield for a range of substituted VCPs.[60] Although the reaction provides inferior results compared to the rhodium and ruthenium systems with respect to the reaction conditions, catalyst loading, and so on, the ability to utilize iron in this type of transformation is significant and has far-reaching implications for the development of this field.

Wender and coworkers also developed the intermolecular rhodium-catalyzed [5 + 2] cycloaddition. Extensive studies identified the methoxyethyl substituted VCP as the optimal precursor, which is readily prepared on a preparative scale and facilitates mild cleavage of the resulting enol ether to the cycloheptanone upon hydrolytic work-up.[61] Moreover, the cationic complex $[(Np)Rh(COD)]SbF_6$ provided an ideal precatalyst, which allowed for very low loadings to be employed at room temperature (0.5 mol%), affording a library of cycloadducts in excellent yield (equation 24).



123 **124** **125**

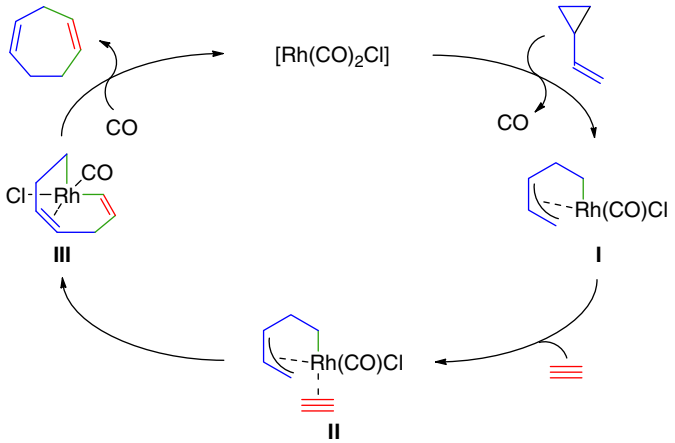
R^1 = alkyl, aryl, EWG, silyl
R^2 = H, alkyl

(24)

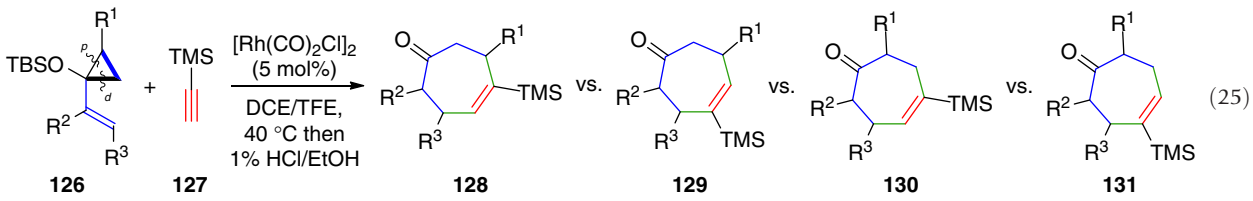
Two plausible mechanisms for the intra- and intermolecular rhodium-catalyzed ['5 + 2'] reactions have been proposed, in which the former is thought to be analogous to 1,6-enyne cycloadditions (*vide infra*) that proceed via initial oxidative addition to furnish a metallacyclopentene intermediate that undergoes *β*-carbon elimination and reductive elimination. The selectivity in the cycloadducts supports this hypothesis, albeit the evidence is circumstantial rather than definitive. Extensive computational studies using density functional theory (DFT) for the intermolecular variant provides insight into the mechanism and suggests that oxidative addition occurs solely with the VCP to generate the η^3-allyl-rhodium species **I** (**Scheme 23**). Coordination of the alkyne provides the 18-electron complex **II**, which undergoes an unusual migratory insertion into the generally less nucleophilic η^3-allyl–rhodium bond (vs. alkyl–rhodium). The calculated transition state energy for the insertion is 13.9 kcal mol^{-1} lower than the corresponding insertion into the alkyl–rhodium bond. A $C(sp^2)$-$C(sp^3)$ reductive elimination of metallacycle **III** provides the cycloheptadiene.[62a,b]

In the intermolecular reaction, the orientation of the alkyne during the insertion step dictates the regioselectivity of the reaction using unsymmetrical alkynes. However, the combination of pseudosymmetric VCPs (**124**) with *in situ* deprotection

provides **125**, in which the regiochemical information is effectively destroyed (equation 24). Table 4 outlines the extension of this process to the selective combination of monosubstituted alkyne **127** with substituted VCPs **126** (equation 25).[62c,d]



Scheme 23 Catalytic cycle for the intermolecular rhodium-catalyzed [5 + 2] cycloaddition between VCP and acetylene.



(25)

Table 4 Regioselective intermolecular [5 + 2] cycloadditions of VCPs and alkynes (equation 25)

	126						
Entry	R^1	R^2	R^3		***128*:*129*:*130*:*131***	*Yield (%)*	*Reference*
1	Me	H	H	**a**	1:1:≥19:1	87	62d
2	H	Me	H	**b**	≥19:1:–:–	85	62d
3	H	H	Me	**c**	≥19:1:–:–	74	62d

In a similar manner to the intramolecular reaction, substituted cyclopropanes can undergo bond cleavage at the proximal or distal position. When R^1 = Me, the reaction affords cycloheptanone **130** as a single constitutional isomer, in which the methyl group is α to the ketone. This product arises from cleavage of the less substituted distal bond of the cyclopropane (*d*), which is consistent with the results observed in the intramolecular process. In addition, the regioselectivity for **130** over **131** is a result of a less congested transition state in the C–C bond forming process, which is 2.2 kcal mol^{-1} lower in energy (entry 1). The steric influence in the transition state is more pronounced when R^2 and R^3 are methylated (entries 2 and 3), which is reflected by the calculated relative energies between the favored and disfavored transition states of 2.3 and 8.0 kcal mol^{-1}, respectively (Figure 4). Although the in-depth analysis of such processes is crucial for future applications in synthetic chemistry, the scope of the regioselective intermolecular [5 + 2] is limited, in most examples, to sterically encumbered trimethylsilyl groups.[62d]

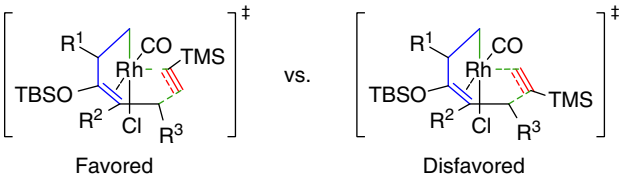
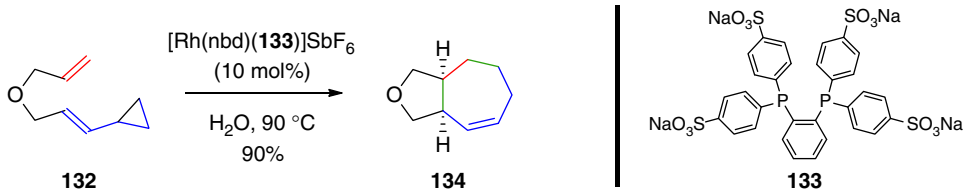


Figure 4 Transition states for alkyne insertion in the intermolecular [5 + 2] cycloaddition.

Additional computational studies also probed the analogous process of VCPs with alkenes and allenes. Although the corresponding intramolecular reactions have been described (*vide infra*), DFT analysis provided an important insight into the lack of reactivity in the intermolecular reaction between VCPs and alkenes.[62b] For example, the rate-limiting step for the reaction of alkynes and allenes with VCPs is the insertion of the exogenous π-component, whereas the rate-limiting step for the corresponding alkenes is the reductive elimination. This can be attributed to a more challenging C(sp^3)-C(sp^3) versus C(sp^2)–C(sp^3) reductive elimination (**Scheme 23**). Although the energy barriers for insertion of the π-components are all similar, the difference in reductive elimination between acetylene and ethylene is 33.6 kcal mol^{-1}. These observations also rationalize why more forcing conditions are required for alkenes in the corresponding intramolecular reaction ($RhCl(PPh_3)_3$/AgOTf (10 mol%), PhMe, 110 °C). Nevertheless, alkene- and allene-tethered VCPs readily undergo this type of transformation, in which new and improved catalysts facilitate these reactions under milder conditions.

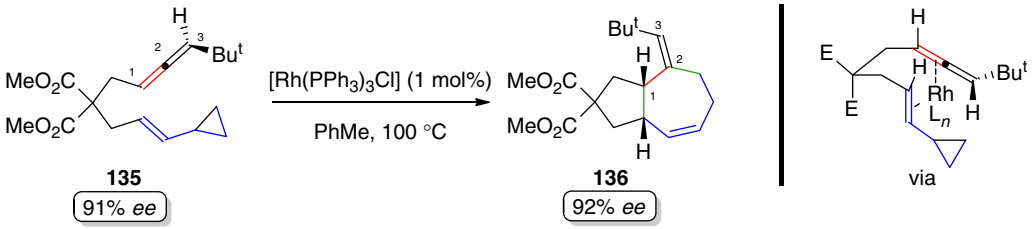
In an effort to improve the economical and environmental factors surrounding homogenous transition metal catalysts in organic media, a water-soluble rhodium-catalyst has been developed.[63] The reusable catalyst is soluble in water because of the incorporation of a tetrasulfonated bis-phosphine ligand, which coordinates to the rhodium via phosphorus. The reactions can be performed in either a methanol/water mixture or water, albeit the low solubility of the alkene-tethered VCPs in these solvents requires the reactions to be performed at high dilution (2 mM). Nevertheless, the low substrate solubility provides a high catalyst-to-substrate concentration, which reduces oligomerization and the formation of intermolecular byproducts often encountered in organic media. Hence, the process provides a highly efficient protocol for the generation of **134**, and the catalyst can be easily recovered by extraction and reused without significant reduction in the overall efficiency of the process (equation 26).



(26)

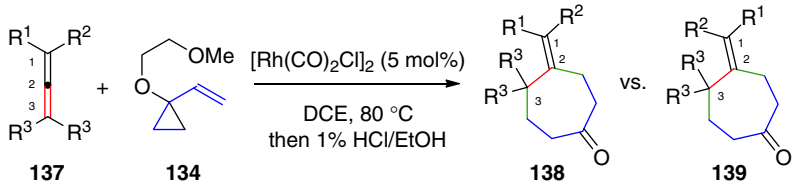
Wender and coworkers also reported the asymmetric version using an axially chiral bis-phosphine, albeit in an organic medium, and highlights the aforementioned challenges. For instance, although excellent selectivities can be achieved for specific substrates, the reaction has limited scope in terms of variations on the cycloheptene ring and requires extended reaction times (up to 8 days).[64]

The intramolecular allene-tethered VCP [(5 + 2)] cycloaddition also provides cycloadducts with two stereogenic centers and affords high *syn*-selectivity in a similar manner to alkene-tethered systems.[65] Allenes provide advantages over other systems because they furnish bicycloheptadienes that contain an *exo*-olefin adjacent to the ring-junction, a motif that is found in a variety of biologically important natural products. This is particularly interesting in light of the fact that alkene-tethered VCP systems do not tolerate terminal alkene substitution (cf. equation 26), which accounts for the number of applications utilizing allene-tethered systems to challenging natural products. In accord with the aforementioned calculations, this process was anticipated to be facile compared to the analogous alkene-tethered reaction, which is evident from the relatively short reaction times (up to 16 h). Another advantage of this system is the potential for stereospecific reactions using enantiomerically enriched allenes. For example, the cycloaddition with the chiral nonracemic allene **135** provides complete chirality transfer to afford **136** in a highly chemo- and diastereoselective fashion (equation 27).[65] The formation of a single geometrical isomer is consistent with the formation of a metallacyclopentane via oxidative addition into the allene–alkene moiety whereby the rhodium coordinates to the opposite face of the sterically demanding *tert*-butyl substituent. The preferential oxidative addition into the C1/C2 allene bond is particularly noteworthy because related rhodium-catalyzed [(2 + 2) + 1] and [(4 + 2)] cycloadditions provide products resulting from the breaking of the C2/C3 allene bond.[1i]



(27)

The intermolecular variant of this process is more challenging due to the formation of geometrical isomers, and mirrors many of the problems encountered in the intermolecular reaction of VCPs with alkynes (equation 28).[66] The bicycloheptanones are generated via the selective insertion of the C2/C3 double bond of the allene, which affords products with quaternary stereogenic centers when R^3 is substituted (**Table 5**). However, the orientation of the allene is nonselective and gives rise to geometrical isomers **138**/**139**, in which typical selectivities range from 1.2:1 to 5:2.

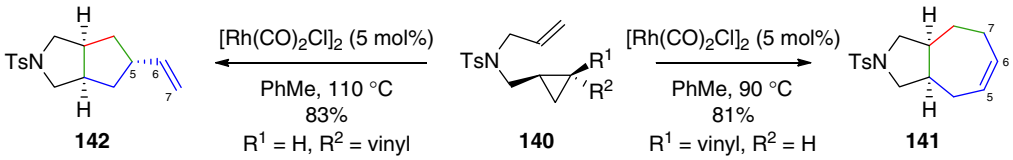


(28)

Table 5 Regioselective intermolecular [5 + 2] cycloadditions of VCPs and allenes (equation 28)

	137						
Entry	*R^1*	*R^2*	*R^3*		***138*:*139***	*Yield (%)*	*Reference*
1	≡-TMS	C_4H_9	Me	**a**	5:2	80	66
2	≡-CN	H	Me	**b**	3:2	99	66
3	≡-Ph	H	Me	**c**	2:1	83	66
4	≡-Ph	H	H	**d**	–	NR	66

In 2008, Yu and coworkers described the rhodium-catalyzed [(5 + 2)] and [(3 + 2)] cycloadditions of alkene-tethered internal VCPs.[67] The internal allylic cyclopropane was utilized, which depending on the diastereoisomer employed led to the formation of five- and seven-membered adducts. For example, the *syn*-substituted cyclopropane afforded the [(5 + 2)] cycloadduct, whereas the *anti*-substituted cyclopropane furnished the [(3 + 2)] product (Scheme 24). The reaction is thought to proceed via oxidative addition into the VCP followed by carbometallation into the pendant alkene. This provides an η^3-allyl-rhodium at C5–C7 which can either undergo reductive elimination at the termini to afford the [(5 + 2)] adduct **141** or at the internal position to furnish the [(3 + 2)] adduct **142**. The location of the olefin in cycloadduct **141** is noteworthy, because this complements the products obtained from terminal VCPs (cf. equation 26).



Scheme 24 Divergent rhodium-catalyzed [(5 + 2)] and [(3 + 2)] cycloadditions of alkene-tethered VCPs.

Overall, the use of transition metals to catalyze ['5 + 2'] cycloaddition reactions of VCPs has been very successful. Although work is still required for the development of a general enantioselective protocol, the ability to utilize enantioenriched VCPs and peripheral stereogenic centers to provide enantiopure cycloadducts is noteworthy. This strategy has been successfully employed in the total synthesis of a number of challenging natural products. For example, tremulenolide A was prepared using a rhodium-catalyzed [(5 + 2)] cycloaddition of an alkyne-tethered VCP, whereas the synthesis of frondosin A utilized a ruthenium-catalyzed reaction (Figure 5). Aphanamol I and dictamnol were also constructed via rhodium-catalyzed cycloadditions of allene-tethered VCPs.[68]

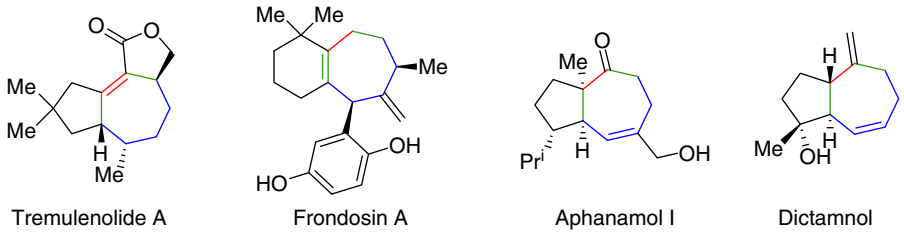
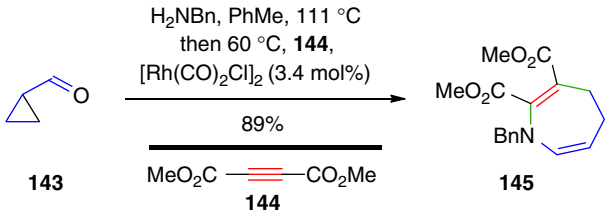


Figure 5 Natural products synthesized via transition metal-catalyzed [(5 + 2)] cycloadditions of VCPs.

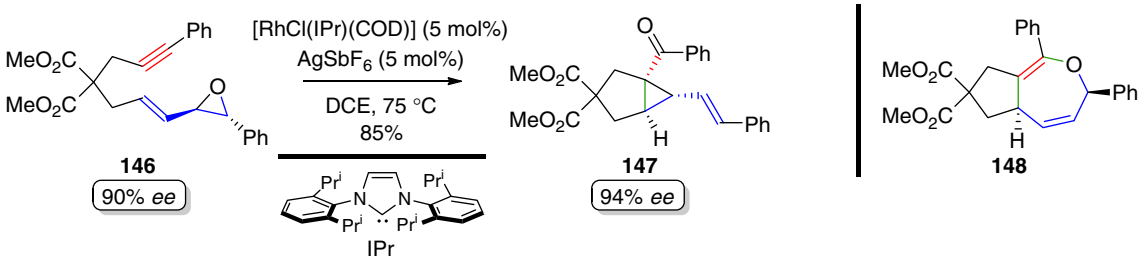
Several adaptations to the more classical VCP cycloaddition chemistry broaden the scope of these transformations to the addition of heteroatoms and the preparation of different ring sizes. For example, the aforementioned [5 + 2] adducts have all focused on the formation of carbocycles, however, two examples have been described that provide access to heterocycles via similar pathways. In 2002, cyclopropyl imines were utilized with activated alkynes in an analogous manner to VCPs (equation 29),[69] to afford seven-membered dihydroazepines in excellent yield on a preparative scale (15 mmol). Interestingly, the

lower reactivity of the *in situ* generated cyclopropylimine mandates the slow addition of the alkyne **144** (12 h) to eliminate competing [2 + 2 + 2] cycloadducts from the combination of two alkynes with the imine.



(29)

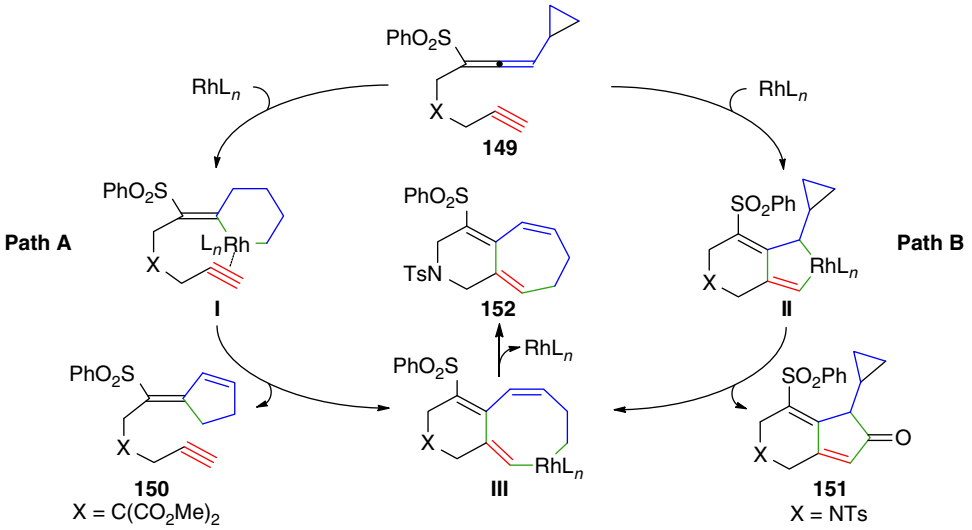
Heteroatom substituents in the cyclopropane ring, namely vinyl epoxides, can also participate in such transformations. The predicted products from this transformation are 2,5-dihydrooxepins, which are known to undergo intramolecular Claisen rearrangement to afford the corresponding aldehydes.[70] Hence, the rhodium-catalyzed rearrangement of vinyl epoxide **146** affords the 2,5-dihydrooxepin **148** *en route* to VCP **147** (equation 30).



(30)

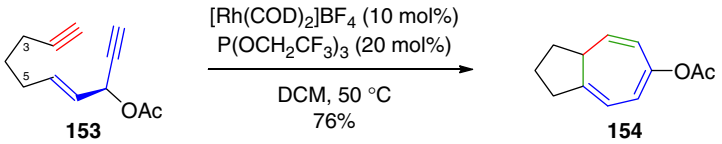
The proposed mechanism is similar to the intramolecular cycloaddition of alkyne-tethered VCPs developed by Wender and Trost, albeit leading to the formation of the heterocyclic cycloadduct **148**. Moreover, it is unclear whether the rearrangement of **148** to afford **147** is a thermal or rhodium-catalyzed process. Nevertheless, the rearrangement favors the formation of **147** by virtue of the stable carbonyl functionality, which compensates for the ring strain in the formation of the cyclopropane. Despite the reversibility of the Claisen rearrangement, enantioenriched vinyl epoxides, such as **146**, afford excellent chirality transfer to the Claisen product **147** (equation 30).

In a recent adaptation to utilizing VCPs, alkyne-tethered allenylcyclopropanes were reported to undergo facile intramolecular [(5 + 2)] cyclization to afford bicyclo[5.4.0] and bicyclo[5.5.0] systems.[71] The reaction occurs exclusively at the allene C=C bond in **149** that is proximal to the cyclopropane to afford the bicyclo[5.4.0]undecatriene **152** in 86% yield (**Scheme 25**). The reaction conditions mimic those previously reported for similar transformations, with $[Rh(CO)_2(dppp)Cl]_2$ (10 mol%) in toluene at 80 °C being optimal. The formation of cycloadduct **152** can occur via two plausible pathways. Oxidative addition into allenylcyclopropane to afford **I**, followed by alkyne insertion should furnish **III**, which on reductive elimination will provide **152** (Path A). Alternatively, oxidative coupling into the enyne moiety of **149** would provide **II**, which could generate the [(5 + 2)] adduct via *β*-carbon elimination and reductive elimination (Path B). It is conceivable that both pathways may be operating depending on the reaction conditions and substrate, because **150** was isolated as a byproduct under the optimal reaction conditions and **151** was isolated when the reaction was performed under an atmosphere of carbon monoxide.



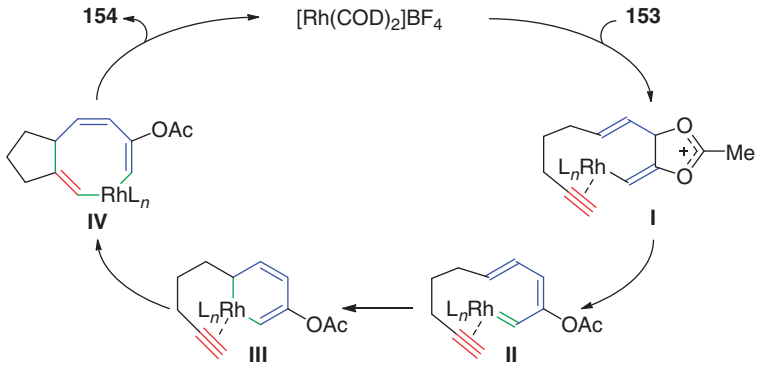
Scheme 25 Rhodium-catalyzed [(5 + 2)] cycloaddition of alkyne-tethered alleneylcyclopropanes.

Recently, the development of the rhodium-catalyzed [(5 + 2)] cycloaddition, which employs propargylic acetates rather than strained rings, further highlights the versatility of this process. The vinyl propargylic acetate provides a five-carbon synthon, which undergoes intramolecular cycloaddition with tethered π-components (equation 31).[72] For example, enediyne **153** affords **154**, which represents a synthetically useful intermediate; however, a major limitation of this reaction is that substituents at C3 or C5 do not provide useful levels of stereocontrol.



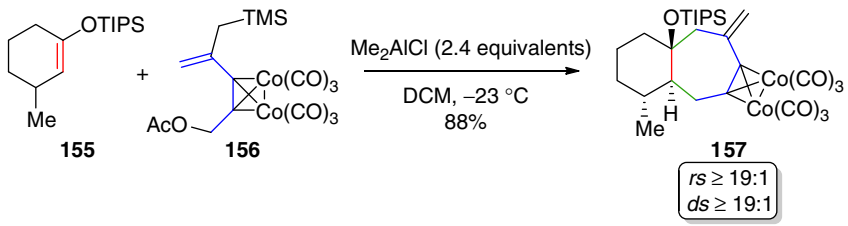
(31)

Propargylic acetates afford Rautenstrauch intermediates similar to **I** via a 1,2-acyloxy migration, which rearrange to afford the rhodium(I)-carbene (**II**). Electrocyclization of **II** to provide **III**, followed by migratory insertion of the pendent alkyne affords **IV**, which undergoes C(sp^2)–C(sp^2) reductive elimination to provide cycloadduct **154**. Additional support for the formation of a rhodium–carbene **II** was established through the isolation of a small amount of a cyclopropane byproduct, generated from the reaction with the olefin of the 1,5-cyclooctadiene ligand. Interestingly, performing the reaction in the presence of excess 1,5-cyclooctadiene furnished the [2 + 1] adduct as the major product. Despite the well-established rearrangement reactions of propargylic acetates in the presence of gold and platinum complexes, in addition to Brønsted acids, none of these systems promote the [(5 + 2)] cycloaddition (**Scheme 26**).



Scheme 26 Rhodium-catalyzed [(5 + 2)] cycloaddition via a Rautenstrauch intermediate.

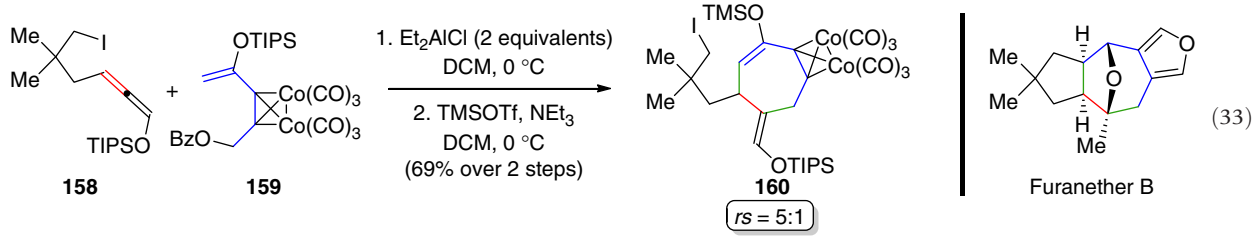
The construction of seven-membered carbocycles from a [5 + 2] cycloaddition using conventional organic chemistry has been relatively unexplored, which is somewhat surprising given the number of [3 + 3] cycloadditions that employ this type of chemistry. Nevertheless, there are examples of sequential nucleophilic substitution reactions of substrates that contain reactive nucleophilic and electrophilic moieties that participate in formal [5 + 2] cycloadditions to generate highly functionalized polycycles. For example, **155** and **156**, which have nucleophilic and electrophilic sites, react to furnish the cycloadduct **157** in excellent yield (equation 32).[73a] The reaction affords excellent diastereoselectivity for the formation of the *anti,anti*-stereotriad by using the resident stereogenic center to direct the allylation. The stereoselectivity for the formation of the *anti*-ring junction is controlled by the facial attack of the allyl silane on the intermediary oxocarbenium ion, which forms from the direct alkylation of the silyl enol ether **155** with **156**. Interestingly, acyclic silyl enol ethers afford the *syn* ring junction irrespective of the nature of the starting olefin, which further supports the proposed stepwise mechanism. In addition, the formation of five-membered adducts from the intramolecular cyclization of **156** were not observed in these reactions.



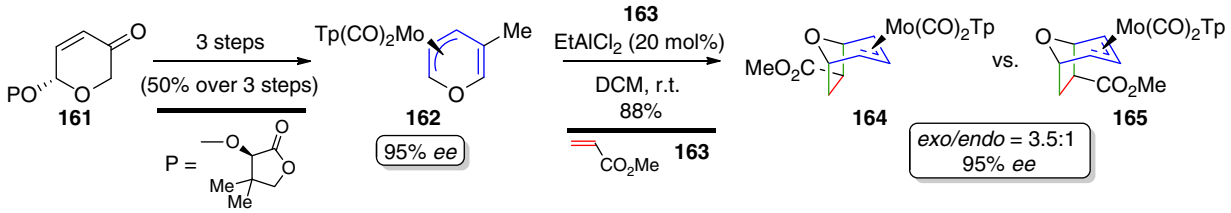
(32)

This concept was recently adapted to allow silyl enol ethers, instead of allyl silanes, as the nucleophilic coupling partner on the cobalt species. Although, the replacement of the silyl enol ether with a silyloxyallene provides comparable reactivity, the reactions

are significantly less selective (*rs*=5:1). This process was highlighted in a 15-step synthesis of the lactarane natural product, furanether B (equation 33).[73b]



In a series of reports, Liebeskind and coworkers described the synthetic utility of enantiomerically enriched molybdenum complexes, which provide five-carbon synthons.[74] The air stable complexes can be prepared on gram scale with high enantiopurity by employing a diastereomerically pure chiral nonracemic precursor, such as **161**, which provides the enantiomerically enriched π-allyl molybdenum species via inversion of configuration. Addition of MeMgBr to the ketone and quenching with trifluoroacetic anhydride/triethylamine afforded, after elimination, the highly enantioenriched molybdenum complex **162**. The bulky complex contains a trispyrazolylborate (Tp) ligand to effectively block the β-face in the [5 + 2] cycloaddition with methyl acrylate (**163**) to afford a mixture of *exo*- and *endo*-cycloadducts (**Scheme 27**). The reaction is highly stereospecific affording **164**/**165** with 95% enantiomeric excess, albeit with modest *exo*/*endo* selectivity. Several demetallation protocols, including iododemetallation with iodine, oxidative demetallation with ceric ammonium nitrate (CAN) and protodemetallation with strong acids, afford highly functionalized bicyclo[3.2.1] systems with excellent selectivity. These products resemble similar [3 + 3] cycloadducts previously reported and it is important to note that the terminology that describes a given cycloaddition is a result of the movement of electrons and not necessarily the position of the newly created bonds (cf. equations 2 and 4). For example, the movement of electrons dictates that **162** is a five-carbon synthon and not a three-carbon synthon.

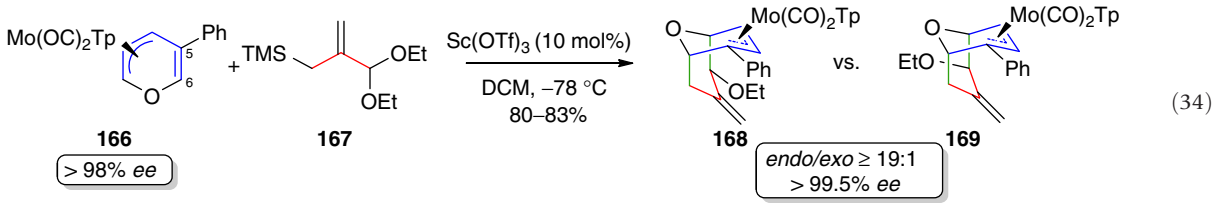


Scheme 27 Lewis acid-catalyzed [5 + 2] cycloaddition of η^3-molybdenum complexes.

5.14.2.4 ['5 + *n*'] Cycloadditions

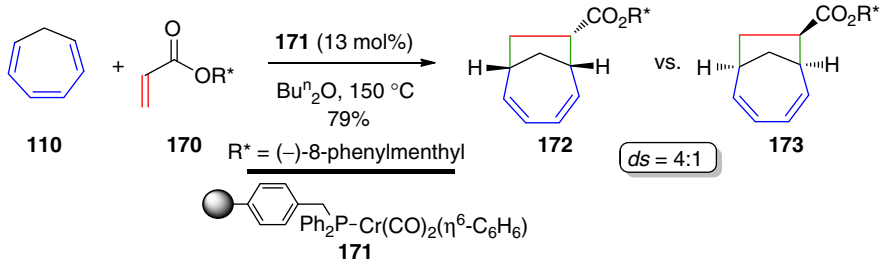
This section describes higher-order ['5 + *n*'] cycloadditions, where *n*=3–5, which have great potential for the rapid and stereoselective construction of eight-, nine-, and ten-membered carbocycles. Consistent with the theme of this chapter, photochemical [5 + 4] cycloadditions are described in Chapters 5.04 and 5.15. Despite the synthetic potential of this class of reactions, it is somewhat surprising that this area has received little consideration.

In this context, the extension of the synthetic utility of η^3-molybdenum complexes to the [5 + 3] cycloaddition was accomplished using oxyallyl cations to provide enantioenriched oxa- and aza-bridged eight-membered rings.[75] Substitution at C5 can be tolerated and affords the corresponding [5 + 3] adducts with excellent *endo*-selectivity and with complete chirality transfer (equation 34). However, the analogous C6 substituted molybdenum complexes afford [3 + 2] products, due to the C5–C6 bond behaving as a two-carbon synthon. This change in reactivity can be explained by a stepwise mechanism in which the formation of the [5 + 3] cycloadduct arises from initial attack by C6 in **166** with C3 of the oxocarbenium ion derived from **167**, followed by S_N2' addition of the allyl silane at C2 in **166**. When C6 is substituted, C5 is inherently more nucleophilic and is responsible for the initial attack onto **167**, followed by S_N2' of the allyl silane at C6 in the molybdenum complex to generate [3 + 2] cycloadducts.



5.14.2.5 ['6 + 2'] Cycloadditions

There are significantly fewer methods for the construction of medium sized rings compared to small rings, which can primarily be attributed to the challenges associated with their construction. As a result, ['6 + *n*'] cycloadditions or higher have been adapted to generate highly functionalized fused and bridged polycyclic structures from readily available precursors. The early development of this reaction involved metallated cycloheptatrienes, which provided six-carbon synthons, however, the necessity for precomplexed and stoichiometric quantities of transition metals to facilitate the transformation made it undesirable.[76] Recently, these limitations have been overcome with the development of catalytic systems using chromium and cobalt which not only eradicate the requirement for initial light irradiation, but also eliminate potential photochemical [2 + 2] byproducts that were previously observed. One of the most impressive accounts in this area has been the polymer-supported chromium-catalyzed reaction of cycloheptatriene **110** with the electron-deficient alkene **170** (equation 35).[77]

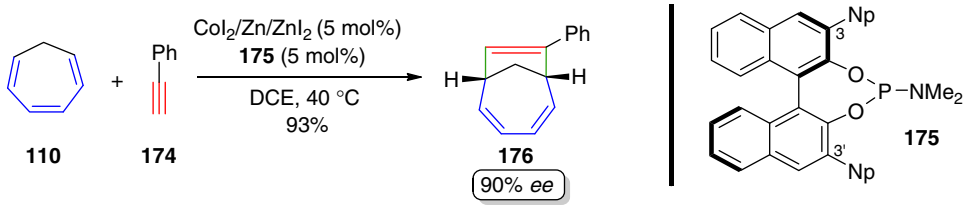


110 + **170** → **172** (*ds* = 4:1) vs. **173** (35)

171

A major drawback of the chromium-catalyzed process compared to other transition metals is the high toxicity and the difficulty associated in removing trace quantities of the transition metal catalyst. In this context, the polymer-supported chromium-complexes, which furnish the cycloadducts via filtration, provide a convenient solution for the removal of the chromium catalyst. For example, the isolated cycloadducts **172**/**173** contain less than 0.53 ppm chromium and the recovered and recycled chromium complex **171** provides similar turnover and efficiency.

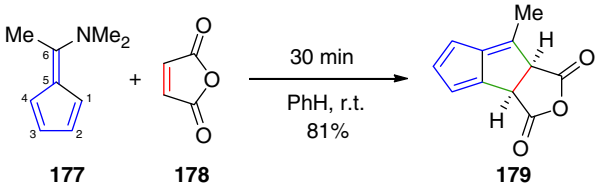
The asymmetric cobalt-catalyzed [6 + 2] cycloaddition using a chiral monodentate ligand has also been developed.[78] Treatment of cycloheptatriene **110** with phenylacetylene (**174**) in the presence of a phosphoramidite-modified cobalt-complex furnished the desired cycloadduct **176** in excellent yield and with excellent enantiomeric excess (equation 36). Interestingly, the amino component on the ligand has little impact on the enantioselectivity of the reaction, whereas the 1,1′-bi-2-naphthol (BINOL) backbone is extremely sensitive to modifications. For example, bulky aryl substituents at C3 and C3′ are optimal for the formation of the desired cycloadduct, albeit the reaction is limited to bulky terminal alkynes as the 2π-component.



110 + **174** → **176** (90% *ee*) | **175** (36)

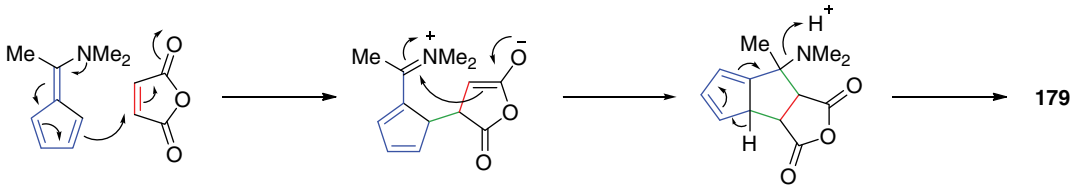
The reaction was expanded to include terminal allenes as 2π-components in a nonasymmetric fashion utilizing 1,3-bis(diphenylphosphino)propane (dppp) as an achiral bidentate phosphine ligand.[79] The most striking feature of this transformation is the stereospecific formation of tri- and tetrasubstituted *E*-alkenes in the cycloadduct, which is a result of the stereoselective incorporation of the distal allene bond.

Substituted fulvenes provide six-carbon synthons in a variety of [6 + 4] cycloadditions (*vide infra*), which nicely complements their ability to provide two- and four-carbon synthons in [2 + 2] and [4 + 2] cycloadditions, respectively. Nevertheless, the development of the [6 + 2] cycloaddition has been limited to a single example, namely the spontaneous room temperature reaction of 6-aminofulvene **177** with maleimide (**178**) to afford the tricyclic adduct **179** in 81% yield (equation 37).[80]



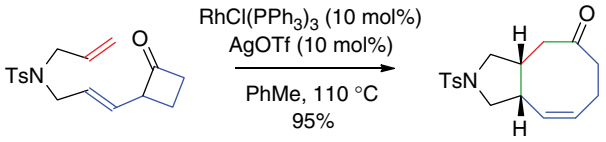
177 + **178** → **179** (37)

Scheme 28 outlines the proposed mechanism for the cycloaddition, which involves stepwise conjugate addition of the fulvene at C1 to the maleimide to furnish a zwitterionic intermediate. Enolate addition to the intermediary iminium ion followed by the elimination of protonated dimethyl amine affords the desired cycloadduct.



Scheme 28 Thermal [6 + 2] cycloaddition of fulvenes with electron-deficient alkenes.

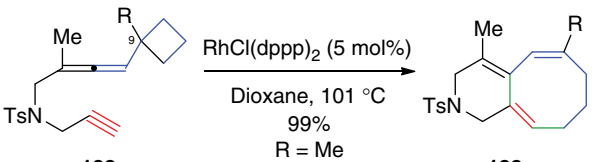
The extension of the concepts outlined in the development of the metal-catalyzed [(5 + 2)] cycloadditions provides the basis for the corresponding [(6 + 2)] cycloaddition (*vide supra*). For example, the [(5 + 2)] cycloaddition of VCPs with tethered 2π-components generates a variety of bicyclo[5.3.0] adducts, which relies on the ring strain of the cyclopropane to promote ring expansion. This concept was extended to cyclobutanones, which contain a similar amount of ring strain (29.5 kcal mol^{-1} vs. 27.5 kcal mol^{-1}), to furnish the corresponding eight-membered [(6 + 2)] cycloadducts (equation 38).[81]



180 **181** (38)

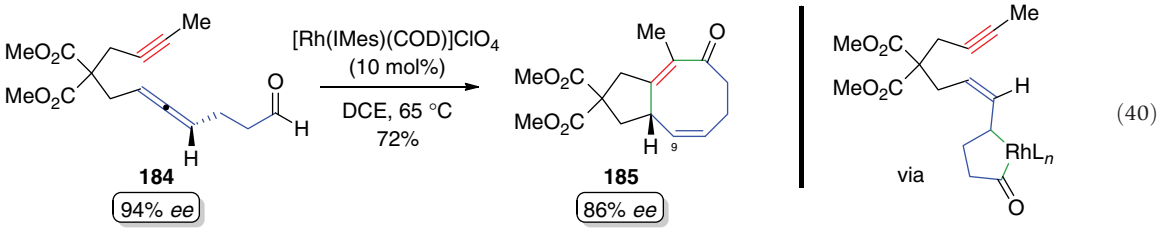
In an analogous manner to the VCP variant, the reaction concentration is critical for efficiency, in which high dilution is required to minimize oligomeric byproducts. Interestingly, the reactivity of the π-component is opposite to the VCPs, in which the alkynyl-tethered vinylcyclobutanones are unreactive in contrast to the alkene- and allene-tethered counterparts. Additionally, the reaction is amenable to the introduction of quaternary carbon stereogenic centers at either ring junction.

Mukai and coworkers described the extension of alkyne-tethered allenylcyclopropanes to the corresponding cyclobutane derivatives (cf. Scheme 25).[82] Treatment of the alkyne-tethered allenylcyclobutane **182** with the rhodium complex $RhCl(dppp)_2$ promoted intramolecular cycloaddition to afford the bicyclo[6.4.0] system **183** in excellent yield (equation 39). The mechanism is consistent with the process outlined in Scheme 25 (Path B), because the lack of substitution at C9 (R≠H) results in competitive β-hydride elimination (vs. β-carbon elimination) of the rhodacyclopentene intermediate to provide ene-cycloisomerization byproducts with varying degrees of chemoselectivity. Hence, synthetically useful yields in this process are only achieved when R≠H.



182 **183** (39)

A particularly impressive example of a formal rhodium-catalyzed [(6 + 2)] cycloaddition was reported by Sato and coworkers, in which they demonstrated that intramolecular cyclization of the alkynyl-tethered allenal **184** furnished the cyclooctadienone **185** in good yield (equation 40).[83] The reaction is mechanistically intriguing because it is thought to resemble a hydroacylation pathway rather than the more common rhodacyclopentene intermediate observed via direct oxidative addition into a 1,6-unsaturated moiety.

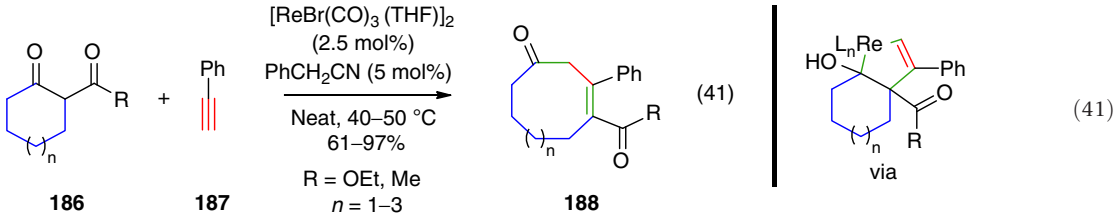


184 94% *ee* **185** 86% *ee* (40)

Hence, the cycloaddition is consistent with an initial oxidative addition into the C–H bond of the aldehyde, followed by the hydrometallation onto the proximal allene bond, which favors the formation of the five- rather than the six-membered rhodacycle. The η^1-allyl then undergoes σ–π–σ isomerization to generate a rhodacycloheptanone. The relative proximity of the pendant alkyne promotes facile insertion and reductive elimination to generate the cycloadduct. Several aspects of this work are

noteworthy; firstly, the stereospecific hydrometallation and isomerization step to furnish enantioenriched products, and secondly, deuterium labeling of the aldehyde affords the cycloadduct with 100% incorporation at C9 to support the mechanistic proposal. The reaction can also tolerate alkene-tethered allenals, which generate *syn*-fused bicycles, however, the ability to utilize alkynes is particularly significant because these products complement those generated in the rhodium-catalyzed cyclization of alkenyl-tethered vinylcyclobutanones, which fail for alkyne-tethered systems (cf. equation 38).

In 2006, Kuninobu and coworkers reported the rhenium-catalyzed insertion of acetylenes into cyclic *β*-diketones and *β*-keto esters (equation 41).[84] Although the precise mechanism of the reaction is unknown, one proposed pathway is that the reaction proceeds via oxidative addition of the rhenium into the acetylene and enol form of **186** to generate a rhenacyclopentene intermediate. Reductive elimination of the metallacyclopentene generates a 6,4-bicycle, which upon ring-opening through a retro-aldol reaction, generates the eight-membered ring. A particularly attractive feature of this transformation is the ability to extend this chemistry to [7 + 2] and [8 + 2] cycloadditions by simply increasing the number of atoms in **186** to provide nine- and ten-membered carbocyclic intermediates in comparable yields (n = 2–3). A similar one-pot [2 + 2]/ring-opening sequence was reported by Carreira and co-workers, in which the reaction of *in situ* generated benzynes with potassium keto-enolates facilitates the synthesis of bicyclic scaffolds.[85] Interestingly, the authors isolated the expected [2 + 2] adduct and demonstrated that the addition of a suitable base promoted the retro-aldol to afford the formal [5 + 2] cycloadduct.

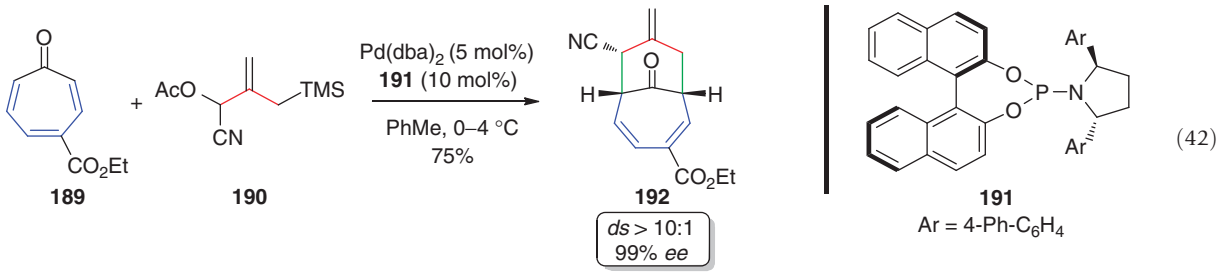


186 **187** **188** (41)

(41)

5.14.2.6 ['6 + 3'] Cycloadditions

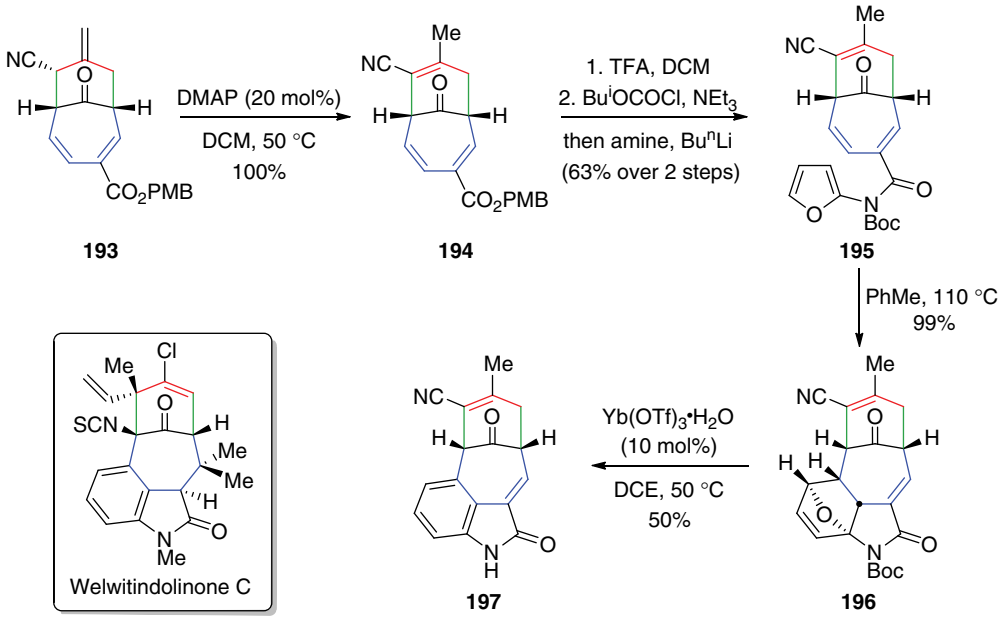
One of the most impressive developments in the ['6 + 3'] cycloaddition class has been the successful union of two well-established components, namely, cycloheptatrienes (or tropones) with TMM complexes as six- and three-carbon synthons, respectively. Initially developed in 1987 by Trost and coworkers, the same research group took advantage of the successful implementation of chiral phosphoramidites in the related [3 + 2] cycloaddition between TMM complexes and electron-deficient alkenes. This highlights the generality of TMM complexes as three-carbon surrogates in ['3 + m'] cycloadditions, because very little deviation in the reaction conditions was required for the development of the [6 + 3] version. For instance, treatment of the tropone derivative **189** with the TMM precursor **190** with the chiral phosphoramidite-modified palladium-complex furnished the bicyclo[4.3.1]-decadiene **192** in good yield and with excellent diastereo- and enantioselectivity (equation 42).[86a]



189 **190** **192** **191** (42)

X-ray crystallographic analysis of one of the cycloadducts concluded that the exocyclic alkene is within close proximity to the endocyclic 1,3-diene, which prompted the investigation of a potential [3,3]-sigmatopic rearrangement. Interestingly, microwave irradiation of the cycloadduct **192** at 170 °C provided the bicyclo[3.3.2]decadiene Cope adduct. Nevertheless, this process hampered efforts toward the synthesis of welwitindolinone C, which required the conversion of the exocyclic alkene in **193** to the *endo*-isomer **194** to suppress the [3,3] sigmatopic rearrangement (**Scheme 29**). Conversion to the amide **195**, followed by a thermal intramolecular [(4 + 2)] Diels–Alder cycloaddition generated **196** as a single diastereoisomer. Deprotection of the carbamate in **196** resulted in spontaneous dehydration of the oxabicycle to provide the oxindole **197**, which represents the tetracyclic core of the natural product.[86b]

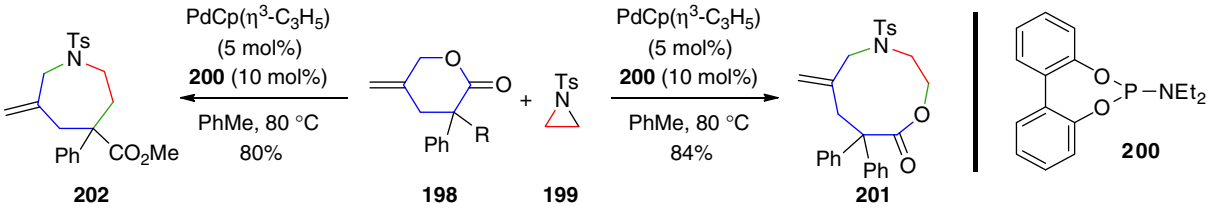
In 2005, Lu and coworkers further expanded the repertoire of cycloadditions involving tropones with the development of a phosphine-catalyzed [6 + 3] cycloaddition.[87] The reaction between tropones and Morita–Baylis–Hillman adducts (cf. **17**) afforded bicyclo[4.3.1]decane systems in good yield with no detectable levels of competing cycloadditions. Similar to the [3 + 3]



Scheme 29 Sequential [6 + 3] and [(4 + 2)] cycloadditions for the synthesis of the core of welwitindolinone C.

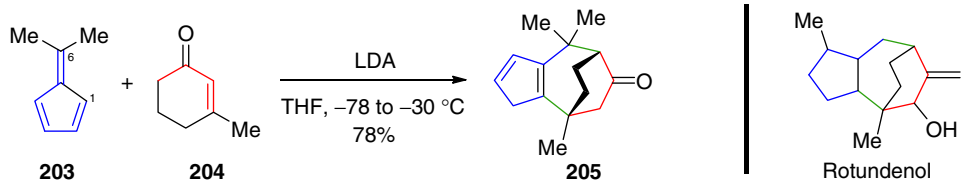
cycloaddition described earlier, *tert*-butyl carbonates provide the corresponding *tert*-butoxide anion, which acts as an internal base for the reaction (cf. Scheme 5). It is noteworthy that tropones can also undergo [4 + 2] and [8 + 2] cycloadditions with electron deficient alkenes.[1a,88]

A rare example of a ['6 + *n*'] cycloaddition that does not generate bridged bicycles was reported using γ-methylidene-δ-valerolactones and aziridines (Scheme 30).[89] This combination, under palladium catalysis, generates nine-membered rings with excellent efficiency. Moreover, the substitution of the γ-methylidene-δ-valerolactones dictates the outcome of the transformation since ester substituents (R=CO$_2$Me) provide [4 + 3] cycloadducts via a decarboxylative pathway.



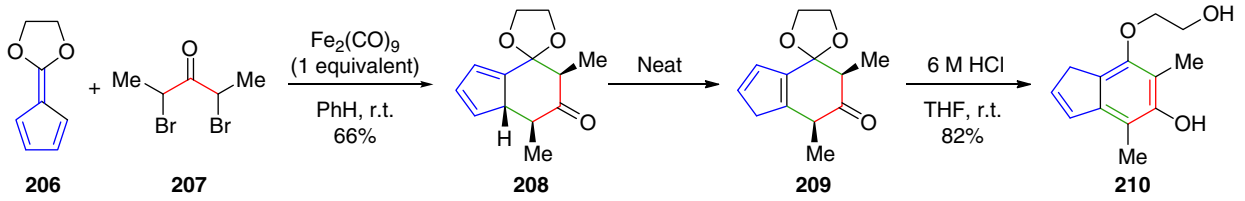
Scheme 30 Divergent [6 + 3] and decarboxylative [4 + 3] cycloadditions of γ-methylidene-δ-valerolactones and aziridines.

As described in Section 5.14.2.5 along with tropones and cycloheptatrienes, fulvenes have six π-electrons that behave as six-carbon synthons in higher-order cycloaddition reactions and, analogously to tropones, they also undergo [6 + 3] cycloadditions. Consistent with the 6-aminofulvene, 6,6-dimethylfulvenes mimic α,β-unsaturated carbonyls, which are inherently electron deficient. For example, the lithium enolate of **204** attacks C6 of the fulvene **203** to generate a new carbon–carbon bond, which enables the anion at C1 to undergo an intramolecular Michael addition onto the α,β-unsaturated ketone, which upon protonation generates the carbocycle **205** (equation 43).[90a] It is noteworthy that in one simple operation, readily available starting materials can generate an intermediate that resembles the natural sesquiterpene, rotundenol.



(43)

Oxyallyl cations also participate in the [6 + 3] cycloaddition with activated fulvenes to provide bicyclo[4.3.0]nonadienes in a highly stereoselective manner (Scheme 31).[90b] The mechanism for the cycloaddition is thought to be a stepwise process similar to that previously described for electron-rich fulvenes in the related [6 + 2] cycloaddition (cf. Scheme 28). Nevertheless, although this process generates α,α′-disubstituted ketones with good stereocontrol, it is particularly sensitive to the type of substituents on the fulvene. For example, 6-monoalkyl- and 6,6-dialkylfulvenes do not participate in the [6 + 3] cycloaddition, but preferentially react as four-carbon synthons to provide [4 + 3] cycloaddition products.

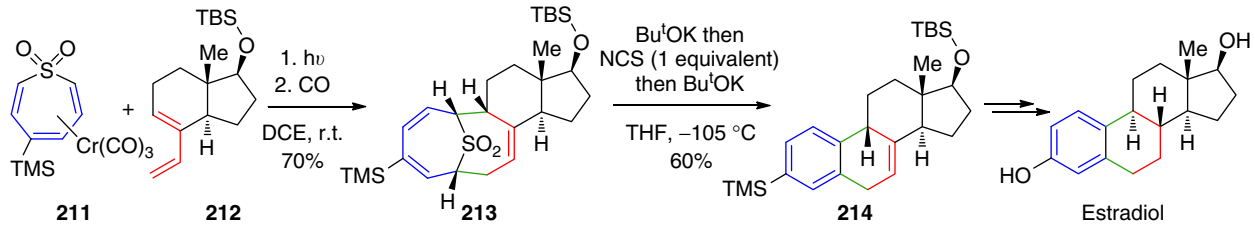


Scheme 31 [6 + 3] Cycloaddition reaction of fulvene ketene acetal with 2-oxyallyl cations.

5.14.2.7 ['6 + *n*'] Cycloadditions

Prior to the first report of a ['6 + 4'] cycloaddition, Woodward and Hoffmann's prediction provided the impetus for the development of this transformation. Hence, this process provided the focus of various synthetic and theoretical investigations, because the cycloadducts represent complex intermediates that would otherwise be difficult to prepare using conventional methods. As a result of these investigations, several reviews by Rigby have provided up-to-date accounts of their application in organic synthesis.[1a,d] The following section will briefly report on more recent state-of-the-art developments in this exciting area.

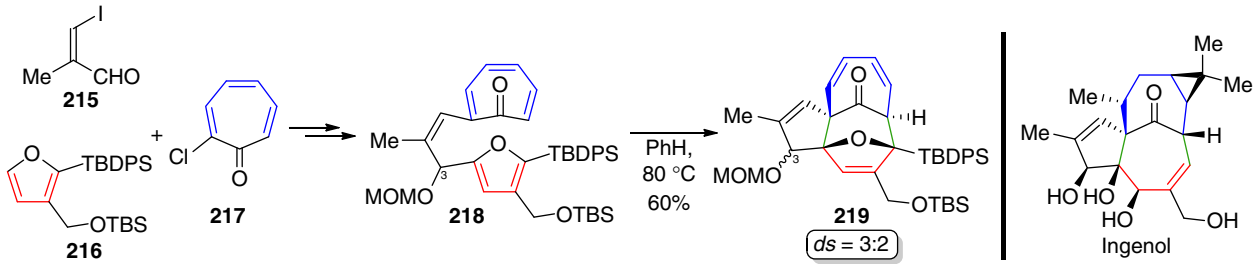
In 1999, Rigby and coworkers reported the [6 + 4] cycloaddition of metallated 6π systems with dienes for the synthesis of complex tetracyclic intermediates, which was employed as a key step in an elegant synthesis of estradiol (Scheme 32).[91] As described previously, irradiation of metallated six-carbon synthons is required to dissociate a ligand, and thereby initiate the reaction to afford the metallated [6 + 4] adduct. In this example, subjecting the crude material to an atmosphere of carbon monoxide facilitates decomplexation of the metal to generate **213**. It is important to note that the cyclic sulfones can undergo a Ramberg–Bäcklund ring contraction to provide bicyclo[3.3.0]decane systems in an efficient manner. Additionally it is possible for the sulfone to provide a tether, which would afford a monocyclic ten-membered ring upon reduction, a strategy that would be highly desirable because acyclic six- and four-carbon synthons in a [6 + 4] cycloaddition have been unsuccessful in this regard (*vide infra*).



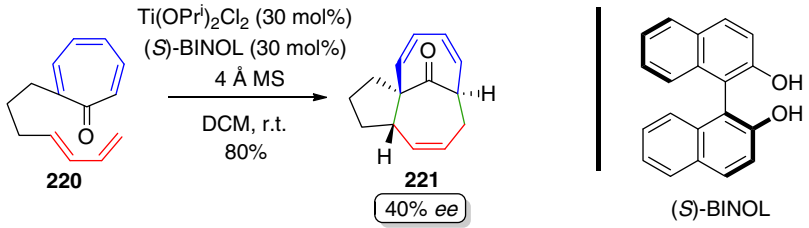
Scheme 32 Total synthesis of estradiol via an intermolecular [6 + 4] cycloaddition.

The thermal intramolecular cycloaddition of furanotropones, which do not require a metallated 6π synthon, was reported by Rigby and Chouraqui for the synthesis of oxabridged polycycles (Scheme 33).[92] The rapid construction of the precursor **218** from the vinyl iodide **215**, furan **216** and tropone **217** is particularly attractive because the final cycloadduct contains all of the required functionality for a convergent synthesis of ingenol. Moreover, the reaction occurs under relatively mild conditions, because tropones have a lower activation barrier than cycloheptatrienes in these types of cycloadditions.[93] Nevertheless, a minor limitation with this methodology is the poor diastereocontrol from the C3 methoxymethyl ether, albeit the actual cycloaddition is completely selective, due to the reaction proceeding through a well-established *exo* transition state.

Additional studies by Rigby and Fleming culminated in the first enantioselective [6 + 4] cycloaddition, which proceeded in the presence of a chiral Lewis acid catalyst at room temperature (equation 44).[94] For example, the (*S*)-BINOL-modified titanium catalyst furnished tricycle **221** from tropone **220** in excellent yield. Although the enantioselectivity was poor, this provided proof-of-principle for what is likely to be the first of several studies on enantioselective Lewis acid-catalyzed [6 + 4] cycloaddition reactions.

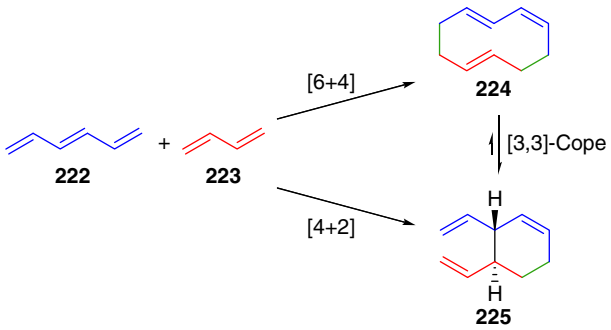


Scheme 33 Synthesis of the core of ingenol via an intramolecular [6 + 4] cycloaddition.



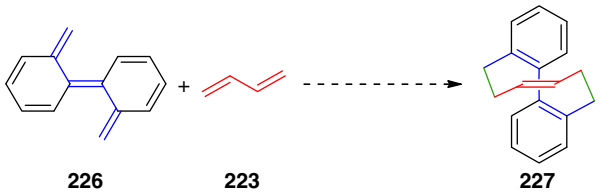
(44)

The successful implementation of acyclic components in the [6 + 4] cycloaddition reaction has been an ongoing challenge for synthetic chemistry, primarily because of competing [4 + 2] cycloadditions. Moreover, the formation of [4 + 2] adducts can also result from a favorable [3,3]-Cope rearrangement of the [6 + 4] adduct.[93,95] Hence, the preconception that the cyclization of the triene **222** with diene **223** to provide the ten-membered cycloadduct **224** would be unsuccessful, because of the facile formation of the rearranged cycloadducts, is supported by DFT studies (Scheme 34). Nevertheless, despite the fact that the 10-membered cycloadducts contain several unsaturated bonds, including *E*-alkenes, many have lower strain energies than cyclodecane, which indicates that this factor is not contributing to the failure of this type of process.



Scheme 34 Failure of the [6 + 4] cycloaddition from heptatriene and butadiene.

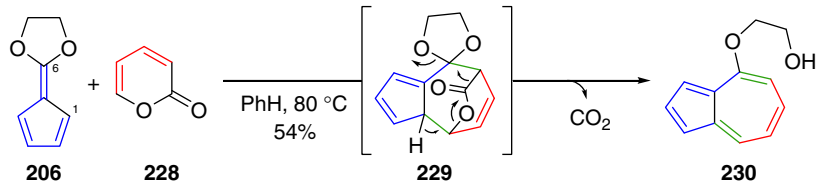
In an alternative approach, Alder and coworkers predicted that **226** and **223** should react spontaneously to afford the ten-membered ring without concomitant formation of the [4 + 2] cycloadduct (equation 45).[95] Moreover, the computed activation energy of the Cope rearrangement suggests that it should not be a spontaneous reaction, since the substituents will be deconjugated. However, this process is purely hypothetical, because this prediction has not been successfully demonstrated at this juncture.



(45)

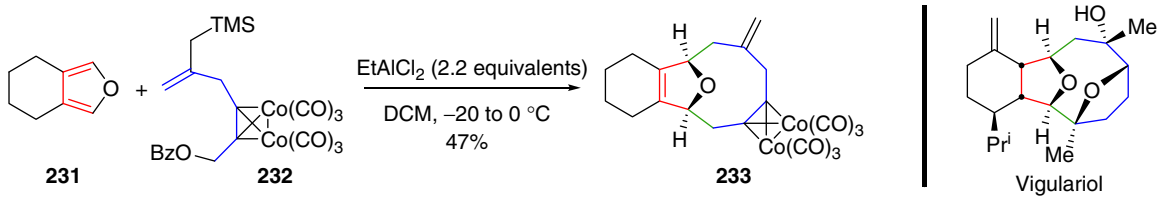
In contrast, the fulvene-derived six-carbon synthon **206** undergoes a thermal [6 + 4] cycloaddition with the butadiene equivalent **228**, which upon decarboxylative aromatization of **229** generates the azulene cycloadduct **230** in moderate yield

(equation 46). Although 6-aminofulvenes can be employed in this reaction, the yields for the formation of the azulenes are generally low, whereas alkylfulvenes are completely unreactive as six-carbon components.[96] This behavior is rationalized by frontier molecular orbital (FMO) theory, which suggests that larger coefficients at C6 (cf. **177** and **206**) promote the [6 + 4] cycloaddition by increasing the energy of the next highest occupied molecular orbital (NHOMO).



(46)

Continuing on the theme of six-carbon synthons, the final example in this section involves the extension of a five-carbon synthon outlined in Section 5.14.2.3. Hence, the addition of a methylene unit to the dicobalt acetylene complex provides a six-carbon synthon to facilitate a [6 + 4] cycloaddition with furan derivatives. For example, treatment of furan **231** with **232** in the presence of a Lewis acid, affords the corresponding nine-membered ring commonly found in the cladiellin family of diterpenes, which includes vigulariol (equation 47). Although the reaction afforded poor yield of the cycloadduct, monosubstituted furans furnish the corresponding cycloadducts with improved yield (up to 85%).[97]



(47)

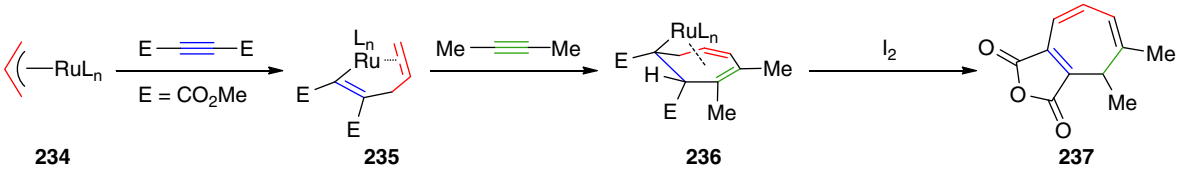
5.14.3 ['*m* + *n* + *o*'] Cycloadditions

The intermolecular three-component cycloaddition is intrinsically more difficult than two-component variants, because in the most challenging scenario they require the successful union of three different π-components. Hence, the ability to prepare the 1:1:1 adducts over competing 1:2 adducts as well as products from dimerization and trimerization highlights the challenges associated with the development of novel ['*m* + *n* + *o*'] cycloadditions. It is therefore unsurprising that transition metals have played a critical role in the development of this field, because they facilitate the selective and systematic construction of systems that are generally not accessible via classical pericyclic reactions, often in a chemo-, regio-, and stereoselective manner. The following section will describe ['3 + 2 + 2'], ['4 + 2 + 2'] and ['4 + 3 + 2'] cycloadditions, however, ['2 + 2 + 2'] (*see* Chapter 5.31) and ['2 + 2 + 1'] (*see* Chapter 5.24) cycloadditions are not discussed.

5.14.3.1 ['3 + 2 + 2'] Cycloadditions

The ['3 + 2 + 2'] cycloaddition is one of the least explored classes of cycloaddition reactions. Nevertheless, some of the developments in this class represent groundbreaking achievements in providing highly functionalized seven-membered rings. The paucity of new developments in this field is presumably the result of relatively few three-atom synthons that can participate in transition metals catalyzed reactions, and as a result, these have been largely limited to π-allyls, Fischer carbenes and cyclopropanes.

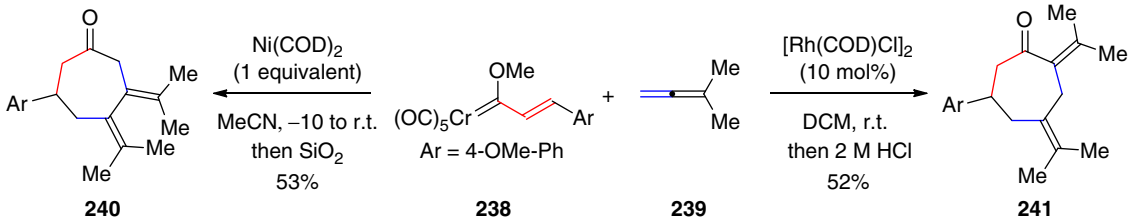
In the 1990s, Stryker and coworkers reported a number of transition metal-mediated [3 + 2 + 2] cycloaddition reactions of metal π-allyls with two alkynes.[98] The insertion of the first alkyne into the precomplexed π-allyl (**234**) affords the ruthenium complex **235**, which is followed by the insertion of the second alkyne to generate the seven-membered carbocycle **236**, in which the metal can undergo iodinolysis to afford the bicycloheptatriene **237** (Scheme 35). Interestingly, the isolation of the intermediates **235** and **236** coupled with the fact that the cycloadduct can either be formed in a single step or sequentially supports the proposed mechanism. The unusual η^1,η^4-bonding mode in **236** (E = CO_2Me), which was established by nuclear magnetic resonance, is thermodynamically more



Scheme 35 Transition metal-mediated [3 + 2 + 2] cycloaddition.

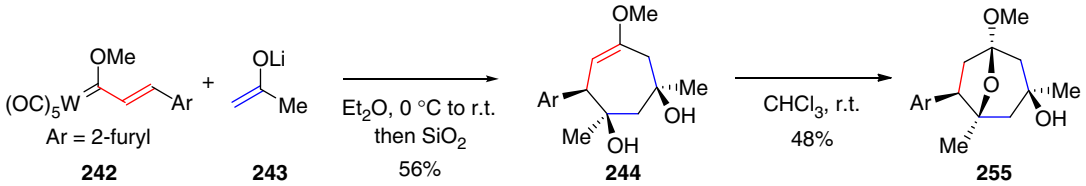
stable than the more commonly invoked η^5-cycloheptadienyl species. This mechanism is also considered to be similar for the corresponding iridium, cobalt, and palladium reactions of this type.[98,99]

Although Fischer carbenes have been used extensively as two-carbon synthons in cycloaddition reactions (cf. **Scheme 16**), the aryl substituted chromium-carbene **238** was recently introduced as a three-carbon synthon in a [3 + 2 + 2] cycloaddition with allenes (**Scheme 36**).[100] The regioselectivity of the reaction is intriguing, with nickel affording **240** and rhodium furnishing the complementary regioisomer **241**. Interestingly, the formation of the constitutional isomers is thought to be a result of a switch in the reaction mechanism rather than differences in the orientation of the allene in the migratory insertion step. Although **240** is formed as a single diastereoisomer, because the proximity of the alkenes restricts atropisomerism (diastereoisomers not depicted for clarity), heating above 80 °C promotes atropisomerism to afford a 2:3 mixture of diastereoisomers.



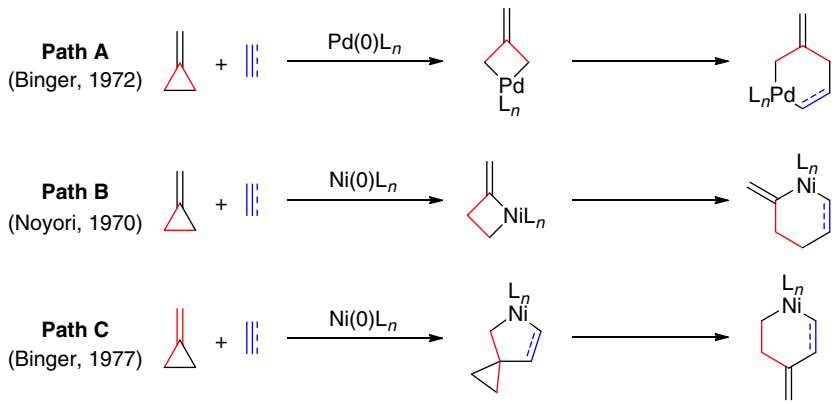
Scheme 36 Regiodivergent [3 + 2 + 2] cycloadditions via nickel-mediated and rhodium-catalyzed processes.

The reaction was expanded to lithium enolates, which eliminated the necessity to use additional transition metals, albeit the carbene **242** still requires stoichiometric tungsten (**Scheme 37**).[101] The reaction furnished cycloadduct **244** as a single diastereoisomer, which contains two ternary alcohols. Interestingly, on standing in chloroform, traces of hydrochloric acid promoted the cyclization of **244** to afford the oxabicycle **255** in 48% yield, which is a particularly attractive entry into these types of cycloadducts.



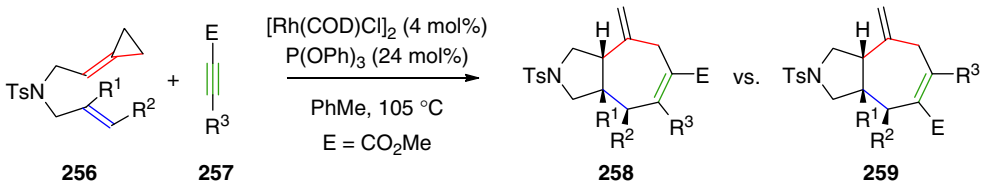
Scheme 37 [3 + 2 + 2] cycloaddition of tungsten-carbenes and lithium enolates.

Noyori and Binger proposed three different mechanisms during the 1970s to rationalize the cycloadducts formed from the reaction of transition metals with methylenecyclopropanes (**Scheme 38**).[102] For example, Binger proposed that palladium undergoes oxidative insertion into the distal cyclopropane bond to afford the palladacyclobutene intermediate (Path A), shortly after Noyori's initial discovery that nickel proceeds via initial proximal insertion (Path B). Nevertheless, these two pathways do not rationalize all of the observed cycloadducts, which prompted Binger to propose a third pathway (Path C) that involves a formal [2 + 2] oxidative addition to afford a metallacyclopentene, followed by a cyclopropylmethyl–butenyl rearrangement. It is noteworthy that, despite the similarities of the three pathways, the methylenecyclopropane represents a different synthetic equivalent in each example. Hence, the position of the olefin in the metallacyclohexene is β, α, and γ for Path A, B, and C, respectively, which provides the potential for the development of regiodivergent processes. This groundbreaking work provided the impetus for a plethora of [3 + 2] cycloadditions using various transition metals.



Scheme 38 Reactivity of methylenecyclopropane in the presence of transition metals.

In 2008, Evans and Inglesby reported the first rhodium-catalyzed [(3 + 2) + 2] cycloaddition of alkylidenecyclopropanes (ACPs), which react via a process reminiscent of Path A. The combination of **256** and alkyne **257**, in the presence of the rhodium(I) complex derived from $[Rh(COD)Cl]_2$ and triphenylphosphite, furnished the cycloheptadienes **258**/**259** in a highly regio- and diastereoselective manner (equation 48).[103] The ease of preparation of the precursor **256** and subsequent reaction with alkynes makes this an extremely attractive approach to [5.3.0] systems, which are ubiquitous in bioactive natural products. Interestingly, the substrate and alkyne substitution impacts the selectivity (Table 6), for example, when $R^1/R^2/R^3 = H$, the reaction affords poor regiocontrol (entry 1), whereas substitution at R^1, R^3, and R^2 affords progressively greater selectivity (entries 2–4). It is noteworthy that all reactions of this type furnish the cycloadducts as a single diastereoisomer, thereby making this an important development in this area.

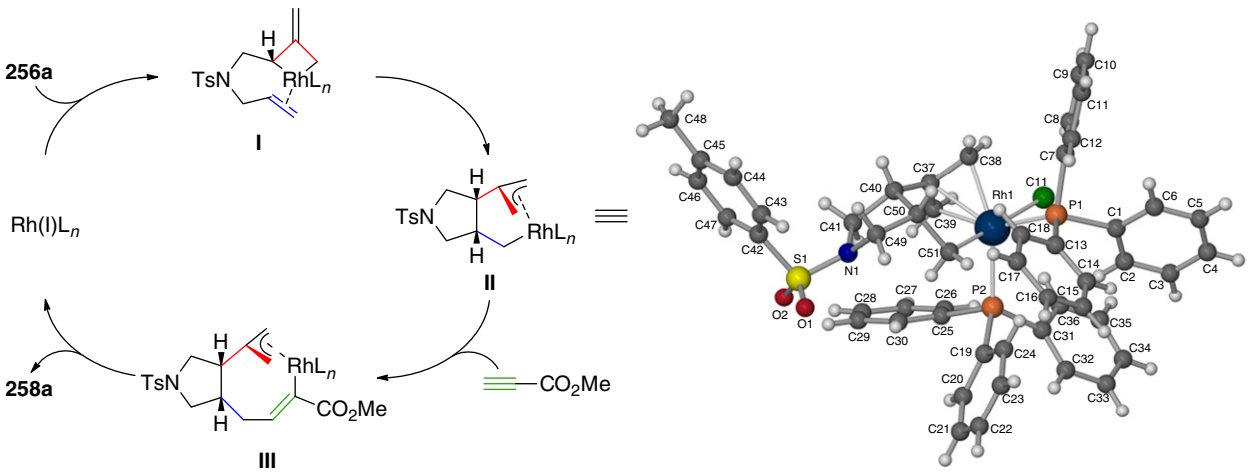


256 **257** **258** **259** (48)

Table 6 Regio- and diastereoselective rhodium-catalyzed [(3 + 2) + 2] cycloadditions of ACPs with alkynes (equation 48)

	256		***257***				
Entry	R^1	R^2	R^3		***258*:*259***	*Yield (%)*	*Reference*
1	H	H	H	**a**	2:1	90	103
2	Me	H	H	**b**	5:1	85	103
3	H	H	Me	**c**	10:1	80	103
4	H	Me	H	**d**	≥19:1	85	103

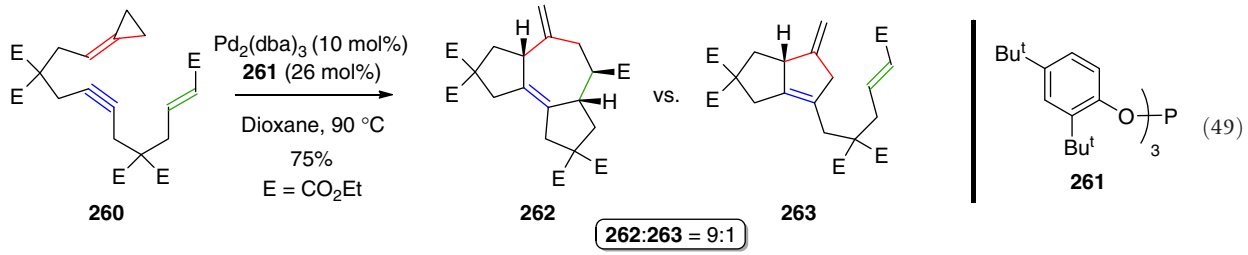
Scheme 39 outlines the proposed mechanism for this transformation, which rationalizes the observed regio- and diastereoselective outcome. Oxidative insertion of rhodium(I) into the distal bond of the cyclopropane, followed by rearrangement affords metallacyclobutene **I**. Carbometallation to the pendant alkene affords the rhodium(III) intermediate **II**, which upon alkyne insertion into the rhodium–alkyl bond and reductive elimination affords **258a**. Support for this mechanistic hypothesis was elegantly established via the isolation of rhodacycle **II**, which was demonstrated to promote the conversion of **256a** to **258a**, thereby confirming the catalytic competency of the intermediate. Moreover, the rhodium complex showed remarkable stability and did not undergo competitive reduction elimination to afford bicyclo[3.3.0]adducts.



Scheme 39 Catalytic cycle for the rhodium-catalyzed [(3 + 2) + 2] cycloaddition of ACPs and alkynes.

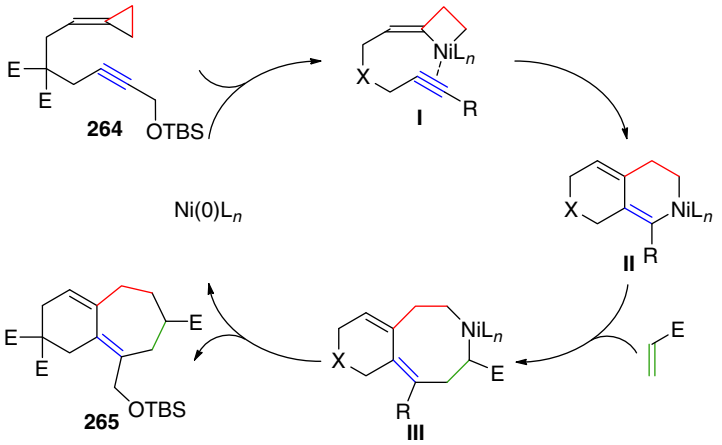
Contrary to the reactivity of rhodium, palladium-catalyzed reactions involving ACPs are prone to premature reductive elimination to furnish bicyclo[3.3.0]adducts. For example, the corresponding intramolecular [(3 + 2 + 2)] cycloaddition of **260** affords the desired tricycle **262** in competition with the undesired bicyclic adduct **263**.[104] This limitation significantly impacted the

development of palladium-catalyzed higher-order cycloadditions of this type, which has prompted the examination of nickel catalysis.



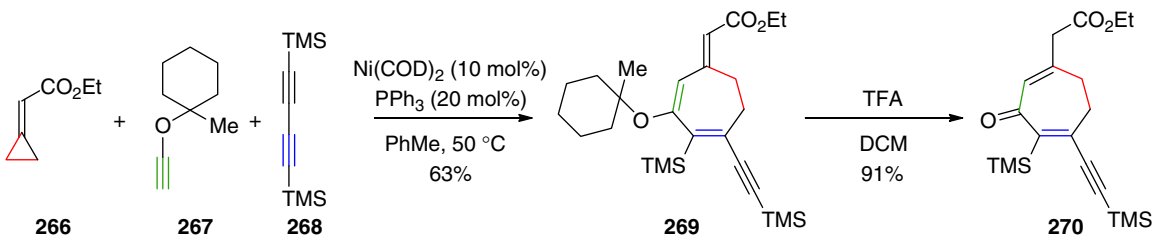
(49)

In accord with the mechanism outlined by Noyori (Path B), the ACP **264** provides the bicyclo[5.4.0]undediene **265** (Scheme 40). This process is consistent with proximal addition followed by carbometallation to afford metallacycle **II**, which on alkene insertion and reductive elimination affords the desired cycloadduct **265** as a single constitutional isomer.[105] The formation of intermediate **I** was supported by DFT and via the isolation of byproducts from competitive alkene insertion into **I** followed by reductive elimination to afford five-membered [3 + 2] cycloadducts.



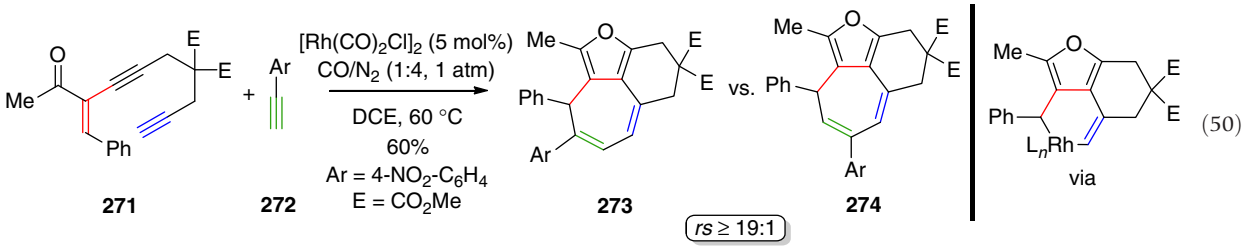
Scheme 40 Catalytic cycle for the nickel-catalyzed [(3 + 2) + 2] cycloaddition of ACPs and alkenes.

Cyclopropylidene acetates react with alkynes in the presence of a nickel(0) catalyst to afford the corresponding [3 + 2 + 2] cycloadducts. Several reports by Saito et al. have illustrated that this reaction is consistent with the selective oxidative coupling of the two alkynes, followed by insertion of ethyl cyclopropylidene acetate (**266**) in either an intra- or intermolecular fashion (Scheme 38; Path C).[106] A particularly impressive feature with this process is that the intermolecular reaction can employ two different alkynes, which provides extraordinary versatility and thereby provides a library of cycloheptadiene products in a rapid and economical manner. Recently, the ynol ether **267** was successfully coupled with **266** and **268** to provide the cycloadduct **269** in 63% yield.[106c] The advantage of employing ynol ethers is that the resulting enol ethers can be readily cleaved to effectively allow the insertion of an 'ethanal' synthon, which represents a motif that has been challenging to incorporate directly (Scheme 41).



Scheme 41 Nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate with two different alkynes.

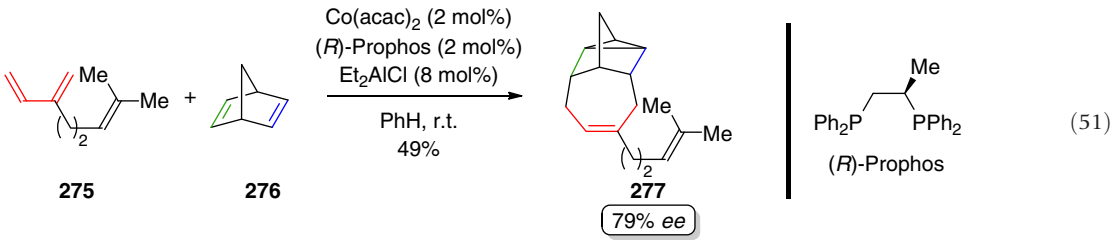
One of the few transition metal-catalyzed [(3 + 2) + 2] cycloadditions that eliminated the requirement for cyclopropanes was in the development of diyne-enones.[107] This motif provides a three-carbon surrogate between β-carbon of the enone and the internal alkyne in the presence of a rhodium catalyst, with the driving force for metallacycle formation being the construction of a furan from the cyclization of the carbonyl. Although alkyne insertion is generally more favorable into the rhodium–vinyl bond to promote reductive elimination to the cycloadduct **273**, the analogous insertion into the rhodium–alkyl bond provides an alternative pathway.



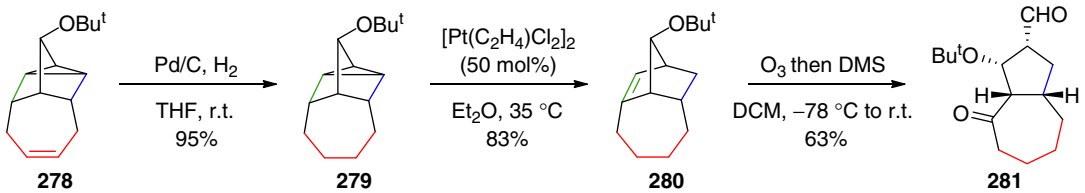
5.14.3.2 ['4 + 2 + 2'] Cycloadditions

The ['4 + 2 + 2'] cycloaddition has attracted significantly more interest than the related ['3 + 2 + 2'] process, presumably because of the dearth of four-carbon synthons. In this context, 1,3-dienes provide one of the most versatile forms of this synthon, which react in the presence of transition metals with various 2π-components to prepare eight-membered rings. Medium rings are extremely difficult to prepare from readily available building blocks using conventional chemistry, which is presumably why this process has attracted so much attention. Moreover, the process is generally atom-economical and tolerant to an array of functionality, which makes this a very powerful synthetic strategy.

One of the earliest examples of a transition metal-catalyzed [4 + (2 + 2)] cycloaddition reaction utilized a strained norbornadiene (**276**) to provide the necessary reactivity for this cycloaddition.[108] Lautens and coworkers later reported the enantioselective variant of this processes.[109] For instance, treatment of **276** with butadiene **275** in the presence of a chiral cobalt catalyst, furnished the polycycle **277** in modest yield and enantioselectivity (equation 51).



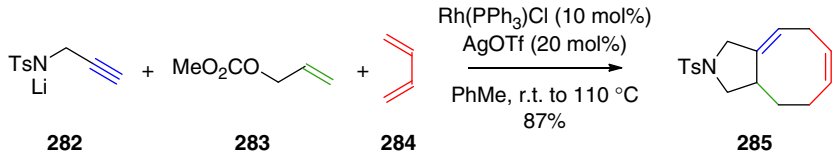
Snyder and coworkers expanded the scope of the achiral [4 + (2 + 2)] cycloaddition with functionalized norbornadienes and thus provided a more compelling rationale for the synthetic utility of this process with the conversion of the cycloadducts into useful bicyclo[5.3.0]decanes (**Scheme 42**).[110] For example, hydrogenation of the cycloadduct **278** to provide the saturated polycycle **279**, followed by platinum-mediated ring opening, afforded **280** in excellent yield. The mechanism of the ring-opening is thought to involve initial oxidative insertion to afford a platinacyclobutane, followed by a series of hydride transfers to furnish the thermodynamically stable trisubstituted alkene. Finally, ozonolysis of tricycle **280** gave the bicyclo[5.3.0]decane **281** as a single diastereoisomer. It is noteworthy that although the product from this derivatization resembles the bicyclo[5.3.0]adducts accessible via a [(3 + 2) + 2] cycloaddition, this approach offers alternative bond forming and bond breaking processes.



Scheme 42 Derivatization of [4 + (2 + 2)] cycloadducts to furnish bicyclo[5.3.0]decanes.

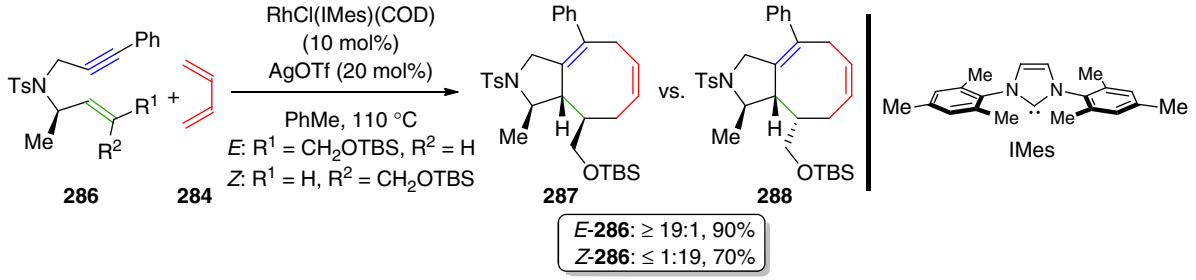
In 2002, Evans and coworkers described the first rhodium-catalyzed [4 + (2 + 2)] cycloaddition of tethered 1,6-enynes with butadiene. A particularly attractive feature with this reaction is the ability to couple the cycloaddition with an allylic substitution to prepare the reactive 1,6-enynes. For instance, the lithium anion **282** and allylic carbonate **283** react at room temperature in the presence of the rhodium catalyst and butadiene (**284**) to furnish the 1,6-enyne, which upon elevating the temperature to 110 °C

promoted the rhodium-catalyzed [4 + (2 + 2)] cycloaddition and provided the cycloadduct **285** in excellent overall yield (equation 52). Although preformed 1,6-enynes tolerate various tethers, including nitrogen, sulfur, and oxygen, the carbon-tethered 1,6-enynes were unsuccessful, which is somewhat unusual for these type of reactions.[56,111]



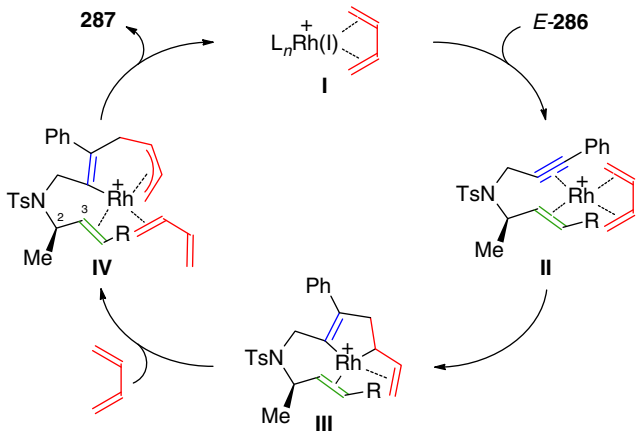
(52)

Additionally, the incorporation of a stereogenic center at the allylic position of the 1,6-enyne provided an excellent source of stereoinduction, in which 1,2-disubstituted alkenes undergo stereospecific insertion to provide three contiguous stereogenic centers in a highly controlled process. For example, *E*-**286** affords the *anti*,*anti*-cycloadduct **287** in 90% yield as a single diastereoisomer, whereas *Z*-**286** furnishes the *anti*,*syn*-diastereoisomer **288** with comparable efficiency and selectivity (equation 53). It is noteworthy that treatment of *E*-**286** to the analogous Pauson–Khand conditions (carbon monoxide atmosphere) provided the [(2 + 2) + 1] cycloadduct with poor diastereocontrol, which implied that the stereochemical-determining step for the two processes is different.[56,111]



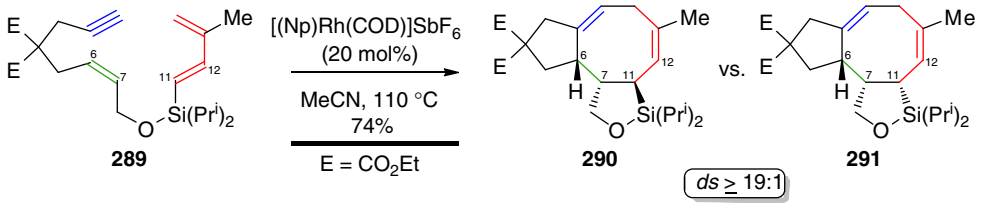
(53)

High-level DFT calculations provided support for an alternative mechanism, wherein preferential oxidative addition of rhodium(I) into the alkyne and butadiene olefin is favored over the more classical oxidative addition into the 1,6-enyne, which is well established for the Pauson–Khand reaction (**Scheme 43**). Moreover, metallacycle **IV** is significantly more stable than **III**, which has an additional butadiene molecule coordinated. Interestingly, alkene insertion into **IV**, which leads to the *anti*-metallacycle (C2–C3) is 3.27 kcal mol^{-1} lower in energy than the corresponding *syn*-metallacycle, which clearly explains the contrasting levels of diastereocontrol between the [4 + (2 + 2)] and [(2 + 2) + 1] cycloadditions.



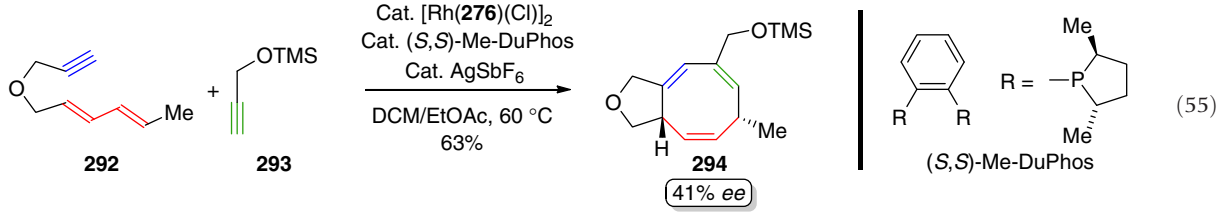
Scheme 43 Mechanism of the intermolecular rhodium-catalyzed [4 + (2 + 2)] cycloaddition.

Critical limitations with the intermolecular rhodium-catalyzed [4 + (2 + 2)] cycloaddition are the lack of regiocontrol with unsymmetrical butadiene derivatives and the inability to utilize carbon–tethers which severely limits the ability to apply this process to target-directed synthesis. In 2004, Evans and Baum provided a convenient solution to these problems by utilizing a temporary silicon-tether, which rendered the process both regiospecific and highly diastereoselective (equation 54).[111c] Similar to the intermolecular variant (cf. equation 53), the reaction is stereospecific with respect to alkene incorporation, which provides access to *syn*- and *anti*-diastereoisomers at C6/C7. Additionally, the reaction provides exclusively the *anti*-diastereoisomer with respect to C7/C11, which was attributed to nonbonding interactions in the transition state between the proton at C11 olefin with one of the isopropyl groups on the silicon-tether.



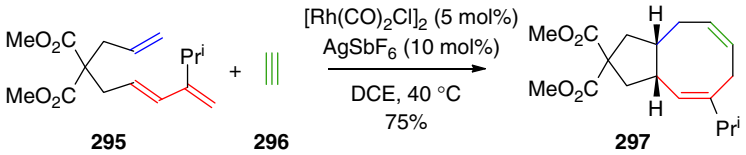
(54)

Gilbertson and DeBoef concurrently reported the construction of cyclooctatrienes via a related [(4 + 2) + 2] cycloaddition of tethered 1,3-dienynes with alkynes, in which the alkyne insertion is highly regioselective for 1,4-disubstituted 1,3-butadienes (equation 55). Interestingly, this reaction evolved from the serendipitous isolation of the [(4 + 2) + 2] cyclodimer of **292** during an investigation into the intramolecular rhodium-catalyzed [(4 + 2)] cycloaddition. Nevertheless, the formation of the dimer is difficult to completely suppress, even in the presence of an excess of alkyne (5 equivalents).[112]



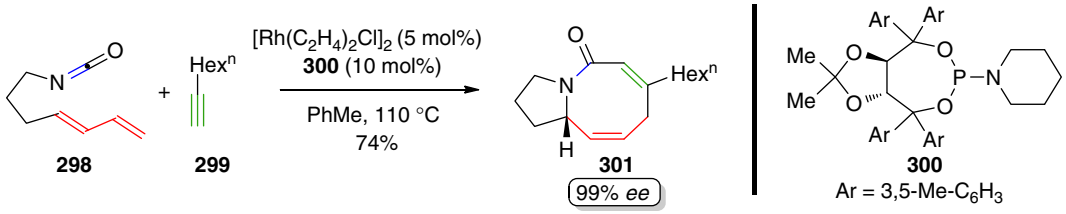
(55)

Wender and coworkers expanded the scope of the [(4 + 2) + 2] cycloaddition to alkenyl-tethered 1,3-dienes with alkynes (equation 56), which is based on their previous work on the [(2 + 2) + 1] Pauson–Khand reaction using 1,3-dienes as alkyne equivalents.[113] For example, triene **295** reacts with acetylene (**296**) in the presence of catalytic rhodium(I) to furnish the cyclooctadiene **297** in good yield. In contrast to the process outlined by Gilbertson, the reaction suffers from poor selectivity with unsymmetrical alkynes (cf. equation 55).



(56)

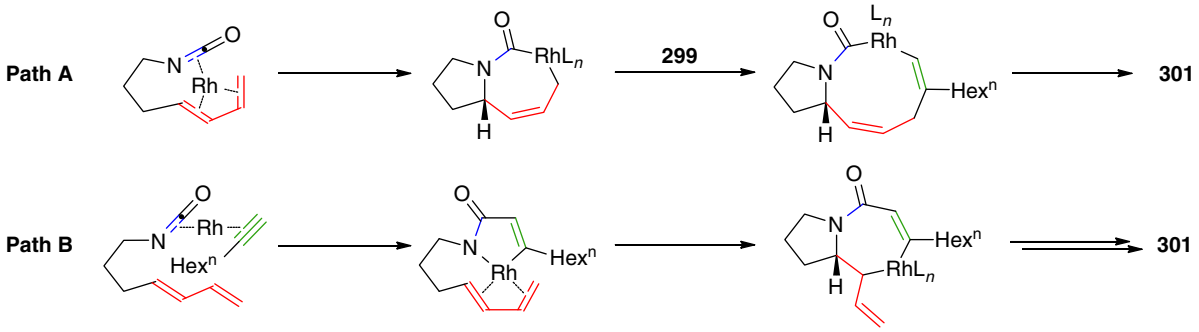
The only highly enantioselective [(4 + 2) + 2] cycloaddition reported to date is the rhodium-catalyzed reaction of dienyl isocyanates with alkynes (equation 57).[114] The reaction provides bicyclo[6.3.0]azocine systems with excellent enantioselectivity for a number of monosubstituted alkynes. Although the piperidine (vs. pyrrolidine) substituent on the phosphoramidite ligand does not impact the level of enantioselectivity, it is crucial for high conversion.



(57)

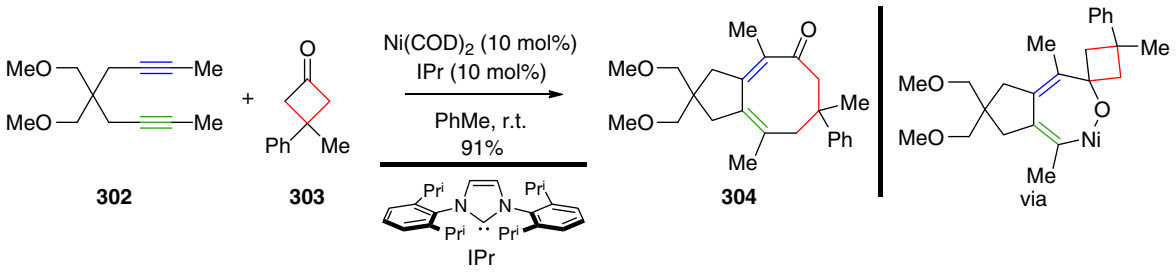
The reaction proceeds via an alternative mechanism to that proposed for the related [(2 + 2) + 2] cycloaddition between alkynes and isocyanates, which involves the direct intermolecular oxidative addition between the alkyne and isocyanate components. In contrast, the 1,3-dienyl isocyanates are proposed to undergo oxidative addition with rhodium(I) to afford the metallacycloheptene intermediate, which is followed by alkyne insertion and reductive elimination to furnish **301** (Path A). The deviation in reaction mechanism is supported by the fact that, although the alkene geometry and 1,3-dienyl substitution impact isocyanate reactivity, the level of enantioselectivity remains consistent, which suggests that the alkyne is not involved in the enantiodetermining step. Nevertheless, the nature of the alkyne does impact the reaction mechanism, because Path B becomes a competing pathway for more nucleophilic alkynes (Scheme 44).

Despite the plethora of examples that employ 1,3-dienes, cyclobutanones also provide excellent four-carbon synthons. For example, the reaction of **302** with **303** in the presence of the nickel–NHC catalyst affords the [4 + (2 + 2)] cycloadduct in excellent



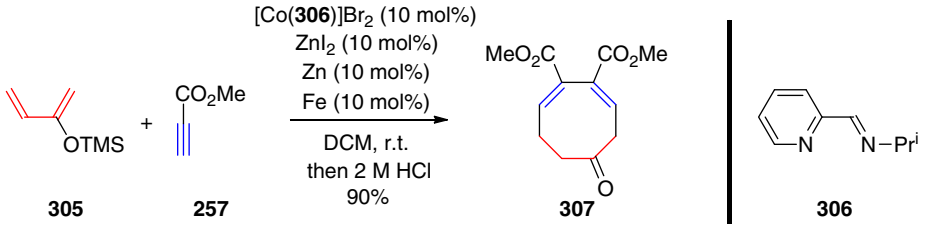
Scheme 44 Plausible pathways for the rhodium-catalyzed [(4 + 2) + 2] cycloaddition leading to bicyclo[6.3.0]azocines.

yield (equation 58). Interestingly, direct oxidative insertion into the cyclobutanone is not thought to be involved in the catalytic cycle, but the carbonyl of **303** acts as a 2π-component and inserts into a nickelacyclopentadiene generated through oxidative addition into **302**. The resultant oxanickelacycloheptadiene then undergoes cyclobutane ring-opening via β-carbon elimination followed by reductive elimination to provide **304**. The nickel–NHC catalyst also successfully converts unsymmetrical 1,6-enynes into the corresponding cycloadducts with excellent selectivity, albeit in poor yield.[115]



(58)

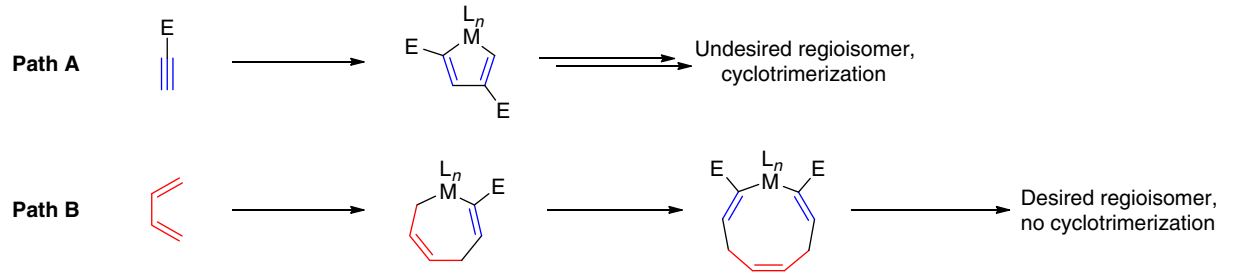
In 2008, Hilt and Janikowski reported the cobalt-catalyzed intermolecular [4 + 2 + 2] cycloaddition of two alkynes and a 1,3-butadiene derivative (equation 59). Although the reaction is cobalt-catalyzed, the addition of iron powder is critical for reducing competitive side reactions and increasing the overall efficiency. For example, the cycloaddition of **305** with methyl propiolate (**257**) in the presence of the catalyst mixture afforded the cyclooctadienone **307** in 90% yield after the acid-catalyzed deprotection of the silyl enol ether.[116]



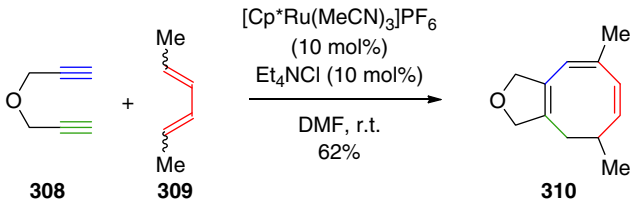
(59)

Remarkably, an excess of the alkyne component is not required, which suggests that the mechanism does not proceed via oxidative addition into the alkynes because this would lead to a high degree of cyclotrimerization (Scheme 45; Path A). The regioselectivity is however indicative of metallacycle formation between the 1,3-diene and one alkyne, followed by insertion of the second alkyne and reductive elimination (Scheme 45; Path B).

Saá and coworkers reported an approach to eight-membered rings via a formal [4 + (2 + 2)] cycloaddition, which involved an unusual 8π-electrocyclization of a 1,3,5,7-tetraene.[117] The reaction was discovered while probing the direct ruthenium-catalyzed [4 + (2 + 2)] reaction of 1,6-diynes with butadienes, however, the resulting substitution in the cyclooctatriene was not consistent with a direct cycloaddition. For example, the reaction of the 1,6-diyne **308** with excess **309** in the presence of the ruthenium catalyst affords the cycloadduct **310** in modest yield (equation 60).

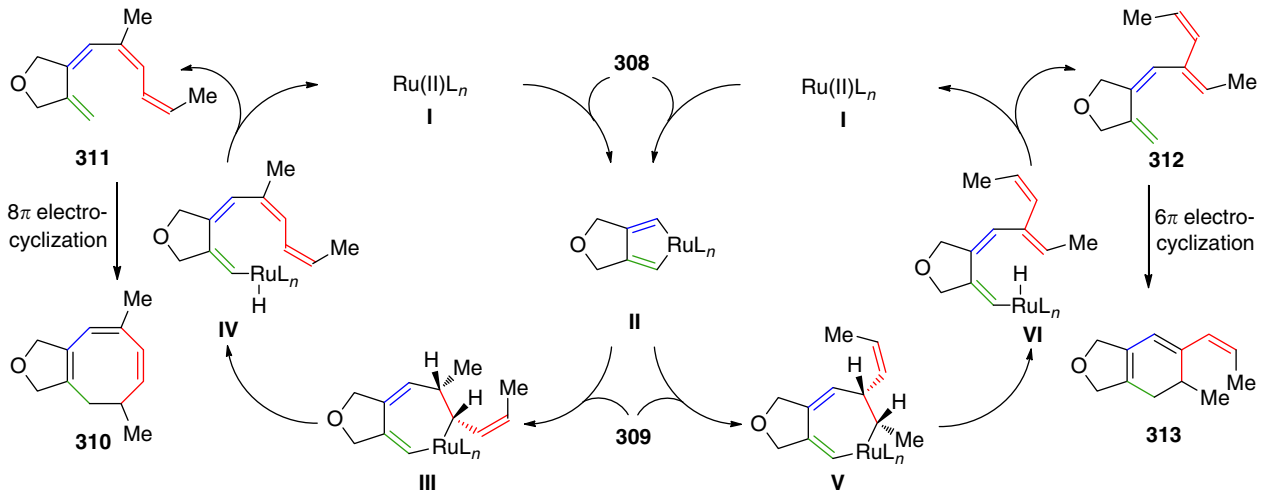


Scheme 45 Mechanistic ralionale for the regioselective cobalt-catalyzed [4 + 2 + 2] cycloaddition.



(60)

As predicted for this type of electrocyclization reaction, alkene geometry impacts the feasibility of the cyclization, in which only the *Z*-isomers of **309** react in the ene-cycloisomerization reaction to afford the corresponding *Z*-1,3,5,7-tetraene **311** which leads to the smooth conrotary cyclization to afford **310** (Scheme 46). Additional control experiments demonstrated that *E*,*E*-**309** was unreactive and afforded none of the cycloadduct. It is noteworthy that this reaction is selective for the formation of the eight-membered adduct whereas other 1,3-dienes afford large amounts of six-membered adducts as a result of poor regioselective insertion into ruthenacycle **II**. This leads to the tetraene **312**, which undergoes a disrotary 6π-electrocyclization reaction to afford **313**.

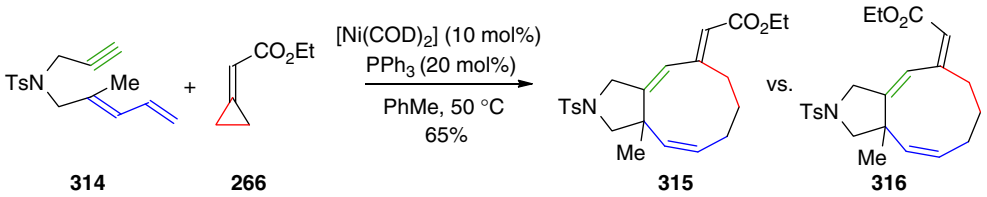


Scheme 46 Sequential intermolecular ruthenium-catalyzed ene-cycloisomerization/8π electrocyclization.

5.14.3.3 ['4 + 3 + 2'] Cycloadditions

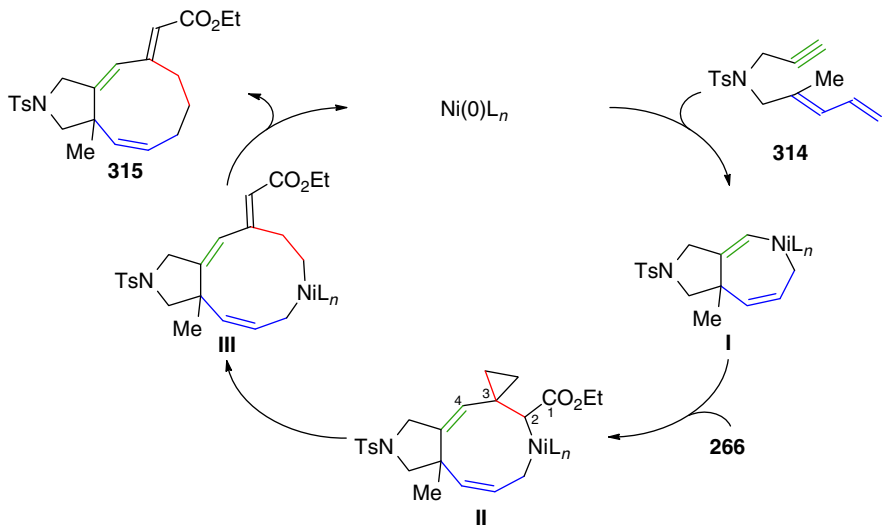
The ['4 + 3 + 2'] cycloaddition is one of the least studied transformations in this area and it is therefore understandable that examples of this complex process have only recently been developed, because it requires the coupling of three extremely different components. Moreover, the ability to overcome inherent low energy barriers that provide alternative cycloadducts can be challenging. Despite the fact that the dienyne **314** readily participates in transition metal-catalyzed [(2 + 2) + 2], [(4 + 2)] and [(4 + 2) + 2] cycloadditions, none of these adducts were observed in the [(4 + 2) + 3] process with the ACP **266**. For example, the

slow addition of **266** to a solution of **314** and the nickel complex in toluene at 50 °C affords **315** as a single geometrical isomer, albeit related examples proceed with poor geometrical selectivity (equation 61).[118]



(61)

The reaction proceeds via initial oxidative addition into **314** to generate the nickel(II) intermediate **I** (Scheme 47). Regioselective insertion of ethyl cyclopropylideneacetate (**266**) into the nickel–vinyl (vs. nickel alkyl) bond affords the nine-membered metallacycle **II**, which upon cyclopropylmethyl–butenyl rearrangement and reductive elimination affords the [(4 + 2) + 3] cycloadduct. The formation of exocyclic alkene geometrical isomers is rationalized by the relative conformation of the metallacyclic intermediates. For example, when the dihedral angle between C1–C2 and C3–C4 in metallacycle **II** is large, the selective cyclopropylmethyl–butenyl rearrangement furnishes metallacycle **III** with *trans*-stereochemistry, whereas a small dihedral angle favors the *cis*-geometry. Therefore, the nature of the tether and ligands on the metal center dramatically impact the level of stereocontrol in this transformation.



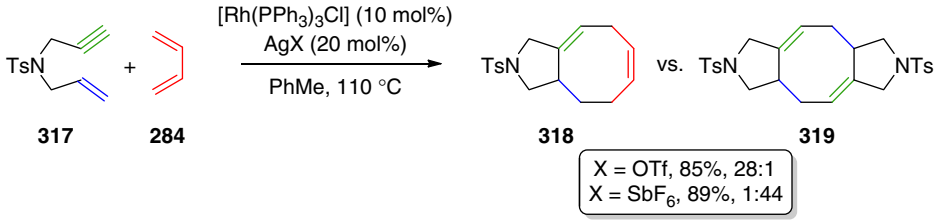
Scheme 47 Mechanism of the nickel-catalyzed [(4 + 2) + 3] cycloaddition.

5.14.4 ['*m* + *n* + *o* + *p*'] Cycloadditions

5.14.4.1 ['2 + 2 + 2 + 2'] Cycloadditions

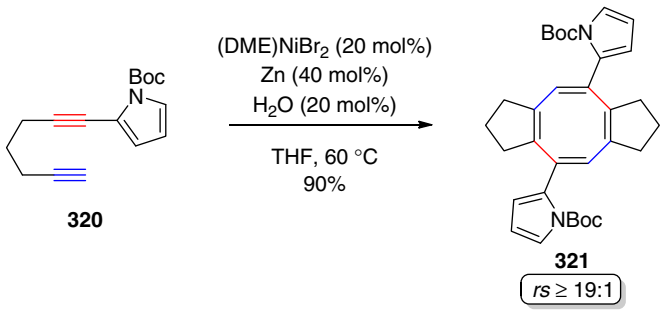
The transition metal-catalyzed [2 + 2 + 2 + 2] cycloaddition[1p] was first reported in 1948 by Reppe who demonstrated the nickel tetramerization of acetylene to furnish cyclooctatetraene,[119] which remains one of the most impressive examples of a four component cycloaddition because the products can be readily ring contracted to afford a range of substituted benzenes. Moreover, the one-step synthesis of cyclooctatetraene represents a significant improvement over the earlier 10-step synthesis and formed the basis for an industrial process. Despite efforts to expand the scope of the reaction by employing unsymmetrical alkynes, poor regio- and stereoselectivity have severely limited the productive translation of this process into more challenging systems.[120]

In 2002, during the investigation into the rhodium-catalyzed [4 + (2 + 2)] cycloaddition (*vide supra*), Evans and coworkers serendipitously discovered that modification of the counter-ion resulted in the selective formation of the [(2 + 2) + (2 + 2)] dimer **319** (equation 62). The complementary reactivity of the two outer-sphere counter-ions was attributed to the propensity of the hexafluoroantimonate modified catalyst to promote butadiene oligermerization, hence reducing its effective concentration and promoting homodimerization.[111a]



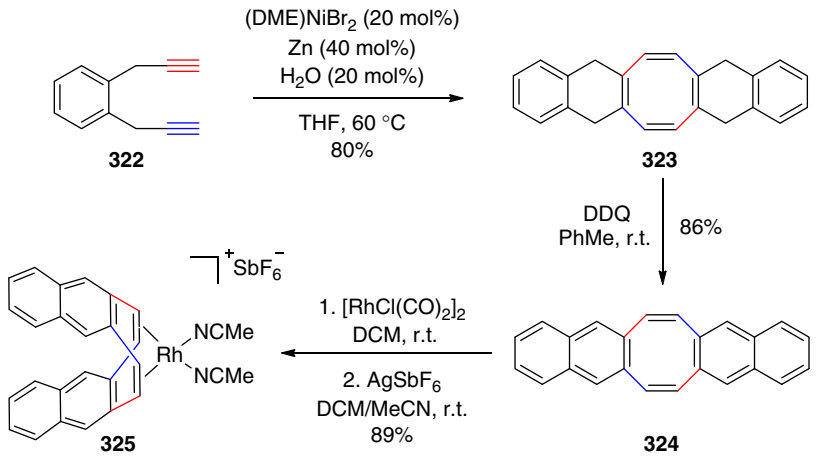
(62)

Recently, nickel complexes have also been demonstrated to promote this type of reaction, albeit the competitive [(2 + 2) + 2] dimerization adducts were, in many examples, the major product.[121] Nevertheless, along with the initial discovery by Reppe, many of the examples in this class utilize four alkyne components and ultimately afford cyclooctatetraenes. In 2007, Wender reported the nickel-catalyzed dimerization of 1,6- and 1,7-diynes for the synthesis of cyclooctatetraenes.[122] The reaction is highly selective (>50:1) for the formation of the [(2 + 2) + (2 + 2)] adduct versus [(2 + 2) + 2] adducts when a large catalyst loading is used (40 mol%), however, at a lower catalyst concentration (1 mol%) the [(2 + 2) + 2] adduct predominates. This provided support for the mechanism outlined by Wilke, which invokes a bimetallic dimerization of two nickallacyclopentadiene intermediates generated via oxidative addition of the *in situ* formed nickel(0) into the diyne.[123] Recent advances have expanded the scope to unsymmetrical diynes, which proceed with excellent regioselectivity when one of the acetylene substituents is aromatic (equation 63).[124]



(63)

In contrast to their numerous applications in natural product synthesis, cyclooctatetraenes have also been utilized as ligands in the synthesis of stable transition metal complexes. For example, Wender and coworkers reported the preparation of the tetracyclic [(2 + 2) + (2 + 2)] cycloadduct **323**, which undergoes oxidation to generate the dinaphtho[*a*,*e*]cyclooctatetraene **324** (Scheme 48).[125] They demonstrated that this intermediate acts as a bidentate ligand for rhodium(I)- and iridium(I)-complexes in a similar manner to 1,5-cyclooctadiene. Furthermore the ability to tune the reactivity of **324** via a two-step bromination/palladium-catalyzed coupling allows for the rapid synthesis of a number of sterically and electronically diverse metal complexes. Interestingly, rhodium complex **325** shows varied, but often superior selectivity to the rhodium complex [(Np)Rh(COD)]SbF_6 in the intermolecular [5 + 2] cycloaddition between VCPs and alkynes (cf. equation 24). In contrast, **325** showed comparable results to [(Np)Rh(COD)]SbF_6 in the intramolecular [(5 + 2)] reactions of alkynyl- and alkenyl-tethered VCPs (cf. equations 21 and 26).



Scheme 48 Application of cyclooctatetraenes in the synthesis of stable transition metal complexes.

In an advancement on the issues relating to the practicalities of the nickel-catalyzed [(2 + 2) + (2 + 2)] dimerization of 1,6-diynes, Okamoto and coworkers recently devised a strategy that circumvented the necessity to employ high catalyst loadings.[126] Since there had been previous support for the aforementioned bimetallic mechanism, they hypothesized that the effective substrate-to-catalyst concentration could be increased by performing the reaction in a biphasic medium and hence low catalyst loading may be tolerated if the nickel is adequately modified with water-solubilizing ligands. They demonstrated that an organic/ionic liquid mixture (toluene/imidazolium salt, 20:1 (v/v)) proved successful in providing good yields with 5 mol% of the catalyst, albeit competing [(2 + 2) + 2] and polymerization byproducts were still observed.

5.14.5 Conclusion

The development of higher-order cycloaddition reactions has aided in the formation of hitherto unknown molecular architecture that would otherwise be difficult to construct. The past 20 years has resulted in an exponential growth of this exciting field with the development of highly stereoselective syntheses of cyclic structures. Moreover, the atom- and step-economy of many of these reactions represents unparalleled versatility in the art of preparing complex polycyclic structures. Despite these achievements, this area remains in its infancy and is thereby likely to continue to develop as the search for new and improved reactions continue to be at the forefront of synthetic sequences.

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5.15 The Arene–Alkene Photocycloaddition

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Glossary

Exciplex An electronically excited complex of definite stoichiometry, 'nonbonding' in the ground state. For example, a complex formed by the interaction of an excited molecular entity with a ground state counterpart of a different structure.

Intersystem crossing An isoenergetic radiationless transition between two electronic states having different multiplicities. It often results in a vibrationally excited molecular entity in the lower electronic state, which then usually deactivates to its lowest vibrational level.

Photocycloaddition Intermolecular photochemical process leading to carbo- or heterocyclic ring systems by formation of two new single bonds, either by a concerted process or by multistep processes.

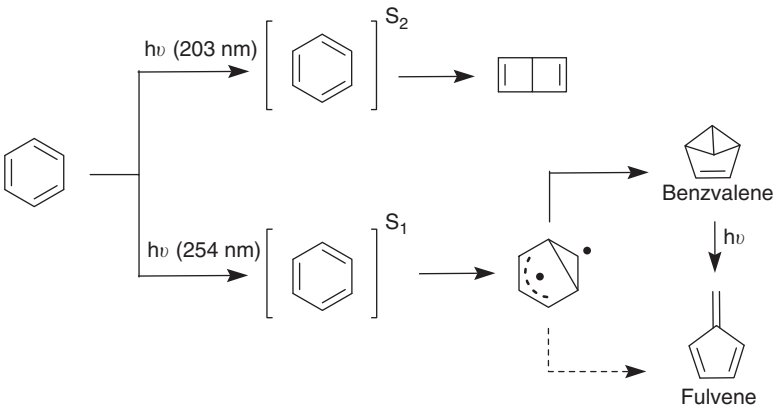
Singlet state A state having a total electron spin quantum number equal to 0.

Triplet state A state having a total electron spin quantum number of 1.

5.15.1 Introduction

Photocycloadditions can be carried out in various modes,[1] and are not limited to simple alkenes. A benzene core, which is very stable under thermal conditions, can become highly reactive on excitation with photons. Conversion into benzvalene[2] and fulvene,[3] when excited to its first excited state, or to Dewar benzene[4] via excitation to its second excited-state (**Scheme 1**) will occur.[5]

In the presence of an alkene, a photocycloaddition with benzene derivatives takes place. Three different modes are known for this reaction, the [2 + 2] or *ortho*, the [3 + 2] or *meta*, and the [4 + 2] or *para* photocycloaddition (**Figure 1**). The descriptors *ortho*, *meta*, and *para* only indicate the connectivity to the former aromatic ring, and do not have any implication with regard to the reaction mechanism. Arene–alkene photocycloadditions are among the most theoretically intriguing and synthetically promising discoveries in organic chemistry. They provide an efficient synthetic access to a range of natural and nonnatural compounds from simple, readily available precursors.



Scheme 1 Photochemistry of benzene.

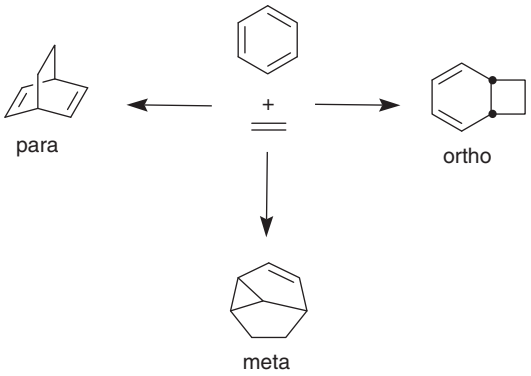


Figure 1 The three modes of the arene–alkene photocycloaddition.

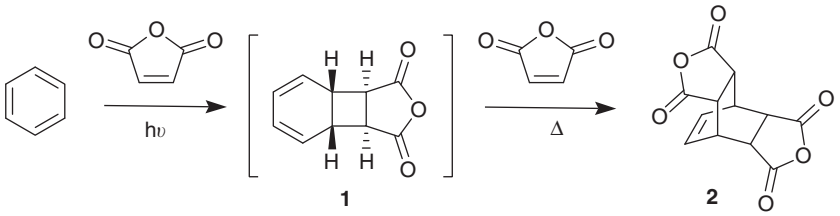
These remarkable reactions, which have no counterpart in thermal chemistry, have inspired physical organic chemists, synthetic organic chemists, and theoretical chemists during a period of more than 50 years.[6] There are beautiful examples of applications in organic synthesis, but the potential of the intermolecular variants have by no means been fully exploited. Theoretical description of the processes were intensively investigated and have led to an improved understanding, but are far from complete, especially with regard to the stereochemical aspects. This chapter starts with a brief historical perspective and carries on with simple theoretical considerations and mechanistic insights, where stereochemical and regiochemical issues are highlighted. In so doing, a special emphasis will be placed on the intramolecular variant of the *meta* photocycloaddition because it is very well documented in the literature and has been used many times in organic synthesis. The subsequent sections deal with applications in total syntheses and discuss the influence of the substitution patterns with regard to the structures that can be delineated thereof. The *ortho* and particularly the *para* photocycloadditions are discussed in Sections 5.15.6 and 5.15.7 of this chapter. They have not received as much attention and literature is few and far between. Additionally, the processes that have been described are low yielding and so far not applicable to organic synthesis, but bear a huge potential for further developments.

5.15.2 Historical Perspective

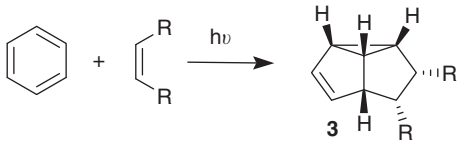
The first 'classical' $[2\pi + 2\pi]$ photocycloaddition of benzene was described by Angus and Bryce-Smith in 1959.[7] They attempted to trap fulvene produced during the irradiation of benzene by conducting the reaction in the presence of maleic anhydride. Instead of the expected Diels–Alder product, they obtained a novel adduct **2**, which was shown to be formed via initial *ortho* cycloaddition and subsequent Diels–Alder reaction (Scheme 2).

However, Ayer, Bradford, and Büchi had obtained similar *ortho* products approximately 4 years earlier and recorded their findings in a patent.[8] These early discoveries stimulated interest in the photochemistry of other arene–alkene systems, leading to a codiscovery of a second type of cycloaddition by Wilzbach and Kaplan[9] and by Bryce-Smith et al. in 1966.[10] In this reaction, an alkene is bound to the arene in a 1,3- or *meta* fashion (Scheme 3).

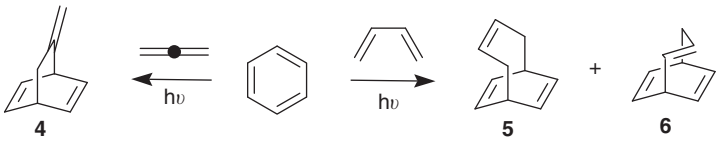
Shortly thereafter, the first examples of 1,4-bonding or para photocycloadditions to the initial arene ring were discovered (Scheme 4).[11]



Scheme 2 The first [2 + 2] photocycloaddition by Angus and Bryce-Smith in 1959.

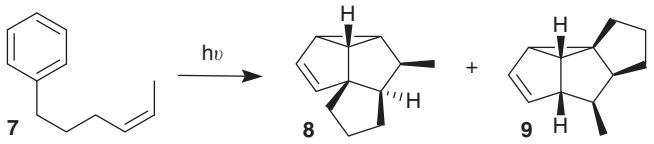


Scheme 3 The discovery of the *meta* photocycloaddition in 1966 by Wilzbach, Kaplan, and Bryce-Smith.



Scheme 4 The discovery of the *para* photocycloaddition.

In 1969, Morrison and Ferree reported the first examples of an intramolecular arene–alkene photocycloaddition, discovered in the course of their exciting studies of bichromophoric compounds (Scheme 5).[12]



Scheme 5 The first intramolecular *meta* photocycloaddition by Morrison and Ferree in 1969.

Especially, the complexity of the products **8** and **9** formed during the intramolecular variant immediately drew the awareness of the synthetic community to this reaction.[6c,13] Subsequently, considerable effort has been invested to understand and further develop benzene photocycloadditions. This has resulted in some spectacular results, among which the application of the *meta* photocycloaddition in the total synthesis of natural products is worth mentioning, particularly by Wender et al.,[14] who pioneered this field. The topic has been reviewed on several occasions mainly by Cornelisse,[6g] Mattay,[15] Wender,[16] Hoffmann,[6i] and de Keukeleire,[6h] with a strong focus on the *meta* mode.

5.15.3 Mechanistic Considerations

A number of processes can take place when an arene is irradiated in the presence of an olefin, including exciplex formation, excitation transfer, isomerization, addition, and cycloaddition. These pathways can lead to substitutions, *ene*-addition products, and to *ortho*, *meta*, or *para* cycloadducts. Control of these different modes is crucial if one aims to obtain defined photocycloadducts in synthetically useful yields. In 1974, Bryce-Smith et al.[17] devised a rule that has become famous for its predictive power: $\varphi_{ortho} > \varphi_{meta}$ when 9.6 eV < IP (alkene) < 8.65 eV. In general, *ortho* cycloaddition is the preferred process with relatively powerful donor and acceptor alkenes, whereas for alkenes with a similar ionization potential (IP) as benzene (9.24 eV), *meta* addition is the preferred process.[18] Bryce-Smith et al.[19] have discussed some deviations from the rule and remarked that the range 8.65–9.6 eV may prove a little too restricted to cover all addends. Gilbert et al.[20] have argued that IPs only of structurally closely related alkenes can be compared in a meaningful manner with regard to the efficiencies of *ortho* versus *meta* cycloadditions.

Nevertheless, successful predictions of many systems concerning the preferred mode of ethane–benzene photocycloaddition have been carried out.[21] Houk[22] came to the same conclusion by deriving the Bryce-Smith/Gilbert generalization on the basis of

orbital interactions. He also found that the *ortho* adduct is favored when the alkene is either a better donor or a better acceptor than benzene. Mattay[15a,23] also derived a rule, which enables the prediction of the mode of reaction between an arene and an alkene if the donor and acceptor properties of the reactants are known. The *ortho* and *meta* photocycloadditions as well as electron-transfer reactions leading to substitution on the arene or on its side chain are considered. Mattay's rule is based on the Weller theory of electron transfer. He considers the free enthalpies of electron transfer according to the Rehm–Weller equation:

$$\Delta G = F\left[E^{ox}_{1/2}(D) - E^{red}_{1/2}(A)\right] - \Delta E_{excit} + \frac{e^2 N}{4\pi a \varepsilon_0}\left[\frac{1}{e} - \frac{2}{37.5}\right] \quad (1)$$

where $E^{ox}_{1/2}(D)$ = oxidation potential of the donor; $E^{red}_{1/2}(A)$ = reduction potential of the acceptor; ΔE_{excit} = excitation energy; $F = 96\,490$ C; $e = 1.602 \times 10^{-19}$ C; $\varepsilon_0 = 8.854 \times 10^{-12}$ Fm^{-1}; ε = dielectric constant of the solvent (ε of acetonitrile is 37.5); $N = 6.023 \times 10^{23}$ mol^{-1}; a = encounter distance, 7 Å; the energies are in eV.

Olefins possessing poor electron-donor or poor electron-acceptor abilities preferentially yield *meta* cycloadducts in photoreactions with benzene; this is the case if $\Delta G > 1.4 - 1.6$ eV (Figure 2).[24] All other alkenes undergo *ortho* cycloaddition. In photoreactions of alkenes with substituted benzenes similar correlations with the ΔG values exist. For example, in reactions of alkenes with benzonitrile, the rule correctly predicts that electron transfer prevails if $\Delta G < 0$, addition of the alkene to the nitrile group occurs if $0 < \Delta G < 0.5$, *ortho* addition in the region $0.5 < \Delta G < -1.7$ and *meta* addition if $\Delta G > -1.7$ eV. The boundaries of the ΔG areas are not very sharp and in overlapping regions two types of reaction with one alkene are observed. However, a biradical intermediate was proposed in the photocycloaddition mechanism, but all attempts to trap a biradical or a zwitterionic intermediate have so far been unsuccessful. A very clever study to test the presence of a biradical intermediate was carried out by Reedich and Sheridan.[25] They incorporated a diazo group into the last formed bond of the cyclopropyl ring (compound **10**) in the *meta* photocycloadduct.[26] If a biradical is an actual intermediate in the course of the reaction, extrusion of nitrogen from **10** should form the same products as the *meta* photocycloaddition. Indeed, they were able to isolate the same products formed by the *meta* photocycloaddition (Scheme 6).

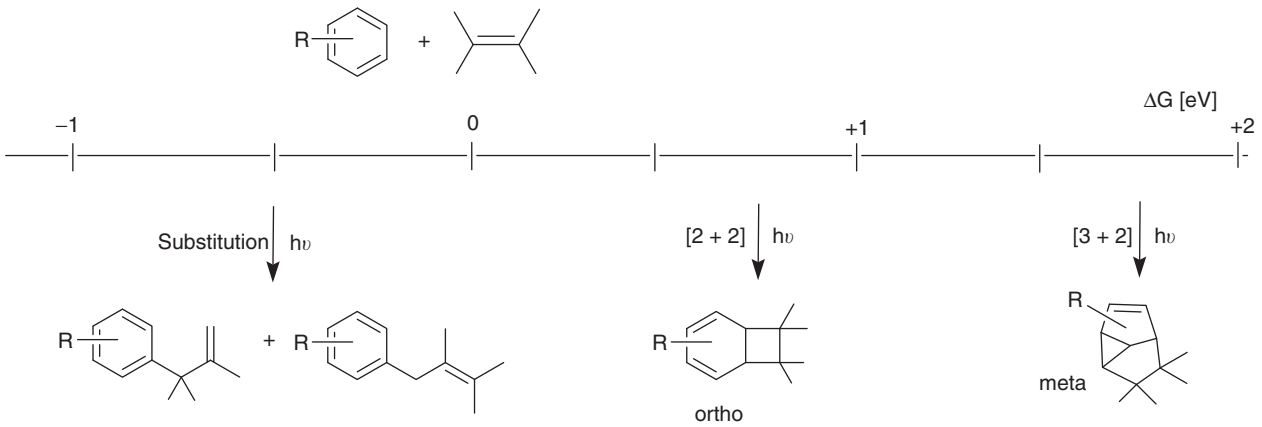


Figure 2 Mode selectivity in dependence of the free enthalpy of radical formation.

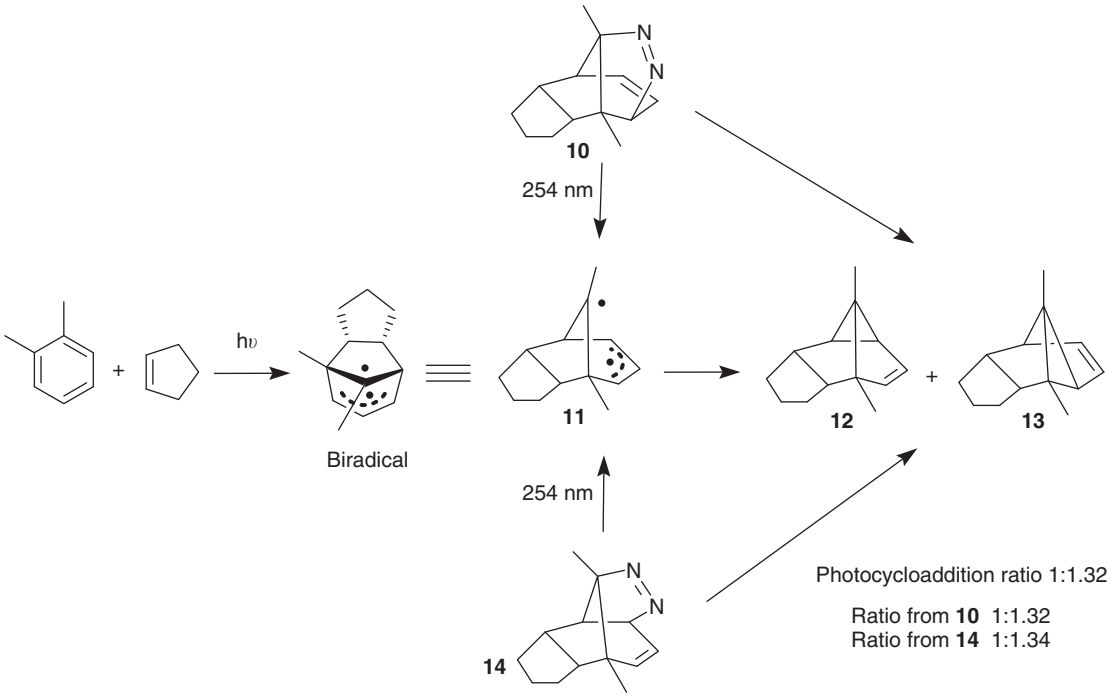
Even very similar ratios of the two distinct stereoisomers **12** and **13** were found to be formed from the diazo compounds **10** and **14** as well as from the photocycloaddition of *o*-xylene to cyclopentadiene. These findings indicated the participation of a biradical structure **11** in the *meta* photocycloaddition pathway; however, it remains unclear whether this biradical is an intermediate with a well-defined half-life or if it is just a transitory species.[27]

5.15.4 The *Meta* Photocycloaddition

Among the three modes of arene–alkene photocycloaddition reactions the *meta* product exhibits the largest increase in molecular complexity. The author, therefore, considered it useful to pinpoint the most representative drawings used in literature to the reader (Figure 3). The numbering is in accordance to the International Union of Pure and Applied Chemistry rules. Each representation emphasizes specific features of the structure. Picture I clearly shows the bond formation between C5 and C8, whereas structures II and IV display the symmetry of the product best. Diagram III is most suitable when stereochemical issues are discussed, as it illustrates the spatial approach of the olefin to the aromatic ring.

5.15.4.1 Regioselectivity

As soon as substituents are attached, either to the aromatic ring or the alkene, regioselectivity becomes an issue. There are two distinct regioselectivities involved in the *meta* photocycloaddition.



Scheme 6 Mechanistic investigations on biradical formation.

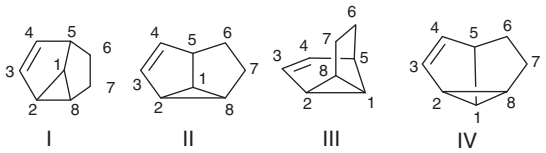


Figure 3 Different representations of the *meta* photocycloaddition adduct.

The first concerns the substitution pattern of the aromatic ring. Electron-donating and electron-withdrawing groups on the benzene ring exhibit a different influence on the polarized intermediate in the course of the reaction. It is generally observed that the alkene addition takes place preferentially 2,6 across the benzene ring if the substituent is electron donating (Scheme 7(a)), and preferentially 2,4 across the benzene with an electron-withdrawing substituent (Scheme 7(b)).[6b,6c,6e–j,15a,28]

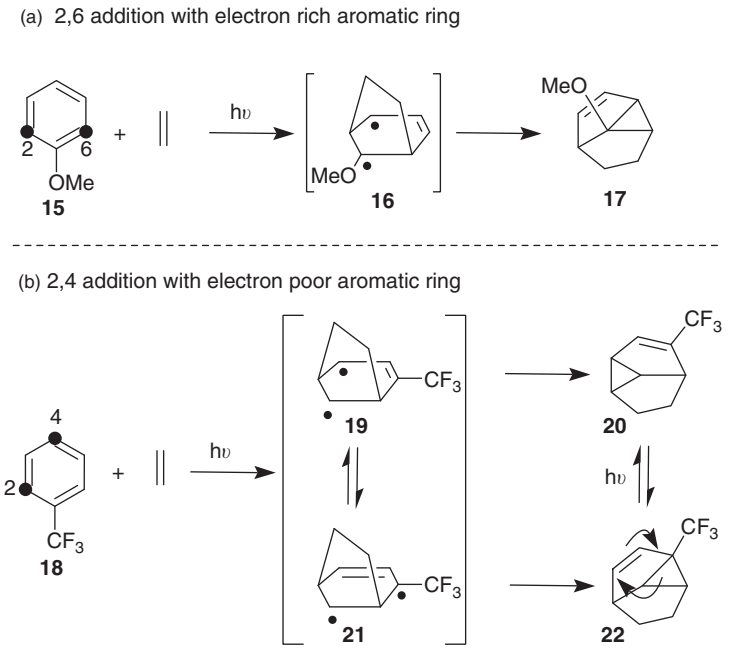
The second regioselectivity originates from the recombination of the biradical formed in the course of the reaction. This regioselectivity is inconsequential only in one case: if the olefin is symmetrical and the aromatic ring bears an electron-donating group (Scheme 7(a)). If the olefin is symmetrical and the benzene ring contains an electron-withdrawing group, two regioisomers are formed, which can be interconverted by a vinylcyclopropane rearrangement (Scheme 7(b)).

Irradiation of benzene in the presence of an unsymmetrical olefin gives two distinct products with respect to the position of the cyclopropane ring compared to the olefin substituents (Scheme 8, compounds **24** and **26**). These compounds are referred to as 1,2-adduct **26** and the 1,3-adduct **24**, which again originate from the two possible biradical recombinations. In both products the cyclopropane ring is in allylic position to the double bond, but the distance between the olefin substituents (*gem*-dimethyl group) and the cyclopropane ring is either vicinal (1,2-adduct) or in the *meta* position (1,3-adduct) (indicated by the black dots in **24** and **26**, Scheme 8). Both regioisomers are interconvertible through a vinylcyclopropane rearrangement (Scheme 8).[19a,21]

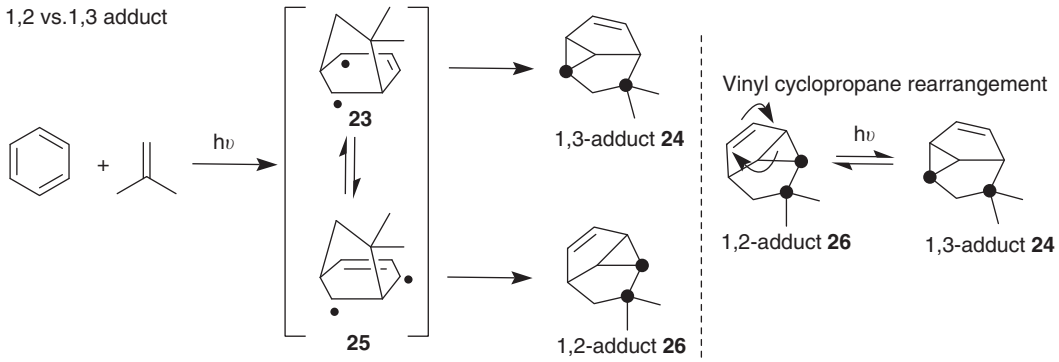
Meta photocycloadditions usually show good intrinsic regioselectivities with respect to the substitution pattern of the aromatic ring, but lack regioselectivity in the recombination step of the biradical, which results in cyclopropane formation.[29]

5.15.4.2 Stereoselectivity (*Endo* vs. *Exo*)

The *meta* photocycloaddition creates a compound containing up to six stereocenters in a single step from planar achiral starting materials. The reaction can either occur from the *exo* or the *endo* exciplex, defining four out of the six possible stereocenters directly. Recombination of the diradical in the last step puts the last two stereocenters in place. In terms of stereocontrol the *exo*/*endo* selectivity is, therefore, of utmost importance, and extensive investigations have been carried out to rationalize the experimental findings.



Scheme 7 Regioselectivity of the *meta* photocycloaddition with respect to the substituent on the aromatic ring.



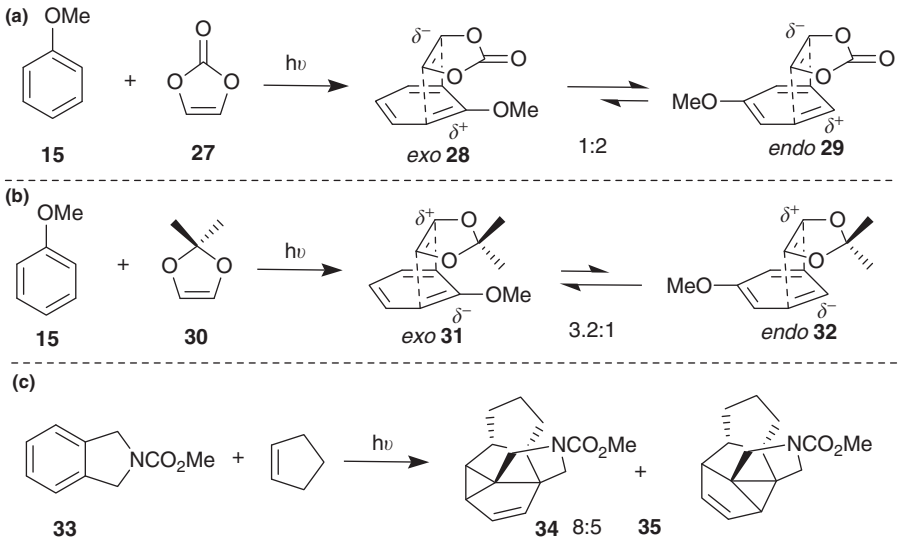
Scheme 8 Regioselectivity with respect to biradical recombination and cyclopropane formation.

An interesting example is provided by the *meta* cycloadditions of anisole with vinylene carbonate **27** and dioxole **30** (Scheme 9). Reactions of **27** give an *exo*/*endo* cycloadduct ratio of 1:2, whereas for alkene **30** a reversed preference is found, i.e., *exo*/*endo* 3.2:1 (Scheme 9(b)). In contrast to what would be expected on the basis of steric effects, a larger substituent on the arene, such as a trimethylsilyloxy group, gives even greater *exo* selectivity (9.3:1). This can only be explained if charge-transfer processes are considered. Thus polarization arising during the cycloaddition with **27** would electrostatically stabilize the *endo* addition mode **29** and destabilize the *exo* mode **28**, the latter due to charge repulsion between the vinylene carbonate subunit and the alkoxy group of the arene. However, the more electron-rich dioxole **30** can serve as a donor in the cycloaddition, in which case charge repulsion is minimized along with steric effects in the *exo* orientation **31**. Intermolecular *meta* photocycloadditions involving alkyl- or alkoxy-substituted arenes and simple alkenes usually proceed with *endo* selectivity as can be seen in Scheme 9(c). The product mixture stems from the recombination of the cyclopropane and is not related to the *endo*/*exo* problem. In contrast, intramolecular photocycloadditions generally give high, if not exclusive, *exo* selectivity and will be discussed in the following chapter.[28]

5.15.5 Intramolecular *Meta* Photocycloadditions

5.15.5.1 *Endo* versus *Exo* Selectivity

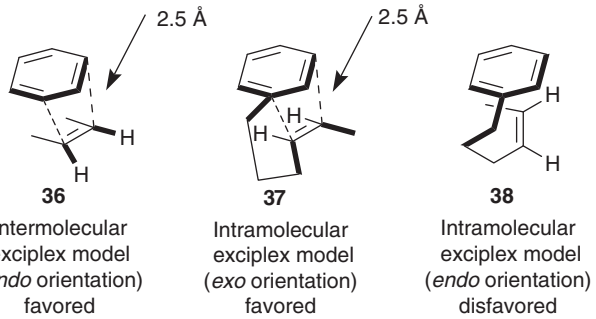
The first intramolecular *meta* photocycloaddition was reported in 1969 by Morrison and Ferree.[12] The intramolecular reaction was shown to be very efficient when three atom tethers were employed, but the quantum yield drops considerably when four atom tethers were involved,[30] apart from some exceptional cases when the flexibility of the tether is restricted and a



Scheme 9 *Endo* versus *exo* selectivity in the intermolecular *meta* photocycloaddition.

suitable conformation can be found.[31] The influence of the incorporation of oxygen in the tether has been reviewed by de Keukeleire.[32] The *exo*/*endo* selectivities mentioned above change completely in intramolecular reactions. In this mode, the *endo* approach of the alkene cannot be achieved without introducing significant strain, which usually outweighs secondary orbital interactions, and thus *exo* rather than *endo* adducts are obtained.[30]

This difference in selectivity has been rationalized in numerous studies by Wender's group on the basis of steric effects associated with the formation and reaction of an exciplex.[33] In this analysis (Scheme 10), the plane of the alkene and that of the excited-state arene are oriented in a parallel fashion and separated by a distance of approximately 2.5 Å, in reasonable agreement with previous studies on exciplex systems.[24b,34] The intermolecular reaction would then involve exciplex **36**, in which an *endo* orientation is preferred due to secondary orbital interactions and, depending on substitution, electrostatic effects. In the corresponding intramolecular exciplexes, the favorable orbital alignment for *meta* cycloaddition is preserved only if an *exo* orientation **37** is adopted, as the *endo* exciplex **36** is poorly aligned. Moreover, *meta* cycloaddition proceeding via **38** would lead to the formation of a product with a highly strained *trans*-fused bicyclo[3.3.0]octane subunit. The corresponding *exo* cycloaddition process leads to a less-strained *cis*-fused bicyclo[3.3.0]octane product.

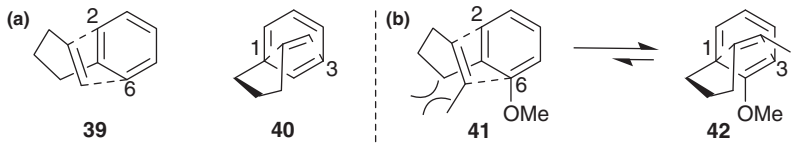


Scheme 10 Inter- versus intramolecular exciplex model.

5.15.5.2 Mode Selectivity

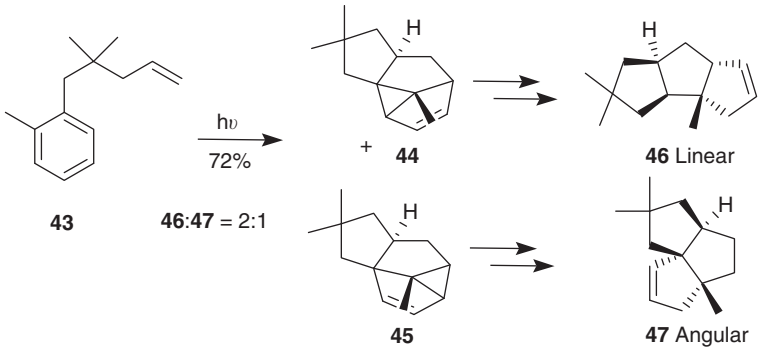
Besides the *endo* versus *exo* selectivity issues in the intramolecular mode, either 2,6- (**39**) or 1,3-addition (**40**) to the tether can be observed (Scheme 11(a)).[35] 1,3-Addition is usually observed selectively when electron-donating groups are attached to the aromatic moiety *ortho* to the tether, or if the olefin contains additional *cis* substituents; this is due to repulsion of the substituents on the olefin with the hydrogen atoms of the tether in the *exo*-addition, which prevents the 2,6-addition mode **41** (Scheme 11(b)). Concerning the double-bond geometry in the course of the photocycloaddition, the general rule applies that the geometry of the double bond is retained unless it is a sterically encumbered olefin. In this case, excitation transfer from the arene to the alkene can occur.

Intramolecular *meta* photocycloadditions that occur at positions 1,3 relative to the tether may give either a linear or an angular isomer (Scheme 12).[36] Calculations of the relative stabilities are a useful tool to predict the selectivity. If no additional



Scheme 11 Explanation of mode selectivity in the intramolecular *meta* photocycloaddition.

substituents are present, the linear compounds are slightly more stable.[30] However, some examples show that this selectivity can be changed.[37] The linear and angular isomer names are derived from the opening of the cyclopropane ring to afford linearly and angularly fused triquinanes.

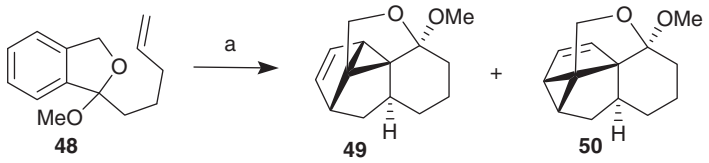


Scheme 12 Linear versus angular product a matter of selective biradical recombination to the cyclopropane ring.

5.15.5.3 The Influence of the Tether Length

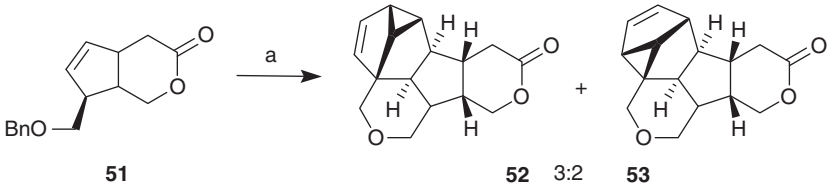
As briefly mentioned, the intramolecular *meta* photocycloaddition displays a significant difference whether a three-[12,38] or four-atom tether length is applied. It was shown that the quantum yields significantly dropped when changing from a three- to a four-atom tether.[6d] One reason might be the strong increase in conformational freedom in the latter case. This might have discouraged further use in complex natural product synthesis, and only a few examples are known. In those cases (shown in Schemes 13 and 14) inherent conformational restraints are responsible for the good yields obtained.

Wender and DeLong's study on tether length used cyclic acetal **48** with a four-atom tether (Scheme 13).[39] This exerts conformational restrictions on the system, and thus products **49** and **50** could be obtained in unusual high yields of 68% of both regioisomers (60% conversion).



Scheme 13 Wender and DeLong's four-atom tether study. Reagents and conditions: (a) hυ (Vycor filter) 60% conversion 68% yield.

In a similar manner, De Keukeleire and coworkers took out the *meta* photocycloaddition on substrate **51** bearing a four-atom tether. The photoadducts **52** and **53** were obtained in 42% yield as 3:2 mixtures of regioisomers originating from cyclopropane formation (Scheme 14).[32,40]



Scheme 14 De Keukeleire's study. Reagents and conditions: (a) hυ (254 nm) 60% Rayonet reactor 42% yield.

5.15.5.4 Diastereoselectivity in the *Meta* Photocycloaddition

Morales et al. have observed diastereoselectivity by the introduction of a chiral center in the α-position to the aromatic moiety on the tether.[38a] In fact, the control element for the intramolecular photocycloaddition is the benzylic position on the tether. If this position bears a stereogenic center, high diastereoselectivities can be expected. Diastereoselectivity in the *meta* photocycloaddition is a synonym for π-facial selectivity. The selectivity originates from allylic strain as displayed in Figure 4 (bold bonds). The tether adopts a distorted *syn*-pentane conformation with the large substituent (L) in the equatorial position. Diastereoselective approaches with chiral induction at position 3 of the tether have also been reported.[41]

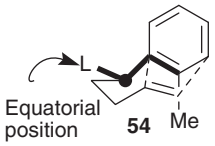
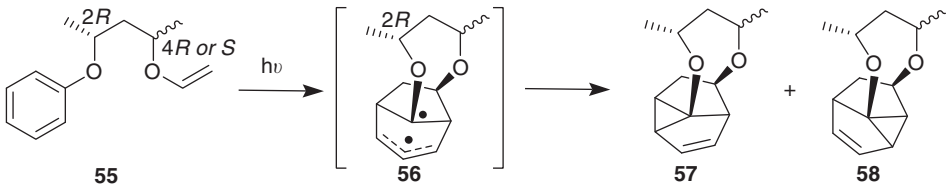


Figure 4 Diastereoselectivity in the intramolecular *meta* photocycloaddition – the ^{1,3}A-starin model.

5.15.5.5 Enantioselective *Meta* Photocycloadditions

The *meta* photocycloaddition has the ability to transform two-dimensional planar molecules into spatial chiral molecules. Therefore, many attempts have been made to carry out this process in an enantioselective fashion. The most commonly used strategy in an intramolecular photocycloaddition is the introduction of a chiral center on the tether, and to carry out the reaction in a diastereoselective way. This approach was first implemented into the total synthesis of (±)-α-cedrene published by Wender et al. in 1981.[33] Further studies aimed to understand and predict the diastereoselectivity of this photocycloaddition were undertaken. Sugimura et al. have shown that chiral 2,4-pentanediol tethers are very efficient for face differentiation (Scheme 15),[42] in which the 2-position of the tether in **55** completely directs the diastereoselectivity of the reaction. Precursors with (2*R*)-configuration react exclusively at the *Si*-face of the vinyl group, and form the (*R*)-configuration at the newly formed stereocenter. Nevertheless, regioselectivity issues in the formation of the cyclopropane ring lead to product mixtures, and both regioisomers are obtained. Van der Eycken et al. carried out a *meta* photocycloaddition in a chiral cavity (*β*-cyclodextrin), which afforded the photocycloaddition products in 17% *ee*.[43]



Scheme 15 Auxillary controlled cycloadditions.

5.15.5.6 Elaboration of Cycloadducts

The value of the arene–alkene *meta* cycloaddition arises from its capacity to produce a cycloadduct with three new rings and up to six new stereocenters. This is an impressive feature even if compared with the highly regarded Diels–Alder reaction. Furthermore, the cycloadduct is a commonly encountered structural motif in many natural products containing cyclopentanes such as triquinanes, cycloheptanes, bicyclo[3.2.1]octanes, and bicyclo[3.3.0]octanes. The *ortho* and the *para* mode provide less of an increase in molecular complexity, but nevertheless afford a new ring and four contiguous stereocenters. However, the core structures obtained in the *meta* photocycloaddition require further elaboration (Figure 5), especially cleavage of the cyclopropyl ring, in order to be useful in total synthesis of naturally occurring polycyclic systems. Many results have been achieved by a variety of research groups to diversify the molecular scaffolds accessible by this synthetic route: the cyclopropyl ring of the *meta* product is either opened to give a bicyclo[3.3.0]octane system (**59**, **63**, **64**, **65**, and **66**), or it is cleaved to give bicyclo[3.2.1]octane derivatives (**60, 61**, and **62**) (Figure 5). Acidolysis of *meta* photocycloaddition compounds opens the cyclopropane ring on protonation of the double bond, and leads to compounds **59** and **60**.[44] The formation of these two diverging carbon frameworks depends on the substituent at position 1. Although R^1 = H affords hexahydropentalene **59**, bicyclo[3.2.1]octane derivatives **60** are obtained if R^1 is an alkyl group.

Other electrophiles such as bromine add to the double bond and thus trigger the opening of the cyclopropane moiety to give compounds of type **61**.[33] Penkett demonstrated that in the course of an epoxidation reaction with *m*-CPBA the cyclopropane ring was opened to directly give an allylic alcohol of type **61** (with E = OH).[45] A Heck-type reaction with concomitant opening of the cyclopropane ring is facilitated by a methoxy group at C-1[46] to give bicyclo[3.2.1]octane derivatives of type **60**. Thermolysis results in [1,5]-sigmatropic shifts, either of hydrogen,[47] or a carbon atom[48] to yield tetrahydropentalenes **64**. Radical opening of the

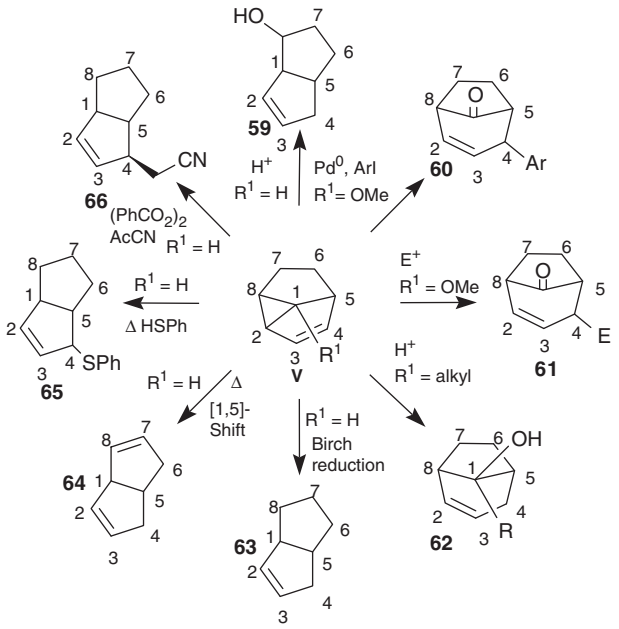


Figure 5 Possible elaborations of photoadducts.

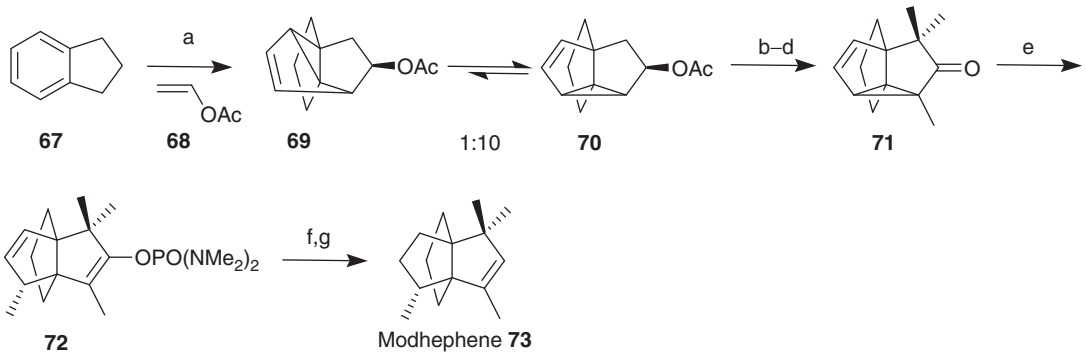
cyclopropyl ring for instance under Birch reaction conditions delivers the reduced hexahydropentalene of type **63**.[49] Radicals such as thiophenoxy radicals can also add to the double bond and induce the opening of the cyclopropane ring to afford compound **65**.[36,50] Acetonitrile radicals can be added to the olefin and open the cyclopropane ring to yield a hexahydropentalene **66**.[51]

5.15.5.7 Applications in Total Synthesis

To expediently use the *meta* photocycloaddition in natural product synthesis, certain criteria have to be fulfilled. The photocycloaddition precursor has to be easily accessible, the cycloaddition itself should be selective or the isomers at least separable. And last but not the least, the conversion of the cycloaddition product to the target structure should not be cumbersome. Paul Wender's group pioneered this field, but of course other groups have also made significant contributions. As mentioned above, the syntheses discussed in the following section are grouped according to the substitution pattern of the aromatic ring.

5.15.5.8 Intermolecular Variants

Total synthesis of modhephene **73** (Scheme 16):[29]

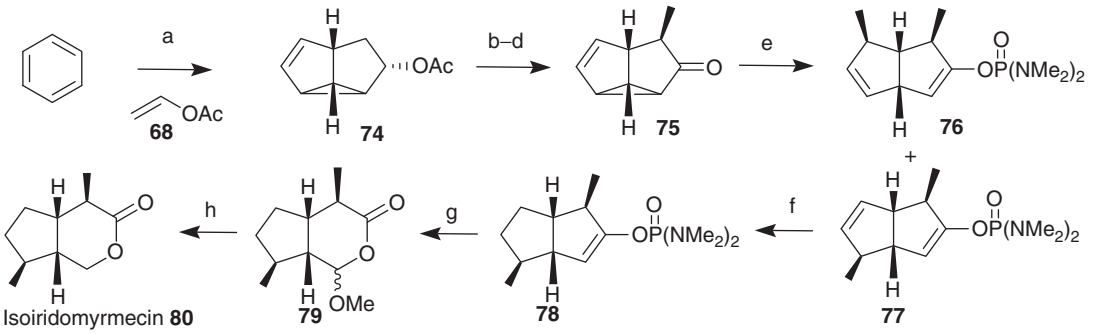


Scheme 16 Wender's synthesis of modhephene: Reagents and conditions: (a) hυ (Vycor filter) cyclohexane, 21%; (b) KOH, MeOH, 86%; (c) $Ba(MnO_4)_2$, 95%; (d) *t*-BuOK (15 equivalents), MeI, THF, 68%; (e) Me_2CuLi, THF, −78 °C, $ClPO(NMe_2)_2$, then Me_2NH, 76%; (f) Li, $EtNH_2$, THF, *t*-BuOH, 0 °C, 93%; (g) H_2, PtO_2, 100%.

Modhephene (Scheme 16) represents an intermolecular application of the *meta* photocycloaddition in total synthesis and varies in this respect from the previous applications. Dihydroindane and vinylacetate underwent the photoreaction to give

regioisomers **69** and **70** (10:1 for the desired compound **70**). The acetate group was cleaved under basic conditions and the resulting alcohol oxidized to the ketone, which was extensively methylated in the α-position to give compound **71**. Homo-1,4-addition of dimethyl-cuprate to **71** introduces the missing methyl group stereoselectively with opening of the cyclopropane ring to give **72**. The resulting enolate was trapped as phosphodiamidate. Subsequent Birch reduction delivered modhephene **73**.

Total synthesis of isoiridomyrmecin **80** (Scheme 17):[52]



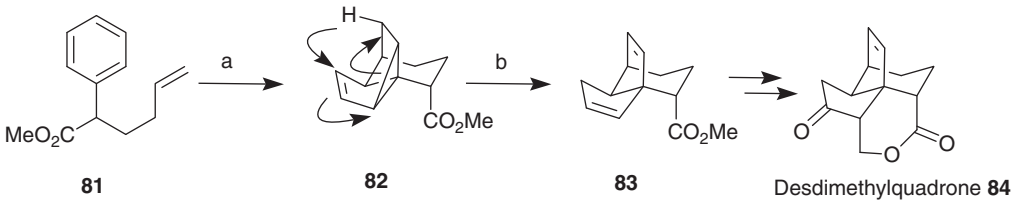
Scheme 17 Synthesis of isoiridomyrmecin, photocycloaddition and cyclopropane cleavage. Reagents and conditions: (a) hυ (Vycor filter); (b) $LiAlH_4$ (89%); (c) MnO_2 (95%); (d) LDA, −78 °C, MeI (75%); (e) Me_2CuLi, THF, −78 °C, then $Cl_2PO(NMe_2)$, then Me_2NH (100%); (f) H_2, PtO_2 (90%); (g) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_4$ (92%, 1:1-epimers); (h) $NaBH_3CN$, H_2O, THF, H_2SO_4 (68%).

The synthesis of this natural product builds on an intermolecular *meta* photocycloaddition as a key step. In accordance with theoretical investigations the *endo*-adduct was formed, albeit in low yields.[53] Anyway the cheapness of starting materials compensates for the low yields. Photoadduct **74** was converted to ketone **75** by deacetylation, oxidation, and methylation. Conjugate addition with dimethyl-cuprate cleaved the cyclopropane ring. The enolate formed in this reaction was trapped as phosphordiamidates **76** and **77** (4.5:1 in favor of **77**). Removal of the disubstituted olefin with Adam's catalyst afforded compound **78**. This was subjected to ozonolysis to give acylal **79**, which was reduced to iridomyrmecin **80** with sodium cyano-borohydride.

5.15.5.9 Intramolecular *Meta* Photocycloadditions

5.15.5.9.1 Monosubstituted arenes

Synthetic studies toward desdimethylquadrone **84** (Scheme 18):[54]



Scheme 18 Synthetic study toward desdimethylquadrone. Reagents and conditions: (a) hυ (Vycor filter) 10%; (b) 220 °C.

Quadrone is a tetracyclic sesquiterpene structure. With regard to the *meta* photocycloaddition two synthetic studies on simplified derivatives have been carried out. The first approach was carried out by Metha et al., who used an intermolecular mode to form decarboxyquadrone,[55] and the second one by Wender and Wolanin, which utilized an intramolecular approach. Photocyclization of **81** gave tetracycle **82** in low yield (10%) but very selective as a single product. Thermolysis of photoadduct **82** triggered a [1,5]-H-shift yielding product **83**. Addition across the tether is in accord with theory, stating that addition always takes place across the strongest donor.

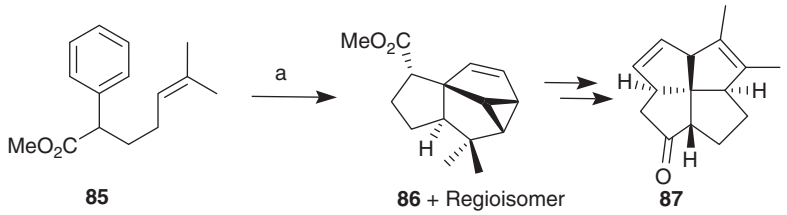
Synthetic studies toward fenestrane structure types **87** (Scheme 19):[50a,56]

This example published by Keese and coworkers comprises a parallel example to the synthesis of desdimethylquadrone with respect to the mode of addition (across the strongest donor group). Keese et al. carried out this synthesis starting from **85** when investigating fenestrane systems like **87**.

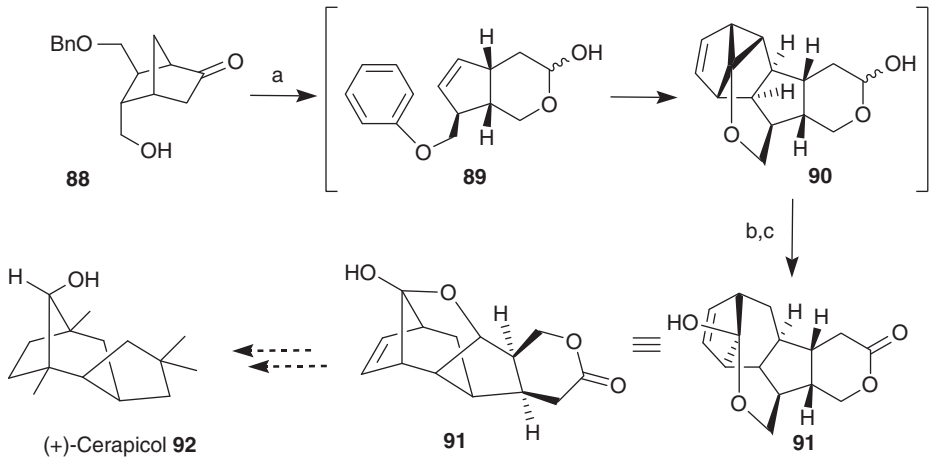
Synthetic studies toward cerapicol **92** (Scheme 20):[32,40]

De Keukeleire obtained product **90** during studies on tandem Norrish type-I/*meta* photocycloaddition reactions. The substrate **88** first underwent a Norrish type-I reaction yielding lactol **89**. This in turn reacted in the photocycloaddition to give, after oxidation and cleavage of the cyclopropane ring, polycycle **91** in 34% overall yield.

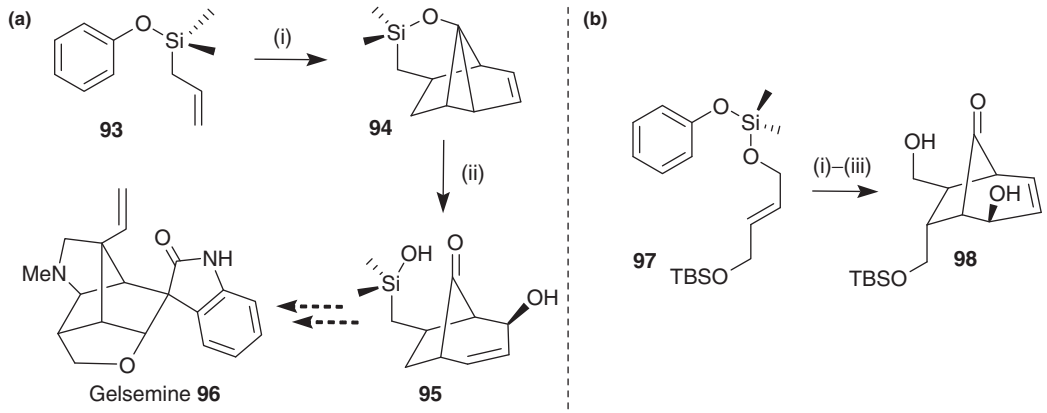
Synthetic studies toward gelsemine **96** (Scheme 21):[45,46,57]



Scheme 19 Synthetic study of fenestranes. Reagents and conditions: (a) hυ (Vycor filter) 10%.



Scheme 20 Synthetic studies toward cerapicol. Reagents and conditions: (a) hυ, cyclohexane–EtOAc (5:1); (b) PDC, CH_2Cl_2 (34% overall); (c) dil. HCl (>95% yield).

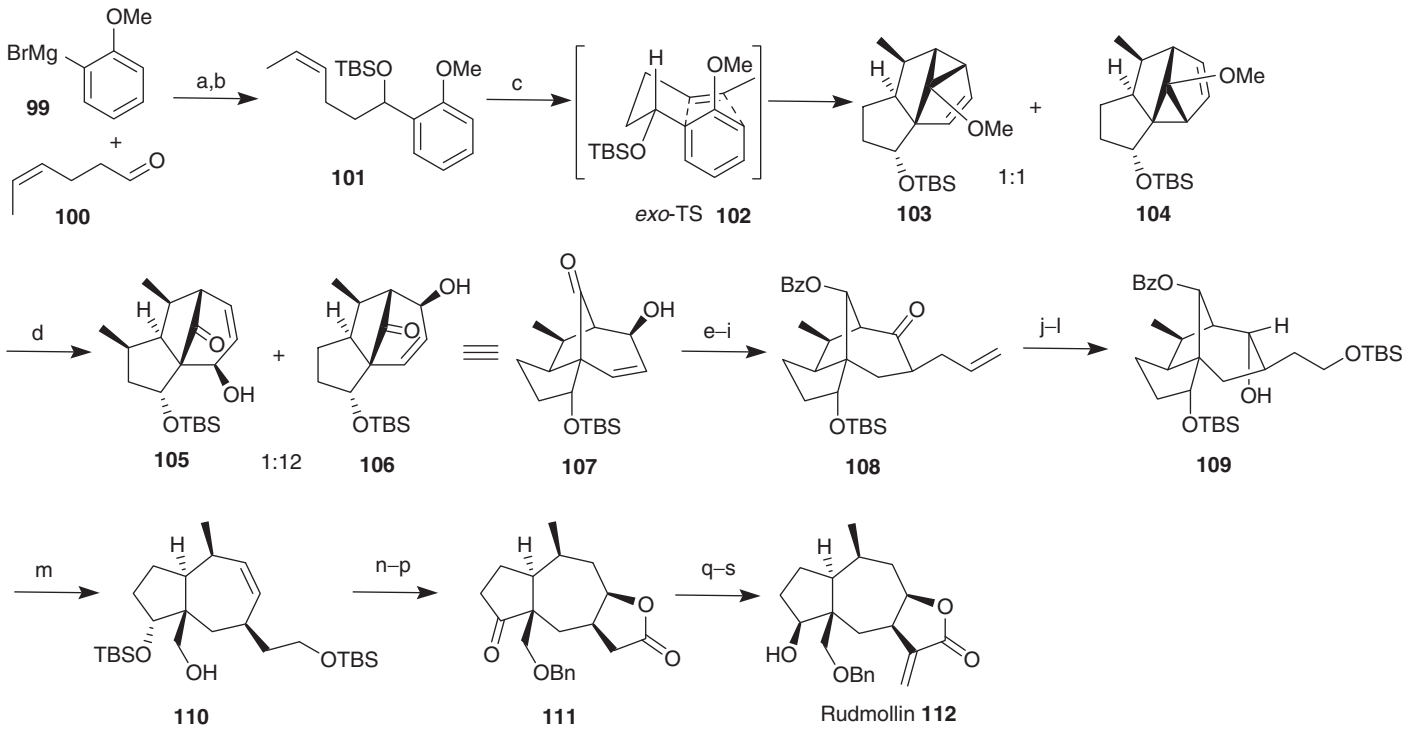


Scheme 21 (a) Synthetic studies toward gelsemine. Reagents and conditions: (i) hυ, hexane (38%); (ii) *m*-CPBA (56%). (b) Synthetic studies toward gelsemine. Reagents and conditions: (i) hυ (low pressure mercury lamp), cyclohexane, 4 h; (ii) *m*-CPBA, CH_2Cl_2; (iii) MeOH, PPTS, 4 days (11% overall).

Fleming and coworkers took out pioneering studies on the utility of silicon tethers in the *meta* photocycloaddition.[58] Following these initial studies, Penkett et al. carried out studies on the versatility of this reaction in the total synthesis of gelsemine **96**. Photolysis of **93** gave rise to cycloadduct **94** in 38% yield and some *ortho*-product (16%, not displayed). Fragmentation of the cyclopropane ring mediated by *m*-CPBA formed product **95**, which contained the signature structure element of gelsemine, the bicyclo[3.2.1]octane core (Scheme 21(a)). The subtle reactivity of the system can be seen in Scheme 21(b). When the photoadduct derived from **97** was treated with *N*-iodo-succinimide compound **98** was formed instead, which originates from bond cleavage of the cyclopropane bond distal to the double bond.

5.15.5.9.2 1,2-Disubstituted arenes

Total synthesis of rudmollin **112** (Scheme 22):[59]

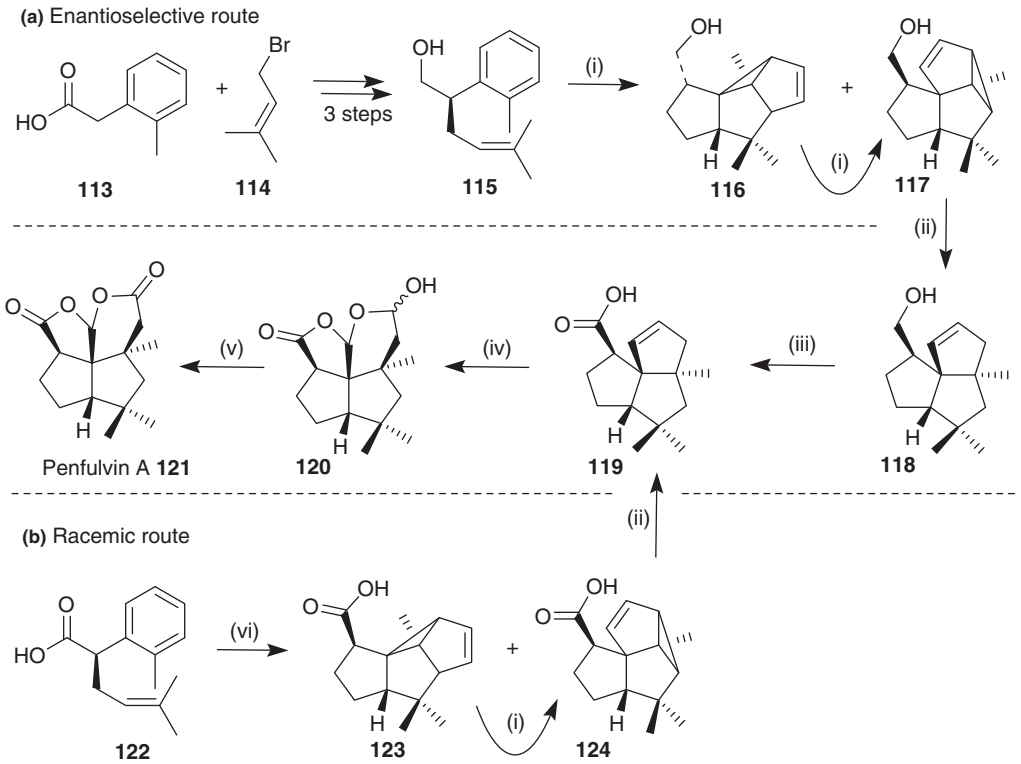


Scheme 22 Wender's synthesis of rudmollin. Reagents and conditions: (a) THF, 0 °C, then **100**, 98%; (b) TBSCl, DMF, NEt_3, DMAP, 97%; (c) hυ (Vycor filter) pentane, 63%; (d) $Hg(OAc)_2$, THF, H_2O (71% **106** + 6% **105**); (e) $NaBH_4$, MeOH, 94%; (f) MnO_2, CH_2Cl_2, 93%; (g) H_2, 5%Pd/C, Et_2O, 99%; (h) $(PhO)_2O$, DMAP, NEt_3, DMF, 50 °C, 95%; (i) KHMDS, DME, 0 °C, then BEt_3, THF, allyl iodide, 50% (j) $NaBH_4$, $CeCl_3$, MeOH, 72% (α:β = 3:1); (k) O_3, MeOH, CH_2Cl_2, −78 °C then $NaBH_4$ 98%; (l) TBSCl, imidazole, DMF, 97%; (m) MsCl, pyridine, then $LiAlH_4$, DME, 0–25 °C, 84%; (n) KH, THF, BnBr, 96%; (o) HF-H_2O, CH_3CN, THF, Jones acetone, 82%; (p) I_2, *sym*-collidine, CH_3CN, Bu_3SnH, AIBN, PhH, 80 °C, 53%; (q) $NaBH_4$, MeOH, −78 to 25 °C, 92%; (r) H_2 (40 psi), 10% Pd/C, 70% $HClO_4$ (catalyst), MeOH, 82%; (s) $(Me_2N)_3CH$, 90 °C, then DIBAL, THF, 0 °C, 54%.

Rudmollin **112** was also synthesized by the Wender group. Its overall oxidation state is far higher than the previous examples and, therefore, more postcycloaddition modifications are necessary. Again the photoaddition precursor is rapidly accessible (**99**/**100**→**101** Scheme 22). In this synthesis, the tether contains a *Z*-double bond, and thus the *exo*-transition state **102** was formed. Regiomers **103** and **104** were obtained in a 1:1 ratio, but were both submitted to the next step – an oxy-mercuration with concomitant fragmentation – to give a 12:1 mixture in favor of the desired regioisomer **106**. This was reduced to the diol, and treatment with manganese dioxide selectively reoxidized the allylic alcohol, giving an enone-system. The double bond was hydrogenated, the remaining alcohol benzoylated and the ketone was alkylated with allyl iodide yielding **108**. Ketone **108** was reduced to give 3:1 in favor of the α-isomer **109**. The double bond was cleaved by ozonolysis, and the resulting aldehyde was reduced and selectively protected with TBSCl at the primary position giving **110**. Mesylation of the secondary alcohol in **110** with subsequent treatment with lithium aluminum hydride resulted in fragmentation to give compound **111**. Benzylation of the primary alcohol, iodolactonization and Barton–McCombie dehalogenation introduced the γ-lactone. The *exo*-methylene-double bond was introduced by a procedure from Wassermann[60] yielding rudmollin **112**.

Total synthesis of penifulvins A[61] **121**, B **129**, and C **134**.[62]

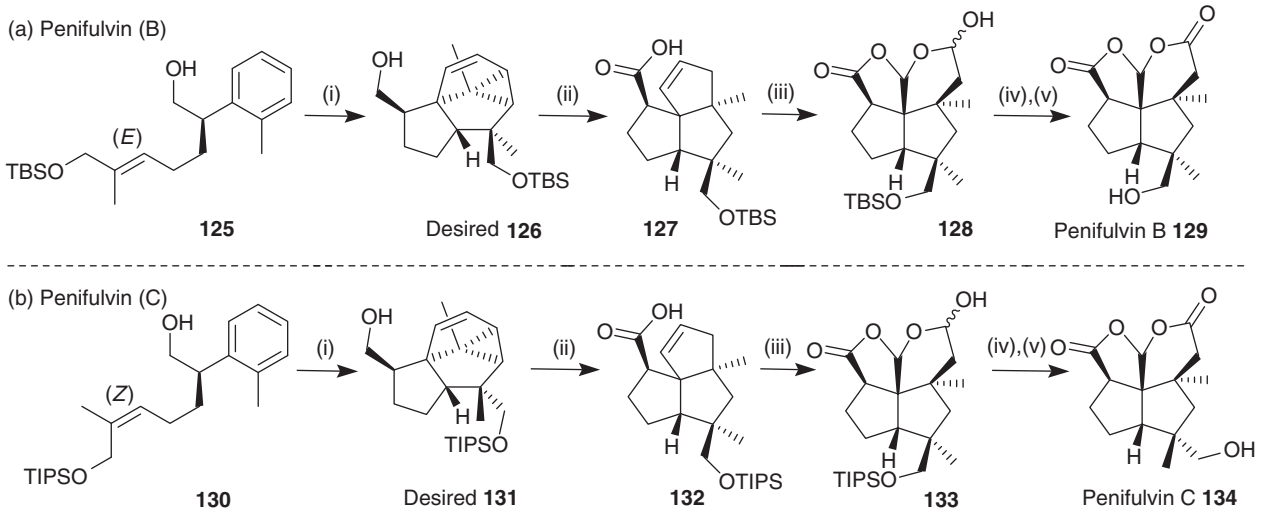
The synthesis of penifulvin A **121** was carried out both in racemic and in an enantioselective fashion. Thereby carboxylic acid **122** was obtained from alkylation (racemic synthesis, Scheme 23(b)). The benzylic stereocenter was established by Myer's alkylation[63] (enantioselective synthesis Scheme 23(a)). Irradiation of **115** and **122**, respectively, afforded a 1:1 mixture of regioisomers (**116** and **117** (enantioselective)/ **123** and **124** (racemic)) in each case, which could be separated and resubjected to photoequilibration conditions. Birch reduction of the cyclopropane moieties gave **118** and **119**. In the enantioselective route, compound **118** was oxidized to the carboxylic acid **119** and subjected to ozonolysis, which afforded acylal **120** in 78% yield. This in turn was oxidized to penifulvin A **121**.



Scheme 23 Gaich's synthesis of penifulvin. (a) Reagents and conditions: (i) hυ, pentane, 22 °C, 2 h, (Series (a)**: 116:117** R = CH_2OH, optically active, 70% yield; (ii) $EtNH_2$, Li, THF, −78 °C, 7 h, 72%; (iii) IBX, DMSO, 22 °C, 20 min, then $NaClO_2$, 2-methyl-2-butene, *tert*-BuOH, NaH_2PO_4, 1 h, 92%; (iv) O_3, DCM, −78 °C, 2 min, then thiourea, 22 °C, 40 min, 78%; (v) PDC (4 equivalents), DCM, 22 °C, 20 min, then AcOH (20 equivalents), 20 min, 82%; (vi) hυ, pentane, 22 °C, 2 h, Series (b)**: 123:124** R = CO_2H, racemic, 62% yield.

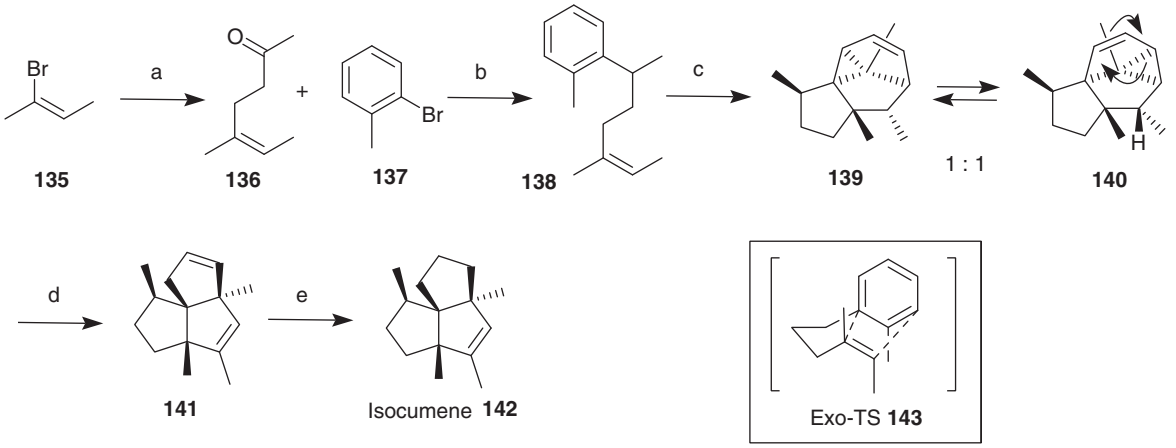
The total syntheses of penifulvin B **129** and C **134** (Scheme 24) were carried out in an analogous way to the synthesis of penifulvin A **121**. They comprise a special feature, which underscores the power of the *meta* photocycloaddition. The two natural products are epimers with respect to the quaternary stereocenter next to the primary alcohol. This stereocenter was to be constructed in the course of the cycloaddition from the double bond. If the geometry of the double bond correlates to the stereochemistry in the respective photoadducts, the synthesis of penifulvin B **129** required photoprecursor **125** with the *E*-double bond, whereas the synthesis of penifulvin C **134** required precursor **130** containing the *Z*-double bond. Indeed the photoadducts

126 and **131**, originating from the two respective geometric double-bond isomers, exhibited the opposite stereochemistry at this carbon atom. Till date this is the only example in the literature where a quaternary stereocenter is formed in this position.



Scheme 24 Gaich's synthesis of penifulvins B and C. Reagents and conditions: (i) hυ, pentane, 22 °C, 2 h, 64% (combined yields); (ii) $EtNH_2$, Li, THF, −78 °C, 7 h, 86%; (iii) IBX, DMSO, 22 °C, 20 min, then $NaClO_2$, 2-methyl-2-butene, *tert*-BuOH, NaH_2PO_4, 1 h, 96%; (iv) O_3, DCM, −78 °C, 2 min, then thiourea, 22 °C, 40 min, 36%; (v) PDC (4 equivalents), DCM, 22 °C, 20 min, then AcOH (20 equivalents), 20 min, 83%; 50% HF–pyr, CH_3CN, 82%.

Total synthesis of isocumene **142** (Scheme 25):[47]

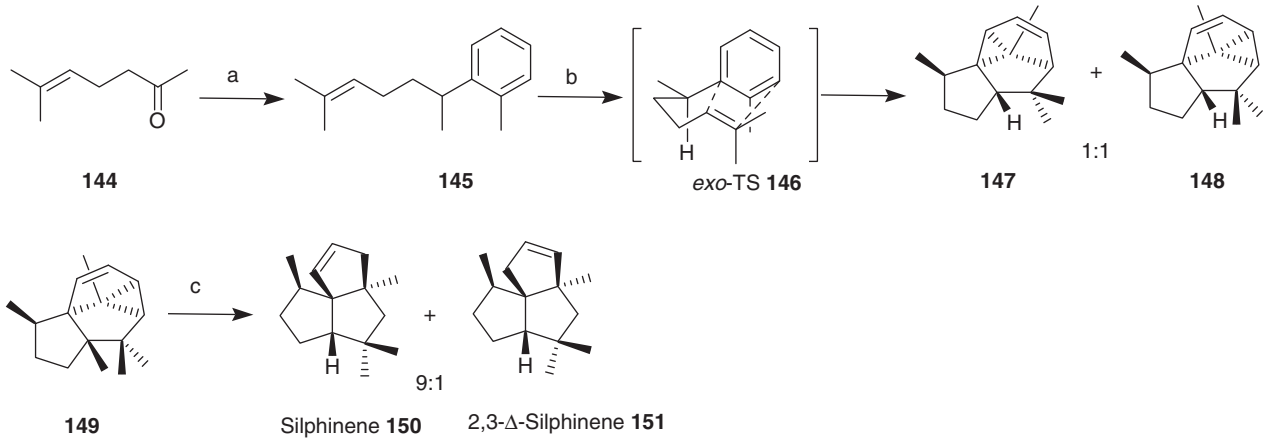


Scheme 25 Wender's synthesis of isocumene: Reagents and conditions: (a) Li, Et_2O then CuI, −65 °C, MVK, 56%; (b) *ortho*-bromotoluene, Li, Et_2O, r.t., then **136** then NH_3, −78 °C, 78%; (c) hυ (Vycor filter) cyclohexane, 72%; (d) 235–240 °C, 69%; (e) H_2, 5% Pd/C, hexane, 98%.

Isocumene **142**, a member of the pentalene family, was synthesized by Wender et al. via photoaddition precursor **138** yielding isomers **139** and **140**. In this case only one isomer was of further use in the synthesis, but fortunately the undesired **140** could be equilibrated to the desired isomer **139** on further irradiation. Dehydro-isocumene **141** was obtained via a 1,5-H-shift when heating to 240 °C.[64] The last step was a selective hydrogenation of the less substituted double bond yielding isocumene **142** (Scheme 25).

Total synthesis of silphinene **150** (Scheme 26):[65]

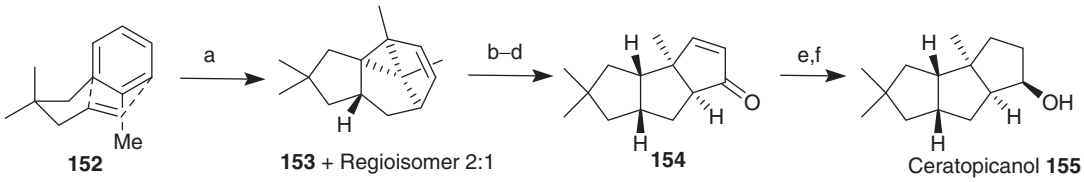
Silphinene **150** is a structure biogenetically related to penifulvins. Wender et al. performed a most elegant and rapid access to this compound without the introduction of any unnecessary functional group (Scheme 26). As in the foregoing syntheses, the stereochemical course of the cycloaddition was governed by the $A^{1,3}$-allyl-strain model (see transition state **146**) leading to regioisomers **147** and **148**. The tricyclic carbon-skeleton was set up in this way except that the cyclopropane ring needed to be



Scheme 26 Wender's synthesis of silphinene. Reagents and conditions: (a) Li, Et_2O, then *ortho*-bromotoluene, then NH_4Cl, 87%; (b) hυ (Vycor filter) pentane, 72%; (c) Li, $MeNH_2$, −78 °C, 74%.

cleaved. This was achieved by a Birch reduction giving silphinene **150** and its 2,3-Δ-double-bond isomer **151** in a 9:1 ratio for the desired natural product.

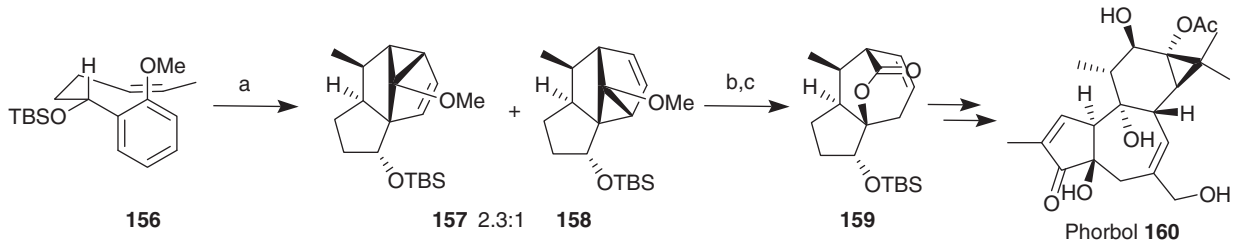
Total synthesis of ceratopicanol **155** (Scheme 27):[36]



Scheme 27 Total synthesis of ceratopicanol. Reagents and conditions: (a) hυ (254 nm) cyclohexane, 72%; (b) PhSH, 100 °C, ultrasound, 97%; (c) CSA, Li, NH_3, −78 °C, 80%; (d) CrO_3–3,5-dimethylpyrazole, 60%; (e) LDA, −78 °C, MeI, 97%; (f) $NaBH_4$, MeOH, 60%.

Chanon et al. have accomplished an effective synthesis of ceratopicanol **155** (Scheme 27). The combined yield in the *meta* photocycloaddition reaction from precursor **152** is 72%, giving two regioisomers; the major and desired one being the linear product **153** is displayed. The angular product was recycled. Radical addition of thiophenol cleaved the cyclopropane ring and the thiophenol was removed under Birch conditions. Chromium-mediated oxidation furnished ketone **154**, which was converted to ceratopicanol **155** in two further steps.

Synthetic studies toward phorbol **160** (Scheme 28):[59]

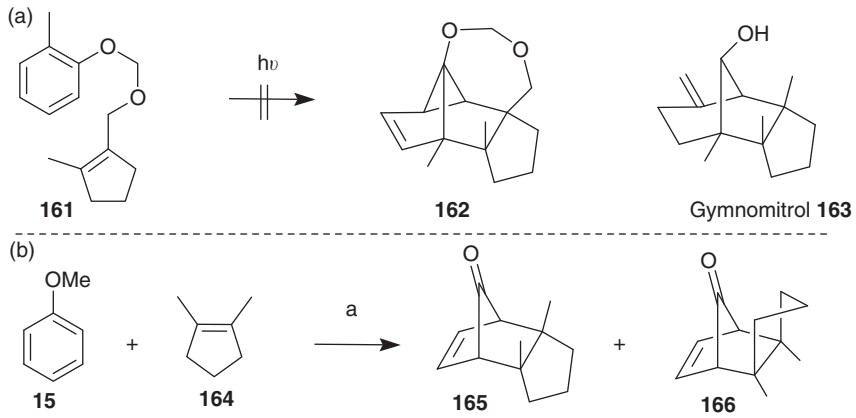


Scheme 28 Synthetic route to phorbol. Reagents and conditions: (a) hυ (Vycor filter) 63%; (b) H_2SO_4, H_2O, acetone reflux then TBSCl, NEt_3; (c) TMSOTf, $(TMSO)_2$, DCM −30 °C.

In the synthetic study to phorbol **160** the *meta* photocycloaddition of **156** yielded a mixture of regioisomers **157** and **158**. The major isomer **158** was subjected to cleavage of the cyclopropane ring under acidic conditions, and Baeyer–Villiger oxidation gave lactone **159**. It was planned to elaborate **159** to phorbol **160**. Product **159** contains the signature 5–7-fused ring system with the tertiary alcohol group.

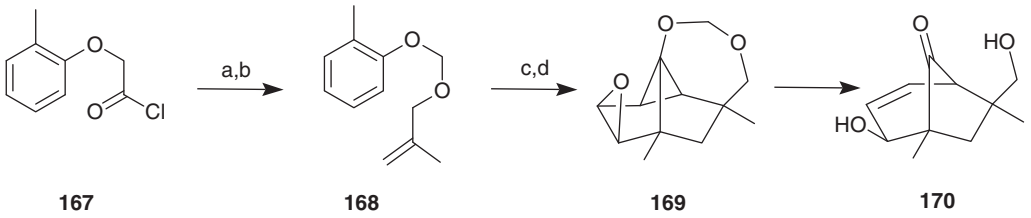
Synthetic studies toward gymnomitrol **163** (Scheme 29):[57,66]

Penkett's synthetic study to gymnomitrol **163** displays one of the few examples of a *meta* photocycloaddition with a four-atom tether. The key to success in these transformations is the conformational lock of the substrate making it suited for the reaction.



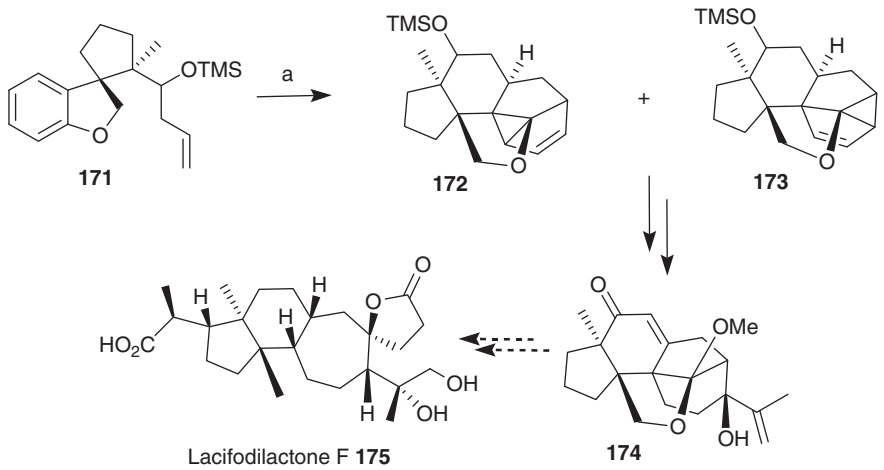
Scheme 29 Attempted photocycloaddition approaches to gymnomitrol. Reagents and conditions: (a) hυ (253.7 nm), cyclohexane, then H_3O^+ (0.1%).

As can be seen in Scheme 29(a) an intramolecular approach turned out to be unsuccessful due to steric hindrance of the tetrasubstituted double bond. The intermolecular reaction gave 0.1% yield of a 1:5 mixture of **165** to **166**, whereas the intramolecular reaction of **161** to **162** delivered no product at all. Only when switching to the less encumbered system **168**, the intramolecular cycloaddition product **169** could be obtained in 17% yield (Scheme 30).



Scheme 30 Attempted photocycloaddition approaches to gymnomitrol. Reagents and conditions: (a) $(PPh_3)_4RhCl$, 170 °C; (b) methallyl alcohol, 50% NaOH, 86%; (c) hυ (253.7 nm), cyclohexane, 17%; (d) DMDO, DCM-acetone (1:1), 0 °C, 100%; (e) HCl(aqueous), acetone, r.t., 55%.

Synthetic studies toward lacifodilactone **175** (Scheme 31):[67]

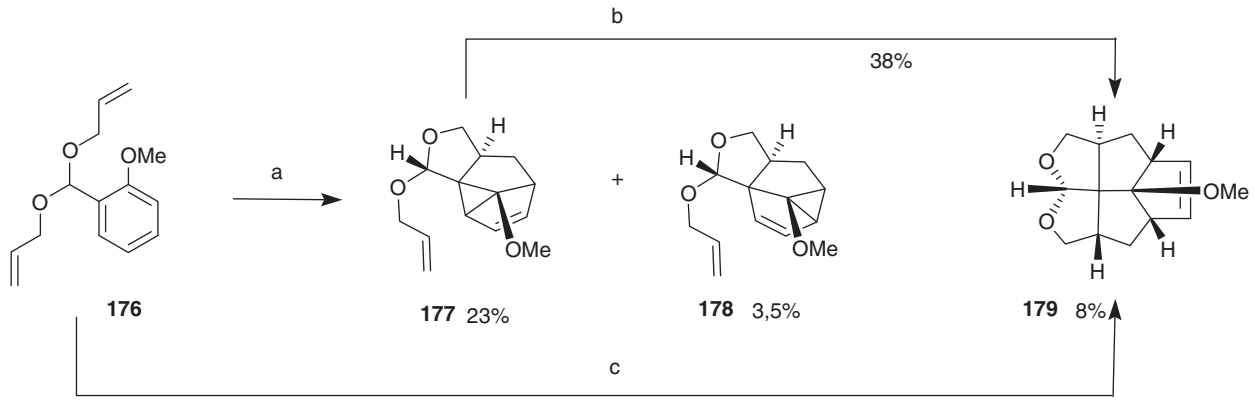


Scheme 31 Studies toward lacifodilactone F. Reagents and conditions: (a) hυ (254 nm) 89%.

A recently published approach to lacifodilactone F **175** by Wang and Chen also featured a four-atom tether. The *spiro* moiety in **171** helped to conformationally restrict the tether and enabled the reaction in impressive 89% yield of **172** and **173**. Further elaboration to **174** gave access to an advanced intermediate en route to the natural product.

A tandem *meta* photocycloaddition/[3 + 2]-cycloaddition approach to fenestranes **179** (Scheme 32):[68]

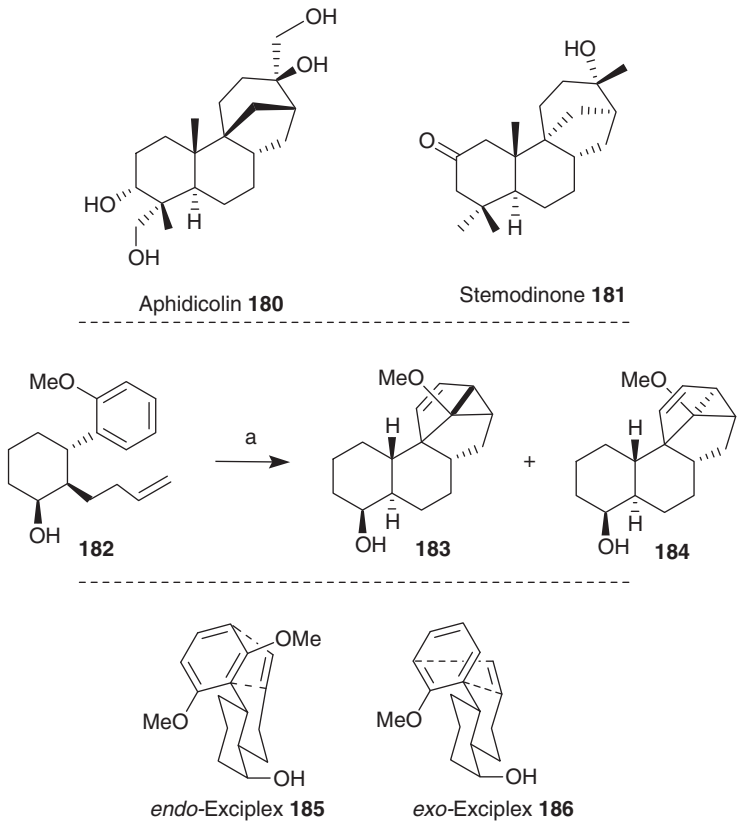
The fenestrane structure has been targeted several times by total synthesis.[69] Recently, Penkett and coworkers described a tandem approach to fenestrane **179**. Their synthesis started from bisallyl acetal **176**. Irradiation in cyclohexane yielded product



Scheme 32 Tandem *meta* photocycloaddition/[3 + 2]-cycloaddition. Reagents and conditions: (a) hυ (254 nm), cyclohexane 4 h; (b) hυ (254 nm), cyclohexane 16 h; (c) hυ (254 nm), cyclohexane 18 h.

177 with 23% and regioisomer **178** with 3.5%. Prolonged exposure of the desired regioisomer **177** to the same reaction conditions resulted in fenestrane formation with 38% yield.

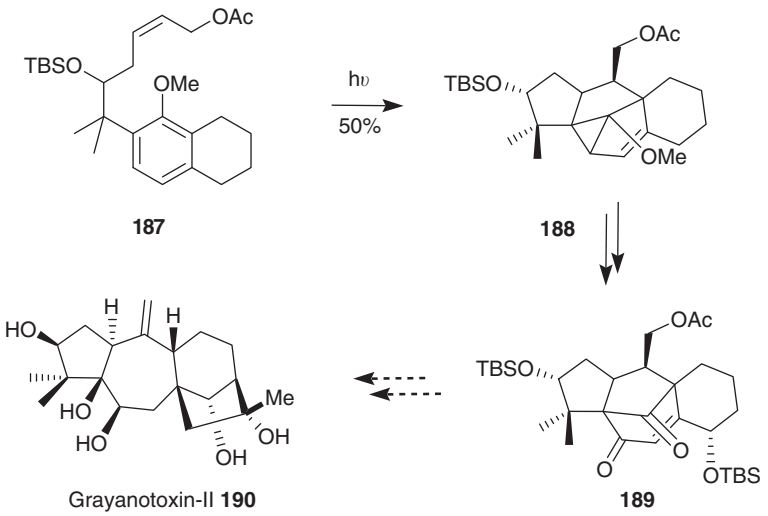
Synthetic studies toward aphidicolin **180** and stemodinone **181** (Scheme 33):[31]



Scheme 33 An approach to the aphidicolin and stemodinone ring systems. Reagents and conditions: (a) hυ (low pressure mercury vapor lamp), cyclohexane, **183**:**184** = 1.2:1 (90%).

In the attempt to provide the carbon-skeleton of aphidicolin **180** and stemodinone **181**, a four-atom-tether cycloaddition of **182** was accomplished. Besides the rarely found four-atom-tether, this is the only example where a *meta* photocycloaddition selectively (1.2:1) proceeds via an *endo*-transition state **185** to give **183** in 90% yield combined with the *exo*-adduct **184** stemming from **186**. Products **183** and **184** are, therefore, not regioisomers but diastereomeric in nature. As expected, the aromatic methoxy group controls the regiochemistry of the cycloaddition.

Synthetic studies toward grayanotoxin-II **190** (Scheme 34):[6f,70]



Scheme 34 Synthetic studies toward grayanotoxin-II.

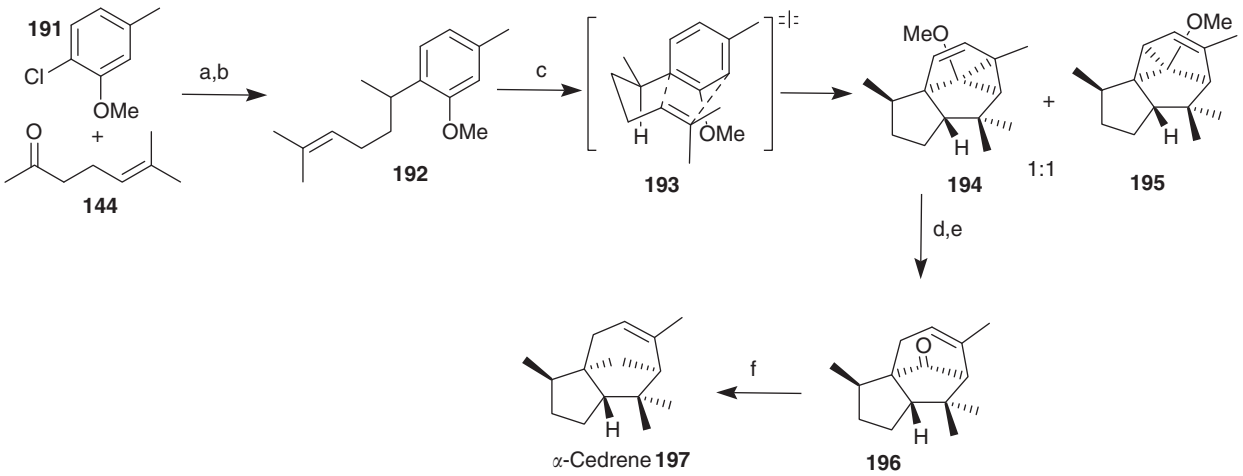
Wender and Oliviero designed a synthetic approach to grayanotoxin-II **190** starting with a tetrasubstituted arene **187**. Nevertheless this apparently hindered system **187**, which comprises a four-atom-tether, gave the desired photoadduct **188** in 50% yield. The carbon framework was thus set up and elaborated to intermediate **189**.

5.15.5.9.3 Trisubstituted arenes

With a trisubstituted arene as starter unit in the *meta* photocycloaddition a more complex carbon scaffold can be accessed, which is able to deliver more hindered photoadducts and thus the rise molecular complexity is drastically increased. So far two different substitution patterns on the arene have been investigated, the 1,2,4- and the 1,2,3-pattern. The next section deals with total syntheses of the first category.

1,2,4-Trisubstituted arenes:

Total synthesis of cedrene **197** (Scheme 35):[33]

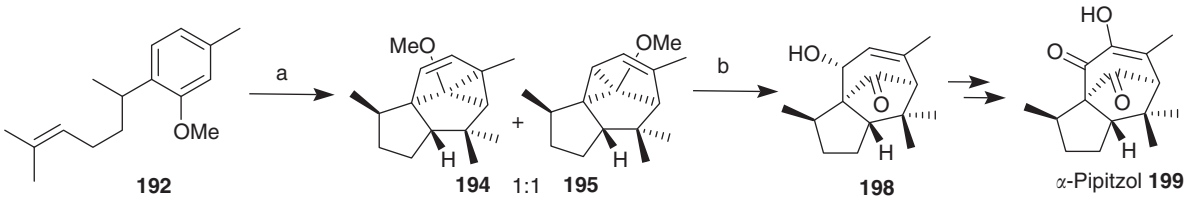


Scheme 35 Wender's synthesis of α-cedrene. Reagents and conditions: (a) Li, Et_2O, then **150**; (b) Li, NH_3, then NH_4Cl, 74% over two steps; (c) hυ (Vycor filter) pentane, 65%; (d) Br_2, CH_2Cl_2; (e) Bu_3SnH (neat), 59% over two steps; (f) NH_2NH_2, KOH, $(OHCH_2CH_2)O$, 200 °C, 58%.

The first example comprises the total synthesis α-cedrene **197** by Wender et al. Synthesis of the cycloaddition precursor **192** was achieved by addition of an aryllithium species generated from **191** to ketone **144**. The benzylic alcohol was reduced to give **192**. The stereogenic center in **192** allowed the stereoselectivity of the photocycloaddition to be controlled in such a way that, according to the $A^{1,3}$-strain model in **193**, the proton stayed in-plane with the aromatic ring. The regioisomers **194**/**195** were

converted to ketone **196** via a bromonium ion-induced fragmentation reaction of the cyclopropane ring. The allylic bromides were defunctionalized in a Barton–McCombie reaction, yielding only one double-bond isomer **196**. This compound was further defunctionalized in a Wolff–Kishner reduction to give α-cedrene **197**.

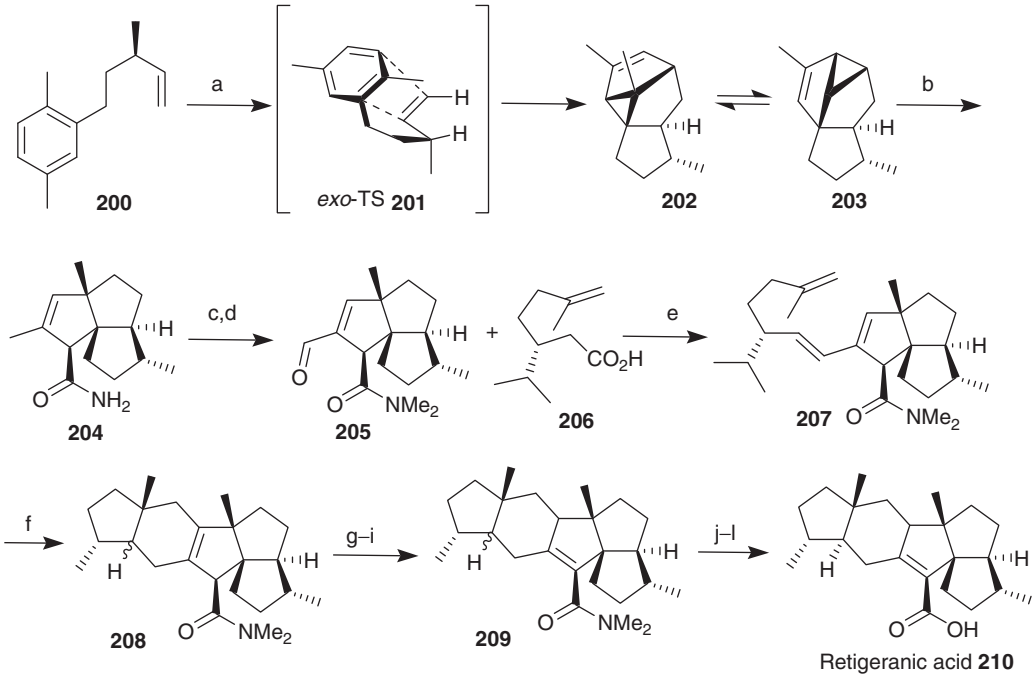
Total synthesis of pipitzol **199** (Scheme 36):[60b,71]



Scheme 36 Wender and Howbart's synthesis of pipitzol. Reagents and conditions: (a) hυ (Vycor filter) 65%; (b) I_2, THF.

Wender and Howbert accomplished a synthesis of pipitzol **199** utilizing the same photocycloaddition adducts **194** and **195** as in the synthesis of cedrene **197**. The synthesis was completed by different functional group interconversions after the photochemical key step.

Total synthesis of retigeranic acid **210** (Scheme 37):[72]

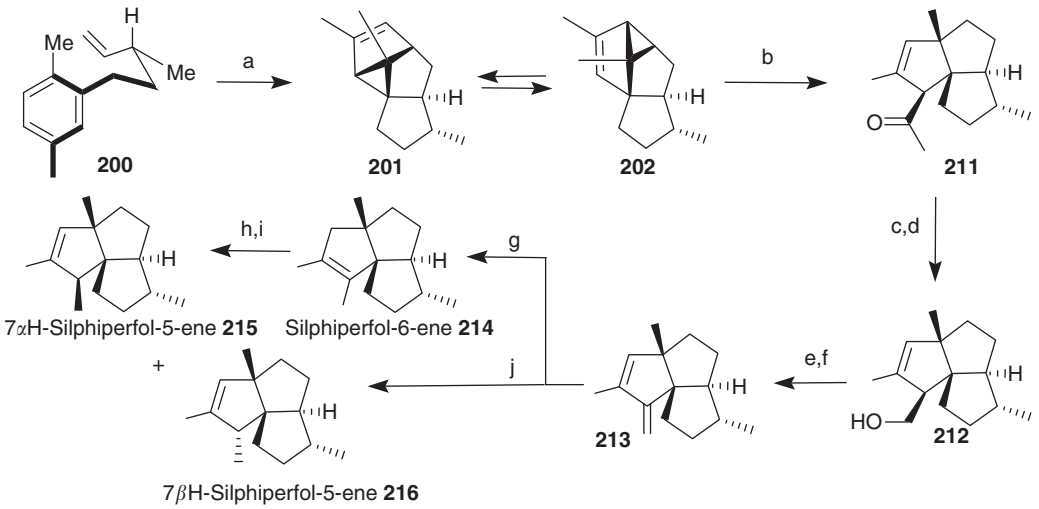


Scheme 37 Wender's synthesis of retigeranic acid. Reagents and conditions: (a) hυ (Vycor filter) pentane, 72%; (b) hυ (pyrex filter) acetone, $HCONH_2$, *t*-BuOH; (c) KOH, DMSO, MeI, 80%; (d) SeO_2, *t*-BuOOH, $(CH_2Cl_2)_2$, Δ, 53%; (e) **206**, LDA, 50 to 0 °C then **205** (at −78 to 25 °C, AcOH, *N,N*-dimethylformamide dimethyl acetal, Δ, 65%; (f) 230 °C, $PhCH_3$, 65%; (g) *m*-CPBA, NaOAc, CH_2Cl_2; (h) *t*-BuOK, DMSO, 100 °C; (i) 10%-Pd/C, H_2, PhH, 400 psi; (j) $LiAlH_4$, THF, (k) PDC, CH_2Cl_2; (l) oxidation to the carboxylic acid.

Retigeranic acid **210** is a more complex pentacyclic structure, containing four cyclopentane and one cyclohexane rings. Photoprecursor **200** was generated in six steps. The two photoadducts **202** and **203** were equilibrated to the desired regioisomer **203**, which was elaborated to compound **204**. Thereby radical ring cleavage of the cyclopropane ring introduced the carbon atom that finally represents the carboxylic acid in the natural product. Methylation of the amide of **204** and allylic oxidation gave compound **205**, which was reacted with **206** to give triene **207**. On heating to 230 °C a Diels–Alder reaction took place to form the cyclohexane and the terminal cyclopentane ring. Further functional group manipulations finally lead to the natural product.

Total synthesis of silphiperfol-6-ene **214** and 7αH-silphiperfol-5-ene **215** (Scheme 38):[73]

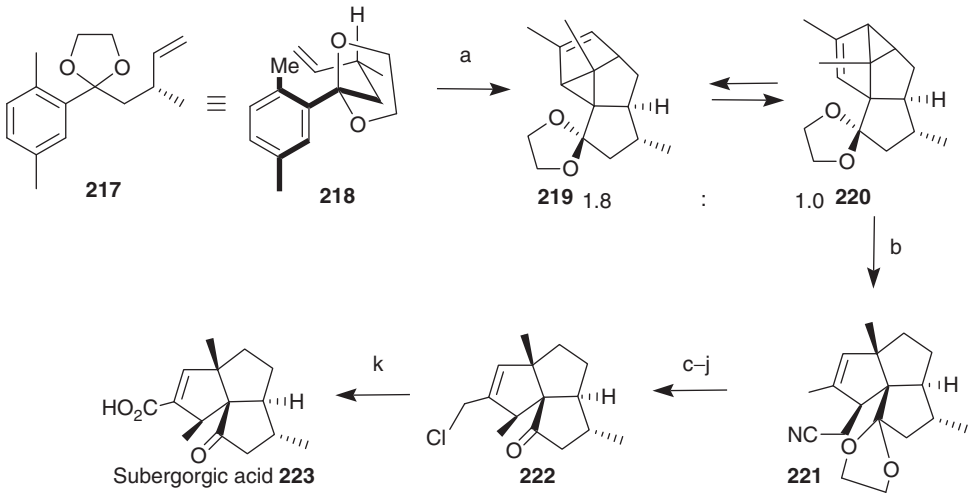
The photoreaction substrate **200** was prepared according to a procedure by McEnroe and Hall.[74] Irradiation of **200** proceeded from the conformation shown in Scheme 38, and gave in *exo*-selective fashion photoadducts **201** and **202** in 72% yield with a ratio of 1.9:1 in favor of **201** – the linear product. Fortunately, the authors were able to photoequilibrate the mixture to the desired regioisomer. Concomitant cleavage of the cyclopropane with introduction of the ketone functionality via addition of acetaldehyde



Scheme 38 Synthesis of silphiperfol-6-one and 7αH-silphiperfol-5-ene. Reagents and conditions: (a) hυ (Vycor filter), 72%; (b) hυ (pyrex) MeCHO, 0 °C, 60%; (c) Br_2, NaOH, reflux 95%; (d) LAH, THF, reflux 91%; (e) $PhNO_2SeCN$, *n*-Bu_3P, THF (99%); (f) H_2O_2, THF (78%); (g) Li, NH_3, Et_2O, −33 °C (91%); (h) *n*-BuLi, $(EtO)_2POCl$, THF-TMEDA (4:1) (76%); (i) Li, *t*-BuOH, $EtNH_2$, THF, 0 °C (55%); (j) $(Ph_3P)_3RhCl$, benzene:ethanol 3:1, (89%) **215**:**216** = 1:2.8.

gave **211**. Bromoform reaction followed by reduction to the corresponding alcohol resulted in the formation of product **212**. Elimination of the alcohol gave diene **213**, which yielded the desired natural product silphiperfol-6-ene **214** under Birch type conditions. In contrast, reduction of the terminal double bond of **213** with Wilkinson's catalyst provided a 2.8:1 mixture of 7αH-silphiperfol-5-ene **216** and 7βH-silphiperfol-5-ene **215**. The latter was synthesized in a stereoselective fashion by conversion of alcohol **212** to a diethyl phosphonate and subsequent reduction with lithium in ethylamine.

Total synthesis of subergorgic acid **223** (Scheme 39).[51]



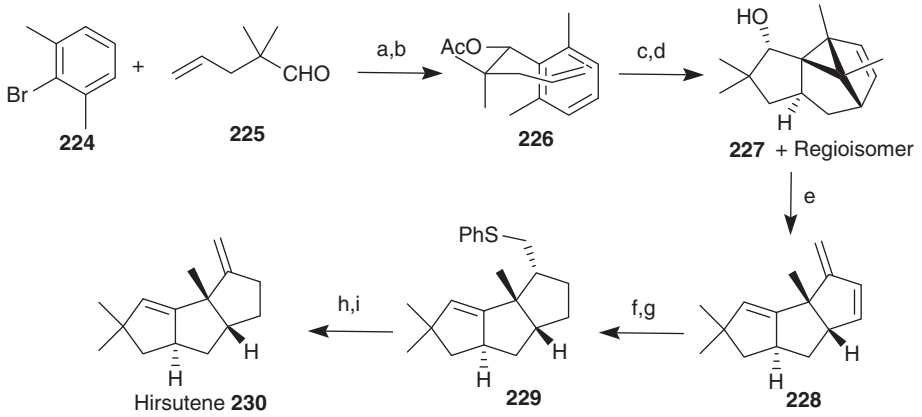
Scheme 39 Synthesis of subergorgic acid. Reagents and conditions: (a) hυ (Vycor filter), cyclohexane (42%); (b) dibenzoyl peroxide, CH_3CN, reflux (67%); (c) K, 18-crown-6, toluene (90%); (d) *m*-CPBA,(80%); (e) *N*-cyclo-hexyl, *N*-isopropylamine, MeMgBr (70%); (f) SOCl2, pyridine (85%); (g) DMSO, $AgBF_4$, Et_3N (85%) then $NaClO_2$.

In the synthesis of subergorgic acid **223**, Wender and deLong explored the influence of steric hindrance adjacent to the benzene ring. In this example, the steric hindrance is exerted by the acetal group in **217**. Photolysis of **217** gave rise to a 1.8:1 regioisomeric mixture of **219** and **220**, whereby three contiguous quaternary carbon centers were formed. Only the angular product **220** was ring-opened via a radical fragmentation reaction, catalyzed by dibenzoylperoxide, to give compound **221**. This was converted to chloro-ketone **222**, starting with the defunctionalization of the nitrile.[75] Epoxidation with *m*-CPBA followed by epoxide opening and allylic chlorination gave **222** in four steps. The final transformations contained a Kornblum oxidation followed by a Pinnick oxidation to the carboxylic acid of subergorgic acid **223**.

1,2,3-Trisubstituted arenes:

This specific substitution pattern of the arene allows for the construction of at least three contiguous quaternary carbon centers, all of them located at the cyclopropane ring. No doubt this synthetic challenge would be difficult to solve otherwise.

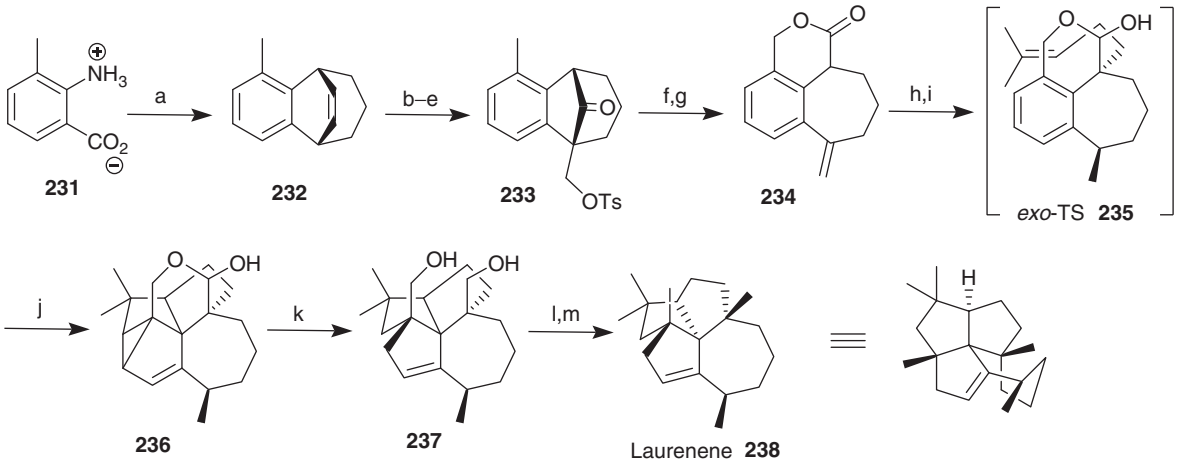
Total synthesis of hirsutene **230** (Scheme 40):[56a]



Scheme 40 Total synthesis of hirsutene. Reagents and conditions: (a) Mg, Et_2O; (b) Ac_2O, DMAP 79%; (c) hυ (Vycor filter) 23%; (d) $LiAlH_4$, Et_2O; (e) CSA, PhH, 71%; (f) PhSH, 100 °C, 78%; (g) H_2, DCM, $[Ir(cod)PyPCy_3]PF_6$; (h) $NaIO_4$,MeOH 86%; (i) 170 °C, $P(OMe)_3$ 60%.

Wender and Howbart prepared the photoprecursor **226** of this total synthesis in a straightforward three-step sequence. Photolysis of **226** gave adduct **227** plus its regioisomer. Although the double bond is terminal and not a *Z*-double bond, the addition takes place in a 1,3-mode across the *ortho*-donor, presumably due to less steric hindrance compared to the 2,6-addition mode which normally takes place. Elaboration of the hirsutene carbon framework was pursued by cyclopropane ring opening with camphorsulfonic acid yielding **228** after elimination reaction. Radical thiophenole addition to the *exo*-olefin of **228** allowed for the selective removal of the disubstituted double bond with Crabtree's catalyst, leading to compound **229**. Restoration of the *exo*-methylene group by elimination of the corresponding sulfoxide of **229** gave hirsutene **230** in approximately 60% yield.

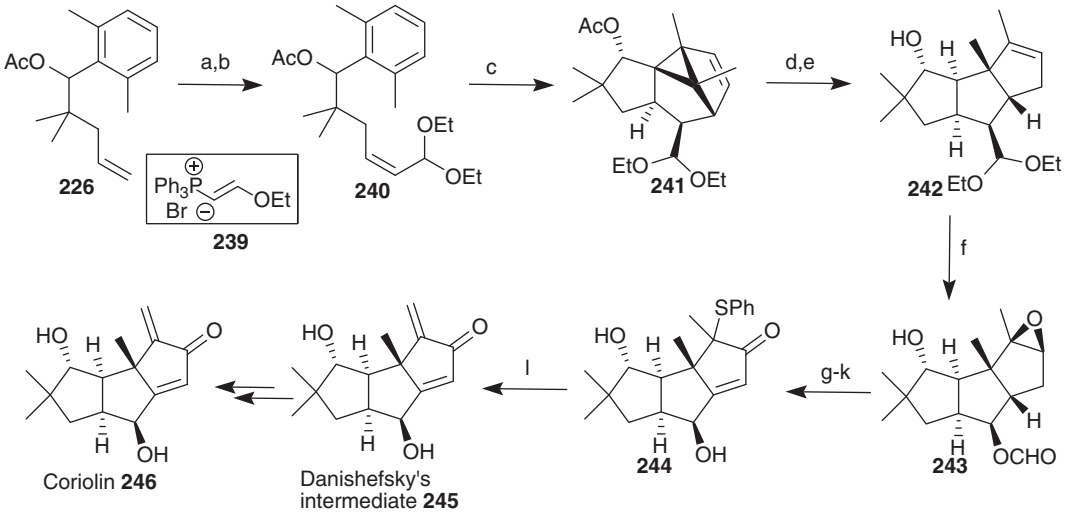
Total synthesis of laurenene **238** (Scheme 41):[37]



Scheme 41 Wender's synthesis of laurenene. Reagents and conditions: (a) isopentyl nitrite, Cl_3CCO_2H, cycloheptadiene, CH_2Cl_2, 84% brsm; (b) O_3, DMS, NEt_3, 68%; (c) $Zn(BH_4)_2$, Et_2O, 98%; (d) TsCl, 72%; (e) PCC, 98%; (f) NBS, AIBN, then KOH, 72%; (g) H_2, Pt, 96%; (h) LDA, DMPU, hompoprenyl iodide, 48%; (i) $LiALH_4$, THF, 95%; (j) hυ, ($BiCl_3$-filter), 51%; (k) Li, $MeNH_2$, −60 °C, 96%; (l) KHMDS, HMPA, $ClPO(NMe_2)_2$, 55%; (m) Li, $EtNH_2$, 65%.

Laurene **238** is one of the most complex natural products synthesized by using the *meta* photocycloaddition. It belongs to the diterpenes and has a fenestrane-type structure. The synthesis of the photoaddition precursor **235** was a little bit more laborious but proceeded through standard steps from amino acid **231**. Photocycloaddition of **235** gave compound **236**. The cyclopropane ring was removed in a Birch reduction to give **237**, and, after several defunctionalization reactions, laurenene **238** was obtained.

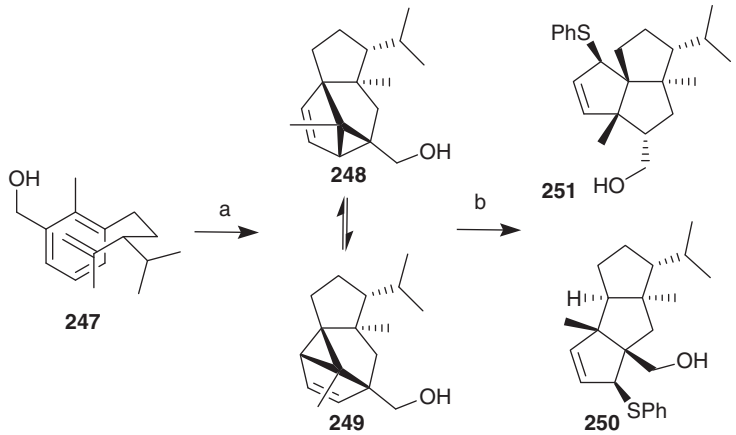
Total synthesis of coriolin **246** (Scheme 42):[50a]



Scheme 42 Formal total synthesis of coriolin. Reagents and conditions: (a) O_3, MeOH, 61%; (b) NaOEt, DCM; (c) hυ (Vycor filter) 15%; (d) PhSH, 100 °C, 72%; (e) Li, NH_3, Et_2O 80%; (f) *m*-CPBA, DCM, H_2O, 67%; (g) BF_3, PhH; (h) LDA, TMSCl; (i) $Pd(OAc)_2$, CH_3CN;%; (j) LDA, $PhSSO_2Ph$, 42% four steps; (k) AcOH:H_2O:THF (3:1:1) 100%; (l) *m*-CPBA, EtOAc, heat.

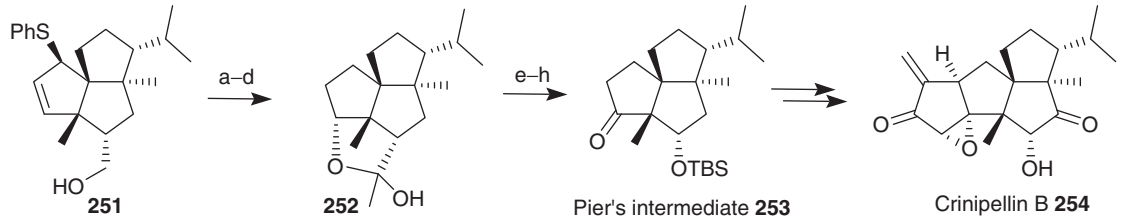
There are two routes to coriolin **246** via a *meta* photocycloaddition reaction. One is closely related to the synthesis of hirsutene **230** and is not mentioned here, as the same photoadduct was used.[76] A second more direct route to coriolin **246** started from compound **226**. Ozonolysis and Wittig olefination gave rise to photoprecursor **240**, which was transformed into **241** in 15% yield. The relatively modest yield is explained by extreme steric hindrance. Radical cyclopropane ring opening with thiophenol was followed by removal of the sulfur under Birch conditions to furnish the linear triquinane system **242** in 80% yield. Treatment of **242** with *m*-CPBA in moist dichloromethane not only introduced the epoxide, but, after acid-catalyzed cleavage of the acetal moiety, a concomitant Baeyer–Villiger oxidation gave compound **243**. Lewis acid-catalyzed epoxide rearrangement formed a ketone, which was transformed into an α,β-unsaturated ketone by Saegusa oxidation. Thiophenoxide was introduced in the α-position to the carbonyl via an addition/elimination process leading to compound **244**. Cleavage of the formiate group and oxidative elimination of the sulfur group furnished compound **245**, a known intermediate of Danishefsky's synthesis of coriolin **246**.[77]

Total synthesis of crinipellin B **254** (Schemes 43 and 44):[50b]



Scheme 43 Formal total synthesis of coriolin. Reagents and conditions: (a) hυ (Vycor filter) 33%; (b) PhSH, 100 °C, 68%.

Wender and Dore accomplished the total synthesis of crinipellin B **254**. This approach required a rather complex precursor **247** for the photocycloaddition. Its synthesis is not displayed here. Despite its complexity, the cycloaddition gave rise to 33% yield of the regioisomers **248** and **249**. On treatment of the product mixture with thiophenol the cyclopropane moiety was cleaved and the two products **250** and **251** were formed which could be separated by flash column chromatography.



Scheme 44 Formal total synthesis of coriolin. Reagents and conditions: (a) Me_3OBF_4, DCM, reflux, 74%; (b) H_2, Pd/C 10%, EtOAc, 97%; (c) $RuCl_3$, $NaIO_4$, 72%; (d) MeLi, THF $-78\,^{\circ}C$, 95%; (e) *m*-CPBA, $CHCl_3$, 55%; (f) Dess–Martin reagent, DCM, 87%; (g) $Ba(OH)_2$, MeOH, 0 °C, 80%; (h) TBSOTf, NEt_3, DCM, $-78\,^{\circ}C$, 86%.

The desired angular product **251** was further elaborated to lactol **252**. To this end, **251** was methylated and the sulfonium-ion was displaced by the primary alcohol, to give the tetrahydrofuran ring of **252**. Hydrogenation of the double bond was followed by oxidation to the lactone, which was converted to lactol **252** by methyllithium addition. Baeyer–Villiger oxidation with *m*-CPBA gave a monoprotected diol, which was oxidized to the ketone. Subsequent cleavage of the acetate with barium hydroxide and reprotection gave compound **253**, called Pier's intermediate. The synthesis was completed starting from this compound.

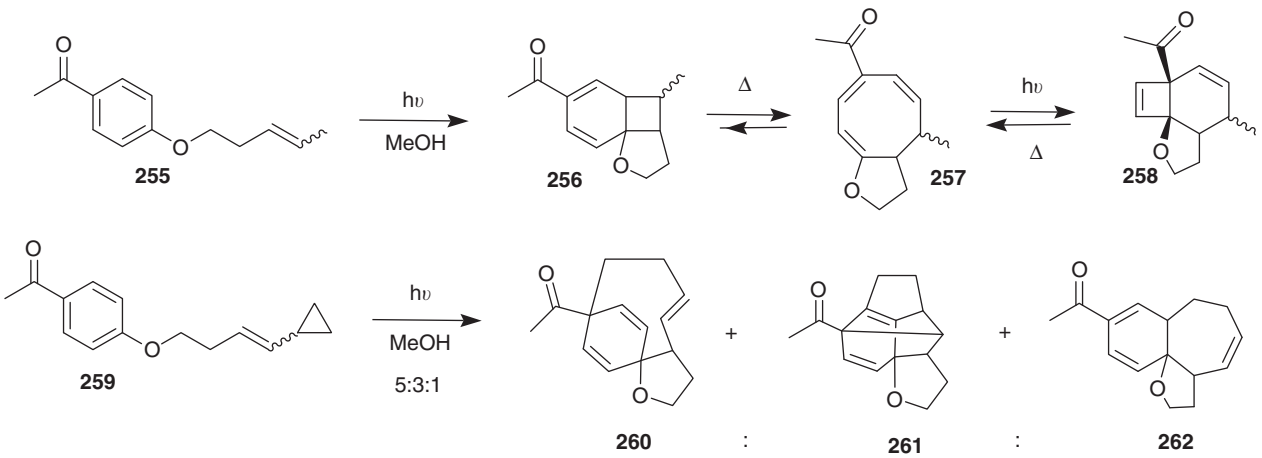
5.15.6 Examples of Applications of the *Ortho* Photocycloaddition

There is little data on the *ortho* photocycloaddition and its selectivity in the literature. The regioselectivity of the *ortho* photocycloaddition is dependent on the electronic properties of the two reaction partners.[15a] This selectivity is low and decreases with diminishing degree of charge-transfer processes. The role of charge transfer is also supported by the fact that regioselectivity is usually higher in polar solvents where charge separation is favored.[21,67,78] Substituted olefins may add in an *exo* or *endo* fashion. Electron-deficient alkenes give mixtures of both possible products; electron-rich compounds however, show stereoselectivity toward the *exo* products. *Ortho* photocycloaddition can also take place from the triplet excited-state by sensitization. This state is believed to have a higher biradical and less zwitterionic character.[79]

5.15.6.1 *Ortho* Photocycloadditions followed by Rearrangment Reactions

Ortho photocycloadducts are known to be inherently unstable, therefore often consecutive reactions take place, which give stable products that can often be isolated in high yields.

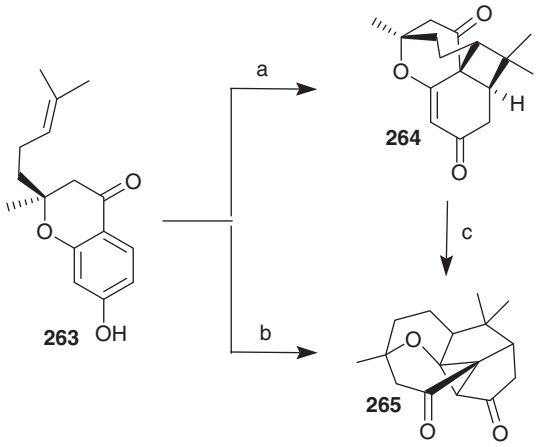
Photocycloadditions of alkanophenones (Scheme 45):



Scheme 45 *Ortho* photocycloadditions of alkanophenones.

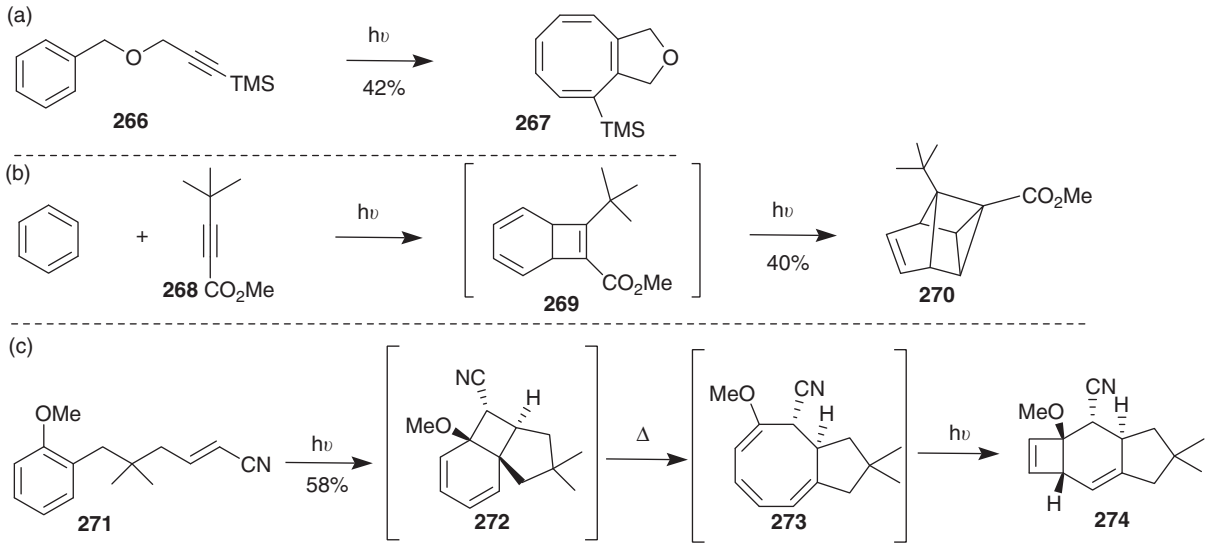
Ortho photocycloaddition of triplet excited benzenes have been extensively studied by Wagner and his group. They investigated [2 + 2] photocycloadditions of alkanophenones **255** and **259**, occurring from the triplet excited-state and via 1,4-biradicals.[80] Such radicals have been proven by the insertion of a cyclopropyl radical trap **259** in the olefin. On irradiation of this modified starting material, the *ortho* cycloadduct **256** could no longer be isolated (Scheme 23),[81] but the brigdehead like compounds **260** and **261** were formed instead.

A very good example for consecutive reactions was published by Kalena et al. some years ago,[82] who observed that 2-alkenyl-7-hydroxy-4-chromanone **263** undergoes *ortho* photocycloaddition to afford tetracyclic compounds **264** and **265** (Scheme 46). Depending on the solvent used, the final product **265** is either formed directly or product **264** is formed first, which undergoes consecutive rearrangement to **265**.



Scheme 46 Reagents and conditions: (a) hυ, (>300 nm) PhH, 25%; (b) hυ, (>300 nm) MeOH, 38%; (c) hυ, 63%.

The *ortho* addition mode with benzenes is almost exclusively observed with alkynes such as **266** (Scheme 47). The photocycloaddition products usually undergo ring opening to cyclooctatetraenes **267** (Scheme 47(a))[83] or to other rearrangement products **270** on further irradiation (Scheme 47(b)).[84] This reaction provides access to bicyclo[4.2.0]octanes **272**, which undergo thermal electrocyclic ring opening to yield eight-membered ring systems like **273**, for example. Irradiation of **273** yields tricycle **274** (Scheme 47(c)).[79,85]

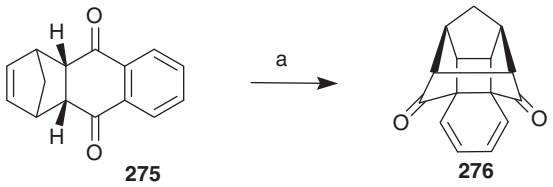


Scheme 47 *Ortho* photocycloadditions followed by rearrangement reactions. Reagents and conditions: (a) hυ, 42%; (b) hυ, 40%; (c) hυ, heat, then hυ, 58%.

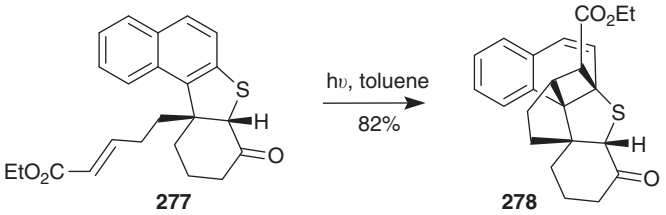
5.15.6.2 Stable *Ortho* Photocycloaddition Products

There are some rare examples where the [2 + 2]-cycloadduct is stable enough to be isolated as such, and in good yield (Schemes 48 and 49).

Naphthoquinones are known to undergo *ortho* cycloaddition (Scheme 48). Recently a very unconventional [2 + 2] photocycloaddition has been reported to afford the caged polycyclic structure **276** from **275**.[86] The attachment of the double bond very



Scheme 48 *Ortho* photocycloaddition of naphthoquinones. Reagents and conditions: (a) hυ, EtOAc, 78%.



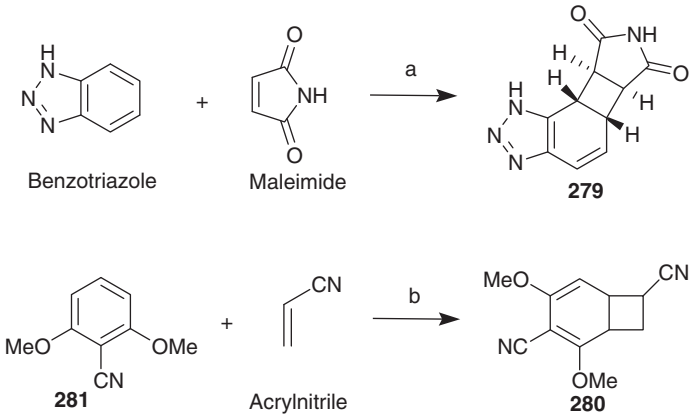
Scheme 49 Naphthalenes undergo *ortho* photocycloaddition.

close to the aromatic moiety leads to the desired cage compound **276** during the photocycloaddition in high yield. The product is stable enough to be isolated and recrystallized.

The *ortho* photocycloaddition with naphthalenes (Scheme 49):

Naphthalenes preferably undergo *ortho* photocycloadditions, whereas higher arenes usually react with olefins in a [2 + 2], [4 + 2], or [4 + 4] cycloaddition mode.

Benzotriazoles, when irradiated in the presence of maleic imide, form stable [2 + 2]-photocycloadducts **279** in 39% yield (Scheme 50). The same applies for 1,5-dimethoxy benzonitrile **281** with acrylnitrile, but in much better yields of 70%.[87]

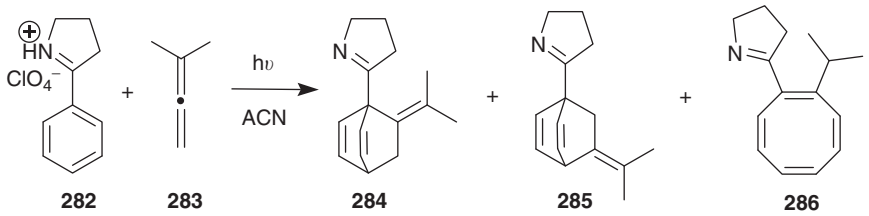


Scheme 50 Reagents and conditions: (a) hυ, MeCN, 39%; (b) hυ, 70%.

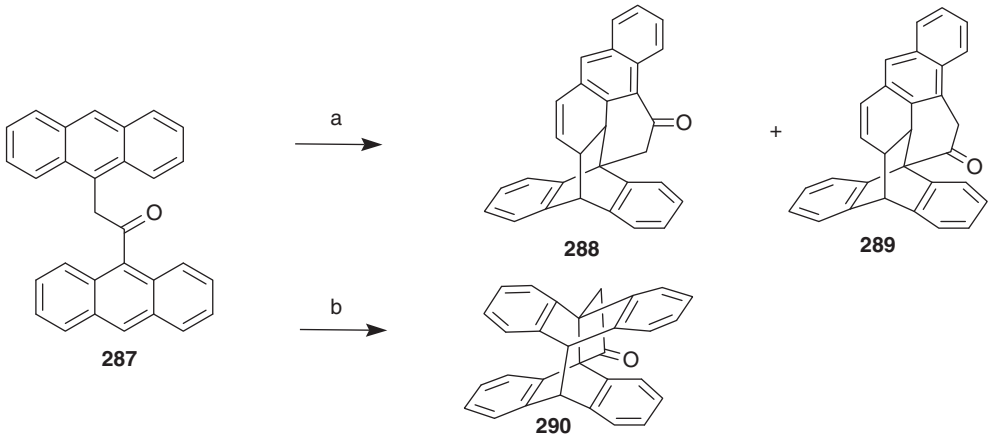
5.15.7 Applications of *Para* Photocycloaddtions

Para photocycloadditions give access to bicyclo[2.2.2]octadiene systems by a formal Diels–Alder type reaction and are rarely observed. Therefore little is known about this mode of transformation. It is known that higher aromatics are more likely to undergo *para* cycloadditions,[88] and that it is the main reaction course when allenes are involved.[11d] If the irradiation is carried out in the presence of conjugated dienes or a second arene, this photocycloaddition can also be performed in a [4 + 4] mode to afford bicyclo[4.2.2]decatrienes and more complex homocycles.[88,89] A high-yielding example of a *para* photocycloaddition with an allene has been published by Haddaway et al. (Scheme 51).[90]

Nonsensitized irradiation of dianthryls **287** usually triggers the [4 + 4] photocycloaddition[88] pathway leading to **290**, but on sensitizing to the triplet excited-state, the [4 + 2] mode prevails and products **288** and **289** are obtained (Scheme 52). Such [4 + 4] photocycloadditions have also been observed intermolecularly with very high yields.[91]

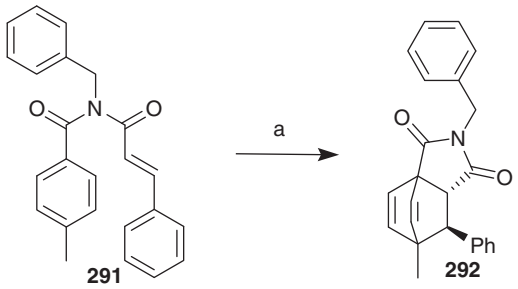


Scheme 51 Reagents and conditions: (a) hυ, MeCN **284:285:286**=38:6:2%.



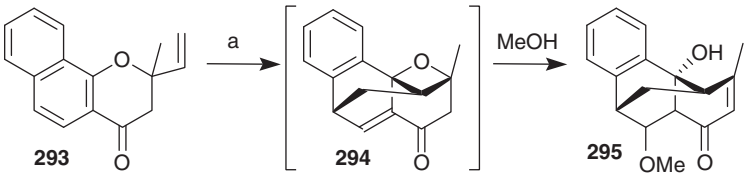
Scheme 52 Reagents and conditions: (a) hυ, **288**:**289**=75:22, diacetyl, 97%; (b) hυ, 98%.

Only a few high-yielding examples leading to *para* products are reported in literature. However, one case is the intramolecular photocycloaddition of a cinnamoylamide and a benzamide in **291** moiety (Scheme 53).[92] This reaction is very efficient and leads to high yields of the bicyclo[2.2.2]octadiene derivative **292**.



Scheme 53 Reagents and conditions: (a) hυ, benzil, PhH, 93%.

The cinnamoylamide **291** is sensitized by benzil to its triplet excited state. The proposed mechanism involves the reaction of the olefin with the *ipso* position of the aromatic ring, affording a *spiro* biradical intermediate. Recombination of these radicals proceeds until formation of the final compound is accomplished. Kohmoto showed that similar enamides linked to a naphthyl moiety underwent preferably *ortho* photocycloaddition if the naphthyl moiety is sensitized.[93] Irradiation of a naphthyl precursor **293** with only two atoms in the tether to the olefin furnished the *para* photocycloadduct **295** formed via **294** (Scheme 54).[94]



Scheme 54 Reagents and conditions: (a) hυ, MeOH, 20%.

5.15.8 Conclusion

In summary, this chapter has highlighted the mechanistic features and synthetic applications of the alkene–arene photocycloaddition. This research field has received an ever-increasing attention over the past five decades culminating in a variety of elegant and efficient syntheses. The efficiency and elegance stems from a drastic increase in molecular complexity in a single chemical operation, building polycyclic carbon scaffolds with up to six stereocenters. For the *meta* photoreaction already sophisticated mechanistic models exist and are further refined, which is important concerning the control of the absolute stereochemistry in this process. In this respect a lot of research needs to be done, as there is no tool to control the absolute stereochemistry in this reaction with resonable enantiomeric excess to date. Although *meta* photocycloadditions have been exploited over the past 40 years, the *ortho* and *para* reactions still require more detailed investigations. Given the way in which such cycloadducts can be further manipulated, their synthetic potential is vast. Therefore, it is very clear that these transformations will continue to be a central topic in the future of organic synthesis.

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5.16 Cyclobutene Ring Opening Reactions

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Glossary

Annulation A transformation in which a new ring is attached to a parent molecule through the formation of two new bonds.

Cycloaddition A reaction in which two or more unsaturated molecules are combined to form a cyclic adduct with a net reduction of the bond multiplicity. The unsaturated entities can be parts of the same molecule.

Cyclobutene A four-membered carbocycle containing one double bond.

Electrocyclic reaction A molecular rearrangement transforming fully conjugated linear π-electron systems into cyclic structures. A σ-bond is formed between the termini with a decrease by one in the number of π-bonds (electrocyclization). Or the reverse process of the reaction mentioned above (cycloreversion, elecrocyclic ring opening reaction).

Torquoselectivity The selectivity on the rotational direction of substituents in electrocyclic ring opening reactions. The substituents undergo either 'inward' or 'outward' rotation.

5.16.1 Introduction

Numerous examples of ring opening reactions of cyclobutenes and benzocyclobutenes have appeared since 1985. The major focus of those studies has been on the investigation of the torquoselectivity, the sequential utilization of the resulting 1,3-dienes in electrocyclization reactions, and applications to natural product syntheses. This review features the typical examples.

5.16.2 Cyclobutene Ring Opening

The Woodward–Hoffmann rules allow the conrotatory ring opening of cyclobutenes.[1] The energy gap between the allowed conrotatory transition state and the forbidden one depends on the planarity of the transition structure, as supported by both experiments and calculation.[2] In case *cis*-3,4-dimethylcyclobutene is fused to another cyclic structure, planarity increases with the conrotatory transition structure and the energy gap is reduced, as evidenced by the experimentally observed $\Delta\Delta G^{\ddagger}$ values (Figure 1).

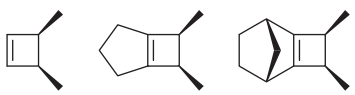
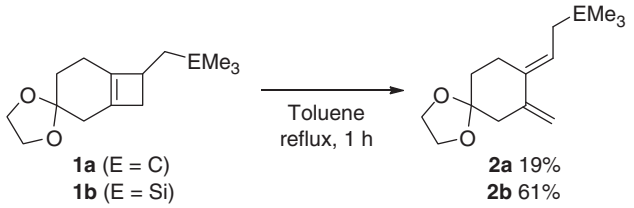


Figure 1 Differences in free energies of activation ($\Delta\Delta G^{\ddagger}$).

The accelerating effects of a neopentyl group and a trimethylsilylmethyl group were compared. On heating in refluxing toluene for 1 h, neopentylcyclobutene **1a** gave the diene product **2a** only in 19% yield, whereas (trimethylsilylmethyl)cyclobutene **1b**

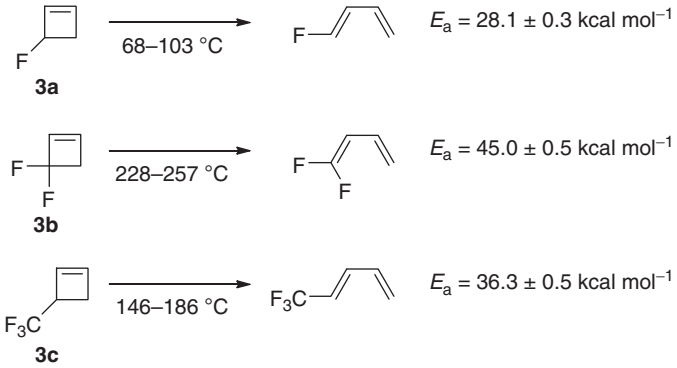
 doi:10.1016/B978-0-08-097742-3.00517-6

afforded diene **2b** in 61% yield (Scheme 1).[3] The rate acceleration was attributed to the σ-donating ability of the C–Si bond, which is associated with the β-effect of silicon.



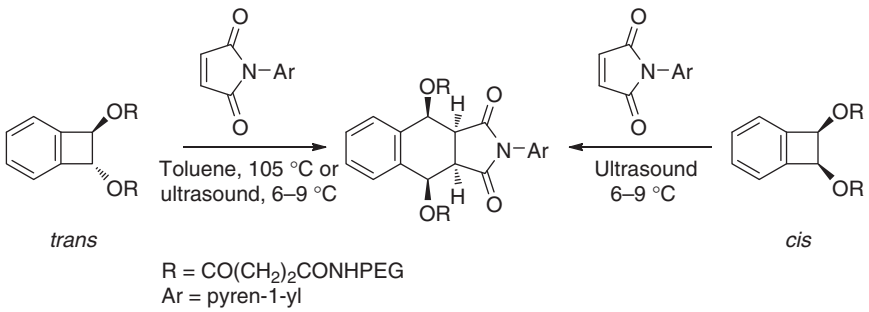
Scheme 1 Thermal ring opening of neopentyl- and trimethylsilylcyclobutenes.

The thermal ring opening of fluorinated cyclobutenes in the gas phase was also studied.[4] The reaction of 3-fluorocyclobutene **3a** occurred at lower temperature than that of cyclobutene itself, and the thermodynamically less stable *E*-diene was selectively formed (Scheme 2). In contrast, 3,3-difluorocyclobutene (**3b**) and 3-(trifluoromethyl)cyclobutene (**3c**) were more reluctant to undergo ring opening than cyclobutene. The activation energy for the ring opening of **3b** was greater than that of the monofluoro analog **3a** by 16.9 kcal mol^{-1}. The rearrangement of **3c** led to a mixture of dienes with the thermodynamically more stable *E*-diene predominating. Cyclobutene **3c** exhibited an activation energy similar to that of cyclobutene.



Scheme 2 Thermal ring opening of fluorinated cyclobutenes **3**.

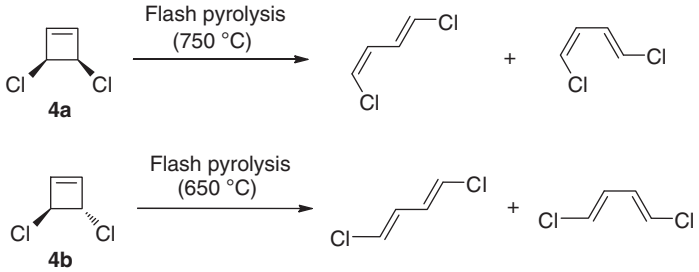
Unusual rotational behaviors were observed in an ultrasound-induced electrocyclic ring opening reaction of 1,2-disubstituted benzocyclobutenes (Scheme 3).[5] The *trans*-isomer yielded a product resulting from conrotatory ring opening, whereas the *cis*-isomer yielded a product resulting from disrotatory ring opening. As a result, the same product stereochemistry arose from the two diastereomers because of the mechanical forces associated with ultrasound. The violation of the Woodward–Hoffman rule was theoretically studied.[6]



Scheme 3 Ultrasound-induced ring opening of benzocyclobutene in MeCN solution.

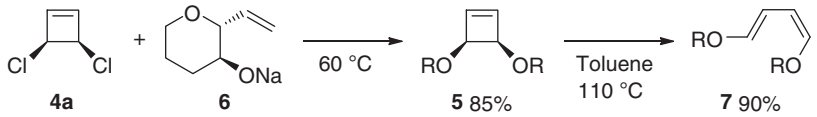
The products of flash pyrolysis of *cis*- and *trans*-3,4-dichlorocyclobutenes were trapped in a matrix (Xe, 12 Kelvin (K)). The *E,Z*-diene produced from *cis*-3,4-dichlorocyclobutene (**4a**) was found to exist in both the s-*cis* and the s-*trans* comformation

(Scheme 4). Likewise, the *E,E*-diene produced from *trans*-3,4-dichlorocyclobutene (**4b**) was also found in both the s-*cis* and s-*trans* conformations.[7] A lower activation energy was observed for the ring opening of **4b**.



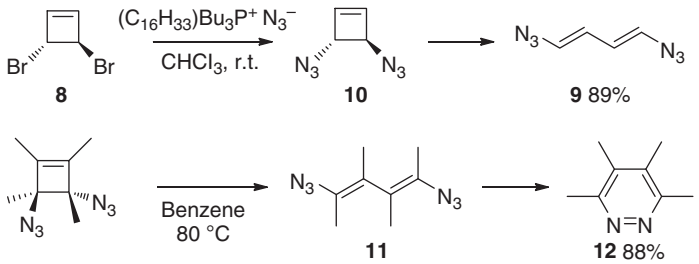
Scheme 4 Flash pyrolysis of *cis*- and *trans*-3,4-dichlorocyclobutenes.

Dialkoxycyclobutene **5** was prepared by a reaction of *cis*-3,4-dichlorocyclobutene (**4a**) with 2 equivalents of *tert*-alkoxide **6** (Scheme 5). When **5** was heated in refluxing toluene, the *E,Z*-diene **7** was the only product formed by conrotatory ring opening.[8]



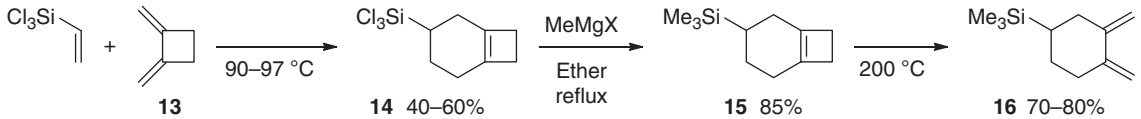
Scheme 5 Synthesis and ring opening of dialkoxycycobutene **5**.

The first synthesis of 1,4-diazidobuta-1,3-dienes was performed via ring opening of cyclobutenes.[9] When *trans*-3,4-dibromocyclobutene (**8**) was treated with tributylhexadecylphosphonium azide in $CHCl_3$ at 20 °C, (*E,E*)-3,4-diazidobuta-1,3-diene (**9**) was obtained as the major product through facile ring opening of *trans*-diazidocyclobutene (**10**) (Scheme 6). However, the corresponding *cis*-diazidocyclobutene was reluctant to undergo ring opening. A tetramethyl-substituted derivative **11** could be formed at 80 °C, which was transformed into pyridazine **12** on prolonged heating.



Scheme 6 Ring opening of 3,4-diazidocyclobutenes.

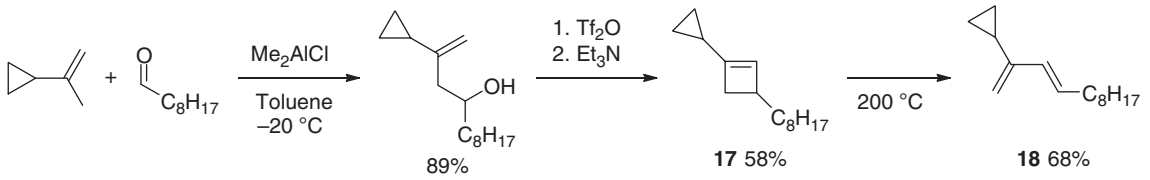
The Diels–Alder reaction of 1,2-dimethylenecyclobutane **13** with vinyltrichlorosilane afforded cyclobutene **14** (Scheme 7). After reaction of **14** with methyl Grignard reagent, the resulting cyclobutene **15** underwent thermal ring opening at 200 °C to give l,2-dimethylenecyclohexane **16**.[10]



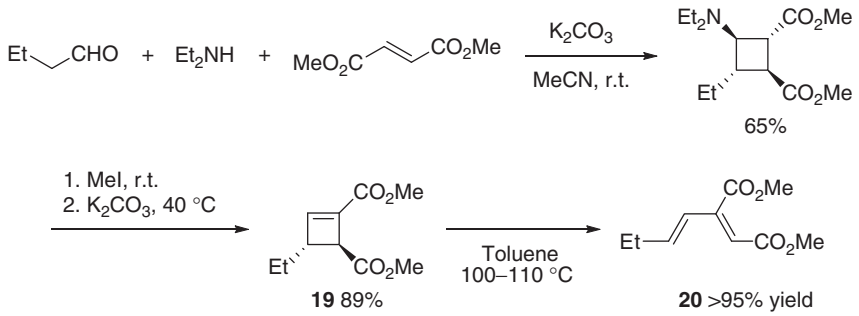
Scheme 7 Ring opening of cyclobutene **15** giving 1,2-dimethylenecyclohexane **16**.

1-Cyclopropylcyclobutene **17** underwent ring opening rather than vinylcyclopropane–cyclopentene rearrangement to give 1,3-diene **18** when heated at 200 °C (Scheme 8).[11]

A thermal ring opening reaction of **19** occurred at 100–110 °C to give 1,3-diene **20** as a single isomer (Scheme 9).[12]

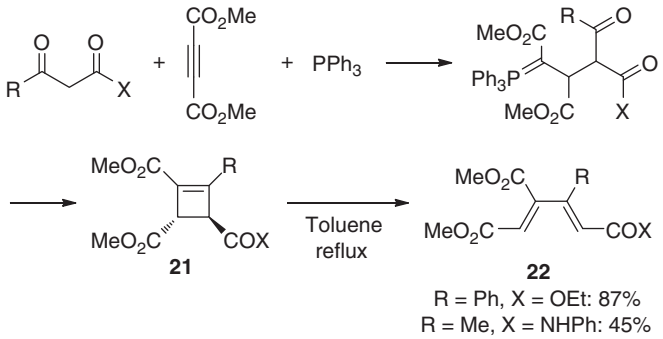


Scheme 8 Synthesis and ring opening of 1-cyclopropylcyclobutene **17**.



Scheme 9 Synthesis and ring opening of cyclobutene **19**.

Cyclobutenes were prepared by a stereoselective intramolecular Wittig reaction of a vinyltriphenylphosphonium salt with 1,3-dicarbonyl compounds. The cyclobutenes **21** underwent electrocyclic ring opening in refluxing toluene to produce the electron-deficient 1,3-dienes **22** (Scheme 10).[13]



Scheme 10 Synthesis and ring opening of cyclobutenes **21**.

Chiral cyclobutanone **23** was prepared by photochemical [2 + 2] cycloaddition between chromium alkoxycarbene complexes **24** and chiral ene-carbamate **25** (Scheme 11). Enolization followed by silylation produced the silyl enol ethers **26** which underwent facile conrotatory ring opening to give dienes **27** on standing at room temperature (r.t.).[14] When the enolate was trapped with acetic anhydride or methyl chloroformate, the corresponding dienes were directly formed.

[2 + 2] Cycloaddition of tetracyanoethene (TCNE) with donor-substituted alkynes followed by electrocyclic ring opening produced 1,1,4,4-tetracyanobutadienes (Table 1).

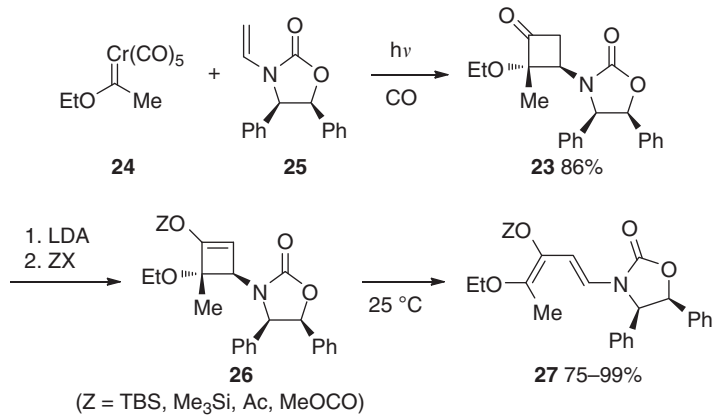
The analogous cycloaddition–cycloreversion occurred regioselectively with tetracyanoquinodimethane (TCNQ), affording a new family of nonplanar charge-transfer chromophores (Scheme 12).[18]

Methanolysis of the *N*-acetyl cyclobutene-lactam **28a** in the presence of LiOH at r.t. resulted in ring opening to give *E,Z*-diene **29a** (Scheme 13).[19] When the *N*-Boc, *N*-benzyl, and nonprotected cyclobutene-lactams **28b–d** were subjected to the methanolysis, *E,E*-dienes **29b–d** were obtained via isomerization under the basic conditions.

A platinum-catalyzed [2 + 2] cycloaddition reaction of a 1,7-enyne at 60 °C afforded cyclobutene **30**, which was converted into 1,3-diene **31** on heating at 120 °C (Scheme 14).[20]

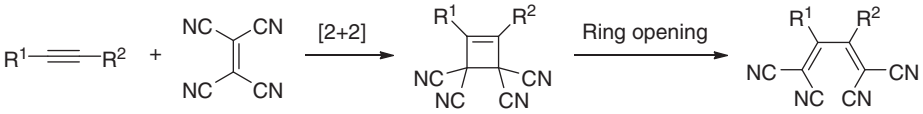
Although the bicyclo[5.2.0]nona-1(9),2-diene **32**, obtained by gold(I)-catalyzed [2 + 2] cycloaddition of a 1,6-dien-8-ynes, was stable in CD_2Cl_2, it slowly underwent ring opening in $CDCl_3$ due to a trace amount of HCl present in this solvent (Scheme 15).[21]

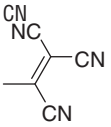
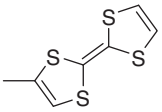
The silyl ether **33**, which was synthesized from cyclobutenedione monoethylenedithioketal, underwent ring opening with outward rotation of the siloxy group at 50 °C to give diene **34** (Scheme 16).[22] The subsequent Diels–Alder reaction of **34** with

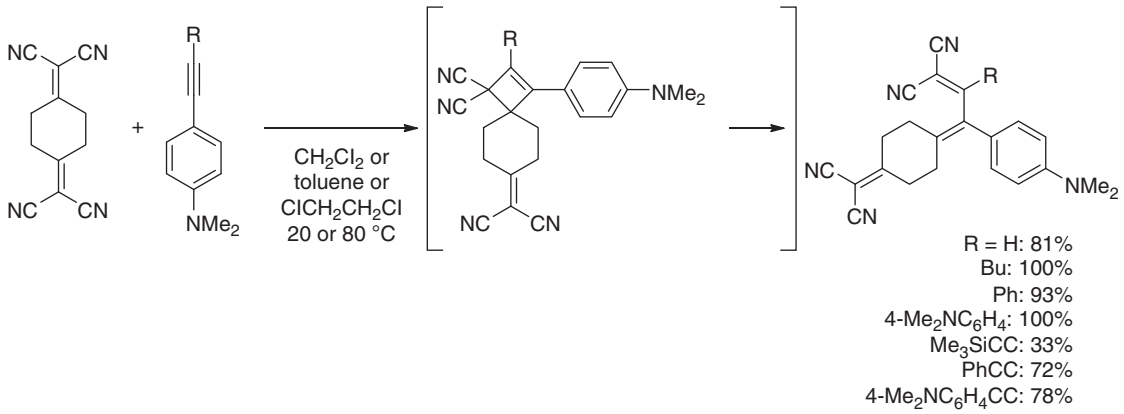


Scheme 11 Synthesis and ring opening of cyclobutenes **26**.

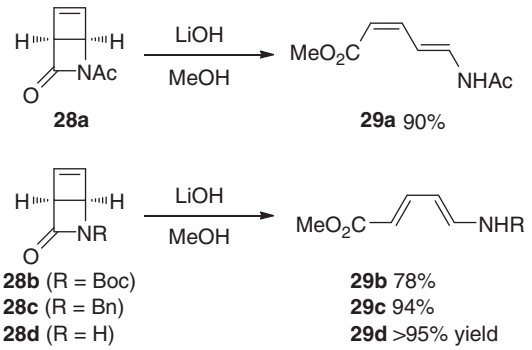
Table 1 Synthesis of 1,1,4,4-tetracyanobutadienes via [2 + 2] cycloaddition–ring opening sequence



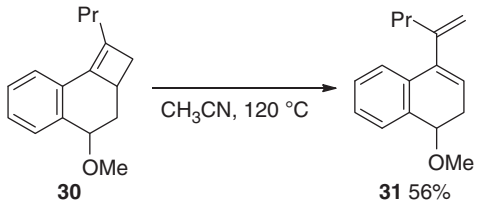
R^1	R^2		*Yield (%)*	*References*
4-$(Me_2N)C_6H_4$	H	Benzene, 20 °C	97	15
4-$(Me_2N)C_6H_4$	4-$(Me_2N)C_6H_4$	THF, 20 °C	100	16
4-$(Me_2N)C_6H_4$	4-$(Me_2N)C_6H_4C{\equiv}C$	Benzene, 20 °C	96	16
2-thienyl	Ph	150 °C	80	16
4-$(Me_2N)C_6H_4$	CN	THF, 20 °C	97	16
4-$(Me_2N)C_6H_4$		TCE, 120 °C	66	17
4-$(Me_2N)C_6H_4$		Benzene, 25 °C	79	17



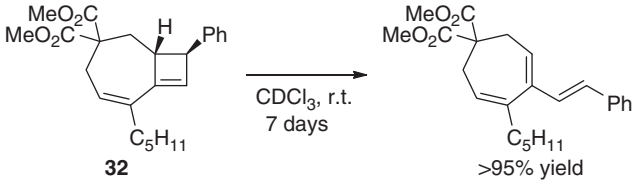
Scheme 12 Reaction of arylalkynes with TCNQ.



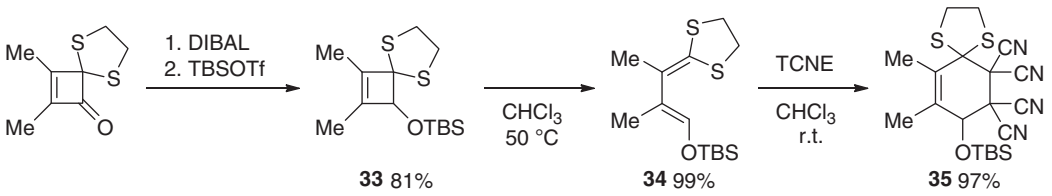
Scheme 13 Ring opening of cyclobutene-lactams **28**.



Scheme 14 Ring opening of cyclobutene **30** derived from platinum-catalyzed [2 + 2] cycloaddition of enyne.

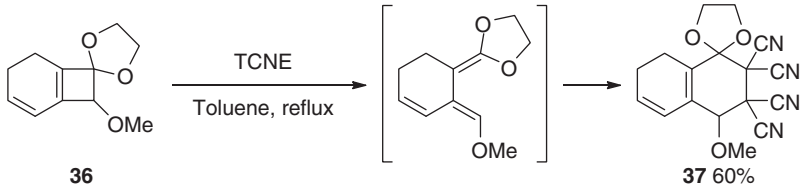


Scheme 15 Ring opening of bicyclo[5.2.0]nona-1(9),2-diene **32**.



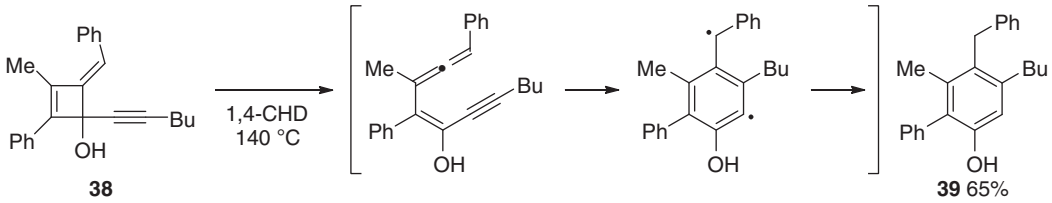
Scheme 16 Ring opening of cyclobutene **33**.

TCNE afforded adduct **35** in high yield. Likewise, thermal ring opening of cyclobutene **36** in the presence of TCNE gave the corresponding Diels–Alder adduct **37** (Scheme 17).[23] A twofold Diels–Alder cycloaddition of a biscyclobutene tethered to C_{60} was carried out in toluene under high dilution conditions to give *rac*- and *meso*-diastereomers of the bis-adduct in a 1:1 ratio.[24]

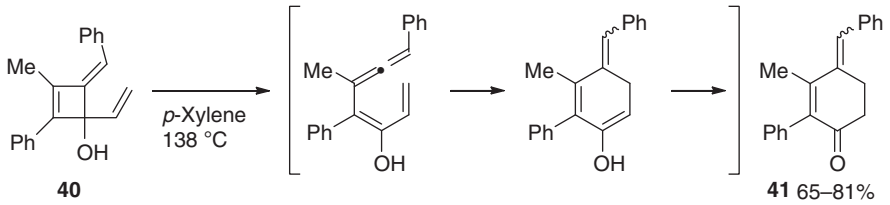


Scheme 17 Ring opening of cyclobutene **36**.

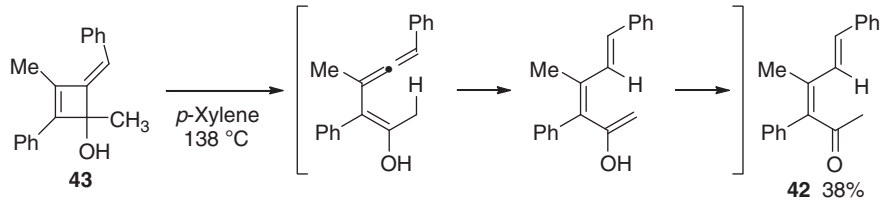
The ring opening of cyclobutenes bearing unsaturated groups provides an opportunity for the synthesis of ring-expanded carbocycles by subsequent electrocyclic reactions. On thermal reaction of 4-alkynyl-4-hydroxy-3-benzylidenecyclobutene **38** at 140 °C, phenol **39** was formed through electrocyclic ring opening, cycloaromatization, and H-abstraction (Scheme 18).[25] Reaction of 4-alkenyl-4-hydroxy-3-benzylidenecyclobutene **40** in refluxing *p*-xylene gave an *E*/*Z* mixture of 4-benzylidenecyclohexenones **41** (Scheme 19). Dienone **42** was obtained when 4-methyl-4-hydroxy-3-benzylidenecyclobutene **43** was heated in refluxing *p*-xylene (Scheme 20). A thermal reaction of 4-allenyl-4-hydroxy-3-benzylidenecyclobutene **44** afforded an *o*-quinodimethane intermediate, which immediately rearranged to the benzocyclobutene **45** (Scheme 21).[26]



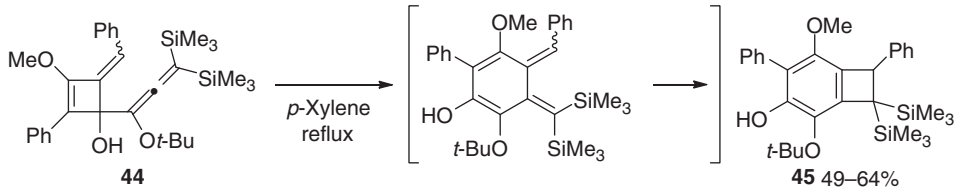
Scheme 18 Ring opening–cyclization of alkynyl(benzylidene)cyclobutenol **38**.



Scheme 19 Ring opening–cyclization of alkenyl(benzylidene)cyclobutenol **40**.



Scheme 20 Ring opening–cyclization of alkyl(benzylidene)cyclobutenol **43**.

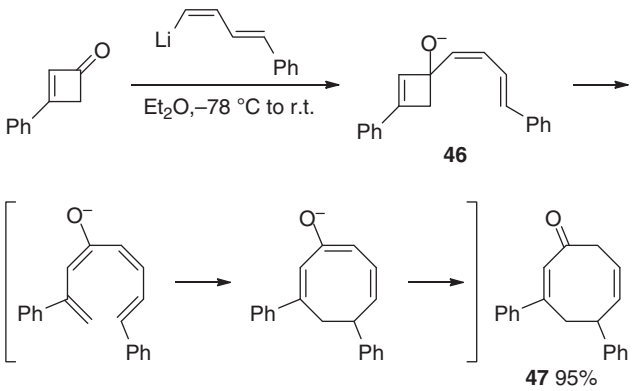


Scheme 21 Ring opening–cyclization of allenyl(benzylidene)cyclobutenol **44**.

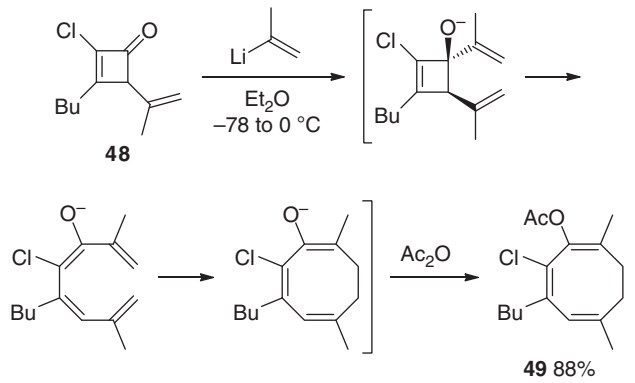
When 3-phenylcyclobutenone was reacted with dienyllithium at −78 °C and the resultant reaction mixture was gradually warmed to r.t., the ring opening of cyclobutene **46** initially formed proceeded and was followed by an 8π electrocyclization to afford the eight-membered ring ketone **47** as a sole product in high yield (Scheme 22).[27]

Addition of alkenyllithiums to 4-alkenylcyclobut-2-enones **48** also led to the production of eight-membered ring products **49** via such a ring opening–8π electrocyclization sequence (Scheme 23).[28]

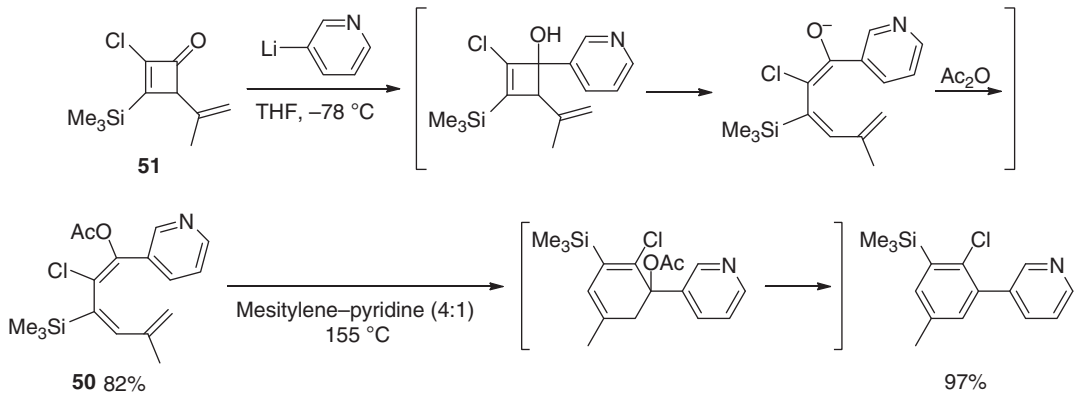
However, it required a higher temperature for the aryl-substituted triene **50**, generated by addition of aryllithium to alkenylcyclobutenone **51**, to undergo 6π electrocyclization (Scheme 24).[29]



Scheme 22 Ring opening–8π electrocyclization of dienylcyclobutenol **46**.



Scheme 23 Synthesis of cyclooctatriene **49** via ring opening–8π electrocyclization.

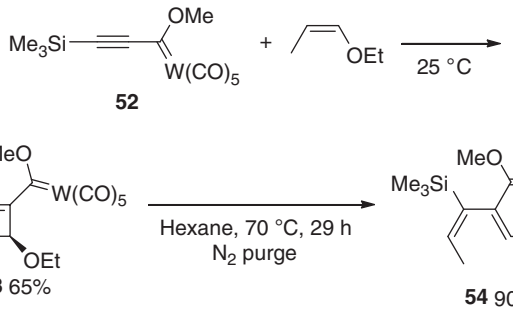


Scheme 24 Ring opening-6π electrocyclization.

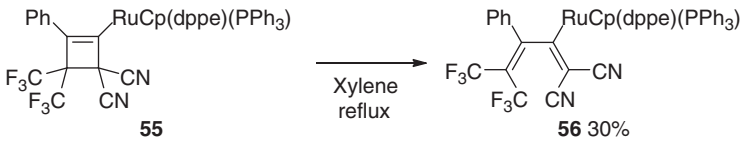
[2 + 2] Cycloaddition of the alkynylcarbene tungsten complex **52** with (*Z*)-ethyl prop-1-enyl ether afforded the cyclobutenylcarbene complex **53**, which underwent stereoselective electrocyclic ring opening at 70 °C to give the butadienylcarbene complex **54** (Scheme 25).[30] Carbon monoxide was expelled during the reaction to form the chelate complex **54**.

The cyclobuten-1-yl ruthenium complex **55** underwent thermal ring opening to give the buta-1,3-dien-2-yl ruthenium complex **56** (Scheme 26). In the electrocyclic reaction of **57**, the two CO_2Me substituents both rotated inward (Scheme 27).[31]

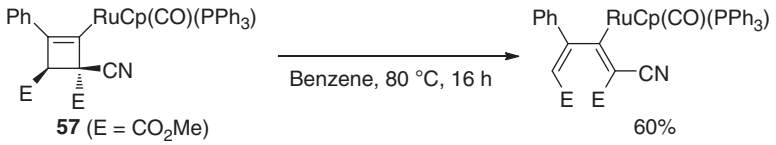
No ring opening of the four-membered ring occurred with the η^5-bicyclo[3.2.0]hepta-l,3-dienylcobalt(I) complex **58** bearing a COD ligand. In contrast, complex **59** having a tetraphenylcyclobutadiene ligand underwent ring opening at 200 °C and further reacted with dimethyl fumarate to afford the [4 + 2] cycloadduct **60** (Scheme 28).[32]



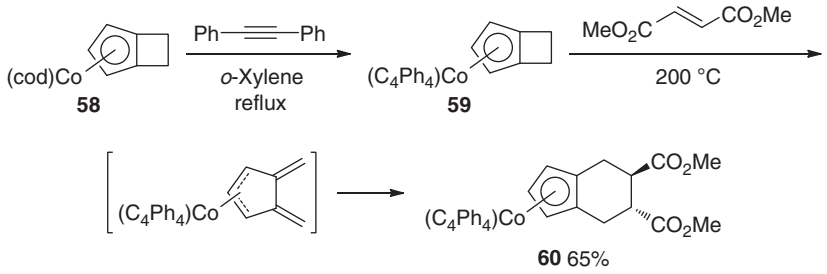
Scheme 25 Ring opening of cyclobutenylcarbene tungsten complex **53**.



Scheme 26 Ring opening of cyclobuten-1-ylruthenium complex **55**.

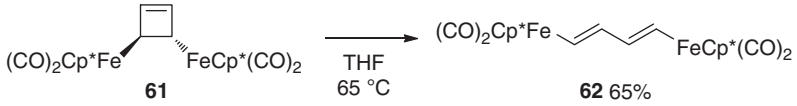


Scheme 27 Ring opening of **57**.



Scheme 28 Ring opening of bicycloheptadienylcobalt(I) complex **59**.

The reaction of $Cp^*Fe(CO)_2K$ with *cis*-3,4-dichlorocyclobutene at –25 °C gave the diiron cyclobutene complex **61** which was converted to the butadienediyl complex **62** on heating (Scheme 29).[33]



Scheme 29 Ring opening of diiron cyclobutene complex **61**.

The ring opening reaction of *cis*-3,4-bis(trimethylsilyl)cyclobutene proceeds remarkably faster than that of *cis*-3,4-dimethylcyclobutene.[34] The significant rate acceleration was explained by assuming that (1) a stabilization of the transition state by electron delocalization from the cyclobutene HOMO to the Si–CH_3 σ^* orbital, (2) the destabilization of the ground state by intramolecular interaction between the C–Si σ orbitals and the π orbital of cyclobutene, and (3) the steric repulsion between the two bulky trimethylsilyl groups in a *cis* arrangement (Figure 2).

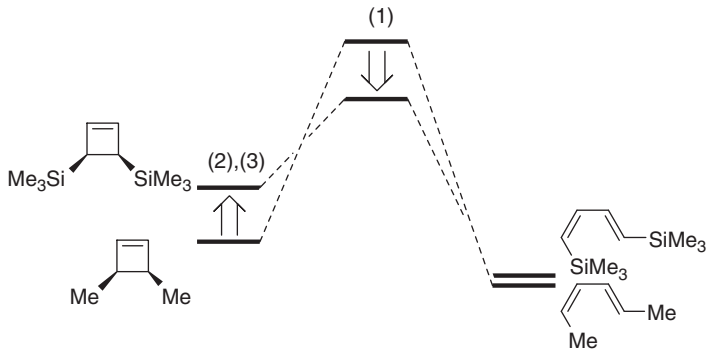
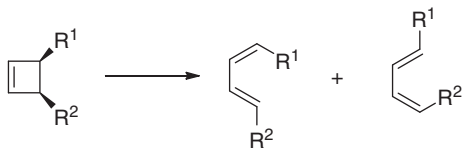


Figure 2 Three factors accelerating the ring opening reaction of *cis*-3,4-bis(trimethylsilyl)cyclobutene.

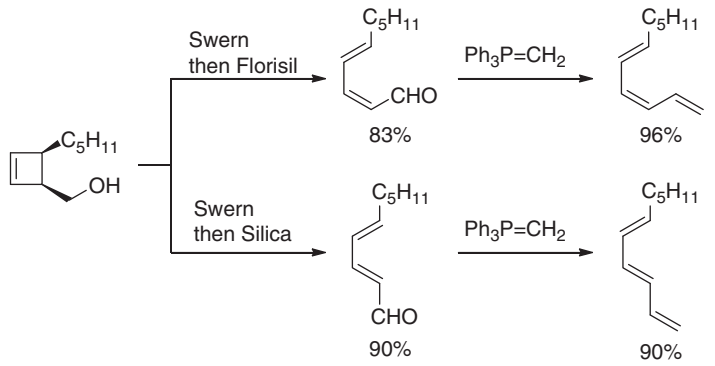
The conrotatory ring opening of unsymmetrically disubstituted cyclobutenes having different substituents at the 3- and 4-positions in a *cis* relationship can give two allowed *E,Z*-dienes (Table 2). The ratios disclose the electronic and steric preferences in rotational direction, i.e., the torquoselectivity.[35] Moderate selectivities were observed with combinations of electron-withdrawing substituents like ester/acid, ester/ester, and ester/acid chloride. The preference of various acid-derived groups toward inward conrotation follows the order: $COCl > CO_2H \approx CO_2(2\text{-Naph}) > CO_2Me$. Preferential inward rotation of a bulikier $CO_2(2\text{-Naph})$ group over a CO_2Me group is accounted for by assuming the greater π-donor capacity of OMe compared to OAr. In contrast, a formyl substituent exhibited a much stronger preference for inward conrotation.

Table 2 Ring opening of *cis*-3,4-disubstituted cyclobutenes



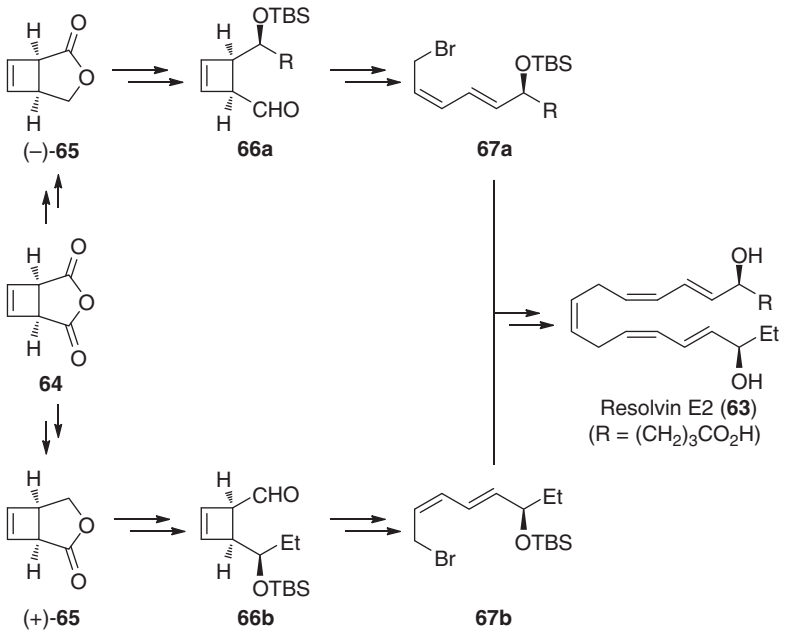
R^1	R^2	*Conditions*	*Ratio*
CO_2H	CO_2Me	Toluene, 110 °C, 1 h	2:1
CO_2H	CO_2(2-naphthyl)	$ClCH_2CH_2Cl$, 83 °C, 10 h	1:1
CO_2(2-naphthyl)	CO_2Me	Toluene, 110 °C, 2 h	1.4:1
COCl	CO_2Me	Toluene, 110 °C, 1 h	4:1
CHO	CH_2OPMB	CH_2Cl_2, <20 °C, <0.5 h	>20:1
CHO	Et	CH_2Cl_2, <20 °C, <0.5 h	>20:1

The strong preference of a formyl group for inward conrotation was exploited in the synthesis of naturally occurring isomeric trienes from a single precursor (Scheme 30).[36] Quenching the Swern oxidation at 20 °C and isolation by silica gel led to the formation of the more stable (*E,E*)-isomer.



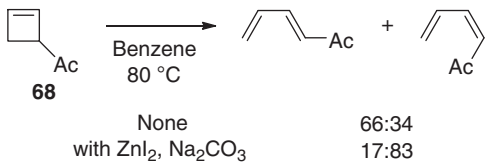
Scheme 30 Synthesis of trienes via ring opening of cyclobutene.

Inward preference of a formyl group was also successfully exploited in a total synthesis of resolvin E2 (**63**), which is derived from eicosapentaenoic acid. Desymmetrization of the anhydride **64** gave both enantiomers of lactone **65**, which were transformed to alkylated diols (Scheme 31). A subsequent Swern oxidation of the diols afforded the formylcyclobutenes **66**, which underwent facile ring opening (at −78 °C to r.t.) to furnish the *E,Z*-dienes **67a** and **67b** in 86% and 81% yields, respectively. Finally, they are coupled to afford product **63**.[37]



Scheme 31 Synthesis of resolvin E2 (**63**).

Thermal ring opening of the 3-acetylcyclobutene (**68**) resulted in a mixture of *E*- and *Z*-dienes, with the *E*-diene predominating (Scheme 32). This preference was reversed by addition of Lewis acidic ZnI_2.[38] The reversal of the torquoselectivity was theoretically studied.



Scheme 32 Study on the torquoselectivity of the ring opening of 3-acetylcyclobutene (**68**).

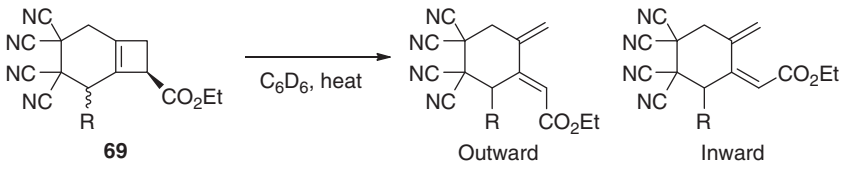
The torquoselectivity was also studied in thermal ring opening reactions of bicyclo[4.2.0]oct-1(6)-ene-7-carboxylates **69** (Table 3). Outward rotation of the CO_2Et group was sterically disfavored by the C5 substituent R. Product ratios obtained from the *trans*-isomers were comparable to those derived from the *cis*-isomers.[39]

A phenyl group exhibits a torquoselectivity-preference for outward rotation. Accordingly, cyclobutene **70a** opened at 80 °C to give *E*-diene **71a** in 24 h (Scheme 33). On the other hand, ring opening of the triester-substituted phenylcyclobutene **70b** completed in 5 min at r.t. to give *Z*-diene **71b** exclusively. However, a computational study supported a high selectivity for outward rotation. This disagreement was explained by assuming that the resulting (*E*)-dienyl ester cyclized to a pyran; its subsequent reopening led to the thermodynamically more stable isomer.[40]

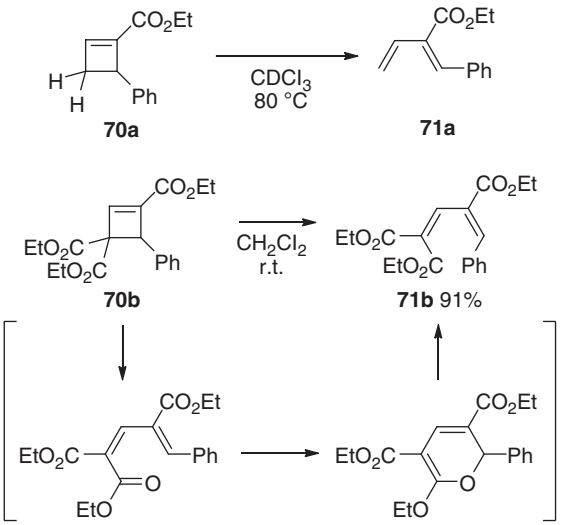
When heated at 140 °C, the *t*-butylcyclobutene **72** underwent ring opening with outward rotation of the *t*-butyl substituent to give exclusively the *trans*-isomer (Scheme 34). However, 3-(trimethylsilyl)cyclobutene **73** furnished a mixture of *cis*- and *trans*-isomers, with the former predominating (69:31).[41] The reaction of **73** ($k = 0.53\ h^{-1}$ at 140 °C) was faster than that of **72** ($k = 0.32\ h^{-1}$ at 140 °C). The observed inward preference and accelerating effect of the silyl substituent can be explained by assuming electron-accepting interactions of the energetically low lying σ^* orbital of the silicon atom with the HOMO orbital of the inward transition state.

Cyclobutenone **74** was treated with a silylcuprate at −78 °C and the resultant 1,4-adduct was trapped with Ac_2O to afford 3-silyl-1-cyclobutene **75** (Scheme 35). When heated in refluxing benzene for 2 h, compound **75** underwent a ring opening

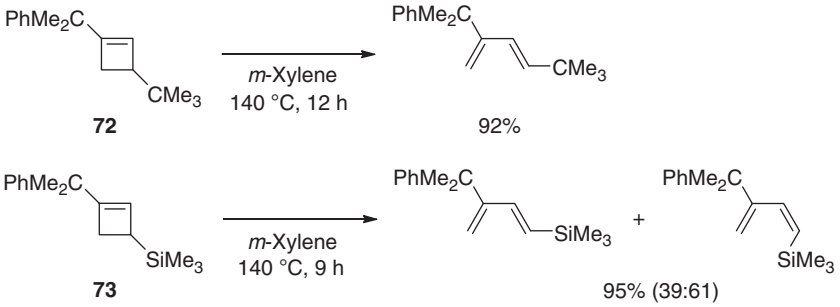
Table 3 Torquoselectivity in thermal ring opening of cyclobutenes **69**



R	*Outward:inward*
H	17:1
trans-Me	4.2:1
trans-i-Pr	1:1.5
trans-c-Hex	1:1.4
cis-Me	2.6:1
cis-i-Pr	1:1.4
cis-c-Hex	1:1.2

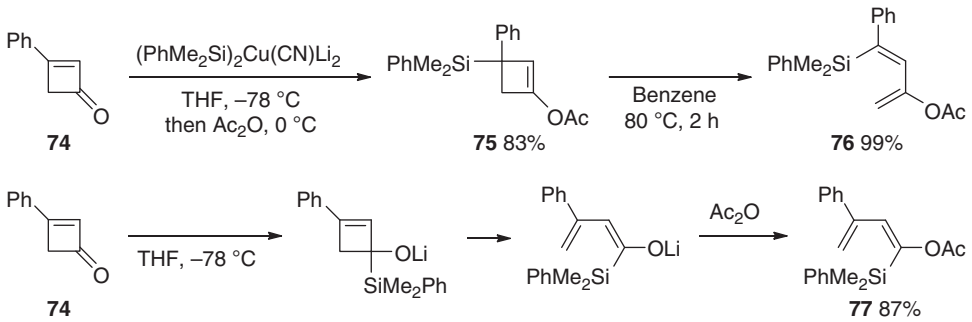


Scheme 33 Ring opening of 3-phenylcyclobutenes **70**.



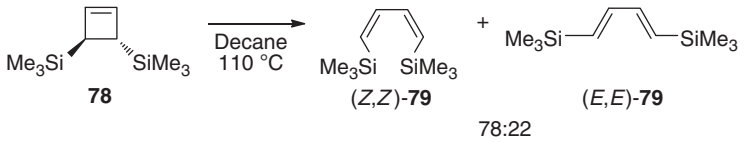
Scheme 34 Ring opening of cyclobutenes **72** and **73**.

reaction with inward rotation of the silyl group to furnish the (*Z*)-1-silyl-1,3-diene **76**. However, when **74** was treated with silyllithium at –78 °C and subsequently with Ac_2O, the expected cyclobutene derivative was not isolated. Instead, the (*Z*)-1-silyl-1,3-diene **77** was directly obtained.[42]



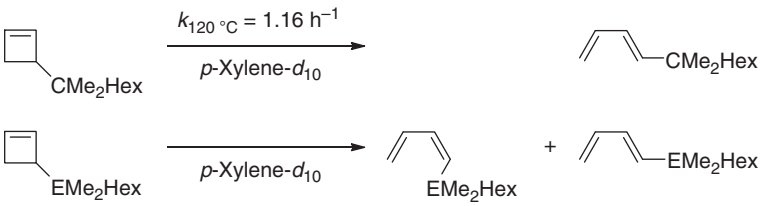
Scheme 35 Ring opening of silyl-substituted cyclobutenes.

trans-3,4-Disilylcyclobutene **78** underwent ring opening in a conrotatory fashion ($t_{1/2}$=1.7 h) to afford a mixture of dienes (Scheme 36).[43] *Z,Z*-**79** predominated over *E,E*-**79**, with a ratio of 78:22. The two trimethylsilyl substituents preferred inward rotation despite the significantly greater steric constraints occurring during this pathway.



Scheme 36 Study of the torquoselectivity of the thermal ring opening of *trans*-3,4-disilylcyclobutene **78**.

The thermal ring opening reaction of a series of cyclobutenes bearing group 14 elements at the 3-position was studied (Scheme 37).[44] Carbon-substituted cyclobutenes followed an outward pathway to afford the corresponding *E*-dienes exclusively. However, the silyl, germyl, and stannyl substituents rotated in both outward and inward directions, giving a mixture of *E*- and *Z*-isomers. The structural features of the calculated transition state and population analysis suggested that the preferential formation of the *Z*-isomer could be also ascribed to the donor/acceptor interaction between the HOMO and the σ^* orbital of the group 14 elements.

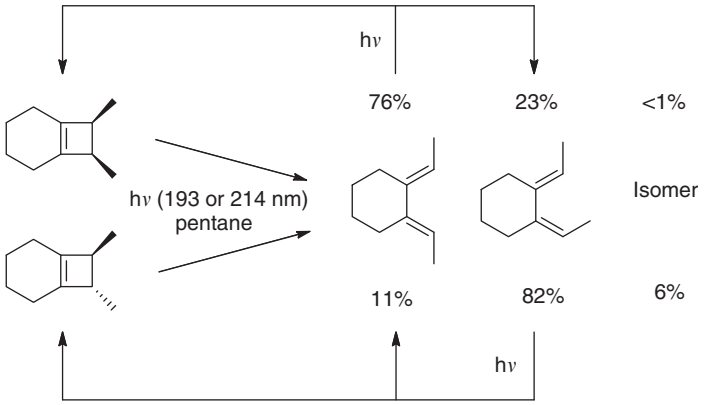


E	$k_{120\ °C}$	*Z*:*E*
Si	0.87 h^{-1}	76:24
Ge	0.21 h^{-1}	47:53
Sn	0.55 h^{-1}	71:29

Scheme 37 Ring opening of cyclobutenes bearing group 14 elements at the 3-position.

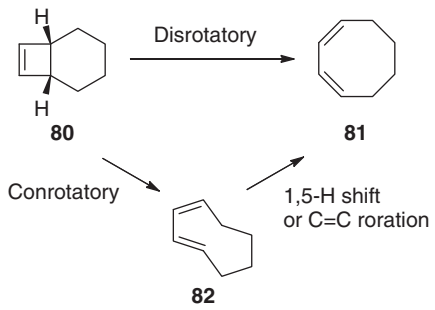
Direct photochemical reactions of *cis*- and *trans*-7,8-dimethylbicycl0[4.2.0]oct-1(6)-ene in pentane solution with 193 or 214 nm light resulted in the formation of (*E,E*)- and (*E,Z*)-1,2-diethylidenecyclohexane (Scheme 38).[45] Under these conditions, the reaction of a solution of the *E,E*-diene yielded *E,Z*-diene as well as *cis*-cyclobutene, whereas the *E,Z*-diene yielded *E,E*-diene together with the *trans*-cyclobutene. The ring closure of *E,E*- and *E,Z*-dienes occurred with >90% stereospecificity. The results stand in marked contrast to those obtained with *cis*- and *trans*-1,2,3,4-tetramethylcyclobutenes under similar conditions; these compounds afforded mixtures of isomeric 3,4-dimethyl-2,4-hexadienes with only a slight preference for the formally allowed product. The difference was attributed to the lower activation energy for the bicyclic cyclobutenes and the conformational rigidity of the dienes.

Thermal ring opening of cyclobutenes fused at the 3- and 4-positions results in ring expansion reactions that are useful for the synthesis of carbo- and heterocycles of various ring sizes. However, the mechanistic issue related to the stereochemistry of



Scheme 38 Photoinduced ring opening of *cis*- and *trans*-7,8-dimethylbicyclo[4.2.0]oct-1(6)-ene.

the resulting cyclic diene has been the subject of debate and still remains unsettled. For example, the ring opening of *cis*-bicyclo[4.2.0]oct-7-ene (**80**) to *cis*,*cis*-cycloocta-1,3-diene (**81**) was first reported in 1965.[46] Baldwin et al. examined a deuterium kinetic isotope effect using deuterated bicyclo[4.2.0]oct-7-ene.[47] The results were inconsistent with a mechanistic scenario involving *cis*,*trans*-cycloocta-1,3-diene (**82**), which led the authors to conclude that a direct disrotatory ring opening route was the preferred mechanism (Scheme 39).



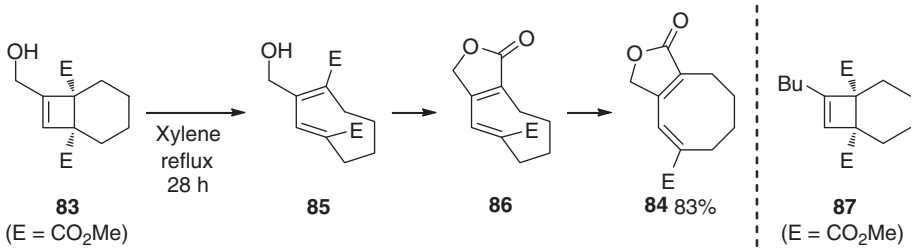
Scheme 39 Ring opening of *cis*-bicyclo[4.2.0]oct-7-ene (**80**).

However, de Lera et al. carried out a high-level computational study to ascertain the conrotatory electrocyclic ring opening followed by double-bond isomerization as the lowest-energy pathway for the net *anti*-Woodward–Hoffmann rearrangement of **80**–**81**.[48] They also examined the reaction of lower bicyclic homologs with [3.2.0], [2.2.0], and [2.1.0] skeletons. This investigation indicated a mechanistic change from a conrotatory ring opening–isomerization pathway toward a direct *anti*-Woodward–Hoffmann disrotatory pathway (Table 4).[49]

Table 4 Ring opening of *cis*-bicyclo[m.n.0]alkenes

Cyclobutene	*Pathway*
	A conrotatory ring opening followed by a higher energy direct *E*–*Z* isomerization
	
	A disrotatory electrocyclic opening is highly competitive with the conrotatory ring opening *E*–*Z* isomerization mechanism
	Thermal opening only through the disrotatory pathway to cyclopentadiene

The conrotatory ring opening of bicyclo[4.2.0]oct-7-ene could occur at temperatures as low as 110 °C. However, the resulting *cis*,*trans*-cycloocta-1,3-diene was too reactive to be isolated. It spontaneously underwent ring closure back to the cyclobutene. However, heating cyclobutene diester **83** in refluxing xylene furnished butenolide **84** in 83% yield (Scheme 40).[50] Lactonization took place with the initial conrotatory ring opening product **85** to give the *cis*,*trans*-cycloocta-1,3-diene-fused butenolide **86**.

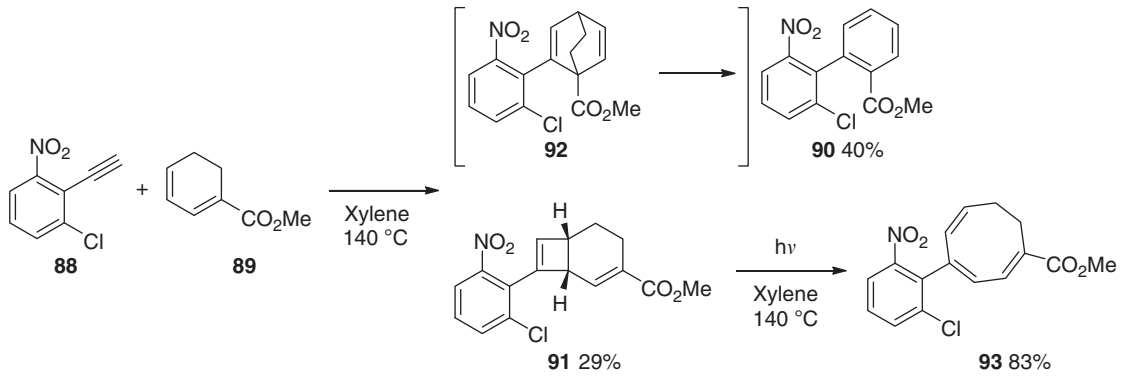


83 (E = CO_2Me) **85** **86** **84** 83% **87** (E = CO_2Me)

Scheme 40 Ring opening of cyclobutene diester **83**.

It failed to close back to the cyclobutene, but instead underwent isomerization to the more stable *cis,cis*-isomer **84** through a 1,5-hydrogen shift and the subsequent tautomerization. On the contrary, no reaction was observed with the butyl derivative **87**.

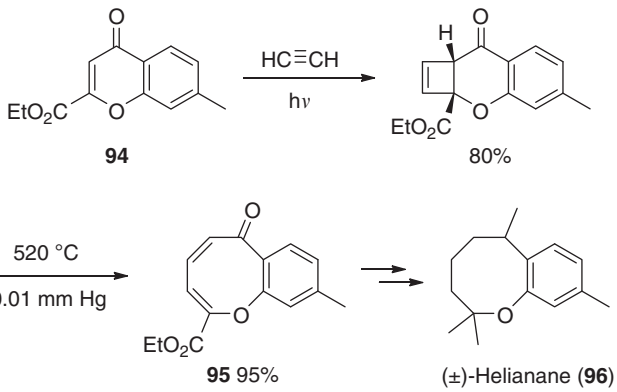
Heating of a mixture of 1-chloro-2-ethynyl-3-nitrobenzene (**88**) and 1-carbomethoxy-cyclohexadiene (**89**) at 140 °C in xylene resulted in the formation of two products **90** and **91** in a 1.3:1 ratio (Scheme 41).[51] The major biaryl **90** arose from a [4 + 2] cycloaddition forming the [2.2.2] bicycle **92** followed by [4 + 2] cycloreversion extruding ethylene, whereas the minor cyclobutene **91** was formed by [2 + 2] cycloaddition. Treatment of the isolated cyclobutene **91** at 160 °C resulted in the formation of two products: the biaryl **90** and the cyclooctatriene **93**. However, exposure of cyclobutene **91** to the light emmitted by a 120 W halogen bulb at 140 °C led to the formation of the cyclooctatriaene **93** as the sole product in good yield.



88 **89** **92** **90** 40% **91** 29% **93** 83%

Scheme 41 Reaction of **88** and **89**.

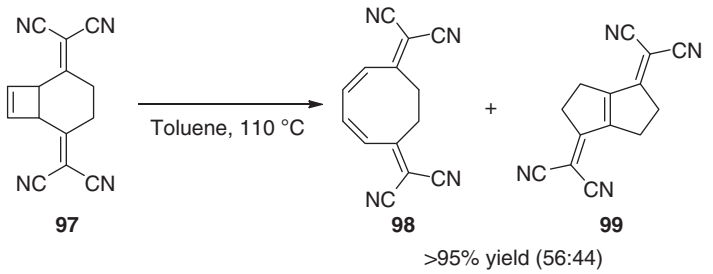
A photochemical reaction of acetylene with 4-chromenone **94** followed by flash vacuum thermolysis (520 °C, 0.01 mm Hg) caused a two-carbon ring expansion of the pyranone ring, giving benzo[*b*]oxocin-6-one **95** in excellent yield (Scheme 42).[52] The oxocinone **95** was then successfully converted to helianane (**96**), a heterocyclic sesquiterpene isolated from a marine sponge.



94 80% **95** 95% (±)-Helianane (**96**)

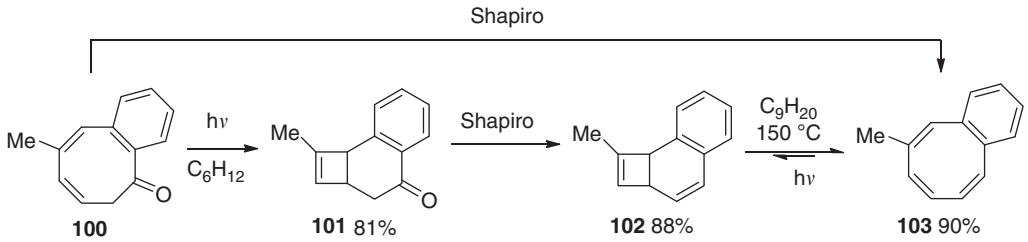
Scheme 42 Synthesis of (±)-helianane (**96**).

2,5-Bis(dicyanomethylene)bicyclo[4.2.0]octa-7-ene **97** underwent a thermal reaction at lower temperature (110 °C) to give cycloocta-1,3-diene **98**, the normal ring-opened product, and hexahydropentalene **99**, a rearranged product (Scheme 43).[53]



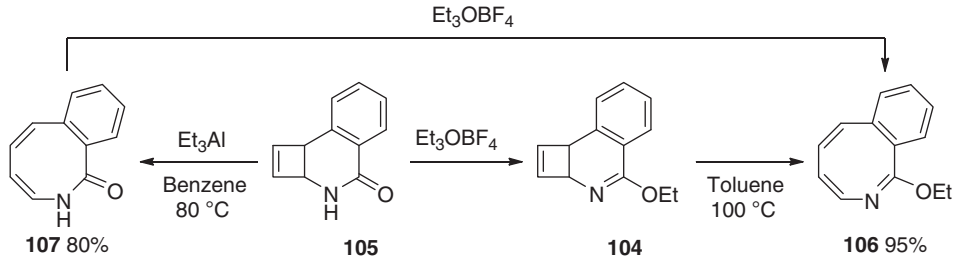
Scheme 43 Thermal reaction of **97**.

The ketone **100** cyclized on irradiation to give the bicyclo[4.2.0] system **101**, which was then transformed to **102** by the Shapiro reaction (Scheme 44). On heating at approximately 150 °C, **102** underwent ring opening to give the cyclooctatetraene derivative **103** quantitatively. Photoinduced conversion of **103** to the triene **102** was excessively slow.[54]



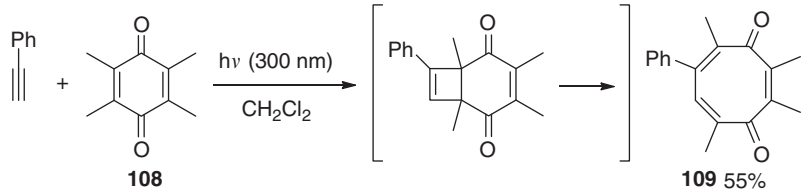
Scheme 44 Ring opening of cyclobutene **102**.

When the iminoether **104**, which was prepared from **105** and Et_3OBF_4, was heated in toluene at 100 °C, 1-ethoxybenzo[*c*]azocine **106** was obtained (Scheme 45).[55] However, heating of **105** in benzene in the presence of Et_3Al at 80 °C resulted in ring opening to give the benzoazocinone **107**. Treatment of **107** with Et_3OBF_4 gave **106**.



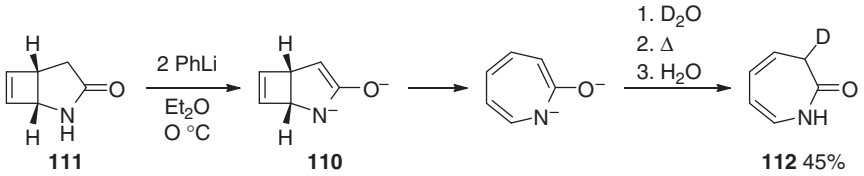
Scheme 45 Ring opening of cyclobutene **104**.

Irradiation of a mixture of duroquinone (**108**) and phenylacetylene (excess) afforded **109** via a [2 + 2] cycloaddition followed by ring opening of the cyclobutene moiety thus formed (Scheme 46).[56]



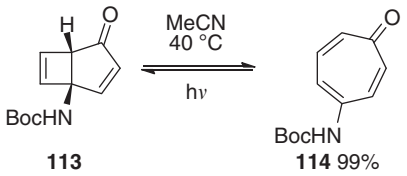
Scheme 46 Photochemical reaction of duroquinone (**108**) and phenylacetylene.

Dianion **110**, generated by deprotonation of 2-azabicyclo[3.2.0]hept-6-en-3-one **111**, underwent ring opening to afford 1*H*-azepin-2(3*H*)-one **112** after hydrolysis (Scheme 47).[57]



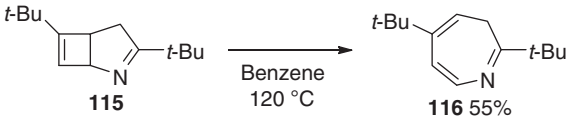
Scheme 47 Ring opening of dianion **110**.

4-Aminocyclohepta-2,4,6-trienone was formed on heating of 5-aminobicyclo[3.2.0]hepta-3,6-dien-2-one **113** at 40 °C (Scheme 48).[58] On the contrary, the cyclobutene **113** was regenerated from the trienone **114** on irradiation by a 4π-electrocyclization.



Scheme 48 Ring opening of **113**.

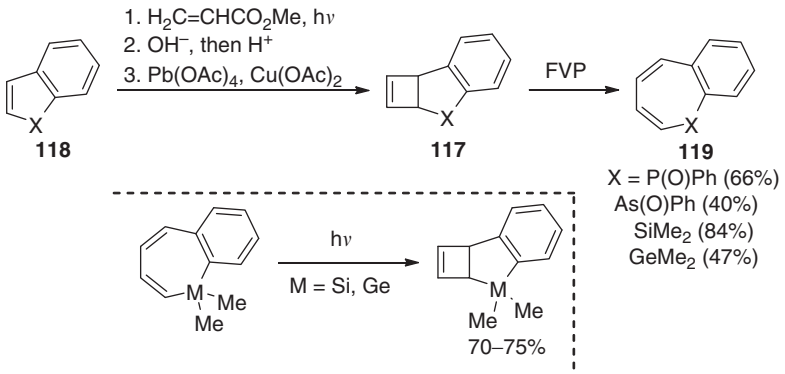
The thermal reaction of 3,6-di-*tert*-butyl-2-azabicyclo[3.2.0]hepta-2,6-diene **115** gave 2,5-di-*tert*-butyl-3*H*-azepine **116** as a single product (Scheme 49).[59] The activation energy of the ring opening was determined by a kinetic study to be 28.7 kcal mol^{-1}.



E_a = 28.7 kcal mol^{-1}

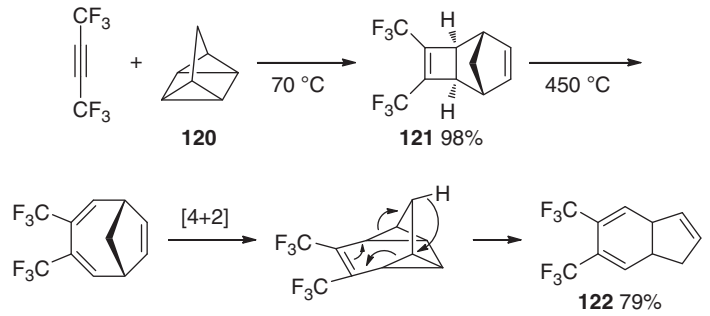
Scheme 49 Ring opening of **115**.

Benzo[*b*]cyclobuta[*d*]heteroles **117** are prepared by photoinduced [2 + 2] cycloaddition of benzoheteroles **118** with methyl acrylate and the subsequent oxidative decarboxylation with $Pb(OAc)_4$ (Scheme 50). Flash vacuum pyrolysis ($1.1–6.0 \times 10^{-5}$ mm Hg, 450–550 °C) of benzo[*b*]cyclobuta[*d*]heteroles **117** gave benzo[*b*]heteropines **119**.[60] The ring opening failed to occur when the substrates were simply heated at 180 °C. The silepine and germepine easily reverted back to the starting tricyclic compounds in good yields on irradiation in benzene.



Scheme 50 Synthesis and flash vacuum pyrolysis of benzo[*b*]cyclobuta[*d*]heteroles **117**.

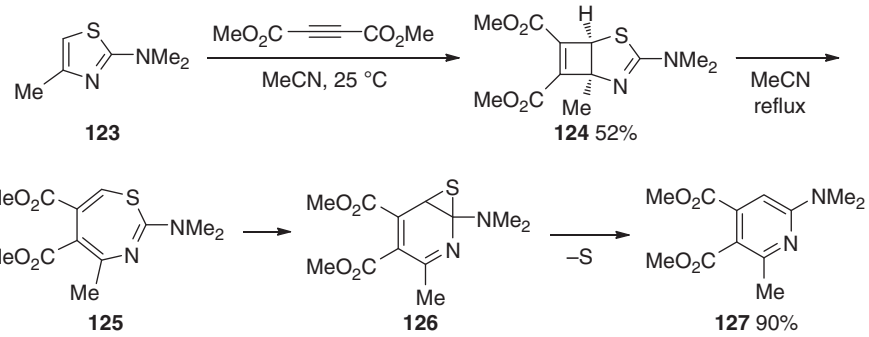
Thermal reaction of hexafluorobut-2-yne with quadricyclane (**120**) gave the 1:1 adduct **121** by a [$_\sigma$2$_s$ + $_\sigma$2$_s$ + $_\pi$2$_s$] pathway (Scheme 51). Flow pyrolysis of the cyclobutene **121** at 450 °C yielded bicyclo[4.3.0]nona-2,4,7-triene **122**.[61] Bicyclononatriene



Scheme 51 Thermal reaction of hexafluorobut-2-yne with quadricyclane (**120**).

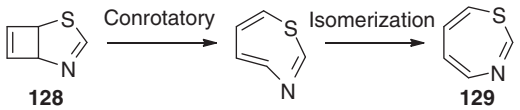
122 arose by a nonconcerted ring opening of cyclobutene **121**, an intramolecular Diels–Alder reaction, and a rearrangement involving a 1,2-hydrogen shift.

The reaction of 2-aminothiazole **123** with dimethyl acetylenedicarboxylate afforded dimethyl 6-amino-3,4-pyridinedicarboxylate **124** (Scheme 52).[62] The initial [2 + 2] cycloaddition proceeded via a two-step mechanism through zwitterionic intermediate. The formal disrotatory electrocyclic ring opening of the cyclobutene ring led to 1,3-thiazepine **125**, which rapidly gave its valence isomer, the 7-thia-2-azanorcaradiene **126** through a symmetry-allowed disrotatory 6π-electrocyclic ring closure. Finally, desulfurization gave rise to the pyridine **127**.



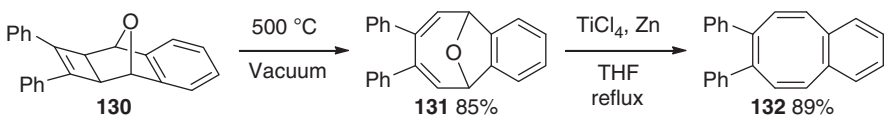
Scheme 52 Reaction of 2-aminothiazoles **123** with dimethyl acetylenedicarboxylate.

Density functional theory calculations were performed on the thermal ring opening reaction of 2-thia-4-azabicyclo[3.2.0]-hepta-3,6-dienes **128** (Scheme 53).[63] It was predicted that, regardless of the nature of the heteroatoms at positions 2 and 4 of the bicyclo[3.2.0]hepta-3,6-diene core, the electrocyclic ring opening reactions would follow the Woodward–Hoffmann-allowed conrotatory pathway leading to the corresponding *cis,cis,trans*-isomer and finally to the corresponding heterocyclic system **129** with *cis,cis,cis* geometry through double-bond isomerization.



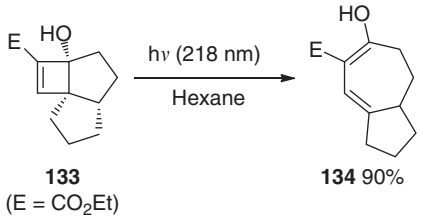
Scheme 53 Theoretical study of the ring opening of **128**.

Nickel-catalyzed [2 + 2] cycloadditions of oxabenzonorbornadienes and alkynes provided cyclobutene derivatives such as **130**, which underwent ring opening on flash vacuum pyrolysis (500 °C) to afford diene **131** (Scheme 54).[64] Deoxygenation of the diene with $TiCl_4$ and Zn in refluxing tetrahydrofuran (THF) afforded the corresponding cyclooctatetraene derivative **132**.



Scheme 54 Flash vacuum pyrolysis of cyclobutene **130**.

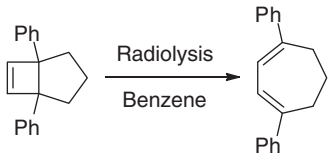
A photochemical reaction of tricyclic cyclobutene **133** bearing a hydroxy group at the ring junction furnished the corresponding hydroazulenic derivative **134** in excellent yields (Scheme 55).[65]



133 (E = CO_2Et) **134** 90%

Scheme 55 Photochemical reaction of tricyclic cyclobutene **133**.

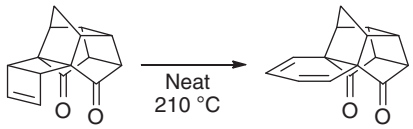
Ring opening of 1,5-diphenylbicyclo[3.2.0]hept-6-ene **135** proceeded via a triplet state by γ-radiolysis and pulse radiolysis to give 1,4-diphenylcyclohepta-1,3-diene **136** quantitatively (Scheme 56).[66]



135 **136**

Scheme 56 Radiolysis of cyclobutene **135**.

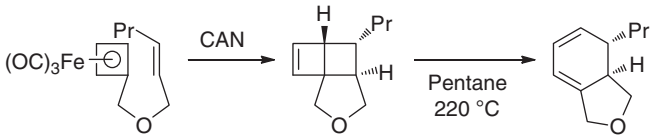
The polycyclic diene **137** was obtained in excellent yield through thermally induced cyclobutene ring opening of **138** (Scheme 57).[67]



138 **137** 96%

Scheme 57 Thermal ring opening of **138**.

Oxidation of cyclobutadiene–iron(0) complex of the type **139** with cerium ammonium nitrate under high dilution conditions afforded fused cyclobutenes such as **140** (Scheme 58).[68] The subsequent thermal ring opening of the cyclobutene moiety produced the fused cyclohexadiene **141**.



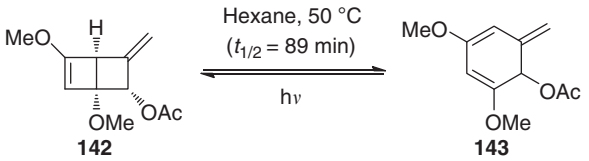
139 **140** 70% **141** 97%

Scheme 58 Formation and ring opening of fused cyclobutene **140**.

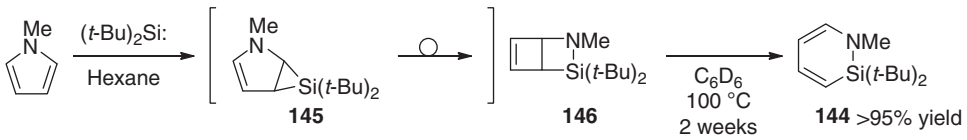
The conversion of 5-methylenebicyclo[2.2.0]hex-2-ene **142** to 5-methylenecyclohexa-1,3-diene **143** was found to be first order ($t_{1/2}$ = ~10 h at r.t., 89 min at 50 °C) (Scheme 59).[69]

Di-*tert*-butylsilylene, generated by photolysis, reacted with *N*-methylpyrrole to furnish 2-aza-3-silabicyclo[2.2.0]hex-5-ene **144** (Scheme 60).[70] An intermediate [2 + 1] cycloadduct **145** rearranged to the bicyclic cyclobutene **146**, which on heating underwent an electrocyclic ring opening reaction to give the corresponding 1-aza-2-silacyclohexa-3,5-diene **144**.

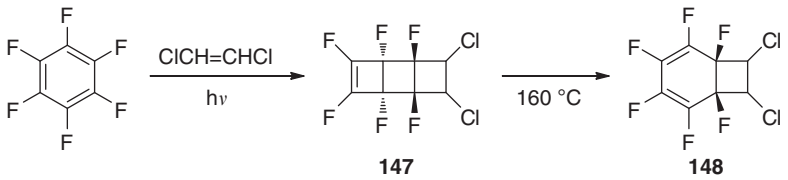
Photoinduced cycloaddition of 1,2-dichloroethylene with hexafluorobenzene yielded a stereoisomeric mixture of tricyclooctenes **147** (Scheme 61). Heating of **147** at 160 °C produced the bicyclic dienes **148**.[71]



Scheme 59 Conversion between **142** and **143**.

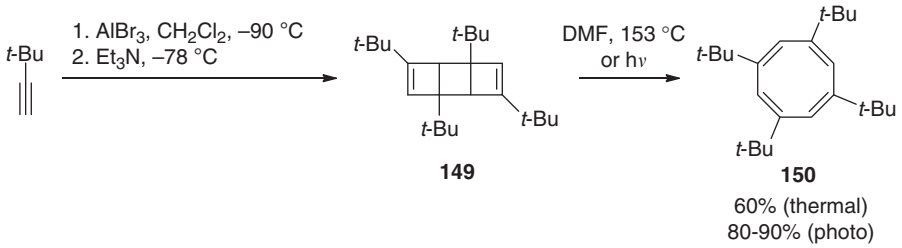


Scheme 60 Formation and ring opening of bicyclic cyclobutene **146**.



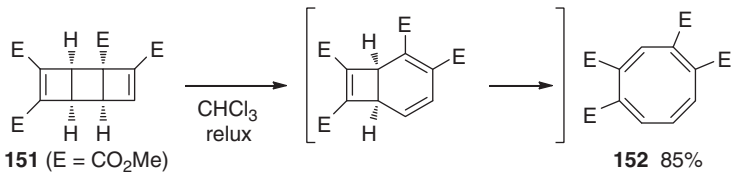
Scheme 61 Formation and ring opening of tricyclooctenes **147**.

The thermal conversion of cyclobutadiene dimer, tricyclo[4.2.0.0^{2,5}]octa-3,7-diene, to cyclooctatetraene was first reported in 1975.[72] *tert*-Butylacetylene underwent regioselective tetramerization in the presence of $AlBr_3$ and Et_3N to afford the cyclobutadiene dimer **149** (Scheme 62).[73] Thermal ring opening of this dimer occurred in refluxing DMF to produce 1,3,5,7-tetra-*tert*-butylcyclooctatetraene **150**. A photochemical reaction of **149** also gave **150** in higher (80–90%) yield.



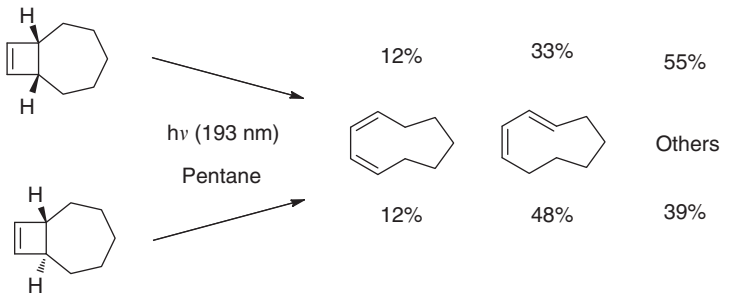
Scheme 62 Formation of cyclooctatetraene **150** via cyclobutadiene dimer **149**.

Cyclobutadiene-1,2-dicarboxylate, disengaged from its iron(0) tricarbonyl complex, dimerized through cycloaddition to furnish tricyclooctadiene **151** (Scheme 63). When tricyclooctadiene **151** was heated in refluxing $CHCl_3$, the 1,2,4,5-tetrasubstituted cyclooctatetraene **152** was formed in 85% isolated yield.[74]



Scheme 63 Thermal reaction of tricyclooctadiene **151**.

When *cis*- and *trans*-bicyclo[5.2.0]non-8-enes were irradiated with far-UV (185–214 nm) light, *cis,cis*-, and *cis,trans*-cyclonona-1,3-dienes were formed via formal electrocyclic ring opening along with other products (Scheme 64).[75] A nonconcerted pathway involving homolytic C–C bond cleavage and the subsequent relaxation of the resulting biradical intermediates was assumed.



Scheme 64 Photochemical reaction of *cis*- and *trans*-bicyclo[5.2.0]non-8-enes.

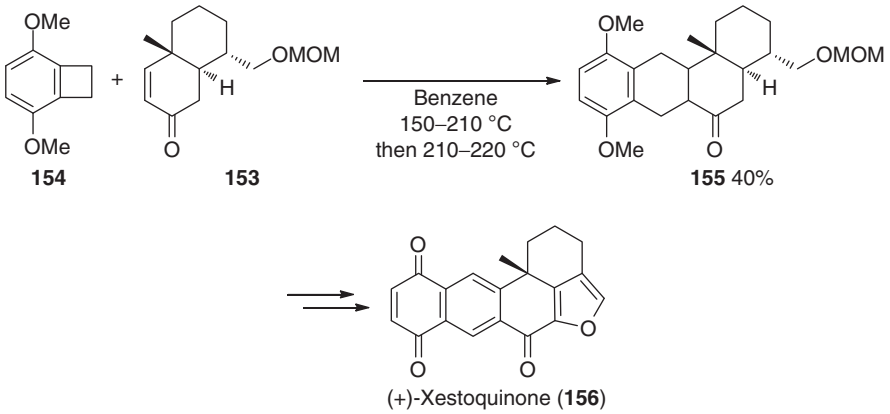
5.16.3 Benzocyclobutenes

Benzocyclobutenes serve as precursors of *o*-quinodimethanes (*o*QDMs) which are generated through an electrocyclic ring opening reaction. Two major synthetic applications of the formed *o*-quinodimethanes are [4 + 2] cycloadditions and 6π electrocyclizations. Both reactions furnish new six-membered rings. Excellent reviews on the chemistry of benzocyclobutenes have recently been published.[76]

Unlike the case of the electrocyclic reaction of monocyclic cyclobutenes, the efficiency is difficult to assess for the reaction of benzocyclobutenes, because the *o*QDM produced readily undergoes cycloreversion to regain aromaticity. The cycloreversion, however, can be avoided by rapid capture of the *o*QDM with highly reactive dienophiles such as maleic anhydride.

5.16.3.1 [4 + 2] Cycloaddition of *o*-Quinodimethanes

The Diels–Alder reaction of enone **153** with 3,6-dimethoxybenzocyclobutene (**154**) at temperatures greater than 200 °C gave the tetracyclic product **155**, which was converted via five steps to (+)-xestoquinone (**156**), a marine natural product (Scheme 65).[77]



Scheme 65 Synthesis of (+)-xestoquinone (**156**).

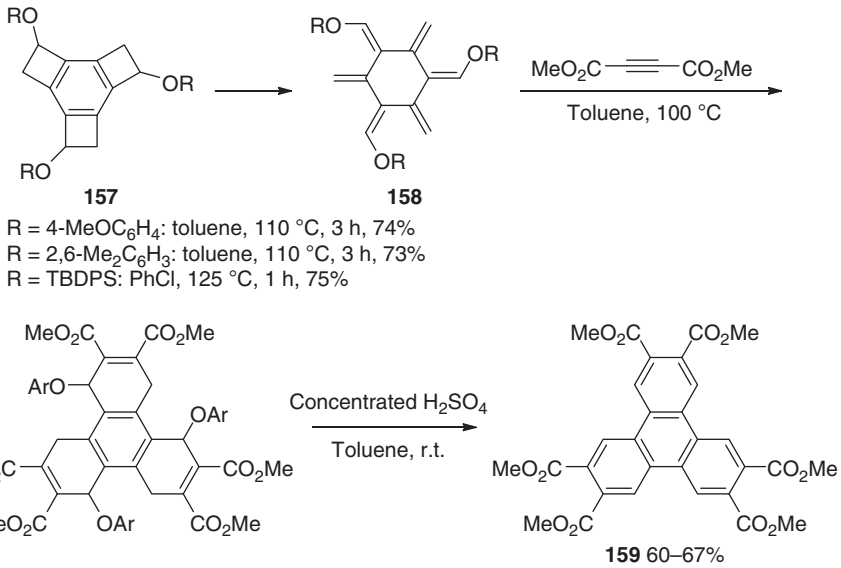
Ring opening of alkoxy-substituted tricyclobutabenzenes **157** generated hexaradialenes **158**, which underwent threefold [4 + 2] cycloaddition to produce triphenylenes **159** (Scheme 66).[78]

Benzocyclobutenol **160** underwent a [4 + 2] cycloaddition with benzoquinone in refluxing toluene to afford the tricyclic quinone **161** after dehydration (Scheme 67).[79] The product was converted into anthracene diquinone on oxidation.

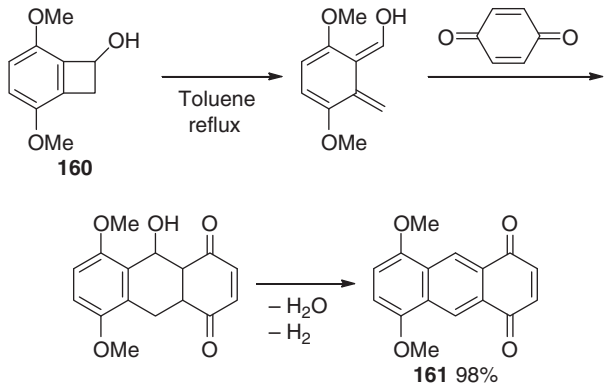
Fullerenes are reactive enough dienophiles to undergo Diels–Alder cycloaddition reactions with quinodimethanes derived from benzocyclobutenol and its methyl ether to afford the corresponding [4 + 2] cycloadducts.[80]

Cyclobutenol **162**, prepared by reduction of benzocyclobutenedione monothioketal, smoothly rearranged to aldehyde **163** at r.t. via ring opening and subsequent 1,5-hydrogen shift (Scheme 68).[81] However, the corresponding silyl ether was stable enough to be stored at r.t. The silyl ether **164** existed in equilibrium with the corresponding ring-opened product **165** (Scheme 69). Color changed when the diene (yellow at r.t.) converted to the benzocyclobutene (colorless at 0 °C). Various dienophiles were reacted with the silyl ether. Whereas the reaction with dimethyl acetylenedicarboxylate gave the expected [4 + 2] cycloadduct, the use of 1,4-naphthoquinone as the dienophile prompted a hetero Diels–Alder reaction to form isochromane **166** as the major product.

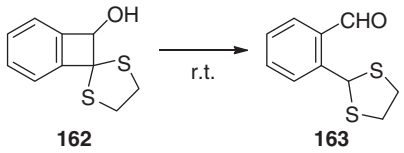
When benzocyclobutenol **167** and halonaphthalene **168** were treated with LiTMP in refluxing THP, two reactive species, a quinodimethane and a benzyne, were generated and coupled together, leading to the construction of anthracene skeleton **169** through dehydration (Scheme 70).[82]



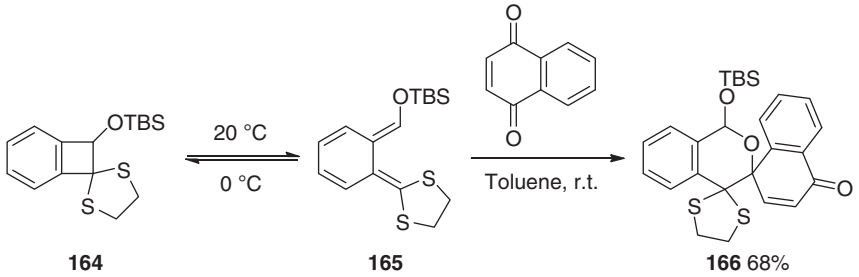
Scheme 66 Synthesis of triphenylenes **159** via hexaradialenes **158**.



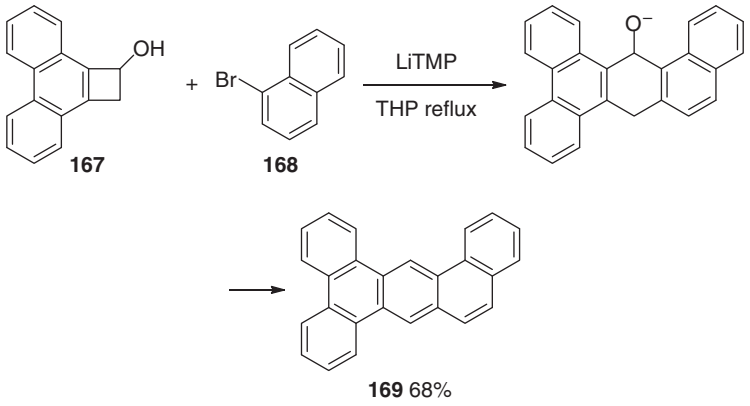
Scheme 67 Ring opening–[4 + 2] cycloaddition of benzocyclobutenol **160**.



Scheme 68 Rearrangement of neat benzocyclobutenol **162** on standing.

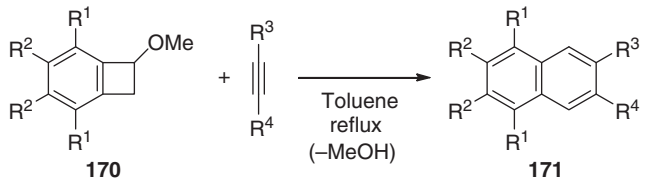


Scheme 69 Ring opening–hetero-Diels–Alder reaction of siloxybenzocyclobutene **164**.



Scheme 70 Synthesis of anthracenes.

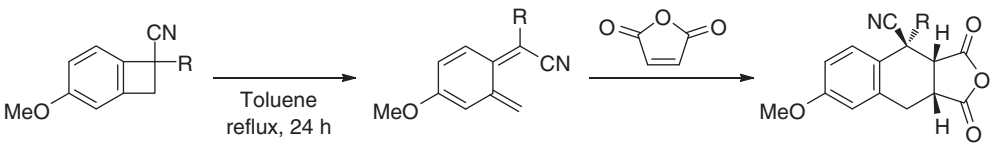
The Diels–Alder reaction of 1-methoxybenzocyclobutenes **170** and alkynes followed by elimination of methanol offered an efficient route to multisubstituted naphthalenes **171** (Scheme 71).[83]



R^1 = OMe, R^2 = H, R^3 = R^4 = CO_2Me: 95%
R^1 = H, R^2 = OMe, R^3 = R^4 = CO_2Me: 84%
R^1 = H, R^2 = OMe, R^3 = CO_2Me, R^4 = H: 93%
R^1 = H, R^2 = OMe, R^3 = CO_2Me, R^4 = Br: 82%

Scheme 71 Synthesis of multisubstituted naphthalenes via Diels–Alder reaction of 1-methoxybenzocyclobutenes **170**.

1-Cyanobenzocyclobutenes **172** thermally reacted with maleic anhydride to afford [4 + 2] cycloadducts **173** (Scheme 72).[3] The cyano group exhibited an inward torquoselectivity; an *endo* addition of maleic anhydride followed. A notable accelerating effect was observed with a silylmethyl substituent. The σ-donating ability of the C–Si bond facilitated the electrocyclic ring opening. This is closely related to the accelerating effect of an anionic oxy substituent, which is also a good electron donor.

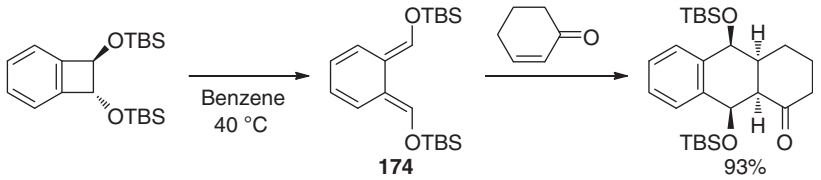


R = H: 9%
R = CH_2t-Bu: 30%
R = CH_2SiMe_3: 68%

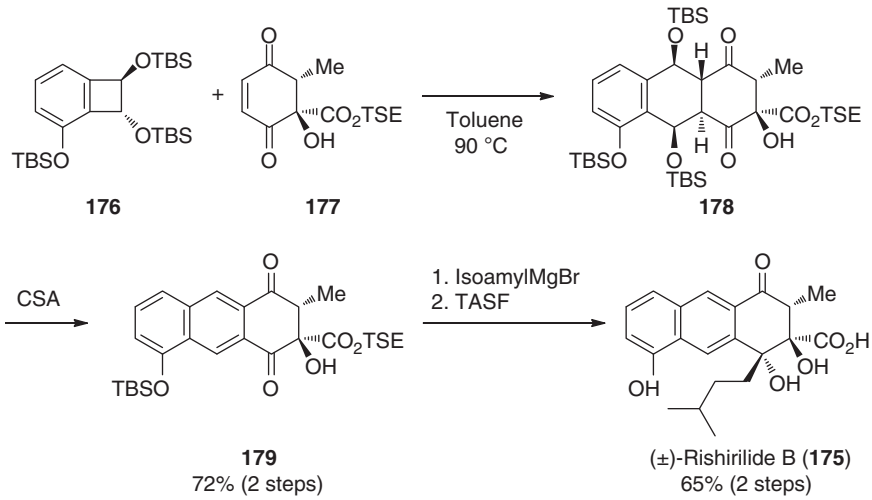
Scheme 72 Thermal reaction of 1-cyanobenzocyclobutenes **172**.

The ring opening of *trans*-1,2-disilyloxybenzocyclobutenes was studied by Danishefsky.[84] The two *trans*-attached siloxy groups underwent outward rotation in a conrotatory manner to generate the *E*,*E*-diene **174**, which subsequently reacted with cyclohexenone in an *endo* fashion (Scheme 73).

The total synthesis of (±)-rishirilide B (**175**) utilized the [4 + 2] cycloaddition of the *o*-quinodimethane (*o*QDM) as the key step (Scheme 74).[85] Cycloaddition of *trans*-disiloxycyclobutene **176** with the unsymmetrical enedione **177** occurred in a regio- and *endo*-selective manner to afford the desired tricyclic product **178** in 90% yield. Dehydration and aromatization were induced by the action of camphorsulfonic acid to give **179**. Monoalkylation of **179** with isoamylmagnesium bromide followed by desilylation with tris(dimethylamino)sulfonium afforded **175**.

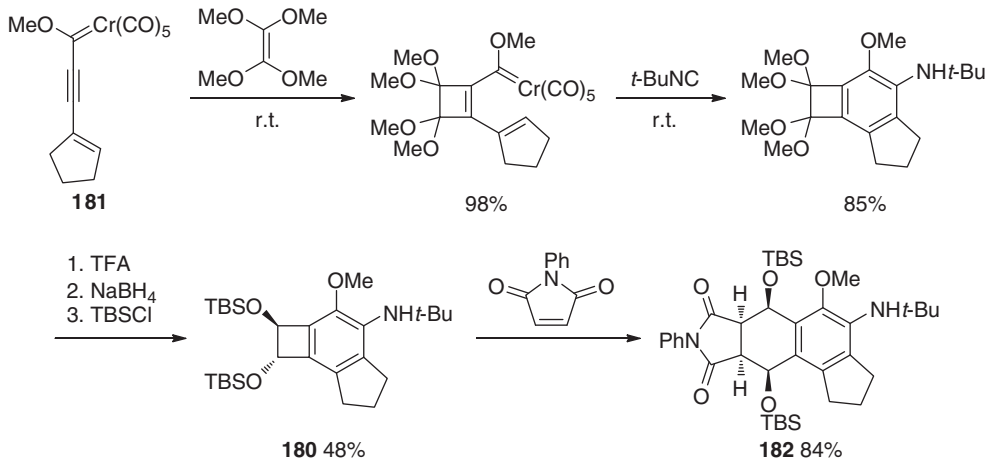


Scheme 73 Ring opening of *trans*-1,2-disilyloxybenzocyclobutenes.



Scheme 74 Synthesis of (±)-rishirilide B (**175**).

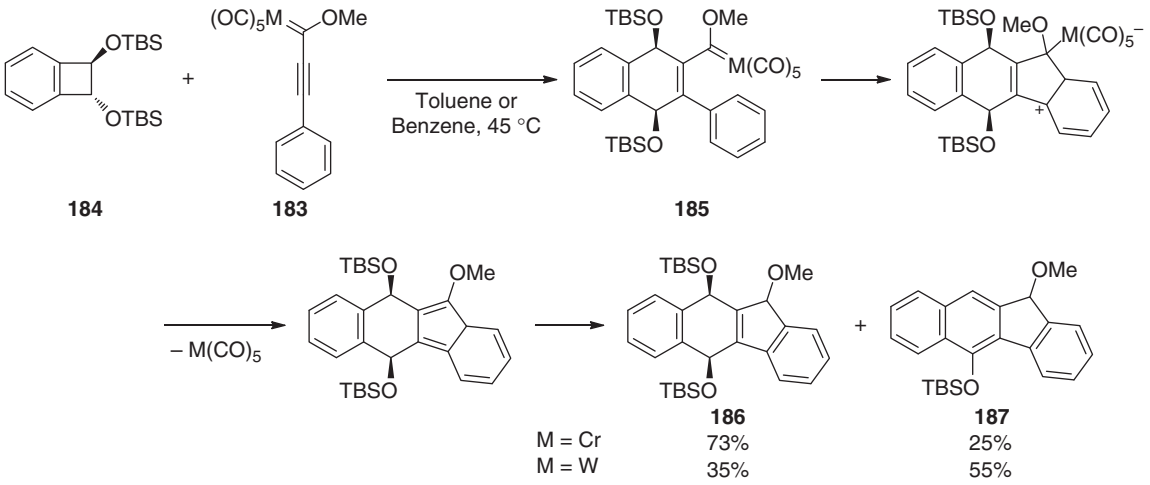
The densely functionalized *trans*-disiloxycyclobutene **180**, synthesized from [(2-alkenylcyclobutyl)carbene]chromium complexe **181** and an isocyanide, reacted with dienophiles to give *endo*-cycloadduct **182** (Scheme 75).[86] However, the corresponding *cis*-disiloxycyclobutenes required an elevated temperature (160 °C) to react with the dienophiles.



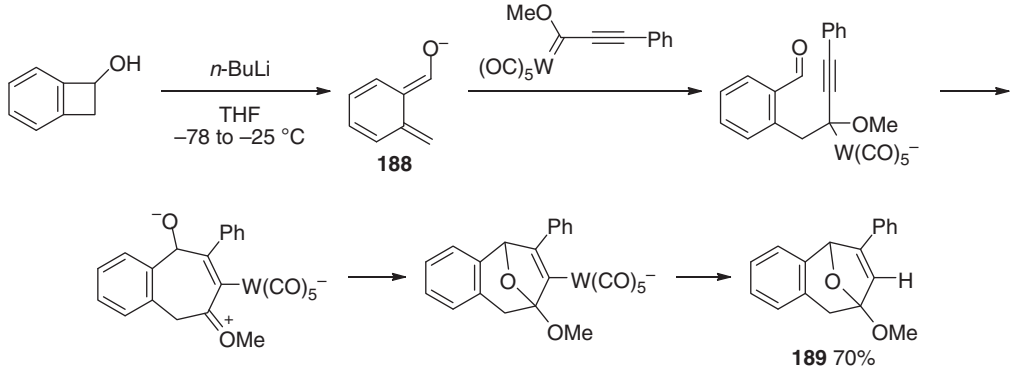
Scheme 75 Synthesis and reaction of *trans*-disiloxycyclobutene **180**.

When arylethynylcarbene metal complexes of chromium and tungsten **183** were reacted with *trans*-disiloxycyclobutene **184**, the initially formed [4 + 2] cycloadducts **185** underwent further annulation to afford benzo[*b*]fluorine derivatives **186** and **187** (Scheme 76).[87]

A reaction of the *o*QDM **188**, generated at −25 °C from lithium benzocyclobutenoxide, with an alkynylcarbene tungsten complex gave the formal [4 + 3] cycloadduct **189** exclusively (Scheme 77).[88] The *o*QDM behaved as a vinylogous enolate rather than as a 1,3-diene.

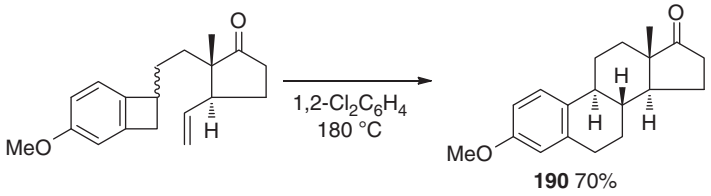


Scheme 76 Reaction of *trans*-disiloxycyclobutene **184** with arylethynylcarbene metal complexes **183**.



Scheme 77 Reaction of *o*QDM **188** and alkynylcarbene tungsten complex.

The synthesis of tetracyclic compounds such as steroids by using the *o*QDM cycloaddition has been extensively studied.[89] The intramolecular Diels–Alder reaction was efficiently utilized in the synthesis of estrone methyl ether **190** (Scheme 78).[90]



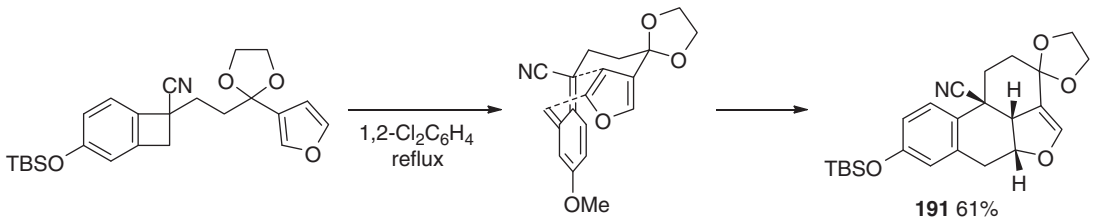
Scheme 78 Synthesis of estrone methyl ether **190**.

A series of furan-fused tetracyclic compounds such as **191** was synthesized via intramolecular [4 + 2] cycloaddition of *o*QDM for the evaluation of their antiviral activity (Scheme 79).[91] The reaction was exclusively *endo*-selective.

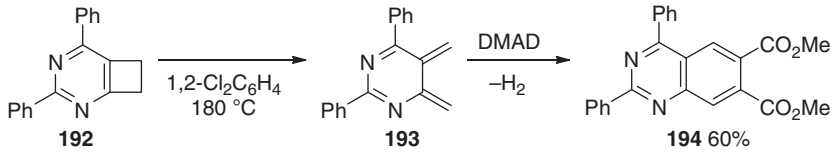
The [4 + 2] cycloaddition via *o*QDM analogs was used also for the construction of heteroaromatic rings. Pyrimidine analogs of benzocyclobutene **192** underwent ring opening in refluxing 1,2-dichlorobenzene to generate diene **193**, which reacted with dienophile to afford quinazoline derivative **194** (Scheme 80).[92]

(2-Formylphenyl)methanide, generated *in situ* by treatment of benzocyclobutenol **195** with LiTMP, reacted with nitriles to form isoquinolines (Scheme 81).[93] The reaction was applied to the total synthesis of hypecumine (**196**).

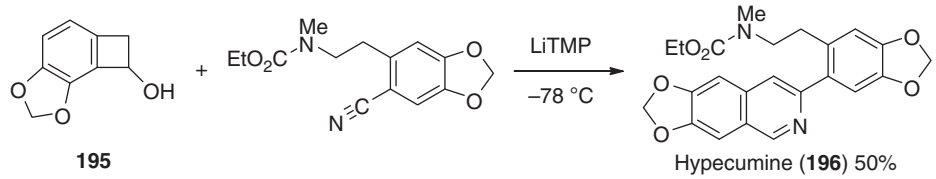
Simple thermal hetero Diels–Alder reactions with dienophiles like aldehydes and imines proceeded to give isochromans and tetrahydroisoquinolines (Scheme 82)[94]; a complete *endo* selectivity was observed. An electron-donating group on the aromatic



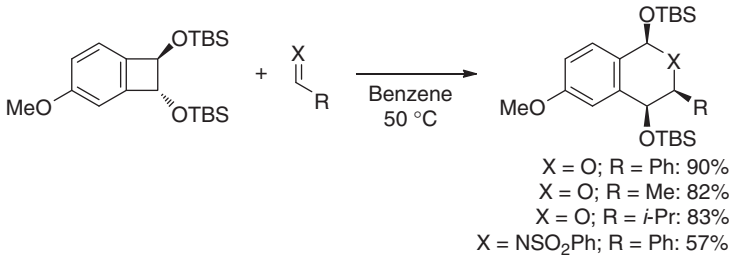
Scheme 79 Intramolecular [4 + 2] cycloaddition of *o*QDM.



Scheme 80 [4 + 2] Cycloaddition affording quinazoline derivative **194**.



Scheme 81 Synthesis of hypecumine (**196**).



Scheme 82 Hetero Diels–Alder reaction giving isochromans and tetrahydroisoquinolines.

ring accelerated the reaction. Furthermore, the reaction of the unsymmetrically substituted disilyloxybenzocyclobutenes exhibited complete regioselectivity.

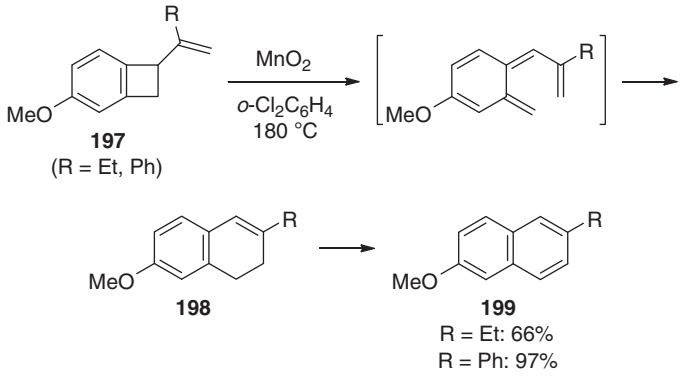
5.16.3.2 6π Electrocyclization

Electrocyclic reactions of *o*QDM are also useful for the synthesis of six-membered carbo- and heterocycles. Ring opening of benzocyclobutene is followed by 6π electrocyclization of the resulting *o*QDM.

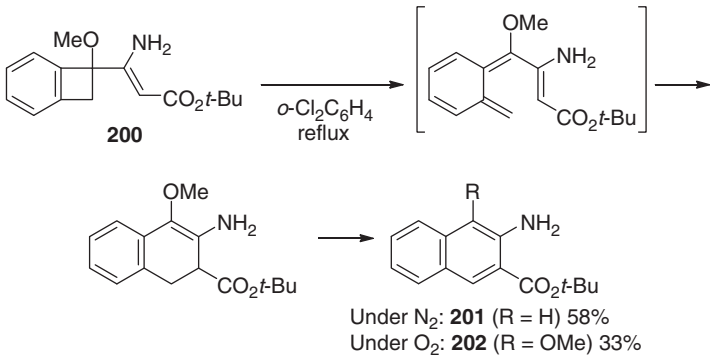
Alkenylbenzocyclobutenes **197** underwent such a cascade to afford dihydronaphthalanes **198**, which were oxidized by MnO_2 to provide the corresponding naphthalene derivatives **199** (Scheme 83).[95]

An analogous cascade reaction of 1-methoxy-1-alkenylbenzocyclobutene **200** having a β-aminoacrylate side chain under nitrogen atmosphere gave 3-amino-2-naphthalenecarboxylate **201** after removal of methanol (Scheme 84).[96] However, the reaction performed under oxygen atmosphere afforded the corresponding 4-methoxy derivative **202**. Synthesis of a potent Src kinase inhibitor utilized this thermal rearrangement of benzocyclobutenes.[97]

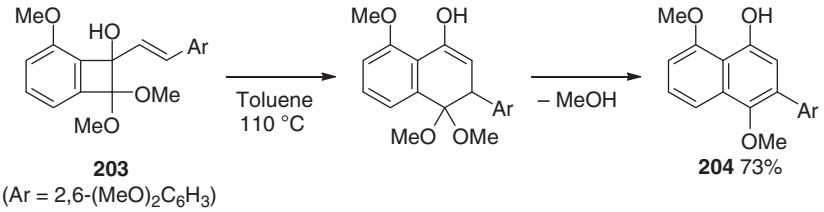
Heating of 1-arylethenylbenzocyclobuten-1-ol **203** in refluxing toluene gave the expected β-phenylnaphthalene **204** via ring opening and subsequent ring closing (Scheme 85).[98] In contrast, treatment of the benzocyclobutene with lithium



Scheme 83 Formation of naphthalenes via ring opening–6π electrocyclization.

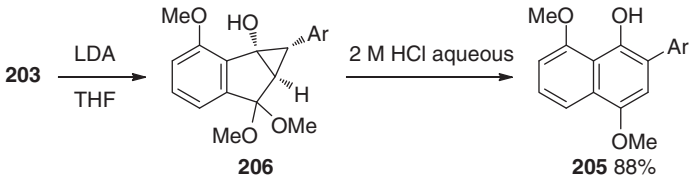


Scheme 84 Synthesis of 3-amino-2-naphthalenecarboxylates **201** and **202**.



Scheme 85 Thermal ring opening–ring closing of **203**.

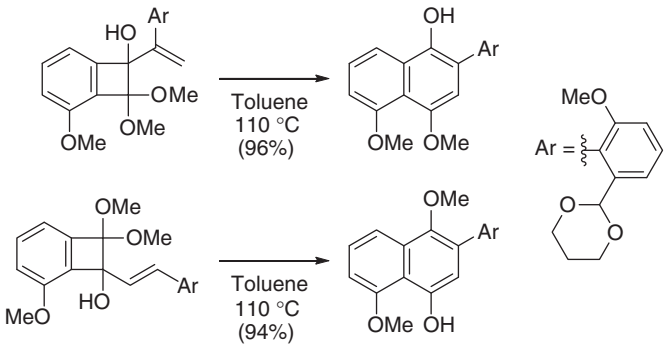
diisopropylamide afforded isomer **205** (Scheme 86). The skeletal rearrangement observed in the latter base-promoted reaction could be accounted for by assuming involvement of cyclopropanol species **206** as the intermediate.



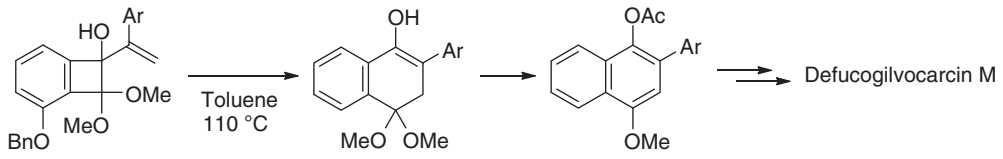
Scheme 86 Base-promoted skeletal rearrangement of **203**.

β-Phenylnaphthalene structures were accessed from two benzocyclobutenes having α- and β-styryl groups (Scheme 87).[99]

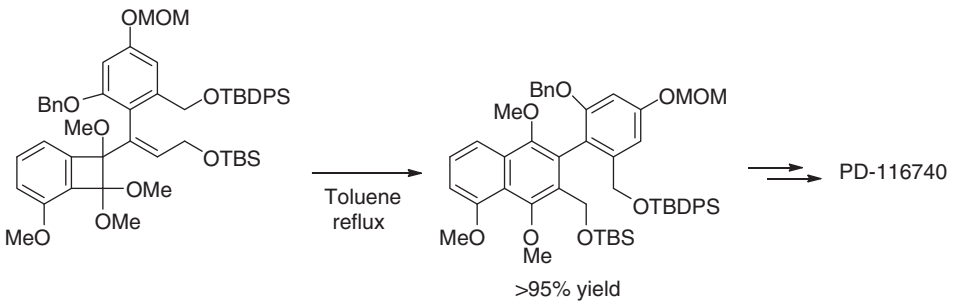
Several antibiotics were synthesized using the 6π elecrocyclization of *o*QDMs (Schemes 88 and 89).[100] The ring expansion reaction of (1-arylalkenyl)benzocyclobutenes gave β-arylnaphthalenes in excellent yield.



Scheme 87 β-Phenylnaphthalene from styryl-substituted benzocyclobutenes.

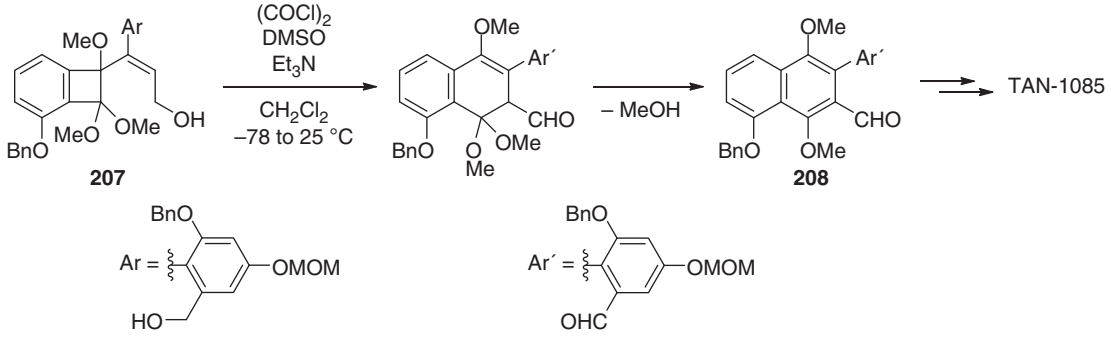


Scheme 88 Ring opening-6π elecrocyclization giving β-arylnaphthalenes (1).



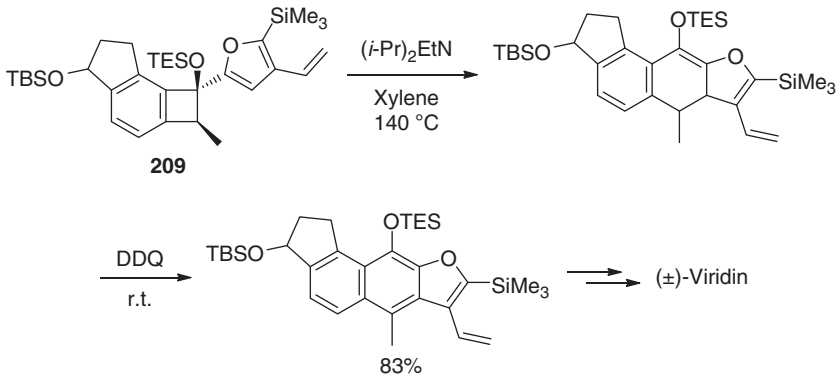
Scheme 89 Ring opening-6π elecrocyclization giving β-arylnaphthalenes (2).

When a reaction mixture formed by Swern oxidation of benzocyclobutene **207** having an allylic alcohol side chain was kept at 25 °C, ring opening and 6π ring closing occurred in sequence to afford aryl aldehyde **208** (Scheme 90).[101] This remarkable rate enhancement of the pericyclic processes was rationalized by assuming a cooperative effect of the electron-donating and electron-withdrawing substituents in their conrotatory motion.



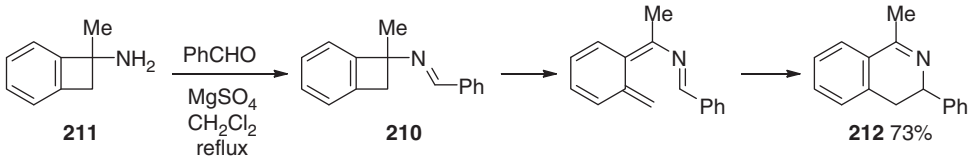
Scheme 90 Oxidation and subsequent thermal reaction of **207**.

A furanosteroidal antibiotic viridin was synthesized based on a strategy including a thermal ring enlargement reaction of the furanylbenzocyclobutene **209** (Scheme 91).[102]



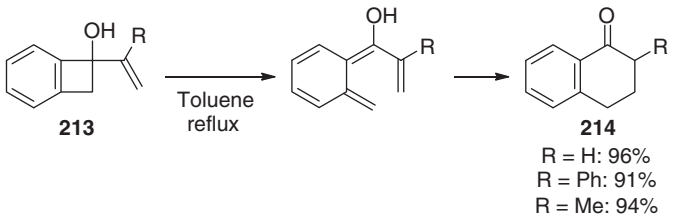
Scheme 91 Thermal ring enlargement of furyl-substituted benzocyclobutene **209**.

The formation of heteroaromatic rings via the 6π electrocyclization of *o*QDMs has also been studied.[103] Imine **210** derived from 1-aminobenzocyclobutenes **211** underwent a ring opening–ring closing sequence at 160 °C to afford 3,4-dihydroisoquinolines **212** (Scheme 92). The reaction was applied to the total synthesis of (±)-coralydine.



Scheme 92 3,4-Dihydroisoquinolines **212** via ring opening–ring closing.

Electrocyclic ring expansion of 1-alkenylbenzocyclobuten-1-ols **213** produced 1-tetralone derivatives **214** after keto–enol tautomerization (Scheme 93).[104]



Scheme 93 Ring expansion of alkenylbenzocyclobutenols **213** producing 1-tetralones **214**.

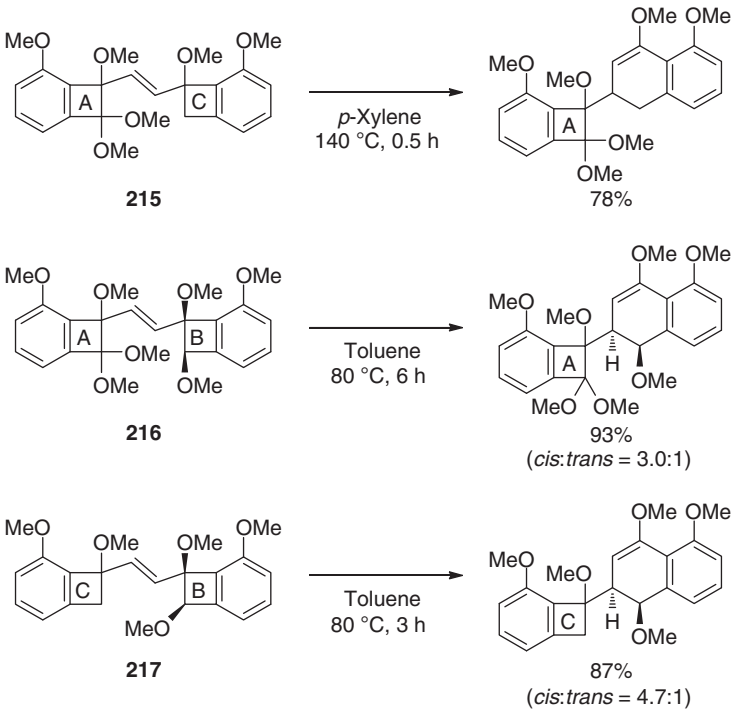
The reactivity of the two different four-membered rings in compounds **215**–**217** was compared (Scheme 94).[105] When **215** was reacted, the C-ring underwent ring expansion exclusively. In contrast, the reaction of **216** and **217** selectively gave the products occurring from ring expansion of the B-ring.

Orbital considerations based on a conrotatory ring opening followed by a disrotatory six-electron ring closure fail to accord with the stereochemistry observed in the products. This was attributed to a *cis*/*trans* isomerization of the starting benzocyclobutene through a biradical species. The resulting B-ring having two *trans* oxy-substituents is more reactive than the A- and C-rings.

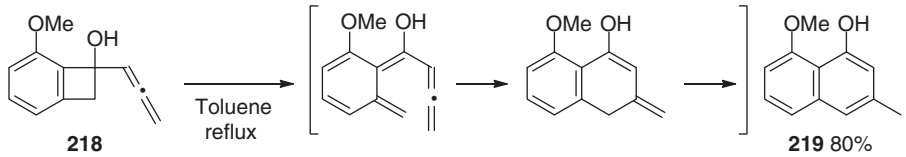
Thermal ring expansion of benzocyclobutenol **218** substituted with an allenyl group afforded the 3-methyl-1-naphthol **219** after migration of the exocyclic C=C bond into the ring (Scheme 95).[106]

1-Alkynylbenzocyclobuten-1-ols **220** were transformed into naphthol derivatives **221** on heating at 110 °C (Scheme 96).[104]

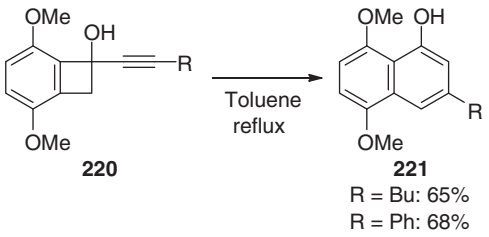
2-Benzylidenebenzocyclobuten-1-ol underwent analogous ring expansion reactions. However, they required higher temperatures, presumably because the allenyl analog of *o*QDMs was more difficult to generate.[107] 4-Benzylidene-1-tetralone **222** was formed from vinyl derivative **223** through ring opening at 190 °C and subsequent keto–enol tautomerization (Scheme 97). A mechanism involving a diradical species was assumed for the transformation of the alkynyl derivative **224** (Scheme 98). A phenyl group could also participate in the 6π electrocyclization, leading to the formation of 10-benzylideneanthrone **225** (Scheme 99).



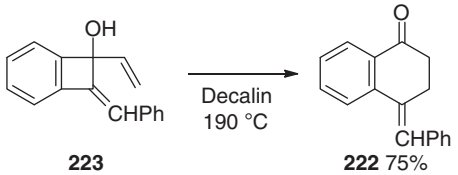
Scheme 94 Ring opening of bis(benzocyclobutene)s **215**–**217**.



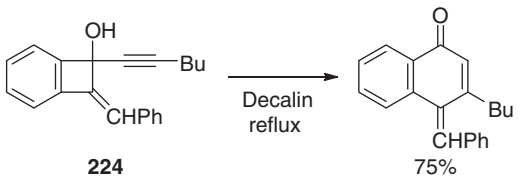
Scheme 95 Ring expansion of allenylbenzocyclobutenol **218**.



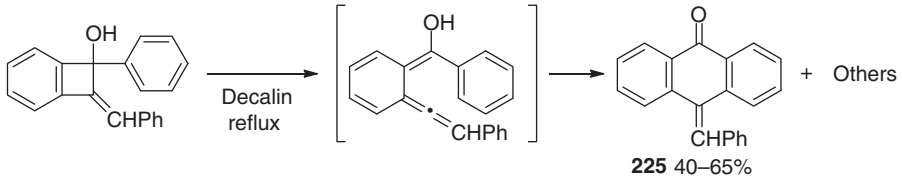
Scheme 96 Ring expansion of alkynylbenzocyclobutenols **220**.



Scheme 97 Ring expansion of alkenyl(benzylidene)benzocyclobutene **223**.



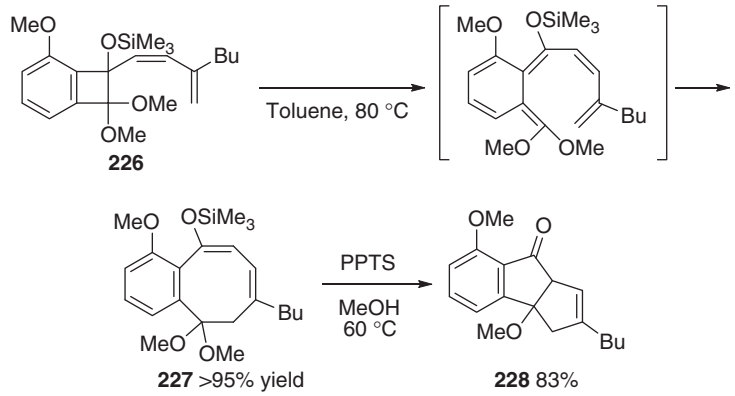
Scheme 98 Ring expansion of alkynyl(benzylidene)benzocyclobutene **224**.



Scheme 99 Ring expansion to 10-benzylideneanthrone **225**.

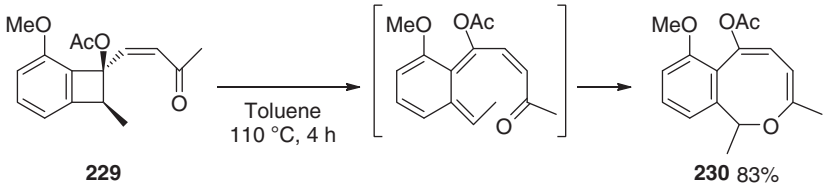
5.16.3.3 8π Electrocyclization

Construction of eight-membered rings via an 8π electrocyclization involving *o*QDM is viable if the benzocyclobutene precursors have a 4π side chain. For example, the dienylbenzocyclobutene **226** underwent the thermal four-carbon ring expansion at 80 °C to give the eight-membered product **227** (Scheme 100).[108] Treatment of the product with an acid (pyridinium *p*-toluenesulfonate) in methanol-induced transannular cyclization to afford the tricyclic product **228**.



Scheme 100 Thermal four-carbon ring expansion of dienylbenzocyclobutene **226**.

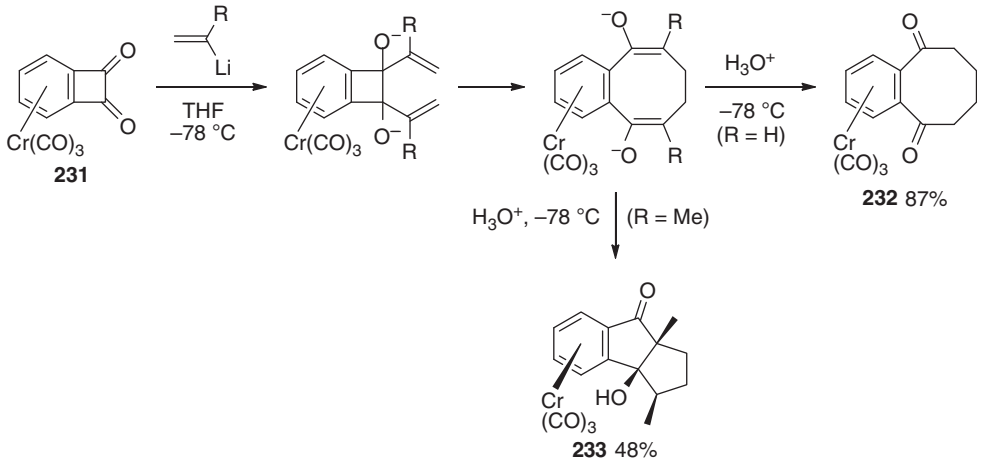
An analogous ring expansion by four atoms occurred with benzocyclobutenes having an α,β-unsaturated carbonyl group **229** to produce the eight-membered ether, benzoxocine **230** (Scheme 101).[109]



Scheme 101 Ring expansion of **229** giving benzoxocine **230**.

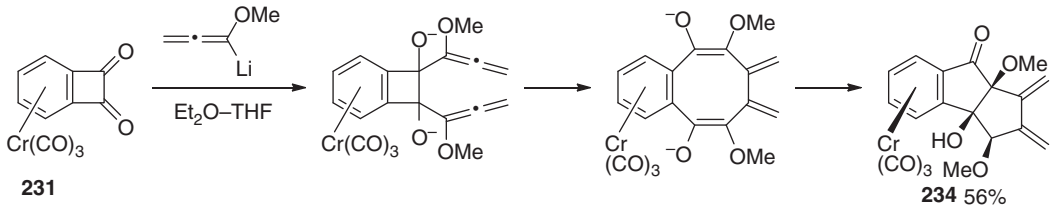
Introduction of two alkenyl groups on the cyclobutene ring offers another approach to eight-membered rings. When the tricarbonylchromium(0) complex **231** of benzocyclobutenedione was treated with vinyllithium, the tricarbonylchromium(0) complex of the eight-membered ring diketone **232** was obtained after hydrolysis (Scheme 102).[110] The two vinyl groups were introduced from the opposite side of the chromium and took a synperiplanar orientation, thereby assisting in the double anionic

oxy-Cope rearrangement. In the reaction with propenyllithium, an intramolecular aldol reaction followed to produce the tricyclic compound **233**.



Scheme 102 Double anionic oxy-Cope rearrangement of dialkenylbenzocyclobutenes.

The addition–ring opening reaction with an allenyllithium also resulted in the formation of a tricyclic compound **234** (Scheme 103).[111]



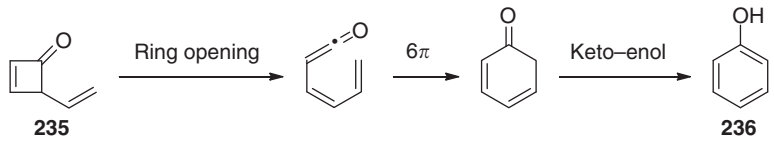
Scheme 103 Addition–ring opening reaction of tricarbonylchromium(0) complex **231**.

5.16.4 Cyclobutenones

Heating of cyclobutenones generates reactive vinylketenes, which serve as the 4π component in 6π electrocyclization reactions or [4 + 2] annulation reactions to produce densely substituted phenol and quinone derivatives.

5.16.4.1 6π Electrocyclization

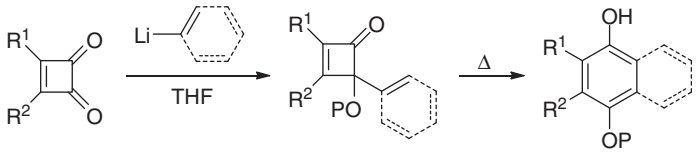
Cyclobutenones having an unsaturated functionality at the 4-position such as **235** undergo ring opening, 6π electrocyclization, and keto–enol tautomerization in sequence to afford phenol derivatives **236** (Scheme 104). A number of applications of this transformation have appeared.

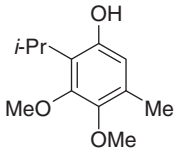
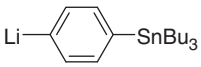
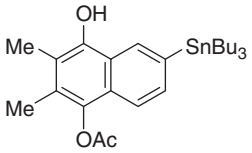
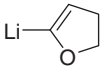
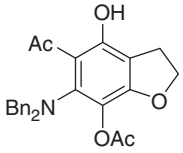
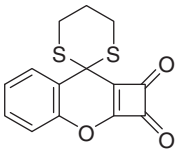
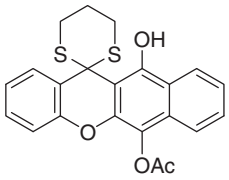
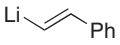
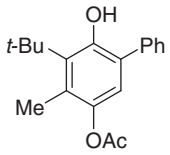
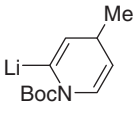
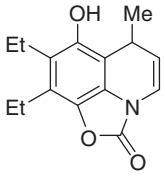


Scheme 104 Phenol synthesis from 4-vinylcyclobutenones **235**.

The requisite cyclobutenones are easily prepared by addition of organolithium reagents to substituted cyclobutenediones (Table 5). A good regioselectivity was observed with unsymmetrical cyclobutenediones. A heteroatom substituent deactivates the distal carbonyl group through resonance delocalization. As a result, nucleophilic addition occurred at the proximal carbonyl group. Thermal ring expansion of the adducts in refluxing xylene gave the corresponding benzannulation products in excellent yields.[112,113] Treatment of cyclobutenediones containing a vinylogous amide functionality with alkenyllithiums gave

Table 5 Cyclobutenone benzannulation (1)[a]



R^1	R^2		P	Product	Yield (%)	References
i-Pr	OMe		Me		70	116
Me	Me		Ac		96	117
Ac	NBn_2		Ac		92	118
		PhLi	Ac		81	119
t-Bu	O*i*-Pr		Ac		73	120
Et	Et		H		65	121

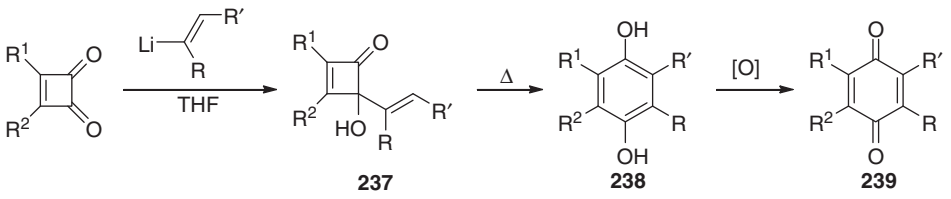
[a]Ring opening was performed at 69–165 °C.

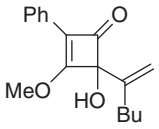
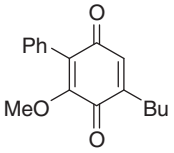
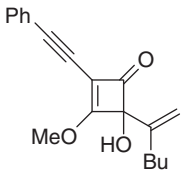
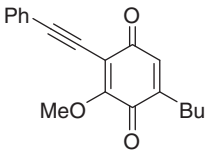
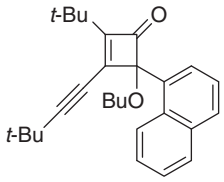
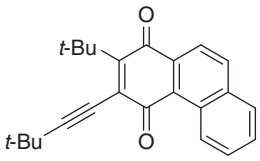
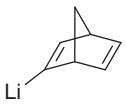
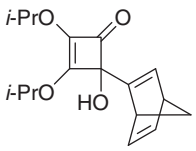
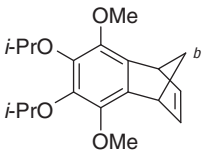
4-hydroxy-4-alkenylcyclobutenones, which underwent ring expansion to provide acyl amino phenol derivatives.[114] Highly substituted xanthones were synthesized by the reaction of dithiane-protected benzopyrone-fused cyclobutenediones with alkenyllithiums.[115] The 1,2-adducts were exceptionally prone to benzannulation; aromatized products were formed slowly even at r.t. In the reaction of cyclobutenediones having a *t*-butyl substituent, the addition of unsaturated carbon nucleophiles occurred regiospecifically at the carbonyl group distal to the *t*-butyl substituent.[116] After thermolysis of the adducts, the *t*-butyl group was removed under acidic conditions to afford 2-unsubstituted hydroquinone monoacetates. Adducts obtained from the reaction of 1-Boc-2-lithio-1,4-dihydropyridines and 3,4-disubstituted cyclobutenediones underwent thermal ring expansion to afford 1,4-dihydroquinolin-5-ols.[117] The 4-hydroxy substituent on the cyclobutenone ring displaced the *t*-butoxy residue of the Boc group, generating an oxazolone ring.

Electrocyclic ring opening–ring closing of nonprotected 4-alkenyl-4-hydroxycyclobutenones **237** gave the hydroquinones **238**, which were easily converted to the corresponding quinones **239** on oxidative workup (**Table 6**).[118–120]

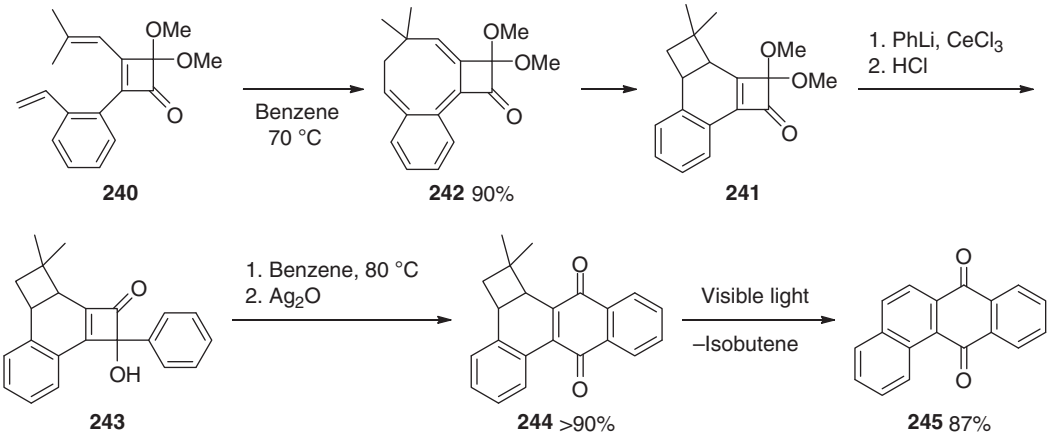
Cyclobutenone **240** isomerized to the tetracyclic cyclobutenone **241** on heating. The transformation involved an 8π electrocyclization to give cyclooctatriene **242**, which was followed by a 6π electrocyclic ring closure (**Scheme 105**). Arylation of the

Table 6 Cyclobutenone benzannulation (2)[a]



R^1	R^2	Li–R	237	Yield (%)	239	Yield (%)	References
Ph	OMe			78		87	122
PhC≡C	OMe			48		80	122
						86	123
O*i*-Pr	O*i*-Pr			81		73	124

[a]Ring opening was performed at 85–138 °C.
[b]Product was converted to methyl ether.

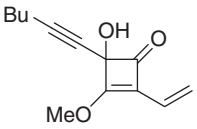
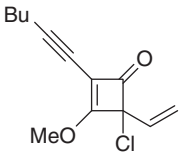
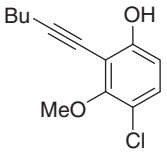
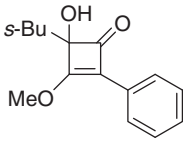
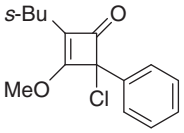
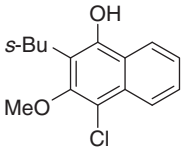
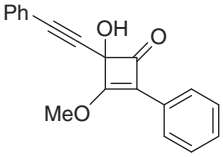
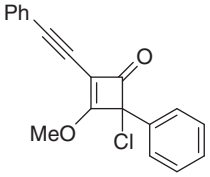
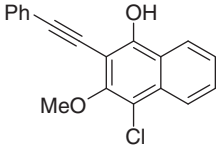


Scheme 105 Benzannulation of **243**.

carbonyl group followed by acid hydrolysis gave cyclobutenone **243**, which was then heated. The resulting ring-expanded hydroquinone was directly oxidized to quinone **244**. When irradiated, **244** underwent an efficient photofragmentation reaction to yield the benzo[*a*]anthracene-7,12-dione **245**, a compound representing the basic framework of the angucycline group of antibiotics.[121]

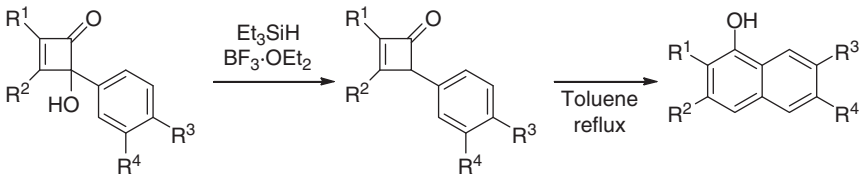
When 4-hydroxycyclobutenones of the general type **246** were treated with thionyl chloride, chlorination took place preferentially at the carbon which could generate the more stable carbocation. The resulting 4-chlorocyclobutenones **247** were converted into highly substituted *p*-chlorophenol derivatives **248** (Table 7).[122]

Table 7 Cyclobutenone benzannulation (3)

246	***247***	*Yield (%)*	***248***	*Yield (%)*
		80		48
		93		80
		59		76

2,3,4-Trisubstituted cyclobutenones **249** were prepared by Lewis acid-mediated reduction of the corresponding 4-hydroxycyclobutenones **250** with Et_3SiH. Their thermal reaction afforded 2-naphthols **251** in excellent yields (Table 8).[123]

Table 8 Cyclobutenone benzannulation (4)



250 **249** **251**

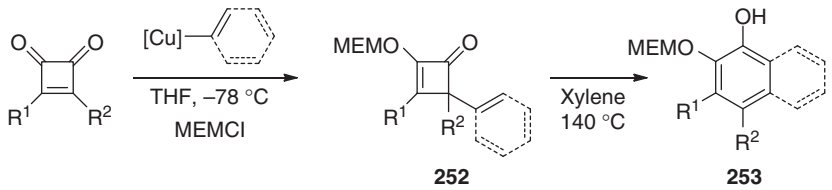
R^1	R^2	R^3	R^4	*Yield (%)*
Bu	O*i*-Pr	H	H	96
BuC≡C	O*i*-Pr	H	H	87
3,4-$Me_2C_6H_3$	OMe	OMe	OMe	85
Ph	O*i*-Pr	OMe	H	64

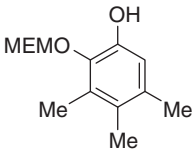
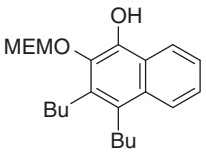
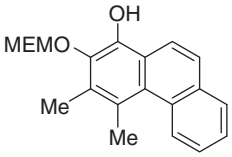
Conjugate addition of alkenyl- and arylcopper reagents led to the formation of the 4-alkenyl- and arylcyclobutenones **252**, which were converted to 1,2-dioxygenated aromatics **253** on heating (Table 9).[124]

4-Alkyenyl and 4-arylcyclobutenones **254** were synthesized by a palladium-catalyzed cross-coupling reaction of 4-chlorocyclobutenones **255** with alkenyl- and arylstannanes. On heating at 100 °C, the cyclobutenones **254** were transformed into the corresponding phenol derivatives **256** in good yields (Table 10).[125] A cross-coupling reaction and a thermal ring opening occurred subsequently in one-pot. When 2-stannylnaphthalenes were used as the cross-coupling partners, an electrocyclic reaction took place at the α-position to selectively furnish angularly fused products.[113] The reaction with stannylquinones afforded naphtho- and anthraquinones.[126] Furan- and thiophene-fused aromatics were also synthesized.[127] A cross-coupling–rearrangement sequence with 4-chlorocyclobutenones and 3-stannylcyclobutenones gave benzocyclobutenedione monoketals.[128]

A number of natural products were synthesized using the cyclobutenone chemistry. A reaction of dimethyl squarate **257** with *i*-PrMgCl followed by hydrolysis gave compound **258** (Scheme 106). Treatment of **258** with isopropenyllithium followed by quenching with Me_3SiCl resulted in the 4-isopropenylcyclobutenone **259**, which was directly subjected to thermolysis at 69 °C to give the monoprotected phenol **260**. Methylation and subsequent desilylation of the crude product gave espintanol (**261**).[112]

Table 9 Cyclobutenone benzannulation (5)



R^1	R^2	[Cu]–R	***253***	Yield (%)
Me	Me	(1-Propen-2-yl)(2-thienyl)Cu(CN)Li_2		95
Bu	Bu	$Ph_2Cu(CN)Li_2$		83
Me	Me	(1-Naphthyl)$_2$Cu(CN)Li_2		64

4-Vinylcyclobutenone **262** derived from diisopropyl squarate underwent thermal ring expansion at 160 °C to produce the corresponding hydroquinone, which was directly methylated to give **263** (Scheme 107). Cyclobutenone **264** was also synthesized in three steps from diisopropyl squarate. The aryllithium reagent generated from **263** added onto the more electrophilic carbonyl group of **264**. The resulting adduct **265** underwent the second thermal benzannulation to produce hydroquinone **266**, which yielded echinochrome A (**267**) after oxidation and deprotection.[129]

Perezone (**268**), a naturally occurring sesquiterpene hydroxyquinone, was synthesized starting from di-*t*-butyl squarate via the thermal rearrangement of the 4-alkenylcyclobutenone **269** (Scheme 108).[130]

Introduction of a dienyl or arylethenyl substituent at the 2-position of the cyclobutenones led to the generation of dienyl or arylethenyl ketene intermediates **270** suitable for the 6π electrocyclic ring closing reaction (Table 11).[131] Thermal reaction of 2-alkenylcyclobutenones **271** followed by treatment with trifluoroacetic acid produced naphthofurans **272**. Both geometrical isomers gave the desired furan, although the *E*-isomer took a significantly longer time to react than the *Z*-isomer.

Condensation of 3,4-diarylcyclobutenediones **273** with indole derivatives occurred in the presence of *p*-toluenesulfonic acid to afford carbazole derivatives **274** (Scheme 109).[132] The reaction proceeds through an acid-promoted diarylation of the cyclobutenediones and a subsequent thermal ring expansion.

The thermal rearrangement of cyclobutenones was further extended to 4-allenylcyclobutenones and cyclobutenimines. 4-Allenylcyclobutenone **275** underwent a ring expansion on heating in refluxing toluene to afford the fully substituted hydroquinone **276** (Scheme 110).[133]

The thermal rearrangement of cyclobutenimines **277** in refluxing *p*-xylene afforded *p*-aminophenols **278** (Scheme 111).[134] The ring expansion of 4-methoxy-4-phenylcyclobutenimines **279** gave α-aminonaphthalenes **280** (Scheme 112).

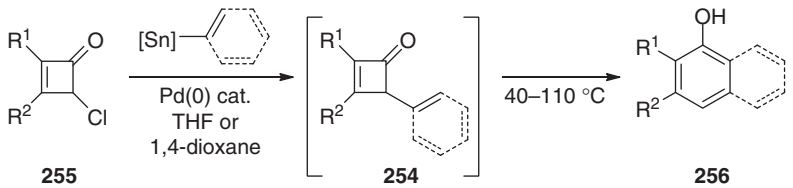
4-Alkynylcyclobutenones **281** were also used as the precursor for the six-membered ring formation (Table 12).[134,135] However, the reaction proceeds via a mechanism involving a diradical or a zwitterion species.

4-(Trimethylsilylpropynyl)cyclobutenones **282** underwent a thermal reaction in refluxing *p*-xylene to give quinones **283** (Scheme 113).[136] In contrast, a thermal ring expansion of 4-(trimethylsilylpropenyl)cyclobutenones **284** followed by oxidation with Ag_2O afforded the regioisomeric quinones **285**.

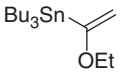
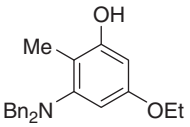
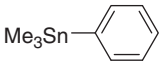
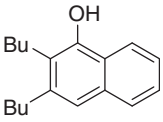
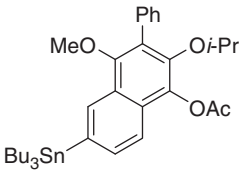
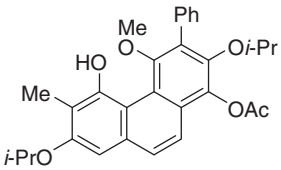
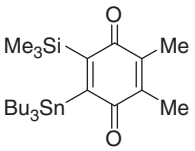
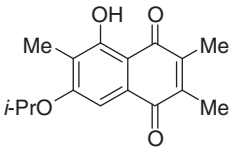
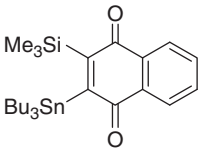
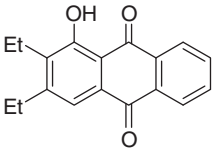
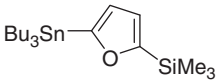
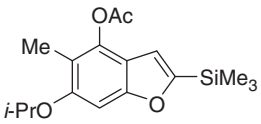
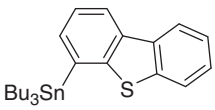
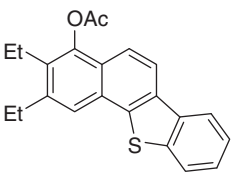
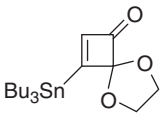
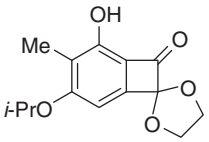
A thermal reaction of alkynyl alkynyloxy cyclobutenone **286** in refluxing *p*-xylene led to the production of methylenebenzofuran **287** (Scheme 114).[137] Initial electrocyclic ring opening of the cyclobutenone gave the conjugated ketene **288**, which generated a diradical species **289** on ring closure. Subsequently, the aryl radical **289** cyclized in a 5-*exo* mode to give another diradical species **290**. The vinylic radical abstracted a H-atom from the proximal butyl group. A second H-atom abstraction then followed to furnish the product **287**.

However, diyne-substituted cyclobutenones **291** rearranged to spirocyclic epoxides **292** (Scheme 115).[138] Initial formation of the ynenylketenes **293** led to the generation of the diradicals **294**. The more reactive carbon radical center underwent

Table 10 Cyclobutenone benzannulation (6)

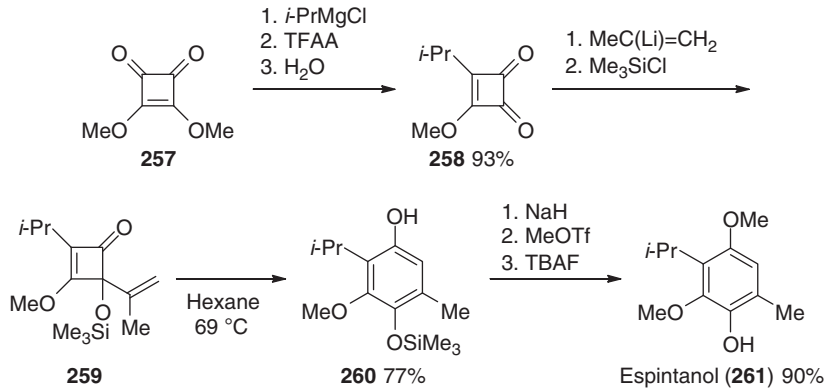


255 **254** **256**

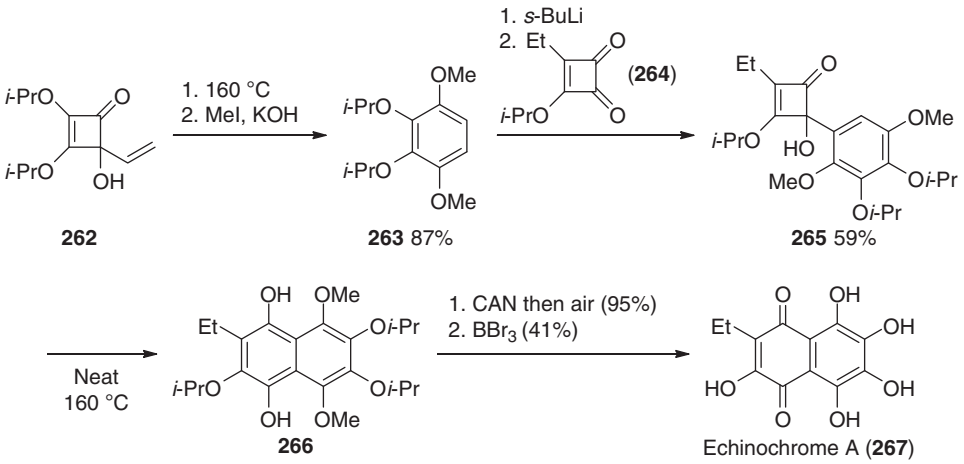
R^1	R^2	[Sn]–R	**256**	Yield (%)	References
Me	NBn_2			74	129
Bu	Bu			77	129
Me	O*i*-Pr			63	117
Me	O*i*-Pr			81	130
Et	Et			95	130
Me	O*i*-Pr			78	131
Et	Et			78	131
Me	O*i*-Pr			95	132

exo-cyclization onto the proximal alkyne moiety to give **295**. The resulting vinyl radical then abstracts a H-atom from the adjacent methoxy group to generate **296**, which formed the spiroepoxides **292**.

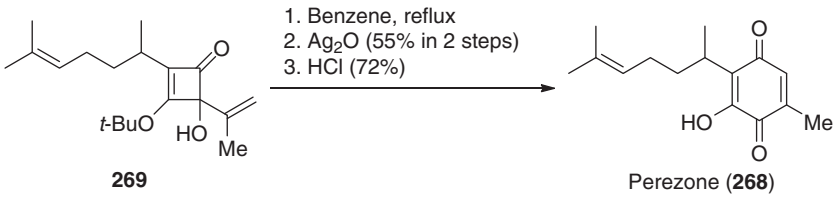
Although a thermal reaction of the 4-alkynyl-4-hydroxycyclobutenones of type **297** also caused similar ring expansion, the resulting products were not spiroepoxides but quinones **298** (Scheme 116).



Scheme 106 Synthesis of espintanol (**261**).



Scheme 107 Synthesis of echinochrome A (**267**).



Scheme 108 Synthesis of perezone (**268**).

Heating of the squaric acid-derived 4-(3-*N*-methyl-*N*-arylpropynyl)cyclobutenones **299** in refluxing chlorobenzene gave benzophenanthridines **300**. An electrocyclic ring opening of the cyclobutenone, ring closure to a diradical intermediate **301**, and a radical arylation took place in sequence (Scheme 117).[139]

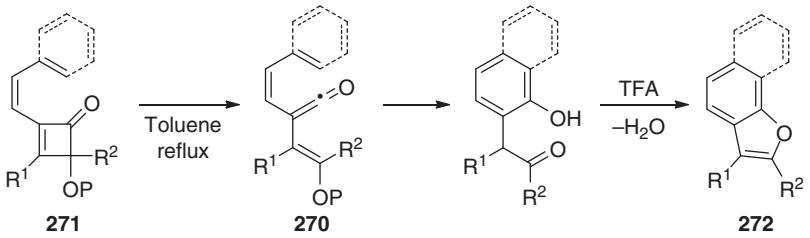
A concise total synthesis of cribrostatin 6, an antimicrobial and antineoplastic agent, involved a tandem electrocyclic ring opening–radical cyclization sequence (Scheme 118).[140]

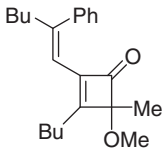
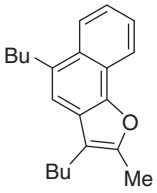
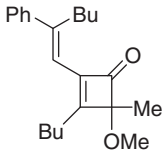
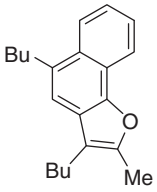
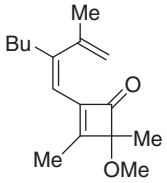
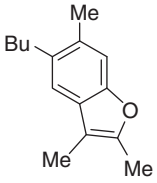
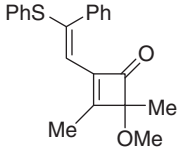
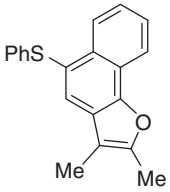
4-(1-Pyrrolyl)-4-siloxycyclobutenone **302** thermally rearranged to 5-hydroxy-8-siloxyindolizine **303**, which was oxidized to the indolizine-5,8-dione **304** (Scheme 119).[141] When the reaction was performed in the presence of dimethyl acetylenedicarboxylate, the indolizine precursor were trapped by an [8 + 2] cycloaddition to give pyrroloindolizine **305**.

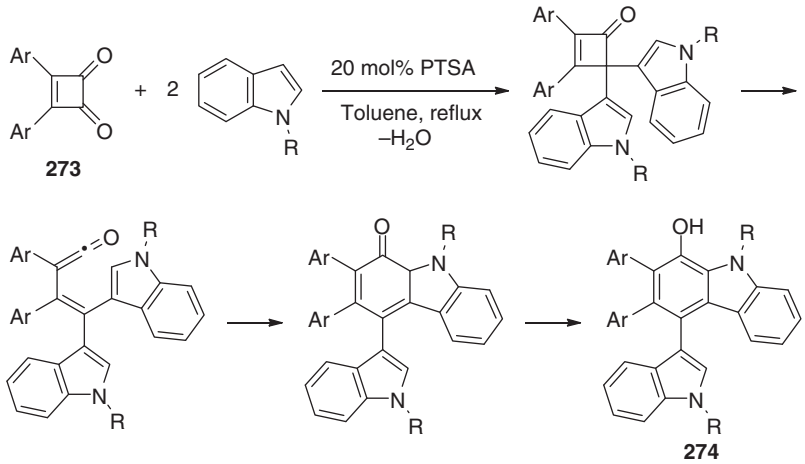
5.16.4.2 [4 + 2] Annulation

Heteroatom-substituted alkynes undergo thermal benzannulation to afford phenols. The vinylketene-based benzannulation strategy developed by Danheiser et al. proceeds via a cascade process involving four successive pericyclic reactions (Table 13).

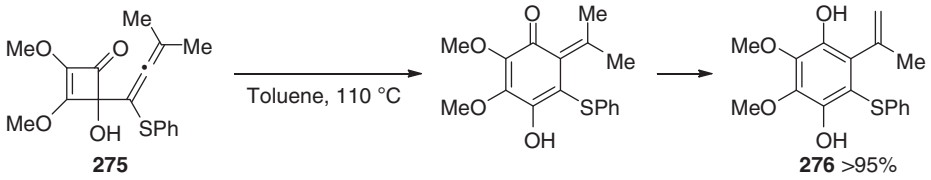
Table 11 Thermal reaction of 2-alkenylcyclobutenones **271**



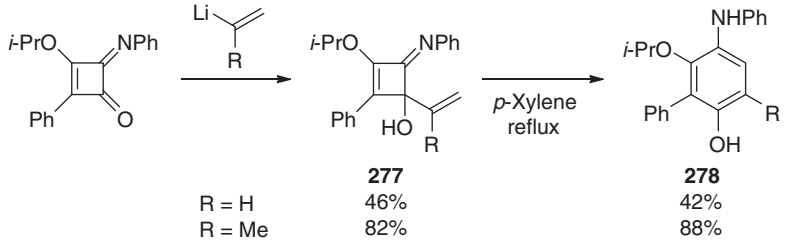
271	*272*	*Yield (%)*
		75
		45
		55
		88



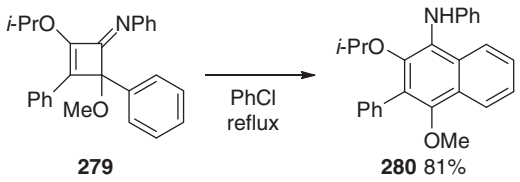
Scheme 109 Diarylation and subsequent ring expansion of cyclobutenediones **273**.



Scheme 110 Thermal rearrangement of 4-allenylcyclobutenone **275**.

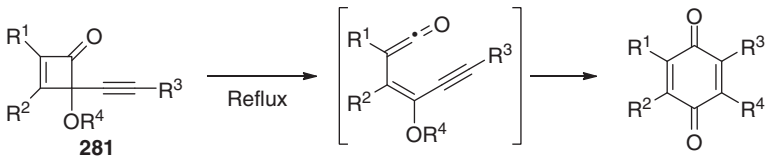


Scheme 111 Thermal rearrangement of cyclobutenimines **277**.



Scheme 112 Thermal rearrangement of cyclobutenimine **279**.

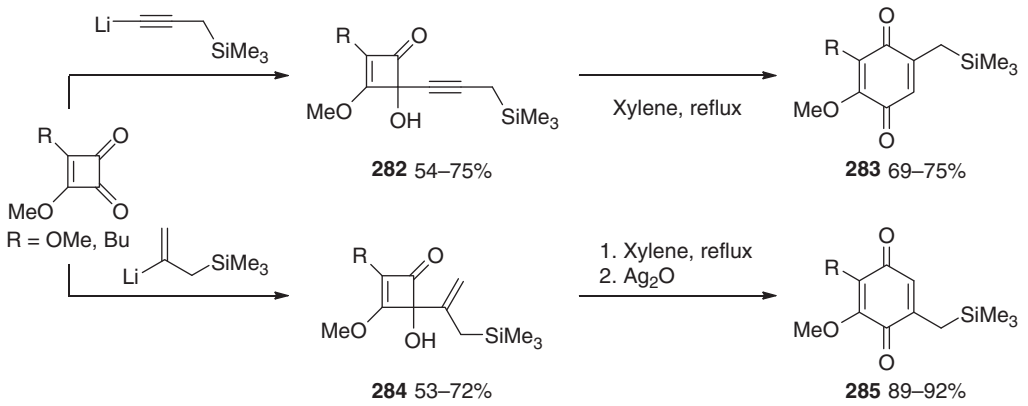
Table 12 Cyclization of 4-alkynylcyclobutenones **281**



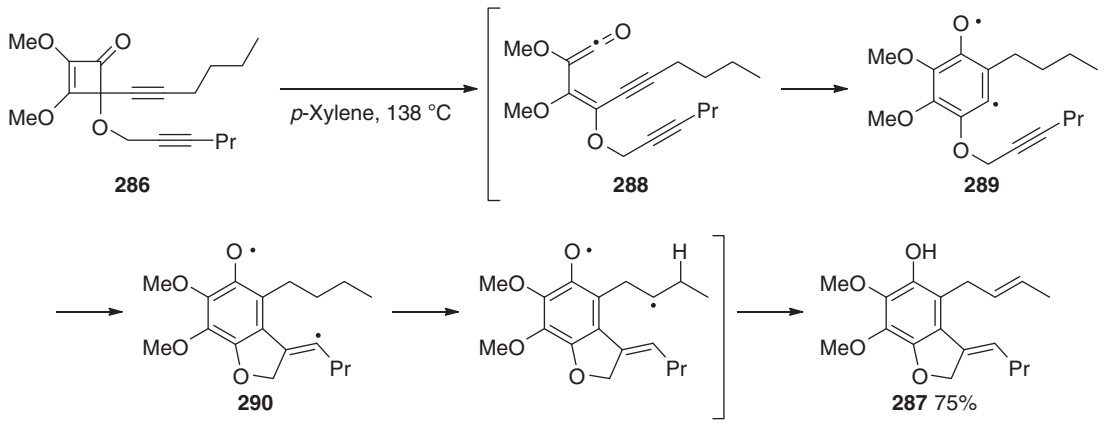
R[1]	*R*[2]	*R*[3]	*R*[4]	*Solvent*	*Yield (%)*	*References*
Bu	O*t*-Bu	Bu	H	Xylene	89	134
Me	O*t*-Bu	H	H	MeCN	79	134
OMe	OMe	Bu	H	Xylene	78	139
OMe	OMe	H	$SiMe_3$	Xylene	75	139

Heating of a cyclobutenone derivative of the general type **306** at temperatures greater than 80 °C induces an electrocyclic ring opening to generate vinylketene **307**, which undergoes a regiospecific [2 + 2] cycloaddition with the ketenophilic acetylene derivative **308** (X = OR, SR, NR_2).[142,143] Ring opening of the resulting 4-vinylcyclobutenone **309** then furnishes dienylketene **310**, which undergoes a 6π electrocyclization to afford a cyclohexadienone. Tautomerization finally yields the highly substituted phenol **311**. Either thermal or photochemical activation prompted benzannulation of ynamides.[144] Microwave irradiation could be also used for the benzannulation.

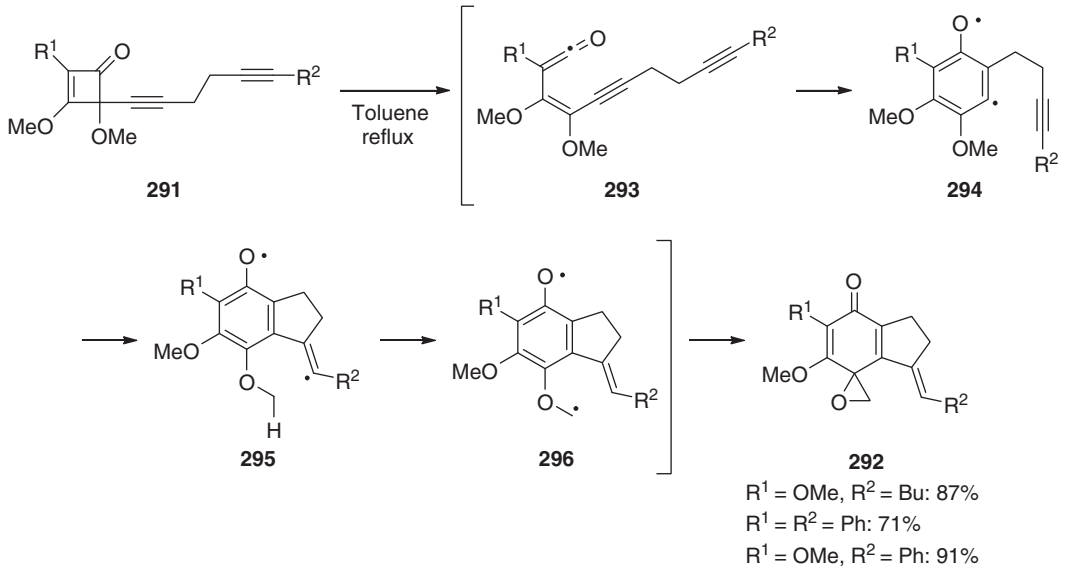
The synthesis of the sesquiterpene phenol (–)-ascochlorin was based on the [4 + 2] annulation strategy (Scheme 120).[145] A solution of the cyclobutenone **312** and the alkoxyacetylene **313** was initially irradiated, and then briefly heated to complete conversion to the desired aromatic product.



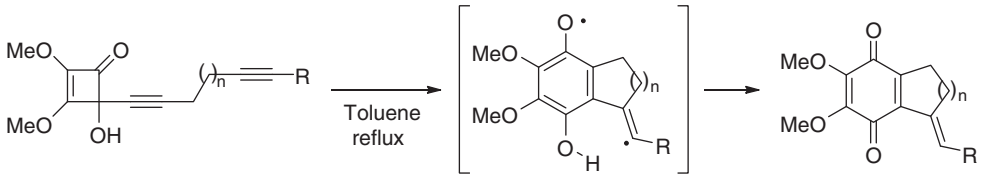
Scheme 113 Thermal ring expansion of **282** and **284**.



Scheme 114 Thermal reaction of alkynyl alkynyloxy cyclobutenone **286**.



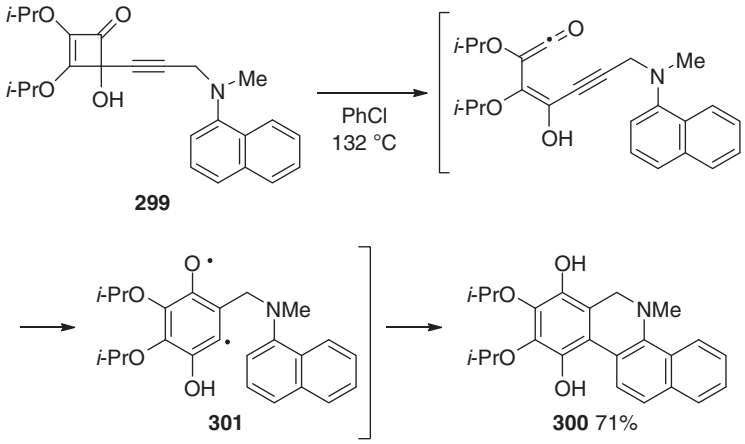
Scheme 115 Rearrangement of diyne-substituted cyclobutenones **291**.



297 **298**

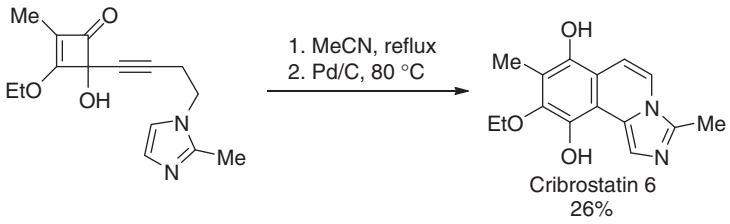
n = 2, R = Bu: 80%
n = 3, R = Ph: 63%

Scheme 116 Formation of quinones **298** via rearrangement of **297**.



299 **301** **300** 71%

Scheme 117 Formation of benzophenanthridines **300** via thermal reaction of **299**.



Cribrostatin 6
26%

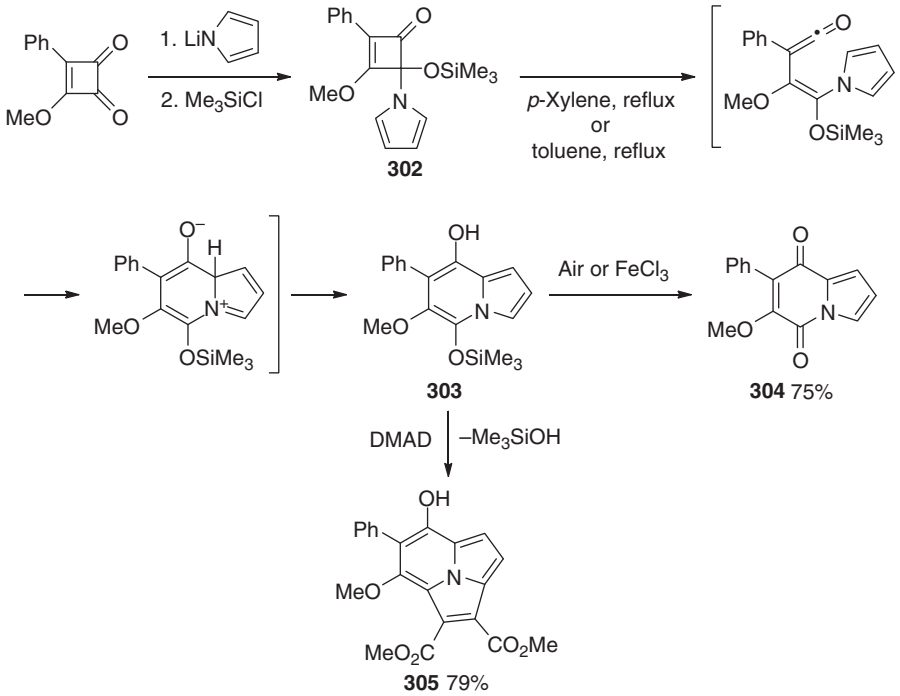
Scheme 118 Synthesis of cribrostatin 6.

Intermolecular annulation of the cyclobutenone **314** with siloxyacetylene **315** afforded phenol **316**, which was then desilylated and methylated (Scheme 121). Treatment of the resulting diene **317** with the Grubbs catalyst led to the corresponding paracyclophane by head-to-tail cyclodimerization. Heterogeneous hydrogenation followed by cleavage of the methyl ether with BBr_3 completed the synthesis of (–)-cylindrocyclophane F.[146]

The cyclobutenone **318** reacted with (η^3-indenyl)Co(PPh_3)$_2$ to give the η^4-vinylketene complex **319**. The following reaction with alkynes produced phenols **320** (Scheme 122).[147]

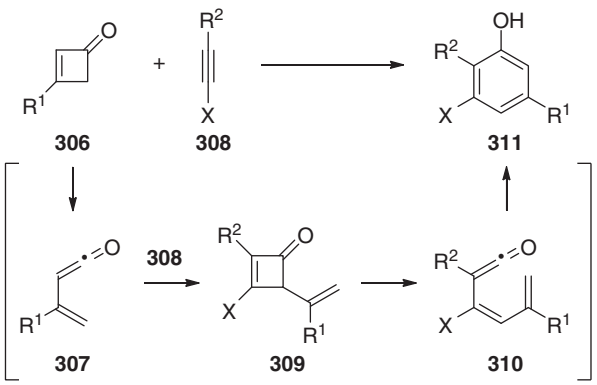
The [4 + 2] annulation of cyclobutenones has also been catalyzed by a nickel(0) complex (Table 14). The reaction of cyclobutenones **321** and internal alkynes **322** occurred even at 0 °C to afford phenols **323** in good yields.[148] Poor regioselectivity was observed with unsymmetrical alkynes. 3,4-Disubstitution was allowed on the cyclobutenones. The vinylketene [4 + 2] cycloaddition with boryl-substituted alkynes provided an entry to boryl-substituted phenols.[149] Excellent regioselectivity was observed in most cases when such boryl-substituted alkynes were used.

Although the [4 + 2] annulation reaction catalyzed by Ni(cod)$_2$ failed to occur with a 2,3-disubstituted cyclobutenone, it became viable with a rhodium catalyst to afford a phenol in a moderate yield (Scheme 123).[150] Even electron-deficient alkenes participated in the rhodium-catalyzed reaction. The initially produced cyclohexenones were oxidized to phenols through hydrogen transfer to the alkenes (Scheme 124).



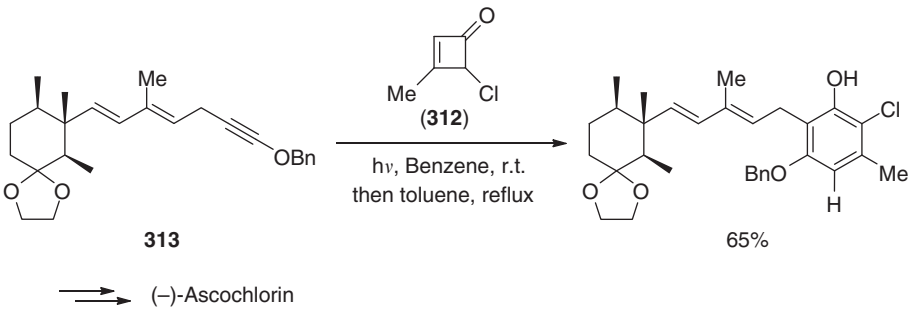
Scheme 119 Thermal rearrangement of 4-(1-Pyrrolyl)-4-siloxycyclobutenone **302**.

Table 13 Benzannulation between cyclobutenones **306** and alkynes **308**

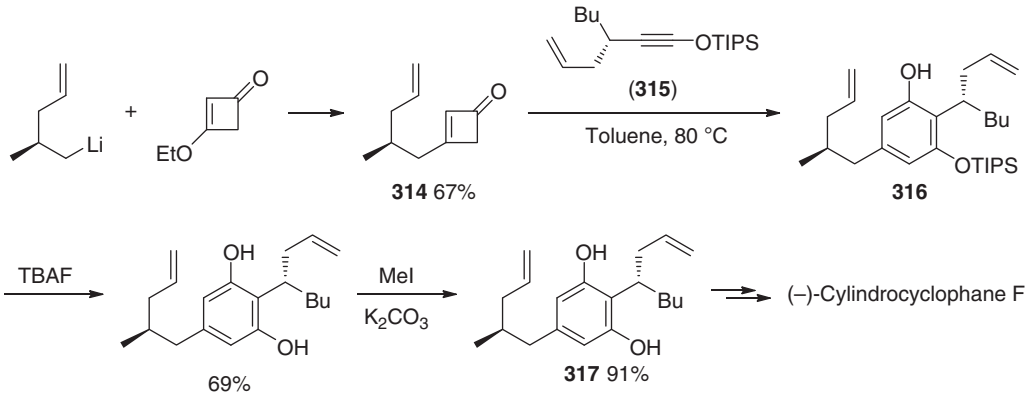


306	***308***		*Conditions*	*Yield (%)*	*References*
R^1	*R^2*	*X*			
Me	Me	OMe	Benzene, 80 °C	71	146
Bu	Me	SMe	$CHCl_3$, 80 °C	82	146
Me	Hex	NMe_2	Benzene, 150 °C	74	146
Bu	*i*-Pr	OSi(*i*-Pr)$_3$	Benzene, 95 °C	96	147
Bu	Hex	N(Me)CO_2Me	Toluene, reflux	80	148
Bu	Hex	N(Me)CO_2Me	hν (254 nm), toluene, r.t.	66	148
Bu	Hex	N(Me)CO_2Me	μw (70–90 W), benzene	74	148
Bu	Me	N(Me)Ts	Toluene, reflux	81	148

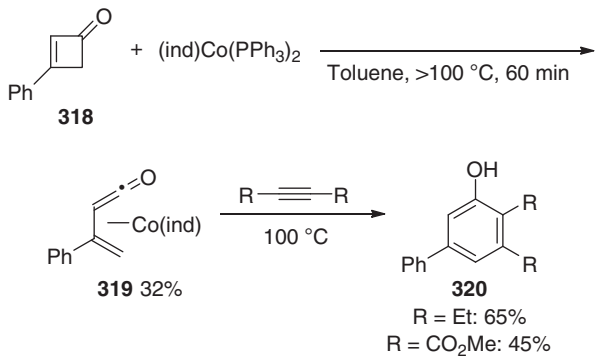
The thioketal derivatives of 2-silylcyclobutenone such as **324** readily underwent electrocyclic ring opening to generate reactive silyl(vinyl)ketene, which further reacted with TCNE to afford the corresponding [4 + 2] cycloadduct **325** (Scheme 125).[151]



Scheme 120 Benzannulation between cyclobutenone **312** and alkoxyalkyne **313**.



Scheme 121 Benzannulation between cyclobutenone **314** siloxyalkyne **315**.



Scheme 122 Reaction of η^4-vinylketene **319** complexes with alkynes.

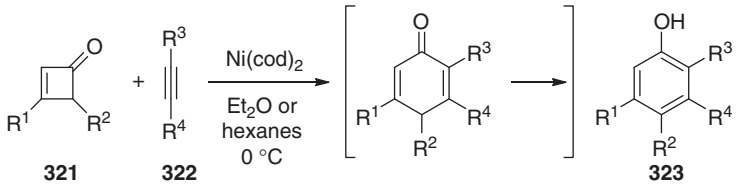
Thermolysis of benzocyclobutenone **326** in refluxing 1,2-dichlorobenzene in the presence of fullerene (C_{60}) affords fullerene-fused 1-tetralone **327** (Scheme 126).[152]

5.16.4.3 [2 + 2] Cycloaddition

When 4-allyl-4-arylcyclobutenones **328** were heated, [2 + 2] cycloaddition and 6π electrocyclization could occur in a competitive manner (Table 15). The selectivity between the two pathways varied according to the substituents. The naphthol **329** resulted in preference to the bicyclo[3.2.0]heptenone **330** from 4-allyl-2-hexynylcyclobutenone. This preference was reversed for 4-allyl-2-phenylcyclobutenone. A bicyclo[3.2.0]heptenone was exclusively formed from 2-*t*-butyl-4-methallylcyclobutenone.

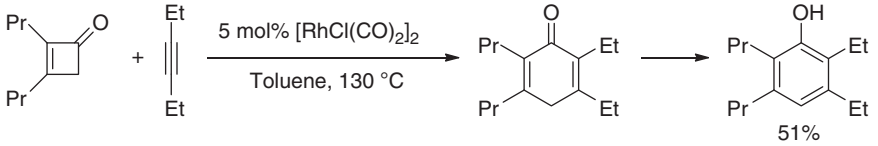
3-(3-Butenyl)-2-isobutenyl-4-siloxycyclobutenone **331** underwent torquoselective electrocyclic ring opening, giving the vinylketene intermediate **332** (Scheme 127).[153] Subsequent intramolecular [2 + 2] cycloaddition with the allylic double bond afforded **333**. Treatment of this compound with aqueous acid resulted in the formation of the corresponding aldehyde with a diastereomeric ratio of 10:1. After reduction of the formyl group to a methyl group, vinyllithium was added to the ketone to

Table 14 Nickel-catalyzed [4 + 2] annulations

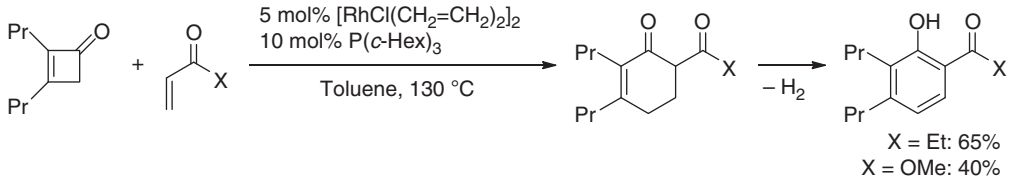


321 **322** **323**

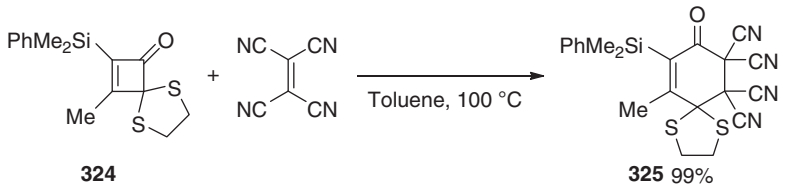
321		*322*		*Yield (%) (regio)*	*References*
R[1]	*R*[2]	*R*[3]	*R*[4]		
Bu	H	Et	Et	76	152
Ph	H	Me	*i*-Pr	81 (50:50)	152
Ph	Me	Et	Et	60	152
Bu	H	Me_3Si	B(pin)	81 (>98:2)	153
Ph	H	Bu	B(pin)	54 (85:15)	153
Ph	Me	Bu	B(pin)	68 (>98:2)	153
Bu	H	B(pin)	Ph	76 (67:33)	153



Scheme 123 Rhodium-catalyzed [4 + 2] annulation reaction of cyclobutenones with alkynes.

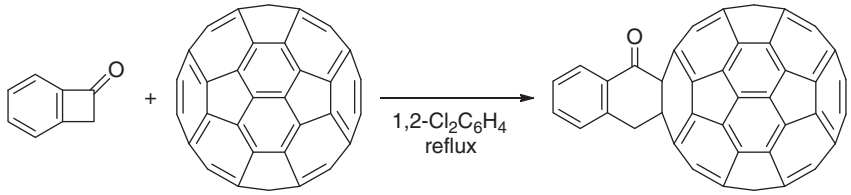


Scheme 124 Rhodium-catalyzed [4 + 2] annulation reaction of cyclobutenones with alkenes.



324 **325** 99%

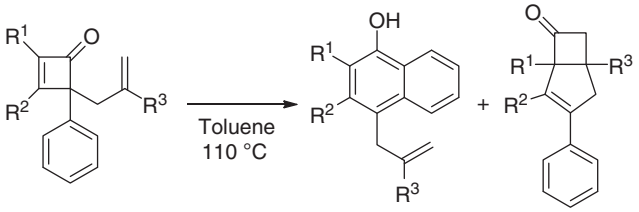
Scheme 125 [4 + 2] Cycloaddition of 2-silylcyclobutenones **324** with TCNE.



326 **327** 49%

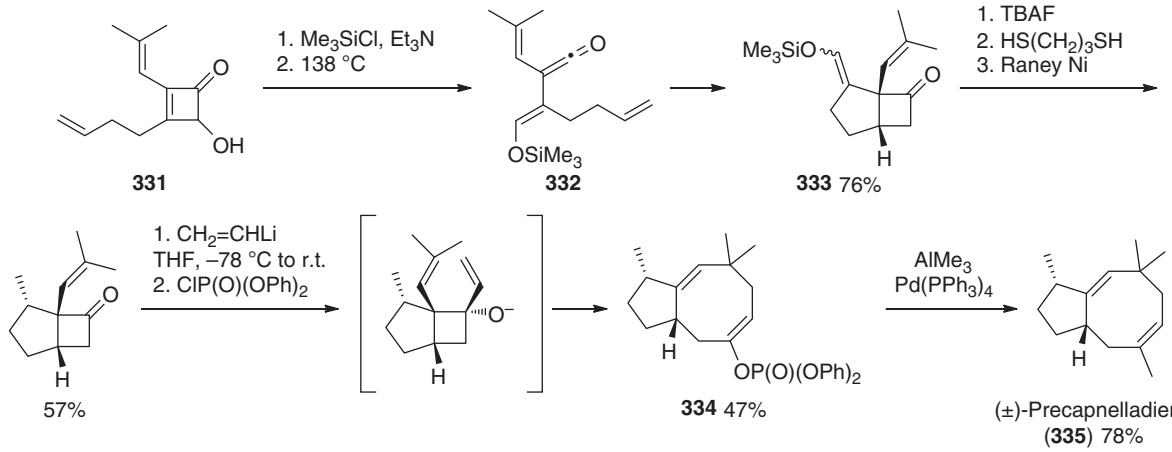
Scheme 126 [4 + 2] Cycloaddition of benzocyclobutenone **326** with C_{60}.

Table 15 6π-Electrocyclization and [2 + 2] cycloaddition of 4-allyl-4-arylcyclobutenones **328**



328 **329** **330**

R^1	R^2	R^3	*Yield (%)*	***329:330***
C≡CBu	O*i*-Pr	H	88	2:1
Ph	O*i*-Pr	H	92	1:2.1
Ph	O*i*-Pr	Me	99	1:4
t-Bu	OMe	Me	98	[2 + 2] only



331 **332** **333** 76%

57% **334** 47% (±)-Precapnelladiene (**335**) 78%

Scheme 127 Synthesis of (±)-precapnelladiene (**335**).

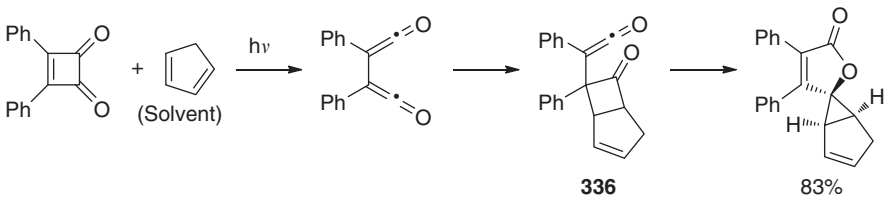
induce an oxy-Cope ring expansion. The resulting enolate was trapped as its diphenyl phosphate derivative to afford **334**. Exposure of **334** to $AlMe_3$ in the presence of catalytic $Pd(PPh_3)_4$ provided (±)-precapnelladiene (**335**).

5.16.5 Cyclobutenediones

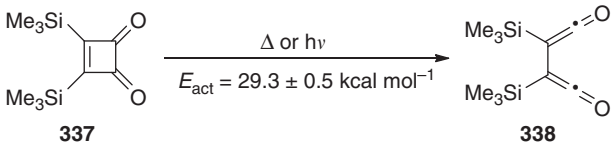
The photoinduced ring opening reaction of cyclobutene-1,2-diones giving 1,2-bisketenes was discovered in 1961.[154] However, 1,2-bisketenes facilely undergo thermal ring closure back to the cyclobutene-1,2-diones. Hence, 1,2-bisketenes have been observed only at low temperatures, mostly in matrices. Tidwell et al. found that bissilyl bisketenes were thermodynamically more stable than the cyclobutenediones at r.t. This finding led them to extensively study the spectroscopic and chemical properties of 1,2-bisketenes.

The irradiation of a variety of substituted cyclobutene-1,2-diones in the presence of cyclopentadiene led to the formation of 1:1 adducts.[155] They result from the cycloaddition of the photochemically generated bisketenes with cyclopentadiene and the following rearrangement of the α-ketenylcyclobutanones **336** (Scheme 128).

Ab initio calculations indicated that bisketene is less stable than cyclobutenedione by only 6.9 kcal mol^{-1}, and that electropositive substituents exert large stabilizing influences on ketenes to favor the acyclic bisketene structure. Heating of 3,4-bis(trimethylsilyl)cyclobutenedione (**337**) at 100 °C for 1 h gave complete conversion to bissilyl bisketene **338** (Scheme 129).[156] Irradiation of **337** with light of 350 nm wavelength for 12 min also formed **338** in 70% yield. Degassed bissilyl bisketene **338** in $CDCl_3$ remained unchanged after 45 days at 2 °C. The kinetics of the conversion of **337** to **338** on heating in



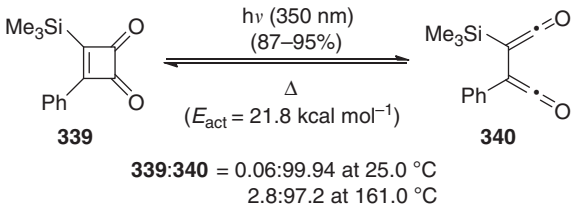
Scheme 128 [2 + 2] Cycloaddition of photochemically generated bisketenes with cyclopentadiene.



Scheme 129 Ring opening of 3,4-bis(trimethylsilyl)cyclobutenedione (**337**).

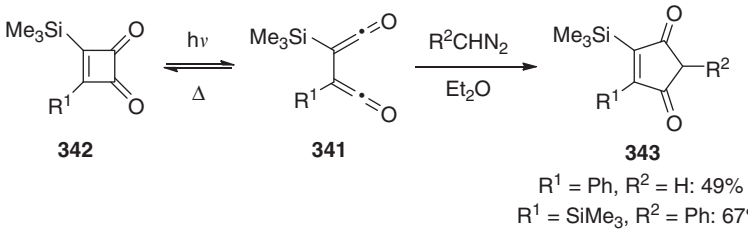
$CDCl_3$ in a sealed tube were monitored by ^1H NMR, which allowed the energy of activation to be determined as $E_{act} = 29.3 \pm 0.5$ kcal mol^{-1}.

The interconversion of cyclobutenediones **339** with the corresponding bisketenes **340** was studied experimentally and theoretically (Scheme 130).[157]



Scheme 130 Interconversion of cyclobutenediones **339** with bisketenes **340**.

[4 + 1] Cycloaddition reactions of bisketenes **341**, generated on photochemical treatment of the corresponding cyclobutenediones **342**, with diazomethanes at r.t. led to the formation of cyclopent-4-ene-1,3-diones **343** (Scheme 131).[158]

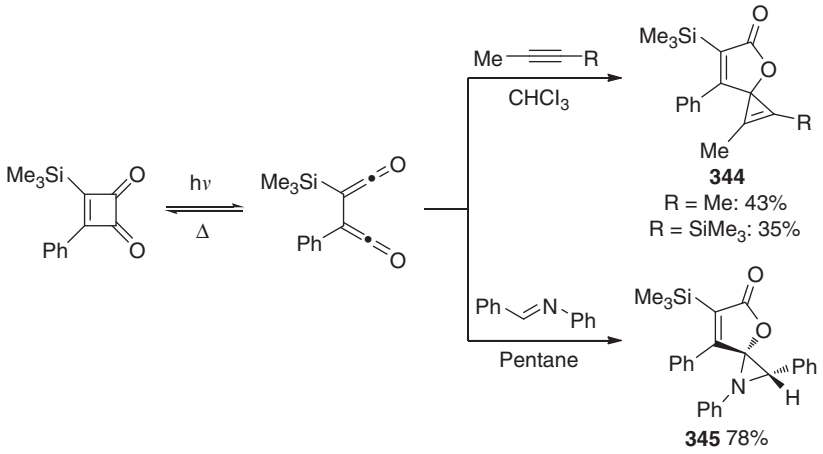


Scheme 131 [4 + 1] Cycloaddition reaction of bisketenes **341** with diazomethanes.

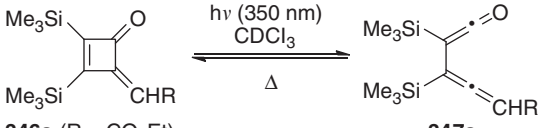
Irradiation of cyclobutenedione with light of 350 nm wavelength at 5 °C for 1 week in the presence of 2-butyne or 1-(trimethylsilyl)propyne furnished the spirocyclic cyclopropenes **344** (Scheme 132).[163] A photochemical reaction of cyclobutenedione formed bisketene, which then reacted with an imine to give spirocyclic aziridine **345** in good yield.[159]

Irradiation of 2,3-bis(trimethylsilyl)-substituted alkylidenecyclobutenones **346** caused quantitative conversion to the allenylketenes **347** which were stable enough to be isolated at r.t. (Scheme 133).[160] As predicted by molecular orbital calculations, the alkylidenecyclobutenones **346** underwent thermal equilibration with the corresponding allenylketenes **347** at 100 °C. The equilibrium constants **346a**:**347a** and **346b**:**347b** were 1.0 and 0.029, respectively. The measured rate constant for the ring opening of the bissilylcyclobutenedione **337** to form the bisketene **338** at 99.0 °C was 9.45×10^{-4} s^{-1} (Scheme 134). It was 110 times greater than that for the ring opening of **346b** at 98.8 °C.

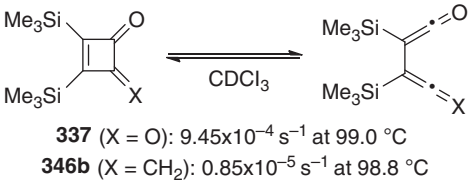
The photochemical reaction of benzocyclobutenedione **348** produceed the bisketene **349** and the carbene **350** (Scheme 135). Benzyne was ultimately produced under matrix conditions. Irradiation of **348**, with light of 290 nm wavelength produced **349**, which was isolated in Ar matrix at 11 K[161]; the isomerization is photoreversible. Thus, photolysis of **349** at $\lambda > 320$ nm regenerated



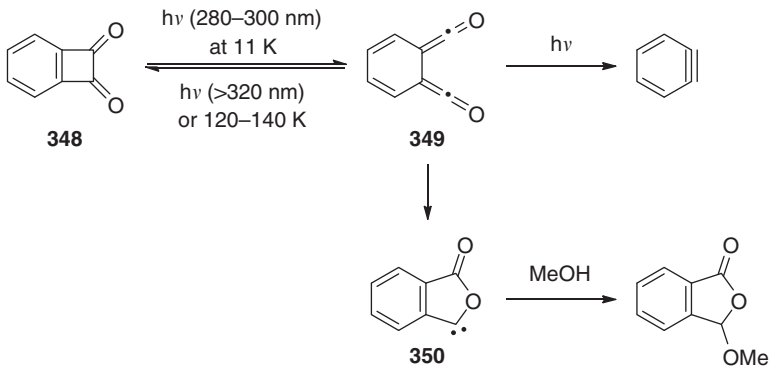
Scheme 132 Photochemical reaction of bisketene with alkynes and inimes.



Scheme 133 Ring opening of alkylidenecyclobutenones **346**.



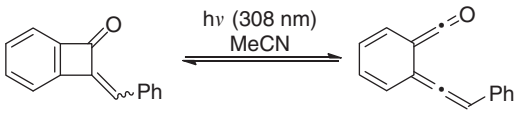
Scheme 134 Ring opening of bissilylcyclobutenedione **337** and alkylidenecyclobutenone **346b**.



Scheme 135 Photochemical reaction of benzocyclobutenedione **348**.

348. It could be repeated several times before the bisketene was finally converted to benzyne. The carbene **350** lived for about 20 μs in toluene and could be trapped by typical carbene scavengers such as alcohols.[162]

A stereoisomeric mixture of the benzylidenebenzocyclobutenone **351** underwent photoinduced isomerization via the intermediate ketene-allene **352**, which had a lifetime of ~26 μs (**Scheme 136**).[163]



351 **352**

Scheme 136 Photoinduced isomerization of benzylidenebenzocyclobutenone **351**.

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5.17 1,3-Cyclohexadiene Formation Reactions: 6π and Higher-Order Electrocyclizations

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Glossary

Cascade/Domino reactions A consecutive series of reactions, wherein each step generates the functionality required for the following reaction.

Density functional theory (DFT) A quantum mechanical modeling method, often used to investigate the electronic structure of molecules computationally.

Electrocyclization, electrocyclic reaction A type of pericyclic reaction, wherein the two termini of a linearly conjugated polyene form a new σ-bond at the expense of a π-bond.

endo*/*exo Stereochemical descriptors that refer to the face a particular substituent lies on in polycyclic ring systems. The convex face, or the side bearing the smaller bridge in bicyclic systems is generally denoted as *exo*, whereas *endo* is commonly used to describe the concave face or the side possessing the larger bridge in bicyclic systems.

Pericyclic reaction A reaction that occurs with a cyclic transition state and simultaneous, concerted bond-breaking/bond-forming events.

Torquoselectivity The rotational stereoselectivity (inward vs. outward directed rotation) of substituents in controtatory or disrotatory electrocyclic reactions.

Woodward–Hoffmann rules A set of rules based on orbital symmetry that allow, inter alia, for predicting the stereochemical course of pericyclic reactions.

5.17.1 Introduction

An important subclass of pericyclic reactions, 6π electrocyclizations can be used to form six-membered rings with predictable stereochemistry and high levels of selectivity. Of historical significance, the reaction's discovery was implicated in the formulation of the Woodward–Hoffmann rules,[1] but only in more recent years has this reaction class begun to enjoy a more prominent role in organic synthesis. Since the vital role played by pericyclic reactions in vitamin D biosynthesis was elucidated,[2] numerous examples of electrocyclic reactions participating in biosynthetic pathways have been identified,[3] often seen in reaction cascades that rapidly generate molecular complexity.

This review aims to underscore the growing significance of this reaction class as a useful synthetic tool for six-membered ring formation, and does not cover electrocyclic ring-opening reactions. It is organized by first examining all-carbon systems, discussing general reactivity and stereoselectivity, before moving on to cases that include oxygen and nitrogen. Finally, since higher order 8π electrocyclizations are often followed by 6π electrocyclic ring closure, these reaction cascades will receive special attention, highlighting their proposed involvement in the biogenesis of various natural products. While this chapter is certainly

not a comprehensive account on 6π electrocyclization reactions, the reader is referred to a number of excellent reviews already published on this topic.[4] The rules of the conservation of orbital symmetry will not be detailed here either, instead the authors wish to provide a simple reminder of the stereochemical course of thermal and photochemical electrocyclization reactions in the ground and first excited states (Table 1).

Table 1 Summary of rotational stereoselectivity in electrocyclization reactions

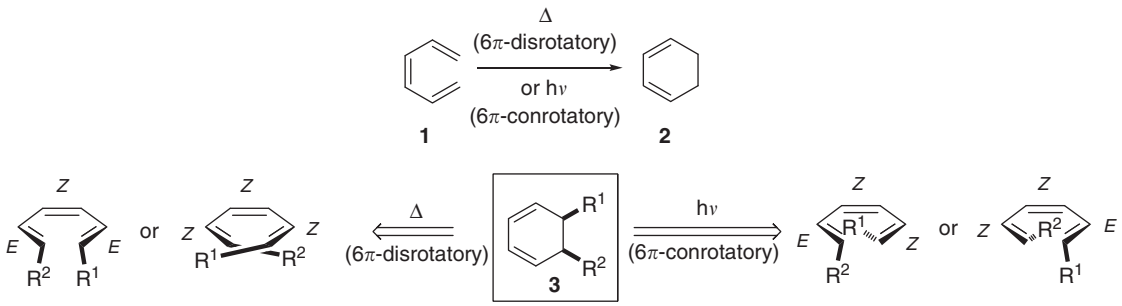
Number of electrons	*Thermal*	*Photochemical*
4π	Conrotatory	Disrotatory
6π	Disrotatory	Conrotatory
8π	Conrotatory	Disrotatory

Source: Reproduced from Beaudry, C.; Malerich, J.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

5.17.2 6π Electrocyclizations of 1,3,5-Hexatrienes

5.17.2.1 General Reactivity of 1,3,5-Hexatriene Systems

In its simplest form, 6π electrocyclic ring closure is the isomerization of a (3*Z*)-1,3,5-hexatriene **1** to a 1,3-cyclohexadiene **2** either thermally or photochemically, generating a σ–bond at the expense of a π–bond (Scheme 1). Retrosynthetically, a simple unsymmetrical 1,3-cyclohexadiene **3** can potentially arise from any of four different 1,3,5-hexatriene geometric isomers, all possessing a (*Z*)-configured central alkene, depending on the reaction conditions employed (thermal or photochemical) and on the torquoselectivity.[5] This powerful transformation, which forms six-membered rings with high stereochemical fidelity, has been underused in target-oriented synthesis compared to other pericyclic processes, such as the Diels–Alder reaction (*see* Chapters 5.09, 5.10, 5.11, 5.12, and 5.21) or sigmatropic rearrangements.[6] Since the discovery of 6π electrocyclizations in the early 1960s,[7] the limited development of related synthetic methodologies has been ascribed to the difficulties associated with preparing 1,3,5-hexatrienes with stereochemically defined alkene geometries, as well as the high thermal barrier of the ring-closing reaction (often requiring >150 –200 °C), bringing with it problems concerning functional group tolerance and competing pericyclic side-reactions, chiefly [1,5]- and [1,7]-hydrogen shifts.[4,8] In recent decades, however, the problem of olefin geometry control has been largely overcome with the advent of modern transition-metal mediated cross-coupling reactions, enabling numerous studies that have culminated in an understanding of several factors that accelerate thermal ring closure.



Scheme 1 The 6π electrocyclization manifold.

The discovery of various 1,3,5-hexatriene systems that undergo facile ring closure (*vide infra*) has provided the impetus for theoretical investigations into the rate-enhancing effects of substituents that perturb the electronics of the triene system.[9] In congruence with experimental evidence, the results of several computational studies using density functional theory (DFT) and MP2 methods have identified that introducing an electron-withdrawing substituent (CO_2Me, NO_2, SO_2Ph or $C{=}N^+Me_2$) at the 2-position has a profound effect on the rate of cyclization, capable of decreasing the activation energy barrier by up to 7–25 kcal mol^{-1}.[10] Furthermore, tactical positioning of electron acceptor/donor groups has been forecasted to drastically increase the rate of 6π electrocyclization, predicting that ring closure could occur even at room temperature in some cases. This acceleration has been attributed to a captodative[11] effect, which results in favorable electronic interactions that are stronger in the transition state than in the reactant structure (Figure 1).[9]

A steric or geometric bias that stabilizes or preorganizes the reactive triene s-*cis* conformation can significantly improve the rate of electrocyclization, as observed in 8π-6π reaction cascades that take place under relatively mild conditions, as well as in some extreme cases of steric confinement, where even symmetry disallowed electrocyclizations (i.e. thermal 6π conrotatory) have been observed due to geometrical constraints preventing the normal symmetry-allowed pathway from occurring.[12] Additionally,

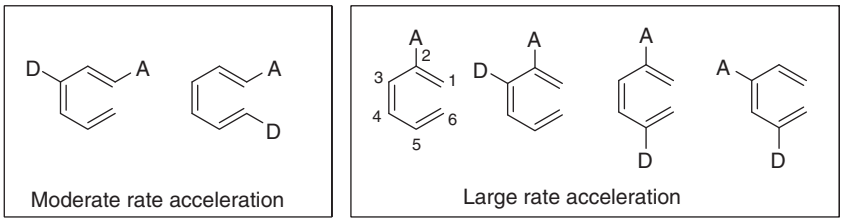
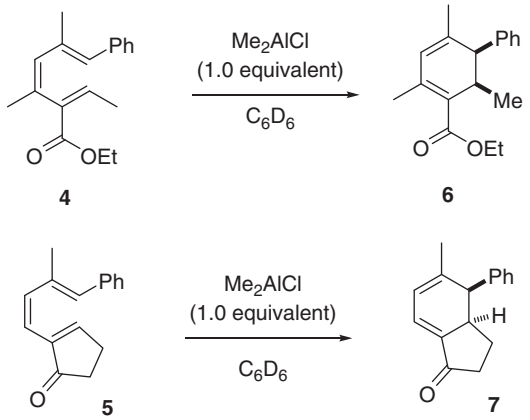


Figure 1 Substituent effects on 6π electrocyclizations of 1,3,5-hexatrienes. Reproduced from Yu, T.; Fu, Y.; Lei, L.; Guo, Q. *J. Org. Chem.* **2006**, *71*, 6157.

reactions that either liberate strain energy or gain in aromatic stabilization energy on ring closure often proceed at lower temperatures.[4a] Conversely however, it has been demonstrated that substitution at the termini of 1,3,5-triene systems typically results in reduced reaction rates by raising the kinetic barrier toward cyclization, energetically disfavoring the reactive conformation and in some cases facilitating alkene isomerization via [1,7]-H shifts.[4a]

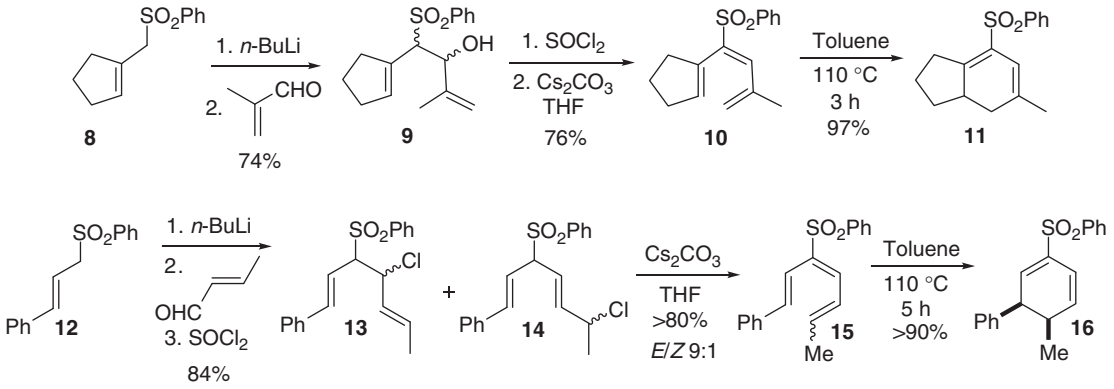
A number of potential avenues exist for catalyzing 6π electrocyclizations of 1,3,5-hexatrienes.[13] One theoretical study using the B3LYP/6–311G* method predicted a significant drop in activation energy (>10 kcal mol^{-1}) for the electrocyclic ring closure of 1,3,5-hexatriene **1** to 1,3-cyclohexadiene **2** by Li^+ complexation through an electrostatic interaction that was proposed to stabilize the transition state.[14] Transition metals have also proven capable of directly complexing the transition states of related pericyclic reactions.[15] For 1,3,5-hexatriene systems that bear substituents, catalysis by Lewis/Brønsted acids or hydrogen-bonding catalysts are viable concepts. Proof of principle was only recently demonstrated by using an aluminum Lewis acid to accelerate the ring closure of 2-carboxy substituted trienes **4** and **5**.[10c] Specifically, in the presence of one equivalent of Me_2AlCl, rate enhancements of 13- and 55-fold were observed for the formation of cyclohexadienes **6** and **7** respectively, each arising from the expected thermal disrotatory pathway (Scheme 2). Varying the Me_2AlCl concentration gave evidence of catalytic turnover, but catalyst loadings of at least 17 mol% were required to increase the reaction rate. Somewhat more recently, a screening of Lewis acid additives revealed that $MeAlI_2$ promotes the same electrocyclization of triene **5** with a 600-fold rate increase over the uncatalyzed reaction.[16] This study also established the first example of a catalytic asymmetric carba-6π electrocyclization by exposing triene **5** to a chiral Lewis acid, albeit only modest enantioselectivities were observed (57–77% *ee*). Still, there is room for development and these preliminary findings have provided a starting point for the design of practical catalytic asymmetric methodologies.



Scheme 2 Lewis acid catalysis of 6π electrocyclizations. Reproduced from Bishop, L.; Barbarow, J.; Bergman, R. G.; Trauner, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8100.

5.17.2.2 Electrocyclization as a Tool for the Synthesis of Six-Membered Rings

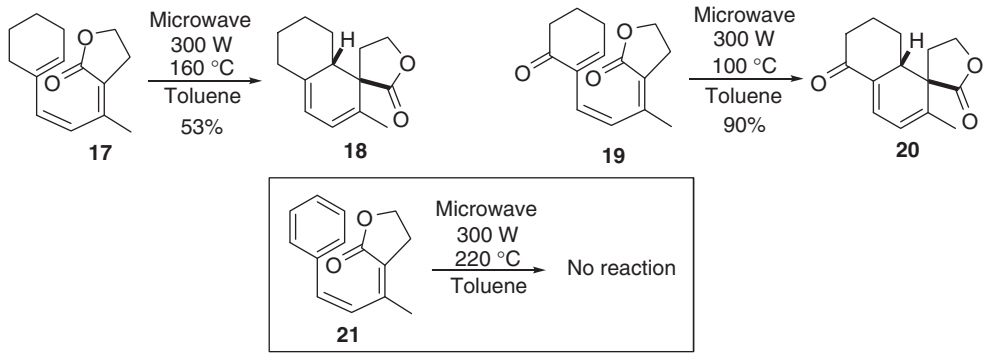
6π Electrocyclizations, although not as powerful as the Diels—Alder reaction, do provide a versatile and practical approach to functionalized six-membered rings, provided the precursor triene can be efficiently constructed. In a recent example, the phenylsulfonyl substituent acts as a versatile synthetic handle that serves a multipurpose role for the construction of six-membered carbocycles via 6π electrocyclizations.[17] In a manner reminiscent of Julia-Lythgoe olefination, (3*E*)-3-phenysulfonyl hexatrienes **10** and **15** with excellent isomeric purity for the central alkene ($>98\%$) were synthesized by α-lithiation of the corresponding allyl sulfones **8** and **12**, followed by trapping with an α,β-unsaturated aldehyde and subsequent dehydration (Scheme 3). The resulting triene systems **10** and **15** were sufficiently activated by the phenylsulfonyl group to afford 6π electrocyclization adducts **11** and **16**



Scheme 3 6π electrocyclization of 3-sulfonyl-1,3–5-hexatrienes. Reproduced from Brändage, S.; Leijonmarck, H. *Chem. Commun.* **2004**, 292.

in superb yields under relatively mild conditions in refluxing toluene. The products are 1,3-cyclohexadienes that are susceptible to further regioselective manipulations, possessing two electronically differentiated alkenes and a flexible, easily modified functional group.[18]

A clear manifestation of electronic effects can be seen from the attempted 6π electrocyclization of various 1,3,5-hexatrienes with an incorporated γ-lactone moiety (Scheme 4).[19] Lactone **17** successfully underwent thermal disrotatory electrocyclization to 1,3-diene **18** in modest yield by microwave irradiation at 160 °C, whereas inclusion of an electron-withdrawing group at the 2-position, as in enone **19**, led to a drastic rate improvement, requiring only 100 °C to deliver 1,3-diene **20** in 90% yield. However, lactone **21**, in which the triene system is embedded within an aromatic ring, did not engage in electrocyclic ring closure, even when submitted to forcing conditions (thermally at 220 °C, flash vacuum pyrolysis at up to 600 °C or photochemically by irradiation at 254 nm, with or without I_2 present). This was presumably due to the unfavorable energetics concordant with a loss of aromaticity.

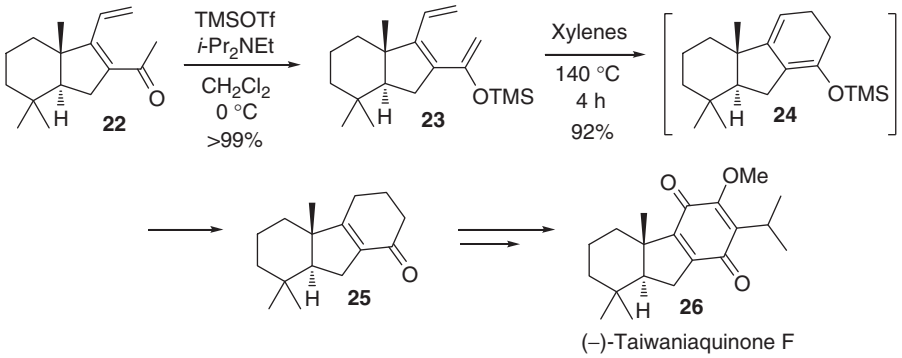


Scheme 4 Formation of 2-oxospiro[4.5]decanones by 6π electrocyclization. Reproduced from Pouwer, R.; Schill, H.; Williams, C.; Bernhardt, P. *Eur. J. Org. Chem.* **2007**, 4699.

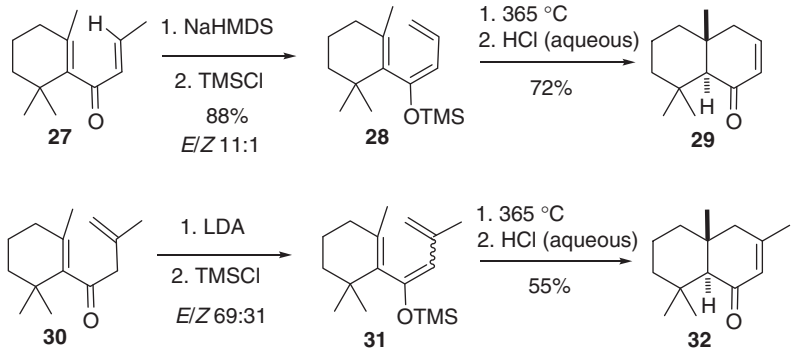
One simple solution to constrain the requisite central *cis*-alkene geometry is to include the double bond within a cyclic system. Such an approach was utilized for the synthesis of several taiwaniaquinoids that featured a 6π electrocyclization as the key step (Scheme 5).[20] Dienone **22**, derived from the chiral pool building-block (+)-sclareolide, was transformed into silyl enol ether **23**, which smoothly underwent electrocyclic ring closure in refluxing xylenes to give enone **25** via 1,3-diene **24**, indicating that compounds possessing a strong electron donor at the 2-position can also undergo electrocyclization with reasonable reaction rates, provided the triene is preorganized.

Similarly, γ-deprotonation of the divinyl ketone **27** or α-deprotonation of the allyl vinyl ketone **30** can give rise to 3-oxo-substituted 1,3,5-hexatrienes **28** and **31** respectively, with modest to good *E*/*Z* selectivity (Scheme 6).[21] Pyrolysis of the silyl enol ethers **28** and **31** in a quartz tube at 365 °C led to electrocyclic ring closure and upon acidic aqueous workup, *trans*-decalones **29** and **32** could be isolated in moderate yield. In contrast to the relatively facile 6π electrocyclization of the 2-oxo-1,3,5-hexatriene **23** (Scheme 5), the cyclization of 3-oxo-1,3,5-hexatrienes **28** and **31** required much higher reaction temperatures, underscoring the importance of substituent effects in these systems.

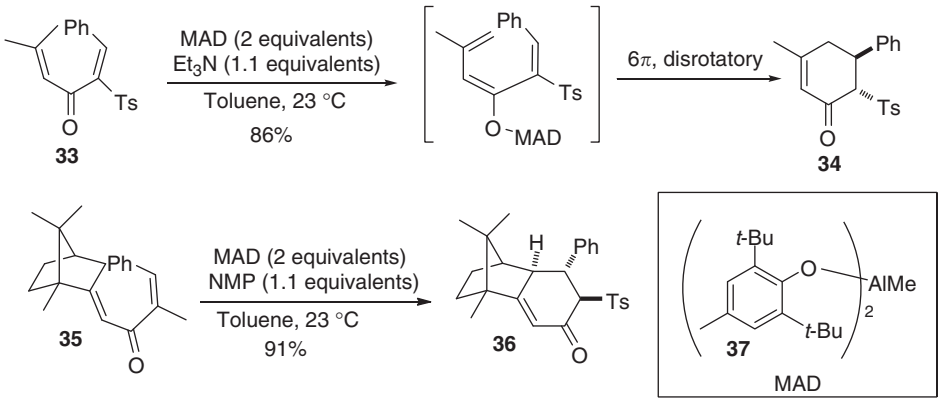
In contrast to the previous example, exceptionally rapid 6π electrocyclizations are observed for 3-oxidohexatrienes bearing an electron-withdrawing group in the 2-position, which can be produced from 2-sulfonylated divinyl ketones **33** and **35** by γ-deprotonation (Scheme 7).[22] Using a bulky aluminum Lewis acid (**37**) and a weak amine base to ensure formation of the required *E*-enolate, disrotatory 6π electrocyclic ring closure proceeded with remarkable efficiency at room temperature, furnishing *trans*-enones **34** and **36** after diastereoselective protonation during the aqueous workup. Alternatively, similar 3-oxidotriene



Scheme 5 Synthesis of the taiwaniaquinoids using a 6π electrocyclization strategy. Adapted from Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; *et al. Chem. Commun.* **2009**, 592, and Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; *et al. Org. Biomol. Chem.* **2009**, *7*, 5146.

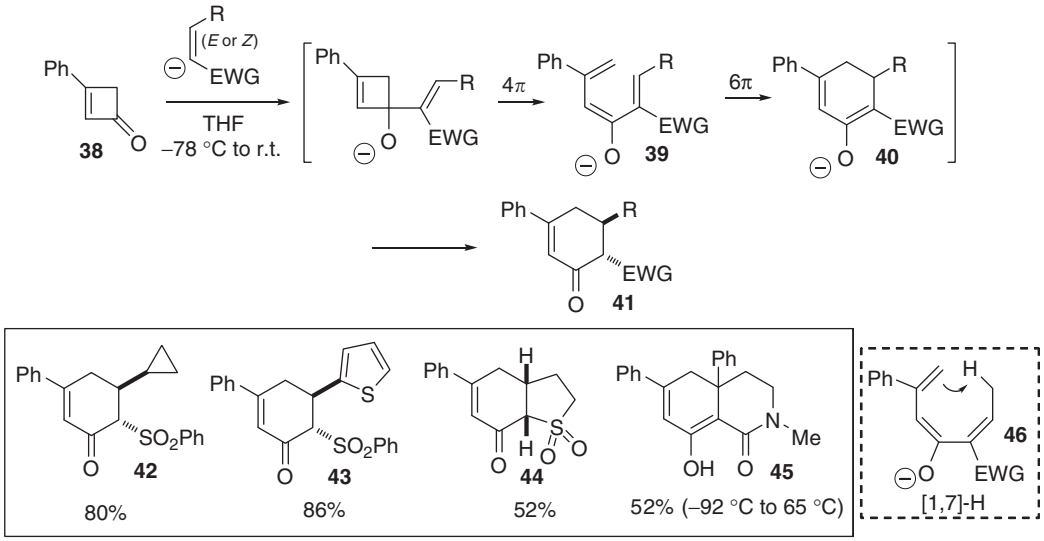


Scheme 6 Preparation of 3-oxo-1,3,5-hexatriene systems by deprotonation/trapping. Reproduced from Fehr, C.; Galindo, J.; Guntern, O. *Tetrahedron Lett.* **1990**, *31*, 4021.



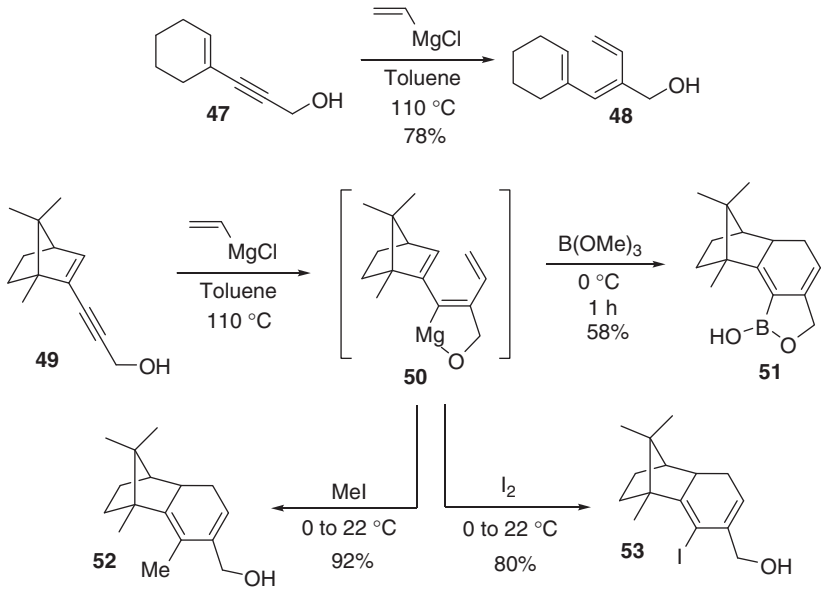
Scheme 7 6π electrocyclization of 2-sulfonyl-3-oxidohexatrienes generated via γ-deprotonation. Reproduced from Magomedov, N.; Ruggiero, P.; Tang, Y. *Org. Lett.* **2004**, *6*, 3373.

intermediates of type **39** can be generated *in situ* by addition of an appropriate nucleophile to cyclobutenone **38**, triggering a conrotatory 4π electrocyclic ring-opening (*see* Chapter 5.16) driven by the release of ring strain, occurring with outward rotation of the oxide group to form the desired (*E*)-enolate (Scheme 8).[23] Intermediate 3-oxidotriene **39** can be anticipated to undergo facile 6π electrocyclic ring closure since it would lead to 1,3-diene **40**, which is the more stable enolate anion. Notably, the presence of an electron-withdrawing group is essential for the 6π cyclization to occur, evidenced by the addition of β-(*E*)-lithiostyrene to cyclobutenone **38**, wherein the reaction cascade stops after the cyclobutene ring-opening step. Protonation of the intermediary enolate **40** then gives access to various substituted cyclohexenones **41**, overall using very mild conditions. Interestingly, it was found that substrates bearing allylic hydrogens *trans* to the electron-withdrawing group, as in enolate **46**, preferentially underwent a [1,7]-H shift over 6π electrocyclization. The exception to this was cyclopropane **42**, where a [1,7]-H shift would have produced a highly strained methylenecyclopropane.



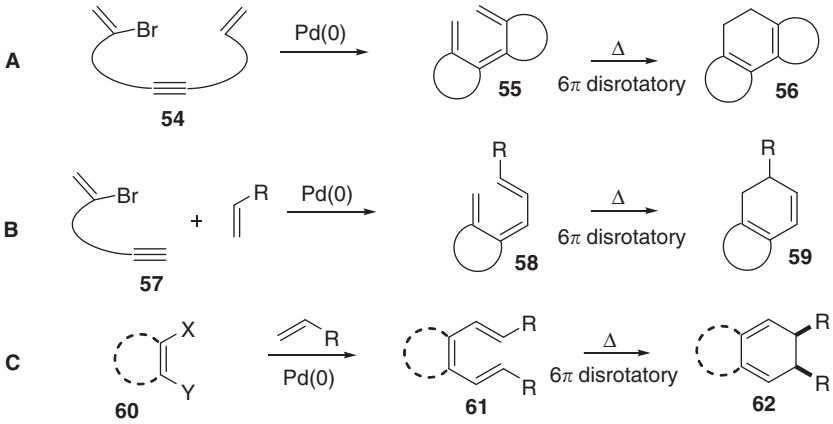
Scheme 8 Conversion of cyclobutenones to cyclohexenones using a 4π/6π electrocyclization cascade. Reproduced from Magomedov, N.; Ruggiero, P.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624.

The carbomagnesation of 4-vinyl propargyl alcohols offers convenient access into 1,3,5-hexatrienes with complete control of the central alkene geometry. Treating propargyl alcohol **47** with vinyl magnesium chloride in refluxing toluene furnishes 1,3,5-hexatriene **48** in good yield; however, subsequent 6π electrocyclization proceeded rather inefficiently, requiring a reaction temperature of 250 °C (Scheme 9).[24] However, unusually facile cyclization was observed employing [2.2.1] bicyclic systems such as alcohol **49**, which underwent *in situ* 6π electrocyclic ring closure from the *exo* face via magnesium chelate **50** that afterward could be quenched with a variety of different electrophiles to afford functionalized 1,3-cyclohexadienes. The rapidity of the electrocyclization has been ascribed to the rigidity of the magnesium-chelated [2.2.1] bicyclic system. Additionally, the alleviation of ring strain from the norbornene-type system may play a role in enhancing the rate.



Scheme 9 Carbometallation with vinyl Grignard reagents as an entry to 1,3,5-hexatriene systems. Reproduced from Tessier, P.; Nguyen, N.; Clay, M.; Fallis, A. *Org. Lett.* **2005**, *7*, 767.

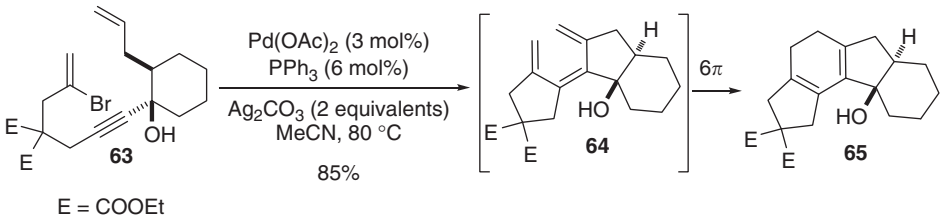
As a powerful $C(sp^2) - C(sp^2)$ bond forming method, the Heck reaction can be applied to construct 1,3,5-hexatriene systems for 6π electrocyclization using three general strategies (Scheme 10).[25] First, the all-intramolecular approach (**A**) starting from a bromodienyne **54** would, following oxidative insertion of Pd(0), proceed with *syn* carbopalladation of the alkyne to give the required *cis*-alkene geometry and lastly undergo an intramolecular Heck reaction to deliver bicyclic 1,3,5-triene **55**. This substrate class would be fixed in the s-*cis* conformation, a feature expected to greatly facilitate its electrocyclic ring closure. Second,



Scheme 10 Array of possible domino Heck reaction/6π electrocyclization cascades. Reproduced from de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413.

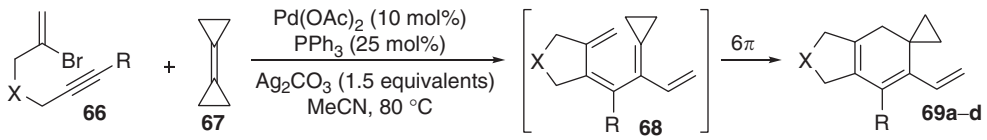
an intra-intermolecular design (**B**) would involve termination of the cascade with an external Heck acceptor, yielding triene **58** with one newly formed ring. Finally, an all-intermolecular process would employ a 1,2-difunctionalized *cis*-alkene **60** that could either participate in a double Heck reaction or in two sequential Heck reactions to build up a 1,3,5-hexatriene of type **61**. Each of these approaches has been explored and will be highlighted in the following examples.

Exposure of vinyl bromide **63** to catalytic $Pd(OAc)_2/PPh_3$ resulted in an efficient threefold domino sequence, featuring two successive intramolecular Heck reactions and ending with a 6π electrocyclization (Scheme 11).[26] Most remarkably, the final cyclization was effected at only 80 °C, ascribed to the enforced s-*cis*/s-*cis* conformation of triene **64**. The addition of either a Ag(I) or Tl(I) salt was necessary to prevent palladium-mediated alkene isomerizations in triene **64** prior to the 6π electrocyclic ring closure.



Scheme 11 Intramolecular Heck cascade terminated by a 6π electrocyclization. Reproduced from Meyer, F. E.; Brandenburg, J.; Parsons, P. J.; de Meijere, *A. Chem. Commun.* **1992**, 390.

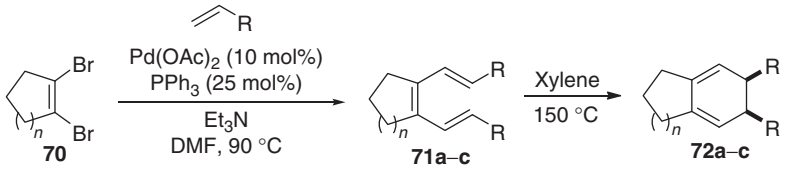
Employing very similar reaction conditions, vinyl bromides of type **66** underwent palladium-mediated cyclization and trapping by an external Heck acceptor, that is the highly strained methylenecyclopropane **67**, producing an intermediate triene **68** after cyclopropane ring-opening and β-hydride elimination (Scheme 12).[27] Again, facile 6π electrocyclization was observed, occurring at only 80 °C, owing to both the relative conformational inflexibility of the intermediate methylenecyclopropane **68**, as well as the significant liberation of strain energy upon ring closure to form spirocyclic cyclopropanes of type **69**.



69	X	R	Yield (%)
a	$C(COOMe)_2$	*t*-Bu	56
b	$C(COOMe)_2$	TBS	65
c	O	Ph	71
d	NTs	Ph	44

Scheme 12 Intra-intermolecular Heck/6π electrocyclization leading to spirocylic cyclopropanes. Reproduced from Schelper, M.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 582.

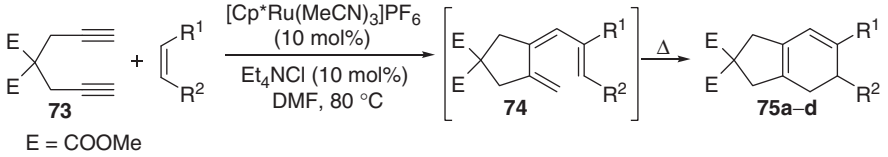
The double Heck reaction of cyclic 1,2-dibromo alkenes **70** represents a general method to access 1,3,5-hexatrienes **71**, possessing *cis* central alkene geometry and identical groups at the termini of the triene system (Scheme 13).[28] In contrast to the previous two examples, due to the conformational flexibility of such hexatrienes **71**, higher temperatures (150 °C) were found to be required for their efficient electrocyclic ring closure.



72a: *n* = 1; R = COOMe; 94%
72b: *n* = 1; R = Ph; 50%
72c: *n* = 2; R = COOMe; 89%

Scheme 13 1,3,5-Hexatriene synthesis by double Heck reaction of 1,2-dibromo alkenes. Reproduced from Voigt, K.; Lansky, A.; Noltenmeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521.

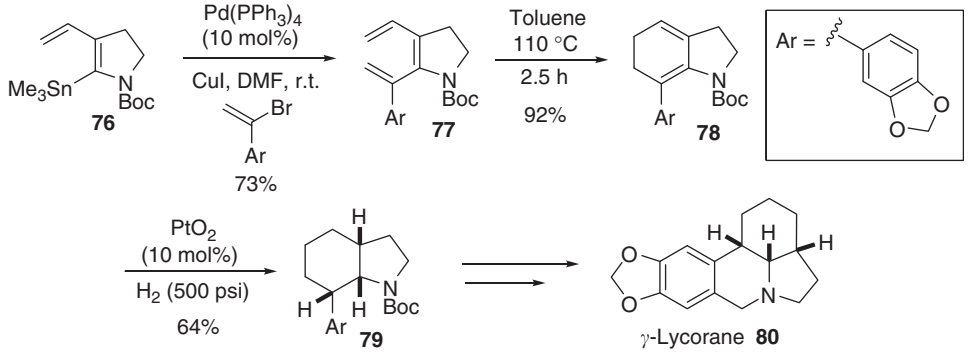
Monocyclic 1,3,5-triene intermediates such as **74**, bearing similarities to methylenecyclopropanes **68** (Scheme 12), can be prepared transiently by the ruthenium-catalyzed coupling of a diyne **73** and an acyclic (*Z*)-alkene (Scheme 14).[29] The coupling is regioselective, provided the alkene substituents are sufficiently different, sterically and electronically. The relatively mild conditions needed for the subsequent electrocyclization to cyclohexadienes **75**, similar to the related examples already presented, is likely due to the geometry of the triene intermediates. Examples **75a–c** would be expected to exhibit particularly rapid electrocyclic ring-closing, since they possess both an electron acceptor in the 2-position and an electron donor in the 5-position of their triene **74** progenitors. Interestingly, when cyclic alkenes were used instead, a [2 + 2 + 2] mechanism was found to be operative that yielded isomeric 1,3-cyclohexadiene products.[30]



75	R^1	R^2	Yield (%)
a	COOMe	H	62
b	CN	H	46
c	COOMe	COOMe	61
d	CH_2OTMS	H	58

Scheme 14 Ru-catalyzed diyne-alkene coupling/6π electrocyclization cascade. Reproduced from Varela, J.; Rubin, S.; González-Rodriguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9262.

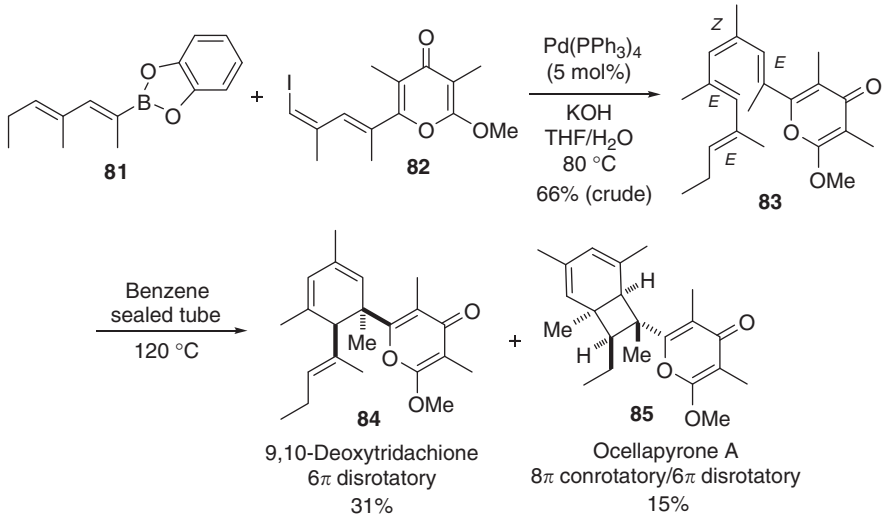
Tactical substrate design can render the 6π electrocyclization a valuable synthetic tool for 6-membered ring annulation, as seen in a recent total synthesis of γ-lycorane **80** (Scheme 15).[31] 3-Amino-1,3,5-trienes, such as **77**, conveniently accessible by Stille



Scheme 15 The total synthesis of γ-lycorane featuring a 6π electrocyclization as the key step. Reproduced from Huntley, R.; Funk, R. L. *Tetrahedron Lett.* **2011**, *52*, 6671.

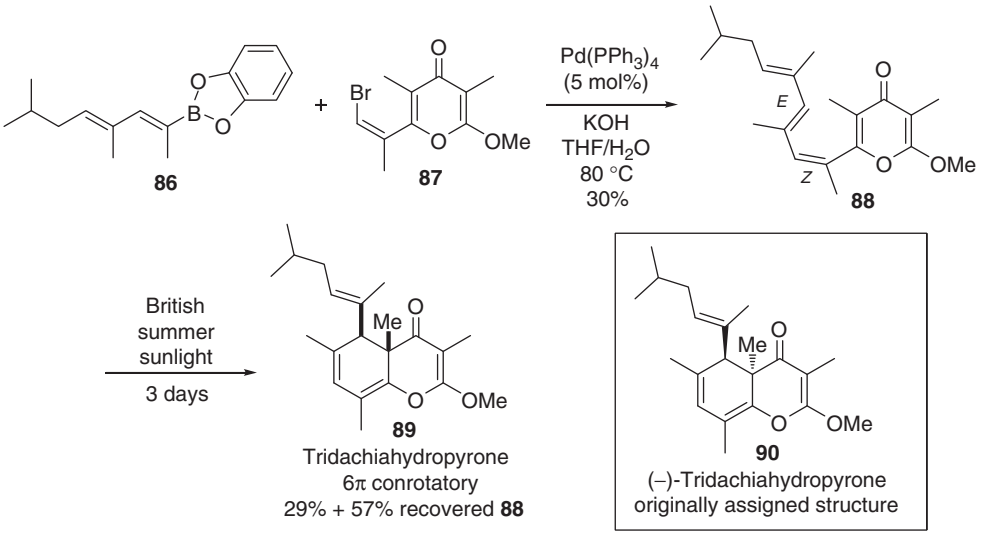
coupling between a vinyl stannane **76** and a vinyl bromide, have been found to undergo electrocyclic ring-closing under comparatively mild conditions (*vide infra*). Simply refluxing a toluene solution of amino-triene **77** for 2.5 h yielded 1,3-cyclohexadiene **78** in 92% yield. High-pressure hydrogenation afforded a single diastereomer of tetrahydroindole **78** that was later transformed into (±)-γ-lycorane **80** in two steps.

A family of γ-pyrone containing polyketide natural products, originating from molluscs of the order *Sacoglossa*, are proposed to feature various electrocyclization modes in their biosynthesis.[32] One natural product of this class, (±)-9,10-deoxytridachione **84**, was prepared in a highly convergent manner by a biomimetic cross-coupling/electrocyclization approach (Scheme 16).[33] Along these lines, a Suzuki coupling of vinyl boronate **81** and vinyl iodide **82** gave crude (*E*,*Z*,*E*,*E*)-tetraene **83**, which on heating in a benzene solution, underwent disrotatory 6π electrocyclic ring closure to afford the desired γ-pyrone natural product **84** in 31% yield. In addition, cyclohexadiene **85**, the product of alkene isomerization and a subsequent 8π/6π electrocyclization cascade, was also obtained from the reaction mixture in 15% yield and was later isolated as a natural product itself.



Scheme 16 The biomimetic synthesis of deoxytridachione and ocellapyrone A. Reproduced from Rodriguez, R.; Adlington, R.; Eade, S.; *et al. Tetrahedron* **2007**, *63*, 4500.

A unique member of the tridachiapyrone natural products, tridachiahydropyrone **89**, possesses a rearranged polypropionate skeleton and appears to result from a 6π electrocyclization that involves the γ-pyrone ring (Scheme 17).[34] Its structure was originally assigned as compound **90** (Scheme 17), the expected product from a thermal disrotatory 6π electrocyclic ring closure. However, a total synthesis of compound **90** called this structural assignment into question and instead suggested



Scheme 17 The biomimetic synthesis and structural revision of tridachiahydropyrone. Reproduced from Sharma, P.; Griffiths, N.; Moses, J. *Org. Lett.* **2008**, *10*, 4025.

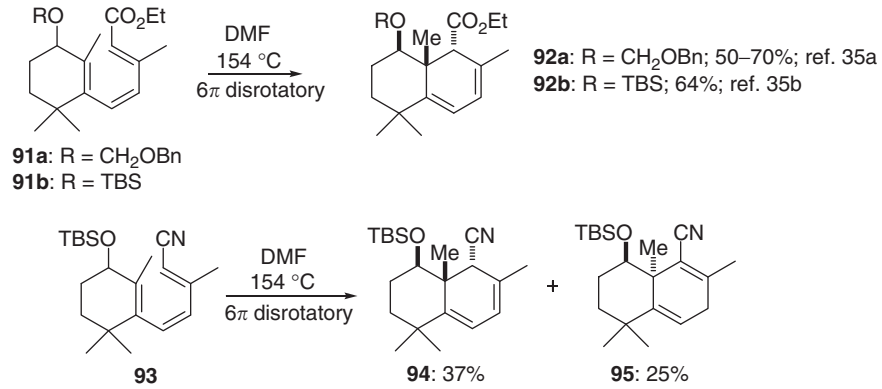
tridachiahydropyrone **89** as the true structure. This was later successfully confirmed by a total synthesis relying on a photochemical conrotatory 6π electrocyclization of γ-pyrone **88**, which was assembled in modest yield via the Suzuki coupling of vinyl boronate **86** with vinyl bromide **87**.

5.17.2.3 Asymmetric Reactions: Induced Diastereoselectivity

5.17.2.3.1 Thermochemical processes

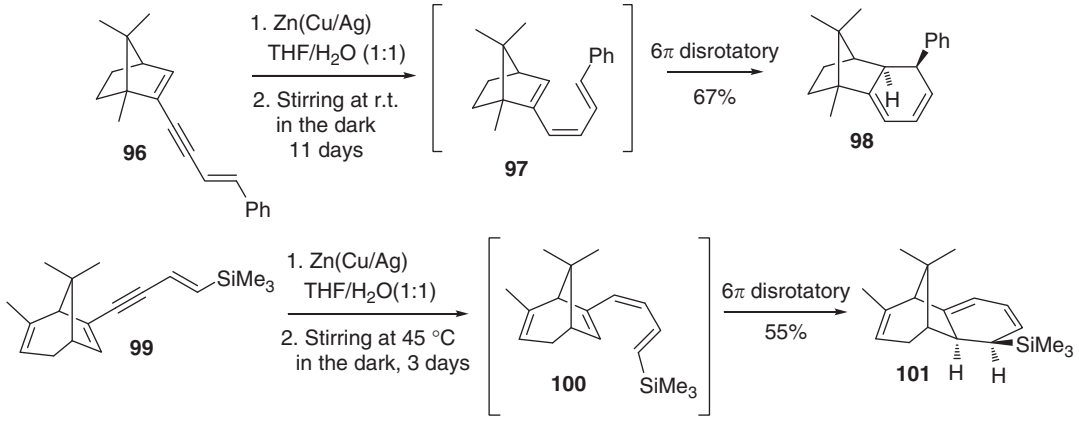
Compared to other pericyclic reaction manifolds, the development of enantioselective 6π electrocyclization methodologies has received scant attention, especially the all-carbon 1,3,5-hexatriene systems. By contrast, the diastereoselectivities of these reactions has received much more attention. Although the simple diastereoselectivity is governed by the Woodward–Hoffmann rules and can be predicted with high fidelity, the induced diastereoselectivity is more involved. Although there remains no general method for stereocontrol of such reactions, it is an active area of research with valuable potential applications in synthesis.

The electrocyclization products of β-ionone-derived esters **91a** and **91b** were obtained as single diastereomers and have served as building blocks for natural product synthesis,[35] demonstrating that torquoselective 6π electrocyclic ring closure can be directed by a stereocenter with a sufficiently bulky substituent at the triene terminus (Scheme 18). However, when the analogous nitrile-substituted triene **93** was submitted to the same conditions, both 1,3-diene **94** and 1,4-diene **95** (from alkene migration postelectrocylization) were isolated in similar quantities, indicating the reaction had proceeded with very little diastereoselectivity. This lack of selectivity was attributed to the nitrile functional group possessing a much smaller steric footprint compared to the ethyl ester, highlighting the subtle nuances involved in the stereocontrol of these systems, which often must be considered on a substrate-to-substrate basis.



Scheme 18 Diastereoselective 6π electrocyclizations of β-ionone derivatives. Adapted from Venkataraman, H.; Cha, J. K. *J. Org. Chem.* **1989**, *54*, 2505, and Jung, M. E.; Min, S.-E. *Tetrahedron* **2007**, *63*, 3682.

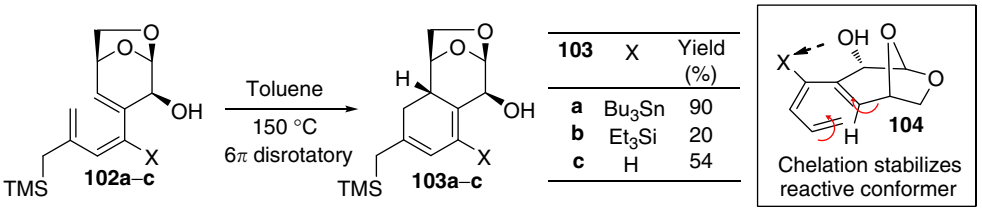
Annexing the 1,3,5-hexatriene motif with a chiral strained bicyclic alkene can allow for highly stereoselective 6π electrocyclizations, as in the case of the camphor-derivative **97** or the [3.2.1] bicycle **100** that were prepared by the stereoselective half-reduction of dienynes **96** and **99** respectively, using zinc activated by $Cu(OAc)_2$ and $AgNO_3$ (Scheme 19).[36] Strikingly, the ensuing electrocyclizations took place efficiently at room temperature, or at slightly elevated temperatures, but did require particularly long



Scheme 19 Strained bicyclic alkenes as a steric buttress for diastereoselective 6π electrocyclizations. Reproduced from Benson, C. L.; West, F. G. *Org. Lett.* **2007**, *9*, 2545.

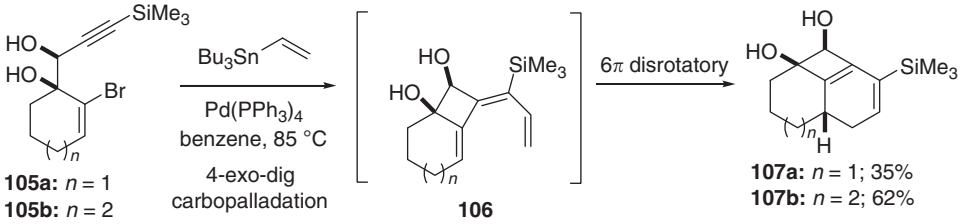
reaction times. The bicycle likely imposes a rotational barrier on the appended carbon chain, thereby increasing the population of the reactive s-*cis* conformer. A possible cooperative driving force may be the release of ring strain in transitioning from an endocyclic alkene, such as **97**, to an exocyclic alkene **98**. In general, the 6π electrocyclization occurred from the *exo* face of the bicycle with complete diastereoselectivity in compliance with the expected mode of disrotatory ring closure.

An interesting torquoselective 6π electrocyclic ring closure was employed in studies toward the asymmetric total synthesis of potent sodium channel blocker tetrodotoxin (Scheme 20).[37] Trienes **102a–c** were found to undergo electrocyclization stereoselectively from the *exo* face of the bicyclic acetal moiety. A chelation model **104** was suggested, since the nature of the substituent X neighboring the free alcohol had a profound effect on the reaction yield. It was proposed that when X = $SnBu_3$ (**102**), the free alcohol is able to form a rigid chelate, increasing the population of the s-*cis* conformer required for cyclization. Indeed, replacement by X = H (**102c**) negatively impacted the yield, whereas the use of a bulky nonchelating group that would be expected to disfavor the s-*cis* conformation, such as X = $SiEt_3$ (**102b**), resulted in a marked decline in reaction efficiency.



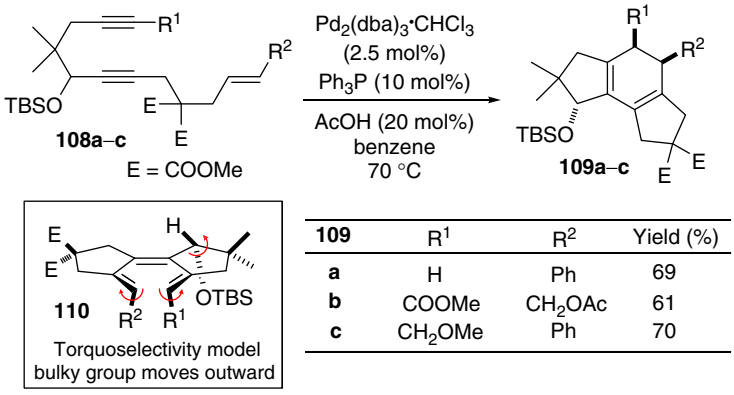
Scheme 20 Chelation-enhanced reactivity of a 6π electrocyclization en route to tetrodotoxin. Reproduced from Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron* **1998**, *54*, 6639.

Other unusual strained cyclic systems have proven capable of controlling the stereochemical outcome of 6π electrocyclizations, such as bis-methylenecyclobutanes **106** that could be generated from vinyl bromides **105a** and **105b** via domino 4-*exo*-*dig*-carbopalladation/Stille coupling (Scheme 21).[38] It was proposed that trienes of type **106** are conformationally preorganized toward 6π electrocyclic ring closure, enabling the production of strained cyclobutene-diols **107a** and **107b** as single diastereomers at relatively low temperature in refluxing benzene.



Scheme 21 The synthesis of strained cyclobutene-diols via a Pd-mediated cascade. Reproduced from Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845.

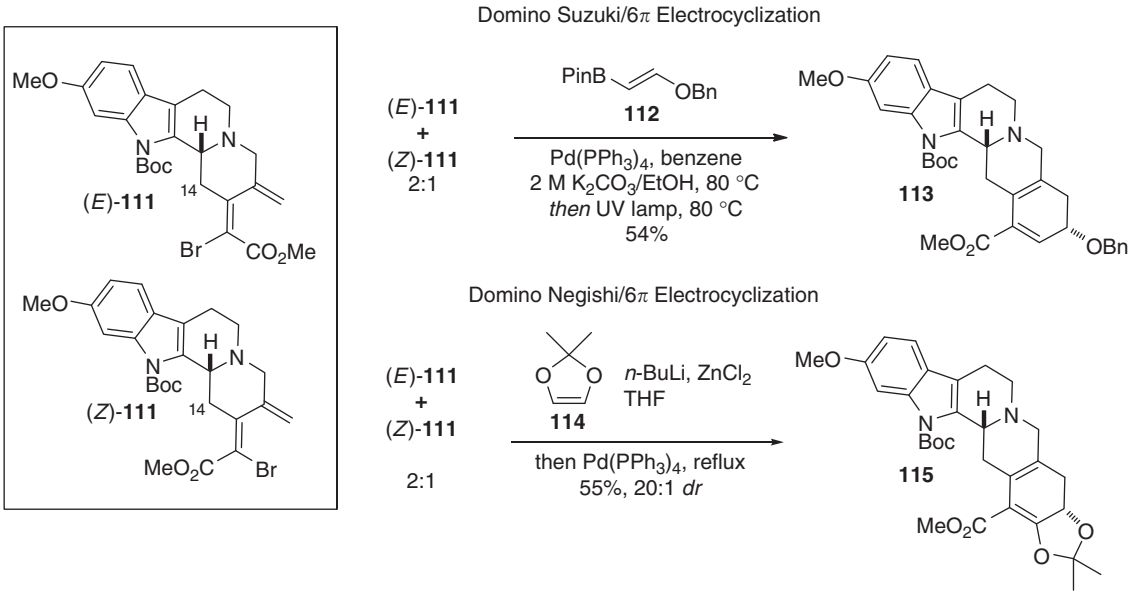
Somewhat more subtle elements of substrate control can be operative, as is the case with the diastereoselective palladium-catalyzed cascade cyclization of enediynes **108a–c** (Scheme 22).[39] A lone remote stereocenter proved capable of directing the



Scheme 22 Torquoselective cycloisomerization/Heck/6π electrocyclization cascade. Reproduced from Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791.

stereochemical course of the reaction. The reaction cascade was initiated by the palladium-catalyzed cycloisomerization of an enediyne **108**, followed by an intramolecular Heck reaction to generate an intermediate 1,3,5-hexatriene **110**. Torquoselective disrotation occurred in an outward fashion, avoiding torsional strain between the bulky silyl group and the adjacent ring system (Scheme 22). As seen in previous examples within this chapter (Scheme 11), hexatrienes of type **110** are conformationally predisposed toward 6π electrocyclic ring closure, so it is perhaps unsurprising that tricyclic products **109a–c** are formed efficiently at only 70 °C.

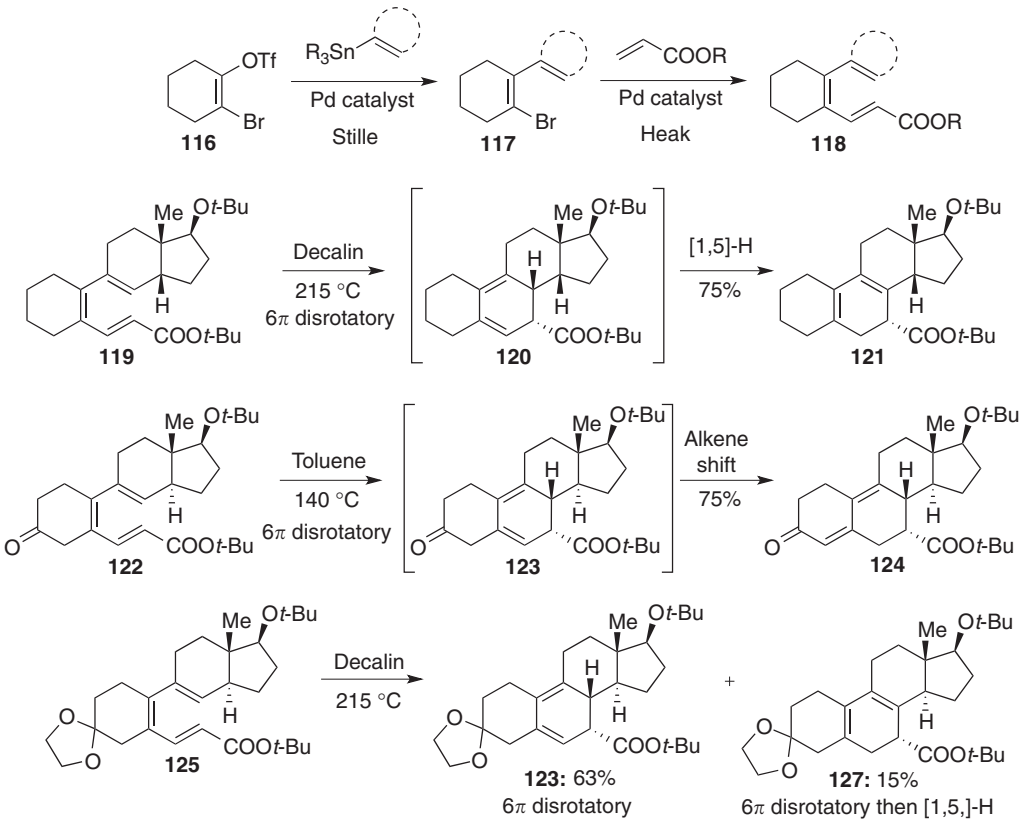
In a related example, complete 1,6-stereoinduction was observed in a domino cross-coupling/6π electrocyclization approach to the reserpine alkaloids (Scheme 23).[40] The mixture of alkene geometric isomers (*E*)-**111** and (*Z*)-**111** was found to successfully undergo Suzuki coupling with vinyl boronate **112**, transiently producing a 1,3,5-triene intermediate. Subsequent irradiation of the reaction mixture with a UV lamp affected isomerization of the central alkene geometry, allowing for productive thermal 6π electrocyclic ring closure, giving 1,3-cyclohexadiene **113** as a single diastereomer. Alternatively, a Negishi coupling strategy proved equally effective, by generating the corresponding organozinc derivatives of alkene **114** via deprotonation and transmetalation, followed by exposure to the mixture of vinyl bromides (*E*)-**111** and (*Z*)-**111** and a Pd(0) catalyst in refluxing THF. In this case, 1,3-cyclohexadiene **115** is formed with high diastereoselectivity, without requiring UV irradiation, attributed to Pd-mediated isomerization of the central alkene geometry. The observed remotely induced diastereoselectivity was proposed to arise from a steric interaction between the methyl ester and the C-14 methylene unit in the electrocyclic transition state.



Scheme 23 A diastereoselective 6π electrocyclization approach to the reserpine alkaloids. Reproduced from Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. *Org. Lett.* **2012**, *14*, 5388.

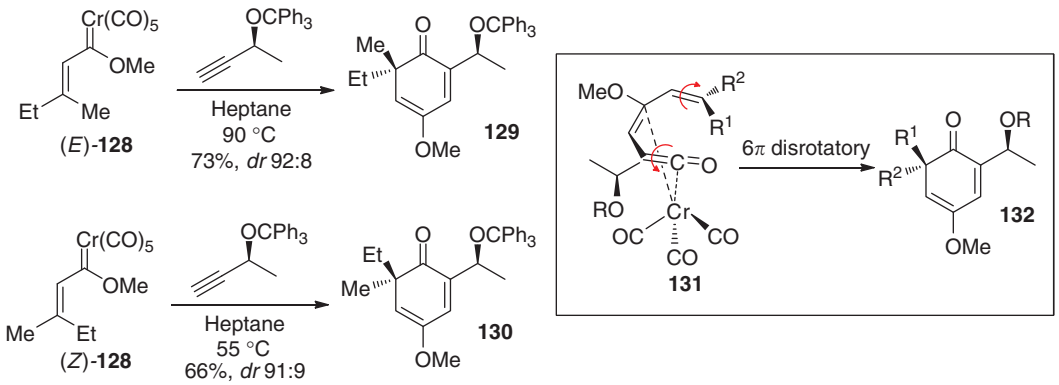
The double Heck reaction of (*Z*)-1,2-bromoalkenes already presented is a viable method to access symmetrical 1,3,5-hexatrienes with a (*Z*)-configured central double bond (Scheme 13), whereas, unsymmetrical 1,3,5-hexatrienes **118** can be conveniently prepared by the sequential cross-coupling of a 2-bromo-enol triflate **116** (Scheme 24).[41] This approach has been used for the diastereoselective synthesis of various substituted steroidal frameworks.[42] For example, *cis*-hydrindane-fused triene **119** underwent clean diastereoselective thermal 6π electrocyclization at 215 °C for 45 min with outward disrotatory ring closure, followed by a [1,5]-hydrogen shift to yield diene **121**. Electrocyclization with outward rotation was also observed for *trans*-hydrindane-fused triene **122**, proceeding at lower temperature to transiently form diene **121** that isomerized to enone **124** under the reaction conditions. The reaction outcome appears to be governed by thermodynamics, as heating of ketal-protected triene **125** at 215 °C for 45 min gave a separable mixture of the 6π electrocyclization product **126** and diene **127**, arising from [1,5]-hydrogen shift post electrocyclization, in a 4:1 ratio. Re-subjecting the rearranged diene **127** to the reaction conditions returned a similar mixture of dienes **126** and **127**, indicating the [1,5]-hydrogen shift is reversible and that diene **126** is the thermodynamic product. In light of this, it is generally difficult to predict the exact reaction outcome in these systems, as the thermodynamic profiles of each substrate/product mixture must be considered individually.

The diastereoselective synthesis of cyclohexadieneones from the union of a chromium Fischer carbene complex (*see* Chapter 5.25) and a chiral alkyne has been proposed to occur via the disrotatory 6π electrocyclization of a chromium–ketene complex **131** (Scheme 25).[43] The resulting products **132** possess a quaternary carbon center derived from 1,4-stereoinduction. Overall, the transformation was found to be stereospecific, since starting from either chromium complex (*E*)-**128** or its geometric isomer (*Z*)-**128** yields the diastereomeric dienones **129** and **130** respectively, each with comparable diastereoselectivity. Interestingly, the



Scheme 24 The synthesis of steroid scaffolds by torquoselective 6π electrocyclization. Adapted from Sünnemann, H. W.; Banwell, M.; de Meijere, A. *Eur. J. Org. Chem.* **2007**, 3879; Sünnemann, H. W.; de Meijere, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 895, and Sünnemann, H. W.; Hofmeister, A.; Magull, J.; de Meijere, A. *Chem. Eur. J.* **2007**, *13*, 3739.

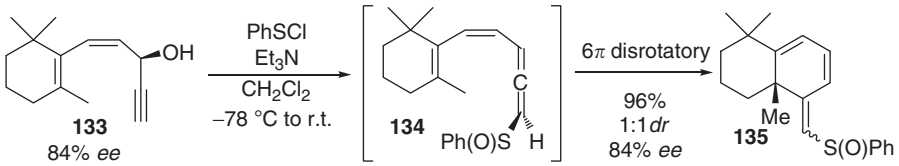
model for stereoinduction was suggested to involve an initial transfer of chiral information to the chromium coordination sphere, which directs outward disrotation of triene **131** to minimize disfavorable steric interactions between the R^1 substituent and the metal center.



Scheme 25 Stereoselective cyclohexadieneone annulations using Fischer carbene complexes. Adapted from Hsung, R.; Wulff, W. *J. Am. Chem. Soc.* **1994**, *116*, 6449, and Hsung, R.; Quinn, J.; Weisenberg, W.; *et al. Chem. Commun.* **1997**, 615.

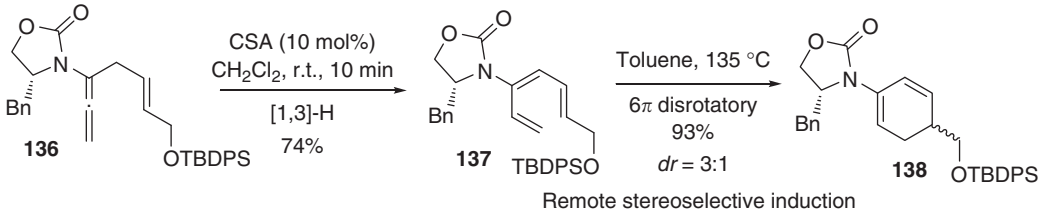
One of the earlier reported examples of a diastereoselective 6π electrocyclization to yield an enantiomerically enriched product involved the stereospecific chirality transfer from allene **134**, generated *in situ* from enantioenriched alcohol **133** by a [2,3]-sigmatropic rearrangement (Scheme 26) (*see* Chapter 5.21).[44] The chiral allene **134** underwent disrotatory electrocyclic ring closure at room temperature to yield 1,3-cyclohexadiene **135** as a 1:1 mixture of alkene isomers, but with no erosion of enantioenrichment.

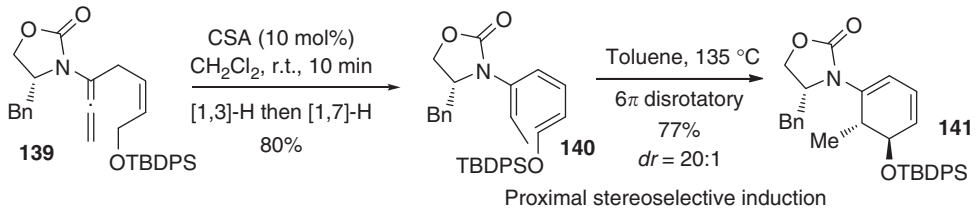
It has also been demonstrated that the diastereoselectivity of 6π electrocyclizations can be controlled through the use of a removable chiral auxiliary. The acid-promoted [1,3]-hydrogen shift of chiral allenamides, such as **136**, affords chiral hexatriene

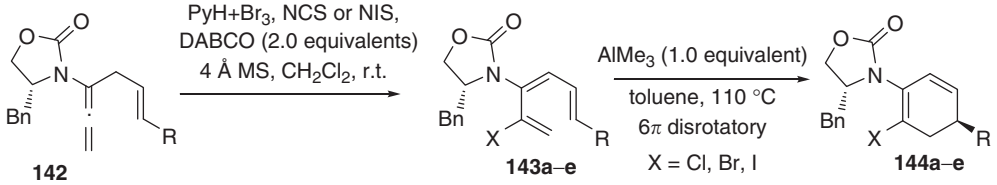


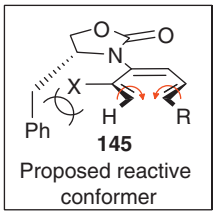
Scheme 26 Chiral allene directed diastereoselective 6π electrocyclic ring closure. Reproduced from Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034.

137 selectively with respect to the central alkene geometry (Scheme 27).[45] Heating of hexatriene **137** at 135 °C in toluene resulted in the highly efficient electrocyclic ring closure to diene **138** as a 3:1 mixture of diastereomers, an impressive level of selectivity considering it represents 1,6-stereoinduction. Counter to allenamide **136**, its olefinic isomer allene **139**, when treated with acid to trigger a [1,3]-hydrogen shift, further rearranged via [1,7]-hydrogen shift to triene **140**, fortuitously bearing the chiral auxiliary closer to the hexatriene terminus. In this case, thermal disrotatory electrocyclization produced diene **141** with significantly greater diastereoselectivity. More effective 1,6-stereoinduction could be achieved by steric buttressing of the auxiliary with a halogen

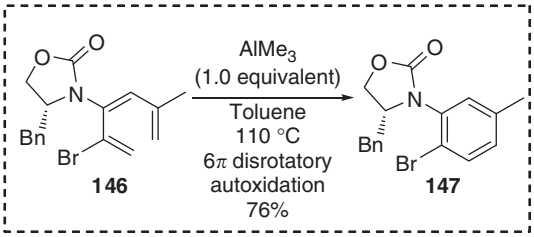








144	R	X	Yield (%)	*dr*
a	Ph	Br	95	90:10
b	$CH_2OTBDPS$	Br	79	88:12
c	CH_2NTsPh	Br	86	90:10
d	CH_2NTsPh	Cl	84	88:13
e	CH_2NTsPh	I	91	90:10

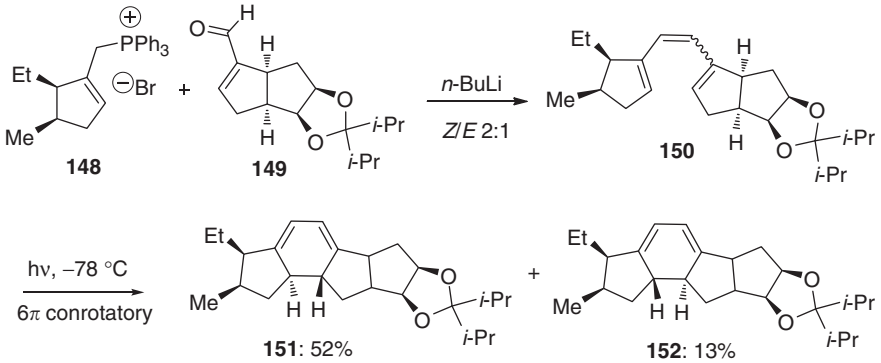


Scheme 27 Stereoselective 6π electrocyclizations directed by a chiral oxazolidinone auxiliary. Adapted from Hayashi, R.; Hsung, R.; Feltenberger, J.; Lohse, A. *Org. Lett.* **2009**, *11*, 2125; Hayashi, R.; Feltenberger, J.; Hsung, R. *Org. Lett.* **2010**, *12*, 1152; Hayashi, R.; Walton, M.; Hsung, R.; Schwab, J.; Yu, X. *Org. Lett.* **2010**, *12*, 5768; Hayashi, R.; Feltenberger, J.; Lohse, A.; *et al. J. Org. Chem.* **2011**, *7*, 410, and Hayashi, R.; Ma, Z.; Hsung, R. *Org. Lett.* **2012**, *14*, 252.

substituent, as was the case with trienes **143a-e**, which smoothly underwent 6π electocyclization in the presence of $AlMe_3$ to uniformly give synthetically useful levels of diastereoselectivty (approximately 9:1 *dr*).[46] A model **145** was put forward to rationalize the observed selectivity (Scheme 27), invoking that inward disrotation would be expected to minimize disfavorable steric interactions with the benzyl group of the auxiliary. It is worth noting that halogenated hexatrienes bearing a substituent at the C-5 position, such as bromo-triene **146**, were prone to oxidative aromatization under the reaction conditions.

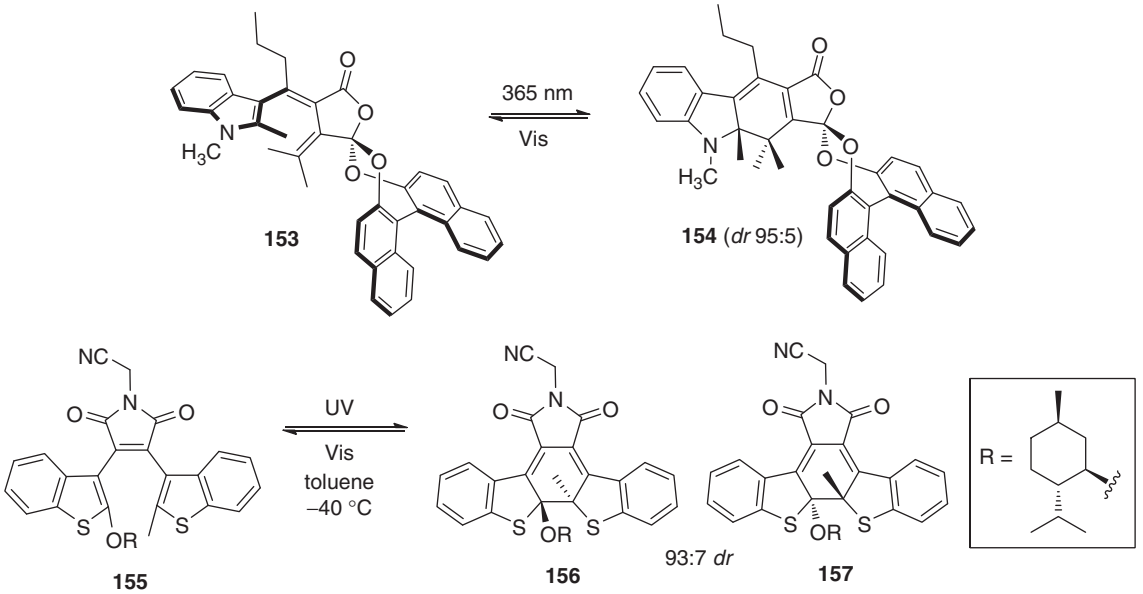
5.17.2.3.2 Photochemical processes

Photochemical 6π electrocyclizations have seen far less use in recent target-oriented syntheses than their thermal counterparts. Occurring with conrotatory ring closure and often at much lower reaction temperatures, the photochemical variant tends to exhibit torquoselectivity that reflects the relative population of conformers in the starting material's ground state.[47] For instance, this was noted in the total synthesis of ikarugamycin,[48] wherein phosphonium salt **148** and aldehyde **149** were used to prepare the advanced triene intermediate **150** with modest *Z*/*E* selectivity (Scheme 28). Subsequent irradiation of triene **150** at low temperature resulted first in the requisite *E* to *Z* alkene isomerization, followed by a 6π conrotatory electrocyclization to yield dienes **151** and **152** as a 4:1 ratio of diastereomers. It was proposed that this ratio is indicative of the inherent bias for the left-handed helical conformer of (*Z*)-triene **150** over its right-handed form.



Scheme 28 The photochemical 6π electrocyclization key step from ikarugamycin's total synthesis. Reproduced from Whitesell, J.; Minton, M. *J. Am. Chem. Soc.* **1987**, *109*, 6403.

It follows logically that it should be possible to affect the stereochemical outcome of photochemical 6π electrocyclizations using a chiral auxiliary. The feasibility of such an approach has been demonstrated by studies on chiral photochromic switches, which are compounds that interconvert between two isomers on irradiation with different wavelengths of light (Scheme 29).[49]



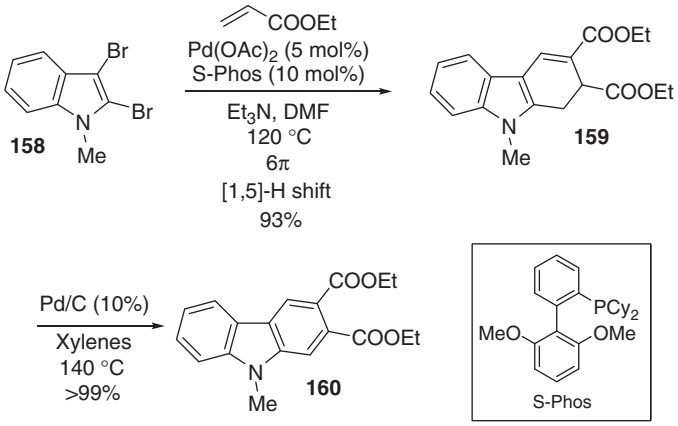
Scheme 29 Diastereoselective 6π electrocyclizations of chiral photochromic switches. Adapted from Yokoyama, Y.; Uchida, S.; Yokoyama, Y.; Sugawara, Y.; Kurita, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3100, and Yamaguchi, T.; Uchida, K.; Irie, M. *J. Am. Chem. Soc.* **1997**, *119*, 6066.

A large subset of photochromic switches rely on photochemical 6π electrocyclizations, typically employing 1,3,5-triene systems with one or more of the alkenes embedded within a (hetero)aromatic ring. For example, indolylfulgide **153**, possessing an appended (*R*)-BINOL motif, preferentially adopts one helical conformation that undergoes photochemical conrotatory ring-closing by irradiation at 365 nm, leading to cyclohexadiene **154** as virtually a single diastereomer.[50] Cycloreversion was also possible by simply exposing cyclohexadiene **154** to visible light. Similarly, it was possible to diastereoslectively photoisomerize diarylethene **155** bearing a menthyl auxiliary, which gave a 93:7 ratio of diastereomers at the photostationary state.[51] Perhaps unsurprisingly, diastereoselectivity in these systems often proves sensitive to solvent and reaction temperature, factors which also effect the relative populations of conformers in the ground state.

5.17.2.4 Electrocyclization as a Benzannulation Strategy

5.17.2.4.1 Thermochemical processes

The 1,3-cyclohexadiene products of 6π electrocyclizations are often easily further transformed into aromatic rings, either by the action of an external oxidant or autoxidation, particularly when fused to other aromatic or conjugated systems. For example, a general two-step benzannelation methodology for a number of 1,2-dibromoarenes and 1,2-dibromoheteroarenes,[52] including dibromoindole **158**,[53] has been developed, featuring an initial double Heck/6π electrocyclization cascade (**Scheme 30**). The transiently formed 1,3-cyclohexadiene undergoes a final [1,5]-hydrogen shift *in situ*, restoring aromaticity to the indole system **159**. Dehydrogenation of indole **159** was effected using palladium on carbon in refluxing xylenes, affording carbazole **160** in excellent yield.

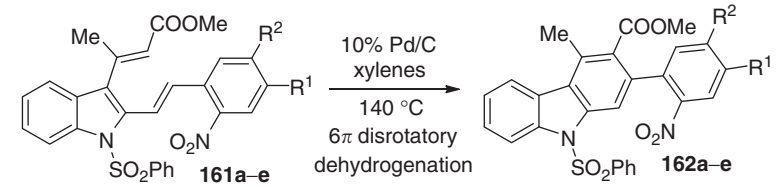


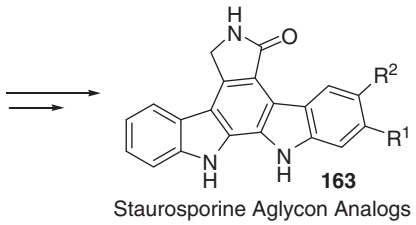
Scheme 30 Benzannealation of 1,2-dibromoarenes via 6π electrocyclization. Reproduced from Hussein, M.; Tengho Toguem, S.-M.; Ahmad, R.; *et al. Tetrahedron* **2011**, *67*, 5304.

In recent years, 6π electrocyclizations have become increasingly prominent as a tactic to prepare aromatic rings that are either sterically-crowded or possess otherwise difficult-to-access substitution patterns. Since many of the required triene precursors are now conveniently accessible through cross-coupling methodologies, numerous examples of this strategy have appeared in target-oriented synthesis within the past decade. For instance, the synthesis of several staurosporine aglycon analogs **163**, posessing a fully-substituted benzene core, were addressed using this approach (**Scheme 31**).[54] Highly substituted divinylindoles **161a-e** were treated with palladium on carbon in refluxing xylenes, triggering a 6π electrocyclic ring closure with concomitant dehydrogenation, efficiently producing various substituted biphenyls **162a-e**.

An unconventional retrosynthetic disconnection of 3,4-disubstituted indoles **169** along the lines of a 6π electrocyclization leads back to triene carbamtes **165**, which are easily prepared via the Stille coupling of an α-halo-enone **164** and an appropriate amino-vinyl stannane (**Scheme 32**).[55] Triene carbamates **165** undergo facile 6π electrocyclic ring closure, in accord with the substituent electronic effects already discussed (**Figure 1**). The cyclohexadiene intermediates **166** were not isolated, but rather treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to effect oxidative aromatization, delivering protected anilines **167** and **168**, each in exceptional yield. Further elaboration to the indole nucleus was efficient and needed only two additional steps. This particular method was used in an approach to the total synthesis of the natural product welwistatin, wherein the structurally complex triene carbamate **170** underwent electrocyclic ring closure/oxidative aromatization without incident and was later converted into indole **172**, demonstrating the level of substrate intricacy tolerated by this methodology.[56] Additionally, an approach to the natural product dragmacidin E using this indole formation strategy has been reported.[57] Similar reaction conditions were successful at converting triene carbamate **173** into the protected arene **174**, which was also later transformed into a fused indole.

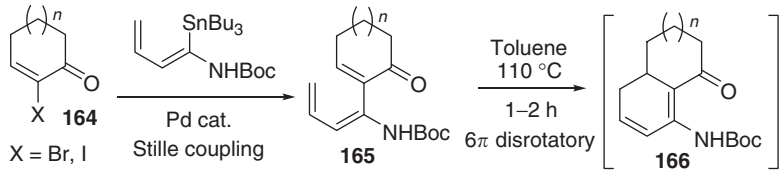
A related approach to *cis*-trikentin B **179** builds the indole benzenoid nucleus using a 6π electrocyclization (**Scheme 33**).[58] Relying again on a Stille reaction, vinyl stannane **175** was coupled with an enol triflate, allowing for the expedient synthesis of

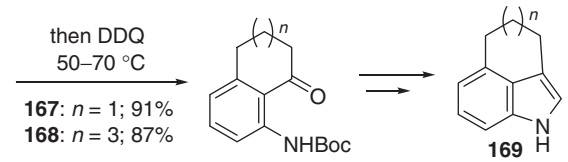


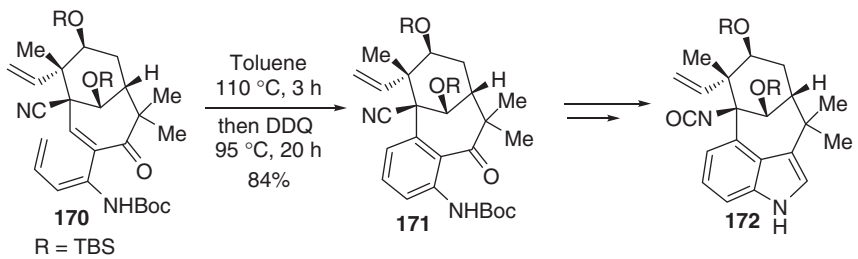


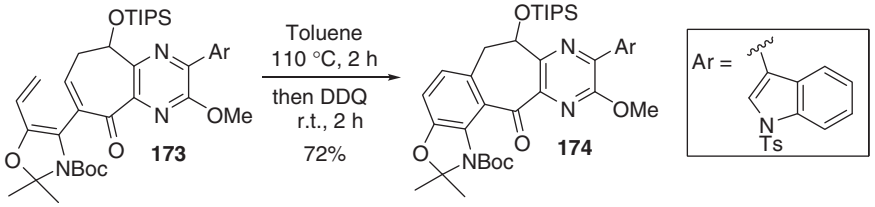
162	R^1	R^2	Yield (%)
a	H	H	85
b	OMe	OMe	90
c	Cl	H	93
d	H	F	84
e	OCH_2O		89

Scheme 31 A 6π electrocyclization/dehydrogenation approach to staurosporine aglycon analogs. Reproduced from Gobi Rajeshwaran, G.; Mohanakrishnan, A. K. *Org. Lett.* **2011**, *13*, 1418.





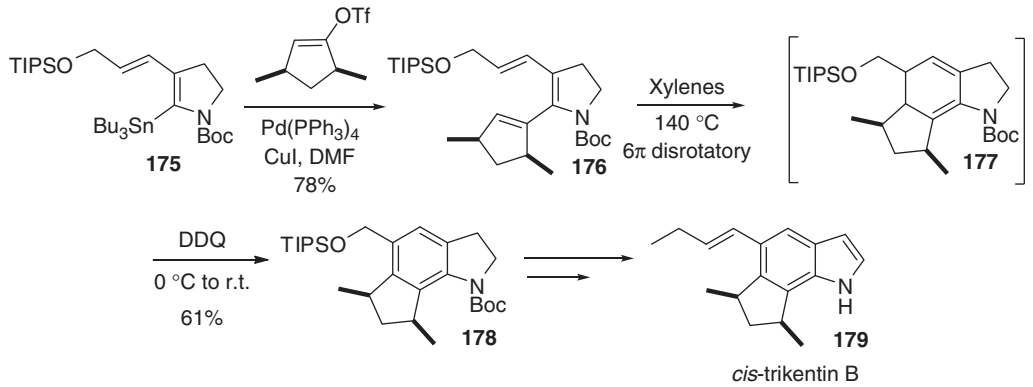




Scheme 32 Indole synthesis by the 6π electrocyclization of triene carbamates. Adapted from Greshock, T.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946; Greshock, T.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643, and Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775.

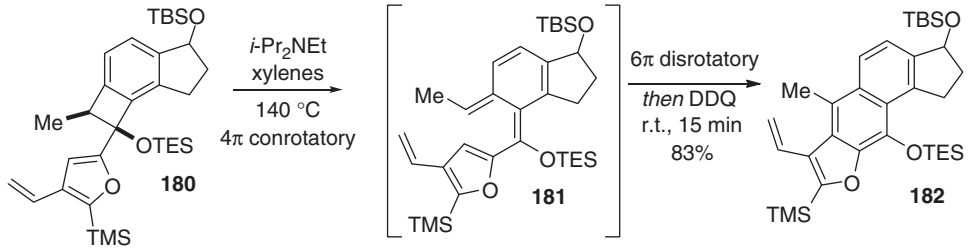
triene carbamate **176**. In turn, electrocyclic ring closure of triene **176** required slightly higher temperatures than triene carbamates **170** and **173** shown in the previous example, possibly due to the absence of the electron-accepting ketone in the former case. Subsequent *in situ* oxidation with DDQ at 0 °C furnished protected indoline **178**, which was successfully transformed into *cis*-trikentin B in four steps.

The synthesis of highly substituted naphthalenes has also merited from the 6π electrocyclization/benzannulation strategy, as seen in an excerpt from the total syntheses of viridin, a furanosteroidal antibiotic, and of the antibiotic TAN-1085. In the case of



Scheme 33 The total synthesis of *cis*-trikentin B. Reproduced from Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403.

viridin, a substituted benzocyclobutene **180** was used to generate the intermediate 1,3,5-triene **181** via thermal 4π electrocyclic ring-opening (*see* Chapter 5.16) at 140 °C in xylenes (Scheme 34).[59] It is typical of triene systems such as **181**, which is an *o*-quinone dimethide, to undergo 6π electrocyclization at relatively low temperatures, driven by the formation of an aromatic ring upon ring closure.[4] Following the 6π electrocyclization, oxidative aromatization with DDQ gave tetracycle **182** in 83% yield, which is particularly efficient for a threefold domino reaction of this nature.



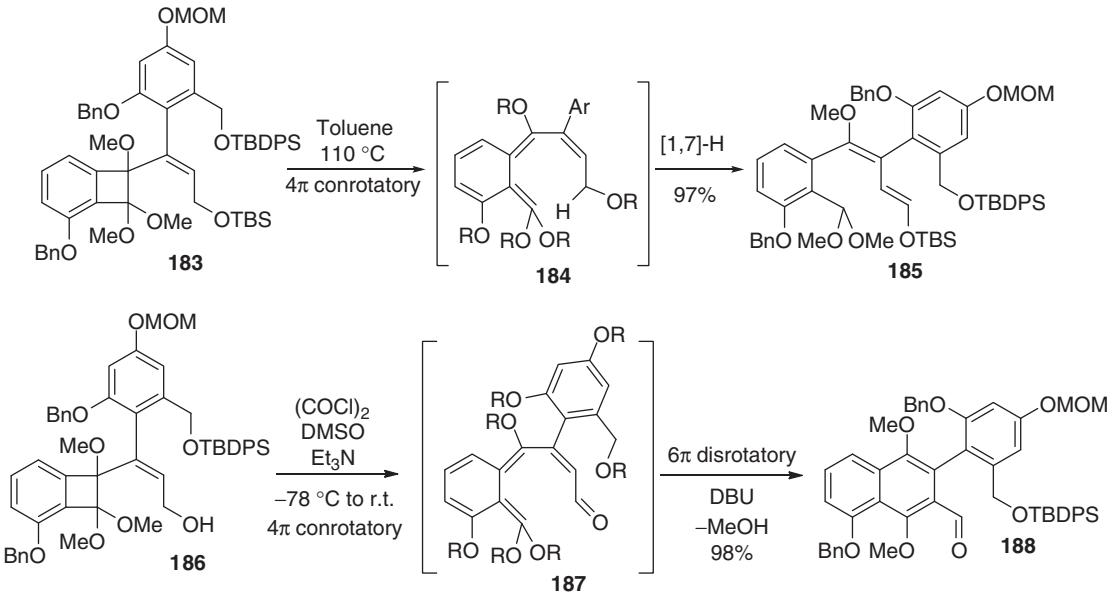
Scheme 34 Electrocyclization/aromatization cascade from the total synthesis of viridian. Reproduced from Anderson, E.; Alexanian, E.; Sorenson, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998.

The total synthesis of TAN-1085 also included the 4π electrocyclic ring-opening (*see* Chapter 5.16)/6π electrocyclic ring-closing by design (Scheme 35). However, even though the initial 4π electrocyclic ring-opening of benzocyclobutene **183** in refluxing toluene proceeded without incident, the resulting triene system **184** instead underwent a remarkably high-yielding [1,7]-hydrogen shift, producing 1,4-dienol ether **185**.[60] A simple, yet astonishingly effective solution to this problem was to render the [1,7]-hydrogen shift pathway inoperative by oxidizing allylic alcohol **186** to the aldehyde under Swern conditions.[61] This modified the substrate electronics, such that the electrocyclic ring-opening/ring-closing cascade took place below room temperature, ultimately forming the sterically congested benzaldehyde **188** in exceptionally high yield after aromatization via base-mediated elimination of methanol.

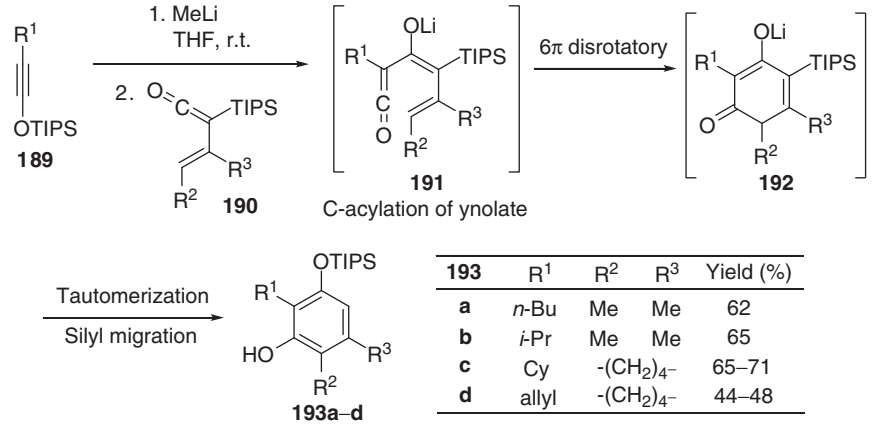
The 6π electrocyclization of *sp*-hybridized carbon containing triene systems, such as alkynes, ketenes or allenes often gives aromatic products directly by tautomerization, requiring no additional oxidation step.[4b] Accordingly, trialkylsilyl vinyl ketenes **190**, which are stable toward silica gel chromatography, can be used to prepare highly substituted phenols (Scheme 36).[62] Adding the lithium ynolate derived from silyl ether **189** to vinyl ketene **190** generates a new ketene **191** via C-acylation, eliciting 6π electrocyclization at room temperature and forming intermediate dienone **192**. Subsequent tautomerization to the phenol was accompanied by 1,3 carbon-to-oxygen silyl migration, giving access to various substituted phenols **193a–d** in moderate to good yield.[63]

Ketene 6π electrocylizations have also found application in an expedient synthesis of the chiral ligands VANOL and VAPOL.[64] In the latter case, phenylacetylene was heated in the presence of the enolizable acid chloride **194**, which underwent *in situ* ketene formation, followed by a thermal [2 + 2] cycloaddition (*see* Chapter 5.02) to give cyclobutenone **195** (Scheme 37). Subsequent 4π electrocyclic ring-opening (*see* Chapter 5.16) formed a second ketene **196** that engaged in 6π electrocyclization, followed by a tautomerization to the corresponding phenol **198**. A high temperature oxidative dimerization provided racemic VAPOL **199** that could be separated into its constituent enantiomers by means of a classical resolution.

In analogy to ketenes, allene containing 1,3,5-triene systems also participate in thermal 6π electrocyclizations with typical activation energies that are significantly lower than the parent 1,3,5-hexatriene manifold. One particularly convenient method for the preparation of allenes, base-mediated isomerization of a propargyl ether,[65] was used to trigger allene 6π electrocyclizations in

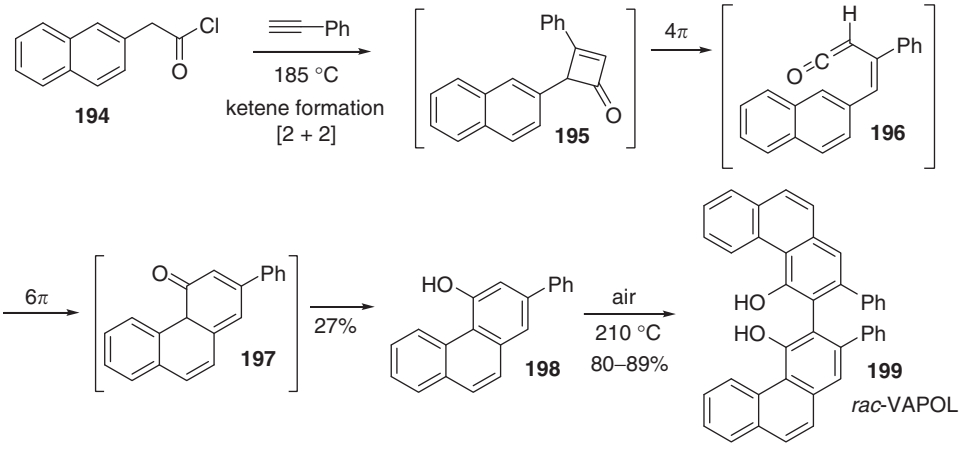


Scheme 35 The key 4π/6π electrocyclic cascad from the synthesis of TAN-1085. Adapted from Ohmori, K.; Mori, K.; Ishikawa, Y.; *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 3167, and Mori, K.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5633.



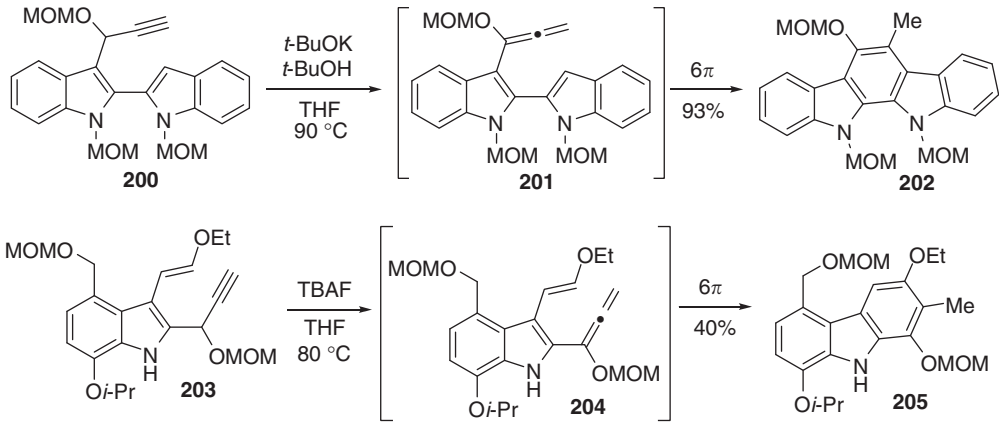
193	R^1	R^2	R^3	Yield (%)
a	*n*-Bu	Me	Me	62
b	*i*-Pr	Me	Me	65
c	Cy	-$(CH_2)_4$-		65–71
d	allyl	-$(CH_2)_4$-		44–48

Scheme 36 The synthesis of highly substituted phenols from trialkylsilyl vinyl ketenes. Adapted from Austin, W.; Zhang, Y.; Danheiser, R. *Org. Lett.* **2005**, *7*, 3905, and Austin, W.; Zhang, Y.; Danheiser, R. *Tetrahedron* **2008**, *64*, 915.



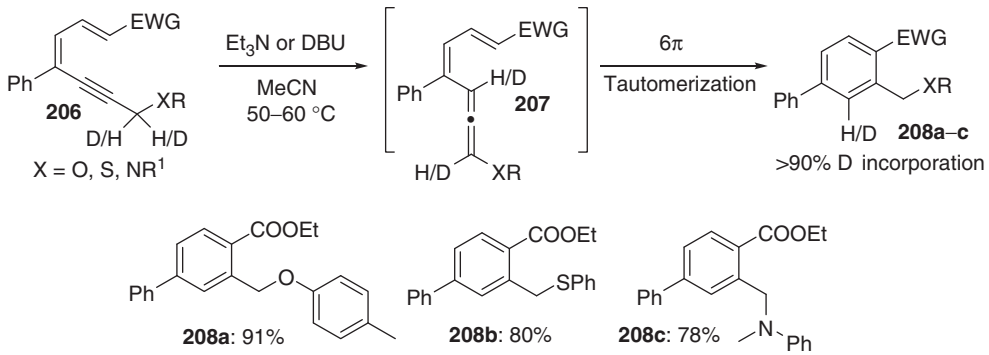
Scheme 37 The synthesis of (±)-VAPOL using an electrocyclization cascade. Reproduced from Ding, Z.; Osminski, W. E. G.; Ren, H.; Wulff, W. D. *Org. Process Res. Dev.* **2011**, *15*, 1089.

the total syntheses of calothrixin B and carbazomadurin A (Scheme 38). Along these lines, propargyl ether **200** was treated with potassium *tert*-butoxide in THF at 90 °C, leading to the efficient production of arene **202** possessing a fully-substituted central aromatic ring.[66] The same reaction conditions were not successful using propargyl ether **203**, an intermediate from the carbazomandurin A synthesis, but changing the base to tetra-*n*-butylammonium fluoride (TBAF) resulted in isomerization to allene **204** and successful electrocyclic ring closure to highly substituted arene **205**, albeit in modest yield.[67]



Scheme 38 Allene 6π electrocyclizations in the synthesis of calothrixin B and carbazomandurin A. Reproduced from Yamabuki, A.; Fujinawa, H.; Choshi, T.; *et al. Tetrahedron Lett.* **2006**, *47*, 5859.

Using other heteroatoms to promote alkyne-to-allene isomerizations to initiate 6π electrocyclization has also been investigated. Simple dieneynes **206** incorporating a propargylic oxygen, nitrogen or sulfur atom were readily accessible using cross-coupling chemistry (Scheme 39).[68] Treating these substrates with an amine base at slightly elevated temperatures was sufficient to educe isomerization to allene **207** and drive the subsequent 6π electrocyclization forward. Isotopic labeling studies showed that the isomerization occurs predominantly with transfer of deuterium, resulting in a high degree of deuterium incorporation in the product arene **208**. A large number of 1,2,4-trisubstituted arenes of type **208a–c** were accessible in good yield using this methodology.

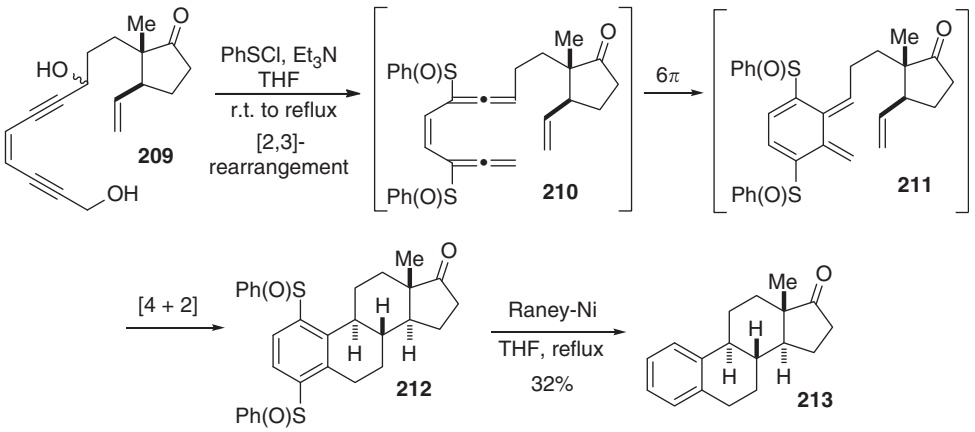


Scheme 39 Heteroatom assisted alkyne-to-allene isomerization accompanied by 6π electrocyclization. Adapted from Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674, and Zhou, H.; Xing, Y.; Yao, J.; Lu, Y. *J. Org. Chem.* **2011**, *76*, 4582.

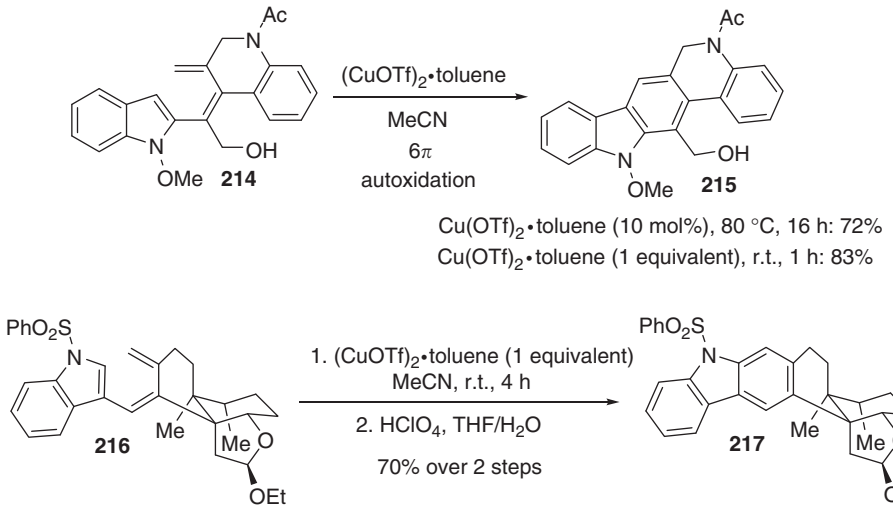
Including two allenes in a 1,3,5-triene system can result in 6π electrocyclization to generate an *o*-quinone dimethide. This has been demonstrated by the formation of intermediate ene-diallene **210** from the sulfur-promoted double [2,3]-sigmatropic rearrangement (*see* Chapter 5.21) of bis-propargyl alcohol **209** (Scheme 40).[69] The ensuing 6π electrocyclic ring-closing begat *o*-quinone dimethide **211**, which underwent an intramolecular Diels–Alder reaction to terminate the cascade. Erasure of the sulfoxide substituents from the rapidly assembled steroidal framework **212** could be accomplished by treatment with Raney-nickel, giving ketone **213** in 32% overall yield from propargyl alcohol **209**.

During the course of studies on the total synthesis of calothrixins A and B, the conversion of 1,3,5-triene **214** to arene **215** was met with difficulty, failing under both forcing thermal and photochemical conditions (Scheme 41).[70] This prompted a screening of additives aimed at promoting the reaction,[71] revealing that a copper(I) salt was effective in catalyzing the 6π electrocyclization at elevated temperature in MeCN. Furthermore, using a stoichiometric quantity of the copper(I) salt caused the reaction to

proceed efficiently at room temperature. Although the exact mechanism of rate enhancement is unclear, it has been proposed the copper species acts as a Lewis acid. These conditions were later applied in another total synthesis, that of tubingensin A,[72] wherein 1,3,5-triene **216** was transformed into carbazole **217** by a copper-mediated 6π electrocyclization/aromatization followed by acetal hydrolysis.



Scheme 40 Sequential pericyclic reactions of ene-diallenes. Reproduced from Kitagaki, S.; Ohdachi, K.; Katoh, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 95.

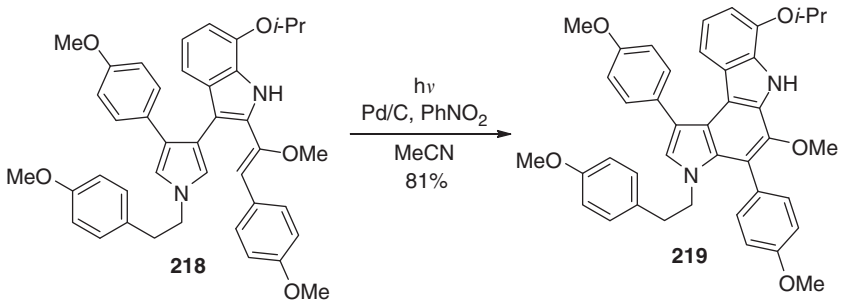


Scheme 41 Copper-catalyzed 6π electrocyclizations. Adapted from Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Org. Lett.* **2011**, *13*, 3356, and Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193.

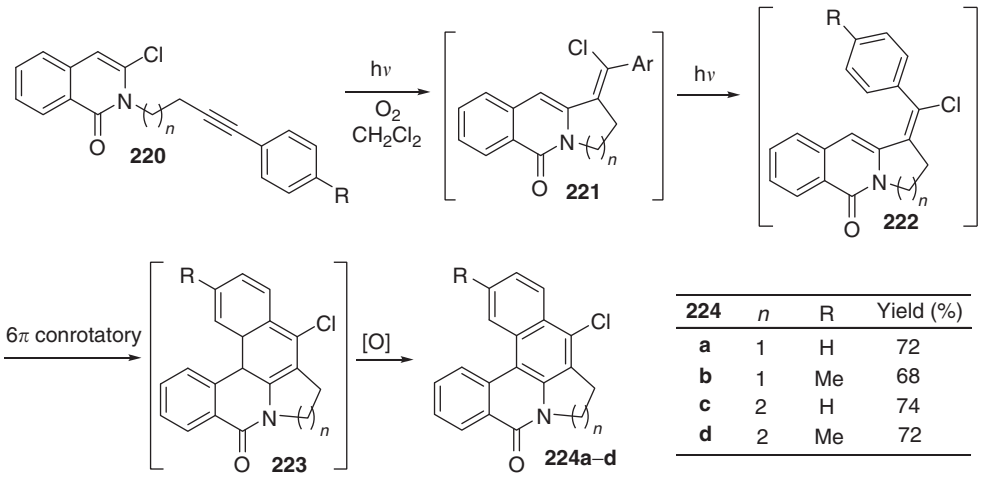
5.17.2.4.2 Photochemical processes

As seen thus far, 6π electrocyclization followed by oxidative aromatization is a particularly effective strategy for making carbazoles. This is true for photochemical electrocyclic ring closure as well, especially when the substrate bears a suitable chromophore and is not susceptible to alkene isomerizations. The total synthesis of the telomerase inhibitors dictyodendrin B, C and E made use of such a transformation. Irradiation of enol ether **218** using a 250 W mercury lamp, followed by aromatization of the initially formed adduct by the addition of palladium on carbon and nitrobenzene gave pyrrolocarbazole **219** in good yield (Scheme 42).[73]

Photochemical 6π electrocyclizations can also be engineered into cascade sequences, enabling the rapid synthesis of polycyclic aromatic structures. For example, 3-chloroisoquinolone **220** undergoes homolytic C–Cl bond cleavage on irradiation with UV light, generating a carbon-centered radical that undergoes a 5-*exo-dig* cyclization with concomitant chlorine radical trapping to afford intermediate vinyl chloride **221** (Scheme 43).[74] A light-induced alkene isomerization to vinyl chloride **222** results in spontaneous 6π electrocyclization to amide **223**, followed by autoxidation, giving access to a number of benzo[*a*]phenanthridein-5-ones **224a–d**.



Scheme 42 Photochemical 6π electrocyclization in the total synthesis of dictyodendrin B. Adapted from Fürstner, A.; Domostoj, M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620, and Fürstner, A.; Domostoj, M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087.

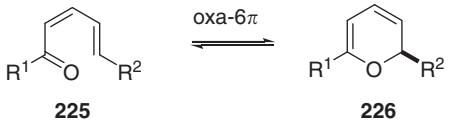


224	*n*	R	Yield (%)
a	1	H	72
b	1	Me	68
c	2	H	74
d	2	Me	72

Scheme 43 Photochemical radical cyclization/6π electrocyclization cascade of 3-chloroisoquinolones. Reproduced from Wang, R.; Lu, S.-C.; Zhang, Y.-M.; Shi, Z.-J.; Zhang, W. *Org. Biomol. Chem.* **2011**, *9*, 5802.

5.17.3 Oxa-6π Electrocyclizations

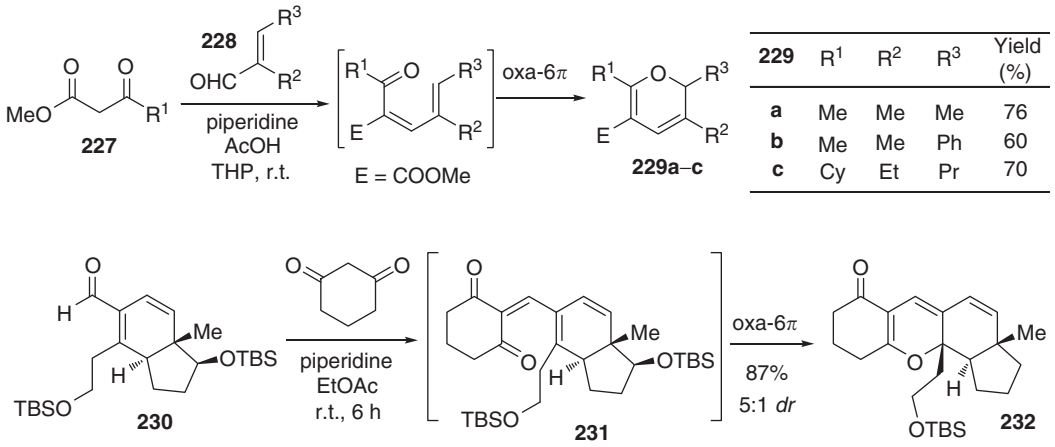
Replacing a terminal carbon in a 1,3,5-hexatriene with an oxygen atom, as in dienone **225**, drastically perturbs the system, significantly decreasing the activation energy barrier toward 6π electrocyclization (Equation 1).[4] The reason for this has been cited as a combination of the decreased steric demand of oxygen compared to a substituted carbon, as well as the direct participation of the oxygen nonbonding lone pairs in the electrocyclic process. Reactions of this type, where bonding and nonbonding orbitals exchange roles have been termed 'pseudopericyclic' and have been the subject of theoretical studies.[75] The oxa-6π electrocyclization interconverts an oxatriene system **225** with the corresponding α-pyran **226**, and has been predicted to be essentially thermoneutral.[4a] Therefore, the equilibrium between the two forms is sensitive to relatively small offsets in energy (1–3 kcal mol^{-1} for K = 10–100), which can be determined by numerous factors such as the steric/electronic nature of substituents, conformational bias or strain energy. The reaction produces one new stereocenter, but selectivites are often governed by thermodynamics, due to the reaction's reversibilty. It is however, a relatively common process in biosynthesis,[3] and many natural products have been found that include either a dihydropyran motif, or a derivative thereof. Several biomimetic syntheses and related studies have been carried out that support the involvement of pericyclic reaction cascades in a number of biosynthetic pathways (*vide infra*).



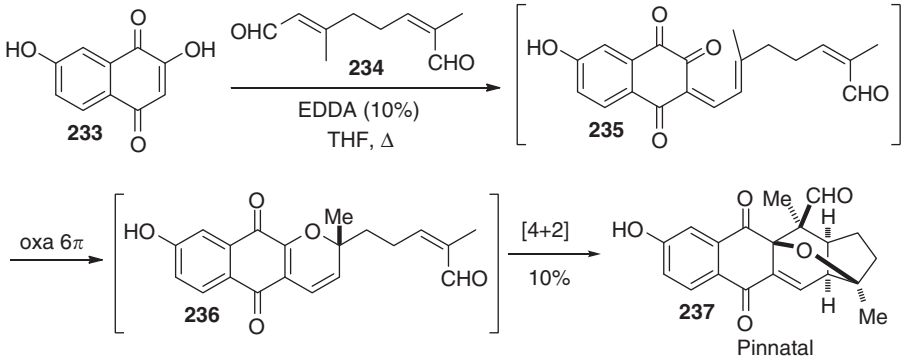
(1)

One of the more common and versatile strategies for constructing substituted dihydropyrans is via domino Knoevenagel/6π electrocyclization (Scheme 44).[76] For instance, acyclic acetoacetates **227** may be condensed with enals **228** bearing a C2

substituent ($R^3 \neq H$) to favor 1,2-addition with (*E*)-selectivity, granting access to dihydropyrans **229a–c** in good yield at ambient temperature.[77] Several natural product syntheses have employed similar domino sequences, among them being an approach to the cortistatins,[78] wherein enal **230** was condensed with cyclohexane-1,3-dione under Knoevenagel conditions to give diketone **231** that spontaneously cyclized to dihydropyran **232** in 5:1 dr with respect to the newly formed stereocenter. This type of sequence has been proposed to occur in various biosynthetic cascades, and has been used in biomimetic approaches to natural products. An illustrative example is provided by the condensation of naphthoquinone **233** with dialdehyde **234** in the presence of ethylenediamine diacetate (EDDA) (Scheme 45).[79] The initial condensation product, triketone **235**, underwent an oxa-6π electrocyclic ring closure, followed by an intramolecular hetero Diels–Alder reaction (*see* Chapter 5.10) to afford the natural product pinnatal **237** in low yield. Significantly higher yields could be obtained starting from the same naphthoquinone **233** by executing stepwise transformations rather than the threefold domino process.



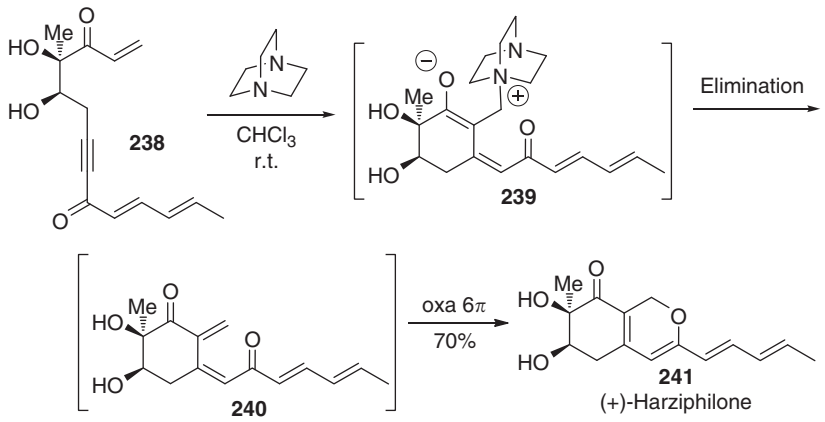
Scheme 44 The Knovenagel/oxa-6π electrocyclization route to dihydropyrans. Adapted from Peng, W.; Hirabaru, T.; Kawafuchi, H.; Inokuchi, T. *Eur. J. Org. Chem.* **2011**, 5469; Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413, and Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408.



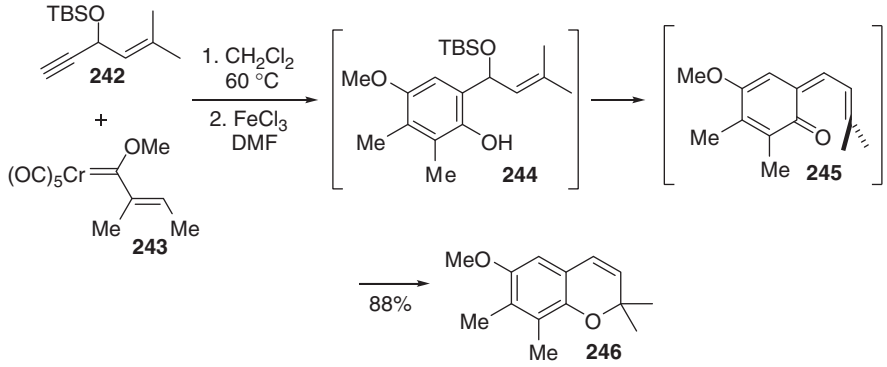
Scheme 45 Cascade Knovenagel/oxa-6π electrocyclization in the biomimetic synthesis of pinnatal. Reproduced from Malerich, J.; Maimone, T.; Elliot, G.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276.

An interesting method to generate the requisite oxatriene system includes the nucleophilic cycloisomerization of diketone **238** (Scheme 46).[80] To this effect, nucleophilic conjugate addition of 1,4-diazabicyclo[2.2.2]octane (DABCO) to enone **238** and subsequent intramolecular conjugate addition of the resulting enolate to the alkyne acceptor formed the Baylis–Hilman-like zwitterion **239**. Elimination of DABCO unmasked the oxatriene **240**, which then underwent facile oxa-6π electrocyclization to give (+)-harziphilone.

Chromenes, which are present in a variety of natural products, are often prepared by oxa-6π electrocyclization onto an aromatic ring. However, it has also been demonstrated that both rings of a chromene **246** may be constructed simultaneously (Scheme 47).[81] Combining enyne **242** with Fischer carbene **243** (*see* Chapter 5.25) resulted first in benzannulation to form phenol **244**, which readily ejected the silyl ether to give *o*-quinone methide **245** that engaged in 6π electrocyclic ring closure to restore aromaticity. The corresponding chromium arene complex (not shown) of **246** was then treated with an iron (III) salt to oxidatively remove chromium, enabling the isolation of chromene **246** in excellent yield.

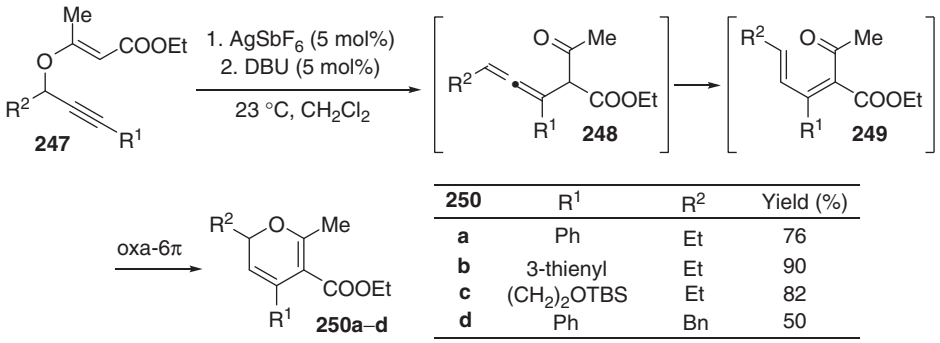


Scheme 46 The synthesis of (+)-harziphilone using a Baylis–Hilman/oxa-6π electrocyclization cascade. Reproduced from Stark, L.; Pekari, K.; Sorenson, E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12064.



Scheme 47 Fischer carbene-mediated synthesis of chromenes. Reproduced from Majumdar, N.; Korthals, K.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *134*, 1357.

The Claisen rearrangement of propargyl vinyl ethers, either thermal or metal-catalyzed,[82] represents an additional avenue for the generation of oxatriene systems, particularly when the vinyl terminus bears a suitable electron-withdrawing group as in propargyl ether **247** (Scheme 48). Activation of the alkyne moiety with a silver(I) salt elicited a propargyl-Claisen rearrangement, giving rise to allene **248**. Subsequent base-promoted isomerization to the oxatriene system **249** was facilitated by the presence of the ethyl ester, after which 6π electrocyclization led to the efficient production of various substituted dihydropyrans **250a–e**.

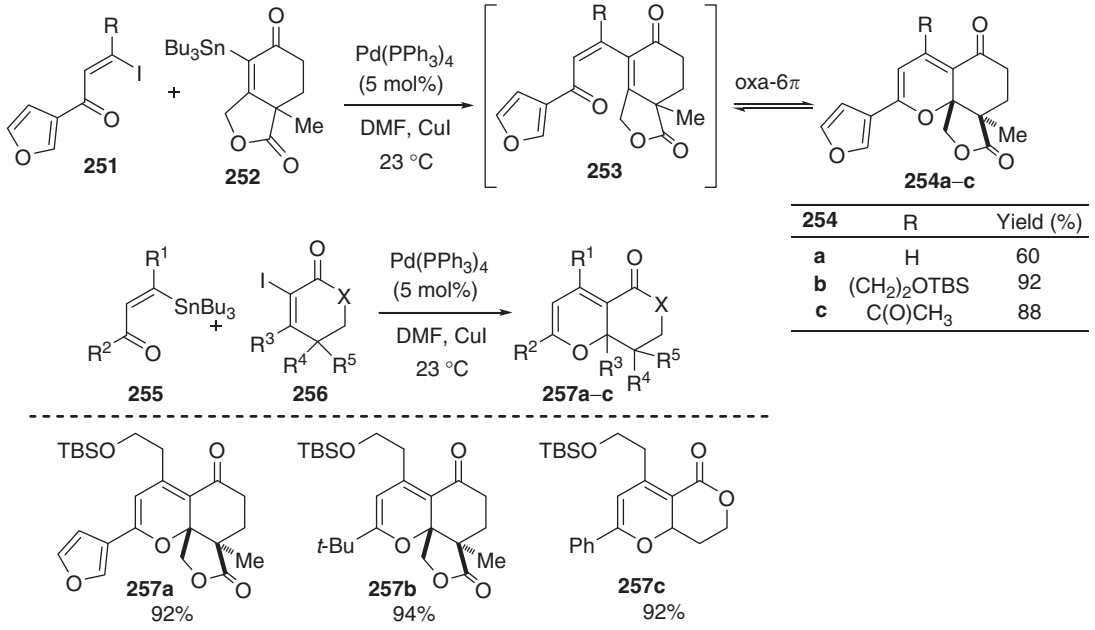


250	R^1	R^2	Yield (%)
a	Ph	Et	76
b	3-thienyl	Et	90
c	$(CH_2)_2OTBS$	Et	82
d	Ph	Bn	50

Scheme 48 The propargyl-Claisen rearrangement as a means to access dihydropyrans. Reproduced from Menz, H.; Kirsch, S. *Org. Lett.* **2006**, *8*, 4795.

A powerful diastereoselective Stille coupling/oxa-6π electrocyclization methodology was borne out of an approach to the polycyclic pyran core of the natural product saudin.[83] The cross-coupling of racemic 2-stannyl-enone **252** and vinyl iodide **251** in the dark (to prevent alkene isomerization) at room temperature efficiently furnished dihydropyrans **254a–c** as single diastereomers via a

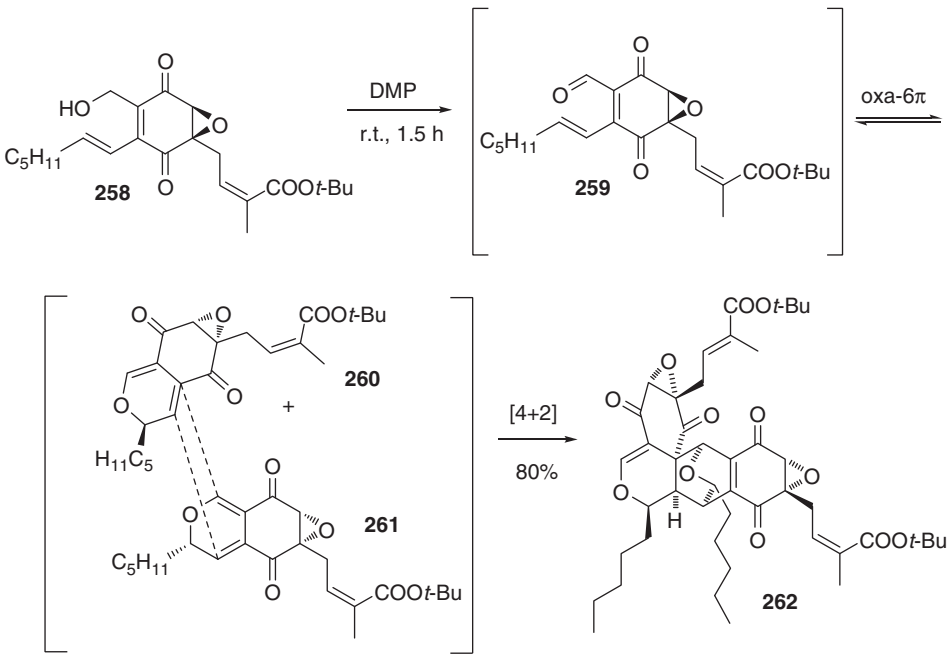
pentadienone **253** (Scheme 49).[84] Reversing the coupling partner's polarities, using a vinyl stannane **255** and a 2-iodo enone **256** led to comparable reaction yields, making this a highly versatile entry into bi/tricyclic pyran-containing scaffolds.[85]



254	R	Yield (%)
a	H	60
b	$(CH_2)_2OTBS$	92
c	$C(O)CH_3$	88

Scheme 49 Synthesis of the polycyclic core of saudin using an oxa-6π electrocyclization strategy. Adapted from Tambar, U.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413; Tambar, U.; Kano, T.; Zepernick, J.; Stoltz, B. M. *J. Org. Chem.* **2006**, *71*, 8357, and Tambar, U.; Kano, T.; Zepernick, J.; Stoltz, B. M. *Tetrahedron Lett.* **2006**, *48*, 345.

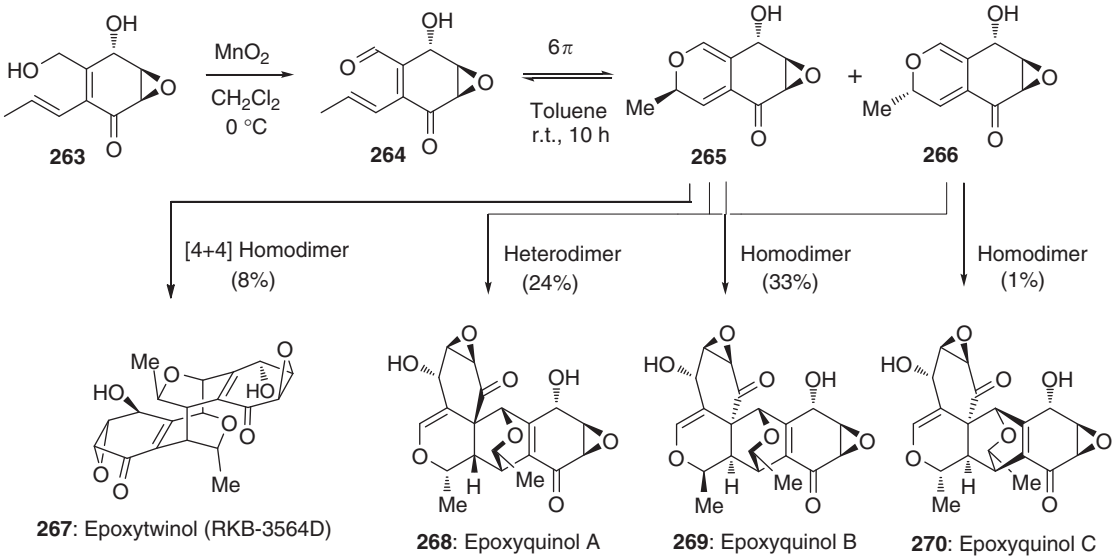
Several dimeric natural products have been discovered which incroporate oxa-6π electrocyclizations into their biosynthetic pathways. For example, the epoxyquinone natural product (+)-torreyanic acid has been proposed to originate from the Diels–Alder heterodimerization (*see* Chapter 5.09) of two diastereomeric 2*H*-pyrans **260** and **261**, which in turn are formed by a nondiastereoselective oxa-6π electrocyclic ring-closing (Scheme 50).[86] This hypothesis has been verified by synthesis, whereby



Scheme 50 The biomimetic total synthesis of (+)-torreyanic acid. Adapted from Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095, and Kleinke, A. S.; Li, C.; Rabasso, N.; Porco, J. A., Jr. *Org. Lett.* **2006**, *8*, 2847.

enantiomerically pure allylic alcohol **258** was oxidized with Dess–Martin periodinane, initiating the cascade via aldehyde **259**. The ensuing unselective oxa-6π electrocyclization gave a mixture of 2*H*-pyran diastereomers **260** and **261** that underwent Diels–Alder cross-dimerization to deliver the *tert*-butyl ester of (+)-torreyanic acid **262** as a single diastereomer in good yield. The selectivity appears to stem from an *endo*-selective Diels–Alder that orients the alkyl side chains *anti* to each other and occurs with facial selectivity *anti* to the epoxide.

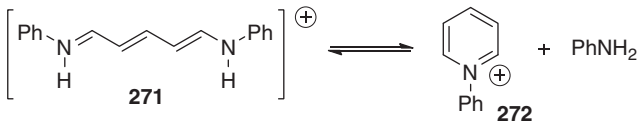
In the same vein, a biomimetic approach to the epoxyquinols A **268**, B **269**, and C **270**, as well as epoxytwinol **267** was established based on a similar reaction sequence (Scheme 51).[87] Selective oxidation of allylic alcohol **263** under mild conditions allowed for the isolation of pentadienal **265**, which on stirring in toluene at room temperature underwent a nondiastereoselective oxa-6π electrocyclization and then various modes of dimerization to yield a mixture of the epoxyquinols A-C and epoxytwinol **267**, all of which had also been previously isolated from the same soil fungus. Epoxyquinol C **270** is known to be formed from epoxyquinol A **267** by microwave irradiation,[88] and epoxytwinol **267** gradually converts to epoxyquinol B **269** on standing, which suggests the reactions are reversible and the observed product mixture is a consequence of thermodynamics. The high selectivity and spontaneous reactivity of the oxa-6π/dimerization manifold hints that enzymes are unlikely to be involved in the process.



Scheme 51 Dimerization modes of epoxy-2*H*-pyrans. Reproduced from Shoji, M.; Kishida, S.; Kodera, Y.; *et al. Tetrahedron Lett.* **2003**, *44*, 7205.

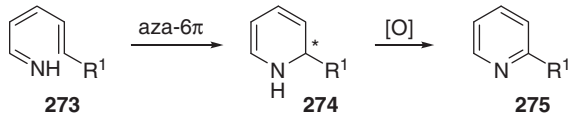
5.17.4 Aza-6π Electrocyclizations

Useful synthetic reactions involving aza-6π electrocyclizations of 1-azatrienes have been known for over a century, predating the mechanistic understanding of such processes. Of particular note is the ring-opening/ring-closing of König's salts **271** and pyridinum cations, that were studied by Zincke,[89] as well as Marvell (Equation 2).[90]



(2)

In general, aza-6π electrocyclic ring closure of 1-azatrienes **273** to 1,3-dihydropyridines **274** is exothermic, barring any additional substituent effects that might strongly perturb the system (Equation 3).[4a] The products are often easily oxidized to pyridines **275**, which has in many cases been used as an efficient route to such compounds. Aza-6π electrocyclizations tend to possess lower activation energy barriers than their 1,3,5-hexatriene counterparts, but usually occur at lower rates than oxa-6π electrocyclizations. Substitution at the *N*-terminus can have a profound effect on reaction rates for (*E*)/(*Z*) configurationally stable imines or oximes, where (*E*)-substrates normally cyclize more rapidly due to sterics.[4] There are three possible isomeric azatriene systems, all of which are able to participate in electrocyclic reactions,[4] but 1-azatrienes are the most well-studied and will be the main focus of this section.

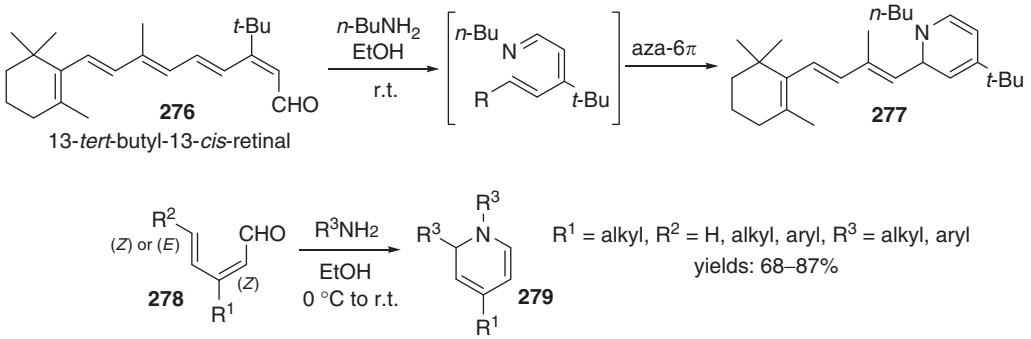


(3)

5.17.4.1 Formation of 1,2-Dihydropyridines

5.17.4.1.1 Thermochemical processes

In the late 1980s, it was discovered that 13-*tert*-butyl-13-*cis*-retinal **276** condenses with *n*-butylamine to form 1,3-dihydropyridine **277** quantitatively at room temperature (Scheme 52).[91] This provided the inspiration for studying the formation of simple 1,3-dihydropyridines **279** by the condensation reaction between a dienal **278** and a primary amine.[92] In the early report, the investigators expressed curiosity toward the propensity of 13-*cis*-retinal **276** to undergo aza-electrocyclization so readily, while the parent oxa-system does not cyclize to the corresponding 1,3-dihydropyran. A likely explanation is that the oxa- and aza-electrocyclizations both occur, but are reversible and the more thermodynamically stable product predominates in each case. Kinetic parameters for the general aza-6π-electrocyclization were measured, and the activation energies were found to be in the range of 17.5–22.5 kcal mol^{-1}, which is approximately 5–10 kcal mol^{-1} lower than typical all-carbon 1,3,5-hexatriene systems. The methodology is also quite useful, and efficiently produces substituted 1,3-dihydropyridines **279** provided a (2*Z*)-dienal **278** is employed.



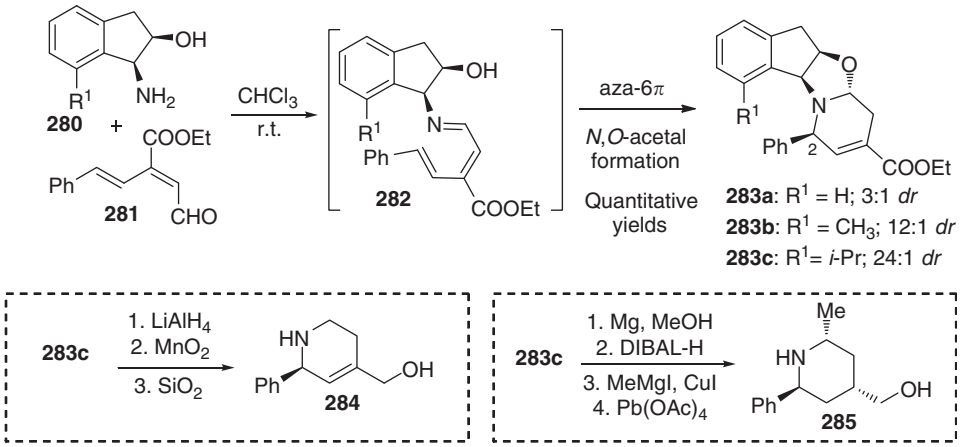
Scheme 52 Formation of 1,3-dihydropyridines by condensation/6π electrocyclization. Adapted from De Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4051; Maynard, D.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763, and Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

Condensing a chiral amine with a dienal can allow for diastereoselective aza-6π electrocyclizations and removable chiral auxiliaries have been used with some success. For example, 2-aminoindanol chiral auxiliaries **280** were shown to readily condense with dienal **280**, forming the corresponding 1-azatrienes **282** that undergo aza-6π electrocyclic ring-closing accompanied by tautomerization/*N*,*O*-acetal formation to give tetrahydropyridines **283a–c** in moderate to good diastereoselectivity with respect to the 2-position (Scheme 53).[93] The products are essentially 1,3-dihydropyridine synthons and can be easily modified to give useful synthetic building blocks. Auxiliary removal can be accomplished by treating the product *N*,*O*-acetal **283c** in series with $LiAlH_4$ and then MnO_2, followed by silica gel to afford the enantioenriched tetrahydropyridine derivative **284**. Additionally, substituted piperidines **285** can be synthesized asymmetrically in good overall yield by stereoselective conjugate reduction of unsatutared ester **283c** with Mg in methanol, ester reduction with diisobutylaluminum hydride (DIBAL-H), ring-opening of the *N*,*O*-acetal by Grignard addition and finally oxidative cleavage of the aminoindanol auxiliary with $Pb(OAc)_4$.

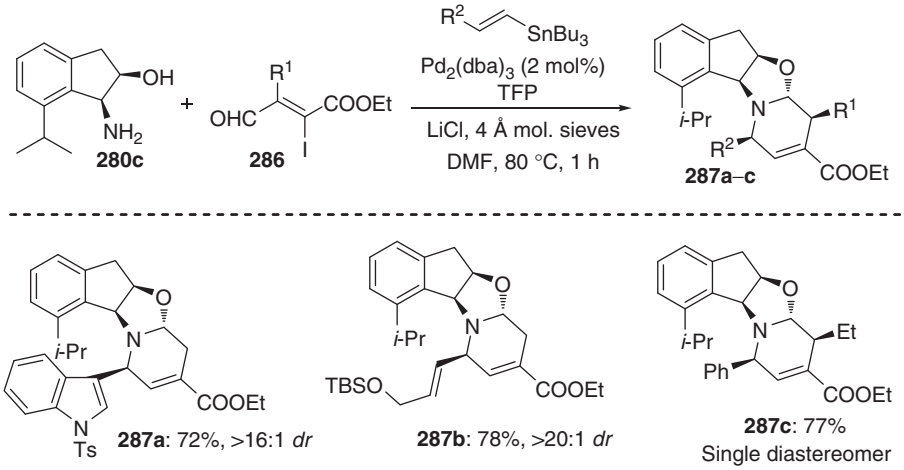
Using the 2-aminoindanol auxiliary **280c** deemed to be optimal in the previous example, it was possible to streamline the methodology, making it a multicomponent reaction featuring the Stille coupling of a *β*-iodo-enal **286** and an appropriate vinyl stannane (Scheme 54).[94] The R^2 substituent was limited to attachment via a non-sp^3 hybridized carbon, but alkenes could be used such as in tetrahydropyridine **287b**, which were later reduced to install an alkyl side chain. The value of this method has been exemplified by its use in the total synthesis of several piperidine alkaloids.[95]

Vinylogous amides **288** bearing a removable chiral auxiliary have also been used to direct stereoselective aza-6π electrocyclic ring closures (Scheme 55).[96] Using an iminium ion as the electrophile rather than an enal promoted selective 1,2-addition with loss of piperidine to give chiral 1-azatriene **289** that underwent reversible 6π electrocyclization to give 1,3-dihydropyridine **290** as the more thermodynamically stable diastereomer. Subsequent removal of the auxiliary was possible via palladium-catalyzed hydrogenolysis of the benzylic C–N bond.

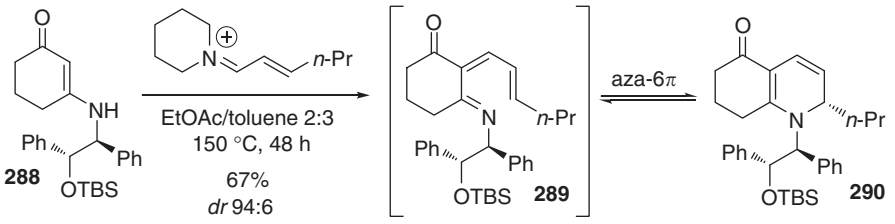
Repositioning the chiral functional group to the *C*-terminus of the imminium ion **291** was somewhat less effective, typically resulting in lower levels of diastereoselectivity (Scheme 56).[97] Generally, during the aza-electrocyclization step, bulkier *C*-terminal and *N*-terminal substituents exhibited a trade-off of higher selectivity at the cost of a lower yield, whereas using smaller



Scheme 53 Aza-6π electrocyclization using a 1,2-aminoindanol-derived chiral auxiliary. Reproduced from Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906.



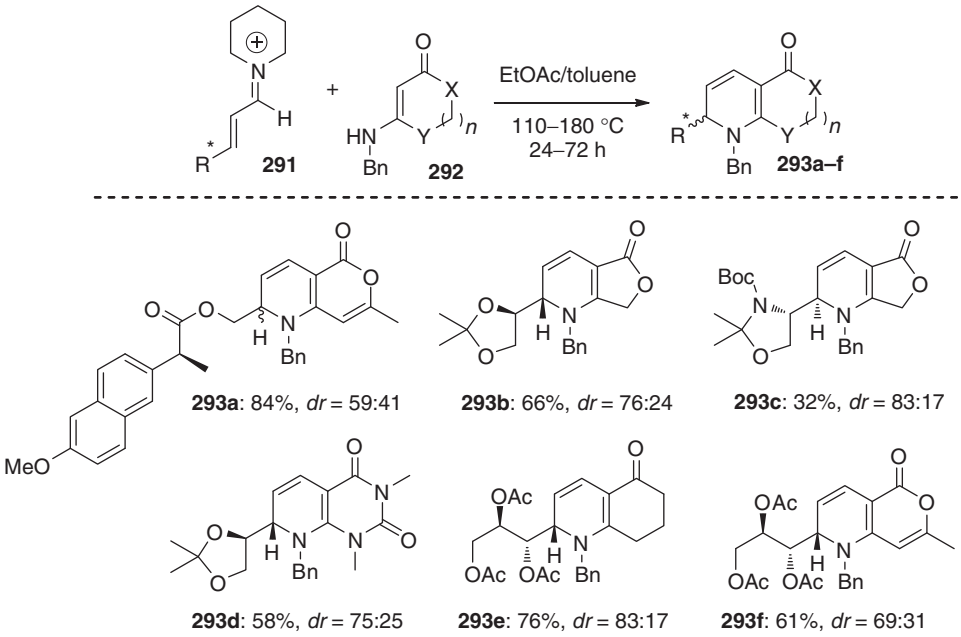
Scheme 54 Multicomponent Stille coupling/aza-6π electrocyclization. Reproduced from Kobayashi, T.; Nakashima, M.; Hakogi, T.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3809.



Scheme 55 Chiral auxiliary-controlled diastereoselective formal [3 + 3] cycloaddition. Reproduced from Sklenicka, H.; Hsung, R.; McLaughlin, M.; *et al. J. Am. Chem. Soc.* **2002**, *124*, 10435.

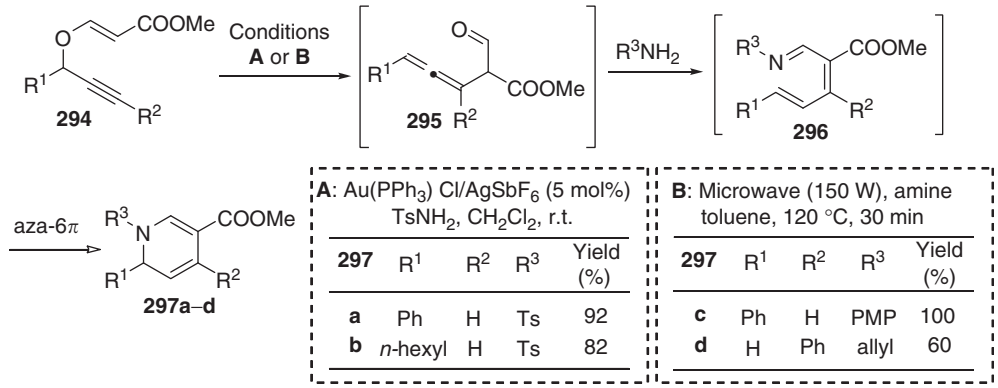
substituents sacrificed diastereoselectivity for increased yields. It was possible to thermally equilibrate a 1:1 mixture of lactone **293b** to favor the major diastereomer, but doing so required significantly higher temperature (250 °C) compared to that of the reaction temperature, suggesting that thermodynamics may not be the determining factor in reaction selectivity and some element of kinetic control may be operative.

As seen earlier in this chapter in Scheme 48, the propargyl-Claisen rearrangement of propargyl vinyl ethers **294** bearing a suitable electron-withdrawing group at the vinyl terminus offers convenient entry into 1-oxatriene systems via base-mediated isomerization of allene intermediates **295** (Scheme 57). The Claisen rearrangement (*see* Chapter 5.20) can be carried out



Scheme 56 Torquoselective 6π electrocyclization of 1-azatrienes with *C*-terminal chiral substituents. Reproduced from Sydorenko, N.; Hsung, R.; Vera, E. *Org. Lett.* **2006**, *8*, 2611.

thermally under microwave irradiation at elevated temperature,[98] or at room temperature in the presence of a gold(I)/silver(I) catalytic system.[99] The normal mode of oxa-6π electrocyclization can be intercepted by a primary amine, generating a 1-azatriene intermediate **296** that undergoes aza-6π electrocyclic ring-closing to give substituted 1,3-dihydropyridines **297a–d**.



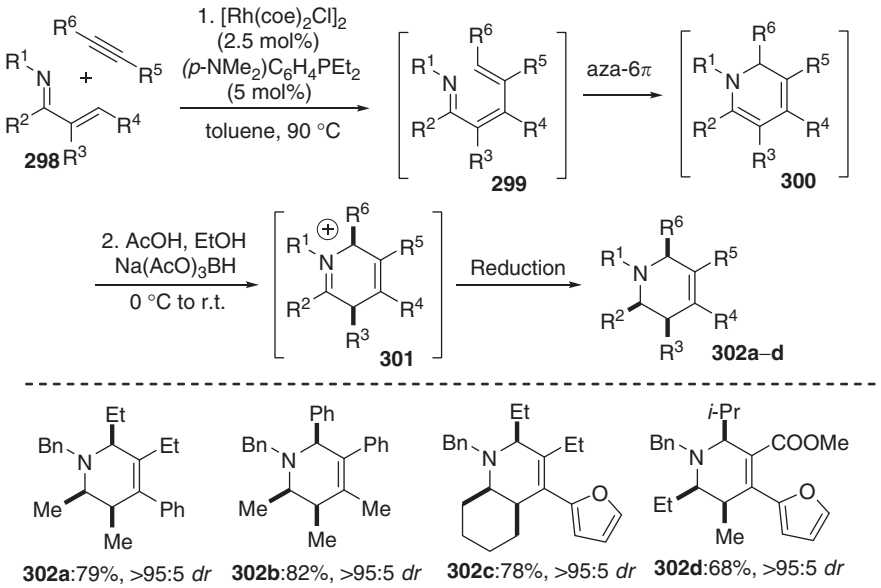
297	R^1	R^2	R^3	Yield (%)
a	Ph	H	Ts	92
b	*n*-hexyl	H	Ts	82

297	R^1	R^2	R^3	Yield (%)
c	Ph	H	PMP	100
d	H	Ph	allyl	60

Scheme 57 1,3-Dihydropyridine synthesis via propargyl-Claisen/aza-6π electrocyclization. Adapted from Tejedor, D.; Méndez-Abt, G.; García-Tellado, F. *Chem. Eur. J.* **2010**, *16*, 428, and Wei, H.; Wang, Y.; Yue, B.; Xu, P.-F. *Adv. Synth. Catal.* **2010**, *352*, 2450.

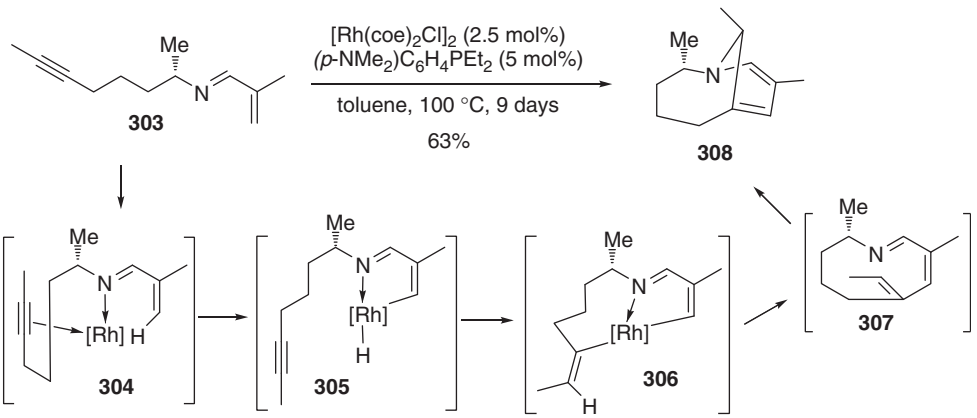
The rhodium(I)-catalyzed β-C–H bond activation (*see* Chapter 5.32) of α,β-unsaturated imines **298** and subsequent addition across alkynes can be used as a means of access to fully-substituted 1-azatrienes **299** that undergo *in situ* aza-6π electrocyclization to 1,3-dihydropyridines **300** (Scheme 58).[100] The 1,3-dihydropyridine **300** can be isolated, or tautomerized to the iminium species **301** using acetic acid, followed by reduction with a borohydride reagent to yield single diastereomers of various fully-substituted tetrahydropyridines **302a–d** in good yield.

When the alkyne functionality is instead tethered to the α,β-unsaturated imines through the nitrogen, unusual strained bicyclic 1,3-dihydropyridine systems **308** can be obtained by rhodium(I)-catalyzed cycloisomerization/aza-6π electrocyclization (Scheme 59).[101] The proposed catalytic cycle begins with bidentate coordination of the metal center to the chiral imine **303** via its alkyne and imine lone pair to give complex **304**. The rhodium center is then posited to undergo C–H insertion with the proximal alkene to form the rhodium-hydride complex **305**, which is followed by intramolecular hydrorhodation of the alkyne to afford



Scheme 58 Tetrahydropyridine synthesis by C–H activation/aza-6π electrocyclization/reduction. Reproduced from Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064.

10-membered rhodacycle **306**. Subsequent reductive elimination to triene **307** and aza-6π electrocyclization would give rise to the strained *anti*-Bredt enamine **308** as a single diastereomer.

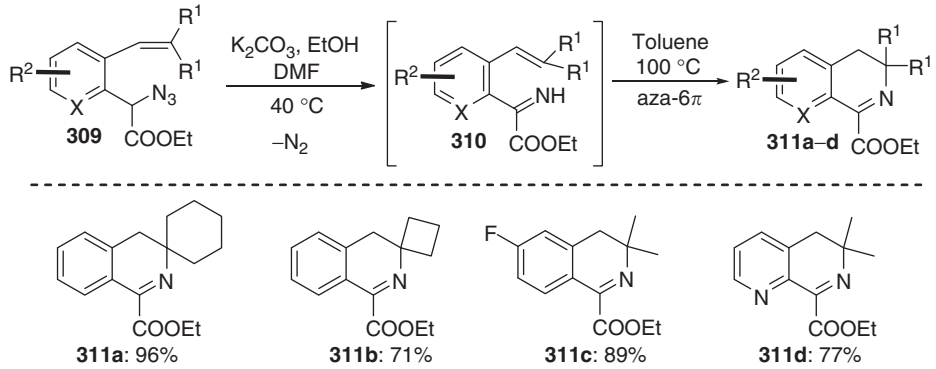


Scheme 59 Synthesis of anti-Bredt bicyclic enamines by Rh-catalyzed cycloisomerization/6π electrocyclization. Reproduced from Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452.

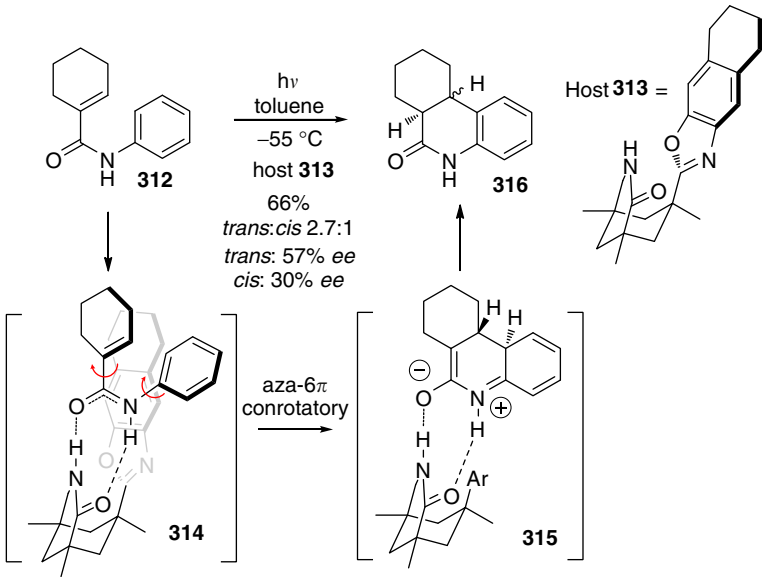
An additional mode of entry to 1-azatriene systems is the base-mediated decomposition of α-azido esters **309** (Scheme 60).[102] Gentle heating of such azides **309** with a mild base was found to induce elimination of N_2 to form 1-azatrienes of type **310**. Dilution of the reaction medium with toluene and increasing the temperature to 100 °C permitted aza-6π electrocyclic ring closure that was followed by tautomerization to give dihydroisoquinolines **311a–d**. It is noteworthy that electrocyclizations of *N*-H imines are quite rare.[103]

5.17.4.1.2 Photochemical processes

A number of studies have been conducted aimed at developing enantioselective photochemical aza-6π electrocyclizations using a host–guest inclusion strategy,[104–106] but so far have mostly led to only modest levels of asymmetric induction. For instance, irradiation of anilide **312** in the presence of the chiral host **313** at −55 °C in toluene produces *trans*- and *cis*-tricycle **314** in a 2.7:1 ratio with 57% and 30% *ee* respectively (Scheme 61).[104] The selectivity model entails a host–guest complex **314** that is held together by a bidentate hydrogen-bonding interaction. The guest's cyclohexene moiety is proposed to reside in the host's chiral pocket and torquoselective outward conrotation is proposed to minimize unfavorable steric interactions with the host's axial tetrahydronaphthalene substituent, rendering the cyclohexene Si-face susceptible to attack from the aromatic ring. Finally, the



Scheme 60 Synthesis of 1-azatrienes from α-azido esters and subsequent aza-6π electrocyclization. Reproduced from Wei-Quang Hui, B.; Chiba, S. *Org. Lett.* **2009**, *11*, 729.



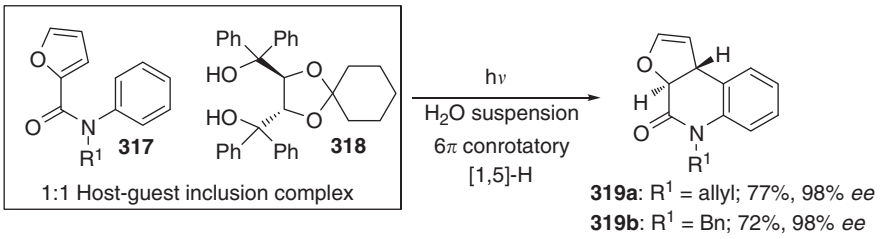
Scheme 61 Solution phase asymmetric photochemical aza-6π electrocyclization in a host-guest inclusion complex. Reproduced from Bach, T.; Grosch, B.; Strassner, T.; Herdtweck, E. *J. Org. Chem.* **2003**, *68*, 1107.

tricyclic product **316** is liberated from the host by diastereoselective protonation of intermediate **315**, providing a reason for the observed disparity in enantiomeric excesses between the *cis* and *trans* products.

The solution phase photochemical conversion of acrylanilides **312** to the corresponding tricyclic amides **316** has been known for some time and occurs readily,[107] presenting a challenge for the development of an asymmetric process since the background reaction leading to racemic product is relatively facile. Very high levels of asymmetric induction have been observed, however, for the solid phase photochemical conversion of aryl and furyl carboxyanilides **317** to tricyclic amides **319** by irradiation of a crystalline 1:1 host–guest complex suspended in water.[105] The reaction is believed to proceed by conrotatory ring closure dictated by the chirality of the inclusion complex, followed by a suprafacial [1,5]-hydrogen shift driven by the gain in aromatic stabilization energy. The solid-state structures of various related host–guest complexes have been studied and some were characterized by X-ray crystallography (Scheme 62).[106]

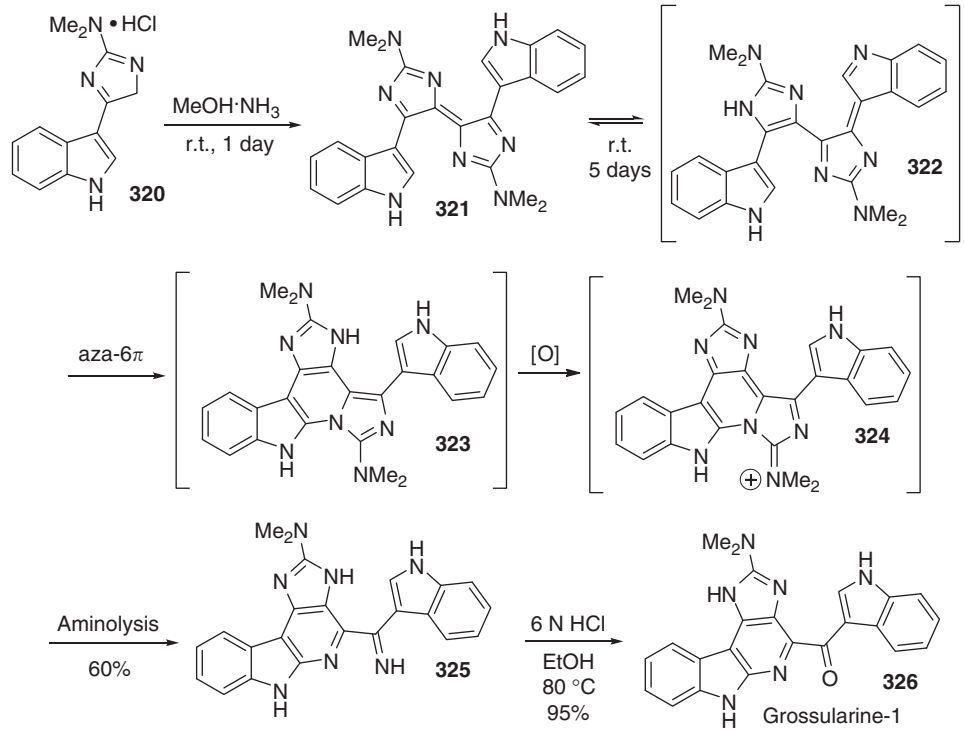
5.17.4.2 Aza-6π Electrocyclizations as a Method to Access Pyridines

As with all-carbon 1,3,5-hexatriene systems, 1-azatrienes offer a point of entry to aromatic compounds via 6π electrocyclization and subsequent oxidation. This sequence was proposed to be involved in the biosynthesis of grossularine-1 **326**, an α-carboline metabolite that exhibits pronounced effects against human tumor cell lines.[108] This proposal was confirmed by an elegant synthesis of grossularine-1 **326** in two steps from indole **320** (Scheme 63).[109] To this effect, indole **320** upon standing in methanol saturated with ammonia, underwent oxidative dimerization to bis-indole **321** that tautomerized to a 1-azatriene **322**,



Scheme 62 Solid phase asymmetric photochemical aza-6π electrocyclization in a host-guest inclusion complex. Reproduced from Toda, F.; Miyamoto, H.; Kanemoto, K.; *et al. J. Org. Chem.* **1999**, *64*, 2096.

which in turn participated in an aza-6π electrocyclization to form 1,3-dihydropyridine **323**. An oxidation event resulted in putative guanidinium cation **324**, which after aminolysis allowed for the isolation of *N*-H imine **325** in a remarkable 60% overall yield from indole **320**. Simple imine hydrolysis under acidic conditions gave the natural product grossularine-1 **326**.

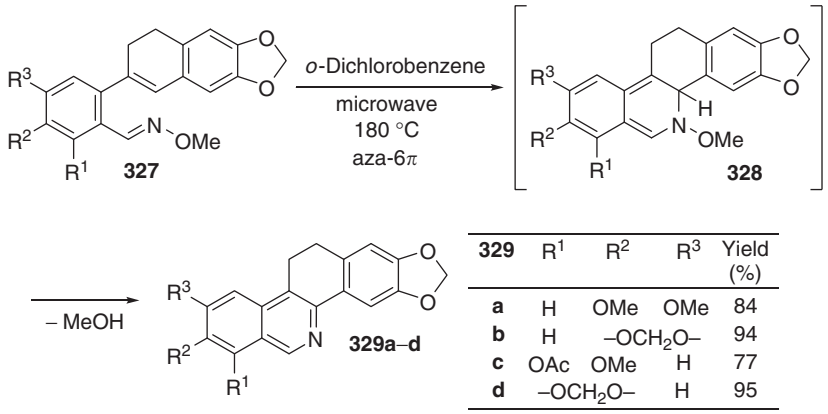


Scheme 63 Biomimetic synthesis of grossularine-1. Reproduced from Miyake, F.; Yakushijin, K.; Horne, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 3280.

The subsequent oxidative aromatization step can be omitted from pyridine synthesis by including an appropriate leaving group on the triene *N*-terminus, as is the case with oximes and oxime ethers. A range of natural products have been synthesized using this particular strategy.[110] Of note is the preparation of a large number benzo[*c*]phenanthridine alkaloids, natural products possessing a wide range of interesting pharmacological properties,[111] starting from substituted oxime ethers **327** (Scheme 64).[112] Heating the latter to 180 °C with microwave irradiation results in aza-6π electrocyclization to a pentacycle **328**, which readily eliminates methanol to yield various phenanthridines **329a–d**.

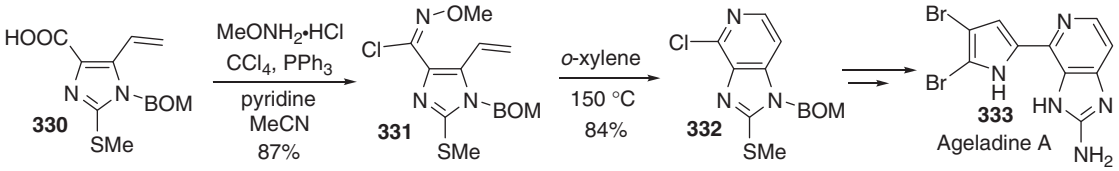
The aza-6π electrocyclization of oxime ethers can provide expedient access to pyridines with substitution patterns that are more difficult to make by conventional cyclocondensation methods. In a total synthesis of ageladine A **333**,[113] a zinc matrixmetalloproteinase inhibitor, carboxylic acid **330** was directly converted into α-chloro oxime ether **331** (Scheme 65).[114] Thermal aza-6π electrocyclic ring closure by heating in *o*-xylene, followed by the elimination of methanol, gave pyridine **332**, which was later successfully used to assemble the natural product ageladine A **333**.

A number of related methodologies have been developed using the rhodium-catalyzed β-C – H bond activation of α,β-unsaturated imines and ketoximes for the synthesis of highly substituted pyridines (See also Scheme 58).[115] Using Wilkinson's catalyst, ketoximes **334** have been shown to undergo β-C – H bond functionalization and addition across alkynes to give pentadienyl oxime intermediates **335**, which are susceptible to aza-6π electrocyclization accompanied by dehydration under the reaction conditions (Scheme 66).[116]

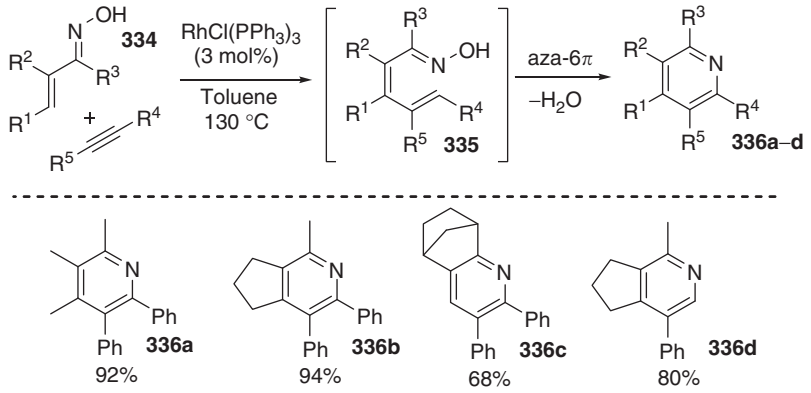


329	R^1	R^2	R^3	Yield (%)
a	H	OMe	OMe	84
b	H	$-OCH_2O-$		94
c	OAc	OMe	H	77
d	$-OCH_2O-$		H	95

Scheme 64 The total synthesis of benzo[*c*]phenanthridine alkaloids using an aza-6π electrocyclization. Reproduced from Ishihara, Y.; Azuma, S.; Choshi, T.; *et al. Tetrahedron* **2011**, *67*, 1320.



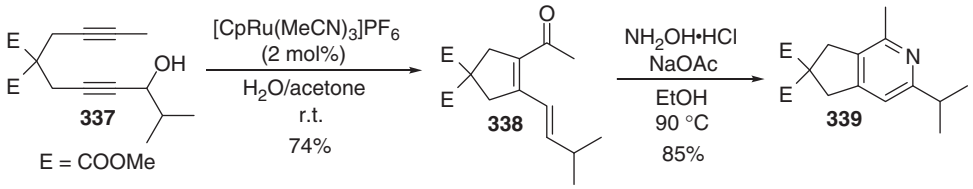
Scheme 65 Aza-6π electrocyclization of an α-chloro oxime ether. Reproduced from Kikugawa, Y.; Fu, L. H.; Sakamoto, T. *Synth. Commun.* **1993**, *23*, 1061.



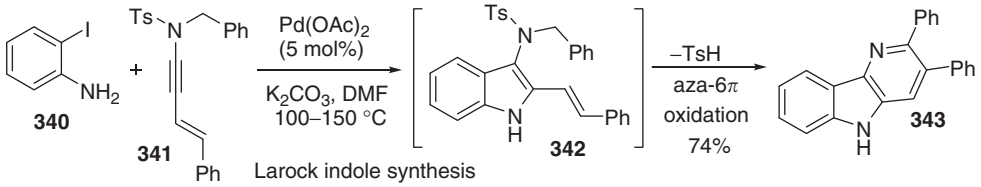
Scheme 66 Rh-catalyzed one-pot synthesis of pyridines from ketoximes and alkynes. Reproduced from Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325.

Direct condensation of hydroxylamine hydrochloride with a dienyl ketone **338** can result in the formation of a substituted pyridine **339** by oxime formation, aza-6π electrocyclization and dehydration (Scheme 67).[93,117] In this case, cyclic dienyl ketones **338** were prepared by the ruthenium-catalyzed cycloisomerization of diynol **337** and a range of five-membered ring-fused 2,3,4,6-substituted pyridines **339** could be prepared in only a few steps.[118]

The use of both 2- and 3-azatrienes to synthesize pyridines has been described as well, although to a much more limited extent.[4] Nevertheless, some interesting methodologies making use of these approaches have been reported, such as using *N*-tosyl-enynamines **341** as alkyne acceptors in the Larock indole synthesis (Scheme 68).[119] Along these lines, employing iodoaniline **340** as a coupling partner, intermediate indole **342** is produced, which undergoes base-mediated elimination of the *N*-tosyl group to form a 2-azatriene system (not shown) that engages in a 6π electrocyclization and concomitant autoxidation to yield δ-carboline **343**. This mechanistic proposal was based on the fact that both indole **342** and the aforementioned 2-azatriene intermediate could both be isolated from the reaction mixture when the reaction was performed at lower temperatures.

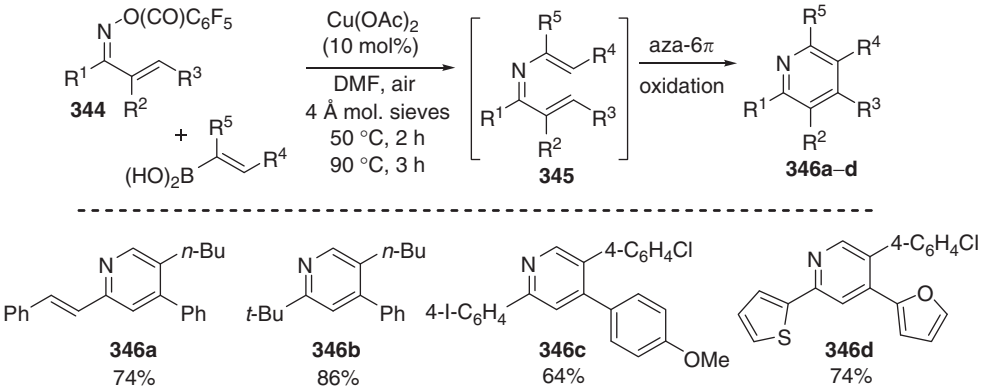


Scheme 67 Sequential Ru-catalyzed cycloisomerization and pyridine synthesis via ketoxime formation. Reproduced from Schiess, P.; Chia, H.; Ringele, P. *Tetrahedron Lett.* **1972**, *13*, 313.



Scheme 68 Synthesis of δ-carbolines by chaining the Larock indole synthesis with 2-azatriene 6π electrocyclization. Reproduced from Cao, J.; Xu, Y.; Kong, Y.; *et al. Org. Lett.* **2012**, *14*, 38.

Of additional note is the copper-catalyzed C–N coupling of an α,β-unsaturated ketoxime *O*-pentafluorobenzoate **344** with a vinyl boronic acid, which proceeds via 3-azatriene intermediate **345** to generate highly substituted pyridines **346a–d** by aza-6π electrocyclization and subsequent autoxidation (Scheme 69).[120] The reaction is remarkably functional group tolerant, and leaves aryl halides (including iodide), esters, nitriles and nitro groups untouched. The R^1 substituent is limited to groups that do not posses C(sp^3) – H bonds, since it enables [1,5]-hydrogen shifts that compete with the desired 6π electrocyclization.



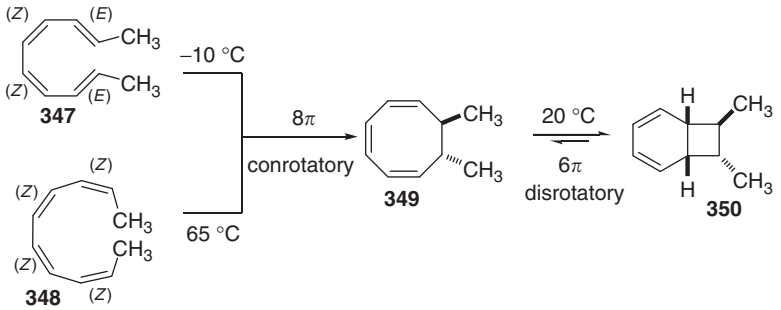
Scheme 69 A modular synthesis of pyridines via C–N coupling and 6π electrocyclization of a 3-azatriene. Reproduced from Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

5.17.5 8π-6π Electrocyclization Cascades

5.17.5.1 General Reactivity of 1,3,5,7-Octatetraene Systems

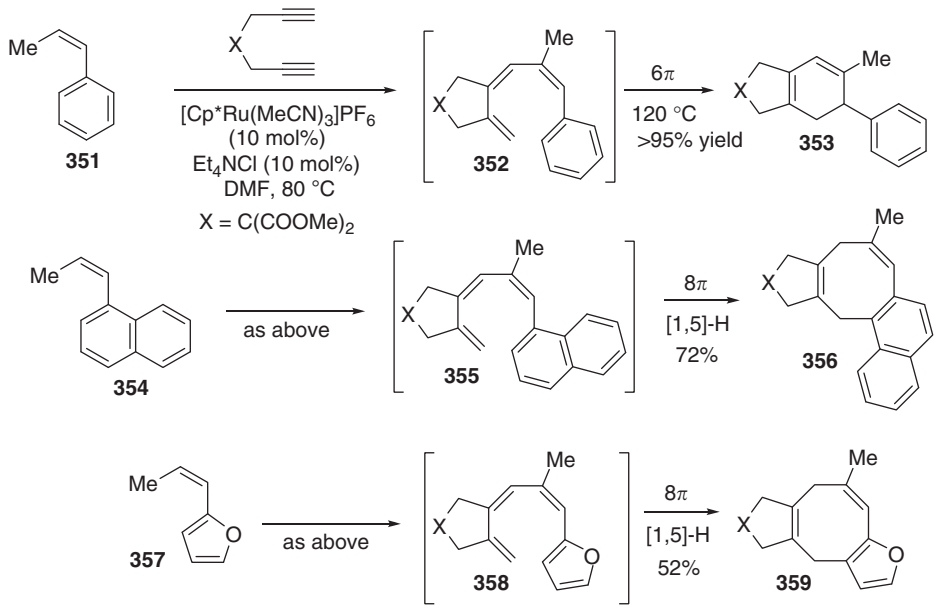
Conjugated tetraenes with (*Z*,*Z*)-substituted double bonds in their center, such as **347** or **348**, undergo rapid conrotatory 8π electrocyclization to afford cyclooctatrienes **349**, which is usually followed by a disrotatory 6π electrocyclization affording bicyclo[4.2.0]octa-2,4-diene products **350** (Scheme 70).[4] This unusually facile second ring closure is attributed to the fixed (*Z*)-alkene stereochemistry of the central double bond and the cyclic geometry, which brings the 1,3,5-triene termini into close proximity. Early on, it was recognized that 1,3,5-cyclooctatriene is in equilibrium with bicyclo[4.2.0]octa-2,4-diene at 80 °C via 6π electrocyclic ring-closing/ring-opening.[121] The conrotatory nature of 8π electrocyclizations has been firmly established, believed to occur by a Möbius aromatic transition state.[122] Its helical character has been proposed to account for the increased rate of cyclization over typical 6π processes, owing to a lack of strain and steric congestion in the transition state at the reacting termini of the tetraene.[123] It is worth noting that the same product (**349**) can arise from two different tetraene precursors whose two terminal

double bonds are both of opposite configuration (**347** vs. **348**). As with other electrocyclizations possessing low activation energy barriers, the 8π electrocyclization is also often reversible and thus under thermodynamic control, complicating the predictability of the various isomers resulting from such cascades.



Scheme 70 The 8π-6π electrocyclization cascade.

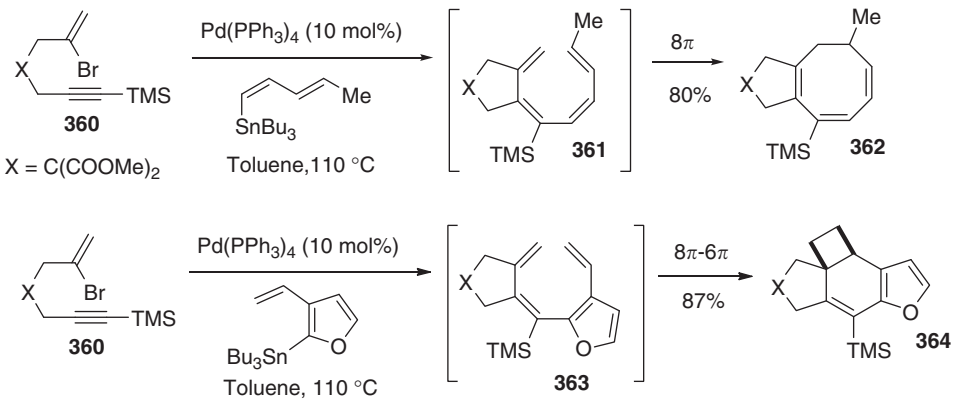
Although the 8π cyclization mode of 1,3,5,7-tetraenes tends to be significantly faster than 6π cyclization, there are certain cases where the two pathways compete, particularly under reaction conditions that allow for alkene isomerization,[4] since two (*Z*)-configured alkenes are required for the 8π cyclization. Interestingly, replacing one of the alkenes in the tetraene system with an aromatic ring can cause the two electrocyclization pathways to diverge, depending on the nature of the arene (Scheme 71).[124] For instance, the ruthenium-catalyzed cycloisomerization of diynes and addition to alkenes, such as styrene **351**, produces a 1,3,5,7-tetraene intermediate **352** that undergoes 6π electrocyclization at 120 °C to furnish 1,3-cyclohexadiene **353** in quantitative yield. Conversely, if the reaction is carried out with an arene other than benzene, as in naphthalene **354** or furan **357**, the intermediate tetraenes **355** and **358** preferentially react by 8π electrocyclization with concomitant [1,5]-hydrogen shift to restore aromaticity. This behavior has been attributed to the lesser degree of aromaticity in the latter substrates.



Scheme 71 Competition between 8π and 6π electrocyclizations decided by degree of aromaticity. Reproduced from García-Rubin, S.; Varela, J.; Castedo, L.; Saá, C. *Org. Lett.* **2009**, *11*, 983.

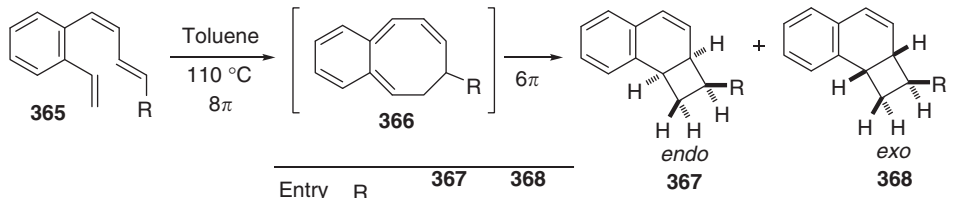
Even though 6π ring closure commonly succeeds 8π electrocyclizations, substrates with rings fused to the tetraene system can halt the cascade after the first step by imposing geometric constraints that disfavor the 6π ring-closing, or render competing processes operative, such as the [1,5]-hydrogen shift seen in the previous example. However, in some cases tetraene systems with fused rings can participate in 8π-6π cascades if there is a sufficient driving force for the second step. To illustrate, tetraene **361**, generated from the domino 5-*exo-dig* carbopalladation/Stille coupling of enyne **360**, undergoes facile 8π electrocyclization to 1,3,5-triene **362** without subsequent 6π ring-closing (Scheme 72).[125] By contrast, exchanging the Stille coupling partner gives rise

to tetraene **363** with an embedded furan ring, which engages in an 8π-6π cascade that is driven by rearomatization of the furan and proceeds in high efficiency despite forming a strained cyclobutane **364**.



Scheme 72 An 8π-6π cascade driven by a gain in aromaticity. Reproduced from Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323.

When an aromatic ring is incorporated at the 3,4-position of a tetraene system rather than at the terminus, the 8π-6π cascade mode is strongly favored. Heating 3,4-benzo-fused tetraene **365** induces 8π cyclization to the triene system **366**, which is also an *o*-quinone dimethide, that undergoes a second electrocyclization to restore aromaticity and give bicyclo[4.2.0]octa-2,4-diene products **367**/**368**, with bulkier substituents leading to preferential formation of the *endo* product (Scheme 73).[126]

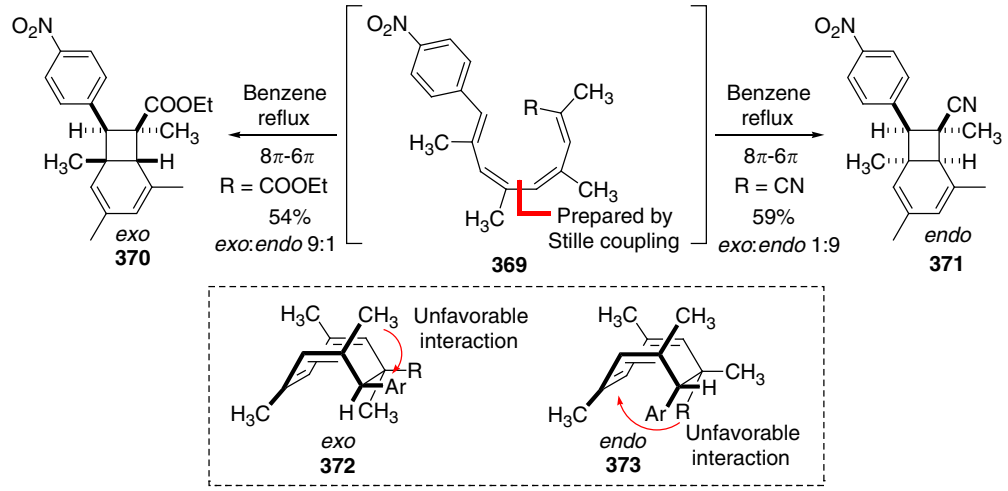


Entry	R	367 (%)	368 (%)
a	Me	33	11
b	Ph	73	–
c	2-furyl	56	–

Scheme 73 The 8π-6π cascade cyclization of [3,4]-benzo-octatetraenes. Reproduced from Skorić, I.; Pavoševic, F.; Vazdar, M.; *et al. Org. Biomol. Chem.* **2011**, *9*, 6771.

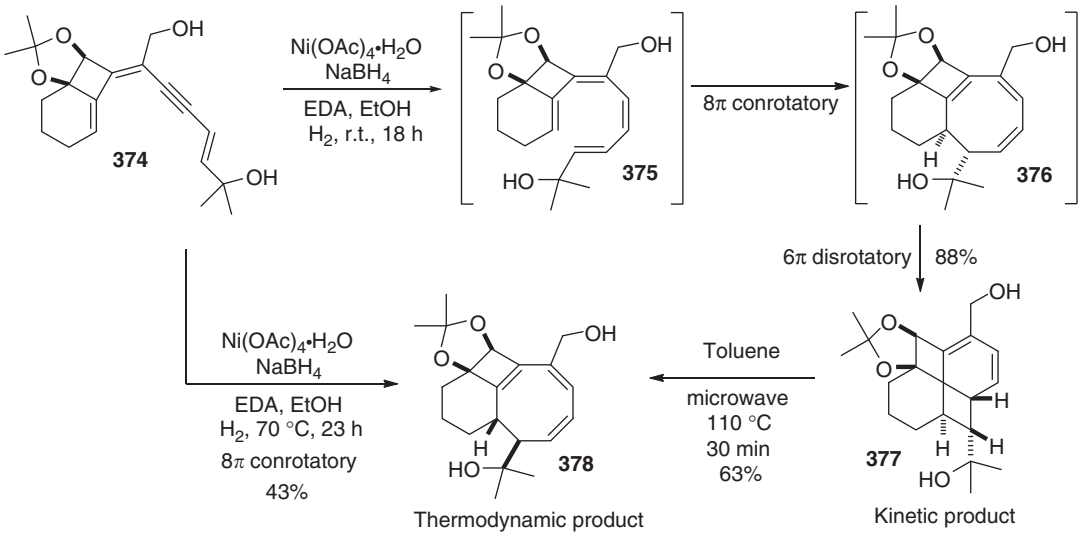
If the tetraene system has different substituents at its termini, diastereomeric *endo*/*exo* bicyclo[4.2.0]octa-2,4-diene products can be generated from the 6π electrocyclization step. The selectivity outcome can sometimes be difficult to predict, since it depends on the substituent interrelationships and can exhibit dramatic switches in *endo*/*exo* product distribution (Scheme 74).[127] For example, tetraene **369**, that was prepared *in situ* by Stille coupling, underwent 8π electrocyclization with subsequent *exo* selective 6π ring closure to bicyclo[4.2.0]octa-2,4-diene **370** when R═COOEt, but when R═CN, the 6π cyclization favored the *endo* bicyclo[4.2.0]octa-2,4-diene **371** instead. To account for this, a simple qualitative model was proposed based on the presumed conformer leading to 6π electrocyclization. The *exo* mode of cyclization **372** is presumed to incur an unfavorable steric interaction between the aryl group and the adjacent methyl substituent, making the *endo* mode **373** generally preferred for this type of substrate unless the R group is relatively large, in which case the R group prefers to be oriented outward from the cyclic system. In this example, the reduced steric demand of a nitrile substituent favors the *endo* product **371**, whereas the energetic benefit of orienting the ester substituent outward in *exo*-**372** outweighs the unfavorable aryl/methyl interaction and results in the predominant formation of *exo*-**370**.

Although induced stereoselectivity in 8π-6π cascades is little understood and has not been sufficiently studied, there are some examples where a high degree of substrate control was observed. An example in the synthesis of strained [4.6.4.6]-fenestradiene **377**, wherein enyne **374** was reduced with nickel boride at room temperature to give intermediate tetraene **375** (Scheme 75).[128] The ensuing 8π conrotatory/6π disrotatory ring closure yielded the product fenestradiene **377** as a single diastereomer. The initial conrotatory 8π cyclization was proposed to occur via a Möbius aromatic *M*-helical transition state, with the tetraene oriented on the same convex face as the acetonide moiety, which was supported by DFT calculations.[129] Further mechanistic studies revealed that fenestradiene **377** is actually the kinetic product, as reduction of enyne **374** at higher temperatures led to the formation of



Scheme 74 Control of bicyclo[4.2.0]octa-2,4-diene *endo*/*exo* selectivity by choice of substituent. Reproduced from Parker, K. A.; Lim, Y.-H. *Org. Lett.* **2004**, *6*, 161.

triene **378** instead, which was assigned as the thermodynamic minimum in this particular system. The cascade was shown to be reversible, since microwave heating of fenestradiene **377** also induced conversion into triene **378**.

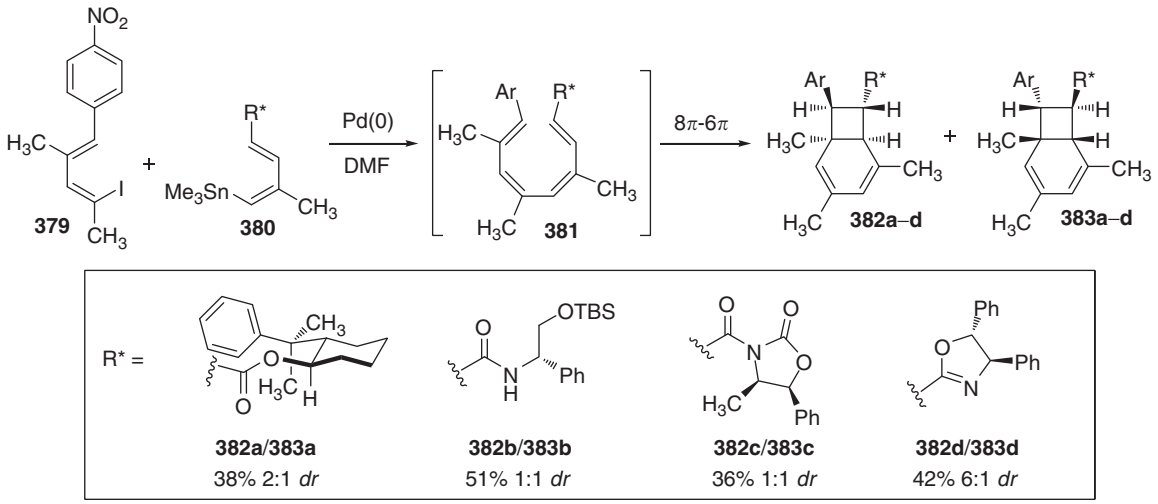


Scheme 75 Synthesis of fenestradienes base on an 8π-6π electrocyclization cascade. Reproduced from Hulot, C.; Blond, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046.

Inducing asymmetry in 8π-6π electrocyclizations through the use of a removable chiral auxiliary has been met with very limited success. The Stille coupling of vinyl iodide **379** to a small range of chiral vinyl stannanes **380** with subsequent 8π-6π electrocyclization to form diasteromeric bicyclo[4.2.0]octa-2,4-dienes **382a–d**/**383a–d** was used as a test system to screen for asymmetric induction (Scheme 76),[130] since tetraenes of this type are known to undergo *endo*-selective 6π electrocyclization (Scheme 74). Although modest levels of selectivity were observed using the menthol-based auxiliaries **382a**/**383a** at the tetraene terminus, oxazoline **382d**/**383d** gave synthetically useful levels of stereoinduction.

5.17.5.2 Biomimetic 8π-6π Reaction Cascades

In what is now considered a classic example, the feasibility of 8π-6π cascades in biomimetic synthesis was first demonstrated by a synthesis of the endriandric acids in the early 1980s (Scheme 77).[131] This family of natural products includes members such as endriandric acid methyl esters A **394** and B **395**, which each possess eight stereogenic centers, but occur in nature as racemates.



Scheme 76 Asymmetric induction in 8π-6π electrocyclization cascades with a removable chiral auxiliary. Adapted from Parker, K. A.; Wang, Z. *Org. Lett.* **2006**, *8*, 3553, and Kim, K.; Lauher, J. W.; Parker, K. A. *Org. Lett.* **2012**, *14*, 138.

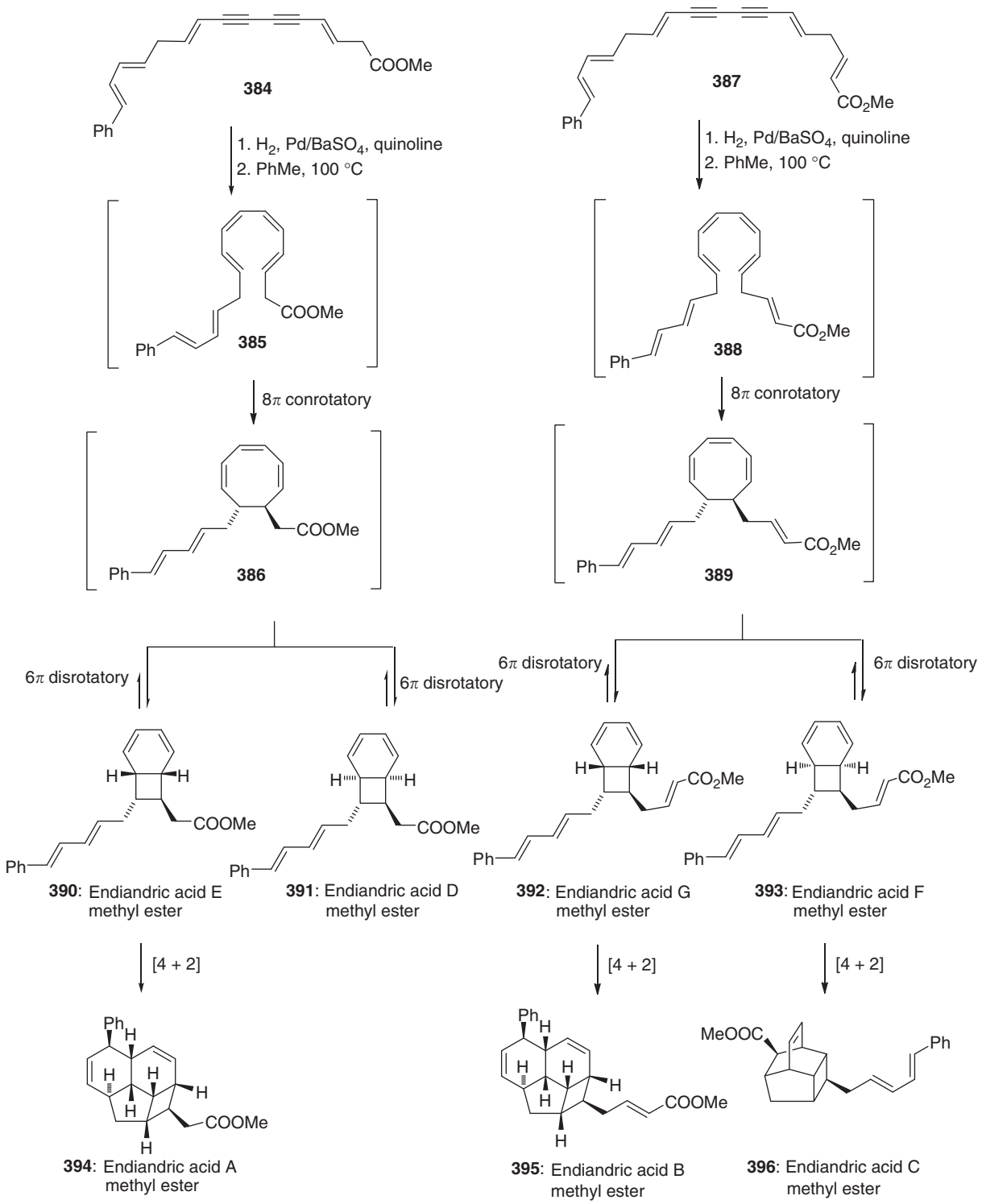
This observation led to the original hypothesis that an 8π-6π electrocyclization/Diels–Alder cascade (*see* Chapter 5.11) was involved in their biosynthesis, starting from achiral polyenes **385**/**388**, without the intervention of enzymes.[131] This spawned an elegant biomimetic synthesis, wherein (*Z*)-selective hydrogenation of diynes **384**/**387** at room temperature resulted directly in the formation of endriandric acid methyl esters E **390**, D **391**, G **392** and F **393** via the 8π-6π electrocyclization cascade (Scheme 77). Alternatively, heating a mixture of endriandric acid methyl esters G **392** and F **393** to 100 °C gave endriandric methyl esters B **395** and C **396**, arising from an intramolecular Diels–Alder reaction. Similarly, endriandric acid methyl esters E **390** and D **391** converged to endriatic acid methyl ester A **394** upon heating the mixture to 100 °C. It is worth noting that endriatic acid methyl ester A **394** cannot be formed directly by endriandric acid methyl ester D **391**, implying the 6π electrocyclization is reversible and that **391** first converts to endriandric acid methyl ester E **390**, funnelling the entire mixture through the intramolecular Diels–Alder pathway. This conjecture was further supported by the conversion of endriandric acid methyl ester E **390** to and equilibrium mixture of E **390**/ D **391** by heating at 70 °C in toluene.

Since this landmark achievement, several additional natural products believed to originate from 8π-6π cascades have been identified, some of which have been targeted by synthetic chemists. In particular, diastereomeric polyketides SNF4435 C **402** and D **403**, isolated from a culture broth of *Streptomyces spectabilis*,[132] have been the subject of a number of synthetic studies (Scheme 78).[133] In contrast to the endriandric acid family, the SNF4435 compounds were isolated as single enantiomers, which were proposed to result from the partially diastereoselective 8π ring-closing of chiral γ-pyrone **399** to form 1,3,5-triene diastereomers **400** and **401**. The subsequent 6π electrocyclization was expected to be completely *endo*-selective, since the corresponding *exo* isomers were not detected in the original isolation study. Indeed, the generation of γ-pyrone **399** from the Stille coupling of vinyl stannane **397** and vinyl iodide **398** ultimately delivers SNF4435 C **402** and D **403** in 67% and 22% yields respectively, which resembles the ratio of the mixture isolated from nature.

Further speculation into the biosynthetic origin of SNF4435 C **402** and D **403** led to re-examining the metabolic profile of *S. orinoci*, an organism that produces spectinabilin **404** under various sets of conditions (Scheme 79).[134] It was postulated that intermediate *E*,*Z*,*Z*,*Z*-tetraene **399**, from the total synthesis of SNF4435 C **402** and D **403**, arises biosynthetically from the photoisomerization of spectinabilin **404**, followed by the 8π/6π electrocyclization cascade depicted in Scheme 79. Indeed, when fermentation and workup of *S. orinoci* was carried out in the dark, no SNF4435 C **402** or D **403** were detected. However, exposure of either the culture or pure spectinabilin **404** to daylight resulted in the formation of SNF4435 C **402** and D **403**, along with small amounts of an additional metabolite orinocin **405**, which appears to be produced from the SNF4435 natural products via retro [2 + 2] cycloaddition. It was also possible to detect mesitylene in the mixture using gas chromatography/mass spectroscopy, providing additional support for the involvement of this mechanism. These studies indicate that the SNF4435 compounds owe their biogenesis to a nonenzymatic alkene photoisomerization of spectinabilin **404** and put forth that mesitylene is in fact a natural product, which can be traced back biosynthetically to an 8π/6π electrocyclization/retro [2 + 2] cycloaddition cascade.

Polyketide natural products isolated as single enantiomers from the marine fungus *Emericella variecolor*, the shimalactones A **411** and B **412**, are also believed to be the consequence of a biosynthetic pathway featuring a moderately torquoselective 8π electrocyclization, followed by a highly diastereoselective 6π electrocyclization (Scheme 80).[135] This too is supported by a synthetic study, in which the enantiomerically enriched alcohol **406** was cross-coupled with oxabicyclo[2.2.1]heptane **407**, resulting in a spontaneous 8π-6π cascade at room temperature that afforded the two diasteromeric shimalactone natural products **411** and **412** in a 5:1 ratio.

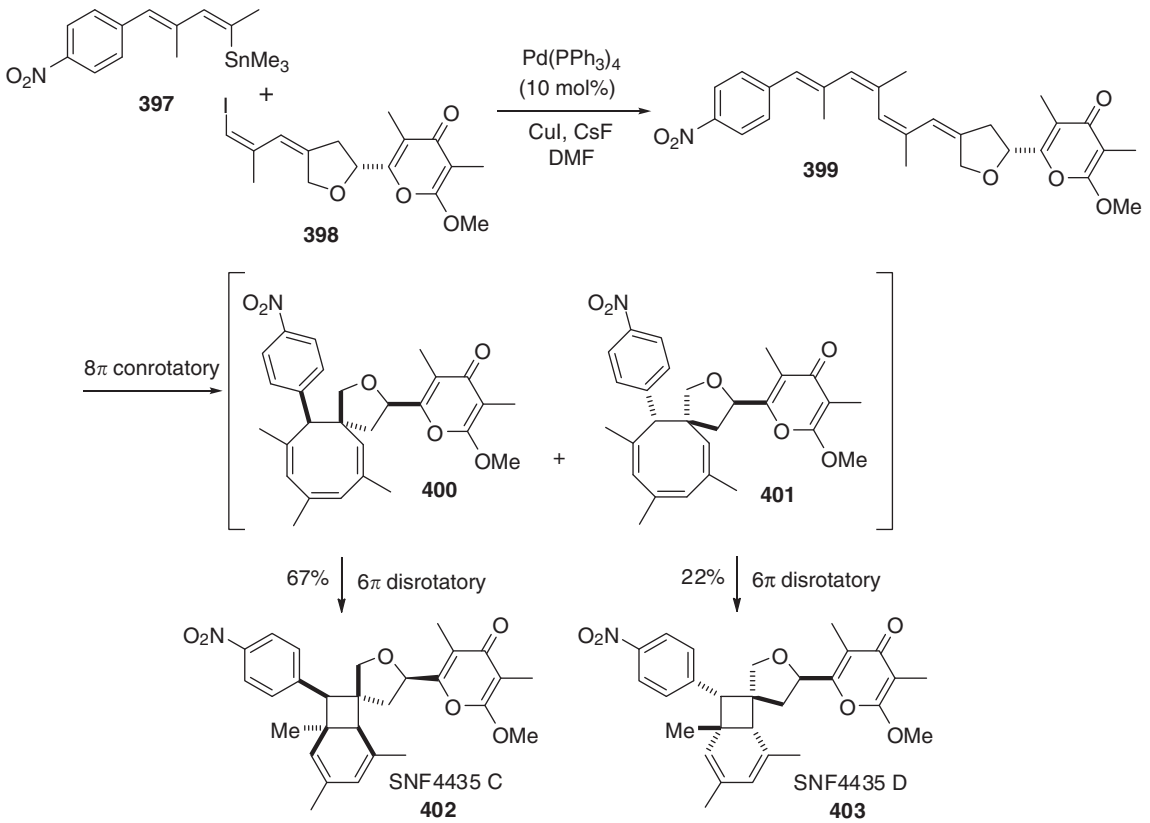
The bicyclo[4.2.0]octane motif present in the sesquiterpene natural product (–)-coprinolone **416** has led to speculation that an 8π-6π cascade is involved in its biogenesis (Scheme 81). Preliminary investigations have demonstrated that trienone **413** can



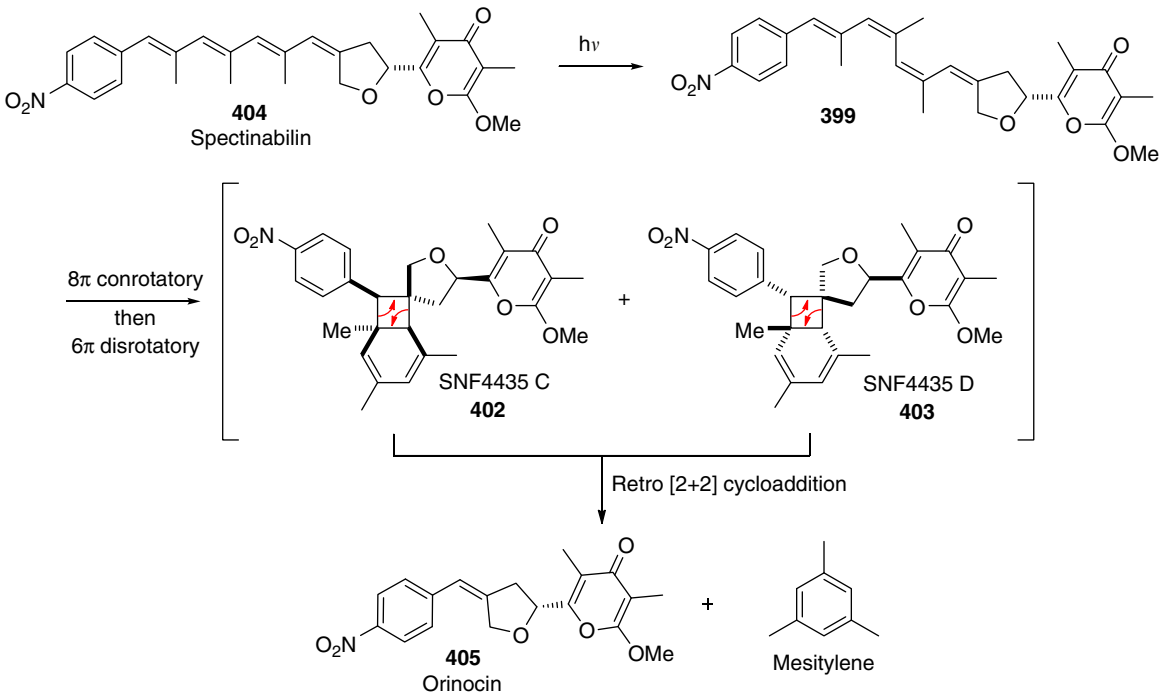
Scheme 77 Biomimetic synthesis of the endriatic acids. Reproduced from Beaudry, C.; Malerich, J.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

transiently form a 1,3,5,7-tetraene system **414** via keto–enol tautomerism in methanol at 110 °C, which undergoes 8π-6π electrocyclization in modest yield.[136] The product enone **415** possesses the same relative stereochemistry as the natural product (–)-coprinolone **416**, lending some support to the biosynthetic hypothesis.

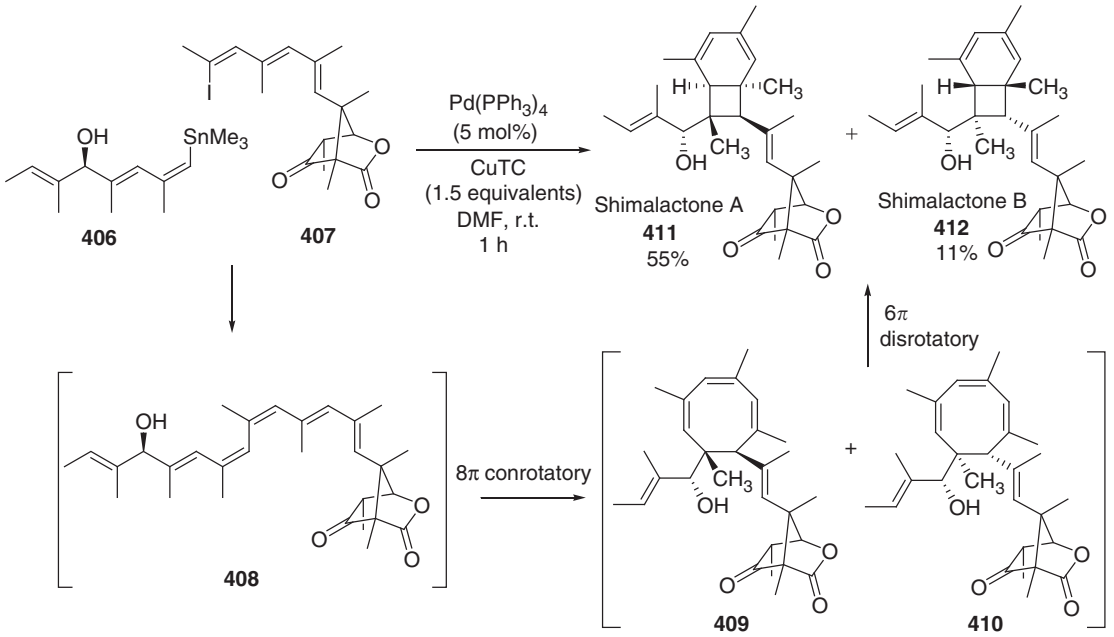
The Bcl-xL/Bak interaction inhibitor kingianin A **417**,[137] a natural product isolated from the bark of the Malaysian *Endiandra kingiana* Gamble, has been proposed to form biosynthetically from an *endo*-Diels–Alder dimerization of the corresponding homochiral bicyclo[4.2.0]octa-2,4-diene *endo*-**418** (Scheme 82).[138] The natural product was isolated as a racemate, suggesting that



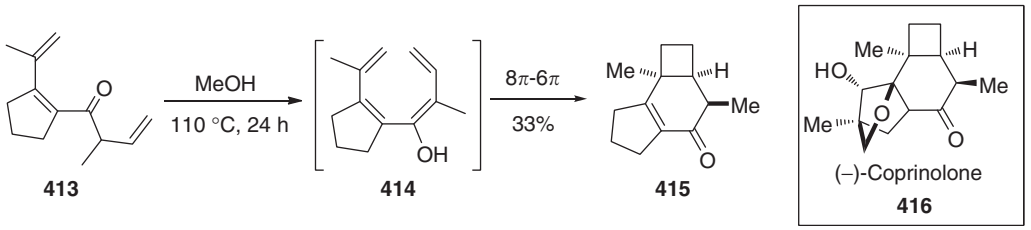
Scheme 78 Biomimetic synthesis of SNF4435 C and SNF4435 D. Reproduced from Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968.



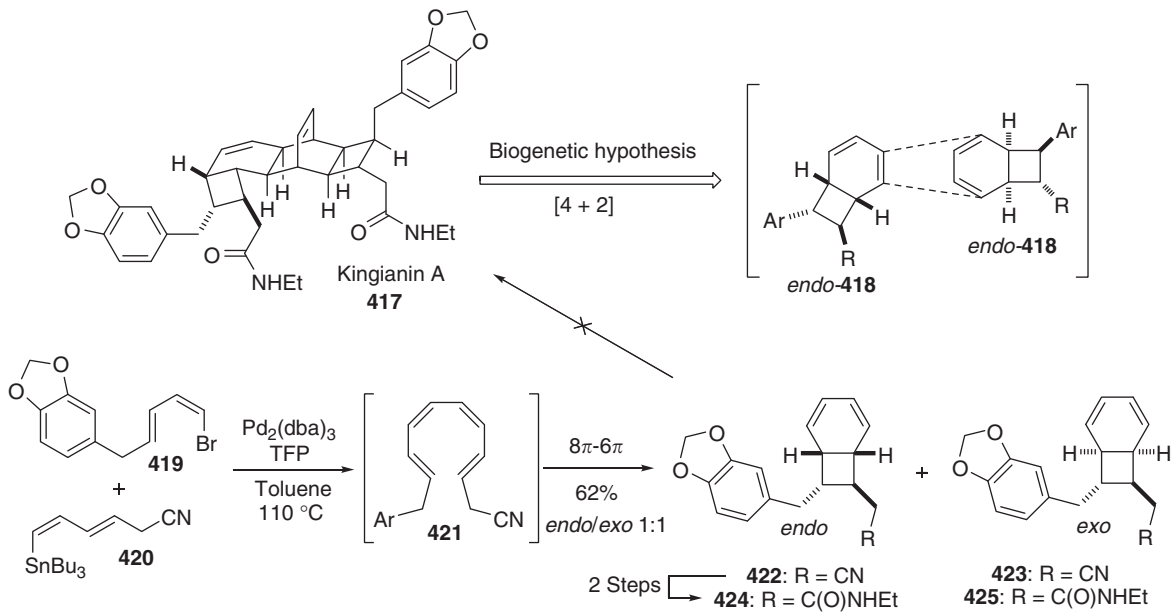
Scheme 79 Biosynthetic origin of SNF4435 C/D from a photoinduced electrocyclization cascade. Reproduced from Müller, M.; Kusebauch, B.; Liang, G.; *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 7835.



Scheme 80 Biomimetic synthesis of shimalactones A and B. Reproduced from Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149.



Scheme 81 Keto–enol tautomerism induced 8π-6π electrocyclization cascade toward the synthesis of (–)-coprinolone. Reproduced from Lawrence, A. L.; Hermann, W. A.; Jacobsen, M. F.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* **2006**, 8717.



Scheme 82 Approach to kingianin A based on a speculated biosynthesis involving 8π-6π electrocyclization/dimerization. Reproduced from Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47*, 10605.

an enzyme may not be involved in its biosynthesis. A synthetic study aimed to verify this hypothesis, forming the requisite (*E*,*Z*,*Z*,*E*)-tetraene **421** from the Stille coupling of vinyl bromide **419** and vinyl stannane **420** at 110 °C in toluene.[139] The ensuing electrocyclization cascade occurred with an unselective 6π step, leading to a 1:1 separable mixture of *endo*-**422** and *exo*-**423** diastereomers. Counter to the proposed biosynthesis, various forcing conditions (195 °C) were unsuccessful at promoting the formation of kingianin A **417** from either *endo*/*exo* diastereomer of nitriles **422**/**423** or amides **424**/**425**. It was demonstrated that the 6π electrocyclization is reversible in this case, as prolonged heating of either bicyclo[4.2.0]octa-2,4-diene diastereomer **424**/**425** converged to a 1:1 equilibrium mixture. Therefore, it does not rule-out that the dimerization of a homochiral bicyclo[4.2.0]octa-2,4-diene **418** is somehow implicated in the biosynthesis of kingianin A **417**, raising the interesting question of how such a dimerization could occur *in vivo*.

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5.18 The Nazarov Cyclization

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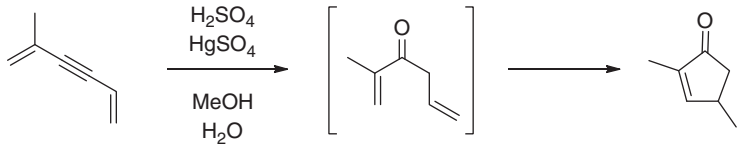
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Glossary

Chirality transfer Creation of one or more new stereocenters/axes if chirality in a molecule under the influence of a preexisting stereocenter/axis of chirality, with simultaneous destruction of the original stereocenter/axis of chirality.
Electrocyclization A pericyclic, orbital symmetry-controlled cyclization of an extended π-system, forming a new σ-bond and a new ring.
***endo* isomer** A diastereomer of a bridged bicyclic compound in which the substituent(s) in question is (are) located *syn* to the longest bridge.
***exo* isomer** A diastereomer of a bridged bicyclic compound in which the substituent(s) in question is (are) located *anti* to the longest bridge.
Organocatalysis Enhancement of the rate of a reaction through the addition of a nonmetallic catalyst (typically a small organic molecule).
Oxyallyl cation A delocalized allylic cation bearing oxygen substitution at the central carbon (C-2).
Pericyclic reaction An orbital symmetry-controlled reaction involving a cyclic transition state with concerted bond formation and cleavage.
Torquoselectivity A preference for one of two possible directions of rotation during either electrocyclic opening or closure.
Vinylogous A structure or process that through the addition of one or more π bonds permit conjugation of two moieties that were directly attached in the original version.
Wagner–Meerwein rearrangement A cationic rearrangement, common in polycyclic ring systems, involving the 1,2-migration of hydrogen, alkyl, or aryl substituents to a carbocationic center from the neighboring atom.

5.18.1 Introduction

The Nazarov cyclization[1] has emerged as an effective means for converting divinyl ketones to cyclopentenones since its discovery in 1903 by Vorländer,[2] with later structural correction in 1955.[3] It gained popularity following the investigations by Nazarov et al. into the hydration of dienynes with mercury salts to form cyclopentenones in the 1940s and 1950s (Scheme 1).[4]



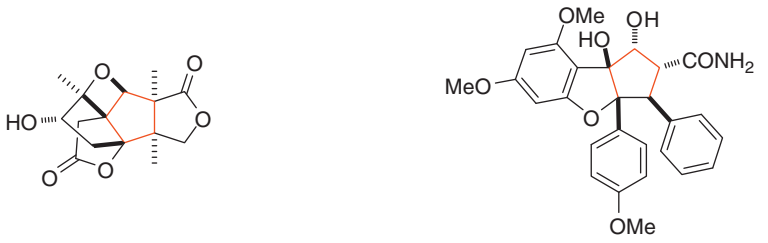
Scheme 1

Since this time, studies have effectively elucidated the mechanism of this transformation, developed means to control regioselectivity in the elimination event, intercepted the oxyallyl cation, and showcased new methods to access the pentadienyl cation intermediate.[1] The Nazarov cyclization has also been shown to be effective in the synthesis of numerous natural products. Highlights of these syntheses include the synthesis of (±)-merrilactone A, where the Frontier group used a Nazarov cyclization to form the C-ring (Figure 1–1).[5] The Frontier group also used an oxidative entry to the Nazarov cyclization in their synthesis of (±)-rocaglamide (Figure 1–2).[6] Furthermore, Williams utilized a Nazarov cyclization to form the cyclopentenone present in (+)-fusicoauritone (Figure 1–3),[7] whereas Tius utilized the reaction in his synthesis of (+)-mandinoline A and its cyclopentendione epimer (+)-mandinoline B (Figure 1–4).[8]

5.18.1.1 Mechanism and Activation

The mechanism for the Nazarov cyclization was covered in detail in the previous edition of Comprehensive Organic Synthesis, and will therefore be addressed only briefly.[1a] In its conventional form, the reaction begins with activation of a cross-conjugated dienone (5) forming a pentadienyl cation (6) (Scheme 2).[3,9] This cation is a conjugated 4π system capable of undergoing an electocyclization,[10] closing the ring in a stereospecific conrotatory fashion. This electrocyclization forms a 2-hydroxycyclopentenyl cation (7), which then undergoes proton elimination and enol tautomerization to form a cyclopentenone (8).

Activation of divinyl ketones has traditionally been done with stoichiometric amounts of strong Brønsted or Lewis acids,[1b] limiting the scope of dienones to those that could tolerate such harsh conditions. Recent findings by the Greaney group have shown that cyclization can occur in the absence of acid, instead mediated by higher reaction temperatures and the use of a microwave reactor.[11] By subjecting dienones with substituents at both α-positions, conversion to cyclopentenones can be seen in good to excellent yield (equation 1). The solvent choice was shown to be imperative, as only dimethylacetamide and the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate ($EMImBF_4$) were successful solvents.



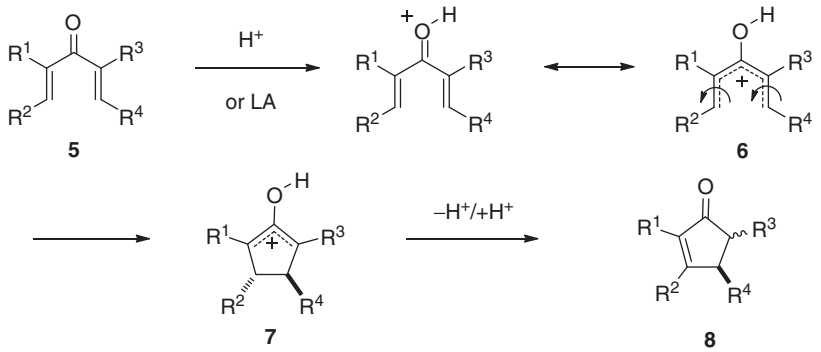
(±)-Merrilactone A **1**

(±)-Rocaglamide **2**

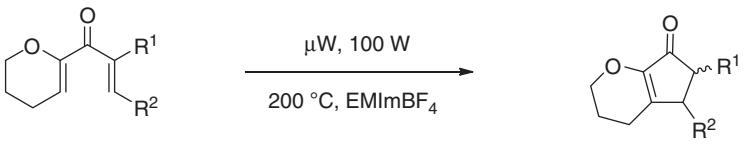
(+)-Fusicoauritone **3**

(+)-Mandinoline A **4**

Figure 1 Selected natural product syntheses utilizing Nazarov cyclizations.



Scheme 2

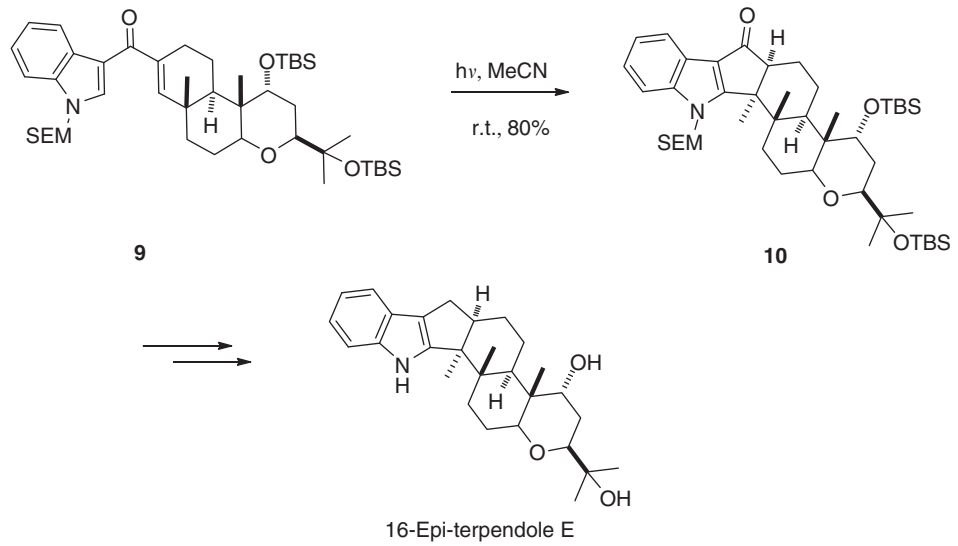


(1)

R^1 = Me, R^2 = Et, 61%
R^1 = Me, R^2 = H, 82%
R^1, R^2 = $(CH_2)_4$, 71%
R^1 = Ph, R^2 = Ph, 56%

5.18.1.1.1 Photochemical activation

The Nazarov cyclization can also be initiated by photolysis. When dienones are subjected to photolytic conditions, the ring closure occurs via a disrotatory electrocyclization, setting the *β*-position stereocenters in the opposite *syn*/*anti* relationship to that of the thermal conditions.[10] The Giannis group showcased a photochemical Nazarov in their synthesis of 16-*epi*-terpendole E. The enone was irradiated with 350 nm light, forming the desired cyclopentenone in 80% yield, before being carried out through four more steps to get to the target molecule (Scheme 3).[12]



Scheme 3

5.18.1.2 Directing Groups

For a long time, a major issue inhibiting the widespread utilization of the Nazarov cyclization in synthesis lay in its final mechanistic step, the elimination. For an unsymmetrical dienone, there are four possible elimination options, leaving the alkene in either an *endo* or an *exo* disposition, and on either side of the ring (Figure 2).

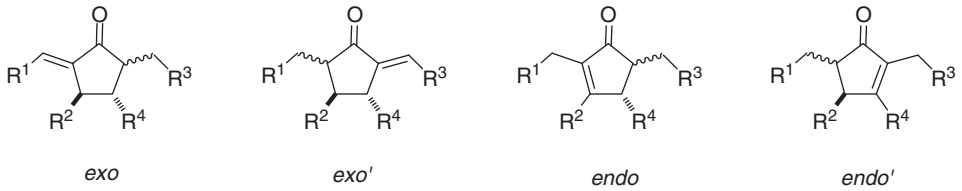
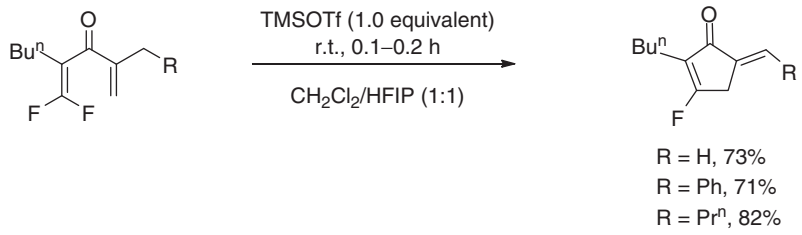


Figure 2 Possible alkene regioisomers.

To address the regioselectivity problem, Denmark et al. developed the silyl-directed Nazarov reaction. The results of these studies, as well as their tin-based counterparts, have been discussed in detail in the previous edition of Comprehensive Organic Synthesis.[1a]

5.18.1.2.1 Effects of fluorine

In contrast to the directing effect of silicon, which installs the alkene selectively with concomitant loss of the silyl group, fluorine was shown by Ichikawa et al. to have a β-destabilizing effect, and directed the elimination to the other side of the ring.[13] By subjecting β-difluoro substituted dienones to trimethylsilyl trifluoromethansulfonate (TMSOTf), elimination was found to occur on the opposite side of the ketone from the fluorines and exclusively in an exocyclic manner. The sequence concluded with elimination of one of the fluorides to afford a second C=C bond (equation 2).

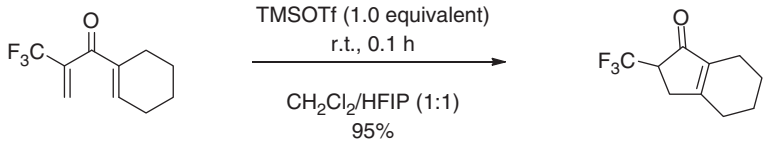


(2)

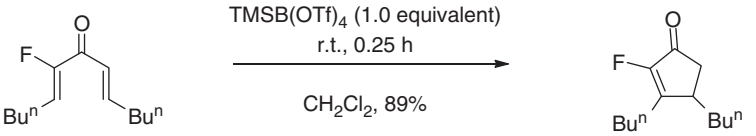
R = H, 73%
R = Ph, 71%
R = Pr^n, 82%

Ichikawa also showed that fluorine atoms at the α-position of the dienone can exert useful directing effects. Placement of a trifluoromethyl group at an α-position led to reactivity analogous to the β-substituted case, directing the elimination to the other side of the ring.[14] However, in these cases, elimination was shown to favor the endocyclic alkene, and elimination of a fluorine to

form the second double bond was not observed (equation 3). Placement of fluorine at the α-position of the dienone reversed the selectivity of the elimination as fluorine has an α-stabilizing effect on cations.[15] In this case, elimination occurred toward the fluorine atoms to afford 2-fluorocyclopentenone in high yield (equation 4).



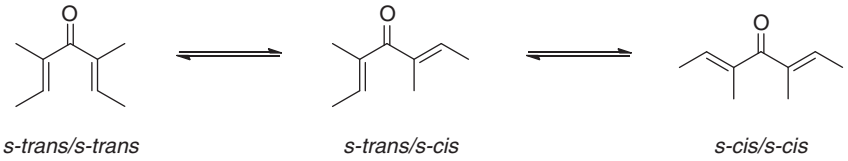
(3)



(4)

5.18.1.3 Substituent Effects

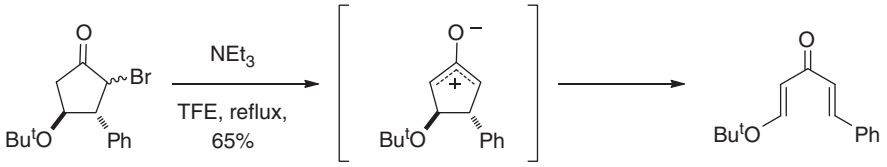
The degree of substitution on dienone substrates has significant effects on the Nazarov cyclization. Alkyl substitution at positions 2 and 4 of the dienone is especially important. Substitution with an alkyl group at either of these positions is believed to increase the population of the reactive *s-trans/s-trans* conformer, facilitating cyclization (Scheme 4).[16] When a hydrogen occupies the α-position, the s-*cis* conformers dominate, leading to diminished reactivity.



Scheme 4

5.18.1.3.1 The retro-Nazarov

β-Electron-donating substituents such as alkoxy groups stabilize the pentadienyl cation intermediate, leading to an increase in the activation barrier for electrocyclization, consequently reducing the rate of cyclization. A particularly germane case of this phenomenon is seen in the Harmata group's discovery of the retro-Nazarov reaction.[17] When α-bromo cyclopentanones bearing β-alkoxy groups were subjected to a base such as triethylamine in refluxing trifluoroethanol, an acyclic dienone results presumably through the intermediacy of a 2-oxidocyclopentenyl cation that undergoes retrograde Nazarov reaction (Scheme 5).

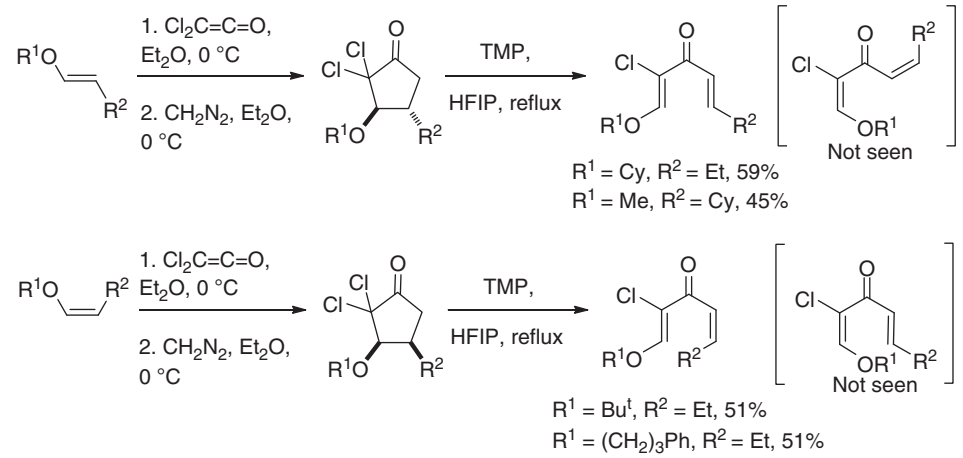


Scheme 5

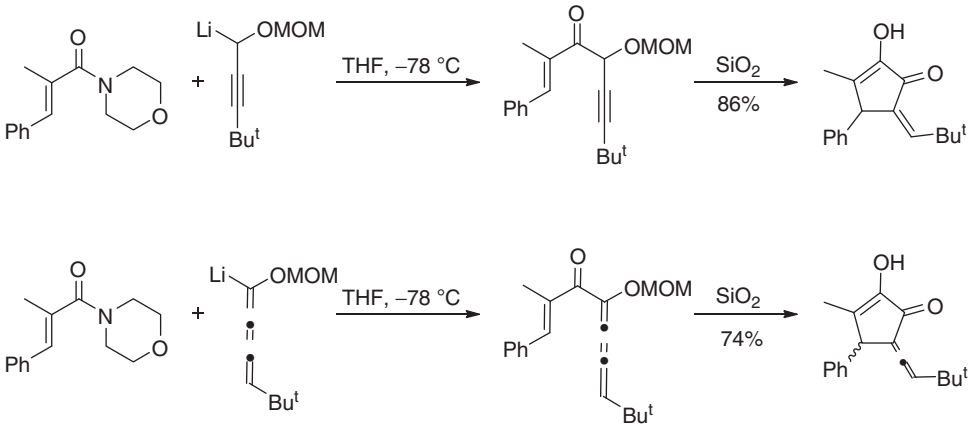
The Harmata group developed this methodology further, finding that vinyl ethers could be selectively transformed through two steps to either the *syn*- or *anti*-cylopentanones with *gem*-dichloro substitution.[18] When these were subjected to retro-Nazarov conditions, they observed remarkable torquoselectivity, forming a single dienone in each case. Each substrate favored the dienone with a (*Z*)-alkoxychloro alkene (i.e., with the alkoxy group *trans* to the ketone), with no detectable quantity of the (*E*)-conformer (Scheme 6).

5.18.1.3.2 Electron-donating groups

Electron-releasing groups at C-2 seem to increase the reactivity of dienones, a phenomenon thought to result from stabilization of the intermediate cyclopentenyl cation.[16] Tius and coworkers have exploited this phenomenon to synthesize a variety of compounds from alkoxy-allene[19] and – cumulene[20] substrates under exceedingly mild conditions (e.g., elution through silica gel) (Scheme 7).



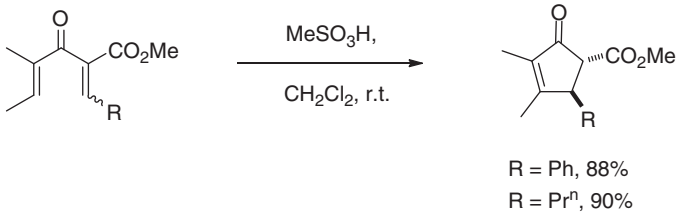
Scheme 6



Scheme 7

5.18.1.3.3 Electron-withdrawing groups

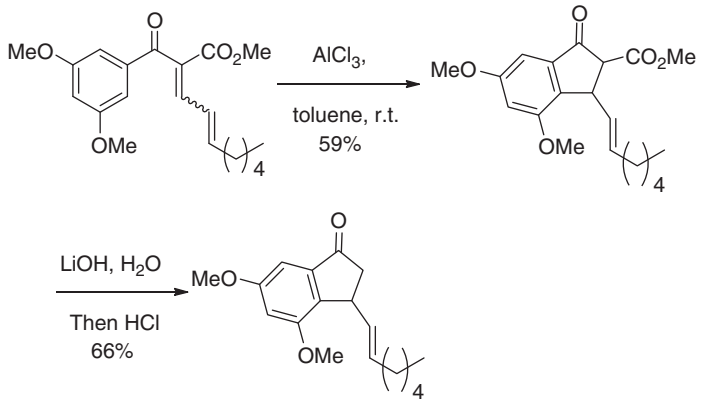
Electron-withdrawing groups at C-2 or C-4 can effectively control the regiochemistry of the elimination (equation 5).[21] The presence of such a group on the intermediate allyl cation should promote greater positive charge density at the opposite terminus, leading to selective elimination on that side. The Sarpong group also showed that esters in the α-position can be easily removed after cyclization and replaced with hydrogen, accessing substrates that were not accessible from the appropriate dienone due to the *s-trans* conformer being favored (Scheme 8).[22]



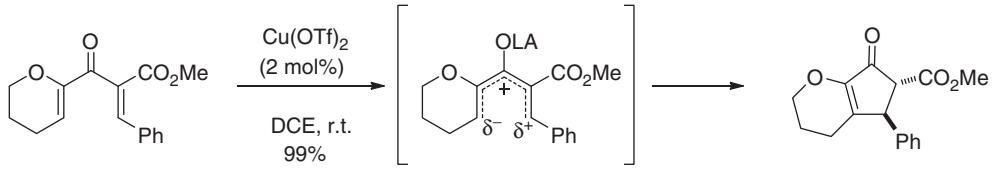
(5)

5.18.1.3.4 Polarized substrates

The Frontier group described the additive effect of electron-donating and -withdrawing groups at C-2 and C-4, permitting Nazarov cyclization under unusually mild conditions.[23] These 'polarized' dienones were shown to complex to copper and iridium catalysts and convert to cyclopentenones in excellent yields (Scheme 9).



Scheme 8



Scheme 9

5.18.2 Asymmetric Nazarov Cyclization[1i,24]

As noted above, the Nazarov reaction is a pericyclic reaction in which the relative configuration at newly formed stereocenters in the cyclized products is governed by the preservation of the orbital symmetry.[10] In the absence of any stereochemical bias, the reaction proceeds with equal amounts of clockwise and counterclockwise conrotation, resulting in a racemic mixture. Recent research efforts have been devoted to the control of absolute configuration by imparting a specific direction of conrotation through the introduction of internal or external asymmetric induction (Figure 3). In Section 5.18.2.1, the development of methodologies and strategies in this field will be discussed.

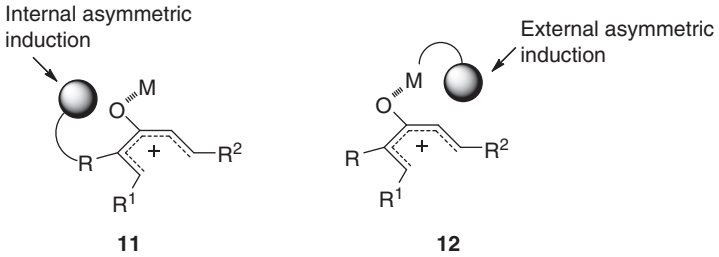


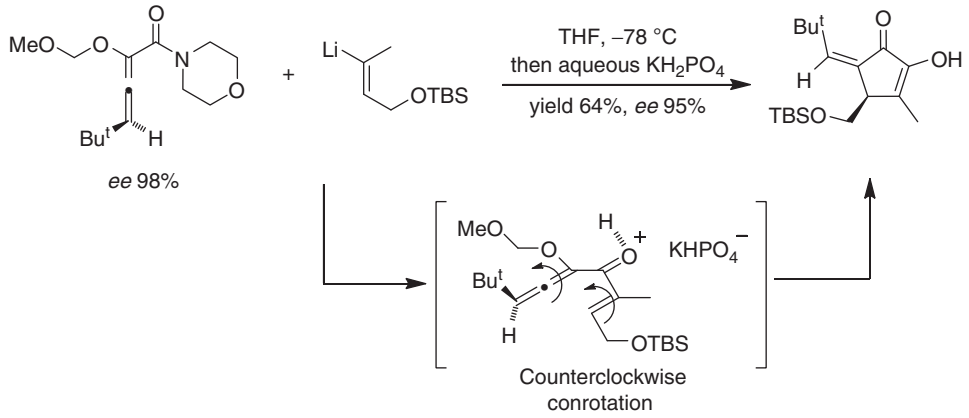
Figure 3 Approaches to asymmetric induction.

5.18.2.1 Internal Asymmetric Induction

5.18.2.1.1 Chirality transfer

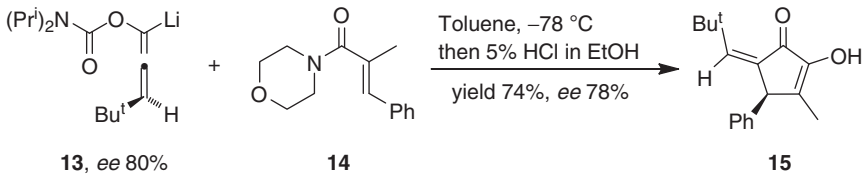
Denmark et al. first demonstrated chirality transfer via silicon-directed Nazarov reaction of a substrate on which the silyl group resides on a stereogenic center.[25] The stereogenic silicon substituent directs the counterclockwise conrotation of the pentadienyl cation by providing continuous electronic stabilization that is not feasible in the clockwise rotation owing to geometrical constraints. Their pioneering work was covered in the previous edition of Comprehensive of Organic Synthesis and will not be discussed further.[1a] Although the early Denmark example employed asymmetric induction from an sp^3 hybridized carbon center, Tius and coworkers described another promising example where high level of axial-to-tetrahedral chirality transfer was observed during cyclization of a chiral allenyl ketone. The sense of rotation was dictated by the steric bias on the distal allene moiety.

As exemplified in Scheme 10, the *tert*-butyl group prefers to rotate away from the pentadienyl system, thus giving a *Z-exo*-olefin as the major isomer plus near-perfect transfer of asymmetry from the allene.[26] However, the nontrivial task of enantioselective preparation of chiral silanes or allenyl amides has limited their further applications.



Scheme 10

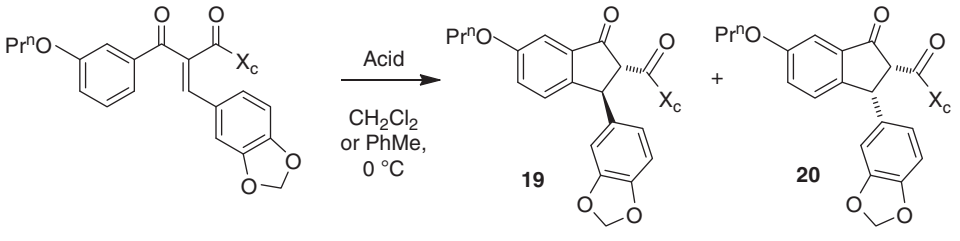
In 2001, Hoppe and coworkers reported an efficient enantioselective synthesis of allenyl carbamates by *n*-BuLi/(−)-sparteine-mediated isomerization of the corresponding alkynes, which can nicely apply to the asymmetric Nazarov reaction described above. Along the same line, Hoppe, Grimme, Tius, and coworkers published an alternative approach to optically active 5-alkylidene-2-cyclopentenones (e.g., **15**) featuring the addition of lithiated chiral allenyl carbamate **13** to the unsaturated amide **14** followed by treatment with protic acid (equation 6). With the same efficiency of chirality transfer, this method proves to be a superior choice in terms of synthetic ease than its previous version.[27]

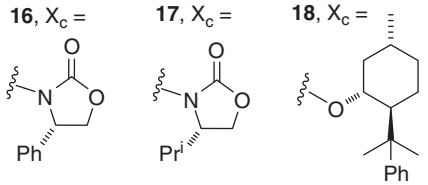


(6)

5.18.2.1.2 Chiral auxiliaries

Pridgen et al. reported the first apparent example of asymmetric 4π-electrocyclization controlled by a pendent chiral auxiliary in 1999 (Scheme 11). In the presence of tin tetrachloride, the cyclization of phenyl oxazolidinone **16** is more stereoselective than its analog **17**. Also, attachment of an 8-phenylmenthoxy group, as in compound **18**, offers a slightly more efficient asymmetric



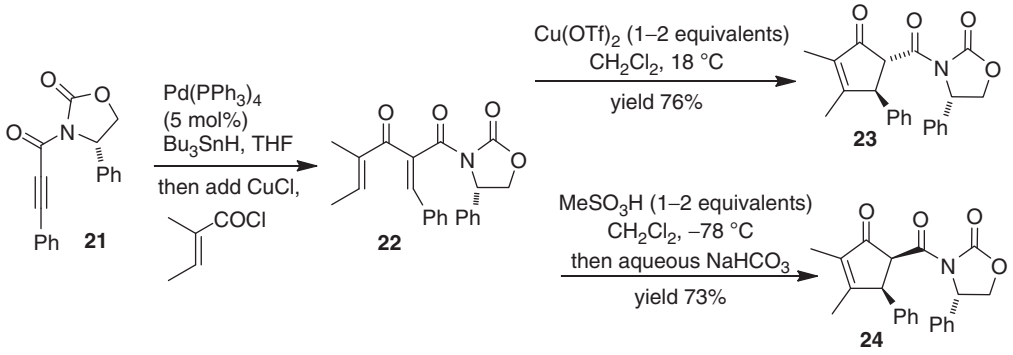


Substrate	Acid (equivalent)	yield (%)	Product ratio (**19**:**20**:other)
16	$SnCl_4$ (1.1)	85	88:12:0
16	$MeSO_3H$ (2)	88	85:15:0
16	$TiCl_4$ (1.1)	60	70:30:0
17	$SnCl_4$ (1.1)	74	71:16:14
18	$SnCl_4$ (1.1)	90	92:4:4

Scheme 11

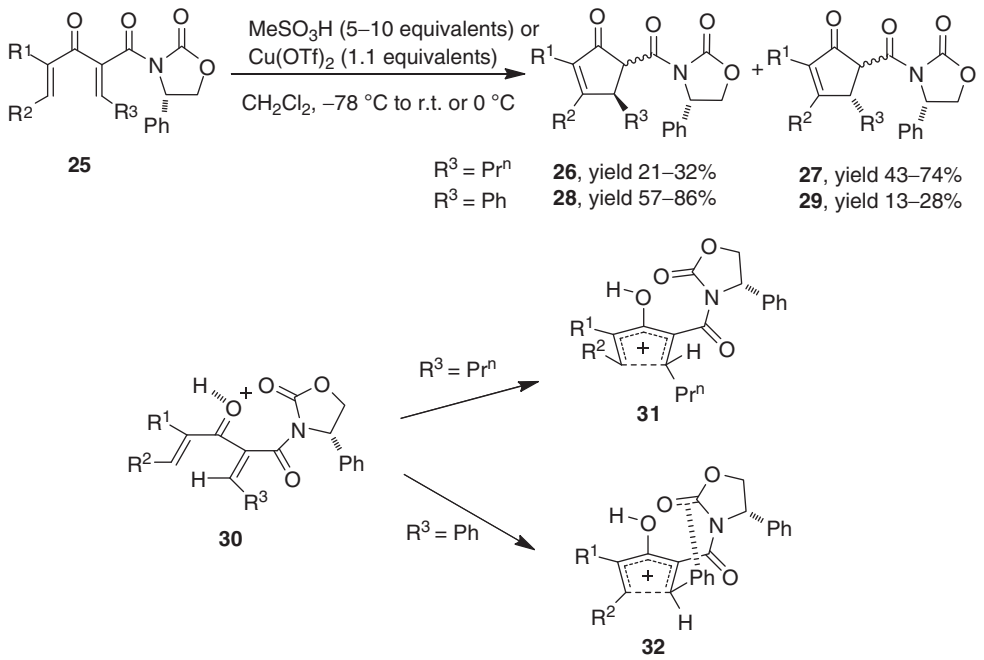
induction, implying that proper modifications of this component may further increase the diastereoselectivities of the cyclization. Comparable results with Lewis and Brønsted acid argues against the intermediacy of a rigid chelate.[28]

Flynn and coworkers reported a modular synthesis of cross-conjugated dienones substituted with Evans' chiral oxazolidinone by a palladium-mediated hydrostannylation/cross-coupling sequence, which represents a synthetically useful extension of Pridgen's work (Scheme 12).[21b] Different acid catalysts were examined, with results indicating that the Nazarov cyclization of **22** could be diverged to give *cis*- or *trans*-cyclopentenones in good yields and excellent diastereoselectivities. The exclusive formation of *cis*-**24** by reaction of **22** with triflic acid at low temperature is presumed to result from kinetic control. This protocol offers a convenient approach to access either of two diastereomeric products **23** and **24** in enantiomerically enriched form.



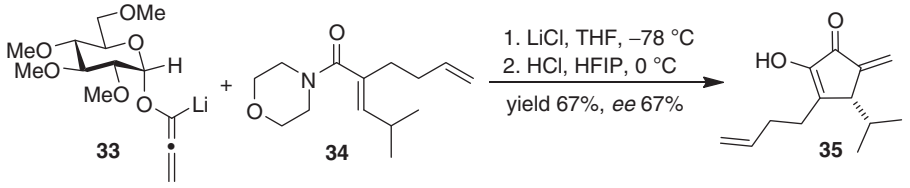
Scheme 12

Subsequent to their preliminary studies, Flynn and coworkers extensively explored the scope of the auxiliary controlled Nazarov reaction.[29] Initially, an evaluation of different auxiliary groups shows that chiral phenyloxazolidinone imposes the best torquoselectivity during cyclization. Additionally, they found that both the steric and electronic nature of the substitutients on the dienone **25** affect the stereoselectivity significantly in this system. Evidence for this can be seen in the reversal of torquoselectivity with differing R^3 groups (Scheme 13). When R^3 = alkyl, it is anticipated that the oxazolidinone-oriented perpendicular to the plane of the pentadienyl cation would avoid steric repulsion to the alkyl substitution, thus favoring the clockwise rotation (see transition state **31**). For R^3 = Ph, the authors rationalize the switched stereochemistry by a favorable secondary orbital interaction between the phenyl group and the carbamate moiety in a counterclockwise rotation, leading to transition state **32**. Nevertheless, several examples in this work exhibit poor to moderate stereoselectivities, albeit the combined yields of isomeric products are generally high.

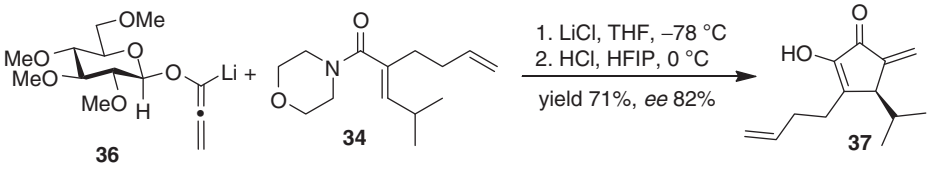


Scheme 13

In 2000, Harrington and Tius described an asymmetric Nazarov reaction of allenyl vinyl ketones, where a D-glucose-derived chiral auxiliary is attached to the proximal allenyl carbon.[30] In comparison with the earlier axial→tetrahedral chirality transfer approach, this method does not require the presence of a substituent on the distal allene carbon (required for a stereogenic allene). In this method, an additional step to remove the chiral auxiliary is not necessary because it is lost during the course of cyclization, in contrast to the related oxazolidinone-based protocols. Notably, the use of the lithiated β-anomeric allene **36** altered the absolute sense of electrocyclization, providing even higher enantioselectivity (equation 8). These findings permit a simple way to synthesize both enantiomers **35** (equation 7) and **37** (equation 8) from readily available D-glucose.



(7)



(8)

With extensive modifications over years, Banaag and Tius disclosed their optimized chiral auxiliaries and reaction conditions for the allenyl version of the Nazarov reaction that offers excellent control on both directions of conrotatory electrocyclization.[31] A coherent mechanistic proposal for the origin of stereoselectivity was fully elucidated, highlighting the donor–acceptor interaction between the ring oxygen and pentadienyl cation, which enhance the proximity of the auxiliary to the developing carbon–carbon bond, and the face-blocking function of axial substituents during cyclization (**Figure 4**). Notably, the enantioselective installation of a quartenary center to the cyclopentenoid products could be accomplished in good yields by employing the fully substituted conjugated amide as a coupling partner (**Scheme 14**).

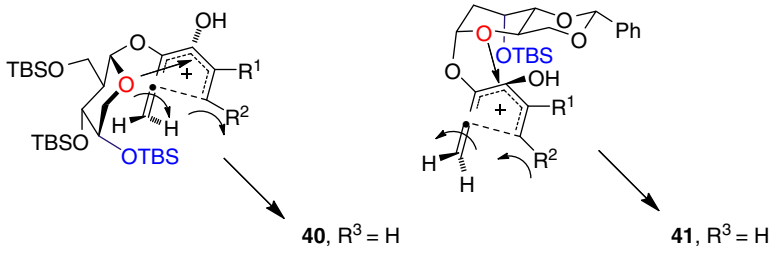
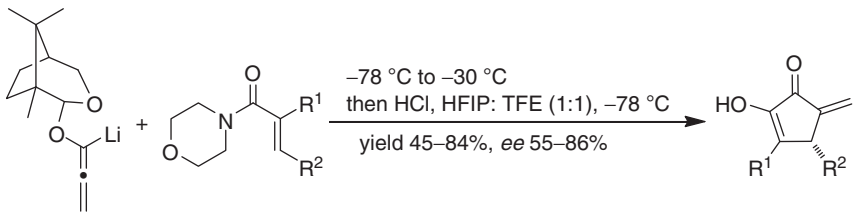
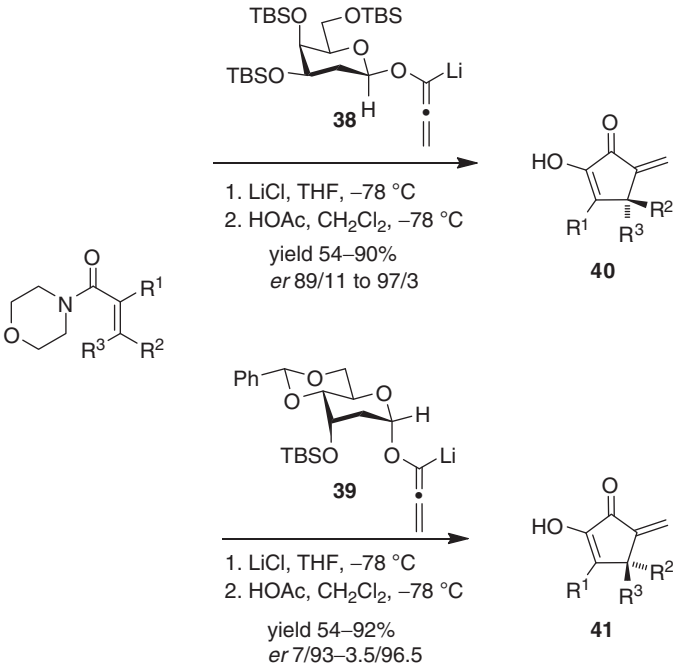


Figure 4 Models for torquoselectivity.

The Tius group explored another type of traceless auxiliary derived from camphor in the context of an enantioselective total synthesis of roseophilin employing an asymmetric Nazarov cyclization as a key step.[32] Later, the scope of that process was examined in detail. However, the control of torquoselectivity during the cyclization in this system is moderate compared to the reaction of exhaustively optimized **38** or **39** (**Scheme 14** versus equation 9).[33] An alternative role of the camphor-derived auxiliary group was demonstrated in the diastereoselective interrupted Nazarov reaction of allenyl ketone substrates. Further discussions on that topic will be given later in the chapter.



(9)

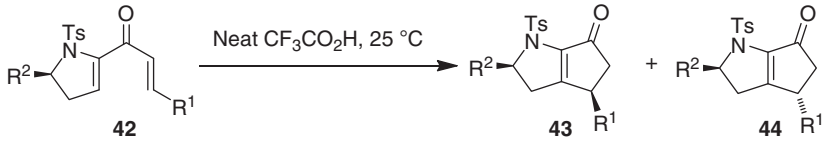


Scheme 14

5.18.2.1.3 Diastereoselective Nazarov reaction of nonracemic substrates

Encasing a portion of the dienone nucleus within a ring containing one or more stereocenters offers another strategy for control of the absolute sense of conrotatory electrocyclization. Early examples of this approach are discussed in the previous edition of Comprehensive Organic Synthesis.[1a] As a general observation, the steric bulk exhibited by the substituent(s) on the stereogentic center and its distance from the developing tetrahedral centers are the two major factors determining the level of torquoselectivity.

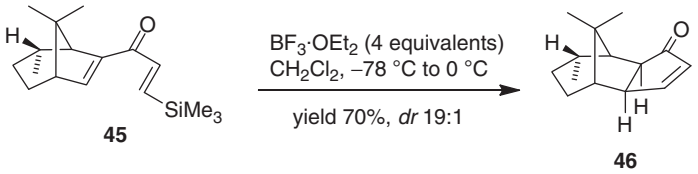
More recently, Occhiato et al. examined the diastereoselective Nazarov reaction of enantiopure dihydropyrrole derivatives **42** in the presence of neat trifluoroacetic acid (Scheme 15).[34] The remote stereocenter located on the heterocycle was able to provide good torquoselective control, albeit in moderate chemical yields. The major product **43** is believed to originate from counterclockwise conrotation in which steric clash between R^2 and the developing cyclopentenyl cation is minimized, consistent with earlier examples[1a] where the steric repulsion between R^2 and pentadienyl cation would be minimized during the course of cyclization.



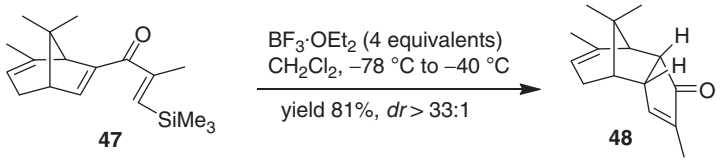
R^1 = Me, R^2 = CH_2OH, yield 42%, *dr* 10:1
R^1 = Pr^i, R^2 = Me, yield 40%, *dr* 1:0 (only diastereomer)
R^1 = Pr^i, R^2 = CH_2OH, yield 27%, *dr* 7:1
R^1 = Pr^i, R^2 = $(CH_2)_2CH = CH_2$, yield 43%, *dr* 1:0 (only diastereomer)

Scheme 15

West and coworkers examined the silicon-directed Nazarov reaction of chiral divinyl ketones where one olefin is embedded in a bridged bicyclic system.[35] The observed *exo* selectivity in the formation of **46** from **45** is consistent with known preferences for electrophilic attack on related bicyclic alkenes (equation 10). Correspondingly, a homologous system, bridged bicyclic 1,3,5-trienes, displayed complete selectivity in favor of electrocyclization from the *exo* face.[36] However, an unexpected reversal of torquoselectivity to afford the *endo* product **48** was found in the reaction of **47** (equation 11). The authors attributed this profound stereochemical effect of a remote olefin to conformational preferences within the six-membered ring of the bicyclic system.



(10)

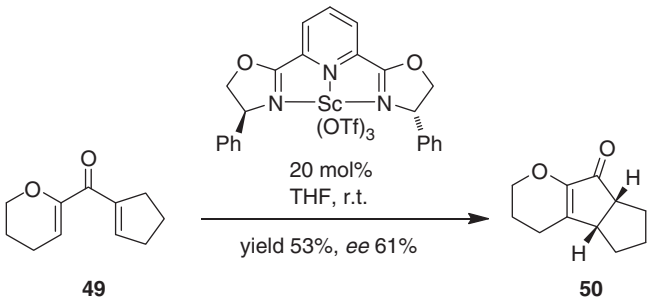


(11)

5.18.2.2 External Asymmetric Induction[1j,37]

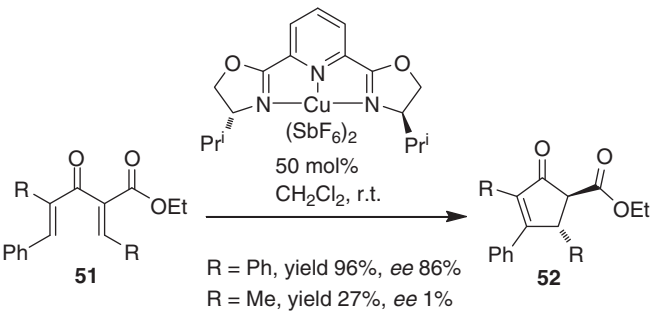
5.18.2.2.1 Metal Lewis acid asymmetric induction

Conventionally, the Nazarov cyclization of cross-conjugated dienones is subject to Brønsted or Lewis acid catalysis. This mechanistic feature offers a platform for the development of catalytic asymmetric versions of the reaction. However, it is somewhat surprising that the first such achievement was reported only recently, six decades after Nazarov's pioneering research. Trauner and coworkers employed 20 mol% of a Sc(III)/PyBOX (2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine) complex to catalyze the cyclization of **49** to afford the tricyclic product **50** with moderate enantioselectivity (equation 12).[37] The authors speculated that the dihydropyran oxygen fulfilled two critical roles. First, substitution of an ether oxygen at the 2-position of the pentadienyl system should stabilize the intermediate cyclopentenyl cation through resonance. Second, chelation of the scandium ion by both the ether and the carbonyl oxygens should enhance the transmission of stereochemical information from the PyBOX ligand to the developing cyclopentenyl cation.



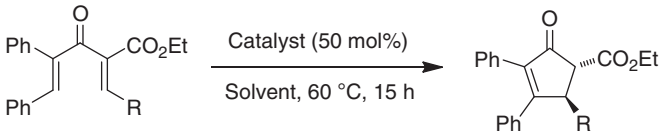
(12)

Shortly after Trauner's report, Aggarwal and Belfield described the use of Cu(II)/PyBOX complexes to promote Nazarov cyclization of 2-acyldienones (equation 13).[38] For these substrates, the yield and enantioselectivity of cyclization were found to be extremely sensitive to the substitution pattern of the dienones, as seen in the large difference for **51** when R = Ph versus Me. Overall, the high catalyst loading of this reaction underscored the central issue of product inhibition for the development of a catalytic transformation.

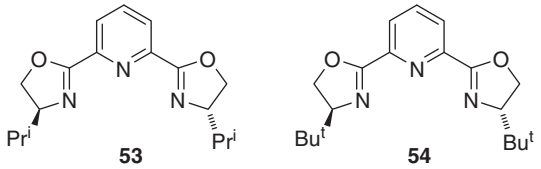


(13)

To broaden the library of metal Lewis acids capable of promoting the asymmetric Nazarov cyclization, Kawatsura and Itoh et al. screened various combinations of iron or cobalt salts, chiral PyBOX ligands, and solvents (**Scheme 16**).[39] The authors concluded that the Fe(II)/PyBOX Lewis acid complex is superior to the Co(II)/PyBOX catalyst for most 2-carboxydienones in terms of yield and enantioslectivity. The results also revealed that the electron density of the β-aryl group has significant impact on the overall performance of the cyclization that clearly limited the substrate scope. Nevertheless, this process still suffered from the demand of high catalyst loading, consistent with Aggarwal's earlier observation[38] for systems of this type.



Substrate	Catalyst	Solvent	Yield (%)	*ee* (%)
R = 4-$MeOC_6H_4$	$Co(ClO_4)_2{\cdot}6H_2O$/**53**	CH_2Cl_2	70	8
R = 4-$MeOC_6H_4$	$Fe(ClO_4)_2{\cdot}6H_2O$/**54**	CH_2Cl_2/hexane(2:1)	81	0
R = 4-$CF_3C_6H_4$	$Co(ClO_4)_2{\cdot}6H_2O$/**53**	CH_2Cl_2	36	51
R = 4-$CF_3C_6H_4$	$Fe(OTf)_2$/**54**	Toluene	53	89
R = 4-$NO_2C_6H_4$	$Co(ClO_4)_2{\cdot}6H_2O$/**53**	CH_2Cl_2	23	12
R = 4-$NO_2C_6H_4$	$Fe(OTf)_2$/**54**	Toluene	13	80



Scheme 16

Tang and coworkers explored the suitability of tris(oxazoline) ligands to amplify the asymmetric environment around the electrocyclization transition state of polarized dienones such as **55**. Their design allowed for two possible binding modes, via either chelation by both carbonyls (**58**) or chelation by the dienone carbonyl and the dihydropyran ring oxygen (**59**) (Figure 5).[40] In the event, the complex of copper (II)/*tris*(oxazoline) ligand **57** was the most efficient asymmetric catalyst for the Nazarov reaction of **55**, furnishing **56** in high yields and enantioselectivities (Scheme 17). It is notable that this process tolerated a range of R substituents at C-5, although electron-poor arenes and alkyl groups required extended reaction times.

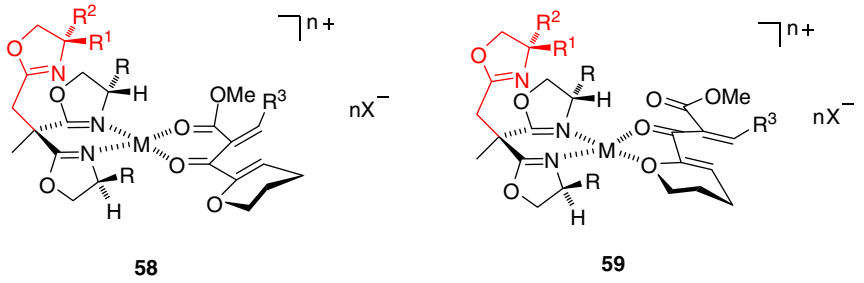
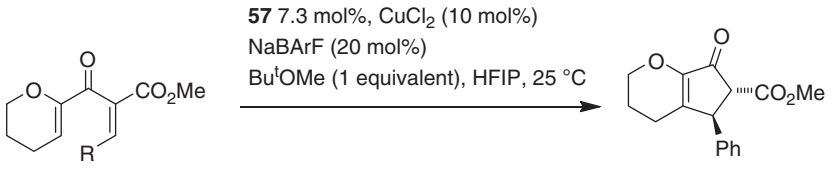
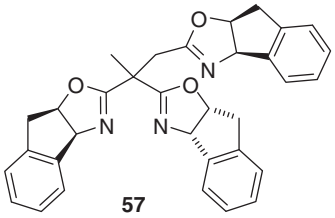


Figure 5 Possible chelation modes.

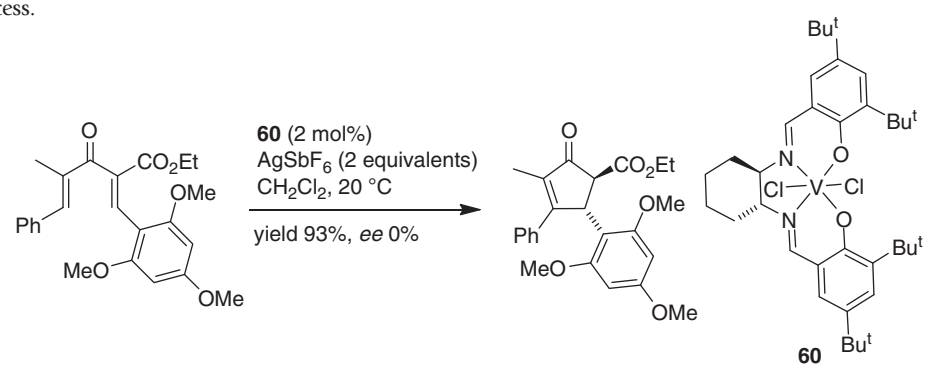


R	*t* (h)	Yield (%)	*ee* (%)
Phenyl	26	90	92
4-methoxyphenyl	18	80	96
4-fluorophenyl	50	53	93
Cyclohexyl	5 days	44 (88 brsm)	78



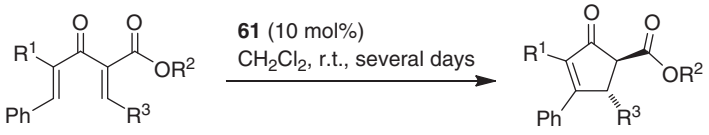
Scheme 17

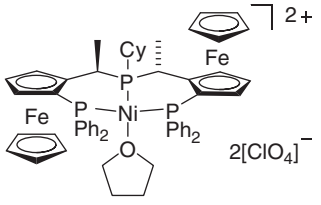
The first vanadium-catalyzed Nazarov reaction was reported for dialkylidene β-keto esters by Togni and coworkers, with remarkable turnover frequencies.[41] As an extension to their own work, a preliminary attempt to utilize a chiral vanadium salen complex **60** for asymmetric catalysis was not fruitful, resulting in racemic cyclopentenone products (equation 14). Nonetheless, the high catalytic activity of these V(IV) complexes offers a strong impetus to carry out further optimization studies of the asymmetric process.



(14)

The known Lewis acidic behavior of the Ni(II)/Pigiphos complex in mediating various types of reactions inspired Walz and Togni to pursue its application in the catalytic asymmetric Nazarov reaction.[42] An examination on the substituent effects indicated that varying the steric and electronic properties of the ester moiety (R^2) would cause the erosion of both yields and enantioselectivities. Moreover, electron-rich aryl groups R^3 are beneficial to the overall process (Scheme 18). The requirement for extremely long reaction times with the Ni(II)/Pigiphos catalyst **61** identifies an area for further improvement of this promising system.





61

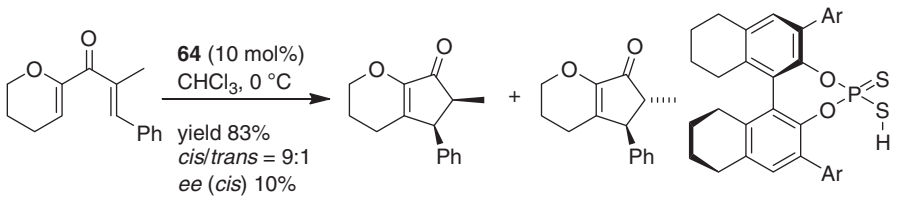
R^1	R^2	R^3	Yield (%)	*ee* (%)
Ph	Et	TMP	85	87
Me	Et	TMP	84	86
Me	Et	PMP	32	71
Me	Pr	TMP	80	82
Me	Bn	TMP	58	45
Me	Np	TMP	No reaction	n/a

Scheme 18

5.18.2.2.2 Organocatalytic asymmetric induction

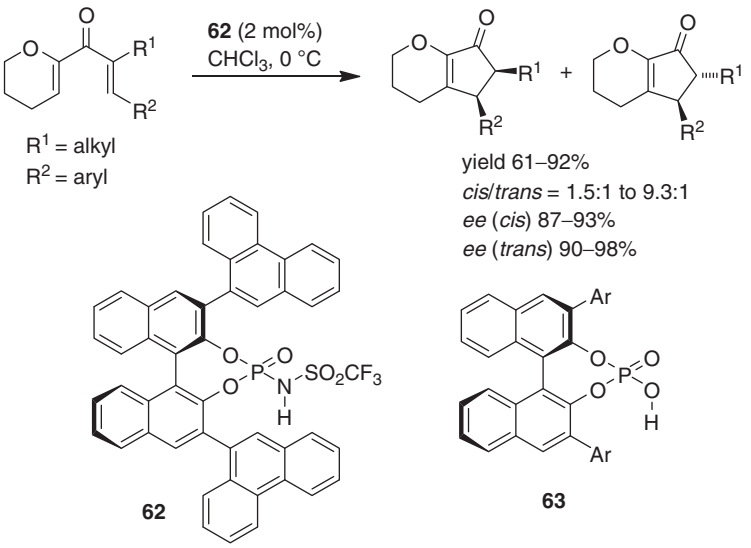
Rueping et al. demonstrated that the sense of conroratory electrocyclization could be controlled using asymmetric organocatalysis, presumably via a chiral ion-pair mechanism.[43] Although several chiral BINOL phosphate-derived Brønsted acids were evaluated for the Nazarov reaction of various dihydropyran-containing dienones, *N*-triflyl phosphoramide **62** was found to be more stereoselective than the corresponding phosphoric acid **63**. As an alternative to the metal-catalyzed process, this method features lower catalyst loadings and excellent enantiocontrol; however, only moderate *cis*/*trans* diastereoselectivities were obtained (Scheme 19).

Blanchet and coworkers explored a dithio analog **64** of BINOL phosphoric acid **63** as a new organocatalyst for the asymmetric Nazarov reaction, where the acidity of the promoter was postulated to be essential to both reactivity and enantioselectivity (equation 15).[44] In the event, the level of torquoselectivity using **64** was disappointingly low, although the *cis*/*trans* diastereoselectivity was somewhat higher than that obtained with **62**.



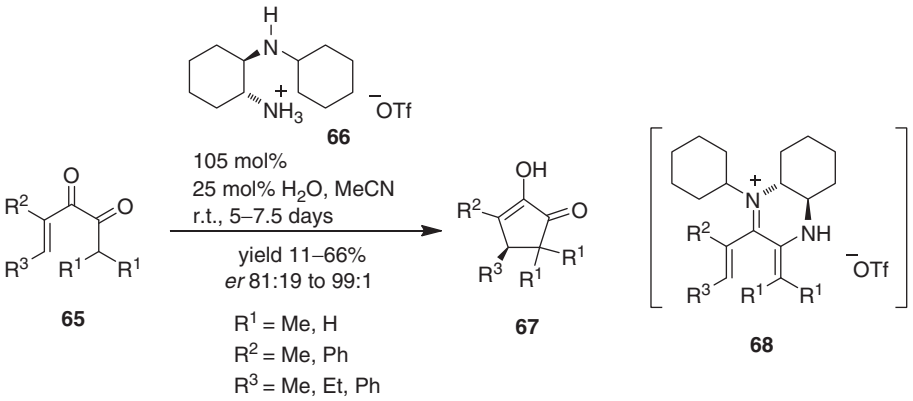
64, Ar = 3,5-$(CF_3)_2C_6H_3$

(15)



Scheme 19

Tius and coworkers disclosed a novel approach for controlling the absolute sense of electrocyclization through the generation of a presumed enamine–iminium intermediate **68** from α-diketone **65** and stoichiometric diamine monotriflate **66** (Scheme 20).[45] The cyclized covalent intermediate, a transpositional enamine-iminium species, was hydrolyzed during aqueous workup to release an α-hydroxycyclopentenone **67** in remarkable optical purity. The chemical yields of this relatively slow process varied from 11% to 66%.

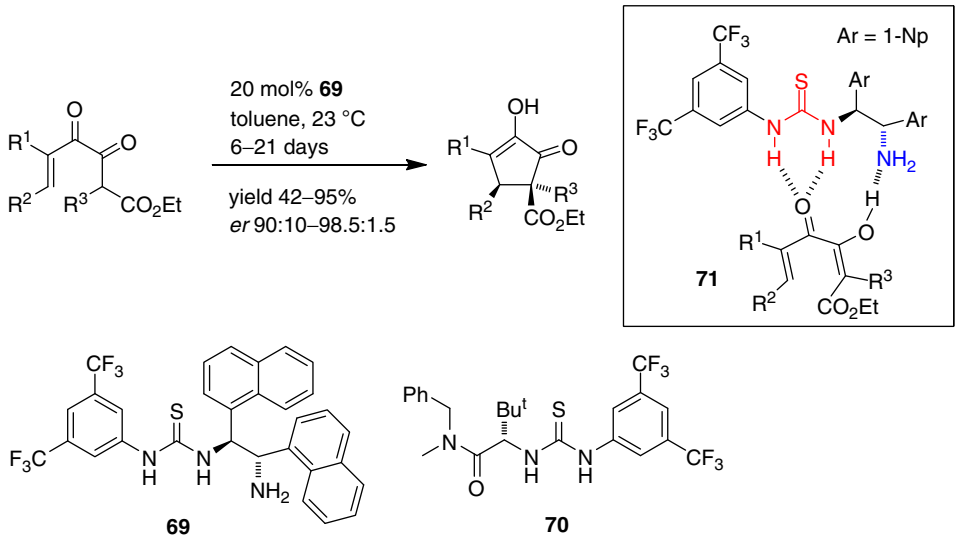


Scheme 20

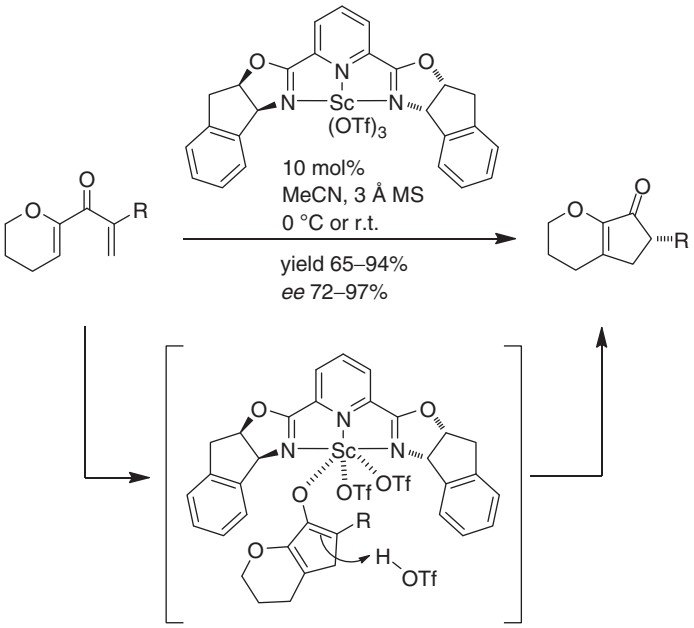
Tius and coworkers devised thiourea-derived bifunctional catalysts for the Nazarov reaction of enolic diketoesters to provide highly functionalized cyclopentenones in moderate to good yields and in enantiomeric ratios that range from 90:10 to 98.5:1.5 (Scheme 21).[46] A notable advantage of this protocol is that two contiguous stereogenic centers, one of which is a quartenary center, could be readily installed. The fact that catalyst **70** lacking a basic amine group was not an effective catalyst highlighted the cooperative function between acidic thiourea moiety and basic primary amine residing in **69**, as indicated in the model **71**.

5.18.2.2.3 Electrocyclization/enantioselective protonation

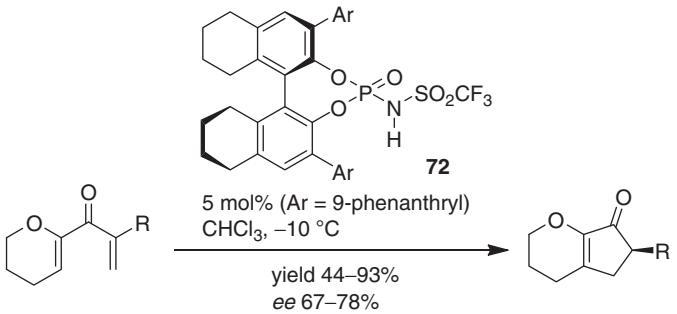
Enantioselective protonation[47] is a common means for establishing absolute configuration in biosynthetic pathways. Liang and Trauner described a new strategy toward asymmetric Nazarov reactions where the enantioselectivity was determined during the final protonation of the enolate intermediate instead of the electrocyclization step (Scheme 22).[48] The yields and enantiomeric ratios obtained in this process are promising, but currently the substrate scope is limited to highly reactive dihydropyran-containing dienones. Rueping and Ieawsuwan described a strategy similar to Liang and Trauner's, using the partially reduced *N*-triflylphosphoramide organocatalyst **72** (equation 16).[49]



Scheme 21



Scheme 22



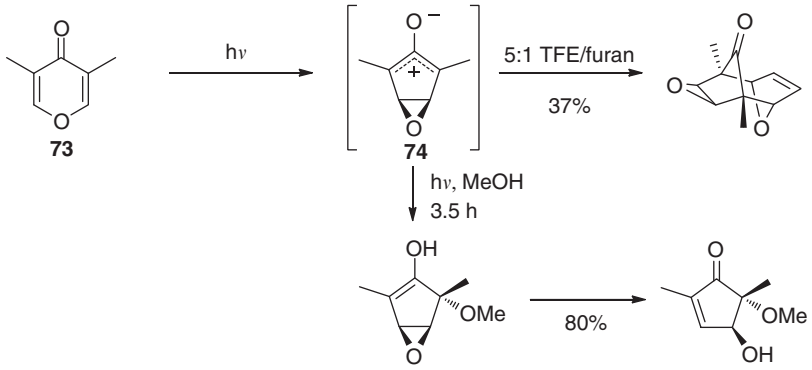
(16)

5.18.3 The Interrupted Nazarov Reaction

Although the conventional Nazarov reaction has considerable value for the construction of cyclopentenones, recently there has been growing interest in utilizing the unique reactivity of various intermediates occurring during the process to form additional strategic bonds. Specifically, the 2-oxidocyclopentenyl cation **7** (Scheme 1) formed on electrocyclization can participate in a variety of nucleophilic trapping or cycloaddition reactions. However, the dienol or dienolate species resulting from elimination can react with a range of electrophiles. This concept of diverting the Nazarov process from its normal path with an added reagent has been labeled the interrupted Nazarov reaction.

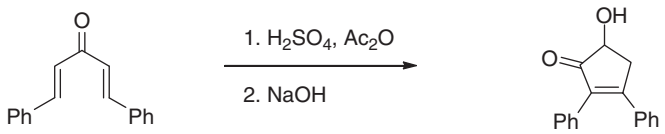
5.18.3.1 Early Interrupted Nazarov Reactions

The first examples which intentionally exploited 2-oxido-cyclopentenyl cation reactivity were observed during photo-Nazarov cyclizations. Trapping of the oxyallyl intermediate **74** generated from photochemical Nazarov cyclization of 4-pyranone **73** was found to occur in a bimolecular fashion with hydroxylic solvent[50,51] or in [4+3] cycloadditions with furan (Scheme 23).[50] West et al. demonstrated the corresponding intramolecular process using pendent hydroxyl traps to form fused bicyclic products.[52] They also found that carbon-based nucleophiles such as olefins, arenes, and dienes could be tethered to 4-pyranones to generate bi- and tricyclic ring systems.[53–55] The photo-Nazarov methodology had a relatively limited scope and required the use of a polar, nonnucleophilic solvent such as trifluoroethanol.



Scheme 23

The similarity of the intermediate in conventional Nazarov reactions and that formed in the photochemical process suggested the possibility of generalizing this trapping strategy beyond a specialized class of 4-pyranone substrates. In fact, long before the mechanism of the Nazarov reaction was understood, Vorländer and Schroedter observed a ketol product from treatment of dibenzylideneacetone with acetic anhydride and sulfuric acid (equation 17), which was most likely the result of trapping of the cyclopentenyl cation intermediate with water, bisulfate, or acetate. Although not appreciated at the time as an example of the interrupted Nazarov reaction, this process offered clear evidence in support of the notion that the Nazarov intermediate could be trapped with nucleophiles.[2] Section 5.18.3.2 will highlight some of the recent advances in domino and tandem processes resulting in interception of the intermediates formed in thermal Nazarov cyclizations. For an in-depth discussion the reader is referred to a review published by West and coworkers.[1g]

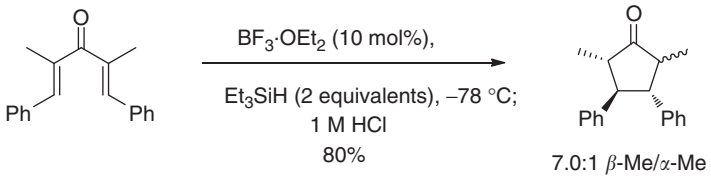


(17)

5.18.3.2 Reductive Nazarov Reaction

An important advantage of the interrupted Nazarov cyclization is the retention of the two stereocenters formed in the electrocyclization step to make functionalized cyclopentanones. Giese and West utilized triethylsilane as a Lewis acid-tolerant hydride source to trap the 2-oxido-cyclopentenyl cation and form cyclopentanones in good yields (equation 18).[56] Nazarov cyclization was followed by a regioselective delivery of hydride at the less substituted end of the 2-oxido-cyclopentenyl cation, rationalized by the preferred formation of a more substituted enolate. Hydride addition favors addition from the seemingly more hindered face to afford a *trans–trans* relative stereochemistry.[57] The reductive Nazarov reaction efficiently captured the oxyallyl cation intermediate

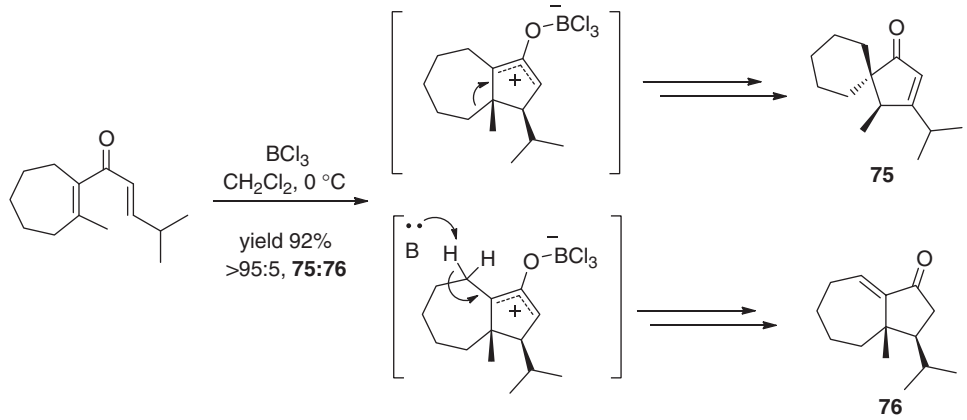
conserving the newly formed stereocenters. Another important observation was the capability to carry out the reaction using catalytic amounts of Lewis acid.



(18)

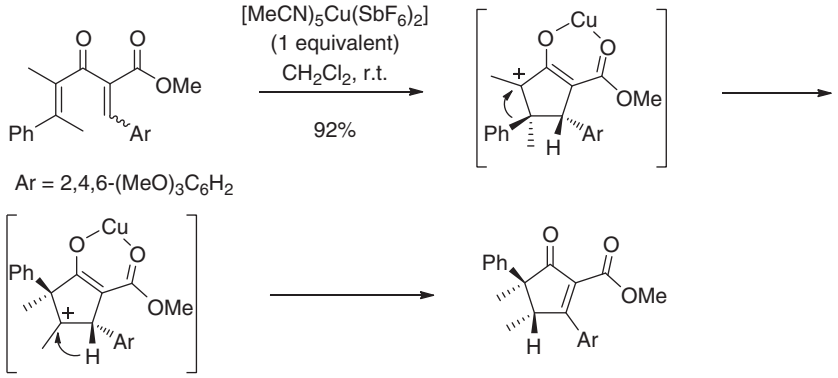
5.18.3.3 Tandem Nazarov Cyclization – Skeletal Rearrangments

Although exploring the synthesis of hydroazulene ring systems using the Nazarov reaction, Chiu and Li found that they could also access spiro[4.5]decanones resulting from Wagner–Meerwein rearrangment of the 2-oxido-cyclopentenyl intermediate.[58] However, this methodology appears to be limited to the formation of spiro[4.5]decanones, as the corresponding spiro[4.4]nonanones are formed as a mixture with the classical Nazarov product (Scheme 24).



Scheme 24

Frontier and coworkers have also developed a methodology utilizing [1,2]-shifts to intercept the oxyallyl cation formed following Cu(II) promoted Nazarov cyclization to prepare highly substituted cyclopentanones.[59] Simple dienones bearing an electron-withdrawing substituent on one of the α-carbons can undergo Nazarov cyclization followed by two sequential chemoselective and stereospecific [1,2]-migrations to cyclopentenone products. The chemoselectivity of the migrations can be predicted based on the migratory aptitude of the substituents, although steric demand also plays a role, as seen in the preferential migration of hydride rather than the bulky 2,4,6-trimethoxyphenyl (TMP) group. (Scheme 25). By employing a bis(oxazoline) ligand, the reaction could be performed enantioselectively. Additionally, the Frontier group showed that when one of the dienone alkenes was part of a cyclohexene, the resulting 1,2-shift led to a ring contraction and formation of a spirocyclic ring junction at the α-position.[60]

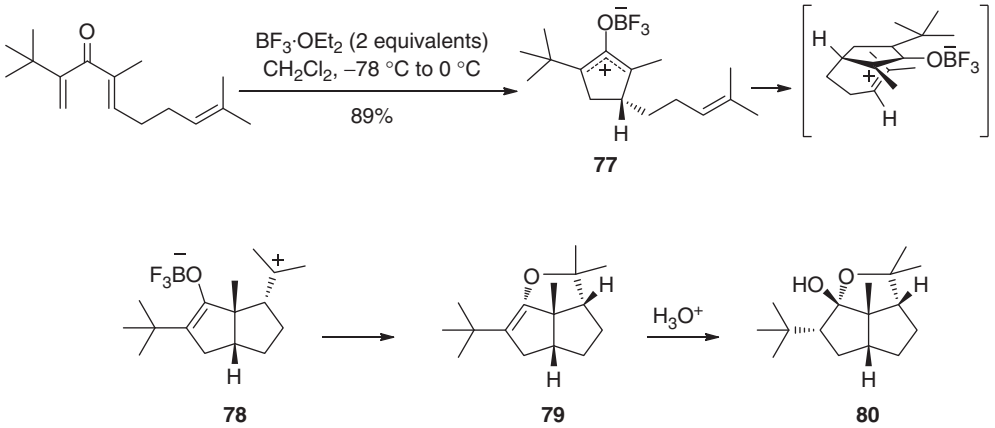


Scheme 25

5.18.3.4 C–C Bond Formation

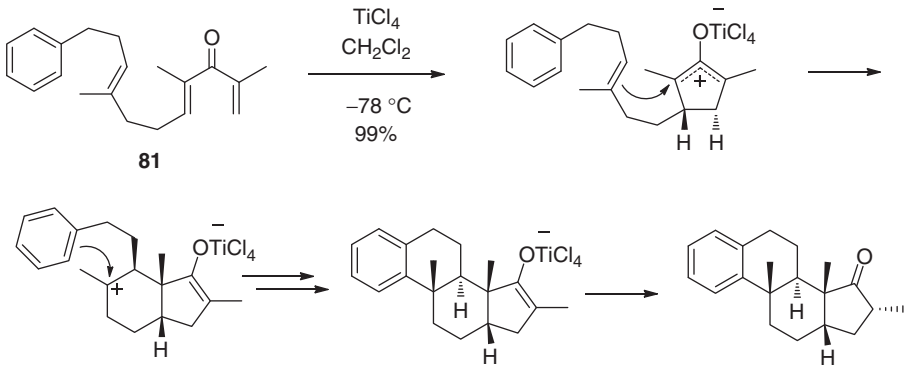
5.18.3.4.1 Intramolecular olefin trapping

In 1998, West and coworkers reported the first intentional interception of the 2-oxidocyclopentenyl cation intermediate generated by a thermal Nazarov cyclization.[61] In this process cross-conjugated dienones bearing an olefin tether were treated with $BF_3{\cdot}OEt_2$ to form a single polycyclic hemiketal product, with consequent formation of two new carbon–carbon bonds and four or five new stereocenters. The products observed were the result of 4π-conrotatory Nazarov cyclization generating a 2-oxidocyclopentenyl cation intermediate **77** (Scheme 26), which underwent cationic cyclization to the tethered olefin resulting in tertiary carbocation **78**. Trapping of this cation by the boron enolate would give the strained enol ether **79**, the hydrolysis of which leads to the observed hemiketal diquinane product **80**.

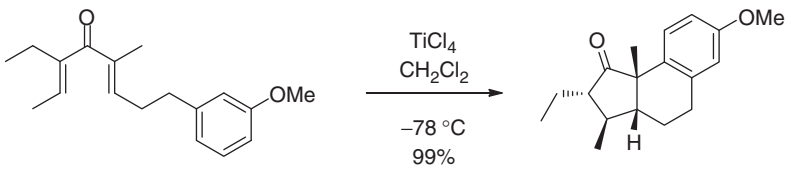


Scheme 26

Cascade polycyclizations with aryl-terminated trienones such as **81** are also possible.[62] Initial trials using protic acid or $BF_3{\cdot}OEt_2$ furnished only simple Nazarov cyclization or truncated monocyclization products. Lower reaction temperatures and stronger Lewis acid were used in an effort to increase the lifetime of the carbocation intermediates with hopes of achieving the polycyclization cascade. In the event, $TiCl_4$ at −78 °C was found to successfully convert the aryltrienone substrate to the desired tetracyclic product in 99% yield with complete diastereoselectivity (Scheme 27). Tethered arenes could also be used to directly trap the Nazarov oxyallyl cation intermediate (equation 19),[63,64] affording benzohydrindenones in good yields.



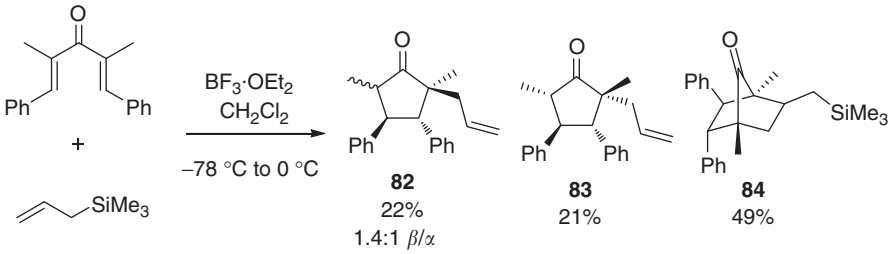
Scheme 27



(19)

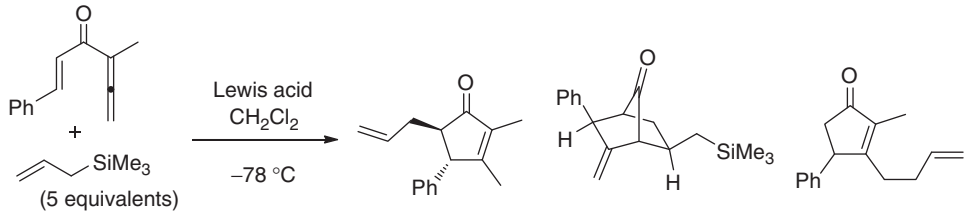
5.18.3.4.2 Intermolecular olefin trapping

The success of intramolecular trapping by π-nucleophiles spurred investigation of the corresponding bimolecular processes. Initial studies employed simple allylsilanes, chosen for their known nuclophilic reactivity and Lewis acid stability. Dibenzylidene-3-pentanone was treated with $BF_3{\cdot}OEt_2$ in the presence of allyltrimethylsilane to afford a diastereomeric mixture of allylated cyclopentanones **82** and **83**, along with the bicyclo[2.2.1]heptanone product **84** derived from [3+2] cycloaddition (equation 20).[65] Products **83** and **84** are thought to arise from the same silicon-stabilized carbocation, which can be trapped by the enolate or undergo silyl elimination. Formation of the [3+2] product could be maximized by using a less labile allylsilane, such as allyltriisopropylsilane. In the case of unsymmetrical dienones, nucleophilic attack occurred exclusively at the less substituted end of the oxyallyl cation intermediate to provide the more stable enolate. Interestingly, complementary diastereoselectivity could be obtained by using a different Lewis acid.



(20)

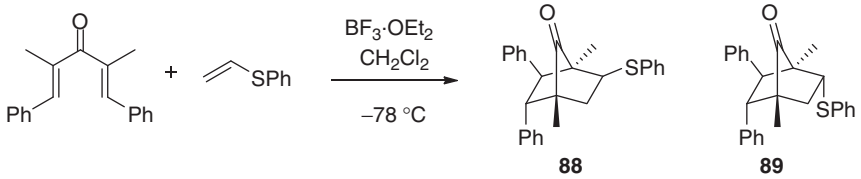
More recently, an allenyl vinyl ketone substrate was shown by Marx and Burnell to undergo efficient trapping with allylsilanes (Scheme 28).[66] Mixtures of allylated cyclopentenone **85** and [3+2]-adduct **86** were formed using $BF_3{\cdot}OEt_2$. However when $Cu(OTf)_2$ or $InCl_3$ were used to promote the Nazarov cyclization, an allylated product **87** arising from exocyclic trapping of the extended cationic intermediate was also formed.



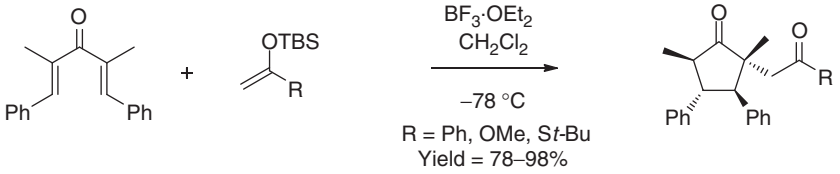
	85	86	87
$BF_3{\cdot}OEt_2$	27%	54%	–
$Cu(OTf)_2$	20%	10%	42%
$InCl_3$	22%	–	56%

Scheme 28

Recently, a variety of other electron-rich olefins with enolate-like reactivity have been used to trap the Nazarov oxyallyl intermediate. Mahmoud and West observed exclusive [3+2] trapping with vinyl sulfides to generate sulfide-substituted bicyclo[2.2.1]heptanones (equation 21) with no evidence of trapped cyclopentanone products.[67] In contrast, nucleophilic silyloxyalkenes were used to generate 1,4-dicarbonyl systems containing highly substituted cyclopentanones and up to five new stereocenters in what was termed a 'homologous Mukaiyama reaction.'[68] When simple divinyl ketone substrates were treated with, $BF_3{\cdot}OEt_2$ in the presence of silyl enol ethers, silyl ketene acetals, or mixed ketene *S*,*O*-acetals, trapping occurred such that the more stable enolate was formed on interception of the oxyallyl cation (equation 22). Similar reactivity involving an allyl vinyl ketone and enol ethers was observed by Marx and Burnell.[66]



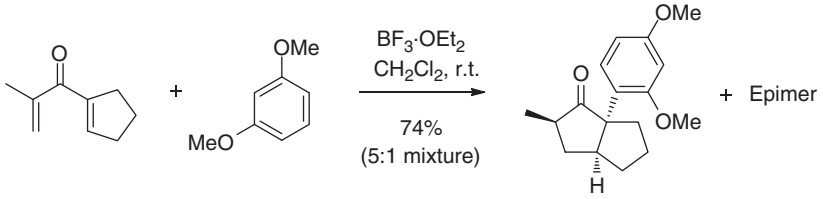
(21)



(22)

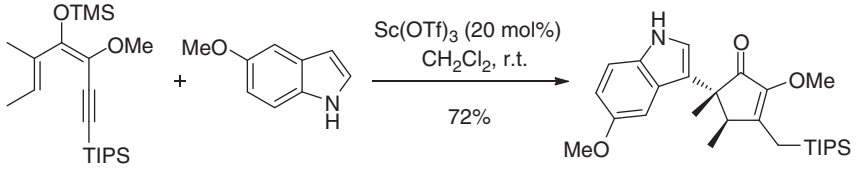
5.18.3.4.3 Intermolecular arene trapping

In 2008, West and coworkers found that similar enolonium-type reactivity could be observed for Nazarov intermediates containing at least one fused cyclopentane ring. Treatment of the corresponding dienones with $BF_3{\cdot}OEt_2$ in the presence of electron-rich arenes furnished products resulting from electrophilic aromatic substitution onto the cyclized 2-oxidiocyclopentenyl Nazarov intermediate.[69] Furans, thiophenes, protected pyrroles, protected indoles,[70] and electron-rich benzene rings were all efficiently trapped. The regioselective attack at the bridgehead (equation 23) is attributed to the formation of the less strained enolate on trapping of the oxyallyl cation. Consistent with the intramolecular studies, less electron-rich aromatic rings failed to undergo the domino process, and instead simple eliminative Nazarov products were isolated.



(23)

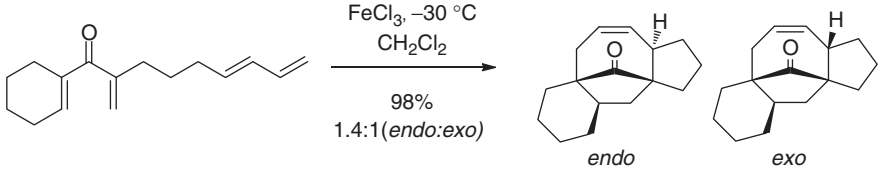
In the same year, Tius and coworkers reported conceptually related work utilizing unprotected indoles as aromatic nucleophiles.[71] In the study, enediyne substrates were cyclized in the presence of catalytic $Sc(OTf)_3$. The resulting cationic Nazarov intermediate was trapped by a variety of indoles at the nuclophilic C-3 position (equation 24). The trapping was reasonably efficient, provided the indoles were electron-rich and sterically unencumbered.



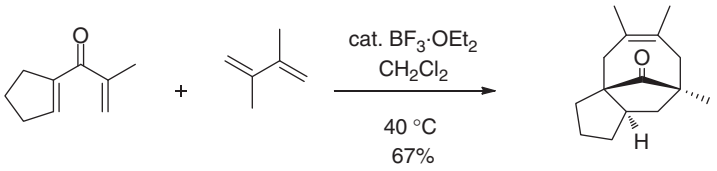
(24)

5.18.3.4.4 [4+3]-Cycloaddition reactions

An alternative mode of trapping the oxyallyl intermediate to the nucleophilic processes described above would be through concerted [4+3]-cycloaddition utilizing the oxyallyl intermediate as a dieneophile. This [4+3]-cycloaddition can also be considered to be a formal [4+4]-cycloaddition given that the reactive 2-oxidocyclopentenyl cation intermediate is enclosed within a ring, furnishing a keto-bridged cyclooctene product. West and coworkers tested this concept using a series of divinyl ketones bearing diene tethers. Treatment with $FeCl_3$ at low temperature led to the desired polycyclic products in excellent yield as a mixture of diastereomers (equation 25).[72] Although exclusive approach of the diene from the more accessible face of the cyclopentenyl cation was seen, reaction via either *endo* or *exo* transition states was possible, and both products were typically obtained. The analogous intermolecular [4+3]-cycloaddition process is also efficient (equation 26).[73] Catalytic activation of simple dienones by $BF_3{\cdot}OEt_2$ in the presence of simple cyclic and acyclic dienes formed the [4+3]-cycloadducts in good to excellent yield with complete facial selectivity.

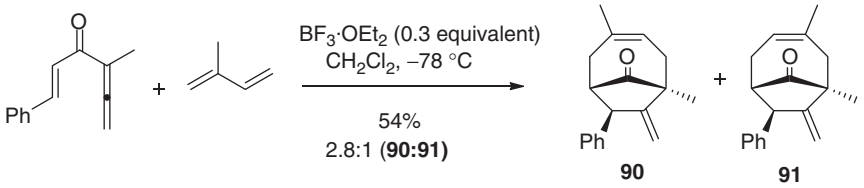


(25)



(26)

Marx and Burnell examined the [4+3] reactivity of an allenyl vinyl ketone, and found that efficient trapping was seen using $BF_3{\cdot}OEt_2$ at low temperatures in the presence of simple dienes (equation 27).[66] In cases employing more substituted dienes, [3+2] trapping products were observed as the major products. This was attributed to low populations of the *s-cis* conformation required for a concerted [4+3]-cycloaddition process.

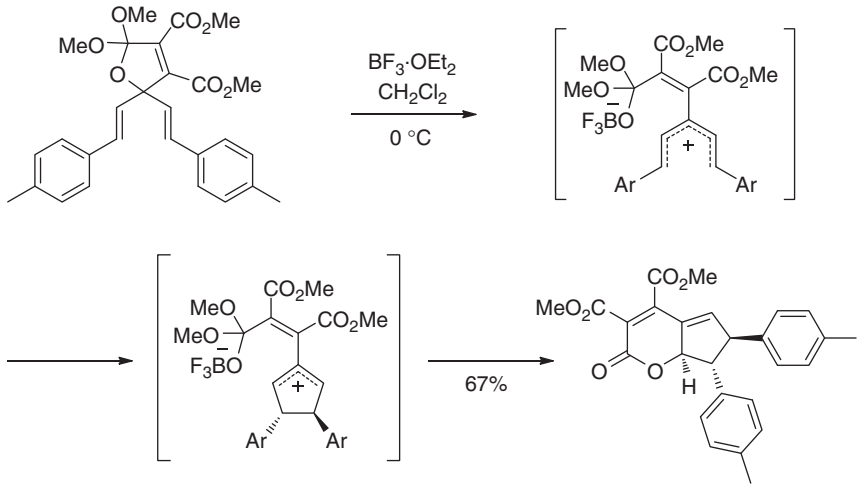


(27)

5.18.3.5 Heteroatom Trapping

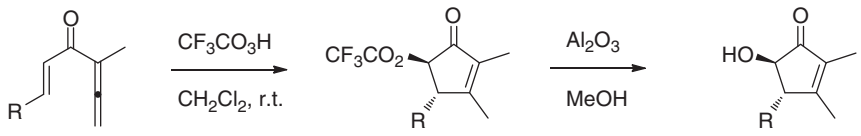
5.18.3.5.1 Oxygen nucleophiles

In 2002, Nair et al. used nontraditional *gem*-divinyl dihydrofuran substrates in an intramolecular oxygen interrupted Nazarov reaction (Scheme 29).[74] When the substrates were treated with $BF_3{\cdot}OEt_2$, a cascade was initated by ring opening to generate a pentadienyl cation that underwent Nazarov cyclization to form the cyclopentadienyl cation intermediate. Subsequent trapping by the *ortho* ester borate oxygen gave the complex bicyclic lactone products and three new stereocenters.



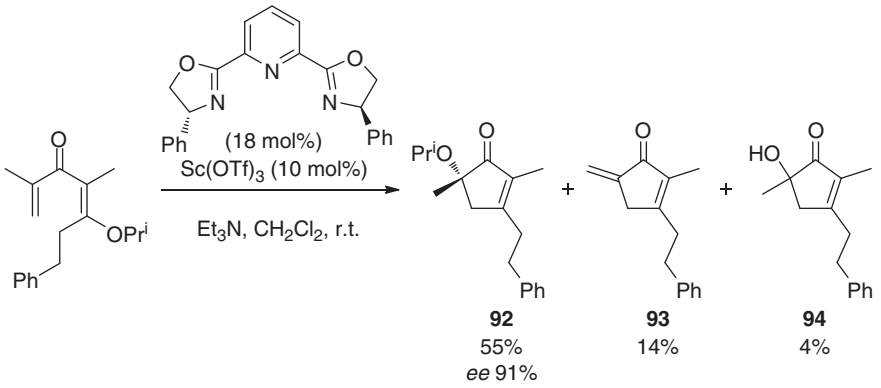
Scheme 29

Marx and Burnell observed that efficient trapping of the cyclopentenyl cation generated by acid promoted Nazarov cyclization of select allenyl vinyl ketones with trifluoroacetic acid. The resulting trifluroacetate esters could be smoothly converted to α-hydroxycyclopentenones on elution through basic alumina (Scheme 30).[75] However, some allenyl vinyl ketones failed to undergo trapping, generating the simple Nazarov product, or underwent Michael addition into the allene before cyclization could occur.[76]



Scheme 30

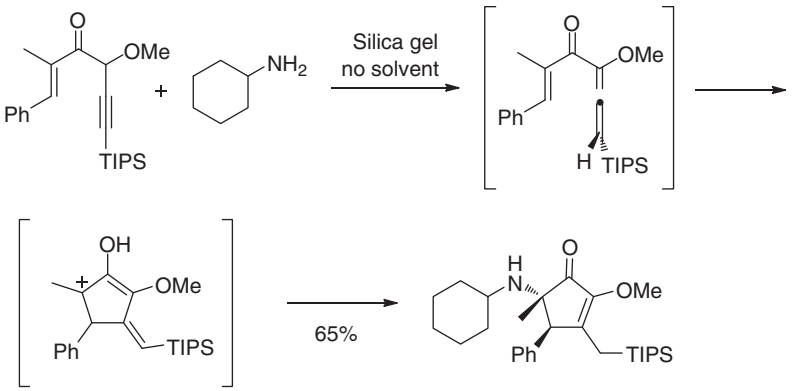
In 2009, Yaji and Shindo reported an asymmetric interrupted Nazarov reaction catalyzed by a $Sc(OTf)_3$–Pybox complex to generate enantioenriched α-alkoxy cyclopentenoes with good yield and moderate ee (equation 28).[77] Deuterium labeling was used to support intermolecular delivery of the alkoxy nucleophile rather than an intramolecular [1,3]-shift.



(28)

5.18.3.5.2 Nitrogen nucleophiles

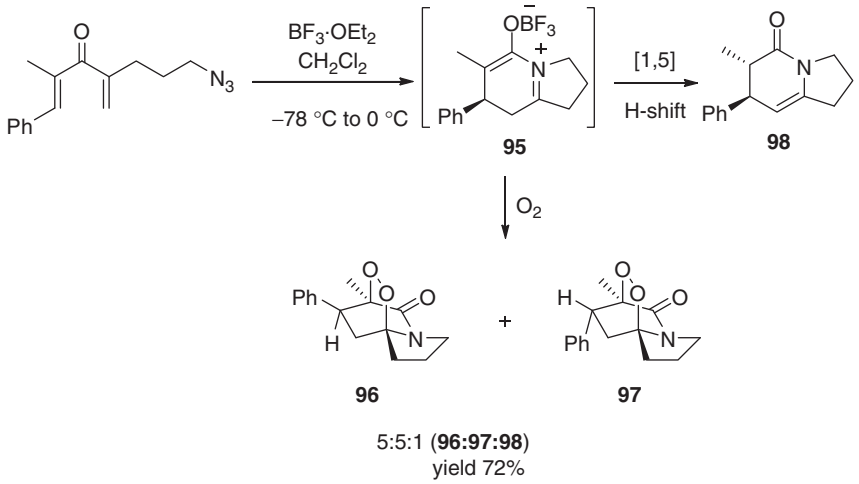
In 2005, Dhoro and Tius reported the first examples of nitrogen as a nucleophile for the interrupted Nazarov reaction.[78] Silica gel was used to promote Nazarov cyclization of *in situ*-formed allenyl vinyl ketones in the presence of a variety of primary and secondary amines (equation 29). Under solvent-free conditions the highly reactive cyclopentadienyl cation could be trapped by the amine, notable due to the readily available elimination pathways that are not seen even in the presence of basic amine. The success of this reaction can be attributed to the high reactivity of the allene ether species, and its close proximity to the nucleophilic amine in the solvent-free conditions. By employing a camphor-based chiral auxiliary on the allene ether, control of the torquoselectivity in the conrotatory cyclization was seen.[79]



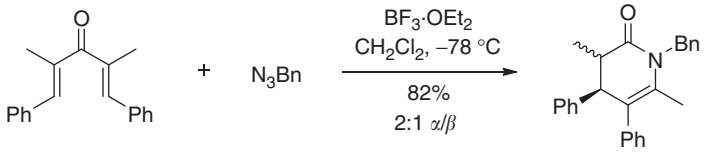
(29)

West and coworkers demonstrated the use of azides to intercept the 2-oxido-cyclopentenyl cation Nazarov intermediates.[80–82] Initial studies focused on intramolecular reactivity, using azide-tethered dienones (**Scheme 31**).[80] Treatment with $BF_3{\cdot}OEt_2$ at low temperature furnished indolizidine endoperoxides **96** and **97** as the major products, along with trace amounts of **98**. The authors suggest that all of these products arise from the 1,4-dipolar intermediate **95**. Careful exclusion of oxygen from the reaction allowed the exclusive formation of **98**. However, the reaction was optimized to favor the peroxy-bridged products by performing the reaction in the presence of oxygen, providing an additional useful handle for further transformations.

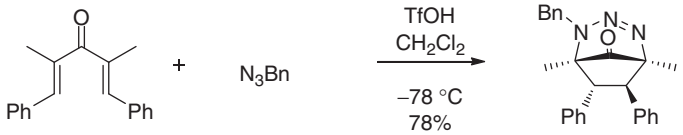
Intermolecular azide trapping of 2-oxidocyclopentenyl cations generated from simple dienones has also been studied.[81] On treatment with $BF_3{\cdot}OEt_2$, Nazarov cyclization followed by azide attack and domino ring expansion produced substituted dihydropyridones from simple starting materials (equation 30). *Trans*-dihydropyridones were the major or exclusive product; however, the lack of complete stereospecificity at the α-carbonyl position argued against a concerted [1,5]-hydrogen shift mechanism, and an alternative pathway was proposed. In contrast to the intramolecular study, no evidence of peroxy-bridged products was seen. In a more recent study an alternative mode of intermolecular azide trapping was observed.[82] When simple dienones were instead treated with strong Brønsted acid in the presence of azides, products resulting from apparent [3+3]-cycloaddition were observed, generating bridged bicyclic triazines, in contrast to the Schmidt-type products observed in the earlier studies (equation 31).



Scheme 31



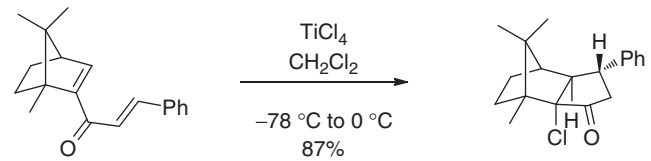
(30)



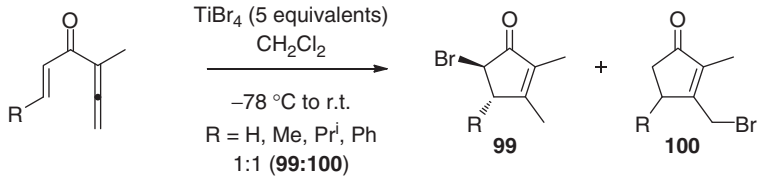
(31)

5.18.3.5.3 Halide nucleophiles

The first examples of nuclophilic halide trapping of the Nazarov oxyallyl cation were reported by White and West in 2005. When bridged bicylic dienones were treated with stoichiometric titanium(IV) chloride, Nazarov cyclization occurred and the resulting oxyallyl cation was trapped with Lewis acid-derived chloride (equation 32).[83] However, this methodology appears to be limited to hindered bicyclic dienones. Additionally, alkyl shift pathways have been found to compete with the halide trapping step. In 2009, Burnell and coworker reported a low yielding inadvertent halide trapping of the Nazarov 2-oxidocyclopentenyl cation intermediate by incorporation of chloride from $AuCl_3$.[75] Subsequent work sought to generalize the halide trapping process.[84] It was found that allenyl vinyl ketones underwent Lewis acid-mediated Nazarov cyclization, followed by halide trapping in the presence of excess Lewis acid. Moderate to low yields of regioisomeric mono-halogenated cyclopentenones were observed (equation 33).



(32)



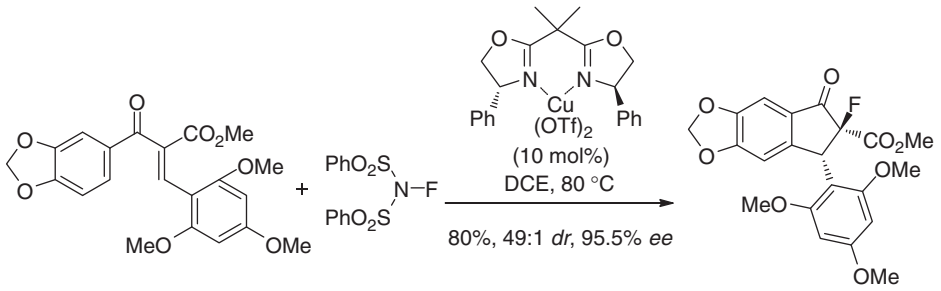
(33)

5.18.3.6 Electrophilic Trapping

All examples discussed so far have involved the interception of the cyclopentenyl cation formed immediately following Nazarov cyclization. The enolate formed on elimination can also be used in domino processes by interception with suitable electrophiles.

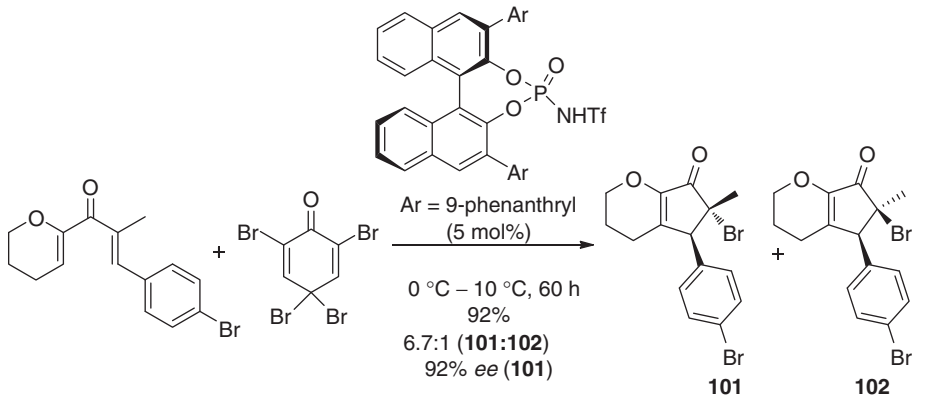
5.18.3.6.1 Trapping with electrophilic halogen sources

Ma and coworkers reported the synthesis of fluorinated indanones in a catalytic Nazarov cyclization/electrophilic fluorination sequence.[85] Alkylidine β-ketoesters were treated with a copper(II) Lewis acid in the presence of *N*-fluorobenzenesulfonimide (NFSI). Nazarov cyclization was followed by elimination with rearomatization, and the resulting copper enolate was then captured with electrophilic fluorine to give the fluorinated 1-indanone. The reaction was also studied using an asymmetric copper(II)-bis(oxazoline), which provided the desired products with moderate enantioselectivity. The same group has also published related methodology for trapping with electophilic fluorine,[86] chlorine, and bromine.[87] In these studies, a one-pot Knoevenagel condensation/Nazarov cyclization/halogenation sequence generates the halogenated 1-indanone products from β-ketoesters. Itoh and coworkers used a Nazarov cyclization/electrophilic fluorination strategy similar to that described above. Divinyl ketones bearing an α-ester were treated with an iron(II) Lewis acid in the presence of NFSI to give rise to fluorinated cyclopentenones.[39]



(34)

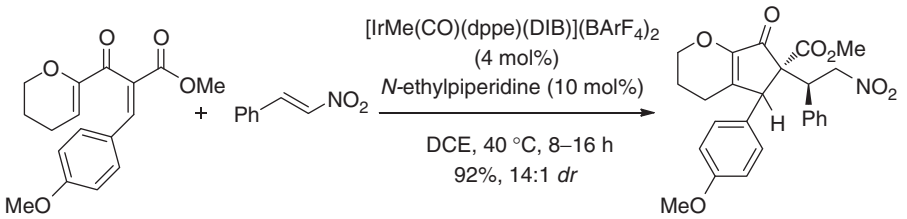
Recently, a conceptually related study by Rueping and Ieawsuwan gave rise to enantiomerically enriched α-halocyclopentenones via an asymmetric Brønsted acid-catalyzed Nazarov cyclization/electrophilic halogenation sequence.[88] Polarized dienone substrates were treated with a chiral BINOL-based *N*-triflylphosphoramide in the presence of the electrophilic bromine source 2,4,4,6-tetrabromocyclohexa-2,5-dienone. Torquoselective Nazarov cyclization followed by elimination led to an enol that was diastereoselectively captured by bromine from the opposite face as the β-substituent. The process was moderate to high yielding with synthetically useful enantiomeric excess, although long reaction times at low temperature were required.

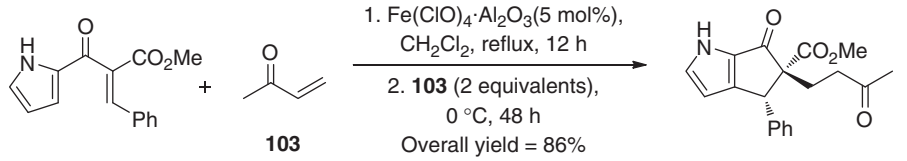


(35)

5.18.3.6.2 Trapping with Michael acceptors

The enolate intermediate of the Nazarov process has also been successfully utilized in conjugate additions. Frontier and coworkers reported the first examples of a tandem Nazarov cyclization/Michael addition (equation 36).[89] When polarized push–pull dienones were subjected to catalytic iridium(III) and amine base in the presence of nitro-alkenes, Nazarov cyclization and elimination occured, followed by Michael addition of the resultant enolate into the nitro alkene. In the process three new stereocenters were formed. The Michael addition is relatively fast, suggesting activation of the nitroalkene by coordination to the Lewis acid. In a similar study, Itoh and coworkers found that pyrrole-containing dienones could undergo Nazarov cyclization in the presence of alumina-supported iron(III) perchlorate, and subsequent Michael addition of the enolate into α,β-unsaturated ketones and aldehydes to generate the desired cyclopentenone Michael adducts (equation 37).[90]



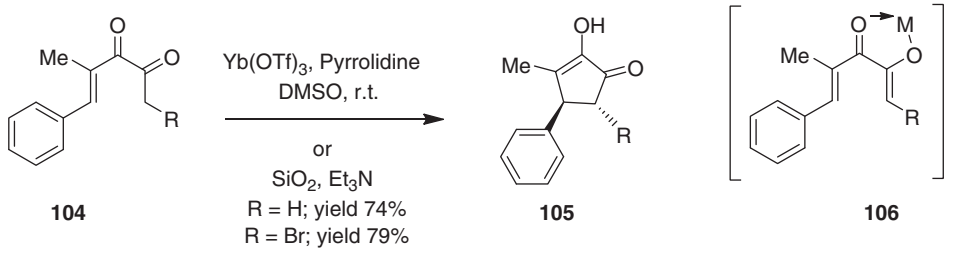


5.18.4 Alternative Activation Strategy

In its traditional format, the Nazarov reaction proceeds via activation of a cross-conjugated dienone with Lewis or Brønsted acid, followed by conrotatory electrocyclization of the resulting pentadienyl cation. However, some possible applications are precluded by limitations in substitution pattern or reagent compatibility. As a result, there has been considerable recent activity focused on alternative routes to the key pentadienyl cation.

5.18.4.1 Activation Through Diketones

α-Diketones are potential pentadienyl cation precursors via tandem enolization/carbonyl activation. α-Hydroxycyclopentenones were first reported to be formed from enediones in 1965 through a Nazarov-type cyclization of a chelated metalloenolate intermediate.[91] Later, Tius and coworkers described the cyclization of diketones **104** using $Yb(OTf)_3$ and pyrrolidine as base, which gave diosphenols **105** (Scheme 32).[92] The intramolecular Michael addition of the metal enolate derived from **104** is precluded by poor orbital overlap (a 5-*endo-trig* ring closure disfavored by Baldwin's rules). Instead, an electrocyclic ring closure involving the internally chelated metalloenolate **106** analogous to the Nazarov cyclization could better account for the formation of **105**.

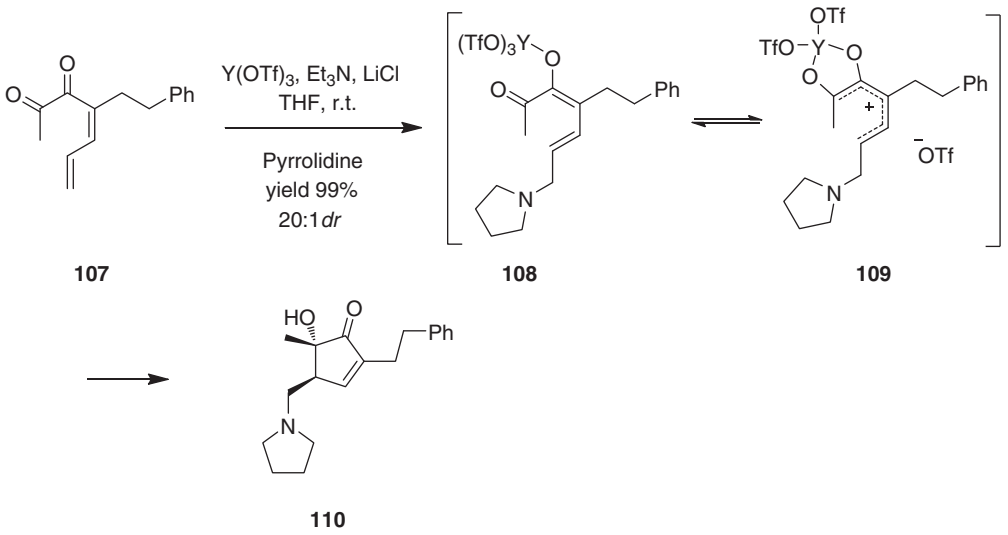


Scheme 32

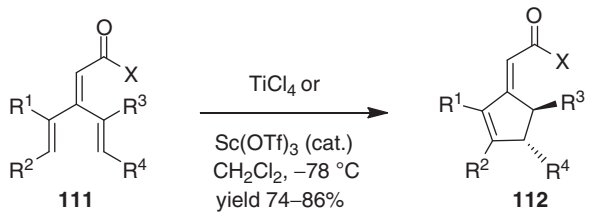
However, the Frontier group found that treatment of dienyl diketone **107** under similar conditions provided α-hydroxycyclopentenone **110** with installation of the pyrrolidine moiety in the molecule (Scheme 33).[93] In the proposed mechanistic rationale, a Lewis acid-promoted conjugate addition of the nucleophile to the diketone **107** would form intermediate **108**. A pentadienyl cation **109** could then be formed through activation of the keto-carbonyl moiety, which then undergoes a Nazarov-type cyclization to give **110**.

5.18.4.2 Vinylogous Nazarov Reaction

The general convention for substrate activation in Nazarov cyclization is through complexation to a C-3 carbonyl moiety. Variation of substitution at C-3 position raises challenges with regard to initiation of the reaction. West and coworkers have demonstrated that a cross-conjugated trienes **111** can also undergo successful Nazarov cyclization in the presence of $TiCl_4$ or $Sc(OTf)_3$ to furnish the cyclized products **112** (equation 38).[94] Replacement of the carbonyl moiety with enoate, enamide, enone, or enal functionality did not impede cyclization. Notably, only a single diene regioisomer **112** was furnished with the endocyclic olefin being *trans* to the carbonyl group.



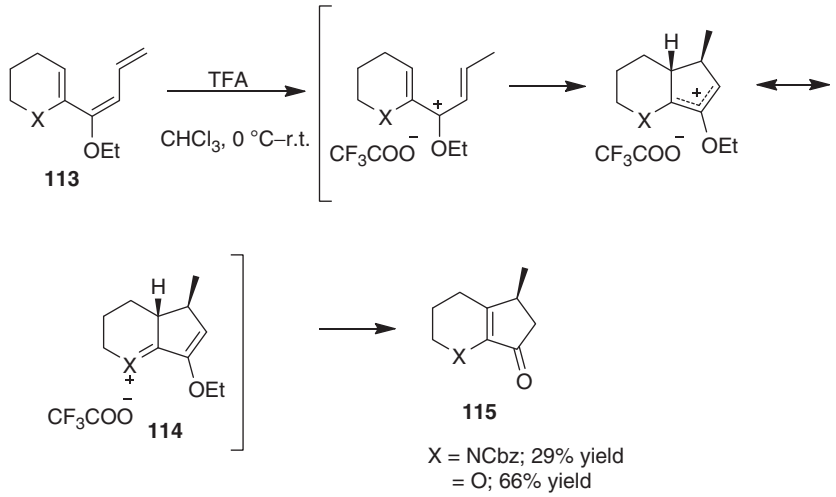
Scheme 33



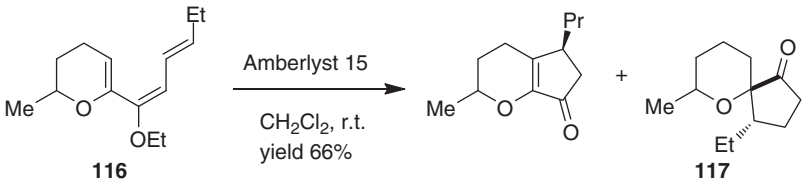
(38)

5.18.4.3 Activation Through Trienes

The Occhiato group has highlighted that proper activation of electron-rich trienes such as **113** derived from the lactam or lactone triflates can also trigger an efficient Nazarov cyclization to construct N- and O-containing heterocycles **115** with high diastereoselectivity (Scheme 34).[95] The presence of the heteroatom in the ring is critical for the stabilization of the oxallyl cationic intermediate **114**, which also accounts for the mildness of the reaction conditions. A spirocyclic by-product **117** was also observed during the cyclization of the dihydropyran derivative **116** via competing protonation of the dihydropyran olefin (equation 39).[96]



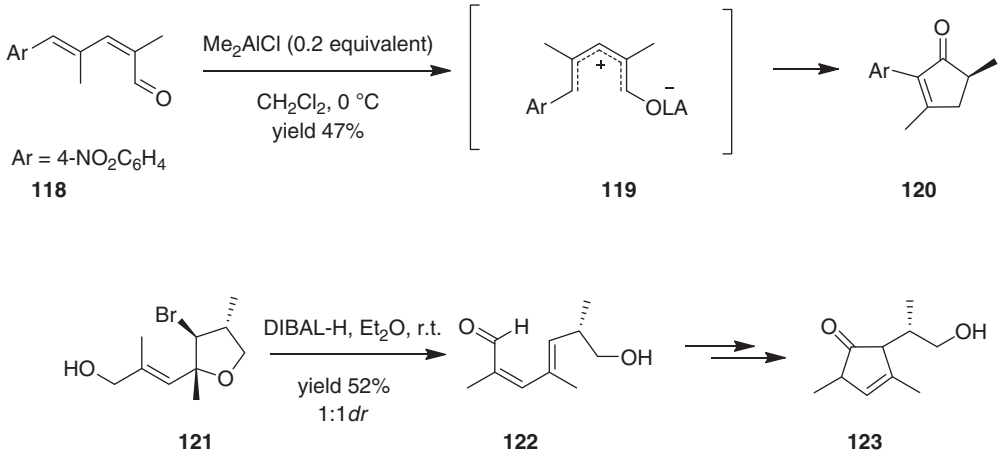
Scheme 34



(39)

5.18.4.4 Iso Nazarov

The electrocyclization of linearly conjugated dienals under Lewis acidic conditions, referred to as the iso-Nazarov reaction, has been studied recently. The Trauner group first reported the formation of cyclopentenone **120** from pentadienal **118** in the presence of a Lewis acid (Scheme 35).[97] The product **120** is assumed to form through a 4π electrocyclization of an oxy-pentadienyl cation **119**. An unusual rearrangement-cyclization of 2-alkenyl-3-bromotetrahydrofuran **121** under DIBAL-H reduction conditions was reported by the Jung group in 2007.[98] The cyclopentenone **123** is presumably formed via the iso-Nazarov cyclization of the activated form of dienal **122**. The acidic impurities from the DIBAL-H are most likely to catalyze this conversion.



Scheme 35

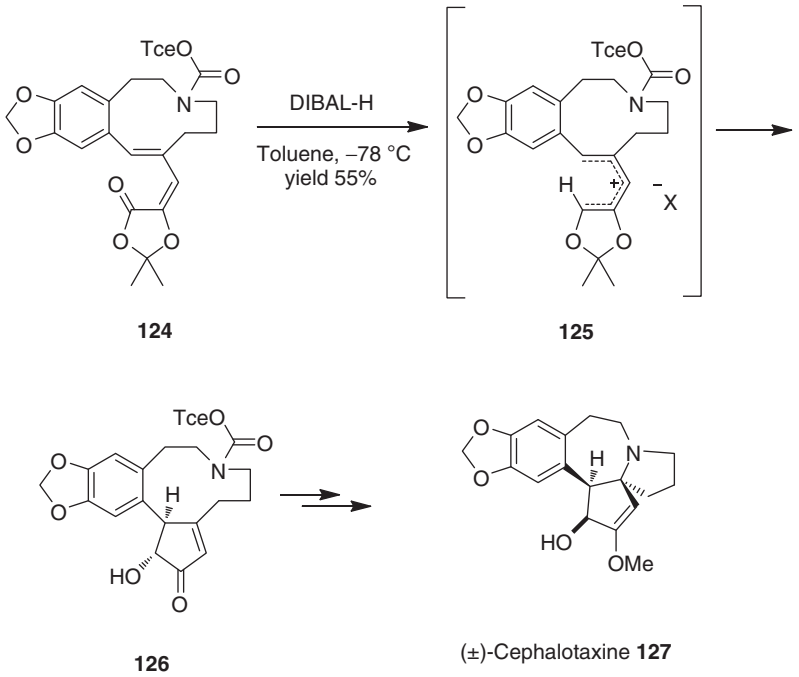
A similar type of electrocyclization strategy (reductive oxy-Nazarov reaction) has been developed by the Li group in conjunction with their studies toward the natural product cephalotaxine **127** (Scheme 36).[99] This transformation involved DIBAL-H reduction of vinylalkylidene dioxolanone **124** to form a tethered 1,2-oxidopentadienyl cation **125**, which then underwent a conrotatory ring closure to give cyclopentenone **126** in a regio- and stereospecific fashion.

5.18.4.5 Alkoxy Allenes

Another potential route to pentadienyl cations involved electrophilic activation of vinyl allenes. In their recent approach to the natural product rocaglamide, Frontier and coworkers applied this strategy through oxidative activation. Treatment of the alkoxy allene **128** with excess *m*-CPBA gave the cyclized product **129** stereospecifically, but in moderate yield (Scheme 37).[6] This tandem sequence involved an initial regioselective epoxidation of allenol ether **128** to generate allene oxide **130**. Epoxide opening under acidic conditions unveiled the pentadienyl cation **131** which then underwent a conrotatory ring closure to form the fused tricyclic product **129**. This strategy has also been extended to simpler vinyl alkoxyallenes.[100]

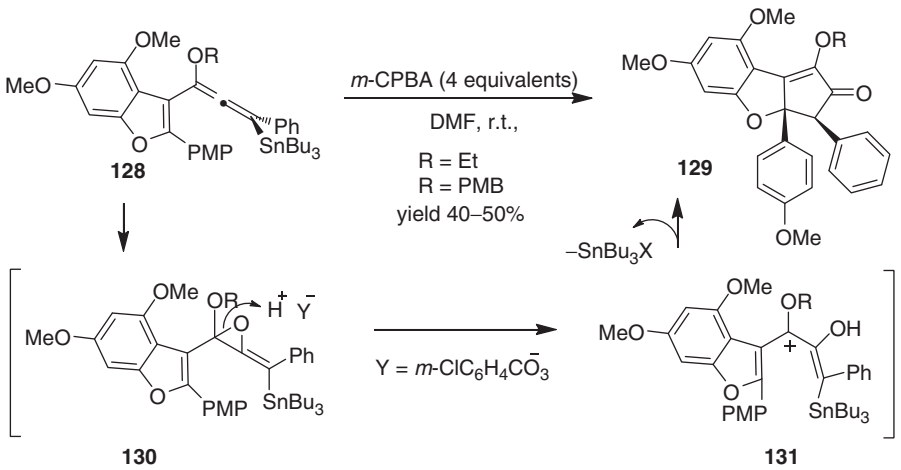
5.18.4.6 Brønsted Acid Activation of Vinyl Allenes

Brønsted acid activation offers another method for accessing pentadienyl cations from vinyl allenes (Scheme 38).[101] Vinyl siloxyallene such as **133** formed *in situ* from enyne **132** were shown to undergo a 4π electrocyclization on Brønsted acid (TFA)-mediated activation to form cyclopentenones **134** and **135** in good yields. However, the regiocontrol for deprotonation at the termination step was poor.



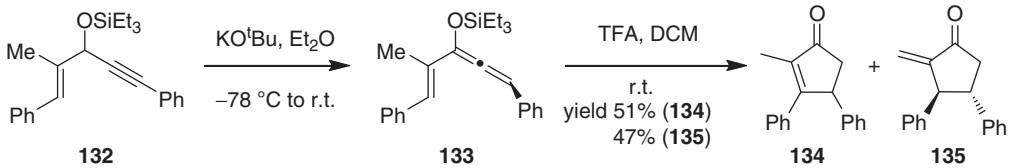
124 125 126

Scheme 36



128 129 130 131

Scheme 37



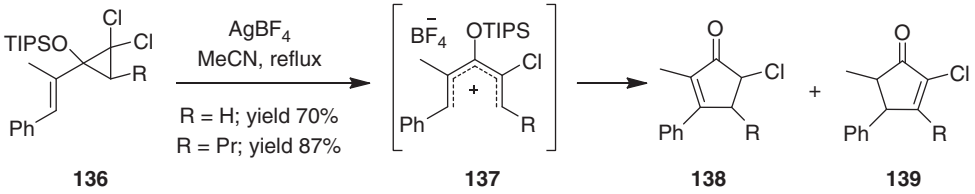
132 133 134 135

Scheme 38

5.18.4.7 Dihalocyclopropane Nazarov Reaction

Disrotatory electrocyclic ring opening of dihalocyclopropanes under thermal or silver-assisted conditions is quite well known. The resulting chloroallyl cations can undergo a variety of trapping processes. A dihalocyclopropane, when properly substituted with an

alkene unit, could potentially provide a novel route to a pentadienyl cation capable of undergoing Nazarov cyclization. Grant and West have demonstrated that alkenyl- and silyloxy-substituted cyclopropane **136**, in the presence of Ag(I), opens to pentadienyl cation **137**.[102] Subsequent 4π electrocyclic closure and elimination would then provide chlorocyclopentenones **138** or **139** (Scheme 39). Complete regioselectivity in the elimination step in favor of more substituted alkene product **138** was observed in cases lacking alkyl substitution on the cyclopropane.



136 **137** **138** **139**

Scheme 39

5.18.4.8 Cyclization via *In Situ* Generation of Nazarov Intermediate

Several different strategies have been developed over the past few years to access species bearing the pentadienylic moiety analogous to the Nazarov intermediate for cyclopentannulation.

5.18.4.8.1 Metal-mediated activation of alkynes

Divinylmetallocarbenes should be expected to display pentadienylic character analogous to Lewis or Brønsted acid-activated divinyl ketones. A common way of generating such type of metallocarbenes is through Au-mediated activation of alkynes. Sanz et al. reported the first gold-catalyzed tandem reactions of propargylated indoles triggered by a 1,2-indolyl migration.[103] Interestingly, propargyl indole **140** with an aryl group at the propargyl position gave **142** as the sole product whereas **143** was formed when **141** was the substrate (Scheme 40). Both products **142** and **143** are believed to be formed through a common intermediate **144** after a 1,2-indole migration.[103a,104] When there is an aryl group at the propargylic position, an intramolecular attack of the aryl group on the carbene carbon leads to the intermediate **145**. Finally, rearomatization and subsequent protodemetallation generates **142**. However, when there are two alkyl groups at the propargyl position, the carbene intermediate may involve in a Nazarov type cyclization to give **146**. Ultimately a similar rearomatization followed by protodemetallation gives the usual aura-Nazarov product **143**.[104]

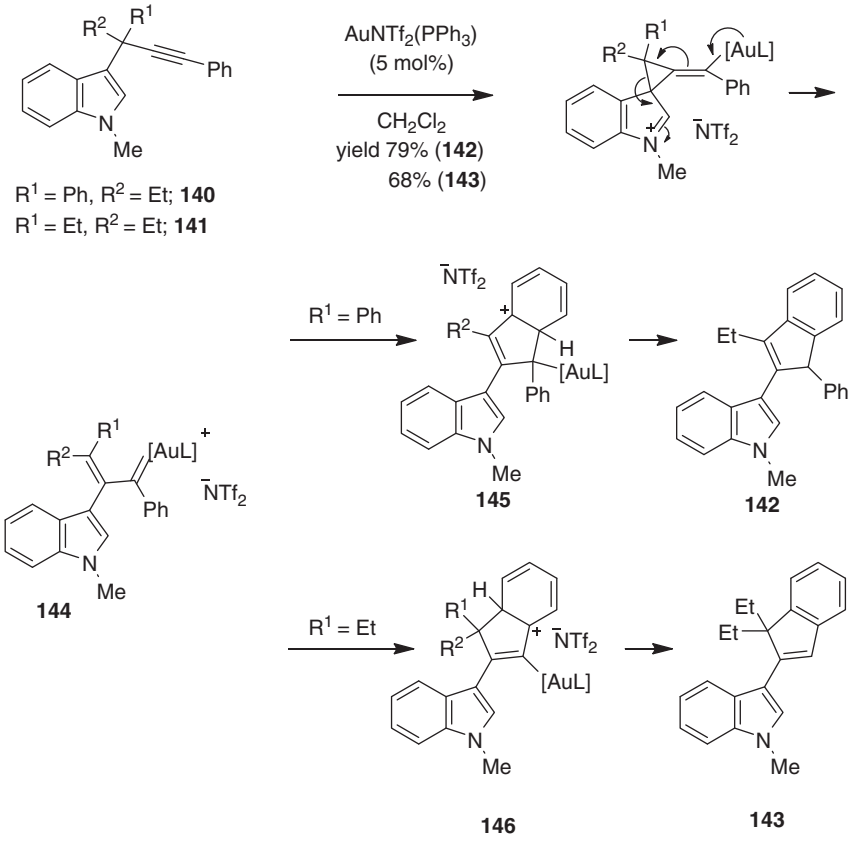
An interesting domino cyclization of propargylic acetate **147** has been reported by the Malacria group using a gold(I) catalyst.[105] An initial [3,3]-rearragement of the acetate group of **147** leads to the intermediate **148** which then undergoes a metallo-Nazarov cyclization to generate a cyclopentenylidene gold complex **149** (Scheme 41). A subsequent cyclopropanation of **149** provides the tetracyclic product **150** as a single diastereomer in excellent yield. This methodology has been applied to a short total synthesis of capnellane.[105b] A similar domino protocol of [3,3] rearrangement and Nazarov cyclization of enynyl acetate **151** to cyclopentenone **153** has been studied by the Zhang group.[106] Best results were obtained using wet dichloromethane as solvent, prompting the authors to propose a water-assisted proton transfer via **152**.[106b]

Vinylcarbenoid intermediates can also be generated by other transition metal catalysis. Indenes **155** and **156** have been formed from propargyl ester **154** by platinum or ruthenium-mediated activation.[107] Metal-mediated activation of the alkyne moiety in **154** with a subsequent 1,2-acetyl shift generated a vinylcarbenoid species **157** (Scheme 42). In the presence of a platinum catalyst, a mixture of isomers **155** and **156** were formed, whereas the use of a ruthenium catalyst yielded predominantly isomer **156**. An alternative reaction mechanism via metallacycle **158** has been proposed for the ruthenium-mediated reaction.

Gold-mediated activation of alkynes can also lead to a Nazarov-type cyclization via a pentadienyl cationic intermediate without involving a vinylcarbenoid species (Scheme 43).[108] The 1,6-yne-allene **159**, for example, undergoes a domino 6-*endo-dig* cyclization via Au(I)-π-alkyne intermediate **160** and a subsequent Nazarov cyclization to generate a tricyclic compound **161** in moderate yield. The $PtCl_2$/CO catalyst system has also been shown to be efficient in catalyzing 2-alkenyl-(1′-hydroxy-4-en-2-ynyl) benzenes **162** through a similar tandem process to generate cyclopentanaphthalene derivatives **163** regioselectively.[109]

Another method of generating the pentadienyl system **165** in the presence of a gold cation can be through heteroenyne metathesis of 1,3-enynyl carbonyls **164** (Scheme 44).[110] In this case, Au (III) activates the alkyne and carbonyl moieties simultaneously. The trienones **166** are generally formed in excellent yields with good olefin regioselectivity and also high diastereoselectivities.

Various other ways of generating the 3-oxygenated pentadienyl cations have been reported in recent years. A tandem cyclization of diyne **167** and oxocarbenium ion **168** in the presence of $FeCl_3$ catalyst has been reported to provide highly functionalized indenes **169** (Scheme 45).[111] In this example, diyne **167** undergoes a [2+2] cycloaddition with the oxocarbenium ion **168** generated from benzaldehyde acetal by Lewis acid catalysis, to form oxete **170**. Ring opening leads to the pentadienyl cation **171**



Scheme 40

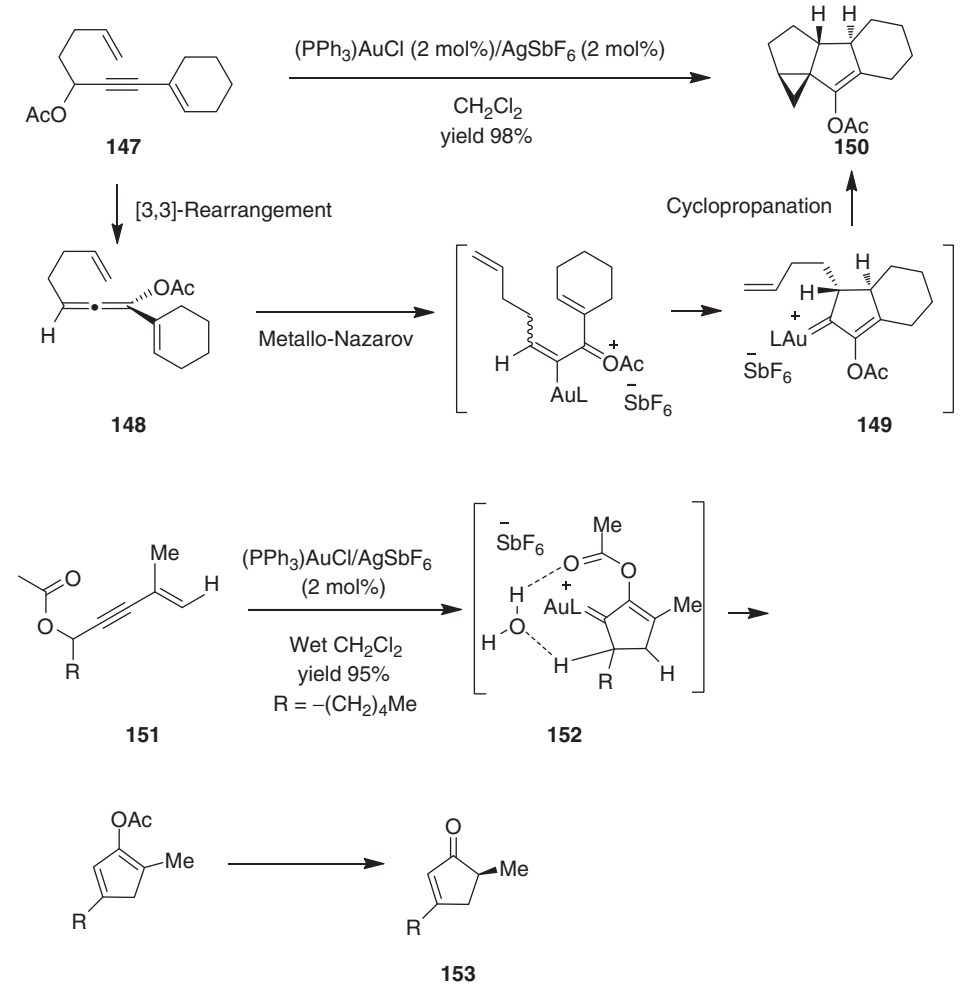
which subsequently undergoes a 4π electrocyclization to generate another oxocarbenium cation **172**. The tethered alkyne moiety then intercepts the oxocarbenium ion and subsequent attack by chloride ion provides the indene **169** as the final product.

5.18.4.9 *In Situ* Generation of Allenyl Vinyl Ketone

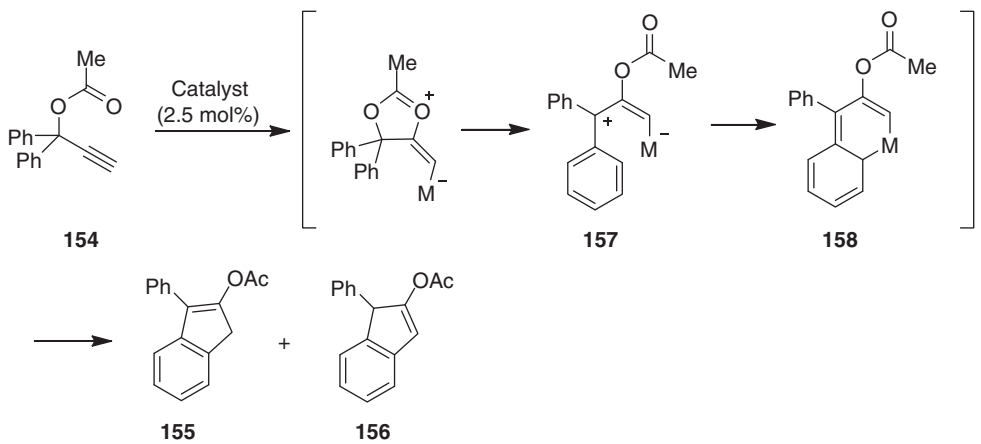
Nazarov cyclization of allenyl vinyl ketone is quite well developed and has been discussed in detail in Section 5.18.3.5.3. Tang and coworkers have developed a method for the *in situ* generation of allenyl vinyl ketone **175** and subsequent Nazarov cyclization (Scheme 46).[112] In this process the starting unsaturated diazocarbonyl compound **173** underwent a Wittig olefination with ketene **174** to provide the allenyl vinyl ketone intermediate **175**. Subsequent cyclization under acidic conditions gave the cyclopentenone **176**. This reaction provides an efficient one-pot alternative access to sensitive allenyl vinyl ketones which can then undergo a facile cyclization to provide cyclopentenone derivatives with high yield and excellent *Z* stereoselectivity.

5.18.4.10 Imino Nazarov

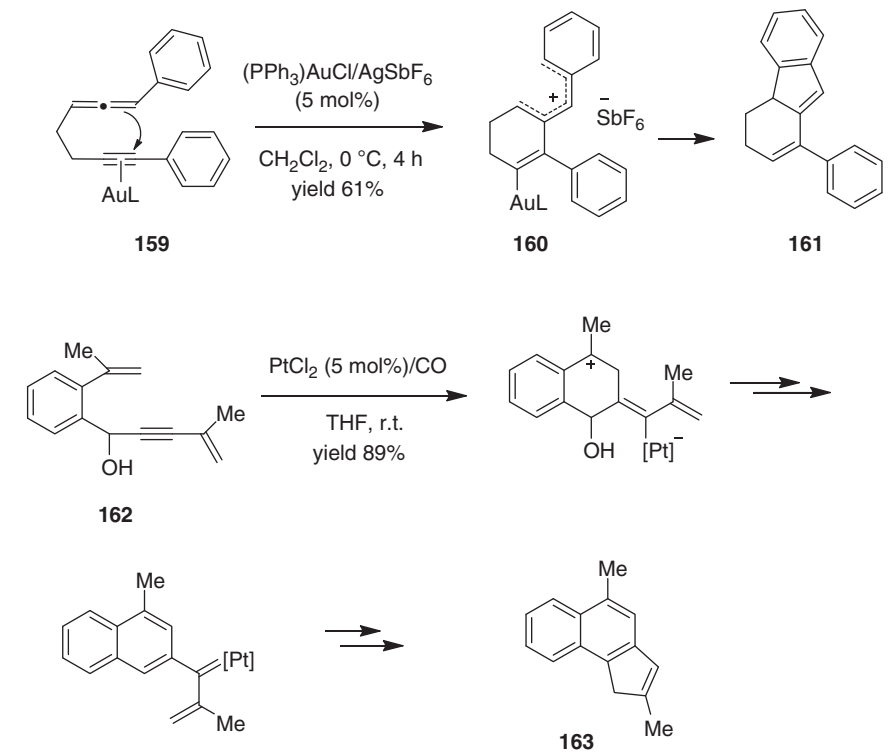
In 2001 Tius et al. first reported the formation of α-aminocyclopentenones **179** in a single operation from α,β-unsaturated nitriles **177** and allenyl nucleophiles **178** (Scheme 47).[113] The cyclopentannulation event was described by the authors as an imino Nazarov cyclization. The amines were converted to the corresponding acetamides **180** for ease of handling and storage. Theoretical calculations by the Smith group rule out the possibility of a classical imino Nazarov cyclization due to an unfavorable equilibrium for the cyclization.[114] However, the formation of the α-aminocyclopentenones **179** is favored by the irreversible loss of the methoxymethyl cation after the cyclization step. Cyclopent-2-imines **187** have been reported to be formed through an interesting tandem reaction sequence involving a gold-catalyzed activation of propargyl tosylates **181** followed by further reaction with activated aldimine **182** (Scheme 48).[115] According to the proposed reaction mechanism, an initial activation of the alkyne moiety by gold(I) leads to the 1,2-tosyl rearrangement inducing an alkyl migration to give **183**. A further elimination provides the diene **184** which then reacts with the activated aldimine **182** to form a highly strained azetine species **185**. Finally, a divinyl imine **186** is formed via the electrocyclic ring opening of **185**. In the presence of the gold complex, **186** then undergoes a Nazarov-like cyclization to give the cyclopentenyl imine product **187**. The formation of cyclopentimine products through the final Nazarov cyclization can also be termed as an imino Nazarov cyclization.



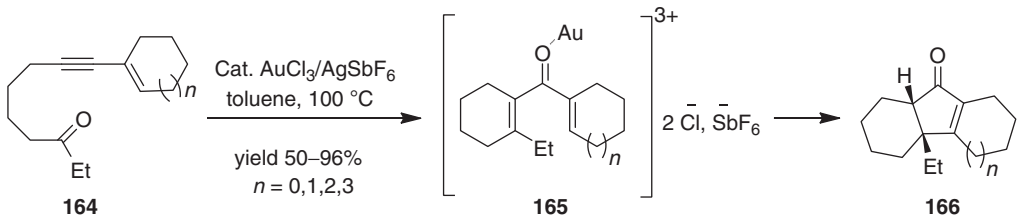
Scheme 41



Scheme 42



Scheme 43



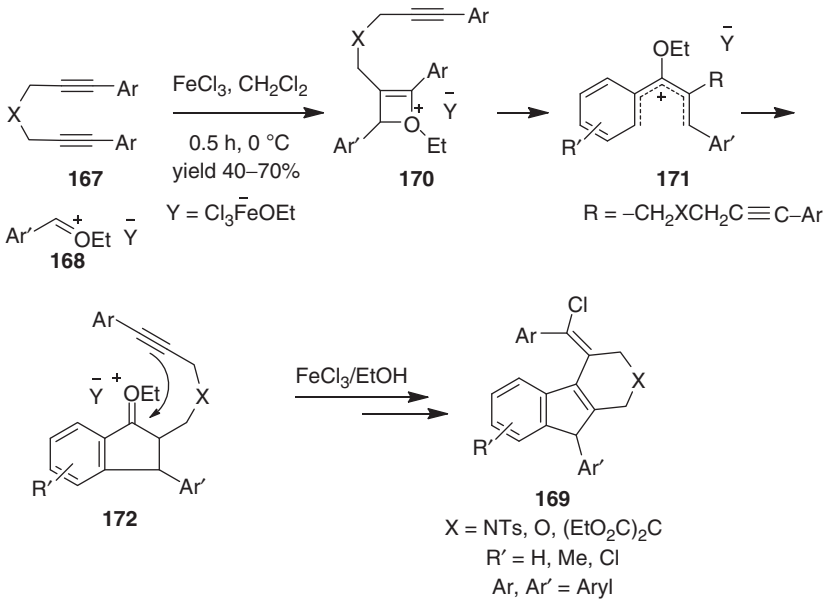
Scheme 44

5.18.4.11 Aza-Nazarov

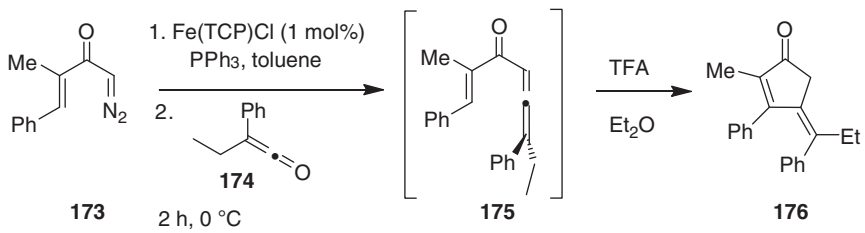
Replacement of 1,4-pentadien-3-ones with 1-aza-1,4-pentadien-3-ones can potentially lead to the formation of pyrroles. Ciufolini and Roschangar first coined the name aza-Nazarov reaction during their synthetic endeavor toward camptothecin where a quinoline-containing enone gave an indolizine product in the presence of $Yb(fod)_3$.[116] Later, the Würthwein group showed that hydrazones of type **188** having nitrogen in the 1-position undergo smooth cyclization to give **189** in accordance with their theoretical estimates (Scheme 49).[117] Compound **189** was generally trapped by acetylation to give **190**, due to its instability. Further studies were carried out with indoline **191**; it was found that indole **193** was an effective leaving group to produce the substituted 1*H*-pyrrole **192**.[118] Klumpp et al., however, reported the aza-Nazarov cyclization of 2-azapentadienone **194** to form a fused bicyclic product **196** (Scheme 50).[119] Although the presence of nitrogen at the 2-position was calculated to confer a high activation energy for cyclization, the reaction occurred smoothly when the substrates were *N*-acyliminium salts **194**, in the presence of acid catalysts.[119a] On the basis of theoretical calculations Klump and coworkers suggested that the formation of superelectrophilic species such as **195** is key to the success of these reactions.

5.18.4.12 Cyclization of Pentadienyl Carbocation Generated through Dehydration

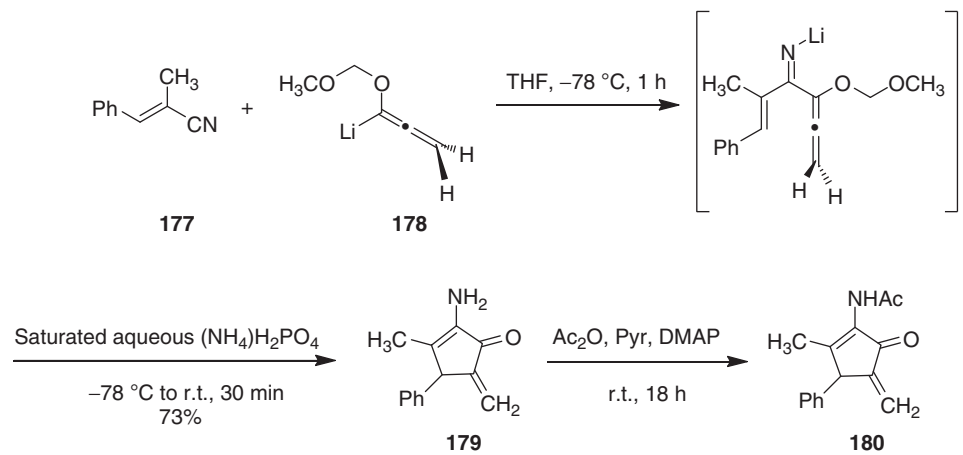
Another alternative route to a pentadienyl carbocation for a potential 4π-electrocyclization could be achieved via dehydration of a divinyl alcohol. An allenic version of this protocol has been reported by Malacria and Gandon to provide a direct route to benzofulvenes **199** or **200** starting from α-hydroxyallenes (Scheme 51).[120] In case of the monosubstituted α-hydroxyallene



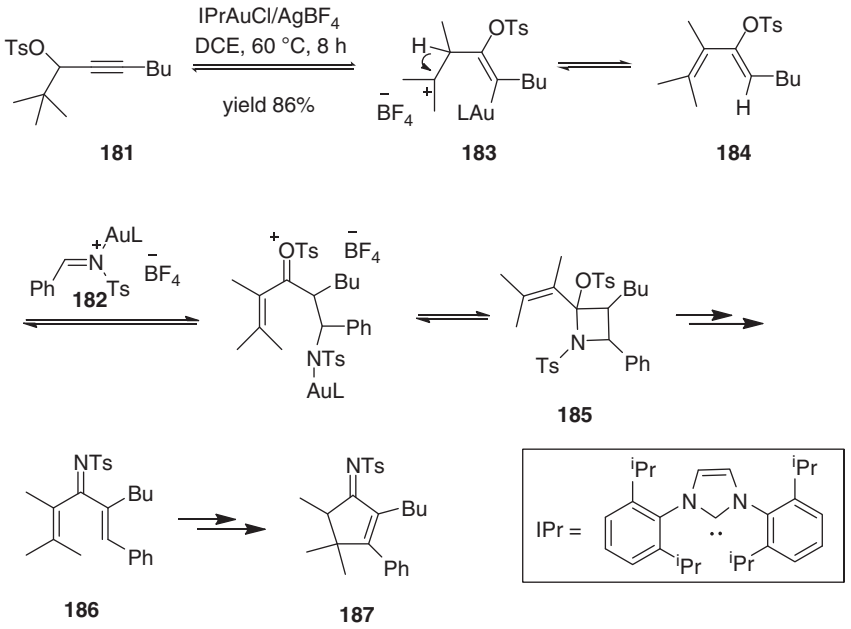
Scheme 45



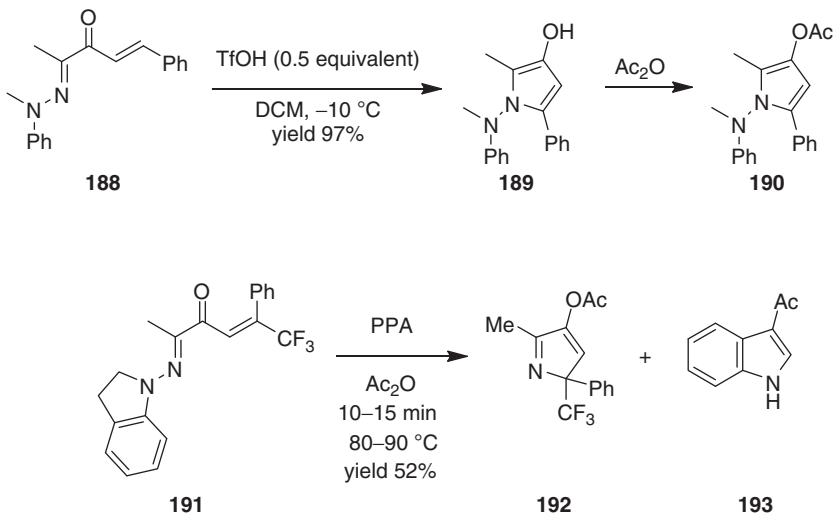
Scheme 46



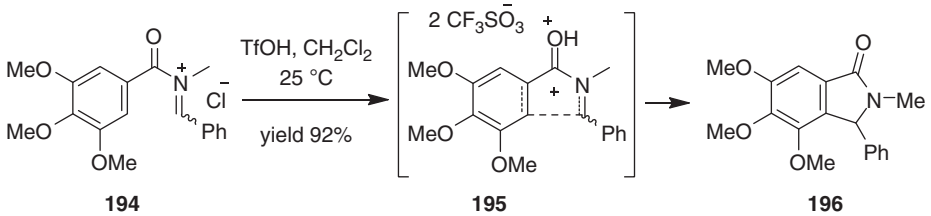
Scheme 47



Scheme 48

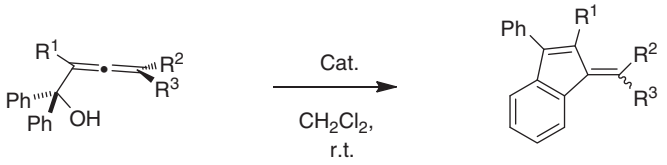


Scheme 49



Scheme 50

substrate **197**, $ZnCl_2$ proved to be a superior catalyst, whereas for di- and tetrasubstituted allenes such as **198**, AgOTf, TfOH and phosphomolybdic acid (PMA) gave the best results. Interesting polycyclic scaffolds **202** have been synthesized in a similar fashion from diaryl alcohols **201** by the Panda group (Scheme 52).[121] The presence of an electron-donating group activates the cyclization of the pentadienyl carbocation, whereas lack of substitution leads to a sluggish cyclization and also allylic isomerization of the



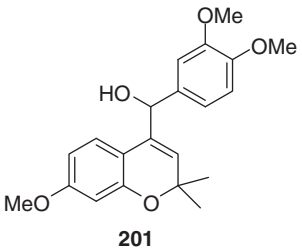
$R^1 = R^2 = R^3 = H$; **197**

$R^1 = R^2 = R^3 = Me$; **198**

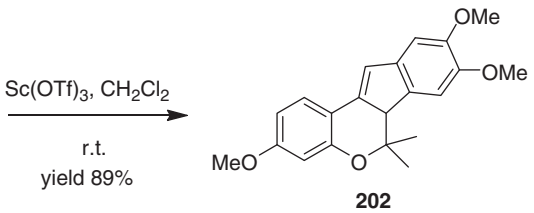
$ZnCl_2$ (200 mol%) $R^1 = R^2 = R^3 = H$; **199**; yield 77%

AgOTf (1 mol%) $R^1 = R^2 = R^3 = Me$; **200**; yield 92%

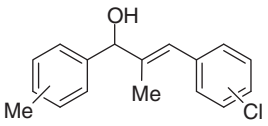
Scheme 51



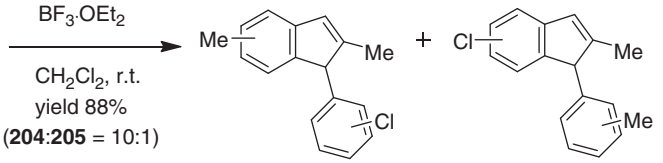
201



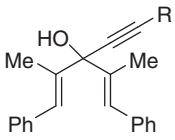
202



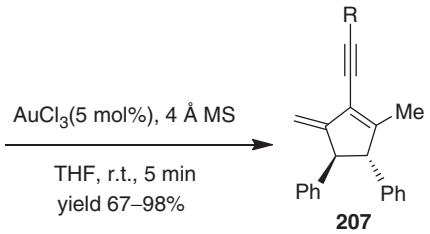
203



204 **205**

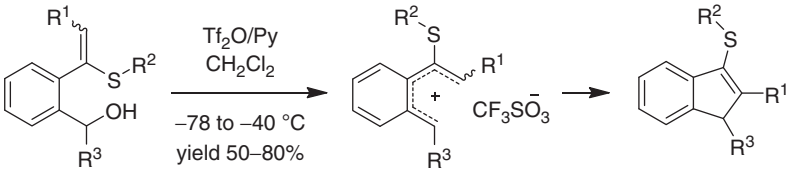


206



207

R = $SiMe_3$, Bu^n, Ph, OEt



208 **209** **210**

R^1 = H, Me, Pr^n, Ph
R^2 = Me, Et, Ph
R^3 = Et, Pr^n, Bu^t, Ph, vinyl

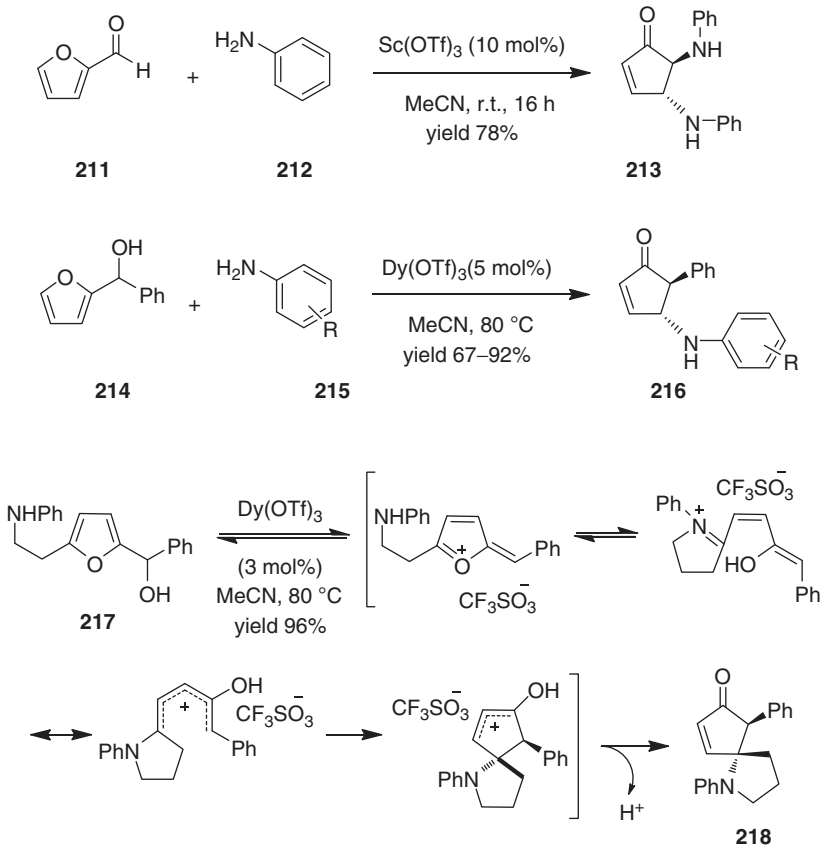
Scheme 52

product. 1,3-Diarylallylic alcohols **203** have been shown to provide 1-aryl-1-H-indenes **204** and **205** under similar Lewis acid-mediated conditions.[122] The reaction is proposed to proceed through dehydration of the alcohol to form the corresponding 1,3-diarylallylic carbocation. Presence of a substituent is necessary at the 2-position of the diarylallic alcohols **203** to attain the reactive conformation for 4π electrocyclization. A dehydrative cyclization was also observed by Rieder and West during their studies on the Meyer–Schuster rearrangement of alkynyl carbinols **206** under gold(III)-catalyzed conditions.[123] Exclusive formation of the cyclized alkyne **207** in good to excellent yields was observed when the reaction was carried out in the presence of molecular sieves. The stereochemical outcome of this dehydrative cyclization confirmed a Nazarov-type electrocyclization pathway. Zhou et al., however, have reported a sulfur-mediated dehydration of [2-(1-thio-vinyl)phenyl]alcohols **208** to generate the pentadienyl cation **209**, followed by Nazarov-type cyclization leading to 3-thio-1*H*-indenes **210**.[124]

5.18.4.13 Piancatelli Reaction

In 1976, Piancatelli et al. reported a protocol for the synthesis of various 4-hydroxycyclopentenones via acid-catalyzed rearrangement of 2-furylcarbinols.[125] The overall transformation is believed to proceed through a domino sequence that involves a 4π electrocyclic ring closure of a pentadienyl cation, closely resembling the Nazarov cyclization. However, the synthetic application of this rearrangement has been largely limited because of the requirement of stoichiometric amounts of acid as activator, dilute reaction conditions, and excess water.

In 2007, the Batey group reported the synthesis of 4,5-diaminocyclopent-2-enones **213** under Lewis acidic conditions from furan-2-carbaldehyde **211** and aniline **212** (Scheme 53).[126] Product **213** is formed with exclusive *trans* diastereoselectivity. The overall transformation is proposed to follow a domino pathway involving an initial condensation followed by ring-opening and electrocyclization, very similar to the Piancatelli reaction. In 2010, Alaniz and coworkers developed a mild catalytic aza-Piancatelli protocol for the synthesis of 4-amino-5-alkylcyclopentenones **216** from readily available 2-furylcarbinols **214** and aromatic amines **215**.[127] 5 mol% of $Dy(OTf)_3$ was optimal for the conversion with good yields and high *trans* diastereoselectivity. Generally, product isomerization is hard to control in the Piancatelli rearrangement which could be avoided in the present protocol due to the mild nature of $Dy(OTf)_3$. The aza-Piancatelli rearrangement has further been extended by the Alaniz group toward the synthesis of azaspirocycles **218** using 2-furylcarbinols with an aminoalkyl side chain **217**.[128] The Reddy group has recently reported a very similar aza-Piancatelli rearrangement to construct *trans*-4,5-disubstituted cyclopentenones under mild conditions using very low catalyst loading (0.03 mol% PMA).[129] The intramolecular aza-Piancatelli rearrangement also



Scheme 53

proceeds with good *trans* diastereoselectivity, consistent with a 4π electrocyclization. Substrates bearing an electron-donating group adjacent to the alcohol and an electron-withdrawing group on the nucleophilic nitrogen were most efficient in the intramolecular pathway. The intramolecular aza-Piancatelli rearrangement provides an efficient approach to the construction of challenging azaspirocycle motifs **218** by forming the tertiary stereocenter and the spirocyclic system in a single operation.

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5.19 Cope, Oxy-Cope, and Anionic Oxy-Cope Rearrangements

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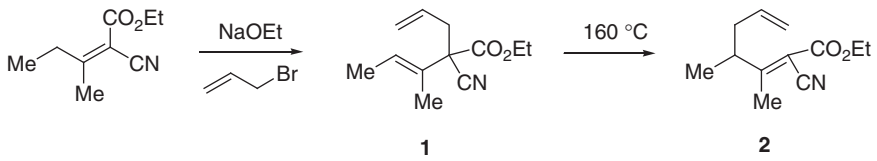
Glossary

Chiral auxiliary Covalently attached chiral residue that controls a desired diastereoselective bond-forming process.
Concerted reaction Reaction with a single transition state for bond breaking and bond making.
Domino reaction Transformation with multiple bond-forming processes run under identical reaction conditions, in which each subsequent reaction occurs at the functional group newly formed in the previous step.
Endo Space inside a vaulted, bicyclic structure.
Exo Space outside a vaulted, bicyclic structure.
Medium-size ring Carbo- or heterocyclic ring with 8–12 members.
Sigmatropic rearrangement Migration of a σ-bonded atom or group along a π-system.
Synchronous reaction Reaction with simultaneous bond breaking and bond making.

5.19.1 Introduction

The all-carbon [3.3]-sigmatropic rearrangement of 1,5-dienes, serendipitously discovered by AC Cope and his group in 1940 during the distillation of the allylated malonic cyanoester **1** (equation 1),[1] comprises the suprafacial migration of an allyl fragment along a second allyl moiety with concomitant σ- and π-bond reorganization to arrive at the doubly conjugated

product **2**. In the course of this process one new σ-bond and two new π-bonds are predictably established at unambiguously defined locations within the product.



1 **2** (1)

In contrast to the related Claisen rearrangement of allyl vinyl ethers that takes advantage of the formation of a carbonyl group in the course of the reaction, the Cope rearrangement is principally a thermoneutral and hence reversible process, which derives its driving force from interaction with the substituents attached. In particular, carbonyl and related substituents with the capacity to conjugate with the developing double bonds turned out early on to be well suited to shift the equilibrium to the product side. A breakthrough for the utility of the Cope rearrangement in synthetic organic chemistry came with the development of the oxy-Cope reaction, which benefits from an irreversible enol–keto tautomerization subsequent to the actual rearrangement. The discovery that a negative charge on the oxy substituent leads to dramatic rate accelerations in the anionic version of the oxy-Cope rearrangement further extended the applicability of this process. In addition, release of ring strain and aromatization of the product can contribute significantly to the ease and driving force of the Cope rearrangement.

This chapter will briefly outline the basic principles of this reaction and then focus primarily on recent developments since 1991. For additional information, the reader is referred to the respective chapter 7.1 in the first edition of this book and a number of excellent review articles.[2]

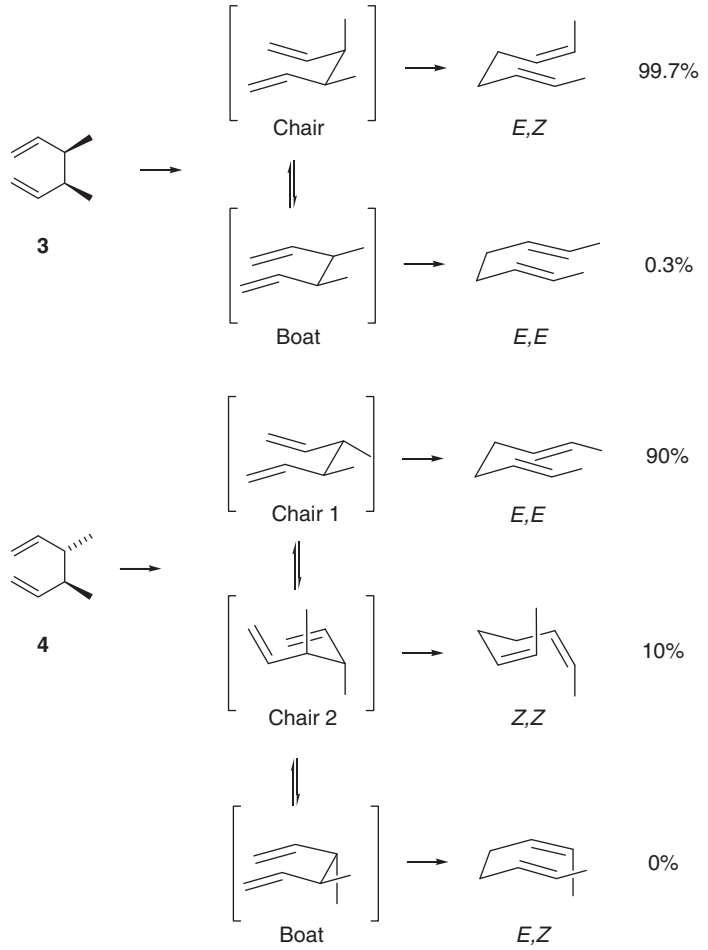
5.19.1.1 Transition State and Mechanism

The Cope rearrangement proceeds through a cyclic, strictly intramolecular, and concerted transition state with inversion of the migrating allyl group. The activation enthalpy for the reaction of the parent 1,5-hexadiene has been measured as 33.5 kcal mol^{-1} with an activation entropy of -13.8 cal mol^{-1} K.[3] Through a number of ingenious experiments, Doering and Roth discovered the exact transition state conformation for rearrangements of acyclic 1,5-dienes.[4] Thus, the Cope rearrangement of *meso*-3,4-dimethyl-1,5-hexadiene (**3**) furnished 99.7% of (2*E*,6*Z*)-2,6-octadiene and only 0.3% of the corresponding *E*,*E*-isomer on heating at 225 °C (Scheme 1). In addition, the C_2-symmetric stereoisomer **4** gave rise to 90% of the *E*,*E*-isomer, 10% of the *Z*,*Z*-isomer, and none of the *E*,*Z*-isomer. These observations reveal a highly stereospecific reaction pathway and suggest a chair transition state conformation which prevails over a boat-like structure by at least 5.7 kcal mol^{-1}.

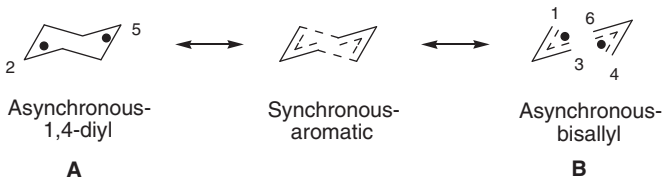
Although the preference for chair-like transition states holds true for acyclic and thus flexible 1,5-hexadienes, boat transition structures may energetically be accessible and even prevail in cyclic 1,5-dienes, which suffer from geometrical constraints. For example, in *cis*-1,2-divinylcyclopropanes, which rearrange spontaneously at ambient temperature, only a boat conformation with eclipsing substituents can bring the two vinyl groups in sufficiently close proximity such that bond formation can occur. For the same reason, most *cis*-1,2-divinylcyclobutanes rearrange through boat transition states too, whereas *cis*-1,2-divinylcyclopentanes can accommodate both conformations and *cis*-1,2-divinylcyclohexanes employ chair conformations exclusively.

The exact nature of the transition state of the Cope rearrangement has been a matter of intense debate in the course of time. Specifically the question whether it is a truly synchronous process with simultaneous bond making and bond breaking resulted in a host of theoretical studies.[5] Although a full discussion of this topic would be beyond the scope of this chapter, some important conclusions should be mentioned here:

(1) The Cope rearrangement of the parent 1,5-hexadiene involves a concerted, aromatic, and synchronous transition state as described above.
(2) Radical-stabilizing substituents such as phenyl and cyano groups located both at C2 and C5 within the 1,5-diene system lead to an asynchronous transition structure with advanced bond making between C1 and C6, which is best described by a cyclohexane-1,4-diyl biradical resonance structure **A** (equation 2).
(3) However, radical-stabilizing substituents at C1, C3, C4, and C6 within the 1,5-diene system result in very long interallylic bond lengths and a transition state that resembles two weakly interacting allyl radicals as depicted in resonance structure **B**. Here, bond breaking between C3 and C4 precedes bond making between C1 and C6. Doering described this phenomenon as a chameleonic transition structure of the Cope rearrangement,[5c] whereas Borden coined the term of a variable transition structure depending on the exact substitution pattern of the 1,5-hexadiene.[5d]



Scheme 1

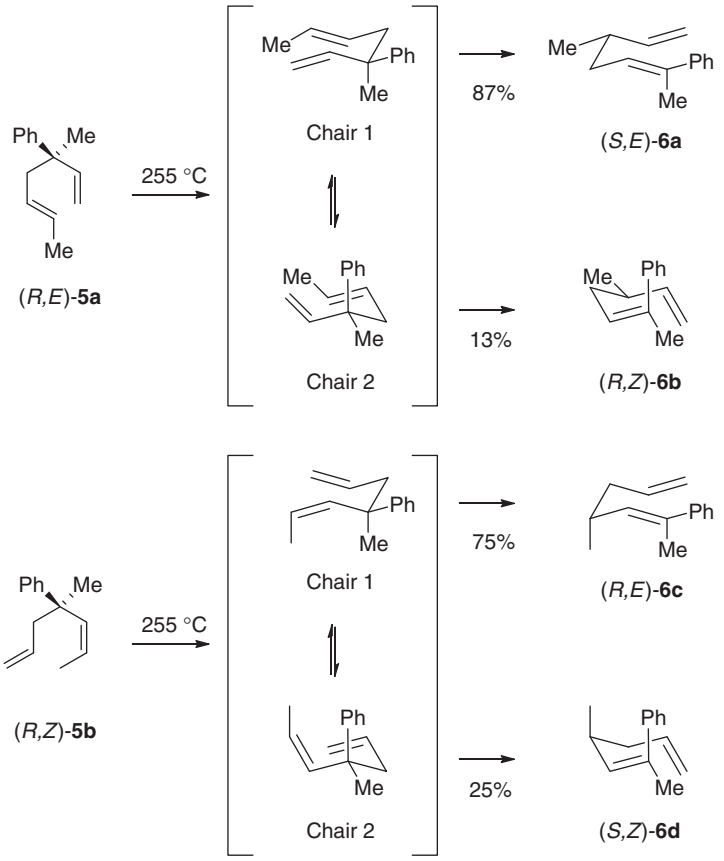


(2)

5.19.1.2 Double Bond Configuration and Chirality Transfer

Based on the preference for chair transition states, C3- and C4-substituents within the 1,5-diene strongly prefer equatorial positions, which results in the formation of *E*-configured Cope products accordingly. Thus, the thermal rearrangement of **4** furnished 90% of the *E*,*E*-configured diene originating from chair 1 with both methyl groups in equatorial positions and only 10% of the *Z*,*Z*-diene resulting from chair 2 with the methyl groups in the unfavorable axial positions (Scheme 1). The preference for the equatorial position of a given substituent and hence the formation of the *E*-alkene increases with the steric size of that substituent. Such A-values for the equatorial/axial preference of substituents in cyclohexanes are a good measure for estimating the proportion of the *E*-alkene in a stereoisomeric mixture of Cope products. If two substituents are attached to the same carbon atom, the larger of them will occupy the equatorial position in the preferred transition state. In oxy-Cope rearrangements, however, the polarity of the solvent and the existence of a charged species, such as in the anionic version, may affect the *E*/*Z* ratio of the product. In general, nonpolar solvents and the absence of charge increase the proportion of *E*-alkene in the stereoisomeric mixture of Cope products.

The stereospecificity of the Cope rearrangement has important implications for chiral 1,5-dienes carrying prochiral alkene groups. Hill et al.[6] first demonstrated unambiguously that the pair of stereoisomeric dienes (*R*,*E*)-**5a** and (*R*,*Z*)-**5b** rearranged on heating exclusively either to a mixture of (*S*,*E*)-diene **6a** and (*R*,*Z*)-diene **6b** or (*R*,*E*)-diene **6c** and (*S*,*Z*)-diene **6d**, respectively (Scheme 2). The two stereoisomers formed in each reaction resulted from the two competing chair-like transition states and consequently had opposite configurations at both the new chiral center and the double bond. No crossover stereoisomers were observed within the limits of detection, indicating stereospecificity of at least 97%. The equatorial preference of the larger phenyl substituent in the respective chair transition state 1 dictated the stereoselectivity of the Cope rearrangement in favor of the formation of *E*-alkenes (*S*,*E*)-**6a** and (*R*,*E*)-**6c**.



Scheme 2

This highly stereospecific reaction path and the unique ability to predictably relay the absolute configuration of an existing stereogenic center along the 1,5-diene via a chair-like transition structure to a prochiral sp^2 center have undoubtedly contributed to the significance and popularity of the Cope rearrangement in synthetic organic chemistry.

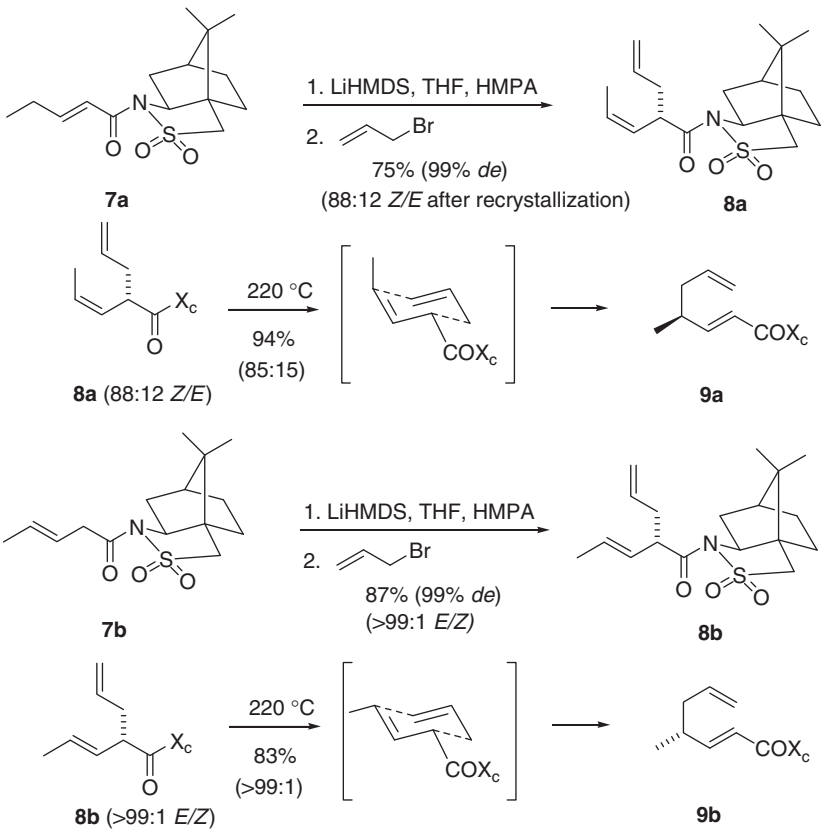
5.19.2 Thermal Cope Rearrangements

5.19.2.1 With Acyclic Unstrained 1,5-Dienes

The equilibria within Cope rearrangements are shifted toward the thermodynamically more stable 1,5-dienes, which may contain either more highly alkyl-substituted or resonance-stabilized alkenes. Rather drastic reaction conditions are typically employed in purely thermally induced processes with reaction temperatures ranging from 160 to 240 °C in most cases due to the high activation enthalpy. The reaction shown in equation (1) is the archetypical example of such a transformation and represents a very useful general strategy until today. An α,β-unsaturated carbonyl compound is converted into the corresponding dienolate by vinylogous enolization, which is alkylated with an allyl electrophile regioselectively at the α-carbon atom to generate the requisite 1,5-diene in one synthetic operation. This 1,5-diene now contains either one or even two carbonyl groups at C3 as a result of the deconjugative allylation process. In the course of the Cope rearrangement, one of the double bonds is shifted back into

conjugation with the carbonyl group(s) which provides the driving force of the rearrangement. A compilation of instructive synthetic examples can be found in Chapter 7.1.2 of the first edition of this book.

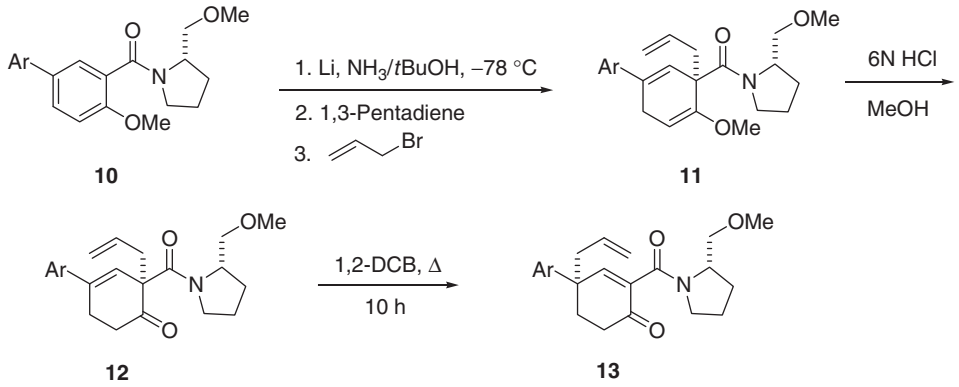
Nakai and coworkers reported the first asymmetric version of this strategy employing a chiral auxiliary.[7] Vinylogous deprotonation of α,β-unsaturated imide **7a** and subsequent asymmetric allylation gave rise to the predominantly *Z*-configured 1,5-diene **8a** (88:12 *Z*/*E* after recrystallization) with >99% *de*. The Cope rearrangement was then effected by heating this diene to 220 °C in naphthalene, which furnished an 85:15 stereoisomeric mixture of products **9a** and **9b** in high yield (Scheme 3). Thus, an 88:12 mixture of *Z*/*E*-stereoisomers was almost stereospecifically converted into an 85:15 mixture of diastereomers. The large carboximide group apparently controlled the diastereoselectivity of this process by its strong preference for the equatorial position in the chair transition state. Likewise, asymmetric allylation of the stereochemically homogenous *E*-configured 1,5-diene **7b** yielded a single diastereomer of *E*-diene **8b**, which was rearranged under the same conditions to furnish Cope product **9b** in good yield, again as a single diastereomer. This study clearly reveals the power of combining an asymmetric enolate-based reaction with the highly stereospecific Cope rearrangement in the context of acyclic stereocontrol and specifically the facile switch of absolute product configuration by changing the corresponding alkene stereochemistry (for the corresponding asymmetric aldol-Cope-sequence see the silyloxy-Cope rearrangement of aldol products in Section 5.19.7.3).



Scheme 3

The combination of an asymmetric Birch reduction-allylation sequence with a thermal Cope rearrangement has been exploited by Malachowski et al. for the highly stereoselective synthesis of carbocyclic quaternary centers.[8] Auxiliary-controlled Birch reduction of a series of *o*-anisidic amides **10** generated dienolates *in situ*, which were trapped with allyl bromide to furnish 1,5-dienes **11** in typically good yields and excellent diastereoselectivity (Scheme 4 and Table 1). Acidic hydrolysis of the enol–ether moiety gave rise to the doubly activated 1,5-dienes **12**, which on heating in 1,2-dichlorobenzene for 10 h underwent a highly stereospecific Cope rearrangement to furnish the thermodynamically more stable isomers **13** in yields ranging from 50% to 80% and as single diastereomers. Microwave irradiation could shorten the reaction time significantly to only 1 h, and identical yields were obtained. The Cope products formed via this strategy were successfully further converted into the alkaloids (+)-mesembrine and (–)-lycoramine.

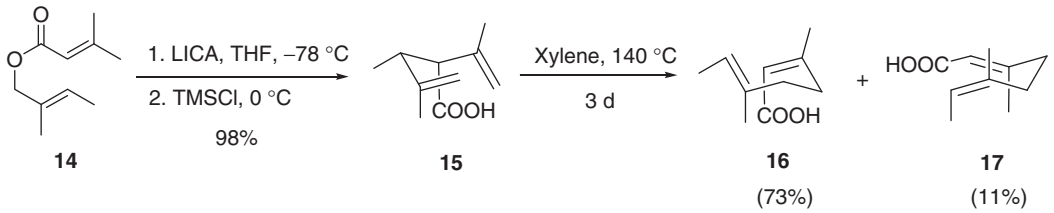
The Cope rearrangement can be coupled to an Ireland–Claisen rearrangement as shown by Kraft et al. in the context of a synthesis of a constitutional isomer of nerol with interesting olfactory properties.[9] Claisen rearrangement of allyl ester **14** under Ireland's conditions gave rise to the 1,5-diene **15**, which on refluxing in xylene furnished the conjugated acid **16** in 73% yield carrying the desired 2*Z*,6*E*-configuration along with 11% of its stereoisomer **17** with opposite double bond geometries (Scheme 5).



Scheme 4

Table 1 Asymmetric Birch-allylation-Cope sequence (Scheme 4)[8]

No.	*Ar*	dr	*Yield of **11** (%)*	*Yield of **12** (%)*	*Yield of **13** (%)*
1	Ph	35:1	62	64	80
2	4-MeO–Ph	50:1	58	89	80
3	3,4-$(MeO)_2$–Ph	>99:1	70	95	80
4	2,3-$(MeO)_2$–Ph	>99:1	70	96	50



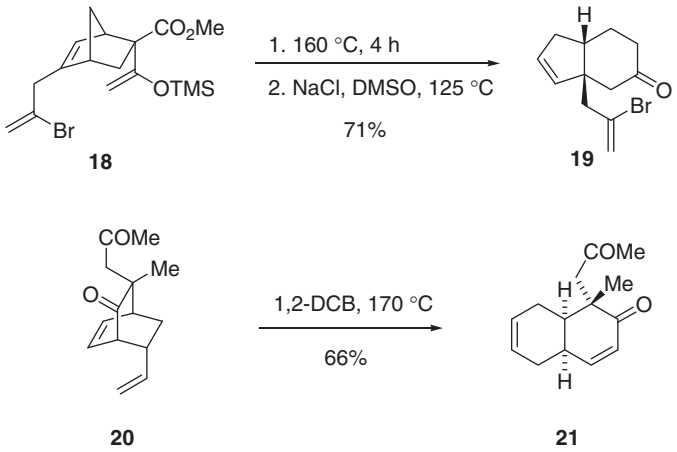
Scheme 5

5.19.2.2 With Strained Bicyclic 1,5-Dienes

1,5-Dienes embedded within strained bicyclic compounds enjoy a natural driving force to undergo Cope rearrangements as they result in the release of ring strain. Therefore, processes involving vinyl-substituted bicyclo[2.2.1]heptenes and bicyclo[2.2.2]octenes, respectively, have been widely employed as suitable substrates for the Cope rearrangement, as long as the vinyl group is on the *endo*-side of the molecule so that a concerted rearrangement can occur. Oxy-Cope and anionic oxy-Cope rearrangements (AOC) make up for the most part of this category based on the facile synthetic accessibility of the requisite 3-oxy-1,5-dienes by highly *endo*-stereoselective organometallic vinyl group additions toward bicyclic ketones. However, regular 1,5-dienes are excellent substrates for this strategy as well.

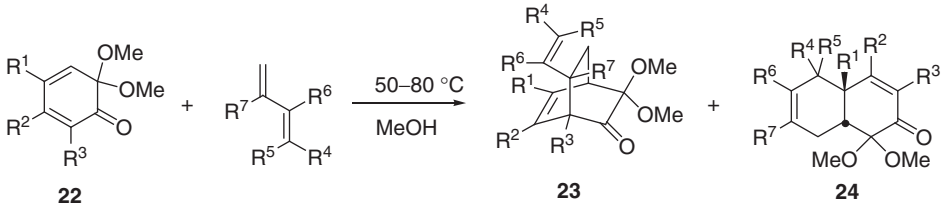
Thus, 1,5-diene **18** with a bicyclo[2.2.1]heptene backbone, which was obtained through catalytic enantioselective Diels–Alder reaction as key step, underwent a highly stereoselective Cope rearrangement on heating at 160 °C for only 4 h to furnish *cis*-hydroindenone **19** in 71% isolated yield after decarboxylation.[10] **19** was subsequently converted into the plant growth regulator, gibberellic acid. Likewise, bicyclo[2.2.2]octenone **20** underwent a smooth thermal Cope rearrangement to deliver the corresponding *cis*-decalin **21** in moderate yield and as a single diastereomer (Scheme 6).[11]

Through inverse electron demand, Diels–Alder cycloadditions of cyclohexa-2,4-dienones and acyclic 1,3-dienes, vinyl-substituted bicyclo[2.2.2]octenones were generally accessible and then converted into *cis*-decalins via Cope rearrangement. In particular, *o*-benzoquinones **22**, masked as ketals, which were obtained through (diacetoxy)iodobenzene-mediated oxidation of the corresponding *o*-methoxy phenols, have been reacted with various 1,3-dienes to furnish mixtures of vinyl-substituted bicyclo[2.2.2]octenones **23** along with the desired *cis*-decalins **24** directly on heating at 50–80 °C (Scheme 7 and Table 2). The Diels–Alder adducts **23** were separated and heated at 200–220 °C in mesitylene for 1–2 h to deliver the Cope product **24** in typically good overall yields.[12]



18 19 20 21

Scheme 6



22 23 24

HC(OMe)$_3$, Mesitylene, 200–220 °C

23a, **24a**: R^1=CO_2Me, R^2=R^3 =R^4=R^5=H, R^6=R^7=Me
23b, **24b**: R^1=CO_2Me, R^2=R^3 =R^5=R^6=R^7=H, R^4=Me
23c, **24c**: R^1=CO_2Me, R^2=R^3 =R^5=R^6=R^7=H, R^4=OAc
23d, **24d**: R^1=CO_2Me, R^2=R^4=R^5=H, R^3=OMe, R^6=R^7=Me
23e, **24e**: R^1=CO_2Me, R^2=R^5=R^6=R^7=H, R^3=OMe, R^4=Me
23f, **24f**: R^1=CO_2Me, R^2=R^5=R^6=R^7=H, R^3=OMe, R^4=OAc
23g, **24g**: R^1=R^3=H, R^2=CO_2Me, R^4=R^5=H, R^6=R^7=Me
23h, **24h**: R^1=R^3=H, R^2=CO_2Me, R^4=Me, R^5=R^6=R^7=H

Scheme 7

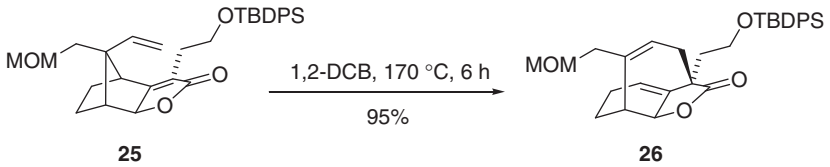
Table 2 Diels–Alder–Cope sequence toward *cis*-decalins **24** (**Scheme 7**)[12]

No.	*Product*	*Diels–Alder reaction*				*Cope rearrangement*			
		Temperature (°C)	*Ratio **23:24***	*Yield of **23** (%)*	*Yield of **24** (%)*	*Temperature (°C)*	*Time (h)*	*Yield of **24** (%)*	*Total yield of **24** (%)*
1	**a**	80	1:2	29	53	220	24	95	91
2	**b**	50	2:1	55	25	200	50	91	–
3	**c**	80	2:1	62	34	200	40	87	88
4	**d**	80	0:1	–	81	–	–	–	81
5	**e**	50	6:1	64	11	200	24	85	–
6	**f**	80	4:1	61	16	200	40	91	71
7	**g**	80	4:1	56	14	220	24	86	62
8	**h**	50	1:0	81	–	200	50	87	–

A number of natural products containing a *cis*-decalin structure were successfully synthesized according to this general scheme, including eremopetasidione, 3β-angeloyloxyfuranoeremophilane, and 3β-methacryloylfuranoeremophilane.[13]

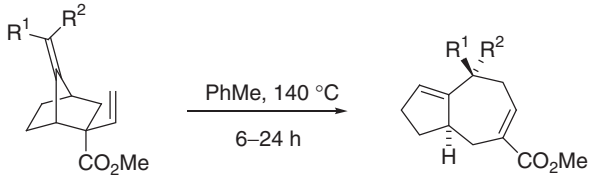
The vinyl substituent may also be attached to the bridgehead atom of a norbornane skeleton to furnish a 1,5-diene, which undergoes a strain-release thermal Cope rearrangement (equation 3). In the course of synthesis of the tetracyclic core of CP-225,

917 the strained lactone **25** was submitted to a Cope rearrangement at 170 °C for 6 h to deliver the tricyclic lactone **26** in 95% yields.[14]



25 **26** (3)

2-*exo*-Vinyl-7-alkylidenenorbornanes **27** underwent facile Cope rearrangements in toluene at 140 °C to furnish hexahydroazulenes **28** in good to excellent yields (Scheme 8 and Table 3).[15] At first glance, this smooth rearrangement appeared unexpected, as significant molecular distortion was required on the side of the bridgehead alkylidene group in order to interact with the exocyclic vinyl group. This rearrangement additionally benefits, however, from the shift of the double bond into conjugation with the ester group. When the ester group was reduced to a hydroxymethyl group, incomplete conversions and low yields were observed even at elevated temperatures and extended reaction times. The starting 1,5-dienes **27** were readily prepared through Diels–Alder reaction of fulvenes and methyl acrylate with subsequent introduction of the *exo*-vinyl group via diastereoselective enolate alkylation and elimination of a suitable leaving group.



27 **28**

Scheme 8

Table 3 Cope rearrangement of 2-*exo*-vinyl-7-alkylidenenorbornanes **27** (Scheme 8)[15]

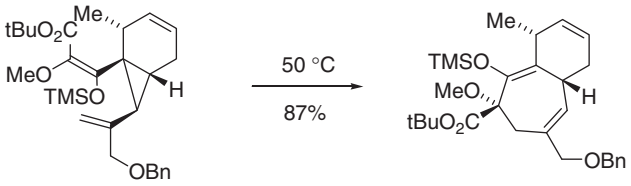
No.	R^1	R^2	*Time (h)*	*Yield (%)*
1	Me	Me	24	94
2	H	H	12	Quantitative
3	H	CO_2Et	6	Quantitative
4	H	OMe	18	95
5	–S–CH_2–CH_2–CH_2–S–		24	90

5.19.3 Ring Expansion of *cis*-1,2-Divinylcycloalkanes

5.19.3.1 *cis*-1,2-Divinylcyclopropanes

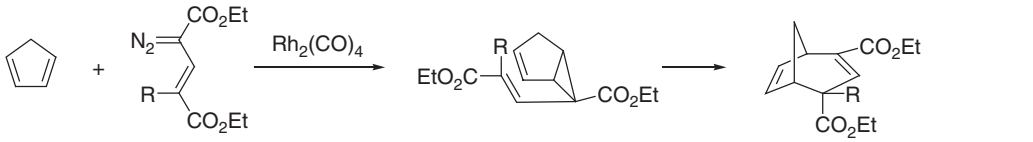
cis-1,2-Divinylcyclopropanes rearrange spontaneously to 1,4-cycloheptadienes at ambient temperature, as a good amount of the activation enthalpy is provided by the release of ring strain. The half-life of the parent *cis*-1,2-divinylcyclopropane toward rearrangement has been measured as being only 90 s at 35 °C and 25 min at 11 °C, so that most of the starting divinylcyclopropanes can only be isolated at low temperatures. Accordingly, any synthetic method for the preparation of *cis*-1,2-divinylcyclopropanes, which themselves require ambient or even elevated temperatures, will frequently furnish the rearranged 1,4-cycloheptadiene instead. Substituents on the double bonds, however, increase the activation barrier of the rearrangement so that elevated reaction temperatures may be necessary. The stereoisomeric *trans*-1,2-divinylcyclopropanes are completely inert toward the [3.3]-sigmatropic process and must be isomerized at higher temperatures to the *cis*-isomers in order for the Cope rearrangement to proceed. Calculations suggest a highly concerted reaction mechanism with only boat-like transition state conformations being accessible because of geometrical constraints.[16]

This process is among the most useful methods for the synthesis of seven-membered carbocycles and has been employed frequently in natural product synthesis. An illustrative example of the power of this strategy in the context of complex molecule synthesis is the straightforward preparation of the [5.4.0]-core structure of the natural product, phorbol (equation 4).[17]



(4)

By combining the actual Cope rearrangement with the preceding cyclopropanation, Davies and coworkers have been able to establish a very elegant domino-type strategy toward 1,4-cycloheptadienes in one synthetic operation. For example, the Rh(II)-catalyzed reaction of vinyldiazoacetate **29a** and cyclopentadiene gave rise to the bicyclo[3.2.1] system **31a** in 98% yield directly (Scheme 9). A highly *cis*-stereoselective cyclopropanation started the sequence furnishing the presumed *cis*-1,2-divinylcyclopropane **30a**, which spontaneously rearranged to **31a**.[18]



29a: R = H
29b: R = OMe

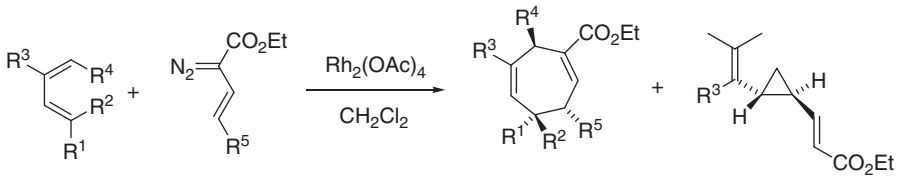
30a: R = H
30b: R = OMe (74%)

31a: R = H (98%)
31b: R = OMe (>95% yield)

Scheme 9

Supporting evidence for this mechanism was obtained from the reaction of the more highly substituted vinyldiazoacetate **29b**. Under otherwise identical reaction conditions, the *cis*-divinylcyclopropane **30b** was isolated in 74% yield, which resisted a spontaneous rearrangement most likely on the basis of steric effects. However, heating of a solution of **30b** in toluene under reflux initiated a quantitative Cope rearrangement to furnish the bicyclic compound **31b**.

This protocol could be successfully extended to acyclic 1,3-dienes as well (Scheme 10 and Table 4). In the case of unsymmetrical 1,3-dienes **32**, the cyclopropanation predictably occurred at the least substituted double bond and delivered 1,4-cycloheptadienes **33** in typically good yields. The stereoselectivity of the initial cyclopropanation step proved to be dependent on



32

29a: R^4 = CO_2Et
29c: R^4 = CH=CHPh

33

34

Scheme 10

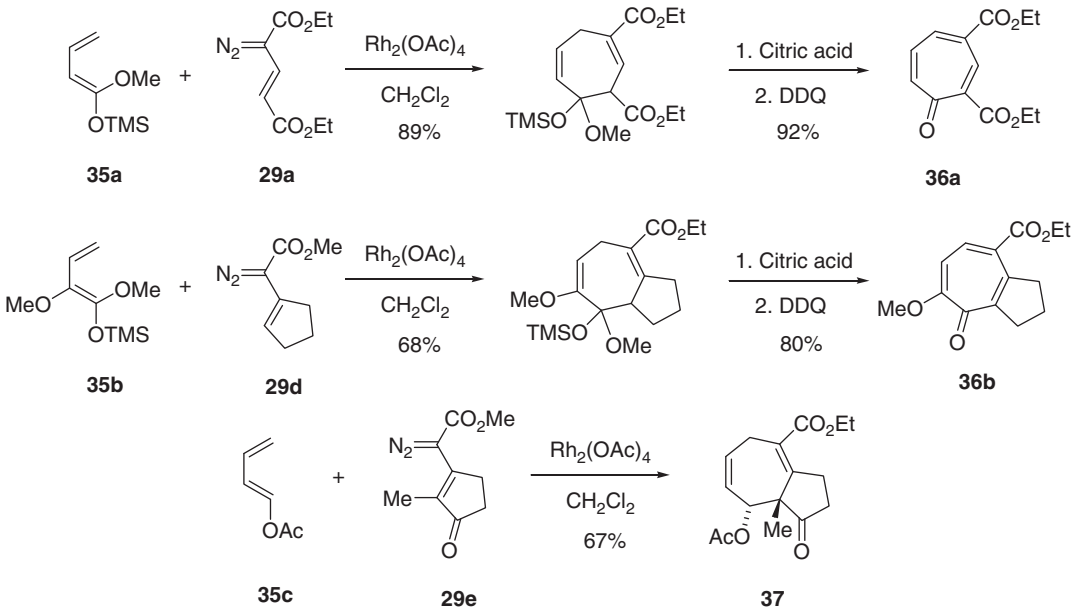
Table 4 Domino cyclopropanation/Cope rearrangement (Scheme 10)[18]

No.	***32***	*R^1*	*R^2*	*R^3*	*R^4*	*R^5*	*Yield of **33** (%)*	*Yield of **34** (%)*
1	**a**	Me	Me	H	H	CO_2Et (**29a**)	58 (**33a**)	14 (**34a**)
2	**a**	Me	Me	H	H	CH=CHPh (**29c**)	80 (**33b**)	
3	**b**	Me	Me	Me	H	CO_2Et (**29a**)	63 (**33c**)	14 (**34c**)
4	**b**	Me	Me	Me	H	CH=CHPh (**29c**)	59 (**33d**)	
5	**c**	Me	H	H	H	CH=CHPh (**29c**)	75 (**33e**)	
6	**d**	H	Me	H	H	CH=CHPh (**29c**)	68 (**33f**)	
7	**e**	Me	H	H	Me	CH=CHPh (**29c**)	53 (**33g**)	

the vinyldiazoacetate employed. With **29a** ($R^5 = CO_2Et$) as vinylcarbenoid precursor, significant amounts of the *trans*-divinylcyclopropanes **34** were formed, which did not undergo the Cope rearrangement for geometrical reasons and were isolated as such. With **29c** ($R^5 = CH{=}CHPh$), however, a highly *cis*-stereoselective cyclopropanation occurred giving rise exclusively to the corresponding 1,4-cycloheptadienes **33** via the domino cyclopropanation/Cope rearrangement.

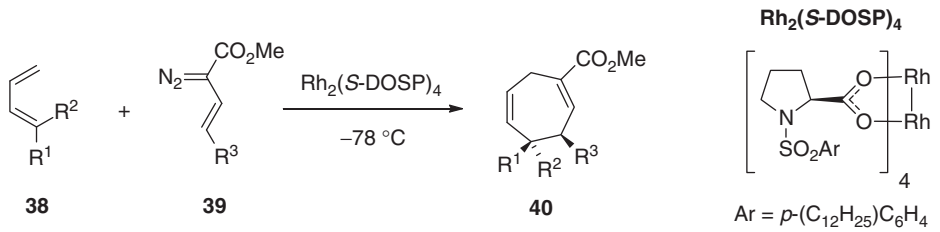
The concerted and highly stereospecific reaction pathway of the sigmatropic process was proven by the reaction of the stereoisomeric *E*- and *Z*-1,3-pentadienes, **32c** and **32d**, respectively, which exclusively furnished the stereoisomeric *cis*- and *trans*-cycloheptadienes, **33e** and **33f**, respectively (Table 4, Number 5 and 6). In the case of **32e** carrying two disubstituted alkenes, the cyclopropanation occurred chemoselectively at the *Z*-alkene moiety, whereas the *E*-alkene remained completely untouched (Number 7).

In contrast to reactions with alkyl-substituted 1,3-dienes, vinyldiazoacetate **29a** reacted with vinylketene silyl-*O,O*-acetals such as **35a** under $Rh_2(CO)_4$-catalysis with complete *cis*-stereoselectivity and furnished doubly oxygenated cycloheptadienes, which on acidic hydrolysis and oxidation gave rise to tropolone **36a** in excellent overall yield (Scheme 11). A fused tropolone **36b** was accessible as well via this strategy by embedding the vinyldiazoacetate double bond into the ring system of **29d**, whereas the corresponding reaction of **29e** with *E*-1-acetyoxy-1,3-butadiene (**35c**) directly furnished hydroazulene **37**.



Scheme 11

By developing an enantioselective cyclopropanation process, Davies and coworkers were able to obtain highly enantiomerically enriched 1,4-cycloheptadienes via this strategy. They employed the highly reactive rhodium(II) (*N*-dodecylbenzenesulfonyl)-*S*-prolinate (Rh_2(S-DOSP)$_4$) as chiral catalyst, which decomposed vinyldiazoacetates **39** in the presence of 1,3-dienes **38** even at temperatures as low as $-78\ ^\circ C$ to afford the corresponding 1,4-cycloheptadienes **40** in moderate to good yields and excellent enantioselectivities (Scheme 12 and Table 5).[18b] The diastereoselectivity of the cyclopropanation/Cope rearrangement was again governed by the double bond configuration of the starting 1,3-diene. The natural product 5-*epi*-vibsanin E was synthesized according to this strategy.[18c] An intramolecular version of this process furnished fused 1,4-cycloheptadienes in moderate selectivities.[18d]

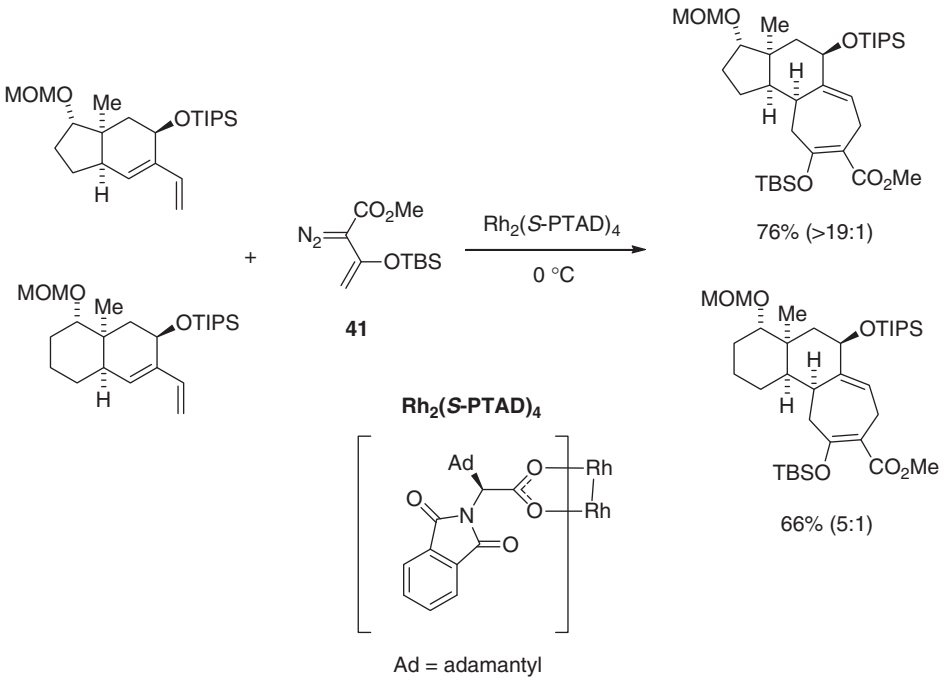


Scheme 12

Table 5 Rhodium-catalyzed, enantioselective cyclopropanation/Cope rearrangement (Scheme 12)[18b]

No.	R^1	R^2	R^3	*Yield (%)*	ee *(%)*
1	Ph	H	Me	87	98
2	Ph	H	Ph	83	98
3	Ph	H	CH=CHPh	84	93
4	Ph	H	$CH=CH_2$	56	96
5	OTBS	H	Ph	Not reported	93
6	Me	H	Ph	51	98
7	Me	H	CH=CHPh	82	95
8	H	Me	Ph	47	96
9	H	Me	CH=CHPh	62	98

1,3-Dienes embedded into bicyclic systems furnished fused 5-6-7- and 6-6-7-tricyclic structures on reaction with 2-(silyloxyvinyl)diazoacetate **41** and the adamantyl glycine-derived catalyst Rh_2(*S*-PTAD)$_4$ (Scheme 13).[18e] Besides the additional functional group, which could be used advantageously for further synthetic manipulations, the silyloxyvinyldiazoacetate **41** generally provided much better stereodifferentiation in the cyclopropanation step than that by the parent vinyldiazoacetate. One of the reaction products was subsequently converted into the terpene natural products, (–)-barekol and (+)-barekoxide.

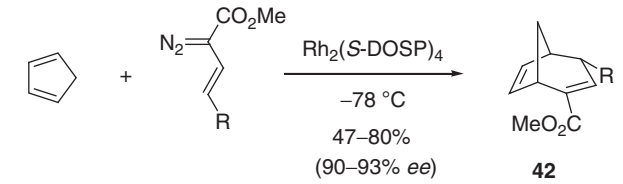


Scheme 13

Cyclic 1,3-dienes such as cyclopentadiene gave rise to bicyclo[3.2.1]octadienes **42**, which constitute formal [4 + 3]-cycloaddition products. In each case, the *endo*-stereoisomers were formed exclusively and the enantioselectivities ranged from 90% to 93% *ee* (Scheme 14). This reaction could be successfully extended to heterocyclic 1,3-dienes and delivered 8-oxabicyclo[3.2.1]octadienes from furans[18f] as well as the corresponding tropanes **43** from *N*-protected pyrroles and **41** with Rh_2(*S*-PTAD)$_4$ as the catalyst in 2,2-dimethylbutane as the solvent (Scheme 14 and Table 6).[18g]

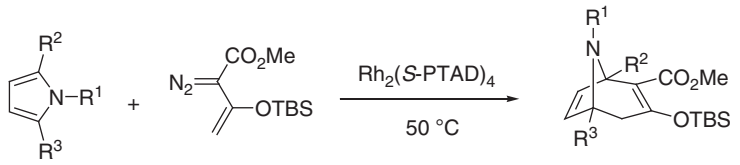
Stoltz and coworkers developed an alternative strategy to access 5-7- and 6-7-bicyclic structures via the Cope rearrangement of *cis*-1,2-divinylcyclopropanes. With vinyl cyclopropyl diazoketones **44** as starting material, a silver-catalyzed Wolff rearrangement was initiated under carefully optimized reaction conditions. The ketene produced as intermediate engaged the vinylcyclopropane residue in the [3.3]-sigmatropic process *in situ* to generate bicyclo[5.3.0]decadienones **45** in excellent yields and as single stereoisomers (Scheme 15).[19] For terminal vinyl cyclopropanes as reaction partners for the ketene, a photochemical activation of the diazoketones was found to be superior.

Yet another elegant synthetic access to *cis*-1,2-divinylcyclopropanes relies on organoiron methodology. Addition of alkenyl Grignard reagents to the (1-methoxycarbonyl-pentadienyl)iron(1 +) cation **46** generates the corresponding (2-alkenylpent-3-en-1,5-diyl)iron complexes, which on ceric(IV) ammonium nitrate (CAN)-oxidation eliminate the metal fragment and furnish *cis*-divinylcyclopropanes **47**. Owing to the electron-withdrawing nature of the ester group which stabilizes the distal cyclopropane



42

R = Me, Ph, CH=CPh, CH=CH$_2$

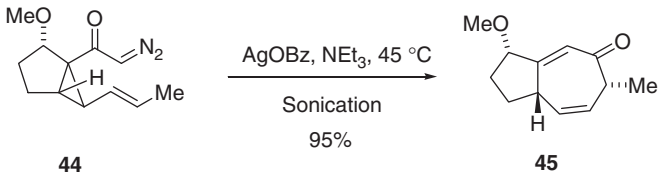


41 43

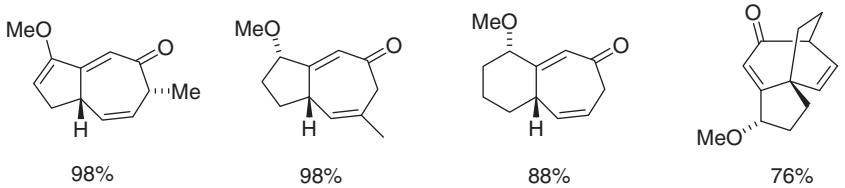
Scheme 14

Table 6 Rhodium-catalyzed, enantioselective synthesis of tropones **43** (Scheme 14)[18g]

No.	*R*^{1}	*R*^{2}	*R*^{3}	*Yield (%)*	ee *(%)*
1	Boc	H	Me	69	96
2	Boc	Me	Me	72	98
3	Boc	H	CO_2Me	71	89
4	Ph	H	H	64	97
5	*p*-Me–Ph	H	H	68	94

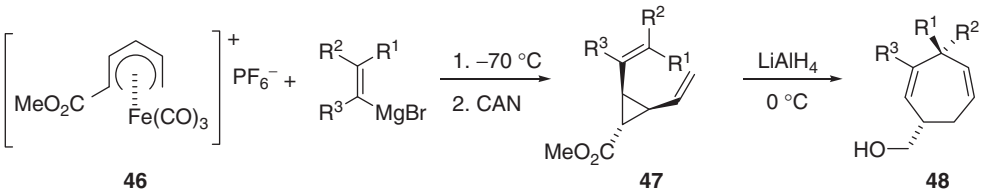


44 45



Scheme 15

ring bond, such *cis*-divinylcyclopropanes are frequently stable at ambient temperature and require heating up to 125 °C in order to rearrange to the corresponding 1,4-cycloheptadienes depending on the substitution. A milder and more general alternative includes $LiAlH_4$-reduction of the ester moiety at 0 °C, which directly gave rise to 1,4-cycloheptadienes **48** in generally good yields via the presumed hydroxymethyl-substituted cyclopropanes (Scheme 16 and Table 7).[20]



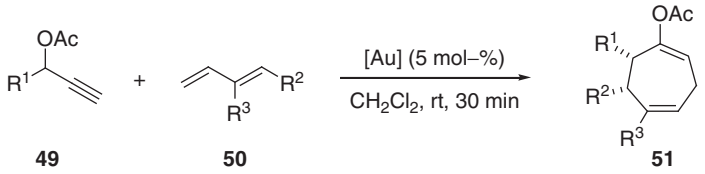
46 47 48

Scheme 16

Table 7 Organoiron-mediated synthetic access to and Cope rearrangement of *cis*-1,2-divinylcyclopropanes **47** (Scheme 16)[20]

No.	R^1	R^2	R^3	*Yield of* ***47*** *(%)*	*Yield of* ***48*** *(%)*
1	H	H	H	39	83
2	Me	H	H	61	81
3	Me	Me	H	71	80
4	H	H	Me	46	82
5	H	H	Ph	44	33
6	H	$-CH_2CH_2CH_2-$		50	76

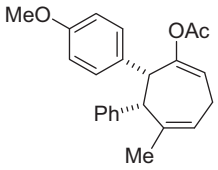
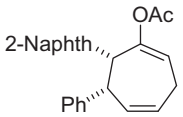
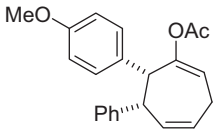
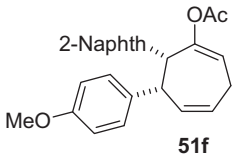
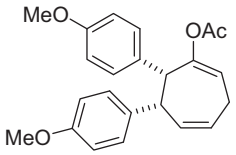
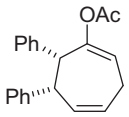
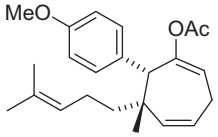
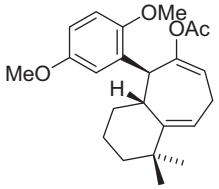
The capacity of cationic gold(I)-complexes to induce a 1,2-acyloxy migration of propargyl esters resulting in the formation of vinyl-substituted gold carbene complexes paved the way for an elegant gold(I)-catalyzed synthesis of seven-membered carbocycles with 1,3-dienes. Thus, reaction of propargyl acetates **49** with 1,3-dienes **50** under Au(I)-catalysis delivered *cis*-6,7-substituted 1,4-cycloheptadienes **51** via Cope rearrangement of the presumed *cis*-divinylcyclopropanes through a boat-like transition state conformation (Scheme 17 and Table 8).[21] This reaction could be rendered enantioselective using a chiral gold(I)-complex, which catalyzed the formation of 1,4-cycloheptadiene **51h** from the corresponding propargyl pivaloate and 1,3-diene in good yield and diastereoselectivity and with >90% *ee*. This bicyclic 1,4-cycloheptadienyl acetate represents a direct synthetic precursor of the natural product frondosin.



49 **50** **51**

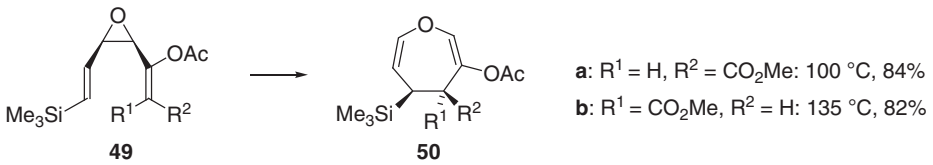
Scheme 17

Table 8 Gold(I)-catalyzed synthesis of *cis*-6,7-substituted 1,4-cycloheptadienes 51 (Scheme 17)[21]

No.	*Product*	*Yield (%)*	*No.*	*Product*	*Yield (%)*
1	 **51a**	85	5	 **51e**	72
2	 **51b**	92	6	 **51f**	55
3	 **51c**	77	7	 **51g**	80
4	 **51d**	37	8	 **51h**	68 (> 6:1 *dr*, >90% *ee*)[a]

[a]Chiral gold catalyst: $[(S)$-MeO-DTBM-BIPHEPAu$_2]Cl_2$ (2.5 mol%) and $AgSbF_6$ (5 mol%).

The Cope rearrangement of *cis*-1,2-divinylcyclopropanes can be extended to divinyl-substituted small ring heterocycles. A prominent example of this category is the [3.3]-sigmatropic rearrangement of *cis*-2,3-divinyl epoxides **49**, which required slightly higher reaction temperatures of 100–150 °C and again proceeded stereospecifically via boat-like transition structures. Highly valuable 4,5-dihydrooxepins **50** were formed as products in good yields. The double bond configuration of **49** determined which diastereomer of **50** was formed (Scheme 18).[22] *E*-configured substrates required higher reaction temperatures than that required by those with *Z*-double bonds.

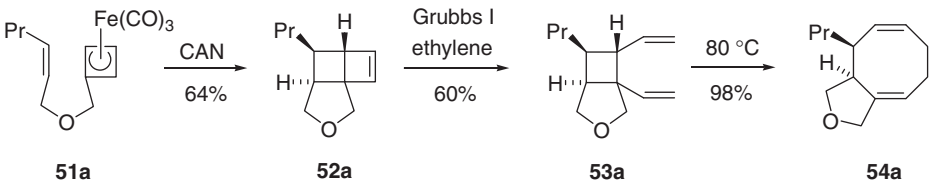


Scheme 18

5.19.3.2 *cis*-1,2-Divinylcyclobutanes

Cope rearrangements of *cis*-1,2-divinylcyclobutanes are almost as facile as those of *cis*-1,2-divinylcyclopropanes as can be estimated from the similar strain energy of the two small rings. However, the parent compound *cis*-1,2-divinylcyclobutane is actually stable at room temperature and requires heating at 120 °C to cleanly rearrange to *Z*,*Z*-1,5-cyclooctadiene.[23] As already seen with *cis*-1,2-divinylcyclopropanes, substituents on the double bonds retard the reaction.

A very common synthetic strategy to furnish *cis*-1,2-divinylcyclobutanes in a highly straightforward manner is based on cycloadditions to assemble the four-membered ring. Snapper et al. have further built on that concept and developed an elegant procedure to synthesize fused cyclooctadienes. For example, the iron carbonyl complex of cyclobutadiene **51a**, which was tethered to an unactivated alkene, was oxidatively decomplexed and the liberated cyclobutadiene moiety underwent an instantaneous, intramolecular [4 + 2] cycloaddition to furnish the cyclobutene-containing 5-4-4 ring system **52a**. On a Ru-catalyzed ring-opening cross metathesis with ethylene, the requisite *cis*-1,2-divinylcyclobutane **53a** was obtained, which on heating gave rise to oxabicyclo[6.3.0]undecadiene **54a** in excellent yield as a single stereoisomer (Scheme 19).[24]

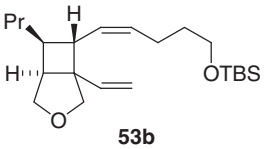
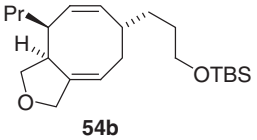
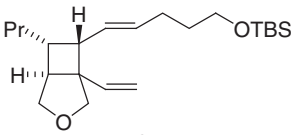
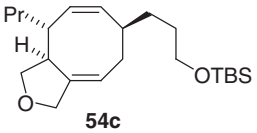
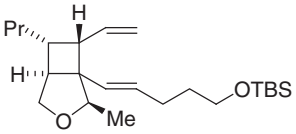
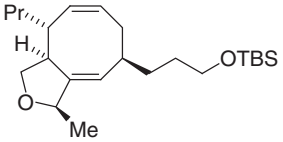
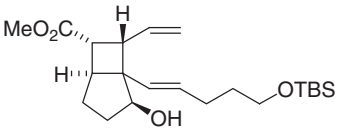
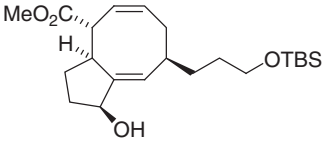
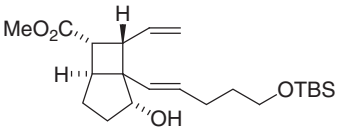
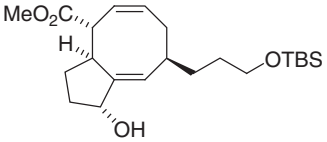
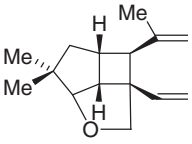
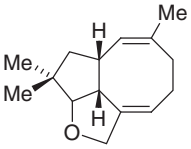


Scheme 19

To access more highly substituted and functionalized bicyclic cyclooctadienes, which possess greater value in the context of natural product synthesis, the ring-opening cross metathesis was also performed with unsymmetrical, substituted alkenes. The ring-opening metathesis (ROM) products were obtained with moderate to good levels of regiocontrol and excellent stereoselectivity furnishing exclusively the *E*-stereoisomers. On heating at 200 °C, the *cis*-1,2-divinylcyclobutanes **53b–f** underwent a stereospecific Cope rearrangement to furnish oxabicyclo[6.3.0]undecadienes, **54b–d**, and bicyclo[6.3.0]undecadienes, **54e** and **54f**, again as single stereoisomers in good to excellent yields (Table 9). The relatively harsh reaction conditions were required because of the highly substituted cyclobutane ring. Substrates lacking a β-alkyl substituent on the cyclobutane ring underwent the sigmatropic rearrangement in refluxing benzene in the same pot. This methodology was successfully applied in a total synthesis of the sesquiterpene natural product, asteriscanolide.[24c]

In a complimentary approach, [2 + 2] photocycloadditions were employed to install the requisite cyclobutane ring. Thus, irradiation of the cyclobutene–cyclopentenone system **55** using a medium pressure Hanovia Hg lamp with a Pyrex filter initiated an intramolecular [2 + 2] cycloaddition to furnish photoadduct **56** in almost quantitative yield (Scheme 20). Thermal fragmentation of the highly strained dicyclobuta[*a*,*c*]cyclobutane **56** at 235 °C gave rise to the desired *cis*-1,2-divinylbutane **57**, which was prevented from undergoing an instantaneous Cope rearrangement through the existence of the lactone bridge. LAH reduction of **57**, however, released the strained system; heating at 140 °C triggered a [3.3] sigmatropic rearrangement via the depicted boat-like transition state to generate dicyclopenta[*a*,*d*]cyclooctadiene **58** in excellent yield.[25] Alternatively, the lactone bridge was opened through an allylic substitution reaction with an organocopper reagent, and the resulting ester rapidly rearranged to cyclooctadiene **59** at 120 °C in 96% yield (Scheme 20).

Table 9 Cope rearrangement of fused *cis*-1,2-divinylcyclobutanes **53** (200 °C, 1 h, benzene) (Scheme 19)[24]

No.	*Substrate*	*Product*	*Yield (%)*
1	 **53b**	 **54b**	70
2	 **53c**	 **54c**	97
3	 **53d**	 **54d**	90
4	 **53e**	 **54e**	96
5	 **53f**	 **54f**	99
6	 **53g**	 **54g**	74 (combined yield for ROM and Cope)

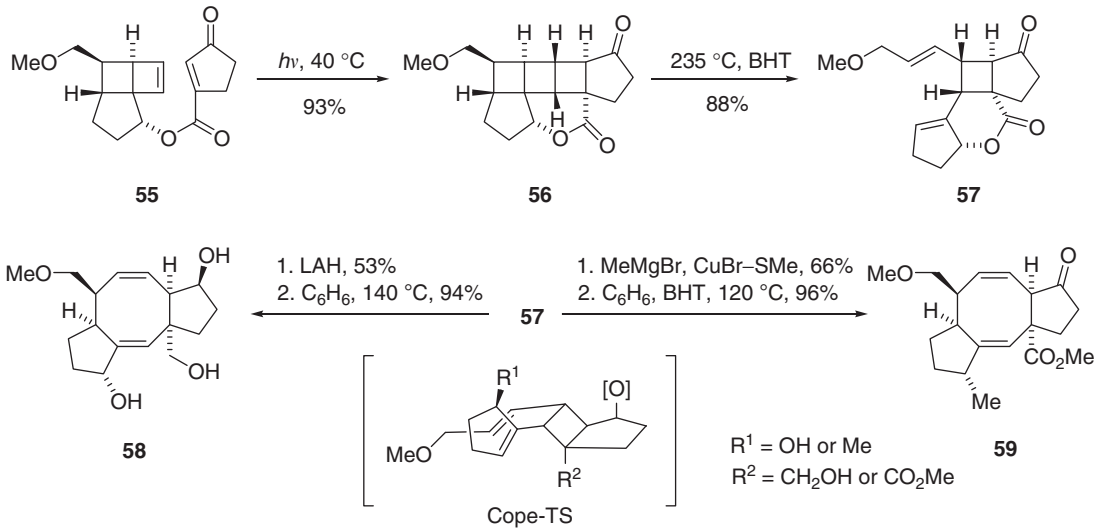
The ring expansion of 1,2-divinyl-substituted four-membered rings can also be performed on heterocyclic systems. Thus, azetidinone-tethered 1,5-dienes **60** smoothly rearranged to eight-membered lactams **61** on heating at 120 °C in a sealed tube in toluene (Scheme 21 and Table 10).[26] With optically pure *β*-lactam **60e**, obtained from asymmetric[2 + 2]cycloaddition of a ketene and an imine controlled by a chiral auxiliary on the lactam nitrogen atom, optically pure **61e** was produced as a single diastereomer (Number 5).

5.19.4 Ring Contraction of Medium Rings

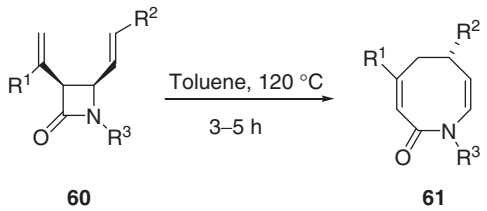
5.19.4.1 1,5-Cyclononadienes

As medium size rings suffer from significant transannular strain but cyclopentanes are almost strainless, the thermal equilibrium between *cis*-1,2-divinylcyclopentane **63** and (*Z*,*Z*)-1,5-cyclononadiene (*Z*,*Z*-**62**) lies on the side of the smaller ring (95:5 in favor of **63** at 220 °C) (Scheme 22). On the basis of its configuration, *Z*,*Z*-**62** can only adopt a boat-like transition state conformation. However, due to the greater flexibility of five-membered rings, *E*,*Z*-configured 1,5-cyclononadiene, *E*,*Z*-**62**, can easily rearrange to **63** quantitatively as well, employing a chair transition state which requires significantly lower temperatures.[27]

E-Configured cycloalkenes are inherently planar-chiral compounds and their 8- and 9-membered congeners typically have racemization barriers high enough, so that the individual enantiomers can be separated. An interesting planar-to-central chirality transfer has been observed with cyclic ether **64**, which on Pd(II)-catalyzed Cope rearrangement (see Section 5.19.6) furnished



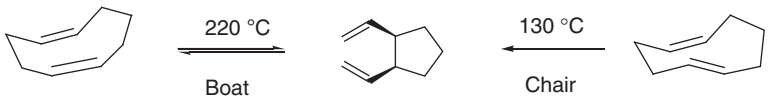
Scheme 20



Scheme 21

Table 10 Ring expansion of azetidinone-tethered 1,5-dienes 60 (Scheme 21)[26]

No.	R^1	R^2	R^3	*Product*	*Yield (%)*
1	H	CO_2Me	PMP	**61a**	86
2	H	COMe	PMP	**61b**	85
3	Me	CO_2Me	PMP	**61c**	90
4	H	Ph	Bn	**61d**	79
5	Me	Ph	(*R*)–CH(Me)Ph	**61e**	83

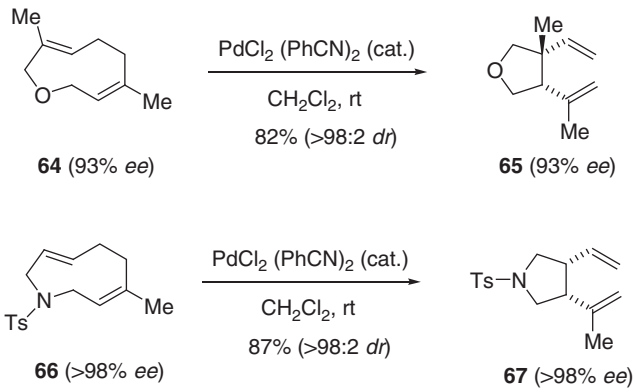


Scheme 22

cis-1,2-divinyl tetrahydrofuran (THF) **65** in good yield and complete chirality transfer (Scheme 23).[28a] Its aza-analogue **66** underwent this transformation in a similar manner delivering *cis*-1,2-divinyl pyrrolidine **67** in 87% yield as a single enantio- and diastereomer, which was further converted into the neurotransmitter stimulator, (–)-kainic acid.[28b]

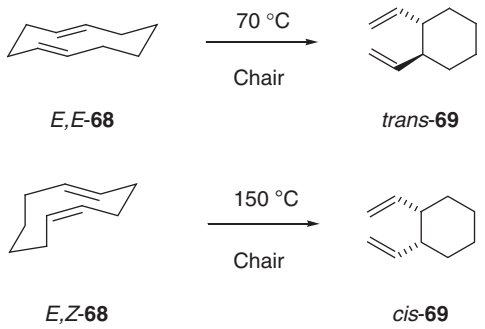
5.19.4.2 1,5-Cyclodecadienes

1,5-Cyclodecadienes **68** rearrange quantitatively to divinylcyclohexanes **69** furnishing both stereoisomers stereospecifically depending on the configuration of the starting 1,5-diene. *E,E*-1,5-cyclodecadiene, *E,E*-**68,** rearranges exclusively to *trans*-1,2-divinylcyclohexane *trans*-**69** at 70 °C, whereas *Z,E*-**68** is converted into *cis*-**69** specifically at 150 °C.[29] In both cases, the rather



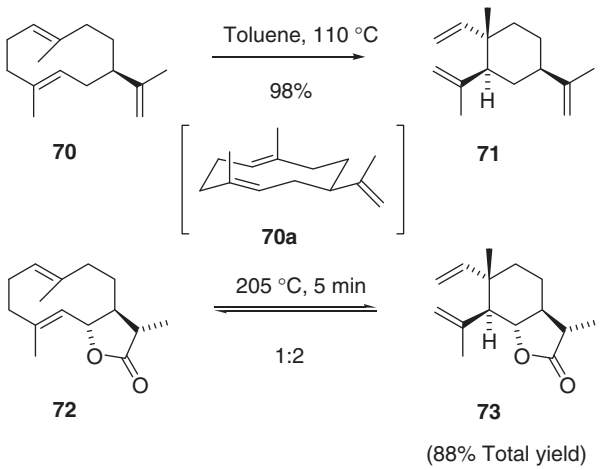
Scheme 23

flexible structure of the six-membered ring, which is formed in the course of the Cope rearrangement, allows the involvement of a favorable chair transition state conformation (Scheme 24).



Scheme 24

A prominent example where this rearrangement plays a major role is found in the sesquiterpene class of natural products named germacranes. They contain an *E,E*-1,5-cyclodecadiene skeleton as central structural motif and easily undergo thermal Cope rearrangements either during distillation or by gas chromatography analysis to furnish elemanes.[30] Thus, germacrene A (**70**) is readily converted to *trans*-*β*-elemene (**71**) in quantitative yield on refluxing the solution in toluene (Scheme 25). The isopropenyl group at the stereogenic center in **70** efficiently controls the diastereoselectivity of the rearrangement by its preference for the equatorial position in transition state **70a**. Likewise, many other germacrenes undergo Cope rearrangements in high yields during distillation to afford the corresponding elemenes.[30]

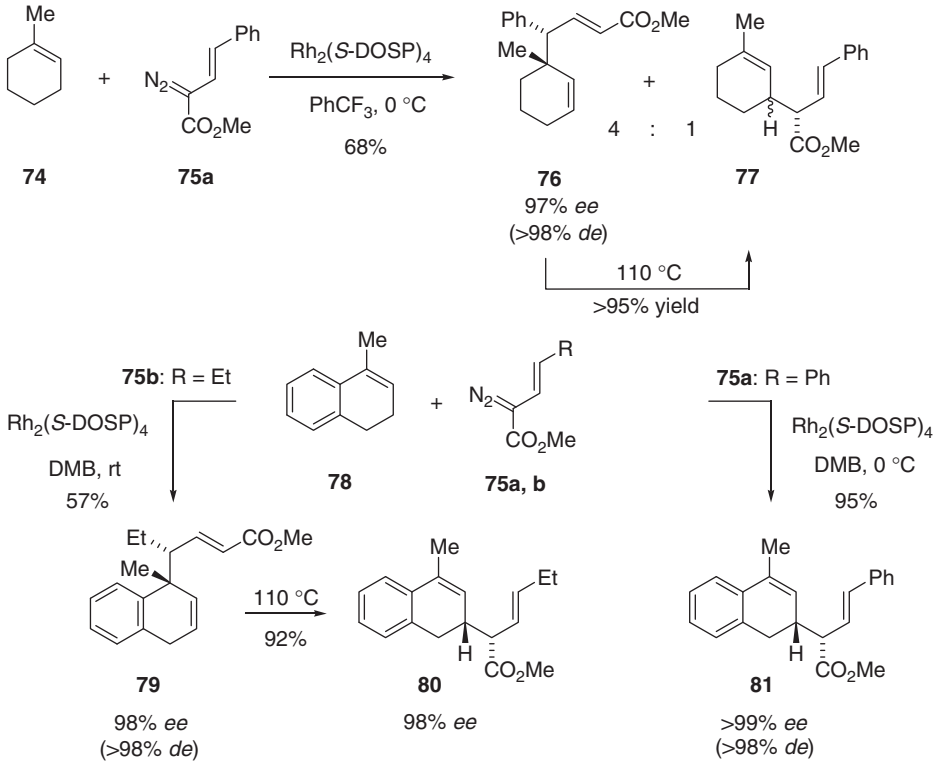


Scheme 25

More highly substituted cyclodecadienes may furnish, however, equilibrium mixtures of germacrenes and elemenes depending on the exact substitution pattern. In addition to some examples listed in Chapter 7.1.5.4 of the first edition of this book, this phenomenon was observed in a synthesis of (+)-vernolipin.[31a] Thus, thermal Cope rearrangement of germacrolide **72** produced an equilibrium mixture of elemanolide **73** and germacrolide **72** in a ratio of 2:1 on heating at 205 °C for 5 min in a sealed tube. The recovered germacrolide was used again in two more rounds, giving rise to elemanolide **73** in a total yield of 88% after three cycles (Scheme 25).

5.19.5 CH Activation/Cope Rearrangement

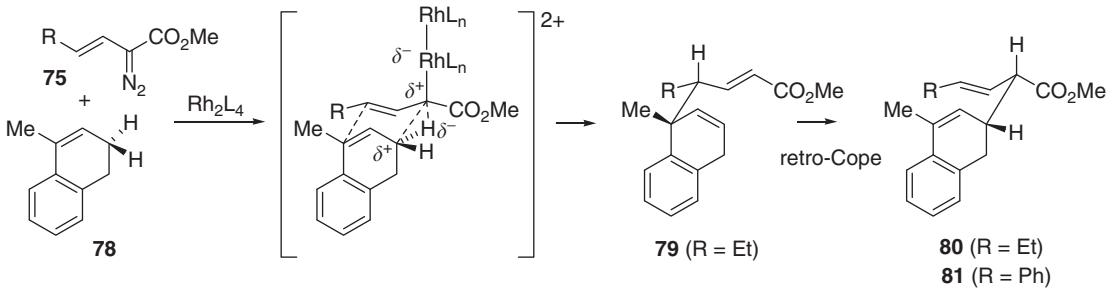
Electron-rich cycloalkenes, when treated with donor–acceptor-substituted diazo compounds, can undergo a very powerful and highly stereoselective Rh(II)-catalyzed combined CH activation/Cope rearrangement. Thus, the Rh_2(S-DOSP)$_4$-catalyzed reaction of 1-methylcyclohexene **74** and styryldiazoacetate **75a** furnished a 4:1 mixture of CH activation/Cope rearrangement product **76** and the apparent direct CH activation product **77** in 68% combined yield (Scheme 26).[32a] **76** was formed with outstanding levels of stereocontrol: a single diastereomer was produced with 97% *ee*. The apparent direct CH activation product was obtained as a mixture of two diastereomers, of which the major diastereomer was formed with 97% *ee*. However, a control experiment revealed that **77** was actually the thermodynamically more stable product, as heating of **76** in refluxing toluene cleanly and quantitatively converted **76** into **77**.



Scheme 26

However, reaction of 4-methyl-1,2-dihydronaphthalene (**78**) with **75a** (R=Ph) under otherwise almost identical reaction conditions furnished exclusively the apparent direct CH activation product **81** in excellent yield as a single diastereomer and enantiomer, whereas vinyldiazoacetate **75b** (R=Et), on reaction with **78**, delivered the CH activation/Cope rearrangement product **79** in moderate yield and again very high levels of diastereo- and enantioselectivity (Scheme 26).[32b] **79** could subsequently be converted into **80** in excellent yield and complete chirality transfer on heating in refluxing toluene for 6 h.

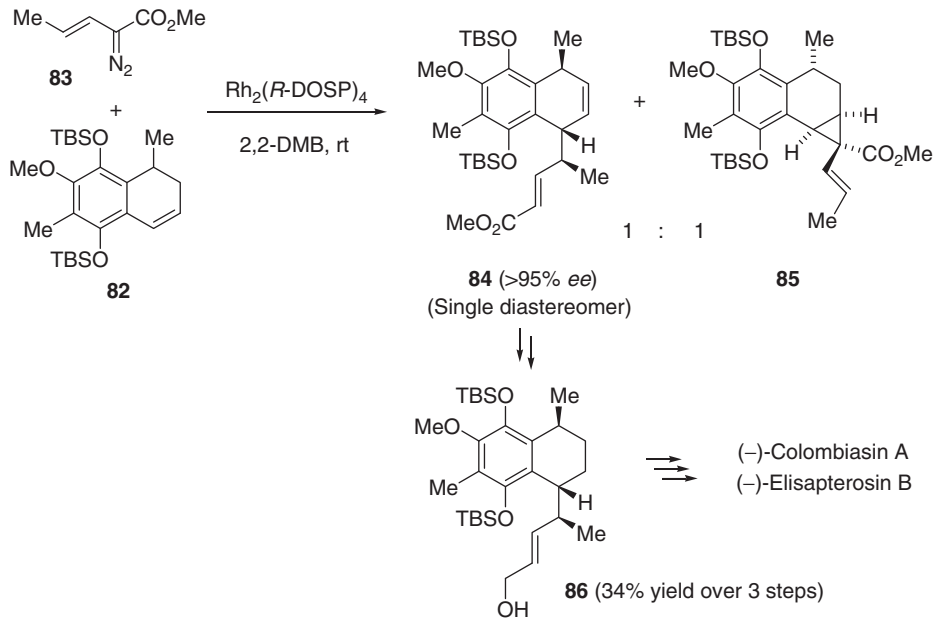
A detailed mechanistic analysis including density functional theory (DFT) calculations revealed a more complicated reaction course for the formation of the CH activation/Cope rearrangement products, **76** and **79**, respectively. It comprised a concerted, yet highly asynchronous hydride-transfer/vinylogous C–C bond-forming event as depicted in Scheme 27.[32c] The relative and absolute configuration found in **76** and **79** was fully consistent with a catalyst-controlled α-selective hydride transfer, and the C–C bond formation occurring in a typical chair transition state conformation. The apparent direct CH-activation products **77**, **80**, and **81** actually originated from a thermodynamically driven retro-Cope rearrangement of the initial CH insertion/Cope products. The discrepancy between the



Scheme 27

reactions of vinyldiazoacetates **75a** and **75b** with **78** was due to the exceptional ease with which the retro-Cope rearrangement took place in the case of **75a,** even at temperatures as low as 0 °C, delivering the more highly conjugated product, **81,** directly.

With chiral racemic 1-methyl-1,2-dihydronaphthalenes as the substrates, an enantiomer differentiation event was observed in this CH activation/Cope rearrangement sequence. Thus, in the course of the total syntheses of the diterpenes (–)-colombiasin A and (–)-elisapterosin B, Davies and coworkers reacted (*E*)-2-diazo-3-pentenoate (**83**) with 1-methyl-1,2-dihydronaphthalene **82** and catalytic Rh_2(*R*-DOSP)$_4$ to generate a 1:1 mixture of the CH activation/Cope rearrangement product **84**, which was formed as a single diastereomer with >95% *ee* along with cyclopropane **85** (Scheme 28).[32d] **84** was subsequently hydrogenated and reduced to alcohol **86**, which was purified by chromatography and 34% yield was obtained over three steps (68% yield in theory based on the racemic starting material). The two enantiomers of **82** apparently responded differently to the reaction with the chiral rhodium vinylcarbenoid, resulting very selectively in CH-activation for one enantiomer and cyclopropanation for the other. The selectivity of these reactions has been found to be markedly influenced by the nature of the chiral catalyst, vinyldiazoacetate and dihydronaphthalene.[32e] The same phenomenon has been employed advantageously in total syntheses of the diterpenes (+)-erogorgiaene[32f] and (+)-elisabethadione by the Davies group.[32g]

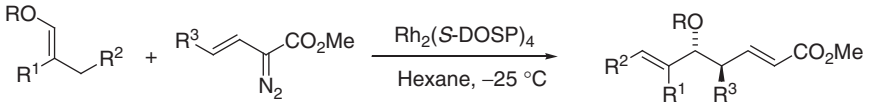


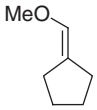
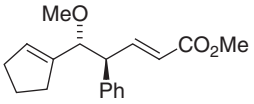
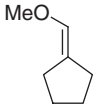
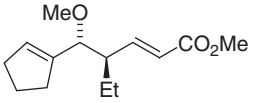
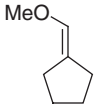
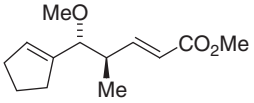
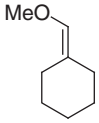
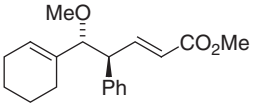
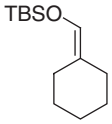
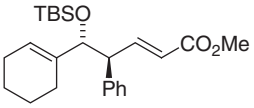
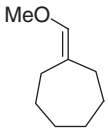
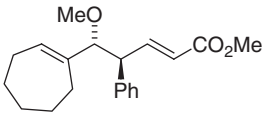
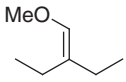
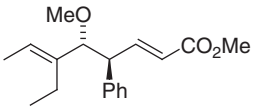
Scheme 28

This methodology was successfully extended to reactions of, for example, 4-silyloxy-1,2-dihydronapthalenes giving rise to chiral tetralones,[32b] 4-acetoxy-6,7-dihydroindoles, which furnished 4-substituted indoles,[32h] and vinyl ethers establishing a formal vinylogous Mukaiyama aldol process (Table 11).[32i] The latter reaction is especially remarkable as it provides an efficient surrogate for a fundamental C–C bond-forming reaction. Good yields and excellent diastereo- as well as enantioselectivity are attractive features of this process, which is currently, however, limited to symmetrical β-disubstituted vinyl ethers.

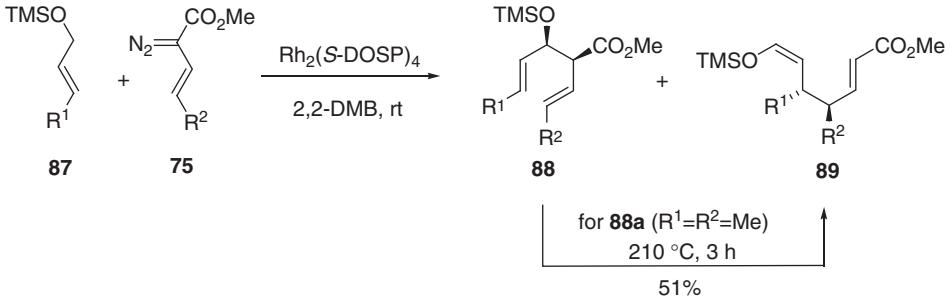
A closely related reaction developed by Davies et al. starts from allyl silyl ethers **87**, which on Rh_2(*S*-DOSP)$_4$-catalyzed reaction with vinyldiazoacetates **75** furnished mixtures of direct CH insertion products **88** and combined CH-activation/Cope

Table 11 Formal vinylogous Mukaiyama aldol reaction[32i]



No.	*Ether*	R^3	*Product*	ee *(%)*	*Yield (%)*
1		Ph		99	78
2		Et		98	87
3		Me		93	67
4		Ph		99	88
5		Ph		98	75
6		Ph		99	89
7		Ph		99	74

rearrangement products **89** (Scheme 29 and Table 12).[32k] Both products were formed as single diastereomers and with enantioselectivities of more than 90% *ee* for the styryldiazoacetate **75b** (but more moderate selectivities for alkyl-substituted vinyldiazoacetates). The similar selectivities observed for **88** and **89** pointed to a very similar pathway involved for both reaction manifolds. The purely 1,6-dialkyl-substituted 1,5-diene **88a** was subsequently converted into **89a** in a thermally induced silyloxy-Cope rearrangement (see Section 5.19.7.3).



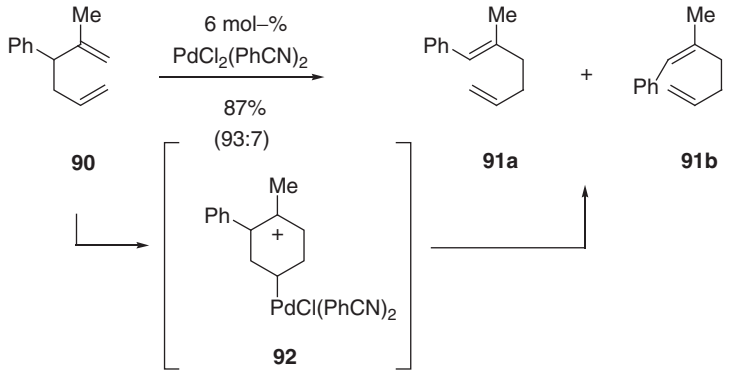
Scheme 29

Table 12 Combined CH activation/siloxy-Cope rearrangement (Scheme 29)[32k]

No.	R^1	R^2	*Yield (%)*	***88*:*89***	dr *for* ***88***	ee *for* ***88*** *(%)*	dr *for* ***89***	ee *for* ***89*** *(%)*
1	Me	Me	48	1.0:1.2	>99:1	81	>99:1	82
2	Me	Ph	82	1.0:1.3	>99:1	90	>99:1	91
3	MeCH=CH–	Ph	85	1.0:4.2	>99:1	91	>99:1	93
4	Ph	Ph	98	1.0:1.4	>99:1	91	>99:1	91
5	Ph	Me	66	1.6:1.0	>99:1	76	>99:1	78
6	Ph	Et	57	2.7:1.0	>99:1	80	>99:1	81
7	Ph	MeCH=CH–	73	1.0:1.6	>99:1	83	>99:1	83

5.19.6 Metal-Catalyzed Cope Rearrangements

Palladium(II) salts have been known since 1966 to promote the Cope rearrangement at ambient temperature.[33a] In 1980, Overman et al. discovered that catalytic amounts of $PdCl_2(PhCN)_2$ were sufficient to convert 2-methyl-3-phenyl-1,5-hexadiene (**90**) into a stereoisomeric mixture of Cope products, **91a** and **91b,** in a 93:7 ratio and in 87% combined yield (Scheme 30).[33b] The reaction conditions were extremely mild and rate accelerations on the order of 10^{10} relative to thermal Cope rearrangements were observed.



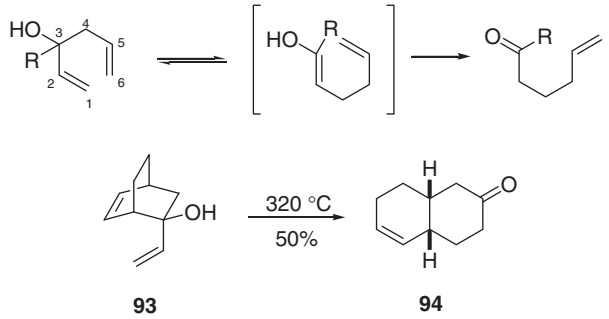
Scheme 30

This reaction does not follow a concerted mechanism but involves two discrete steps: the first one involves a rate-limiting Pd(II)-initiated cyclization to yield a 4-palladacyclohexyl cation intermediate **92**, which is followed by elimination of $PdCl_2(PhCN)_2$ to furnish the final Cope products in the second step (cyclization-induced rearrangement). The observation that exactly one cation-stabilizing substituent at either C2 or C5 of the 1,5-diene is required for the reaction to proceed is fully consistent with this mechanistic analysis, which was further substantiated through the kinetic analysis of the Cope rearrangement of various electron-deficient 2-aryl-1,5-dienes.[33c] With chiral 1,5-dienes, a complete transfer of chirality toward a prochiral sp^2 center was observed, indicating the same chair topology as in thermal Cope rearrangements. Accordingly, the Pd(II)-catalyzed Cope rearrangement has been successfully employed in synthetic organic chemistry as shown in Scheme 23. For example, chiral oxa- and aza-1,5-cyclononadienes were converted into 3,4-substituted THF and pyrrolidines, respectively, with full stereochemical control.[28] Also, the conversion of germacrone and germacranolides into elemenone and elemanolides, respectively, was facilitated under Pd(II)-catalysis.[31b,c]

Pd(0)-species such as $Pd(PPh_3)_4$ have been found to be able to catalyze the Cope rearrangement as well.[34a] Here, the rearrangement proceeds through bis(η^3-allyl)Pd(II)intermediates, however, which are generated by oxidative addition of Pd(0) into carbon–carbon σ-bonds. In addition, a Pd(0)-catalyzed domino allylation-Cope rearrangement of allyl 3-butenoates was achieved by decarboxylative sp^3–sp^3 coupling.[34b]

5.19.7 Oxy-Cope Rearrangement

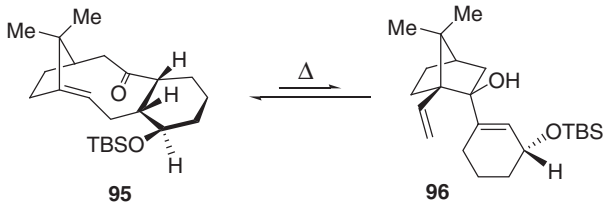
The discovery of the thermal oxy-Cope rearrangement greatly broadened the applicability of [3.3]-sigmatropic processes in the synthesis of complex structures. In analogy to the classical Cope rearrangement, a shift of double bonds occurs to generate new double bonds between C2 and C3 and C4 and C5, respectively (Scheme 31). As a hydroxyl group is attached to C3, the product of the rearrangement can undergo a facile and rapid enol–keto tautomerization to furnish a ketone or an aldehyde with a strong carbonyl bond. However, rather drastic thermal conditions are still necessary for the rearrangement to proceed. Berson and Jones



Scheme 31

discovered this reaction in 1964 while heating 2-*endo*-vinyl-2-*exo*-hydroxybicyclo[2.2.2]octene (**93**) at 320 °C to obtain *cis*-$\Delta^{5,6}$-octalone-2 (**94**), providing a facile entry into functionalized *cis*-decalins after hydrogenation.[35]

The first thermally induced retro-oxy-Cope rearrangement was reported by Paquette in 1991 (equation 5).[36] When a solution of **95** was refluxed in toluene for 5 days, 35% of **96** could be isolated along with 61% of recovered starting material. Subjecting **96** to identical reaction conditions resulted in the same distribution as observed before, proving that the oxy-Cope rearrangement was indeed reversible. Apparently, transannular strain in **95** provided enough driving force to partially compensate for the loss of binding energy of the carbonyl group.

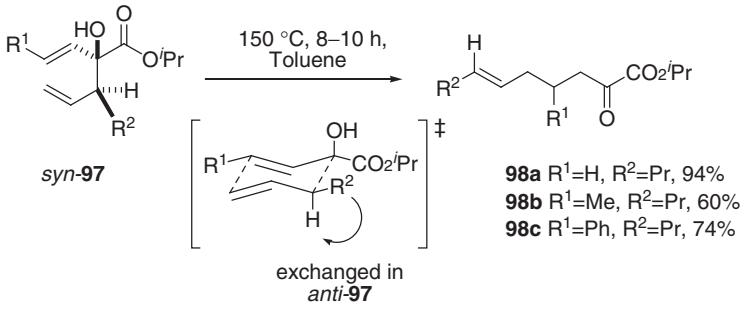


(5)

Although earlier studies of the oxy-Cope rearrangement dealt with investigations into the stereoselectivity of the reaction, geometry of transition states, kinetics, and substrate scope, in the past two decades the oxy-Cope rearrangement has witnessed a vast number of applications in complex molecule synthesis and cascade reactions to assemble polycyclic scaffolds.

5.19.7.1 Application in Synthesis – Acyclic Examples

Reports on the participation of acyclic 1,5-dienes in the oxy-Cope rearrangement are rare due to the lower driving force and selectivity when applying conformationally more flexible and less rigid systems. By heating 1,5-hexadienes *syn*-**97** in a sealed tube, Hiersemann could obtain α-keto esters **98** in good yields and *E*-diastereoselectivities (Scheme 32).[37]

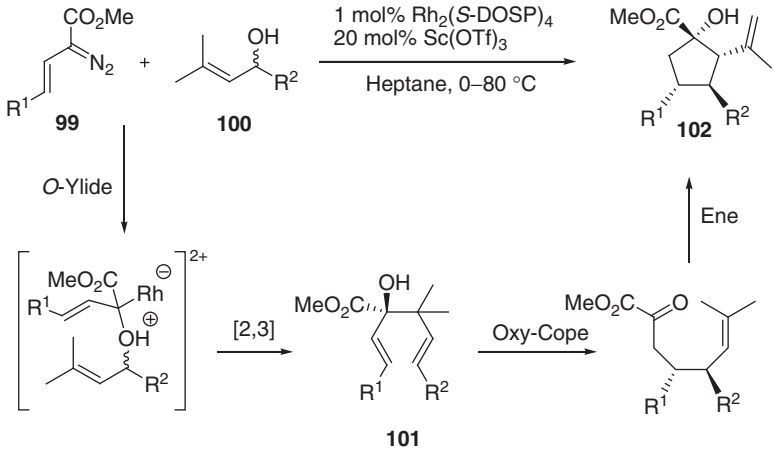


Scheme 32

The high selectivities of the rearrangement could be explained with the advantageous chair-like transition state. When changing to the anticonfigured substrates, the additional axial substituent caused the selectivity and rate of the reaction to deteriorate drastically. Hiersemann later found that α-keto esters such as **98** underwent ene reactions with good to moderate selectivities when subjected to harsher conditions, giving functionalized cyclopentanes.[37]

A very elegant, asymmetric one-pot access to highly functionalized cyclopentanes **102** via similar intermediates was demonstrated by Davies and coworkers.[38] They developed a domino sequence in which styryldiazoacetates **99** and racemic allyl alcohols

100 underwent Rh(II)-catalyzed tandem oxygen ylide formation/[2,3]-sigmatropic rearrangement to give rise to highly enantioenriched dienols **101**, which underwent an oxy-Cope rearrangement on heating followed by ene cyclization to arrive at multiply substituted cyclopentanols with excellent diastereo- and enantioselectivity (Scheme 33 and Table 13).



Scheme 33

Table 13 Rh(II)-catalyzed oxygen ylide formation/[2,3]-sigmatropic/oxy-Cope rearrangement/ene cyclization (Scheme 33)[38]

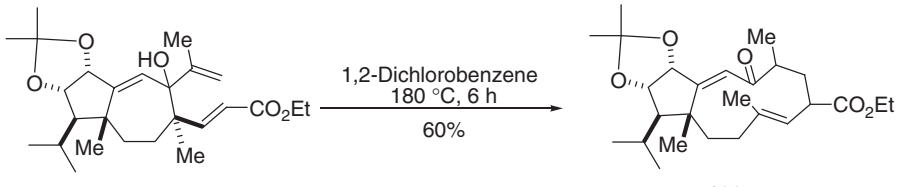
No.	R^1	R^2	*Yield (%)*	dr	ee *(%)*
1	Ph	Me	95	>20:1	82
2	Ph	*i*-Pr	67	>20:1	80
3	Ph	*i*-Bu	73	>20:1	80
4	Ph	allyl	86	>20:1	76
5	Ph	*n*-Hex	80	>20:1	78
6	Ph	$-CH_2OTBS$	65	>20:1	78
7	Ph	CH_2SiMe_3	59	>20:1	84
8	Et	Ph	63	>20:1	64
9	*p*-(OMe)C_6H_4	Ph	94	>20:1	87
10	*p*-BrC_6H_4	Ph	48	>20:1	92

5.19.7.2 Application in Synthesis – Cyclic Examples

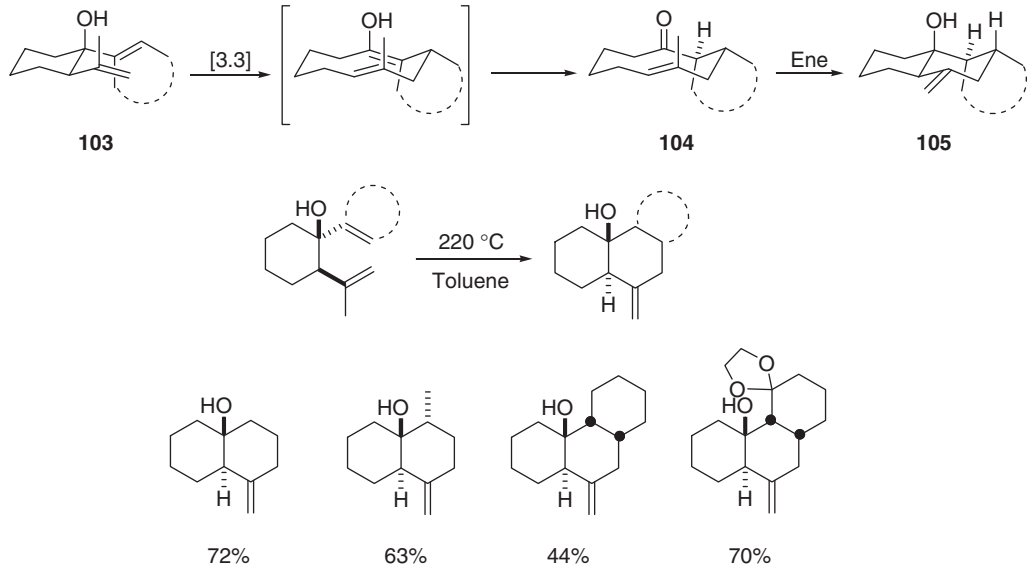
Barriault and coworkers applied the thermal oxy-Cope rearrangement of a variety of 1,2-divinylcyclohexanols **103** for the construction of polycyclic ring systems.[39] After the sigmatropic process, the intermediate ketones **104** underwent spontaneous transannular ene reactions with high diastereoselectivity to give polycycles **105** (Scheme 34). A number of functionalized decalins were successfully generated by this method, giving the products in moderate to good yields and with complete diastereoselectivity.

On extending this methodology, they assembled the *trans*-decalin core of the diterpenoid teucrolivin A **107** via a cascade oxy-Cope/Claisen/ene reaction with complete diastereoselectivity (Scheme 35). This cascade reaction was applied toward the synthesis of several other decalin scaffolds of natural products.

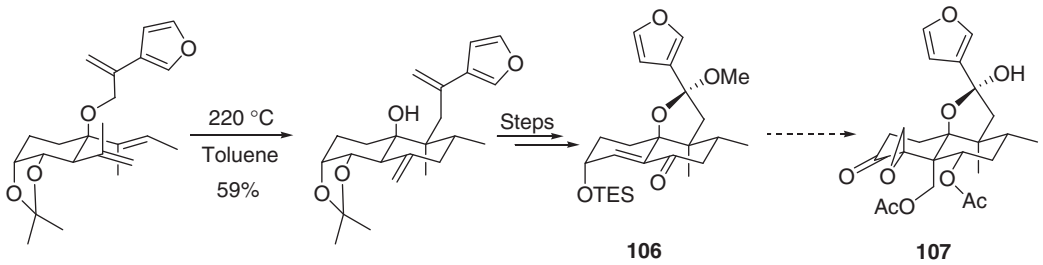
Mehta and coworkers constructed the 5,11-fused bicyclic framework present in dolabellane-type diterpenoids (equation 6).[40] Under thermal conditions, they could induce the sigmatropic shift in **108** to access the cycloundecadienone **109** as a single diastereomer. Attempts to employ the anionic variant of the oxy-Cope rearrangement failed.



108 109 (6)

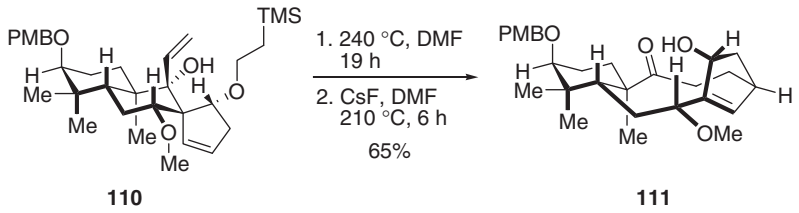


Scheme 34



Scheme 35

During the total syntheses of the diterpenoids (–)-*O*-methylshikoccin and (+)-*O*-(methylepoxy)shikoccin, Paquette and coworkers transformed **110** into **111** by an oxy-Cope rearrangement followed by *in situ* deprotection to give the target molecule in good yield as a single isomer (equation 7).[41]



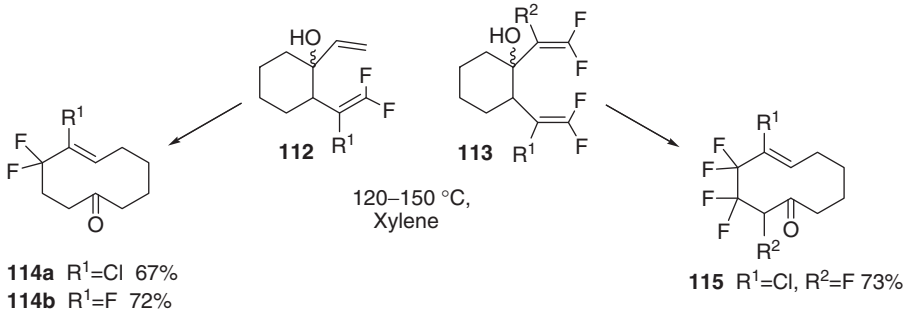
(7)

Rearrangement of the highly fluorinated divinylcyclohexanols, **112** and **113**, under thermal conditions gave access to cyclodecenones, **114** and **115**, respectively, containing up to five fluorine atoms (Scheme 36).[42] The exceptional driving force for the oxy-Cope process strongly overrode the typically prevalent ring contraction of cyclodecadienes. This method by Percy constituted the first route toward the synthesis of cyclic fluoroketones, which were otherwise impossible to obtain.

5.19.7.3 The Silyloxy-Cope Rearrangement

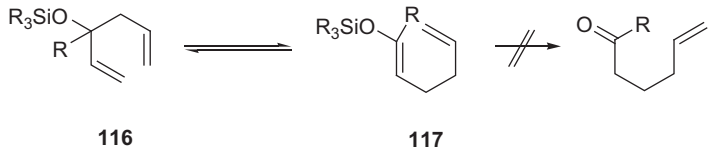
5.19.7.3.1 With cyclic substrates

One of the major drawbacks of the oxy-Cope rearrangement is the competing retro-ene fragmentation, which always occurs whenever it is geometrically possible. To avoid this side reaction, the hydroxyl group has been frequently protected as an ether or ester making the oxy-Cope rearrangement the exclusive pathway.[43] In a similar manner, the silyloxy-Cope rearrangement using 3-silyloxy-1,5-dienes **116** as substrates has been developed furnishing silyl enol ethers **117** as products, which cannot tautomerize to



Scheme 36

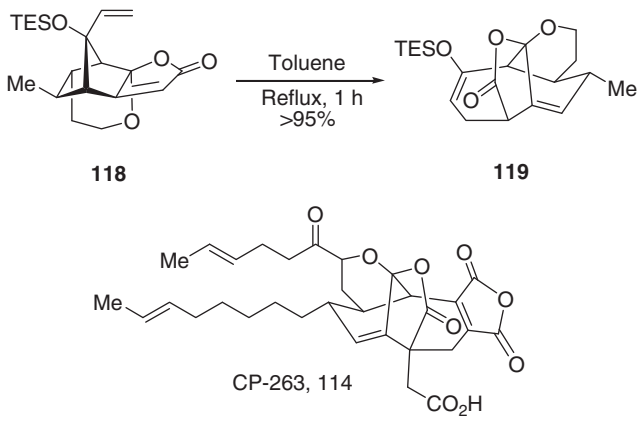
the corresponding aldehydes or ketones under the reaction conditions (Scheme 37). This process, however, still greatly benefits from the enol–ether conjugation in the product.



Scheme 37

The application of the silyloxy-Cope rearrangement in cyclic substrates is rarely documented and deals exclusively with the assembly of the core structure of the phomoidride family of natural products. The natural product, phomoidride B, also known as CP-263, 114, and derivatives thereof were found to be active against protein farnesyl transferase and hence might serve as lead structures in the design of anticancer drugs. Also, due to their challenging structure, their synthesis has generated considerable interest among synthetic chemists.

In an attempt to synthesize the tricyclic core structure of the phomoidrides, Leighton and coworkers found that heating of a solution of **118** in toluene led to smooth conversion to silyl enol ether **119** as a single compound (Scheme 38).[44] Remarkably, the reaction was completed within 1 h in refluxing toluene based on the embedded strain of the lactone spiroketal **118** that was released on rearrangement, despite the bridgehead double bond in the product. Subsequent reports applied similar approaches adding more substituents to the core structure and combining preceding reactions in a tandem fashion with the sigmatropic rearrangement.

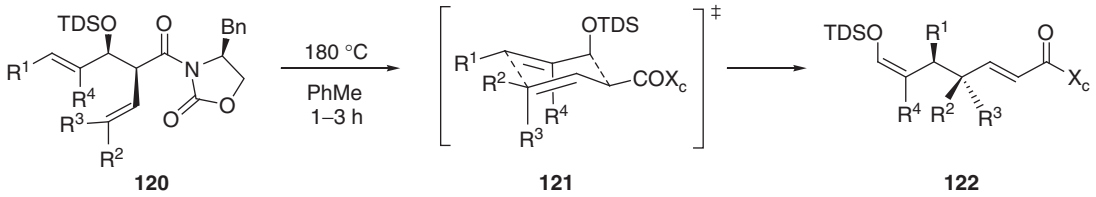


Scheme 38

5.19.7.3.2 With acyclic substrates

Chiral aldol products have been introduced as suitable substrates for the silyloxy-Cope rearrangement. First demonstrated by Schneider and coworkers, 3-silyloxy-1,5-dienes **120**, which were prepared via an Evans *syn*-aldol reaction with subsequent silylation, underwent rapid and highly stereoselective thermal Cope rearrangements on heating for 1–3 h at 180 °C in toluene in a sealed flask (Scheme 39 and Table 14).[45] Alternatively, microwave irradiation was applied, which sharply reduced the reaction

times to only 15–20 min in dimethylformamide as solvent.[45d] The exceptional diastereoselectivity arises from the chair-like transition state conformation **121**, in which the bulky carboximide substituent occupies the pseudoequatorial position, whereas the rather slim silyl ether favors the pseudoaxial position. The uncommonly high rate of this process presumably originates from the different electronic properties of the two allyl fragments, resulting in a highly dipolar transition structure with a resonance structure resembling an allyl cation and allyl anion couple.[46] Kinetic studies using aldol products with different oxy substituents and different carboxyl groups clearly revealed that strongly electron-releasing oxy groups and strongly electron-withdrawing carboxyl groups accelerate the Cope rearrangement substantially, whereas less electron-releasing oxy groups and less electron-withdrawing carboxyl groups retard the reaction. DFT calculations convincingly supported these results and predicted activation barriers very close to the experimental results. A broad range of different substituents could be accommodated in the aldol components, and the products **122** were typically obtained with excellent yields and diastereoselectivities (**Table 14**).



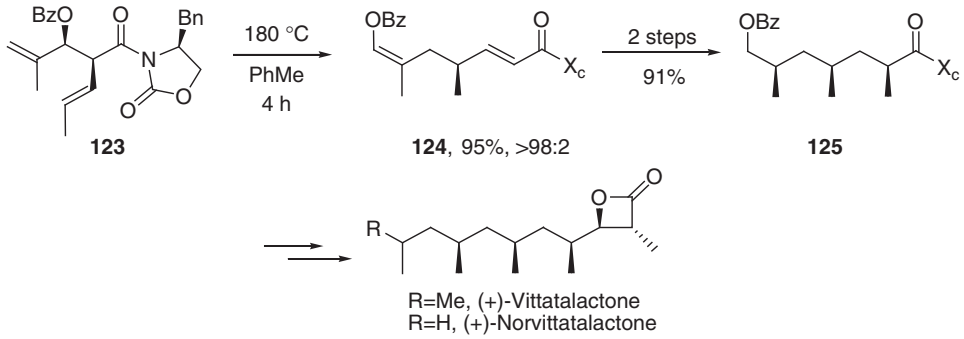
Scheme 39

Table 14 The silyloxy-Cope rearrangement of *syn*-aldol products **120** (**Scheme 39**)[45]

No.	R^1	R^2	R^3	R^4	dr	*Yield (%)*
1	Me	H	H	H	92:8	92
2	Ph	H	H	H	>95:5	88
3	$SiMe_2Ph$	H	H	H	88:12	90
4	Me	Me	H	H	>95:5	87
5	Me	H	Me	H	>95:5	86
6	Me	Me	H	Me	>95:5	89
7	H	Me	H	Me	>95:5	91
8	*n*-Pr	Me	H	H	95:5	82
9	*n*-Pr	H	Me	H	>95:5	82
10	$SiMe_3$	Me	H	H	>95:5	82

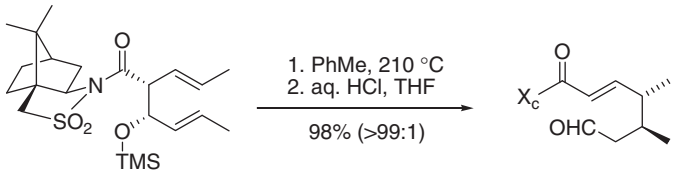
The straight-chain Cope products **122** have proven to be versatile synthetic intermediates due to their functional group pattern and have been successfully converted into optically pure and polysubstituted tetrahydropyrans, piperidines, terpenols, 1,3,5…-polyol chains, and highly functionalized cyclohexanes.[47]

A related oxy-Cope rearrangement of the benzoyl-protected aldol product **123** has been performed in the context of the first noniterative and straightforward synthetic approach toward polydeoxypropionate natural products. Enol benzoate **124** was obtained both in excellent yield and diastereoselectivity on heating **123** at 180 °C for 4 h. On the basis of the coordinating benzoate group, a highly diastereoselective catalyst-controlled hydrogenation with a chiral iridium catalyst delivered a dideoxypropionate building block which was further converted into trideoxypropionate **125** via an auxiliary-controlled enolate methylation (**Scheme 40**).[48] This methodology was successfully applied toward the asymmetric synthesis of the cucumber beetle pheromones, (+)-vittatalactone and (+)-norvittatalactone.



Scheme 40

Independently, Black and Nakai and their groups reported thermal Cope rearrangements of 3-silyloxy-1,5-dienes derived from aldol products as well. Although Black employed the same Evans-type substrates, Nakai took advantage of the Oppolzer sultam as a chiral auxiliary to obtain the *syn*-aldol product **126**. Again, the silyloxy-Cope rearrangement proceeded rapidly to give rise to Cope product **127** in excellent yield and stereoselectivity (equation 8).[49]



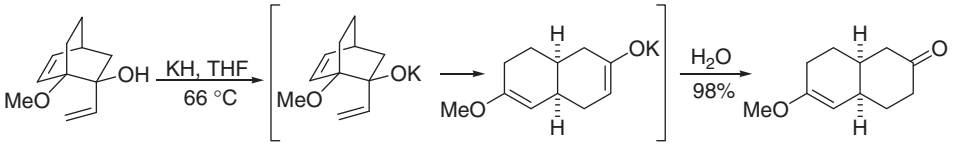
126 **127** (8)

5.19.8 AOC

Until today, the AOC has been the most extensively investigated and synthetically employed variant of the Cope rearrangement. The majority of the literature that refers to the term 'oxy-Cope' in fact deals with the anionic variant. Owing to its mild reaction conditions and thus functional group tolerance, the AOC has been widely used for the assembly of complex, polycyclic scaffolds of natural products often in the context of cascade reactions with the AOC being only a part of the entire sequence. There have been more than 70 reports over the past 20 years employing the AOC as the key step in total syntheses. The subchapters of the AOC's synthetic applications can thus only scratch the surface of what has been published within the past two decades.

5.19.8.1 Rate Acceleration

Discovered in 1975 by Evans and coworkers, the AOC of **128** using potassium hydride (KH) as base to generate the corresponding potassium alkoxide resulted in observed rate accelerations of 10^{10}–10^{17} to afford the rearranged enolate **129**, which was then protonated to ketone **130** (Scheme 41).[50] The reaction rate displayed strong counter ion dependence, and the potassium alkoxide proved to be the optimal substrate, especially when crown ether such as 18-crown-6 was added, which resulted in additional 180-fold rate acceleration. This indicated that ion pair dissociation was important for maximal rate increase, allowing for much milder reaction conditions compared with the neutral oxy-Cope rearrangement.



128 **129** **130**

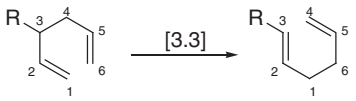
Scheme 41

Baumann and coworkers investigated Cope rearrangements of different 1,5-dienes **131** using DFT methods to explain the drastic changes in reaction rate.[51] The $n \rightarrow \sigma^*$-orbital interaction between the oxygen lone pair and the σ^*-orbital of the neighboring C3–C4 bond readily destabilizes the σ-bond which is being broken in the course of the rearrangement and hence decreases the activation enthalpy for the Cope rearrangement. It could be shown that the more negatively charged the substituent R in **131** is, the longer and thus weaker the C3–C4 bond becomes, which nicely parallels the observed rate accelerations (Scheme 42).

Additional rate accelerations of the AOC could be achieved by resonance effects. Installing oxygen or sulfur moieties at the terminal carbon atom of the bridgehead vinyl group in **132** accelerated the Cope rearrangement toward **133** by 1.4- and 3.45-fold, respectively (Scheme 43).[52] During the assembly of the diterpenoid vinigrol, an additional unsaturation significantly accelerated the sigmatropic process. Although **134** required heating under reflux in THF for over 22 h to give rise to **135**, the additional unsaturation in **136** greatly facilitated the process and led to a quantitative rearrangement to furnish **137** within just 2 h at room temperature.[53]

5.19.8.2 Stereoselectivity

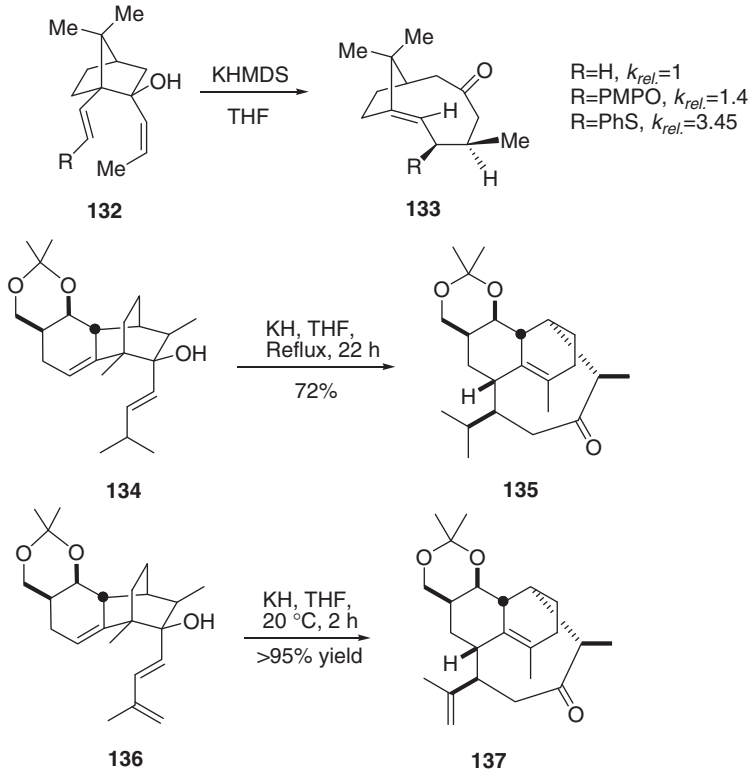
The control over the diastereoselectivity of the AOC of chiral acyclic substrates has attracted much attention recently. Because these acyclic systems are less rigid than their cyclic counterparts, one chair-like transition state conformation may flip easily into the other chair conformation, furnishing opposite enantiomers as products. In the Cope rearrangements of *E*- and *Z*-**138**, the



131

R	Bond distance (Å) C3 – C4	$\Delta G^{\ddagger}$ (kcal mol^{-1})	k (s^{-1})
H	1.548	36.3	1.63×10^{-14}
OH	1.552	33.8	1.05×10^{-12}
$O^{\ominus}$	1.604	6.3	1.64×10^{8}

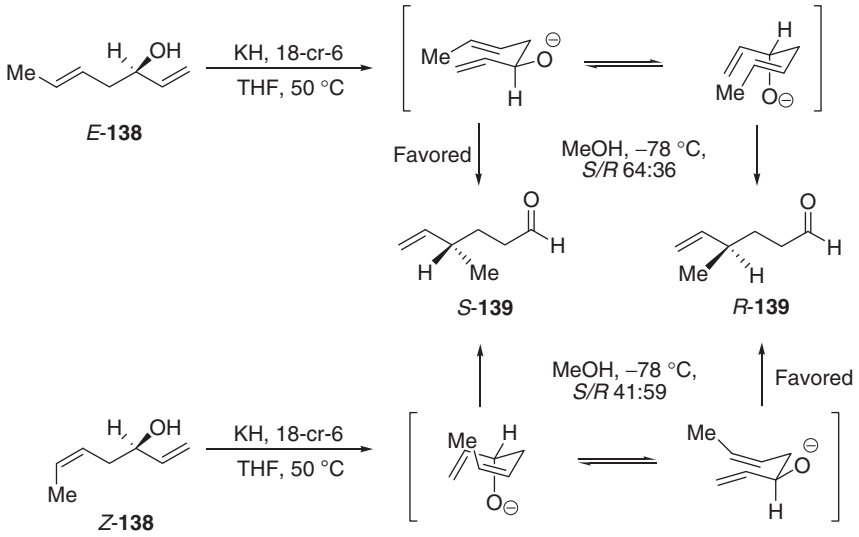
Scheme 42



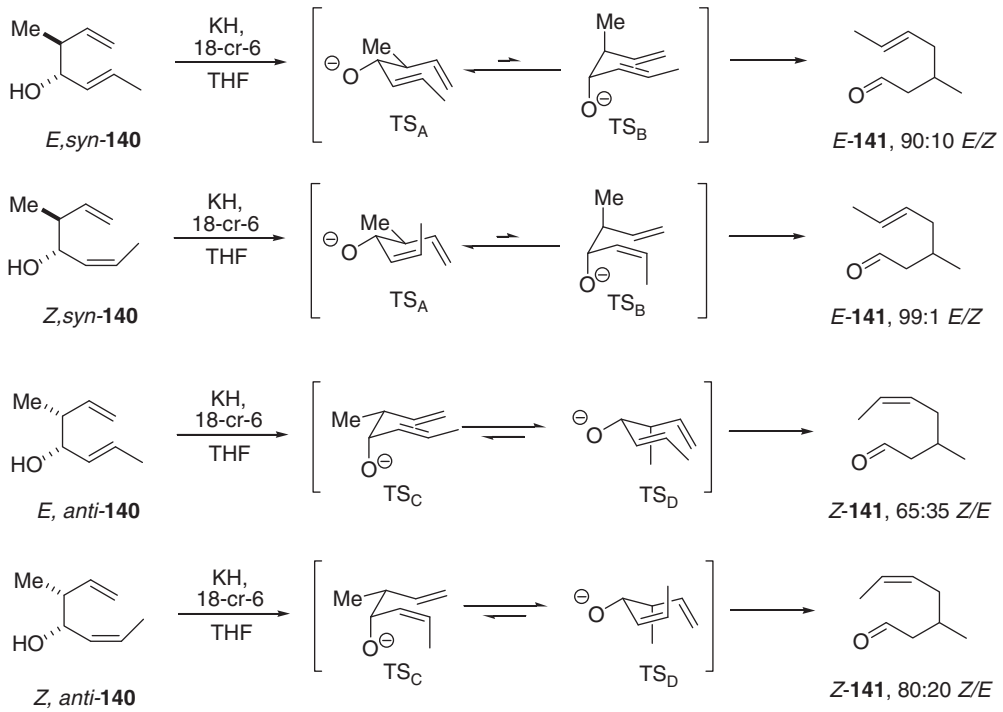
Scheme 43

efficiency of chirality transfer depends exclusively on the orientational preference of the alkoxide substituent (Scheme 44).[54] The reactions were quenched at low temperature by the addition of methanol to give rise to mixtures of *S*- and *R*-**139**, which were obtained with the indicated ratios. In both cases the oxyanion substituent favors the pseudoequatorial position in the transition state of the sigmatropic process. However, the selectivity proved to be quite low and may well be overridden by a change of the substitution pattern.

In the course of the total syntheses of the natural products, (+)-furanal and (–)-antirhine, Nakai and coworkers showed that improved diastereoselectivity can be achieved by placing an alkyl substituent on the carbon atom adjacent to the carbinol center (Scheme 45).[55] They very accurately studied the dependence of product configuration on the starting relative configuration between the two chiral centers as well as the double bond geometry. It turned out that the preference for the equatorial position of the oxy group prevailed in all cases studied, albeit to a different extent. Thus, the pair of diastereomeric 1,5-dienes, *E,syn*-**140** and *Z,syn*-**140,** both rearranged with high diastereoselectivity to *E*-**141** because the adjacent methyl group enforced the preference for transition state A (TS_A) with both substituents occupying pseudoequatorial positions. In the case of *Z,syn*-**140,** TS_B suffered from additional 1,3-diaxial interactions with the *Z*-configured methyl group, making TS_A the almost exclusive pathway for the Cope rearrangement (99:1 vs. 90:10 *E*/*Z*).



Scheme 44



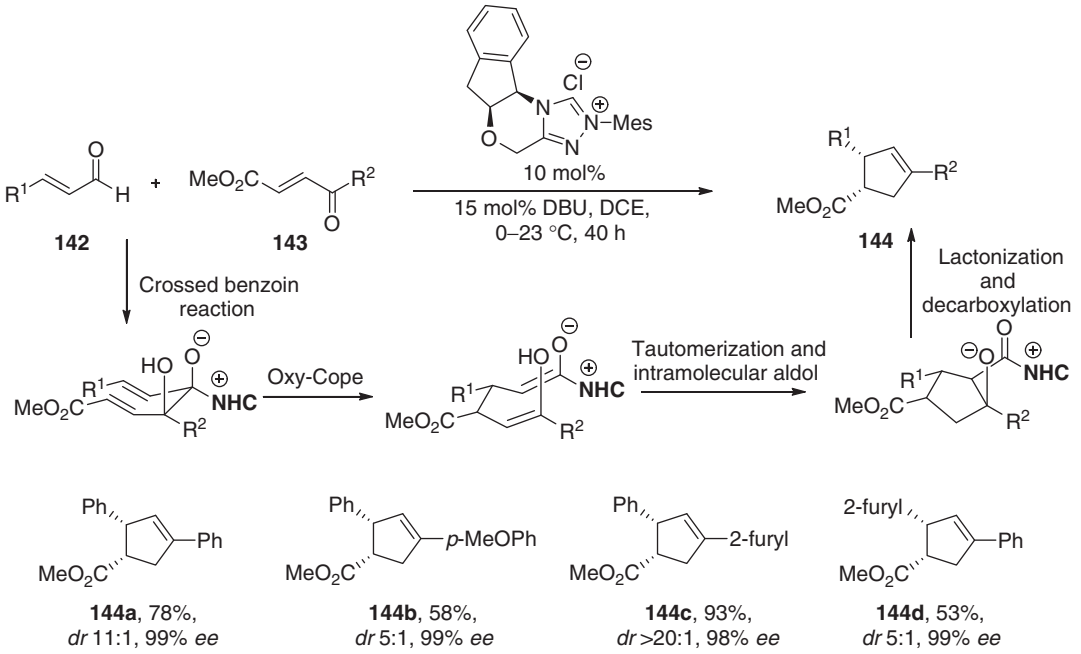
Scheme 45

For 1,5-dienes *anti*-**140**, only one of the substituents was able to occupy the favorable pseudoequatorial position and, based on the *Z*-configuration in product *Z*-**141**; this was the oxy group originating from TS_D. In the case of *Z,anti*-**140**, the diastereoselectivity was again higher because the competing TS_C once again suffered from unfavorable 1,3-diaxial interactions with the *Z*-configured methyl group (80:20 *Z*/*E* vs. 65:35 *Z*/*E*). In subsequent studies, Lee et al. also investigated the orientational preference of the oxyanion group and the effect on the diastereoselectivity of the AOC.[56]

5.19.8.3 Application in Synthesis – Acyclic Examples

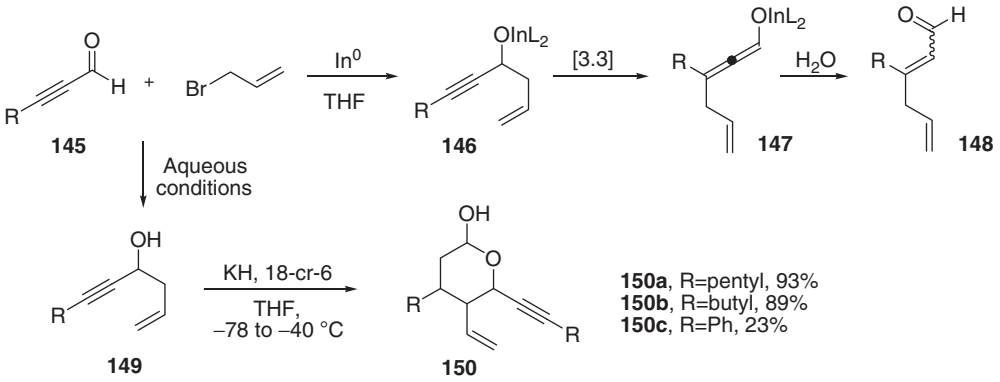
As in the neutral oxy-Cope rearrangement, examples involving acyclic substrates in the AOC are rather scarce. Bode et al. reported an interesting cascade reaction in which a highly enantioselective *N*-heterocyclic carbene (NHC)-catalyzed benzoin reaction between cinnamaldehydes **142** and 4-oxoenoates **143** preceded the oxy-Cope rearrangement, which was followed by an

intramolecular aldol/lactonization/decarboxylation sequence (Scheme 46).[57] This extremely elaborate cascade reaction gave rise to highly functionalized cyclopentenes **144** in excellent stereoselectivity and good to very good yields.



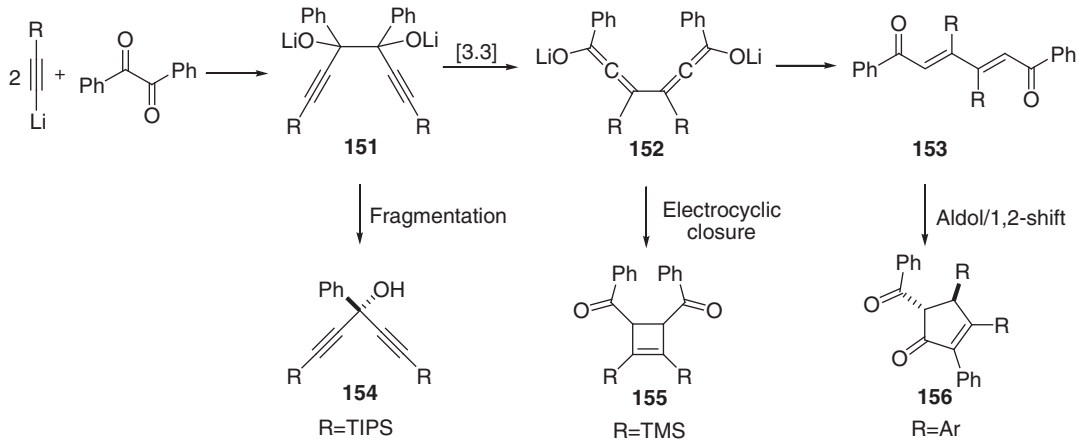
Scheme 46

When Mitzel and coworkers conducted the indium-promoted coupling of propargyl aldehydes **145** with allyl bromide under anhydrous conditions, they observed the formation of aldehydes **148** which were derived from an oxy-Cope rearrangement of **146** followed by hydrolysis of the resulting allenol intermediate **147** (Scheme 47).[58] They were able to selectively generate alcohol **149** when running the reaction in a protic medium. Subjecting **149** to the typical AOC conditions surprisingly resulted in the formation of lactol **150** in moderate to very good yields as a mixture of two diastereomers. The origin of this lactol formation was partial fragmentation of **149** back to the propargylic aldehyde **145,** which then reacted with the intermediate allenol to form the cyclic lactols **150**.



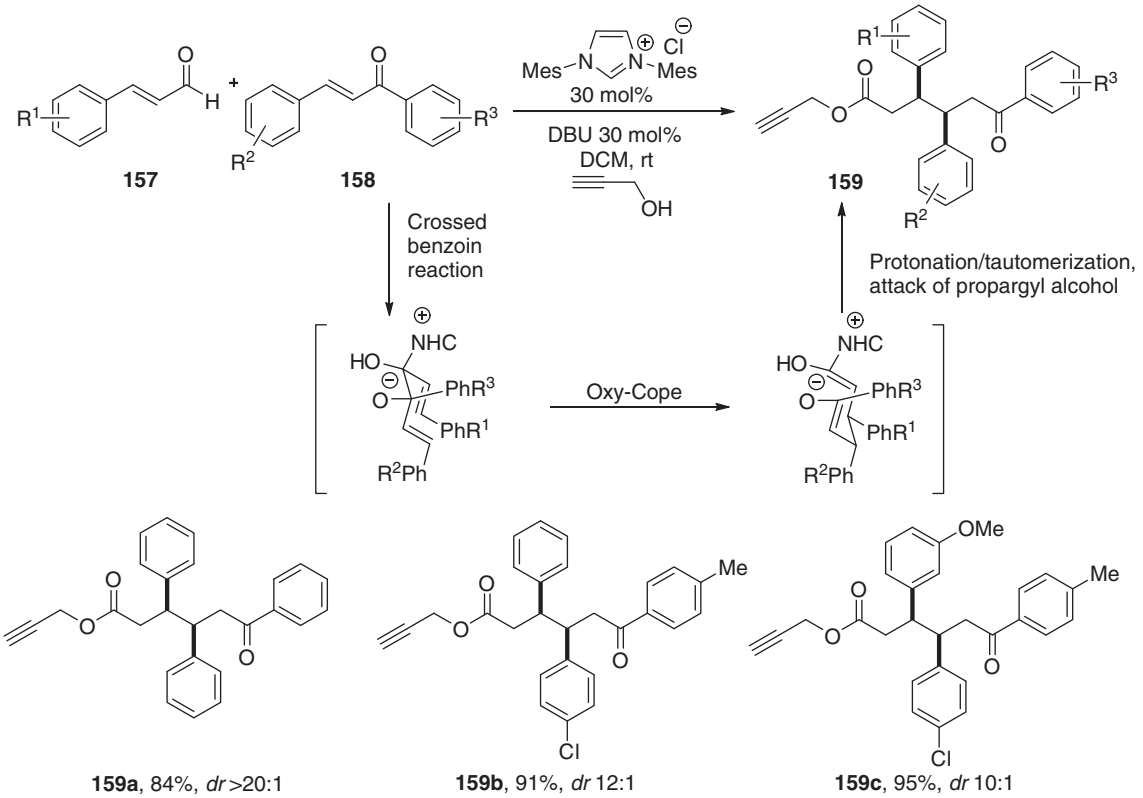
Scheme 47

Another participation of alkynes in the AOC was demonstrated by the group of Alabugin.[59] After addition of two equivalents of Li-alkynes to benzil, the dianionic intermediate **151** could be incorporated into different cascade transformations depending on the choice of the substituent R on the alkyne moiety (Scheme 48). If bulky groups like triisopropylsilyl were present, the intermediate dianion was incapable of undergoing the sigmatropic rearrangement resulting in fragmentation to give carbinol **154**. In the case of smaller silyl substituents, the dianionic oxy-Cope rearrangement (DAOC) proceeded, followed by 4π-electrocyclic ring closure to yield cyclobutene **155** as a mixture of 2 diastereomers. Subsequent to the Cope step, substrates with aromatic substituents underwent an aldol condensation closing the cycle in a favorable 5-(*enolexo*)-*exo-trig* fashion followed by a 1,2-phenyl migration to give the functionalized cyclopentenones **156**.



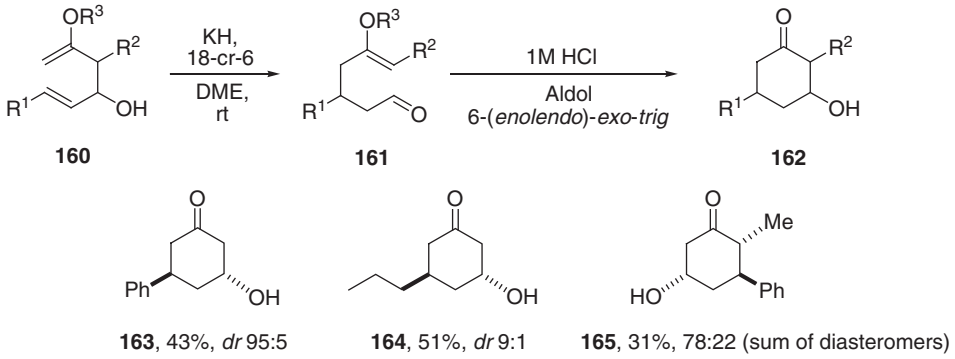
Scheme 48

Chen and coworkers developed an access to functionalized *syn*-ε-ketoesters **159** employing a crossed benzoin/oxy-Cope/esterification cascade (Scheme 49).[60] A number of differently substituted cinnamaldehydes **157** were reacted in an NHC-catalyzed crossed benzoin reaction with enones **158**. The benzoin intermediates underwent an oxy-Cope rearrangement followed by esterification with propargyl alcohol to give ε-ketoesters **159** in very good yields and diastereoselectivities. In few cases, depending on the substitution pattern, an *anti*-diastereoselective reaction was observed.



Scheme 49

Hartley and coworkers developed an AOC of acyclic, racemic enol ethers **160** furnishing enol ether aldehydes **161** that underwent a subsequent cyclization in a 6-(*enolendo*)-*exo-trig* intramolecular aldol reaction on acidic workup to give rise to β-hydroxy cyclohexanones **163–165** with up to three stereocenters (Scheme 50).[61]

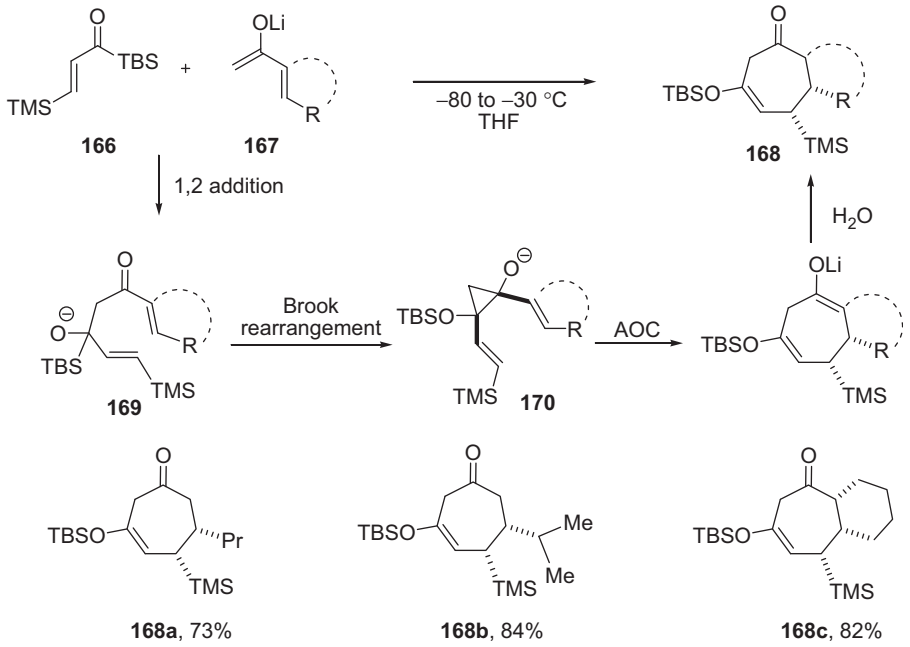


Scheme 50

5.19.8.4 Application in Synthesis – Cyclic Examples

5.19.8.4.1 Medium size rings

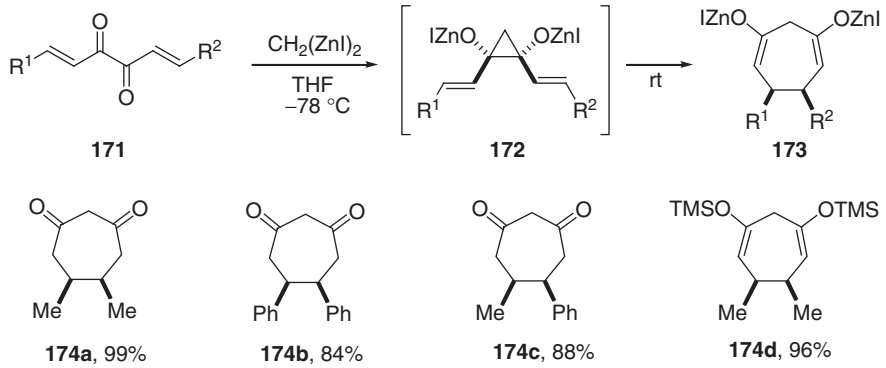
As discussed before (Section 5.19.3), the inherent strain of small rings can be exploited to provide a substantial driving force for the Cope rearrangement. Thus, the AOC has been employed frequently to synthesize medium size rings from highly strained three- and four-membered rings. Takeda and coworkers applied this strategy toward the synthesis of functionalized 3-cycloheptenones **168** in a very elegant cascade reaction (Scheme 51).[62] Reaction of lithium dienolates **167** with acyl silanes **166** furnished intermediate 1,2-addition products **169** that underwent a spontaneous Brook rearrangement to form *cis*-1,2-divinylcyclopropanediols **170**, followed by a rapid AOC to give rise to the desired *cis*-configured 3-cycloheptenones **168**.



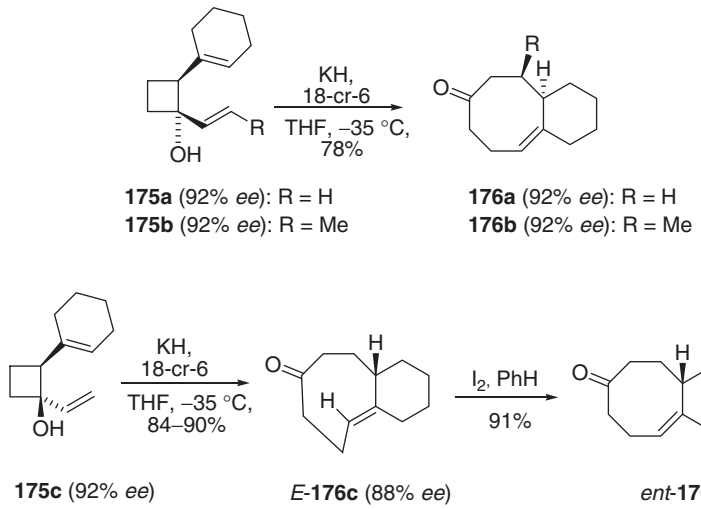
Scheme 51

Matsubara and coworkers developed another synthetic access to seven-membered rings by the stereospecific rearrangement of zinc alkoxides of *cis*-1,2-divinylcyclopropanediols **172** generated from 1,2-diketones **171** by cyclopropanation with bis(iodozinc)methane (Scheme 52).[63] The zinc alkoxides underwent the AOC on warming to room temperature and were either hydrolyzed to furnish cycloheptane-1,3-diones **174a-c** or trapped by the addition of an electrophile, for example, trimethylsilyl chloride (TMSCl), to give silyl dienol ether **174d**.

This methodology was successfully extended to the synthesis of annulated eight-membered rings starting from 1,2-divinylcyclobutanols (Scheme 53).[64] Enantiomerically highly enriched *cis*-1,2-divinylcyclobutanols, **175a** and **175b,** underwent the AOC to furnish bicyclo[6.4.0]dodecenones, **176a** and **176b**, respectively, with complete chirality transfer. Unexpectedly, *trans*-1,2-divinylcyclobutanol **175c** underwent the [3.3]-sigmatropic rearrangement under identical conditions as well and the product *E*-**176c** was obtained with only slightly reduced enantiopurity supporting a concerted reaction mechanism. *E*-**176c** incorporating



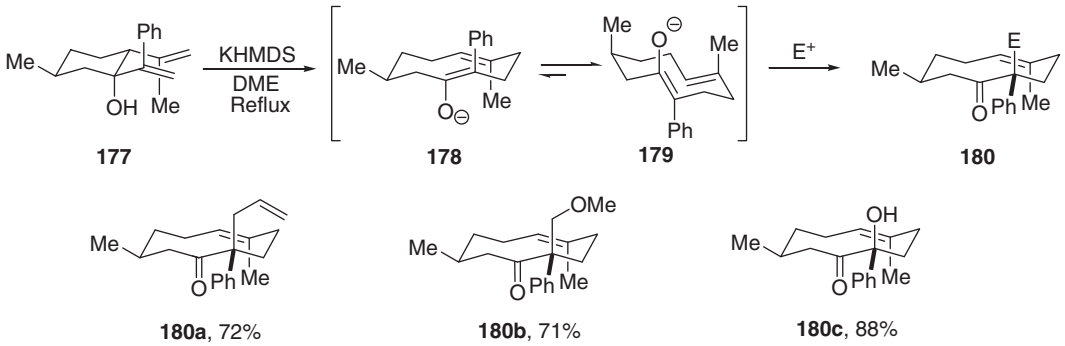
Scheme 52



Scheme 53

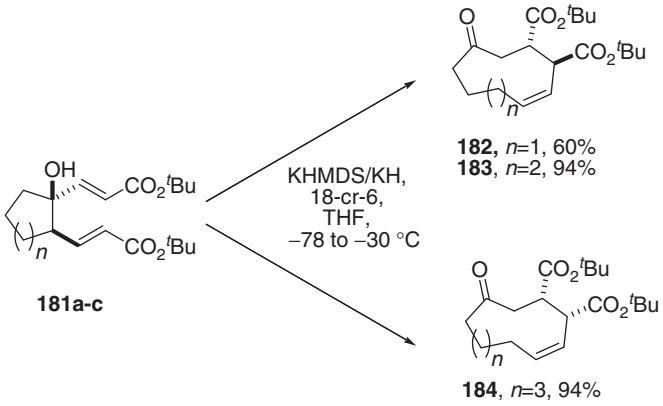
both planar and central chirality could easily be converted by isomerization with iodine into the corresponding *Z*-olefin, which constitutes the enantiomer of **176a**. A similar approach was demonstrated by Snapper et al., giving rise to annulated cyclic nine- to eleven-membered cycloalkenones.[65]

Barriault and coworkers subjected enantiomerically pure divinylcyclohexanols **177** to the AOC and trapped the intermediate enolates **178**/**179** with different electrophiles to give cyclodecenones **180a-c** bearing a quaternary stereocenter with complete transfer of chirality (Scheme 54).[66] Surprisingly all products had the opposite relative configuration than what was predicted, indicating that the initially formed enolate **178** underwent a rapid rotation to enolate conformation **179** after the sigmatropic process. The versatility of this strategy was demonstrated by the formal total synthesis of (–)-mesembrine.



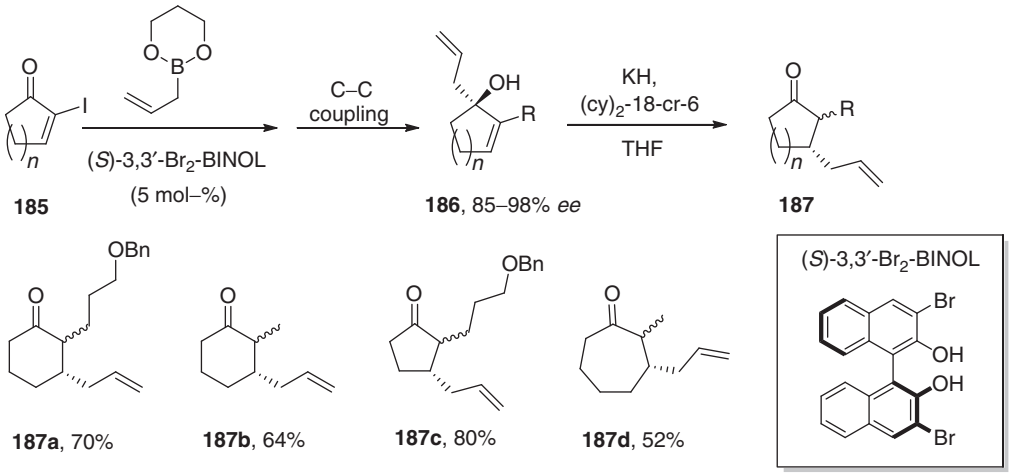
Scheme 54

Larger ring sizes were accessible from *trans*-1,2-divinylcyclopentanols, -hexanols, and -heptanols **181a-c** (Scheme 55).[67] After careful optimization of the reaction and quenching conditions, cyclononenone **182**, cyclodecenone **183**, and cycloundecenone **184** were obtained in good to excellent yields. Although the relative *trans*-configuration of **182** and **183** indicated the intermediacy of chair transition state conformations, it was concluded based on the unexpected relative *cis*-configuration of **184** that the AOC of divinylcycloheptanol **181c** had apparently proceeded through a boat-like transition state conformation.



Scheme 55

A formal conjugate allylation of α-substituted cycloalkenones was established by the group of Taber through the AOC.[68] Various carbinols **186** were obtained through enantioselective 1,2-addition of allylboronate to enones **185** and a subsequent C–C coupling. The allyl group was then transposed in a highly suprafacial process furnishing 3-allylated cycloalkanones **187** in the course of the AOC with full chirality transfer (Scheme 56). In that way, cyclic ketones **187a-d** with five- to seven-membered rings were easily accessed.

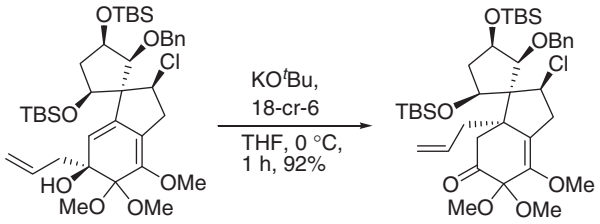


Scheme 56

5.19.8.4.2 Polycyclic ring systems

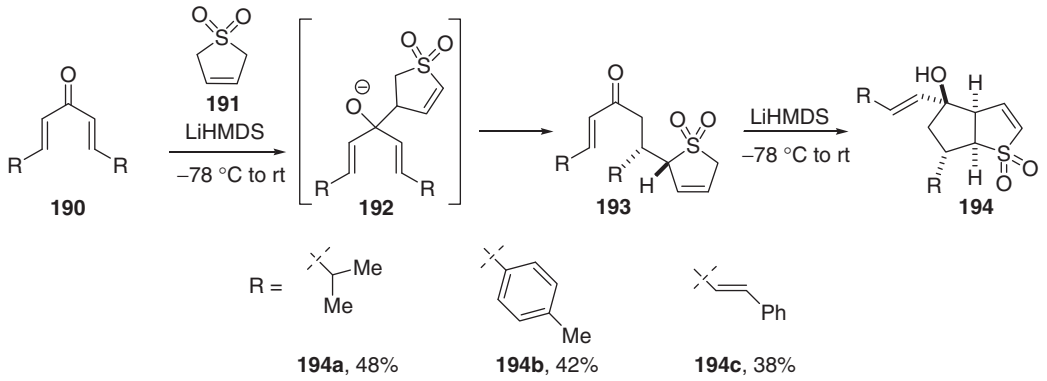
Aside from simple ring expansions, the AOC has been widely used to assemble more complex, annulated polycyclic ring systems. The sigmatropic process is often embedded in larger reaction cascades, each step of which leads to the formation of an additional ring system.

A remarkable example of functional group tolerance as well as excellent diastereoselectivity in an AOC was recently demonstrated by Castle and coworkers in the course of the total synthesis of (–)-acutumine.[69] They installed an all-carbon quaternary stereocenter by the AOC of the highly functionalized dienol **188** under very mild conditions, giving rise to ketone **189** in excellent yield and as a single diastereomer (equation 9). The conjugation of the additional enol ether with the homoallylic alcohol most likely accelerated this reaction.



188 **189** (9)

Wulff and coworkers used a cascade reaction to access orthogonally functionalized bicyclic sulfones **194** (Scheme 57).[70] Treatment of a solution of ketones **190** and sulfone **191** with lithium hexamethyldisilazide (LiHMDS) resulted in the formation of the 1,2-addition intermediates **192**, which underwent the AOC on warming the solution to room temperature. If the initial oxy-Cope product **193** was treated *in situ* with another equivalent of LiHMDS, a second aldol-type addition took place to give bicyclic sulfones **194a-c** with four contiguous stereogenic centers as single diastereomers.

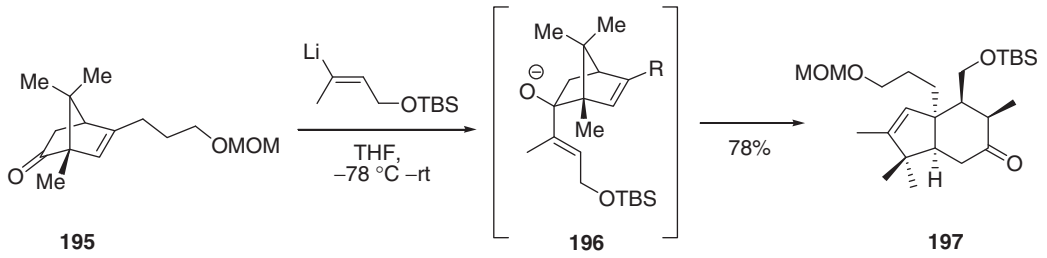


190 **192** **193** **194**

194a, 48% **194b**, 42% **194c**, 38%

Scheme 57

The synthesis of the enantiomerically pure core structure of the insect antifeedant dumsin was realized by Paquette and coworkers, who employed an AOC as the key step (Scheme 58).[71] Diastereoselective addition of a vinyl lithium compound to ketone **195** led to intermediate **196**, which rearranged smoothly to the bicyclic ring system **197** in good yield.



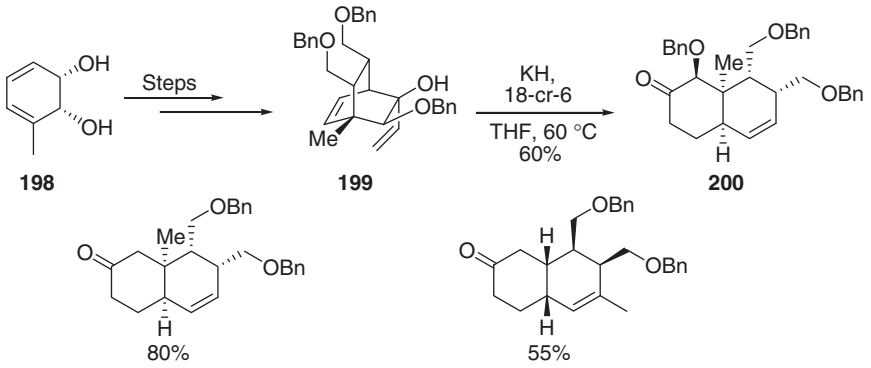
195 **196** **197**

Scheme 58

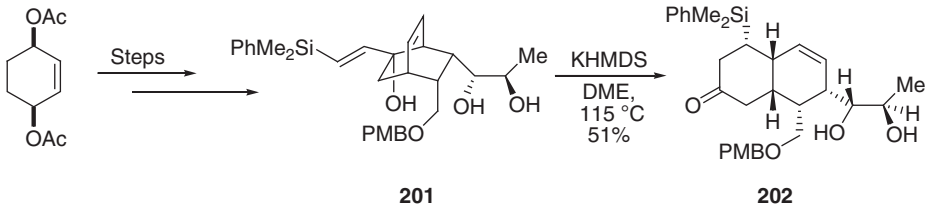
Banwell developed an elegant synthesis of enantiopure *cis*-decalin cores employing the AOC (Scheme 59).[72] Microbially derived *cis*-1,2-dihydrocatechol **198** was transformed into **199** via a straightforward, eight-step reaction sequence including a Diels–Alder reaction. Subjecting **199** to typical AOC conditions gave the *cis*-decalin **200** in 60% yield. Modification of the substrate structure gave access to similar decalins in equally good yields for the last step.

The *cis*-decalin unit of the antitumor macrolides superstolide A and B was generated using an AOC by Jin and coworkers (Scheme 60).[73] Applying a chemoenzymatic desymmetrization approach with *Candida rugosa* lipase, enantiopure **201** was obtained from a *meso*-diacetate. The rearrangement of **201** gave rise to **202** in only moderate yield due to the unprotected diol moiety present in the molecule. When the diol was protected as an acetonide, a base-promoted elimination set in under the rearrangement conditions.

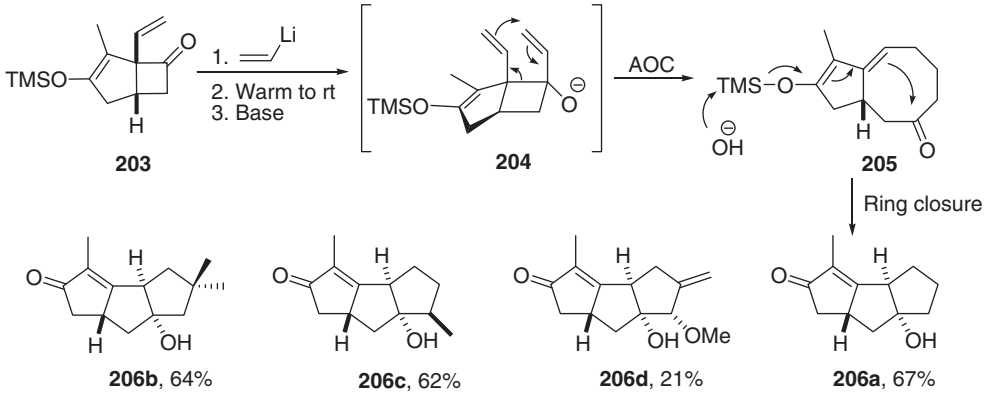
In a series of reports, Moore and coworkers constructed tricyclic polyquinanes in a three-step reaction sequence (Scheme 61).[74] Stereocontrolled *exo*-addition of vinyl lithium to bicyclo[3.2.0]heptenone **203** furnished the alkoxide **204,** which rearranged on



Scheme 59



Scheme 60



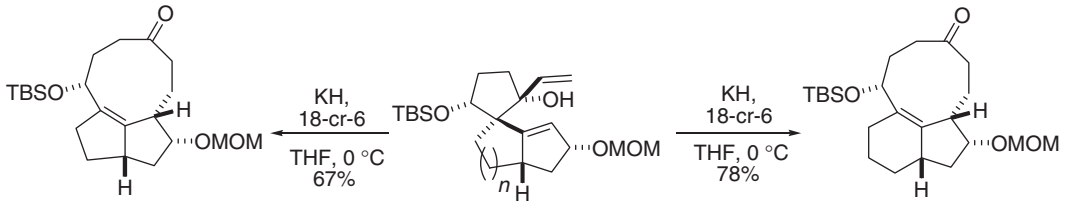
Scheme 61

warming to room temperature to give rise to Cope product **205**. Treatment of **205** with base initiated a transannular vinylogous aldol reaction and formation of the tricyclic ring structure of polyquinane **206a** in 67% overall yield. By variation of the vinyl lithium species, differently substituted polyquinanes **206b-d** could be accessed as well in typically good overall yields.

An extremely rapid AOC was employed in the preparation of the carbocylic ring system of the aquariolide diterpene **208a**. Starting from spirocyclic dienol **207a**, the 5-5-9-ring system of the natural product was obtained in good yield at 0 °C (Scheme 62).[75] Also, the six-membered analogue **208b** could be accessed by this facile oxy-Cope rearrangement.

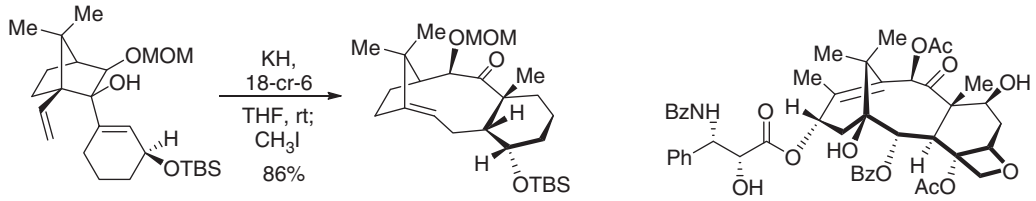
In a series of reports, Paquette and coworkers evaluated the capacity of the AOC for the assembly of potential taxol precursors from different enantiopure starting materials.[76] The tricyclic core structure **210** was obtained in very good yield by the AOC of **209** under very mild reaction conditions followed by the highly diastereoselective trapping of the generated enolate with methyl iodide (Scheme 63).

Likewise, the dicyclopenta[*a,d*]cyclooctene core of the ceroplastin sesterpene was accessed using the AOC (equation 10).[77] On deprotonation, **211** underwent an extremely rapid AOC in only 20 min at room temperature to give the core unit **212** in good yield.



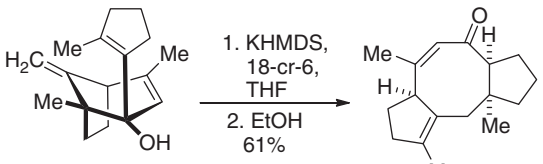
208a, *n*=1 **207a/b** **208b**, *n*=2

Scheme 62



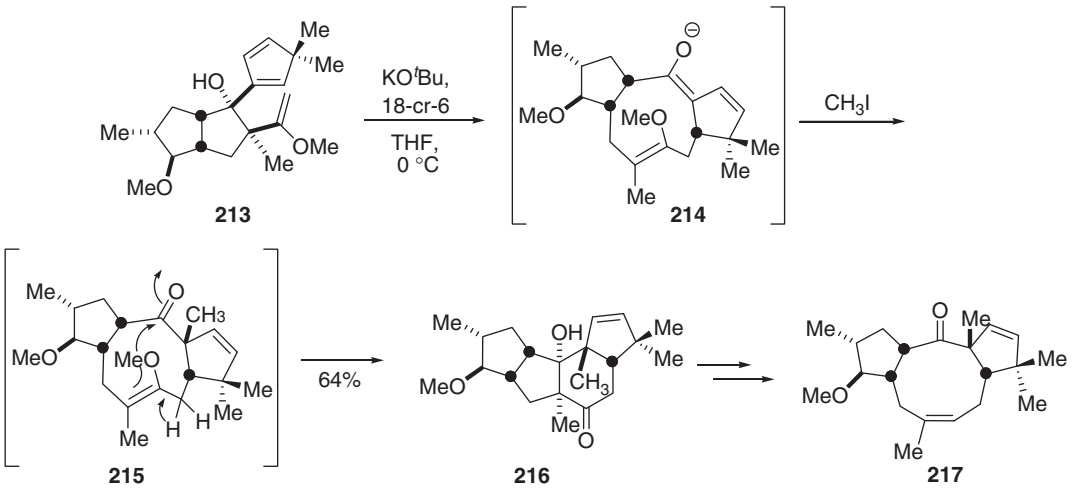
209 **210**

Scheme 63



211 **212** (10)

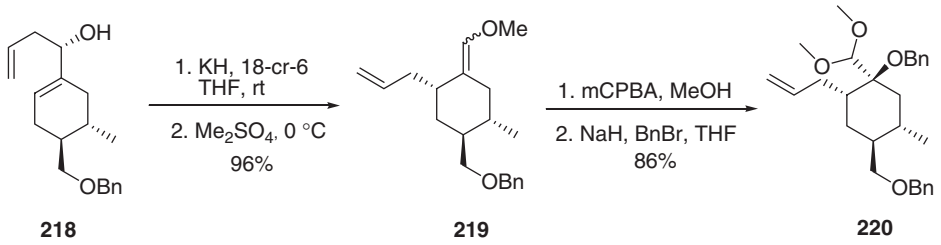
A very impressive example of an AOC embedded in a multiple reaction sequence was demonstrated by the group of Paquette during the assembly of the 5-9-5-tricyclic framework of the diterpenoid natural products, jatrophatrione and citlalitrione (Scheme 64).[78] The rapid AOC of *cis*-1,2-divinylcyclopentanol **213** led to the intermediate enolate **214**, which was stereoselectively alkylated *in situ* with methyl iodide to furnish intermediate **215**. This compound underwent a spontaneous transannular ene cyclization resulting in the tetracyclic 5-5-6-5-scaffold **216** in a remarkable overall yield of 64%. **216** was eventually converted into the desired diterpenoid structure **217** in a four-step sequence.



213 **214** **215** **216** **217**

Scheme 64

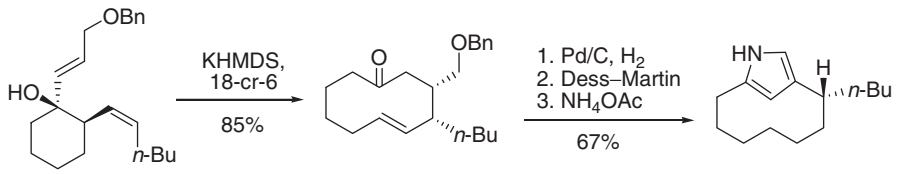
During the total synthesis of the antitumor antibiotic, (–)-okilactomycin, Smith and coworkers rearranged **218** under typical AOC conditions and trapped the intermediate enolate with dimethyl sulfate to obtain **219**, which was further oxidized and benzylated to furnish acetal **220** in excellent overall yield (Scheme 65).[79] A direct oxidation of the intermediate enolate as well as the generated silyl enol ether failed or gave low yields.



218 **219** **220**

Scheme 65

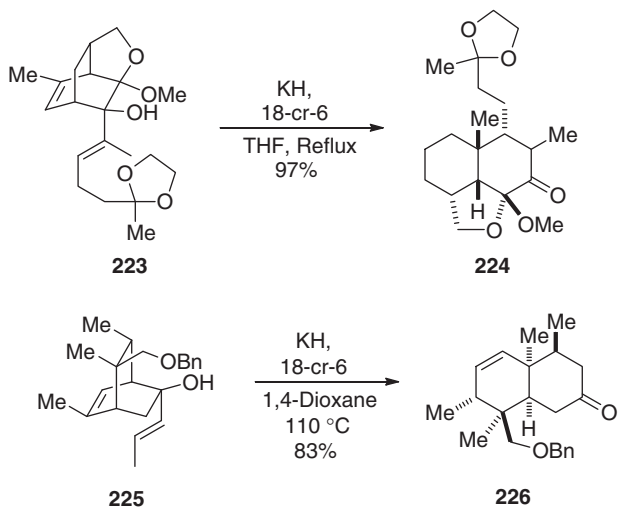
To obtain the crucial 10-membered ring of the prodigiosin alkaloid streptorubin B, Thomson and coworkers utilized an AOC of *trans*-1,2-divinylcyclohexanol **221** to obtain **222** in very good yield and with complete stereochemical transfer (Scheme 66).[80] In a subsequent three-step sequence, they installed the annulated pyrrole ring setting the stage for the endgame of the total synthesis.



221 **222**

Scheme 66

As discussed in Section 5.19.8.4.1, the AOC is often used to generate the decalin core of complex natural products. This methodolody was exploited by Liao and coworkers with the quantitative rearrangement of **223** to give the functionalized decalin derivative **224** in excellent yield, which served as the key intermediate toward the total syntheses of the sesterpenic acids, bilosespenes A and B (Scheme 67).[81] They also applied this methodology to obtain the decalin core structure **226** of another diterpenic acid in very good yield starting from carbinol **225**.[82]

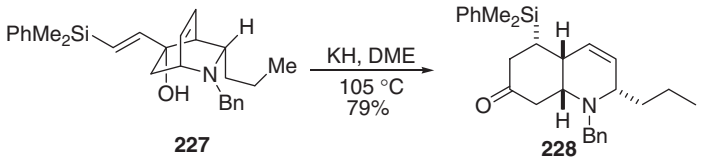


223 **224**

225 **226**

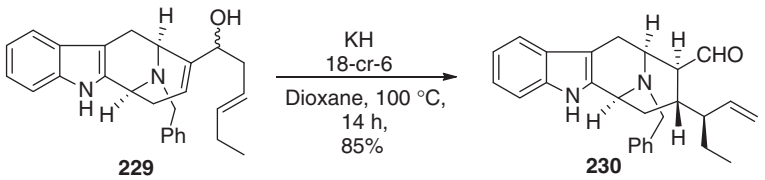
Scheme 67

Heteroanalogues of the decalin core can also be accessed by the AOC as was nicely shown by Polniaszek et al.[83] During the total synthesis of the alkaloids, 195A and 2-*epi*-195B, the azabicyclo[2.2.2]octenol **227** underwent an AOC on treatment with KH and heating in dimethoxyethane to give rise to the decahydroquinolone **228** in good yield (equation 11).



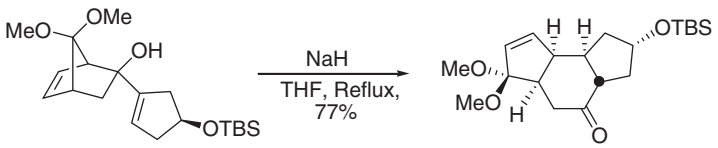
227 228 (11)

In a series of publications, Cook and coworkers demonstrated the usefulness of the AOC for the assembly of ajmaline-related indole alkaloids, which exert interesting biological activities. Refluxing of the potassium alkoxide of **229** in dioxane gave rise to aldehyde **230** in very good yield and complete stereocontrol, from which the total synthesis of (+)-ajmaline was completed in only seven additional steps (equation 12).[84]



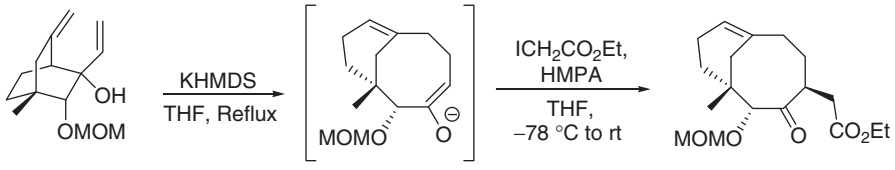
229 230 (12)

Over the past decades, the group of Paquette has made major contributions to the AOC and demonstrated its synthetic potential in numerous syntheses of natural products. The AOC of carbinol **231** served as a key step toward the spinosyn A core structure **232** (equation 13).[85] Interestingly, the use of KH at room temperature led to decomposition and byproduct formation, whereas the use of sodium hydride in refluxing THF allowed for smooth rearrangement. As a consequence of the substantial strain release that came with the dismantling of the norbornene ring, no crown ether needed to be added.



231 232 (13)

A key intermediate toward the total synthesis of the sesquiterpene lactones vulgarolide and deoxocrispolide was obtained by the AOC of **233** to give rise to the intermediate enolate **234** (Scheme 68).[86] Proceeding with remarkable facility, the rearrangement was completed in just 20 min and the generated enolate was trapped with ethyl iodoacetate at low temperature to furnish alkylated **235** with complete diastereoselectivity and with very good yield in two steps.

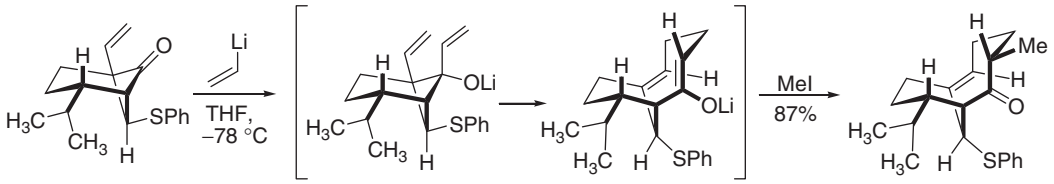


233 234 235, 78%

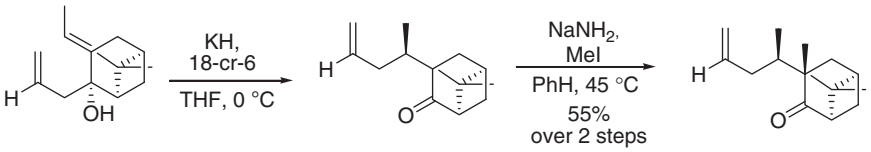
Scheme 68

An even more impressive alkylative trapping of an intermediate enolate was demonstrated by Paquette et al. during their total synthesis of (–)-salsolene oxide.[87] Clean *exo*-addition of vinyl lithium to ketone **236** gave rise to the intermediate alkoxide **237** which, due to its inherent ring strain, spontaneously underwent the oxy-Cope rearrangement to furnish enolate **238** (Scheme 69). The enolate anion was trapped by the addition of an excess methyl iodide to furnish **239** in excellent yield and diastereoselectivity.

In a total synthesis of (+)-nootkatone, Laine and coworkers employed the AOC of **240** to generate ketone **241** (Scheme 70).[88] Trapping of the intermediate enolate species proved to be problematic, forcing them to opt for a two-step approach in which the crude product of the rearrangement was isolated and deprotonated with sodium amide. Alkylation with methyl iodide gave the desired precursor **242** for (+)-nootkatone in good yield over these two steps.



Scheme 69

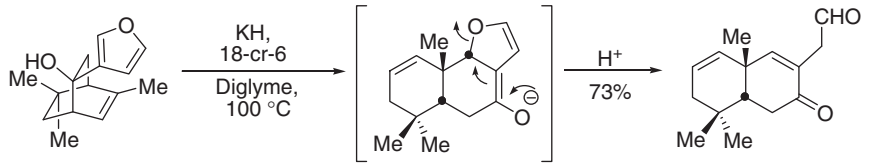


Scheme 70

5.19.8.5 Aromatic Oxy-Cope Rearrangement

For aromatic groups to participate in oxy-Cope rearrangements, the π-electron delocalization has to be disrupted, which makes the sigmatropic process less favorable. Nevertheless, a few examples have been developed in which aromatic systems undergo AOC.

During the total synthesis of (+)-pallescensin A, the group of Paquette employed furyl carbinol **243** in which the furyl moiety was part of the 1,5-diene system (Scheme 71).[89] Elevated temperatures and the use of 18-crown-6 as complexing agent were necessary to promote the sigmatropic process at elevated temperature to furnish the intermediate enolate **244**, which underwent β-elimination of the alkoxide ion to give rise to aldehyde **245**.



Scheme 71

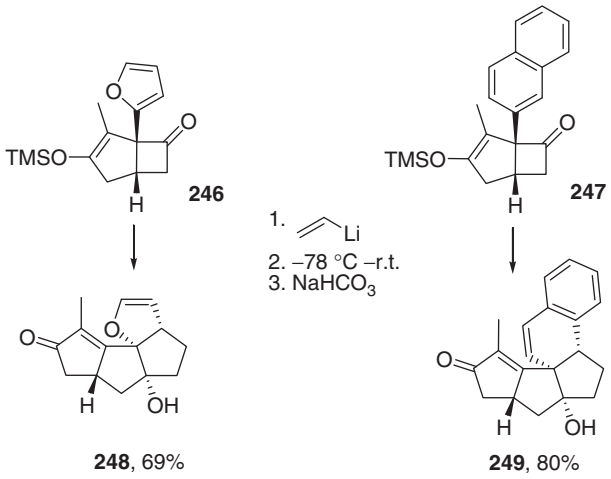
The participation of furyl and naphthyl groups in the AOC was also shown by Moore and coworkers (Scheme 72).[90] They obtained the linear-fused polyquinanes, **248** and **249**, by vinyl lithium addition to the cyclobutanones, **246** and **247**, respectively, and subsequent AOC and transannular ring closure on basic workup (see Scheme 62 for detailed mechanism).

Karikomi and coworkers employed an aromatic AOC to access chiral [5]helicene **252** (Scheme 73).[91] Starting from enantiopure carbinol **250**, the phenanthrene moiety participated in the rearrangement leading to ketone **251** which was aromatized in a four-step sequence to give helicene **252**. The enantiopurity of the product was found to be the same as in the starting material, which showed that the central chirality of **250** was completely transferred into the helical chirality of **252**.

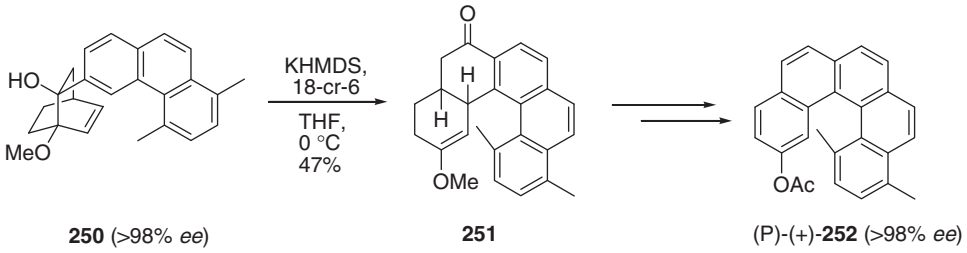
Although the preceding examples involved only one double bond being part of an aromatic system, Huq and coworkers demonstrated that substrates **253** were able to undergo AOC with both double bonds as parts of aromatic systems participating in the sigmatropic process (Scheme 74).[92] On hydrolysis, the intermediate enolate dianion **254** isomerized to give products **255** with a restored aromatic system.

5.19.8.6 DAOC

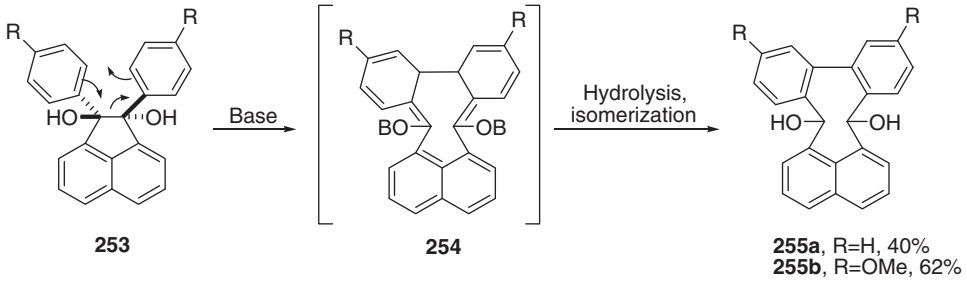
Although known since the early 1980s,[93] doubly charged systems have only recently been increasingly utilized in the dianionic variant of the oxy-Cope rearrangement. The group of Paquette conducted extensive studies on the DAOC of vinyl lithium adducts of squarate esters.[94] When added to squarate esters **256**, the two organometallic additions will furnish two stereoisomers, **257a** and **257b**, with the vinyl substituents in the *trans*- or *cis*-configuration, respectively (Scheme 75). Because only the *cis*-diastereomer is able to undergo the sigmatropic process, a certain level of stereocontrol of the second addition was achieved by incorporation of



Scheme 72

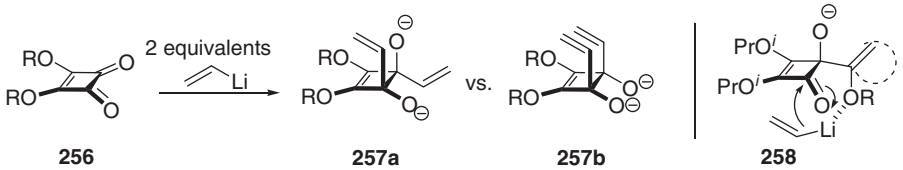


Scheme 73



Scheme 74

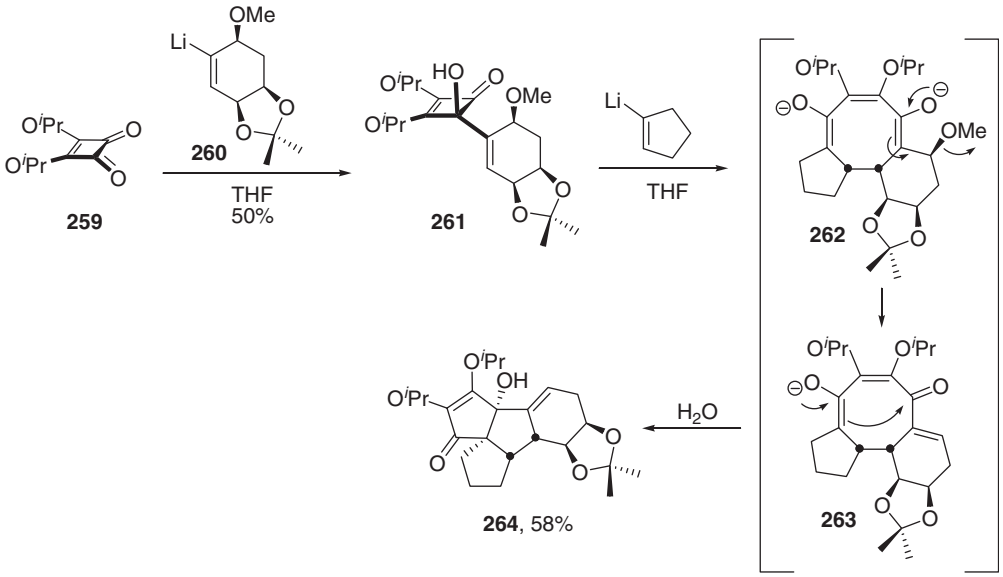
an ether oxygen substituent in the first organometallic reagent, which served to direct the second vinyl lithium equivalent as shown in **258**.



Scheme 75

Addition of one equivalent of the optically pure organolithium reagent **260** to squarate ester **259** gave 50% of the monoadduct **261**, which could easily be separated from the diastereomeric adduct by chromatography (Scheme 76).[95]

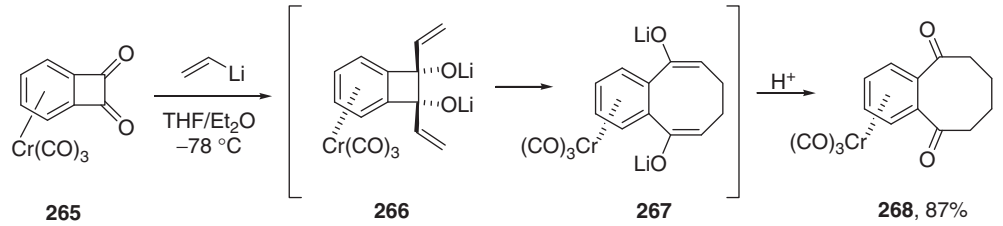
Treatment of **261** with an excess of cyclopentenyllithium preferentially gave the *cis*-adduct, which underwent DAOC to dienediolate **262** followed by *β*-elimination to give ketone **263**, which was then attacked in a transannular aldol reaction by the



Scheme 76

second enolate present to furnish the highly functionalized polyquinane **264** in good overall yield and complete transfer of chirality over the cascade sequence.

Butenschön and coworkers used the arenetricarbonylchromium(0) complex **265** to selectively obtain the *cis*-adduct **266** on addition of an excess of vinyl lithium (Scheme 77).[96] The bulky tricarbonylchromium moiety was effectively shielding one side of the molecule, allowing for nucleophilic attack of both vinyl groups only from the other face. The *in situ*-generated *cis*-configured dianion underwent spontaneous DAOC to give rise to dienediolate **267**, which on hydrolysis was converted into diketone **268** in very good overall yield.

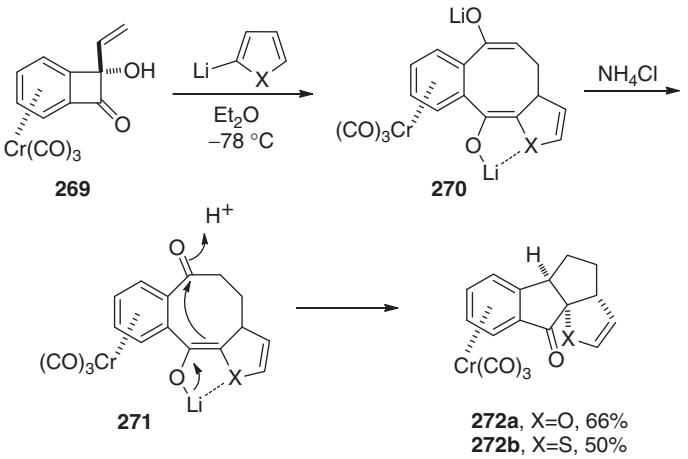


Scheme 77

Interruption of the organolithium addition at the stage of the monoadduct **269** and subsequent treatment of the resulting product with a variety of organolithium reagents contributed to the diversity of this approach. In a special example, a lithiated furane or thiophene was added to **269** to obtain the intermediate dienediolate **270**, accounting for the first example of a DAOC in which an aromatic system was involved (Scheme 78).[97] The heteroatom present in the furan and thiophene ring stabilized the neighboring enolate such that controlled hydrolysis under mild conditions led to ketone **271**, which was then engaged in a transannular aldol reaction to give rise to the polycyclic scaffolds **272a/b** in good overall yields.

5.19.9 Conclusions

The Cope rearrangement of 1,5-dienes is among the most fundamental C–C bond-forming reactions currently available to synthetic chemists. It is unique in forming C–C σ-bonds between unfunctionalized carbon centers in a highly stereospecific and predictable manner. It creates stereogenic centers and stereogenic double bonds with high fidelity in chair-like transition states whenever they are geometrically accessible. A wealth of theoretical investigations have recently shed light on the mechanism of the Cope rearrangement and on the exact nature of the transition state in particular. Taking advantage of the inherent strain in small rings, the Cope rearrangement is among the most useful and versatile methods to access medium size rings starting from *cis*-1,2-divinyl-substituted cyclopropanes and cyclobutanes as the substrates. Coupled with asymmetric enolate-based reactions, conjugation-driven Cope rearrangements have been successfully employed in the context of acyclic stereocontrol. The oxy- and



Scheme 78

anionic oxy-Cope variants proceed under much milder conditions and have proven highly useful in the synthesis of polycyclic natural products. A large number of total syntheses of complex natural products have relied on the power of the AOC in particular.

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5.20 Claisen Rearrangements

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Glossary

Chiral auxiliary Asymmetric fragment that is temporarily incorporated into an organic compound so that a subsequent synthetic step can be carried out asymmetrically. Out of the two possible enantiomers, only one will be selectively obtained after removal of the original auxiliary in a third step of the synthetic sequence.

Chiral ligand Enantiomerically pure organic compound which is used in combination with a metal atom producing a chiral catalyst for asymmetric synthesis. The ligand chirality is transferred to the reaction product, which as a result is obtained enantioselectively.

Enantioselectivity Degree to which one enantiomer of a chiral product is preferentially produced in a reaction, as a consequence of the presence of an additional source of chirality.

Organocatalyst Organic compound capable of increasing the rate of a chemical reaction either by temporary covalent binding or by noncovalent interactions with the substrate.

Pericyclic This term is applied to concerted reactions wherein the transition state has a cyclic geometry and multiple carbon–carbon bond-making and -breaking events take place.

Sigmatropic rearrangement Type of organic intramolecular pericyclic reactions wherein the carbon skeleton of the substrate is transformed in a structural isomer by way of a σ-bond migration from one terminus of a π-bonded system to its more distant terminus with simultaneous shift of the π system.

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5.20.1 Introduction

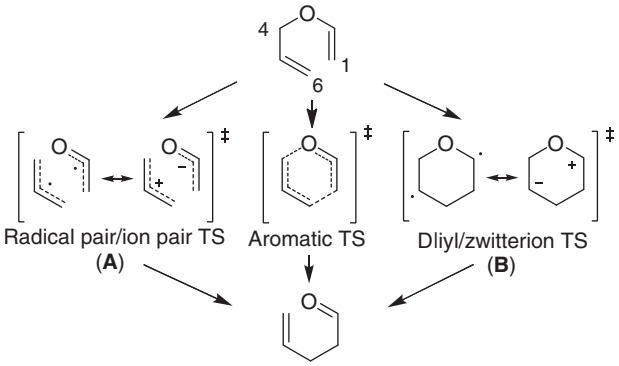
In 1912, Rainer Ludwig Claisen discovered the intramolecular rearrangement of an allylic fragment from the O-position of β-naphthol to the vicinal C-position of the arene.[1] Soon, it was evident that the scope of the reaction was far beyond the use of aryl vinyl ethers. Additionally, the highly ordered transition state involved allowed predicting the stereochemical outcome of the process. These features, along with the good availability of the starting materials, established the rearrangement as a powerful tool for the synthesis of new complex structures. Consequently, many aspects related to mechanism, reaction conditions, asymmetric variants, and synthetic applications have been extensively reviewed.[2]

A century later, this chapter is aimed to cover the most relevant advances in the Claisen rearrangement since the publication of the first edition of *Comprehensive Organic Synthesis* (*COS*) in 1991.[2g] However, this overview is not intended to be exhaustive, so not all the relevant examples are included. The first part of the chapter deals with methods for the preparation of allyl vinyl ethers, as well as mechanistic and kinetic aspects of the Claisen rearrangement with special attention on the use of catalysts. In this section, only the use of achiral catalysts is covered as the catalyzed asymmetric rearrangement is discussed later in the chapter. Next, different [3,3]-sigmatropic rearrangements closely related to the title reaction are presented. The second part of this overview is focused on the stereoselective version of the rearrangement. Two approaches to control the stereoselectivity of the reaction have been considered depending on whether the elements of stereocontrol are embedded in the allyl vinyl ether moiety (intra-annular stereoselectivity) or are external to it (extra-annular stereoselectivity). A significant part of this section refers to recent diastereo- and enantioselective approaches in which the stereoselectivity of the reaction can be controlled by a remote stereocenter covalently bonded to the allyl vinyl ether moiety or by a chiral catalyst. Examples of the synthesis of natural or biologically active compounds are shown in each section. Due to the wealth of data, sections concerning the photo,[3] aza,[4] zwitterionic amino,[5] thia,[6] phospha,[7] and metallo[8] as well as retro-Claisen rearrangements[9] have been omitted. Tandem processes involving Claisen rearrangements are covered in a different chapter (*see* Chapter 5.21). Literature examples were mostly taken from reports published between 1991 and 2012, in order to provide information that is complementary to the first edition of *COS*.

5.20.2 Aliphatic Claisen Rearrangement

5.20.2.1 Mechanistic Overview

The term 'aliphatic Claisen rearrangement,' which describes the thermal isomerization of an allyl vinyl ether into a γ,δ-unsaturated carbonyl compound, is applied to a $[\pi^2s + \sigma^2s + \pi^2s]$ reaction proceeding through a six-membered cyclic transition state,[1] classified as a [3,3]-sigmatropic rearrangement following the Woodward–Hoffmann rules[10] and frontier orbital theory.[11] The initially postulated aromatic transition state for the rearrangement, involving concerted and synchronous σ- and π-type 2p overlappings of both allylic fragments of the substrate,[12] has been thoroughly revised over the years. Studies of the secondary kinetic deuterium isotope effects on the σ-bond dissociation and the new σ-bond formation during the rearrangement revealed two nonaromatic alternate structures for the transition state (**Scheme 1**),[13] an oxoallyl–allyl radical pair, also represented by an ionic pair (**A**), and a 1,4-diyl or zwitterionic intermediate (**B**). An early dissociation of the C4–O bond produces pair **A**, whereas intermediate **B** results from an advanced C1–C6 bond formation. Kinetic studies demonstrated a large extent of C4–O bond dissociation in the transition state, thus favoring the radical-pair structure **A**,[14] in accordance with the similarly dissociative transition state postulated for the enzymatic [3,3]-sigmatropic rearrangement of chorismic acid to prephenic acid.[15] Numerous theoretical calculations predicting similar plausible structures for the transition state of the aliphatic Claisen rearrangement have been reported.[16,17]



Scheme 1

A three-step pathway for the rearrangement has been proposed from the observation of the molecular changes occurring during the reaction on vibrational excitation in the electronic ground state by a stimulated Raman process.[18] The initial formation of a bis-allyl-like intermediate as a result of the C4–O-bond weakening is followed by incipient formation of a C1–C6 bond giving

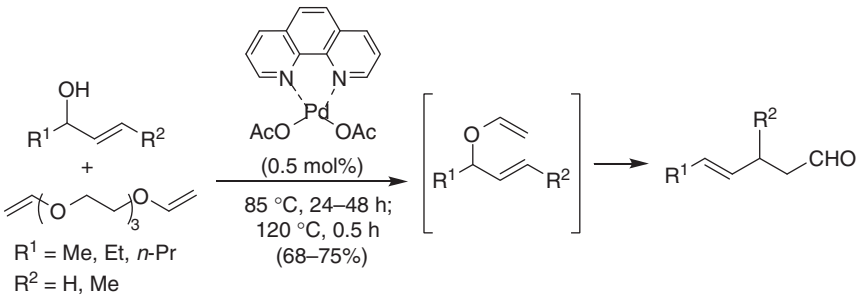
an aromatic-like intermediate species. In a third step, the rearrangement product is obtained after the simultaneous C4–O-bond breaking and C1–C6-bond formation.

Recently, the comparison of the experimental $\Delta G^{\neq}$ values for different aliphatic Claisen rearrangements with the benchmark calculated free energy barriers for the gas-phase reactions provided a calculated structure for the transition state,[19] which closely resembles the fairly dissociative structure postulated on the basis of kinetic isotope effects.[20]

Regarding the only two permitted conformations for the six-membered cyclic transition state of a *supra–supra* process (i.e., chairlike and boatlike geometries), both theoretical methods[16,21–23] and the experimentally observed asymmetry transfer from the π-bonds of the substrate to the new σ-bond of the product clearly suggest that the chairlike transition state is lower in energy than the analogous boatlike transition state.

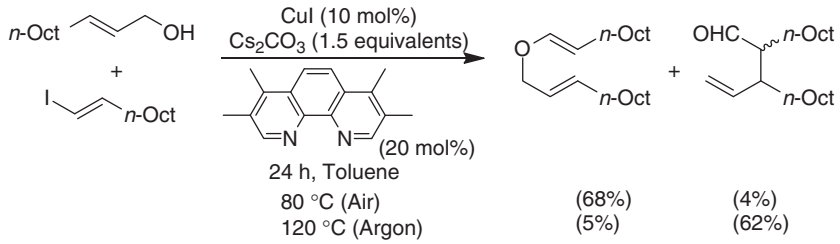
5.20.2.2 Synthesis of Allyl Vinyl Ethers

The initially reported methods for the preparation of allyl vinyl ethers consisted of either the acid- or base-promoted cleavage of allyl ketals,[24,25] or a mercury-catalyzed transfer of a vinyl group from vinyl ethers to allylic alcohols.[26–29] The usually low yields reported for the above protocols along with the high toxicity of mercury(II) salts prompted the development of improved approaches to the synthesis of allyl vinyl ethers. *O*-vinylation reaction of allylic alcohols with commercial triethyleneglycol divinyl ether was proved to be successful for the preparation of allyl vinyl ethers, which *in situ* rearranged into γ,δ-unsaturated aldehydes (Scheme 2).[30]



Scheme 2

O-allylation reactions have also been used for the preparation of allyl vinyl ethers.[31] Perhaps, one of the most attractive new protocols for the synthesis of allyl vinyl ethers involves metal-promoted C–O coupling reactions. The copper-catalyzed coupling reaction of a vinyl halide and an allylic alcohol under Ullmann-type conditions in the presence of tetramethyl-1,10-phenanthroline afforded a method for the synthesis of allyl vinyl ethers, which could be isolated or, if desired, directly transformed into the Claisen products on changing the reaction temperature (Scheme 3).[32]



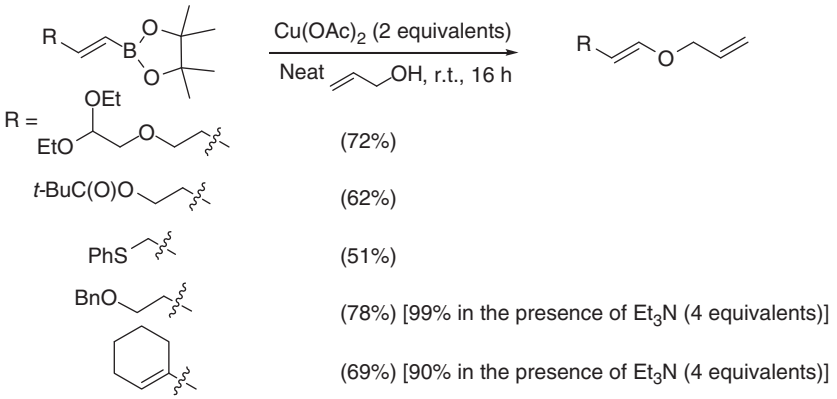
Scheme 3

The $Cu(OAc)_2$-promoted coupling reaction of pinacol vinyl boronates and allylic alcohols has been developed as a mild and functional-group-tolerant method for the synthesis of isolable allyl vinyl ethers. The addition of a tertiary amine to the reaction medium proved beneficial (Scheme 4).[33]

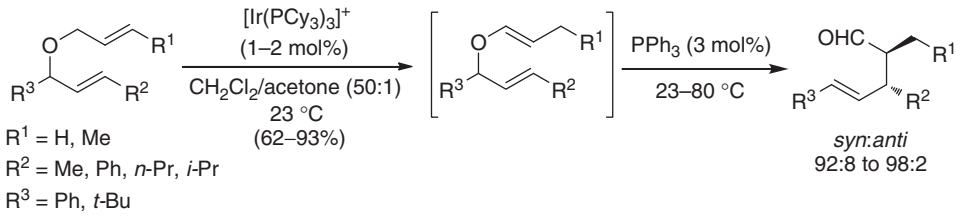
Although different Ni(0)-,[34] Ru(II)-[35] and Ir(I)-based[36–38] complexes have been described as catalysts for the isomerization of bis(allyl) ethers, the resulting allyl vinyl ethers are usually not easily isolable but rearrange *in situ* to the γ,δ-unsaturated aldehydes (Scheme 5).[36]

The 1,4-elimination reaction of 1-allyloxy-4-methoxy-(2*Z*)-alkenes with *n*-butyllithium is a general method for the stereoselective preparation of allylic (1*Z*,3*E*)-dienyl ethers, which can be transformed into the Claisen products on treatment with an organoaluminum reagent (Scheme 6).[39]

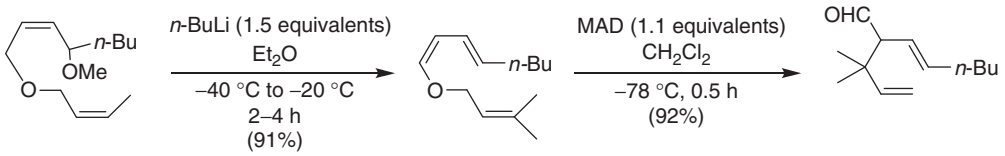
Cyclic allyl vinyl ethers (3,4-dihydro-2*H*-1,4-oxazines) have been prepared by $PtCl_2$-catalyzed isomerization of alkynyl epoxides, and were further converted to piperidine derivatives by Claisen rearrangement (Scheme 7).[40]



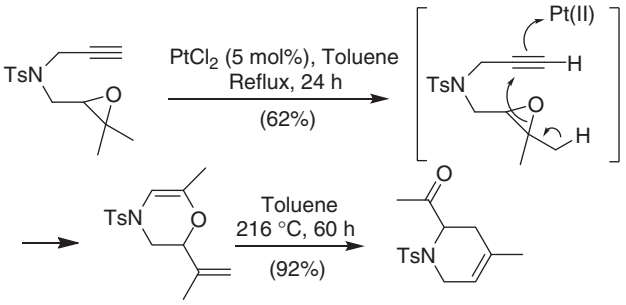
Scheme 4



Scheme 5



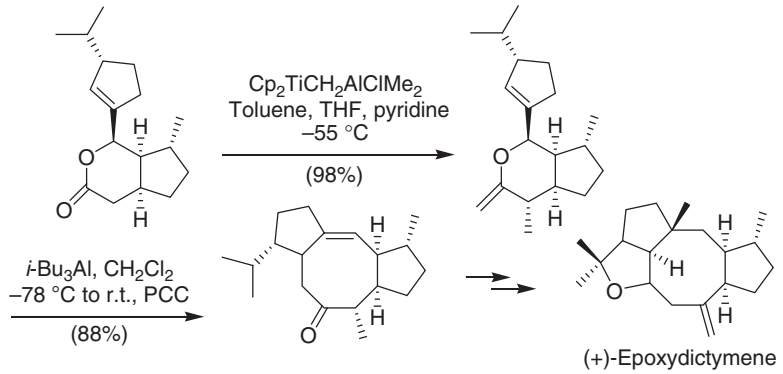
Scheme 6



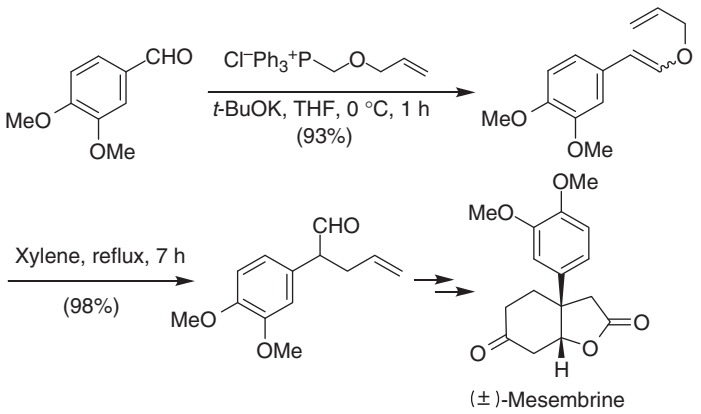
Scheme 7

Olefination reactions have also been traditionally used for the construction of allyl vinyl ethers. In this sense, the use of the Tebbe reagent ($Cp_2Ti(\mu\text{-}CH_2)(\mu\text{-}Cl)AlMe_2$) has provided good yields from allyloxy carbonyl compounds.[41–43] This was the method of choice for the preparation of the substrate which underwent an aluminum-promoted Claisen rearrangement, described as the key step in the total synthesis of the diterpene (+)-epoxydictymene (Scheme 8).[44]

Wittig olefination of carbonyl derivatives with allyloxy triphenylphosphonium chloride afforded isolable allyl vinyl ethers.[45] This protocol provided the starting material for the thermal Claisen rearrangement utilized as a key step in the synthesis of the alkaloid (±)-mesembrine (Scheme 9).[46]



Scheme 8



Scheme 9

5.20.2.3 Kinetic Aspects of the Aliphatic Claisen Rearrangement

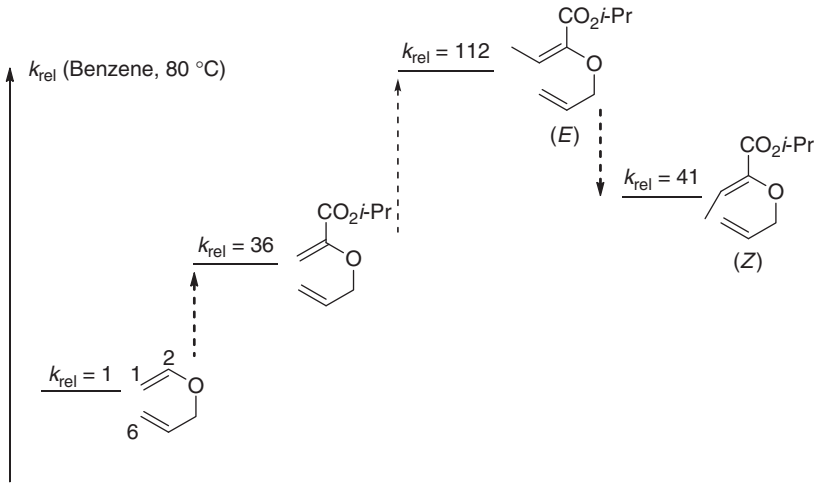
5.20.2.3.1 Influence of substituents on the rearrangement rate

The effect of disparate functional groups installed at different sites of the allyl vinyl ether on the rearrangement rate has been thoroughly examined. Depending on the predominant electron-withdrawing (or donating) character or the radical-stabilizing properties of the groups, as well as their position at the substrate skeleton, different structures for the transition state of the rearrangement, ranging from the radical pair **A** to the diyl structure **B** (Scheme 1), have been proposed. Electron-withdrawing cyano[47,48] and trifluoromethyl[49] groups, as well as electron-donor alkoxy[50] and trialkylsiloxy[51–54] substituents, have received particular attention in the literature. In general, a marked accelerating influence on the reaction rate has been reported for both electron-donor and electron-acceptor substituent positions at C2 and C4 of the allyl vinyl ether framework. These results have been confirmed by a number of theoretical calculations.[55]

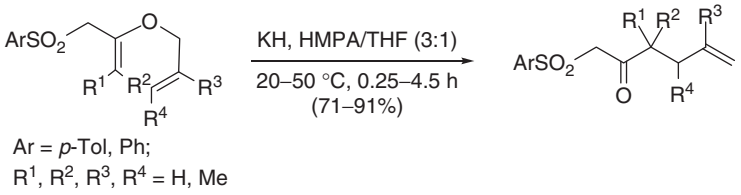
The accelerating role played by an alkoxycarbonyl group at C2 in the kinetics of the Gosteli–Claisen rearrangement[56] has been evidenced by computational studies.[57] Thus, a 36-fold rate acceleration by such a group was reported. The presence of one or more electron-donor alkyl groups at C1, C6, or both amplified the effect on the rate, in particular for *E*-configured substrates (Scheme 10).

The theoretically predicted positive effect of electron-donor substituents at C2 on the rate of the aliphatic Claisen rearrangement[58] was experimentally verified with substrates having a sulfur[59] or phosphorus[60,61] stabilized carbanionic center bonded to C2 of allyl vinyl ethers. These studies gave rise to the so-called carbanionic Claisen rearrangement, which affords γ,δ-unsaturated ketones regioselectively under unusually mild conditions, which are attributed to the π-donor effect of a carbanion. Arylsulfonyl groups are the only sulfur-based anion-stabilizing groups capable of accelerating the rearrangement (Scheme 11). The use of potassium hydride as the base in neat hexamethylphosphoramide (HMPA) as the solvent gave the best results, since these conditions maximized the charge on the carbanionic atom.

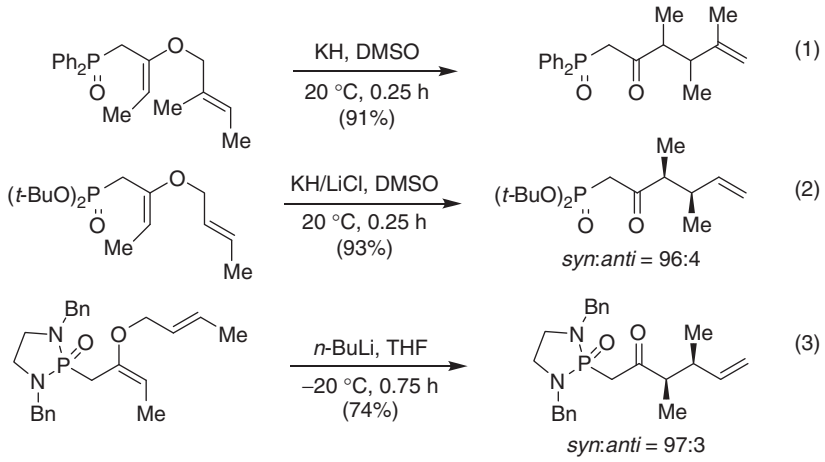
Different phosphorus-based groups have also been reported as anion-stabilizing functions capable of accelerating the Claisen rearrangements. Thus, phosphine oxides (Scheme 12, equation 1),[60] phosphonates (Scheme 12, equation 2),[60] and



Scheme 10



Scheme 11



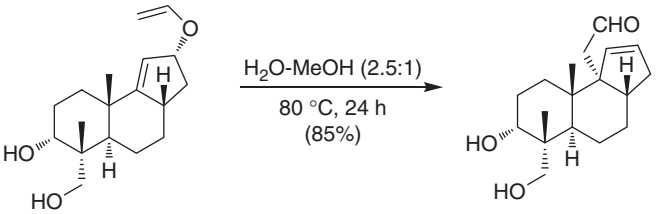
Scheme 12

phosphonamides (Scheme 12, equation 3)[61] stabilize a carbanionic charge on a carbon atom bonded to the C2 position of the substrates, producing a large acceleration of the Claisen rearrangement (Scheme 12).

5.20.2.3.2 Influence of solvents and temperature on the rearrangement

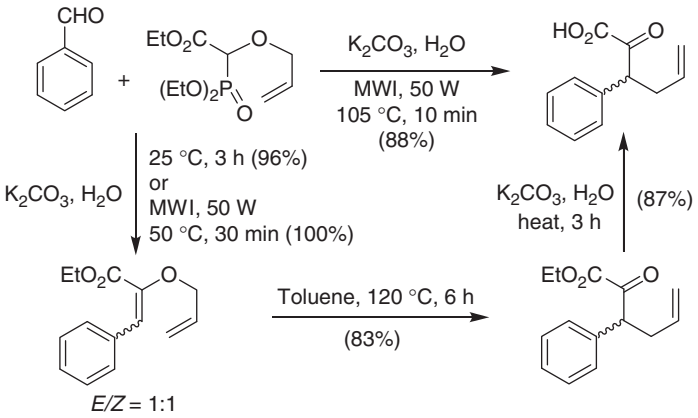
The role of solvents in the aliphatic Claisen rearrangement has been largely examined over the years. Experimental data[15,62–64] and theoretical calculations[65,66] have shown the positive effect of water on the rate of the reaction. This effect has been attributed to hydrophobic interactions and to the hydrogen-bond donating properties of water, as well as to the contribution of solvent polarization to the activation energy of the rearrangement.[67] Sometimes, the addition of small amounts of a cosolvent (typically methanol or dimethyl sulfoxide) facilitates the solubility of the substrate. The Claisen rearrangement reported as the key step in

the synthesis of aphidicolin proceeded with poor yield (20%) under gas-phase thermal conditions, whereas the Claisen product was obtained in an 85% isolated yield in water–methanol (Scheme 13).[68]



Scheme 13

Microwave irradiation (MWI) has also proved to be beneficial for the thermal rearrangement, the synthetic potential of which has been broadly demonstrated in the synthesis of natural and unnatural products.[69] The benefits of MWI are evident from multistep sequences wherein a Claisen rearrangement is one of the involved reactions (*see* Chapter 5.21). The tandem three-step, one-pot Horner–Wadsworth–Emmons olefination/Claisen rearrangement/hydrolysis sequence described in water under MWI for the synthesis of homoallylic α-ketoacids[70] was clearly more advantageous than the stepwise conventional sequence (Scheme 14).



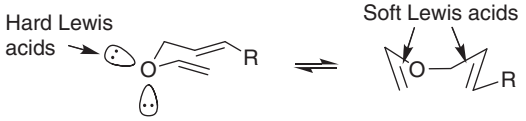
Scheme 14

5.20.2.3.3 Catalyzed aliphatic rearrangements

A marked enhancement of the rearrangement rate may be achieved in the presence of catalysts under mild experimental conditions. The use of both metal catalysts and organocatalysts has been reported to this end.

5.20.2.3.3.1 Metal catalysis

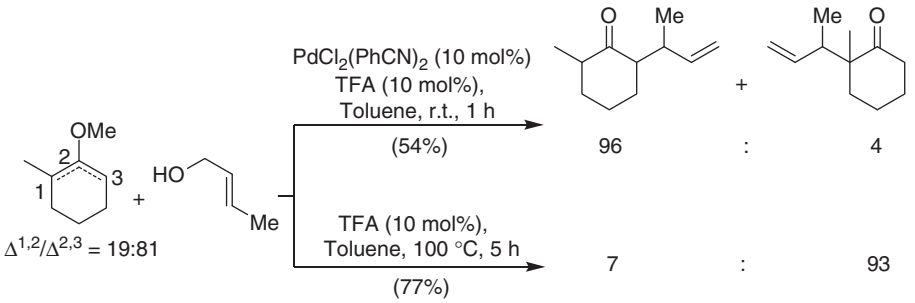
The Claisen rearrangement is efficiently catalyzed by Lewis acids through metal coordination to either one of the lone electron pairs at the oxygen atom or simultaneously to the allyl and vinyl double bonds (Scheme 15). Hard Lewis acids prefer the oxygen electron pair as the coordination site, and a chairlike transition state is predominant in the rearrangement. Contrarily, soft Lewis acids (typically, Hg(II)- and Pd(II)-based acids) usually coordinate to both π-bonds of the substrate, which behaves as a bidentate ligand adopting a boatlike geometry in the favored transition state of the rearrangement.



Scheme 15

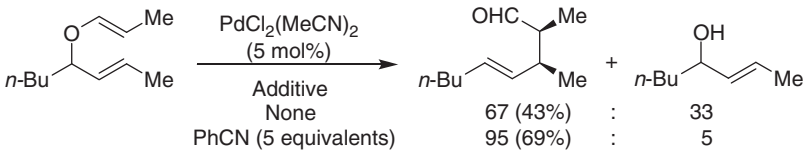
Since the initial report of $PdCl_2(CH_3CN)_2$-promoted aliphatic Claisen rearrangements,[71] many examples describing the use of catalysts based on Pd(II) have been published. The stereochemical outcome of all of them has been explained in terms of a

marked preference for the boatlike transition state.[72–75] Additionally, Pd(II)-catalyzed rearrangements were reported to provide different regioselectivities to those obtained by noncatalyzed thermal rearrangements. These different results were attributed to the different rates of the rearrangement of the less and the more substituted enol allylic ethers, which are interconvertible in the presence of the Pd-catalyst (Scheme 16).[76]



Scheme 16

The low yields reported for the Pd(II)-catalyzed Claisen rearrangement of α-unsubstituted allyl vinyl ethers, which are due to undesired hydrolysis as a side reaction,[77] have been improved in the presence of PhCN or *i*-PrCN as additives capable of limiting the formation of the allylic alcohol (Scheme 17).[78]

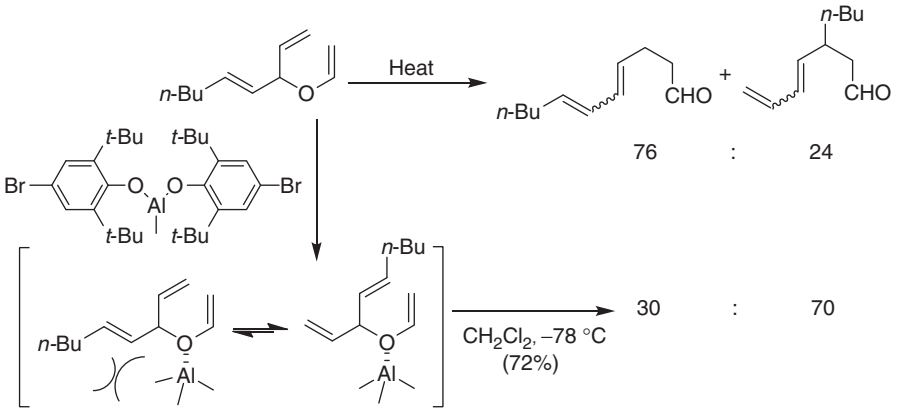


Scheme 17

The rearrangement of aliphatic allyl vinyl ethers proceeds under mild conditions in the presence of aluminum Lewis acid catalysts. The use of Et_2AlSPh or Et_2AlCl-PPh_3 produces the corresponding γ,δ-unsaturated aldehydes or ketones in moderate to good yields.[79]

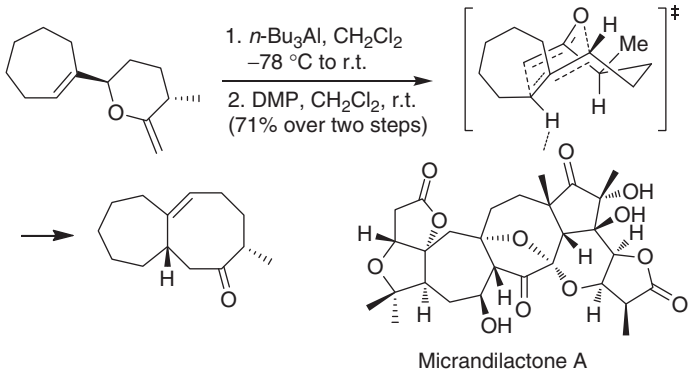
The stereoselectivity of the Al-catalyzed rearrangements clearly demonstrates the marked preference of the organoaluminum reagents for selective coordination to one of the oxygen electron lone pairs, favoring a chairlike conformation for the transition state of the reaction, as will be discussed later in this chapter.

This coordination mode was also responsible for the observed inversion in the regioselectivity of the rearrangements of bisallyl vinyl ethers, which thermally reacted preferentially through the less substituted allylic double bond, but gave the opposite regioisomer under aluminum catalysis (Scheme 18).[80]



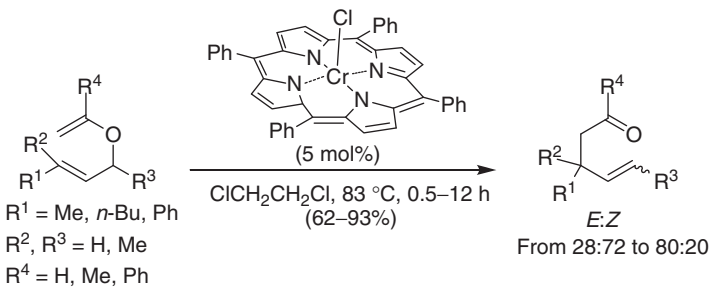
Scheme 18

The central 7–8 fused bicyclic core of the nortriterpenoid micrandilactone A was constructed by a mild *i*-Bu_3Al-catalyzed Claisen rearrangement via a chairlike transition state (Scheme 19).[81]



Scheme 19

The catalytic activity of Cu(II), Sn(IV), and Ti(IV) Lewis acids in the Claisen rearrangement has also been examined.[28] However, the synthetic applicability of these species is restricted because practically equimolecular mixtures of [1,3]- and [3,3]-rearrangement products were formed. Improved levels of regioselectivity in the Claisen rearrangement of allyl vinyl ethers were achieved in the presence of catalytic amounts of a metalloporphyrin, Cr(TPP)Cl. The complete regioselectivity of the reaction was attributed to the concerted nature of the rearrangement under weak Lewis acid catalysis, capable of depressing the formation of ionic intermediates (Scheme 20).[82]



Scheme 20

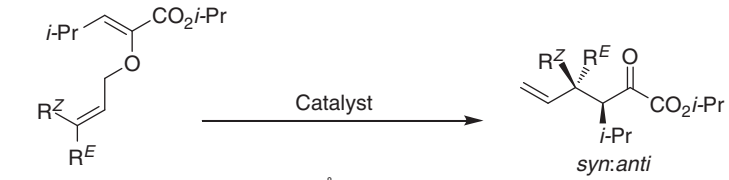
Different Lewis acids such as $Cu(OTf)_2$,[83] $Yb(OTf)_3$,[83] $Bi(OTf)_3 \cdot 4H_2O$,[84] and $MgCl_2$[85] have been reported to catalyze the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers, with disparate *anti*/*syn* selectivities (Scheme 21). Thus, (*Z*,*Z*)-configured substrates afforded high levels of *syn*-selectivity, whereas (*Z*,*E*)-configured allyl vinyl ethers reacted with practically no selectivity.

5.20.2.3.3.2 Organocatalysis

Hydrogen bonding stabilization of the transition state has been described as responsible for the reported organocatalytic acceleration of different Claisen rearrangements. Thus, a marked enhancement of the rate was described for the rearrangement of electron-donor-substituted allyl vinyl ethers (Scheme 22).[86,87]

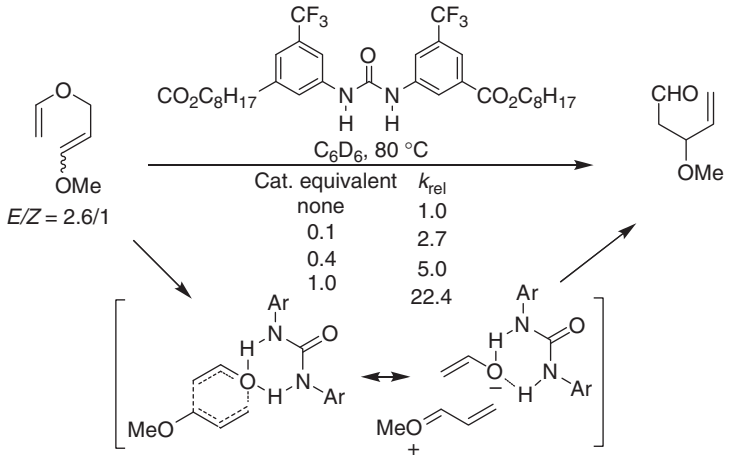
1,3-Bis[3,5(trifluoromethyl)phenyl]thiourea failed to catalyze the rearrangements of 2-alkoxycarbonyl-substituted allyl vinyl ethers.[88] However, an *N*,*N*′-diphenylguanidinium salt induced substantial rate enhancement in the rearrangement of differently substituted allyl vinyl ethers, probably due to the stabilization of the transition state by hydrogen bonding (Scheme 23).[89]

A bisamidinium catalyst was also capable of accelerating the rearrangement of a 2-trifluoromethyl allyl vinyl ether (Scheme 24).[90] The transition state stabilization by the formation of a double hydrogen bond between the catalyst and the oxygen atom of the substrate was invoked as responsible for the observed rate enhancement.

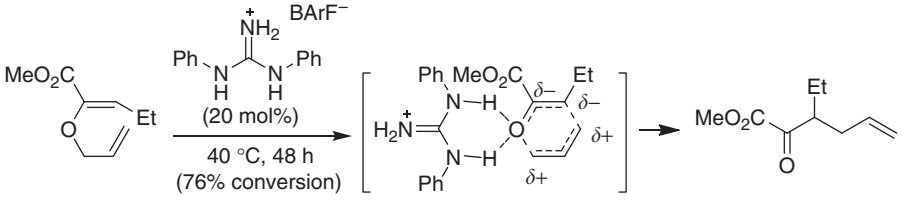


R^Z = *n*-Pr; R^E = H	*$Cu(OTf)_2$, 3 Å MS, CH_2Cl_2 25 °C, 24 h (99%)	93:7
	*$Yb(OTf)_3$, 3 Å MS, CH_2Cl_2 25 °C, 24 h (99%)	91:9
	*$Bi(OTf)_3{\cdot}4H_2O$, toluene 25 °C, 2–25 h (78%)	98:2
R^Z = H; R^E = *n*-Pr	*$Cu(OTf)_2$, 3 Å MS, CH_2Cl_2 25 °C, 24 h (97%)	55:45
	*$Yb(OTf)_3$, 3 Å MS, CH_2Cl_2 25 °C, 24 h (95%)	69:31
	*$Bi(OTf)_3{\cdot}4H_2O$, toluene 25 °C, 2–25 h (82%)	59:41

Scheme 21



Scheme 22

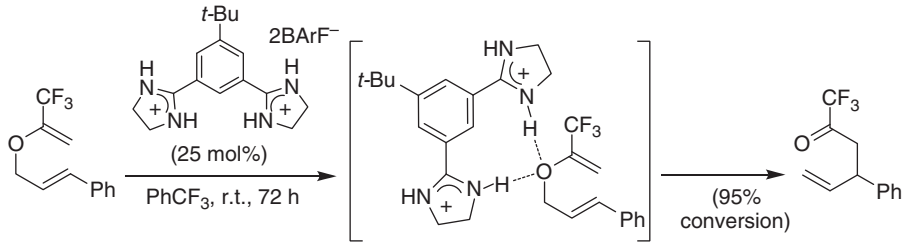


Scheme 23

5.20.3 Other [3,3]-Sigmatropic Rearrangements

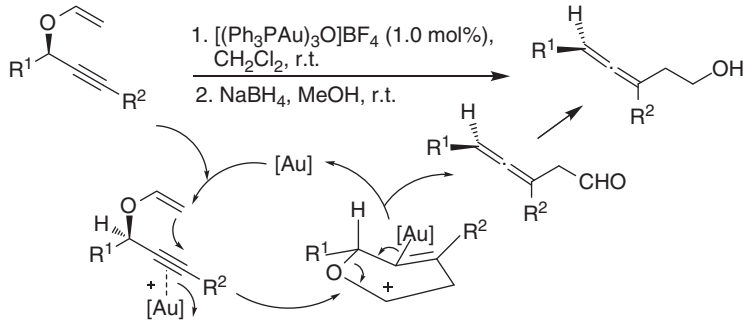
5.20.3.1 Aliphatic Claisen Rearrangement of Propargyl Vinyl Ethers

Propargyl vinyl ethers have also been reported to undergo [3,3]-sigmatropic rearrangements, usually under catalytic conditions. The synthetic utility of the resulting allene derivatives is frequently evidenced by their straightforward transformations into a



Scheme 24

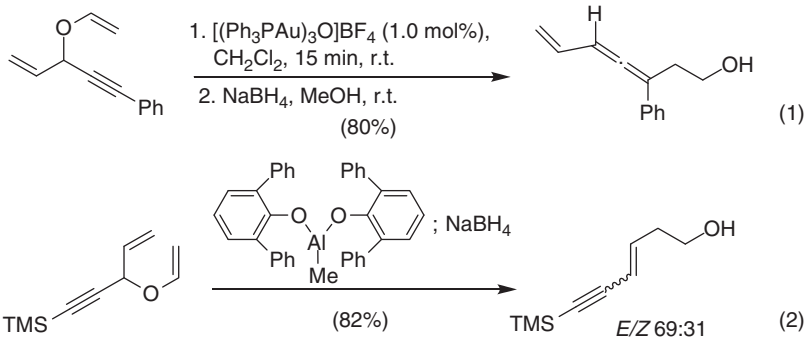
variety of organic arrays. A series of propargyl vinyl ethers underwent smooth Claisen rearrangement in the presence of catalytic amounts of the gold-oxo complex $[(Ph_3PAu)_3O]BF_3$.[91] The addition of $NaBH_4$ to the reaction medium afforded homoallenic alcohols in high yields. When starting from enantiomerically enriched propargyl vinyl ethers, the central chirality of the carbinol was effectively transferred to the axial chirality in the allene product (**Scheme 25**). Surprisingly, under Ph_3PAuBF_4 catalysis, no chirality transfer was detected and the rearranged product was almost racemic. The catalytic system $Ph_3PAuOTf$, in turn, produced erosion in the yield because of competing [1,3]-rearrangement. The proposed mechanism involves a 6-*endo-dig* addition of the enol ether portion onto the gold(I)–alkyne complex and subsequent Grob-type fragmentation, affording the *β*-allenic aldehyde and the regeneration of the Au(I) catalyst.



Substrate *ee* (%)	Yield (%)	*ee* (%)
R^1 = Ph; R^2 = H (92)	78	88
R^1 = Me; R^2 = $-(CH_2)_3Ph$ (79)	84	77
R^1 = Ph; R^2 = $SiMe_3$ (92)	98	92

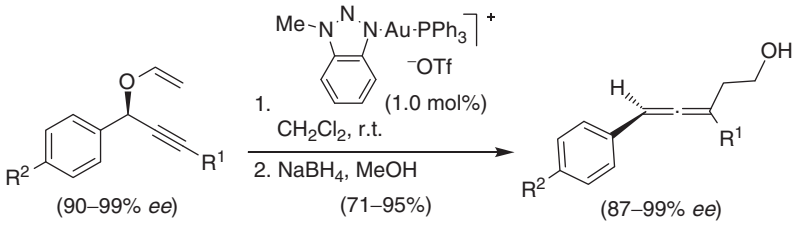
Scheme 25

Vinyl ethers capable of reacting either via allylic or propargylic Claisen rearrangement exhibit a high selectivity for the acetylenic pathway under Au(I)-catalyzed conditions (**Scheme 26**, equation 1). Contrarily, reactions catalyzed by hard Lewis acids are selective for the allylic rearrangement (**Scheme 26**, equation 2).[28]



Scheme 26

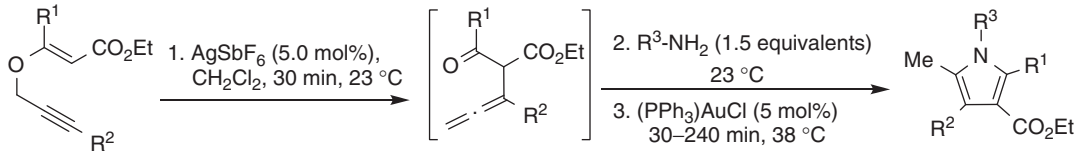
More recently, 1,2,3-triazole–Au complexes have been reported as efficient catalysts capable of promoting propargyl vinyl rearrangements in high yields. These homogeneous catalysts chemoselectively activate the starting alkynes, thus avoiding their undesired isomerization to allenes and, therefore, providing excellent levels of chirality transfer in the rearrangement (Scheme 27).[92]



R^1 = H, *n*-Bu, TMS
R^2 = F, NO_2, CO_2Me, Me

Scheme 27

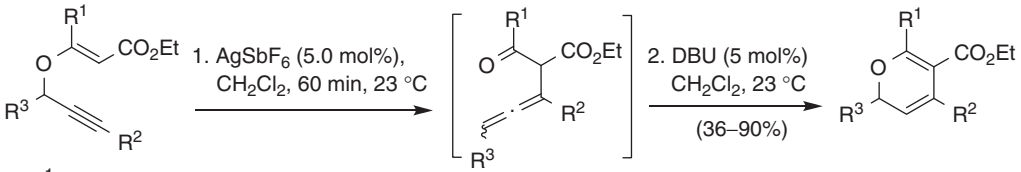
Ag(I) salts effectively catalyze the propargyl-Claisen rearrangement. $AgBF_4$ has been reported to promote the reaction at room temperature in benzene.[93] Under $AgSbF_6$ catalysis, a series of propargyl vinyl ethers rearranged to generate allenic ketones, which were further condensed with a primary amine to give, after Au(I)-catalyzed 5-*exo*-*dig* cyclization, highly substituted 5-methylpyrroles.[94] This Ag(I)-catalyzed propargyl-Claisen rearrangement proceeded rapidly at room temperature in CH_2Cl_2 in high yields with low catalyst loadings (Scheme 28).



R^1 = Me, *n*-Pent, Ph
R^2 = H, Me, TBS, $CH_2(c\text{-}C_6H_{11})$, Ph, 2-MeO(C_6H_4), 3-thienyl
R^3 = Ph, 4-MeO(C_6H_4), 1-naphthyl

Scheme 28

A protocol consisting of $AgSbF_6$-catalyzed propargyl-Claisen rearrangement followed by base-catalyzed isomerization and 6π-oxa-electrocyclization has been successfully applied to the synthesis of monocyclic 2*H*-pyrans from propargyl vinyl ethers (Scheme 29).[95]



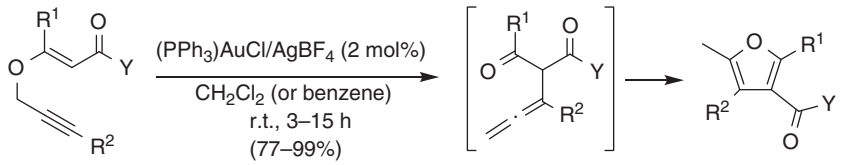
R^1 = Me, *n*-Pent, Ph
R^2 = Ph, 2-MeO(C_6H_4), 4-PhO(C_6H_4), 4-*t*-Bu(C_6H_4), $CH_2(c\text{-}C_6H_{11})$, 3-thienyl
R^3 = Me, Et, *i*-Pr, CH_2Ph, Ph

Scheme 29

The cationic triphenylphosphine–gold(I) complex formed from $(PPh_3)AuCl$ and $AgBF_4$ was reported to catalyze the Claisen rearrangement of a series of propargyl vinyl ethers, which afforded, after heterocyclization of the intermediate allenyl carbonyl derivatives, tri- and tetrasubstituted furans in good yields (Scheme 30).[96]

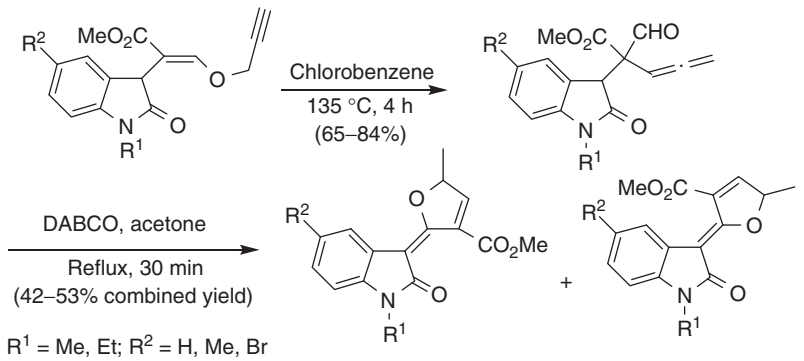
The thermal propargyl-Claisen rearrangement has not been extensively reported in the literature. However, the thermal rearrangement of propargyl vinyl ether derivatives was described to give allene carbonyl intermediates, which were further used for the synthesis of highly functionalized allene-appended oxindoles (Scheme 31).[97]

MWI has also been reported to accelerate the propargyl-Claisen rearrangement, which was described as the key step in the total synthesis of the triterpenoid azadirachtin, allowing the formation of the sterically congested C8–C14 bond (Scheme 32).[98]



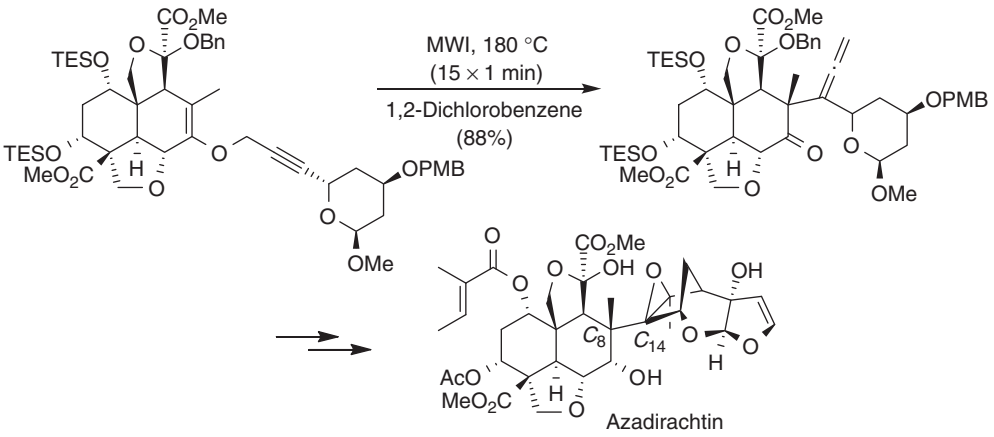
R^1 = H, Me, *n*-Pent, Ph
R^2 = H, Me, Ph, 2-MeO-C_6H_4
Y = OMe, OEt, Ph

Scheme 30



R^1 = Me, Et; R^2 = H, Me, Br

Scheme 31

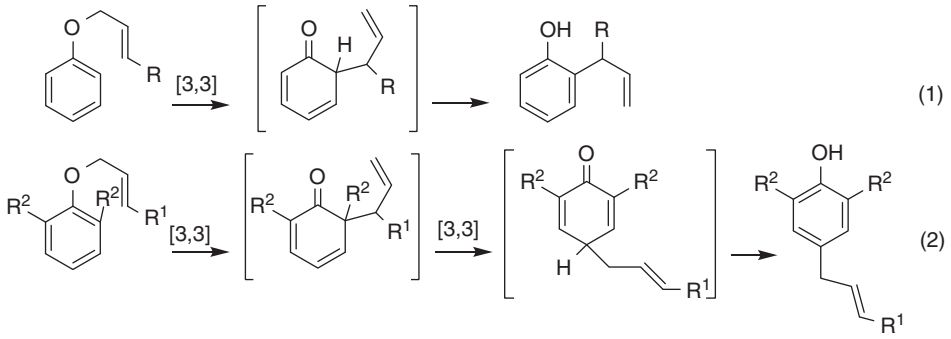


Scheme 32

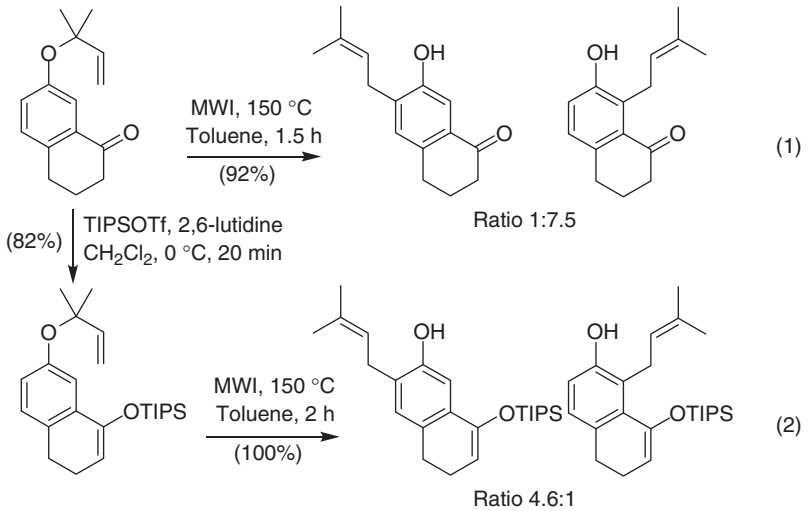
5.20.3.2 Aromatic Claisen Rearrangement

The so-called aromatic [3,3]-sigmatropic rearrangement of allyl aryl ethers developed simultaneously with the aliphatic version of the reaction.[99–101] The initial *ortho*-dienone resulting from the rearrangement immediately enolizes into the corresponding *ortho*-allyl phenol (*ortho* Claisen rearrangement, Scheme 33, equation 1). When the *ortho* position in the substrate is occupied by a substituent, the intervening *ortho*-allyl dienone evolves into the corresponding *para*-allyl phenol via a second [3,3]-rearrangement (*para* Claisen rearrangement, Scheme 33, equation 2).

Experimental results and theoretical calculations agree in predicting the regioselectivity of the rearrangement when both *ortho* positions are not equivalent. Thus, a *p*-acceptor keto group at the *meta* position directs the rearrangement to the sterically less favored *ortho*-substituted product (Scheme 34, equation 1). Contrarily, a bulky silyl enol ether group at the *meta* position gives preferentially the *para*-substituted product (Scheme 34, equation 2).[102]

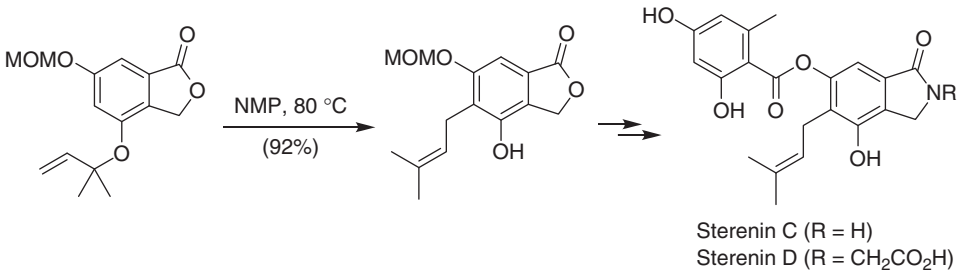


Scheme 33



Scheme 34

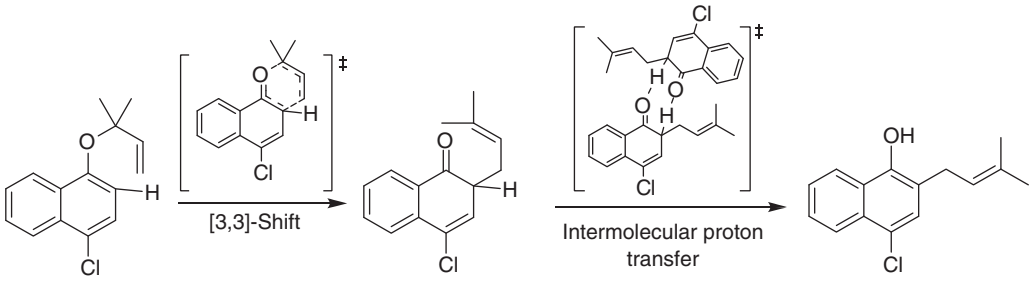
A thermally induced regioselective aromatic Claisen rearrangement has been described as a key step for the introduction of the prenyl group in the context of the synthesis of the glucocorticoid inhibitors sterenins C and D (Scheme 35).[103]



Scheme 35

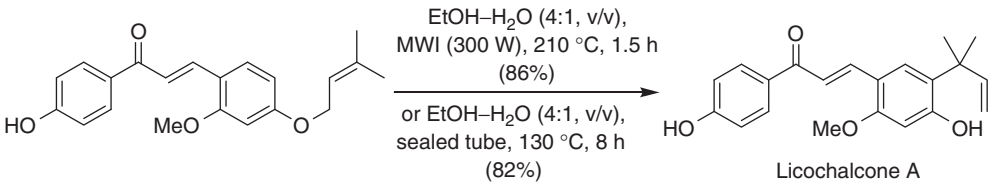
Recently, theoretical calculations on the aromatic Claisen rearrangement of 1-(4-chloronaphthyl) 1,1-dimethylallyl ether have demonstrated that, out of the two steps involved in the aromatic Claisen rearrangement, the initial [3,3]-intramolecular shift is the rate-limiting step for the water-catalyzed reaction;[104] in contrast, under neat conditions, the subsequent proton transfer takes place intermolecularly and is the rate-limiting step (Scheme 36).[105] The obtained calculated energy profile evidenced the rate accelerating role played by water as a catalyst of the aromatic Claisen rearrangement via hydrogen-bonding with the oxygen of the substrate.[104]

Accordingly, a rate enhancement of the reaction in an aqueous medium has been reported for many different allyl aryl ethers. The rearrangement of this class of compounds in organic solvents or under solvent-free conditions was much slower.[106] Thus, a water-accelerated aromatic Claisen rearrangement was reported as one of the key steps of the synthesis of the biologically active



Scheme 36

compound gambogin.[107] Similarly, an aromatic Claisen rearrangement of a prenyl ether in an ethanol–water cosolvent system has been recently reported as the crucial final step for a concise preparation of the biologically active derivative licochalcone A (Scheme 37).[108]

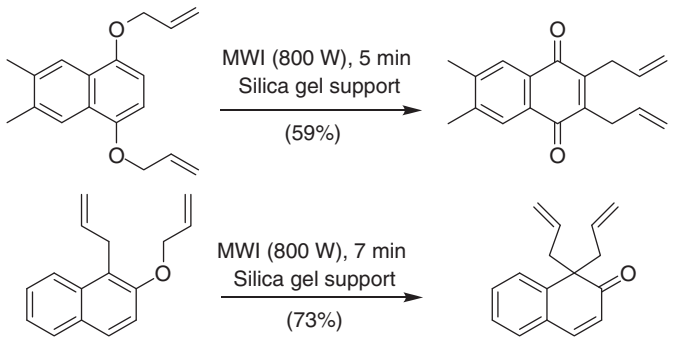


Scheme 37

The use of a microreaction system with high pressure/high temperature water has been recently developed as an efficient method to rearrange allyl methylphenyl ethers into the corresponding *o*-allyl phenols with high yields and selectivities.[109] A hydrogen bond between the solvent and the substrate was invoked to account for the excellent results of the reactions.

High temperatures are typically required for the noncatalyzed aromatic Claisen rearrangements. The use of a continuous flow reactor was described as a convenient method for scaling-up the rearrangement of 1-[4-(allyloxy)phenyl]ethanone in high yields and short reaction times, potentially avoiding the safety and chemical hazards involved in large-scale batch reactors.[110]

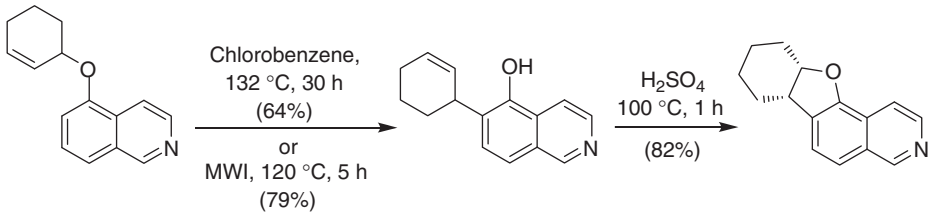
The use of MWI has been profusely reported to accelerate the aromatic Claisen rearrangement, as compared with the conventional thermal process.[111–113] Particularly interesting are the results of the microwave-assisted aromatic Claisen rearrangements of 1,4-bis-hydroxybenzene derivatives, which provide bis-allyl ketones on a silica gel support under environmentally benign solvent-free conditions (Scheme 38).[114]



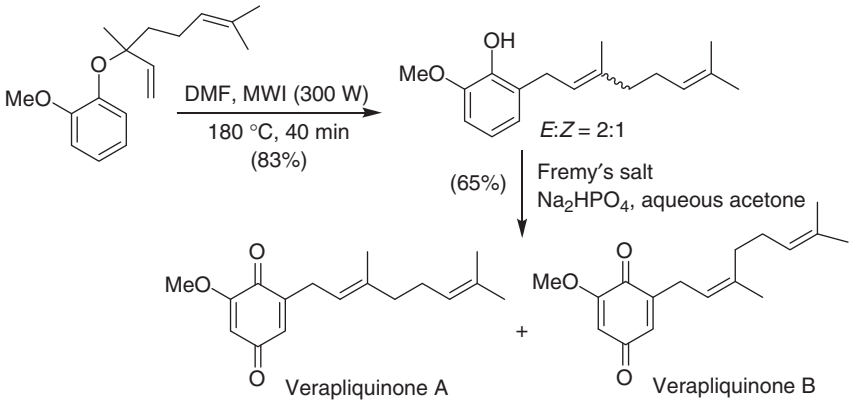
Scheme 38

Microwave-assisted aromatic Claisen rearrangements of allyloxyisoquinolines have been reported as a useful procedure for the construction of a key intermediate in the synthesis of furo[3,2-*f*]isoquinolines derivatives, which are valuable phosphodiesterase IV inhibitors. As compared with the conventional thermal rearrangement, the microwave-accelerated process worked at lower temperatures and needed shorter reaction times (Scheme 39).[115]

MWI proved similarly useful in accelerating the aromatic Claisen rearrangement reported as a key step in the context of the synthesis of the marine benzoquinones verapliquinones A and B (Scheme 40).[116]



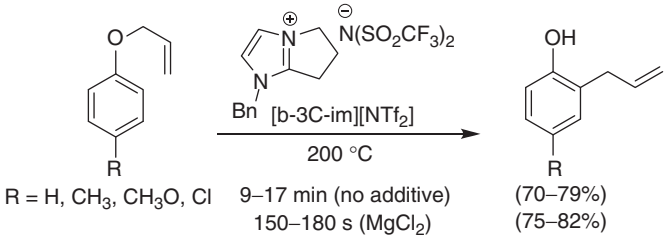
Scheme 39



Scheme 40

The combined use of MWI and the bicyclic imidazolium ionic liquid [b-3C-im][NTf_2] as solvent has been successfully applied to an aromatic Claisen rearrangement, producing good yields in very short ($\leq$ 3 min) reaction times. The presence of a Lewis acid (i.e., $MgCl_2$) as an additive shortened the required reaction times even further and slightly improved the yields (Scheme 41).[117]

Aromatic Claisen rearrangements under MWI in toluene doped with the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) as the reaction medium have also been reported.[118]

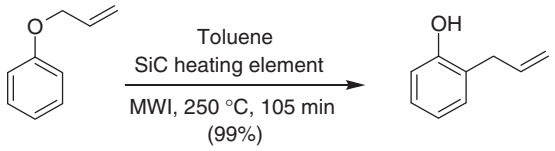


Scheme 41

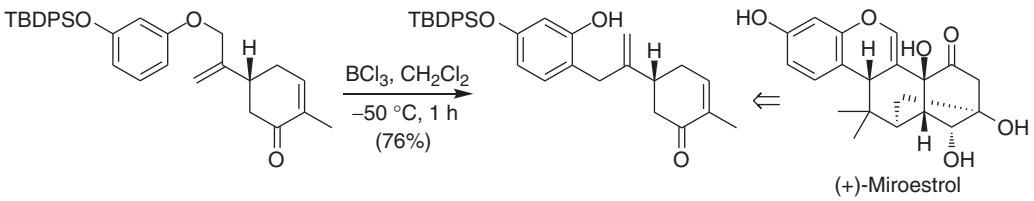
However, the use of microwave energy to accelerate aromatic Claisen rearrangements has been traditionally restricted to microwave-absorbing solvents (i.e., ethanol, methanol, dimethyl sulfoxide, and, to a small extent, water). The problem of low microwave absorption of nonpolar solvents was circumvented by utilizing a cylinder of sintered silicon carbide as passive heating element. This strongly microwave-absorbing material transfers the generated thermal energy to the aromatic rearrangement media, affording the Claisen products in high yields (Scheme 42).[119]

The benefits of microwave heating for the aromatic Claisen rearrangement at small scale have been recently reported as easy to scale-up to a manufacturing capability equivalent to pilot-plant scale by way of a commercial continuous flow microwave reactor.[120,121] For effective scale-up of microwave-assisted Claisen rearrangements, a continuous flow system avoids the problems inherent to the limited penetration depth of microwaves in most solvents, which is particularly noticeable when working at large-scale.

Significant rate enhancement of the aromatic Claisen rearrangement in the presence of boron trichloride has been extensively reported.[2,122] However, the use of BCl_3 usually generates undesired side products, which restricts the synthetic applicability of this catalyst. Nevertheless, the presence of specific substituents on the aromatic ring of the starting allyl aryl ether (typically a silyloxy function) mediates the BCl_3-catalyzed rearrangement such that high levels of regioselectivity are procured.[123] This has been particularly useful for the regioselective synthesis of resorcinol carvonyl ethers, described as formal key intermediates in the synthesis of miroestrols (Scheme 43).[124]

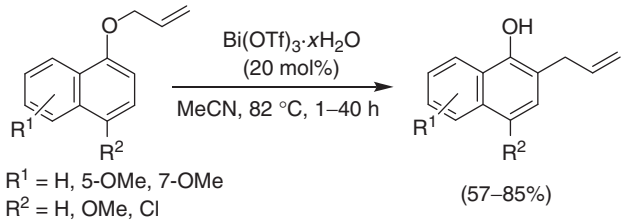


Scheme 42



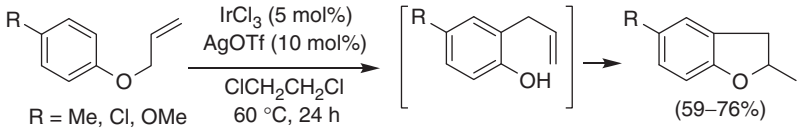
Scheme 43

Bismuth triflate has also been reported as a catalyst for the Claisen rearrangement of allyl naphthyl ethers.[125] The synthetic versatility of the regioselectively obtained *ortho*-allyl naphthols (Scheme 44), along with the low toxicity and good stability of the catalyst, makes these $Bi(OTf)_3$ catalytic conditions an attractive protocol for the synthesis of biologically active compounds.



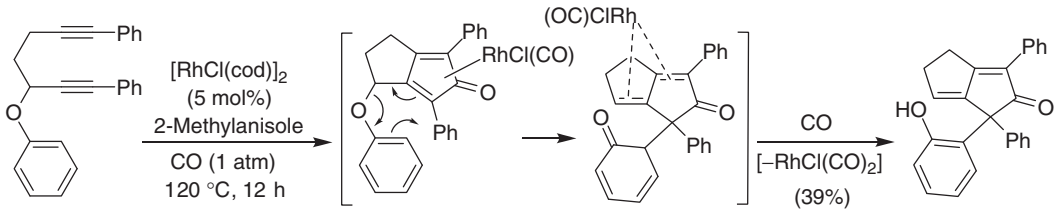
Scheme 44

An effective one-pot combination of an aromatic Claisen rearrangement and a subsequent hydroaryloxylation of the rearranged phenols takes place in good yields in the presence of a catalytic amount of iridium(III) chloride and silver triflate as additive (Scheme 45).[126] Although the reported mild conditions are useful for synthesizing differently substituted dihydrobenzofurans, the reaction proved sensitive to the degree of substitution of the starting olefinic fragment.



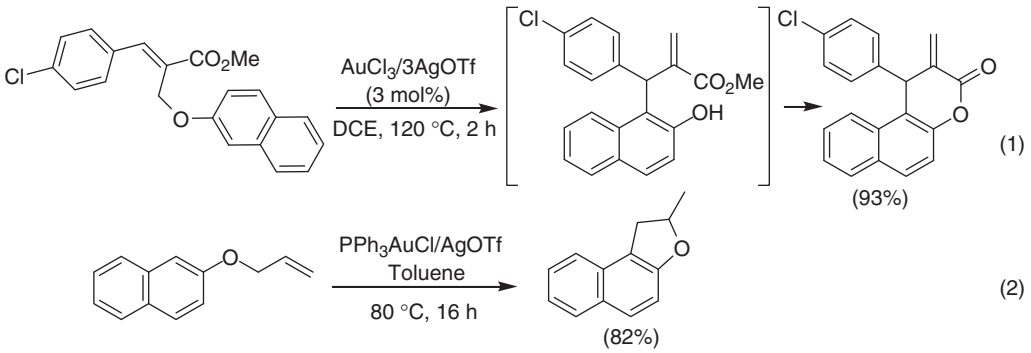
Scheme 45

The aromatic Claisen rearrangement has also been reported under mild conditions from an aryloxy-substituted RhCl(CO) (cyclopentadienone) complex, prepared *in situ* by a Rh-catalyzed [2 + 2 + 1] carbonylation of suitably substituted diynes (Scheme 46).[127] Despite the high interest of the intervening Rh complex, the reported yields for the rearranged products are only moderate.



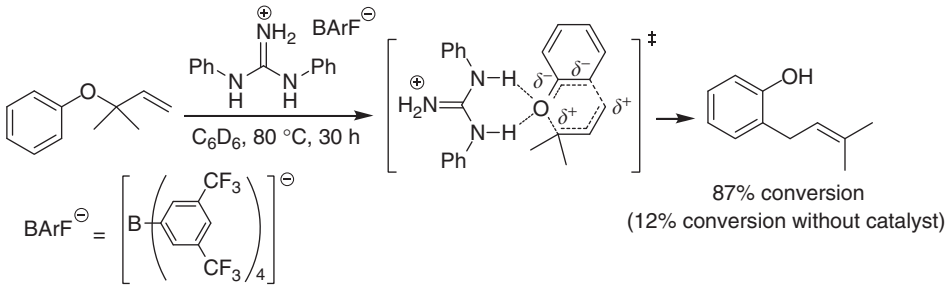
Scheme 46

Combined gold/silver catalytic systems have been successfully applied for achieving Claisen rearrangements of allyl aryl ethers under mild conditions. Both $AuCl_3$/AgOTf and PPh_3AuCl/AgOTf systems have been reported as efficient catalysts for the rearrangement of different aromatic substrates. Subsequent *in situ* cyclizations of the rearranged products have afforded ready access to either 3,4-dihydrocoumarins (Scheme 47, equation 1)[128] or dihydrobenzofurans (Scheme 47, equation 2).[129] The formation of isomeric rearranged products under specific experimental conditions (typically lower temperatures) has been attributed to competitive [1,3] versus [3,3] sigmatropic rearrangements.[128] If desired, the formation of the dihydrobenzofurans could be inhibited in the presence of Proton-sponge®, and the rearranged *o*-allyl phenols could be isolated in good yields.[130]



Scheme 47

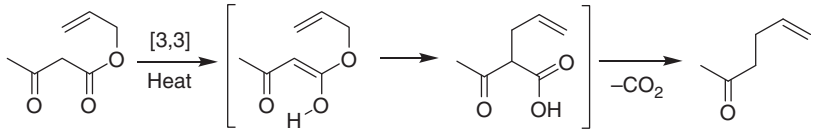
Guanidinium hydrogen bond donors, used in substoichiometric quantities, have been reported to induce rate enhancement in the rearrangement of allyl aryl ethers (Scheme 48).[89] However, to date, the organocatalytic version of the aromatic Claisen rearrangement has been poorly exploited.



Scheme 48

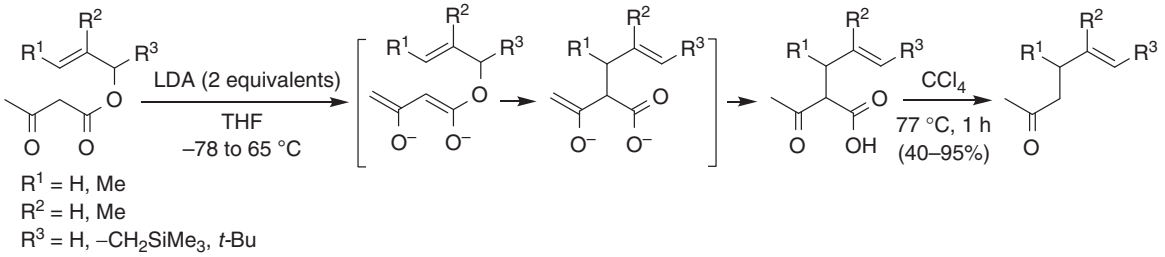
5.20.3.3 Carroll Rearrangement

The Carroll rearrangement was described as a complementary variant of the aliphatic Claisen rearrangement, consisting of the thermal transformation of allylic *β*-keto esters into *β*-keto acids, via a [3,3]-sigmatropic rearrangement, and subsequent decarboxylation to produce *γ*,δ-unsaturated ketones (Scheme 49).[131–133]



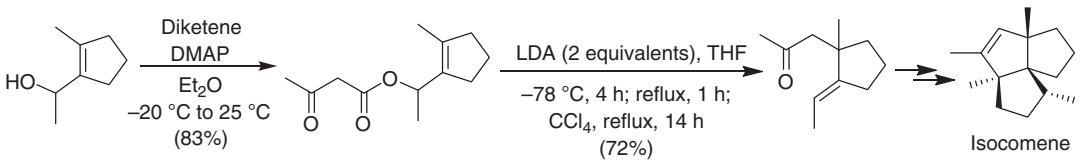
Scheme 49

The initially reported high temperatures required for the reaction could be avoided in the presence of a base (e.g., Al(*i*-PrO)$_3$,[134,135] NaOAc,[136] NaH,[137] *s*-collidine[138]). *γ*,δ-Unsaturated ketones have been obtained in good yields from the corresponding allylic acetoacetates, on treatment with lithium diisopropylamide (LDA) (2 equivalents) at −78 °C, via rearrangement of the intervening dianions and subsequent decarboxylation on heating in CCl_4 (Scheme 50).[139] α-Substituents on the allylic fragment of the substrate proved beneficial to the rearrangement.



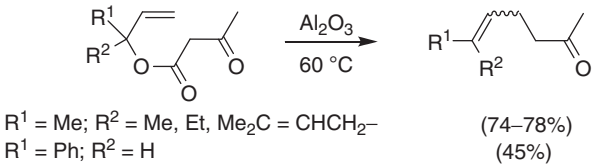
Scheme 50

These optimized conditions for the rearrangement of allylic β-keto esters have been reported as the key steps in the preparation of a variety of biologically active compounds. An example is outlined in Scheme 51. The reported improved procedure for the preparation of allylic β-keto esters, consisting of the reaction of an allylic alcohol with diketene in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP), afforded the desired acetoacetate, which, on treatment with LDA (2 equivalents) and further heating, produced the γ,δ-unsaturated ketone serving as a key intermediate in the formal total synthesis of the sesquiterpene isocomene (Scheme 51).[140]



Scheme 51

An enhancement of the rate of the Carroll rearrangement was reported by performing the reaction with the substrates adsorbed on Al_2O_3 in the absence of any solvent.[141] These conditions have proved particularly useful for acetoacetates derived from tertiary allylic alcohols (Scheme 52).



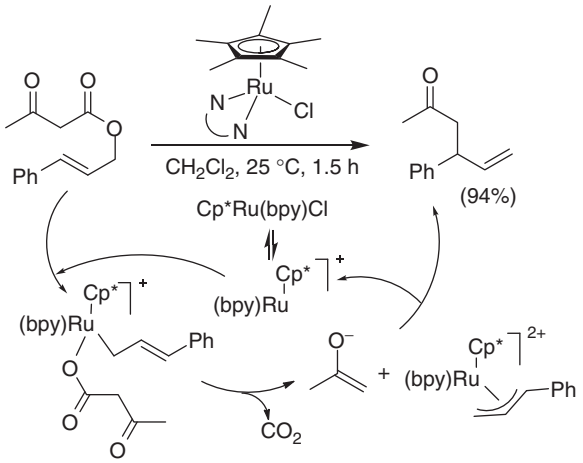
Scheme 52

Different metallic derivatives have been reported as efficient catalysts for the Carroll rearrangements. In the presence of catalytic amounts of $Ti(OEt)_4$[142] or $Pd(PPh_3)_4$,[143] Carroll-type rearrangements of differently substituted allylic β-keto esters proceed smoothly to produce the corresponding γ,δ-unsaturated ketones.

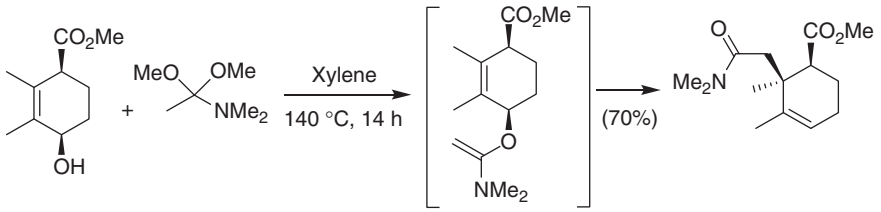
Bipyridyl(pentamethylcyclopentadienyl)ruthenium chloride has also been used as a selective catalyst for the transformation of allylic β-keto esters into γ,δ-unsaturated ketones (Scheme 53).[144] Although the reaction is described as a formal decarboxylative Carroll rearrangement, the proposed mechanism involves ruthenium π-allyl intermediates, which are selectively attacked at the more substituted allyl terminus.

5.20.3.4 Eschenmoser Rearrangement

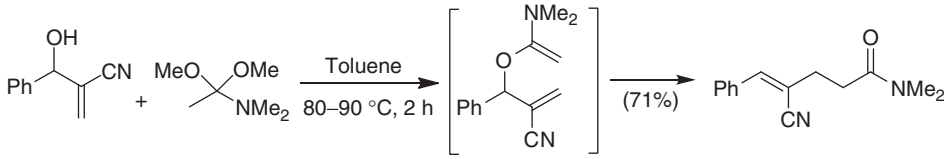
The Eschenmoser rearrangement was originally reported in 1964 as a valuable method for the synthesis of γ,δ-unsaturated amides.[145] The process consists of the *in situ* formation of an unstable ketene *N,O*-acetal (by reaction of an allylic alcohol with an amide acetal, typically *N,N*-dimethylacetamide dimethyl acetal, followed by alcohol elimination) and its subsequent [3,3]-sigmatropic rearrangement to afford a γ,δ-unsaturated amide. The electron-donating amino substituent on the carbon fragment involved in the rearrangement accelerates the process in comparison with the classical Claisen variant. Consequently, mild experimental conditions are required, which makes the rearrangement tolerant with a wide range of functional groups (Scheme 54).[146] Similarly, Baylis–Hillman adducts have proved to be convenient substrates for the Eschenmoser rearrangement (Scheme 55).[147]



Scheme 53

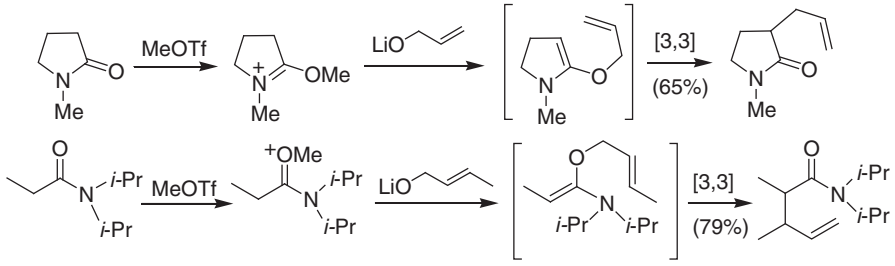


Scheme 54



Scheme 55

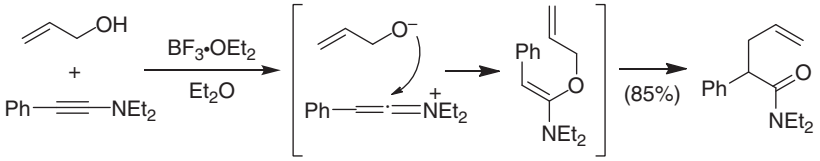
However, the method of choice for the preparation of more elaborated ketene *N,O*-acetals derived from sterically hindered or poorly nucleophilic acyclic and cyclic amides consisted of the alkylation of the starting amides with ethyloxonium tetrafluoroborate[148] or methyl triflate,[149–151] and subsequent heating of the intervening amidinium salts in the presence of allylic sodium or lithium alkoxides. The *in situ* generated ketene *N,O*-acetals immediately rearrange to the γ,δ-unsaturated amides (Scheme 56).



Scheme 56

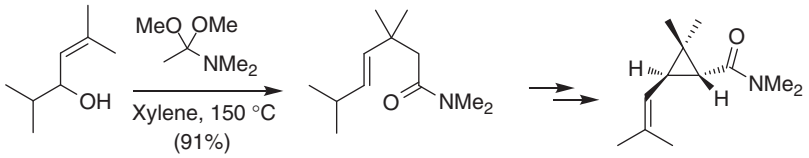
The preparation of ketene *N,O*-acetals has also been reported by reaction of an allylic alcohol and 1-(diethylamino)propyne (ynamine). High temperatures or a catalytic amount of $BF_3 \cdot OEt_2$ are usually required for the initial formation of the ketene

N,O-acetal and its subsequent *in situ* rearrangement. This variant of the Eschenmoser rearrangement is known as the ynamine–Claisen rearrangement or Ficini rearrangement (Scheme 57).[152,153]



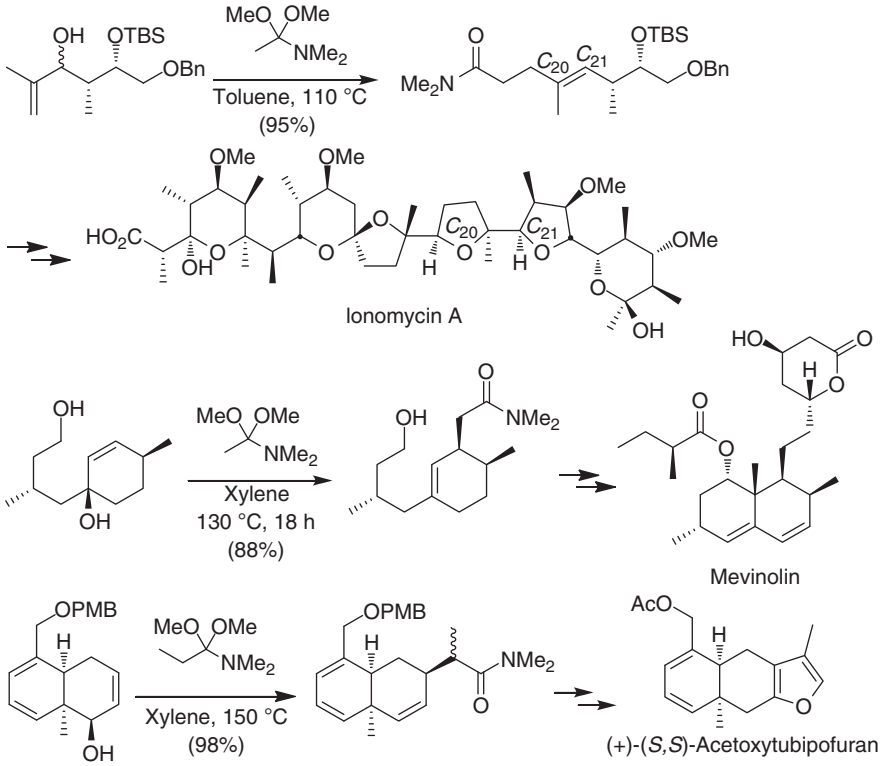
Scheme 57

The Eschenmoser rearrangement has been described as the key step of the synthesis of a pyrethroid amide derivative (Scheme 58).[154]



Scheme 58

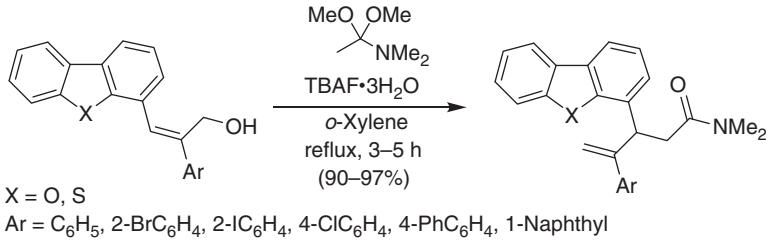
Eschenmoser rearrangements of both acyclic and cyclic allylic alcohols have been reported as convenient routes for the preparation of key intermediates in the syntheses of a variety of biologically active compounds.[155–159] Some selected examples are represented in Scheme 59.[155,156]



Scheme 59

The drastic experimental conditions usually required in the Eschenmoser rearrangement may restrict its synthetic applicability. The use of tetra-*n*-butylammonium fluoride trihydrate has been reported as highly useful phase-transfer catalyst, allowing the

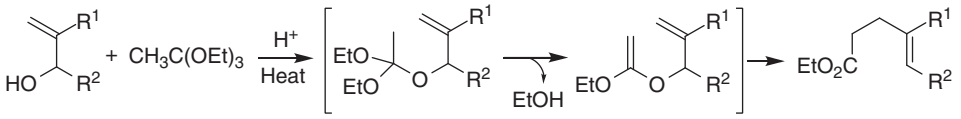
Eschenmoser rearrangement of sterically congested allylic alcohols to take place in high yields in the presence of *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene or xylene (Scheme 60).[160]



Scheme 60

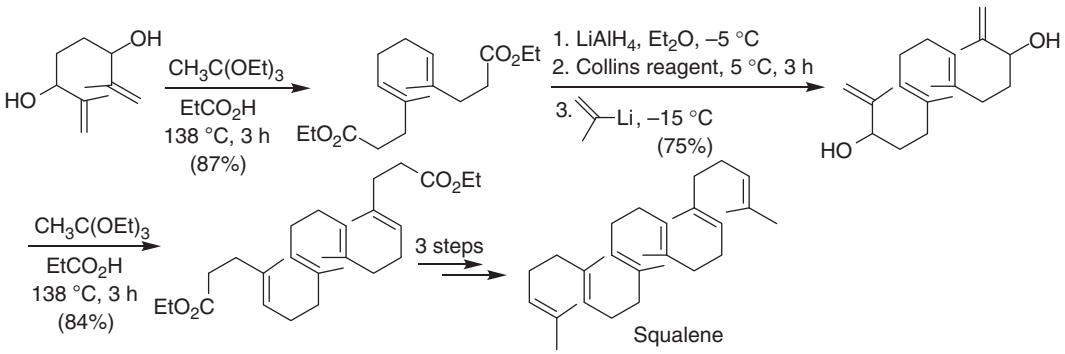
5.20.3.5 Johnson Rearrangement

The Johnson rearrangement was first reported in 1970 as the acid-catalyzed condensation of an allylic alcohol with an excess of orthoester. The initially formed mixed orthoester evolves into a mixed ketene acetal, which *in situ* rearranges into a γ,δ-unsaturated carboxylic ester (Scheme 61).[161]



Scheme 61

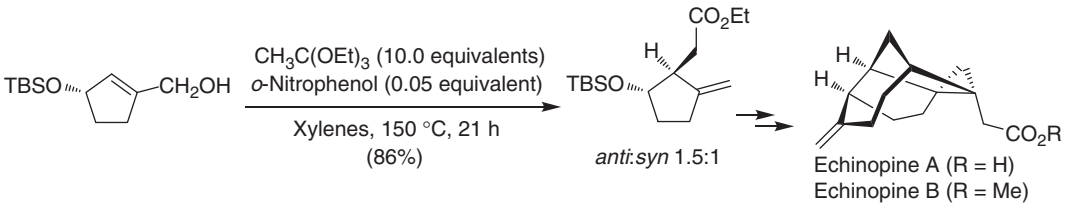
Two general procedures have been described for the preparation of the mixed orthoesters, which are precursors of the *O*-allyl ketene acetals, the latter being the actual substrates of the rearrangement. One of them consists in the acid-catalyzed transesterification of trimethyl orthoacetate with a properly substituted allylic alcohol. Although the initially formed mixed orthoesters can be isolated under $MgCl_2$ catalysis,[162] trace amounts of a weak acid (typically propionic acid) permitted the reaction of allylic alcohols with an excess of orthoacetate to go to completion and give the rearranged *trans*-γ,δ-unsaturated esters, which are used as intermediates in the synthesis of many natural products. Thus, the initially reported synthesis of squalene makes use of two orthoester rearrangements (Scheme 62).[161]



Scheme 62

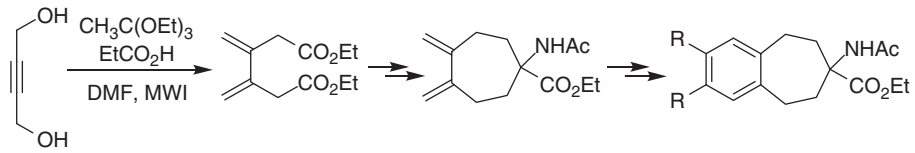
The second method of choice for the preparation of the intervening mixed orthoesters is the addition of an allylic alcohol to a ketene acetal. The use of $PdCl_2$(COD) as the catalyst,[163] *t*-BuOH as the solvent,[164] or, more recently, uncatalyzed solvent-free conditions[165] have been reported to this end.

A rate enhancement of the orthoester rearrangement in the presence of a catalytic amount of *o*-nitrophenol has been reported in the context of the syntheses of biologically active alkaloid (+)-galanthamine[166] and the sesquiterpenes echinopines A and B (Scheme 63).[167]



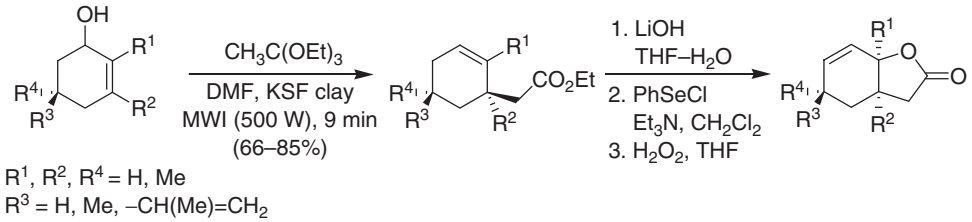
Scheme 63

Although the Johnson rearrangement usually requires high temperatures, the microwave-assisted processes have also been reported. The combined use of a catalytic amount of propionic acid and MWI allowed a double Johnson rearrangement to produce diethyl 3,4-bismethyleneadipate, which was utilized as intermediate for the synthesis of benzocycloheptane-derived amino acids (Scheme 64).[168]



Scheme 64

The combination of montmorillonite KSF clay as a solid acid catalyst and MWI has also been reported to produce clean Johnson rearrangement products from cycloalkenols, which were subsequently transformed into *cis* bicyclic unsaturated lactones (Scheme 65).[169]



Scheme 65

Heterogeneous catalysis based on silica-supported sodium hydrogen sulfate ($NaHSO_4$-SiO_2)[170] or iodine adsorbed on silica (I_2-SiO_2)[171] also accelerates the Johnson rearrangement of differently substituted Baylis–Hillman adducts.

Some metallic compounds have proved to be efficient catalysts for the Johnson rearrangement. Thus, $PdCl_2(PPh_3)_2$[163] and triisobutylaluminum[172] cleanly promote both the *in situ* alcohol elimination from the starting mixed orthoester, and the immediate rearrangement. These catalytic conditions have been reported for the preparation of γ,δ-unsaturated esters [Pd catalysis (Scheme 66, equation 1)] or γ,δ-unsaturated alcohols [Al catalysis (Scheme 66, equation 2)] in high yields under mild conditions.

The acidic conditions reported for the Johnson rearrangement are usually compatible with the presence of diverse heteroatomic substituents on the allyl vinyl framework. Alkoxy,[173] halo,[174] sulfenyl,[174] and phenylseleno[175] substituents on the orthoester component have proved compatible with the experimental conditions of the rearrangement. An α-sulfinyl orthoester was used to prepare dienoate esters by way of a Johnson rearrangement and subsequent pyrolytic sulfoxide 1,2-elimination in the course of a synthesis of precursors of 1α,25-dihydroxyvitamin D_3 (Scheme 67).[176]

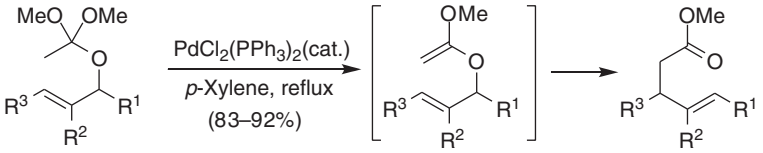
Heteroatomic substituents on the allylic alcohol have also been reported. The Johnson rearrangement of a *trans*-dichlorinated allylic alcohol with methyl orthoacetate was developed as the key step of the synthesis of the antitumor agent halomon (Scheme 68).[177]

The Johnson rearrangement of boron-substituted allylic alcohols produced 1,3-disubstituted allylboronic esters in high yields (Scheme 69).[178]

The functionality of the products resulting of the Johnson rearrangements allows their transformation into synthetically useful building blocks. In this sense, the synthesis of the core quaternary carbon center present in tetradirectional dendrimeric frameworks has been prepared by a Johnson rearrangement (Scheme 70).[179]

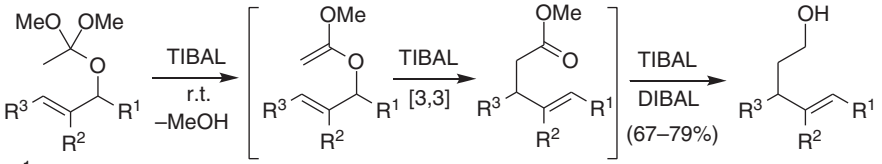
The Johnson rearrangement of γ-trifluoromethyl γ-alkyl allylic alcohols has been developed as an efficient strategy for the construction of CF_3-substituted quaternary carbon atoms (Scheme 71).[180]

The use of unsaturated cyanohydrins as the allylic component of the Johnson rearrangement has emerged as a useful protocol for the preparation of δ-ethoxycarbonyl α,β-unsaturated nitriles in good yields, although large excess amounts of both acid and triethyl orthoacetate are required (Scheme 72).[181]



(1)

R^1 = H, Ph, $Ph(CH_2)_2$
R^2 = H, OEt
R^3 = H, Me, Ph, $Ph(CH_2)_2$

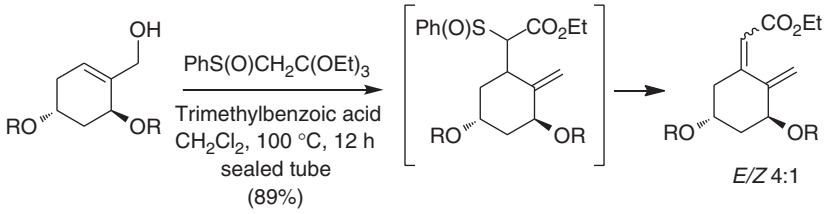


(2)

R^1 = Me, Et, n-C_6H_{13}
R^2 = H, Me
R^3 = H, Et, n-C_5H_{11}, Ph, o-$MeOC_6H_4$

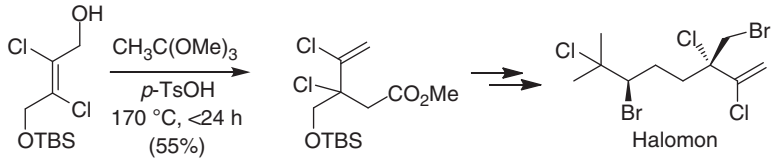
Z:*E*
14:86 to 17:83

Scheme 66

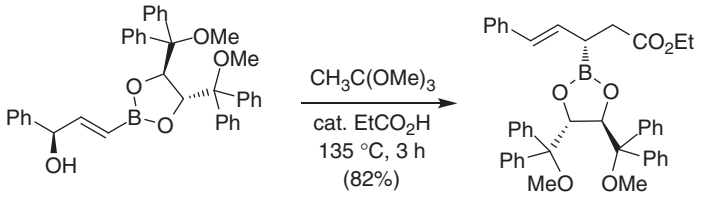


E/*Z* 4:1

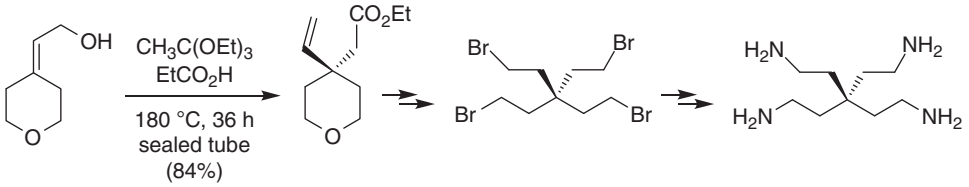
Scheme 67



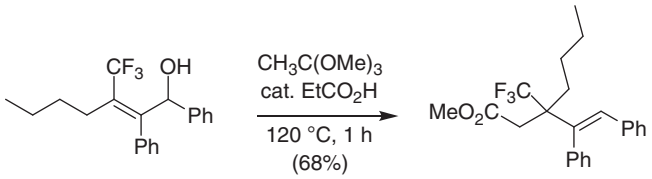
Scheme 68



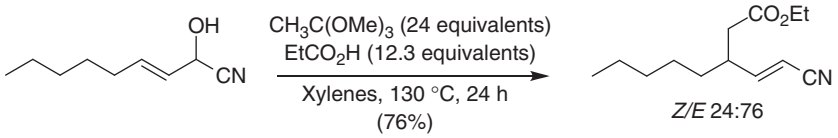
Scheme 69



Scheme 70

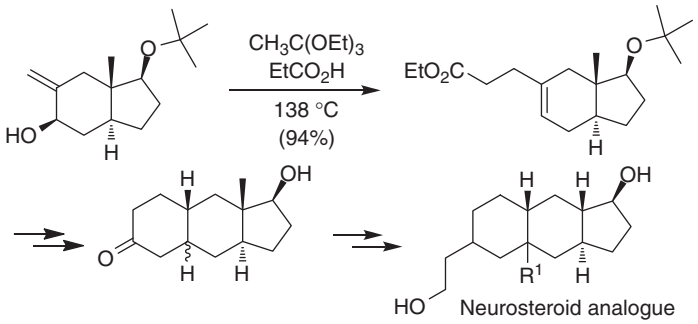


Scheme 71



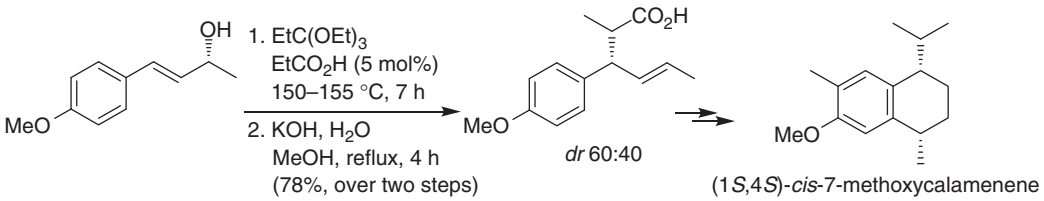
Scheme 72

A Johnson rearrangement has also provided a ready access to an intermediate used for the preparation of 1,6-difunctionalized dodecahydrobenz[*f*]indenes, precursors of linear tricyclic neurosteroid analogs (Scheme 73).[182]



Scheme 73

In the context of the synthesis of natural products, the Johnson rearrangement has served as a valuable tool for the efficient incorporation of specific structural fragments into the target molecules. Thus, the isopropyl unit at the benzylic position of the terpenoid-like (1*S*,4*S*)-*cis*-7-methoxycalamenene was constructed via a Johnson rearrangement (Scheme 74).[183]



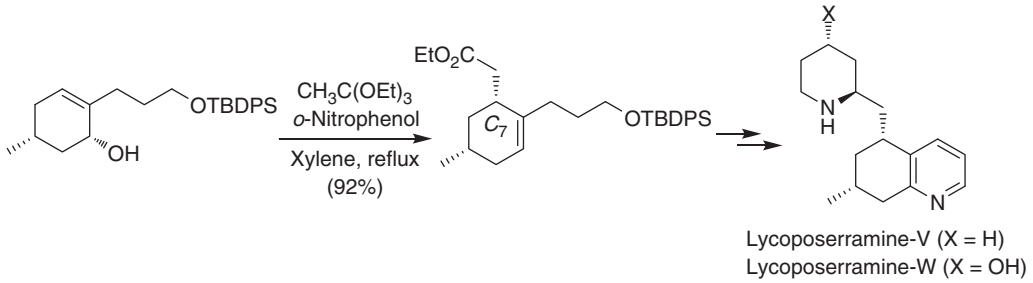
Scheme 74

The carbon residue at C7 in the key intermediate of the synthesis of the phegmarine-type alkaloids lycoposerramine V and W was introduced by a thermal orthoester rearrangement (Scheme 75).[184]

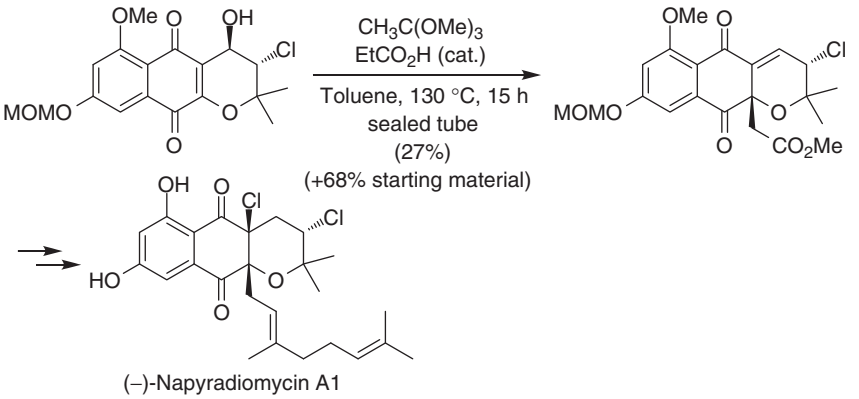
Similarly, an acid-catalyzed orthoester rearrangement has been reported as the key step in the synthesis of the halogenated biologically active compound (–)-napyradiomycin A1 (Scheme 76).[185]

5.20.3.6 Ireland Rearrangement

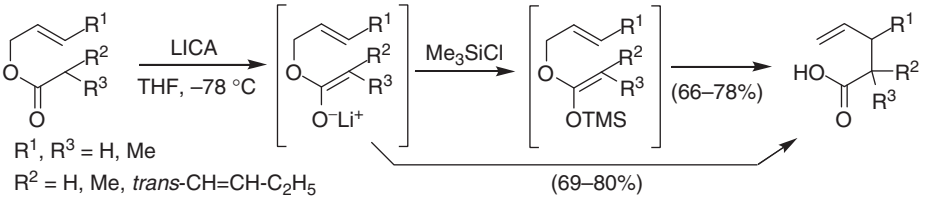
The Ireland rearrangement was originally described in 1972 as the concerted intramolecular reorganization of an enolate anion derived from an allyl ester into a γ,δ-unsaturated carboxylic acid. When this intermediate enolate is quenched with trimethylsilyl chloride, the resulting *O*-allyl-*O*-silyl ketene acetal rearranges readily, usually at low temperatures under basic or neutral conditions (Scheme 77).[186]



Scheme 75

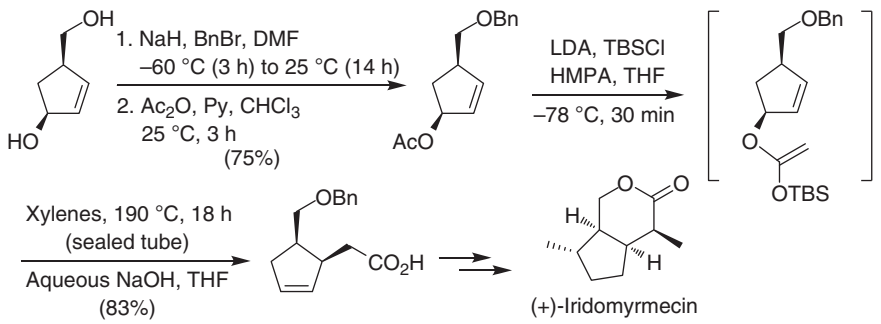


Scheme 76



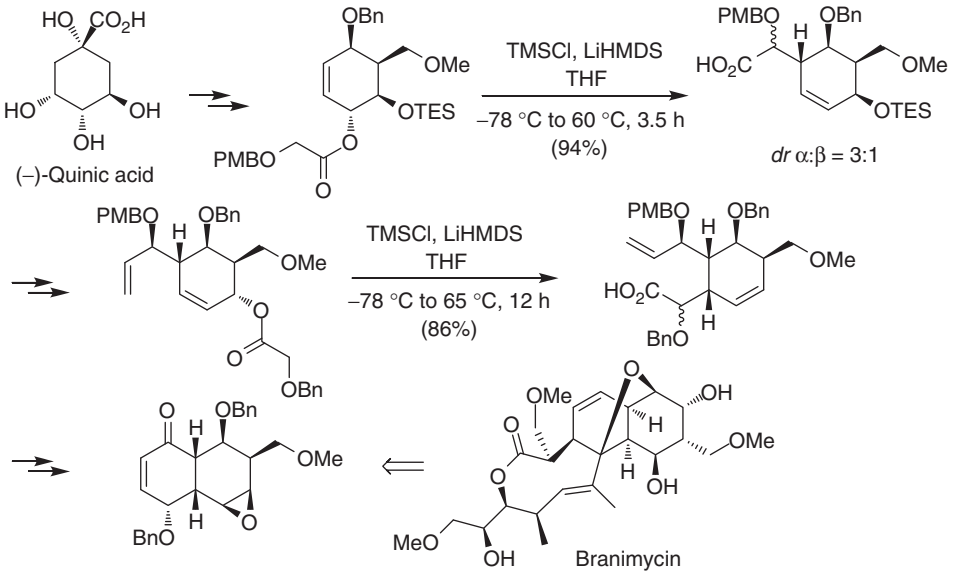
Scheme 77

Although several syntheses of the precursor *O*-allyl-*O*-silyl ketene acetals have been reported, two procedures are particularly worth mentioning. Deprotonation of allylic esters and subsequent enolate-trapping with Me_3SiCl or *t*-$BuMe_2SiCl$ generates a silyl ketene acetal which rearranges *in situ*. On hydrolysis of the intervening silyl ester, a γ,δ-unsaturated carboxylic acid is formed. This protocol has been applied to the synthesis of many biologically active compounds. The *O*-allyl-*O*-silyl ketene acetal used as the substrate of the Ireland rearrangement reported in the synthesis of the insecticidal iridoid (+)-iridomyrmecin was prepared by way of this method (Scheme 78).[187]



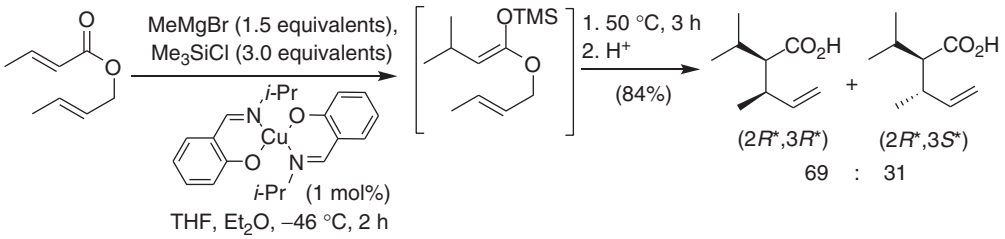
Scheme 78

Two successive Ireland rearrangements, performed under the above conditions, have been utilized for installing the monosubstituted double bonds required for the construction of the *cis*-fused decalin core present in the antibiotic branimycin (**Scheme 79**).[188]



Scheme 79

Conjugate addition to allylic α,β-unsaturated esters followed by *O*-silylation of the intervening enolates has also been described as an efficient procedure for the preparation of *O*-allyl-*O*-silyl ketene acetals, which *in situ* undergo rearrangement to give γ,δ-unsaturated acids. In this sense, conjugate additions of organocopper reagents,[189,190] lithium ester enolates,[191] trialkylphosphines,[192] 1,4-diazabicyclo[2.2.2]octane (DABCO),[193] or alkyl radicals[194–196] to allylic α,β-unsaturated esters and rearrangement of the intervening allyl silyl ketene acetals have been reported. A copper(II)-catalyzed conjugate addition of Grignard reagents to allylic crotonates and the subsequent *in situ* rearrangement of the resulting intermediates to produce 2-allyl 3-alkyl carboxylic acids is represented in **Scheme 80**.[189]

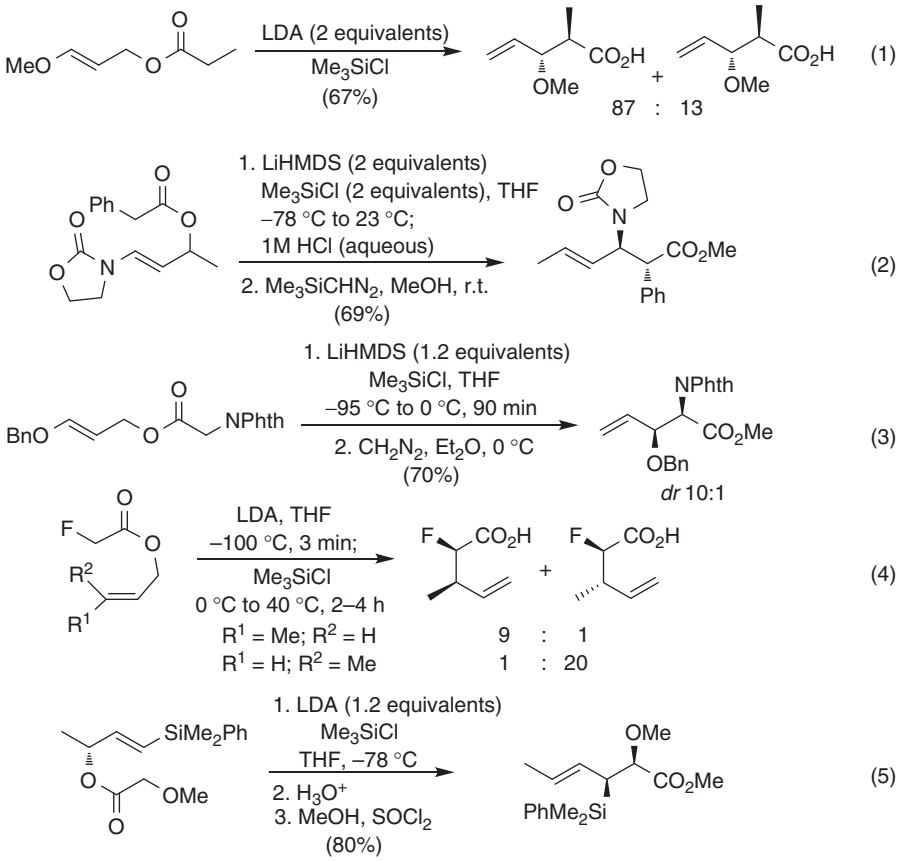


Scheme 80

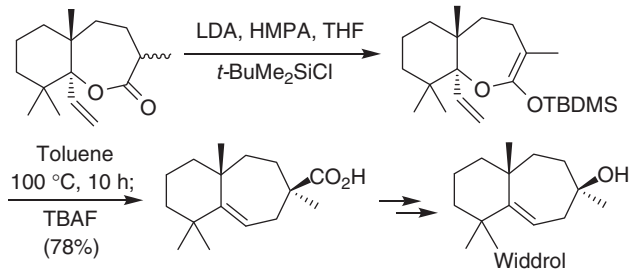
The usually mild conditions reported for the Ireland rearrangement render it compatible with a wide range of functional groups in the substrate. The presence of heteroatom substituents either at the ester or at the allylic fragment generates differently substituted unsaturated acids. Thus, esters of alkoxy allylic alcohols give *anti*-β-alkoxy acids (**Scheme 81**, equation 1).[197,198] Similarly, an enamide moiety in the alcohol portion of the rearrangement substrate provides *anti*-β-amino acids (**Scheme 81**, equation 2).[199] In turn, heteroatomic functions at the ester fragment give α-heteroatom-substituted γ,δ-unsaturated carboxylic acids (**Scheme 81**, equations 3 and 4).[200,201] The Ireland rearrangement of glycolates, bearing an alkoxy substituent at the ester fragment, derived of silyloxy allylic alcohols affords diastereoisomerically enriched α-alkoxy-β-silylhexenoates, which have proved to be efficient chiral carbon nucleophiles (**Scheme 81**, equation 5).[202]

The Ireland rearrangement of vinyl lactones has been described as an elegant route to functionalized cycloalkanes under smooth conditions.[203] This protocol has been utilized as the key step in a stereospecific total synthesis of the sesquiterpene widdrol (**Scheme 82**).[204]

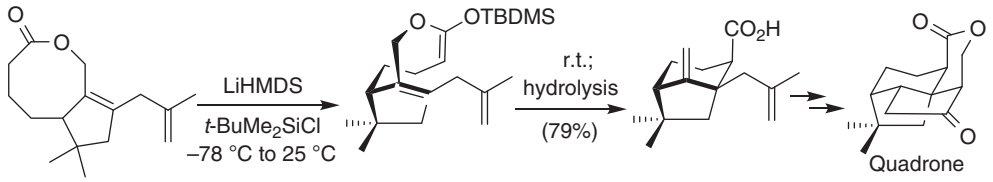
Similarly, the bridged cycloalkane intermediate in the synthesis of (±)-quadrone was prepared by the lactone version of the Ireland rearrangement (**Scheme 83**).[205]



Scheme 81



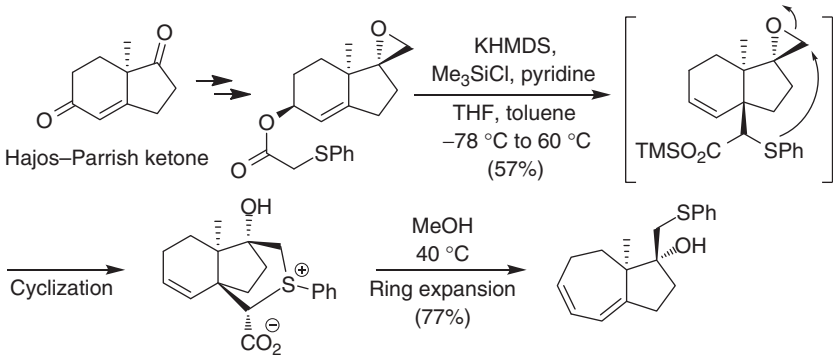
Scheme 82



Scheme 83

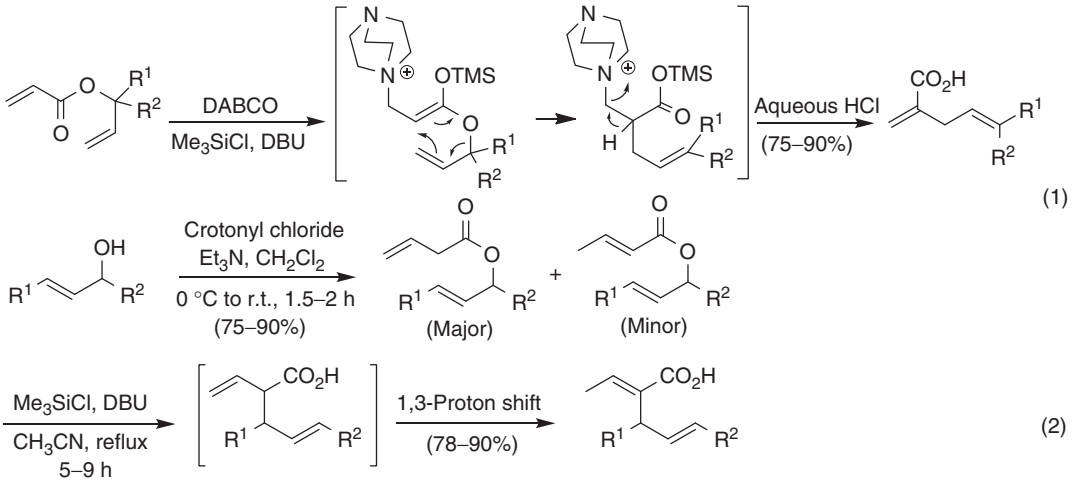
The bicyclo[5.3.0]decane ring system possessing an angular methyl group is a skeleton common to naturally occurring pseudoguaianes, and has been readily synthesized by way of an Ireland rearrangement of a thiophenyl acetate – prepared from the Hajos–Parrish ketone – and a subsequent ring expansion reaction of the rearranged intermediate (Scheme 84).[206]

The DABCO-catalyzed Ireland rearrangement of allylic acrylates in the presence of an excess amount of Me_3SiCl and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been reported to produce α-methylene-γ,δ-unsaturated carboxylic acids



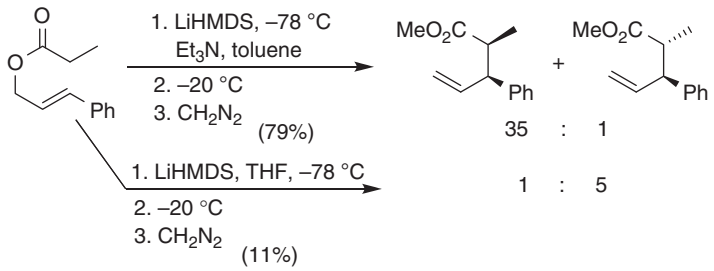
Scheme 84

(Scheme 85, equation 1).[207] This methodology has been efficiently expanded to a range of allylic but-3-enoates. The combined use of DBU and Me_3SiCl promotes the formation of the silyl ketene acetal and its rearrangement/isomerization reactions to afford a variety of 2-ethylidene-γ,δ-unsaturated carboxylic acids (Scheme 85, equation 2).[208]



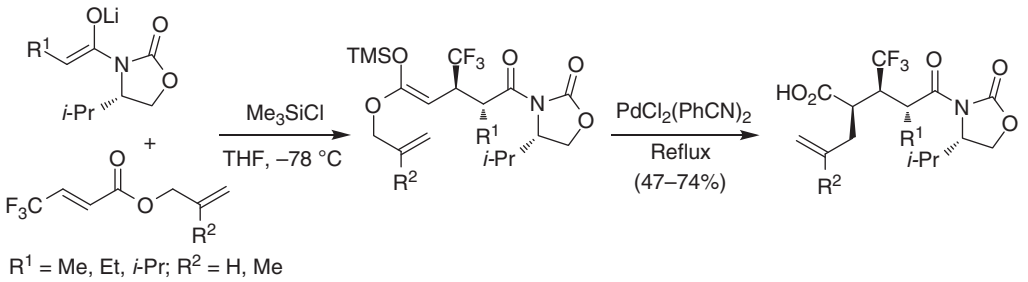
Scheme 85

Lithium hexamethyldisilazide (LiHMDS) in triethylamine/toluene produces Et_3N-solvated allylic enolates, which exhibits a marked acceleration of their Ireland rearrangements (~20 times faster) when compared with the analogous rearrangements in neat tetrahydrofuran (THF). The stereoselectivity of these processes was also reported to be reversed (Scheme 86).[209] Enolization of the ester in Et_3N/toluene affords the *Z* enolate predominantly. Subsequent Claisen rearrangement at −20 °C proceeds with excellent diastereoselectivity. When the enolization takes place in neat THF the rearrangement took place only in 11% yield with lower diastereoselectivity. The low yield could be due to a poor enolization or a poor rearrangement from the *E* enolate.[210]



Scheme 86

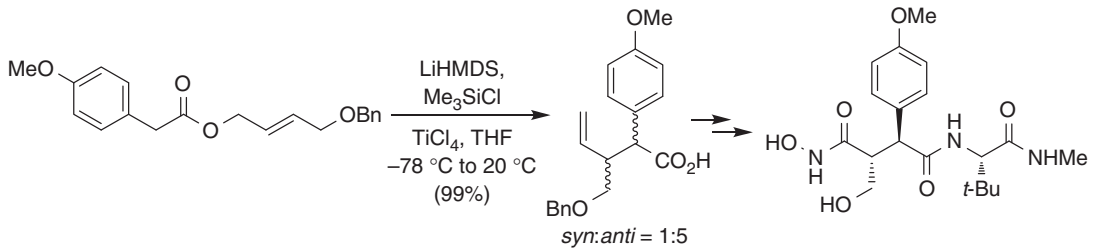
Different metallic additives have proved efficient in accelerating the Ireland rearrangement. For example, catalytic amounts of $PdCl_2(PhCN)_2$ are beneficial for the rearrangement of silyl ketene acetals (Scheme 87).[211]



R^1 = Me, Et, *i*-Pr; R^2 = H, Me

Scheme 87

The combined use of LiHMDS/Me_3SiCl with catalytic amounts of $TiCl_4$ accelerates the Ireland rearrangement as compared with the uncatalyzed process.[212] These improved Ireland rearrangement conditions have been applied as a key step for the synthesis of succinate-based hydroxamate inhibitors of tumor necrosis factor-converting enzyme and matrix metalloproteases (Scheme 88).[213]

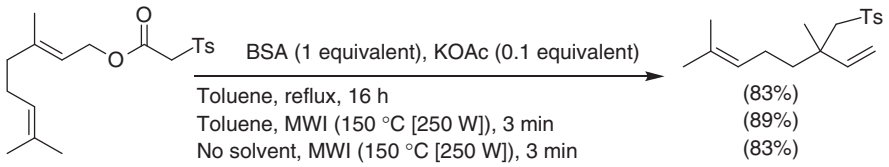


syn:*anti* = 1:5

Scheme 88

5.20.3.7 Decarboxylative Claisen Rearrangement

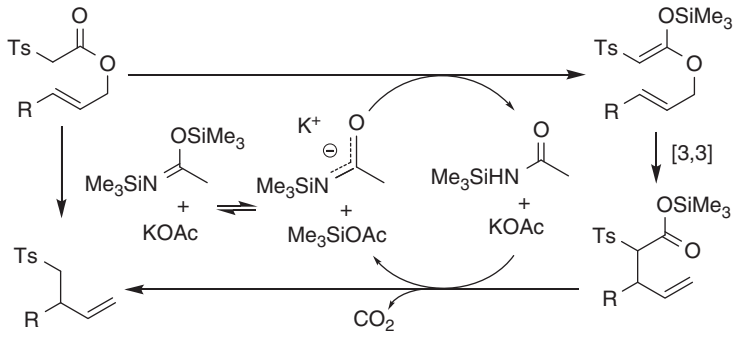
A novel variant of the Ireland–Claisen rearrangement, in which an electron-withdrawing α-substituent is present at the ketene acetal skeleton, has been developed. The one-pot rearrangement-decarboxylation sequence takes place smoothly in a highly regio- and stereoselective manner, regardless of the substitution pattern at the allylic portion of the substrate. Sulfonyl groups have proved to adapt successfully to this decarboxylative Claisen rearrangement to yield homoallylic sulfones in high yields.[214,215] Treatment of allylic tosylacetates with substoichiometric amounts of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate afforded α-tosyl silyl ketene acetals, which *in situ* underwent thermal rearrangement followed by acetate-induced desilylation-decarboxylation to provide γ,δ-unsaturated sulfones in one step. Similar results were achieved by brief exposure to MWI (Scheme 89).



Scheme 89

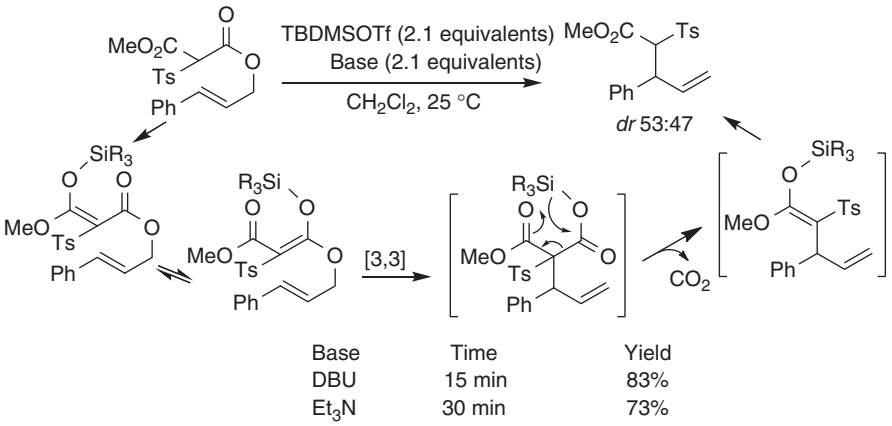
A catalytic cycle involving acetate as a silyl transfer reagent was proposed (Scheme 90).

Decarboxylative Claisen rearrangement conditions have also been successfully applied to allyl methyl esters of tosylmalonic acid to provide an effective regiospecific access to the products of the formal allylation of methyl tosylacetate. Both reagent systems, BSA/KOAc and DBU/TBDMSOTf, proved useful for these substrates, which afforded, under mild conditions, the allylated methyl tosylacetates by a sequence not requiring acetate in the decarboxylation step. A mechanism involving silatropic



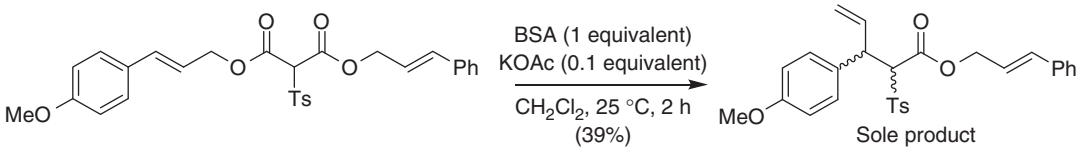
Scheme 90

rearrangement of the intervening silyl esters would account for the results obtained in the presence of silyl triflates and DBU (Scheme 91).[216]



Scheme 91

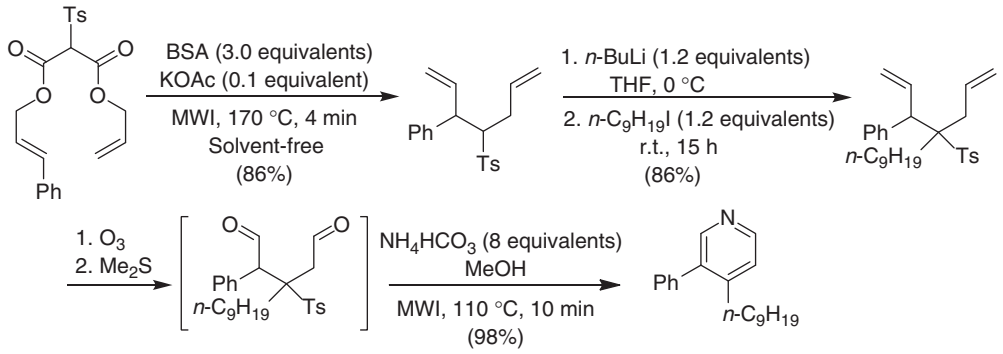
A first-order rate constant was determined for the decarboxylative Claisen rearrangement of these allyl methyl 2-tosylmalonate esters and a rate enhancement was observed for those substrates possessing an electron-rich aryl group bonded to the allylic double bond. These data are indicative of a positive charge development at the benzylic position during the rearrangement and, therefore, are consistent with a dipolar transition state for the reaction.[217] In complete agreement with these kinetic studies, substituted bis(allyl) 2-sulfonylmalonates underwent a highly regioselective rearrangement-decarboxylation sequence when treated with BSA/KOAc. Thus, allylic side-chains bearing remote vinylic electron-rich substituents rearranged preferentially (Scheme 92).[218]



Scheme 92

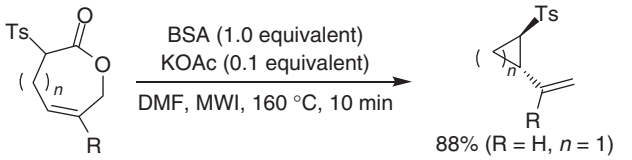
When bis(allyl) 2-tosylmalonates were treated with the BSA/KOAc reagent combination under MWI, a double decarboxylative Claisen rearrangement sequence took place and provided substituted 1,6-heptadienes, which were subsequently transformed into polysubstituted pyridines (Scheme 93).[219]

When substrates possessing heteroaromatic rings were exposed to the decarboxylative Claisen rearrangement conditions, the corresponding dearomatized products were formed. Particularly interesting are the alkylidene-substituted indolines prepared by microwave-assisted decarboxylative rearrangement reactions of substituted acetate derivatives of 3-(hydroxyalkyl)indoles.[220] These dearomatized products were conveniently transformed into polyfunctionalized compounds due to the synthetic versatility of the exocyclic methylene group.



Scheme 93

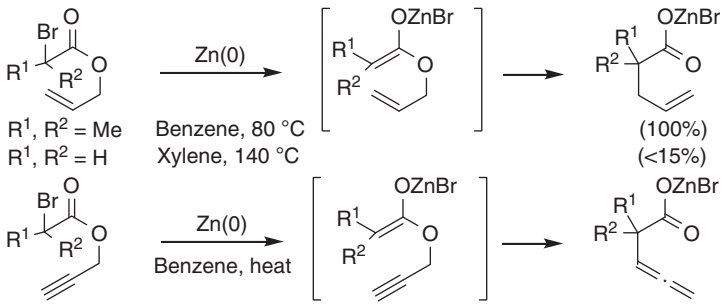
Transannular, decarboxylative Claisen rearrangement reactions of seven- and eight-membered unsaturated lactones bearing an α-arylsulfonyl substituent have been reported for the diastereoselective synthesis of *trans*-sulfur-substituted vinylcyclopropanes[221] and vinylcyclobutanes[222] in high yields (Scheme 94).



Scheme 94

5.20.3.8 Reformatsky Rearrangement

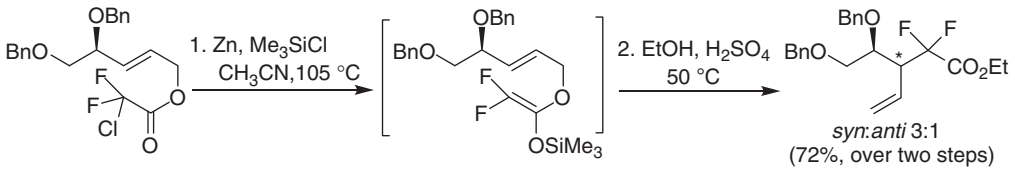
The [3,3]-sigmatropic rearrangement of zinc allylic ester enolates, which provides an access to zinc carboxylates of γ,δ-unsaturated carboxylic acids, is known as the Reformatsky rearrangement.[223] This rearrangement, compatible both with allylic and propargylic substrates, requires the *in situ* formation of the zinc enolates by zinc-mediated dehalogenation of *O*-allyl (or *O*-propargyl) α-bromo esters (Scheme 95). Under the initially reported conditions (heating at moderately high temperatures in a hydrocarbon solvent in the presence of an excess of zinc dust), the allylic α-bromo esters reacted smoothly under nonacidic and nonbasic conditions. The undesired condensation of the zinc enolate giving 1,3-dicarbonyl compounds is minimized with alkyl-substituted enolates, which give the highest yields of rearrangement products.



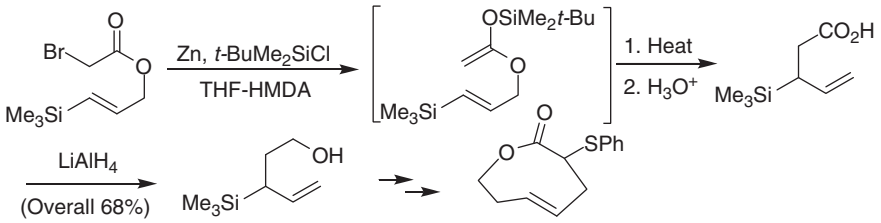
Scheme 95

The presence of Me_3SiCl is frequently required for the zinc-promoted Reformatsky rearrangement to take place,[224] and, as a consequence, a silyl ketene acetal is proposed as the reaction intermediate. The reaction has been used for the synthesis of *gem*-difluoro-substituted γ,δ-unsaturated acids, which has been reported as a key step in the preparation of fluorine-containing carbocyclic nucleosides (Scheme 96).[225,226] The chirality of the substrate is transferred during the rearrangement.[226]

This modified Refortmatsky rearrangement has been satisfactorily used for the preparation of a key intermediate in the synthesis of medium-sized lactones (Scheme 97).[227]

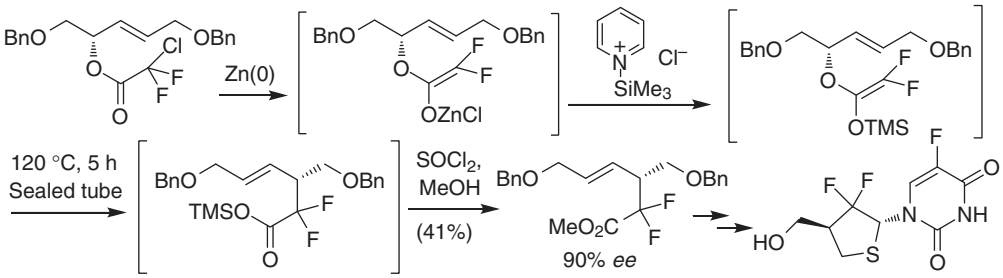


Scheme 96



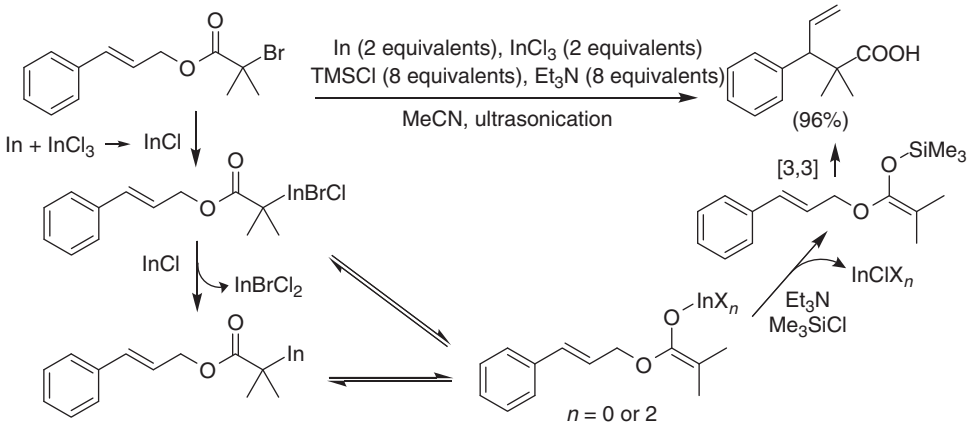
Scheme 97

In the context of the asymmetric synthesis of *gem*-difluorinated nucleoside analogs, the addition of pyridine to the reaction mixtures of the Reformatsky rearrangement has proved useful for improving both the yield and the stereoselectivity of the reaction.[228] The additive activates the silyl chloride, thus facilitating the conversion of the initially formed zinc enolate into the *O*-silyl ketene acetal, which undergoes the rearrangement (Scheme 98).



Scheme 98

Recently, a modified indium-mediated Reformatsky rearrangement was reported.[229] It consists of the reaction of substituted allyl (or propargyl) α-bromoacetates with indium and indium(III) chloride in the presence of Me_3SiCl and Et_3N under ultrasonication. The scope of the method has proved general for a large variety of substrates, including those which are base sensitive. The proposed mechanism implies the formation of indium ester enolates, which are converted into the silyl ketene acetal, the rearrangement of which generates the corresponding carboxylic acid (Scheme 99).



Scheme 99

5.20.4 Stereoselective Claisen Rearrangement

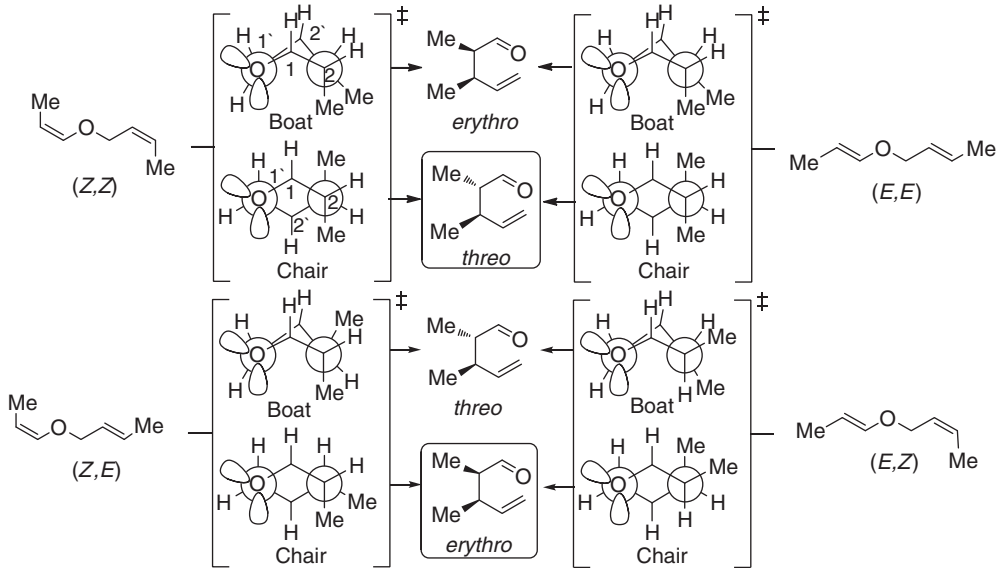
5.20.4.1 General Aspects

The highly ordered cyclic transition state involved in the Claisen rearrangement, along with the steric restrictions imposed by the orbital symmetry rules, effect a reliable transfer of stereochemistry from starting materials to products. There are two approaches to control the stereoselectivity of the reaction that we will refer to as 'intra-annular stereoselection' and 'extra-annular stereoselection,' depending on whether the elements of stereocontrol are embedded in the allyl vinyl ether moiety or are external to it. In the intra-annular stereoselection, there are three possible elements of stereocontrol that will determine the stereochemistry of the products: the geometry of the vinyl ether bond, the geometry of the allyl double bond, and the configuration at C4. In the extra-annular stereoselection, the diastero- and enantioselectivity of the reaction can be controlled either by a remote stereocenter covalently linked to the allyl vinyl ether moiety or by a chiral catalyst.

5.20.4.2 Intra-annular Stereoselection

5.20.4.2.1 Transition state geometry

The generally accepted geometry for the transition state of the Claisen rearrangement in acyclic systems is a chair conformation, controlled by the steric[230] and electronic[53] features of the system. The gas-phase rearrangement of acyclic (*Z*,*Z*)-, (*E*,*E*)-, (*Z*,*E*)-, and (*E*,*Z*)-allyl vinyl ethers into the corresponding *erythro* and *threo* products proceeds preferentially through chairlike transition states in order to minimize steric interactions, as shown in the Newman projections represented in **Scheme 100**.[2j] The chairlike transition state determines that the geometry of the vinylic and the allylic double bonds in the starting material controls the relative stereochemistry of the two new stereogenic centers created through the sigmatropic process.



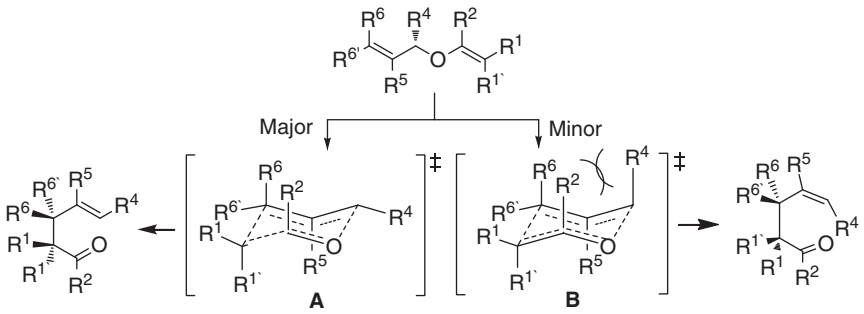
Scheme 100

In the presence of a substituent at C4 ($R^4 \neq H$), there are two possible chairlike transition states that place the C4 substituent in a pseudoequatorial (**A**) or pseudoaxial (**B**) position (**Scheme 101**). The preference for transition state **A**, in which R^4 occupies a pseudoequatorial position, determines the prevalence of *E* alkenes as major products in the rearrangement of acyclic systems.

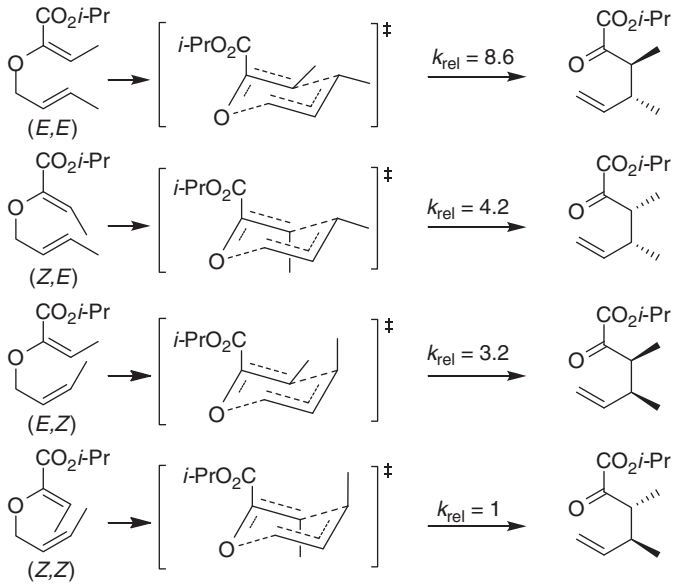
Kinetic studies on the uncatalyzed [3,3]-rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers, first reported by Gosteli in 1972,[56] have evidenced that these substrates, regardless of the geometry of both vinylic and allylic olefins, have a clear preference for reacting through a chairlike transition state. The reaction rates, however, are closely dependent on the substituents and the geometry of the double bonds in the substrate (**Scheme 102**).[57]

Recent computational studies have proved that the thermal aromatic Claisen rearrangement also proceeds through a chairlike transition state. The observed *E*/*Z*-product selectivity, ranging between 90:10 and 98:2, was attributed to the progression of the rearrangement through differently favored chairlike conformers.[231]

Claisen and Claisen-related [3,3]-sigmatropic rearrangements evolving through the most stable chairlike transition state have been applied to the synthesis of a number of natural products.[232,233] In the presence of hard Lewis acid catalysts (typically aluminum or titanium), selective coordination to one of the two electron lone pairs at the oxygen atom of the substrates favors a chairlike conformation for the transition state.[234] The asymmetric synthesis of (−)-saudin uses a Lewis acid ($TiCl_4/Me_3Al$)-mediated Claisen

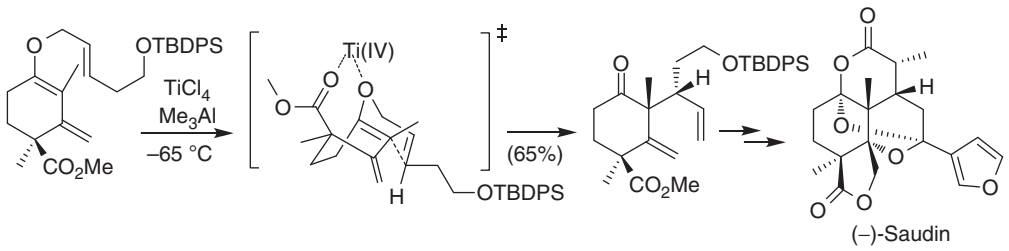


Scheme 101



Scheme 102

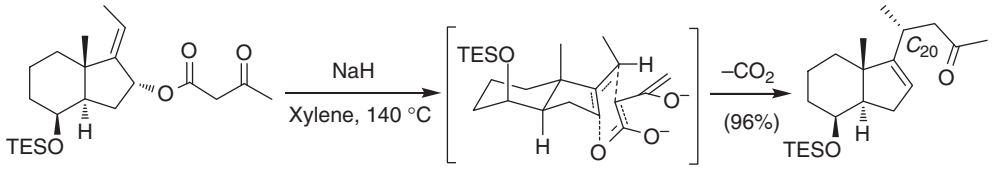
rearrangement of an allyl vinyl ether to introduce the correct configuration at the two quaternary carbon atoms (C13 and C16). The facial selectivity derives from a bidentate coordination by Ti(IV) of both the oxygen atoms of the vinyl ether and the ester, enforcing the boatlike conformation in which the rearrangement takes place via the chairlike transition state on the less hindered $\alpha-$face (Scheme 103).[235]



Scheme 103

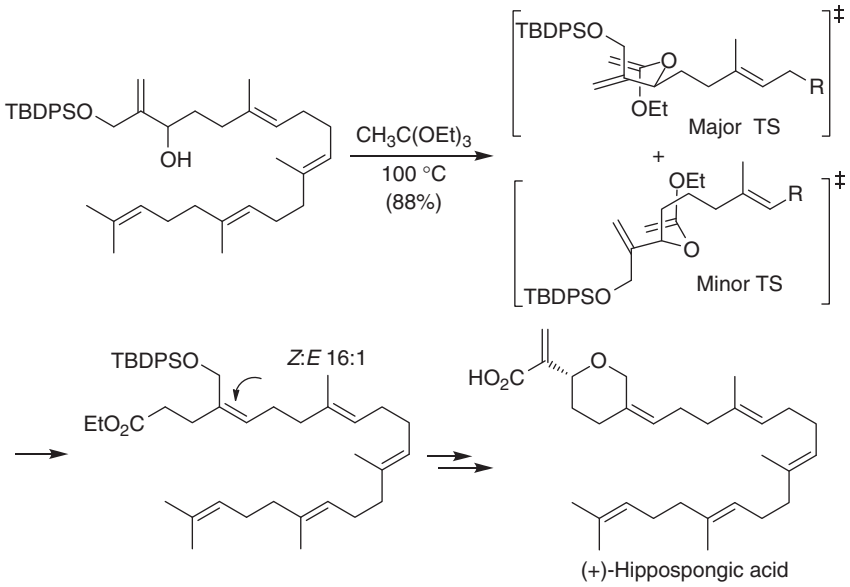
The six-membered chairlike cyclic transition state of the Carroll rearrangement, reported for the stereocontrolled synthesis of functionalized vitamin D_3 side-chain units with the natural C20 (*S*) configuration, is responsible for the excellent chirality transfer from the starting allylic β-keto ester to the rearranged ketone (Scheme 104).[236]

In the total synthesis of the gastrulation inhibitor (+)-hippospongic acid A, the Johnson rearrangement of an allylic alcohol bearing a TBDPS-protected hydroxymethyl group at C2 afforded the corresponding γ,δ-unsaturated ester as a 16:1 *Z*:*E* olefin



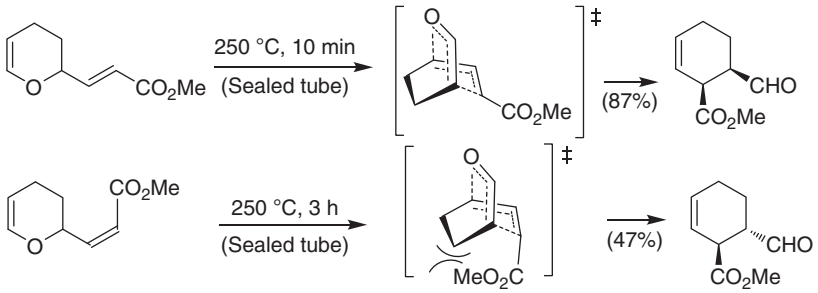
Scheme 104

mixture. The most favorable chairlike transition state bearing the long carbon chain in an equatorial orientation gave the desired major olefin, whereas the minor isomer derived from the alternate chair conformer where the steric interactions with the bulky TBDPS ether are minimized (Scheme 105).[237]



Scheme 105

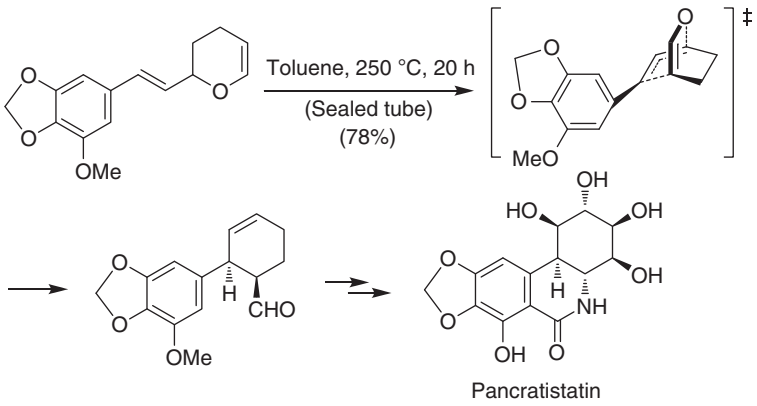
Although it is well accepted that the Claisen rearrangement proceeds through a chairlike transition state for acyclic systems, the rearrangement takes place through a boatlike transition state for pyranoid- and furanoid-glycals bearing an endocyclic vinylic double bond. Thus, the Claisen rearrangement of 3,4-dihydro-2*H*-pyranylethylenes proceeds preferentially through a boatlike transition state to afford differently substituted cyclohexenes. This boat conformation explains the stereochemistry as well as the relative reactivity depending on the geometry of the allylic double bonds of the substrates (Scheme 106).[238]



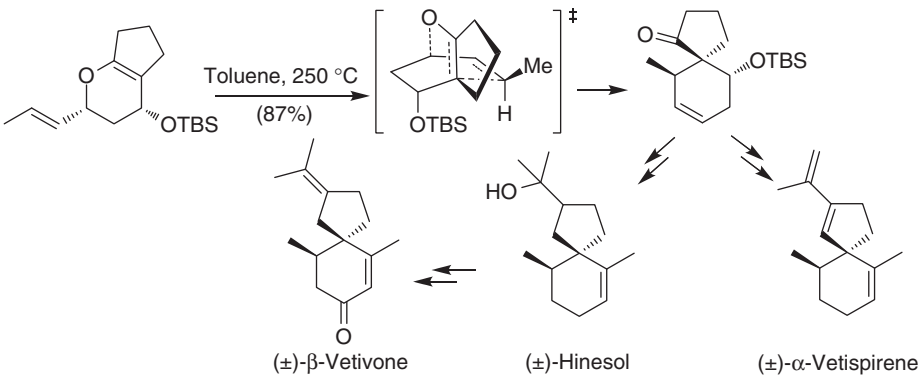
Scheme 106

A similar protocol has been described as a highly diastereoselective key step in the synthesis of the antitumor alkaloid pancratistatin (Scheme 107).[239]

A highly stereoselective thermal Claisen rearrangement of bicyclic dihydropyran derivatives through a boatlike transition state provided multifunctionalized spiro[4.5]decanes.[240] This methodology was used for the construction of the key intermediate in the synthesis of the vetivane sesquiterpenes (±)-α-vetispirene, (±)-hinesol, and (±)-β-vetivone (Scheme 108).[241]



Scheme 107



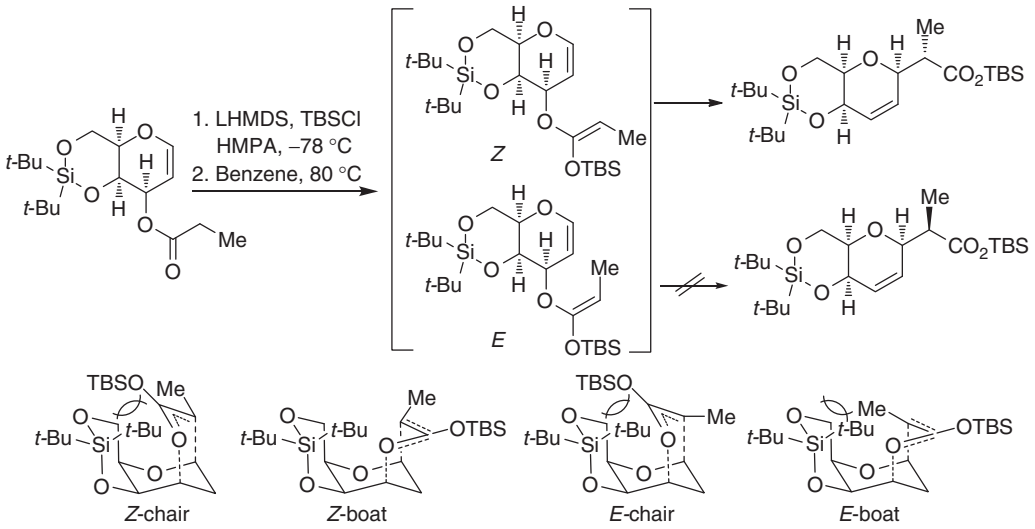
Scheme 108

When the stereoselectivity is not good enough, modifications in the starting material can sterically modulate the activation energy for the rearrangement to improve the overall diastereoselectivity. This strategy has been used recently in the total synthesis of the marine natural products halicondrins.[242] The first attempts to perform an Ireland–Claisen rearrangement on a glycal derivative (lacking a silyl ether bridge) to synthesize the C27–C38 fragment of halicondrin B, resulted in an 8:1 mixture of diastereoisomers. It was reasoned that the introduction of a silyl ether bridge in the glycal structure could affect the activation energy for the Claisen rearrangement, improving the overall stereoselectivity of the process. Using the conditions reported by Ireland, the starting glycal was converted to *O*-silyl ketene acetals (*Z*/*E* 7.3:1 ratio) which, on heating, afforded a single diastereoisomeric carboxylate (Scheme 109). The (*Z*)-ketene acetal reacts through a boatlike transition state (*Z*-boat) to avoid the steric destabilization present in the chairlike transition state (*Z*-chair). However, for the (*E*)-ketene acetal both transition states appear to have a severe steric destabilization. Thus, the rearrangement takes place preferentially for the (*Z*)-*O*-silyl ketene acetal through a boatlike transition state, resulting in an improvement of the overall diastereoselectivity.

In simple cyclohexenols, the geometry of the transition state depends on the geometry of the vinyl ether (Table 1).[243] For *Z*-silyl ketene acetals (R^c = Me), the rearrangement takes place preferentially through a boatlike transition state, whereas for *E*-silyl ketene acetals (R^t = Me) the transition state prefers a chairlike geometry. Transition states **TS1** and **TS2** explain the different pathways for *Z*- and *E*-silyl ketene acetals. When R^c = Me and R^t = H, the chairlike transition state **TS1** is destabilized as compared to the boatlike conformer **TS2** due to the steric interaction between the substituent X and the cyclohexene ring. However, when R^t = Me and R^c = H, the interaction between R^t and the carbocycle destabilizes the transition state **TS2** relative to **TS1**.

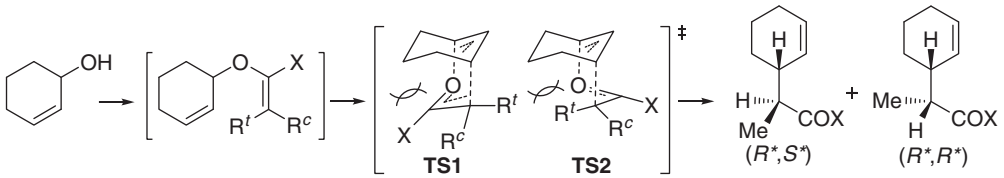
From cyclic enol ethers, it is possible to control the geometry of the transition state by proper choice of the catalyst (Scheme 110).[72] In the presence of 2,6-dimethylphenol, the *E-anti* diastereoselectivity is explained by a chairlike transition state. However, using a Pd(II) catalyst the rearrangement takes place through a boatlike transition state, where the diene acts as a bidentate ligand to give the major *E-syn* product.

The transannular Ireland–Claisen rearrangement of medium or large ring lactones proceeds through a boatlike transition state usually due to restrictions imposed by the macrocycle. A recent example depicted in Scheme 111 shows the transannular rearrangement of a ζ-lactone through a boatlike transition state to afford a *cis*-vinylcyclobutane as a single diastereomer.[222] This reaction has served as the key step in the formal synthesis of (±)-grandisol.



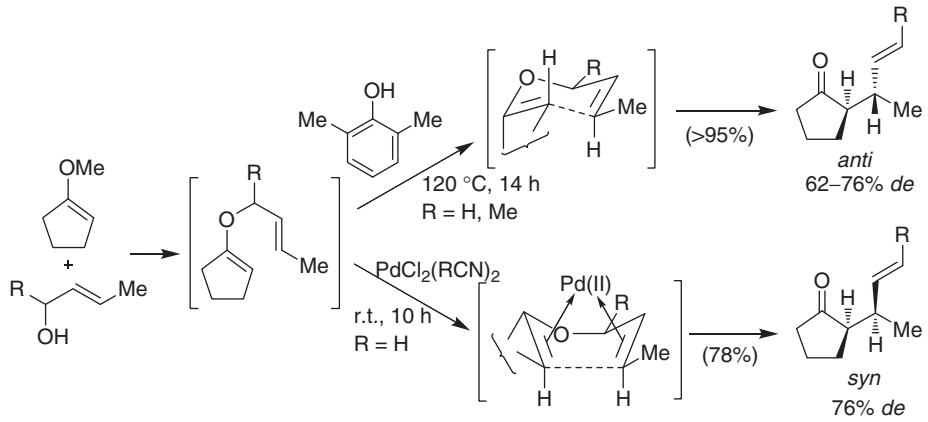
Scheme 109

Table 1 Ireland rearrangement of 2-cyclohexenols



Entry	*Conditions*	*X*	R^t	R^c	*(R*,S*):(R*,R*)*	*Transition state*	*Yield (%)*
1	LDA, THF; *t*-BuMe$_2$SiCl; Δ	$OSiR_3$	Me	H	85:15	Chair	47
2	LDA, HMPA/THF; *t*-BuMe$_2$SiCl; Δ	$OSiR_3$	H	Me	75:25	Boat	36

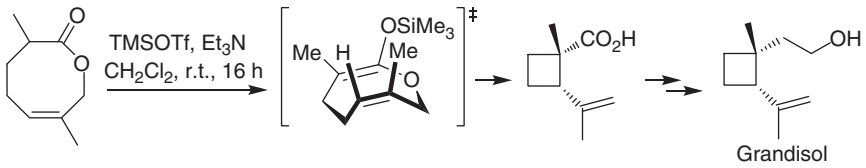
Source: Reproduced from Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062.



Scheme 110

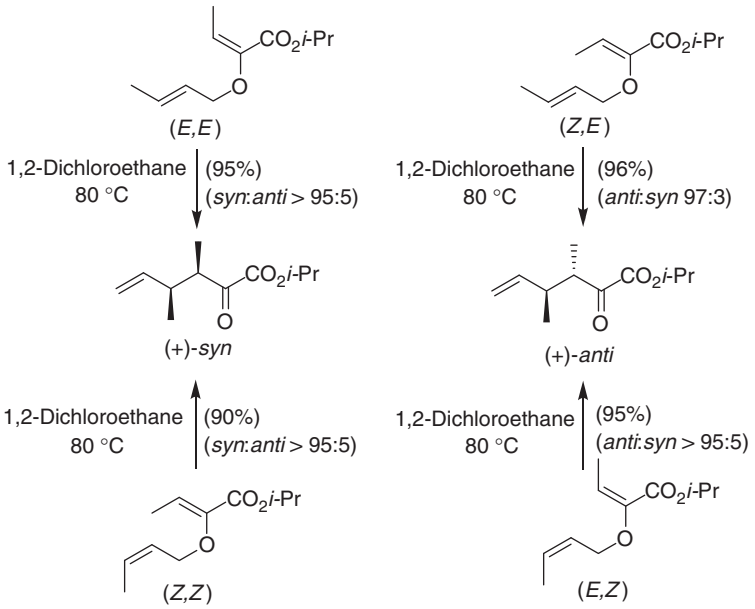
5.20.4.2.2 Enol ether geometry

As mentioned above, due to the highly ordered transition state of the Claisen rearrangement, the enol ether and the allylic double bond geometries determine the relative configuration of the new stereocenters created in the process. Therefore, different strategies to control the enol ether geometry have been developed. Considering the marked preference of aliphatic allyl vinyl ethers for evolving through a chairlike transition state, the relative stereochemistry of the two vicinal stereocenters of the rearranged product



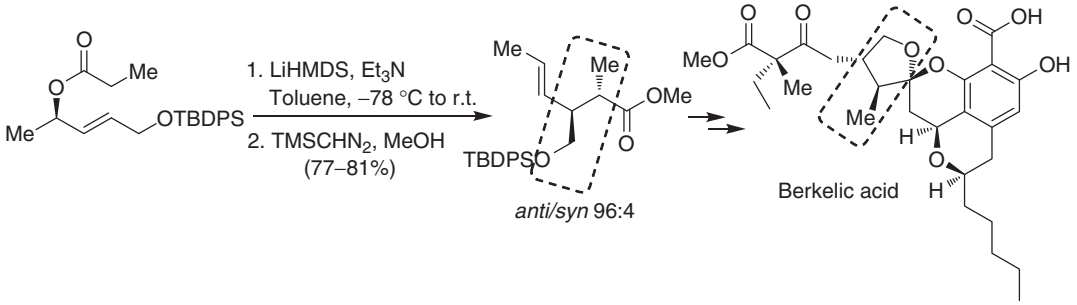
Scheme 111

will depend on the geometry of the enol ether on assuming a fixed geometry at the allylic olefin. 2-Alkoxycarbonyl-substituted allyl vinyl ethers have proved especially attractive substrates for examining the influence of the enol ether geometry on the stereochemical outcome of the rearrangement.[57,75] For *E*-configured allylic substrates, those with an (*E*)-enol ether double bond rearrange to the *syn* product, whereas a (*Z*)-enol ether double bond gives the *anti* product. Contrarily, *Z*-configured allylic substrates evolve to the *syn* or *anti* product when starting from (*Z*)- or (*E*)-enol ethers, respectively (Scheme 112).



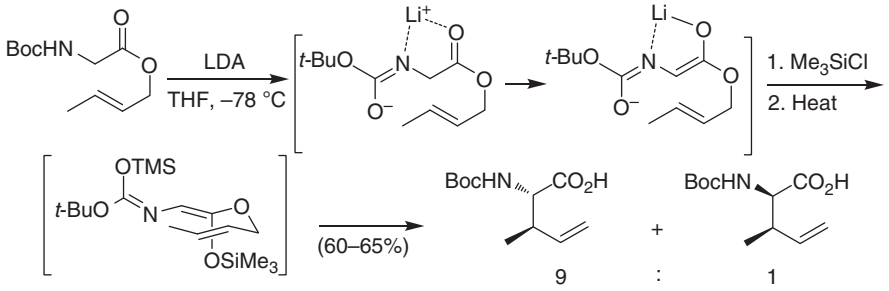
Scheme 112

One of the factors that contributes to the versatility of the Ireland–Claisen rearrangement is the possibility to easily control the *E*/*Z* stereochemistry of the enol ether. Using LDA as base, in THF or THF/HMPA as solvent systems, it is possible to selectively obtain the *E* or *Z* silyl ketene acetal intermediates, respectively.[244] Consequently, a highly reliable and predictable transfer of stereochemistry from the starting material to the product can be realized. Although in most cases synthetically useful *E*/*Z* stereoselectivities are obtained, it is still necessary to find more efficient methods. As previously mentioned, an unprecedented *E*/*Z* selectivity has been observed in the enolization of acyclic esters using a combination of lithium hexamethyldisilazide in Et_3N/toluene (see Scheme 86).[209] The efficiency of the process makes it one of the most significant modern developments in Claisen chemistry. These conditions have been recently applied to the total synthesis of berkelic acid (Scheme 113).[245]



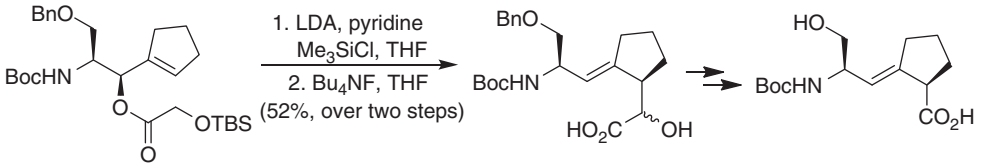
Scheme 113

The presence of heteroatom substituents at the α-position of the ester fragment effectively controls the stereochemistry of the allyl silyl ketene acetal. An *N*-acylamino substituent at the α-position of the carboxylic acid moiety can determine the enolate stereochemistry and hence the stereochemical course of the process. The initial coordination of the Li^+ between the carbonyl oxygen atom and the anionic nitrogen substituent generates the *E* enolate, which rearranges through a chairlike transition state to afford the *threo* product (Scheme 114).[246] This methodology has been applied to the synthesis of highly substituted α-amino acids in good yields and high stereoselectivities.[200,247]



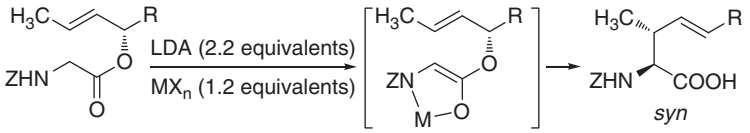
Scheme 114

Oxygen substituents at the α-position of *O*-allylic esters also proved effective in the chelation control of the Ireland rearrangements; this methodology was utilized in the context of different synthetic sequences.[248,249] During the synthesis of the amide isostere of the dipeptide Ser-*trans*-Pro, the (*E*)-alkene was formed with high levels of diastereoselectivity through the use of a chelation-controlled Ireland rearrangement of a protected allylic glycolate (Scheme 115).[250]



Scheme 115

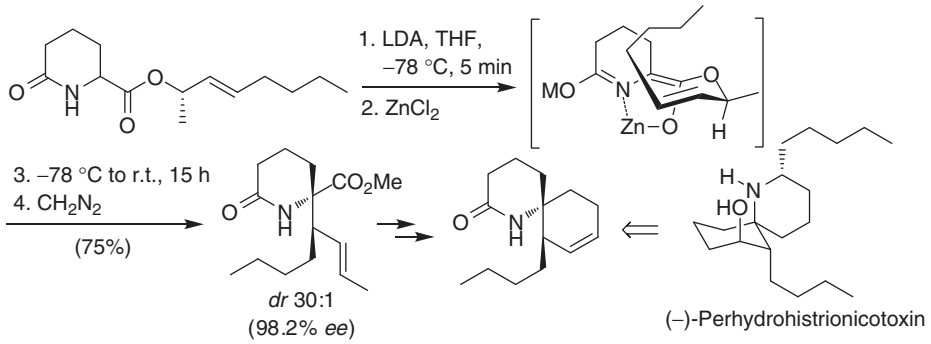
Esters derived from α-amino acids allow a good control over the enolate formation through chelation with a metal salt through the so-called chelate version of the Claisen rearrangement, which is a variation of the previously discussed ester enolate rearrangement. Deprotonation of *N*-protected amino acid allylic esters with LDA and subsequent addition of a metal salt (typically $ZnCl_2$) affords an intermediate chelated zinc enolate, which rearranges on warming to room temperature to produce the unsaturated amino acids (Scheme 116). The higher stability of the chelated zinc-enolates, as compared to the corresponding lithium enolates, makes these intermediates considerably more advantageous as substrates for the rearrangement. As the enolate geometry is determined by chelation and a chairlike transition state is preferred, compounds with a *syn* relative configuration are formed diastereoselectively in the rearrangement of (*E*)-allylic esters.[251]



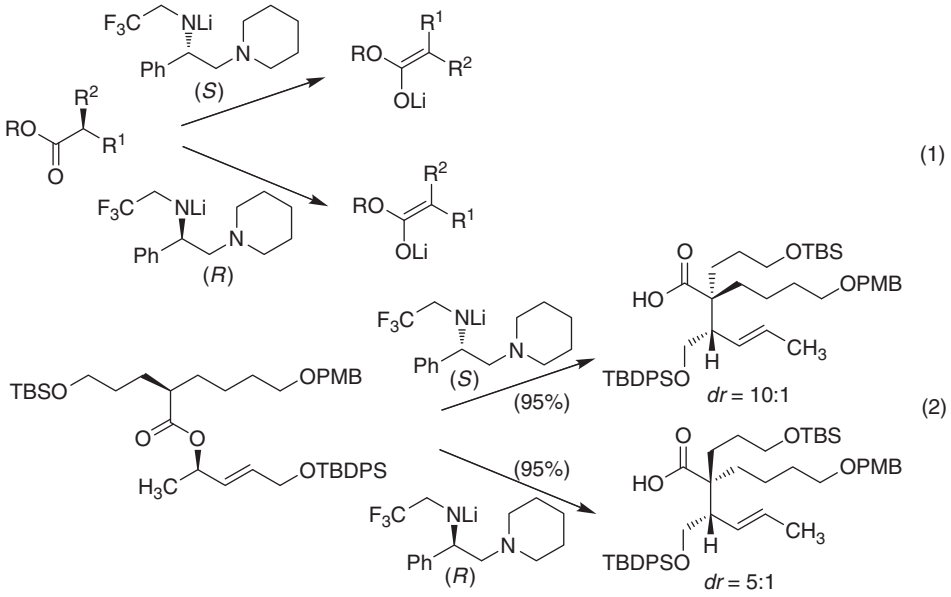
Scheme 116

The utility of this strategy has been nicely exemplified in a formal synthesis of the non-natural alkaloid (–)-perhydrohistrionicotoxin, in which a cyclic amino acid chelate Claisen rearrangement was used as the key step.[252] Again, the zinc chelation dictated the enolate geometry of the intermediate, the rearrangement of which, via a chairlike transition state, proceeded with a high level of π-facial selectivity (Scheme 117).

One of the deficiencies of the Ireland–Claisen rearrangement is the low diastereoselectivity observed for α-branched esters due to lack of geometry control in the enol ether formation. Recently, an unprecedented stereoselective enolization of α-branched esters using chiral lithium amide bases has been reported (Scheme 118, equation 1).[253] By choosing the right enantiomer of the base, both enolates can be selectively prepared from the corresponding allylic ester (Scheme 118, equation 2).



Scheme 117



Scheme 118

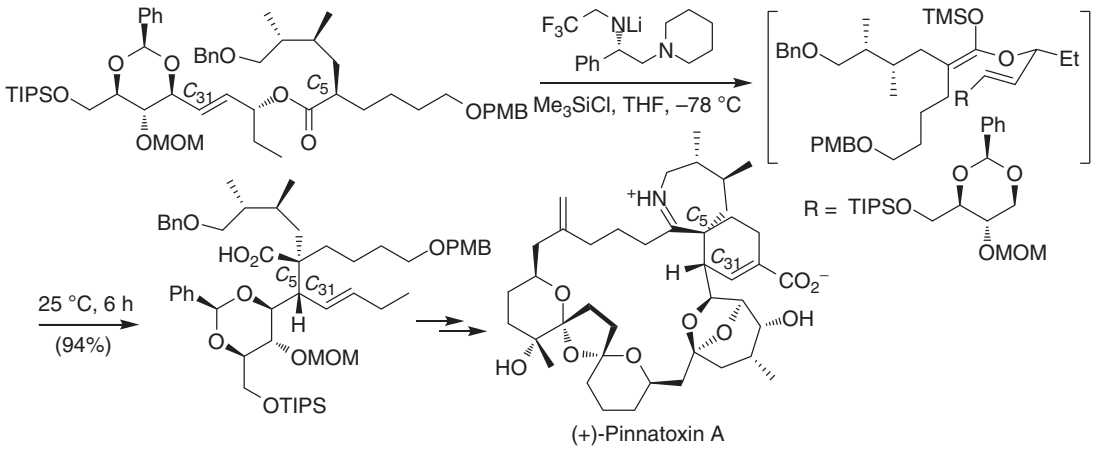
The two vicinal stereogenic centers – quaternary C5 and tertiary C31 – present in the marine toxin (+)-pinnatoxin A were constructed by way of a highly stereoselective Ireland rearrangement of an α-branched ester.[254,255] The stereoselective enolization of the ester precursor using a Koga-type chiral lithium amide produced high levels of diastereoselectivity in the rearrangement (Scheme 119).

The use of rhodium carbenoids constitutes another way of controlling the geometry of trisubstituted enol ethers (Scheme 120). Treatment of differently substituted α-diazo ketones with an allylic alcohol in the presence of a rhodium catalyst proceeds through O-H insertion via a rhodium-stabilized ylide, and allows the selective formation of the *Z*-enol ether, which rearranges to afford the tertiary (*R*)-alcohol.[256] Alternatively, a dicarbonyl allyloxy derivative, prepared in three steps from the α-diazo ketone, gives selectively the *E*-enol ether, which evolves to the (*S*)-alcohol through a sigmatropic rearrangement.

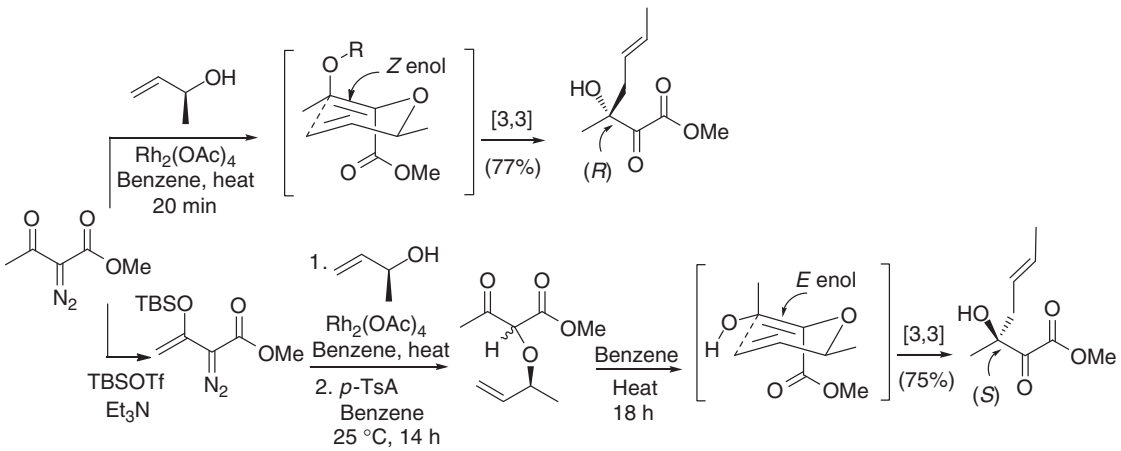
(*E*)-Silyl ketene acetals can also be generated by treatment of allyl acrylates with a rhodium catalyst in the presence of a phosphine ligand and a silane (Scheme 121).[257] These (*E*)-silyl ketene acetals undergo an Ireland–Claisen rearrangement with good diastereoselectivity. Again, the geometry of the silyl ketene acetal is the crucial control element.

Sometimes, the vinyl double bond geometry is controlled by steric interactions. This is the case for *N*,*O*-ketene acetals, synthesized by reaction of propionamide salts and lithium alkoxides (Scheme 122).[149] The *Z*-enolate is more stable than the *E*-enolate due to destabilizing interactions between the nitrogen substituents and the enamine substituent at the β position. The *Z*-enolate reacts faster to give the Eschenmoser rearrangement product.

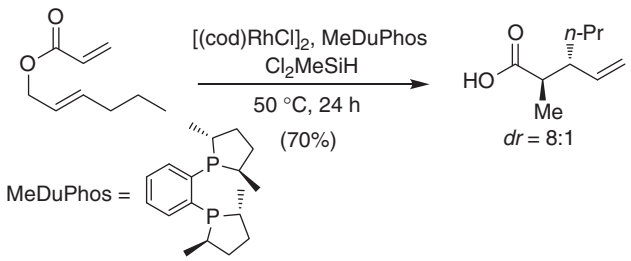
Allylic *N*,*O*-acetals can also be synthesized by addition of allylic alcohols to ynamines through a keteniminium intermediate (Ficini–Claisen rearrangement). At elevated temperatures, the *E*-ketene acetal is preferentially formed and rearranges to give the corresponding γ,δ-unsaturated amide with moderate diastereoselectivity (Scheme 123). In the presence of a Lewis acid, the thermodynamically favored *Z*-ketene acetal is generated, which on rearrangement affords the diastereomeric amide.[258] This method is somewhat limited by the instability of ynamines and their somewhat difficult preparation.



Scheme 119



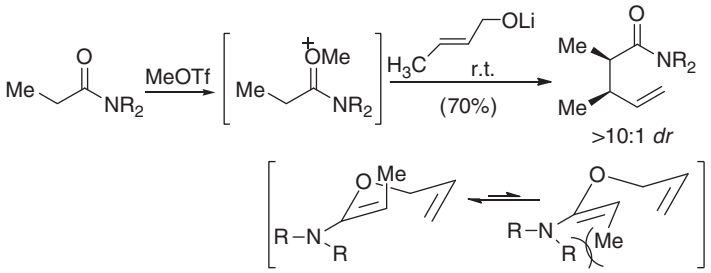
Scheme 120



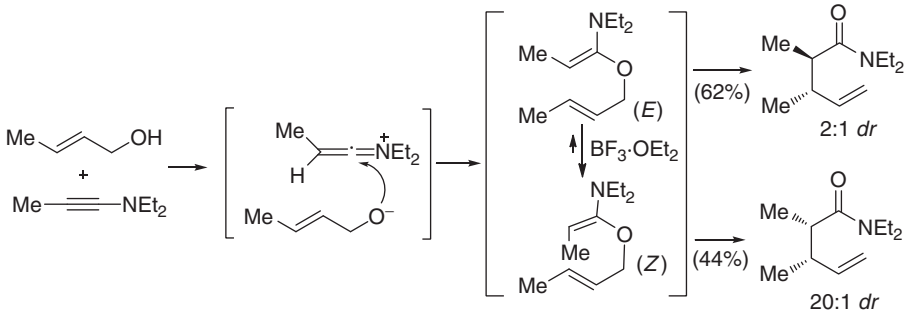
Scheme 121

5.20.4.2.3 Allylic double bond geometry

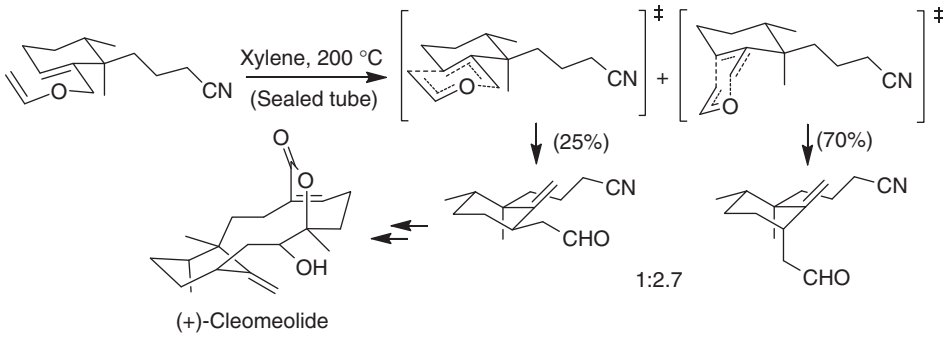
The choice of the allylic double bond geometry in the starting materials is crucial to obtain the desired relative configuration in the rearranged products. This is especially important in the total synthesis of naturally occurring or biologically active products, as a result of the high intra-annular diastereoselectivity of the reaction. In the total synthesis of the macrocyclic diterpene lactone (+)-cleomeolide, a thermal aliphatic Claisen rearrangement allowed the construction of the methylenecyclohexane fragment. The endocyclic nature of the trisubstituted allylic double bond of the precursor ether was responsible for the diastereomeric ratio of the rearrangement products; the minor one was further transformed into the natural product. The axial or equatorial arrangement of the newly formed C–C bond was dependent on the evolution of the rearrangement through either of the two possible chairlike transition states (Scheme 124).[259]



Scheme 122



Scheme 123



Scheme 124

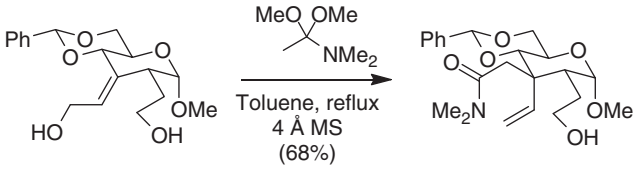
The stereochemical outcome of the Eschenmoser rearrangement utilized for the synthesis of carbocycles from carbohydrate derivatives proved to be dependent on the olefin geometry at the exocyclic allylic fragment of the chosen diol (Scheme 125).[260]

In this context, the Carroll version of the Claisen rearrangement had been used to install the C20 stereogenic center of sterol side chains. Only the *E*-isomer of the starting allyl *β*-keto ester affords the natural configuration (20*R*) at C20 present at cholesterol, whereas the *Z*-isomer gives the opposite configuration (20*S*). The differences detected in the yields for both rearrangements (90% from *E*-allylic ester and 62% from *Z*-isomer) derive from the axial arrangement of the methyl group in the transition state for the *Z*-isomer relative to its equatorial positioning in the transition state for the *E*-isomer (Scheme 126).[137]

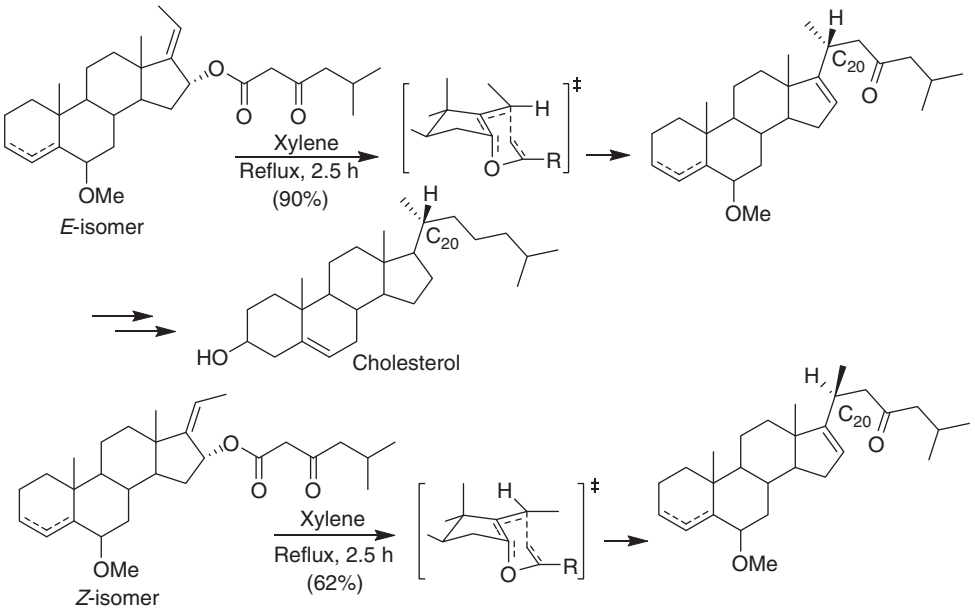
Sometimes, a change in the allylic double bond geometry can shut down the Claisen rearrangement. A recent example can be found in the one-pot synthesis of spirocyclic oxindoles through intramolecular Ullmann coupling and Claisen rearrangement (Scheme 127).[261] Although the starting *E*-configured indole substrate undergoes the one-pot sequence with excellent yield and diastereoselectivity, the *Z*-isomer only affords a complex mixture. This result can be rationalized considering destabilizing steric interactions between the *cis*-olefin and the hydrogen atoms of the dihydropyran ring in a boatlike transition state.

5.20.4.2.4 Configuration at C4

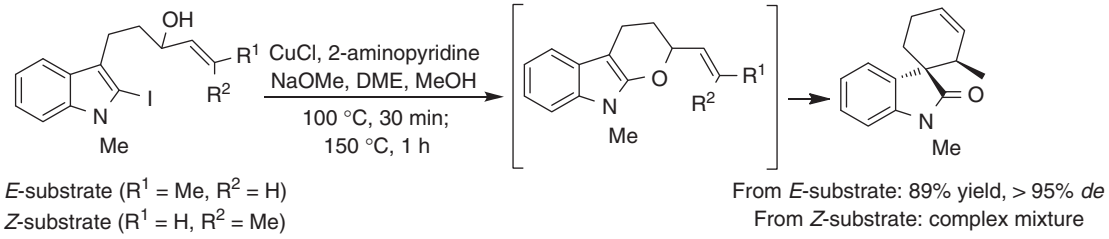
In allyl vinyl ethers with a substituent next to the ether oxygen and, therefore, with an asymmetric center at C4, the highly ordered cyclic transition state of the Claisen rearrangement determines a chirality transfer from C4 to the newly formed stereocenter at C6 and, accordingly, also at C1 (Scheme 128).[262] In acyclic systems, the substituent bonded to the stereogenic C4 atom prefers to



Scheme 125



Scheme 126



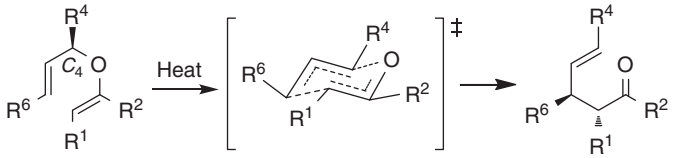
Scheme 127

occupy a pseudo-equatorial position in the chairlike transition state. This preference controls the geometry of the new double bond in the Claisen products (see Section 5.20.4.2.1). Numerous examples describing the applicability of this efficient chirality transfer during the Claisen rearrangement have been reported.[263] The 1,3-chirality transfer evidences the suprafacial nature of the thermal intramolecular rearrangement.[264]

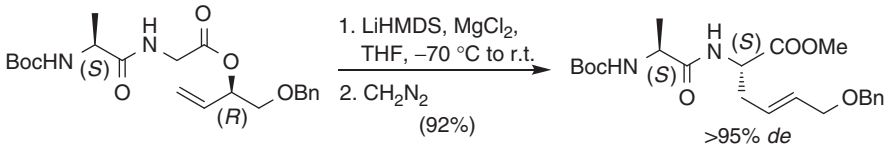
This chirality transfer has been applied to the synthesis of diastereomerically pure peptides (Scheme 129).[265] The geometry of the vinylic double bond is controlled by formation of a chelated magnesium enolate. The chirality of the allylic stereocenter is transferred to the product allowing for the generation of (*R*)- or (*S*)-amino acids. The stereocenter in the vicinal amino acid does not have any influence on the rearrangement.

The chirality of enantiomerically pure *E*-allylic *syn*-diols derived from tartaric acid has been effectively transferred through sequential sigmatropic rearrangements under Eschenmoser's conditions (*see* Chapter 5.21). When the sequence commenced with a trisubstituted olefin, two contiguous stereocenters, including a quaternary carbon atom, were constructed in the process (Scheme 130).[266]

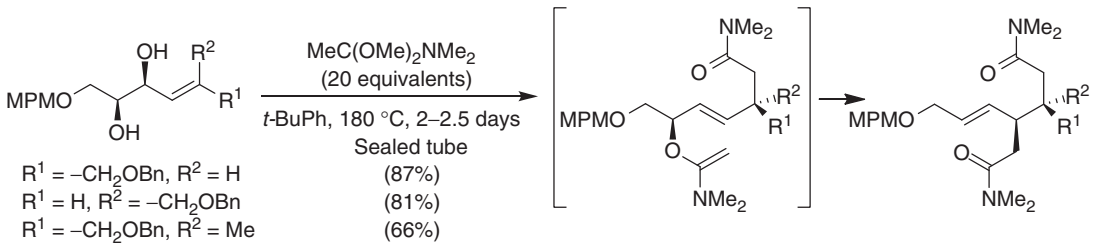
An excellent chirality transfer has been also observed in the holmium-catalyzed Claisen rearrangement of chiral allyl vinyl ethers derived from cyclic 1,2-diketones, especially with sterically less hindered substrates (Scheme 131).[267] The allyl vinyl ethers



Scheme 128



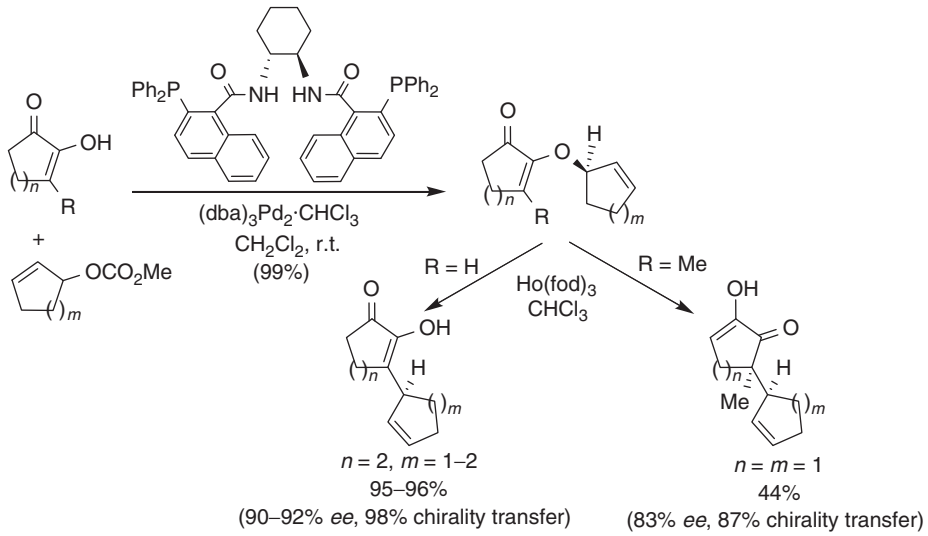
Scheme 129



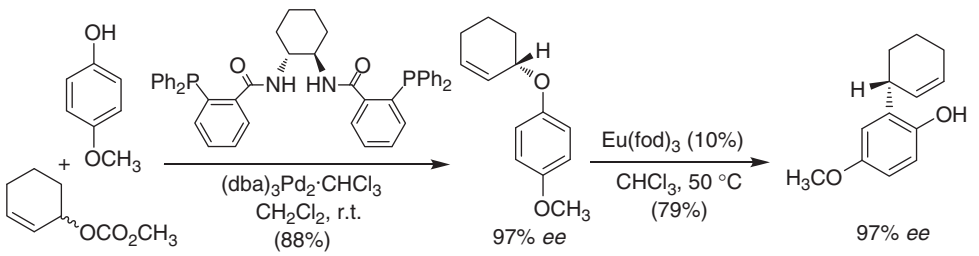
Scheme 130

were prepared by enantioselective palladium-catalyzed allylic *O*-alkylation of the corresponding 3-substituted cyclic 1,2-diketones in the presence of a C_2-symmetric chiral ligand.

A similar concept was applied to the aromatic Claisen rearrangement. The requested chiral allyl vinyl ethers were prepared by enantioselective *O*-alkylation of hydroquinone monomethyl ether, following a methodology similar to that described in Scheme 131.[268] The rearrangement proceeded with excellent chirality transfer in the presence of a catalytic amount of $Eu(fod)_3$ as the Lewis acid catalyst (Scheme 132).

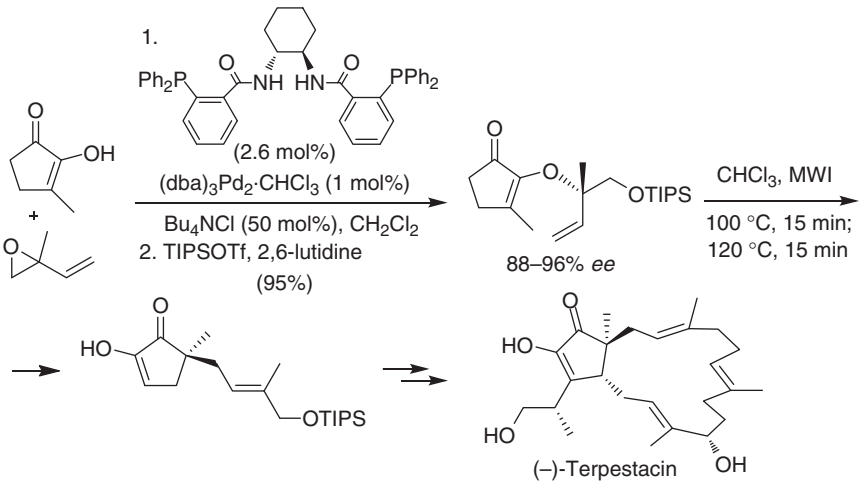


Scheme 131



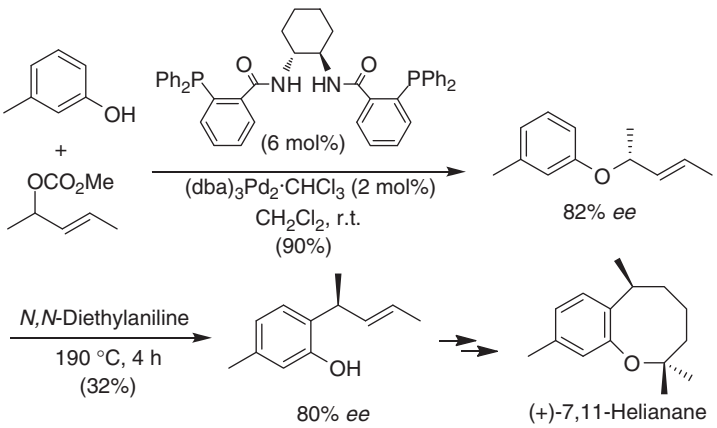
Scheme 132

An asymmetric version of this strategy has been reported as a key step in the synthesis of naturally occurring (–)-terpestacin.[269] The highly enantioselective Pd-catalyzed asymmetric allylic alkylation between commercially available 3-methyl-1,2-cyclopentanedione and isoprene monoepoxide, followed by *in situ* silylation of the adduct, provided the allyl vinyl ether, the chirality of which was efficiently transferred by a Claisen rearrangement under microwave conditions to the *C*-alkylation product (Scheme 133).



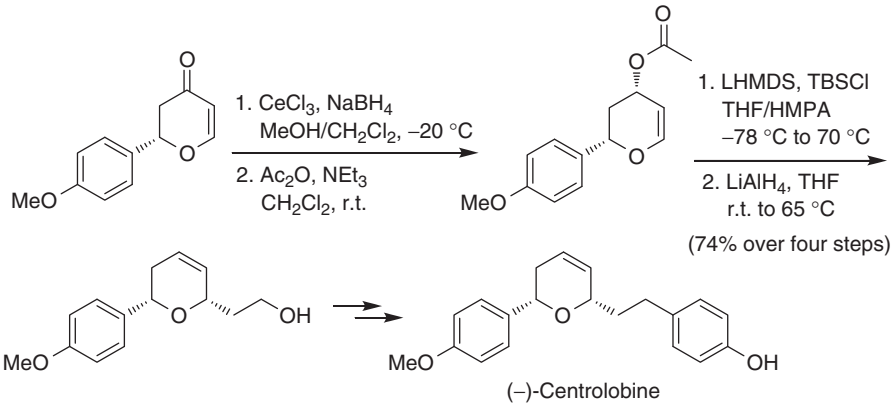
Scheme 133

A sequence of palladium-catalyzed asymmetric allylic alkylation reaction, followed by thermal aromatic Claisen rearrangement, which took place with excellent transfer of stereochemical information, has been recently applied to the synthesis of the marine sesquiterpene (+)-7,11-helianane (Scheme 134).[270]



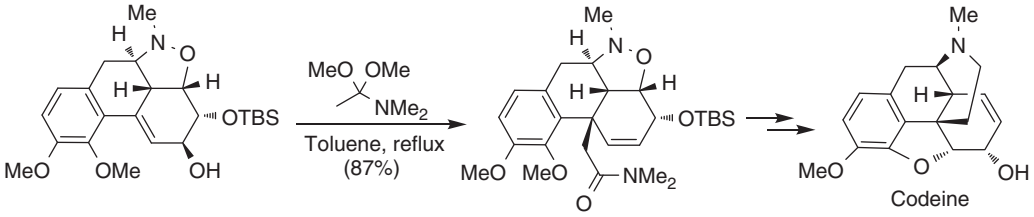
Scheme 134

The combination of a selective Luche reduction of the carbonyl function and a highly stereoselective Ireland rearrangement has been developed as an efficient route to chiral *cis*-6-substituted 2-(2-hydroxyethyl)5,6-dihydro-2*H*-pyrans.[271] This methodology has been satisfactorily utilized in the total synthesis of the antibiotic (–)-centrolobine (**Scheme 135**).



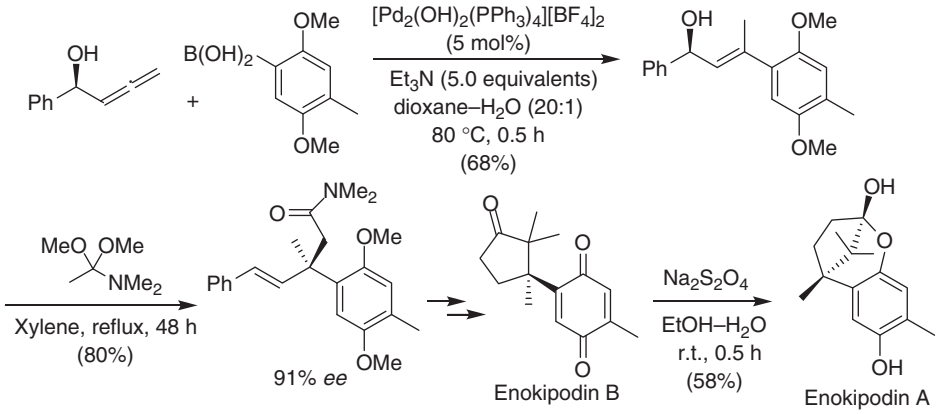
Scheme 135

The chirality of C4 in the allyl vinyl ether can also be transferred intramolecularly to create quaternary stereocenters.[272] These processes are self-immolative sequences, combining an enantioselective transformation, which creates a chiral center, and a subsequent enantiospecific sigmatropic rearrangement, whereby the initial chirality is destroyed and transferred to a newly created quaternary carbon atom. This strategy has been widely applied in the synthesis of complex naturally occurring or biologically active compounds possessing at least one stereogenic quaternary carbon atom.[273–276] In this context, one of the quaternary stereocenters of codeine has been recently installed by an Eschenmoser rearrangement (**Scheme 136**).[277]



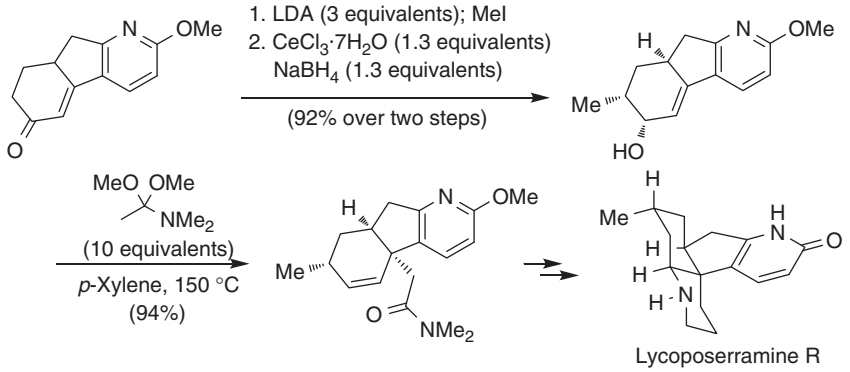
Scheme 136

Similarly, the asymmetric quaternary carbon atom of the sesquiterpenoids enokipodins A and B was constructed via an enantiospecific Eschenmoser rearrangement (**Scheme 137**).[278] The optically active starting allyl vinyl ether was prepared by the palladium-catalyzed addition of an arylboronic acid to an optically active allenic alcohol, the chirality of which had been previously generated by an enantioselective carbonyl reduction with the (*R*)-CBS (Corey–Bakshi–Shibata) reagent and BH_3.



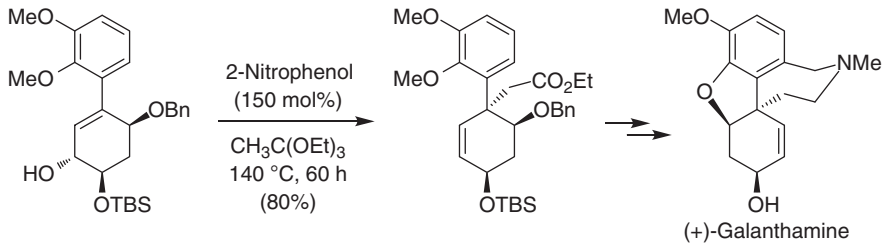
Scheme 137

A stereoselective Eschenmoser rearrangement was developed to create the all-carbon quaternary center contained within the alkaloid lycoposerramine R (Scheme 138).[279] The starting allylic alcohol was diastereoselectively prepared by way of α-methylation of a suitably substituted enone and subsequent Luche reduction.



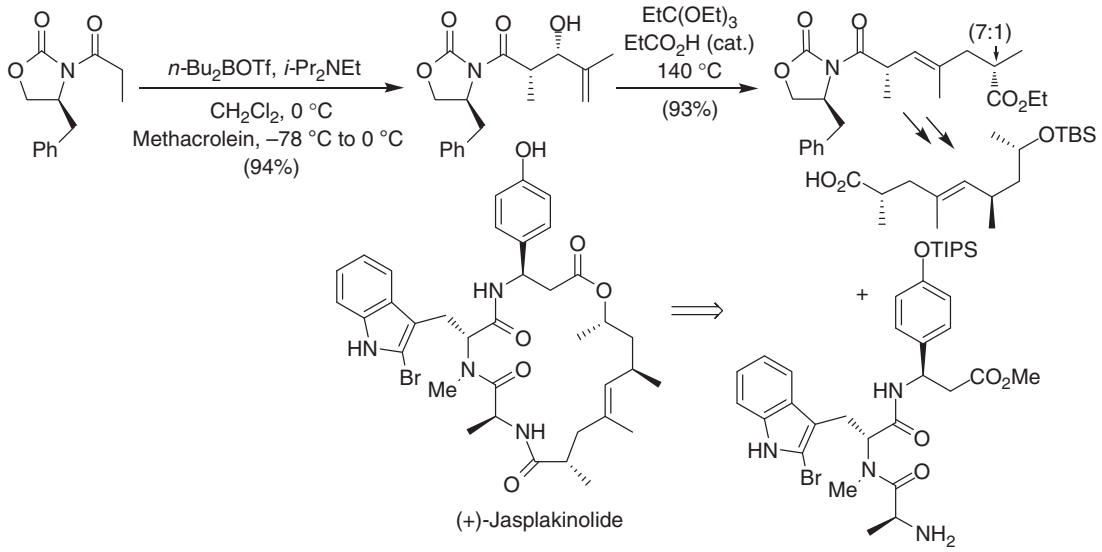
Scheme 138

The chirality of a cyclohexenol derived from D-glucose was efficiently transferred in the course of a Johnson rearrangement to stereoselectively generate the quaternary carbon center present in (+)-galanthamine (Scheme 139).[166]



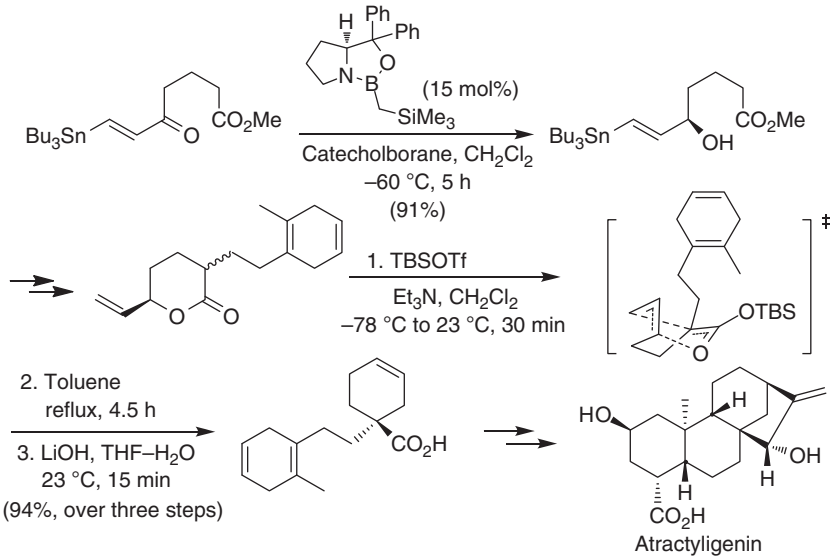
Scheme 139

The chairlike transition state for the Johnson rearrangement of an allylic alcohol, which, in turn, had been prepared by an auxiliary-assisted aldol addition, was responsible for the efficient 1,4-chirality transfer observed in a convergent synthesis of the cyclic depsipeptide (+)-jasplakinolide (Scheme 140).[280] The highly stereoselective rearrangement afforded the stereogenic α-methyl carbonyl functionality and the *E*-olefin geometry present in the polyketide fragment of the natural product.



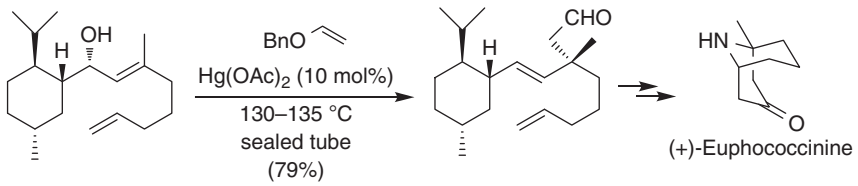
Scheme 140

In the synthesis of atractyligenin, an Ireland rearrangement of a lactonic silyl enolate was described as the key step, evolving through a favored boatlike transition state. In this way the chirality of a secondary alcohol generated by an oxazaborolidine-catalyzed (CBS) reduction of an enone was efficiently transferred to the quaternary carbon stereocenter present in the key intermediate (Scheme 141).[281]



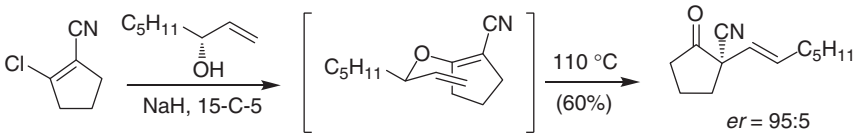
Scheme 141

The construction of quaternary stereocenters has also been addressed via thermal aliphatic Claisen rearrangements with excellent chirality transfer from the starting allyl vinyl ethers.[282] In the context of the synthesis of the naturally occurring alkaloid (+)-euphococcinine, the quaternary carbon stereocenter present in the key intermediate was created by a thermal aliphatic Claisen rearrangement. The requested allylic alcohol was obtained by stereoselective addition of a vinylaluminum reagent to *p*-menthyl-3-carboxaldehyde and its chirality was efficiently transferred during the rearrangement (Scheme 142).[283]



Scheme 142

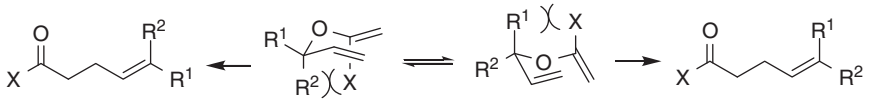
The Claisen rearrangement of cyano-substituted endocyclic enol ethers, synthesized by a conjugate addition–elimination reaction of allylic alkoxides to 2-chlorocycloalkenecarbonitriles, allows for the stereoselective formation of cyclic oxonitriles with a quaternary stereocenter (Scheme 143).[284] The enantiomeric ratios were typically greater than 9:1.



Scheme 143

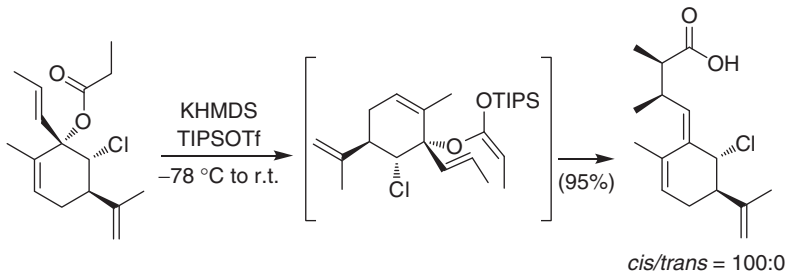
In tertiary allyl vinyl ethers, the outcome of the Claisen rearrangement become less obvious since both chairlike transition states suffer from 1,3-diaxial interactions (Scheme 144).

In this context, the Ireland rearrangement of tertiary bis-allylic esters derived from cyclohexenones has been reported to afford tri- and tetrasubstituted alkylidenes with unprecedented levels of stereoselectivity.[285] Scheme 145 shows an example in which a silyl ketene acetal rearranges through a transition state with the C6 carbon of the cyclohexenone occupying a pseudo-equatorial



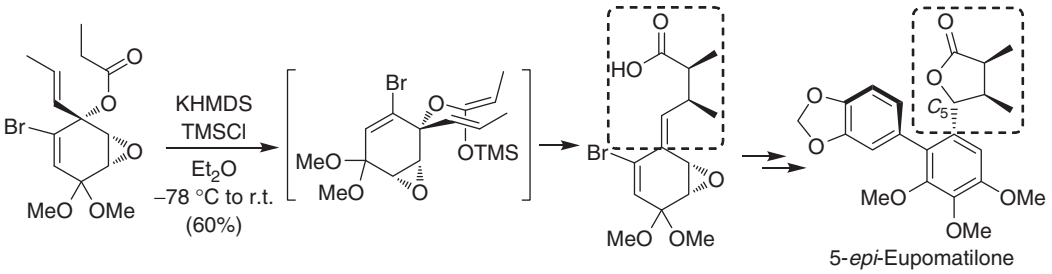
Scheme 144

position. Interestingly, the higher-energy exocyclic alkene is formed. Once again, the chirality of the allylic stereocenter is transferred to the two new stereocenters in the product and to the new geometry of the double bond.



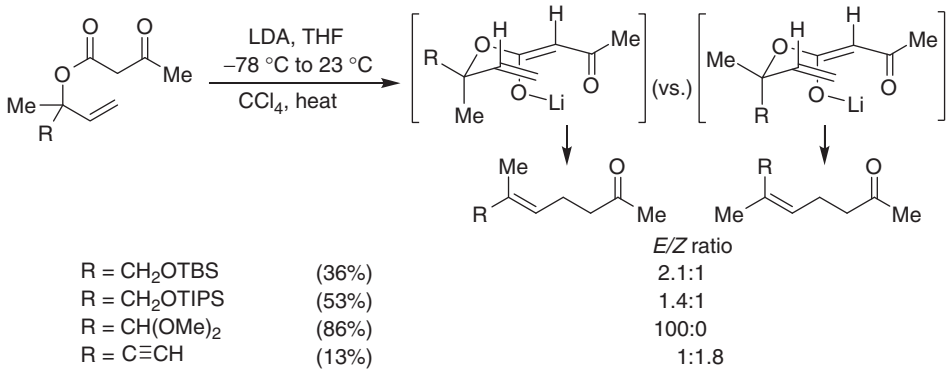
Scheme 145

This strategy has been applied to the total synthesis of a member of the eupomatilone family (Scheme 146).[285a] In this case the exocyclic alkene with the opposite stereochemistry was obtained.



Scheme 146

The Carroll rearrangement of β-keto esters derived from tertiary allylic alcohols has also been reported. The reaction takes place through the most stable chairlike transition state, which is closely dependent on the steric differences between the substituents at the allylic C4 position and, therefore, dictates the olefin geometry of the obtained γ,δ-unsaturated methyl ketones (Scheme 147).[286]

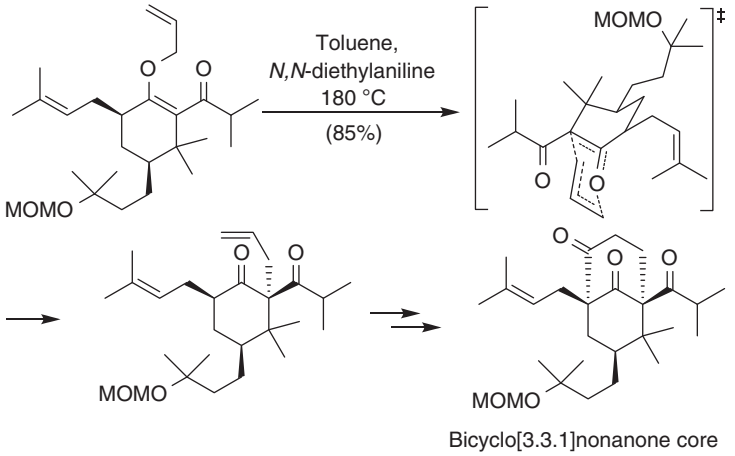


Scheme 147

5.20.4.3 Extra-annular Stereoselection

The presence of additional stereocenters not directly participating in the six-membered cyclic transition state of the rearrangement may control the extra-annular diastereoselectivity and, accordingly, determine the stereochemical pathway of the process.

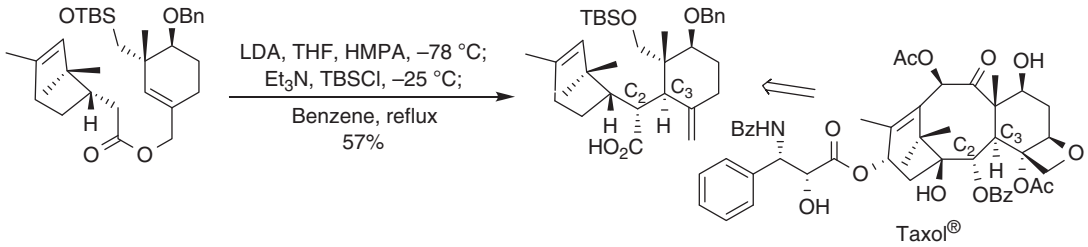
A diastereoselective thermal Claisen rearrangement was devised as the key step of the synthesis of the highly congested bicyclo[3.3.1]nonanone core of natural acylphloroglucinols. The stereochemistry of the asymmetric centers present at the allyl vinyl ether used as the substrate dictated the axial C–C bond formation in the rearrangement and, hence, controlled the configuration of the newly formed quaternary stereocenter (Scheme 148).[287]



Scheme 148

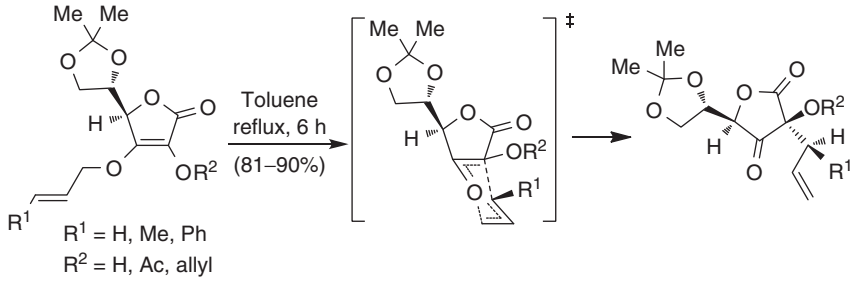
Heteroatomic stereogenic centers adjacent to both the vinylic and the allylic olefins of the starting materials of the Ireland[288,289] and Johnson[290] rearrangements have caused good *exo*-pericyclic stereocontrol in the reactions. Similarly, structural restrictions existing in chiral substrates have proved useful as asymmetric inducers of the diastereoselectivity of the rearrangements.[291]

The chirality of additional asymmetric centers present in the substrate of the key Ireland rearrangement step used for the generation of the C2–C3 bond in taxanes exerted a positive influence on the stereocontrol of the reaction (Scheme 149).[292]



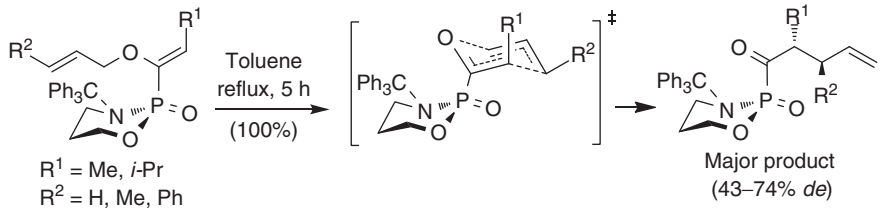
Scheme 149

The influence of chiral auxiliaries on the stereochemical outcome of [3,3]-sigmatropic rearrangements has been investigated. In the synthesis of C2-functionalized gulono-γ-lactone derivatives from L-ascorbic acid, a highly diastereoselective thermal Claisen rearrangement was used to install an allyl fragment in the lactone core of the products. The steric constraints imposed by the bulky chiral 1,2-*O*-isopropylidene-1,2-ethanodiol moiety on the vinyl portion on the top face of the substrate determined the preference of the rearrangement to occur almost exclusively from the bottom face through the favored chairlike transition state (Scheme 150).[293]



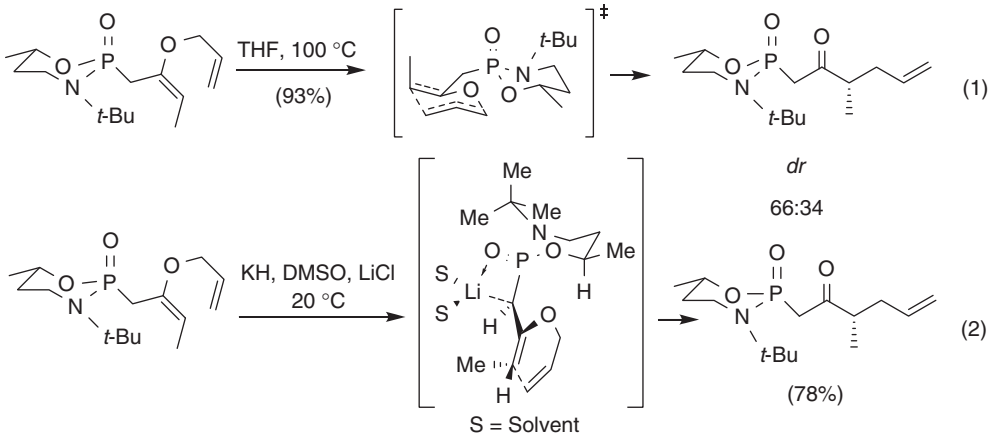
Scheme 150

A chiral 1,3,2-oxazaphosphorinane directly bonded to the vinyl olefin of the rearrangement substrates provided modest to good diastereoselectivities resulting from the evolution through the favored chairlike transition state minimizing the electronic repulsion from the ring oxygen electron lone pair (Scheme 151).[294]



Scheme 151

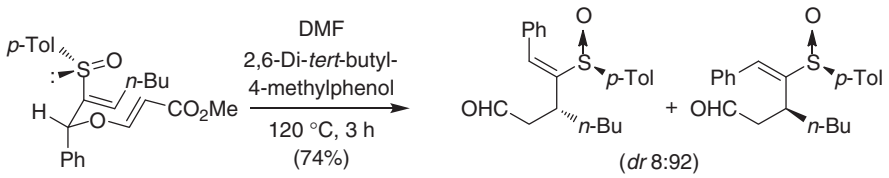
A moderate degree of asymmetric induction was achieved by using a chiral, nonracemic 1,3,2-oxazaphosphorinane bonded by a methylene unit to the vinyl olefin of the ether framework. The favored rearrangement proceeded by bond formation on the *Re* face, thus avoiding steric interactions with the most hindered face of the chiral auxiliary (Scheme 152, equation 1).[295] The diastereoselectivity of the rearrangement of these substrates was substantially improved under basic conditions, whereby the 1,3,2-oxazaphosphorinane moiety acted as the anion-stabilizing group. In the presence of Li^+ as the counterion, the chirality was effectively transferred in the course of the carbanionic Claisen rearrangement, presumably as a result of the course of the rearrangement through an sp^2-hybridized anion, which is strongly complexed to lithium (Scheme 152, equation 2).[296]



Scheme 152

The C_2-symmetric *N*,*N*′-dibenzyl-1,3,2-diazaphospholidine was also investigated as a chiral auxiliary of the reaction, both under neutral and basic conditions.[61,296] Although these rearrangements exhibited a good internal induction (intra-annular diastereoselectivity), the degree of extra-annular diastereoselectivity exerted by the chiral auxiliary was rather moderate.

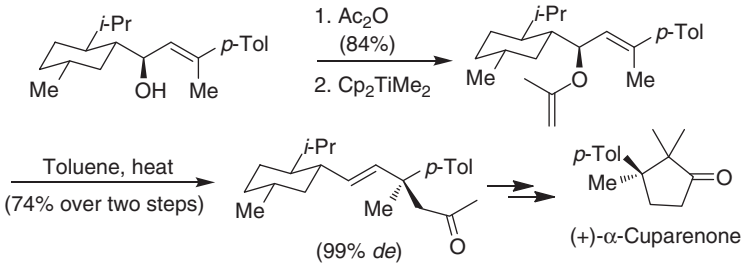
Chiral auxiliaries located on the allylic portion of the starting vinyl allyl ethers have also been reported in the aliphatic Claisen rearrangement.[297] A chiral sulfinyl functionality positioned at the allylic fragment of an allyl vinyl ether proved capable of controlling the diastereoselectivity of the thermal Claisen rearrangement due to its ability to differentiate between the diastereotopic faces of the neighboring double bonds.[298] The presence of an additional stereocenter at C4 defined the matched or mismatched contribution of both stereogenic elements in the reaction, which was also modulated by the geometry of the allylic double bond (Scheme 153).[299] Interestingly, allyl vinyl ethers with a (*Z*)-vinyl sulfoxide rearranged through a chairlike transition



Scheme 153

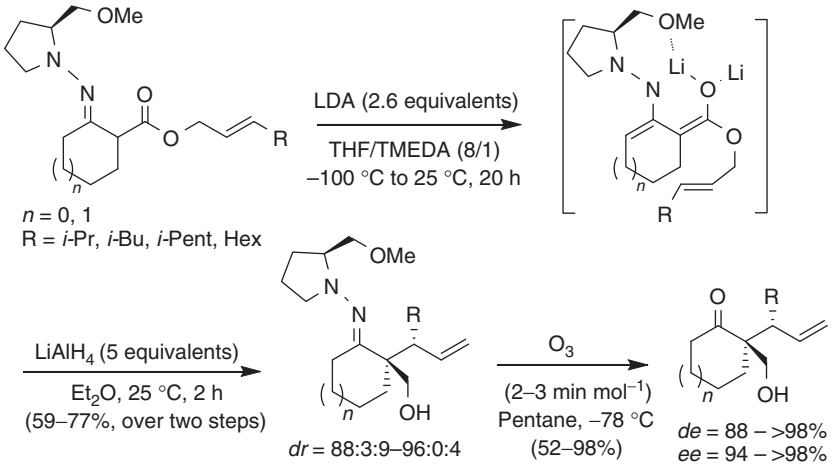
state which places the allylic substituent in a pseudoaxial position to avoid interactions with the sulfoxide moiety. The stereochemical outcome of these rearrangements was explained from an (s)-*cis* C═C/S═O conformation around the C–S bond for the chairlike transition state.

A completely stereoselective Claisen rearrangement was reported during the synthesis of the sesquiterpene (+)-cuparenone. The cooperative action of a chiral auxiliary directly bonded to the allyl fragment of the allyl vinyl ether along with the fixed configuration at C4 dictates a highly diastereoselective course of the reaction (Scheme 154).[300]



Scheme 154

Functionalized ketones bearing adjacent quaternary and tertiary stereocenters have been synthesized with high diastereo- and enantioselectivities by way of a Carroll rearrangement utilizing a chiral auxiliary. The rearrangement of dianions derived from SAMP-type β-hydrazonoesters, followed by reduction with $LiAlH_4$, and regeneration of the carbonyl function has been reported as a route to γ,δ-unsaturated β′-hydroxyketones with two stereogenic centers at the α and β positions. The intermolecular chelation of the lithium by the methoxymethyl (MOM) group of the chiral β-hydrazonoester differentiates both diastereotopic faces for the allylic approach in the chairlike transition state of the rearrangement (Scheme 155).[301]

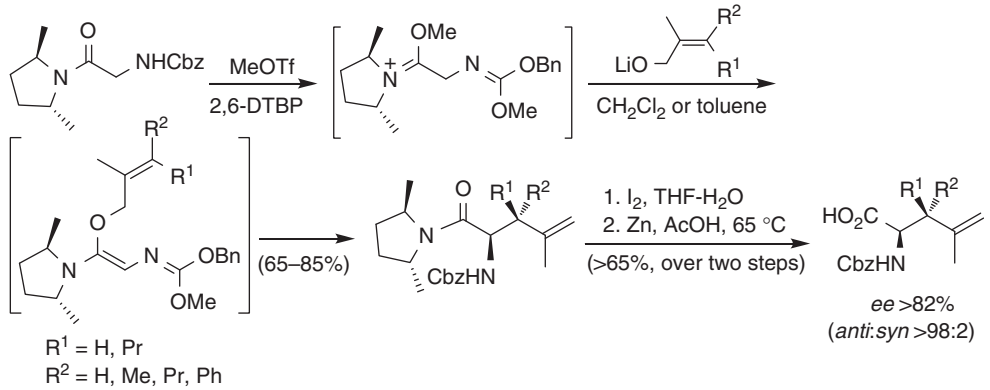


Scheme 155

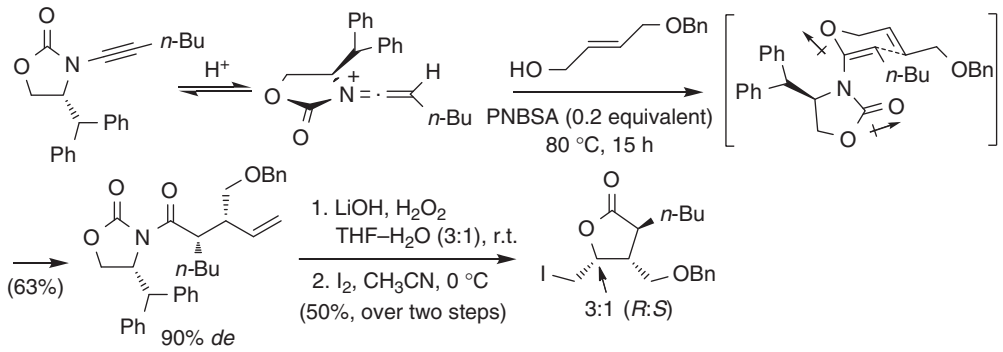
The presence of chiral auxiliaries on the nitrogen portion of *N,O*-ketene acetals has also provided high levels of diastereoselectivity in the Eschenmoser rearrangement.[150,302,303] The C_2-symmetric chiral auxiliary (2*R*,5*R*)-dimethylpyrrolidine has provided high levels of diastereoselectivity in an Eschenmoser rearrangement, which has been reported as a valuable tool for the synthesis of optically active *anti*-β-substituted γ,δ-unsaturated α-amino acids (Scheme 156).[304,305]

High levels of diastereoselectivity have been achieved utilizing a chiral oxazolidinone group as a chiral auxiliary in the Ficini–Claisen rearrangement of a range of ynamides.[306] The (*E*)-ketene aminal resulting from the addition of an allylic alcohol to the less hindered diastereotopic face of the initially formed iminium salt rearranged through a chairlike transition state in the conformation that minimized the dipole interaction between the urethane C═O bond and the vinyl C–O bond. In this conformation, the chiral auxiliary determined the preferred approach of the allylic olefin to the less hindered side of the vinyl double bond, leading to the major *syn* isomers from *trans*-substituted allylic alcohols (Scheme 157). This strategy has provided ready access to synthetically useful diastereomerically enriched lactones.

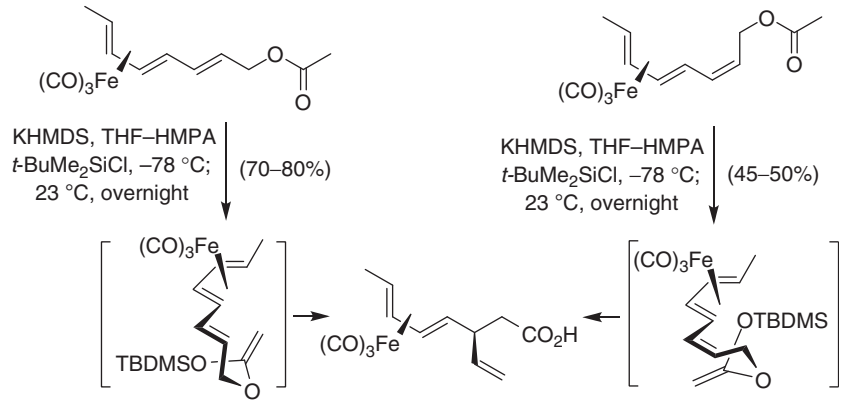
The use of chiral auxiliaries in diastereoselective Ireland rearrangements has also been investigated.[307–309] A chiral η^4-diene iron(tricarbonyl) complex provided high levels of stereocontrol in the Ireland rearrangement of trienylic esters. The excellent diastereofacial selectivity led to the formation of the new C–C bond *anti* to the $Fe(CO)_3$ group (Scheme 158).[310] The reaction proved to be completely diastereoconvergent, regardless of the *E*/*Z* geometry of the allylic olefin in the substrate.



Scheme 156



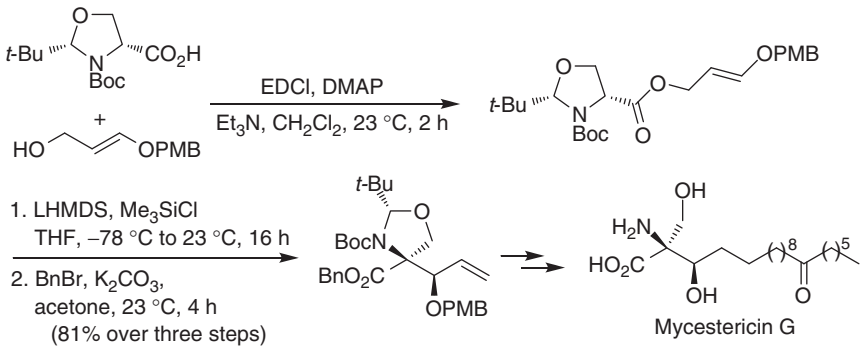
Scheme 157



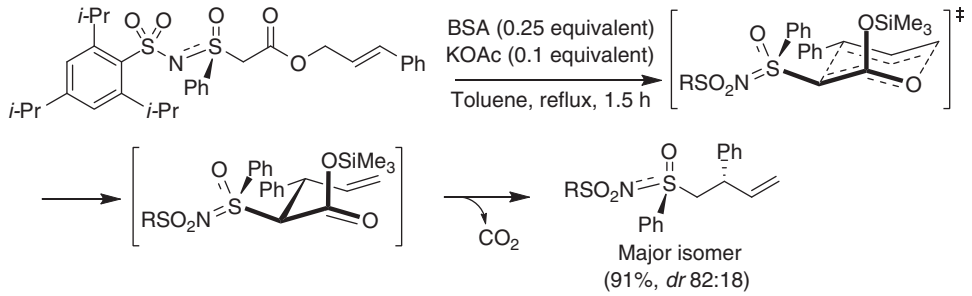
Scheme 158

Excellent levels of remote stereocontrol have been recently reported in the Ireland rearrangement of a chiral oxazolidine enol ether, which has been described as the key step of the synthesis of the natural immunosuppressant agent mycestericin G (Scheme 159).[311]

The asymmetric version of the decarboxylative Claisen rearrangement has been studied on substrates bearing an *N*-arylsulfonylsulfoximine group as a chiral sulfone surrogate.[312] The reaction proceeds with good yields and diastereoselectivities. This stereochemical outcome has been rationalized by a pseudochair transition-state model for the rearrangement of the intermediate (*Z*)-sulfoximine-substituted silyl ketene acetals. By assuming an antiperiplanar conformation of the $ArSO_2N$ group to the ketene acetal C–C double bond, the favored approach of the allylic fragment – *syn* with respect to the sulfoximine oxygen atom and *anti* to the phenyl group – will account for the configuration of the major isomer obtained in the reaction (Scheme 160).

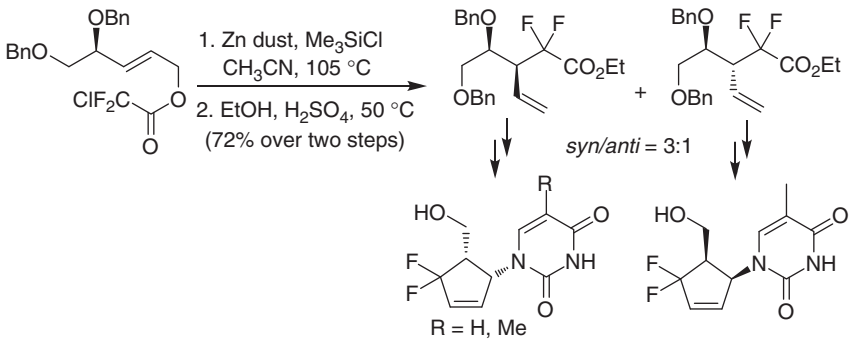


Scheme 159



Scheme 160

The presence of an additional asymmetric center on the allylic fragment also proved effective in the stereocontrol of a silicon-induced Reformatsky rearrangement which gave the key building block for the synthesis of difluoromethylenated nucleosides (Scheme 161).[313]



Scheme 161

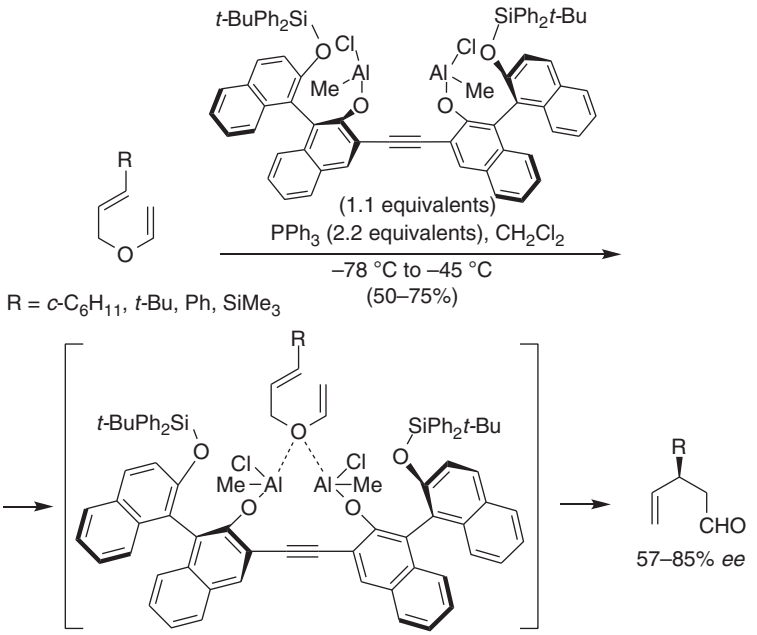
5.20.4.4 Enantioselective Rearrangements and Asymmetric Catalysis

The presence of chiral enantiopure catalysts, cocatalysts, or solvents in the reaction media of the Claisen rearrangement may generate an asymmetric environment in the transition state, which, in turn, will be responsible for the degree of stereoselectivity achieved in the reaction.

5.20.4.4.1 Chiral metal catalysts

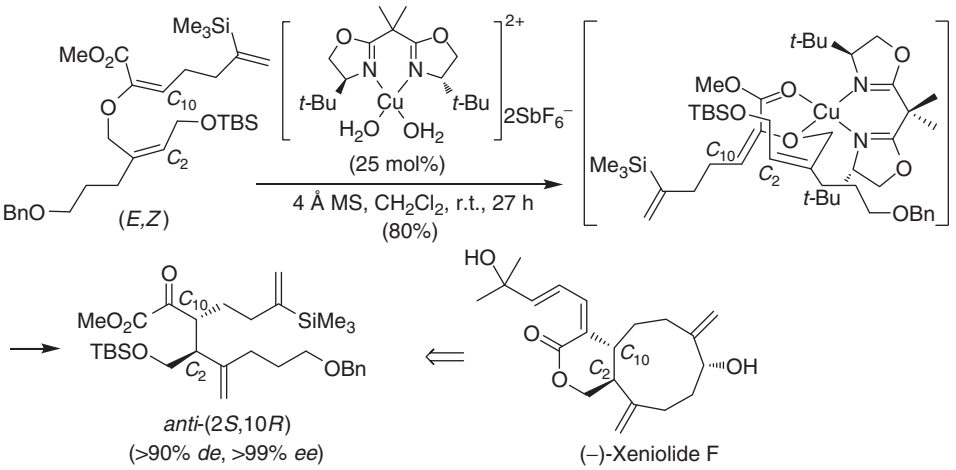
High levels of enantioselectivity in the Claisen rearrangement have been achieved over the past two decades by utilizing Lewis-acid catalysts bearing chiral ligands, which are capable of differentiating the two possible chairlike conformations for the transition state. Bulky chiral organoaluminum reagents have been reported to simultaneously accelerate the rearrangement of differently

substituted allyl vinyl ethers and discriminate the two possible chairlike conformations for the transition state, therefore affording one of the enantiomers preferentially.[314–316] A double coordination of chiral bis(organoaluminum) Lewis acids with the oxygen atom in the allyl vinyl ethers has also been reported to lead to asymmetric induction in the Claisen rearrangement (Scheme 162).[317]



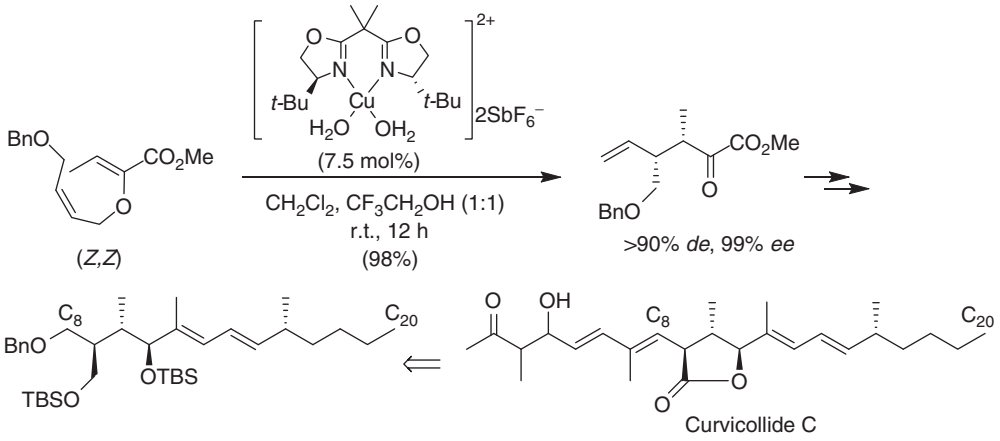
Scheme 162

Chiral bis(oxazoline) copper(II) complexes have been reported as powerful catalysts for the enantioselective aliphatic Claisen rearrangements of a range of 2-alkoxycarbonyl-substituted allyl vinyl ethers.[318] Both [Cu(*tert*-Bu-box)](OTf)$_2$ and [Cu(*tert*-Bu-box)](H$_2$O)$_2$(SbF$_6$)$_2$ catalysts provided excellent enantio- and diastereoselectivities in the rearrangement of the distorted square planar substrate/catalyst complex, proceeding through a chairlike transition state with the allylic ether portion approaching the vinyl ether fragment from the face opposite to the bulky *tert*-butyl substituent on the bisoxazoline ligand. These copper-catalyzed asymmetric Claisen rearrangements have been reported as the key step for the synthesis of some naturally occurring compounds.[319] In the context of the synthesis of the marine xenicane diterpene (–)-xeniolide F, the rearrangement of a highly functionalized (*E,Z*)-α-alkoxycarbonyl-substituted allyl vinyl ether in the presence of substoichiometric amounts of chiral [Cu{(*S,S*)-*tert*-Bu-box}](H$_2$O)$_2$(SbF$_6$)$_2$ proceeded with excellent *anti* diastereoselectivity, affording the desired enantiomerically pure key synthetic intermediate (Scheme 163).[319a]



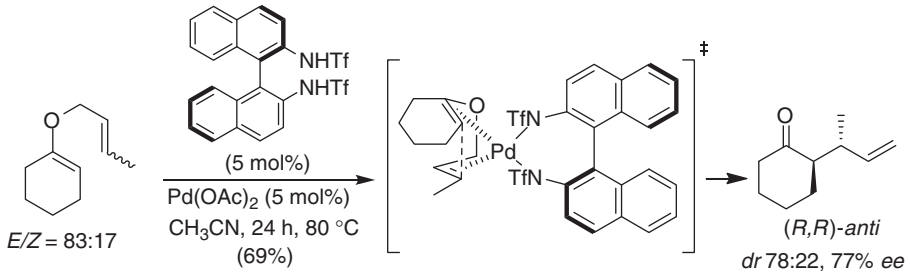
Scheme 163

This strategy has also been described as a valuable tool for the enantio- and diastereoselective C-C bond construction in the key step of the synthesis of the C8–C20 fragment of antifungal polyketide curvicollide C (Scheme 164).[319]



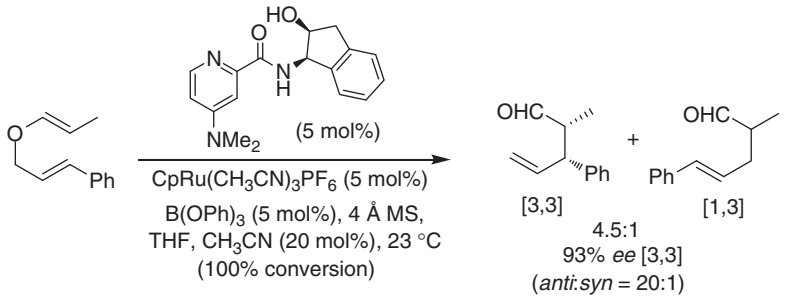
Scheme 164

Chiral palladium complexes have also been used as catalysts for the enantioselective Claisen rearrangement. The Claisen rearrangement of cyclic (*E*)-allyl vinyl ethers proceeded in moderate yields with good *anti*/*syn* selectivities and enantioselectivities in the presence of catalytic amounts of the [(*R*)-diamino-binaphthyl trifluoromethanesulfonylamide]-palladium complex [(*R*)-DABNTf], as a result of the preferred rearrangement of the major (*E*)-allyl vinyl ether via a chiral bidentate boatlike transition state [the minor (*Z*)-substrate proved unreactive under the catalytic conditions] (Scheme 165).[320]



Scheme 165

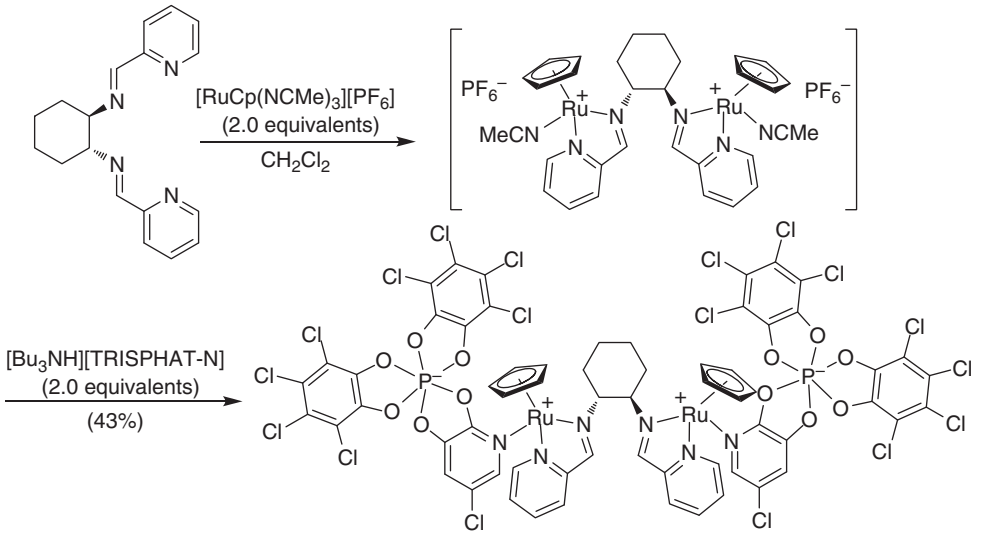
A cooperative catalytic system consisting of a chiral ruthenium(II) complex (readily obtained by reacting $[CpRu(CH_3CN)_3]PF_6$ with a chiral ligand) and the Lewis acid cocatalyst $B(OPh)_3$ provided high enantio- and diastereoselectivities in the Claisen rearrangements of 1,6-disubstituted allyl vinyl ethers, although the efficiency of the reaction was limited to C6-aryl-substituted substrates (Scheme 166).[321] The minor competing [1,3]-rearrangement regioisomer was detected under all the assayed conditions, which may be indicative of a mechanism initiated by C–O bond cleavage.



Scheme 166

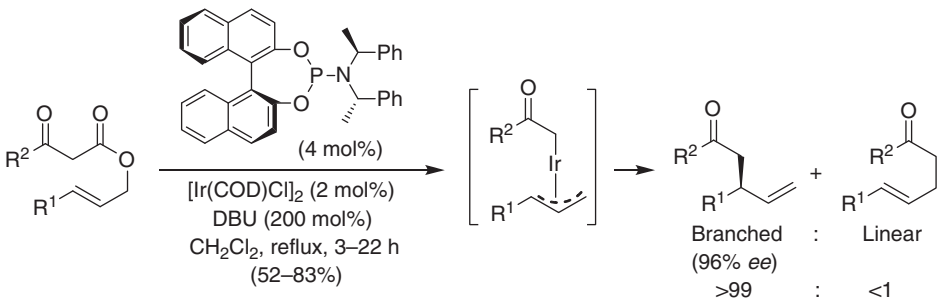
In the past years, a number of highly asymmetric Carroll rearrangements have been reported in the presence of chiral metal complexes as efficient catalysts capable of inducing high levels of stereoselectivity. The chiral palladium catalyst generated *in situ* from $Pd_2(dba)_3 \cdot CHCl_3$ and the optically active Trost bisphosphine ligand produced a high degree of asymmetric induction in the Carroll rearrangement of allyl α-acetamido-β-ketocarboxylates, giving optically active γ,δ-unsaturated α-amino ketones.[322] However, it has been the use of chiral ruthenium catalysts, which has been most widely investigated for achieving enantioselective versions of the Carroll rearrangement. The combined use of CpRu half-sandwich complexes – $[CpRu(NCCH_3)_3][PF_6]$ or $[CpRu(\eta^6\text{-naphthalene})][PF_6]$ – and enantiopure pyridine imine ligands provided high levels of regio- and enantioselectivities.[323]

A dinuclear zwitterionic complex, where the catalytically active chiral metallic species is stabilized by a hexacoordinated phosphorus anion (TRISPHAT-N), has proved highly efficient as a catalyst in the asymmetric Carroll rearrangement of a variety of allyl β-keto esters providing high levels of enantioselectivity (85% *ee*) (Scheme 167).[324]



Scheme 167

The catalytic system comprising $[Ir(COD)Cl]_2$ and a phosphoramidite ligand has also provided high regio- and enantioselectivities in the transformation of γ-substituted allyl β-ketocarboxylates into branched γ,δ-unsaturated ketones. Although the reaction is a formal Carroll rearrangement, the proposed mechanism involves C–O bond scission and further enolate–allyl recombination (Scheme 168).[325]

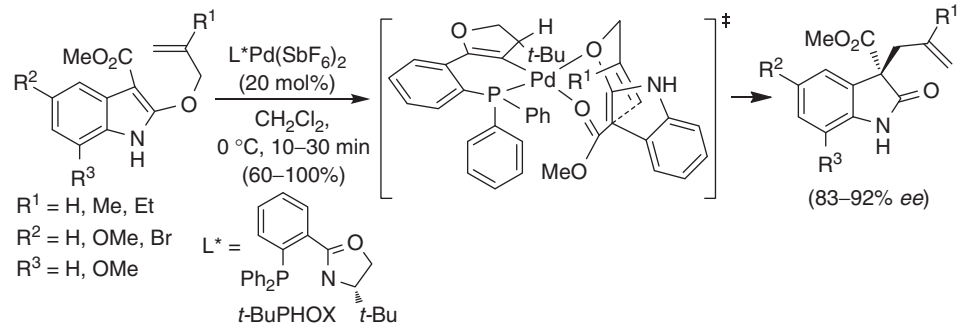


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-FC_6H_4, 2-furyl, Me, *n*-C_5H_{11}
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-Naphthyl

Scheme 168

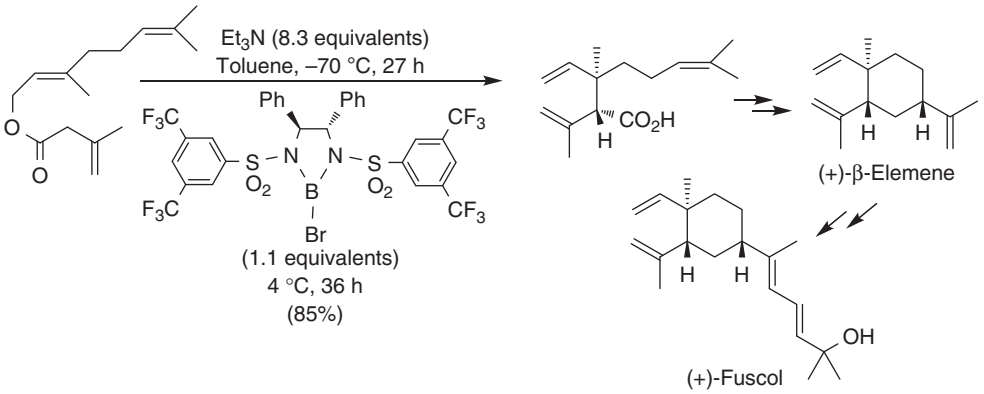
A catalytic enantioselective Eschenmoser rearrangement of aromatic substrates in the presence of the chiral *t*-BuPHOX palladium complex afforded a range of enantiomerically enriched allyl oxindoles bearing a quaternary stereocenter.[326] A two-point coordination of the substrate to the Lewis acidic palladium complex provided a rigid chiral environment to the favored chairlike transition state (Scheme 169).

This catalytic enantioselective methodology utilizing alkynyl substrates has been recently applied to the asymmetric synthesis of allenyl oxindoles bearing a quaternary stereocenter.[327]



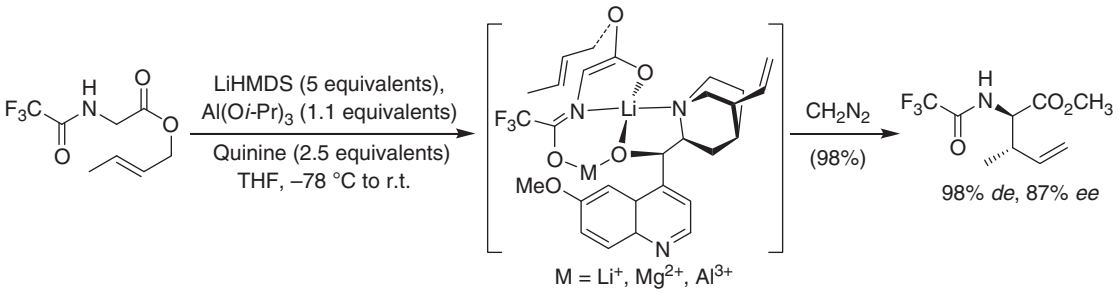
Scheme 169

A chiral boron Lewis acid has allowed for a highly enantioselective Ireland rearrangement of an achiral allylic ester. This reaction has been described as the key step in the asymmetric synthesis of the anti-inflammatory agent precursor (+)-fuscol, via the intermediate terpenoid (+)-β-elemene (Scheme 170).[328]



Scheme 170

The incorporation of chiral ligands [(–)-phenylglycinol, (–)-valinol, (–)-pseudoephedrine, (–)-ephedrine, cinchona alkaloids] to the coordination sphere of the chelating metal [$ZnCl_2$, $EtAlCl_2$, BCl_3, $CaCl_2$, $MgCl_2$, $Mg(OEt)_2$] in the bidentate enolate complex, which acts as the substrate for the chelate Claisen rearrangement, has also been developed as a useful strategy for asymmetric induction.[329] In this sense, the combined use of cinchona alkaloids (quinine or quinidine) and $Al(OiPr)_3$ afforded diastereo- and enantiomerically enriched amino acids in high yields.[330] This methodology has provided ready access to sterically congested amino acids with a β-quaternary center in a highly diastereo- and enantioselective manner.[331] When allylic amino esters bearing an *N*-protecting trifluoroacetyl group were treated with LiHMDS as the base, $Al(OiPr)_3$ [or $Mg(OEt)_2$] as the chelating salt, and quinine (or quinidine) as the chiral ligand, a rigid chiral bimetallic complex was formed by coordination of the bidentate ligand quinine to the lithium enolate and further stabilization of this complex by incorporation of a second metal ion (Li^+, Al^{3+}, or Mg^{2+}). This rigid chiral environment in the transition state accounts for the high enantioselectivity of the rearrangement (Scheme 171).[330]

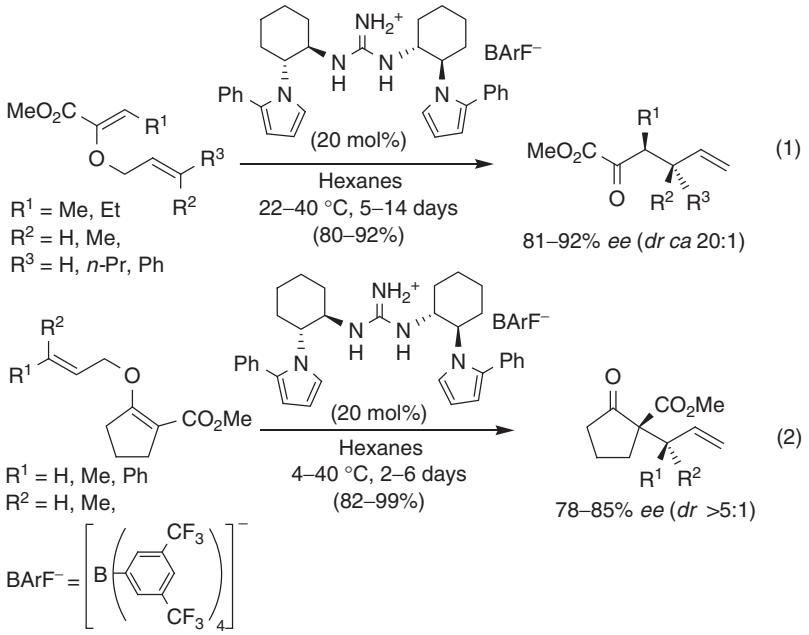


Scheme 171

5.20.4.4.2 Chiral organocatalysts

Very few examples of the use of chiral organocatalysts in asymmetric Claisen rearrangements have been reported to date.

C_2-Symmetric guanidinium ions derived from *trans*-1-pyrrolo-2-aminocyclohexane are effective chiral organocatalysts for the enantioselective rearrangement of 2-alkoxycarbonyl-substituted alicyclic allyl vinyl ethers derived from α-ketoesters (Scheme 172, equation 1).[89] These catalytic conditions have provided ready access to molecules containing tertiary and quaternary stereocenters with high enantio- and diastereoselectivities. However, no enantioselectivity was induced in the rearrangement of nonsubstituted allyl vinyl ethers. Similarly, the rearrangement of cyclic *O*-allyl β-ketoesters in the presence of the above chiral guanidinium catalyst also provided the rearranged products with high levels of enantioselectivity (Scheme 172, equation 2).[332]



Scheme 172

Experimental observations and computational models have predicted a double hydrogen-bonding interaction of the guanidinium catalyst with the allyl vinyl ether substrate with both the ether oxygen atom and the ester group. This hydrogen-bond interaction stabilizes the developing negative charge in the transition state. An additional secondary interaction between the π-system of the catalyst's phenyl substituent and the allylic fragment of the substrate will contribute to stabilize the favored six-membered chairlike transition state and will hence determine the excellent stereocontrol of the rearrangement (Figure 1).[333]

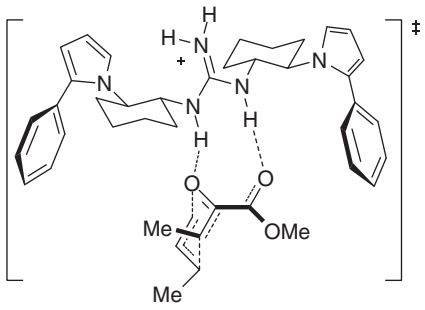


Figure 1 Favored transition state for the organocatalyzed rearrangement. Reproduced from Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062.

5.20.5 Conclusions and Outlook

Twenty years after the publication of the first *Comprehensive Organic Synthesis* chapter on the Claisen rearrangement, this reaction remains an excellent tool for the synthesis of complex molecules. Crucial to its continued importance are the advances made in

the synthesis of the starting materials required for the rearrangement. Metal-catalyzed coupling reactions and metal-promoted double bond isomerizations now allow easier access to allyl vinyl ethers. Additionally, new conditions have been found for the synthesis of silyl ketene acetals with unprecedented *E*/*Z* selectivities. However, the most significant advances have undoubtedly been made in the field of asymmetric catalysis, although some limitations do still exist. In particular, most of the examples described to date require the presence of a group able to coordinate to a metal or an organocatalyst. This is probably the aspect of the Claisen rearrangement that offers the most room for new discoveries in the coming years.

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5.21 Consecutive Sigmatropic Rearrangements

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Glossary

***A* value** Utilized in conformational analysis, it is the difference in free energy (ΔG) between conformations having an axial substitution (high energy) and an equatorial substitution the lower energy conformation (low energy) for the same functional group.

Domino reaction A domino process involves two or more reactions occurring in succession without the addition of new reagents or modification of the conditions, whereby the intermediates are not isolated.

Interdependent rearrangement An interdependent rearrangement involves a reciprocal relationship between the intermediates formed during the reaction.

Sigmatropic rearrangement A sigmatropic rearrangement is a pericyclic reaction wherein an allylic σ-bond migrates along a π-system to form a new σ-bond.

5.21.1 Introduction

Architecturally complex natural products have been a source of inspiration for synthetic organic chemists for over 100 years. Although many methods to generate new C–C, C–O, C–N, etc., bonds have been established, the rapid assembly of complex organic structures remains a significant challenge. Sigmatropic rearrangements are important tools in this regard and, when combined in consecutive operations, the resulting processes are powerful synthetic transformations.

A sigmatropic rearrangement is a pericyclic reaction wherein an allylic σ-bond migrates along a π-system to form a new σ-bond. These concerted reactions proceed through well-ordered transition states, hence the stereochemical outcome of a sigmatropic rearrangement is usually predicted with ease. This predictable stereoselectivity, coupled with the fact that at least one π-bond relocates during each event, means that the sequencing of sigmatropic reactions into consecutive rearrangements is an attractive synthetic strategy. The conspicuous advantages of such sequences relate to their ability to rapidly elaborate complex frameworks bearing many new stereogenic centers. Evidently, sequences of sigmatropic rearrangements lead to more efficient syntheses and can be considered as a component of more sustainable synthetic chemistry practices.[1]

Consecutive sigmatropic rearrangements involve two or more discrete events that follow one another in a synthetic sequence. These two events can either be dependent on, or independent of, one another. For example, a so-called 'aromatic *para*-Claisen rearrangement' involves two [3,3]-sigmatropic rearrangements, an initial Claisen rearrangement followed by a Cope rearrangement. The Claisen rearrangement necessarily must occur first, so that the required functionality is set up for the Cope rearrangement. This is not the case, however, for the two sigmatropic shifts involved in the double 'aromatic *ortho*-Claisen rearrangement' of the diallyl ether of catechol to form 2,5-diallyl catechol.

A further distinction is possible within the subclass of processes involving two or more interdependent sigmatropic rearrangements. In one scenario, the two processes occur in a true 'domino' sense, whereby the intermediate(s) cannot be isolated and only the starting material and final product of the consecutive sigmatropic rearrangement sequence can be detected. On the other end of the spectrum, each discrete step of the consecutive sigmatropic rearrangement sequence can be conducted separately and isolation of the intermediate(s) is possible. These factors are determined by the relative rates of the contributing rearrangements, of course. Although there are practical implications stemming from these issues; as far as the present chapter is concerned, the

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authors have elected to include examples from all conceivable permutations. They note that there is still controversy over the use of terms such as cascade, domino, consecutive, sequential, one pot, etc., and have attempted to use terminology consistently throughout this chapter and they hope that there will be no confusion over their intended meaning.

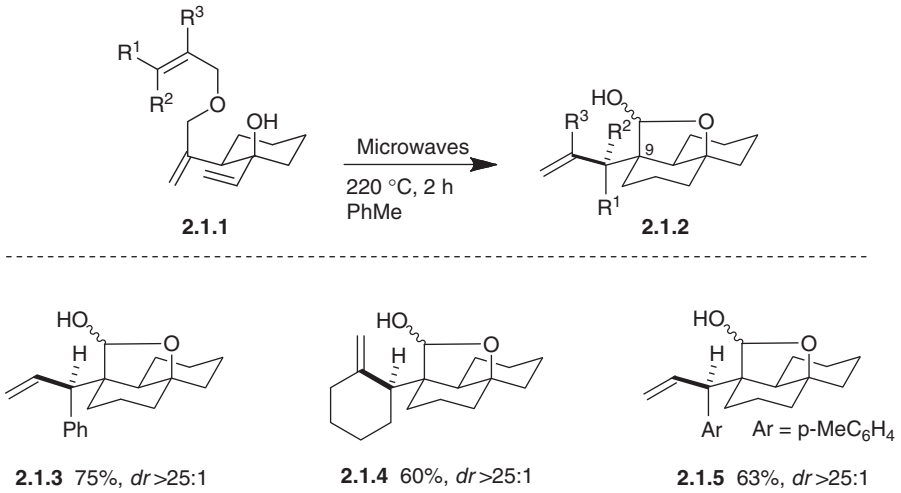
Finally, this chapter focuses on transformations published since the first edition of Comprehensive Organic Synthesis (i.e., since 1991). The authors have subclassified the content of this chapter according to the type of sigmatropic rearrangements involved. As might be expected, sequences involving [3,3]-sigmatropic shifts are in the majority.

5.21.2 [3,3]-[3,3] Rearrangement

5.21.2.1 Interdependent Sequences

5.21.2.1.1 Cope–ene–Claisen

The stereocontrolled synthesis of quaternary carbon centers is a challenge often encountered in diterpene synthesis. Although there exists a broad range of methods capable of generating new carbon–carbon bonds, the formation of quaternary centers is among the most restrictive in organic chemistry.[2] Barriault and Denissova described a domino oxy-Cope–ene–Claisen reaction of allyl ether **2.2.1** to generate decalin frameworks **2.1.2** possessing at least three contiguous stereocenters (Scheme 1).[3] Depending on the pattern of substitution on the terminal allyl ether (i.e., R^1 and R^2) in precursor **2.1.1**, a tertiary or quaternary stereocenter was incorporated adjacent to C9. The broad scope and high diastereoselectivity of this approach are exemplified by the generation of decalins **2.1.3**–**2.1.5**.



2.1.1 **2.1.2**

2.1.3 75%, *dr* >25:1 **2.1.4** 60%, *dr* >25:1 **2.1.5** 63%, *dr* >25:1

Scheme 1

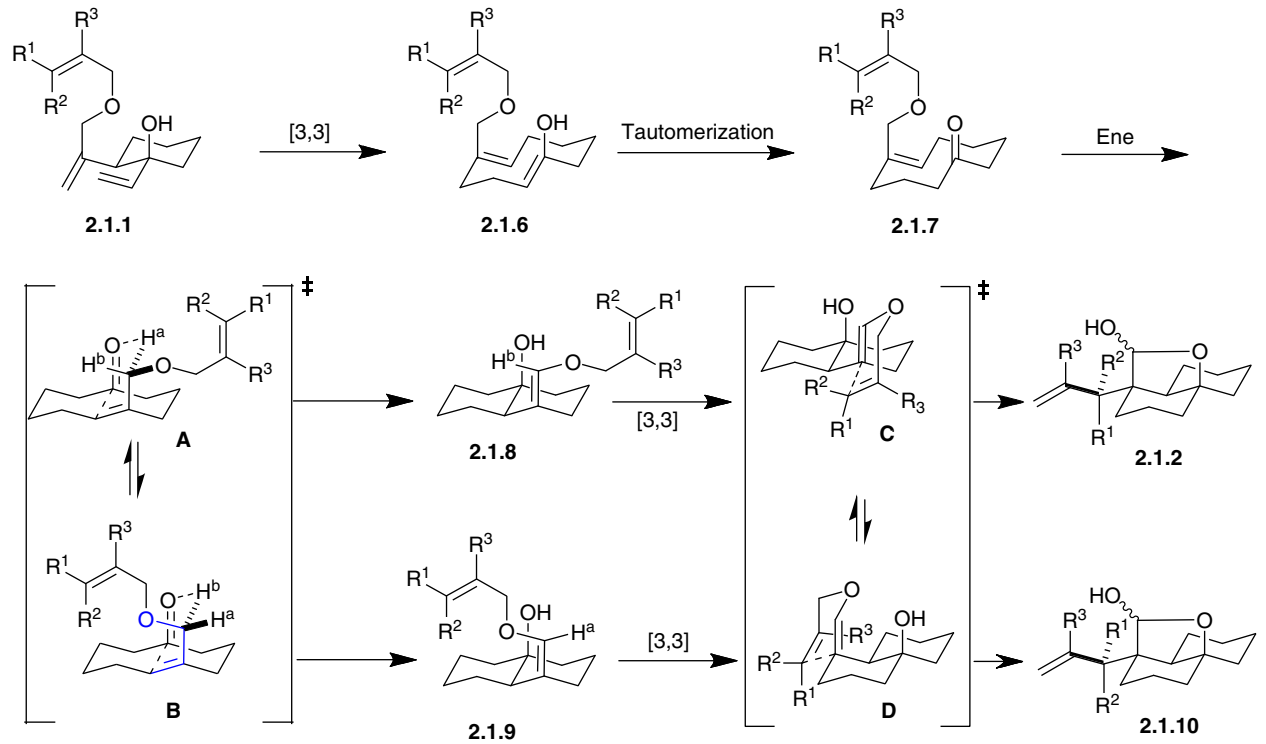
The mechanism and the high diastereoselectivity of the reaction can be rationalized as follows (Scheme 2). Microwave heating of 1,2-divinylcyclohexanol allyl ether **2.1.1** is proposed to give enol **2.1.6**, which after a rapid tautomerization would furnish ketone **2.1.7**. There are two possible transition states (**A** or **B**) for the subsequent transannular ene reaction of ketone **2.1.7**. A close examination of transition state **B**, however, reveals the presence of severe 1,3-allylic strain between the allyl ether group and the macrocyclic ring (in blue). As a result, enol ether **2.1.9** is disfavored relative to geometrical isomer **2.1.8**. Finally, a Claisen rearrangement of **2.1.8** via transition state **C** furnishes a hydroxyaldehyde, which then cyclizes to form lactol **2.1.2** as the major isomer. The minor isomer lactol **2.1.10** is formed via transition state **D**.

This domino oxy-Cope–ene–Claisen sequence has been employed to prepare an advanced intermediate en route to the natural antibiotic tetradecamycin (**2.1.11**) (Scheme 3).[4] Thus, Barriault and Warrington reported the conversion of propargyl alcohol **2.1.15** to decalin **2.1.14** in 87% yield. The latter was transformed into the advanced intermediate **2.1.13** through a short sequence.

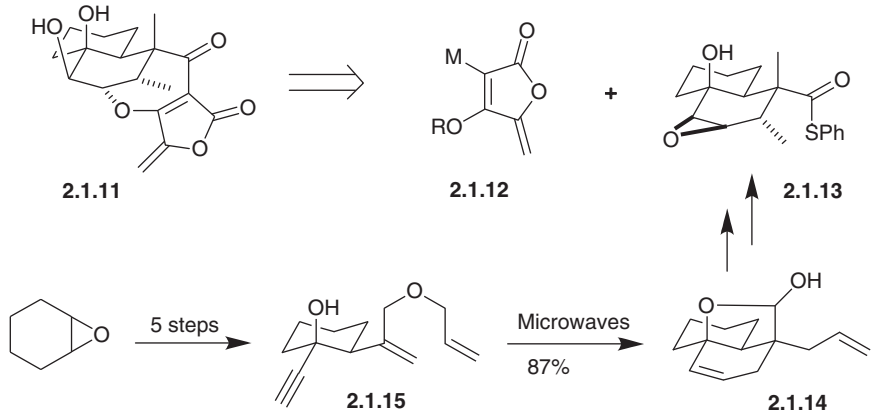
5.21.2.1.2 Cope–Claisen–ene

The stereocontrolled formation of two or more contiguous quaternary stereocenters is a significant challenge, particularly in cyclic systems. Barriault and Sauer developed a domino oxy-Cope–Claisen–ene sequence of allyl ethers **2.2.1** to produce decalins **2.2.2** possessing quaternary stereocenters at C9 and C10 in high yield and diastereoselectivity. This type of scaffold is embedded in several natural diterpenes including myrocin C (**2.2.3**) and teucrolivin A (**2.2.4**) (Scheme 4).[5]

On microwave irradiation, it is proposed that allyl ether **2.2.5** is converted to enol ether **2.2.6** via an oxy-Cope reaction (Scheme 5). The latter is positioned to undergo a Claisen rearrangement providing ketone **2.2.8**. This can be directly converted into **2.2.11** or undergo a rapid conformational interchange to produce **2.2.9**, which leads to the formation of **2.2.10**. It is



Scheme 2

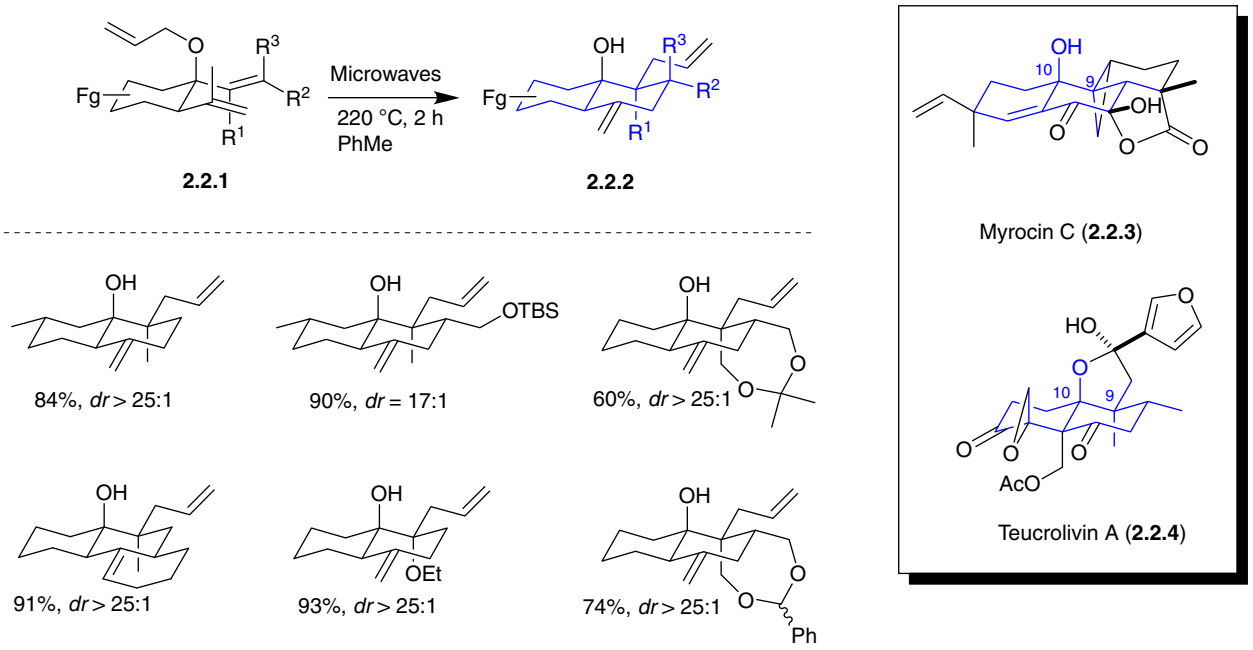


Scheme 3

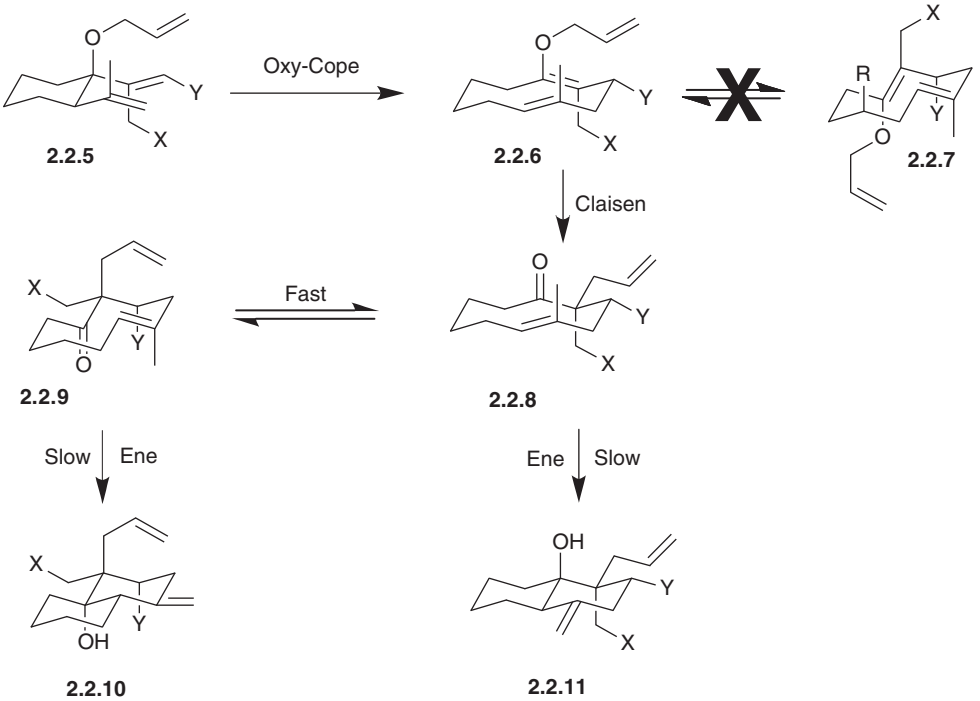
important to note that the conformational preference of macrocycles **2.2.6**, **2.2.8** and **2.2.9** dictates the stereochemical outcome of the final product.[6]

Experimental evidence and DFT calculations demonstrated that the ring inversion of **2.2.6**–**2.2.7** does not occur at 220 °C. It would appear that the 'through-the-annulus' rotation of either substituent of the tetrasubstituted alkene has a prohibitively high-energy barrier,[7] with the Claisen rearrangement of **2.2.6**–**2.2.8** being a much faster process. Conversely, the ring inversion of ketone **2.2.8**–**2.2.9** is a faster process than the ene reaction. As a result, the diastereoselectivity can be rationalized using the Curtin–Hammett principle.[8]

In 2008, Barriault and coworkers reported a stereoselective synthesis of complex carbocycles **2.2.14** from five- and six-membered ring propargyl ethers **2.2.12** and dienophiles **2.2.13** via four successive pericyclic reactions (Scheme 6).[9] This transformation combined a domino oxy-Cope–Claisen reaction and a subsequent hydroxyl-directed Diels–Alder reaction. In all cases, only one diastereoisomer was observed ($dr > 25{:}1$) in yields ranging from 36% to 49%. The attractive feature of the proposed process resides in the ability to generate, in one pot, four new C–C bonds and as many as four new contiguous stereogenic centers (**2.2.28**) leading to complex carbocyclic frameworks (**2.2.18**–**2.2.28**).

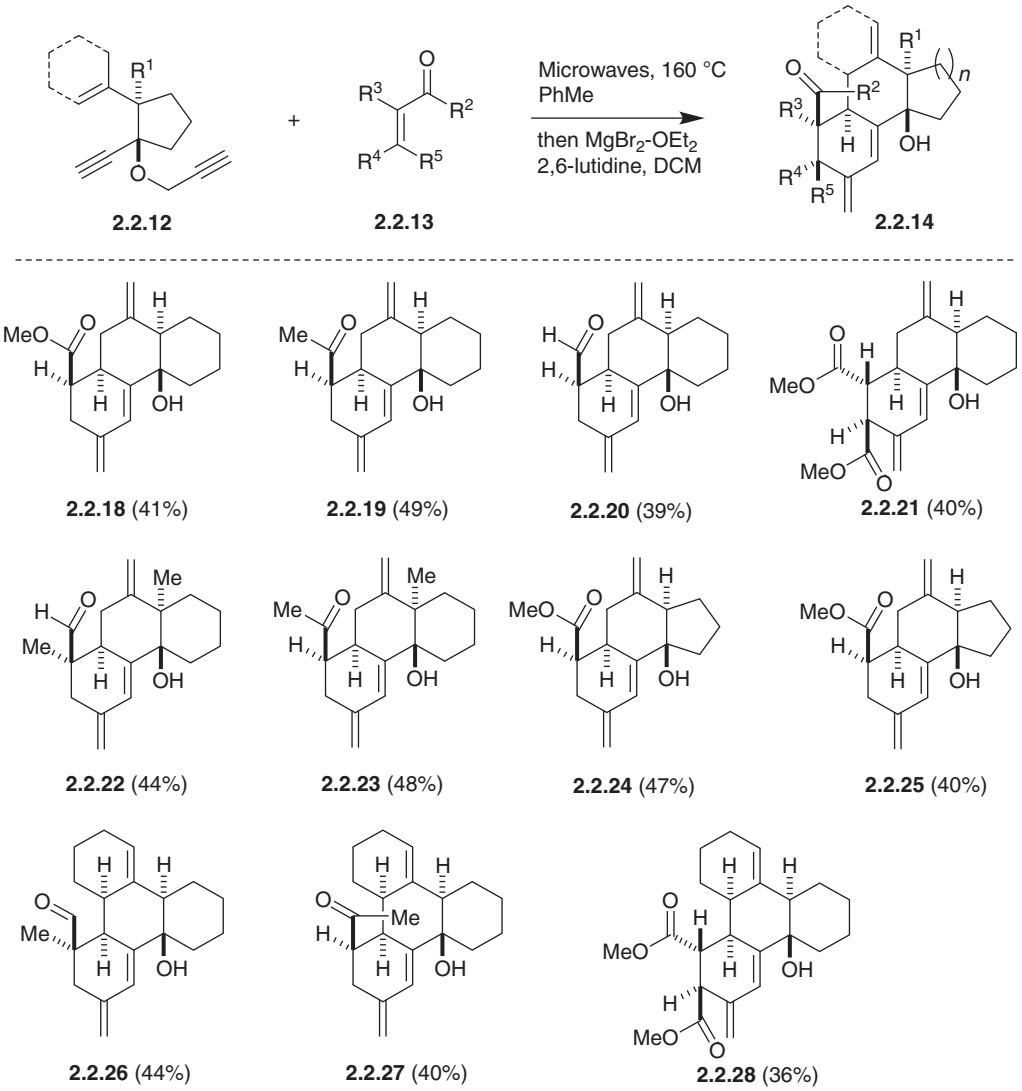


Scheme 4



Scheme 5

Microwave irradiation of **2.2.12** triggered the oxy-Cope reaction to produce allene **2.2.15** (Scheme 7). This highly strained macrocycle rearranges to generate enone **2.2.16** which undergoes a transannular ene reaction to deliver allene **2.2.17**. The latter was subsequently treated with a magnesium-based Lewis acid and a dienophile (**2.2.13**). The resulting hydroxyl-directed Diels–Alder reaction gives a single cycloadduct **2.2.14** in overall yields ranging from 36% to 48%. Transition state **TS-A** was proposed to account for the observed diastereoselectivity.



2.2.12 **2.2.13** **2.2.14**

2.2.18 (41%) **2.2.19** (49%) **2.2.20** (39%) **2.2.21** (40%)

2.2.22 (44%) **2.2.23** (48%) **2.2.24** (47%) **2.2.25** (40%)

2.2.26 (44%) **2.2.27** (40%) **2.2.28** (36%)

Scheme 6

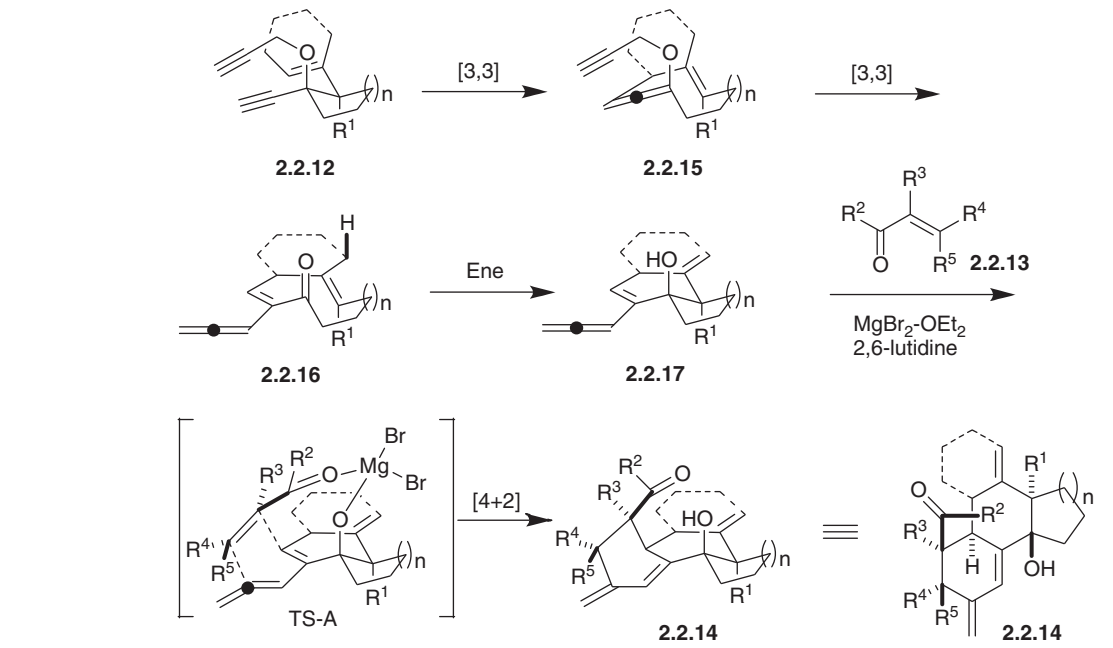
5.21.2.1.3 Claisen–Cope

Kraft et al. synthesized constitutional isomers of nerol by consecutive Ireland–Claisen and Cope rearrangements.[10] Thus, treatment of ester **2.3.1** with lithium cyclohexylisopropylamide (LICA) and trimethylsilyl chloride (TMSCl) in THF at −78 °C produced the silyl enol acetal **2.3.4** stereoselectively. This *Z*-configured alkene participated in an Ireland–Claisen rearrangement via a chair-like transition state to produce, after an aqueous work-up, carboxylic acid **2.3.5** as the sole isomer. On heating to 140 °C for 3 days, 1,5-diene **2.3.5** was converted into a 1:7 ratio of **2.3.2** and **2.3.3** in 84% yield. Acid **2.3.5** can undergo the Cope rearrangement via two chair-like transition states **2.3.6** and **2.3.7**. Because the *A* value of a methyl group is slightly larger than that of a carboxylic acid group, conformation **2.3.7** should be favored over **2.3.6**, thereby producing **2.3.3** as the major isomer (Scheme 8).

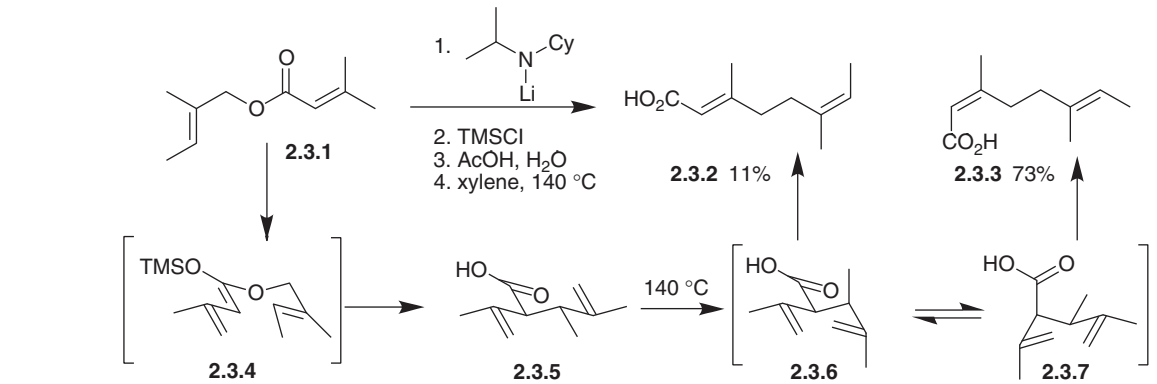
Natural coumarins such as (+)-trachypleuranin A (**2.3.11**) isolated from *Harboria trachypleura* were synthesized using an aromatic *para*-Claisen rearrangement (Scheme 9). Thus, domino Claisen–Cope rearrangements of phenyl prenyl ether **2.3.8** and intramolecular transesterification occurred in refluxing diethylaniline to give advanced intermediate **2.3.9** in 81% yield.[11] Natural products such as **2.3.11** have been shown to potentiate the action of anthraquinones as multidrug resistance efflux pump inhibitors.

5.21.2.1.4 Claisen–Claisen

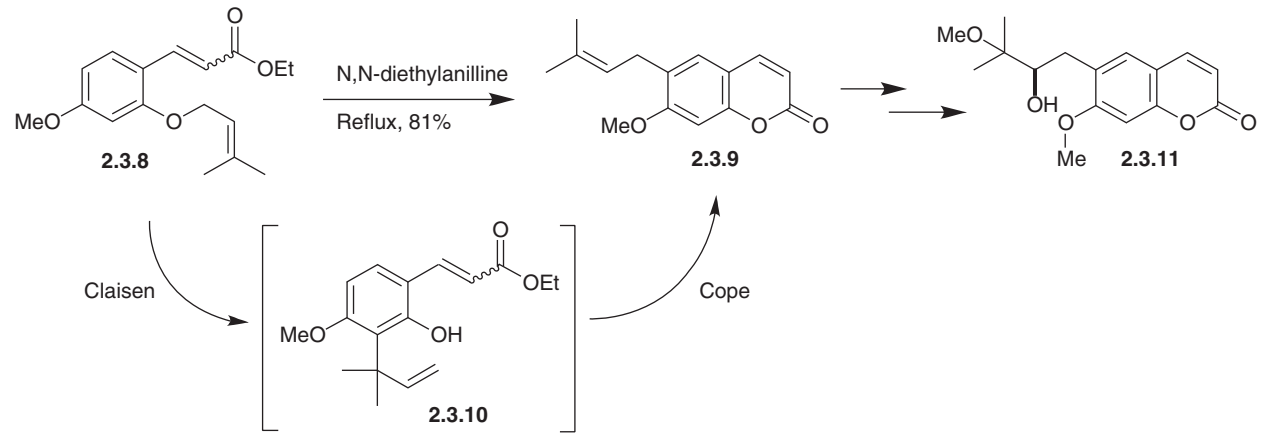
The examples described so far involve sequences of different sigmatropic rearrangements to construct new carbon–carbon bonds. In this section, the authors focus on the sequences involving only Claisen rearrangements. Seminal work from Hiratani reported the use of domino aryl Claisen rearrangements for the synthesis of ligands, sensors, and supramolecular building blocks (Scheme 10).[12] Thus, under thermal conditions, readily prepared di-ethers **2.4.1** are converted to monoether/monophenols **2.4.2**,



Scheme 7

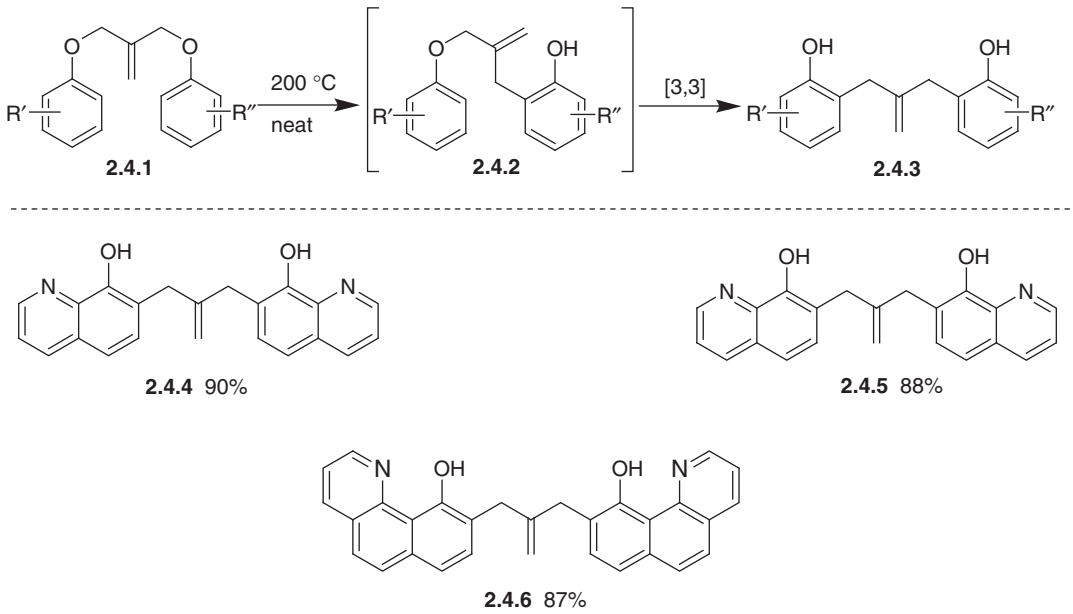


Scheme 8



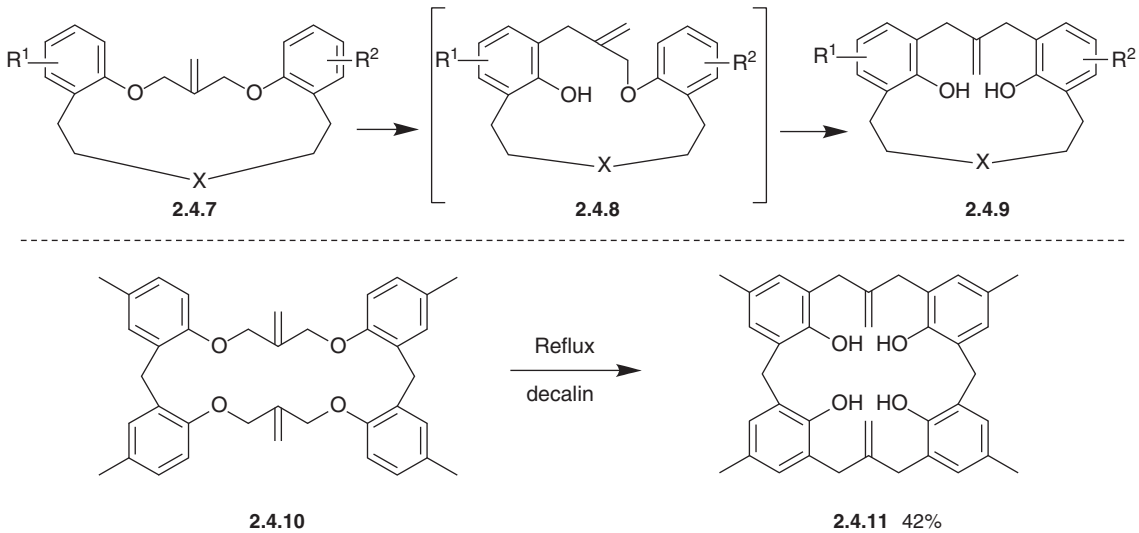
Scheme 9

which further rearrange to di-phenols **2.4.3**. Quinolone-containing ligands **2.4.4**–**2.4.6** were prepared in high yield using this approach.



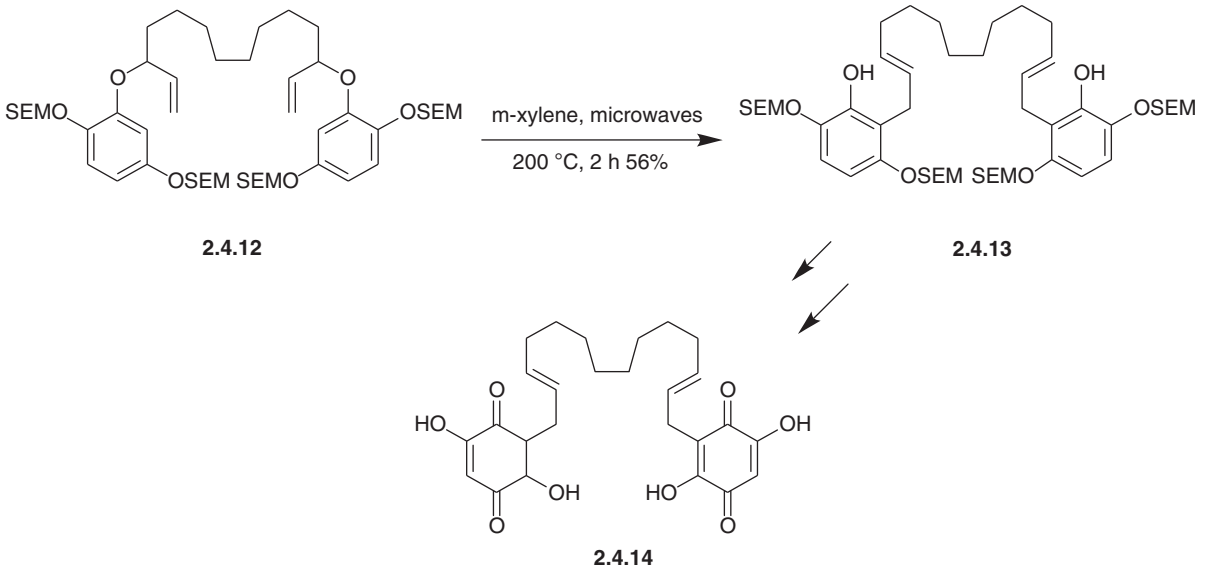
Scheme 10

Incorporation of a tether connection between the *ortho*-positions of the two aromatic rings allowed the sequence to be carried out within a macrocyclic context (i.e., **2.4.7**→**2.4.8**→**2.4.9**). In an extension of this work, macrocycle **2.4.10**, containing two diaryl methane units, was converted to calixarene **2.4.11** in 42% yield via a sequence of four consecutive Claisen rearrangements (Scheme 11).[13] This is a unique approach to compounds that are useful in host–guest chemistry.



Scheme 11

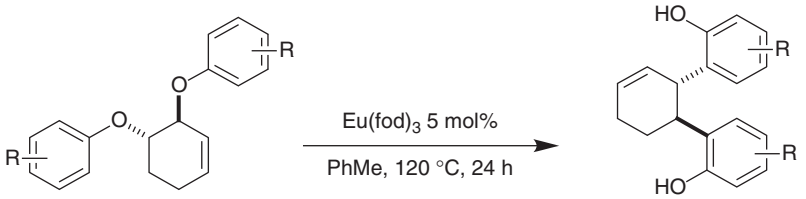
In a related example, Moody utilized a double Claisen rearrangement of a substrate containing two separate aromatic allyl ethers **2.4.12**, connected through a octamethylene chain (Scheme 12).[14] The product di-phenol **2.4.13** was converted to the proposed structure of lanciaquinone **2.4.14**. In some respects, this synthesis is reminiscent of Johnson's classic two-directional synthesis of squalene from 1970, which involves orthoester Johnson–Claisen rearrangements at the two ends of a growing acyclic chain.[15]



2.4.12 **2.4.13** **2.4.14**

Scheme 12

Batey has introduced a different twist on the twofold aromatic *ortho*-Claisen rearrangement theme. Thus, the rearrangement of the allyl aryl ether group of diaryloxy-cyclohexenes **2.4.15** (Scheme 13) sets up a new allyl aryl ether, which allows the second Claisen rearrangement.[16] The conversion of **2.4.15** to **2.4.16** proceeds with the replacement of two C–O bonds with two C–C bonds and is accompanied by smooth transfer of stereochemistry.

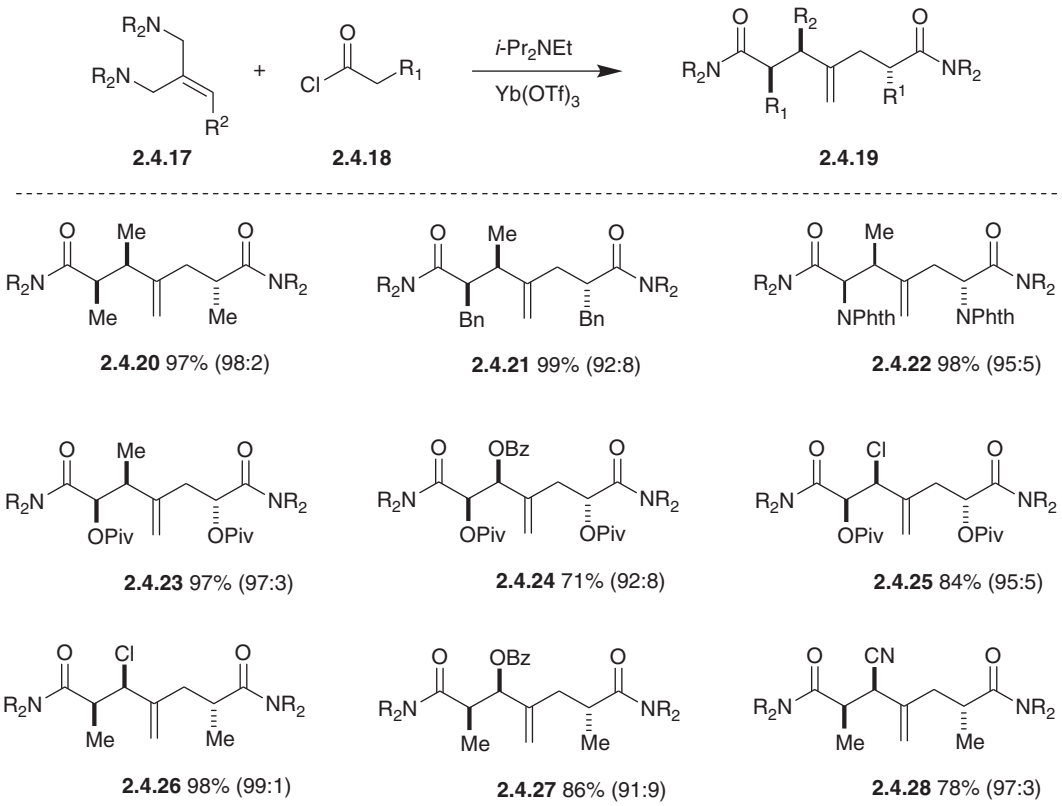


2.4.15 **2.4.16**
up to 93%
and 99% *ee*

Scheme 13

Polypropionate units are frequently encountered in bio-active natural products and the asymmetric aldol reaction has been the dominant method to prepare such motifs for many years. That the Claisen rearrangement represents an attractive alternative method for polypropionate unit synthesis is demonstrated in the next example. Drawing inspiration from the work of Bellus and Malherbe,[17] MacMillan and Dong reported a highly stereoselective synthesis of complex acyclic 2,3,6-trisubstituted-1,7-dioxoheptanes **2.4.19** via a tandem Bellus–Claisen rearrangement of diamine **2.4.17** and acyl chloride **2.4.18** (Scheme 14).[18] This double [3,3]-shift proves to be tolerant to substantial structural variations (i.e., R^1 and R^2) in the two precursors. Substituted-1,7-dioxoheptanes **2.4.20–2.4.28** that incorporate alkyl, halo, cyano, alkoxy, and amino substituents were prepared in high yield and high diastereoselectivity (71–99% yield, 92:8 to 98:2 *syn–anti*). The advantage of this method resides in its capacity to build functional group- and stereocenter-rich acyclic chains that are not readily available using conventional chemical processes.

The process (Scheme 15) commences with elimination of the elements of HCl from the acyl chloride to form the ketene, which suffers nucleophilic addition by one of the two amine groups of substrate **2.4.29.** One can rationalize that destabilizing steric interactions will disfavor transition state **2.4.31** relative to **2.4.30**, thereby resulting in [3,3] rearrangement product **2.4.32**. Given that the nucleophilic addition of the amine **2.4.29** to the ketene is reversible,[19] the slower reacting *Z*-isomer **2.4.31** presumably reverts back to precursors and all starting material is thereby channeled through to amide **2.4.32**. A second ketene addition then generates an ammonium enolate that can adopt two chair-like transition states for [3,3] sigmatropic rearrangement, namely, **2.4.33** and **2.4.34**. The minimization of 1,2-allylic strain (C5–C5a) in **2.4.33** imposes destabilizing interactions between the axial methylene group (morpholine ring) and the amide chain, whereas the same torsional restriction in **2.4.34** orients the side chain away from the ring. As a result, the Bellus–Claisen rearrangement proceeds via transition state **2.4.34** to give diamide **2.4.35** as the major diastereoisomer.



Scheme 14

Over the past few years, Chida's group has developed elegant applications of sequential [3,3]-sigmatropic rearrangements of allylic diols in total synthesis. The targets prepared include A-315675 (**2.4.39**), the synthesis of which involved a double Overman rearrangement as a key step (Scheme 16).[20] Thus, treatment of diol **2.4.36** with trichloroacetonitrile and 1,5-diazabicyclo [5.4.0]undec-5-ene (DBU) produced imidate **2.4.37**, which on heating under basic conditions delivered amide **2.4.38** in 63% yield over two steps. A short sequence from this double sigmatropic rearrangement product led to the natural product.

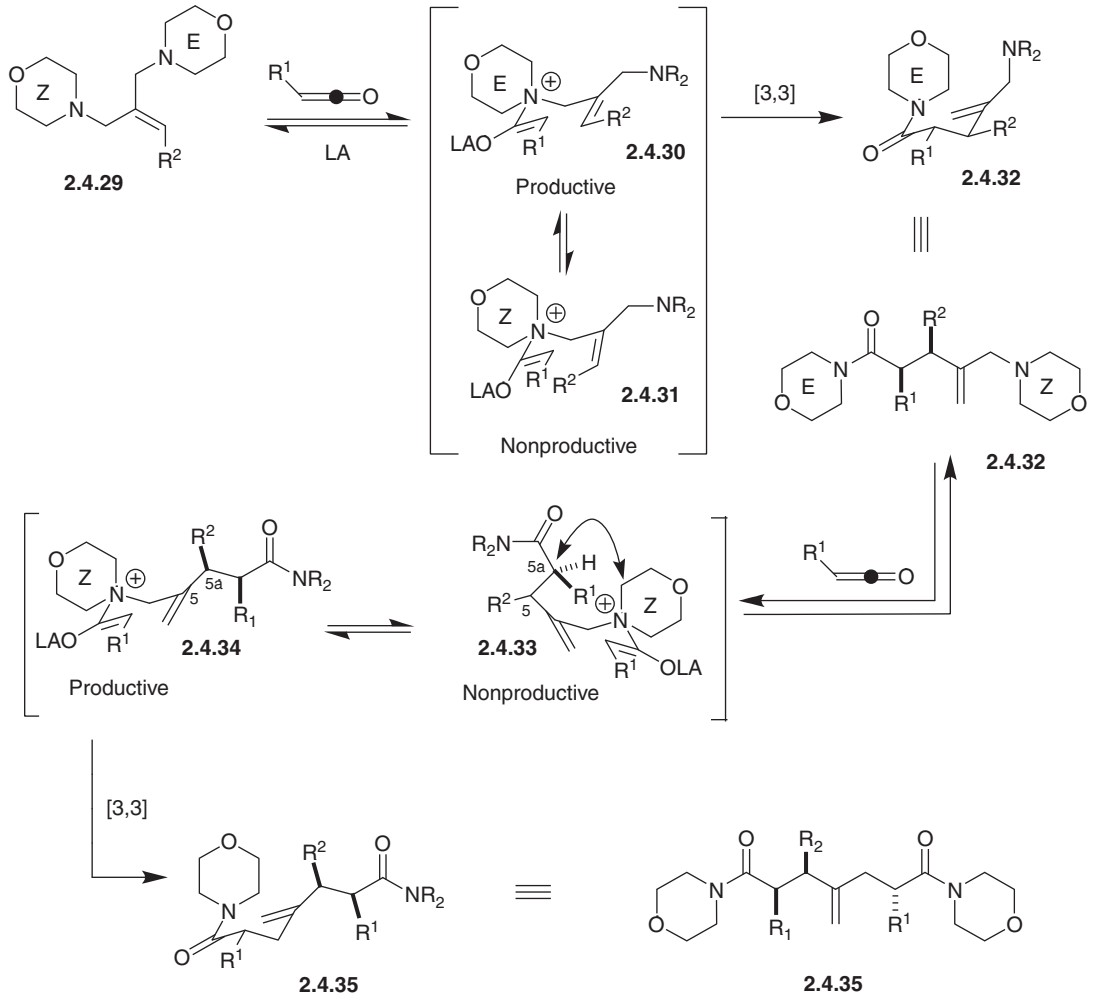
The Chida group applied a variation on this theme to the synthesis of kainic acid.[21] In this case, the initial Claisen rearrangement of **2.4.40** proceeded through cyclic orthoamide **2.4.41** and *N,O*-ketene acetal **2.4.42** intermediates to form allylic alcohol **2.4.43.** A subsequent Overman rearrangement, in a separate synthetic transformation, gave amide **2.4.44** (Scheme 17) en route to the natural product.

The Chida group also reported a formal total synthesis of (–)-morphine (**2.4.49**) employing a double orthoester Johnson–Claisen rearrangement as a key step (Scheme 18).[22] Thus, *trans*-diol **2.4.45** was treated with trimethylorthoacetate in the presence of a catalytic amount of 2-nitrophenol at 140 °C to give the corresponding substituted cyclohexene **2.4.48** in 36% yield. The reaction proceeds via intermediates **2.4.46** and **2.4.47**, with complete transfer of stereochemistry from substrate to product. The double *ortho*-Claisen rearrangement reported later by Batey (Scheme 13) bears a close similarity to this approach.[16]

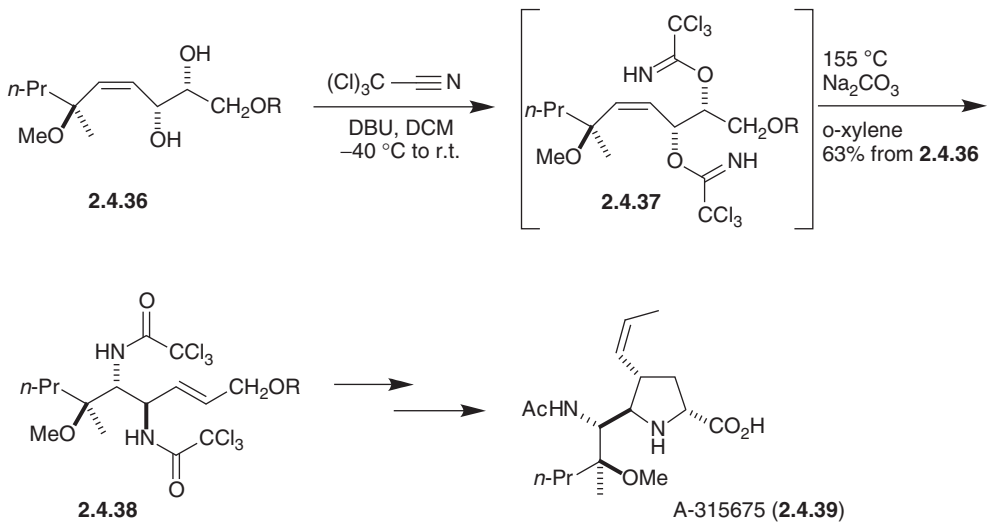
5.21.2.1.5 Claisen–Claisen cycloaddition

4-Oxatricyclo[4.3.1.0]decan-2-ones are fascinating ring systems found in several natural products isolated from the genus *Garcinia* of the *Guttiferae* family of plants.[23] Among them, forbesione (**2.5.2**) was isolated from the plant *Garcinia forbesii* (Scheme 19).[24] Quillinan and Scheinmann proposed a biogenesis of these scaffolds from 6-allylxanthones, by way of a double Claisen rearrangement followed by a Diels–Alder reaction.[25] In 2001, Nicolaou et al. reported the successful synthetic realization of this domino sequence and its application in the biomimetic synthesis of 1-*O*-methylforbesione (**2.5.3**).[26] In the event, the *O*-methylated natural product **2.5.3** was obtained as the major isomer in 63% yield on heating allylxanthone **2.5.1** at 120 °C in DMF for 20 min.

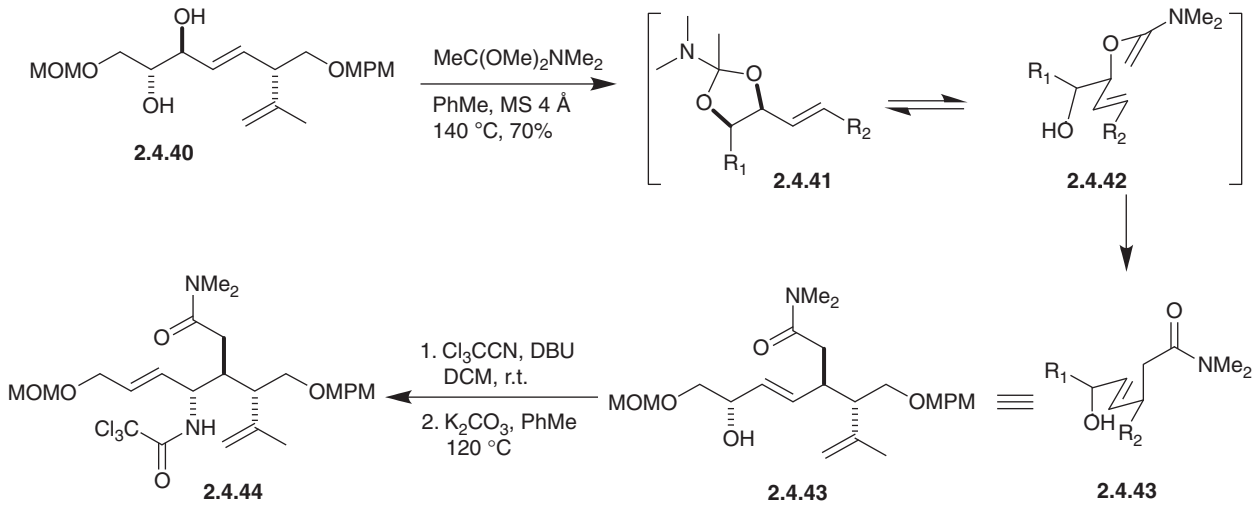
The cascade pericyclic reaction sequence is triggered by a [3,3]-sigmatropic rearrangement involving the α,α-dimethylallyl substituent at C-6 (Scheme 20). The less substituted alkene substituent attached to the resulting cyclohexadienone **2.5.5** undergoes an intramolecular Diels–Alder cycloaddition to afford the cycloadduct **2.5.6.** A regioselective *ortho*-Claisen rearrangement of the other allyl aryl ether group delivers the desired product **2.5.3** in 63% yield. A competitive Claisen rearrangement involving the C-5 allyl group gave intermediate **2.5.7**, which after an analogous Diels–Alder reaction and [3,3]-sigmatropic shift



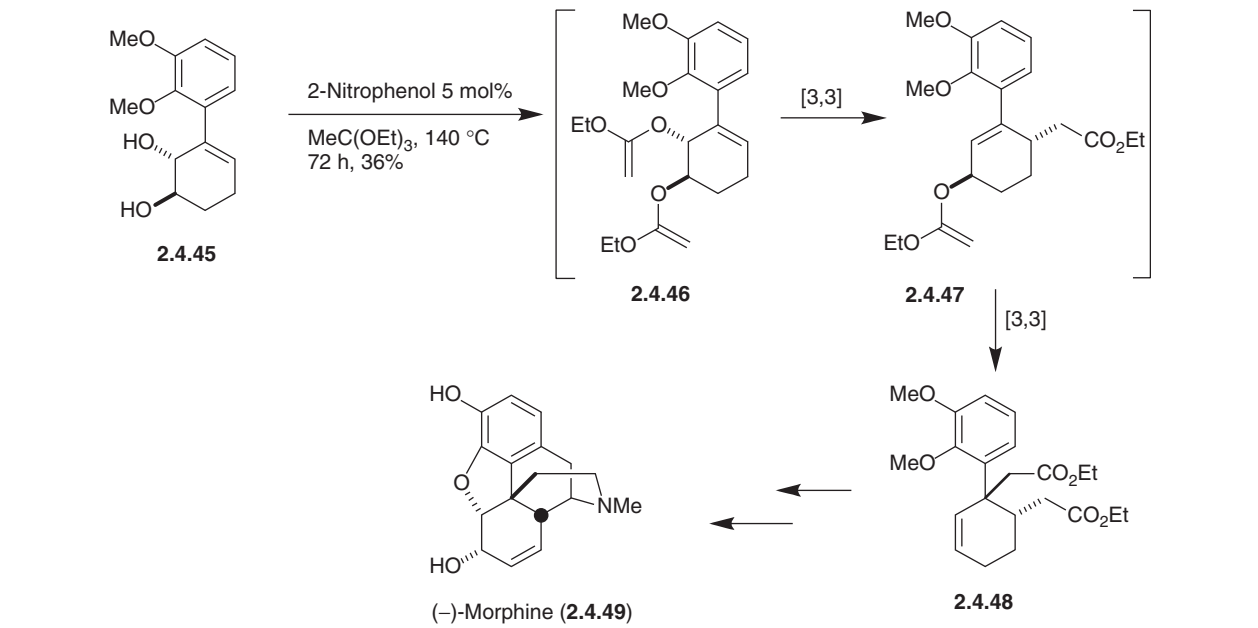
Scheme 15



Scheme 16



Scheme 17



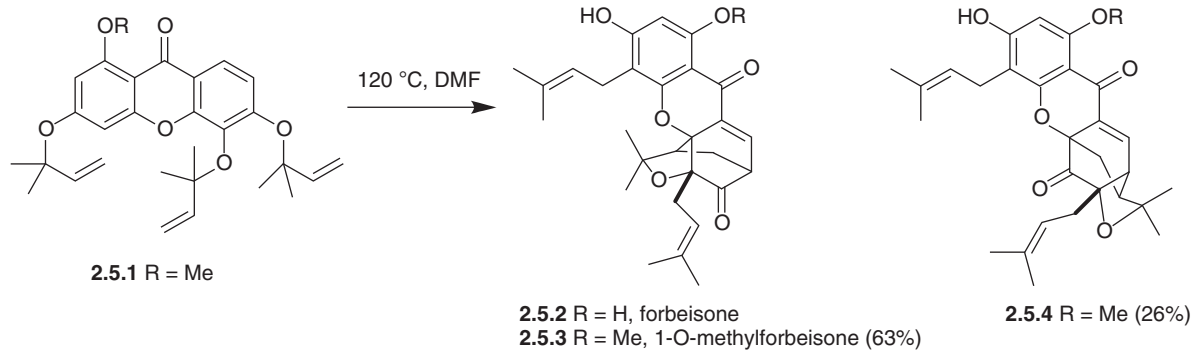
Scheme 18

led to the minor isomer **2.5.4** (26% yield). The order of events in this overall transformation with respect to the two Claisen rearrangements has not been reported, hence the sequences shown in Scheme 20 are simply used for convenience.

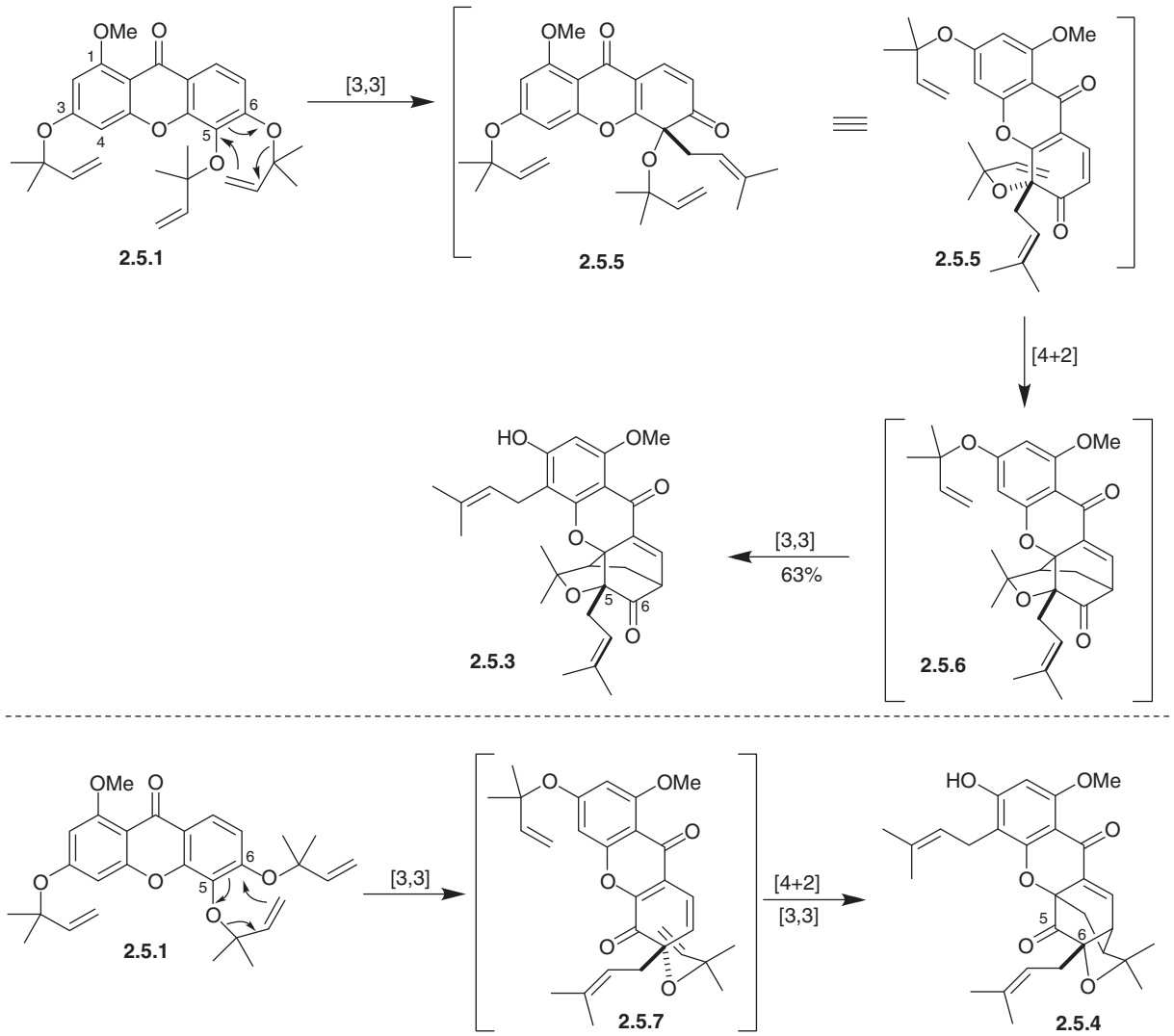
It has been postulated that the biosynthesis of the bicyclo[3.2.0]heptane framework of the artochamins involves a double Claisen rearrangement followed by a [2 + 2]-cycloaddition.[27] Nicolaou et al. evaluated this proposed pathway in a bioinspired total synthesis of artochamins H (**2.5.12**), I (**2.5.13**), and J (**2.5.14**) (Scheme 21).[28] Thus, stilbene **2.5.8** was heated at 180 °C in xylene with a catalytic amount of Ph_3PO to give tetracycle **2.5.9** in 55% yield as 5:1 diastereomeric mixture. An initial double *ortho*-aromatic Claisen rearrangement and *in situ* double *tert*-butyloxycarbonyl (Boc)-deprotection led to catechol **2.5.10**. The latter underwent an intramolecular formal [2 + 2]-cycloaddition, as formulated in structure **2.5.11**, to provide the desired product **2.5.9**, which was converted in four steps into Artochamins H-J. Mechanistic studies suggested that formation of the cyclobutane ring proceeds via a stepwise ionic pathway. Irrespective of the true biosynthesis and the mechanism of the ring forming process, this approach is an efficient method to construct the carbon framework of the artochamins.

5.21.2.1.6 Double [3,3]-sigmatropic rearrangements on alkynes

In this double orthoester Johnson–Claisen rearrangement developed by Ishino, an alkyne diol such as **2.6.1** participates in a [3,3]-sigmatropic shift to form an allene **2.6.3**, which in turn undergoes a second [3,3]-sigmatropic shift resulting in a conjugated



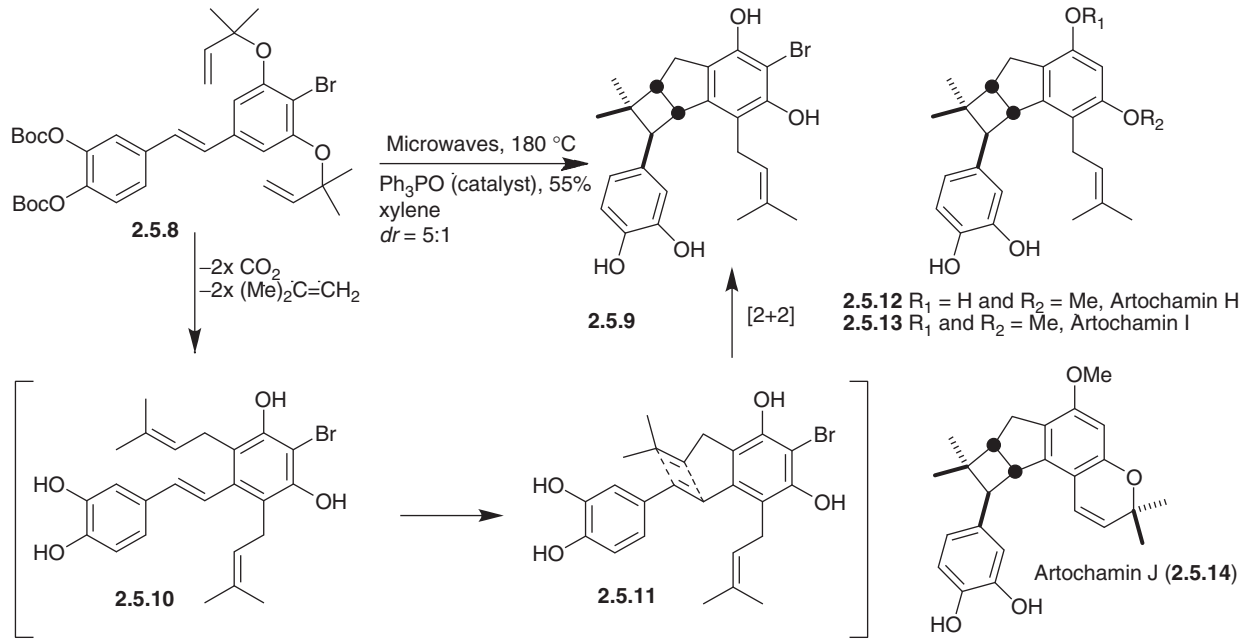
Scheme 19



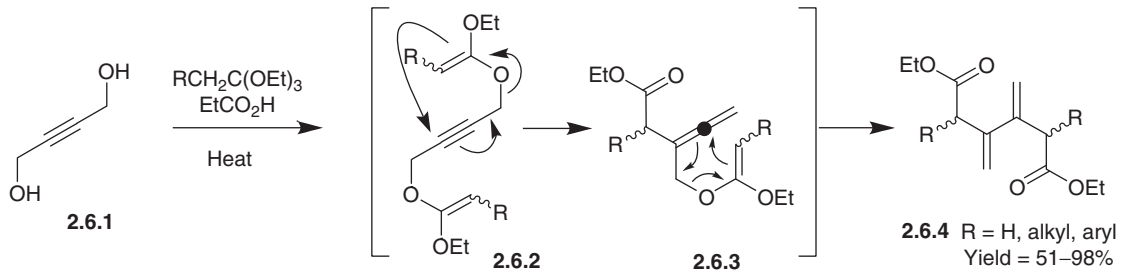
Scheme 20

1,3-butadiene **2.6.4** (Scheme 22).[29] The reaction proves tolerant to various substituents on the trialkyl orthoalkanoate to give allylic substituted products.

In a conceptually related study, Banert et al. reported the synthesis 1,2-difunctionalized 1,3-butadienes through a sequence of [3,3]-shifts of terminal alkynes **2.6.5** (Scheme 23, equation 1).[30] Although trichloroacetamide- (XYZ=NHCOCCl$_3$),

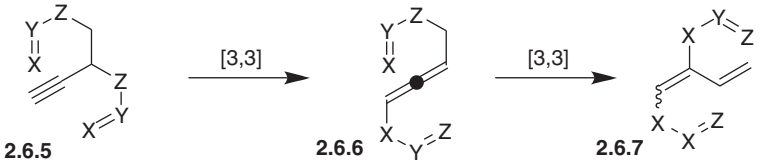


Scheme 21



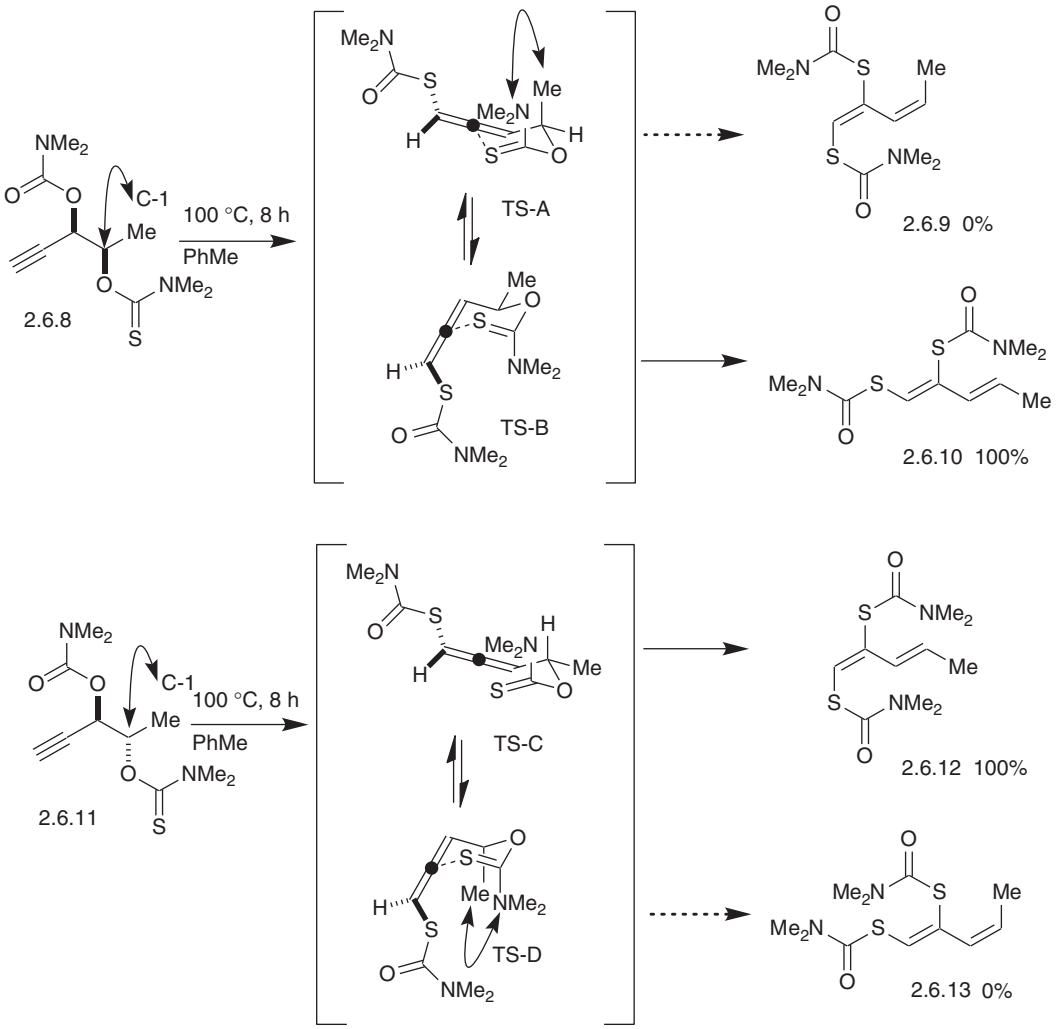
Scheme 22

thioester- (XYZ=SCOPh), thiocarbamate- (XYZ=SCONMe$_2$), thiocarbonate- (XYZ=SCO$_2$Ar), and dithiocarbonate- (XYZ=S-C(O)SMe) substituted alkynes **2.6.5** were converted to 1,3-dienes **2.6.7** in good yields, these compounds were obtained as a (separable) mixture of *E* and *Z* isomers. In a subsequent study, the reaction was found to be highly stereoselective with substrates carrying a stereocenter at C-1.[31] Thus, separate heating of the thiocarbamates diastereomers **2.6.8** (*syn*) and **2.6.11** (*anti*) gave the *E,Z*-dienes **2.6.10** and *E,E*-dienes **2.6.12,** respectively, each as a single geometrical isomer in quantitative yields. A close examination of the chair-like transition states **TS A-D** reveals the presence of severe 1,3-diaxial interactions between the axially oriented methyl and thiocarbamate groups in **TS-A** and **TS-D**. The stereoisomeric products derived from these transition states, namely, **2.6.9** and **2.6.13**, are not observed. The isolated products **2.6.10** and **2.6.12** result from transition states **TS-B** and **TS-C**, respectively, which lack these destabilizing interactions.



(1)

In the Banert examples, the order of events is known, because the propargylic substituent must rearrange first. With other substrates, the mechanism is less certain. Hopf demonstrated that pyrolysis of alkyne **2.6.14** at temperatures ranging from 290 to 350 °C gave aldehyde **2.6.15** in 87% yield (Scheme 24).[32] One can imagine a mechanism involving an initial Claisen or Cope rearrangement. Because only the product from an initial Claisen rearrangement, **2.6.16**, was observed in the reaction mixture, it is



Scheme 23

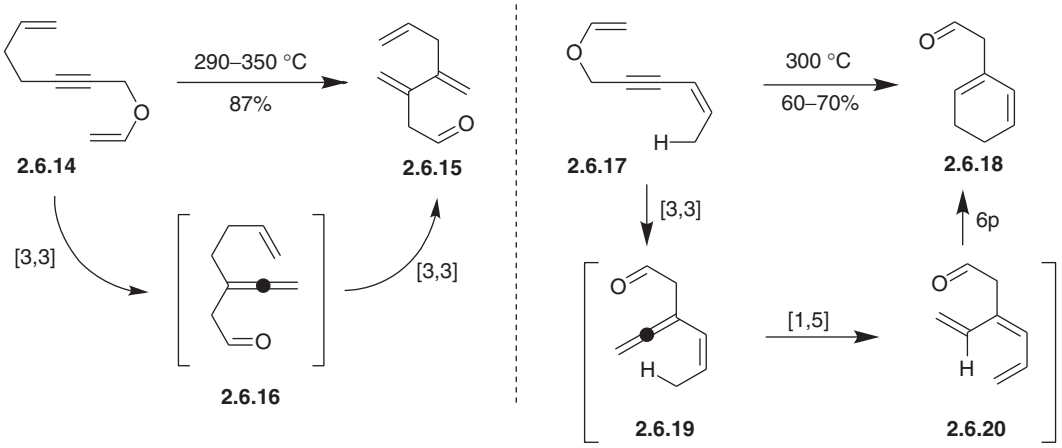
this pathway that operates. The allene **2.6.16** is converted to aldehyde **2.6.15** via a Cope rearrangement. In a related example, the pyrolysis of enol ether **2.6.17** gave aldehyde **2.6.18** in 60–70% yields. The domino process commences with a Claisen rearrangement to produce allene **2.6.19**. The latter undergoes the expected [1,5]-sigmatropic shift to produce aldehyde **2.6.20**, which on 6π electrocyclization gives **2.6.18**. It was found that cyclization of **2.6.17** at higher temperatures produced toluene via decarbonylation and aromatization.

Hopf also attempted the double Claisen rearrangement of the divinyl ether of butyne-1,4-diol but these efforts were met with limited success.[32] This type of consecutive sigmatropic rearrangement has been successfully achieved by Ishino, however, using a double orthoester Johnson–Claisen rearrangement (Scheme 22).[28a,b] More recent studies by Hong et al. reported the stereoselective synthesis of (*E*)-1,2,3-trisubstituted dienes **2.6.22** (R=alkyl, aryl) from substituted propargyl diols **2.6.21** via a double Johnson–Claisen rearrangement.[33] It was proposed that the ketene acetal of the primary alcohol is formed first, which after [3,3]-sigmatropic rearrangement furnishes allene **2.6.23**. The latter is transformed to a secondary ketene acetal **2.6.24**, which undergoes a second Claisen rearrangement to produce 1,3-diene **2.6.22**. The high selectivity of the process is presumably the result of the chair-like transition state **TS-A** being favored over boat-like transition state **TS-B** in the second Claisen rearrangement. The R– and $-CH_2CO_2Et$ substituents are *cis*-oriented in **TS-A**, thus giving rise to *E*-diene **2.6.22** (Scheme 25).

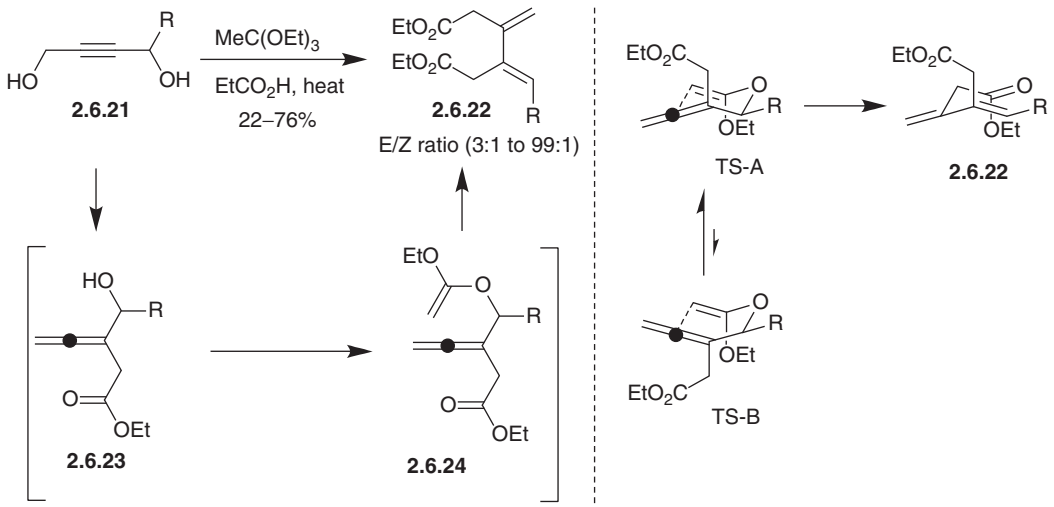
5.21.3 [3,3]-[i,j] Rearrangement

5.21.3.1 Claisen-[2,3]-Shift

Zakarian and Pelc devised a clever synthesis of the A/G spirocyclic fragment **3.1.2** of pinnatoxin A (**3.1.1**) via a domino Claisen/Mislow–Evans rearrangement (Scheme 26).[34] The sulfoxide **3.1.3** (as a mixture of diastereomers at the sulfur center) was heated at



Scheme 24



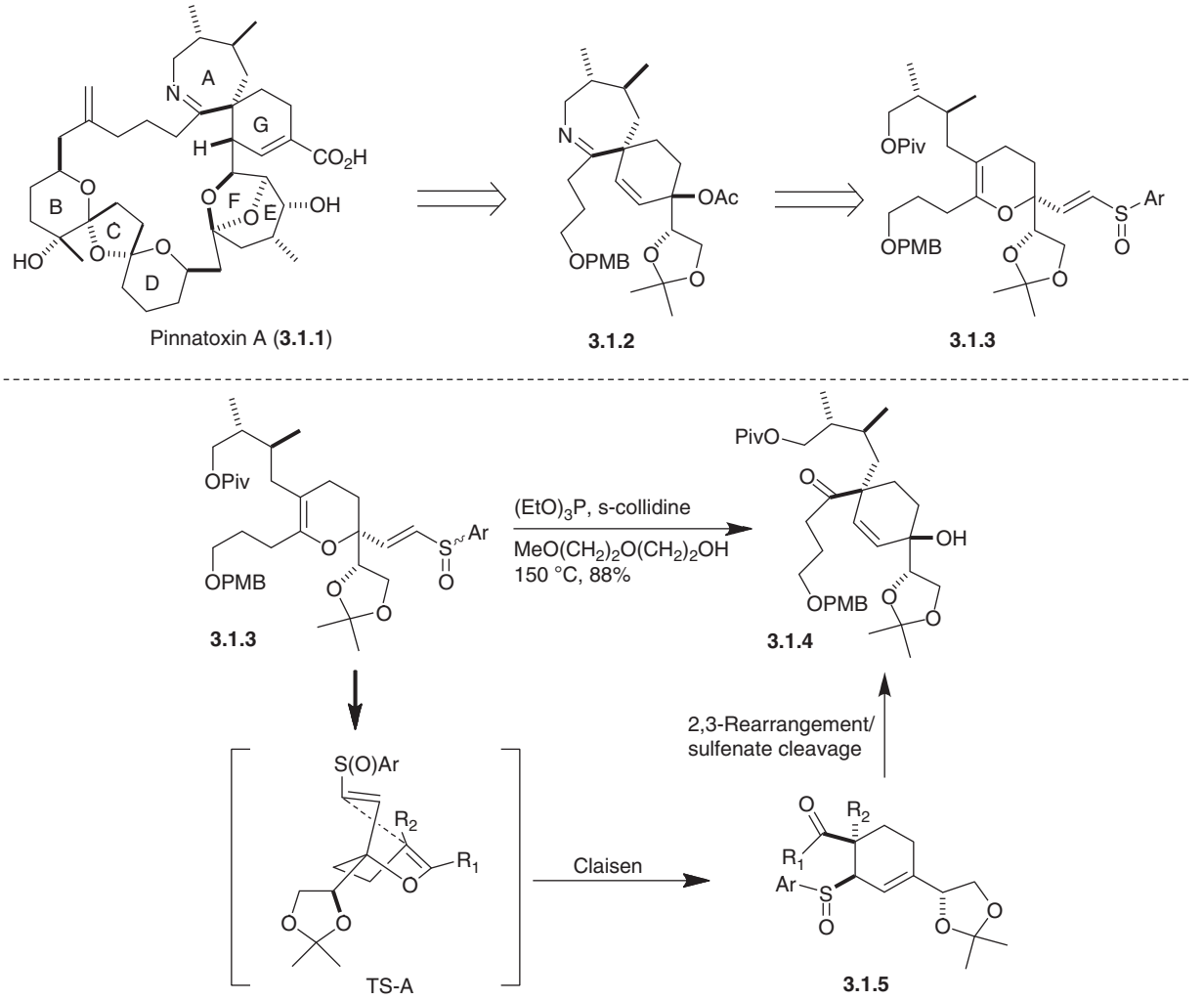
Scheme 25

150 °C in the presence of Ph_3PO and 2,6-collidine to give **3.1.4** in 88% yield as a single isomer. The domino reaction is triggered by a [3,3]-sigmatropic shift proceeding via transition state **TS-A** to furnish allylic sulfoxide **3.1.5**. A subsequent [2,3]-sigmatropic shift (Mislow–Evans reaction) forms an allyl sulfenate, which is cleaved to allyl alcohol **3.1.4** by triethyl phosphite. The latter was converted over several steps into the target subunit **3.1.2**.

The same group applied a related strategy to the synthesis of mesembrine (**3.1.10**), an alkaloid found in *Sceletium* plants (Scheme 27).[35] The direct domino [3,3]/[2,3] sigmatropic rearrangement was not applicable in this case, so a stepwise approach was pursued involving a Claisen rearrangement of alkenyl sulfide **3.1.6** followed by oxidation to the sulfoxide and a Mislow–Evans reaction to give the desired alcohol **3.1.9**. Interestingly, despite the presence of alkenyl sulfide **3.1.6** as an *E*/*Z* mixture, the stereochemical outcome of the Claisen rearrangement is consistent with only the *E*-isomer reacting. This led the authors propose an *E*/*Z* equilibration under the reaction conditions. Presumably, severe 1,3-allylic interactions in the *Z*-isomer **TS-B** make this transition state disfavored relative to that of the *E*-isomer, **TS-A.**

Posner et al. developed a new synthetic method to 4-oxo-2-alkenoate esters **3.1.16** from propargyl alcohols **3.1.11** and sulfoxide reagent **3.1.12** (Scheme 28).[36] This one pot transformation presumably proceeds via a [3,3]-sigmatropic rearrangement of Michael addition product **3.1.13**, followed by a [2,3]-shift of the allenyl sulfoxide **3.1.14** to give dienyl sulfenate **3.1.15**. Hydrolysis gives functionalized 4-oxo-2-alkenoates **3.1.17**–**3.1.23** in yields ranging from 52% to 80% as a mixture of *E*/*Z* isomers. This approach represents an efficient and convenient route to functionalized trisubstituted dienophiles, because it proceeds in one step from readily available propargylic alcohols and the bench stable reagent **3.1.12**.

Majumdar et al. observed a novel domino sigmatropic reaction during the thermolysis of propargylic sulfoxide **3.1.26** (Scheme 29).[37] Oxidation of sulfide **3.1.24** followed by refluxing in CCl_4 produced the rearranged structure **3.1.25** in 62–71% yields. This novel cascade reaction proceeds first by a [2,3]-sigmatropic rearrangement of the sulfoxide to produce sulfenate



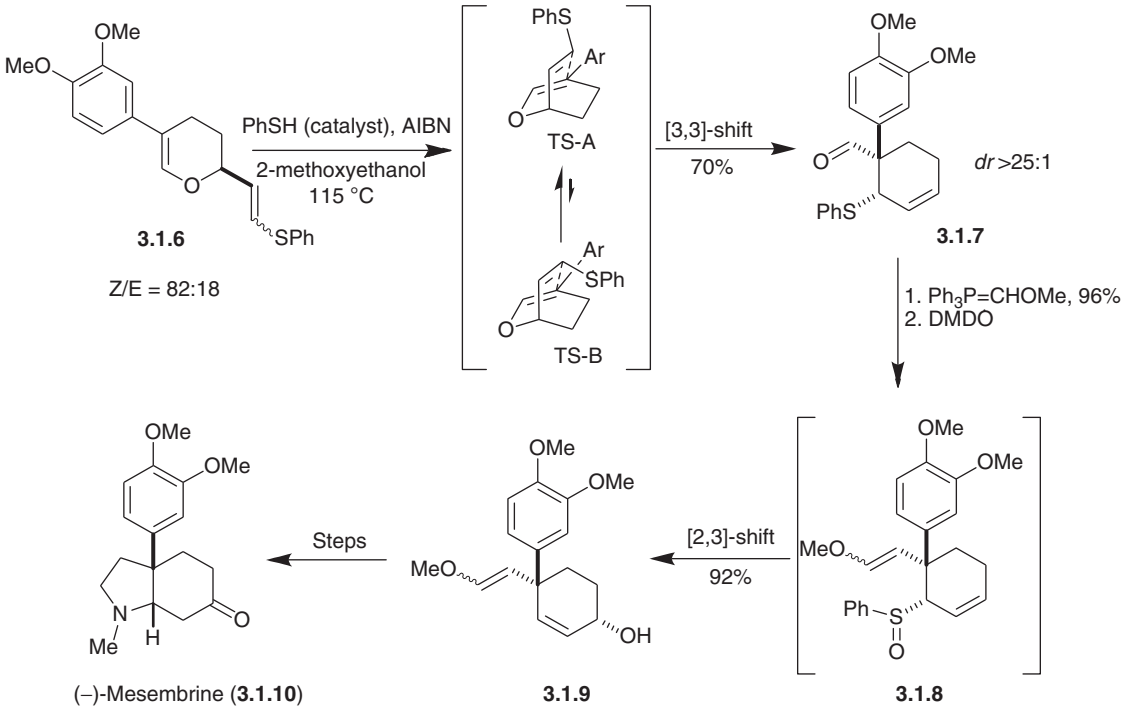
Scheme 26

intermediate **3.1.27**. This transient intermediate undergoes a [3,3]-sigmatropic rearrangement to give enone **3.1.28**. Tautomerization of the thione functionality affords thio-enol **3.1.29**, which undergoes an intramolecular Michael addition to give the observed product **3.1.25**.

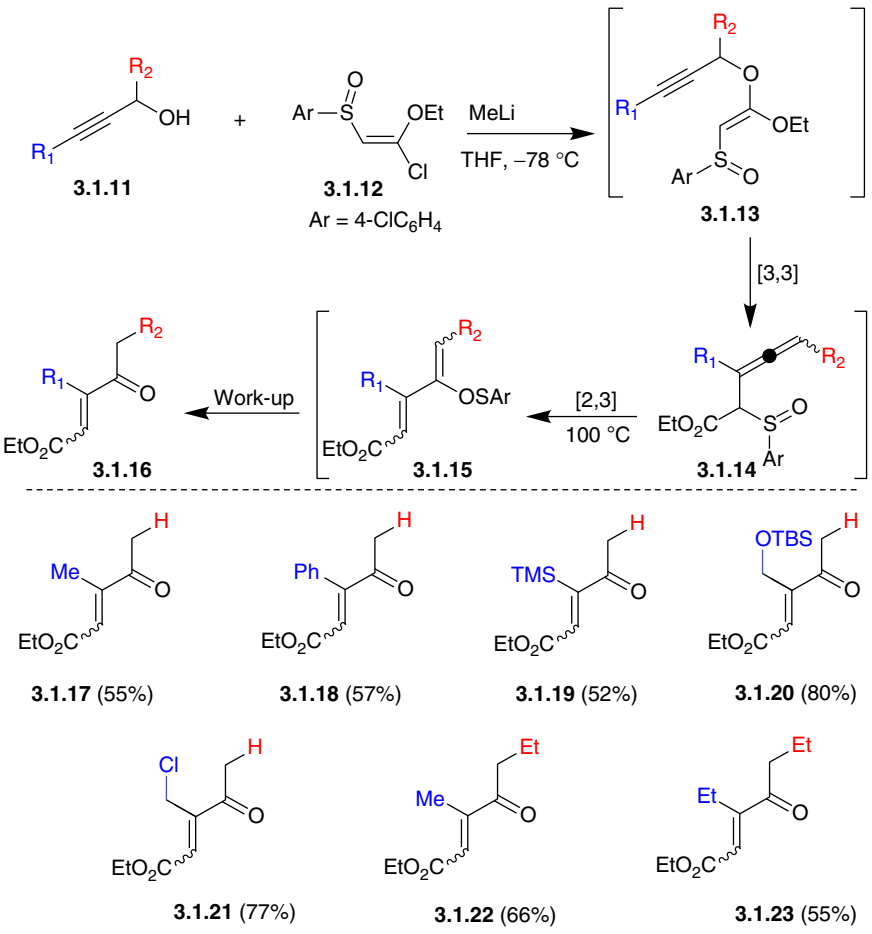
In an extended version of their earlier studies (see Schemes 16–18), Chida and coworkers reported the synthesis of agelastatin A using a sequence of two [3,3]-sigmatropic rearrangements followed by a [2,3]-shift (Scheme 30).[38] Thus, treatment of diol **3.1.30** with trichloroacetonitrile gave di-imidate **3.1.31**, which under basic conditions rearranged to give diamide **3.1.33** in 58% yield. Subsequent oxidation of the allylic sulfide **3.1.33** afforded allylic sulfoxide **3.1.34**, which underwent a [2,3]-shift yielding alcohol **3.1.35** on phosphite-mediated heterolysis of the intermediate sulfenate.

5.21.3.2 [1,5]-[3,3](-[3,3]) Shift

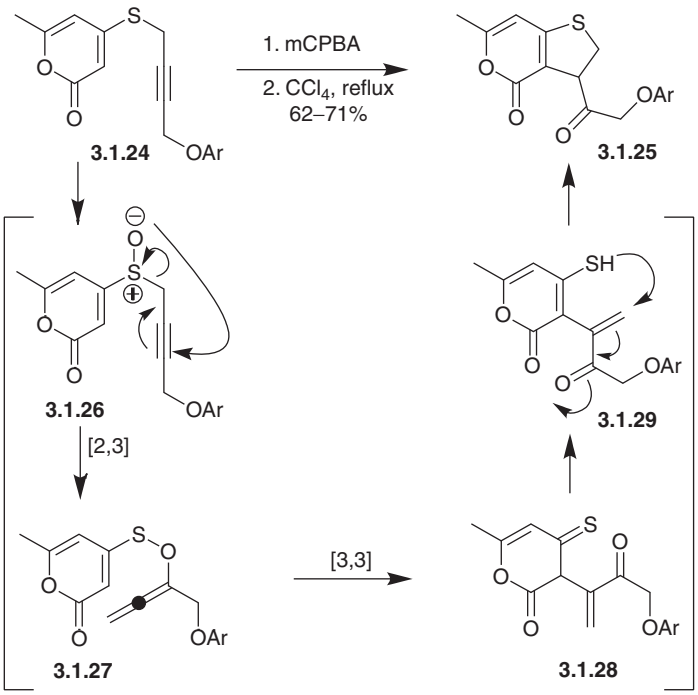
Vanderwal and coworkers have reported the synthesis of unsaturated amides via a thermal pericyclic rearrangement of Zincke aldehydes.[39] In the course of their studies, they found that Zincke aldehydes **3.2.1** and **3.2.4** were transformed into intramolecular Diels–Alder adducts **3.2.2**/**3.2.5** and dihydropyridones **3.2.3**/**3.2.6** (Scheme 31).[40] Further investigations featuring computational studies provided mechanistic insights into the cascade reaction.[41] It was found that Zincke aldehyde **3.2.7** undergoes [1,5]-hydrogen shift to produce a reactive ketene intermediate **3.2.8**, which cyclizes through nucleophilic addition to form the zwitterionic species **3.2.9**. The latter constitutes a common intermediate by which both bicyclic amide **3.2.12** and dihydropyridone **3.2.15** are generated, as shown in Scheme 31 via path a and path b, respectively. In the former, a 6π-electrocyclic ring opening sets up an intramolecular Diels–Alder reaction. In the latter, either a single (**3.2.3**) or a double (**3.2.6**) Cope rearrangement occurs.



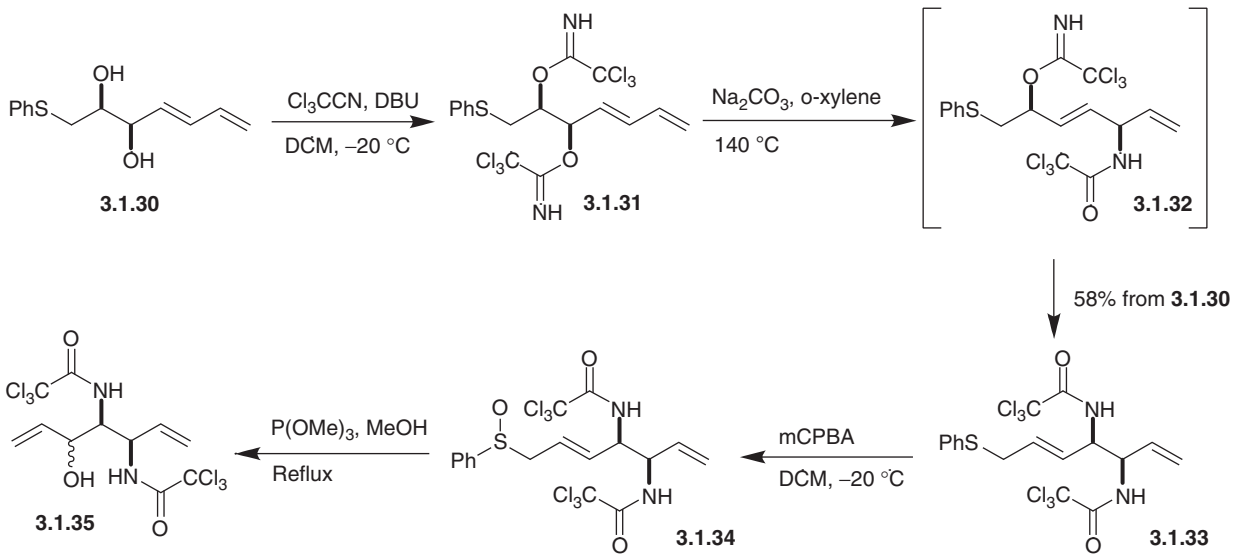
Scheme 27



Scheme 28



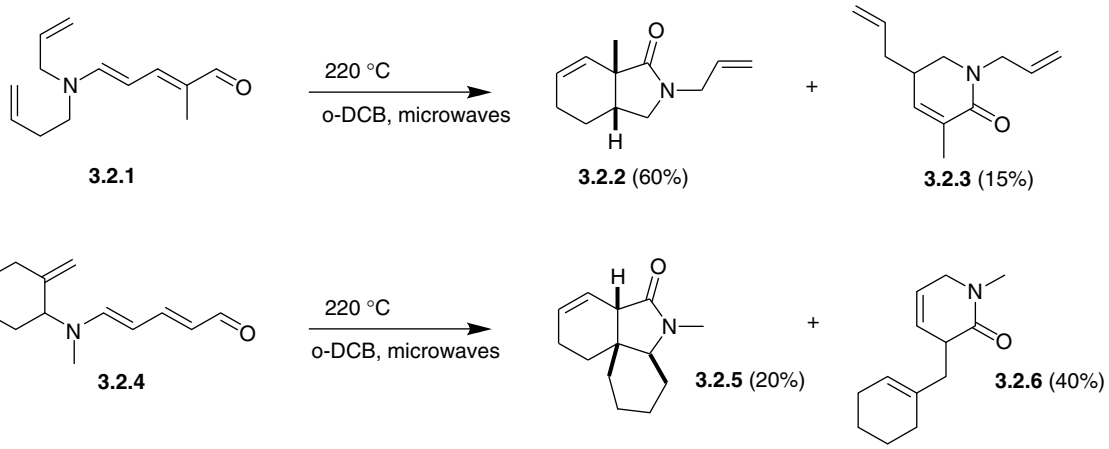
Scheme 29

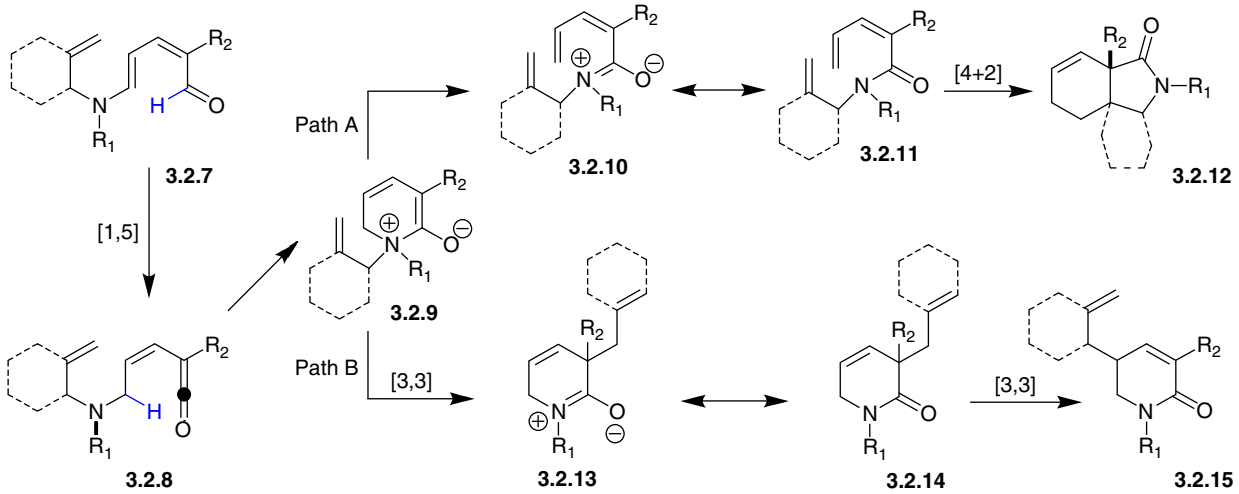


Scheme 30

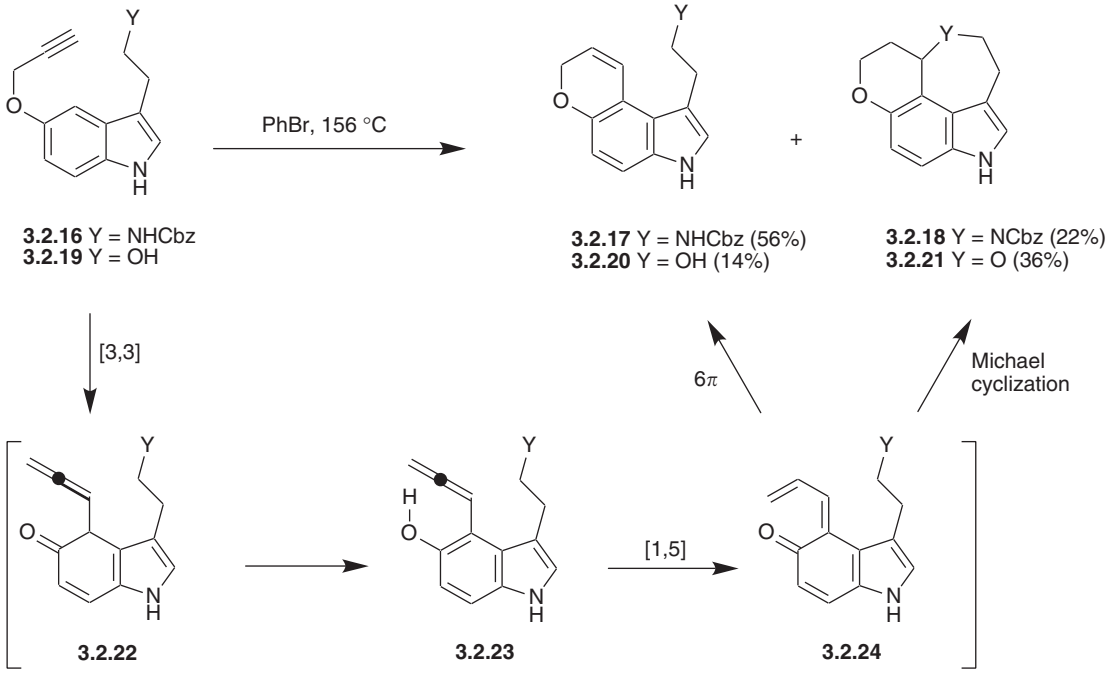
Evidently, the substitution pattern of the allylic chain has a direct influence on the outcome of the reaction. The observed product ratios were consistent with computational findings.

Macor and coworkers reported the thermal conversion of 5-propargyloxyindoles to tricyclic indoles via a [3,3]-[1,5]-sigmatropic shift sequence, *en route* to serotonin analogs (Scheme 32).[42] Propargyloxyindole **3.2.16** was heated in bromobenzene at 156 °C to give tricycle **3.2.17** in 56% yield, along with tetracyclic indole **3.2.18** in 22% yield. The mechanism for the formation of tricycles **3.2.17** involves Claisen rearrangement of propargyl aryl ether **3.2.16** to give allenyl cyclohexadienone **3.2.22**, which after tautomerization would produce allenyl phenol **3.2.23**. The latter is poised to undergo a [1,5]-hydrogen shift to generate quinone methide **3.2.24**, which can be converted to **3.2.17** via a 6π electrocyclization. The formation of tetracycle **3.2.18** could arise from intermediate **3.2.24** through an intramolecular 1,4-addition of the nucleophilic group on the side chain (i.e., Y) followed by





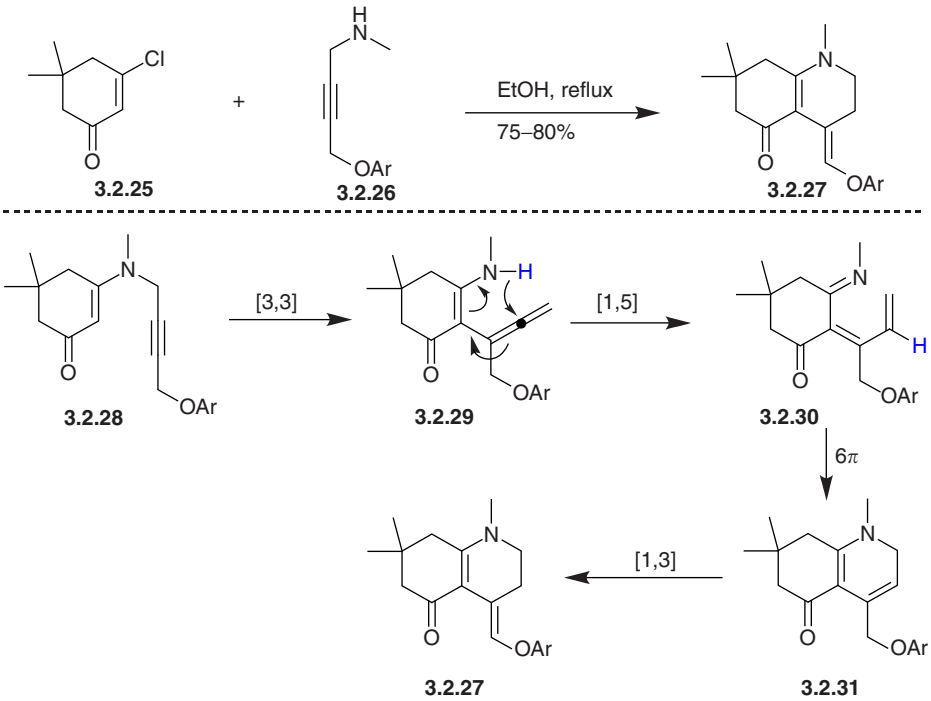
Scheme 31



Scheme 32

cyclization (i.e., of the phenol to the terminal alkene). The isolation and resubmission of **3.2.17** in the same reaction conditions did not produce **3.2.18**. Products **3.2.17** and **3.2.18** could be derived from common intermediate **3.2.24**. It was hypothesized that the increase of the nucleophilicity of the side chain should favor the formation of the tetracyclic product. Replacement of the NHCbz group by a primary alcohol (**3.2.19**) led to a higher yield of the tetracycle **3.2.21** (36%) relative to the tricycle **3.2.20** (14%), providing some support for this possibility.

An aza-Claisen rearrangement-[1,5]-hydrogen shift sequence has also been used in the annelation of piperidine rings (Scheme 33).[43] Thus, heating a mixture of 3-chloro enone **3.2.25** and propargyl amines **3.2.26** produced hydroquinolones **3.2.27** in 75–80% yield. In all cases, the rearrangement took place through the amine intermediate **3.2.28**. The formation of the products can be explained by an initial [3,3]-sigmatropic rearrangement of the propargyl alkenylamine **3.2.28** to generate an intermediate enamine-allene **3.2.29**. A [1,5]-hydrogen shift followed by 6π-electrocyclization gives the endocyclic intermediate **3.2.31**, which leads to the final product by [1,3]-hydrogen shift.



Scheme 33

5.21.4 Conclusion

The results reviewed in this chapter highlight the synthetic power of sequences involving sigmatropic rearrangements. Studies directed toward the development of new synthetic methods, total synthesis, medicinal chemistry, and host–guest chemistry have all benefitted from the introduction of such sequences. It is perhaps not surprising that [3,3]-shifts dominate the landscape of consecutive sigmatropic rearrangements. Although sequences comprising exclusively sigmatropic rearrangements are powerful, their true potential becomes even more apparent when they are coupled with other bond-forming reactions, such as cycloadditions. It is surely in this guise that these processes will continue to flourish for many years to come.

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5.22 Rearrangements of Vinylcyclopropanes, Divinylcyclopropanes, and Related Systems

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[†]Deceased, 2010; portions of the divinylcyclopropane section are excerpted from: Piers, E. In Comprehensive Organic Synthesis; Trost, B., Ed.; Vol. 5, Chapter 8.2, Pergamon, Oxford, 1991.

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5.22.1 Vinylcyclopropanes

5.22.1.1 Introduction

It has been more than 125 years since von Baeyer[1] and Perkin[2] reported the first syntheses of cyclopropane derivatives and von Baeyer[1] formulated of the "theory of ring strain." The chemistry of small-ring compounds has risen to prominence in the past 50 years. The popularity especially of three-membered rings as intermediates in synthetic transformations has been due primarily to their latent energy content and to the seemingly endless chemical transformations in which these compounds and their derivatives can participate. New applications and novel permutations of the basic systems continue to appear at a fast pace. The fascinating chemistry associated with the strain of these intermediates continues to find wide applicability in the field of synthetic methodology and in the total synthesis of complex molecules.

The following discussion highlights those transformations of vinylcyclopropanes and their derivatives that are selective with regard to the regio- and stereochemistry of products. The discussion of such transformations is done from the position of a synthetic practitioner interested in their actual use. At the end of both major sections, a survey of useful and general methodologies based on these transformations is provided along with a tabular compilation of total syntheses featuring these rearrangements as key steps.

5.22.1.2 Theoretical and Mechanistic Considerations of the Vinylcyclopropane System

5.22.1.2.1 Bonding and energetics of cyclopropane systems

The bonding in cyclopropane requires that the sp^3 hybrids be misaligned by approximately 22° from the imaginary line connecting the carbon atoms, as shown in Figure 1. The result is the so-called bent or banana bond, which has approximately 20% less orbital overlap than the corresponding bond in ethane. The Coulson–Moffitt[3] model **1** and the Walsh[4] model **2** use three sp^3-hybridized CH_2 groups and three sp^2-hybridized CH_2 groups, respectively. The overall hybridization of cyclopropane carbon–carbon bonds is thus $sp^{2.3}$; this greater *p*-character can be invoked in rationalizing the similarity of cyclopropane chemistry to that of alkenes. Because the bond angles are considerably less than the ideal 109.5°, cyclopropane suffers from significant angular (Baeyer) strain and hydrogen repulsions, as well as from torsional (Pitzer) strain from eclipsed carbon–hydrogen bonds.

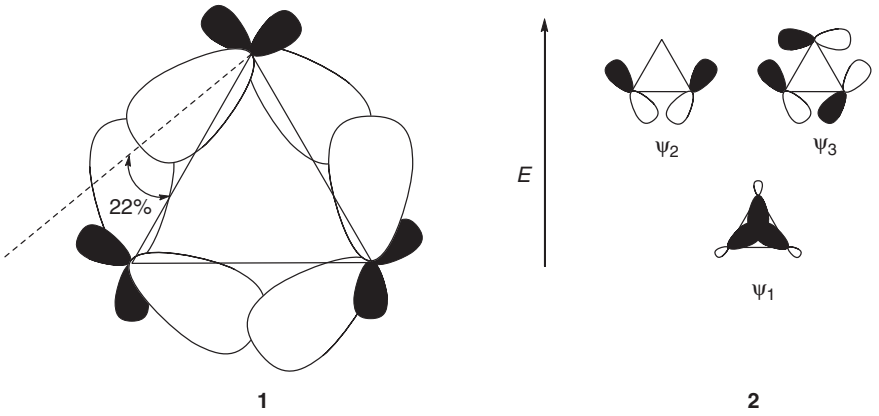


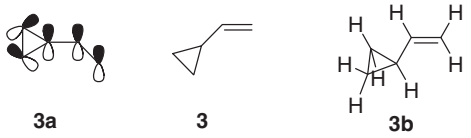
Figure 1 Bonding in cyclopropane.

A unique treatment of cyclopropane was advanced by Dewar,[5] who introduced the concept of σ-aromaticity, which explains some of its anomalous chemical and physical properties. The notion of σ-conjugation implies that three σ-bonds form a cyclic system of six electrons; thus cyclopropane is aromatic by the $(4n+2)$ rule. This explanation accounts well for its strain energy. The actual value (27.5 kcal mol^{-1})[6] is much lower than the predicted value of 104 kcal mol^{-1} (1 cal = 4.2 J), calculated from the C–C–C bending force constants obtained spectroscopically.[5,7] A similar comparison for cyclobutane (antiaromatic by the above notion and the $4n$ rule) underestimated the strain energy.[8] σ-Aromaticity also accounts for such observations as ^{1}H NMR chemical shifts and the reactivity of cyclopropane toward electrophiles.

The cyclopropane ring is subject to a number of chemical transformations that are only possible because of its unique bonding and high energy content. It is the energy content (27.5 kcal mol^{-1}) that drives the diradical opening of cyclopropane, especially so if one (or both) of the resulting radicals becomes a part of a delocalized allylic system, as in the case of vinyl- or divinylcyclopropanes. The resonance stabilization energy of an allylic radical system (12.6 kcal mol^{-1})[8] can be used to explain the lower activation energy for reactions involving vinylcyclopropane (34–55 kcal mol^{-1}) compared with the activation energy for reaction resulting from diradical processes that involve only the cyclopropane ring (59–66 kcal mol^{-1}).[9–13]

The vinylcyclopropane unit contains the strain energy of the cyclopropane ring (27.5 kcal mol^{-1}), and it is this energy content that is primarily responsible for its reactive options. Thermal ring fission can occur by any one of three mechanisms: [1,5] sigmatropic hydrogen shift, $[2\sigma_s+2\pi_s]$ concerted reorganization to cyclopentene, or a diradical fission followed by further reactions of the diradicals (recombination or hydrogen abstraction). This discussion has received considerable attention in both the mechanistic and the synthetic sense and has been the subject of several reviews.[9,14–25]

The bonding in vinylcyclopropane **3** is such that an *s-trans-gauche* conformational equilibrium exists to allow for maximum orbital overlap of the asymmetric component of cyclopropane orbitals with the π- or π^*-orbitals of the ethylene unit, as shown in **3a**. From thermochemical studies it appears that conjugation of an alkene with cyclopropane stabilizes the system by 1.2 kcal mol^{-1}.[26,27] The conformational equilibrium for vinylcyclopropane was shown to consist of an *s-trans* minimum **3b** and two *gauche* conformers that are equal in energy and destabilized by 1.43 kcal mol^{-1} with respect to the *s-trans* conformation. The barrier to interconversion has been determined to be 3.92 kcal mol^{-1}.[28]



3a **3** **3b**

The details of bonding and spectroscopic properties of cyclopropane derivatives have been reviewed.[13,27,29] In addition, the properties and energetics of cyclopropyl cations, anions, radicals, anion radicals, and cation radicals have been amply reviewed, and comparisons have been made with their corresponding alkenic counterparts.[13,27,30,31] Recently, theoretical calculations in a study of properties have been performed on vinylcyclopropyl cation radicals,[32] anion radicals,[33–35] and neutral radicals.[34]

5.22.1.2.2 Reactive tendencies

For a synthetic chemist the analogy between cyclopropanes and alkenes is an appropriate one. Virtually every reaction that an alkene undergoes has a counterpart in the repertoire of transformations possible with cyclopropanes. Thus, conjugation of a cyclopropane to an alkene makes it possible to invoke a number of reaction modes and reactive intermediates that can be compared directly to their alkenic counterparts.

How a particular vinylcyclopropane will be electronically perturbed toward a specific mode of reactivity depends on the substitution of either the cyclopropane or the vinyl portion. All of the principal reactions of vinylcyclopropanes proceed via transition states that require stabilization by activating groups and/or release of the ring strain. To understand and to alter the reactive tendencies of substituted vinylcyclopropanes, we must understand the components of the possible transition state and the probable reactive intermediates involved. **Table 1** shows the principal reaction pathways of the vinylcyclopropane system in the context of their intermediates, products, and alkenic equivalents.

The cyclopropylcarbinyl radical **4**, the cyclopropylcarbinyl cation **5**, and the cyclopropylcarbinyl anion **6** all dominate the expected reactivity of vinylcyclopropanes as one of these forms will be expected to be a major contributor to either a radical or a polar transition state. It is important to consider the various reactive subunits in some detail in order to understand the "big picture" reactivity of a vinylcyclopropane system, especially as perturbed by additional substituents.

The dominant contributor to the reactivity of vinylcyclopropanes in any radical reaction is the form **4a**, the cyclopropylcarbinyl radical system. The opening of a cyclopropylcarbinyl radical to a butenyl radical is among the fastest radical processes known, with a rate constant of 1.3×10^8 s^{-1}.[36,37] The various stereoelectronic effects of this rearrangement have been reviewed.[38,39] The structure of **4a**, deduced from its electronic spin resonance spectrum[40,41] and in agreement with calculations (STO-36 basis set),[42] is in the bisected conformation shown, predicted to be 1.4 kcal mol^{-1} more stable than its perpendicularly oriented counterpart. Above −100 °C, only the butenyl radical **4b** can be detected. Substituent effects do not seem to operate when the substituents are on the cyclopropane (i.e., product stabilization).[43] The cyclopropylcarbinyl cation and anion have structures similar to **4a**, bisected conformations **5** and **6**, respectively. A concise summary of solvolytic and mechanistic data for system **5** has appeared.[27] Reviews of the chemistry of cyclopropylcarbinyl anions and carbenes are also available.[12,13]



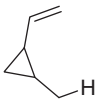
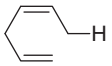
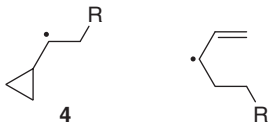
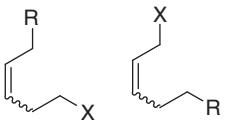
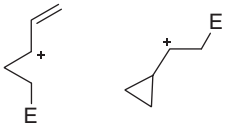
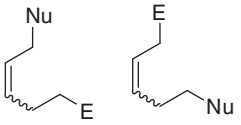
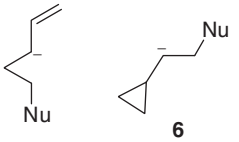
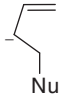
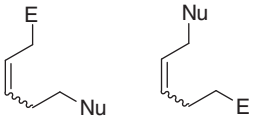
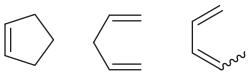
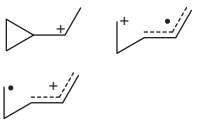
4a **4b**



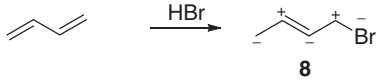
5 **6**

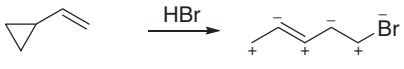
To understand how substituents, especially heteroatoms, change the reactivity of these systems, the basic transformations shown in **Table 1** should be kept in mind. The number of possibilities is limitless, especially on the recognition that, depending on the substituents, any one of the above contributing structures **4**, **5**, or **6** can become operational on the mode of subsequent rearrangement of the vinylcyclopropane when such rearrangements occur from the homolytic or heterolytic manifolds. The question of concerted rearrangements, or $[2\pi_s+2\sigma_s]$ processes, is more difficult to address. Evidence exists on both sides of the argument with no clear-cut rules for or against a universally accepted mechanism. The next section presents the debate concerning this topic in more detail.

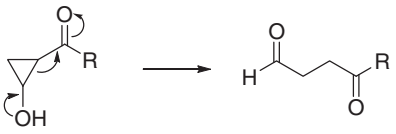
Table 1 Principal reaction modes of vinylcyclopropanes

Reaction type	*Reactive intermediate*	*Alkenic counterpart*	*Product(s)*
[1,X] Sigmatropic migration	 [1,5 shift]		
Radical addition	 **4** (Cyclopropylcarbinyl radical)		
Electrophilic addition	 **5** (Cyclopropylcarbinyl cation)		
Nucleophilic addition	 **6** (Cyclopropylcarbinyl anion)		
Radical cleavage			
One-electron oxidation	 **7** radical-cation		

In terms of retrosynthetic or disconnective reasoning, cyclopropane is an ideal molecular building block. Because it can be expected to act as an alkene, all of the standard reactions can be performed with it. As it has an extra carbon, however, it serves as a marvelous "synthetic wedge tool"[12] that can be used to either disrupt existing symmetry or consonance or to introduce it to the target. The concepts of synthetic consonance and dissonance formulated by Evans[44,45] or the "cyclopropane trick" analogy of Seebach[46] are ideal in understanding the synthetic utility of cyclopropanes. Thus, for example, equilibrium addition of HBr to 1,3-butadiene yields 1-bromo-2-butene **8** (equation 1), in which the halide enjoys an allylic relationship with the alkene. Similar addition to a vinylcyclopropane (equation 2) will, however, produce 1-bromo-3-pentene **9** where the same relationship is homoallylic. One can immediately see that the charge parity in the product alkenes has been inverted by the introduction of the odd carbon, and thus inverted reactivity of such alkenes can be expected in subsequent synthetic steps. This criterion is extremely important in synthetic schemes involving long-range planning and placement of functional groups. This property of cyclopropane has been exploited in the pioneering efforts of Wenkert, who developed 1,4-dicarbonyl compound synthesis based on the ability of oxycyclopropylcarbinyl systems such as **10** to act as pseudo enols (equation 3).[20,47,48]


8 (1)


9 (2)



10 (3)

Finally, the introduction of cyclopropane or vinylcyclopropane into organic compounds provides an opportunity to cross the odd/even manifolds in further synthetic steps aimed at the preparation of compounds of increased molecular complexity. Traditionally, any synthesis that involves cyclic intermediates with an odd number of atoms (or acyclic intermediates with an even number) is more difficult because proper charge parity or consonance cannot be observed. A cyclopropane unit then functions as a topological operator in those cases where such crossover is desired.[49–51]

The most fascinating features of vinylcyclopropane reveal themselves upon the introduction of not only substituents, but also heteroatoms. The number of possible permutations of molecular connectivity in a system such as **Z** (Figure 2) is virtually limitless. (Consider the series of connectivity operations for a chemical system composed of an odd number of atoms with an external operator X. Although there is only one way to connect A and X, there are now six ways to connect X through the ring opening of the three-membered ring system (**i**) and 120 such different connections in the ring opening of the heterovinylcyclopropane (**ii**) and its interactions with X.[52]) The complexity of connectivities of **Z** with an external operator X is related through the factorial (!) function and becomes even greater when the presence or the position of substituents in **Z** or the complexity of X is added for consideration. The success in predicting the reactivity of a system such as **Z** depends on the nature of component atoms, substituents, electronic perturbations, and the preference of some mechanistic pathways over others. To consider selective transformations of a system that has in excess of 120 possibilities may seem frivolous; fortunately there exists a number of simplifying parameters that provide for surprising selectivity as well as predictability of the rearrangements of any hetero-substituted system of type **Z**.

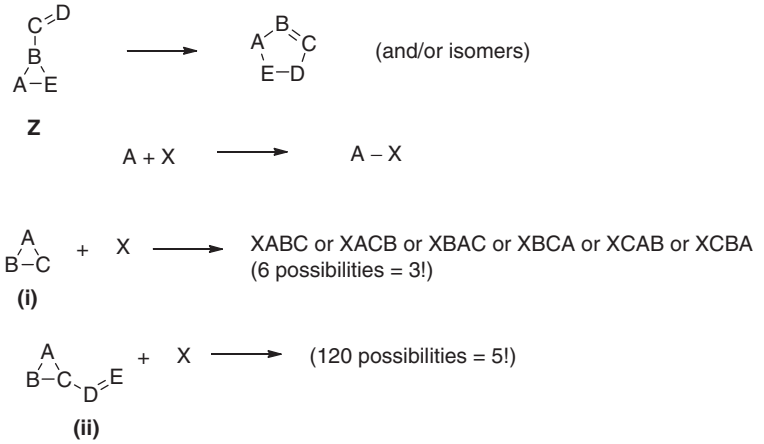
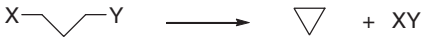


Figure 2 Permutations in connectivity.

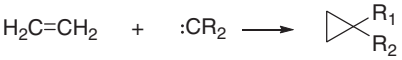
In the context of specific transformations, for example the vinylcyclopropane–cyclopentene rearrangement, substituent effects have been quantitatively addressed and are discussed in the appropriate sections. Donor/acceptor principles have been applied to thermal, heterolytic, and transition metal-catalyzed rearrangements and have been reviewed.[16,21,53–56] These take into account the possible intermediate structures listed in Table 1 and are used to explain the reactivity of a particular cyclopropane system. In the discussion that follows, emphasis is given to the processes that are uniformly selective with regard to regio-, stereo-, and enantiochemical integrity of the products.

5.22.1.2.3 Guide to preparation

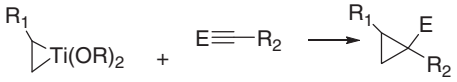
The inherent energy content of the cyclopropane ring demands that the method of introduction of a cyclopropyl subunit itself relies either on highly reactive intermediates or on irreversible or energetically, if not entropically, favored processes. Thus the synthesis of cyclopropane derivatives can be classified into four major categories: 1,3 bond forming sequences (equation 4);[57–59] carbene or carbenoid routes (equation 5);[60–65] insertion of η^2 complexes of alkenes to electron-deficient unsaturated compounds (equation 7);[66–74] and rearrangement pathways (equations 8 and 9).[75–78]



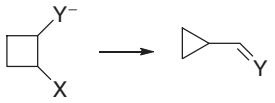
(4)



(5)



(6)



(7)



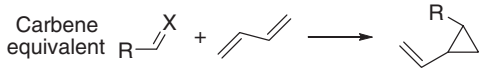
(8)

The procedures for the synthesis of cyclopropane derivatives, especially by the carbenoid route[57,59–63,79–84] or the ylide route (1,3-displacement),[19,20,59,85–88] have been amply reviewed.

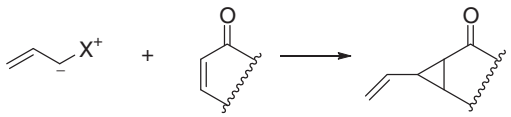
Equally well reviewed are the reactions of cyclopropanes and their use in synthetic methodology.[53,54–56,70,89] For the preparation of the more common cyclopropane derivatives, the use of suitably functionalized cyclopropyl building blocks that are commercially available is recommended.

Vinylcyclopropanes are most easily prepared by one of the following methods:

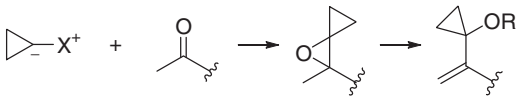
1. Cyclopropanation of conjugated dienes (inter- and intramolecular) by carbenes or carbenoids (equation 9)[51,83]
2. Permutations of the reactions of allylic ylides with Michael acceptors (equation 10)[19,20,59]
3. Ring opening of oxaspirocyclopentanes (equation 11)[19,20,90,91] and
4. Kulinkovich reaction of titanium diene intermediates with esters/amides/nitriles/thioacetals (equation 12)[69,70,73,74]



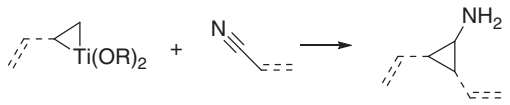
(9)



(10)



(11)



(12)

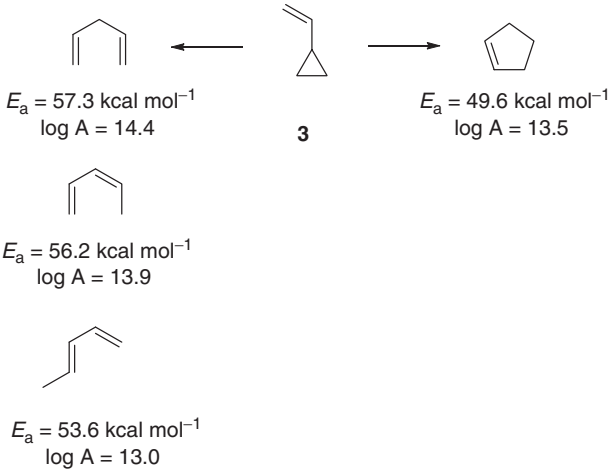
Indirect methods of formation can be used, for example, Wittig reaction of acylcyclopropanes and rearrangement pathways;[58,59] and in certain specific cases where the vinylcyclopropanes are immediately reacted further, by thermolysis of 1,4-dienes via [1,5] shift sigmatropic reactions.[51,92] The preparations of vinyloxiranes, vinylaziridines, cyclopropylcarbonyls, and cyclopropylimines have been reviewed in different contexts (addition of ylides to carbonyl compounds, interaction of azides or diazo compounds with alkenes, etc.), but their preparations have not been summarized under a common heading; however, any reference dealing with the use of these compounds will provide a guide to one or more methods of their synthesis.

5.22.1.3 Rearrangements of Vinylcyclopropanes

The vinylcyclopropane system is subject to a wide variety of transformations ranging from thermolysis and photolysis to nucleophilic, electrophilic, and radical ring-opening reactions as well as transition metal-catalyzed rearrangements and cycloadditions. A common trait in all such transformations is the release of the ring strain and further reaction of the intermediates thus generated. Until 1990s the most commonly recognized transformations of vinylcyclopropanes were those resulting from thermally induced bond reorganizations.

There are two major pathways available to vinylcyclopropanes on thermolysis: rearrangement to cyclopentene and ring opening to alkenes or dienes. The ability to predict which of these transformations is the most likely depends to a great extent on

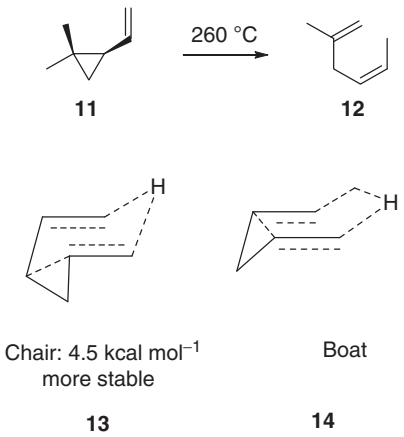
the substituents and on the precise conformational definitions and the orientation of the π-system of the vinyl group to the cyclopropane. The thermal cleavage of vinylcyclopropane can in principle provide any of the products depicted in Scheme 1. The analysis of the mechanistic pathways has been reviewed and widely accepted mechanism of such rearrangements includes a diradical intermediate/transition state.[22]



Scheme 1

5.22.1.3.1 [1,5] Shift pathways

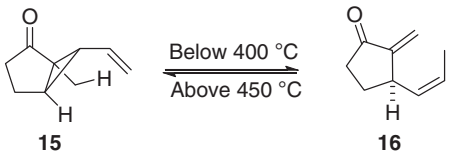
Under some circumstances, the [1,5] sigmatropic shift of a hydrogen from an alkyl group oriented *cis* to the vinyl group is the lowest energy pathway available to a vinylcyclopropane.[10,11,92] The classic experiments that led to the understanding of this process were performed by Winstein[93] and Frey.[92,94,95] The rearrangement of vinylcyclopropane **11** proceeded at 260 °C to furnish only the *cis*-alkene **12** (equation 13).[94] The rearrangement usually proceeds with an activation energy of 30–35 kcal mol^{-1} [9–11] and is thought to involve a chair-like (**13**) rather than a boat-like (**14**) transition state. Most of these rearrangements are stereospecific, yielding only the *cis*-alkene.



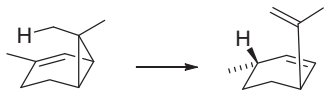
(13)

The transformation has been shown to be reversible by careful study of the temperature profiles of flash vacuum pyrolysis (FVP) of either *cis*-methylvinylcyclopropane **15** or diene **16** (equation 14).[96] Only above 400 °C did the vinylcyclopropane show the expected tendency toward diradical cleavage, a process that requires a substantially higher activation energy (15–20 kcal mol^{-1} higher) than the concerted [1,5] shift. This rearrangement also occurs stereospecifically in endocyclic vinylcyclopropanes such as **17** (equation 15).[97] The migration of the hydrogen atom is governed by the principles of sigmatropic rearrangements, that is, the pathway of the hydrogen atom is suprafacial.[98] The effect of substituents and their stereochemistry in this rearrangement was investigated.[99]

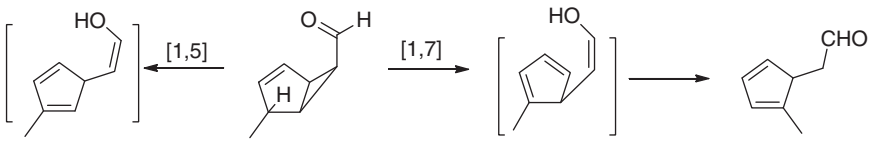
The fact that suitably sterically biased *cis*-alkylvinylcyclopropanes participate in these types of reactions attests to the ability of the cyclopropane ring to transfer conjugative properties and to act as a pseudo-ene unit. Competing pathways of higher order may become dominant in those cases where the transition state is stabilized by extended conjugation, as in the case of **18** and its predominant [1,7] hydrogen shift (Scheme 2).[100]



15 **16** (14)



17 (15)

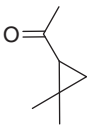
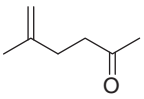
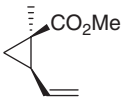
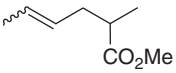
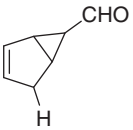
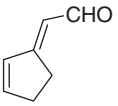
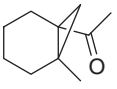
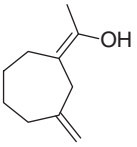
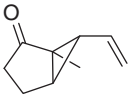
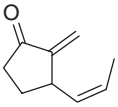


9% **(18)** 91%

Scheme 2

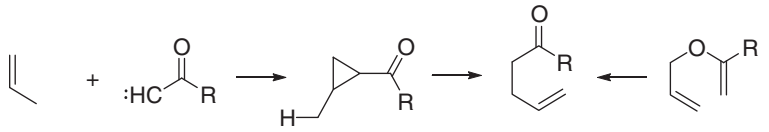
Oxygen, nitrogen, and carbon atoms can equally well participate in the "vinyl" system. Table 2 provides a survey of some synthetically useful rearrangements of this type. In all cases shown in Table 2 the formation of the alkene is regioselective and in most cases it is stereospecific as well, according to the principles outlined below. The distinction between boat and chair transition states depends on the precise conformation of the reacting system, and this factor can be somewhat manipulated experimentally.

Table 2 Thermal rearrangements of *cis*-alkylvinylcyclopropanes

Cyclopropane	*Temperature (°C)*	*Alkene*	*Yield*	*References*
	300			95,101
	150		89.4	102
	280		82.5 (*trans*) 17.5 (*cis*)	102
	120			100,103,104
	200		80	105
	360		80	96

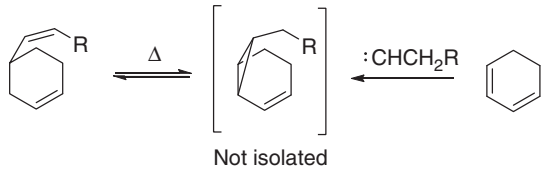
The synthetic utility of this process can be seen by evaluating the examples in Table 2. For example, because the cyclopropane serves as a pseudo alkene and because the [1,5] shift requires a six-membered transition state, it relates conceptually to the Cope and Claisen rearrangements. The γ,δ-unsaturated carbonyl compounds in Table 2 are those that would otherwise be obtained via

Claisen or orthoester Claisen rearrangements, which are normally effected under strongly acidic or strongly basic conditions (Scheme 3).



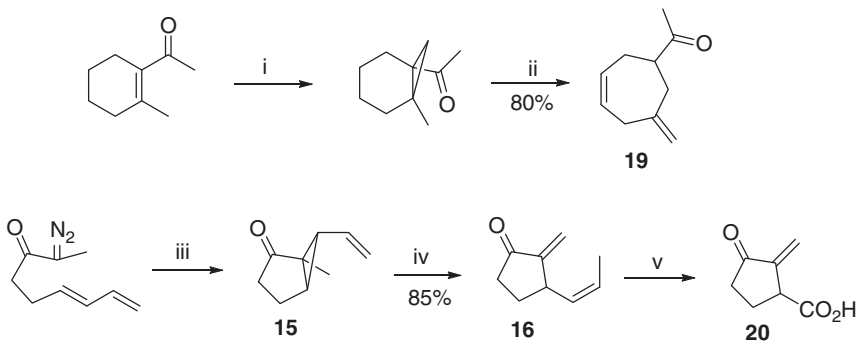
Scheme 3

For compounds of small molecular weight, the [1,5] shift pathway may therefore be superior in the ease of preparation, simplicity, and cost. In those instances where 1,4-dienes are easily constructed with the alkene predisposed *cis*, the resulting conversion to vinylcyclopropanes may in fact be superior to the use of carbenoid-based reagents in those instances where the resulting vinylcyclopropanes need not be isolated (Scheme 4). The retro-ene reaction of 1,4-dienes requires temperatures that induce immediate further reactive options in the vinylcyclopropane as soon as it is generated.[96]



Scheme 4

Two examples that show selectivity in synthetic applications are the synthesis of cycloheptanone **19**,[105] which involves ring expansion via a [1,5] hydrogen shift, and the synthesis of sarkomycin **20** (Scheme 5).[96,106] In both of these protocols, the intermediate cyclopropyl ketone or vinylcyclopropane system could be rearranged to dihydrofurans or cyclopentenes, respectively, by the appropriate adjustments in the experimental conditions.[9,51]



i. $LiAlH_4$; Simmons–Smith cyclopropanation, Collins oxidation; ii. 200 °C, 2 h;
iii. $Cu(acac)_2$, PhH, Δ; iv. 450 °C, Pyrex; v. O_3, CH_2Cl_2, Me_2S; Jones oxidation

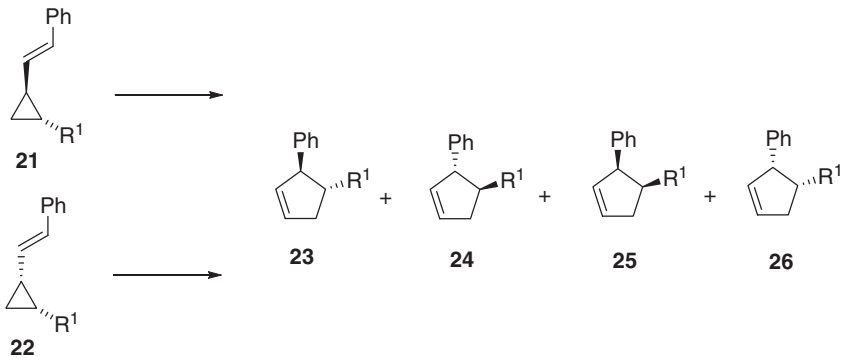
Scheme 5

5.22.1.3.2 Vinylcyclopropane–cyclopentene rearrangements

The thermal rearrangement of vinylcyclopropanes to cyclopentenes is probably the most recognized mode of reactivity of the vinylcyclopropyl system and the one that has received the most attention. Discovered independently by Neureiter in 1959,[107] Vogel,[108] and Overberger and Borchert in 1960[109] it was scrutinized in detail during the 1960s. Mechanistic details of the thermal vinylcyclopropane–cyclopentene rearrangement have been reviewed.[22,23]

The fundamental issue at the time revolved around the concerted $[2\pi_s+2\sigma_s]$ versus diradical nature of the rearrangement. No resolution of this question materialized as both mechanisms were invoked to explain specific cases.[9–13] The experimental evidence in the majority of cases studied, however, supports a diradical-type cleavage of the vinylcyclopropane system and a reclosure of the allylic diradical with an average activation energy of approximately 45 kcal mol^{-1}, or approximately 15 kcal mol^{-1} higher than the competing [1,5] shift pathway discussed in the Sections 5.22.1.3 and 5.22.1.3.1. What is puzzling is the apparent stereospecificity

of the rearrangement of optically pure vinylcyclopropanes such as **21** (equation 16).[110] The presence of "forbidden" products, (−)-**23** and (+)-**23**, would suggest a biradical mechanism, but the high degree of retention of optical purity (80.1±0.4% at 60 °C, 68.8±0.5% at 120 °C) rules out any freely rotating diradical species.[110,111] This observation implies that if the regiochemistry of the rearrangement is controlled, the stereo- and enantiochemical consequences will follow.



(16)

Further studies conducted since 1990,[112–117] thus support, to a varying extent, a diradical-type cleavage of the vinylcyclopropane system and a reclosure of the allylic diradical with an average activation energy for unsubstituted vinylcyclopropane–cyclopentene rearrangement system of approximately 51.7±0.5 kcal mol^{-1}, as recently determined.[118] This value is approximately 6 kcal mol^{-1} higher than the one previously measured. Introduction of activating groups lowers the E_a for diradical opening by 5–20 kcal mol^{-1}.[114]

One of the major drawbacks is the apparent scrambling of enantiospecificity and sometimes stereospecificity. Opening and reclosure of vinylcyclopropane occurs more readily than the rearrangement to cyclopentene. Usage of *cis*- and *trans*-alkene can lead to the same manifold of products with different ratios. The use of optically pure vinylcyclopropanes indicated that both "allowed" (*antarafacial retention*, *ar*, and *suprafacial inversion*, *si*) and symmetry "forbidden" (*antarafacial inversion*, *ai*, and *suprafacial retention*, *sr*) products are formed although with different ratios. For example, for two cases of **21** and **22**, the distribution of products of (*sr*+*ai*) and (*si*+*ar*) pathways are shown in the **Table 3**.[119,120] In vicinally disubstituted donor–acceptor vinylcyclopropanes (i.e., functionalities on adjacent carbons), the transition state is believed to involve to some extent 1,3-zwitterionic intermediates.[54] The actual level of radical–zwitterionic character is likely influenced by the choice of solvent.[121]

Table 3 Distribution of products of the thermal rearrangement of enantiomerically pure vinylcyclopropanes **21** or **22**

Substrate, R^1	***23***	***24***	***25***	***26***	*References*
21, R^1=Me	44	20	25	11	119
21, R^1=Ph	67	12	17	4	120
22, R^1=Me	90 (mix)		10 (mix)		119
22, R^1=Ph	91 (mix)		9 (mix)		120

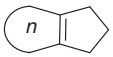
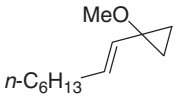
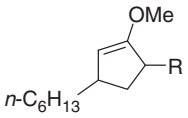
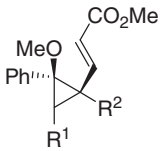
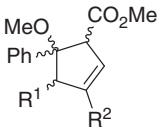
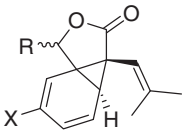
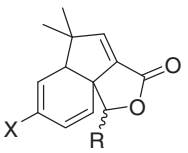
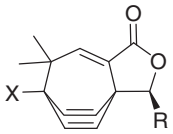
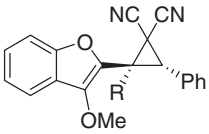
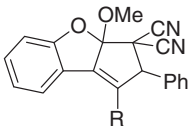
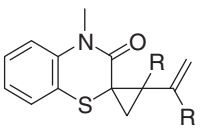
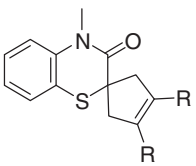
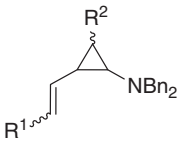
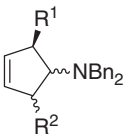
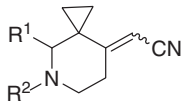
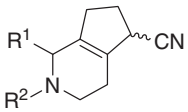
The molecular topology of this rearrangement is fascinating in its potentially limitless permutations. As indicated in Section 5.22.1.2.2, any one of the five atoms in the vinylcyclopropyl system may be replaced with almost any other atom (C, Si, P, N, O, S, etc.), and the overall reorganization to an unsaturated five-membered ring system remains operational. Thus cyclopropyl aldehydes, imines, ketones, and esters yield the corresponding heteroatom analogs of cyclopentene, as do vinyloxiranes, vinylaziridines, and vinylthiiranes. When electronegative elements are contained within the vinylcyclopropane framework, the mechanism may change from a diradical to a dipolar one.

In the parent system **3**, only one bond is activated toward a cleavage that produces an allylic radical. In more substituted cases, however, different degrees of activation may exist, and these will control the rate as well as the regiochemistry of the rearrangement. Some examples of recent synthetic utilization of the thermal vinylcyclopropane–cyclopentene rearrangement are presented in **Table 4**.

Nonthermal rearrangements can proceed under significantly milder conditions. For example, a radical-cation of vinylcyclopropane has a barrier of rearrangement of only 21.7 kcal mol^{-1}.[134] The photolytic vinylcyclopropane–cyclopentene rearrangement usually proceeds with the same stereoselectivity as the thermal rearrangement. It can be performed under direct irradiation or with photosensitizers and has been subject of several reviews.[135,136] It is interesting to note that, in some cases, the outcome of the photochemical rearrangement can be different: the vinylcyclopropane–cyclopentene rearrangement takes place in the presence of the photosensitizer and the cyclopropylcarbonyl–lactone rearrangement under direct irradiation conditions (see **Scheme 6**).[137]

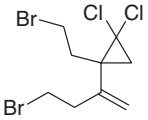
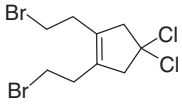
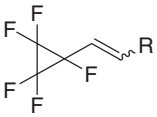
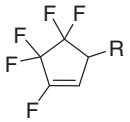
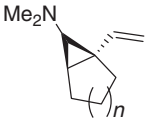
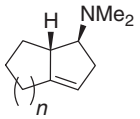
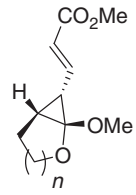
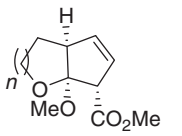
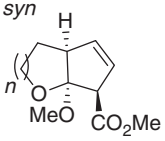
Photosensitized reactions are believed to proceed through single-electron transfer (SET).[138] Studies on cyclopropanes substituted with electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) at position 1 (point of the connectivity of the vinyl group) of the cyclopropane ring showed that the former substrates tend to form an open-chain radical, which attacks

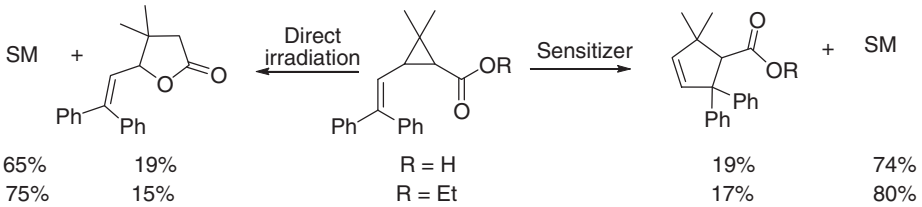
Table 4 Thermal rearrangements of vinylcyclopropanes

Starting material (SM)	*Conditions*	*Product*	*Yield (%)*	*References*
	500 °C		68–88	122
n-mono/bycliclic				
	300 °C		87, 80	123
R = H, CH_2CO_2Me				
	Decalin, benzonitrile, 190 °C; or: DMF, 150 °C		74–100	53
R^1,R^2 = alkyl, aryl, H				
	130–180 °C, benzene	 VCP  Cope	Vinylcyclopropane–cyclopentene rearrangement: 63–96 Cope: 0–37	124
X = H, Me, Cl, Ph R = H, Me				
	150 °C, toluene, 4 days		33–40 + SM	125
R = H, CO_2Me				
	230 °C, benzene, 6 h		95–97	126
R = H, Me				
	400–600 °C, 10^{-5} mbar		27–95	127
R^1=H, alkyl, Ph R^2=H, alkyl, Ph				
	550 °C, 10^{-2} mbar		60–77	128
R^1 = Alkyl, aryl R^2 = Alkyl				

(*Continued*)

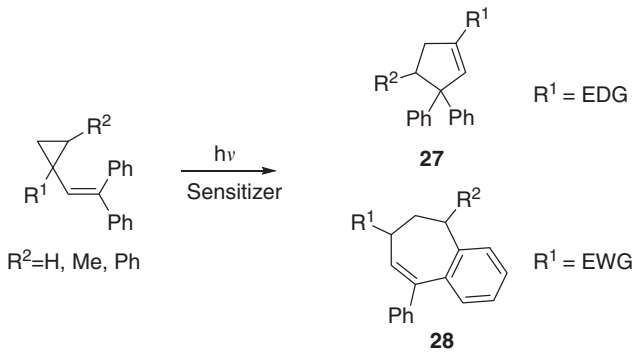
Table 4 Continued

Starting material (SM)	*Conditions*	*Product*	*Yield (%)*	*References*
	480 °C, 5×10^{-5} mbar		Mass recovery 90	129
 R = H, Me	80–140 °C		Not reported	130
 n = 1,2,3	n=1, 500 °C, 10^{-5} mbar n=2, decalin 220 °C n=3, decalin 240 °C		n=1, 89 n=2, 90 n=3, 84	131
 n = 1,3	110 °C, toluene; 132 °C, chlorobenzene	 *syn*  *syn* n = 1, 3	n=1, *syn:anti*=4:96, 65 n=3, *syn:anti*=99:1, 45	132,133



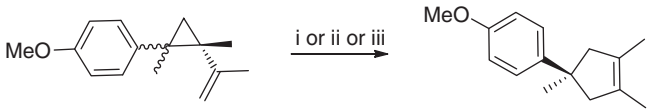
Scheme 6

the aromatic ring and undergoes divinylcyclopropane–cycloheptadiene rearrangement to form compounds **28**. With electron-donating substituents on the cyclopropane, the products of the classical vinylcyclopropane–cyclopentene rearrangement, namely **27**, were formed (equation 17).



(17)

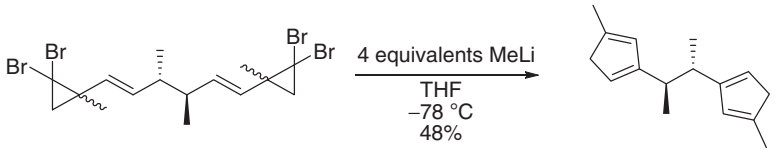
Cation–radical rearrangement mechanism and periselectivity have been studied.[139] Upon reaction with an amidyl radical source (i) in equation 18, the product of the rearrangement was formed. The same product was formed under conditions of one-electron oxidation in (ii) equation 18 and photochemical rearrangement (iii) in equation 18. Almost identical stereoselectivity and product distribution led to the conclusion that all three reactions operate under the same mechanism. These methods present a complementary approach to the thermal rearrangement. Formal periselectivity of the latter one is different and a main product of it would be the retro-ene product.



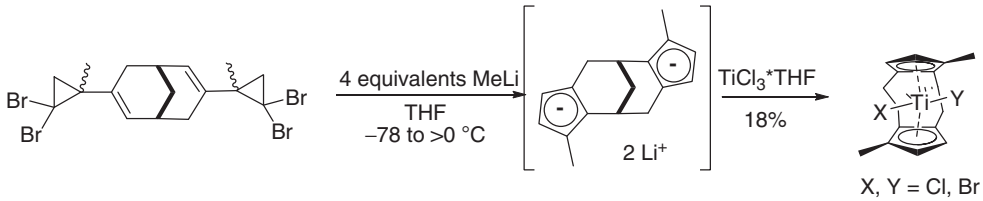
(18)

i. $(p\text{-}ClC_6H_4)_3\overset{\bullet+}{N}SbF_6^-$; ii. Fe(1,10-phenantroline)$_3^{3+}(PF_6^-)_3$; iii. hν, 350 nm

The Skattebøl rearrangement, shown in equations 19 and 20, constitutes a rare case of the vinylcyclopropane–cyclopentene rearrangement. It is used especially for the generation of cyclopentadienyl anions[140,141] and is believed to proceed through the formation of carbene intermediates.



(19)



(20)

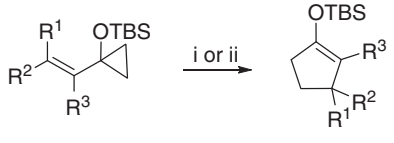
Lewis acids are known to facilitate the vinylcyclopropane–cyclopentene rearrangement under mild conditions. For this protocol to be effective the cyclopropane ring must contain a functionality that can interact with the Lewis acid in order to stabilize charged zwitterionic intermediates. Some recent examples of these rearrangements are shown in **Table 5**.

5.22.1.3.2.1 Metal-catalyzed rearrangements

5.22.1.3.2.1.1 Vinylcyclopropane–cyclopentene rearrangements

The metal-catalyzed vinylcyclopropane–cyclopentene rearrangement has a much shorter history of development than the thermal version. The major difference from thermal rearrangement lies in the fact that the thermal rearrangement requires high temperatures to ensure cleavage of the C–C bond to diradicals with very similar energy, which in turn produce mixtures of products. Because metal insertion takes place at significantly lower temperatures through a concerted pathway, the stereoselectivity of the outcome can be controlled much more efficiently than in the case of thermal rearrangements. In addition, the use of chiral ligands provides an opportunity to control enantioselectivity, which cannot be achieved using other conditions unless at least one chiral center retains its original configuration. This aspect was sufficiently demonstrated through the early work of Hudlicky.[152] A general discussion on the topic of the transition-metal-catalyzed rearrangement of vinylcyclopropanes and related systems is provided in several reviews.[89,153,154]

Initially rhodium, low valent nickel, and copper catalysts were used.[155] Ryu and Sonoda[156] discovered that the catalytic system Ni(0)/PPh_3 can catalyze vinylcyclopropane–cyclopentene rearrangements of activated 1-silyloxyvinylcyclopropanes in good yields (equation 21).



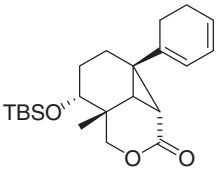
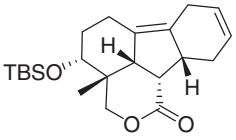
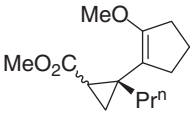
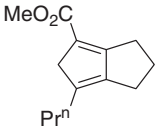
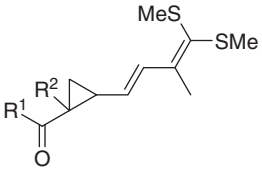
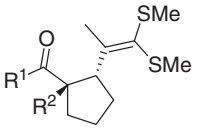
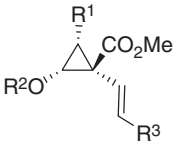
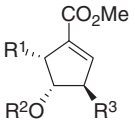
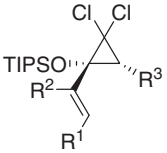
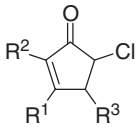
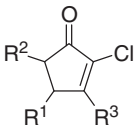
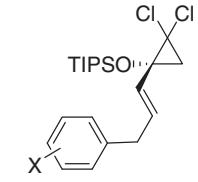
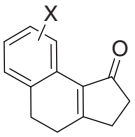
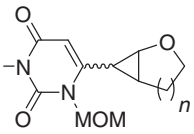
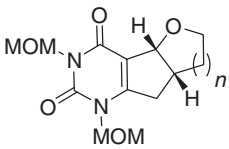
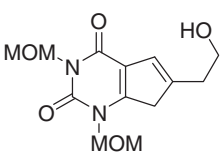
$R^{1,2,3}$=H,Me,Bu,Ph

78–90%

(21)

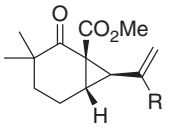
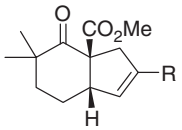
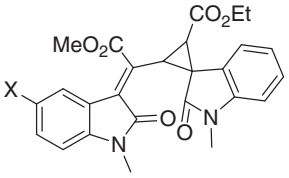
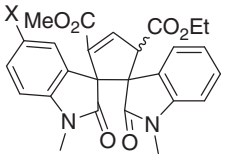
i. $Ni(COD)_2$ 10 mol%, PPh_3 20 mol%, PhMe, reflux, 17 h;
ii. $NiCl_2(PPh_3)_2$ 5 mol%, Zn 10 mol%, PhMe, reflux, 20–40 h

Table 5 Lewis acid-mediated rearrangements of vinylcyclopropane systems

Starting material	*Conditions*	*Product*	*Yield (%)*	*References*
	Et_2AlCl, CH_2Cl_2, 0 °C		93	142
	(a) Et_2AlCl, CH_2Cl_2, r.t. (b) $AlMe_3$, Et_2O, reflux		(a) 75 for *cis*, 90 for *trans* (b) 48 for *cis*, 56 for *trans*	143
 R^1 = aryl R^2 = H, alkyl	$SnCl_4$, CH_3NO_2		61–85	144
 R^1 = H, alkyl, aryl R^2 = Et R^3 = Ph, Me	Me_2AlCl, CH_2Cl_2, –78 °C[a]		61–87	145,146
 $R^{1,2,3}$ = H, alkyl, aryl	$AgBF_4$, CH_2Cl_2 or TFE, r.t.	 	45–87	147
 X = OH, OMe, Br, Me	$AgBF_4$, MeCN, reflux		39–80	148
methoxymethyl (MOM)–  *n*=1,2	Me_2AlCl, CH_2Cl_2, –78 °C to 0 °C	 	51 for *n*=1 88 for *n*=2 20 for *n*=1	149

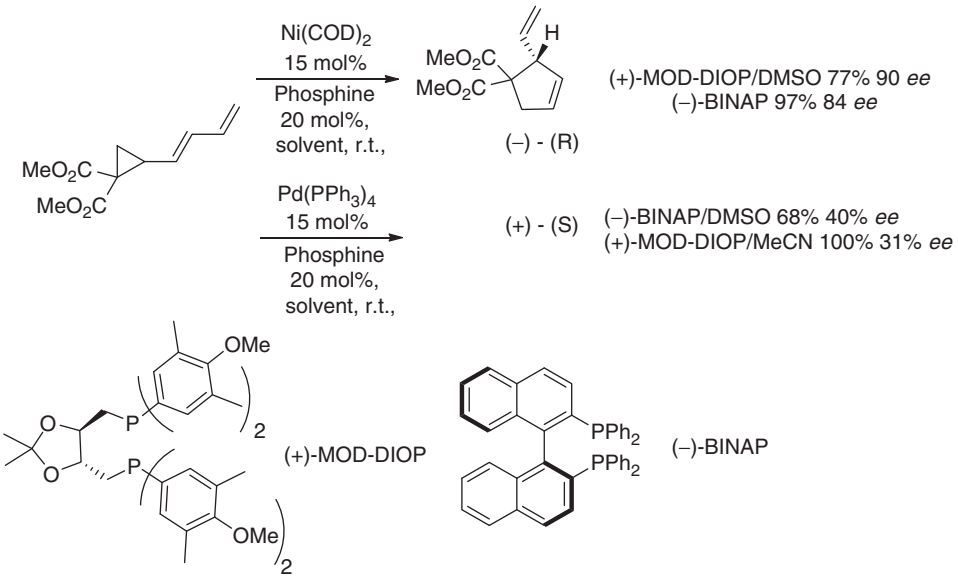
(*Continued*)

Table 5 Continued

Starting material	*Conditions*	*Product*	*Yield (%)*	*References*
	MgI_2, MeCN, 40 °C		74–86	150
 X = H, Br	$MgBr_2$, THF reflux		89–98	151

[a]Significant erosion of enantiomeric excess (*ee*) for monocyclic substrates, retention of *ee* for bicyclic substrates.
Abbreviations: TFE, trifluoroethanol; TIPS, triisopropyl silyl.

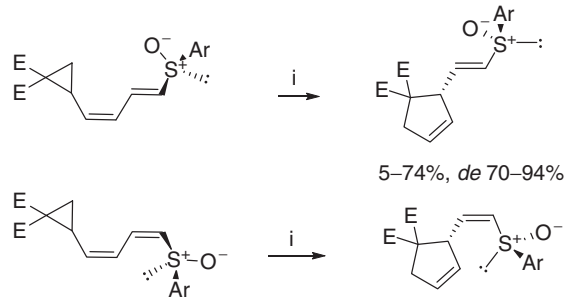
An enantioselective version of the vinylcyclopropane–cyclopentene rearrangement was developed by Hiroi,[157] who studied a wide range of metal catalysts, ligands, and solvent systems. Best results were obtained with Ni(1,5-cyclooctadiene; $COD)_2$/(+)-MOD-DIOP/DMSO, which produced the desired compound with 90% *ee*. It is interesting to note that the use of $Pd(PPh_3)_4$ under the same conditions[158] gave complete inversion of the enantioselectivity for the same substrates, albeit with lower *ee*. This suggests different modes operating in Ni- versus Pd-catalyzed rearrangements. Other metals, such as Cr, Mo, Pt, and W either failed to promote the rearrangement or their use did not lead to significant enantioselectivity (Scheme 7).



Scheme 7

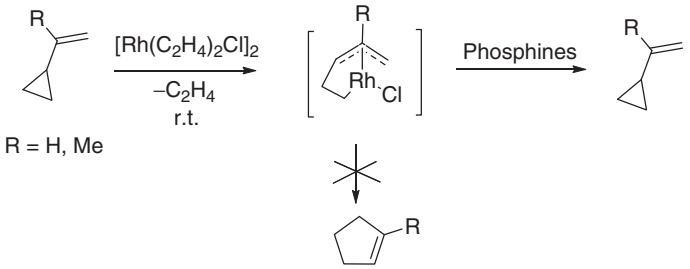
A chiral sulfoxide auxiliary was used by Hiroi in the rearrangement shown in Scheme 8.[159] High levels of diastereomeric excess (*de*) (90–94%) were observed and the unexpected retention of configuration of the diene double bond was noted.

Most of the early discoveries of rearrangements catalyzed by Ni and Pd were made on "activated" vinylcyclopropane systems, either those containing EWGs on the cyclopropane ring, whose presence is thought to facilitate oxidative addition of the metal, or those containing an extended diene system, which would help precoordination of the transition metal. Rhodium catalysis did not require such additional functionalities in order to undergo C–C bond insertion, but in the case of simple unsubstituted vinylcyclopropanes a stable complex is formed that does not undergo a further transformation to cyclopentene, as shown in Scheme 9.[160] Cyclopropylallenes and cyclopropylalkynes can be considered to be activated systems. Examples of rearrangement of cyclopropylallenes with rhodium are known, as shown in equations 22, 23 and Table 6.[161,162]

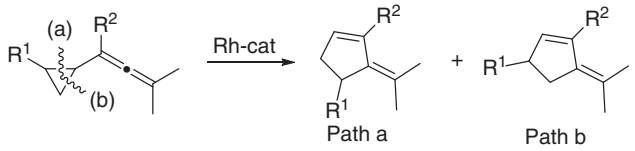


E = CO_2Et
Ar = *p*-tolyl, 1-(2-methoxynaphthalene)
Diphospine ligand = dppe, 1,1-bis(diphenylphosphino)propane (dppp), 1,1′-bis(diphenylphosphino)ferrocene, dppb, 1,2-bis(diphenylphosphino)hexane
i. $Pd_2(dba)_3$*$CHCl_3$10 mol%, diphosphine ligand 20 mol%, PhMe, r.t., 18 h

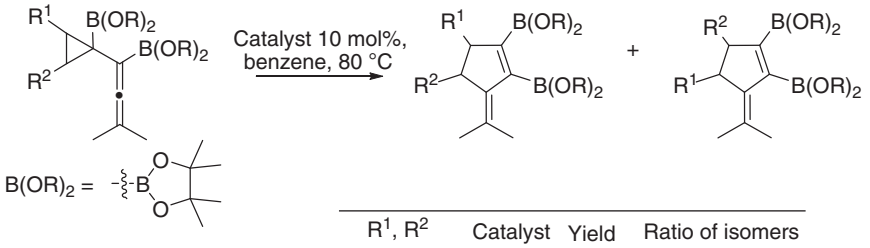
Scheme 8



Scheme 9



(22)



(23)

Catalyst = **A** $[Rh(MeCN)_2(cod)]BF_4$, **B** $[Rh(cod)_2]BF_4$, **C** $[RhCl(cod)]_2$

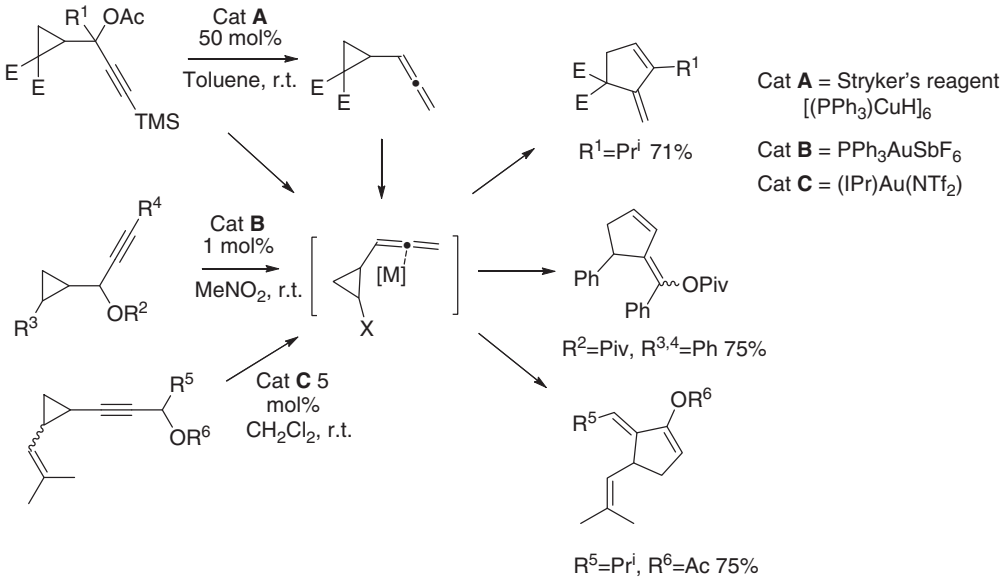
R^1, R^2	Catalyst	Yield	Ratio of isomers
Vinyl, H	**A**	46%	80:20
Ph,H	**B**	79%	55:45
$–(CH_2)_4–$	**B**	58%	–
$–CH_2(CH_2)_2O–$	**C**	46%	57:43

The regioselectivity of the rearrangement can be somewhat controlled[161] by using either a cationic or a neutral rhodium catalyst, as indicated in Table 6. Transient cyclopropylallenes generated *in situ* from propargyl acetates can also be rearranged under

Table 6 Rhodium-catalyzed rearrangement of vinylcyclopropylallenes as shown in equation 22

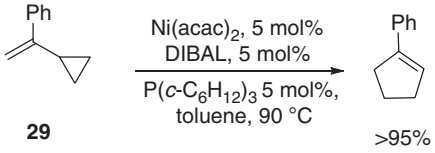
Substituent	*Catalyst*	*Ratio a:b*	*Yield (%)*
R^1=H, R^2=CO_2Bn	$RhCl(PPh_3)_3$; $[Rh(COD)_2]^+BF_4^-$	–	88
R^1=*n*-Pr, R^2=CO_2Bn	$RhCl(PPh_3)_3$	12:88	89
R^1=*n*-Pr, R^2=CO_2Bn	$[Rh(PPh_3)_3]^+$ BF_4^-	1:99	98
R^1=Ph, R^2=H	$[Rh(PPh_3)_3]^+$ BF_4^-	8:92	98
R^1=Ph, R^2=H	$[Rh(COD)_2]^+BF_4^-$	95:5	95
R^1=Ph, R^2=CO_2Me	$RhCl(PPh_3)_3$	44:56	73
R^1=Ph, R^2=CO_2Me	$[Rh(COD)_2]^+BF_4^-$	97:3	78

copper[163] and gold catalysis.[164,165] Both reactions are believed to proceed through similar allenic–metal complexes, as shown in Scheme 10.



Scheme 10

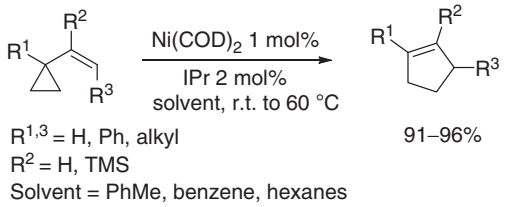
The unactivated vinylcyclopropane **29** was shown by Suginome and Ito to isomerize in the presence of Ni(pentane-2,4-dione; acac)$_2$/PCy_3/diisobutylaluminium hydride (DIBAL).[166] It is interesting to note that in an earlier chapter by Nishida[155f] the same substrate was shown to be inactive under $Ni(COD)_2$/PBu_3 conditions.



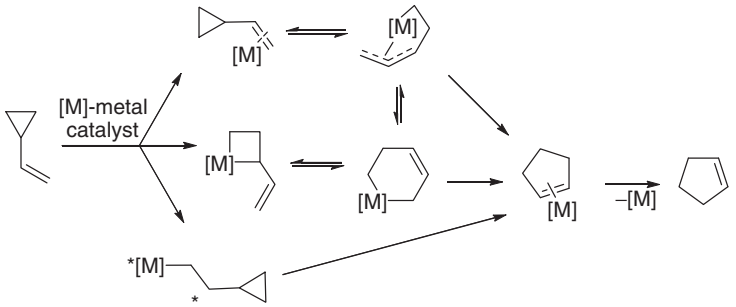
(24)

In 2004 Louie[167] discovered that the rearrangement of unactivated vinylcyclopropanes can be performed with a catalytic system consisting of $Ni(COD)_2$/N-heterocyclic carbene (NHC). (NOTE: Although the term "NHC" is widespread in the literature, the authors suggest refraining from the usage of this terminology. As there is no experimental proof that such species are true carbenes (they are in fact zwitter-ions!) the term NHC is misleading, inaccurate, and incorrect. It is only a resonance form of the zwitterion, not a true reactive entity. The metal complexes of such species should be referred to as carbenoids.) Utilization of sterically hindered "NHC" ligands allowed this reaction to proceed at significantly lower temperatures (room temperature to 60 °C) than with phosphine ligands, equation 25. Later this reaction was also utilized by Murakami[168] for bicyclic systems.

Louie and Tantillo studied the mechanism of the rearrangement under the Ni catalytic system.[169] They showed that the rearrangement is likely to proceed via sequential formation of an alkene complex followed by the opening of the cyclopropane and formation of complexes with different hapticity, as shown in Scheme 11.



(25)

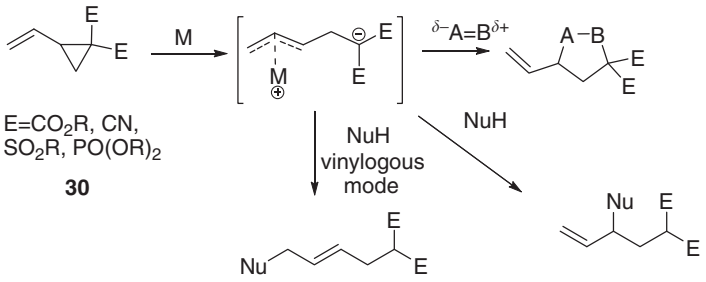


Scheme 11 Reproduced from Wang, S. C.; Troast, D. M.; Conda-Sheridan, M.; *et al. J. Org. Chem.* **2009**, *74*, 7822–7833, with permission from ACS.

5.22.1.3.2.1.2 Metal-catalyzed opening and [3+2] cycloadditions

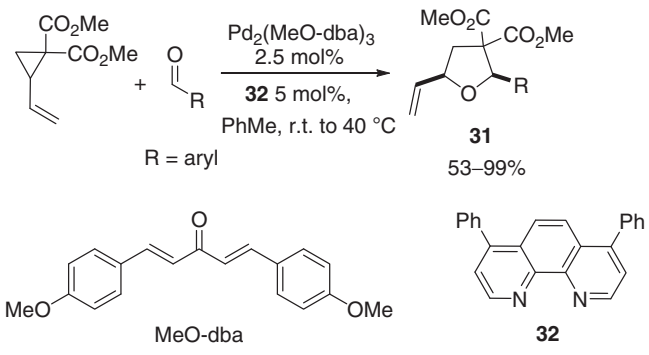
When a vinylcyclopropane is substituted with an electron withdrawing group (EWG), donor/acceptor symmetry causes the electrons to flow in one particular direction. Such a system, for example **30**, is susceptible to insertion of a transition metal followed by nucleophilic addition or cycloaddition of unsaturated compounds. Control of the outcome of the three possible modes of reaction is available by changing the metal and/or the ligand environment. As well, the use of chiral complexes can provide access to chiral compounds. Similar reactivity can be observed via Lewis acid mediated cycloaddition. This particular subject has been thoroughly covered in recent reviews.[54–56]

Most developed metal-catalyzed insertions involve palladium catalysis, proceeding via the formation of η^3-metal complexes. The regioselectivity of cycloaddition is dictated by the electronic effects of the second coupling partner as shown in Scheme 12.



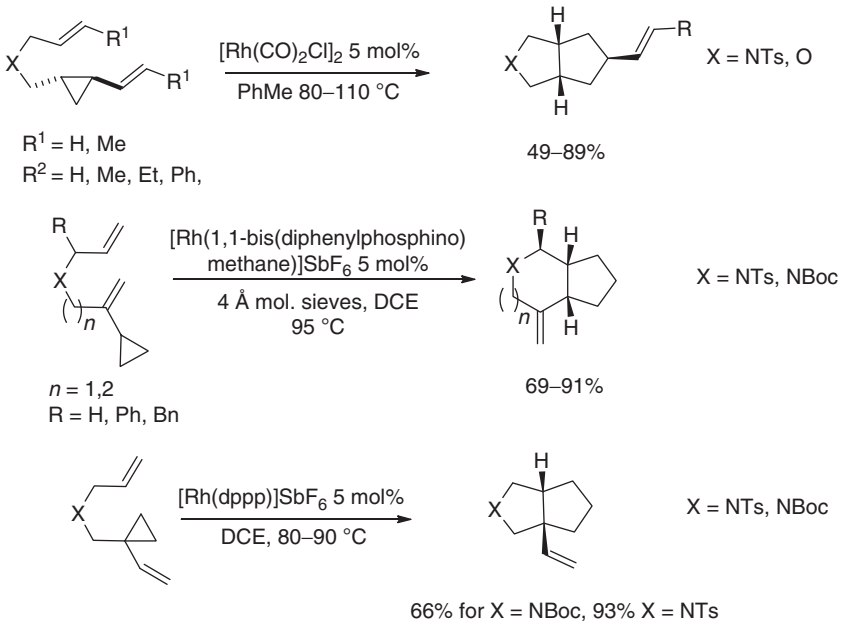
Scheme 12

The first example of such a [3+2] cycloaddition of an activated vinylcyclopropane as 1,3-dipolar equivalent with an activated alkene was described by Tsuji in 1985.[170] Different unsaturated fragments have been used as partners for coupling with activated cyclopropanes. Johnson[171] showed that aldehydes also undergo such cycloadditions. The main products are 2,5-disubstituted tetrahydrofurans (THFs) **31**. It was shown that electron-poor aldehydes perform better under the chosen reaction conditions (equation 26).



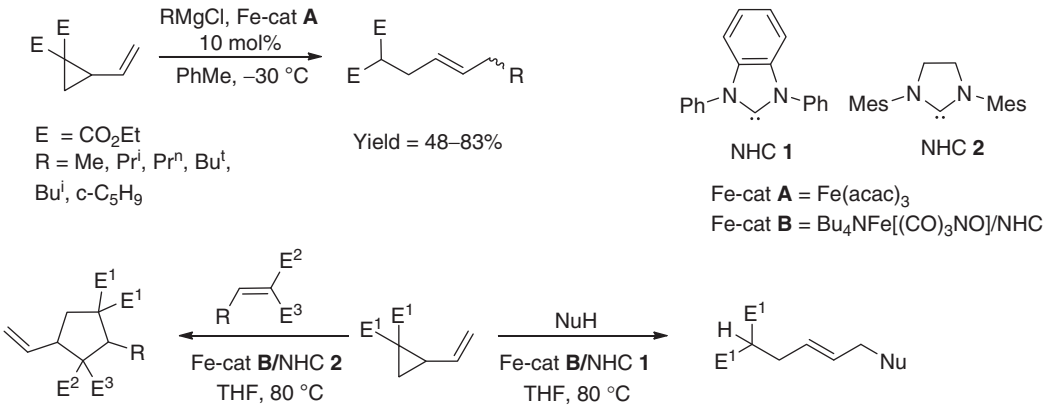
(26)

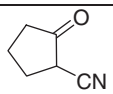
Rhodium-catalyzed [3+2] intramolecular cycloadditions of unactivated vinycyclopropanes were shown to proceed selectively[172] under the same conditions employed for the [5+2] cycloadditions (see Section 5.22.1.3.2.4). The configuration of the vinylcyclopropane plays a crucial role in the outcome of such process as shown in Scheme 13.



Scheme 13

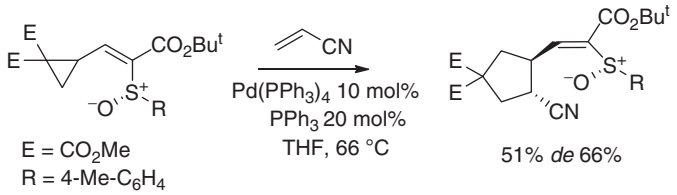
Complexes of iron[173,174] were shown to be efficient and inexpensive catalysts in formal [3+2] cycloadditions as well as in nucleophilic opening. Fürstner[173] has shown that activated vinylcyclopropanes undergo nucleophilic opening by Grignard reagents in the presence of $Fe(acac)_3$ to produce allylic products. A more recent study by Plietker[174] showed that the mode of reactivity catalyzed by the $Bu_4N[Fe(CO)_3NO]$/NHC system can be altered by modifying the NHC ligand as shown in Scheme 14.



	R, E^2, E^3	E^1	NuH	
		SO_2Ph		96%
95%	H, SO_2Ph, SO_2Ph	CO_2Me	$CH_2(CN)_2$	70%
79%	H, SO_2Ph, SO_2Ph	$CO_2CH_2CF_3$		
82%	Ph, CN, CN	CN		

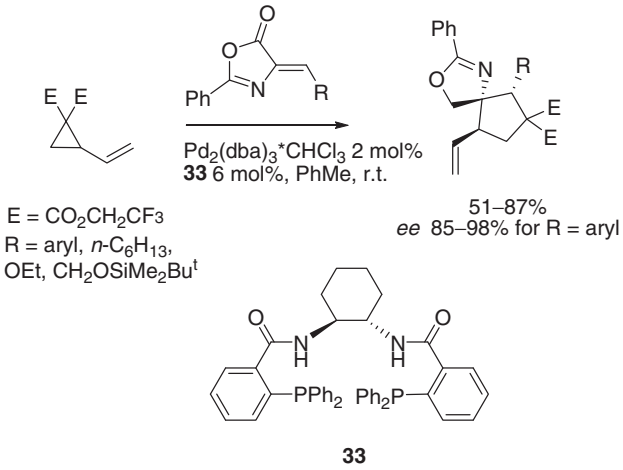
Scheme 14

Asymmetric versions of a formal [3+2] cycloadditions have a much shorter history. One of the first examples was performed by Hiroi who used chiral auxiliaries.[175] Despite the modest diastereoselectivity, the starting material can be easily accessed in an enantiodivergent way.



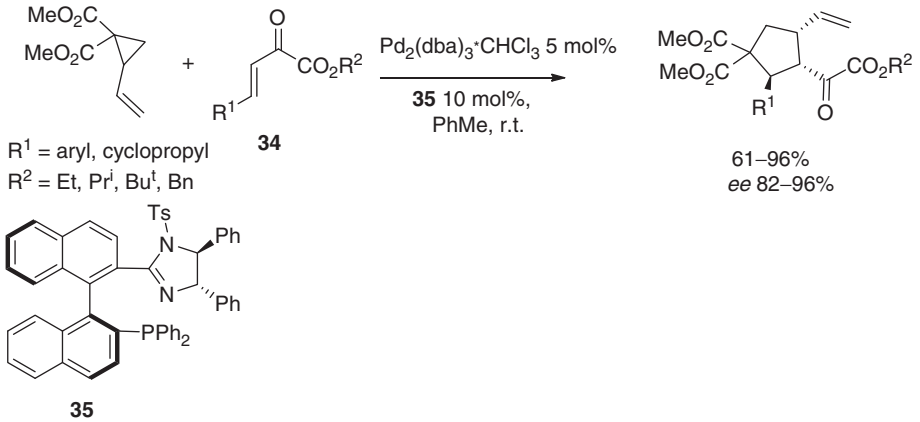
(27)

Trost[176] developed an asymmetric version of the [3+2] cycloaddition with alkylidene azalactones as the ene fragment. Additional activation of the cyclopropyl ring was required by introduction of electron-poor trifluoroethyl esters in order for the reaction to proceed in good yield. The reaction provided products with high enantioselectivity and high diastereomeric ratios (>19:1 for R=aryl) (equation 28).



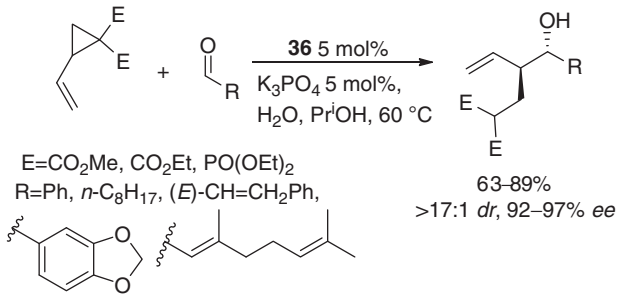
(28)

A similar approach was also described by Shi.[177] Palladium catalysis was shown to be quite efficient with the new type of chiral ligands **35**. Starting from standard activated cyclopropanes and activated alkenes **34**, chiral cyclopentanes were produced with good yields and high enantioselectivity (equation 29).

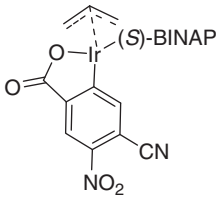


(29)

Unusual regioselectivity was observed with the iridium catalyst **36** during the coupling of aldehydes with activated vinylcyclopropanes. In contrast to the analogs coupling under palladium catalysis,[171] the introduction of iridium led to the opposite regioselectivity of aldehyde insertion. Homoallylic alcohols were produced with good yields and high enantioselectivity (equation 30).

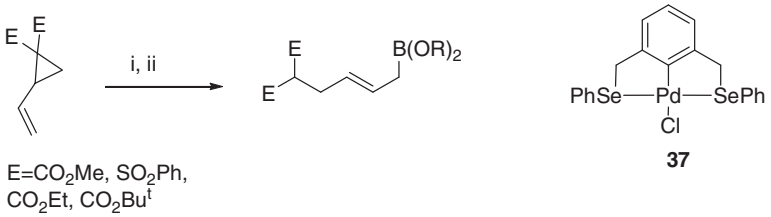


(30)



36

Different functional groups can be introduced via metal-catalyzed insertion. One of the most useful examples is the borylation of vinylcyclopropanes. The use of the palladium pincer complex **37** was shown[178] to lead selectively to *E*-allyl boronates. Similar transformations were also performed with the $Ni(COD)_2$/phosphine system under milder conditions and were shown to be less demanding with regard to the activation of the cyclopropane ring by EWGs (**Scheme 15**).[179]

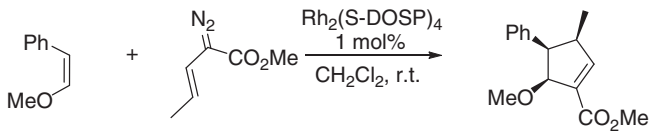


37

Scheme 15

5.22.1.3.2.2 Formal [4+1] cycloadditions catalyzed by metals

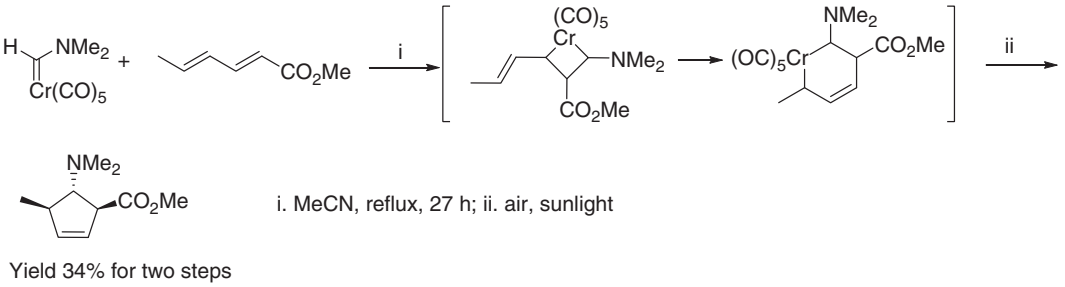
In some cases no cyclopropanes are isolated during attempted cyclopropanations of electron-rich enolates by vinyl carbenoids. Such a difference in the product outcome has been observed by Davies.[145] Depending on the nature of the rhodium catalyst, it was possible to isolate either a cyclopropane or a cyclopentene. The latter outcome was believed to proceed via charged intermediates, which lead directly to the cyclopentene, the product of a "formal" [4+1] annulation, (equation 31).



79%, 98% *ee*

(31)

Hegedus[180] discovered that the addition of an electron-rich chromium carbene to methyl sorbate provided the product of the formal [4+1] cycloaddition in one step. It is believed to form through sequential addition and rearrangement of a chromium complex, followed by reductive elimination, as shown in Scheme 16.

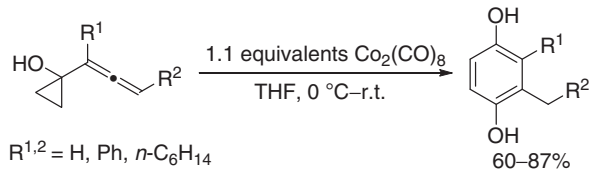


Scheme 16

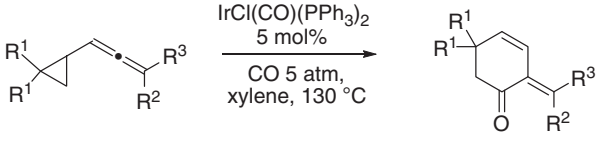
5.22.1.3.2.3 [5+1] Cycloadditions

The formal [5+1] rearrangement has a significantly shorter history than other cycloadditions of the vinylcyclopropane system. Before 1990, only a limited number of examples of vinylcyclopropane–cyclopentene rearrangements with stoichiometric iron carbonyls were explored.

The first version of the [5+1] cycloaddition with metals other than Fe was discovered for "activated" vinylcyclopropane system containing allene and/or oxygen substituents on the cyclopropane ring. Cobalt [181] and iridium[182] catalysts were among the first to be investigated. Mechanistic studies of such cycloadditions were carried out with $Fe(CO)_5$.[183] Taber[184] showed that this transformation can be used for the synthesis of enantiopure cyclohexenones. A catalytic version of the [5+1] cycloaddition catalyzed by $Co_2(CO)_8$ was developed by de Meijere,[185] and similar activity was observed for $[Rh(CO)_2Cl]_2$ (equation 34). Only vinyl cyclopropanes with substituents on both the double bond and the cyclopropane ring undergo rearrangement under such conditions. Cationic rhodium catalysts, which were developed for [5+2] cycloadditions (*vide infra*), proved applicable in some cases to [5+1] cycloaddition with unactivated vinylcyclopropane systems[186] (equation 35 and Table 7). Yu and coworkers described[187] formal [5+1]/[2+2+1] cycloadditions (equation 36). The scope of this transformation is limited to 5-5-6 system. The product of such transformation possesses elements of homo-angular triquinane skeletons.

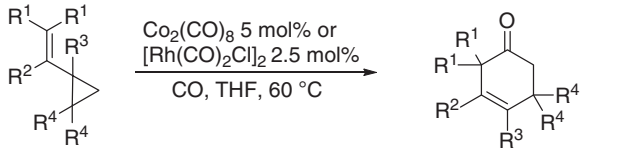


$R^{1,2}$ = H, Ph, *n*-C_6H_{14} (32)



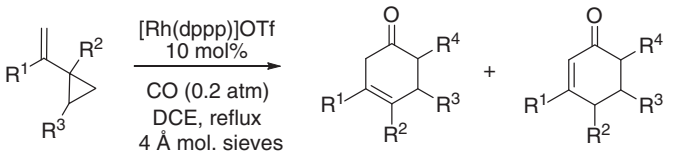
R^1 = H, Ph
$R^{2,3}$ = Me, Ph, H

63–83% (33)



R^1, R^4=$(CH_2)_2$, H
R^2=Me, Ph, *c*-C_3H_7
R^3=Me, vinyl, $O(CH_2)_2OMe$

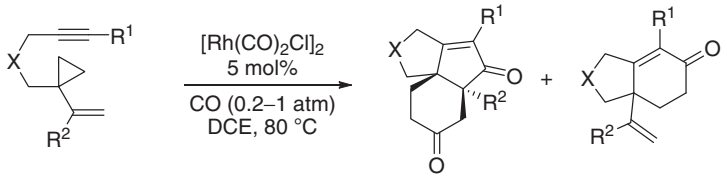
$Co_2(CO)_8$ 16–89%
$[Rh(CO)_2Cl]_2$ 0–95% (34)



38 39 (35)

Table 7 Rhodium-catalyzed [5+1] cycloaddition of unactivated vinylcyclopropanes (equation 35)

Substituents	*Yield of **38** (%)*	*Yield of **39** (%)*
R^1=aryl, CH_2NTs R^2,R^3,R^4=H	41–74	7–43
R^1,R^3,R^4=H, R^2=Ph, CH_2OBn	80, 42	–
R^1,R^2,R^4=H, R^3=CH_2OBn CH_2OBn, CH_2OH, CH_2OTBS	41–68	11
R^1,R^4=H,R^2,R^3=$(CH_2)_4$	56	–



X = $C(CO_2Me)_2$, NTs, O
R^1 = alkyl, TMS
R^2 = H, Me

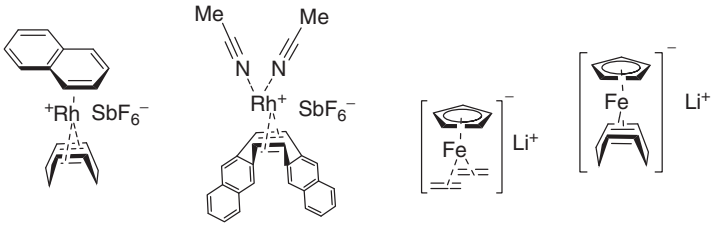
40 41 (36)

Table 8 Representative examples of distribution of products in formal [5+1]/[2+2+1] reaction (equation 36)

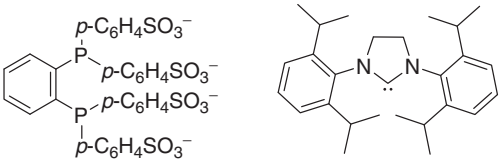
Substituents	*Yield of **40** (%)*	*Yield of **41** (%)*
X=NTs R^1=Pr^i, R^2=H	72	9
X=$C(CO_2Me)_2$ R^1=Bu^t, R^2=H	74	–
X=O R^1=Pr^i, R^2=H	87	–
X=NTs R^1=Pr^i, R^2=Me	31	46
X=$C(CO_2Me)_2$ R^1=Bu^t, R^2=Me	55	18

5.22.1.3.2.4 [5+2] Cycloadditions

A [5+2] cycloaddition or rearrangement between vinylcyclopropane and an unsaturated two-carbon partner has been an attractive goal for synthetic chemists over the years, as it offers the possibility to generate multifunctionalized polycyclic structures containing seven-membered rings. This topic has been reviewed extensively over the past 10 years.[188] Seminal work was presented by Wender,[189] who described intramolecular cycloadditions of vinylcyclopropanes and alkynes with Wilkinson`s catalyst. The addition of AgO trifluoromethanesulfonate (Tf) has shown to lower the catalyst loading significantly and shorten the reaction time. More efficient catalysts were discovered,[190] such as $[Rh(CO)_2Cl]_2$ with higher functional group compatibility and improved selectivity. It has been shown that cationic Rh(I) complexes are most likely to be the active intermediates in such reactions. For example, other Rh catalysts that induced the [5+2] transformation at room temperature included those developed by Gilbertson[191] ((Rh(1,2-bis(diphenylphosphino)ethane; dppe)$(CH_2Cl_2)_2$]SbF_6) and Zhang ([Rh(1,4-bis(diphenylphosphino) butane; dppb)Cl]$_2$/$AgSbF_6$).[192] The recent development in this field is the discovery of the tendency of the arene complexes **42**[193] and **43**[194] to catalyze [5+2] cycloadditions with exceptional effectiveness and wide substrate scope at room temperature. Arene complex **42** allowed the migration of the double bond in the final product to be suppressed, which was a common problem with $[Rh(CO)_2Cl]_2$. [Rh(nbd)Cl]$_2$/$AgSbF_6$ (nbd=norbornadiene) was shown to accomplish successfully the transformation in water in the presence of the water soluble phosphine **46**.[195] The use of a water–methanol mixture as the solvent facilitated the isolation of nonpolar products. High formal dilution helps to suppress unwanted side reactions.



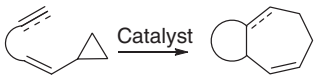
42 43 44 45



46 47

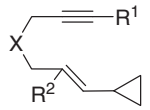
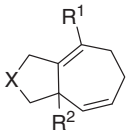
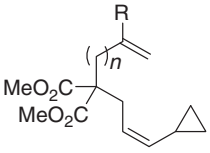
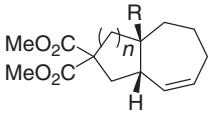
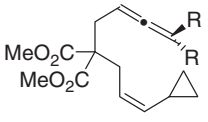
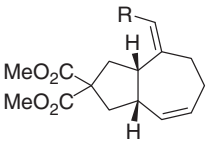
Because of the prohibitive cost of rhodium, other metal complexes have been investigated as alternatives in the catalysis of the [5+2] cycloaddition. Trost[196] found the commercially available $[CpRu(MeCN)_3]PF_6$ complex to be an effective catalyst at room temperature but with somewhat lower yields that the rhodium system **42**. Low-valent iron complexes of type **44** and **45** were utilized by Fürstner[197] for similar reactions. The $Ni(COD)_2$/SIPr system developed by Louie[198] was active in a limited number of cases (Table 8).

The scope of this reaction was later expanded to include alkenes and allenes as the cycloaddition partners.[199–201] The general reaction is depicted in Scheme 17, and representative examples of rhodium-catalyzed reactions are presented in Table 9. Only geminally disubstituted alkenes are suitable substrates for cycloaddition. Chiral allenes underwent the rearrangement enantioselectively. Vicinally disubstituted alkenes produced inseparable mixtures of products.[201]



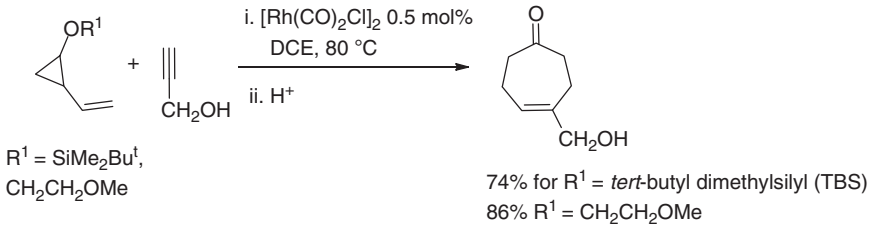
Scheme 17

Table 9 Rhodium-catalyzed [5+2] cycloadditions

Starting material (SM)	*Conditions*	*Product*	*Yield(s) (%)*	*References*
 R^1 = Me, TMS, Ph, CO_2Me R^2 = H, Me X = O, $C(CO_2Me)_2$	10 mol% $Rh(PPh_3)_3Cl$, PhMe, reflux or 0.5 mol% $Rh(PPh_3)_3Cl$, AgOTf, PhMe, reflux		74–88	189
 R = H, Me *n* = 1, 2	10 mol% $Rh(PPh_3)_3Cl$, PhMe 100–110 °C or 0.1 mol% $Rh(PPh_3)_3Cl$, AgOTf, PhMe, reflux		77–94	200, 201
 91% *ee*	10 mol% $Rh(PPh_3)_3Cl$, benzene, 100 °C	 92% *ee*	96	199

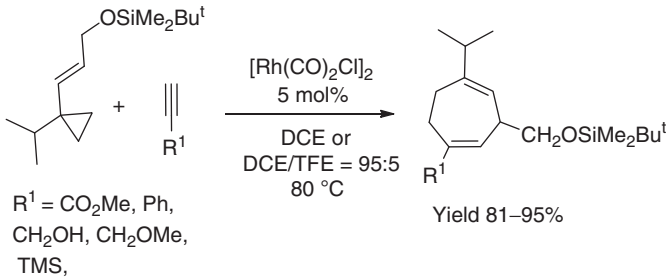
5.22.1.3.2.5 Intermolecular [5+2] cycloadditions

The intermolecular version of the [5+2] cycloaddition, first described by Wender[202] for alkynes and vinylcyclopropanes, poses a greater challenge than the intramolecular case. It was shown that additional coordinating siloxy or carboxy groups[203] on the vinylcyclopropane ring helped to facilitate such reactions. The scope of alkyne substrates has been shown to be quite extensive, including electron-rich, electron-poor, and terminal alkynes, as depicted in equation 37. The reaction has also shown to be chemoselective toward the alkyne moiety in enynes. The use of alkynes containing coordinating groups has led to higher yields of the cycloaddition products.



(37)

Reactions with "unactivated" vinylcyclopropanes are possible at higher temperatures; however, these vinylcyclopropanes must contain bulky substituents on position 1 of the cyclopropyl ring and/or oxygen coordinating substituents on the alkene portion of the vinylcyclopropane as shown in equation 38.[204]

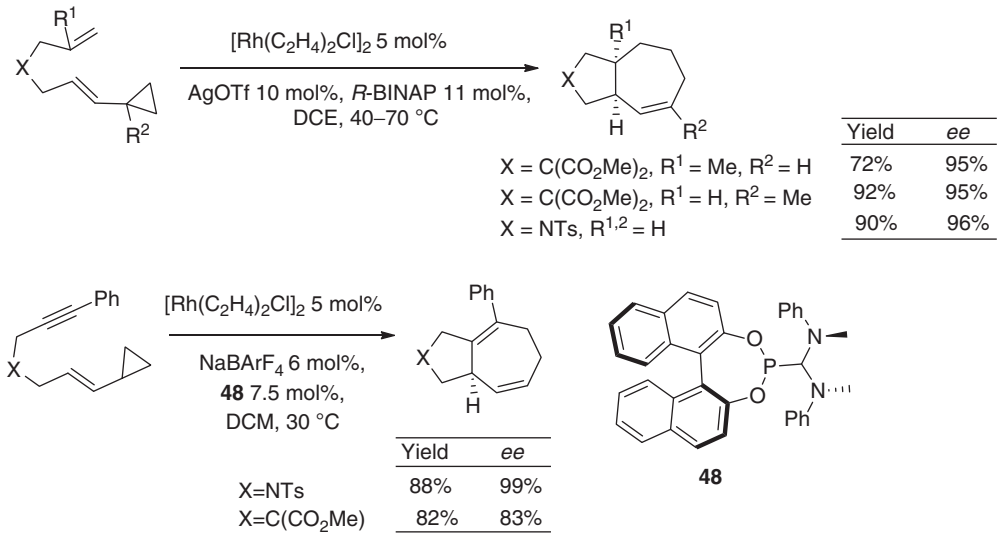


(38)

Wender[205] later discovered that intermolecular vinylcyclopropane–alkyne cycloadditions can be performed at room temperature and low loading (0.2–0.5%) with the cationic complex $[Rh(C_{10}H_8)cod]^+$ SbF_6^-. Simple allenes do not undergo cycloaddition, but it has been shown that extra coordinating groups such as alkynes, alkenes, and nitriles facilitate the cycloaddition.[206] Alkenes are not suitable substrates for intermolecular cycloadditions of this type.

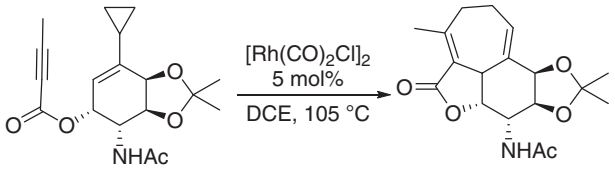
5.22.1.3.2.6 Asymmetric [5+2] cycloadditions

There are very few examples of enantioselective [5+2] cycloadditions. Wender[201] observed the first example for the vinylcyclopropane–alkene system by using $[Rh(C_2H_4)_2Cl]_2$/AgOTf with (–)-CHIRAPHOS; however, only 63% *ee* was obtained. Later[207] he showed that the best ligand for such transformations is *R*-BINAP. The highest *ee* was achieved for *gem*-disubstituted alkene fragments. In case of an alkyne or an unsubstituted alkene moiety, low *ee*'s were obtained. Hayashi[208] discovered a new catalytic system which was useful in achieving high *ee*'s for vinylcyclopropane–alkyne coupling, as shown in **Scheme 18**.

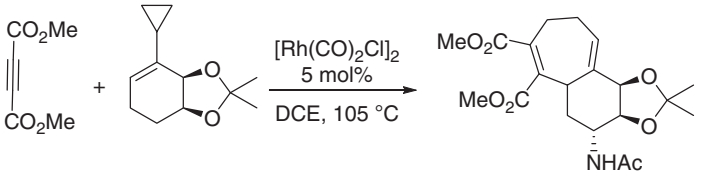


Scheme 18 $NaBAr^F_4$, sodium tetrakis[3,5-bis (trifluoromethyl)phenyl]borate.

Recently, Hudlicky [209] studied the [5+2] cycloaddition with vinylcyclopropanes in which the olefin was constrained into a ring, as shown in equations 39 and 40; however, the yields were extremely low in both inter- and intramolecular applications. Calculations have shown a 16° misalignment of the olefin with the cyclopropane (see Figure 3). (Illustration provided by Dr. Travis Dudding (the structure was optimized with density functional theory (DFT) using B3LYP/6–31G(d)).) The yield of the cycloaddition was later improved to 22% for the intramolecular version.[210]



49 22% (39)



50 Traces (40)

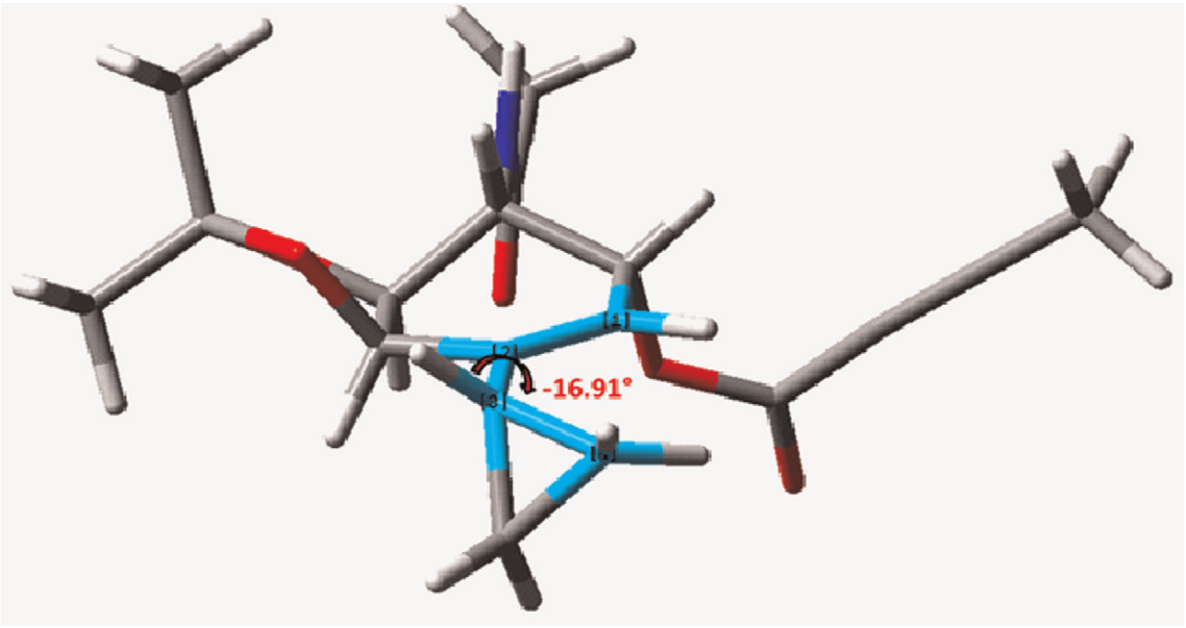
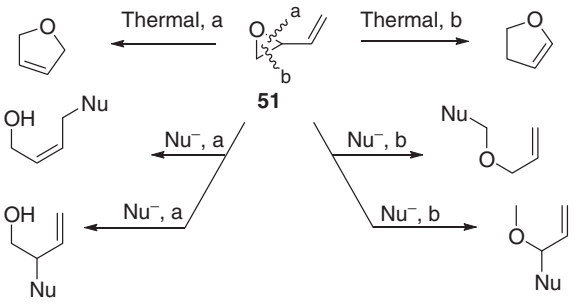


Figure 3 Predicted geometry of compound **49**.

5.22.1.4 Rearrangements of Vinyloxiranes and Cyclopropyl Carbonyls

5.22.1.4.1 Vinyloxiranes

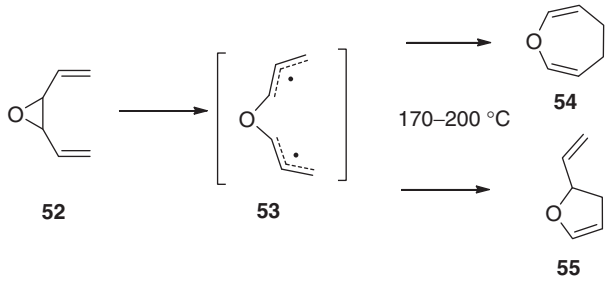
Rearrangements of vinyloxiranes proceed in an analogous fashion to those of the corresponding vinylcyclopropane, with two notable exceptions. First, they generally require a lower activation energy and therefore take place under milder conditions. Second, most of the thermal rearrangements proceed through zwitterionic or ylide-like intermediates, which are uncommon in carbocyclic cases. The nucleophilic opening of systems such as **51** is more complex because of the coordinative abilities of oxygen and the increased number of possible nucleophilic interactions (Scheme 19). Nevertheless, there is some parallel behavior and predictability in vinyloxirane rearrangements.



Scheme 19

5.22.1.4.1.1 Thermal isomerization

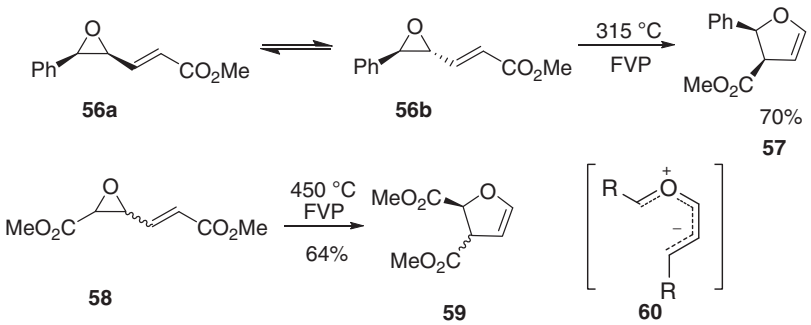
The study of benzene oxide–oxepin tautomerism, reviewed in the late 1960s, revealed a competing pathway in the rearrangements of *trans*-divinyloxiranes of type **52** (Scheme 20).[211,212] The corresponding *cis* isomer gave only oxepin **54**, whereas the *trans* isomer gave a 7:3 mixture of dihydrofuran **55** and oxepin **54**. The activation parameters implied that the intermediate was biradical **53** (*cis*-oxide: $\Delta H^{\ddagger} = 24.6$ kcal mol^{-1}, $\Delta S^{\ddagger} = -11.3$ cal deg^{-1} mol^{-1}; *trans*-oxide: $\Delta H^{\ddagger} = 36$ kcal mol^{-1}, $\Delta S^{\ddagger} = -0.4$ cal deg^{-1} mol^{-1}).[211] These values indicate processes far lower in energy than those operating in the vinylcyclopropane rearrangement, whereas their difference (11 kcal mol^{-1}) led to the conclusion that the rearrangement was concerted for the *syn* isomer and biradical for the *trans* compound.



Scheme 20

The mechanism has since been studied on a number of occasions, and it is generally agreed that concerted, electrocyclic closures of ylides are operating in the formation of either oxepins or vinylfurans.[213–217] The rate of racemization of optically pure vinyloxiranes has been shown to be 6 times faster than the isomerization to the dihydrofuran.[213] Alternatively, cleavage of a vinyloxirane to a carbon–oxygen diradical pair or to a carbene–carbonyl pair has been considered for processes that do *not* usually lead to the formation of dihydrofuran[213,215,218] (though there is a notable exception, see ref.[218]). Corresponding [1,5] shift pathways are also known for those oxiranes that contain a *cis*-oriented alkyl group having at least one hydrogen.[215]

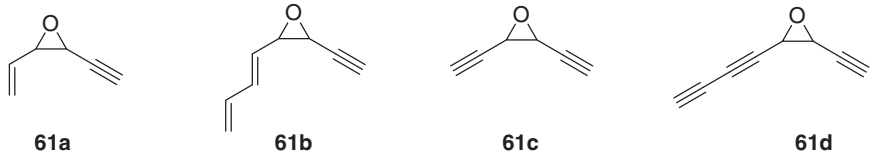
The regio- and stereoselectivity of this rearrangement was found to be excellent.[214] Thus the rearrangement of either isomer of vinyloxirane **56** yielded dihydrofuran **57** stereoselectively, whereas that of vinyloxiranes **58** led to a mixture of *cis* and *trans* isomers (Scheme 21); *cis*/*trans* isomerization was also accomplished photochemically.[219] The results were rationalized by involving ylides



Scheme 21

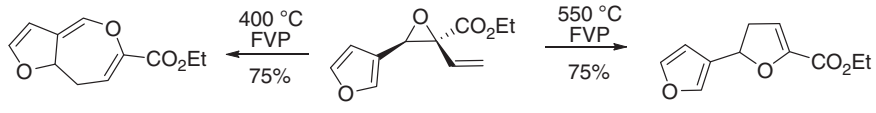
of type **60** and this allowed $[2\pi_s+2\sigma_a]$ or $[2\pi_a+2\sigma_s]$ closures for the former case and biradicals for the latter, although the epimerization may have taken place after the rearrangement because of the presence of an acidic proton.[214]

A number of substituents can be placed on the periphery of the vinyloxirane system. For example, alkynyl- and dienyl-oxiranes of the general structures represented by **61a** to **61d** were extensively studied. Their isomerization to various oxidation states of oxepins competed in some cases with the formation of the corresponding vinylfurans.[167,214,215,217,220]



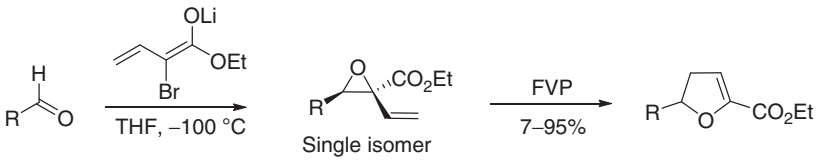
61a **61b** **61c** **61d**

The control of furan versus oxepin manifolds has been addressed. Vinyloxiranes of type **62** yielded oxepins **63** at lower temperatures, whereas higher temperatures gave dihydrofurans (**64**; Scheme 22),[221] indicating that the Cope-type rearrangement of *cis*-divinyloxirane may be controlled by precisely defining the temperature profile of the FVP.[221,222] A [2+3] dihydrofuran annulation methodology was developed based on this rearrangement. Vinyloxiranes **65** were generated by the stereospecific addition of the lithium dienolate of ethyl α-bromocrotonate to aldehydes, and the subsequent pyrolysis to dihydrofurans **66** (Scheme 23) proceeded in excellent isolated yields (except for R = Bu^n, Pr^i).[221]



63 **62** **64**

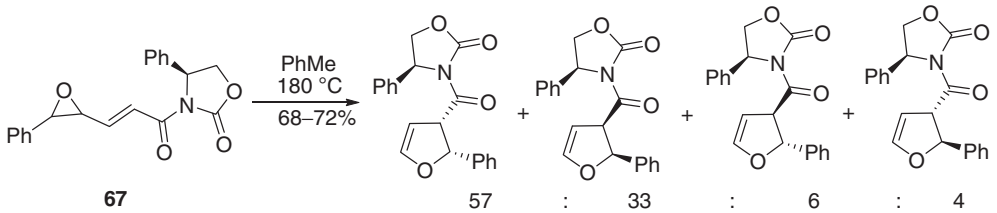
Scheme 22



65 **66**

Scheme 23

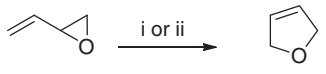
The thermal rearrangement of vinyloxiranes equipped with a chiral auxiliary group, such as **67**, was studied by Steel,[223] but only limited chiral induction was achieved because of the small energy difference in the corresponding transition states (equation 41).



67 (41)

The 2-vinyloxirane–2,5-dihydrofuran rearrangement is a transformation of interest for industrial applications.[224,225] A combination of Lewis acids such as trialkyltin iodides,[225] zinc halides,[224] and iodide salts can be used as shown in Scheme 24.

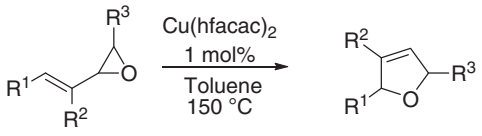
Njardarson[226] found that Bis(hexafluoroacetylacetonato)copper(II) ($Cu(hfacac)_2$) is a convenient catalyst for laboratory application of the rearrangement to a wide range of vinyloxiranes **70** to 2,5-dihydrofurans **71**. The process occurs under milder conditions than those employed for the conventional thermal rearrangement. Complete stereoselectivity was observed in these rearrangements (equation 42).



68 **69**

i. LiCl*H_2O 5 mass%, $ZnCl_2$ 3 mass%, NMP, 130 °C, 99%;
ii. (n-C_8H_{17})$_3$(n-$C_{18}H_{37}$) P^+I^- 3.5 mass%, (n-C_8H_{17})$_3$ SnI 0.5 mass%, 100 °C, 94%

Scheme 24



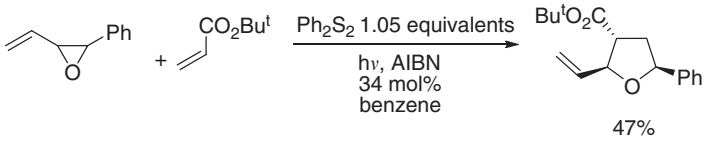
(42)

70 **71**

$R^{1,3}$-alkyl, H
R^2 = p-MeC_6H_4, H, alkyl

Yield 59–97%

Radical addition of alkenes to vinyloxiranes to yield THFs is analogous to the similar reaction of vinylcyclopropanes (equation 43),[227] with the same regio- and stereoselectivity, with a predominance of *syn* isomers having the regiochemistry indicated in **72**.[228] Radical polymerization of vinyloxiranes has also been reported.[229] The rearrangements of vinyl thiiranes proceed in a similar fashion to those of vinyloxiranes. The general field of thermal rearrangements of three-membered heterocycles containing oxygen, sulfur, or nitrogen was reviewed.[230] A vast majority of the literature on the rearrangements of vinyloxirane systems deals with those cases where Cope-like rearrangements of the divinyloxiranes are possible. The expansions of such systems to oxepins and further rearrangements and transmutations of, for example, vinylalkynyloxiranes to vinylcyclopropyl aldehydes have also been studied and reviewed.[222,228,230]



47%

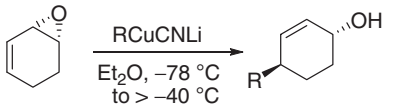
(43)

72

5.22.1.4.1.2 Nucleophilic opening

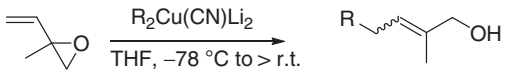
Vinyloxiranes react with nucleophiles in three regiochemically distinct ways: with α, β, and vinylogous modes of opening. The subject has been of considerable interest in the context of acyclic stereoselection and generation of allylic alcohols in an iterative fashion. Cyclic vinyloxiranes react with organocuprates with inversion of configuration (*anti*) and in a vinylogous mode (equation 44), not by the expected S_N2 reaction that simple oxiranes are known to undergo. This subject has recently been summarized.[231,232]

The conformation of cyclic vinyloxirane is restricted, whereas the acyclic vinyloxiranes, like vinylcyclopropanes, enjoy a conformational equilibrium, which determines the (*E*):(*Z*) ratio of the allylic alcohols that result from interactions with nucleophiles. For example, vinyloxirane **73** gave a *E*:*Z* = 4:1 ratio of allylic alcohols **74** (equation 45) with $Ph_2Cu(CN)Li_2$, but a 7:2 ratio when (2-$C_5H_5NCH_2$)$_2$Cu(CN)Li_2 was used.[233]



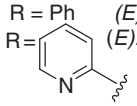
R = Ph 65%
Me 95%

(44)



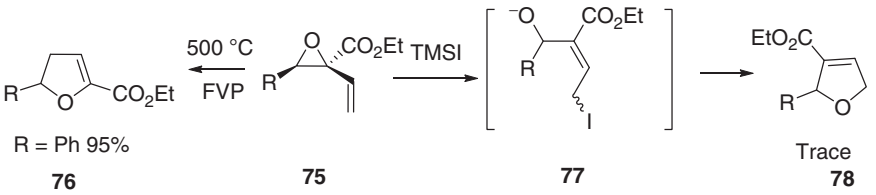
73 **74**

R = Ph (*E*):(*Z*) = 3.4:1 96%
R = (*E*):(*Z*) = 7:2 73%



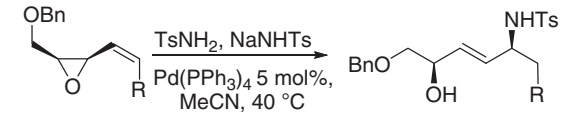
(45)

Although the 2,5-substitution pattern inherent in **76** is furnished through thermolytic rearrangements, the 2,3-isomer would result from an S_N2' opening of **75** to allylic iodide **77**, which would cyclize to 2,3-functionalized dihydrofuran **78** (Scheme 25).[221a,234] Only marginal results were obtained with vinyloxiranes under the conditions adapted from similar opening of vinylcyclopropanes with trimethylsilyl (TMS) iodide and titanium tetrachloride.[235]

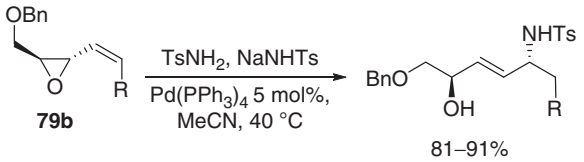


Scheme 25

Palladium-catalyzed nucleophilic opening of vinyloxiranes received attention in connection with the *cis*-dihydroxylation reported by Trost in 1985.[236] However, Pd-catalyzed S_N2' addition of nucleophiles is not a predominant mode for vinyloxiranes. Baeckvall[237] described opening of enantiomerically pure *cis*- and *trans*-vinyl epoxides **79** with NaNHTs in the presence of Pd $(PPh_3)_4$. The reaction proceeded with high regio- and stereoselectivity.

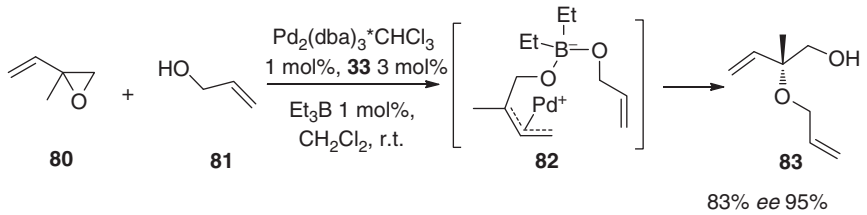


(46)

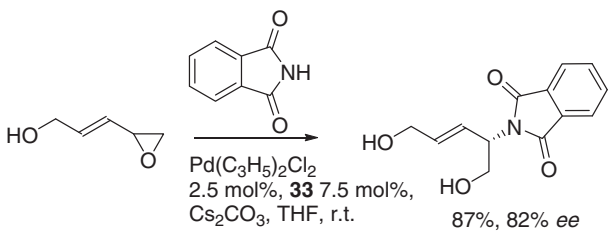


(47)

Trost[238] described a general approach for asymmetric opening of vinyloxiranes **80** with alcohols **81**. Starting from racemic epoxides, it was possible to achieve dynamic resolution with a wide range of alcohols. The reaction was believed to proceed via a π-allyl palladium complex **82**. In order to increase the nucleophilicity of the alcohol and change the reaction to an intramolecular mode triethylborane was added as cocatalyst. High enantiomeric excess (80–98%) was achieved. Trost[239] also showed that under similar conditions the opening of vinyloxiranes can be achieved with nitrogen nucleophiles containing acidic N–H bonds, such as the case of phthalimide, in good yields and with high enantiomeric excess (up to 98% *ee*) (equation 49).

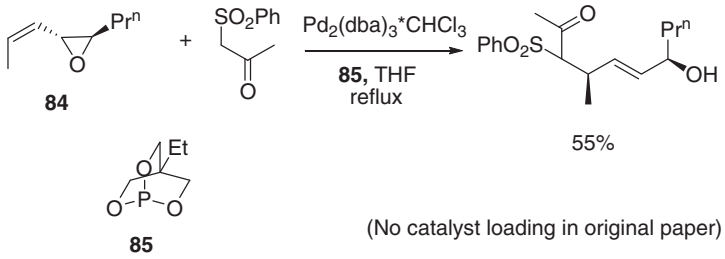


(48)

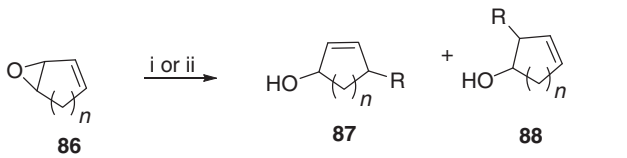


(49)

Vinyloxiranes also undergo opening with carbon nucleophiles. With soft nucleophiles and products formed via π-allyl metal intermediates, S_N2' addition can be expected, whereas hard nucleophiles tend to form products of S_N2 addition. Certain methods can lead to the selective formation of either S_N2 or S_N2' products depending on the conditions and additives. Trost[240a] studied the addition of soft carbon nucleophiles to a chiral vinyloxirane **84** and showed that the reaction proceeds smoothly with retention of configuration (equation 50). He and his group[240b] also described conditions for selective asymmetric S_N2 opening of vinyloxiranes utilizing Pd-catalyzed conditions. Some alkynyl lithium salts can serve as soft nucleophiles and the mode of addition to the vinyloxirane can be controlled. A combination of copper salts and chiral phosphoramidite **48** (see Scheme 18) was utilized for the asymmetric resolution of cyclic vinyloxiranes **86** with alkyl zinc[241] and alkyl aluminum reagents.[242] Different ligands and sources of copper were studied (equation 51).



(50)

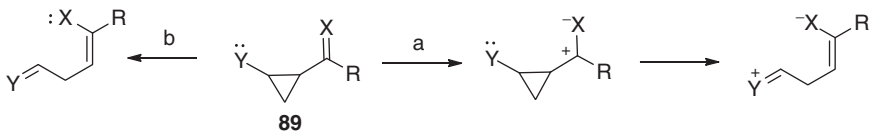


(51)

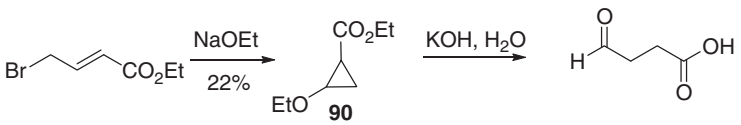
i. Me_2Zn $Cu(OTf)_2$ 3 mol%, **48** 6 mol%, toluene, –70 °C
ii. Me_3Al CuTC 1 mol%, **48** 2 mol%, THF, –70 °C

5.22.1.4.2 Cyclopropyl carbonyls

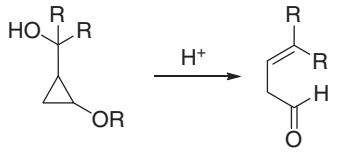
When the vinylcyclopropane system contains a heteroatom within the alkene portion, it is highly susceptible to rearrangements governed by donor–acceptor principles. Under appropriate conditions the ring closure of systems such as **89**, in addition to normal diradical pathways, can occur by two additional mechanisms: unraveling of a cyclopropylcarbinyl cation system (path a) or the action of a lone pair of an additional donor atom (or a full anion) resembling the unraveling of a cyclopropylcarbinyl anion (path b; Scheme 26). Ideally, both processes can reinforce one another to lead easily to rearrangements of systems such as **90** to the corresponding 1,4-dicarbonyl compounds, reported as early as 1938 (Scheme 27).[243] Recognition that the cyclopropylcarbinyl cation cleaves to provide additional unsaturation led to the methodology of acid- or base-catalyzed unraveling of systems of type **91** to the corresponding β,γ-unsaturated carbonyls (equation 52).[244] Only one review on the topic of synthesis and reactivity of cyclopropyl carbonyls and imines has been published in the past 20 years.[245]



Scheme 26

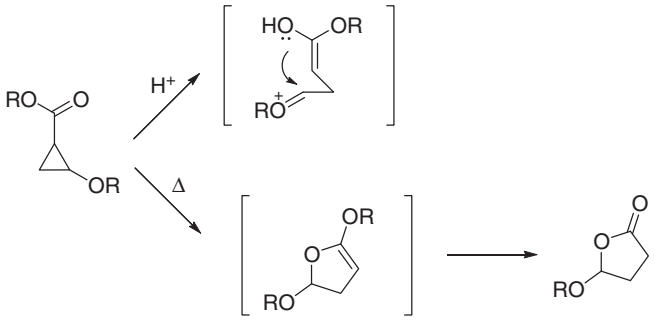


Scheme 27



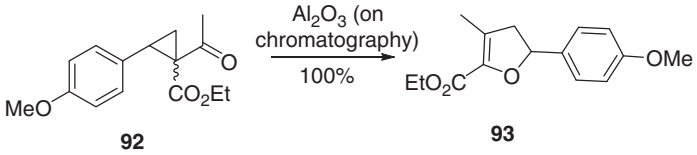
91 50% for R=Ph (52)

The above processes constitute the foundation on which Wenkert developed a general synthetic methodology applicable to terpenoid and alkaloid syntheses.[47,48] The carbonyl can be viewed as a hetero-vinyl moiety participating in the overall (hetero-vinyl)-cyclopropane–cyclopentene rearrangement, as shown in Scheme 28, even though the mechanism involves the cyclopropylcarbinyl rearrangement.

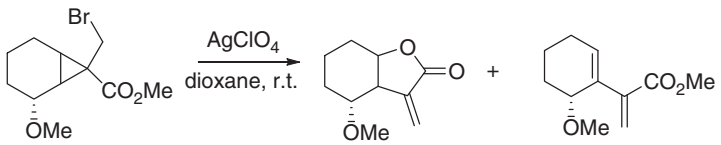


Scheme 28

Either isomer of **92** was converted into dihydrofuran **93** on alumina as an alternative to acid-catalyzed conditions (equation 53).[246] One methodology for α-methylene lactone synthesis relies on the solvolysis of cyclopropyl esters of type **94** to give α-methylene lactone **95** with Li_2CO_3 in dioxane (equation 54). The formation of the undesired diene **96** was diminished by the use of $AgClO_4$.[247]

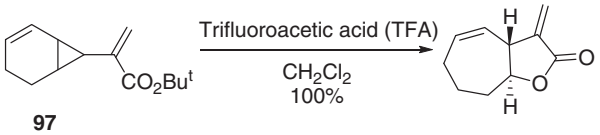


92 **93** (53)



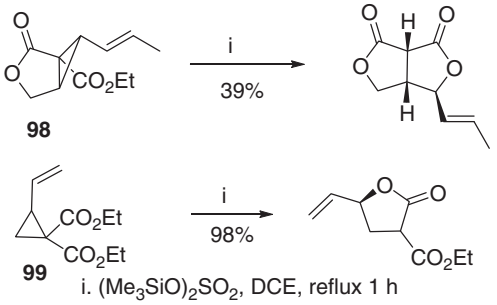
94 **95** 85% **96** 15% (54)

Vinylcyclopropanes containing carboxylates react selectively through the agency of the carbonyl group in acid-catalyzed rearrangements, as shown in equation 55.[248] It is noteworthy that neither of the two alternative pathways, the divinylcyclopropane Cope rearrangement of **97** or cyclopentene rearrangement(s), takes place. Further examples of carboxylate over vinyl selectivity are seen in the rearrangements of cyclopropanes **98** and **99** to the corresponding tetrahydrofuranones (Scheme 29).[249]



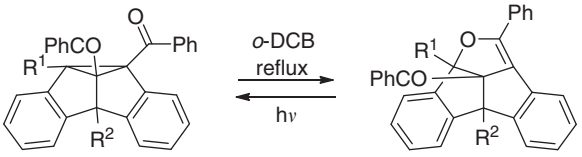
97 (55)

Thermal rearrangements of various dibenzosemibullvalenes have been described.[250] On heating, the compounds underwent clean rearrangements to the corresponding dihydrofurans **100**. It is interesting to note that under direct irradiation the products are converted back to the starting cyclopropyl ketones, in contrast to direct photoconversion of cyclopropyl carbonyl to



Scheme 29

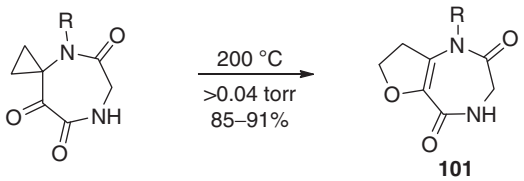
gem-disubstituted dimethyl dihydrofurans,[137] (equation 56; compare to Scheme 6). FVP was applied by de Meijere[251] to produce complex diazepine products such as **101** (equation 57). Treatment of activated silylcyclopropyl ketones with acids[252] in aprotic conditions or with excess of TMS triflate[253] lead to conversion to the corresponding 2,3-dihydrofurans or cyclobutanones. Most substrates provided highest conversion with TMS triflate, as shown in Scheme 30 and Table 10.



(56)

R^1=H, R^2=*t*-Bu
R^1=H, R^2=COMe
R^1=COMe, R^2=Me
R^1=COPh, R^2=Me
R^1=*p*-ArOMe, R^2=H

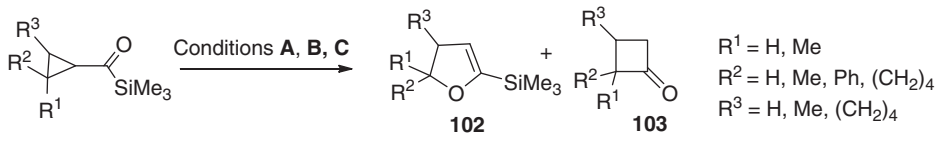
100



(57)

101

R = $CH_2(C_6H_4)$-*p*-OMe, $CH_2(C_6H_4)$-*p*-Cl



102 **103**

R^1 = H, Me
R^2 = H, Me, Ph, $(CH_2)_4$
R^3 = H, Me, $(CH_2)_4$

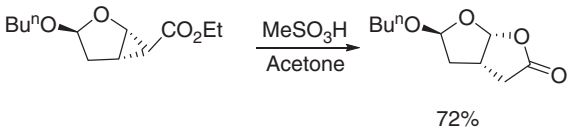
Conditions **A** H_2SO_4 THF/1,2-dimethoxyethane (DME) 60 °C
Conditions **B** TfOH, DME, –20 °C
Conditions **C** Me_3SiOTf 1–5 equivalents, CH_2Cl_2, –78 °C

Scheme 30

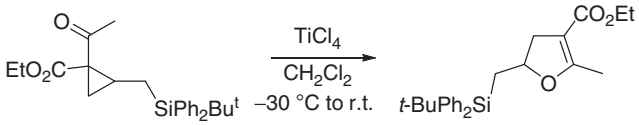
Table 10 Acid-catalyzed rearrangement of silyl cyclopropyl ketones (Scheme 30)

R^1,R^2,R^3	*Conditions*	*Product (Yield %)*
H, Ph, H	**A**	**103** (70)
Me, Me, H	**A**	**102** (69)
H, Ph, H	**B**	**102** (75)
H, Ph, H	**C**	**102** (99)

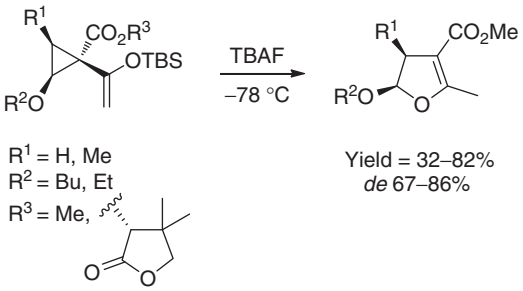
Theodorakis[254] utilized the acid-catalyzed rearrangement of bicyclic systems to produce bicyclic lactones (equation 58). Lewis acids have also been used for similar rearrangements in order to stabilize opened, charged intermediates. Yadav[255] and Johnson[256] showed that 1-acyl-2-vinylcyclopropanes can be rearranged with $Ni(cod)_2$[256] or with a range of Lewis acids[255] (equation 59). In analogy with the anion accelerated vinylcyclopropane–cyclopentene rearrangement, such as the one used in specionin synthesis (see **Table 12** and ref. 381) cyclopropyl carbonyls masked as silyl enol ethers rearrange, via the corresponding enolate anions, as shown in equation 60 and described by Davies.[257] The rearrangements proceed with good diastereoselectivity but with complete racemization in the absence of a chiral auxiliary.



(58)



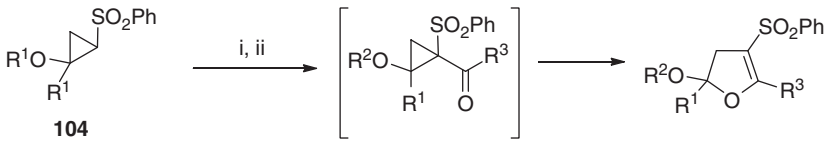
(59)



(60)

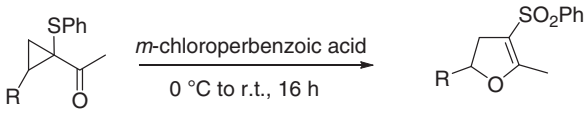
5.22.1.4.2.1 *Transient cyclopropyl carbonyls*

Cyclopropane systems that contain donor and acceptor substituents on vicinal carbons are predisposed to undergo opening and rearrangement to more stable dihydrofuran moieties (equation 61). Suitable substrates can be generated by metalation of sulfonyl cyclopropanes such as **104**[123,258] and lithium salts can be quenched by acyl imidazoles (Im). On heating to room temperature, these compounds rearrange to dihydrofurans. Oxidation of cyclopropyl sulfides with electron-rich aryl substituents to the corresponding sulfones leads to rearrangement to dihydrofurans (equation 62).[259] Upon insertion of carbenoid intermediates to electron-rich enol ethers derived from α,β-unsaturated ketones the resulting cyclopropane intermediates can undergo further rearrangement to dihydrofurans.[260]



(61)

i. BuLi, –78 °C, THF; ii. R^3COIm, –78 °C to r.t.

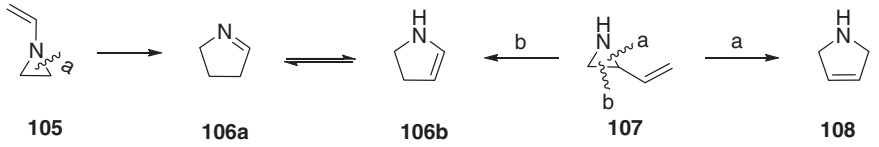


(62)

5.22.1.5 Rearrangements of Vinylaziridines and Cyclopropyl Imines

5.22.1.5.1 Rearrangement of vinylaziridines

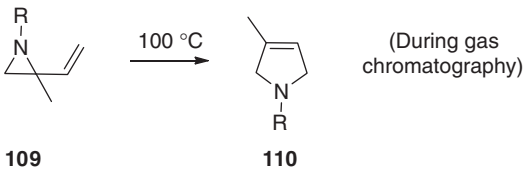
Like vinyloxiranes, vinylaziridines are subject to a number of rearrangements that parallel the pathways available to vinylcyclopropanes. Unlike them, however, vinylaziridines undergo extremely well-controlled nucleophilic opening to furnish pyrrolines under nonthermolytic conditions. They are easily prepared from alkenes and azides via triazolines.[261] Because of the valency of nitrogen there are two topographical isomers possible, **105** or **107**, each leading to a different tautomer of pyrroline **106a** or **106b**, and an additional isomer, 3-pyrroline **108**, available through cleavage of bond **a** in **107** (Scheme 31). This remarkable property of vinyl- aziridines translates into the selective preparation of all possible isomers of pyrroline, 1-, 2-, and 3-pyrroline, by careful "tuning" of the reactivity of **105** and **107** through substituent effects and the knowledge of probable reaction intermediates. Much of the thermal and photochemical behavior of vinylaziridines may be rationalized through either diradical or zwitterionic (azomethine ylide) intermediates. This subject has been thoroughly summarized.[51,230,262,263]



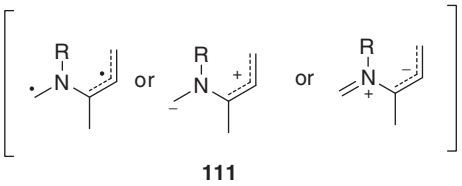
Scheme 31

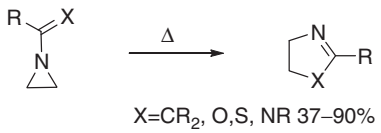
5.22.1.5.1.1 Thermal rearrangements of vinylaziridines

Vinylaziridines such as **109** have been rearranged thermally to 3-pyrrolines (equation 63),[264,265] presumably through one of the species **111**. Substituents play an important role in the likelihood of these intermediates.[266] The energy of activation for carbon–nitrogen bond cleavage has been estimated to be 12–14 kcal mol^{-1} (compared with 27 kcal mol^{-1} for cyclopropane).[267] Vinylaziridines of type **112** (R = alkyl) furnish 1-pyrrolines **113** or, if X is another heteroatom, the corresponding heterocyclopentenes (equation 64).[265,268]



(63)

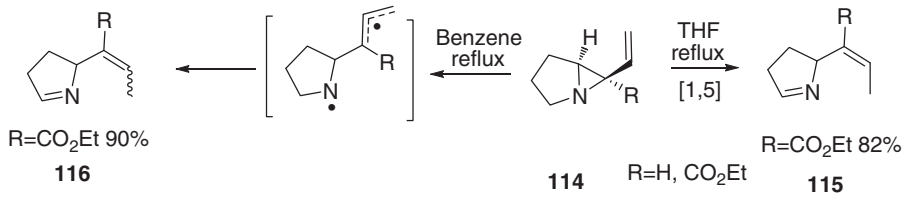




(64)

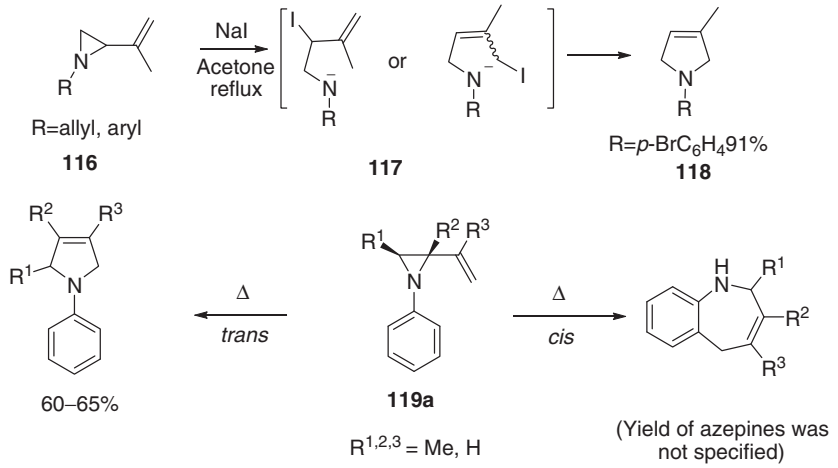
The competing reaction involves the formation of imines (presumably via diradicals and hydrogen migration), as proposed by Logothetis to account for the formation of imines in the thermolysis of aziridines.[269] Imine formation is sometimes observed as a competing pathway in the thermolysis of *N*-substituted vinylaziridines[270] and can also be rationalized by a process analogous to a [1,5] homodienyl shift.[230,271,272] In cyclic systems with proper stereochemistry (*endo*) this process may predominate, as evidenced by the isolation of only the (*E*)-alkene **115** (R = CO_2Et; Scheme 32).[271,272]

Reaction of vinylaziridines **116** with NaI in refluxing acetone led to 3-pyrrolines **118** (Scheme 33).[273,274] When the *N*-substituent contains an additional alkene as in the case of **119a**, the possibility of an intervening Cope-like rearrangement will complicate pyrroline formation. The selectivity between these two pathways usually depends on the stereochemistry of the



Scheme 32

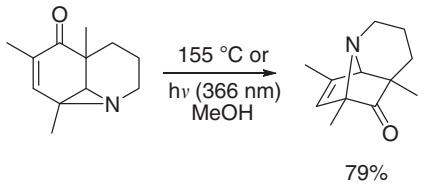
vinylaziridine, and the temperature of the rearrangement (higher temperatures favor the pyrroline formation as the Cope rearrangement is frequently reversible.) No *cis*/*trans* isomerization was observed in the case of **119a**.[275] The divinylaziridine rearrangement as well as the [1,5] shift pathways of vinylaziridines can be controlled according to the principles found valid with vinylcyclopropanes or vinyloxiranes. Some aspects of the rearrangements of vinylaziridines have been reviewed.[23,45,230,263,276]



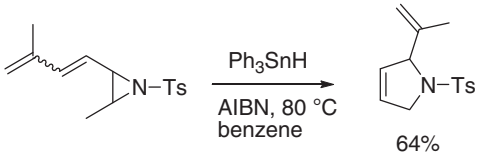
Scheme 33

Photochemical rearrangements have also been reported, as shown in equation 65.[277,278] Transition-metal-catalyzed rearrangement [palladium(0)] of a dienylaziridine has been reported in one case,[279] and a radical opening of a dienylaziridine led to pyrroline formation under the conditions of radical initiation with azobisisobutyronitrile (AIBN)/Ph_3SnH (equation 66).[280] For those vinylaziridines that contain additional unsaturation, the corresponding aza equivalent of a divinylcyclopropane Cope rearrangement is the usual pathway.[281] The pyrroline–azepine pathways are usually controllable by determining temperature profiles for the reactions. Higher temperatures favor pyrroline formation.

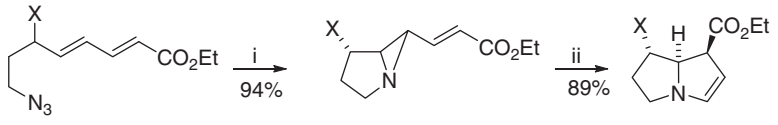
Compared to vinylcyclopropanes, vinylaziridines have not enjoyed wide applicability in synthetic schemes or for annulation before the discovery and development of [4+1] pyrroline annulation (Scheme 34).[51,271,272,282–284] Activation of the dienes with EWGs proved necessary for the formation of vinylaziridines **121** (through intermediate triazolines and their thermal decomposition).[284] Noteworthy is the selectivity in bond activation in **121** (Scheme 34).



(65)



(66)

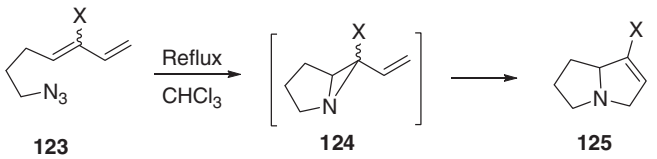


120 X = H, OR **121** **122**

i. PhMe, Δ; ii. 485 °C

Scheme 34

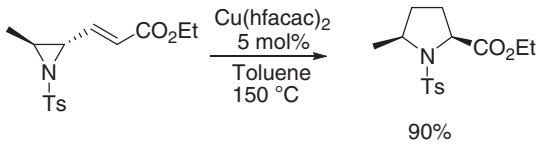
Compounds of type **123** (Scheme 35) have been found to yield pyrrolines **125** through the vinylaziridine–pyrroline rearrangement of **124** (not isolated) in refluxing $CHCl_3$ or THF, albeit in moderate yields (31–62%).[285,286] The heteroatom substitution apparently accelerates the rearrangement. Somfai[287] showed that vinylaziridines may be rearranged to 3-pyrrolines under microwave radiation in presence of salts such as LiI or NaI. Njardarson[288] discovered that electron-deficient $Cu(hfacac)_2$ can promote a smooth rearrangement of electron-deficient vinylaziridines to the corresponding 2,5-dyhydropyrroles (equation 67). He extended the scope of this rearrangement to enantiopure aziridines,[289] in which the reaction proceeded with complete retention of optical purity unlike similar vinylcyclopropane–cyclopentene rearrangements. It is important to note that only electron-poor aziridines (R^1 = *p*-toluenesulfonate (Ts), *p*-nitrobenzenesulfonyl) can be transformed under such conditions.



123 **124** **125**

X = SPh, $OSiMe^2Bu^t$, $OCH(CH_3)OEt$ 31–65%

Scheme 35

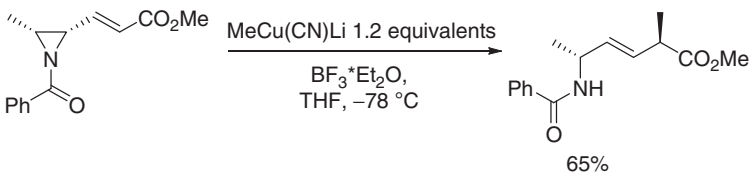


90% (67)

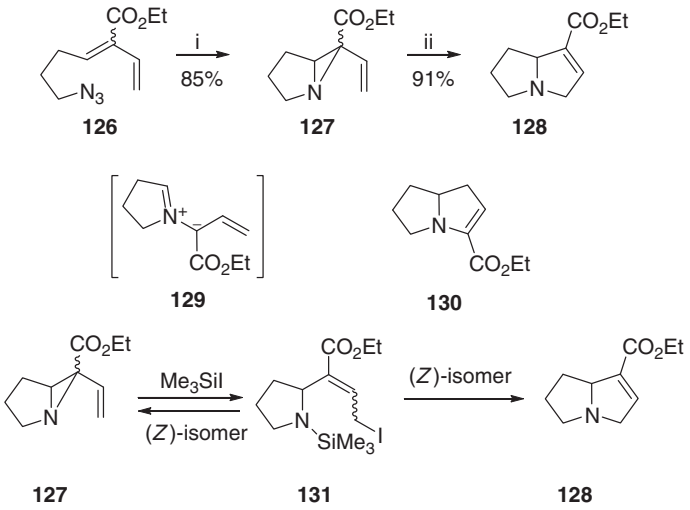
5.22.1.5.1.2 *Nucleophilic opening of vinylaziridines*

The mechanistic details of the nucleophilic opening of vinylaziridines are similar to those operating on vinyloxiranes. Whereas thermolysis of **127** leads to pyrrolizidine **130**,[271,272,284] likely through the agency of azomethine ylide **129**, nucleophilic opening leads exclusively to **128** through intermediate allylic iodides **131**, which are produced as mixtures of (*E*)- and (*Z*)-isomers but are converted into **128** through equilibration and recycling of the (*Z*)-isomer (Scheme 36).[282]

It was shown by Ibuka and coworkers in 1994[290] that copper reagents can open acyclic vinylaziridines in a S_N2' fashion (Scheme 37). The same year Wipf[291] succeeded in opening of *N*-acyl aziridines with cyanocuprates in the presence of BF_3. High *anti*-selectivity was achieved (equation 68). Later Hudlicky[292] applied similar conditions to the opening of cyclic vinylaziridine **132**. The main product was formed as a result of selective *syn*-S_N2' addition. The predominance of the *syn* addition was explained by the high steric demand of the acetonide to proceed in *anti*-fashion (equation 69). Sweeney[293] showed that 2,3-*trans*-3-aryl-2-vinylaziridines can be opened with lithium dialkyl cuprates in exclusive S_N2' fashion (equation 70).

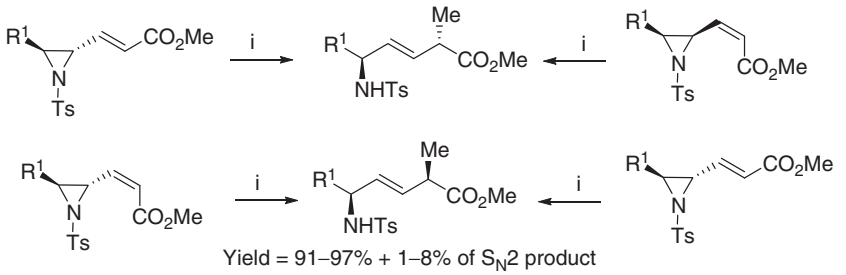


65% (68)



i. Toluene, Δ; ii. Me_3SiI, CH_2Cl_2, –50 °C;

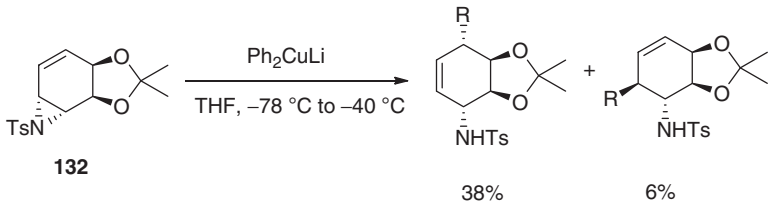
Scheme 36



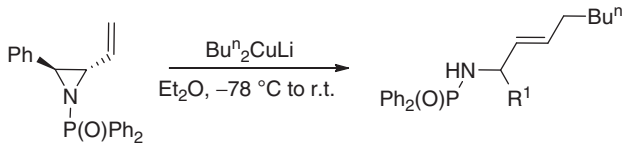
Yield = 91–97% + 1–8% of S_N2 product

R^1 = H, Me i. 3–4 equivalents Me_3ZnLi/30 mol% CuCN or MeCu(CN)Li, THF, –78 °C

Scheme 37

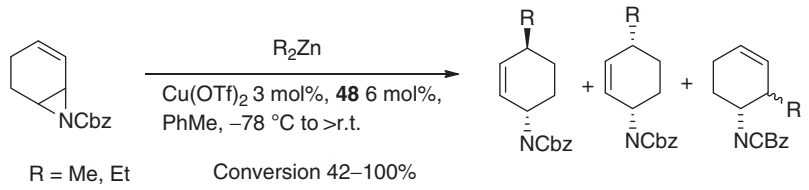


(69)



(70)

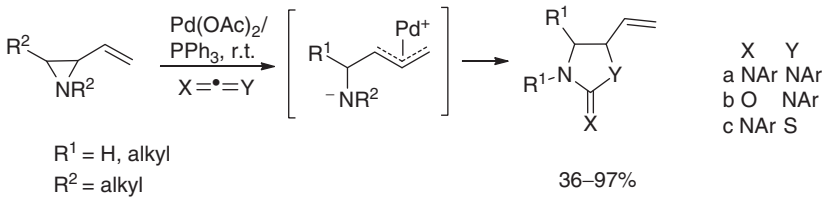
The catalytic enantioselective opening of vinylaziridines in the presence of copper catalysts has been studied by Pineschi.[294] During his work with cyclic vinyl epoxides (see Section 5.22.1.4.1.2), he discovered that cyclic 2-alkenyl *N*-carboxybenzyl (Cbz)-protected aziridines can be opened by alkylzinc reagents in the presence of $Cu(OTf)_2$/phoshoramidite ligands with an enantiomeric excess range of 5–83%. Without the ligand, there were unexpected amounts (50%) of the *syn* product observed, explained by the complexation of the copper with the Cbz group (equation 71). Comasseto[295] screened different organometallic reagents and showed that higher order cuprates gave the best selectivity for S_N2' addition for cyclic and acyclic aziridines.



(71)

5.22.1.5.1.3 Cycloadditions of vinylaziridines

Alper[296] showed that vinylaziridines can undergo cycloadditions with a variety of isocyanates, carbodiimides, and isothiocyanates with $Pd(OAc)_2/PPh_3$ as the catalytic system. The reaction proceeds via formation of a π–allylpalladium complex (Scheme 38, Table 11).

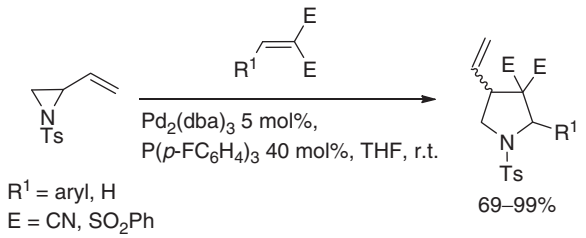


Scheme 38

Table 11 Cycloaddition reaction of vinylaziridines with different unsaturated partners

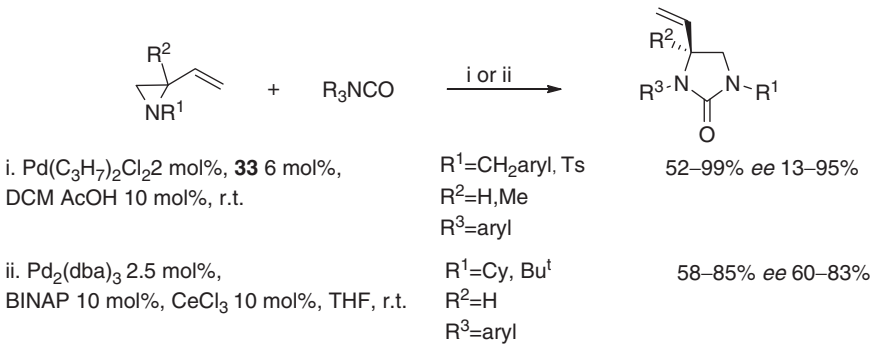
X,Y	*R^1,R^2*	*Yield (%)*
O, PhN	*c*-C_6H_{11}, H	89
PhN, PhN	*c*-C_6H_{11}, H	60
PhN, S	*c*-C_6H_{11}, H	96

Yamamoto[297] described similar cycloadditions with olefins activated by EWGs. The reaction proceeded with high yields but low diastereoselectivities, with ratios of *cis* to *trans* in the range of 23:77–55:45 (equation 72).



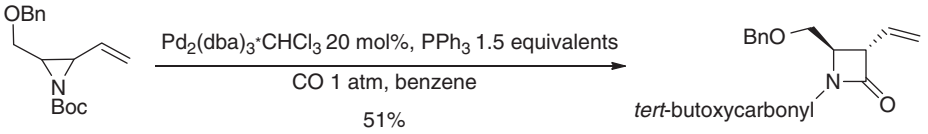
(72)

Trost[298] described the first example of an enantioselective version of the cycloaddition of isocyanates to vinylaziridines in the presence of $Pd(allyl)_2Cl_2/(R,R)$-**33**. The reaction proceeded with good yields and in reasonable enantiomeric excess in the presence of an acidic additive such as acetic acid. Later the same group utilized this transformation in total synthesis.[299] Alper[300] discovered that similar reactivity can be achieved also with BINAP and $CeCl_3$ as an additive (Scheme 39).



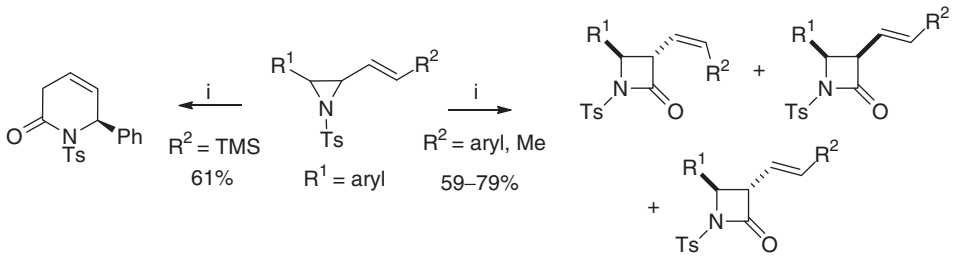
Scheme 39

The first example of a palladium-catalyzed cycloaddition of carbon monoxide to vinylaziridines was described in 1991 by Ohfune (equation 73).[301] Regardless of the configuration of the starting vinylaziridines, only the *trans* β-lactam was formed in moderate yield. Somfai and Tanner[302] utilized this transformation in the synthesis of the carbapenem antibiotic (+)-PS-5.



(73)

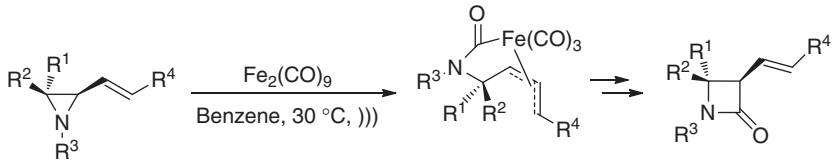
Expanding this methodology to a broader scope of substrates, Aggarwal[303] discovered that changing the solvent significantly alters the stereochemical outcome. He also discovered that silyl-substituted aziridines can produce δ-lactams as the only product of what seems to be a [5+1] cycloaddition, contrary to the typical reaction of such a system to produce β-lactams (Scheme 40).



i. $Pd_2(dba)_3$*$CHCl_3$ 5 mol%, PPh_3 60 mol%, CO 1 atm, PhMe, r.t.

Scheme 40

Iron-mediated processes were described by Ley.[304] Sonication of vinylaziridine with $Fe_2(CO)_9$ produces a stable iron complex that can be reduced and transformed to the β-lactam by oxidation with Me_3NO (Scheme 41).



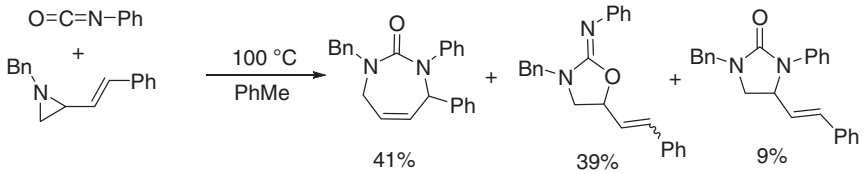
$R^{1,2}$ = H, Me
R^3 = CO_2Me, Bn
R^4 = H, Ac

71–77%

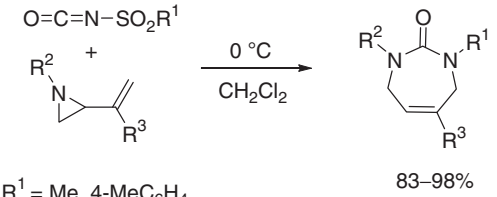
54–69%

Scheme 41

Louie[305] discovered that a formal [5+2]-cycloaddition occurred up on heating electron-rich vinylaziridines with phenyl isocyanates in nonpolar solvents with formation of seven-membered cyclic ureas. Byproducts were five-membered ureas and oxazolidines. It has been shown that only *trans*-substituted aziridines form seven-membered cyclic ureas (equation 74). Recently Saito[306] showed that a similar reaction can proceed at 0 °C with activated mesyl and tosyl isocyanates (equation 75).



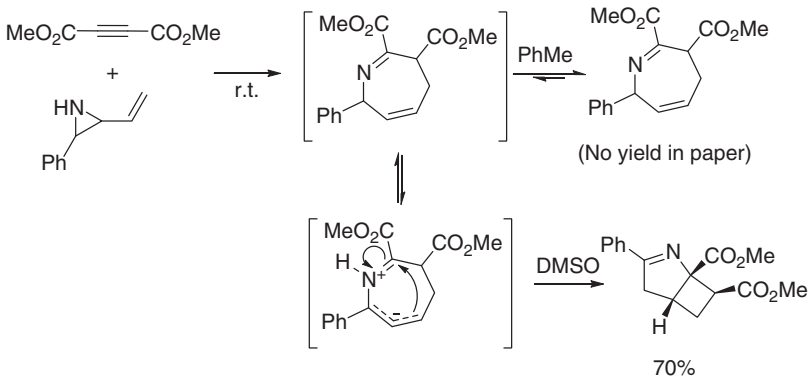
(74)



(75)

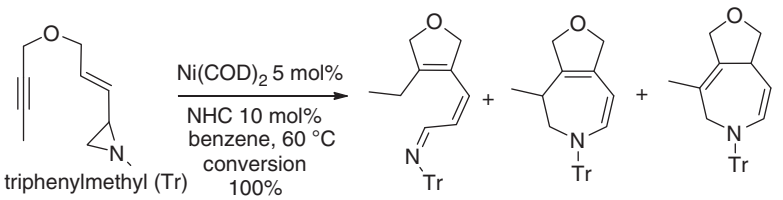
R^1 = Me, 4-MeC_6H_4
R^2 = Bn, *c*-C_6H_{13}, Bu^n, 2,4-dimethoxyphenyl
R^3 = H, Me

Yudin[307] described the reaction of *N*-unsubstituted vinylaziridines with dimethyl acetylenedicarboxylate (DMAD). The use of different solvents led to the formation of dihydroazepines or bicyclic 4,5-systems (Scheme 42).



Scheme 42

The Ni(0)/NHC catalytic system developed by Louie[308] was applied in the intramolecular cycloaddition reaction between alkynes and aziridines. In order to suppress the competing β-hydride shift, a large substituent on nitrogen was required. Screening of various ligands showed that the most efficient ones were SIPr and IMes (equation 76).



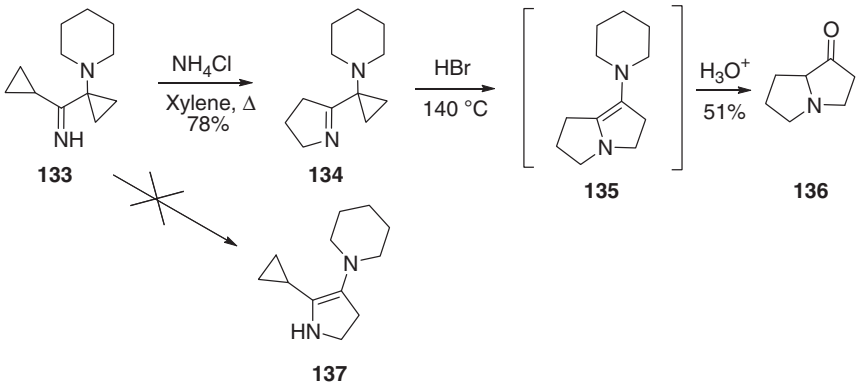
(76)

NHC	**a**	**b**	**c** (ratio)
I*t*-Bu	1	–	–
IMes	–	1	2
IPr	–	1	1
SIPr	–	4	1

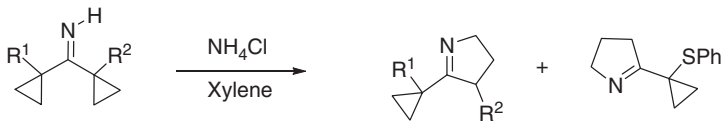
5.22.1.5.2 Cyclopropyl imines

The cyclopropylimine–pyrroline rearrangement (Cloke rearrangement) has been known since 1929, long before the discovery of the parent vinylcyclopropane system.[309] Rearrangements of cyclopropylimines have been studied recently in the context of the effects of heteroatom substitution on rearrangements of cyclopropanes.[245]

Dicyclopropylimine **133** rearranged to pyrroline **134** not to 2-pyrroline **137**, the product expected from the accelerating effect of the amino substituent (Scheme 43). Further reaction and hydrolysis led to pyrrolizidone **136**.[310] The effects of substituents (*N*, *S*) were investigated on substrates shown in equation 77.[247] Sulfur and nitrogen did not exert an effect of the magnitude expected from similar studies on vinylcyclopropanes. It may be attributed to the mechanistic duality of this rearrangement, which may involve nucleophilic opening followed by alkylation. The observed preference for the rearrangement of the less-substituted cyclopropane may have its roots in steric effects and the preference for the nucleophilic attack at the less-substituted site. Stevens obtained a different result.[311,312] The piperidinyl-substituted cyclopropane in **138** rearranged on thermolysis in the presence of an acid with a nonnucleophilic counterion and gave pyrrole **139** up on further acid-catalyzed elimination (equation 78).[311,312]

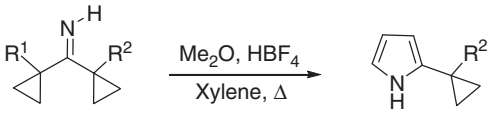


Scheme 43



(77)

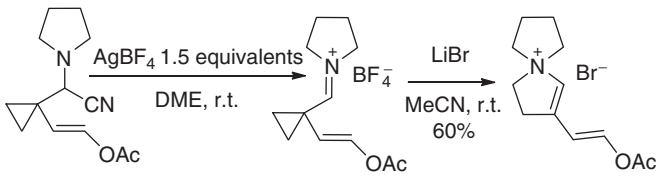
138a R^1 = piperidinyl , R^2 = H	78%	–
138b R^1 = piperidinyl, R^2 = SH	69%	–
138c R^1 = H, R^2 = SPh	28%	22%



(78)

R^1 = piperidinyl		**139**
138a	R^2=H	32%
138b	R^2=SPh	42%

Cyclopropyl imines are usually generated by reduction of nitriles or condensation of carbonyl compounds with amines.[312,313] An alternative to this process involves the generation of cyclopropylimmonium salts such as **141** at room temperature from a cyanohydrin equivalent such as **140** (Scheme 44).[314]

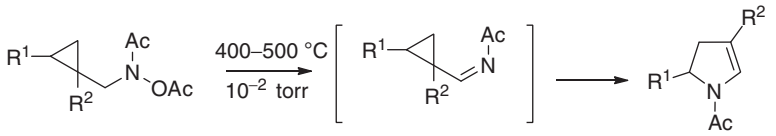


Scheme 44

The rearrangement proceeds thermally under acid catalysis by HBr, NH_4Cl, or via nucleophilic opening and reclosure as in the case of vinylaziridines. Sulfur substitution has been found effective in accelerating the rearrangement as well as serving as a site of further functionalization. This feature has been especially exhibited in the synthesis of pyrrolizidine and *Amaryllidaceae* alkaloids.[312,313]

The synthesis of cyclopropylimines was discussed in detail in a 2007 review.[315] Their rearrangement takes place under conditions similar to those employed for vinylcyclopropane–cyclopentene rearrangements; high temperatures (300–500 °C) are sometimes required. Unsubstituted C-cyclopropyl imine is stable toward heating up to 650 °C in the absence of acid. When Wu[316] studied the FVP of C-cyclopropyl imine, he discovered that *N*-acyl imines, with a stabilizing group on the cyclopropyl ring

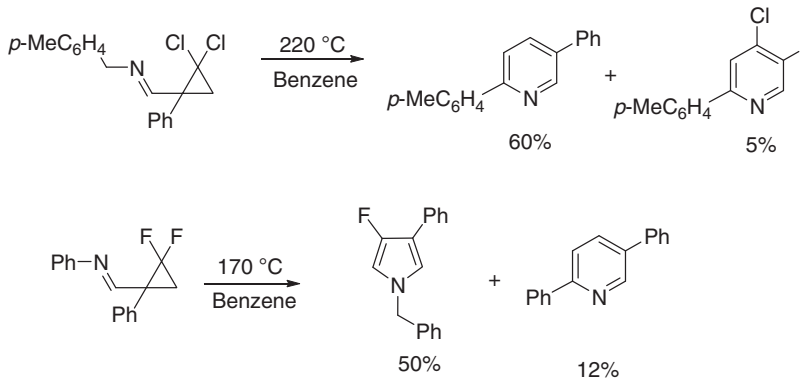
generated *in situ*, undergo rearrangement with moderate yields. In case of unsubstituted and alkyl-substituted cyclopropanes decomposition was observed (Scheme 45).



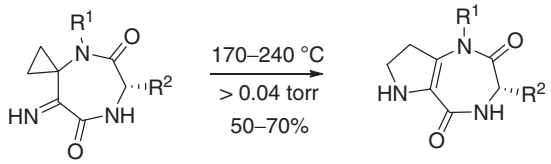
R^1	R^2	%
H	Ph	37
Ph	H	38
PhCO	H	21
H	CO_2Me	35

Scheme 45

Kagabu[317] discovered that *gem*-dihalosubstituted cyclopropyl imines produce heterocyclic compounds under thermal conditions and with different additives (bases, metal oxides, inorganic salts). In the case of *N*-benzyl (Bn) substituted imines, the main products were pyridines. Pyrroles were generated from *N*-alkyl-substituted imines and *gem*-difluoro cyclopentene (Scheme 46). Later the same group[320b] published a more extensive study showing that *N*-substituents without α-protons undergo rearrangements to pyrroles. The mechanism is believed to vary for different substrates. In case of *gem*-difluorocyclopentene, radical cleavage occurs. *gem*-Dichlorocyclopropyl imines undergo the rearrangement via cationic intermediates. De Meijere[251] showed that this rearrangement can generate complex molecules starting from cyclopropyl ketimines (equation 79).

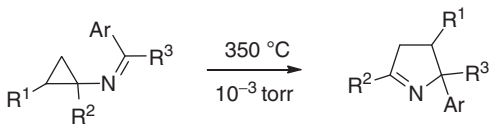


Scheme 46



(79)

N-Cyclopropyl imines undergo much smoother rearrangement. It has been shown by Campos and Rodriguez[318] that with FVP a variety of unsubstituted and aryl-substituted cyclopropyl imines undergo rearrangement to 1-pyrrolines (equation 80).



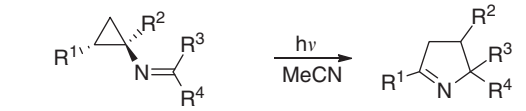
$R^{1,2}$ = H, Ph
R^3 = H, MePh
Ar = Ph, furyl

26–74%

(80)

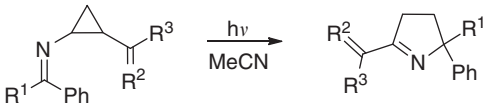
Photochemical rearrangement has been shown to work only for *N*-cyclopropyl imines.[315] The scope of substrates was investigated under direct irradiation and was shown to proceed with good to excellent yields (equation 81). The mechanism was shown to occur

via diradical intermediates,[319] but slow interconversion and control of chromophore excitation allowed greater stereoselectivity compared to thermal vinylcyclopropane–cyclopentene rearrangements. A further study[320] described the influence of substituents and solvents. Complete selectivity toward the cyclopropylimine–dihydropyrrole rearrangement was shown (equation 82).



$R^{1,2,3}$ = H, Me, Ph, CO_2Bu
R^4 = Ph, *trans*-CH=CHPh

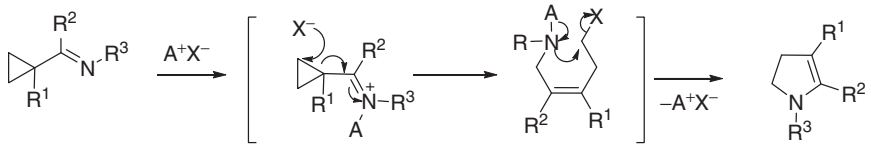
50–98% (81)



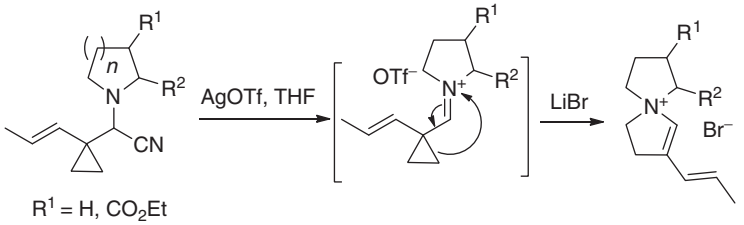
R^1	R^2	R^3	
Ph	CHPh	H	70%
H	O	OEt	75%

(82)

Classical methods for the rearrangement of C-cyclopropyl imines (Cloke rearrangement)[309] entail high temperatures and acidic conditions. A typical reaction involves heating of the substrate to 140 °C in the presence of NH_4Cl;[321] however, milder catalysts may be used, for example TMSCl and NaI,[322] LiCl, LiI, and others. The generally accepted mechanism of the acid-catalyzed rearrangement is depicted in Scheme 47. The cyclopropyl iminium ion can also be generated with AgOTf (Scheme 48). Charged intermediates generated by alkylation of thioimidates were utilized for a similar rearrangement.[323] The mechanism for opening and reclosure is similar to the Cloke rearrangement (Scheme 49).



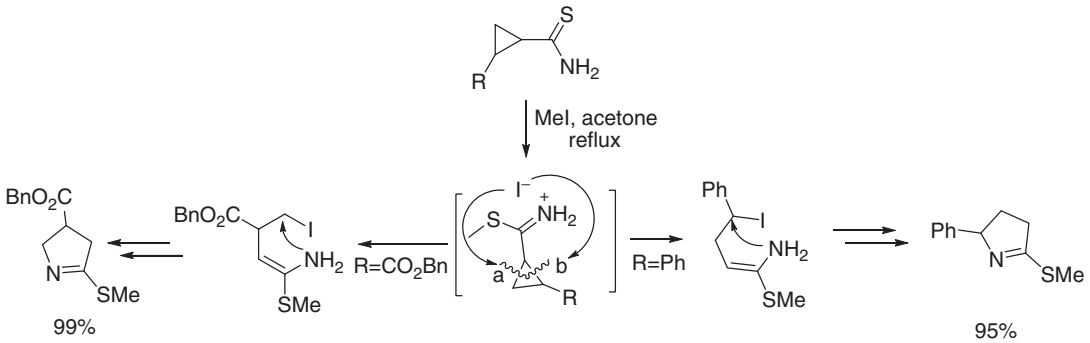
Scheme 47



R^1 = H, CO_2Et
R^2 = H, CH_2CO_2Et
n = 1, 2, 3

65–93%

Scheme 48

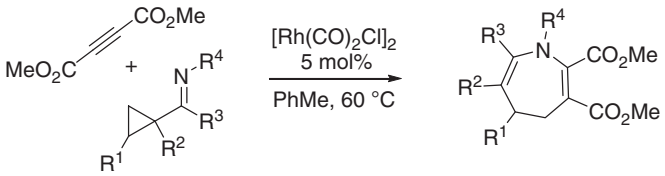


99%

95%

Scheme 49

Wender[324] used intermolecular cycloaddition of DMAD to cyclopropyl imines to produce dihydroazepines in high yields (equation 83).



R^1, R^2 = H, alkyl
R^3 = H, alkyl, Ph
R^4 = Bn, alkyl

61–95% (83)

5.22.1.6 Miscellaneous Systems

It would be difficult to list all of the cases involving the various combinations of heteroatom substitution in a vinylcyclopropane system. It has been recognized that virtually any heteroatom or any degree of unsaturation can be incorporated into the parent vinylcyclopropane system for almost limitless variability in the type of products that can be expected on its rearrangements.[52,325] The general transformations depicted in equation 84 have been summarized and reviewed[18,230,326–329] in the context of the synthesis of five-membered heterocycles. Vinylcyclopropenes, methylenevinylcyclopropanes, and cyclopropylalkynes all undergo the requisite rearrangements to five-membered rings.[9] The products are the corresponding cyclopentadienes or methylenecyclopentenes and their heteroatom analogs. These topics have been reviewed.[9,13,18,329] The mechanism of these transformations ranges from diradical scission to carbene generation and rearrangement.[18,329–331]



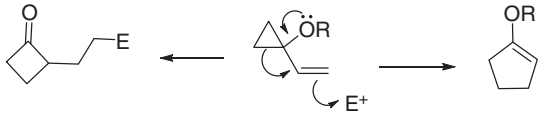
(84)

General discussions and reviews of rearrangements of heterovinylcyclopropane systems with one heteroatom and two or more heteroatoms not discussed in the previous sections (Sections 5.22.1.4 and 5.22.1.5) are available.[332,333] Their rearrangements are governed by principles discussed previously, that is, most stable diradical or ylide intermediate or the least-hindered site for nucleophilic attack in the case of nucleophilic openings. The electronegativity of the heteroatom and the conditions of rearrangement determine the regiochemistry of bond cleavage. With systems containing additional unsaturation, the divinylcyclopropane–Cope rearrangement remains a viable option (see Section 5.22.2).[222]

The use of vinylthiiranes as synthons for 2,5-dihydrothiophenes has been somewhat limited as they readily undergo thermal desulfurization to form dienes. Njardarson[334] recently discovered that vinylthiiranes may be rearranged into 2,5-dihydrothiophenes under conditions similar to those described above for vinyloxiranes and vinylaziridines.

5.22.1.6.1 Isomerizations of oxyvinylcyclopropanes to cyclobutanones

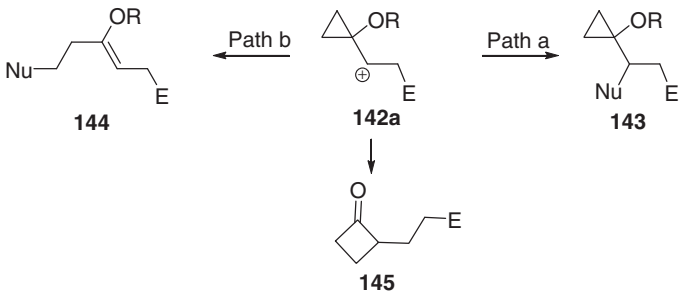
Vinylcyclopropanes substituted with oxygen (or sulfur or selenium) are susceptible to ring expansion to the corresponding cyclobutanone derivatives in addition to the expected rearrangement to cyclopentene (Scheme 50). The oxycyclopropane can be viewed as a pseudo enol in those interactions with electrophiles that involve the vinyl group. The resulting cyclopropylcarbinyl system **142a** will interact with nucleophiles either directly (path a) or through ring opening (path b; Scheme 51). The participation of either bond **a** or **b** in this opening will depend on the precise conformation of **142**, which is in turn dependent on the nature of the cation and its solvation, as well as on the tendency of the cyclopropylcarbinyl cation **142a** to unravel. When proper orbital overlap exists, one of these bonds will participate in opening the cyclopropane to yield **144**, or it will act as an internal nucleophile in its migration (and concomitant ring expansion to **145**).



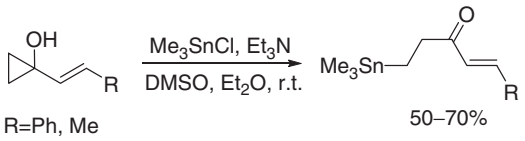
142

Scheme 50

This latter process was developed and extensively utilized by Trost in spirocyclobutanone annulation.[19,20] A less common reaction of oxyvinylcyclopropanes involves normal electrophilic opening of the oxycyclopropane, as, for example, that occurring in the generation of the β-stannyl enone (equation 85).[15]

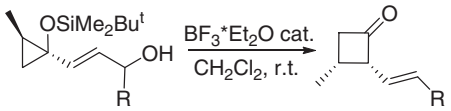


Scheme 51



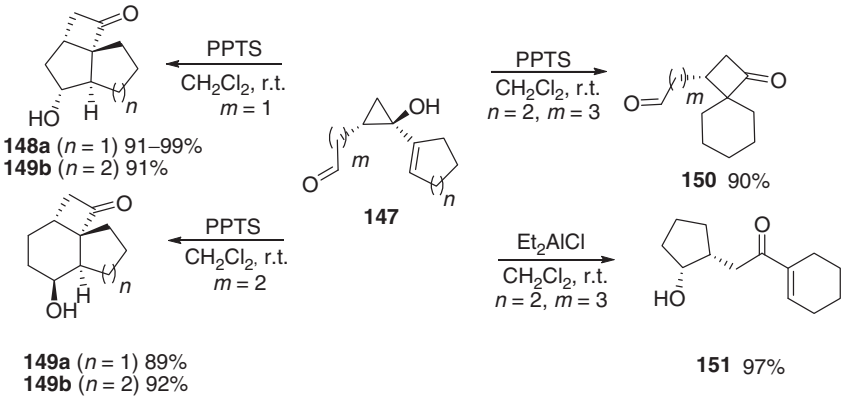
(85)

Salaun showed that optically active silyl ethers of vinylcyclopropanols can be rearranged under mild conditions with $BF_3{*}Et_2O$ with the retention of optical configuration (84–90% *ee*, equation 86).[335]



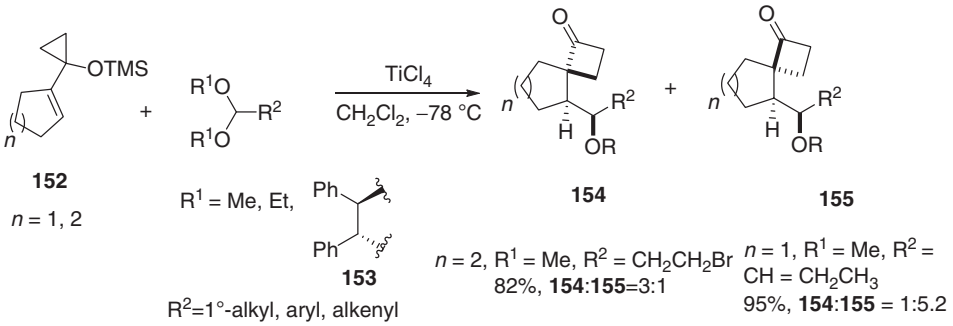
(86)

Cha[336] utilized the acid-catalyzed intramolecular cyclization of vinylcyclopropanols with tethered ω-aldehydes for the synthesis of polycyclic structures. Reactions proceed with good yield and diastereoselectivity. It was shown that, depending on the length of alkyl chain, different stereochemistry of the hydroxyl group can be observed (**Scheme 52**).



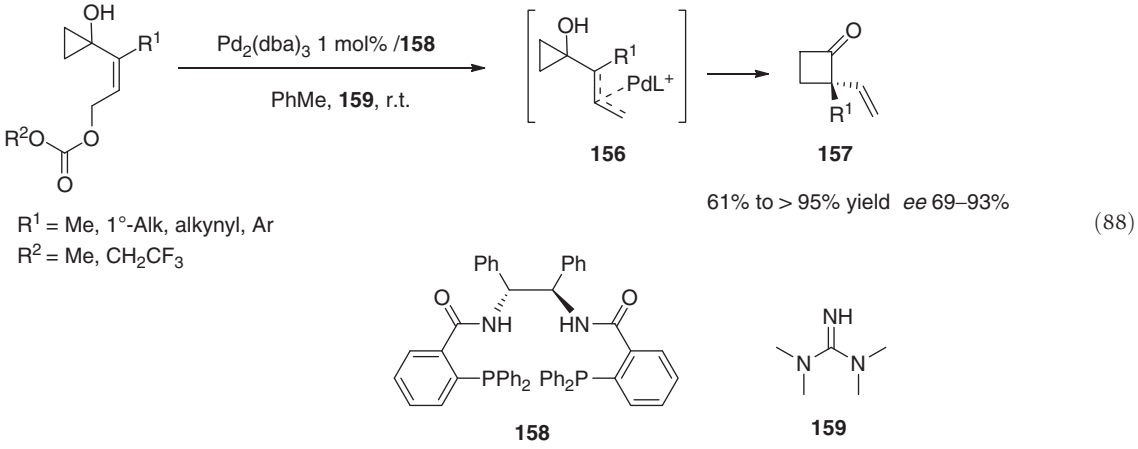
Scheme 52 PPTS, pyridinium *p*-toluenesulfonate.

Cha[337] also explored Lewis acid intermolecular reaction of acetals with vinylcyclopropanols. In the case of α,β-alkenyl substrates good diastereoselectivity was observed (>6:1), compared to modest diastereoselectivity (>3:1) observed in case of alkyl and aryl acetals (equation 87). The chiral auxiliary (*R,R*)-(+)-hydrobenzoin **153** was used[337b,c] in the form of a chiral acetal to provide access to the enantiomerically pure products.



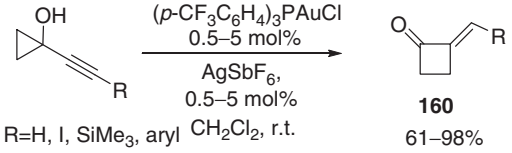
(87)

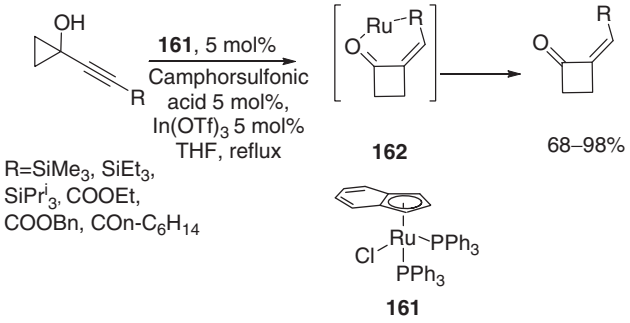
Cationic rearrangements can be performed in the presence of transition-metal complexes. Seminal work on the enantioselective variant of such rearrangements was published by Trost.[338] Reactions proceed in the presence of catalytic amounts of $Pd(dba)_2$ and the chiral bidentate phosphine **158** via formation of the π-allylpalladium complex **156** and proceed with good yields to give chiral vinylcyclobutanones **157** (equation 88). Addition of base such as tetramethylguanidine (**159**) was shown to increase the *ee* but significantly lowered the rate of conversion.



(88)

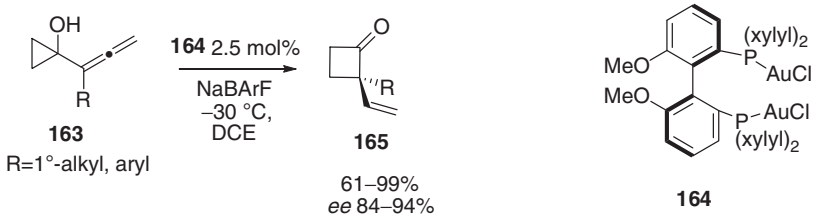
Gold[339] and ruthenium[340] were shown to promote rearrangements of alkynyl cyclopropanols to 2-alkylidenecyclobutanones. Triarylphoshine gold cationic species promoted the rearrangement of a wide range of substrates to *E*-alkene products **160** with high stereoselectivity. The indenyl ruthenium catalyst **161** promotes rearrangement to the sterically less favorable *Z*-alkene. A possible explanation of such an outcome is coordination of ruthenium to the R group in the proposed transitional state **162**, as shown in equation 89.





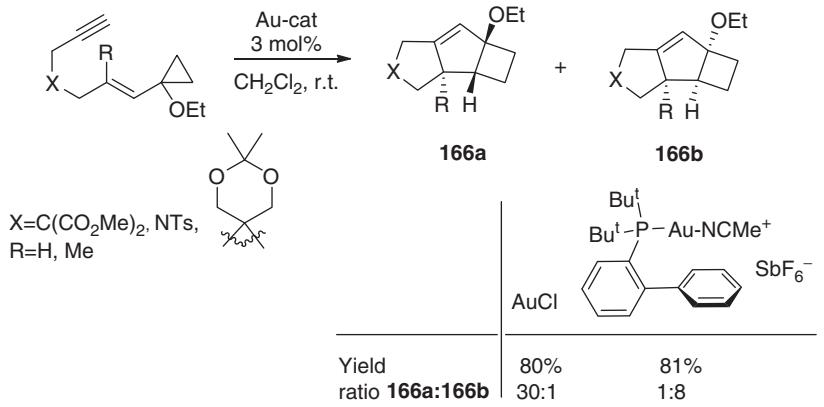
(89)

Toste[341] described enantioselective rearrangements in the presence of the cationic gold catalyst **164**. Allenyl cyclopropanols yielded vinylcyclobutanones under these conditions (equation 90).



(90)

Electrophiles generated from alkynes on addition of gold catalysts were shown to undergo intramolecular annulation to produce [5.5.4] tricyclic systems.[342] The outcome of the reaction can be somewhat controlled by variations in catalysts (equation 91).

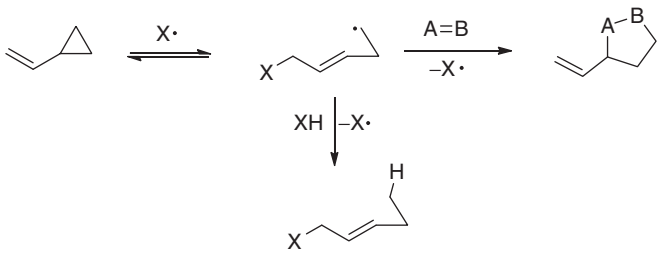


(91)

5.22.1.6.2 Radical reactions and cycloadditions of vinylcyclopropanes

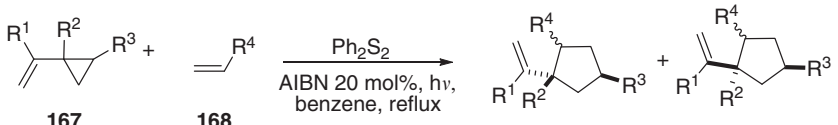
Addition of free-radical species to vinylcyclopropane results either in the abstraction of a hydrogen atom from the cyclopropane or ring opening through the agency of the cyclopropylcarbinyl radical generated on the initial addition.[12]

Radical addition occurs with vinylcyclopropanes containing radical stabilizing group on the cyclopropane ring. There are two general types of reactivity derived from the radical activation of vinylcyclopropanes: the termination of a radical chain by a hydrogen atom source leading to an open-chain product or the addition of an unsaturated fragment A=B in a [3+2] manner leading to cyclic products (Scheme 53). Tin-, sulfur-, and silicon-based radicals add to the vinylcyclopropane system.



Scheme 53

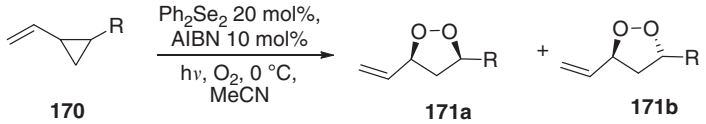
Regioselectivity of radical additions was observed in general and follows the same pattern as metal-catalyzed formal [3+2] cycloadditions. Feldman[343] described radical activation of vinylcyclopropane rings with diphenyldisulfide under thermal and photolytic conditions. A mixture of *syn* and *anti*-isomers was formed. On introduction of an EWG to the cyclopropane ring, preferential formation of the *syn* product **169b** was observed (equation 92).



			Yield
R^1 = Me, R^2 = H, R^3 = CO_2Bu^t, R^4 = OBu^n	3.3	1	94%
$R^{1,2}$ = H, R^3 = OBn, R^4 = CO_2Me	1	1	70%

(92)

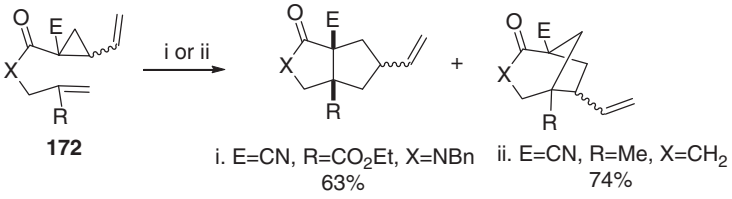
Feldman[344] performed a study on the addition of oxygen to the radical formed from vinylcyclopropanes (equation 93). A mixture of dioxolanes **171** was formed under mild conditions with good regioselectivity in some cases.



			Yield
R = Ph	>10	<1	63%
R = $CO_2CH(CF_3)_2$	<1	>10	65%

(93)

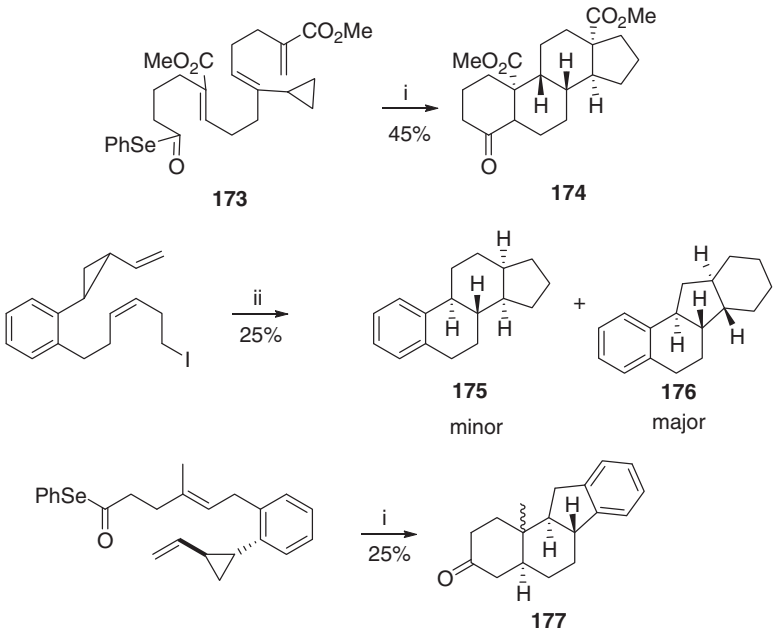
A study of intramolecular cyclizations showed[345] that the regioselectivity can be affected by the electronic configuration of the linker X in compound **172** (Scheme 54); different types of bicyclic systems can be produced starting from the same type of vinylcyclopropane **172**.



i. Ph_2S_2 1 equivalent, hν sunlamp, PhCl, reflux; ii. AIBN cat., benzene, reflux

Scheme 54

Free radical polymerization of substituted vinylcyclopropanes through both 1,2- and 1,5-type additions has also been reported.[346,347] Radical macrocyclization–transannulation in polyene systems containing a vinylcyclopropane moiety provided efficient access to manifolds of polycyclic compounds. Pattenden developed a general approach to diverse analogs of the steroid skeleton. By varying the position of the initial site of radical formation and the position of the vinylcyclopropane moiety in polyene system different types of polycyclic structures could be formed. An unusual type of steroid, **174**,[348] can be formed starting from acyl selenoate **173**. The estrone-type skeleton formation was studied, and conditions were found for the selective formation of **175** and **176**.[349] A similar type of skeleton of C-nor-D-homosteroid **177** was selectively prepared in moderate yield in one step (Scheme 55).[350]



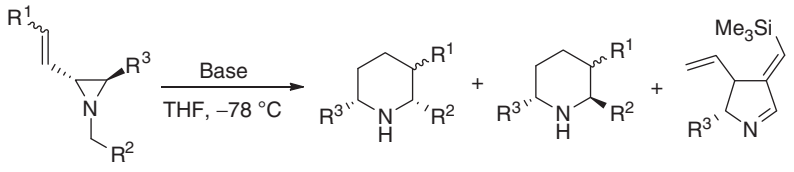
i. Bu_3SnH, AIBN, PhH, Δ; ii. $(Me_3Si)_3H$, AIBN, PhH, Δ

Scheme 55

5.22.1.6.3 [2,3] Rearrangements of vinylaziridines and vinyl epoxides

The first example of an aza-[2,3]-Wittig rearrangement of vinylaziridines was described by Somfai.[351] It was shown that *N*-substituted aziridines with an anion-stabilizing group may be rearranged to piperidines on treatment with base. The best selectivity for formation of *cis*-disubstituted piperidines **179a** was achieved when a carboxylic ester was the stabilizing group and lithium diisopropylamide (LDA) was used as a base (Scheme 56).

Coldham[352] described a similar system that showed the same tendency to produce *cis*-disubstituted piperidines. Vinyl epoxides can be rearranged in a similar [2,3] fashion via oxonium ylides. Only two examples have been published on this rearrangement.[353,354] An oxonium ylide is produced on the attack by the metal carbenoid obtained from the decomposition of a diazo compound (equation 94).

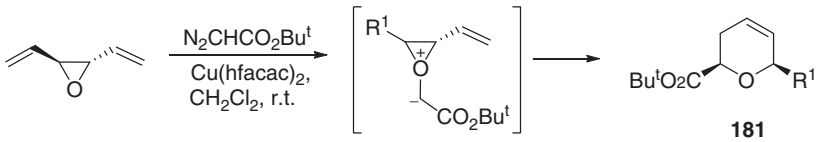


179a **179b** **180**

R^1=H, R^3=Bu^t

178		179a	179b		Yield
LDA	R^2=CO_2Bu^t	Only product	–	–	95%
Bu^{s}Li	R^2= ≡—SiMe$_3$	1.2	1.8	1	95%
KHMDS	R^2=CN	6.6	1	–	80%

Scheme 56

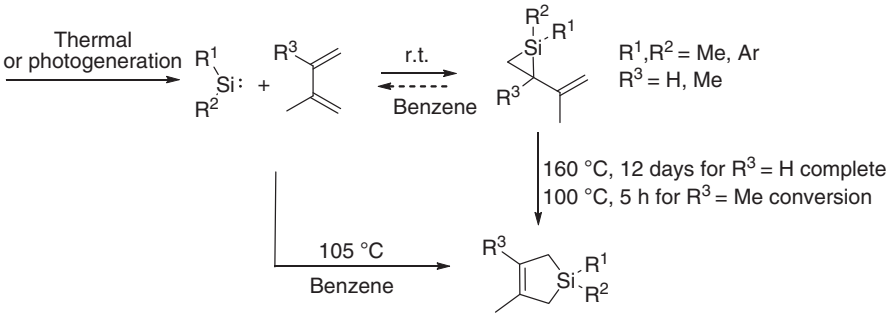


181
70%

(94)

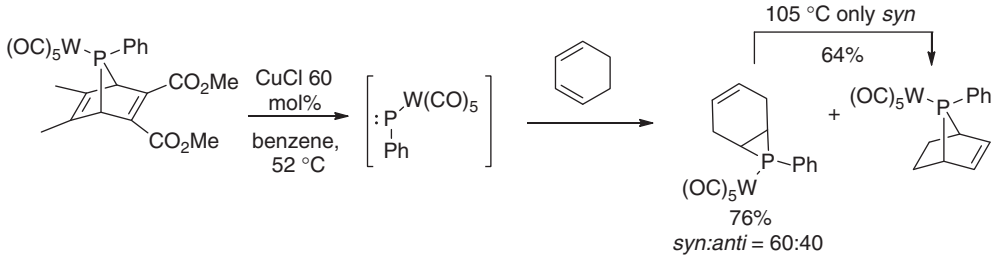
5.22.1.6.4 Rearrangements of silavinylcyclopropanes

Thermal or photochemical[355] generation of silylenes in the presence of 1,4-dienes leads to 3-silolene. Stable vinylsiliranes can be prepared in high yield under mild conditions from bulky silylenes.[356] Such vinylsiliranes can be converted on heating to 3-silolene as shown in Scheme 57. It is unclear whether this reaction proceeds by a mechanism similar to the vinylcyclopropane–cyclopentene rearrangement or by decomposition to silylene and direct [4+1] cycloaddition. Computational studies for silylenes, germylenes, and hypothetical stannylenes have been performed.[357]



Scheme 57

Vinyl phosphirane can be generated via the addition of the corresponding phosphinidene complex to a diene.[358] Rearrangement to the corresponding 3-phospholenes can occur under thermal conditions via a biradical intermediate similar to that in the vinylcyclopropane–cyclopentene rearrangement process, but such a rearrangement can also occur under CuCl catalysis as shown in Scheme 58. In the latter case the process possesses significant concerted features.[359]



Scheme 58

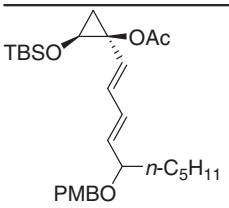
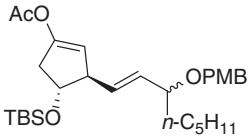
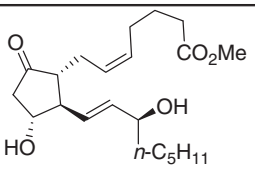
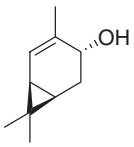
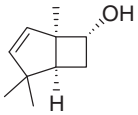
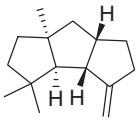
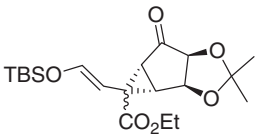
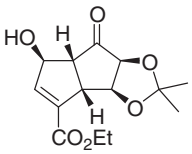
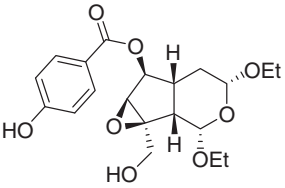
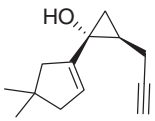
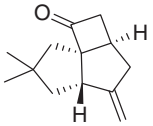
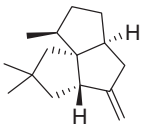
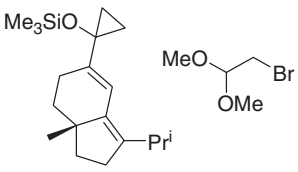
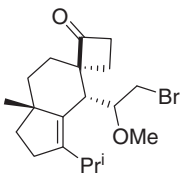
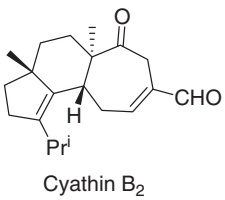
5.22.1.7 Total Syntheses

The vinylcyclopropane–cyclopentene rearrangement and its heterocyclic variants have been featured in a number of general methods of synthesis, most notably those developed by Wenkert, Stevens, Hudlicky, and Wender. Most of these developments were discussed in the first edition of this work published in 1991 or in the review that appeared at the anniversary of Neureiter's discovery.[485]

The list of syntheses performed before 1991 includes the core of prostaglandin by Trost,[360] aphidicolin by Trost,[361] zizaene by Piers,[362] hirsutene by Hudlicky,[363] 11-deoxyprostaglandin E_2 by Salaün,[364] α-vetispirene by Paquette,[365] hinesol by Piers,[366] isocomenic acid, isocomene, and β-isocomene by Hudlicky,[367,368] jasmone and dihydrojasmone by Salaün,[369] coriolin by Wender,[370] spirovetivane by Salaün,[371] silphinine by Wender,[372] dicraenone by Salaun,[373] antheridiogen-an by Corey,[374] epiisocomene by Hudlicky,[375] pentalenene by Hudlicky,[376,377] pentalenic acid by Hudlicky,[377] and retigeranic acid by Hudlicky.[378]

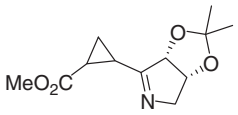
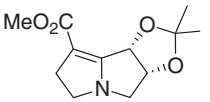
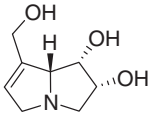
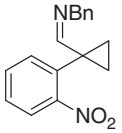
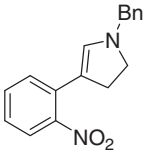
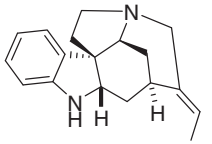
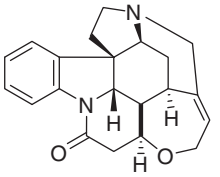
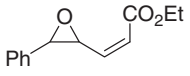
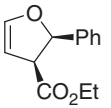
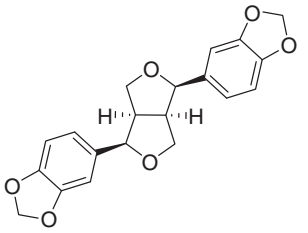
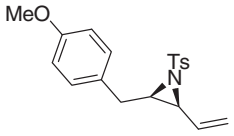
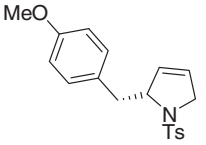
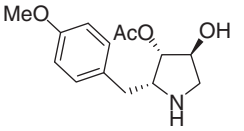
The use of these rearrangements in total synthesis continues and the tables below provide the update in accomplishments since the 1991 version (Tables 12–14).

Table 12 Vinylcyclopropane rearrangement in total synthesis

Starting material (SM)	*Conditions*	*Product*	*Target*	*References*
	Bu_2O, 190 °C		 Prostaglandin E_2 methyl ester	379
	hν, Toluene–petrol ether		 (–) -Δ9 (12)capnellene	380
	Tetra-*n*-butylammonium fluoride (TBAF), THF		 (–)-Specionin	381
	PPh_3AuCl, $AgBF_4$, dichloromethane (CH_2Cl_2)		 Ventricos-7(13)-ene	382
	$TiCl_4$, CH_2Cl_2		 Cyathin B_2	383

Heteroatom-containing analogs of vinylcyclopropanes used in total synthesis before 1991 include mysomine and apoferrosamine by Stevens,[384] mesembrine by Stevens[385] and Keely,[386] shihunine by Breuer,[387] aspidospermine by Stevens,[388] joubertiamine by Stevens,[389] elwesine by Stevens,[390] ^{14}C-nicotine by Comes,[391] sceletium alkaloid A-4 by Stevens,[385c] isoretronecanol and δ-coniceine by Stevens,[392] ipalbidine and septicine by Stevens,[393] supinidine by Hudlicky[271,282] and Pearson,[272] isoretronecanol and traceanthamidine by Hudlicky,[282,284] mitomycin A by Maruyama,[394] dihydroxyheliotridane, hastanecine, and

Table 13 Rearrangements of heteroatom-containing analogs of vinylcyclopropanes in total synthesis

Starting material (SM)	*Conditions*	*Product*	*Target*	*References*
	NH_4Cl, toluene, 140 °C		 (+)-Crotanecine	321
	TMSCl, NaI		 Dehydrotubifoline	322,398
			 Strychnine	
	500 °C, 0.04 mbar		 (±)-Epiasarinin	399
	LiI, MeCN, μwave		 (–)-Anisomycin	287

(*Continued*)

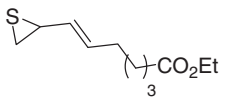
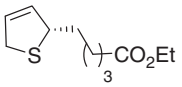
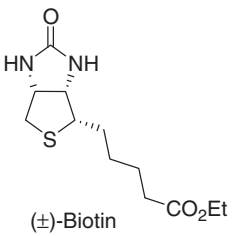
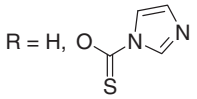
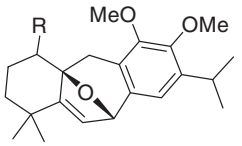
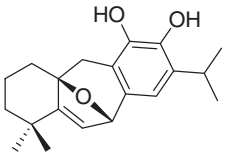
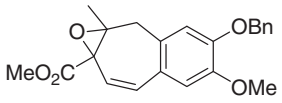
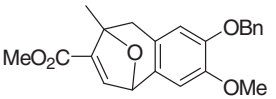
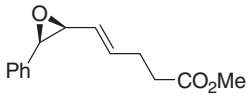
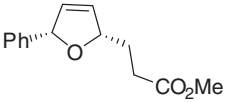
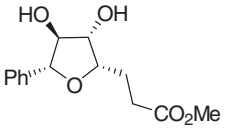
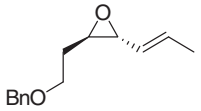
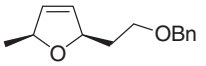
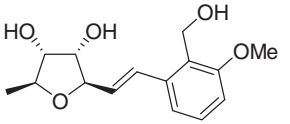
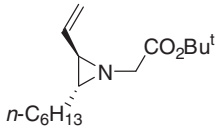
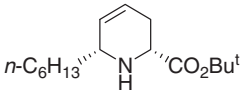
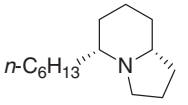
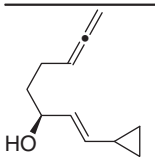
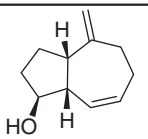
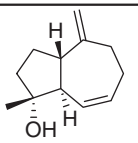
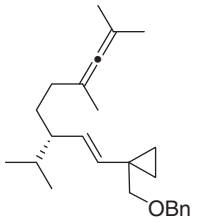
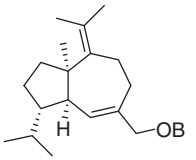
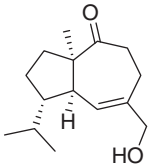
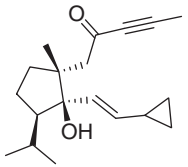
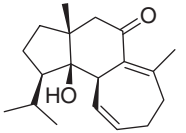
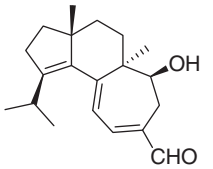
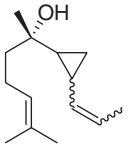
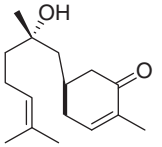
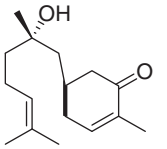
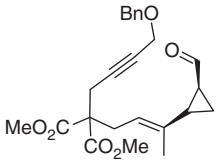
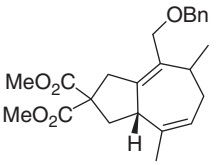
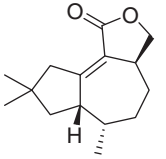
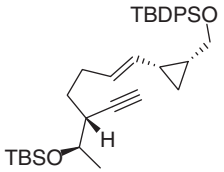
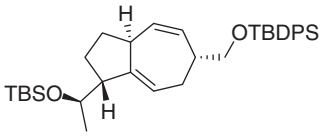
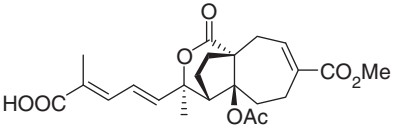
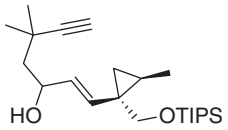
	$Cu(hfacac)_2$, 150 °C		 (±)-Biotin	336
 	TFA		 (±) -Salviasperanol	400,401
	$Cu(hfacac)_2$, 100 °C		 Core of Platensimycin	402
	$Cu(hfacac)_2$, 150 °C		 (+)-Gonithalesdiol	403
	$Cu(hfacac)_2$, 150 °C		 (+)-Varitriol	404
	Lithium diisopropylamide (LDA), THF, −78 °C		 Indolizidine 209D	405

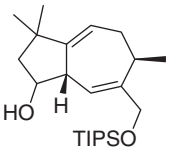
Table 14 Cycloadditions in total synthesis

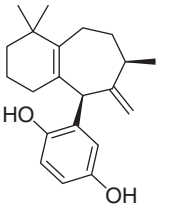
Starting material (SM)	*Conditions*	*Product*	*Target*	*References*
	$[Rh(CO)_2Cl]_2$, toluene, reflux		 (+)-Dictamnol	406
	$[Rh(CO)_2Cl]_2$, toluene, reflux		 (+)-Aphanomol I	407
	$[Rh(CO)_2Cl]_2$, 1,2-dichloroethane (DCE)		 Core of (+)-Allocyathin B_2	408
	Fe(CO)$_5$, *i*-PrOH, hν		 (–)-Delobanone	184
	$[Rh(CO)_2Cl]_2$, toluene, reflux		 Tremulenolide A	409
	$[(C_8H_{10})Rh(COD)]^+$ SbF_6^-, DCE		 (–)-Pseudolaric acid B	410

(*Continued*)



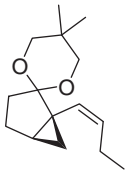
$CpRu(MeCN)_3PF_6$, CH_2Cl_2



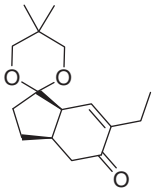


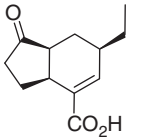
(+)-Frondosin A

411



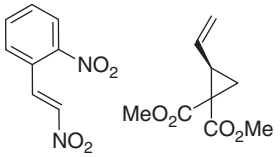
$Fe(CO)_5$, *i*-PrOH, hν



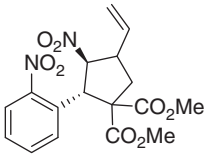


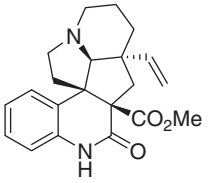
(+)-Coronafacic acid

412



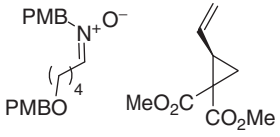
$Pd_2(dba)_3$, dppe, THF



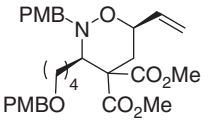


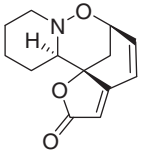
Scandine

413



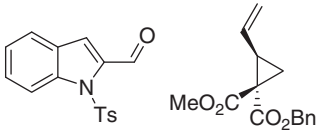
$Yb(OTf)_3$



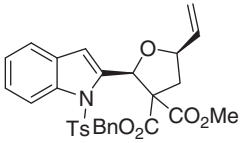


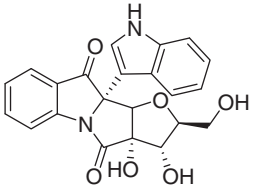
(+)-Phyllantidine

414



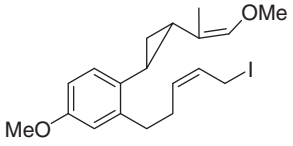
$Sn(OTf)_2$



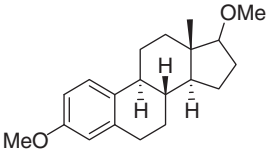


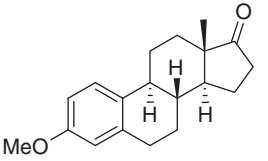
(+)-Isatisine A

415



Bu_3SnH, AIBN





(±)-Estrone

351

trihydroxyheliotridane by Hudlicky,[395,396] eburnamonine by Wenkert,[397a] dehydroaspidospermidine and quebrachamine by Wenkert,[397b] and ipomeamarone by Hudlicky[221] (Tables 13 and 14).

5.22.2 Divinylcyclopropanes

5.22.2.1 Introduction

The facile thermal $\sigma^2s+\pi^2s+\pi^2s$ (Cope) rearrangement of *cis*-1,2-divinylcyclopropane **182** to 1,4-cycloheptadiene **183** was first reported in 1960 by Vogel.[416] In his experiments, Vogel did not isolate **182**, since, under the conditions of its formation (80 °C), **182** rearranges rapidly to **183**. Indeed, it was not until more than a decade later that **182** was isolated and shown to rearrange to **183** with half-lives of approximately 90 s and 25 min at 35 °C[417] and 11 °C,[417,418] respectively.



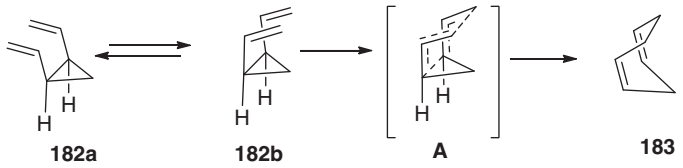
182 **183** **184**

Not unexpectedly, *trans*-1,2-divinylcyclopropane **184** is much more stable than the *cis* isomer **182** and is a readily isolable compound. Nevertheless, at elevated temperatures, for example, 190 °C, **184** undergoes smooth bond reorganization to provide 1,4-cycloheptadiene **183** in essentially quantitative yield.[416a,c] Thus, at the time the Cope rearrangement of 1,2-divinylcyclopropane systems was discovered,[416] it was already clear that both *cis* and *trans* isomers could, in principle, serve as suitable substrates for the reaction. As it turns out, this is an important reaction characteristic, since, in most cases, it makes unnecessary the stereoselective preparation of either the *cis* or *trans* starting material. Since 1960, the thermolysis of 1,2-divinylcyclopropanes has been studied quite extensively to from a mechanistic point of view. However, particularly since 1975, synthetic applications of the rearrangement reaction have been explored, and these studies have shown that the reaction provides a versatile, effective method for the construction of functionalized mono-, bi-, and tricyclic substances.[21,419] In this section, the mechanistic features of the rearrangement will be outlined briefly. The major portion of the discussion will deal with synthetic aspects of this interesting process.

5.22.2.2 Mechanistic Considerations

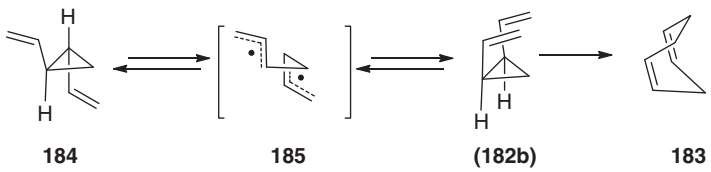
5.22.2.2.1 Rearrangement pathways

It appears to be well accepted that the thermal rearrangement of *cis*-1,2-divinylcyclopropane **182** proceeds in a concerted fashion via a boat-like transition state, in which the vinyl groups lie over the three-membered ring.[10,420,421] Thus, conformational orientation of **182** as shown in **182b** (equation 95), followed by bond reorganization by way of a transition state represented by **A**, provides 1,4-cycloheptadiene **183**, in which both double bonds have *cis* stereochemistry. Concerted rearrangement of **182** via a chair-like transition state derived directly from conformation **182a** would lead to the highly strained *trans,trans*-1,4-cycloheptadiene, and it is clear that such a pathway would be of a much higher energy than that involved in the conversion of **182b**, via (**A**), into **183**.



182a **182b** **A** **183** (95)

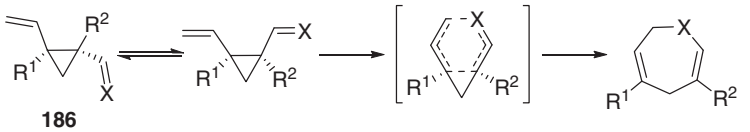
The thermolytic transformation of *trans*-1,2-divinylcyclopropane **184** into 1,4-cycloheptadiene **183** probably proceeds via the pathway shown in equation 96. Homolytic cleavage of the cyclopropane ring of **184** provides the resonance stabilized diradical **185**, which, in addition to reverting to **184**, can undergo bond rotation and subsequent ring closure to give *cis*-1,2-divinylcyclopropane **182**. The latter substance then rearranges, by way of conformation **182b**, into **183**.



184 **185** **(182b)** **183** (96)

The energy of activation E_a for the overall conversion of **184** into **183** has been reported[421,422] to be in the range 32.1–34.3 kcal mol^{-1} (1 kcal≈4.2 kJ). In comparison, the data reported by Brown et al.[417] and Schneider and Rau[423] show that E_a for the rearrangement of **182** to **183** is approximately 19–20 kcal mol^{-1}. Thus, for the conversion of **184** into **183**, the rate-determining step is the isomerization of **184** into **182**, presumably via the diradical **185**. This characteristic is common to most of the known rearrangements of 1,2-divinylcyclopropane systems. That is, for a given pair of isomers, *trans* to *cis* isomerization is generally slower than Cope rearrangement of the *cis* isomer. However, it must be noted that there are exceptions to this generalization, since thermolysis of certain substituted *cis*-1,2-divinylcyclopropanes results only in *cis-trans* isomerization and not in sigmatropic rearrangement (*vide infra*).

The mechanism of rearrangement has been studied by DFT methods. Fabian[424] explored systems containing a heteroatom in the double bond **186**. The activation barrier calculated for the known vinylcyclopropane carbaldehyde–dihydrooxepin rearrangement corresponded well with known data, 23.4 and 23 kcal mol^{-1}, respectively. The barrier for rearrangement of *cis*-divinylcyclopropane, a strongly exothermic reaction, was calculated at 18.8 kcal mol^{-1}. This result corresponds with experimental evidence that *cis*-divinylcyclopropane rearranges below room temperature. Substituents such as OH and CHO lower the activation barrier for rearrangement (equation 97).

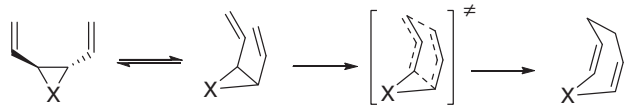


186

X = CH_2, O, S, NH
$R^{1,2}$ = H, OH, CHO

(97)

For systems **187** Zora calculated the barrier of rearrangement and nuclear independent chemical shifts (NICS) for the all-carbon skeleton[425] and for heterocyclic analogs.[426] It was shown that the activation barrier decreases in the series $CH_2 < NH < O < PH < S$, which can be justified by decreasing ring strain of the parent three-membered compounds (equation 98).



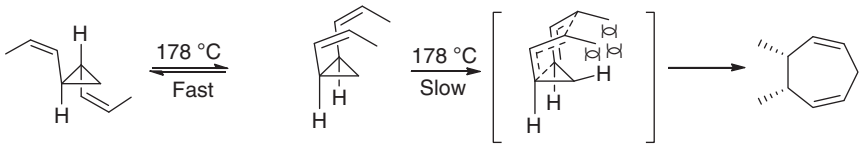
187

X = CH_2, O, NH, NMe, NEt, PH, S

(98)

5.22.2.2.2 Substituent effects

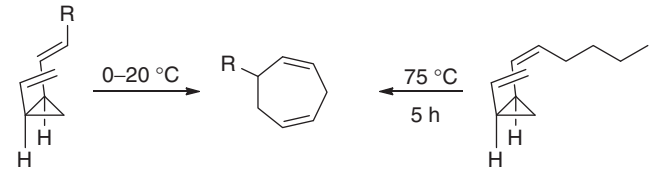
Substituents attached to the terminal carbons of the vinyl groups can have a profound effect on the rate of the Cope rearrangement of *cis*-1,2-divinylcyclopropane systems, Schneider and Rau[423] showed that the *cis,cis,cis* substrate **187** undergoes reversible *cis-trans* isomerization, **188** to **187**, much faster than it undergoes Cope rearrangement to **189** (Scheme 59). In a related study, Baldwin and Ullenius[427] reported that, at 165 °C, the **188**:**187** ratio at equilibrium is approximately 1:4. Furthermore, heating **187** at 178 °C for 4.2 h or 75 h gives, in addition to an equilibrium mixture of **188** and **187**, minor (4%) or significant (35%) amounts of the Cope rearrangement product **189**. Thus, although the sigmatropic bond reorganization of **188** is not precluded, the steric interactions present in the transition state (**E**; Scheme 59) make this a higher energy pathway than the isomerization of **188** to **187**.



187 **188** **E** **189**

Scheme 59

Other studies have also qualitatively demonstrated the effect of substitution patterns on the ease of *cis*-divinylcyclopropane rearrangements. For example, at temperatures in the range 0–20 °C, the substrates **190**–**192** are readily transformed into the cycloheptadienes **193**–**195**, respectively (Scheme 60).[428–430] The rearrangement of **192** to **195** occurs with a half-life of approximately 50 min at 15 °C[430] and is thus marginally slower than the thermal conversion of the parent *cis*- 1,2-divinylcyclopropane **182** into 1,4-cycloheptadiene **183** (Section 5.22.2.1).[417,419] However, complete transformation of **196** into **193** requires heating at 75 °C for 5 h (Scheme 60),[428] again demonstrating the notable rate-retarding effect of a *cis*-substituent.



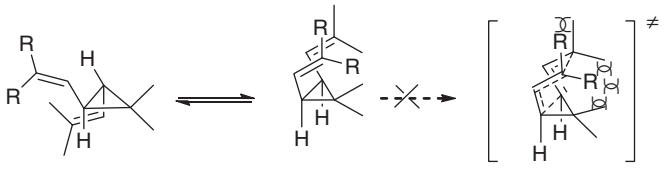
190 R = Bu^n
191 R = (*E*)-1-butenyl
192 R = (*Z*)-1-butenyl

193 R = Bu^n
194 R = (*E*)-1-butenyl
195 R = (*Z*)-1-butenyl

196

Scheme 60

The highly substituted *cis*-divinylcyclopropanes **199** and **200** do not undergo sigmatropic rearrangement at all.[431] Apparently, the highly sterically congested nature of the transition states (**F**) precludes this possibility. Thermolysis of **199** and **200** at 170–180 °C produces only equilibrium mixtures of these substances and the corresponding *trans* isomers **197** and **198**, respectively (Scheme 61).[431]



197 R = H (75%)
198 R = Me (72%)

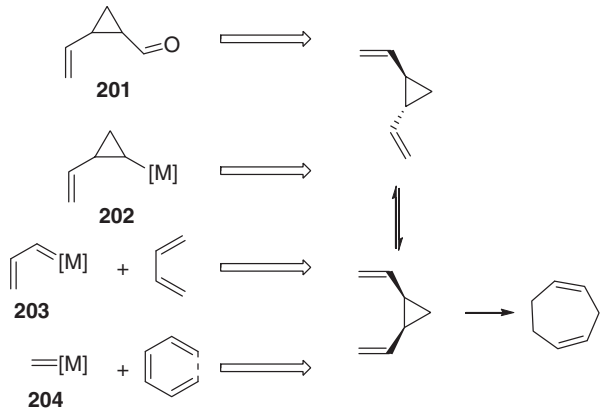
199 R = H (25%)
200 R = Me (28%)

F R = H or Me

Scheme 61

5.22.2.2.3 Guide to preparation

There are a variety of methods for generating divinylcyclopropanes. Some are analogous to those used for the preparation of vinylcyclopropanes (*vide supra*). The following methods are unique to divinylcyclopropane systems, in particular *cis*-divinylcyclopropane systems. Some general approaches are presented in Scheme 62.

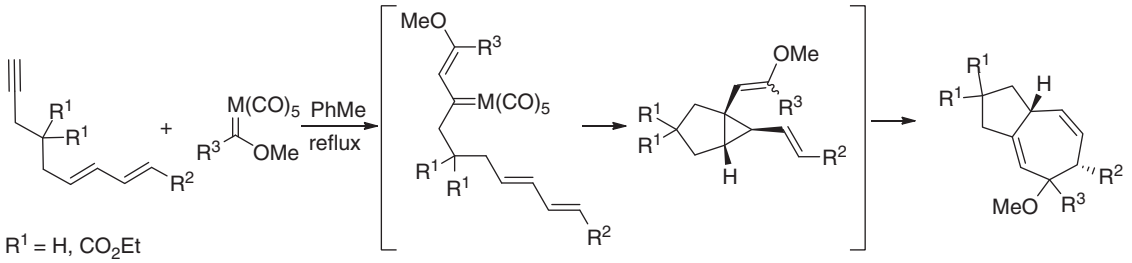


Scheme 62

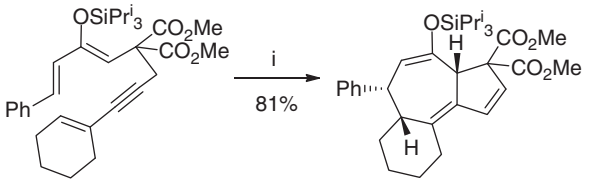
Olefination of cyclopropyl aldehydes of general type **201**[432–434] provided access to a variety of substituted divinylclyclopropanes. Addition of cyclopropyl-containing organometallic reagents of general type **202** to appropriate electrophiles provided yet another means of access to the divinylcyclopropane core. These reagents include Cu,[435] Zn,[436] Zr,[437], and Li[438,439] derivatives.

One of the most developed and general modern methods involves the addition of vinyl carbenoids of type **203** to a diene system. Early examples of use of such carbenoids include addition of Fischer-type carbenes of VI group metals. Harvey[440] utilized insertion of these to alkynes. The vinylcarbenoid **205** formed in this way undergoes intramolecular cyclopropanation to the diene, which in turn rearranges to the cycloheptadiene system **206**. The reaction proceeds in moderate yields in both electron-neutral and electron-poor diene systems (Scheme 63).

A similar approach was utilized by the group of Iwasawa.[441] Insertion of a tungsten complex into the enyne led to the formation of a vinyl carbenoid, which was subjected to cyclopropanation and rearrangement as shown in equation 99.



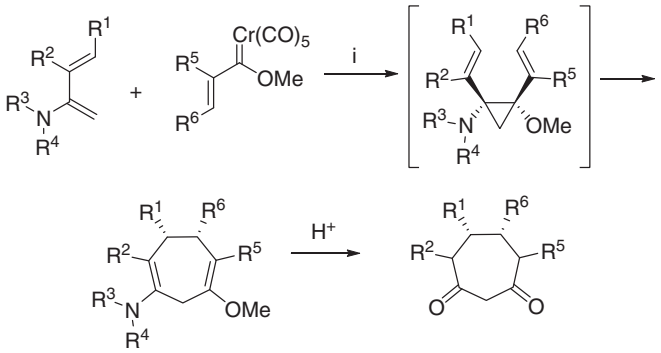
Scheme 63



(99)

i. 5 mol% $W(CO)_6$ 5 mol%, Et_3N 10 mol%, hν, 4 Å sieves, PhMe, r.t.

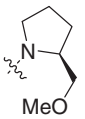
The addition of chromium carbene complexes to electron-rich dienes was studied by Barluenga.[442] The reaction occurred under mild conditions and provided *cis*-divinylcyclopropanes with complete regio- and stereoselectivity. In some cases, the reaction required heating to 60 °C, and some *trans*-product was observed. Studies of reactions in the presence of chiral proline-based auxiliaries showed significant enantioinduction[442b,c] (**Scheme 64**, **Table 15**). Barluenga described similar reactivity for 2-azadiene systems,[443] with preferential insertion into the C=N bond.



i. MeCN, 25 °C or THF, 60 °C

Scheme 64

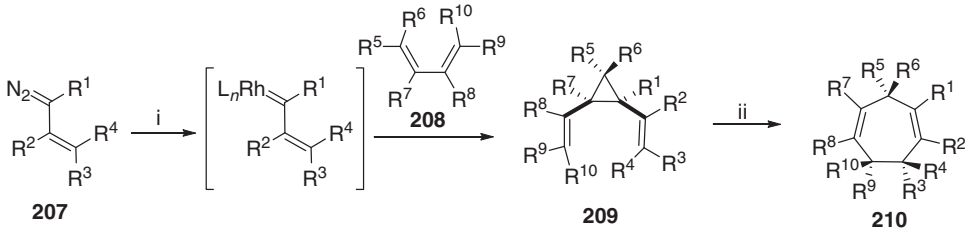
Table 15 Selected examples of addition of chromium carbenes to diene systems

R^1, R^2	R^3, R^4	R^5, R^6	*Yield (%) (*ee[a]*)*
CH_2OH, Me	NR^3R^4=	H, Ph	65 , (95)
			
CH_2OMe, Me	Me, Ph	H, 2-furyl	82

[a]For chiral auxiliaries.

One of the most convenient methods for generating such carbenoids is by the decomposition of diazo compounds of type **207** in the presence of metal catalysts such as salts of rhodium and copper. The rhodium-based approach developed and studied by Davies has been the subject of several reviews.[83,84,444–447]

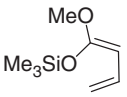
The advantage of this method is that it proceeds with high levels of stereoselectivity and the major product is a *cis*-divinylcyclopropane **209**, which can undergo direct rearrangement to the cycloheptatriene skeleton (Scheme 65, Table 16). The regioselectivity of carbenoid insertion into acyclic dienes can be controlled somewhat by changing the substitution pattern. Preferential cyclopropanation occurred on the least substituted double bond. The reaction can be selectively performed on a *cis*-alkene in presence of the *trans* isomer. Better control can be achieved by substitution with electron-rich functionalities.



i. RhL, solvent; ii. Δ

Scheme 65

Table 16 Selected examples of addition of rhodium carbenes to diene systems

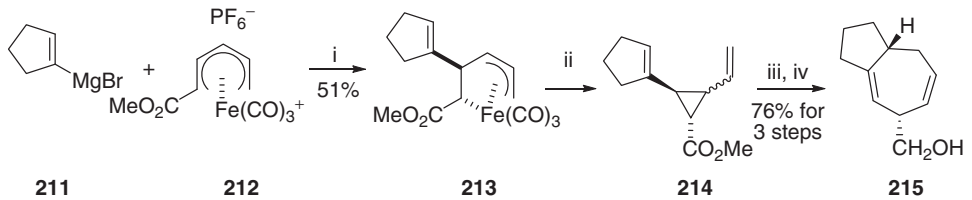
R¹, R², R³, R⁴	***208***	*RhL, solvent*	*Yield (%) (ee[a])*
Me, H, H, H		$Rh_2(OPiv)_4$ pentane	90
Me, H, H, CH=CHPh		$Rh_2(OAc)_4$, CH_2Cl_2	80
Et, H, H, CO_2Et		$Rh_2(OAc)_4$, CH_2Cl_2	92
Et, H, H, Ph		Rh_2(S-DOSP)$_4$, pentane	52 (98)

[a]For chiral version of the transformation.

In most cases, divinylcyclopropanes are transient species and cannot be isolated. Under the reaction conditions they tend to undergo subsequent transformation to cycloheptadienes **210**; however, sterically congested divinylcyclopropanes can sometimes be isolated.

A wide range of substrates has been studied. Cyclic dienes[448], furans,[449] pyrroles[450] have been used; these open access to functionalized bicyclic systems including biologically active tropanes. The addition of metal carbenoids to an aromatic ring with disruption of aromaticity (Büchner reaction) leads to bicyclic norcaradiene structures.[445,451] The reaction also proceeds under copper/rhodium catalysis from diazo compounds. In most cases the intermediate divinylcyclopropanes undergo immediate rearrangement to the corresponding cycloheptatriene system.

Less common methods of preparation of divinylcyclopropanes include oxidative cyclization of allyl iron complexes. Donaldson[452] discovered that vinyl Grignard reagents **211** can be stereoselectively added to a cationic iron complex such as **212**. The product of such reaction, namely **213**, can be oxidized by one-electron oxidants such as cerium ammonium nitrate (CAN) or H_2O_2. Oxidation of the complex leads to decomplexation of iron and rearrangement to *cis*-divinylcyclopropane **214**. After reduction of the ester, this compound undergoes the rearrangement to cycloheptadiene **215** (Scheme 66).

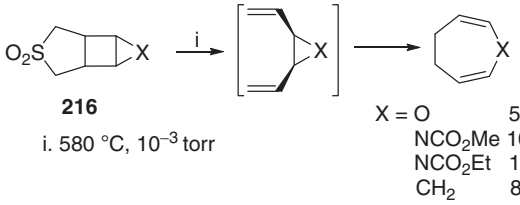


211 **212** **213** **214** **215**

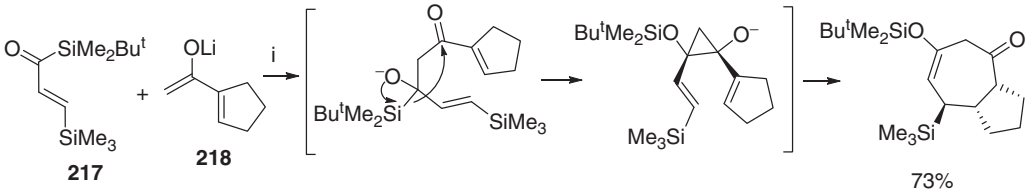
i. DCM, –78 °C; ii. H_2O_2, MeCN, r.t.; iii. $LiAlH_4$, THF; iv. mesitylene, reflux

Scheme 66

Extrusion of SO_2 from tricyclic sulfolanes **216** was explored by Aitken.[453] Fused tricyclic sulfolanes produced the corresponding 7-membered-ring compounds up on FVP in moderate to good yields via formation of *cis*-divinylcyclopropanes (equation 100). Acyl-silanes of general type **217** undergo sequential Brook/Cope rearrangement on addition of dienolates **218** (Scheme 67) as was described by Takeda.[454,455] Matsubara reported that vinylic 1,2-diketones **219** can be transformed into *cis*-divinylcyclopropanes with Zn carbenoids.[456] The reaction proceeded with high stereoselectivity, and the transient divinyl species **167** underwent smooth rearrangements to cycloheptane diketone **221** (Scheme 68). Stephenson[457] studied the utility of a photoredox catalyst in the reaction of cyclopropyl-centered radicals with alkynes. It was shown that radicals are formed under mild conditions and undergo an addition–Cope rearrangement sequence with good yield. The scope of substrates was somewhat limited as only propargylic amides **170** were found to participate in such reactions (equation 101).

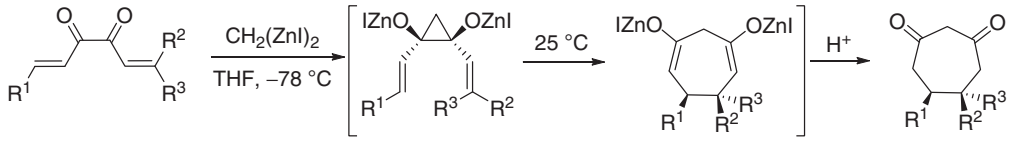


(100)



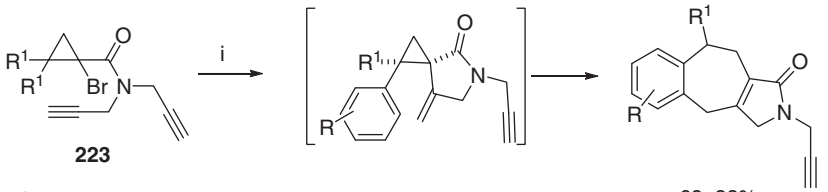
i. THF –80 °C to –30 °C

Scheme 67



R^1 = aryl, Me
$R^{2,3}$ = aryl, Me, H

Scheme 68



(101)

R^1= Ph, 3-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 2-FC_6H_4,

69–88%

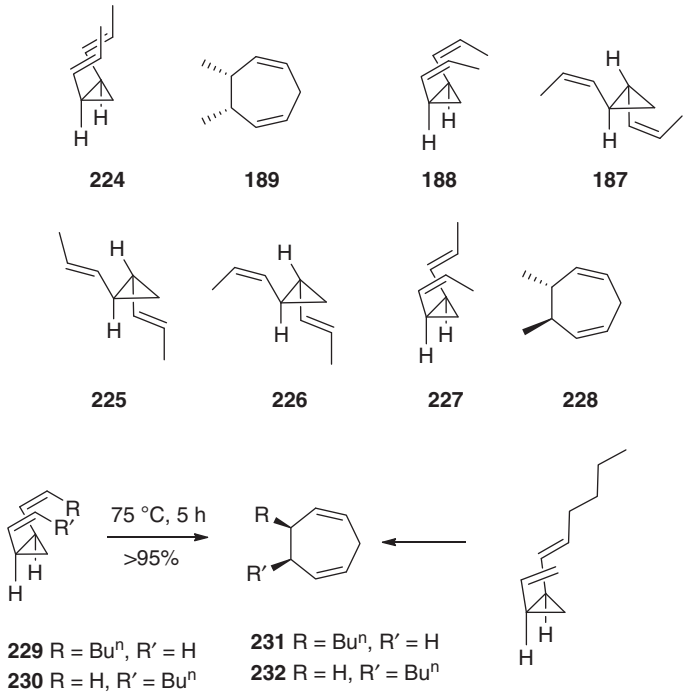
i. 1 mol% Ir(2-pyridin-2-ylphenyl)$_2$(4,4′-di-*tert*-butyl-2,2′-bipyridine) PF_6, Et_3N, DMF, visible light

5.22.2.3 Monocyclic Divinylcyclopropanes

5.22.2.3.1 Stereospecificity

Rearrangement of **224** from –10 to 30 °C provides quantitatively *cis*-6,7-dimethyl 1,4-cycloheptadiene **189**.[423] Furthermore, prolonged heating of **188** at 178 °C produces, in addition to the *trans* isomer **187**, the same sigmatropic rearrangement product

(**189**; Scheme 69).[427] Other studies have shown that thermolyses (178 °C, 4.2 h) of substrates **225** and **226** give, in quantitative yields, the epimeric cycloheptadienes **189** and **228**, respectively.[427] Presumably, these transformations proceed by way of the corresponding *cis*-1,2-di(1-propenyl)cyclopropanes **224** and **227**.[427]



Scheme 69

Collectively, the results summarized above show that, with respect to the stereochemistry of appropriately substituted vinyl groups, the (reversible) *trans* to *cis* isomerization (e.g., **187** to **188**; **224** to **225**; **226** to **227**) and the sigmatropic rearrangement of the *cis*-1,2-divinylcyclopropane systems (e.g., **224** or **188** to **189**; **225** to **228**) are completely stereospecific. In connection with carrying out stereoselective syntheses, the importance of this reaction characteristic is obvious. Indeed, the stereospecific nature of the Cope rearrangement of 1,2-divinylcyclopropanes has been demonstrated with substrates that are structurally more complex than those discussed above. Specific examples will be presented later in this chapter (see Sections 5.22.2.3–5.22.2.6).

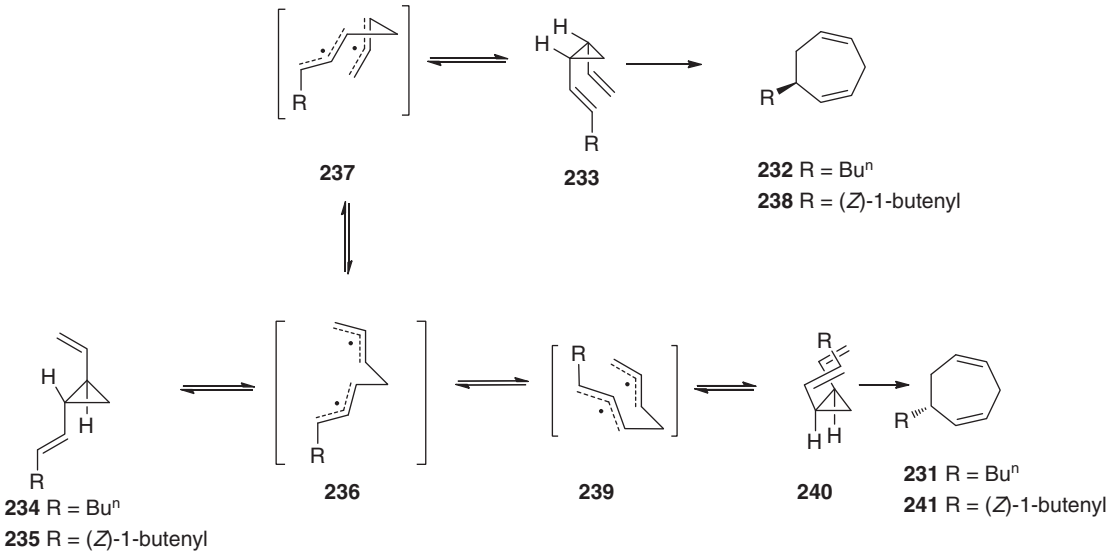
5.22.2.3.2 Enantiospecificity

Relatively little work has been done in this area. In studies related to the total synthesis of the marine natural product (*R*)-(−)-dictyopterene C′ (**231**), Jaenicke and coworkers[458] showed that the enantiomerically pure substrates **229** and **230** rearrange cleanly to the corresponding enantiomerically pure products **231** and **232**, respectively (Scheme 69). Nonnatural (*S*)-(+)-dictyopterene C′ (**232**) is also obtained by rearrangement of (1*R*,2*S*)-1-[(*E*)-1-hexenyl]-2-vinylcyclopropane (Scheme 69).[459] These results show, not unexpectedly, that the Cope rearrangements of rather simply substituted *cis*-divinylcyclopropanes are enantiospecific.

With monocyclic *trans*-1,2-divinylcyclopropanes, chirality transfer is, apparently, poor. Thermolysis of (+)-dictyopterene A (**234**) at 165 °C for 48 h and of (−)-dictyopterene B (**235**) at 103–108 °C for 40 h gives, in each case, a mixture of the two enantiomeric Cope rearrangement products, **231**, **232** and **238**, **241**, respectively (Scheme 70).[460] Although the uncertainty associated with the optical purities and (or) rotations of the various substances involved[458,460] made a quantitative determination of the product ratios difficult, it is evident from the results that enantiomers **232** and **238** predominated marginally over **231** and **241**, respectively. This observation has been rationalized[461] by postulating that, in the intermediate diradical **236**, the allyl system rotates more rapidly, to give **237**, than the more bulky heptenyl or heptadienyl groups, to produce **239**. Ring closure of **237** and **239**, followed by bond reorganization of the (enantiomeric) *cis*-divinylcyclopropanes **233** and **240**, produces the final products.

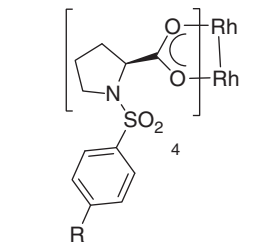
Although further work in this area is desirable, it appears that in the Cope rearrangement of simple *trans*-divinylcyclopropanes, such as **234** and **235**, enantioselectivity is poor. Despite the biradical character of the rearrangement, transfer of chirality can sometimes occur in more complex substrates, such as polycyclic systems.

The enantioselective generation of divinylcyclopropanes is of utmost importance. Because of the concerted nature of the rearrangement, enantioselective cyclopropanation leads to chiral products, according to the well-studied transition state. Davies has expanded the scope of the insertion of vinyl carbenoids to an asymmetric version. Chiral auxiliaries have been utilized[462] with some success, but the diastereomeric excess of products was not high (30%).



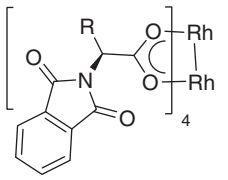
Scheme 70

Later investigations focused on chiral rhodium catalysts. The use of amino acid-based rhodium dinuclear ligands such as **242** and **243** led to impressive levels of enantio- and regiocontrol. Low temperatures and nonpolar solvents such as pentane and toluene were required.



R = Bu^t Rh_2(S-TBSP)$_4$
R = $C_{12}H_{25}^n$ Rh_2(S-DOSP)$_4$

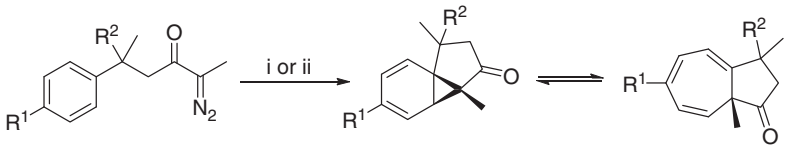
242



R = adamantyl Rh_2(S-PTAD)$_4$
R = Bu^t Rh_2(S-PTTL)$_4$

243

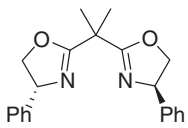
Maguire studied the enantioselective copper-catalyzed Büchner reactions.[463] Bis-oxazoline ligands **244** showed good enantioselectivity and yields for an intramolecular version of the Büchner cyclopropanation (equation 102).



i. $CuPF_6$ 5 mol%, **244** 6 mol%, CH_2Cl_2, reflux
ii. CuCl-$NaBAr_F$ 5 mol%, **244** 6 mol%, CH_2Cl_2, reflux

62–97% *ee* 56–95%
46–57% *ee* 72–80%

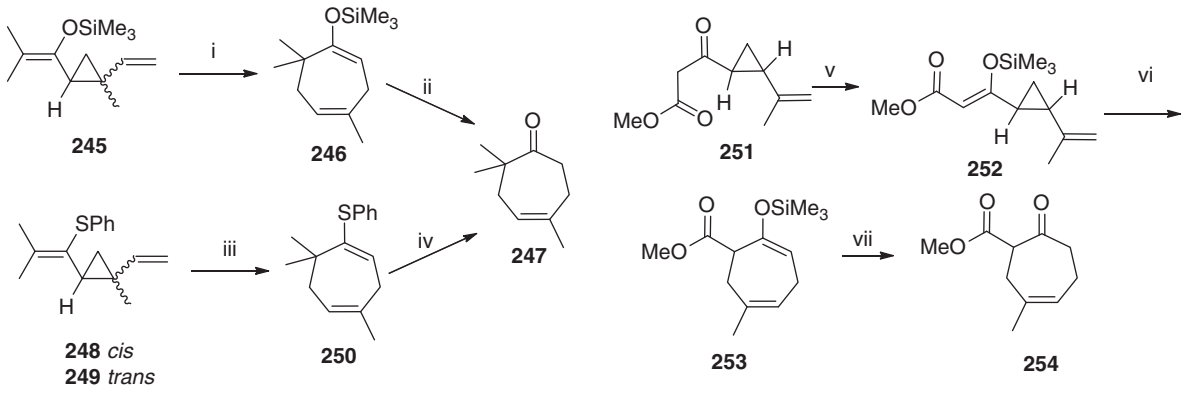
(102)



244

5.22.2.3.3 Synthesis of functionalized cycloheptanes

The use of the Cope rearrangement of 1,2-divinylcyclopropanes for the synthesis of functionalized seven-membered rings has been illustrated in a number of studies. For example, thermolysis of **245** (mixture of *cis* and *trans* isomers), followed by cleavage of the enol silyl ether function in the resultant product **246** provides the natural product karahanaenone (**247**; Scheme 71).[438a] In this

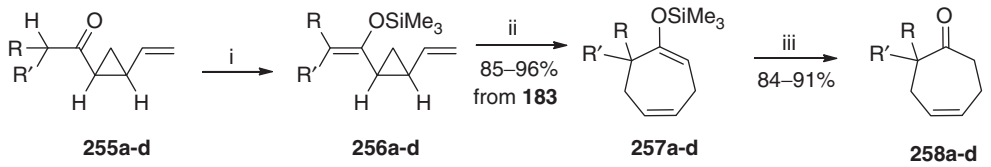


i. 165–175 °C, PhH; ii. Bu^{n}Li, THF; iii. *cis*, 25 °C; *trans*, 160 °C (70%); iv. $HgCl_2$, H_2O-MeCN (45%); v. Me_3SiCl, Et_3N, Et_2O (100%); vi. 210 °C, PhH (96%); vii. KF, MeOH (95%)

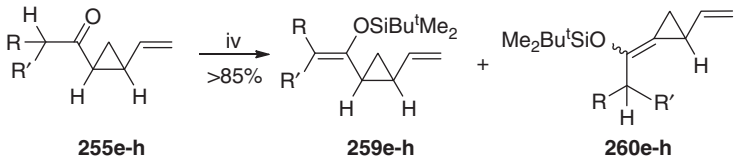
Scheme 71

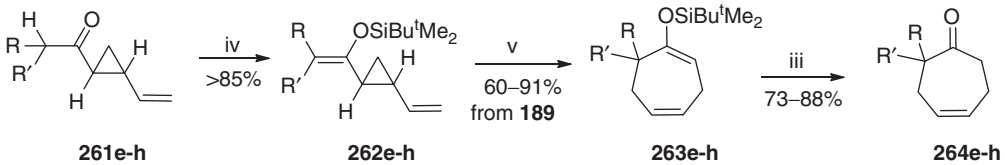
case, as in many others, the fact that **245** was not stereochemically homogenous was of no consequence, since both isomers of **245** cleanly afford the same rearrangement product. Similarly, sigmatropic rearrangement of the isomers **248** and **249** and subsequent hydrolysis of the resultant vinyl sulfide **250** also produces karahanaenone (**247**).[464] The efficient conversion of substrate **251** into the keto ester **254** via a route in which the Cope rearrangement of **252** played a key role has been reported.[465]

In an investigation related to the synthesis of substituted 4-cyclohepten-1-ones,[466] the stereochemically homogenous *cis*-2-vinylcyclopropyl ketones **255a–255d** were converted cleanly into the enol silyl ethers **256** (**Scheme 72**). Thermolysis of the latter substances, followed by acid hydrolysis of the resultant products **257**, gives excellent yields of the ketones **258a–258d**. Interestingly, however, kinetic deprotonation of each of the *cis*-ketones **255e–255h** is not regioselective. Treatment of these substrates with LDA–TBSCl provides mixtures of the enol silyl ethers **259** and **260**, in ratios varying from 4:1 (substrate **255g**) to 1:9 (substrate **255f**). Fortunately, the *trans*-ketones **262e–262h** give synthetically more satisfactory results, since these substances can be converted chemoselectively into the *trans*-divinylcyclopropanes **263**. As expected, Cope rearrangements of compounds **262** require temperatures considerably higher than those employed for the conversion of **256** into **257**. However, the reactions are clean and the products **264**, obtained in good to excellent yields, are readily hydrolyzed to the ketones **258e–258h**.



a: R = Bu^n, R′ = H; **b**: R = Ph, R′ = H; **c**: R, R′ = $(CH_2)_3$; **d**: R, R′ = $(CH_2)_4$



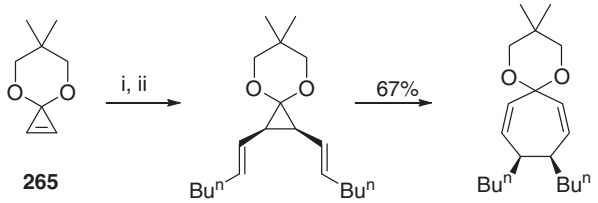


e: R, R′ = $(CH_2)_5$; **f**: R, R′ = $CH_2CMe_2(CH_2)_3$; **g**: R, R′ = $(CH_2)_6$; **h**: R = Bu^t, R′ = H

i. LDA, THF; Me_3SiCl, Et_3N; ii. 100–110 °C, 30 min; iii. HCl, H_2O, MeOH; iv. LDA, THF; Bu^{t}Me$_2$SiCl, HMPA; v. 230 °C, 30–60 min

Scheme 72

In a study of Nakamura, an interesting application of the chemistry of the cyclopropenone acetal **265** was achieved (equation 103).[437] Although this conversion was the only reported example of this novel process, it seems likely that the use of other functionalized and (or) stereochemically modified reagents would provide efficient syntheses of a wide variety of interestingly substituted seven-membered rings.



(103)

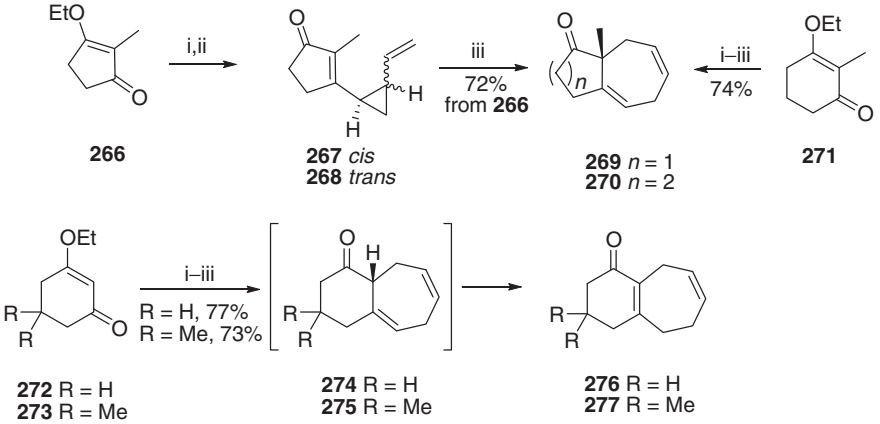
i. $(Bu^n\!\!\sim\!\!\sim)_2CuLi$, THF $-Et_2O$, -70 °C; ii. $Bu^n\!\!\sim\!\!\sim I$, $(PPh_3)_4Pd$, -70 °C to >r.t.

5.22.2.4 β-(2-Vinylcyclopropyl)-α,β-Unsaturated Ketones

5.22.2.4.1 Synthesis of functionalized bicyclo[5.n.0]alkanes and related substances

The Cope rearrangement of 1,2-divinylcyclopropane systems in which one of the vinyl groups is part of an *α,β*-unsaturated ketone moiety has found considerable use in synthesis. A significant number of substrates have been prepared and subjected to thermal rearrangement and some of the products have been employed effectively for natural product syntheses.

The reaction of 2-vinylcyclopropyllithium reagents with *β*-alkoxy enones has served well as a method for preparing *β*-(2-vinylcyclopropyl) enones.[438,439] For example, treatment of **266** with a mixture of *cis*-and *trans*-2-vinylcyclopropyllithium, followed by mild acid hydrolysis of the resultant products, provides the epimeric divinylcyclopropanes **267** and **268** (Scheme 73).[439a] Although **267** rearranges slowly at room temperature, the *trans* substrate **268** requires, as expected, elevated temperatures for rearrangement. Indeed, heating of the mixture of **267** and **268** at 170–180 °C provides **269** cleanly and efficiently.[439a] Thus, not unexpectedly, the stereoselective preparation of the requisite divinylcyclopropane substrates is unnecessary, since both **267** and **268** are readily converted into the same product **269**. In a similar fashion, the enones **271–273** are smoothly transformed into the rearrangement products **270**, **276** and **277**, respectively.[439a] Under the rearrangement reaction conditions, the primary products **274** and **275**, derived from **272** and **273**, undergo isomerization to the more stable enones **276** and **277**, respectively.

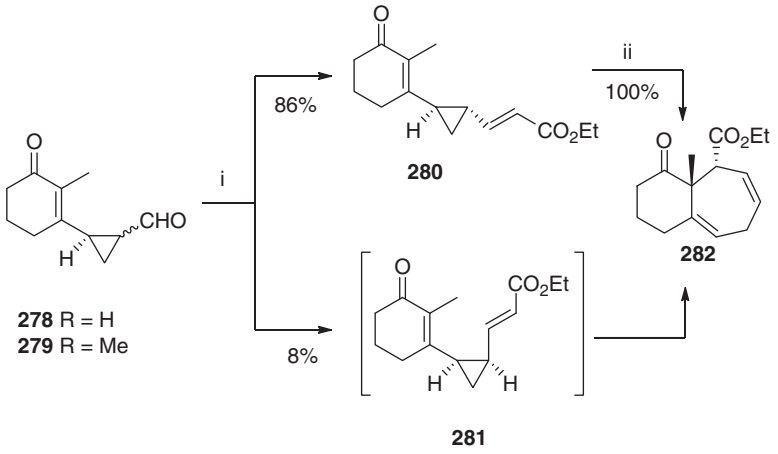


i. 7:3 mixture of *cis*- and *trans*-2-vinylcyclopropyllithium, Et_2O; ii. HCl, H_2O; iii. 170–180 °C, PhH

Scheme 73

Chemoselective Wittig reactions on keto aldehydes, such as **278** and **279**, also provide substrates suitable for sigmatropic rearrangement.[432,433] For example, treatment of **279** (mixture of epimers) with $Ph_3P{=}CHCO_2Et$ provides the *trans*-divinylcyclopropane **280** (86%) and the keto ester **282** (8%), the latter being derived from room temperature Cope rearrangement of the initially formed intermediate **281** (Scheme 74).[433] Thermolysis of **280** produces **282** quantitatively. The efficient conversions of **280** and **281** into the stereochemically homogenous keto ester **282** again illustrates the highly stereoselective nature of the sigmatropic rearrangement of *cis*- and *trans*-1,2-divinylcyclopropane systems.

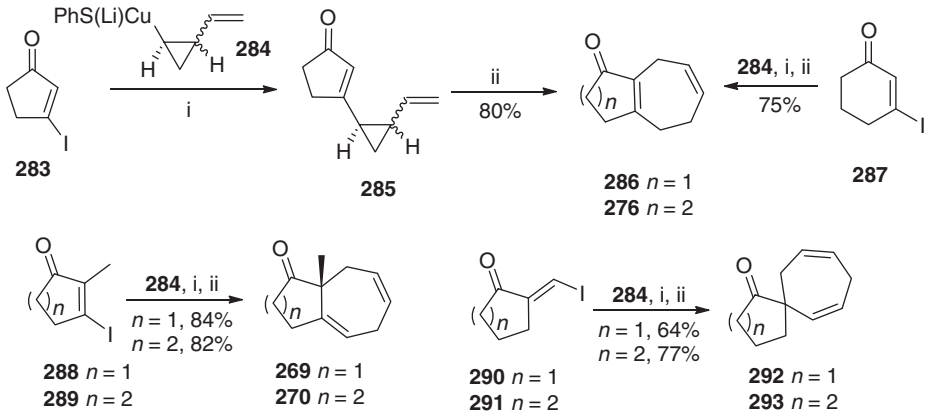
The reaction of cyclopropylcuprate reagents with *β*-iodo enones has proven to be a useful method for preparing *β*-(2-vinylcyclopropyl) enones. For example, reaction of **283** with the cuprate reagent **284** (7:3 mixture of *cis* and *trans* isomers, readily prepared from the corresponding mixture of 1-bromo-2-vinylcyclopropanes), followed by thermal rearrangement of the resultant product **285**,



i. $Ph_3P{=}CHCO_2Et$, THF, 20 °C; ii. 140 °C, xylene, 6 h

Scheme 74

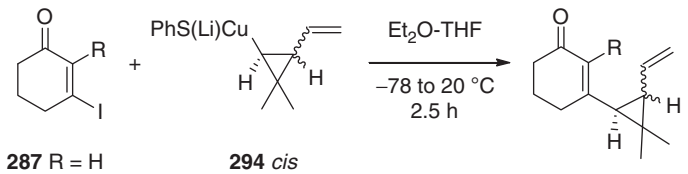
gives the ketone **286** (Scheme 75).[467] Similarly, the substrates **287**–**289** are smoothly transformed into the bicyclic ketones **276**, **269**, and **270**, whereas subjection of the (*E*)-2-(iodomethylene)cycloalkanones **290** and **291** to the same reaction sequence affords the corresponding spirodienones **292** and **293**. Because the iodo enones are readily prepared from 1,3-dicarbonyl compounds[468] and the cuprate reagent **284** is obtained via a separate synthetic route, the overall annulation sequences are convergent, short, and efficient.



i. THF, –78 °C, 1 h; –20 °C, 1 h; 0 °C, 1–2 h; ii. Heat, 180 °C, 30–45 min

Scheme 75

Cuprate methodology can also be used to prepare more highly substituted substrates. Thus, treatment of the 3-iodo-2-cyclohexen-1-ones **287** and **289** with the epimeric, stereochemically homogenous cuprates **294** and **285** produces the divinylcyclopropanes **296**–**299** in excellent yields (equation 104).[468]



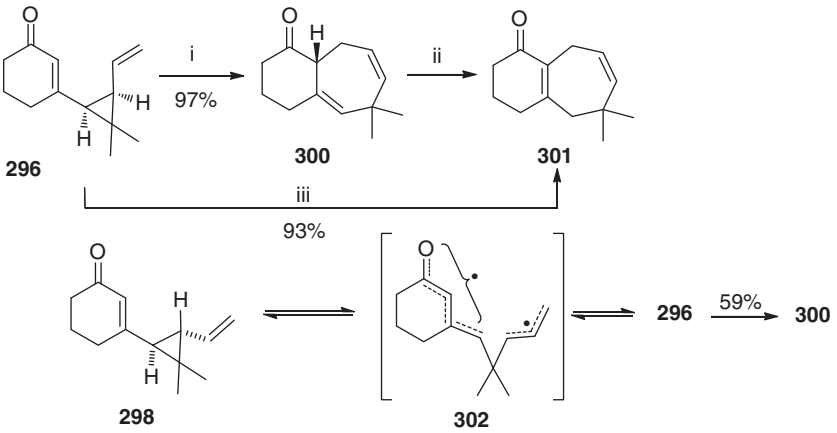
287 R = H
289 R = Me

294 *cis*
295 *trans*

296 R = H, *cis* (88%)
297 R = Me, *cis* (76%)
298 R = H, *trans* (95%)
299 R = Me, *trans* (82%)

(104)

Rearrangement of the epimers **296** and **298** is, in each case, unexceptional (Scheme 76).[468] Thermolysis of **296** in hexane provides the dienone **300**, whereas heating either **296** or **300** at 110 °C (neat) affords the conjugated ketone **301**. Although, as expected, rearrangement of **298** requires much higher temperatures, the same product **301** is formed in good yield. Presumably, this conversion proceeds by way of the stabilized diradical **302** and the *cis*-divinylcyclopropane **296**.

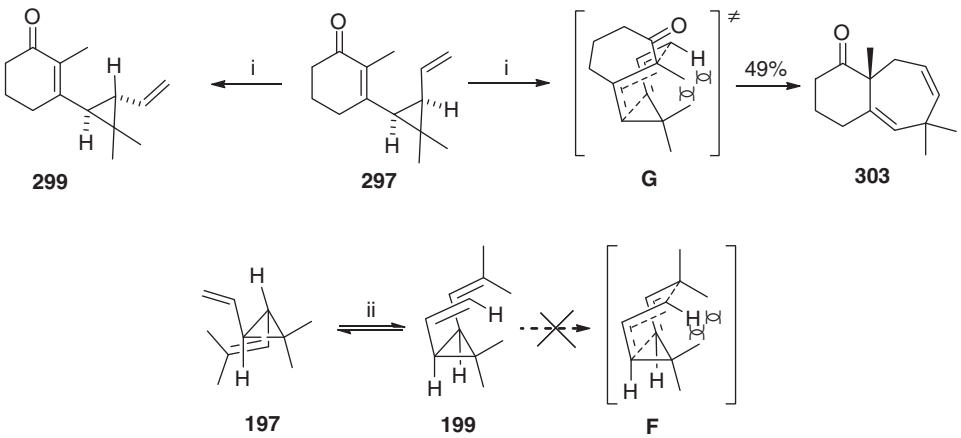


i. hexane, reflux, 4 h; ii. Heat, 110 °C, 10 min; iii. o-dichlorobenzene, 220 °C, 14 h

Scheme 76

The *cis* substrate **297** represents an interesting case. Thermolysis of this material under a variety of conditions produces mixtures of **299** and **303**, in which the latter substance nearly invariably predominates (Scheme 77).[468] For example, heating of **297** in collidine at 140–150 °C gives **299** and **303** in a ratio of approximately 1:2. Under these and other thermolysis conditions, the *trans*-divinylcyclopropane **299** is stable.

As mentioned in Section 5.22.2.2.2, Scheme 61, thermolysis of **199** at 180 °C does not result in Cope rearrangement but provides an equilibrium mixture of **199** and its epimer **197**.[431] Interestingly, in terms of steric congestion, the transition states for Cope rearrangement of **199** and **297**, **F** and **G**, respectively, are similar (Scheme 77). Therefore, it is noteworthy that **297** does undergo sigmatropic rearrangement (albeit in competition with isomerization to **299**), whereas **199** does not. In **297**, of course, one of the substituted vinyl groups is part of an α,β-unsaturated ketone function and, apparently, this structural feature lowers the activation energy of the Cope rearrangement process.

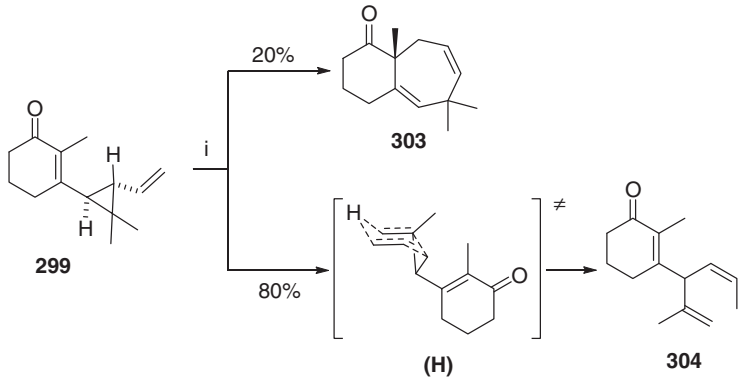


i. Collidine, 140–150 °C, 43.5 h; ii. 180 °C, 3 h

Scheme 77

The *trans* substrate **299** is quite resistant to thermal rearrangement. However, thermolysis of this substance at 220 °C (Scheme 78)[468] provides the Cope rearrangement product **303** and the trienone **304**, in a ratio of 1:4. Product **304** results from a [1,5] sigmatropic hydrogen migration, presumably via a transition state that can be represented by **H**.[421,98] Interestingly, in the thermolysis of **299**, the latter process is energetically more favorable than the alternative Cope rearrangement pathway.

From a synthetic viewpoint, a comparison of the thermolyses of the epimers **297** and **299** (Schemes 77 and 78) illustrates the point, previously mentioned, that, in certain cases in which alternative modes of rearrangement are possible, the stereoselective

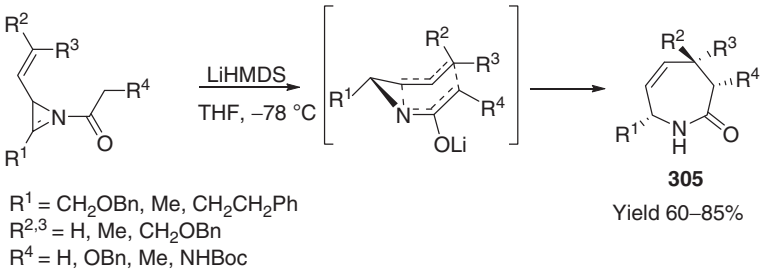


Scheme 78 *o*-DCB, 1,2-dichlorobenzene.

formation of the *cis*-divinylcyclopropane substrate is important. Thus, whereas thermal rearrangement of the *cis* substrate **297** provides the Cope rearrangement product **303** in reasonable yield, thermolysis of the *trans* isomer **299** does not.

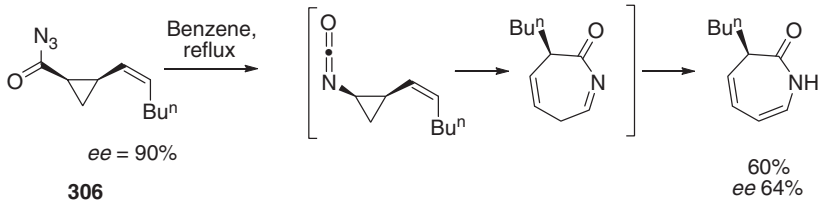
5.22.2.5 Heterocyclic Divinylcyclopropanes

Somfai[469,470] studied rearrangements of *N*-acylvinylaziridines. On their treatment with LiHMDS, the resulting enolate underwent a rearrangement to lactam **305** via a boat-like transition state leading to conservation of chirality in the sp^2-sp^3 transfer of stereochemical information (equation 105).

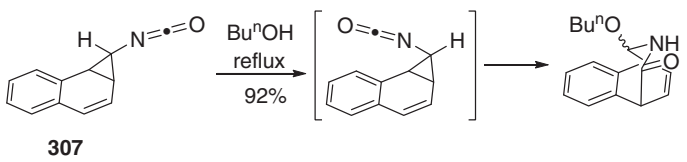


(105)

Müller described a Curtius–Cope rearrangement sequence.[471] It is interesting to note that, despite the mostly concerted character of this rearrangement, some erosion of *ee* occurred in case of **306**, probably because of participation of a biradical mechanism (equation 106). In case of the more substituted compound **307**, complete conservation of stereoselectivity was observed (equation 107).

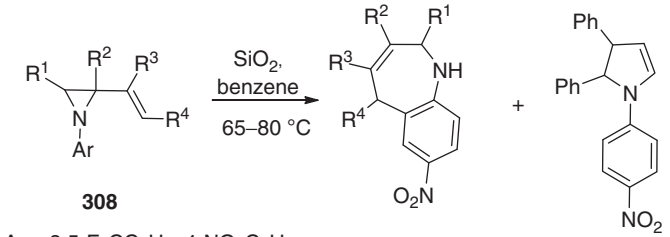


(106)



(107)

N-Aryl vinylaziridines **308** can be rearranged to benzoazepines **309** on heating with silica gel. Gallo[472] studied the formation of such aziridines and their pathways of rearrangement. In case of sterically encumbered aziridines or under strictly thermal conditions without silica gel, dihydropyrroles of type **310** are formed (equation 108).



308

Ar = 3,5-$F_3CC_6H_4$, 4-$NO_2C_6H_4$

309

$R^{1,3}$=H, $R^{2,4}$=Me
Single product 58%

310

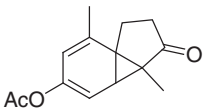
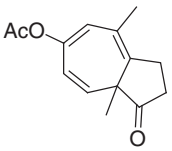
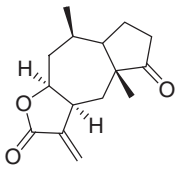
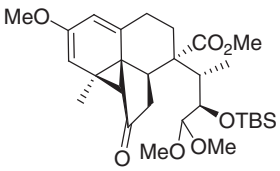
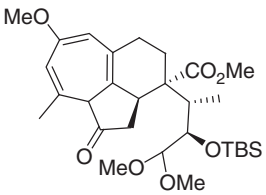
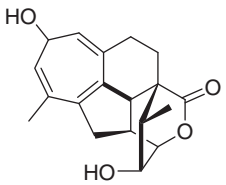
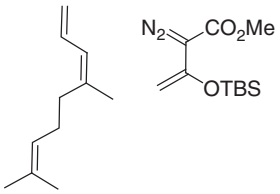
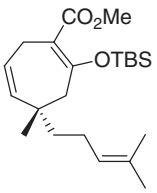
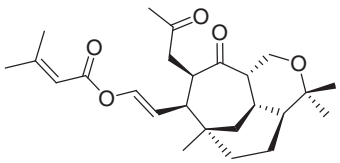
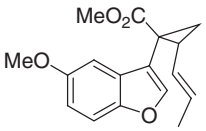
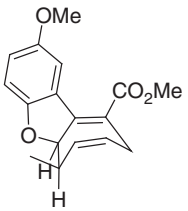
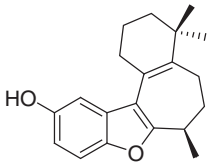
for $R^{1,2}$=Ph, $R^{3,4}$=H,
Single product 70%

(108)

5.22.2.6 Total Syntheses

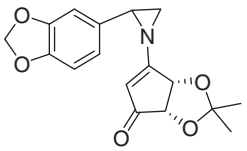
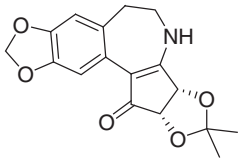
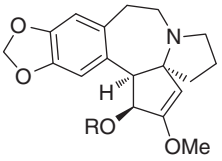
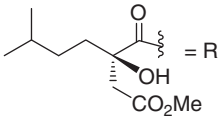
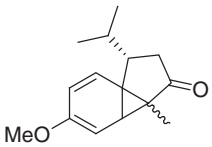
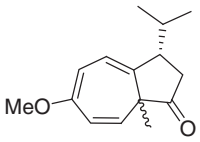
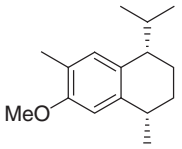
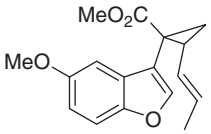
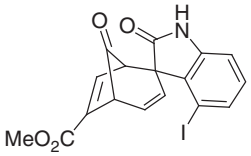
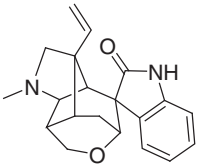
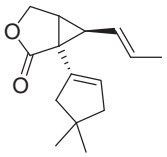
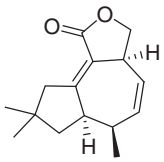
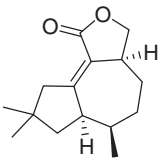
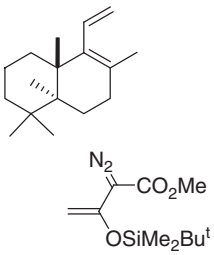
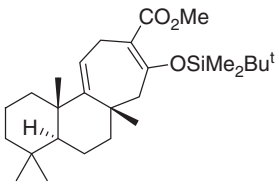
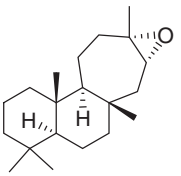
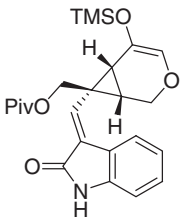
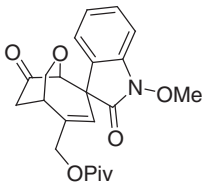
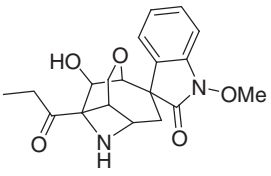
The divinylcyclopropane–cycloheptadiene rearrangement has not been featured in total syntheses as frequently as the vinylcyclopropane–cyclopentene rearrangement. Since the publication of the first edition of this work, only a few applications were reported. These are summarized in Table 17. For previous utilization of this rearrangement see the 1991 edition; notable accomplishments include the syntheses of β-himachalene by Piers[473] and of confertine by Wender.[474]

Table 17 Total syntheses featuring the divinylcyclopropane–cycloheptadiene rearrangement

Starting material (SM)	*Conditions*	*Product*	*Target*	*References*
			 Confertin A	475
	1,8-diazabicyclo[5.4.0] undec-7-ene (DBU)		 Hainanolidol	476
	Rh_2(S-PTAD)$_4$, –10 °C to reflux		 (–) 5-*epi*-Vibsanin	477
			 (+)-Frondosin B	478

(*Continued*)

Table 17 Continued

Starting material (SM)	*Conditions*	*Product*	*Target*	*References*
	Cs_2CO_3, 100 °C, 76%		  (–)-Deoxyharringtonine	479
			 (–)-*cis*-7-Methoxycalamenene	480
	Toluene-MeCN, 90 °C		 (±)-Gelsemine	481
	140 °C		 (+)-5-*epi*-Tremulenolide	482
	Rh_2(*R*-PTAD), hexanes, reflux		 (+)-Barekoxide	483
	Toluene, 70 °C		 Gelsemoxonine	484

5.22.3 Outlook

More than 50 years have passed since Neureiter's discovery of the vinylcyclopropane rearrangement. In the golden age of physical organic chemistry, 1950–70, this rearrangement and the divinylcyclopropane rearrangement were subjected to detailed

mechanistic scrutiny. The applications of both rearrangements to synthesis followed shortly thereafter. Many useful and general methods were derived from these rearrangements and their heteroatom variants. The total synthesis community was also quick to recognize their value, as evidenced by many applications to the synthesis of natural products in both the terpene and alkaloid domains.

After the publication of the chapters dealing with these two rearrangements in the first edition of *Comprehensive Organic Synthesis* in 1991 the frequency of applications in synthesis diminished, perhaps indicating the maturity of the methods. An update published in 2010[485] as a tribute to Neureiter's historical contribution reported a few new applications that surfaced since 1991.

Organometallic chemistry significantly changed the landscape of, especially, the chemistry of vinylcyclopropanes. The attention of the synthetic community has been more focused on the application of transition-metal catalysis especially in the design of new modes of reactivity, such as the higher order cycloadditions discovered by Wender and the redesign of old reactions under enantioselective conditions.

The topology of these reactive substrates offers almost endless combinations of products when one considers the almost infinite combinatorial possibilities resulting from the incorporation of heteroatoms into the reactive manifold. Few of these combinations have been truly exploited in synthesis, and it is the authors' hope that the publication of this chapter will inspire interest in further development of some of the most fascinating transformations in organic synthesis.[486,487]

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5.23 Anion- and Metal-Promoted Rearrangements of Small-Ring Systems

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Glossary

β-Carbon elimination Formation of a carbon–metal species by elimination of the carbon atom in the β-position to the metal. Reversal of the migratory insertion reaction.
Carbon–carbon bond cleavage Rupture of the bond between two carbon atoms.
Charge acceleration Faster reaction rate due to the presence of a positive or negative charge.
Cyclobutane Four-membered carbocycle.
Cyclopropane Three-membered carbocycle.
Strain acceleration Enhanced reaction rate due to the release of ring strain.

5.23.1 Charge-Accelerated Rearrangements: Background

5.23.1.1 Introduction

Exploitation of ring strain as enabling force to promote molecular rearrangements, which do not proceed (or at least not as facile) with conventional substrates, is a well-appreciated strategic tool in organic synthesis. In particular, this encompasses ring-expansion and -cleavage reactions of three- and four-membered rings. Although the exact quantification of the energy benefit of breaking the small ring depends on the specific substrates and reactions, a rough overview of the strain energies is helpful to estimate reactivities. The strain energy of cyclopropane (27.5 kcal mol^{-1}) is very similar to that of cyclobutane (26.5 kcal mol^{-1}) and dramatically higher than that of cyclopentane (7.4 kcal mol^{-1}) (Scheme 1). Despite this similarity, the cyclopropane ring is more susceptible toward ring-cleavage. This can be rationalized by a dissection of the strain in C–C and C–H bond energy contributions. The amount deriving from C–C bonds is 10.1 kcal mol^{-1} higher in cyclopropane than in cyclobutane.[1] This difference is compensated by the stronger C–H bonds (8.0 kcal mol^{-1}) of cyclobutane.[2] Care needs to be taken to estimate the ring strain of substituted substrates. For example, geminal disubstitution reduces the ring strain of cyclobutane by more than 8 kcal mol^{-1} because of the Thorpe–Ingold effect.[3]



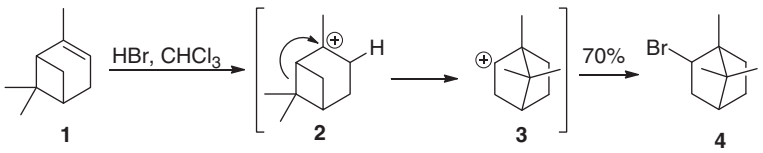
Scheme 1 Strain energies of selected carbocycles.

Although the ring strain is an important feature to increase reactivity, many substrates still suffer from drawbacks of poor reactivity, selectivity, and scope limitations. These shortcomings can often be addressed by exploiting the accelerating properties of a charged substituent on the small-ring compound. In the first edition of Comprehensive Organic Synthesis (COS) in 1991, the

majority of the featured reactions fell in the category of anionic pericyclic rearrangements. Most often, these reactions were stoichiometric comprising a first or second row metal cation. The reaction outcome is dictated by the substrate and the rate is modulated by the nature of the charge. Generally, the faster the reaction, the greater their charge separation and higher their ionic character. Although some additional applications of these reactivities have been reported in the following two decades, the most significant advances were made in the area of transition-metal catalyzed reactions. The transition-metal catalyst enables a host of conceptually new methods, with intermediary appearing charges. These may be more accurately described as coordination complexes or organometallic species. The chapter's main focus is placed on illustrating the possibilities that these new methods enable in combination with strained ring compounds.

5.23.1.2 Cationic Rearrangements

The history of cationic rearrangements of the Wagner–Meerwein type of strained molecules is long. In general, the reaction follows the mechanistic pathway of a 1,2-carbon shift. A generated cyclopropyl methyl or cyclobutyl methyl carbenium ion rearranges into a cyclobutyl or cyclopentyl carbenium ion, which in turn can react further. An important illustration and a classic example is the acid-promoted rearrangement of α-pinene (**1**) (Scheme 2). Simplified, it is the ring-expansion of a vinyl cyclobutane into a cyclopentane. Protonation leads to the tertiary cyclobutyl methyl carbenium ion **2** which rearranges to the camphane cation **3**, which gets subsequently trapped to give 2-bromo camphane **4** in 70% yield.[4]

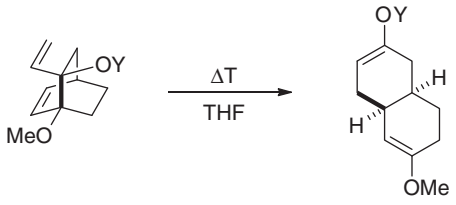


Scheme 2 Prototypical Wagner–Meerwein type of cationic rearrangement.

This reactivity principle has been utilized many times, exploiting the different aspects of this chemistry. It should be noted that these types of purely cationic rearrangements are not covered in this chapter and are treated separately with the appropriate depth in the chapters specifically concerned with Wagner–Meerwein type and related rearrangements in Volume 3 of COS2. A recent review focusing on cyclobutane substrates is available as well.[5]

5.23.1.3 Aza- and Oxyanion-Accelerated Rearrangements

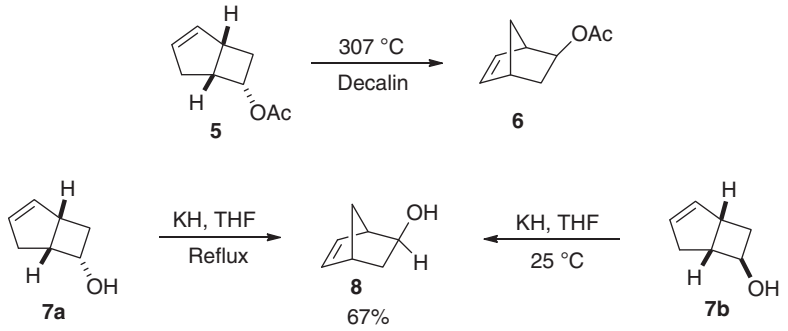
The classical example for anionic-charge accelerated processes is the oxy-Cope reaction. Spectacular rate enhancements of 10^{10}–10^{17} are observed with anionic oxy-substituents compared to their neutral congeners (Scheme 3). Although the neutral process generally requires reaction temperatures between 200 and 400 °C, the corresponding anionic reaction often proceeds at ambient temperature or below.[6] The effect stems both from reactant destabilization and transition state stabilization. Since its discovery, anionic oxy-Cope reactions have been widely utilized in synthetic organic chemistry (*see* Chapter 5.19 of COS2).



Y	Half-life	T (°C)
H	(66 yrs)	66
Na	1.2 h	66
K	1.4 min	66
K	11 h	10
K (HMPA)	4.4 min	10

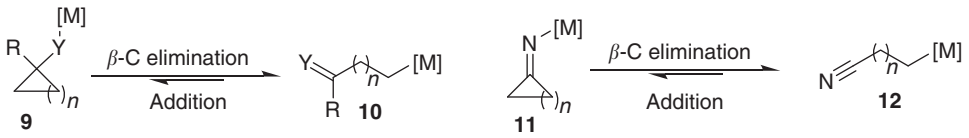
Scheme 3 Rate accelerations and half-lives of anionic oxy-Cope reactions.

A popular prototype of oxyanion-accelerated rearrangements of strained rings is the vinylcyclobutane-to-cyclohexene rearrangement. As exemplified for the rearrangement of **5**–**6**, the notoriously high temperature for the reaction has severely limited synthetic applications (Scheme 4).[7] These limitations can be largely overcome by exploiting the accelerating properties of an appended alkoxide group.[8] Depending on the utilized diastereomer **7a** or **7b**, different mechanistic pathways of the rearrangement are operative, all ending with the same thermodynamic *exo*/*endo* ratio, favoring largely the depicted isomer **8**.



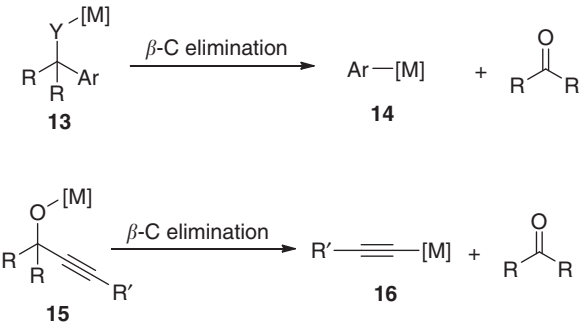
Scheme 4 Anion-accelerated vinyl-cyclobutane rearrangement.

The mechanistic details and synthetic applications of this and related reactions are discussed in detail in the corresponding chapter of COS1. Here, the main focus is placed on new developments of transition-metal oxy- and aza-anions. In this scenario compound **9** builds an important starting point for rearrangements of strained cyclic compounds (Scheme 5). Their softer and less oxyphilic character compared to main group anions, enables a rearrangement process – the β-carbon elimination – giving rise to either a C=O and C=N double bond or a nitrile and an alkyl-metal species.[9] In turn, intermediate **10** undergoes a myriad of valuable follow-up processes, often involving a π-unsaturation in vicinity. However, these π-unsaturations are generally not essential to induce the rearrangement reactivity. However, the reaction requires most often tertiary alcoholates/amides to avoid the concurrent process of β-hydride elimination. For β-carbon elimination of sp^3-hydribized carbon substituents, the energy release of ring opening is required to compensate for the relatively weak C(sp^3)-metal bond (**10** and **12**). In contrast, substrates with sp- and sp^2-hydribized residues (**13** and **15**) give species with significantly stronger carbon-metal bonds (**14** and **16**) and do not mandate this additional driving force. In several cases the relevant alkoxides can be generated as reactive transients by the addition of organometallic species to the strained ketones. This, and alternative methods to their generation as well as the possible downstream reactivities of the species **10** and **12** are overviewed in the following sections.



[M] = Transition metal
Y = N, O; R ≠ H
n = 1, 2

C(sp^2)-[M] and C(sp)-[M] do not require strain release:

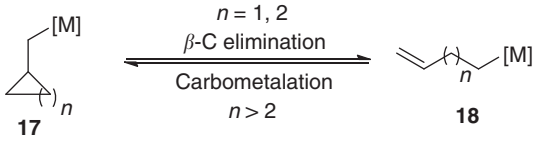


Scheme 5 β-Carbon eliminations from *tert*-alcohols with and without strain.

5.23.1.4 Carbanion-Accelerated Rearrangements

Similar to aza- and oxyanions, major progress in the field of carbanion-accelerated rearrangements has been made with transition-metal catalysis involving discrete carbon-metal bonds. In particular, β-carbon eliminations benefit from the release of ring strain (equation 1). For $n > 2$, the equilibrium largely favors the cyclic form **17**, whereas cyclopropylmethyl and cyclobutylmethyl

intermediates rapidly rearrange to their open forms **18**. Often, the ring opening is preferred over β-H elimination when the appropriate geometrical constraints are met. The range of methods to obtain the crucial intermediates **18** and their subsequent reactivity are discussed. For example, this concept has been applied to higher order cycloadditions such as [5 + 2].

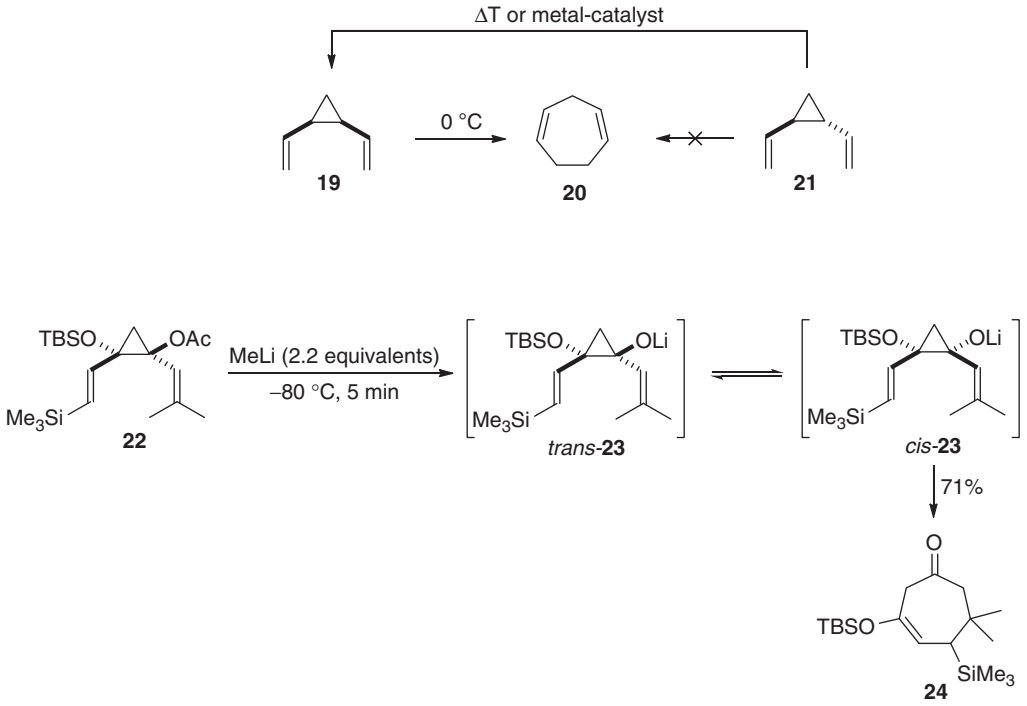


(1)

5.23.2 Charge-Promoted Rearrangements of Cyclopropanes

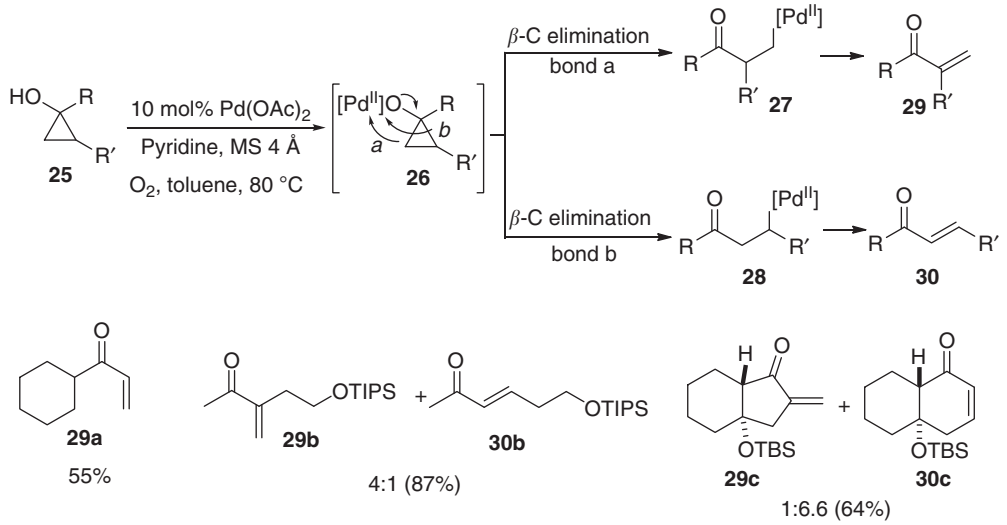
5.23.2.1 Oxyanion-Induced Rearrangements of Cyclopropanes

The divinylcyclopropane rearrangement is a special form of the Cope-rearrangement and provides access to 1,4-cyclohepadienes **20** (Scheme 6).[10] Owing to the release of ring strain, the rearrangement of *cis*-divinyl cyclopropane **19** proceeds already at ambient temperature and below, making it very difficult to isolate **19**. Usually, formation of the divinylcyclopropane and the rearrangement is carried out in the same pot. In contrast, the corresponding *trans*-isomer **21** is stable and does not undergo the rearrangement unless an isomerization (excessive heat or transition-metal-catalysts) to the *cis*-isomer **19** occurs. Similar to anionic oxy-Cope reactions, divinyl cyclopropane rearrangements are also accelerated by appended oxyanions. Takeda found that generation of the lithium alkoxide *trans*-**23** from the unreactive *trans*-acetate **22** promotes a rapid equilibration to *cis*-**23**, which directly cyclizes to cycloheptenone **24**.[11] All steps are fast and take place at −78 °C within 5 min.



Scheme 6 Oxyanion-accelerated divinylcyclopropane rearrangement.

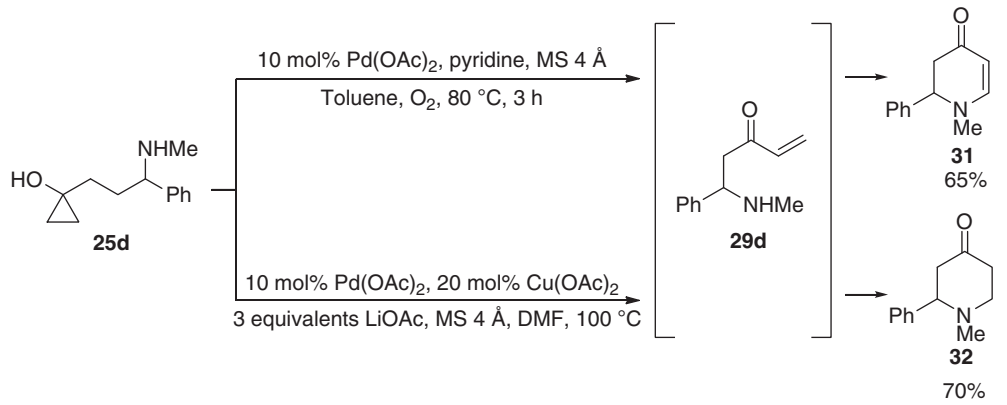
Free *tert*-cyclopropanols are readily accessible from the corresponding esters by the titanium-mediated Kulinkovich reaction.[12] They are a versatile class of substrates for a set of rearrangements initiated by a range of transition-metal catalysts. For instance, Cha reported palladium(II)-catalyzed openings of cyclopropanols **25** under oxidative conditions (Scheme 7).[13] The reactions proceed with molecular oxygen as the terminal oxidant, using catalytic amounts of $Pd(OAc)_2$ and pyridine as base. At first, formation of the palladium(II) alkoxide **26** occurs. Depending on the substitution pattern, a β-carbon elimination – cleaving either bond *a* or *b* – leads to intermediates **27** or **28**. Subsequent β-hydride elimination gives rise to enones **29** or **30**. Oxidation of the formed Pd(0)-species by oxygen turns over the metal complex. For acyclic substrates, cleavage of the



Scheme 7 Palladium(II)-catalyzed β-carbon elimination from *tert*-cyclopropanols.

less substituted bond *a* dominates, whereas for constrained cyclic substrates, selectivities can be reversed, favoring cleavage of bond *b*.

Independently, Okumoto described a similar process with Pd(0)-catalysts.[14] Brandi exploited the reaction further, capitalizing on the formation of the enone **29d** for an aza-Michael addition, leading either to enaminone **31** or to the saturated product **32** (Scheme 8).[15]



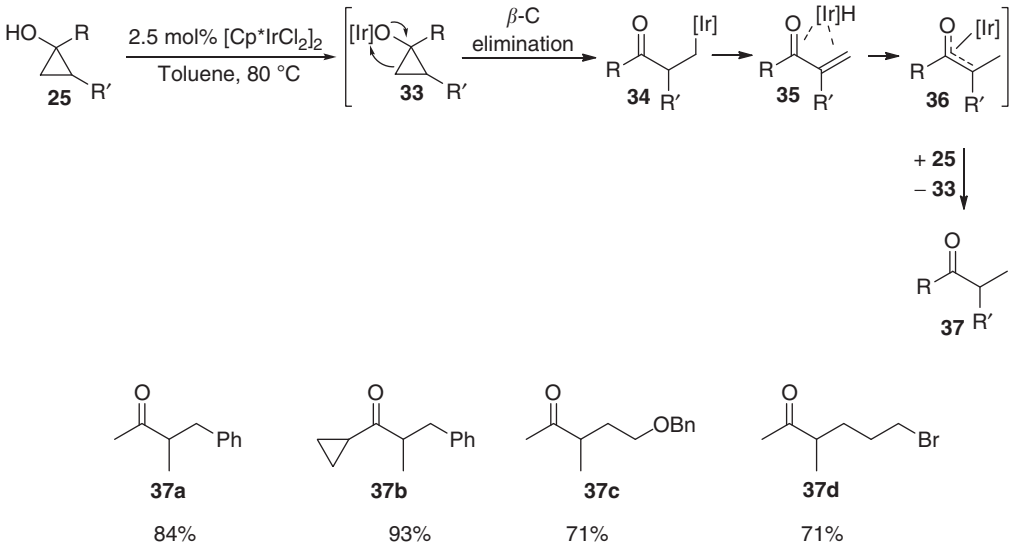
Scheme 8 Palladium(II)-catalyzed β-carbon elimination followed by cyclization.

With other catalysts, similar cyclopropanol substrates can be transformed into saturated ketones as well. In this respect, Funk reported a Ir(III)-catalyzed process using catalytic amounts of $[Cp^*IrCl_2]_2$ (Scheme 9).[16] Contrasting the work of Cha, the less substituted C–C bond of **33** is cleaved selectively, leading strictly to the more stable primary iridium intermediates **34**. β-Hydride elimination leads to enone **35** and an iridium-hydride species, which in turn adds in a 1,4-fashion, leading to the saturated ketone **37** via the oxa-π-allyl species **36**. The reaction is functional group tolerant and generally high yielding.

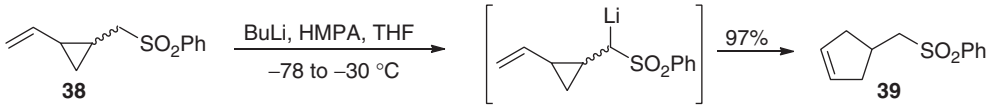
5.23.2.2 Carbanion-Induced Rearrangements of Cyclopropanes

The acceleration potential of carbanionic substituents for small-ring rearrangements was first demonstrated by Danheiser with the vinylcyclopropane (VCP) rearrangement of **38** into cyclopentene **39** (Scheme 10).[17] The potential and the limitation of such lithiated intermediates were covered in the first edition of COS.

Since then, most exciting progress has been made by using transition-metal carbanionic intermediates complementing the classical main group carbanion reactivity. In general, these reactions follow the same principle as the one for oxyanions. The metalated cyclopropylmethyl intermediate **40** undergoes a strain-driven opening to form a homoallyl metal species **41** (equation 2).

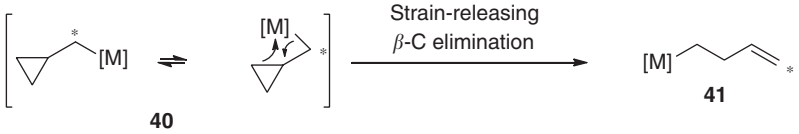


Scheme 9 Iridium(III)-catalyzed β-carbon elimination from *tert*-cyclopropanols.



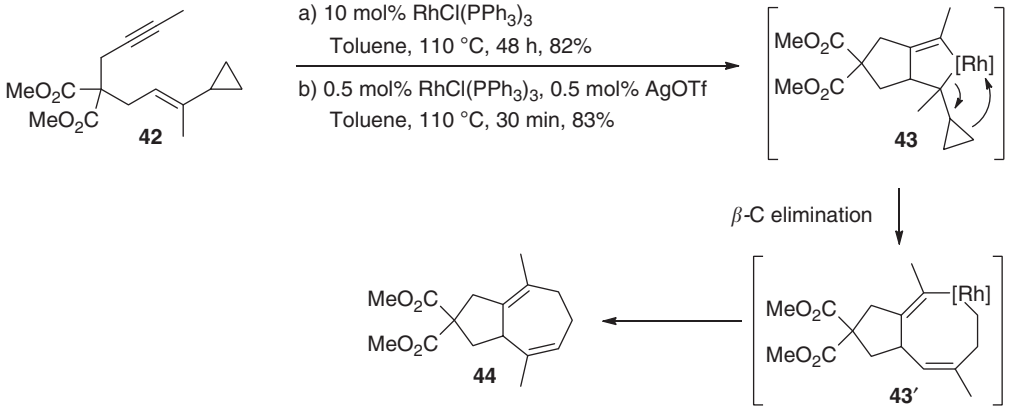
Scheme 10 Carbanion-accelerated vinylcyclopropane rearrangement.

Depending on the catalyst and metal, **41** undergoes specific downstream processing to the individually observed product branches. The generation of the initiating anionic intermediate **40** can be achieved by several methods.



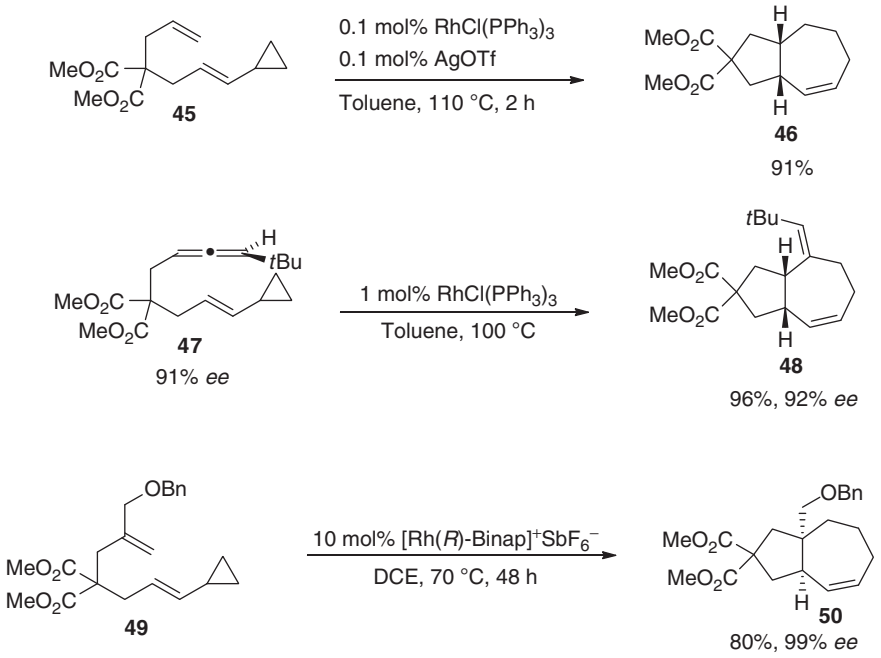
(2)

Common methods for its generation are metal-catalyzed cycloisomerization reactions. Especially Wender's large body of work on rhodium-catalyzed [5 + 2]-cycloadditions of a VCP moiety tethered by a three atom spacer to an alkyne expanded this field vastly. In early studies, Wilkinson's catalyst was utilized, whereas later it was found that a cationic rhodium(I) species is much more reactive (Scheme 11).[18] At first, oxidative cyclization of **42** forming rhodacyclopentene **43** proceeds. Then, strain-driven ring opening by β-carbon elimination leads to a transient rhodacyclooctadiene **43′**, which undergoes reductive elimination to give cycloheptadiene **44**.



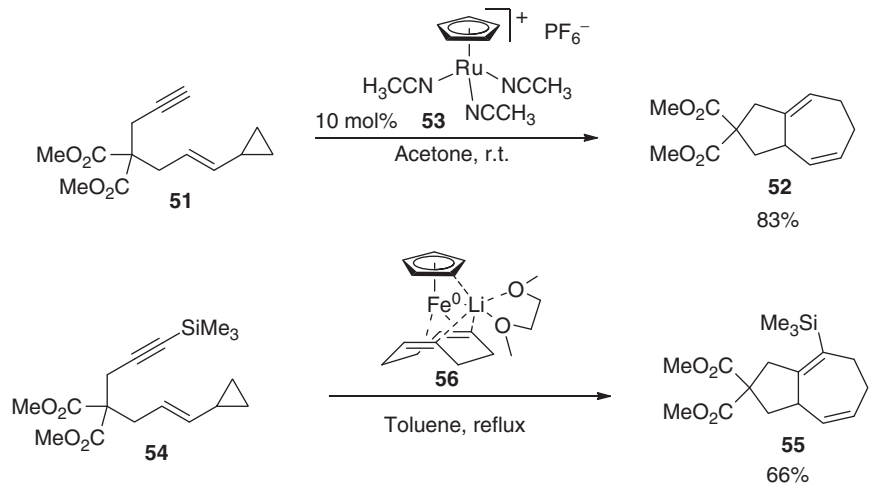
Scheme 11 Wender's rhodium(I)-catalyzed [5 + 2]-cycloadditions.

Subsequently, it was demonstrated that the reaction proceeds as well with olefins instead of alkynes (Scheme 12).[19] As shown for **45**, cycloheptene **46** is obtained. The transformation of a trisubstituted allene **47–48** is enantiospecific.[20] Some enantioselective versions have also been developed.[21] For instance, substrate **49** gave, with *(R)*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (Binap) as chiral ligand, cycloisomerized product **50** in excellent optical purity.



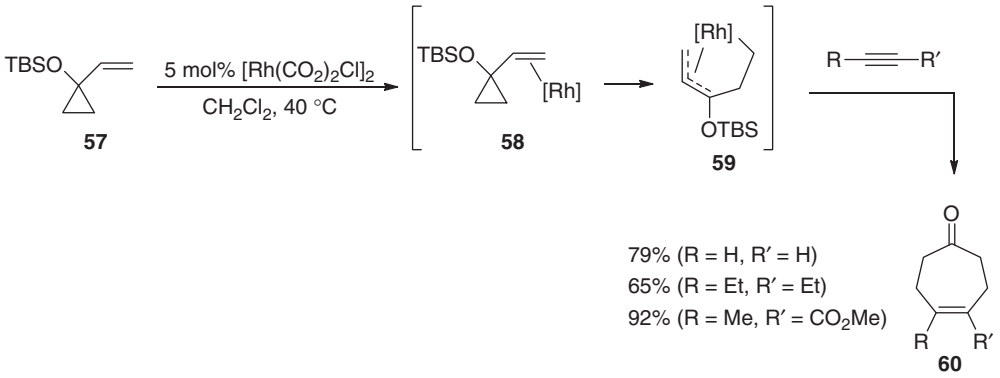
Scheme 12 General scope of rhodium(I)-catalyzed [5 + 2]-cycloadditions.

Although rhodium complexes are until now the most general and best explored metal catalysts for [5 + 2]-cycloadditions, other metal-catalysts promote this transformation as well. For instance, Trost showed that similar substrates **51** undergo the reaction with the cationic ruthenium(II) complex $[CpRu(CH_3CN)_3]PF_6$ (**53**) providing product **52** (Scheme 13).[22] The reaction has a broad scope and proceeds at mild conditions, comparable to the rhodium-catalyzed process. Fürstner reported the use of the well-defined ferrate complex **56**, showing that it is possible to catalyze the cycloisomerization of substrate **54** to bicycle **55** also with a nonnoble metal catalyst.[23]



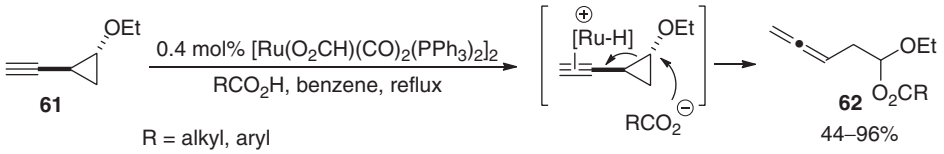
Scheme 13 [5 + 2]-Cycloadditions catalyzed by ruthenium- and ferrate-complexes.

Wender has further developed an intermolecular version (Scheme 14). VCPs **57** needs to be activated by an alkoxy or siloxy group. The scope for the alkyne is broad (acetylene, internal alkynes, and propiolates are tolerated).[24] However, to achieve the reaction, one has to use $[Rh(CO)_2Cl]_2$; Wilkinson's catalyst is not competent. Calculations for this reaction have shown that coordination of a Rh(CO)Cl fragment to the vinyl group (**58**) leads to a cleavage of the cyclopropane delivering intermediate **59**. Insertion of an alkyne and subsequent reductive elimination provides cycloheptane derivative **60**.[25] Further details on these and related metal-catalyzed [5 + 2]-cycloadditions[26] can be found in Chapter 5.14 of COS2, dealing with higher order cycloadditions.



Scheme 14 Intermolecular rhodium-catalyzed [5 + 2]-cycloaddition.

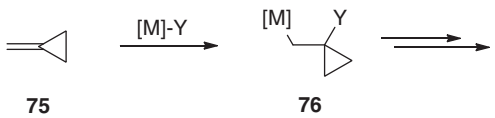
Similarly to the reactions outlined above, activated alkynyl cyclopropanes such as **61** can be activated by ruthenium catalysts (Scheme 15).[27] Dixneuf showed that coordination of a ruthenium hydride species to the alkyne make the cyclopropane moiety susceptible toward nucleophilic attack by a carboxylate. The ring-opening reaction yields allenes **62** and proceeds in fair to excellent yields.



Scheme 15 Ruthenium catalyzed ring-opening of alkynyl cyclopropanes.

Besides these pathways, other strategies to access the cyclopropylmethyl metal intermediates were reported. Shair used aldehydes **63** with an appended vinyl cyclopropane unit as starting materials for an intramolecular hydroacylation, leading to the cyclopropylmethyl intermediate **64** (Scheme 16).[28] β-Carbon elimination opens the cyclopropane ring and gives **65**. Reductive elimination provides access to the cyclooctanone derivative **66**. In general, the reaction is tolerant to a variety of substitution patterns and functional groups. However, the catalytic efficiency is moderate and the yields are often fair. A related approach was reported by Fürstner and Aissa, using vinylidene cyclopropanes **67** and **71** as substrates for the intramolecular hydrorhodation to access the critical intermediates **68** and **72**.[29] Similarly, these reactive species ring open subsequently to compounds **69** and **73**, respectively, before reductive elimination forms products **70** and **74**.

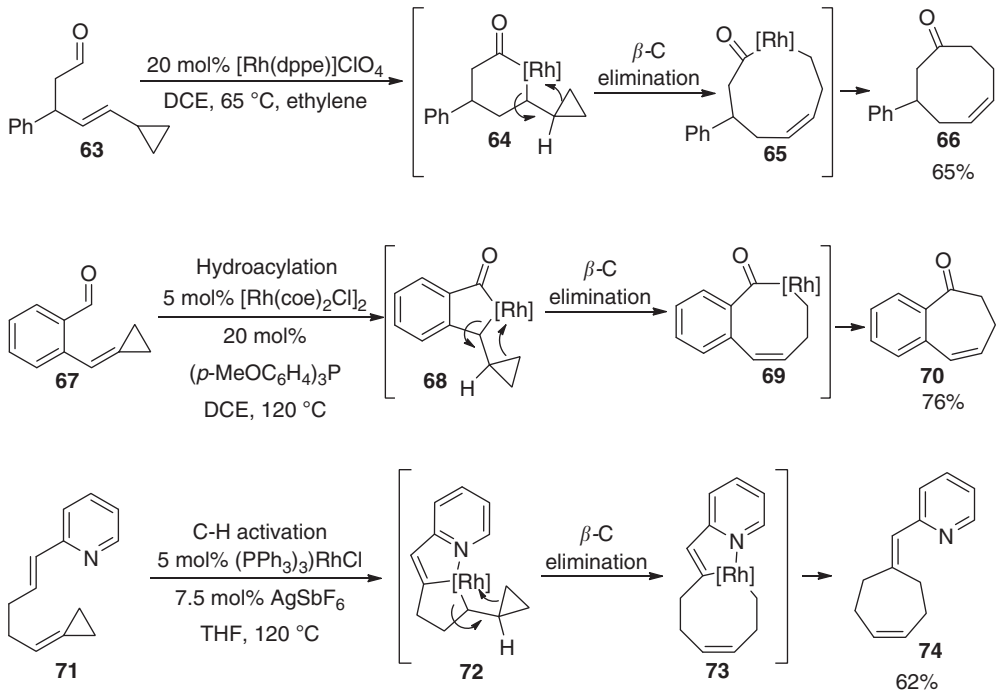
In general, methylenecyclopropanes (MCPs) **75** are highly strained molecules and undergo a variety of addition and ring-opening reactions. Although some of these reactions pass by cyclopropylmethyl metal intermediates like **76** (equation 3), their discussion will go beyond the scope of this chapter and more detailed information can be found in recent reviews.[30]



(3)

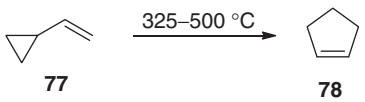
5.23.2.3 Rearrangements of Cyclopropanes Promoted by π-Coordinated Metals

The VCP, (77)-to-cyclopentene (**78**) rearrangement is a classic application field for flash vacuum pyrolysis, capable of delivering the necessary high reaction temperatures (frequently over 500 °C) (Scheme 17).[31] A reasonable reaction temperature and a solid functional group tolerance as well as cleaner stereochemical outcome has been achieved by charge-acceleration. Analogous to the tremendous acceleration effect observed in anionic-oxy-Cope rearrangements, similar observations have been made by Danheiser

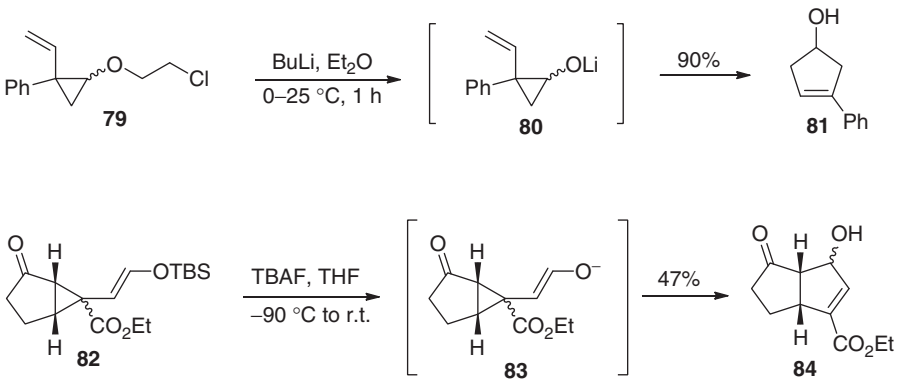


Scheme 16 β-Carbon elimination induced by hydrorhodation.

Thermally promoted parent VCP rearrangement:



Oxyanion accelerated VCP rearrangements:

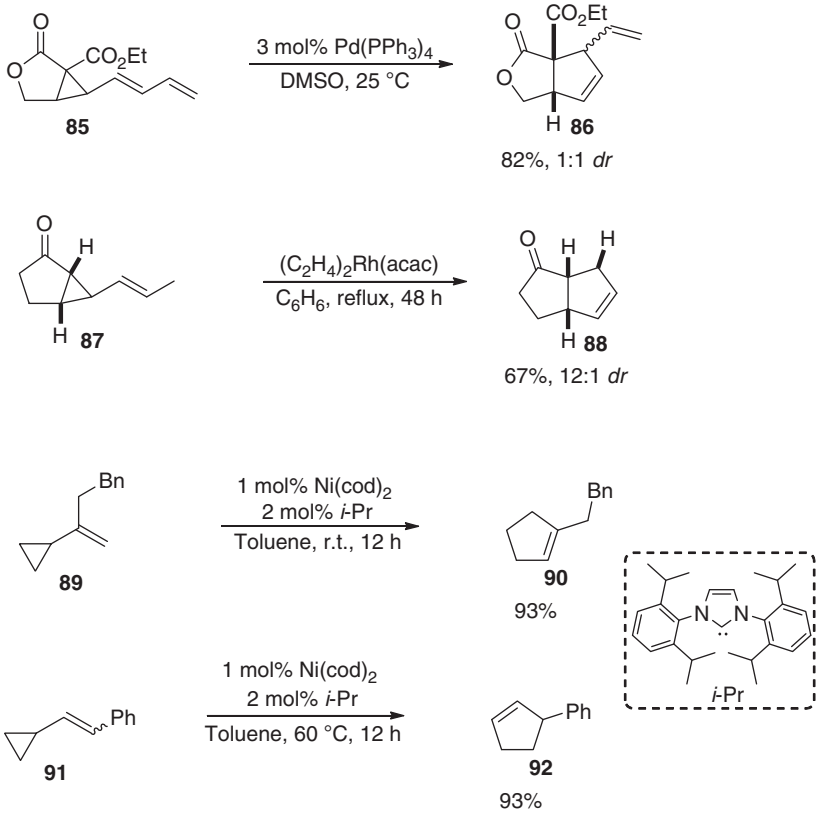


Scheme 17 Thermal and charge-accelerated VCP rearrangements.

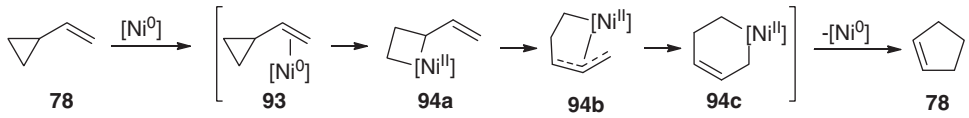
for VCPs bearing deprotonated hydroxyl functionalities.[17] For instance, generation of the lithium alkoxide **80** from **79**, allows for a clean rearrangement to cyclopentenol **81** at ambient temperature. Activated substrates such as **83**, obtained by desilylation from **82**, are even more reactive and readily rearrange to **84**.[32]

In contrast to these advances, substrates lacking the appropriate handle to place a charge remained problematic and required the development of different activation strategies. Transition-metal complexes (Ni, Pd, Rh, Cu, Cr, Mo, and Fe) were reported to catalyze rearrangements from VCP, dramatically lowering the required reaction temperature.[33] In this respect, Pd(0), Rh(I), and Ni(0)-catalyst were the most versatile (for selected examples see Scheme 18). The scope for palladium- and rhodium-catalysts

reactions is limited by and large to activated VCP (**85** and **87**) having an electron-withdrawing substituent, which enhances their propensity for oxidative addition and/or stabilization of anionic ring-opened intermediates. Alternatively, cyclopropyl dienes are well behaved substrates because of their good coordination ability to the metal complexes. These limitations were addressed by a nickel system with a carbene ligand described by Louie.[34] It proved to be highly efficient for completely unactivated VCPs. With a 1,1-disubstituted olefin (**89**), the reaction proceeds at ambient temperature with a catalyst loading of 1 mol%. A 1,2-disubstituted olefin (**91**) requires heating to 60–100 °C. Mechanistically, calculations suggest that coordination of the nickel complex to the double bond (**93**) and, subsequently, a proximity-induced insertion into the strained C–C bond of the cyclopropane gives **94a**. Isomerization to **94c** and finally reductive elimination gives rise to the cyclopentene derivative **78**.[35]



Mechanism of the Ni^0-catalyzed VCP rearrangement:

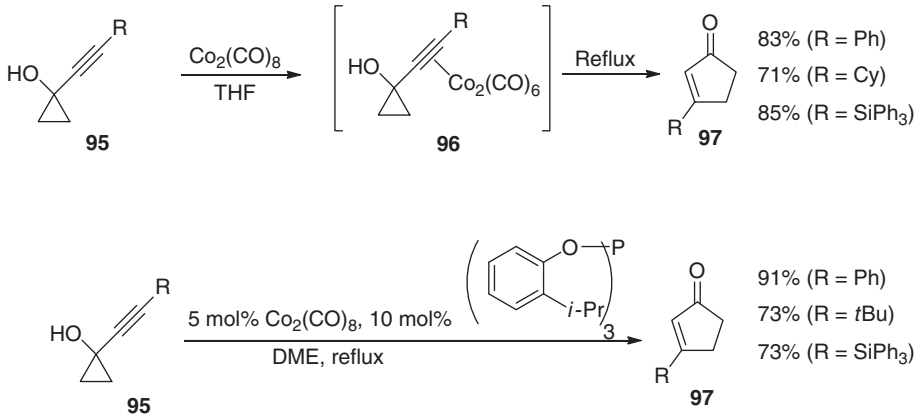


Scheme 18 Transition-metal catalyzed VCP rearrangements.

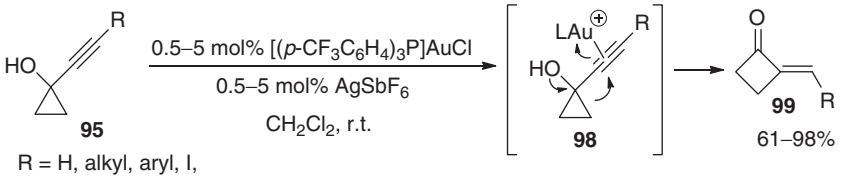
The metal-catalyzed VCP rearrangements were reported along the way of related activation strategies leading to a host of versatile new transformations. The activating nature of the hydroxyl group of cyclopropanol derivatives possessing an adjacent degree of unsaturation (olefin, allene, and alkyne) render them readily rearrangeable on treatment with transition-metal complexes. In an early example, Iwasawa demonstrated the ring opening of 1-alkynylcyclopropanols **95** mediated by dicobalt octacarbonyl (Scheme 19).[36] On heating, the intermediate cobalt complex **96** undergoes a rearrangement delivering cyclopentenone **97** in moderate to excellent yields. The same group later established an efficient catalytic version using a bulky triarylphosphite ligand.[37]

Toste found that exposure of the same substrates **95** to an *in situ* generated cationic gold(I)-catalyst induces a 1,2-shift leading to *trans*-cyclobutenones **99** (Scheme 20).[38] The reaction is induced by π-coordination of the gold(I) complex to the triple bond (**98**). The rearrangement proceeds at ambient temperature and is generally very high yielding.

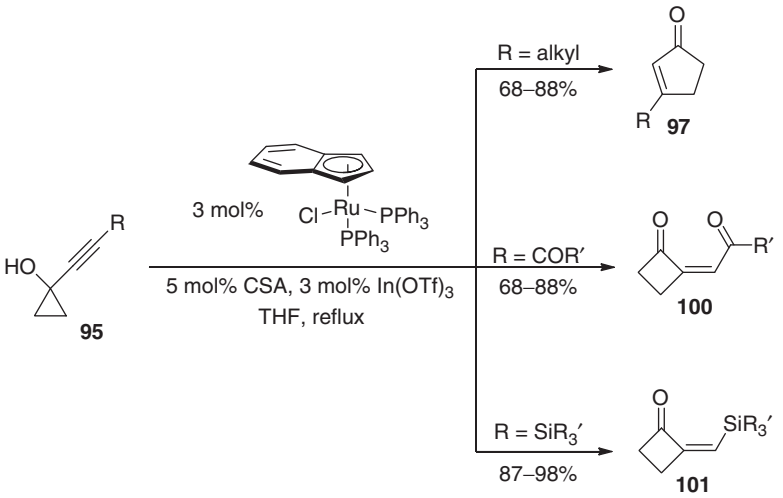
The reaction of 1-alkynylcyclopropanols **95** with a ruthenium(II)-catalyst was reported by Trost.[39] Interestingly, divergent reaction pathways were observed depending on the substituent R (Scheme 21). Electronically 'neutral' alkyl substituents are prone to a C–C insertion providing, similar to the cobalt-catalyzed process, cyclopentenones **97** via a suggested ruthenacyclohexenone.



Scheme 19 Cobalt-promoted rearrangement of 1-alkynylcyclopropanols.



Scheme 20 Gold-promoted rearrangement of 1-alkynylcyclopropanols.

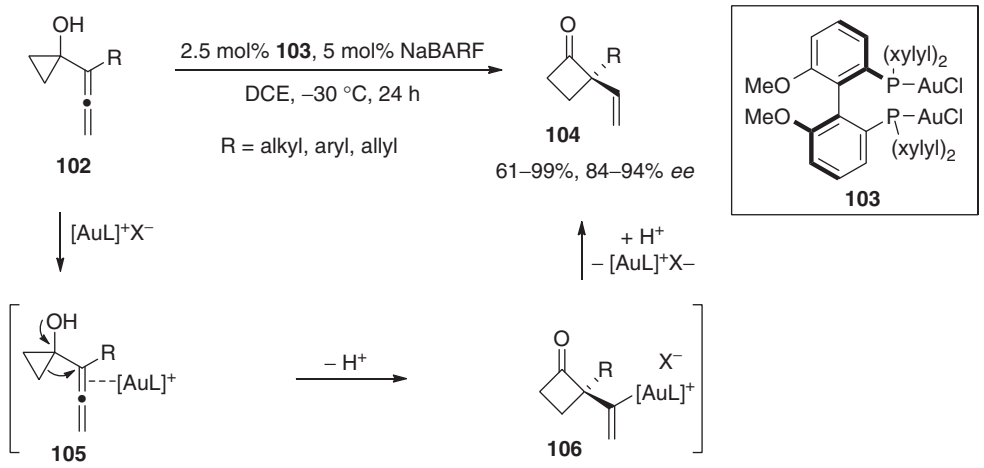


Scheme 21 Ruthenium(II)-promoted rearrangement of 1-alkynylcyclopropanols.

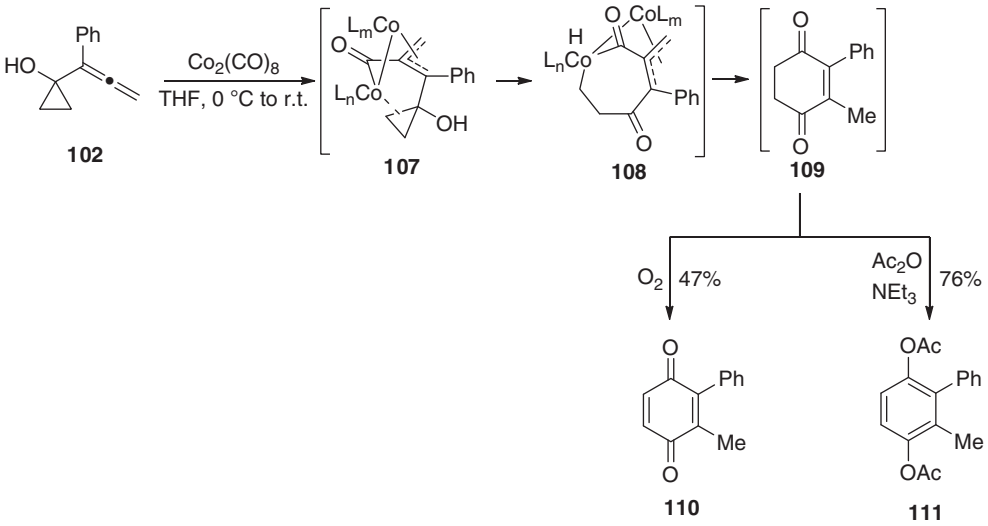
In contrast, electron-donating silyl groups or electron-withdrawing carbonyl groups yield selectively *cis*-cyclobutenones **101** and **100**, respectively. The observed olefin geometry is complementary to the one obtained by the gold-catalyzed process.

Toste reported in 2009 a highly enantioselective rearrangement of 1-allenylcyclopropanols **102** using the chiral bis-gold(I) complex **103** (Scheme 22) to give cyclobutanones **104**.[40] On generation of a competent cationic gold species by anion metathesis with sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate, the reaction proceeds at temperatures as low as $-30\,^{\circ}C$. The reaction tolerates different substitution pattern and works efficiently with a wide range of R-groups. Although coordination of the metal to the allene moiety of **105** induces ring enlargement via vinyl gold species **106**, the reaction can as well becatalyzed in a racemic fashion by simple Bronsted-acids such as $HNTf_2$.

Treatment of similar 1-allenyl cyclopropanols **102** with dicobaltoctacarbonyl at ambient temperature leads to a totally different reaction pathway (Scheme 23). Iwasawa reported the formation of diketone **109**, which rapidly enolizes to the corresponding hydroquinone.[41] Owing to its oxidation sensitivity, this primary product is *in situ* acylated to give **111** in good yield. Alternatively, deliberate exposure to molecular oxygen delivers benzoquinone **110**. The reaction is believed to proceed first by a carbonylation of



Scheme 22 Enantioselective gold-catalyzed rearrangement of allenylcyclopropanols.



Scheme 23 Cobalt-mediated rearrangement of allenylcyclopropanols into hydroquinone derivatives.

the allene moiety leading to **107**. Cleavage of the cyclopropane ring gives rise to intermediate **108**, and subsequent reductive elimination delivers diketone **109**.

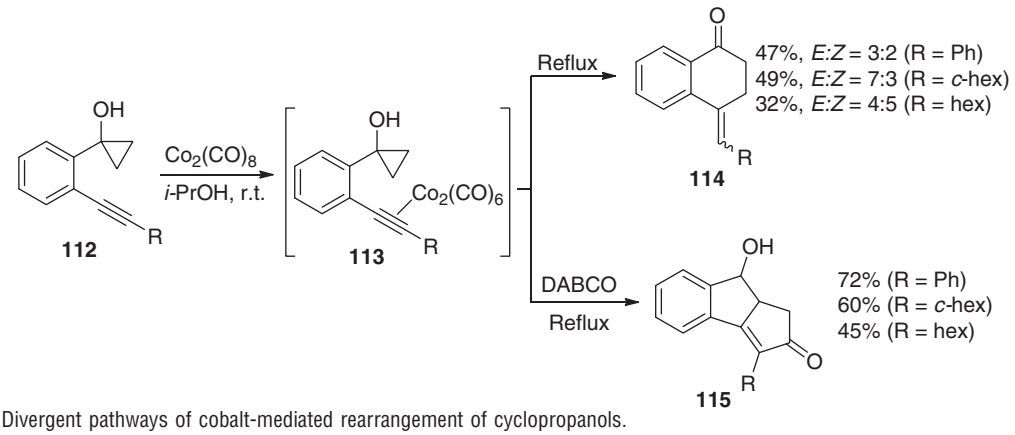
Iwasawa also reported cobalt-mediated rearrangements of 1-aryl cyclopropanols **112** with an appended internal alkyne (Scheme 24).[42] After formation of the alkyne cobalt complex **113** at ambient temperature in isopropanol, heating initiates a *β*-carbon cleavage and promotes subsequent cyclization to ketones **114** in fair yields. The *E*/*Z*-ratio is dependent on the substituent R of the alkyne. When the reaction is carried out in the presence of a base 1,4-diazabicyclo[2.2.2]octane (DABCO), a different pathway becomes operative and Pauson–Khand like products **115** are obtained in fair to good yields.

Trost reported in 2001 an enantioselective rearrangement of cyclopropanols such as **116** equipped with an allylic carbonate-leaving group (Scheme 25).[43] With a palladium(0) species formed with the Trost ligand **117** ionization to intermediate **118** occurs. The addition of tetramethylguanidine is beneficial for the rate of the reaction. From **118**, a selective migration of one of the enantiotopic cyclopropane C–C bond leads to cyclobutanone **104a** in excellent yield and selectivity.

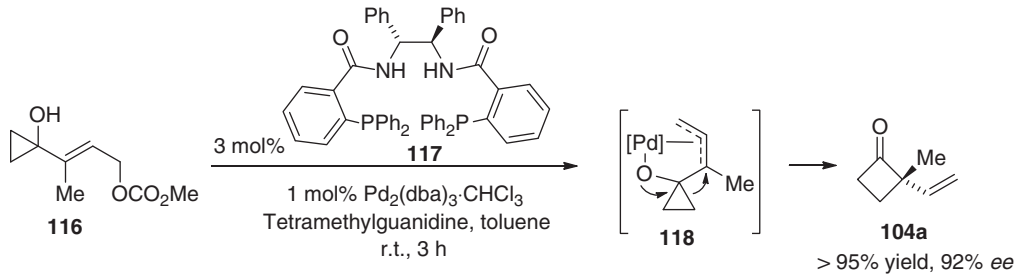
5.23.3 Charge-Promoted Rearrangements of Cyclobutanes

5.23.3.1 Oxyanion-Induced β-Carbon Eliminations

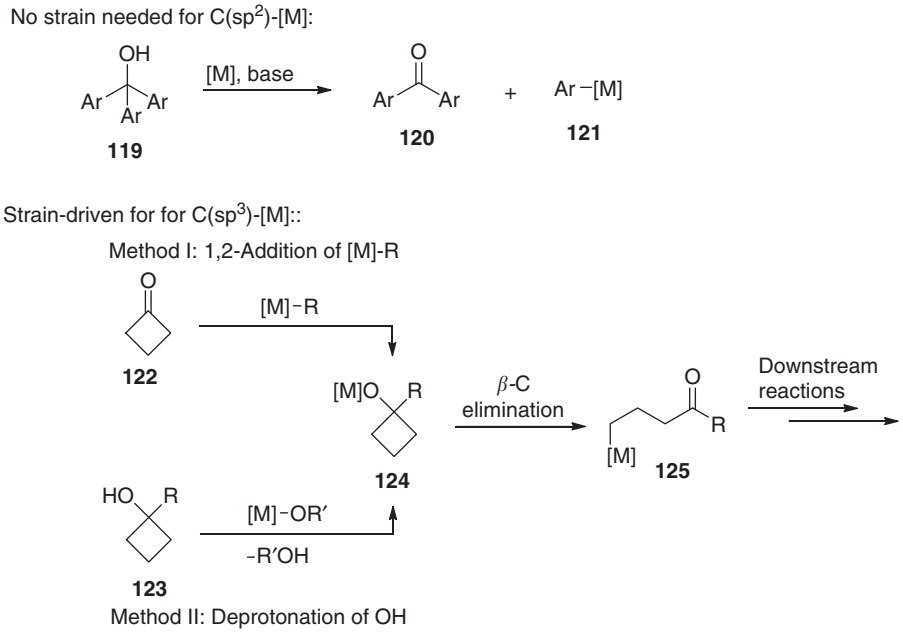
Hartwig has shown that triarylcarbinols **119** undergo a *β*-carbon elimination in the presence of a rhodium(I) catalyst to give aryl rhodium species **121** and benzophenone **120** (Scheme 26).[44] For a similar reaction leading to an alkyl-(instead of the aryl-) rhodium intermediate, additional energy input in the form of ring-strain release is required. In this respect, cyclobutanolates have



Scheme 24 Divergent pathways of cobalt-mediated rearrangement of cyclopropanols.



Scheme 25 Enantioselective palladium(0)-catalyzed rearrangement of cyclopropanols.

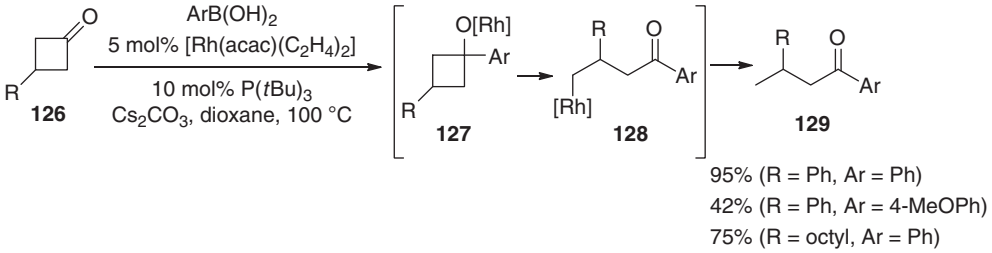


Scheme 26 Anion-promoted β-carbon elimination of *tert*-cyclobutanolate intermediates.

the right balance between reactivity and stability of the starting material and this method became a relatively robust reaction to access, in a complementary way, highly reactive alkyl-metal species **125**. Two general approaches have been described to obtain the metal cyclobutanolate intermediate **124**. It can be either obtained by the addition of an organometallic reagent to a cyclobutanone precursor **122** (Method I) or directly from the corresponding cyclobutanol **113** through deprotonation of the hydroxyl

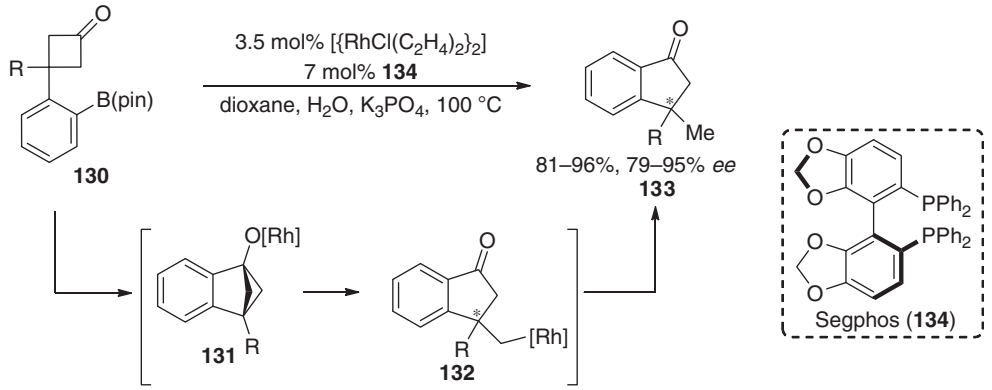
group (Method II). Both methods and the rich downstream chemistry of the alkyl-metal intermediates are discussed in this section.[45]

Following the first approach, Murakami disclosed rhodium(I)-catalyzed intermolecular 1,2-additions of aryl boronic acids to cyclobutanones **126** (Scheme 27).[46] Normal ketones are poor electrophiles in rhodium(I)-catalyzed 1,2-additions, but the higher carbonyl reactivity of a cyclobutanone compared to an unstrained ketone enables this process. However, only a single substituent is tolerated in the 3-position of the cyclobutanone. The rhodium-cyclobutanolate intermediate **127** is then undergoing a β-carbon cleavage reaction to give **128**. Sequential β-hydride eliminations and readditions afford an oxa-π-allylrhodium which is finally protonated to yield arylketones **129**.



Scheme 27 β-Carbon elimination induced by intermolecular 1,2-addition of arylrhodium species.

3,3-Disubstituted cyclobutanones are unreactive toward 1,2-additions of aryl rhodium species. So far, this could only be overcome by performing the reaction in an intramolecular fashion (Scheme 28).[47] Starting from boronic acid **130**, a 1,2-addition leads to the highly strained rhodium-alkoxide **131**, which in turn undergoes a β-carbon elimination to give complex **132**. Protonation via a 1,4-rhodium shift leads to indanones **133**. A differentiation of the two enantiotopic C–C bonds of **131** during the β-carbon elimination step enables the resulting quaternary carbon center to be formed with high enantioselectivity. Segphos (**134**) proved to be the best ligand for this purpose.

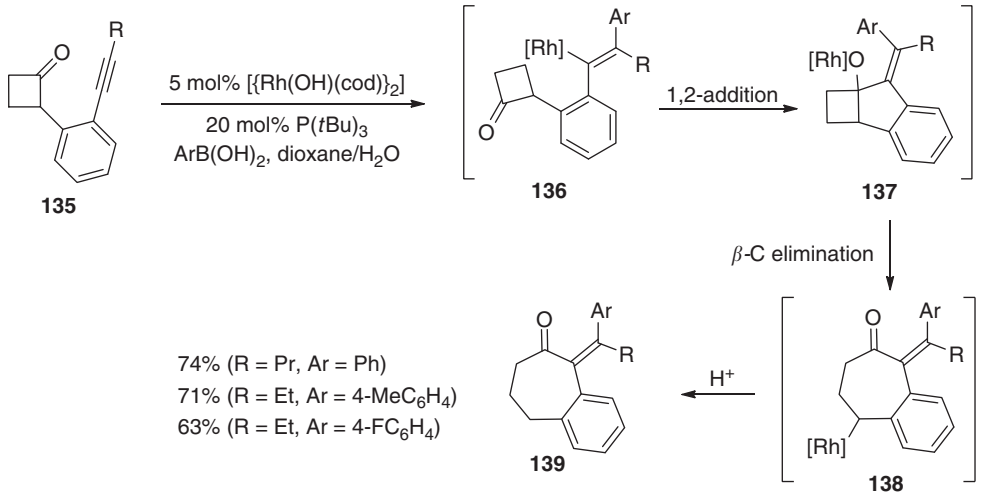


Scheme 28 Intramolecular 1,2-addition followed by enantioselective β-carbon elimination.

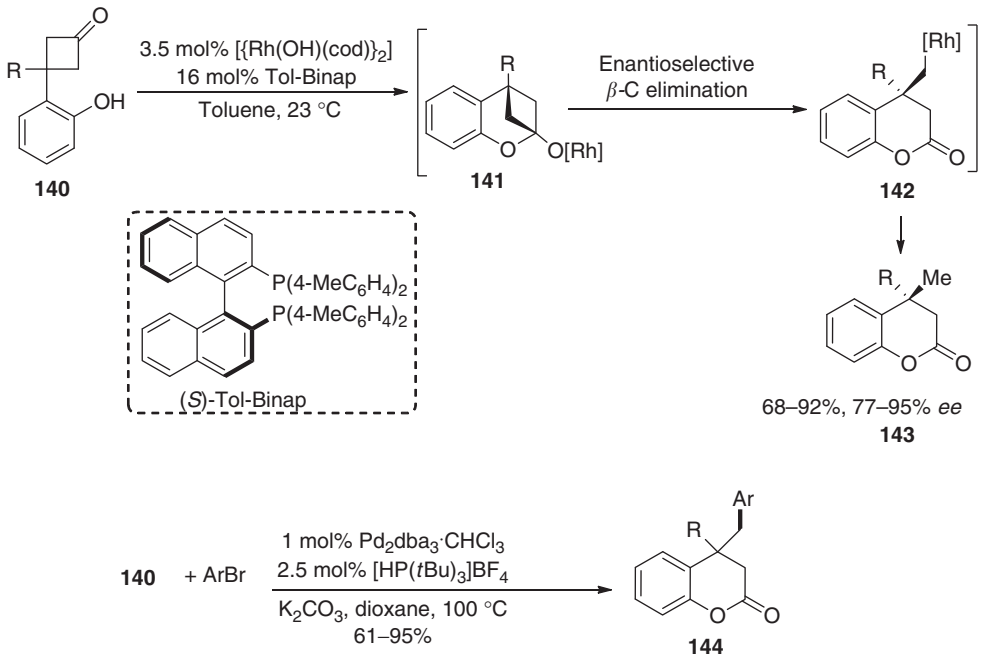
The same authors further designed another handle to render the additions intramolecular. First, regioselective carbo rhodation of the internal alkyne of **135** gives rise to vinyl rhodium species **136** (Scheme 29).[48] A facile intramolecular 1,2-addition across the carbonyl group of the cyclobutanone generates the requisite cyclobutanolate **137**. Regioselective β-carbon elimination leads to the benzylic rhodium species **138**. Two consecutive β-hydride eliminations/readditions provide medium-sized benzoheptanones **139** as the terminal products.

Murakami also reported the generation of the cyclobutanolate intermediates from a cyclobutanone by deprotonation of an *in situ* formed hemiacetal (Scheme 30).[49] The initial step of the reaction is believed to be the deprotonation of the phenolic hydroxyl group of **140**. Cyclization delivers lactolate **141**. The use of Tol-Binap as chiral ligand results in an enantioselective β-carbon elimination. Protodemetalation of the alkylrhodium species **142** gives dihydrocoumarine **143** in good to excellent enantiomeric excess. Arylated dihydrocoumarines **144** were obtained with similar substrates by performing the reaction with a palladium catalyst.[50]

Murakami reported a nickel(0)-catalyzed process using cyclobutanones **145** and internal alkynes. In this reaction, the cyclobutanone serves as a four-carbon atom component in a formal [4 + 2]-cycloaddition providing cyclohexenones **146** (Scheme 31).[51] In 2012, Aissa has extended this reaction to 3-azetidinones **147** and 3-oxetanones **149**, leading to the corresponding heterocycles **148** and **150** in high yields.[52] Like for many other nickel(0)-catalyzed reactions between alkynes and



Scheme 29 Cyclobutanolate formation induced through carborhodation of appended alkynes.

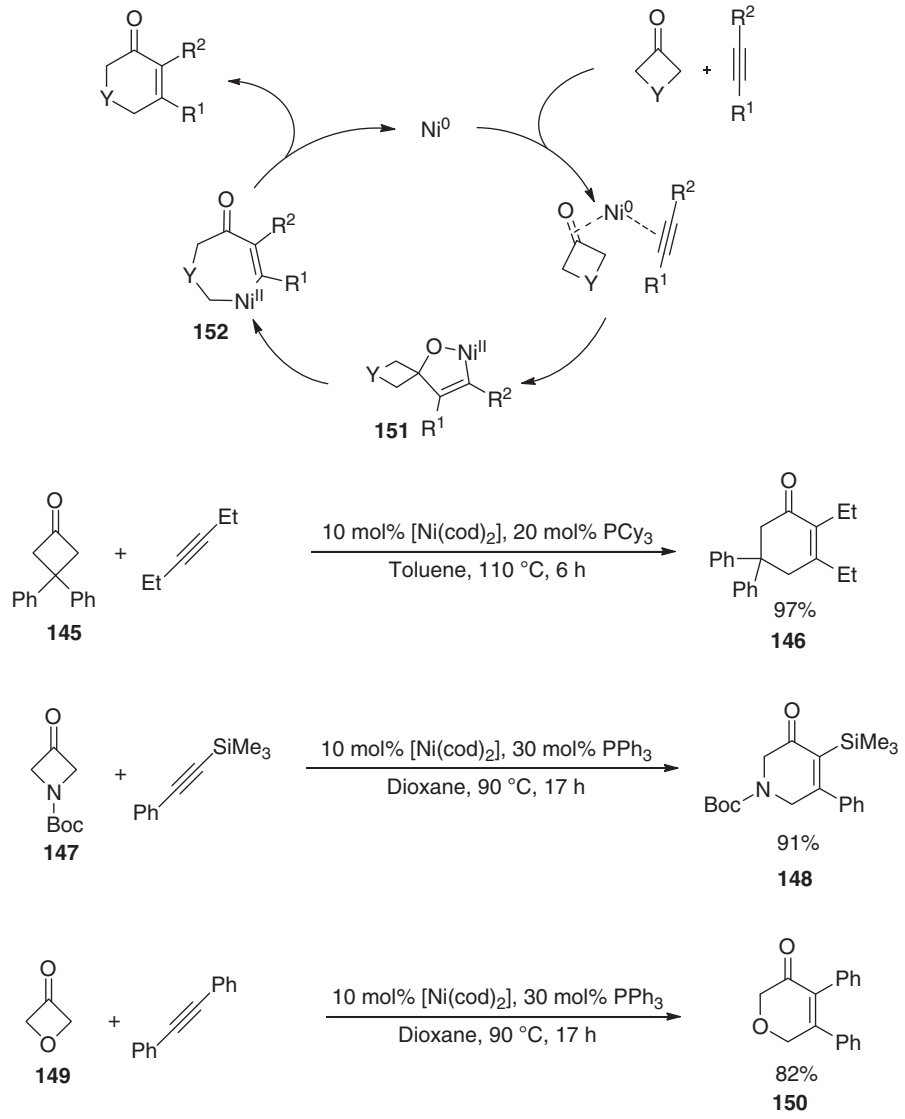


Scheme 30 Deprotonation of lactols promotes enantioselective β-carbon elimination.

carbonyl moieties, oxidative cyclization to form an oxanickelacyclopentene is the central part of the mechanism. A similar intermediate is proposed for the reaction with the strained four-membered ring ketone. Hence, the proposed catalytic cycle is initiated by a simultaneous coordination of the carbonyl group and the alkyne to the Ni(0)-catalyst resulting in a cyclization, which leads to the crucial spiro-oxanickelacycle **151**. The nickel cyclobutanolate collapses subsequently by β-carbon elimination, cleaving the four-membered ring and forming the seven-membered nickelacycle **152**. Reductive elimination forms the observed six-membered rings in moderate to excellent yields and expels the Ni(0)-complex to close the catalytic cycle.

This principal reaction concept was extended to a formal [4 + 2 + 2]-cycloaddition leading to cyclooctadienones **157** (Scheme 32).[53] Tethered diynes **153** provided, on reaction with the nickel(0) catalyst, a nickelacyclopentadiene **154** which reacts in a similar manner with the strained cyclobutanone, now leading to spirocycle **155**. Once again, the *tert*-cyclobutanolate collapses via β-carbon elimination to give **156**, which on reductive elimination yields cyclooctadienones **157**.

Although the nickel-catalyzed reactions do not proceed with olefins instead of alkynes in an intermolecular fashion, a corresponding intramolecular version can accommodate the less reactive olefins as coupling partners (Scheme 33).[54] As before, oxidative cyclization of **158** forms oxanickelacyclopentane intermediate **159**, which undergoes β-carbon elimination to

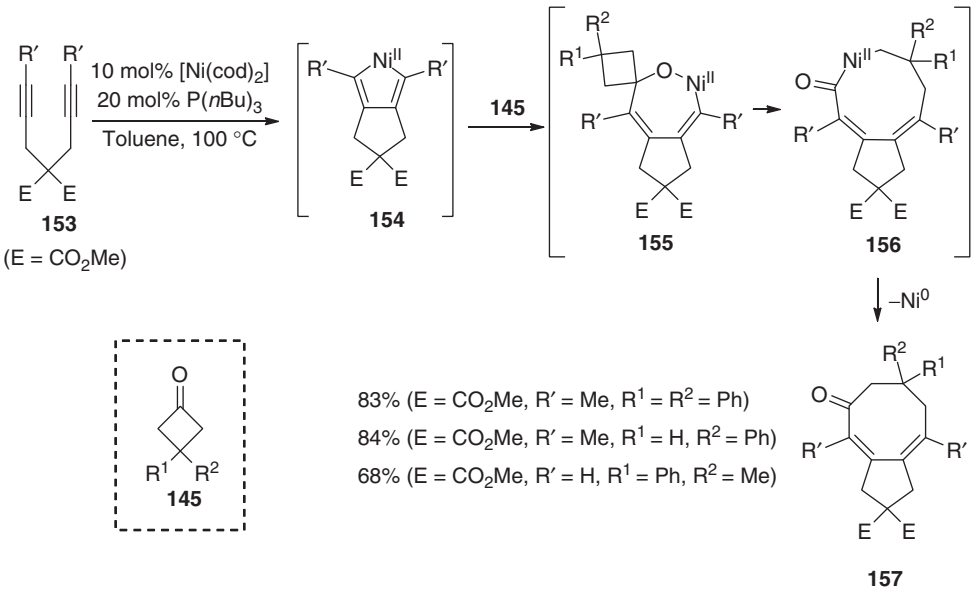


Scheme 31 Nickel-catalyzed [4 + 2]-cycloaddition of strained four-membered ketones and alkynes.

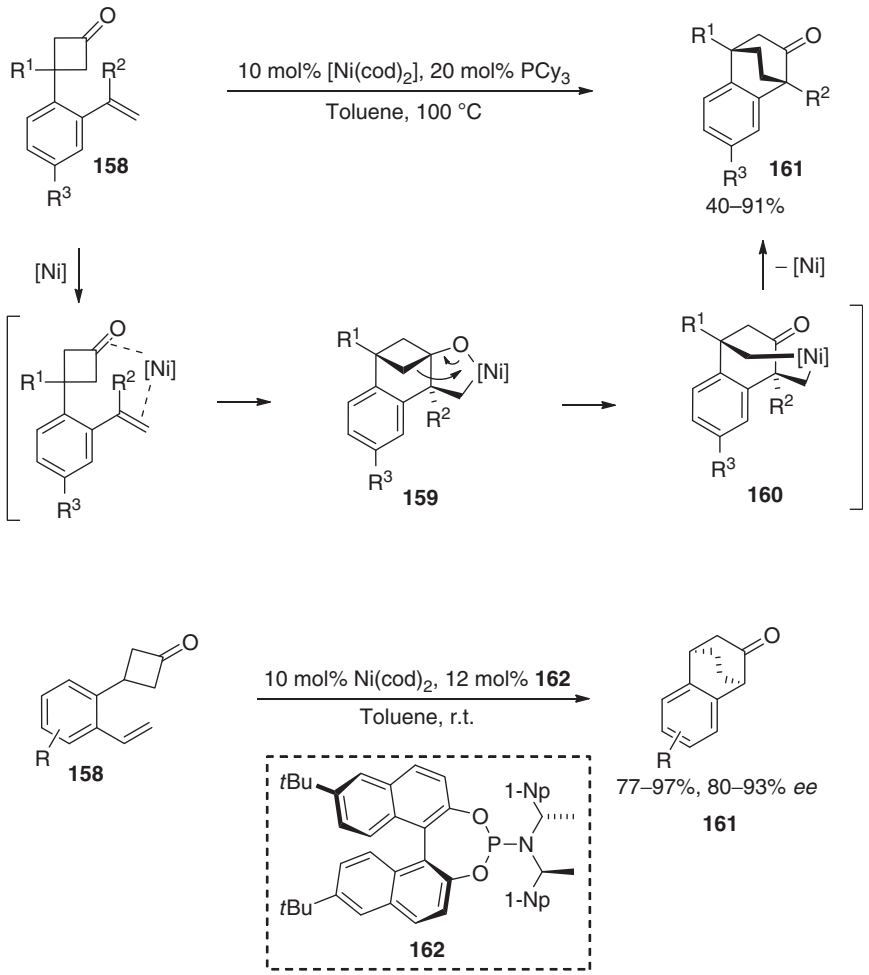
nickelacycles **160**. Reductive elimination closes the catalytic cycle and gives benzobicyclo[2.2.2]octenones **161**. In 2012, an enantioselective version of this reaction has been reported.[55] With the Binol-derived phosphoramidite ligand **162**, high enantioselectivities ranging from 80 to 93% *ee* are obtained for styrene substrates **158**.

The second method to obtain transition-metal cyclobutoxides as precursors for the *β*-carbon elimination process is the direct deprotonation of a preformed cyclobutanol derivative. Although this method requires more elaborated tertiary alcohols as starting materials, its independence from tethered 'enabling' functionalities such as alcohols, alkynes and olefins offsets this shortcoming. Uemura demonstrated in 1999 the viability of this approach. Under oxidative conditions, cyclobutanol **163** was cleaved in the presence of a palladium(II) catalyst to intermediate **164** (Scheme 34).[56] Depending on the substitution R, different pathways are operative. If a *β*-hydrogen atom is present (R = H), *β*-hydride elimination is preferred, resulting in the formation of the *β*,*γ*-unsaturated ketone **165**. If no *β*-hydrogen atom is available (R = Me), a cyclization by a direct arylation of the phenyl group leads to the tricyclic ketone **166**. Reoxidation of the formed palladium(0) species occurs under oxygen atmosphere.

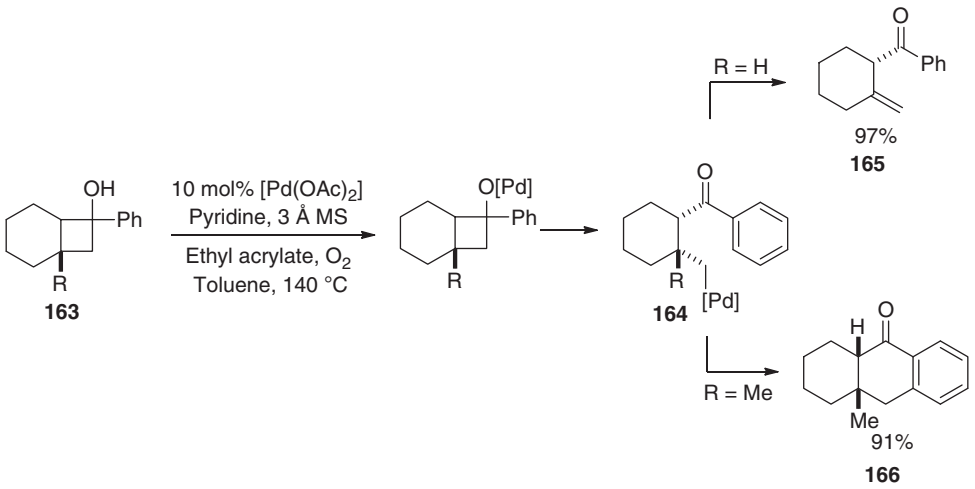
The same group demonstrated that the formed alkylpalladium intermediate can be coupled to aryl halides (Scheme 35).[57] In this scenario, reoxidation of the Pd(0)-species proceeds by an oxidative addition of an aryl bromide or iodide leading to an aryl palladium(II) species. This complex is competent to induce ring-cleavage of **167** and forms the aryl alkylpalladium intermediate **168**. Reductive elimination forms *γ*-arylated ketones **169**. The scope of this process was recently extended by Martin, now allowing an efficient use of aryl chlorides as well as 3,3-unsubstituted cyclobutanols as substrates.[58] Orellana further showed that benzocyclobutanols **170** are selectively cleaved to form the more stable C(sp^2)-Pd bond (**171**) providing ketone **172**.[59]



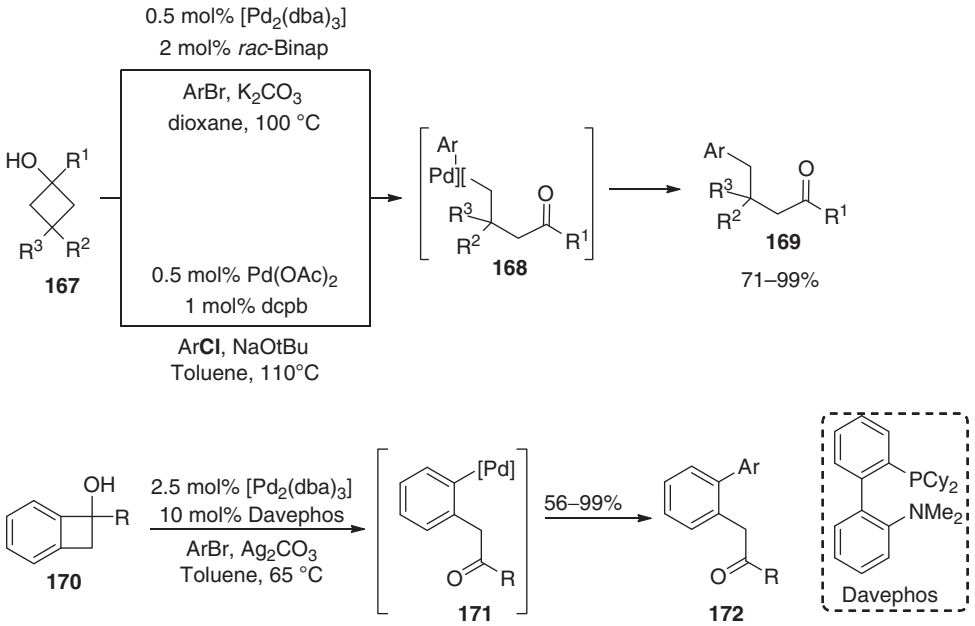
Scheme 32 [4 + 2 + 2]-cycloaddition of cyclobutanones and diynes.



Scheme 33 Intramolecular cyclization/rearrangements with olefins. 1-Np, 1-naphthyl.



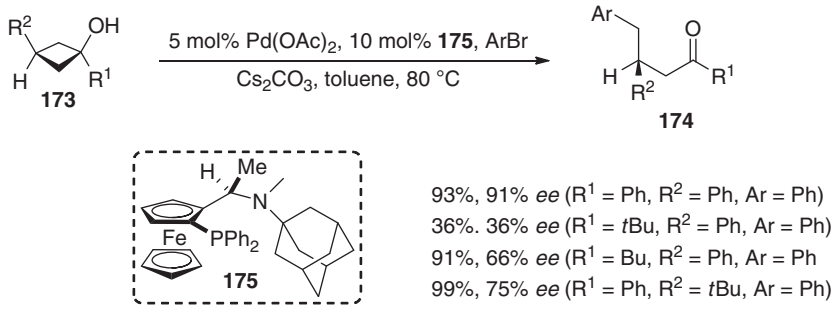
Scheme 34 Uemura's pioneering Pd(II)-catalyzed ring-cleavage of *tert*-cyclobutanols.



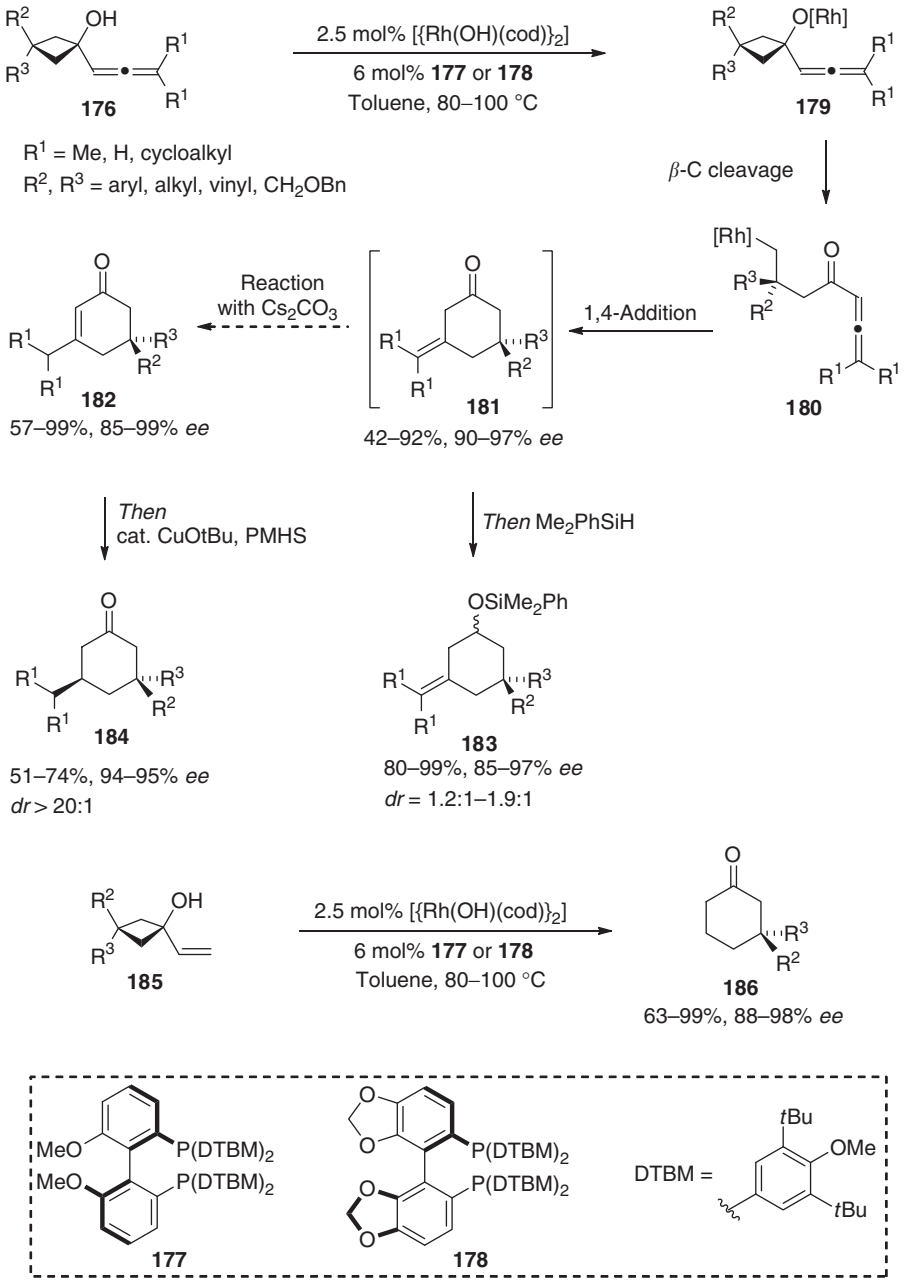
Scheme 35 β-Carbon elimination and trapping of the intermediate by subsequent arylation.

Uemura and coworkers developed an enantioselective version of this process.[60] With the engineered bulky bidentate *P,N*-ferrocenyl ligand **175**, γ-arylated ketones **174** with a tertiary stereogenic center were obtained in excellent enantioselectivities of up to 95% *ee* (Scheme 36). However, 3,3-disubstituted cyclobutanol substrates reacted less selectively, and the selectivity was dependent as well on the substitution pattern.

Rhodium(I) catalysts are also well suited to initiate β-carbon cleavages from metal cyclobutanolates, showing a complementary reaction profile of the arising alkyl-metal intermediate. In 2008, Cramer reported a highly enantioselective rearrangement of allenyl cyclobutanols **176** (Scheme 37).[61] Once the rhodium alkoxide **179** is formed, an enantioselective β-carbon cleavage is triggered, leading to an alkylrhodium intermediate **180** bearing an all-carbon quaternary stereogenic center. Chiral bulky biphosphine ligands such as di(3,5-di-*tert*-butyl-4-methoxyphenyl (DTBM)-MeOBiphep (**177**) or DTBM-Segphos (**178**) allow for excellent enantioselectivities. Subsequent cyclization of **180** by 1,4-addition across the now activated allenyl ketone moiety provides access to cyclohexanones **181** with an exocyclic double.[62] Without auxiliary bases in the reaction mixture and careful work-up, these products can be isolated. In the presence of cesium carbonate, double bond isomerization occurs, leading to enones **182**. As the addition across the allene moiety is faster than β-hydride elimination, cyclobutanols that are only monosubstituted at the 3-position can be used as well. One-pot and cascade pathways were developed, enabling an access to different products. For instance, *in situ*



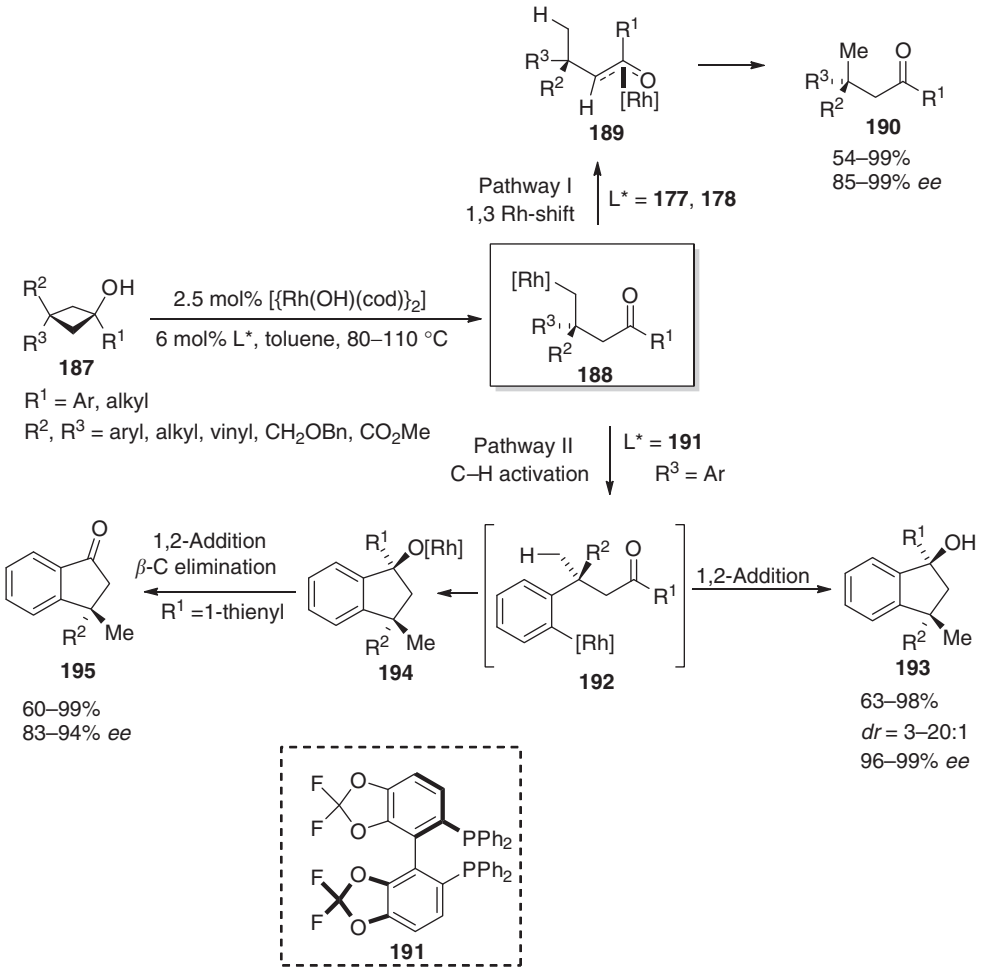
Scheme 36 Enantioselective version of the Pd-catalyzed β-carbon elimination/arylation.



Scheme 37 Reactions of alkylrhodium species formed by β-carbon elimination of *tert*-cyclobutanols.

hydrosilylation providing a protected secondary alcohol **183**, occurs with a silane in the presence of the rhodium catalyst. 1,4-Reduction can be selectively induced with an added copper(I) catalyst and a silane leading to saturated ketone **184**. Vinyl *tert*-cyclobutanols **185**, forming intermediary vinyl ketones cyclize as well, giving rise to cyclohexanones **186**.

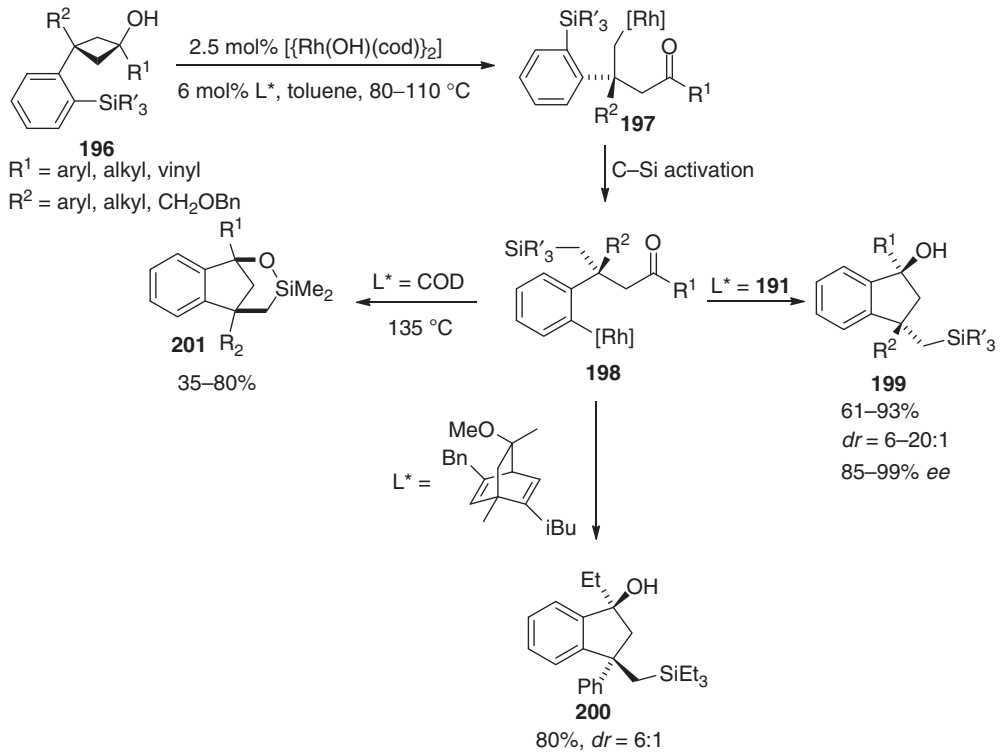
The β-carbon cleavage does not require vinyl or allenyl groups in proximity to proceed. Aryl- or alkyl-substituted cyclobutanols (**187**) rearrange to alkylrhodium intermediates seeking downstream stabilization by other pathways. Apparent protodemetalation of intermediate **188** afford acyclic ketones **190** (Scheme 38, pathway I).[63] However, Cramer showed with labeling experiments that the formation of **190** proceeds by a 1,3-Rh-shift, forming oxa-π-allylrhodium species before protonation. Cramer and Murakami independently found that β-aryl substituted substrates undergo a formal 1,4-rhodium shift, which is supposed to proceed via a C–H bond activation/reductive elimination pathway of hydride (pathway II).[64] An intramolecular addition of the arising aryl rhodium species **192** across the formed carbonyl group yields heavily substituted indanols **193** in a highly enantio- and diastereoselective manner using difluorphos **191** as steering ligand. Remarkably, electron-rich aromatic substituents R^1, e.g., a 1-thienyl group, induced another β-carbon elimination from the rhodium indanolates **194** providing finally indanones **195**.[65]



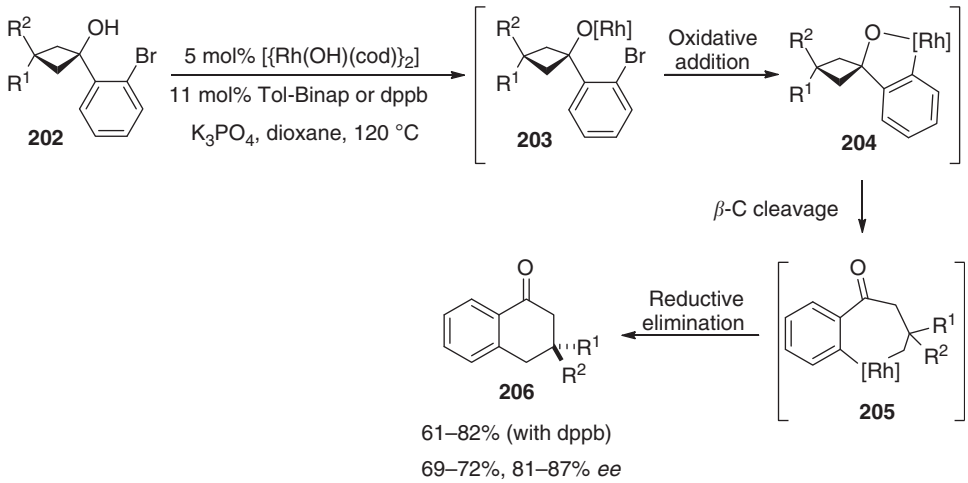
Scheme 38 Ring-cleavage followed by pathways induced by C–H activations.

The transposition of the aromatic hydrogen atom limits the reachable product portfolio strictly to methyl-substituted quaternary stereogenic centers. Addressing this shortcoming, Cramer showed further that functionalizable silyl groups (**196**–**198**) can be used alternatively. Oxidative cleavage followed by reductive elimination leads to silyl-substituted products **199** (Scheme 39).[66] In general, silyl groups with two methyl substituents ensure complete C–Si over C–H activation. For bulkier silyl groups, rhodium catalysts bearing solely a diene as ligand provide selective C–Si activation, whereas phosphine ligands favor C–H activation. In addition, the diastereoselectivity is dependent on the nature of the ligand. Phosphines give rise to indanols **199** and diene ligands to indanols **200** with the opposite diastereoselectivity. Higher reaction temperatures induced a second C–Si activation, thus providing access to tricyclic silyl ethers **201**.

Murakami developed a Rh(I)–Rh(III) redox cycle which allows bromo aryl-substituted *tert*-cyclobutanols **202** to be converted into tetralones **206** by a β-carbon cleavage process (Scheme 40).[67] The suggested mechanism involves oxidative addition of the



Scheme 39 Ring-cleavage, followed by C–Si activation.



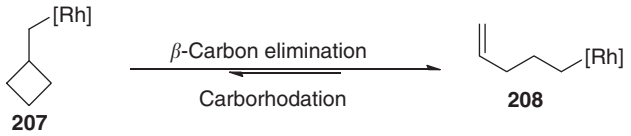
Scheme 40 Cyclobutanol cleavage leading to tetralones.

rhodium alkoxide **203** to give Rh(III)-species **204**. Subsequent *β*-carbon elimination forms **205** and reductive elimination provides **206** in good yields. The process can be conducted asymmetrically and gives good selectivities with Tol-Binap as the chiral ligand.

5.23.3.2 Carbanion-Induced β-Carbon Eliminations

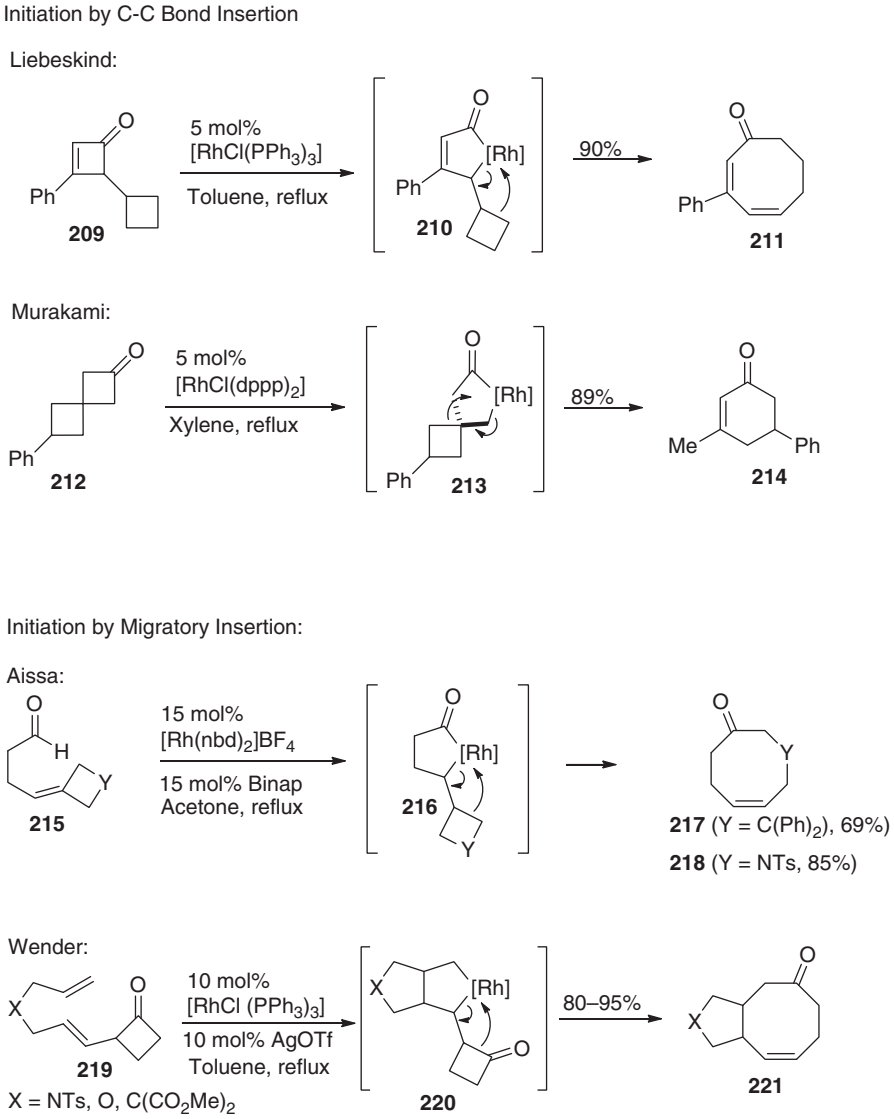
β-Carbon eliminations from cyclobutylmethyl metal species is an unconventional method to access unusual organometallic intermediates from cyclobutane derivatives. This reaction can be seen as the reversal of the carbometalation of a C–C double bond, a '*retro* 4-*exo-trig*' event (equation 4). Compared to the previous Section 5.23.2.1, where a very strong carbonyl bond was

concomitantly generated during the ring opening, the formation of an olefin provides less energy. In contrast to rearrangements of cyclopropyl metal intermediates, the homologous ring-opening reaction of cyclobutyl metal species is already less favored. Owing to the stronger carbon–rhodium bond compared to other transition metals, rhodium catalysts are the favored metal for this process, although a few other examples exist. The β-carbon elimination is nevertheless often faster than other pathways of the organometallic intermediate, namely reductive- and β-H-eliminations, so that its synthetic potential could be explored.



(4)

The crucial organorhodium intermediates can be accessed by several indirect methods involving either an addition across a double bond or a C–C bond activation process (**Scheme 41**). In a leading example, Liebeskind investigated the C–C insertion of rhodium(I) complexes into cyclobutenone **209** in 1993.[68] Rhodacycle **210** is formed with catalytic amounts of Wilkinson's catalyst in refluxing toluene. In turn, this intermediate undergoes β-carbon cleavage of the adjacent cyclobutane and subsequent reductive elimination provides access to cyclooctadienone **211**. Exploiting the insertion of rhodium(I) complexes into the acyl bond of strained ketones, Murakami disclosed a related reaction starting from spirocyclobutanone **212**.[69] The initial C–C bond insertion delivers the cyclobutylmethyl rhodium intermediate **213** and sets the stage for the β-carbon elimination. Final reductive

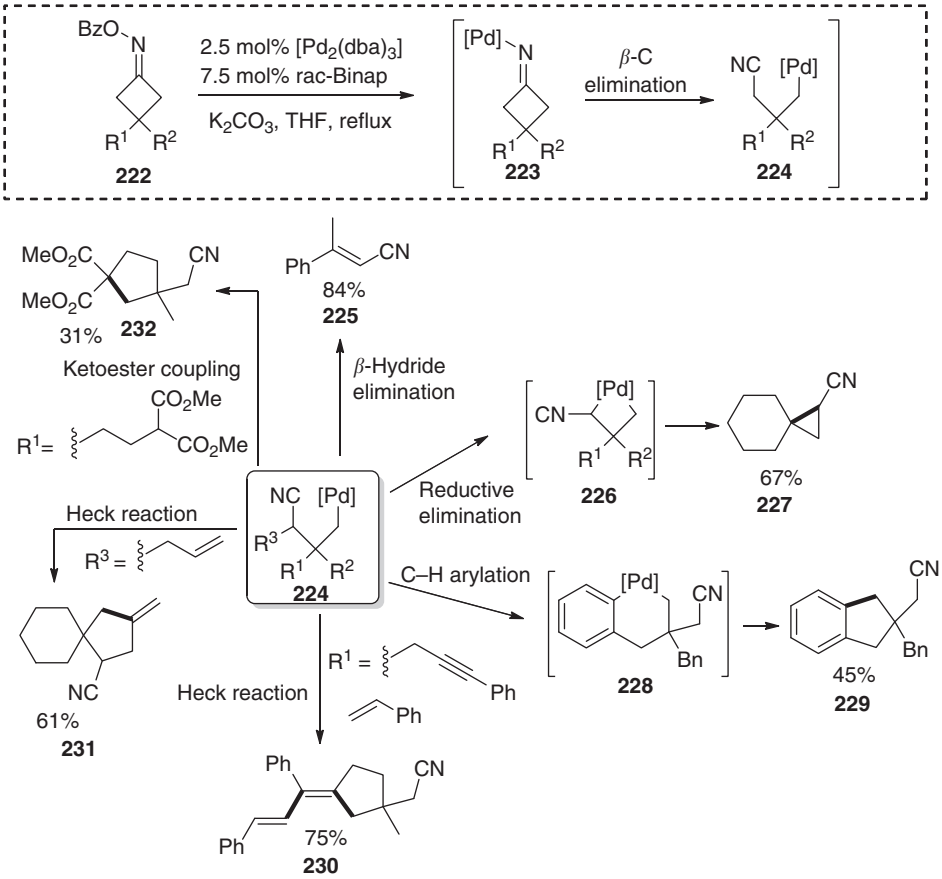


Scheme 41 β-Carbon eliminations induced by cyclobutylmethyl-metal transients.

elimination gives rise to cyclohexenone **214**. A conceptually different method to obtain the direct cyclobutylmethyl metal precursor is the addition of an organorhodium species across a suitable double bond, which consists either of a vinylcyclobutane or a vinylidenecyclobutane. Following the latter approach, Aissa used an intramolecular hydroacylation of **215** to obtain **216**, which collapses under ring-strain release to cyclooctenone **217**.[70] The method is also suited for azetidine derivatives **218** in the place of a cyclobutane. Wender accessed rhodacycle **220** via cycloisomerization of dienes **219**.[71] In contrast to his work on [5 + 2]-cycloadditions with vinyl cyclopropane substrate, the ring opening of the cyclobutylmethyl intermediate is significantly more sluggish. Without the appended carbonyl group on the cyclobutane providing an additional driving force, no ring-opening proceeded. However, in some instances this carbonyl causes side reaction. CO extrusion can take place, leading to the formation of seven-membered rings as side products instead of the desired cyclooctenone **221**.

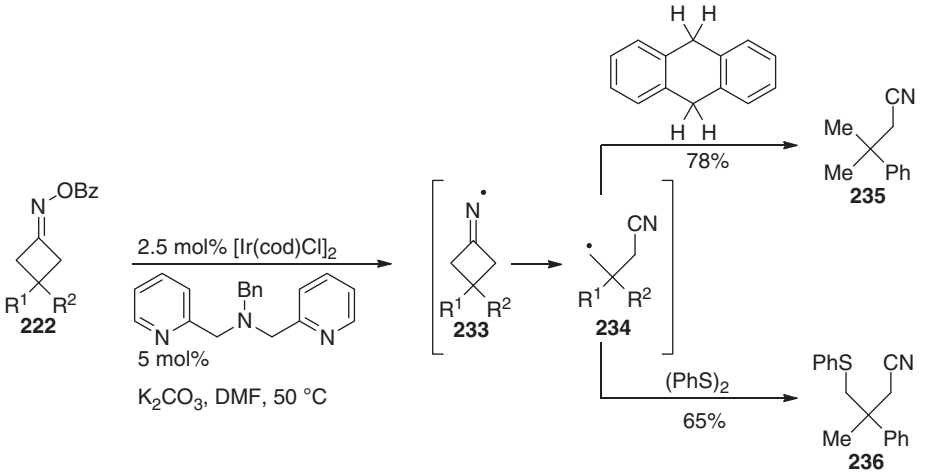
5.23.3.3 Azaanion-Induced β-Carbon Eliminations

The use of metal-nitrogen intermediates to trigger rearrangements has so far received less attention. In addition to the energy released by ring opening, cleavages from C=N double bonds to form nitriles are a good driving force. For instance, Uemura reported an attractive method capitalizing on the generation of a strong CN-triple bond of a nitrile from benzoylated cyclobutanone oximes **222** using a Pd(0)-catalyst (Scheme 42).[72] This process still represents a *β*-carbon elimination (in this case a '*retro*-4-*exo*-*dig*' event). Oxidative addition of the N–O bond generates an iminopalladium(II) species **223**, which is the competent intermediate to undergo *β*-carbon cleavage giving nitriles **224**. In the absence of a suitable acceptor, *β*-hydride elimination and migration of the formed double bond into conjugation yields acrylonitriles **225** (for R^1 and/or R^2=H). In cases where the *β*-hydride elimination pathway is blocked (R^1 and $R^2 \neq H$), cyclopropanecarbonitriles **227** are obtained instead. The reaction is presumed to proceed via an activation of the acidic methylene group in *α*-position to the nitrile to give palladacyclobutane **226**; reductive elimination yields the products **227**. Alternatively, an activation of an aryl-H bond can proceed to yield benzocyclobutane **229** via palladacycle **228**. However, offering a suitable acceptor to intermediate **224** can trigger many of the common reactivities of organopalladium(II) species. For instance, Heck-type processes were obtained when an alkene or alkyne moiety is at a distance for a 5-*exo*-*trig*/5-*exo*-*dig* cyclization (**230** and **231**). Similarly, appended malonates react as C-nucleophiles forming cyclopentane derivatives **232**, though in rather modest yields.



Scheme 42 *β*-Carbon elimination from iminyl Pd(II)-complexes and their reaction manifold.

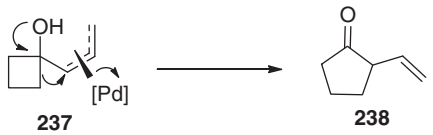
A related ring-cleavage reactivity has been reported by the same authors using iridium complexes (Scheme 43);[73] reduced products **235** are obtained. However, the reaction does not proceed via anionic metal intermediates but is believed to proceed through radical pathways involving species such as **233** and **234**. This conclusion is based on trapping reactions which gave products **236** with diphenyldisulfide in good yields, and enhanced yields of **235** in the presence of a hydrogen donor.



Scheme 43 Iridium-catalyzed ring-cleavage proceeding by radical pathways.

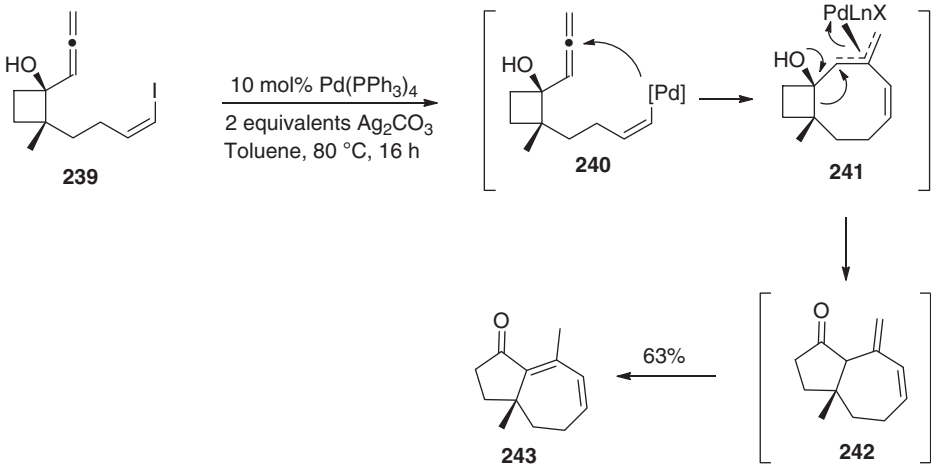
5.23.3.4 Allylmetal-Induced Rearrangements of Cyclobutanols

tert-Cyclobutanols can be triggered to ring expand by activating adjacent C–C double or triple bonds by a range of transition-metal complexes. Very often, this reactivity can be achieved by the generation of an allylmetal intermediate in α-position to the hydroxyl group, typically involving palladium catalysts (equation 5). Formally, the ring-expansion of **237** can be seen as Wagner–Meerwein type of reactivity, which can be modulated by the metal and its surrounding ligand sphere and delivers cyclopentanone derivatives **238**.



(5)

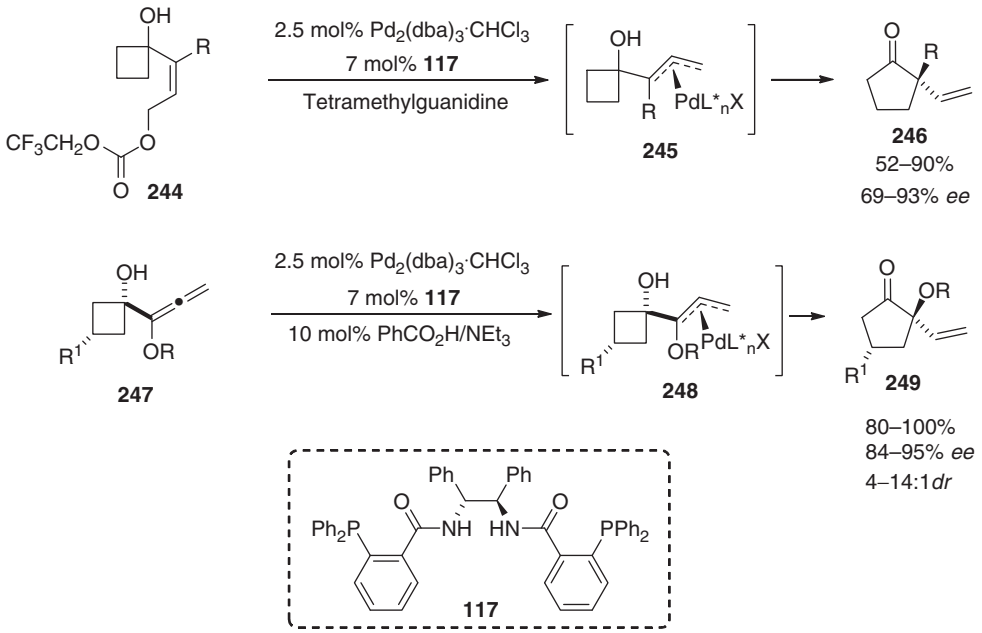
Nemoto proved the viability of this approach using allenyl cyclobutanol **239** as substrate (Scheme 44).[74] An intramolecular carbopalladation initiated via vinylpalladium species **240** from the appended *Z*-vinyl iodide moiety across the allene functionality generates the π-allyl palladium intermediate **241**. This 4,8-bicyclic system primarily formed rearranges to the 5,7-ring system **242**.



Scheme 44 Ring enlargements induced by carbo-palladations of allenyl cyclobutanols.

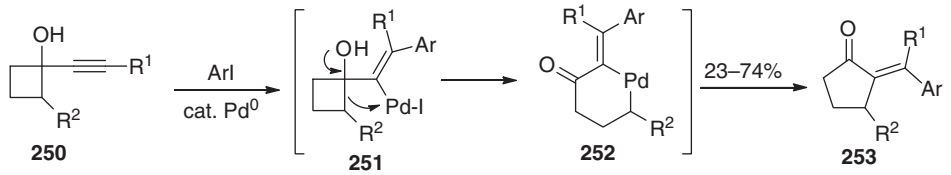
Under the reaction conditions, the *exo*-methylene group is not stable and migrates into conjugation to give the more stable enone **243** as the final product. The scope of the reaction was subsequently extended to an intermolecular version with aryl halides.[75] Based on these findings, related transformations were reported in which the key π-allyl palladium species was generated by a carbopalladation of conjugated dienes[76] or alternatively from propargylic carbonates.[77]

Trost developed an asymmetric version of this kind of ring expansions (Scheme 45). In the initial approach, the requisite π-allyl palladium intermediate **245** was generated from allyl carbonate precursors such as **244**.[43] Good to excellent levels of enantioselectivity were achieved with the Trost ligand **117**. Later, the process could be extended to cyclobutanol substrates **247** bearing an electron-rich alkoxy allene group. Hydropalladation leads to the formation of the allyl palladium species **248** and triggers the enantioselective ring enlargement to give access to a wide range of α-alkoxy cyclopentanones **249** in high diastereo- and enantioselectivity.[78]



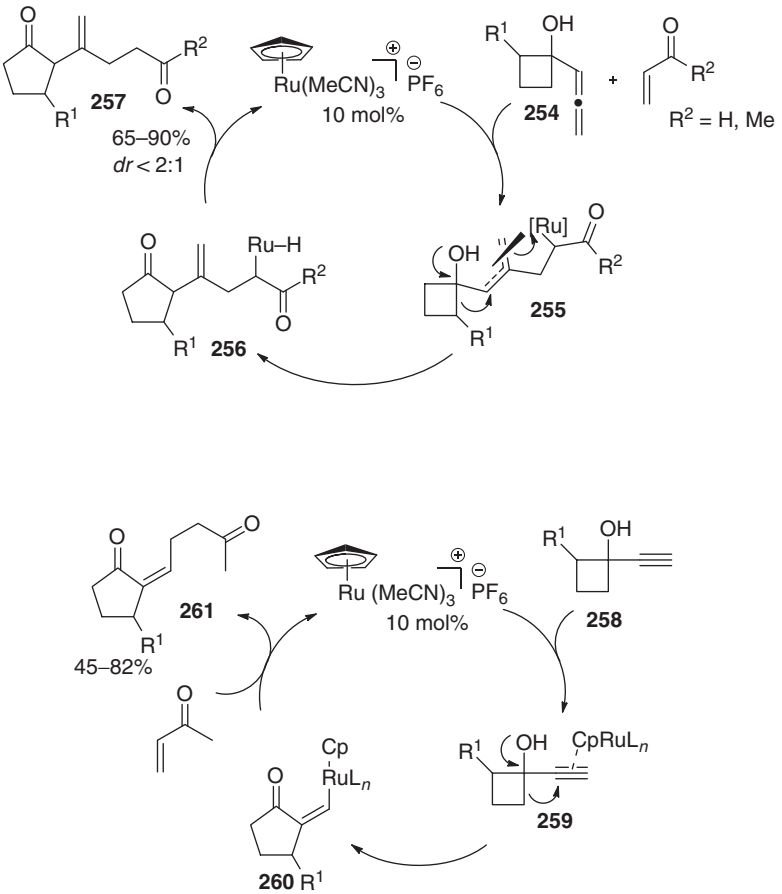
Scheme 45 Palladium-catalyzed enantioselective ring enlargements of cyclobutanols.

Larock reported a related, but mechanistically distinct process for the synthesis of 2-alkylidenecyclopentanones **253** from alkynyl-substituted cyclobutanols **250** (Scheme 46).[79] The authors suggest that the process is initiated by a regioselective carbopalladation of the internal alkyne moiety of the cyclobutanol **250**, giving rise to the vinyl-Pd(II) intermediate **251**. In turn, this vinyl metal species ring expands to give the six-membered palladacycle **252**. Finally, reductive elimination forms cyclopentenones **253** in fair to good yields.



Scheme 46 Cyclobutanol ring-expansion initiated by carbopalladation of internal alkynes.

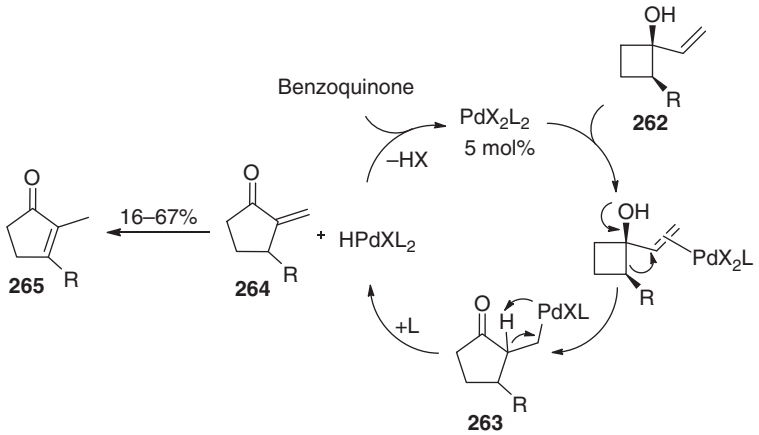
Besides palladium-catalyzed rearrangements via π-allyl intermediates, Ihara showed that ruthenium complexes are competent catalyst for this task (Scheme 47).[80] The required π-allyl intermediate is obtained by an intermolecular reaction of an α,β-unsaturated carbonyl compound (acrolein or methyl vinyl ketone, MVK) and allenylcyclobutanols **254**. It is assumed that an allyl ruthenacyclopentane **255** is formed with the ruthenium(II) complex $[CpRu(CH_3CN)_3]PF_6$. Subsequently, ring-expansion followed by reductive elimination leads to **256** which evolves into cyclopentanones **257** in good yields. Later, the same authors demonstrated as well the feasibility of this transformation with alkynyl-cyclobutanol substrates **258** as the strained ring component.[81] Contrasting the allene substrate **254**, they suggest a π-coordination of the ruthenium catalyst (**259**) promoting the rearrangement to the vinyl ruthenium species **260**. A 1,4-addition to MVK closes the catalytic cycle and gives product **261**.



Scheme 47 Ruthenium(II)-catalyzed intermolecular coupling/rearrangement reactions.

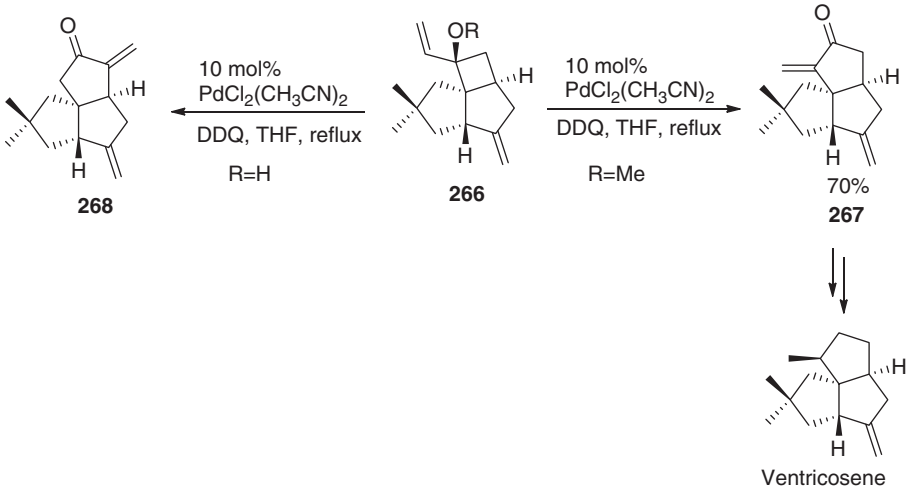
5.23.4 π-Coordinated Metal-Promoted Rearrangements of Cyclobutanes

In a seminal publication, Clark reported in 1985 that Pd(II) salts are active catalysts able to rearrange vinyl cyclobutanols **262** into cyclopentenones **265** (Scheme 48).[82] From a mechanistic perspective, coordination of the Pd(II) to the olefin promotes a Friedel–Crafts type reactivity, leading to cyclopentanone **263** bearing an alkylpalladium group. In turn, *β*-hydride elimination generates cyclopentenone **264**. Under the reaction condition, internalization of the olefin takes place to give **265**. Benzoquinone is often used as stoichiometric oxidant, which is required to reoxidize palladium(0) back to palladium(II) to close the catalytic cycle.



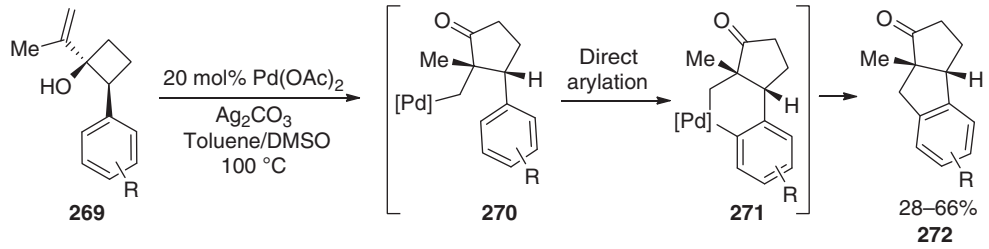
Scheme 48 Palladium(II)-salts promoted rearrangements of vinyl cyclobutanols.

Since the original publication, related methods were reported[83] and the reaction was sporadically employed in the context of natural product synthesis.[84] For example, Toste converted **266** into **267** for a total synthesis of ventricosene (Scheme 49). For the substrate with a free hydroxyl group, migration of the less substituted bond giving the undesired isomer **268** was observed. Protection of the hydroxyl group as its methyl ether induced a selective migration of the more highly substituted C–C bond, producing the required intermediate **267** for the completion of the synthesis of ventricosene.



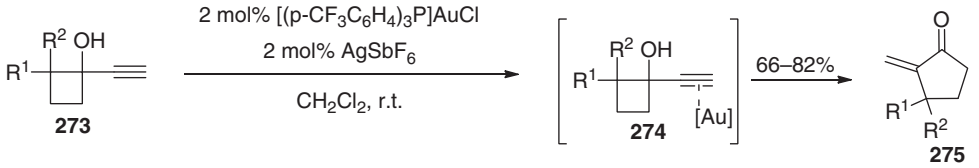
Scheme 49 Synthesis of ventricosene using a Pd(II)-catalyzed ring-expansion.

When substrates bearing 1,1-disubstituted olefins are used, the commonly observed *β*-hydride elimination of the alkylpalladium intermediate is blocked. This feature was recently explored by Orellana, who coupled the ring-expansion process to a downstream direct arylation reaction with a tethered aryl substituent (Scheme 50). This strategy provides access to *cis*-benzoquinanes **272** in moderate yields.[85] Starting with substrates **269**, coordination-promoted rearrangement gives rise to intermediate **270**, which undergoes (in the absence of a more favorable pathway) an activation of the aromatic C–H group leading to palladacycle **271**. Reductive elimination closes the second five-membered ring and gives the benzoquinanes **272**.



Scheme 50 A domino ring-expansion/direct arylation sequence.

Besides the activation of olefin-bearing cyclobutanols, the corresponding reactivity of alkynyl-substituted cyclobutanols was investigated as well. For instance, Toste exploited the strong propensity of gold complexes to act as carbophilic Lewis acids capable of activating carbon–carbon triple bonds, in conjunction with cyclobutanols **273** (Scheme 51). By coordination of an *in situ*



Scheme 51 Gold-catalyzed ring-expansion of alkynyl-cyclobutanols.

formed cationic gold(I) catalyst to the alkyne moiety of the substrate (**274**), the ring rearrangement is triggered forming cyclopentenones **275** in good yields.[38]

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5.24 The Pauson–Khand Reaction

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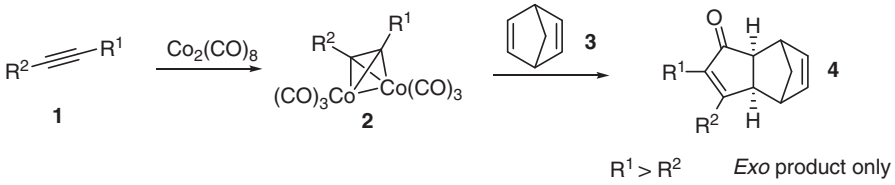
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Glossary

Desymmetrization reaction Reaction creating stereogenic center(s) by chiral catalysts from symmetric achiral substrates, such as *meso*-compounds.
Diversity-oriented synthesis A strategy for quick access to molecule libraries with an emphasis on skeletal diversity.
Promoter An additive, which expedites a reaction by activation of either the catalysts or the reagents.
Reagent-controlled reactions A reaction, the stereoselectivity of which is controlled by chiral catalysts or reagents.
Substrate-controlled reaction A reaction, the stereoselectivity of which is controlled by preexisting stereogenic center(s) in the substrates, not by the catalyst or the reagent; usually achiral catalysts or reagents are employed.
Tandem reaction A consecutive series of reactions completed in one batch. It can be affected by either employing more than one catalyst or reagent, where the product of one reaction is the substrate for another reaction, or by employing a single catalyst.

5.24.1 Introduction to the Pauson–Khand Reaction

Five-membered rings are found as a key portion of the skeleton in many biologically interesting natural products. Of the numerous methods for the preparation of this building block, the transition metal-mediated [2 + 2 + 1] carbocyclization of three components, an alkyne, an olefin, and carbon monoxide (CO), is uniquely straightforward and efficient. This reaction was first discovered and reported during the early 1970s by Pauson and Khand as an unexpected result of their study on the reaction of various (alkyne)hexacarbonyldicobalt compounds with strained olefins (Scheme 1). Shortly thereafter, it was named after its discoverers and so became known as the Pauson–Khand reaction (hereafter, PKR or PK-type reaction).[1]



Scheme 1

Since then, it has attracted a great deal of interest from the synthetic community over the past four decades, because of its distinctive virtues, providing a straightforward synthetic strategy for various natural products, operational simplicity, and compatibility with a wide range of functional groups. In addition, many variations using metals other than cobalt, improvements of the reaction efficiency by promoters, and the development of catalytic versions with a stereoselectivity issue have appeared in the literature. These subsequent developments are complementary to each other, make the transformation better and expand the application scope. Naturally, one can find a number of review articles and easily refer to them for more ideas and details about the reaction.[2]

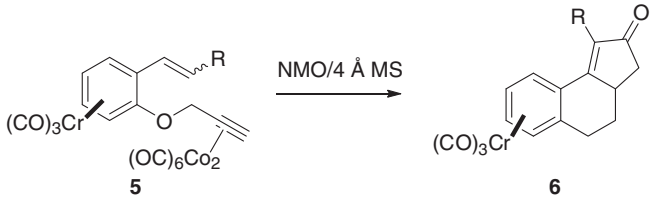
The purpose of this chapter is to update and highlight the recent advances regarding this reaction with critical comments, instead of duplicating the previous review articles.

Despite the fact that the reaction is conceptually straightforward and operationally simple, the original protocol exhibited some distinct limitations together with several virtues. We start our discussion by summarizing the scope and limitations of the original version, with respect to the substrate scope, regiochemistry, and stereochemistry. Then, a discussion of the possible solutions to nearly all of the issues raised regarding the original protocol will be given.

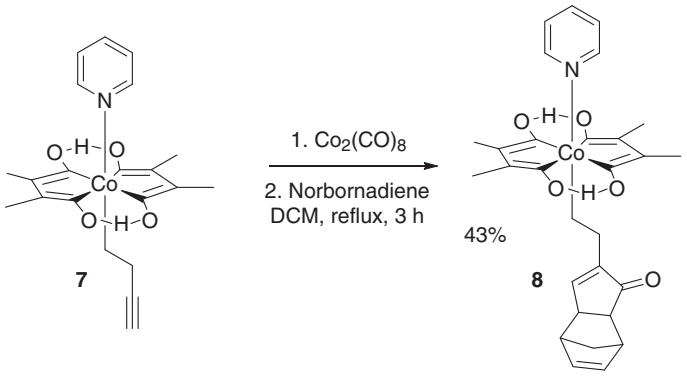
5.24.1.1 Substrate Scope

This reaction tolerated many functional groups, such as ethers, alcohols, carbonyls, acetals, esters, amides, tertiary amines, and even halides as previously summarized.[1b] It is worth mentioning here that even organometallics, including alkynyl allylamino

chromium and/or tungsten Fisher–carbene complexes,[3a] arene–chromium carbonyl complexes **5**,[3b] ferrocene,[3c] and cobalt complexes **7**[3d] are compatible with this reaction. A couple of examples are illustrated in equation 1.



85% (Based on the consumed substrate)



(1)

However, the efficiency of the reaction depends on the nature of the substrates. For example, electron-deficient olefins and/or alkynes were not adequate under the original thermal protocol. Also, it is well known that, from the inception, only strained olefins like norbornene provided reasonable chemical yields in the intermolecular PKR (**Figure 1**).[1,4]

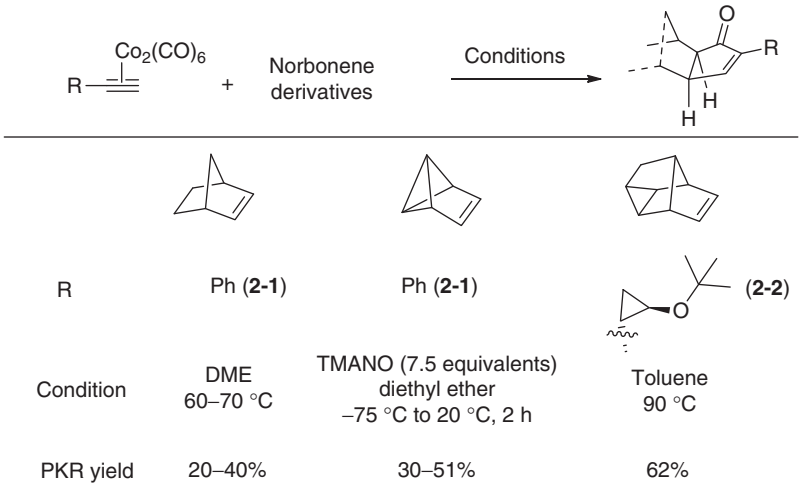
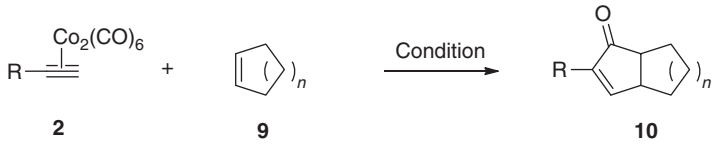


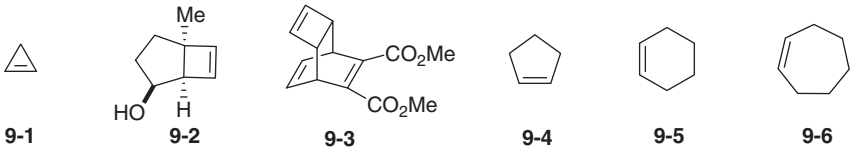
Figure 1 Intermolecular PKR of the strained olefins.

A theoretical study by Milet and coworkers[5] showed that there is a correlation between the reactivity of olefins with a given hexacarbonyldicobalt alkyne complex and the lowest unoccupied molecular orbital (LUMO) of the olefin substrate. They carried out charge decomposition analysis (CDA) calculations and found an excellent correlation between the level of back donation of electrons from the d-orbital of the cobalt atom and the barrier to cobaltacycle formation, which is thought to be the rate-determining step. The back-donation of electrons from the metal to the olefin is facilitated as the LUMO level of the olefin is lowered.[6]

The study also notes that the energy of the LUMO is lowered as the C=C–C angle of the alkene becomes smaller.[7] Based on this argument, the higher reactivities observed with smaller cycloalkenes (cyclopropene to cyclopentene),[5,8,9] than those with larger rings (cyclohexene and cycloheptene),[10] is readily explained (**Figure 2**). For a reasonable reaction with a less reactive cycloalkene, a special promoter is required (see Section 5.24.2.2).



2 9 10

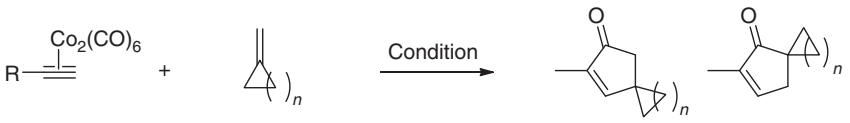


9-1 9-2 9-3 9-4 9-5 9-6

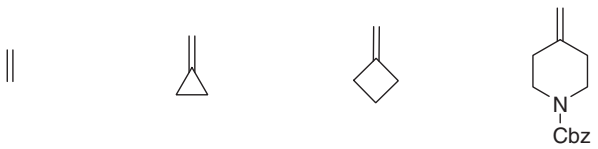
R of **2**		^{t}Bu (**2-3**)	H (**2-0**)	*n*-Hexyl (**2-4**)	Ph (**2-1**)	*n*-Bu (**2-5**)	Ph (**2-1**)
Condition/ yield	Thermal	–	73%[9]	–	–	3%	0%
	Promoted	93%[8]	–	–	97%[11]	68%[12]	85%[12]
	Catalytic	–	–	>98%[10]	–	–	–

Figure 2 Intermolecular PKR of the endocyclic olefins.

In addition, it is also understandable that, although ethylene a substrate free from any strain, is notoriously unreactive, *exo*cyclic olefins are reasonably reactive (Figure 3).



2 11 12-a 12-b



R	Ph (**2-1**)	Me (**2-6**)		Ph (**2-1**)
Condition/ yield	TMANO•H_2O Bubbling of ethylene 55%	Al_2O_3 50 °C 77%[13] (**a**:**b** = 5:1)	Al_2O_3 50 °C 47%[13] (**a**:**b** = 15:1)	Thermal 78%[14] (**a** only)

Figure 3 Intermolecular PKR of the exocyclic olefins.

5.24.1.2 Stereoselectivity

The relative stereoselectivity is high in this intermolecular reaction (Scheme 1).[1] Norbornene or norbornadiene (**3**) reacted with the alkyne–cobalt complex (**2**) to give the *exo* product only. More details about the stereoselectivity for the intramolecular reaction, including the control of the absolute stereochemistry, will be discussed in Section 5.24.4.2.

5.24.1.3 Regioselectivity

The regioselectivity in the PKR is one of the more complicated issues, if the intermolecular reaction is considered.[1b,c] The outcome depends on two factors, the substitution pattern and the electronic nature of the alkynes or alkenes.[11–14]

5.24.1.3.1 Regiochemistry with respect to the alkynes

In the reaction with a given alkene like norbornene (**3-2**), the regiochemical outcome is again controlled by steric and electronic factors. If an unsymmetrical alkyne such as **2** in Figure 4 bearing substituents of different size with similar electronic character is

employed, the major product would be the one having a larger substituent on the α-position with respect to the carbonyl of the product cyclopentenone (**12-a**) (Figure 4).[15]

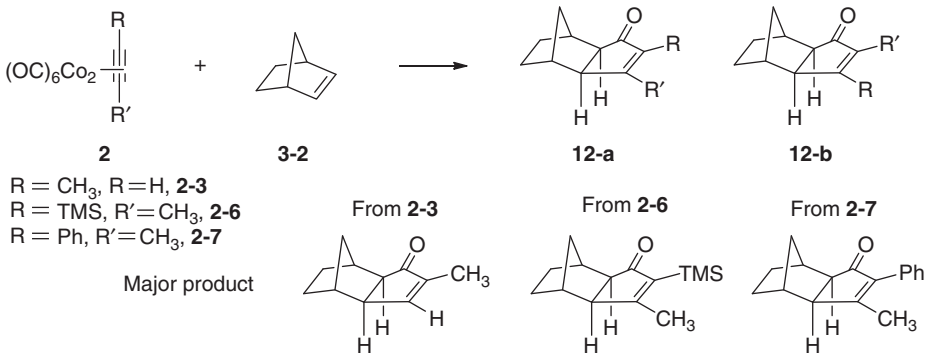
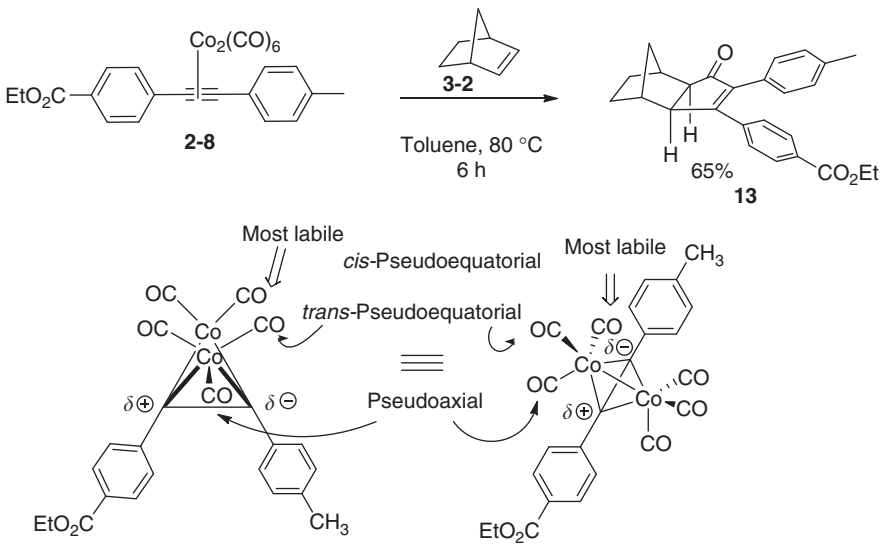


Figure 4 Regioselectivity with respect to alkyne substitution pattern.

However, if the substituents at both ends of the alkyne have different electronic characters but similar size, as in **2-8**, the more electron-deficient substituent prefers to sit on the β-position of the enone in the resultant cyclopentenone **13**. This electronic bias can be accounted for by the facile loss of CO at the *cis*-pseudo equatorial position affected by the '*trans* effect,' as shown in Scheme 2.[16]



Scheme 2

When both effects enforce the same trend, the results apparently reflect the sum of each. In other words, a larger and more electron-rich substituent prefers to be at the α-position of the enone.

However, when both effects act against each other, the outcome will be more difficult to predict. A couple of examples is illustrated in Figure 5. First, when the terminal alkyne (**1-9**) was used, the carboxylate is considered to be the larger group and, thus, only the α-substituted cyclopentenone (**14**) was obtained, regardless of the electronic character of the substituent. However, if the terminal proton is replaced by a methyl group, the effect of the electronic character becomes more influential: **15** is the major product, in contrast to the cases of 1-trimethylsilyl (TMS) propyne (**1-6**) and 1-phenylpropynes (**1-7**), where the steric factor is more significant (compare Figure 5 with Figures 3 and 4).[15]

The bothersome aspect of the regiochemistry is demonstrated more clearly by the reaction between (2-phenylethynyl)heteroaromatic compounds (**1-11**) and norbornene (**3-2**) reported by Fairlamb and coworkers.[17] In most cases, the regioselectivity seemed to follow the general trend previously mentioned. When the counterpart heteroaromatic ring HetAr is similar to or bigger than the phenyl in size, the electronic character seemed to control the reaction pathway; compound **17-a** is obtained as the major product if the heteroaromatic is more electron rich than phenyl, but compound **17-b** if it is more electron poor.

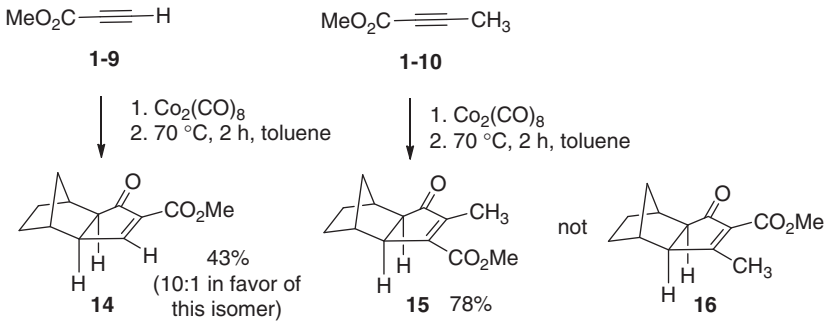
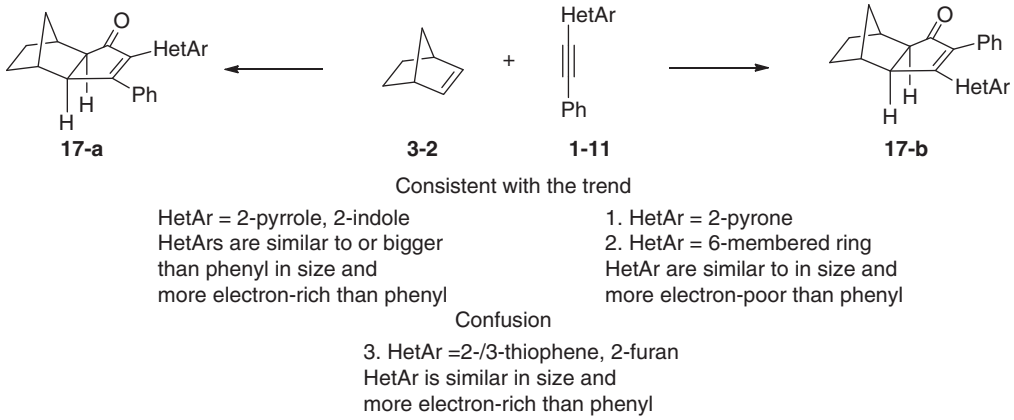


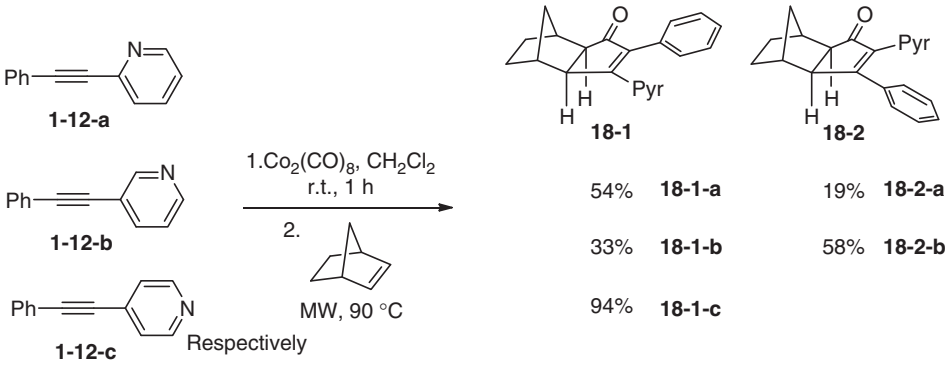
Figure 5 The competition of electronic and steric effects in determining the regiochemistry during the intermolecular PKR.

2-/3-Thiophene and 2-furan, whose sizes are similar to and which are more electron-rich than phenyl, are supposed to give **17-a** as the major product. Experimentally, however, it was found that this is not the case, and it is not easy to give a rationale for the observed results (Scheme 3).



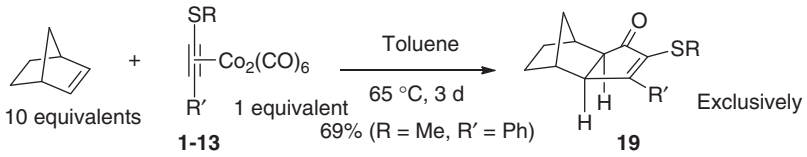
Scheme 3

Furthermore, even with a fixed heteroaromatic like pyridine in **1-12**, not only the electronic character of the heteroaromatic ring but also the position of the heteroatom within the ring seems to influence the regioselectivity. When the nitrogen atom in pyridine is remote from the alkyne, the exclusive formation of **18-1-c** is observed, as expected, but when the nitrogen moves toward the alkyne group, a mixture of regioisomers is obtained (equation 2).



(2)

Heteroatoms directly bonded to the alkyne also exhibit an influence on the regioselectivity. The PKR of the *S*-alkyl-substituted alkyne (**1-13**) with norbornene provided the single regioisomer, in which the *S*-alkyl sits on the α-position in the cyclopentenone **19**, regardless of the electronic character of the other substituent R′ (equation 3).[18] No plausible rationale for this effect has been suggested.

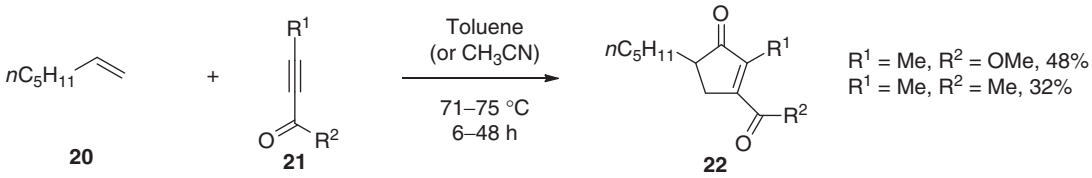


(3)

R, R′ = Me, Me; Me, *t*-Bu; Me, Ph; Me, CO_2Et; *t*-Bu, Me

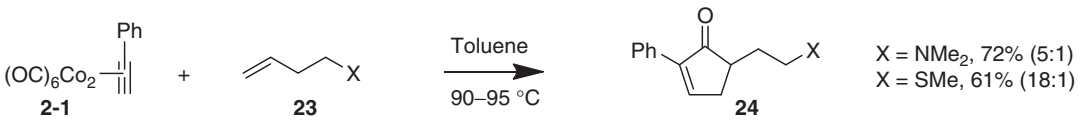
5.24.1.3.2 Regiochemistry with respect to the alkenes

The regiochemistry with respect to the alkene is more complicated than that in the case of the alkyne. Even with terminal alkenes like **20**, nearly equal amounts of the regioisomers are obtained. One exception is the coupling of 1-heptene (**20**) and the dicobalt hexacarbonyl complex of an alkyne **21** conjugated with an electron-deficient group, in which a single product was formed (equation 4).[19]



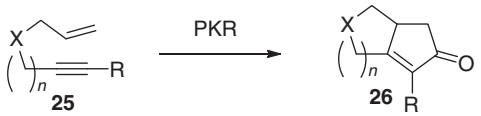
(4)

Krafft showed that the presence of a heteroatom in the substrate **23** that can coordinate the metal will guide the regiochemistry. These examples are thought to be a result of the coordination of the heteroatom to the metal before the insertion of the olefin, thereby fixing the orientation of the alkene to favor the 5-substituted product (equation 5).[20]



(5)

Despite the existence of several successful examples of regioselective PKRs, the formation of a mixture of regioisomers is inevitable in most intermolecular PKRs and a serious drawback when unsymmetrical alkenes and/or alkynes are employed. The synthetic utility of this reaction can be considerably improved by utilizing the intramolecular version. Schore introduced the first intramolecular version forming several rings simultaneously.[21] This has become the most popular synthetic strategy in the synthesis of natural products, because the reaction is more efficient than the intermolecular version and can reduce the complications related to the regiochemistry (Scheme 4).



Scheme 4

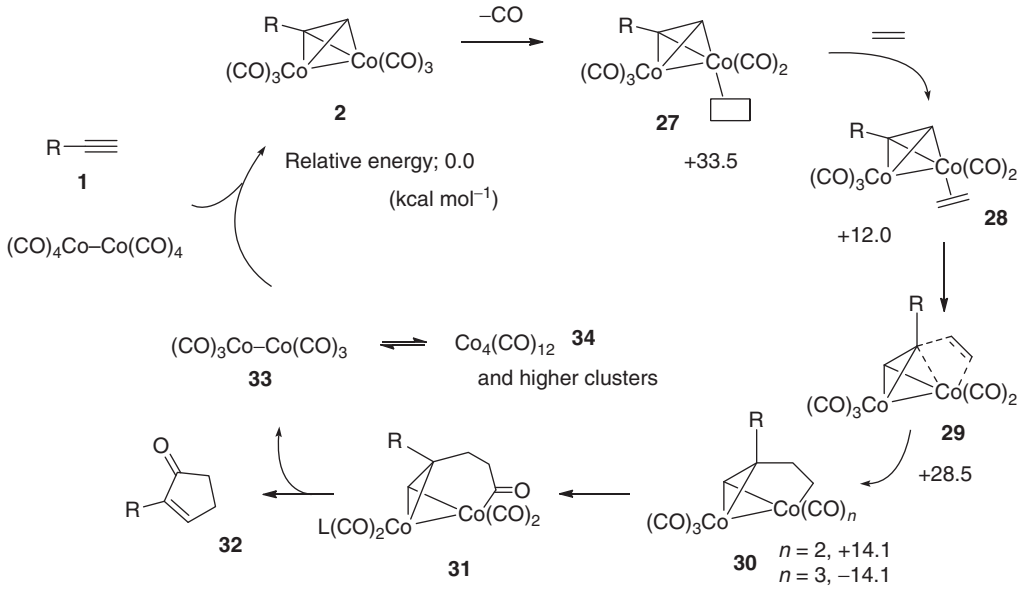
5.24.2 Improvement of the Original Protocol

5.24.2.1 A Proposed Mechanism

Some of the problems mentioned previously can be accounted for by the widely accepted mechanism given in Scheme 5, which was proposed by Magnus[22] and is supported by many theoretical studies.[23]

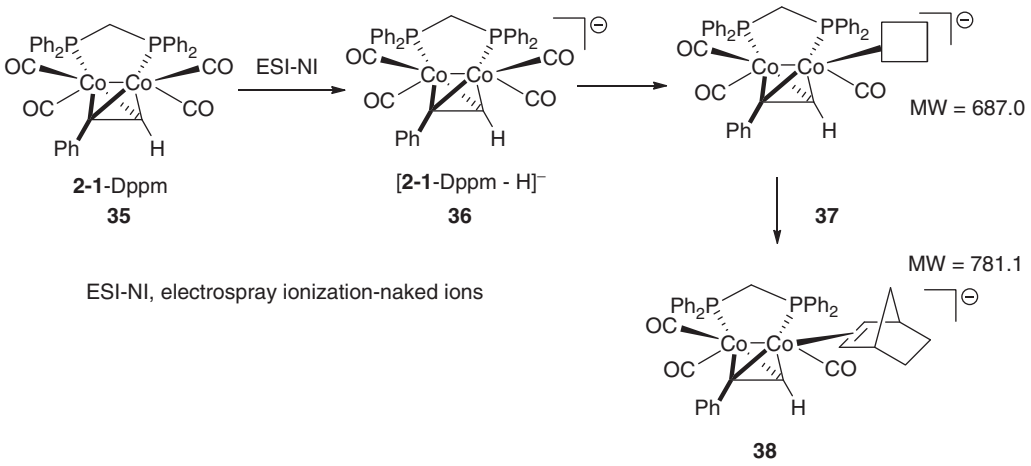
The alkyne–cobalt carbonyl complex (**2**) formed from the alkyne (**1**) and dicobalt octacarbonyl should lose at least one of the CO moieties on the metal to provide the vacancy required for the incoming olefins. Subsequently, the olefin-bound complex (**28**) is oxidatively rearranged to yield a metallacycle intermediate **30** via transition state **29**. The migratory insertion of the CO ligands in **30** provides the homologated-ring intermediate **31**, and the following two successive reductive eliminations afford the cyclopentenone product **32** and the unsaturated dicobalt-carbonyl species **33**.

In this multistep process, the decarbonylation from complex **2** is thought to be the rate-determining step of the overall process and this hypothesis is supported by a couple of experimental data, albeit they are still circumstantial. One piece of evidence is that the overall reaction rate is given as $k = [CO]^{-1.9}[\text{olefin}]^{0.3-1.2}[Co_2(CO)_8]^{1.3}[\text{alkyne}]^{0}$.[24] The process is -1.9th order with respect to



Scheme 5

CO, which means that higher CO concentrations retard the reaction. The concentration of alkyne is irrelevant to the reaction rate. Other evidence comes from the identification of the proposed intermediate. Gimbert and Greene carried out an experiment to trace the proposed intermediates by a tandem mass spectroscopic study coupled with electrospray ionization. Starting from precursor **35** with a modified bisphosphine ligand, the decarbonylated species **37** (*m*/*z* 687) and the olefin complex **38** (*m*/*z* 781) were identified (Scheme 6).[25]



Scheme 6

Nonetheless, none of the proposed intermediates beyond **2** has been isolated and characterized. Very limited cases of trapping of any of the proposed intermediates have been reported.[26] Compounds **40** and **41** were isolated and fully identified by spectroscopic data and crystal structure analysis (Figure 6).[27] Ironically, these isolated intermediates fail to react further to provide the corresponding PKR product even under forcing conditions. This means that the isolable compounds are accidentally interrupted intermediates of the PKR rather than the real active species involved in the cycloaddition reaction. These reactions may represent an example of 'Halpern's law,' that is, only those intermediates are isolable which are not involved in the reaction pathway.[28]

5.24.2.2 Promoter-Assisted PKR

5.24.2.2.1 Physical means

As already mentioned, the requirement of harsh reaction conditions is mainly associated with the first decarbonylation of complex **2**. The first practical and significant rate acceleration had been achieved by the dry support-adsorption method on silica

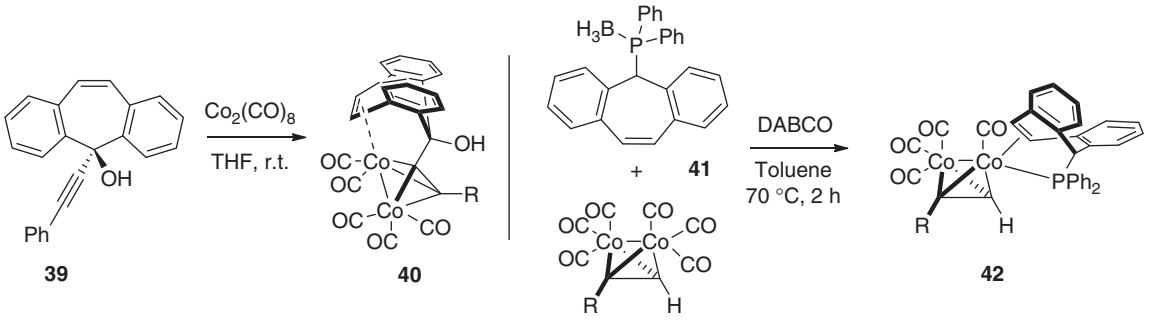
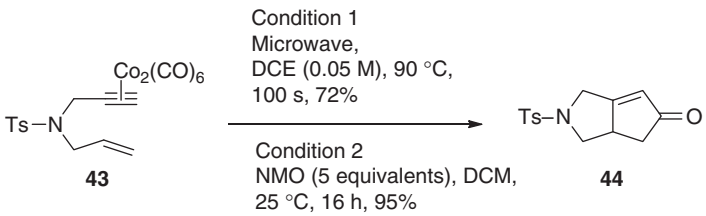


Figure 6 Trapped intermediates during the PKR.

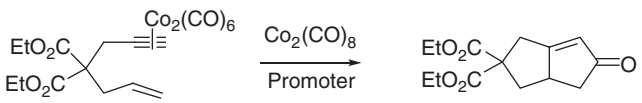
gel or alumina. Smit and Caple used cobalt-complexed enynes adsorbed on silica gel (2 on SiO_2) and obtained the cyclopentenones in good yields by gentle heating for several hours.[29]

The other physical means included irradiation with ultraviolet light and sonication with ultrasound. These methods have been tested and shown positive effects.[30] Most noticeably, Evans and coworker demonstrated excellent promotion by microwaves to expedite the reaction to completion in a minute (equation 6). Nevertheless, the beneficial effect in terms of the chemical yield is not spectacular[31] (**Table 1**).



(6)

Table 1 The promoter-assisted Pauson–Khand reaction with cobalt



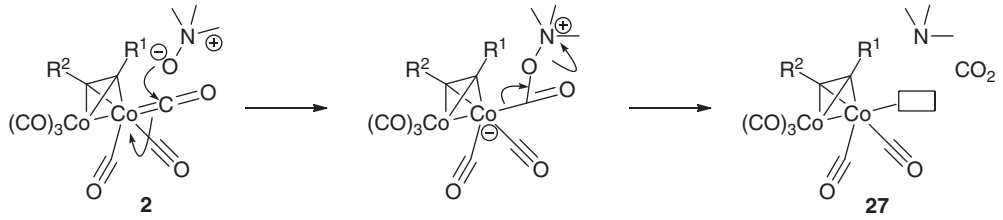
Promoter-assisted condition				*Yield (%)*	*References*
Promoters	*Solvent*	*Temperature (°C)*	*Time (h)*		
By physical means					
SiO_2	–	60	4	74	29
Visible light, UV	Toluene	r.t.	45	78	3c
Microwave	DCE	90	0.3	98	31
By oxidative promoters					
N-Methyl morpholin *N*-oxide	CH_2Cl_2	0–r.t.	3–20	95	32a
Trimethylamine *N*-oxide	CH_2Cl_2	0–r.t.	3	95	32b
TMANO with 4 Å MS	CH_2Cl_2	−10–r.t.	3	45–90	36
Amine *N*-oxide on solid support	THF	r.t.	0.5	91[a]	37
Dimethylsulfoxide	Benzene	40–50	3–20	83–92	38
By nonoxidative promoters					
$RSCH_3$	1,2-DCE	80	0.5–2	22–99	39,40
Sulfide on solid support	1,2-DCE	83	0.5	76[a]	41
TEMPO	Toluene	99	3 days	99	43

[a]The yields were taken from the intermolecular reaction.

Recently, an example was reported in which a stoichiometric PKR was promoted solely by visible light, although the result was not impressive. Only two examples with TMS-acetylene and ferrocenyl acetylene dicobalt-hexacarbonyl complexes were reported to give 78% yield at 59% conversion, with an *endo*/*exo*-ratio of 3:97.[3c]

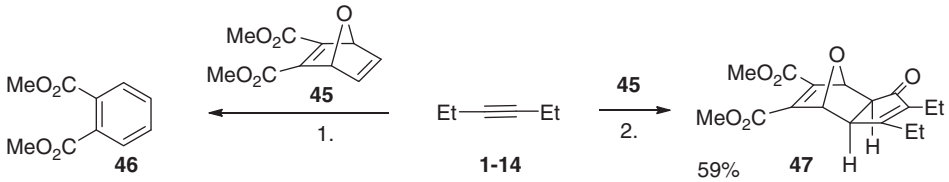
5.24.2.2.2 Oxidative promoters

More general methods have been devised. Schreiber[32a] and Jeong[32b] independently showed that amine *N*-oxides could promote the reaction substantially, affording high yields within a short reaction time. It is thought that these amine *N*-oxides, such as *N*-methylmorpholin *N*-oxide (NMO) and trimethylamine *N*-oxide (TMANO), oxidize at least one of the CO moieties to CO_2 even at ambient temperature. The latter binds much more weakly to the metal and, thus, dissociates readily to afford a vacant site for the incoming olefins (Scheme 7). As a result, the reaction proceeds even at ambient temperature. In addition, after the completion of the reaction, deep purple-colored cobalt oxide clusters are formed, which can be removed by simple filtration.



Scheme 7 An amine *N*-oxide promoter anchored to a solid support.

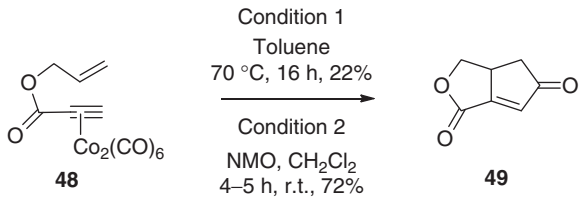
This general approach has now become the method of choice. The beneficial effects of amine *N*-oxide promoters are well documented in the example given in equation 7.[33] Although the aromatized product **46** was obtained instead of the PKR product from the reaction of diethylacetylene **1-14** and compound **45** under thermal conditions, only the desired PKR product **47** was formed with the aid of the amine *N*-oxide (equation 7).



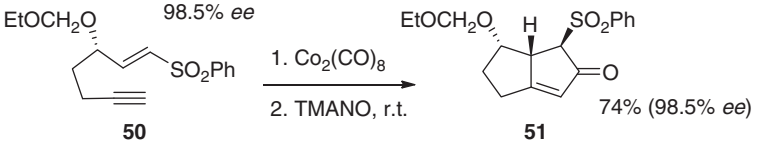
(7)

1. Toluene, 70–80 °C (yield not reported); 2. NMO (6 equivalents), CH_2Cl_2, 0–20 °C, 10–24 h

This condition is good for reactions of electron-deficient alkynes and alkenes as well. The allyl alkynoate **48**[34] and sulfonyl-substituted substrate **50**[35] stereospecifically afforded the corresponding PKR products **49** and **51** in high yield (equations 8 and 9). Especially, a comparison between the thermal and promoter-assisted PKR clearly showed the difference (equation 8).

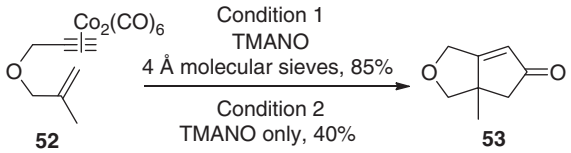


(8)



(9)

The promotion of the cycloaddition reaction by amine *N*-oxides was further improved by addition of molecular sieves (equation 10).[36] Molecular sieves are assumed to retain CO molecules and, thus, increase the conversion without the destruction of the metal clusters. This condition is applicable to less reactive substrates like **52**, which carry a trisubstituted olefin.



(10)

Subsequently, Kerr introduced a promoter anchored to a solid support to facilitate the workup after the reaction. For example, the PKR proceeds to completion when the amine *N*-oxide is anchored to a solid support (**54**) and then the polymeric amine can be recovered by simple filtration (Figure 7). The recovered polymer is cleaned, oxidized again, and then reused without any loss of activity.[37]

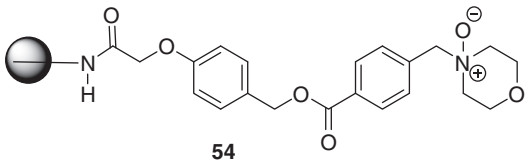
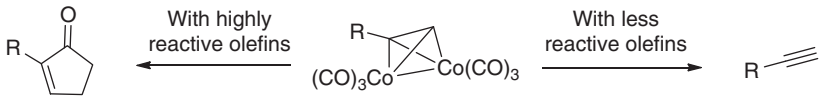


Figure 7 An amine *N*-oxide promoter anchored to a solid support.

Jeong and Pauson revealed that sulfoxides are milder than amine *N*-oxides, but still excellent promoters for the reaction. The slight warming (50 °C) of the mixture was required.[38] Under this condition, the competition between the PKR and demetallation of the alkyne–metal carbonyl complex (see Scheme 8) is substantially suppressed.

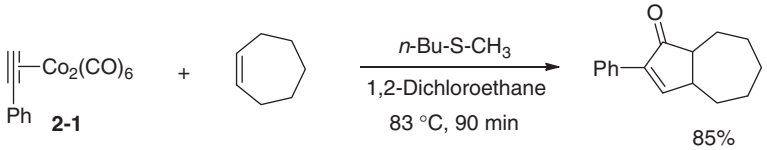


Scheme 8

5.24.2.2.3 Nonoxidative promoters

Although oxidative promoters have been shown to be quite effective, the reaction with less reactive olefins is still troublesome in the presence of an oxidative promoter. The PKR inevitably competes with the demetallation of the alkyne–cobalt carbonyl complex to give the metal-free alkynes. This competition is insignificant if reactive olefins are employed, but prominent if less reactive olefins are used, most likely because the decarbonylation is not discriminative.

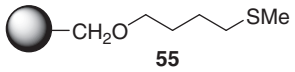
As a result, further optimization to identify milder promoters is critical to make the PKR more favorable. Sugihara reported that dialkylsulfides were effective as nonoxidative promoters in stoichiometric reactions.[12,39] This finding is rooted in the dimethylsulfoxide (DMSO) promoter[38] and Krafft's demonstration[20,26] that a suitably positioned sulfur moiety tethered to the PK precursor increases the reaction efficiency. Although the reaction conditions with these promoters generally require noticeably higher reaction temperatures than those with oxidative promoters, the transformation is completed in substantially shorter periods and gives high chemical yields. Moreover, the sulfur additive promotes the intermolecular PKR with even unstrained and less reactive olefins. A prominent example is the reaction between phenyl acetylene and cycloheptene (equation 11).[12]



(11)

This result has to be compared with the observation that only phenyl acetylene (**1-1**) was obtained with an NMO promoter, whereas the PKR product was formed in only 23% yield under thermal conditions after 3 days. The odorless sulfide, *n*-dodecyl methyl sulfide (DodSMe), was introduced by Kerr to make the reaction innoxious.[40] A sulfide anchored on the solid support (**55**) was also successfully used (Figure 8).[41]

Sugihara et al. demonstrated the enhancement of the reaction rate by using primary amines as a promoter, and this will be discussed in conjunction with the 'hard Lewis base'-catalyzed reaction (Section 5.24.3.1). Before that, it is worth mentioning that ammonia can serve as a promoter in a biphasic system consisting of an aqueous solution of ammonium hydroxide and dioxane. The reaction provided nearly quantitative yields in less than an hour under optimized conditions.[39]

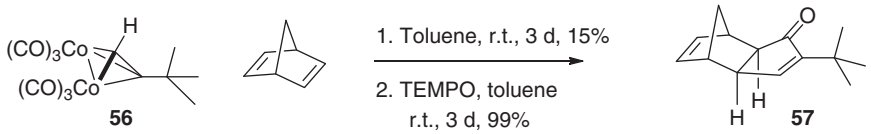


55

Figure 8 A sulfide promoter anchored to a solid support.

5.24.2.2.4 Promotion by single-electron transfer

Ab initio calculations using the complete active space (CAS) method indicated that the Co–Co bond in the alkyne-bridged dicobalt hexacarbonyl complex (**2**) has a singlet diradical character.[42] Based on this study, the PKR was successfully promoted by single-electron transfer. Co–Co bond dissociation in a dicobalt alkyne complex is induced by 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) to afford (η^2-TEMPO)Co(CO)$_2$ without oxygen transfer to CO, which undergoes the PKR efficiently. This protocol is especially efficient for sterically demanding acetylenes such as *tert*-butylacetylene **56** (equation 12).[43]



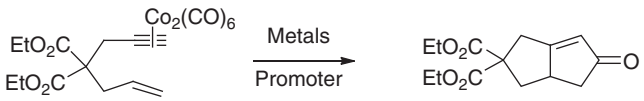
56 57 (12)

5.24.2.2.5 Other metals coupled with a promoter

Group 16 metal carbonyls are also effective in the PKR reaction. Hoye prepared a pre-activated tungsten catalyst (W(CO)$_5$THF) by photochemically replacing one of the CO moieties of W(CO)$_6$ with THF, and successfully applied this complex to the PKR. Only substoichiometric amounts were required and this semicatalytic system constitutes one of the early examples of a metal/promoter couple. It is useful even for substrates bearing electron-withdrawing groups.[44]

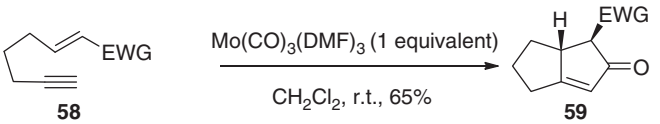
Jeong et al. reported the activation of molybdenum hexacarbonyl *in situ* by DMSO.[45] A mixture of the substrate and Mo(CO)$_6$ (1.0 equivalent) together with more of DMSO (10 equivalents) in toluene and/or benzene was heated to give the corresponding PK products. DMSO can be replaced by tributylphosphine oxide (TBPO).[46] Recently, Carretero showed that Mo(CO)$_3$(DMF)$_3$, obtained by mixing molybdenum hexacarbonyl with DMF for several months, efficiently promotes the PKR reaction (Table 2).[47]

Table 2 The promoter-assisted Pauson–Khand type reaction with other metals



Promoter-assisted condition				*Yield (%)*	*Reference*
Promoters	*Solvent*	*Temperature (°C)*	*Time (h)*		
W(CO)$_5$(THF)	THF	65–110	6–20	60	44
Mo(CO)$_6$/DMSO	Toluene	100	8	76	45
Mo(CO)$_6$/Bu$_3$P=O	Toluene	100	3.5	71	46
Mo(CO)$_3$(DMF)	CH_2Cl_2	r.t.	15 min	83	47

The molybdenum-assisted version made some formidable PK reactions possible. In particular, substrates **58** having electron-deficient olefins, including the phosphonate-conjugated substrate **58d**, work nicely to give the corresponding products **59** (equation 13).[48]



58

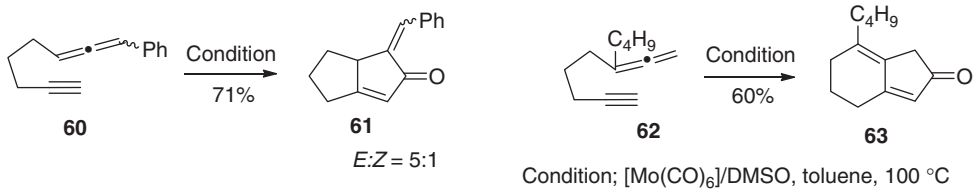
EWG = SO_2Ph; **58a**
EWG = CO_2Et; **58b**
EWG = CN; **58c**
EWG = P(=O)(OEt)$_2$; **58d**

59

59a 80%
59b 55–76%
59c 55–62%
59d 65%

(13)

An allene moiety is an interesting substitute for an olefinic unit and, thus, the application of the PKR to allenes has flourished in recent years. However, the results of the early trials of the PKR with cobalt carbonyl were inconclusive.[49] Brummond et al. demonstrated the efficiency of the combination of molybdenum carbonyl and DMSO in the PKR of allenes.[50] They also showed that the regioselectivity of the reaction could be controlled by the substitution pattern on the allenes. For example, when the 1,3-disubstituted allene **60** was subjected to this condition, the product **61** resulting from the reaction with the internal double bond of the allene was obtained. However, the reaction took place at the terminal double bond when the 3-substituted allene **62** was employed, giving product **63** (equation 14).[50]



(14)

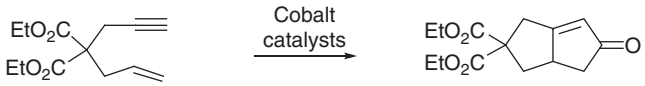
More discussion about the PKR with allenes is found in Section 5.24.5.1.

5.24.3 Catalytic PKR

5.24.3.1 Based on Cobalt

From the very beginning, the catalytic version of the PKR had been envisioned. In fact, Pauson reported an early success in the intermolecular catalytic reaction employing a continuous supply of ethylene (Table 3).[1]

Table 3 The cobalt-catalyzed Pauson–Khand reaction



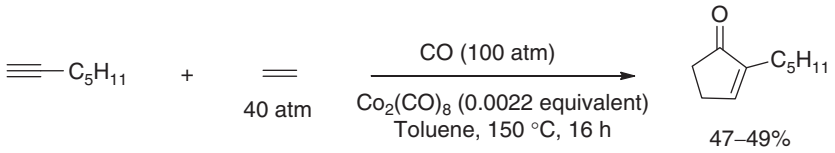
Catalytic condition				*Yield (%)*	*References*
Catalysts	*Solvent*	*CO (atm)*	*Temperature (°C)*		
$Co_2(CO)_8$	Toluene	40	50–55	83	51
	DME	1	90	82	52
	$scCO_2$, XPL	30	90	82	65,67
	Ionic liquid	10	80	90	68
	H_2O/Triton RX	1	70	86	69
$Co_2(CO)_8$/light	DME	1	50	95	53
$Co_2(CO)_8/P(OPh)_3$ or PAr_3	DME	1–3	120	82	54
	DME	1.05	70	80	55
$Co_2(CO)_8/R_3PS$	Benzene	1	70	90	56
$Co_2(CO)_8$/TMTU	Benzene	1	70	96	57
$Co_4(CO)_{11}P(OPh)_3$	sc Ethylene	5	120	94[a]	66
$Co_4(CO)_{12}$	CH_2Cl_2	10	150	92	69
	sc Ethylene	5	150	92[a]	66
$Co_4(CO)_{12}/C_6H_{11}NH_2$	Toluene	1	65–70	94	60
$Co_3(CO)_9(\mu^3\text{-CH})$ (**68**)	Toluene	7	120	98	61
indenyl Cobalt(I) (**69**)	DME	15	100	64	62
Co═NHC (**70**)	DME	1.05	75	73	63
Co(II) salts/reducing agent	CH_2Cl_2	30–40	100	98	64
Co(II) salts/reducing agent	tol/*t*BuOH	1	110	88	64

[a]The yield was based on the used alkynes during the intermolecular reaction.

It has been suggested that the difficulty in making the reaction catalytic is mainly associated with the facile formation of higher cobalt clusters like **34** from the unsaturated cobalt carbonyl species **33** relieved after a catalytic cycle (Scheme 5). Once **34** is formed, high pressure of CO is required to dissociate it to produce $[Co_2(CO)_8]$ again. However, the portion of unsaturated cobalt carbonyl $[Co_2(CO)_{8-n}]$ ($n = 1$ or 2) as the real catalytic species for the next cycle of the reaction would be severely discouraged

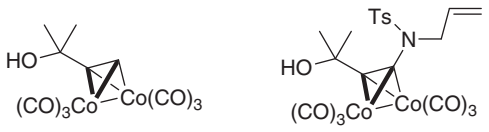
under such condition, and the second cycle would be even more difficult. As a result, many early attempts involving the simple use of a catalytic amount of dicobalt octacarbonyl provided erratic results.

The first successful catalytic reaction was reported in 1990 by Rautenstrauch et al. (Table 3). In their report, the reaction between ethylene (40 bar) and 1-heptyne in toluene was performed in the presence of a catalytic amount of $Co_2(CO)_8$ under a high pressure of CO (100 bar).[51] Although this constitutes the first truly catalytic reaction with a high turnover number (>220), this result was not reproducible. The reported chemical yield did not exceed a certain limit (<50%) and the trimerization of 1-heptyne competed with the desired reaction (equation 15).



(15)

In this endeavor, the purity of $Co_2(CO)_8$ should be high to ensure reproducible results. Many attempts have been made to realize this catalytic reaction. Finally, Livinghouse and coworkers refined the conditions and expanded the scope of the catalytic version.[52] Their first report used photochemically activated $Co_2(CO)_8$ under atmospheric pressure of CO. Next, they found thermal conditions by keeping the reaction temperature in a very narrow range (50–55 °C). For both studies, $Co_2(CO)_8$ must be rigorously purified. An alternative way to ensure the formation of highly purified unsaturated [$Co_2(CO)_6$] is the use of alkyne–dicobalthexacarbonyl complexes. The early attempts of Billigton to use ethyne–[$Co_2(CO)_6$] and recent examples using **64** and **65** are representative (Figure 9).[53]

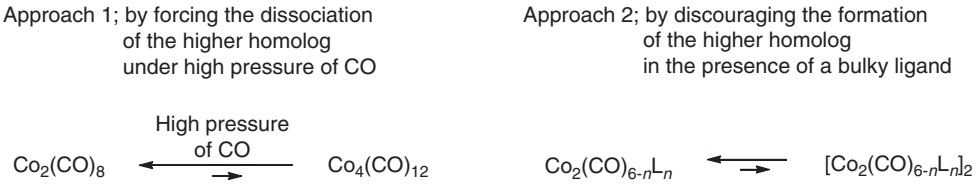


64 **65**

Figure 9 Precursors providing pure unsaturated cobal-carbonyls in a practical manner.

5.24.3.1.1 Various ligand-modified cobalt catalysts

More reliable catalytic PKRs were devised. The bottom line in devising the catalytic PKR is identifying the way to discourage the formation of higher cobalt clusters **34** and to allocate enough time to the unsaturated cobalt carbonyl species **33** for binding the new substrates before making the aggregated clusters (Scheme 9). A highly congested environment was introduced around the cobalt metal by using a sterically bulky external ligand. Once the catalyst is sterically encumbered, it would discourage the dimerization or oligomerization of the unsaturated metal carbonyls (Figure 10).



Scheme 9

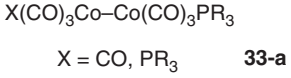
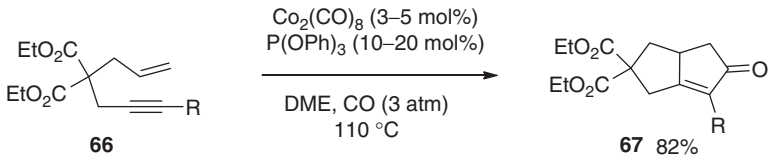


Figure 10 Dicobalt carbonyls armed with bulky ligands.

Jeong et al. made a phosphite-modified cobalt catalyst **33-a** (X=P(OPh)$_3$) which was prepared *in situ* by mixing dicobalt-octacarbonyl (3 mol%) and triphenylphosphite (10 mol%) before the PKR. The best results were obtained when the reaction was carried out at elevated temperature (110 °C) under mild pressure of CO (3 atm) (equation 16).[54]

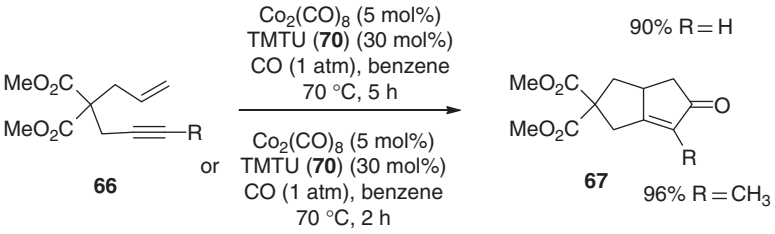


(16)

Although phosphites were used in the original work, it was found that other phosphorus ligands including phosphanes are also effective as long as the solubility of the catalysts in the reaction media is guaranteed. Subsequently, it was shown that the use of premade robust catalysts by coupling with phosphanes and phosphites was effective under a CO atmosphere (1 atm).[55]

Since the successful introduction of catalysts modified by phosphine ligand, the efforts were focused on the identification of other ligands. Hashimoto showed that the addition of phosphane sulfides also results in higher yields and faster conversions for the PKR under atmospheric pressure of CO. This mild promoter provided high TONs and can be applied to an intermolecular PKR under 1 atm of CO.[56]

In addition, thiourea turned out to be a very effective additive.[57a] Among the various thioureas tested, including the bulky and optically pure **71**, tetramethylthiourea (TMTU, **70**) turned out to be the best choice and provided the best results if the metal/ligand ratio was carefully controlled (1:6) (equation 17). Subsequently, the tris-thiourea compound **72** was also introduced for the same purpose (**Figure 11**).[57b]



(17)

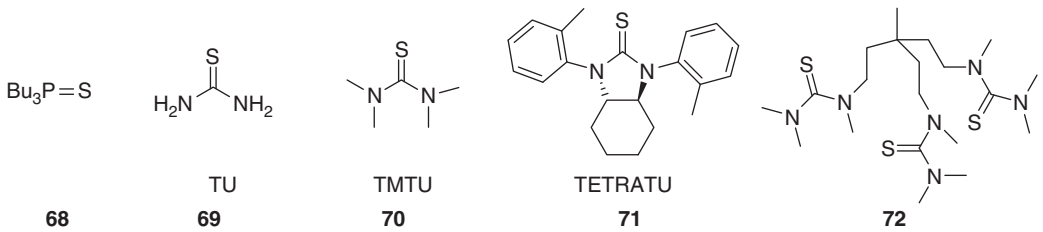


Figure 11 Representative promoters of PKR by cobalt carbonyl bearing sulfur.

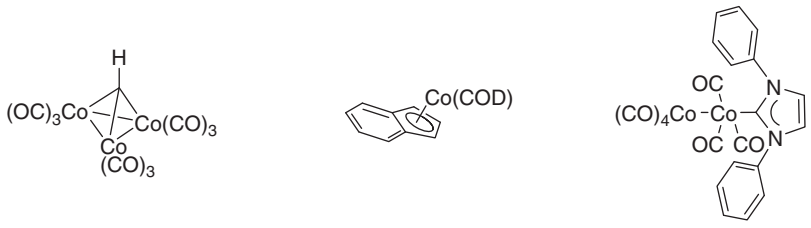
The catalysts modified by phosphorus ligands made the transformations reliable, but this consistency was obtained at the expense of the reaction rate. This is mainly attributed to the electron flow from the ligands to the metal, making the π-back bonding of the metal to the CO much stronger and thus the removal of CO more difficult. The use of 'hard Lewis bases' would be a solution to overcome this problem, because these kinds of ligands are assumed to make the CO of low-valent organotransition metal complexes more labile.[58] However, there is a rather contradictive explanation for the role of the hard Lewis base. The DFT calculation carried out by Milet and Gimbert indicated that the rate effects exerted by most Lewis bases are due to preventing the reversibility of olefin insertion rather than by facilitating the departure of the CO ligand to create a vacant site for the incoming olefin.[59] Anyway, whatever the reason is, the beneficial effect of the 'hard Lewis base' seems to be evident.

It was already discussed that the use of 1,2-dimethoxyethane (DME) as a hard Lewis base additive in toluene was critical to the success in the microwave-promoted PKR (see equation 6).[31] Nevertheless, the use of DME as the solvent is detrimental and the formation of the demetallate parent alkyne **1** was the problem. Water was less efficient under the same conditions, but gave a comparable yield at higher concentrations.

Cyclohexylamine, which was found to be one of the best promoters for the stoichiometric reaction, failed to give a catalytic version under CO pressure (7 atm). However, Krafft et al. elegantly combined cyclohexylamine and cobalt carbonyl (in the form of dicobalt octacarbonyl or tetracobalt dodecacarbonyl (**34**)) in DME and demonstrated its efficiency in catalytic cyclizations. Cyclohexylamine is a sterically bulky amine and is presumed to remain intact on the unsaturated dicobalt species during the catalytic cycle, discouraging the formation of higher homologues and making CO more labile.[60]

Interestingly, cobalt clusters such as alkylidynetricobalt nonacarbonyl, which are easily prepared by the reaction of dicobalt octacarbonyl with trihaloalkane, were utilized for the PKR reaction.[61] Among the clusters investigated, the one having a relatively

small substituent on the bridging carbon, $Co_3(CO)_9(\mu^3\text{-}CH)$ (**68**), turned out to be the best choice (Figure 12). However, a relatively high pressure of CO (7 atm) is required for consistent results.



68 **69** **70**

Figure 12 Cobalt based catalysts other than dicobalt octacarbonyl.

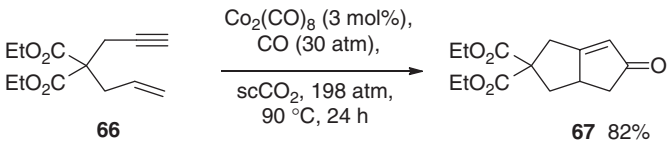
In another study, a mono cobalt(I) species proved its utility for the catalytic PKR. Chung and Jeong reported a new catalyst, [(indenyl)(cod)cobalt(I)] (**69**) (Figure 12), to promote the reaction. Although this catalyst required a high pressure of CO (15 atm) to obtain excellent results, the TON was as high as 97.[62]

The robust NHC–cobalt complex **70** has been used, albeit with slightly inferior efficiency, which might be due to the highly electron-donating character of NHC ligands (Figure 12).[63]

Studies using alternative sources of cobalt have been the subject of research as well, because of the relative instability of $Co_2(CO)_8$. The generation of Co(0) can be effected either by the reduction of $Co(acac)_2$ with $NaBH_4$ in CH_2Cl_2 or the reduction of $CoBr_2$ by Zn in toluene/*t*-BuOH.[64]

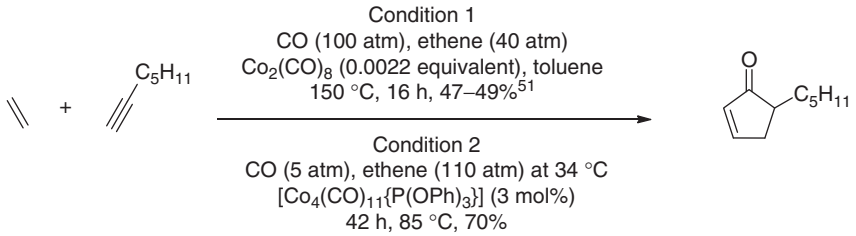
5.24.3.1.2 Cobalt-mediated catalytic PKR in unconventional media

Compressed carbon dioxide, either as a supercritical fluid ($scCO_2$) or expanded liquid (XPL), can be used as a solvent for this reaction. Jeong et al. first demonstrated that the efficiency of the PKR is substantially improved in supercritical CO_2 fluid.[65] The advantages may be due to the high solubility of gaseous reactants including CO, the rapid diffusion of the solutes, and the weakening of the solvation around the reacting species (equation 18).



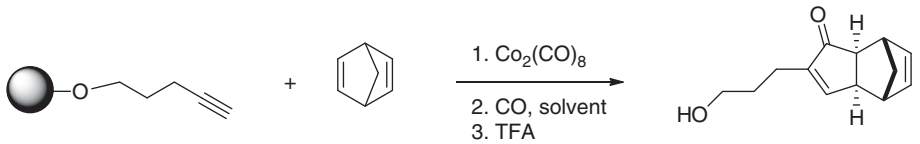
66 **67** 82% (18)

In a subsequent study, the same authors used ethylene both as a substrate and supercritical fluid solvent.[66] This notoriously poor substrate in the PKR served nicely to give 2-substituted cyclopentenones. The reaction efficiency of each alkyne substrate can be tuned by changing the catalyst precursors. Not only $Co_2(CO)_8$ but also the two cobalt clusters $[Co_4(CO)_{12}]$ and $[Co_4(CO)_{11}\{P(OPh)_3\}]$ were used case by case to obtain optimal yields. A comparison with Rautenstrauch's result[51] clearly shows the superiority of this approach (equation 19).



(19)

Furthermore, these media turned out to be especially good for solid-phase organic synthesis, in which efficient mass transfer is critical to success. Leitner and his coworkers demonstrated that the PKR between norbornadiene and the alkyne substrate **71**, which is bound to a solid support, proceeded well in compressed carbon dioxide (equation 20). In this specific case, the reaction in XPL provided better results than that in a supercritical fluid, because the concentrations of both the catalysts and soluble substrate were significantly improved in XPL compared to that in the supercritical phase.[67]



(20)

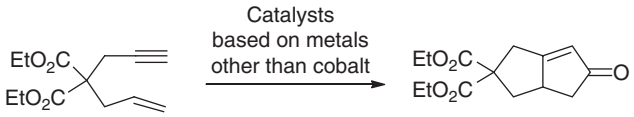
Ionic liquids are a versatile class of solvents for transition metal-mediated reactions, because of their many advantages compared to conventional media, including their nonvolatility. The catalytic PKR was also tested in these media, but only found to provide reasonable chemical yields for a narrow range of substrates.[68]

To reduce the environmental impact of organic solvents in industrial-scale applications, water is considered as a possible alternative, because it is cheap, readily available, nonflammable, and nontoxic. The PKR can also be realized in water in the presence of detergents and surfactants to solubilize the cobalt carbonyls, $Co_2(CO)_8$ and/or $Co_4(CO)_{12}$. The water–Triton X medium using $Co_4(CO)_{12}$ rendered the catalytic thermal PKR in aqueous conditions possible. The efficiency of this protocol exceeds that of the aqueous reactions using stoichiometric amounts of $Co_4(CO)_{12}$ and $Co_2(CO)_8$.[69]

5.24.3.2 Based on Metals Other Than Cobalt

The use of other metals for the PKR has attracted much attention recently in the search of new possibilities (Table 4).

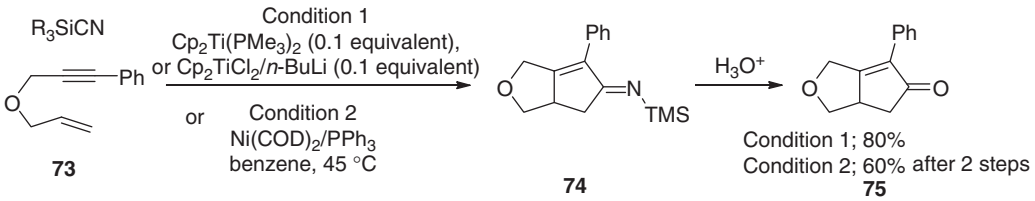
Table 4 The catalytic Pauson–Khand reaction using metals other than cobalt



Catalytic condition				*Yield (%)*	*References*
Catalysts	*Solvent*	*CO (atm)*	*Temperature (°C)*		
$Cp_2Ti(CO)_2$	Toluene	1.2	90	98	70,72
$CpTi(OAr)X_2$	Toluene	1	95	79	73
$Ni(COD)_2/PPh_3$	DMF	Isocyanide	120	85[a]	71
$[Ru_3(CO)_{12}]$	DMAC	15	140	79	74,75
$[RhCl(CO)_2]_2$	Toluene	0.1	80	90	77
$[RhCl(PR_3)_2]/CO$	Toluene	1	110	96	78
$[Rh(COD)(TRIA)]_2$	Xylene	5	130	80	81
$PdCl_2$/TMTU (**70**)	THF	1	50	81	82
$[IrCl(COD)]_2$	Toluene	1	110	75	120

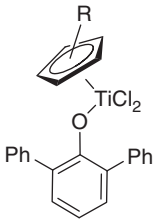
[a]The yield of the PK product was determined after hydrolysis of the resultant imines.

The initial success with early transition metals, such as zirconium and titanium, reported by the Buchwald group, included an indirect cycloaddition between an enyne and isocyanides. The first protocol using catalytic $[Cp_2Ti(PMe_3)_2]$ or Ni(cod) together with CO and triphenylphosphine failed to cyclize the enynes. However, the cyclic imine **74** was obtained when trialkylsilyl isocyanides were used, which eventually hydrolyzed to give the PK product **75**.[70,71] For the nickel-catalyzed PKR, it was revealed that a diamine ligand was superior to the commonly used phosphane ligand. In addition, it was necessary to use sterically bulky isocyanides for the catalytic version. The poisoning of the nickel catalyst by the formation of a nickel–isocyanide complex was an obstacle in this reaction (equation 21).



(21)

Subsequently, the direct incorporation of CO by the titanocene(II) catalyst, $Cp_2Ti(CO)_2$, under a CO atmosphere was accomplished.[72] This catalytic system showed a substantially higher TON and broader functional group compatibility. However, this catalyst failed to react with sterically hindered olefins and alkynes. A subsequent contribution from the same group revealed that the series of aryloxide titanium complexes of type **76** could promote the PKR even with sterically hindered enynes (Figure 13).[73]

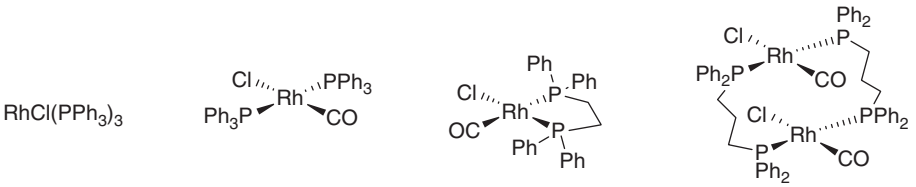


76

Figure 13 Ti-based catalysts for the PKR.

Furthermore, late transition metals such as ruthenium, rhodium, and iridium showed their ability to catalyze the PK reaction. In 1997, two groups reported independently that $[Ru_3(CO)_{12}]$ can be used. The group led by Murai reported the use of dioxane as the solvent,[74] whereas the other led by Mitsudo employed *N*,*N*-dimethylacetamide (DMAC).[75] Both conditions required a high pressure of CO (10–15 atm) and the scope extended only to disubstituted alkynes.

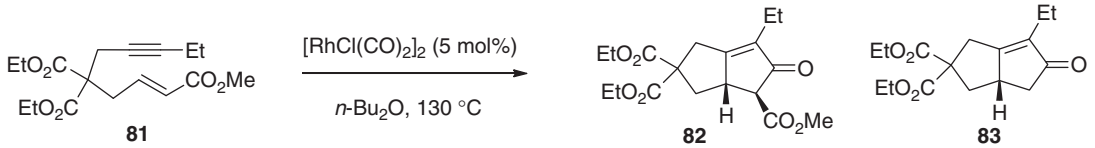
The rhodium catalyzed PKR was also reported by two groups simultaneously and has attracted much more attention.[76] Early studies by Narasaka and coworkers employed $[RhCl(CO)_2]_2$ as a catalyst in dibutyl ether,[77] whereas the report by Jeong et al. employed various phosphine-modified Rh(I) catalysts in noncoordinating solvents such as toluene.[78] The latter has the potential for further development toward the enantioselective version. The requirements for efficient transformation, when phosphine-ligated catalysts are used, are well defined. For example, while complexes such as $RhCl(PPh_3)_3$ (**77**), *trans*-$RhCl(CO)(PPh_3)_2$ (**78**), or RhClCO(dppe) (**79**) require the co-use of silver(I) salts for a faster reaction by making cationic catalysts, the complex *trans*-$[RhCl(CO)(dppp)]_2$ (**80**) efficiently promotes the reaction without the need for any additives (Figure 14).



77 **78** **79** **80**

Figure 14 Various Rh(I) catalysts initially screened for the PKR.

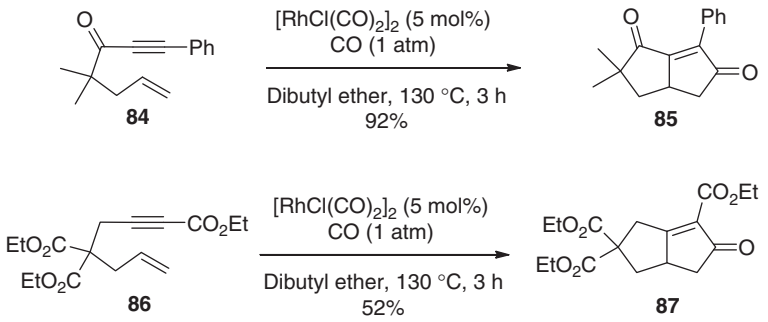
Rhodium catalysts demonstrated some additional unique features, which cobalt catalysts do not have. Electron-deficient alkenes and alkynes were among the previously challenging substrates in the PKR assisted by oxidative promoters. The situation is more favorable when a rhodium(I) catalyst is utilized. The inherently electron-rich rhodium(I) is able to provide a more significant π-back-bonding into the electron-deficient multiple bonds. Thus, it initiates the reaction to furnish the cycloaddition products in a highly efficient manner.[77] It is interesting to note that the concentration of CO should be kept as low as possible to achieve a higher chemical yield in a shorter reaction time (equation 22).



1 atm CO	18 h	19%	68%
0.1 atm CO and 0.9 atm Ar	4 h	59%	31%

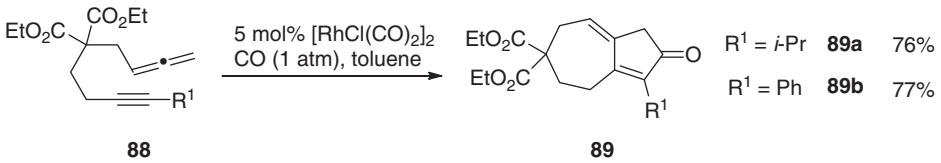
(22)

In addition to the example given above, the alkynone **84** and the alkynoate **86** also gave the PKR products in moderate to excellent yield (equation 23).[77]



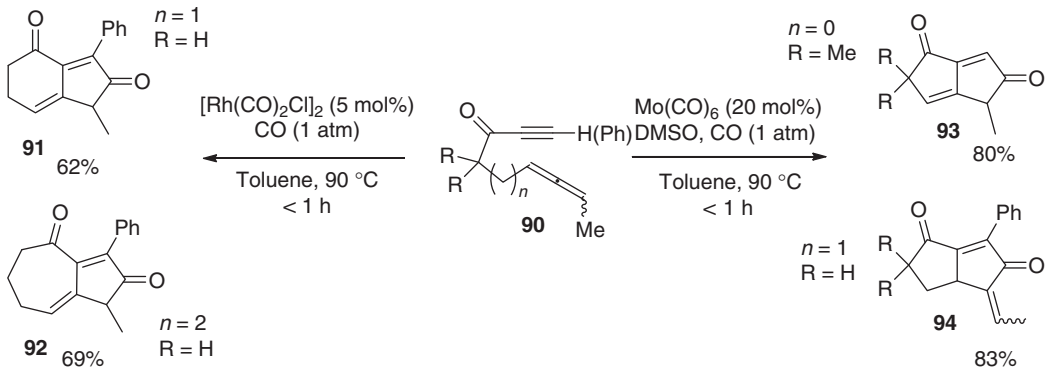
(23)

Another advantage of the Rh(I) catalyst is the preparation of a bicyclo[5.3.0]-decenone system by the PKR. The preparation of a larger ring system than bicyclo[3.3.0]- and [4.3.0] rings remained a big challenge for a long time. The breakthrough came with Rh catalysts, when allenes were used as a substitute for the olefin moiety. The treatment of substrate **88** with either $[RhCl(CO)_2]_2$ or $[RhCl(CO)dppp]_2$ in toluene under 1 atm of CO furnished the bicyclo[5.3.0] compounds **89** in excellent yields (equation 24) (see Section 5.24.6.1).[79]



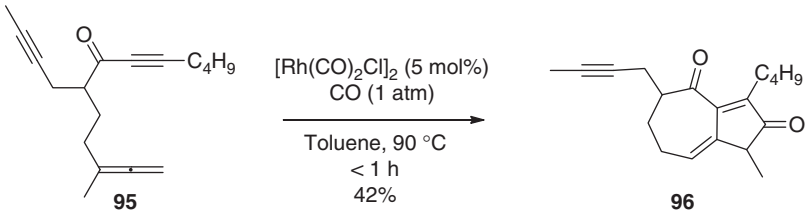
(24)

Interestingly, the regioselectivity of the cycloaddition of the allene–alkynone **90** depends on the catalyst used, for example, Mo versus Rh(I) (equation 25). With compound **90** ($n=1$, R=H), Rh(I) afforded **91** as the product, whereas Mo(0) yielded **94**.



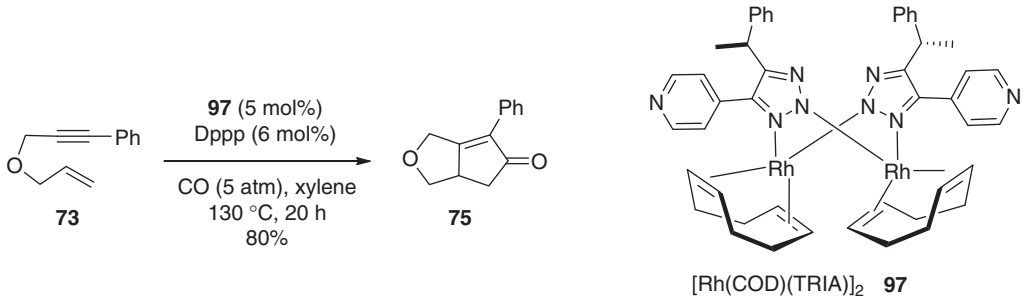
(25)

More interestingly, it was found that the carbonyl-conjugated alkyne in **95** was more reactive than the normal alkyne. Compound **95** afforded **96** exclusively in 42% yield (equation 26).[80]



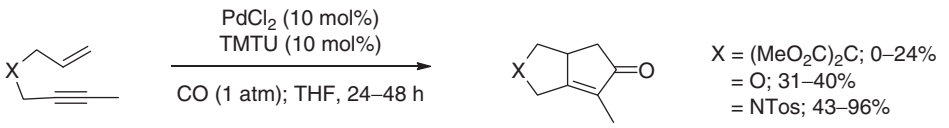
(26)

$[Rh(COD)(TRIA)]_2$ (**97**), obtained from a mixture of $[Rh(COD)Cl]_2$ and 4,5-disubstituted NH-1,2,3-triazole (TRIA) in the presence of KOH, constitutes a new class of Rh(I) catalysts for the PKR. Together with dppp, this complex exhibited decent reactivity under CO pressure (5 atm) (equation 27).[81]



(27)

Palladium(II) coupled with TMTU (**70**) was also introduced as a catalyst for the PKR. The efficiency of this combination is very sensitive to the tethering of the substrates and only substrates having an *N*-Tos tether turn out to be effective (equation 28). In addition, the diastereoselectivity of the reaction is extremely high, and the reaction more effective with electron-deficient alkynes, contrary to the conventional notion. The use of LiCl as an additive expanded the substrate scope widely and improved the efficiency of the reaction significantly.[82]



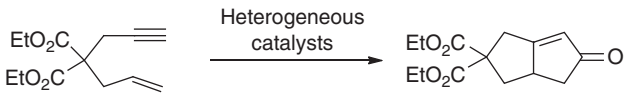
(28)

Catalysts based on iridium(I) were discovered and will be discussed later in the context of enantioselective transformations in Section 5.24.4.2.2.

5.24.3.3 Heterogenized (Immobilized) Catalysts

In view of their environmental advantages and operational simplicity, heterogeneous catalytic systems have been strongly suggested (Table 5). To this end, Gibson and coworkers first introduced polymer-bound cobalt species (**98** and **99-a**).[83a] Subsequently, Portnoy and coworkers immobilized cobalt on dendrimeric phosphane ligands, which have a partial structure of **99-b**.[83c–e] Leitner introduced poly(ethylene glycol) stabilized Co nanoparticles for this transformation (Figure 15).[84]

Table 5 Heterogeneous catalysts for Pauson–Khand reactions



Catalytic condition				*Yield (%)*	*References*
Catalysts	*Solvent*	*CO (atm)*	*Temperature (°C)*		
Polymer-bound Co	THF	1	70	61	83,84
Co on PEG	THF	23	130	89	
Co/silica	DCM	20	130	92	85a
Co/charcoal	THF	20	130	98	85b
Colloidal Co	THF or H_2O	5–20	130	90	85c,d
Entrapped Rh	THF	5	130	90	85e
RuCNC	THF	2-Pyridyl-methyl formate (**112**)	130	98	85f
Co_2/Rh_2, Co_3/Rh on C	THF	1	130	92	86
Raney Co	THF	23	130	95	87
Zr-mesoporous silica	Toluene	30	130	20	88

Chung and Hyeon developed a variety of heterogeneous catalysts, using cobalt metal immobilized on mesoporous silica[85a] or charcoal.[85b] Although these catalysts generally require harsh conditions (high CO pressure and high catalyst loading) to effect the reaction, the reuse of the catalysts without loss of activity may compensate for such drawbacks.

Substantial improvements were made by using cobalt nanoparticles.[79a] Contrary to the previous cases, a much lower CO pressure (5 atm) is sufficient for the completion of the reaction. However, the high loading of catalysts (45 mol%) is still a drawback. Nevertheless, this system can be reused, and one of them is even compatible with water as the solvent.[85]

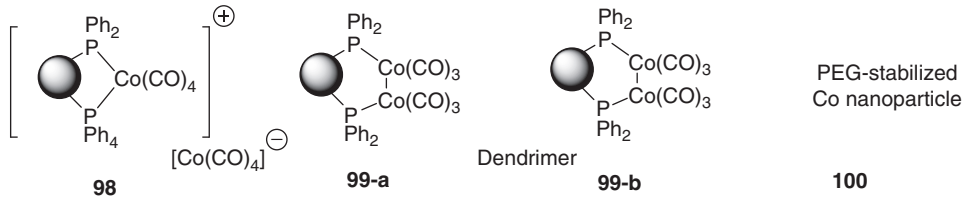
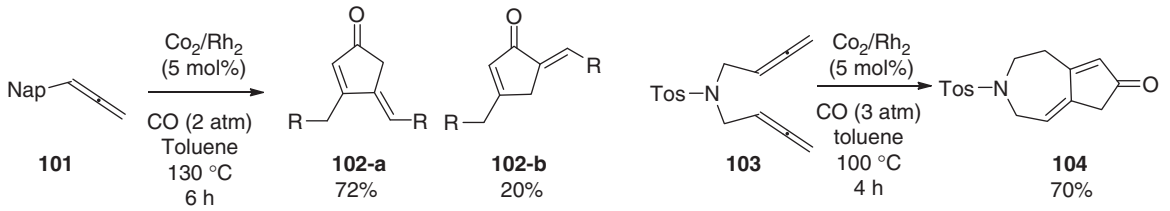


Figure 15 Representative cobalt carbonyl catalysts immobilized on solid supports.

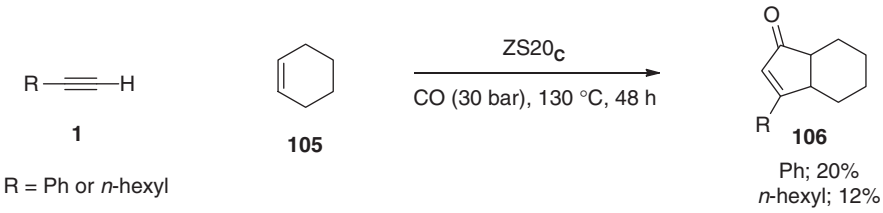
Immobilized Co_2Rh_2 heterobimetallic nanoparticles on charcoal were identified and used for the catalytic reaction either under CO atmosphere or in the presence of crotonaldehyde as the CO source.[86] This catalyst was further used for the carbonylative dimerization of two allenes intra- and intermolecularly (equation 29).[86]



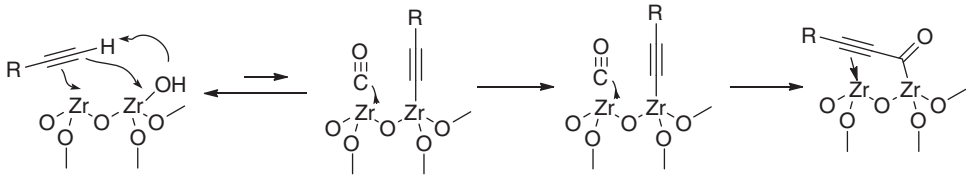
(29)

Commercially available Raney cobalt has also been used for this cycloaddition.[87]

Zirconium–silica mesoporous powders ($ZS20_C$) were found to act as a moderate catalyst for hydroformylations and the PKR. Although the reaction using this catalyst was far less efficient than that with other immobilized catalysts, this is one of the first examples of the use of zirconium for this transformation. Besides this aspect, there are a couple of points worth mentioning. The reaction is good only for terminal alkynes. Even though the chemical yield is not impressive at all, this condition provided *β*-substituted cyclopentenones **106** in contrast to the previous results (equation 30). Based on these observations, the authors proposed the mechanism described in Scheme 10.[88]



(30)

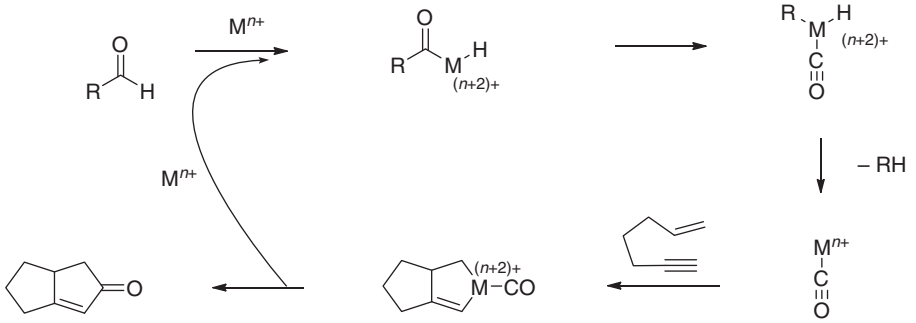


Scheme 10

5.24.3.4 PKR using Alternative CO Sources

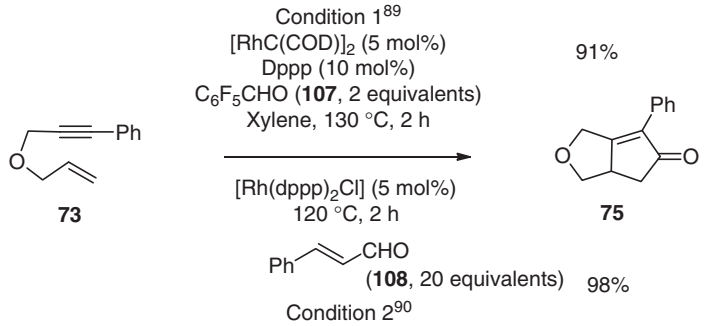
Facile formation of metal carbonyl complexes makes rhodium a very useful catalyst for both the hydroformylation of multiple bonds and the decarbonylation of aldehydes (Scheme 11). Two groups have independently utilized rhodium carbonyl complexes obtained by decarbonylation of aldehydes in the PK reaction.[89]

After an extensive screening of various aldehydes to optimize the conditions, Kakiuchi and Morimoto reported that most of the aromatic aldehydes tested are able to serve as a CO source and that the electronic nature of the aldehydes is responsible for the CO-transfer efficiency. Aldehydes bearing electron-withdrawing substituents are more effective than those bearing electron-releasing substituents. As a result, pentafluorobenzaldehyde (**107**) is chosen for this purpose. No complication by hydroacylation of the alkenes and/or alkynes was observed.[89]



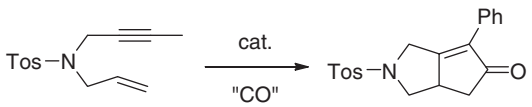
Scheme 11

In a subsequent study, Shibata found that cinnamaldehyde (**108**) can be employed as a CO source as well as a solvent.[90] Refluxing of the enynes **73** greater than cinnamaldehyde (**108**) (20 equivalents) together with 5 mol% $Rh(dppp)_2Cl$ (prepared *in situ* by mixing $[Rh(cod)Cl]_2$ and 2 equivalents of dppp) under argon provided the corresponding bicyclopentenones **75** in nearly quantitative yields (equation 31). The reaction time in the case, where **108** is used, is substantially shorter than that when **107** was used (Table 6).



(31)

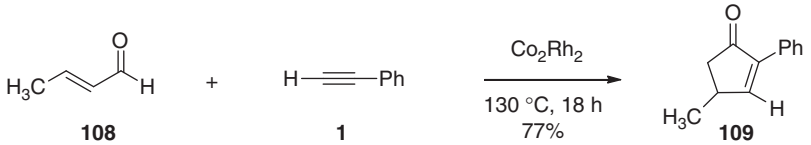
Table 6 The catalytic Pauson–Khand reaction using aldehydes as CO source



Catalyst (mol%)	*Additive (mol%)*	*RCHO (equation)*	*Yield (%)*	*References*
$RhCl(cod)_2$ (5)	Dppp (11)	C_6F_5CHO (2)	95	89a
$RhCl(dppp)_2$ (5)		Cinnamaldehyde (20)	90	90a,b
$RhCl(cod)_2$ (5) or $[Rh(cod)_2]BF_4$ (10)	Dppp (10), TPPTS[a] (10), SDS (200)	HCHO (10)/H_2O	96	89b
$[RhCl(cod)]_2$ (5)	BINAP	Acetylated carbohydrates	51 (61% *ee*)	92a,b

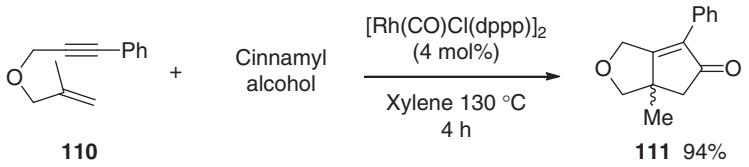
[a]TPPTS, triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt.

Chung successfully used cinnamaldehyde not only as a CO source but also as a reactant styrene source. This PK reaction was achieved using Rh/Co colloidal nanoparticles (equation 32).[91]



(32)

Since aldehydes are formed from alcohols through the metal-assisted dehydrogenation, this tandem process can be further extended. The same catalyst is used for the dehydrogenation of alcohols to aldehydes, then decarbonylation of the resultant aldehyde yields the metal carbonyl, which finally serves in for the PKR (equation 33).[91b]



(33)

Various carbohydrate derivatives with acetate-protected alcohol groups derived from D-glucose, D-mannose, D-galactose, D-xylose, D-ribose,[92a] or glyceraldehyde acetonide[92b] were used as CO sources, albeit the results were modest. Multiple successive CO generations from single carbohydrates such as D-glucose and/or xylitol was tried, but the efficiency is not impressive (Figure 16, see Section 5.24.4.2.2 for more discussion).[91b]

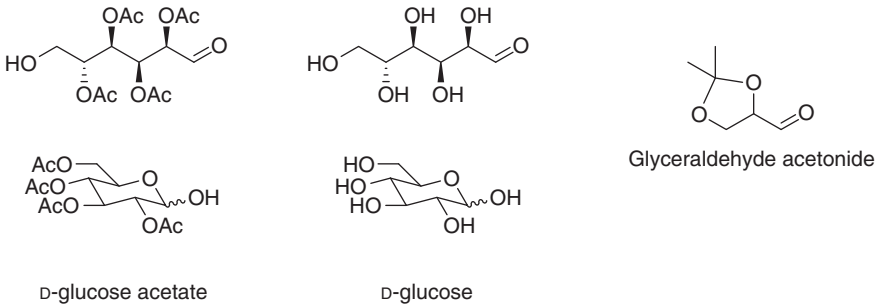
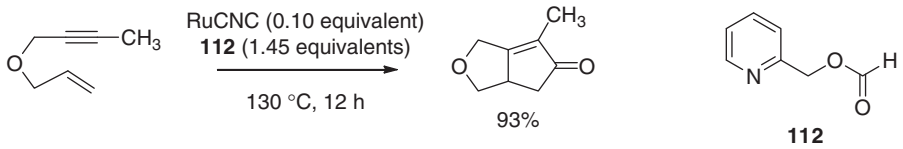


Figure 16 Sugars as CO source for the neutral Rh(I) catalyzed PKR.

Chung introduced a combination of the well-designed CO surrogate **112** and ruthenium colloidal particles (RuCNC) (equation 34).[93]



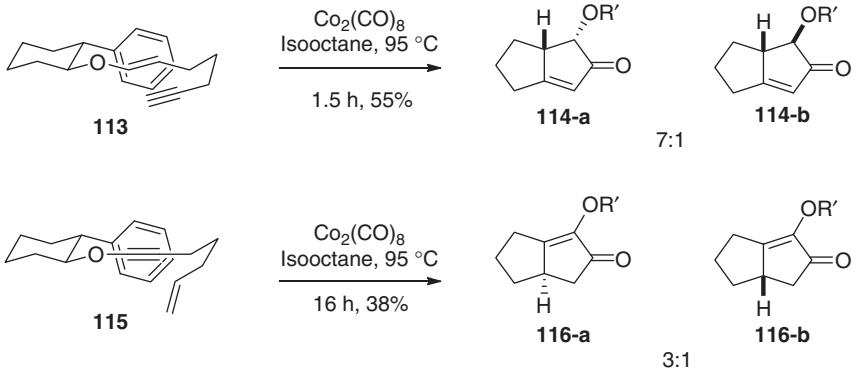
(34)

5.24.4 Asymmetric PKR

In the past two decades, there have been extensive efforts to prepare optically pure PKR products. These efforts include the following two categories: (1) substrate-controlled asymmetric reactions and (2) reagent-controlled asymmetric reactions.

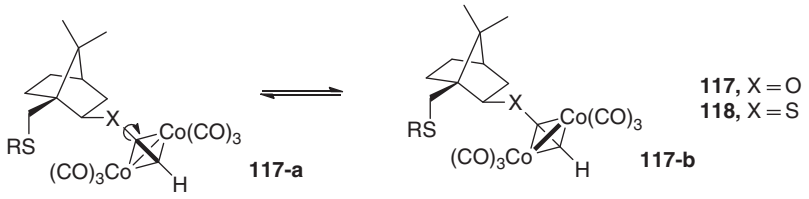
5.24.4.1 Substrate-Controlled Asymmetric PKR

The use of substrates having a removable chiral auxiliary: Early attempts utilizing the substrates **113** and **115**, with the expectation of the blocking of one face of the olefin by a phenyl group, led to modestly diastereoselective PKRs (equation 35).[94]



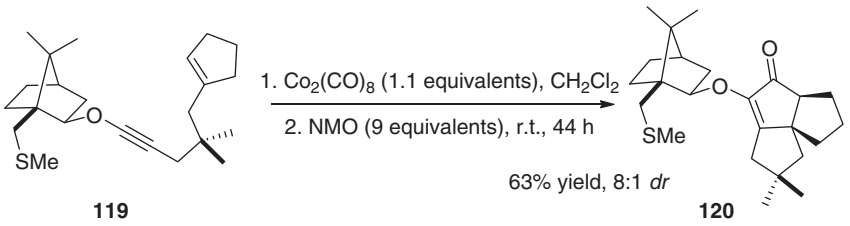
(35)

Moyano and Pericas used the chiral alcohols **117** (X=O) or sulfides **118** (X=S) bearing a suitably positioned extra sulfur appendage. This would make the intermediate structure rigid by a secondary ligation from the auxiliary. As a result, the free rotation of the alkyne cobalt complex moiety along the axis between the alkyne carbon and the heteroatoms would be restricted and high diastereoselectivity be ensured (Scheme 12) when a highly strained olefin such as norbornadiene (**3**) is used.[95a] Otherwise, when a less reactive olefin such as cyclopentene was employed, a 1:1 mixture of diasteromers was obtained in low yield (14%).[95b]



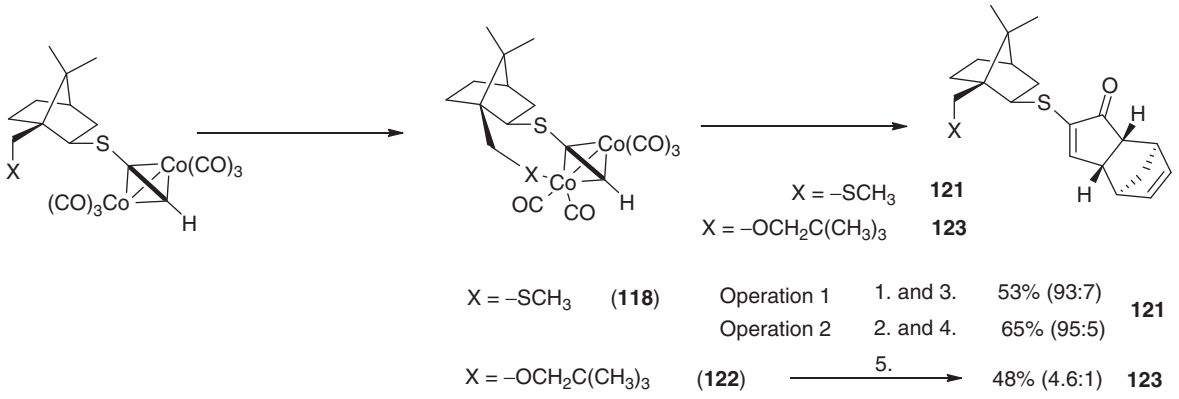
Scheme 12

The tricyclic ring compound **120** was prepared from **119**, an analog of **117**, with high stereoselectivity (equation 36).[96]



(36)

The significance of the secondary prechelation is again supported by the report that compound **118** having a more strongly donating sulfur atom on the appendage provided a substantially higher diastereoselectivity than **122** containing a weaker binding O-atom (equation 37).[97]



(37)

1. (a) $Co_2(CO)_8$, (b) heating at 55 °C; 2. (a) $Co_2(CO)_8$, (b) NMO (3 equivalents) in CH_2Cl_2 3.; 4. norbonadiene, –10 °C;
5. (a) $Co_2(CO)_8$, (b) NMO (6 equivalents), –20 °C, CH_2Cl_2

Substrates bearing other chiral auxiliaries such as Oppolzer's bornanesultam **124** gave excellent results in terms of stereocontrol and yield (Figure 17).[98]

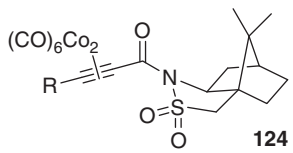
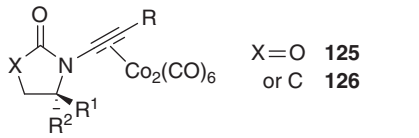
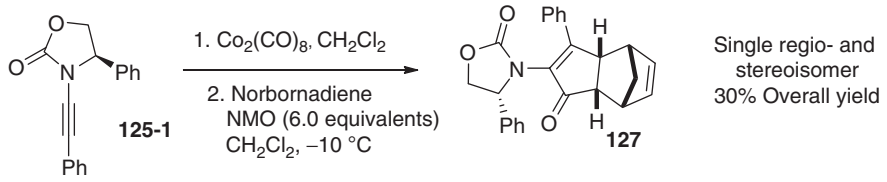


Figure 17 Chiral alkyne-cobalt complex bearing Oppolzer's bornanesultam.

A chiral imidate (**125**) or chiral amides (**126**) were successfully employed for the intermolecular PKR to provide a single diastereomeric product, albeit in low yield.[99]

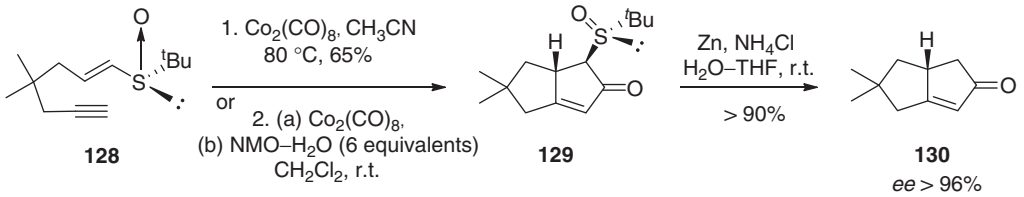
An example of the use of an imidate is summarized in equation 38 and another example using the chiral amide **581** will be given later in equation 155.





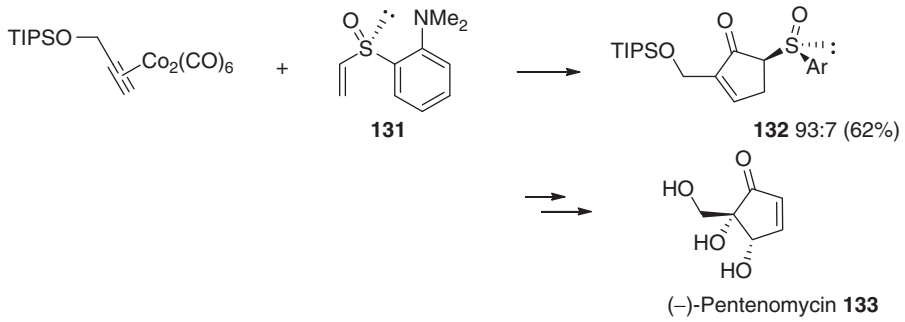
(38)

The chiral sulfoxide group next to the olefinic moiety in **128** controls the stereoselectivity efficiently and provides **129** with high diastereoselectivity. In addition, the mixture of *E* and *Z* vinylsulfoxides **129** gives the same final product **130**, if they are treated with zinc to remove the sulfoxide moiety (equation 39).[97c]



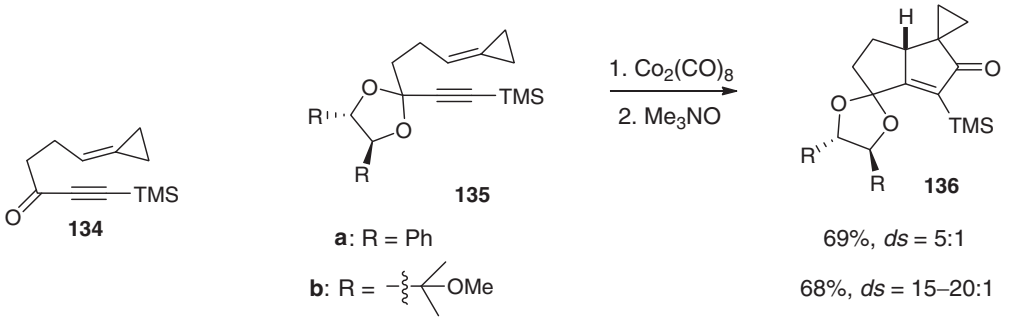
(39)

The chiral sulfoxide in compound **131** could control the diastereoselectivity in an intermolecular PKR as well (equation 40).[100]



(40)

De Meijere introduced a chiral ketal for the ynone substrate **134**. The authors tried to offer a solution for two problems in the PKR of the electron-deficient alkyne **134**. By introducing a chiral ketal on the carbonyl, the newly formed alkyne **135** was then no longer a poor substrate, and a chiral environment was imposed at the same time.[101a] The PKR of substrate **135a** provided **136a** as the major diastereomer. Later, Krafft used a bulkier chiral auxiliary. Compound **135b** gave rise to improved results (ds from 5:1 to 15–20:1) (equation 41).[101d]

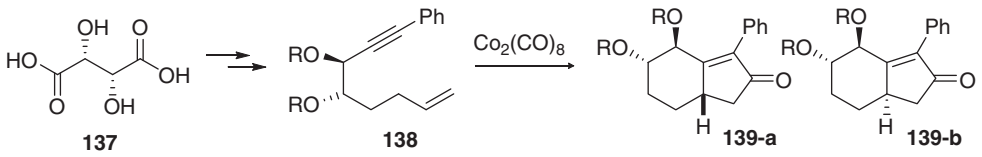


(41)

5.24.4.1.1 Chirality transfer from the preexisting stereogenic center on the substrates

Relative stereocontrol by preexisting stereogenic centers in the reacting substrates has been studied extensively, and the outcome of the reaction is now well predictable.

Mukai and Hanaoka applied this approach to the synthesis of numerous natural products in optically pure form. They prepared numerous 'chirons' from the abundant natural chiral pool, such as dimethyl L-tartrate or L-ascorbic acid, and employed them in the PKR. One example is the previously reported synthesis of the bicyclo[4.3.0] ring with high diastereoselectivity as given in equation 42.[102a] Two more examples will be discussed in Section 5.24.6.1.

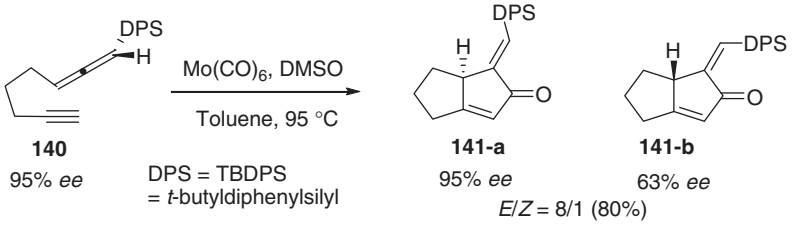


Condition	139-a:139-b	Yield
R, R = TBDMS	1. 100:0	99%
R, R = H	2. 1:99	94%
R, R = $OC(CH_3)_2O$	3. 0:100	56%

Condition: 1. 70–75 °C in MeCN 2. NMO in CH_2Cl_2

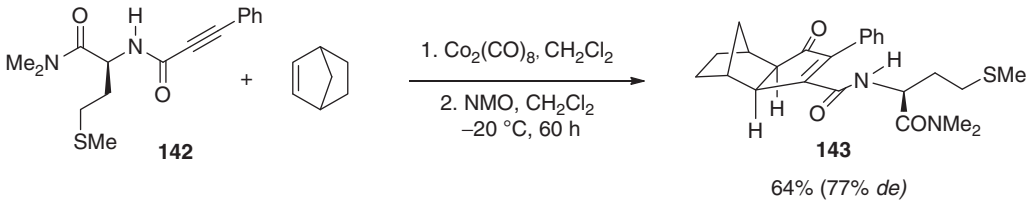
(42)

Brummond's example of successful chirality transfer from a chiral allene **140** in the PKR is also noteworthy (equation 43).[103]



(43)

Hiroi et al. employed the alkynamide **142** derived from (*S*)-methionine to obtain **143** in a regio- and stereoselective manner (equation 44).[104,99]



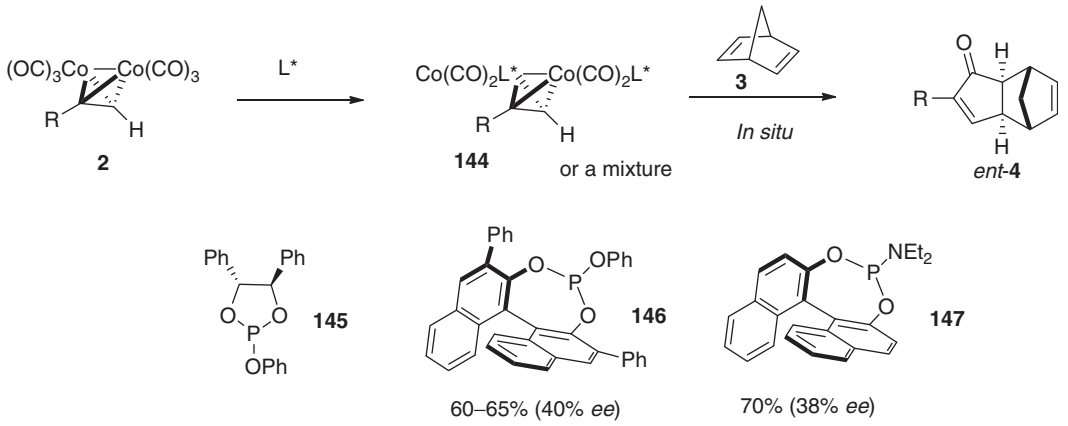
(44)

5.24.4.2 Reagent-Controlled Asymmetric PKR

5.24.4.2.1 Based on cobalt

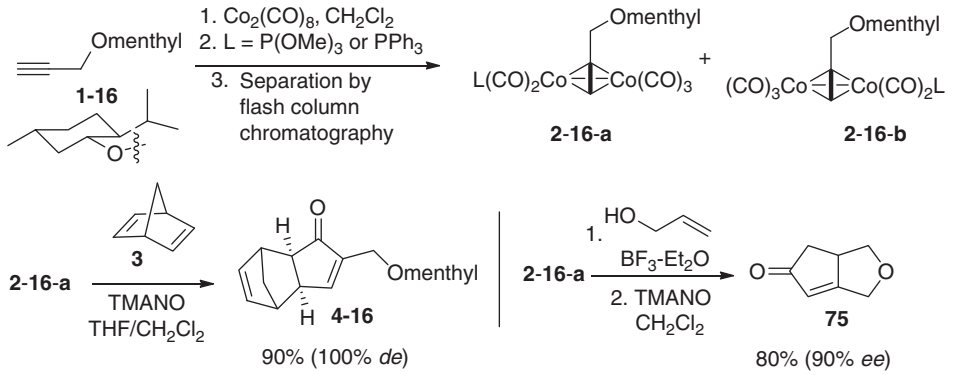
One of the simplest approaches is the modification of the environment around the metal. This can be divided into two categories: (1) the use of a chirally modified alkyne–metal complex formed *in situ* and (2) the use of preformed chiral alkyne–metal complexes.

The first approach is carried out by simply mixing the alkyne-dicobalt hexacarbonyl complexes (**2**) with a chiral phosphorous ligand and, then, the presumed chiral intermediate is subjected to the PKR. It was assumed that two CO, one from each $Co(CO)_3$ moiety, were replaced to form the intermediate **144**. The PKR induced either by thermal conditions or by promoter-assisted conditions would allow the optically enriched product **4** to be obtained. The chiral phosphites, **145** or **146**, were used first.[97] Subsequently, Monophos **147**, a commercially available BINOL-derived monodentate phosphoramidite, was also used for the intermolecular PKR. However, the enantioselectivity was not satisfactory in any of the cases (equation 45).[105]



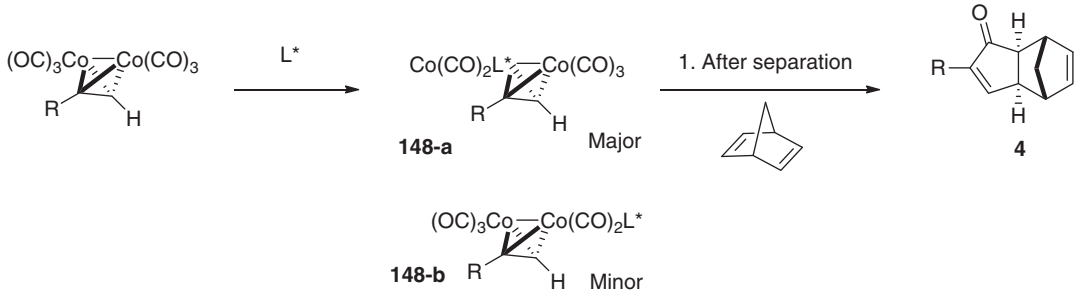
The second approach uses preformed chiral alkyne-cobalt carbonyl complexes. A mixture of diastereomeric metal-alkyne complexes was usually obtained and each diastereomer was separated by column chromatography or other means. Then, the isolated optically pure diastereomer was subjected to the PKR either under thermal or promoter-assisted conditions. When an enantiomerically pure substrate was employed, the PKR was highly stereoselective.

One of the first approaches employed a propargyl alcohol having a menthyl group, **1-16**. The replacement of only one CO afforded a 1:1 mixture of diastereomers, **2-16-a** and **2-16-b**, which were separated by column chromatography. Each diastereomer was employed in the intermolecular PKR reaction with norbornadiene to give the PK product **4-16**, or subjected to the Nicholas reaction with the allyl alcohol followed by the PKR to afford **75** in optically pure form (Scheme 13).[106]



Scheme 13

The next approach is to treat the prochiral alkyne–dicobalt hexacarbonyl complex **2** with chiral ligands. Again, a mixture of diastereomers was obtained, which were separated and then used for the PKR (Scheme 14; for the conditions, see Figure 18 and Table 7).



Scheme 14

All of the ligands used in this category are summarized in Figure 18 and some representative results are listed in Table 7.

Glyphosphate was employed for the first time by Pauson and coworkers. The replacement of only one CO would lead to a 1:1 mixture of diasteromers. Each diastereomer was separated by chromatography and then subjected to the PKR.[107,108]

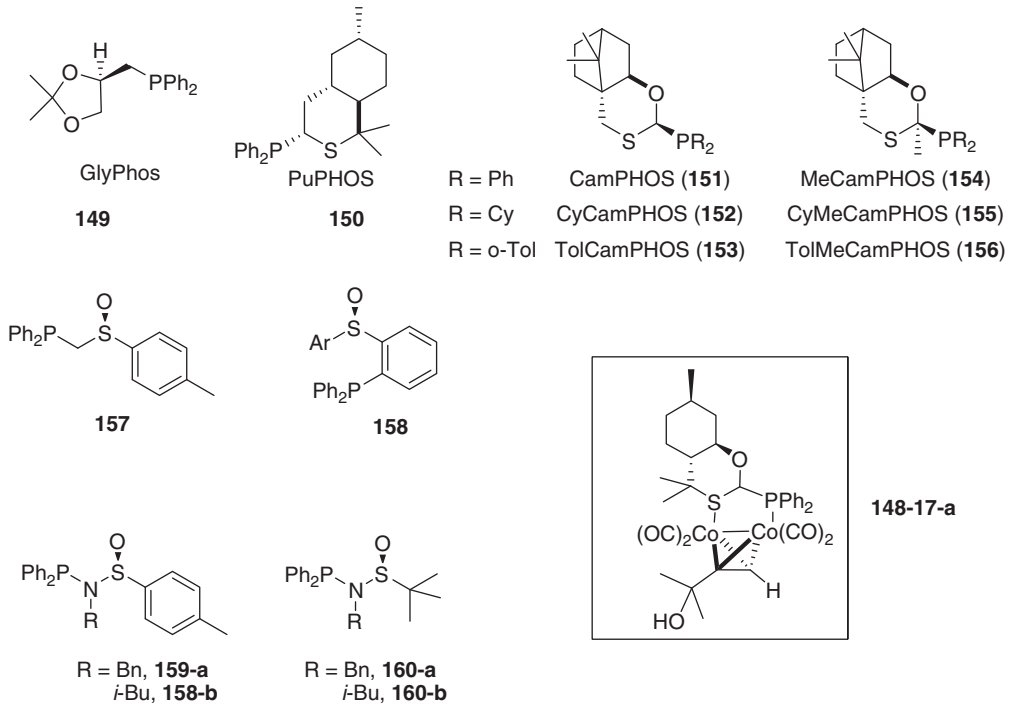
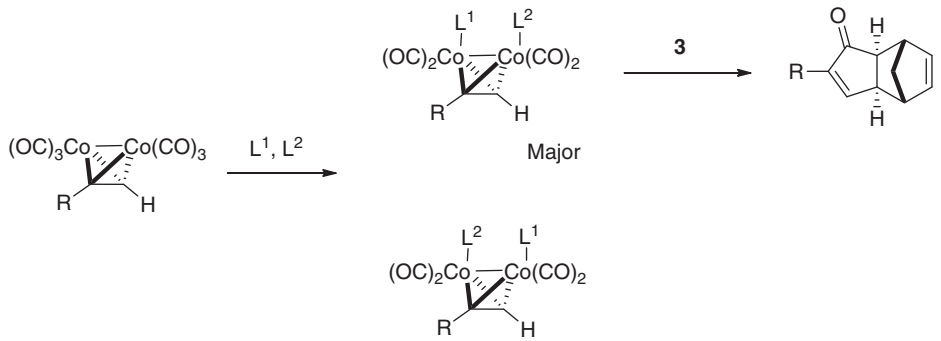


Figure 18 Representative chiral ligands been used for the preparation of optically pure diastereomeric alkyne-metal complexes.

Table 7 Stereoselective intermolecular PKR employing diastereomerically pure alkyne-Co complexes



Entry	*L*	*R*	*Yield of* ***148***	ds *of* ***148***	*PKR condition*	*Yield of* ***4***	ee *of* ***4***	*Reference*
1	**149**	Ph (**1-1**)	–	1:1	NMO	76	99	108
2	**150**	$CMe_2(OH)$ (**1-17**)	84	4.5:1	Thermal	99	99	109a
3	**151**	Ph (**1-1**)	85	1.5:1	Thermal	93	97	109b
4	**151**	$CON(i\text{-}Pr)_2$ (**1-18**)	89	99:1	Thermal	91	91	109c
5	**159-a**	$CH_2OTBDPS$(**1-19**)	85	10:1	NMO	99	92	109e
6	**159-b**	$CMe_2(OH)$ (**1-17**)	81	1.3:1	Thermal	89	28	109f
7	**159-a**	PhCCPh[a] (**1-20**)	83	–	NMO	73	90	109g

[a]Disubstituted alkyne.

Many years later, Greene, Pericas, and Moyano prepared a series of complexes between the cobalt–alkyne and hemi labile P,S ligands with a chiral backbone[109] such as PuPHOS (**39**) and various CamPHOS derivatives (**151-153**), which were readily obtained from (+)-pulegone or camphor, respectively.

The diastereomers derived from **1-17**, obtained in a 4.5:1 ratio when PuPHOS (**150**) was used, were separated. Then the major diastereomer (**148-17-a**) reacted with norbornadiene by the assistance of NMO as promoter to give the PKR product (**4**) in excellent yield as well as enantioselectivity.[109a]

Subsequently, Verdaguer et al. introduced new auxiliaries for the asymmetric PKR bearing chirality on the sulfoxide, for example, P-C-SulfOxide (PCSO) ligands such as **157** and **158** and P-N-SulfOxide (PNSO) ligands such as **159–160**.[109e]

Among the examples in Table 7, entry 4 is noteworthy. For the alkyne substrate **1-18** with an amide substituent, which can participate in the formation of an internal nonclassical hydrogen bond found in **148-18-a** to rigidify the conformation, the diastereoselectivity was dramatically improved by this secondary effect (Figure 19).[109c]

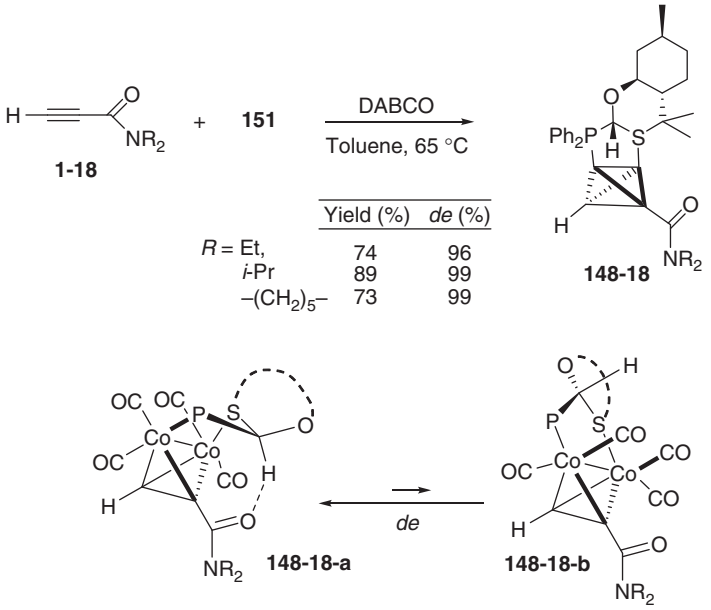
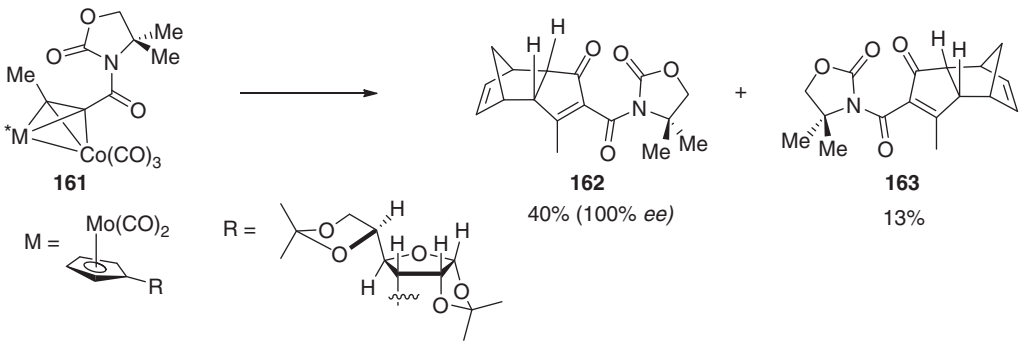


Figure 19 Internal nonclassical hydrogen bonding guided stereoselective intermolecular PKR.

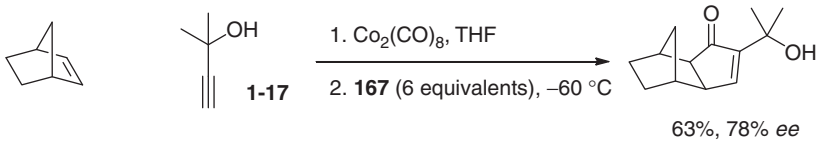
Pericas and Moyano reported an interesting observation that a heterobimetallic (Mo–Co) complex provided the intermolecular PKR products in favor of the *endo*-isomer (equation 46).[110]



(46)

5.24.4.2.1.1 Use of chiral promoters

The use of chiral promoters is an obviously straightforward entry into the enantioselective PKR. The chiral promoter may approach one of the two equivalents cobalts and effect the oxidation of a specific CO group preferentially. However, early attempts to make a vacant coordination site stereoselectively were not encouraging (Figure 20). After much effort, enhanced enantioselectivity at a practical level was obtained by using brucine *N*-oxide (**167**), a bulky amine *N*-oxide, under carefully controlled conditions (− 60 °C) (equation 47).[111]



(47)

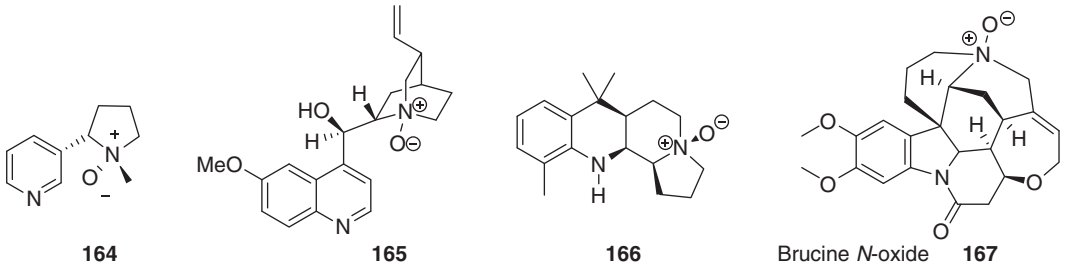
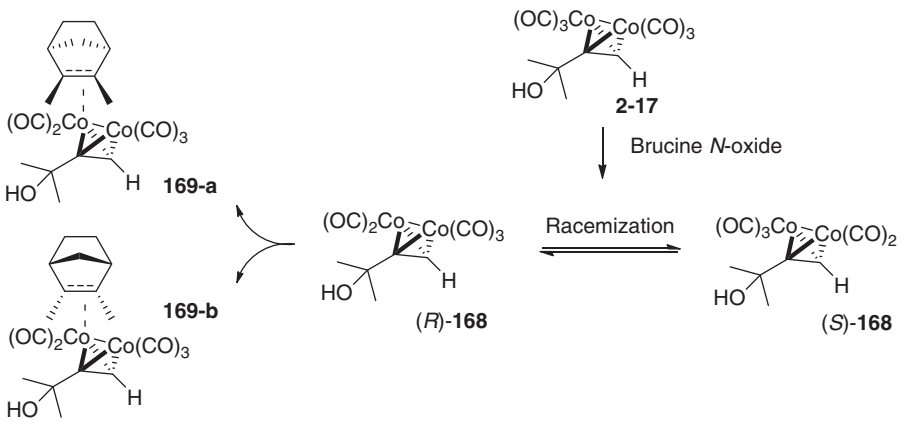


Figure 20 Representative chiral amine *N*-oxide promoters.

A computational study revealed that the partial racemization at the intermediate **168** can hardly be avoided and, thus, the enantioselectivity is noticeably lowered. This racemization can be reduced by elevating the energy barrier between the two intermediates. If the substrate bore an alcohol functionality in it, the barrier was raised through an intramolecular hydrogen bond. Under these circumstances, a significantly higher ee was obtained (Scheme 15).[111e]

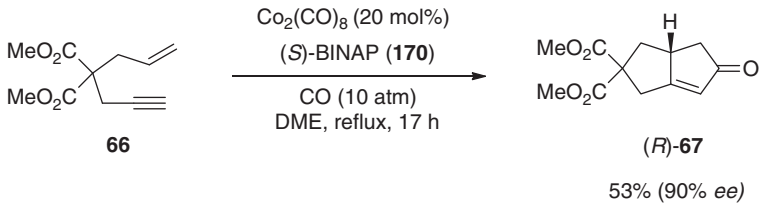


Scheme 15

5.24.4.2.1.2 The use of chiral catalysts

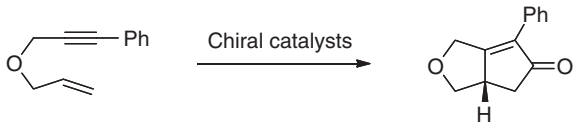
Despite the impressive advances in the catalytic PKR, the development of a catalytic enantioselective version has not kept pace with the other successes (Table 8). Naturally, the use of a cobalt catalyst bearing an external ligand was extended to the use of chiral phosphane or phosphite ligands, but the success of this approach has been extremely limited.

The asymmetric PKR using cobalt modified by the chiral phosphane (*S*)-BINAP (**170**) was reported by Hiroi et al. for the first time (equation 48).[112] However, the narrow scope of the substrates and high catalyst loading seemed to be a major shortcoming. Such a drawback can be explained by the fact that the chemical constitution of the real catalyst was ill-defined. To overcome this problem, Gibson et al. purified complex **171** before the reaction and characterized its structure. Utilizing this compound as a catalyst, a highly enantioselective PKR was realized.[113] Extensive studies to understand the further behavior of **171** to give putative $[Co_2(substrate)(BINAP)(CO)_4]$ complexes followed. Monitoring of the reaction pathway with ^{31}P NMR strongly suggested the occurrence of intermediate **173** in which the Co–Co bond was cleaved by the presence of the pendent alkene during the intramolecular reaction. However, the correlation between this mono cobalt-intermediate and the PK reactivity remained unclear (Figure 21).

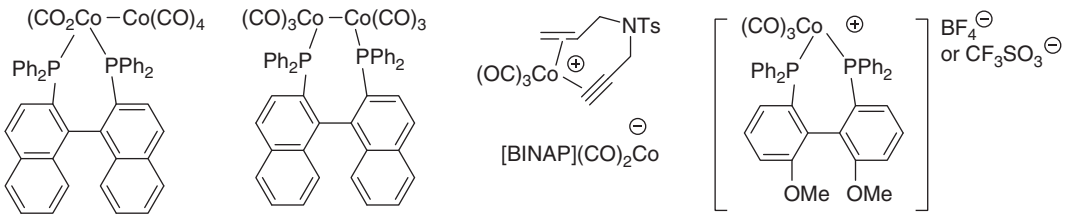


(48)

Table 8 The catalytic enantioselective Pauson–Khand reaction



Enantioselective catalytic condition				*Yield (%)*	ee *(%)*	*References*
Catalytic system	*Solvent*	*CO (atm)*	*Temperature (°C)/ time (h)*			
With cobalt						
$Co_2(CO)_8$/BINAP (**170**)	DCE	1	Reflux, 17	64	90	112,114
$Co_2(CO)_8$ + phosphites (**175**)	Toluene	1	120, 24	75	75	115
Preformed alkyne-BINAP Co(CO)-$Co(CO)_3$	DME	1–3	75, 5	70	89	113
With other metals						
(*S,S*)-(EBTHI)$Ti(CO)_2$	Toluene	1	90, 12	96	85	116
$[RhCl(CO)_2]_2$/(*S*)-BINAP (**170**) or chiral bisphosphines, AgOTf	THF	1	100, 5	88	81	117,118,119
$[IrCl(cod)]_2$/(*S*) tol-BINAP or **182**	Toluene	1	130, 36	80	96	120
$[RhCl(cod)_2]_2$/(*S*)-BINAP	Cinnam aldehyde	0	100, 3–4	89	82	121
$[Rh(cod)Cl]_2$/(*S*)-*tol*BINAP, TPPTS, SDS	H_2O	HCHO	100, 5	61	93	121c
$[Rh(cod)Cl]_2$ (0.05 eq)/(*S*)-PPHOS (**183**) or (*S*)-**184**	H_2O or *t-amyl* alcohol	RCHO	100	97	96	124
$RhCl(cod)_2]_2$/(*S*)-BINAP cinnamaldehyde	Toluene	–	110–115, 24	57	90	125
Co_2/Rh_2/(*R*)-BINAP crotonaldehyde	THF	–	130, 18	93	79	126

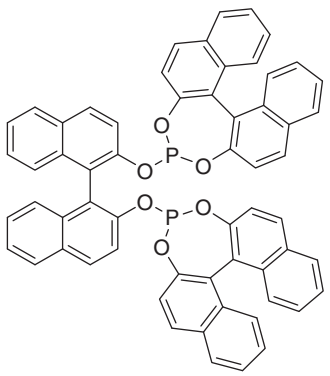


171 **172** **173** **174**

Figure 21 Chiral cobalt carbonyl catalysts modified with bisphosphane ligands.

In the meantime, the cationic chiral monocobalt catalyst [Co(*R*)-MeO-Biphep)$(CO)_3$]X (X = BF_4 or OTf) (**174**) was also reported, although it was found to be slightly less efficient.[114]

Buchwald and Sturla introduced a cobalt-catalyst carrying chiral phosphites (Figure 22).[115] Only modest *ee* values (64%–75%) were reported, however.

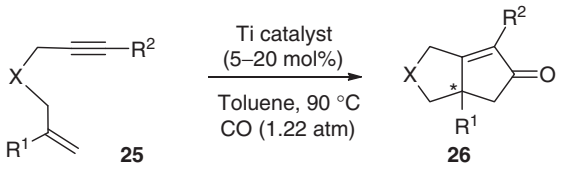


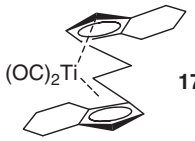
175

Figure 22 Chiral phosphite used for the preparation of a chiral cobalt carbonyl catalyst.

5.24.4.2.2 Based on metals other than cobalt

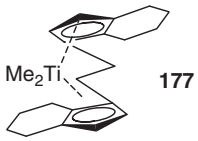
Buchwald and Hicks reported the first asymmetric PKR utilizing a catalytic amount of a chiral titanocene complex. The titanium catalyst (*S*,*S*)-(EBTHI)Ti(CO)$_2$ (**176**) obtained *in situ* from (*S*,*S*)-(EBTHI)TiMe$_2$ (**177**) and CO was efficient for the enantioselective PKR.[116] Not only the *N*-tethered enyne but also *C*- and *O*-tethered substrates provided the corresponding cyclopentenones **26** in excellent yield and enantioselectivity (equation 49).





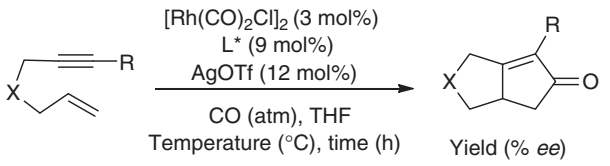
(49)

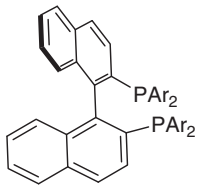
X	R^1	R^2	Yield (%)	*ee* (%)
O	H	Ph	96	85
CH_2	H	Ph	87	70
$C(CO_2Et)_2$	H	Ph	94	92
$C(CO_2Et)_2$	Me	Me	72	90



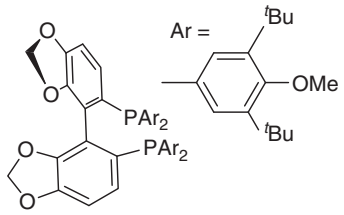
Following the successful application of a rhodium(I) catalyst bearing tunable bidentate phosphine ligands such as dppp, Jeong et al. performed the first rhodium-based enantioselective PK reaction.[117a] Initial results were somewhat unsatisfactory because a high *ee* was obtained only in the case of *O*-tethered substrates. Furthermore, such high *ee* values were often obtained at the expense of the chemical yield.[117b]

Extensive optimization was subsequently performed along with the elucidation of the reaction mechanism for the purpose of clarifying some of the fundamental features. For example, the CO concentration must be kept as low as possible in order for the transformation to be efficient.[117c] The higher enantioselectivity obtained for *O*-tethered substrates than for other congeners is explained by the prechelation by the oxygen atom in the substrate to rhodium in the transition state (**Scheme 16**).[117d] In subsequent years, two notable optimizations were reported. First, the reaction induced by the catalyst obtained from 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) bearing bulky phosphorus substituents, especially 3,5-*xylyl*-BINAP (**178**),





Ar = Ph **(170)**



DTBM–MeO–BIPHEP **(179)**

Ar = 3,5-dimethylphenyl **(178)**

Condition

1. L* = BINAP (**170**)
   CO (1 atm), 80 °C, 2–5 h
2. L* = 3,5-xylylBINAP (**178**)
   CO (0.1 atm), 0–25 °C, 2–5 h
3. L* = DTBM–MeO–BIPHEP (179)
   CO (0.1 atm), 80 °C, 2–5 h

X	R	Condition 1.[117a] Yield (%)	*ee* (%)	Condition 2.[117c] Yield (%)	*ee* (%)	Condition 3.[117f] Yield (%)	*ee* (%)
O	alkyl	40	96	52	99	94	99
	aryl	88	81	99	94	95	92
TsN	alkyl	80	84	96	98	94	99
	aryl	93	74	99	75	96	99
E_2C	alkyl	70	70	60	96	84	91
	aryl	78	42	99	74	99	93

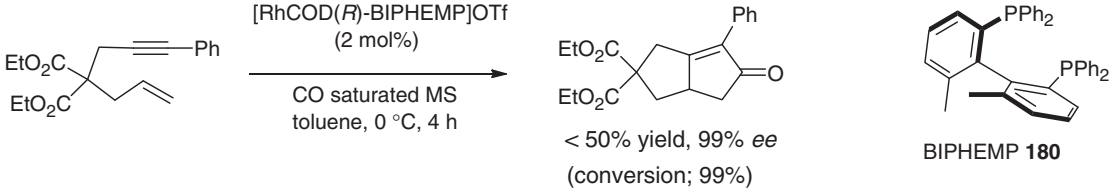
E_2C = $(EtO_2C)C$

Scheme 16

proceeded at ambient temperature, affording much improved enantioselectivities under reduced CO pressure (10% CO in argon at atmospheric pressure).[117c] However, there is still a trade-off between the chemical yield and stereoselectivity for some substrates.

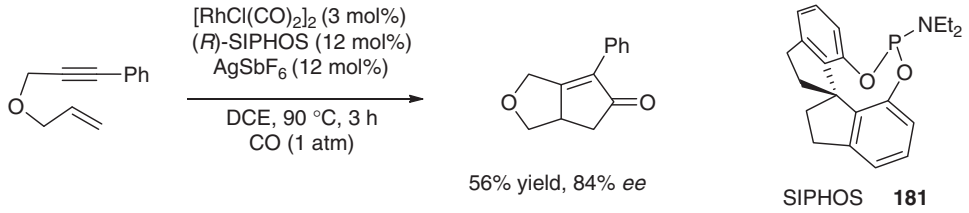
Second, the reaction by catalysts bearing a highly sterically demanding ligand, DTBM–MeO–BIPHEP (**179**), under reduced pressure of CO, but at high temperature, provided the PKR products in higher yields as well as enantioselectivity for a wide range of substrates. Pleasantly, the side product formation is significantly suppressed under this condition.[117f]

Many modifications of the original protocol appeared in the literature in the following years. A molecular sieve CO reservoir was also used as a CO source in place of a CO balloon. With this modification, the reaction temperature was lowered significantly to 0 °C. However, a low concentration of CO often led to a low chemical yield of the PKR product, even after the complete conversion of the starting materials (equation 50).[118]



(50)

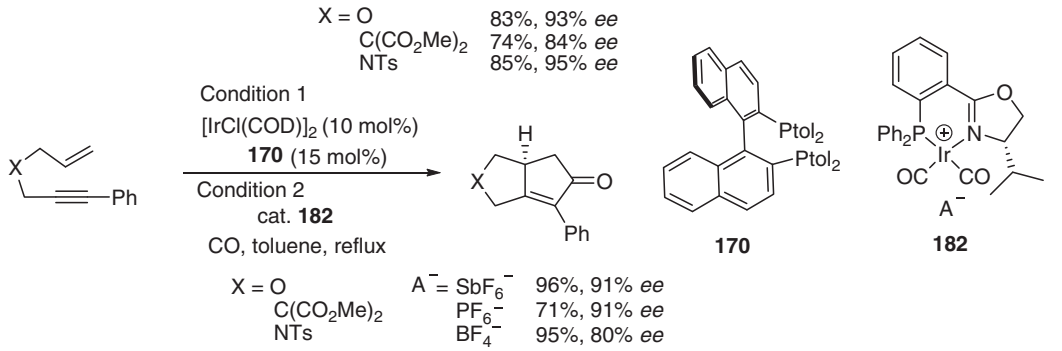
The monodentate phosphoramidite SIPHOS ligand (**181**) was employed to afford the PKR product in dichloromethane with a decent chemical yield and good enantioselectivity (equation 51).[119]



(51)

Following the success with cobalt and rhodium, Ir(I)-based enantioselective catalytic PKRs were attempted. Right after the observation of the catalytic activity of $[IrCl(cod)]_2$ in the PKR in the presence of phosphane ligands, Shibata moved directly to the use of chiral tol-BINAP and examined the enantioselectivity.[120a] The TON and TOF of the reaction were low and the number of examples was limited; however, a high efficiency was observed in terms of the enantioselectivity. Moreover, this catalytic system provided the first asymmetric intermolecular reaction as well.

Subsequently, Pfaltz and coworkers utilized the catalyst **182**. Excellent *ee*'s for a wide range of substrates were realized, especially in the case of oxygen and malonate tethered 1,6-enynes (equation 52).[120b]



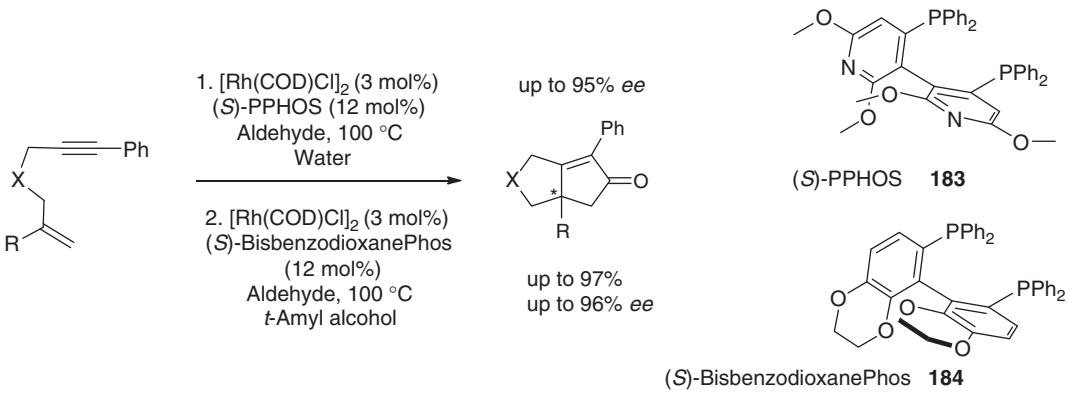
(52)

Asymmetric catalytic versions with Rh(I) using other CO sources have also been reported. Kakiuchi, Morimoto, and Shibata used a neutral rhodium(I) complex bearing chiral ligands together with aldehydes as the CO source. These reactions were comparable to the conventional PKR carried out with cationic Rh(I) under CO pressure in terms of their enantioselectivities and chemical yields.[121] Since this condition used a neutral Rh(I) catalyst, it proved useful in reactions of acid-sensitive substrates (e.g., the acetal-carrying alkyne **193** shown later in equation 58).[122]

Polar protic solvents such as water and alcohols can also be used for these reactions if a solubilizing additive is present. Kakiuchi developed the asymmetric PKR in water using formaldehyde as a water soluble CO source and BINAP-based chiral ligands, after solubilizing them using a surfactant. They were able to obtain evenly high enantioselectivities over a broad range of substrates.[89b]

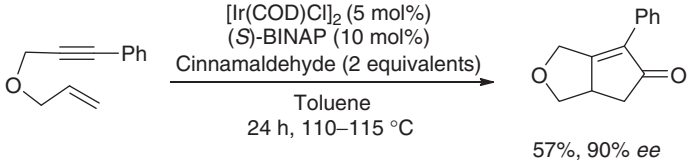
The use of a surfactant can be omitted if the solubility of the ligands in a polar protic solvent is guaranteed. This is the case for catalysts obtained using PPhos and its analogs. Neutral Rh(I) catalysts coupled with PPhos (**183**) or bisbenzodioxane-Phos (**184**)

turned out to be efficient catalysts in water and *t*-amyl alcohol, respectively (equation 53). Reactions with the latter are further expedited by microwave radiation.[123]



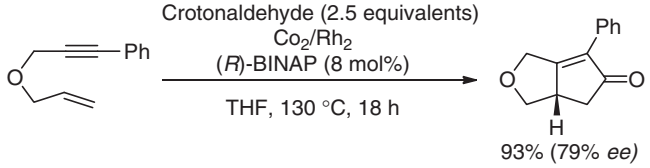
(53)

The iridium catalyst obtained from $[Ir(COD)Cl]_2$ and (*S*)-BINAP (**170**) is also useful for the enantioselective PKR with aldehydes as the CO source, providing a modest yield (57%) but excellent enantioselectivity (90% *ee*) (equation 54). A linear correlation between the *ee* of the ligand and that of the product was confirmed in this specific reaction.[124]



(54)

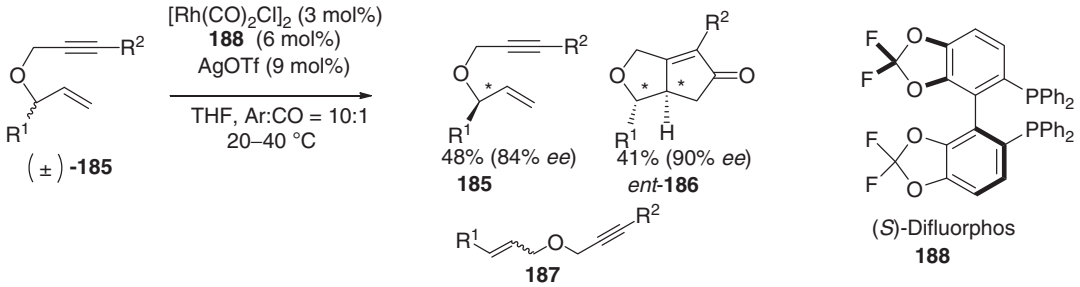
An interesting catalyst, obtained by the adsorption of the chiral ligand BINAP (**170**) on heterogeneous Co_2/Rh_2 particles, is also effective for the enantioselective PKR in the presence of crotonaldehyde (equation 55).[125]



(55)

5.24.4.2.2.1 Application of enantioselective PKR

The kinetic resolution of **185** was realized, although its successful application is limited to R^2 = aryl. It is important to identify the right ligand to suppress the transition metal mediated allylic rearrangement. In this regard, ligand **188**, whose dihedral angle in the corresponding metal complex is smaller than that of BINAP derivatives and for which phosphorus is significantly deshielded, provides a good compromise in terms of the chemical yield and enantioselectivity at ambient temperature (equation 56).[126]

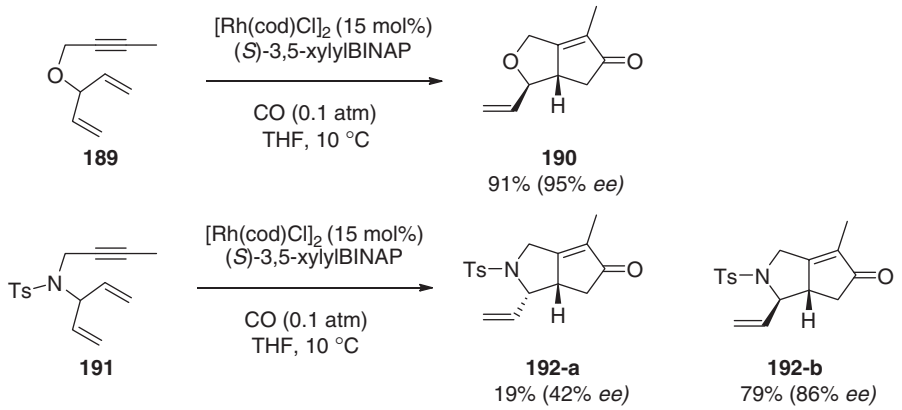


(56)

The desymmetrization of prochiral compounds is more attractive than a kinetic resolution because of the intrinsic problem of the latter that the maximum yield is 50%.

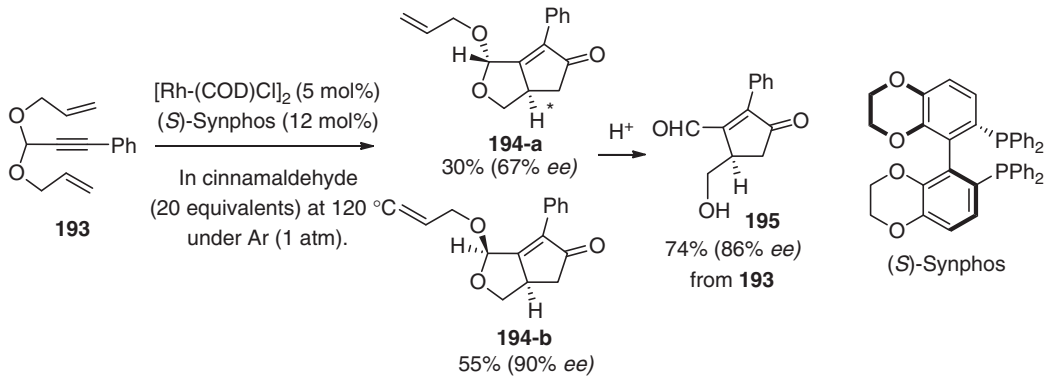
In the desymmetrization of the dienynes **189** and **191** by the asymmetric Rh(I)-based PK-type reaction, the corresponding vinyl-substituted bicyclo[3.3.0]octenones **190** and **192** were obtained with high diastereoselectivity and enantioselectivity,

respectively (equation 57).[117e,127] The interesting observation of the reversal of the diastereoselectivity, depending on the nature of the tether, is rationalized by the precoordination by the heteroatom.[117d]



(57)

The desymmetrization of bisallyl propargyl acetals **193** was accomplished by using a neutral Rh(I) catalyst together with cinnamaldehyde as the CO source. The use of a cationic Rh(I) catalyst was detrimental to this acid-sensitive substrate (equation 58).[122]

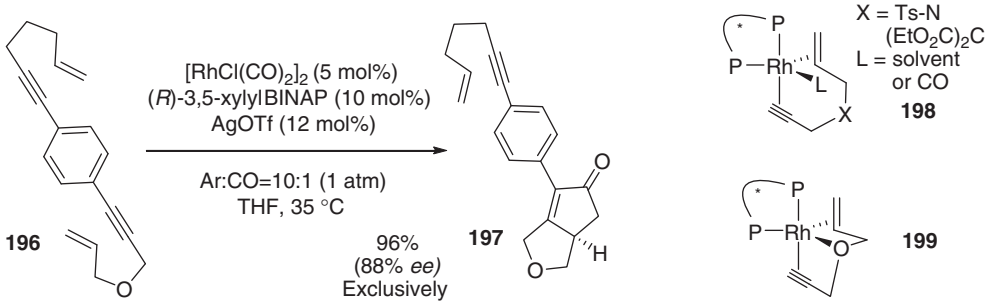


(58)

5.24.4.2.2.2 Chelation-guided reaction

When Rh(I) cationic catalysts are used, the reaction efficiency is significantly dependent on the nature of the tether. Substrates bearing an *O*-tether were superior to their congeners in terms of the reaction rate, chemical yield, and stereoselectivity when subjected to the asymmetric PKR utilizing a cationic rhodium catalyst. This special effect is accounted for by the prechelation of the oxygen atom to the metal center. The chelated precursor **199** allows the facile assembly of each reaction component and has a rigid conformation that results in high enantioselectivity.

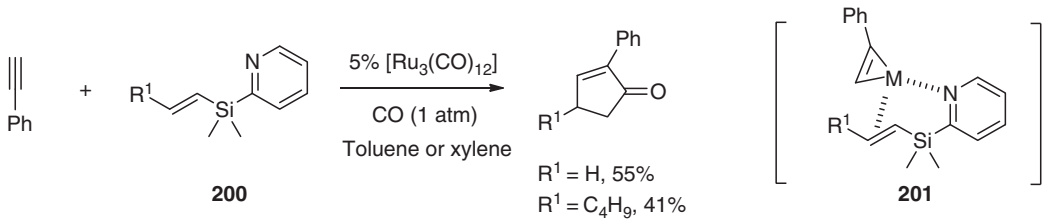
As shown in the competition experiment with **196**, only the *O*-tethered side chain reacted to give product **197** exclusively (equation 59).[117d]



(59)

The importance of chelation during the PKR was demonstrated by the case given in equation 60. Itami and Yoshida reported an elegant surrogate for terminal olefins, dimethyl(2′pyridyl)-vinylsilane (**200**) (equation 60). Since the reaction proceeds through the precomplexation of Ru with the pyridine moiety, the outcome is regioselective to provide the products with the R_1

located at the β-position from the carbonyl. This approach allows the products to be obtained from any terminal olefins with well-defined regiochemistry.[128]



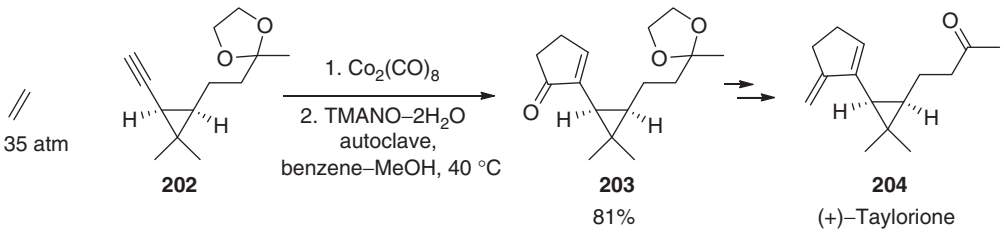
(60)

5.24.5 Some Special Features

5.24.5.1 Substrate Scope

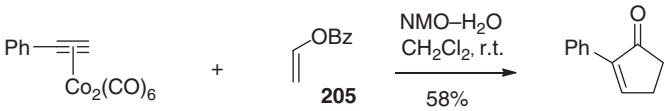
5.24.5.1.1 Ethylene

As we already discussed in Section 5.24.1.1, ethylene is generally a poor substrate for the PKR. Some special treatments are required to utilize ethylene efficiently, as described earlier. For some more examples, Kerr enforced the reaction of **202** by using more of TMANO hydrate in the presence of ethylene under pressure (35 atm) to give **203**, which served as an intermediate for the synthesis of (+) – taylorione **204** (equation 61).[129]



(61)

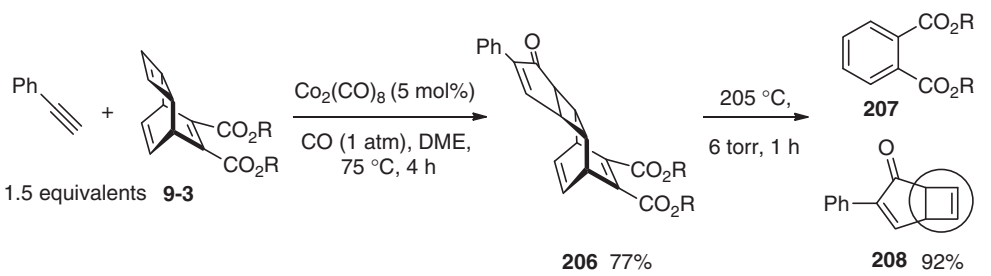
In addition, a couple of ethylene surrogates were reported. Dimethyl(2′-pyridyl)-vinylsilane (**200**) mentioned above is one of them, and the vinyl ester **205** is another. Kerr and Pauson successfully employed **205** as an ethylene substitute, and its reaction with the alkyne–dicobalt carbonyl complex (**2**) gave the desired product at ambient pressure and temperature (equation 62).[130]



(62)

5.24.5.1.2 Cyclobutadiene

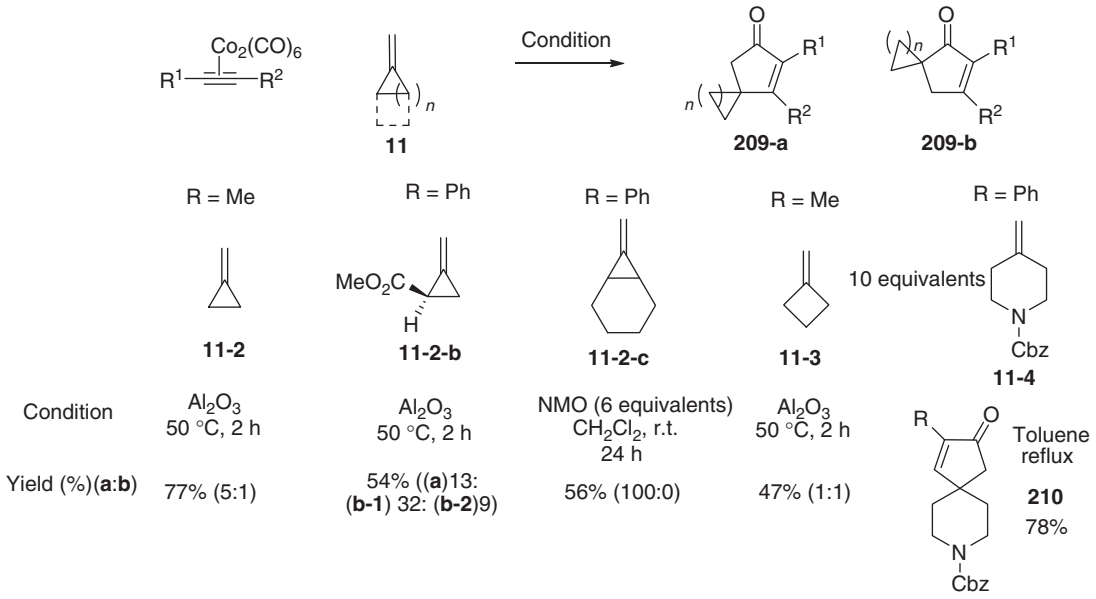
Gibson et al. introduced a well-designed latent cyclobutadiene moiety **9-3**, which reacted with a phenylethyne–cobalt complex (**2-1**) to yield **206**. The PKR took place at the sterically less hindered site to give **206** as a single stereoisomer (equation 63). This product was further subjected to a retro-Diels–Alder reaction at 205 °C under 6 Torr to give **208**.[10]



(63)

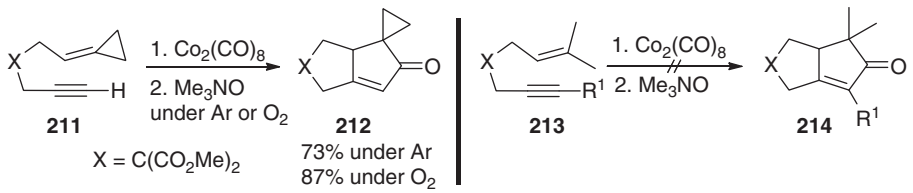
5.24.5.1.3 Exocyclic olefins

When we discussed the substrate scope of the PKR, the reactions of exocyclic olefins, especially those with a small size ring were considered, illustrating the excellent reactivity of highly strained olefins (Section 5.24.1.1). Following the first example of the intermolecular PKR with *exo*-methylenecyclopropane **11-2** reported by Smit with the aid of a solid support,[13] several more examples were reported in the literature (Scheme 17). Summarizing them roughly, usually greater than **11** was reacted with dicobalthexacarbonyl–alkyne complexes (**2**) adsorbed on silica to provide the corresponding PKR products **209** in fair to good yields. The regioselectivity of this reaction was found to be dependent on the nature of the alkynes. With terminal alkyne **1**, the methylenecyclopropanes **11-2** and **11-2-c** provided the corresponding compounds **209-a** as major products, whereas the cyclopropane substrates **11-2-b** bearing carboxylates afforded an isomeric cyclopentenone **209-b** as the major product.[131] Methylenecyclobutane (**11-3**) gave rise to a nearly 1:1 mixture of **209**.[13]



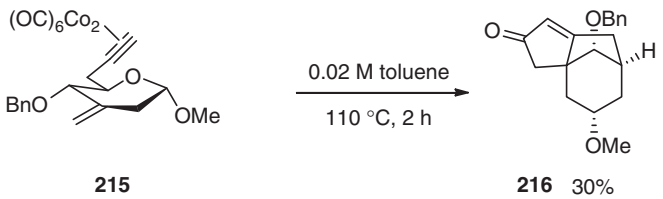
Scheme 17

The intramolecular PKRs of substrates bearing an alkylidenecyclopropane moiety were reported as well. The strain on the olefin is critical to their success. Thus, substrates **211** bearing a cyclopropyl ring on the alkenyl group (tri- and even tetra-substituted) reacted smoothly, affording the corresponding PKR products **212** in moderate to high yield.[132] However, the non-strained olefin **213** bearing a 1,1-dimethylolefin unit did not undergo the cyclization under the same reaction conditions (equation 64).[132]



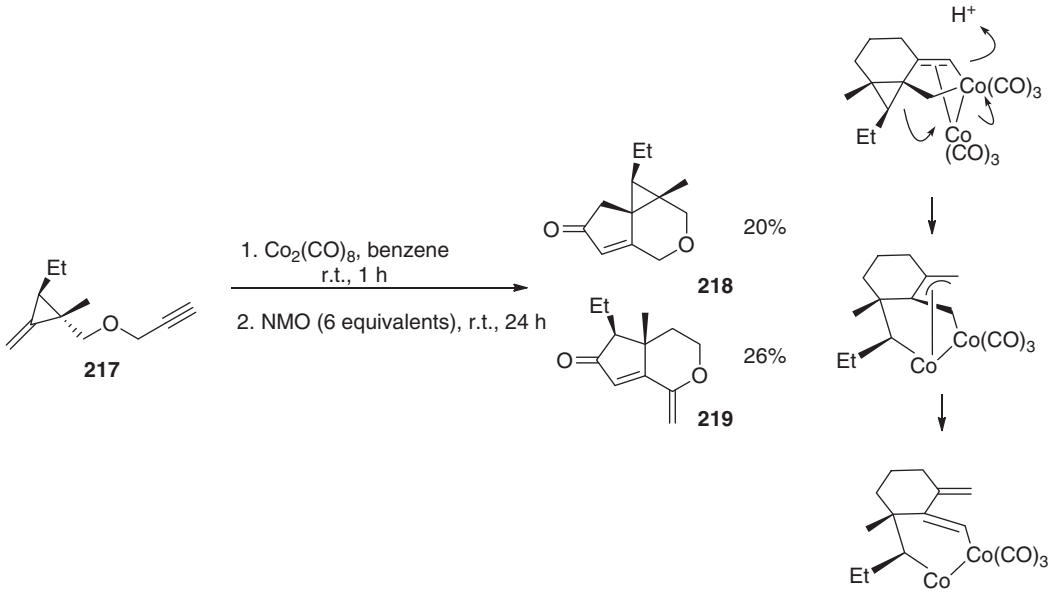
(64)

In analogy to the exocyclic olefin **11-4** with a six-membered ring, where the PKR took place smoothly, substrate **215** underwent the PKR nicely to yield the bicyclic[4.1.0] compound **216**, although the chemical yield was low (equation 65).[132]



(65)

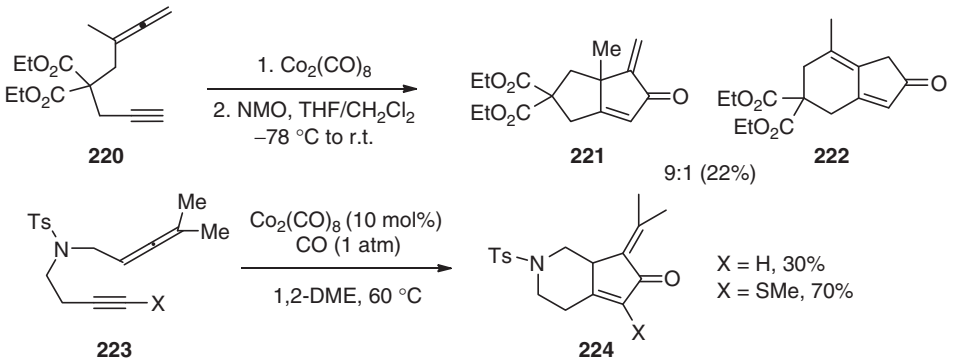
An unusual rearrangement accompanying the intramolecular PKR of substrate **217** was reported by Motherwell. When the reaction was carried out at room temperature, an unusual product **219**, in which none of the carbon atoms of the alkyne were incorporated in the cyclopentenone ring, was obtained as the major product through rearrangement, together with a small amount of the expected PKR product **218** (equation 66).[133]



(66)

5.24.5.1.4 Allenic substrates

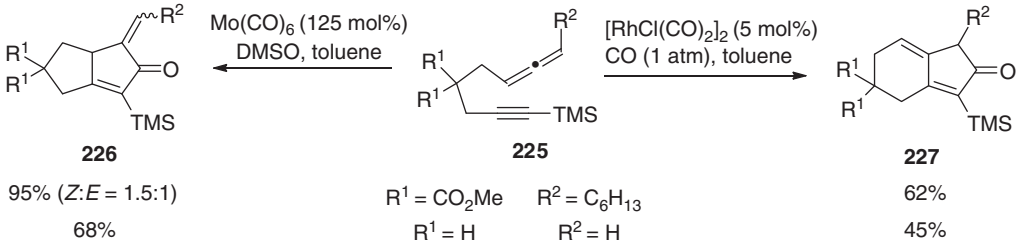
The PKR with some allenes have already been discussed. Benchmark substrates were used to demonstrate the unique features of the newly introduced reagents or catalysts. More examples are summarized here. Some earlier trials employing cobalt metal turned out to be frustrating and gave only limited success (equation 67).[134]



(67)

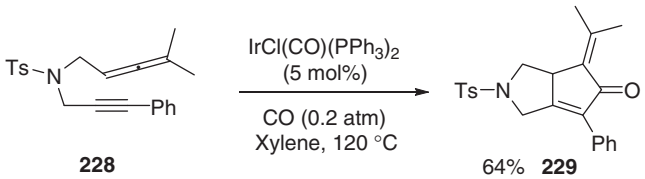
As previously mentioned, molybdenum carbonyl with DMSO[50] and rhodium complexes[79,80] were identified as excellent catalysts for the PKR of allenic substrates, which are complementary in terms of their regioselectivity.

The molybdenum catalyst favored the formation of **226** from **225**, whereas rhodium gave product **227** (equation 68).[122] Although the internal olefin in the allene takes part in the reaction with molybdenum, as previously mentioned, the terminal olefin in the allene reacts with the rhodium catalyst to give a larger ring.[134]



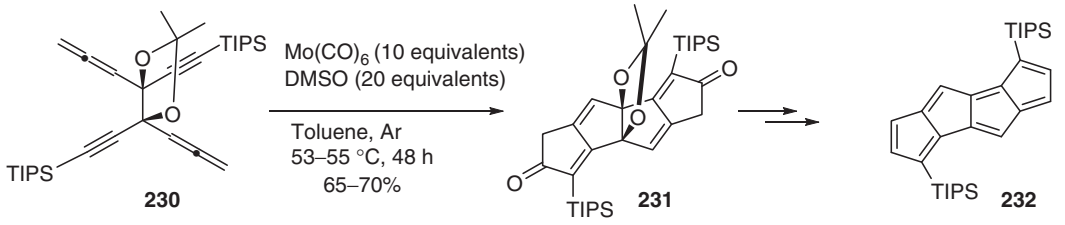
(68)

Iridium was also found to catalyze the PKR through the same reaction, and behaved more like molybdenum in terms of the regioselectivity (equation 69).[135]



228 64% 229 (69)

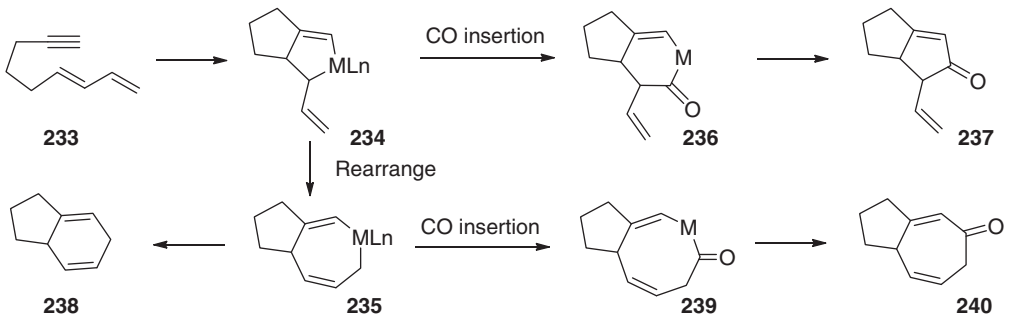
Cook and coworker took advantage of the molybdenum-based methodology and reported one of the most graceful applications of the allenic PKR. They intended to use the PKR reaction to synthesize a theoretically interesting tertracyclic compound **232**, which has 14 π-electrons and is expected to be aromatic in principle. To this end, they applied the PK reaction to various alkynyl allenes and finally employed the diyn-diallene substrate **230** successfully. The double PKR employing molybdenum hexacarbonyl and DMSO more afforded the requisite intermediate **231** in high yield (equation 70).[136]



230 231 232 (70)

5.24.5.1.5 1,3-Dienes and ene-vinylcyclopropane

The PK reaction with 1,3-dienes **233** has many interesting features. First, there must be pathways that compete with the formation of the PK product **237**, leading to the Diels–Alder product **238** and to the homologous PKR product bicyclo[5.3.0]-decadienone **240** (Scheme 18).



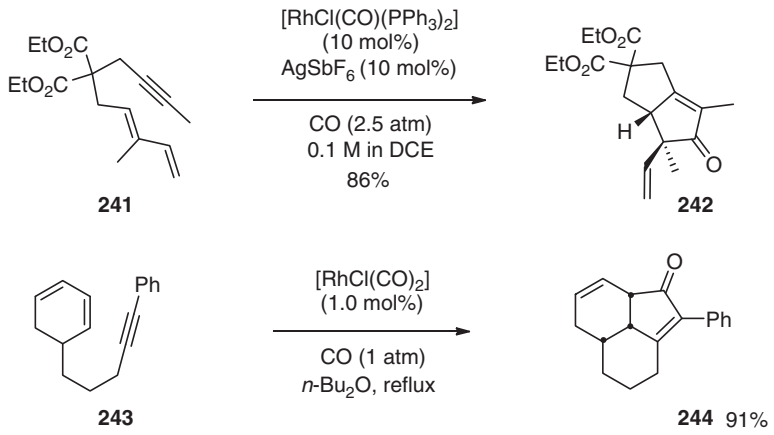
233 234 236 237 238 235 239 240

Scheme 18

In most studies with a sufficient amount of CO, the PKR product **237** was obtained as a major product with the bicyclo[5.3.0]-decadienone **240** as minor product. Because the insertion of CO into **234**, followed by the reductive elimination of the sp^2-hybridized C-atoms of the olefin and carbonyl in **236**, is much more facile than the rearrangement of **234**-**235**, the reaction provided **237** predominantly.

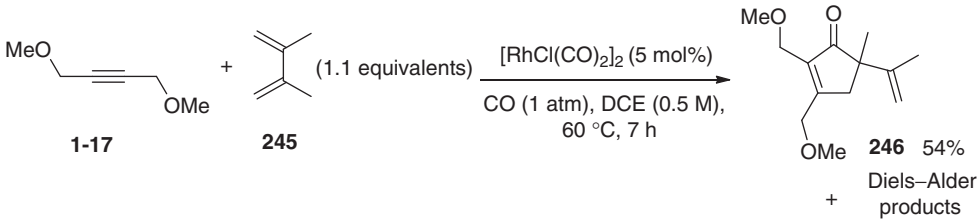
Wender et al. focused their attention on the selectivity of the reaction with the dienynes related to **233** using rhodium catalysts. Disubstituted alkynes gave excellent yields of the PK products, whereas terminal alkynes react less efficiently. Substituents at the 2- and 3-positions of the diene moiety did not slow down the reaction. The stereochemistry of the alkenes are well transferred during the transformation (equation 71).[137]

Yeh et al. employed the conformationally rigid dienes **243** and successfully obtained the PKR products in high yields.[138]



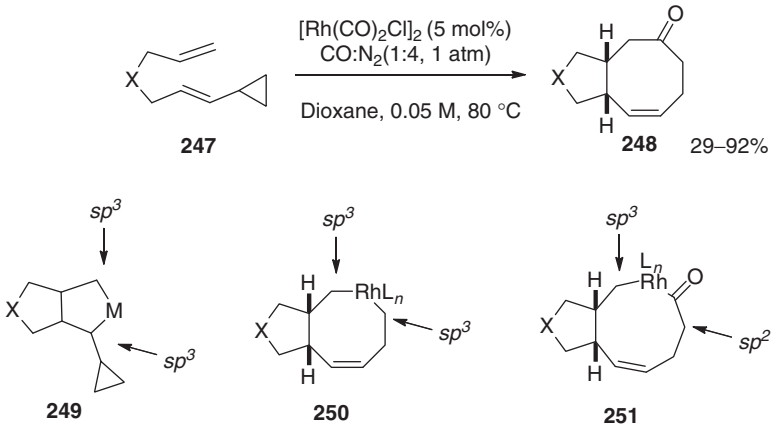
(71)

Later, Wender et al. showed that an intermolecular reaction with the disubstituted alkynes **1-17** and 2,3-dimethylbutadiene (**245**) provided the PKR products in high yields under similar conditions (equation 72).[139]



(72)

Controlling the rate of reductive elimination by changing the hybridization of the carbon atom and introducing strain into the ring allowed bicyclo[6.3.0]-nonadecadienones to be obtained. The product **248** was formed from **247** under similar conditions.[140] Since the reductive elimination of sp^3C-sp^3 C-atoms is much slower, in contrast to the case of **236**, **249** underwent the rearrangement to give **250** with the release of the strain of the cyclopropyl group. Even though **250** was formed, the reductive elimination between the two sp^3C-sp^3 centers is still slow and, thus, the intermediate **250** was intercepted by CO insertion to form **251**. Once **251** was formed, the faster reductive elimination between the sp^3C and sp^2-hybridized C-atoms occurred (equation 73).[140]



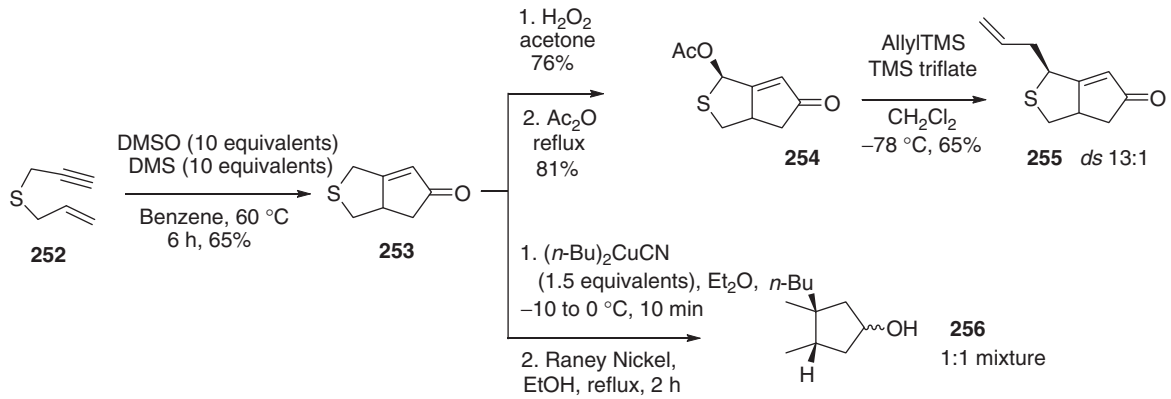
(73)

5.24.5.1.6 Substrates having removable tethers

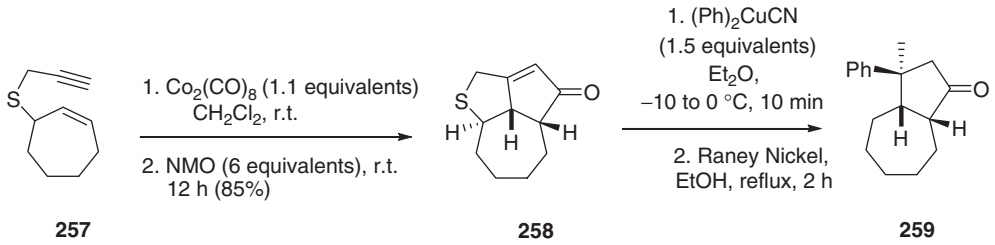
The application of the intermolecular PKR is still largely restricted because of its lack of regioselectivity, especially in the preparation of monocyclic compounds. A detour to make such monocyclic products in high yield with high regioselectivity is necessary, using substrates bearing a removable functional group to take advantage of the regiocontrol of the intramolecular reaction.

Pericas and Jeong independently demonstrated that the sulfur-tethered substrate **252**, when subjected to PKR conditions, afforded the bicyclic product **253**. Then the sulfur tether is removed cleanly by desulfurization with Raney nickel in the presence of hydrogen after all the necessary transformations. Another example uses the Pummerer reaction after the oxidation of sulfur to

sulfoxide to give **254**, which was further subjected to Lewis acid catalysed allylation to furnish **255**. Alternatively, the 1,4-addition to either **253** or **258** with dialkyl-cuprate followed by hydrogenolysis gave rise to **256** or **259**, respectively. It is worth mentioning that the regioselectivity regarding the acetylene part is opposite to that of the intermolecular version (equation 74).[141]



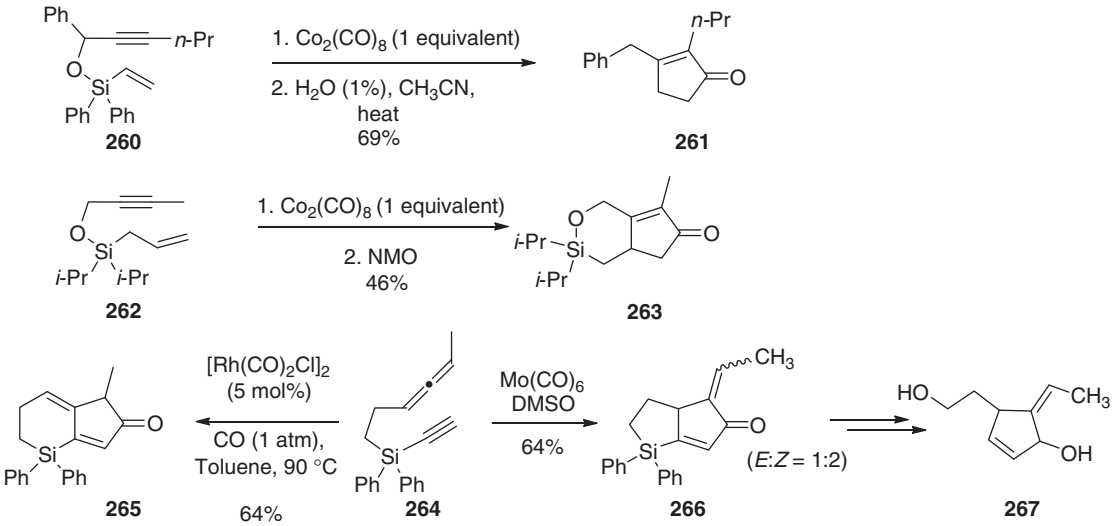
(74)



The use of a silicon atom as a removable tether was envisioned earlier. Since the projected silicon-containing PK products could be functionalized in various ways, such as protodesilylation and Tamao–Fleming oxidation, much effort has been directed to perform the PKR of silicon-tethered substrates (equation 75). However, the outcome in the beginning was far from expected.[142]

Upon optimization of this particular PKR, propargyl vinylsilyl ether **260** always afforded the monocyclic products **261** after the loss of a silicon atom. The yield was moderate, possibly due to the formation of a presumed hydridocobalt species. However, Pagenkopf intensively optimized this transformation and found that a small amount of water substantially improved the yield.[142b,c] Subsequently, the PKR product was obtained when iPr groups were present on the Si atom. However, this reaction is still erratic and gives a very low yield for a limited number of substrates.[142d]

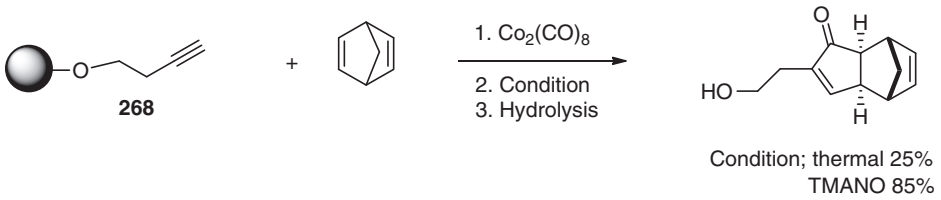
Brummond reported that the silicon-bound products **265** could be obtained from the (allenylethyl)alkynylsilane **264**. Either molybdenum/DMSO or rhodium(I) catalysts afforded the desired products, but the regioselectivity was dependent on the catalyst used. This trend is in line with the dependence of the regioselectivity on the chosen catalysts mentioned previously.[143]



(75)

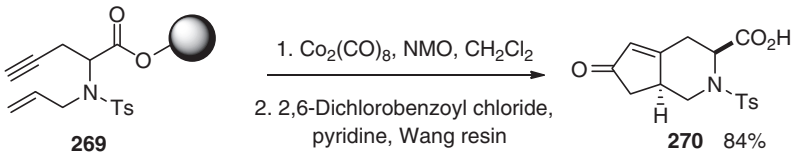
5.24.5.1.7 Substrates on solid support and chemical libraries

The PK reaction with substrates attached to a solid support was first reported by Schore and Kurth to improve the chemical yield of an intermolecular reaction with low-molecular weight alkynol and norbornadienes. An alkynol anchored on silica gel was reacted with norbornadiene and high chemical yield of the PK product was obtained after cleavage from the solid support (equation 76).[144]



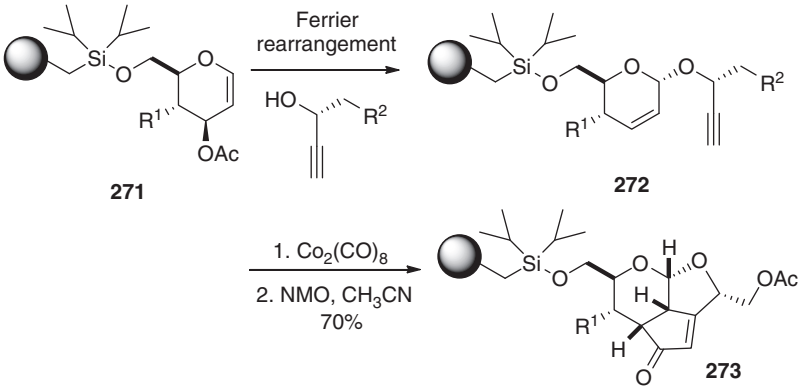
(76)

Later, Bolton extended this approach to an intramolecular reaction to form the bicyclic α-amino acids **270** (equation 77).[145]



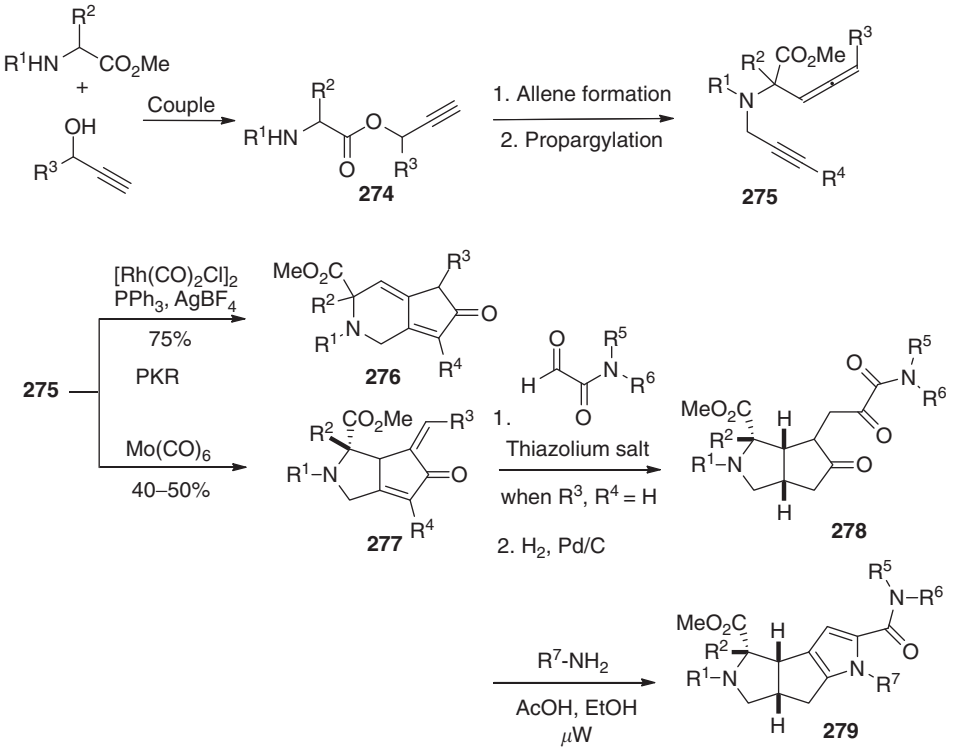
(77)

This approach paved the way to the synthesis of chemical libraries.[146] Schreiber and coworkers showed that this approach is useful for the preparation of compound libraries. One of their examples is the diversity-oriented synthesis of polycyclic scaffolds **273** from a glycal template **271** on solid support by the Ferrier reaction followed by the PKR (equation 78).[147]



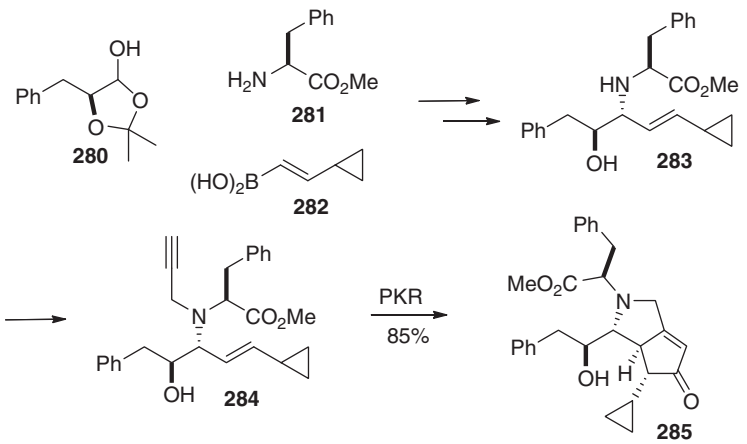
(78)

The solution-phase synthesis of discovery libraries was also reported. Brummond prepared a library consisting of tricyclic pyrrole-2-carboxamides (**279**) by applying the PKR, Stetter, and Paal–Knorr reactions sequentially (equation 79).[148]



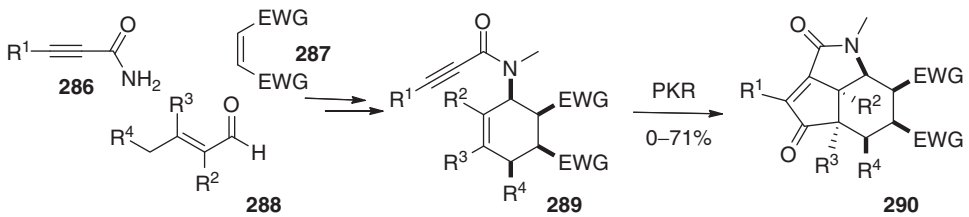
(79)

The Petatis condensation of three components, namely, boronic acids, lactol, and ester-protected amino acids, yielded new *β*-amino alcohols, some of which were subjected to the PKR after propargylation at the *N* atom (equation 80).[149]



(80)

Beller and coworkers used the multicomponent coupling of the aldehyde **288**, amide **286**, and dienophile **287**;[150] the resultant enynes **289** were subjected to the PKR. Some other examples have already been reviewed (equation 81).[147]



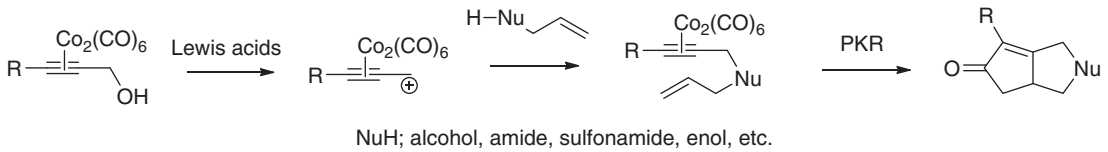
(81)

5.24.5.2 Tandem Approaches Coupled with Other Reactions

Tandem reactions have attracted much interest in recent years, because they allow multiple transformations to be performed in one operation. All of the reports can be classified into two categories: sequential reactions, in which the additional reagents are added or changes of the conditions are required, and single operations with all ingredients in one pot to effect at least more than two transformations.

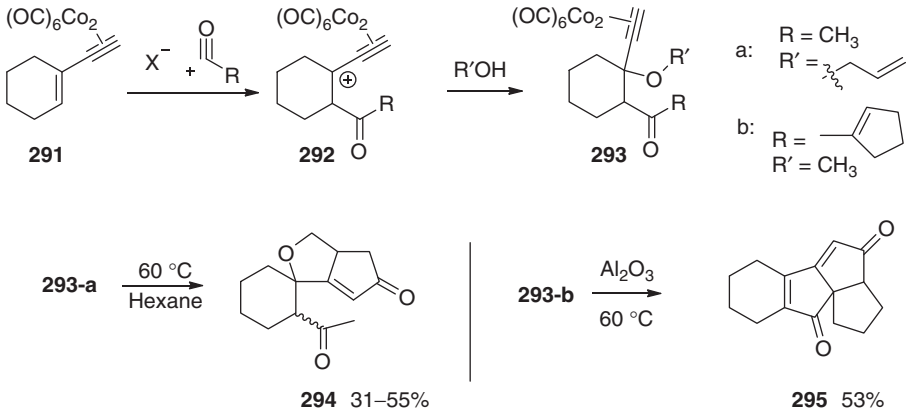
5.24.5.2.1 PKR coupled with the Nicholas reaction

The most popular approach is a combination of the Nicholas reaction and the PKR.[151] Properly functionalized 1,6- or 1,7-enynes for the PKR are readily obtained from propargyl alcohol–dicobalt hexacarbonyl complexes and an allylic and/or homoallylic nucleophile in the presence of a Lewis acid. The resultant enynes are usually subjected to the promoter-assisted PKR without purification to afford the desired PKR products (Scheme 19).[140]



Scheme 19

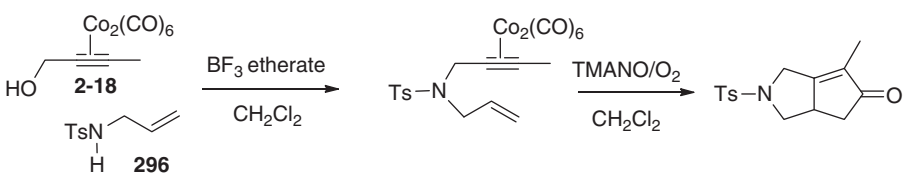
Smit prepared the Nicholas reaction precursor **292-a** by treating a conjugated enyne-dicobalt hexacarbonyl complex **291** with an acylium species. The resultant propargylic cation intermediate was then trapped with an allylic alcohol to give the enyne **293-a**. The PKR of **293-a** gave rise to the PK product **294** (Scheme 20).[29b,152]



Scheme 20

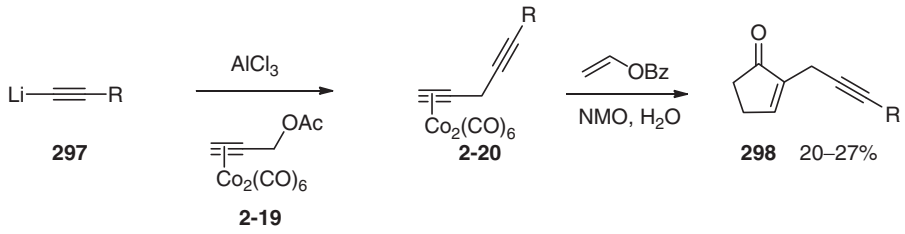
Subsequently, the same group used an olefin-conjugated acylium species to yield **292-b**, and the Nicholas precursor was trapped with methanol. Compound **293-b** was subjected to the PK condition to yield the tetracyclic compound **294-b**.

Cobalt carbonyl–propargyl alcohol derivatives are more popular precursors for the Nicholas reaction. In their first report, Jeong et al. reported that compound **2-18** was subjected to the Nicholas reaction by a Lewis acid in the presence of an allylamide nucleophile **296**. The resultant *N*-tosyl allyl propyne was transformed into the PK product without purification with the aid of an amine *N*-oxide promoter (equation 82).[153a]



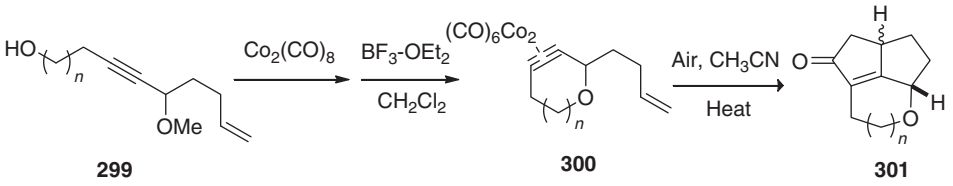
(82)

The regioselectively metal-coordinated dialkyne complex **2-20** was obtained by taking advantage of the Nicholas reaction and used for the intermolecular PKR to obtain **298** (equation 83).[154]



(83)

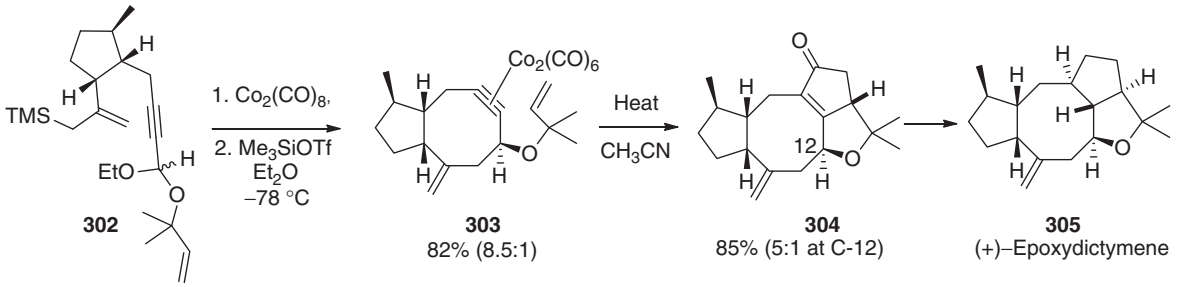
The intramolecular Nicholas reaction followed by the PKR exhibited its synthetic utility as well. Shea and coworkers prepared complex **300** from substrate **299** in the presence of boron trifluoride, which was further subjected to the PKR condition without purification. The tricyclic compound **301** was obtained in high yield (equation 84).[155]



(84)

n = 1, 3% (from **299**), *cis*:*trans* = 66:34
n = 2, 63%, *cis*:*trans* = 37:63
n = 3, 86%, *cis*:*trans* = 55:45

Schreiber and coworkers provide one of the most stylish examples of this approach. The successful synthesis of (+) – epoxydictymene (**305**) relied on the selective activation of an ethyloxy group in the mixed acetal **302** by the Nicholas reaction (selectivity 8:1) followed by a stereoselective PKR (equation 85).[156]

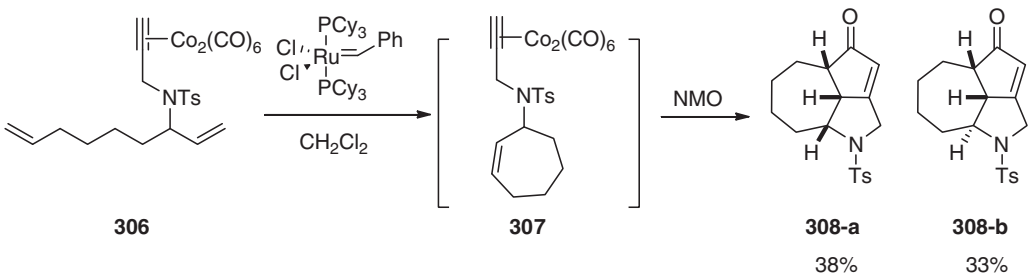


(85)

More examples in this line can be found in the reports of Carbery et al.[157]

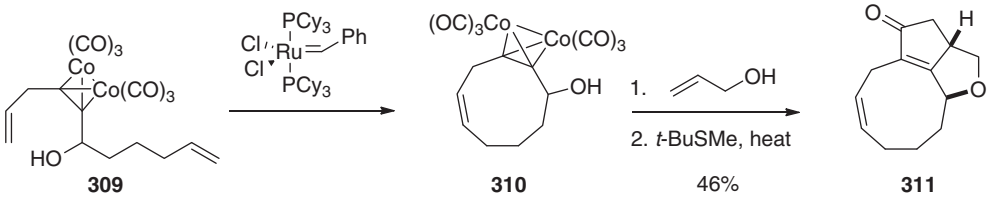
5.24.5.2.2 PKR coupled with RCM

There are several examples utilizing a combination of ring-closing metathesis (RCM) and the PKR. Perez-Castells and coworkers combined RCM and the PKR for the synthesis of tricyclic compounds in one batch. In this approach, the Grubbs catalyst first mediated the RCM of **306**, bearing an alkyne–cobalt carbonyl complexed side chain as an alkyne protecting group for the metathesis stage to give the cobalt complex **307**, which was used directly as a PKR precursor in the next stage, affording **308** (equation 86).[158]



(86)

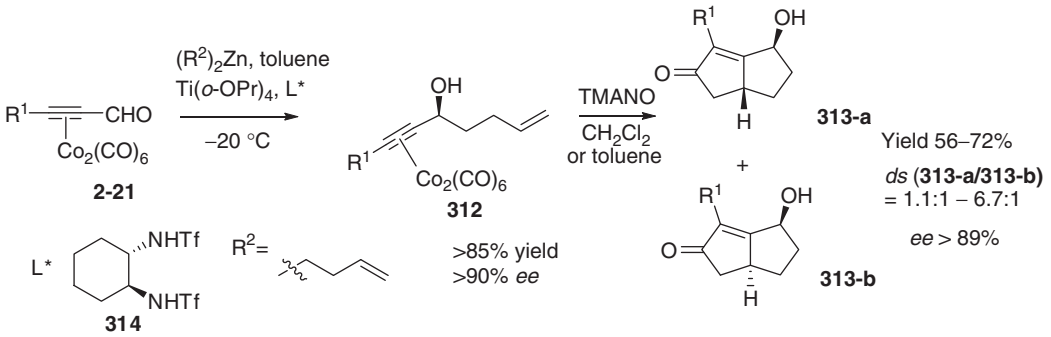
A sequence consisting of a combination of RCM and the Nicholas reaction followed by the PKR was successfully employed by Young et al. to form compound **311** (equation 87).[159]



(87)

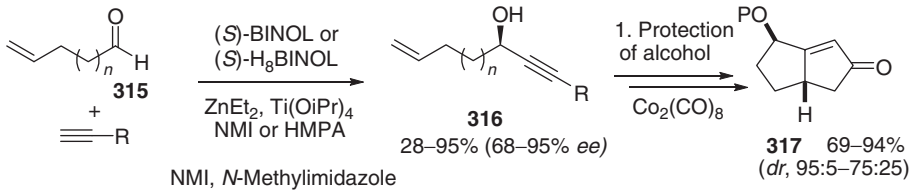
5.24.5.2.3 PKR coupled with carbonyl addition of one component of the resultant enynes

Jeong et al. utilized a cobalt–alkyne complex **2-21** to increase the enantioselectivity of the addition of bis(homoallyl)zinc to propargyl aldehydes by enhancing the steric environment. The reaction provided the optically enriched propargyl alcohol **312** in the presence of a chiral ligand and titanium tetra(isopropoxide) more. The adduct **312** was subjected to the PKR to yield the optically enriched bicyclic compounds **313** (equation 88).[160]



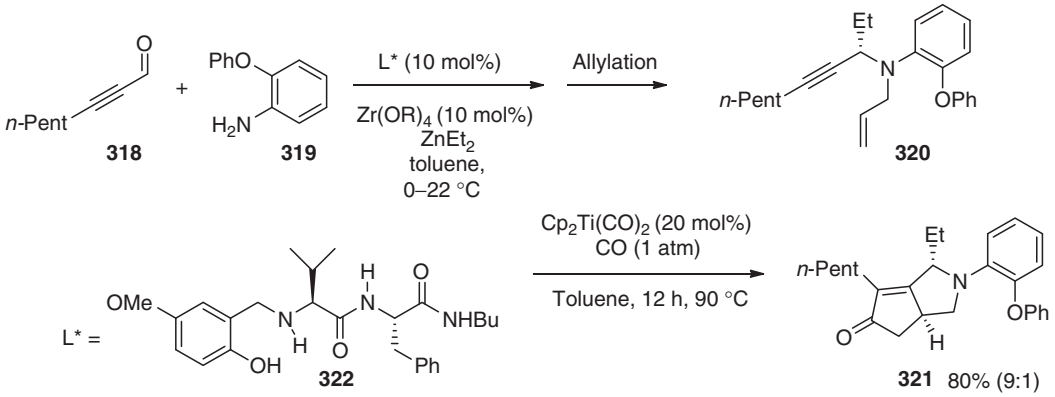
(88)

In contrast, the strategy utilizing the enantioselective addition of a terminal alkyne to the carbonyl **315** followed by the PKR was also reported (equation 89).[161] This example and the following one cannot be classified as a tandem reaction in one pot, but it is worthwhile discussing them also in this section.



(89)

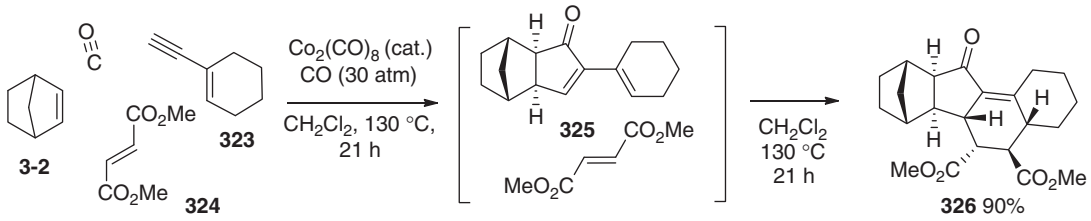
An imine can be used as a substitute for the carbonyl group. The enantioselective addition of diethyl zinc to the imine species in the presence of the chiral ligand **322**, formed from the propynal **318** and aniline **319**, provided the amine compound **320** in high enantioselectivity, which was subjected to the PKR in the presence of a Ti(II) catalyst to give product **321** in high diastereoselectivity (equation 90).[162]



(90)

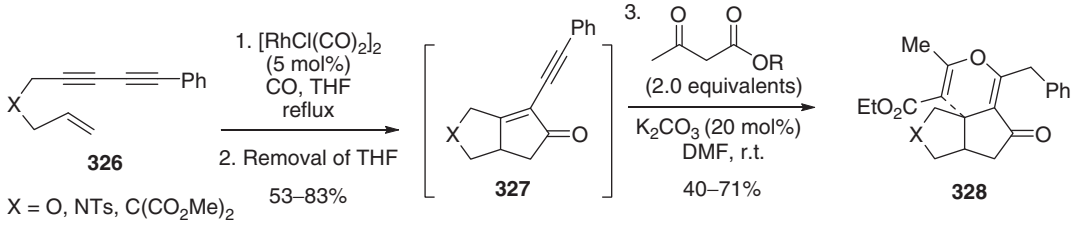
5.24.5.2.4 PKR coupled with post modifications

The PKR between compounds **3-2** and **323** proceeded to yield the diene intermediate **325**, which underwent the Diels–Alder reaction with the fumarate **324** to afford the tetracyclic compound **326** (equation 91).[163] To this end, a mixture of all components was heated in the presence of a catalytic amount of dicobalt octacarbonyl under a high pressure of CO.



(91)

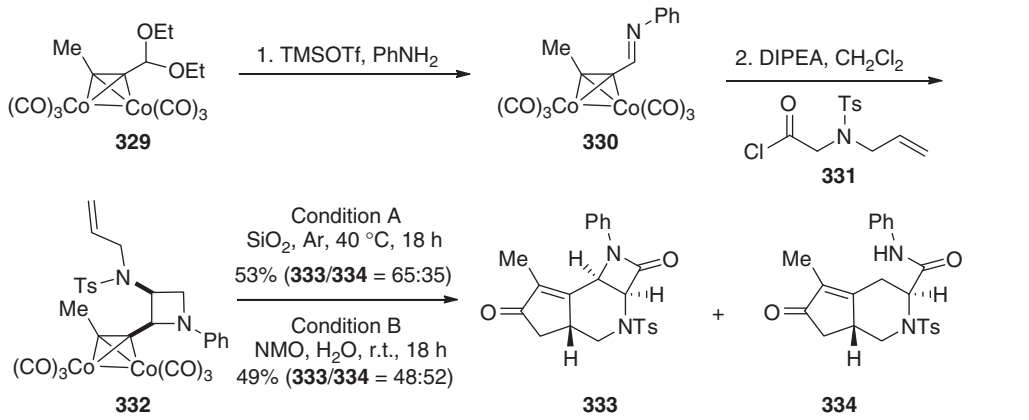
The PKR of substrate **326** catalyzed by a rhodium complex yielded the α-alkynyl enone **327**, which underwent a Michael addition of β-ketoesters to give product **328** (equation 92).[164]



(92)

5.24.5.2.5 PKR coupled with a Staudinger reaction

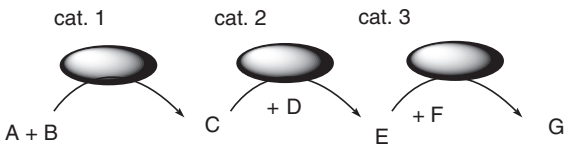
Dicobalt hexacarbonyl complexes of alkynyl imines, which were obtained *in situ* from the corresponding acetal and amines in the presence of a Lewis acid, underwent the Staudinger reaction with the ketene derived from **331**, providing the intermediate **332**. Then the PKR of **332** was performed without purification to afford the tricyclic compound **333** as the major product together with the bicyclic product **334** (equation 93).[165]



(93)

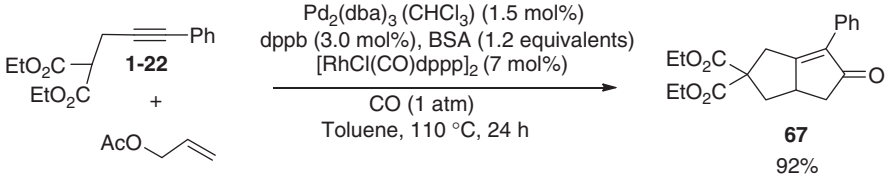
5.24.5.2.6 Mimic of multi enzymatic systems

The most desirable tandem process is a mimic of the multi-enzymatic process in a cell, in which most of the metabolites are synthesized by a programmed sequence of enzymes with high specificity for the substrates, although many other potential intermediates are around the reacting enzymes (Scheme 21).[166]



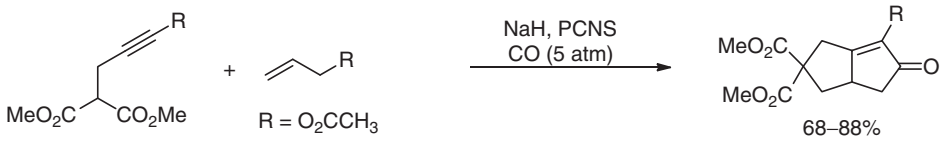
Scheme 21

In particular, Jeong was the first to demonstrate that this concept was feasible with the combination of π-allylic substitution by a palladium catalyst and the PKR by a rhodium catalyst. This two-step transformation is achieved by mixing all of the ingredients and heating the mixture in toluene at 110 °C (equation 94).[167]



(94)

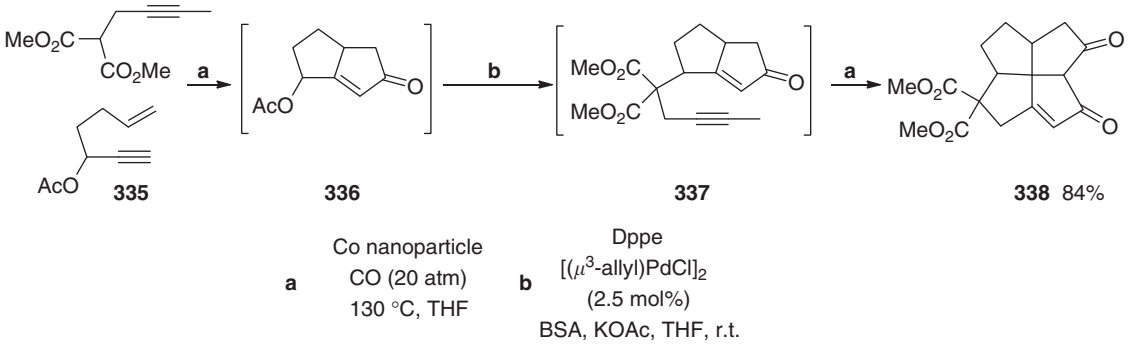
Subsequently, Chung and coworkers extended this concept further. Especially, this group emphasized the use of heterogeneous PKR catalysts for the tandem reaction. By differentiating the catalyst phases, they were able to avoid cross-poisoning between the catalysts (equation 95).[168]



(95)

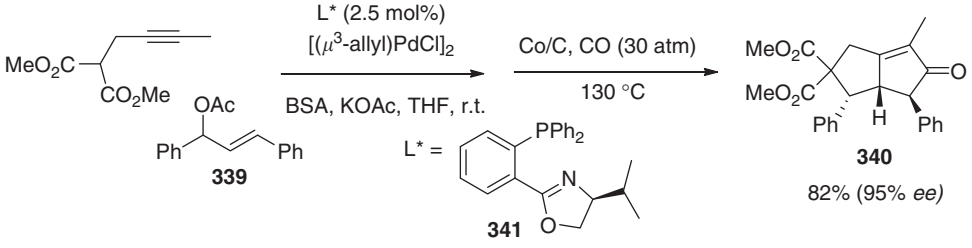
PCNS, palladium and cobalt nanoparticles immobilized on silica

The treatment of enyne **335** with propargyl malonate in the presence of cobalt nanoparticles and an allyl–Pd(II) complex led to the formation of the fenestranes **338** in high yield (84%).[169] π-Allylic substitution took place at the initially formed PK product **336**, before a second PKR afforded the tetracyclic compound **338** (equation 96).



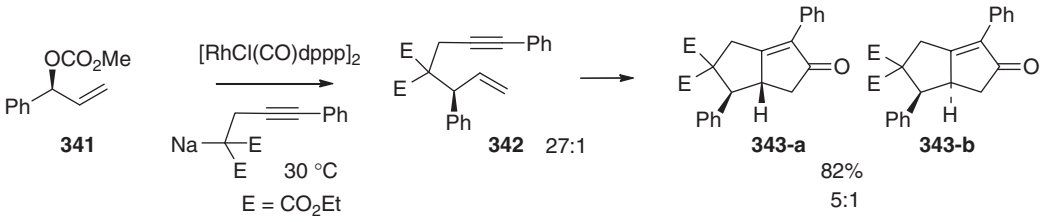
(96)

An optically enriched enyne was obtained from **339** by taking advantage of enantioselective allylation by a chiral palladium catalyst (obtained by mixing a Pd precursor and ligand **341**) and subjected to the PKR employing cobalt on charcoal to give rise to product **340** (equation 97).[170]



(97)

The regio- and diastereoselective rhodium-catalyzed tandem allylic alkylation of **341** with stabilized carbon and heteroatom nucleophiles followed by the Pauson–Khand annulation by the same catalyst was described by Evans and coworkers. The alkylation of an optically active allylic alcohol carbonate **341** proceeded in a regio- and stereospecific manner at 30 °C with π-acidic Rh(I) catalysts. The resultant product **342** then underwent the PKR with the aid of the preexisting catalyst under CO pressure at elevated temperature (equation 98).[17] The moderate diastereoselectivity that is common with the PKR was substantially increased by the introduction of bulkier substituents.



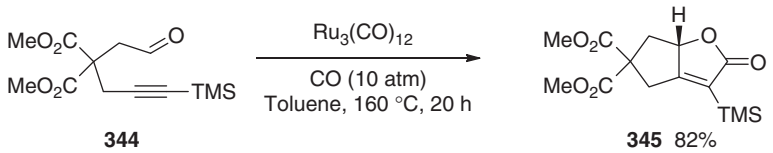
(98)

5.24.5.3 Variations of the PKR

Some notable variations utilizing multiple bonded substitutes for alkynes and alkenes are summarized in this section.

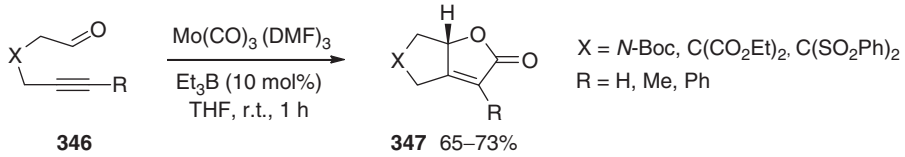
5.24.5.3.1 Carbonyl groups as a substitute for the alkene

Carbonyls can replace alkenes to yield lactones. Because of the higher oxophilicity of ruthenium, Murai and Chatani first discovered that $Ru_3(CO)_{12}$ can catalyze the reaction to provide the lactones **345** (equation 99).[171]



(99)

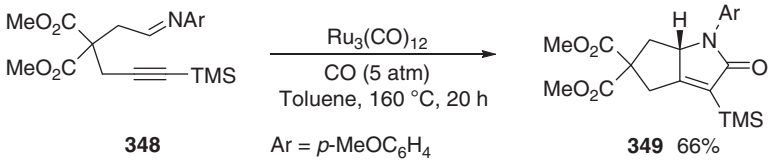
A stoichiomatric amount of the preactivated molybdenum catalyst, $Mo(CO)_3(DMF)_3$ or $Mo(CO)_6$, coupled with DMSO is also active for this transformation (equation 100).[172]



(100)

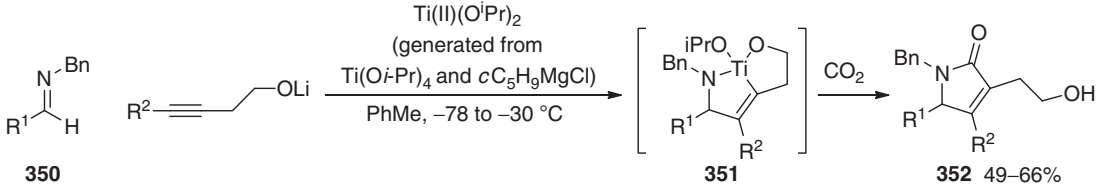
Rhodium was an efficient catalyst too. Moreover, the reaction was completed even under 1 atm of CO with this catalyst, although the substrate scope is severely limited.[173]

The same ruthenium catalytic systems are known to catalyze the reaction with the imines **348** to give the lactams **349** (equation 101).[173]



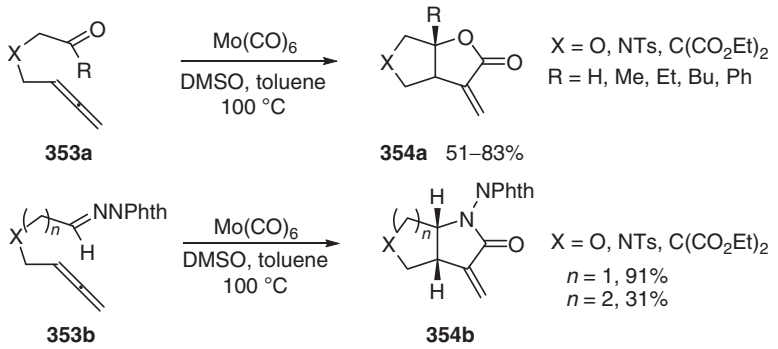
(101)

In addition, the imines **350** could couple with alkynes with the aid of a Ti(II) catalyst to provide γ-lactams of type **352** in decent yield (equation 102).[174]



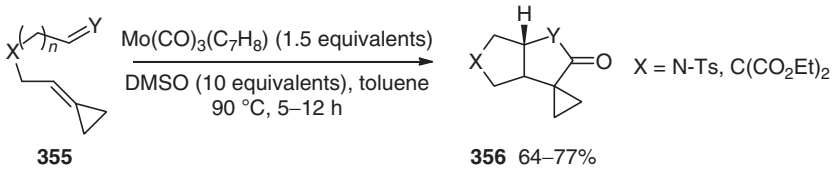
(102)

Furthermore, the double switching of the alkyne to an allene, and of the alkene to a carbonyl or hydrazone allowed α-methylene lactones **354-a** and lactams **354-b,** respectively, to be formed as described in equation 103.[175,176]



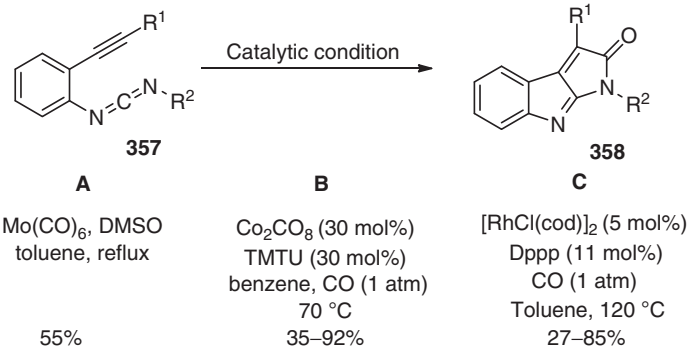
(103)

Replacing the allene by a vinylcyclopropane allowed the α-cyclopropyl-lactone **356** to be obtained under similar conditions (equation 104).[177]



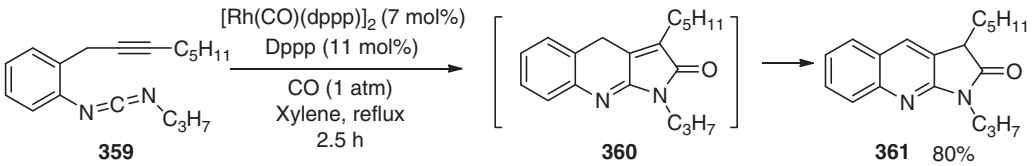
(104)

The carbodiimide **357** successfully replaced the alkenes to afford the pyrrolo[2,3–b]indol-2-one ring system **358** in reasonable yield (**Scheme 22**). Cobalt, molybdenum, and rhodium catalysts are effective for this transformation, which was utilized for the synthesis of various indole alkaloids (see equation 108).[178]



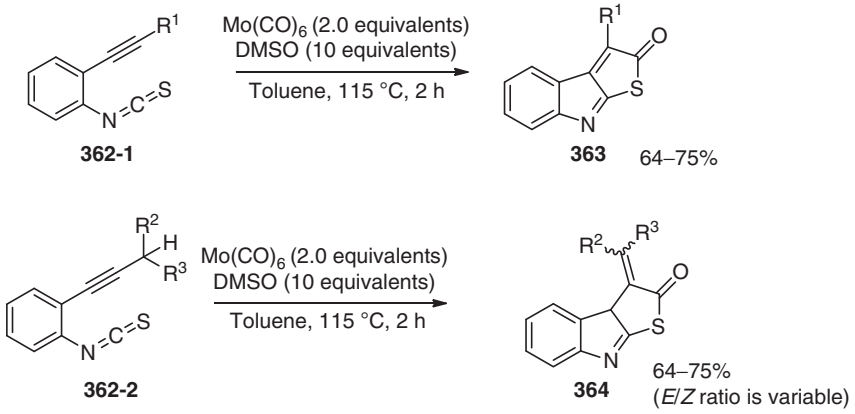
Scheme 22

The quinolines **361** were obtained from the homologous substrate **359** after the cyclization followed by the rearrangement of the olefin in the resultant intermediate **360** under the reaction conditions (equation 105).[179]



(105)

The 2-alkynylphenyl isocyanates **362** were used to afford the 3-substitruted-2*H*-thieno[2,3–b]indol-2-ones **363** and **364**. A stoichiometric amount of $Mo(CO)_6$ or $Co_2(CO)_8$ was effective. A catalytic amount of Rh could also be used but provided another regioisomer as the major product (equation 106).[180]



(106)

5.24.6 Application to Synthesis

5.24.6.1 Natural Products Synthesis

One of the most prominent features of the PKR is that it provides quick access to relatively complex polycyclic compounds. Specially, the intramolecular PKR with properly functionalized precursors allows for the preparation of highly functionalized cyclic intermediates with complete control of the regioselectivity as well as the stereoselectivity.

5.24.6.1.1 Synthesis of alkaloid natural products

Model studies utilizing the PKR for the synthesis of the basic skeleton found in the various alkaloids shown in Figure 23 are summarized in Scheme 23.[181] Various skeletons are easily accessed by the PKR protocol from the substrates based on the indole skeleton having properly located appendages.[182]

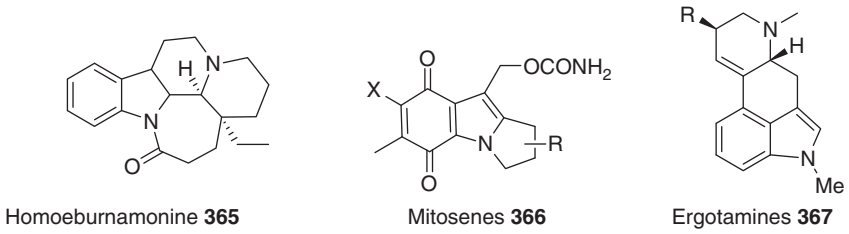
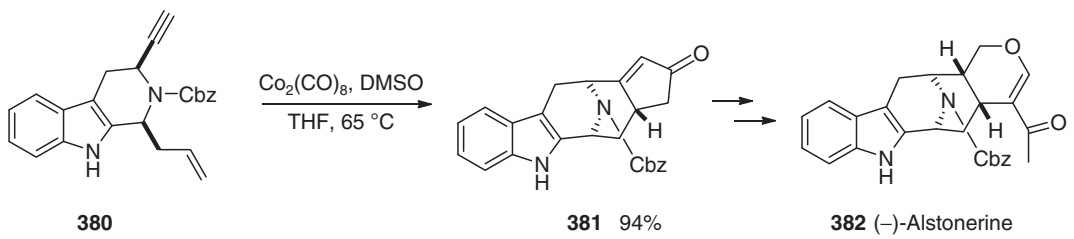
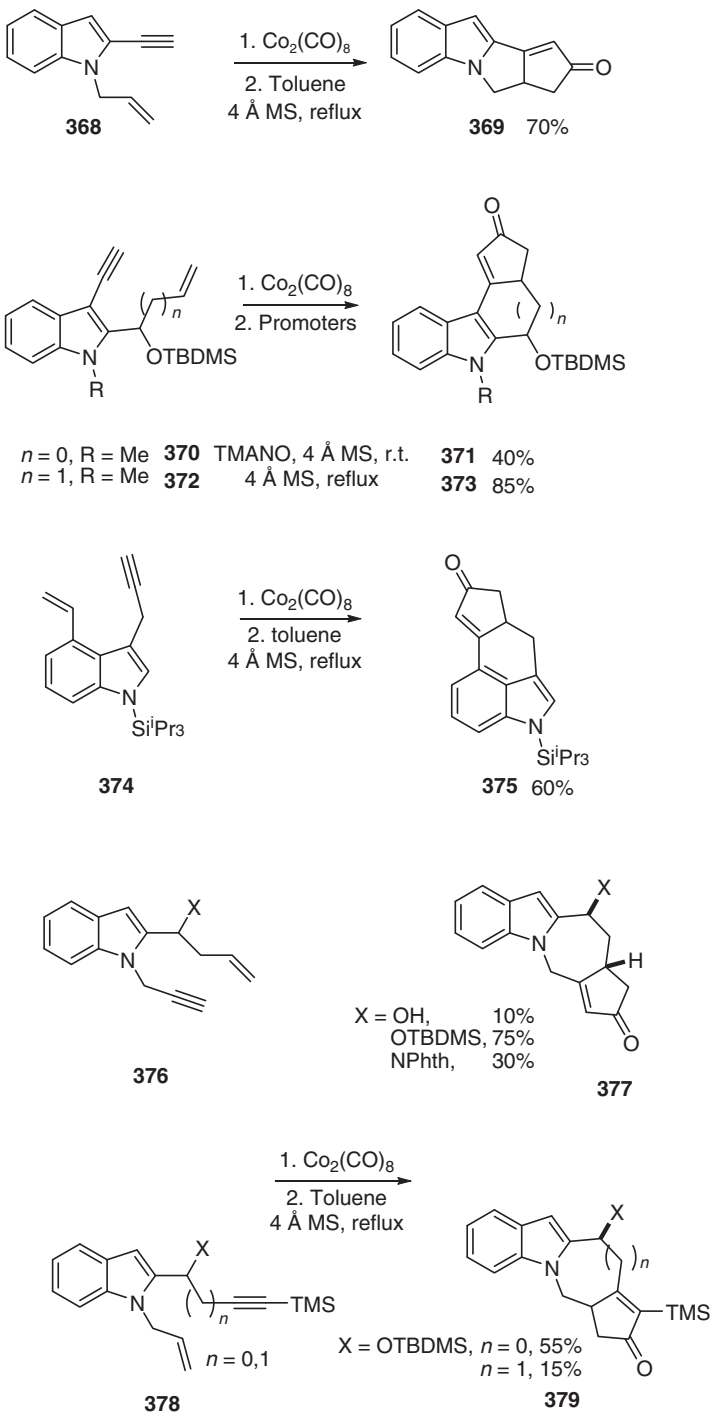


Figure 23 Representative alkaloids natural products being targeted by PKR.

A bridged azabicyclic [3.3.1] skeleton found in the macroline/sarpagine class of indole-based alkaloids such as (–)-alstonerine (**382**) was efficiently assembled by utilizing a stoichiometric PKR with cobalt carbonyl in combination with DMSO. The substrate **380** derived from L-trytophan provided the pentacyclic intermediate **381** in 94% yield (equation 107).[183]

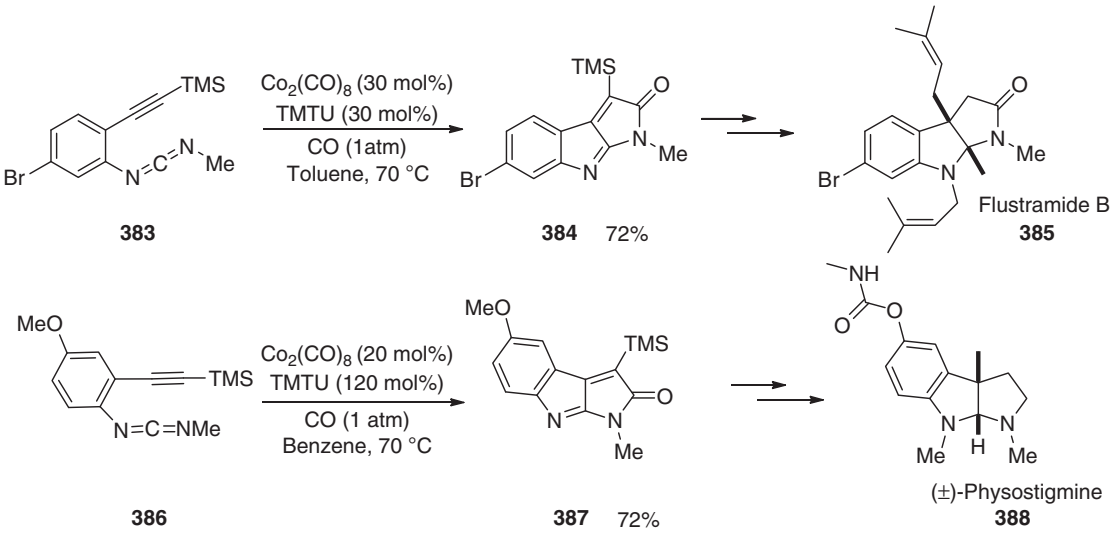


(107)



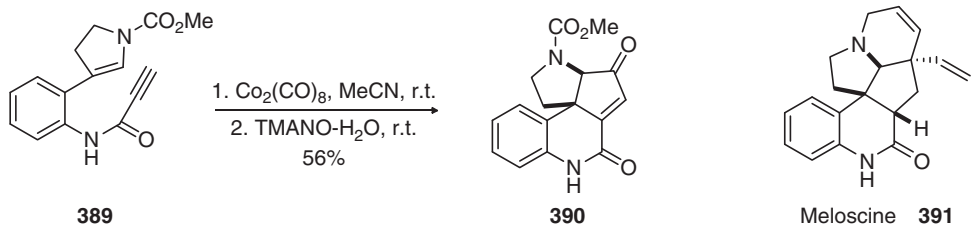
Scheme 23

Other indole alkaloids such as (±)–flustramide B (**385**) and (±)–physostigmine (**388**) were efficiently synthesized by employing the aza-PKR. The carbodiimides **383** and **386** provided **384** and **387** which were then used for the synthesis of **385** and **388**, respectively (equation 108).[178b,c]



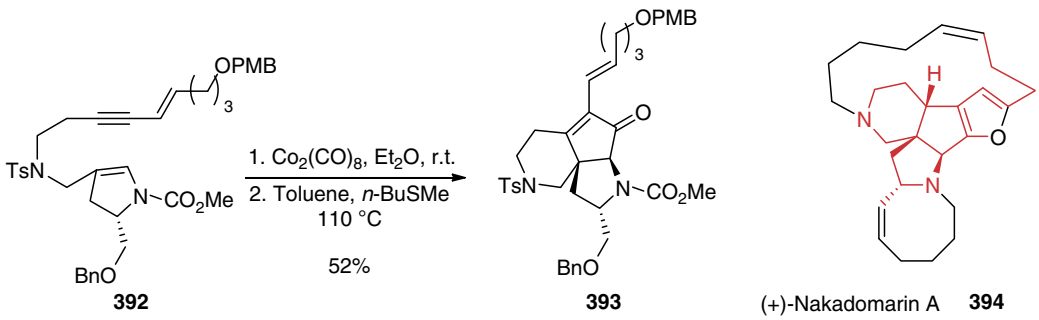
(108)

Meloscine (**391**) is representative of the Melodinus alkaloids, also known as meloquinolins, and has a unique pentacyclic carbon skeleton, which can be synthesized by using the PKR from substrates having enamines. The amine *N*-oxide promoted PKR worked nicely even with the electron-deficient alkyne of compound **389**, resulting in the desired tetracyclic compound **390** in 56% yield (equation 109).[184]



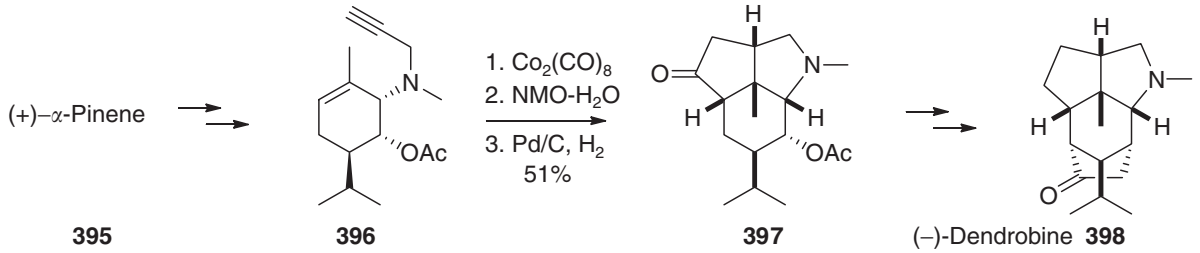
(109)

The same strategy involving the PKR was employed again for the formal synthesis of (+)-nakadomarin[185] and manzamine,[185b] representative manzamine-related alkaloids, starting from substrate **392**. This highlighted the stereoselective formation of the diazatricyclic[6.4.0.0]dodecene skeleton (equation 110).[185]



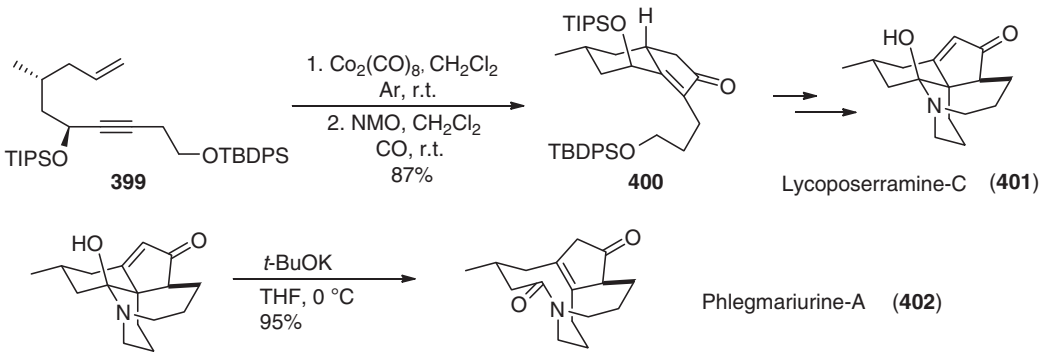
(110)

The formation of the quaternary carbon present in dendrobin (**398**) was readily achieved by the PKR. Takano[186a] and Zard[186b] independently employed the PKR for the synthesis of optically pure (–)-dendrobin (equation 111).



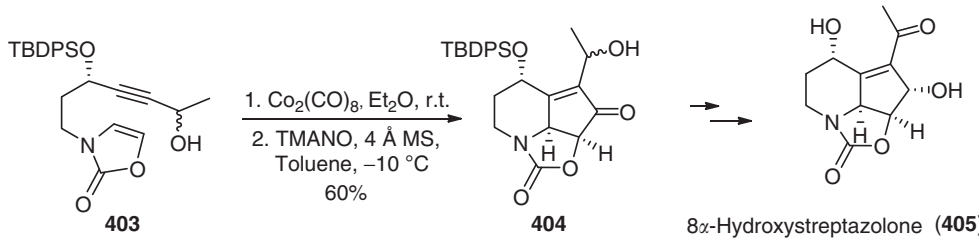
(111)

A key intermediate **400** of the newly identified fawcettimine-type lycopodium alkaloid lycoposerramine-C (**401**) was also synthesized by using the PKR as a key step. A related alkaloid phlegmariurine-A (**402**) was obtained from lycoposerramine-C afterwards (equation 112).[187]



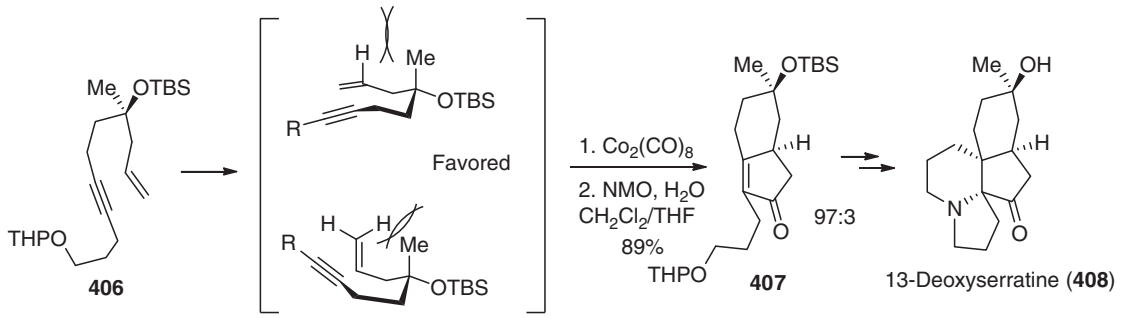
(112)

Mukai's synthesis of 8α-hydroxystreptazolone (**405**) and streptazoline represents an example of the use of an oxazolone derivative in the PKR (equation 113).[188]



(113)

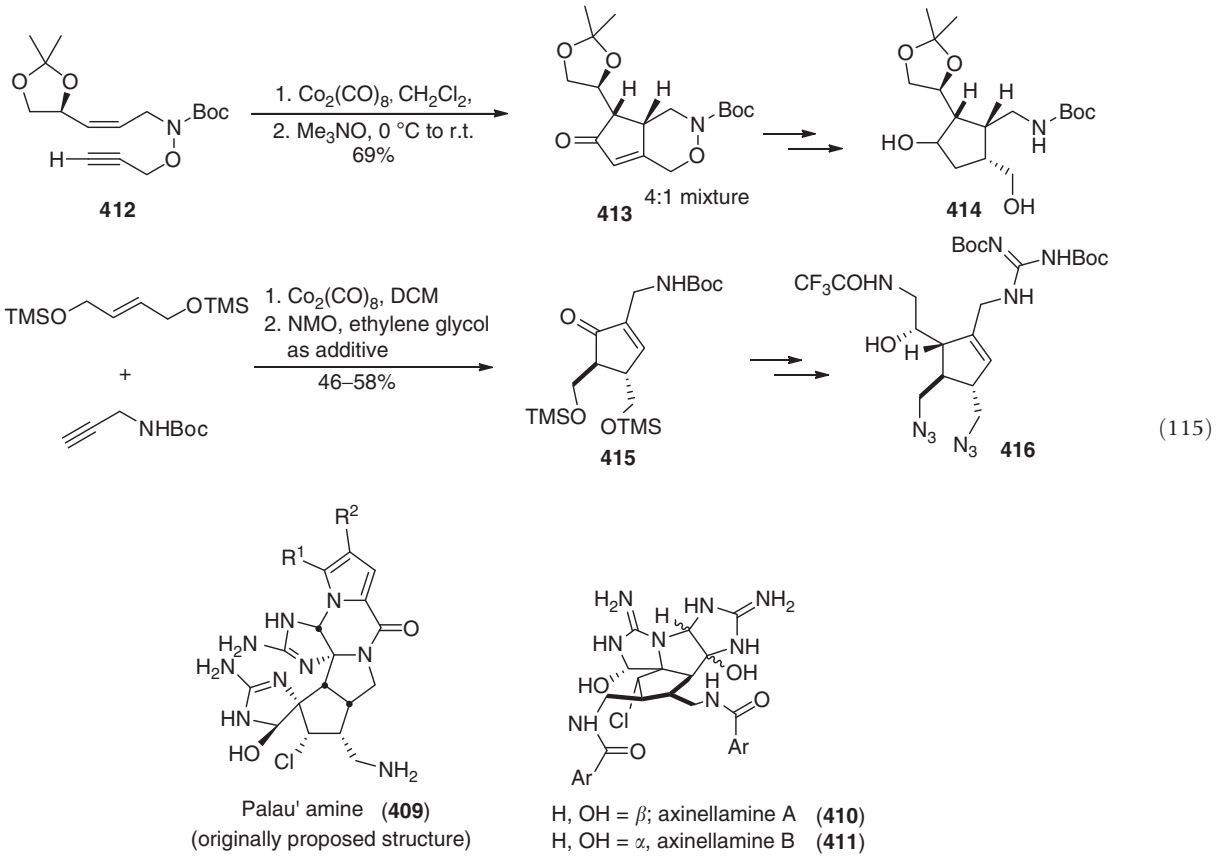
Zard and coworkers recently reported the synthesis of 13-deoxyserratine (**408**). This synthesis includes a highly diastereoselective PKR (equation 114).[189]



(114)

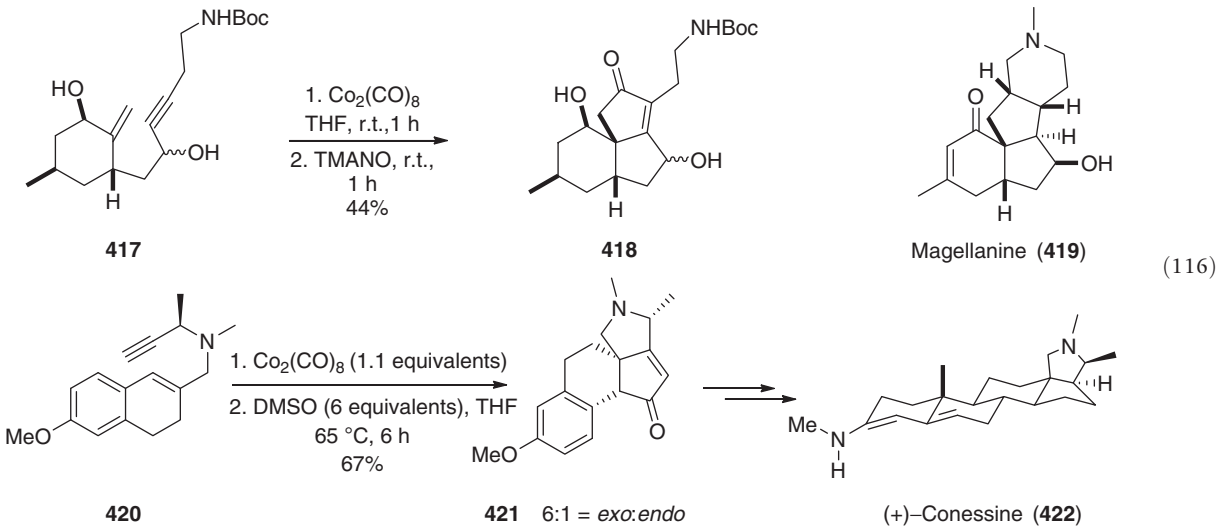
The family of pyrrole–imidazole marine alkaloids (PIA) consists of the Palau'amine (**409**), axinellamines (**410**), and massadines (**411**). They seem to be formidable targets, due to their highly decorated guanidine moieties. Koenig employed the *N–O* linked substrates **412** in the PKR to synthesize the fully functionalized bottom core of Palau'amine **414** and styloguanidine (equation 115).[190a,b]

More recently, the complete synthesis of the axinellamines A (**410**) and B (**411**) was accomplished by Baran and coworkers. The key carbocyclic portion **416** of the target compound was obtained by utilizing the PKR.[190c]



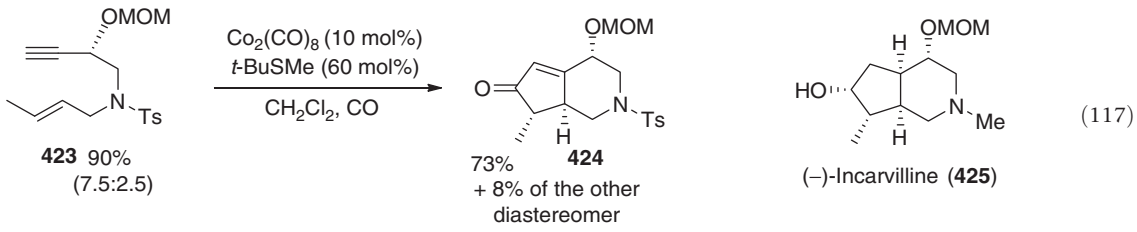
(115)

The efforts made toward the synthesis of portions of (±)–magellanine (**419**)[191a] and (+)–conessine (**422**)[191b] are noteworthy. The exocyclic olefin **417** was successfully employed in the key reaction for the synthesis of **419**, and the vinyl group conjugated to the phenyl ring in **420** served nicely as a PKR substrate for the synthesis of (+)–conessine with good diastereoselectivity (equation 116).



(116)

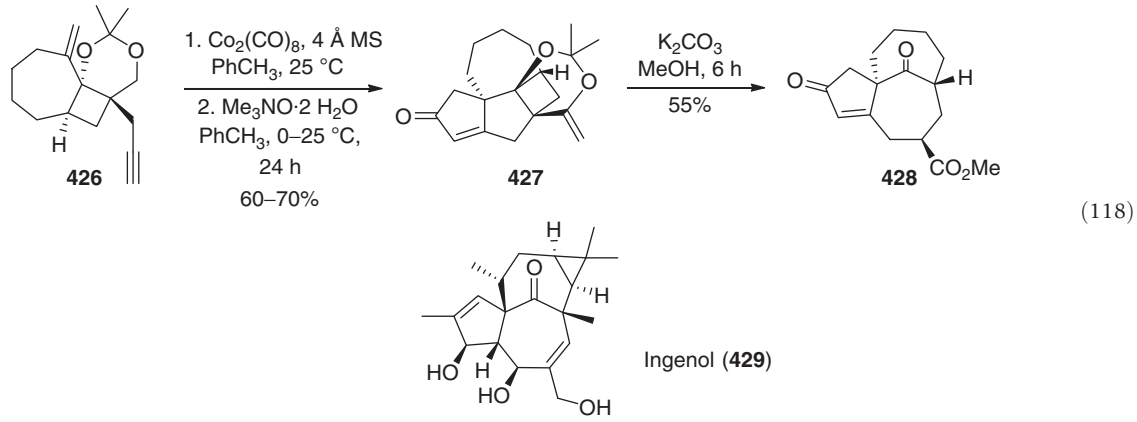
In this line, the homologous substrate **423** was also used to form a bicyclo[4.3.0] skeleton, which would be eventually transformed into a monoterpene alkaloid, (–)-incarvilline, which is a component of incarvillateine (equation 117).[192]



(117)

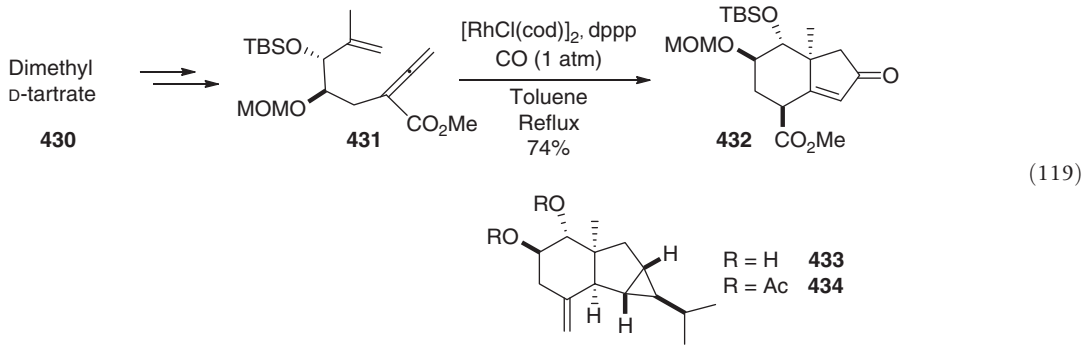
5.24.6.1.2 Synthesis of terpenoid natural products

Winkler's first synthesis of the highly oxygenated diterpenoid ingenol (**429**) in racemic form required 42 synthetic steps from commercially available materials. Subsequently, the authors devised a new synthetic pathway to obtain the key intermediate **428** based on the PKR as a key reaction. The substrate **426** having an exocyclic double bond underwent the PKR smoothly to yield **427** in 60–70% yield (equation 118).[193]



(118)

Two uncommon tricyclic sesquiterpenes **433** and **434** were synthesized for the first time.The key bicyclic [4.3.0]nonenone **432** was synthesized by a variant of PKR from the optically pure precursor **431** derived from dimethyl tartrate. Afterwards, the highly stereoselective construction of the isopropylcyclopropane ring was nicely achieved (equation 119).[194]



(119)

The fusicoccain family of diterpenes is characterized by a fused 5-8-5 carbotricyclic skeleton (Figure 24).

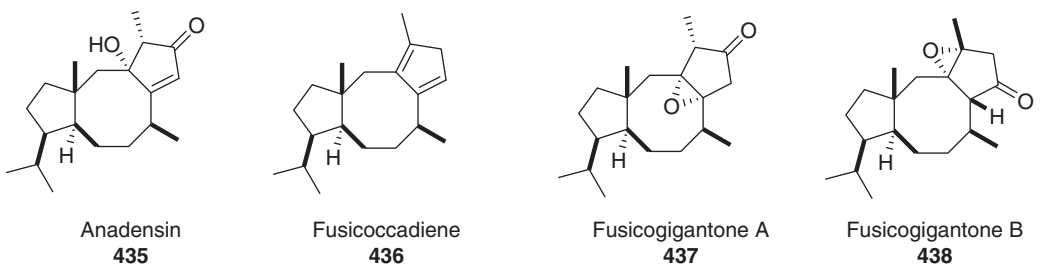
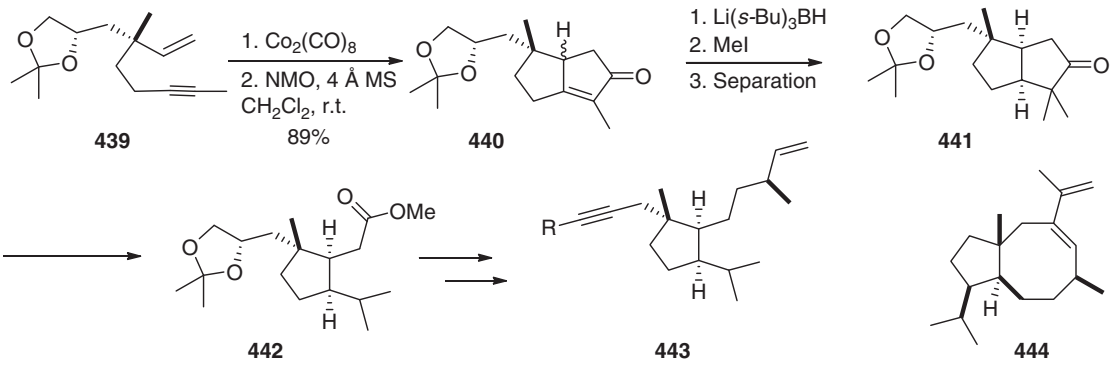


Figure 24 Representative fusicoccain diterpenoids.

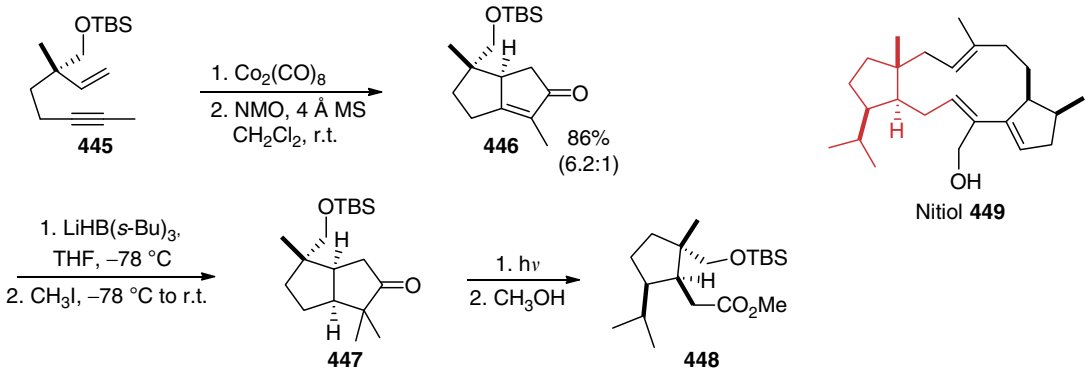
It was proposed that the key bicyclic[6.3.0]ring skeleton in **444**, where the third ring would be introduced, could be formulated from the monocyclic intermediate **443** by enyne metathesis. The key intermediate **443** would be obtained from compound **442** which derives from a Norrish type I fragmentation of the bicyclic precursor **441**.[195]

The introduction of a methyl group on the α-position of the enone was achieved by selective 1,4-hydride addition to the PKR product **440** by L-selectride, followed by trapping of the resultant enolate with the methyl group. The resultant product **441** was subjected to the Norrish Type I fragmentation under UV light (190 nm) to afford the isopropyl-substituted five-membered ring product **442** (equation 120).[195a]



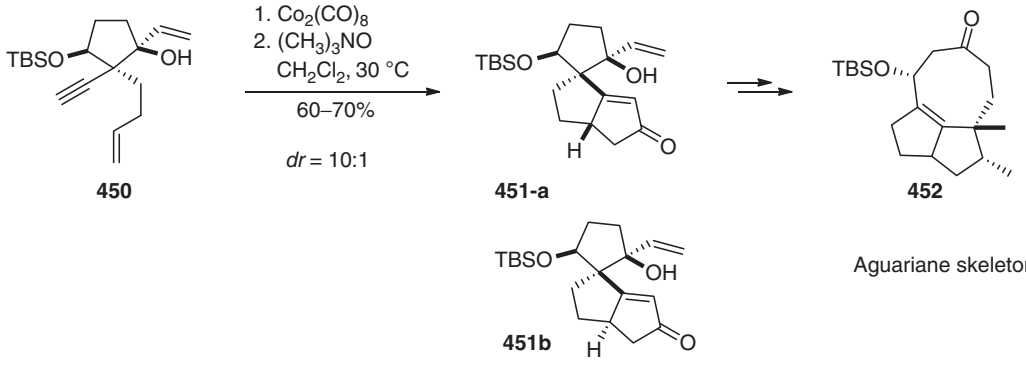
439 **440** **441** **442** **443** **444** (120)

Nitiol (**449**) is characterized by two five-membered rings fused to a central 12-membered macrocycle. Its left five-membered ring was synthesized earlier by utilizing the same strategy (equation 121).[195b]



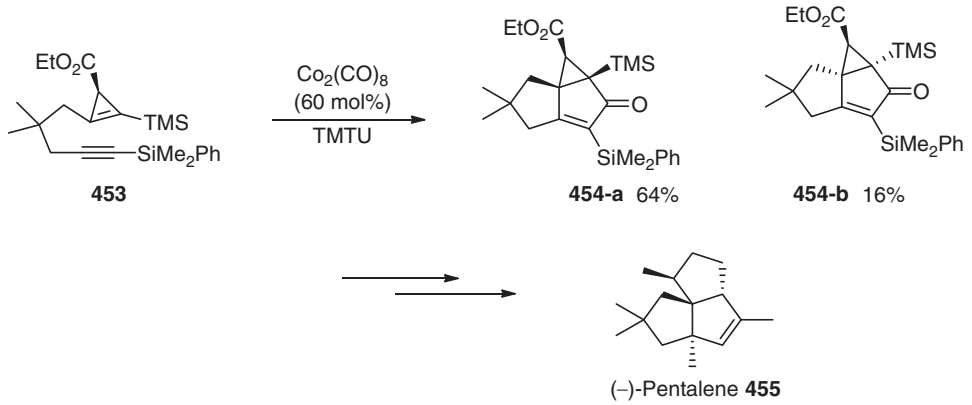
445 **446** **447** **448** Nitiol **449** (121)

Aquariolides are cyclic diterpenes, in which a nine-membered ring is fused to two five-membered rings. The PKR was used to set the stage by affording the intermediate **451** which served in a ring-expanding Cope rearrangement to form the nine-membered ring **452** in a highly diastereoselective manner (equation 122).[196]



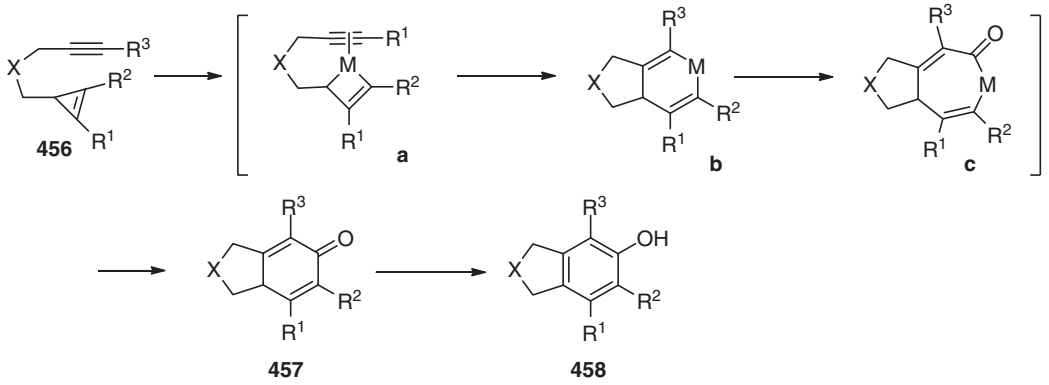
450 **451-a** **451b** **452** (122)

The tricyclic compound **454**, which could be transformed into (–)-pentalene **455**, was formed from substrate **453** by the TMTU-assisted cobalt catalyzed PKR (equation 123).[197]



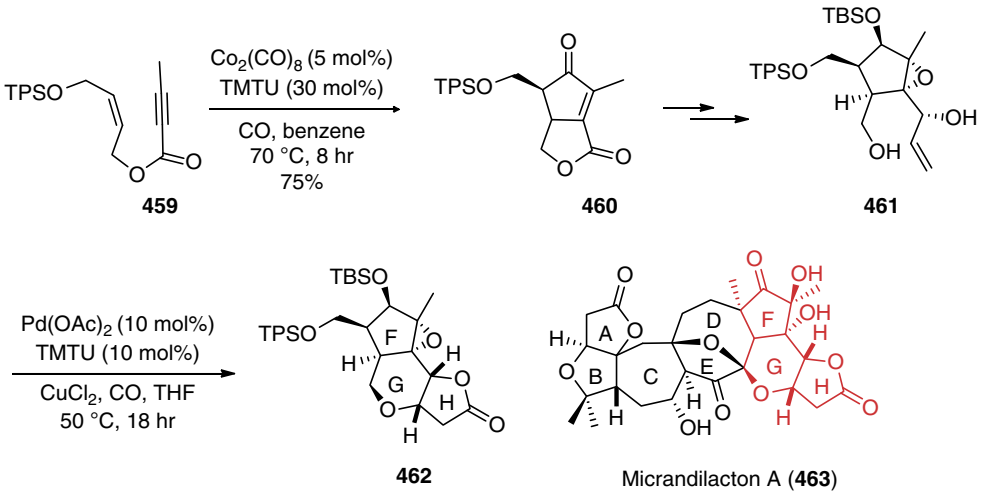
(123)

In conjunction with this, it is worth mentioning about the related [3 + 2 + 1] cycloaddition at this point. Compound **456**, a regioisomer of **453**, in which the olefin in the cyclopropene is distant from the reaction site, underwent a metal insertion into a C–C single bond of the cyclopropene followed by the formation of metallacyclopentane intermediate **b**; a subsequent CO insertion and the reductive elimination afforded a cyclohexadienone **457**, which was tautomerized to the phenolic compound **458** (equation 124).



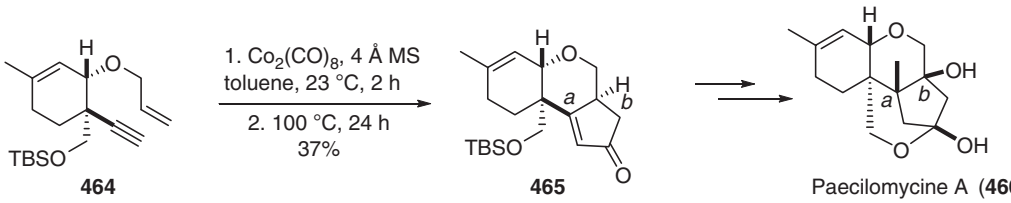
(124)

The critical portion of micrandilacton A (**463**) (FGH ring as assigned in equation 125) was synthesized by a couple of reactions catalyzed by a transition metal. First, the F ring having side chains for the synthesis of the G ring at a later stage was prepared by the PKR. The substrate **459** was subjected to the catalytic reaction employing $Co_2(CO)_8$ and TMTU to form **460**. After proper functionalization, the substrate **461** was set up for the synthesis of **462** in next key step by a palladium catalyzed carbonylative annulation in the presence of TMTU (equation 125).[198]



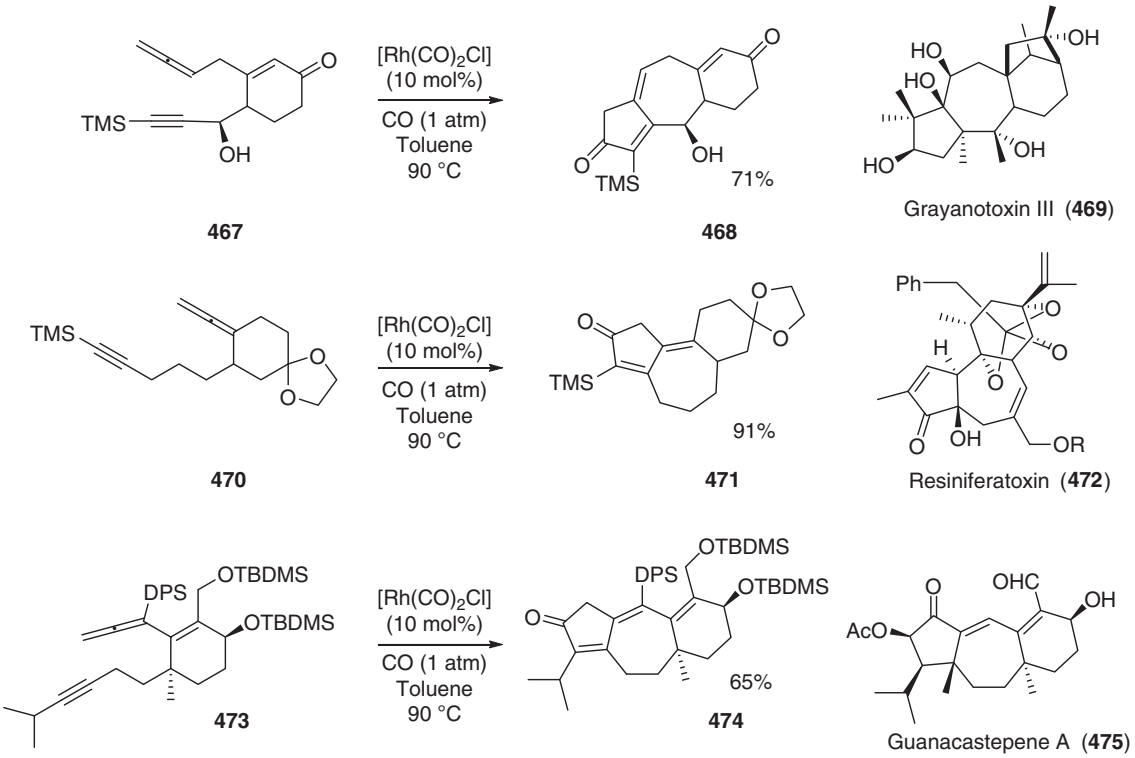
(125)

The key tricyclic skeleton **465** of paecilomycine A (**466**), one of several terpenoids derived from *Paecilomyces tenuipes*, was synthesized by Danishefsky and coworkers from substrate **464** by the thermal PKR using a cobalt reagent (equation 126).[199]



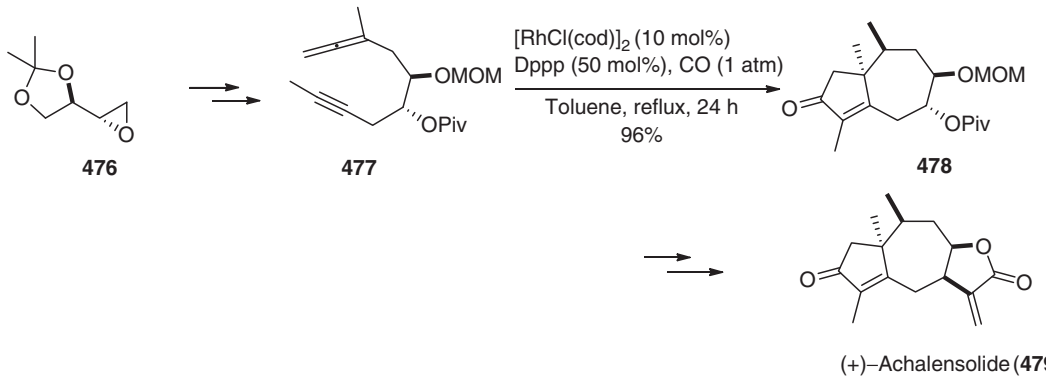
(126)

Guaianolides are a notable class of sesquiterpene lactones, which possess a 5-7-6 ring system. Such polycyclic systems are found in grayanotoxin (**469**), resiniferatoxin (**472**), and guanacastepene A (**475**) and have been shown to be formidable targets for conventional PK reactions. As mentioned earlier, Rh(I) could catalyze the PKR of 1,7 alkynyl allenes to afford such a skeleton, especially the 5-7 ring system. Taking advantage of this result, compound **469** was obtained from **467** via **468**, **472** from **470** via **471**, and **475** from **473** via **474**. All of the resultant PKR products have been further elaborated to the corresponding natural products (Scheme 24).[200]

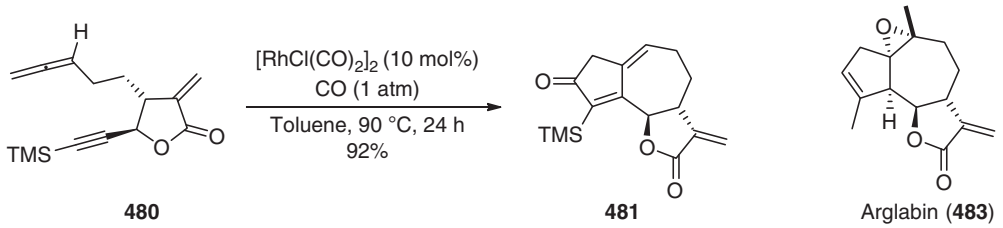


Scheme 24

In addition, guaianolides such as **479** or **483** having an α-methylene butyrolactone were also synthesized. Mukai prepared the requisite bicyclo[5.3.0] ring system **478** first from **477** by the PKR and then introduced the α-methylene lactone ring later in their synthesis of (+) – achalensolide (**479**) (equation 127).[201a] Direct access to the 5-7-5 ring skeleton bearing the α-methylene lactone appendage **481** was realized starting from **480** by Brummond under nearly identical reaction conditions (equation 128).[201b]

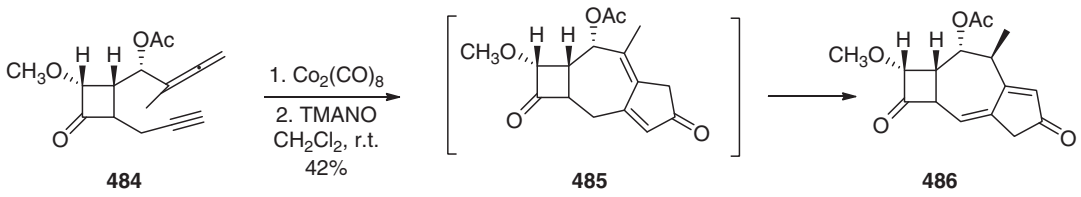


(127)



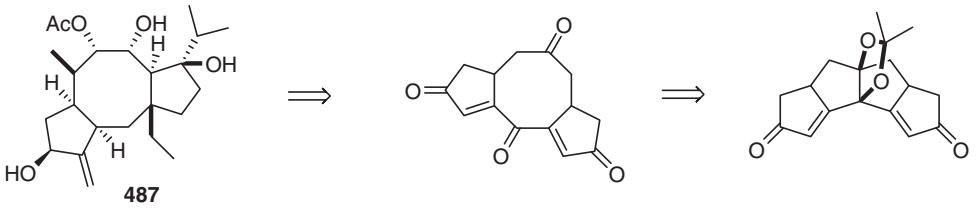
(128)

The extension of this strategy to substrate **484** allowed the 4-7-5 ring system of **486** to be obtained (equation 129).[202]

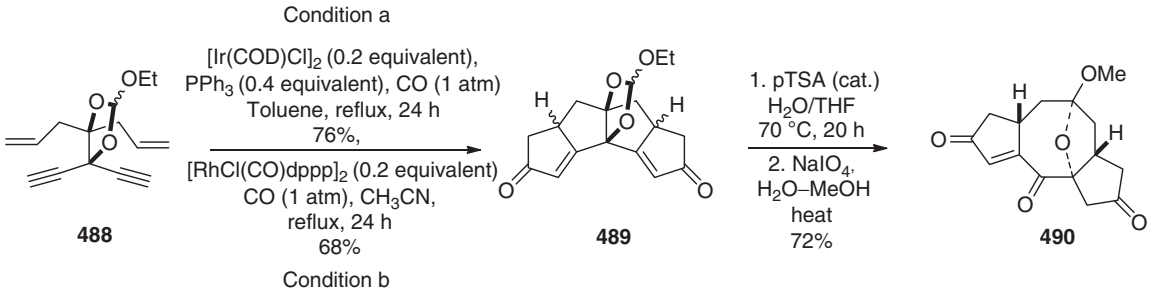


(129)

Access to a 5-8-5 ring system was realized by ring expansion through the double PKR of **488** (Scheme 25, equation 130). The two five-membered rings at the center of the tetracyclic product **489** were transformed into the eight-membered ring of **490** by treatment with an acid and periodate cleavage of the resulting diol.[203]

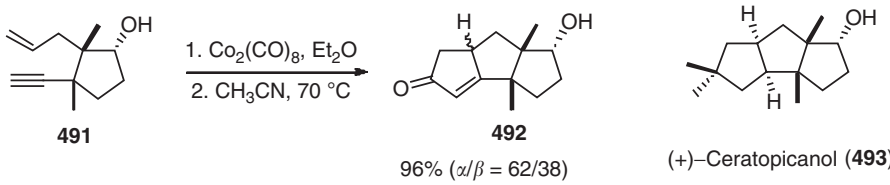


Scheme 25



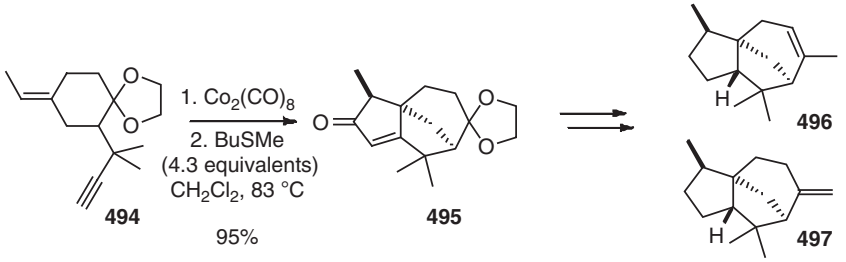
(130)

Persistent synthetic efforts toward the triquinane skeleton by the intramolecular PKR, triggered by a seminal synthesis of *dl*-coriolin by Magnus,[204] have appeared in the literature. These include the synthesis of (+) – ceratopicanol (**493**) by Mukai,[205] the synthesis of the tricyclic moiety of kalmanol by Paquette,[206] and the asymmetric synthesis of 15-nor-pentalene by Pericas and Moyano.[96] The synthesis of (+) – ceratopicanol is illustrated in equation 131. In related work, the synthesis of the D/E ring of the pentacyclic steroid xestoergosterol was described by Krafft.[207]



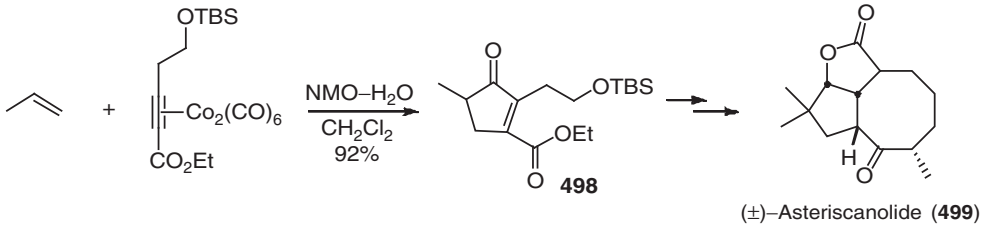
(131)

A number of examples for the formation of quaternary carbon centers by PKR were reported, including the synthesis of α-cedrene and β-cedrene by Kerr an Pauson (equation 132),[208a] and of the core of (–)-tricycloillicinone.[208b]



(132)

In spite of the complication in terms of the regiochemistry, the intermolecular PKR has been used for the synthesis of some natural products. Taking advantage of the regiochemical control based on the electronic nature of the substituent, in which the more electron-withdrawing group on the alkyne goes to the β-position of the enone, a couple of examples were reported. Krafft reported the synthesis of the key skeleton of (±)-asteriscanolide (**499**). The desired regioisomer **498** was formed exclusively by the intermolecular PKR (equation 133).[209a]



(133)

One of the distinctive virtues of the cobalt-mediated PKR is its acceptance to various functional groups, especially oxygen substituents. Iridoids are monoterpenes which often serve as intermediates in the biosynthesis of alkaloids. Chemically, iridoids usually consist of a cyclopentane ring fused to a six-membered oxygen heterocycle. They are among the most challenging synthetic targets, because of their plethora of oxygen functionalities present in a relatively small backbone (**Figure 25**). Utilizing the precursor **503** derived from carbohydrates, this class of target has been efficiently synthesized (equation 134).[210]

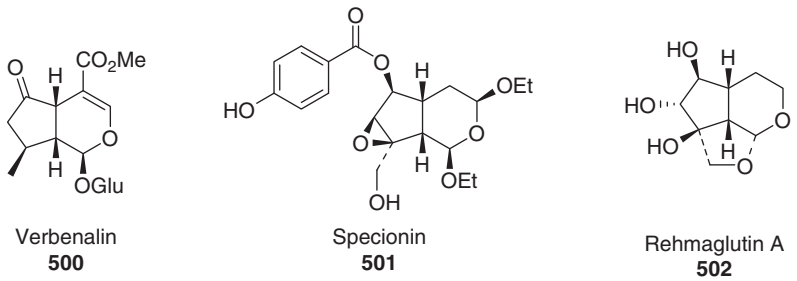
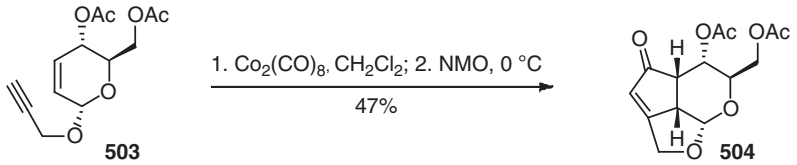
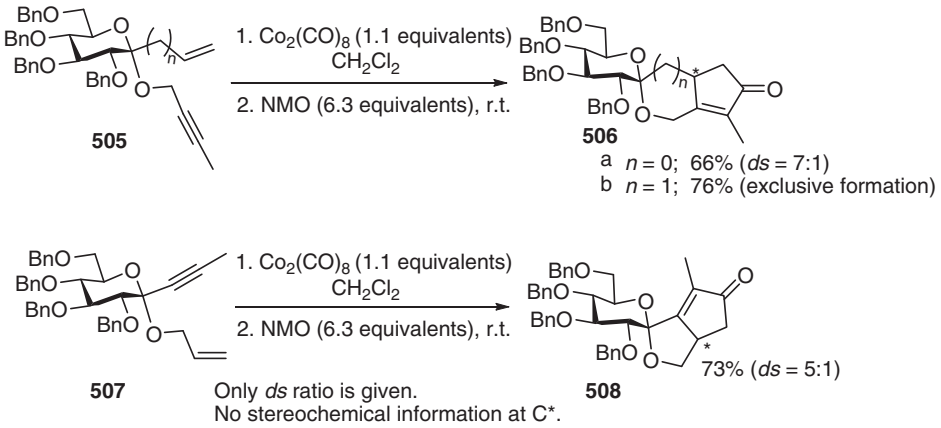


Figure 25 Representative iridoid monoterpenoids.



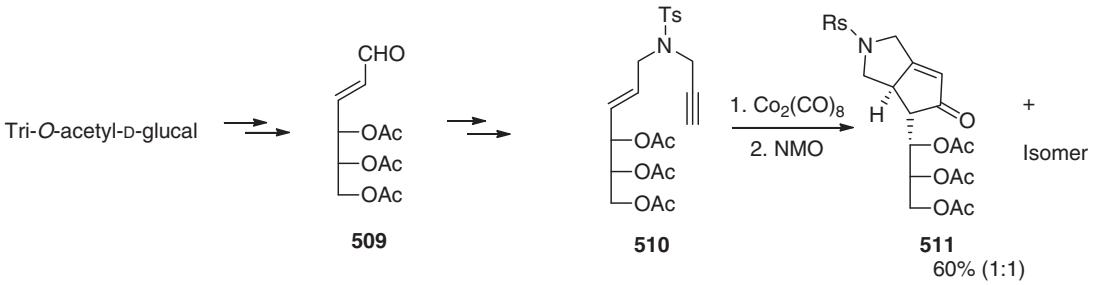
(134)

Along similar lines, the enynes **505** and **507**, having a sugar appendage derived from D-glucose, were utilized for the intramolecular reaction to give products **506** and **508** with good to excellent diastereoselectivity, respectively (equation 135).[211]



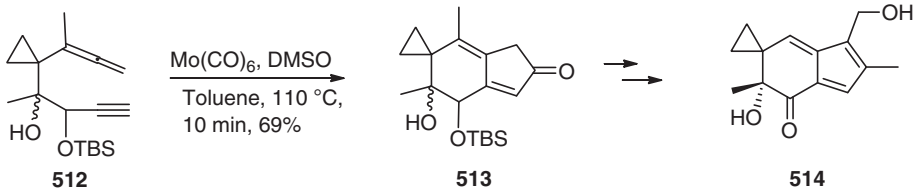
(135)

The *N*-tosyl tethered enyne **510** bearing a sugar side chain was also used to yield the bicyclic compound **511** (equation 136).[212]



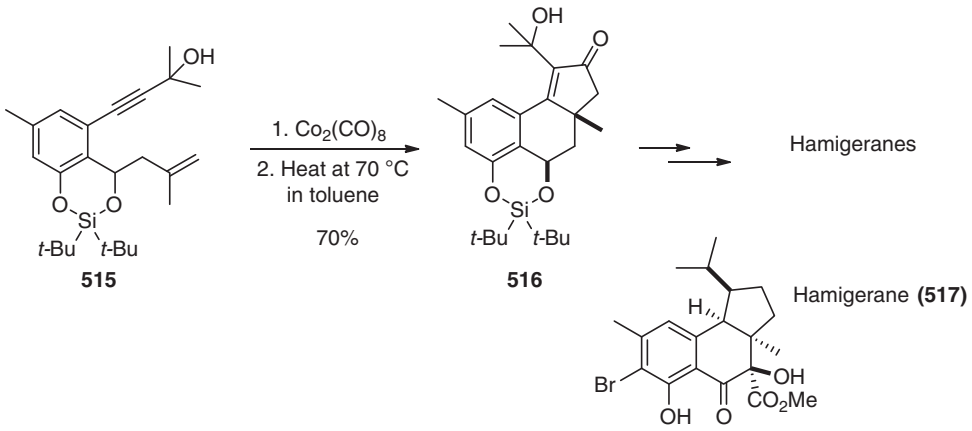
(136)

As seen in Section 5.24.6.1.1, the PKR of the allene-ynes opens up a new type of application. One of the rewards of this approach is the synthesis of highly functionalized compact bicyclic compounds, such as the illudins. Brummond et al. performed the PKR with the properly functionalized allenyne **512** to afford compound **513**, which is transformed into hydroxymethylacylfulvene (HMAF) (**514**) (equation 137).[213]



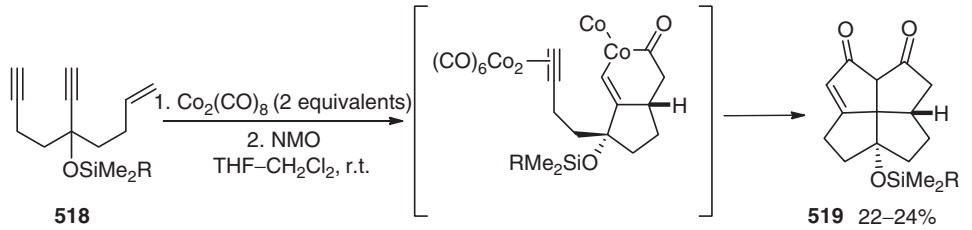
(137)

The core structure of the hamigerane terpenes was constructed by the use of the PKR. Enyne **515**, renderd rigid by silicon-protection, was subjected to thermal PKR to afford product **516** efficiently (equation 138).[214a]



(138)

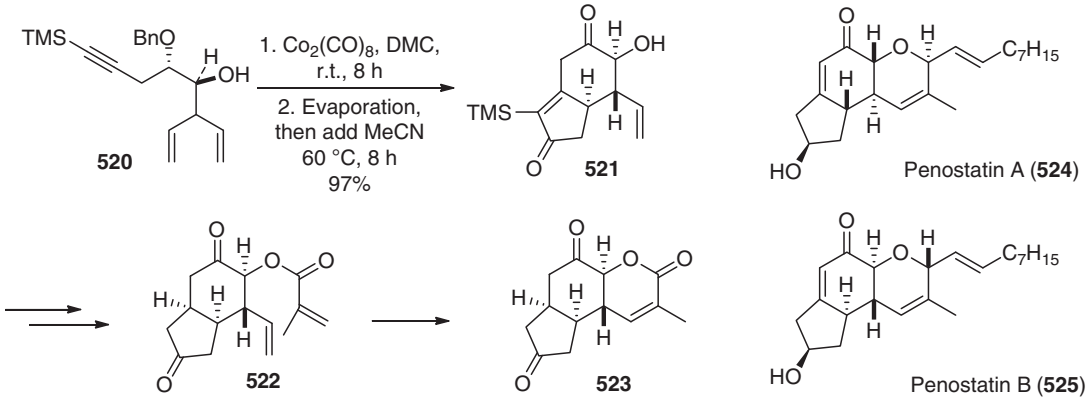
Keese's elegant synthesis of the farnestane [5.5.5.5] ring system through the PKR is particularly attractive (equation 139). Chung and coworkers upgraded this synthesis with the assistance of the improved tandem protocols mentioned in equation 96.[215]



(139)

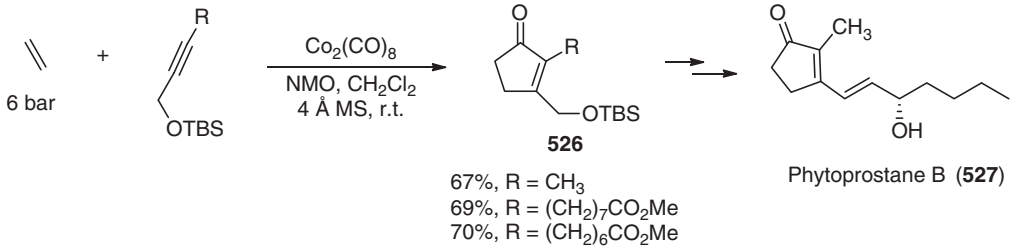
5.24.6.1.3 Synthesis of polyketide natural products

The penostatins A (**524**) and B (**525**) constitute a family of polyketide natural products, whose structure is highlighted by a densely functionalized hexahydrocyclopenta[f]-chromenone skeleton. Among this family, penostatin B (**525**) was synthesized in the natural form for the first time by employing a highly diastereoselective PKR for the construction of the tetrahydroindenone segment. A promoter-assisted PKR was applied to substrate **520** and furnished compound **521** with high diastereoselectivity (>20:1) in 97% yield.[214] The subsequent esterification of **521** with acrylic acid followed by ring-closing metathesis with the Grubbs–Hoveyda catalyst yielded the desired skeleton **523** (equation 140).[216]



(140)

The synthesis of phytoprostane B (**527**) is another example of an intermolecular reaction, in which again the more electron-withdrawing group is placed in the β-position of the PKR product **526** (equation 141).[217]



(141)

5.24.6.1.4 Carbanucleosides

The identification of the carbanucleosides such as (–)-aristeromycin (**531**) and (–)-neplanocin (**532**) as antitumor and antiviral agents has attracted a great deal of interest from the medicinal chemistry community (Figure 26). A couple of synthetic approaches based on the PKR were reported. First, the optically pure cyclopentenone **535** was utilized, which was obtained by the enantioselective catalytic PKR mediated by $Co_2(CO)_8$ and a chiral S-P ligand. The resultant PKR product **533** in optically pure form was transformed into compound **534** in a series of reactions. **535** was then obtained by the retro Diels–Alder reaction of **534** promoted by the Lewis acid $MeAlCl_2$ (equation 142).[218]

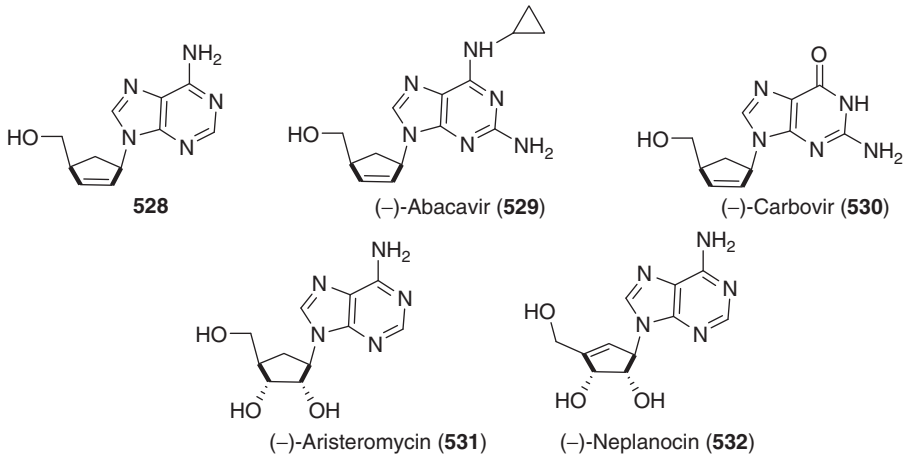
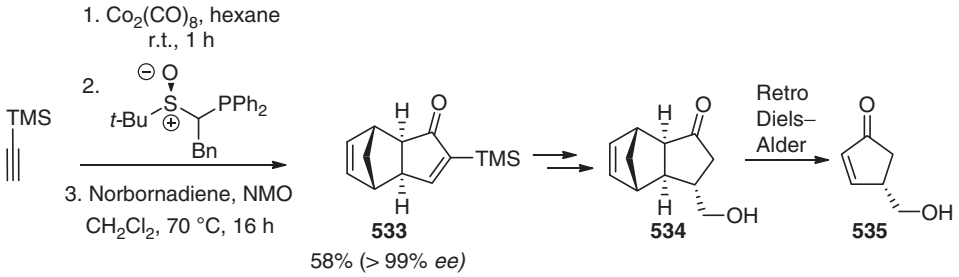
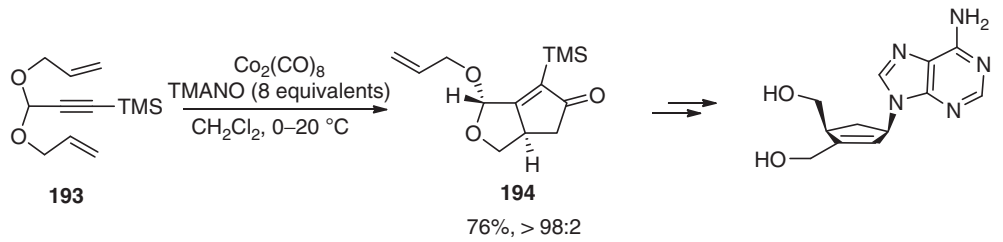


Figure 26 Representative carbanucleotides.



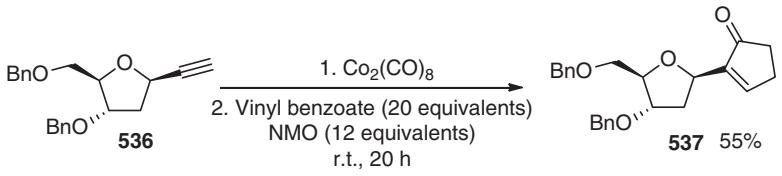
(142)

In conjunction with this, Jeong reported the cycloadditions of the bis(allyl) and bis(homoallyl) acetals of alkynals leading to bicyclic lactols.[219a] Schmalz and coworkers extended their utility to the synthesis of carbocyclic nucleosides via nucleophilic substitution of a π-allylic palladium complex (equation 143).[219b]



(143)

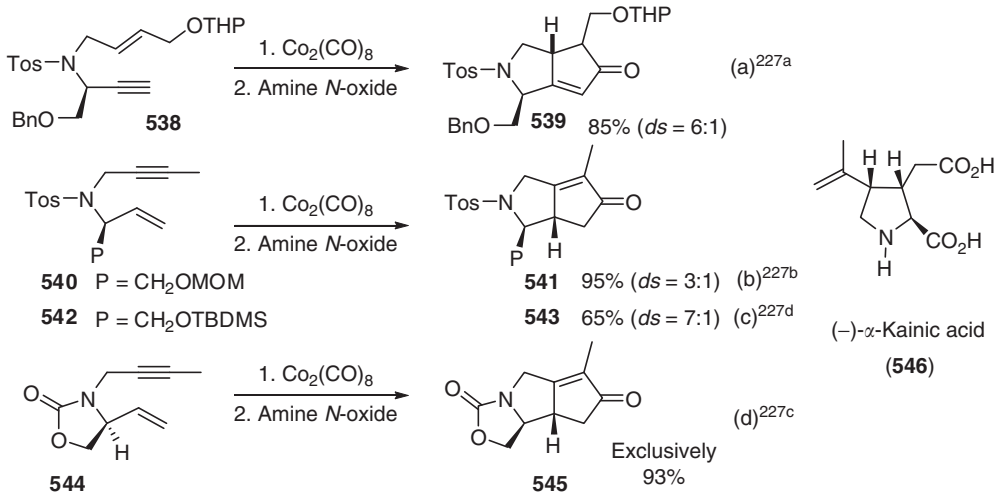
The PKR with the 1-alkynyl-2-deoxy-D-ribose derivative **536** constitutes an example for the use of highly oxygenated sugar-based substrates (equation 144).[220]



(144)

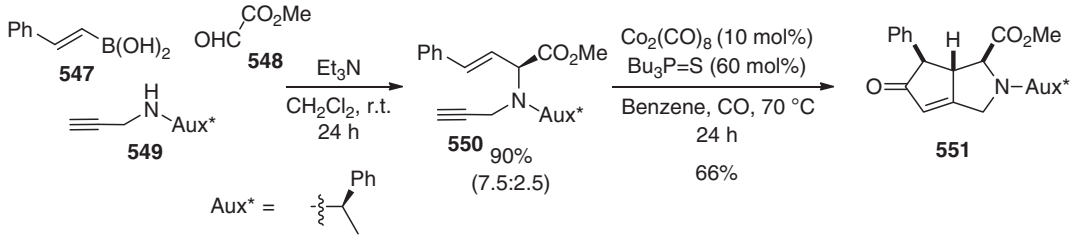
5.24.6.1.5 Amino acid derivatives

An excitatory neurotransmitter, (–)-α-kainic acid (**546**), has frequently served as synthetic target in approaches based on the PKR as a key reaction. Various precursors, such as **538**, **540**, **542**, and **544**, were tested to enhance the diastereoselectivity. Modest to excellent diastereoselectivities were observed with the first three acyclic precursors,[221a,b,d] but perfect stereoselectivity was obtained when the rigid cyclic precursor **544** was used (equation 145).[221c]



(145)

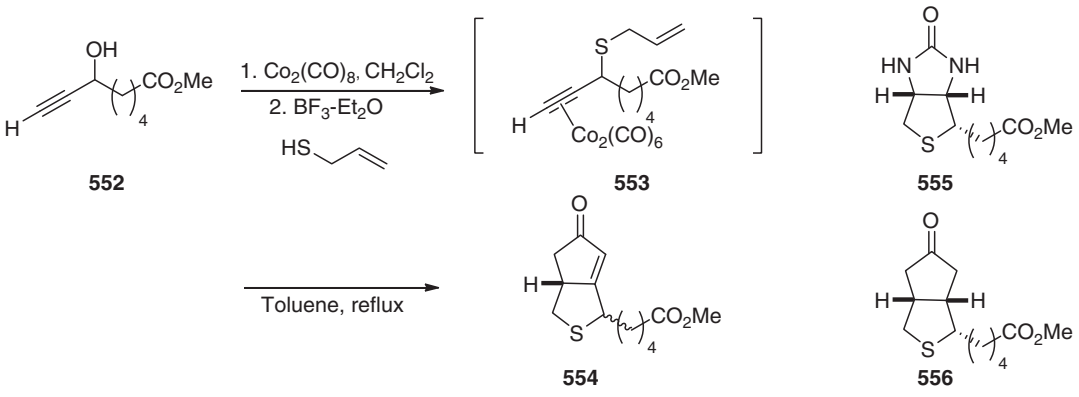
In conjunction with this study, it is noteworthy that a bicyclic proline derivative was obtained in a highly diastereoselective manner. The starting material, **550**, an optically pure enyne amino acid derivative, was prepared by trapping the imine intermediates formed *in situ* by mixing propargyl amine **549** and glyoxylic acid **548** with an alkenyl boronic acid **547**. At this point, the diastereoselectivity is not high and, thus, it is necessary to separate each diastereomer by chromatography. Once the optically pure starting material was subjected to the catalytic PKR condition, the single stereoisomer **551** was obtained (equation 146).[222]



(146)

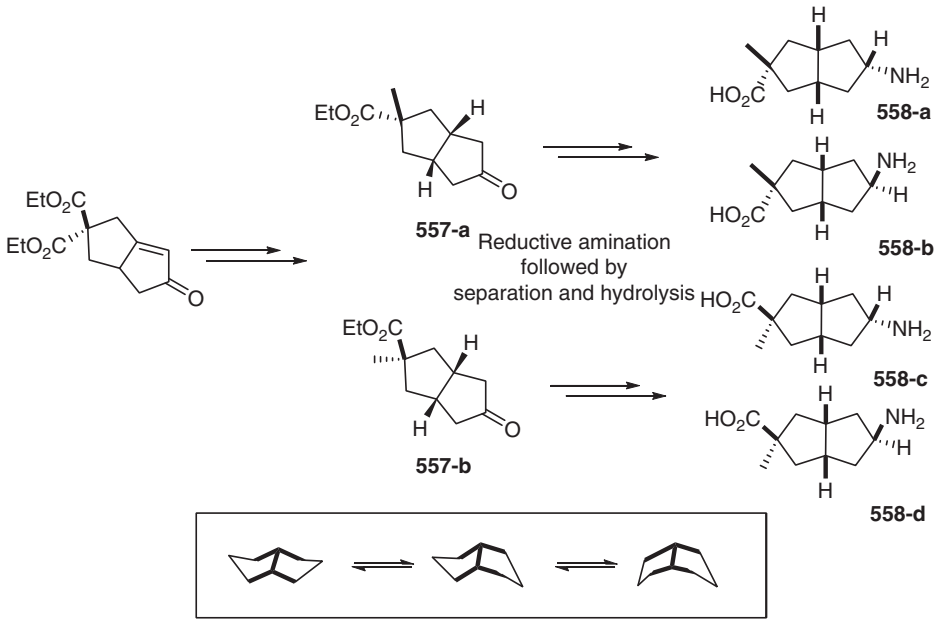
5.24.6.1.6 Unnatural but biorelevent products

Compound **556**, an analog of biotin (**555**), in which the urea moiety of the natural product is replaced by a ketone, was obtained starting from the substrate **552** (equation 147).[223]



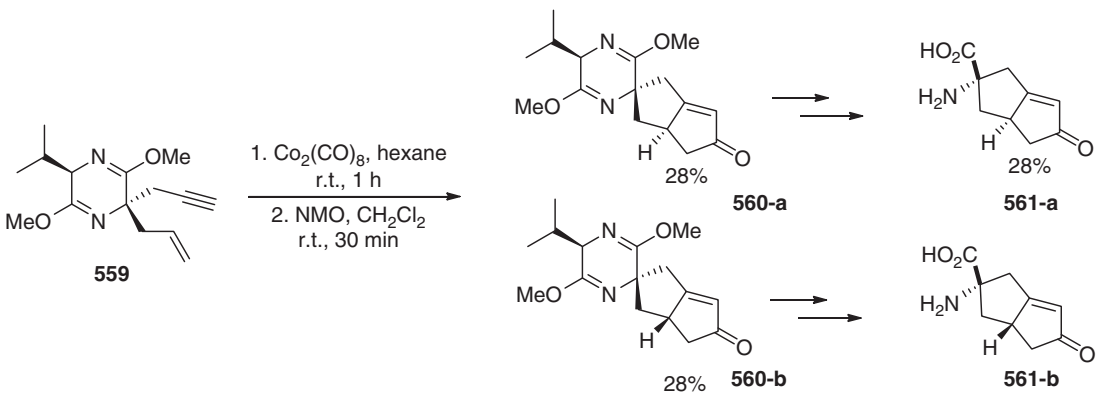
(147)

The ε-amino acid **558** was synthesized from the PKR product **557**, which has a rigid backbone together with flexible ends, and used as a probe for protein folding (equation 148).[224]



(148)

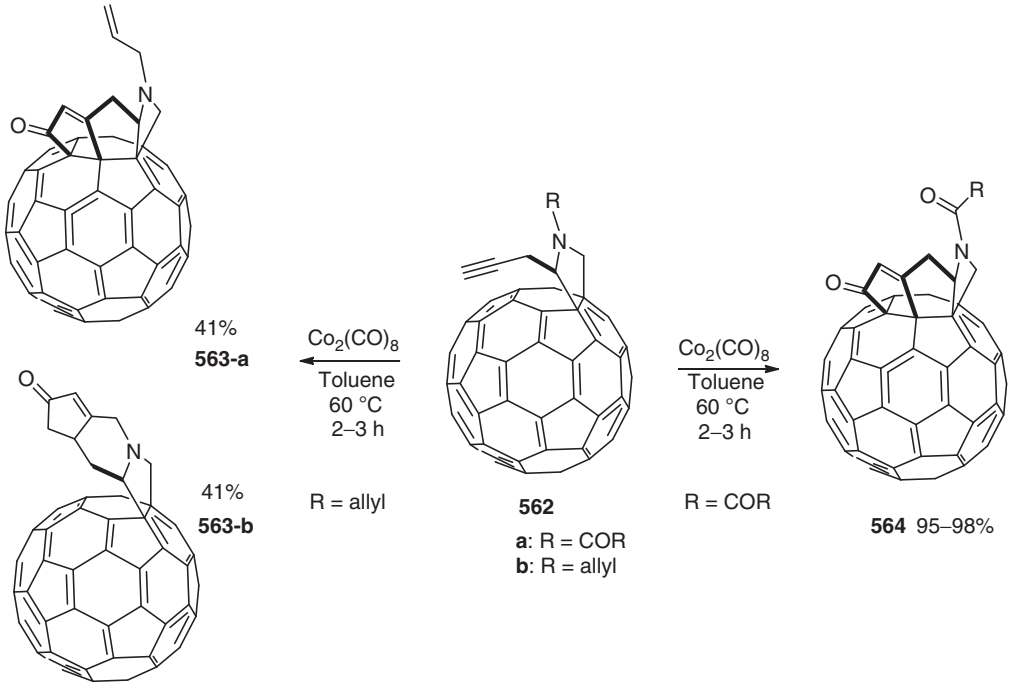
Numerous unnatural cyclic amino acids were synthesized in optically pure form by the transition metal mediated reaction from enyne substrates carrying the Schoellkopf bislactam ether auxiliary. The promoter-assisted PKR of substrate **559** provided a diastereomeric mixture (1:1) of the bicyclic compound **560**, which were separated easily by flash chromatography and then transformed into the corresponding amino acids **561** (equation 149).[225]



(149)

5.24.6.2 Miscellaneous

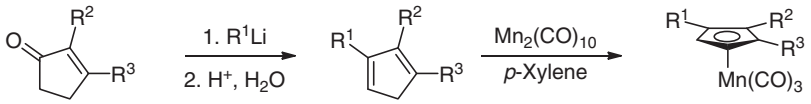
When the fullerene derivative **562-a** was subjected to the PKR, the reaction was forced to take place on C_{60}. However, there are two options when **562-b** is employed, but no significant preference was observed, yielding a 1:1 mixture of **563,** which means that the reactivity of the olefin within C_{60} is comparable to that of the allyl group (equation 150).[226]



(150)

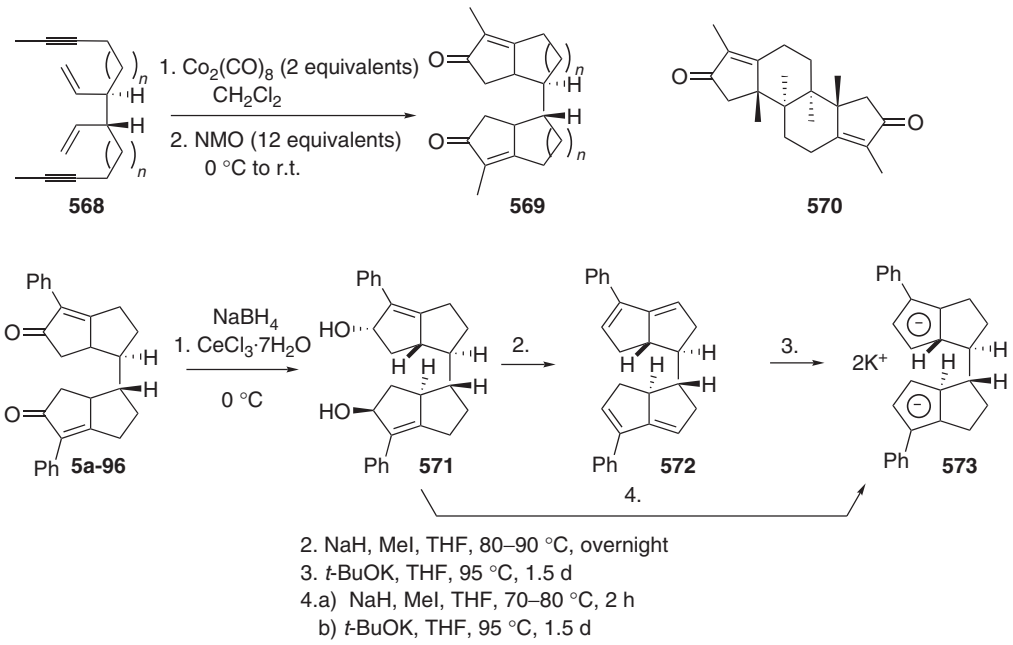
5.24.6.2.1 Cyclopentadienes

Cyclopentenones obtained by the PKR can be used as precursors for Cp-type ligands. These efforts are summarized thoroughly elsewhere. Chung and Jeong demonstrated the efficient transformation of the PKR product into the Cp ligand. Subsequently, many applications followed. A given cyclopentenone was treated with an alkyl lithium reagent, followed by dehydration by an acid to give a mixture of regioisomers of cyclopentadienes **565** (equation 151).[227]



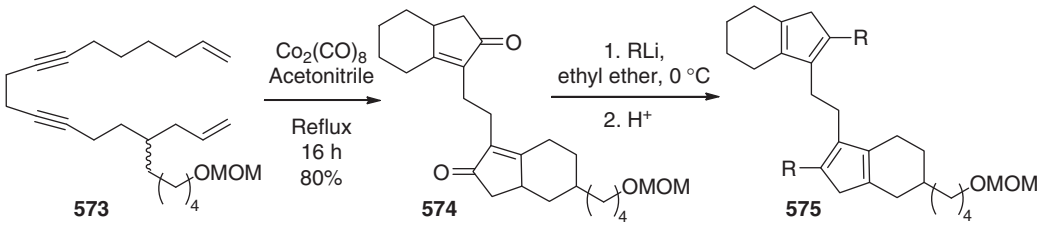
(151)

It is interesting to notice that the double PKR of substrate **567** gave rise to product **568** instead of **569**. This can be accounted for by the fact that the two bicyclic[3.3.0] rings are more favorably formed than the fused [4.3.0] ring, when $n=1$. **568-a** was further modified to give the bis Cp-ligand **572** (equation 152).[228]



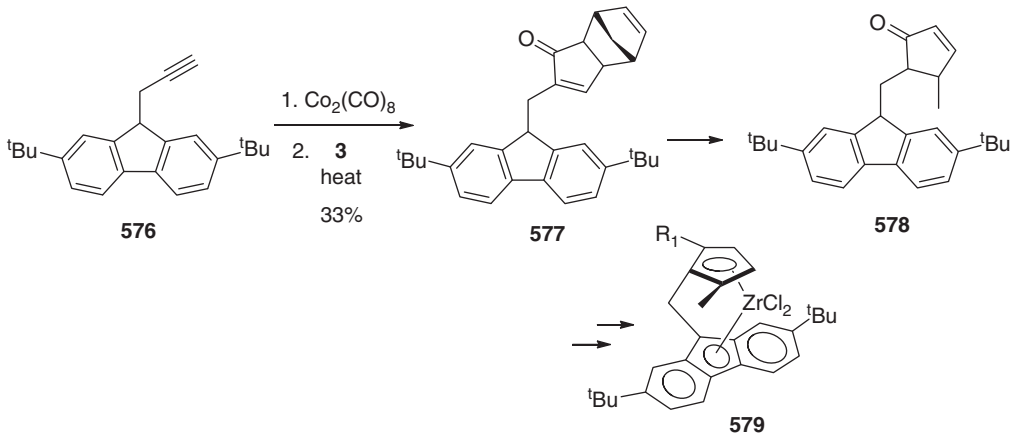
(152)

The same strategy was applied to the synthesis of **575**. The appendage on **575** can be used for the immobilization of this ligand on a solid support (equation 153).[229]



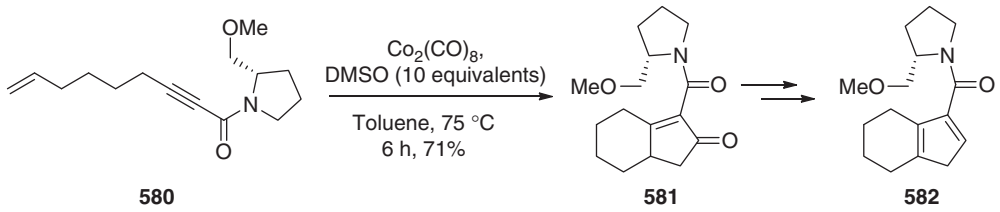
(153)

The derivatives **579**, which were obtained from **578**, were used as catalysts in combination with methylaluminoxane (MAO) for ethylene–norbornene copolymerization and their activity is comparable to that of isopropylene[9-fluorenylcyclopentadienyl]zirconium dichloride under identical conditions.[79a] **578** was derived from **577**, a PKR product of **576**, by a series of reactions including the 1,4-addition of a methyl group and a retro-Diels–Alder reaction (equation 154).[230]



(154)

Moyano and Pericas prepared the cyclopentadiene **582** having a chiral appendage (equation 155; see equation 44).[231]



(155)

5.24.7 Conclusions

The Pauson–Khand reaction is a truly remarkable synthetic method in several respects. It creates much molecular complexity in one-step while retaining the original functionality in the substrate. Every carbon on the pentagon corner can be further functionalized to lead to the desired target products decorated with various functional groups.

The drawbacks imposed on the early version of this transformation, such as the limited substrate scope, low efficiency, and problems associated with regio- and stereoselectivity, have been overcome and/or eliminated by the extensive efforts over the past four decades. Thus, the horizon of the reaction has been greatly widened. More specifically, the finding of promoters for the stoichiometric cobalt-mediated reaction, and the development of catalytic versions, including heterogeneous as well as enantioselective ones, clearly demonstrate that its application to synthetic chemistry in academia and even in industry is more tangible. We have also witnessed the rapid expansion of the substrate scope and are expecting further applications of this method to be developed. With the deepening understanding of the reaction mechanism and accumulated knowledge of its regio- and stereoselectivities, this reaction has become an indispensable tool in organic synthesis.

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5.25 Metal Carbene Cycloadditions

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Glossary

Benzannulation Construction of a benzene ring from a nonbenzene precursor.

Carbene complex A compound that contains a double bond between a carbon and a metal, or the metal complex of a stable carbene species.

Cyclization Construction of a new ring system in a process that creates one bond of the newly formed ring system.

Cycloaddition Construction of a new ring system in a process that creates two or more bonds of the newly formed ring system.

Cyclohexadienone annulations The Dötz benzannulation reaction applied to a β-disubstituted-α,β-unsaturated carbene complex, resulting in a cyclohexadienone system since aromatic ring formation is blocked.

Cyclopentannulation Construction of a five-membered carbocyclic ring system from a precursor that does not already contain the five-membered ring system.

Cyclopropanation Creation of a cyclopropane ring via the coupling of an alkene and a carbene or carbene complex.

Dötz benzannulation reaction The construction of a phenol through reaction of an α,β-unsaturated carbene complex and an alkyne; formally a $[3+2+1]$-cycloaddition incorporating the carbene carbon and unsaturated group, the alkyne, and CO.

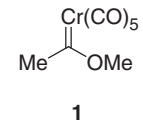
Enynylcarbene complex A carbene complex that contains an alkyne group at the carbene compound, featuring an alkene group attached to the other side of the alkyne.

Olefin metathesis Exchange of the alkene carbons of two or more alkenes, often catalyzed by transition metal carbene complexes.

Tandem reaction A reaction where the initial product is designed to undergo an additional reaction process without isolation of the initial product.

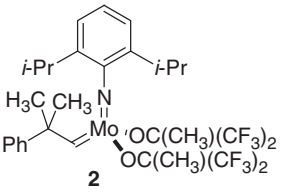
5.25.1 Introduction

This chapter is an update to a chapter by the same title published in the first edition of Comprehensive Organic Synthesis.[1] The literature of carbene complexes in the intervening years has been vast. Emphasis in this chapter is the reactions where new ring systems are formed as a result of the reaction with a carbene complex and emphasizes the period of 1990–2010. This has been divided into two sections, involving reactions at the carbene ligand followed by reactions that initially occur at the metal center. The review has primarily been restricted to reaction processes that lead to an organic structure and is also primarily restricted to reaction processes that involve a stable carbene or isolable carbene complex as one of the reactants. In most cases, only processes that have been demonstrated by a significant number of examples have been presented. There are three general classes of carbene complexes, Fischer carbene complexes, Schrock carbene complexes, and Arduengo carbene complexes. Fischer carbene complexes feature electrophilic carbene carbons and relatively low oxidation state metals. Schrock carbene complexes feature nucleophilic carbene carbons and relatively high oxidation state metals. Arduengo carbene complexes, often referred to as *N*-heterocyclic carbene (NHC) complexes, feature carbene ligands that are moderately stable as free carbenes and display minimal C–M double bond character. Emphasis in this chapter is on Fischer-type carbene complexes, which are electrophilic at the carbene carbon. Schrock carbene complexes are reviewed elsewhere. Arduengo carbene complexes typically undergo no change in their chemical structure in most reactions. The vast majority of the carbene complexes depicted in this review involve the Group 6 metals. The chapter is intended to give an overview and present as many examples as is possible, which demonstrate the synthetic utility of individual processes, and is thus not comprehensive. Major comprehensive review works in this area have been authored by the Barluenga,[2,3] Dötz,[4] and Wulff[5] groups. Many other subject-specific reviews have appeared and are noted; their areas of relevance are discussed. A comprehensive survey of all carbon–metal doubly bonded systems appears annually.[6] The chapter headings employed in the Wulff chapter in Comprehensive Organic Synthesis, 1st edition, have been largely retained in this chapter; however, the proliferation of tandem reaction processes incorporating multiple reaction types has made it difficult to uniquely classify many of the reaction processes.



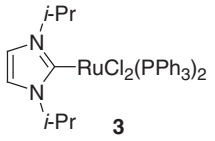
1

A Fischer carbene complex



2

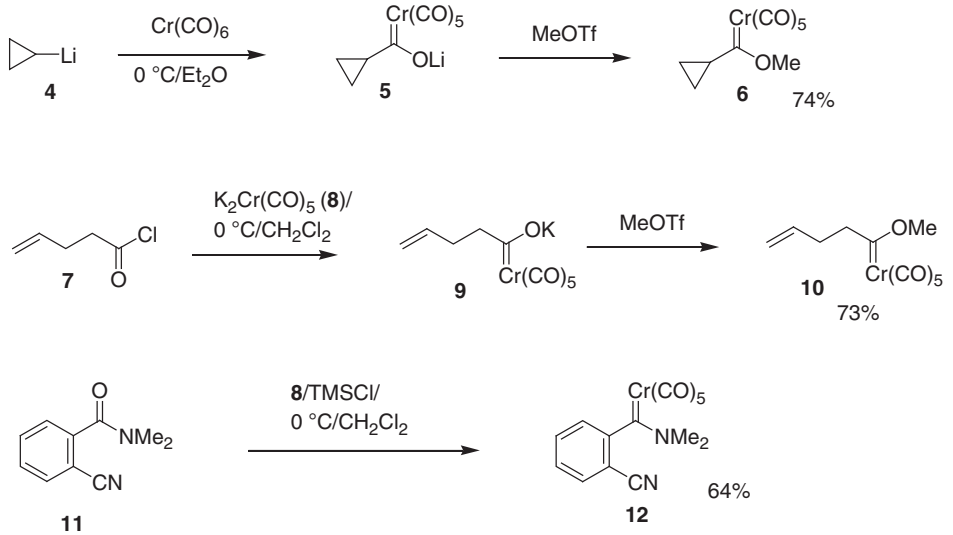
A Schrock carbene complex



3

An Arduengo (or NHC) carbene complex

Carbene complexes employed in these investigations are prepared using primarily two basic methods, depicted in **Scheme 1**. Synthesis of carbene complexes from organolithium reagents (**4**) is known as the Fischer synthesis. The Fischer synthesis is the most commonly employed method for carbene complex preparation. In this conversion, the organolithium reagent is treated with a metal carbonyl derivative, and the resulting acylate complex is treated with a highly reactive alkylating agent. Recent improvements in Fischer synthesis include several papers reporting the use of less expensive iodides in the final alkylation step.[7,8]

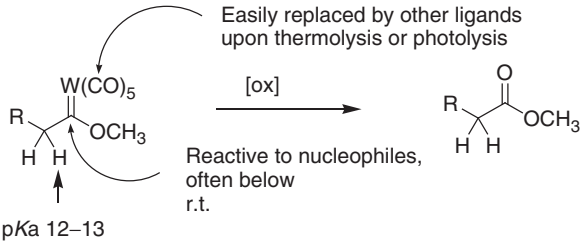


Scheme 1

Most of the carbene complexes depicted in this chapter are synthesized according to this method. The most commonly used alternative method involves the use of acid chlorides (**7**) or amides (**8**) and is known as the Hegedus/Semmelhack synthesis. Alkoxycarbene complexes are prepared from the reaction of acid chlorides with metal carbonyl dianions (**8**), which are then treated with highly reactive alkylating agents as in the Fischer synthesis. Aminocarbene complexes are obtained from the reaction of tertiary amides with metal carbonyl dianions in the presence of silyl chlorides, resulting in the direct formation of the aminocarbene complex. Other lesser employed methods have been documented, including preparation from terminal alkynes via vinylidene complexes and preparation from diazo compounds.

5.25.2 Reactions on the Carbene Ligand: The Metal as Reactivity and Selectivity Auxiliary

The representative reactivity profile for Fischer carbene complexes is depicted in Scheme 2. In several cases, the carbene complex functionality serves as a surrogate for an activated ester or amide. The carbene complex group functions as a strongly electron-withdrawing group and leads to a substantial increase in the acidity of protons at the alpha position. The p*K*a value for protons in simple alkyl complexes is approximately 12–13 for alkoxycarbene complexes[9] and 25–30 for aminocarbene complexes (in acetonitrile).[10] The carbene complex functionality also electronically activates conjugated alkene and alkyne groups for nucleophilic addition processes and other cycloaddition processes commonly associated with α,β-unsaturated carbonyl compounds. The carbene complex functionality is easily transformed into the corresponding carbonyl group through reaction with a variety of mild oxidizing agents. The carbene complex functionality also undergoes nucleophilic acyl substitution-like processes than can transform alkoxycarbene complexes to aminocarbene or thiocarbene complexes. Finally, the carbene complex undergoes numerous reactions at the metal atom.

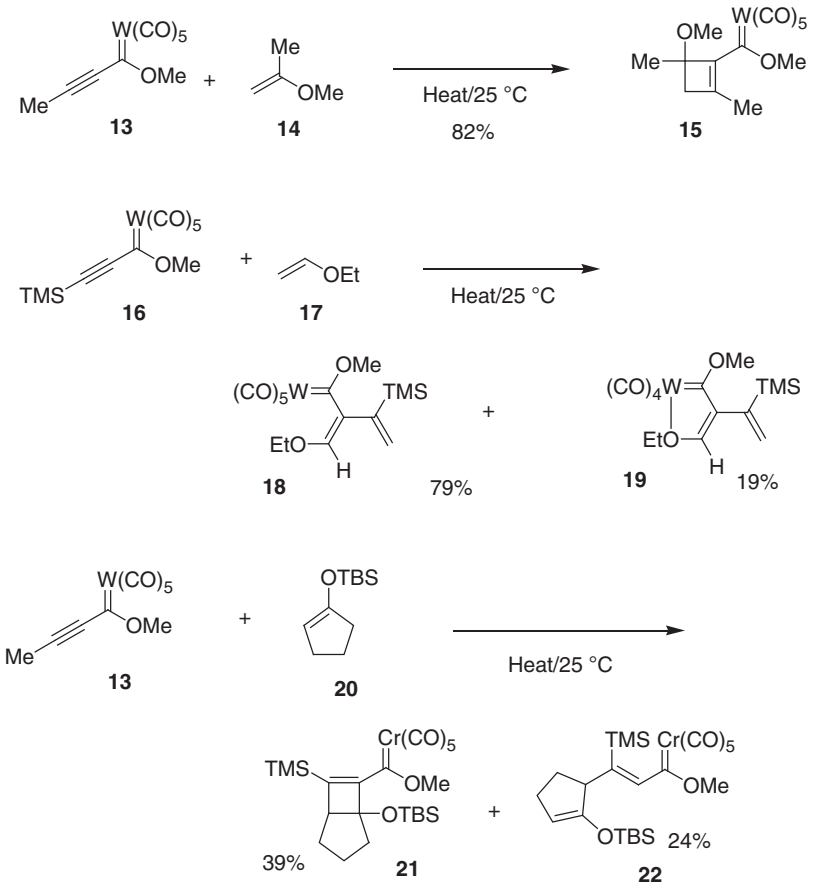


Scheme 2

5.25.2.1 2 + 2 Cycloaddition

As noted in the previous edition of Comprehensive Organic Synthesis, several examples of this process involving primarily the reaction of alkynylcarbene complexes of Group 6 metals and highly electron-rich alkenes, in most cases enol ethers or enamines, had been reported. The reaction occurs under milder conditions than analogous ester systems (typically room temperature). The reaction typically proceeds with retention of configuration and is frequently accompanied by subsequent ring-opening reactions of the initially formed cyclobutenes. Representative examples reported since the previous edition of Comprehensive Organic Synthesis are depicted in Scheme 3. The carbene complexes are easily transformed to the analogous esters through reaction with various oxidants (e.g., DMSO). Most of the examples demonstrated to date involve alkynylcarbene complexes. In numerous cases, addition to the alkyne group of alkynylcarbene complexes is employed for the primary purpose of setting up an electrocyclization process. Examples of this will be presented in a future section. An extensive compilation of [2 + 2]-cycloadditions and ene reactions for alkynylcarbene complexes and either enol ethers or ketene acetals has been reported.[11] These studies demonstrate a competition between ene reaction (product **22**) and [2 + 2] cycloaddition (product **21**). The ene reaction was favored for trimethylsilylalkynylcarbene complexes reacting with acyclic enol ethers and cyclic enol ethers featuring an exocyclic oxygen. In many cases, the products undergo cyclobutene ring opening to afford dienylcarbene complexes. The [2 + 2]-cycloaddition reaction can be accelerated through high-pressure conditions.[12] Coupling of enol ethers with *exo*-methylene cyclic carbene–chromium and –tungsten complexes resulted in a completely diastereoselective [2 + 2]-cycloaddition process.[13]

In most cases, the [2 + 2]-cycloaddition of alkynylcarbene complexes and enamines results in the direct preparation of ring-opened products. The initial coupling of alkynylcarbene complexes (e.g., **23**) and enamines proceeded via dual-reaction pathways (formation of **25** vs. **26**, Scheme 4): (1) [2 + 2]-cycloaddition followed by ring opening of the resulting cyclobutene to afford dienylcarbene complexes (e.g., **27** and **28**) or (2) Michael addition followed by cyclization to afford a cyclopentadiene derivative (e.g., **29**).[14,15] The reactions using dienamines (e.g., **30**) led to dienylcarbene complexes (e.g., **31**) through [2 + 2]-cycloaddition and ring opening, which also transformed to the corresponding cyclopentadienes (e.g., **32**).[16] Conversion of the dienylcarbene complex to the cyclopentadiene (**32**) could be accelerated by transforming the tungsten–carbene complex to a rhodium–carbene complex, which underwent a more rapid cyclization reaction. The reaction using β-aminoketones (e.g., **33**) leads to



Scheme 3

aminobenzene derivatives (e.g., **37**).[17] In this case, the initially formed [2 + 2]-cycloadduct opens to form the enamine **35**, which undergoes an internal condensation process to afford the pyridine derivative.

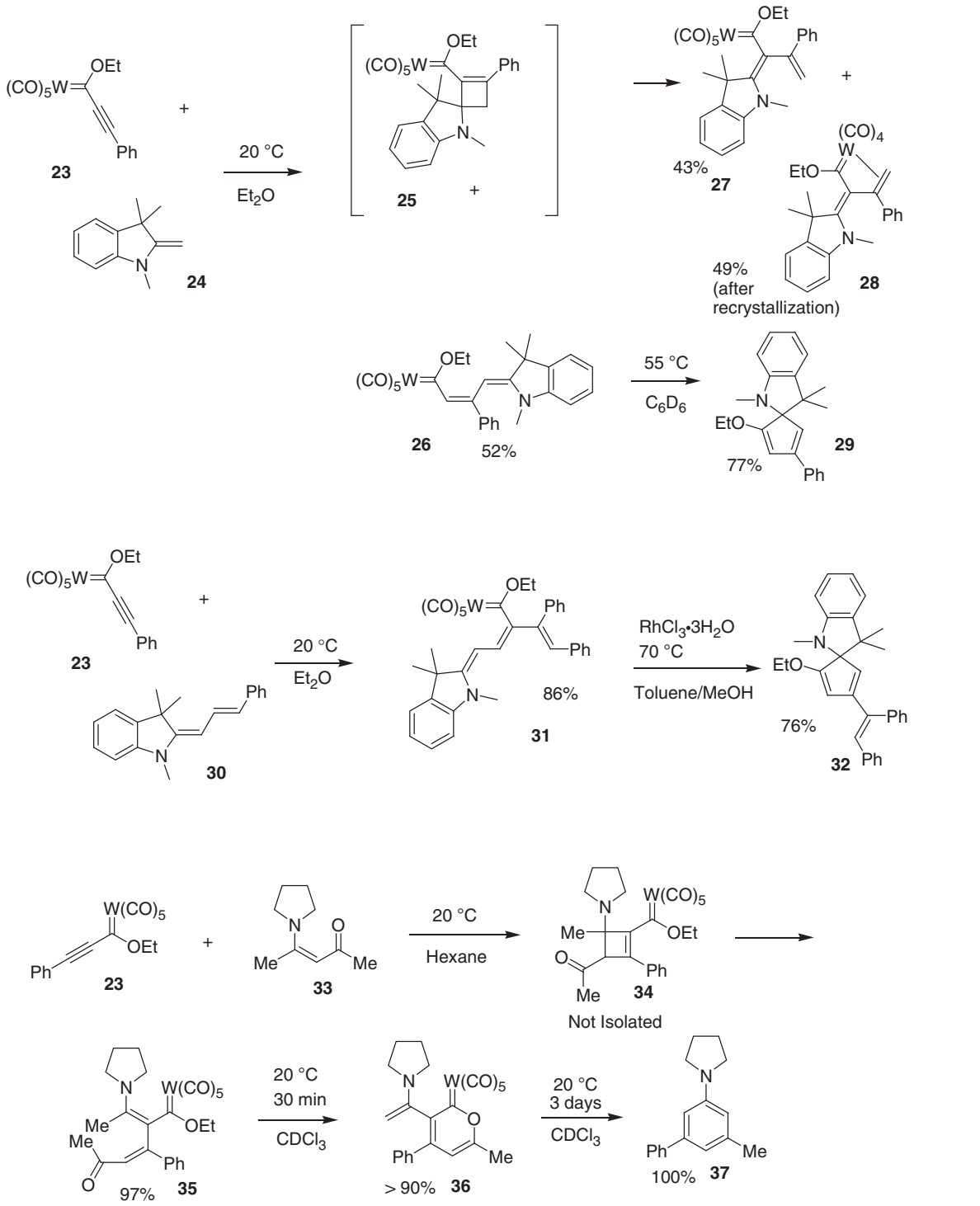
5.25.2.2 3 + 2 Cycloaddition

Several examples of the 1,3-dipolar cycloaddition reaction of alkenyl and alkynylcarbene complexes with various dipoles have been demonstrated. These reaction processes proceed under milder conditions and with higher regioselectivity than reactions employing analogous ester derivatives. The resulting products are easily transformed to esters through oxidation reactions. Some examples of this reaction were reported in the previous edition of Comprehensive Organic Synthesis; however, the range of dipole types has expanded tremendously since that publication.

Examples of 1,3-dipoles that have been reported are depicted in Scheme 5 and include nitrones (e.g., **39**),[18–20] diazo compounds (e.g., **42**),[21,22] diazo ylides,[18] nitrilimines (e.g., **46**),[23] azomethine ylides (e.g., **49**),[24] and azides.[25,26] In most cases, the reaction proceeds with a very high degree of relative asymmetric induction when carbene complexes featuring chiral oxygen or nitrogen carbene substituents were employed. The azomethine ylide cycloaddition process was used as a key step in the enantioselective synthesis of rolipram. A theoretical study of 1,3-dipolar cycloaddition reactions of alkynyl Fischer carbene complexes suggests that the origin of the superior reactivity and regioselectivity arises from a transition state that is more asynchronous than that for esters.[27] Nonconcerted cycloaddition reactions were observed using alkylideneimidazole derivatives.[28]

5.25.2.3 2 + 2 + 1 Cycloaddition

Several examples that employ carbene complexes as reactive auxiliaries in the Pauson–Khand reaction have been reported (Scheme 6). These Pauson–Khand reactions occur at much milder temperatures than typical intramolecular Pauson–Khand reactions. Most of the successful examples involve an alkynylcarbene complex featuring an allylamino group (e.g., **51**).[29,30] The Pauson–Khand reaction involving allylamino(alkynyl)carbene complexes was studied, with emphasis on heteroatom-substituted alkene derivatives.[31] Alkene–carbene complexes (**54**) where X is a thio group and Y is a nonheteroatom afforded mostly Pauson–Khand products (**55**), whereas derivatives of **54** where Y is a heteroatom afforded mostly diene derivative (**56**). The

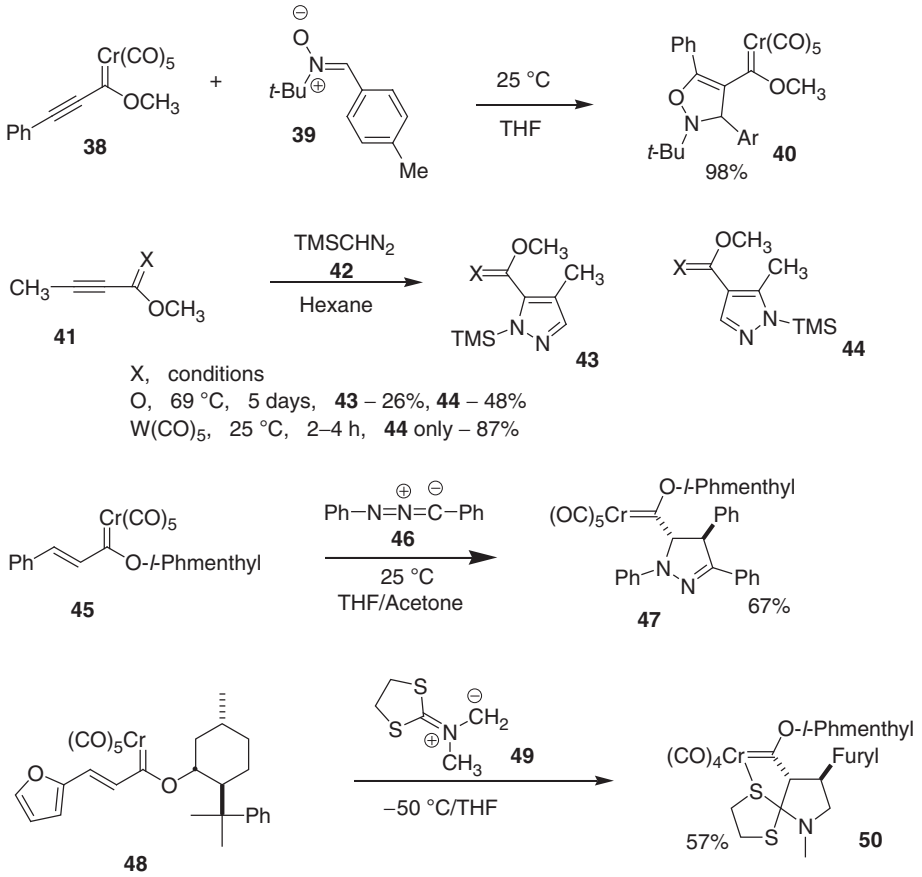


Scheme 4

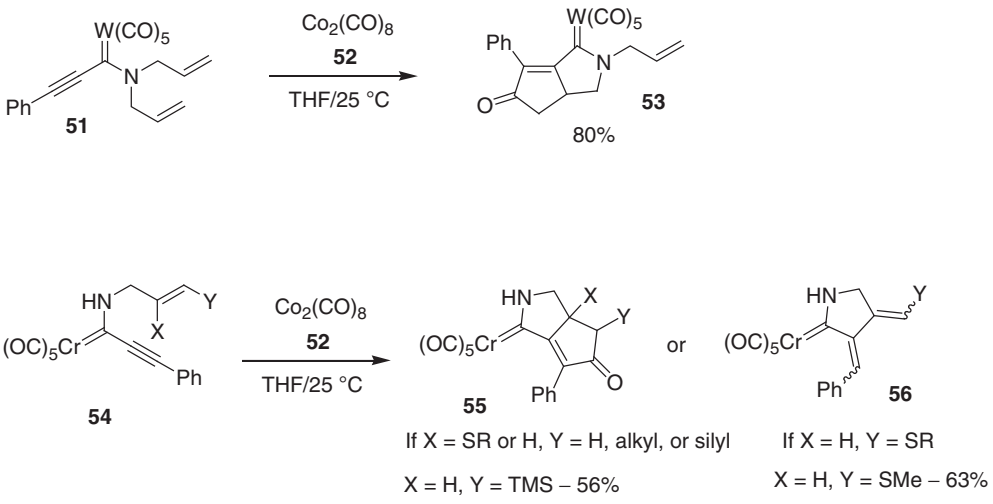
reactivity of alkynylcarbene complexes in the Pauson–Khand reaction was accelerated by fluoride ion.[32] The use of carbene complexes where the alkyne is not conjugated in intermolecular Pauson–Khand reactions has also been reported.[33]

5.25.2.4 4 + 2 Cycloaddition

One of the major synthetic uses of carbene complexes is the Diels–Alder reaction of α,β-unsaturated carbene complexes and dienes[34] (Scheme 7). These complexes are extremely reactive dienophiles. Their reactivity resembles that of α,β-unsaturated esters

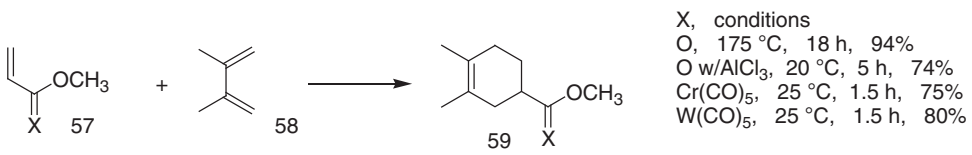


Scheme 5



Scheme 6

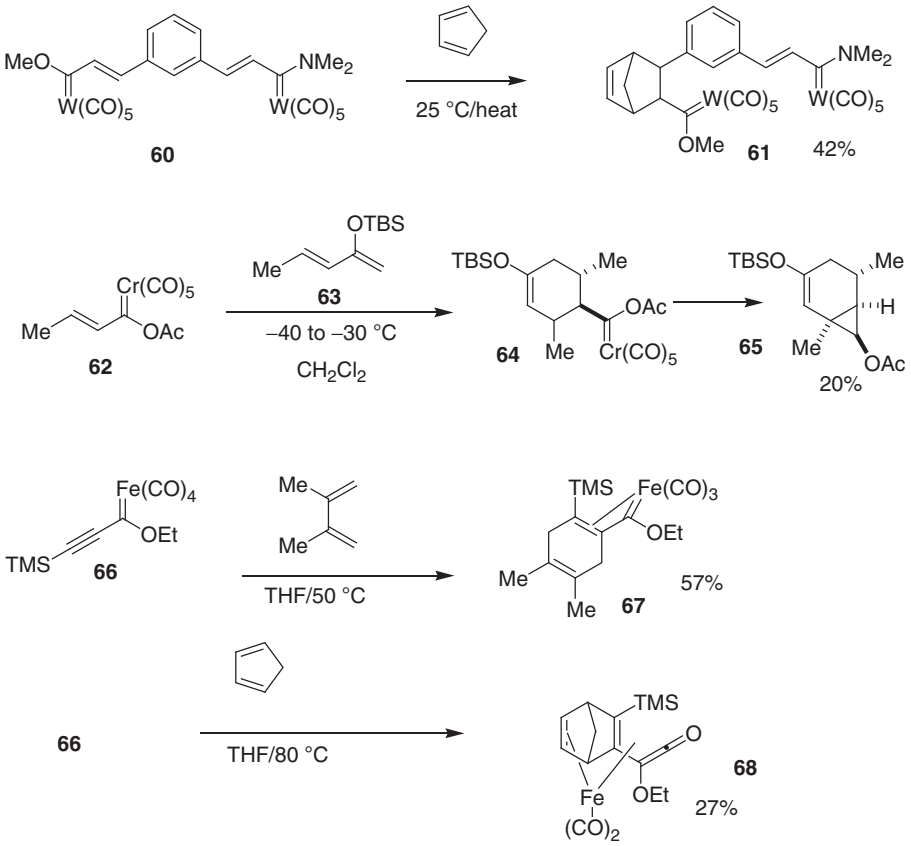
in the presence of Lewis acids, and they offer superior regio- and stereoselectivity in reactions with unsymmetrical dienes relative to α,β-unsaturated esters. Diels–Alder reactions involving α,β-unsaturated carbene complex dienophiles often proceed at room temperature. Oxidation of the carbene complex adducts to the corresponding esters or amides can be accomplished with a variety of reagents under very mild conditions. Numerous synthetic transformations have been demonstrated for the carbene complex functionality. Specific cases that demonstrate these and several other features are discussed in the following paragraphs. A variety of diene types have successfully been employed in this process, including several examples of 2-amino-1,3-dienes[35–37] and



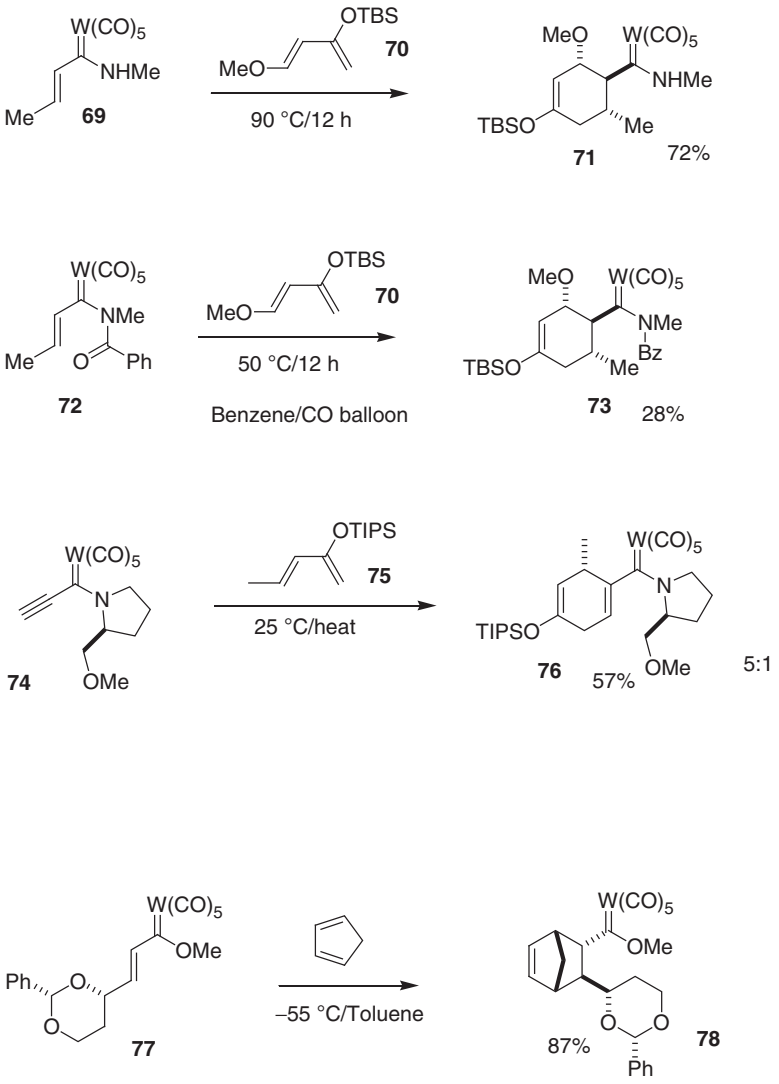
Scheme 7

imino-dienes, which result in pyrimidine derivatives.[38,39] Alkoxycarbene complexes, aminocarbene complexes, and acyloxycarbene complexes have all been successfully demonstrated. Alkoxycarbene complexes are generally more reactive, as noted in the reaction of bis(carbene complex) **60** with cyclopentadiene (Scheme 8).[40] The acyl analogs of both aminocarbene complexes and alkoxycarbene complexes are more activated for the Diels–Alder reactions. The reaction of acetoxycarbene **62** and 2-silyloxydienes afforded bicyclo[4.1.0]heptane derivatives (e.g., **65**) in a process involving Diels–Alder reaction followed by intramolecular C–H insertion, which occurs in competition with direct cyclopropanation.[41] Diverse functionality has been demonstrated for the carbene ligand, including α-alkoxyethenylcarbene complexes.[42] Use of the parent ethynylcarbene complex in the Diels–Alder reaction with cyclopentadiene has also been demonstrated.[43] Although most of the examples employ chromium and tungsten carbene complexes, examples using iron–carbene complexes (e.g., **66**) have also been demonstrated.[44] In some cases, the product vinylcarbene complexes directly afford the ketene complexes (e.g., **68**). In many cases, an initial Diels–Alder reaction is followed up by another process employing the carbene complex functionality; examples of these processes are depicted in a future section.

A diverse array of stereoselective Diels–Alder reactions have been demonstrated for carbene complexes. The use of chiral auxiliaries to effect relative asymmetric induction in Fischer carbene complex reactions has been reviewed.[45] A variety of *exo*-selective Diels–Alder reactions of aminocarbene–tungsten complexes were demonstrated (Scheme 9).[46,47] The *exo*-selectivity derives from steric inhibitions in the approach of the diene from the endo direction. The simple aminocarbene complexes (e.g., **69**) were reactive only with the most reactive dienes, and only the E rotamer was reactive. The *N*-acyl complexes (e.g., **72**) were far more reactive. This reaction can also be conducted asymmetrically if a chiral auxiliary is present on the heteroatom substituent. Moderately diastereoselective Diels–Alder reactions were observed using chiral alkynylcarbene complexes (e.g., **74**).[48] Diastereoselective Diels–Alder reactions were also reported for chiral α,β-unsaturated carbene complex **77**.[49] Stereoselective Diels–Alder reactions were reported for cyclic carbene complexes featuring an *exo*-methylene group and a carbohydrate substituent.[50]



Scheme 8

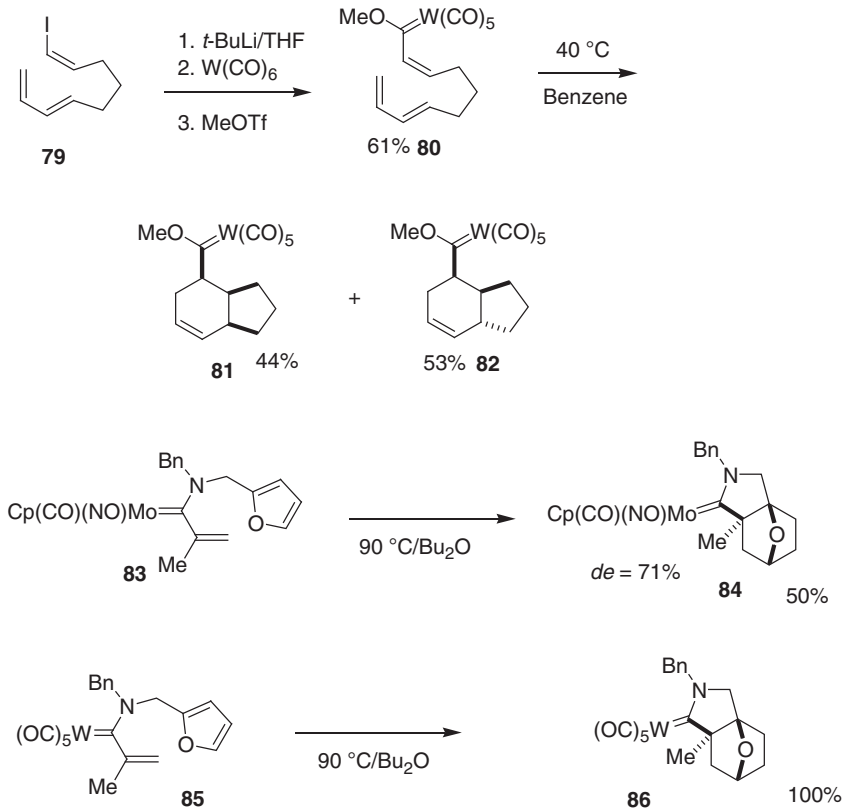


Scheme 9

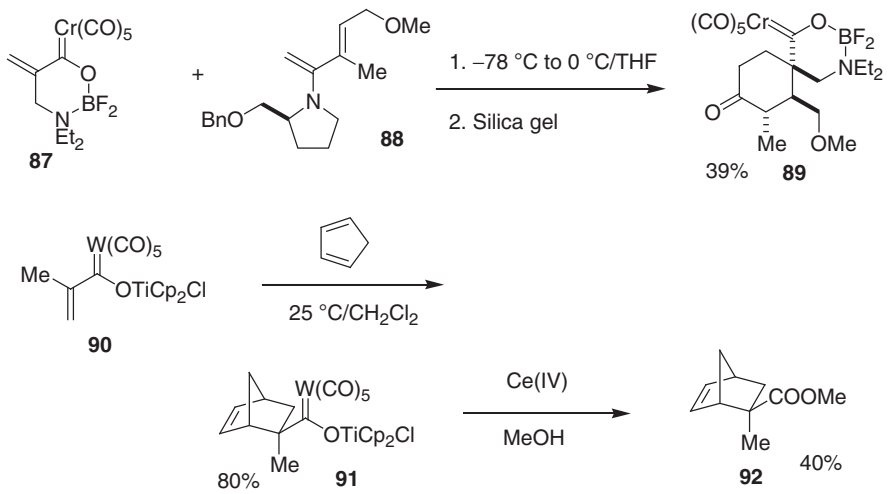
Several examples of intramolecular Diels–Alder reactions involving carbene complexes were also demonstrated (Scheme 10).[51] Carbene complexes containing triene functionality (e.g., **80**) were prepared using the Fischer route and cyclized on mild thermolysis to afford a mixture of *exo* (**82**) and *endo* (**81**) isomers. Chiral-at-molybdenum α,β-unsaturated carbene complexes (e.g., **83**) were prepared and their intramolecular Diels–Alder reactions with appended furan rings examined.[52] A comparison with analogous achiral tungsten– and manganese–carbene complexes and simple ester analogs was also conducted. The diastereoselectivity in the Diels–Alder step was moderate; however, it was better than that observed for achiral-at-metal carbene complexes featuring chiral nitrogen substituents. The molybdenum complexes were less reactive than the $(CO)_5$W- and $Cp(CO)_2$Mn-complexes and provided the lowest yields of Diels–Alder products.

Several examples that involve bimetallic carbene complexes have also been reported (Scheme 11). Use of these complexes is advantageous in that the alkylation step of carbene complex synthesis can be avoided. The reaction of cyclic boryloxycarbene complexes (e.g., **87**) with various dienes afforded the Diels–Alder products under very mild conditions.[53] Use of chiral dienes led to the cycloadducts with a high degree of enantioselectivity. The reaction of titanium acylate α,β-unsaturated carbene complexes (e.g., **90**) and dienes was also *exo*-selective.[54]

Several examples of inverse electron-demand Diels–Alder reactions using dienylcarbene complexes were reported (Scheme 12). A net [3 + 3]-cycloaddition of alkynylcarbene complex **93** and 1,3-diketones led to pyranylidene complexes (**94**), which then undergo Diels–Alder reaction with electron-rich alkenes.[55] Several pyranylidene complexes (**101**) were prepared through the reaction of enyne-carbonyl derivatives (e.g., **97** and **98**) with Group 6 metal pentacarbonyl sources. The intermediate pyranylidene complexes undergo reaction with both electron-rich and electron-deficient dienophiles.[56] Diels–Alder reaction of **101** with electron-deficient acetylenes followed by loss of tungsten hexacarbonyl afforded highly substituted aromatic rings



Scheme 10

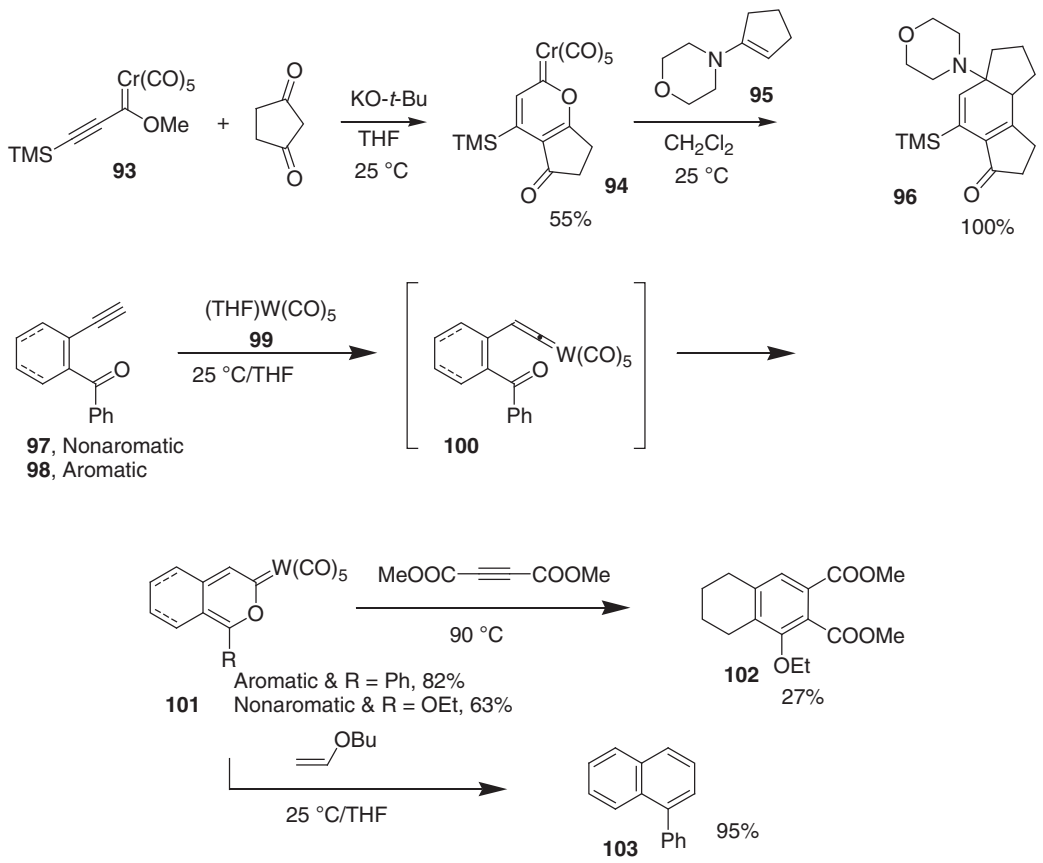


Scheme 11

(e.g., **102**). An analogous reaction process was reported for *o*-ethynylbenzoates and phenylketone analogs.[57] The resulting *o*-quinoidal systems underwent Diels–Alder reactions with enamines and enol ethers to afford naphthalene ring systems.

5.25.2.5 Michael Addition to α,β-Unsaturated Carbene Complexes

Many examples of simple and complex reaction processes initiated by nucleophilic addition to an α,β-unsaturated carbene complex have been documented. Due to the superior electron-withdrawing ability of a carbene complex functionality, this process typically proceeds under milder conditions than analogous Michael additions to purely organic carbonyl compounds. As in the case with purely organic compounds, Michael addition occurs in competition with direct nucleophilic addition to the carbene

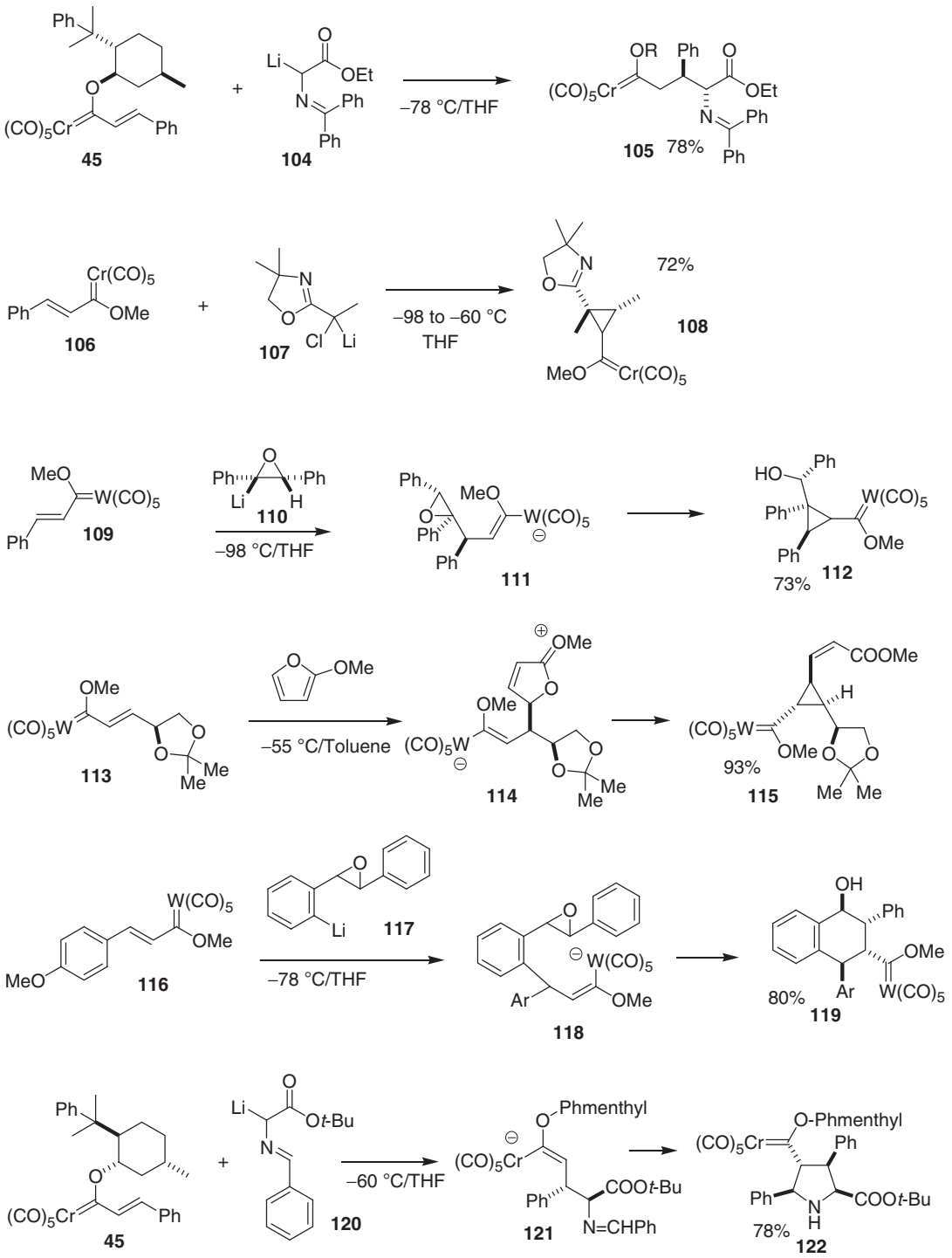


Scheme 12

carbon of these complexes. Many of the reported studies involve both types of processes. Many of the Michael additions to alkynylcarbene complexes are merely the first step in a tandem process involving the resulting alkenylcarbene complex. Examples of these processes will be discussed in a subsequent section.

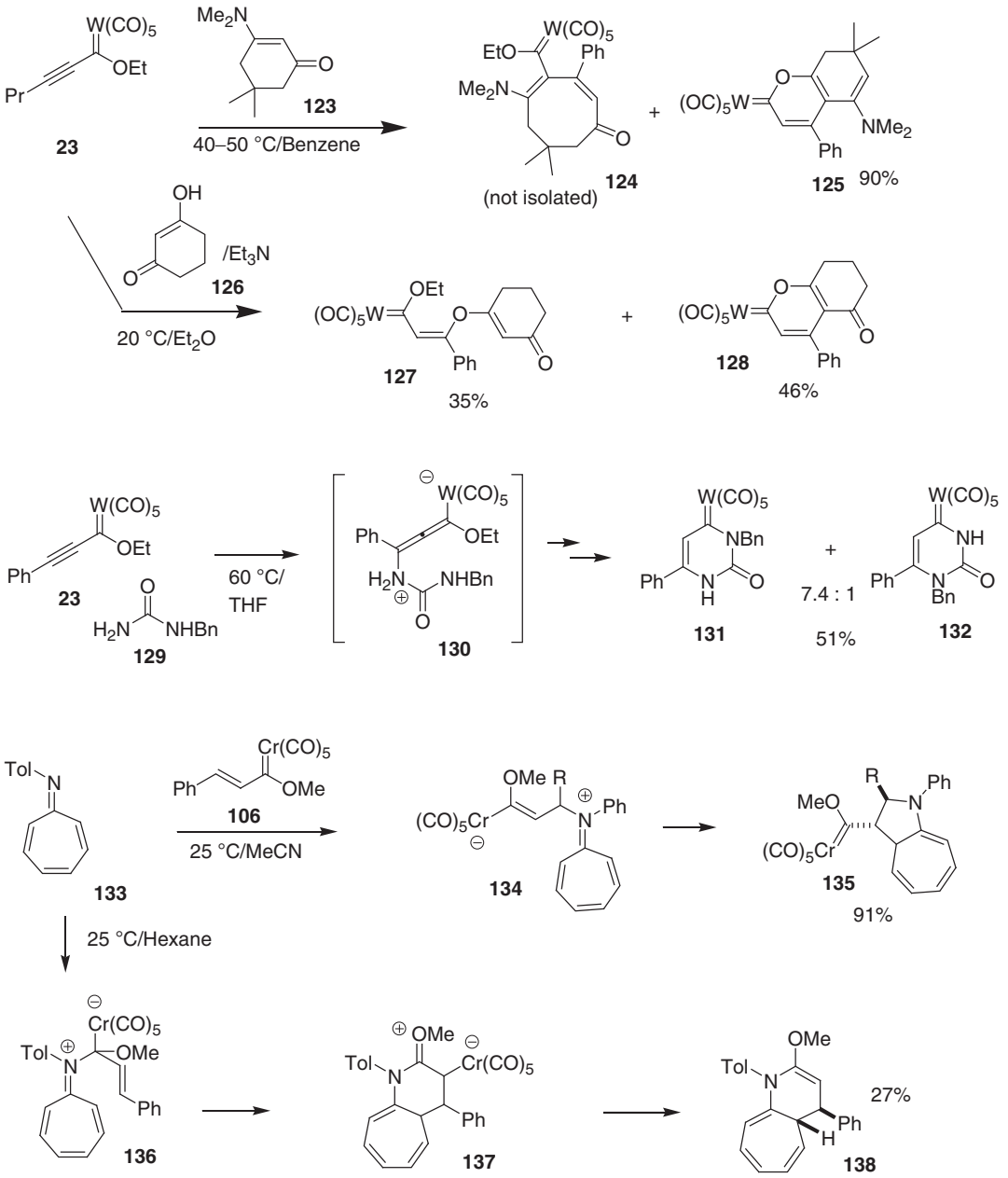
Several examples of simple Michael addition followed by electrophilic quench, resulting in more complex carbene complexes, have been documented. The Michael addition of glycine-derived carbanions (e.g., **104** and Scheme 13) to homochiral α,β-unsaturated alkoxycarbene complexes featuring a chiral alkoxy substituent (e.g., **45**) led to carbene complexes having multiple stereocenters (e.g., **105**) with a very high degree of stereoselectivity.[58] Reactions involving diphenylmethylidene-protected amines were highly selective for formation of the antidiastereomer, whereas reactions involving dibenzyl-protected or disilyl-protected nitrogens were selective for formation of the *syn* diastereomer. In all cases involving the 8-phenylmenthyl chiral auxiliary, the addition was completely face selective. The reaction of organolithium reagents to furyl menthyloxycarbene complexes afforded Michael addition products with a moderate degree of diastereoselectivity.[59] Cyclopropylcarbene–chromium complexes (e.g., **108**) are produced from the coupling of α,β-unsaturated chromium carbene complexes (e.g., **106**) and lithiated α-chloroiminoesters (e.g., **107**).[60] The reaction involves the Michael addition to the carbene complex followed by intramolecular S_N2 reaction. Cyclopropylcarbene tungsten complexes were prepared by Michael addition of lithiated epoxides (e.g., **110**)[61] or epoxide-imin-others to α,β-unsaturated tungsten complexes.[62] Synthesis of chiral cyclopropylcarbene complexes through Michael addition of iodomethyllithium to chiral and enantiomerically pure α,β-unsaturated carbene complexes has also been demonstrated.[63] A novel cyclopropanation reaction was observed in the coupling of chiral α,β-unsaturated tungsten carbene complexes (e.g., **113**) with methoxyfuran, leading to alkenylcyclopropylcarbene complexes (e.g., **115**).[64] A mechanism involving Michael addition to afford a zwitterionic intermediate (**114**) followed by intramolecular S_N2 reaction on the oxonium ion intermediate was proposed. The overall process was highly stereoselective. A net [4 + 2]-cycloaddition reaction was observed in the coupling of *o*-lithiated stilbene oxides (e.g., **117**) with α,β-unsaturated carbene complexes (e.g., **116**).[65] A mechanism involving Michael addition to form intermediate **118**, followed by intramolecular S_N2 reaction at the epoxide in a 6-*endo* fashion was proposed. Pyrrolidine derivatives (e.g., **122**) were prepared through the coupling of chiral and optically pure α,β-unsaturated carbene complexes (e.g., **45**) with imido-enolate derivatives (e.g., **120**).[66] A mechanism involving stereocontrolled Michael addition followed by addition of the resulting anion to the imine was proposed.

Several examples of net [3 + 3]-cycloaddition processes have been reported for alkynylcarbene complexes (Scheme 14). In general, these reactions proceed through Michael addition followed by proton transfer followed by an intramolecular addition to the carbene carbon. The coupling of alkynylcarbene complexes (e.g., **23**) with enaminones (e.g., **123**) led to either ring expanded



Scheme 13

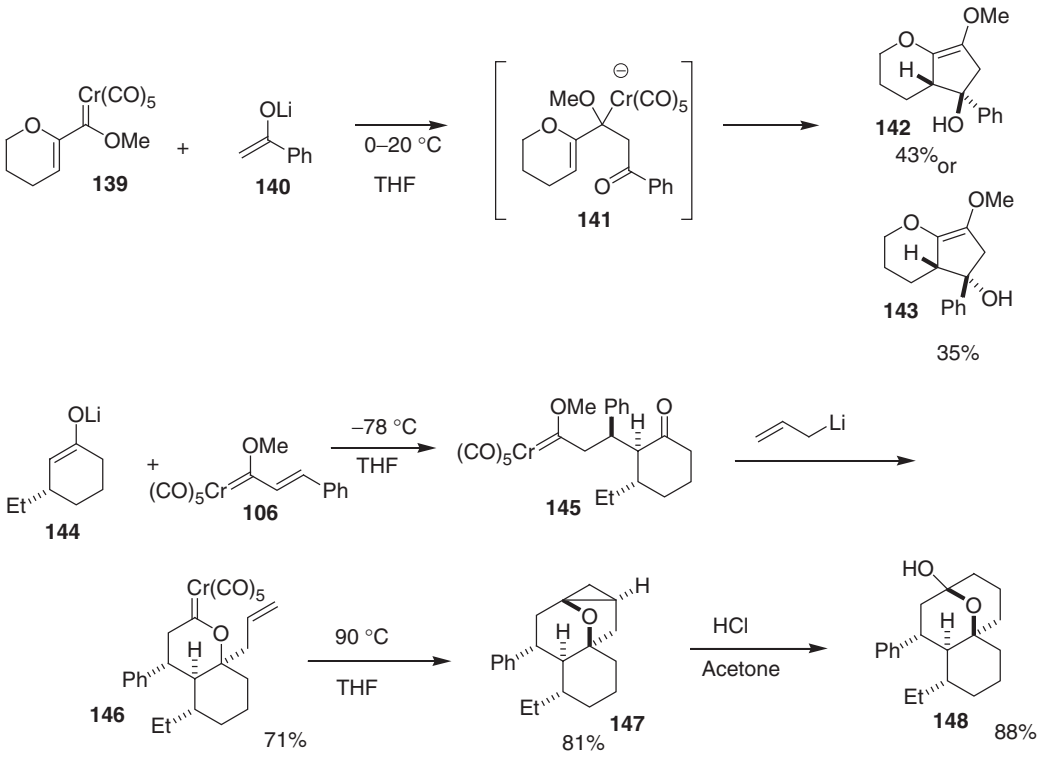
products (e.g., **124**) or cycloaddition products (e.g., **125**).[67] A mechanism involving [2 + 2]-cycloaddition followed by ring expansion was proposed for the formation of cyclooctadienone product **124**. For formation of [3 + 3]-cycloadduct **125**, Michael addition, followed by proton transfer, followed by intramolecular displacement of the ethoxy group was proposed. The analogous reaction with 1,3-diketone enolate led to either products resulting from Michael addition at O (e.g., **127**) or to C-addition products, which later cyclized to carbene complexes of general structure **128**. Several examples of the net cycloaddition of urea derivatives to alkylcarbene complexes leading to uracil-like systems, which form via Michael addition followed by intramolecular heteroatom exchange at the carbene carbon, have been demonstrated.[68,69] Net competitive [8 + 3]- and [8 + 2]-cycloaddition processes were observed in the coupling of alkynylcarbene complexes and aza-heptafulvenes (e.g., **133**).[70,71] Carbene complexes



Scheme 14

that feature a five-membered heterocyclic or an alkene group in the β-position afforded exclusively [8 + 3]-cycloadducts regardless of the solvent employed. The proposed mechanism for the [8 + 2]-cycloaddition involves Michael addition followed by ring closure of the zwitterion (**134**). In the case of [8 + 3]-cycloaddition, direct addition to the carbene carbon followed by intramolecular attack on the ring by the allylchromium intermediate establishes the ring system (**137**), and subsequent loss of chromium affords the final product (**138**). Both processes were highly stereoselective. A variety of carbene complex demetallation reactions were demonstrated for the [8 + 2]-cycloadducts. The reaction of various primary diamines with alkynylcarbene tungsten and chromium complexes leads to cyclic products from Michael addition and carbene carbon addition.[72]

In several cases, addition of an enolate in a Michael fashion or directly to the carbene carbon initiates a cascade process that results in cyclic products (Scheme 15). Cyclopentenols (e.g., **143**) arise through the coupling of α,β-unsaturated carbene complexes (e.g., **139**) with enolates (e.g., **140**).[73] A mechanism involving 1,2-addition followed by nucleophilic addition to the carbonyl group with allylic rearrangement was proposed. The stereochemistry of the reaction was controlled by choice of solvent (ether vs. THF vs. coordinating additives). A novel eight-membered ring synthesis (e.g., formation of **148** from carbene complex **106**) results from the one-pot sequential coupling of a lithium enolate, α,β-unsaturated carbene complex, and an allylic Grignard reagent.[74] This reaction sequence proceeds through Michael addition of a silyl enol ether to the carbene complex, followed by



Scheme 15

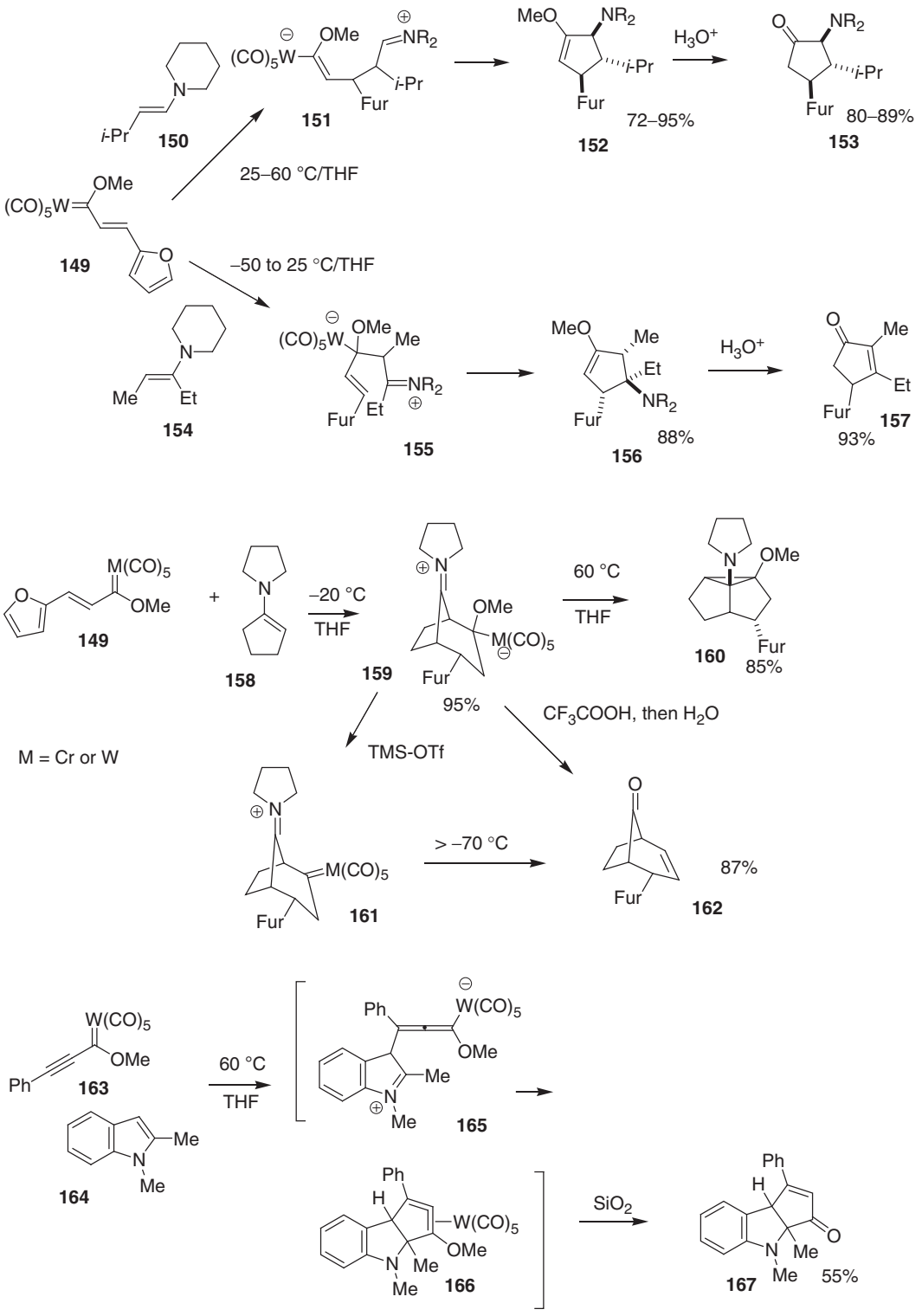
allylation of the ketone group in Michael adduct **145** to form **146** after alkoxide metathesis, followed by intramolecular cyclopropanation and ring opening.

Several cascade processes were initiated through the Michael addition of enamines to α,β-unsaturated carbene complexes (Scheme 16). Cyclopentannulation reactions were reported for the coupling of alkenylcarbene complexes (e.g., **149**) with enamines.[75] Different types of cyclopentenones were obtained, depending on whether the imine is derived from an aldehyde (e.g., **150**) or a ketone (e.g., **154**). Aldehyde-derived imine **150** led to cyclopentenone **153** through Michael addition of the imine followed by attack of the vinyl anionic equivalent **151** at the iminium salt followed by hydrolysis. Ketone-derived imine **154** afforded cyclopentenone **157** through reaction of the imine at the carbene carbon followed by intramolecular addition of the resulting allyl-tungsten species (**156**) to the iminium salt, followed by hydrolysis. Both processes occurred with a high degree of diastereoselectivity, and homochiral products were produced if chiral enamines were employed. Coupling of α,β-unsaturated carbene complexes with cyclic enamines (e.g., **158**) led to bicyclic structures (e.g., **161** and **162**).[76,77] Initially, zwitterionic compound **159** forms through Michael addition, followed by proton transfer to afford an enamine–carbene complex, followed by 1,2-addition. Thermolysis of **159** leads to tricyclic compound **160**, whereas reaction with trifluoroacetic acid leads to bicyclic compound **162**. Alkynylcarbene complexes (e.g., **163**) are highly useful reagents for the annulation of three carbons onto an enamine or an indole ring (e.g., **164**).[78] The mechanism involves Michael addition followed by ring closure to a cyclic allene complex (**165**), which affords the final product (**167**) after protonation/hydrolysis on silica gel. Enantiomerically pure products were obtained if the carbene complex contains a chiral alkoxide group. Michael addition of enamine species to alkynylcarbene complexes was also a key event in a novel synthesis of dihydropyridine derivatives.[79]

5.25.2.6 Addition to Alkynylcarbene Complexes Followed by Electrocyclization

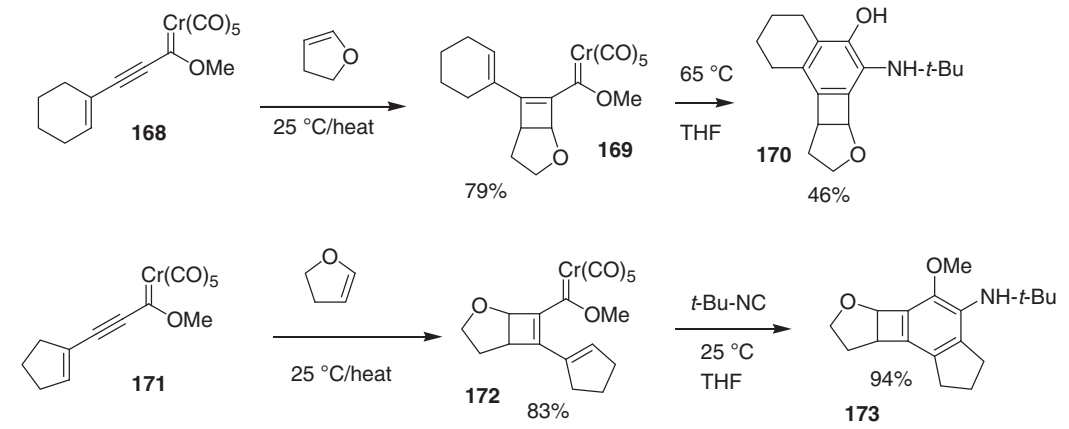
A major application of alkynylcarbene complex involves their conversion to an alkenylcarbene complex through cycloaddition or Michael addition followed by electrocyclization with or without CO or isonitrile insertion. All of the previously mentioned reactions in this section have been utilized in this manner. This research area has been reviewed.[80]

Many examples of [2 + 2]-cycloaddition involving an alkynylcarbene complex and an electron-rich alkene followed by cyclization of the resulting alkenylcarbene complex have been documented (Scheme 17). The coupling of cyclic enol ethers with enynylcarbene complexes (e.g., **168**) afforded cyclobutenylcarbene complexes (e.g., **169**), which underwent cyclization in refluxing THF to afford the corresponding benzocyclobutane derivatives (e.g., **170**).[81] Treatment of the cyclobutylcarbene complexes with isocyanides led to aniline derivatives (e.g., **173**) in a process involving formation of the conjugated ketenimines followed by electrocyclization.

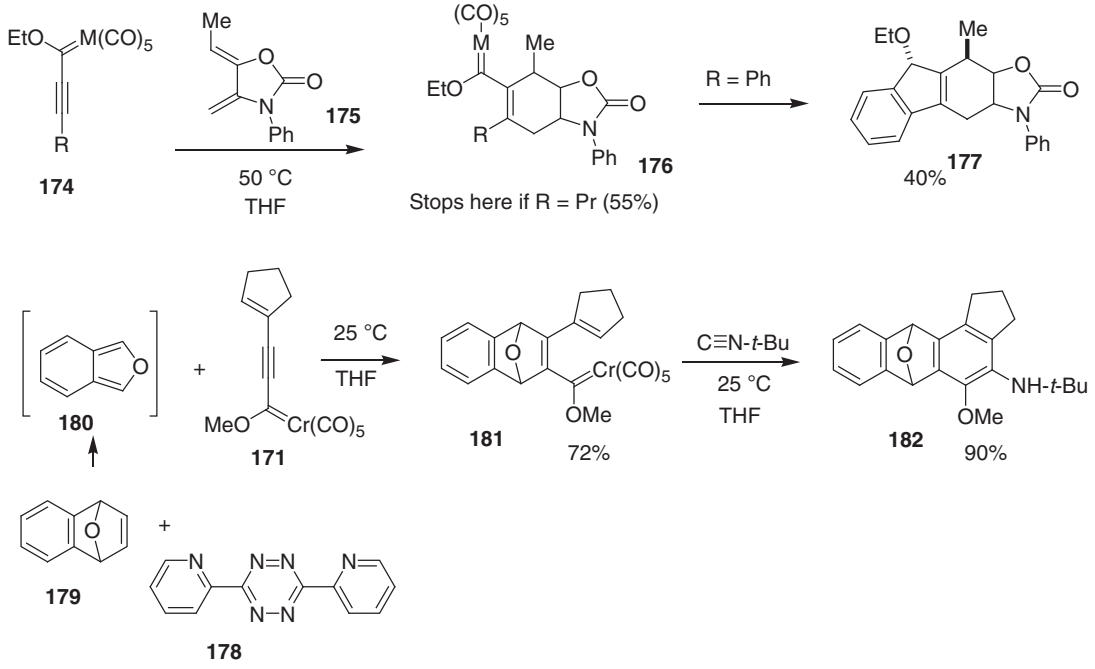


Scheme 16

In several cases, the initial Diels–Alder adducts undergo secondary cyclization processes initiated by the carbene complex functionality (Scheme 18). The reaction of alkynylcarbene complexes of general structure **174** with dienes (e.g., **175**) proceeds through an initial Diels–Alder reaction to afford an alkenylcarbene complex (e.g., **176**).[82] In the case of arylethynylcarbene complexes, tetracyclic compounds (e.g., **177**) were produced in a process involving tandem Diels–Alder reaction followed by cyclization of the alkenylphenylcarbene complex. Diels–Alder reactions were reported for enynylcarbene complexes (e.g., **171**)



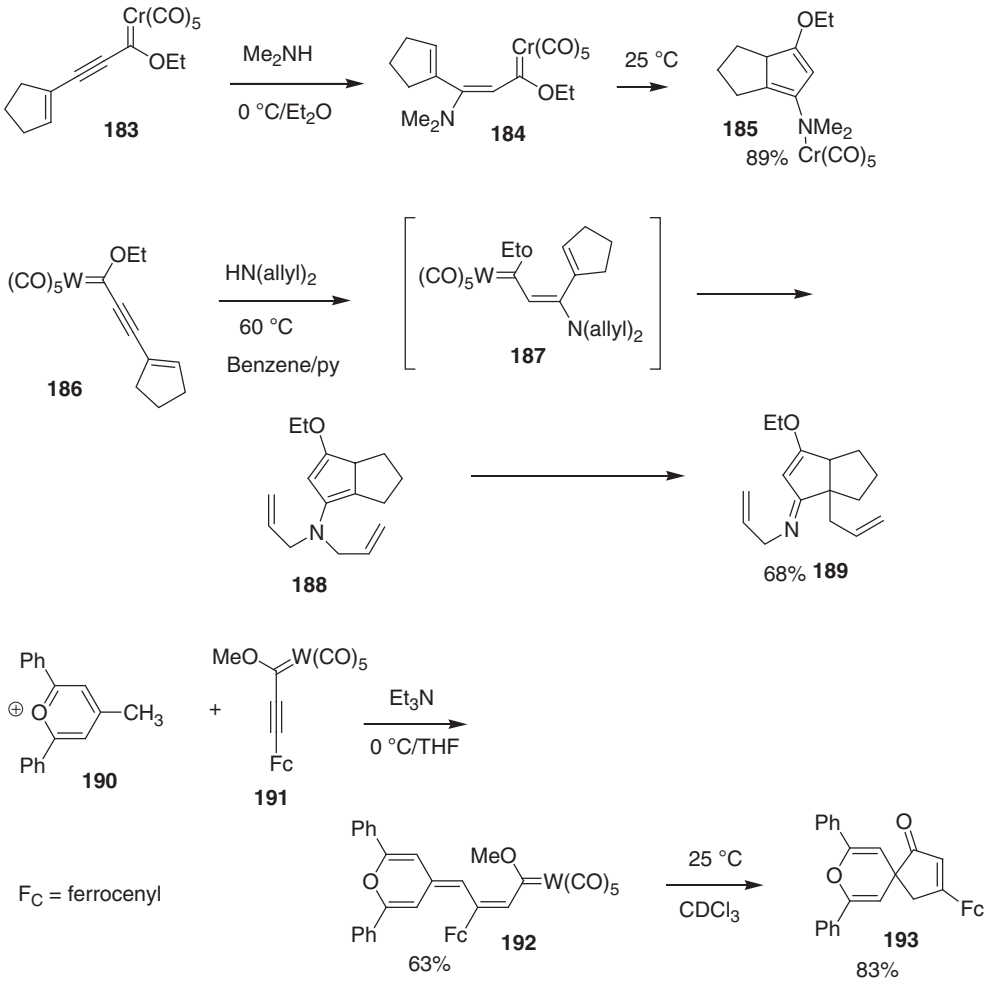
Scheme 17



Scheme 18

and *in situ*-generated isobenzofuran derivatives (e.g., **180**).[83] The reaction of adducts (**181**) with isocyanides or photolysis in the presence of CO leads to the formation of oxygen-bridged anthracene derivatives (e.g., **182**). Tandem Diels–Alder-cyclopentannulation reactions were reported in the coupling of phenylethynylcarbene complexes with *o*-quinonedimethane precursors.[84] The Diels–Alder adducts of pentamethylcyclopentadiene and alkynylcarbene complexes undergo a secondary benzannulation reaction which was observed when the reaction was conducted at 50 °C.[85]

Several examples of the preparation of cyclopentene derivatives through Michael addition of various nucleophiles to enynylcarbene complexes have been reported (Scheme 19). In this reaction, the Michael addition process leads to a dienylcarbene complex system that subsequently undergoes a cyclization process to afford the alkoxycyclopentadiene, which affords the cyclopentone derivatives after hydrolysis. Michael addition of amines to enynylcarbene complexes (e.g., **183**) afforded dienylcarbene complexes (e.g., **184**), which cyclized at room temperature without CO insertion to provide cyclopentadiene derivatives (e.g., **185**).[86] Cyclopentannulation reactions were reported for the coupling of enynylcarbene complexes (e.g., **186**) with allylamines.[87] In these cases, after cyclopentannulation (forming **188**), an amino-Claisen rearrangement occurs to give the C-allylated products (e.g., **189**). Reaction of enynylcarbene complexes with β-aminoenones also proceeded via Michael addition followed by cyclization to the expected cyclopentadiene derivatives.[88] Similar cyclopentannulation reactions were reported in the coupling of enynylcarbene complexes with sulfur nucleophiles.[89] A net cycloaddition process leading to spirocyclic cyclopentenones (e.g., **193**) was observed in the base-catalyzed reaction of methylpyrilium salts (e.g., **190**) and ferrocenyalkynylcarbene

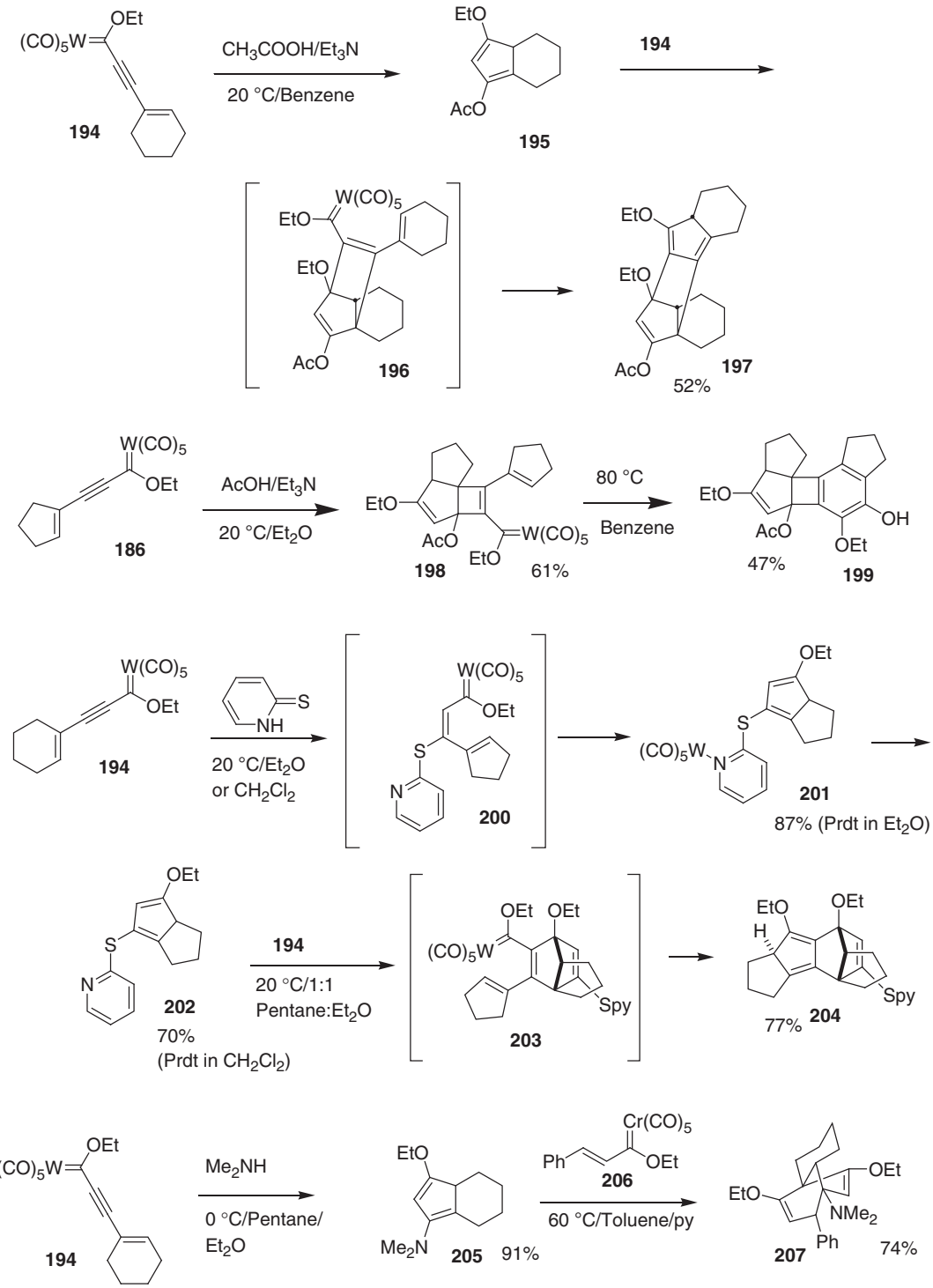


Scheme 19

complexes (e.g., **191**).[90] A mechanism that involves Michael addition to afford dienylcarbene complex **192** followed by cyclization was proposed. The dienylcarbene complex could be observed at low temperature. In some cases, a secondary cleavage of the heterocyclic ring occurred under the reaction conditions.

Many examples that involve the incorporation of one or more carbene units or diene units that result in the rapid construction of complex architectures were also reported (Scheme 20). Addition of carboxylate anions to enynylcarbene complexes led to the expected cyclopentadiene derivatives (e.g., **195**); however, these very rapidly underwent a Diels–Alder reaction with the starting carbene complex to afford complex cyclopentadienes (e.g., **197**) after secondary cyclization.[91] The resulting complexes can undergo additional iterations of this reaction to form rather complex structures. A net dimerization product (**199**) was formed in the coupling of enynylcarbene complex **186** with acetate ion.[92] Michael addition followed by cyclization affords a cyclopentadiene (**198**), which subsequently undergoes a [2 + 2]-cycloaddition with a second mole of carbene. Cyclization of cyclobutene derivative **198** then leads to the observed benzannulation product **199**. Nucleophilic addition of thioamides to enynylcarbene complexes (e.g., **186**) led to the $\alpha,\beta,\gamma,\delta$-unsaturated carbene complex (e.g., **200**), which rapidly cyclized to a cyclopentadiene derivative (e.g., **201**).[93] After decomplexation of tungsten to afford **202**, an additional mole of enynylcarbene complex could be incorporated through Diels–Alder reaction followed by cyclization to afford a complex ring system exhibited by **204**. Capture by alkenylcarbene complex dienophiles also has precedent. Michael addition and thermolysis of enynylcarbene complexes (e.g., **194**) also afforded cyclopentannulation products, which underwent Diels–Alder reactions when thermolysis was performed in the presence of a variety of dienophiles.[94,95] Use of alkenylcarbene complex **206** led to net [4 + 3]-cycloaddition products (e.g., **207**).

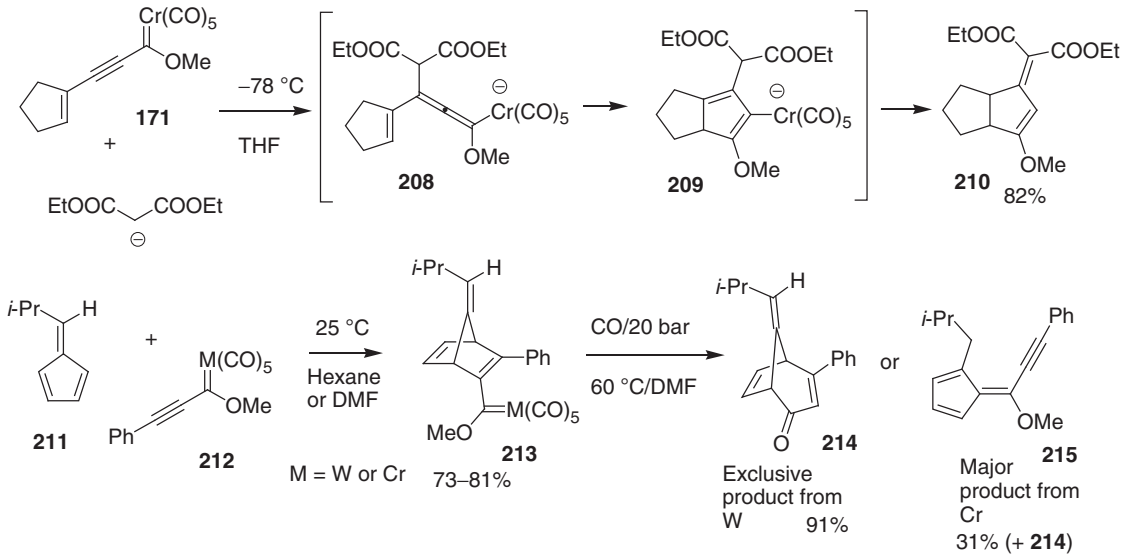
The products from addition to the triple bond of alkynylcarbene complexes were successfully captured by other methods. The addition of stabilized carbanions (e.g., malonate anion) to enynylcarbene–chromium complexes (e.g., **171**; Scheme 21) led to cyclized compounds (e.g., **210**).[96] A mechanism involving Michael addition followed by cyclization with chromium migration, followed by protonolysis of the C–Cr bond was proposed. Diels–Alder reactions were reported for alkynylcarbene complexes (e.g., **212**) and fulvene derivatives (e.g., **211**).[97] The Diels–Alder adducts (**213**) are produced at room temperature; however, heating transforms the Diels–Alder adducts into either of the compounds **214** or **215**. The distribution of the products was highly



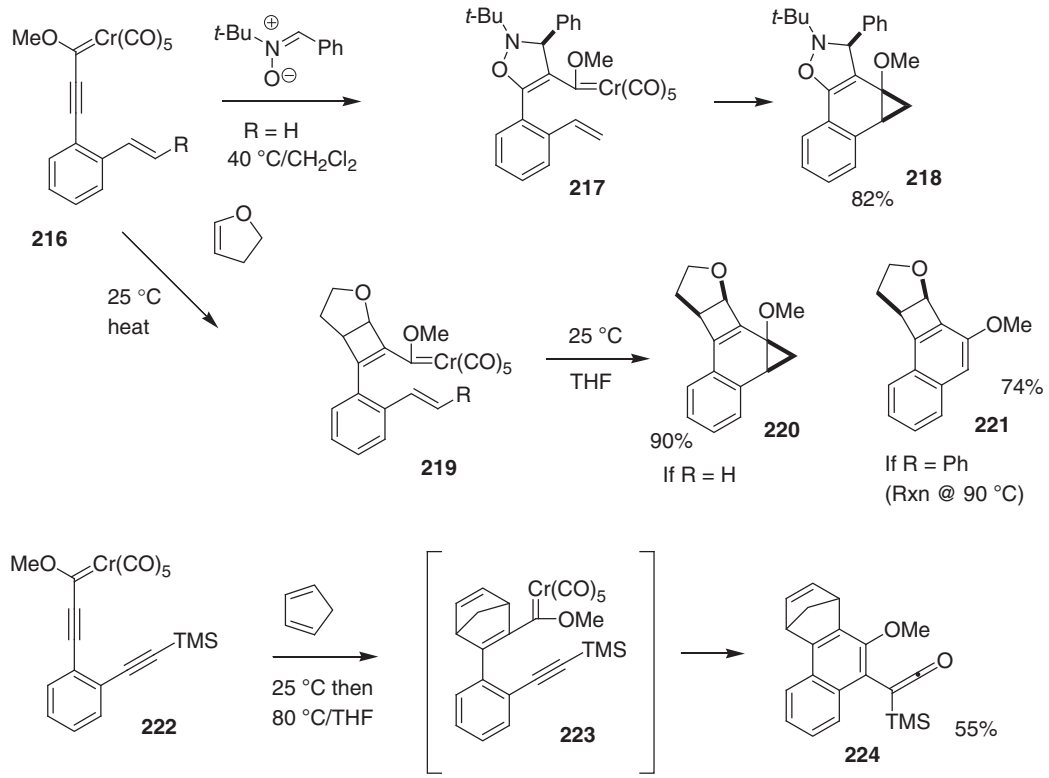
Scheme 20

dependent on the metal. The cyclopentadienes (**215**) were formed only when chromium was employed, although tungsten carbene complexes led exclusively to bicyclo[3.2.1]octadienone systems (**214**).

Alkynylcarbene complexes that feature additional conjugating substituents also undergo additions to the triple bond followed by capture of the resulting alkenylcarbene complex (Scheme 22). Reaction of *o*-styrylalkynylcarbene complexes (e.g., **216**) with various species that add to alkynylcarbene complexes (e.g., nitrones, enol ethers, or dienes) was reported.[98] The intermediate highly conjugated carbene complex (e.g., **217** and **219**) was successfully captured through cyclopropanation (e.g., formation of **212** and **214**) and olefin metathesis (e.g., formation of **221**). A tandem cycloaddition-alkyne insertion sequence was also



Scheme 21



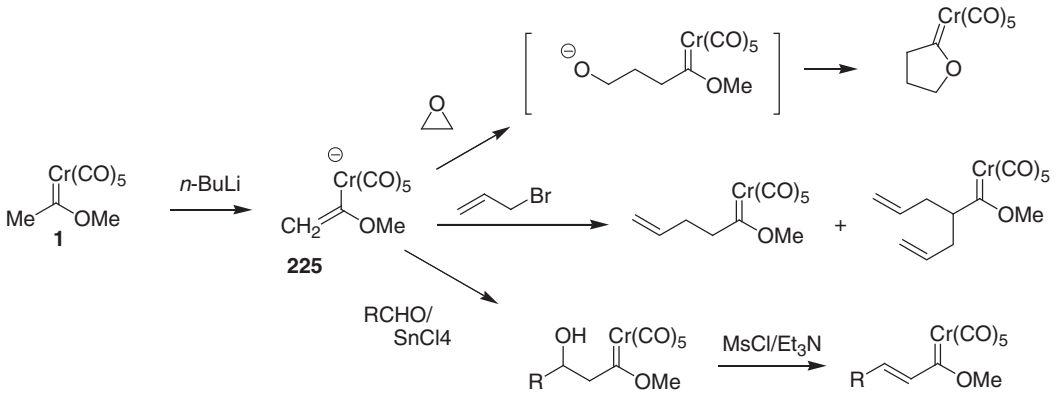
Scheme 22

demonstrated.[99] In this case, a conjugated enediyne–carbene complex (e.g., **222**) undergoes cycloaddition to afford an alkenyl-carbene complex (e.g., **223**), which subsequently undergoes intramolecular alkyne–carbene insertion reaction. In cases of trimethylsilylalkynes, a stable ketene (e.g., **224**) could be isolated. In other cases, ketene trapping products were obtained.

5.25.2.7 Anions of the Carbene Ligand – Reaction with C–X Sigma Bonds

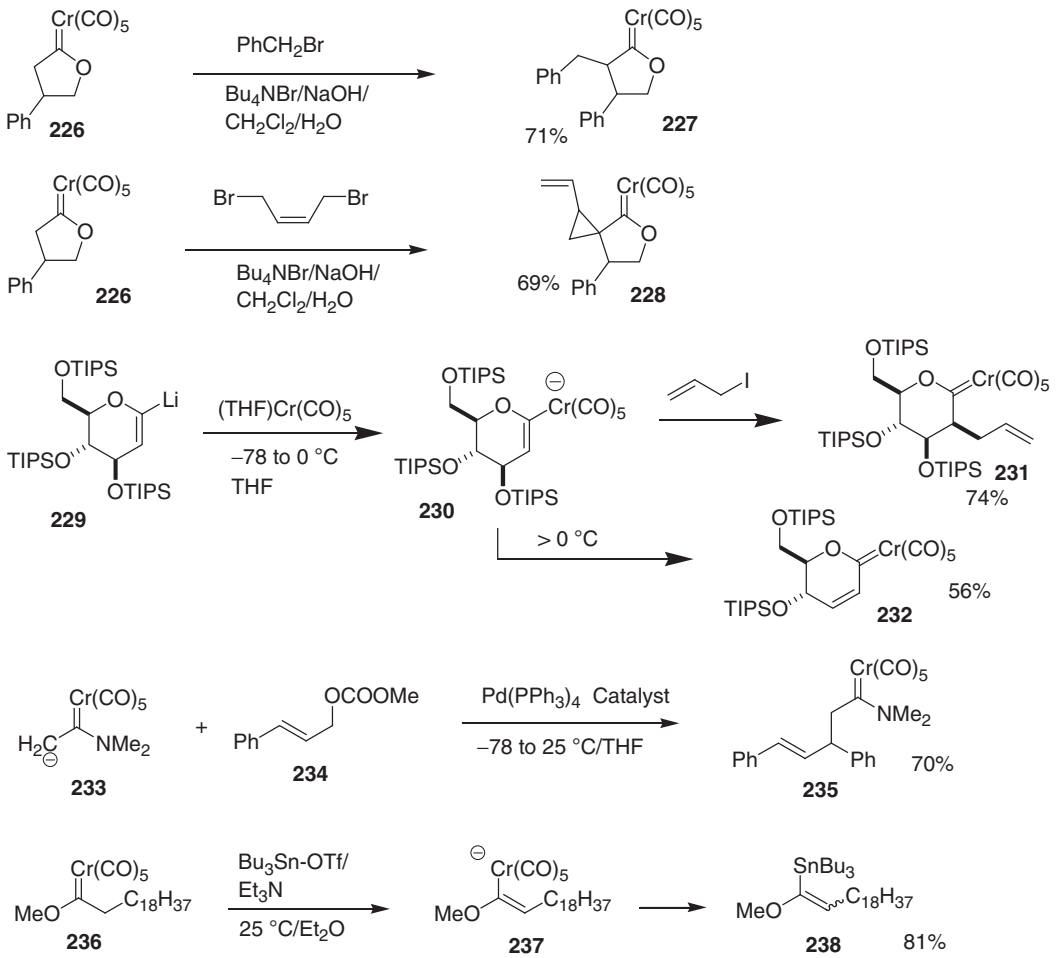
Fischer carbene complexes substantially increase the acidity of α-hydrogens. As such, the compounds are easily deprotonated relative to analogous esters and amides; however, the resulting anions tend to be comparatively unreactive except to the most reactive of electrophiles.

Several examples of deprotonation followed by alkylation with alkyl halides were reported in the previous edition of Comprehensive Organic Synthesis. The coupling of allylic, benzylic, and α-carbonyl halides[100] with the pentacarbonyl derivatives is well-documented; however, dialkylation is sometimes a problem in these reactions. Representative classical transformations of carbene complex-derived anions (e.g., **225**) are depicted in Scheme 23.



Scheme 23

Several examples have been reported where carbene complexes react with carbon atom and heteroatom electrophiles to afford substituted carbene complexes (Scheme 24). Biphasic alkylation in the presence of phase transfer catalysts often leads to alkylated

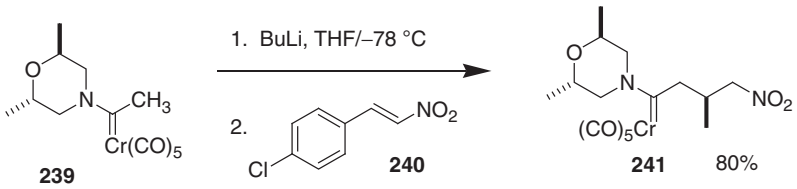


Scheme 24

carbene complexes in higher yields than conventional monophasic alkylation procedures. The reaction of carbene complexes that contain α-hydrogens with allylic halides under phase transfer conditions led to alkylated carbene complexes (e.g., **227**).[101,102] The reaction employing 1,4-dibromo-2-alkenes led to cyclopropylcarbene complexes (e.g., **228**) in a double alkylation process. The alkylation reactions of hydrazinocarbene complexes were also explored and offer advantages for multiple alkylation reactions.[103] Carbene complex-stabilized anions (e.g., **230**) can be alternatively formed from the reaction of alkenyllithium reagents (e.g., **229**) with Group 6 metal pentacarbonyl sources.[104] Anions generated from glycals in this way were allylated with a high degree of diastereoselectivity in favor of the axial diastereomer (e.g., **231**). A β-elimination process resulting in unsaturated carbene complexes (e.g., **232**) was observed if anion **230** was allowed to warm above 0 °C. Successful palladium-catalyzed allylic alkylation was reported for carbanions derived from aminocarbene complexes (e.g., **233**).[105] Other electrophiles that have been successfully coupled to these types of carbanions include (1) polyene–metal complexes,[106] (2) phosphorus electrophiles,[107] and (3) sulfenylating agents.[108] Vinylstannanes (e.g., **238**) were prepared through deprotonation of alkoxycarbene complexes followed by quenching with tributyltin triflate.[109] In addition to the studies with alkoxy pentacarbonyl complexes, a variety of studies employing other types of carbene complexes have been documented. Treatment of carbene complex anions with iodinating agents leads to mixtures of alkenyl iodides and CO-inserted products.[110]

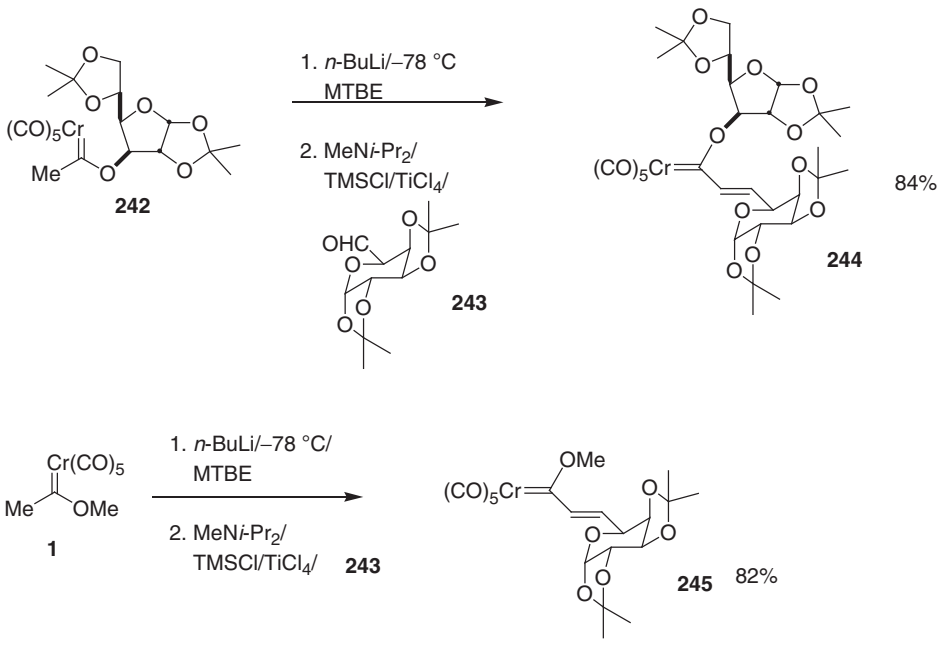
5.25.2.8 Anions of the Carbene Ligand – Reaction with C–X pi Bonds

Several examples of asymmetric Michael addition to nitro styrene derivatives were reported (Scheme 25). Reaction of chiral carbene complex-derived carbanions (e.g., anion from aminocarbene complex **239**) with nitro alkenes led to Michael addition products (e.g., **241**).[111] The addition proceeded with a moderate degree of diastereoselectivity, and was higher for nitrostyrene derivatives featuring an electron-withdrawing group and for Z nitrostyrenes. Diastereoselective Michael addition of a homochiral aminocarbene complex **239** with nitrostyrene derivative **240** was a key step in the asymmetric total synthesis of baclofen.[112]



Scheme 25

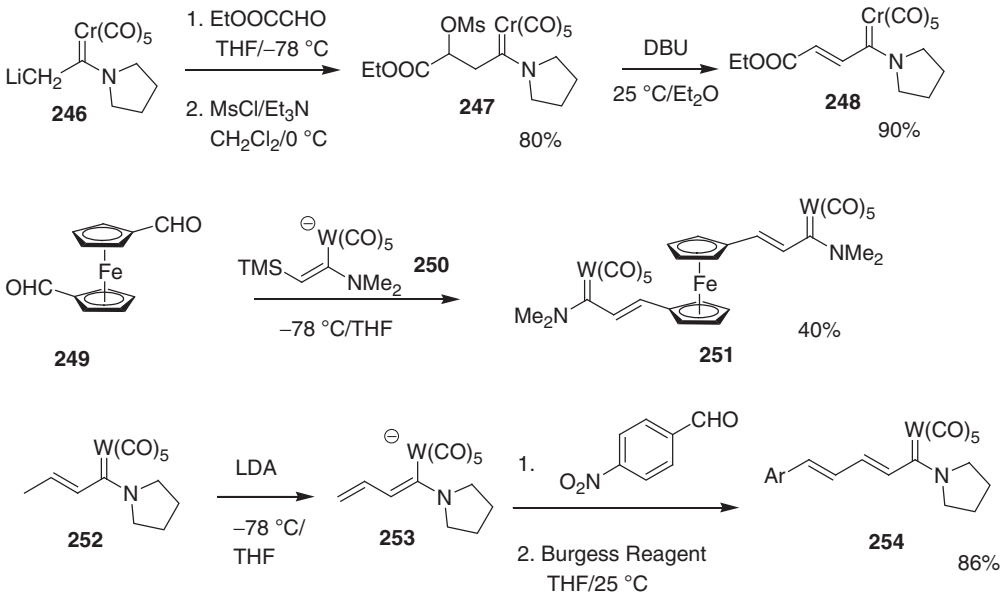
Numerous examples of the aldol condensation employing carbanions derived from alkoxycarbene complexes have been reported since the previous edition (Scheme 26). Since the carbene complex-stabilized anion is of limited reactivity, most of the



Scheme 26

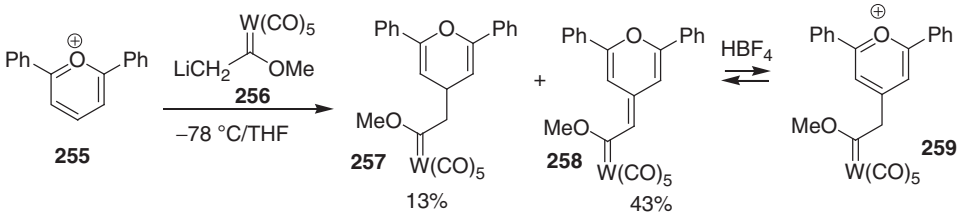
examples employ Lewis acid activators.[113,114] Carbene complex-linked carbohydrate derivatives (e.g., **244**) were prepared through the coupling of carbanions derived from carbohydrate-containing carbene complexes (e.g., **242**) with carbohydrate–aldehydes (e.g., **243**).[115] Related couplings using pyran-containing aldehydes and simple methylcarbene complexes led to aldol-like products (i.e., α,β-unsaturated carbene complexes).[116] Aldol-type reactions were also reported for simple methylcarbene complex **1** with various carbohydrate aldehydes[117] and other chiral aldehydes.[118]

Several examples of aldol reactions that involve aminocarbenes have been documented (Scheme 27). The reaction of aminocarbene–chromium complex-derived carbanion **246** and glyoxal ester, followed by methanesulfonyl chloride afforded the anticipated alkylated carbene complex **247**, which afforded the γ-oxo-α,β-unsaturated carbene complex **248** on base-induced elimination.[119] This aminocarbene complex underwent efficient benzannulation at 60 °C with a variety of alkynes. Hydrocarbon- and ferrocene-bridged carbene complexes (e.g., **251**) were prepared using the Peterson olefination involving dialdehydes (e.g., **249**) and anions derived from α-silylcarbene–tungsten complexes (**250**).[120] A carbene–aldol strategy was also employed for the synthesis of ϕ-ferrocenylhexatrienylcarbene–tungsten complexes from 5-ferrocenyl-2,4-pentadienal.[121] The coupling of hydrazinocarbene complex-stabilized anions with α,β-unsaturated carbonyl compounds and simple carbonyl compounds resulted in dienylcarbene complexes.[122] Dienylcarbene complexes (e.g., **254**) were prepared by γ-deprotonation of α,β-unsaturated carbene complexes (e.g., **252**), followed by treatment with an aromatic aldehyde and dehydration.[123]



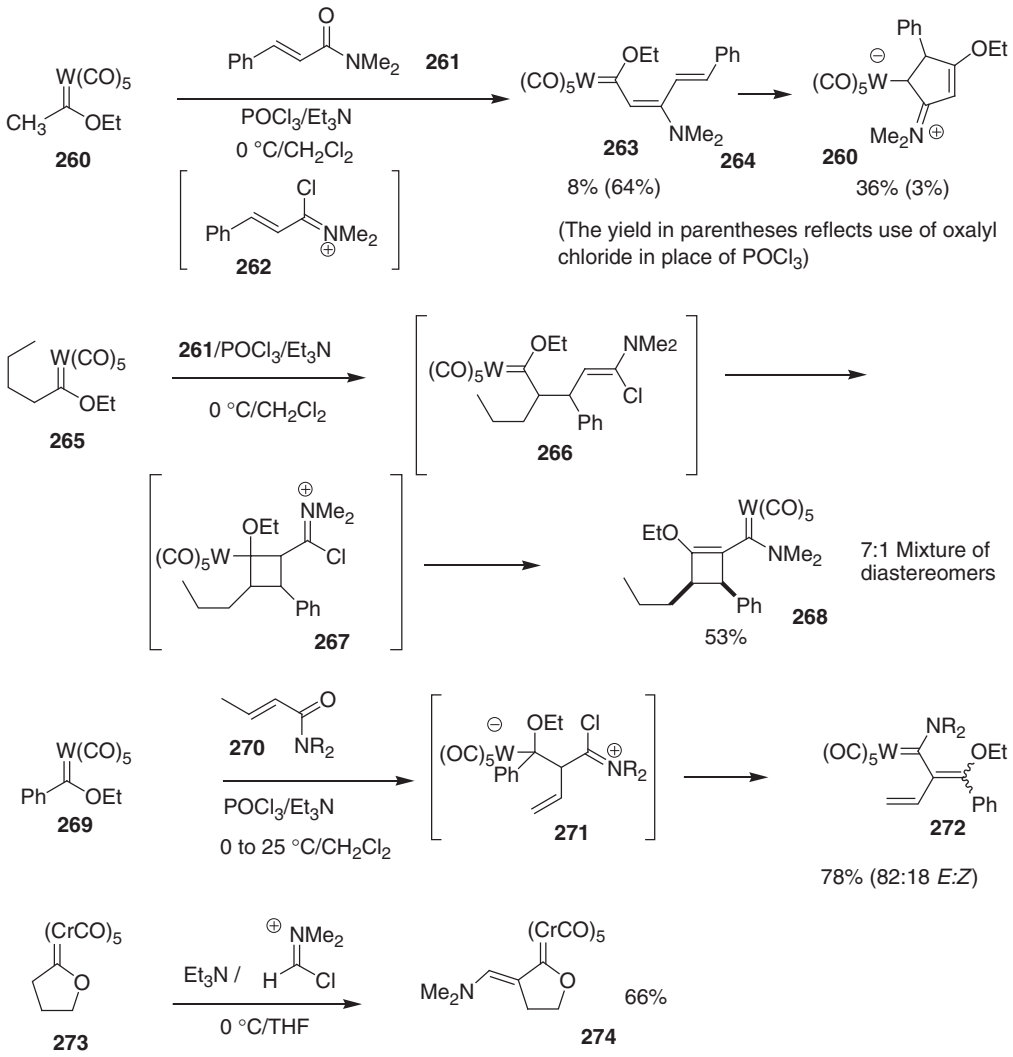
Scheme 27

A large number of reported aldol-type reactions feature pyrilium salts and result in the preparation of donor–acceptor molecules (Scheme 28). The coupling of carbene complex-derived carbanions (e.g., **256**) with pyrilium salts (e.g., **255**) afforded pyran derivatives (e.g., **257** and **258**) featuring a carbene complex-containing substituent in the 4-position.[124] The oxidation of the 4-alkylpyrone to the 4-alkylidenepyrone was induced by the pyrilium salt. Protonation of carbene complex **258** regenerated a pyrilium salt (**259**). Reactions using aminocarbene complexes generally led to compounds analogous to **258**. Additional examples that vary in metal, heteroatom, and length of conjugation spacers were also reported.[125–127]



Scheme 28

Several examples of the coupling of carbene complexes with amide-derived electrophiles have been reported (Scheme 29). The observed reaction pathway depends on the substitution pattern of the chloroiminium salt, and this coupling provides a variety of



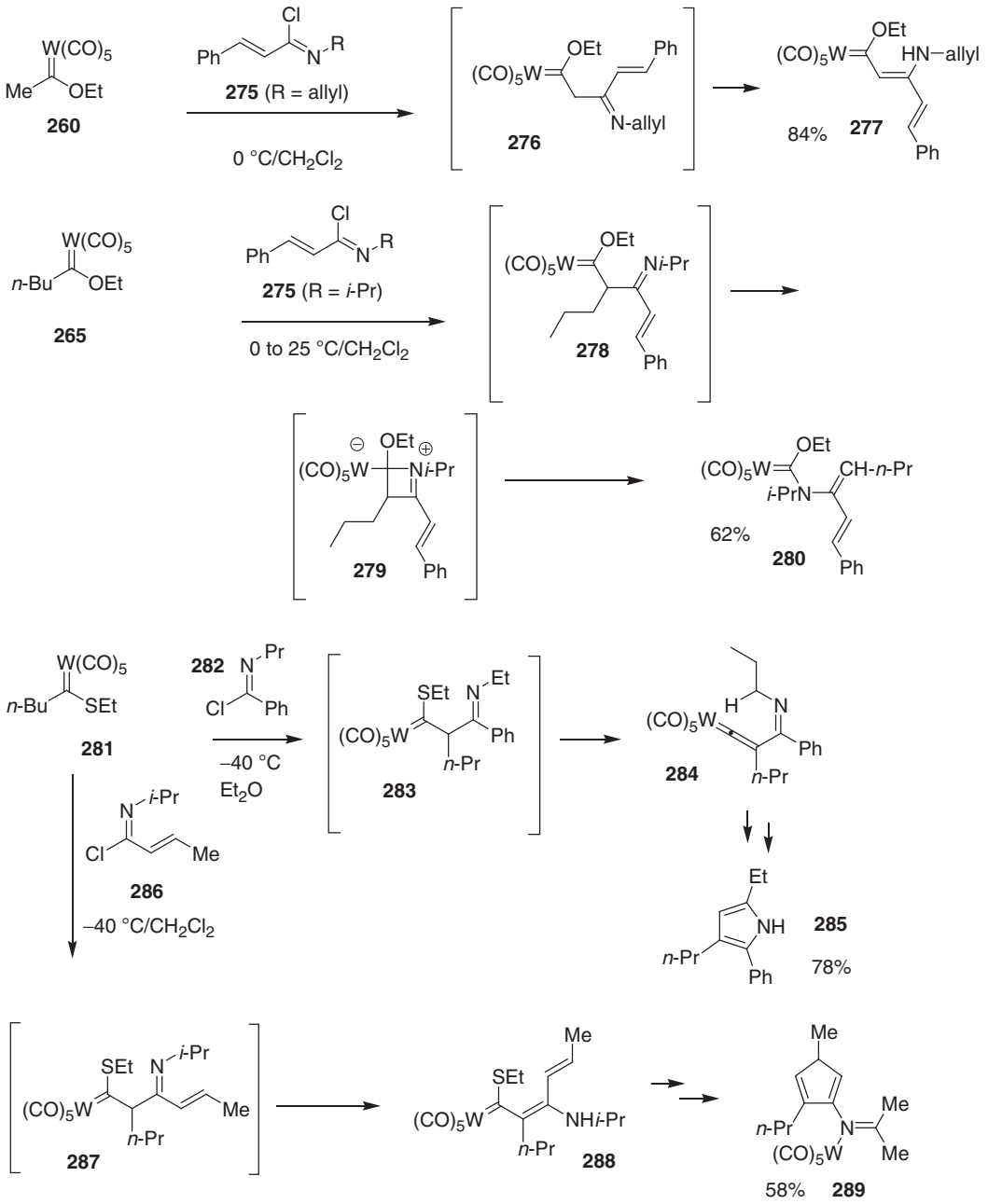
Scheme 29

different product types. Reaction of carbene complex-derived anions with *in situ*-generated chloroiminium salt derivatives initially affords mainly the β-aminocarbene complex (e.g., **263**) via 1,2-addition to the chloroiminium carbon.[128] The β-aminocarbene complex decomposes at room temperature to afford five-membered ring species (e.g., **264**). Higher homologs (e.g., butylcarbene complex **265**) afforded a four-membered ring derivative (e.g., **268**) in a process involving Michael addition followed by intramolecular reaction of the resulting enamine (**266**) with the carbene complex. The coupling of carbene complexes with α,β-unsaturated amides that feature an acidic γ-hydrogen (i.e., **270**) in the presence of $POCl_3$ led to dienylcarbene complexes (e.g., **272**) accompanied by the enol ether hydrolysis products.[129] The reaction of cyclic carbene complexes (e.g., **273**) with Villsmeyer reagents afforded the alkenylcarbene complex (e.g., **274**).[130] Condensation with β-aminoacrolein derivatives afforded dienylcarbene complexes. Analogs featuring additional conjugated alkenes were similarly prepared.

Analogous reaction of neutral iminoyl chlorides (e.g., **275**, Scheme 30) led to β-aminocarbene complexes (e.g., **277**) for the methylcarbene complexes and to dienylaminocarbene complexes (e.g., **280**) for higher homologs.[131] Formation of dienylaminocarbene complex **280** was proposed to occur through intramolecular nucleophilic addition of nitrogen to the carbene carbon followed by electrocyclic ring opening. Thiocarbene complexes (e.g., **281**) led to pyrroles (e.g., **285**) through formation of a vinylidene intermediate (**284**) followed by intramolecular hydrogen transfer and cyclization.[132] Related coupling with α,β-unsaturated iminoyl chlorides (e.g., **286**) afforded predominately the cyclopentadienimine (e.g., **289**) (and isomeric cyclopentadienes) after cyclization of the initially formed dienylcarbene complex (e.g., **288**).[133]

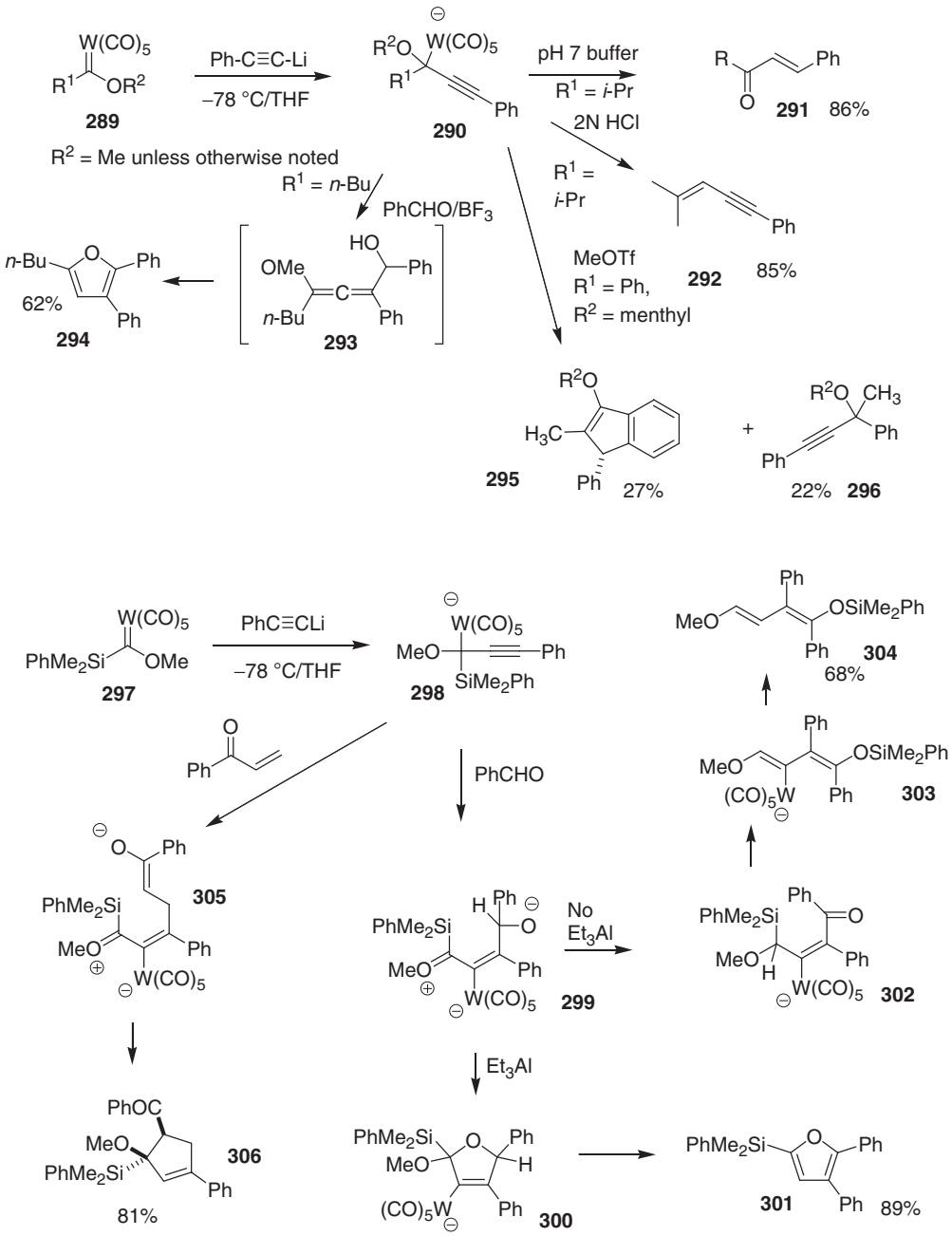
5.25.2.9 Nucleophilic Substitution at and Cleavage of Carbene Ligands

Several new reaction processes were reported for anionic propargyl–tungsten complexes (e.g., **290**, Scheme 31), which were derived from addition of alkynyl anions to Fischer carbene complexes.[134,135] If the complex was simply allowed to warm to 25 °C,



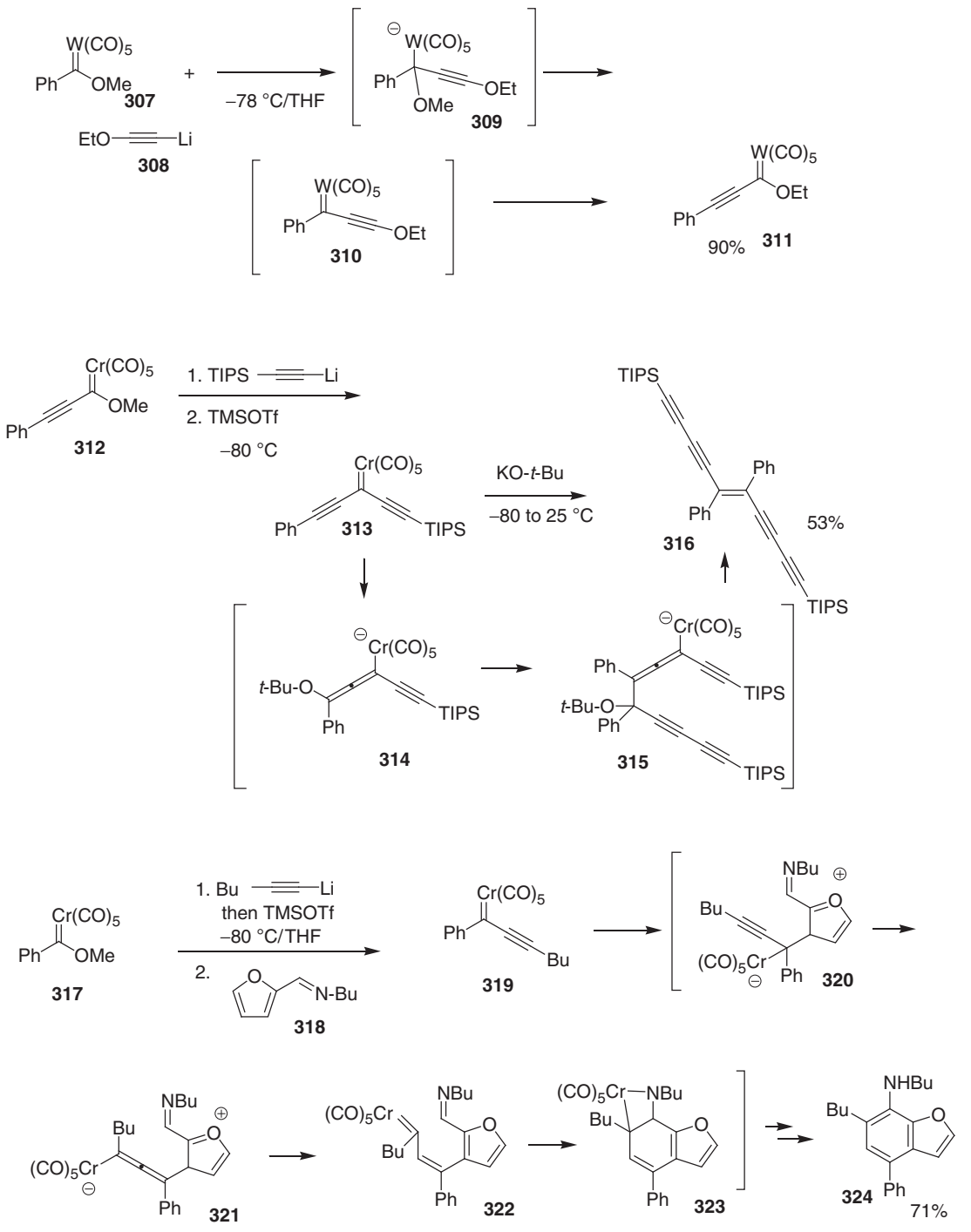
Scheme 30

the α,β-unsaturated ketone **291** was obtained via an allene intermediate. Treatment of propargyl compound **290** with 2M HCl afforded the enyne derivative **292**. Reaction with aldehydes and Lewis acids afforded furan derivatives (e.g., **294**). A mechanism involving electrophilic attack at the γ-position, forming allene **293** followed by acid-catalyzed ring-closure was proposed for furan formation. This methodology was used as the cornerstone for the total synthesis of the antibiotic PI-091.[136] Similar processes were demonstrated for anionic propargyl–tungsten complexes derived from addition of alkynyl anions to arylcarbene complexes.[137] Treatment of this complex with methyl triflate resulted in indene (e.g., **295**) formation, which proceeds via a 1,3-shift of tungsten before alkylation, followed by cyclization. The coupling of silylcarbene complexes (e.g., **297**) with alkynyl anions initially afforded the anionic complex (**298**).[138] The reaction with simple aldehydes afforded either dienes (**304**) or furans (**301**), depending on the presence or absence of triethylaluminum. The proposed mechanism involves attack at the γ-carbon to afford intermediate zwitterion **299**, which undergoes a hydride shift to afford the ketone (**302**), which affords the product (**304**) after 1,5-silicon shift and demetallation. Nucleophilic addition of oxygen to afford the dihydrofuran (**300**) followed by methanol elimination leads to the furan (**301**) in the presence of triethylaluminum. Reaction with α,β-unsaturated ketones led to cyclopentenols (e.g., **306**) in a mechanism involving Michael addition at the γ-position of the enone followed by cyclization.



Scheme 31

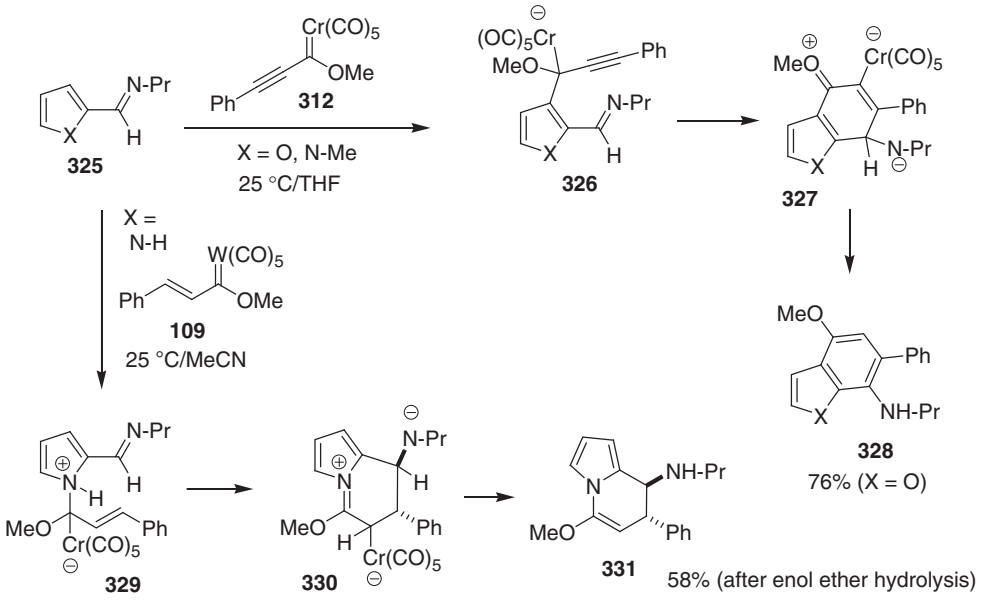
In several examples, the addition of alkynyl anions to carbene complexes leads to formation of alkynylcarbene complexes devoid of heteroatom substitution, which are stable at low temperatures (Scheme 32). A new synthetic route to alkynylcarbene complexes (e.g., **311**) was developed that employs the reaction of carbene complexes with alkoxyacetylide anions (e.g., **308**).[139] Nucleophilic addition to the carbene carbon, followed by loss of methoxide and 1,3-rearrangement yields the alkynylcarbene complexes. The addition of alkynyllithium reagents to carbene complexes devoid of α-hydrogens (e.g., **312**) followed by reaction with trimethylsilyl triflate led to alkynylcarbene complexes devoid of heteroatom stabilization (e.g., **313**).[140] These carbene complexes are stable only at low temperature and form dimers (e.g., **316**) when warmed to room temperature in the presence of potassium *t*-butoxide. Head-to-head as well as head-to-tail dimers were produced, depending on the structure of the carbene complex. A mechanism was proposed that involves Michael addition of *t*-butoxide ion followed by propargylation of a virgin carbene complex resulting in a dimeric anionic complex (**315**), followed by demetallation/alkoxide elimination. Coupling of carbene complexes (e.g., **317**) with alkynyllithiums followed by reaction with furfural imines (e.g., **318**) led to substituted benzofurans (e.g., **324**).[141] Subsequent treatment of the intermediate alkynylcarbene complex with furfural imine proceeds via



Scheme 32

Michael addition of the furan ring to the alkynylcarbene complex (**319**) followed by proton transfer to afford a carbene complex-imine (**322**), followed by [2 + 2]-cycloaddition and β-hydride elimination.

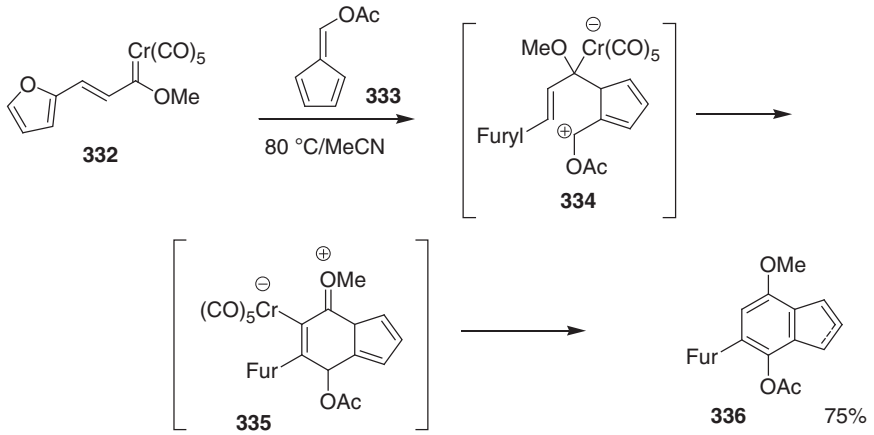
A novel benzannulation process was reported for the coupling of alkynylcarbene complexes (e.g., **312**, Scheme 33) with heteroaromatic aldehyde-derived imines (e.g., **325**).[142] Furan, benzofuran, and *N*-substituted indole derivatives led to the carbocyclic benzannulation products (e.g., **328**) via a mechanism involving nucleophilic addition to the carbene carbon at the 3-position of the heterocyclic ring, followed by simultaneous 1,2-shift of the metal and attack on the imine. A heterocyclic benzannulation product (e.g., **331**) was formed from the coupling of N–H pyrrole and indole-starting materials. A similar mechanism was proposed except that the initial attack occurs at the heterocyclic N atom. Coupling of N–H pyrroles and indoles



Scheme 33

with alkynylcarbene complexes afforded seven-membered ring annulation products which result from initial Michael addition of the imine N atom to the alkyne carbon followed by a 1,3-shift of the metal.

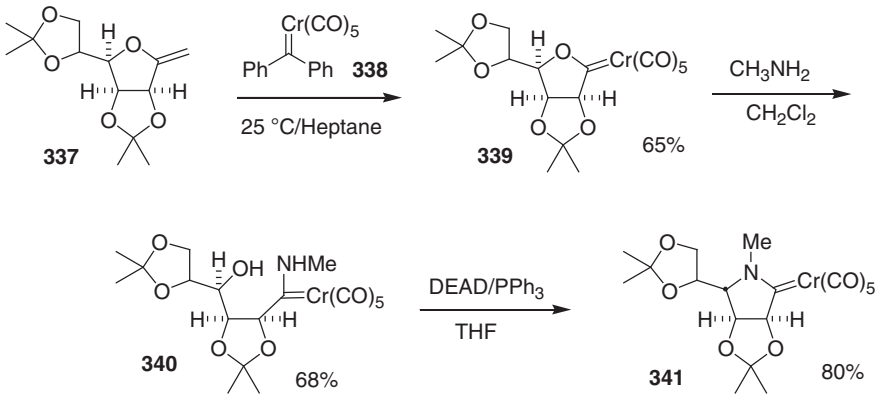
A net [6 + 3]-cycloaddition process was observed in the coupling of α,β-unsaturated chromium carbene complexes (e.g., **332**, Scheme 34) with electron-rich fulvenes (e.g., **333**).[143] The proposed mechanism involves electrophilic attack on the carbene complex at the 2-carbon of the fulvene, affording intermediate **334**, followed by simultaneous 1,3-shift of chromium and nucleophilic attack at the exocyclic carbon of the delocalized cation to afford cyclized intermediate **335**. Subsequent aromatization leads to the cycloaddition product **336**. Compound **336** was obtained as a mixture of alkene regioisomers.



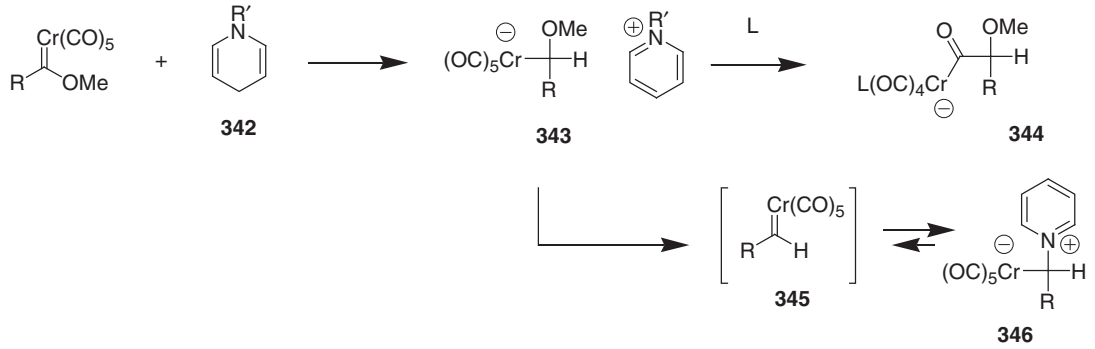
Scheme 34

Synthesis and aminolysis of a variety of carbohydrate-derived carbene complexes have been demonstrated (Scheme 35). Carbene complex **339** was prepared from methylenetetrahydrofuran **337** by an olefin metathesis route.[144] A net conversion of the oxygen heterocycle **339** to the nitrogen heterocycle **341** was effected by the sequence of aminolysis-ring opening followed by a Mitsunobu-type ring closure process. Other examples utilizing carbene complexes for carbohydrate synthesis have been documented, including a three-carbon chain extension process based on the conversion of homopropargyl alcohols to cyclic carbene complexes,[145] and preparation and aminolysis of iron-, chromium-, molybdenum-, and tungsten-alkoxycarbene complexes derived from aldonic acid chloride derivatives and the corresponding metal carbonyl dianions.[146]

Several examples employ the use of dihydropyridines or dihydroquinolines to form ylide complexes, which serve as synthetic equivalents to hydrido-Fischer carbene complexes (Scheme 36).[147–151] Common reaction pathways observed in these systems include initial formation of a stable tetrahedral complex (e.g., **343**) as a pyridinium salt followed by either *in situ* generation of the nonheteroatom-stabilized carbene complex (e.g., **345**), which is in equilibrium with a stable pyridinium ylide complex (e.g., **346**),



Scheme 35

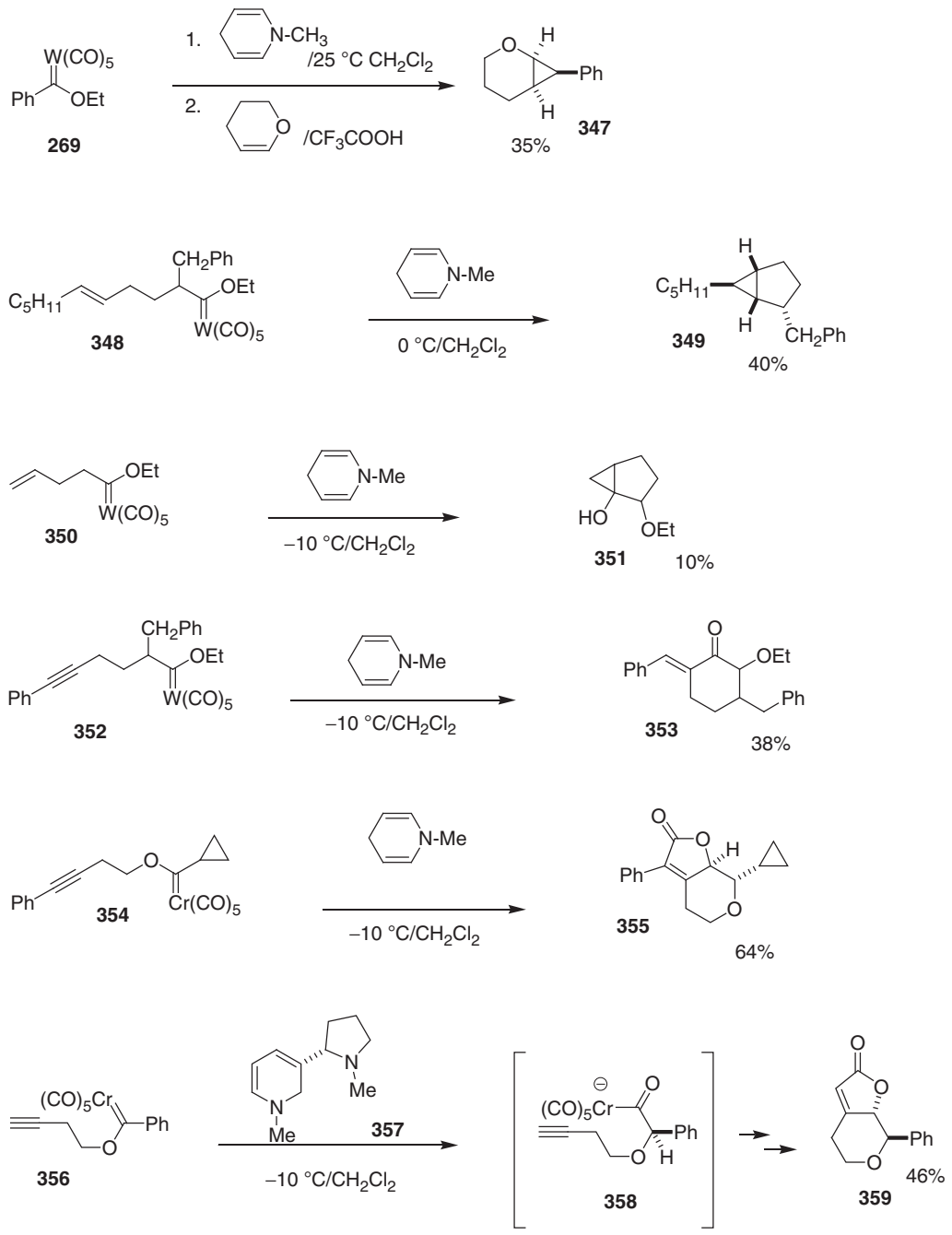


Scheme 36

or CO insertion to generate the acylate complex (e.g., **344**). Specific examples are depicted in Scheme 37. Reaction of the pyridinium salt complexes with electron-rich alkenes led to cyclopropanation products (e.g., **347**) with a high degree of stereoselectivity for the depicted isomer. Direct intramolecular cyclopropanation without isolation of the ylide complexes was observed in the reaction of δ,ω-unsaturated carbene complexes (e.g., **349**) with dihydropyridine derivatives; formation of cyclopropane derivative **349** proceeded with a high degree of stereoselectivity. Alkene complexes which feature a shorter tether (e.g., **350**) afforded hydroxycyclopropanes (e.g., **351**) on treatment with *N*-methyldihydropyridine via a CO-insertion process. Reaction of alkyne–carbene tungsten complexes (e.g., **352**) with *N*-methyldihydropyridine led to CO insertion-cyclization products (e.g., **353**), although chromium analogs (e.g., **354**) afforded multiple CO-insertion products (e.g., **355**).[152] A key step in the formation of compounds **353** and **355** is intramolecular alkyne-insertion reaction of a chromium acylate (analogous to **344**, Scheme 36). Treatment of alkyne–carbene complexes (e.g., **356**) with dihydronicotine (**357**) led to the bicyclic derivatives (e.g., **358**) with a moderate degree of enantioselectivity.[153]

Several examples of related cascade cyclization processes initiated by the addition of nucleophiles to the carbene carbon have been reported (Scheme 38). The coupling of alkynylphenylcarbene–chromium complexes (e.g., **360**) with dihydropyridine derivatives and with carbon nucleophiles (e.g., MeLi) led to indane-fused furanone derivatives (e.g., **363**) through a process involving nucleophilic addition to the carbene carbon, followed by CO insertion and alkyne insertion.[154,155] The process uses three of the CO ligands in the original chromium hexacarbonyl starting material. Related nucleophilic additions to γ,δ-unsaturated carbene complexes (e.g., **364**) led to cyclopentenones (e.g., **365**) through a related mechanistic process involving CO insertion and alkene insertion after the initial addition of carbanion to the carbene carbon.

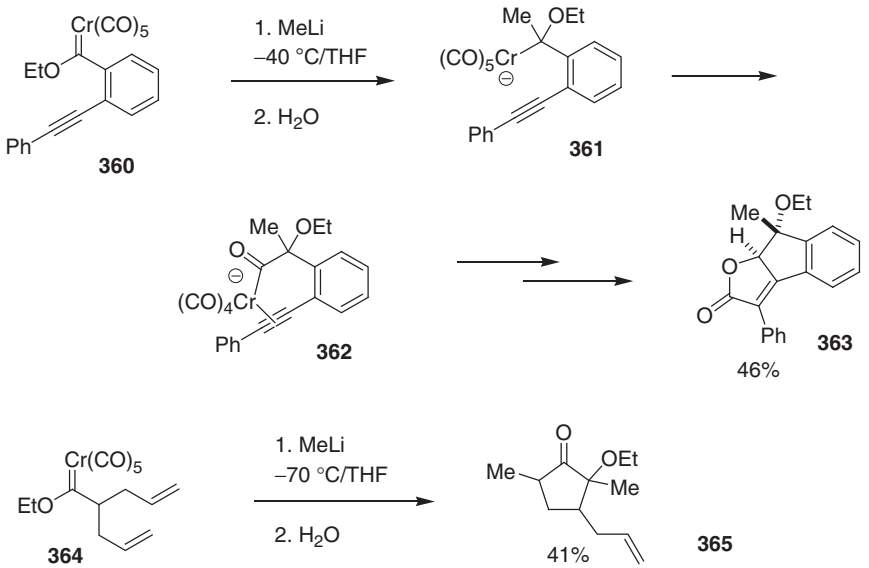
Several examples, where nucleophilic addition of an enolate to a carbene complex carbon initiates a cascade process, have been documented (Scheme 39). The three-component coupling of carbene complexes (e.g., **317**), ketone or ester enolates (e.g., **366**, R = Me), and allylmagnesium bromide was reported.[156,157] Substituted enolates led to five-membered ring derivatives (e.g., **370**) in a reaction sequence involving addition of the enolate to the carbene carbon, followed by addition of allylmagnesium bromide to the ketone, followed by intramolecular alkene insertion and cyclopropanation. Enolates from methyl ketones (e.g., **366**, R = H) afforded six-membered rings (e.g., **372**) by a similar mechanism except that CO insertion occurs from intermediate **368**, which then undergoes a net oxidative addition into the alkene C–H bond to afford the six-membered ring product. In both cases, the reaction was highly stereoselective. New diastereoselective five- and seven-membered ring forming cycloaddition reactions that utilize the coupling of alkenylcarbene complexes (e.g., **109**) and enolates were reported.[158] The ultimate course of the reaction was highly dependent on the structure of the enolate. All of the products form via initial nucleophilic addition of the enolate to the



Scheme 37

carbene carbon to form a tetrahedral intermediate (**373** and **376**). Formation of five-membered rings (e.g., **375**) occurs through addition of a second mole of the enolate to the ketone to provide a pentanoyl–tungsten complex (**374**), which affords the five-membered ring through addition of the carbanion-like chromium-containing carbon to the carbonyl group. Formation of seven-membered rings (e.g., **377**) using the acetone-derived enolate occurs through a similar series of steps; however, the final ring-forming step occurs with allylic rearrangement.

A novel ring expansive cycloaddition of benzocyclobutenols (e.g., **378**, Scheme 40) and alkynylcarbene complexes (e.g., **194**) resulted in seven-membered rings (e.g., **379** and **380**).[159] A mechanism involving opening to the anionic *o*-quinonedimethane **381**, followed by nucleophilic addition to the carbene complex to afford aldehyde–alkynyltungsten complex **382**, followed by 1,2-shift of tungsten and attack at the aldehyde was proposed. The cyclized intermediate **383** either undergoes a hydride shift to produce **379** or attack of the alkoxide at the oxonium ion to afford **380**. Intermediates of nucleophilic addition of enolates to carbene complexes can also be intercepted through reaction with iodine[160] or methyl triflate, the latter process leading to



Scheme 38

cyclopropanes (e.g., **385**).[161] Related processes were reported for amide enolates.[162] A new cycloheptadiene synthesis utilizes the coupling of dienylcarbene–tungsten complexes (e.g., **386**) and enolates.[163] A mechanism involving addition of the enolate to the carbene carbon followed by nucleophilic addition of the resulting pentadienoyl–tungsten complex to the carbonyl group was proposed.

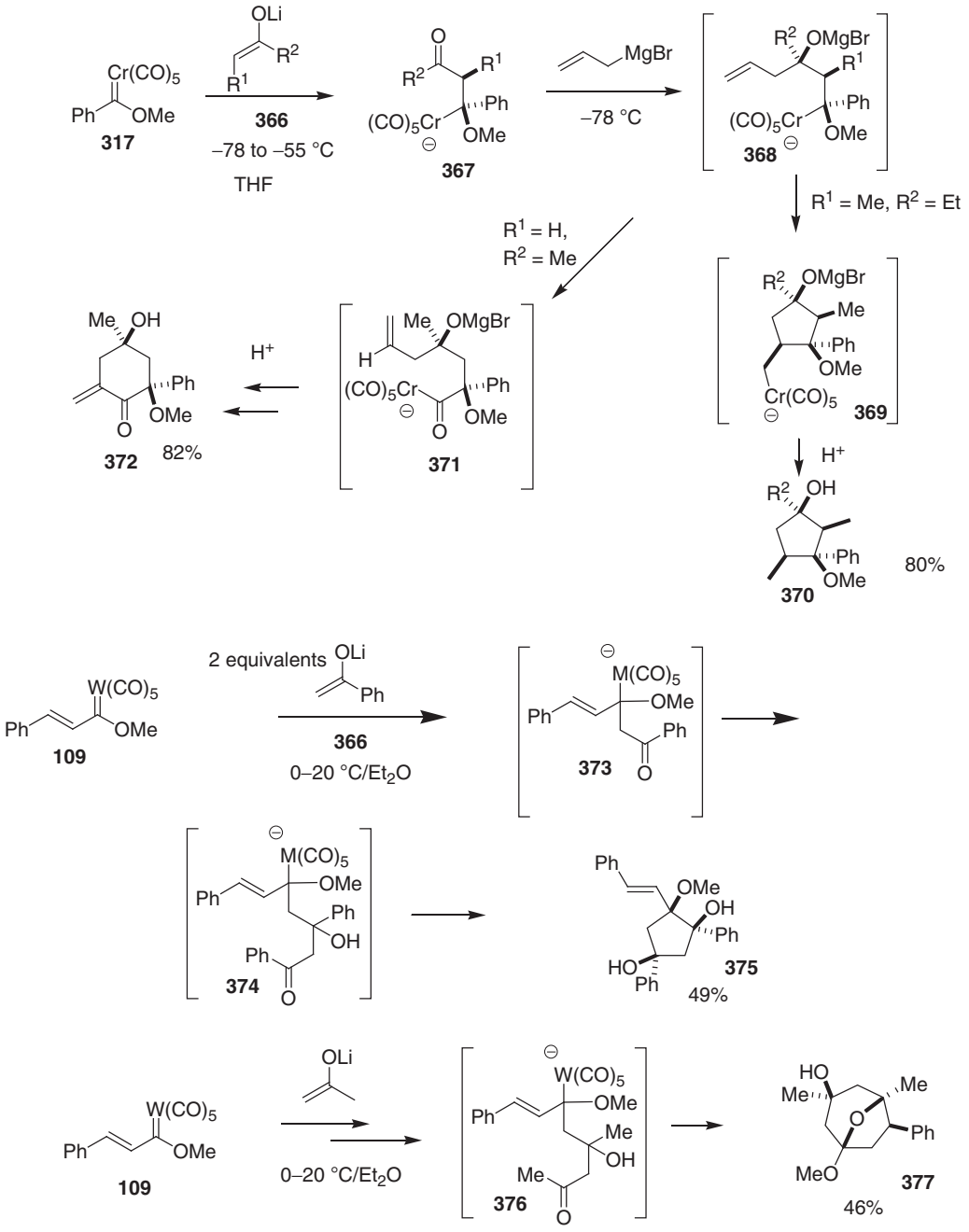
Reaction of ketene acetals (e.g., **391**, Scheme 41) with carbene complexes (e.g., **390**) leads to either cyclopropanation products (e.g., **392**) or five-membered ring lactones (e.g., **393**).[164] All of the reaction products form from the zwitterion **394**, obtained through nucleophilic addition of the alkene carbon to the carbene carbon. The identity of the reaction product was dependent on the R group of the alkoxycarbene complex. Carbene complexes featuring hindered R groups led to cyclopropanone acetals. The methoxy complex led to γ-lactones through a mechanism involving formation of oxonium ion **397**, which then affords the lactone **393** in a sequence involving formation of unstabilized carbene complex **398**, C–H activation, alkyl shift, reductive elimination, and ortho ester hydrolysis. Additional reaction pathways were observed in many of the cases. Use of an α,β-unsaturated carbene complex led to the alkyne product **400** in addition to the expected lactone **399**.[165] Formation of the alkyne occurs through Michael addition followed by conversion of the resulting zwitterionic complex (**401**) to the vinylidene complex (**402**) followed by conversion to the alkyne and ortho ester hydrolysis. The reaction of Fischer carbene complexes and cyclic ketene acetals (e.g., **403**) led to cyclic products resulting from CO insertion (e.g., **406** and **407**).[166] The reaction proceeds via 1,2-addition to afford the zwitterionic complex **404**, which undergoes methoxy group transfer to afford the unstabilized carbene complex **405**, which then undergoes intramolecular C–H insertion. The reaction was employed in a relatively short total synthesis of edanolide.

5.25.3 Reaction at the Metal Center

5.25.3.1 Coupling of the Carbene Ligand with Alkenes and 1,3-Dienes

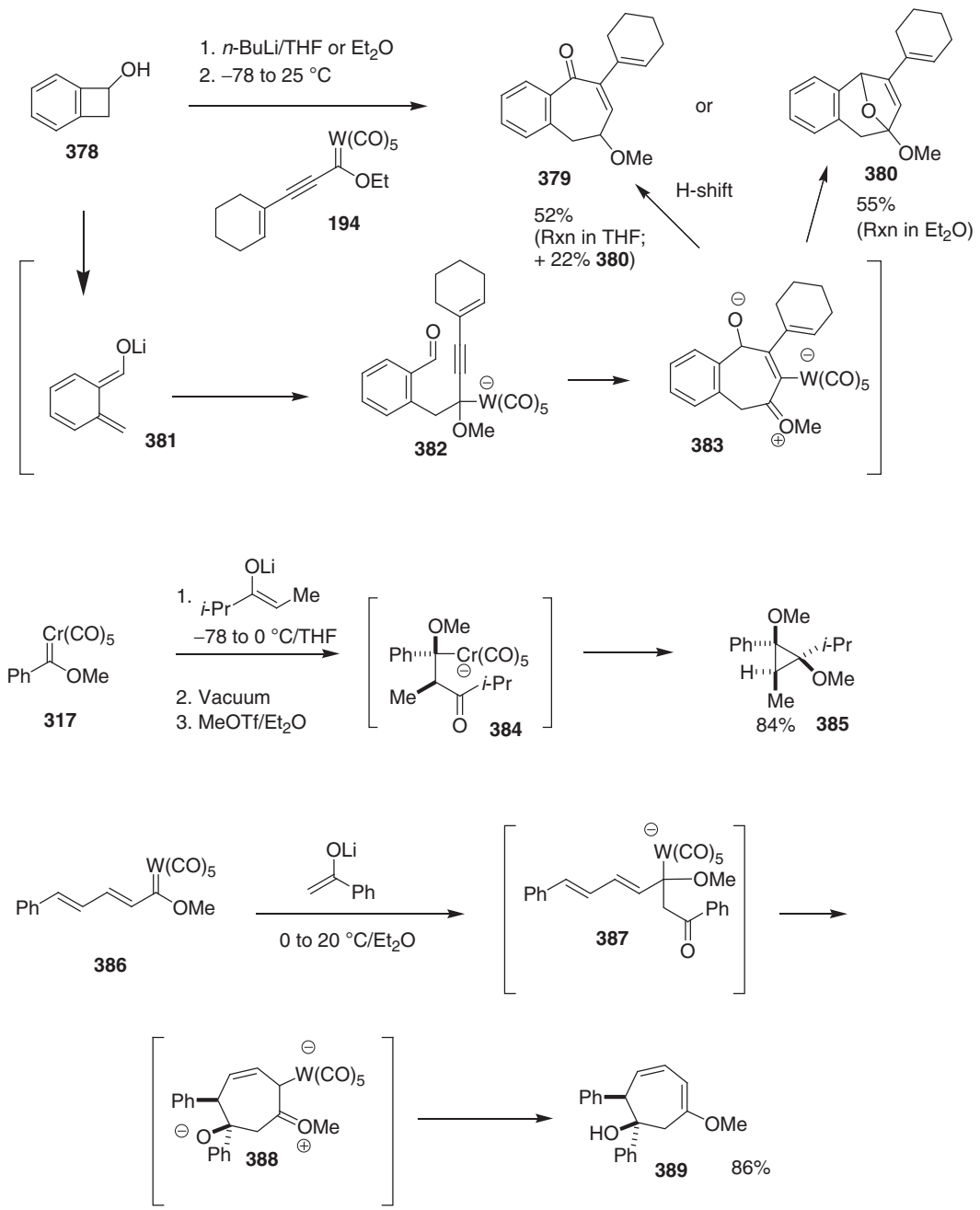
5.25.3.1.1 Three-membered rings via 2 + 1 cycloaddition

One of the early goals after the discovery of carbene complexes was to accomplish the most common transformation of carbenes, cyclopropanation.[167] In most of the early studies of Fischer-type carbene complexes, heteroatom-stabilized Fischer carbene complexes can only cyclopropanate electron-poor alkenes (e.g., **1** + *N*,*N*-dimethylacrylamide, Scheme 42),[168] or electron-rich alkenes under CO pressure. Numerous additional examples of these processes have been amassed since the first edition of Comprehensive Organic Synthesis, and new methods for the cyclopropanation of additional alkyne types have been developed. Cyclopropanation reactions involving glycal–carbene complexes (e.g., **411**) and various electron-deficient alkenes were reported.[169] Varying degrees of diastereoselectivity were observed depending on the aldohexose and the alcohol protecting groups. Cyclopropanation has been extended to conjugated diene substrates (e.g., complex **413** + 2,3-dimethylbutadiene).[170,171] These substrates are generally limited to diene systems that can attain the *s-cis* conformation. This limitation was attributed to required formation of a chelated π-allyl complex as a key intermediate. For the metals of Group 6, the molybdenum carbene complexes appear to be more reactive than the chromium carbene complexes; tungsten carbene complexes are not generally useful cyclopropanating agents except when lacking heteroatom substitution.[172] Cyclopropanation using alkynylcarbene–chromium complexes and electron-deficient alkenes was also reported.[173] Intramolecular cyclopropanation reactions (e.g., conversion of complex



Scheme 39

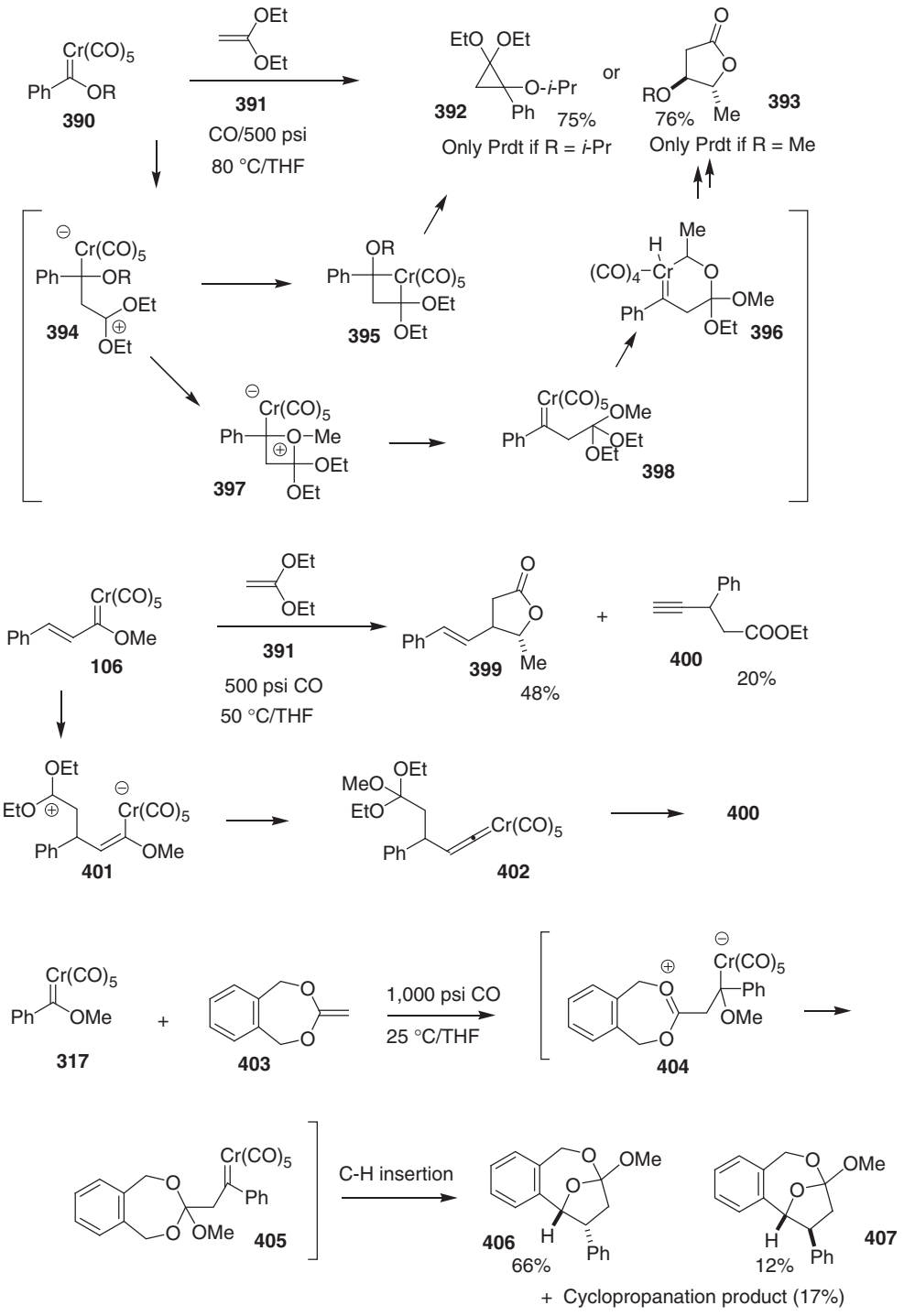
415 to **416**) appear to be more facile and proceed with unactivated alkene groups.[174] The cyclopropanation reaction has been successfully extended to alkenes conjugated to carbon–nitrogen double bonds. Reaction of α,β-unsaturated carbene complexes with 2-alkenyloxazoles (e.g., **417**) at 80 °C led to five-membered ring derivatives (e.g., **419**) after rearrangement of the initially formed cyclopropanes (e.g., **418**).[175] Cyclopropanation reactions of alkenyloximes were similarly reported.[176] Successful cyclopropanation of unactivated alkenes was achieved using α,β-unsaturated chromium carbene complexes (e.g., **106**) in refluxing DMF or THF at high temperature.[177] Only alkenylcarbene complexes and heteroarylcarbene complexes were successful in this reaction. The cyclopropanation of cyclohexene required a 20-fold molar excess of cyclohexene. In cases involving monosubstituted alkenes or *cis* 1,2-disubstituted alkenes, the cyclopropane stereoisomer where the methoxy group and the original alkene substituents are *cis* was produced with a high degree of stereoselectivity. A mechanism involving [2 + 2]-cycloaddition followed by conversion of the resulting σ-allyl/metallacyclobutane complex to a π-allyl complex (e.g., **420**) was proposed to account for the substrate limitations of this process. Solid phase reaction of carbene complexes with alkenes was also reported.[178]



Scheme 40

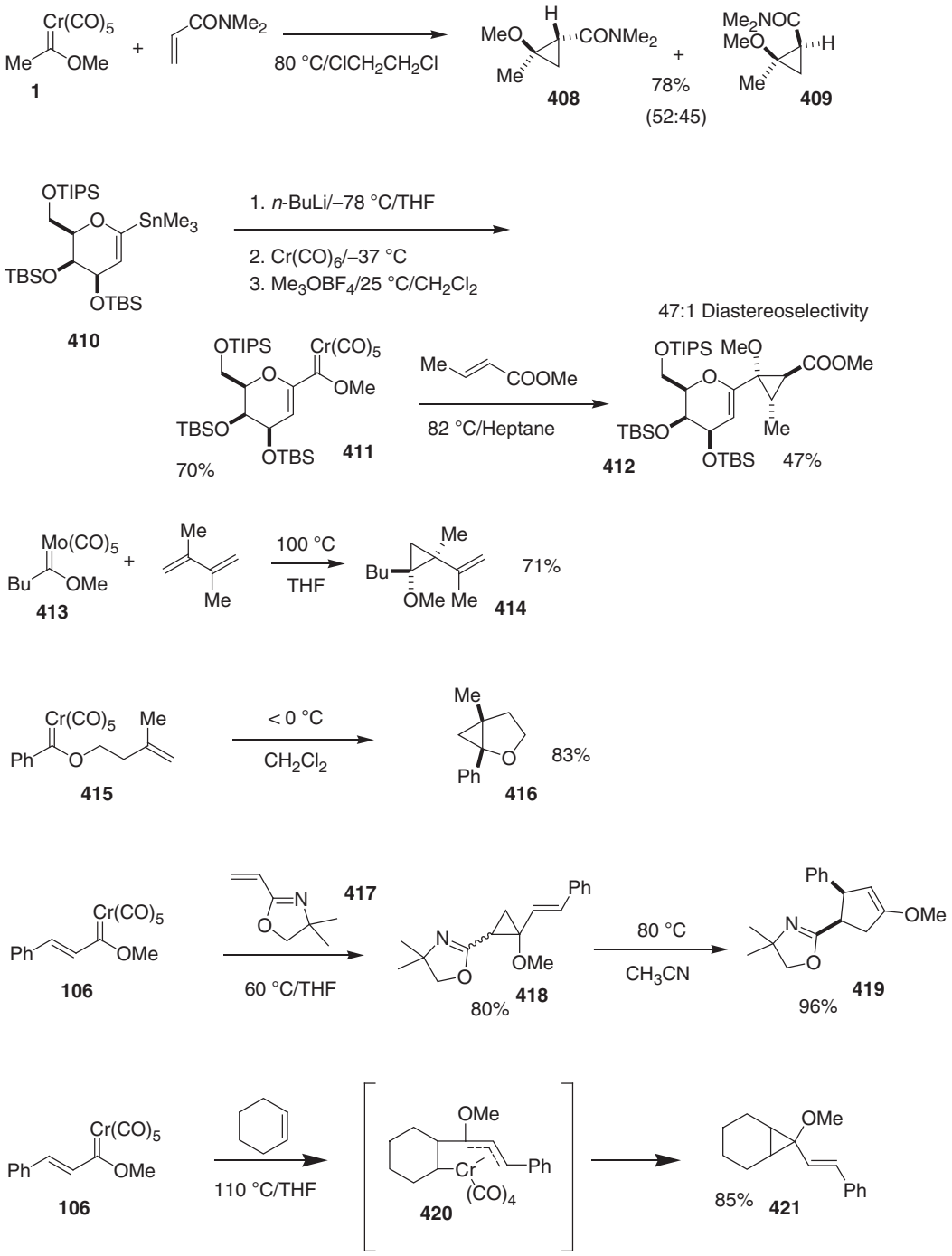
Several successful attempts to activate the relatively unreactive Fischer carbene complex systems were reported (Scheme 43). Most employ the use of carbene complexes that have been deactivated by electron-withdrawing groups. Unstable acetoxycarbene analogs (e.g., **422**) appear to undergo cyclopropanation of electron-rich alkenes quite readily.[179] This reaction process is the cornerstone for the synthesis of prostaglandin derivatives. Chloroethylcarbene complex analogs (e.g., **425**) were noticeably more reactive and could successfully cyclopropanate norbornene, styrene, and 1-hexene.[180] Alkene cyclopropanation can be accomplished using aminocarbene complexes that feature an acyl group at the carbene carbon (e.g., **427**).[181]

Cationic iron carbene complexes undergo cyclopropanation reactions with electron-rich alkenes under very mild conditions (Scheme 44). These complexes are typically unstable but generated *in situ*, and appear to be excellent reagents for cyclopropanation of unactivated alkenes. These iron carbene complexes can be generated via a variety of methods, including protonation of vinyliron species (e.g., **429**), alkylation of thioalkyliron species, or protonation or silylation of alkoxyiron (or hydroxyiron) species (represented by general structure **431**). The thiomethyliron complexes appear to be the most convenient starting materials for carbene transfer.[182] Some degree of asymmetric induction has been observed in the reaction of chiral-at-iron



Scheme 41

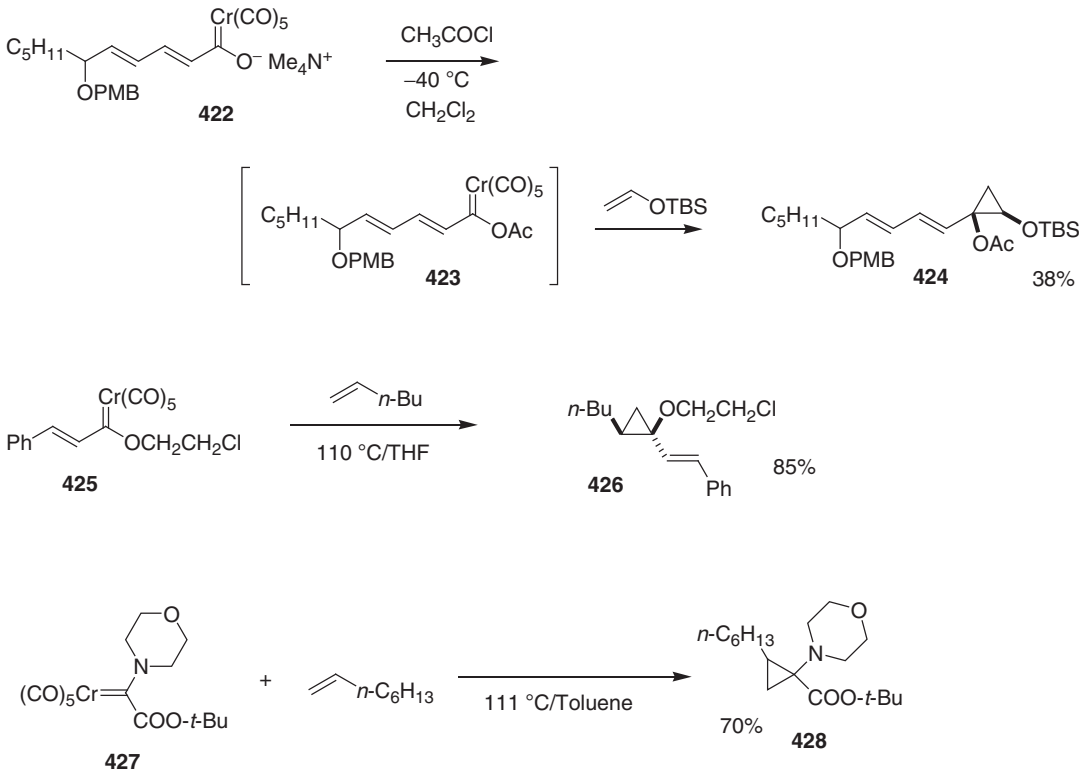
phosphine-substituted iron carbene complexes (e.g., **432**)[183,184] and for iron carbene complexes featuring the arene-chromium chiral auxiliary (e.g., **435**).[185] This method has been used as the cornerstone for a recent synthesis of optically pure cyclopropanecarboxylate derivatives (e.g., **437**). A mechanistic study of the reaction suggested that the reaction occurs via electrophilic attack at the alkene followed by ring closure that occurs with inversion at iron. The equivalent intermediate can be generated from stereo-labeled precursor **438**, which affords the cyclopropane product with clean inversion of the C–Fe bond on treatment with trimethylsilyl triflate.[186] Cation–olefin cascade cyclization processes can be initiated by the generation of iron carbene complexes in polyene systems (e.g., **442**).[187] In the reaction process depicted, the iron carbene complex functions as a carbocation equivalent.



Scheme 42

5.25.3.1.2 Five-membered and larger ring systems

Diverse reaction modes leading to ring sizes other than three were observed in the reaction of carbene complexes with alkenes where either of the cycloaddition partners is carrying an extra alkene group (Scheme 45). Reaction of aminodiene **445** with arylcarbene–chromium complex **317** afforded cyclopentane derivatives (e.g., **447**) via a cyclopropanation–vinylcyclopropane rearrangement sequence.[188] Arylvinylcarbene–chromium complex **448** afforded seven-membered ring derivative **449** via a cyclopropanation–divinylcyclopropane rearrangement sequence on reaction with aminodiene **445**. Alkylvinylcarbene–chromium and tungsten carbene complexes afforded primarily Diels–Alder products. Other reactions involving the coupling of 1,3-dienes with α,β-unsaturated carbene complexes also feature competition between the Diels–Alder and carbene-addition pathways, including (1) the coupling of 2-azadienes with various types of α,β-unsaturated carbene complexes[189] and (2) the coupling of

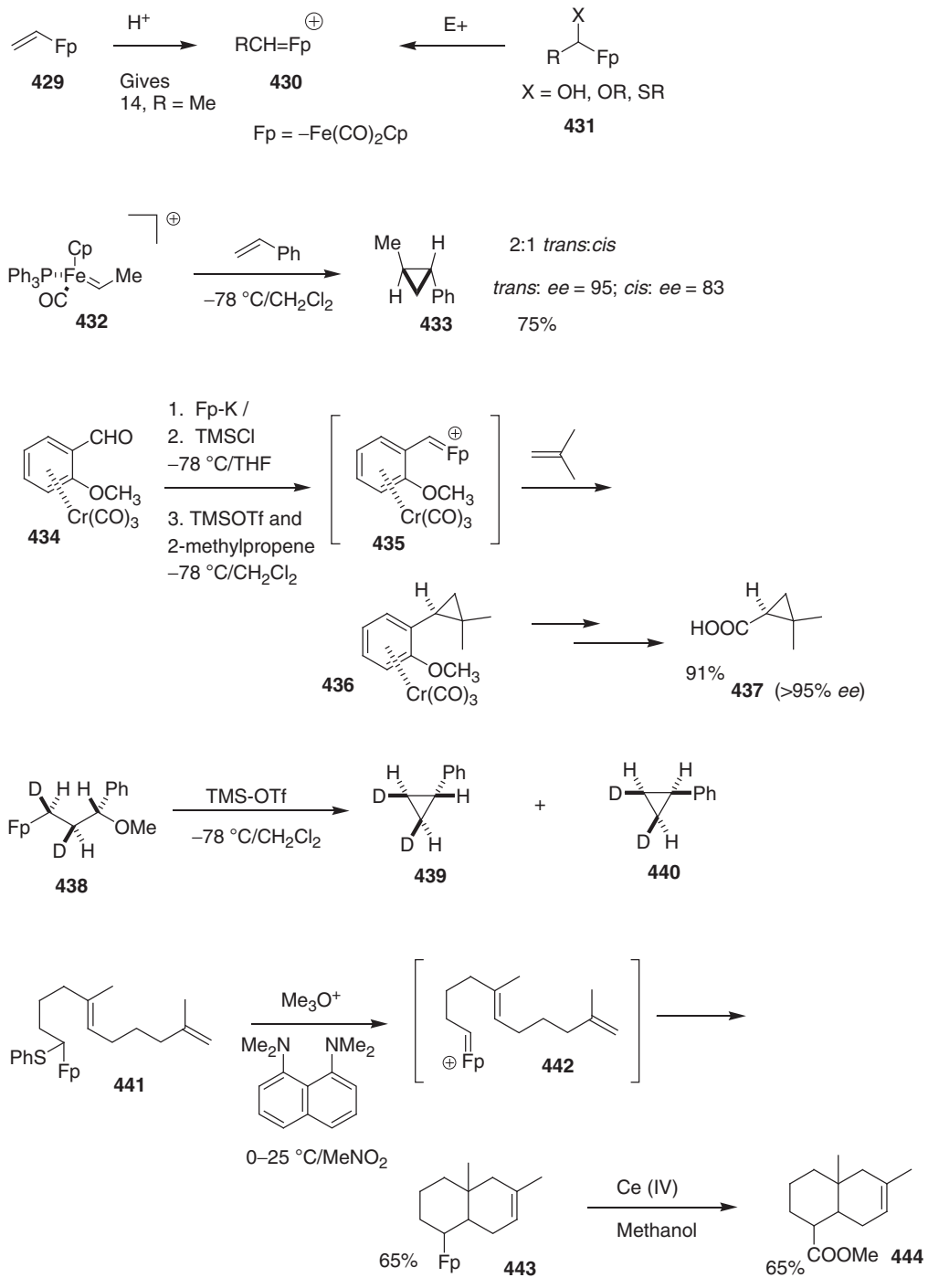


Scheme 43

1-azadienes with alkynylcarbene–chromium complexes.[190] Cyclopropanation was observed in the coupling of electron-rich dienes (e.g., **451**) with (acetoxy)vinylcarbene–chromium complexes (e.g., **450**); the resulting divinylcyclopropanes (**452**) were transformed to cycloheptadiene derivatives (**453**) by treatment with methyllithium.[191] Intramolecular cyclopropanation was observed when chromium carbene acylates were treated with β,γ-unsaturated acid chlorides.[192] The coupling of α,β-unsaturated chromium carbene complexes (e.g., **106**) with silyloxydiene derivatives (e.g., **454**) afforded either five- or seven-membered ring products.[193] Competition between direct cyclopropanation followed by Cope rearrangement, resulting in the formation of cycloheptadiene (e.g., **459**), or direct five-membered ring formation resulting in the formation of cyclopentenes (e.g., **457**), was noted. In the reaction with complex **106**, electron-deficient silyloxydienes (e.g., **454**, R = COOMe) generally afforded five-membered rings, whereas other derivatives led to cycloheptadienones.

The coupling of alkynylcarbene complexes (e.g., **312**, Scheme 46) with strained rings (e.g., norbornene) afforded mixtures of the simple cyclopropanation product **461** and an adduct **465** incorporating CO and two moles of the norbornene.[194] A mechanism involving [2 + 2]-cycloaddition, CO insertion, and simultaneous 1,3 shift of chromium and carbonyl addition led to intermediate carbene complex **464**, which couples with the starting alkene to provide adduct **465**. This carbene complex intermediate can also couple with electron-rich alkenes to provide cyclopropane derivatives (e.g., **466**) accompanied by ring-opened products (e.g., **467**).

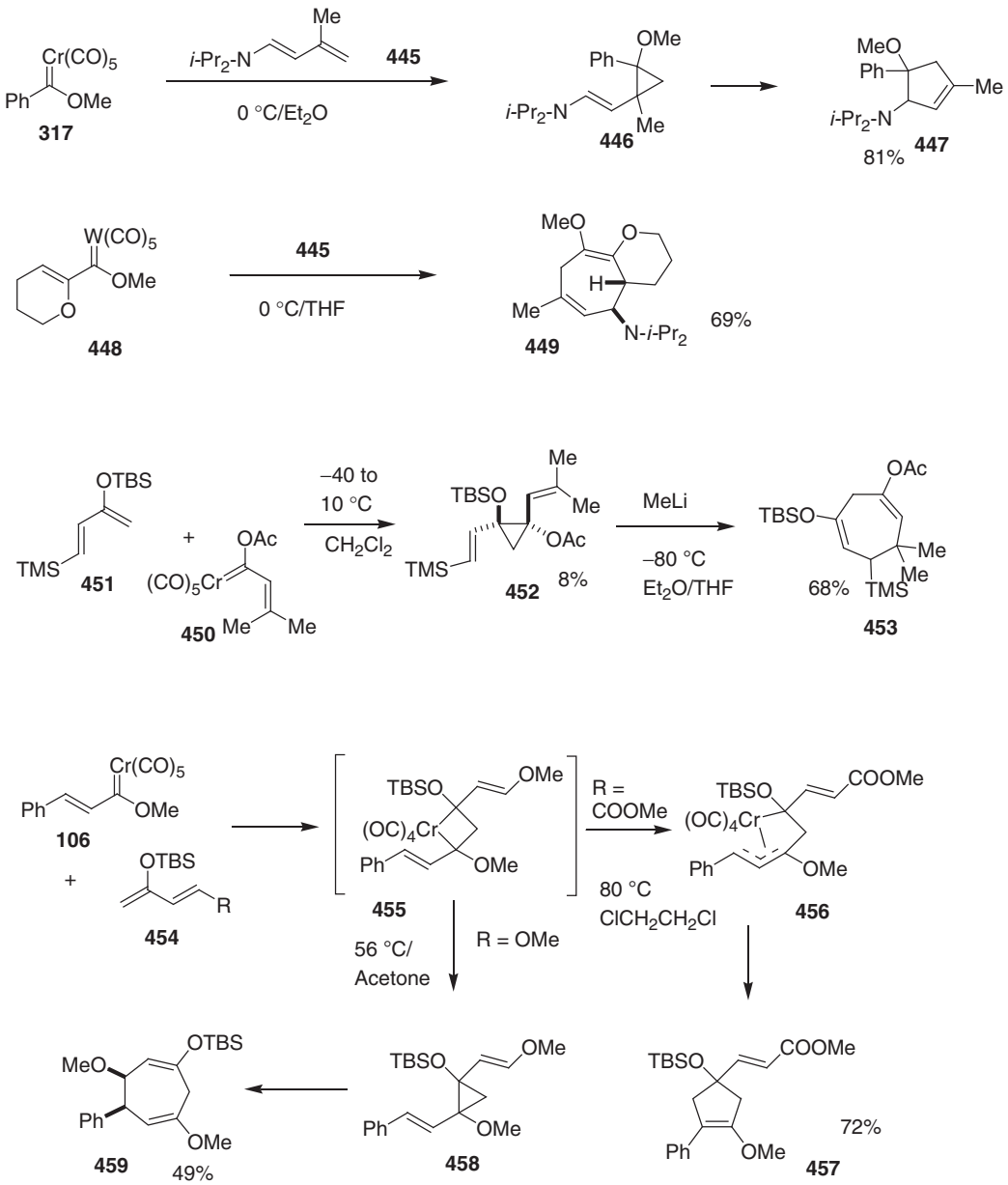
In several cases, the reaction of carbene complexes and alkenes where either partner has an extra alkene group leads to five-membered rings (Scheme 47). Cyclopentenones (e.g., **471**) were obtained from the coupling of α,β-unsaturated Fischer carbene complexes (e.g., **106**) and α,β-unsaturated *N,N*-dimethylhydrazones (e.g., **468**).[195] The pyrrole **474** was a minor product in the reaction. Moderate levels of ee were observed using the chiral alkoxycarbene complexes. Cyclopentenones were produced by nucleophilic addition of the β-carbon of the hydrazone at the carbene carbon followed by addition of the resulting allylmetal group of the initial adduct (**469**) to the vinyldiazonium group. The pyrrole was formed through nucleophilic attack of the imine nitrogen at the carbene carbon followed by intramolecular Michael addition of the organochromium group of **472** to the vinyliminium group. The coupling of alkenylcarbene complex **475** and electron-deficient alkenes affords either the expected vinylcyclopropanes (e.g., **476**) or a cyclopentene derivatives (e.g., **477**).[196] Coupling of α,β-unsaturated carbene–chromium complexes (e.g., **106**) with electroneutral 1,3-dienes (e.g., isoprene) leads to cyclopentane derivatives (e.g., **478** (a [4 + 1] adduct) and **479** (a [3 + 2] adduct)).[197] The distribution was solvent and temperature dependent and, however, exclusive formation of **478** was observed in THF at 120 °C, although **479** was the exclusive product from the reaction conducted at 90 °C in toluene. Exclusively the [3 + 2]-adduct was obtained from the analogous tungsten carbene complexes. The proposed mechanism for the formation of **478** and **479** both involve a metalla-Diels–Alder reaction followed by reductive elimination. The cycloaddition



Scheme 44

mode is determined by whether the metalla-Diels–Alder reaction utilizes the carbene complex as the 2π-component (affording intermediate **480**) or the 4π-component (affording intermediate **481**). The reaction of carbene complexes (e.g., **317**) with alkylidenecyclopropanes (e.g., **482**) also leads to cyclopentenones.[198] A mechanism involving [2 + 2]-cycloaddition to afford **484** followed by cyclopropylcarbinyl metal ring expansion to afford metallacyclopentane **485**, followed by CO insertion and reductive elimination was proposed.

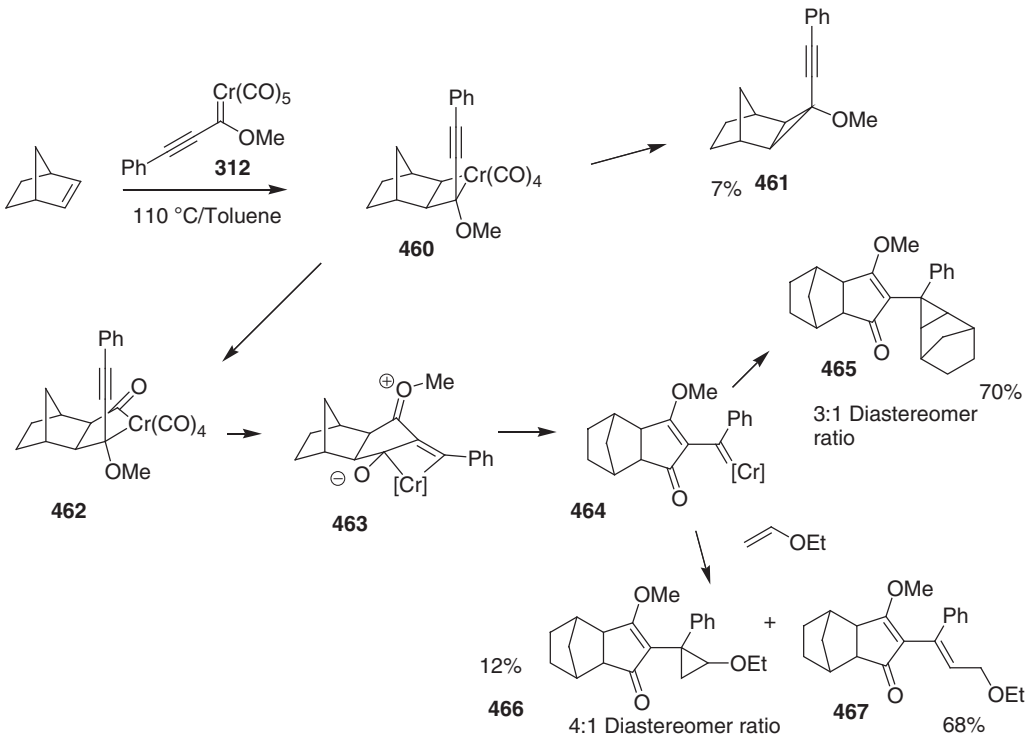
Several examples of the coupling of carbene complexes and alkenes leading to heterocyclic compounds have been reported (Scheme 48). Cyclopropanation or [4 + 1]-cycloaddition using alkenylcarbene–chromium complexes (e.g., **106**) and



Scheme 45

electron-deficient ketones leads to either the cyclopropanation product (e.g., **488**) or furan derivatives (e.g., **486** and **487**), depending on the substrate and reaction time.[199] In most cases, the cyclopropanation product rearranges to the [4 + 1]-cycloadduct on heating. Pyrroles (e.g., **494**) arise through the reaction of aminocarbene complexes (e.g., **490**) and α,β-unsaturated aldehydes.[200] A mechanism involving cyclopropanation to afford a donor–acceptor activated cyclopropane (**492**), followed by ring opening and aldehyde–enamine condensation was proposed.

Several examples of the photolytic coupling of iminocarbene Group 6 metal complexes (e.g., **495**, Scheme 49) and electron-deficient alkenes leading to five-membered ring nitrogen heterocycles (e.g., **498**) have been reported. The reaction pathway is highly dependent on the substitution pattern of the carbene substituents and that of the alkene or alkyne reactant. In the reaction of complex **495** with ethyl acrylate leading to pyrroline **498**, a mechanism involving photo-assisted CO dissociation, followed by complexation and cyclopropanation, followed by photochemically induced transformation of the *N*-cyclopropylimine (**497**) to the 1-pyrroline (**498**) was proposed.[201] The cyclopropylimine derivative **497** could be isolated from the reaction at short reaction times. Photolytic coupling of iminocarbene Group 6 metal complexes and various alkynes led to 1-pyrrolines (e.g., **500**).[202] The reaction with internal alkynes leads to acyclic 2-iminodiene derivatives.



Scheme 46

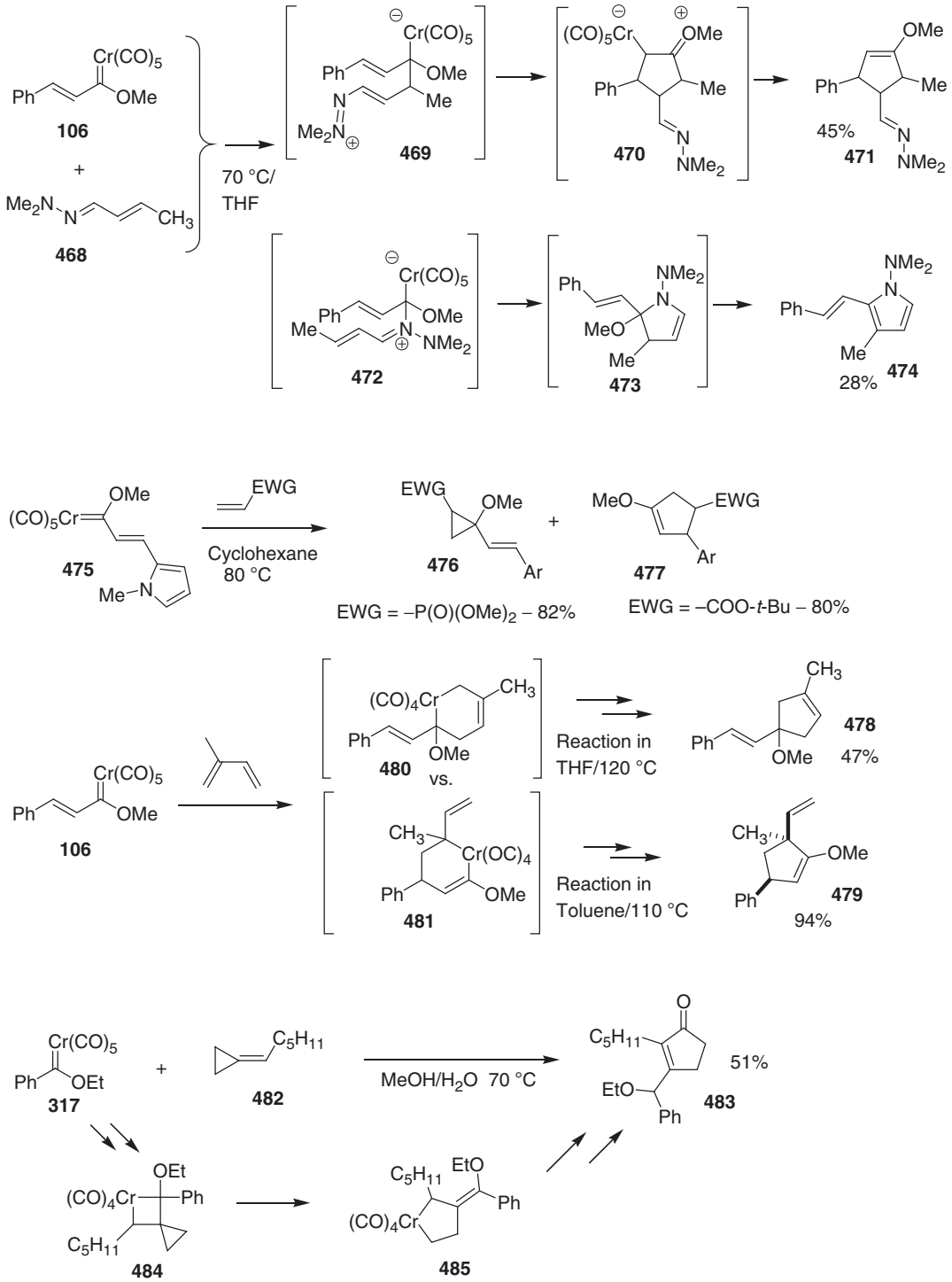
5.25.3.2 Coupling of the Carbene Ligand with Alkynes

5.25.3.2.1 2 + 1 + 1 cycloadditions – cyclobutenones

Cyclobutenone formation is often a minor reaction pathway observed in the coupling of Fischer carbene complexes with alkynes; however, in a very limited number of cases cyclobutenone formation is the major pathway (Scheme 50). Coupling of ferrocenylcarbene complex **501** with alkynes led to predominantly cyclobutenones (e.g., **502**) and furans (e.g., **503**) and not benzannulation products.[203] The product distribution was highly dependent on the metal and on the number of equivalents of alkyne employed. The furan products were more prevalent when the reaction was conducted at high concentration. Alkynylboranes (e.g., **504**) were suitable substrates for benzannulation reactions, resulting in naphthylboronic esters (**505**);[204] however, sterically hindered alkynylboranes afforded predominantly cyclobutenones (**506**). The reactions provided products where the boron inserts β- to the carbene complex functionality; this regioselectivity preference was observed regardless of the steric bulk of the other alkyne substituent.

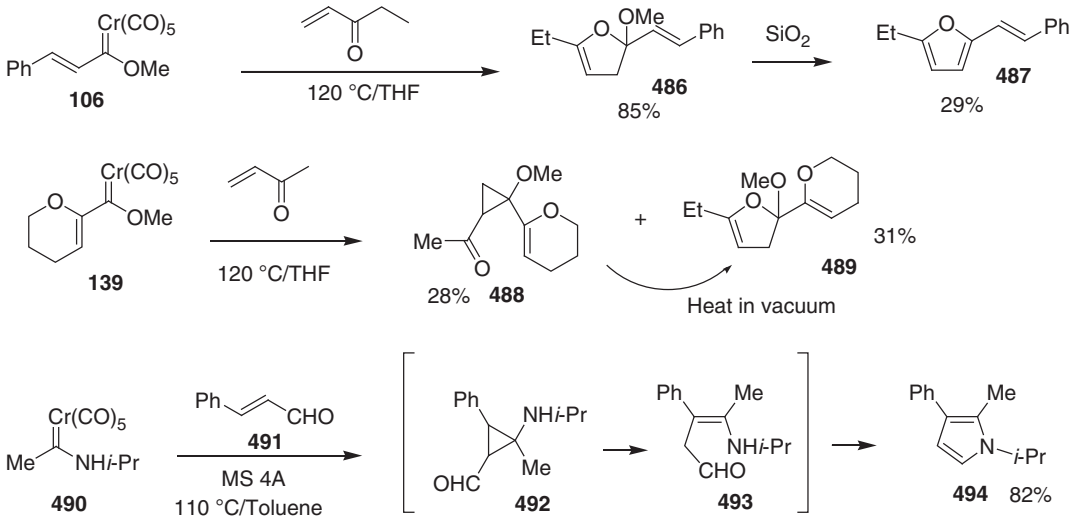
5.25.3.2.2 Five-membered rings[205]

Five-membered ring formation is often observed in the coupling of α,β-unsaturated carbene complexes with alkynes (Scheme 51). Often five- and six-membered ring formations are in competition. The ring formation is primarily determined by whether CO is incorporated, and in several cases conditions have been designed that maximize this five-membered ring-forming process. Certain substitution patterns are, however, far more likely to result in five-membered rings. Benzannulation (six-membered ring formation, see ahead) appears to be a general reaction process only for alkoxy-substituted chromium carbene complexes. Aryl aminocarbene complexes usually afford five-membered ring annulation products (e.g., **507**→**508**)[206] unless the nitrogen is acylated;[207] however, there are cases where benzannulation[119,208] and other ketene-derived products[209] are observed. Molybdenum– and tungsten–carbene complexes typically afford cyclopentannulation products also (e.g., **509**→**510**, **511**).[210,211] Iron carbene complexes afford pyrones (e.g., **512**→**513**/**514**)[212] or furans,[213,214] whereas cobalt carbene complexes afford furans (e.g., **515**→**516**).[215] Five-membered ring formation using alkoxycarbene-chromium complexes appears to be favored in polar coordinating solvents, and under high dilution conditions.[216] Electronic effects in the carbene complex and alkyne, as well as ring size effects for intramolecular reactions all play an important role in directing the course of the reaction. Additional examples of five-membered ring formation are depicted in Scheme 52 and include (1) the reaction of 1,6-methano[10]annulene-substituted tungsten carbene complexes (e.g., **520**) and alkynes leading to five-membered ring derivatives (e.g., **521**),[217] (2) thermolysis of aryl(amino)carbene complexes that feature remote alkyne groups (e.g., **523**) to afford five-membered rings fused to heterocyclic ring systems (e.g., **525**),[218] (3) cyclopentannulation reactions involving the coupling of alkynes and aminocarbene complexes fused to podocarpane rings (e.g., **526**),[219] and (4) coupling of 4-oxygenated-2,6-dimethylphenylcarbene–chromium complexes (e.g., **528**) and various alkynes to afford nonaromatic five- and six-membered ring annulation products (e.g., **529** and **530**).[220]

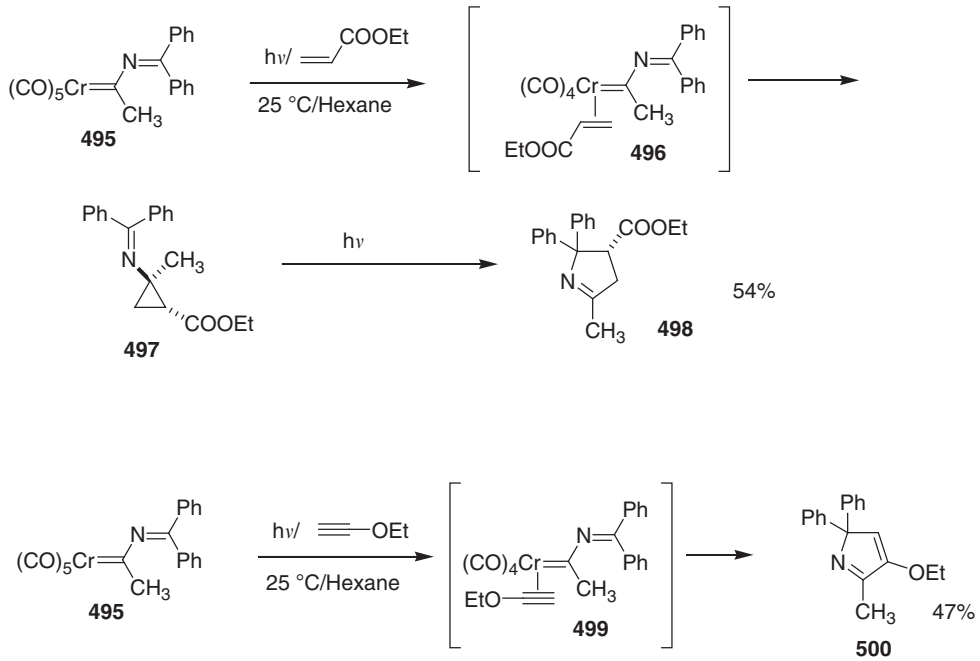


Scheme 47

Several examples of the intramolecular coupling of aminocarbene complex with alkynes leading to pyrrole and pyrrolidinone products have been reported.[221] The general reaction equation is depicted in Scheme 53 and involves alkyne insertion to afford a ketene (**533**) followed by formation of a nitrogen ylide (**534**), which then undergoes a Stevens-type rearrangement to afford the pyrrolidinones. The most thoroughly studied version of this reaction is the intramolecular coupling of aminocarbene–chromium complexes and alkynes (e.g., **538**→**541**, **542**). Thermolysis of **538** initially affords nitrogen ylide derivatives (**540**), which subsequently affords lactam derivatives **541**, **542**.[222] This reaction is also efficient for the formation of six-membered ring analogs.



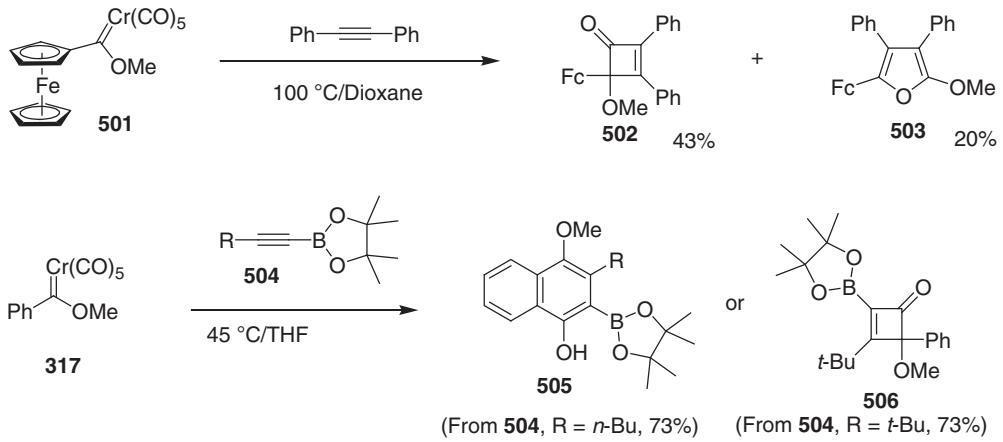
Scheme 48



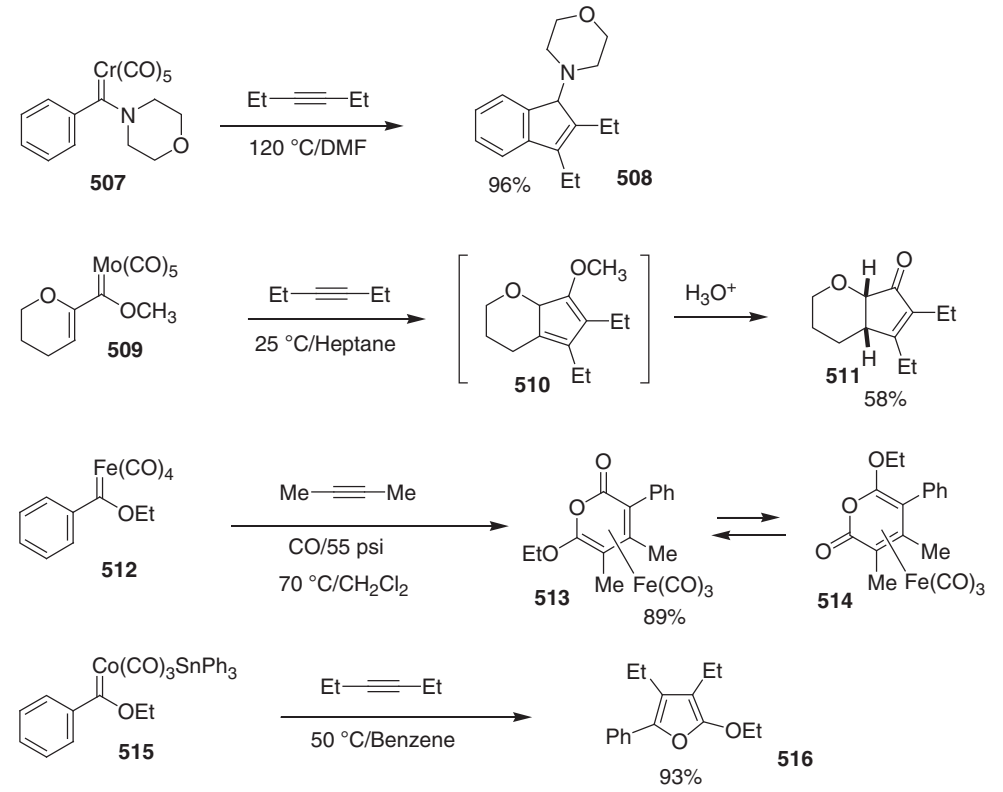
Scheme 49

Several examples of this reaction type have been reported. Intermolecular variants of this process have also been reported (e.g., **543** → **545–548**).[223]

Numerous studies of the reaction of β-amino-α,β-unsaturated carbene complexes with alkynes to afford five-membered ring compounds have been documented (**Scheme 54**).[224,225] Cyclopentadienes (e.g., **552**) were produced from the reaction of alkynylcarbene complexes (e.g., **549**) with amines followed by reaction of the resulting alkenylcarbene complexes with alkynes.[226] This process involves first heating the alkenylcarbene complex to afford an amine-coordinated complex (**551**), which then reacts with an alkyne to afford the cyclopentadiene after cyclization. Hydrolysis affords the observed ketone product (**553**). In many cases the cyclopentadienes undergo Diels–Alder reactions with the alkynes to afford the ring-fused norbornadiene derivatives. The coupling of β-amino-α,β-unsaturated carbene complexes with cyclopropylacetylene derivatives (e.g., **554**) leads to alkylidenecyclopentane derivatives (e.g., **556**) via ring opening of cyclopentadiene derivative **555**.[227] Cyclopentannulation reactions of β-aminoalkenylcarbene–chromium complexes were employed as a key step for syntheses of angularly fused triquinanes.[228] In several examples, useful organic groups were incorporated for the deployment of tandem multiple ring-forming reactions. Reaction with bis(alkenyl)acetylenes (e.g., **558**) led to indanone derivatives (e.g., **561**) in a complex tandem process involving

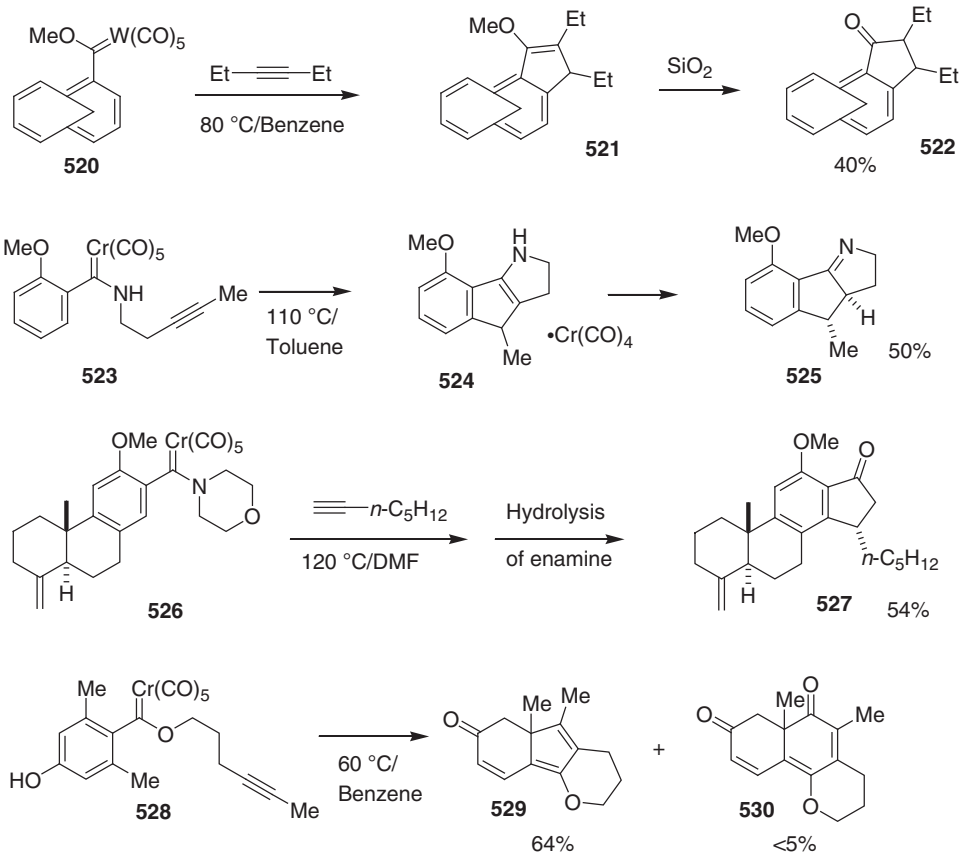


Scheme 50



Scheme 51

formation of the bis(alkenyl)aminocyclopentadiene **559**, followed by electrocyclic ring closure to form cyclohexadiene derivative **560**, followed by elimination of amine, aromatization, and enol ether hydrolysis.[229] The major products are 5-alkylidene-2-cyclopentenones or 2-alkenyl-2-cyclopentenones (e.g., **564**) if β-amino-α,β-unsaturated carbene complexes (e.g., **563**) are coupled with alkynes in ethereal solvents. This reaction process is the basis of a synthesis of the antihypertensive oudenone (**565**).[230] Synthesis of bulgaramine using a related intramolecular cyclopentannulation process was also reported.[231] In several cases, the reaction of β-amino-α,β-unsaturated carbene complexes and multiple equivalents of an alkyne leads to comparatively complex polycyclic ring systems.[232,233] Similar reaction pathways were observed for β-alkoxy-α,β-unsaturated molybdenum carbene complexes reacting with alkynes. The reaction of dioxenylmolybdenum carbene complex **566** and several enyne systems affords complex polycyclic ring systems (e.g., **569**) in a process that involves [3 + 2]-cycloaddition followed by intramolecular Diels–Alder reaction.[234]

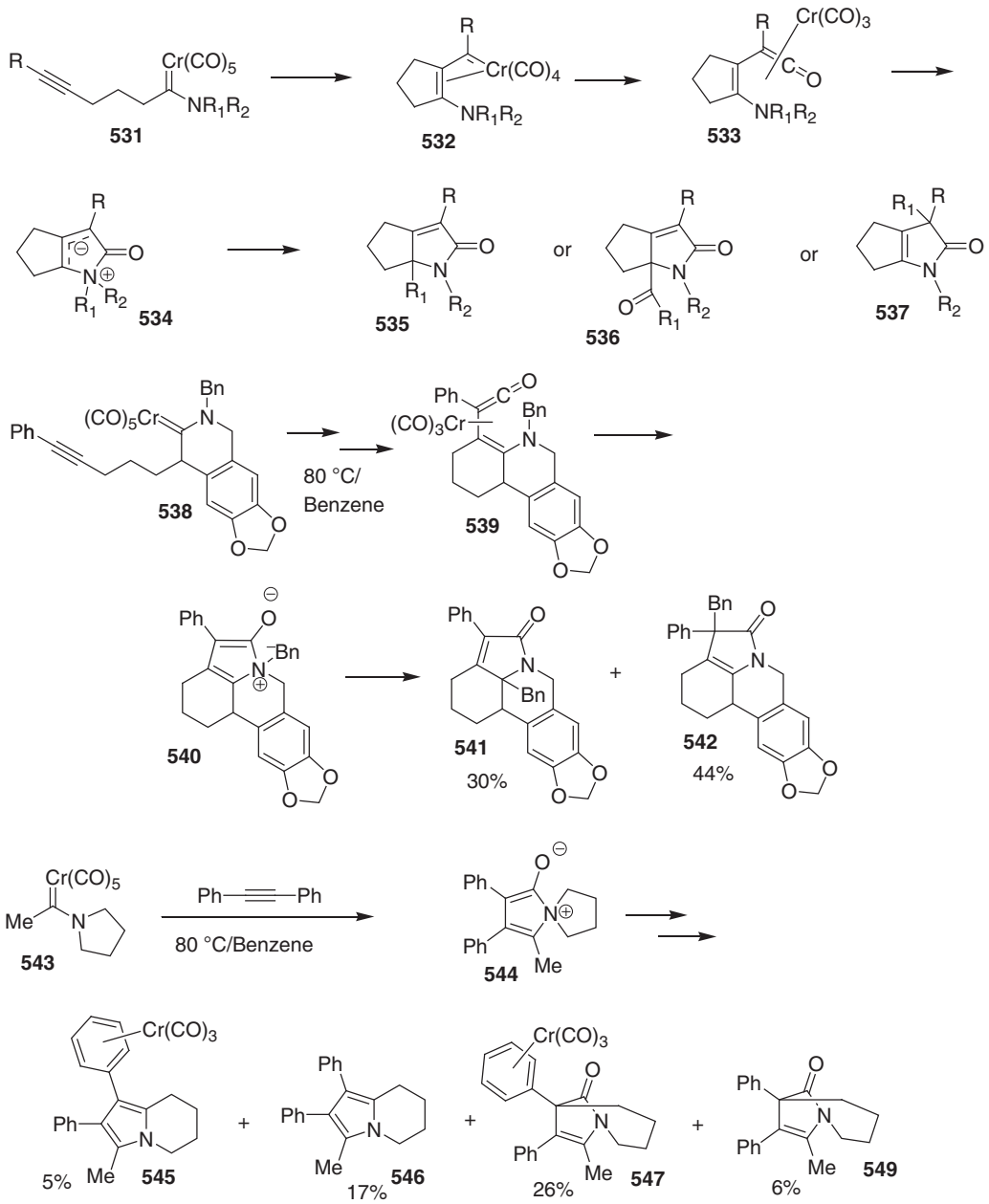


Scheme 52

The coupling of alkynes with cyclopropylcarbene–chromium complexes affords cyclopentenone derivatives (e.g., **6**→**571**, Scheme 55).[235,236] The myriad of reactions that emanate from cyclopropylcarbene-Group 6 metal complexes have been reviewed.[237] The reaction produces a cyclopentadienone intermediate (**570**) through a complex mechanistic process involving loss of ethylene (a formal [4 + 2 + 1–2]-cycloaddition), which is reduced by the chromium byproduct of the cycloaddition process. In some cases the cyclopentadienones (e.g., **573**) can be isolated and are the major products when reactions are conducted in heptane solvent.[238] The reduction process involves cyclopentadienide intermediates (e.g., **576**), which can be intercepted if the starting alkyne features leaving groups in the propargyl position, resulting in alkylidenecyclopentenone derivatives (**6** + **579**→**582**).[239] The intramolecular reaction featuring carbene complexes that have chiral propargyl groups (e.g., **583** and **586**) proceeds stereoselectively to afford five-membered rings with a high degree of stereocontrol, affording the thermodynamically more stable ring system.[240] This process has been used as cornerstone for the preparation of vitamin D synthetic intermediates.[241] Cyclopentenone products similar to those from Section 5.25.3.2.1 can also be produced from the coupling of alkylcarbene complexes with alkynes;[242] however, the reaction is mechanistically quite different. This method is most effective for dialkylacetylenes; cyclobutenones and two-alkyne insertion products are formed as minor byproducts in most of these studies. Compounds of this type have also been observed in the coupling of molybdenum carbene complexes with alkynes,[211,243] and in intramolecular couplings involving aminocarbene complexes.[244] Mixtures of the vinylogous ester isomer **590** and the 4-alkoxy-2-cyclopentenone isomer **591** were obtained in most cases.

The coupling of alkynylcyclobutenols (**592**, Scheme 56), readily derived from cyclobutenediones, with Fischer carbene–chromium complexes leads to cyclopentendione derivatives (e.g., **595**).[245] A mechanism involving alkyne insertion, leading to the unstable but electrophilic vinylcarbene complex intermediate **593**, followed by acyl migration to the electrophilic carbene carbon and demetallation has been proposed. The reaction process is general for a variety of carbene complexes, including alkylcarbene, arylcarbene, vinylcarbene, and cyclopropylcarbene complexes. This reaction is unique to the cyclobutenedione-derived systems; other related systems, including the saturated cyclobutane ring systems, do not undergo the analogous ring expansion process. In cases where there is competition from Dötz-type benzannulation reaction pathways, the ring expansion pathway is the exclusive reaction pathway.

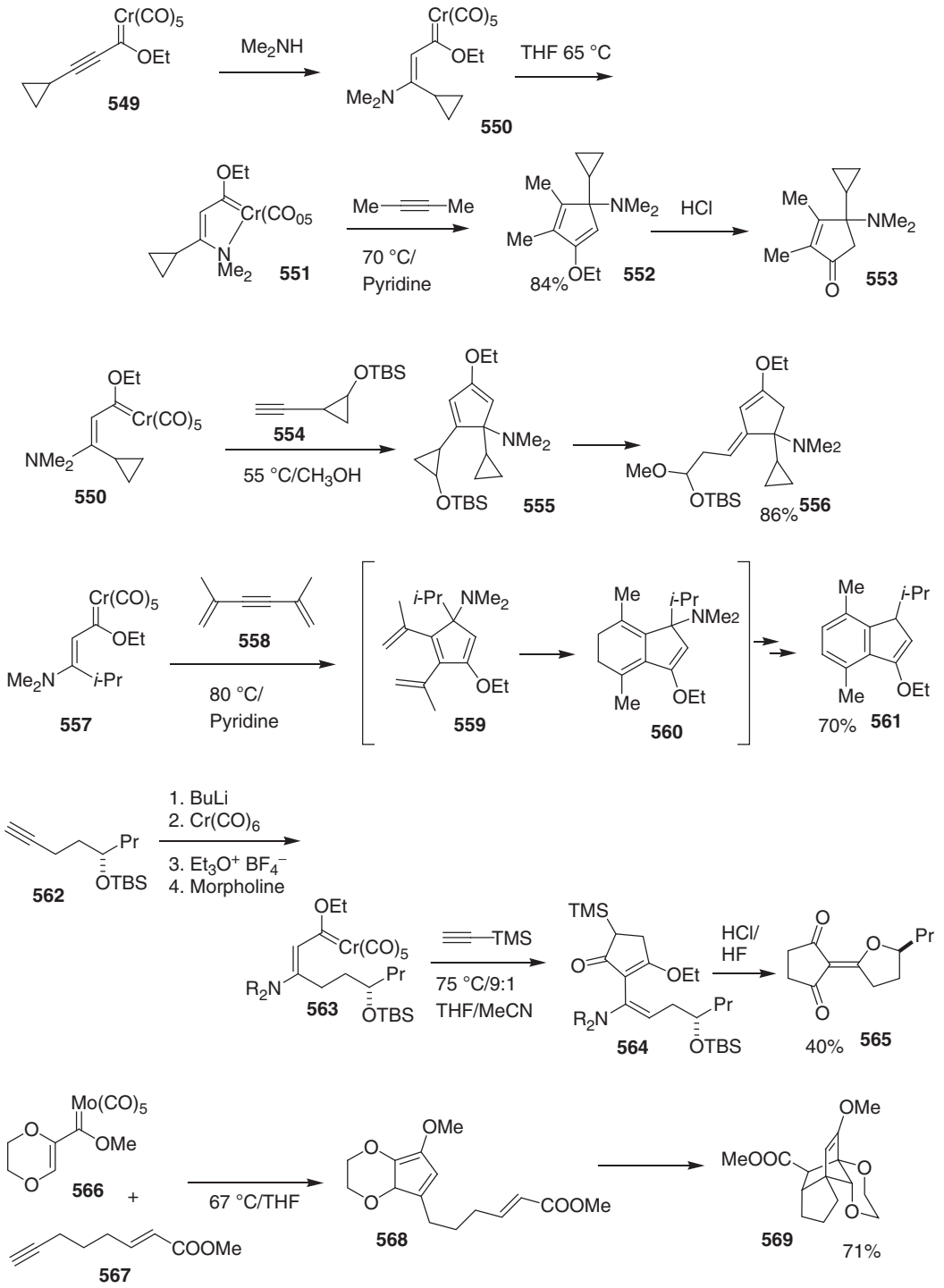
The reaction of methylcarbene complex **1** with enyne–aldehydes (e.g., **596**, Scheme 57) or enyne–ketones led to vinylfuran derivatives (e.g., **599**).[246] A mechanism involving nucleophilic attack of the carbonyl oxygen at the carbene carbon of the vinylcarbene complex intermediate **597** (forming carbonyl ylide **598**) followed by demetallation was proposed. The reaction of



Scheme 53

γ,δ-unsaturated Fischer carbene complexes (e.g., **601**) with enyne aldehydes afforded simple furans (e.g., **602**), which undergo Diels–Alder reactions at elevated temperatures leading to hydronaphthalenes (e.g., **603**).[247]

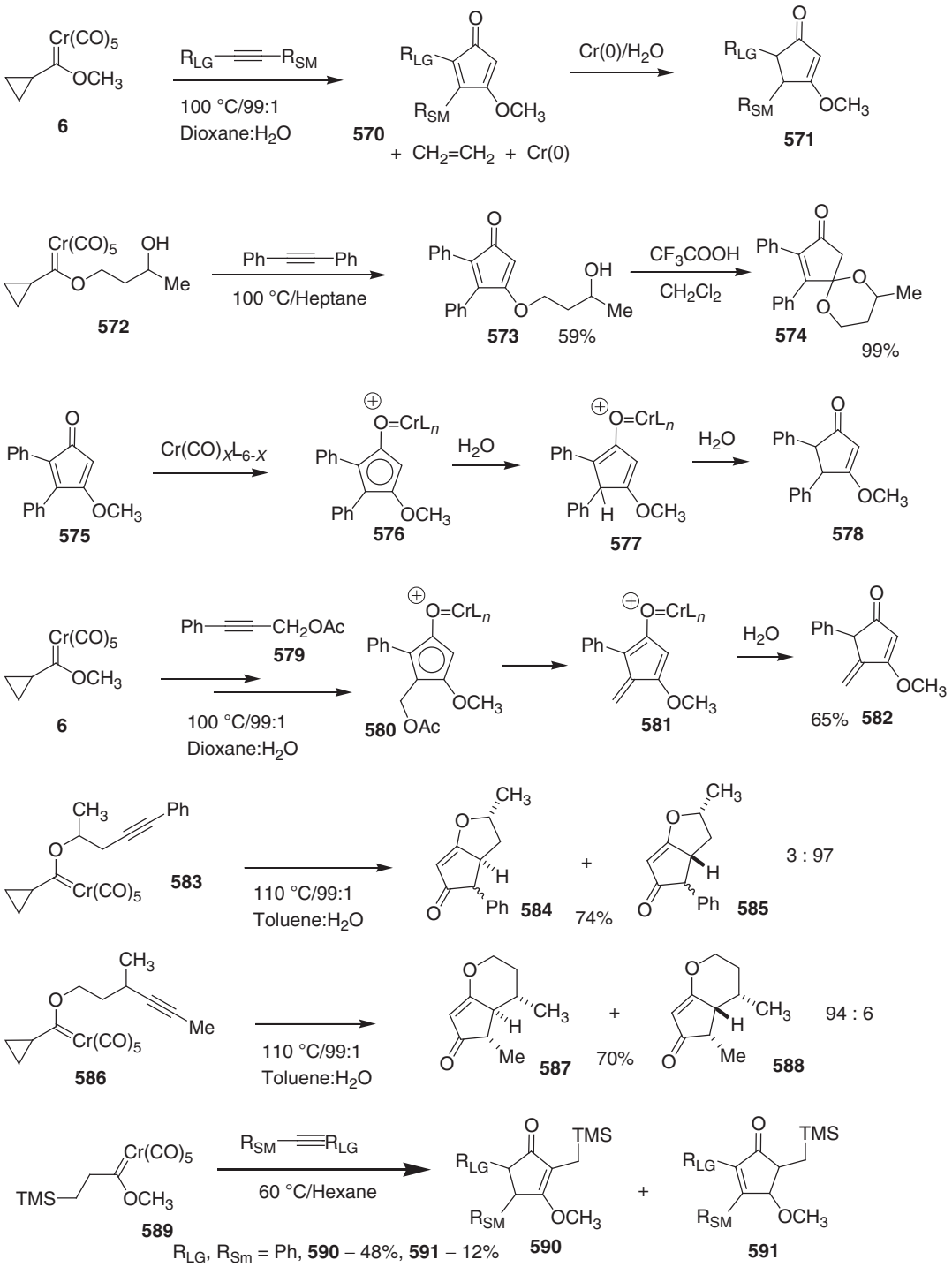
Coupling of carbene complexes with *o*-alkynylbenzaldehyde derivatives (e.g., **604**) led to the generation of isobenzofurans (e.g., **605**) (Scheme 58).[248,249] Simple coupling of carbene complexes with enyne–carbonyl systems resulted in the formation of alkylidenephthalans (e.g., **607**) via a net 1,7-hydrogen shift followed by enol ether hydrolysis. A three-component coupling was observed if the reaction was conducted in the presence of electron-deficient alkenes (e.g., **608**). The intermediate isobenzofuran undergoes a Diels–Alder reaction in this case. Coupling of γ,δ-unsaturated carbene complexes (e.g., **611**, Scheme 59) with *o*-alkynylbenzaldehyde derivatives led to the formation of hydrophenanthrene derivatives (e.g., **613**) in a single reaction pot,[250,251] and proceeds with enhanced efficiency in aqueous solvent systems.[252] A mechanism involving generation of an isobenzofuran (**612**), followed by intramolecular Diels–Alder reaction and oxanorbornene ring opening was proposed. The reaction proceeded with a very high degree of relative asymmetric induction. Additional variants include the preparation of dihydrophenanthrenes using electron-rich systems (e.g., **614**),[253,254] alternate tethering schemes (e.g., **617** + 1 → **620**),[255] and use of pyridine systems in place of benzene ring systems (e.g., **621** + **601** → **622**),[256–259] Less efficient processes include the use of amides in place of



Scheme 54

ketones and aldehydes,[260] and use of β-cyanocarbene complexes in place of γ,δ-unsaturated carbene complexes to afford phenanthrenes.[261]

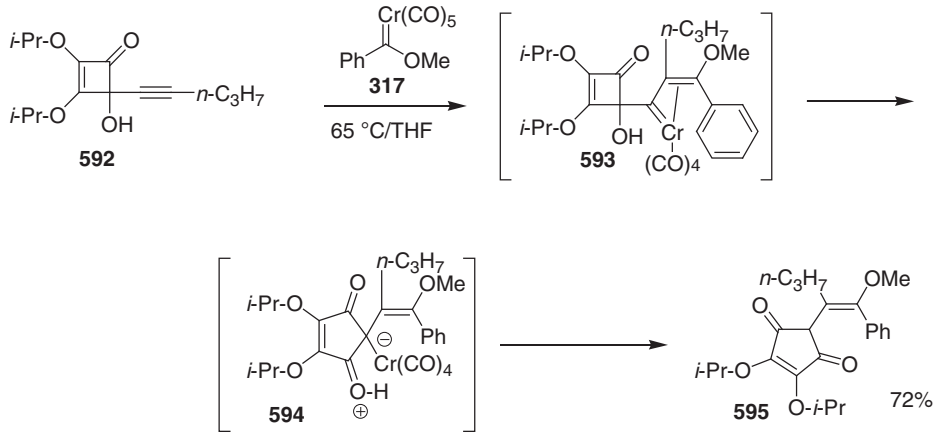
Isobenzofuran intermediates (e.g., **625**, Scheme 60) that are derived from α,β-unsaturated carbene complexes (e.g., **624**) could be captured by dimethyl acetylenedicarboxylate (**626**) to provide [8 + 2]-cycloaddition products (e.g., **628**) as single diastereomers.[262] Both isobenzofuran Diels–Alder products (e.g., **627**) and [8 + 2]-cycloaddition products are typically produced in this reaction, and their ratio varies considerably with the carbene complex and alkyne–ketone substituents. In some cases, the Diels–Alder adducts thermally rearrange to [8 + 2]-cycloadducts.[263] Coupling of simple enyne aldehydes (e.g., **629**) with



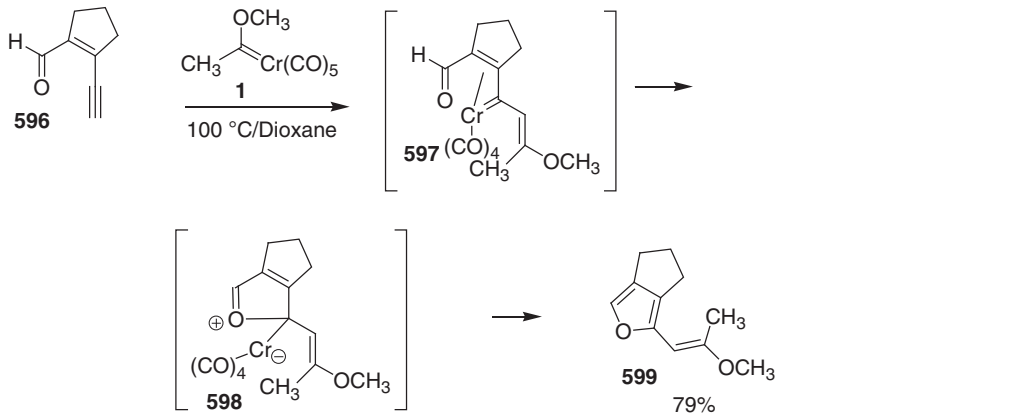
Scheme 55

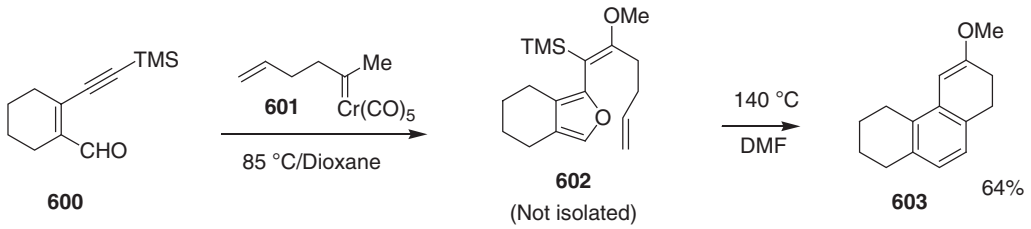
alkenylcarbene complexes leads to dienylfurans (e.g., **630**), which undergo exclusive [8 + 2]-cycloaddition on treatment with dimethyl acetylenedicarboxylate.[264]

Coupling of carbene complexes with enyne–hydrazones (e.g., **632**, Scheme 61) affords pyrrole derivatives (e.g., **634**) through a mechanism involving alkyne insertion followed by nucleophilic addition of the imine nitrogen to the carbene carbon of the intermediate alkenylcarbene complex **633** followed by demetallation.[265] Benzo-fused analogs of these systems have also been demonstrated. The three-component coupling of 2-alkynylbenzaldehyde hydrazones (e.g., **635**), carbene complexes, and electron-deficient alkynes (e.g., **626**) leads to substituted naphthalene derivatives (e.g., **638**).[266] The carbene–alkyne coupling process results in isoindoles (**637**), which undergo Diels–Alder reaction with the alkyne followed by nitrene extrusion to provide the



Scheme 56





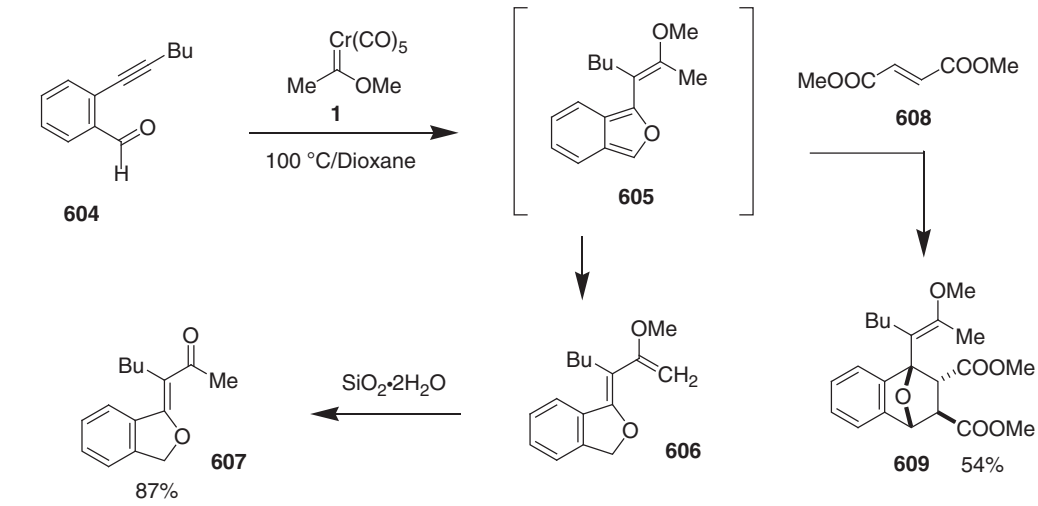
Scheme 57

naphthalene derivatives. Since the isoindole intermediates are more stable than isobenzofurans, the dienophile can be added after generation of the isoindole system.

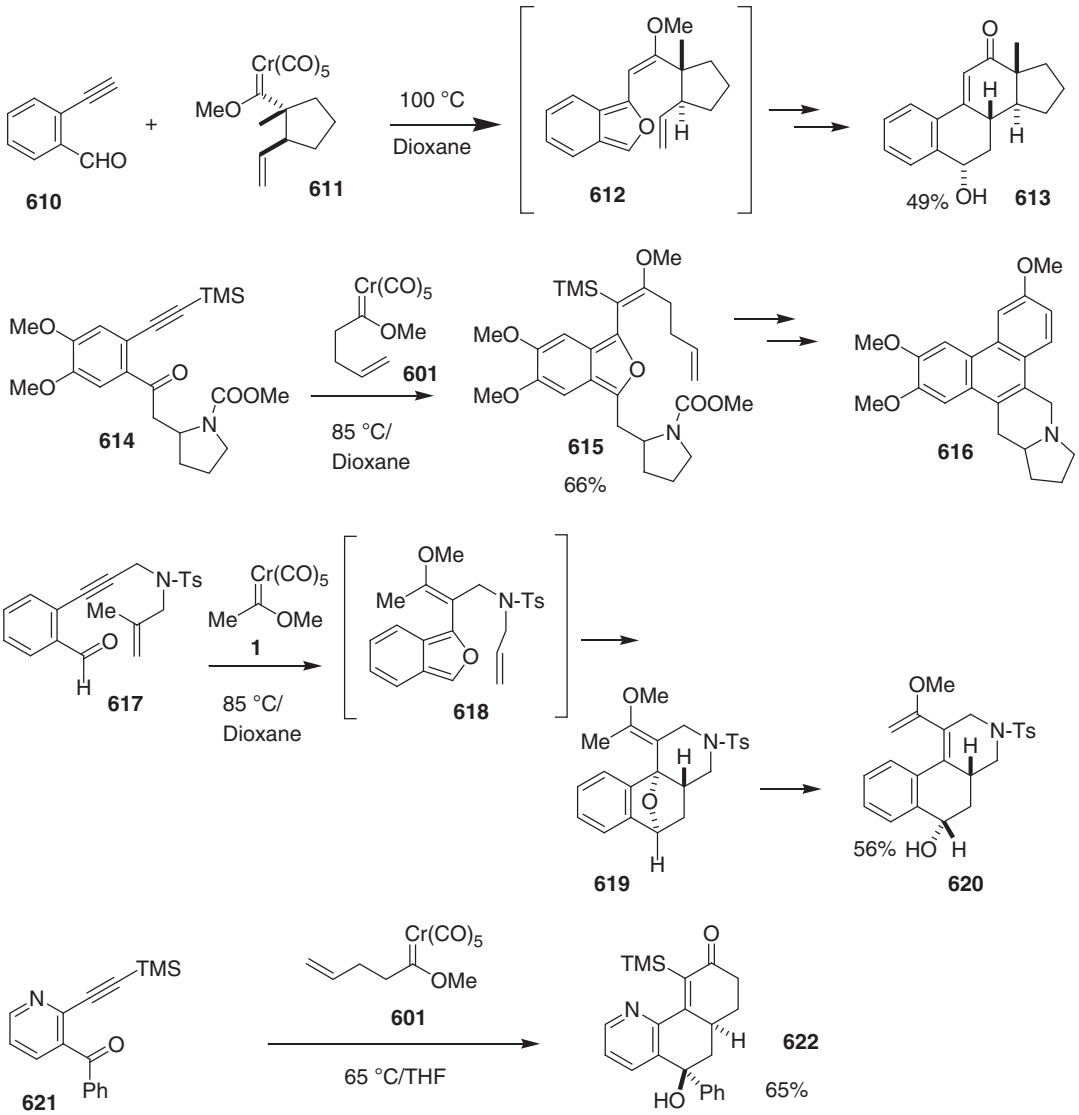
The coupling of iminocarbene complexes (e.g., **639**, **643**, Scheme 62) and alkynes led to pyrroles (e.g., **640**) analogous to those obtained from nitrile ylide cycloadditions.[267,268] These pyrroles were produced in a highly regioselective manner. In most of the cases, hydroxypyridines were minor products; however, these become the major products when using alkoxy-substituted iminocarbene complexes (e.g., **643**). Reaction with nitriles afforded imidazoles (e.g., **641**). Reaction with alkenes led to dihydropyrroles (e.g., **642**). The observed regioselectivity was attributed to resonance structure **639a**, with chromium doing a Michael addition to give the products after electrophilic capture and reductive elimination.

5.25.3.2.3 Six-membered rings

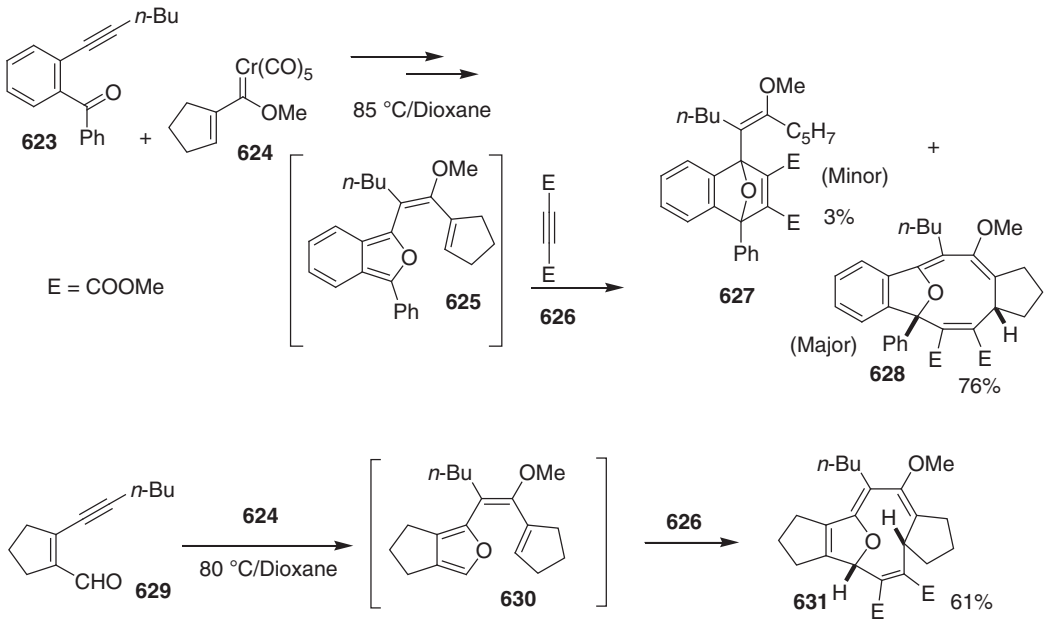
Among the most useful reactions of Fischer carbene complexes is the formation of phenols from the coupling of alkynes with α,β-unsaturated carbene complexes or arylcarbene complexes, which is commonly known as the Dötz benzannulation reaction (Scheme 63).[269] The normal product of this coupling is the *p*-methoxyphenol derivative. The generally accepted mechanism of



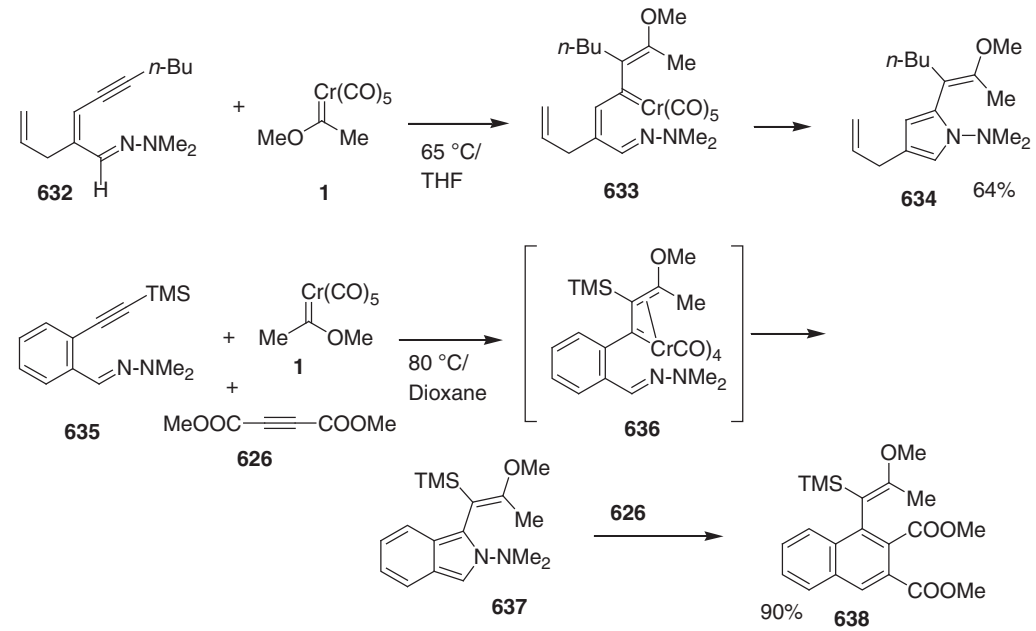
Scheme 58



Scheme 59



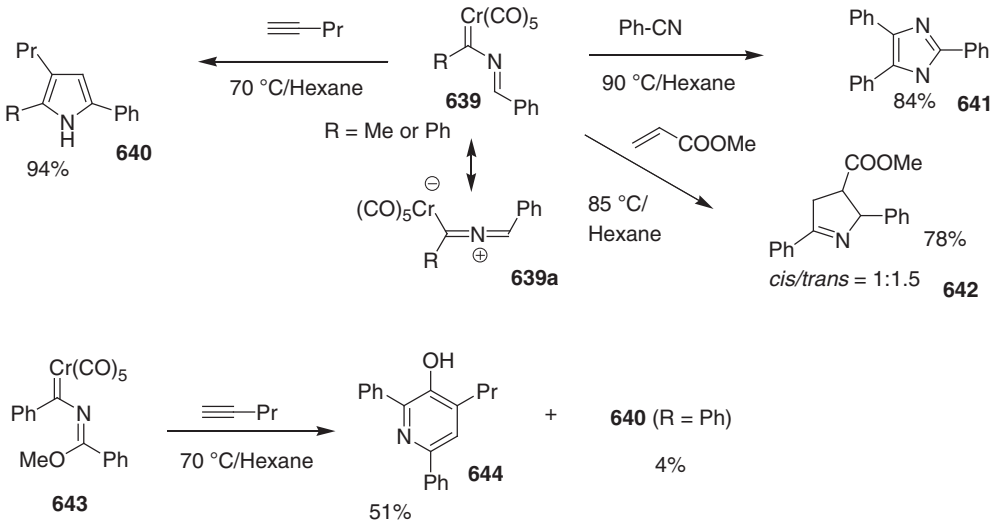
Scheme 60



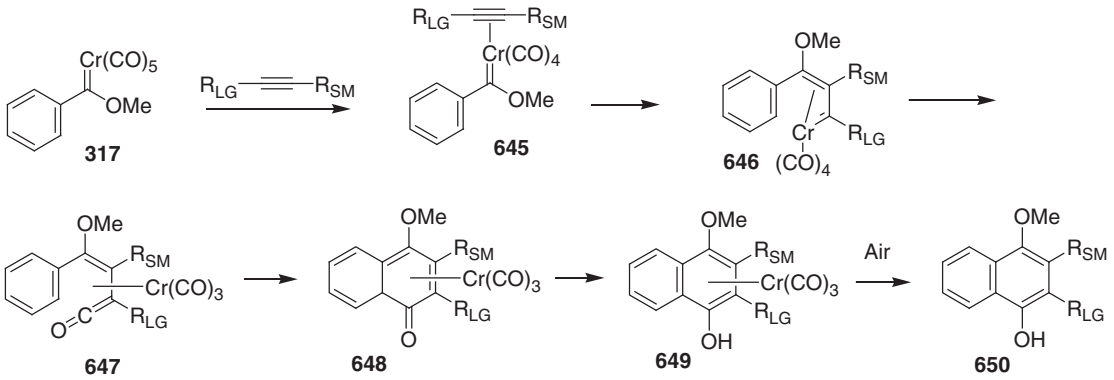
Scheme 61

the Dötz reaction is depicted in Scheme 63. The scope and limit of this reaction have been studied widely, and both inter- and intramolecular versions of this reaction have been reported for a diverse array of highly functionalized alkynes and carbene complexes. Numerous cases where this reaction has been employed for the synthesis of complex molecules have been presented.

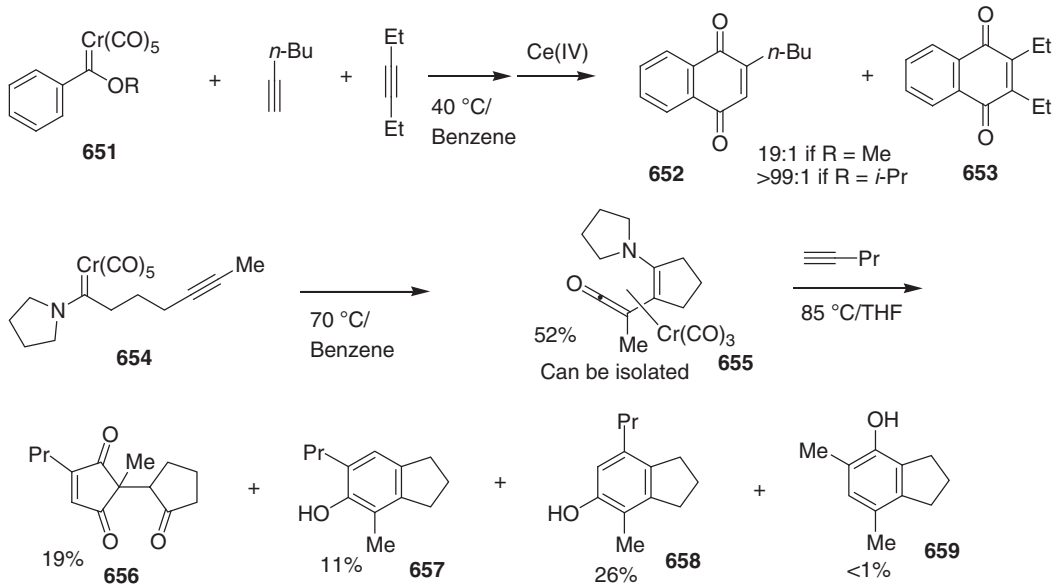
Several fundamental studies that advance the mechanistic understanding of the Dötz benzannulation reaction have been documented. A systematic examination focusing on the relative reactivity of various alkynes in benzannulation reactions was reported.[270] The relative reactivity of alkynes with arylcarbene complexes of general structure **651** (Scheme 64) was governed primarily by sterics, and the degree of selectivity was enhanced through use of sterically demanding carbene complexes. In some cases, intermediates of the Dötz benzannulation can be isolated. A study where the intermediate vinylketene complex can be isolated (**655**), followed by studies of its transformation to phenols (**657–659**) was reported.[271] Stepwise cyclopentannulation



Scheme 62

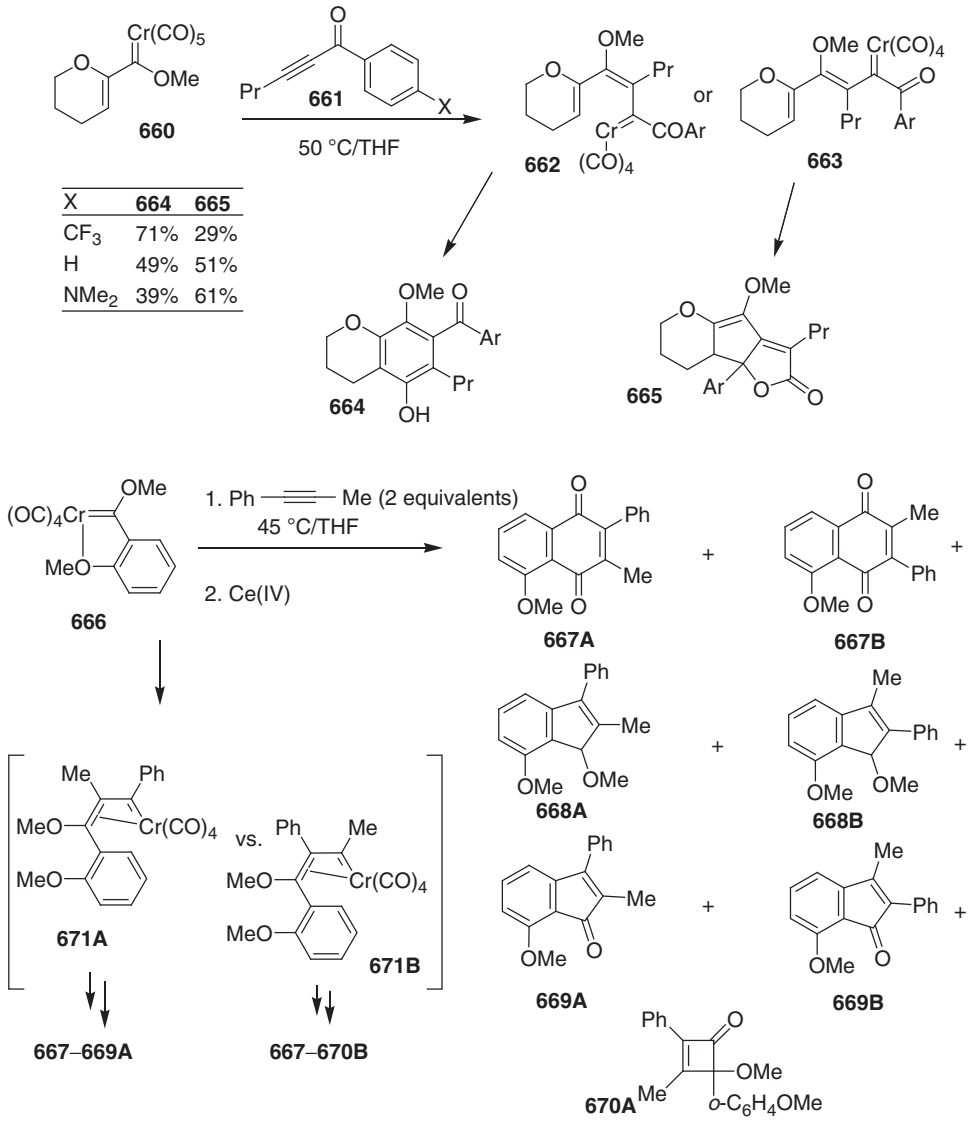


Scheme 63



Scheme 64

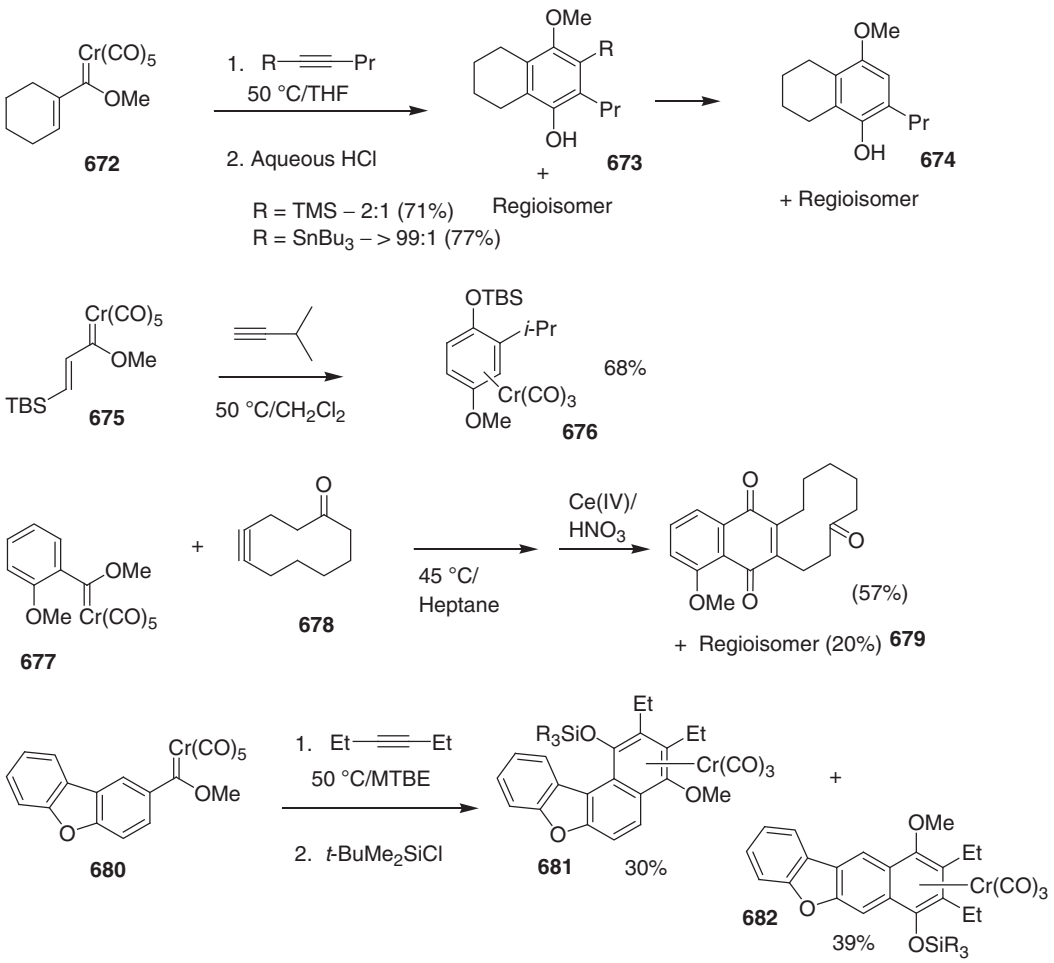
and Dötz benzannulation reactions were demonstrated for the coupling of α,β-unsaturated aminocarbene complexes and dimethyl acetylene dicarboxylate.[272] A detailed study of electronic effects in an early step of the Dötz benzannulation, vinylcarbene complex (**662** and **663**, Scheme 65) formation, was conducted.[273] The reaction of alkenylcarbene complex **660** and the aroylacetylene **661** afforded mixtures of the benzannulation product **664** (from the *Z*-vinylcarbene complex **662**) and the van Halban–White product **665** (from the *E*-vinylcarbene intermediate **663**). The electron density of the aromatic ring had a profound effect on this product distribution. Electron-withdrawing groups favored the benzannulation product due to a preference for *trans* orientation of the methoxy and the more electron-withdrawing substituent at the α-carbon in **662**. A similar electronic dependence was also noted for aryloxycarbene complexes. A detailed mechanistic study of the relationship between regiochemistry and alkyne concentration in the coupling of arylcarbene complexes (e.g., **666**) with alkynes was conducted.[274] The regiochemistry for reaction with 1-phenylpropyne was dependent on the concentration, and attributed to interconversion of the regioisomeric vinylcarbene intermediates (**671A** and **B**) followed by ligation to the alkyne in a later step of the reaction. It was also noted that benzannulation products (**667**) were formed with a higher degree of regioselectivity than the corresponding indene products (**668** and **670**). Two hypothetical pathways for isomerization of **671A** and **B** were deemed reasonable: (1) reversible insertion of the alkyne and (2) isomerization through a cyclopropene intermediate. An unusual bimolecular mechanism was noted in the coupling of *o*-methoxyphenylcarbene complex **666** with alkynes at high concentration. The intramolecular reaction of alkyne-containing carbene complexes and alkynes to afford benzannulation products in competition with cyclopentenediones was studied with respect to reaction conditions and solvents.[275] The Dötz benzannulation reaction can be totally mimicked through



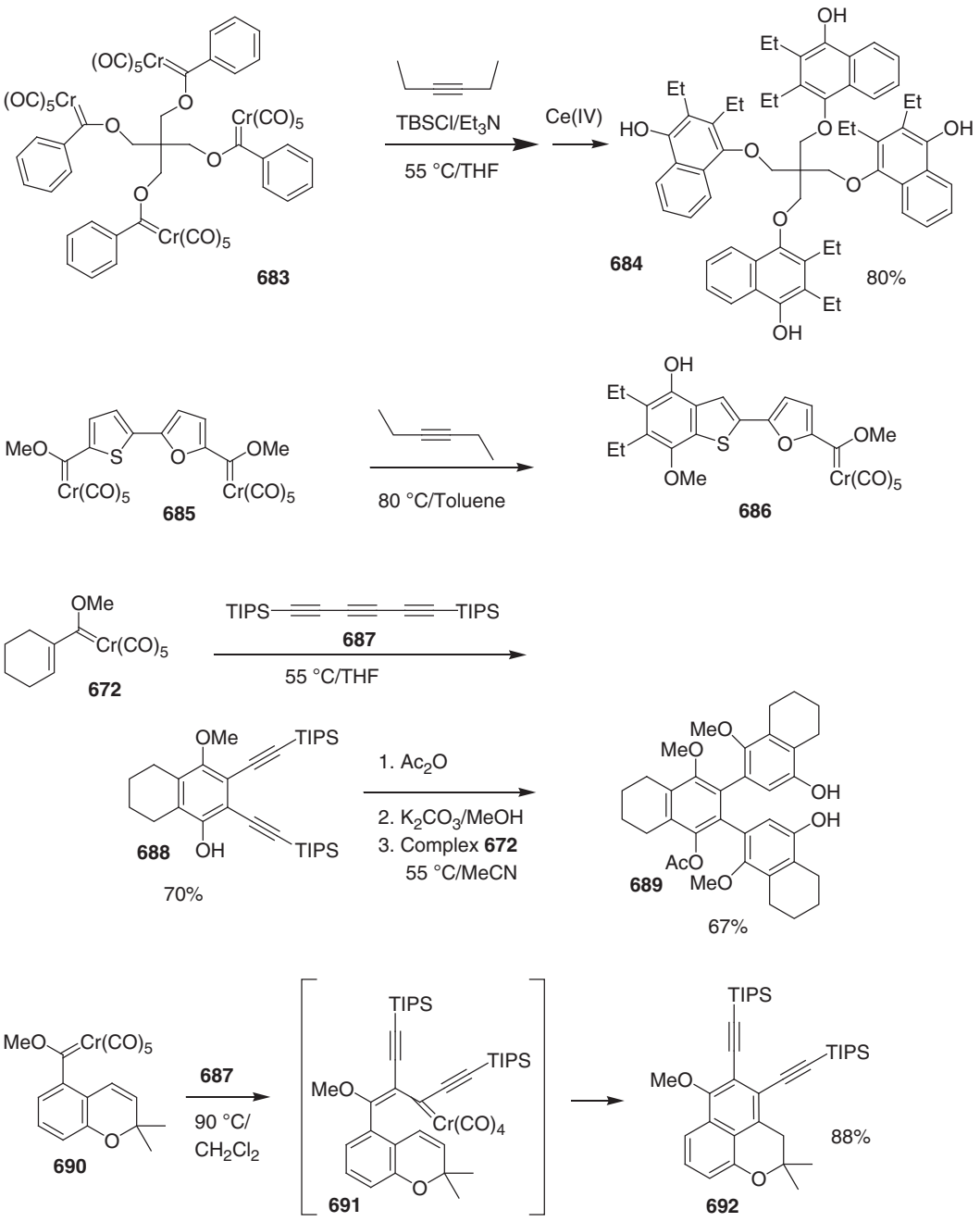
Scheme 65

the rearrangement of alkynylcyclopropenes in the presence of Group 6 metal carbonyl derivatives.[276] Several computationally based studies of the Dötz benzannulation reaction have been reported.[277–282]

Many examples of benzannulation using α,β-unsaturated chromium–carbene complexes and alkynes (commonly known as the Dötz reaction) have been documented since the previous chapter. Several examples are depicted in **Scheme 66**. The use of stannylacetylenes resulted in products not anticipated based on the accepted notion of sterically controlled regiochemistry (see general structure **673**) using unsymmetrical alkynes.[283] To a lesser extent the process was also observed with silylated alkynes. Use of β-silyl-substituted vinylcarbene complexes (e.g., **675**) as synthons for the parent vinylcarbene complex was also reported.[284] In this process, the silicon migrates to the phenolic oxygen to afford a stable arene–chromium complex (**676**). C-aryl glycosides were prepared via the coupling of alkynylglycals with arylcarbene–chromium complexes.[285] Other examples employing carbohydrate-based carbene complexes or alkynes were successfully demonstrated.[286] Successful benzannulations using cyclic alkynes (e.g., **678**) were also reported.[287,288] Aminobenzannulation reactions were observed in the coupling of β-carbomethoxy-α,β-unsaturated aminocarbene complexes with simple alkynes.[289] Both linear and angular fused benzannulation products (formation of **681** vs. **682**) were obtained in the benzannulation of dibenzofuran–carbene complexes with 3-hexyne.[290] Formation of benzannulation products using diphenylacetylene derivatives that feature an ortho carbonyl group on one of the phenyl rings was reported.[291] Quinones fused to benzofurans were prepared through Dötz benzannulation reactions using benzofuranylcarbene complexes.[292] The synthesis of 5,8-quinolinedione derivatives was achieved using benzannulation reactions of dihydropyridylcarbene complexes.[293] Benzannulations using cyclic carbene complexes featuring an exocyclic alkene were also demonstrated.[294,295] Several examples of the use of densely functionalized alkynes in the Dötz benzannulation reaction have been reported.[296–298] The individual naphthyl rings of VAPOL ligands were prepared from arylcarbene complexes.[299] Coupling of tetracarbene complex **683** (**Scheme 67**) with 3-hexyne led to corresponding tetranaphthoxy ether derivative **684**; the crude product before decomplexation of chromium consisted of seven isomers.[300] A modified Fischer synthesis was also employed for the synthesis of heterocyclic bis(carbene) complexes (e.g., **685**).[301,302] Monobenzannulation and dibenzannulation reactions were reported for the bis(chromium) and mixed chromium/tungsten complexes. Other examples of benzannulation in the presence of

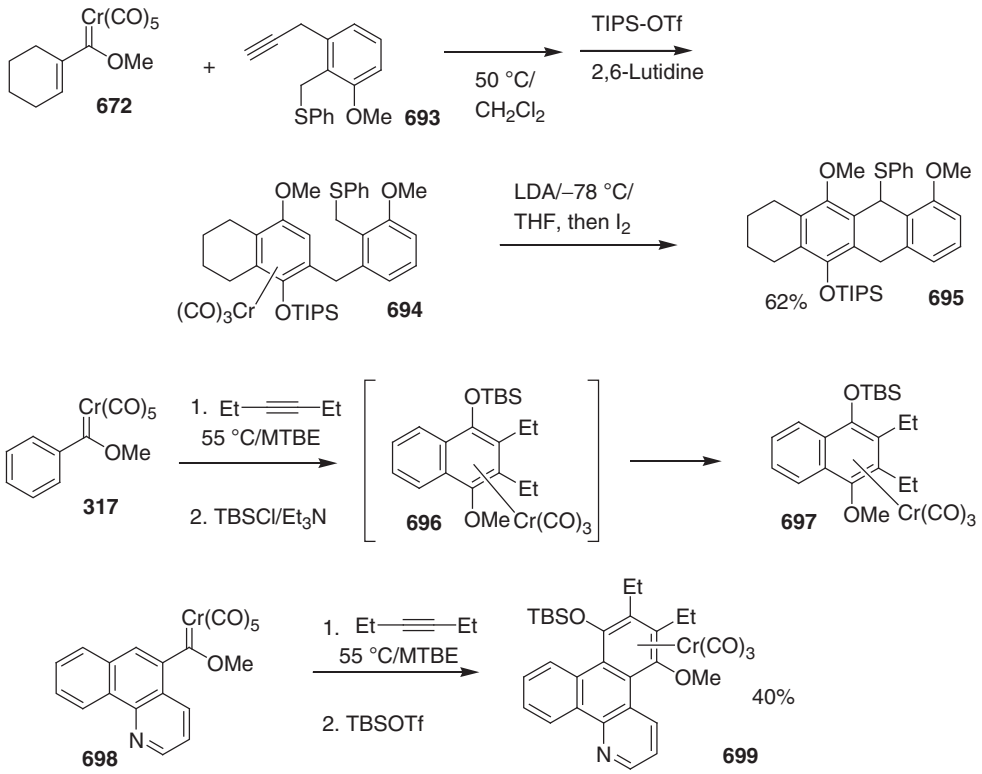


Scheme 66



Scheme 67

a bystander metal carbene complex group have also been reported.[303] Several examples of mono-, di-, and tri-benzannulation reactions were reported for the coupling of carbene complexes with conjugated diynes and triynes. Reaction of triyne **687** and cyclohexenylcarbene complex **672** led to the *o*-dialkyne-substituted naphthol derivative **688**.[304] Acetylation of the alcohol and desilylation of the bis(alkyne) followed by a double benzannulation using two equivalents of the carbene complex **672** led to tris(quinone) precursor **689**. This synthetic sequence was not successful for alkyl analogs of **687** due to preferential benzannulation of the outer triple bonds. The synthesis of naphthopyrans (e.g., **692**) via coupling pyran complex **690** with monoalkynes and triynes was followed by a secondary cyclization process to afford a tricyclic compound (**692**).[305] Benzannulation of 2,2-dimethylvinylcarbene-chromium complex and various alkynes was employed for the preparation of a 5,5-dimethylcyclohexen-1,4-dione combinatorial library.[306] Several technique-based improvements to the Dötz benzannulation reaction were reported, including (1) dry state adsorption,[307] microwave irradiation,[308] (2) solid-phase benzannulation,[309] (3) use of ionic liquid solvents,[310] (4) use of 1,2-dichloroethane as solvent, in which the reaction proceeds at 30 °C,[311] and (5) use of ultrasound

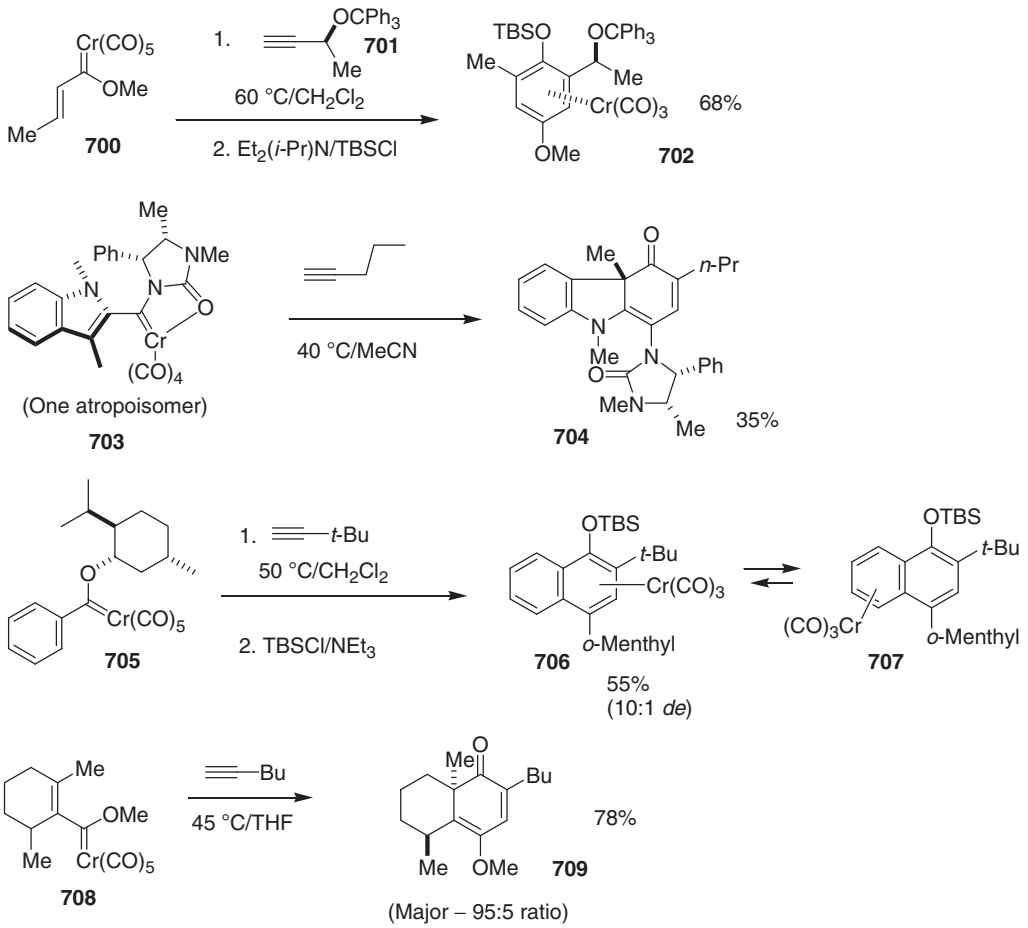


Scheme 68

conditions.[312] Pyrrolocarbene–chromium complexes serve as surrogates for alkoxycarbene complexes in cyclopropanation, benzannulation, and β-lactam syntheses.[313]

Isolation of a stable arene complex typically requires protection of the phenol group before purification. Representative examples of this process are depicted in Scheme 68. Sequential benzannulation followed by nucleophilic addition to the resulting isolable arene–chromium complex was employed for the synthesis of anthracene-type structures (e.g., **695**).[314] In many cases the complexes were subjected to haptotropic rearrangement. Examples of these studies include (1) formation of naphthalene-$Cr(CO)_3$ complexes (e.g., **696**) and subsequent studies of haptotropic rearrangements,[315,316] (2) formation and haptotropic rearrangements of phenanthrene-$Cr(CO)_3$ complexes,[317–319] (3) formation and haptotropic rearrangements of cymantrene-fused aromatic systems,[320] (4) benzannulation of quinoline–carbene complexes (e.g., **698**) followed by studies of haptotropic rearrangements of the resulting arene-complexes (e.g., **699**) (and *N*-complexed analogs),[321] and (5) related studies of stilbene–carbene complexes and azobenzene–carbene complexes.[322]

Numerous examples of stereocontrolled benzannulation or cyclohexadienone annulation leading to arene complexes of defined stereochemistry have been documented (Scheme 69).[43] In many of the cases, a chiral group on the carbene ligand controls the stereochemistry in the benzannulation product. Examples include (1) stereoselective benzannulation using chiral alkynes that contain a propargylic stereocenter (e.g., **701**),[323] (2) stereoselective benzannulations using chiral auxiliary-containing phenyl- and alkenylcarbene complexes,[324] (3) use of chiral ancillaries (e.g., **703**) in benzannulation reactions involving alkynes and Fischer carbene complexes,[325] (4) diastereoselective benzannulation reactions using menthyloxycarbene complexes (e.g., **705**) and studies of the haptotropic isomerization of the resulting naphthalene–chromium complexes,[326] (5) benzannulation using arylcarbene complexes fused to a ferrocene ring,[327] (6) coupling of alkynes with chiral *m*-cyclophanylcarbene complexes, which afforded naphthol–chromium complexes with a moderate degree of stereocontrol,[328] and (7) stereoselective cyclohexadienone annulations using alkenylcarbene–chromium complexes (e.g., **708**) and propargylic alcohol derivatives.[329] Benzannulation of carbohydrate-templated chromium carbene complexes proceeds with a high degree of relative asymmetric induction in some cases.[330] Stereoselective benzannulations that involve atropoisomerism are depicted in Scheme 70. Two diastereomeric benzannulation products were observed from the reaction of nonracemic and axial chiral bis carbene complexes of chromium (**710**) and 3-hexyne.[331] These isomers were converted to a single quinone (e.g., **711**) on oxidation. An atroposelective benzannulation reaction was observed in the coupling of cyclohexenylcarbene complex **713** (obtained by Diels–Alder reaction of alkynylcarbene complex **712** with 2,3-dimethyl-1,3-butadiene) with *o*-tolylacetylene derivatives (e.g., **714**).[332] Both of the expected isomers **715** and **716** were observed; however, either could be obtained as the major product depending on the timing of the addition of the phenol protecting group. The kinetic product **715** was obtained if the reaction was conducted in the presence of the silylating agent. The thermodynamic product **716** was obtained when the silylating agent was added later, or if a less bulky



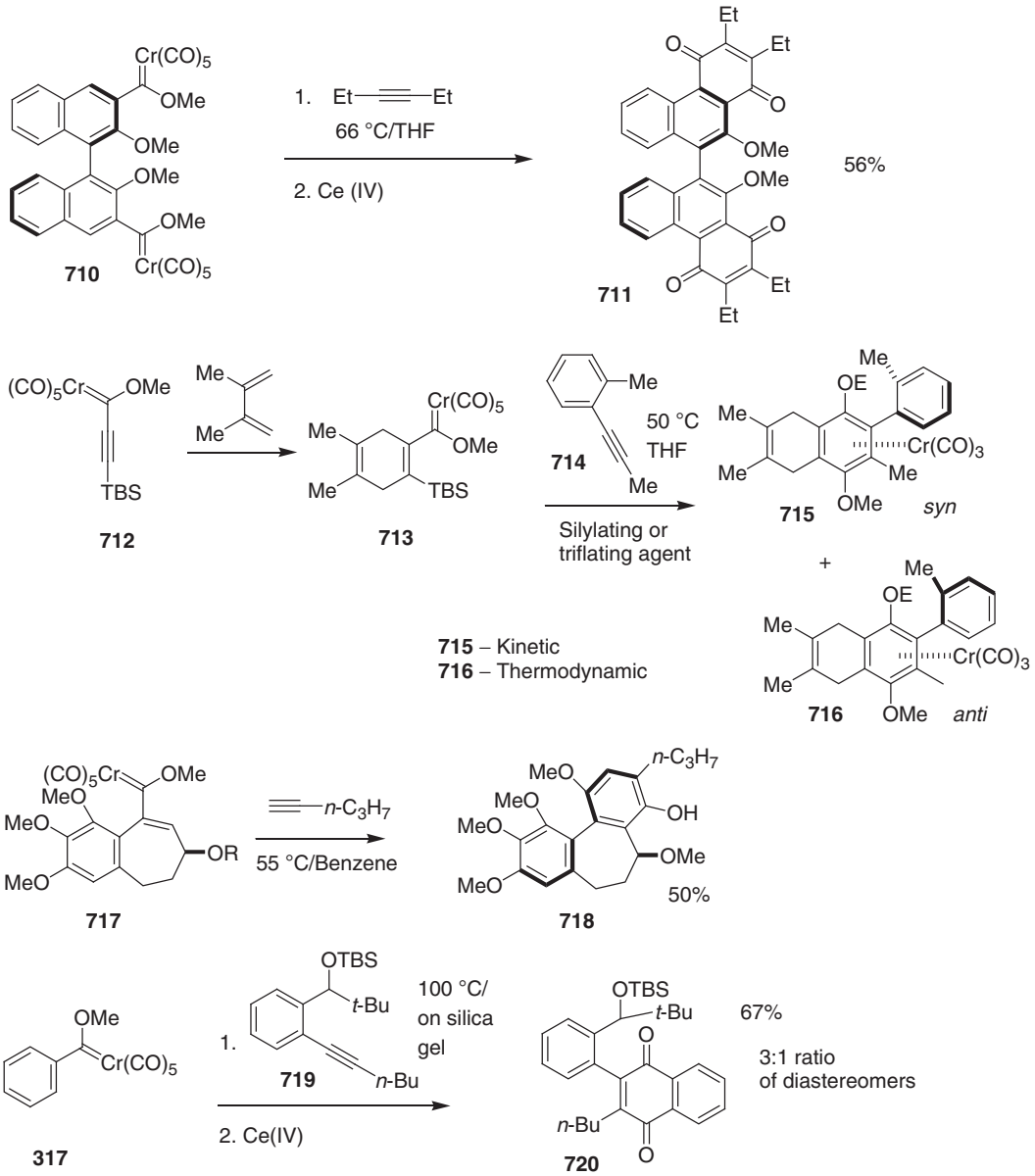
Scheme 69

group like a triflate was attached to the phenol. Atropoisomer-selective formation of benzene rings from coupling of carbene complex **717** with 1-pentyne was employed as a model system for the construction of allocolchicinoids.[333] Atroposelective benzannulation reactions involving arylacetylene derivatives that contain a chiral substituent ortho to the alkyne group (e.g., **719**) were also reported.[334] Helicene-type compounds were formed in the reaction of bis(carbene) complexes linked through binaphthyl systems.[335]

Photolysis of ortho–alkynylcarbene complex **721** (Scheme 71) afforded alkyne–carbene complex **722**, which was stable enough for spectroscopic characterization.[336] Thermolysis of **722** in refluxing methyl *t*-butyl ether led to chrysene derivative **723** (a single diastereomer), which results from an unusual benzannulative dimerization reaction. Direct thermolysis of either the chelated or the nonchelated carbene complex afforded predominantly the carbene dimerization product. The coupling of 2-alkynylphenylcarbene–chromium complexes (e.g., **725**) with alkyne–aldehydes linked through heterocyclic ring systems (e.g., **724**) led to polynuclear aromatic systems (e.g., **728**).[337] A mechanism that involves formation of a heterocycle-fused pyrone derivative (**726**), followed by intramolecular Diels–Alder reaction and elimination of CO_2 was proposed.

Several examples of the construction of unusual molecular architectures using the Dötz reaction have been documented (Scheme 72). The intramolecular coupling of alkynes and alkenylcarbene complexes featuring 6-atom and 13-atom tethers (**729**) led to *m*-cyclophane derivatives (e.g., **730**).[338,339] Optimal formation of the cyclophane was observed employing the 13-atom tether, and mostly dimeric cyclophanes were obtained using the 6-atom tether. The formation of *m*-cyclophanes via the intramolecular coupling of benzo analogs (e.g., **731**) was also observed.[340] Mixtures of *m*- and *p*-cyclophanes (e.g., **734** and **735**) were produced from benzannulation reactions using analogous compounds featuring a 1,1-disubstituted alkene group (e.g., **733**).[341] In addition to the expected *m*- and *p*-cyclophanes, additional products were observed, including cyclopropane **737** *m*-benzannulation product **736**. Formation of *m*-cyclophanes (e.g., **739**) in an intramolecular benzannulation was employed in the total synthesis of phomactin.[342] A complex benzannulation reaction was observed when bis(carbene complex) derivative **740** couples with bis(alkyne) derivatives (e.g., **741**).[343] This coupling resulted in the formation of calixarenes (e.g., **742**) in moderate yields.

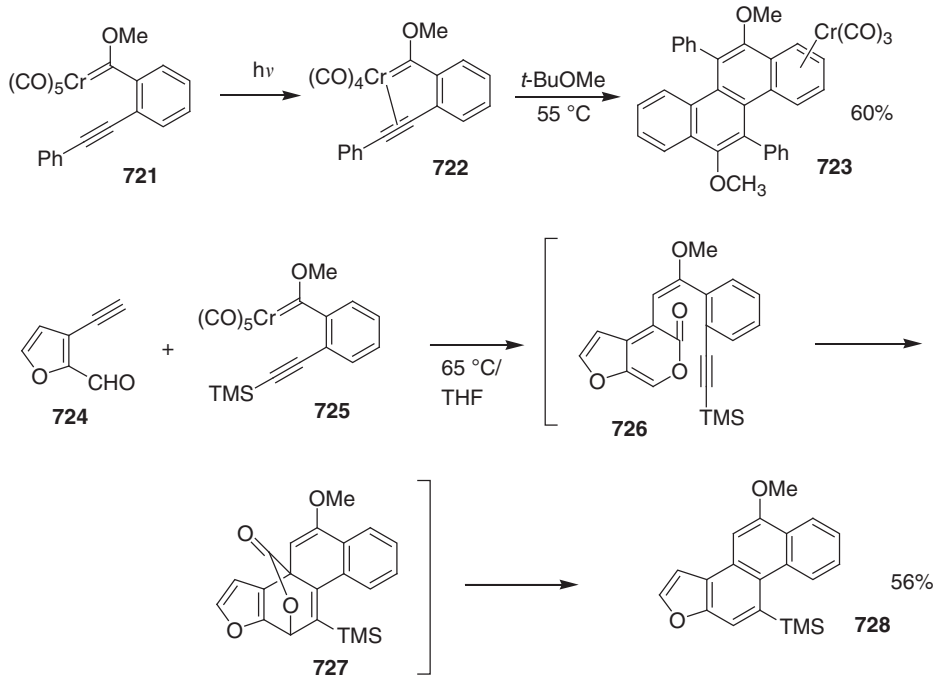
Several examples employing the Dötz reaction as a key step in natural product synthesis have been reported (Scheme 73). The carbon core of menogaril (**745**) was prepared through coupling of arylcarbene complex **743** and an elaborate alkyne (**744**) in



Scheme 70

acetonitrile.[344] A complex intermediate for olivin total synthesis (**748**) was prepared using a similar carbene complex (**746**) and a complex alkyne (**747**).[345] A formal total synthesis of 7-methoxyeleutherin was reported that utilizes the Dötz reaction as the key step.[346] The Dötz reaction was demonstrated for a selenium-containing alkyne, which was a key step for synthesis of naphthoquinone natural products.[347] A complex phenol derivative (**751**) for synthesis of kendamycin segments was prepared through Dötz benzannulation.[348] Benzannulation using dihydrofurylcarbene complex **752** was employed for the total synthesis of aflatoxin B_2.[349] The Dötz benzannulation using indane–alkyne **755** was employed as a key step in a synthetic approach to fredericamycin A.[350] Subsequent aldol reactions then afford the fredericamycin skeleton. Other compounds prepared through benzannulation include eleutherin,[351] curcuquinone,[352] parvaquone,[353] demethoxycardinalin 3,[354] hingconin,[355] and deoxyfrenolicin.[356] The macrocyclic compounds arnebinol (via **758**, Scheme 74)[357] and kendomycin (via **760**)[358] were prepared through intramolecular macrocycle-forming carbene complex–alkyne couplings.

Several examples of benzannulation using aryloxycarbene complexes have been reported (Scheme 75). These complexes are considerably less stable than the analogous alkoxycarbene complexes. Diaryl ethers (e.g., **762**) are produced from coupling of alkynes with aryloxy α,β-unsaturated carbene complexes (e.g., **761**). This process was demonstrated for a variety of aryl- and vinylcarbene complexes.[359] An intramolecular benzannulation process involving 2-alkynylaryloxycarbene complexes (e.g., **763**) was also reported.[360] Benzannulation of an aryloxycarbene complex (**766**) was employed for synthesis of isodityrosine.[361]



Scheme 71

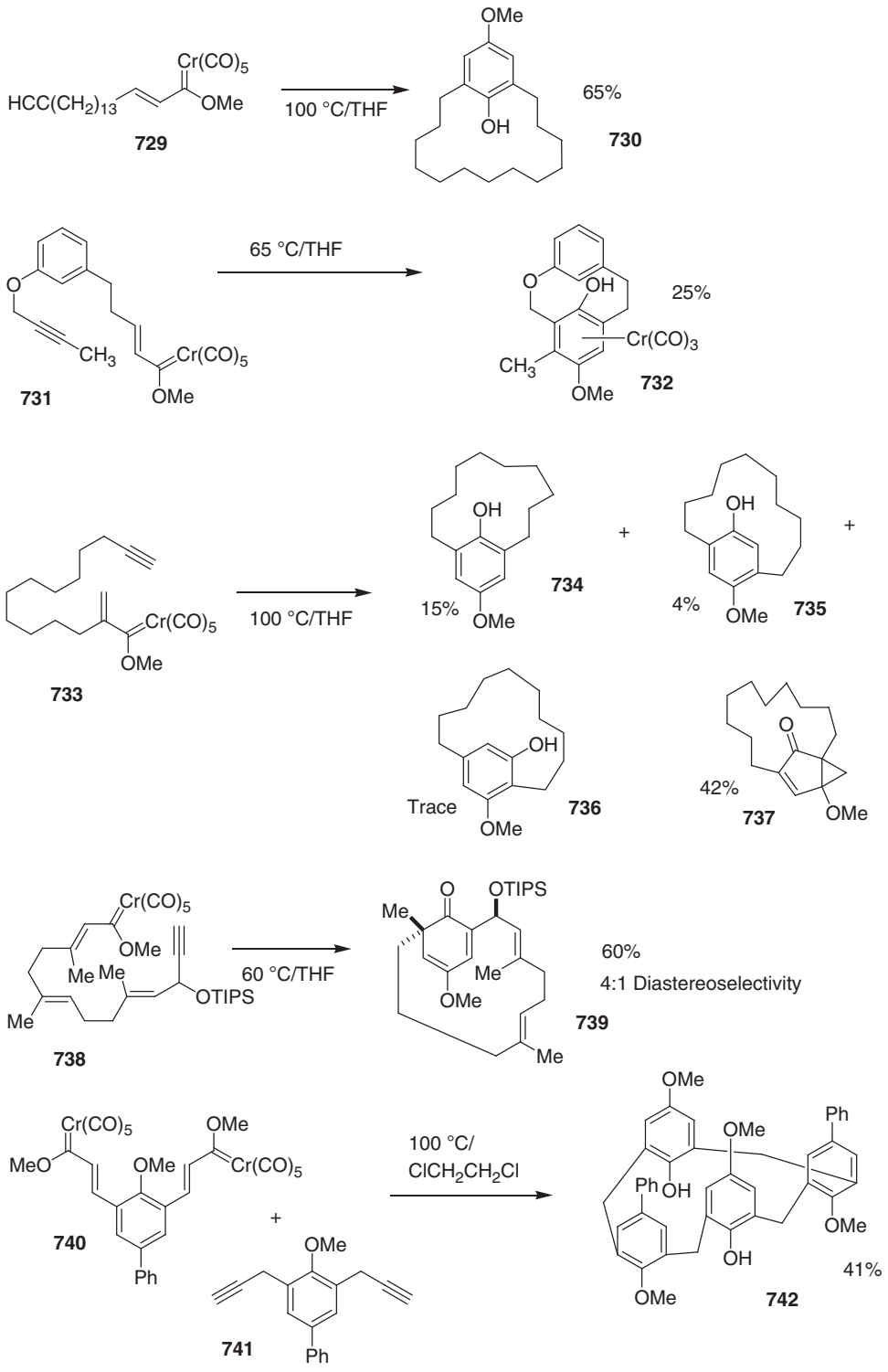
More complex benzannulation processes have also been documented that use Group 6 metal carbonyls (Scheme 76). Benzannulation reactions have been demonstrated for nonheteroatom-stabilized chromium carbene complexes (e.g., **769**).[362] Low-temperature benzannulation reactions were also reported for 2-alkynylglucose derivatives (e.g., **771**) and diphenylcarbene–chromium complex **338**, which occurred at 25 °C.[363] Benzannulations involving alkynes that feature propargylic leaving groups and pendant alkene groups (e.g., **773**) and α,β-unsaturated carbene complexes (e.g., **106**) provide tricyclic compounds (e.g., **776**) in a process involving benzannulation, followed by elimination of the leaving group and formation of the *o*-quinonemethide (**775**), followed by intramolecular Diels–Alder reaction.[364] Coupling of 1,3-disubstituted-indol-2-ylcarbene-chromium complexes (e.g., **777**) and alkynes led to cyclohexadienone annulation products (e.g., **778**), which underwent a secondary thermal rearrangement under the reaction conditions, affording cyclohexadienone **779**; similarly hindered 2,6-disubstituted arylcarbene complexes lead to mostly indenones except in a single case involving an intramolecular reaction.[365]

The benzannulation pathway is largely unique to chromium carbene complexes and a few examples of other Group 6 metals. Some reports of other metals performing Dötz-like benzannulation processes have appeared (Scheme 77). The use of manganese carbene complexes (e.g., **780**) in the Dötz benzannulation reaction has been demonstrated. Both intermolecular[366] and intramolecular[367] processes have been examined. The intramolecular reaction employing complex **783** was assisted through the allelochemical effect achieved by the addition of diphenylacetylene as a spectator alkyne ligand.

Several alternative benzannulations have been designed based on the proposed mechanism. These processes primarily involve alternative procedures to access the reactive intermediates for the mechanism depicted in Scheme 63.

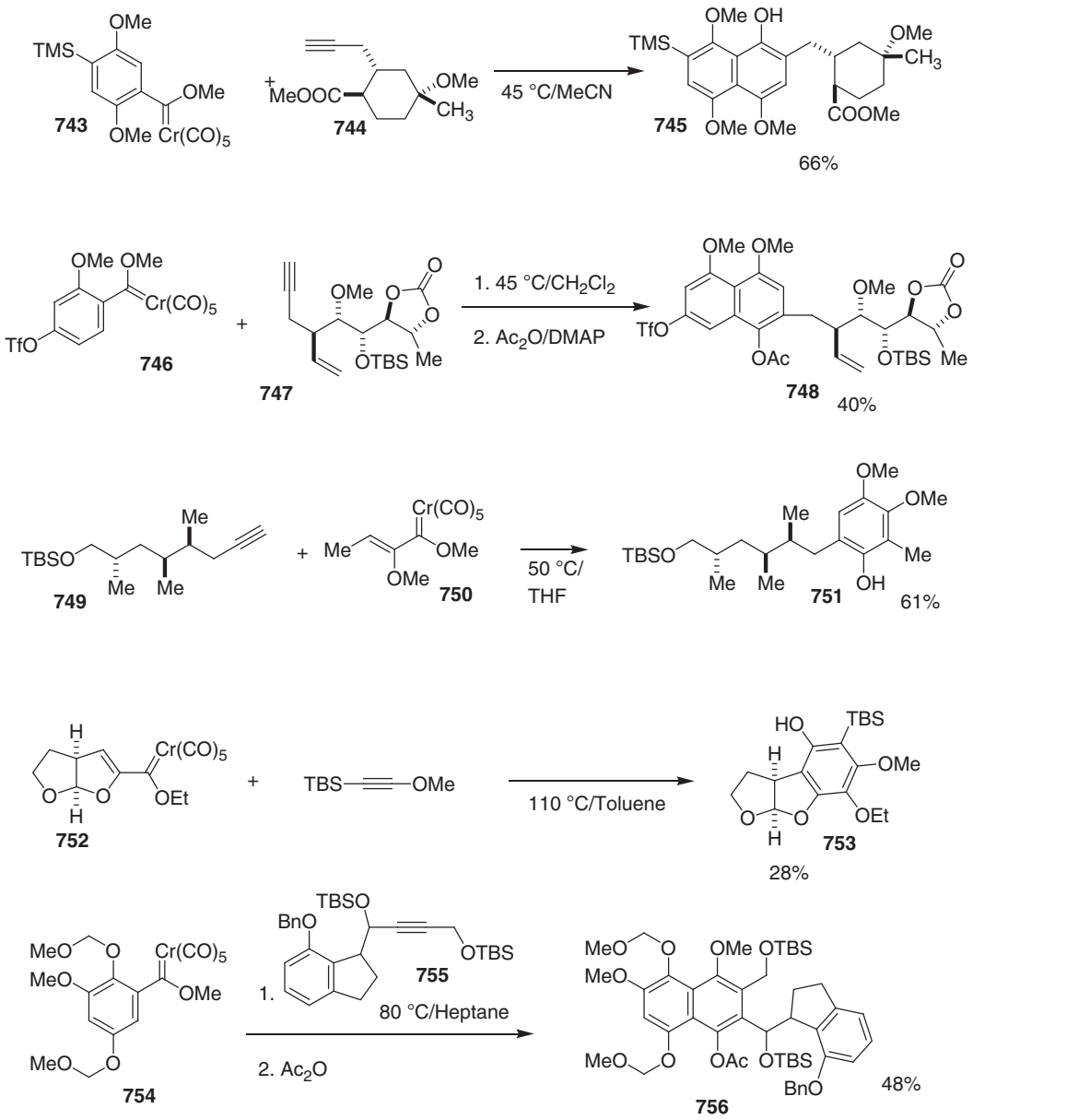
Alternative benzannulation through the coupling of simple carbene complexes with fully conjugated dienylacetylenes (e.g., **785**, Scheme 78) was reported.[368] The initially expected phenol–enol ether derivatives (e.g., **787**) are converted to benzofurans (e.g., **788**) during the oxidative workup procedure. This reaction was used as a cornerstone for formal total synthesis of the natural product egonol through coupling of triene-yne **789** with arylcarbene complex **790**.[369] Coupling of carbene complexes with conjugated dienynes where the middle ring is part of a heterocyclic ring (e.g., **792**) led to the heteroaromatic-fused benzofurans (e.g., **794**) after acidic workup.[370] Naphthalenes were formed in the coupling of carbene complexes with *Z*-alkynylstyrenes.[371]

Coupling of carbene complexes with conjugated enediyne derivatives (e.g., **795**, Scheme 79) led to benzannulation products (**799** and **802**) via a diradical mechanism.[372,373] Formation of the major product **802** involves Moore cyclization of the predicted enyne–ketene intermediate **796**, followed by sequential intramolecular hydrogen atom transfers from intermediate diradical **797** to give an enol ether–phenol (**801**), which is converted to the benzofuran derivative **802** during workup. Reaction of diradical **797** with an external hydrogen atom source (the solvent dioxane) leads to butyl derivative **799**. The initially formed diradical could also be captured in a radical cyclization reaction. Through careful exclusion of hydrogen atom donors, selective remote functionalization processes occur, resulting in allylbenzene derivatives as the major products. The diradical intermediates could also be captured through chlorine abstraction processes, resulting in chlorinated analogs (e.g., **804**). The coupling of carbene complexes



Scheme 72

with conjugated enediynes that feature radical traps was also reported.[374] A free radical-based benzannulation process can also be initiated through thermolysis of aminocarbene complex-linked diynes (e.g., **806**).[375] In this case, the alkyne insertion affords an enyne–ketene (**807**), which undergoes Moore cyclization to afford the diradical (**808**), which reacts with added hydrogen atom donors to afford the benzannulation products.

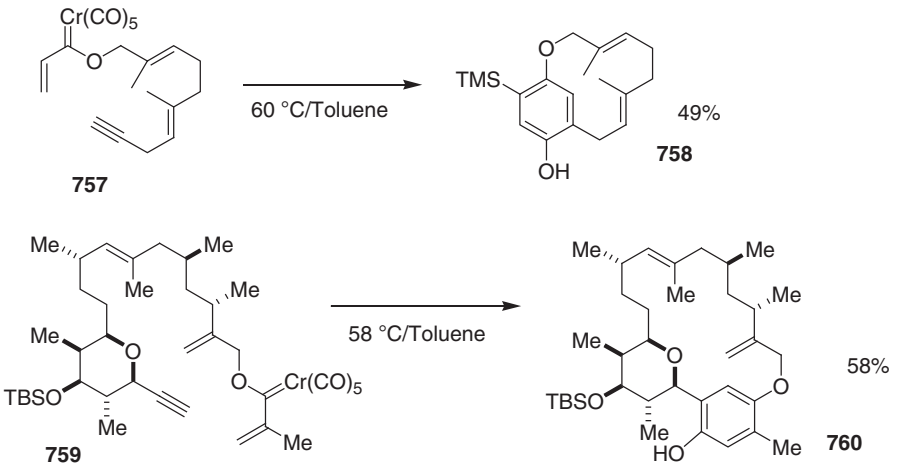


Scheme 73

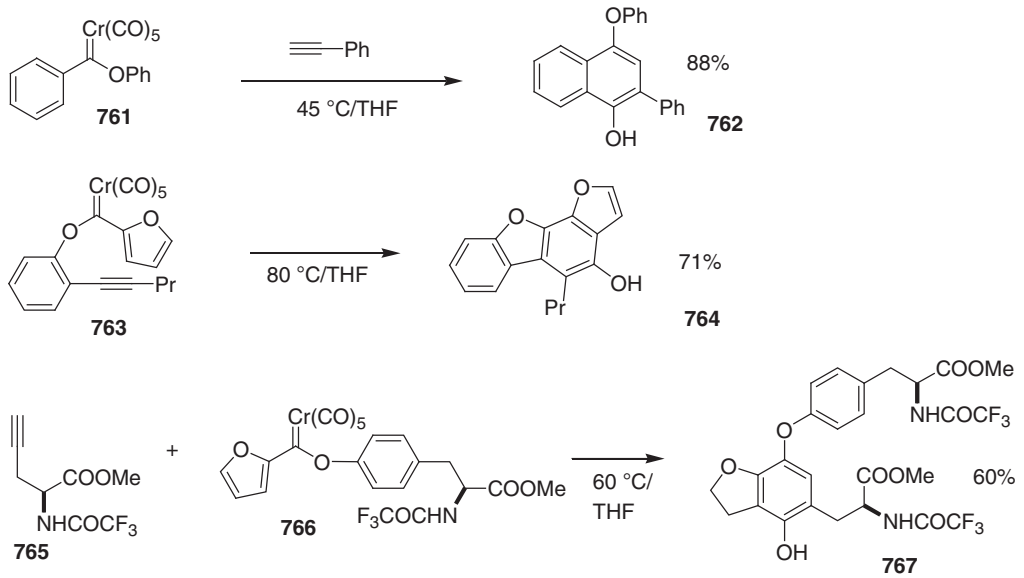
Coupling of enyne aldehydes fused to heteroaromatic ring systems (e.g., **811**, **814**, and Scheme 80) proceeds through *o*-quinoidal-like pyrone ring systems (e.g., **812**).[376] The products derived from these systems incorporate a molecule of CO relative to the arene systems depicted in Scheme 58. The differences for heteroaromatic carboxaldehyde substrates relative to arene analogs have been attributed to the enhanced ring strain in the bicyclo[3.3.0]octatriene systems. The reaction employing γ,δ-unsaturated carbene complexes led to intramolecular Diels–Alder adducts (e.g., **813**). Subtle variations in the reaction pathways for different ring systems were noted and were based on the relative electron-donating ability of different heteroaromatic ring systems. Diels–Alder adducts from furan derivatives (e.g., **815**) undergo a further loss of CO_2 leading to simpler tricyclic ring systems (e.g., **817**); this process was used as the cornerstone for a total synthesis of cadinene natural products. Imidazole-, pyrazole-, and indole-fused analogs have also been successfully demonstrated.[377]

5.25.3.2.4 Seven-membered and larger ring systems

The coupling of alkynes with cyclopropylcarbene-Group 6 metal complexes (**818** and Scheme 81) leads to cycloheptadienones.[378] The homologous Dötz reaction depicted initially affords the cycloheptadinone **819**, which undergoes isomerization to the doubly



Scheme 74

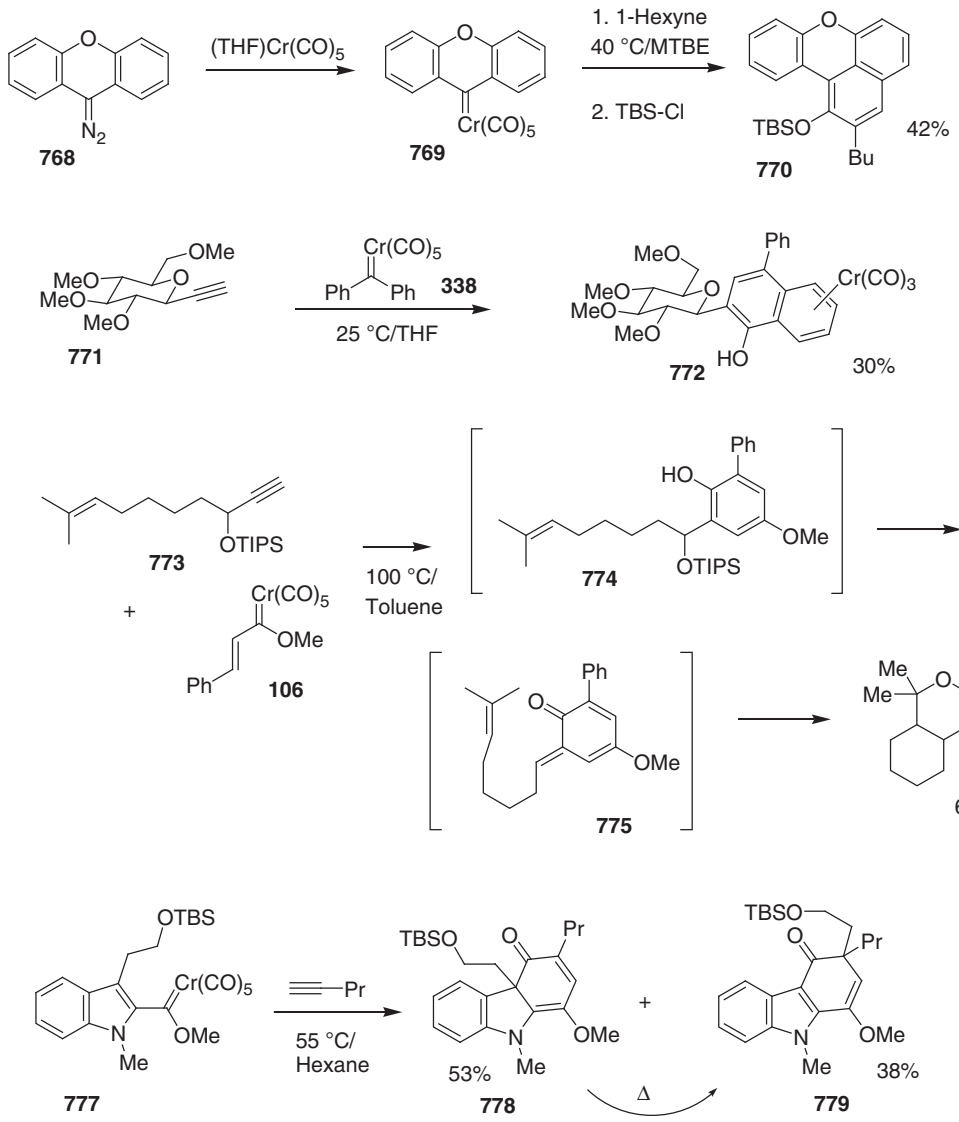


Scheme 75

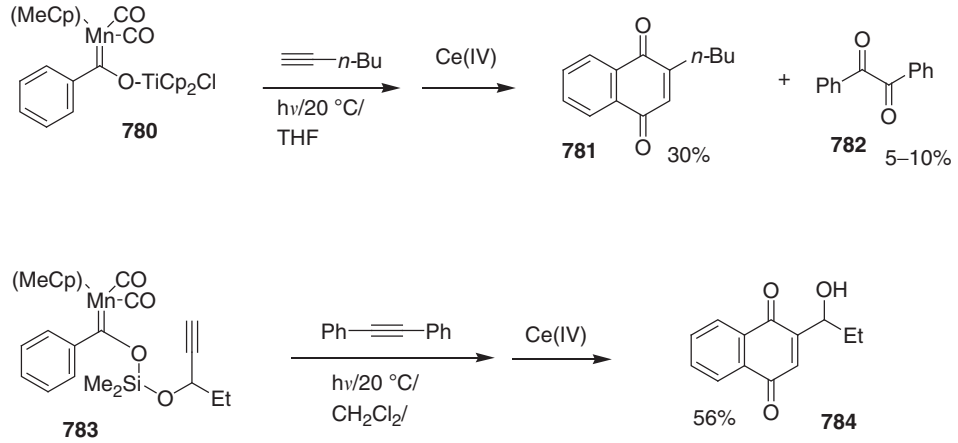
vinylogous ester system **820** under the reaction conditions. This reaction was limited to simple cyclopropane systems and internal alkynes. Coupling of $\alpha,\beta,\gamma,\delta$-unsaturated carbene complexes (e.g., **821**) with monosubstituted acetylenes led to eight-membered ring derivatives (e.g., **822**).[379] The eight-membered ring forming reaction was limited to systems where the α,β-alkene was embedded in a cyclobutene ring, likely due to the ring strain in the unobserved benzannulation product.

5.25.3.2.5 Vinylketene capture and stable ketenes

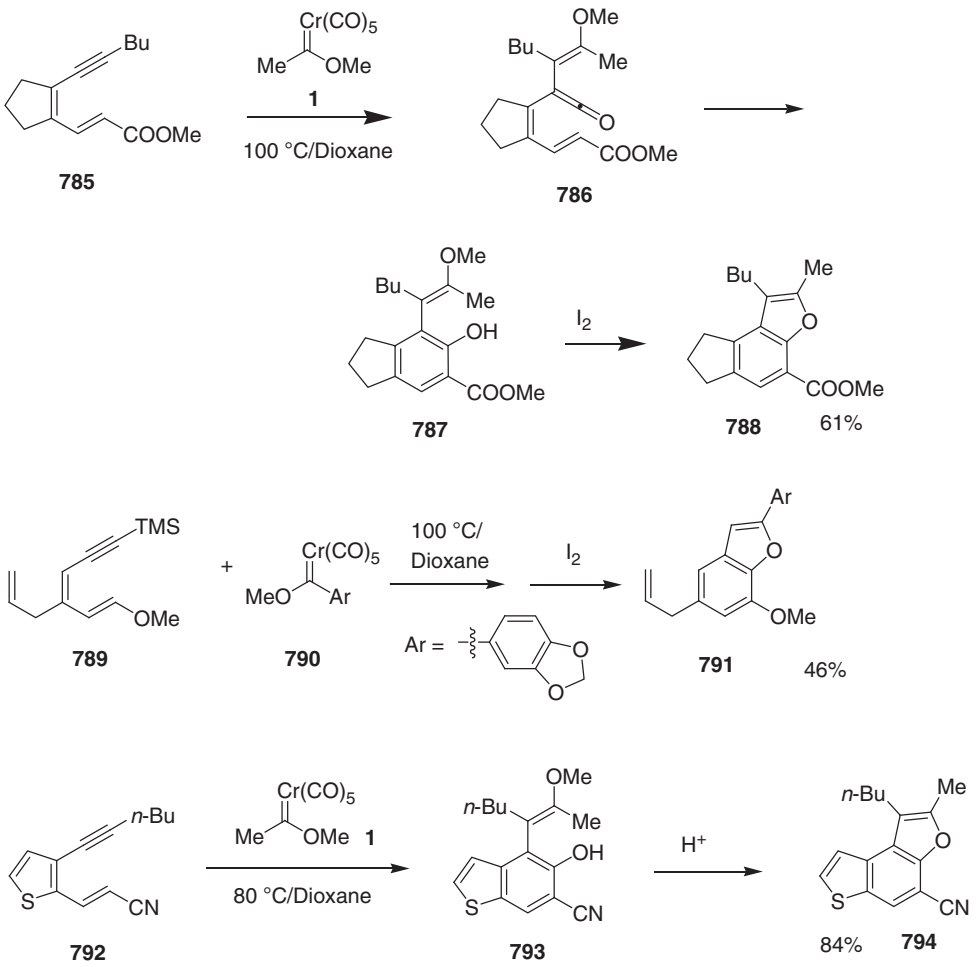
Several reaction processes have been designed, which capture the ketene intermediates of benzannulation reactions (Scheme 82). Capture of intermediate ketene complexes by intramolecular reaction with an alcohol led to β-lactone derivatives (e.g., **826**).[380] The reaction requires activation through the Thorpe–Ingold effect; examples devoid of the gem dialkyl substitution undergo benzannulation processes. Coupling of hindered arylcarbene complexes led to the lactone derivatives under thermal or sonication conditions.[381] The coupling of arylpropargyl alcohols (e.g., **827**) and Fischer carbene complexes under solvent-free conditions led to alkylidene-γ-lactones (e.g., **830**).[382] In these cases the regiochemistry of alkyne insertion is opposite to that from terminal alkyne propargyl alcohols. Subsequent treatment with acid in the air afforded the corresponding furanones (e.g., **831**). This reaction process likely involves the formation of a vinylketene intermediate (**829**),



Scheme 76



Scheme 77



Scheme 78

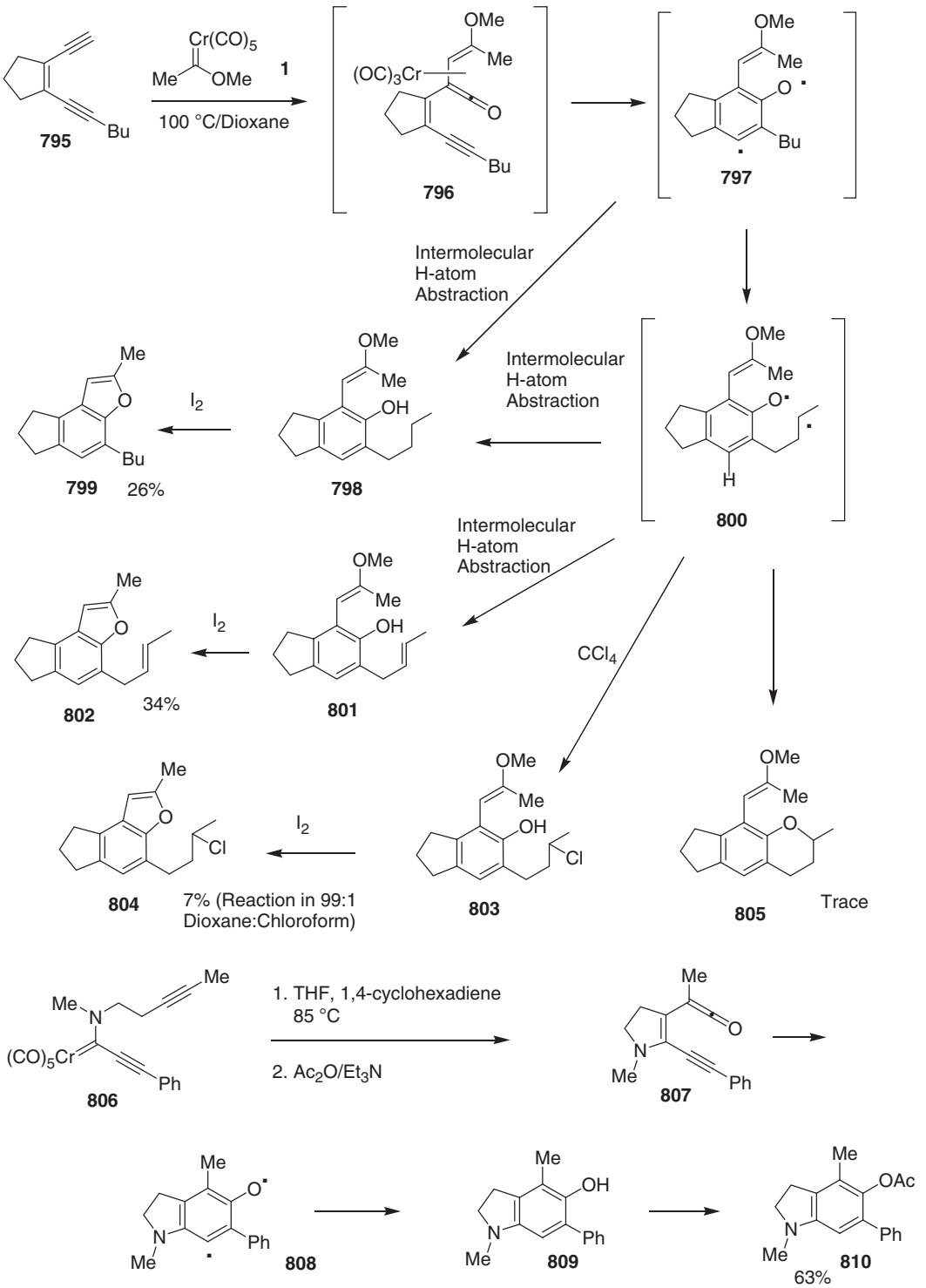
which reacts with the alcohol to afford the lactone. Intramolecular trapping by enol derivatives resulted in cyclopentanone derivatives (e.g., **835**).[383]

In some cases, stable ketenes can be isolated from alkyne–carbene complex coupling processes (Scheme 83). Formation of ketene complexes (e.g., **837**) was observed in the coupling of phenylcarbene complex **317** with sterically hindered silyl phenyl acetylenes (e.g., **836**).[384] Treatment of the ketenes with methylene sources led to cyclopentenones (e.g., **838**). Treatment of the ketene–arene complexes with photolysis or cerium (IV) followed by thermolysis of the resulting free ketenes at 80 °C led to the benzannulation products (e.g., **839**).[385] An intramolecular cyclopentannulation process using aryloxycarbene complexes (e.g., **842**) was also demonstrated.[386] The reaction initially affords stable α-silyl-vinylketene complexes (e.g., **843**), which subsequently react with carbene equivalents to generate cyclopentenone derivatives (e.g., **844**).

5.25.3.2.6 Coupling leading to intercepted products – tandem reactions

In many cases, the vinylcarbene complex intermediate from carbene complex–alkyne coupling can be trapped through reaction with pendant alkene and alkyne groups. A number of investigators have designed serial reaction processes for the vinylcarbene intermediates obtained from the reaction of carbene complexes with alkynes.[387] It is somewhat difficult to classify all tandem reactions equally, and numerous examples that could be classified this way have been presented elsewhere in this chapter. This section emphasizes examples where the 'trap' for the carbene complex is not in conjugation with the initially formed carbene complex.

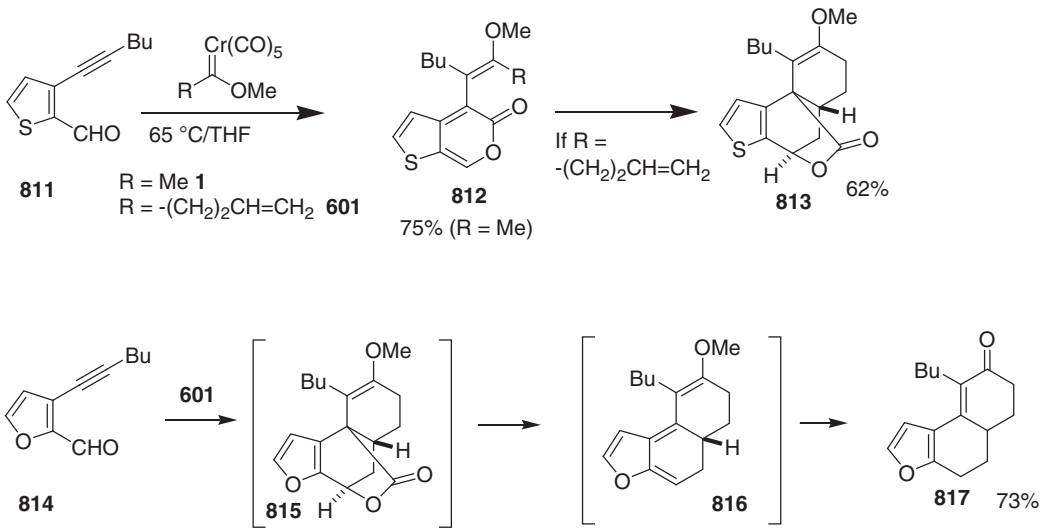
The coupling of Fischer carbene complexes with enynes (e.g., **845**) can proceed through a variety of reaction pathways, including cyclopropanation, ketene addition, and alkene metathesis (Scheme 84).[388] Numerous attempts to suppress the insertion process through use of electron-rich aminocarbene complex analogs,[389] manganese complexes (e.g., **851**),[390] tungsten complexes,[391] and molybdenum carbene complex (e.g., **413**)[392,393] analogs have been successful. The use of various carbene complex acylates was also found to increase the proportion of non-CO inserted products.[394] Formation of six-membered rings



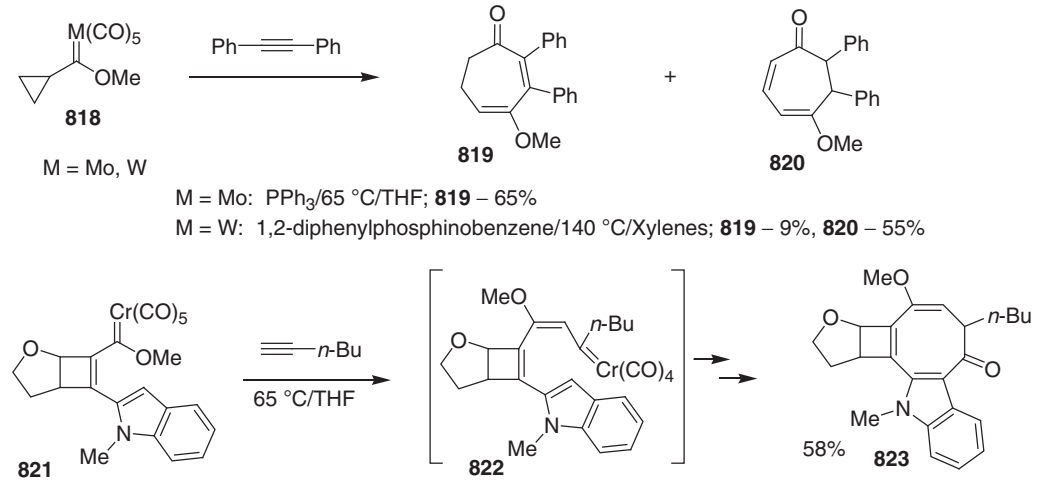
Scheme 79

from 1,7-enynes has also been demonstrated for many of the examples. The reaction pathway observed is highly dependent on the alkene substitution pattern and on the reaction conditions. A higher proportion of olefin metathesis products were observed when more substituted alkene groups were involved. Fischer carbene complexes also catalyze the enyne metathesis reaction pathway if the starting compound has alkene substituents that match the carbene complex substituents (e.g., **856** + **857** → **858**).[395]

The reaction of the dienynes (e.g., **861** and Scheme 85) with a simple carbene complex affords the 5,7-fused ring system (e.g., **864**) after intramolecular cyclopropanation followed by divinylcyclopropane rearrangement (**863** → **864**).[396] The reaction is most



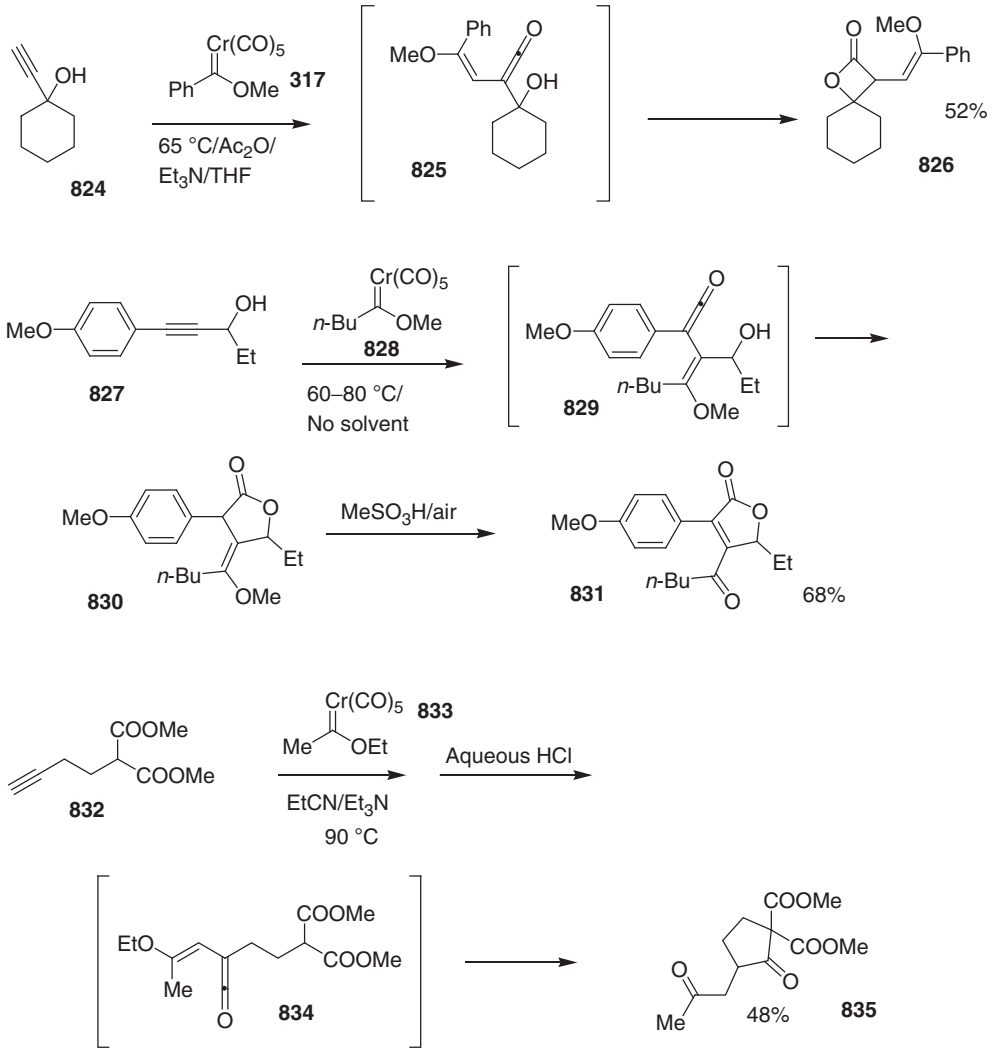
Scheme 80



Scheme 81

efficient when molybdenum carbene complexes are employed. The divinylcyclopropane derivatives can be isolated in some cases if the carbene–alkyne coupling is performed at 40 °C; however, only the hydroazulene derivatives are observed from the reaction conducted at 60 °C. The relative stereochemistry at the asterisked carbons is effectively controlled through stereospecific cyclopropanation followed by Cope rearrangement through a boat transition state. The stereochemistry at the remaining stereocenter is controlled by the alkene geometry of the enol ether, which is established as in the initial alkyne insertion step. An intramolecular version of this reaction has also been reported.[397] Molybdenum carbene complexes react with dienynes where the diene and alkyne functionalities are linked through the 2-position of the diene (e.g., **865**) to afford tricyclic compounds (e.g., **870**).[398] A mechanism involving alkyne insertion to afford vinylcarbene complex **866** followed by intramolecular cyclopropanation was proposed. Divinylcyclopropane **867** then undergoes a Cope rearrangement, followed by methanol loss, followed by electrocyclic ring opening to afford **870**.

Some efforts to enhance the ketene pathway for carbene complex alkyne coupling have been reported. This pathway is most predominant using chromium complexes and enynes that feature more highly substituted alkene groups (e.g., **871**, Scheme 86).[399] The coupling of carbene complexes with dienyne derivatives (e.g., **873**) was examined as a possible synthetic route to taxol derivatives.[400] Coupling of enyne **873** with methylcarbene complexes resulted in regioisomeric cyclobutenones (e.g., **875**



Scheme 82

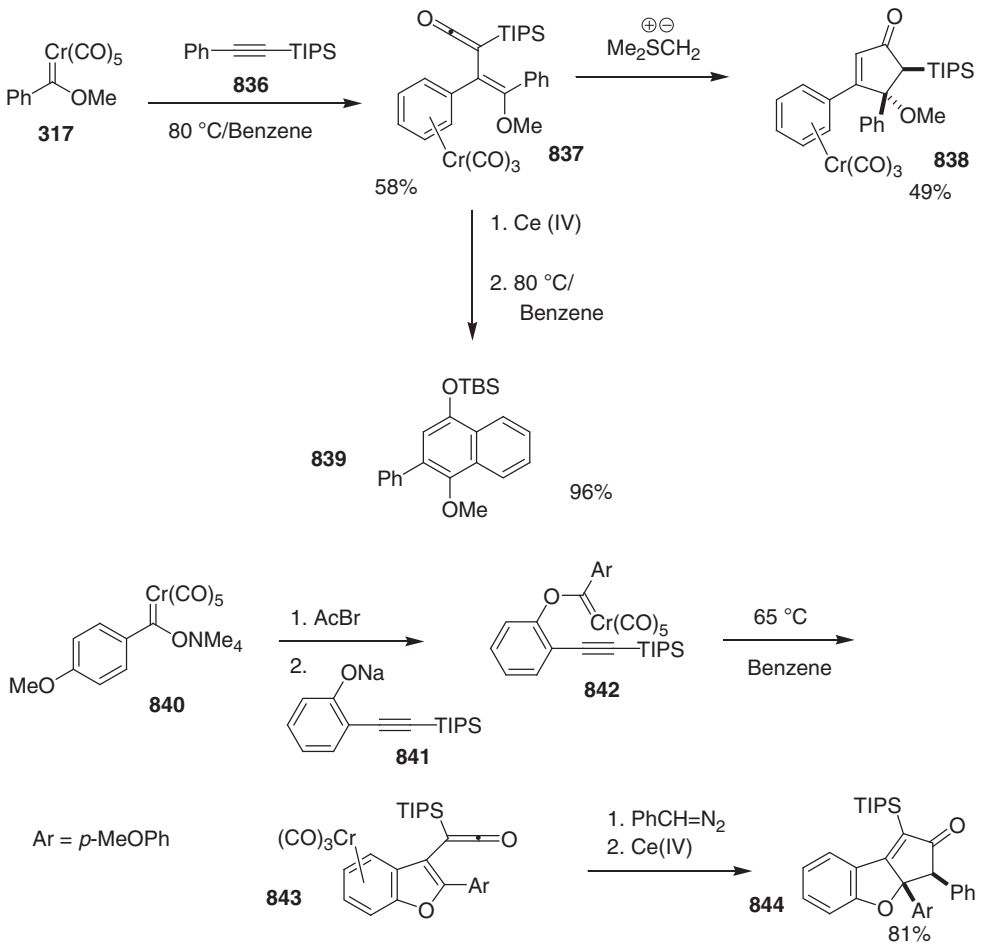
and **876**). Formation of **875** is the desired process for taxol synthesis. A systematic study of this process involving aryloxycarbene complexes (e.g., **874**) revealed that electron deficiency in the ketene favors the desired reaction pathway.

The intermediate vinylcarbene complexes from alkyne–carbene complex coupling can also be intercepted by other alkynes to effect alternative strategies for benzannulation (Scheme 87). Treatment of 1,6-heptadiyne (**877**) with carbene complexes affords the benzannulation products (e.g., **880** and **881**) in high yield.[401] A secondary reduction process of cyclohexadienone **880** leads to phenol derivative **881**. Several tandem reactions have been developed that incorporate this general reaction pathway. The tandem Diels–Alder reaction of triynylcarbene complexes (e.g., **882**) followed by benzannulation was demonstrated in several examples.[402,403] In this process the initial Diels–Alder reaction affords an arylcarbene complex (**883**), which undergoes a series of intramolecular alkyne insertion processes to afford the stereoid skeleton (e.g., **886**).

5.25.3.3 Coupling of Carbene Ligands with Cumulene and C–X pi Bonds

5.25.3.3.1 Allenes

Limited studies of the reactions of carbene complexes and allenes have been demonstrated (Scheme 88). Coupling of allenes (e.g., **887** and **890**) and Fischer carbene complexes affords trimethylenemethane derivatives (e.g., **888** and **891**), which afford cyclopentane derivatives (e.g., **889** and **892**) after subsequent cycloaddition with suitable alkenes.[404] Dialkylidenecyclopentane derivative **889** can be obtained by either isolation of complex **888** and treatment with allene **887**, or by prolonged coupling of complex **857** and allene **887**. The isolated trimethylenemethane derivatives (e.g., **891**) can also couple with alkynes in a separate



Scheme 83

step to provide mixtures of alkylidenecyclopentene (**893**) and alkylidenecyclohexenone derivatives (**894**),[405] which result from CO insertion processes. An efficient cycloaddition reaction occurs when trimethylenemethane complex **891** is treated with maleoyl derivatives, resulting in the exclusive formation of alkylidenecyclopentenes (**893**). Reaction of alkenylcarbene complexes with 1,1-dimethylallene led to 2-alkoxy-1,3-diene derivatives in a net metathesis reaction.[406]

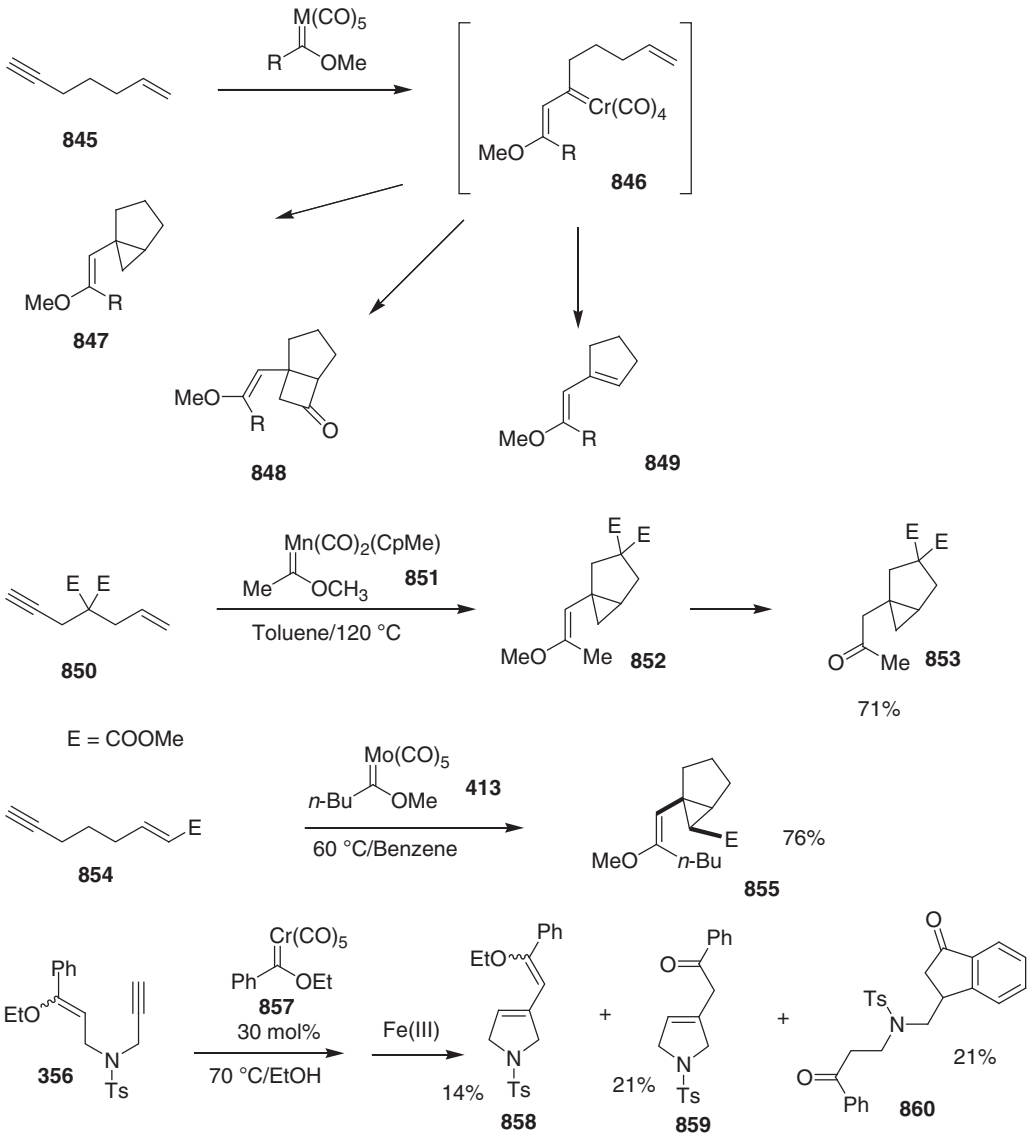
5.25.3.3.2 Imines

Most of the reactions reported with imines involve generation of metal complexes of ketene through photoinduced CO insertion followed by [2 + 2]-cycloaddition. These reactions are discussed in the section on CO and isonitrile insertion.

5.25.3.3.3 Isonitriles and CO

Photoinduced conversion of metal carbene complexes to metal–ketene complexes, followed by subsequent transformation of the ketene is the basis of many metal carbene cycloaddition processes. Several reviews on this topic have appeared.[407] This process is largely mimicked by the thermal reaction with isonitriles, which leads to ketenimines.[408]

Several examples of the coupling of β-lactams through the photolytic coupling of chromium carbene complexes and imines have been reported. Representative examples are depicted in Scheme 89. Penam-type β-lactams (e.g., **898**) were prepared from the photolytic coupling of dihydrothiazoles (e.g., **896**) with carbene complexes.[409] Azapenams were prepared with a very high degree of stereoselectivity through photolytic coupling of dihydroimidazoles (e.g., **899**) with methylcarbene complexes.[410] Synthesis of carbon-linked β-lactams (e.g., **902**) from the reaction of bis carbene complexes (e.g., **901**) with imines (e.g., **899**) was reported using both achiral and homochiral imines.[411,412] In several cases, the photolytic reaction of chromium carbene complexes and alkenes leads to cyclobutanones. The synthesis and photolytic reactions of α-alkoxycarbene–chromium complexes (e.g., **903**) were described.[413] The requisite carbene complexes could only be synthesized via the chromium pentacarbonyl dianion route; the Fischer route using alkoxymethyllithium derivatives failed. Successful cycloaddition with enamide derivatives (e.g., **904**) was

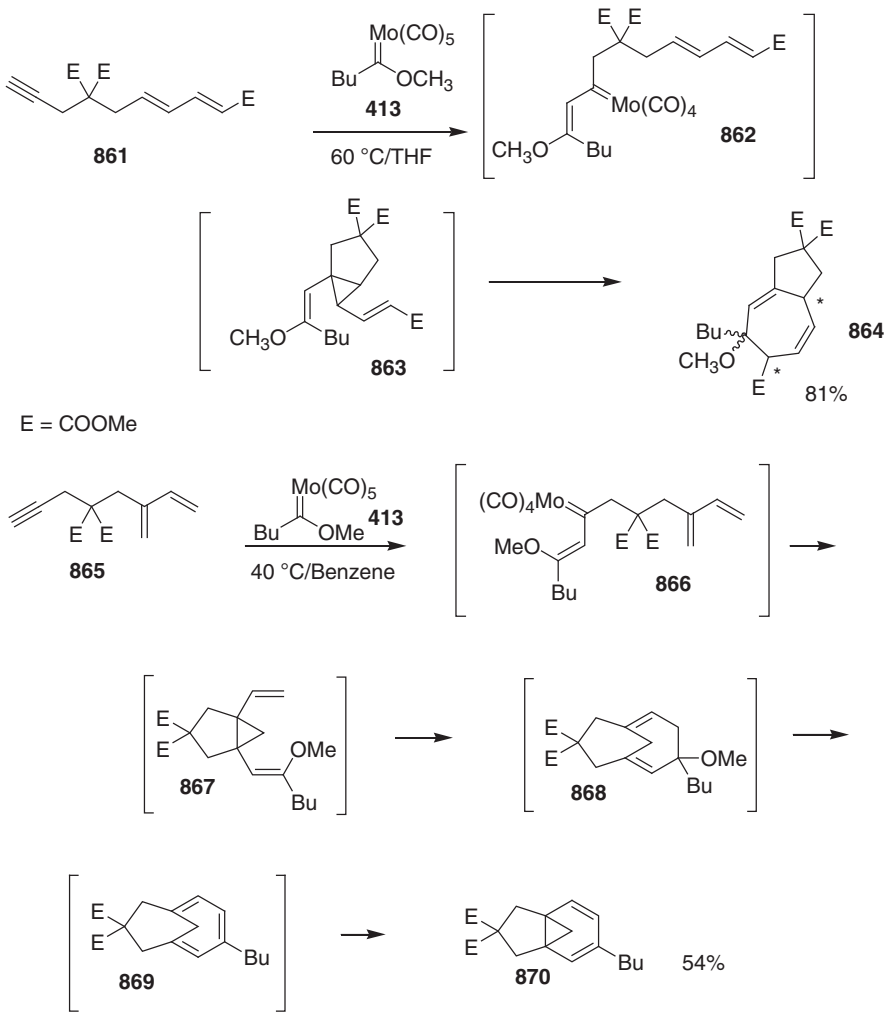


Scheme 84

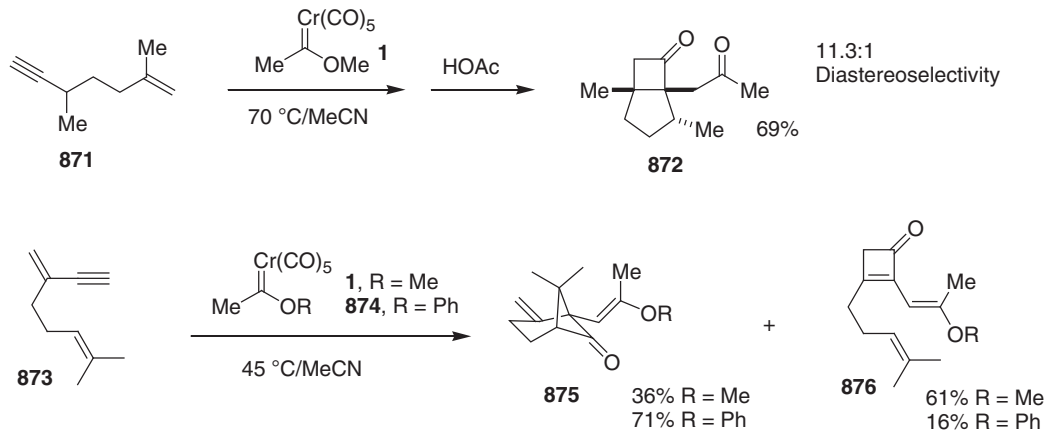
achieved using a DMF–carbazole solution as a filter. The photo-induced CO insertion process is specific to chromium carbene complexes. A combined experimental–theoretical study of the photolytic formation of β-lactams from chromium carbene complexes and imines was undertaken to address the issues that favor photolytic ketene formation over photolytic CO dissociation.[414]

In several cases, photolysis of carbene complexes affords ketenes, which then undergo pericyclic ring closure reactions. Several examples of this process have already been discussed as this process is frequently a follow-up step in several reactions that lead to dienylcarbene complexes. Photolysis of carbene complex **907** (Scheme 90) resulted in carbazole derivatives (e.g., **909**). This process occurs via tandem photolytic ketene generation (**908**) and electrocyclic ring closure.[415] Indolocarbazoles (e.g., **911**) were produced in the photolysis of biindolecarbene derivative **910**.[416] Similar cyclizations of biphenylcarbene complexes (e.g., **912**) led to the corresponding phenanthrenes (e.g., **913**).[417]

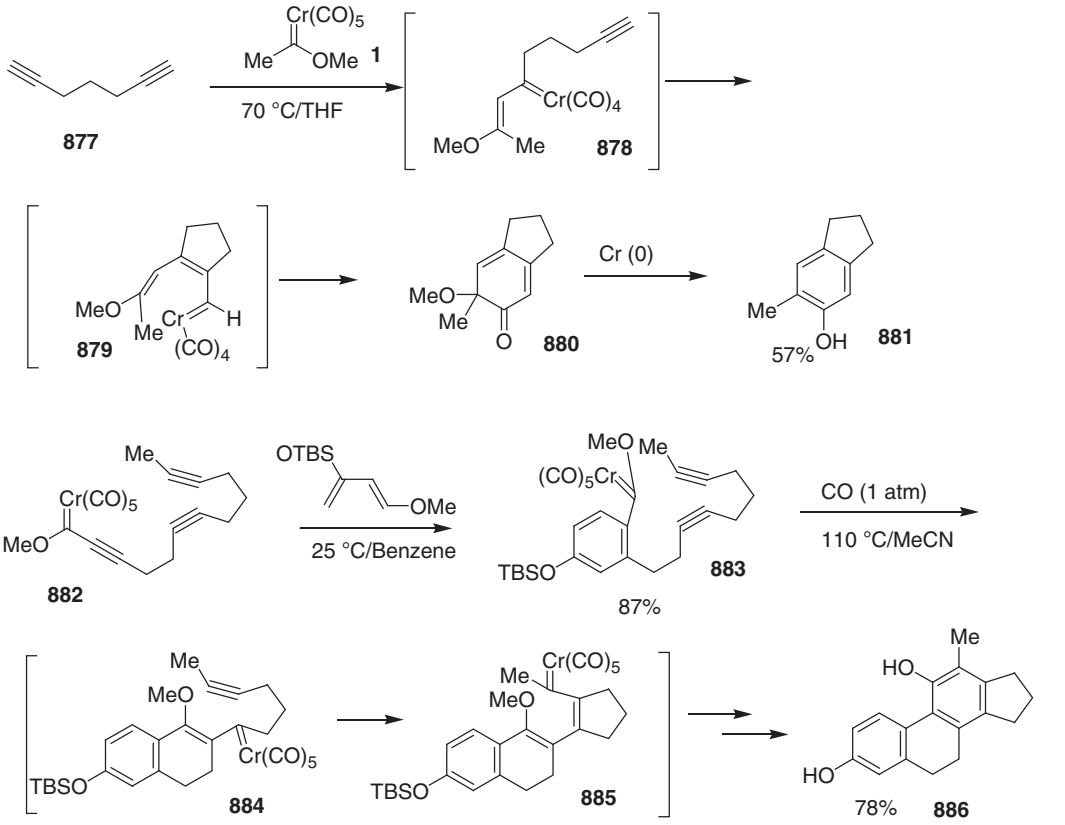
Several examples of the analogous reaction of carbene complexes with isocyanides to afford ketenimines have been reported (Scheme 91). Numerous examples of isocyanide insertion followed by cyclization of the resulting ketenimine were applied to the alkenylcarbene complexes generated from additions to the triple bond of alkynylcarbene complexes (e.g., **914**), resulting in net aminobenzannulation. Several examples of the treatment of dienylcarbene complexes with isocyanides or CO to afford benzannulation products (e.g., **915** and **916**) have been demonstrated.[418,419] Reaction of chromium carbene complex **917** with *t*-butyl



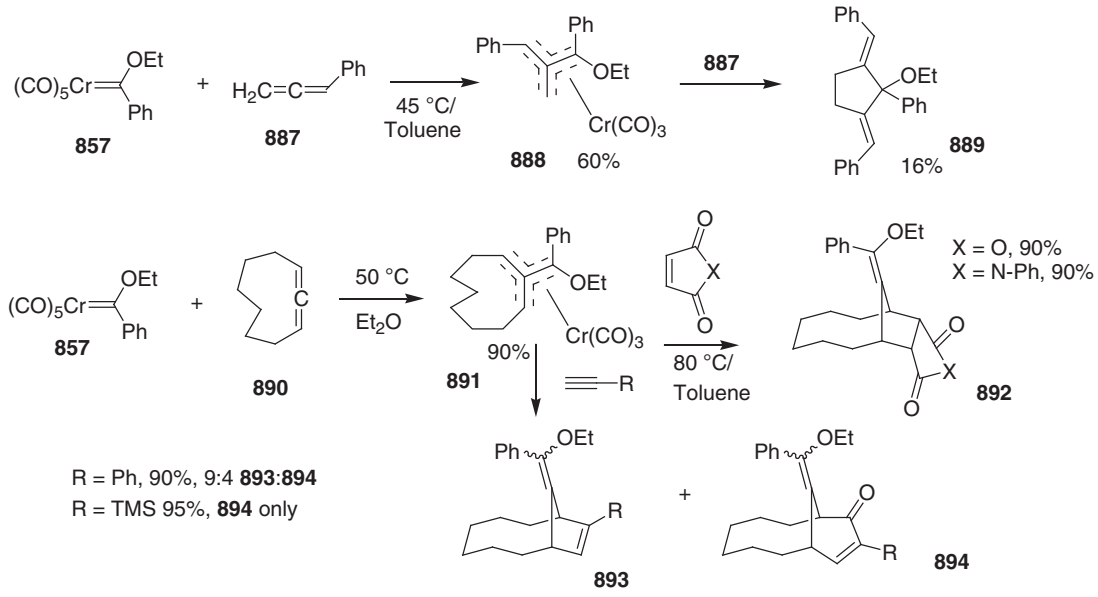
Scheme 85



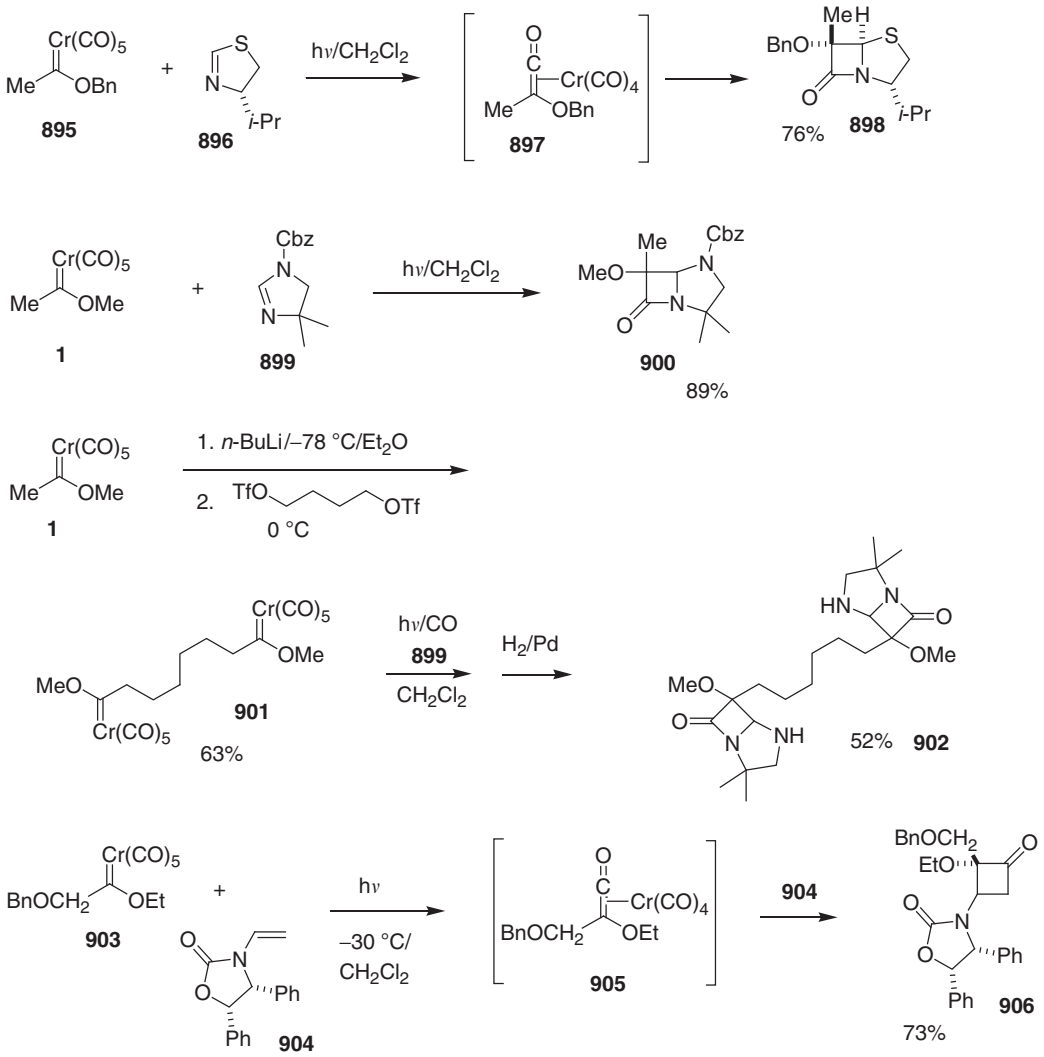
Scheme 86



Scheme 87



Scheme 88



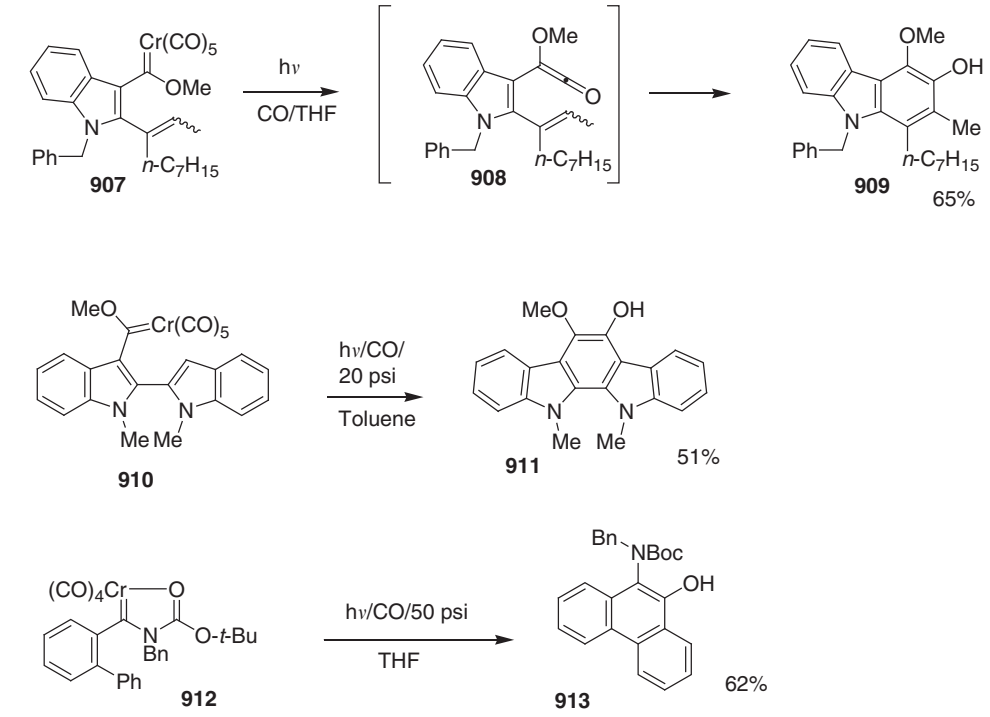
Scheme 89

isonitrile led to aminonaphthalene derivatives **919**, which was employed for the total synthesis of the calphostin natural products.[420]

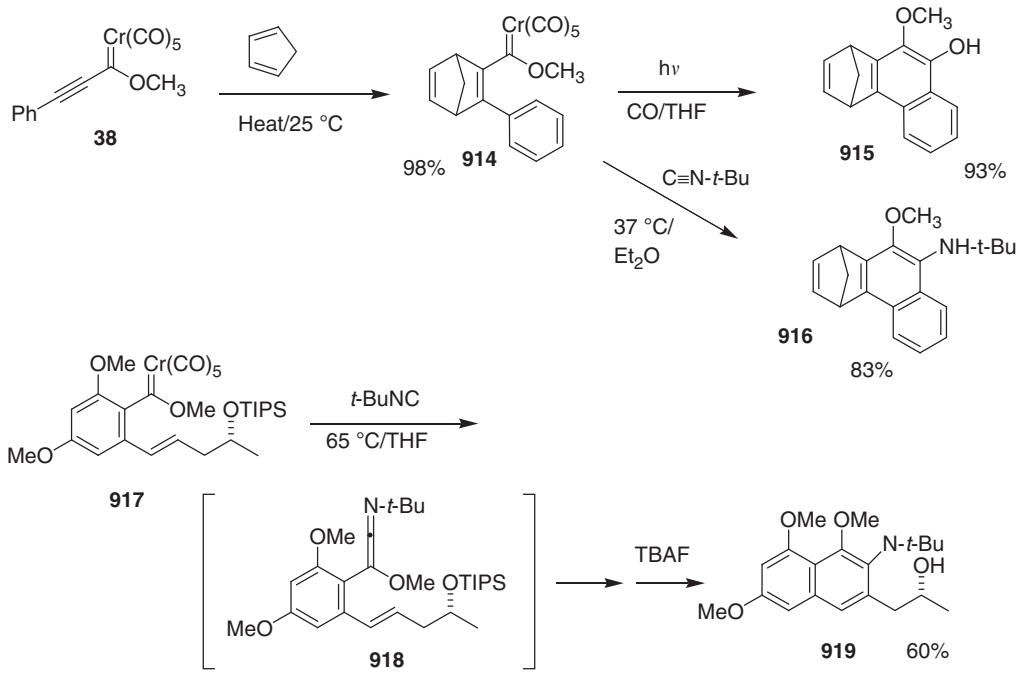
5.25.3.4 Transfer of the Carbene Ligand to Another Metal

In several cases, metal carbene cycloaddition processes require the transfer of the carbene ligand to another metal to accomplish the desired transformation. Some aspects of this research area have been reviewed.[421] The most well-developed processes invoking this reaction pathway are low-temperature carbene complex dimerization and cycloaddition reactions with alkenes, alkynes, and allenes. In a sense, this method is employing a stable transition metal carbene complex as a safe alternative to a diazo compound.

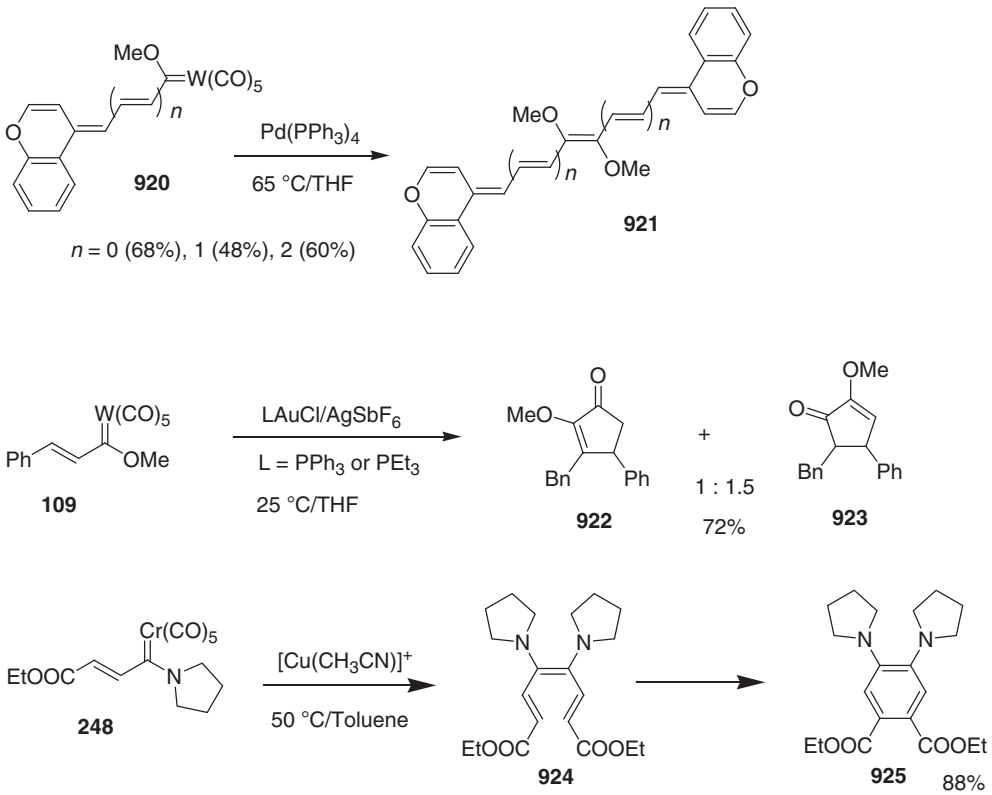
Numerous examples of metal-catalyzed carbene complex dimerization have been reported. Most examples of this process use palladium(II) complexes. Treatment of pyranylidene–carbene complexes (e.g., **920** and Scheme 92) with a palladium(0) catalyst led to the carbene dimerization product (e.g., **921**).[422] Gold complexes catalyze cyclopropanation and carbene dimerization reactions using α,β-unsaturated carbene complex **109**.[423] Treatment of tungsten carbene complex **109** with a gold complex led to dimerization/cyclization products (e.g., **922** and **923**). Copper-catalyzed dimerization of α,β-unsaturated carbene complexes (e.g., **248**) afforded conjugated trienes (e.g., **924**), which underwent electrocyclic ring closure and oxidation to afford 1,2-diaminobenzene derivatives (e.g., **925**).[424]



Scheme 90



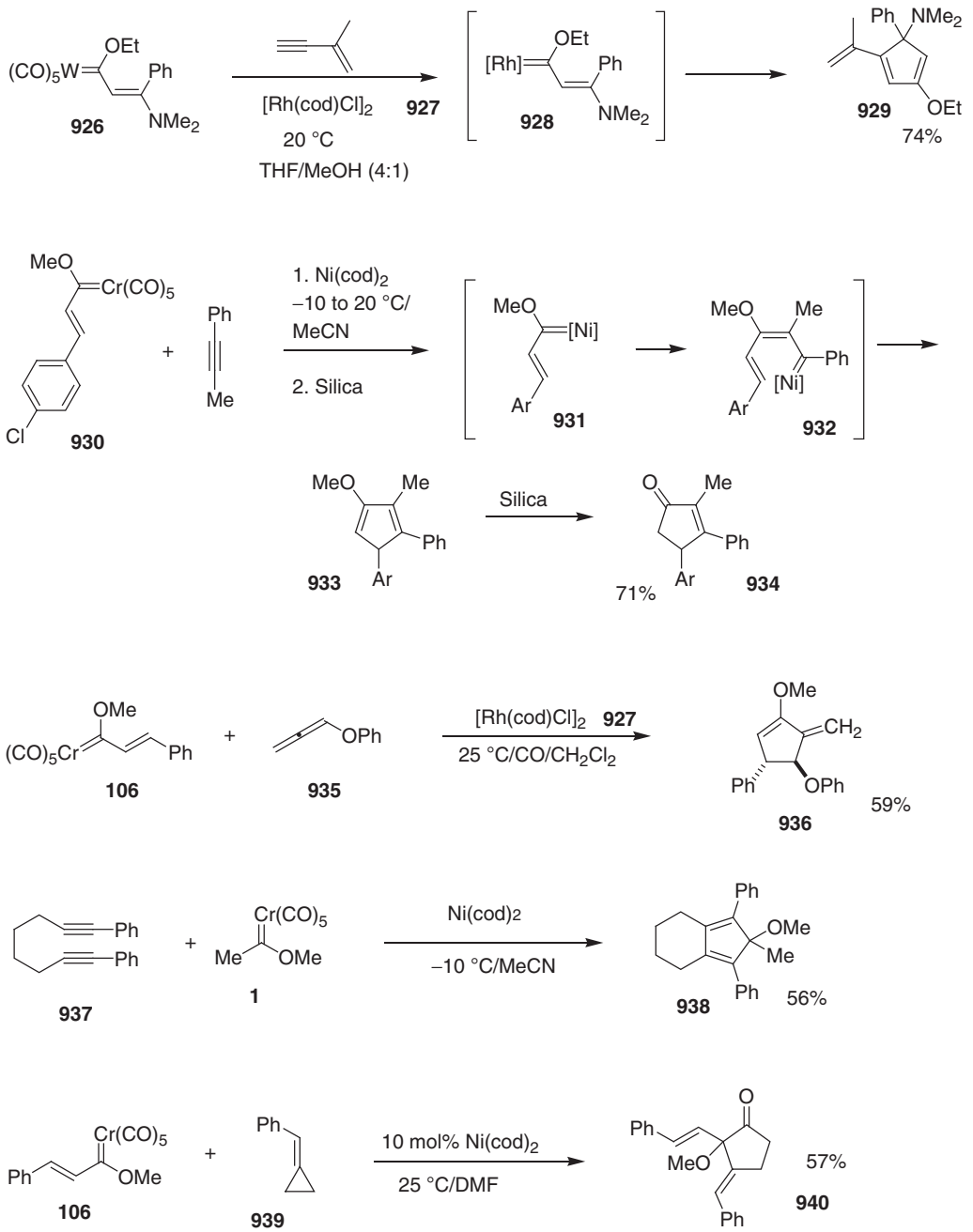
Scheme 91



Scheme 92

Several cases of transition metal-catalyzed multicomponent couplings leading to five-membered rings have been reported (Scheme 93). The coupling of β-aminoalkenylcarbene–tungsten complexes (e.g., **926**) with conjugated acetylenes in the presence of various rhodium complexes (e.g., **927**) proceeded at 20 °C to provide the cyclopentadiene derivatives (e.g., **929**).[425,426] A mechanism involving initial carbene transfer from tungsten to rhodium was proposed. The nickel-catalyzed coupling of α,β-unsaturated Fischer carbene complexes (e.g., **930**) and alkynes led to cyclopentenones (e.g., **934**) in a net [3 + 2]-cycloaddition process.[427] The key step in the proposed mechanism is transfer of the carbene ligand from chromium to nickel to afford a nickel carbene complex intermediate (**931**), which undergoes alkyne insertion followed by cyclization to afford cyclopentadiene–enol ether derivatives (e.g., **933**). Enol ether hydrolysis on silica gel leads to the cyclopentenone products. The coupling of alkenylcarbene complexes (e.g., **106**) with allenes in the presence of a rhodium catalyst (**927**) resulted in the formation of alkylidenecyclopentene derivatives (e.g., **936**).[428] The coupling of two alkynes (or a dialkyne) (e.g., **937**) with a Fischer carbene complex in the presence of a nickel catalyst afforded cyclopentadiene derivatives (e.g., **938**) in a formal [2 + 2 + 1]-cycloaddition process.[429] Nickel carbene complexes were also proposed in the formation of cyclopentanones (e.g., **940**) through nickel-catalyzed cycloaddition reaction of carbene complexes with alkylidenecyclopropanes (e.g., **939**).[430]

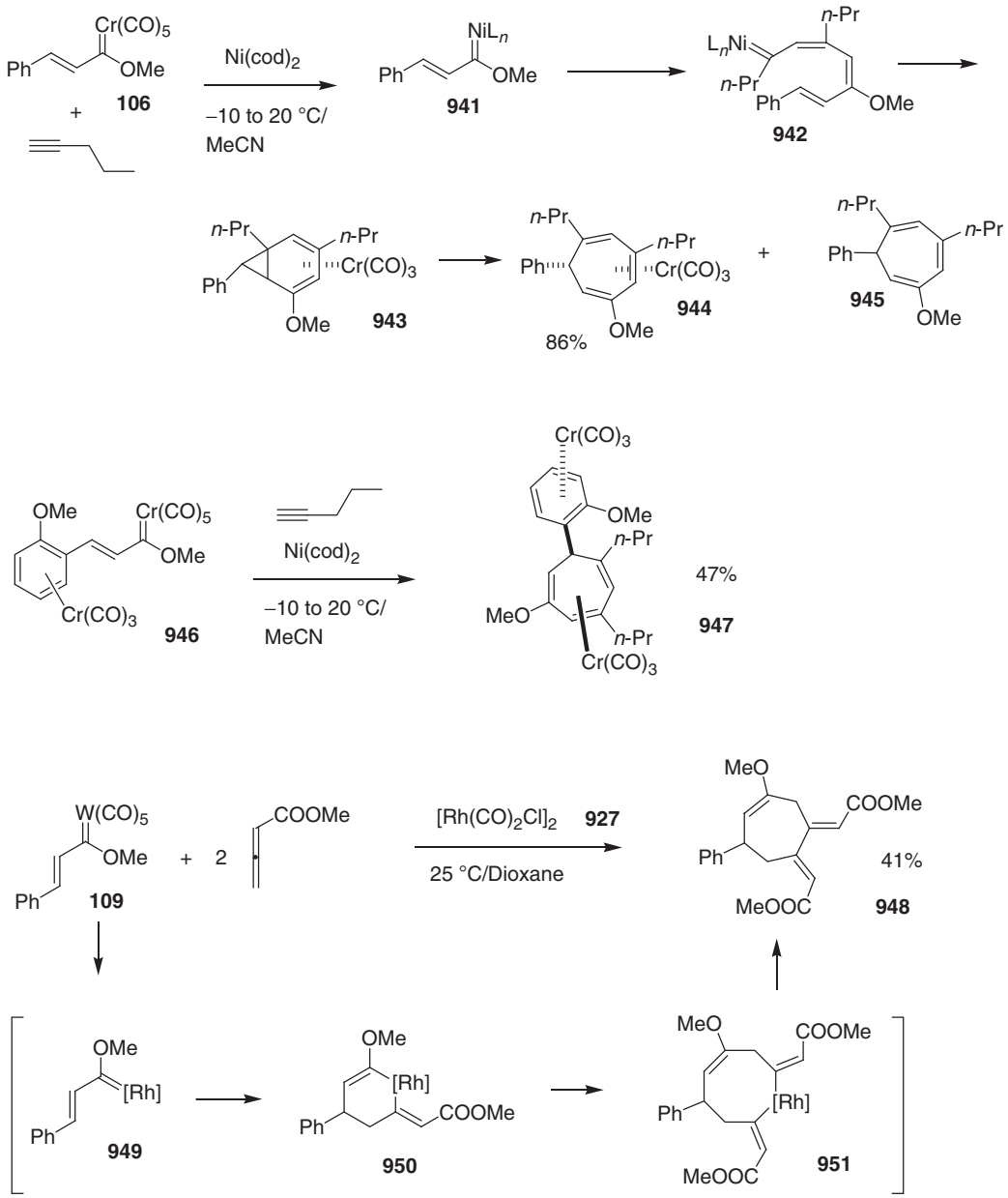
Transition metal-catalyzed seven-membered ring-forming cycloadditions employing carbene complexes have been documented (Scheme 94). Cycloheptatrienes (e.g., **944** and **945**) were synthesized through either the coupling of an alkenylcarbene complex with two equivalents of an alkyne or through coupling of an alkylcarbene complex or arylcarbene complex with three equivalents of an alkyne.[431] A mechanism involving formation of a nickel carbene complex (e.g., **941**) through carbene transfer to nickel, followed by insertion of 2–3 mol of alkyne, followed by intramolecular cyclopropanation to afford an intermediate norcaradiene species (e.g., **943**), followed by an electrocyclic ring opening was proposed. The coupling of chiral alkenylcarbene-$Cr(CO)_3$ complexes (e.g., **946**) with alkynes in the presence of $Ni(cod)_2$ afforded chromium-complexed cycloheptatriene derivatives (e.g., **947**) with a high degree of diastereoselectivity.[432] A net [3 + 2 + 2]-cycloaddition affording bis(alkylidene)cycloheptanones (e.g., **948**) was observed in the rhodium-catalyzed reaction of α,β-unsaturated carbene complexes and allenes.[433] A mechanism involving transfer of the carbene unit to rhodium, followed by metalla-Diels–Alder reaction with an allene to afford the metallacyclohexene (**950**) followed by insertion of a second allene molecule and reductive elimination was proposed. A major side reaction is five-membered ring formation resulting from reductive elimination at the metallacyclohexene (**950**) stage. A similar reaction employing an excess of 1,1-dimethylallene led to cycloheptanone derivatives.[434]



Scheme 93

5.25.4 Conclusions

The use of metal carbene cycloadditions has emerged as an important method for the synthesis of complex ring systems. The most well-developed of these, the Dötz benzannulation reaction, is a powerful tool for aromatic ring construction and has been employed as a cornerstone reaction in many complex natural product syntheses. Through a thorough understanding of the mechanism of this and other processes, tandem reactions that rapidly transform simple molecules into complex systems featuring multiple functionalities and stereocenters have been developed. Although the majority of these reaction processes are stoichiometric in chromium and other transition metals, the source materials (metal hexacarbonyls) are relatively low molecular weight and readily available, and enable transformations that would require multiple operations if performed without these reaction



Scheme 94

processes. It should be noted also that all of the chromium processes depicted involve relatively low oxidation states (0 or +2) and not Cr(VI), the oxidation state associated with harmful health effects. A major underappreciated advantage of stoichiometric chemistry is the ability to perform sequential addition processes on intermediates that would otherwise have no lifetime, and several of these reaction processes take advantage of this unique attribute. Although these reaction processes defy modern-day buzzwords like 'atom economy' and 'catalysis,' they have proven themselves highly useful in advanced synthesis problems.

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5.26 Cross Metathesis

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Glossary

Carbene A molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. Most carbenes are unstable, but persistent carbenes are also known, among them are a class of *N*-heterocyclic ligands often utilized in metal catalysis.

Homodimerization Described also as self-metathesis or homo cross metathesis – a metathetic process during which one alkene substrate yields the product composed of two identical units. This transformation is applied to the synthesis of symmetrical compounds, but is also an issue leading to secondary metathesis pathways when two complicated compounds are utilized.

Isomerization A process by which one molecule is transformed into another molecule with exactly the same atoms, but in a rearranged format. In some molecules and under some conditions, isomerization occurs spontaneously, but it may be a catalytic transformation as well enhanced by, for example, metal-based initiators.

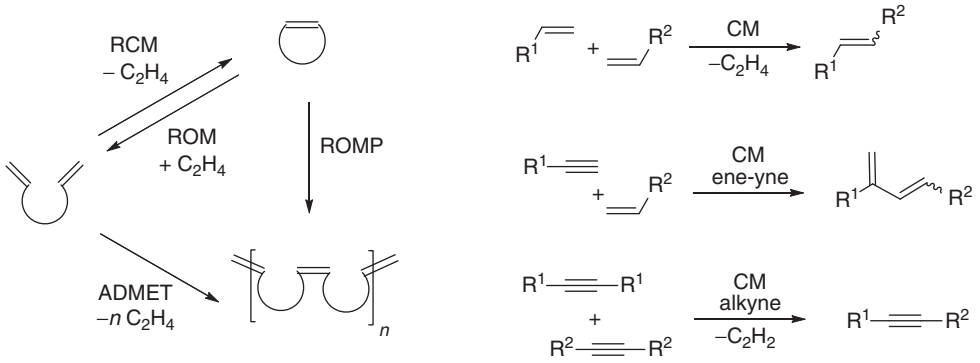
Metathesis An organic metal-catalyzed reaction during which a redistribution of alkene fragments takes place. The mechanism involves the [2 + 2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metallacyclobutane intermediate, which is later rearranged to form the product. Catalysts for this reaction are typically based on ruthenium, molybdenum, or tungsten, enabling a variety of applications.

Stereogenic-at-metal complexes Complexes bearing various ligands with different substitution patterns. This renders the metal a stereocenter and has a profound effect on the enantioselectivity of the catalysts. The main representatives of this class are molybdenum-based complexes containing a partially substituted alkoxide ligand and a pyrrolide moiety.

5.26.1 Introduction

5.26.1.1 General Information

Olefin metathesis[1] is one of the most powerful tools in organic chemistry leading to C–C double-bond formation. The importance of this transformation was underlined by awarding the Nobel Prize to Chauvin, Schrock, and Grubbs in 2005 (http://nobelprize.org/nobel_prizes/chemistry/laureates/2005/chemadv05.pdf). One of the reasons for the success is the variety of possible applications caused by the enormous compatibility of functional groups with the available well defined catalysts. There are examples of utilization of metathesis in the synthesis of natural products,[2] pharmaceuticals,[3] heterocyclic and macrocyclic compounds,[4] or speciality polymers.[5] The great potential of this transformation is partially caused by the fact that metathesis is a set of several different types of reactions: ring-closing metathesis (RCM), ring-opening metathesis (ROM), acyclic diene metathesis (ADMET) polymerization, ROM polymerization (ROMP), and cross metathesis (CM), which are presented in **Scheme 1**.[6]

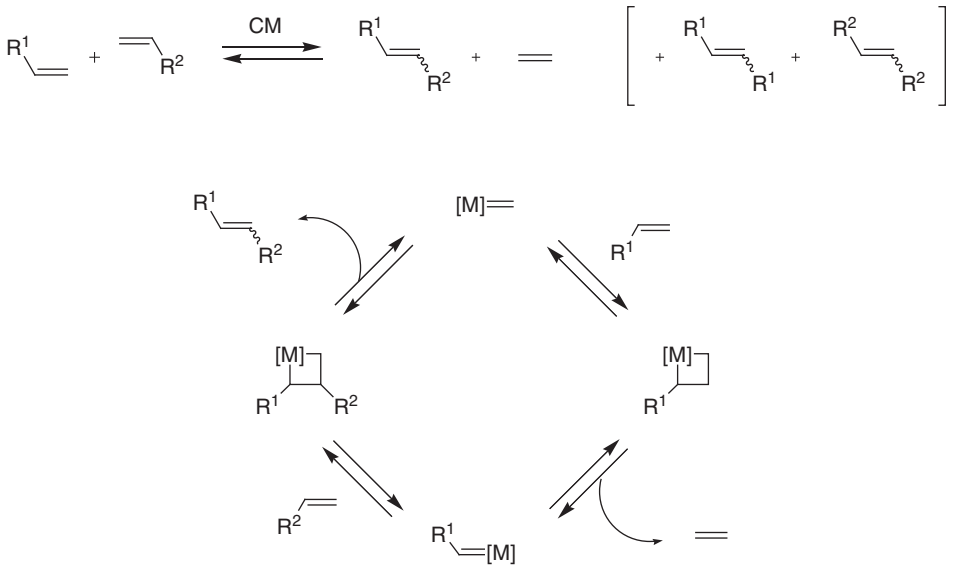


Scheme 1 The main types of olefin metathesis.

It is crucial to underline that, by definition, olefin metathesis is a reaction of two olefinic substrates that are broken and rearranged to form two new olefinic products. Two types of CM shown in the above scheme do not fit into this category. These are the ene-yne CM and alkyne CM – cases when one or both substrates are alkynes. Although this chapter is devoted to CM, those methods will be discussed in Chapters 5.27 and 5.28.

5.26.1.2 Mechanism and Modifications

This review is devoted to discussing CM, its variants and applications, as considerable improvements have been made in this field. The mechanism of this powerful transformation, proposed by Chauvin and Hérisson,[7] is presented in Scheme 2.



Scheme 2 Mechanism of cross metathesis.

The first step is the coordination of the substrate to the catalyst – a transition-metal carbene complex – resulting in the formation of a metallacyclobutane. During the next stage it breaks forming a volatile olefin (ethylene when both the substrates are terminally unsubstituted) and a carbene. The released carbene interacts with the next substrate forming another metallacyclobutane. Decomposition of this species leads to the final product with simultaneous regeneration of the starting metal carbene. It is important to note that all of the steps are reversible, with the release of the volatile alkene being the driving force of the reaction.

5.26.1.3 Commercially Available Catalysts

According to the widely accepted mechanism, the reaction is catalyzed by a transition metal complex. Several metal catalysts have been tested in metathesis reactions, but the best outcome was achieved with molybdenum-, tungsten-, and ruthenium-based ones. A narrow selection of popular, commercially available catalysts is presented in Figure 1. Strem Chemicals offers six molybdenum and seven ruthenium catalysts (including **Ind-I**, **Ind-II**, and **Ind-II′**) were obtained in collaboration with Degussa-Evonik, Ciba

Specialty Chemicals, Umicore, and Zannan Pharma. Since 2003, Sigma-Aldrich has exclusively offered 11 Grubbs and Hoveyda catalysts (including **Gru-I**, **Gru-II** and **Hov-I**, **Hov-II**) produced by Materia Inc. **Gre-I**, **Gre-II**, and several other ruthenium catalysts available from Apeiron Synthesis. This wide selection is a great aid for the community of organic chemists willing to perform metathesis.

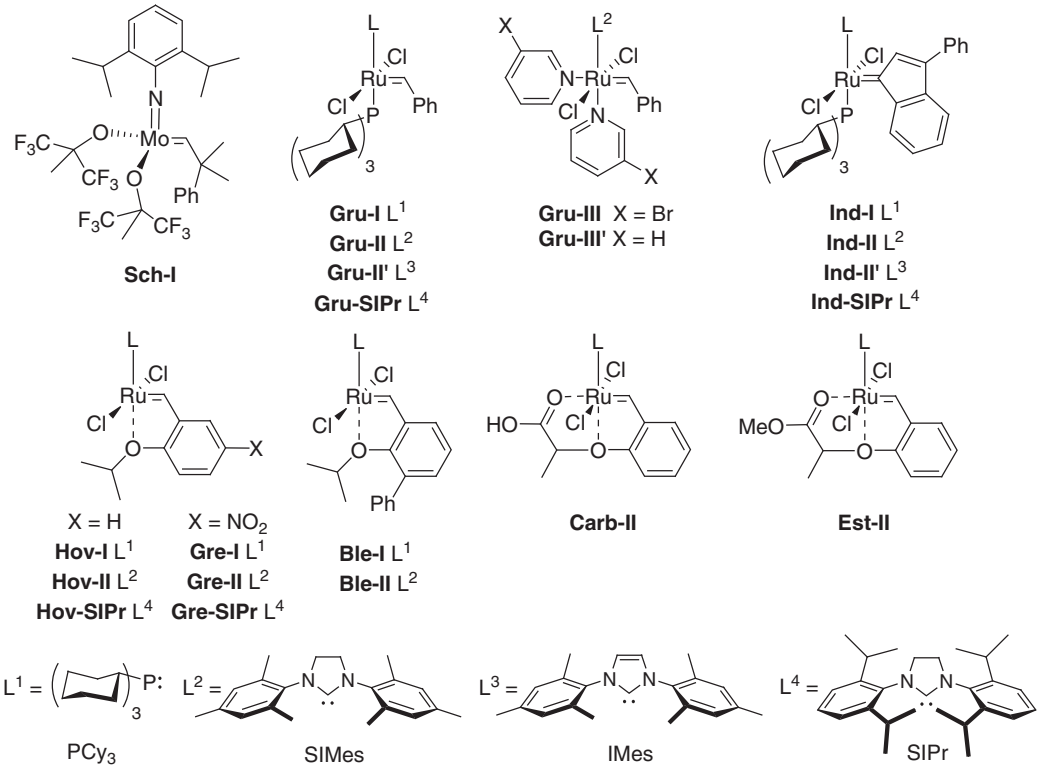


Figure 1 Selected commercially available metathesis initiators. Ph, phenyl.

The most reactive catalysts to date are based on molybdenum. The class represented by **Sch-I**[8] was the first to be developed and possesses enormous synthetic potential. Although the activity of these kinds of initiators is very high, their sensitivity to air and moisture were the limiting factors in industrial applications. The discovery of ruthenium-based benzylidene[9] and indenylidene[10] catalysts, free of these drawbacks, was a real breakthrough. The original variants, known as 'first-generation,' contained two phosphine ligands. Later, one of the phosphines was replaced by an *N*-heterocyclic carbene (NHC) possessing a σ-donor character, thus leading to the 'second-generation' of ruthenium compounds. It is important to note that even slight modifications of the NHC ligand structure leads to changes in the catalytic behavior.[11] A good example is the implementation of chirality to the structure of the catalysts, which has been an important issue in metathesis studies for over a decade. So far the NHC was the only means of introducing chirality in Ru-based catalysts, as the strong bond connecting such ligands to the metal does not break during the catalytic cycle, thus allowing for efficient transfer of stereoinformation. NHCs applied to induce chirality are usually divided into two classes: those of C_1 and C_2 symmetry. Representatives of these classes are presented in **Figure 2**.[12]

Application of *N*-heterocyclic ligands of C_1 symmetry allows the influence of the chiral backbone to be enforced by the increase in the steric hindrance. Depending on the structure of the complex, various *syn*/*anti* rotamer ratios are observed. A variation of this class are bidentate C_1-symmetric NHCs. Their interesting feature is that the backbone does not have to be substituted and, as the ligand is chelating, no Ru-NHC rotation is observed. Moreover, the diastereoselective complexation of the ruthenium atom creates a stereogenic center at the metal (stereogenic-at-Ru complexes). This leads to a highly improved *E*:*Z*-selectivity, which is beneficial in a variety of asymmetric applications such as CM or ring-opening CM (ROCM). Additional modification of the anionic ligands – applying iodides instead of chlorides – magnifies this effect by increasing the steric interactions. Moreover, complexes of this class show outstanding stability. Research on C_1-symmetric NHCs led to further developments in the field. Mol et al. reported on a Grubbs-type initiator derivative bearing the bulky 1-(1-adamantyl)-3-mesityl-4,5-dihydroimidazol-2-ylidine NHC ligand,[13] whose X-ray structure showed a possible weak interaction of one of the adamantyl carbons with the metal center (2.883 Å). As this complex failed to initiate even the simple self-metathesis it was not further developed until, more recently, Grubbs obtained a Hoveyda-type complex (**Ru-V**) bearing the same NHC ligand used by Mol.[12e] In this complex the NHC is chelated to the metal center through a Ru–C covalent bond. Despite its relatively poor activity in metathesis reactions, it has displayed a fairly good *Z*-selectivity in CM. Continuing their efforts, Grubbs et al. obtained several new

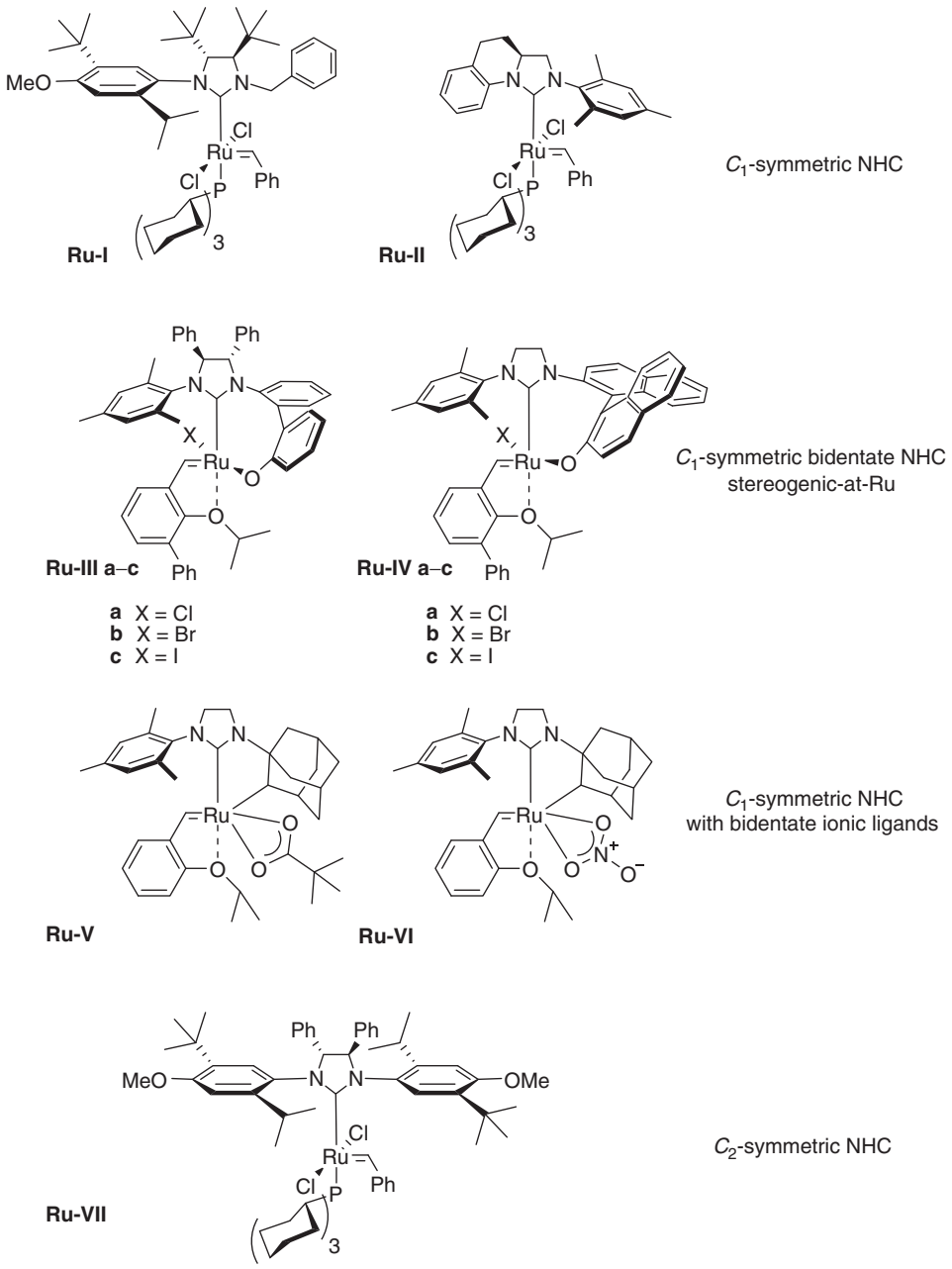
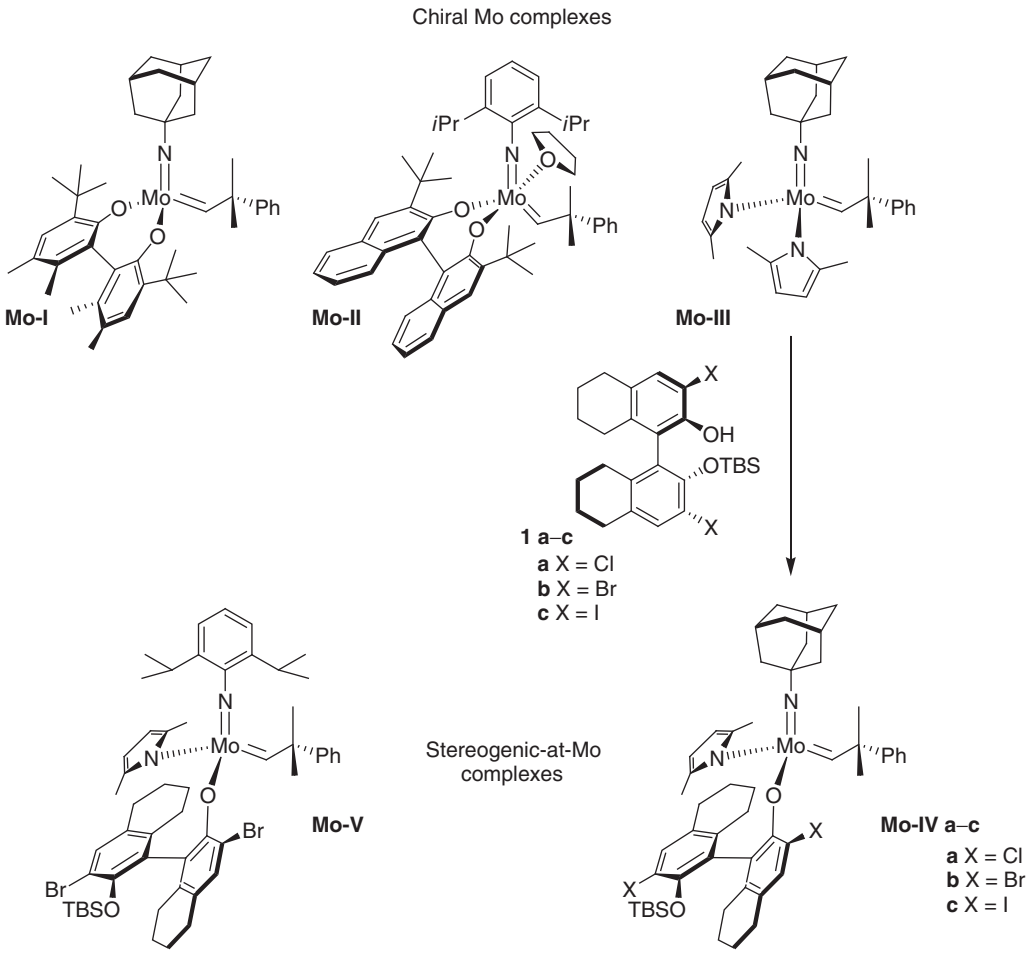


Figure 2 Chiral Ru-based metathesis catalysts.

C–H-activated ruthenium catalysts for *Z*-selective olefin metathesis.[12e,f] It was found that bidentate anionic ligands (e.g., bulky carboxylates, **Ru-V**) led to the best metathesis activity and selectivity, whereas the monodentate ones were usually less optimal. The use of Chen's nitrato ligands[14] in place of carboxylates led to a significant improvement in the catalyst's activity and selectivity (**Ru-VI**).[12f] With these catalysts, turnover numbers approaching 1000 were possible for a variety of CM reactions, including syntheses of industrially relevant products. It shall be noted that, in contrast to Mo- and W-based systems, these catalysts are compatible with polar groups and protic solvents.

The last class of chiral ruthenium compounds is of higher C_2 symmetry. These complexes are highly stable. Another advantage is that the rotation around the Ru-NHC axis is inconsequential. The chiral backbone influences the *N*-aryl substituent's orientation with the aryl *o*-substituents being crucial for selectivity. The general pattern of enantioinduction seems to be the same for all Ru-based complexes. The substrate may coordinate to the complex in different ways, and due to the steric interactions with the NHC, one of the possible intermediates with the bound substrate is ultimately favored. This scenario has been confirmed by theoretical studies.[15]

Installing chirality in the molybdenum complexes requires a different approach, as the ligands do not dissociate during the catalytic cycle, thus strongly influencing the behavior of the complex. Two classes of Mo-based complexes utilized in asymmetric metathesis are presented in Scheme 3.[16]



Scheme 3 Mo-based complexes utilized in asymmetric metathesis. *i*Pr, *iso*-propyl; TBS, *tert*-butyldimethylsilyl.

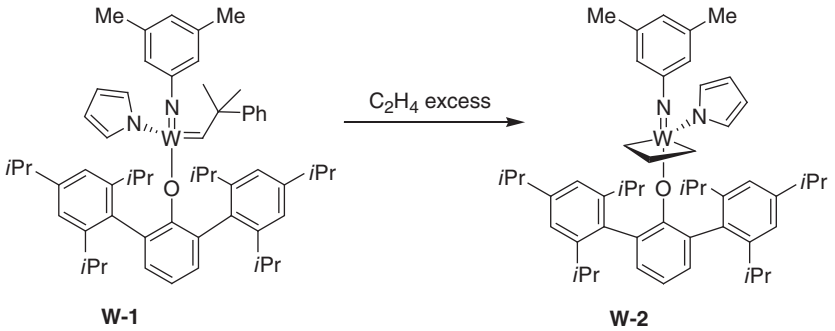
Typical chiral Mo-based complexes contain biphenol and binol derivatives with different substitution patterns. Stereogenic-at-Mo complexes are obtained by utilization of a partially substituted alkoxide ligand and a pyrrolide moiety (the so-called monoalkoxide-pyrrolide (MAP) complexes). The combination of two different monodentate ligands leads to the establishment of a stereocenter at the metal, having a profound effect on the enantioselectivity of the complex. A great advantage of such systems is that they can be generated *in situ*. Although utilization of Mo-based catalysts seems beneficial, they have a major drawback – sensitivity to air and moisture, which still seems to limit their applications. There have been attempts to stabilize the complexes by specially designed additives (2,2′-bipyridine was utilized), which, although successful, resulted in initiators of diminished activity.[17]

Recently, Schrock and Hoveyda found that related tungsten-based MAP catalysts such as **W-1** can be transformed into fairly stable crystalline metallacyclobutane complexes such as **W-2** by exposing the alkylidene to an ethylene atmosphere (Scheme 4).[18] Importantly, it was shown that a number of α-olefins as well as many functionalized alkenes can be homo-metathesized in the presence of this complex in good-to-excellent yields with *Z*-selectivities of >99%.

Despite enormous improvements in the synthesis of chiral catalysts, their large-scale applications to date seem to be limited. The review will discuss principles and means of utilization of the described catalysts in the different variants of CM.

5.26.1.4 Olefin Types

On the basis of the mechanism of CM (Scheme 2) one can easily tell that the reaction of two substrates can lead to up to four products. The possible formation of various metallacyclobutanes and the number of secondary metathesis pathways determine



Scheme 4 Chiral tungsten complexes.

the composition of the product spectrum, which depends on the properties of the substrates taking part in the reaction. Attempts to introduce some categorization of reactivity were made by Grubbs et al.[19] The authors suggested that the relative ability to undergo homodimerization, compared with other olefins, may be the key. This factor, combined with a willingness of the potential homodimers to undergo secondary metathesis, was established as the basis of the original categorization presented in Table 1. Since the publication of this significant paper, important advances have been made in the field, but the classification presented below remains a starting point for any reaction optimization.

Table 1 Olefin categorization according to Grubbs

Olefin type	*Properties*	*Examples*
I	Fast homodimerization, homodimers consumed	Terminal alkenes, allyl silanes, allyl halides, primary allylic alcohols, allyl boronates, allyl phosphonates, protected allyl amines styrenes (no large *ortho* substituent) allyl sulfides, allyl ethers
II	Slow homodimerization, homodimers sparingly consumed	Styrenes (large *ortho* substituent), allyl stannanes, acrylic acid, acrylates, acrylamides, vinyl ketones, vinyl epoxides, vinyl boronates, vinyl dioxolanes, olefins substituted by perfluorinated alkyl groups, secondary allylic alcohols, unprotected tertiary allylic alcohols
III	No homodimerization	Tertiary allyl amines, vinyl sulfones, 1,1-disubstituted alkenes, acrylonitrile, vinyl siloxanes, vinyl phosphonates, protected tertiary allylic alcohols, alkenes flanked by quarternary allylic carbons (all alkyl substituents)
IV	Spectators to cross metathesis	1,1-Disubstituted alkenes, nitroolefins, quarternary allylic carbon containing alkenes, protected tertiary allyl amines, protected trisubstituted allylic alcohols

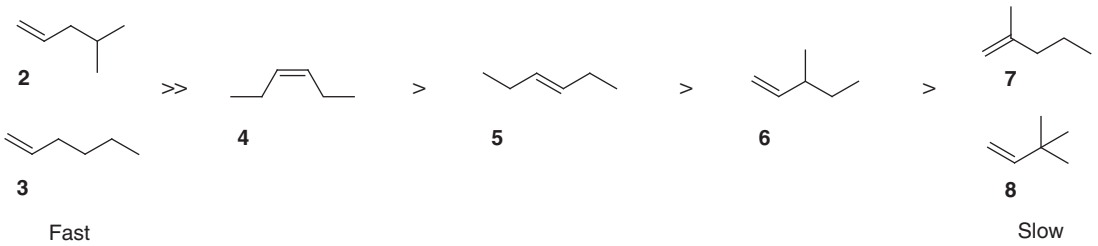
According to this classification, type I olefins undergo homodimerization rapidly, but the resulting dimers are consumed in secondary metathesis processes. Olefins described as type II homodimerize slowly and their homodimers are slowly consumed in the following CM process. Type III olefins do not homodimerize. The last type of olefins – type IV – gives neither homodimerization nor CM products. The classification was applied only to olefins that can be metathesized or are inert toward metathesis initiators, but olefinic compounds that have a deactivating influence on the catalyst were not taken into consideration. It requires emphasis that the above classification, although informative, is not general, as many exceptions were found. Moreover, as the metathesis methodology improves, type IV cases can be placed in different categories, and indeed, since the original classification in 2003, this particular category has been significantly reduced.[20]

A great advantage of the above classification is that it allows the prediction of the reaction selectivity. The rules are presented in Table 2.

Table 2 Rules for selectivity in cross metathesis

	Type I	*Type II*	*Type III*	*Type IV*
Type I	Statistical	Selective	Selective	No reaction
Type II	Selective	Nonselective	Selective	No reaction
Type III	Selective	Selective	Nonselective	No reaction
Type IV	No reaction	No reaction	No reaction	No reaction

It should be noted that Table 2 is based on generalized experimental data, which sometimes leads to results that are slightly different from the ones suggested by the model. One reason for that is the complexity of the problem, as the reactivity of olefins is a combination of steric and electronic factors. These aspects determine not only the selectivity of the reaction but also the relative reaction rates toward the catalyst. Scheme 5 summarizes the data for the ruthenium complex **Gru-I**.[21]



Scheme 5 Relative reaction rates with **Gru-I**.

When we compare the reaction rates of *E*- and *Z*-olefins (**5** and **4**, respectively) with the ruthenium benzylidene **Gru-I**, the catalyst reacts approximately twice as fast with the *Z*-isomer. The explanation seems to be simple: when the *Z*-olefin binds to the metal, the substituents point away from the bulky phosphine; this is not the case for *E*-olefins, which therefore bind more slowly. As the steric bulk increases, the reaction rate decreases placing 2,2-substituted olefins on the right as they do not react under the applied conditions. This results in the above reactivity order. Many studies on the influence of electronic effects have been conducted, which do not seem to be straightforward and cannot be discussed in general.

It should be noted that the above considerations based on the homodimerization rate may lead to certain confusion. Although a lot of examples seem to support this classification, in recent years many papers contain opposing data. Direct application of this concept to the experiments planning may occasionally result in a failure. The review will proceed to describe particular examples and applications of CM.

5.26.2 CM

5.26.2.1 Reaction with Fast Homodimerizing Metathesis Partners

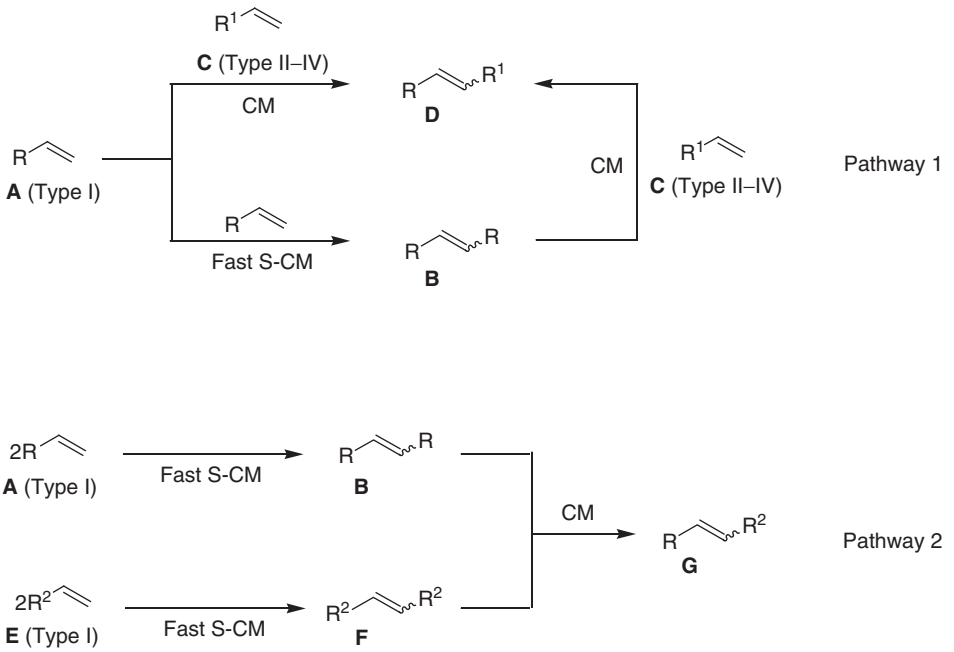
5.26.2.1.1 CM between two partners of type I

According to the general classification proposed by Grubbs,[19] olefins of type I (**A**) undergo self-CM (S-CM, sometimes referred in the literature as 'homo metathesis' or even as 'dimerization') and such 'dimers' (**B**) can also be used in CM with other olefins (Scheme 6). Most terminal alkenes can be classified as Type I olefins. Usually, in order to obtain acceptable selectivity levels, type I olefins (**A**) are used as CM partners for types II–IV olefins (**C**) according to pathway 1. A number of successful examples of this approach have been reported in the literature.

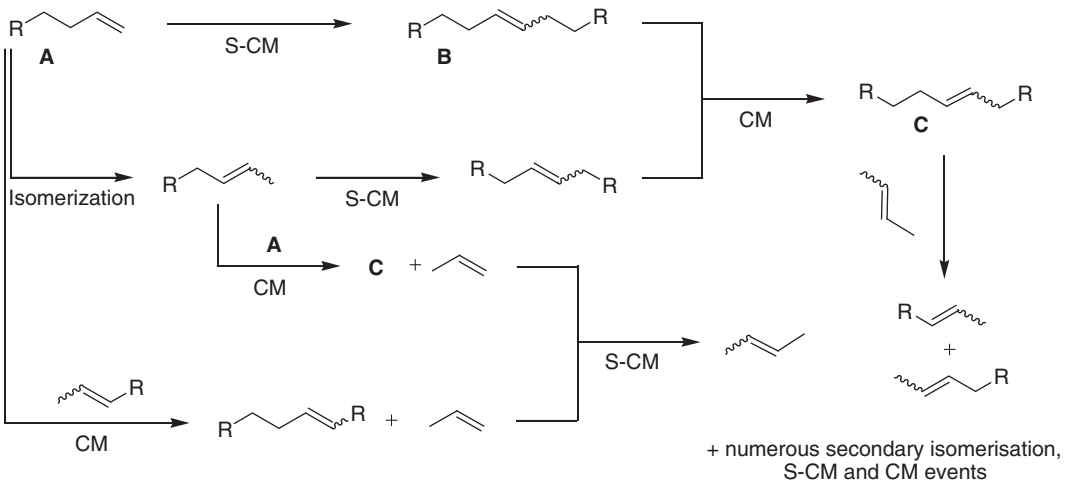
When two different type I olefins, **A** and **E**, undergo a CM reaction, the rates of homodimerization are usually very similar, leading to pathway 2. Therefore, the desired cross product **G** is always accompanied by the respective homo metathesis products **B** and **F**, resulting in a statistical product mixture, which makes the transformation impractical. To obtain good yields of the desired cross product, usually high excess of one of the type I olefins is required. Practically, 2–10 equivalents of one partner may be necessary to obtain a CM product of two type I olefins in a reasonable yield.[22,23] Better results can be obtained by utilizing internal olefins **B** and **F** for the CM reaction. If the CM product **G** can be separated from the substrates and further recycled, such transformation can be of significant practical value. Such strategies involving S-CM (sometimes described as homo metathesis) of simple alkenes can be attractive industrial methods allowing, for example, the conversion of low value feedstock such as Fischer–Tropsch olefin fractions and other *n*-olefins into useful chemicals. Unfortunately, a mixture of products can be formed due to alkene C–C double-bond isomerization during the metathesis reaction. As the products of this transformation can also undergo CM reactions, a range of alkene products is usually formed (Scheme 7).

The number of different processes taking place during such reactions prevented potential applications; therefore, efforts were made to reduce the undesirable reaction pathways. Utilization of first-generation ruthenium complexes was found to be beneficial in such cross metatheses because they do not cause isomerization to a high extent. The more active second-generation catalysts are known to cause shifts of the double bonds more easily, which can be effectively suppressed by the addition of benzoquinones.[24] Czaban et al. recently checked the influence of the reaction parameters on the conversion and selectivity of the metathesis of 1-dodecene (Scheme 8).[25]

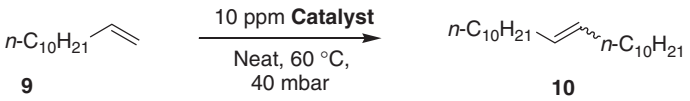
As expected, it was found that the addition of benzoquinone derivative (in this case **11**) tremendously increases the selectivity of the process. The catalyst screening led to less obvious results. The best catalysts were found to be **Gru-II**, **Gre-II**, and **Carb-II**.[26] Despite structural similarities between the utilized catalysts (**Hov-II** and **Gru-II**, **Carb-II** and **Est-II**) the reaction outcomes varied



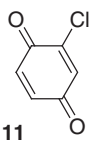
Scheme 6 Reactivity pathways of type I olefins.



Scheme 7 Isomerization problem.



Catalyst	Additive	Conversion (%)	Selectivity (%)
Gru-II	–	64	83
Gru-II	20 ppm **11**	63	98
Hov-II	20 ppm **11**	35	98
Gre-II	20 ppm **11**	51	98
Ind-II	20 ppm **11**	83	82
Carb-II	20 ppm **11**	53	98
Est-II	20 ppm **11**	21	99

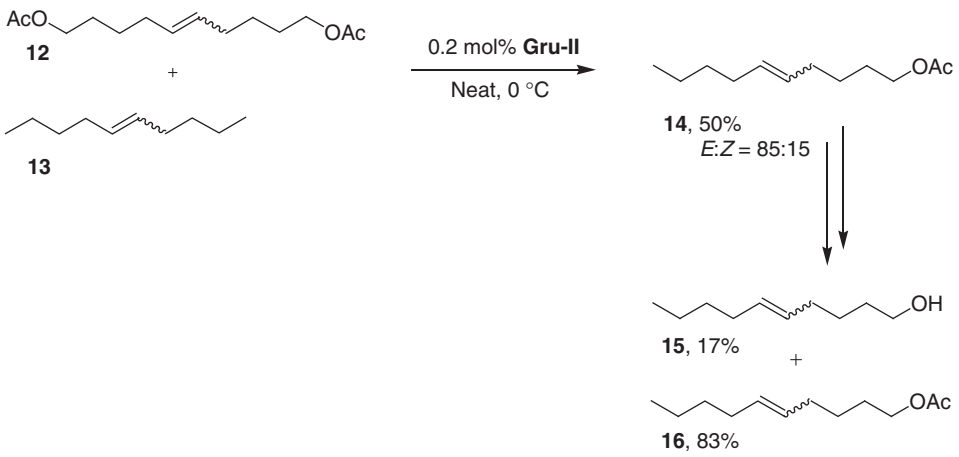


11

Scheme 8 Utilization of quinones in S-CM.

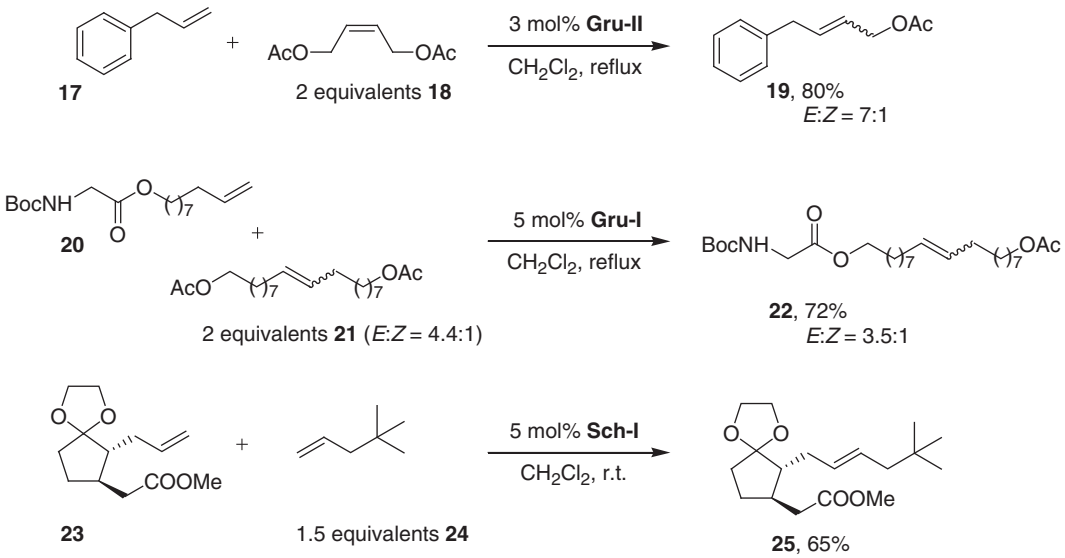
highly, suggesting an electronic effect as the cause of the observed differences. The study also pointed out that another method of increasing the conversion was the efficient removal of ethylene.

The solvent-free CM of **12** and **13** represents an example of the use of two different type I olefins to obtain a commercially relevant product (Scheme 9). Product **14** is readily converted into a pheromone of the peach twig borer moth (mixture of **15** and **16**), which can be used as an environmentally friendly alternative to classical pesticides.[27] In an attempt to design a more cost-effective process, the symmetrical internal olefins **12** and **13** (individually derived from S-CM of the corresponding α-olefins) were equilibrated by CM in the presence of 0.2 mol% of the second-generation Grubbs catalyst. The product was separated by distillation and the starting materials were recycled. The reaction was conducted at 0 °C to minimize unwanted C–C double-bond isomerization. Despite much slower ratios of the CM reaction at low temperatures, these conditions were found optimal as the separation of olefin isomerization byproducts formed at higher temperatures was problematic.[28,29]



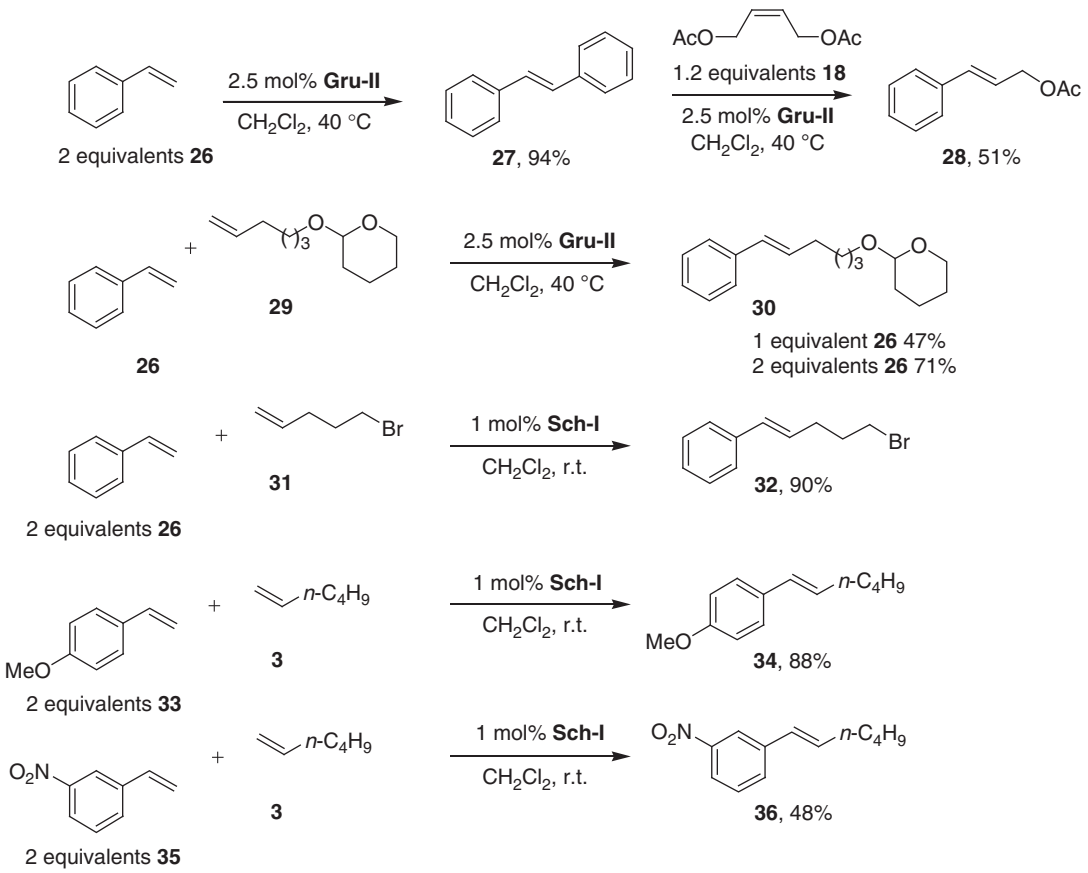
Scheme 9 CM of type I olefins in a commercial application. Ac, acetyl.

CM reactions involving type I olefins are widely reported in the literature, as this route represents an efficient means to generate valuable compounds starting from relatively inexpensive starting materials (Scheme 10).[22,23]



Scheme 10 Examples of CM involving type I olefins. Boc, *tert*-butoxycarbonyl; r.t., room temperature.

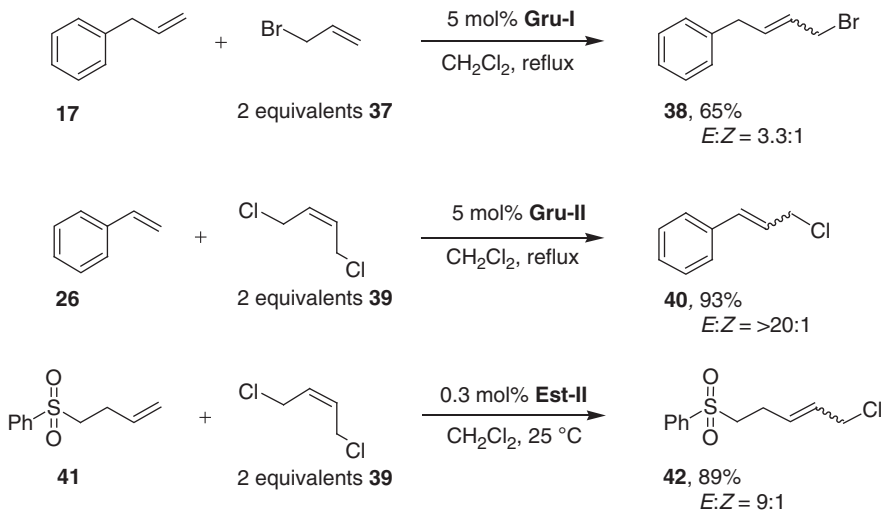
These examples demonstrate the applicability of CM for the synthesis of unsymmetrically substituted and functionalized olefins, where a broad variety of functional groups is tolerated. Further studies proved that styrenes that are not substituted in the *ortho* positions easily undergo S-CM in reactions promoted by **Gru-II**[19] (Scheme 11). Stilbene (**27**) obtained in this reaction reenters CM reactions with other type I olefins. This result clearly indicates that styrene is a type I olefin, at least if active catalysts



Scheme 11 Styrenes as type I partners.

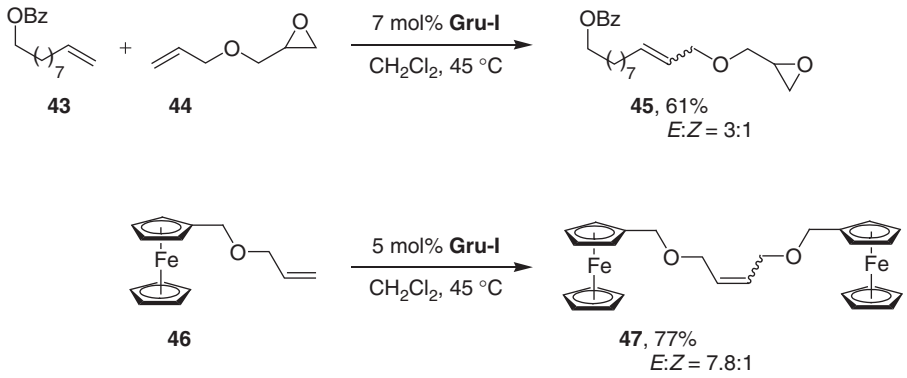
are used. A study concerning the utilization of the molybdenum catalyst **Sch-I** proved that, under properly selected conditions, CM involving styrenes can lead to a variety of synthetically valuable building blocks.[30]

Another class of easily dimerizing CM partners are allyl chlorides and bromides. The example of CM between allylbenzene, a type I olefin, and allyl bromide, promoted by **Gru-I**, was published by Castedo et al. (Scheme 12).[31] Further improvements in terms of yield were made by using the more active **Gru-II**,[32,33] **Hov-II**,[34] and finally **Est-II**[35] catalysts. It was noted that the internal alkene **39** can act as a convenient replacement for the more volatile allyl chloride. However, in the case of allyl fluorides and allyl iodides, the CM reactions are more challenging.



Scheme 12 CM reactions involving allyl halides and type I olefins.

Allylic ethers are another example of olefins efficiently employed in various CM reactions, as demonstrated by a large number of literature reports.[6d] For example, in a CM reaction of the allyl glycidyl ether **44** with benzoate **43**, the cross product **45** is formed in 61% yield (**Scheme 13**). Allylic ethers undergo S-CM easily, leading to useful products, like compound **47**, which was formed from 1-ferrocenecarbinol allyl ether.[22]

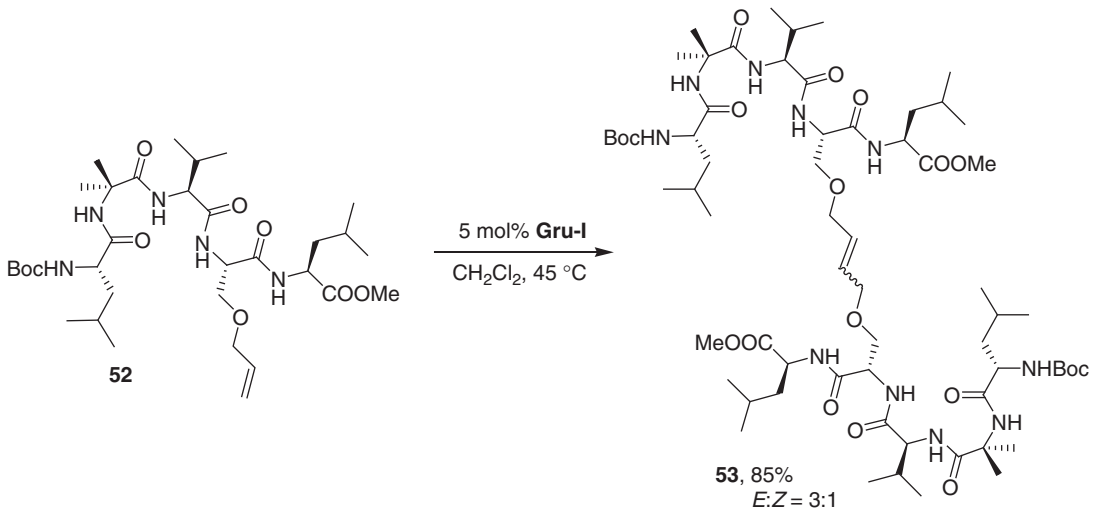


Scheme 13 CM of allylic ethers.

To modify the biological activity of amino acid derivatives and O-allylated peptides, various compounds of this class were subjected to S-CM. Grubbs reported on the synthesis of a series of amino acid and peptide homodimers (**Scheme 14**). O-allyl ethers of protected L-serine (**48**) and L-homoserine (**49**) derivatives, on treatment with **Gru-I**, afforded good yields of their respective homodimers with moderate *E*-selectivity (*E*:*Z* = 3:1). In some cases the self-metathesis was performed *in vacuo*, allowing for a more efficient removal of ethylene, thus shifting the reaction equilibrium to the right. In the presence of the ruthenium catalyst **Gru-I**, a pentapeptide **52** bearing an L-serine O-allyl ether fragment led to the side chain-bridged homodimer **53** in good yield, demonstrating the utility of the self-metathesis methodology for the synthesis of advanced peptidic architectures.[22]

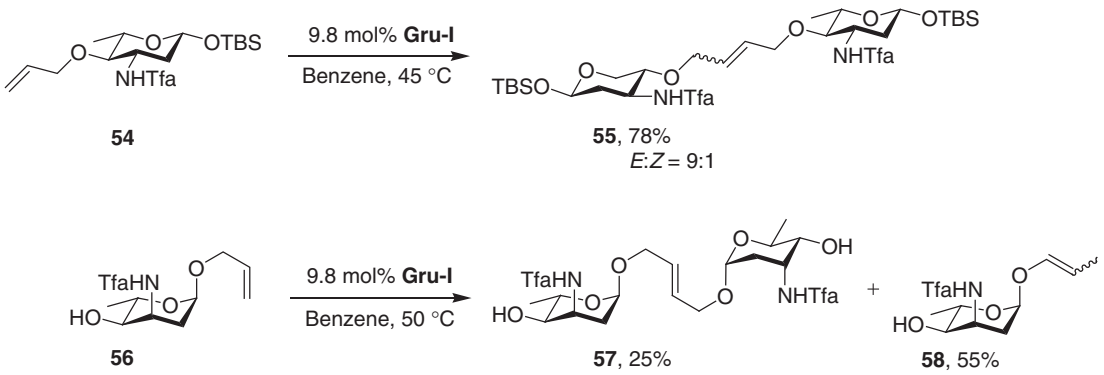


Substrate	Product	*n*	Yield (%)	*E*:*Z*
48	**50**	1	73	2.6:1
49	**51**	2	75	2.7:1



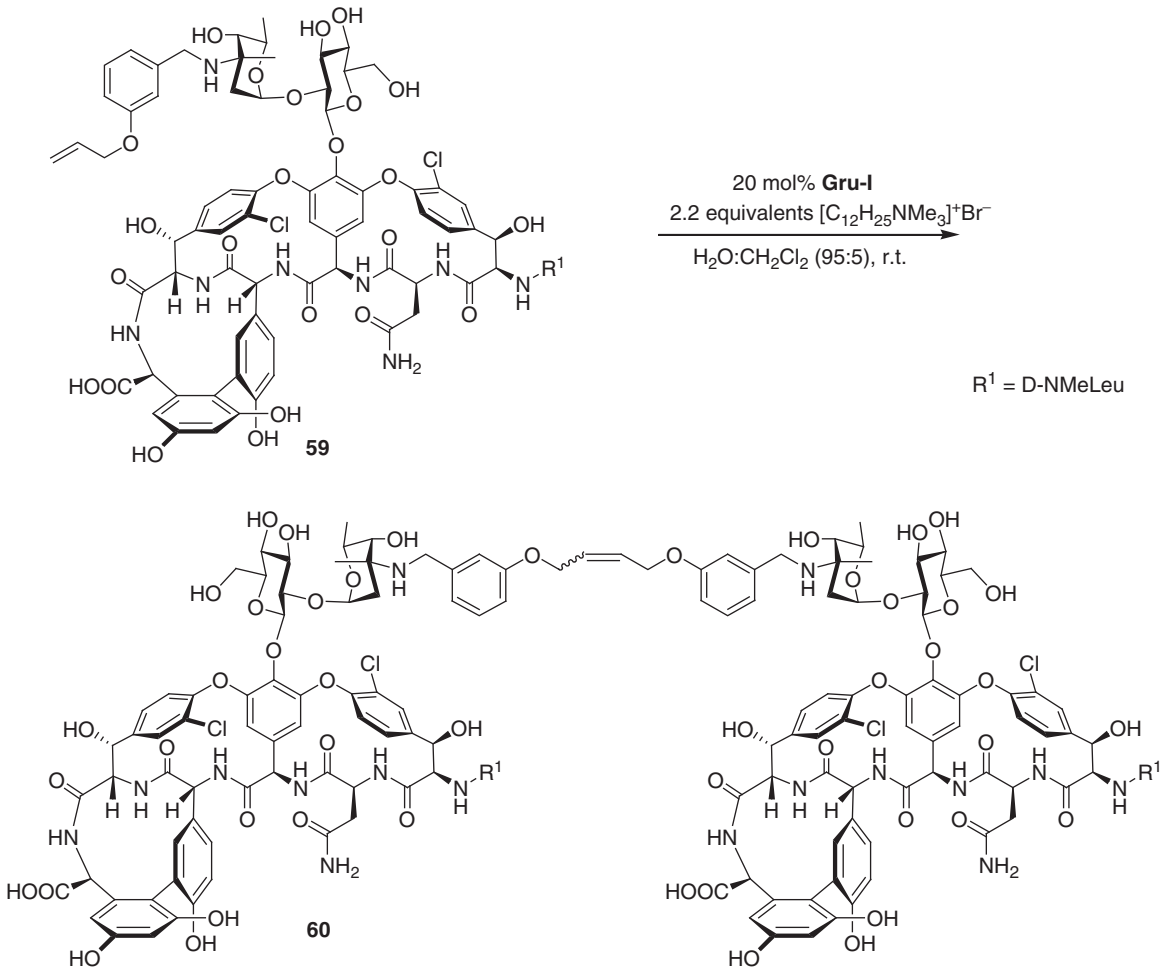
Scheme 14 Self-metathesis of amino acid derivatives.

The preparation of cyclic 1,4-butanediol-linked oligoaminodeoxysugars – potential binders to polynucleotides – was disclosed by Kirschning (Scheme 15).[36] Saccharide dimers, such as **55** and **57** were assembled by self-metathesis reaction of aminodeoxy monosaccharides. The resulting C_2-symmetric *E*:*Z* mixtures were further transformed into the targeted cyclic oligoaminodeoxysugars. The first-generation Grubbs catalyst **Gru-I** turned out to be the catalyst of choice for this reaction. In the case of allyl glycoside **56**, in addition to the expected product **57**, a byproduct **58** was formed that contained a shifted alkenic double bond.



Scheme 15 Dimerization of allylated saccharides. Tfa, trifluoroacetyl.

Another example of the synthetic utility of a metathetical dimerization of allylic ethers (and homoallylic ethers) was provided by Nicolaou and coworkers, who used this method to generate libraries of vancomycin dimers (Scheme 16).[37] It was found that



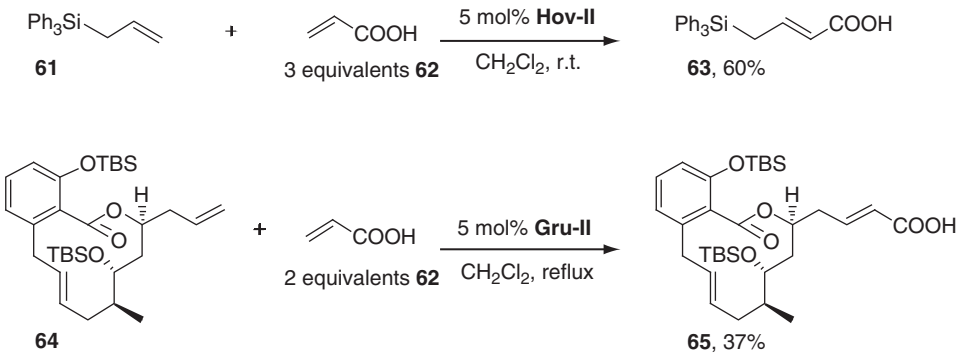
Scheme 16 S-CM of a vancomycin analog.

dimerization of the vancomycin derivative **59** catalyzed by **Gru-I** proceeds best in a heterogeneous mixture composed of water and methylene chloride (95:5 v/v) in the presence of $[C_{12}H_{25}NMe_3]Br$ as the phase transfer catalyst. Under such conditions, dimer **60** was cleanly obtained as the sole product.

The described examples of CM between type I partners prove that the method is particularly useful for the functionalization of advanced intermediates in the organic syntheses or the synthesis of diverse combinatorial libraries. This, along with the construction of dimeric molecules, affords compounds that can potentially exhibit modified biological activity and are therefore of interest for use in molecular biology.

5.26.2.1.2 CM between partners of type I and type II

Although CM of two 1-alkenes, belonging to type I, usually results in a statistical product distribution, the reactions between terminal alkenes and a variety of unsaturated compounds, such as α,β-unsaturated esters, amides, ketones, and nitriles, are usually characterized by excellent selectivity. In this case, according to the Grubbs classification,[19] substrates such as acrylic acid and its derivatives are type II olefins because they undergo homodimerization only to a small extent under typical reaction conditions and hence allow for selective crossing with 1-alkenes (type II + type I). Acrylic acid enters CM with olefins, leading to a number of useful building blocks like compound **63** (Scheme 17).[38] Direct CM of alkene **64** with the same partner was employed in the total synthesis of salicylihalamides A and B.[39]

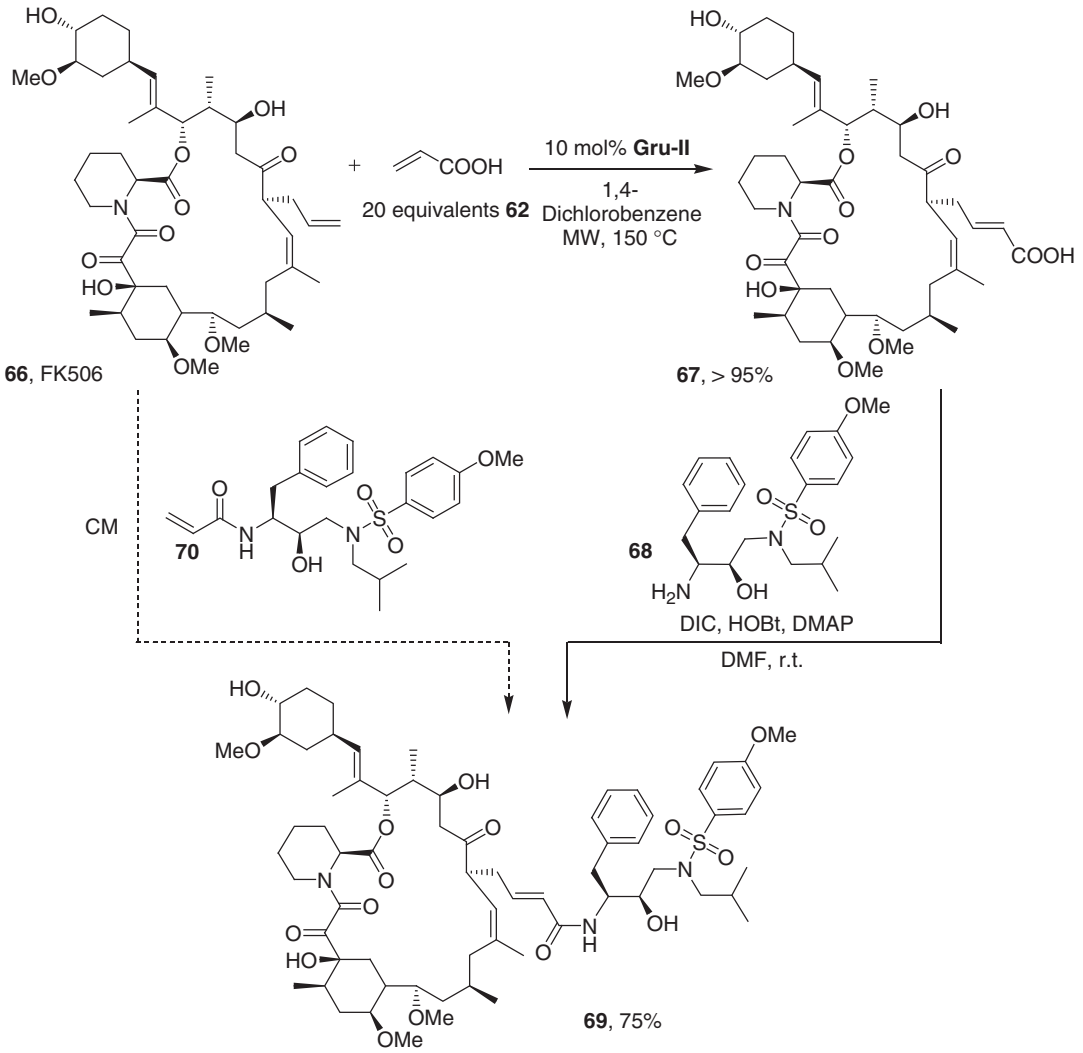


Scheme 17 Examples of CM with acrylic acid.

Under carefully optimized conditions, CM can be used to functionalize natural products in order to change their biological mode of action. Such modular assembly may lead to the formation of compounds that posses interesting biological properties. Using this approach, a powerful immunosuppressant FK506 (**66**), normally used to prevent allograft rejection in transplant patients was modified with an array of functional groups, including a carboxylic acid residue (Scheme 18).[40] Intermediate **67** formed in the CM reaction with acrylic acid was coupled with a core of the known human immunodeficiency virus (HIV) protease inhibitor **68** to produce a bifunctional molecule **69** that exhibits modified antiprotease activity.[40] It shall be noted that this two-step strategy (first CM and then coupling with amine **68**) seems to be much more efficient than a direct attaching of the whole HIV protease inhibitor fragment by a CM reaction with a hypothetical amide **70**. The use of a large excess (20 equivalents) of acrylic acid, required to obtain a good yield of the CM product **67**, is more convenient from the economy point of view as the unreacted acrylic acid can be much more easily removed from the reaction mixture by aqueous extraction than the much more expensive amide partner.

CM of methyl acrylate found utility not only in target-oriented synthesis but also as a tool for the comparison of the activity of various Ru-based catalysts. Grubbs et al. presented a model reaction of **72** and 5-hexenyl acetate (**71**), which is discussed in detail in Scheme 19.[41] Although the first-generation initiators do not catalyze this reaction to a synthetically useful extent, the NHC-based complexes show a much higher reactivity. According to the researchers, the following activity trend was observed within the series of NHC-based catalysts: **Gru-II** > **Hov-II** > **Gru-II′** ≫ **Gru-III**.[19] The only CM product observed is the *E*-isomer, presumably due to the strong preference to form the more stable *E*-configured unsaturated ester. It should be noted that the CM of methyl acrylate and terminal olefins promoted by activated Hoveyda catalyst analogs such as **Ble-II**[42] and **Gre-II**[43] is possible even at ambient temperatures; at elevated temperatures, however, practically all second-generation catalysts can be used, sometimes at much lower loadings.

CM with acrylic acid esters was used in a number of syntheses, which renders this reaction a useful, predictable, and reliable method for the preparation of functionalized molecules, including indoles[44] and steroids (Scheme 20). CM of allylestrone **79** was optimized utilizing various catalysts, with **Gru-II** showing the best results.[45] Kalesse et al. used the CM with methyl acrylate to install the conjugated ester functionality for an intramolecular Michael addition *en route* to the synthesis of the ABC-ring system (**83**) present in hexacyclinic acid and other bioactive compounds.[46] Several metathesis catalysts have been screened in this transformation, and the Hoveyda-Grubbs second-generation catalyst **Hov-II** and its activated analog **Gre-II** were proved to be the



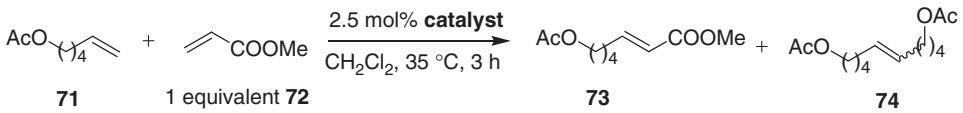
Scheme 18 CM in the modification of FK506. DIC, *N,N*′-diisopropylcarbodiimide; DMAP, 4-(*N,N*-dimethylamino)pyridine; HOBt, hydroxybenztriazole; MW, microwave irradiation.

most potent, leading to the formation of **82** in 80% yield. CM of the same allylestrone **79** with the acrylamide derivative **84** was also evaluated for the synthesis of a 17β-hydroxysteroid dehydrogenase-type 1 inhibitor **86** (Scheme 21).[45]

Grubbs et al. reported a study on CM reactions of various α,β-unsaturated amides with terminal olefins and styrene (Scheme 22).[47] Several unsaturated amide substrates were utilized and it was found that the CM efficiency is affected by the substituents on the amide nitrogen.

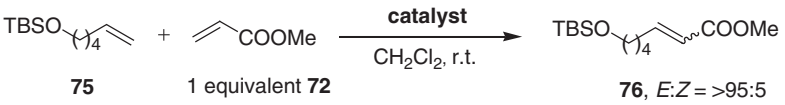
α,β-Unsaturated aldehydes were also proved to be excellent CM partners with terminal olefins. This method allows for an efficient one-step formation of functionalized α,β-unsaturated aldehydes like **95** under mild conditions (Scheme 23).[48] A sequence of three CM reactions, two with acrolein and one with ethyl acrylate, was very elegantly employed by Cossy and BouzBouz in the total synthesis of the C1–C14 fragment of Amphidinol 3 (**102**).[49] In each case the *E*:*Z*-selectivity of the CM step was better than 50:1. The second and the third CM events were fully chemoselective, as only the homoallylic terminal double bond (type I olefin) reacted and the internal C–C double bonds were inert under the applied conditions.

It is to be noted that the strongly odorous and rather unstable acrolein can be easily replaced in CM reactions with a more user-friendly crotonaldehyde (**104**). List and Michrowska reported an efficient, highly enantioselective and diastereoselective total synthesis of ricciocarpin A (**106**) utilizing this CM partner (Scheme 24).[50] Substrate **105** for the key transformation of the total synthesis – the one-pot, three-step organocatalytic, reductive Michael–Tischenko cascade – was easily obtained from **103** by a CM reaction. The CM reaction promoted by 10 mol% of the commercially available Grubbs second-generation catalyst in the presence of crotonaldehyde (**104**) led to the formation of aldehyde **105** with 84% yield. Again, the internal type III double bond of **103** was completely inert during the CM reaction with the α,β-unsaturated aldehyde, allowing for excellent chemoselectivity. With the more active catalyst **Gre-II** only 2 mol% loading was needed to obtain enal **105** in a 90% yield.



71 1 equivalent **72** **73** **74**

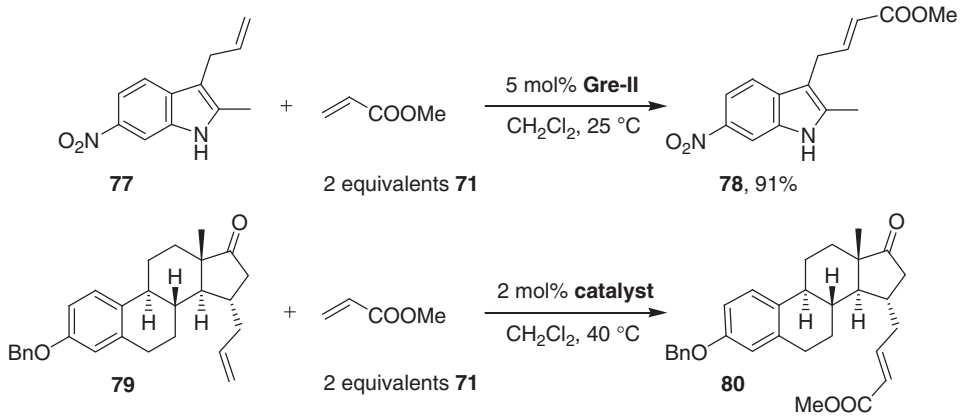
Catalyst	Yield of **73** (%)	
Gru-I	10	80% of **74** was formed
Gru-II	98	
Gru-II'	80	
Hov-II	80	
Gru-III	38	



75 1 equivalent **72** **76**, *E*:*Z* = >95:5

Catalyst	*t* (min)	Yield (%)
2.5 mol% **Ble-II**	20	91
1 mol% **Gre-II**	30	95

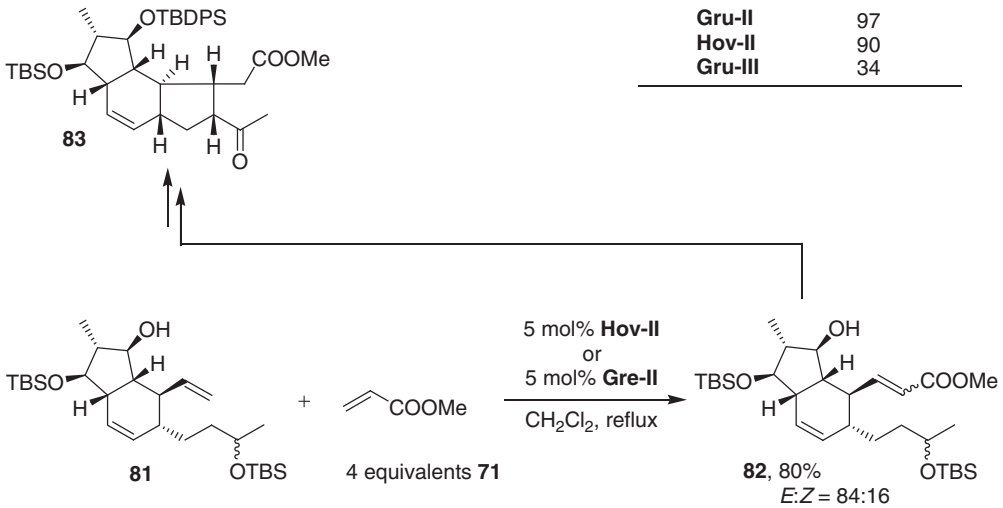
Scheme 19 CM with methyl acrylate.



77 2 equivalents **71** **78**, 91%

79 2 equivalents **71** **80**

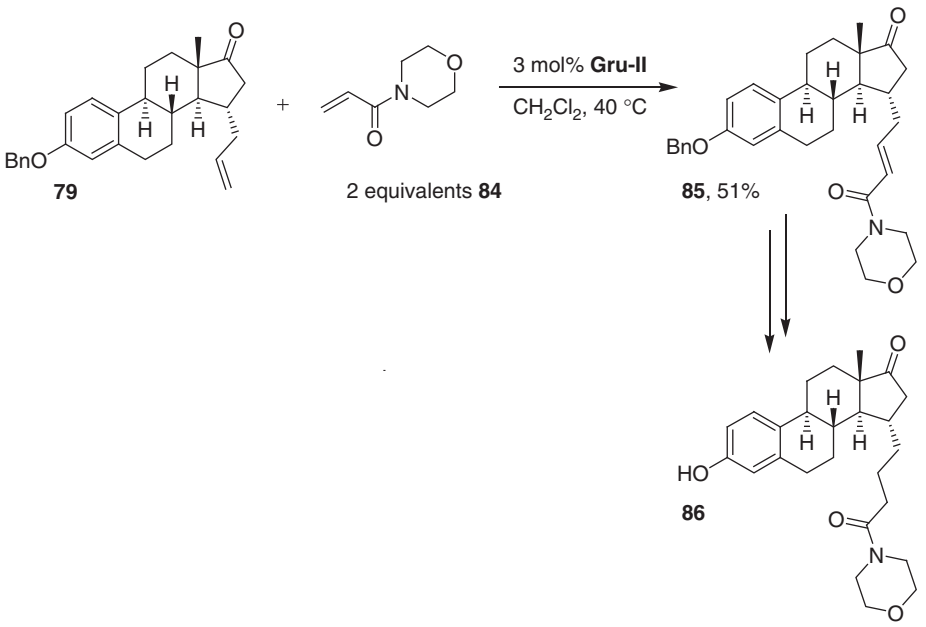
Catalyst	Yield (%)
Gru-II	97
Hov-II	90
Gru-III	34



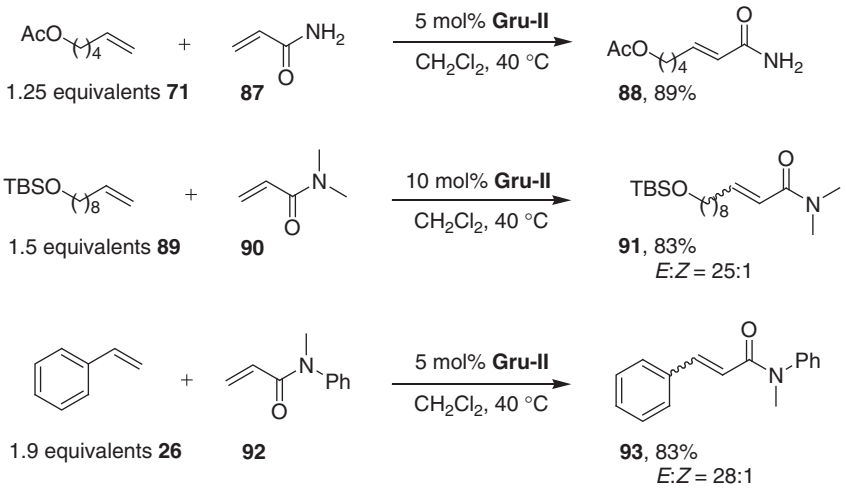
83

81 4 equivalents **71** **82**, 80%
E:*Z* = 84:16

Scheme 20 CM with methyl acrylate in the synthesis of various building blocks. Bn, benzyl; TBDPS, *tert*-butyldiphenylsilyl.



Scheme 21 CM of an estrone derivative.

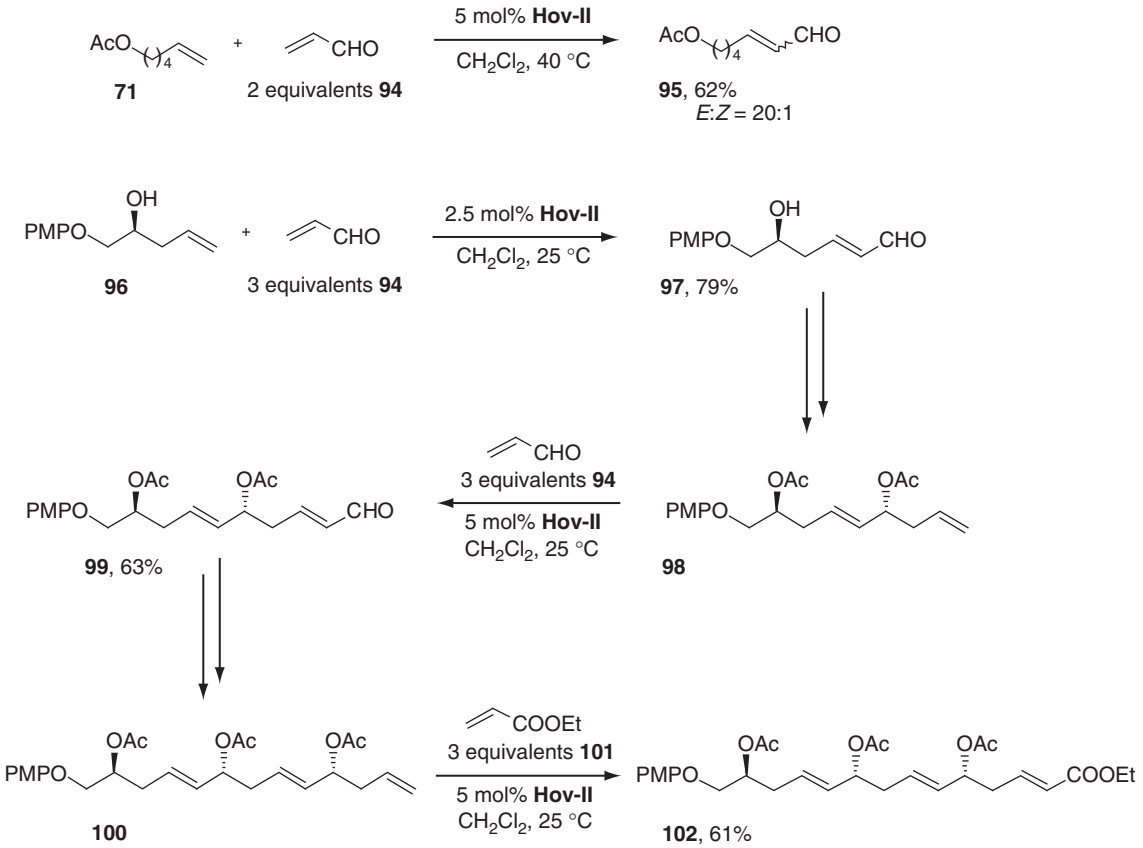


Scheme 22 CM with unsaturated amides.

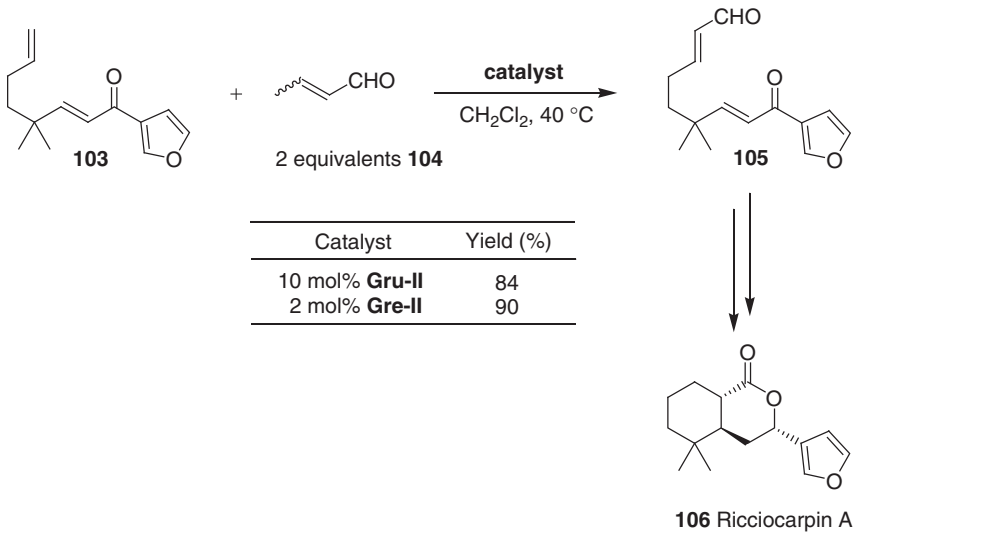
In addition to α,β-unsaturated esters, amides, and aldehydes, α,β-unsaturated ketones are also valuable and relatively easily reacting type II partners in CM transformations. The use of active second-generation Ru catalysts provides good yields in CM reactions between methyl vinyl ketone and type I olefins (Scheme 25).[42,44,48]

The CM with α,β-unsaturated ketones has been used in numerous target-oriented syntheses. Randl and Blechert reported an efficient enantioselective synthesis of (+)-carpamic acid **114**, with the key strategy based on a CM reaction between an α,β-unsaturated ketone and a terminal alkene.[51] Interestingly, it was found that the CM of ketone **112** and alkene **110** afforded the desired product **113** in rather unsatisfactory yields ($<60\%$) due to competing homodimerization of **110** as the major side reaction. When using the protected precursor **111** as the CM partner the homodimerization was almost completely suppressed. The authors suggest that the decreased tendency toward self-metathesis of **111** is related to the increased steric demand of the bulky trimethylsilyl (TMS) group. After applying this modification and utilizing 5 mol% of **Hov-II** as the catalyst, the CM product **113** could be obtained in good yield. The subsequent removal of the protecting group, cyclization, and saponification afforded (+)-carpamic acid **114** in good overall yields (Scheme 26). Using a similar strategy, xenovenine (**118**), indolizidine 209D (**122**), and other natural products were synthesized by the same group[52] (Scheme 27).

Protected and unprotected secondary allylic alcohols are another class of type II olefins, which give products in good yields and stereoselectivities in CM reactions with type I olefins. It should be noted that, depending on the substitution pattern at the allylic



Scheme 23 CM with acrolein in synthetic applications. Et, ethyl; PMP, *p*-methoxyphenyl.

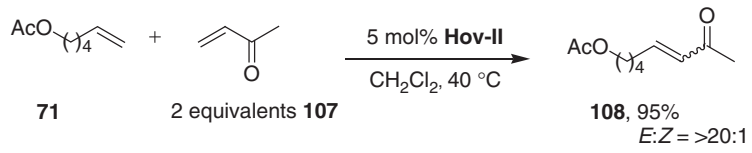


Catalyst	Yield (%)
10 mol% **Gru-II**	84
2 mol% **Gre-II**	90

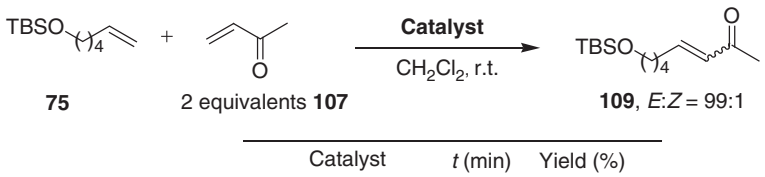
Scheme 24 CM with crotonaldehyde in the total synthesis of riccocarpin A.

position or bulkiness of the protecting group installed at allylic alcohol, these substrates can be sometimes classified as type III olefins (see the next section). Grubbs studied the CM of a number of protected and unprotected allylic alcohols (Scheme 28).[19] It was found that substrates of type II like **123** and **125** react with a number of type I olefins usually in good yields; however, excess of one of the CM partners is required.

An interesting example of a successful CM of the advanced polyfunctional substrate **127** bearing a β-substituted alkene fragment (type II olefin) with the internal olefin **128** (type I partner) was published by Barrett et al. *en route* to the biologically



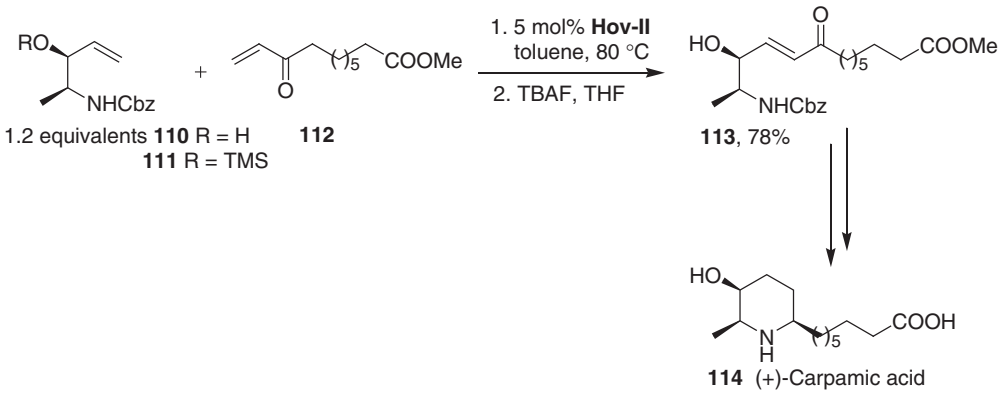
71 2 equivalents **107** **108**, 95%
E:*Z* = >20:1



75 2 equivalents **107** **109**, *E*:*Z* = 99:1

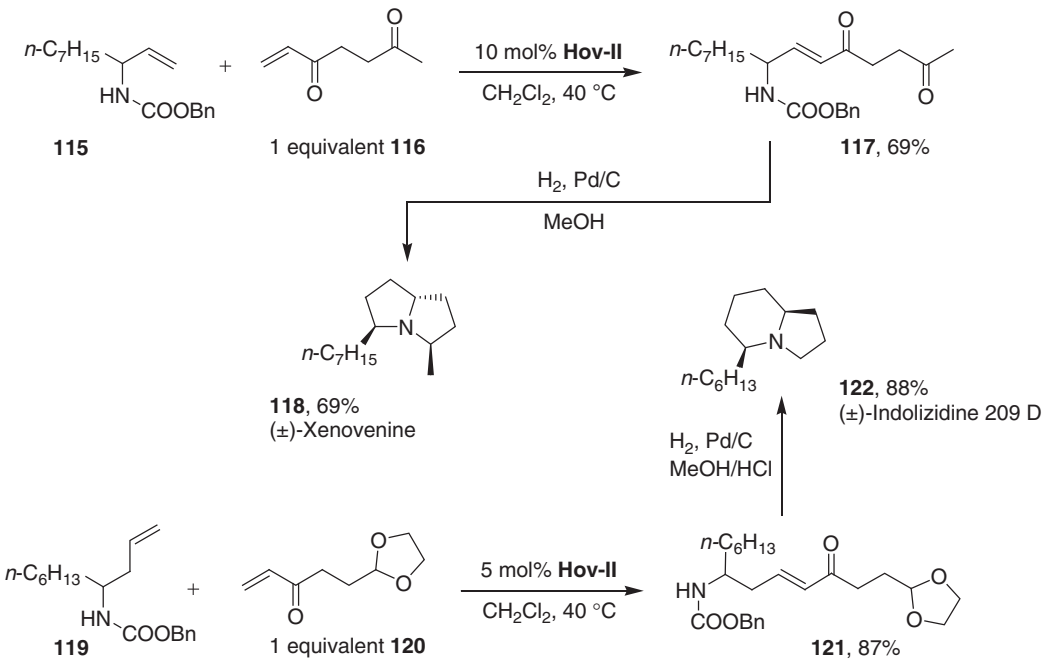
Catalyst	*t* (min)	Yield (%)
2.5 mol% **Gre-II**	30	82
1 mol% **Ble-II**	40	90

Scheme 25 CM between methyl vinyl ketone and type I olefins.



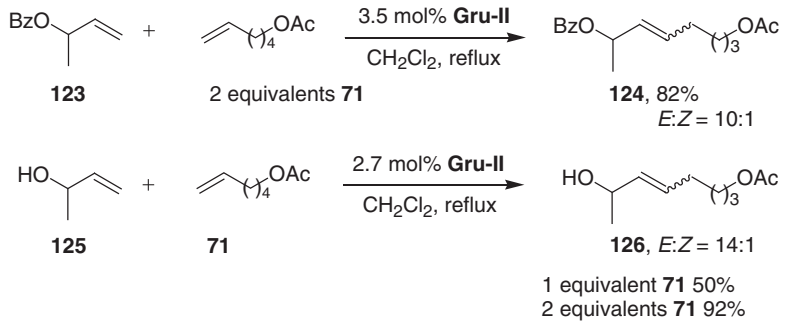
1.2 equivalents **110** R = H
111 R = TMS
112
113, 78%
114 (+)-Carpamic acid

Scheme 26 CM in the synthesis of carpamic acid. Cbz, benzyloxycarbonyl; TBAF, tetrabutylammonium fluoride.



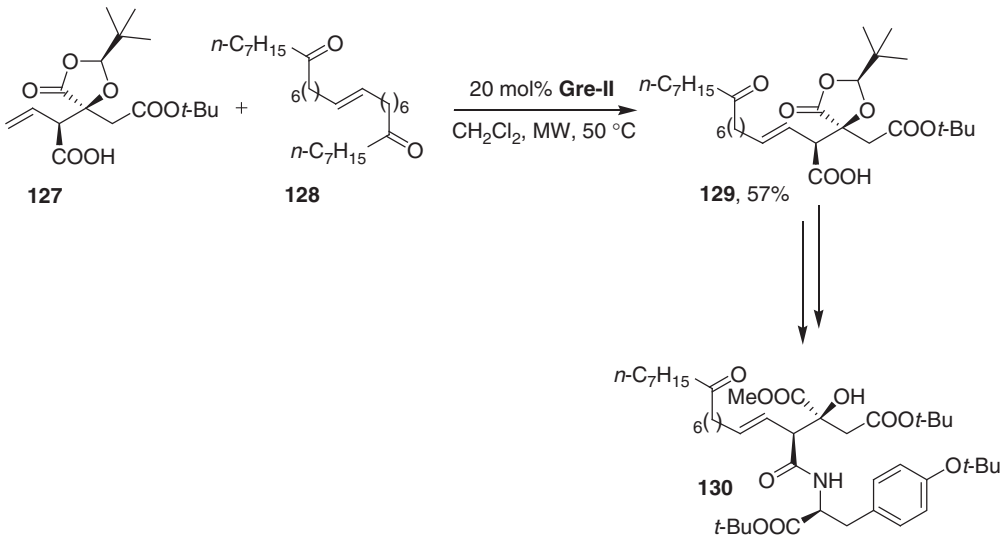
115 1 equivalent **116** **117**, 69%
118, 69%
(±)-Xenovenine
122, 88%
(±)-Indolizidine 209 D
119 1 equivalent **120** **121**, 87%

Scheme 27 CM with vinyl ketones utilized in total syntheses.



Scheme 28 CM involving allylic alcohols.

active viridiofungin derivatives (Scheme 29).[53] After selecting the best catalyst and a careful optimization of the reaction conditions, it was possible to obtain the expected CM product **129** in excellent yields (>95%) as determined by ^{1}H nuclear magnetic resonance (NMR). Unfortunately, extensive chromatography, which was required to remove ruthenium residues from the polar acid **129**, limited the isolated yield to only 57%.[53]



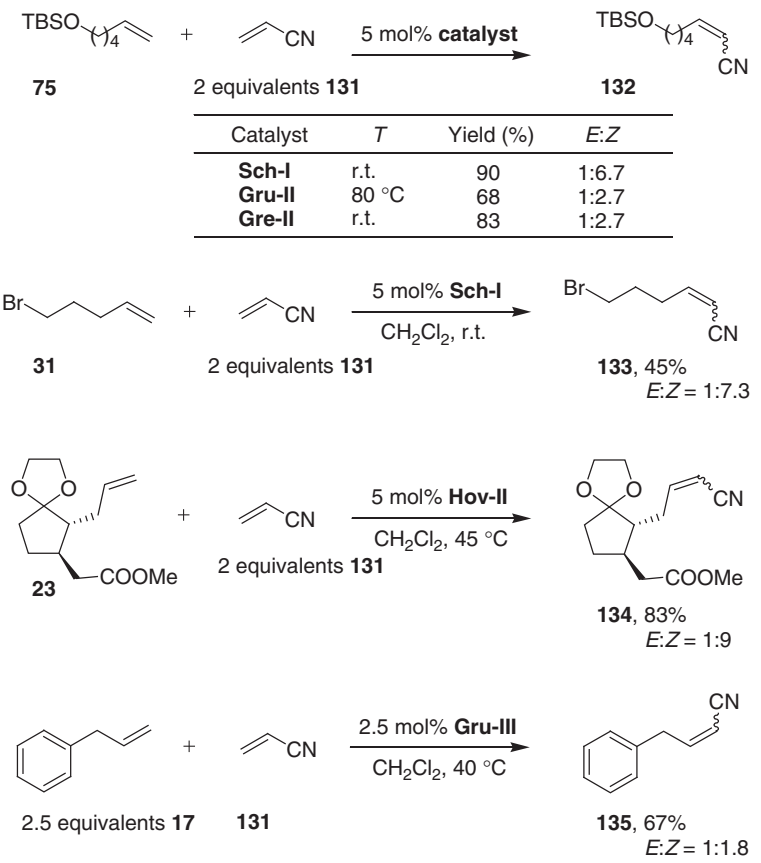
Scheme 29 CM leading to viridiofungin derivative 130. *t*Bu, *tert*-butyl.

Numerous reported results show that α,β-unsaturated compounds are valuable partners in CM reactions. Usually, the best results can be obtained when more active catalysts, like **Sch-I**, **Gru-II**, and especially phosphine-free catalysts (**Hov-II**, **Gre-II**), are used.[54]

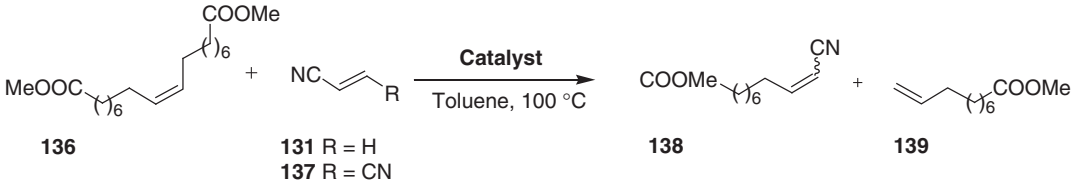
5.26.2.1.3 CM involving partners of type III

Acrylonitrile (**131**) is usually regarded as a rather challenging CM partner, and as a type III olefin according to Grubbs' classification.[19] The CM reactions involving **131** have been successful with Schrock's arylimido molybdenum alkylidene catalyst **Sch-I**,[55] whereas within the Ru-family the best results were obtained with the ether-tethered derivative **Hov-II** (reaction with **23**)[56] and its activated nitro analog **Gre-II** (Scheme 30).[44] There are also literature reports that microwave irradiation combined with the Hoveyda-Grubbs catalyst **Hov-II** allows for an even more effective CM of acrylonitrile.[57] Phosphine-containing ruthenium catalysts, such as **Gru-II**, usually give slightly lower yields; however, addition of copper chloride as a phosphine scavenger is known to highly improve the results.[58] It was shown by Grubbs that the pyridine-containing catalyst **Gru-III** is a very effective catalyst in the CM of terminal olefins and acrylonitrile.[59] Actually, this catalyst was claimed to be the fastest initiator amongst the ruthenium-based catalysts studied. Independently, He et al. provided more examples showing the superiority of the third-generation Ru-catalysts in the CM reaction of acrylonitrile.[60]

The CM of fatty acids and esters, as renewable raw materials, with acrylonitrile **131** was presented by Bruneau and Dixneuf (Scheme 31).[61] Subsequent hydrogenation of the C=C and CN bonds in the metathesis products allows for the generation of linear amino acid monomers that are useful for the production of polyamides. Importantly, the authors were able to utilize fumaronitrile **137** instead of acrylonitrile (the latter is classified as type III olefin,[19] so its 'dimer' is inert in the metathesis process)



Scheme 30 CM of acrylonitrile.



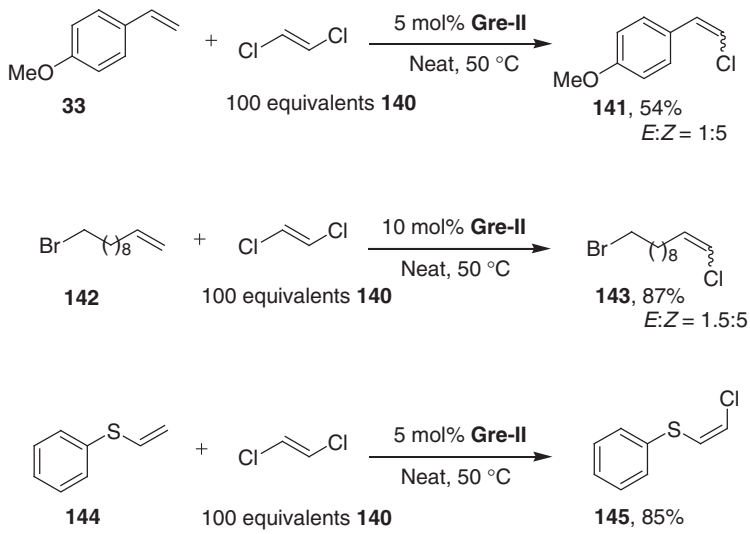
Substrates	Catalyst	Conversion (%)
4 equivalents **131**	5 mol% **Gru-II**	75
4 equivalents **131**	5 mol% **Hov-II**	99
4 equivalents **131**	5 mol% **Ind-II**	61
2 equivalents **137**	1 mol% **Gru-II**	11
2 equivalents **137**	1 mol% **Hov-II**	50
2 equivalents **137**	1 mol% **Ind-II**	18

Scheme 31 Synthesis of nitrile-ester derivatives from renewable oils.

as a source of unsaturated nitrile entity in CM. Reaction of the internal olefin **136** and both nitrile sources led to an interesting result. In the examined cases, **Hov-II** catalyst gave the best results whereas the phosphine-containing catalysts **Gru-II** and **Ind-II** were less effective in this reaction. When utilizing **131** as the cross partner, the reaction led to a mixture of the expected product **138** and large amounts of monoester **139**. Application of fumaronitrile provided the main product with 50% conversion with a loading of only 1 mol% of the ruthenium complex **Hov-II**. When 5 mol% of the same catalyst was used, the conversion was estimated to be 97% leading to the isolation of **138** in 92% yield. The result shows that fumaronitrile, if treated with Hoveyda second-generation catalyst, is a valuable CM partner.[61]

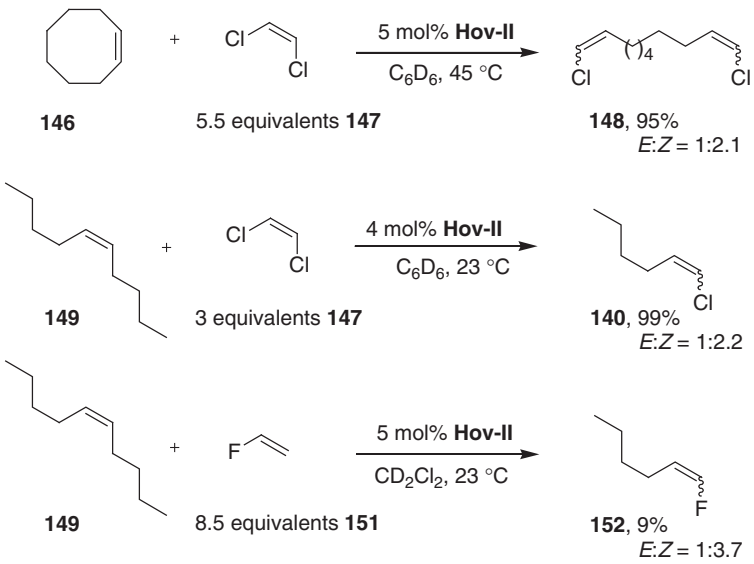
Alkenyl halides are key building blocks in numerous transition-metal-catalyzed syntheses, particularly in various Pd-catalyzed coupling reactions.[62] Unfortunately, it was reported that phosphine-containing Ru catalysts such as **Gru-II** fail to mediate CM of

vinyl halides.[63] On the contrary, CM of various type I alkenes with *E*-1,2-dichloroethylene **140** promoted by phosphine-free catalysts like **Gre-II** and **Est-II** led to the formation of the expected chloroalkenes in acceptable yields (Scheme 32).[64]



Scheme 32 CM with alkenyl halides.

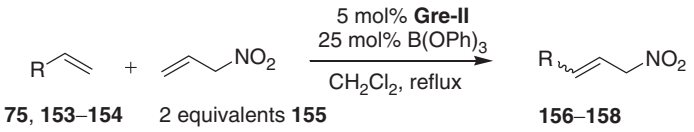
In the same work, Grela et al. studied the reaction of **142** and *E,Z*-1,2-dibromoethylene. The dibromide product, analogous to **143** can be formed, albeit in a much lower yield (34%). Application of *Z*-1,2-dichloroethylene **147** as a CM partner was also examined, but resulted in a decreased yield and selectivity of the product. At the same time, Johnson et al. reported a number of impressive examples of CM reactions promoted by **Hov-II** as the catalyst, such as ROM-CM of cyclooctene **146** and the CM of the internal olefin **149** (Scheme 33).[65] Unfortunately, the reaction with vinyl fluoride **151** was unsuccessful.

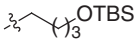
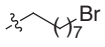
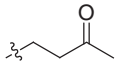


Scheme 33 CM with vinyl halides.

α,β-Unsaturated nitroalkenes are known to be reluctant in CM reactions (type IV olefins).[19] However, nonconjugated nitroolefins, such as 4-nitro-1-butene, 5-nitro-1-pentene and 6-nitro-1-hexene, are typical type I olefins that can be successfully used as partners in CM with olefins.[66] Interestingly, 3-nitropropene **155**, unlike the above-mentioned nitro-containing type I substrates, does not undergo self-metathesis, suggesting that β,γ-unsaturated nitro compounds should be classified as type III substrates in metathesis. CM of terminal alkenes with 3-nitropropene promoted by **Gre-II** in the presence of triphenyl borate leads to the formation of functionalized β,γ-nitroolefins in good yields (Scheme 34).[67] Substituted β,γ-nitroolefins are versatile

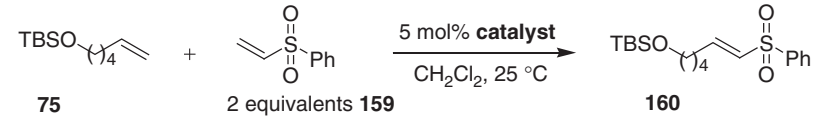
building blocks in organic synthesis, but unfortunately, they are relatively difficult to prepare via the conventional synthetic methods.[68] Therefore, catalytic CM seems to be a convenient alternative.[67]



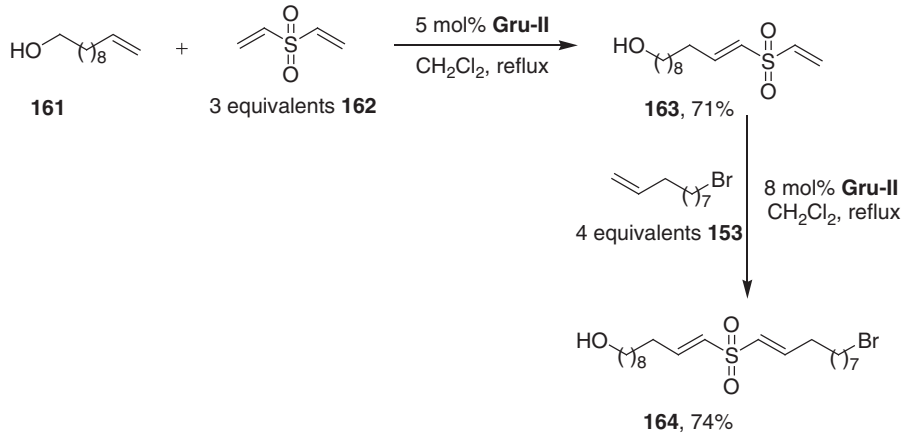
Substrate	Product	R	Yield (%)	*E*:*Z*
75	**156**		70	7.6:1
153	**157**		80	7.5:1
154	**158**		71	16:1

Scheme 34 CM of 3-nitropropene.

Another group of functional compounds useful as building blocks are α,β-unsaturated sulfones. These compounds can be transformed into versatile synthetic intermediates when utilized, for example, as Michael acceptors or as partners in cycloaddition reactions.[69] The ease of further transformations via elimination or either reductive or alkylative desulfonylation renders further advantages. Additionally, vinyl sulfones have recently been shown to potently inhibit a variety of enzymatic processes, providing unique opportunities for drug design and medicinal chemistry (a vinyl sulfone warhead).[70] Compatibility of remote sulfone function (type I olefins) with ruthenium and molybdenum-based metathesis catalysts is well established, thus CM is a well-suited method for their synthesis.[71,72] Although CM of β,γ-unsaturated sulfones (such as allyl phenyl sulfone) has been reported by Grubbs,[73] α,β-unsaturated sulfones (type III olefins) were considered challenging substrates in CM, even for the second-generation Ru catalysts.[74] Grela et al. have described CM of phenyl vinyl sulfone **159** as a simple *E*-selective method for the preparation of substituted unsaturated sulfones (**Scheme 35**). This reaction was catalyzed by the second-generation Grubbs' carbene **Gru-II**, leading to functionalized sulfones in good yields. Later, it was found that application of phosphine-free catalysts such as **Hov-II** and **Gre-II** can sometimes give slightly better yields.[75] Interestingly, in the case of divinyl sulfone **162**, it is possible to selectively



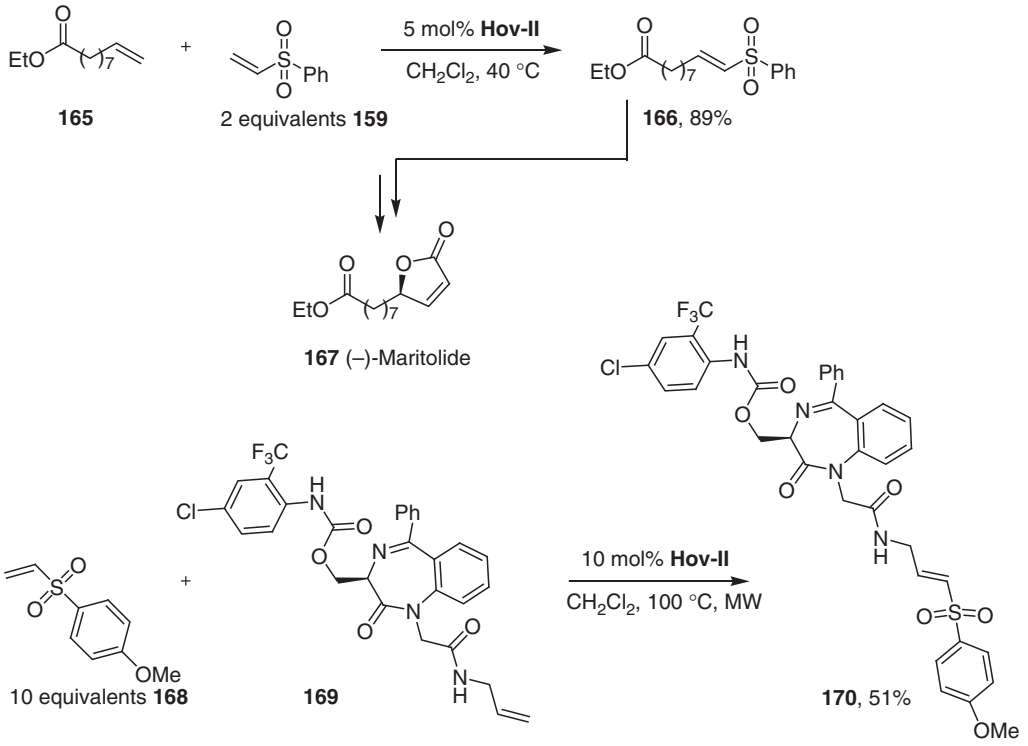
Catalyst	Yield (%)
Gru-II	68
Gre-II	86



Scheme 35 CM with vinyl sulfone partners.

functionalize only one of the two vinyl groups present in this substrate.[76] Next, by repeating the CM event, the second vinyl group can be functionalized by CM, leading to asymmetrically substituted products, such as **164**, with no or only very little scrambling. This result revealed that the CM technology gives easy access to synthetically useful desymmetrized mono- or disubstituted divinyl sulfones with excellent *E*-selectivity under mild conditions.

Given the synthetic potential of sulfones as both Michael acceptors and substrates for cycloaddition reactions, these findings are of interest in organic synthesis, including the total synthesis of natural and biologically active compounds. For example, CM of alkene **165** with **159** led to the functionalized α,β-unsaturated sulfone **166**, which was then easily converted into the furanone natural product (–)-maritolide (Scheme 36).[77] Additional biological activity of vinyl sulfones is connected with covalent inhibition of falcipain-2 (FP-2), a cysteine protease isolated from *Plasmodium falciparum* – the most dangerous parasite species causing malaria. The parasitic cycle can be effectively stopped by irreversible addition of the thiol group of the active site Cys-25 to the electrophilic vinyl sulfone moiety, which behaves as a Michael acceptor. The CM-based synthesis of a new class of peptidomimetic cysteine protease inhibitors based on a 1,4-benzodiazepine scaffold decorated with a vinyl sulfone moiety was described by Ettari et al.[78] Studies on biological activity of compound **170** proved it to be a potent and selective inhibitor of FP-2, displaying antiplasmodial activity.[78] CM reactions involving α,β-unsaturated sulfones were also used for the preparation of quercus lactone,[77] swansonine,[79] myrioxazine A,[80] and other natural products.

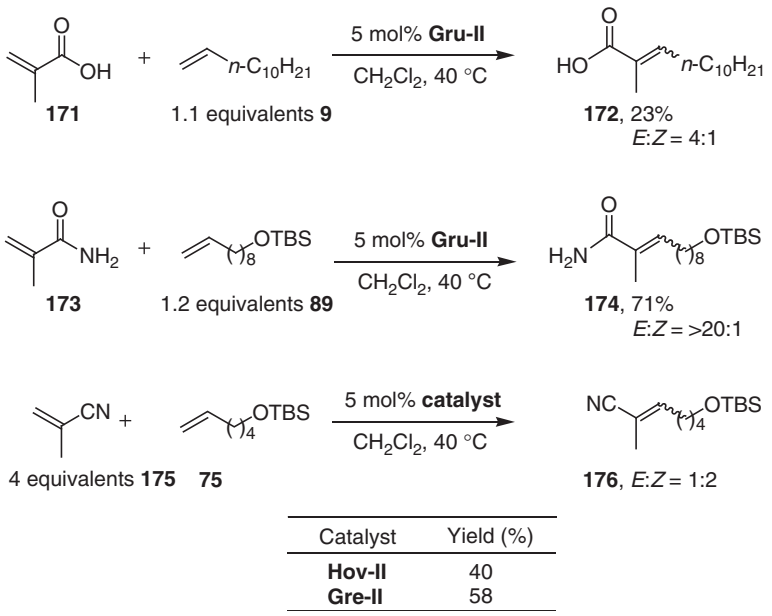


Scheme 36 Vinyl sulfones in CM-based syntheses of biologically active compounds.

Although acrylic acid and its esters can be categorized as relatively reactive type II olefins, metacrylic acid and its esters are much less reactive, thus being type III olefins.[19] CM of type I partners with α-substituted α,β-unsaturated compounds and requires a careful selection of the catalyst to secure a satisfactory yield of the CM products (Scheme 37).[44] However, under optimized conditions this reaction can be very useful.

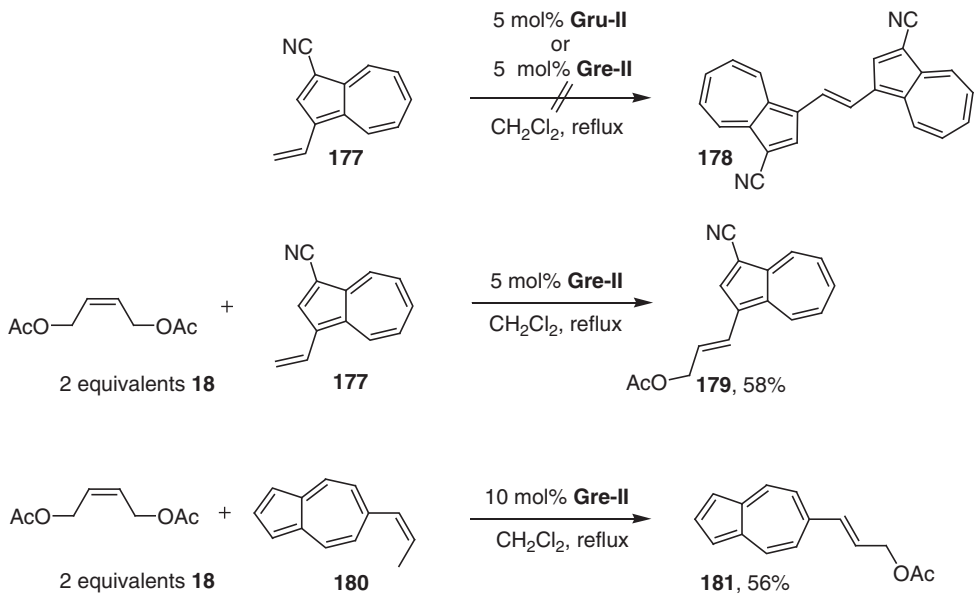
In contrast to non-*ortho*-substituted styrenes, which are type I olefins, vinyl azulenes do not undergo any homo metathesis reaction (Scheme 38).[81] Selected alkenyl-substituted azulenes were subjected to CM reactions with type I olefins to obtain valuable azulene-containing building blocks such as **179** and **181** under very mild conditions.

Grubbs noted that quaternary allylic olefins undergo CM reactions promoted by highly active **Gru-II** with excellent stereoselectivity, leading to the formation of *E*-configured products in good yields (Scheme 39).[19] According to Grubbs, these reactions are the first example of exclusive olefin *E*-selectivity in CM, based solely on the sterics of the alkyl substituents. For example, the unprotected (**182**) and protected tertiary alcohol (**186**) provide excellent yields of the CM products with only the *E*-isomer being observed by ^{1}H NMR. The steric bulk of the tertiary allylic substrates hinders their homo CM in most cases; therefore, these substrates can be classified as type III olefins. Moreover, in the case of **184** no dimerization was observed, allowing for a greater CM product selectivity. It should be noted that these substrates are usually inert in the presence of the first-generation catalysts such as **Gru-I**.[22]



Catalyst	Yield (%)
Hov-II	40
Gre-II	58

Scheme 37 CM with α-substituted α,β-unsaturated compounds.

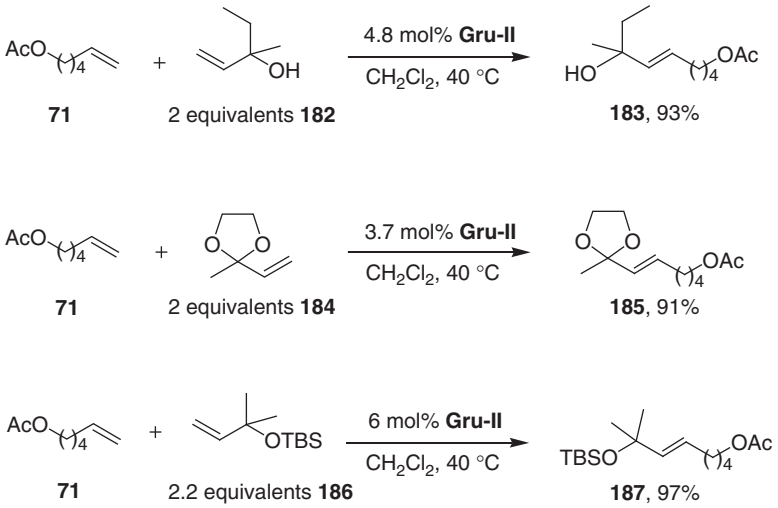


Scheme 38 CM of vinyl azulenes.

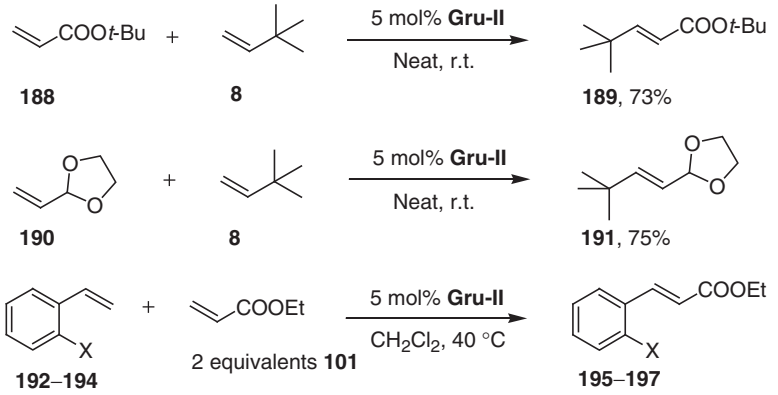
CM reactions involving type III olefins are extremely useful in organic synthesis as they provide highly functionalized building blocks for the preparation of complex molecules. The possibility of attaching highly substituted fragments at a C–C double bond in a stereodefined manner and perspectives of further modification make these reactions a valuable tool for organic synthesis.

5.26.2.1.4 CM reactions involving type II and type III olefins

Selective CM of type II with type III olefins, despite being challenging, are generally very selective, as both partners hardly homodimerize. This leads to the formation of CM products in high yields. However, given the low reactivity of some type III olefins, reduced yields may be obtained, especially when nonoptimal catalysts and conditions are used. Sometimes, excess of the less reactive olefin should be used to achieve good conversions. Usually, the excess of the CM partner can be easily separated from the expected product. For example, neat 3,3-dimethyl-1-butene **8** was successfully used by Grubbs in the CM with various type II olefins (Scheme 40).[19] In the same work, Grubbs et al. investigated the CM of *o*-substituted styrenes with a variety of nontype I olefins such as acrylates. Smaller *ortho*-substituents did not reduce the reactivity of a styrene (for example **192**) with acrylates;



Scheme 39 CM of quaternary allylic olefins.



Substrate	Product	X	Yield (%)
192	**195**	F	72
193	**196**	Cl	62
194	**197**	Br	49

Scheme 40 CM between type II and type III olefins.

however, when electron-withdrawing functionalities[19] or bulky ones (**193** and **194**) were present at the *ortho*-position, the CM yields fell dramatically due to the low reactivity of both the partners even with a reactive catalyst such as **Gru-II**.

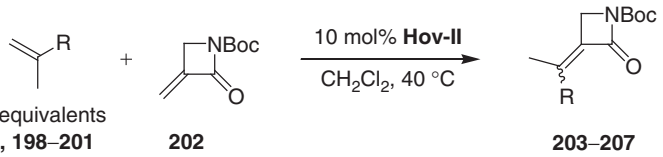
Howell et al. reported the CM of terminal alkenes with the β-lactam **202** to obtain the tetrasubstituted unsaturated β-lactams **203–207** in a surprisingly high yield (Scheme 41).[82] A range of types I–III olefins were utilized as partners in CM catalyzed by **Hov-II**, resulting in numerous α-alkylidene-β-lactams. However, the methodology seems to have a disadvantage: substrates with any α-branching completely prevented the reaction. Nevertheless, these results are the first example of the formation of tetrasubstituted alkenes by a CM reaction.

CM of type II with type III olefins is not as well developed as the variants described before. This is mainly due to the additional difficulties such as a diminished reactivity of the substrates. Taking into consideration the constant introduction of catalysts of enhanced activity and selectivity, further development in the field is predicted.

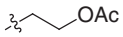
5.26.2.2 Recent Achievements in *Z*-Selectivity Control

One of a few unsolved problems in CM is the lack of stereocontrol of the formed product. Although some fully *Z*- or *E*-selective CM reactions have been reported, mixtures of *E*- and *Z*-isomers have been obtained in less lucky cases. Many bulky olefins or

α,β-unsaturated substrates give predominantly *E*-configured products in CM, but selective access to the corresponding *Z*-olefins is limited in most cases. This constitutes a significant drawback in target-oriented synthesis, preparation of specialty polymers, as well as in other fields where metathesis can be used. For this and other reasons, increasing attention is being focused on the development of *Z*-selective catalysts for olefin metathesis.

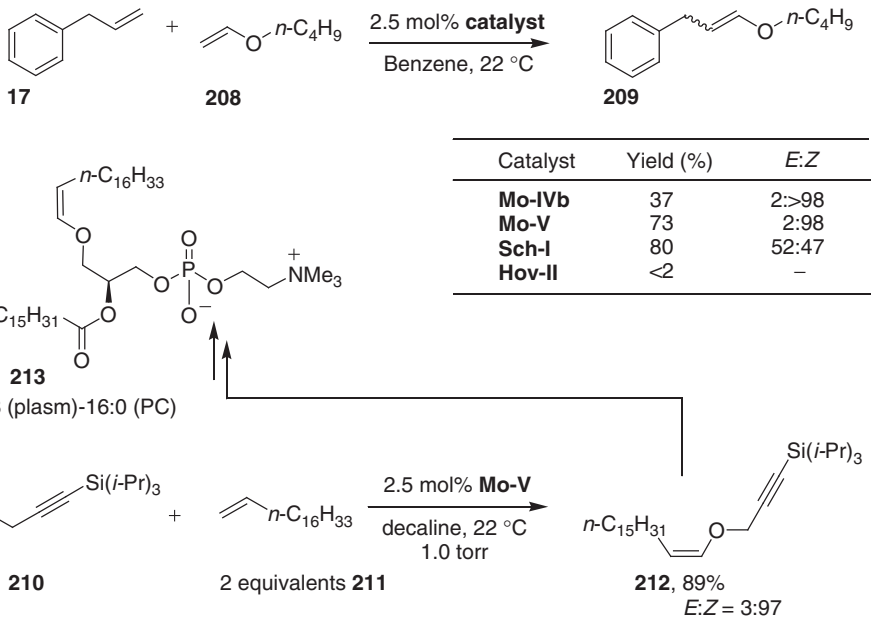


4 equivalents
7, 198–201 **202** **203–207**

Substrate	Product	R	Yield (%)	*E*:*Z*
7	**203**		85	1:1
198	**204**		64	1:1.5
199	**205**		58	1:1.6
200	**206**		81	1:1.5
201	**207**		–	–

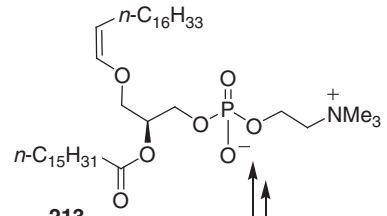
Scheme 41 CM reactions of lactams.

During a study directed toward the development of efficient *Z*-selective CM reactions, Schrock and Hoveyda utilized the stereogenic-at-Mo alkylidenes **Mo-IV** (see Scheme 3) that were recently developed to promote enantioselective RCM.[16e] These complexes were found to promote CM of enol ethers, a class of substrates for which a CM reaction has not been previously reported (Scheme 42). Although the Ru-complex **Hov-II** was ineffective in this transformation, the Mo-based complex **Sch-I** gave very good conversion in a model CM reaction, but with no *Z*-selectivity. Finally, it was found that stereogenic-at-Mo complexes, such as **Mo-IVb** and **Mo-IVd**, promote this reaction in a fully stereoselective way, leading to the disubstituted enol ether **209** in 98% *Z*-selectivity and up to 73% yield. The same authors demonstrated the utility of the catalytic *Z*-selective CM by using it as a key step in a diastereoselective synthesis of an antioxidant plasmalogen phospholipid, C18 (plasm)-16:0 (PC) **213**. As enol ether



17 **208** **209**

Catalyst	Yield (%)	*E*:*Z*
Mo-IVb	37	2:>98
Mo-V	73	2:98
Sch-I	80	52:47
Hov-II	<2	–



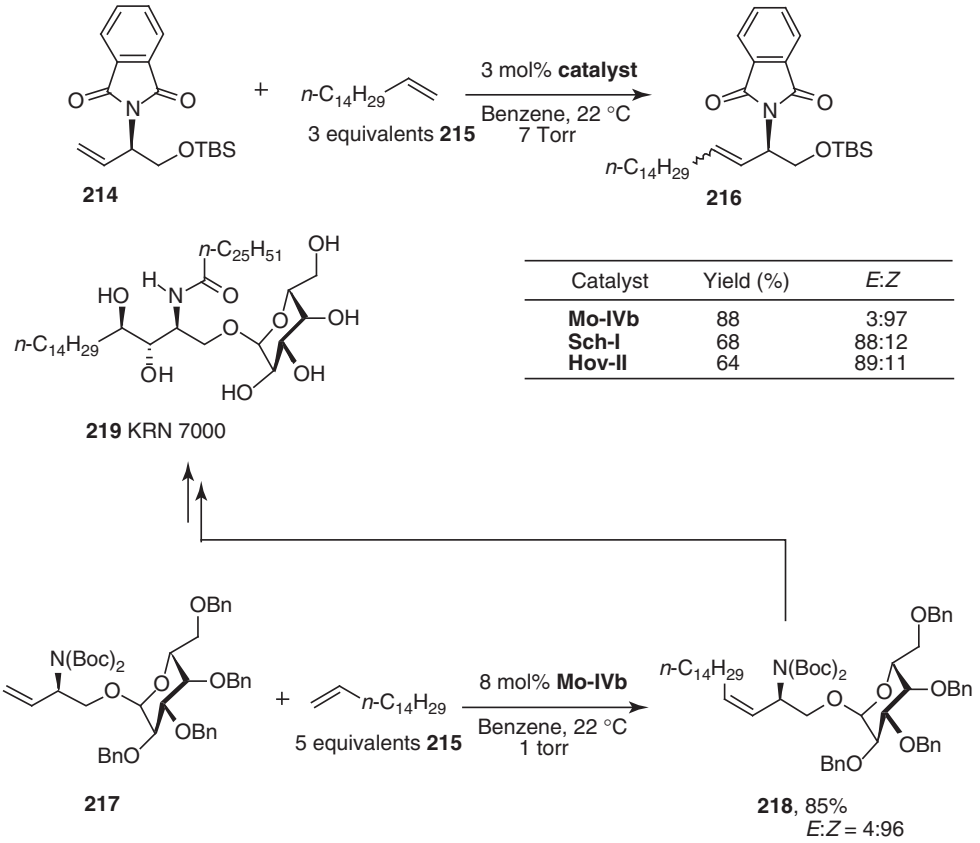
213
C18 (plasm)-16:0 (PC)

210 2 equivalents **211** **212**, 89%
E:*Z* = 3:97

Scheme 42 *Z*-Selective CM of enol ethers with Mo-catalysts.

210 is more difficult to obtain and thus more valuable than the commercially available cheap 1-octadecene **211**, the researchers opted to use an excess of the latter to assure good conversion and chemoselectivity of the process. Unfortunately, increasing the amount of **211** was found to have a diminishing effect on the observed *Z*-selectivity. This was related to the increased ethylene generation from a competing S-CM of **211**. According to the authors, ethylene causes diminished stereoselectivity by increasing the concentration of the Mo-methylidene, which promotes isomerization. To attenuate the negative effect of ethylene, the CM was performed under vacuum. Under such conditions, an efficient CM reaction was made possible with only a relatively slight excess of the aliphatic alkene. It led to the disubstituted enol ether **212**, obtained with 97% selectivity, which was in turn converted to C18 (plasm)-16:0 (PC) **213** in a small number of steps.

Another class of CM reactions that can be conducted selectively with Mo alkylidenes is the transformation involving allylic amides as substrates.[16e] As a large number of biologically active molecules can be obtained from disubstituted alkenes bearing nitrogen at the allylic position, the synthesis of functionalized allylic amines is of great importance. As some allylic amides, such as **214**, can undergo S-CM (type II substrates), it can be difficult to control the chemoselectivity of the reaction (Scheme 43).[2] Preliminary investigations with enantiomerically pure allylic amide **214** and 1-hexadecene **215** indicated that the optimal catalyst is complex **Mo-IVb**, affording the desired *Z*-alkene in 88% yield and with 97% stereoselectivity. As stated before, mild vacuum should be used to assure good *Z*-selectivity of this process. It should be noted that the achiral Mo alkylidene **Sch-I** and the representative Ru-complex **Hov-II** furnish the *E*-isomers predominantly.



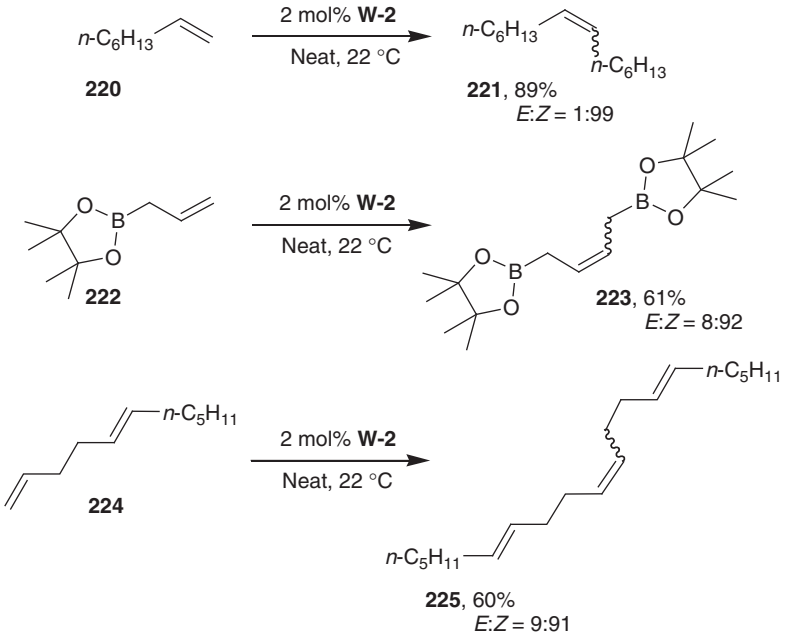
Catalyst	Yield (%)	*E*:*Z*
Mo-IVb	88	3:97
Sch-I	68	88:12
Hov-II	64	89:11

Scheme 43 *Z*-Selective CM involving allylic amides.

The *Z*-selective CM of allylic amides was also utilized in a stereoselective synthesis of the antitumor agent KRN7000 (**219**), thus underlining the utility of the method.[2] The key step – CM of the carbohydrate derivative **217** containing an allylic amide fragment with the terminal alkene **215** – gave a product **218** in 85% yield and with excellent (96%) *Z*-selectivity. Further transformations, such as diastereoselective dihydroxylation, esterification, and carbohydrate deprotection, gave the target molecule **219** in excellent overall yield.

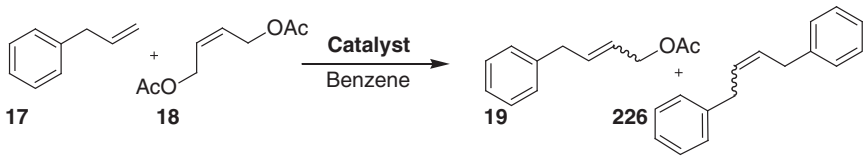
As shown in the previous examples, the MAP complexes are excellent catalysts in *Z*-selective CM. On the basis of the knowledge that tungsten appears to be superior to molybdenum for the *Z*-selective formation of olefins, Hoveyda et al. continued their research in that direction.[18] In fact, the tungsten complex **W2** described in their work allows for homocoupling of olefins with high *Z*-selectivity (Scheme 44). The authors state that the reaction rate and the conversion can be improved by performing the reaction in a neat substrate, whereas elevating the temperature leads to relatively low yields of the product as a consequence of

catalyst decomposition. S-CM of **224** seems to be a particularly interesting example because the resulting triolefin **225** was obtained in 60% yield as *E,Z,E*-isomer with excellent selectivity. It is worth noting that such a formation of a high percentage of a *Z*-homocoupled product in the presence of *E*-olefinic bonds elsewhere in the molecule was observed for the first time.

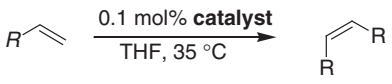


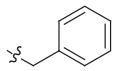
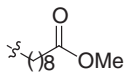
Scheme 44 *Z*-Selective CM with complex W-2.

In contrast to molybdenum- and tungsten-based catalysts, which have shown outstanding *Z*-selectivity in CM and S-CM (homocoupling) of terminal olefins, only a few ruthenium-based catalysts have been reported that show an enhanced *Z*-selectivity.[83] Their selectivity is still not satisfactory for precisely stereocontrolled syntheses. However, the recent development of catalysts bearing bidentate anionic ligands such as **Ru-V** and **Ru-VI** changed this situation. The outcome of the CM of **17** and **18** highly depends on the catalyst (Scheme 45).[84] The *Z*-selectivity is excellent in the reaction promoted by **Ru-V**. The authors



Catalyst	*T* (°C)	*t* (min)	19 Conversion (%)	19 *E*:*Z*	226 Conversion (%)	226 *E*:*Z*
2.5 mol% **Hov-II**	23	1	69.7	10.5	5.9	5.22
5 mol% **Ru-V**	70	30	32.5	0.13	24.8	0.07



Substrate	Product	R	Catalyst	*t* (h)	Yield (%)	*Z* (%)
17	**226**		**Ru-V**	3	73	86
			Ru-VI	3	89	95
227	**228**		**Ru-V**	12	13	90
			Ru-VI	12	75	94

Scheme 45 *Z*-Selective CM with Ru-complexes.

presented a number of similar S-CM reactions of various terminal olefins using as catalyst **Ru-VI** bearing nitrato ligands, which proved to be superior in all cases. Notably, this complex was also able to 'dimerize' some more challenging substrates, such as unprotected alcohols, with excellent conversion and good *Z*-selectivity.

The scientific community witnessed an enormous development of CM over recent years. A variety of substrates considered impossible to metathesize were successfully utilized in CM reactions due to the introduction of new catalysts and conditions. Development of Ru, Mo, and W catalysts enabling selective CM transformations is expected to account for the progress in academic syntheses, where the stereoselective construction of *Z*-olefins is required. There is a great chance that this powerful methodology will be adapted by the chemical industry.

5.26.3 Tandem Metathesis

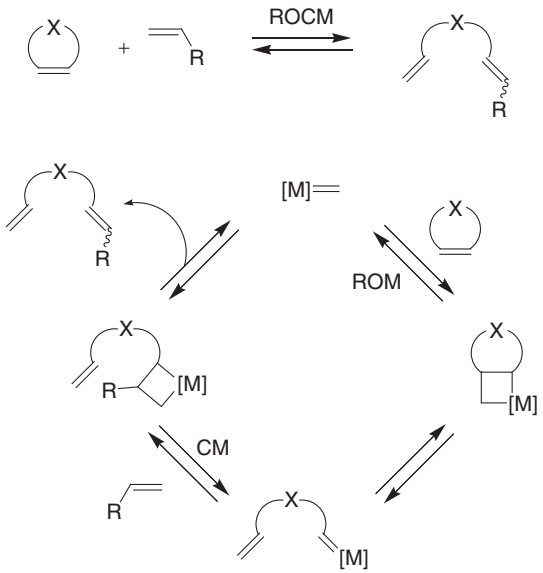
The utility of metathesis reactions is not limited to a single CM step. A double-bond generated in one reaction can serve as a substrate in another transformation, which also may be metathetic. Often such sequences are conducted in a one-pot manner and are called 'tandem metathesis.'

5.26.3.1 Two-Step Domino Metathesis

The simplest metathetic sequences are those consisting of two steps. Examples include ROCM, CM-RCM, or ring-opening/ring-closing sequences (ROM-RCM). In this chapter we will discuss only those that include at least one intermolecular step.

5.26.3.1.1 ROCM

ROCM is a tandem process involving an interchange between an endocyclic olefin and a double bond of an acyclic substrate. The mechanism of this transformation (Scheme 46) is very similar to that of CM discussed previously in Section 5.26.1.2. In the first step, the metal carbene reacts with the cyclic olefin to generate a metallacyclobutane, which after reversion reacts with the acyclic olefin. A second metallacyclobutane is formed and cleaved, resulting in a desired product and regeneration of the starting carbene.



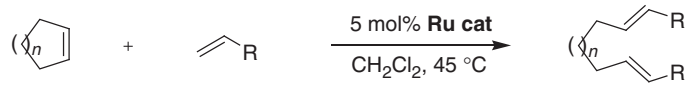
Scheme 46 Mechanism of ROCM.

Contrary to most other types of metathesis, the ROM-CM sequence is in the majority of cases driven by the release of the ring strain energy (release of a volatile alkene is also an option, but usually it is enthalpically disfavored). Considering these mechanistic issues, it seems fairly obvious that the strained cyclic alkenes are the most common substrates. Table 3 summarizes the thermodynamic data for alkenes often utilized as ROCM substrates.[85]

For the ROCM sequence to be efficient, it has to proceed faster than the competing ROMP pathway. The crucial factors are the nature of cyclic olefins and high dilution conditions. In most cases, ROMP can be outperformed. Yet another risk is the possibility that the cross partner undergoes homodimerization. The mentioned problems can be solved by a careful substrate selection, which is absolutely crucial in tandem processes. Although most applications of ROCM include a strained substrate, successful attempts to metathesize unstained carbocycles were also published (Scheme 47).[86]

Table 3 Strain energies of cyclic olefins

Olefin	*Strain energy ΔH_f° (kcal mol^{-1})*
Cyclopropene	53.7
Cyclobutene	29.8
Cyclopentene	5.9
Cyclohexene	1.4
Cyclooctene	6.0
Norbornene	27.2



229 $n = 1$
230 $n = 2$
231 $n = 3$

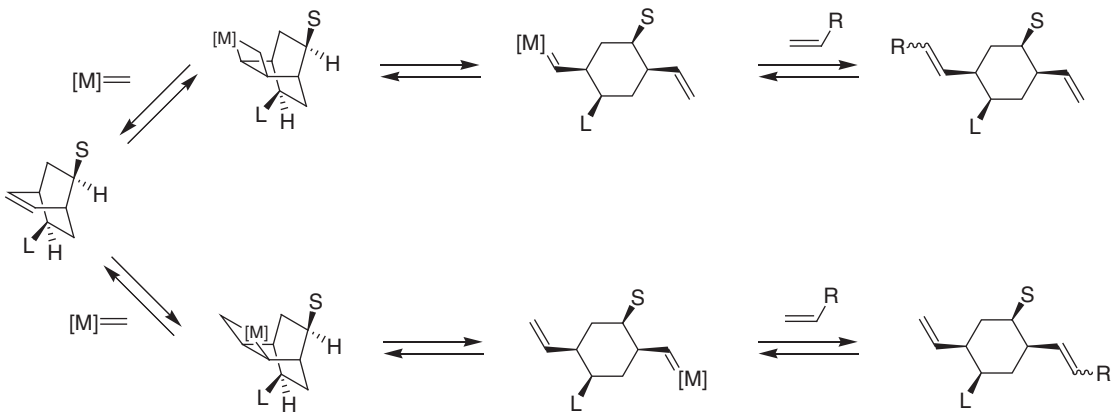
72 R = CHO
62 R = COOMe

232–237

Product	*n*	R	Yield (%) Gru-II	Yield (%) Hov-II
232	1	CHO	30	83
233	1	COOMe	79	90
234	2	CHO	5	45
235	2	COOMe	47	66
236	3	CHO	75	90
237	3	COOMe	80	97

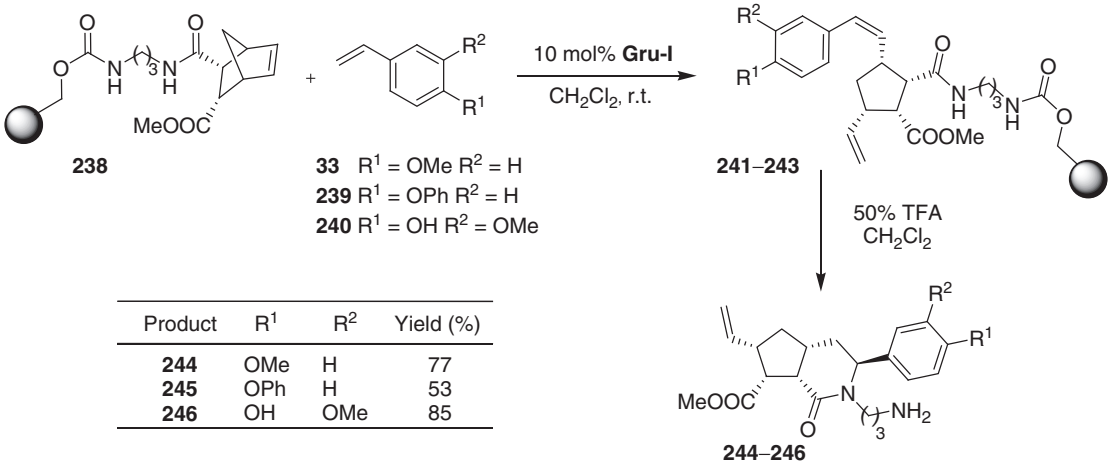
Scheme 47 ROCM of unstrained carbocycles.

Modification of the ring size of the cyclic olefin proved that cycloheptene is a better substrate than cyclopentene, thus underlining the influence of the ring strain on the overall efficiency of the reaction. In all the examples presented in the study, the catalyst **Hov-II** was proven to be superior to **Gru-II**. The most interesting point is that all the products were obtained as *E*-isomers only, but one should note that this selectivity is largely substrate dependent. A mechanistic study by Arjona et al. considered interactions of a substrate bearing a small and a large substituent with ruthenium complexes (Scheme 48).[87]



Scheme 48 Reasons for the selectivity of ROCM.

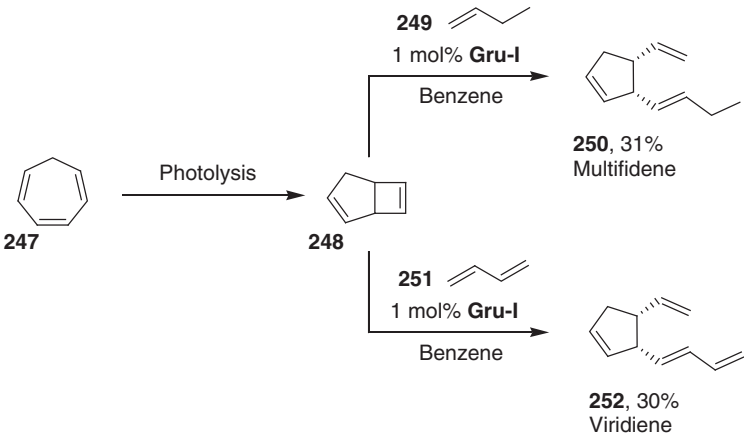
The selectivity can be derived either from the cycloaddition reaction or from the later CM reaction. If the difference between the large and the small substituent is significant, the steric factors affect largely the first stage of the reaction. In such cases, the addition is preferable from the side of the small substituent creating the more favorable metallacyclobutane. This causes the *Z*-isomer to be the major product. The understanding of the mechanism of the reaction was soon followed by methodology studies. Over the years attempts were made to establish a method of utilization of ROCM on solid support. Wang resin-bound norbornenes made that possible.[88] The developed protocol resulted in a variety of substituted cyclopentene-fused piperidinone rings (Scheme 49).



Product	R^1	R^2	Yield (%)
244	OMe	H	77
245	OPh	H	53
246	OH	OMe	85

Scheme 49 ROCM on solid support. TFA, trifluoroacetic acid.

As the studies devoted to ROCM selectivity contributed to the development of knowledge on the subject, the first attempts of applications in target-oriented synthesis soon followed. Scheme 50 presents an example of the synthesis of pheromones of brown algae.[89] Although the results do not seem impressive at first glance, they can be considered to be a milestone in the synthesis of these compounds. Previous syntheses required more than nine steps to produce either compound in approximately 3–8% overall yield. This meant that the synthesis was shortened by 5 times and turned out to be more than 10 times as effective.



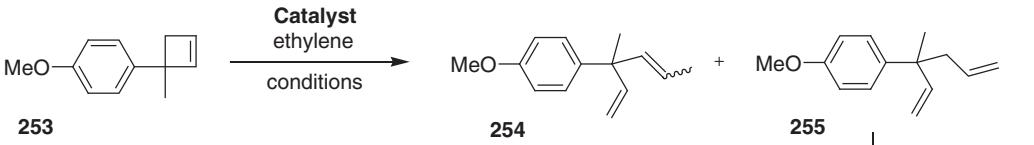
Scheme 50 ROCM in target-oriented synthesis.

Another application of ROCM is the synthesis of (±)-sporochnol,[90] which is isolated from the Caribbean marine alga *Sporochnus bolleanus*, presented in Scheme 51. During this synthesis various conditions were explored. The authors utilized catalysts of first- and second-generation. **Gru-I** gave poor results, allowing product formation only at a loading of 45 mol%. Switching to the second-generation catalyst, **Gru-II** led to improved results. Further variation of solvent, temperature, and catalyst loading allowed the synthesis to be completed with a satisfying result both in terms of yield and isomer ratio.

It is worthy of note that ROCM strategies have also been used in the synthesis of more sophisticated compounds. Furthermore, tandem metathesis processes are increasingly used in sequences with other reactions of significant synthetic potential. The synthesis of (+)-asteriscanolide[91] presented in Scheme 52 can serve as a great example. In this particular sequence, after the ROCM conditions were successfully applied, the reaction mixture was refluxed to allow for a Cope rearrangement of the product primarily formed. Thus, **258** is a product of a one-pot cascade synthesis obtained in more than reasonable yield.

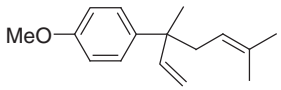
The part devoted to two-step tandem metathesis consisted mainly of examples of the ROCM sequence, as it has been the most investigated, but there are also other possibilities including an intermolecular step, for example, CM followed by RCM (CM-RCM). One of the most important examples of its utilization was the synthesis of the cylindrocyclophanes[92] presented in Scheme 53.

The authors employed a variety of conditions in their synthetic attempts to discover that the Mo-based catalyst **Sch-I** gave the best result in this case. The CM-RCM strategy led to a noticeable increase in the overall yield of the (–)-cylindrocyclophane F synthesis; a previous pathway had required 20 steps with an overall yield of 8.3%, whereas the modified one containing the



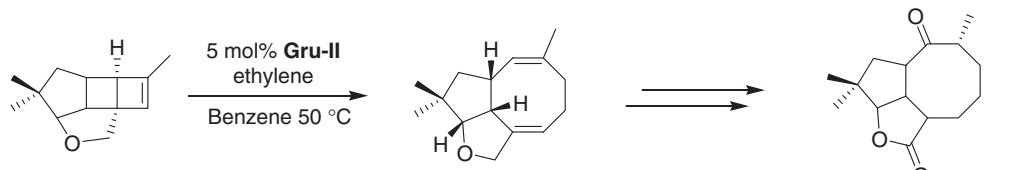
253 **254** **255**

Catalyst	Solvent	*T* (°C)	Time (h)	Yield (**254**:**255**)
10 mol% **Gru-I**	CH_2Cl_2	20	16	–
45 mol% **Gru-I**	CH_2Cl_2	20	120	65% (>5:95)
5 mol% **Gru-II**	Dichloroethane	60	3	52% (>5:95)
7 mol% **Gru-II**	Dichloroethane	60	16	73% (>5:95)
10 mol% **Gru-II**	Toluene	80	48	81% (30:70)



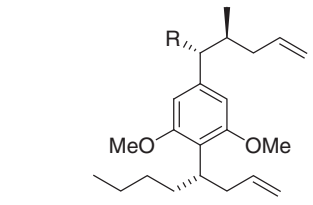
256 (±)-Sporochnol

Scheme 51 Sporochnol synthesis by ROCM.



257 **258**, 74% **259** (+)-Asteriscanolide

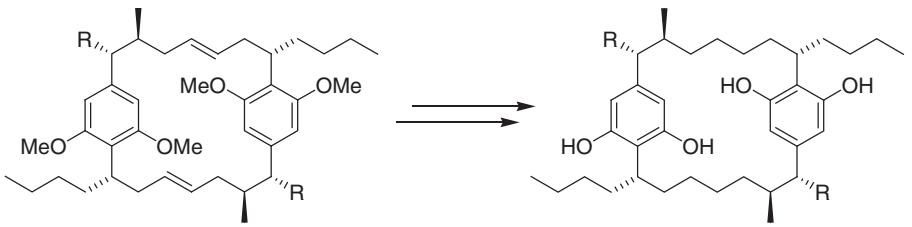
Scheme 52 (+)-Asteriscanolide synthesis.



260 R = H
261 R = OTES

CM-RCM

Product	Catalyst	Solvent	*T* (°C)	Yield (%)
262	15 mol% **Gru-I**	CH_2Cl_2	20	55
262	15 mol% **Gru-II**	CH_2Cl_2	40	48
262	15 mol% **Gru-II**	Benzene	40	58
262	30 mol% **Sch-I**	Benzene	20	72
263	34 mol% **Sch-I**	Benzene	20	77

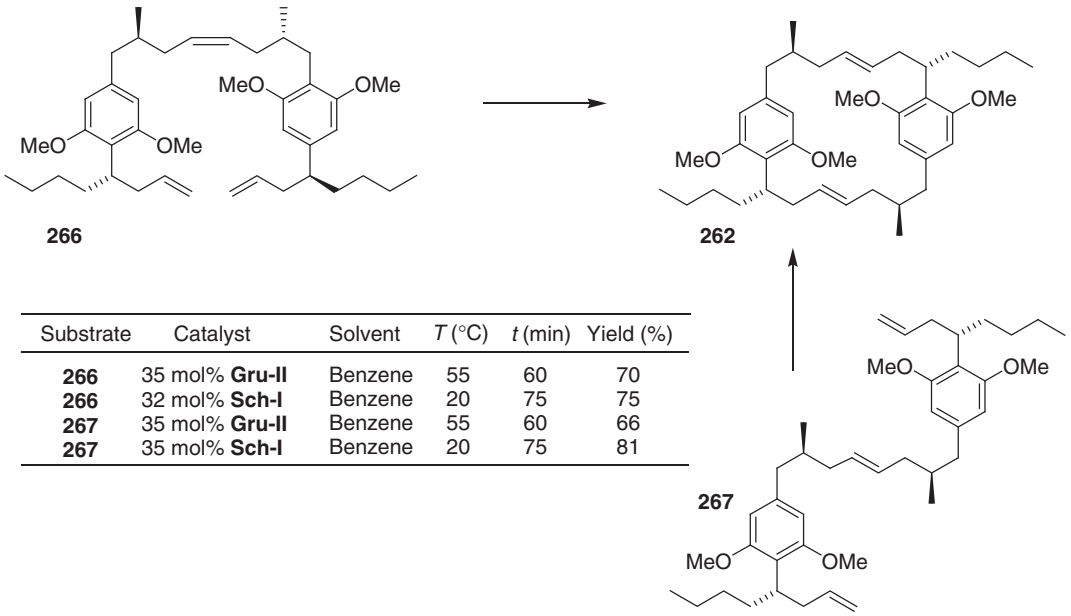


262 R = H
263 R = OTES

264 R = H (–)-Cylindrocyclophane F
265 R = OTES (–)-Cylindrocyclophane A

Scheme 53 Cylindrocyclophane synthesis by a CM-RCM sequence.

metathesis tandem provided the product in only 11 steps with an overall yield of 22%. A noteworthy observation made by the authors was that when substrate **260** was metathesized, only **262** was observed, exclusively as the required *E*,*E*-isomer. The dimerization of compound **260** could lead to up to seven products when all possibilities are taken into account. As only one of those was observed, a conclusion was made that thermodynamic factors contribute largely to the course of the reaction. To prove that, an additional synthetic experiment was performed (Scheme 54).



Substrate	Catalyst	Solvent	T (°C)	t (min)	Yield (%)
266	35 mol% **Gru-II**	Benzene	55	60	70
266	32 mol% **Sch-I**	Benzene	20	75	75
267	35 mol% **Gru-II**	Benzene	55	60	66
267	35 mol% **Sch-I**	Benzene	20	75	81

Scheme 54 Reversibility of CM as a synthetic approach.

The theoretical studies conducted revealed that the observed isomer possessed the lowest energy. Many other research studies had suggested that the reversibility issue leads to the formation of the most thermodynamically stable products. To obtain an experimental proof for this assumption, the authors designed and synthesized trienes **266** and **267**. It was assumed that during the RCM process, they would lead to the formation of an [8,6]-cyclophane. Despite the predispositions of the substrates to do so, the only product observed was the thermodynamically most stable [7,7]-cyclophane **262**. This experiment shows that this kind of tandem metathesis process is self-editing in order to reach the most stable of all possible isomers.

5.26.3.1.2 Asymmetric ROCM (AROCM)

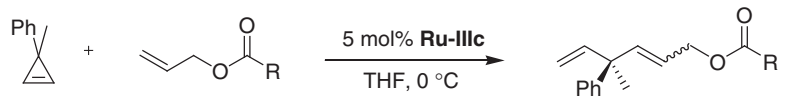
The previous section was devoted to ROCM catalyzed by commercially available achiral complexes. The only means of inducing chirality was the utilization of a chiral substrate, resulting in a diastereoselective process. However, there has been an important improvement – introduction of chirality into the catalyst structure allowed metathesis to be taken to an entirely new level, as enantioselective transformations can now be considered (Scheme 55). With the chiral catalysts described in Section 5.26.1.3 in hand, one can utilize substrates with no chirality and install stereoinformation in an enantioselective metathetic process. One of the most investigated areas of this asymmetric metathesis is the ROM-CM sequence, which – in its asymmetric variant – is abbreviated as AROCM.



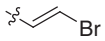
Scheme 55 Inducing chirality in metathesis.

Principles of AROCM are very similar to those of its achiral version. Thus, one of the first cases of its applications utilized a substituted cyclopropene compound as a strained alkene substrate.[93] Metathesis with unsaturated carbonyl compounds afforded the corresponding products that contained a quaternary carbon center (Scheme 56). It is worth noting that a wide variety of functional groups is well tolerated within the reaction. Functionalities such as trisubstituted cyclic alkenes, terminal alkenes, or alkynes are compatible and the resulting products are formed with outstanding enantioselectivities. Since the structures of the obtained products allow further functionalization, they are valuable starting points for the synthesis of sophisticated compounds. The noticeable drawback of this method is that in all cases of diene cross partners some amounts of lactone were formed by RCM.

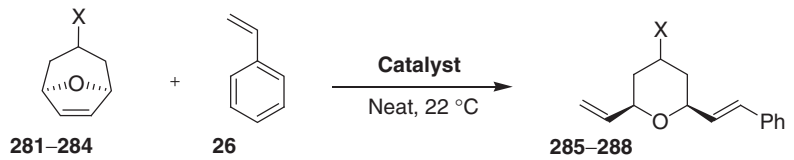
Cyclopropene was not the only strained ring utilized in such reactions. Substituted oxabicycles are often utilized in synthesis, giving access to a range of tetrahydropyrans presented in Scheme 57.[94] The data also allow for a comparison of the chiral ruthenium catalysts. The general conclusion that can be drawn is that in most cases the complex Ru-IIIc is more reactive than Ru-IVc, whereas the enantioselectivity of the products seems to be on a similar level. Further research on catalyst behavior was conducted in AROCM reactions of anhydrides and protected diols (Scheme 58).[95] The study utilized both aromatic and aliphatic



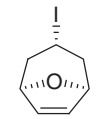
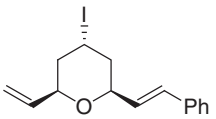
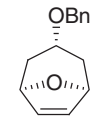
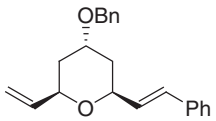
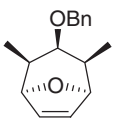
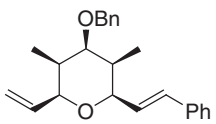
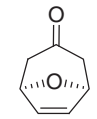
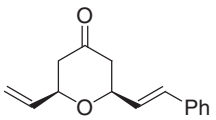
268 **269–274** **275–280**

Substrate	Product	R	Yield (%)	*E:Z*	*ee* of *E* isomer (%)
269	**275**		71	4.5:1	85
270	**276**		83	3:1	87
271	**277**		63	6:1	82
272	**278**		80	7:1	98
273	**279**		69	6:1	98
274	**280**		65	4:1	86

Scheme 56 AROCM with cyclopropene derivative.

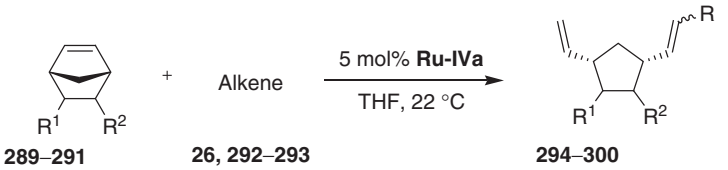


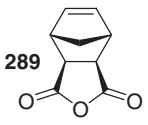
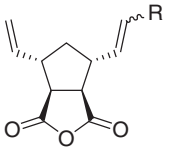
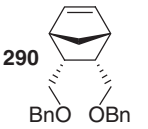
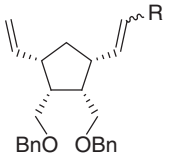
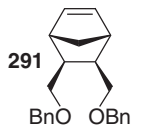
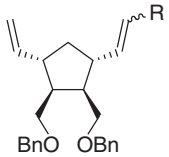
281–284 **26** **285–288**

Substrate	Product	Catalyst	Yield (%)	*ee* (%)
 **281**	 **285**	2 mol% **Ru-IIIc**	70	82
		2 mol% **Ru-IVc**	65	93
 **282**	 **286**	2 mol% **Ru-IIIc**	70	94
		2 mol% **Ru-IVc**	85	90
 **283**	 **287**	5 mol% **Ru-IIIc**	56	81
		5 mol% **Ru-IVc**	44	80
 **284**	 **288**	5 mol% **Ru-IIIc**	71	93
		5 mol% **Ru-IVc**	–	–

Scheme 57 AROCM in tetrahydropyran synthesis.

olefins as cross partners. Interestingly, no meaningful difference was observed among these reactions. A strong influence of the substrate's stereochemistry on the results of the metathesis reaction was noted. A case of the protected diol may serve as an example. The *endo* isomer **290** afforded product **297** in decent yield and enantioselectivity. The *exo* isomer **291** yielded product **300** with a noticeably lower enantioselectivity.



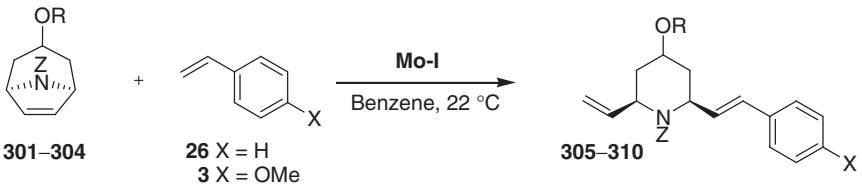
Substrate	Alkene	Product	Yield (%)	*E:Z*	*ee* (%)
 **289**	**26**  Ph		**294** R = Ph	60	95:5	70
	292  Cy		**295** R = Cy	57	96:4	74
	293  *n*-C_5H_{11}		**296** R = *n*-C_5H_{11}	58	95:5	72
 **290**	**26**  Ph		**297** R = Ph	70	>98:2	85
	292  Cy		**298** R = Cy	77	95:5	91
	293  *n*-C_5H_{11}		**299** R = *n*-C_5H_{11}	65	95:5	88
 **291**	**26**  Ph		**300** R = Ph	75	98:2	10

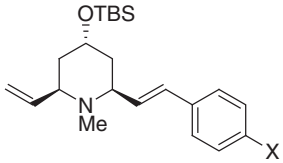
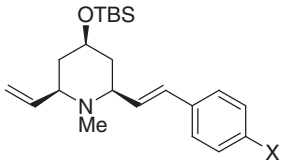
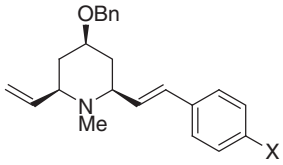
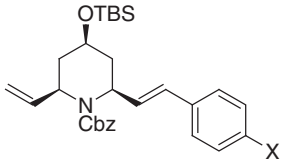
Scheme 58 Ruthenium-catalyzed AROCM reactions.

AROCM studies did not focus on ruthenium-catalyzed reactions only. Molybdenum-based chiral catalysts were utilized in the syntheses of substituted piperidines presented in Scheme 59.[96] The catalyst promotes the reaction effectively, although the level of success depends on the steric and electronic factors of the substrates. Reaction with the electron-rich styrene **3** proceeds faster and in a more enantioselective manner. The nitrogen protective group does not seem to affect the efficiency of the transformation. The same research attempted to compare the behavior of Ru- and Mo-based complexes in piperidine synthesis. The results are summarized in Scheme 60.

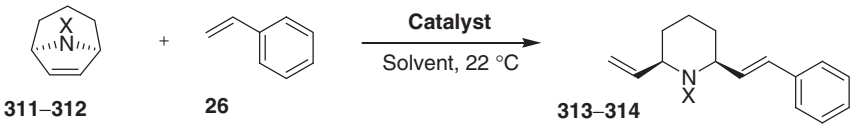
In the cases presented in Scheme 60, **Mo-I** is superior in efficiency. In the discussed examples, the metal catalysts exhibit an opposite enantioinduction, thus constituting a complementary approach for the synthesis of chiral compounds (negative values of enantiomeric excess (*ee*) represent products of opposite configuration). Ruthenium-based complexes seem to catalyze only the reaction of the azabicyclic substrates lacking a C4 substituent; in the other cases, the conversion is rather poor for steric reasons. Further comparison of the catalytic abilities of different catalysts was conducted in metathesis reactions of enol ethers presented in Scheme 61.[97] The only examined ruthenium complex (**Hov-II**) gave poor results despite acceptable conversions, which might be due to a competing oligomerization pathway in this case. This is further proven by an even lower yield in case of metathesis with a more sterically demanding substrate **208**. The Ru-catalyzed reaction was moderately *E*-selective, whereas in the same example **Sch-I** provided both the isomers in equal ratios. When stereogenic-at-Mo complexes were applied, the *Z*-selectivity improved noticeably. In all cases, the reaction tended to proceed less enantioselectively when the cross partner **316** was utilized. This may stem from an increased steric hindrance when compared with **208**. All **Mo-IV** catalysts in the study were obtained *in situ* from the same amount of precursors. This leads to the conclusion that, when bigger halogen substituents in the complex structure were utilized, the catalysts are generated more efficiently. The mentioned exchange seems to have little or no effect on the outcome of the reaction. Thus, considering the preparative pathway, catalyst **Mo-IVb** was selected for further tests in the AROCM of carbocyclic compounds and enol ethers (Scheme 62).

Higher enantioselectivities were observed with a cyclopropene substrate. The significantly lower enantiomeric ratio (*er*) for the benzyl-protected substrate **320** can be explained by the elevated temperature required for its transformation. Generally, the benzyl



Product		Catalyst loading (mol%)	Yield (%)	*ee* (%)
	**305** X = H	5	90	85
	**306** X = H	5	95	94
	307 X = OMe	5	92	89
	**308** X = H	5	86	96
	**309** X = H	10	93	90
	310 X = OMe	10	65	80

Scheme 59 Azabicycles as AROCM substrates.

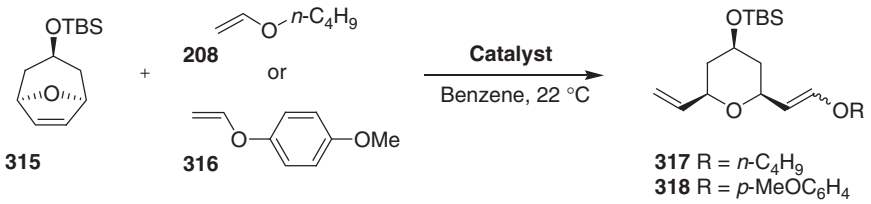


Product	Catalyst	Yield (%)	*ee* (%)
313 X = Cbz	10 mol% **Mo-I**	80	82
	10 mol% **Ru-IIIa**	70	–90
314 X = COOEt	5 mol% **Mo-I**	72	90
	10 mol% **Ru-IIIa**	66	–94

Scheme 60 Nitrogen protective group influence in AROCM.

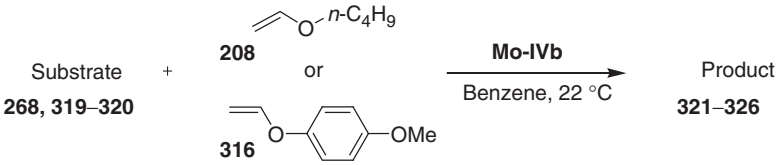
protection was found to be an obstacle during the reaction. Its smaller size (compared with the *tert*-butyldimethylsilyl (TBS) group) did not turn out to be beneficial, as it might allow for chelation between the substrate and the Mo-catalyst. Interestingly, a tendency to give higher enantioselectivities was noticed for certain cyclic compounds, when a larger excess of vinyl ether was utilized. What seems peculiar is that increasing the amount of the acyclic partner did not alter the *Z*-selectivity in any of the examined cases.

Although AROCM is a relatively new research area, it has immediately gained attention in the context of possible applications. One of the most recent examples is its application in the total synthesis of baconipyrone presented in Scheme 63.[98] The different catalysts employed in the study gave similar results. Generating 2 mol% of **Ru-IIIc** *in situ* noticeably improved the yield of **287**



Product	Catalyst	Yield (%)	*Z:E*	*er*
317	1 mol% **Hov-II**	32	25:75	–
318	1 mol% **Hov-II**	<5	–	–
317	1 mol% **Sch-I**	10	50:50	–
318	1 mol% **Sch-I**	14	80:20	–
317	0.5 mol% **Mo-IVa**	87	>98:2	98:2
318	0.5 mol% **Mo-IVa**	80	>98:2	92:8
317	0.6 mol% **Mo-IVb**	89	>98:2	99:1
318	0.6 mol% **Mo-IVb**	90	>98:2	98.5:1.5
317	0.7 mol% **Mo-IVc**	87	>98:2	98:2
318	0.7 mol% **Mo-IVc**	85	>98:2	98.5:1.5

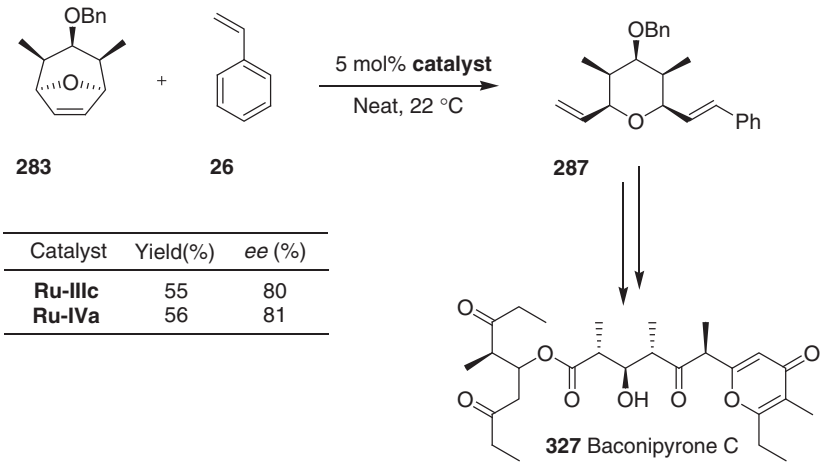
Scheme 61 ROCM enol ether reactions.



Substrate	Product	Vinyl ether equivalents	Catalyst loading (mol%)	Yield (%)	*Z:E*	*er*
268	**321** R = *n*-C_4H_9	10	3	79	>98:2	94.5:5.5
	322 R = *p*-$MeOC_6H_4$	2	3	71	>98:2	96.5:3.5
319	**323** R = *n*-C_4H_9	1.1	0.6	52	97:3	79.5:20.5
		10	0.6	90	96:4	86.14
	324 R = *p*-$MeOC_6H_4$	1.1	0.6	34	95:5	68:32
		10	0.6	90	94:6	85:15
320	**325** R = *n*-C_4H_9	20	0.6 (60 °C)	61	84:16	85:15
	326 R = *p*-$MeOC_6H_4$	20	0.6 (60 °C)	73	98:2	85:15

Scheme 62 AROCM of strained rings with enol ethers.

(64%, 89% *ee*). The described case proves that there is room for further improvements of the efficiency of metathetic steps by application of *in-situ*-generated catalysts. In spite of that, AROCM is already a valuable source of optically enriched compounds that can be accessed by significantly shortened pathways. Mo- and Ru-based chiral catalysts have been developed, which let the field flourish. The former provide better reaction outcomes, but the latter are tolerant toward a wider substrate scope. Further development is to be expected as ever more new chiral complexes are introduced.

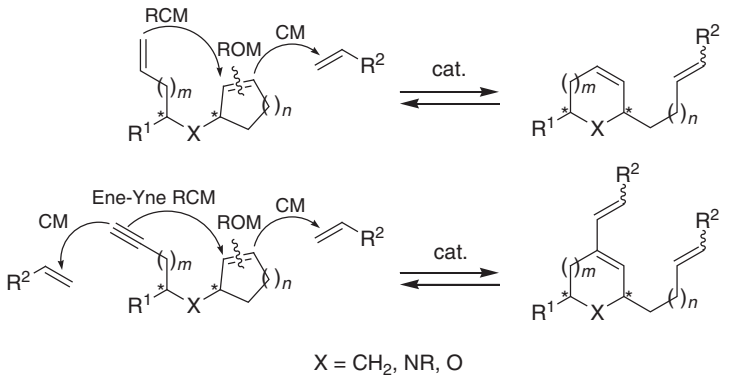


Catalyst	Yield(%)	*ee* (%)
Ru-IIIc	55	80
Ru-IVa	56	81

Scheme 63 Baconipyrone synthesis.

5.26.3.2 Transformations Involving Several Metathesis Steps

In the previous paragraphs, only two-step sequences of metathesis were discussed. However, this is not the only possibility, as cascade reactions can consist of more metathetic steps. The most common way of utilizing such transformations is ring-rearrangement metathesis known as RRM.[99] The general concepts of this transformation are presented in Scheme 64, but it should be noted that only those examples that possess at least one intermolecular step are described here.

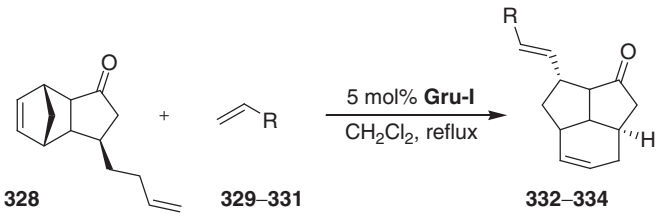


Scheme 64 General principle of RRM.

The RRM processes have the same features as the single metathesis reaction steps that are combined. Thus the driving forces are the same – release of ring strain or the formation of a volatile alkene. The most important feature of RRM is the preservation of stereochemical information contained in the substrate and its transfer to the product, which seems to be particularly important for applications of RRM processes in the synthesis of biologically active molecules, being often fused carbo- or heterocycles. An interesting example of fused-ring synthesis by means of RRM was presented by Prunet et al. (Scheme 65).[100]

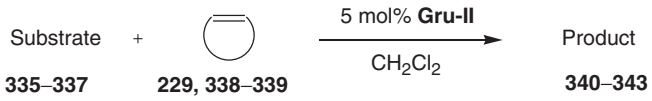
The authors examined the formation of tricyclic frameworks by a ROM-RCM-CM sequence. In all cases the result of the intermolecular step was an *E*-olefin only. Surprisingly, the reaction proceeded more efficiently when a substituted olefin was utilized as the cross partner instead of ethylene. In contrast to the other substrates, ethylene is a gas and as such cannot favor the domino process over competing polymerization. Attempts were made not only to form cyclic products but also to utilize cyclic substrates in ring-expansion reactions. A study containing applications of a ROM-CM-RCM sequence is presented in Scheme 66.[101] Modification of either substrate enables the size and substitution pattern of the resulting product to be adjusted, which leads to a powerful strategy for macrocycle formation. The conducted research proved that a number of factors such as the substitution of the acyclic substrate and the ring size of the cyclic one affect the product formation. The effect of concentration on product distribution was also investigated.

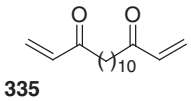
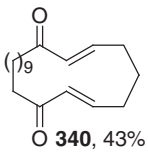
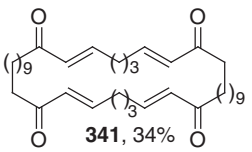
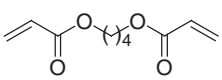
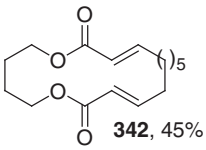
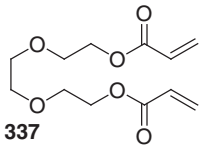
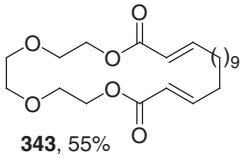
In several synthetic applications selectivity of the reaction is a major issue. This seems to be a problem especially when the intermolecular step of the sequence may take part in more than one place (Scheme 67).[102] In the presented ROM-ene-yne-RCM-CM sequence, substituted cyclopentene derivatives were targeted. The authors obtained olefin **346** as the expected product of



Substrate	Product	R	Yield (%)
329	**332**	H	64
330	**333**	CH_2SiMe_3	88
331	**334**	$CH_2P(O)OEt_2$	61

Scheme 65 Tricyclic framework synthesis by RRM.



Substrate	Ring size	Concentration	Product, yield	
 **335**	**229** 5	5 mM	 **340**, 43%	 **341**, 34%
	229 5	25 mM	**340**, 13%	**341**, 30%
 **336**	**338** 8	5 mM	 **342**, 45%	
 **337**	**339** 12	5 mM	 **343**, 55%	

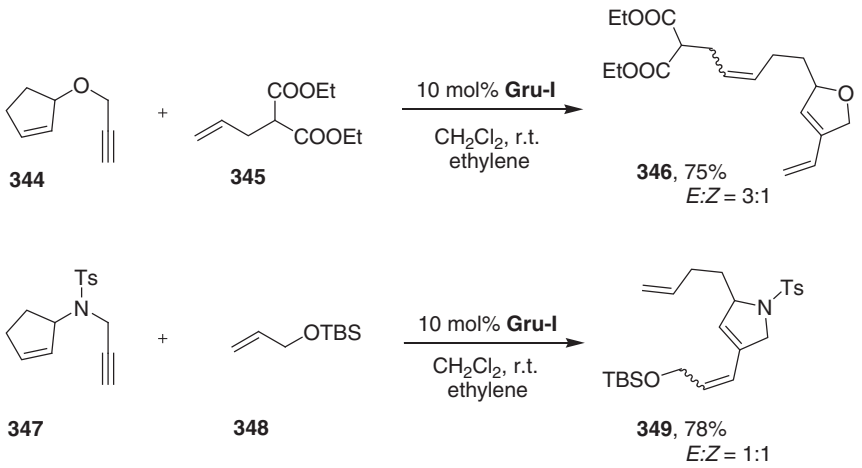
Scheme 66 Ring expansion by a ROM-CM-RCM sequence.

RRM. Surprisingly, the analogous transformation of substrates **347** and **348** led to another outcome. This regioselectivity may probably be explained by electronic or steric effects of the particular substrate pair, but the mechanism is still unknown.

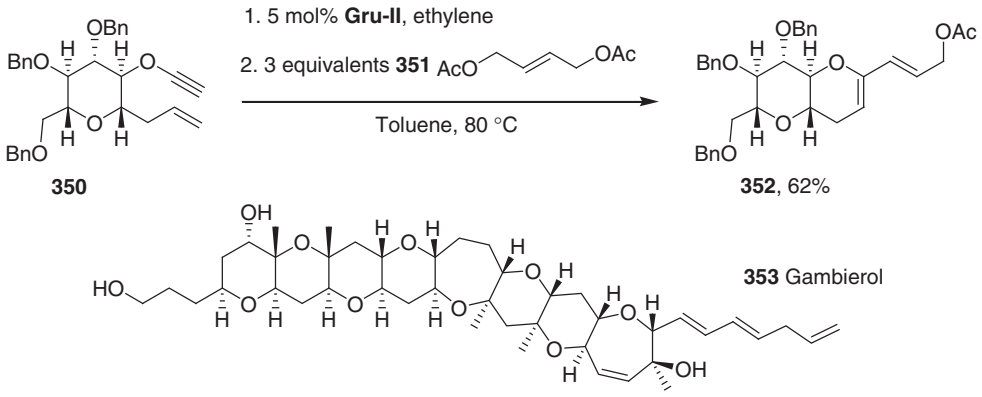
Although problematic in some cases, RRM transformations have found application in the syntheses of various natural products. An example of the construction of polyether substructures common in biologically active compounds is shown in Scheme 68.[103] The utilized metathetic sequence provided product 352 in an overall yield of 62%, proving the efficiency of this methodology.

Another natural product synthesized by this methodology was (–)-lasubine.[104] The reaction between **354** and **355** presented in Scheme 69 resulted in the *E*-configured product **356** in a 48% yield. The main drawback of this approach is the concurrent CM reaction between the substrates, which causes byproduct formation.

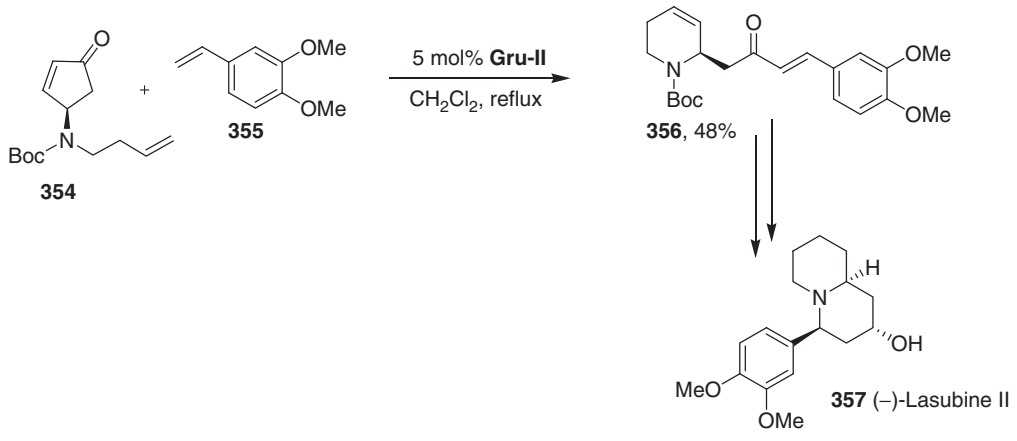
The ROM-RCM-CM methodology was utilized by Phillips et al.[105] to synthesize (+)-cylindramide A (Scheme 70). The bicyclic substrate **358** was metathesized in a ROM-RCM sequence with compounds **360** or **363**. In the first approach a mixture of products



Scheme 67 Selectivity of RRM.



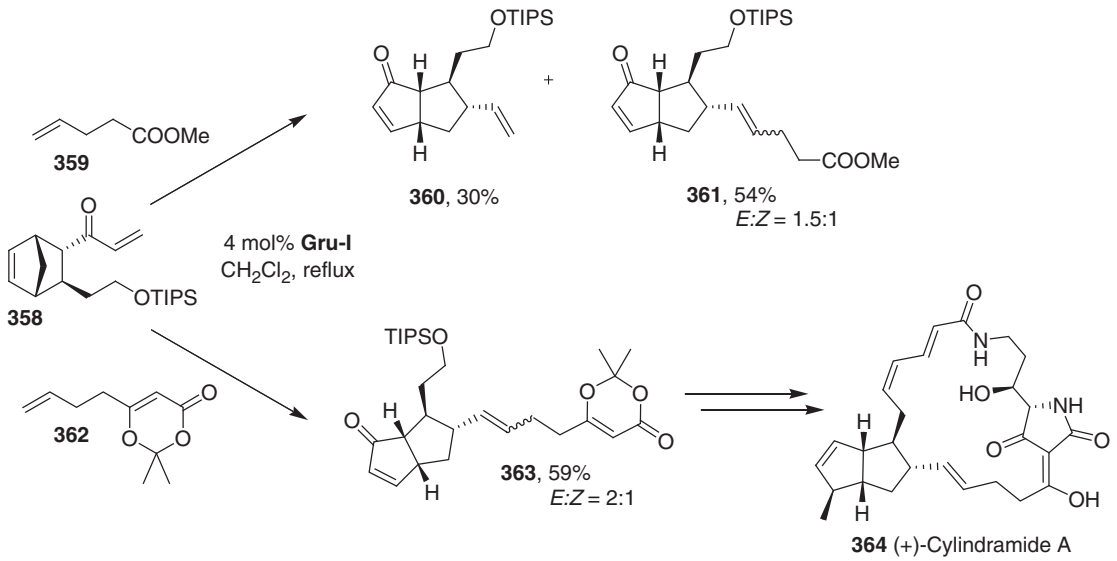
Scheme 68 Synthesis of polycyclic ether framework.



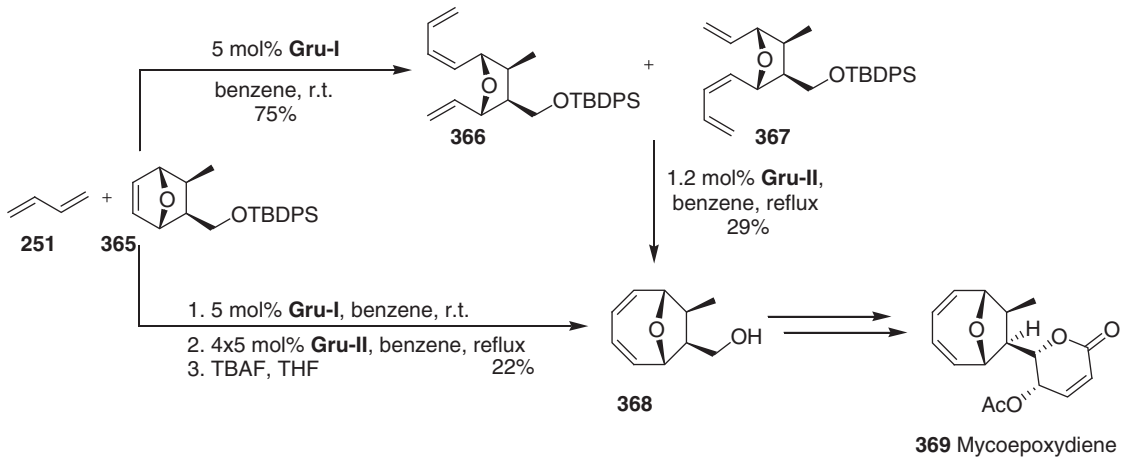
Scheme 69 RRM synthesis of (–)-lasubine.

was obtained, indicating an incomplete CM step when using **359** as the reaction partner. Utilizing olefin **362** as the cross partner led to a complete conversion of **358** and better selectivity.

Another natural product obtained by this methodology is mycoepoxydiene (Scheme 71).[106] This compound was synthesized utilizing two different protocols. The first one divided the sequence into two separate steps: ROM-CM and RCM, whereas the other



Scheme 70 Synthesis of (+)-cylindramide A by means of RRM. TIPS, triisopropylsilyl.

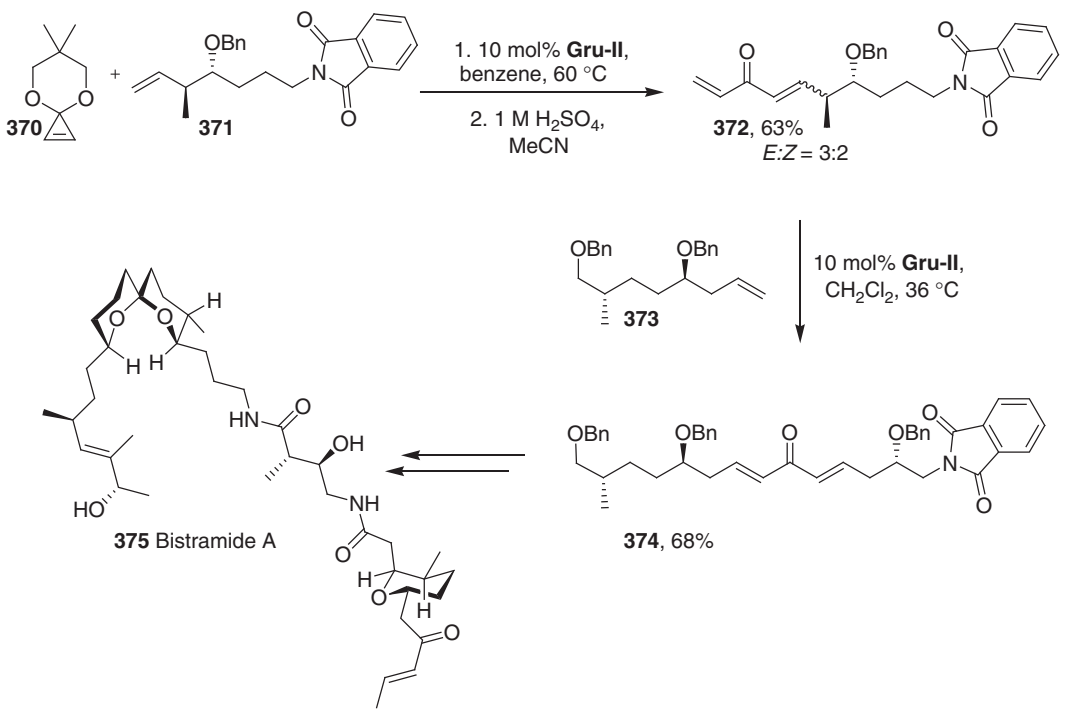


Scheme 71 Mycoepoxydiene synthesis utilizing different protocols.

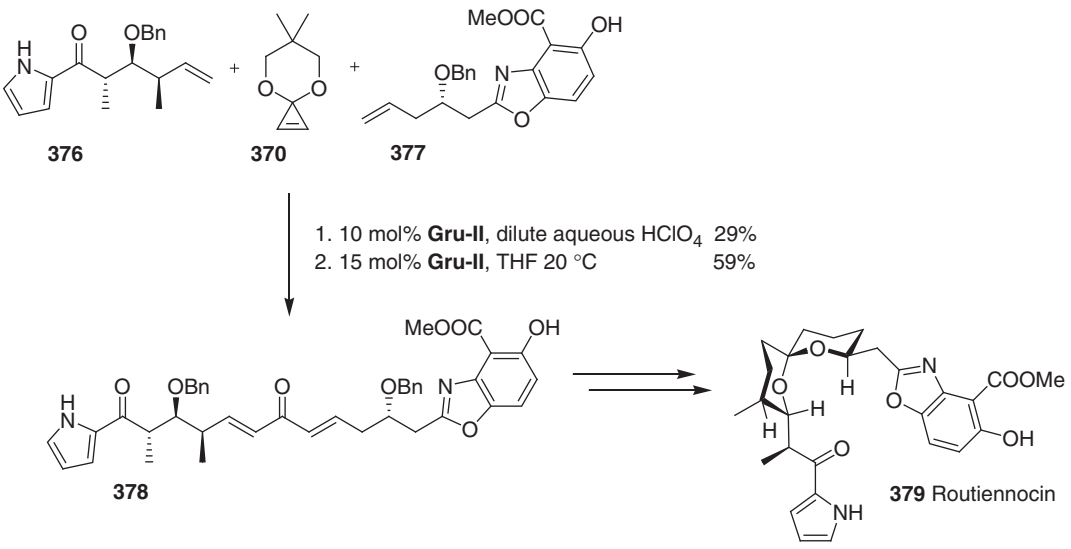
was a stepwise one-pot procedure. The second procedure turned out to be more effective overall, although it has to be noted that it utilized a much higher catalyst loading during the CM step.

Most RRM synthetic pathways contain only one intermolecular step, as incorporating another such transformation usually doubles the difficulty of obtaining the expected product. Therefore, such transformations are usually conducted in a stepwise manner. The synthesis of bistramide A[107] presented in Scheme 72 is a great example of such an approach. The first stage of the synthesis is a ROCM between **370** and **371**. After the formation of **372**, the next cross partner **373** is added resulting in the formation of **374** as the product of the sequence. The same concept was successfully utilized in the synthesis of another complicated compound – routiennocin[108] (Scheme 73).

The last and probably the most sophisticated example of RRM is a synthesis of (–)-centrolobine, an antibiotic isolated from the heart wood of *Centrolobium robustum*, which is presented in Scheme 74.[109] Among many synthetic approaches toward that rather simple structure, a sequence comprising a diastereoselective variant of RRM (dRRM) followed by CM proved to be superior. During a RRM, an existing stereocenter can be transferred from the side chain to the ring (or vice versa), but their total number remains unchanged. The diastereoselective variant, however, usually involves prochiral rings with a stereocenter in the side chain, which after metathesis leads to carbo- or heterocycles containing a new stereocenter. The greatest challenge of such a



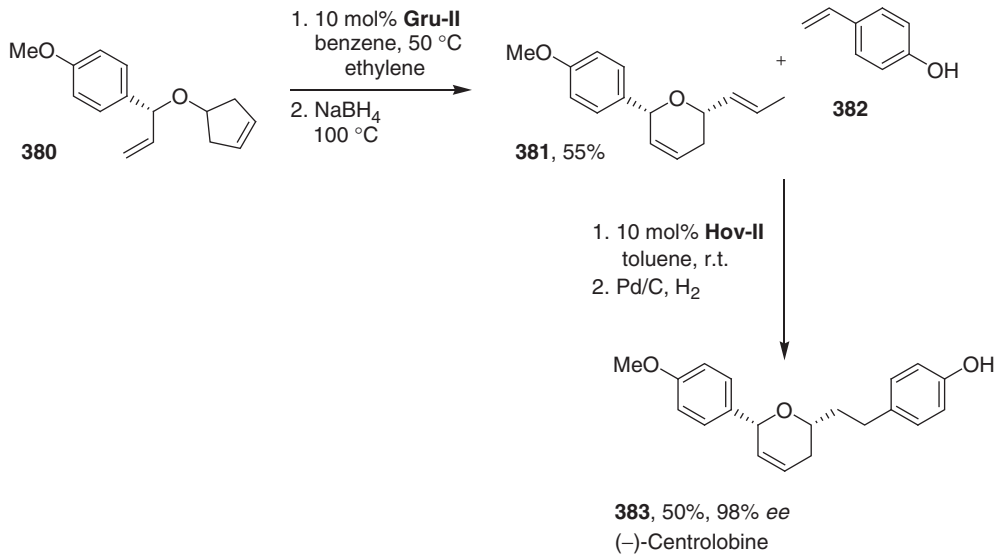
Scheme 72 Synthesis of bistamide utilizing ROM-CM-CM sequence.



Scheme 73 Routiennocin synthesis.

transformation is the formation of the rearranged product in an acceptable diastereoselectivity, which was nicely achieved in the discussed example.

As proven above, tandem sequences have found applications in many syntheses. They provide access to complex structures that would otherwise be very difficult to obtain. Apart from the obvious advantages, some issues remain to be solved. One of the most serious ones is the often poor diastereo- and enantioselectivity, which are crucial in natural product chemistry. The final issue, probably the most limiting for large-scale applications, is that natural product synthesis usually requires high catalyst loadings, which are unacceptable for the industry. Solving those problems would certainly lead to widespread use of tandem metathesis sequences in the synthesis of specialty chemicals.



Scheme 74 dRRM in natural product synthesis.

5.26.4 Outlook/Perspectives

Functionalized olefins are important building blocks in organic synthesis. Catalytic olefin CM in all its flavors is a convenient route to functionalized olefins from simple alkene precursors. One of the most appealing facets of this transformation is that a carbon–carbon double bond produced in CM can be substituted by heteroatom-containing groups (in this respect, CM can be seen as a formal C-H activation reaction of the olefinic substrate). Additionally, advanced architectures such as polycyclic frameworks can be relatively easily prepared using multicomponent processes, where a CM reaction is paired with another metathetical transformation, such as ROM or RCM.

A lot of effort has been made toward understanding of the mechanism and the origin of selectivity in CM transformations. Of note, the general empirical model for olefin reactivity in CM, developed by Grubbs, provides a simple yet convenient tool for the prediction and design of new selective CM reactions. Development of new efficient catalysts and conditions is another key factor, which allows the use of previously incompatible substrates. Although some problems related to controlling of chemo- and stereoselectivity during CM reactions remain unsolved, this reaction has already become a valuable tool for organic chemists and further development is expected.

Acknowledgments

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5.27 Ene–Yne Metathesis

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Glossary

Alkylidene-first mechanism In an ene–yne metathesis, a mechanistic sequence where the alkene reacts first to form a reactive metal carbene. This is sometimes called the 'ene-then-yne' mechanism.

Diversity-oriented synthesis Synthesis activity that aims to create various cyclic or polycyclic templates to project functional groups in three-dimensional space. This approach offers a complement to the structural diversity represented in Nature and aims to access additional three-dimensional arrays of organic functional groups.

Double-directional synthesis A bifunctional or symmetrically functionalized substrate is extended by bond formation in two directions at once or sequentially.

***Endo*-selectivity (in ene–yne metathesis reactions)** In a ring-closing enyne metathesis, the alkene carbon becomes bonded to the more distant alkyne *sp*-hybridized carbon. This process may be triggered by the addition of ethylene to the alkyne, or by ring closing of an alkene-derived alkylidene to produce an endocyclic metal carbene intermediate. This is common in macrocyclizations.

Metallotropic shift An alkynyl-substituted metal carbene undergoes propargylic transposition to form a new alkynyl-substituted metal carbene. This has been used to migrate metal carbenes so that they can participate in cascade metathesis sequences.

Methylene-free ring synthesis The use of an unsaturated four-carbon chain to build a cyclohexadiene ring from an alkyne without any methylene (CH_2) sources. Lack of methylene sources favors the metathesis cascade that produces a cyclized product.

Mori's conditions The use of an ethylene atmosphere to increase yields of ring-closing enyne metathesis products.

RCEYM Ring-closing ene–yne metathesis.

Relay metathesis or relay ring-closing metathesis The use of a more reactive alkene to position a new metal carbene through a ring-closing metathesis. This can be used

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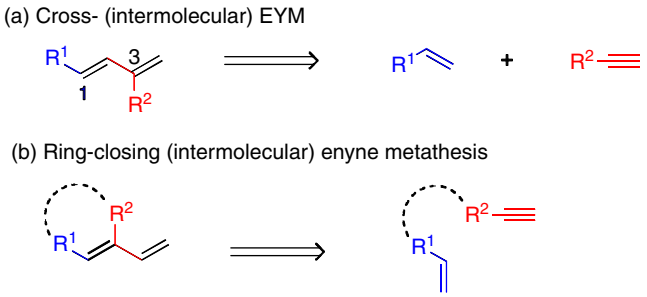
to make metal carbenes that would be otherwise difficult to form, or as a means to position a metal carbene at a desired site to initiate metathesis cascades.

Ring rearrangement metathesis The intramolecular exchange of a cycloalkene with an alkyne to form a new cycloalkene or unsaturated heterocycle.

Transalkylidenation Conversion of a metal carbene to a new metal carbene by reaction with an alkene. This is a fundamental process in alkene metathesis. For example, the Grubbs benzylidene $L_nCl_2Ru{=}CHPh$ is converted to $L_nCl_2Ru{=}CHR$ by reaction with $RCH{=}CH_2$. The process occurs via a ruthenacyclobutane intermediate.

5.27.1 Introduction

Ene–yne metathesis (EYM) is a synthetically useful method for the synthesis of 1,3-dienes. Conjugated dienes are valuable building blocks for organic synthesis. For example, conjugated 1,3-dienes are widely used in Diels–Alder reactions for the synthesis of six-membered rings. With catalytic EYM, the 1,3-diene is synthesized in a single reaction step from alkene and alkyne reactants. Notably, the alkene and alkyne reactants do not require preactivation: Their π-bonds provide the origin for their reactivity. The ruthenium carbenes are uniquely matched to react with π-bonds, which is the origin of their remarkable chemoselectivity. This preference is also known as functional group tolerance. The EYM reaction is a catalytic transformation and usually employs the mild and readily available Grubbs carbene catalysts. The ruthenium carbenes known as the Grubbs catalysts promote EYM with excellent chemoselectivity (Scheme 1).



Scheme 1 Enyne and EYM.

Carbon–carbon bond coupling between an alkene and an alkyne with π-bond reorganization is EYM. When the reaction occurs between two separate molecules in an intermolecular reaction, it is known as a 'cross' EYM (Scheme 1, panel a). In simple terms, the reaction can be described as a cleavage of the alkene π-bond and the attachment of the individual carbene components across the triple bond with a defined regiochemistry. Accordingly, a 1-alkene combines with a 1-alkyne to give a 1,3-disubstituted 1,3-diene. The alkene must be reactive with the metal carbene being used. If the reactants are joined by a tether, as in a 1,ω-enyne, then the reaction is intramolecular and known as ring-closing *1,n*-enyne metathesis (RCEYM). The RCEYM produces the 1,2-disubstitution pattern with ring formation (Scheme 1, panel b). This reaction is successful for the synthesis of a wide assortment of carbocycles and heterocycles. For the synthesis of small rings, the tether geometrically restricts the ene and yne fragments from joining in the 1,3-orientation; instead they join with 1,2-substitution on the 1,3-diene. In this chapter, intermolecular reactions will be denoted as EYM and intramolecular ring-closing metathesis (RCM) of 1,*n*-enynes will be called 'enyne' metathesis. Collective or generic references to metathesis of each molecularity will be called 'ene–yne metathesis'.

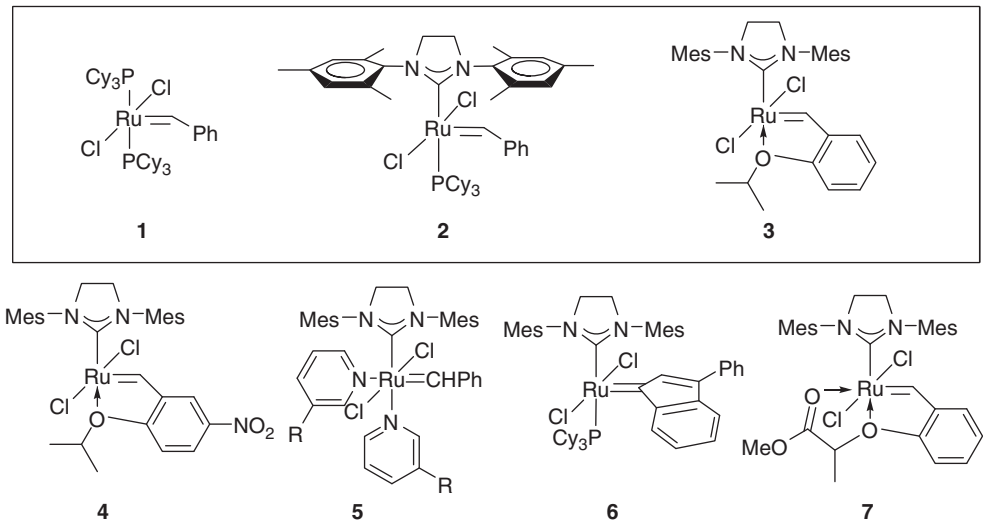
EYM is used in diverse synthetic applications. The intermolecular EYM between alkenes and alkynes produces acyclic dienes. The EYM is also used to create rings. The simple RCM of an enyne produces a diene that is contained in the newly formed ring. This version of EYM has seen applications to the widest variety of complex small molecules in organic synthesis. These applications have progressed to more complex cascading processes, where multiple rings are formed in a metathesis cascade. A number of excellent review articles have appeared.[1–4] Mechanistic aspects of the EYM will be discussed before the synthetic examples.

5.27.1.1 Catalyst Overview

The development of EYM has paralleled improvements in well-defined ruthenium carbene catalysts. Katz and Sivavec showed the catalytic effectiveness of RCEYM in 1985.[5] However, the use of early transition metal carbene complexes limited the reaction's effectiveness and scope of application. After a decade, Mori's group applied the metathesis to challenging nitrogen heterocycle synthesis.[6–8] However, the real breakthrough came from alkene metathesis when the Grubbs group reported a well-defined, group VIII ruthenium carbene complex.[9] This led to a number of applications by Grubbs and Fu, which captured the attention of the synthetic community (ruthenium,[10] molybdenum[11]). Having already investigated catalytic enyne metathesis, the Mori's group revisited the problem using the ruthenium carbene complex and found an excellent reactivity in enyne metathesis.[12] Mori and

coworkers followed this work with additional studies using ethylene, which have helped advance enyne metathesis in the synthetic community.[13–15]

Much of the recent work in metathesis has gravitated toward the use of the second-generation Grubbs carbene complex **2** (Scheme 2). During the past several years, synthetic chemists have embraced the Grubbs catalyst because of its availability, bench stability, improved reactivity, and chemoselectivity for alkenes and alkynes. The Grubbs catalysts are extremely easy to use. Chemoselectivity is also called functional group tolerance. The evolution of catalysts from gloveboxes to the benchtop has made metathesis a standard tool in the synthetic chemist's arsenal. Due to ease of use and catalyst availability, the use of metathesis in a synthetic plan has become very easy. This has facilitated exploratory chemistry and adventurous synthetic pursuits. Moreover, it can partly explain the explosion in metathesis applications and the widespread use of the Grubbs catalyst. The widely accepted utility of this catalytic carbon–carbon bond formation led to recognition of the groundbreaking work and leadership from Grubbs,[16] Schrock,[17] and Chauvin,[18] who were awarded the Nobel Prize in Chemistry in 2005.



Scheme 2 The Grubbs family of ruthenium carbenes used in metathesis.

Although the Grubbs catalysts **1** and **2** are primarily used in EYM, several new carbene complexes have seen increased use. New carbenes are continually being developed for challenging applications in alkene metathesis, to give improved stereoselectivity and for asymmetric applications. The bisphosphine complex **1** is called the first-generation Grubbs complex.[19,20] Carbene complex **2** is known as the Grubbs second-generation complex. Ruthenium carbene complex **2** bears a single *N*-heterocyclic carbene (NHC) ligand, reported by the Grubbs group in a highly cited 1999 paper.[21] The ruthenium complex containing the unsaturated NHC ligand, IMes, is the Nolan catalyst.[22,23] The replacement of a tricyclohexylphosphine ligand with a coordinating ether in the arylidene ligand was developed by Hoveyda and coworkers. With the saturated NHC ligand, dihydroIMes, the chelated complex **3** is known as the Hoveyda–Blechert complex, as it was independently developed by the Hoveyda[24,25] and Blechert research groups[26] (the catalyst is also sometimes called the Hoveyda–Grubbs complex). The electron-poor complex **4** is the Grela complex,[27] which has a more weakly coordinated ether and, like the Hoveyda–Blechert complex, is phosphine-free. The Grela complex also falls into the Hoveyda–Blechert family, and a new bidentate complex **7** has also been employed for enyne RCEYM. The indenylidene catalyst **6**, sometimes called the Umicore catalyst, has also been used for EYM with performance comparable to that of the Grubbs complex **2**.[28–30] In catalysis, activity refers to a combination of catalyst attributes including favorable initiation rates and long propagation lifetime (catalyst longevity). Though the phosphine-free initiators are more active, they are not necessary for most applications. Typically, these phosphine-free catalysts are reserved for cases where catalyst longevity at higher temperatures is desired, or in cases involving less reactive alkenes such as enones or enoate esters. The pyridine adduct **5** is known as the Grubbs pyridine solvate.[31] All of these complexes derive their lineage from the first well-defined ruthenium carbene discovered by the Grubbs group in 1993,[9] the ground breaking discovery that opened the door to this entire family of ruthenium carbene catalysts. As of this writing, the second-generation Grubbs carbene **2** and the Hoveyda–Blechert complex are the most widely used catalysts for EYM. New catalysts continue to be developed and this assessment is merely a static snapshot of an evolving and active research area in catalyst development (in the fields of both alkene and EYM).

5.27.1.2 General Considerations

The Grubbs-type complexes **1**, **2**, **3**, **4**, and **6** are commercially available and easy to use. The carbene complexes are not hygroscopic and can be weighed in the air under normal laboratory conditions. The shelf-life of the complexes is quite good and

they can be stored for extended periods in a darkened cabinet under nominal atmospheric conditions. Purification of commercial lots is generally not necessary and not recommended. Some carbene complexes can be purified by column chromatography with varying material losses; the second-generation carbene can be purified this way, but substantial loss of material occurs. The Hoveyda–Blechert chelated complexes are generally easy to purify by column chromatography on silica gel with good mass recovery.[24] Usually purification is needed only if degradation is observed by ^{1}H or ^{31}P NMR spectroscopy. The Grubbs first-generation carbene **1** gives a diagnostic proton signal at δ 20.02 ppm (CD_2Cl_2) and a single ^{31}P resonance at δ 36.61 ppm (CD_2Cl_2).[19] The second-generation Grubbs carbene **2** gives a diagnostic proton signal at δ 19.16 ppm (CD_2Cl_2) and a single ^{31}P resonance at δ 31.41 ppm (CD_2Cl_2).[21] The Hoveyda–Blechert carbene **3** gives a diagnostic proton signal at δ 16.56 ppm ($CDCl_3$) and has no phosphorus nucleus.[24]

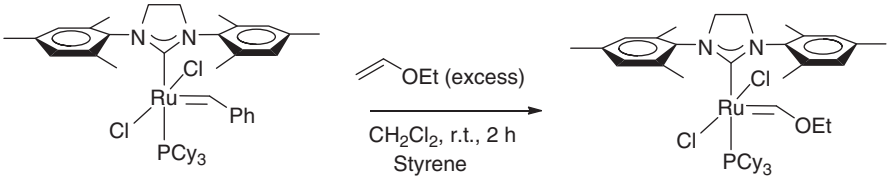
Metathesis can be performed in a wide variety of solvents. The most common solvents are dichloromethane, benzene, and toluene. Alkene metathesis initiation studies have shown that catalyst **2** reacts effectively in CH_2Cl_2, benzene, toluene, and tetrahydrofuran (THF).[32] Due to the greater thermal stability of carbene complex **1**, higher boiling solvents such as benzene and toluene are commonly employed. Solvents such as ether, THF, and 1,2-dimethoxyethane (DME) have seen little use in metathesis. Interestingly, though THF is not commonly used, it is a good solvent for *Z*-selective alkene cross-metathesis.[33–35] Carbene complex **2** has poor solubility in methanol and water. In the best cases, metatheses can be performed in degassed, commercially available solvents.

Alkene concentrations vary depending on the molecularity of the application. Typical RCM or RCEYM employ high dilution (1–20 mM) of diene or enyne. In the intermolecular or cross-EYM (CEYM), the alkene is used in molar excess (3–6 equivalents) and the concentrations as high as 1 M are not unprecedented. The mechanistic studies show that alkene concentration is important in the rate-determining step of one carbene complex, the commonly used second-generation complex **2**. Cross-metathesis typically uses 0.02–0.1 M alkyne as the limiting reagent. An ethylene additive is sometimes used with catalyst **1** in promotion of RCM of 1,*n*-enynes. Ethylene is not commonly used in cross-metathesis applications due to the possible formation of ethylene–alkene cross-metathesis products. When used, ethylene delivery is not always specified. Typically, an ethylene atmosphere is achieved with an ethylene-filled balloon.

5.27.1.3 Quench and Removal of Ruthenium

At the end of a metathesis reaction, the ruthenium carbene activity must be quenched and the residual metal must be removed from the isolated organic product. In most cases, the ruthenium carbene catalyst is used at a loading between 2 and 10 mol%. In some of the earlier applications with catalyst **1**, no quench method was necessary because the catalyst decomposed during the reaction. Similarly, sampling the recent literature shows that quenching methods are not always used. Since the newest Grubbs carbenes are particularly robust, quenching is highly recommended. Many metatheses catalyzed by **2** occur quickly, and due to the thermal stability of the carbene complex, active metal carbenes derived from **2** remain at the end of the organic reaction. Longer reactions or those conducted under heating will decompose the metal carbenes to metathesis-inactive ruthenium-containing species. Thus, the purification procedure must successfully remove different forms of the metal, both carbenic and noncarbenic Ru(II) species. Because of the many ruthenium species present, a removal procedure must inactivate the metathesis-active intermediates and convert the remaining nonmetathesis reactive metal species into those that are readily removed.

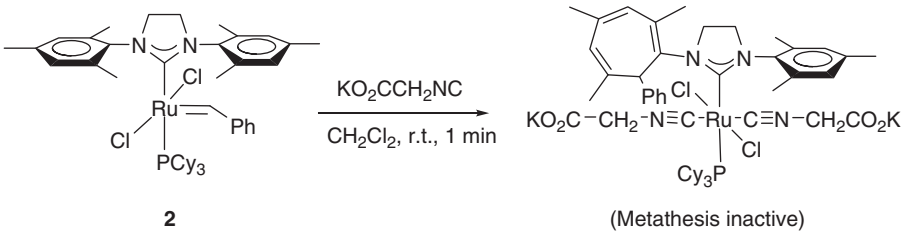
Quenching carbenes does not necessarily aid in the removal of ruthenium from the organic products. By far the most common way to stop a metathesis reaction is to add an enol ether such as ethyl vinyl ether after the limiting reactant has been consumed. This requires a brief period of heating to convert the remaining metathesis-active alkylidenes into stable Fischer carbenes which are not cross-metathesis active[36,37] (equation 1). Although this procedure is effective for stopping EYM, it does not aid in the removal of all the ruthenium by-products. A decomposed form of ruthenium(II) that is no longer a metal carbene is incapable of reacting with the enol ether.



2 93% (1)

Though there are many methods to remove ruthenium, there are two that are widely used and recommended. Often a crude metathesis reaction has a lingering yellow color associated with residual ruthenium. A mild oxidative procedure was reported by Georg et al.[38] using either DMSO or $O{=}PPh_3$ as an oxygen transfer agent. This is an attractive method due to its simplicity and mildness. Though the mechanism is not known, the oxidant is thought to convert the metal species into polar oxides that can be removed during column chromatography. The Georg procedure is an effective way to remove the yellow color associated with ruthenium residue in the crude sample. The main disadvantage of this procedure is that it is very slow: Oxidation requires 12–24 h to fully convert the ruthenium into polar species. Nonetheless, the mildness and simplicity have led to the wide use of this procedure.

A polar isocyanide procedure is dually effective in both quenching the carbene activity and removing the ruthenium (equation 2). The main advantage of the procedure is its very rapid reaction rate (1 min is typical), and the use of small amounts of isocyanide KO_2CCH_2NC (40–50 mol%) and that it results in a demonstrated 'quench' of carbenic activity for a wide variety of Grubbs carbenes.[39] The 'quench' destroys metathesis activity completely and arrests any further metathetic processes. The quench of carbene activity is accomplished by transferring the carbene into one of the aromatic rings of the NHC ligand (e.g., in complex **2**)[39,40]: an intramolecular Buchner cyclopropanation, which is followed by a norcaradiene-to-cycloheptatriene rearrangement. Catalysts bearing NHC ligands are the most active and are currently the most commonly used catalysts in organic synthesis applications. However, it should be noted that the first-generation Grubbs complex **2** also undergoes an effective quench and is itself transformed into a polar, removable Ru(II) complex, albeit by a distinct pathway.[41] After the isocyanide-promoted Buchner insertion, a simple plug filtration (silica gel) or a column chromatography step removes the polar – and metathesis-inactive–ruthenium isocyanide complex.

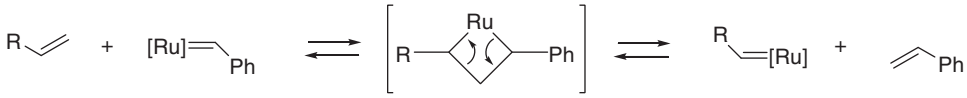


2 (2)

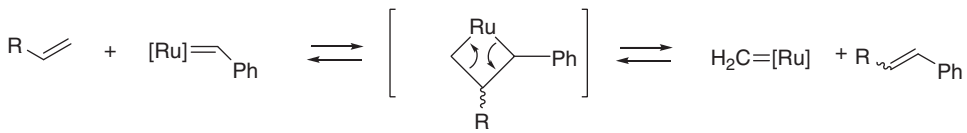
5.27.2 Mechanism of EYM

The EYM mechanism began as a source of controversy, but detailed mechanistic studies developed into a generally accepted mechanism. The confusion had been complicated by many factors: the use of different carbene catalysts (e.g., of different generations), differing reactivity of alkenes (e.g., 1-hexene vs. acrolein), 'borrowing' intermediates from alkene metathesis, the difficulty in differentiating mechanisms experimentally, and the propensity of any new synthetic application to ascribe a mechanism without decisive mechanistic experiments. (These problems arise partly due to the cross-fertilization of the literature from mechanistic organometallic chemistry to synthetic organic chemistry and partly from the pace at which new reactions can be synthetically exploited and published as compared with mechanistic studies. Mechanistic studies are usually much slower to performed.) Mostly these concerns have been dispelled; however with certain combinations of alkene and alkyne reactants, the mechanism may vary. With certain catalysts, the rate-determining steps may be different. Before a detailed catalytic cycle is presented, the authors will briefly discuss fundamental carbene pathways and the relationship to alkene metathesis (for the catalytic cycle, see Scheme 4 *vide infra*).

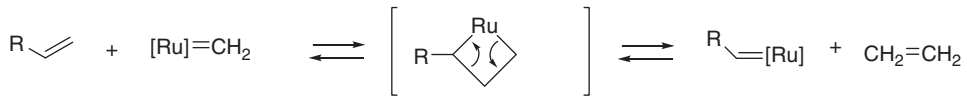
EYM is a catalytic process involving ruthenium carbene intermediates. Of course, ruthenium carbenes are well known to be reactive intermediates in alkene metathesis. From alkene metathesis, the benzylidene initiates with an added 1-alkene. Fundamentally, the metal carbene catalyst undergoes cycloaddition with the alkene in two different ways. This process may occur with regiochemistry indicated in equations 3–5.



(3)



(4)



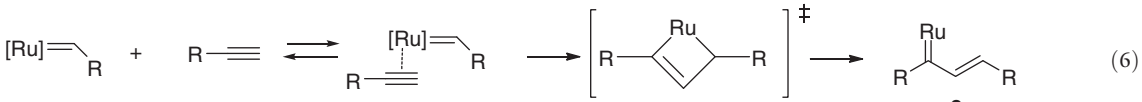
(5)

The pathway in equation 3 is called transalkylidenation, a process that transforms one alkylidene ligand (or in this case a benzylidene) into another alkylidene ligand. An alkylidene is the organic fragment of a metal carbene. This is the initiation step in alkene metathesis; the equilibrium lies to the right when the alkene is in excess of the catalyst, and in many cases styrene is the more stable alkene. This fundamental process generates the needed alkylidene that is required for cross-metathesis. Alternatively, the alkene may react with the opposite regiochemistry in a process that leads to alkene cross-metathesis (equation 4). In this case, the intermediate ruthenacyclobutane has 1,2-disubstitution. Retrograde [2 + 2] extrudes a 1,2-disubstituted alkene and a

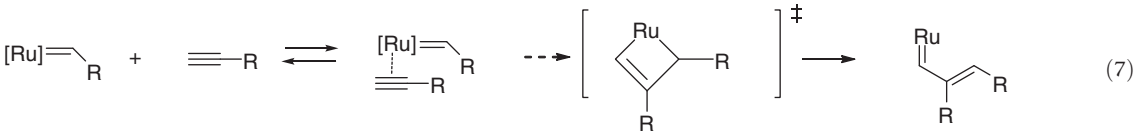
$Ru{=}CH_2$ species. Of these two pathways, the initiation step is faster than cross metathesis. Transalkylidenation of equation 3 is favored due to the lower energy 1,3-disposition of substituents on the metallacyle intermediate of equation 3. The cross-metathesis pathway is slower because the 1,2-disubstituted ruthenacyclobutane intermediate is higher in energy. These intermediates are relevant to the high-energy ruthenacycles encountered in EYM.

In terms of alkene metathesis, the methylidene plays an important catalytic role. Productive alkene cross-metathesis must follow the regiochemistry of equation 4 to give a 1,2-disubstituted alkene product. The methylidene is formed after a cross-metathesis, exemplified by the reaction of equation 4. The methylidene product of equation 4 is a reactive species that propagates catalysis. Subsequent transalkylidenation with excess 1-alkene ultimately releases ethylene (equation 5). Excess alkene and loss of ethylene help drive the equilibrium of equation 4 forward (to the right side). As it does, it regenerates the alkylidene, the reactive metal carbene intermediate that is needed for the next catalytic turnover.

The metallacycle reactive intermediates in EYM resemble those in alkene metathesis, but they are higher in energy. In fact, density functional theory (DFT) calculations suggest that ruthenacyclobutenes are actually transition states.[42] To access metallacyclobutenes, the metal carbene undergoes $2\pi + 2\pi$ cycloaddition with the alkyne. As in the case of metal carbene cycloadditions with 1-alkene, this reaction can follow two different pathways that differ in regiochemistry (equations 6–7). Alkyne binding occurs by ligand exchange with the tricyclohexylphosphine ligand (note that the Cy_3P ligand is omitted for clarity in the equations). The resulting η^2 complex reorganizes via the ruthenacyclobutene to give a vinyl carbene **8**. As in the above examples, the alkyl groups can be either 1,3- or 1,2-substituted on the ring. Though alkyne binding is more favorable than alkene binding, the high energy of the ruthenacyclobutene transition states allow preequilibrium events such as ligand exchange and metal carbene exchange reactions. Metal carbene exchange reactions such as initiation and transalkylidenation are described in equations 3–5. Because the alkene is typically in molar excess, formation of the alkylidene tends to be dominated by equations 3 and 5, and this populates the alkylidene 'resting state.' This sets the stage for an alkylidene-first mechanism. (When the alkene is ethylene, the reaction proceeds through the $Ru{=}CH_2$ intermediate. The Grubbs benzylidene carbene complexes form the $Ru{=}CH_2$ intermediate when exposed to ethylene. The methylene species is highly reactive and not selective. In the second-generation Grubbs carbene, it becomes kinetically deactivated by coordination to tricyclohexylphosphine. Higher ethylene concentrations may help protect the reactive carbene from kinetic deactivation by phosphine coordination.)



(6)

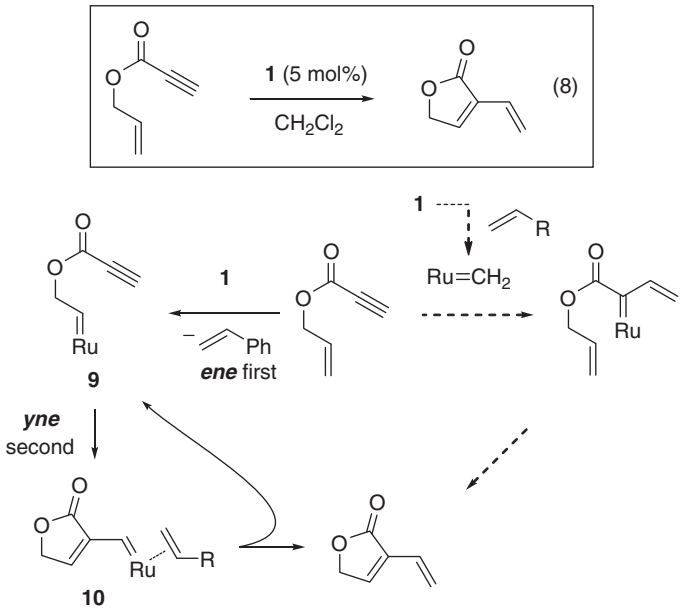


(7)

Current mechanistic and kinetic evidence points to an alkylidene-first mechanism. Mechanistic studies were done because of inconsistencies in the literature, partly due to mechanistic assertions in the synthetic literature and the fact that different catalysts were being used. The mechanistic controversy surrounded the question as to which occurs first – reaction of the metal carbene with the alkene or alkyne. Though alkene reactivity varies considerably, it is generally believed that the Grubbs initiator reacts with the alkene first to produce an alkylidene. The alkylidene is the reactive intermediate that reacts with the alkyne. (Some of the confusion is due to a reasonable assumption that a terminal alkyne should bind better to the Grubbs benzylidene complex such that the alkyne should react first. The alkyne does bind better in preequilibrium,[43] but reorganization via ruthenacyclobutene intermediates is a higher energy process than transalkylidenation via 1,3-disubstituted ruthenacyclobutanes. It is a Curtin–Hammett scenario where facile alkyne binding does not dictate alkyne insertion.)[43] Reaction with the alkene is called the 'alkylidene-first' mechanism; it is rooted in the transalkylidenation of alkene metathesis. The metal alkylidene reacts with a 1-alkyne via the regiochemistry of equation 6. This mechanistic scenario is to be differentiated from the alkyne-first mechanism where a ruthenium methylidene (methylene) is the reactive metal carbene intermediate, and reacts with the alkyne with the opposite regiochemistry. (In some cases, ene–yne cross-metathesis does begin by reaction with an alkyne in cases where the alkene may be particularly unreactive. For instance, alkynes can react exclusively with the initiator in a oligomerization reaction).[44,45]

Early mechanistic studies of RCEYM suggested an 'alkylidene-first' reaction mechanism based on NMR studies. In RCM depicted in equation 8, Hoye recognized that there were two possibilities: reaction of $[Ru]{=}CH_2$ with the alkyne directly or initial transalkylidenation to generate an alkylidene **9** (**Scheme 3**).[46] These two possibilities invoke different metal carbenes as reactive species and suggest an order of reactivity. The reaction of $Ru{=}CH_2$ with the alkyne is called the methylidene-first pathway. The initiation of the alkene moiety with the Grubbs catalyst gives rise to an alkylidene; since the alkylidene forms first, it is called the alkylidene-first mechanism. The difference distills down to what metal carbene is reacting with the alkyne.

If the ene-then-yne pathway is followed, it was predicted that vinyl carbene intermediate **10** should accumulate. ^1H NMR experiments showed the buildup of an alkylidene concomitant with initiation by the Grubbs benzylidene **1**, as evidenced by the



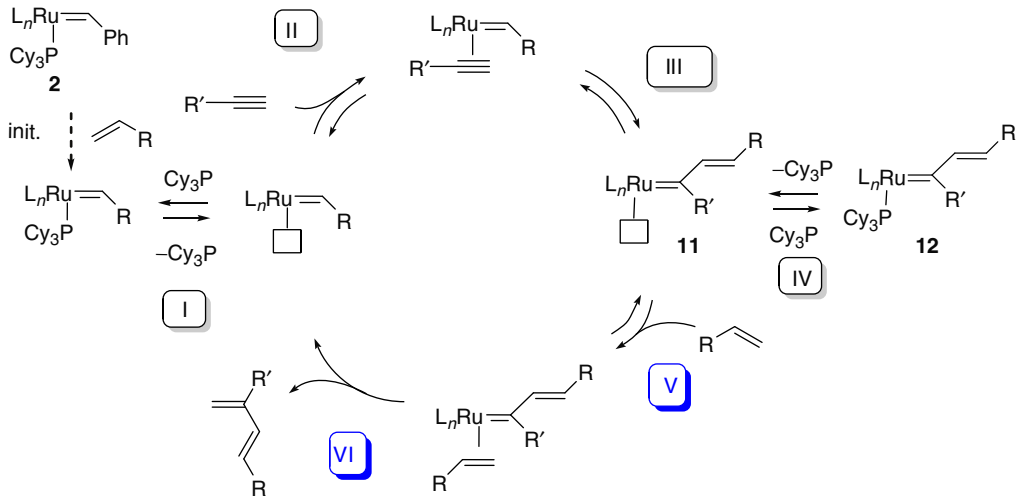
Scheme 3 Alkylidenation-first mechanism in a bifunctional enyne substrate (RCEYM).[46]

loss of the benzylidene CH signal and the production of styrene. Styrene could only be formed if the Grubbs catalyst reacted with the alkene present in the bifunctional substrate. In the last critical step, the alkene reacts with the vinyl carbene to generate the product and more alkylidene, which continues in catalysis. Hoye and Vos refer to this as an 'ene-then-yne' pathway; this terminology is widely used in the literature for describing the mechanism of RCEYM. Similarly, using carbene **2** in an RCEYM, Kozmin et al. suggested that an 'alkylidene-first' mechanism was operative.[47] These authors examined the reactivity of each unsaturated fragment of the enyne and found that the alkene reacted to give the corresponding alkylidene, whereas the alkyne did not react. These two studies suggested that alkylidenes formed faster than the reaction rate between [Ru]=CH_2 and alkynes. These studies were performed with the first- and second-generation Grubbs carbene complex and arrived at the same conclusion in support of an alkylidene-first mechanism. This is presumed to be the basic mechanism, with perturbations depending on the relative reactivity of the unsaturated reactants.

An accepted mechanism has emerged based on mechanistic investigations and kinetic studies of the reaction mechanism (Scheme 4). Direct mechanistic evidence of the EYM is derived from kinetic analysis using the second-generation Grubbs catalyst **2**. Zero-order dependence on the alkyne concentration indicates that the alkyne is not involved in the rate-determining step. First-order dependence was found for both the ruthenium complex and the terminal alkene. This kinetic evidence suggested that either step V or step VI was the rate-determining step (alkene binding or metallacycle formation/collapse). Based on DFT calculations, Lippstreu and Straub suggested that the cycloreversion step VI is rate limiting,[42] which is consistent with experimental kinetic data. Supporting evidence for the alkylidene-first mechanism was presented above and is supported by another critical study of the regiochemistry of vinyl carbene reactions with styrenes.[49] The mechanism shown in Scheme 4 is based on this kinetic study. The kinetic study was performed on a limited set of alkyne and alkene substrates, and a large excess of the alkene was employed for pseudo-order conditions. These conditions resemble those normally used for intermolecular EYM. Typically the alkene is used in molar excess, but not always.[50]

A modest increase in propargylic substitution gave faster reaction rates. An increase in steric bulk resulted in faster reaction for propargylic benzoates. To test whether chelation by oxygen atoms located in the propargylic position was inhibiting the reaction rate, the corresponding hydrocarbons were examined, devoid of oxygen functionality. In comparison with their lower hydrocarbon analogs, it was found that secondary substitution at the propargylic center resulted in faster reaction rate than a primary carbon chain. Alkynes with the same propargyl substitution reacted with similar rates. In contrast, tertiary substitution at the propargylic site resulted in diminished reaction rates. With the second-generation Grubbs catalyst, there is not a chelation effect for ester functionality located at the propargylic position.

The resting state at the vinyl carbene intermediate explains the effect of propargyl substitution on reaction rate. The mechanistic picture brings into focus the partitioning of the 14-electron vinyl carbene intermediate **11**. Greater substitution at the propargylic position may increase the rate of catalysis by destabilizing unproductive resting state **12**. Substitution of **12** at the site labeled R′ in Scheme 4 might destabilize the phosphine complex, increasing the concentration of the vinyl carbene **11**. With EYM promoted by phosphine-free catalysts like the Hoveyda–Blechert complex, there is no phosphine-bound resting state that may partly explain their high activity once initiated. However, phosphine-bound resting states can also protect the highly reactive intermediate **11** when alkene concentration is low (e.g., near the end of the reaction). Thus, a subtle balance is needed for a good

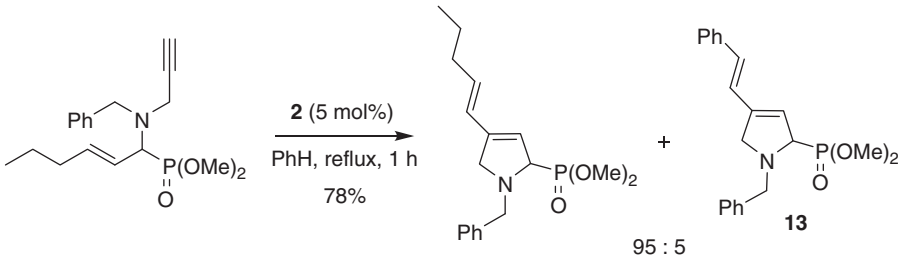


Scheme 4 Mechanism for intermolecular enyne metathesis based on kinetic studies.[48]

catalyst – high activity but protection from decomposition. Since decomposition pathways are only partly understood, the optimal structural features of a superior catalyst are not completely clear.

Which catalyst is used and under what reaction conditions can result in a change in the rate-determining step or divert the EYM to another pathway. For example, different kinetic orders for reactants and catalysts were found for the first-generation Grubbs complex.[51] Although this does not change the sequence of events of the catalytic mechanism, it shows that the rate-determining step can change. This is governed by the 'resting state' of the catalyst and the intrinsic barriers of the fundamental processes. One of the most rapid areas of growth has been in catalyst development. In recent years, there has been an increased use of the Hoveyda–Blechert 'phosphine-free' catalyst, largely due to its thermally robust nature. The higher reactivity of the catalysts can lead to alkyne oligomerization either at low alkene concentrations or with alkenes that are not very reactive with the Grubbs complex.[45] (This can be gauged from inspection of the Grubbs selectivity model for alkene metathesis. The less reactive alkenes are in the type III and type IV family. With these less reactive alkenes, one may expect greater competition from alkyne oligomerization reactions, similar to what one observes with the traditional Schrock catalyst.) In other words, the effectiveness of EYM is determined by a balance of reactivity between the alkene and the alkyne.

In RCEYM, the general reactivity appears to be ene-then-yne by an alkylidene-first mechanism. However, with less reactive alkenes, the timing may switch leading to an yne-then-ene pathway. One case that appears to react at the alkyne-first is shown in equation 9.[52] In this case, the alkene is internal and substituted with an allylic heteroatom, which suggests that its reactivity will be diminished considerably compared with 1-hexene. In addition to the expected RCEYM product, a new product **13** was obtained. The styrene-transfer product **13** in equation 9 supports the viability of the alkyne-first pathway because the Grubbs benzylidene catalyst **2** gave alkyne insertion followed by RCEYM. This initiation step would furnish a Ru=CHC$_3$H$_7$ species that would propagate catalysis. Importantly, it reveals that intermolecular reactions are kinetically feasible compared with alkene initiation and intramolecular ring closing onto the pendant alkyne, which is understood as the 'normal' or most common pathway. The latter pathway is thought to dominate in RCEYM. This example points out that more challenging bifunctional substrates, which possess unsaturated functionality of vastly different reactivity, may diverge from the normal processes.



(9)

It is difficult to reliably (or quantitatively) predict alkene versus alkyne reactivity. Though the example in equation 9 is not too surprising given the alkene's steric and electronic properties, a reactivity model is lacking to predict the outcome in more complex cases. In equation 9, which reacts first is not a major concern as long as the RCEYM provides the expected product. In Section 5.27.7, the site selectivity for initiation on a dienyne is controlled by relative alkene reactivity, which directly influences the ring sizes formed. More importantly, as reactivity is retarded on each unsaturated component, a complete loss of enyne metathesis reactivity will be observed, which neither higher temperatures nor higher catalyst loadings will remedy. Less reactive unsaturated

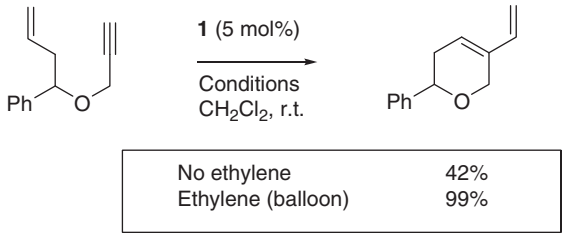
functionality will be encountered increasingly as chemists wish to push the reaction into more challenging cases or those with an increased number of electron-withdrawing groups. What is still missing in ene–yne or enyne metathesis is a predictive model of alkyne versus alkene reactivity. In the next few years, hopefully a model will emerge from the current body of literature and guide future applications.

The mechanism of EYM commonly follows an alkylidene-first pathway that defines the order of reactivity as ene-then-yne. For reactions catalyzed by **2**, the rate-determining step involves alkene association such that higher alkene concentrations (or molar excesses) contribute to a productive EYM. Importantly, the alkene concentration and the intrinsic reactivity of the alkene are important determinants of 'manifold selectivity': maintaining the catalytic EYM over competing reactions such as alkyne oligomerization. This helps explain the beneficial role of ethylene. The role of ethylene in promoting RCEYM under Mori's conditions is a combination of mode selectivity, stabilization of reactive intermediates with respect to decomposition, and more favorable turnover of the vinyl carbene intermediate.

Continued discussion of the mechanism of RCEYM will follow in the next section describing the role of ethylene. The observations related to the ethylene effect are directly relevant to the mechanism of the intramolecular enyne metathesis.

5.27.2.1 Role of Ethylene in Ring-Closing Enyne Metathesis (Mori's Conditions)

The helpful effect of ethylene on RCM of 1,ω-enynes is known as 'Mori's conditions.'[14] Ethylene exerts a subtle effect because it does not seem to appear in the products. Ethylene is not necessary for 'atom economy' since the alkene of the enyne is able to contribute both the alkylidene and methylene moieties in the metathetical union with alkyne. For example, RCM of a simple enyne gave low yield under inert atmosphere, but under an atmosphere of ethylene (an ethylene balloon) a high yield was obtained (equation 10). The exact role played by ethylene is probably the combination of stabilization of reactive intermediates, acceleration of catalyst turnover, and interdiction of alkyne oligomerization pathways. Catalyst turnover can be accelerated at higher alkene concentration. The importance of alkene concentration had been noted in earlier studies by Hoye[46] and Lee,[53] and a mechanistic and kinetic explanation offered by Diver and Keister.[48] Because enyne metathesis is dependent on alkene concentration and proceeds best with molar excess of alkene, it proves useful to provide an 'auxiliary alkene' such as ethylene, especially where higher enyne concentrations cannot be used for fear of enyne oligomerization/polymerization.



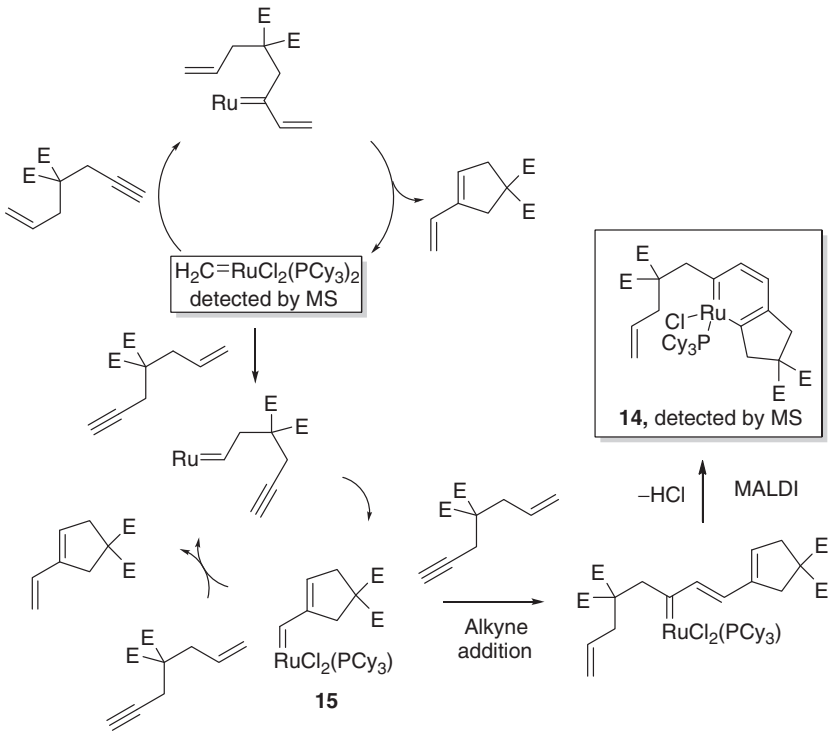
(10)

The ethylene effect is primarily due to the need for higher concentrations of alkene to maintain catalysis. The sagely study by Hoye clearly showed that alkene concentration was critical for the success of an RCEYM. The authors found that increased enyne concentration (0.1 mol l^{-1}) gave an efficient RCM.[46] This is counterintuitive since high dilution is employed in bifunctional substrates to encourage ring closure and to limit oligomerization. This is the first example showing that solution concentration of the enyne affects the 'rate' of RCEYM.

The role of ethylene in RCEYM has been addressed in mechanistic and kinetic studies. Due to the uncertainty regarding the role of ethylene, a detailed study was needed. First, an elegant mechanistic study was conducted by Lloyd-Jones.[54] In this investigation, the authors showed that ^{13}C-labeled ethylene produced vinyl carbene turnover, showing that ethylene turns over the vinyl carbene by what the authors termed a 'second cycle,' via reaction with the auxiliary alkene, ethylene. In other words, ethylene assists the turnover of the intermediate vinyl carbene (see **Scheme 3**, where R=CH_2). This is consistent with the concentration effect observation by Hoye and Vos[46] and the mechanistic proposal by Diver et al. in CEYM with ethylene speeding up the turnover step.[55]

Further insight into the ethylene effect has been provided by observations made using matrix-assisted laser desorption/ionization (MALDI) mass spectral analysis under inert atmosphere conditions.[44] Fogg and coworkers had developed mass spectral analysis as a tool for studying intermediates and decomposition products of ruthenium carbenes relevant to metathesis. The RCEYM of the malonate shown in **Scheme 5** was considered in terms of both the ene-then-yne and the yne-then-ene pathway. The RCM was investigated under nitrogen or ethylene. Under an ethylene atmosphere, a Ru=CH_2 resting state was detected by MALDI MS analysis. (The authors suggest that this is due to initiation with the alkene end of the enyne. The high molar concentration of ethylene populated the Ru=CH_2 species. Note that these mass spectral data were observed with the first-generation Grubbs catalyst **1**.) Under nitrogen, a decomposition species was found which had incorporated two molecules of enyne substrate **14**. At longer reaction times, a molecular ion was observed consistent with six enynes having reacted with the ruthenium carbene. The dimer and oligomer observed under nitrogen (in the absence of ethylene) are suggestive of alkyne oligomerization through a vinyl carbene intermediate.

This study sheds further light on the role of ethylene because it limits intermolecular pathways. It was recognized that vinyl carbene reactions may proceed with alkene through RCEYM (intramolecular) or with alkyne by an intermolecular process. The reaction with an alkyne can repeat itself giving rise to higher molecular weight species. This helps explain the low mass recoveries

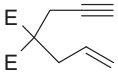
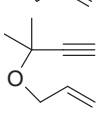
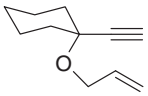


Scheme 5 Evidence of alkyne dimerization/oligomerization pathways in RCEYM.[44]

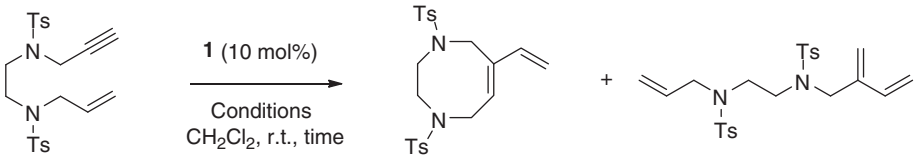
in simple RCEYM reactions without the use of 'Mori's conditions.' In the absence of added ethylene, intermediate **15** prefers to react with additional alkyne subunits of enynes in *inter*molecular EYM. This pathway leads to higher molecular weight products that are intractable and explains the low mass balance observed in these reactions. (Fogg et al.[44] also showed that the oligomerizations are not reversible using the first-generation Grubbs carbene **1**. The observation of higher molecular weight oligomers obtained from alkyne oligomerization provides critical insight into the dichotomy of enyne metathesis versus alkyne oligomerization.) In the presence of ethylene, these pathways are shut down and ethylene assists in turning over vinyl carbenes. This is consistent with previous suggestions.

Increased propargylic substitution results in better mass balance and decreased need for ethylene. Under conditions without ethylene (Table 1), comparison of the first- and the second-generation Grubbs catalyst shows that each is susceptible to alkyne oligomerization (entries 1 and 2).[44] Alkyne oligomerization has been observed in EYM using the Hoveyda–Blechert catalyst.[45] Low conversions were seen after 24 h and remarkably very low yields of dienes were found, suggesting that little conversion to product had occurred. Monosubstitution on the alkyne propargylic position enhanced conversion, but did not appreciably increase the yield (entries 3 and 4). Only disubstitution gives significantly enhanced conversions and yields (entries 5–8). In the more hindered cases, the second-generation Grubbs complexes are needed due to their higher reactivity with sterically hindered substrates.

Table 1 Ring-closing ene–yne metathesis yields vs. propargylic substitution (without ethylene)

Entry		*Catalyst*	*Time (h)*	*Alkyne conversion (%)*	*Diene yield (%)*
1		1	24	33	18
2		2	24	17	3
3		1	–	–	–
4		2	24	42	3
5		1	–	–	–
6		2	20	>99	67
7		1	–	–	–
8		2	20	>99	71

For RCM, the use of ethylene is not always beneficial as it can lead to intermolecular EYM. For example, if ring closure is slow, the competitive ethylene–alkyne cross-metathesis can be expected. Formation of eight-membered rings is particularly difficult. Ring closing under standard inert atmosphere conditions gave a low yield of the RCM product (equation 11); resorting to ethylene atmosphere gave none of the desired ring closure product, but produced solely the ethylene cross-metathesis product, a 2-substituted butadiene (equation 11).[56]



(11)

No ethylene	35%	–
Ethylene (balloon)	–	84%

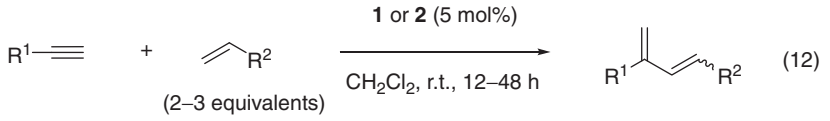
5.27.3 Cross-EYM

Cross-metathesis between alkene and alkyne generates acyclic 1,3-dienes. This carbon–carbon bond coupling can be described as a cross-coupling of alkyne and alkene with π-bond reorganization. These unsaturated reactants do not require preactivation for carbon–carbon bond coupling: They are generally reactive with the ruthenium carbene. The metathesis is thought to initiate from the alkene, so it is critical that the alkene is reactive with the Grubbs ruthenium carbene initiator. The cross-metathesis produces a 1,3-disubstitution pattern on the resulting diene. A limitation of the EYM cross-coupling is the production of *E*/*Z* mixtures in these acyclic reactions. High concentration or molar excess (2–6 equivalents based on alkyne) of the alkene is favored, but it is not absolutely required. When reactivity of each unsaturated reactant is high, it is possible to use equimolar amounts of the alkene and alkyne. Though terminal alkynes are employed most of the time, internal alkynes are sufficiently reactive for cross-metathesis. However, internal alkyne–alkene couplings are plagued with regiochemistry problems and best reserved for reactions with symmetrical alkene/alkyne substrates (see Section 5.27.3.2).

5.27.3.1 Cross-EYM with 1-Alkenes

Simple aliphatic 1-alkenes, used in molar excess, perform best in cross-enyne metathesis with either generation Grubbs complex. Blechert reported the first cross-enyne metathesis using the first-generation Grubbs carbene complex (equation 12).[57] Several terminal alkynes were examined and led to products with a 1,3-disubstitution pattern. A variety of different 1-alkenes were found to participate in the reaction, giving the conjugated 1,3-diene products as *E*/*Z* mixtures (Table 2).

Table 2 Cross-enyne metathesis[57,58]

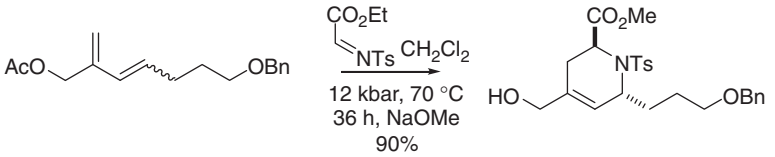


(12)

Entry	*R*^{1}	*R*^{2}	*Catalyst*	*Yield (%)*
1	$BnOCH_2CH_2CH_2$–	$–CH_2SiMe_3$	1	86
2	$BnOCH_2CH_2CH_2$	$–CH_2CH_2CH(CO_2Me)_2$	1	76
3	$BnOCH_2CH_2CH_2$	$–CH_2OTBS$	1	83
4	Cyclohexyl–	$–CH_2SiMe_3$	2	69
5	Me_3Si–	$–CH_2SiMe_3$	2	77
6	$TrOCH_2CH_2$–	$–CH_2SiMe_3$	2	98

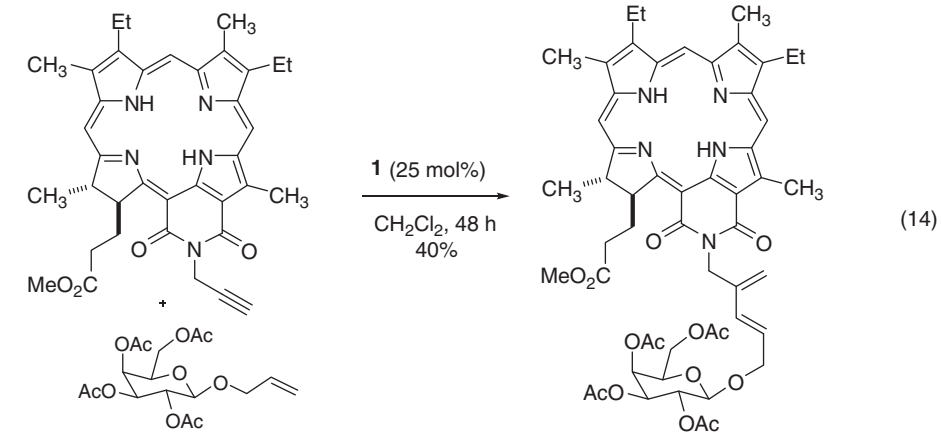
Follow-up studies using the second-generation Grubbs complex showed substantial improvements in propargylic substituted alkynes and trimethylsilyl (TMS) acetylene (entries 4–6).[58] Entries 4 and 5 shown in Table 1 did not give products using the first-generation carbene complex **1**. An *E*/*Z* mixture of stereoisomers in the vicinally disubstituted bond of the 1,3-diene is typical of the intermolecular (ene–yne) metathesis. In some cases, higher *E*-selectivity has been achieved by secondary metathesis[59] or by the use of ethylene additive.[60] The acyclic 1,3-diene products are useful building blocks in ring

construction. Not surprisingly, they give cycloaddition; an example of a high-pressure hetero Diels–Alder reaction is illustrated in equation 13.[61]

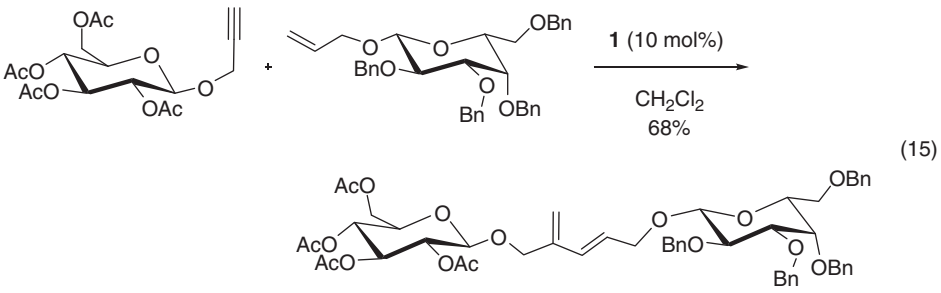


(13)

Fairly complex functional groups can be carried in the alkene or alkyne reactant so long as they are removed from the reacting sites (Scheme 6). For example, a porphyrin attached to the alkyne via a propargylic imide proved to be an effective way to conjugate the *O*-allyl galactoside (equation 14).[62] Similarly, a 1,3-diene-linked disaccharide could be prepared from unsaturated reactants with acetal functionality in the allylic and propargylic positions (equations 14 and 15).[63]



(14)



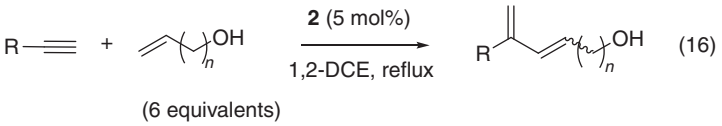
(15)

Scheme 6 Some complex substrates in CEYM.[62,63]

CEYM can be performed with free hydroxyl functionality in the alkene reactant. Though allylic alcohols were found to be problematic in early metathesis studies, they have been found to react efficiently in CEYM (equation 16).[64] Catalyst decomposition to ruthenium hydride species occurs when heating with primary alcohols, so the metathesis had to be accelerated by higher temperature and the use of excess alcohol reactant. These two experimental parameters are the easiest to change, and often the most successful. The CEYM was successful for an assortment of homologous unsaturated alcohols. With respect to the alkyne, oxygen-containing functional groups were tolerated at the propargylic and homopropargylic position (Table 3). Notably, a free hydroxyl group in the alkyne reactant is not permitted in this reaction. The reactions were quenched using the polar isocyanide[39] that assisted in the purification of products.

Under optimized conditions, it is possible to conduct EYM cross-coupling with equimolar amounts of unsaturated reactants. As previously noted, CEYM has typically been done with an excess of the alkene reactant. Since the rate-determining step of CEYM showed alkene dependence, it was understandable that a CEYM should benefit from a molar excess of the alkene. To make CEYM truly 'atom economical,'[65,66] a reactive alkyne would have to be paired with a reactive alkene in equimolar amounts. Diver and Clark found that equimolar amounts of very reactive alkene and alkyne substrates with 10 mol% of catalyst **2** or **3** gave a high-yielding diene synthesis (Table 4).[50] Several alkenes were examined, including a series of protected and unprotected alkenols. Additionally, enantiopure *syn*-allylic alcohols were shown to perform well in the cross-metathesis with branched alkynes. The allylic chiral center was preserved in product **16** which in this case was found to be solely the *E*-isomer. Under atom economy,

Table 3 Allylic alcohols and homologs in cross ene–yne metathesis[64]

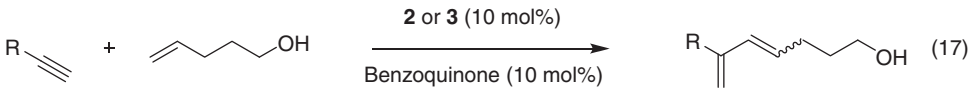


(16)

Entry	*R*	n	*Yield (%)*
1	CH_2OBz	1	74
2	CH_2OBz	2	91
3	CH_2OBz	3	70
4	CH_2OTHP	1	58
5	CH_2CH_2OTBS	2	72
6	$CH_2CH_2N(Ts)Ph$	1	453

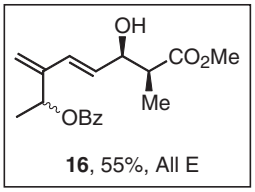
slower cross-metatheses can lead to unwanted by-products arising from 1,5-hydride shift. Benzoquinone was added to suppress an undesirable 1,5-hydride shift in all CEYM cases involving unprotected alkenols. 1,5-Hydride shift was not found in cases where nonalcohol-containing functionalities were present in the alkene.

Table 4 Atom economy in ene–yne metathesis cross-coupling[50]



(17)

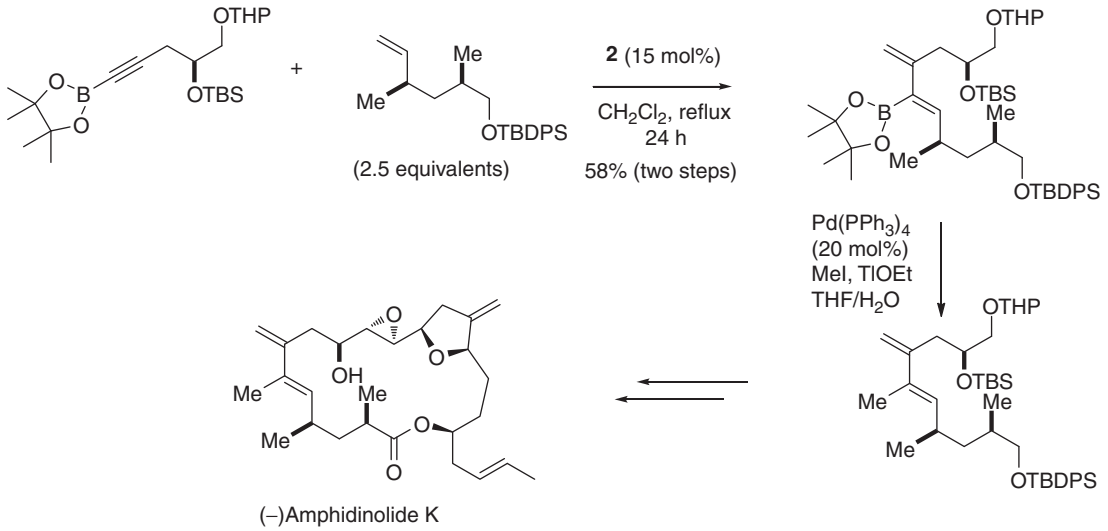
Entry	*R*	E/Z	*Yield (%)*
1	$-CH(OBz)CH_3$	1.8:1.0	90
2	$CH(OAc)CH_2Ph$	1.5:1.0	79
3	$CH_2CH_2CH_2CH_2OTBS$	3:1	68



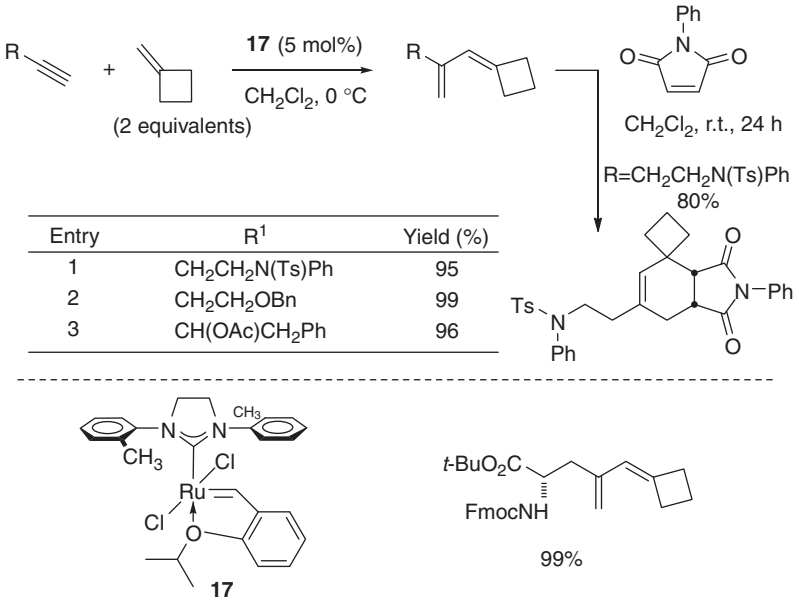
16, 55%, All E

CEYM has been used successfully in the total synthesis of amphidinolide K.[67] The macrocyclic ring of the natural product features a 1,3-diene with trisubstitution on one of the alkene moieties. Though this could be directly accessed by CEYM using an internal alkyne, a mixture of regioisomers was expected. Lee et al. devised a bold solution using a two-step sequence using a boronate to direct the regiochemistry of the EYM step. Starting with a terminal alkyne, the boronate is installed and directly subjected to cross-metathesis with excess alkene, giving a single regioisomer of the product (**Scheme 7**). It is worth noting that the alkene bears secondary allylic substitution and a chiral center; this is rare in CEYM. The boronate was converted to the trisubstituted alkene through Suzuki coupling using MeI. In addition to providing an elegant solution to carbon–carbon bond coupling in the total synthesis, this approach may prove generally useful to access higher substitution on the diene substructure. (The regiochemistry is guided by steric and electronic factors from the alkyne. Sterically, the ligands on the metal avoid the boronate. Electronically, it is unfavorable to place the carbene on the carbon bearing the electropositive boron atom.)

Strain can be used to promote reaction of geminally substituted alkenes with 1-alkynes.[68] Normally, geminal (1,1-disubstituted) alkenes are nonreactive in EYM because they do not initiate with **2** and cannot participate in the alkylidene-first mechanism. According to the alkylidene-first mechanism of enyne metathesis,[44,46–49,51,69] the alkene must be able to react with the Grubbs catalyst. Yet by the Grubbs model,[70] 1,1-disubstituted alkenes are unreactive with the second-generation Grubbs carbene. To overcome this lack of reactivity, ring strain in the alkene can be used to drive the initiation (this principle was used by Grubbs to form geminally substituted ruthenium carbenes)[71] and give CEYM (**Scheme 8**). A variety of initiators were screened for this reaction, with the best reactivity registered by the phosphine-free Hoveyda–Blechert-type catalysts. Interestingly, these reactions could be conducted at low temperatures. Typical CEYM are run at ambient temperature (25 °C); more difficult ones are performed over extended periods in refluxing toluene. The strain relief that drives the cycloaddition with the metal carbene also drives cycloaddition, permitting low-temperature cycloaddition chemistry.



Scheme 7 CEYM in synthesis of Amphidinolide K.[67]



Entry	R^1	Yield (%)
1	$CH_2CH_2N(Ts)Ph$	95
2	CH_2CH_2OBn	99
3	$CH(OAc)CH_2Ph$	96

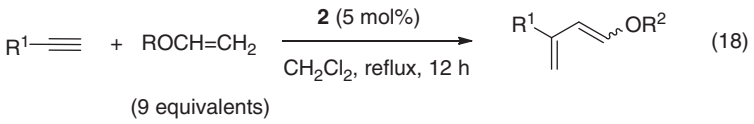
Scheme 8 Strain-assisted EYM (and cycloaddition step).[68]

An important distinction between alkene and EYM is highlighted in the case of enol ethers. Though less reactive than aliphatic alkenes, enol ethers participate in EYM.[37] Enol ethers such as ethyl vinyl ether are commonly used to quench alkene metatheses before isolation of product (equation 1). The resulting ruthenium Fischer carbenes are not sufficiently reactive to give further alkene metathesis. Yet EYM is different than alkene metathesis because it benefits from an enthalpic driving force in forming the conjugated diene products. A critical variable that can be optimized when employing reluctant alkenes is molar excess. The mechanistic study with **2** suggests why this is helpful.[48] Accordingly, a large excess of enol ether gives EYM that is complete in a matter of minutes (equation 18; **Table 5**). Vinylogous ruthenium Fischer carbenes are likely to be intermediates in the reaction. Despite the stability of these intermediate Fischer carbenes, excess alkene helps accelerate catalysis in the turnover step (see Section 5.27.2). A variety of terminal alkynes participate in this transformation, though the reaction proved sensitive to substitution at the propargylic position.

5.27.3.2 Internal Alkynes

Since the earliest examples of enyne metathesis, internal alkynes were shown to have good reactivity.[12] However, the major limitation in their use has been lack of control of regiochemistry. The orientation preference of the metal carbene (metal

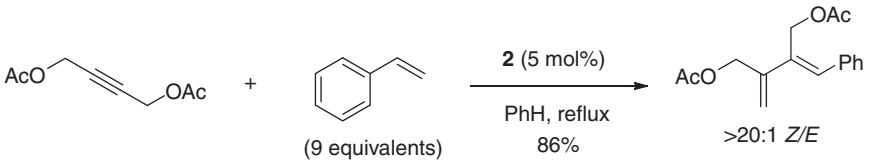
Table 5 Enol ether–alkyne cross-metathesis producing electron-rich 1,3-dienes[37]



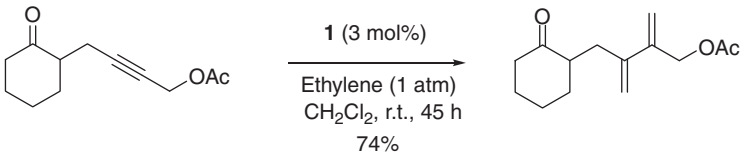
(18)

Entry	R^1	R^2	*Yield (%)*
1	$CH(OAc)CH_2Ph$	Et	88
2	$CH_2OTBDPS$	Et	99
3	$CH(OBz)CH_3$	*n*-Bu	95
4	$CH_2N(Ts)(n\text{-Bu})$	*n*-Bu	92

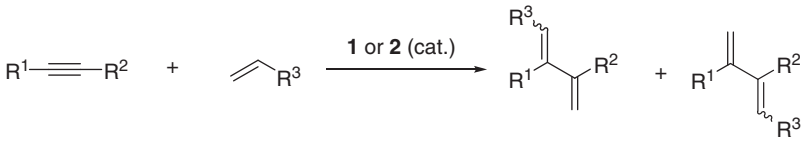
alkylidene) is determined by differential alkyne substitution and stability of the resulting vinyl carbenes. With internal alkynes bearing two different alkyl groups, there is poor distinction between the two ends. Nonetheless, cross-metathesis has been successfully employed with internal alkynes using a symmetrical alkyne[49] (equation 19), a symmetrical alkene[15] (equation 20), or both (not shown). If each of the two components is not symmetrically substituted, then a mixture of regioisomers results (equation 21).



(19)



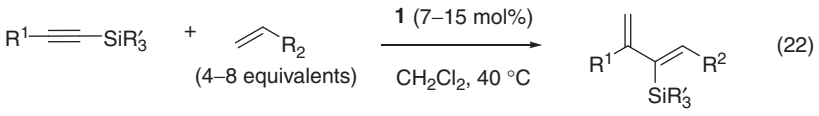
(20)



(21)

A slight steric difference in internal alkyne substitution gives a regioselective EYM. Lee and coworkers developed a regioselective cross-enyne metathesis between TMS-substituted alkynes and a wide variety of 1-alkenes (**Table 6**).[69]

Table 6 Regioselective cross ene–yne metathesis of internal alkynes[69]



(22)

Entry	R^1	R^2	R'_3	*Yield (%)*
1	$AcOCH_2$	CH_2OAc	Me_3	63
2	$AcOCH_2$	$CH_2OC_6H_4CH_3$	Me_3	43
3	$AcOCH_2$	$CH_2CH_2CH_2Br$	Me_3	53
4	$MeOCH_2$	CH_2CH_2OAc	$Ph_2(MeO)$	64

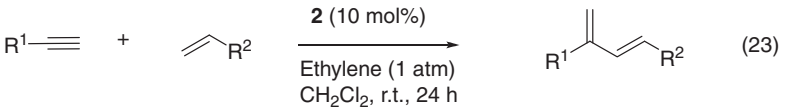
In addition, $(RO)Ph_2Si$-substitution was effectively tolerated on the alkyne. The newly formed bond was produced with high *Z*-selectivity. The origin of the high regio- and stereoselectivity is probably due to an alkylidene-first mechanism, which leads to the preferential formation of one metallacycle intermediate.

5.27.3.3 Ethylene-Assisted CEYM

Ethylene has been used in the CEYM involving higher alkenes. There are two principal reasons justifying its use. First, ethylene may improve the *E*-selectivity. Second, ethylene may allow milder reaction conditions. However, using ethylene must be done with good judgment, for ethylene is itself a reactive alkene and can give ethylene–alkyne cross-metathesis. There are few cases where ethylene can be used with another alkene – in this combination the other alkene should dominate reactions with the Grubbs carbene. (Mori's conditions refer to the use of ethylene in promoting an RCM of a 1,ω-enyne, not ethylene as a reactant in cross-metathesis.)

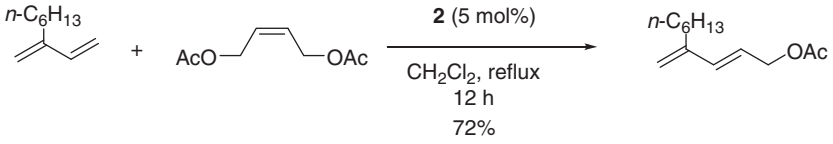
Ethylene as an additive enhances stereoselectivity in cross-metathesis of 1-alkynes with select alkenes.[60] Simple aliphatic alkenes such as 1-hexene give *E*-diene with ethylene present in a closed system (equation 23; **Table 7**). Though a variety of alkenes successfully produce the *E*-diene, some alkenes do not give high selectivity.[59,72] The relationship of alkene reactivity to *E*-selectivity is not completely understood. Though many possible roles of ethylene are imaginable, the most likely explanation for the most *E*-selective examples is the intermediacy of 2-substituted-1,3-butadienes. These would be the product of ethylene cross-metathesis. Grubbs has also described a highly *E*-stereoselective alkene–diene cross-metathesis using 2-substituted-1,3-butadienes.[73] The 2-butadiene starting materials can be accessed by ethylene–alkyne cross-metathesis (equation 24).

Table 7 Stereoselective CEYM[60]



(23)

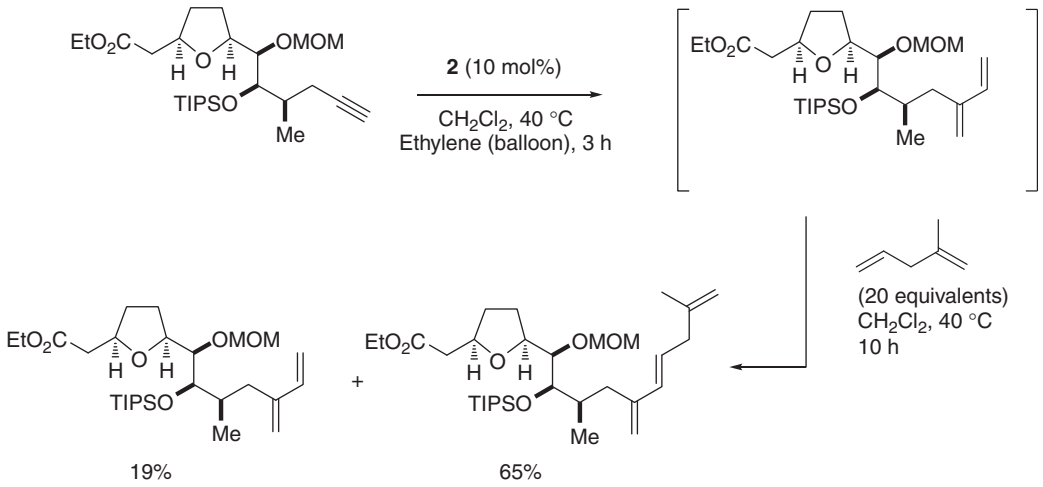
Entry	*R^1*	*R^2*	E/Z	*Yield (%)*
1	$BnOCH_2CH_2$–	*n*-C_4H_9	*E* only	82
2	$TBDPSOCH_2CH_2$	$CH_2CH_2CO_2Et$	>20:1	62
3	$TsOCH_2CH_2$	CH_2CH_2Br	>20:1	64
4	$TsOCH_2$	CH_2O*n*-Bu	3:1	42
5	$AcOCH_2CH_2$	CH_2SiMe_3	1:6:1	86



(24)

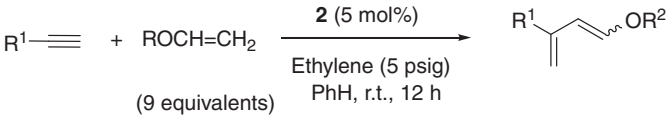
Lee and coworkers synthesized the macrolide amphidinolide E using a CEYM to introduce the C_{19}–C_{26} triene segment of the highly unsaturated natural product isolated from the dinoflagellate *Amphidinium* sp.[74] In the metathesis step, the authors first conducted an ethylene cross-metathesis to give an intermediate butadiene (3 h), the ethylene balloon was removed and a large excess of the skipped 1,4-diene was added and the vial sealed (**Scheme 9**). Because of the two different substitution patterns on each alkene, the less substituted alkene is more reactive and the geminal alkene does not give rise to any cross-metathesis products. Higher stereoselectivity was obtained by conducting the cross-metathesis as a diene–alkene cross-metathesis. Nonetheless, the butadiene is not completely reactive and 19% yield of the ethylene cross-metathesis product was obtained after 24 h. This synthesis stands as an important milestone in the use of stereoselective cross-metathesis in total synthesis.

To improve the effectiveness of enol ether–alkyne cross-metathesis, ethylene was used as a coadditive.[55] Because the enol ether–alkyne cross-metathesis is demanding, these reactions are heated to speed up the ligand exchange processes and accelerate the vinyl carbene turnover step. However, heating results in destruction of the metal carbene and the concomitant formation of ruthenium hydride species.[75,76] Instead of higher temperatures, other means of accelerating the slow catalytic step was desired. An auxiliary alkene, ethylene, was used to speed up the vinyl carbene turnover step, which was presumed to be the slow step of the catalytic cycle. This led to improved reaction scope and resulted in lower reaction temperatures (**Table 8**). Silyl enol ethers could be coaxed to react since the temperatures were lower. Previously, it had been found that heating silyl enol ethers with the Grubbs catalyst gave decomposition to a hydrocarbonyl ruthenium complex.[77] Since lower temperatures can be used with ethylene assistance, this catalyst deactivation pathway can be averted. As a result, the ethylene/enol ether–alkyne 'cometathesis' could be used to generate Danishefsky-type dienes that are extremely useful in thermal and Lewis acid-promoted cycloaddition (another important cross-metathesis method to make electron-rich dienes uses alkynyl ethers).[47,78]



Scheme 9 Stereoselective with the unprotected hydroxyl group present in EYM via 2-substituted butadiene.[74]

Table 8 Diene products from ethylene-assisted enol ether–alkyne cross-metathesis[55]



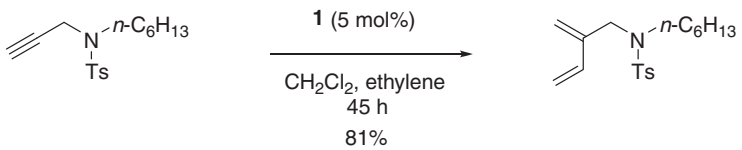
(25)

Entry	*R^1*	*R^2*	*Yield (%)*
1	$BzSCH_2CH_2$	Et	91
2	$BzSCH_2$	Ac	92
3	$MOMOCH_2CH_2$	Et	91
4	$BnOCH_2CH_2$	TBS	72
5	$BzOCH(CH_3)$	TSB	91
6	$BzSCH(CH_3)$	TBS	93

5.27.3.4 CEYM with Ethylene

The CEYM between alkynes and ethylene is an effective way to synthesize substituted 1,3-butadienes. Using an atmosphere of ethylene gas supplied through a balloon, Mori demonstrated an effective cross-metathesis with a variety of terminal and internal alkynes.[15] The procedure produces 2-substituted-1,3-butadienes from terminal alkynes and 2,3-disubstituted-1,3-butadienes from internal alkynes. The cross-metathesis has seen many more examples of terminal alkyne reactions than those of internal alkynes, though each substituted alkyne is reactive. Though the intramolecular RCM with Grubbs' carbenes demonstrates excellent functional group tolerance, intermolecular reactions are more demanding. Ethylene has the advantage that it can be employed in molar excess at ambient or moderately elevated pressures. Moreover, the excess ethylene reactant is easy to remove at the end of the reaction.

An example of ethylene–alkyne cross-metathesis is shown in equation 26.[15] The ethylene is supplied through the use of a balloon. Good reactivity was found with both terminal and internal alkynes, though none of the substrates had additional propargylic substitution. Under these conditions using carbene **1**, long reaction times are generally needed.

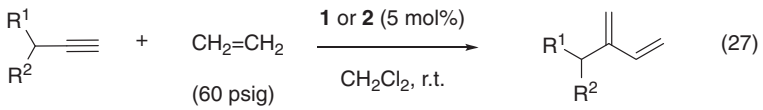


(26)

To tackle higher propargylic substitution and additional functionality on the alkyne, there are additional requirements (equation 27). Improvement in substrate scope was possible through either increased ethylene concentration[79] or use of the second-generation Grubbs complex.[80] Modest increase in ethylene pressure results in higher solution concentration of ethylene.

Due to the dependence of EYM on alkene concentration, this resulted in an improvement in reaction rate. Faster cross-metathesis helped the less reactive α-branched terminal alkynes to react (Table 9). In these cases, no purification of ethylene was needed. It should be noted that 60 psig (pounds per square inch gauge) is approximately 4 bar (4×10^5 Pa), easily achievable using pressure glassware that is available in most synthesis labs (stainless steel autoclaves are not needed).

Table 9 Butadienes synthesized at higher ethylene pressure[79]



(27)

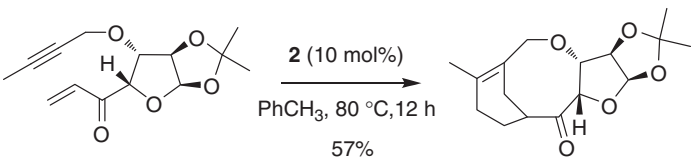
Entry	*R^1*	*R^2*	*Catalyst*	*Yield (%)*
1	Ph	OAc	2	78
2	$PhCH_2CH_2$	OBz	2	57
3	Np	OBz	2	75
4	Ph	OH	1	N.R.
5	Ph	OTBS	1	N.R.
6	Ph	OH	2	73
7	Ph	OTBS	2	91
8	$PhCH_2$	SBz	2	99
9	$PhCH_2CH_2$	SAc	2	97
10	CH_3	SBz	1	11
11	CH_3	SBz	2	87

Oxygen functionality and additional substitution in the alkyne can be overcome by the use of the second-generation Grubbs catalyst at higher ethylene pressures.[80] When there are Lewis basic and potentially coordinating heteroatoms positioned in close proximity to the alkyne, the intermediate vinyl carbene may become kinetically trapped by chelation (entry 4). Chelation slows down the rate of catalysis because the coordinating group has to be exchanged for ethylene to complete the catalytic cycle. Improved reactivity was achieved by joining high ethylene pressure with the more reactive second-generation carbene (entries 4 vs. 6 and 5 vs. 7). As the previous discussion of mechanism indicates, higher concentrations of alkene benefit rate, but high ethylene concentration may also help stabilize reactive intermediates. In the case of the second-generation Grubbs carbene, higher solution concentration of ethylene may prevent both decomposition and rebinding of the Cy_3P ligand, which generates a dormant form of the methylidene.[81] For a planned ethylene–alkyne cross-metathesis with sterically hindered alkynes rich with oxygen functionality, higher pressure of ethylene and the second-generation Grubbs catalyst is recommended.

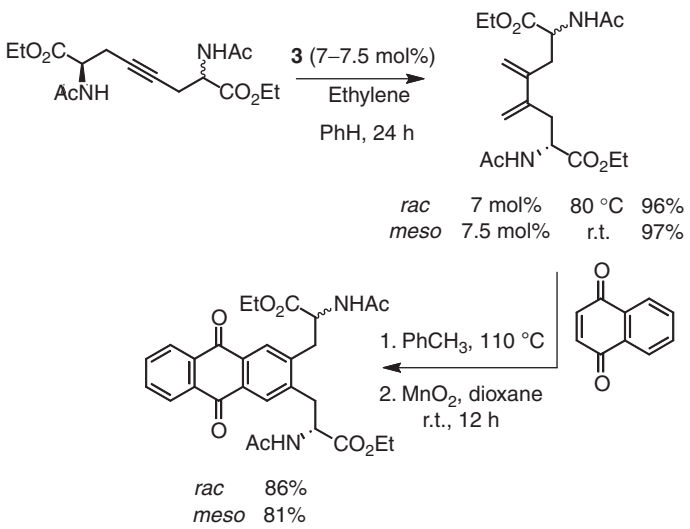
For metathesis with the Grubbs carbenes, sulfur functionality in the unsaturated reactant has presented a difficulty. The affinity of sulfur for late transition metals is well known. During catalysis, the metal carbene can become ligated by sulfur and therefore discourage further reactions such as productive EYM. Use of thiol ester protecting groups proved successful in attenuating the basicity of the sulfur lone pair, resulting in a successful ethylene cross-metathesis (entries 8–11).[82] Thiol acetates and thiol benzoates were prepared by Mitsunobu reaction of the corresponding alkynols. In entry 10, it can be seen that the first-generation carbene **1** as well as the second-generation complex **2** did not perform. For alkynes containing sulfur functionality, higher ethylene pressures proved helpful.

Kotha and coworkers developed a novel CEYM/Diels–Alder sequence to apply to the synthesis of substituted phenylalanines.[83,84] In this example, ethylene CEYM using the Hoveyda–Blechert second-generation catalyst was followed by a Diels–Alder reaction (Scheme 10).[85] The cycloadduct was oxidatively aromatized with MnO_2. This simple and effective method was used to make several other analogs of cystine mimetics in good yields.

EYM is often used in conjunction with subsequent [4 + 2] cycloaddition. This tandem approach was used to access taxol hybrid structures. With several unsuccessful RCM approaches to the central eight-membered ring, Kaliappan and coworkers sought a tandem approach accentuating the utility of each individual reaction.[86] In the metathesis event, an ethylene cross-metathesis was employed to access the substrate for a type II intramolecular Diels–Alder reaction (equation 28).

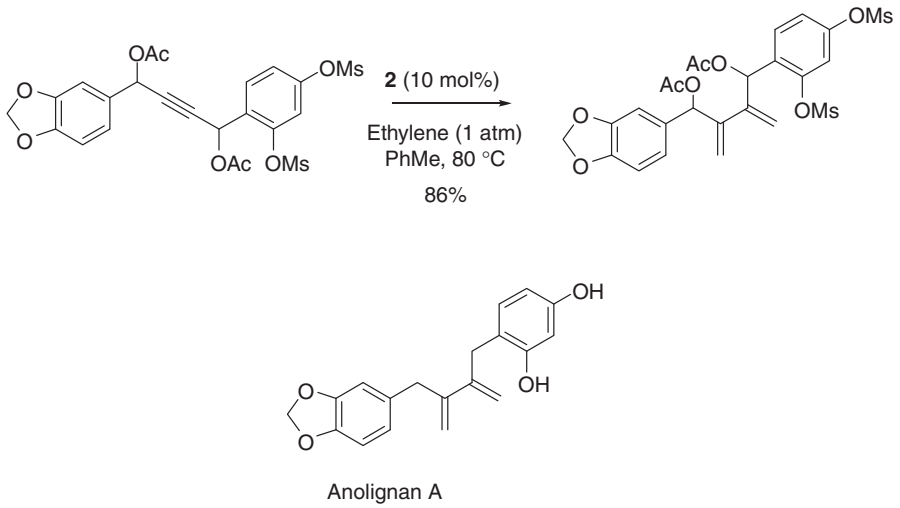


(28)



Scheme 10 Synthesis of amino acid analogs by metathesis/cycloaddition/oxidation.[85]

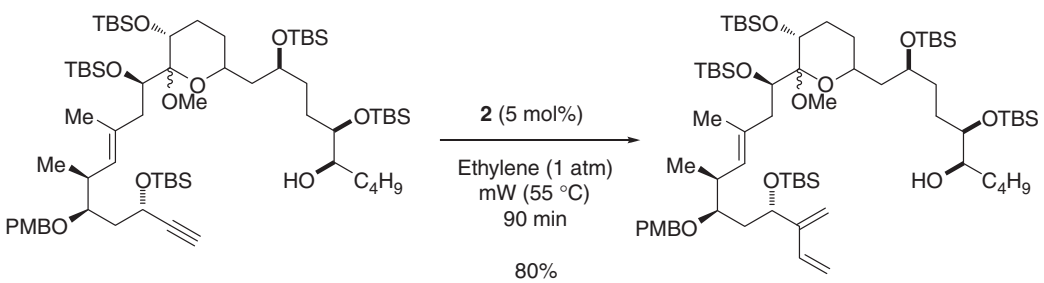
Ethylene–alkyne cross-metathesis has been used in natural product synthesis. Anolignan was prepared using an ethylene metathesis with the second-generation Grubbs complex performed at higher temperature (**Scheme 11**).[87]



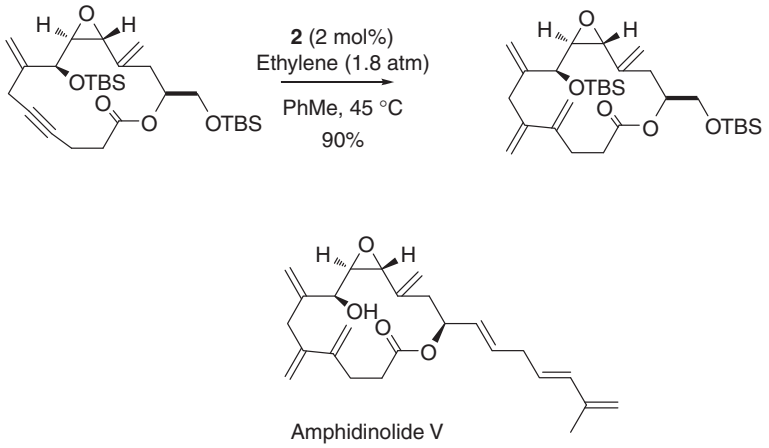
Scheme 11 Mori's approach to anolignan by ethylene–alkyne cross-metathesis.[87]

Fürstner demonstrated an impressive use of ethylene–alkyne metathesis on an unsaturated cycloalkyne to furnish the macrocyclic framework of amphidinolide V (**Scheme 12**).[88,89]

While scouting routes to amphidinolide N, Nicolaou and coworkers carried out a successful ethylene metathesis on a complex synthetic intermediate (equation 29).[90] For this same substrate, other EYM proved problematic.



(29)



Scheme 12 Fürstner's synthesis of Amphidinolide V by ethylene–alkyne cross-metathesis.[88]

In summary, both the first- and second-generation Grubbs catalysts can be used in ethylene–alkyne cross-metathesis. Ethylene as the simplest and lowest molecular weight alkene is easy to use in excess and easy to remove. For more difficult cases, such as those with α-branching in the propargylic position or those alkynes replete with oxygen-containing functionality (such as alkyl ethers), the reactions benefit from higher ethylene pressure. Given the wide availability of the second-generation Grubbs carbene, it is advisable to employ this catalyst in combination with slightly elevated ethylene pressures if the cross-metathesis is difficult. Though the terminally unsubstituted 1,3-dienes are somewhat rare, they can be found in Nature. To that end, the use of ethylene–alkyne cross-metathesis has been successfully used in total synthesis.

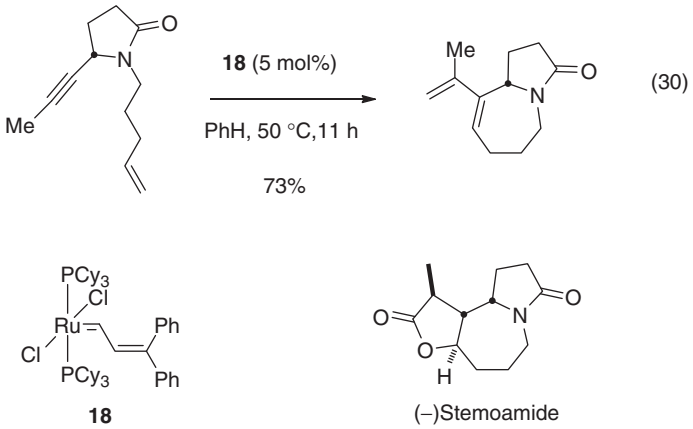
5.27.4 Ring-Closing Applications

5.27.4.1 Ring-Closing Enyne Metathesis with Ruthenium Carbenes

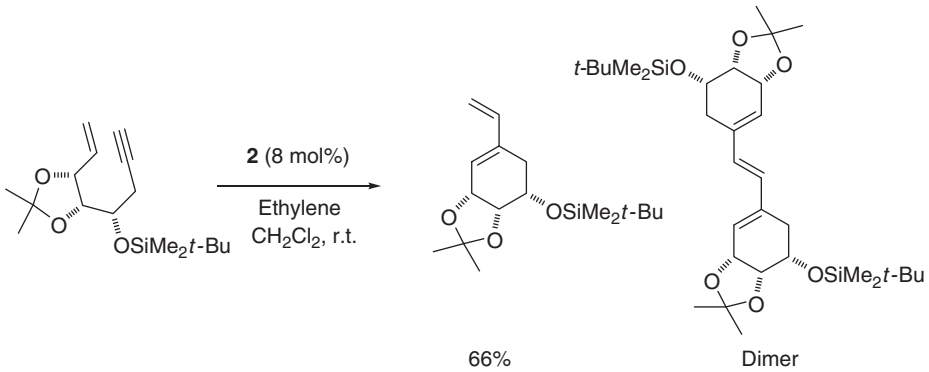
RCEYM is a well-established method for the synthesis of rings. A variety of carbocyclic and heterocyclic rings can be formed using this protocol. The synthesis of small rings is relatively straightforward using metathesis methods.[3,16] Larger rings can also be formed under typical macrocyclization conditions involving high dilution of the enyne reactant. The RCEYM is used to form carbocycles and heterocycles, and is successful even in the presence of a high density of functional groups such as those found in carbohydrates and natural products. RCEYM has been used in natural product synthesis. More applications utilize the RCEYM in tandem with other processes, such as cycloaddition or a second cross-metathesis reaction. These have become attractive due to their ability to rapidly assemble polycyclic structures. Reactions that involve metathesis cascades are discussed in greater detail in Section 5.27.7. During the development of RCEYM methods and applications to a range of small molecules, there are distinct phases where different generations of catalysts were used. Currently, the second-generation Grubbs carbene is widely employed for RCEYM, though in earlier examples and for the simplest cases, the first-generation Grubbs complex was successfully used. Modern use of this chemistry may employ either Grubbs catalyst, depending on the application. The most difficult ring closures to make small rings or those containing highly substituted alkenes require longer lived and thermally robust catalysts like the Hoveyda–Blechert catalyst. Lastly, RCEYM with the first-generation Grubbs carbene benefits from the presence of ethylene. Many early examples used 'Mori conditions' to improve the yield of the 1,3-diene product. The role of ethylene has been explained in Section 5.27.2.1.

Mori and Kinoshita illustrated a beautiful use of RCEYM as a key step in their synthesis of the *Stemona* alkaloid stemoamide (Scheme 13).[91] This was a landmark contribution because it demonstrated that the new Grubbs carbenes could be used to promote enyne metathesis in complex molecule synthesis. The Grubbs catalyst **18** was a tremendous advance over early transition metal Fischer carbenes, which lacked the activity, selectivity, and functional group tolerance of the well-defined ruthenium carbene complex.

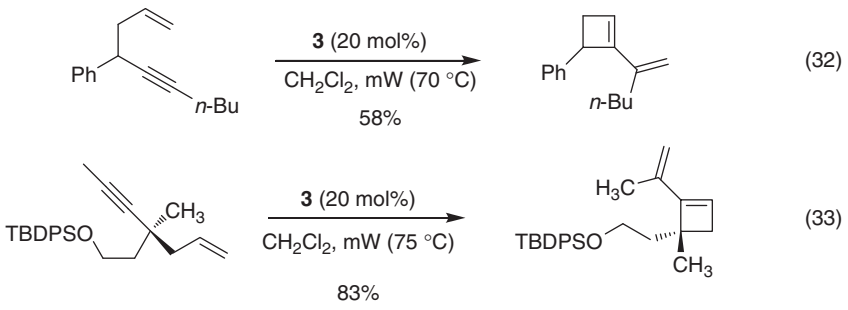
RCEYM has been used successfully in many oxygen-rich environments. In particular, the second-generation Grubbs carbenes feature a combination of increased reactivity and high chemoselectivity; significant attributes in oxygen-rich environments, where induction and chelation reduce reactivity. Accordingly, ring closure with the second-generation Grubbs complex gives the vinylcyclohexene product in good yield.[92] Without ethylene, the vinyl carbene dimerizes, illustrating another dimension to the ethylene effect in RCEYM. Ethylene limits the formation of an undesired dimeric by-product by 'turning over' the vinyl carbene intermediate to product. This prevents an intermolecular reaction with the alkyne of another enyne reactant, which leads to the dimer (equation 31).



Scheme 13 RCEYM en route to Stemoamide.[91]



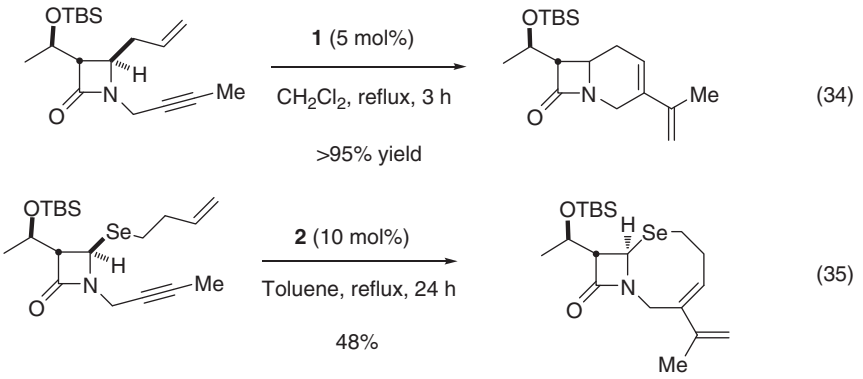
Formation of strained four-membered rings is possible by RCEYM. Reactivity gains have been achieved with the second-generation Grubbs carbenes simply due to the ability to heat difficult reactions for a longer period. However, at refluxing toluene temperatures, thermal decomposition of **2** becomes problematic. For difficult metatheses that require higher temperatures, the Hoveyda–Blechert complex **3** has distinguished itself. Recently, microwaves have been used to bring about metathesis. Use of the complex **3** under microwave heating promoted RCEYM to form strained cyclobutene rings (equation 32; **Scheme 14**).[93]



Scheme 14 Four-membered rings by microwave-assisted ring-closing enyne metathesis.[93,94]

A similar approach was employed by Goess et al. to make grandisol (equation 33).[94] The use of high catalyst loading and microwaves promoted the difficult ring-closing step. Notably, a quaternary carbon center resides at the propargylic position, which is unusual even for intramolecular enyne metathesis.

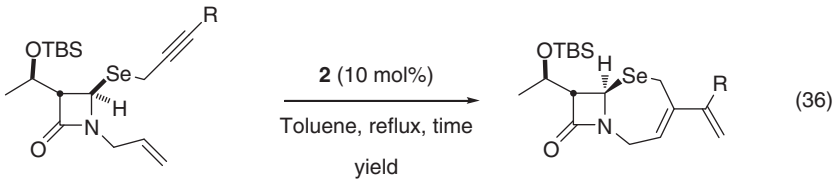
RCEYM can be used to access privileged heterocyclic ring systems such as the carbapenams and their structural analogs. The RCM conditions are mild such that the delicate β-lactam ring system remains intact during annulation (**Scheme 15**).[95,97] Larger B rings were made with selenium present in the nascent ring using the second-generation Grubbs catalyst (equation 34).[96] This reaction proved quite challenging due to the ring size and the presence of the selenium atom (see Section 5.27.3.4 for an example of sulfur in CEYM). Neither the first-generation Grubbs carbene or lower reaction temperatures were sufficient to promote this



Scheme 15 RCEYM to form β-lactams.[95,96]

reaction (equation 35). Internal alkynes performed well in the RCM, but a terminal alkyne failed (equation 36; Table 10) possibly due to alkyne polymerization under the forcing reaction conditions.

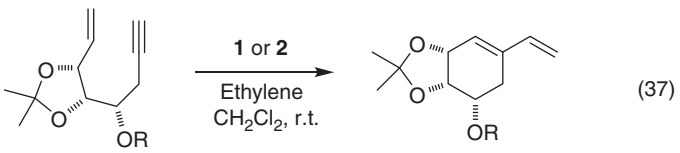
Table 10 RCM on β-lactam-containing substrates



Entry	*R*	*Time (days)*	*Yield (%)*
1	H	4	0
2	Me	2	44
3	Ph	1	59

Polyhydroxylated carbocyclic rings are found in biologically important molecules and natural products. Due to their importance, Madsen and Poulsen developed an RCEYM strategy to readily access carbocyclic rings from carbohydrates (equation 37).[92] The authors attempted the RCEYM in the presence of an unprotected alcohol located at the homopropargylic position. At room temperature and in the presence of ethylene, they found no reaction (N.R.) with catalyst **1** or **2**. Raising the temperature to 40 °C gave decomposition of the enyne. Blocking this position with a *t*-butyldimethylsilyl (TBS) protecting group gave RCEYM under ethylene to form the desired carbocycle in good yield (Table 11).

Table 11 RCEYM with homopropargylic oxygen functionality[92]

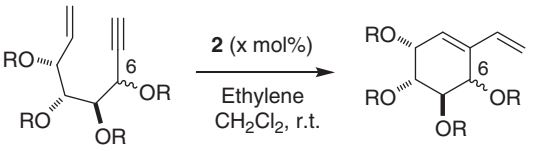


Entry	*R*	*Catalyst*	*Yield (%)*
1	H	1	N.R.
2	H	2	N.R.
3	TBS	2	66

Highly oxygenated enynes undergo RCEYM to form six-membered carbocycles. Similar to the examples above, polyhydroxylated enynes bearing homopropargylic and propargylic oxygen functionality were subjected to ring closing with the

second-generation Grubbs carbene **2**.[98,99] Interestingly, either benzyl or acetyl protecting groups were tolerated (equation 38, Table 12); these protecting groups are commonly used in sugar chemistry. In addition, each diastereomer was evaluated separately and found to give efficient RCM.

Table 12 RCEYM in a highly oxygenated environment[98,99]

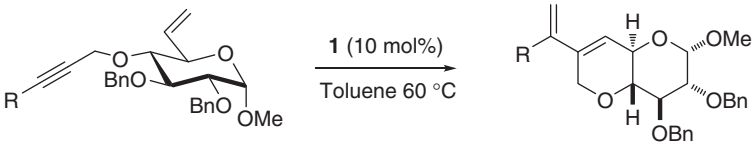


(38)

Entry	*C6 stereochemistry*	*Loading (mol%)*	*Yield (%)*
R=Bn			
1	β	15	55
2	α	15	66
R=Ac			
3	β	10	72
4	α	10	76

As a means of ring fusion toward bicyclic dienes, van Boom and coworkers performed RCEYM on protected 2-vinyl pyranose and 2-vinyl furanose.[100] These readily available carbohydrates were transformed into pyranopyrans and pyranofurans in the presence of the first-generation Grubbs catalyst **1**. Low conversion was observed with a terminal alkyne; however an internal alkyne gave good yield (equation 39; Table 13). A similar difference in yield was also found in the furanose case (equation 40; Table 14).

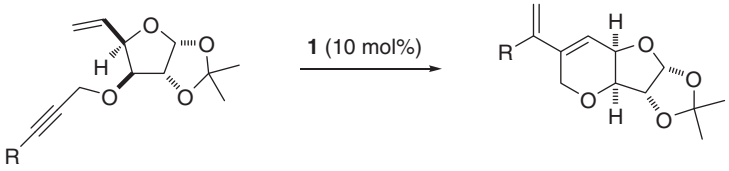
Table 13 RCEYM in a highly oxygenated pyranose environment[100]



(39)

Entry	*R*	*Yield (%)*
1	H	24
2	CH_2OTBS	73

Table 14 RCEYM in a highly oxygenated furanose environment[100]

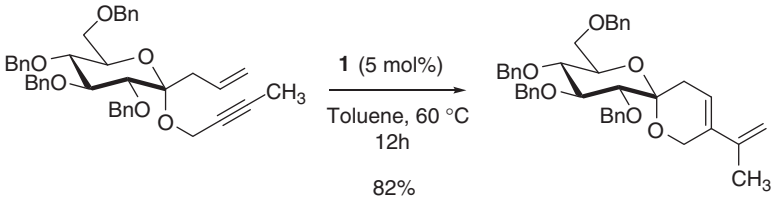


(40)

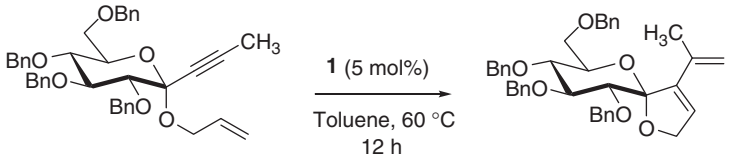
Entry	*Conditions*	*R*	*Yield (%)*
1	Toluene, 60 °C 24 h	H	51
2	CH_2Cl_2, reflux, 6 h	CH_2OTBS	94

Highly functionalized spirofused oxacycles are accessible from carbohydrate-based enynes by RCEYM. van Boom et al. converted ketoglycosidic enynes into dienyl spiroacetals in the presence of the first-generation Grubbs carbene.[101] The

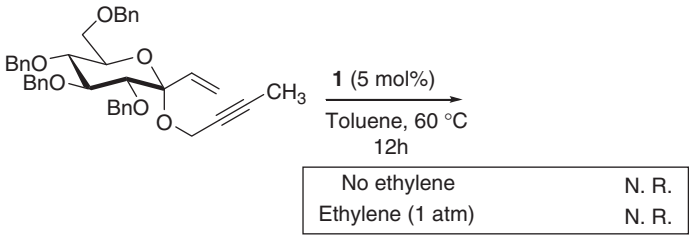
first two reactions (equations 41 and 42) were successful, producing the desired spirocycles in good yields, whereas the third reaction (equation 43) proved unsuccessful as the starting enyne was found to be unreactive. Conversion to product did not improve in the last case under extended reaction times or increased catalyst loadings. The ability of the catalyst **1** to initiate at the alkene may be diminished due to the steric hindrance associated with the highly substituted anomeric center.



(41)

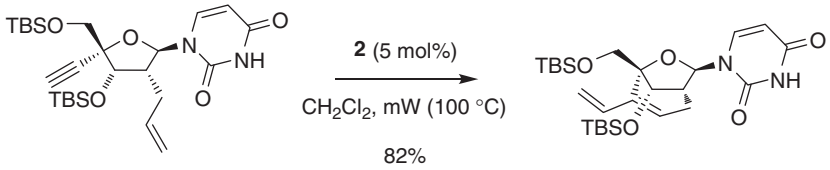


(42)



(43)

RCEYM can be used to synthesize bicyclic structures in the presence of nitrogen heterocycles such as pyrimidines. Nielson and coworkers recognized the potential of enyne metathesis in their synthesis of a bicyclic 2′-deoxynucleoside, a carbocyclic-locked nucleic acid analog (equation 44).[102] The enyne was subjected to the second-generation Grubbs catalyst using microwave heating for 2 h, giving the bicyclic structure in 82% yield.



(44)

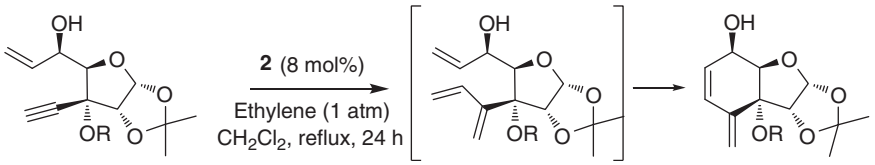
A tandem metathesis sequence allowed access to an unusual ring-closure mode. In an RCEYM, forming a new ring by closure onto the proximate carbon of an alkyne would lead to a smaller ring. If a pendant alkene could be made to close onto the distal carbon, a larger ring would result. This is called *endo*-selectivity and is atypical of small ring closures using ruthenium carbene intermediates. *Endo*-selectivity was achieved by Kaliappan and coworkers who envisioned a tandem ethylene cross-metathesis/RCM sequence as a means to access 4-methylene-2-cyclohexanols.[103] This substructure obtained from equation 45 is contained in the natural products otteliones and loloanolides (**Table 15**). The reaction was conducted under ethylene, triggering an ethylene–alkyne metathesis first. The intermediate vinyl appendage of the 1,3-diene can combine in an alkene RCM to furnish the product. Subsequent Dess–Martin oxidation of the alcohol resulted in the 4-methylene-2-cyclohexenone framework.

5.27.4.1.1 Nitrogen-containing heterocycles

The RCEYM has been used to furnish a variety of nitrogen-containing heterocycles. Nitrogen heterocycles pose a challenge to metal carbene-mediated chemistry because of the electron-withdrawing nature of the nitrogen atom and because nitrogen protecting groups may coordinate to the carbene intermediates. In this section, some challenging examples are provided, mostly employing the second-generation Grubbs catalyst **2**. Bicyclic nitrogen heterocycles are also obtained using metathesis methods.

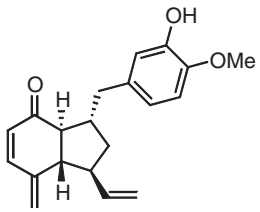
The use of a sulfoximine linker in the enyne leads to a heterocyclic sulfoximine by RCEYM (equation 46).[104] In the case of terminal alkynes, good yields were also obtained along with a dimeric product that could not be completely eliminated by

Table 15 An unusual ring closure mode for enyne metathesis[103]

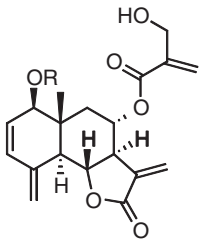


(45)

Entry	*R*	*Yield (%)*
1	Me	83
2	Et	89
3	Bn	87
4	MOM	88

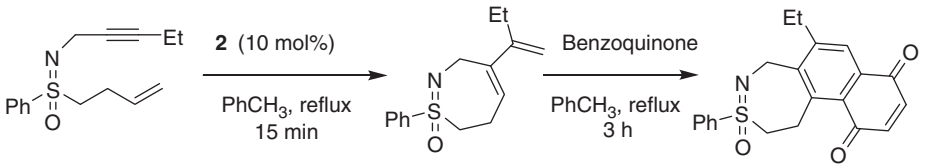


Otteliones



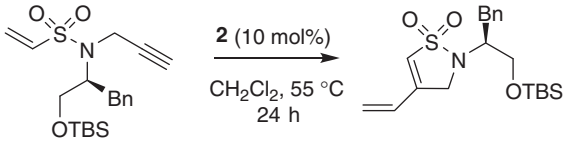
R = H, loloanolide B
R = OAc, 1-*O*-acetylloloanilide B

dilution or use of ethylene. The resulting 1,3-dienes underwent further transformation such as a Diels–Alder aromatization with benzoquinone, allowing access to benzofused sulfoximines. Attempts to perform further RCEYM reactions on enynes with longer tether lengths to produce larger heterocyclic rings were unsuccessful.

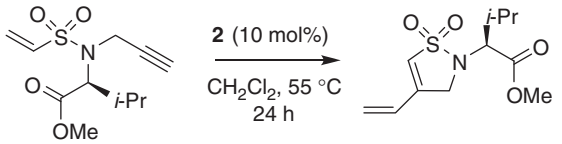


(46)

RCEYM can be performed with a vinyl sulfonamide and a terminal alkyne to produce an endocyclic sultam; this is an unusual heterocycle. Heterocyclic ring systems appear in many pharmaceutical agents and are extremely important in drug development. Given this and their versatility, heterocycle synthesis has become a major focus for chemical library synthesis by diversity-oriented synthesis (DOS). With this goal in mind, Hanson and coworkers synthesized skeletally diverse sultams (equations 47 and 48).[105] RCEYM reactions provide unique access to functionalized heterocyclic ring systems from linear unsaturated elements with heteroatom linkers. Initiating metathesis at an electron-deficient site or near coordinating heteroatoms can be difficult. In this case, vinyl sulfonamides are difficult substrates due to the electron-poor nature of the alkene. Generally, this problem can be solved using the more active Hoveyda–Blechert catalyst **3**, but in this case longer periods of heating with Grubbs carbene **2** proved successful.



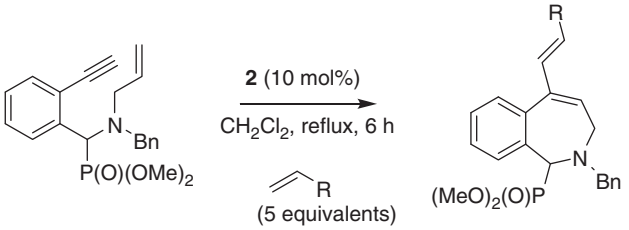
(47)



(48)

Cyclic α-aminophosphonates are accessible by RCEYM. Benzofused seven-membered ring systems have received much attention in the synthetic community due to their appearance in a variety of natural products and similarity to privileged structures such as to the benzodiazepines. Moreover, benzofused heterocycles bearing phosphonates have interesting biological properties. Stevens and coworkers planned the synthesis of phosphono-substituted benzazepines using RCEYM as their key strategy (equation 49; Table 16).[52] Obtaining the desired 1,3-diene posed a challenge due to the slow conversion of the initially formed butadiene to the 1,3-diene. To speed up conversion to the 1,3-diene, an additional 5 equivalents of alkene were added after the first 2 h of reaction. At the end of the reaction, approximately 10% of butadiene remained unreacted but proved separable by flash chromatography.

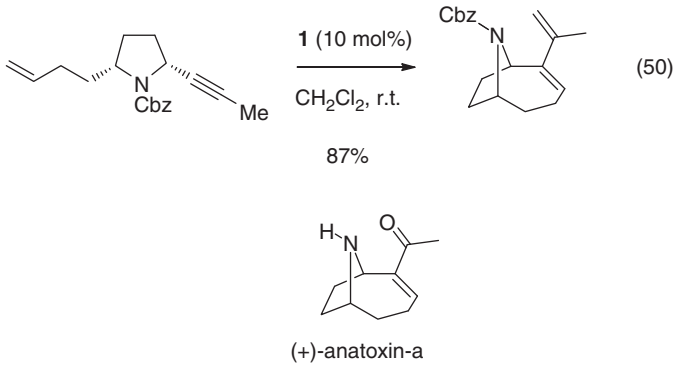
Table 16 RCEYM to access phosphono-substituted azepines[52]



(49)

Entry	*R*	*Yield (%)*	E/Z *ratio*
1	Ph	78	*E* only
2	CH_2 $SiMe_3$	74	66:34
3	$CH_2CH_2C(O)CH_3$	68	67:33

Bicyclic nitrogen heterocycles have been synthesized by RCEYM. The groups of Martin[106] and Mori[107] had independently pursued two closely related strategies toward anatoxin-a. For brevity, the Martin approach is detailed. The enyne precursor was synthesized from D-methyl pyroglutamate.[106] In the RCEYM step, the enyne was found to cyclize efficiently (under Ar) to give the bridged azabicycle under nominal conditions (equation 50). The exocyclic geminal alkene of the diene product was elaborated by osmylation and oxidative cleavage of the 1,2-diol. After protecting group removal (TMSI), the natural enantiomer of (+)-anatoxin was formed (Scheme 16).

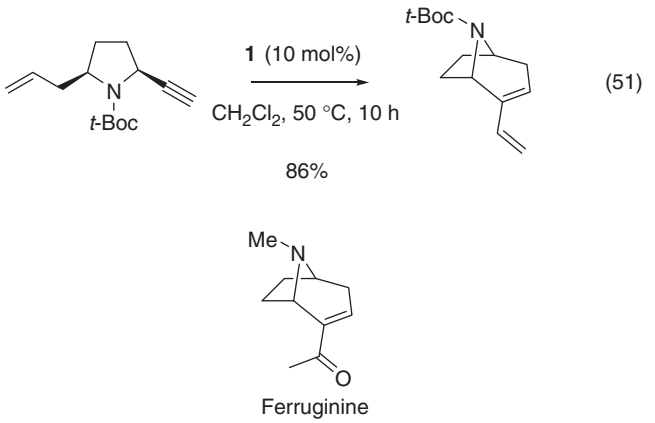


(50)

Scheme 16 Ring-closing approach to the aza bicyclic ring system of anatoxin.

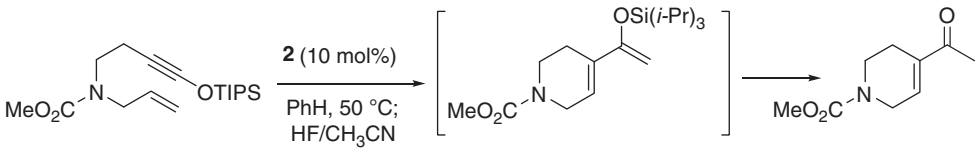
The bicyclic ring system of the alkaloid (+)-ferruginine was assembled by RCEYM (Scheme 17). Aggarwal et al. screened catalysts **1**, **3**, and **5** in this reaction, but monitoring reaction progress indicated that these more active catalysts were destroying the 1,3-diene product after its initial formation.[108] This is an unusual example of an RCEYM that occurs better with the less reactive first-generation carbene **1**. A Wacker-type oxidation sequence was used to transform the exocyclic geminal alkene to a methyl ketone.

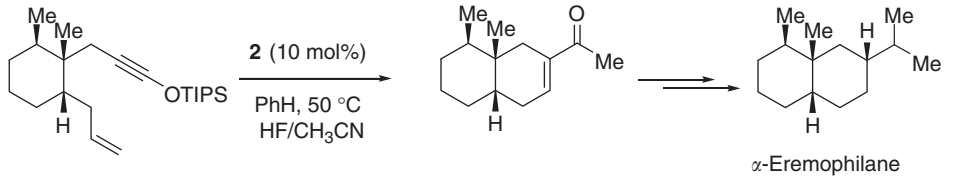
RCEYM can be used to access other functionality besides 1,3-dienes. Coupling a tandem transformation with the enyne metathesis provides access to enones in a 'one-pot' process. Normally, enyne metathesis produces a vinyl cyclohexene; however, Kozmin et al. recognized that if the alkyne bore an oxygen atom, the product could be converted into a methyl ketone.[47] Use of silyl alkynyl ethers in the RCM followed by deprotection of the intermediate silyl enol ether gives the product methyl ketones after



Scheme 17 RCEYM approach to [3.2.1] azabicycle.[108]

acid-catalyzed enol-keto tautomerization (equation 52). This metathesis/deprotection/tautomerization sequence was applied to the synthesis of α-eremophilane (equation 53).[109]

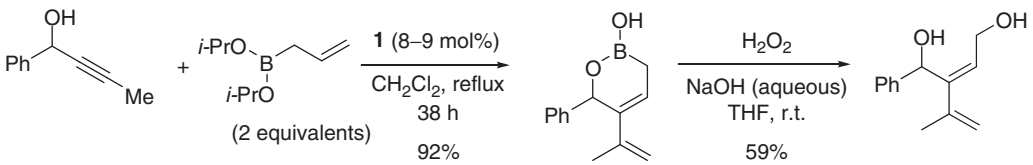




5.27.4.1.2 Other heterocycles

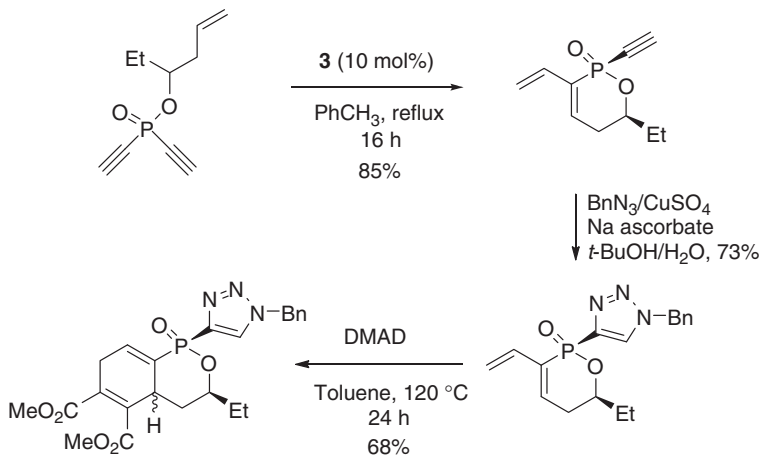
Though they had previously shown that phosphorus-containing compounds are suitable for metathesis, Gouverneur and coworkers developed the first example of a diastereoselective ene-diyne metathesis to form various chiral P-stereogenic heterocycles (Scheme 18).[110] To achieve full conversion, 10 mol% of the Grubbs catalyst **2** or the Hoveyda–Grubbs catalyst **3** was necessary, in conjunction with elevated reaction temperature. Through optimization, it was also found that the second-generation Hoveyda–Blechert catalyst in refluxing toluene gave the highest diastereoselectivity (18:1). This was much higher than with the first-generation Grubbs catalyst **1** (3:1) or Grubbs catalyst **2** (10:1). These stereochemically distinct phosphorus heterocycles are unique stereogenic templates and could lend themselves to further functionalization on either the alkyne (Huisgen 3 + 2 cycloaddition) or 1,3-diene moieties (Diels–Alder reaction).

The use of a transient linker to bring together the unsaturated elements was elegantly employed by Schreiber and Micalizio to furnish boroxines (Scheme 19).[111,112] However, the cyclic boronate could be oxidized to the enol that produced the corresponding enone after enol-keto tautomerization. The cyclic boronates could also be subsequently hydrolyzed to provide acyclic dienes (equation 54). The use of a linker switches a slower intermolecular EYM to the intramolecular manifold, increasing the reaction rate and enforcing the endocyclic alkene geometry. The mixed boronate ester offers functionality that can be harnessed for subsequent C–C bond formation.

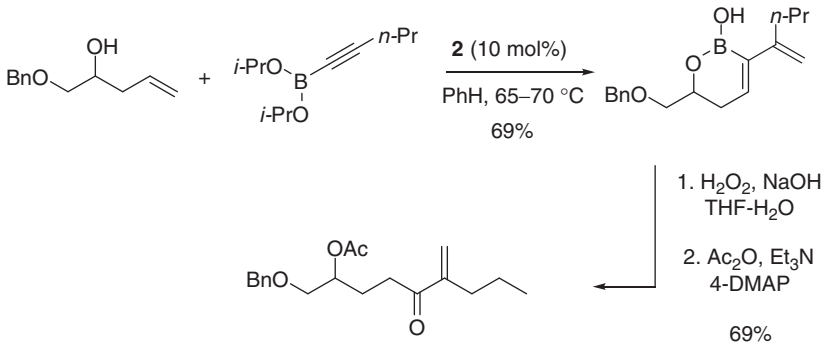


5.27.4.1.3 Application to carbocyclic natural products

Morken constructed the seven-membered ring found in dihydroxanthatin by RCEYM (equation 55).[113] The treatment of the requisite enyne with 5 mol% of **2** produced the expected RCEYM product. After enolate alkylation, the diene was subjected to

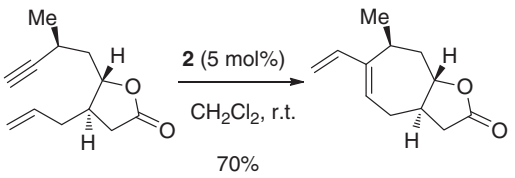


Scheme 18 Desymmetrization RCM on diyne.[110]

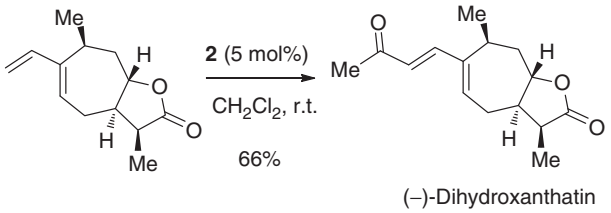


Scheme 19 Transient boronate linker organizing RCEYM.[111,112]

cross-metathesis with methyl vinyl ketone (equation 56). This procedure could have been achieved in one pot using **3**; however, the authors found it tactically superior to perform the metathesis stepwise to selectively enolize the lactone.



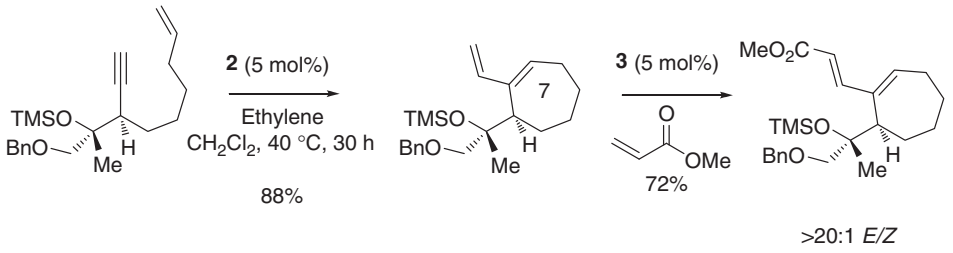
(55)



(56)

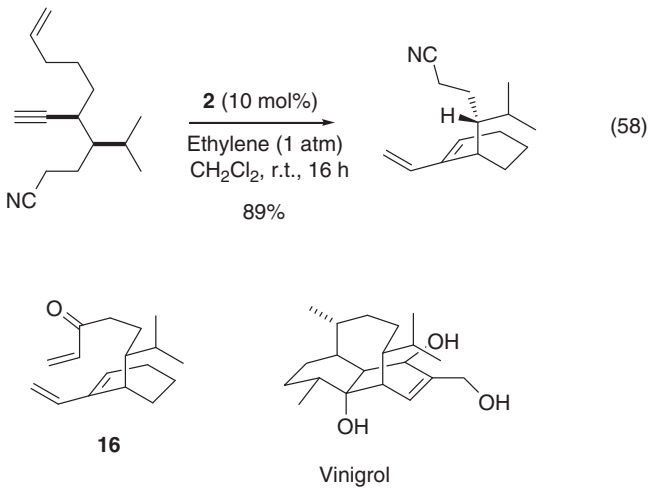
(–)-Dihydroxanthatin

An efficient RCM was used to make the seven-membered C-ring of lancifodilactone.[114] In this case, a rather hindered homopropargylic alkyne underwent reaction with carbene **2**, as long as the homopropargylic alcohol was protected as the TMS ether (equation 57). In the second cross-metathesis with methyl acrylate, the Hoveyda–Blechert complex **3** was employed to achieve good yield and high *E*-selectivity. This example serves to illustrate different strengths of the carbene promoters **2** and **3**.



(57)

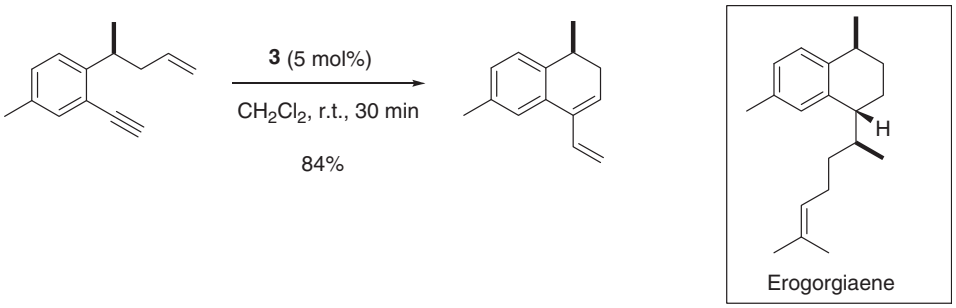
Access to six-membered rings using metathesis is advantageous because it can be used to set up subsequent annulation. For example, the resulting vinyl cyclohexene is capable of Diels–Alder cycloaddition (Scheme 20).[115] In subsequent transformations, Barriault and coworkers converted the nitrile into the enone **16**, which underwent a Lewis acid-catalyzed Diels–Alder reaction to provide the carbon framework of the tricyclic core of the diterpenoid vinigrol.



(58)

Scheme 20 RCEYM used to set up intramolecular cycloaddition.[115]

The Hoveyda–Blechert complex also promotes simple RCEYM. In their synthesis of erogorgiaene, Hoveyda and coworkers employed an RCEYM using complex **3** (equation 59).[116]



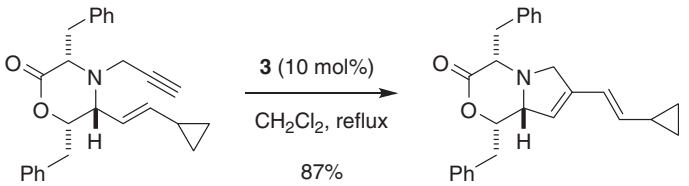
(59)

5.27.4.1.4 For diversity generation and in diversity-oriented synthesis

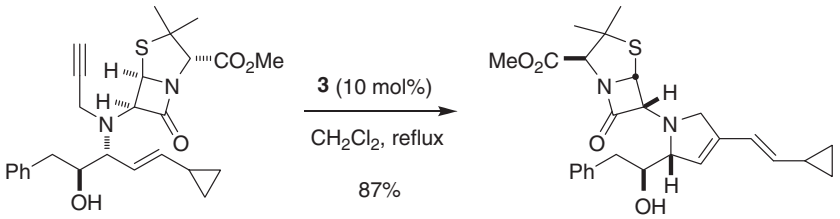
The EYM is well suited to DOS. The DOS aims to create various cyclic or polycyclic templates to project functional groups to give a quasi systematic and wide representation of three-dimensional space. This approach is inspired by complex natural products, which evolved for a particular function. Enyne metathesis is a very attractive enabling technology for the rapid assembly of the core structures because it can be used to make a wide variety of ring sizes, tolerates many functional groups, and supplies products that are amenable to subsequent transformation (e.g., cycloaddition). In this section, a few reactions that fall into this family are highlighted. In Section 5.27.7, cascade reactions are also utilized for the assembly of polycyclic arrays and are detailed in that section.

Two representative examples from DOS illustrate the functional group tolerance of the RCEYM (equations 60 and 61). Chiral scaffolds can be employed to generate heterocyclic rings bearing chiral centers, and the alkene does not need to be terminal. Many

examples in this section include terminal alkenes closing onto alkynes. In this case, Schreiber et al. showed that an alkene bearing a cyclopropyl group participates in RCEYM onto an alkyne that contains a basic amine in the propargylic position (equation 60).[117] In the second example, a privileged heterocyclic ring, that of the penicillin ring (with a divalent sulfur atom and a β-lactam ring), is carried as a spectator during a remarkably efficient RCEYM (equation 61). These two examples illustrate that the enynes can be adorned with a rich array of functionality without deleterious effect on the catalytic enyne metathesis.

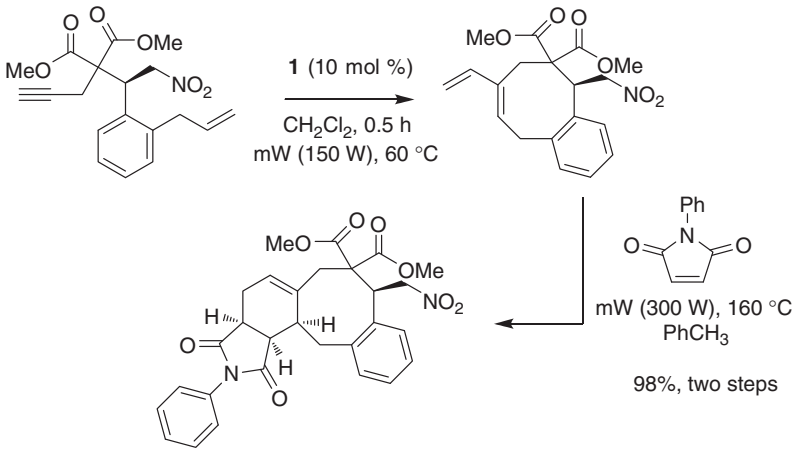


(60)



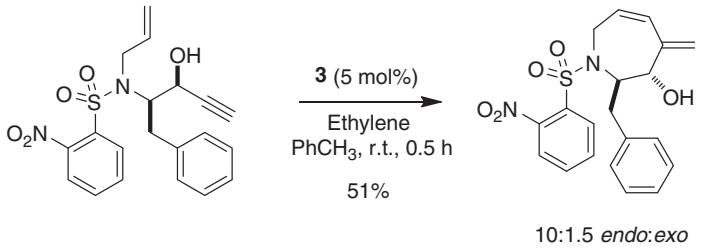
(61)

Multifunctional diene scaffolds were accessed through RCEYM as a means of generating skeletal diversity. Porco and coworkers conducted the RCM step under Mori's conditions using ethylene and microwave heating (**Scheme 21**).[118] The 1,3-diene was not isolated but directly subjected to a thermal [4 + 2] cycloaddition with *N*-phenylmaleimide. The microwave heating allows rapid throughput and high chemical yield (98% over two steps).



Scheme 21 Skeletal diversity by enyne metathesis and cycloaddition.[118]

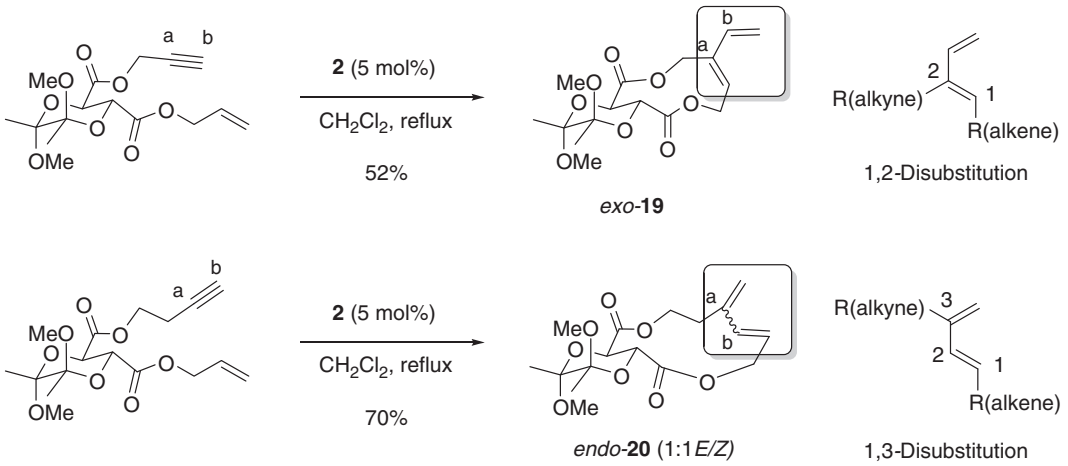
Schreiber et al. built stereochemical and skeletal diversity into a set of small molecules using multiple approaches involving RCEYM (equation 62).[119] The RCEYM in Equation 62 gave an unusual result, proceeding with *endo*-selectivity when using the Hoveyda–Grubbs catalyst under an ethylene atmosphere. Significantly, a free hydroxyl group is present at the propargylic position. Free alcohols in the propargyl position tend to be problematic in CEYM, except those involving ethylene. The free hydroxyl group was important for the high *endo*:*exo* selectivity; if it was protected, the *exo*-mode RCM dominated.



(62)

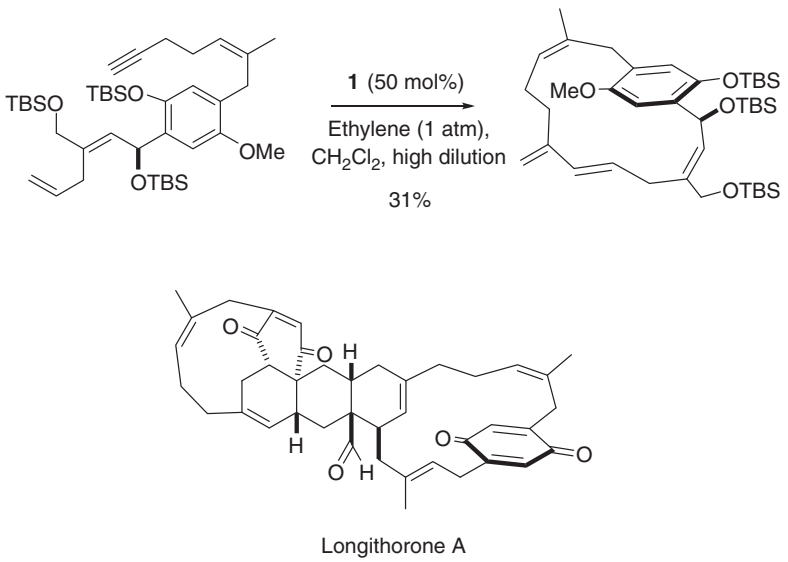
5.27.4.1.5 Macrocyclic ring closure

In larger RCEYM, there are two orientations that can be obtained, which affect the ring size formed. If the ring is smaller than 10 members, then ring constraint forces the enyne to come together with the 1,2-disubstitution pattern (**19**, Scheme 22). This is called *exo*-selectivity because the intermediate vinyl carbene leading to *exo*-**19** features the ruthenium exocyclic to the newly formed ring. However, if the ring is very large, the ene and yne react with the regiochemistry observed for the intermolecular reaction (as in **20**). In this case, the vinyl carbene forms endocyclic to the macroring formed. Lee and Hansen studied this in a systematic way and rationalized the data in terms of reactive intermediate stabilities.[120] With slightly greater flexibility in the enyne tether, the ring closure may result in the larger ring size by switching regiochemical preference. In general, rings smaller than 10 members will form with the 1,2-disubstitution pattern (*exo*-selectivity); rings in the 10–11 range are borderline cases, and larger rings result in the 1,3-disubstitution pattern on the 1,3-diene (*endo*-selectivity). The 1,3-disubstitution results from CEYM. A study of macrocyclization in a related system has also appeared, with an emphasis on DOS.[121]



Scheme 22 Ring-closure mode selectivity.[120]

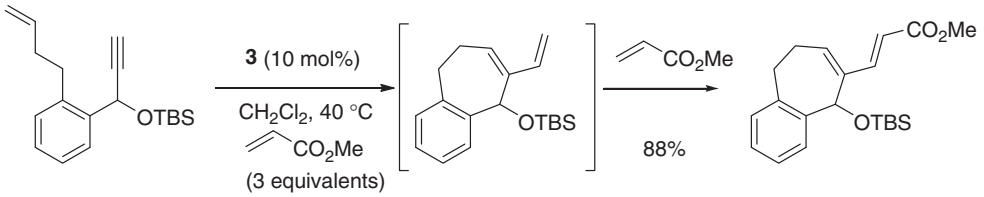
In a remarkable macroring-closing enyne metathesis, Shair and coworkers produced two cyclophanes that were used to assemble the seven ring systems found in longithorone A.[122] Due to the difficulty of the ring closure, high loading of the Grubbs catalyst was used along with ethylene. The synthesis of one cyclophane is illustrated in Scheme 23. This cyclophane comprised the right half of longithorone A.



Scheme 23 Macroring closure en route to Longithorone A.[122]

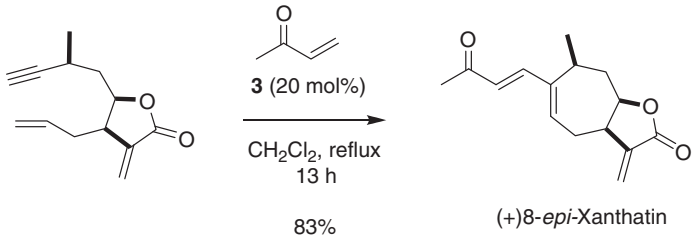
5.27.4.1.6 With tandem cross-metathesis

Since the Hoveyda complex is well suited to reactions employing electron-deficient alkenes, tandem reactions are possible using these alkenes subsequent to RCEYM.[123] Though carbene **3** is capable of reaction with enoates, it is more reactive with simple aliphatic alkenes. In equation 63, the initial reaction occurs on the alkene of the enyne that undergoes ring closure to give an intermediate vinyl cycloheptene species. With complex **3**, both the ring closing and the cross-metathesis with the added alkene took place in a single-reaction flask without further addition of catalyst. The second step can be regarded as a slower and more difficult diene-enoic ester cross-metathesis. It is interesting to note that the reaction temperature can be controlled in this example so as to limit possible Diels–Alder reaction between the intermediate and the excess electron-poor alkene.



(63)

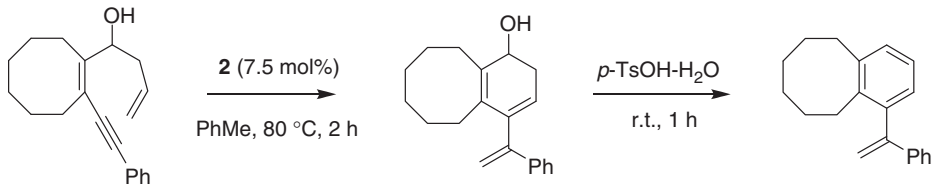
Martin used a tandem cross-metathesis-based approach to make the related diterpene 8-*epi*-xanthatin using the Hoveyda–Blechert complex **3** (equation 64).[124]



(64)

5.27.4.1.7 Ring-closing/aromatization

Substituted arenes can be prepared by an RCEYM/dehydration sequence. RCEYM was carried out with a 1,5-octadien-7-yn-4-ol and second-generation Grubbs carbene (equation 65).[125] On formation of the triene, the alcohol was subjected to mild dehydration conditions (*p*-toluenesulfonic acid (*p*-TsOH)) to trigger elimination and engender aromaticity in the six-membered ring. This novel one-pot process was carried out with a large repertoire of substrates offering an efficient one-pot access to substituted styrenes. A related RCEYM/keto-to-enol tautomerization is also described.[125]



(65)

Ethylene	Yield
None	74%
(1 atm)	96%

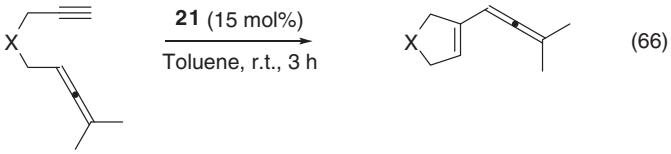
RCEYM has seen wide application as a ring-forming method. It is tolerant of a variety of functional groups and can accommodate electron-withdrawing functionality positioned within or residing outside the newly formed ring. For carbocycles, the scope is wide, tolerant of oxygen substitution, and used in complex molecule synthesis. The Grubbs catalysts typically cause ring-closing of 1,*n*-enynes in the *exo* mode. Use of ethylene in some cases leads to *endo*-ring closure. The next section details more examples of *endo*-selectivity using Schrock–Hoveyda molybdenum carbene catalysts. The use of RCEYM in alkaloid synthesis has a long history dating back to Mori's landmark synthesis of stemoamide. Applications to more unusual nitrogen heterocycles and use in DOS are modern themes. Though the Hoveyda–Blechert complex can be used to promote enyne metathesis just as the second-generation Grubbs complex, its niche application is electron-deficient alkenes and forcing reaction conditions needed to make small rings. This complex is the most widely used phosphine-free variation of the Grubbs ruthenium carbenes, but variants such as the Grela catalyst **4** are also useful for enyne metathesis. Complex **3** has proven particularly effective under demanding metathesis conditions or those involving enones, enoates, or enals.

5.27.4.2 Ring-Closing Applications with the Molybdenum Carbene Catalysts

The Schrock molybdenum catalyst has not been widely used in enyne metathesis. This can be attributed to the catalysts' high reactivity with terminal alkynes: Alkyne polymerization outcompetes enyne metathesis. In the best cases, 1,ω-enyne substrates may undergo RCEYM with competitive polymerization taking place. A few years ago, there were no examples of RCEYM using the Schrock catalyst.[3] In recent years, the Schrock catalyst has seen far greater application in asymmetric alkene metathesis applications and in *Z*-selective alkene metathesis. Improving the design of asymmetric catalysts has led to a collateral benefit for enyne metathesis: improved cross-selectivity. (This refers to the cross-reaction between an alkene and an alkyne as opposed to homopolymerization of alkynes.) This highlights that major developments often follow from improvements in catalyst design. As any student of organometallic chemistry might expect, subtle changes in catalyst structure may have a profound effect on reactivity and selectivity.

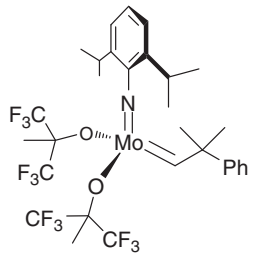
The parent Schrock catalyst was found to promote the RCEYM of an allene–yne.[126] This is a well-balanced case of intramolecular reactivity over alkyne polymerization (**Table 17**). Based on initiation studies, the authors favored a mechanism where the molybdenum allenylidene formed and then reacted with the alkyne, followed by ring closure. Though the ether linkage failed due to chelation with the oxophilic metal, a basic amine gave successful enyne metathesis.

Table 17 Allene–alkyne RCM[126]



(66)

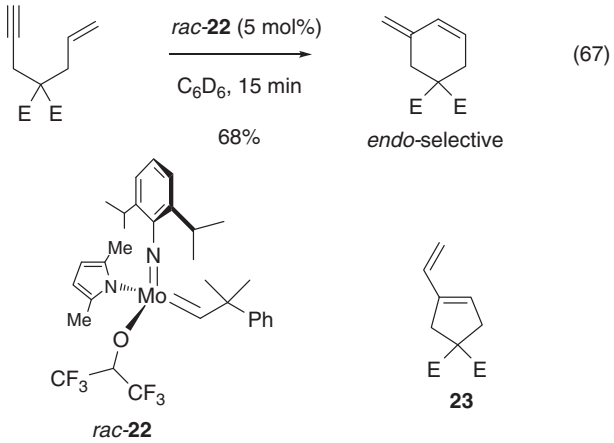
Entry	*X*	*R*	*Yield (%)*
1	NTs	H	71
2	NTs	Me	68
3	NBn	H	73
4	$C(CO_2Et)_2$	H	95



21 (Schrock catalyst)

By changing the ligands in the Schrock complex, RCM of 1,ω-enynes is possible.[127] Chirality in the Schrock molybdenum carbene environment is achievable by either substituting the two alkoxy groups for a chiral diol,[128] or using four different ligands to make the metal center stereogenic. In both ways, the Schrock and Hoveyda research team has generated highly selective catalysts for asymmetric RCM applications[129,130] and *Z*-selective alkene metathesis.[131–133] The Schrock complex **21** has two alkoxy groups bound to the molybdenum center. The chiral-at-molybdenum carbene complex **22** bears one alkoxy group and one pyrrolide ligand directly bound to the metal.[127,134] This slight alteration in ligand environment (changing one alcohol ligand to a pyrrole ligand) resulted in enyne metathesis reactivity. Mono pyrrolide catalyst **22** promotes RCM (equation 67).[127] Interestingly, the ring size formed from a 1,6-enyne is not the same as would be expected based on RCEYM promoted by ruthenium carbenes. The mode selectivity observed in equation 67 is called *endo*-selectivity (it has also been called the β-addition mode). Interestingly, this ring closure 'mode selectivity' is different from that observed with the Grubbs ruthenium carbene, where *exo*-selectivity is observed in small-membered rings. With ruthenium carbenes, the five-membered ring **23** would have been produced by *exo*-addition (**Scheme 24**). This complementary mode selectivity suggests a niche for the molybdenum (and tungsten catalysts).[135] In rare cases where ruthenium catalysts have been used, an initial ethylene cross-metathesis is required to guide *endo*-selectivity. Use of the stereogenic-at-metal complex has provided two asymmetric applications in RCEYM.[134]

The catalyst structure in the Schrock–Hoveyda catalysts influences 'mode selectivity' of ring closure. With one pyrrolide ligand already in place, changing the alkoxy group in the four-coordinate molybdenum catalyst has a profound effect on the ring closure mode selectivity (**Table 18**). For instance, the heteroleptic catalyst **23** gives primarily the *exo* ring closure mode, but changing to catalyst **24** results in exclusively *endo*-mode. This example illustrates how the ligands surrounding the metal atom determine

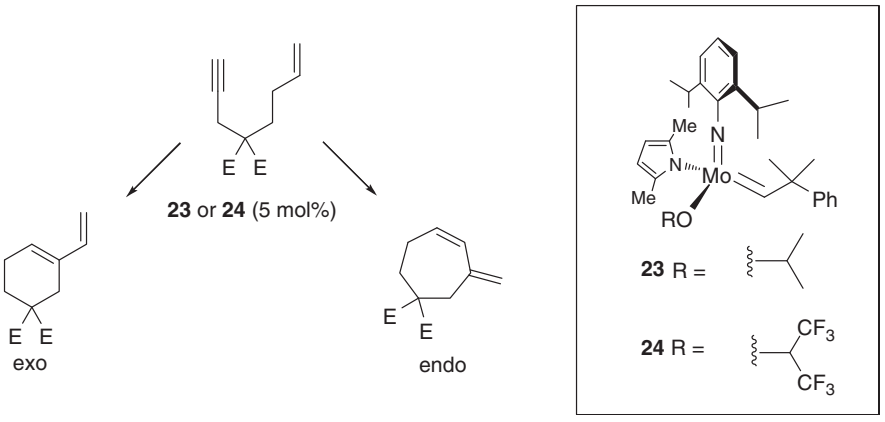


Scheme 24 Schrock–Hoveyda molybdenum carbene-promoted RCEYM.[127]

reactivity profile and how a class of catalysts once dismissed for enyne metathesis has emerged with both the reactivity and a degree of selectivity previously unseen.

Table 18 Molybdenum ligand environment affects the mode of ring closure[75]

Entry	*Catalyst*	*Ratio*(exo:endo)	*Yield (%)*
1	23	80:20	79
2	24	0:100	70

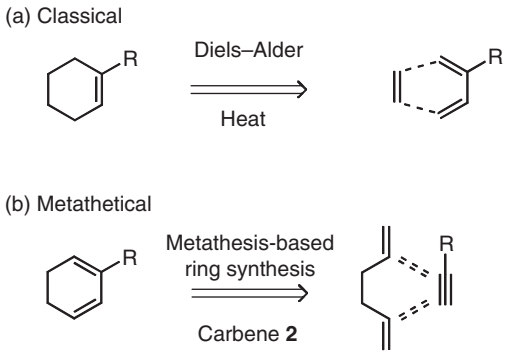


The new Schrock catalysts have improved selectivity and may have improved functional group tolerance compared with the parent Schrock catalyst. Although the outlook is hopeful, there has been a higher barrier to the use of the Schrock complex due to its moisture sensitivity and its lower functional group tolerance for alcohols and ethers. Recently, the Schrock catalysts have been rendered significantly more bench stable through complexation with 2,2′-bipyridine.[136] This practical advance will facilitate the use of these catalysts in synthetic laboratories. For RCEYM, the reactivity issue has been solved through tailored catalyst design. With continued improvements in the synthesis of *in situ* catalysts and their recognized versatility, the perceived barrier to using these complexes is expected to be less significant. Though one can argue that Mo(IV) is too oxophilic to use in complex molecule total synthesis, one is reminded of the early, successful ring-closing alkene metathesis approach to fluvirucin (Sch 38516) by Hoveyda,[137] where a protected sugar and amide withstood the metathesis conditions. Most likely, immediate use of the Schrock subfamily of catalysts will capitalize on the unusual enyne metathesis ring closure mode selectivity and the potential for enantioselectivity, due to the unique stereogenic environment at the metal center.

5.27.5 Ring Synthesis

Rings can be formed by EYM between 1,ω-dienes and alkynes.[138] To accomplish this ring synthesis, both a CEYM and *in situ* RCM would occur in the same reaction. The use of a 1,5-diene such as 1,5-hexadiene as a four-carbon donor to an alkyne results in the synthesis of 1,3-cyclohexadienes. Larger rings can be formed by cross-metathesis/ring closing performed on enyne substrates.

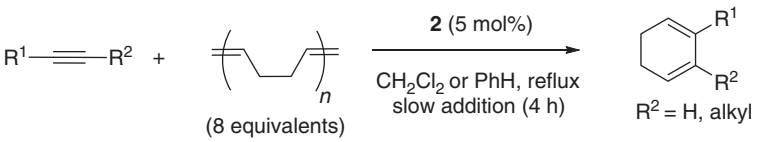
Cross-metathesis between dienes and alkynes provides a powerful ring synthesis of 1,3-cyclohexadienes. For example, the venerable Diels–Alder reaction forms a six-membered ring by a cycloaddition between an alkene and 1,3-diene. In a similar vein, a two-carbon plus four-carbon additive metathesis reaction would form the six-membered ring with a conjugated diene present. To take the analogy with the Diels–Alder reaction one step further, the newly formed six-membered ring contains a 1,3-diene rather than a cyclohexene, the 'residual unsaturation' characteristic of the Diels–Alder cycloadducts (**Scheme 25**). Of course, the Diels–Alder reaction is superior due to its simplicity: It only requires heat to bring the reactants together in the ordered transition state. The methylene-free ring synthesis joins two carbons from the alkyne with four carbons from the diene reactant. The ring synthesis is promoted by the Grubbs carbene **2** and is favored by π-reorganization. Unlike the Diels–Alder reaction, the ring synthesis results from several discrete metathesis steps and is not concerted. The products of methylene-free ring synthesis are themselves amenable to subsequent Diels–Alder reaction serving in the capacity of 1,3-diene.



Scheme 25 Six-membered ring-building approaches.

The methylene-free tandem metathesis approach offers a synthetically useful ring synthesis (**Table 19**). The reaction is preparatively useful and can be conducted on a larger scale at reduced catalyst loadings.[141] Either 1,5-cyclooctadiene or polybutadiene can be used as the alkene reactant. Because there are no terminal methylene groups, this is termed 'methylene-free conditions.' These conditions are thought to permit equilibration between *E*- and *Z*-vinyl carbene intermediates. In more difficult cases, such as those employing coordinating heteroatoms on the alkyne or internal alkynes, higher concentrations of 1,5-cyclooctadiene or the polymer polybutadiene are needed.[139] Some representative products are illustrated in **Table 19**.

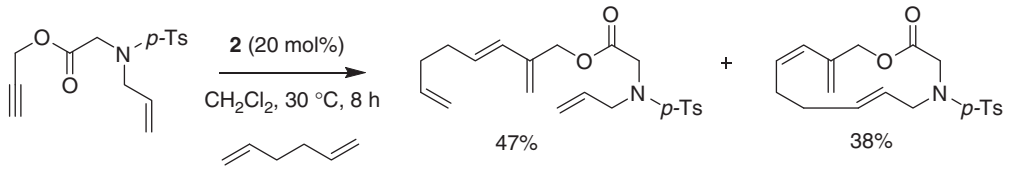
Table 19 Methylene-free enyne metathesis: Formation of 1,3-cyclohexadienes[139,140]



(68)

Entry	*R^1*	*R^2*	*Yield (%)*
1	$(EtO_2C)_2CHCH_2$	H	82
2	$BnOCH_2CH_2$	H	70
3	$BocN(Ts)CH_2CH_2$	CH_3	72
4	$TsOCH_2CH$	H	72
5	$TsNHCH_2CH$	H	73
6	$AcOCH_2$	C_2H_5	65
7	MeO_2C	Me	53

EYM has been used as a key step in a diversity-oriented approach to macrocyclic structures through a cross-metathesis/ring-closing ring synthesis. Kotha and Singh generated a diverse collection of macroheterocyclic derivatives by CEYM with 1,5-hexadiene followed by a macroring-closing metathesis (equation 69). This cascade reaction is effective in producing macroheterocycles. In addition, a tetraene product was isolated due to *E*-diene formation. The mixture of products reflects the nonstereoselective cross-metathesis. The isolated *E*-tetraene was resubjected to the second-generation Grubbs catalyst **2**, but failed to undergo RCM.

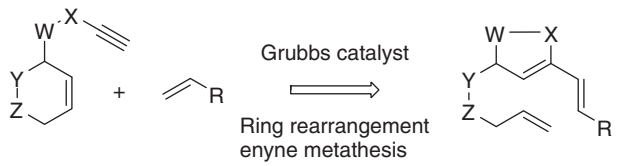


(69)

5.27.6 Ring-to-Ring Conversions by EYM

5.27.6.1 Ring Rearrangement Enyne Metathesis

RCEYM onto a pendant cycloalkene shuffles the ring. In the process, the existing cycloalkene (YZ linker atoms) is converted into a new ring incorporating the atoms that separated the cycloalkene and alkyne in the first place (linker atoms W–X, equation 70). Often the linker W–X includes a heteroatom, which distinguishes this metathesis as a useful conversion of carbocyclic rings to heterocyclic rings.

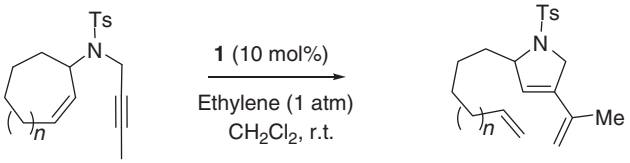


(70)

To the best of the authors' knowledge, the reaction was developed independently by Blechert[142] and Mori.[143] Blechert dubbed the process to be a 'ring rearrangement;[142,144–147] this terminology will be used throughout this section. The ring rearrangement is driven forward to products by π-bond reorganization, the same enthalpic driving force of enyne metathesis. Typically, a carbocycle is broken, whereas a heterocycle is formed.

The ring rearrangement enyne metathesis occurs in the presence of added ethylene. To a first approximation, the mildness of the rearrangement inversely correlates with the stability of the cycloalkene. Seven- and eight-membered cycloalkenes perform well in the ring rearrangement promoted by the first-generation Grubbs complex **1** (Table 20).[143] Though the carbocycle to heterocycle forward reaction may seem surprising, it is driven by the π-bond reorganization of the enyne metathesis, and it is not due to the stability of the new ring system formed.

Table 20 Ring rearrangement with added ethylene[143]



(71)

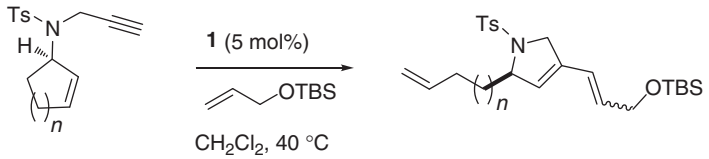
Entry	n	*Time (h)*	*Yield (%)*
1	1	24	56
2	2	1	75

Other alkenes can be added in the ring rearrangement enyne metathesis. Initial studies by Mori had focused on ethylene,[143] yet Blechert found that other alkenes could be incorporated into the resulting 1,3-diene (Table 21).[142]

In this example, the alkylidene is formed from the added silyl allyl ether that reacts with the alkyne, then triggers ring rearrangement onto the pendant cycloalkene to produce the triene product (Scheme 26). The site of reaction by the metal carbene can be influenced by propargylic ethers, which lead to alkene incorporation on the cycloalkene if propargylic ethers are present (not shown).[142]

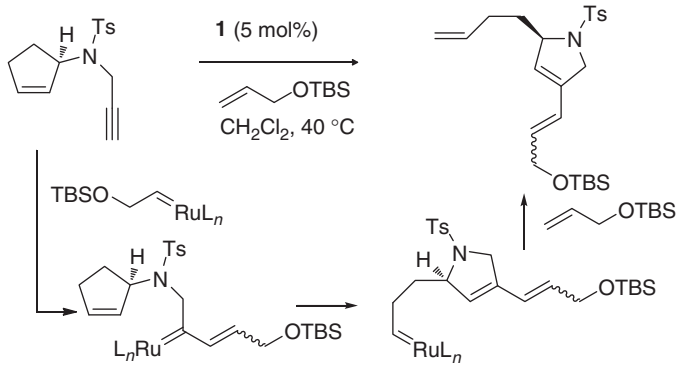
Mori observed diastereospecific ring rearrangements with cyclohexenes bearing an endocyclic chiral center.[143] In these two examples, each conducted under ethylene, initial ethylene–alkyne metathesis produces a vinyl carbene (see inset of Scheme 27). To undergo ring rearrangement, the vinyl carbene must approach the pseudoaxial silylether to access the ruthenacyclobutane giving ring closing. This is impeded in the conformer shown. In the *trans*-diastereomer, this interaction is not present because the silylether resides in a pseudoequatorial position. The absence of this steric interaction allows the RCM onto the cyclohexene ring to proceed uneventfully (equation 74). The resulting triene is poised for intramolecular Diels–Alder cycloaddition after oxidation of the allylic alcohol.

Table 21 Ring rearrangement enyne metathesis with a higher alkene[142]

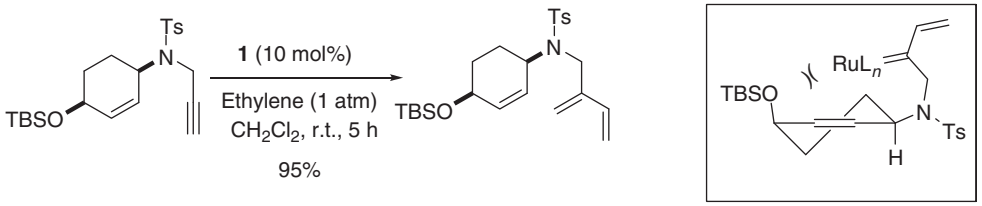


(72)

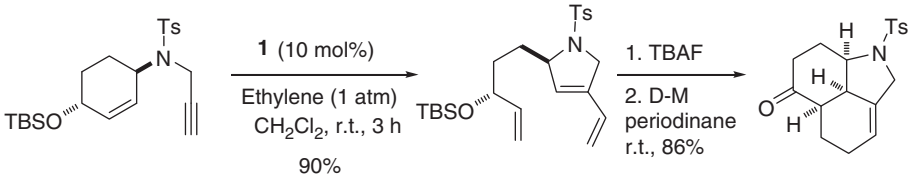
Entry	n	*Yield (%)*
1	1	78
2	2	85
3	3	81



Scheme 26 Sequence of carbene reactions in ring rearrangement.



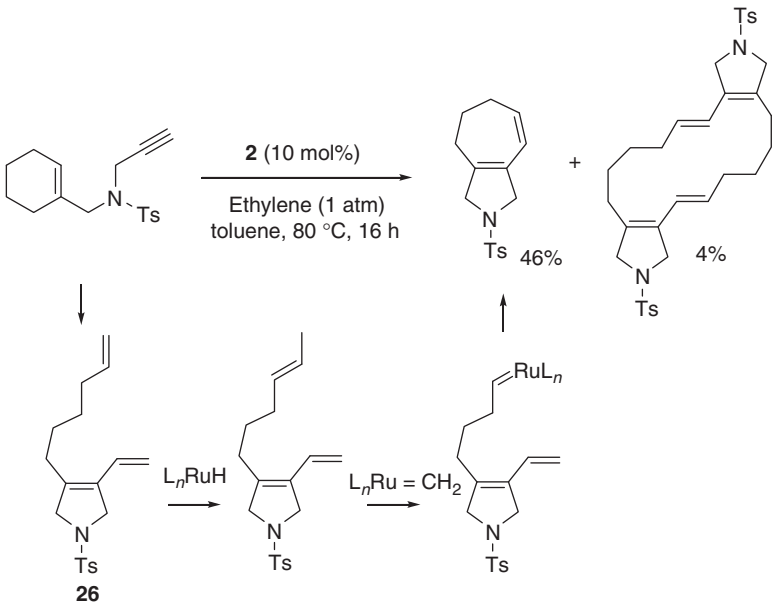
(73)



(74)

Scheme 27 Diastereospecific ring rearrangement enyne metathesis.[143]

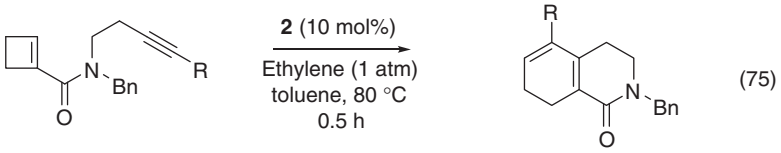
The increased reactivity of the second-generation Grubbs carbene permitted more difficult ring rearrangements onto more highly substituted cyclohexenes. The first-generation carbene **1** could not open the cyclohexene and instead promoted ethylene cross-metathesis. Under more forcing conditions possible with **2**, a seven-membered ring carbocycle was obtained along with a trace dimeric product (Scheme 28).[148] The seven-membered ring was not expected; addition of the six-membered ring to the alkyne should have formed an eight-membered ring. The forcing conditions caused alkene isomerization via the intermediate triene **26**. Ruthenium hydride-promoted alkene isomerization is followed by reinitiation and RCM on the pendant diene, which resulted in the truncated ring rearrangement product. Under less forcing conditions (refluxing CH_2Cl_2), the desired eight-membered ring product was obtained as a minor coproduct along with the 1,3-cycloheptadiene and dimer.



Scheme 28 Unexpected truncation product under more forcing ring rearrangement.[148]

Strained cycloalkenes also give the ring rearrangement (Table 22).[149] Given the potential for the cyclobutene to undergo competing ring-opening metathesis polymerization, ethylene is added. This is quite typical in RCM or metathesis cascades involving strained cycloalkenes. The added ethylene helps suppress polymerization of the strained cycloalkene. This net process is similar to the intermolecular synthesis of 1,3-cyclohexadienes using methylene-free conditions.[140]

Table 22 Ring rearrangement to form isoquinoline derivatives[149]



(75)

Entry	*R*	*Yield (%)*
1	H	61
2	Me	56
3	Ph	82

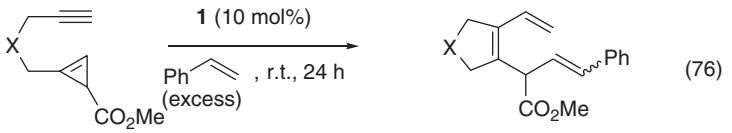
Ring rearrangement with cyclopropene-containing reactants provides skipped triene products. Ring opening of the cyclopropene is triggered by an external alkene such as styrene (equation 76; Table 23). As in the example above, an added alkene used in molar excess helps prevent homopolymerization of the strained cycloalkane, as demonstrated previously by Snapper et al. in selective ring-opening cycloalkene-alkene cross-metathesis.[150] The regioselectivity of the cyclopropene ring opening positions the carbene proximal to the alkyne. Ring closing onto the pendant alkyne results in the ring-rearranged product (equation 76).[151]

Metathesis cascades are extremely efficient for rapidly generating skeletal diversity. In Scheme 29, metathesis events are controlled in a stepwise process that capitalizes on catalyst attributes.[152] The overall process most likely begins with ethylene cross-metathesis joining the strained norbornene with the alkyne. The second-generation Grubbs catalyst would broker the formation of the seven-membered ring. To facilitate purification of the intermediate triene from the ruthenium catalysts, a polar isocyanide[39] is used to quench the catalysts and facilitate the removal of the organometallic impurities. Using microwave irradiation allowed Spring et al. to accelerate the metathesis and conduct a cycloaddition on the diene subunit to gain access to an additional ring.

5.27.6.2 Synthesis of 1,3-Cycloheptadienes

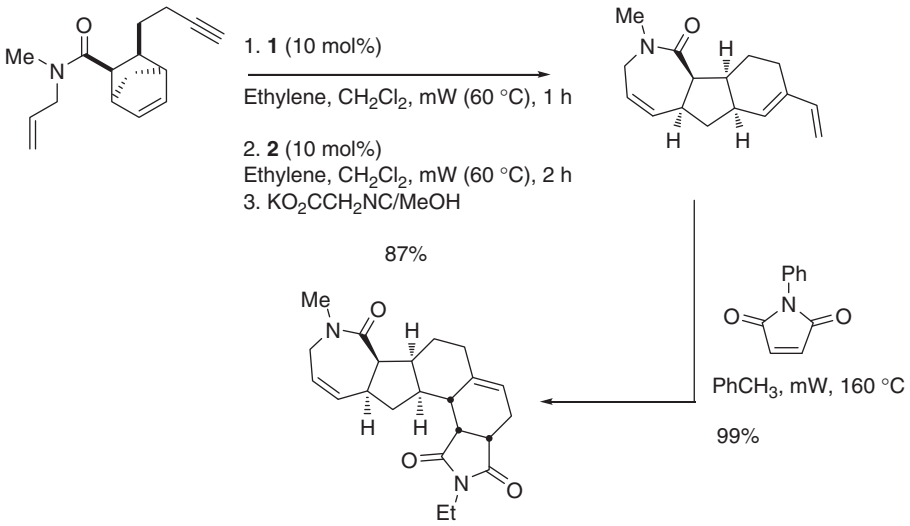
Like the ring rearrangement, an existing ring can be converted into a larger ring by net alkyne insertion. This is a ring expansion EYM that occurs as a result of a cascade process. In contrast to the ring rearrangement described in Section 5.27.6.1, ring

Table 23 Ring rearrangement involving cyclopropenes



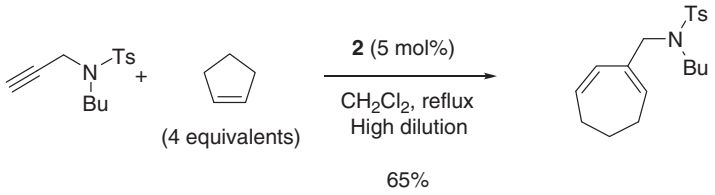
(76)

Entry	*X*	*Yield (%)*	E/Z *ratio*
1	NTs	60	1:1.5
2	O	55	1:1.4



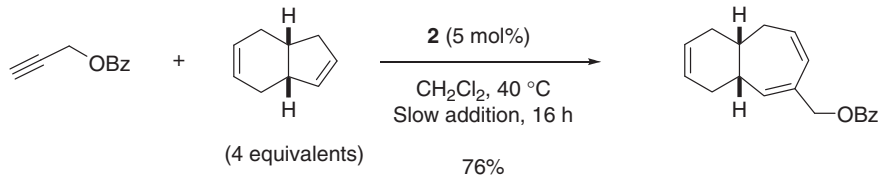
Scheme 29 Cascade metathesis to generate skeletal diversity.[152]

expansion is an intermolecular process. This makes the reaction more challenging. Moreover, because of the decreased reactivity with cycloalkenes in the intermolecular manifold, competing reactions such as alkyne polymerization become problematic. As a result, high dilution of the alkyne is needed along with a molar excess of the cycloalkene. An example of the ring expansion with cyclopentene is shown in equation 77. [153]



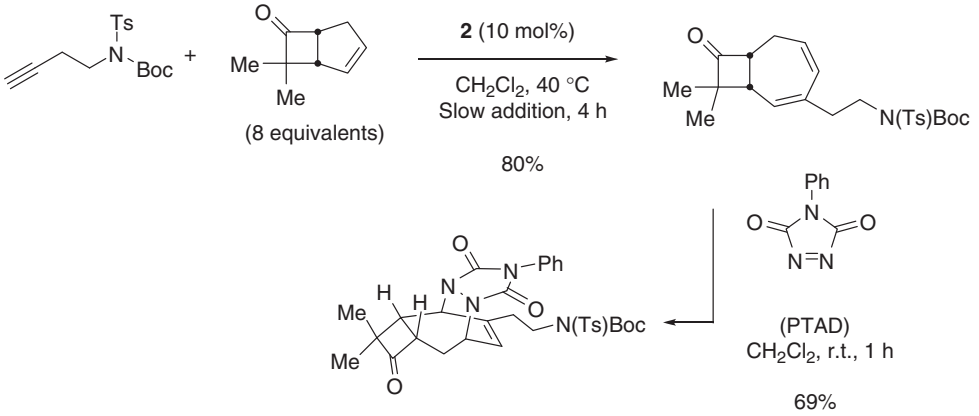
(77)

In bicyclic systems, the double bond in the five-membered ring reacts selectively. There are two issues: which alkene will react (site selectivity) and what is the orientation of the alkyne substituent in the product (regioselectivity). The ring opening of bicyclic diene proved highly selective and produced a single product[154] (equation 78). To obtain the desired product, slow addition of the reactive components to the Grubbs catalyst was needed via syringe pump addition. These reaction conditions benefit from a robust second-generation Grubbs catalyst, which must survive for an extended period of heating. Because ruthenacyclobutane ring openings are not generally stereoselective, the origin of the stereoselectivity is thought to arise from *E*/*Z* isomerization of vinyl carbenes occurring *in situ*.



(78)

To guide regioselectivity in bicyclic systems, a bulky group at the allylic position is required. In the bicyclic ketone shown, the geminal dimethyl substituents guide the ring opening of the cyclopentene and give a single cycloheptadiene product (Scheme 30). Facile [4 + 2] cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) gives a crystalline tetracyclic product.



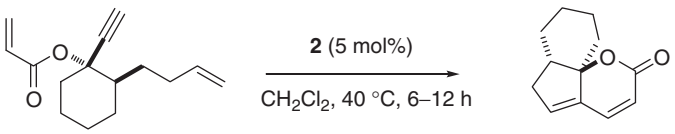
Scheme 30 Regioselectivity in the ring expansion of a bicyclic cyclopentene.[154]

5.27.7 Cascade Enyne Metathesis

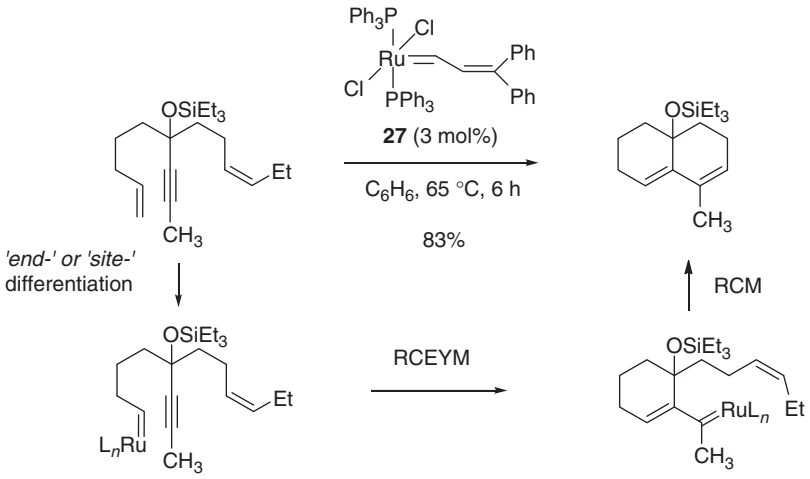
Cascade dienyne metathesis is a powerful ring-building method that furnishes multiple rings from acyclic precursors. Ring-forming reactions are very powerful transformations since many biologically active molecules contain one or several ring systems. The potential of cascade metathesis to produce different polycyclic ring systems from common precursors by using differential alkene reactivity has become an important method of generating skeletal diversity. A common theme in these reactions is the exploitation of the different reactivity of the alkenes, an important concept that borrows heavily from mechanistic understanding of alkene metathesis (the Grubbs model). The metathesis cascade begins with reaction of one alkene, ring closure onto the alkyne, and the next ring-forming metathesis by closure on the other alkene. Control can be achieved in unsymmetrical dienynes by rendering one alkene more reactive toward the metal carbene. Higher reactivity is achieved in less substituted alkenes that are not electron deficient. This serves to orchestrate the first ring closure onto the alkyne. The alkyne serves as a 'relay' linking the two ring closure events. Interestingly, the RCEYM is generally favored over a possible alkene–alkene RCM. The most commonly used catalysts are the Grubbs ruthenium benzylidene complexes **1** and **2**. A variety of small and medium-sized rings can be formed in this metathesis cascade. However, bulky groups may significantly slow down the RCEYM and attempted the eight-membered ring formation may lead to truncation products arising from undesired alkene isomerization side reactions.

The differential substitution of the pendant alkenes controls the ring size of the bicyclic system formed. Dienyne undergoes cascade metathesis with an earlier Grubbs catalyst **27** to provide the bicyclo[4.4.0]decane (Scheme 31).[155,156] This process begins by metal carbene formation on the 1-alkene, which achieves end differentiation. Had the other more substituted *cis*-alkene initiated, a bicyclo[5.3.0]decane would have resulted. Experimentally, these intramolecular metathesis cascades can be favored over intermolecular reactions by conducting the reaction at high dilution.

The same concepts of end differentiation apply to electronically distinct alkenes. In this case, the more electron-rich alkene initiates the cascade reaction (equation 79). The electron-poor acrylate reacts more slowly.[157] Interestingly, this study found that the initial RCEYM always out competed the ring-closing alkene–alkene metathesis. Along with the approach to securinine in the previous section, relative alkene reactivity provides useful information when planning metathesis cascades. In this case, the metathesis sequence produces bicyclic lactones containing the conjugated 1,3-diene.

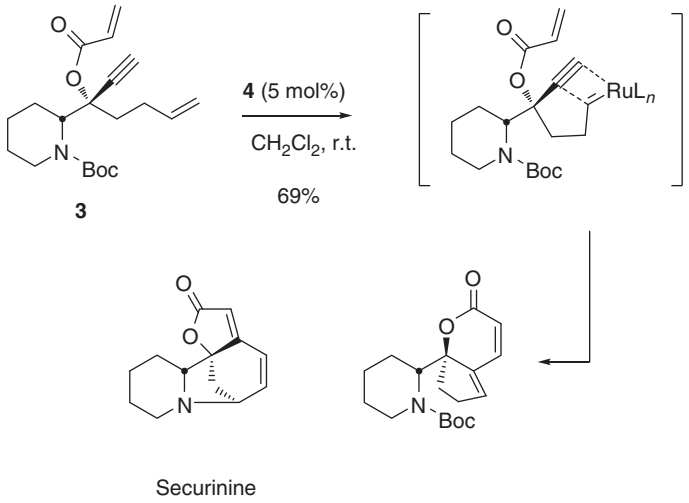


(79)



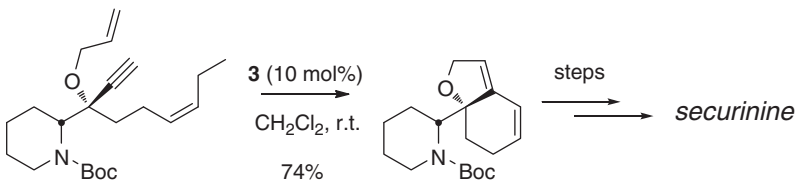
Scheme 31 Metathesis polycyclization and end group differentiation.[155]

A tandem RCEYM that involves an electron-deficient alkene benefits from phosphine-free catalysts. Honda and coworkers prepared the *securinega* alkaloid securinine by a tandem enyne metathesis. The reaction began at the more electron-rich terminal alkene to give the observed product, which does not have the same bicyclic ring system found in securinine (**Scheme 32**).[158] The initial ring closure produced the five-membered ring rather than the desired six-membered ring present in securinine.



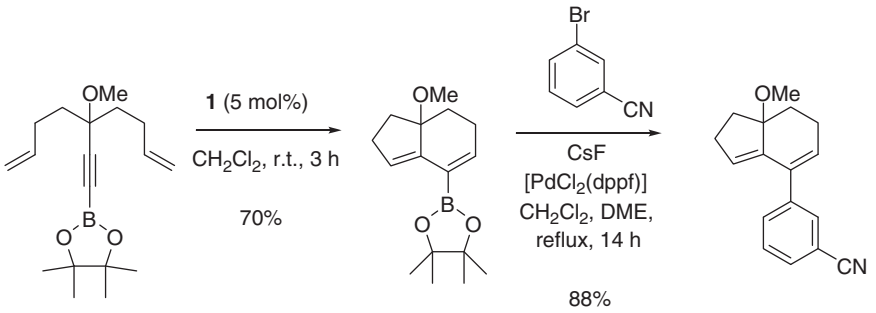
Scheme 32 Site differentiation with phosphine-free grela catalyst **4**.[158]

To obtain the desired bicycle, the initiation profile had to be reversed. In other words, the alkene of the enoate had to be rendered more reactive so it would initiate the cascade. From the Grubbs reactivity model of alkene cross-metathesis, terminal aliphatic alkenes are the most reactive with the Grubbs catalysts.[70] Dienyne bearing an allyl ether was used to initiate the cascade (equation 80). Simultaneously, the 'lower' alkene's reactivity had been tempered by converting it to a less reactive internal alkene. After a series of allylic oxidations, the synthesis of the alkaloid securinine was completed.



(80)

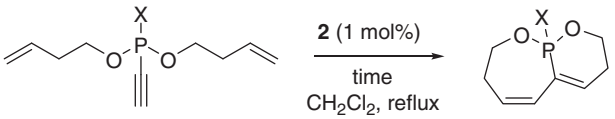
Boron-substituted alkynes participate in cascade cyclization to give products amenable to Suzuki coupling. Cascade metathesis with first-generation carbene **1** gave the bicyclic diene, which was cross-coupled with an aromatic ring under Pd(0) catalysis (equation 81).[159]



(81)

Phosphorus heterocycles can be accessed by a tandem ring-closing dienyne metathesis (equation 82; Table 24). The phosphorus-substituted alkyne proved reactive, despite its electron-deficient nature. Interestingly, the phosphine borane underwent successful RCEYM without reduction of the Grubbs catalyst. In this example, the equivalent reactivity of the terminal alkene means that the cascade can start at either end to produce the observed heterocycle.

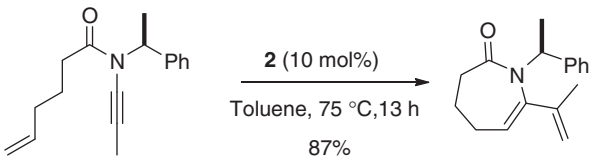
Table 24 Phosphorus-containing oxa-bicyclics



(82)

Entry	*X*	*Time (h)*	*Yield (%)*
1	O	0.5	76
2	BH_3	16	75

Electron-rich alkynes also participate in cascade ring-closing dienyne metathesis to bicyclic dienes with a nitrogen atom at a bridgehead position (equation 83).[160] These heterocycles are unsaturated homologs of the indolizidine alkaloids. If the second ring closure is difficult, such as in the eight-membered ring formation, the reaction may terminate after a single RCEYM to give a monocyclic product (entry 1; Table 25). When the second ring-forming step is slow, the by-products associated with double-bond migration are observed (entry 2). Competing reactions leading to by-products can be anticipated due to high temperatures required to form eight-membered rings, a process disfavored due to the negative entropy associated with ring closure. With two similar ends of dienyne, the reaction cascade begins at either side to give a 1:1 mixture of bicyclic products. If the initiation is inhibited at one site, the other more reactive terminal alkene triggers the cascade giving predominantly one bicyclic product. A similar example can be found in Section 5.27.6.1.

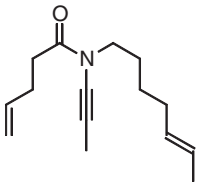
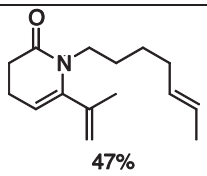
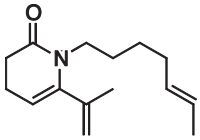
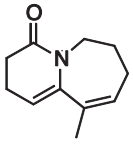
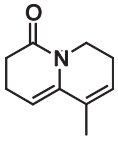
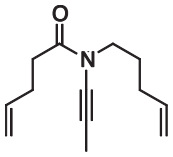
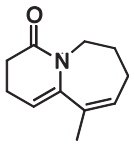
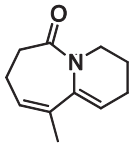
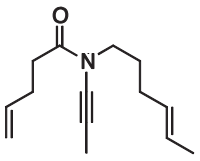
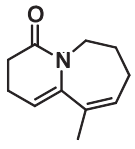
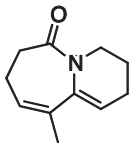


(83)

The cascade metathesis has also been used as an entry point to bicyclic ring systems that contain seven-membered rings. Seven-membered rings can be found in a variety of natural products. The polycyclization has been employed to gain access to the guanacastepene carbotricyclic framework[161,162] (equation 84; Table 26). A variety of substituents on the alkyne were tolerated in the metathesis, with the exception of a TMS group that is presumably too bulky to permit the alkyne insertion step. Interestingly the ring-closing cascade begins from the vinyl appendage of the diene, and this requires the use of the more reactive second-generation Grubbs catalyst.

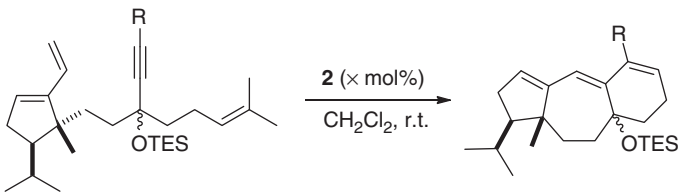
The unsaturated tricyclic ring system of colchicine was made through a polycyclization by cascade metathesis[163] (Scheme 33). A free propargylic hydroxyl group prevented the metathesis, so protection as the TMS ether was required (a similar solution has been used in a related RCEYM).[114] (To the authors' knowledge, the only cases where a free propargylic hydroxyl group is allowed is ethylene–alkyne cross-metathesis.) In this case, a clever oxidative [3,3] sigmatropic rearrangement was used to alter the diene substitution pattern and accomplish the oxidation of the secondary chromate ester. The epimers proved inconsequential as the oxidative rearrangement converged to the enone product. The PCC oxidative rearrangement is an interesting organic transformation applied to the dienes obtained through enyne metathesis.

Table 25 Tandem ring-closing dienyne metathesis of ynamides catalyzed by **2**

Entry	*Dienyne*	*Product(s), Yield (%)*
1		 47%
2		 52%  26%
3		 38%  38%
4		 60%  10%

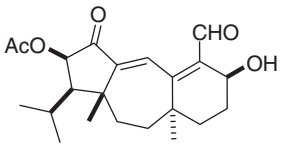
Conditions: **2** (5–10 mol%), toluene, 75 °C, 12 h

Table 26 Cascade metathesis approach to guanacastepene[161]



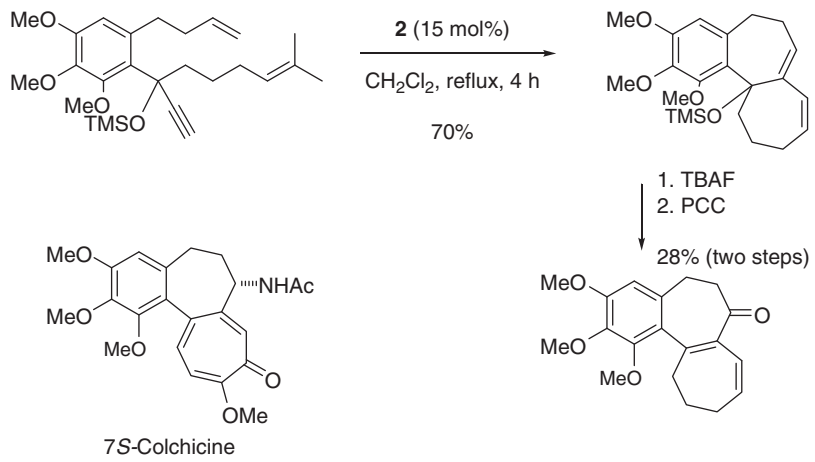
(84)

Entry	*R*	*Loading*	*Yield (%)*
1	H	7.5	80
2	Me	7.5	70
3	$SiMe_3$	7.5	N.R.
4	CO_2Me	10	93



Guanacastepene A

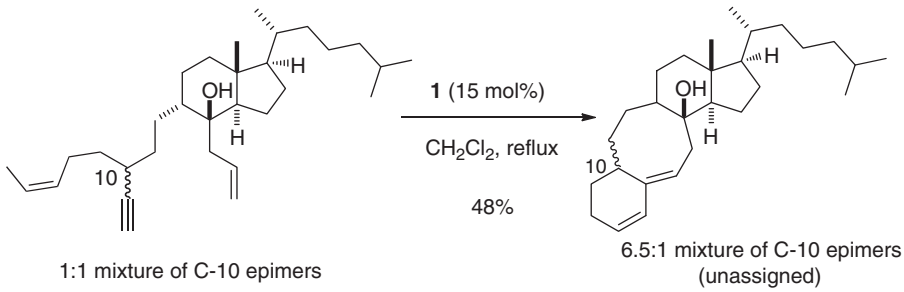
In the above two examples, the introduction of the alkyne into the reactant is difficult to control, which required that the diastereomeric mixture be carried through the synthesis. This serves to highlight one of the difficulties in the synthetic preparation of the required polyunsaturated substrates (dienynes in this case). In more rigid systems with existing stereocenters, the presence



Scheme 33 Polycyclization approach to colchicines.[163]

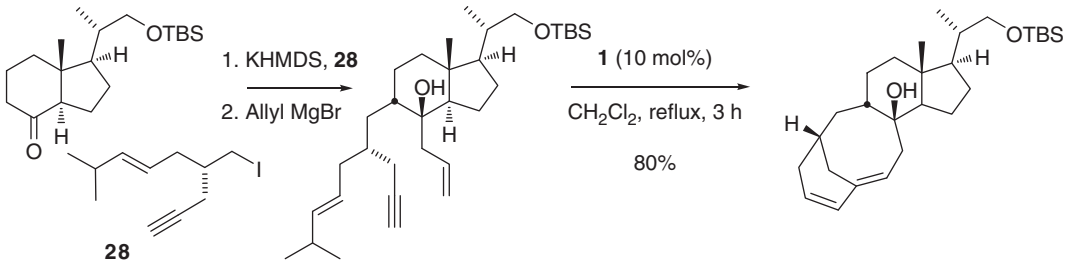
of epimers might result in kinetic differentiation, as observed by Clark et al. previously.[164] Some evidence of this diastereodifferentiation can be found in the next example.

The metathesis cascade can also furnish eight-membered rings. In the first ring closure, an eight-membered ring is formed in the synthesis of a vitamin D_3 transition-state analog[165] (equation 85). In this case, the first-generation Grubbs carbene was employed, and the cyclization was conducted under high-dilution conditions (4.7 mM in CH_2Cl_2). A 1.7:1.0 mixture of diasteromers resulted in a product consisting of a 6.5:1 mixture of C-10 diastereomers yield, which suggests that one epimer cyclized more favorably than the other.



(85)

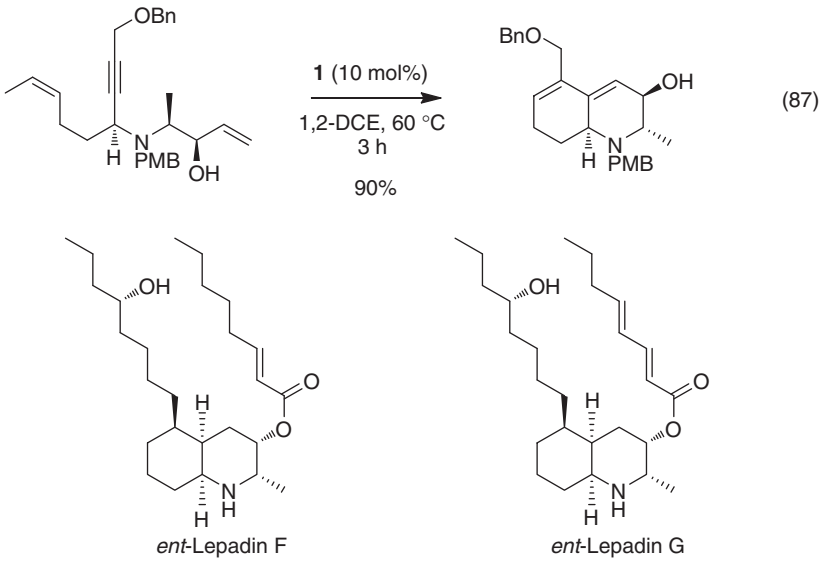
Remarkably, the strained bicyclic [5.3.1] ring system found in taxol can be formed by a metathesis cascade. In this study, Granja et al.[166,167] found that the catalyst **1** gave the best results in their approach to 'taxosteroids' (equation 86). The cascade is initiated at the homoallylic alcohol to form the eight-membered ring in the initial enyne metathesis ring closure. To ensure end differentiation of the alkenes and to avoid formation of the alternative bicycle starting from a five-membered ring, the kinetic decelerating substitution of the pendant alkene was systematically evaluated. An optimum balance of reactivity was achieved by the use of the isopropyl-substituted alkene, as a trisubstituted alkene did not undergo the second ring closure. This study shows that a successful bicyclization depends on the proper choice of alkene substitution to achieve end differentiation.



(86)

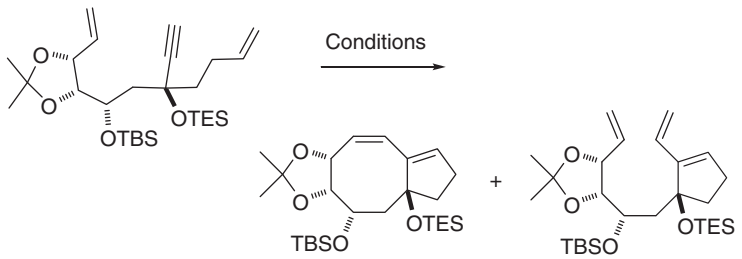
Tandem dienyne RCM can access bicyclic systems containing a heterocyclic ring. As a key step in their synthesis of lepadin F and G, the skeletal synthesis by tandem dienyne metathesis was achieved in a 90% yield (equation 87, Scheme 34).[168] The hexahydroquinoline ring system was carried forward to provide the first total synthesis of lepadin F and G.

In a highly oxygenated environment, the reactivity difference between the first- and second-generation Grubbs carbenes determined the success of the second ring closure. The first-generation catalyst **1** gave RCEYM beginning with the most reactive



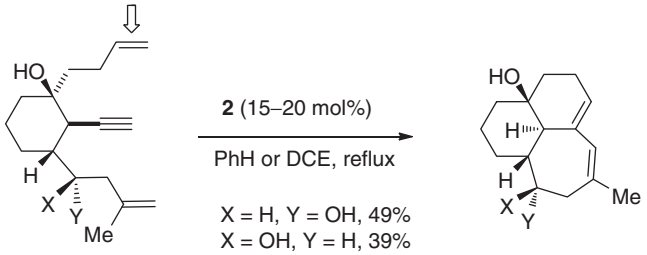
Scheme 34 Dienyne metathesis cascade approach to the lepadins.[168]

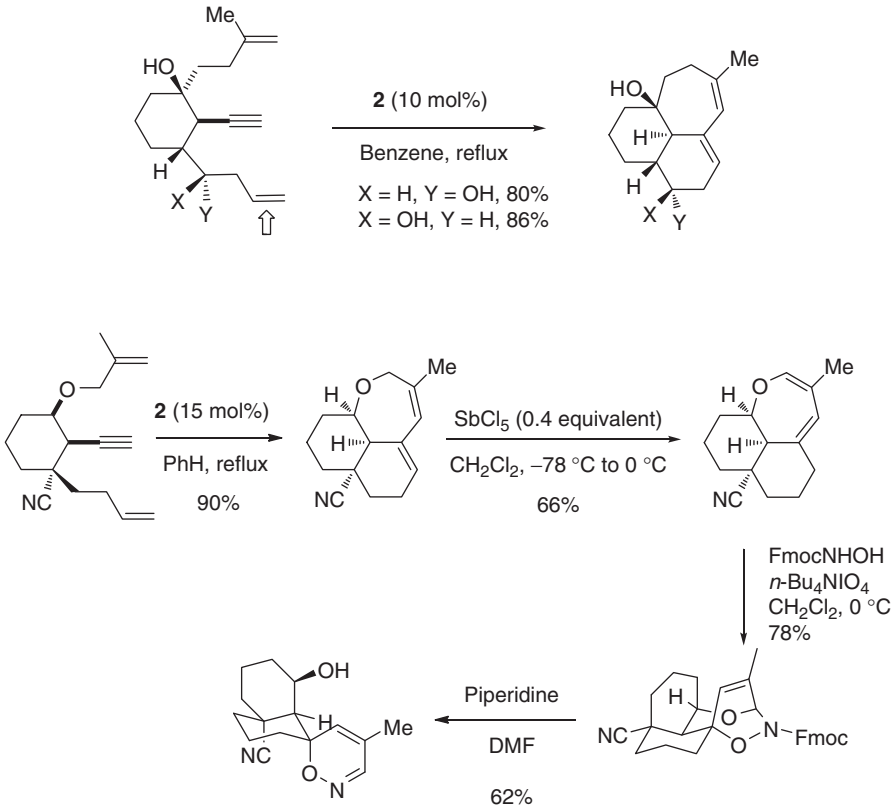
alkene and the reaction stopped at the triene stage (equation 88).[169] To encourage the second cyclization, the more reactive Grubbs complex **2** was employed.



1 (20 mol%), PhH, reflux, 17 h	–	85%
2 (10 mol%), CH_2Cl_2, reflux, 24 h	94%	–

Polycyclization using tandem RCEYM proved to be an effective strategy to generate diverse structural analogs of the anti-trypanosomal agent artemisinin. An advantage of the site differentiation is the ability to access different cyclic core structures, depending on the placement of the initiating alkene (equations 89 and 90).[170] This approach is highly attractive for the construction of unique polycyclic frameworks that could be used in directed library synthesis or DOS. To complete the synthesis of structural analogs, dienyl isomerization was required. After screening several different Brønsted and Lewis acids, catalytic SbF_5 was used to produce the endocyclic diene (**Scheme 35**). The endocyclic diene underwent cycloaddition with an *in situ*-generated acyl nitroso dienophile giving a cycloadduct, which rearranged during Fmoc deprotection to the unusual spirofused oxazine.

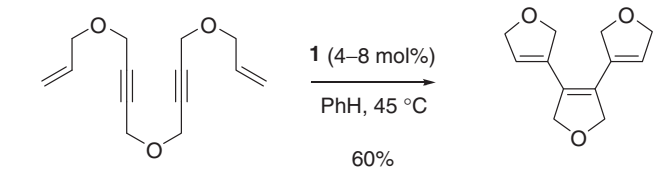




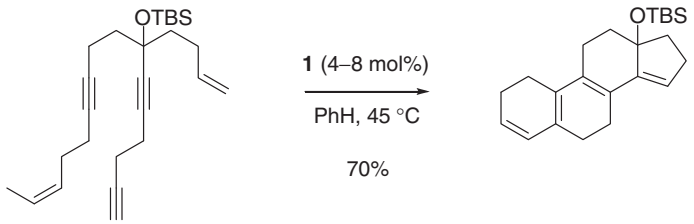
(90)

Scheme 35 Cascade metathesis and dienyl isomerization sequence.[170]

Polycyclization by cascade metathesis proceeds with multiple alkynes situated in between the starting and terminating alkenes. Arranged in this way, the additional alkyne(s) react with the intermediate vinyl carbenes to produce new vinyl carbenes, which eventually terminate. Oxygen heterocycles (equation 91) are easily made as well as the steroid-like tetracycle (equation 92).[171]

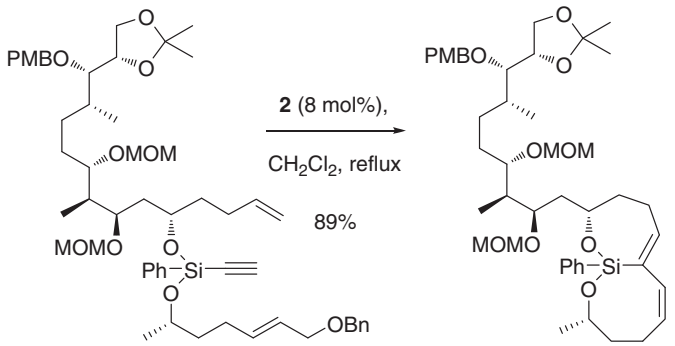


(91)



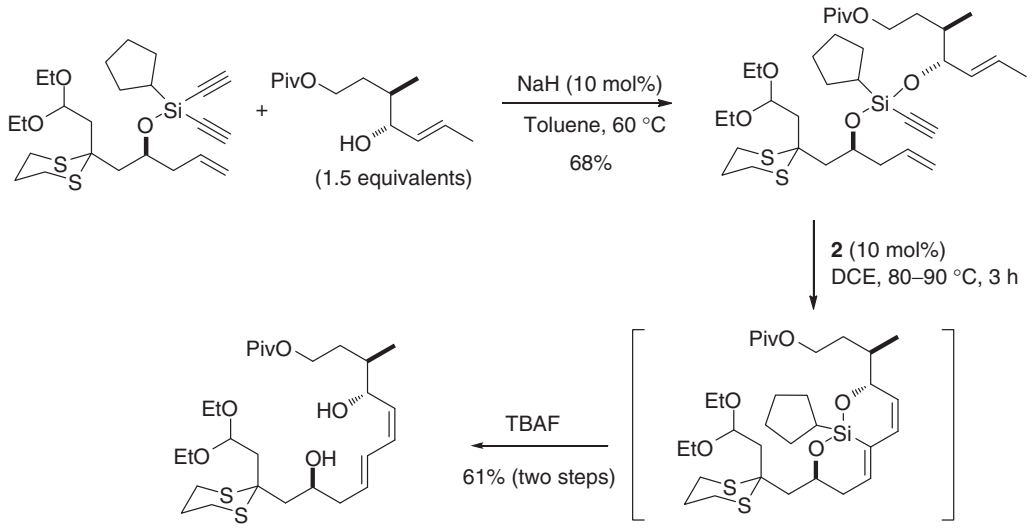
(92)

Siloxane linkers can be used to preorganize unsaturated reactants and then removed to provide stereocontrolled synthesis of 1,3-dienes.[172] This strategy was employed by Kim and Lee for the construction of the unsaturated carbon framework of tartrolon B (equation 93). The silicon atom is used to temporarily connect the alkyne and alkene fragments, similar to the use of boronate linkers by Schreiber and Micalizio.[111,112] Reactivity differences in the two alkenes achieve site differentiation, which resulted in the initial formation of the seven-membered ring. Once the cascade RCM has occurred, the silicon is removed by desilylation using a fluoride source such as TBAF. In this tandem sequence of reactions, various end substitutions on the 1,3-diene can be obtained.



(93)

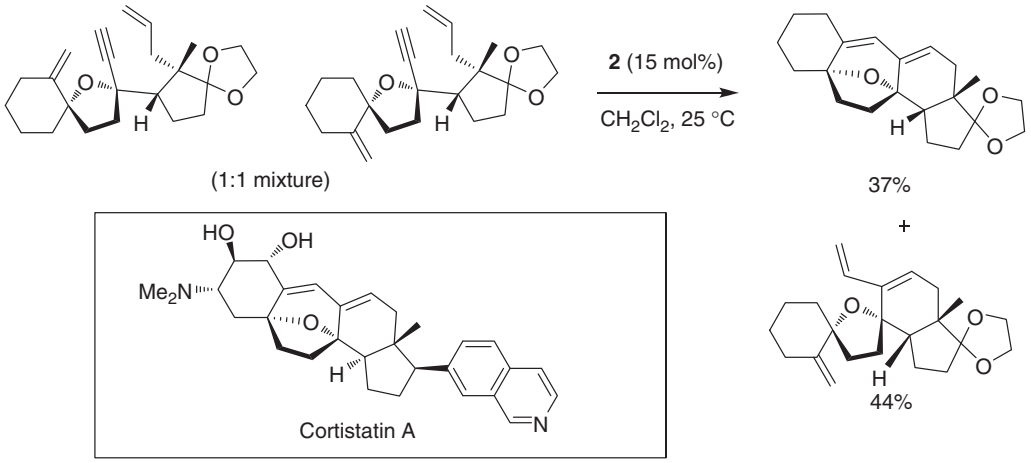
The temporary siloxane linker was used to furnish the 1,3-diene segment of cochleamycin. Access to the mixed silaketal is provided by base-catalyzed replacement of an acetylide with the secondary alcohol. The mixed silaketal sets the stage for the cascade EYM. The control of the rings formed utilized end differentiation, where the more reactive unsubstituted alkene triggered the cascade process (**Scheme 36**). Stereospecific removal of the siloxane was accomplished with TBAF. More recent approaches to the stereoselective synthesis of macrocyclic dienes include the use of site-specific ring-closing alkene–diene metathesis,[173] but this is not detailed in this chapter.



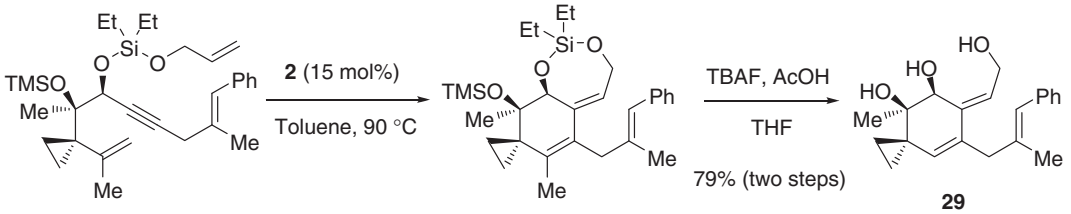
Scheme 36 Siloxane-mediated cascade EYM for stereocontrolled diene synthesis.

The polycyclic core of cortistatin A was accessible by cascade dieneyne RCM. Stolz and coworkers utilized a 1:1 mixture of diastereomers in the cascade metathesis that was triggered by the second-generation Grubbs carbene (**Scheme 37**).[174] As a result, a 37% isolated yield of the desired core ring system was obtained, along with 44% yield of a by-product arising from the other diastereomer. Interestingly, the alternate diastereomer gives a single RCM since the geminal alkene is not able to capture the vinyl carbene intermediate. This shows that cascade enyne metathesis is a rapid method for the construction of the carbocyclic core of cortistatin A.

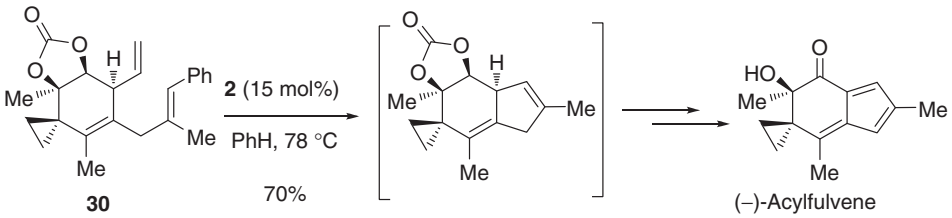
A casacade RCM was used to assemble the core ring system of the spirotricyclic natural product acylfulvene.[175] The metathesis cascade (which was studied extensively in model systems)[176] was initiated by the second-generation Grubbs complex to afford an intermediate tricyclic diene, which was deprotected *in situ* to give the triol **29** (equation 94). The bond-forming events are orchestrated by alkene reactivity; the most reactive allyl ether initiated the cascade and the less reactive geminally disubstituted alkene terminated it. After the tandem reaction, the 1,3-diene was reductively transposed using the Myers protocol for the *in situ* generation of the diazene, giving **30**. This synthetic tactic manages to convert the conjugated 1,3-diene into a 1,4-diene. After the transposition, a ring-closing alkene metathesis of **30** gained access to all three rings of the natural product (–)-acylfulvene (equation 95). This combination of tandem enyne metathesis and a clever diene isomerization stands as an inspiring example of cascade metathesis in the service of total synthesis.



Scheme 37 Cascade metathesis approach to Cortistatin A.[174]

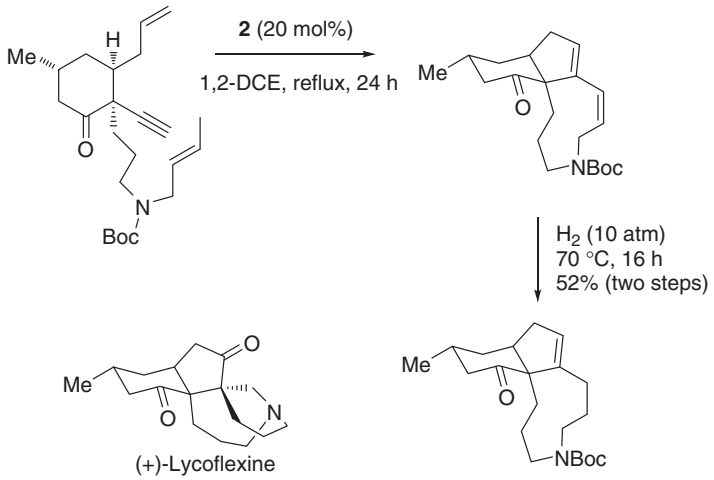


(94)



(95)

A concise tandem ring-closing dienyne metathesis was used to assemble the core polycyclic framework of the alkaloid lycoflexine.[177] The ring-closing event was initiated at the more reactive terminal alkene to first form the five-membered ring (Scheme 38). Strikingly, the second ring closure generated the nine-membered azacyclic ring. The 1,3-diene was semihydrogenated in a site-selective reduction step where the residual Grubbs catalyst was transformed into a ruthenium hydride, giving a ruthenium hydride catalyst that selectively reduced the diene fragment. Such use of tandem catalysis under hydrogenation (H_2) or transfer hydrogenation conditions has been previously employed in ring-closing alkene metathesis/hydrogenation tandem reactions.[75]



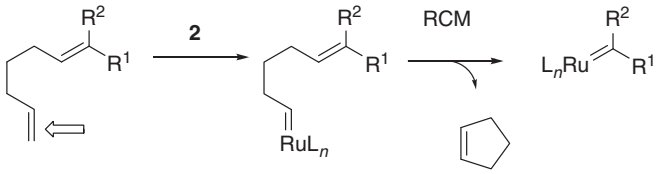
Scheme 38 Cascade metathesis approach to the alkaloid lycoflexine.[177]

5.27.8 Choreographed Movement of Metal Carbenes in Enyne Metathesis Cascades

In the previous section, differential alkene reactivity guided the movement of the carbene to the alkyne, thereby controlling ring size in the resulting bi- or polycyclic frameworks (end differentiation). In this section, a directing alkene is used to guide the metal carbene to a less reactive site through RCM. In the process, the five-membered ring is extruded and lost. This tactic allows for the formation of a metal carbene that would otherwise be difficult or impossible to form. This choreographed movement of metal carbenes is called 'relay RCM' (rRCM). It has been used several times in alkene metathesis literature to guide RCM. The applications to enyne metathesis are somewhat fewer, but ironically it is here that the reaction was discovered. Some recent applications have conjoined rRCM in tandem with distinct reactions such as metallotropic shift.

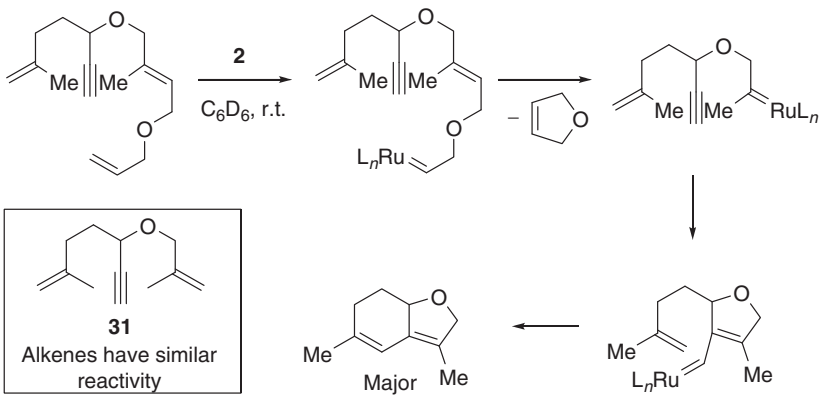
5.27.8.1 Relay Metathesis or rRCM

The relay ring-forming metathesis strategy developed by Hoye is designed to use a favorable RCM to position the metal carbene, usually at a less reactive alkene site. The relay metathesis strategy overcomes the problem of generating reactivity at an unreactive or less reactive alkene site. Hoye and coworkers[178] developed a procedure where a pendant alkene serves as an initiation locus (equation 96). The strategy cleverly exploits alkene reactivity preferences to orchestrate a metathesis cascade. Initiation at the terminal alkene leads to the intermediate metal carbene that undergoes RCM. The RCM step is associated with the loss of a cyclic alkene that translocates the carbene to a site that was not accessible by direct, intermolecular catalyst initiation.



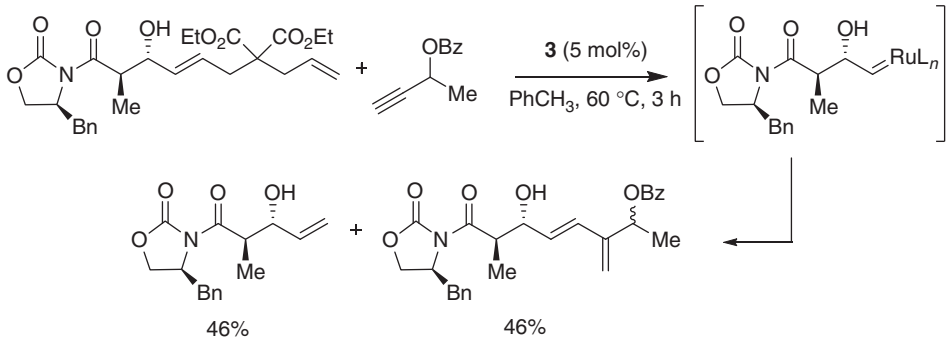
(96)

In addition to its utility for cyclizing unreactive dienes, this strategy can be used to steer metathesis when more than one option is available. The dienyne **31** shown in the inset of Scheme 39 contains two relatively unreactive alkenes. Cascade metathesis is triggered nearly equally at each site, giving a mixture of two products. By adding a terminal alkene three atoms away from the desired site of reaction, higher selectivity is obtained to give one major product due to choreographed metathesis as depicted in Scheme 39. The terminal alkene is the initiating point and through the RCM positions the metal carbene appropriately. Geminally substituted alkenes are difficult to initiate with the Grubbs carbenes; one case of strain assistance was seen previously.[68] The rRCM achieves site selectivity when the starting material has two reactive alkenes. If the relay is triggered on the other side, the opposite site selectivity is obtained producing the alternate bicyclic ring system that contains a pyran ring (product not shown).



Scheme 39 Site selectivity with rRCM.[178]

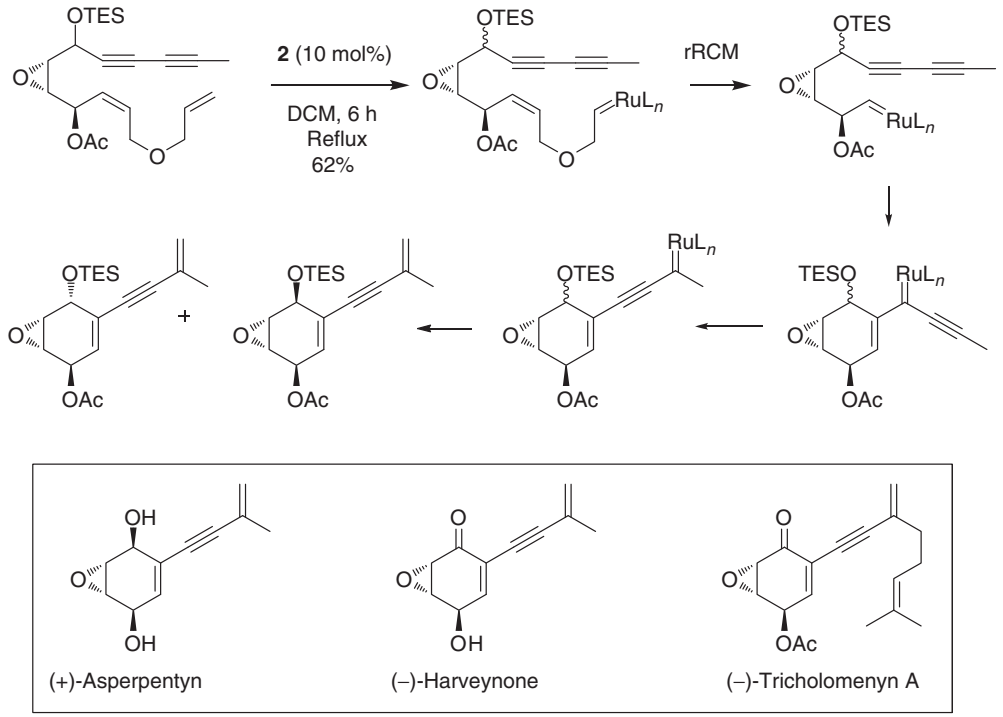
Using the rRCM strategy, Diver and coworkers set the stage for a CEYM.[179] A dienal underwent a catalytic Evans aldol reaction (reaction not shown), and subsequently the Hoveyda–Blechert carbene **3** was used to trigger the relay metathesis in the presence of an external alkyne. The rRCM extrudes a cycloalkene to form an intermediate metal carbene (Scheme 40). In this way, ene–yne cross-metathesis occurs *in situ* with butynyl benzoate, providing a highly functionalized 1,3-diene in a good yield. With 1:1 stoichiometry of alkene and alkyne, the intermediate metal carbene did not completely react with butynyl benzoate such that some *anti*-allylic alcohol was isolated as a coproduct.



Scheme 40 rRCM/CEYM sequence.[179]

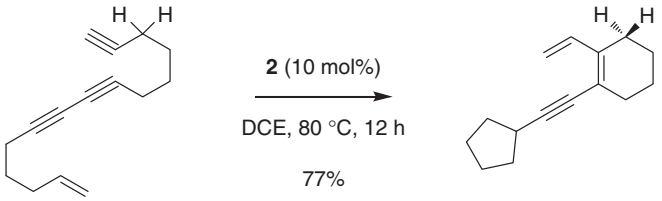
5.27.8.2 Ring-Closing Enyne Metathesis with Metallatropic Shift

Relay ring closing has been conjoined with RCEYM and metallatropic shift as an approach to oxygenated natural products containing an unsaturated sidechain. Lee and coworkers began with a mixture of diastereomers and subjected them to tandem enyne metathesis metallotropic [1,3]-shift for a concise total syntheses of (+)-aperpentyn, (–)-harveynone, and (–)-tricholomenyn A (Scheme 41).[180] The two diastereomers were formed collectively in 62% yield and proved separable by flash chromatography. These were carried forward to give the desired natural products.

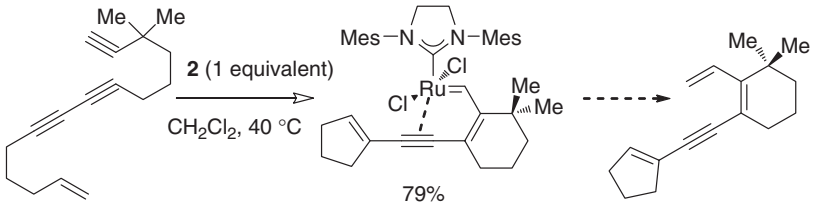


Scheme 41 Access to natural products using polycyclization/metallatropy cascade.[180]

While studying metathesis cascades involving metallatropic shift, Lee and coworkers identified a stable ruthenium alkylidene complex bearing a coordinated alkyne.[181] In one case, a diendiyne gave the expected cascade product (equation 97). With the geminally substituted dimethyl analog, exposure of the entriyne to 1 equivalent of catalyst **2** in refluxing DCM for 6 h gave an alkyne-chelated ruthenium alkylidene complex instead of the expected metathesis product (equation 98). This stable metal carbene was formed through an RCEYM, metallatropic shift, and another RCEYM to produce the vinyl carbene. The rigidity of the cyclohexene ring enforces a favorable coordination geometry that discourages ligand exchange and hence limits the last step of metathesis.



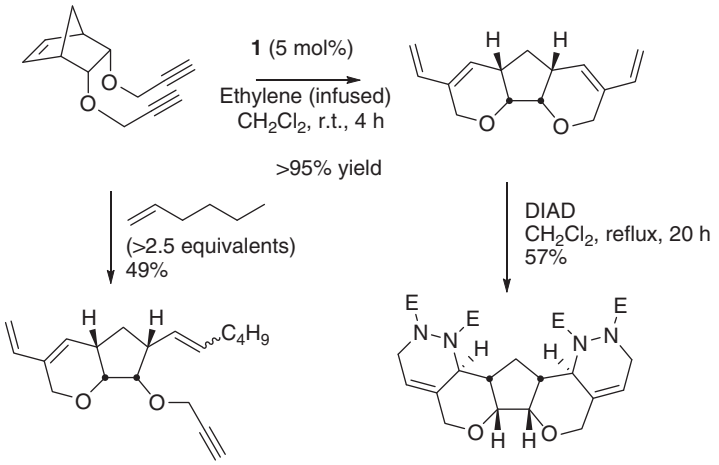
(97)



(98)

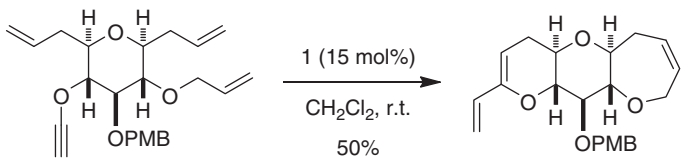
5.27.9 Double-Directional Synthesis

A particularly dramatic example of the ring rearrangement enyne metathesis employed a strained norbornene that reacted with two alkynes in a two-directional manner. In this case, each alkyne underwent RCM with the proximate end of the cycloalkene, giving the linear tricycle (Scheme 42).[182,183] The two 1,3-dienes were subsequently trapped in a cycloaddition step to form the linear pentacycle. With an added aliphatic alkene, ring opening of the norbornene takes place first and only one alkyne participates in ring closure, giving the bicyclic diene.



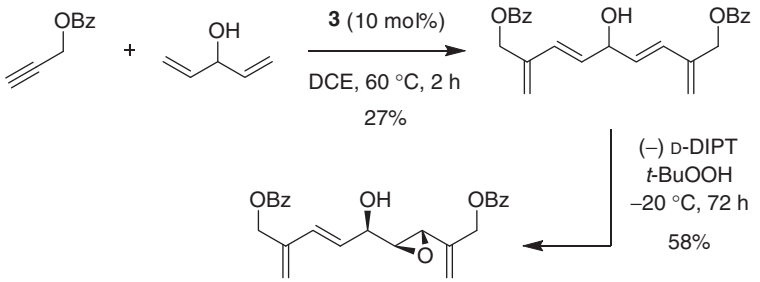
Scheme 42 Double-ring rearrangement enyne metathesis.[182]

Double-directional synthesis involving enyne and alkene metathesis was employed to access the polyether framework found in the ciguatoxins and brevetoxins. Polycyclic ethers such as those found in CTX-30 are a synthetic challenge due to the complexity of their polycyclic ring system. Clark and Hamelin found a two-directional double RCM to be a useful strategy in the synthesis of polycyclic ethers containing complex medium-sized rings (equation 99).[184] The example depicted below uses 15 mol% of the first-generation Grubbs catalyst to perform RCEYM and a ring-closing alkene metathesis simultaneously. This resulted in an efficient synthesis of the ABC ring system found in CTX-3C.



(99)

Achieving stoichiometric equivalency in CEYM permits the use of a bifunctional alkene substrate for a linear two-directional synthesis. Under standard cross metathesis conditions, this would be inconceivable because the alkene is used in molar excess. An excess of the alkene would have prevented double substitution of a diene reactant. In this case, divinyl carbinol was reacted with a twofold excess of propargyl benzoate to give the resulting tetraene in 27% yield (Scheme 43).[50] With the unprotected hydroxyl group present in the product, a site-selective desymmetrization was achieved through a directed sharpless asymmetric epoxidation.



Scheme 43 Two-directional EYM with divinylcarbinol.[50]

5.27.10 Conclusion and Outlook

EYM provides an efficient catalytic method for diene synthesis using simple unsaturated reactants. The reaction shows excellent functional group tolerance characteristic of the Grubbs ruthenium carbenes. That the ruthenium carbenes are widely available and easy to use can explain the wide range of applications in organic synthesis. Some of the appeal is the accessibility of the simple reactants and the reactivity of the resulting 1,3-dienes. The unique reactivity of 1,3-dienes can be harnessed in cycloaddition reactions. This sequence translates into a rapid gain in structural complexity. Interest in enyne metathesis has closely followed interest in complex molecules and heterocycles, and there has been increasing use of metathesis in total synthesis. These successes have helped to maintain momentum in the field, further emboldened by successful EYM used in tandem with other bond-forming processes. These successes, combined with continuing improvements in substrate scope and a refined understanding of reaction mechanism, have made EYM a useful synthetic method for C–C bond construction.

RCM has seen diverse applications to a variety of ring sizes and for the construction of different heterocyclic rings. Some recent topics that utilize the economy of the enyne metathesis and recognize the utility of the 1,3-diene product include DOS, or the synthesis of platforms that array functional groups in a stereodefined way. It was also seen that a number of tandem reactions are joined with the enyne metathesis, some distinct bond-forming processes such as cycloaddition or metallotropic shift, and others involving additional metathesis steps. The cascade metathesis applications have tremendous potential to generate polycyclic structures in one step. The potential chemistry here is expansive and is open to the imagination and limited perhaps only by the level of difficulty in obtaining the acyclic polyeneyne precursors. Control of the formed ring in polypendant dienynes is controlled through alkene reactivity, which in turn achieves site differentiation. Control of carbene positioning has been achieved through orchestrated movement of carbenes known as relay enyne metathesis.

In CEYM applications, a molar excess of the alkene is typically used to drive the EYM forward. However, in the best cases, nearly equimolar amounts of the alkene and alkyne can be used. In these cases, the EYM is a carbon–carbon cross-coupling, with a reorganization of the π-bonds. Some of the other exciting applications include the ring rearrangements to form heterocyclic rings, and ring construction and ring expansion methods.

There are still growth areas for EYM. Some of the unresolved difficulties in EYM include poor control of alkene geometry, high catalyst loadings, and oftentimes the need for a large excess of alkene reactant. Some applications such as ring building capitalize on *in situ* isomerization to access the *Z*-geometry. *Z*-Selectivity is unsolved in acyclic EYM and there are currently no catalysts to overcome this shortcoming, despite the very recent advances in *Z*-selective alkene metathesis catalysts. Though the mechanism has been studied, the rate profile with a wide assortment of alkynes and alkenes has not been fully elucidated. This will be useful to guide future synthetic efforts with less reactive unsaturated reactants.

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5.28 Alkyne Metathesis

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Glossary

Alkyne metathesis Reaction leading to the mutual exchange of the alkylidyne units between a pair of (nonterminal) acetylene derivatives.

Ancillary ligands Permanent ligands to a transition metal catalyst that are not directly involved in the catalytic process, yet may exert a strong influence on activity and stability.

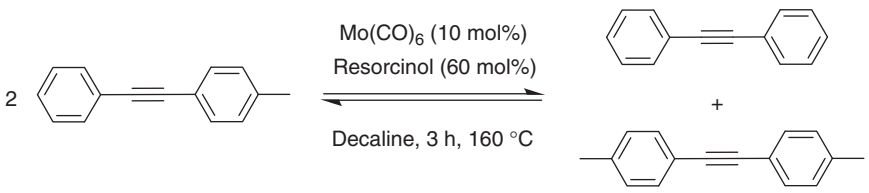
Ate-complex Salt, the anion of which is a negatively charged transition metal complex.

Fischer carbyne Transition metal complexes discovered by Prof. E. O. Fischer, which are distinguished by a triple bond between a carbon-based ligand and a transition metal in a low oxidation state; prototype examples are $[Br(CO)_4M{\equiv}CPh]$ (M = Cr, Mo, W); their LUMO is largely made up by the π^*-orbitals of the metal–carbon bond, which renders such complexes susceptible to nucleophilic attack at the carbyne carbon atom.

Schrock alkylidyne Transition-metal complexes discovered by Prof. R. R. Schrock, featuring a triple bond between a carbon-based ligand and a transition metal in (usually) the highest possible formal oxidation state (d°). The tungsten complex $[(t\text{-BuO})_3W{\equiv}CCMe_3]$ serving as a standard catalyst for alkyne metathesis represents a prototype example; Schrock alkylidyne complexes are nucleophilic at the alkylidyne carbon atom.

5.28.1 Introduction

The tremendous success of alkene metathesis during the past two decades[1–3] has overshadowed the fact that π-systems other than olefins can also be scrambled by related mutual exchange processes with the aid of transition metal catalysts. For nonterminal alkynes, this is known since 1968, when Penella and coworkers disclosed that the two inequivalent alkylidyne units of 2-pentyne get statistically redistributed on exposure of this substrate to a heterogeneous catalyst consisting of WO_3 (6.8% *w*/*w*) on silica.[4] The impact of this discovery on synthesis remained limited, not least because of the very harsh reaction conditions (200–450 °C) that led to competing polymerization. A few years later, Mortreux and coworkers showed that the same type of transformation, which was called 'alkyne metathesis' from there on, can also be achieved in homogeneous phase (**Scheme 1**).[5] Specifically, a mixture of $Mo(CO)_6$ (10 mol%) and resorcinol (60 mol%) in decaline at 160 °C was found to equilibrate 1-methyl-4-(phenylethynyl)benzene within 3 h to a mixture comprising the substrate (55%), diphenylacetylene (23.5%), and bis(*p*-tolyl)acetylene

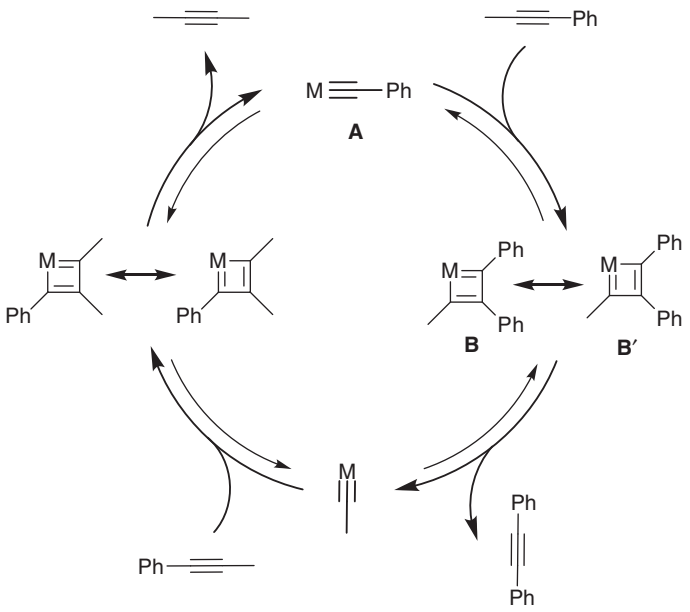


Scheme 1 Original discovery of alkyne metathesis in homogeneous phase.

(21.5%). The fact that the products were formed in equal amounts, within the limits of detection, was taken as an indication that a metathetic process must have taken place in solution.[5,6]

Many variants of this original catalyst recipe were explored later on by changing the molybdenum source, the phenol activator, the solvent, and/or by using additional additives. Although the actual catalyst species formed *in situ* has not been unambiguously characterized so far, it is highly likely that it is a molybdenum alkylidyne endowed with one or more phenolate ligands (or a blend of several such species). This open question notwithstanding, 'Mortreux-type' mixtures still enjoy some popularity because of the preparative convenience and the use of cheap and bench-stable ingredients. Their scope, however, is limited by the typically harsh conditions and a restricted functional group tolerance (see Section 5.28.2).

A significant leap forward was made when the mechanism of alkyne metathesis could be established beyond doubt. Penella et al. originally envisaged a scenario based on direct [2 + 2] cycloadditions/cycloreversions of the two alkyne substrate molecules;[4] in contrast to this proposal, Katz and McGinnis advocated a mechanism following the logic of the Chauvin cycle of olefin metathesis (Scheme 2).[7] Specifically, they suggested that a catalyst species **A** comprising a carbon–metal triple bond as the reactive unit undergoes a formal [2 + 2] cycloaddition with the substrate to give a metallacyclobutadiene complex that is adequately described by the two mesomeric extremes **B** and **B′**. Cycloreversion of **B′** forms the product and regenerates a competent catalyst entity, which then undergoes the exact same steps to close the catalytic cycle.



Scheme 2 Generally accepted mechanism of alkyne metathesis spelled out for the conversion of 1-phenyl-1-propyne to tolane and 2-butyne; the latter needs to be removed from the mixture to drive the reaction forward, otherwise an equilibrium is reached.

Somewhat surprisingly however, the Fischer–carbyne complexes[8] known at the time when this mechanistic proposal was published were essentially inactive, even though they comprise a carbon–metal triple bond. According to the conventions of organometallic chemistry, the metal center in Fischer–carbynes is usually considered 'low-valent' and the carbyne unit counted as a monoanionic ligand.[9] It was only after the discovery of their 'high-valent' relatives, the so-called Schrock alkylidynes,[2,10,11] that the mechanistic hypothesis depicted in Scheme 2 could be brilliantly validated.[12,13] Many Schrock alkylidynes of tungsten, molybdenum, and rhenium exhibit good-to-excellent catalytic activities; the corresponding metallacyclobutadiene complexes formed in the [2 + 2] cycloaddition step were shown to be intermediates rather than transition states. They actually represent the catalyst resting state since the loss of the product alkyne from the metallacycle is rate-determining, at least for the specific tungsten complexes invesigated. Details are outlined in Section 5.28.3.

The catalytic activity and the functional group tolerance of Schrock alkylidynes is largely determined by the chosen ancillary ligands. Whereas alkylidynes bearing halide-, (branched) alkyl-, carboxylate-, or thiolate ligands were found by and large inadequate, the use of *tert*-alkoxides, branched fluorinated alkoxides, sterically hindered phenolates, certain amides, imidazoline-2-iminato groups, and in particular, silanolates have been employed with great success in various formats. Figure 1 displays the most common Schrock alkylidynes, although other variants have also been described. All of these complexes are quite sensitive to moisture and need to be handled and stored under inert atmosphere.

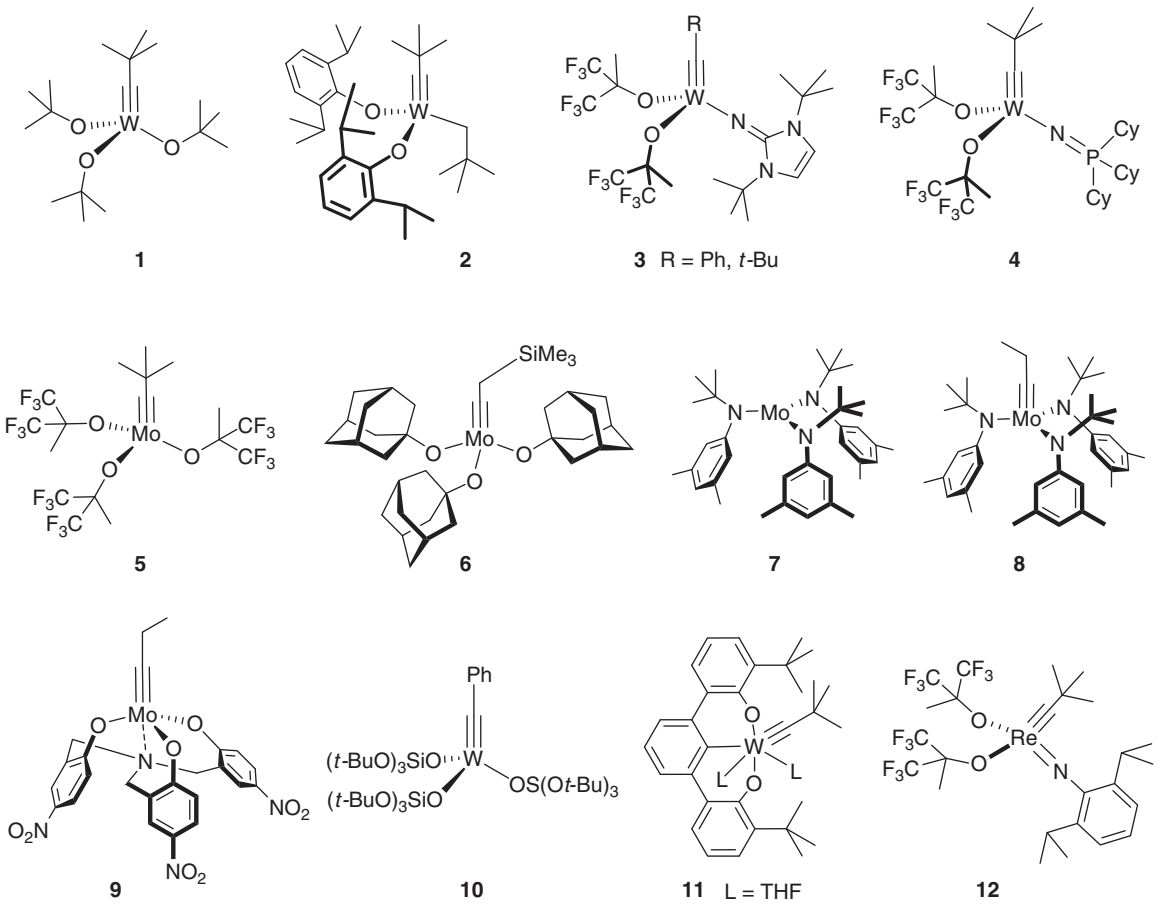


Figure 1 Assortment of established alkyne metathesis catalysts bearing *tert*-alkoxides, fluorinated alkoxides, amides, phenolates, or neopentyl groups as ancillary ligands; in case of complex **7**, the alkylidyne unit is generated *in situ* on treatment with CH_2Cl_2 and exposure to the alkyne substrate, see Section 5.28.3.2.

The list of possible ancillary ligands was recently extended to cheap triarylsilanolates, which impart particularly favorable properties onto the corresponding alkylidynes (see Sections 5.28.3.2 and 5.28.3.3). Complexes such as **13** and **14** belong to the most active metathesis catalysts known to date (Figure 2).[14,15] At the same time, such alkylidyne complexes can be rendered bench-stable on complexation with 1,10-phenanthroline or 2,2′-bipyridine; the active species is easily regenerated from the resulting adducts on treatment with metal salts as simple as $ZnCl_2$ or $MnCl_2$.[14,15] Therefore, phenanthroline complexes such as **15** combine an excellent performance and application profile with a much improved user-friendliness, and should lend themselves to broad applications in organic chemistry and polymer science.

This chapter will focus on the preparative aspects of alkyne metathesis, whereas the organometallic background is touched only to the extent that the reader can put the recent catalyst development into proper perspective.[16–22] For more information, the comprehensive and authoritative reviews of the preparation, structure, and reactivity of metal alkylidyne complexes should be consulted.[2,10,11] In analogy to alkene metathesis, several distinctly different application modes of alkyne metathesis can be envisaged, which demonstrate that this methodology is relevant for small molecule chemistry and polymer science alike (Scheme 3). Among them, ring-closing alkyne metathesis (RCAM),[23,24] alkyne cross metathesis (ACM, $R^1 \neq R^2$),[25–27] alkyne-self-metathesis (ACM, $R^1 = R^2$), and the stepwise acyclic diyne metathesis polymerization (ADIMET)[28] have so far gained the greatest relevance.

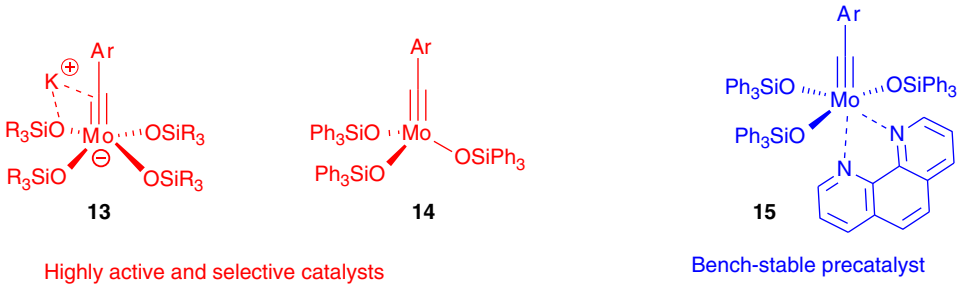
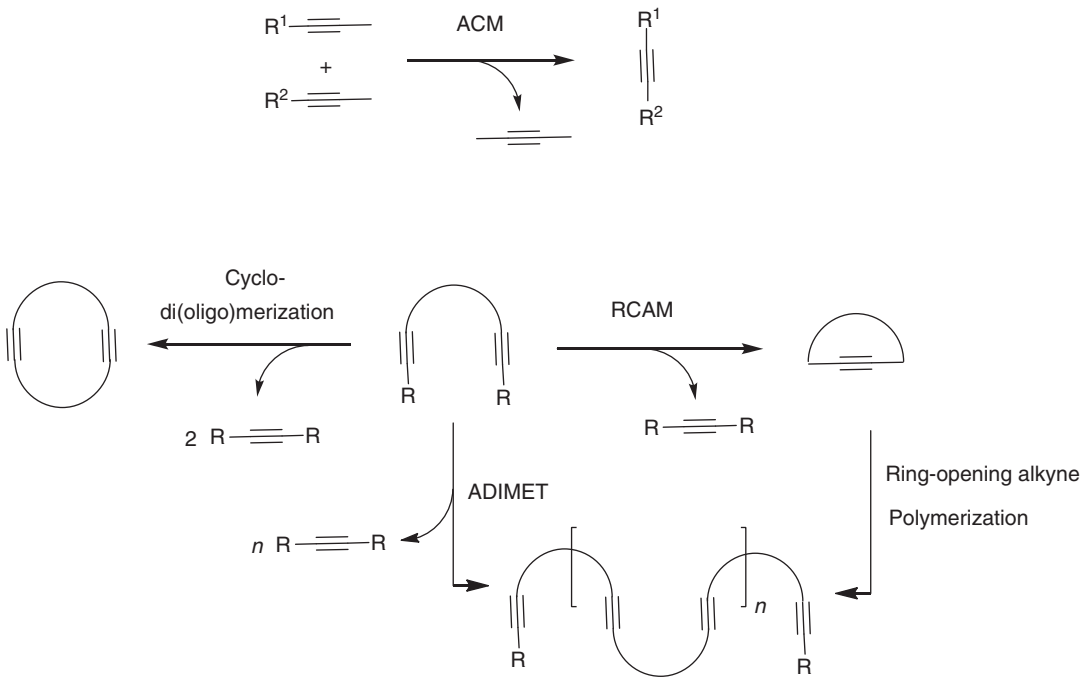




Figure 2 Sample of the bench-stable molybdenum alkylidyne/1,10-phenanthroline adduct **15b** (Ar = *p*-$MeOC_6H_4$–), which serves as a convenient precatalyst for alkyne metathesis reactions of all sorts and is compatible with a host of polar and unpolar functional groups; adduct **15** derives from the parent complexes **13** and **14**, which are arguably the most active and selective alkyne metathesis catalysts known to date (see Section 5.28.3.2).



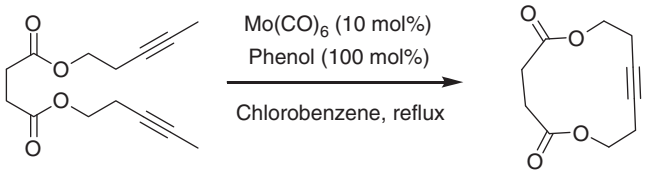
Scheme 3 Basic modes of alkyne metathesis.

5.28.2 Mortreux-Type Catalysts

As mentioned in Section 5.28.1, a mixture of $Mo(CO)_6$ and resorcinol accounted for the first alkyne metathesis reaction in homogeneous phase; this system operated at 160 °C in decaline as the solvent.[5] Soon after this important discovery had been disclosed, it was shown that other molybdenum sources can also be used, although $Mo(CO)_6$ remained the most popular choice for its convenience and ready availablity.[29] Although structurally undefined species generated *in situ* from $MoO_2(acac)_2$ and alkylaluminum reagents showed higher activity on modification with phenol additives, such catalysts were hardly used in later investigations.[30] Scattered reports on the use of $W(CO)_6$ instead of $Mo(CO)_6$ can also be found.[31]

Over the years, the performance of a large variety of substituted phenols was tested in combination with $Mo(CO)_6$.[29,32–34] The data suggest that electron-withdrawing substituents are generally advantageous and allow the necessary reaction temperature to be lowered, at least to some extent. Based on the results of simple RCAM experiments, 2-fluorophenol, and 2-fluoro-5-methylphenol were proposed as being optimal, whereas pentafluorophenol failed completely (**Table 1**).[35,36] In striking contrast to these results, however, pentafluorophenol scored best in a related screening exercise based on an ACM reaction of propynyl ferrocene, whereas 2-fluorophenol was clearly suboptimal (**Table 2**).[37,38] No obvious explanation for these disparate findings can be given nor could any correlation between the pK_A of the phenol and the activity of the resulting catalyst be established. It is also of note that *ortho*-, *meta*-, and *para*-nitrophenol performed either poorly or gave no conversion at all in either assay. This result stands in striking contrast to the widespread use of nitrophenolates as ancillary ligands for structurally defined molybdenum alkylidynes, which will be discussed in more detail in Section 5.28.3.2.

Table 1 Screening of different phenol additives in a model ring-closing alkyne metathesis (RCAM) reaction catalyzed by a Mortreux-type catalyst mixture[a]



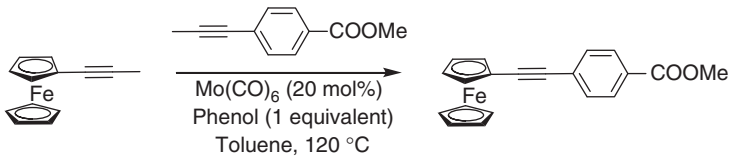
Entry	*Phenol*	*GC conversion (%)*[b]	*GC yield (%)*[b]
1	2-Fluorophenol	95	83
2	2-Fluoro-5-methylphenol	94	81
3	3,4-Dichlorophenol	90	69
4	4-Chlorophenol	83	53
5	4-Trifluoromethylphenol	80	51
6	2-Chlorophenol	64	28
7	2,4-Dichlorophenol	45	33
8	3-Nitrophenol	45	23
9	3,5-Bis(trifluoromethyl)phenol	30	25
10	4-Fluorophenol	60	15

[a]No reaction was observed, inter alia, with pentafluorophenol, 2-nitrophenol, and 4-nitrophenol.
[b]After 6 h reaction time.

Further attempts were made to allow Mortreux-type mixture to operate under milder conditions by the use of additional coligands. In this context, 1,2-di(phenyloxy)ethane[39] and 1,2-dichloroethane[40] were reported to exert beneficial effects, although their mode of action remains speculative. Furthermore, it was recommended to generate the as yet unknown active species before the addition of the actual substrate by heating the molybdenum source and the chosen phenol in the presence of a sacrificial alkyne; after this activation step, the temperature can be lowered before the actual substrate is introduced.[41] Although these empirical protocols showed some promise, they did not yet find widespread application; therefore the knowledge base about their scope remains narrow.

The phenol additive is always used in excess relative to $Mo(CO)_6$ and even more than 1 equivalent compared to the substrate is not uncommon (**Scheme 4**). At temperatures ≥ 100 °C, however, free phenol in solution is by no means innocent and can damage various functional groups. Therefore, many of the reported applications of Mortreux-type mixtures deal with substrates that are barely functionalized or carry only rather stable substituents. Noteworthy examples include early applications of RCAM to the synthesis of various macrocyclic ethers and lactones including the valuable perfume ingredients ambrettolide and civetone (see Section 5.28.6.4.2),[24,42–44] the insect repellant aza-macrolide epilachnene,[24] the cytotoxic alkaloid motuporamine C (see Section 5.28.6.4.6),[45] and some naturally occurring cyclophanes of the turrinane series;[46] in the latter case, it was shown that ultrasonication of the reaction mixture leads to a significant rate acceleration without affecting the yield by much. A more recent

Table 2 Screening of different phenol additives in an ACM reaction of propynyl ferrocene[a]



Entry	*Phenol*	*Yield (%)*
1	Pentafluorophenol	80
2	4-Fluorophenol	63
3	2-Chlorophenol	62
4	2,4,5-Trichlorophenol	60
5	2-Fluorophenol	54
6	4-Chlorophenol	49
7	2,4-Dichlorophenol	48
8	Pentachlorophenol	45

[a]No reaction was observed with 2-, 3-, or 4-nitrophenol.

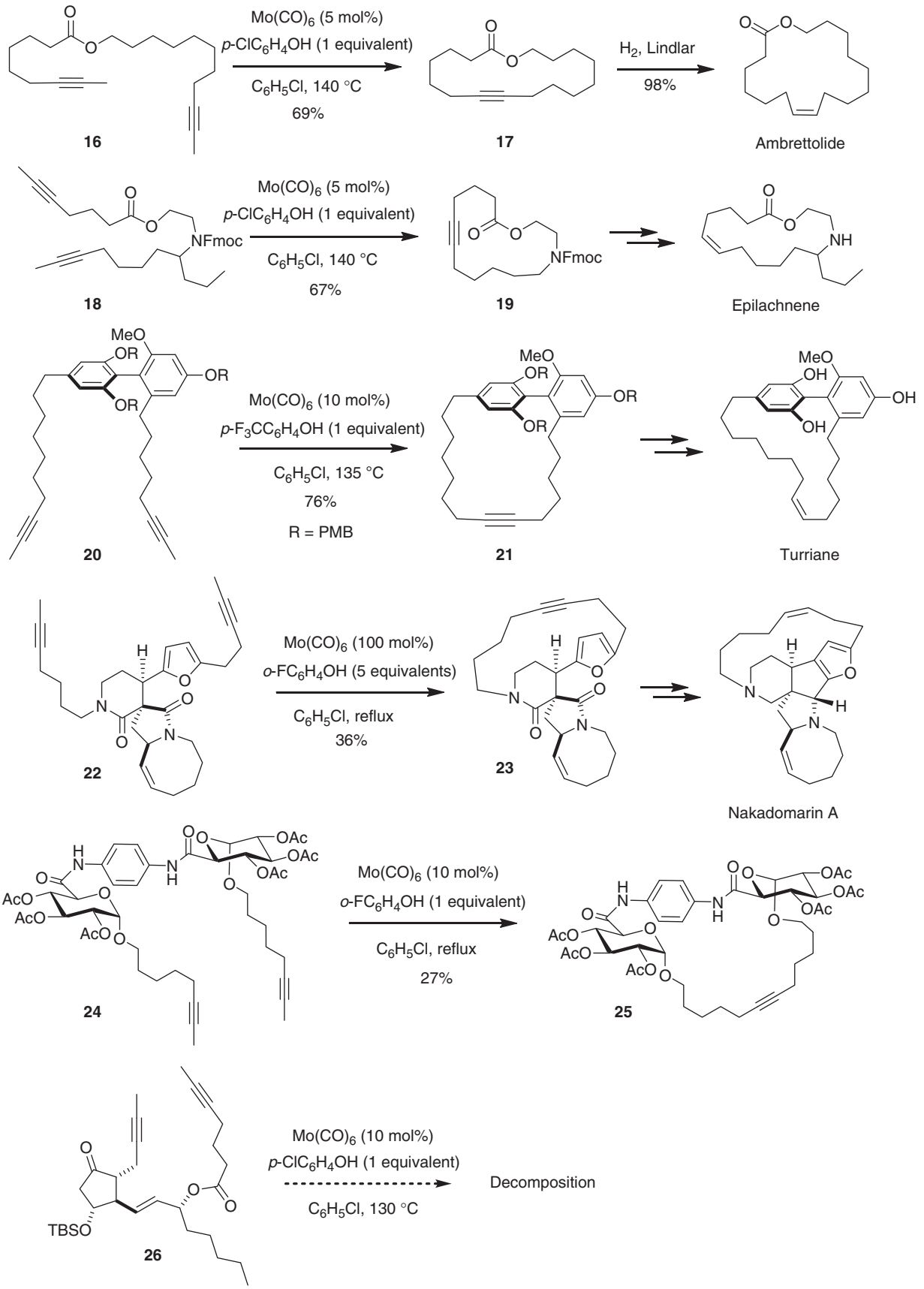
case refers to a total synthesis of the complex alkaloid nakadomarin A, even though the yield of the desired cycloalkyne **23** was only modest despite the high catalyst loading.[47] Likewise, the productivity was poor in an application to the glycolipidic array **25**.[48] The attempted cyclization of the arguably more sensitive prostaglandin derivative **26** by a Mortreux-type catalyst failed since the substrate was merely decomposed. In contrast, this particular diyne could be cyclized without incident and in good-to-excellent yields with the molecularly defined catalysts **1** (65%) or **7**/CH_2Cl_2 (81%).[49]

Whereas the limited compatibility of Mortreux-type mixtures with polar groups is a severely limiting factor for applications in advanced organic synthesis, they turned out highly enabling for material science where less functionalized substrates can still lead to valuable products. Of particular interest are various poly(arylene-ethynylene) (PAE) derivatives with promising electronic and optical properties (**Scheme 5**). The PAE's obtained by ADIMET tend to show fewer defects and higher molecular weights than the corresponding materials prepared by traditional Sonogashira-type cross coupling.[50] The nature of the side chains attached to the monomers is the prime determinant for solubility of the growing chain and hence for the attainable degree of polymerization. Although a detailed discussion of this topic (as well as of other applications of alkyne metathesis to polymer chemistry)[51] is beyond the scope of this chapter, the representative repeat units depicted in **Scheme 5** clearly indicate that ADIMET powered by Mortreux catalyst mixtures allowed various carbo- and heterocyclic arene-building blocks to be processed, including carbazole- and ferrocene-based units. In this context, however, it is of note that other authors found propynylated ferrocene derivatives to undergo competing addition of the *p*-chlorophenol to the triple bond when subjected to mixtures of $Mo(CO)_6$/*p*-ClC_6H_4OH in chlorobenzene under the standard conditions.[52] This result shows again that the presence of excess phenol is a seriously limiting factor for applications of Mortreux-type catalyst mixtures in general. Yet another sidetrack is the possible consumption of the alkyne substrate by a [2 + 2 + 2] cycloaddition process, which actually became the major reaction pathway for certain substrates when Mortreux-type mixtures are employed.[26,53]

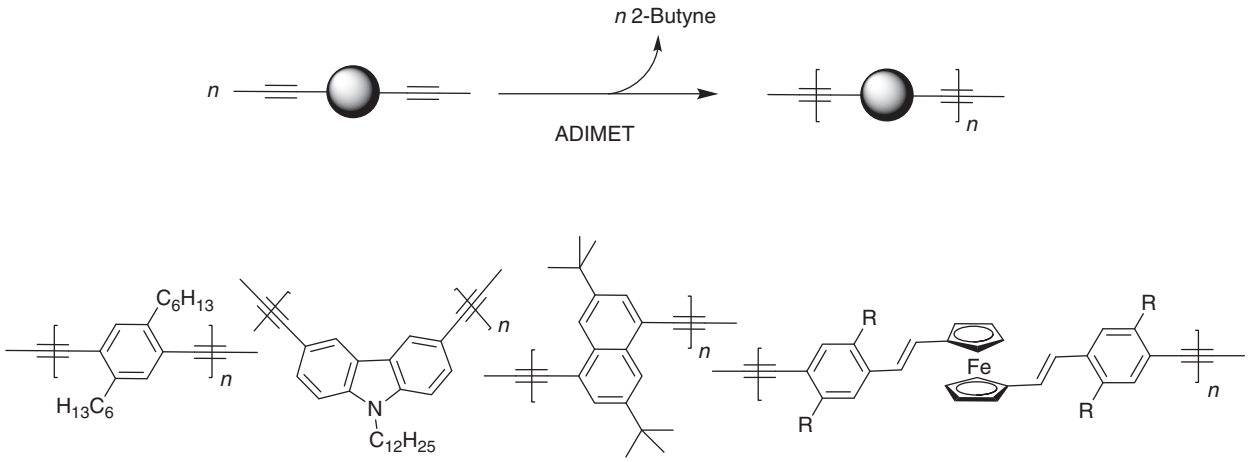
5.28.3 Schrock Alkylidyne Complexes

5.28.3.1 General Characteristics

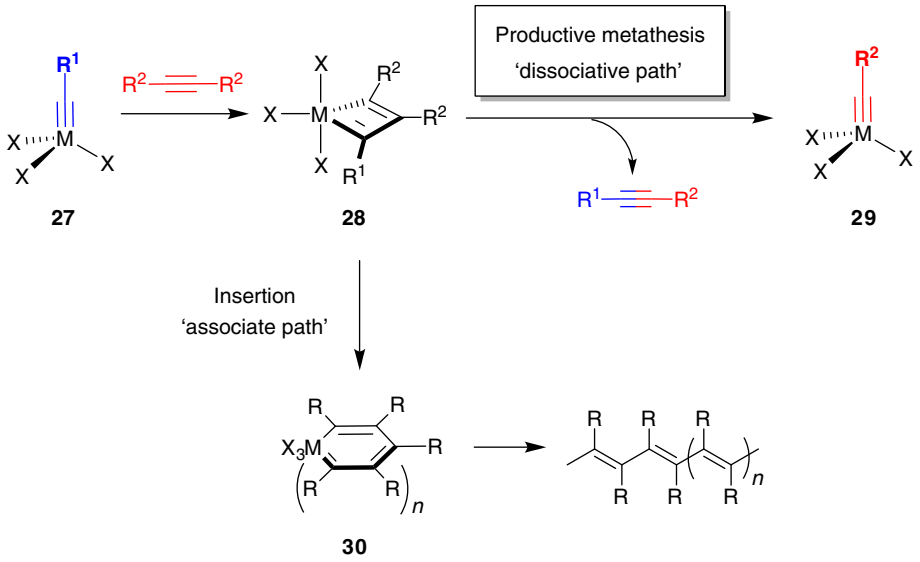
The advent of complexes containing a triple bond between a carbon ligand and a high-valent metal center, commonly called Schrock alkylidynes after their inventor,[2,10,11] allowed the mechanistic proposal originally made by Katz[7] to be elegantly confirmed. Specifically, it was shown that certain high-valent alkylidynes of tungsten, molybdenum, and rhenium exhibit good-to-excellent catalytic activity, which was far higher than that of any Mortreux-type mixture known at the time. Moreover, several representative metallacyclobutadiene complexes of the general structure **28** formed in the elementary [2 + 2] cycloaddition step between an alkylidyne **27** and an alkyne substrate could be isolated and fully characterized (**Scheme 6**).[54,55] Kinetic studies indicated that they might actually be the catalyst resting states, since the release of the product from such metallacyclobutadiene complexes was found to be rate determining, at least for the specific examples of tungsten complexes investigated. Although metallacyclobutadienes of molybdenum (**28**, M = Mo) are less well characterized, they are believed to be isostructural with but likely less stable than their tungsten analogs (**28**, M = W). Overall, these early classical investigations into Schrock alkylidynes formed a sound basis for the development of ever more active and selective catalysts for alkyne metathesis.



Scheme 4 Applications of Mortreux-type catalyst mixtures to natural product chemistry.



Scheme 5 Repeat units of representative PAE derivatives prepared by acyclic diyne metathesis polymerization using Mortreux-type catalyst mixtures.



Scheme 6 Possible competition between a dissociative pathway and an associative channel, which may result in substrate polymerization.

In addition to the nature of the central metal, the ancillary ligands turned out to be of utmost importance for the performance of the catalysts. The nature of the substituent R^1 on the alkylidyne unit of **27**, which is lost in the first turn of the catalytic cycle, affects the onset rate of the reaction, the stability of the complex and the ease of its preparation. However, the inherent catalytic activity of a given alkylidyne is largely determined by the anionic ancillary ligands X.[56] Although an in-depth discussion is beyond the scope of this chapter, the available data suggest that the anionic ligands must be sterically demanding as well as moderately electron-withdrawing. Metal neopentylidyne complexes **27** ($R^1 = CMe_3$) endowed with X = chloride, neopentyl, -SR, -NR_2, or certain carboxylate groups were found by and large inactive;[57,58,75] in contrast, the use of either bulky phenolates or branched alkoxides afforded catalysts of appreciable activity.[59] Among them, [(*t*-BuO)$_3$W≡CCMe$_3$] (**1**) served as the valuable lead compound and continues to represent a benchmark in the field of alkyne metathesis;[12,13] this complex is also commercially available. The use of branched fluorinated alkoxides instead of *tert*-butoxides leads to even more active species.[60] This effect is particularly evident from the molybdenum series, where the parent complex [(*t*-BuO)$_3$Mo≡CCMe$_3$] showed little, if any, activity, whereas its fluorinated cousin with $-OC(Me)(CF_3)_2$ ligands in lieu of the *tert*-butoxides exhibits appreciable catalytic performance.[61–63] If the ancillary groups are too small and the central metal quite Lewis acidic, however, as is the case for M = W and X = $-OCH(CF_3)_2$, the productive metathesis channel can be outperformed by an associative pathway (**27** → **28** → **30**), which ultimately result in polyacetylene formation.[60] This course is particularly easy for small, unhindered alkynes and therefore potentially relevant for the fate of 2-butyne formed as the generic byproduct in all alkyne metathesis reactions of acetylene substrates capped by a methyl group. Polymerization of 2-butyne, however, keeps the catalyst busy and away from doing its actual

job ('pseudo-poisoning effect');[64] successful catalyst design must close this associative channel by proper adjustment of the steric and electronic environment about the chosen central metal.

Another important factor is the Lewis acidity of the central metal, which can be regulated via the ancillary ligands X. One has to note, for example, that even the parent complex [(*t*-BuO)$_3$W≡CCMe$_3$] (**1**) is incompatible with substrates containing (moderately) basic nitrogen or divalent sulfur.[24] This limitation is likely caused by coordination of such donor sites onto the high-valent metal center with a formal d^0 electron count (not considering π-back donation). Because of this pronounced Lewis acidic character, complex **1** was also found to deprotect certain acetal groups and can seriously damage or even destroy acid-sensitive substrates (for representative examples, see Section 5.28.6.4). At the same time, however, the alkylidyne carbon atom of this and related complexes shows nucleophilic character, which is sufficiently high for reactions with the carbonyl groups of benzaldehyde, acetone, ethyl formate, and even DMF.[65]

The combination of a fairly Lewis acidic metal center and a markedly nucleophilic alkylidyne unit seriously limits the applicability and scope of [(*t*-BuO)$_3$W≡CCMe$_3$] (**1**) and relatives, since advanced organic chemistry is all about the ability to manipulate functional groups with the highest possible level of chemoselectivity. To increase the scope of alkyne metathesis in general, it was therefore mandatory to develop more tolerant catalysts without compromising their activity. To this end, different approaches have been pursued, the most prominent of which can be summarized as follows:

1. The Lewis-acidity imparted onto the W^{VI} center of pertinent alkylidynes by branched (fluorinated) alkoxides can be counterbalanced with the aid of electron-releasing substituents. To this end, complexes such as **2**–**4** characterized by a mixed ligand sphere with a push/pull environment have been prepared (**Figure 1**).[66–69] Complex **3** in particular was reported to be highly active and compatible with esters, ethers, thioethers, nitro groups, and aryl chlorides. A more comprehensive picture of its performance, however, cannot yet be drawn from the limited dataset currently available.[70]
2. Replacement of tungsten by the inherently less Lewis acidic molybdenum seems to pay dividends when it comes to the design of chemoselective alkyne metathesis catalysts for organic synthesis and polymer chemistry. A successful and widely used precatalyst is the molybdenum trisamide [(Ar)(*t*-Bu)N]$_3$Mo (**7**, Ar=3,5-dimethylphenyl) which is activated with CH_2Cl_2 to generate a molybdenum alkylidyne *in situ* (see Section 5.28.3.2).[71,72] Closely related is the complex [(Ar)(*t*-Bu)N]$_3$Mo≡CCH$_2$CH$_3$ (**8**),[73,74] which derives from the same precursor **7** on treatment with higher *gem*-dichlorides (Section 5.28.3.2). Exchange of the bulky amide ligands by nitrophenol has been used to fine-tune the Lewis acidity even further, which enabled many interesting applications, notably in material science.
3. Molybdenum alkylidyne complexes endowed with triarylsilanolate groups as the ancillary ligands arguably show the best application profile known to date.[14,15] As will become evident from the discussion in Section 5.28.3.2, the silanolates synergize with the high-valent molybdenum center, leading to highly active and, at the same time, remarkably selective catalysts. A raft of complexes of this type has been prepared, amongst which the ate-species **13** and its neutral analog **14** are the most practical and useful variants, which are easy to make on a multigram scale (**Figure 2**); such complexes are currently about to be commercialized. Their performance was carefully investigated with a large set of inter- as well as intramolecular alkyne metathesis reactions.[14,15] The direct comparison of **13a** · Et$_2$O with the standard Schrock alkylidyne [(*t*-BuO)$_3$W≡CCMe$_3$] (**1**) depicted in **Figure 3** demonstrates the far superior performance of the molybdenum silanolate complex; at the same time, **13** and relatives tolerate a host of functional groups, including very sensitive ones that are incompatible with e.g., [(*t*-BuO)$_3$W≡CCMe$_3$]. Specifically, esters, ethers, silyl ethers (TESO-, TBSO-, TBDPSO-, TIPSO-), thioethers, sulfonates, ketones, amides, carbamates (Boc, Fmoc, Teoc), aldols, acetals (including MOM- and THP- groups), spiroketals, epoxides, vinyl epoxides, aryl-X groups (X=F, Cl, Br), aldols, alkyl chlorides, propargyl acetates as well as trifluoromethyl- and nitro groups pose no problem; even the triple bond of nitriles is kinetically inert. All kinds of alkenes are fully compatible, independent of whether they are terminal, internal, or conjugated to a carbonyl group; 1,3-dienes as well as skipped alkenes are inert too. Moreover, various types of heterocycles such as pyridine, thiophene, thiazole, indole, carbazole, pyrone, and so on are tolerated. In view of this excellent profile, complexes of type **13** and **14** are ideally suited for advanced synthetic applications. For the practitioner it is also important to note that such complexes are rendered bench-stable on complexation with 1,10-phenanthroline or 2,2′-bipyridine; the active principle is easily released from the resulting adducts **15** with the aid of cheap metal salts such as $MnCl_2$ or $ZnCl_2$ (for a more detailed discussion, see Section 5.28.3.2).[14,15]

5.28.3.2 Preparation of the Standard Schrock Alkylidyne Complexes

The classical route to Schrock alkylidynes consists in the alkylation of a high-valent metal salt such as WCl_6 or – preferably – [(MeO)$_3$WCl$_3$] with a sterically hindered alkylmetal reagent, typically neopentylmagnesium chloride.[75,76] The intermediate primarily formed is unstable and undergoes two consecutive α-elimination reactions with formation of the neopentylidyne entity (**Scheme 7**). The resulting air-sensitive product **32** is treated with anhydrous HCl to give the corresponding trichloro–alkylidyne complex **33**, which itself is catalytically inert but serves as a valuable starting material for the preparation of various active complexes by salt metathesis with suitable ancillary ligands as exemplified for **1a–e**. Although this chemistry – a priori – also works in the molybdenum series, the yields tend to be lower and problems with the scale-up have been documented in the literature.[61,62]

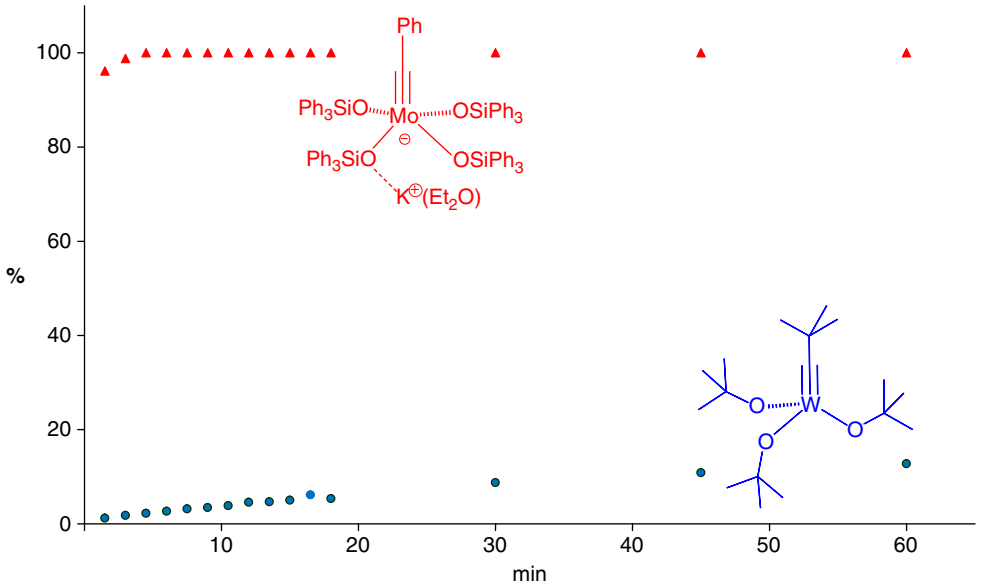
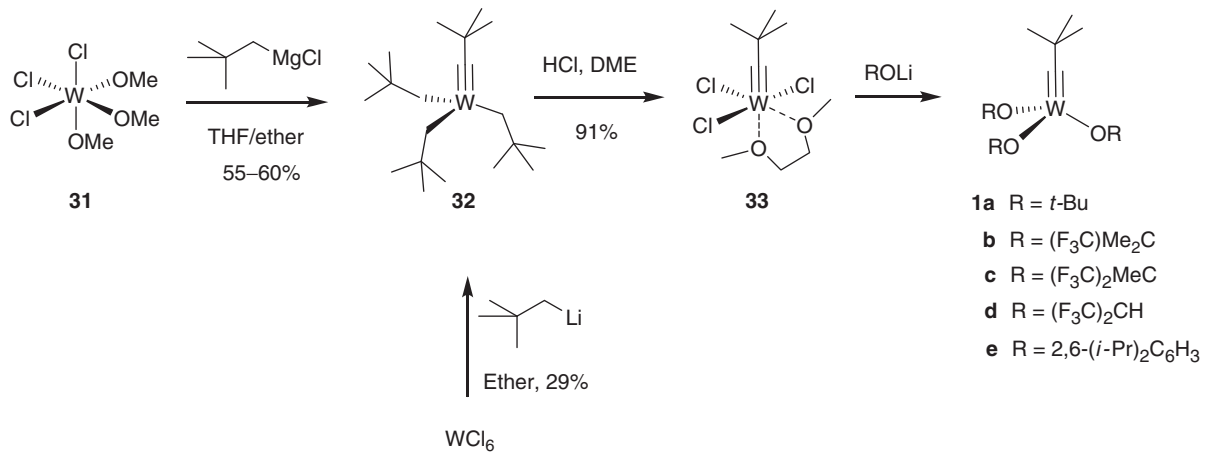


Figure 3 Comparison of the performance of the Mo-alkylidyne ate-complex **13a** · Et_2O (red) with the tungsten alkylidyne **1** (blue) in the conversion of 1-phenyl-1-propyne to tolane. The reaction was performed at ambient temperature with 1 mol% catalyst loading in the presence of MS 5 Å to trap the released 2-butyne (see Section 5.28.5).

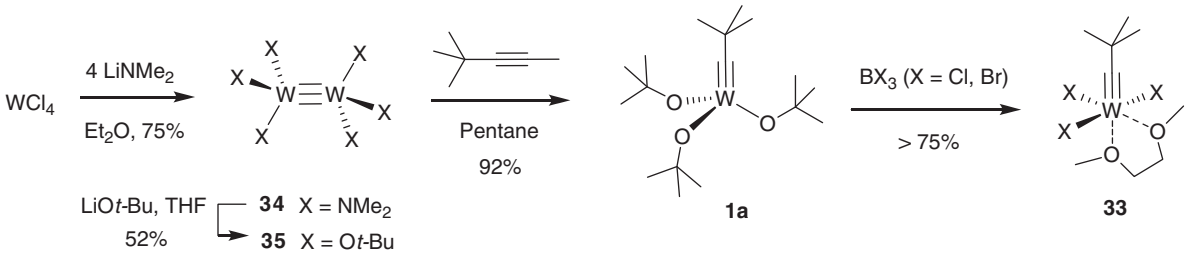


Scheme 7 The classical 'Schrock route' for the preparation of tungsten neopentylidyne complexes.

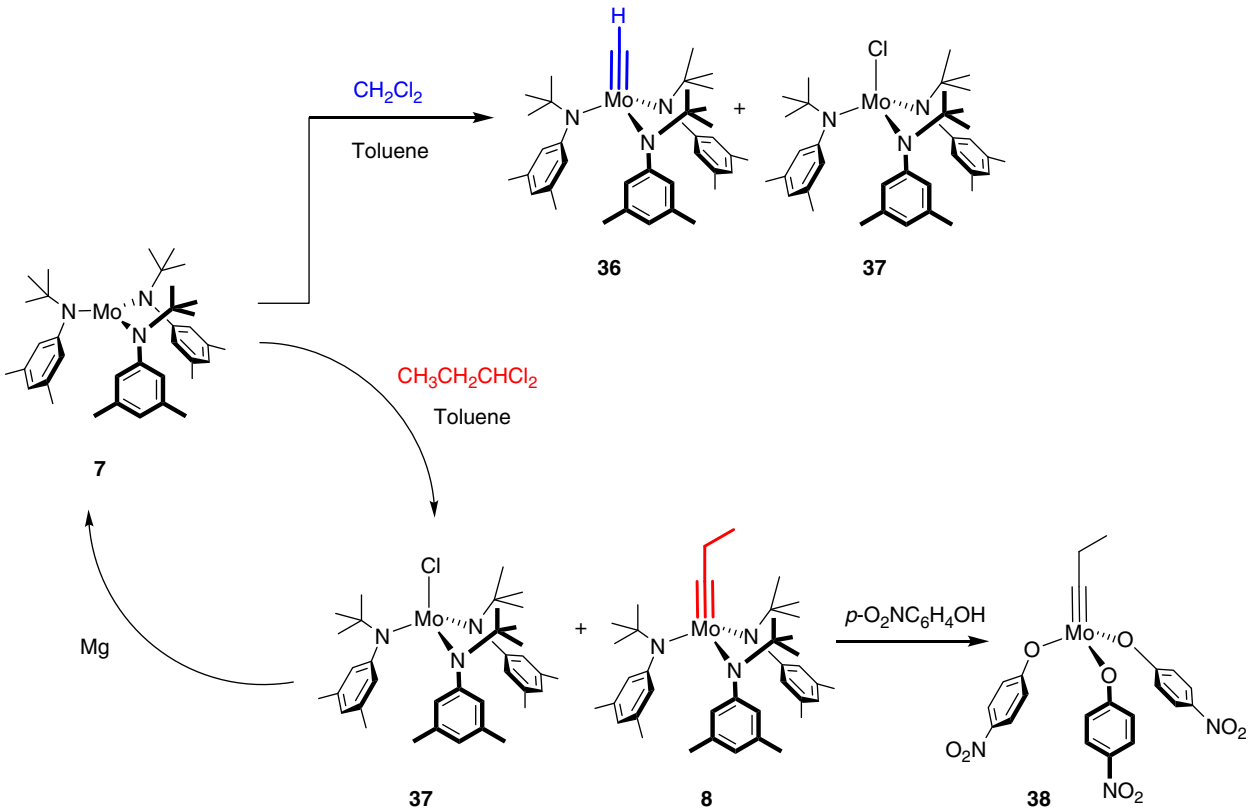
An alternative route to complex **1** relies on the metathetic cleavage of the tungsten–tungsten triple bond of the precursor complex $[(t\text{-BuO})_3W{\equiv}W(Ot\text{-Bu})_3]$ (**35**) with neoheptyne,[77] which in turn is available on a multigram scale from WCl_4 and $LiNMe_2$ (Scheme 8).[78] Unfortunately, this chemistry is once again not easily translated into the molybdenum series, where it is unclean and low yielding. If desirable, **1** can be converted into $[X_3W{\equiv}CCMe_3(dme)]$ (**33**, X = Cl, Br) using BX_3 as the reagent, which provides another access route to this valuable building block.[79]

For the exploration of the potential of molybdenum alkylidynes, it was necessary to develop alternative synthesis routes. Among the different solutions proposed in the literature,[80] the conversion of the trisamido Mo(+3) complex **7** into Mo(+6) alkylidyne complexes represented an important advance.[71,72] This development was triggered by the observation that the treatment of **7** with CH_2Cl_2 leads to a mixture of different molybdenum species, of which the methylidyne complex **36** and the monochloride complex **37** are the major constituents (Scheme 9). This mixture does not need to be separated but is metathesis-active as such;[71,72] therefore, the combination **7**/CH_2Cl_2 found numerous applications in the past, because of its excellent activity and remarkable functional group tolerance (see Sections 5.28.6.3 and 5.28.6.4).

Replacement of CH_2Cl_2 by other *gem*-dihalides provides nonterminal molybdenum alkylidynes, which are more robust and allow for the reconversion of the accompanying chloride **37** into the starting complex **7** on reduction with magnesium turnings (Scheme 9). This 'reductive recycle strategy' ultimately transforms the entire substrate into the desired molybdenum alkylidyne.[73,74,81] Propylidyne **8** thus formed from **7** and 1,1-dichloropropane can be isolated and its catalytic activity adjusted on



Scheme 8



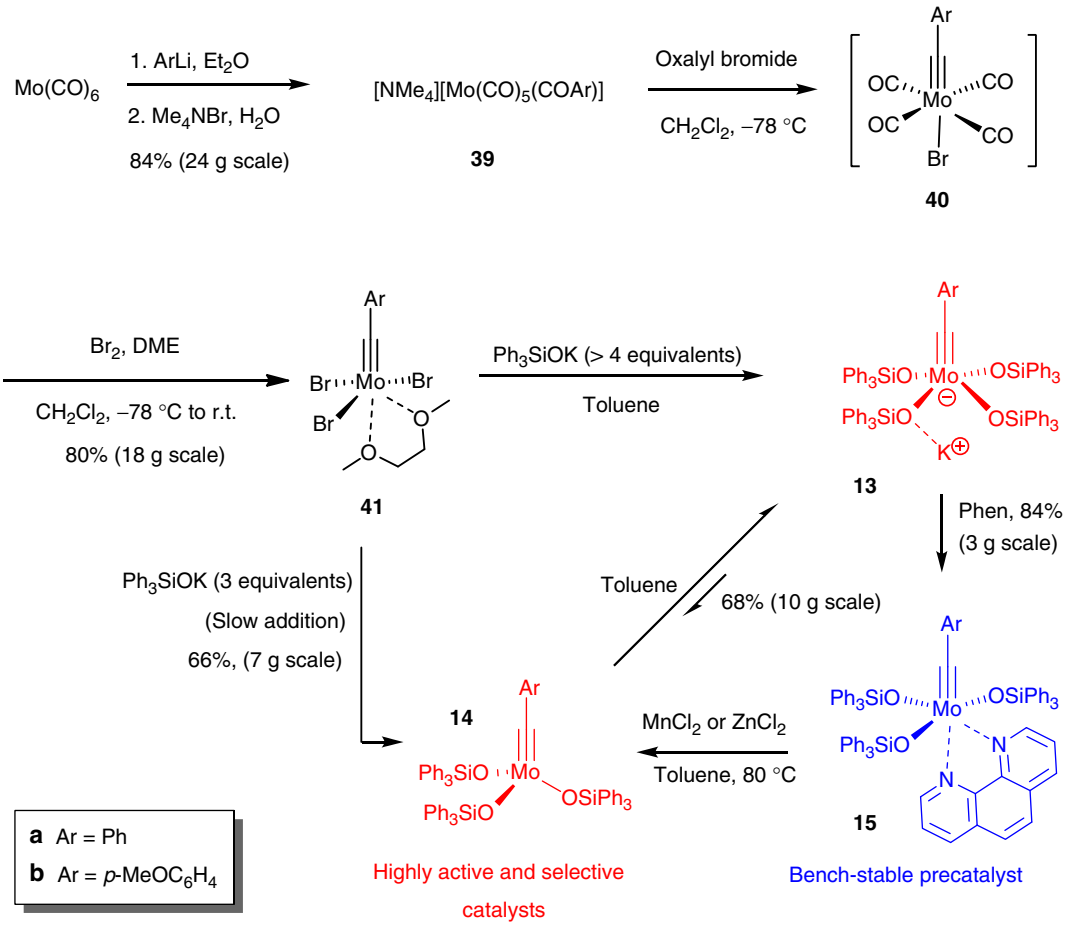
Scheme 9

mixing with electron-deficient phenol additives, preferably 2-nitro-, or 4-nitrophenol. These additives replace the amide groups by nitrophenolates and hence afford more electron-deficient catalyst species such as **38**. An analogous ligand exchange process has been used to introduce the chelate ligand of complex **9** (Figure 1), which was also described as highly metathesis active.[82] Moreover, immobilized catalyst variants could be made from complex **8** on reaction with the surface –OH groups of silica.[83]

The combinations **7**/CH_2Cl_2 or **8**/nitrophenol found widespread use in alkyne metathesis, both in the realm of natural product synthesis as well as in the material science arena. However, the popularity of these powerful catalysts is limited by the fact that complex **7** serving as the starting material in either case is exceptionally sensitive. Not only is this species instantaneously destroyed by air or moisture, but it even reacts with molecular nitrogen at ambient temperature.[84] Therefore it is mandatory to work under Argon in rigorously dried and purified solvents using proper organometallic techniques (Schlenk-lines, glove box).

This handicap was recently overcome by a new type of catalysts for alkyne metathesis, which are much more user-friendly. As has already been mentioned, 1,10-phenanthroline- or 2,2′-bipyridine adducts such as **15** are bench-stable and can be handled without any particular precautions (Scheme 10).[14,15] They are prepared on multigram scale by adapting a sequence that links the chemistry of low-valent Fischer-carbyne complexes with that of their high-valent Schrock alkylidyne relatives.[85,86] Specifically, the reaction of $Mo(CO)_6$ with an aryllithium reagent followed by cation exchange provides the Fischer carbene **39**, which converts into the corresponding Fischer-carbyne **40** on treatment with oxalyl bromide. **40** does not need to be isolated but is best oxidized directly to the tribromo alkylidyne complex **41** with Br_2 in CH_2Cl_2 in the presence of 1,2-dimethoxyethane (DME). These

transformations are high yielding and nicely scalable as long as the reaction temperature during the oxidation steps is properly controlled.[15] In practical terms, the use of *p*-methoxyphenyl lithium in the first step turned out to be optimal, because it imparts advantageous solubility properties onto all downstream complexes (**13b–15b**, **41b**), which are easy to isolate and purify.[15] It should be mentioned that a similar sequence of reactions is also successful in the tungsten series.[70]

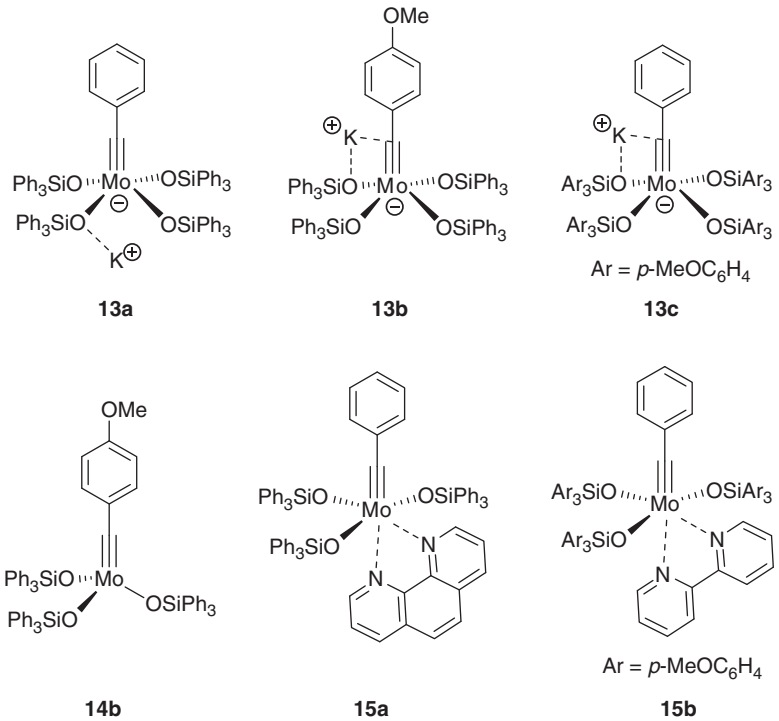


Scheme 10 Scalable and modular preparation of molybdenum alkylidyne complexes endowed with triarylsilanolate complexes; the yields are specified for Ar = *p*-MeO-C_6H_4 (**b** series). The same route can also be followed using other ArLi reagents and silanolates other than Ph_3SiO–, cf. Ref. 15. For specific examples of preferred catalysts prepared by this route, see **Figure 4**.

Complexes **41a**,**b** and relatives serve as convenient starting materials for the preparation of highly metathesis-active molybdenum alkylidyne complexes by ligand exchange via salt metathesis. A thorough screening campaign showed that triarylsilanolates are privileged ancillary ligands, with triphenylsilanolate and tris(*p*-methoxyphenyl)silanolate being optimal in practical terms (**Scheme 10** and **Figure 4**).[14,15] They are cheap and provide highly active catalysts, which are nicely crystalline and hence easy to isolate. Complexes **14b** and **13a**,**b** are the most reactive ones, whereas the use of complex **13c** is advantageous when working with highly unpolar alkyne substrates; the *p*-methoxy groups render the silicon-containing byproducts formed on work-up of the reaction mixtures quite polar and hence facilitate the product isolation in such cases. If desirable, however, other silanolates can also be used and lead to complexes with tailor-made properties and impressive activities.[15]

The reaction of **41** with Ph_3SiOK in toluene forms the ate-complex **13** as the preferred product independent of the chosen stoichiometry. For preparative purposes, it is therefore recommended to use ≥ 4 equivalents of Ph_3SiOK to ensure high yields. The fourth silanolate ligand on **13**, however, is sufficiently labile to get lost when treated with 1,10-phenanthroline or 2,2′-bipyridine. The resulting adducts of type **15** are air-stable for extended periods of time (> 2 years) and hence easy to handle.[14,15] Although **15** itself is inactive (all coordination sites of the molybdenum center are blocked), the stabilizing chelate ligand can be readily removed with $MnCl_2$ or $ZnCl_2$ in anhydrous toluene to deliver the catalytically active neutral alkylidyne template **14** (**Scheme 10**). Although this activation will occur even at ambient temperature, it is recommended to perform this step at ≈60–80 °C to ensure fast rates.

The lability of the fourth silanolate of the ate-complex **13** is also deemed responsible for the fact that this species itself is highly metathesis-active. In solution, **13** equilibrates with a small amount of the corresponding neutral complex of type **14**, which is thought to represent the actual catalyst (**Scheme 10**). Access to these exquisitely active neutral alkylidyne species in analytically



13a 13b 13c

14b 15a 15b

Figure 4 Specific examples of molybdenum alkylidyne complexes endowed with silanolate ligands prepared by the route shown in **Scheme 10**, which are preferred catalysts for alkyne metathesis (see Section 5.28.6). For the ate-complexes **13**, the location of the potassium counterion is drawn as found in the crystal structures of the complexes, see Ref. 15.

pure form has also been achieved, albeit only in a few select cases.[15] Specifically, slow addition of 3 equivalents of Ph_3SiOK to a solution of precursor complex **41b** carrying a *p*-methoxybenzylidyne unit allowed the neutral product **14b** to be formed in decent yield on a multigram scale (**Scheme 10**). The structures of this complex and of many of its relatives have been unambiguously determined by X-ray diffraction. Molybdenum alkylidynes endowed with silanolate ligands are about to be commercialized for use in alkyne metathesis.

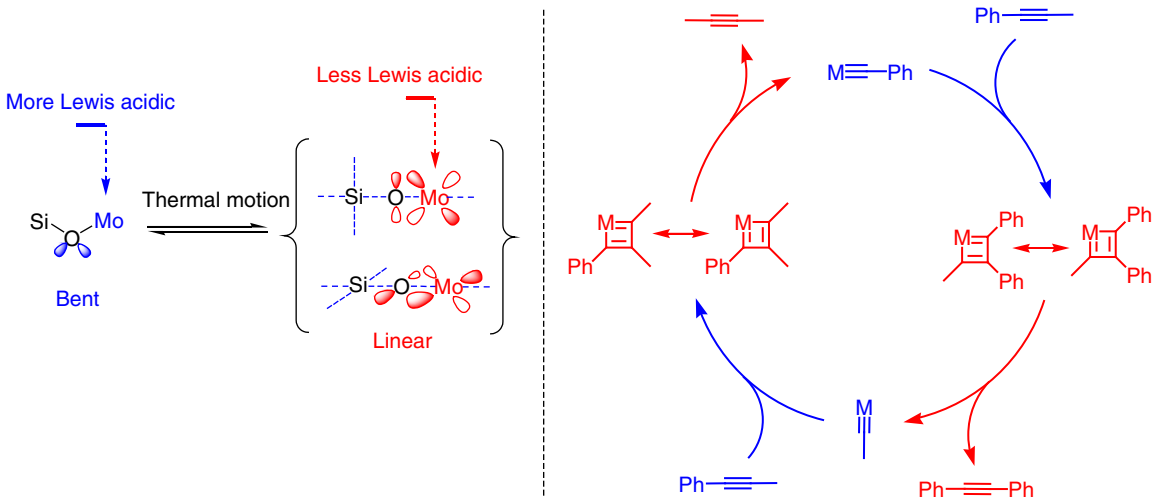
5.28.3.3 Silanolate Effect and the Fate of the Catalysts

Although a detailed discussion of the organometallic background is beyond the scope of this review, a few comments on the beneficial effects of triarylsilanolates on the stability, activity, and functional group tolerance of molybdenum alkylidyne complexes seem appropriate. One might perceive Ph_3SiO-groups as being very bulky, but the available crystallographic information actually shows that the Mo-center in a complex of type $[(Ph_3SiO)_3Mo{\equiv}CAr]$ (**14**) remains well accessible for neutral (and anionic) donors.[14,15] Therefore, one may conclude that the silanolate ligand sphere does not impede substrate binding and hence presents no serious kinetic barrier for productive alkyne metathesis.

However, triarylsilanolates render the periphery crowed enough to disfavor the collision of two alkylidynes. Because bimolecular decomposition pathways account for much of the thermal decay of alkylidyne catalysts, the effective shielding provided by the greasy rim of the triarylsilanolates increases the catalyst lifetime and, as a consequence, the total turnover number.[15] Similarly important is the fact that $R_3Si–O$ bonds are quite robust when bound to a Lewis acidic metal center such as Mo^{VI}, whereas the analogous $R_3C–O$ bonds of tertiary alcohols (a class of ligands with a long history in alkyne metathesis, cf. **Figure 1**) break much more readily with formation of stabilized tertiary cations. Hydrolysis constitutes the most serious threat for complexes of the general type $[(R_3SiO)_3Mo{\equiv}CAr]$ and adducts thereof, independent of whether they are anionic (**13**) or neutral (**14**).[15]

In addition to these steric arguments, triarylsilanolates exert a very unique electronic effect, which renders the derived alkyne metathesis catalysts particularly productive. Siloxides are weaker net donors than alkoxides because $p_\pi \rightarrow d$ donation has to compete with backbonding of the two electron pairs of oxygen into the low lying Si-C $\sigma*$ orbitals.[87,88] Furthermore, the donor capacity is innately angle-dependent: electron donation into the vacant metal d-orbitals is maximized when the Mo–O–Si bond angle Θ is close to 180 °C, because both orthogonal electron pairs of oxygen can then engage in $O \rightarrow Mo$ bonding (**Scheme 11**). In contrast, bending of the Si–O–Mo hinge gives only one O-lone pair the chance to overlap with an empty metal d-orbital and should therefore lead to higher Lewis acidity at the central atom.

The available crystallographic data for a host of neutral and anionic molybdenum alkylidyne complexes indicate that the bending and stretching of the Mo–O–Si hinges is very facile and the silanolate ligand sphere therefore unusually floppy.[14,15] This

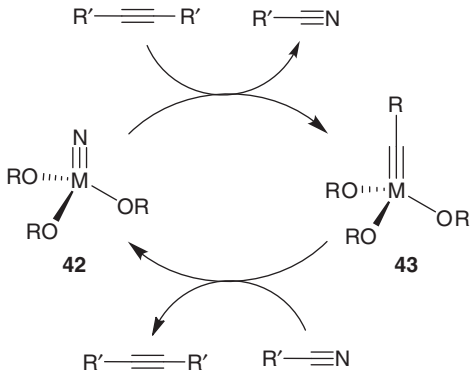


Scheme 11 The floppiness of the silanolate ligand sphere is thought to translate into a gentle up- and downregulation of the Lewis acidity of the molybdenum center, which may help the catalyst to meet the alternating electronic demands during the catalytic cycle.

thermal motion, however, means that the electronic influence of the R_3SiO-ligand sphere is not static either: on bending, the Lewis acidity of the Mo^{VI} center is gently increased which favors uptake of an alkyne substrate as well as the subsequent metallacycle formation; in contrast, stretching of the Si–O–Mo hinge assists the release of the product. In this context, it is important to recognize that any metathesis catalyst has to meet opposing electronic requirements during a single turn-over, as color coded in Scheme 11. By virtue of their suppleness, silanolates are thought to help the operative alkylidyne unit in adjusting to these alternating electronic demands along the reaction coordinate.[15]

5.28.4 Metal–Nitride Complexes as Precatalysts

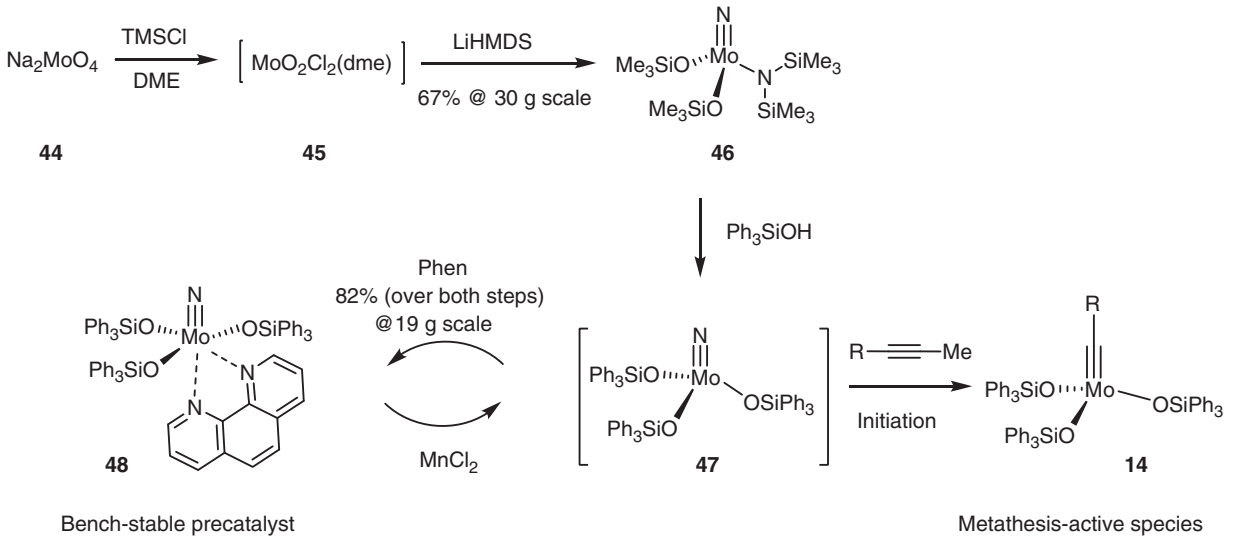
It is known for a long time that certain metal alkylidynes eventually react with nitriles in a metathetic process that is largely driven by the high thermodynamic stability of the resulting nitride complexes.[65,89] Strikingly, however, it was recently shown that the reaction can be reversed, provided that electron-withdrawing ancillary ligands are bound to the metal (Scheme 12).[90,91] Such ligands are thought to destabilize the more polarized M≡N bond of a nitride more than the rather unpolar M≡CR bond of a Schrock alkylidyne. In line with this notion, molybdenum- and tungsten nitrides **42** (M = Mo, W) endowed with fluorinated branched alkoxide ligands were found to react with 3-hexyne at elevated temperatures to give the corresponding propylidyne complexes **43**.



Scheme 12 The discovery of a reversible interchange between certain metal nitrides **42** (M = Mo, W, R = $-C(Me)(CF_3)_2$, $-CMe_2(CF_3)$) and the corresponding metal alkylidynes **43** opened the door for the use of metal nitrides as precatalysts for alkyne metathesis and alkyne-nitrile cross metathesis reactions.

The originally used nitride species **42** were prepared by azide decomposition and the fluorinated alcohols are rather expensive.[90,91] Gratifyingly though, a much more practical alternative could be found with nitride **46**, which is available on multigram scale, without recourse to any dangerous azide precursors, from cheap sodium molybdate, trimethylchlorosilane (TMSCl), and

lithium hexamethyldisilazide (LiHMDS) (Scheme 13). Reaction of this material with commercial Ph_3SiOH exchanges the ligands to give **47**, which turned out to be a competent precatalyst for alkyne metathesis reactions of all sorts.[14,15,92] **47** slowly converts into an alkylidyne of the general type $[(Ph_3SiO)_3Mo{\equiv}CR]$ on treatment with an alkyne substrate. Therefore, this particular precatalyst exhibits by and large the same excellent scope and functional group tolerance as the preformed alkylidyne complexes **13** and **14** discussed above. The necessary nitride-to-alkylidyne conversion, however, is best accomplished at somewhat elevated temperatures. Thus, reactions catalyzed by **47** are typically carried out at 80 °C, whereas the analogous reactions effected by prefomed alkylidynes such as **14** usually proceed at ambient temperature.[14,15]

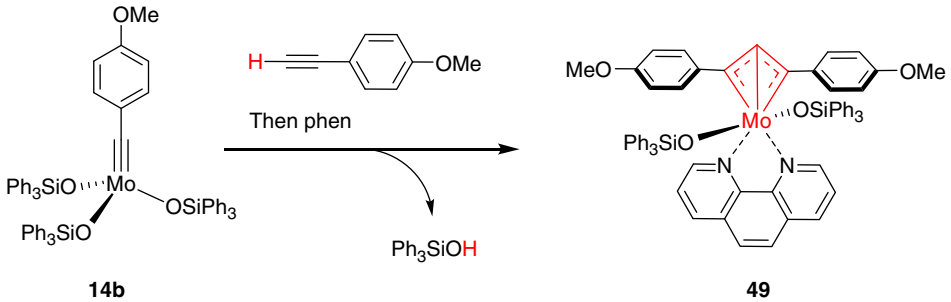


Scheme 13 Convenient and scalable preparation of molybdenum nitride complexes endowed with silanolate ligands, which qualify as effective precatalysts for alkyne metathesis.

As expected, nitride **47** can also be stabilized by complexation with 1,10-phenanthroline or 2,2′-bipyridine.[14,15] The resulting adducts such as **48** are indefinitely air stable and therefore very convenient to work with. As in the alkylidyne series, the stabilizing nitrogen chelate ligand can be removed and the metathesis-active template released on treatment of **48** with $MnCl_2$ or $ZnCl_2$ in anhydrous toluene. Since the preparation of **48** is straightforward, scalable, and requires only very cheap starting materials, this complex constitutes a serious alternative choice for the practitioner of alkyne metathesis.[14,15] Very much like its alkylidyne siblings, it has already passed the test of natural product total synthesis (see Section 5.28.6.4).

5.28.5 Reaction Set-up

At the present stage of development, terminal alkynes cannot be used as the substrates for catalytic alkyne metathesis; they do not lead to sustained turn-over but destroy Schrock alkylidyne complexes by a peculiar C–H activation mechanism at the stage of the metallacyclobutadiene. This has been confirmed crystallographically on more than one occasion (Scheme 14).[15,62,93–95]



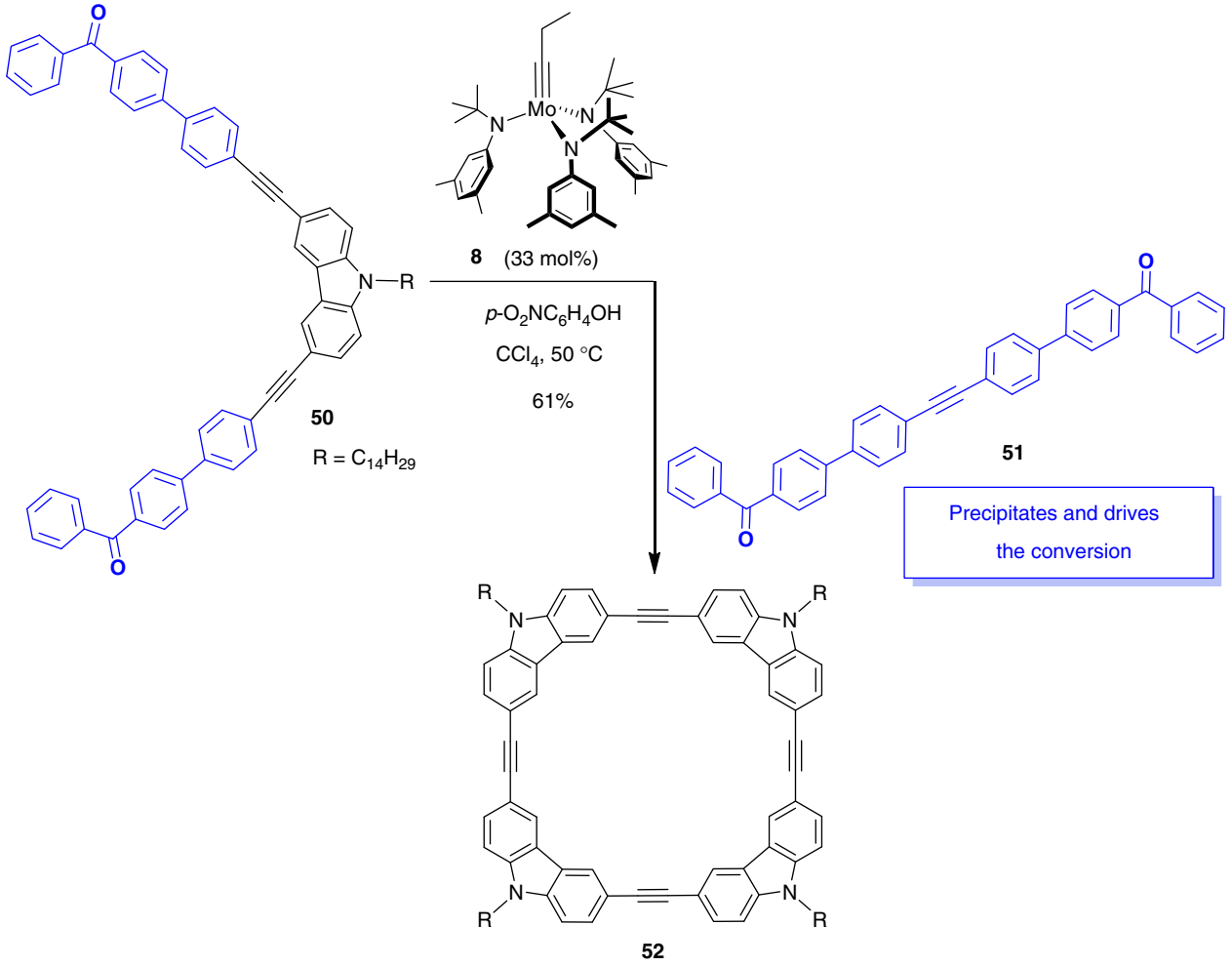
Scheme 14 Established pathway leading to the deactivation of metal alkylidynes on exposure to terminal alkyne substrates; the structure of the product was established by X-ray diffraction, see Ref. 15.

As a consequence, internal alkynes must be used, among which acetylenes capped with a methyl group are most readily accessible and hence most common. Their use leads to the formation of 2-butyne as one of the products, which has to be removed

from the mixture in order to drive the reaction forward and make it preparatively meaningful. In view of the low boiling point of 2-butyne of 27 °C, most of it will evaporate if the reactions are carried out at elevated temperatures and/or if gentle vacuum is applied. Vacuum-driven reactions, however, are not convenient as the solvent will also distill off, at least in part, which changes the concentration of the reaction mixture and may require monitoring and occasional replenishing. High boiling solvents can compensate for this inconvenience, but they usually render the work-up and product isolation more tedious.

In addition to the possible impact on the overall conversion, the accumulation of 2-butyne is also potentially detrimental for the catalyst. Certain Schrock alkylidynes are capable of engaging in a competing associative mechanism, in which further insertion of a given substrate into the metallacycle is faster than cycloreversion with release of the metathesis product (**Scheme 6**). This polymerization manifold is obviously more likely for smaller alkyne substrates and hence most probable for 2-butyne. Because it prevents the catalyst from doing its actual job, 2-butyne may exert a so-called 'pseudo-poisoning' effect.[64]

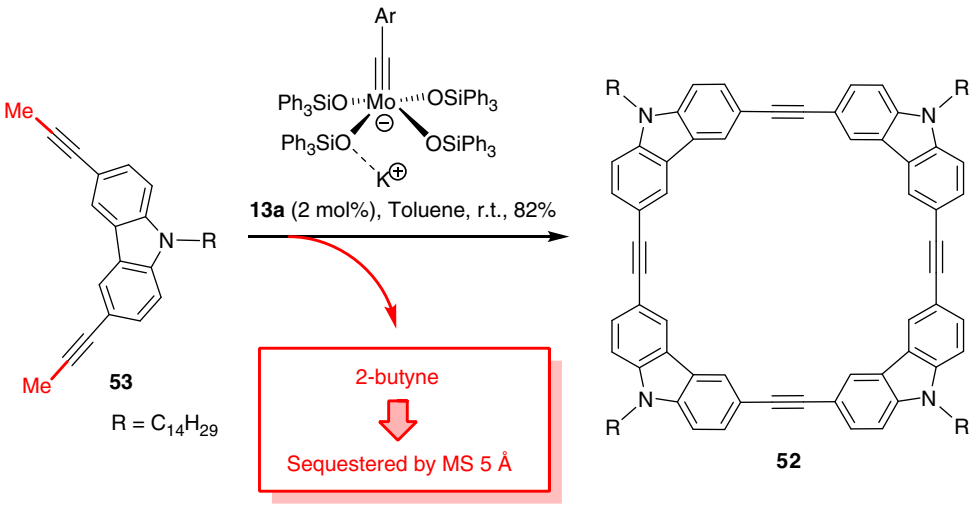
An obvious way around the problem is the use of alkyne substrates carrying larger end-groups than methyl; this strategy, however, is less attractive from the viewpoint of 'atom economy' as more of the material input ultimately ends up in the waste stream. Yet, it has been carried to the extreme in what is called 'precipitation-driven alkyne metathesis' (**Scheme 15**).[64,96] To this end, tailor-made substrates such as **50** were used; on metathesis, the contained 4-benzoyl-biphenyl termini end up in compound **51**. Since this product is only sparingly soluble in either CCl_4 or 1,2,4-trichlorobenzene, the conversion is driven to completion by its precipitation and the desired shape persistent macrocycle **52** isolated in good yields (61–81%).[64,97] Note, however, that the byproduct **51** has a molecular weight of no less than 538 and the preparation of the required substrate **50** mandates more than one extra step.



Scheme 15 Prototype example of a precipitation-driven alkyne metathesis reaction.

A much more practical alternative relies on the use of molecular sieves, in particular MS 5 Å.[14] The pores of this material are able to entrap 2-butyne without getting blocked by the toluene solvent molecules. As a consequence, methyl-capped alkynes can be used as the substrates and the reactions be performed at ambient temperature (or even below), where 2-butyne will hardly evaporate; yet, quantitative conversion is reached since the added MS 5 Å effectively sequesters this byproduct and thereby drives

the conversion to completion.[14] As an additional bonus, the molecular sieves keep the reaction medium dry and hence retard or even stop the deleterious hydrolysis of the catalysts, which remains a serious decomposition pathway for molybdenum alkylidynes carrying silanolate ligands. Furthermore, MS 5 Å binds traces of water that might be inadvertently introduced when $ZnCl_2$ or $MnCl_2$ are employed to activate bench-stable precatalysts such as the phenanthroline or bipyridine adducts **15a**,**b**, respectively. Since molecular sieves are cheap and, if desirable, can be recovered and reactivated, their use is recommended independent of the chosen catalyst. Out of the many successful applications of the use of MS 5 Å, some of which are featured in the later sections of this chapter, the preparation of the very same cyclotetramer **52** is quoted here. As can be seen from Scheme 16, the yield of this particular product was even better than that obtained under precipitation-driven conditions, on exposure of the methyl-capped substrate **53** to catalyst **13a** (or alternatively, to either the nitride- or alkylidyne-phenanthroline adducts **48** or **15** in combination with $MnCl_2$).[14] It is also of note that the required catalyst loading of **13a** (2 mol%) was significantly lower than that in case of catalyst **8** (33 mol%) used in Scheme 15.



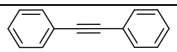
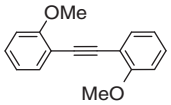
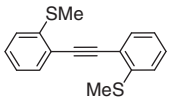
Scheme 16 Molecular sieves allow 2-butyne (bp = 27 °C) formed as the byproduct in metathesis reactions of alkynes capped with methyl groups to be conveniently sequestered and hence the reactions to be performed at (or even below) ambient temperature.

5.28.6 Synthetic Applications of Alkyne Metathesis

5.28.6.1 Alkyne Self-Metathesis Reactions

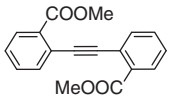
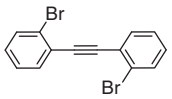
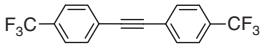
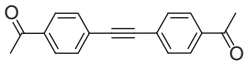
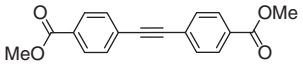
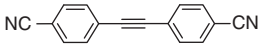
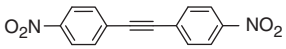
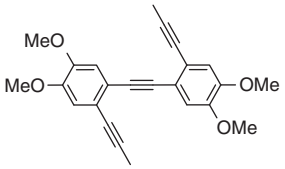
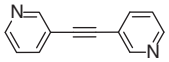
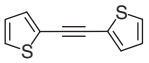
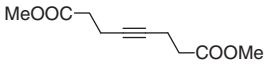
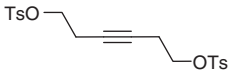
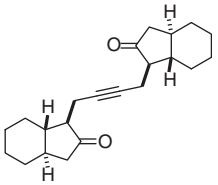
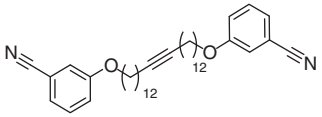
With the advent of ever more effective catalysts, the number of reactions in which alkyne substrates were 'dimerized' (with loss of 2-butyne) has considerably grown. Although by no means comprehensive, the examples compiled in Table 3 provide an overview and attest to the excellent state of the art. As can be seen, aliphatic and aromatic substrates are equally amenable to this reaction, and a considerable number of functional groups were found compatible with the latest generation of catalysts represented by complexes **13**, **15**, or **48**.[14,15] This included heterocyclic motifs as well as potential donor sites comprised of divalent sulfur or moderately basic nitrogen atoms, showing that these complexes fare extremely tolerant to catalyt poisoning. It also makes little

Table 3 Intermolecular metathesis reactions of alkynes of the type RC≡CMe affected by some representative precatalysts; the data for complexes **13**, **15**, and **48** are taken from Ref. 14 and 15; for the other data, see the cited literature

Entry	*Product*	**48**[a] *(%)*	**15**[b] *(%)*	**13a**[c] *(%)*	**13c**[c] *(%)*	**7**[27] *(%)*	$Mo(CO)_6$[d] *(%)*
1		99	99	99	98		
2		96	97	97	99[e]	68	0[27]/ 98[41]
3		87	96[f]	98[f]			

(*Continued*)

Table 3 Continued

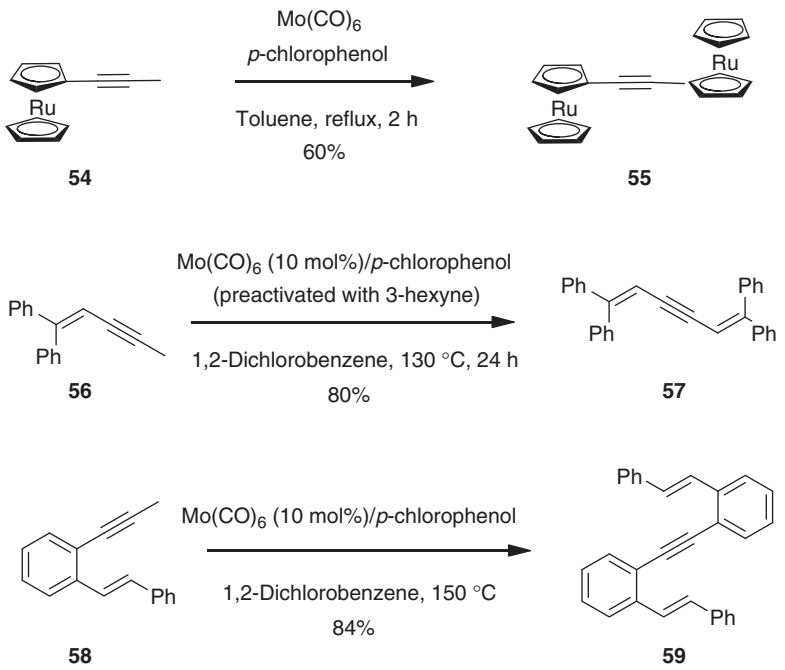
Entry	*Product*	**48**[a] *(%)*	**15**[b] *(%)*	**13***a*[c] *(%)*	**13***c*[c] *(%)*	**7**[27] *(%)*	*Mo(CO)*$_6$[d] *(%)*
4		72[g]	97[h]	95		76	0[27]
5			94[i]	94[h]			
6		94	95	93			
7		<40[g]	84	84			
8			93[i]	99[j]			
9					86[e]	58	15[27]
10			69[i]				
11				61			
12		76[g]	88[f]	90[f]	62[e]		
13		86	87	88	98[k]	0	0[27]
14		85	91	89			
15		95	92	92			
16			88	92			
17		81	89	87			

[a] **48** (10 mol%), $MnCl_2$ (10 mol%), MS 5 Å, toluene, 80 °C, 30 min, then addition of the substrate and reaction at 80 °C unless stated otherwise.
[b] **15a** (5 mol%), $MnCl_2$ (5 mol%), toluene, 80 °C, 30 min; then addition of the substrate and MS 5 Å, and reaction at ambient temperature.
[c] **13** (2 mol%), toluene, ambient temperature, MS 5 Å.
[d] In the presence of a substituted phenol.
[e] With 10 mol% of **13c** at 110 °C.
[f] At 50 °C.
[g] At 100 °C.
[h] With **15b** (5 mol%), $ZnCl_2$ (10 mol%), toluene, MS 5 Å, ambient temperature, >95% yield conversion after 6 h.
[i] Complex **15b** was used.
[j] Using 10 mol% of the catalyst.
[k] With 5 mol% of **13c**.

difference if the polar substituent resides *ortho*-, *meta*-, or *para*- to the alkyne group to be metathesized. In the same context, the kinetic stability of nitriles has to be emphasized (entries 9 and 17), as such groups may by cleaved by Schrock alkylidyne complexes as already outlined in Section 5.28.4. The example shown in entry 16 illustrates that chiral centers next to an enolizable carbonyl group are not racemized (for further illustrations of this aspect, see Section 5.28.6.4), and an elimination-prone primary tosylate remained untouched (entry 15). Aromatic aldehydes, however, still represent a challenge, although some examples are known in which this group remained intact.[27] Interestingly, when working with nitride precatalysts such as **46**–**48**, aldehydes actually get transformed into the corresponding nitriles by an as yet unknown mechanism, which represents a potentially valuable transformation in its own right.[92]

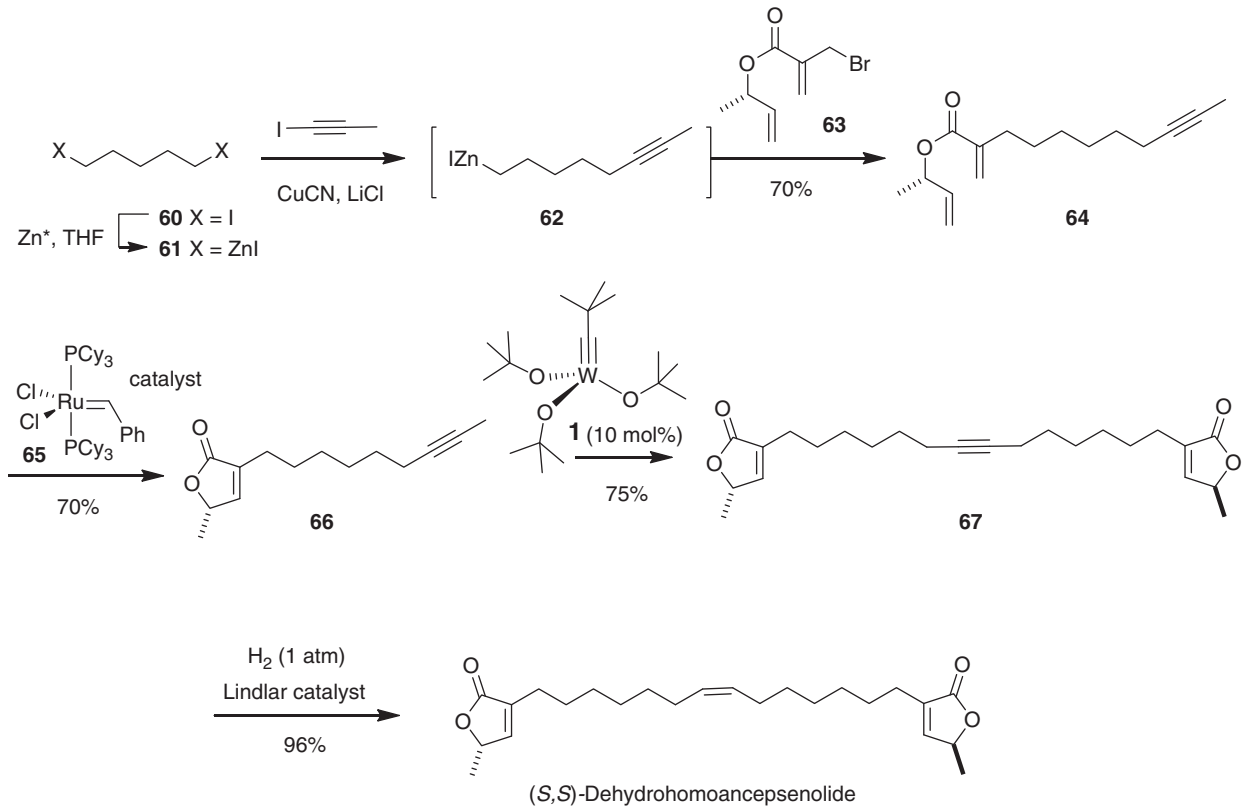
The data also suggest that molybdenum alkylidynes endowed with triarylsilanole ligands and their molybdenum nitride counterparts exhibit essentially the same application profile in chemical terms. It should be noted, however, that the initiation of **47** by nitride-to-alkylidyne exchange is best performed at slightly elevated temperatures and the reactions therefore usually carried out at $\geq 80\ ^{\circ}C$ (see Section 5.28.4). This boundary does not exist for preformed alkylidynes, which can be used at ambient temperature if the intrinsic activity of the chosen substrate permits.[14,15] Moreover, the necessary catalyst loading is typically higher when working with nitride precatalysts such as **48**. As expected, however, it makes no difference whether the active species is released from a bench-stable phenanthroline (bipyridine) adduct with the aid of $MnCl_2$, or whether an unstabilized complex is used (compare the performance of **15** vs. **13a**,**b**).

In addition to the examples shown in **Table 3**, a few other peculiar cases deserve mentioning at this point (**Scheme 17**). Propynylated ruthenocene (**54**) for instance reacted quite efficiently under Mortreux conditions to give the corresponding dinuclear product **55**.[98] Conjugated enynes such as **56** and **58** also behaved well under similar conditions, with or without preactivation of the Mortreux-type catalyst by sacrificial 3-hexyne before the addition of the substrate (see Section 5.28.2).[41,99]



Scheme 17

An early application of an alkyne self-metathesis reaction to natural product total synthesis is shown in **Scheme 18**.[100] The C_2-symmetric acetogenin (*S*,*S*)-dehydrohomoancepsenolide could be made available by a concise sequence of reactions, starting with a zinc-induced, copper-mediated three-component coupling reaction.[101] To this end, insertion of activated zinc into both C–I bonds of 1,5-diiodopentane (**60**) followed by addition of only 1 equivalent of CuCN to the resulting diorganozinc intermediate **61** gave a 1,5-heterobimetallic species, which was first reacted with 1-iodo-1-propyne at the copper end, followed by addition of the bromomethyl acrylate ester **63** to provide product **64** in 70% yield in a single operation. This material was treated with the first-generation Grubbs catalyst **65** to forge the corresponding butenolide **66**, which was then subjected to alkyne metathesis in the presence of the standard tungsten alkylidyne complex **1**. A final Lindlar reduction of the dimeric product **67** thus formed completed the total synthesis of this particular target of marine origin.[101] The most noteworthy chemical feature of this productive sequence is the chemical orthogonality of alkene- and alkyne metathesis, which transpires from the consecutive manipulation of the olefinic and acetylenic sites in **64** with the aid of an alkylidene and an alkylidyne complex. This characteristic is highly enabling, as will become evident from several more intricate examples described in Section 5.28.6.4.



Scheme 18

5.28.6.2 Cyclodimerization and Cyclooligomerization Reactions

A special case of self-metathesis relates to the cyclo-oligomerization of suitable bis-propynylated arene derivatives, which leads to shape-persistent macrocycles with interesting material properties. The carbazole tetramer **52** as a prototype example has already been discussed in Section 5.28.5 in the context of precipitation-driven alkyne metathesis. Many related cases are known in the literature; a few representative examples are compiled in Table 4. The fact that alkyne metathesis is inherently reversible arguably constitutes the biggest advantage of this methodology over alternative syntheses of such cyclooligomeric products. This dynamic covalent character allows the initially formed product mixture to equilibrate and hence the thermodynamically most favorable product to accumulate in solution. To this end, however, it is necessary that the different products initially formed *in situ* do not precipitate from the mixture. The solubility of such polyaromatic compounds is largely determined by the length and nature of the alkyl chains attached to the monomeric building blocks, which therefore need to be carefully chosen.

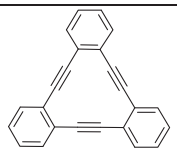
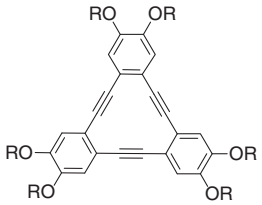
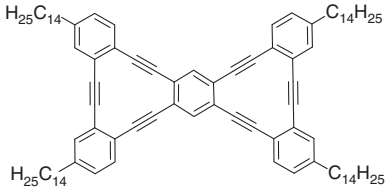
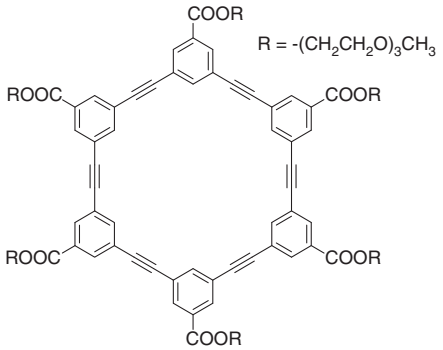
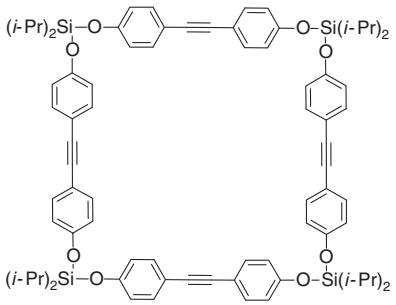
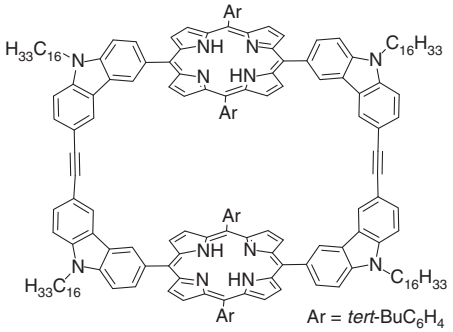
The cyclodimerization of a homologous series of conformationally unrestricted and unfunctionalized diynes has also been reported using a mixture of $Mo(CO)_6$ and 4-(trifluoromethyl)phenol in boiling toluene.[107] The yields remained rather low in most cases, except for the formation of cyclooctadeca-1,10-diyne (**69**) and cyclotetracosa-1,13-diyne, which formed quite efficiently (Scheme 19). The reasons why these particular cyclic diynes are generated much more productively than their immediate homologs are not obvious.

5.28.6.3 Alkyne Cross Metathesis

For ACM to be productive, it is necessary that the two reaction partners are sufficiently different in steric and/or electronic terms;[14,25–27] otherwise, a statistical mixture of products is formed, which is usually difficult to separate. In many of the reported cases, a couple comprising one aromatic and one aliphatic alkyne partner was crossed, and the corresponding products were obtained in good to excellent yields. Even alkynes terminated by a TMS-group could be employed, which are much less reactive than their analogs terminated by a methyl cap and therefore do not react with themselves to any significant degree.[27] The same argument holds true for propargylic alcohol derivatives, which undergo self-metathesis only very reluctantly and therefore cross well.[14] Table 5 shows a selection of representative cases.

Several applications of ACM to natural product chemistry have been reported, among which the preparation of a library of prostaglandin derivatives (Scheme 20)[27,49] and the synthesis of gallicynoic acid I (**78**, Scheme 21)[92] are noteworthy. ACM also

Table 4 Selected examples of cyclooligomeric products formed by alkyne metathesis

Entry	Product	Catalyst	Conditions	Yield (%)	References
1		**1** (20%)	Toluene, 80 °C, 8 h	54	102
2		**1** (20%)	Toluene, 80 °C, 140 h	28 (R = Me)	102
3		**8** (10%)[a]	CCl_4, 30 °C, 22 h	86[b] (R = hexyl)	103
4		**1** (50%)	Toluene, 80 °C	46	104
5		**8** (10%)[a]	CCl_4, 30 °C, 22 h	77[b,c]	96
6		$Mo(CO)_6$ (10%)[d]	1,2-Dichlorobenzene, 140 °C, 17 h	18[e]	105
7		**9** (8%)	CCl_4, 45 °C, 16 h	60[b]	106

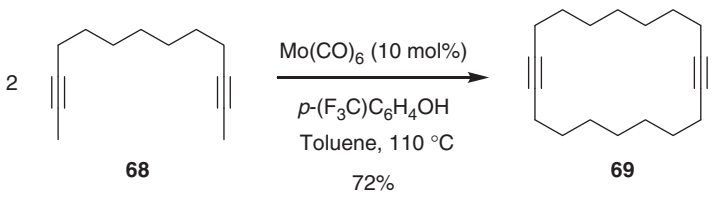
[a] In the presence of *p*-$O_2NC_6H_4OH$.

[b] Prepared by the 'precipitation-driven' method described in Section 5.28.5.

[c] Gram scale.

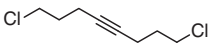
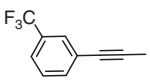
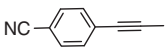
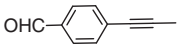
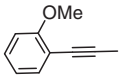
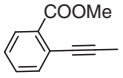
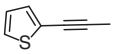
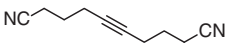
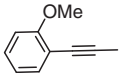
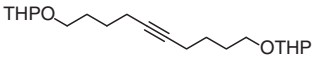
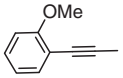
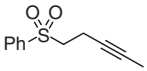
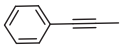
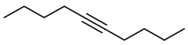
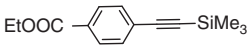
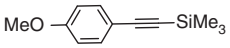
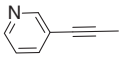
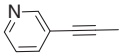
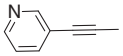
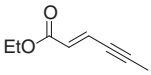
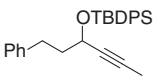
[d] In the presence of 4-chlorophenol (60 mol%).

[e] Together with 14% of the corresponding cyclotrimer.



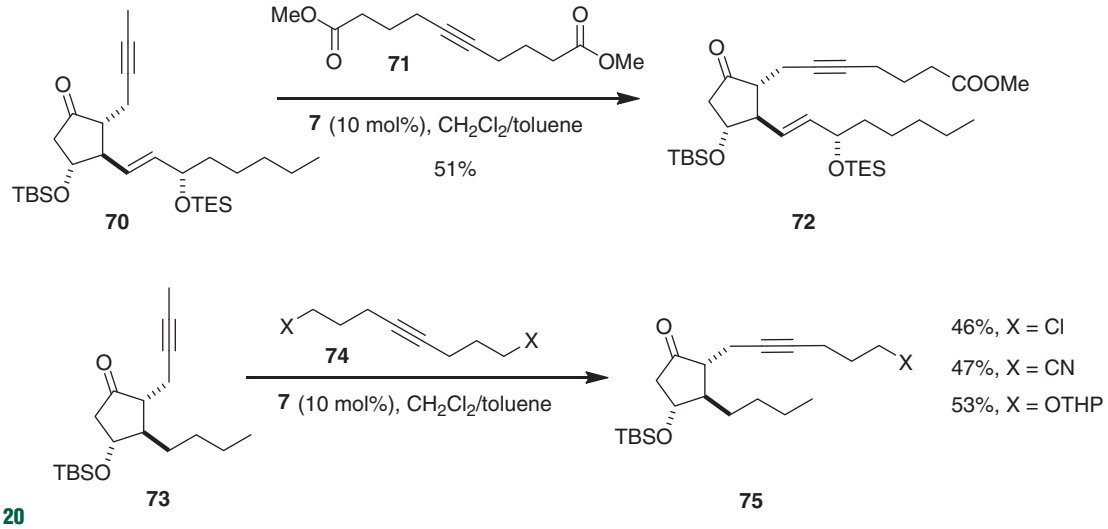
Scheme 19

Table 5 Representative ACM reactions performed in toluene

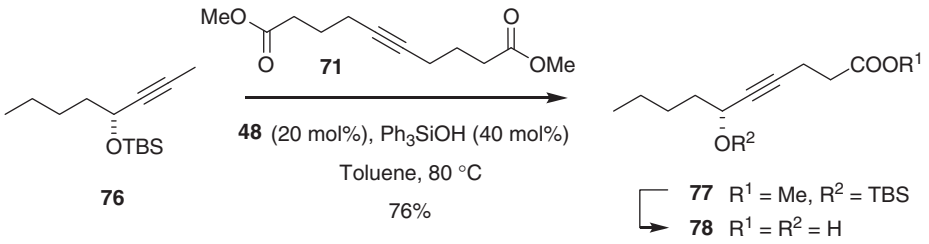
Entry	*Substrates*		*Catalyst*	*Temperature (°C)*	*Yield (%)*	*References*
1			**7**/CH_2Cl_2	80	70	27
2			**7**/CH_2Cl_2	80	70	27
3			**7**/CH_2Cl_2	80	47	27
4			**7**/CH_2Cl_2	80	67	27
5			**7**/CH_2Cl_2	80	62	27
6			**7**/CH_2Cl_2	80	55	27
7			**7**/CH_2Cl_2	80	82	27
8			**7**/CH_2Cl_2	80	68	27
9			**7**/CH_2Cl_2	80	71	27
10			**7**/CH_2Cl_2	80	65	27
11			**7**/CH_2Cl_2	80	60	27
12			**48**	100	76[a,b]	14
13			**13a**	r.t.	65[b]	14
14			**15**	r.t.	72[c]	14
15			**15**	r.t.	62[c]	14
16			**15**	r.t.	61[c]	14

[a]In the presence of $MnCl_2$.
[b]In the presence of MS 5 Å.
[c]Activation of the precatalyst with $MnCl_2$ in toluene at 80 °C for 30 min followed by addition of the substrate and MS 5 Å, and reaction at room temperature.

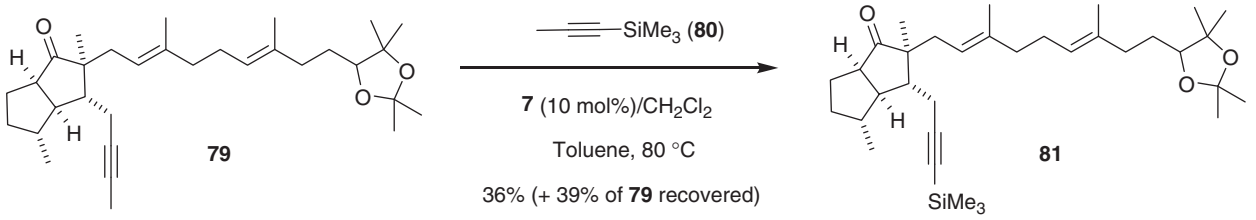
served in a study toward the total synthesis of terpestacin, during which compound **81** was prepared from **80** and 1-trimethylsilyl-1-propyne in reasonable yield based on recovered starting material (Scheme 22).[108]



Scheme 20



Scheme 21



Scheme 22

5.28.6.4 Ring-Closing Alkyne Metathesis

5.28.6.4.1 General aspects

The advent of RCAM shortly before the turn of the millennium increased the preparative significance of alkyne metathesis to a large extent.[23,24,72] The reaction was originally developed to address a stereochemical problem that conventional ring-closing alkene metathesis (RCM) was unable to solve, but it has evolved since then into a much more general tool for organic synthesis.

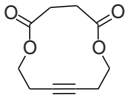
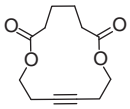
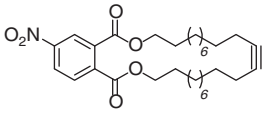
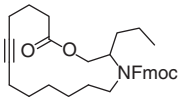
It is now common knowledge that RCM provides access to cyclic products of virtually all ring sizes but tends to afford *E*/*Z*-mixtures when applied to medium and macrocyclic rings.[109–112] The isomer ratio is difficult to predict; it depends on the chosen catalyst, the particular reaction conditions, and even the reaction time since the reversible nature of RCM engenders a (slow) equilibration. A priori, this process should accumulate the thermodynamically more stable isomer in solution, which is often – but not always – the *E*-configured cycloalkene. Many examples are documented in the literature, however, which demonstrate that even remote substituents and/or the nature of the chosen protecting groups exert a pronounced influence on the

isomer ratio in RCM-based macrocyclizations.[109–112] Inherently *E*-selective alkene metathesis catalysts are currently unknown, and the first-generation of *Z*-selective catalysts has been published only very recently.[113,114]

RCAM was originally developed as a reliable entry point into stereodefined macrocyclic alkenes of either series.[23,24] The cycloalkynes formed by RCAM can either be subjected to Lindlar-type reductions to give *Z*-alkenes or to a Birch-type reduction process, which opens access to the complementary *E*-alkene series with good to excellent levels of selectivity. As will become apparent from the discussion below, this concept has worked out very well and was scrutinized by many applications to the total synthesis of natural products of different levels of complexity. It should be noted at this point, however, that the classical Birch reduction can be advantageously replaced by a ruthenium-catalyzed *trans*-selective hydrosilylation followed by protodesilylation;[115] this methodology is compatible with many functional groups.

Despite the original strategic goal of making stereodefined cycloalkenes accessible by an RCAM/semireduction sequence, it is obvious that the scope of RCAM is by no means limited to this particular type of application. Cycloalkynes can be converted into a host of other structural motifs by taking advantage of different alkyne-selective postmetathesis transformations. The recent progress in the development of alkynophilic π-acid catalysts, notably those based on platinum and gold, provide ample opportunities in this regard.[116–118] Some illustrative case studies along these lines have already been published and many more can be awaited. Table 6 displays a few selected examples of RCAM reactions used to test the different catalyst systems.

Table 6 Screening of different catalysts in model RCAM reactions

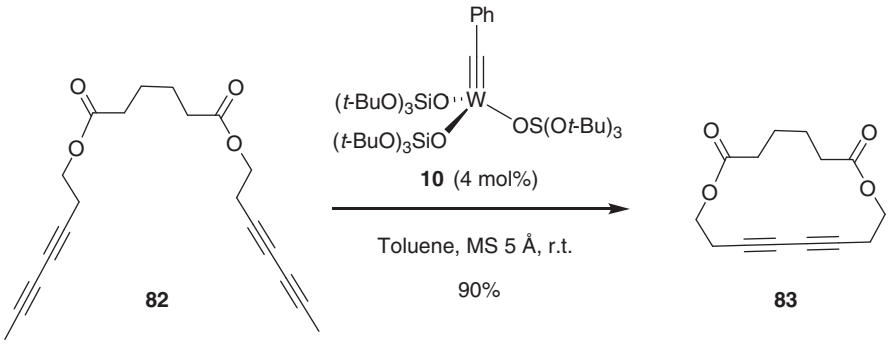
Entry	*Product*	*Catalyst*		*Conditions*	*Yield (%)*	*References*
1		$Mo(CO)_6$[a]	5 mol%	Chlorobenzene, 140 °C	64	24
2		$Mo(CO)_6$[b]	10 mol%	Chlorobenzene, 140 °C	83	36
3		**1**	5 mol%	Chlorobenzene, 80 °C	73	24
4		**7**[c]	10 mol%	Toluene/CH_2Cl_2, 80 °C	91	72
5		**48**[d]	10 mol%	Toluene, 80 °C	91	14
6		**13a** · Et_2O	2 mol%	Toluene, r.t., MS 5 Å	73	14
7		**15**[d]	5 mol%	Toluene, r.t., MS 5 Å	78	14
8		$Mo(CO)_6$	10 mol%	Chlorobenzene, 140 °C	83	36
9		**1**	5 mol%	Chlorobenzene, 80 °C	79	24
10		**7**[c]	10 mol%	Toluene/CH_2Cl_2, 80 °C	81	72
11		**48**[d]	10 mol%	Toluene, 80 °C	85	14
12		**13a** · Et_2O	2 mol%	Toluene, r.t., MS 5 Å	92	14
13		**15**[d]	5 mol%	Toluene, r.t., MS 5 Å	90	14
14		**7**[c]	10 mol%	Toluene/CH_2Cl_2, 80 °C	69	72
15		**13a** · Et_2O	2 mol%	Toluene, r.t., MS 5 Å	85	14
16		$Mo(CO)_6$[a]	5 mol%	Chlorobenzene, 140 °C	67	24
17		**1**	5 mol%	Chlorobenzene, 80 °C	71	24
18		**13a** · Et_2O	2 mol%	Toluene, r.t., MS 5 Å	90	14

[a]In the presence of *p*-ClC_6H_4OH (1 equivalent).
[b]In the presence of *o*-FC_6H_4OH (1 equivalent).
[c]Activated with CH_2Cl_2 used as cosolvent.
[d]Activated with $MnCl_2$.

Another highly advantageous characteristic, which paid already many dividends in synthesis, is the orthogonal character of alkyne- and alkene metathesis. It has been demonstrated on many occasions that the available alkyne metathesis catalysts, in particular those of the latest generation, do not touch C–C double bonds of any kind, be they terminal, internal, or conjugated with electron-withdrawing or -donating groups;[14,15] 1,3-dienes are equally tolerated and even highly sensitive skipped 1,4-dienes were shown to survive undamaged. As a consequence, RCAM is predestined for applications to target molecules that present more than one π-system, as will become evident from some of the examples compiled below.

In terms of ring size, RCAM has allowed carbo- and heterocycles of ring sizes ≥ 11 to be formed, with the strain of the cycloalkynes being the limiting factor. In case of an 11-membered ring, the cyclodimerization of the substrate was a major side reaction (see Section 5.28.6.2.),[23,24] which completely takes over in attempted formations of even smaller cycles.

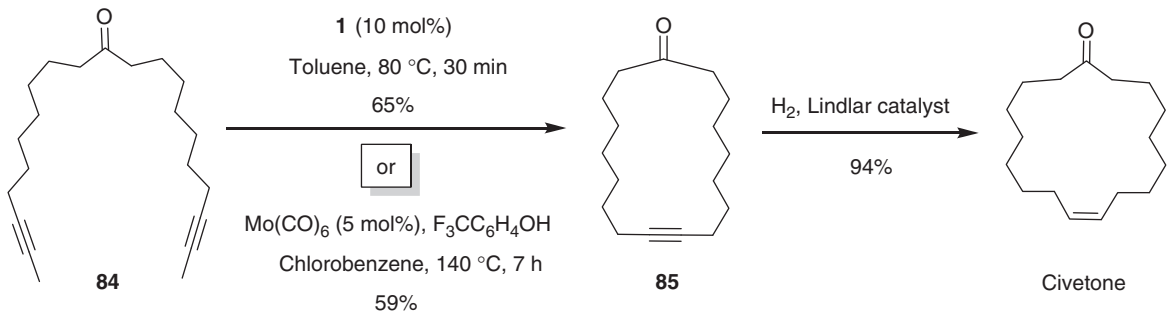
Very recently, catalytic ring-closing metathesis reactions of conjugated diyne substrates have also been accomplished in which dimethyldiacetylene is cleaved off and cyclic 1,3-diyne products are formed (Scheme 23).[119] The reaction was again best performed in the presence of MS 5 Å, using the tungsten alkylidyne **10** modified by siloxide ligands.[120]



Scheme 23

5.28.6.4.2 Olfactory compounds

Many unsaturated macrocyclic lactones and ketones exhibit pleasant olfactory properties, which are often determined by the configuration of the double bonds embedded into the macrocyclic frames. Prominent examples are the perfume ingredients civetone and (*R*,*Z*)-5-Muscenone®, the musk-odored lactone ambrettolide or the camphor- and minty-odored yuzu lactone. Because of their rather simple structures yet industrial relevance, these and related compounds frequently served as testing grounds for the various generations of alkyne metathesis catalysts.[24,42,121] As already mentioned in Section 5.28.2, several such targets could be made in respectable yields even with Mortreux-type catalyst mixtures, although the tungsten alkylidyne **1** was at least as effective but required much shorter reaction times, as exemplified in Scheme 24 for the case of civetone.[42]

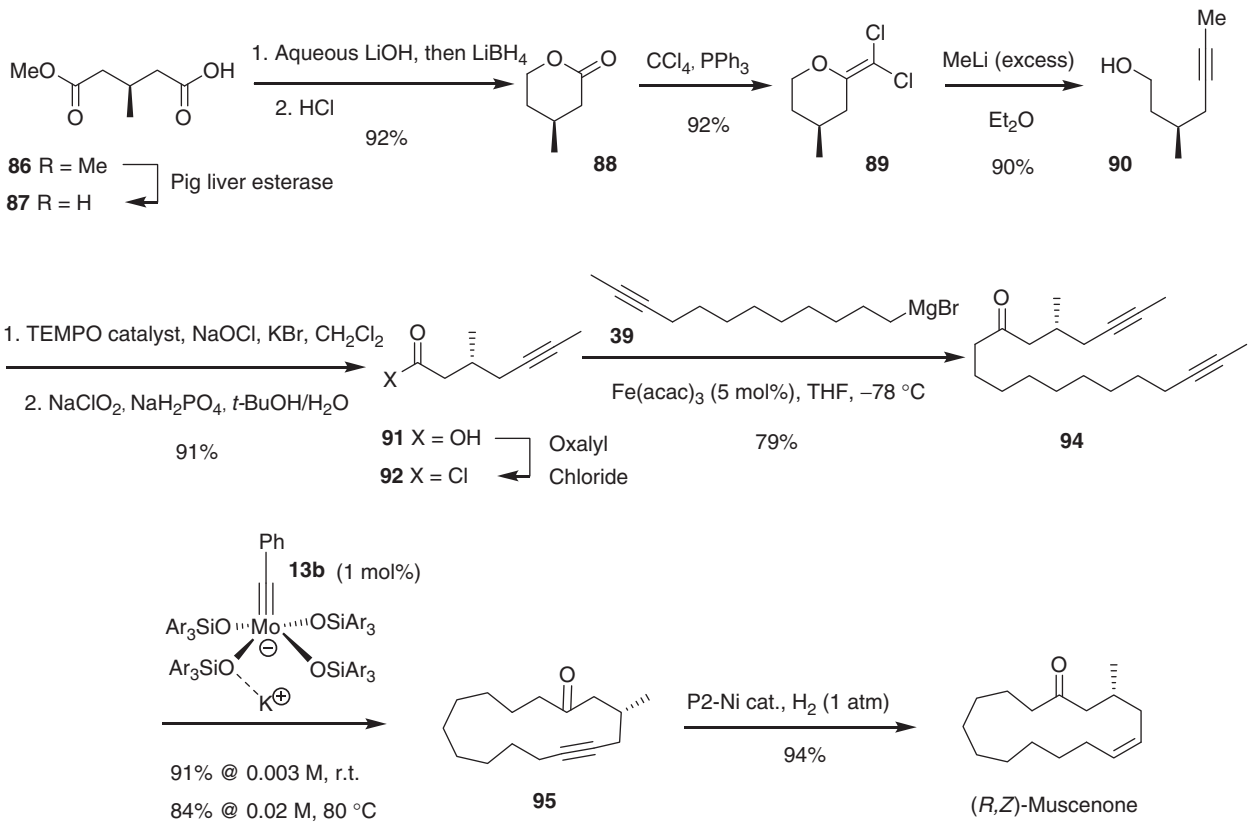


Scheme 24

A comparison of the civetone synthesis with the preparation of the commercially used perfume ingredient (*R*,*Z*)-5-Muscenone® presented in Scheme 25 is instructive as it gives a feeling for the advances in catalyst design during the last decade.[122] Interestingly, the preparation of Mucenone was solely built on base-metal catalysis (Fe, Mo, Ni), featuring an iron-catalyzed cross coupling reaction for the formation of the necessary substrate **94** from acid chloride **92** and the alkyl Grignard reagent **93**.[123,124] The cyclization of diyne **94** to the 15-membered cycloalkyne **95** was effected within 30 min at ambient temperature using only 1 mol% of the molybdenum alkylidyne ate-complex **13b**, when the reaction was carried out under high-dilution conditions (0.003 mol l^{-1}). Interestingly, it was possible to increase the substrate concentration by almost one order of magnitude to 0.02 mol l^{-1} without much loss in yield, provided that the cyclization was performed at 80 °C.[122] Under these conditions, the substrate initially converts into a product mixture comprising **95** and various dimeric and oligomeric compounds. Due to the covalent dynamic character of alkyne metathesis, however, this mixture eventually converges to the desired cyclic monomer at the chosen higher temperature.

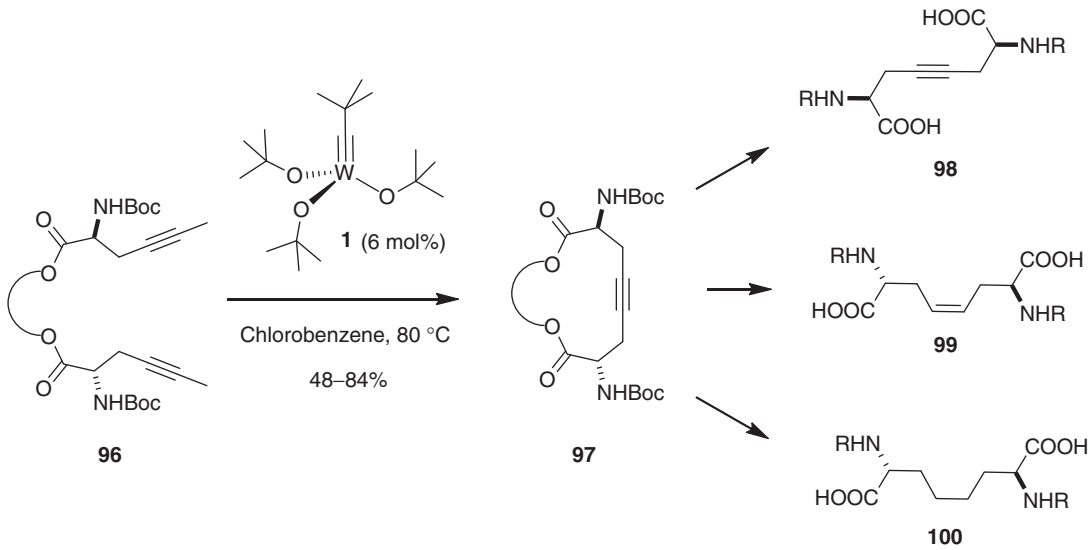
5.28.6.4.3 Amino acid derivatives

The functionality presented by protected amino acids and peptides poses no problem for the tungsten alkylidyne complex **1**. This excellent compatibility transpires from the successful applications to a small set of cystine isosteres **98**–**100**, in which the chemically and metabolically labile disulfide bridge of the natural product was replaced by either a carbon–carbon triple-, double-, or single bond; the efficiency of ring closure, however, depended on the chosen diol tether (Scheme 26).[125] The same



Scheme 25

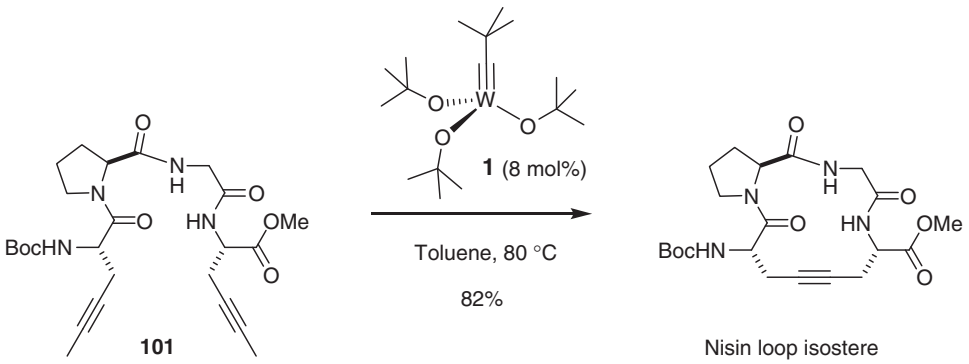
tactics could also be applied to the preparation of orthogonally protected cystine isosteres for incorporation into larger peptides, as well as to variety of other acetylene-containing amino acid derivatives.[126]



Scheme 26

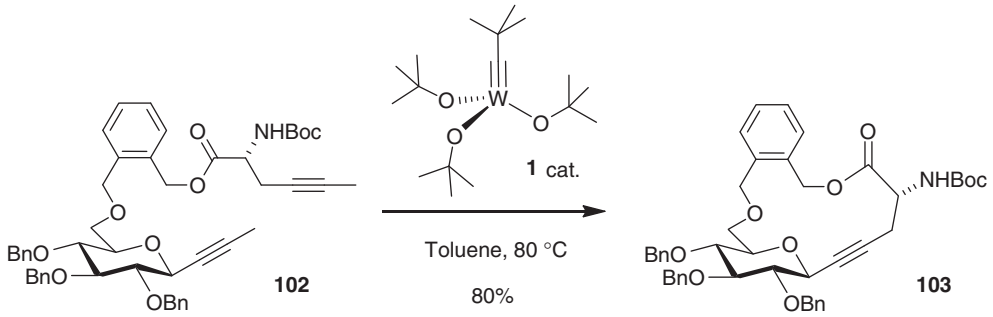
RCAM also served the preparation of several isosteres of the individual loops of the lantibiotic nysin Z.[127,128] The most effective case is shown in Scheme 27, which benefits from a certain degree of conformational preorganization of the substrate **101** by the turn-inducing proline unit. Peptidic diynes devoid of such a cyclization-friendly conformation gave lower yields and

required longer reaction times. The beneficial effect of proline was later used to prepare various other cyclic β-turn motifs by a similar strategy.[129]



Scheme 27

Related cyclization reactions were successfully applied to the preparation of glycopeptide isosteres starting with substrates, in which *C*-glycosidic acetylenes such as **102** reacted intramolecularly with a tethered 2-butynyl glycine entity.[130] Depending on the particular connectivity pattern, either the desired cyclic monomers such as **103** or cyclodimeric products were obtained with the aid of the tungsten catalyst **1** (Scheme 28).

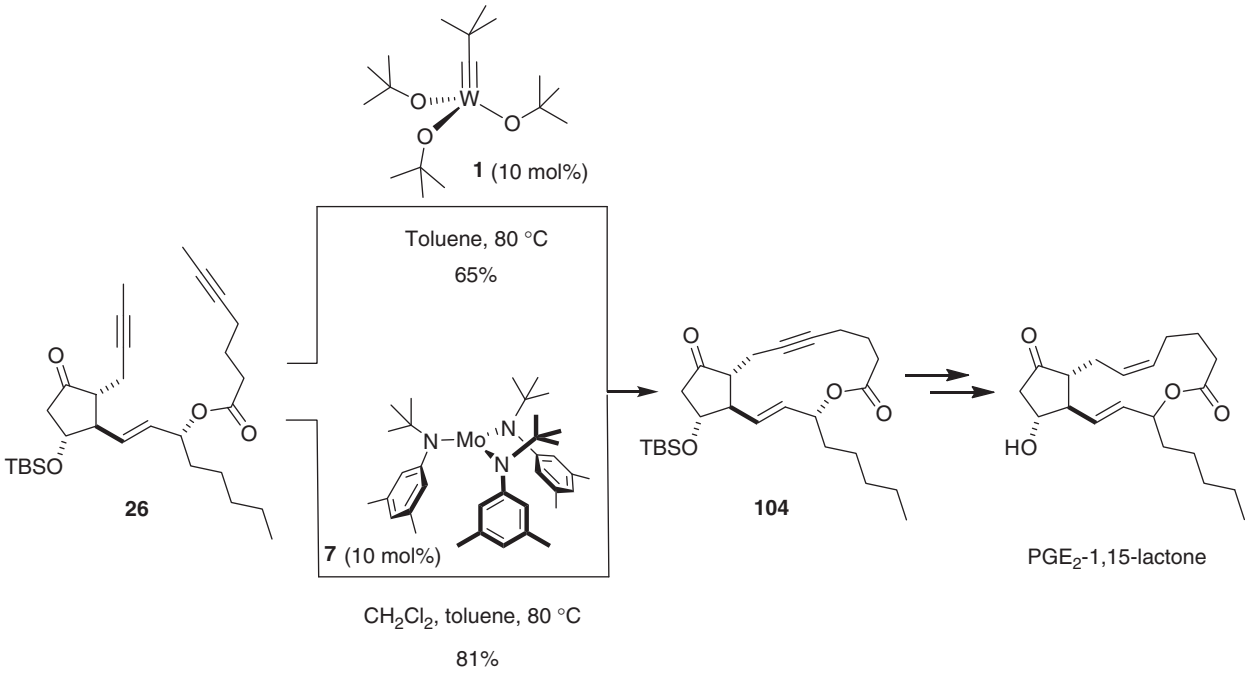


Scheme 28

5.28.6.4.4 Prostaglandins and oxylipins

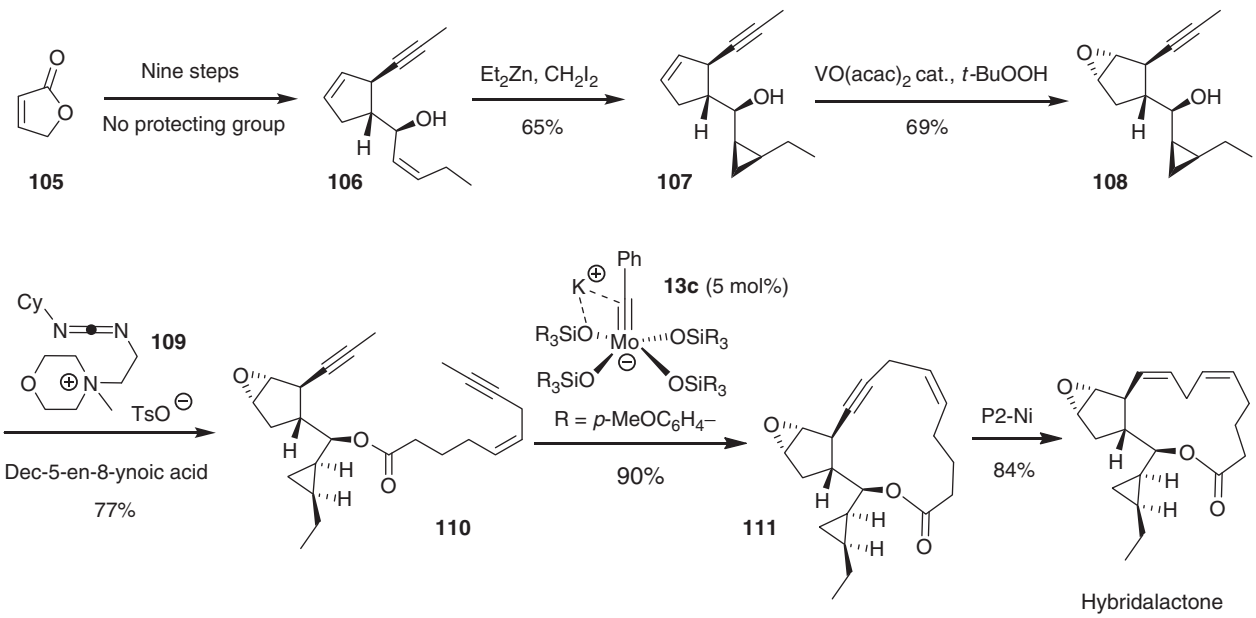
The intrinsic lability of prostaglandins renders this product class a formidable testing ground for the efficiency of the various alkyne metathesis catalysts available to the practitioner. The significant differences in their performance are evident from an early application to the total synthesis of prostaglandin E_2–1,15-lactone, a naturally occurring prodrug that is hydrolyzed on demand to the parent prostaglandin E_2 by various esterases (Scheme 29).[49,131] Attempts to cyclize diyne **26** by Mortreux-type catalysts met with failure as the substrate was destroyed (Scheme 4). In contrast, the use of the classical tungsten alkylidyne **1** afforded the desired cycloalkyne **104** as the immediate precursor of the target in appreciable yield but was outperformed by the combination **7**/CH_2Cl_2. A small set of nonnatural prostaglandin analogs could be obtained analogously by varying the length and substitution pattern of the acid segment in the cyclization precursor.[49]

The structurally rather unusual marine eicosanolid hybridalactone constitutes an even more demanding case (Scheme 30).[132] In an attempt to adhere to the most stringent conditions imposed on contemporary total synthesis, the required cyclization precursor **110** was prepared without recourse to any protecting group maneuvers in excellent overall yield starting from the commercial butenolide **105**. Key to success were two consecutive and highly chemo- and stereoselective functionalizations of the alkene sites in **106**, both of which were guided by the allylic –OH group serving as a relay substituent. First, this group assured a β-selective cyclopropanation of the *Z*-configured allylic alcohol to give product **107** before it directed the subsequent vanadium-catalyzed epoxidation to the α-face of the endocyclic olefin. With all seven contiguous chiral centers of the target being set, the stage for macrocyclization was reached on esterification of **108** with dec-5-en-8-ynoic acid. This seemingly routine step was actually rather difficult and worked well only when mediated by a specially modified cationic carbodiimide **109** escorted by a tosylate counterion. Any more nucleophilic anion present in the mixture (for instance, the chloride released when using the respective acid chloride for the acylation) was found to open the epoxide ring of **108**, which is unusually reactive. Gratifyingly, the resulting diyne **110** was cyclized with exceptional ease using catalyst **13c**, whereas the classical tungsten alkylidyne **1** destroyed this

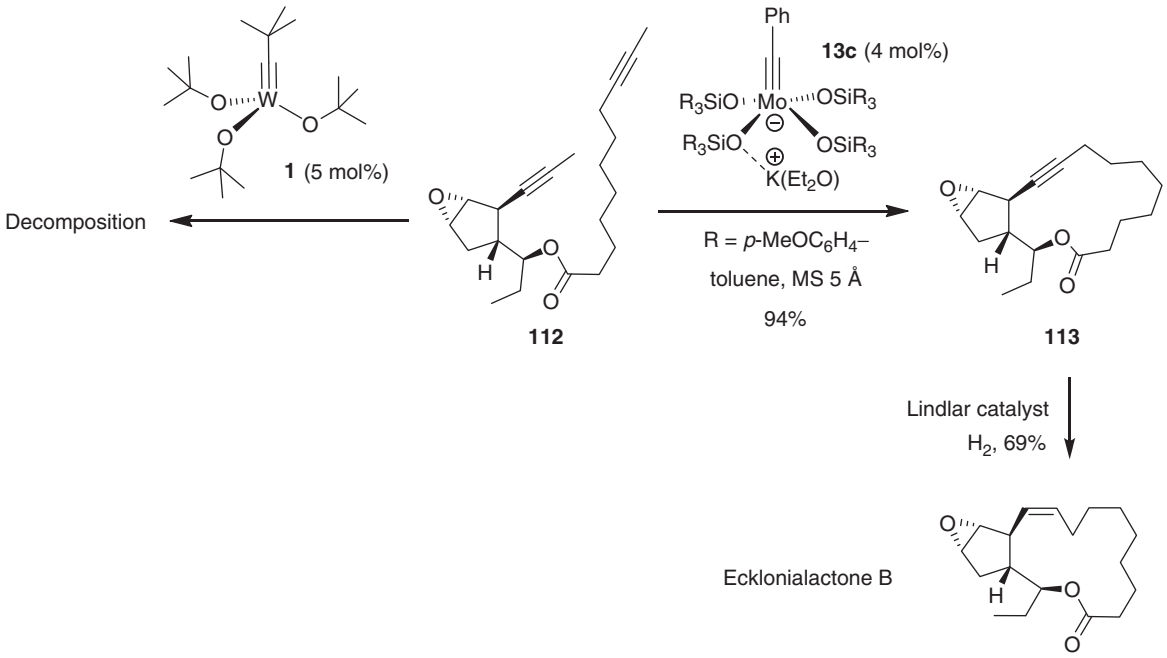


Scheme 29

fragile substrate (and related compounds, see Scheme 31).[132] The *p*-methoxyphenyl groups on the silanolate ligands of **13c** facilitate the purification of the resulting cycloalkyne **111**, because they render the silicon-containing residues formed on work up rather polar and hence easy to remove from the fairly lipidic product. A selective reduction of **111** over nickel boride (P2-Ni made from $Ni(OAc)_2 \cdot 4\,H_2O$ and $NaBH_4$) installed the skipped 1,4-diene unit and completed the total synthesis of this interesting marine natural product.[132] Various natural and nonnatural analogs were also obtained by analogous routes, including the C18-oxylipin derivatives ecklonialactone A, B, and C. The approach to these latter compounds also highlighted the much improved application profile of the molybdenum alkylidynes of type **13** as compared with the classical Schrock catalyst **1** (Scheme 31).[132,133]



Scheme 30

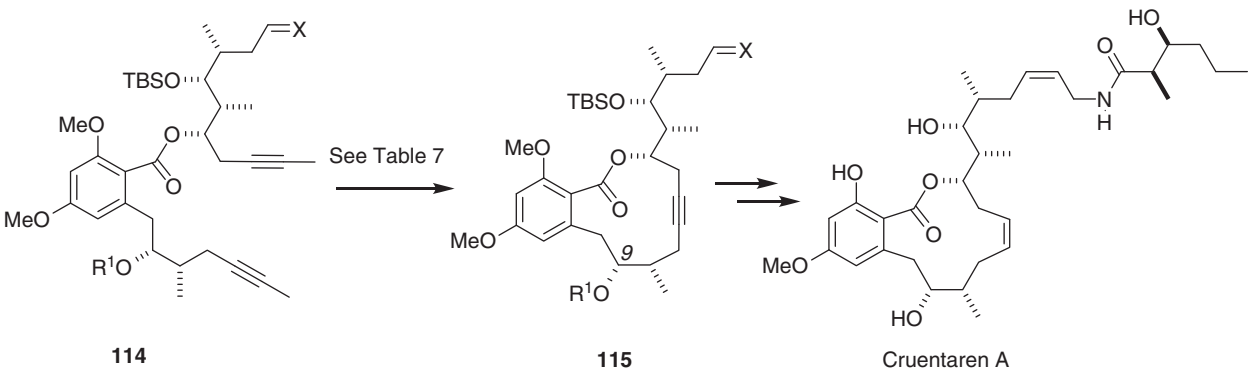


Scheme 31

5.28.6.4.5 Macrolides incorporating Z- or E-configured alkenes

The fact that three research groups independently pursued the total synthesis of the highly cytotoxic F-ATPase inhibitor cruentaren A via RCAM/semireduction as the key strategic transformation may reflect the growing popularity of the method within the synthetic community. At the same time, the three approaches nicely feature the rapid advance in catalyst development made in recent years.

Specifically, Vintonyak and Maier forged the highly functionalized 12-membered ring **115a** with the aid of the Schrock tungsten alkylidyne catalyst **1** (Scheme 32 and Table 7, entry 1)[134,135] and then carried the cycloalkyne trough to the very end of the synthesis. It served to keep the –OH group at C.9 away from the transannular lactone and hence effectively prevented undesirable ring contraction with formation of a δ-lactone from occurring. After attachment of the lateral chain, a Lindlar reduction revealed the two *Z*-olefins residing in the ring and the tether in a single operation. This successful blueprint was promptly extended to the preparation of a set of cruentaren-analogs for biological testing.[136]



Scheme 32

In parallel work, the Fürstner group was able to cyclize the even more decorated precursor **114b** to product **115b**, which already contained the *Z*-alkene in the lateral chain (X=CHCH$_2$OTHP).[137,138] Attempts to perform this reaction with the tungsten alkylidyne **1a**, however, only led to cleavage of the THP-acetal due to the significant Lewis acidity of this particular catalyst (Table 7, entry 2). Gratifyingly, the combination **7**/CH_2Cl_2 was found more chemoselective, furnishing the desired product in 87% yield (entry 3). This transformation was revisited when the latest generation catalysts endowed with siloxide ligands became available. As expected, complex **13a** furnished product **115b** with similar efficiency but required a significantly lower loading of

Table 7 RCAM reactions en route to cruentaren A as shown in **Scheme 32**

Entry		*R^1*	*X*	*Catalyst*	*T (°C)*	*Yield (%)*	*References*
1	**115a**	TIPS	H, ODMB	**1** (10 mol%)	85	91	134
2	**115b**	TBDPS	$CHCH_2OTHP$	**1** (10 mol%)	80	–[a]	137
3	**115b**	TBDPS	$CHCH_2OTHP$	**7** (10 mol%)[b]	80	87	137
4	**115b**	TBDPS	$CHCH_2OTHP$	**13a** (2 mol%)	80	82	139
5	**115c**	TIPS	$CHCH_2OPMB$	**47** (40 mol%)[c]	110	75	139

[a]Only the THP-group in the substrate was cleaved.
[b]Activated with CH_2Cl_2.
[c]Used in form of the pyridine adduct.
Abbreviations: TBDPS, *tert*-butyl-diphenylsilyl; TIPS, tri-isopropylsilyl.

only 2 mol% (entry 4). A few standard operations then allowed **115b** to be converted into cruentaren A in high overall yield. In the next stage of the project, the approach could be successfully reprogrammed to the preparation of a collection of designer-analogs of this potent cytotoxic agent, all of which contained deep-seated structural point mutations.[138] Gratifyingly, three of these fully synthetic compounds turned out to be as or even more cytotoxic than the parent natural product cruentaren A itself against L-929 mouse fibroblast cells, reaching IC_{50} values as low as 0.7 ng ml^{-1}.

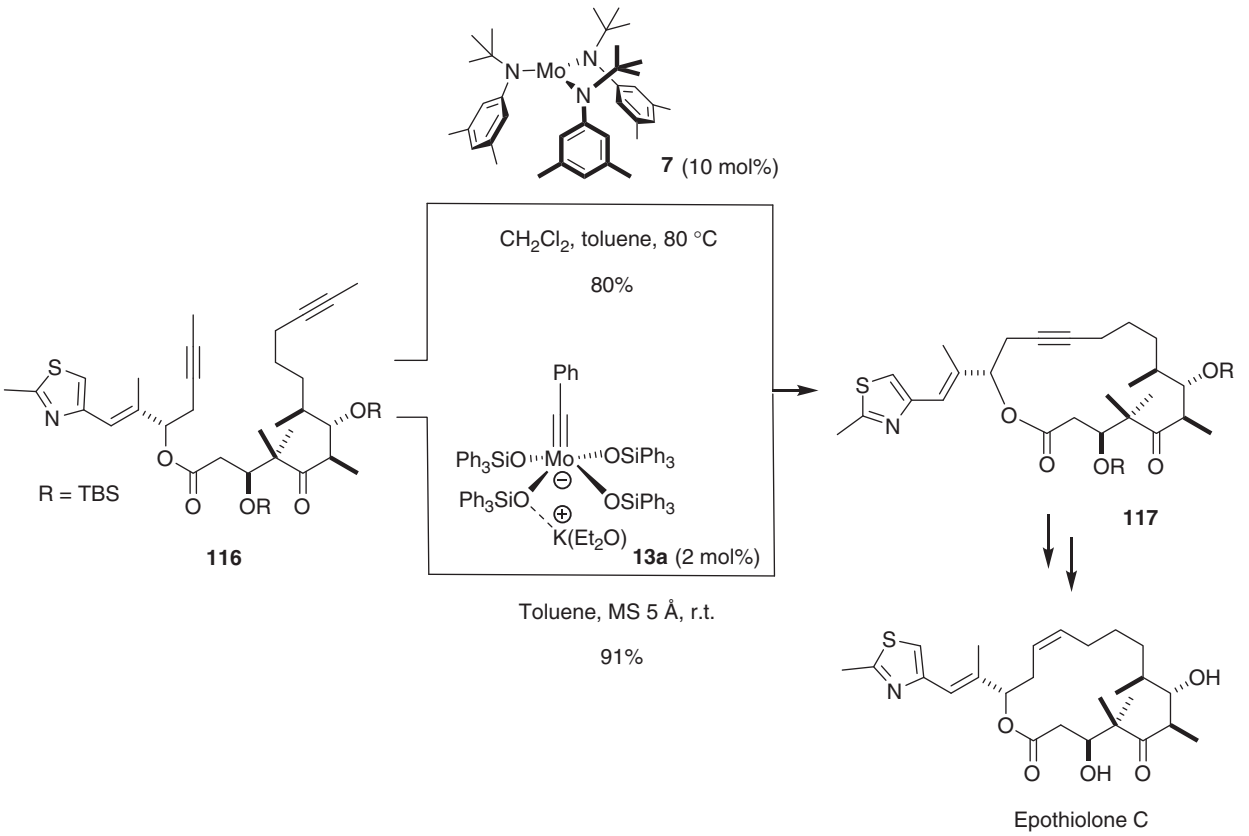
Barrett and coworkers reported yet another synthesis of cruentaren A via RCAM using the pyridine adduct of the molybdenum nitride **47** as the precatalyst to forge the macrocycle.[139] Because the initiation of this precatalyst by nitride-to-alkylidyne exchange is slow and requires heating, a fairly high loading (40%) was used to ensure a sufficient concentration of the active species in solution and hence a short reaction time in order to minimize the thermal decomposition of the polyfunctionalized substrate (Table 7, entry 5). Although this key step resembles the earlier syntheses of **115**, the innovative preparation of the cyclization precursor **114c** by a biomimetic *de novo* synthesis of the resorcyclide unit deserves particular mentioning.

A similar comparison of the productivity of the different available catalysts can also be made in the case of epothilone C, a prominent target in natural product synthesis in general and metathesis chemistry in particular (**Scheme 33**). The first synthetic approaches toward the epothilones based on RCM were all facing the same problem that the macrocycle could be closed in high yields but with little – if any – selectivity in favor of the required *Z*-alkene.[140] Since this selectivity issue arose only in the final stages of the multistep sequences leading to the target and the produced isomer mixtures were found difficult to separate, the epothilones showcased the urgent need for the development of more stereoselective metathesis catalysts. To this end, the combination of RCAM/Lindlar reduction provided the first viable solution (**Scheme 33**).[72,141] It was the then brand new trisamido complex **7** in combination with CH_2Cl_2, which allowed the polyfunctionalized diyne **116** to be cyclized in high yield in toluene at 80 °C. Neither was the aldol substructure damaged nor was the sulfur- and nitrogen donor sites present in this substrate interfering with the catalyst. After the development of the molybdenum alkylidyne complexes endowed with triarylsilanolate ligands, this particular transformation was reinvestigated.[14] As expected, catalyst **13a** was not only even more productive but also required a lower loading even when operated at ambient temperature. Semireduction of the resulting cycloalkyne **117** followed by global deprotection gave epothione C in excellent yield and isomerically pure form. It is, however, fair to say at this point that the very recent progress in the design of *Z*-selective olefin metathesis catalysts has also enabled a stereoselective synthesis of epothilone C by conventional RCM.[113]

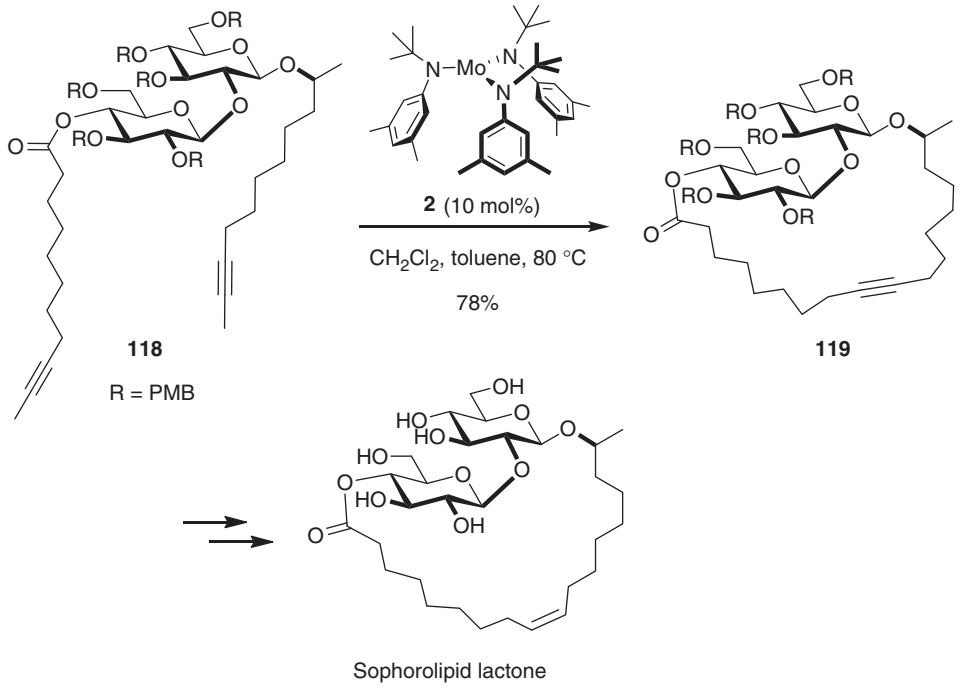
Another challenging application from a different area relates to the stereoselective total synthesis of the glycoconjugate sophorolipid lactone, which comprises an isolated *Z*-alkene within its fatty acid tether (**Scheme 34**). Once again, RCAM followed by semihydrogenation provided a satisfactory solution and showed at the same time that polyoxygenated substrates and glycosidic linkages pose no problems for molybdenum-based catalysts.[142,143]

A recent total synthesis of the sponge metabolite tulearin C shows that RCAM/semireduction also excels in the stereocomplementary formation of *E*-olefins from adequate cycloalkyne precursors (**Scheme 35**).[144] This result must be seen in the light of a previous investigation, in which the macrocyclic frame of a tulearin had been forged by conventional RCM, but with an unfavorable *E*/*Z*-ratio of 1.9:1.[145] This outcome shows that the lack of inherently *E*-selective olefin metathesis catalysts can be a serious setback for target-oriented synthesis, in particular since all attempts to improve on the result by changing the reaction parameters or modifying the substrate were to no avail.

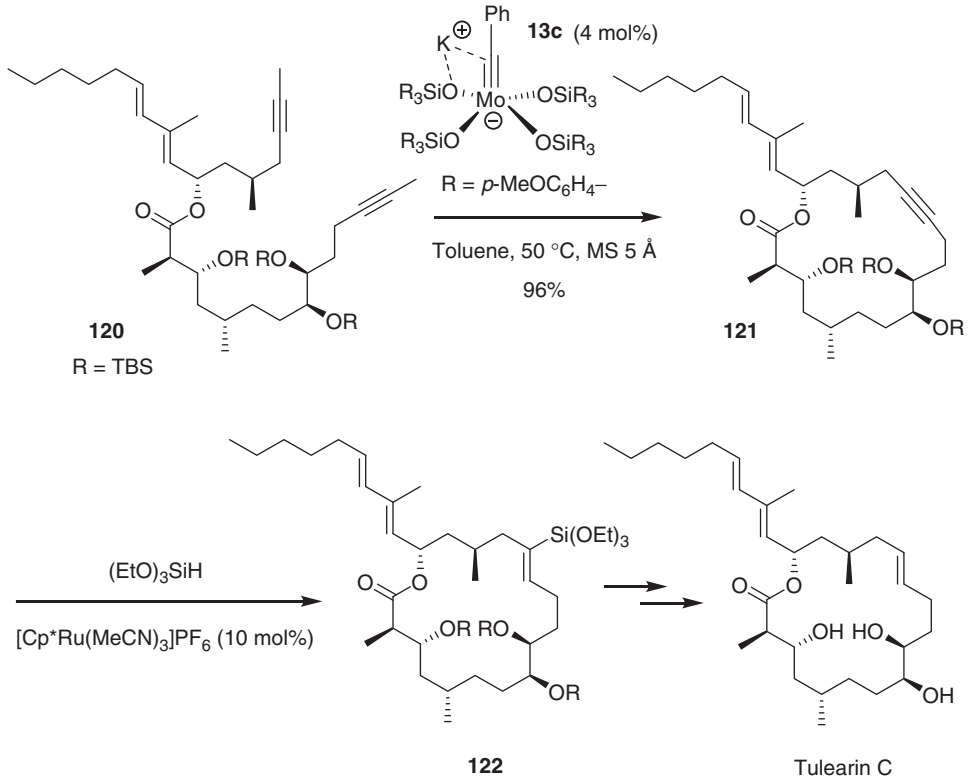
This shortcoming of RCM can be circumvented by an RCAM/semireduction sequence. As shown in **Scheme 35**, this tactics furnished tulearin C with exquisite stereochemical purity. Specifically, cyclization of diyne **120** using the highly active and selective ate-complex **13c** as precatalyst in the presence of MS 5 Å as additive gave the corresponding cycloalkyne **121** in almost quantitative yield, although the contained dienyl-alcohol motif as well as the aldol subunit are both fairly sensitive. A subsequent *trans*-hydrosilylation catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$ followed by global deprotection of **122** furnished tulearin C in a very satisfactory yield and excellent *E*-selectivity. The formal *trans*-reduction of the alkyne by a ruthenium-catalyzed hydrosilylation followed by cleavage of the resulting alkenyl silane with a mild fluoride source, originally developed by Trost and coworkers,[115] is widely applicable in the context of cycloalkynes and cyclic enynes and tolerates many relevant functionalities, as this and other studies from the author's laboratory have demonstrated.[146–148]



Scheme 33



Scheme 34



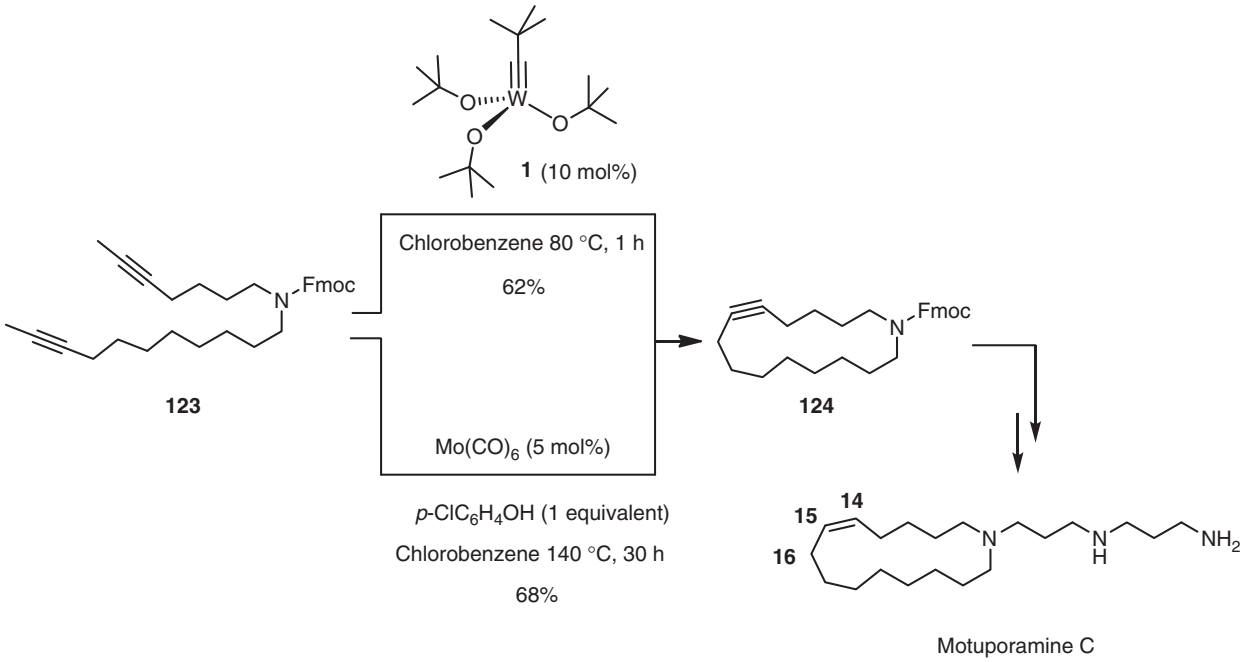
Scheme 35

5.28.6.4.6 Alkaloids

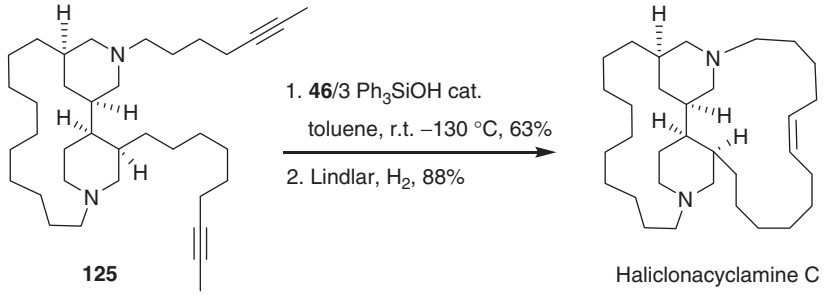
The structurally rather simple but biologically very promising spermine alkaloid motuporamine C served as an early testing ground.[45] Since the isolation team had been unable to determine whether the $\Delta^{14,15}$-alkene or the $\Delta^{15,16}$-isomer represented the natural product, both compounds were selectively prepared as depicted in **Scheme 36** for one of them. RCAM forged the macrocycle either with the aid of the tungsten alkylidyne **1** or with an *in situ* Mortreux-type mixture, which were similarly effective in case of this barely functionalized substrate. A subsequent Lindlar reduction then gave the required *Z*-alkene, which was easily advanced into the target. With both positional isomers in hand, it was possible to show that the $\Delta^{14,15}$-alkene depicted in **Scheme 36** was identical with natural motuporamine C in all spectroscopic and analytical regards.[45]

Whereas the early and more Lewis acidic alkyne metathesis catalysts such as **1** are inhibited by coordination to basic N-atoms, the new molybdenum nitride and alkylidyne complexes bearing silanolate ligands are usually compatible with such donor sites and hence qualify particularly well for applications in the alkaloid series. This notion is exemplified by a total synthesis of the tetracyclic alkylpiperidine alkaloid haliclonacyclamine (**Scheme 37**).[149] In the penultimate step, the elaborate substrate **125** containing two *tert*-amines was successfully cyclized and the resulting product swiftly advanced to the targeted natural product. Of all the catalysts tested, only $[(Ph_3SiO)_3Mo{\equiv}N]$ (**47**) generated *in situ* from nitride **46** and Ph_3SiOH was able to effect this transformation without getting blocked by the tertiary amines. Since **47** must convert into an alkylidyne *in situ* in order to exert its catalytic activity (see Section 5.28.4, **Scheme 13**), it is reasonable to assume that preformed molybdenum alkylidynes such as **13**–**15** would be equally or even more effective in this particular transformation.[14,15]

The macrocyclic perimeter of the complex marine alkaloid nakadomarin A (**128**) has invited many teams to scrutinize the performance of RCAM in target-oriented synthesis (**Scheme 38**). After an early model study had suggested that the ring can be closed by this reaction in excellent yield (**126**→**127**),[24] several teams succeeded in implementing this strategy into actual total synthesis endeavors. Specifically, the group of Funk showed that the tungsten alkylidyne **1** and the molybdenum nitride complex **47** are roughly equipotent in the conversion of **129** into **130**, but the latter is much cheaper and easier to handle.[150] Dixon and coworkers employed the tungsten catalyst **1** to cyclize the somewhat more elaborate substrate **131**, which contained two additional double bonds; once again, the alkylidyne was found to select exclusively for the alkynes and left the olefins unchanged.[151] Somewhat surprisingly, the most elaborate substrate **22** with the strained eight-membered ring already in place, was cyclized by the Dixon group in a second approach with the aid of a more archetypic Mortreux-type catalyst, which required very harsh conditions.[47] Although the desired product **23** could be isolated, the yield remained low despite the very high catalyst loading (see Section 5.28.2).



Scheme 36



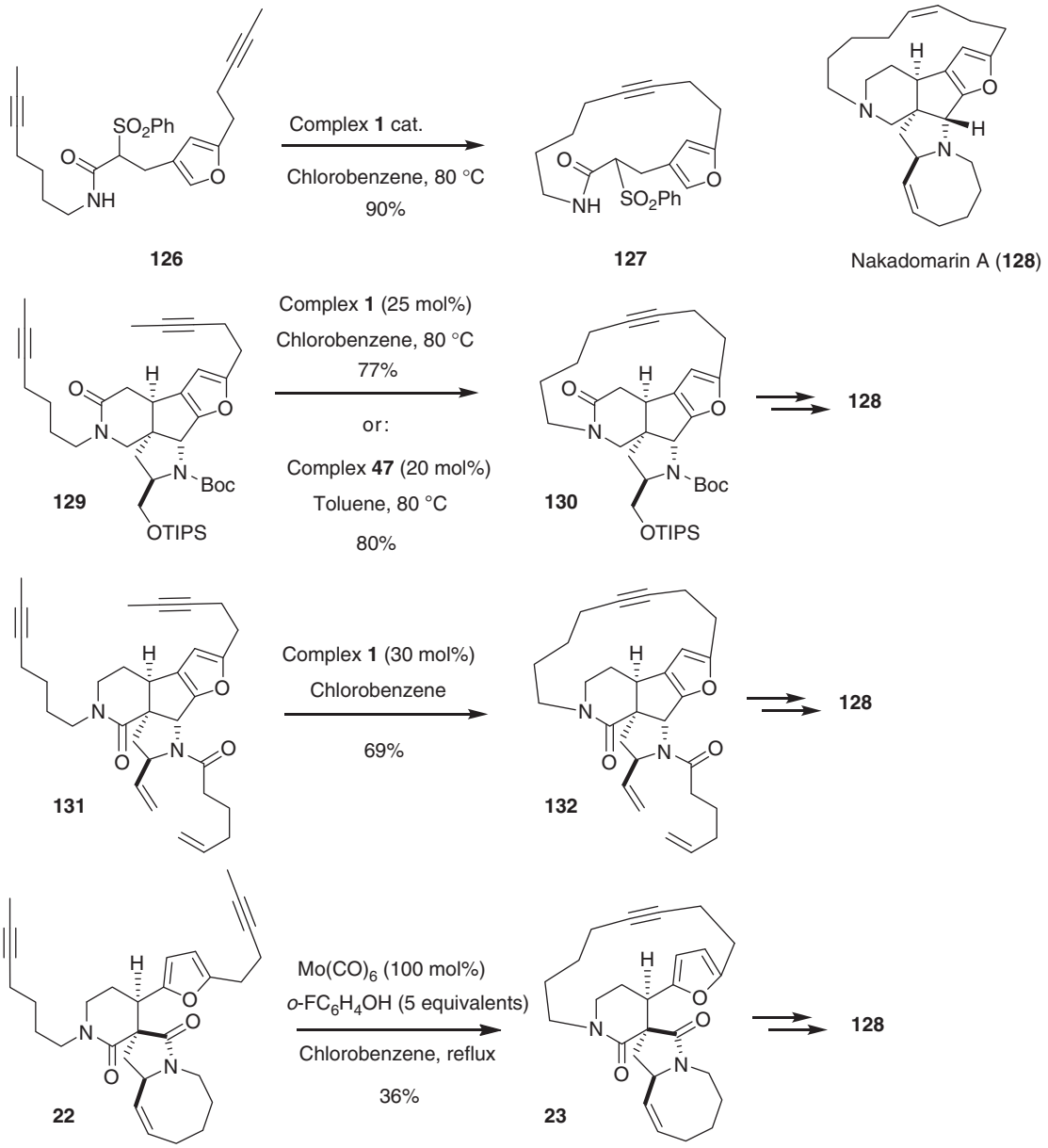
Scheme 37 The compatibility of the molybdenum catalysts bearing silanolate ligands with basic amines was the key enabling feature for a total synthesis of the alkylpiperidine alkaloid halichlonacyclamine C.

5.28.6.4.7 Conjugated dienes

An important limitation of contemporary alkene metathesis relates to the stereoselective formation of conjugated dienes or polyenes, because the standard catalysts do not properly distinguish between the different double bonds of the required substrates. Although a couple of successful examples are known in the literature, many attempted syntheses of cyclic 1,3-dienes were plagued by the preferential activation of the inner double bond of a given substrate, which ultimately results in ring contraction. Moreover, the newly formed bonds are usually formed as *E*/*Z*-isomer mixtures, which complicates matters even further and makes cumbersome separations necessary. Only recently has a more rational RCM-based approach to 1,3-dienes been devised, in which the inner double bond of a given substrate is substituted by a silyl group that serves as a protecting and as a stereodirecting group alike.[152]

The proven orthogonal character of alkyne metathesis provides a serious alternative. Early model studies had shown that only the two acetylene units of an enyne–yne substrate will react, whereas the conjugated alkene site passes uncompromised.[147,148] The resulting enyne product can then be stereoselectively transformed into the desired diene, which allows the regio- and stereochemistry of the product to be reliably dialed in. This notion is illustrated by the total syntheses of lactimidomycin (Scheme 39) and latrunculin A (Scheme 40). Both targets contain an *E*,*Z*-configured diene; in the former case, this motif was formed at the *E*-olefinic site, whereas in the latter case, it was the *Z*-alkene substructure, which served as the site of disconnection, thus showing the flexibility of the RCAM-chemistry.

The major challenge in the total synthesis of the cell-migration inhibitor lactimidomycin is related to the significant strain inherent to the 12-membered head group that comprises seven sp^2-hybridized C-atoms (Scheme 39). Although it may seem counterintuitive at first sight to try to forge this substructure via alkyne metathesis, this plan could be reduced to practice on counterbalancing the extra strain by editing the enoate double bond out at the stage of ring closure.[153] The success of this tactics,

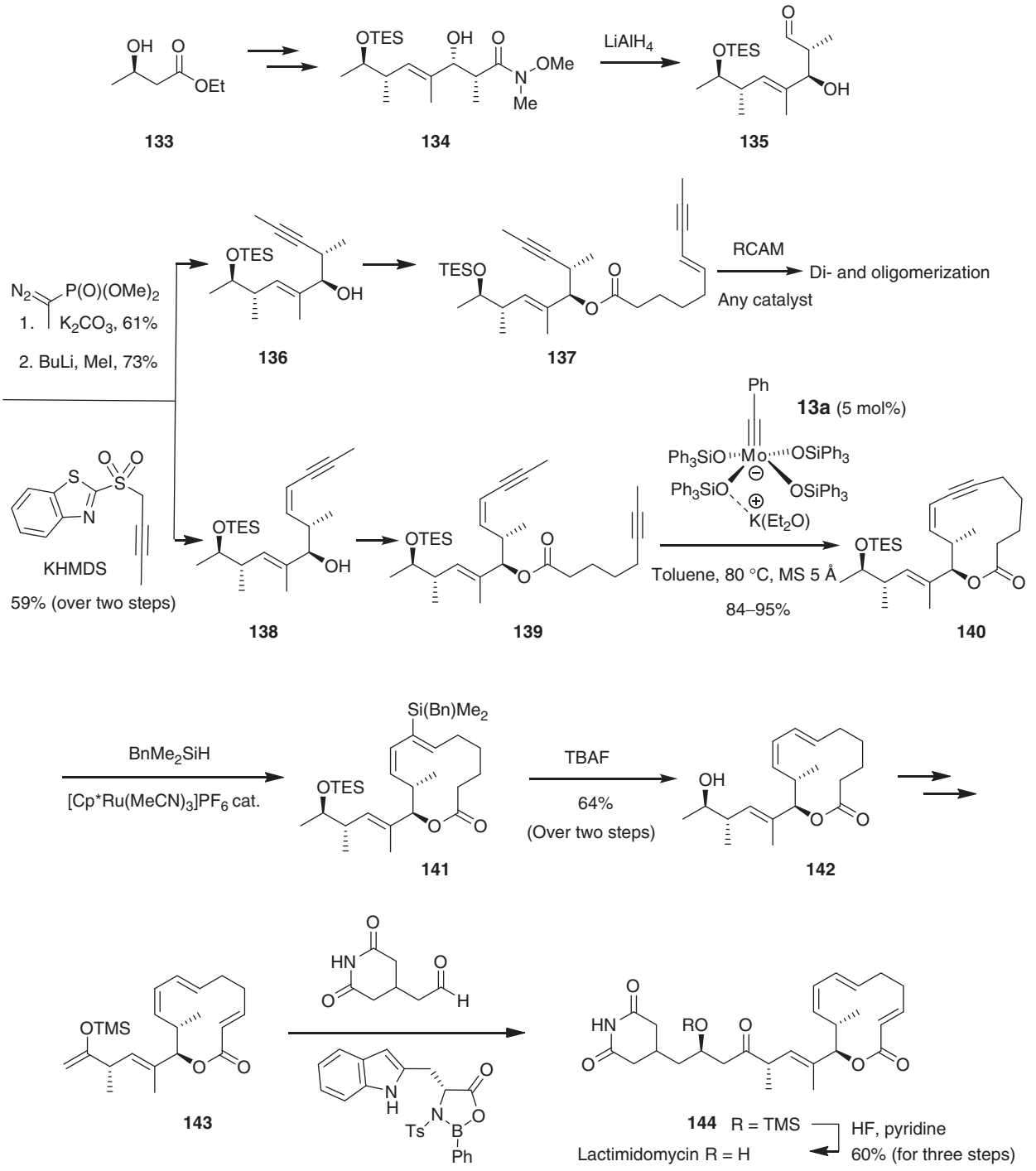


Scheme 38 Comparison of different RCAM-based approaches to nakadomarin A.

however, depended on the site of ring closure, whereas compound **137** afforded only di- and oligomeric products but no significant amount of the desired cyclic monomer, the isomeric substrate **139** cyclized smoothly; this different pattern is readily understood if one considers that **137** would lead to a 12-membered lactone comprising a supposedly linear alkyne and an *E*-alkene, whereas product **140** is somewhat less strained because the preexisiting alkene in the ring is *Z*-configured.

In any case, compound **139** was ring closed in excellent yield on a gram scale to cycloalkyne **140** by recourse to the powerful molybdenum ate-complex **13a** in the presence of MS 5 Å. Although this catalyst is metathesis-active at or even below room temperature, this particular transformation had to be carried out at 80 °C, which is ascribed to the strain that has to be built up.[153] A subsequent ruthenium-catalyzed *trans*-hydrosilylation followed by a simultaneous C- and O-desilyation of the resulting product **141** gave **142**, which was then elaborated into the target. The final stages of the synthesis relied on an asymmetric Mukaiyama aldol reaction of silyl enolether **143** to complete the lateral chain of **144** while setting the as yet missing chiral center.

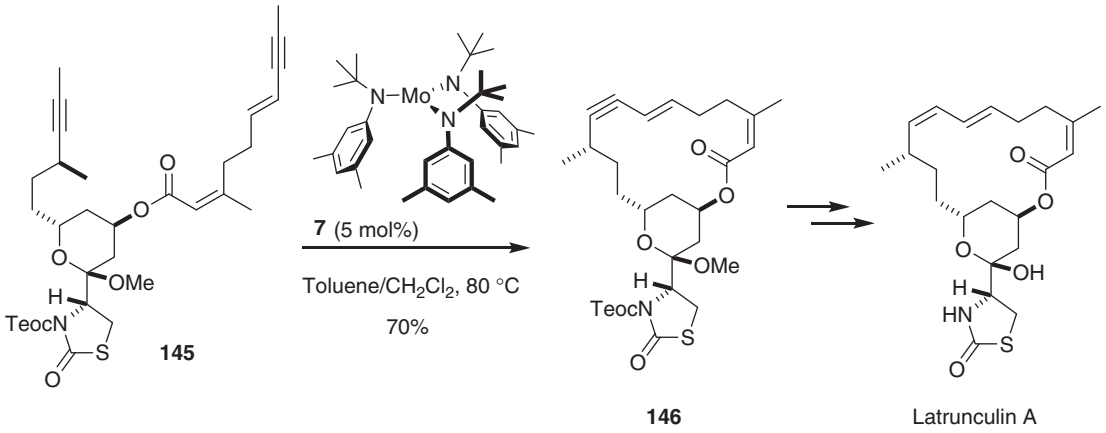
As outlined above, considerations of ring strain had dictated the choice of the *E*-alkene as the optimal assembly point for lactimidomycin. No such superordinate aspects need to be considered in the case of the potent actin-binding macrolide latrunculin A (Scheme 40).[154,155] This valuable tool for chemical biology was made available by a convergent approach via the elaborate enyne **145** decorated by an unusual thiazolidinone unit. Gratifyingly, neither this rare sulfur-containing heterocycle nor the elimination-prone tertiary glycoside posed any problem in the macrocyclization, which was catalyzed by the combination



Scheme 39

7/CH_2Cl_2 in toluene as the then most effective catalyst. A series of routine protecting group manipulations and a Lindlar reduction allowed **146** to be transformed into the targeted natural product in high yield.

This project was then extended to the total synthesis latrunculin B, C, S, and 16-*epi*-latrunculin B, as well as to the preparation of a set of nonnatural analogs comprising deep-seated structural 'point mutations' within their framework that would not be easily available otherwise; the produced compounds are summarized in Scheme 41, with structural modifications relative to the parent natural lead being indicated in red.[155,156] Even though the sulfur atom was edited out in some members of this panel (e.g., **147**), the cyclization would not proceed with the tungsten alkylidyne complex **1** (Scheme 41). Therefore, these and other examples clearly attest to the superior functional group tolerance of molybdenum-based catalysts for alkyne metathesis. A detailed



Scheme 40

biological assessment of the compound collection shown in Scheme 41 allowed us to demonstrate that the excision of two seemingly innocent peripheral methyl branches from the latrunculin backbone results in increased potency of these actin microfilament-disrupting agents while streamlining the synthesis.[156,157] This investigation is therefore deemed a good example for the power of 'diverted total synthesis' in general.[158]

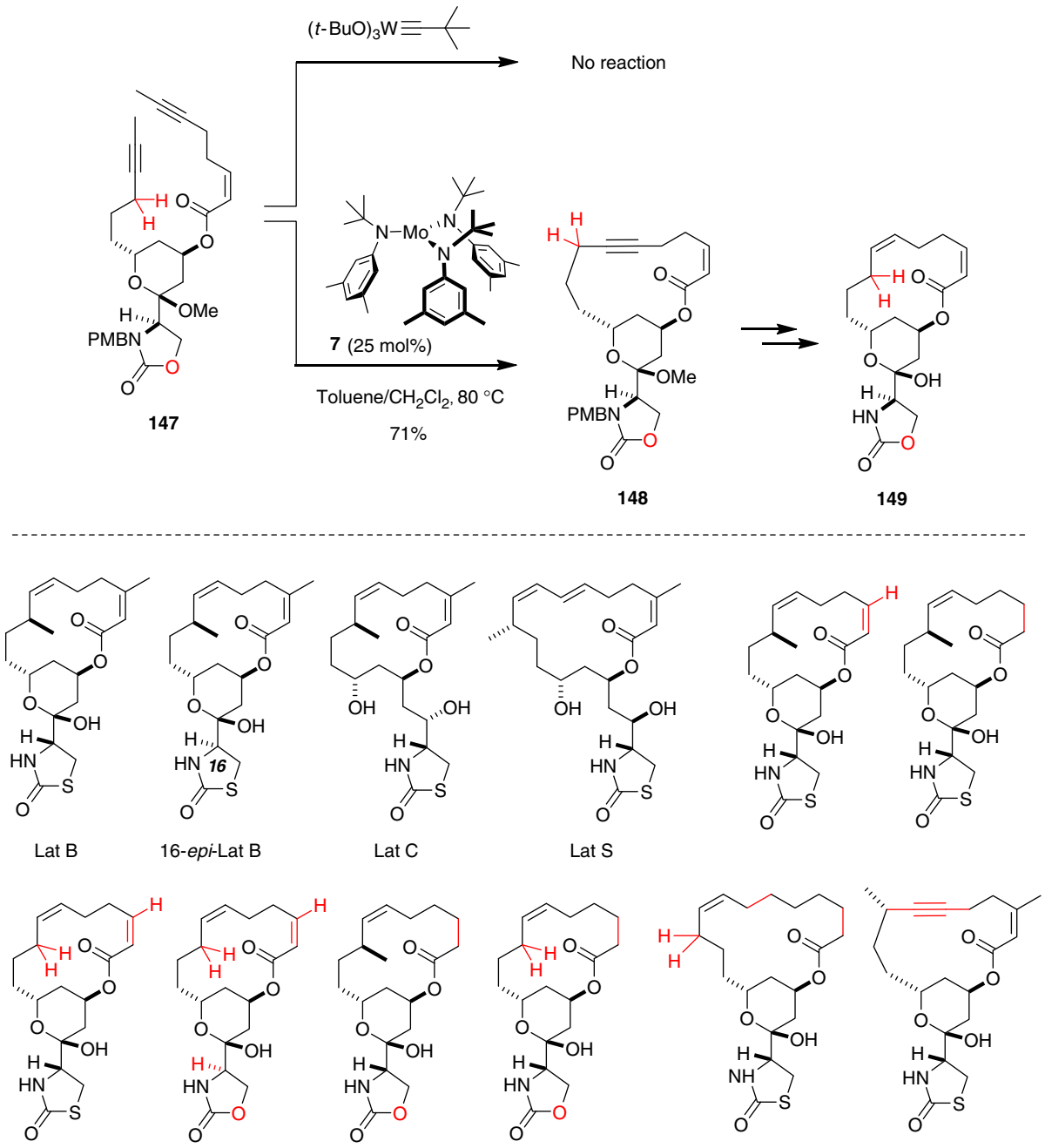
The total synthesis of the rare marine metabolite amphidinolide V at the conspicuous 1,3-diene substructure made up by the two vicinal *exo*-methylene branches of this target inspired a conceptually very different application of alkyne metathesis (Scheme 42).[159] It was reasoned that a sequence of RCAM followed by enyne cross metathesis might allow this motif to be built up by an unconventional approach. To this end, the required cyclization precursor **155** was prepared by a convergent route starting from bromide **150** and trifluoroborate **151** as the building blocks. After their merger by a Suzuki coupling followed by elaboration of the allylic alcohol subunit in **153** to the corresponding epoxy-aldehyde **154**, a stereoselective addition of a functionalized dialkenylzinc reagent followed by protection of the newly formed –OH group as a TBS-ether gave the required diyne **155**. This sensitive material, which incorporates an alkenyl epoxide, an alkoxy epoxide, and a skipped, nonthermodynamic enyne motif, could be cyclized in excellent yield with the aid of **7**/CH_2Cl_2. None of these fragile structural elements suffered any harm during this transformation, which highlights the outstanding functional group tolerance of the catalyst. The resulting cycloalkyne **156** was then subjected to an enyne cross metathesis with ethylene gas, which was effected by the second-generation Grubbs ruthenium carbene **157** to set the vicinal methylene branches decorating the macrocyclic frame of this particular target. The resulting product **158** was cleanly transformed into amphidinolide V by means of a few standard operations.[159]

Since the structure originally assigned to amphidinolide V by the isolation team left some ambiguity, all conceivable stereomers of this compound were prepared following the same synthesis blueprint.[159,160] In addition to solving a structural conundrum and providing precious material for biological testing, the success of this campaign confirms the reliability of alkyne metathesis in general. Moreover, after the advent of the new siloxide-bearing molybdenum alkylidynes, the ring closure of **155** to **156** was revisited as a particularly stringent test reaction. As expected, the ate-complex **13a** was not only similarly effective in terms of yield (81%) as the combination **7**/CH_2Cl_2 originally used, but also required a much lower loading (2 mol% vs. 30 mol% of **7**).[14]

5.28.6.4.8 Alkyne metathesis in the heterocyclic series

The total synthesis of neurymenolide A, an unusually sensitive pyrone derivative of eicosanoid origin, is deemed one of the most stringent tests for the performance of RCAM published to date (Scheme 43).[161] This compound contains three *Z*-alkenes as well as one *E*-configured olefin in its lipidic chain and would hardly withstand any of the known alkene metathesis catalysts. By virtue of the skipped arrangement of the unsaturations, this target compound and all of its immediate precursors are exceptionally sensitive and may even decompose on contact with silica. Yet, neurymenolide A could be formed in high yield by a sequence comprising a new gold-catalyzed hydroxy-pyrone synthesis and a subsequent alkyne metathesis as the key operations.[161] It is of note that the gold catalyst **162** activates only the alkyne that is conjugated to the carbonyl for the formation of the heterocyclic ring within substrate **161** that contains no less than six different sites of unsaturation (not counting the enolized *β*-keto ester). Equally remarkable is the chemoselectivity of the subsequent RCAM of the resulting compound **163**. Alkylidyne **13c** was absolutely critical because it operates under very mild conditions and selectively activates the alkynes, but leaves the truly fragile olefinic array untouched. This example therefore nicely underscores the outstanding tolerance and activity of the new molybdenum alkylidyne complexes ligated with triarylsilanolate groups and features at the same time that alkyne metathesis is strictly orthogonal to olefin chemistry. This very property allowed the site of ring closure as well as the configuration of the newly formed double bond derived from the cycloalkyne precursor to be unambiguously predetermined, which was critical for success.[161]

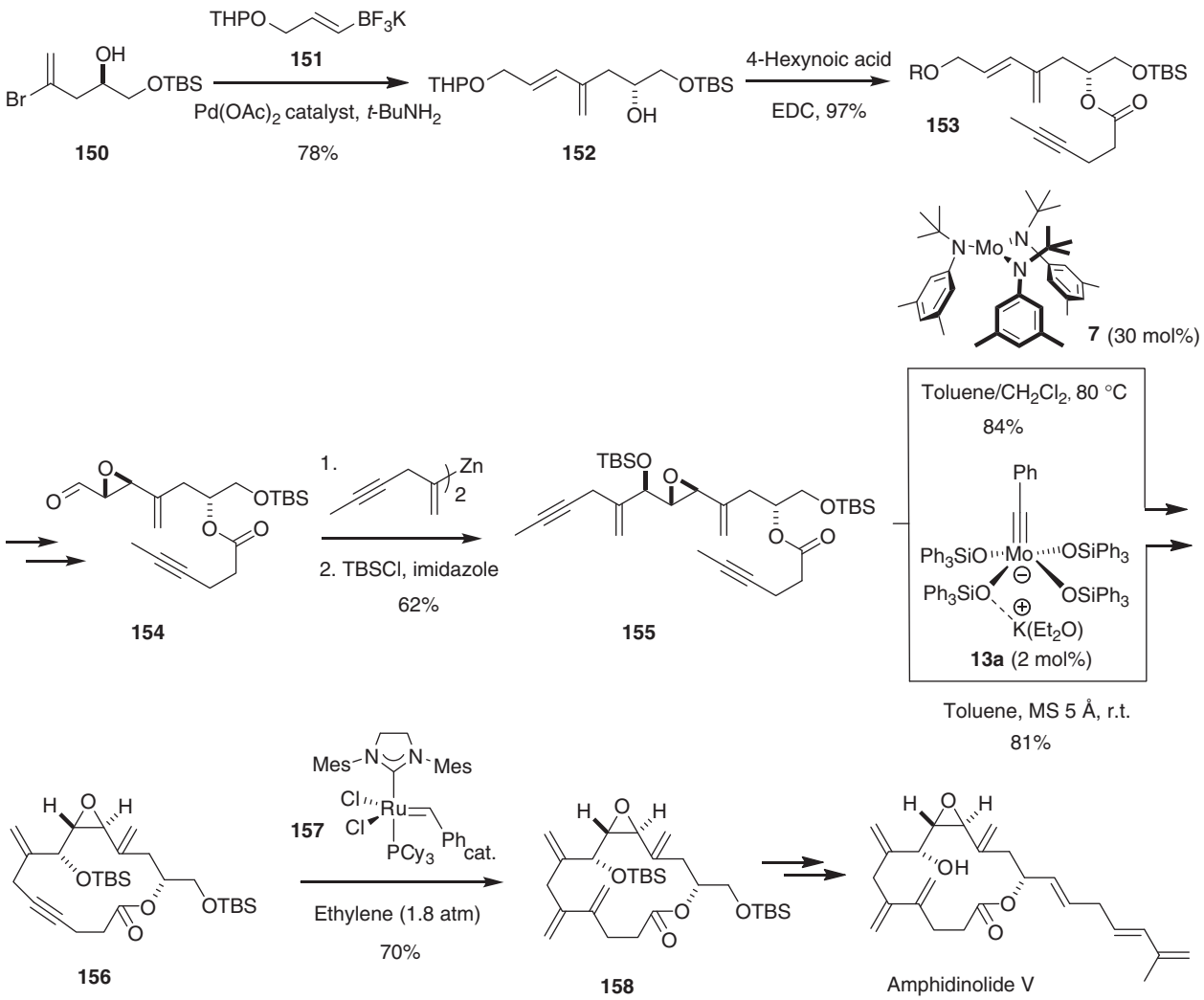
The cycloalkynes formed by RCAM can also be used as carbonyl equivalents for the preparation of heterocyclic motifs. A concise total synthesis of citreofuran illustrates this notion, in that product **167** formed by cyclization of diyne **166** with the



Scheme 41 Catalyst dependence in the preparation of a fully synthetic analog of latrunculin B together with the set of naturally occurring latrunculins and latrunculin-related compounds prepared via RCAM; structural point mutations relative to the parent natural products are indicated in red.

tungsten alkylidyne **1** was gently converted into the macrotricyclic scaffold of the target on exposure to mildly acidic conditions (Scheme 44).[162] It is believed that the ketone undergoes a transannular 5-*exo*-*dig* attack onto the slightly strained triple bond in vicinity, followed by aromatization of the resulting intermediate. A final deprotection of compound **168** thus formed unmasked optically active citreofuran.

A much more sophisticated example can be found in a recent total synthesis of the potent phosphatase inhibitor spirastrellolide F (Scheme 45).[163] In this particular case, the highly decorated macrocyclic perimeter was forged at the 'southern' spiroketal site made up by the B- and C-rings. The necessary substrate was obtained in high overall yield from the three building blocks **169**–**171**, which were assembled by hydroboration of **170**, Suzuki coupling of the resulting alkylborane with triflate **171**, and esterification of the resulting product with the elaborate acid segment **169**. Diyne **172** thus formed underwent an essentially quantitative RCAM in 30 min reaction time at ambient temperature when exposed to 8 mol% of the molybdenum alkylidyne ate-complex **13a** in the

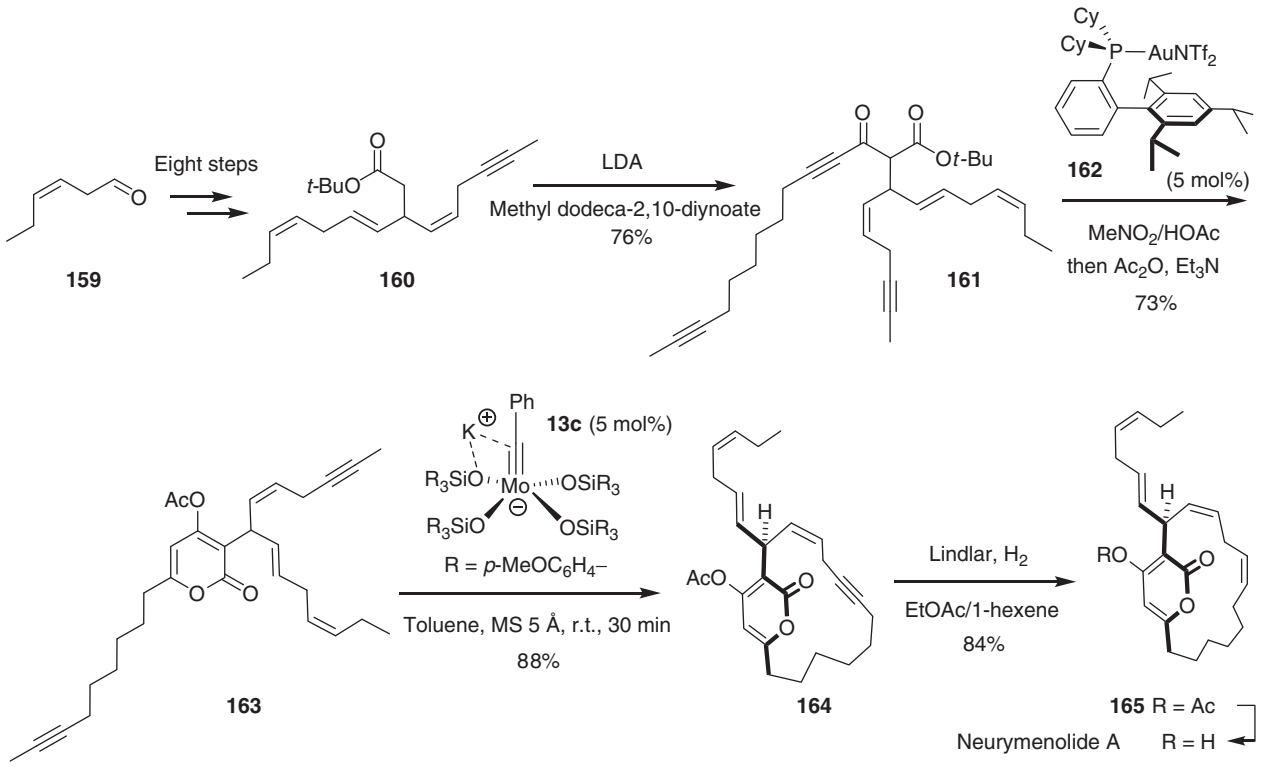


Scheme 42

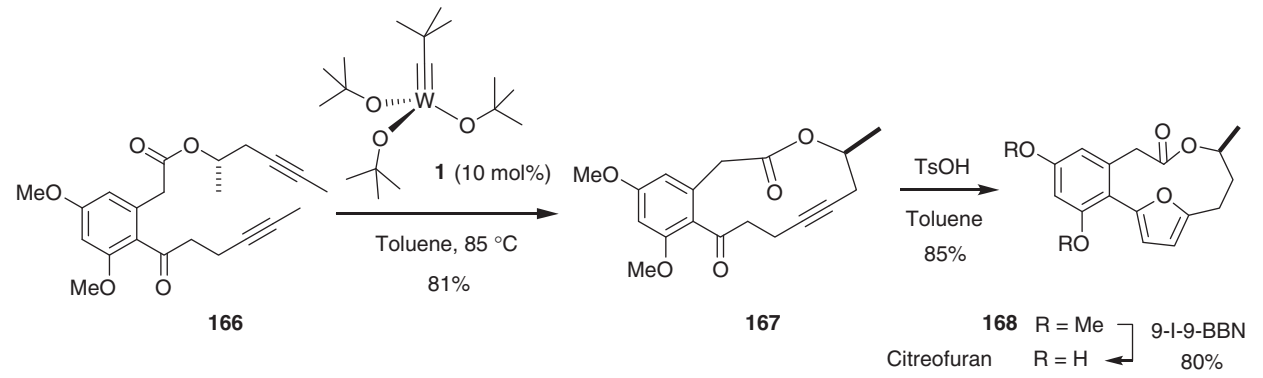
presence of MS 5 Å. Product **173** was isolated from the mixture in 87% yield, which illustrates the outstanding performance and functional group tolerance of this latest generation of alkyne metathesis catalysts.[163] After deprotection of the two *p*-methoxybenzyl (PMB) ether groups, the necessary transannular ketalization of **174** was accomplished in two consecutive operations. In the event, treatment of **174** with the bulky cationic gold catalyst **175** enforced a regioselective 6-*endo-dig* attack of the C.13–OH group onto the alkyne, which gave enol ether **177** in respectable yield. Acid treatment of this labile intermediate prompted the sterically more hindered hydroxyl group at C.21 to engage in the necessary second cyclization with formation of ketal **178**. The integrity of this compound was confirmed by X-ray diffraction before it was elaborated into spirastrellolide F by stereoselective reduction of the *exo*-methylene group and attachment of the lateral chain via a Kocienski olefination as the key steps.[163]

5.28.6.4.9 RCAM in the organometallic series

Collectively, the examples discussed above illustrate the outstanding compatibility of alkyne metathesis catalysts with all sorts of polar and unpolar functional groups as displayed by natural products and nonnatural compounds of interest for life sciences or material research. This gratifying profile is further completed by a number of examples, in which RCAM was used to tailor the ligand sphere of unsaturated coordination compounds. This allowed a set of unusual chelate complexes of rhenium, ruthenium, and platinum to be forged, which would be difficult to make otherwise; a few representative cases are compiled in Scheme 46. The example of the rhenium complex **179** is particularly noteworthy, whereas the tungsten alkylidyne **1** allowed the kinetic product *fac*-**180** to be formed, a rearrangement to the thermodynamically more stable *mer*-disposed product **181** could not be avoided when working with a Mortreux-type mixture, which mandates a much higher reaction temperature to become operative.[164,165]



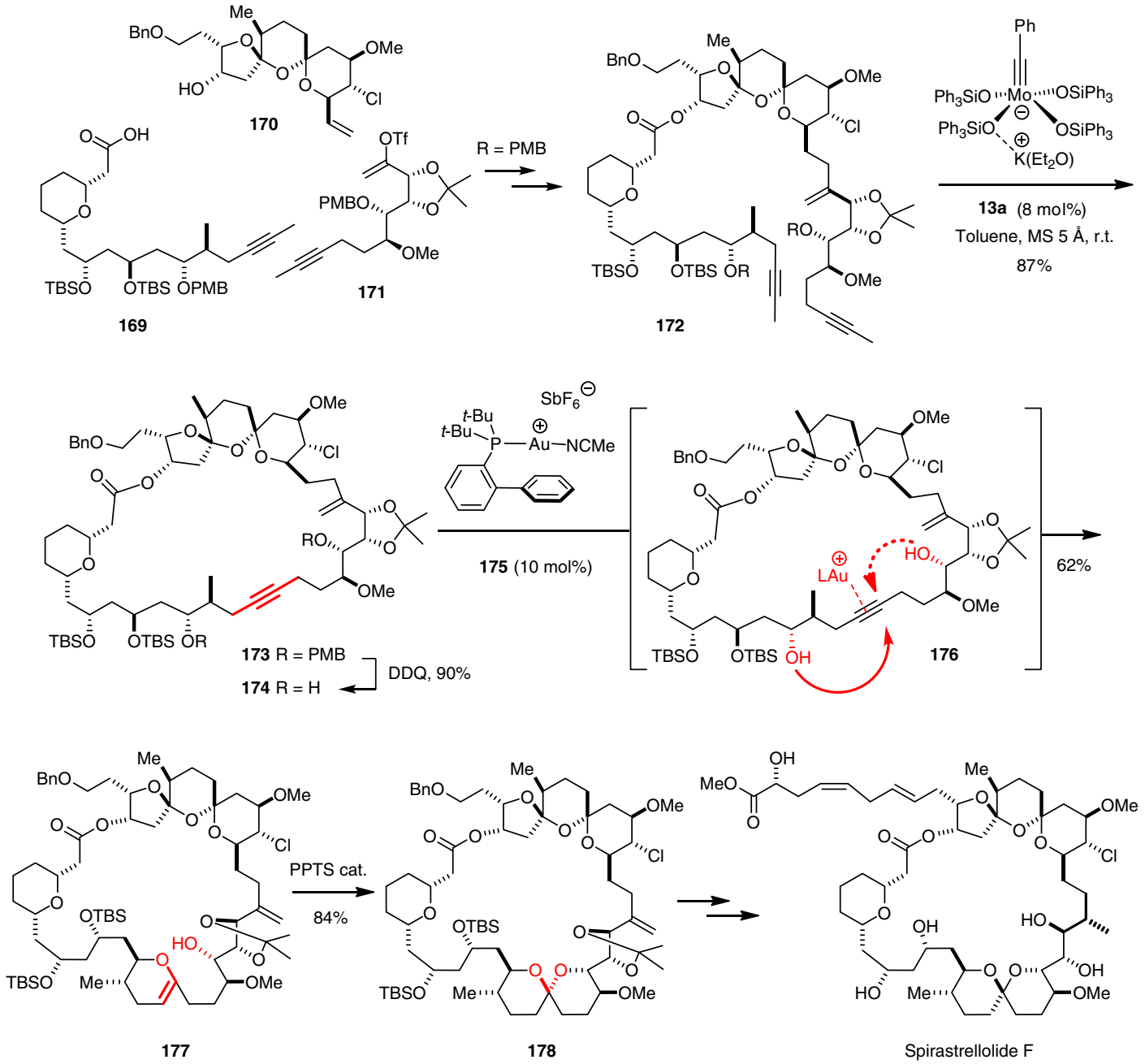
Scheme 43



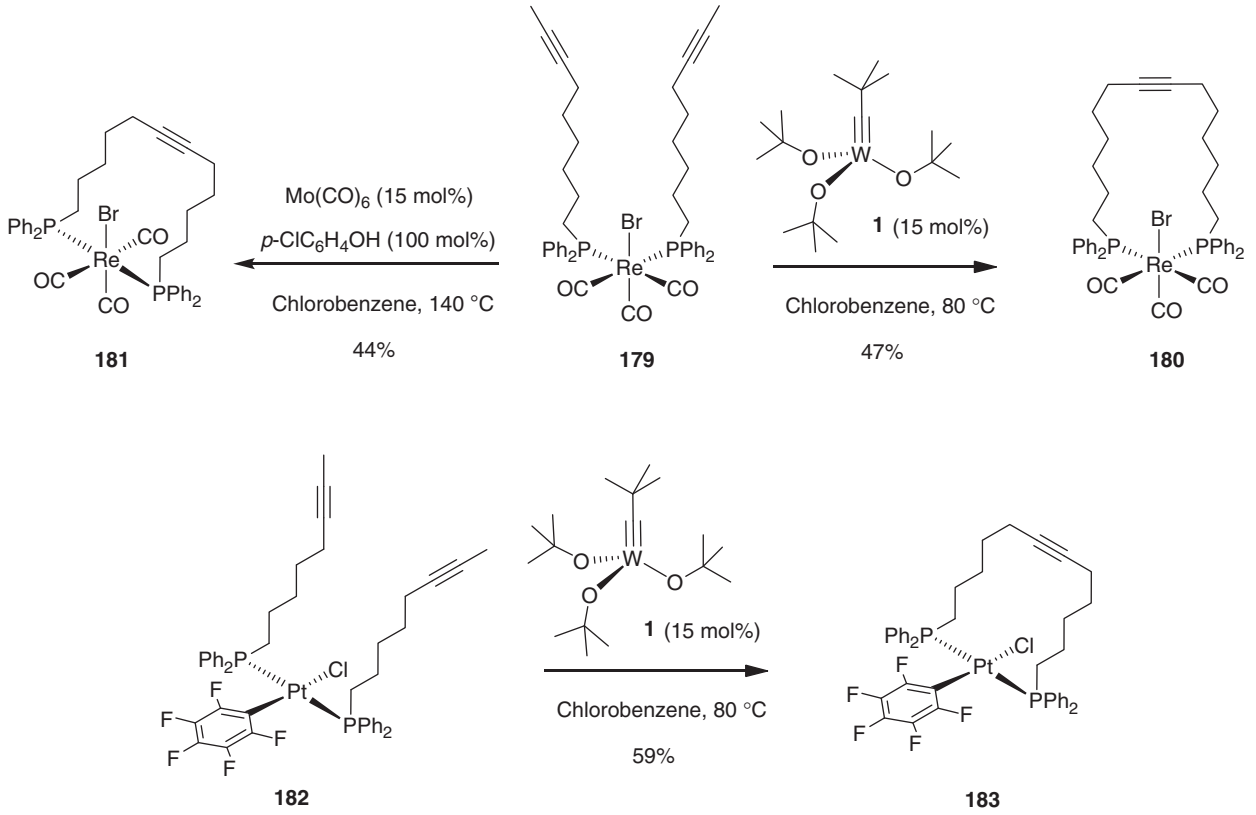
Scheme 44

5.28.7 Conclusions and Outlook

It is fair to say that alkyne metathesis did not play a significant role in preparative chemistry for several decades after its discovery, even though the mechanism of this reaction had been elucidated early on and effective catalyst were available following simple-to-use *in situ* protocols. Yet, the limited compatibility of some of these catalyst preparations together with the harsh reaction conditions were not overly attractive. As in the olefin metathesis arena, the decisive impulse for the development of this method into a useful preparative tool came from fundamental studies into the organometallic chemistry of transition metal alkylidynes. Catalysts based on such mechanistically well-behaved entities show remarkable performance and acquired, with a certain lag time, a truly outstanding compatibility with functional groups that rivals the rightfully praised tolerance of the very best alkene metathesis catalysts known to date. At the same time, the catalysts became user-friendly, as bench-stable variants have been described that are easy to work with. Therefore alkyne metathesis should find many more applications in the future, as there is now little barrier left for its use even by practitioners who are less familiar with organometallic techniques. Since alkynes can be


Me
BnO
OMe
HO
Cl
170
OH
O
OTf
PMBO
OMe
TBSO
OTBS OPMB
171
169
R = PMB
Ph
Ph3SiO
Mo
OSiPh3
K(Et2O)
13a (8 mol%)
Toluene, MS 5 Å, r.t.
87%
RO
TBSO
OTBS OR
172
SbF6
t-Bu
P
Au
NCMe
175 (10 mol%)
LAu
HO
62%
176
173 R = PMB
174 R = H
DDQ, 90%
PPTS cat.
84%
177
178
MeO
Spirastrellolide F

Scheme 45



Scheme 46

converted into many different structural motifs, the structural space that can be covered by alkyne metathesis in concert with creative postmetathesis transformations is expected to be large and many opportunities for explorative investigations along these lines can be envisaged.

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5.29 Ring-Closing Metathesis

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Glossary

Alkylidene complex Transition metal complex with an alkylidene or carbene ligand. Alkylidene complexes are characterized by a metal–carbon double bond.

Backbite mechanism Describes the attack of a reactive center at the terminus of a growing chain onto a reactive functional group at an inner position.

Chiral pool The entity of natural products occurring in enantiomerically pure form. Compounds from the chiral pool are often used as starting materials in the synthesis of enantiomerically pure target molecules.

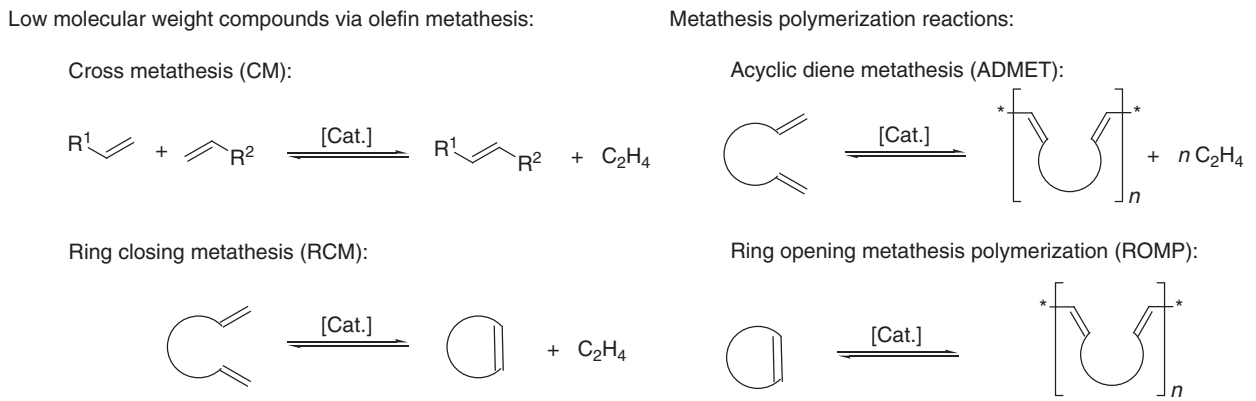
Multicomponent reaction Reaction leading from three or more starting materials to one single product in a defined and controlled order of events.

***N*-Heterocyclic carbene (NHC)** Unusually stable carbenes, in which the divalent carbon atom is part of a heterocycle. NHCs are often highly nucleophilic and good σ-donor ligands in complexes with transition metals.

Tethered reaction A synthetic strategy that involves the temporary connection of two molecules via a labile bond (the tether) and a subsequent, facilitated, cyclization. Cleavage of the tether liberates the desired acyclic molecule.

5.29.1 Introduction

Olefin metathesis reactions can be described as a transition metal catalyzed mutual exchange of alkylidenes, resulting in the formation of alkenes from other alkenes by formal scission of carbon–carbon double bonds and recombination of the alkylidene units. In principle, every olefin metathesis reaction is reversible, although numerous examples exist where the back reaction is merely a theoretical option. After its incidental discovery in the 1950s during investigations into Ziegler–Natta-type olefin polymerization reactions, olefin metathesis rapidly emerged as an important topic in polymer and industrial chemistry.[1] Investigations into the mechanism[2] and the nature of the actual catalysts became a domain of organometallic chemistry and stimulated many projects dealing with the synthesis and reactivity of transition metal–carbene complexes. Olefin metathesis reactions can take place in an inter- or intramolecular fashion and yield low molecular weight compounds or polymers (Scheme 1).

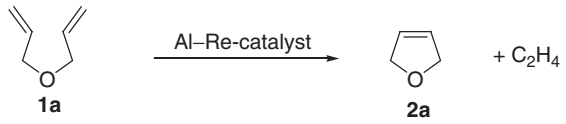


Scheme 1 Inter- and intramolecular olefin metathesis reactions.

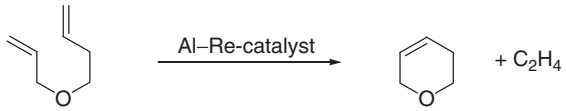
For the intermolecular version, the term cross metathesis (CM) is commonly used;[3] and in those cases where $R^1 = R^2$, occasionally the term self-metathesis or homodimerization can be found in the literature. For intramolecular olefin metathesis reactions, α,ω-dienes are required as starting materials. These reactions result in the formation of carbo- or heterocycles and are therefore named ring-closing metathesis (RCM) reactions. Both enthalpic and entropic factors contribute to the success of these reactions. RCM reactions that involve the buildup of ring strain are disfavored and, consequently, the reverse reaction, called ring opening metathesis (ROM), will be preferred.[4] Beneficial for RCM reactions is the formation of a volatile alkene, normally ethene or propene, which is removed from the reaction mixture, thereby shifting the equilibrium to the side of the cyclic product. Two metathesis polymerization reactions[5] may interfere with the RCM and ROM reactions: acyclic diene metathesis (ADMET)[6] is the polymerization of α,ω-dienes and thus, in principle, a competing reaction of RCM, whereas the ROM polymerization[7] occurs with strained cyclic olefins. This chapter focuses on RCM reactions (*see* Chapter 5.26). CM reactions are covered in a separate chapter and will therefore only be mentioned if they are relevant in the context of a particular RCM reaction. Ring closure reactions involving the metathesis of C–C triple bonds, ring closing enyne metathesis (*see* Chapter 5.27),[8] and ring closing alkyne metathesis[9] reactions (*see* Chapter 5.28) are also discussed in separate chapters in this volume.

A search for the topics 'ring-closing metathesis' or 'ring-closing olefin metathesis' in the ISI-Web of Science, conducted in August 2012, reveals that either of these terms has been used in more than 6000 publications, which have been cited more than 173 000 times. These figures are even more impressive if one considers that the term 'ring closing olefin metathesis' has been used

for just 20 years, when it was introduced by Fu and Grubbs.[10] However, there have been earlier reports describing the cyclizative olefin metathesis of α,ω-dienes, albeit without using the term 'ring-closing metathesis'. For example, Bashkirov et al. reported in 1978 that two simple allyl ethers **1a,b** react in the presence of an unspecified Al–Re-catalyst to 2,5-dihydrofuran and α-2,3-dihydropyran, respectively in 'high rate and a selectivity of 100%',[11] unfortunately without stating an yield (equations 1, 2). The RCM of diallyl silanes with the same heterogeneous catalyst system was reported shortly afterward as a side reaction in the ADMET of these substrates, yielding silacyclopentenes in low yields.[12–15]

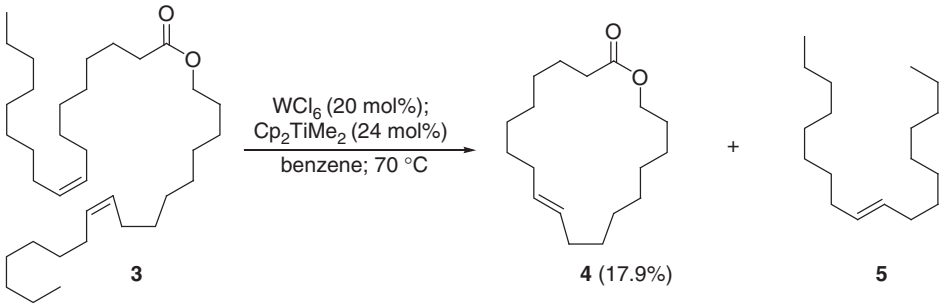


1a **2a** (1)



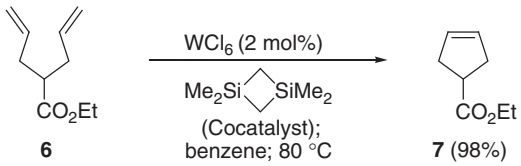
1b **2b** (2)

In 1980, Tsuji and Hashiguchi[16] and Villemin[17] independently reported the first synthesis of macrocycles using RCM. These researchers used WCl_6/Cp_2TiMe_2 and $WCl_6/SnMe_4$, respectively; both catalyst systems are clearly inspired by Ziegler-type catalysts used for olefin polymerization. As highlighted in equation 3, Tsuji and Hashiguchi could obtain the macrolactone **4** from the fatty acid-derived precursor **3** only in a moderate yield, which was attributed by the researchers to a rather low tolerance of the catalyst system against functional groups.



3 **4** (17.9%) **5** (3)

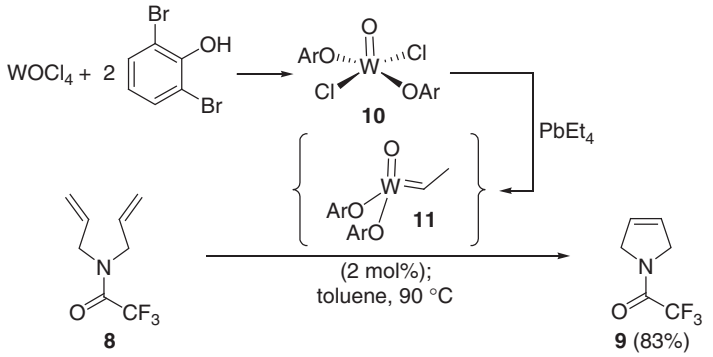
A few reports published in the early 1990s suggest, however, that the limitations of these tungsten-catalyzed RCM reactions are more likely caused by the particular challenges of macrocyclization reactions rather than poor functional group tolerance. For example, Bespalova et al.[18] were able to synthesize cyclopentene **7** via RCM of the diallyl compound **6** in the presence of 2 mol% of a WCl_6/silacyclobutane catalyst system in nearly quantitative yields (equation 4).



6 **7** (98%) (4)

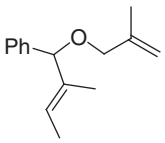
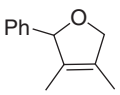
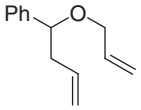
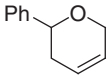
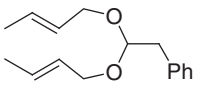
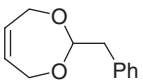
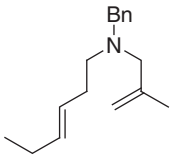
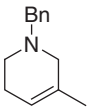
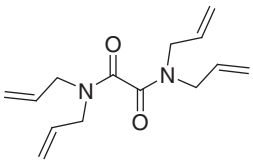
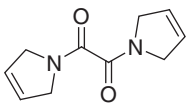
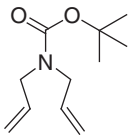
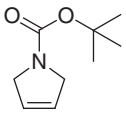
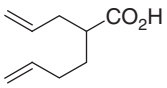
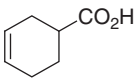
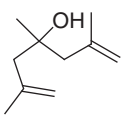
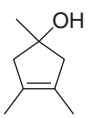
Shortly afterward, Nugent et al. disclosed their catalytic system for 'cyclic metathesis, a combination of $WOCl_4$, 2,6-dibromophenol, and $PbEt_4$'.[19] Using this catalytic system, numerous five- and six-membered carbo- and heterocycles, such as **9**, were synthesized in high yields. The actual catalyst was also investigated in some detail: $WOCl_4$ and 2,6-dibromophenol react under nucleophilic displacement of two chlorides to a bis-phenoxy tungsten complex **10**, which is activated *in situ* by the addition of the cocatalyst $PbEt_4$. The researchers propose that the actual catalyst is a tungsten ethylidene complex **11**, which was, however, not isolated and characterized (**Scheme 2**).

Although interesting and synthetically valuable results were achieved in RCM reactions using the two-component tungsten-based catalytic systems mentioned above, these could not prevail against the structurally defined homogeneous Mo (**C1**)[20] and Ru-catalyst (**C2**)[21,22] discovered shortly before by Schrock et al. and Grubbs et al. The structural formulae of these catalysts are depicted in Section 5.29.2 (**Table 2**), together with those of the commonly used derivatives of **C2**. In the context of this historical discussion, only a few representative examples published in the early days of Mo- and Ru-catalyzed RCM will be mentioned (**Table 1**). These seminal examples already reveal some of the most characteristic differences between Mo- and Ru-catalyzed RCM



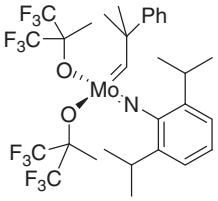
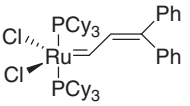
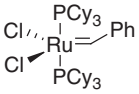
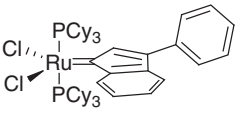
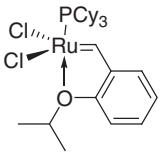
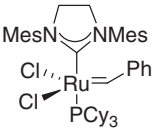
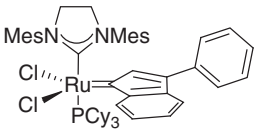
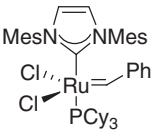
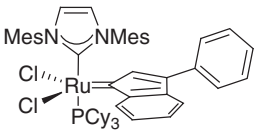
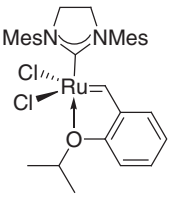
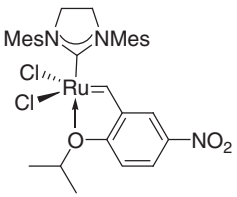
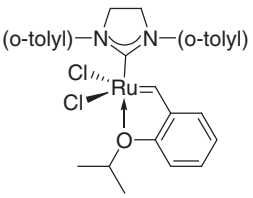
Scheme 2 Tungsten-catalyzed RCM reaction.

Table 1 Early days RCM reactions catalyzed with **C1** or **C2**[a]

Entry	*α,ω-Diene*	*RCM product*	*Catalyst (mol%)*	*Yield (%)*	*References*
1			**C1** (5)	93	10
2			**C1** (5) **C2** (4)	92 86	10 23
3			**C1** (5) **C2** (4)	89 87	10 23
4			**C1** (4)	86	24
5			**C1** (4) **C2** (2–4)	89 89	24 23
6			**C2** (2)	91	23
7			**C2** (2)	87	23
8			**C1** (4)	84	25

[a]All reactions were conducted in benzene at ambient temperatures.

Table 2 Well defined Mo- and Ru-precatalysts used in RCM reactions

No.	*Structure*	*References*	*No.*	*Structure*	*References*
C1		20	**C2**		21,22
C3		31	**C4**		32,33
C5		34	**C6**		35
C7		36,37	**C8**		38
C9		39	**C10**		40,41
C11		42	**C12**		43

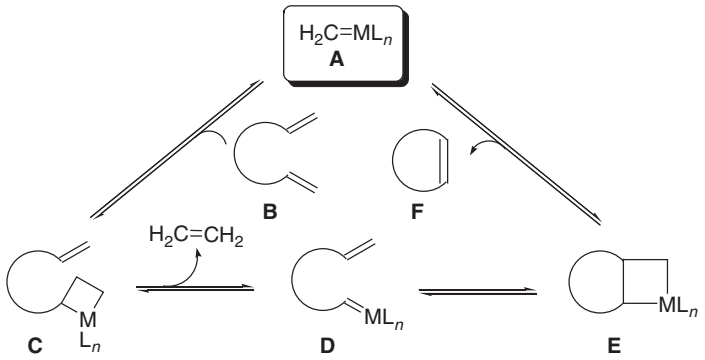
reactions. The Mo-catalyst **C1** is very active and, in contrast to **C2**, tolerates tertiary amines, and is capable of forming tetrasubstituted double bonds. On the contrary, RCM reactions catalyzed with **C2** can be performed in nonpurified solvents under air (which is impossible for **C1**). An additional advantage of **C2** is a significantly higher tolerance toward functional groups, in particular protic functional groups, which are normally not tolerated by **C1** (for a notable exception, see **Table 1**, entry 8).

Over the past two decades, catalyst evolution has led to the development of a plethora of new Mo- and Ru-alkylidene complexes with beneficial properties in RCM and olefin metathesis in general. One of the most notable advancements is the discovery of Ru-alkylidenes with one *N*-heterocyclic carbene ligand, which show reactivities comparable to those observed for **C1** while maintaining the functional group tolerance of **C2**.[26] The objective of this chapter is to provide an overview of synthetic applications of RCM and to highlight the general synthetic strategies involving RCM steps. Therefore, the mechanistic aspects and progress in catalyst development will not be discussed in detail; however, fundamental mechanistic considerations and an overview of common catalysts used in RCM are provided in the following section.

5.29.2 The Mechanism of RCM and a Selection of Commonly Used Catalysts

The accepted mechanism of RCM reactions is an adaptation of Chauvin's orginal mechanism for olefin metathesis reactions in general.[2] This mechanism accounts for the alkylidene structure of the actual catalysts and for the reversibility of RCM reactions.

The catalytic cycle involves the formation of metallacyclobutane **C** from the alkylidene complex **A** and an α,ω-diene **B**, which then undergoes cycloreversion to a new alkylidene complex **D**, and intramolecular cycloaddition to a bicyclic metallacyclobutane **E**, which reacts in a final cycloreversion with regeneration of the catalytically active species **A** and formation of the RCM product **F** (Scheme 3).

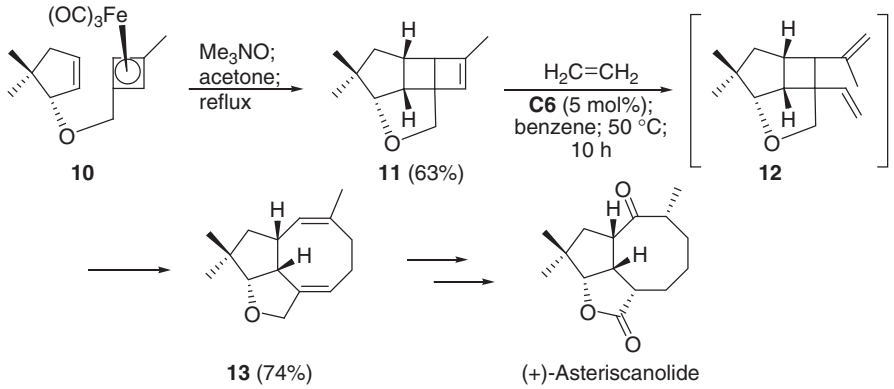


Scheme 3 Mechanism of RCM reactions.

Numerous important details of Mo- and Ru-catalyzed RCM reactions are not considered in this simplified mechanistic scenario and the reader is referred to more specialized review articles for this information.[27–30] In lieu of a comprehensive discussion of catalyst development, just the structures and references for the most common catalysts used in RCM reactions are listed in Table 2 and correlated with a numbering scheme, which will be used throughout this chapter. Structures of other catalysts will be shown in the appropriate section.

Apart from the choice of the best catalyst, a number of other questions arise when an RCM reaction is implemented in a synthesis: Is the intended ring size conveniently accessible, or are certain ring sizes disfavored? In which way will substituents affect the cyclization rate? Which is the ideal solvent for a given RCM? Is it necessary to consider dimerization or ADMET as a side reaction? If so, do these reactions occur under thermodynamic or kinetic control, and are there opportunities to avoid them and favor the RCM reaction? Answers to these questions are mostly based on empirical data, gathered in the literature over the past two decades. However, over the past few years first steps toward simulation approaches have been undertaken which rely on spectroscopic investigations, kinetic measurements, and computational methods. Although these approaches cannot yet replace the consideration of literature precedence, they might perspectively assist in planning and executing RCM reactions by suggesting parameters such as the substrate concentration and the preferred solvent, choice of catalyst, (minimum) catalyst loading, and reaction temperature. Some aspects of general importance are briefly discussed below:

1. Effects of ring size on cyclization rates.[44] Due to the reversibility of the olefin metathesis reaction, cyclopropenes and cyclobutenes are not formed in RCM reactions but undergo the reverse reaction, ROM, with the release of ring strain.[4] Such ROM reactions can be combined with an RCM step, resulting in synthetically very useful domino reactions, which will be discussed in detail in Section 5.29.11. The combination of ROM with a CM reaction is strictly speaking beyond the scope of this chapter, but such reactions have evolved as synthetically valuable methods. Therefore, Snapper's total synthesis of (+)-asteriscanolide is discussed as an instructive example,[45] outlined in Scheme 4. The cyclobutene **11** required as a starting material was obtained from Fe–cyclobutadienyl complex **10** by oxidative decomplexation. Treatment of **11** with the second-generation catalyst **C6**

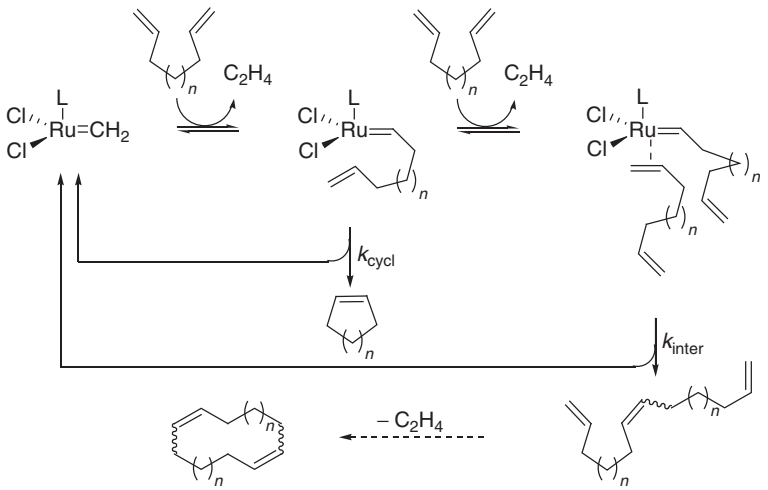


Scheme 4 Synthesis of (+)-asteriscanolide via ROM–CM.

under an ethylene atmosphere and at slightly elevated temperatures gave cyclooctadiene **13** via a sequence of ROM–CM and a thermal Cope rearrangement.

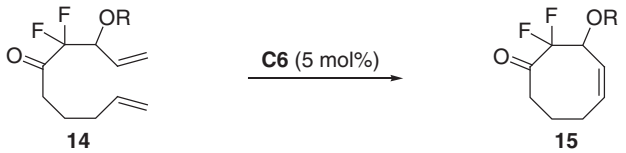
As for many other cyclization reactions, the formation of five- and six-membered rings by RCM is normally fast. However, to rank the RCM-rates for these two ring sizes is not simple; based on the literature precendence it has generally been assumed that five-membered ring systems are formed more rapidly than six-membered rings, but a recent electrospray ionization mass spectrometry study on the RCM of unsubstituted α,ω-dienes suggests that the formation of cyclohexene from 1,6-octadiene is significantly faster than the corresponding reaction giving cyclopentene and cycloheptene.[46] This ranking has been corroborated by an nuclear magnetic resonance (NMR)-spectroscopical investigation into the kinetics of RCM reactions for these simple substrates,[47] and by computational methods, which also suggest that the formation of cyclohexene is thermodynamically more favorable than cyclopentene formation by several orders of magnitude.[48] In contrast, the formation of medium-sized rings (ring sizes from 7 to 11) using RCM can be difficult,[49] because, as for many other cyclization methods, enthalpic (ring strain) and entropic constraints have to be overcome. For macrocyclizations (ring size ≥ 11), the buildup of ring strain is normally not a major problem, but cyclization may be retarded due to a larger distance between the chain ends.

2. Metathesis cyclization versus ADMET. Over the past few years the application of the concept of 'effective molarities' (EM) to olefin metathesis reactions has been discussed in the literature. The kinetic effective molarity EM^k is defined as the ratio of the rate constants for cyclization (k_{cycl}) and intermolecular reaction (k_{inter}): for the thermodynamic effective molarity, the ratios of the corresponding equilibrium constants K are considered.[50] These parameters have been proposed to evaluate the overall efficiency of RCM reactions by taking the competition between ADMET and RCM into account. The mechanistic scenario might be further complicated by a cyclization of dimers or oligomers, as outlined in **Scheme 5**.



Scheme 5 RCM versus dimerization.

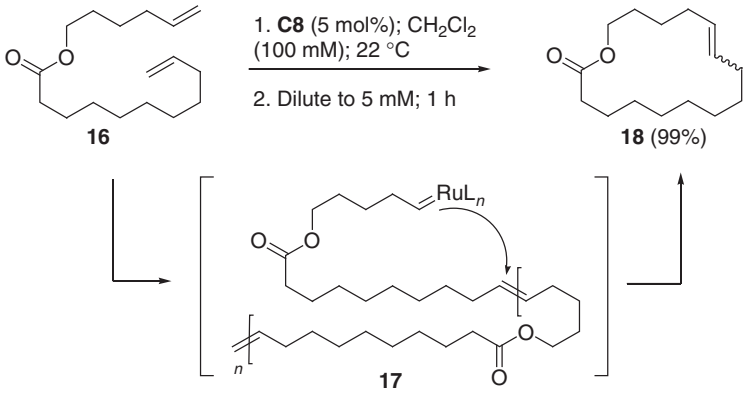
The competition between inter- and intramolecular olefin metathesis is normally limited to medium-sized rings and macrocycles. It is possible to suppress undesired dimerization in many cases by applying high dilution conditions; however, scale up becomes a serious problem in such cases. Percy et al. could show for the RCM-based synthesis of a set of cyclooctenones **15** that the rate and efficiency can be modulated by a protecting group R. These researchers also succeeded in measuring EM for different substrates (equation 5).[51]



(5)

Although the fastest RCM was observed for allylic alcohol (R=H), this reaction was not the most efficient, because introduction of a benzoate (R=Bz) could very effectively suppress dimerization, although the reaction rate was lower than for the free alcohol. The experimental determination of EM for the RCM of dienes **14** could be directly translated into a synthetically advantageous experimental protocol, because it was found that precursor **14** with R=Bz undergoes RCM at an initial

substrate concentration of 20 mM, which is unusually high for this particular ring size. However, the initial formation of dimers or oligomers in an intended RCM does not necessarily mean that the reaction is not feasible or that the initial substrate concentration is too high. Fogg et al. discovered that for many α,ω-diene precursors leading to medium-sized rings or macrocycles, oligomer formation is dominant in the early phase of the reaction, but that ring closure to the desired RCM product can occur via a backbite mechanism. Owing to this possibility, oligomer formation might even be advantageous; if substrate **16** was exposed to catalyst **C8** at 100 mM, rapid oligomerization occurred. Subsequently, diluting the reaction mixture to 5 mM induced cyclization via a backbite mechanism, resulting in the efficient formation of macrocycle **18**. This protocol turned out to be more efficient than conducting the RCM under high dilution conditions from the beginning, because this decelerates the reaction between substrate **16** and the catalyst, which can result in a decreased overall yield due to competing catalyst decomposition (Scheme 6).[52]



Scheme 6 Backbite mechanism for RCM from oligomers.

3. Solvent effects. The most commonly used solvents for RCM reactions are dichloromethane, 1,2-dichloroethane, benzene, and toluene. Recently, the RCM of diallyl malonate, a commonly used test substrate, has been investigated in different solvents including uncommon ones such as acetic acid and acetone using the second-generation catalyst **C6**.[53] The researchers proposed a kinetic model that considers the individual steps of the RCM, i.e., phosphine dissociation to give the catalytically active 14-e species, the subsequent metathesis reaction as one single step, and the irreversible catalyst decomposition[54] as a deactivating step. Determination of kinetic data for the individual steps in different solvents allows the simulation of product formation versus reaction time. This study reveals that the overall productivity of a certain metathesis reaction in a particular solvent is governed by a 'fine balance between initiation, catalytic turnover, and catalyst deactivation'.[53] For instance, dichloromethane is a good solvent for RCM reactions because decomposition of the catalytically active species is very slow. Quite surprisingly, acetic acid was identified as an even better solvent for the RCM reaction studied, albeit for different reasons. In acetic acid, catalyst decomposition is faster than in dichloromethane, but initiation and catalytic turnover also occur much more rapidly, resulting in an overall superior performance. This result was corroborated by experiments on preparative scale.[53,55] The underlying kinetic model, proposed by Adjiman, Taylor et al., has recently been criticized as 'significantly simplified' in certain points by Percy et al., who published a refined approach for the simulation of RCM reactions based on the kinetic data for the individual steps.[56] Significantly improved yields have been observed for several 'difficult' metathesis reactions with second-generation catalysts, if the common solvents were replaced by fluorinated aromatic hydrocarbons (e.g., C_6F_6 or $C_6F_5CF_3$).[57–59] On the basis of X-ray structure data, Grela et al. suggested that the effect is caused by an enhanced initiation, which might in turn result from π–π-stacking interactions between the aromatic substituents of the *N*-heterocyclic carbine (NHC) ligand and the fluorinated aromatic hydrocarbons.[60]

5.29.3 Five-Membered Ring Systems

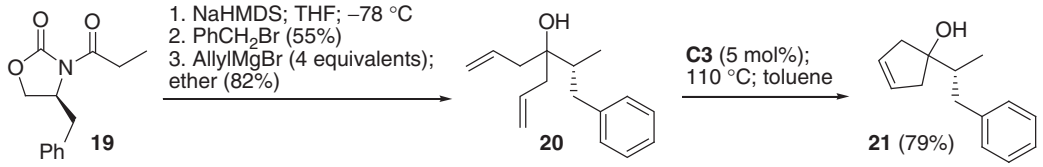
5.29.3.1 Five-Membered Carbocycles

Over the past two decades numerous RCM reactions of α,ω-heptadienes leading to functionalized cyclopentenes have been described. In particular, hydroxylated derivatives, cyclopentitols, play an important role as natural and nonnatural target molecules. Specialized current review articles on cyclization approaches to cyclopentitols[61] and metathesis approaches to carbanucleosides[62] are available.

5.29.3.1.1 Synthesis of precursors by addition of organometallics to carbonyl compounds

Addition of excess allyl metal compounds to carboxylic acid derivatives is a straightforward route to diallyl carbinols with identical allyl groups, which serve as precursors for symmetrical cyclopentenols. Apart from esters, amides have also been used as

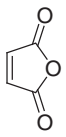
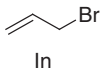
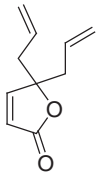
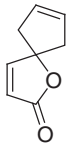
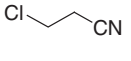
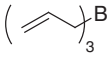
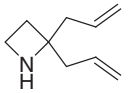
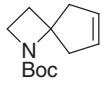
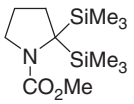
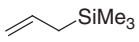
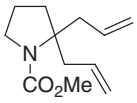
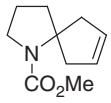
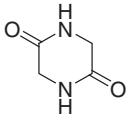
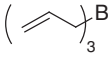
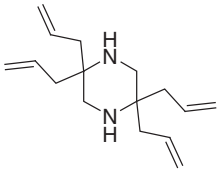
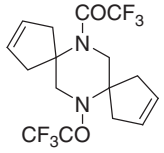
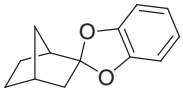
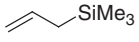
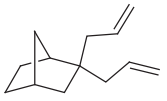
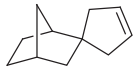
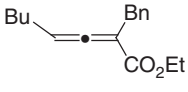
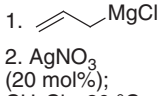
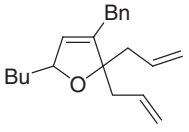
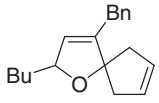
precursors, for example, the acylated Evans auxiliary resulting from a diastereoselective alkylation of **19**. Cleavage of the auxiliary with excess allyl-Grignard reagent yields **20**, which undergoes RCM to cyclopentenol **21** with the first-generation catalyst **C3** only at elevated temperatures, whereas no reaction was observed at ambient temperatures (Scheme 7).[63]



Scheme 7 Enantiopure cyclopentenols via Evans alkylation.

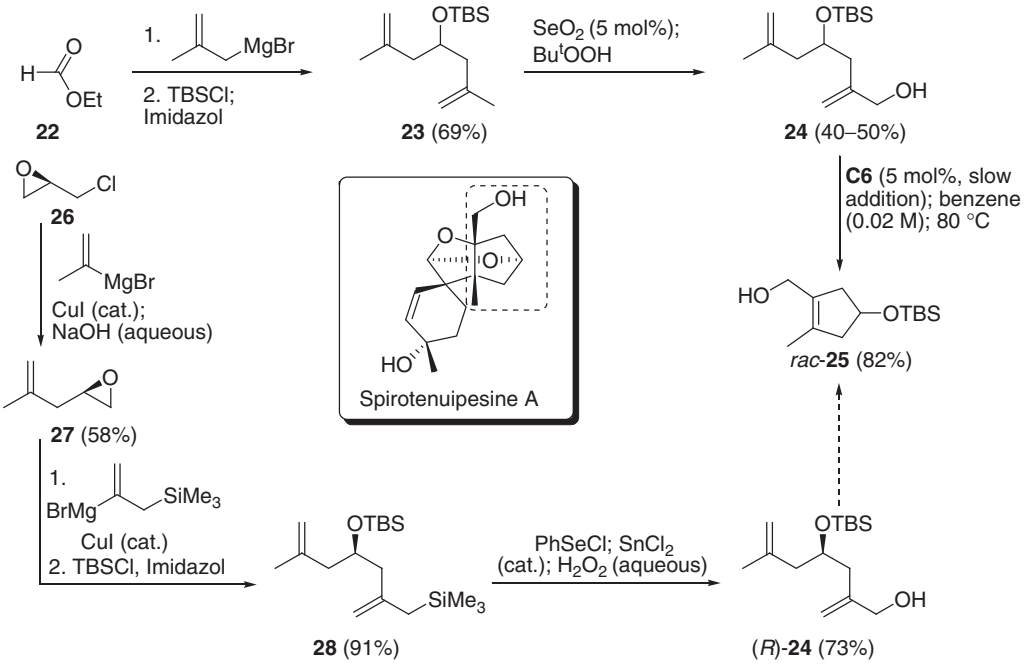
Occasionally, undesired double bond isomerization reactions occur when RCM reactions are conducted in refluxing toluene. For the RCM of **20** and several derivatives, this can be avoided by using the more reactive second-generation catalyst **C6**, which catalyzes this reaction at an ambient temperature with catalyst loadings as low as 1 mol%.[64] The double allylation of carbonyl compounds and subsequent RCM has also been used for the synthesis of spirocyclopentenes and representative examples are listed in Table 3. Remarkably, in contrast to the RCM of diallyl carbinols with an unprotected OH group, for most examples listed in Table 3 the less reactive first-generation catalyst **C3** gives satisfactory results at ambient or slightly elevated temperatures. For the example listed in entry 6 a rather high amount of catalyst **C6** has been used at 40 °C. However, it is not clear whether these conditions are mandatory or if comparable results could have been obtained with a first-generation catalyst.

Table 3 Diallylmetalation and subsequent spirocyclization via RCM

Entry	*Substrate*	*Allyl metal compound*	*RCM precursor*	*Yield (%)*	*RCM conditions*	*RCM product*	*Yield*	*References*
1				64	**C3** (5 mol%); CH_2Cl_2; 20 °C		87	65
2				91	1. Boc_2O 2. **C3** (1.3 mol%); CH_2Cl_2; 40 °C		93	66
3				46	**C3** (5 mol%); benzene; 20 °C		77	67
4				64	1. $(CF_3CO)_2O$; 2. **C3** (2 mol%); CH_2Cl_2; 22 °C		89	68
5				65	**C3** (5 mol%); CH_2Cl_2 (0.05 M); 20 °C		80	69
6				98	**C6** (5 mol%); CH_2Cl_2; 40 °C		86	70

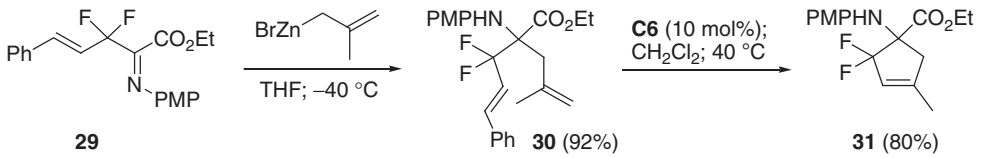
Although double allylation of esters, amides, or nitriles, as described above, is a straightforward route to RCM precursors, it has only rarely been used in actual target molecule syntheses, because for such applications symmetrical cyclopentenes are normally

not required, and the differentiation between enantiotopic or diastereotopic allyl groups is often difficult. This point has been illustrated by Danishefsky et al., who required enantiomerically pure cyclopentene **25** in a total synthesis of the fungal metabolites spirotenuipesines A and B (Scheme 8).[71,72]



Scheme 8 Two syntheses of the cyclopentene building block for spirotenuipesines A and B.

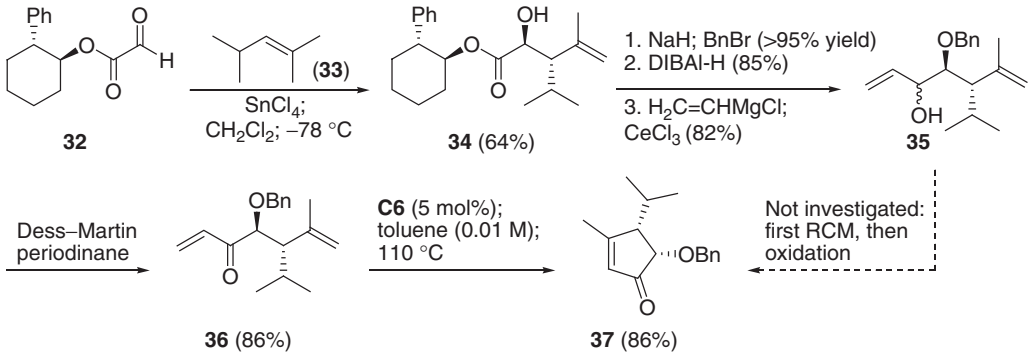
The shortest route starts from ethyl formiate (**22**), which is converted to **23** by double addition of methallylmagnesium chloride. Selenium catalyzed allylic oxidation yields racemic **24**, which undergoes RCM to the required cyclopentene **25** using **C6** in refluxing benzene. The construction of tetrasubstituted double bonds via RCM is challenging and normally requires significantly higher catalyst loadings or even more reactive catalysts. In this case, rather high dilution was combined with a slow addition of the precatalyst to the reaction mixture, resulting in a good yield of 82%.[71] Alternatively, a route to enantiomerically pure (*R*)-**24** from *R*-epichlorohydrine (**26**) was pursued, which involves the subsequent Cu-catalyzed addition of two vinyl-Grignard reagents and a final oxidative cleavage of the allylsilane **28**.[72] Other strategies toward unsymmetrical cyclopentenes are based on the addition of organometallic reagents to aldehydes, ketones, or imines. Fustero et al.[73] exploited this approach in a synthesis of fluorinated cyclopentene-α-amino acids, which are potentially useful building blocks for the synthesis of conformationally constrained peptides (Scheme 9). The required precursors, for example **30**, were obtained by chemoselective addition of allylic zinc reagents to imines such as **29**. RCM of **30** requires 10 mol% of the second-generation catalyst **C6** and proceeds with loss of styrene. This example illustrates that the formation of volatile alkenes such as ethene or propene is not necessarily required to shift the equilibrium toward product formation.



Scheme 9 Synthesis of fluorinated cyclic amino acids.

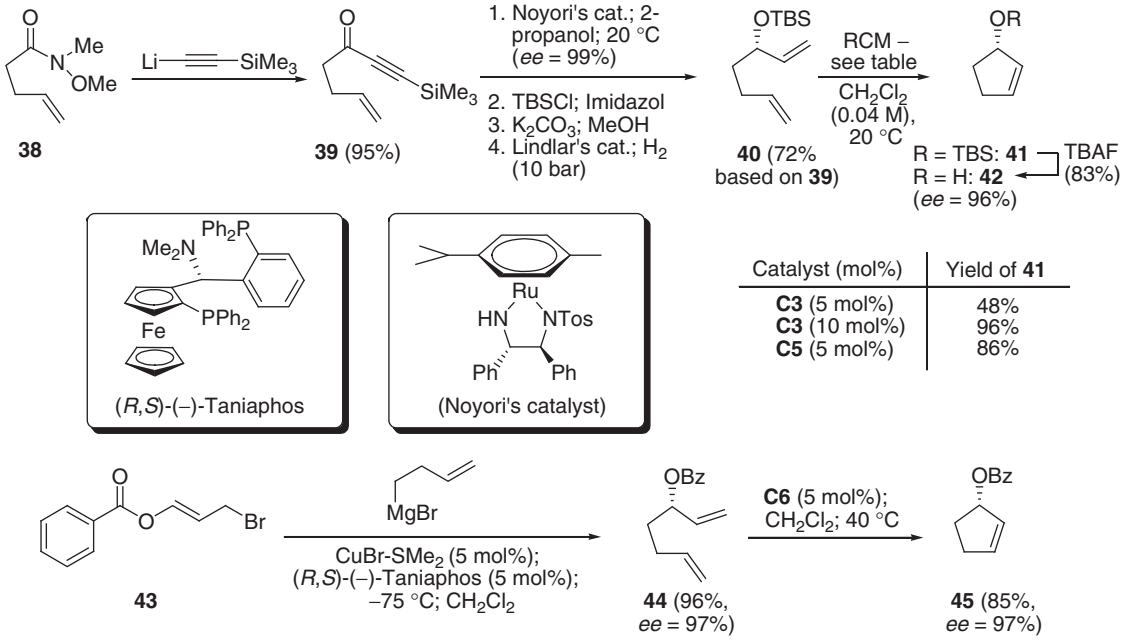
A challenging cyclopentenone formation has been reported by Trauner et al. in the course of a total synthesis of guanacastepene E (Scheme 10).[74] In this example, the chirally modified glyoxylate **32** reacts with 2,4-dimethyl-2-pentene (**33**) in the presence of a Lewis acid to homoallylic alcohol **34**, which is converted by a sequence of benzylation, reduction of the ester with diisobutylaluminumhydride (DIBAl-H), and addition of vinyl magnesium bromide to allylic alcohol **35**. Oxidation of **35** gave enone **36**, which underwent RCM in the presence of **C6** in refluxing toluene. An alternative strategy, which has not been reported for this particular example, would rely on a reversed order of the two final steps, i.e., RCM of the allylic alcohol **35**, followed by oxidation of the resulting cyclopentenol. This order of events turned out to be advantageous in some cases, for

example, Nay's synthesis of a harringtonolide fragment,[75] because RCM of an electron-deficient double bond is avoided, and OH-directing and activating effects[76] might facilitate the metathesis step. However, if the metathesis reaction is slow (which has to be expected in the case of **35**) rapid isomerization to ethyl ketones will most likely occur.[77]



Scheme 10 Synthesis of cyclopentenone fragment in the total synthesis of guanacastepene E.

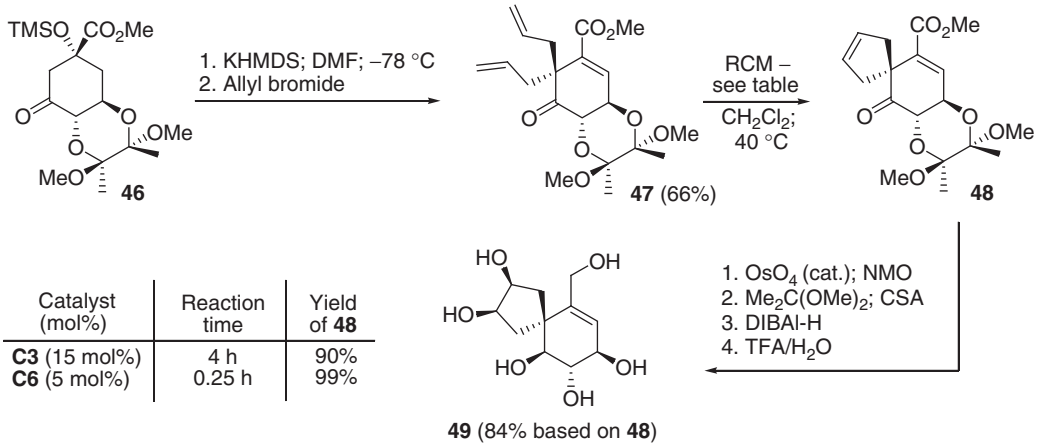
An RCM-based synthesis of enantiopure 2-cyclopentenol (**42**), a useful building block for several target molecule syntheses, relies on the addition of an alkynyl lithium reagent to a Weinreb amide **38**, followed by enantioselective reduction of ketone **39**[78] and Lindlar reduction of the alkyne (Scheme 11). RCM of the *tert*-butyldimethylsilyl (TBS)-protected precursor **40** was investigated using the first-generation Grubbs' catalyst **C3** and first-generation Grubbs–Hoveyda catalyst **C5** in CH_2Cl_2 at an ambient temperature. With a catalyst loading of 5 mol%, the conversion remained incomplete for **C3**, whereas quantitative conversion and synthetically useful yields were obtained with 10 mol% of **C3** or 5 mol% of **C5**.[79] An alternative approach to a protected *S*-2-cyclopentenol **45** uses a Cu-catalyzed enantioselective allylic substitution with butenyl magnesium bromide as a nucleophile and benzoate **43** as a starting material. RCM precursor **44** was obtained in nearly quantitative yields and high *ee*, and subsequently cyclized to **45** using the second-generation catalyst **C6** (Scheme 11). The modest reactivity of the TBS- or benzoate-protected precursors **40** and **44** might be attributed to steric reasons. In particular, TBS-protecting groups attached to allylic OH-groups were found to retard the rate of RCM reactions, and it is therefore often advantageous to remove the protecting group before the RCM step.[80] The enantioselective Cu-catalyzed allylic substitution with butenyl-Grignard reagents and phosphoramidite ligands, and subsequent RCM have also been conducted as one-pot reactions, giving various enantiopure cyclopentenes.[81]



Scheme 11 Alternative syntheses of protected *S*-2-cyclopentenol.

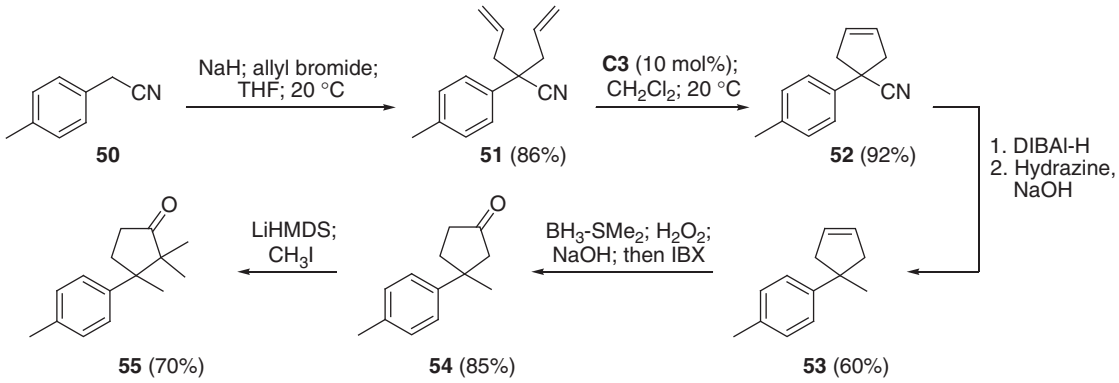
5.29.3.1.2 Synthesis of precursors by α-functionalization of carbonyl compounds

A straightforward route to symmetric cyclopentenes is the double allylation of enolates, in particular those derived from 1,3-dicarbonyl compounds, followed by RCM. The synthesis of conformationally constrained spirocyclic glycosidase inhibitors is a typical example for this approach (Scheme 12).[82] Dicarbonyl compound **46**, derived from quinic acid, was converted by deprotonation and treatment with excess allyl bromide to the RCM precursor **47**. RCM of **47** using the less reactive catalyst **C3** did not give satisfactory results, because an excessively high catalyst loading was required. In contrast, with **C6** a quantitative yield of **48** was obtained within considerably shorter reaction times and with lower catalyst loading. Spirocyclopentene **48** was then converted stereoselectively in four steps to product **49**, which showed a moderate inhibitory activity of a β-galactosidase.



Scheme 12 Synthesis of potential glycosidase inhibitors.

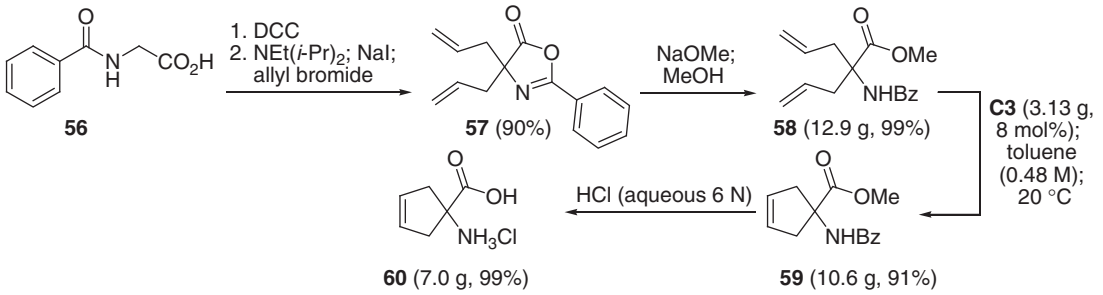
The problem of cyclopentene desymmetrization remains for other target molecule syntheses using double allylation and subsequent RCM. In the syntheses of *rac*-cuparenone[83] and *rac*-1,13-herbertenediol[84] this has been solved by hydroboration–oxidation and by allylic oxidation using pyridinium dichromate (PDC), respectively. The cuparenone synthesis is outlined as a representative example in Scheme 13.[83] As for the previous example, the catalyst loading required for this spirocyclization is very high, which might not only be attributed to steric constraints but also to partial catalyst deactivation by the cyano group.



Scheme 13 Synthesis of *rac*-cuparenone (**55**).

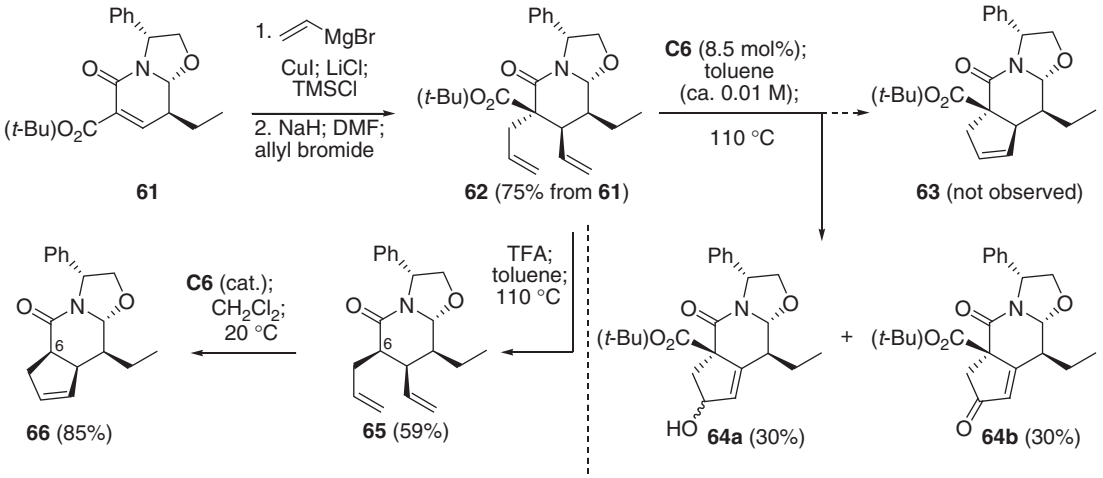
Similar approaches have been pursued by several groups for the synthesis of conformationally constrained cyclopentene α-amino acids **60** (see also Scheme 9 and discussion). As starting materials for the double allylation, Schöllkopf' bis-lactim ethers,[85] isocyanoacetate,[86] or a hippuric acid-derived oxazolone have been used. The synthesis starting from hippuric acid (**56**) was performed on multigram scale and is summarized in Scheme 14.[87] Notably, and particularly important for reactions on larger scale, an initial substrate concentration of approximately 0.5 M can be used.

An alternative route to cyclopentene precursors relies on a sequence of conjugate addition of a vinyl metal compound to an α,β-unsaturated carbonyl or dicarbonyl compound, followed by mono-α-allylation. This approach makes unsymmetrical cyclopentene units accessible and is particularly useful for bicyclic systems. Bosch et al. investigated a route along these lines with a



Scheme 14 Multigram scale synthesis of 1-aminocyclopent-3-ene-1-carboxylic acid hydrochloride (**60**).

view toward the synthesis of enantiomerically pure polysubstituted piperidine libraries (Scheme 15).[88] Starting from **61**, the required metathesis precursor **62** was obtained by Cu-mediated addition of vinyl magnesium bromide, followed by α-allylation. Interestingly, the desired RCM product **63** was not observed, instead two products **64a** and **64b** resulting from allylic oxidation of **63** were isolated in equal amounts. The researchers attribute the formation of these products to residual oxygen in the reaction mixture and a release of strain associated with the migration of the double bond. It is not fully clear whether the allylic oxidation occurs spontaneously or Ru-catalyzed; however, it is evident that the bulky ester group at the 6-position is responsible for this outcome, because a precursor **65** resulting from ester cleavage and decarboxylation reacts smoothly to cyclopentene **66** without concommitant or subsequent allylic oxidation. A comparable result was observed for the 6-epimer of **65**, giving the *trans*-configured diastereomer of **66**.

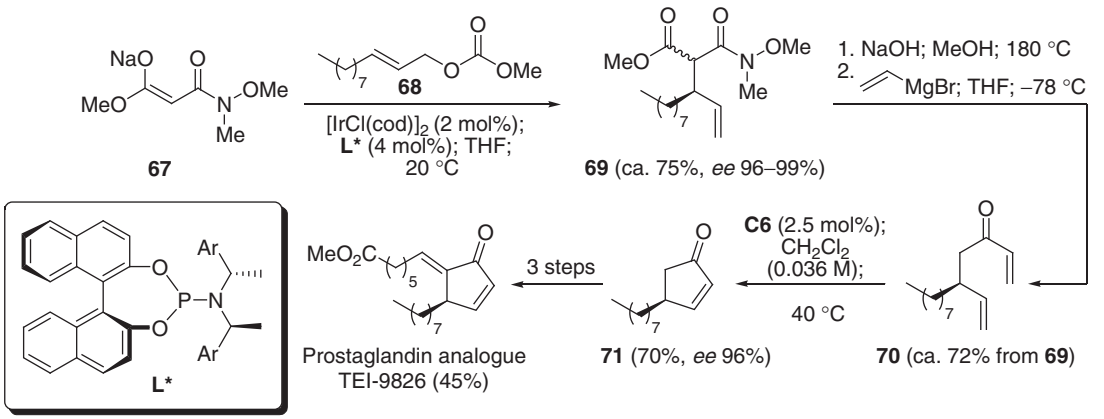


Scheme 15 Conjugate addition/α-allylation sequence for the synthesis of RCM precursors.

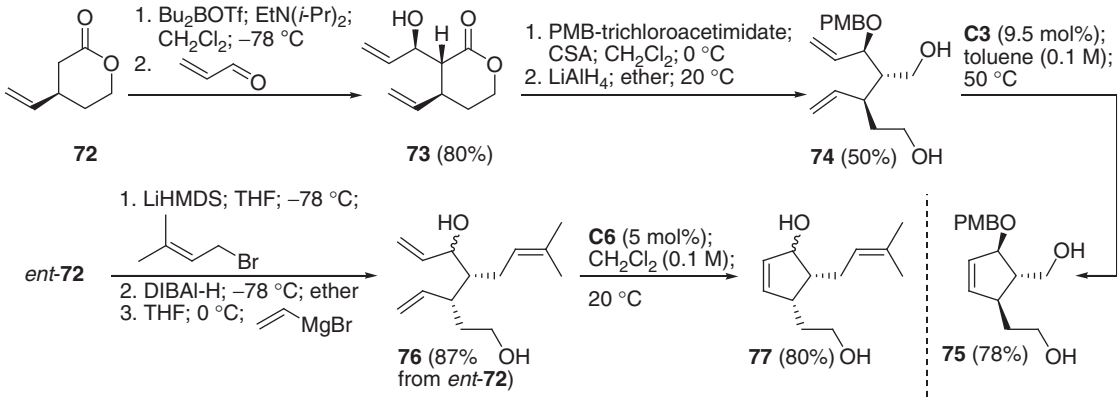
The Cu-catalyzed enantioselective allylic substitution with alkenyl metal compounds has been discussed in the previous section. A related strategy toward RCM precursors was developed by Helmchen et al. It involves the Ir-catalyzed allylation of enolates derived from 1,3-dicarbonyl compounds, for example, Weinreb-amide **67** (Scheme 16).[89] The strategy has, inter alia, been applied to the synthesis of the cytotoxic prostaglandin analog TEI-9826. In the first step, enolate **67** was allylated with carbonate **68** in the presence of an Ir-(I)-precatalyst and chiral phosphoramidite ligand L*. The resulting product **69** was obtained in very high *ee*, and subsequently converted by saponification/decarboxylation and addition of the vinyl-Grignard reagent to the RCM precursor **70**. RCM of **70** yields the required cyclopentenone **71** in good yield and excellent optical purity. The synthesis of the target molecule TEI-9826 was accomplished by aldol addition and elimination. The sequence can be conveniently modified for the synthesis of 2-methyl-2-cyclopentenones by replacing vinyl magnesium bromide by the Grignard reagent resulting from 2-bromopropene. In these cases, the RCM step was performed with comparable catalyst loadings, dilution, and isolated yields.

Stereoselective aldol addition reactions of enolates and enals have also emerged as a useful method for the synthesis of RCM precursors. An example is the synthesis of preclavulone-A methyl ester, which starts from lactone **72**, obtained in enantiomerically pure form by resolution (Scheme 17).[90]

Conversion of **72** into the corresponding boron enolate and subsequent treatment with acrolein gave aldol adduct **73** as a single diastereomer in good yields. The RCM precursor **74** was obtained by protection of the secondary alcohol and reductive cleavage of the lactone. RCM was accomplished in good yield with the first-generation catalyst **C3** at slightly elevated temperatures. In the same study, the researchers investigated a route to the *cis*-epimer, which involved a ring-closing metathesis of precursor **76**. Surprisingly, this reaction failed with **C3**. It is not clear whether this failure must be attributed to the allylic OH



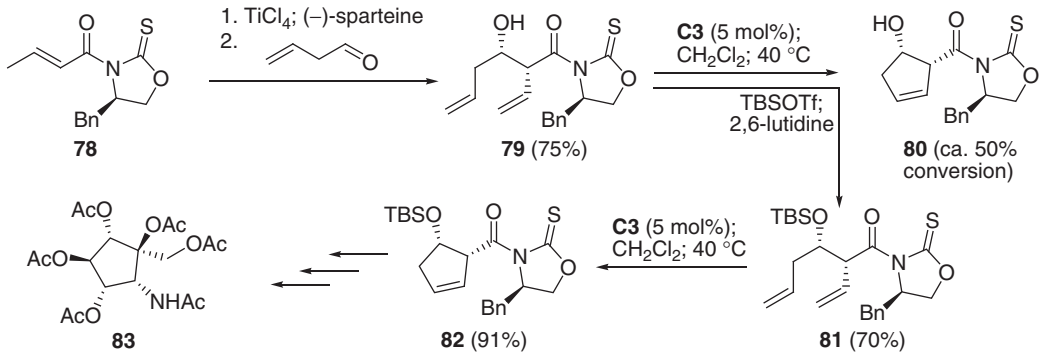
Scheme 16 Cyclopentenones via enantioselective allylic substitution and RCM.



Scheme 17 Diastereoselective aldol addition using a boron enolate.

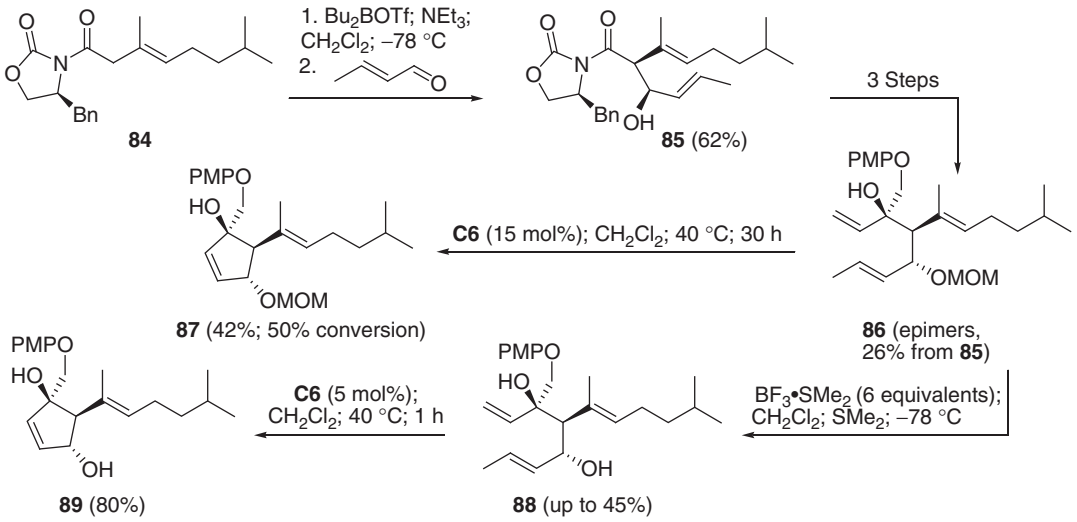
group or the pendant prenyl side chain. Gratifyingly, however, with the aid of the second-generation catalyst **C6** the cyclization proceeds at an ambient temperature.

The asymmetric aldol addition-RCM strategy has been applied to the synthesis of several target molecules with densely functionalized cyclopentane cores by Crimmins et al. One example is their approach to the trehalase inhibitor trehazolin, which is outlined in Scheme 18.[91] Starting from oxazolidinthione **78**, a stereoselective aldol addition was achieved with 3-butenal in the presence of $TiCl_4$/(–)-sparteine with high *syn*-selectivity and in good yields. Attempted RCM of aldol adduct **79** did not proceed to completion, but stopped at ca. 50% conversion. Interestingly, the same result was observed for the analogous oxazolidinone (synthesized from the corresponding boron enolate); thus, catalyst inhibition by coordination to the sulfur can be excluded. However, after protection of the hydroxy group as a TBS ether the RCM proceeded smoothly to yield cyclopentene **82**, which was functionalized in several steps to the advanced trehazoline precursor **83**.



Scheme 18 Auxiliary controlled asymmetric aldol addition and RCM.

It should be noted that it is not possible to draw the general conclusion that protection of allylic hydroxy groups is always beneficial. Eustache et al. investigated several cyclopentene forming RCM reactions in the course of a project directed at the elucidation of structure–activity relationships of potential angiogenesis inhibitors based on the fumagillin structure (Scheme 19).[92] Evans-aldol methodology was used to synthesize **85**, which was then converted in three steps to two epimers of the methoxymethyl (MOM)-protected RCM precursor **86**. Separation of the epimers was possible, and both were found to undergo cyclization only slowly, requiring very high catalyst loadings of 15 mol% of **C6**. Nevertheless, the reaction stopped at 50% conversion after 30 h, and an isolated yield of just 42% of **87** could be obtained. The researchers suspected that the low reactivity of **86** was caused by the MOM-protecting group, which was therefore removed and the resulting allylic alcohol **88** was then subjected to RCM. Remarkably, this reaction went to completion in the presence of a considerably lower amount of the second-generation catalyst **C6** within 1 h, resulting in an isolated yield of 80% of cyclopentene **89**.

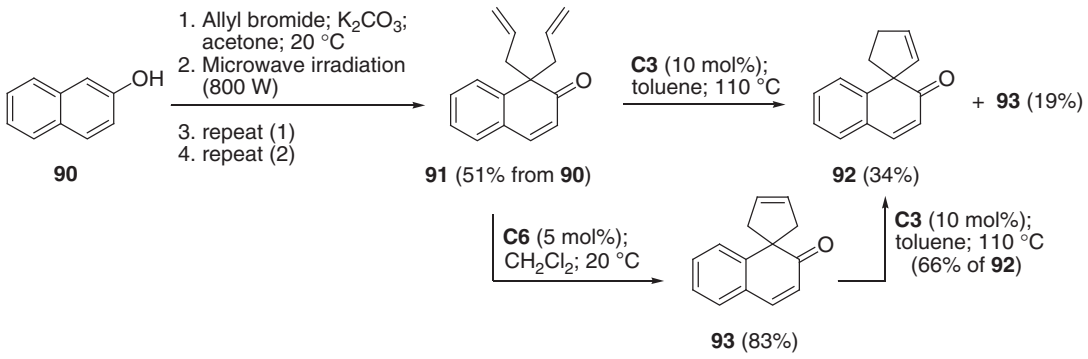


Scheme 19 Protecting group effects in the RCM-approach toward fumagillin analogs.

5.29.3.1.3 Synthesis of precursors involving Claisen rearrangement

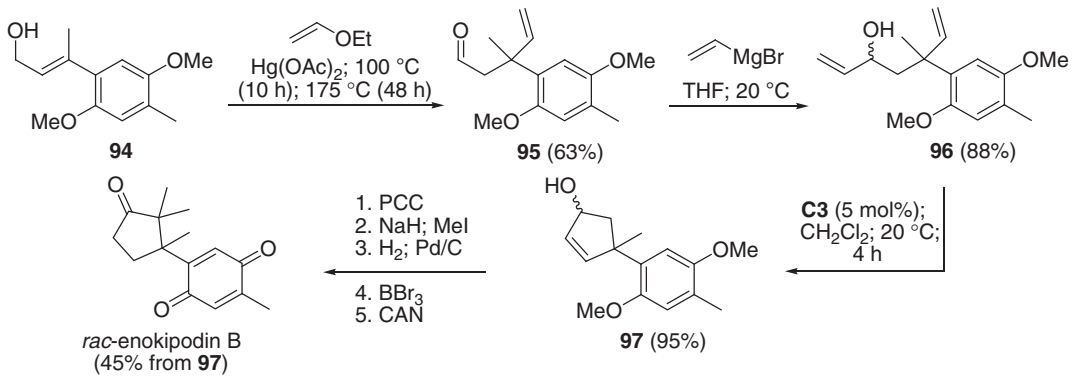
The Claisen rearrangement (*see* Chapter 5.20) and its variants are very useful for the synthesis of cyclopentene precursors, and numerous applications have been published. For example, the iterative O-allylation/Claisen rearrangement of 2-naphthol (**90**) yields the diallylated ketone **91** under microwave irradiation in good yields (Scheme 20).[93] RCM of **91** was found to be very slow in the presence of catalyst **C3**, making a high catalyst loading and elevated temperatures necessary. Under these conditions an undesired double bond isomerization occurs, and **92** was identified as the major product. In contrast, with the second-generation catalyst **C6** the reaction proceeds smoothly at an ambient temperature and with a lower amount of precatalyst. The researchers demonstrated that the double-bond migration is indeed Ru-catalyzed, because **93** can be converted to its isomer **92** in the presence of the first-generation catalyst **C3**, whereas no isomerization occurs in the absence of a Ru-catalyst.

Srikrishna et al. have used the combination of Claisen rearrangement and RCM in a manifold of sesquiterpene syntheses.[94] As an example, the synthesis of enokipodin B is outlined in Scheme 21:[95] starting from allyl alcohol **94**, a one-pot vinylation/Claisen



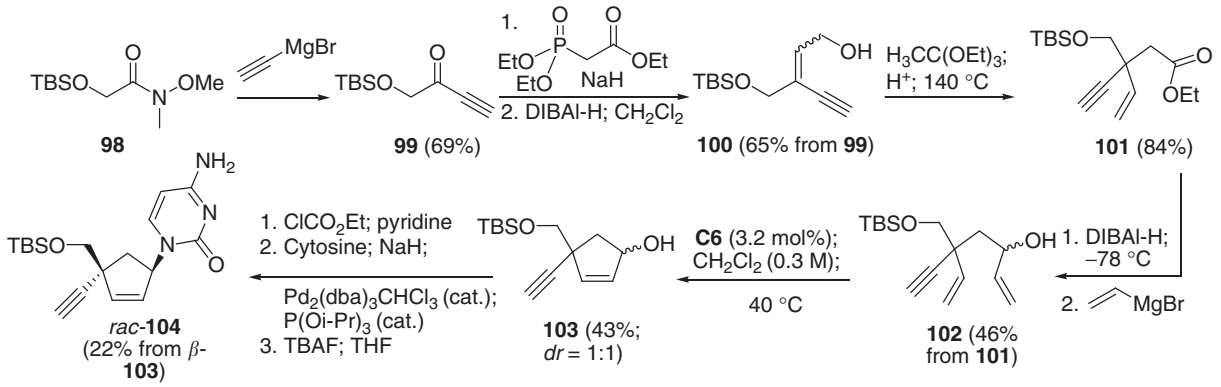
Scheme 20 O-Allylation/Claisen rearrangement/RCM sequence to spirocycles.

rearrangement to give the substituted pent-4-enal **95** was performed. By addition of vinyl magnesium bromide the RCM precursor **96** was obtained, which underwent smooth ring closure in the presence of **C3** to give cyclopentenol **97** in nearly quantitative yields. Compound **97** was then converted in five steps to the target molecule enokipodin B.



Scheme 21 Claisen rearrangement/RCM toward enokipodin B.

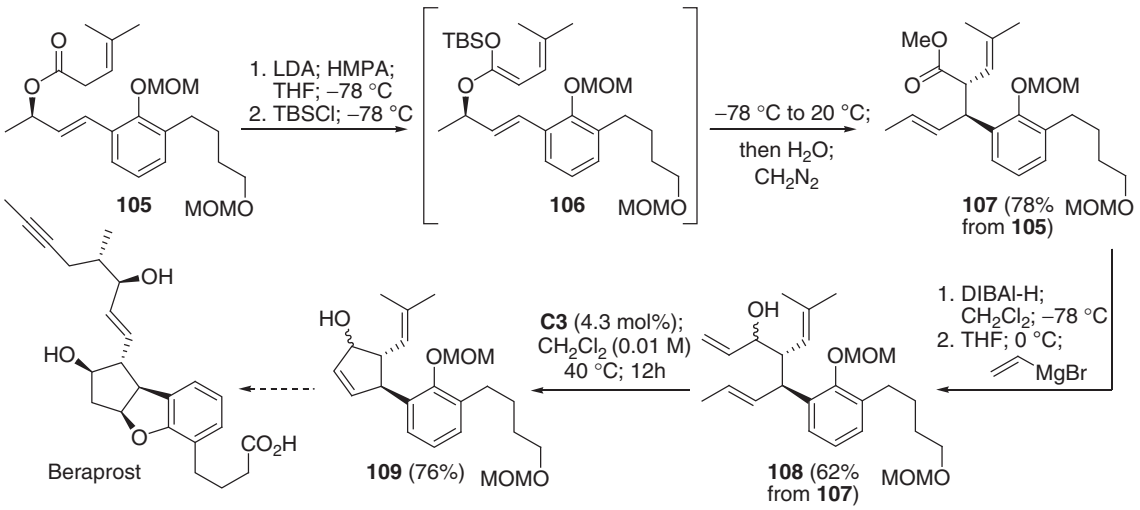
In many syntheses, the Johnson variant or the orthoester variant of the Claisen rearrangement has been advantageously used instead of the Claisen rearrangement itself. This has been exemplified in several contributions by Hong et al., who investigated synthetic approaches to carbonucleosides that rely on Johnson–Claisen rearrangement, RCM, and Pd-catalyzed allylic alkylation (Scheme 22);[96] starting from the glycolate-derived Weinreb amide **98**, precursor **100** was obtained through alkinyl Grignard addition, Horner–Wadsworth–Emmons (HWE)-reaction, and reduction. Treatment with triethyl orthoacetate at 140 °C in the presence of acid gave the Claisen rearrangement product **101**, which was converted by reduction and addition of vinyl magnesium bromide into a mixture of diastereomeric alcohols **102**. RCM of **102** was accomplished using the second-generation catalyst **C6** and resulted in the formation of diastereomeric cyclopentenols **103** in a moderate yield of 43%. The modest yield can be attributed to a competing ring closing enyne metathesis; unfortunately, no yield was reported for this product. The sequence was completed with single diastereomers of **103**, by conversion of the hydroxy group into a carbonate leaving group and Pd-catalyzed allylic substitution using deprotonated cytosine as a nucleophile.



Scheme 22 Carbonucleosides via Claisen rearrangement, RCM, and allylic alkylation.

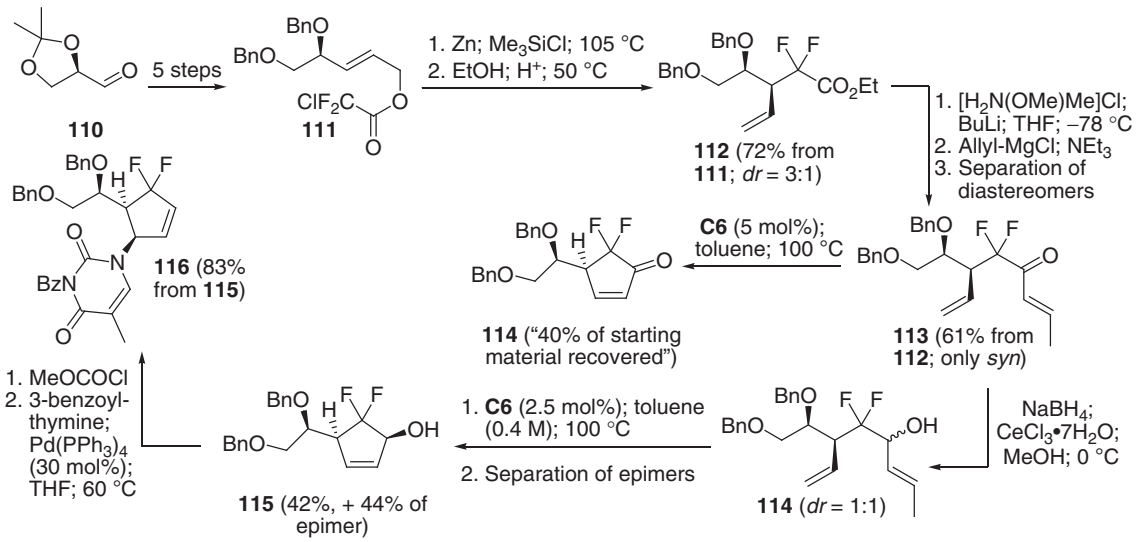
Variants of the Claisen rearrangement, which can be performed under milder conditions and in a stereoselective fashion, have been developed and combined with RCM in synthetic sequences. Among these, the Ireland–Claisen rearrangement is the most commonly used method, which is exemplified by a synthesis of the antiplatelet drug, beraprost (Scheme 23).[97] Allyl ester **105** was first converted into the (*Z*)-silyl ketene acetal **106**, which underwent stereospecific rearrangement on warming to an ambient temperature. Aqueous workup, followed by treatment with diazomethane provided ester **107** as a single diastereomer. The RCM precursor **108** was obtained through reduction with DIBAl-H and Grignard addition. It was cyclized to cyclopentenol **109**, without OH-protection, using a moderate amount of the first-generation catalyst **C3** at 40 °C.

The Reformatsky–Claisen reaction has been exploited for the synthesis of fluorinated carbonucleosides (Scheme 24).[98] The required precursor **111** was synthesized in five steps from protected glyceraldehyde **110**. The Reformatsky–Claisen rearrangement required the presence of zinc as a reducing agent at elevated temperatures and resulted in the formation of ester **112** in moderate diastereoselectivity. This compound was converted into the RCM precursor **113**; however, RCM did not proceed with satisfactory



Scheme 23 Synthesis of beraprost via Ireland–Claisen rearrangement/RCM.

conversion, which was attributed to the highly electron-deficient nature of one C–C double bond. Therefore a Luche reduction was used to obtain an allylic alcohol **114**. Both epimers of **114** underwent RCM smoothly at a remarkably high initial substrate concentration of 0.4 M to give cyclopentenol **115** and *epi*-**115** in equal amounts. Palladium-catalyzed allylic alkylation was used for the introduction of the protected nucleobase 3-benzoyl thymine, which proceeded to give a good yield but required a rather high loading of the Pd-precatalyst.



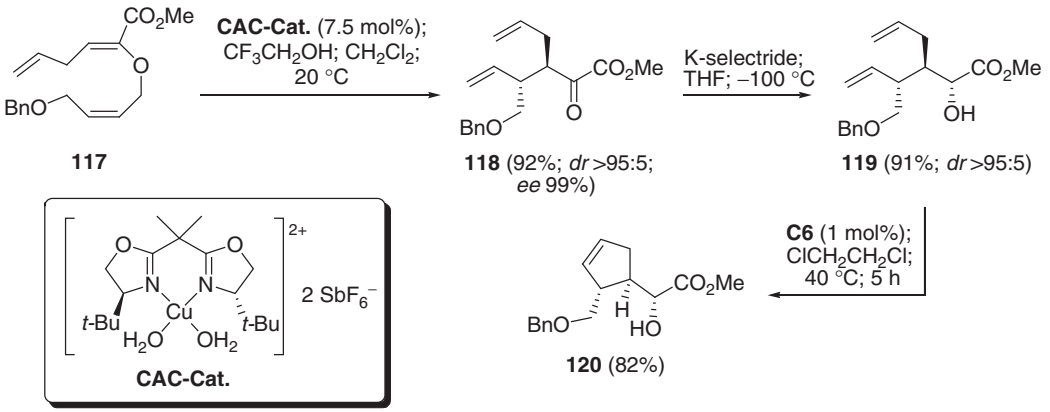
Scheme 24 Carbonucleosides via Reformatsky–Claisen reaction and RCM.

The catalytic asymmetric Claisen rearrangement, developed by Hiersemann et al., was combined with RCM in the synthesis of a cyclopentane fragment of (–)-ecklonialactone B (Scheme 25).[99] Starting from ketene acetal **117**, the rearrangement product **118** was obtained in a high yield as a single stereoisomer. Stereoselective reduction gave the RCM precursor **119**, which was converted to cyclopentene **120** in good yield with a comparatively low catalyst loading.

5.29.3.1.4 Synthesis of precursors from 'chiral pool' starting materials

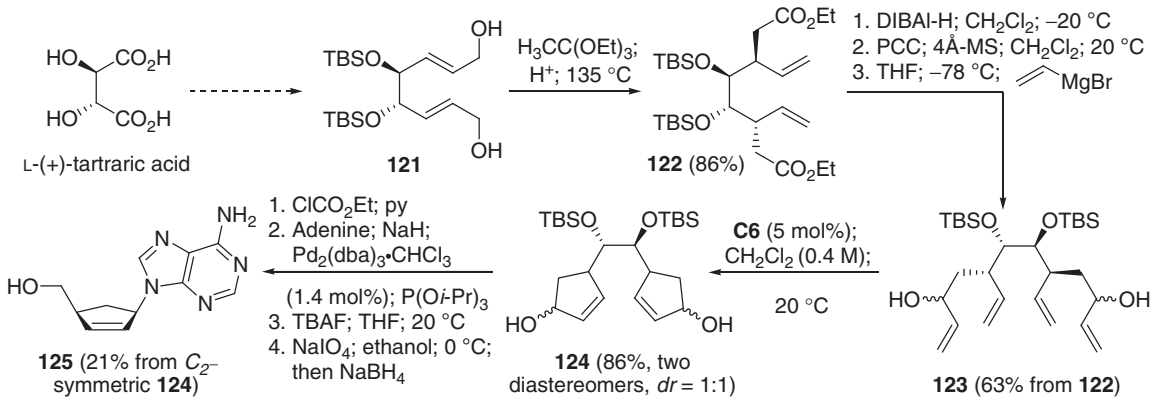
In the preceding sections, the authors focused on synthetic methods for the construction of appropriate metathesis precursors. Although in some of the examples discussed so far, starting materials derived from natural products have been used, this section will be dedicated specifically to the exploitation of chiral pool compounds. In particular, α-hydroxy acids, α-amino acids, and carbohydrates have been used for the stereoselective synthesis of many RCM precursors.

An example for the efficient use of L-(+)-tartrate has been published by Fang and Hong (Scheme 26).[100] Conversion into diol **121** was achieved through routine steps. Subsequently, **121** was subjected to the conditions of a Johnson–Claisen rearrangement, resulting in the highly diastereoselective formation of **122**. Elaboration of the diester into the diallylic alcohol **123** gave a mixture



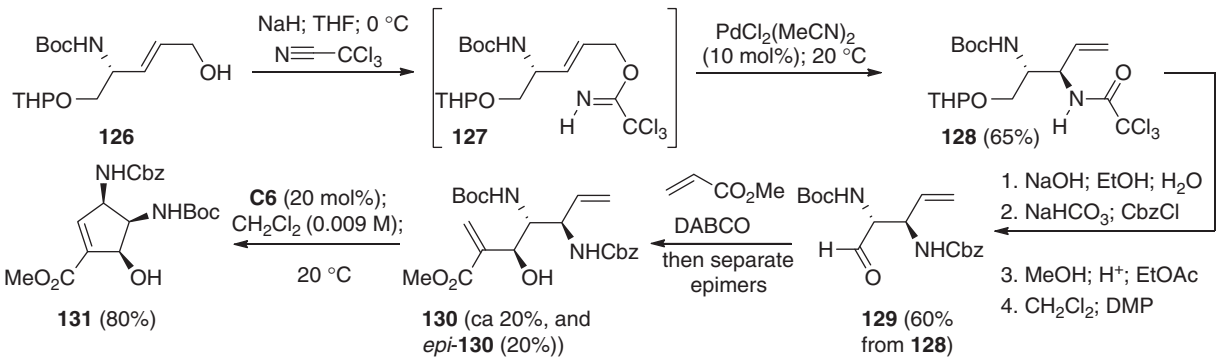
Scheme 25 Catalytic asymmetric Claisen rearrangement and RCM.

of two diastereomers, which underwent RCM smoothly to afford bis-cyclopentenol **124**. Separation of the C_2-symmetric epimer, conversion of the OH-groups into carbonate groups, Pd-catalyzed allylic substitution with deprotonated adenine, and desilylation gave a C_2-symmetric diol, which was finally subjected to a periodate cleavage, giving two equivalents of carbonucleoside **125** after reductive workup.



Scheme 26 Enantiopure carbonucleosides from L-(+)-tartrate.

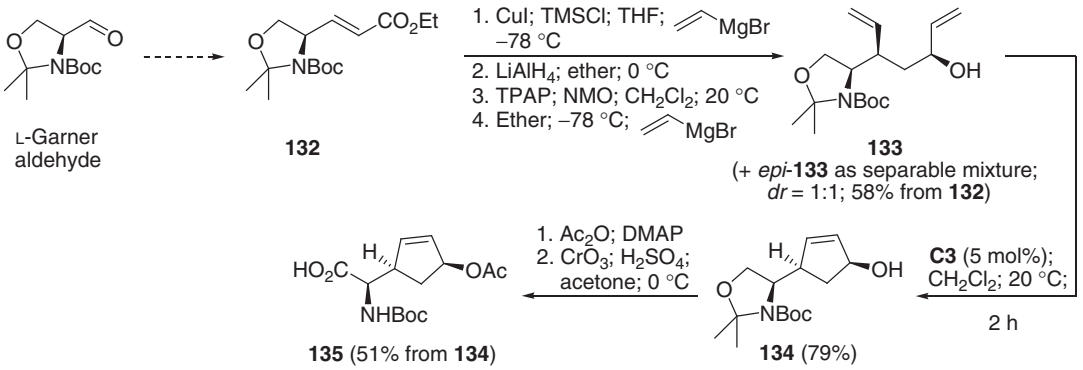
L-serine is one of the most commonly used amino acids in organic synthesis. Here, two examples of how serine-derived starting materials can be used in the synthesis of aminocyclitols will be discussed. With a view toward diaminocyclitols as potential neuraminidase inhibitors, the serine-derived allylic alcohol **126** was converted to the vicinal *anti*-diamine **128** by treatment of the alkoxide with trichloroacetonitrile followed by a Pd-catalyzed aza-Claisen rearrangement of the initially formed trichloroacetimidate **127** (Scheme 27).[101] Aldehyde **129** is available in four steps from **128**, which is then subjected to a Baylis–Hilman reaction to furnish the RCM precursor **130** and its epimer. The epimers were separated and subjected individually to RCM conditions. Not surprisingly, considering the electron-deficient nature of one of the double bonds involved and the



Scheme 27 Diaminocyclitols from L-serine.

required formation of a trisubstituted double bond, the first-generation catalyst **C3** was found to be inactive; however, by using the second-generation catalyst **C6** (albeit with a very high catalyst loading and at rather high dilution) cyclization to both **131** and its epimer were accomplished in good yields. Interestingly, by thermal aza-Claisen rearrangement the *syn*-diastereomer of **128** becomes available, and the researchers also repeated the entire sequence for *syn*-**128**. Thus, all diastereomeric RCM precursors of **130** were separately synthesized and individually subjected to RCM. All RCM reactions proceeded under similar conditions and the products were obtained in comparable yields.

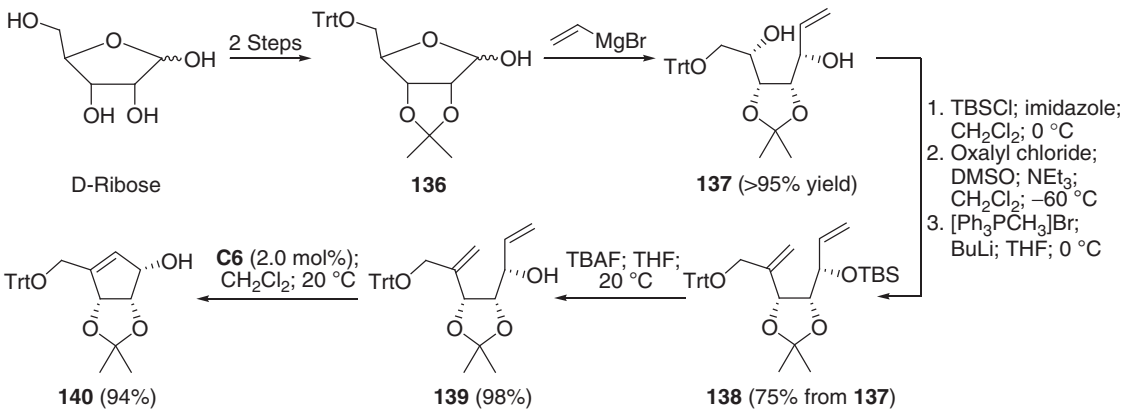
A commonly used building block derived from L-serine is Garner's aldehyde, which has been used in several syntheses of enantiopure cyclopentenol derivatives. A recent example is outlined in Scheme 28.[102] The starting point is ester **132**, which is converted through conjugate addition, reduction of the ester group, oxidation to the aldehyde, and addition of vinyl magnesium bromide into a 1:1 mixture of allylic alcohols **133** and *epi*-**133**. The epimers were separated and subjected to RCM, which proceeded smoothly without protection of the OH-group. Under the reported RCM conditions, both diastereomers reacted with a comparable rate and yield to the corresponding cyclopentenols **134** and *epi*-**134** (not shown). By acetylation and Jones oxidation the desired *N*-*tert*-butyloxycarbonyl (Boc)-protected amino acid **135** and its epimer could be obtained. The researchers also devised a route to the enantiomers of **135** and *epi*-**135** from cheap L-serine, which was converted to D-Garner aldehyde in five steps.



Scheme 28 Stereodivergent route to cyclopentenyl glycine derivatives.

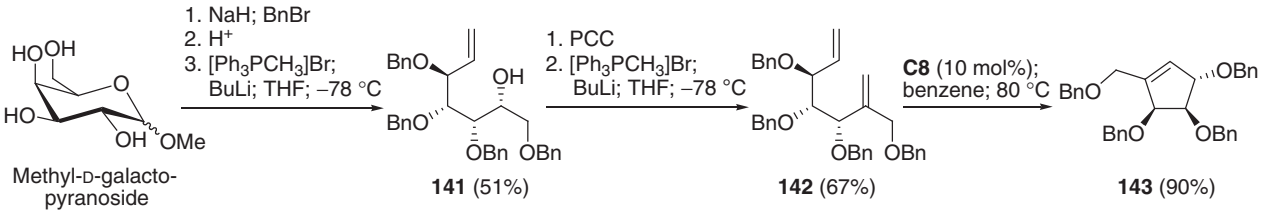
By far the most important chiral pool starting materials for RCM-based syntheses of cyclopentenes (and cyclohexenes, see Section 5.29.4.1) are carbohydrates.[103] Three important methods for the synthesis of the required RCM precursors have emerged: (i) addition of vinyl metal compounds to the carbonyl carbon of a carbohydrate; (ii) Wittig and other olefination reactions; and (iii) reductive elimination of iodoglycosides.

The addition of vinyl metal compounds to protected lactols often proceeds with high or even perfect diastereoselectivity. A representative example is highlighted in the following: aiming at the synthesis of carbonucleosides as potential antiviral agents, D-ribose was converted to the protected furanose **136**, which reacted quantitatively with vinyl magnesium bromide to allylic alcohol **137** as a single diastereomer.[104] After regioselective TBS protection and oxidation of the remaining secondary alcohol to a ketone, the second C–C double bond was introduced using a Wittig olefination. The TBS-protected precursor **138** did not undergo RCM, even if excessive amounts of first- or second-generation catalysts were used. However, after desilylation, the resulting allylic alcohol **139** underwent RCM smoothly on a 10 g scale in the presence of 2 mol% of the second-generation catalyst **C6** (Scheme 29).



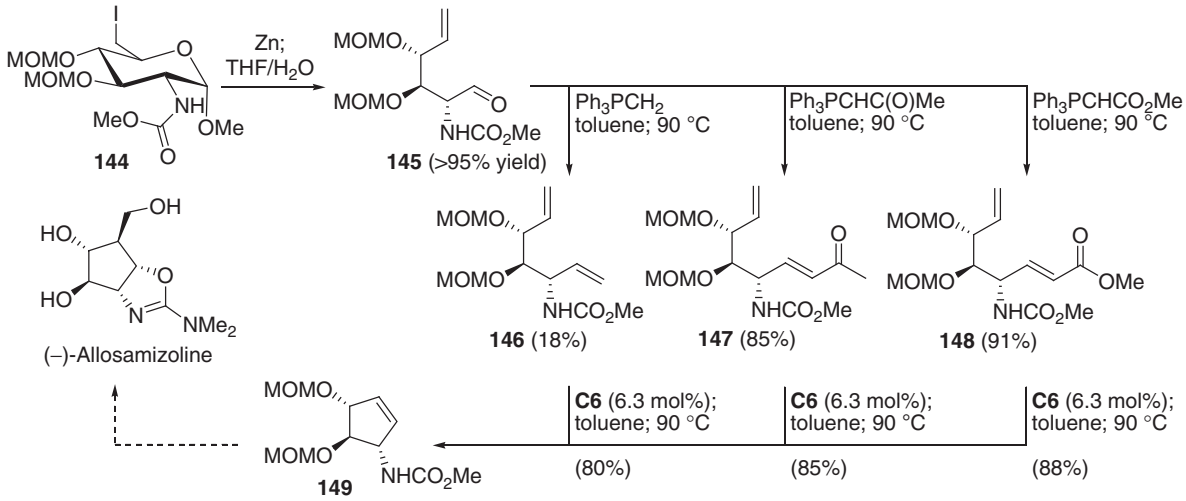
Scheme 29 Synthesis of RCM precursor from D-ribose.

An example for a dual application of the Wittig olefination is summarized in Scheme 30.[105] The sequence, starting from D-galactose, leads to a protected cyclopentitol **143** with a diastereomeric substitution pattern relative to **140** (Scheme 29). In this example, the RCM step was conducted with the tetrabenzylated precursor **142**, making significantly higher catalyst loadings and elevated temperatures necessary.



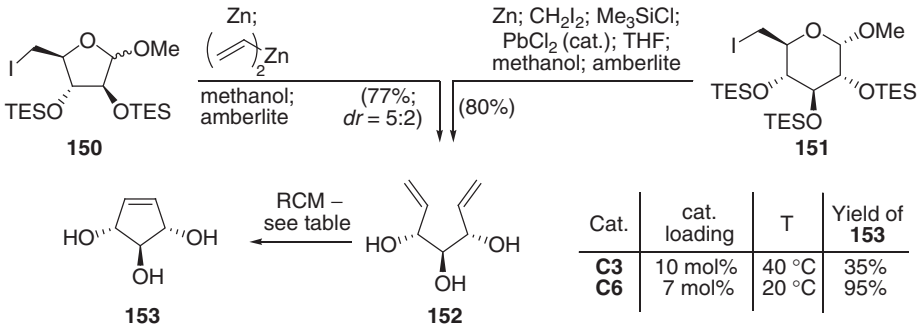
Scheme 30 Synthesis of RCM precursor from D-galactose.

The third method often used for the construction of alkenes from carbohydrates, the zinc-mediated elimination of iodoglycosides, has been combined with an olefination of carbonyl groups in most examples. This is illustrated in the RCM-based synthesis of (–)-allosamizoline, the aglycon of the chitinase inhibitor allosamidin (Scheme 31).[106] The aldehyde **145** obtained on treatment of iodoglycoside **144** (derived from D-glucosamine) with zinc was then subjected to a Wittig olefination. As the supposedly most reactive precursor **146** was obtained in only 18% yield, the Wittig reaction was repeated with stabilized ylides to give precursors **147** and **148** in high yields. In spite of the electron-deficient nature of one of the double bonds participating in the RCM step, cyclopentene **149** was obtained from all three precursors in preparatively useful yields with acceptable amounts of precatalyst **C6**.



Scheme 31 Synthesis of the cyclopentene core of (–)-allosamizoline.

Madsen et al. devised protocols for sequential one-pot reductive elimination/vinylation and reductive elimination/olefination syntheses of polyhydroxylated α,ω-dienes from deoxy-iodo carbohydrates (Scheme 32).[107]

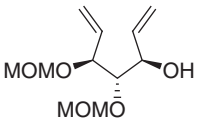
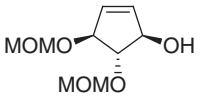
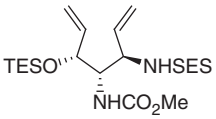
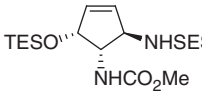
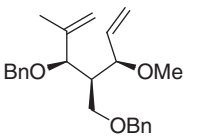
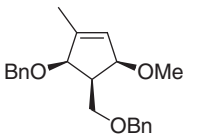
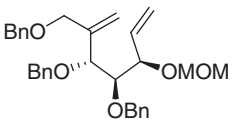
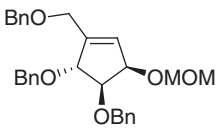
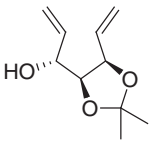
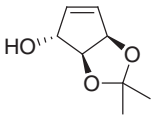
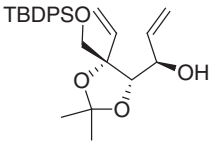
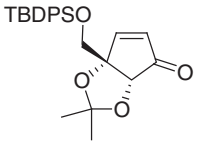
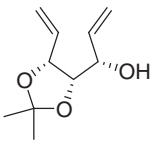
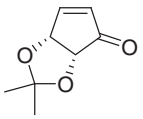
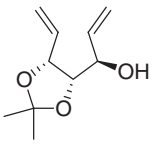
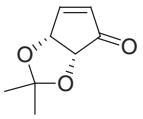


Cat.	cat. loading	T	Yield of **153**
C3	10 mol%	40 °C	35%
C6	7 mol%	20 °C	95%

Scheme 32 Sequential zinc-mediated elimination toward RCM precursors.

From arabino derivative **150**, diene **152** is available in moderate diastereoselectivity through reduction with zinc, addition of divinylzinc, and final acidic workup. The same diene was obtained from the gluco derivative **151** as a single isomer by zinc-mediated reduction for the formation of one double bond and Takai-type olefination of the aldehyde for the construction of the second C–C double bond. Both protocols involve acidic workup with methanol, resulting in the removal of the TES-protecting groups. Subsequent RCM was accomplished with the unprotected triol **152**, which underwent smooth cyclization to cyclopentene **153** only in the presence of the second-generation catalyst **C6**, whereas incomplete conversion was observed with **C3** even with higher amounts of catalyst and at elevated temperatures. Additional instructive examples for the RCM-based syntheses of cyclopentenes from carbohydrates are listed in Table 4.

Table 4 Examples for the synthesis of carbohydrate-derived cyclopentenes through RCM

Entry	*Carbohydrate*	*RCM precursor*	*RCM product*	*RCM conditions*	*Yield (%)*	*References*
1[a]	D-glucose			**C6** (0.2 mol%); CH_2Cl_2 (0.05 M) 20 °C	92	108
2[b]	D-glucosamine			**C10** (2 mol%); C_6H_6 (0.04 M); 80 °C	≈80	109
3	D-glucose			**C6** (7 mol%); C_6H_6 (0.15 M); 80 °C[c]	89	110
4[c]	D-mannose			**C3** (10 mol%); toluene; 60 °C; 33 h	12	111
5				**C1** (20 mol%); toluene; 60 °C; 2 h	74	111
6				**C6** (10 mol%); toluene; 60 °C; 2 h	78	111
7				**C8** (10 mol%); toluene; 60 °C; 1.5 h	74	111
8[d]	D-mannose			**C3** (0.05 mol%); CH_2Cl_2 (0.1 M); 20 °C; 24 h	89	112
9[e,f]	D-mannose			1. **C7** (0.7 mol%); CH_2Cl_2 (0.15 M); 20 °C; 70 h 2. PDC (2 equivalents)	93	113
10[e]	D-ribose			1. **C8** (1.5 mol%); CH_2Cl_2 (0.2 M); 24 °C 2. PCC (1.5 equivalents)	79	114
11[e]	D-mannose			1. **C3** (1 mol%); CH_2Cl_2 (0.26 M); 20 °C; 48 h 2. PDC (2 equivalents)	89	115

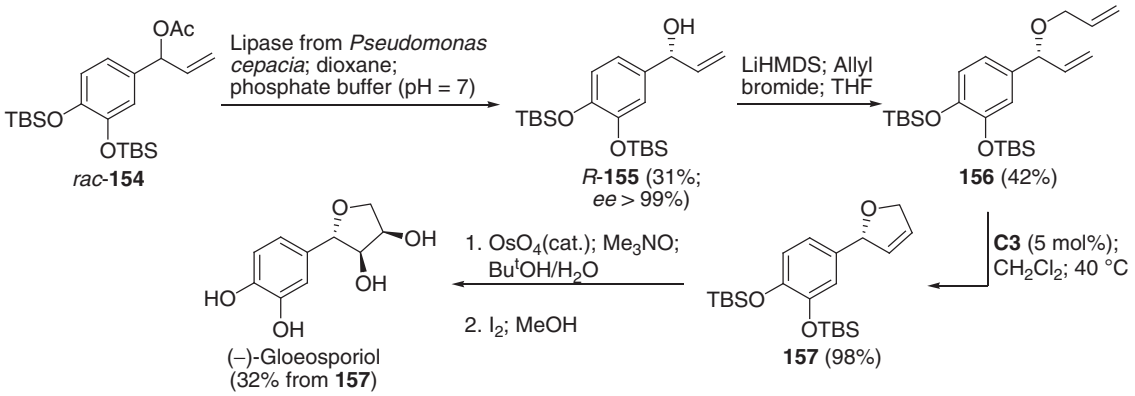
[a] RCM conducted on a 50 g scale.
[b] RCM conducted in the presence of impurities from previous steps.
[c] No conversion with **C3** in refluxing benzene for 2 days.
[d] RCM conducted on 88 g scale.
[e] One-pot RCM–Cr-mediated oxidation.
[f] RCM conducted on a 33 g scale.

5.29.3.2 Five-Membered Heterocycles

5.29.3.2.1 Five-membered oxacycles

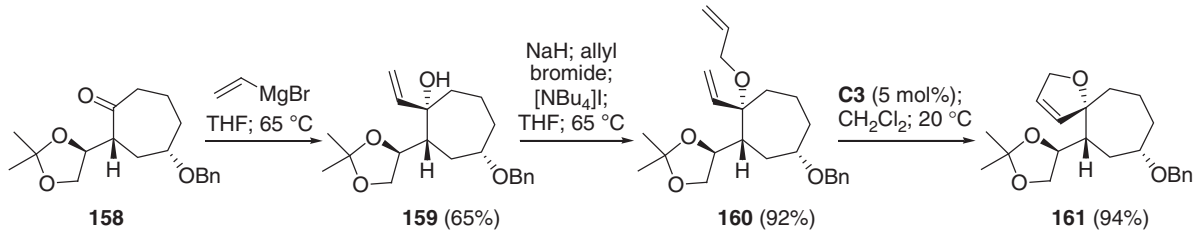
5.29.3.2.1.1 α-Substituted dihydrofurans

Monosubstituted diallylethers are normally highly reactive substrates in RCM reactions, and in most cases the first-generation catalyst **C3** should be sufficiently active to convert the precursors into 2-substituted 2,5-dihydrofurans in high yields at ambient or only slightly elevated temperatures. An example is the synthesis of enantiomerically pure (–)-gloeosporiol, a secondary metabolite of a phytopathogenic fungus (Scheme 33).[116] Routinely, the synthesis of RCM precursors such as **156** starts from aldehydes or ketones, which react with vinyl-Grignard reagents to racemic homoallylic alcohols. Often a kinetic resolution with lipases is used to obtain enantiopure alcohols,[117] which are then allylated to the desired RCM precursors. In the present case, **156** underwent RCM to 2-aryl-2,5-dihydrofuran **157** smoothly, which was then diastereoselectively dihydroxylated, resulting – after desilylation – in the formation of (–)-gloeosporiol with an optical purity higher than 99%.



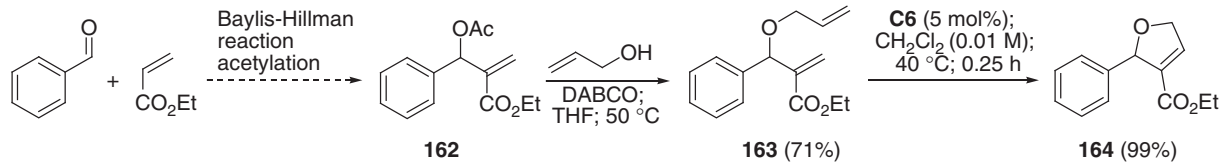
Scheme 33 Synthesis of (–)-gloeosporiol through RCM of a diallyl ether.

In the course of a study directed at the synthesis of Schisandra nortriterpenoids, a highly diastereoselective addition of vinylmagnesium bromide to a substituted cycloheptanone **158** was exploited for the synthesis of the RCM precursor **160** (Scheme 34).[118] Although this precursor is sterically more congested than **156** (Scheme 33), RCM to the spirocyclic compound **161** proceeded in nearly quantitative yields with the same catalyst loading.



Scheme 34 Synthesis of a Schisandra-nortriterpenoid building block through RCM.

As for the synthesis of cyclopentenes, RCM reactions leading to dihydrofurans with a triple-substituted double bond require higher catalyst loadings, elevated temperatures, or the use of more active second-generation catalysts. In particular, this is necessary if electron-deficient double bonds are involved in the RCM step, as outlined in Scheme 35.[119] In this example, one of the two double bonds of the precursor comes from an acetate of a Baylis–Hillman adduct (**162**). The second double bond is introduced by nucleophilic substitution with allyl alcohol to give the RCM precursor **163**, which underwent RCM in the presence of **C6**. As in most cases when a triple-substituted double bond is formed in the RCM step, comparatively high dilution has been

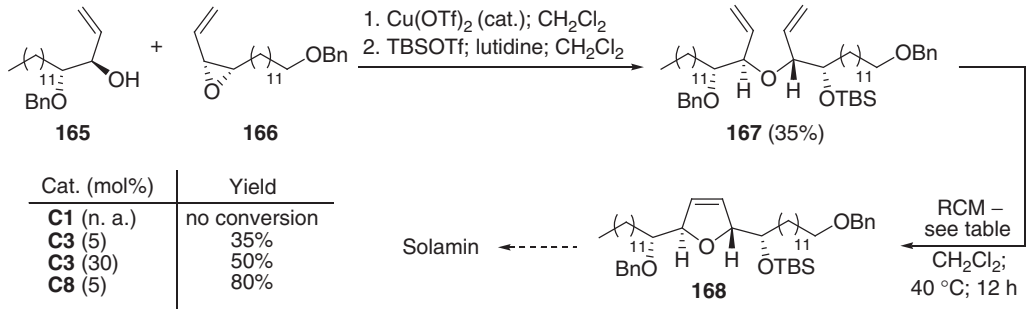


Scheme 35 2,3-Disubstituted 2,5-dihydrofurans through RCM of Baylis–Hillman-adducts.

applied to suppress competing dimerization through self-metathesis. In a related strategy, Baylis–Hillman-adducts have been used by Donohoe et al. to synthesize dihydrofurans equipped with a leaving group, which undergo elimination of ethanol leading to furans.[120]

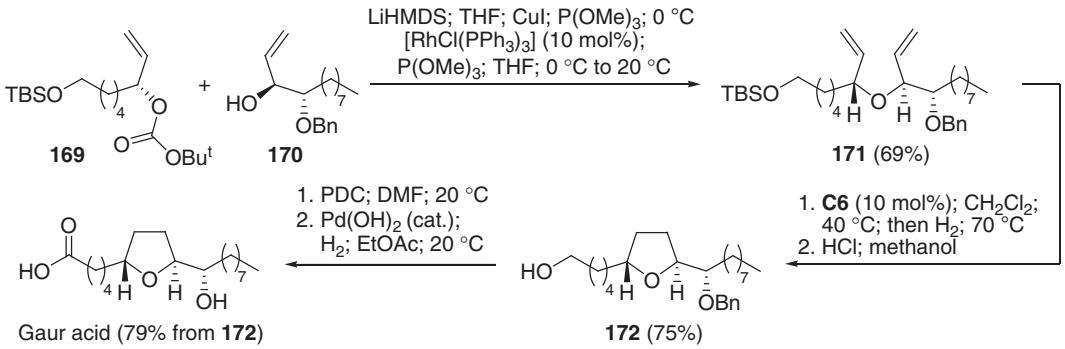
5.29.3.2.1.2 α,α′-Disubstituted dihydrofurans

For quite some time, the synthesis of appropriately substituted precursors has been a major obstacle in accessing 2,5-disubstituted dihydrofurans through RCM. One solution relies on a regio- and stereoselective opening of vinyl epoxides with allyl alcohols, and a representative example is outlined in the following (**Scheme 36**).[121] Aiming at the synthesis of the *Annona* acetogenin solamin, alcohol **165** and vinyl epoxide **166** were coupled in the presence of catalytic amounts of Cu-(II)-triflate to furnish diene **167** in moderate yields after TBS protection. Various catalysts and conditions were tested to accomplish RCM, but only low yields could be obtained with **C3** at reasonable catalyst loadings. Surprisingly, the highly active molybdenum catalyst **C1** failed completely, which might be attributed to its high sensitivity toward air and moisture, whereas the second-generation catalyst **C8** worked well, providing the desired dihydrofuran **168** in good yields at acceptable catalyst loadings. A similar strategy has been pursued in the synthesis of an amphidinolide C segment, where the crucial RCM step was accomplished with catalyst **C6**.[122]



Scheme 36 2,5-Disubstituted dihydrofurans through RCM.

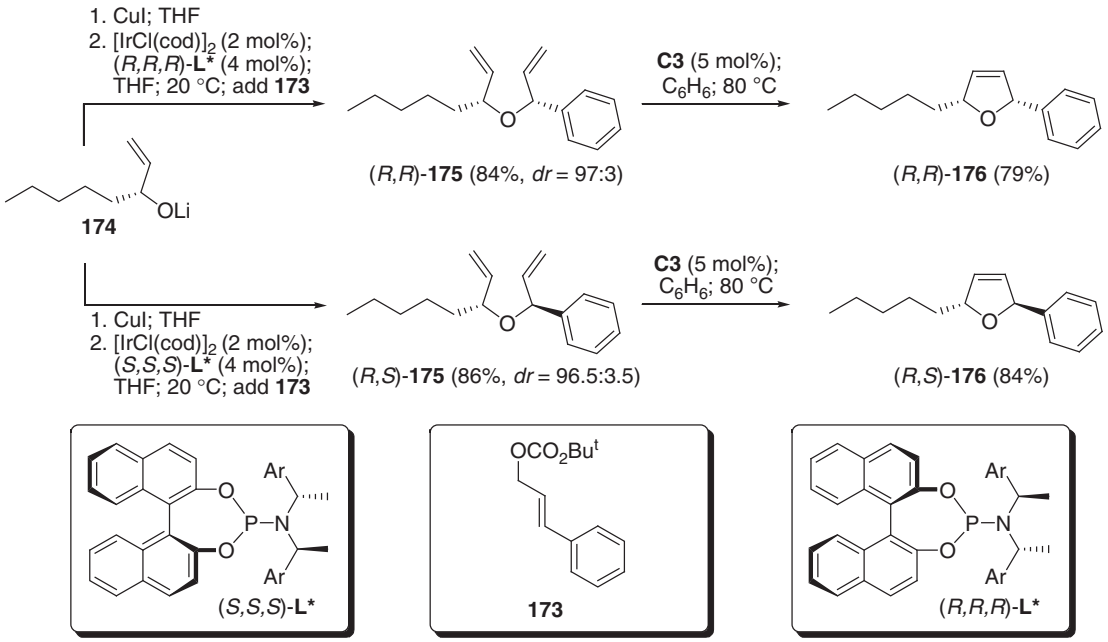
The discovery that Rh- and Ir-catalyzed allylic nucleophilic substitution reactions provide a convenient access to products with a terminal C–C double bond has been a major advantage in the synthesis of RCM precursors. The approach reported by Evans et al.[123] to the natural product gaur acid illustrates how a stereo- and regiospecific Rh-catalyzed allylic substitution and an RCM can be advantageously combined in the synthesis of target molecules (**Scheme 37**). The enantiomerically pure carbonate **169** undergoes a regio- and stereospecific Rh-catalyzed nucleophilic substitution with the Cu-alkoxide of allylic alcohol **170** to give the RCM precursor **171** as a single diastereomer. RCM was achieved with the second-generation catalyst **C6**, and the newly formed double bond was *in-situ* hydrogenated, using the metathesis catalyst in a tandem transformation (see Section 5.29.12 for a more detailed discussion of such transformations). After desilylation, the resulting *trans*-configured tetrahydrofuran **172** was converted into the natural product in two steps.



Scheme 37 Synthesis of Gaur acid through Rh-catalyzed allylation and RCM.

Alternatively, achiral carbonates can be used with chiral catalysts. To this end, Hartwig et al. introduced the combination of Ir(I)-precatalysts and phosphoramidite ligands (**Scheme 38**).[124] For example, Li-alkoxide **174** reacts with the achiral carbonate **173** in the presence of enantiomeric Ir-catalysts (generated *in situ* from all-*R* or all-*S* phosphoramidites, respectively) to the diastereomeric precursors (*R*, *R*)-**175** and (*R*, *S*)-**175** in high regio- and stereoselectivity. In contrast to the examples

quoted above, both undergo smooth RCM in the presence of 5 mol% of the first-generation catalyst **C3** in refluxing benzene.

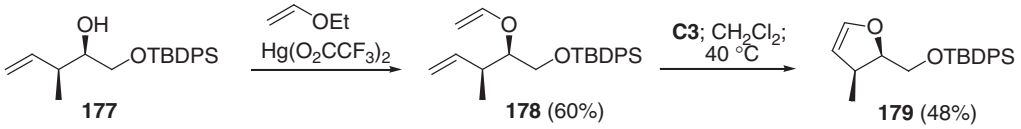


Scheme 38 Synthesis of RCM precursors through enantioselective Ir-catalyzed allylation.

More recently, Kocovský et al. exploited the Ir-catalyzed allylic substitution-RCM sequence for the synthesis of various aryl-C-ribonucleosides. For substrates that are sterically similarly congested as **175** it was found that the amount of catalyst **C3** can be reduced to 1 mol%, and that the temperature can be reduced to 40 °C for the RCM step.[125]

5.29.3.2.1.3 Five-membered cyclic enol ethers

In contrast to the RCM of diallyl ethers, vinyl ethers react slower and often require increased catalyst loadings, more active catalysts, higher dilution, and elevated temperatures. The decreased reactivity is commonly attributed to the intermediate formation of Fischer-type carbene complexes, if initiation occurs at the electron rich C–C double bond.[126] Another obstacle in the RCM of enol ethers is the synthesis of the precursors, which is often achieved by Hg^{2+}-mediated vinylation of homoallylic alcohols with ethyl vinyl ether. An example has been described by Williams et al., who required the 4,5-dihydrofuran **179** in the course of their lankacyclinol synthesis (Scheme 39).[127] Unfortunately, no catalyst loading was reported for this example.

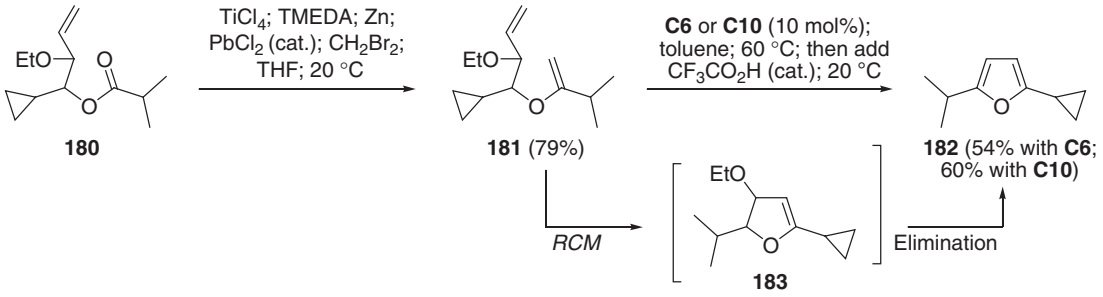


Scheme 39 Vinylation of homoallylic alcohols and enolether RCM toward lankacyclinol.

A different approach to enol ethers was pursued by Donohoe et al. in their one-pot synthesis of furans (e.g., **182**) via RCM and acid-catalyzed elimination (Scheme 40).[128] They used a modified Takai olefination to obtain the required precursors, for example, **181**, from esters such as **180**.

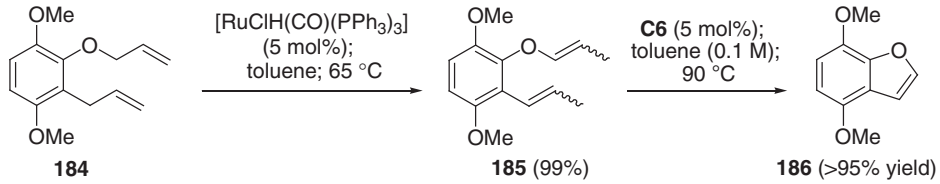
The RCM step was catalyzed by **C6**, and the resulting dihydrofurans **183** were treated, without isolation, with catalytic amounts of acid to promote the elimination of ethanol. The researchers report that in some cases the chromatographic purification of the product was hampered by the presence of phosphine, but this problem could be solved by using the phosphine-free catalyst **C10**. Apart from the simplified workup, better yields and shorter reaction times were observed with this catalyst.

Sometimes it is advantageous to synthesize the required RCM precursors from allyl compounds via isomerization. A significant number of examples for this strategy have been published by van Otterlo et al. In the following a synthesis of benzo[b]furans based on Ru-hydride catalyzed double-bond migration and subsequent RCM is highlighted (Scheme 41).[129] Allyl ether **184** was



Scheme 40 One-pot enolether RCM elimination for the synthesis of furans.

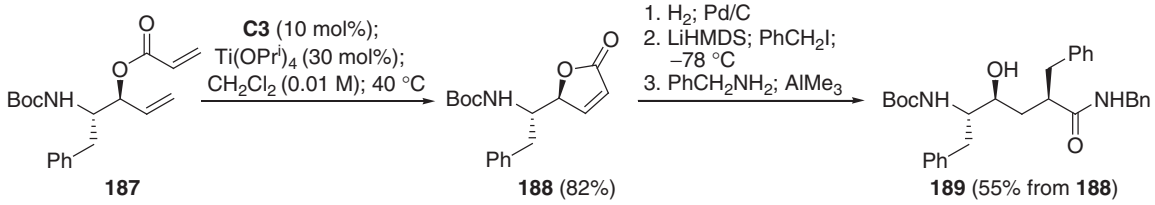
treated with a catalytic amount of a Ru-hydride complex to undergo quantiative isomerization to the vinyl ether **185**, which was then cyclized to the benzo[b]furan **186** with moderate loadings of catalyst **C6**.



Scheme 41 Ru-catalyzed isomerization and RCM for the synthesis of benzofurans.

5.29.3.2.1.4 α,β-Unsaturated five-membered lactones (butenolides)

Like substrates with one electron-rich double bond, for example, enol ethers, substrates with an electron-deficient double bond are significantly less reactive than allyl ethers. The problems associated with this type of RCM and its high synthetic value become evident from an early example published by Ghosh et al. in 1998 (Scheme 42).[130] They discovered that the RCM of acrylates such as **187** proceeds only very slowly, making rather high catalyst loadings of **C3** necessary. It should be taken into account that at this time the second-generation NHC-ligated catalysts were not yet available, and therefore alternative measures were investigated to improve the rate of the RCM. The researchers reasoned, supported by the previous observations published by Fürstner and Langemann in the course of macrocyclizations,[131] that the decreased reactivity originates from the formation of rather stable chelates after initiation. It is in line with this assumption that the addition of the Lewis acid $Ti(OPr^i)_4$ as a cocatalyst significantly accelerates the cyclization, resulting in the formation of butenolide **188** in 82% yield. Lactone **188** was diastereoselectively converted into the dipeptide isostere **189**, a useful intermediate in the synthesis of protease inhibitors.

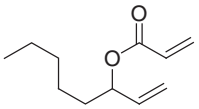
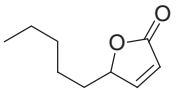
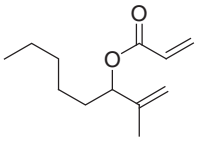
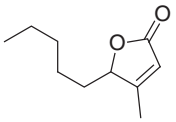
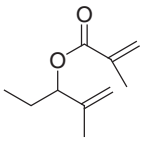
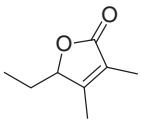
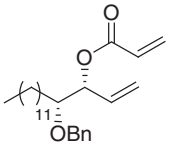
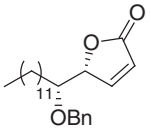
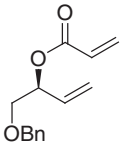
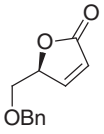
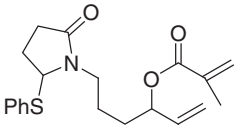
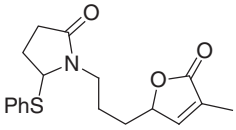
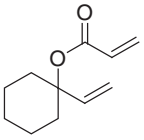
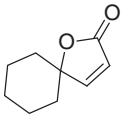


Scheme 42 Toward dipeptide isosteres through acrylate RCM.

In spite of the significant acceleration achieved by the addition of a Lewis acidic cocatalyst, the amount of first-generation Ru-catalysts (such as **C3**) required for useful rates of conversion is still very high, typically in the range of 10 mol% (occasionally in the range of 5 mol%).[132] In this regard, a significant progress was achieved with the discovery of second-generation catalysts. Shortly after the NHC-complexes **C6**–**C9** were first described in the literature, Fürstner et al. published an extensive study on the performance of these novel catalysts in 'difficult' RCM reactions, including the cyclization of various acrylates listed in Table 5 (entries 1–3).[39] In many cases, in particular if both the double bonds of the starting material are monosubstituted, catalyst loadings of 5 mol% or less are sufficient to obtain high yields of the desired butenolide. However, an obstacle that could not be overcome with the more active second-generation catalysts is the necessity to use rather low initial substrate concentrations, typically in the range of 0.01–0.05 M. A systematic study on the effect of catalyst loading and dilution in the RCM of acrylates suggests that, regardless of the catalyst loading, a critical initial substrate concentration exists for each RCM precursor.[133]

If this concentration is exceeded, the rate of conversion will decrease significantly, and this cannot be corrected by increased catalyst loadings. In contrast to some reports in the literature,[137] competing homodimerization is not the reason for the decreased

Table 5 Synthesis of butenolides through RCM of acrylates

Entry	Precursor	Conditions	Butenolide	Yield (%)	References
1		**C8** (5 mol%); toluene (0.02 M); 80 °C; 2 h		93	39
2		**C8** (5 mol%); toluene (0.04 M); 80 °C; 2 h		92	39
3		**C8** (5 mol%); toluene (0.1 M); 80 °C; 40 h		63	39
4		**C6** (5 mol%); toluene (0.025 M); 80 °C; 24 h		80	134
5		**C6** (4 mol%); CH_2Cl_2 (0.01 M); 40 °C; 5 h		98	135
6		**C6** (10 mol%); CH_2Cl_2 (0.1 M); 40 °C; 3h		79	136
7		**C7** (2.5 mol%); toluene (0.02 M); 80 °C; 1.5 h		85	133

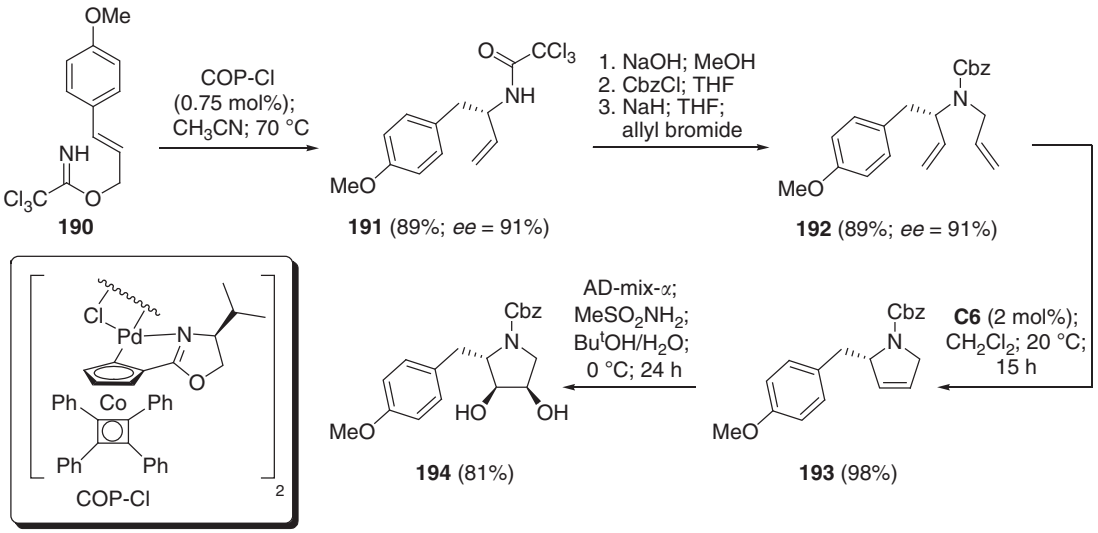
rate of RCM at higher concentrations in this particular case, because, whenever incomplete conversion was observed, only unreacted starting material and RCM products could be detected. Interestingly, higher initial substrate concentrations are tolerated with increasing degree of substitution of the double bonds (Table 5, entries 2, 3, 6).

5.29.3.2.2 Five-membered azacycles

5.29.3.2.2.1 α-Substituted dihydropyrroles

The most striking difference between oxa- and azacycle formation via RCM is that precautions have to be taken in the latter case to reduce the nucleophilicity of the heteroatom. In most cases this is achieved with electron-withdrawing groups such as the acetates, carbonates, or tosylates. Occasionally, however, synthetically useful results are obtained with tertiary amines, in particular benzyl amines, or after temporary conversion of a secondary amine into the corresponding hydrochloride.[138] For the synthesis of enantiomerically pure RCM precursors, diastereoselective transformations of carbohydrates,[139–141] enantio- or diastereoselective transformations of amino acid derivatives,[142,143] enantioselective allylic amination,[144,145] diastereoselective addition of organometallics to oximes,[146] or enantioselective imidate rearrangements[147] have been used. Synthetic strategies and methods for stereocontrol used in these precursor syntheses resemble those used for the synthesis of other RCM precursors (see Sections 5.29.3.1 and 5.29.3.2). Therefore, only an example for the successful implementation of an Overman- or imidate rearrangement catalyzed by a cobalt oxazoline palladacycle (COP-Cl, Scheme 43) will be discussed.[147]

Starting from prochiral imidate **190**, an enantioselective imidate rearrangement to the allyl amine **191** is achieved with the dimeric Pd-catalyst COP-Cl. Introduction of the benzyloxycarbonyl (Cbz)-protecting group and allylation yields diallyl amide **192**, which cyclizes smoothly in the presence of **C6** at an ambient temperature to dihydropyrrole **193**. Dihydroxylation with



Scheme 43 Toward dihydropyrroles via enantioselective imidate rearrangement and RCM.

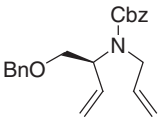
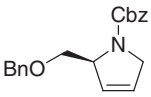
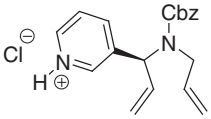
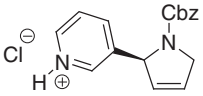
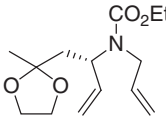
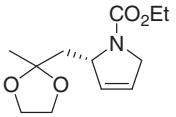
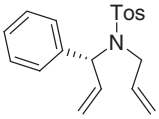
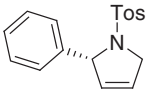
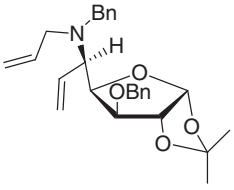
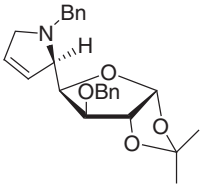
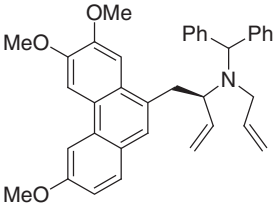
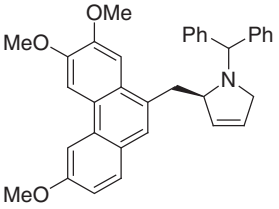
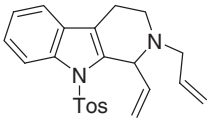
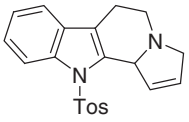
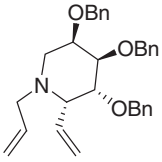
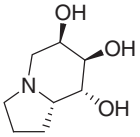
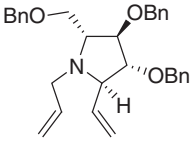
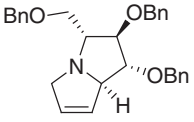
AD-mix-α proceeds with high diastereoselectivity, giving product **194**, a Cbz-protected epimer of the naturally occurring antibiotic anisomycin. In Table 6 some representative examples for RCM reactions leading to 1,2-disubstituted 2,5-dihydropyrroles are summarized. The commonly used electron-withdrawing N-protecting groups are Cbz (entries 1 and 2) or ethoxy carbonate (entry 3). In the case of the example listed in entry 2, pyridine was converted into hydrochloride before RCM. This RCM product was then converted in few steps into nicotine in > 99% *ee*,[144] whereas the dihydropyrrole in entry 3 served as a precursor for the alkaloid (+)-hygrine.[143] Tosylates (entry 4) are the less commonly used N-protecting groups in RCM reactions, although it could be demonstrated that the yields are comparable to those obtained with an ethoxy carbonate group for analogous RCM precursors.[145] In entries 5 and 6, examples for the successful conversion of tertiary amines are given. Although RCM of the benzyl-protected diallyl amine in entry 5 requires a rather high catalyst loading of 10 mol% of **C3**,[139] just 2 mol% of the same catalyst are sufficient to convert the diphenylmethyl-protected diallyl amine listed in entry 6 into the corresponding dihydropyrrole, an intermediate en route to the phenanthroindolizidine alkaloid (–)-antofine.[142] Obviously, sterically more demanding protecting groups reduce the unfavorable coordination of nitrogen to the metathesis catalyst, resulting in higher turnover numbers and lower catalyst loadings. Successful RCM reactions of diallyl amines have also been reported with sterically less demanding substituents at the nitrogen atom, in particular when nitrogen is part of a ring. In the example listed in entry 7, a long reaction time of 3 days was required for a good yield of the RCM product, but the amount of catalyst could be limited to 5 mol%.[148] In contrast, by using 10 mol% of the same catalyst, the reaction time could be significantly reduced for the structurally similar example in the entry 9.[140] A successful cyclization of an unhindered tertiary amine using a first-generation catalyst was achieved after temporary conversion of the precursor into the hydrochloride (entry 8). In this example, a very high catalyst loading of 25 mol% of **C3** was required, and the RCM product was hydrogenated *in situ* to give the bicyclic amine in 82% overall yield.

5.29.3.2.2.2 α,α′-Disubstituted dihydropyrroles

For the synthesis of precursors for 1,2,5-trisubstituted dihydropyrroles, regioselective nucleophilic opening of butadiene oxides with amines have been used in several syntheses. As a representative example, Trost's synthesis of the naturally occurring unusual amino acid (–)-bulgecinine is outlined below (Scheme 44).[150]

Starting from racemic butadiene oxide **195** and enantiomerically pure oxazolidinone **196** the RCM precursor **197** was obtained in good diastereoselectivities and overall yields using a Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) followed by benzylation of the primary alcohol. Protection of the primary alcohol was found to be mandatory for successful RCM. Even with benzyl ether **197** the RCM reaction proceeded slowly, and the best yields of **198** were obtained by portionwise addition of catalyst **C6**. For the synthesis of the target molecule a regio- and stereoselective hydroboration of the double bond was required, which was accomplished using 9-*H*-9-borabicyclononane (9-H-9-BBN). The synthesis of (–)-bulgecinine was completed in five further steps. Additional examples for RCM reactions leading to 1,2,5-trisubstituted dihydropyrroles are listed in Table 7. The example in entry 1 shows the RCM of an epimer of **197** (see Scheme 44). A significantly higher catalyst loading and longer reaction times are required, although the effect of the relative configuration on the rate of the RCM step has not been explicitly investigated for this example. In entry 2, the RCM of the unprotected analog of **197** with **C6** is reported, which apparently contradicts the results reported by Trost et al. (see above). It should, however, be noted that for this example no catalyst loading was reported. From the example in entry 3 it becomes obvious that less active first-generation catalysts such as **C3** are only of limited value for this type of transformation, because no less than 50 mol% of catalyst are required to obtain 73% yield of product. In the last example in entry 4, the formation of an azabicyclooctane is reported. Ring closure proceeds with

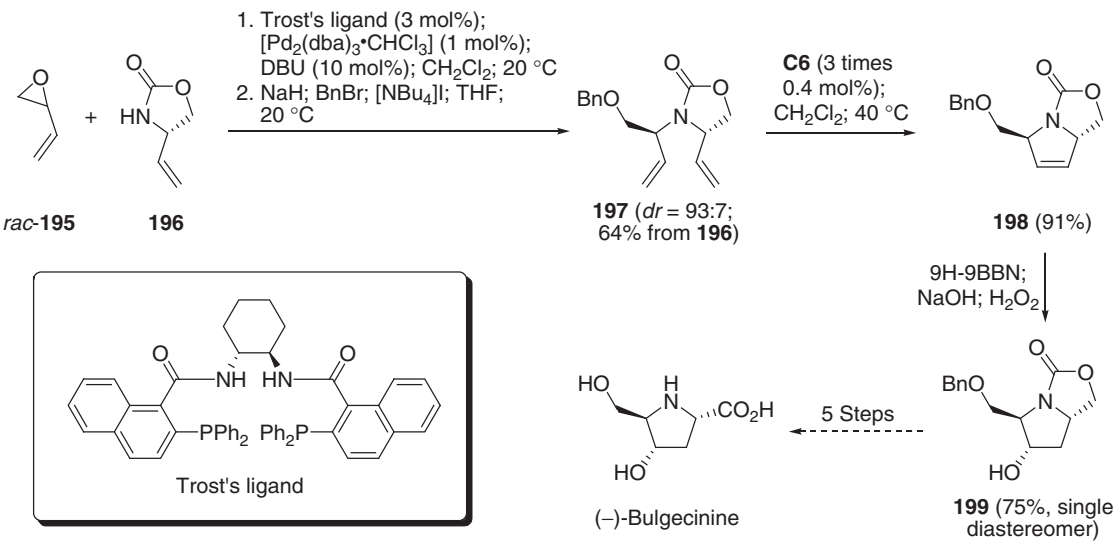
Table 6 Synthesis of 1,2-disubstituted 2,5-dihydropyrroles through RCM

Entry	*Precursor*	*Conditions*	*Dihydropyrrole*	*Yield (%)*	*References*
1		**C3** (10 mol%); CH_2Cl_2 (0.1 M); 20 °C		96	146
2		**C6** (5 mol%); CH_2Cl_2; 40 °C		92	144
3		**C6** (8 mol%); CH_2Cl_2; 20 °C		99	143
4		**C3** (5 mol%); CH_2Cl_2; 40 °C		95	145
5		**C3** (10 mol%); CH_2Cl_2 (0.2 M); 20 °C; 12 h.		84	139
6		**C3** (2 mol%); CH_2Cl_2 (0.05 M); 20 °C; 24 h		92	142
7		**C6** (5 mol%); toluene; 20 °C; 3 days		76	149
8		1. HCl (1.25 M in MeOH) 2. **C3** (25 mol%); CH_2Cl_2; 45 °C; 24 h 3. Pd/C; H_2		82	141
9		**C6** (10 mol%); toluene; 80 °C; 14 h		87	140

surprising efficiency, considering that a strained bicyclic product is formed, and requires only 10 mol% of the first-generation catalyst **C3**.

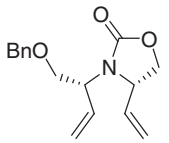
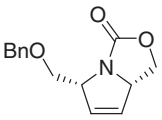
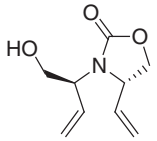
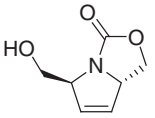
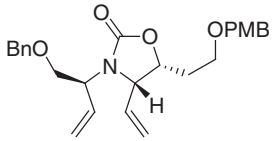
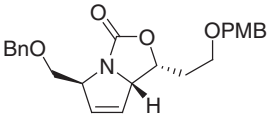
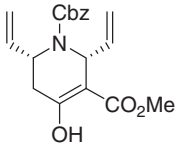
5.29.3.2.2.3 Five-membered cyclic enamides

Five-membered cyclic enamides are also accessible by RCM. The required starting materials can be synthesized by Tebbe olefination of acetamides or by isomerization of allylic amides. Examples for the synthesis of dihydropyrroles and indoles have been described. As for the oxa-analogs more active catalysts are required in most cases, but for sterically



Scheme 44 Synthesis of (–)-bulgecinine via DYKAT and RCM.

Table 7 Synthesis of 1,2,5-trisubstituted 2,5-dihydropyrroles through RCM

Entry	*Precursor*	*Conditions*	*Dihydropyrrole*	*Yield (%)*	*References*
1		**C6** (3 mol%); CH_2Cl_2; 40 °C; 15 h		96	150
2		**C6** (no catalyst loading stated); CH_2Cl_2; 40 °C		71	151
3		**C3** (25 mol%); CH_2Cl_2; 40 °C; 24 h; then add second portion of **C3** (25 mol%); 40 °C; 24 h		73	152
4		**C3** (10 mol%); CH_2Cl_2 (0.01 M); 20 °C; 15 h		86	153

unconstrained substrates, first-generation catalysts might also give satisfactory results. Some representative examples are listed in Table 8.

5.29.3.2.2.4 α,β-Unsaturated five-membered lactams

Ring-closing metathesis of acrylamides is associated with similar problems as RCM of acrylates (Table 9). To obtain good yields of unsaturated γ-lactams, normally high amounts of first-generation catalysts (entry 1), or moderate loadings of second-generation catalysts are required. Initial substrate concentrations normally do not exceed 0.1 M. For the example shown in entry 2, microwave irradiation and standard oil bath heating were compared. The researchers found that microwave irradiation reduces the reaction time to 30 min, compared with the 20 h taken under conventional heating conditions.

Table 8 Synthesis of five-membered cyclic enamides through RCM

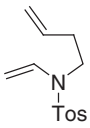
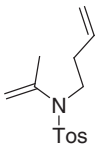
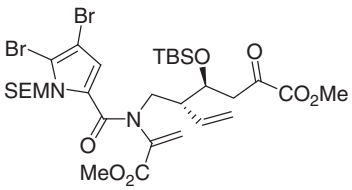
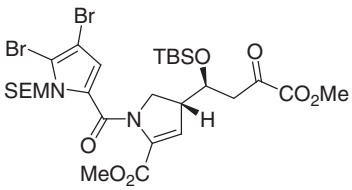
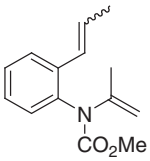
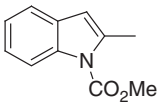
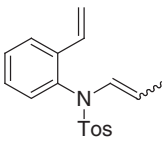
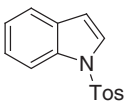
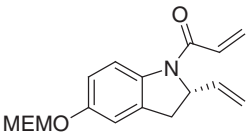
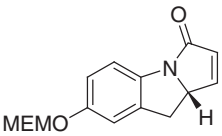
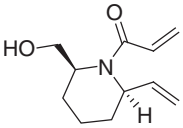
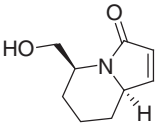
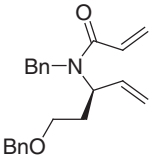
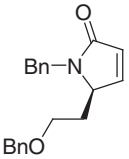
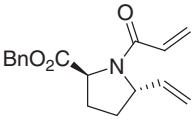
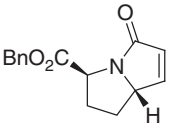
Entry	*Precursor*	*Conditions*	*RCM product*	*Yield (%)*	*References*
1		**C3** (5 mol%); CH_2Cl_2 (0.016 M); 20 °C; 16 h		84	154
2		**C3** (5 mol%); CH_2Cl_2 (0.016 M); 40 °C; 2 h		59	154
3		**C8** (5 mol%); $ClCH_2CH_2Cl$ (0.016 M); 84 °C; 2 h		86	
4		**C6** (5 mol%); CH_2Cl_2 (0.1 M); 40 °C; 48 h		80	155
5		**C6** (6 mol%); toluene; 110 °C; 4 h		85	156
6		**C6** (5 mol%); toluene (0.0125 M); 80 °C; 1 h		94	157

Table 9 Synthesis of γ-lactams through RCM

Entry	*Precursor*	*Conditions*	*γ-Lactam*	*Yield (%)*	*References*
1		**C3** (25 mol%); CH_2Cl_2; 40 °C; 48 h		75	158
2		**C6** (4.4 mol%); toluene (0.03 M); μ-wave irradiation at 180 °C for 0.5 h		72	159
3		**C6** (5 mol%); CH_2Cl_2 (0.01 M); 40 °C; 12 h		90	160
4		**C6** (10 mol%); toluene (0.1 M); 70 °C; 18 h		55	161

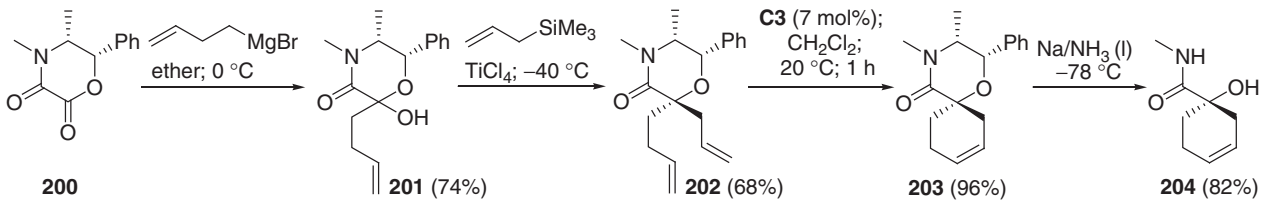
5.29.4 Six-Membered Ring Systems

5.29.4.1 Six-Membered Carbocycles

To a certain extent the methods used for the synthesis of RCM precursors for functionalized cyclohexenes resemble those for five-membered carbocycles. Therefore, they will not be covered in the same depths as in Section 5.29.3.1, but representative examples will be discussed to illustrate how the methods can be adapted to access RCM precursors for functionalized cyclohexenes.

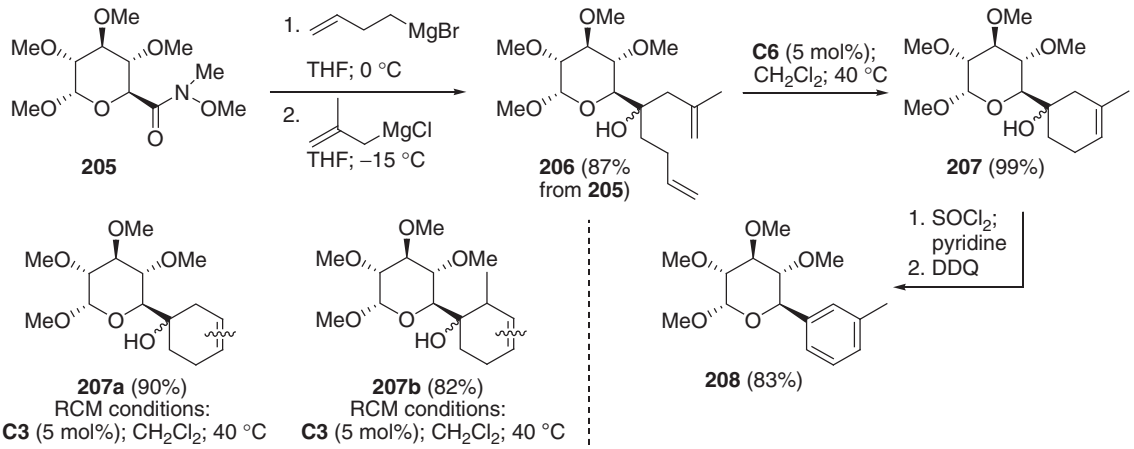
5.29.4.1.1 Synthesis of precursors by the addition of organometallics to carbonyl compounds

One approach to cyclohexene precursors involves the sequential addition of two different organometallics to a carboxylic acid derivative. Useful chemo- and stereoselectivities can, for instance, be achieved with the cyclic ephedrine derivative **200** (Scheme 45).[162] En route to the quinic acid precursor **204**, the morpholine derivative **200** was first treated with butenyl magnesium bromide, followed by a highly diastereoselective Lewis-acid mediated allylation of hemiacetal **201** with allyltrimethylsilane. RCM of diene **202** was fast with the first-generation catalyst **C3** at an ambient temperature and provided spirocycle **203** in nearly quantitative yields. Reduction with Na in liquid ammonia furnished **204**, which was further elaborated to quinic acid.



Scheme 45 Sequential butenylation/allylation for the synthesis of cyclohexene precursors.

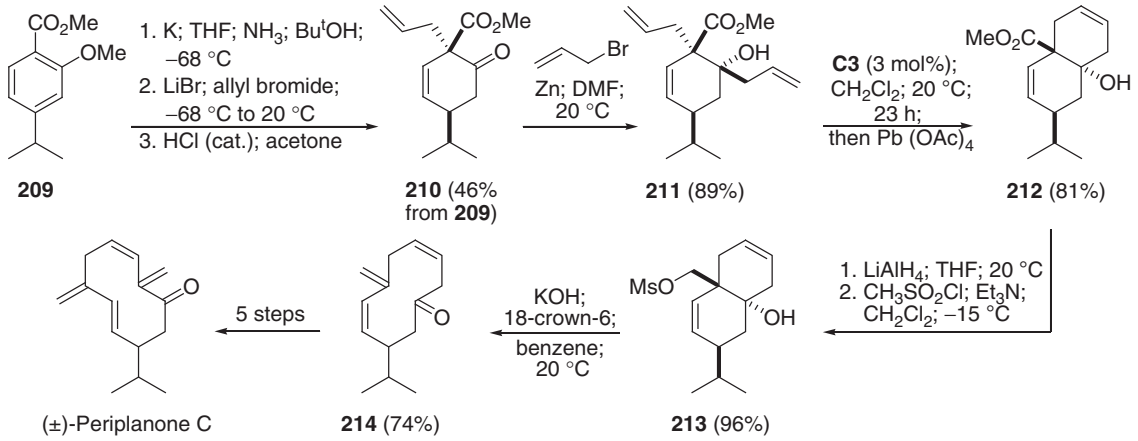
Weinreb amides also allow the selective sequential addition of two different organometallic reagents. This has been used for the synthesis of cyclohexenols, which were then converted to substituted benzenes by elimination and oxidation (Scheme 46).[163] The sequence is illustrated for the synthesis of a *C*-aryl glycoside **208**: starting from Weinreb amide **205**; a butenyl and a 2-methylpropenyl Grignard reagent are successively added to give the RCM precursor **206**. For the RCM of **206**, comprising one geminally disubstituted double bond, the second-generation catalyst **C6** was used. Cyclohexenol **207** was obtained in nearly quantitative yields. It underwent aromatization by elimination, followed by oxidation with DDQ to give *C*-aryl glycoside **208**. For the RCM reactions leading to **207a** and **207b**, which did not involve the construction of a trisubstituted double bond, the less active catalyst **C3** gave good yields under otherwise identical conditions.



Scheme 46 From Weinreb amides to benzenes via RCM and elimination/oxidation.

An alternative strategy toward cyclohexene precursors involves sequential trapping of an enolate with an allyl electrophile, followed by addition of an allyl nucleophile to the adjacent carbonyl group. This tactic is illustrated by the first steps of a synthesis of periplanone C (Scheme 47).[164] Interestingly, in this example the RCM is used to set the stage for a ring enlargement, giving access to a ring size that is normally difficult to obtain in a stereoselective manner.

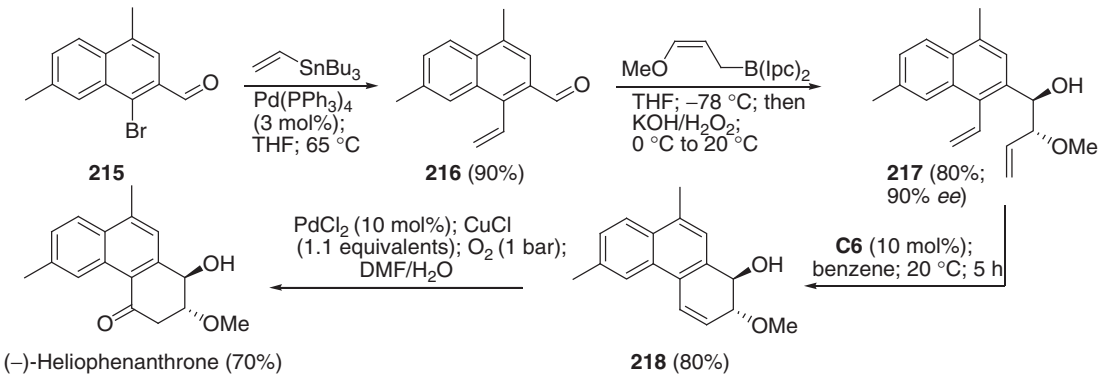
The sequence starts with a stereoselective Birch-reduction/allylation of the substituted benzene **209**, which proceeds with a *dr* of 7:1. An allyl zinc reagent is added to the resulting ketone **210** to give the RCM precursor **211** as a single diastereomer. RCM was



Scheme 47 From benzenes to decaline derivatives through Birch reduction and RCM.

accomplished in a good yield using a moderate amount of **C3** at ambient temperatures. To facilitate chromatographic purification of cyclohexene **212**, Ru-residues were oxidized with $Pb(OAc)_4$ after the RCM had been completed.[165] Reduction of the ester and conversion of the primary alcohol into the mesylate set the stage for the base-induced fragmentation of **213** to the 10-membered cyclic ketone **214**. From **214**, the synthesis of (±)-periplanone C was completed in five further steps.

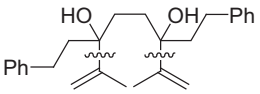
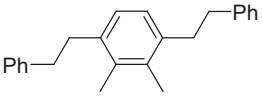
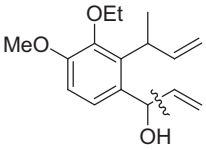
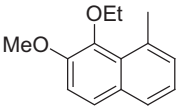
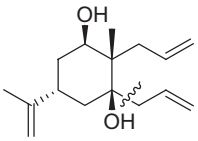
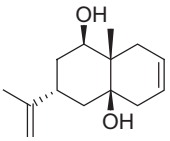
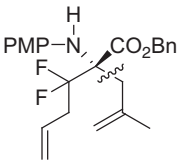
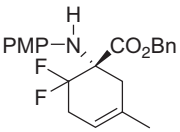
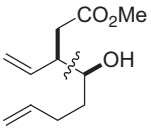
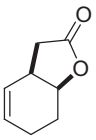
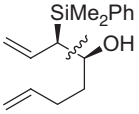
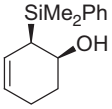
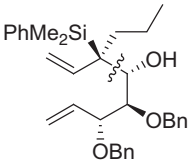
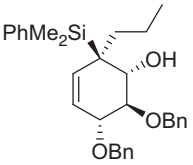
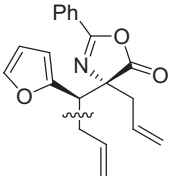
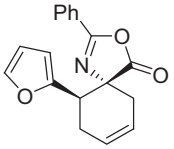
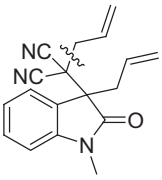
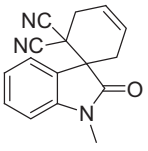
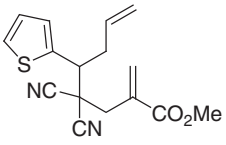
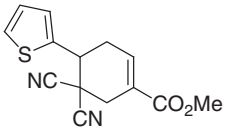
Apart from polar allyl metal compounds, allyl boron, allyl tin, and allyl silicon compounds were found to be particularly useful for constructing RCM precursors. A recent example is the protecting group-free synthesis of the plant constituent (–)-heliophenanthrone (Scheme 48).[166] Starting from naphthalene **215**, the first C–C double bond was introduced via Stille coupling, followed by a highly diastereoselective and enantioselective allylboration to give the RCM precursor **217** in 80% yield. RCM was accomplished using a surprisingly high loading of catalyst **C6**. The resulting cyclohexene **218** was then converted in one step to the target molecule via a regioselective Wacker oxidation.



Scheme 48 Synthesis of (–)-heliophenanthrone.

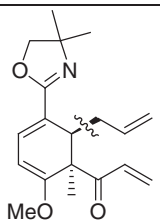
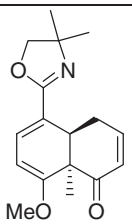
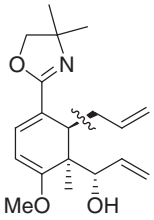
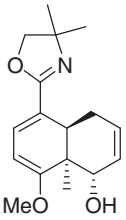
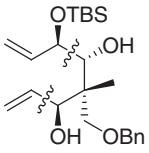
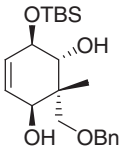
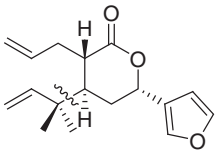
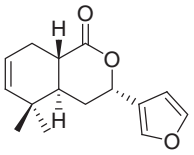
Some additional examples for the RCM of functionalized 1,7-octadienes, which were synthesized from carbonyl compounds through the addition of organometallics and enolate alkylation, are listed in Table 10. The authors wish to comment only on a few examples. The *in situ* RCM-aromatization listed in entry 1 is hampered because the formation of a tetrasubstituted double bond through RCM is a notoriously difficult process. No conversion was observed with precatalysts **C6** or **C10**, and the necessity to use excessively high catalyst loadings of Schrock's catalyst (**C1**) might be attributed to its sensitivity toward protic functional groups. For the example listed in entry 5, the RCM precursor was synthesized *in situ* via allylboration of pent-4-enal, and the allyl boronate was in turn generated *in situ* via a Pd-catalyzed borylation with bis-(pinacolato)diborane (B_2pin_2). The entire sequence, including the RCM step, was conducted in one flask in the presence of dimethyl sulfoxide (DMSO) and methanol, which might explain the unconventional choice of catalyst. The two examples shown in entries 6 and 7 illustrate how steric congestion both at the reacting double bonds, and also at the adjacent positions can lead to a decreased reactivity, necessitating higher catalyst loadings and prolonged reaction times. In the example listed in entry 11, RCM proceeded with unsatisfactory yields even if a second-generation catalyst **C9** was used, due to the presence of an electron-deficient double bond. This problem could be overcome by reducing the ketone, and subjecting the secondary alcohol shown in entry 12 to RCM. In this case, **C3** was sufficiently reactive to promote cyclization to cyclohexene in very good yield.

Table 10 RCM of α,ω-dienes obtained via addition reactions to carbonyl compounds[a]

Entry	Precursor	Conditions	Product	Yield (%)	References
1[b,c]		**C1** (2 × 20 mol%); C_6H_6; 80 °C; 60 h; then add *p*-TSA; 80 °C		66	167
2[b]		**C3** (5 mol%); CH_2Cl_2; 20 °C; 2 h; then add SiO_2; 20 °C; 12 h		89	168
3		**C3** (5 mol%); C_6H_6; 80 °C		94	169
4[d]		**C6** (5–15 mol%); CH_2Cl_2 (0.02 M); 40 °C		95	170
5[e]		**C10** (5 mol%); DMSO/MeOH/H_2O-mixture; 50 °C; 20 h		68	171
6		**C6** (5 mol%); CH_2Cl_2; 40 °C; 1 h		94	172
7		**C6** (10 mol%); toluene; 80 °C; 3 days		88	172
8		**C3** (5 mol%); CH_2Cl_2; 40 °C; 5–8 h		92	173
9		**C6** (5 mol%); CH_2Cl_2; 20 °C; 2 h		90	174
10		**C6** (5 mol%); CH_2Cl_2; 20 °C; 16 h		72	175

(*Continued*)

Table 10 Continued

Entry	Precursor	Conditions	Product	Yield (%)	References
11		**C9** (5 mol%); toluene; 80 °C; 24 h		48	176
12		**C3** (10 mol%); CH_2Cl_2; 40 °C; 14 h		87	176
13		**C6** (3 mol%); C_6H_6; 70 °C; 0.75 h		83	177
14		**C3** (1.7 mol%); CH_2Cl_2; 25 °C; 16 h		97	178

[a]Bonds formed through the addition of organometallics to carbonyl groups are marked with wavy lines.
[b]Dehydration was conducted *in situ* without isolation of the RCM product.
[c]No conversion was observed with **C6** or **C10**.
[d]PMP = 4-methoxyphenyl.
[e]RCM precursor obtained *in situ* from pent-4-enal through allylboration with an *in-situ* generated boronate.

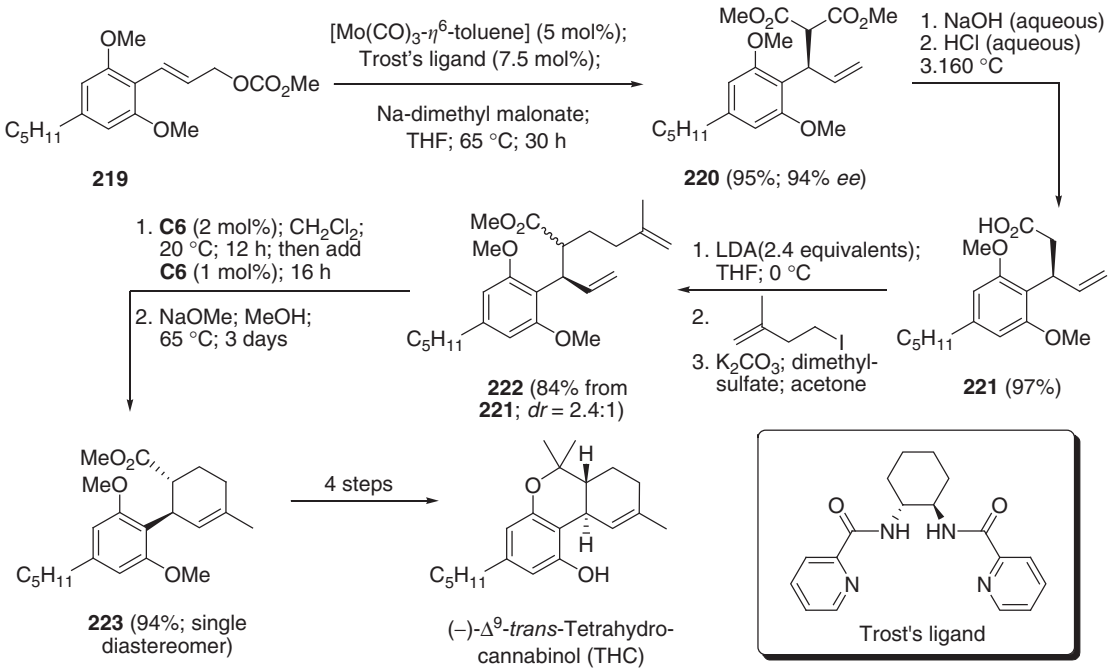
5.29.4.1.2 Synthesis of precursors by α-functionalization of carbonyl compounds

As described for the synthesis of cyclopentene precursors in Section 5.29.3.1.2, asymmetric transition metal-catalyzed enolate allylation has also emerged as a useful approach toward functionalized 1,7-octadienes, which can be subsequently cyclized to functionalized cyclohexenes. One example to illustrate this strategy is Trost's tetrahydrocannabinol synthesis (Scheme 49),[179] which relies on an Mo-catalyzed allylation of Na-malonate leading to the terminal alkene **220** with high regio- and enantioselectivities. Compound **220** was converted to acid **221** by saponification and decarboxylation. Alkylation of the enolate obtained from **221** with 4-iodo-2-methylbut-1-ene, followed by esterification, gave the RCM precursor **222** in good yields as a mixture of diastereomers. The mixture was subjected to RCM using 2 mol% of **C6** in dichloromethane at 20 °C, but the conversion was found to be incomplete and therefore an additional 1 mol% portion of **C6** was added. After base-mediated epimerization, the *trans*-configured cyclohexene **223** was isolated, which was then converted in four further steps to the target molecule, *trans*-tetrahydrocannabinol.

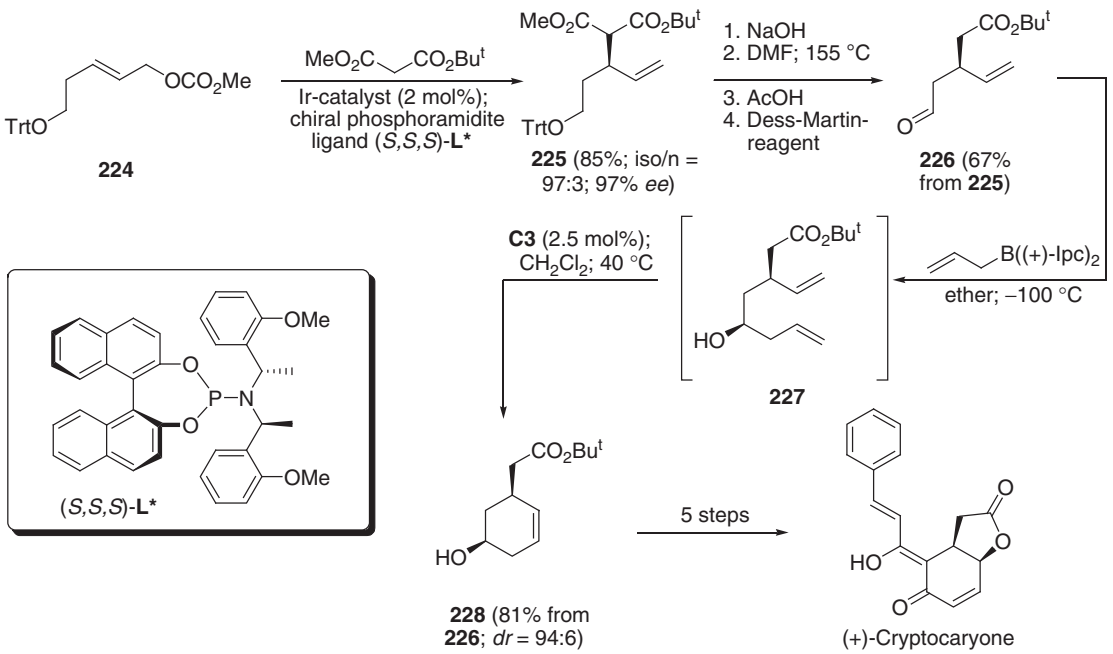
The combination of Ir-precatalysts and chiral phosphoramidite ligands is also very useful for the regio- and enantioselective synthesis of branched allylic substitution products, as illustrated by Helmchen's synthesis of the natural product (+)-cryptocaryone (Scheme 50).[180] The substitution product **225** was converted into aldehyde **226** in four steps, and the second alkene moiety was introduced via Brown allylboration. Diene **227** was then subjected to RCM without complete removal of the byproducts from the previous step. Nevertheless, cyclization proceeded smoothly with a moderate catalyst loading of **C3** to furnish the *cis*-configured cyclohexene **228** in good yield, which was elaborated in five steps into the target molecule.

5.29.4.1.3 Synthesis of precursors involving Claisen rearrangement

The Claisen rearrangement and its variants have already been discussed in some detail in Section 5.29.3.1.3 as a method for the synthesis of cyclopentene RCM precursors. Therefore, only two examples will be discussed in this section to illustrate how synthetic strategies based on Claisen rearrangements can be adapted to obtain cyclohexene precursors. The first example is a total



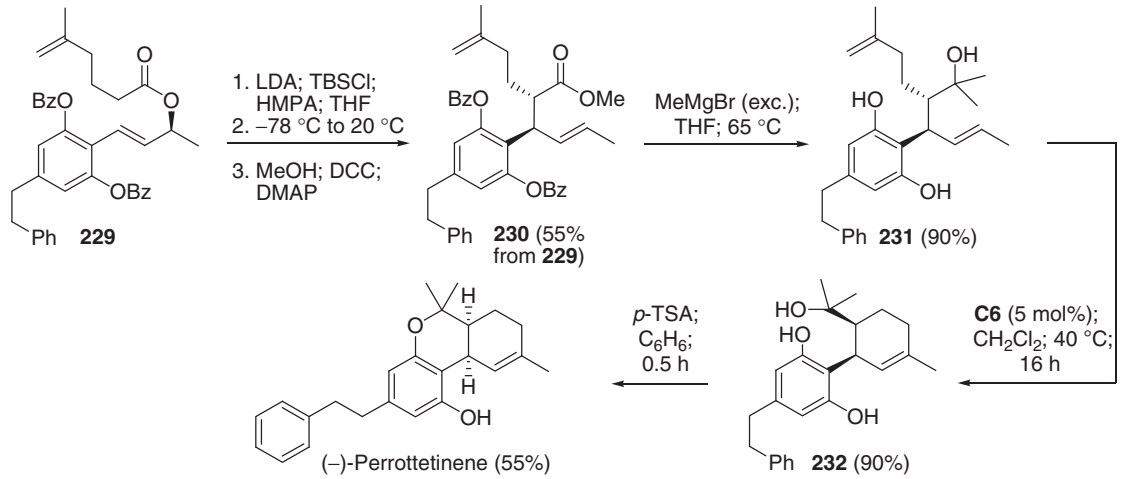
Scheme 49 Trost's tetrahydrocannabinol synthesis via Mo-catalyzed allylation/RCM.



Scheme 50 Helmchen's (+)-cryptocaryone synthesis via Ir-catalyzed allylation/RCM.

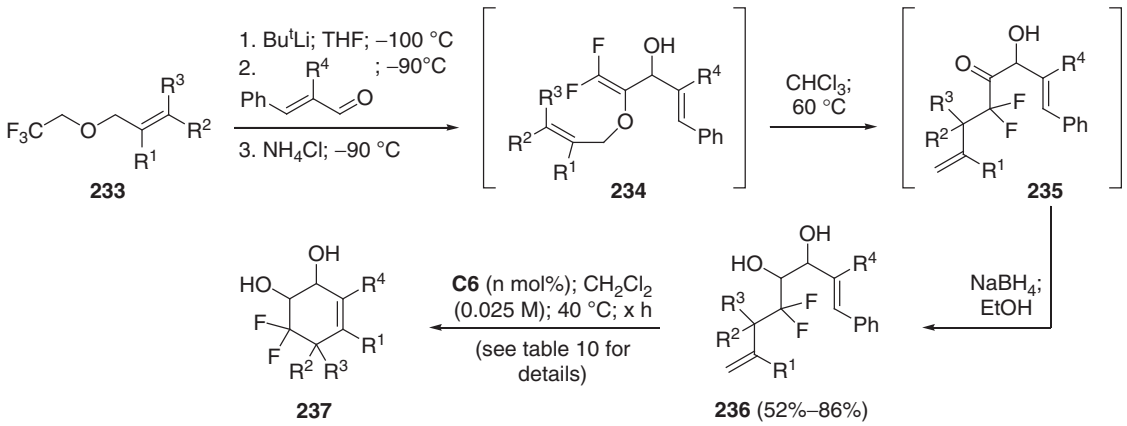
synthesis of the natural product (–)-perrottetinene, which relies on the combination of an Ireland–Claisen rearrangement of ester **229** and an RCM reaction as the key steps (Scheme 51).[181]

Before RCM, the Ireland–Claisen rearrangement product **230** was treated with excess MeMgBr to convert the methyl ester into the tertiary alcohol, and to cleave the benzoate groups. The RCM precursor **231** then underwent cyclization smoothly with 5 mol% of **C6** to give cyclohexene **232** in high yields. From **232**, the target molecule was obtained in one step by acid-catalyzed dehydration. The researchers point out that catalyst inhibition by coordination of the phenol to the Ru-center, a complication which has been observed for CM reactions of ortho-hydroxy styrenes,[182] is apparently not a problem in this case. The second



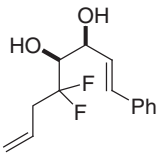
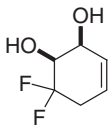
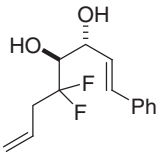
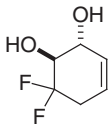
Scheme 51 Total synthesis of (–)-perrottetinene through Ireland–Claisen rearrangement/RCM.

example to be discussed in some detail is a concise route to difluorinated, polysubstituted cyclohexenes based on Claisen rearrangement and RCM (Scheme 52 and Table 11).[183] A set of precursors **233** was converted by metallation and addition of α,β-unsaturated aldehydes into *gem*-difluorinated enol ethers **234**, which underwent Claisen rearrangement to ketones **235** on heating. These were reduced to a set of RCM precursors **236** with a *vic*-diol structure. The RCM reactions were accomplished with the second-generation catalyst **C6** in refluxing dichloromethane. The researchers found that in all examples the initial substrate concentration should not exceed 0.025 M, because otherwise significant amounts of byproducts were formed.



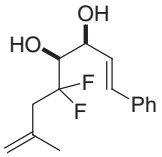
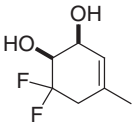
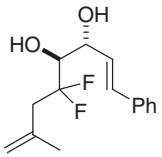
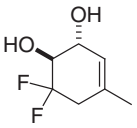
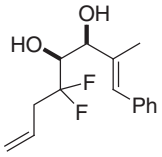
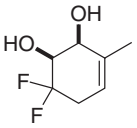
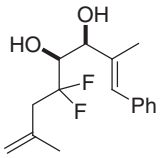
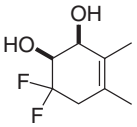
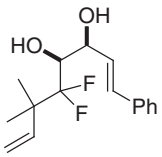
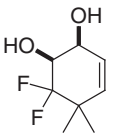
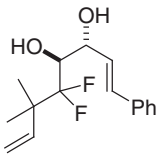
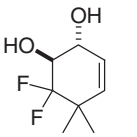
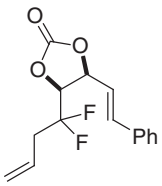
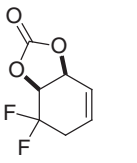
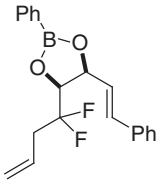
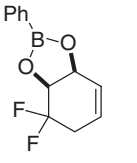
Scheme 52 RCM precursors via metallation/Claisen rearrangement of fluorinated ethers.

Table 11 RCM of dienes **236** to cyclohexenes **237**[a,183]

Entry	*Precursor*	*Product*	*Catalyst loading*	*Reaction time (h)*[b]	*Yield (%)*
1			0.5 mol%	0.75	76[c]
2			0.5 mol%	0.75	81

(*Continued*)

Table 11 Continued

Entry	*Precursor*	*Product*	*Catalyst loading*	*Reaction time (h)*[b]	*Yield (%)*
3			4 mol%	30	79
4			5 mol%	48	90
5			2.5 mol%	48	77
6			8.5 mol%	48	81
7			5 mol%	5	83
8			5 mol%	18	80
9			5 mol%	39	56[d]
10			5 mol%	3	43[e]

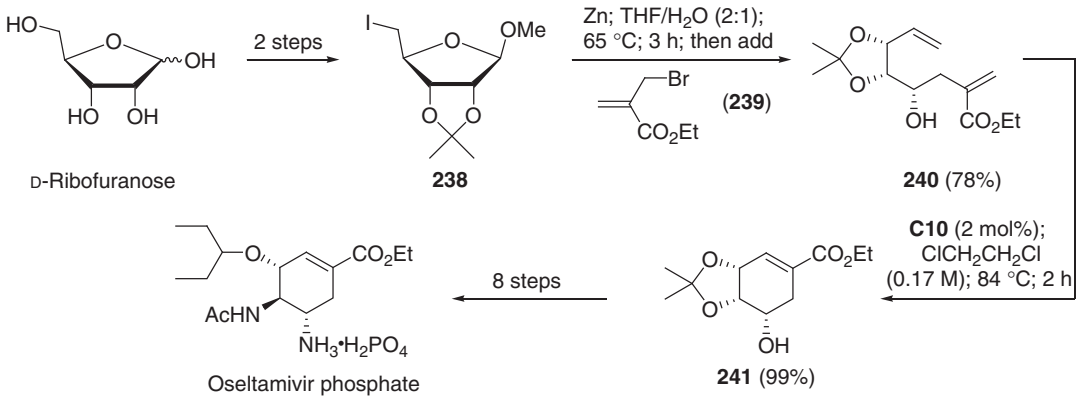
[a]General conditions (see **scheme 52**): **C6**; CH_2Cl_2 (0.025 M); 40 °C.
[b]Time for 100% conversion of diene **236**.
[c]Product obtained in 4 g-quantities.
[d]Conversion of starting material remained incomplete.
[e]Full conversion of starting material.

The RCM reactions of precursors **236** were studied in considerable detail and valuable information on the interconnection of catalyst loading, reaction time, and steric constraints could be gathered. Representative examples from this study and the experimentally determined minimum catalyst loadings and reaction times are summarized in Table 11.[183] For the sterically less constrained epimeric dienes in entries 1 and 2, full conversion was observed in short reaction times at a remarkably low catalyst

loading of 0.5 mol%. The researchers report that reducing the catalyst loading further to 0.25 mol% is possible, but only at the expense of dramatically increasing reaction times. In those cases leading to cyclohexenes with trisubstituted double bonds, catalyst loadings in the range of 2.5–5 mol% are equired, and reaction times are between 1 and 2 days. Particularly challenging are RCM reactions resulting in the construction of tetrasubstituted double bonds, as illustrated by the example in entry 6. Not surprisingly, this example requires a comparatively high catalyst loading and a prolonged reaction time. The two examples listed in entries 7 and 8 suggest that an expected rate acceleration by the *gem*-dimethyl effect is probably outweighed by additional steric hindrance, as these substrates require significantly higher catalyst loadings and longer reaction times compared with the examples in entries 1 and 2. Similarly, incorporating the two OH-groups in an annellated five-membered ring leads to a strongly decreased cyclization rate, which has been rationalized by the buildup of ring strain in the RCM step. Remarkable in these examples is the persistence of the catalytic activity over comparatively long periods of time. This has been attributed to the terminal phenyl substituent in the starting dienes, which will result in the regeneration of a more stable Ru-benzylidene species, rather than a Ru-methylidene species, after each catalytic cyle.

5.29.4.1.4 Synthesis of precursors from 'chiral pool'-starting materials

As for the stereoselective synthesis of cyclopentene precursors, starting materials from the chiral pool are also very important for accessing α,ω-octadienes. Once again α-hydroxy acids, α-amino acids, and carbohydrates have been extensively used for this purpose. One example to illustrate the use of carbohydrates is a formal total synthesis of the drug oseltamivir phosphate (Tamiflu™) from D-ribose (Scheme 53).[184] First, D-ribose was converted into iodide **238**, which underwent Zn-mediated reductive fragmentation to a substituted pent-4-enal. Addition of the allyl-Zn-reagent generated *in situ* from **239** proceeded in a *dr* of 5:1 to provide **240** in 78% yield after separation from the minor epimer. RCM of **240** to cyclohexene **241** went to completion within just 2 h in the presence of a comparatively small amount of the Grubbs–Hoveyda catalyst **C10** in refluxing dichloroethane. From the RCM product **241** the antiinfluenza drug oseltamivir phosphate is available in eight steps.



Scheme 53 Formal RCM-based total synthesis of oseltamivir phosphate from D-ribose.

An alternative approach to the same target molecule starts from L-serine (Scheme 54),[185] which was converted in several known steps to **242**. Swern oxidation, followed by moderately diastereoselective addition of vinyl magnesium bromide ($dr = 5:1$) furnished the RCM precursor **243**. The first-generation catalyst **C3** was sufficiently active for the formation of cyclohexenol **244** with a trisubstituted double bond, even though a rather large amount of catalyst was used. Remarkably, after MOM protection of the secondary alcohol, precursor **245** required the more active second-generation catalyst **C6** to obtain the desired cyclohexene **246** in synthetically useful yields. Further examples for the utilization of ex-chiral pool compounds for the RCM-based synthesis of functionalized cyclohexenes are summarized in Table 12.

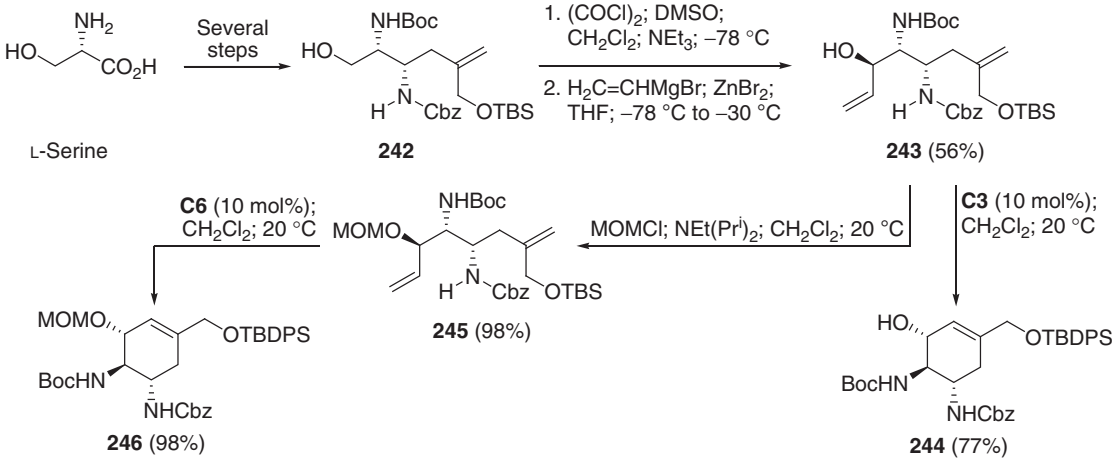
5.29.4.2 Six-Membered Heterocycles

5.29.4.2.1 Six-membered oxacycles

As for the synthesis of five-membered oxacycles in Section 5.29.3.2.1, reactions leading to dihydropyrans with only one substituent α to the ether oxygen (general structure **248**) will be discussed first, and then transformations yielding α,α'-disubstituted dihydropyrans, followed by examples for the synthesis of six-membered cyclic enol ethers. Finally, the formation of α,β-unsaturated δ-lactones through RCM will be discussed.

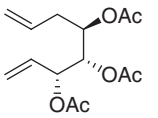
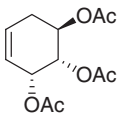
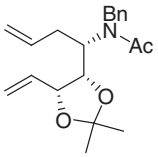
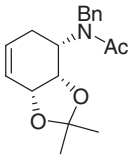
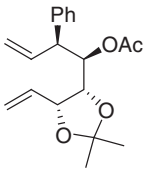
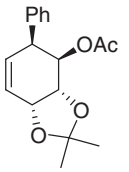
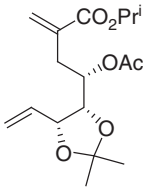
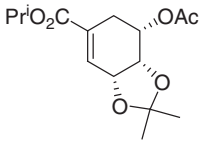
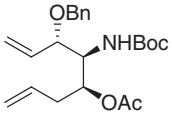
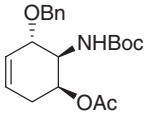
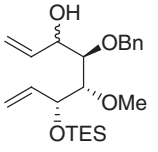
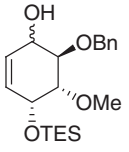
5.29.4.2.1.1 α-Substituted dihydropyrans

In most cases, RCM reactions leading to 2,3-disubstituted 3,6-dihydro-2*H*-pyrans (**248**), lacking a substituent at the 6-position, proceed smoothly with moderate catalyst loadings of first-generation catalysts at ambient or only slightly elevated temperatures. More active catalysts, higher catalyst loadings, and higher temperatures might be necessary if trisubstituted or even tetrasubstituted



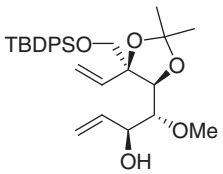
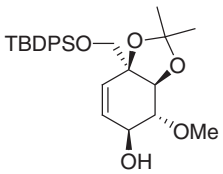
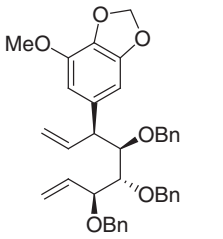
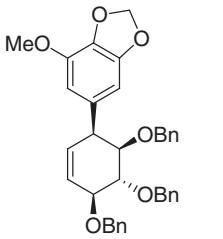
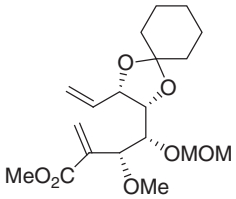
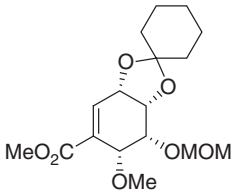
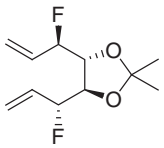
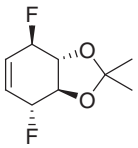
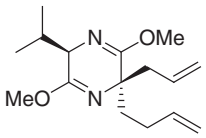
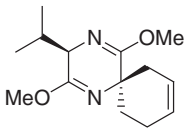
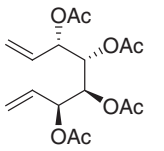
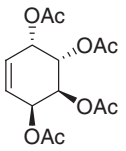
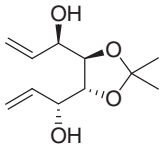
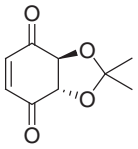
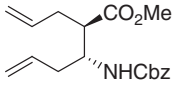
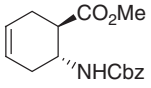
Scheme 54 Formal RCM-based total synthesis of oseltamivir phosphate from L-serine.

Table 12 Examples for the synthesis of cyclohexenes from chiral pool compounds via RCM

Entry	*Chiral pool compound*	*RCM precursor*	*RCM product*	*RCM conditions*	*Yield (%)*	*References*
1	D-mannose			**C3** (5 mol%); CH_2Cl_2; 20 °C	98	107
2	D-ribose			**C3** (10 mol%); CH_2Cl_2; 20 °C	94	107
3	D-ribose			**C6** (5 mol%); CH_2Cl_2; 40 °C	95	107
4	D-ribose			**C6** (10 mol%); CH_2Cl_2; 40 °C	56[a]	107
5	D-mannitol			**C6** (5 mol%); CH_2Cl_2; 20 °C	95	186
6	D-ribose			**C3** (10 mol%); CH_2Cl_2; 20 °C; 2 h	98	187

(*Continued*)

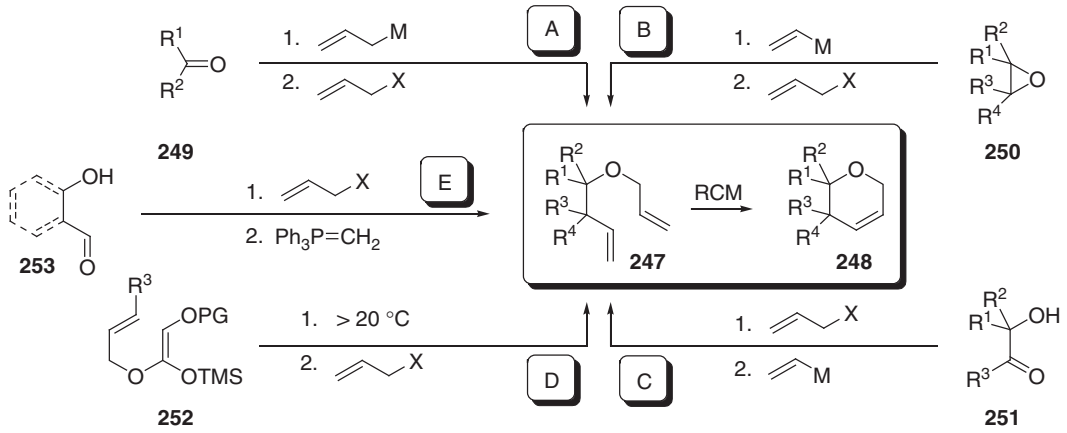
Table 12 Continued

Entry	*Chiral pool compound*	*RCM precursor*	*RCM product*	*RCM conditions*	*Yield (%)*	*References*
7	D-mannose			**C6** (1.2 mol%); toluene (0.13 M); 80 °C; 1.5 h	94[b]	188
8	D-xylose			**C3** (3.8 mol%); CH_2Cl_2; 20 °C	96	189
9	D-ribose			**C10** (7 mol%); toluene; 110 °C; 18 h	86	190
10	D-mannitol			**C6** (5 mol%); CH_2Cl_2; 40 °C; 3 h	70	191
11	glycine; L-valine			**C3** (2 mol%); C_6H_6; 60 °C; 5 h	95	85
12	L-tartrate			**C6** (7.5 mol%); CH_2Cl_2; 40 °C	96[c]	192
13	D-tartrate			**C6** (2 mol%); CH_2Cl_2; 40 °C; 2 h; DMP; 0 °C	82[d]	193
14	*R*-allyl glycine			**C3** (5 mol%); CH_2Cl_2; 40 °C	96	194

[a]32% of starting materials were recovered.
[b]RCM conducted on a 5.4 g scale.
[c]Low yields and significant decomposition were observed with the analogous tetrabenzoate or tetraol.
[d]After completion of the RCM, Dess–Martin periodinane was added to the mixture at 0 °C.

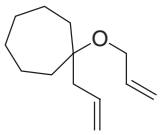
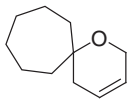
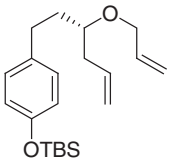
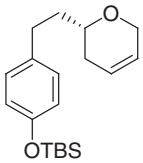
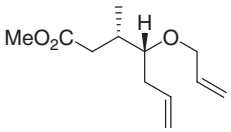
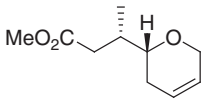
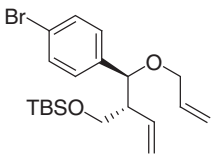
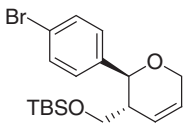
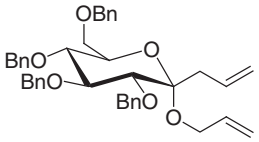
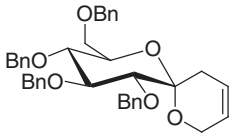
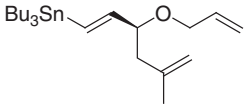
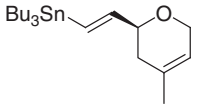
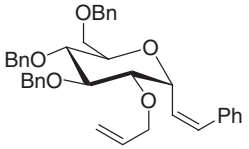
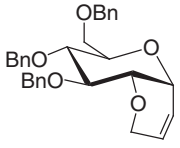
double bonds are formed in the RCM step. Some general routes to RCM precursors **247** are highlighted (Scheme 55) and representative examples for their RCM are summarized below (Table 13).

Probably the most common method for the synthesis of allyl homoallyl ethers **247** involves addition of allyl metal compounds to carbonyl compounds **249**, followed by Williamson ether synthesis of the resulting homoallylic alcohols



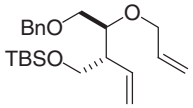
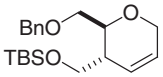
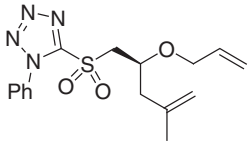
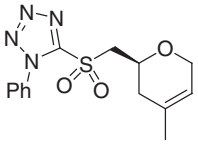
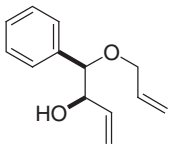
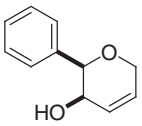
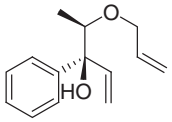
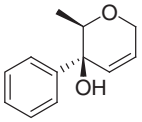
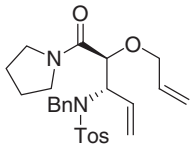
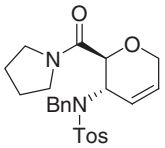
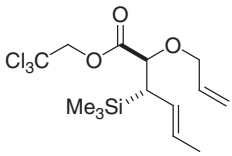
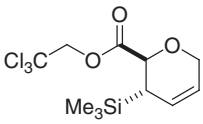
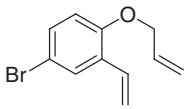
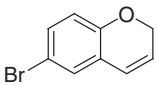
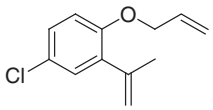
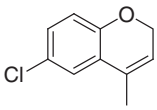
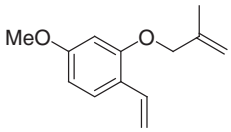
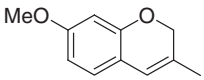
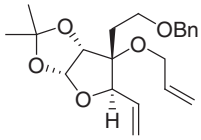
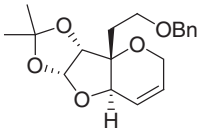
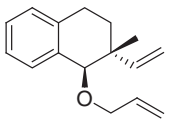
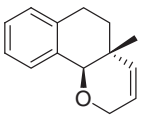
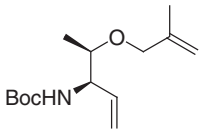
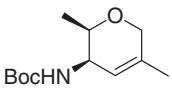
Scheme 55 General routes to dihydropyran precursors **247.**

Table 13 Synthesis of dihydropyrans via RCM (refer to **Scheme 55** for general routes)

Entry	*Route*	*RCM precursor*	*RCM product*	*RCM conditions*	*Yield (%)*	*References*
1	A			**C3** (2 mol%); CH_2Cl_2 (0.2 M); 20 °C; 0.5 h	90	201
2	A			**C3** (2.5 mol%); toluene (0.3 M); 80 °C; 2 h	86	196
3	A			**C3** (3 mol%); CH_2Cl_2; 20 °C; 2 h	96	208
4	A			**C3** (5 mol%); CH_2Cl_2; 20 °C; 8 h	91	209
5	A			**C3** (6 mol%); toluene; 60 °C	88	210
6	A			**C1** (15 mol%); toluene; 20 °C	81	197
7	B			**C3** (5 mol%); toluene; 50 °C	82	199

(*Continued*)

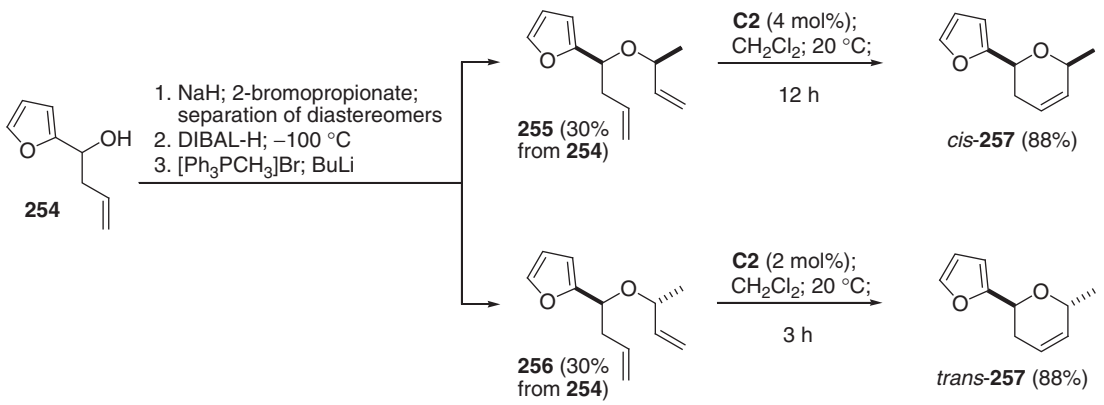
Table 13 Continued

Entry	Route	RCM precursor	RCM product	RCM conditions	Yield (%)	References
8	B			**C3** (3 mol%); CH_2Cl_2; 20 °C	97	198
9	B			**C6** (3 mol%); CH_2Cl_2 (0.015 M); 20 °C; 3 h	95	200
10	C			**C3** (5 mol%); CH_2Cl_2; 20 °C	69	201
11	C			**C3** (3 mol%); CH_2Cl_2; 20 °C	86	211
12	D			**C6** (10 mol%); CH_2Cl_2; 40 °C	81	204
13	D			**C3** (5 mol%); C_6H_6 (0.01 M); 80 °C; 1–3 h	68	205
14	E			**C3** (2 mol%); CH_2Cl_2 (0.2 M); 20 °C; 2 h	99	206
15	E			**C3** (2 mol%); CH_2Cl_2 (0.2 M); 20 °C; 2 h	94	206
16	E			**C3** (6 mol%); C_6H_6 (0.2 M); 60 °C; 2 h	93	206
17	E			**C3** (5 mol%); CH_2Cl_2; 20 °C	93	212
18	E			**C3** (7.6 mol%); CH_2Cl_2; 20 °C	77	213
19	E			**C6** (1 mol%); C_6H_6; 80 °C	>95	207

(route A).[195,196] One reason for the popularity of this approach is the availability of several reliable enantioselective allylation methods, such as Brown-allylboration (*see* Chapter 2.01) (entry 6)[197] or Leighton's allylation (*see* Chapter 2.02) (entry 2).[196] Alternatively, epoxides **250** are cleaved with appropriate vinyl metal compounds, again followed by allylation of the intermediate homoallylic alcohol (route B).[198] For the example listed in entry 7, a glycal epoxide was used as a starting material, which was cleaved with an acetylide, followed by Lindlar reduction and O-allylation to provide the RCM precursor.[199] In the case of entry 9, a laulimalide side chain precursor was obtained from enantiomerically pure glycidol by nucleophilic opening with a 2-propenyl cuprate. Notably, the tetrazole sulfone moiety does not interfere with the RCM reaction.[200] A third method starts from α-hydroxy carbonyl compounds **251**, which are first allylated and then treated with a vinyl metal compound (route C, entries 10, 11).[201] For this route the choice of the etherification method is often crucial, because α-hydroxycarbonyl compounds tend to undergo racemization or Wittig rearrangement to carbinols under the strongly basic conditions of a Williamson ether synthesis.[202] These problems can be circumvented by using either Ag_2O as a base in combination with allyl halides,[201] or by Pd-catalyzed allylation of aliphatic alcohols with allyl carbonates.[203] A less general but highly stereospecific and synthetically useful route to RCM precursors involves sigmatropic rearrangements, for example, of silyl ketene acetals such as **252**, followed by etherification of the resulting homoallyl alcohols (route D, entries 12,13).[204,205] A fifth class of precursor syntheses starts from β-hydroxy aldehydes or ketones and involves O-allylation followed by olefination of the carbonyl group (route E). This sequence has often been used for benzoannellated systems and therefore salicylic aldehydes **253** are common starting materials (entries 14–16),[206] but application of this route to the synthesis of aliphatic derivatives has also been described, for example, toward the *de-novo* synthesis of carbohydrates (entry 19).[207]

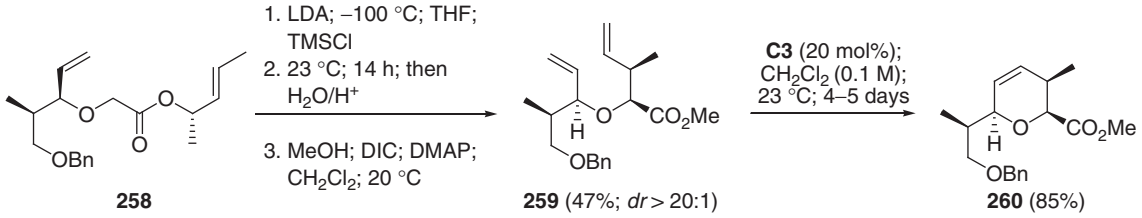
5.29.4.2.1.2 α,α′-Substituted dihydropyrans

The synthesis of 2,6-disubstituted dihydropyrans was initially hampered by a lack of synthetic methods to access the required precursors stereoselectively. An early approach starts with the etherification of homoallylic alcohols such as **254** with 2-bromopropionates (**Scheme 56**).[214] Separation of the diastereomeric esters, reduction to the aldehyde followed by Wittig olefination furnished the diastereomeric RCM precursors **255** and **256** separately. The reactivity in the subsequent RCM depends on the relative configuration; interestingly, the formation of *trans*-**257** occurs significantly faster and with a lower amount of catalyst than the formation of the *cis*-epimer.



Scheme 56 RCM-based approach to 2,6-disubstituted dihydropyrans.

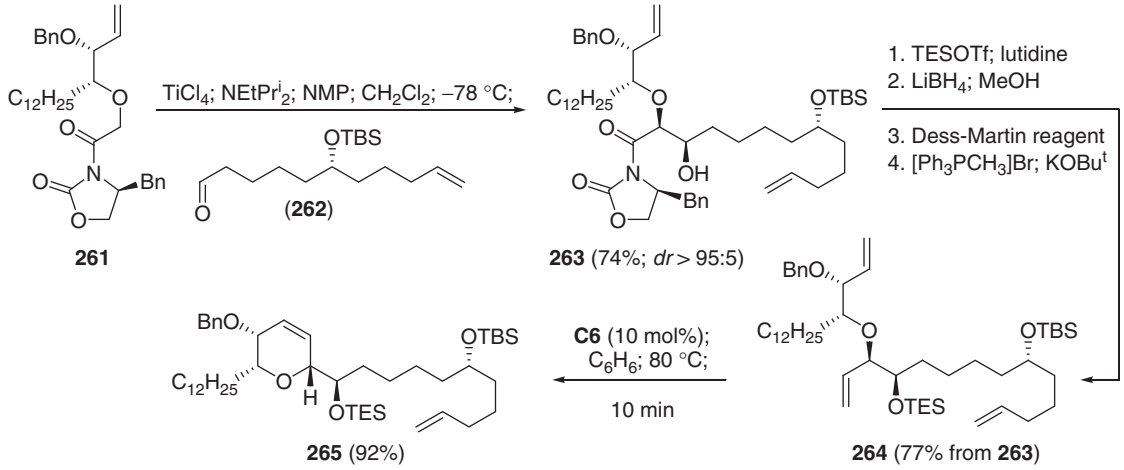
Shortly afterwards, Burke et al. described a diastereoselective approach to dihydropyrans based on a sequence of Ireland–Claisen rearrangement of glycolates and RCM (**Scheme 57**).[205] This example was published in 1998, shortly before the more active second-generation catalysts were discovered, and it illustrates how steric congestion leads to decreased reaction rates



Scheme 57 Synthesis of dihydropyrans via Ireland–Claisen rearrangement and RCM.

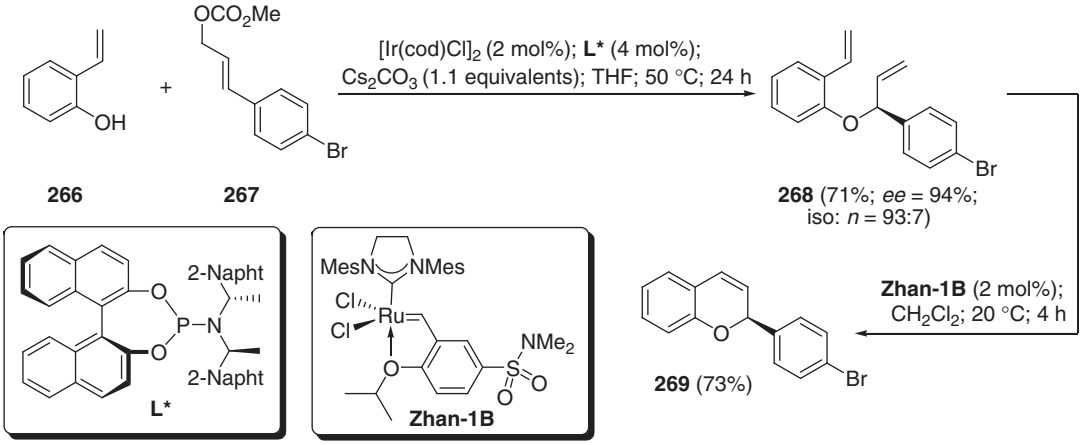
with first-generation catalysts, resulting in long reaction times (several days) and excessively high catalyst loadings of up to 20 mol%.

Another route, intensively investigated by Crimmins et al., also relies on glycolates as starting materials (Scheme 58).[215] For example, the synthesis of a fragment of the annonaceous acetogenin pyragonicin starts from glycolate **261**, which was reacted with aldehyde **262** to the aldol addition product **263** in high diastereoselectivity. Reductive removal of the oxazolidinone, followed by Dess–Martin oxidation and Wittig olefination, gave the RCM precursor **264**, which was cyclized within 10 min to dihydropyran **265** using the second-generation catalyst **C6**. A comparison with the example outlined in Scheme 57 underlines the significant improvement that can be achieved for the cyclization of highly substituted precursors if the more active second-generation catalysts are used.



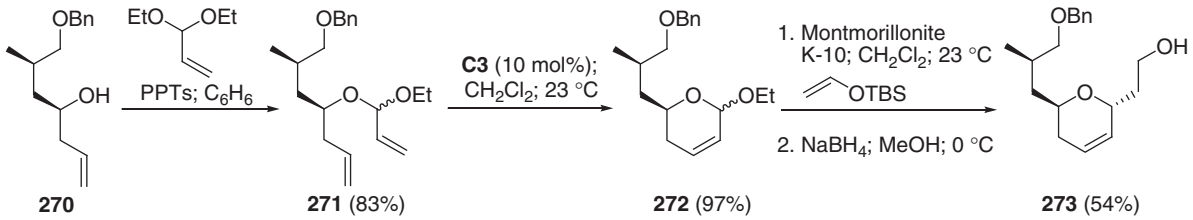
Scheme 58 Auxiliary controlled aldol addition of glycolates and RCM.

Transition metal catalyzed O-allylation reactions have also been used to access α,α′-disubstituted dihydropyrans stereoselectively. This is illustrated by an Ir-catalyzed regio- and enantioselective allylation of phenols such as **266**, which, in combination with RCM, furnishes 2-substituted chromenes **269** (Scheme 59).[216] In this example, the less common Zhan-1B catalyst has been used. It should be noted that chromenes with very similar substitution patterns had previously been obtained by others using 4 mol% of **C6**.[217]



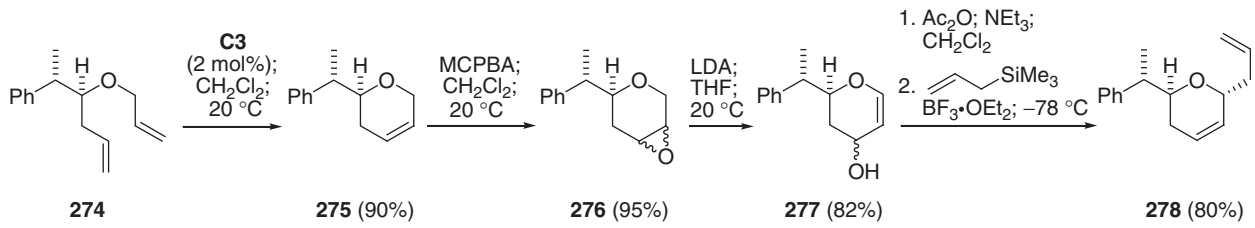
Scheme 59 Synthesis of chromenes via Ir-catalyzed allylation and RCM.

An alternative RCM-based approach to α,α′-disubstituted dihydropyrans relies on a subsequent introduction of one side chain. Via this strategy, it is possible to circumvent the stereoselective synthesis of acyclic precursors and exploit the normally more rigorous stereocontrol for substitution reactions of cyclic molecules. Such an approach has been pursued in Ghosh's total synthesis of laulimalide for the construction of the *trans*-configured 2,6-disubstituted dihydropyran fragment (Scheme 60).[218]



Scheme 60 Toward laulimalide via RCM and *trans*-selective nucleophilic substitution.

First, the homoallylic alcohol **270** was converted into a diastereomeric mixture of the mixed acrolein acetals **271** by treatment with acrolein diethyl acetal in the presence of acid. Alternatively, homoallylic alcohols can be reacted with methoxy allene in the presence of catalytic amounts of $Pd(OAc)_2$, as previously described by Rutjes et al., to give similar RCM precursors.[219] Dienes **271** underwent RCM in the presence of **C3** to yield a mixture of the epimeric cyclic acetals **272** in nearly quantitative yields. Under Lewis-acidic conditions, attack of the silyl enol ether occurs as expected from a pseudoaxial orientation, to provide – after reduction of the intermediate aldehyde – the *trans*-configured dihydropyran **273** as a single diastereomer. Alternatively, dihydropyrans such as **275**, lacking a substituent at the 6-position, have been epoxidized and subjected to a regioselective base-induced epoxide opening, giving cyclic enol ethers **277** with a hydroxy group at the 4-position. Converting the OH-group into a leaving group, and subjecting these derivatives *in situ* to the conditions of a carbon-Ferrier rearrangement gives access to *trans*-configured dihydropyrans such as **278** (Scheme 61).[201]



Scheme 61 RCM/epoxidation/base-induced rearrangement sequence.

5.29.4.2.1.3 Six-membered cyclic enol ethers

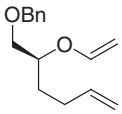
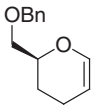
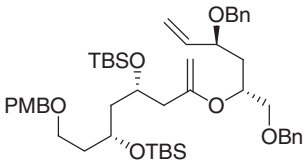
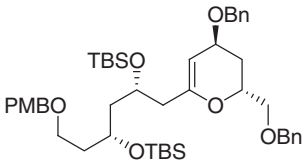
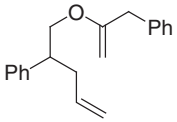
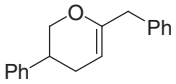
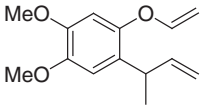
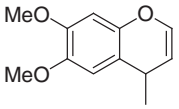
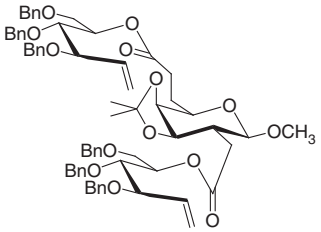
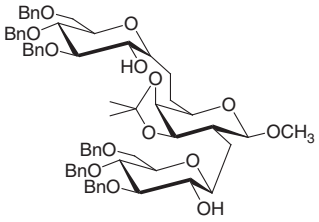
Similar to five-membered cyclic enol ethers, the formation of six-membered cyclic enol ethers is significantly slower compared with allyl ether metathesis. Consequently, more active catalysts, higher catalyst loadings, elevated temperatures, and comparatively low initial substrate concentrations are required. Table 14 provides an overview of some representative examples. As outlined for the example in entry 5, the precursors are often synthesized from esters using Tebbe or Takai-olefination reactions. First-generation catalysts, for example, **C3**, can be used only for sterically less congested substrates and are not suitable for the construction of cyclic enol ethers with trisubstituted double bonds.

5.29.4.2.1.4 α,β-Unsaturated six-membered lactones

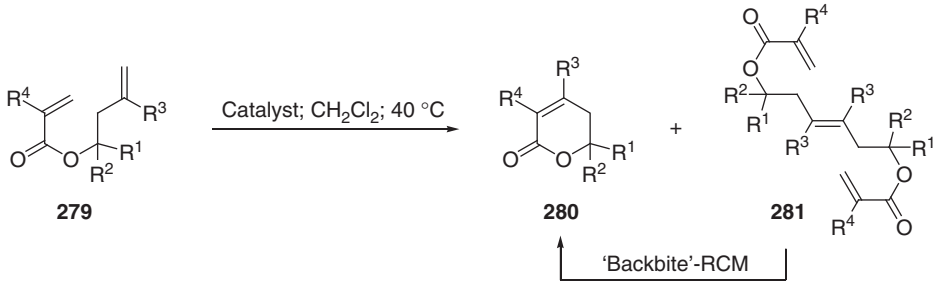
A fourth group of reactions to be discussed in this section is the RCM of acrylates derived from homoallylic alcohols, resulting in the formation of α,β-unsaturated δ-lactones. These transformations, like the RCM of allyl alcohol acrylates (Section 5.29.3.2.1), also suffer from a comparatively low reactivity of the electron-deficient double bond, resulting in the necessity to apply high catalyst loadings, more active catalysts or Lewis-acidic additives, and normally high dilution conditions. Owing to the ubiquitous occurrence of α,β-unsaturated δ-lactones as structural elements in various natural products, the RCM of homoallylic acrylates has nevertheless been intensively investigated and numerous examples have been published. A detailed study by D'Annibale et al.[137] revealed that in contrast to common preconceptions first-generation catalysts can promote this particular type of RCM in many cases, albeit at the expense of rather high catalyst loadings (Scheme 62). The researchers could prove by NMR-experiments that initiation occurs at the homoallylic double bond of precursors **279**, and that – in particular with first-generation catalysts **C3** and **C5** – substantial amounts of self-metathesis products **281** are formed along with the desired RCM products **280**. Notably, these dimers cyclize via a backbite mechanism (see Section 5.29.2 for a more general discussion) to lactones **280** on addition of the second-generation catalysts **C6** or **C10**. In some cases, a substituent R^1 or R^2 was found to facilitate the RCM, in particular if a tetrasubstituted double bond ($R^3 = R^4 = Me$) is formed in the metathesis step.

The RCM step used in the synthesis of (+)-cryptocarya diacetate is an example for a comparatively facile homoallylic acrylate RCM, as it proceeds efficiently with just 3 mol% of **C6** at a remarkably high initial substrate concentration of 0.3 M (Scheme 63).[224] The *syn*-1,3-diol motif found in the target structure was synthesized via a highly diastereoselective aldol addition of 'super-silyl'-protected enol ether **283** to aldehyde **282**, catalyzed by triflimide. Subsequent diastereoselective addition of allyl

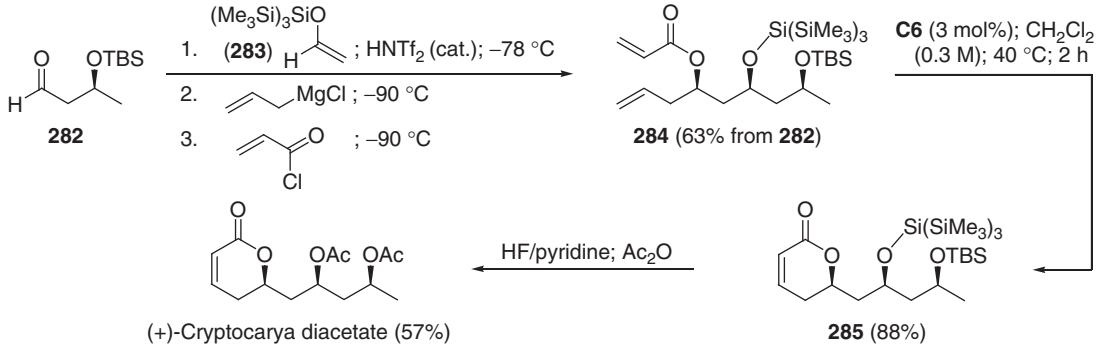
Table 14 Enol ether RCM for the synthesis of dihydropyrans

Entry	Precursor	RCM conditions	Dihydropyran	Yield (%)	References
1		**C3** (20 mol%); C_6H_6 (0.017 M); 80 °C; 0.5 h		69	126
2		**C6** (18 mol%); C_6H_6 (0.09 M); 45 °C; 2 h		81	220
3		**C1** (12 mol%); pentane; 20 °C; 3.5 h		84	221
4		**C6** (5 mol%); toluene; 20 °C		98	222
5[a]		1. $TiCl_4$; Zn; TMEDA; CH_2Br_2 2. **C6** (35 mol%); toluene; 60 °C 3. $BH_3 \cdot THF$; H_2O_2; NaOH		49	223

[a]Yield over three steps.



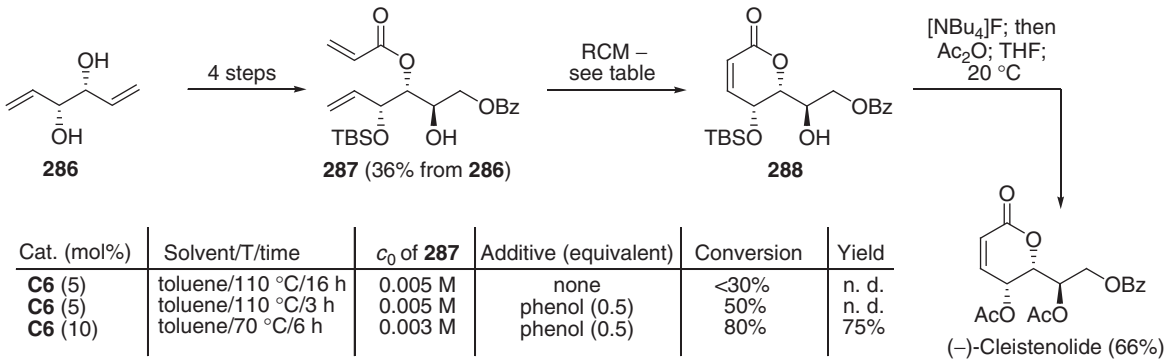
Scheme 62 RCM of homoallylic acrylates versus self-metathesis.



Scheme 63 Homoallylic acrylate RCM in the synthesis of cryptocarya diacetate.

magnesium chloride, followed by conversion of the intermediate homoallylic alcohol into the acrylate furnished the RCM precursor **284**. After RCM, both silyl groups in **285** were removed and the hydroxy groups acylated to give the target compound (+)-cryptocarya diacetate.

A synthesis of the natural product (–)-cleistenolide illustrates how sterically demanding substituents in the γ-position adversely influence the rate of the RCM step (**Scheme 64**).[225]



Cat. (mol%)	Solvent/T/time	c_0 of **287**	Additive (equivalent)	Conversion	Yield
C6 (5)	toluene/110 °C/16 h	0.005 M	none	<30%	n. d.
C6 (5)	toluene/110 °C/3 h	0.005 M	phenol (0.5)	50%	n. d.
C6 (10)	toluene/70 °C/6 h	0.003 M	phenol (0.5)	80%	75%

Scheme 64 Homoallylic acrylate RCM in the synthesis of (–)-cleistenolide.

In this example, the required homoallylic acrylate **287** was obtained from the C_2-symmetric mannitol-derived diene **286** in four steps, i.e., monosilylation, Sharpless epoxidation, acrylate formation, and epoxide opening with benzoic acid. For the RCM of **287** numerous conditions were tested, and a selection is highlighted in the table inserted in **Scheme 64**. With 5 mol% of the second-generation catalyst **C6**, the conversion remained unsatisfactory even after 16 h. Inspired by a literature report describing the beneficial effect of added phenol in CM reactions,[226] this option was tested next. The conversion improved significantly to 50% in a considerably shorter period of time. Eventually, the use of 10 mol% of **C6** in combination with added phenol at a very low initial substrate concentration of 0.003 M turned out to be the optimum, resulting in an isolated yield of 75%. The synthesis of cleistenolide was completed by a one-pot desilylation–acetylation reaction. A comparison with related examples reveals that the choice of γ-OH-protecting groups has a significant impact on the rate of the RCM step (**Table 15**). Unfortunately, a removal or exchange of protecting groups before the RCM is not always possible; for example, in the case of the cleistenolide synthesis discussed above, all attempts to cleave the TBS group in **287** resulted in an extensive scrambling of the acrylate group. As can be seen from entry 1, taken from a different synthesis of cleistenolide, a sterically less demanding *para*-methoxybenzyl (PMB)-protecting group allows the RCM to be performed with lower amounts of catalyst and at a higher substrate concentration. In many cases unprotected allylic hydroxy groups are tolerated (entry 2), although it should be noted that allyl alcohols are sometimes prone to irreversible double-bond migration to the corresponding ethyl ketones or fragmentation to methyl ketones under metathesis conditions.[77] The RCM listed in entry 3 is hampered not only by a sterically demanding TBSO-group in the allylic position, but also by the presence of a dithiane moiety. Nevertheless, a synthetically useful yield could be obtained with the phosphine-free catalyst **C10** under microwave irradiation. RCM of acrylates without any substituent in the allylic position (entries 7, 8) is normally facile with comparatively low loadings of second-generation catalysts or first-generation catalysts in combination with $Ti(OPr^i)_4$ as a Lewis-acidic additive, even if, as in entry 9, a trisubstituted double bond is formed.

5.29.4.2.2 Six-membered azacycles

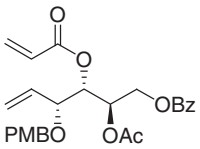
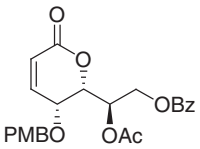
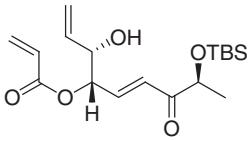
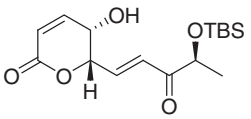
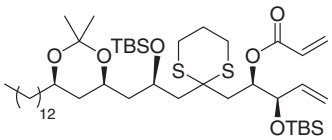
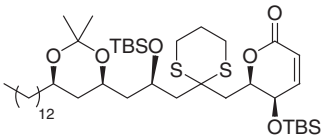
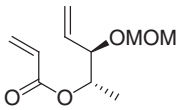
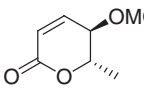
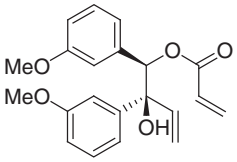
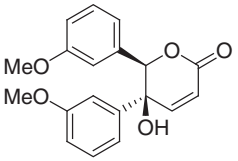
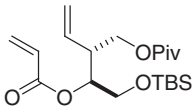
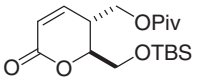
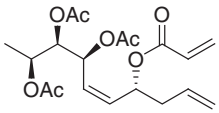
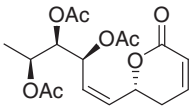
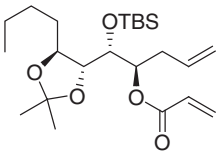
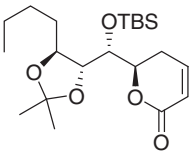
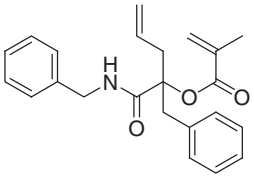
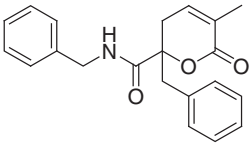
Six-membered azacycles are, together with six-membered oxacycles and their five-membered counterparts, the most important heterocycles accessible through RCM. Consequently, a plethora of examples have been described and only a representative selection can be shown here. Similar to the formation of five-membered azacycles, the donor capacity of the nitrogen has to be reduced to prevent catalyst inhibition.

5.29.4.2.2.1 Substituted tetrahydropyridines

Enantiomerically pure RCM precursors for substituted tetrahydropyridines have been obtained through enantioselective transformations or via modification of chiral pool starting materials. An example for the former approach is Felpin's synthesis of (*S*)-anatabine and various other tobacco alkaloids (**Scheme 65**).[233]

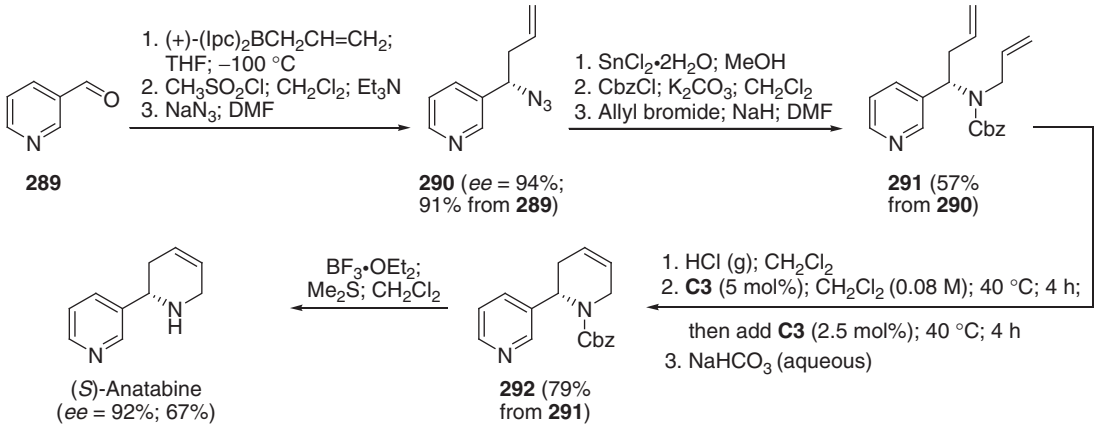
Starting from pyridine-3-carbaldehyde (**289**), azide **290** was obtained through enantioselective allylboration, conversion of the homoallylic alcohol into the mesylate and S_N2-reaction with NaN_3 in 94% *ee*. Conversion of **290** into the required RCM precursor **291** was achieved in three steps. RCM was successful after intermediate conversion of the pyridine into the hydrochloride; under these conditions, tetrahydropyridine **292** was isolated after basic workup in 79%, using catalyst **C3** in a total amount of 7.5 mol%. Addition of the catalyst in two portions turned out to be crucial, as incomplete conversion was observed if 10 mol% of the catalyst were added in one portion under otherwise identical conditions. The researchers reasoned that this might be caused by the acidic

Table 15 Homoallylic acrylate RCM

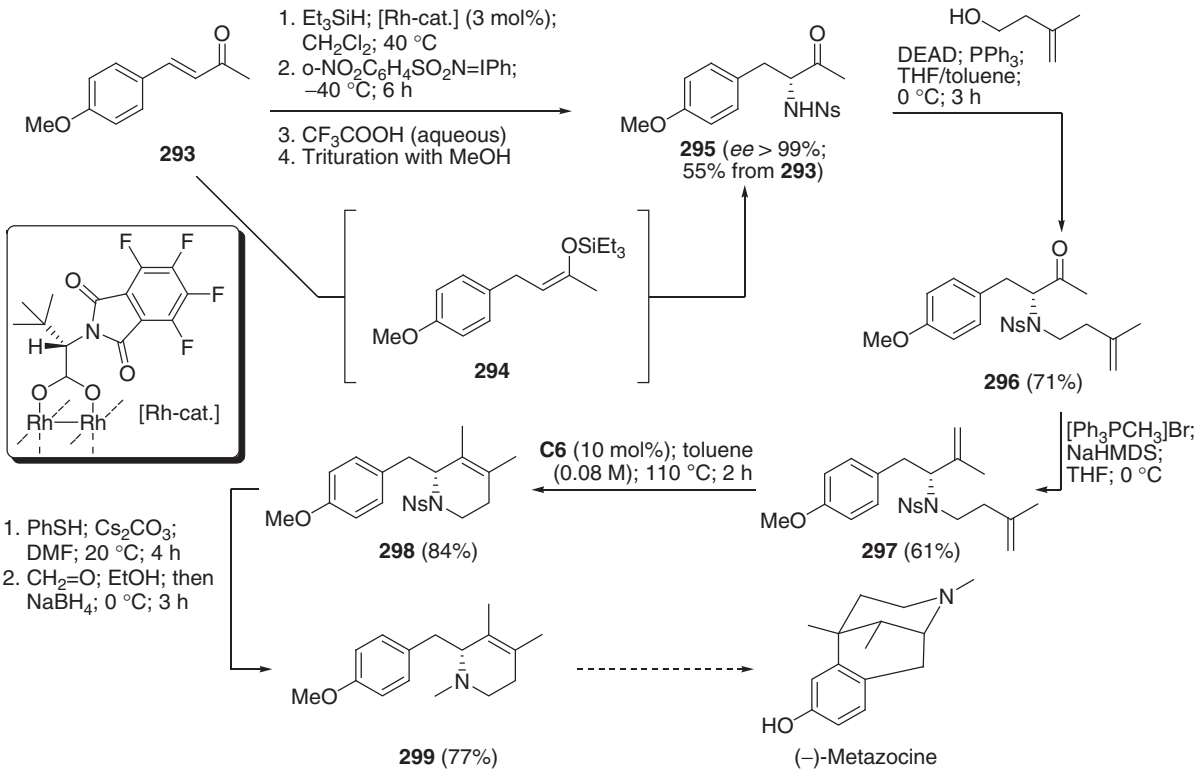
Entry	Precursor	RCM conditions	Dihydropyran	Yield (%)	References
1		**C6** (5 mol%); CH_2Cl_2 (0.01 M); 40 °C; 12 h		69	227
2		**C10** (5 mol%); $ClCH_2CH_2Cl$ (0.005 M); 80 °C; 12 h		68	228
3		**C10** (10 mol%); toluene (0.1 M); 150 °C; μ-wave (150 W); 4 h		65	229
4		**C3** (5 mol%); CH_2Cl_2 (0.04 M); $Ti(OPr^i)_4$ (1 equivalent); 40 °C; 12 h		84	134
5		**C6** (4 mol%); toluene (0.02 M); 70 °C; 1 h		95	211
6		**C6** (5 mol%); toluene (0.02 M); 110 °C; 5 h		84	198
7		**C6** (2 mol%); CH_2Cl_2 (0.01 M); 40 °C; 2 h		94	230
8		**C3** (2 mol%); CH_2Cl_2 (0.005 M); $Ti(OPr^i)_4$ (0.3 equivalent); 40 °C; 16 h		90	231
9		**C9** (5 mol%); toluene (0.1 M); 70 °C		62	232

conditions, which are presumbably detrimental for the stability of the metathesis catalyst. An enantioselective Rh-catalyzed α-amination of an *in-situ* generated silyl enol ether has been used, in combination with a challenging RCM as the key steps in a formal total synthesis of (–)-metazocine (Scheme 66).[234] In a sequential catalytic transformation, enone **293** underwent conjugate addition of triethylsilane, and the *in-situ* generated silyl enol ether **294** was then enantioselectively α-aminated, catalyzed by the depicted chiral catalyst. The RCM precursor **297** was obtained via Mitsunobu reaction and Wittig olefination.

RCM of **297** requires 10 mol% of **C6** and results in the formation of tetrahydropyridine **298**, with a tetrasubstituted double bond. Such transformations are generally considered to be challenging but manageable, provided that the more active second-generation catalysts are used. Grubbs et al. described several examples of reactions that proceed with comparable yields but lower catalyst loadings using less common NHC-alkylidene complexes.[43] The RCM product **298** was subsequently converted



Scheme 65 Synthesis of (*S*)-anatabine via allylboration.

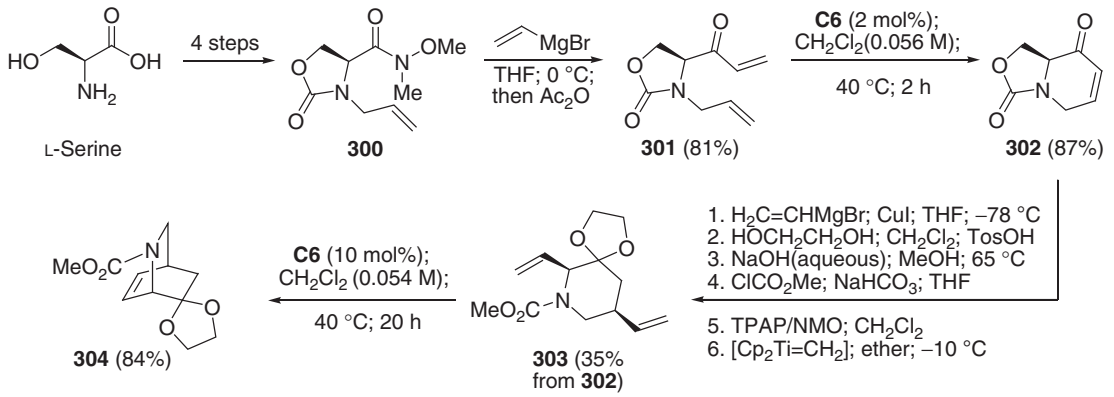


Scheme 66 Metazocine via enantioselective Rh-catalyzed α-amination and RCM.

in two steps into the tetraalkylated tetrahydropyridine **299**, which had previously been used as a precursor for the synthesis of the target molecule.

Amino acids are obviously well suited ex-chiral-pool starting materials for the synthesis of RCM precursors. In particular, proline and serine have found numerous applications, and one example, the synthesis of the azabicyclooctane fragment of the vinca alkaloid (+)-catharanthine from L-serine, is highlighted below (Scheme 67).[235]

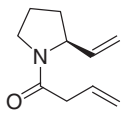
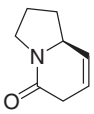
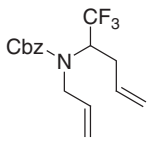
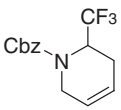
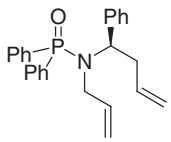
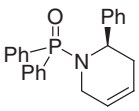
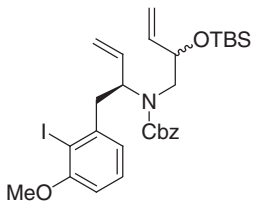
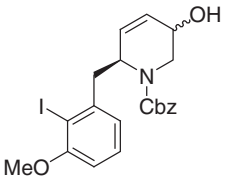
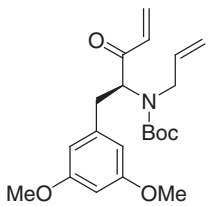
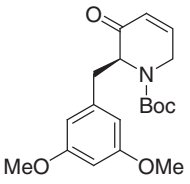
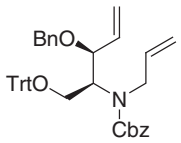
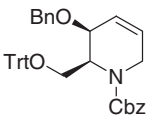
Thus, L-serine was converted in four steps into the Weinreb amide **300**, which served as a precursor for enone **301**. The first RCM step of the sequence was accomplished with a comparatively low amount of **C6** in just 2 h. The resulting RCM product **302** was then converted into the precursor **303** for the second, more challenging RCM step. The crucial step of the sequence leading to **303** is the conjugate addition of a vinyl cuprate to enone **302**, which proceeds with the desired high *cis*-diastereoselectivity. The second double bond required for the next RCM was established via hydrolysis of the oxazolidinone, oxidation of the primary alcohol, and Tebbe olefination. RCM of **303** was successful with a significantly increased catalyst loading of **C6** and a prolonged



Scheme 67 Synthesis of a (+)-catharanthine fragment through dual RCM.

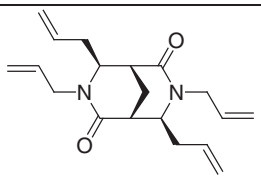
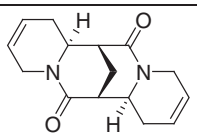
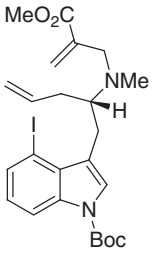
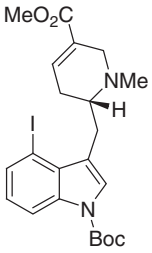
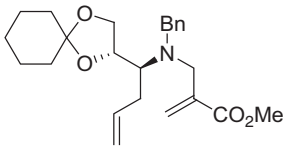
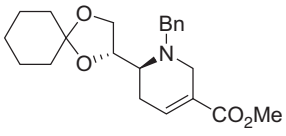
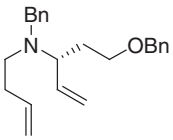
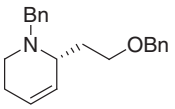
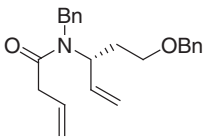
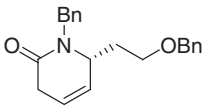
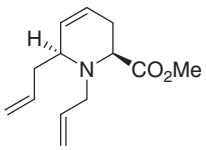
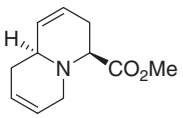
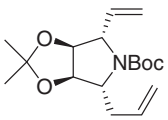
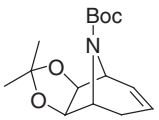
reaction time of 20 h. The researchers reasoned that the piperidine ring in precursor **303** needs to adopt an unfavorable boat conformation for the RCM to proceed. In Table 16, some additional examples for RCM reactions leading to variously substituted tetrahydropyridines are summarized.

Table 16 Substituted tetrahydropyridines through RCM

Entry	*Precursor*	*RCM conditions*	*Dihydropyran*	*Yield (%)*	*References*
1		**C2** (5 mol%); C_6H_6 (0.029 M); 20 °C; 3 days		93	236
2		**C3** (1 mol%); CH_2Cl_2 (0.1 M); 20 °C; 5 h		91	237
3		**C6** (5 mol%); CH_2Cl_2 (0.1 M); 40 °C; 1 h		98	238
4[a]		1. **C6** (5 mol%); toluene (0.025 M); 80 °C; 6 h 2. TBAF; THF		89	239
5[b]		**C6** (3 mol%); CH_2Cl_2 (0.03 M); 25 °C; 12 h		83	240
6		**C3** (5 mol%); CH_2Cl_2 (0.07 M); 20 °C; 12 h		91	186

(*Continued*)

Table 16 Continued

Entry	Precursor	RCM conditions	Dihydropyran	Yield (%)	References
7		**C3** (2 mol%); CH_2Cl_2; 20 °C		97	241
8[c]		**C6** (5 mol%); toluene (0.01 M); TosOH (1.1 equivalents); 55 °C; 10 h		88	242
9		**C6** (3 mol%); toluene (0.125 M); 90 °C; 4 h		54	243
10		**C6** (3x1 mol%; addition in equal intervals); toluene (0.125 M); 90 °C		92	
11		**C6** (5 mol%); CH_2Cl_2 (0.05 M); 40 °C; TosOH (1.0 equivalent); 10 h		85	160
12		**C6** (5 mol%); CH_2Cl_2 (0.01 M); 40 °C; 12 h		90	160
13[d]		**C8** (1 mol%); toluene (0.02 M); 80 °C; 6 h		77	244
14		**C3** (10 mol%); CH_2Cl_2; 40 °C; 1.5 h		95	245

[a]Yield over two steps.
[b]Yield over two steps starting from crude starting material; RCM conducted on 5 g-scale.
[c]No conversion in CH_2Cl_2 at 40 °C.
[d]Reaction failed with the first generation catalyst **C3**.

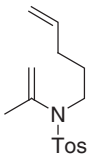
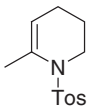
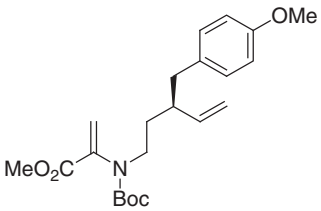
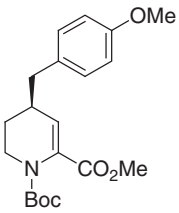
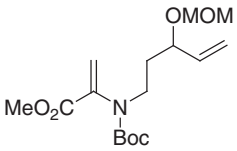
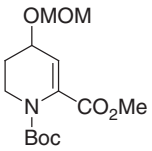
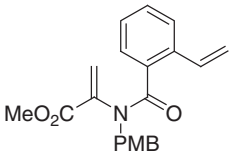
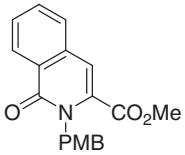
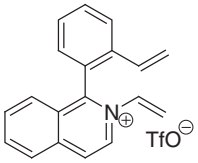
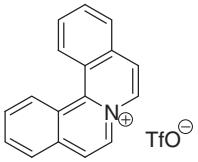
5.29.4.2.2.2 Six-membered cyclic enamides

As previously discussed for five-membered cyclic enamides, the RCM leading to their six-membered counterparts normally requires more active second-generation catalysts and often elevated temperatures. A selection of examples is presented in **Table 17**.

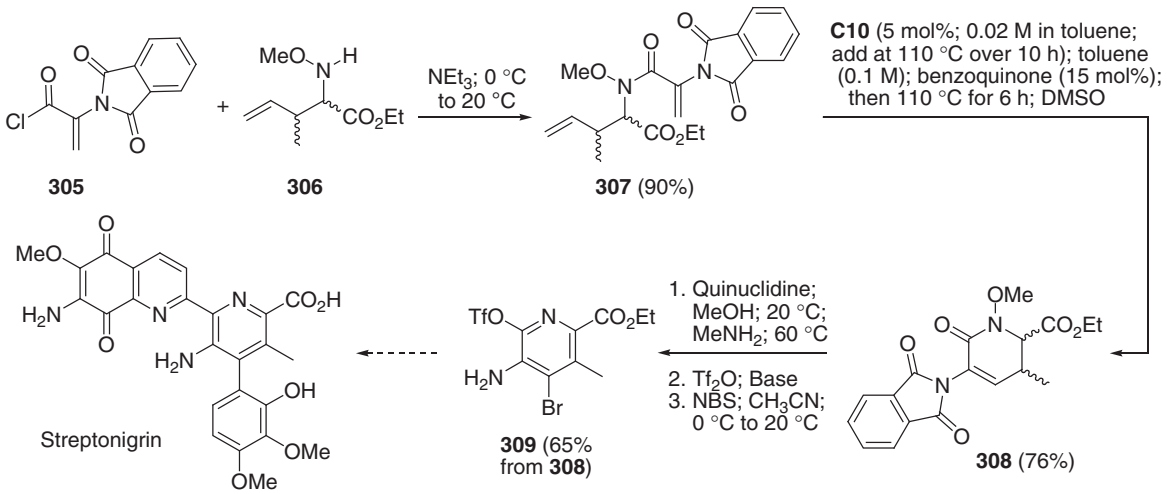
5.29.4.2.2.3 α,β-Unsaturated six-membered lactams

In many cases where homoallylic acrylamides were subjected to RCM, the resulting α,β-unsaturated lactams were not the actual target structures but intermediates en route to substituted piperidines or pyridines, as outlined below for Donohoe's synthesis of the pyridine core of the aminoquinone antitumor antibiotic streptonigrin (**Scheme 68**).[249]

Table 17 Synthesis of six-membered cyclic enamides through RCM

Entry	Precursor	Conditions	RCM product	Yield (%)	References
1		**C3** (5 mol%); CH_2Cl_2 (0.016 M); 40 °C; 24 h		26	154
2		**C8** (5 mol%); toluene (0.016 M); 80 °C; 6 h		75	
3		**C6** (10 mol%); toluene (0.002 M); 80 °C; 4 h		90	246
4[a]		**C6** (10 mol%); toluene; 80 °C; 1,4-benzoquinone (20 mol%); 18 h		75	246
5		**C6** (5 mol%); toluene (0.1 M); 80 °C; 0.5 h		82	247
6		**C10** (5 mol%); $ClCH_2CH_2Cl$ (0.05 M); 130 °C; 4 h		53	248

[a]Product was obtained along with the starting material (22%). In the absence of benzoquinone, extensive isomerization of the starting material to the MOM-enol ether was observed.



Scheme 68 Toward streptonigrin via homoallylic acrylamide RCM, followed by elimination.

The RCM precursor **307** was obtained by condensation of the *in-situ* generated acyl chloride **305** and the *O*-methyl hydroxyl amine **306**. The cyclization of **307** required optimization, but eventually the phosphine-free catalyst **C10** was found to catalyze this reaction when added slowly as a solution in toluene with a syringe pump over a period of 10 h. Addition of benzoquinone

was required to suppress undesired double-bond isomerization reactions of the substrate, and DMSO was used to oxidatively destroy the metathesis catalyst after completion of the RCM in order to facilitate the chromatographic purification. Lactam **308**, obtained in gram quantities via this route, was then converted into the pentasubstituted pyridine **309** by elimination of methanol, aromatization by trapping of the enol form as a triflate, and bromination. It should be noted that this is a particularly challenging example, and that numerous other derivatives are accessible using less carefully controlled conditions. Some representative examples are listed in Table 18. Entries 1 and 2 once again illustrate the superior reactivity of second-generation catalysts if electron-deficient double bonds are involved in the RCM step. However, if the more reactive double bond is sterically encumbered, for example, due to a bulky protecting group in the allylic position (entry 3), even highly reactive catalysts such as **C6** often fail to give satisfactory results. For the same reasons the RCM of the isomeric precursors in entries 4 and 5 or 6, respectively, proceeds with a significantly different rate, although in both cases a trisubstituted double bond is formed. For the example listed in entry 4, a sterically less constrained styrene double bond facilitates initiation at this position, which is followed by rapid cyclization, resulting in a nearly quantitative yield. In contrast, the regioisomer in entry 5 undergoes RCM only very slowly, resulting in a poor yield even if a significantly higher amount of catalyst is used. This result can most likely be explained by assuming that the initiation at both double bonds is unfavorable for steric or electronic reasons, respectively. For this particular example, the yield can be improved by a solvent switch from dichloromethane to benzene (for a general discussion on solvent effects, see Section 5.29.2). The examples shown in entries 9 and 10 illustrate that in certain cases good results can be obtained even with the first-generation catalysts, but that a nitrogen-protecting group and a sterically unencumbered initiation site are mandatory.

5.29.4.2.2.4 Combinations of multicomponent reactions and RCM

Azacycles are among the most important structural motifs in medicinal chemistry and play a major role as target structures for the synthesis of combinatorial libraries. A combination of multicomponent reactions with transition metal-catalyzed transformations, in particular RCM, has emerged as a useful strategy for generating structural complexity and diversity. In this section, two examples will be outlined briefly. An approach toward bridged bicyclic lactams has been published by researchers from Abbott (Scheme 69),[255] who obtained RCM precursors, for example, **314**, through Ugi multicomponent reactions. The double bonds required for the subsequent RCM were introduced in this example by using ω-unsaturated carboxylic acids, for example, **312**, and amines, for example, allyl amine (**311**). In other examples, one of the double bonds participating in the RCM came from the aldehyde component. RCM of **314** was accomplished with 10 mol% of **C6**; after completion of the RCM reaction, DMSO was added to facilitate chromatographic removal of catalyst residues. Lactam **315** was eventually subjected to a diastereoselective intramolecular Heck reaction to the bridged bicyclic lactam **316**, using a Pd-precatalyst immobilized on a polystyrene backbone.

The second example illustrates the combination of a van Leusen three-component reaction and RCM for the synthesis of structurally diverse bicyclic imidazoles (Scheme 70).[256]

The RCM precursor **318** was obtained through coupling of tosyl methyl isocyanide (**317**), carboxylic acid **312,** and allyl amine (**311**) under basic conditions. RCM of **318** proceeded smoothly, in spite of the nucleophilic imidazole present in the precursor, when catalyst **C6** was used. Replacing 3-butenoic acid (**312**) with 4-pentenoic acid leads to precursors for azepine derivatives.

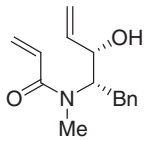
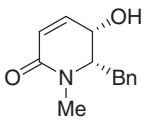
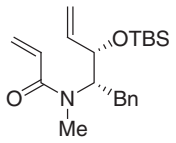
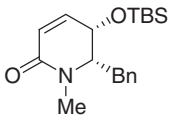
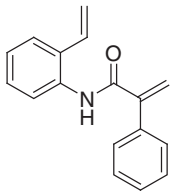
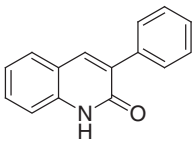
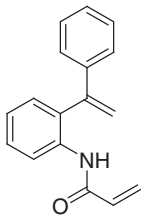
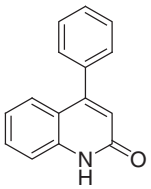
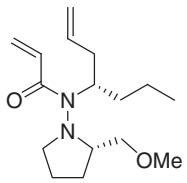
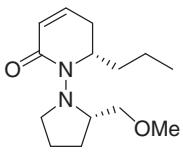
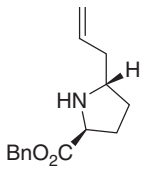
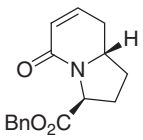
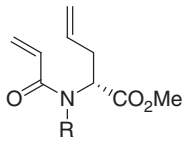
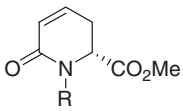
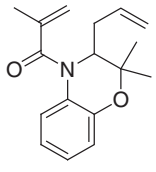
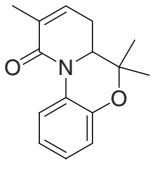
5.29.5 Medium-Sized Ring Systems and Macrocycles

The formation of medium-sized rings is generally hampered by enthalpic and entropic constraints,[49] and this is also true for most RCM reactions leading to seven- to ten-membered carbo- or heterocycles. As a consequence, lower initial substrate concentrations (to suppress undesired self-metathesis) and higher catalyst loadings than for similarly substituted five- or six-membered rings are normally required. Although the number of examples is considerably smaller than that for five- and six-membered rings, a plethora of reactions has been published over the past 20 years. This section is subdivided only according to the ring size, and carbo- and heterocycles are, in contrast to the previous sections, discussed under the same subheading.

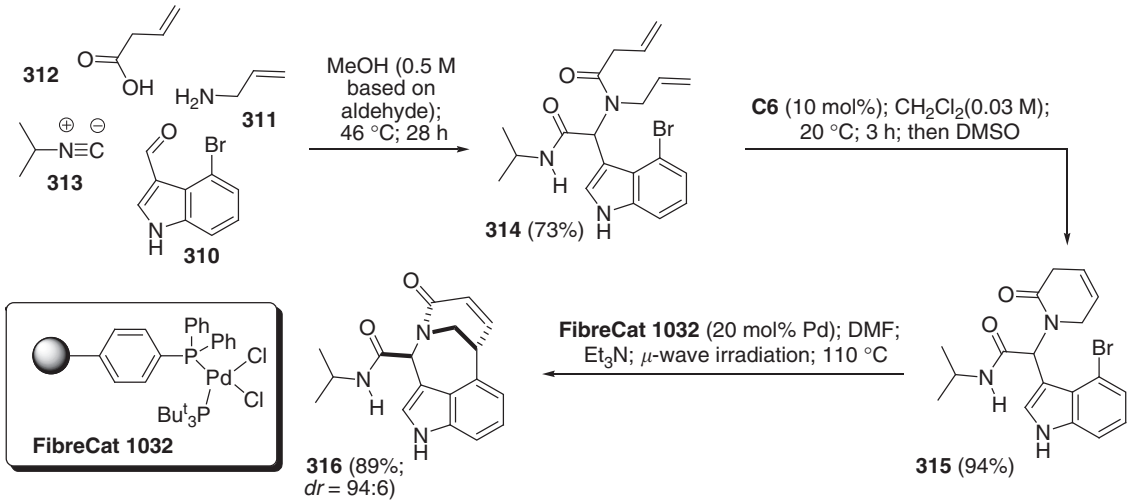
5.29.5.1 Seven-Membered Ring Systems

Over the past decade, after the discovery of the more active and robust second-generation metathesis catalysts, RCM has been applied in the synthesis of several terpenoid natural products comprising seven-membered carbocycles, including strained bridged or polycyclic systems. The RCM step is occasionally highly challenging, making very high catalyst loadings, high reaction temperatures, and long reaction times necessary, which might induce undesired side reactions. For these reasons, synthetic modifications of the RCM precursor are sometimes inevitable to facilitate the subsequent RCM reaction. As a very recent example, the RCM step of Kigoshi's (–)-13-oxyingenol synthesis and attempts toward its optimization are outlined below (Scheme 71).[257]

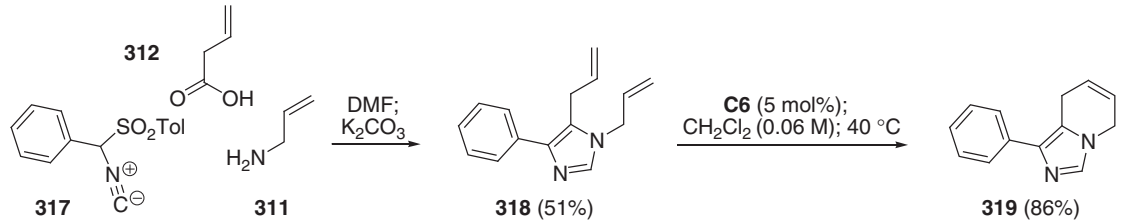
Table 18 Synthesis of α,β-unsaturated six-membered lactams through RCM

Entry	*Precursor*	*Conditions*	*RCM product*	*Yield (%)*	*References*
1		**C3** (15 mol%); CH_2Cl_2 (0. 15 M); 20 °C; 12 h		Trace	250
2		**C6** (5 mol%); CH_2Cl_2 (0.15 M); 20 °C; 6 h		84	
3		**C6** (60 mol%); CH_2Cl_2 (0.15 M); 40 °C; 48 h		61	250
4		**C6** (5 mol%); CH_2Cl_2 (0.01 M); 40 °C; 7.5 h		99	251
5		**C6** (10 mol%); CH_2Cl_2 (0.01 M); 40 °C; 7.5 h		38	251
6		**C6** (10 mol%); C_6H_6 (0.01 M); 22 °C; 7.5 h		53	
7		**C6** (10 mol%); CH_2Cl_2 (0.1 M); 20 °C; 24 h		68	252
8		1. Acryloyl chloride; Na_2CO_3; acetone 2. **C6** (7 mol%); toluene (0.04 M); 40 °C		63	161
9		R = H: **C3** (5 mol%); CH_2Cl_2 (0.05 M); 40 °C		20	253
10		R = PMB: **C3** (5 mol%); CH_2Cl_2 (0.05 M); 40 °C		93	
11		**C9** (5 mol%); toluene; 70 °C		76	254

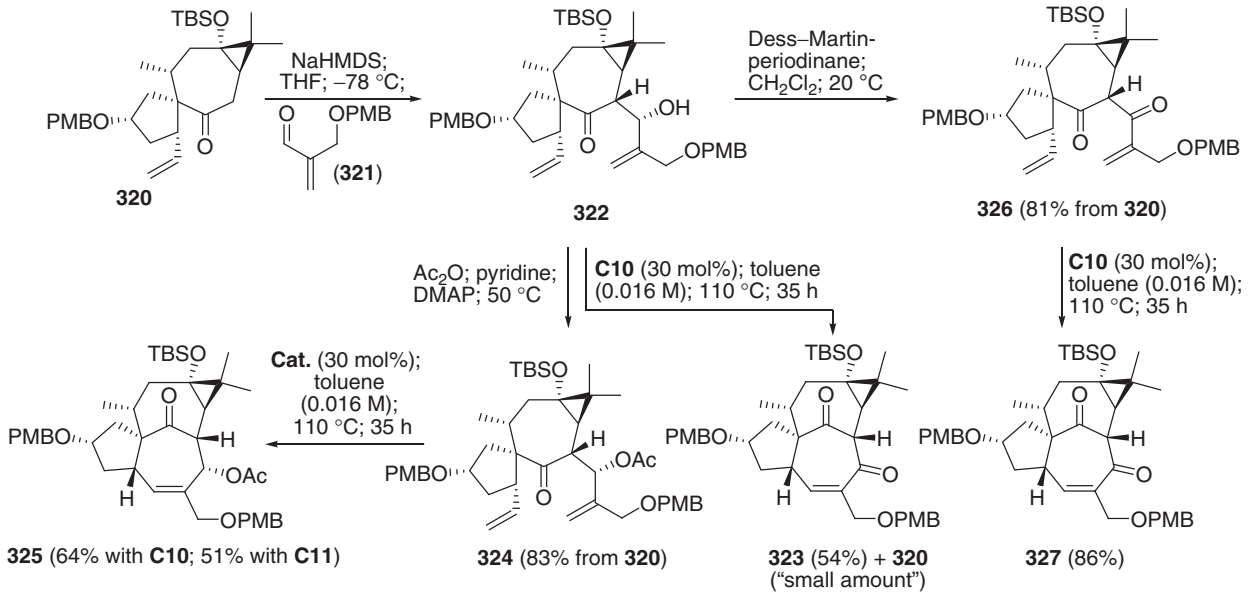
The first RCM precursor tested in this study, diene **322**, was directly obtained from a highly diastereoselective aldol addition of **320** and aldehyde **321**. Under the standard RCM conditions, the desired product **323** was obtained in 54% yield, but a retro-aldol reaction occurred to some extent. This could be avoided by protection of the hydroxy group as acetate **324**; however, neither the Grubbs–Hoveyda catalyst **C10** nor Grela's nitro-substituted catalyst **C11** gave satisfactory yields of **325**. The best yield was



Scheme 69 Bridged bicyclic lactams via Ugi reaction, RCM, and Heck reaction.



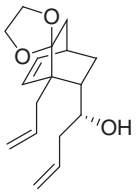
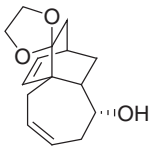
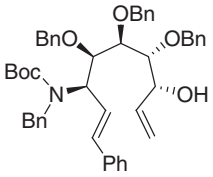
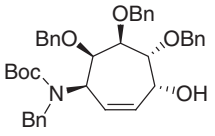
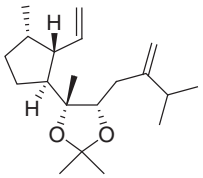
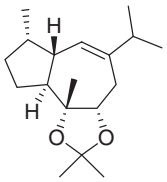
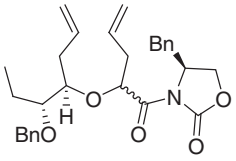
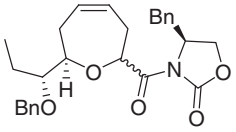
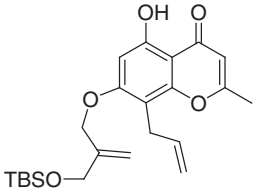
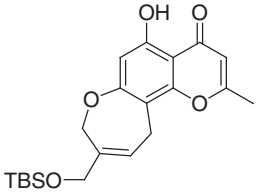
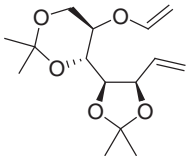
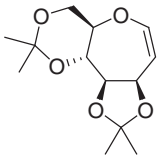
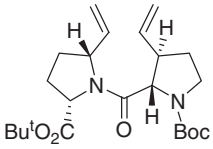
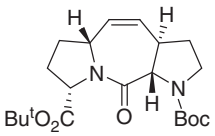
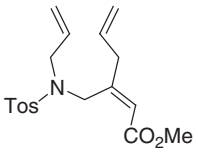
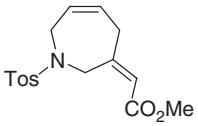
Scheme 70 Bicyclic imidazoles via van Leusen reaction and RCM.



Scheme 71 Toward 13-oxyingenol through RCM.

eventually obtained after oxidation of the secondary alcohol to the enone **326**, which underwent RCM in high yields to furnish the 1,3-diketone **327**. Obviously, conversion of the alcohol into the ketone results in reduced steric and conformational constraints during the RCM step, which outweighs the reduced reactivity of the electron-deficient double bond. Table 19 provides a representative selection of further examples for RCM reactions leading to seven-membered rings.

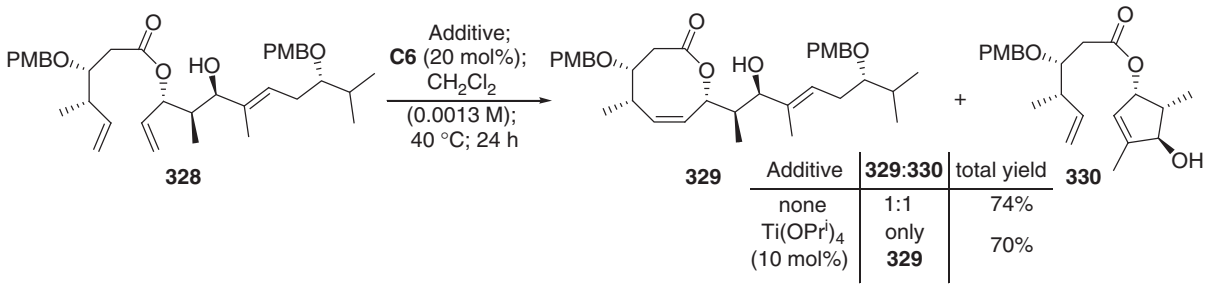
Table 19 Synthesis of seven-membered rings through RCM

Entry	Precursor	Conditions	RCM product	Yield (%)	References
1		**C3** (4.4 mol%); CH_2Cl_2 (0.014 M); 20 °C; 5 h		94	258
2		**C6** (10 mol%); CH_2Cl_2 (0.02 M); μ-wave irradiation at 100 W; 90 °C; 1.5 h		77	259
3		**C6** (20 mol%); CH_2Cl_2 (0.01 M); 40 °C; 36 h		99	260
4		*trans*-configuration: **C3** (5 mol%); CH_2Cl_2 (0.005 M); 40 °C; 8 h		49	261
5		*cis*-configuration: **C3** (5 mol%); CH_2Cl_2 (0.005 M); 40 °C; 2 h		98	
6		**C6** (10 mol%); CH_2Cl_2 (0.002 M); 40 °C; 2.5 h		98	262
7		**C6** (20 mol%); CH_2Cl_2 (0.005 M); 40 °C; 12 h		25	263
8		**C1** (20 mol%); toluene (0.002 M); 60 °C; 12 h		89	
9		**C6** (10 mol%); CH_2Cl_2 (0.04 M); 40 °C; 24 h; then DMSO; 12 h		91	264
10		**C10** (2 mol%); CH_2Cl_2 (0.02 M); 40 °C; 3 h		87	265

5.29.5.2 Eight-Membered Ring Systems

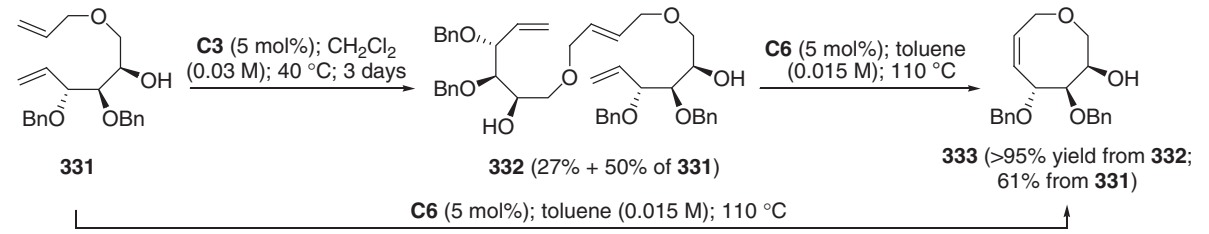
The formation of eight-membered carbo- and heterocycles is often complicated by competing self-metathesis of the precursors or by the formation of cycles with a more favorable ring size, if alternative double bonds are available for RCM. An example for the

latter complication has been observed during the synthesis of octalactin A (Scheme 72).[266] In this case, cyclopentene **330** was formed as a side product during RCM of **328**, caused by initiation of the catalyst at the double bond adjacent to the acyl substituent and subsequent intramolecular attack of the trisubstituted double bond next to the unprotected secondary hydroxy group. Interestingly, this cyclization was completely suppressed by the addition of $Ti(OPr^i)_4$ as a cocatalyst, resulting in the exclusive formation of **329** in good yields.



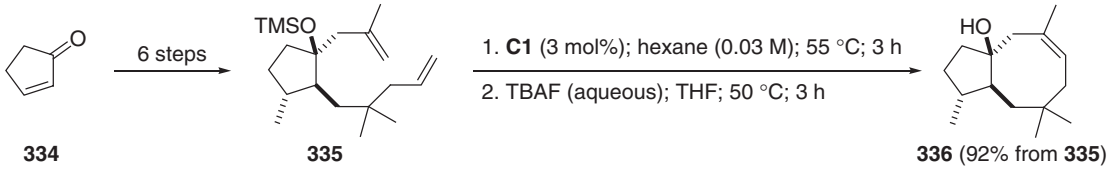
Scheme 72 Competing cyclization modes in the synthesis of octalactin A.

In contrast to the formation of ring-contracted products, as outlined in Scheme 72, self-metathesis of the RCM precursor does not necessarily mean a complete failure of the desired RCM reaction, because the formation of the cyclic product might still be possible via a backbite mechanism (Scheme 73).[267] For example, precursor **331** undergoes selective dimerization via the sterically less demanding allyl ether to give **332**, which does not react in a subsequent RCM if first-generation catalyst **C3** is used, even after a prolonged reaction time of 3 days. In the presence of **C6**, however, **332** cyclizes via backbite metathesis to the desired product **333** in quantitative yields. The same product could be obtained directly from **331** when the second-generation catalyst **C6** was used from the outset.



Scheme 73 Competing self- and ring-closing metathesis, and RCM via backbite mechanism.

Nevertheless, it should be noted that RCM is a useful method for the synthesis of eight-membered rings and that in certain cases even trisubstituted double bonds can be constructed. An early example is Fürstner's dactylol synthesis (Scheme 74),[268] which starts from cyclopentenone (**334**). In six steps, comprising a one-pot conjugate addition–aldol condensation, precursor **335** and its epimer were obtained. With Schrock's catalyst **C1** RCM proceeded smoothly with moderate catalyst loadings; however, protection of the tertiary alcohol turned out to be mandatory as the RCM failed completely for the carbinol.

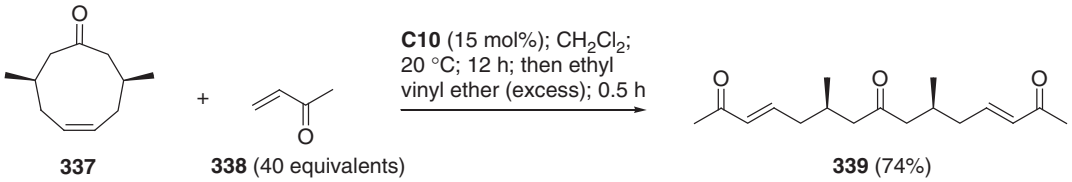


Scheme 74 Final steps of a dactylol synthesis.

5.29.5.3 Nine-Membered Ring Systems

The considerable ring strain of medium-sized rings in general and nine-membered rings in particular becomes evident from a recently published example, in which a clean ROM of a cyclononene in the presence of methyl vinyl ketone was exploited for the synthesis of a meso-triketone (Scheme 75).[269] Cyclononenone **337** was obtained via an anionic oxy-Cope rearrangement, and

ROM to triketone **339** proceeded smoothly with **C10** and a significant excess of methyl vinyl ketone (**338**). In this example, the metathesis activity of the catalyst was quenched by the addition of ethyl vinyl ether before isolation of the product.

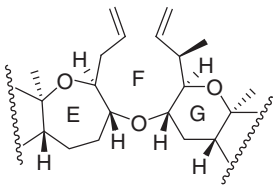
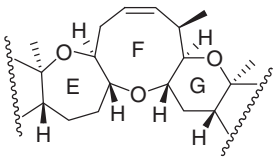
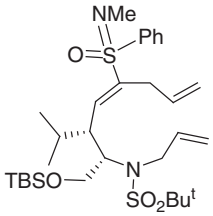
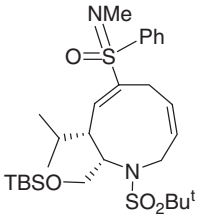
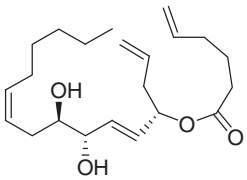
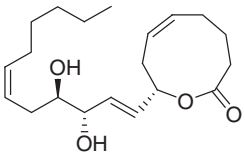


337 **338** (40 equivalents) **339** (74%)

Scheme 75 Toward bidirectional synthesis via ROM of a cyclononene.

In some other examples, RCM reactions leading to nine-membered rings have been shown to proceed in synthetically useful yields, although sometimes at the expense of rather high catalyst loadings (Table 20). In particular, these RCM reactions have been used for constructing the central oxacyclononene ring of several polyether toxins, for example, gambieric acid. This subject has been reviewed,[270] and a recent example is listed in entry 1.

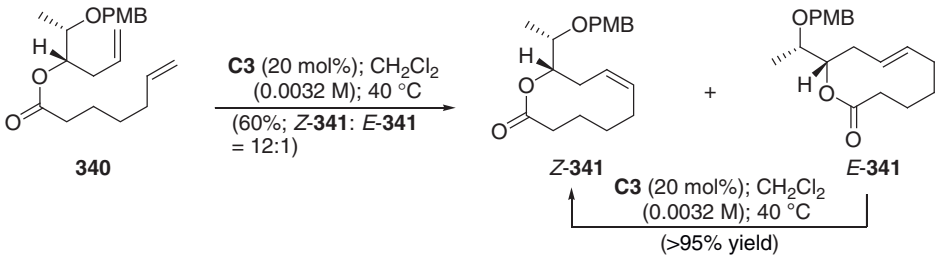
Table 20 Synthesis of nine-membered rings through RCM

Entry	*Precursor*	*Conditions*	*RCM product*	*Yield (%)*	*References*
1		**C6** (20 mol%); CH_2Cl_2 (0.001 M); 40 °C; 1.5 h		>95	271
2		**C6** (10 mol%); toluene (0.005 M); 110 °C; 24 h		85	272
3		**C6** (10 mol%); CH_2Cl_2 (0.004 M); 40 °C; 0.5 h		78	273

5.29.5.4 Ten-Membered Ring Systems

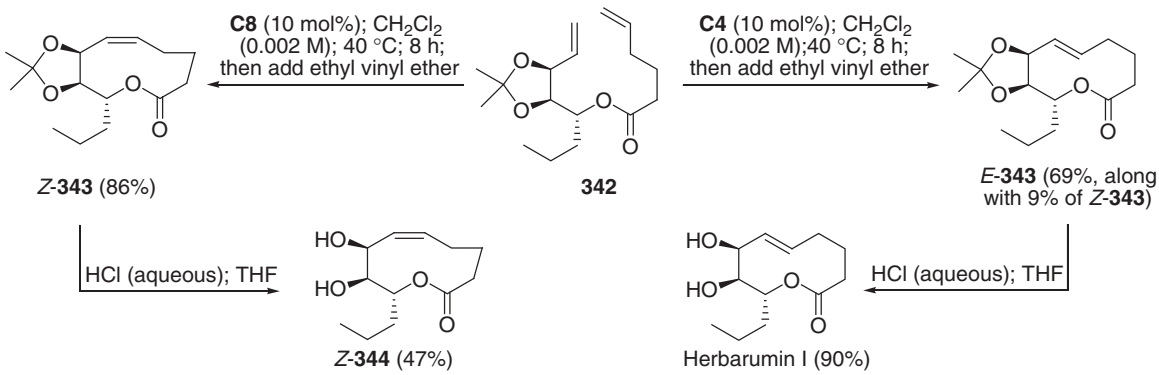
For this ring size control of the configuration of the newly formed double bond is a major issue. Several examples have been investigated, because the ten-membered lactone pattern is a common structural element in many natural products, which have attracted considerable attention over the past few years. In an early example for this type of RCM reaction, Kalesse et al. presented experimental and theoretical evidence that the control of *E*/*Z*-selectivity is subject to thermodynamic versus kinetic control (Scheme 76).[274] In the course of an epothilone synthesis, **340** was subjected to RCM using the first-generation catalyst **C3**, as the second-generation catalysts were not yet available at that time. The researchers discovered that with a rather high amount of the catalyst cycloalkene *Z*-**341** is the predominant product, but that the *E*-isomer, after chromatographic separation, can be completely converted into the *Z*-isomer on renewed exposure to the metathesis catalyst through a sequence of ring opening and ring-closing metathesis. From this observation, it was concluded that *Z*-**341** is the thermodynamically favored RCM product, and this was corroborated by computational methods, revealing that *Z*-**341** should be 9 kcal mol^{-1} more stable than *E*-**341**.

The advent of the significantly more active NHC-ligated Ru-catalysts in 1999 opened new opportunities for controlling the stereochemical course of an RCM reaction through a choice of the catalyst. Examples for this catalyst-controlled approach were



Scheme 76 Control of *E*/*Z*-selectivity for a 10-membered lactone formation.

presented by Carda, Marco et al. for the synthesis of microcarpalide[275] and by Fürstner et al. for the synthesis of herbarumins I and II (Scheme 77).[276] In the latter example, semiempirical calculations revealed that the RCM product *Z*-**343**, leading to the nonnatural herbarumin analog *Z*-**344**, should be 3.5 kcal mol^{-1} more stable than *E*-**343**, which on deprotection gives the natural product herbarumin I. Consequently, formation of the thermodynamically more stable product had to be expected with the more active second-generation catalysts, whereas use of a less active first-generation catalyst might furnish the kinetically preferred product, i.e., *E*-**343**. The experimental results are indeed in line with these assumptions, as the desired *E*-isomer was obtained using the first-generation indenylidene complex **C4**, whereas the second-generation catalyst **C8** cleanly provided the *Z*-isomer. In both cases, the metathesis activities of the catalysts were quenched by the addition of ethyl vinyl ether after complete consumption of the starting material.



Scheme 77 Control of *E*/*Z*-selectivity through choice of the catalyst.

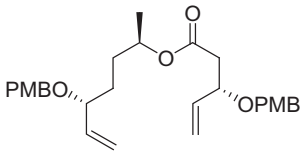
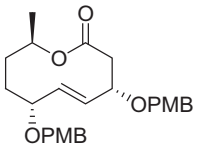
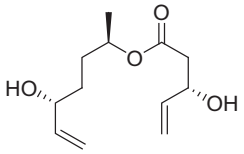
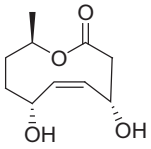
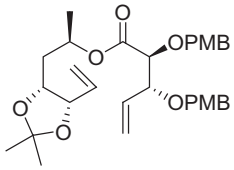
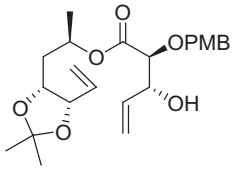
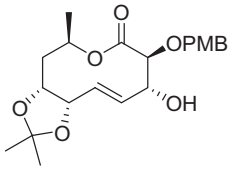
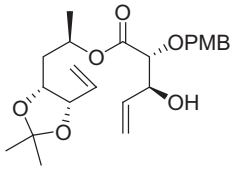
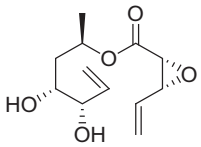
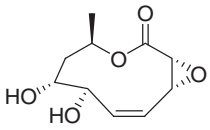
If a catalyst controlled stereoselective formation of the newly formed double bond is not feasible, modification of the RCM precursor is often the last resort to obtain the desired RCM product and to avoid a complete revision of the synthetic strategy. Sometimes, removal or introduction of a protecting group has already a significant impact on the outcome of an RCM reaction. Some examples are compiled in Table 21.

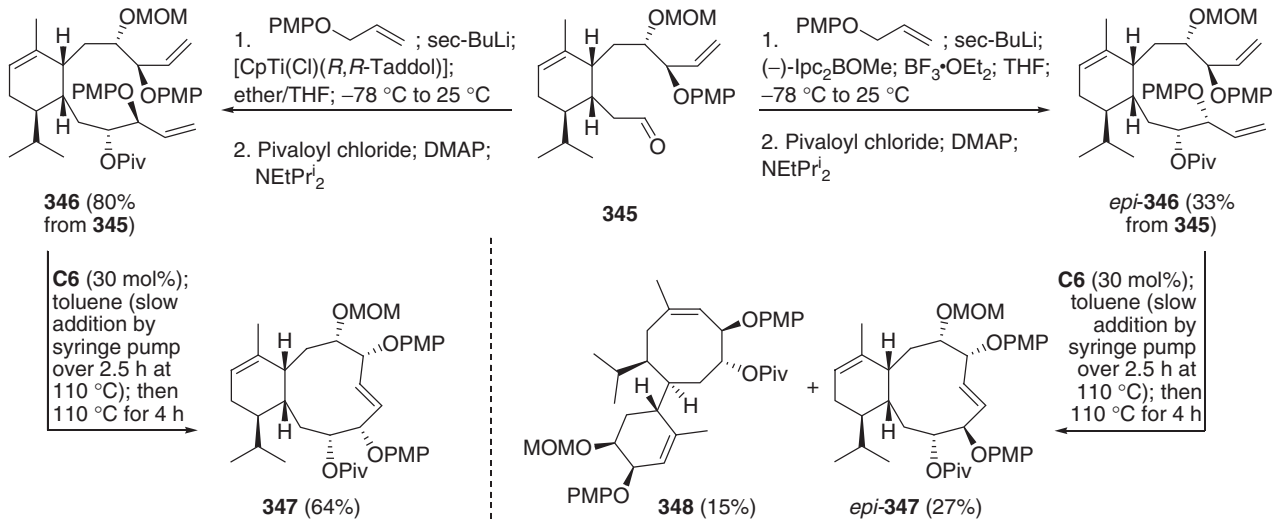
Although the identification of the thermodynamically preferred geometrical isomer by theoretical methods may assist in choosing the appropriate catalyst in many cases, there are examples where this approach fails. Gennari et al. discovered, during a study directed at the synthesis of the marine natural product eleutherobin, that the RCM of diene **346** proceeded with complete *E*-selectivity even under forcing conditions, although computational methods revealed that the *Z*-isomer of **346** should be more stable (Scheme 78).[279] On the basis of the DFT calculations, the researchers reasoned that the preferred *E*-selectivity originates from lower energies of the intermediate *trans*-ruthenacyclobutanes compared with their *cis*-analogs, and that – once the cycloalkene is formed – a ROM is no longer possible due to the sterically constrained environment of the C–C double bond. A further remarkable outcome of this study is that even minor configurational changes can have a significant impact on the result of the metathesis reaction. Apart from **346**, which was obtained from **345** via Duthaler–Hafner oxyallylation, the researchers also examined the RCM of its epimer, *epi*-**346**, which was the major product of a Brown-allylboration of the same precursor **345**. Application of the same RCM-protocol gave *E*-configured *epi*-**347** in significantly lower yields, along with a considerable amount of **348**, resulting from a ring opening/double RCM sequence.

5.29.5.5 Macrocycles (Ring Size > 10)

As for most synthetic methods used for macrocyclization, macro-RCM requires normally high dilution or pseudo-high dilution conditions to suppress the formation of dimers or oligomers. However, as outlined in Section 5.29.2, extremely high dilution

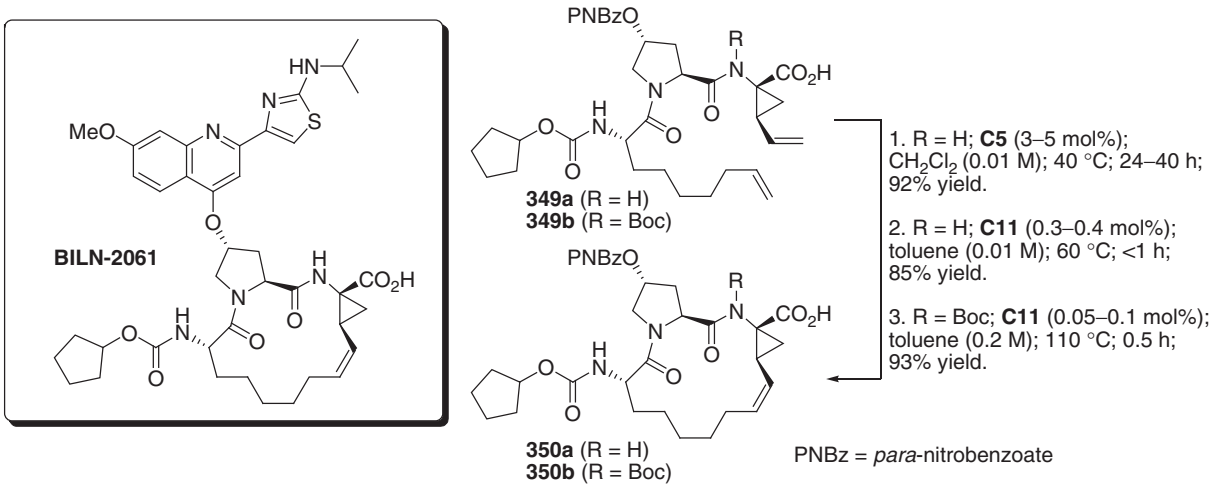
Table 21 Control of double-bond geometry through modification of the RCM precursor

Entry	Precursor	Conditions	RCM product	Yield (%)	References
1		**C8** (10 mol%); CH_2Cl_2 (0.001 M); 40 °C; 8 h		78	277
2		**C8** (10 mol%); CH_2Cl_2 (0.001 M); 40 °C; 8 h		76	277
3		**C6** (2.7 mol%); C_6H_6 (0.002 M); 80 °C; 6 h	Complex mixture of products	–	278
4		**C6** (2.7 mol%); C_6H_6 (0.002 M); 80 °C; 6 h		64	278
5		**C6** (2.7 mol%); C_6H_6 (0.002 M); 80 °C; 6 h	Complex mixture of products	–	278
6		**C6** (7 mol%); CH_2Cl_2 (0.003 M); 40 °C; 1 h		38	278



Scheme 78 Toward eleutherobin via RCM.

might be counterproductive in some cases, because often a considerable proportion of the RCM product is formed from dimers or oligomers via a backbite mechanism, and using low initial substrate concentrations will not only reduce the extent of self-metathesis, but also intermolecular reactions of the catalyst and the substrate. This will result in an overall reduced rate for the RCM. The application of RCM to the synthesis of macrocyclic natural products has been reviewed by Gradillas and Pérez-Castells, and their review includes an extensive compilation of reaction conditions such as catalyst, catalyst loading, solvent, substrate concentration, and reaction temperature.[280] These data show that most macro-RCM reactions are conducted with initial solvent concentrations in the low millimolar range and with catalyst loadings of up to 20 mol%. For these reasons, it is not surprising that RCM was not considered in drug development and production beyond the laboratory scale, because implementation into process development will be extremely challenging. It can, however, be safely assumed that in the majority of target molecule syntheses using macrocyclic RCM these critical parameters have not been fully optimized, because the RCM precursors require laborious multistep syntheses, and are therefore available only in small quantities. In addition, kinetic and thermodynamic data for ring closing and self-metathesis reactions have rarely been obtained. These data can be used for the calculation of kinetic and thermodynamic EM, which have recently emerged as a useful guiding principle for planning and optimizing macrocyclic RCM (see Section 5.29.2 for a brief general discussion).[51] An instructive example in this regard comes from a group at Boehringer Ingelheim, who developed a large-scale synthesis of the hepatitis-C protease inhibitor BILN-2061 (**Scheme 79**).[281]

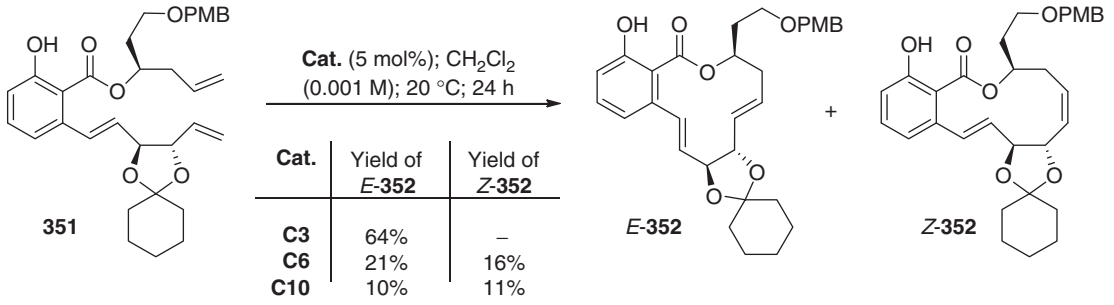


Scheme 79 Development of a metathesis-based large-scale synthesis of BILN-2061.

In the original first-generation process, precursor **349a** with R=H was used in combination with the first-generation catalyst **C5** (RCM condition 1) in Scheme 79. Although the yields of **350a** were quite good, the high dilution, the large amount of catalyst, and the long reaction times were not acceptable on pilot plant scale. Two of these problems could be solved by using Grela's *para*-nitro-substituted catalyst **C11**, which made a reduction of the catalyst loading well below 1 mol% possible, and lead to a reaction time shorter than 1 h (RCM condition 2) in Scheme 79. The high dilution problem, however, remained, and prompted the researchers to measure EM for the RCM of **349a** by running the reaction at various initial substrate concentrations. This investigation revealed that EMs for **349a** are quite unfavorable and lead to the introduction of Boc as a bulky, electron-withdrawing protecting group at the nitrogen adjacent to the cyclopropane moiety. It turned out that for this modified precursor **349b** initiation of the metathesis exclusively occurs at the sterically less hindered double bond, whereas the unprotected precursor **349a** initiates at the double bond adjacent to the cyclopropane ring, which might lead to a chelation of the Ru and a retardation of the RCM. In addition, various computational methods revealed that introduction of a Boc group significantly reduces the ring strain of **350b** compared with **350a**, presumably because rotation around the neighboring endocyclic amide bond is no longer frozen.[282] This effect translates into a 19-fold increased thermodynamic effective molarity for the RCM of **349b** compared with **349a**, and even a 27-fold increase could be realized by conducting the RCM at 110 °C. In practice, this means that high yields of the RCM product **350b** are obtained at concentrations as high as 0.2 M, which is probably unprecedented for RCM macrocyclizations.

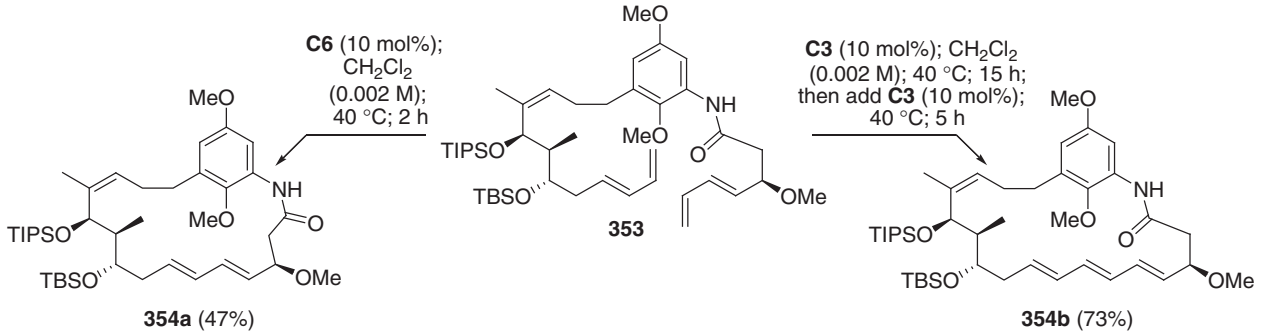
Other problems associated with macrocycle formation via RCM resemble to some extent those discussed above for medium-sized rings. In particular, control of *E*/*Z*-selectivity is often an issue, as outlined below for the example of a study directed at the synthesis of 12-membered salicylic macrolides (**Scheme 80**).[283] Interestingly, the highest yield and the best stereoselectivity was observed with a comparatively low amount of first-generation catalyst **C3**, whereas both **C6** and **C10** resulted in lower yields of cyclic products and poor *E*/*Z*-selectivity. One might assume that the reaction proceeds under kinetic control with the first-generation catalyst **C3** but under thermodynamic control with the more active second-generation catalysts. However, the researchers present evidence that even RCM reactions catalyzed by **C6** and **C10** are kinetically controlled. They reason that the observed selectivity arises from (i) a higher stability of the intermediate *trans*-ruthenacyclobutane (which fragments to *E*-**352**)

compared with the *cis*-ruthenacyclobutane (the mechanistic precursor for *Z*-**352**) and (ii) different rate determining steps for the first- and second-generation catalysts.



Scheme 80 *E*/*Z*-Selectivity control in macrocycle formation.

Another problem, which might occur if cyclic polyenes are the target molecules, is ring contraction, as outlined below (Scheme 81).[284] With the more active catalyst **C6**, the internal double bond of one conjugated diene is attacked with release of butadiene, resulting in the formation of **354a** instead of the desired target molecule **354b**. Gratifyingly, the conjugated triene moiety in **354b** became available with the first-generation catalyst **C3**.



Scheme 81 Ring contraction in the synthesis of cyclopolyenes.

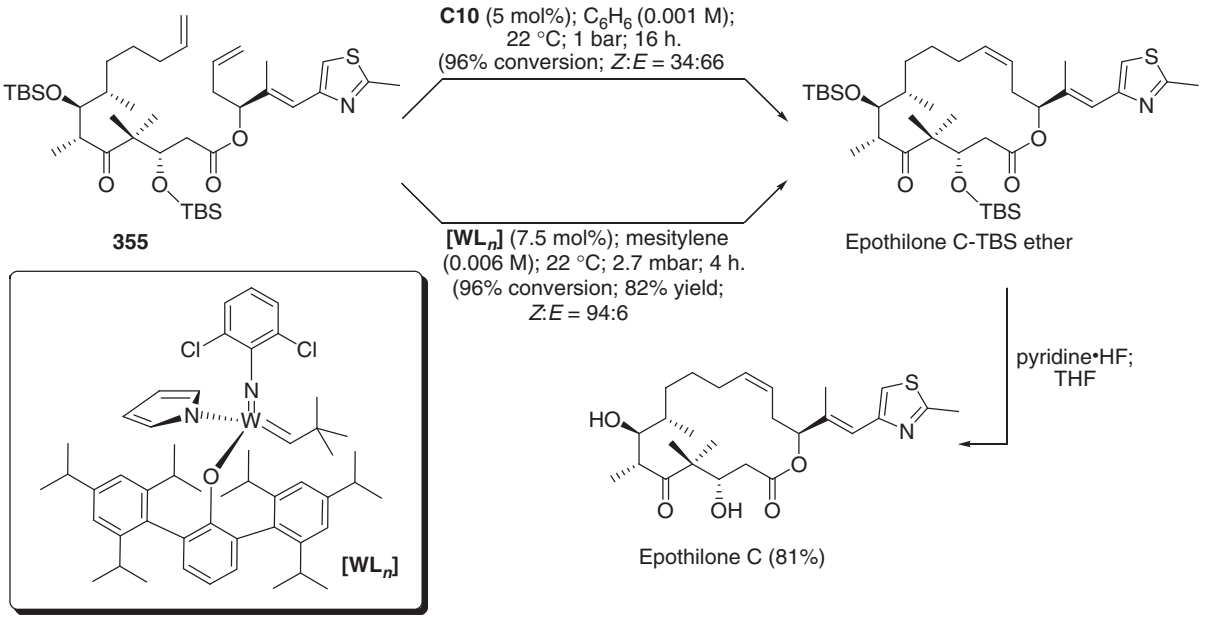
Recently, it was shown that stereoselectivity problems and undesired ring contraction can in many cases be efficiently suppressed if a sterically demanding silyl group is temporarily attached to a diene moiety participating in an RCM reaction. This strategy makes *E*,*Z*-configured conjugated macrocyclic dienes accessible.[285] Apart from these substrate-controlled solutions for the *E*,*Z*-selectivity problem, recently there has been significant progress made using a catalyst-controlled approach. Schrock, Hoveyda et al. developed a series of 'stereogenic-at-metal' catalysts which can not only be used for the efficient differentiation of enantiotopic vinyl groups (see Section 5.29.10, Scheme 92),[286] but also for *Z*-selective CM[287] and RCM.[288] This application is illustrated for a long-standing problem in the metathesis-based natural product synthesis, the *Z*-selective syntheses of the epothilones[289–292] (Scheme 82).

5.29.6 Heterocycles with Less Common Heteroatoms

The majority of heterocycles synthesized via RCM are five- or six-membered and contain just one oxygen or nitrogen ring atom. Other heteroatoms are by far less common (Table 22): these include phosphorus (entries 1, 2) and sulfur (entries 3–10) in various oxidation states, and some examples for boron heterocycles, mostly in combination with other electron-donating heteroatoms (entries 11, 12) and silacycloalkenes (entries 13, 14). The synthesis of P- and S-heterocycles based on RCM has been reviewed by Hanson et al.[293] Examples for metathesis-based formation of heterocycles with more than one heteroatom (entries 15, 16) are also comparatively rare.

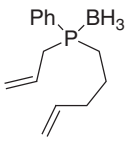
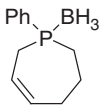
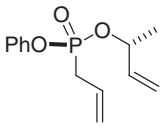
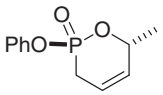
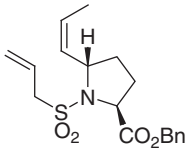
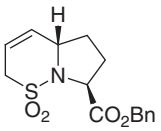
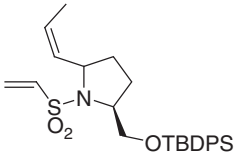
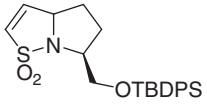
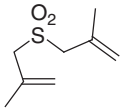
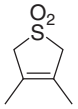
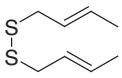
5.29.7 RCM Reactions Involving Heteroatom-Substituted Double Bonds

In this section, the authors discuss only examples where a heteroatom is attached to a double bond participating in an RCM and where this heteroatom is not an endocyclic part of the newly formed ring (Table 23). Metathesis reactions of



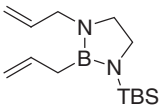
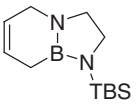
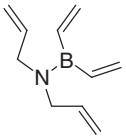
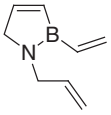
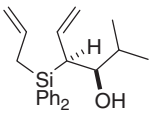
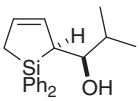
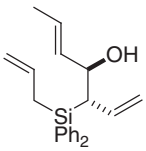
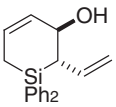
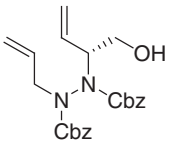
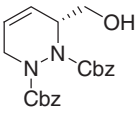
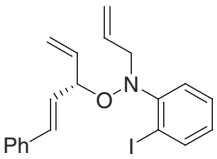
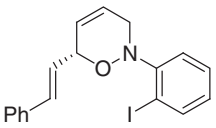
Scheme 82 Synthesis of epothilone C via *Z*-selective RCM.

Table 22 Metathesis-based heterocyclization for less common heteroatoms

Entry	*Precursor*	*Conditions*	*RCM product*	*Yield (%)*	*References*
1[a]		**C3** (4 mol%); CH_2Cl_2 (0.02 M); 40 °C; 9 h		94	294
2		**C3** (3 mol%); CH_2Cl_2 (0.009 M); 40 °C		68	295
3		**C3** (3 mol%); CH_2Cl_2 (0.01 M); 20 °C; 3 h		98	296
4		**C6** (5 mol%); toluene (0.01 M); 110 °C; 2 days		79	296
5		**C6** (5 mol%); CH_2Cl_2 (0.05 M); 40 °C; 24 h		99	297
6[b]		**C6** (5 mol%); CD_2Cl_2 (0.1 M); 40 °C; 4 h		>95	298
7		**C3** (5 mol%); CD_2Cl_2 (0.1 M); 40 °C; 12 h		0	298

(*Continued*)

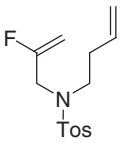
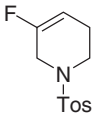
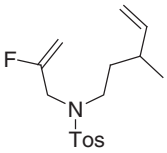
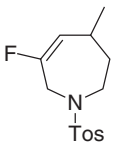
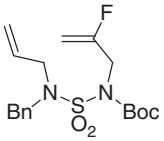
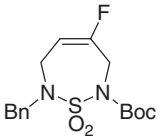
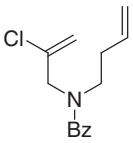
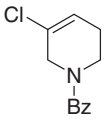
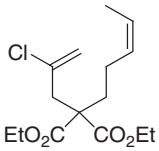
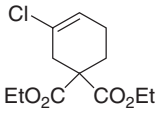
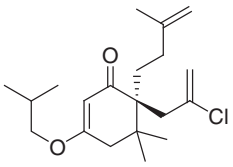
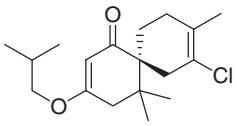
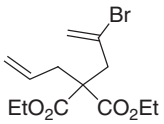
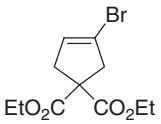
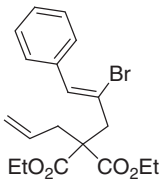
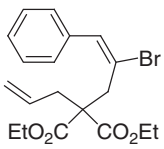
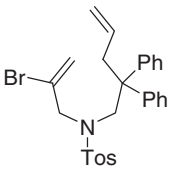
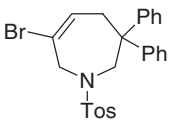
Table 22 Continued

Entry	Precursor	Conditions	RCM product	Yield (%)	References
8[c]		**C6** (5 mol%); CD_2Cl_2 (0.1 M); 40 °C; 4 h		6	298
9		**C1** (10 mol%); C_6H_6 (0.05 M); 20 °C; 3 h		54	299
10		**C2** (10 mol%); C_6H_6 (0.05 M); 20 °C; 3 h		0	299
11		**C3** (4 mol%); CH_2Cl_2 (0.13 M); 20 °C; 2 h		55	300
12		**C3** (5 mol%); CH_2Cl_2 (0.5 M); 25 °C; 9 h		62	301
13		**C3** (2 mol%); C_6H_6 (0.11 M); 80 °C; 6 h		93	302
14		**C3** (2 mol%); C_6H_6 (0.11 M); 80 °C; 12 h		57	302
15		**C6** (1 mol%); CH_2Cl_2 (0.014 M); 40 °C; 1 h		91	303
16		**C6** (10 mol%); C_6H_6 (0.17 M); 70 °C; 10 h		79	304

[a]No conversion with Ru-catalysts and the free phenyldialkyl phosphane.
[b]Yield with **C3** under otherwise identical conditions: 15%.
[c]Formation of 40% of the self-metathesis product.

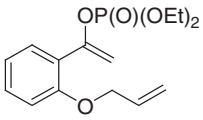
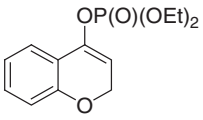
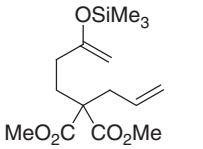
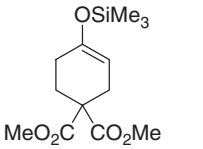
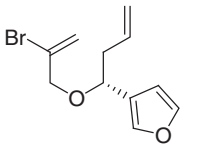
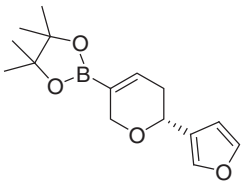
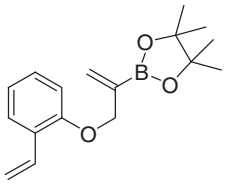
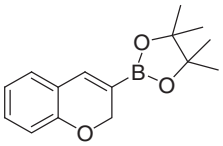
heteroatom-substituted double bonds have previously been reviewed by Brown and Satcharoen[305] and by Eustache et al.[306] Potentially highly useful from a synthetic point of view are metathetical cyclizations of vinyl halides; although RCM of vinyl fluorides might provide a convenient entry into fluorinated heterocycles as potential pharmaceutically active molecules (entries 1–3), the heavier halides offer the opportunity for further functionalization of the RCM products via cross-coupling reactions. Unfortunately, vinyl chlorides, which undergo RCM reactions at synthetically useful rates and selectivities (entries 4–6), are less reactive in this respect, whereas the more reactive vinyl bromides were for many years believed to be unreactive in olefin metathesis reactions. Recently, a surprising solution for this problem was devised by Dorta et al.,[307] who discovered that terminally unsubstituted vinyl bromides, such as the precursor in entry 7, decompose the second-generation catalyst **C6** with concommitant formation of styrene, when both are mixed in equimolar amounts. This observation explains why attempted catalytic RCM reactions of vinyl bromides failed. Remarkably, a quantitative conversion to the RCM product with liberation of styrene was observed when a phenyl substituent was introduced *Z* to the bromine (entry 8), whereas no conversion was observed for the *E*-isomer (entry 9). In their communication, the researchers present a plausible mechanistic rationale to explain this surprising outcome, along with 16 other examples to highlight the scope of the method; one of these is listed in entry 10. Apart from vinyl halides, enol ethers and enamides can also participate in RCM reactions. An example for the successful conversion of an enamide has been discussed in Section 5.29.4.2.2.3 in the course of Donohoe's streptonigrin synthesis.[249] Examples for the RCM of enol ethers are listed in entries 11 and 12. Enol phosphates are potentially useful as substrates for cross-coupling reactions, whereas the RCM of a silyl enol ether will, after desilylation, furnish a cyclic ketone. In entries 13 and 14, two examples for the RCM of vinyl pinacolatoboronates are given. The first successful RCM reactions of vinyl boronic acids and vinyl boronates were published by Renaud et al. in 1998 using the first-generation catalysts **C2** and **C3**.[308] The researchers discovered that the free boronic acids require longer reaction times and higher catalyst loadings than the analogous boronates. Later, second-generation catalysts were preferably used for this type of transformation, although occasionally still very long reaction times are necessary. The example

Table 23 RCM of heteroatom-substituted double bonds

Entry	*Precursor*	*Conditions*	*RCM product*	*Yield (%)*	*References*
1		**C6** (5 mol%); toluene (0.01 M); 100 °C; 1 h		97	309
2		**C6** (5 mol%); toluene (0.01 M); 100 °C; 1 h		94	309
3		**C6** (6 mol%); CH_2Cl_2 (0.03 M); 40 °C; 5 h		90	310
4		**C6** (10 mol%); C_6H_6 (0.004 M); 65 °C; 4–10 h		90	311
5		**C6** (10 mol%); C_6H_6 (0.004 M); 65 °C; 4–10 h		98	311
6		**C12** (5 mol%); C_6H_6 (0.1 M); 60 °C; 18 h		97	312
7		**C6** (2 mol%); C_6H_6 (0.1 M); 60 °C; 24 h		0	307
8		**C6** (2 mol%); C_6H_6 (0.1 M); 60 °C; 0.5 h		90	307
9		**C6** (2 mol%); C_6H_6 (0.1 M); 60 °C; 24 h		0	307
10		**C6** (5 mol%); CH_2Cl_2 (0.1 M); 40 °C; 3 h		67	307

(*Continued*)

Table 23 Continued

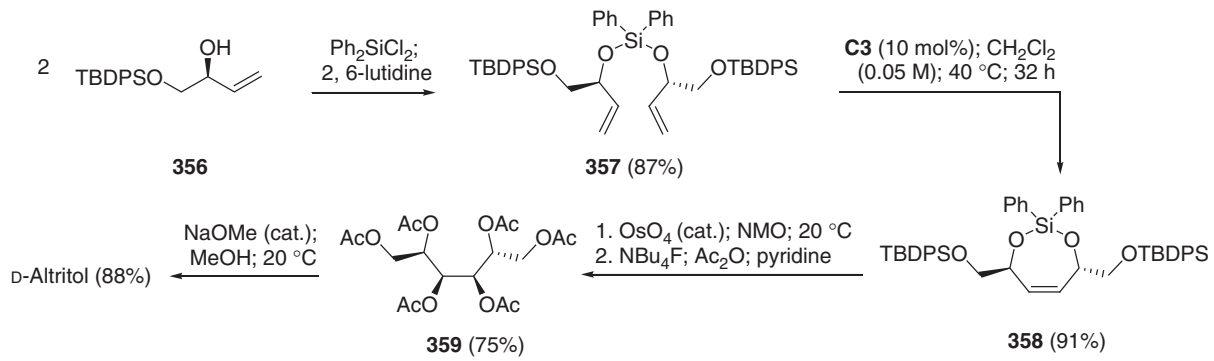
Entry	Precursor	Conditions	RCM product	Yield (%)	References
11		**C6** (5 mol%); CH_2Cl_2; 40 °C		99	313
12		**C6** (7 mol%); C_6H_6 (0.005 M); 65 °C; 1 h		99	314
13[a]		1. Bu^tLi; ether; −78 °C; 2-isopropoxy-tetramethyl-1, 3,2-dioxaborolane; −78 °C to 20 °C 2. **C6** (10 mol%); C_6H_6 (0.03 M); 20 °C; 4 h		45	315
14		**C10** (5 mol%); C_6H_6 (0.01 M); 22 °C; 60 h		71	316

[a]Yield over two steps.

listed in entry 13 is taken from Snapper's synthesis of cacospongiolide B analogs;[308] in this case the reported yield refers to the vinyl bromide used to synthesize the actual RCM precursor via halogen–lithium exchange and subsequent borylation. The precursor in the last example in entry 14 was synthesized using a Cu–NHC-complex catalyzed borylation of a propargyl ether with pinacolatodiboron.

5.29.8 Tethered RCM

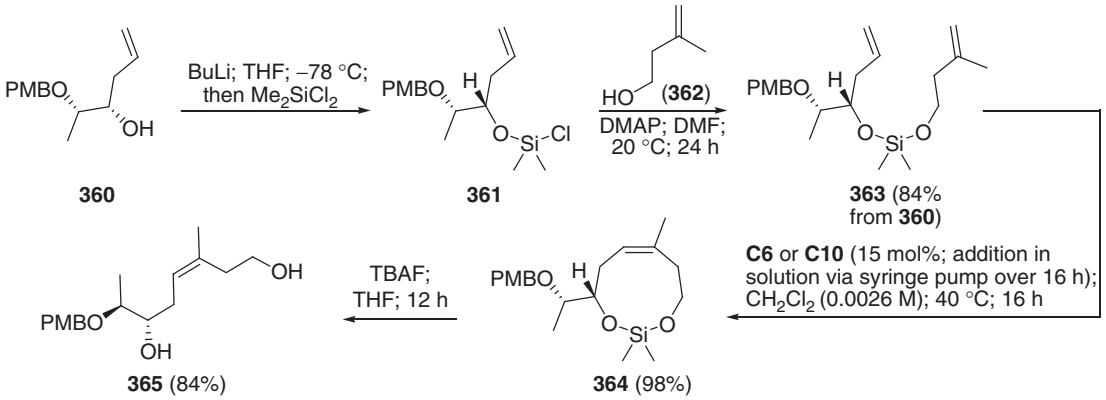
Tethered reactions are an important strategy to overcome entropic and selectivity drawbacks of many intermolecular reactions. The strategy involves the temporary connection of two molecules via a labile bond and a subsequent cyclization, which occurs ideally with improved yields and stereoselectivities compared with the intermolecular variant. Eventually, cleavage of the tether liberates the desired acyclic product. Particularly useful tethers contain silicon–carbon or silicon–oxygen bonds and were originally developed for radical cyclization reactions.[317] Later, these silicon tethers have been used to solve the *E*/*Z*-selectivity problem normally associated with olefin CM reactions.[3] Although RCM reactions leading to five- to eight-membered cycloalkenes necessarily proceed *Z*-selectively, CM reactions normally show moderate to high *E*-selectivity. An early application of the tether concept in olefin metathesis was published by Evans et al. and addresses this particular problem (**Scheme 83**).[318] Silylation of



Scheme 83 Silicon-tethered RCM-dihydroxylation sequence.

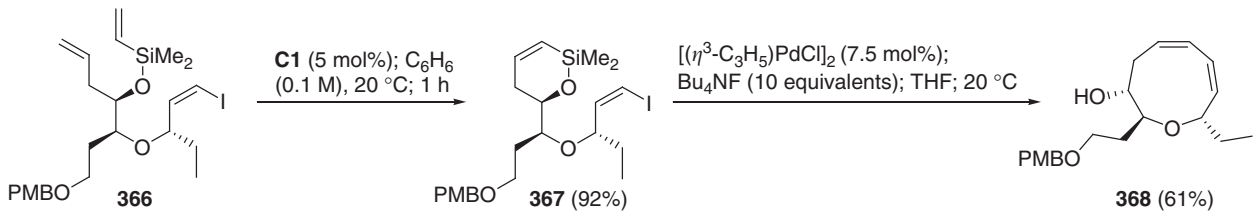
allylic alcohol **356** with dichlorodiphenyl silane gave silyl ether **357**, which underwent RCM with **C3** to the C_2-symmetric seven-membered cycle **358**. Osmium-catalyzed dihydroxylation, followed by cleavage of the tether with fluoride and treatment with acetic anhydride lead to the isolation of peracetylated D-altritol **359**.

Another problem of CM reactions is the formation of homodimers if olefins of the same type are used. In these cases, a statistical distribution of products must be expected. It has been demonstrated by several groups that temporary silicon-tethered RCM is a suitable method to circumvent this particular obstacle as well. For example, the C10–C15 fragment of epothilones B and D has been synthesized using a silicon-tethered RCM of an unsymmetrical silyl acetal **363**, which was obtained from alcohols **360** and **362** by stepwise condensation with dichloro dimethyl silane (Scheme 84).[319] The researchers point out that carefully controlled conditions for the RCM step are crucial in this example; quantitative yields of the RCM product **364** could only be obtained by extremely slow addition of catalysts **C6** or **C10** to a solution of **363**. Addition of the catalyst in one portion always resulted in yields of only 50%.



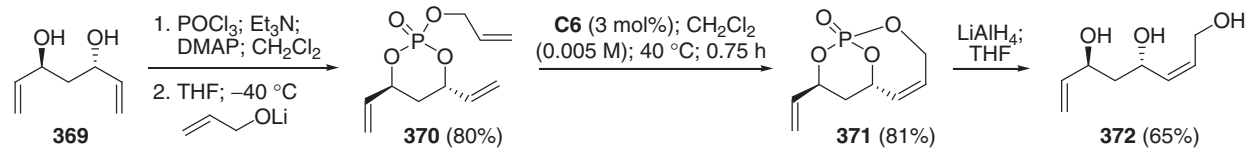
Scheme 84 Synthesis of C10–C15 fragment of epothilones B and D via silicon-tethered RCM.

As mentioned above, silicon tethers may also rely on Si–C bonds, which offer additional opportunities for the post-RCM cleavage of the tether. For example, Denmark and Yang used the cyclic vinylsiloxane **367**, synthesized via RCM of **366** using Schrock's catalyst **C1**, for a Pd-catalyzed intramolecular cross-coupling reaction en route to the natural product (+)-brasilenyne (Scheme 85).[320]



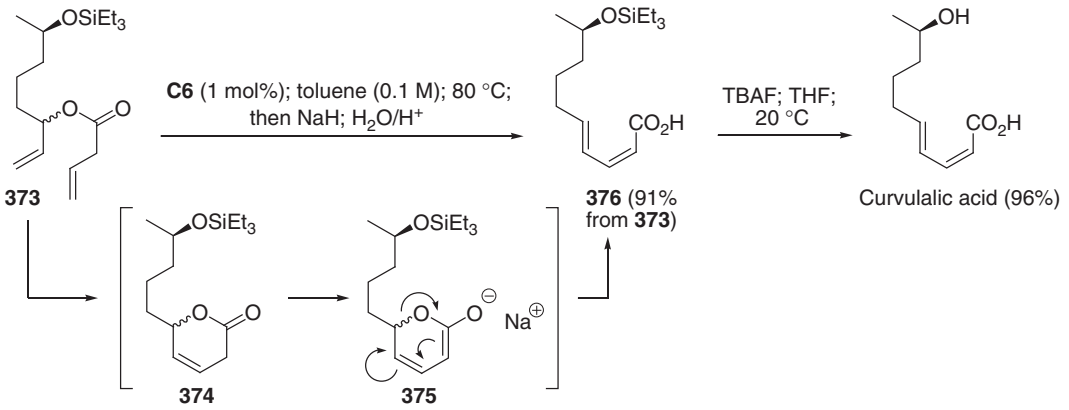
Scheme 85 Silicon-tethered RCM and subsequent cross coupling.

Over the past few years several examples for the efficient use of phosphate-tethered RCM reactions were published by Hanson et al. (Scheme 86).[321,322] For example, phosphate **370**, obtained via condensation of the C_2-symmetric diol **369** with $POCl_3$ and subsequent substitution of the remaining chloride with a Li-alkoxide, was cyclized to the bicyclic phosphate **371** in high yields. Reduction of **371** furnished triol **372** as a single *Z*-isomer. The phosphate-tethered RCM can be extended to a bidirectional synthesis by subjecting **371** to a CM before cleavage of the tether.[323]



Scheme 86 Temporary phosphate-tethered RCM.

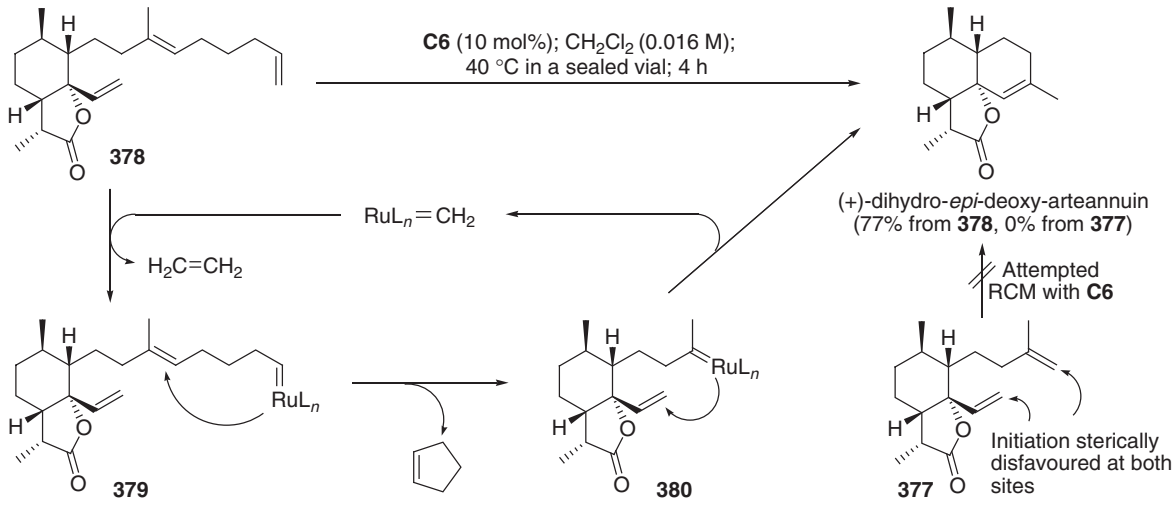
In most tethered RCM reactions the tether is removed tracelessly at some point after the cyclization by reduction or hydrolysis. It might, however, be an interesting option to keep the tether in the molecule as a functional group after cleavage. An example of this approach is outlined for the synthesis of the natural product curvulalic acid (Scheme 87)[324] via a one-flask RCM-deprotonation-electrocyclic ring opening sequence of butenoate **373**, which proceeds cleanly and highly stereoselectively to give the (2*Z*,4*E*)-configured dienoic acid **376**. After deprotection, the target molecule was obtained in nearly quantitative yields.



Scheme 87 Synthesis of *Z*,*E*-dienes via one-flask tethered RCM/electrocyclic ring opening.

5.29.9 Relay Ring-Closing Metathesis

The examples of RCM reactions presented in the previous sections suggest that at least one double bond of the diene precursor should be sterically and electronically unencumbered for the RCM to proceed at a reasonable rate and hence with a synthetically useful catalyst loading. It can be concluded that in these cases the initial attack of the metal–carbene species will occur at the sterically less hindered and electronically neutral site, but that – once initiation took place – the subsequent steps are reasonably fast and less influenced by steric or electronic drawbacks of the second double bond. This reasoning is the basis for the relay RCM (RRCM) concept originally developed by Hoye et al. to overcome reactivity problems in RCM reactions arising from insufficient rates of initiation.[325] The concept and some early applications have been reviewed by Wallace.[326] Here, the method is illustrated by the example of the total synthesis of the sesquiterpene dihydro-*epi*-deoxyarteannuin B (Scheme 88).[327]



Scheme 88 Illustrative example of an application of the RRCM concept.

Precursor **377** was found to be completely unreactive in attempted RCM reactions because both the terminal double bonds are sterically congested and the initial attack of the Ru-carbene at either site is hindered. However, the extended precursor **378** reacts smoothly to the target molecule, because initiation at the least hindered double bond is facile, the resulting Ru-carbene **379** then attacks the internal trisubstituted double bond via a backbite mechanism with concommitant formation of cyclopentene and a new Ru-carbene intermediate **380**. Once this Ru-carbene is formed, the catalytic cycle of the RCM can proceed, ethene is liberated,

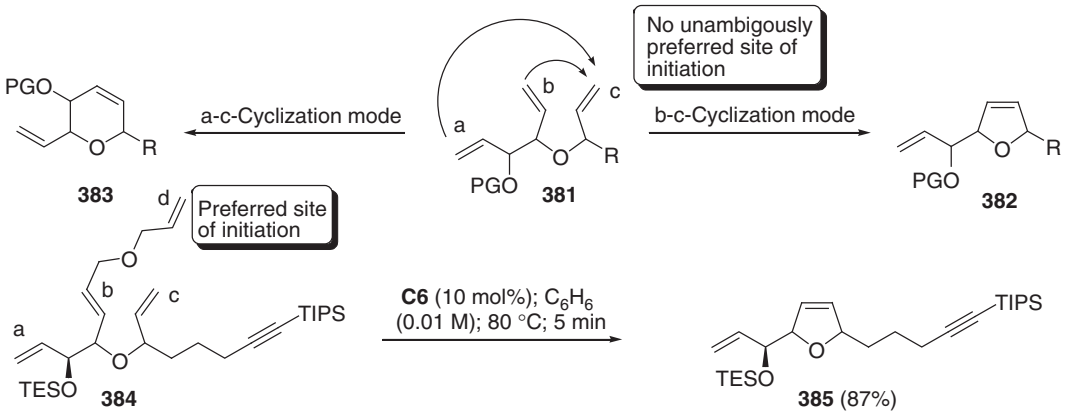
and the catalytically active species is regenerated. Apart from this example several interesting applications of RRCM have been published since the original disclosure[325] of the concept by Hoye et al. Recent examples include a RRCM-assisted macrocyclization in the synthesis of peloruside A[328] and a synthesis of the natural product penostatin B, where RRCM is used to trigger initiation at an electron-deficient acrylate moiety.[329] RRCM strategies can also help to overcome selectivity problems observed for certain RCM substrates with more than two double bonds. This aspect is covered in Section 5.29.10.

One should, however, bear in mind that in spite of numerous highly effective applications of the RRCM concept, the 'use of an RRCM strategy by no means guarantees a successful outcome',[330] as was recently stated by Hoye et al. in a very instructive account of synthetic approaches toward callipeltoside A.

5.29.10 Control of Regio- and Stereochemistry Issues Through RCM Reactions

Regio- and stereoselectivity issues may arise for substrates with more than two double bonds amenable for RCM. The subject has been reviewed,[331,332] and in this section different selectivity issues and their solutions are exemplified.

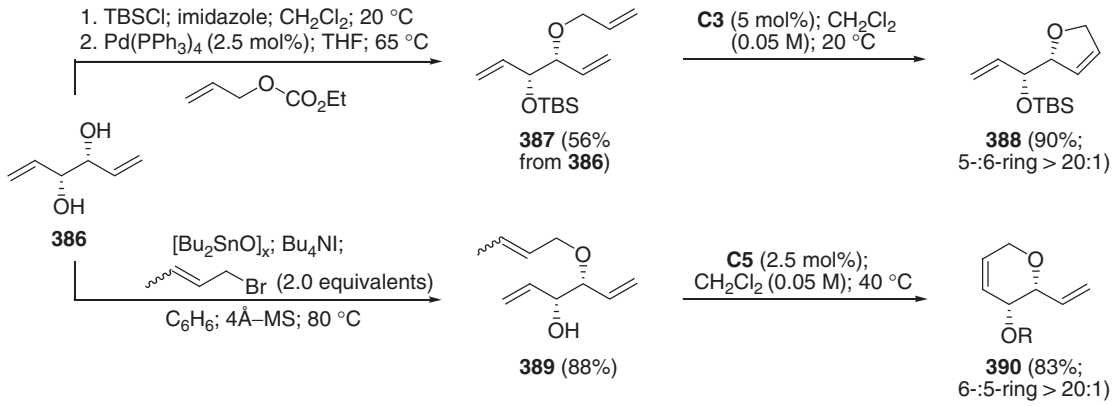
Regioselectivity of a given RCM reaction may affect the resulting ring size; for this reason, the term 'ring size selectivity' has been occasionally used. The following example to illustrate the problem and strategies to its solution comes from Crimmins' synthesis of the acetogenin natural product (–)-mucocin (Scheme 89).[333] In preliminary experiments it was discovered that precursors of the general structure **381** undergo RCM only with insufficient regioselectivity, leading to mixtures of the five- and six-membered rings **382** and **383**. This observation suggests that there is no preference for initiation at one of the three double bonds a, b, and c. A selective formation of the desired five-membered ring might be accomplished if the catalyst is directed exclusively to double bond b, because from this point only the cyclization mode b-c is feasible. Indeed, a ring size selective synthesis of the dihydrofuran fragment **385** could be realized through an RRCM strategy (see Section 5.29.9 for details) using precursor **384**, which preferentially initiates at the least hindered double bond d and then undergoes transfer of the Ru to position b with the formation of the 2,5-dihydrofuran **385**.



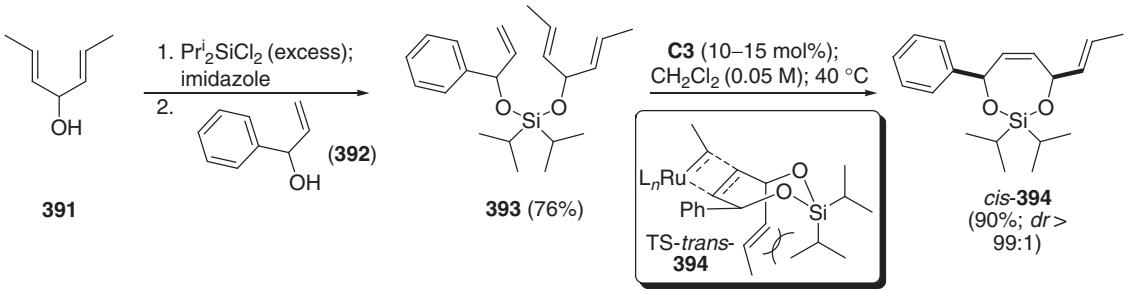
Scheme 89 Ring size selectivity issue in the synthesis of (–)-mucocin.

Another strategy to effectively influence ring size selectivity relies on hydroxyl group-directing effects. Such effects have also been exploited and rationalized by mechanistic considerations for diastereoselective ROM–CM sequences by Hoveyda et al., who proposed an H-bonding interaction between allylic OH-groups and the chloro ligands of the Ru-catalyst.[76] In the example outlined below, enantiopure dihydrofurans and dihydropyrans were synthesized selectively starting from the C_2-symmetric diene **386** (Scheme 90).[334] The TBS-protected allyl ether **387** reacts in high yield and selectivity exclusively to the dihydrofuran **388**, presumably due to initiation at the linear allyl ether and subsequent cyclization at the less hindered double bond. In contrast, the crotyl ether **389** cyclizes with similar yield and selectivity to the dihydropyran **390**, which can be rationalized by assuming that the OH-group steers the catalyst (most likely via H-bonding with the chloro ligands, *vide supra*) to the adjacent C–C double bond. In this case, a crotyl ether was used instead of an allyl ether to additionally increase the steric demand of the linear allyloxy substituent and suppress initiation at this site. Without the terminal methyl group, five- and six-membered oxacycles are formed in equal amounts. However, the first-generation Hoveyda–Grubbs catalyst **C5** had to be used for this substrate, because conversion remained incomplete with the less active catalyst **C3**. Interestingly, all NHC–Ru-catalysts tested in this study were unsuitable to mend the problem, because a complete erosion of selectivity was observed.

Diastereoselectivity becomes an issue in RCM reactions of trienes with two diastereotopic double bonds. The first examples for this type of RCM were published by Huwe and Blechert, who obtained up to 92% *de* and found that opposite relative configurations of the RCM products were obtained with the Ru-catalyst **C3** and the Mo-catalyst **C1**.[335] To illustrate the principle, an interesting example is highlighted below, in which a diastereoselective differentiation of diastereotopic groups is achieved through a tethered RCM (Scheme 91).[336]



Scheme 90 Control of ring size selectivity through OH-directing effects.



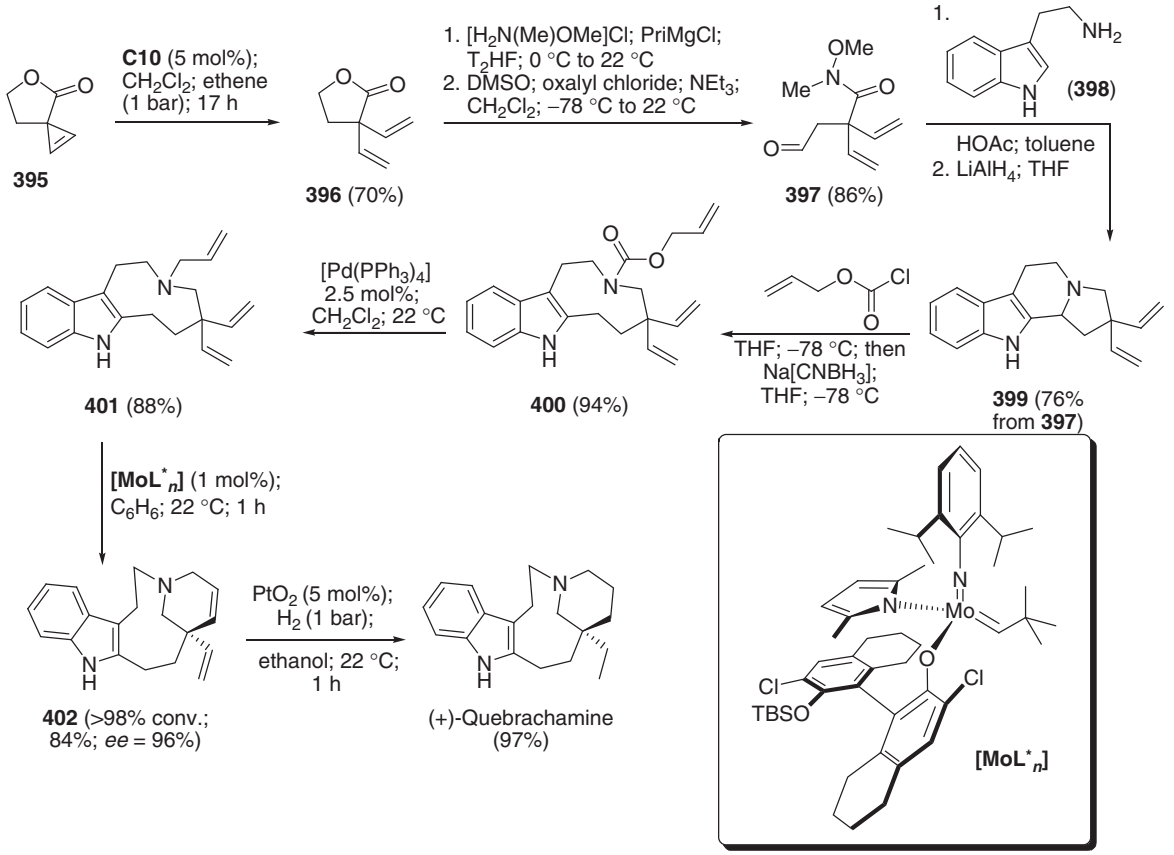
Scheme 91 Highly diastereoselective tethered RCM.

As for other tethered RCM reactions, precursor **393** was synthesized via stepwise condensation of alcohol **391** with a dichlorodialkyl silane and allylic alcohol **392**. With catalyst **C3**, which needs to be added to the reaction mixture in portions over a period of several hours, the *cis*-configured product **394** (and several related examples) were obtained in diastereomeric ratios generally better than 20:1. The steric demand of the alkyl substituents at the silicon is crucial for the success of the reaction, which can be understood from the proposed transition state (see Inset in Scheme 91). The disfavored transition state TS-*trans*-**394** is presumably destabilized by steric repulsion between the vinyl substituent not participating in the RCM and the pseudoaxially oriented isopropyl substituent at the silicon.

Enantioselective RCM can be considered as the ultimate challenge in the field discussed in this section. Considerable efforts were made to obtain chirally modified catalysts that are highly active, yield high enantioselectivities, and are applicable to a broad range of substrates at the same time. The topic has been the subject of very instructive and up-to-date reviews by Hoveyda et al. (with a focus on applications in natural product synthesis)[337] and Kress and Blechert (a recently published tutorial review that outlines general construction principles of the catalysts and mechanistic considerations to rationalize the observed enantioselectivities).[338] In the context of this overview, we illustrate for one example, the enantioselective synthesis of the alkaloid quebrachamine and how the differentiation of enantiotopic vinyl groups by RCM using a chiral Mo-catalyst can be implemented in a total synthesis (Scheme 92).[286] The synthesis of the RCM precursor starts from a γ-butyrolactone, which is converted in a few steps to the spirocyclic lactone **395**. At this stage the two enantiotopic vinyl groups (to be differentiated several steps later) are introduced by a ROM using catalyst **C10**. By nucleophilic ring opening with an *in-situ* generated Mg-amide and subsequent Swern oxidation aldehyde **397** was obtained, which reacts with tryptamine (**398**) in a Pictet–Spengler reaction to give the tertiary amine **399**. Acylation of nitrogen with allyl chloroformiate, followed by reduction furnished amide **400**, which was then subjected to an intramolecular Pd-catalyzed N-allylation, giving the required precursor **401** for the enantioselective RCM, which was successful with the chiral Mo-catalyst depicted in the Insert. Notably, in contrast to many other chiral metathesis catalysts, this complex does not only contain a chiral ligand, but the metal itself is a stereocenter ('stereogenic-at-Mo-complexes'), accounting for the high levels of enantioselectivity observed. The synthesis of (+)-quebrachamine is completed by hydrogenation of the two double bonds of the RCM product **402**.

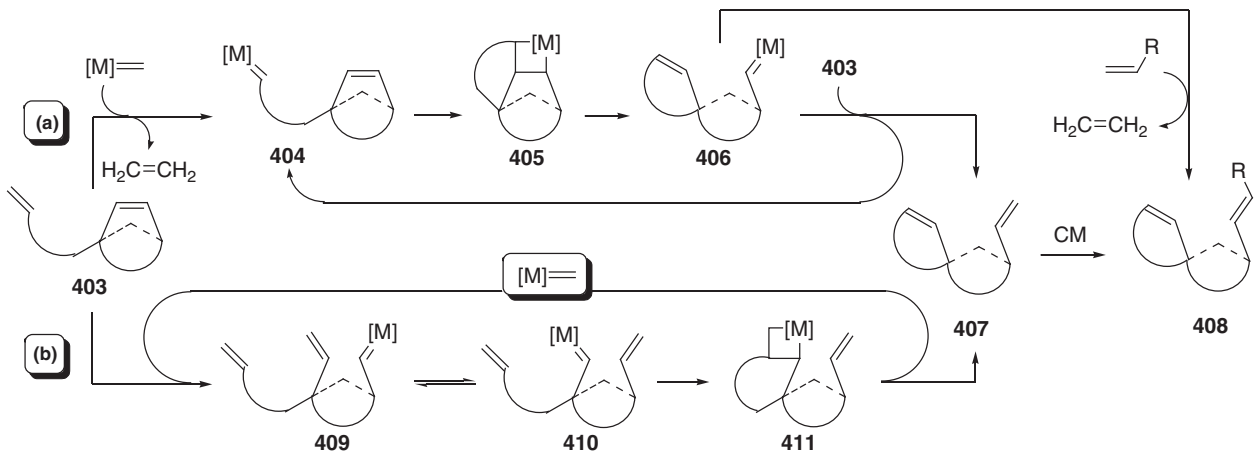
5.29.11 Ring Rearrangement Metathesis (Domino Reactions)

According to Tietze's definition, a domino reaction is understood as 'a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the



Scheme 92 Total synthesis of (+)-quebrachamine via enantioselective RCM.

previous step.'[339] Homogeneous olefin metathesis catalyzed by Mo- and Ru-complexes was still in its infancy when this definition was published in 1993, but shortly afterwards a group of metathesis reactions was discovered that fits the above definition of a domino reaction perfectly, the ring rearrangement metathesis reactions (RRM). The field has been extensively reviewed,[340,341] and the authors will therefore limit themselves to discussing the concept with a few representative examples. In a typical RRM, a strained cycloalkene (bridged or monocyclic) with a pendant ω-unsaturated alkyl substituent (**403**) reacts to another less strained cycloalkene with a different ω-unsaturated side chain (**407**). The driving force for these reactions can be a release of ring strain, decreased steric interactions of other substituents attached to the starting carbo- or heterocycle, and/or removal of a volatile alkene from the reaction mixture. In principle, two mechanisms are conceivable (Scheme 93).



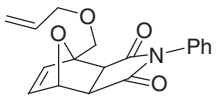
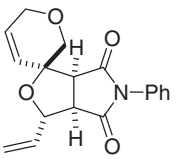
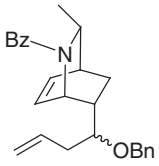
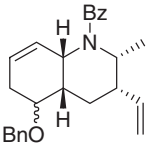
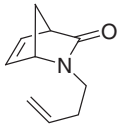
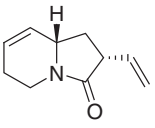
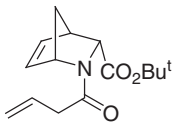
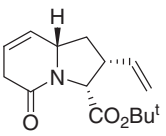
Scheme 93 Schematic presentation of different mechanistic scenarios for RRM reactions.

Mechanism (*a*): Initiation occurs at the least hindered double bond (typically the pendant side chain) to give a carbene complex **404**, followed by intramolecular attack of the carbene at the endocyclic double bond of the strained cycloalkene (metallacyclobutane **405**), resulting in a ring opening of the strained ring with release of ring strain and concomitant formation of a new, less strained cycle (ROM/RCM sequence) with a pendant metal–carbene moiety (**406**). Termination of the sequence occurs either by transfer of the carbene to the next substrate **403** (no small molecule alkene formed) with the formation of **404**, or by a CM with an added alkene (giving **408**) or by a second RCM event (not shown in the general scheme). In the latter cases a volatile alkene is released.

Mechanism (*b*): The catalyst initially attacks the strained cycle with immediate loss of ring strain, leading to the new metal carbenes **409** and/or **410**. These carbene complexes are interconvertible, but **410** can be removed from the equilibrium by a subsequent 'normal' RCM with the pendant ω-unsaturated side chain via metallacyclobutane **411**. Again, no volatile alkene is set free unless the new ω-unsaturated substituent is engaged in a subsequent metathesis reaction (either CM or RCM).

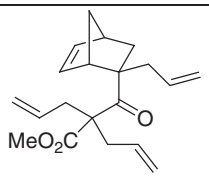
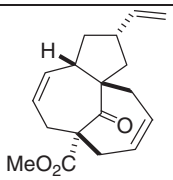
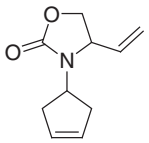
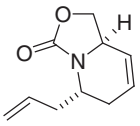
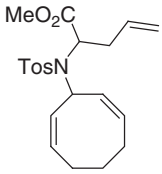
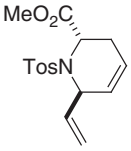
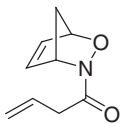
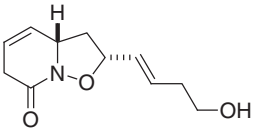
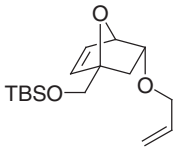
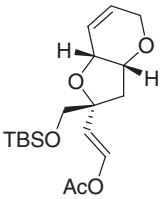
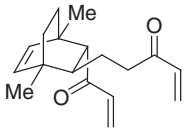
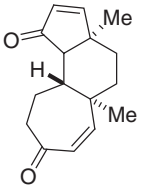
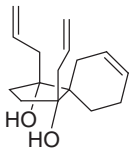
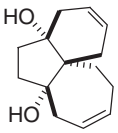
Metathesis transformations proceeding along these lines offer vast opportunities for the rapid and highly stereoselective construction of hetero- and polycyclic systems, because very often norbornenes and heteronorbornenes can be used as substrates, which are conveniently available via stereoselective Diels–Alder reactions. The absolute and relative configuration of the starting materials is then transferred through the RRM sequence into the desired products. It should be noted that a considerable number of transformations classified as ring rearrangement metathesis reactions involve one or two C–C triple bonds. These enyne metathesis reactions are beyond the scope of this chapter and covered separately in this volume (*see* Chapter 5.27). For these reasons, the principle of RRM is illustrated in Table 24 exclusively for alkenes. In the example listed in entry 1, the ω-unsaturated side chain is attached to the bridgehead of the strained bicyclic system. As can be deduced from the general scheme outlined above, spirocycles are the products in these cases. If, as in entry 2, the pendant side chain is attached to an atom adjacent to the bridgehead of the bicyclic starting material, annellated bicyclic products will result. As can be seen from entries 3–7, the RRM is frequently conducted under an atmosphere of ethene. In practice, this is often accomplished by saturation of the solvent with ethene before the reaction. For the example in entry 5, an additional 'conventional' RCM step occurs, resulting in the formation of an additional cycloheptenone ring. Entries 6 and 7 nicely illustrate that diastereoselective RCM can also be combined with an RRM sequence. In these examples, the halves of the cyclopentene and cycloheptadiene ring are diastereotopic, and the RRM sequence consequently becomes diastereoselective, with the *dr* of 14:1 observed for the example in entry 7 being remarkably high for this type of reactions. This example deserves another comment: after the RRM sequence one would expect a hepta-1,6-dienyl side chain α to the ring nitrogen; however, cyclopentene is cleaved off via a backbite mechanism and a vinyl side chain remains. Entries 8 and 9 illustrate the elongation of the ROM/RCM sequence by a CM step with pent-4-ene-1-ol (entry 8) and vinyl acetate (entry 9), respectively. Entries 10 and 11 show examples of RCM/ROM/RCM-sequences. Notably, for the example in entry 10, both pendant double bonds are electron deficient, making initiation at these sites less likely and suggesting a preferred pathway via general intermediate **409** (Scheme 93), which may also account for the comparatively high catalyst loading that was required.

Table 24 Examples for ring rearrangement metathesis reactions

Entry	*RRM-precursor*	*Conditions*	*RRM-product*	*Yield (%)*	*References*
1		**C6** (2 mol%); CH_2Cl_2 (0.01 M); 20 °C		95	342
2		**C6** (1 mol%); toluene (0.01 M); 80 °C; 2 min.		74	343
3[a]		**C3** (5 mol%); CH_2Cl_2 (0.025 M); ethene (1 bar); 20 °C; 24 h		60	344
4[b]		**C6** or **C10** (10 mol%); CH_2Cl_2 (0.01 M); ethene (1 bar); 40 °C; 12 h		58–63	345

(*Continued*)

Table 24 Continued

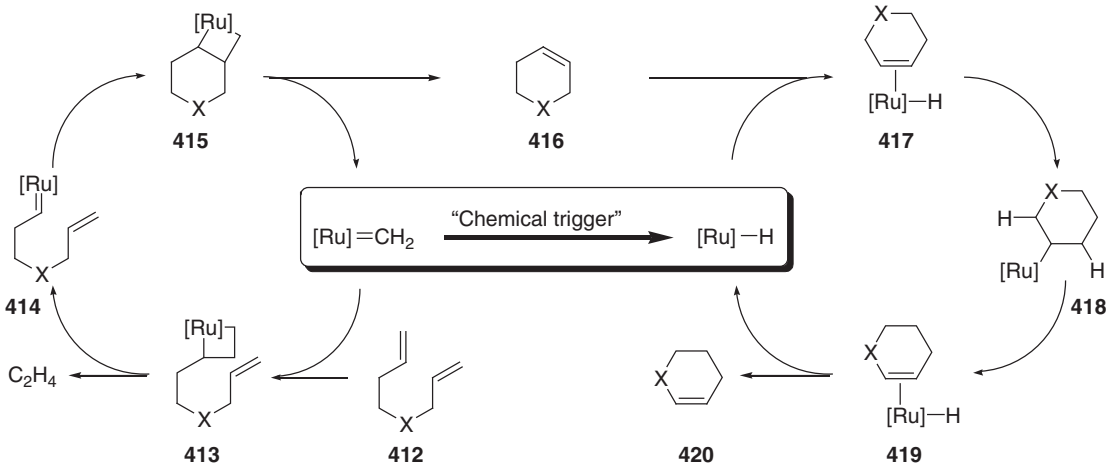
Entry	*RRM-precursor*	*Conditions*	*RRM-product*	*Yield (%)*	*References*
5		**C3** (10 mol%); CH_2Cl_2 (0.014 M); ethene (1 bar); 20 °C; 2 h		59	346
6[c]		**C5** (2 mol%); CH_2Cl_2 (0.02 M); ethene (1 bar); 20 °C		89	347
7[d]		**C6** (5 mol%); CH_2Cl_2 (0.02 M); ethene (1 bar); 20 °C		95	347
8[e]		**C6** (2.5 mol%); CH_2Cl_2 (0.5 M); pent-4-ene-1-ol (4 equivalents); 40 °C		77	348
9		**C10** (9 mol%); C_6H_6 (0.01 M); vinyl acetate (10 equivalents); 60 °C; 4 h		95	349
10[f]		**C6** (20 mol%, portionwise addition over several hours); toluene (0.01 M); ethene (1 bar); 20 °C; 12 h		43	350
11		**C6** (10 mol%); C_6H_6 80 °C; 2 h		90	351

[a]Isolated along with the starting material (30%) and ROM-product (7%).
[b]Obtained with small amounts of a dehydrogenation product (a pyridone).
[c]*dr* = 5:1 in favor of the *trans*-isomer.
[d]*dr* = 14:1 in favor of the *trans*-isomer; cyclopentene is released after ROM/RCM step.
[e]Isolated together with 10% of the ethenolysis product.
[f]Yield also refers to the two previous steps.

5.29.12 Sequential RCM–Non Metathesis Transformations (Tandem reactions)

The domino metathesis reactions discussed in the previous section are characterized by the presence of just one catalytically active species (i.e., a metal–carbene complex), which promotes all steps of the sequence via essentially the same mechanism (i.e., the Chauvin mechanism). In addition, no functional group interconversion occurs during the sequence, which means that alkenes are converted via a domino metathesis transformation into other alkenes. Apart from these reactions, a second class of sequential metathesis reactions has emerged over the past decade, which are conceptually different from the domino or ring rearrangement

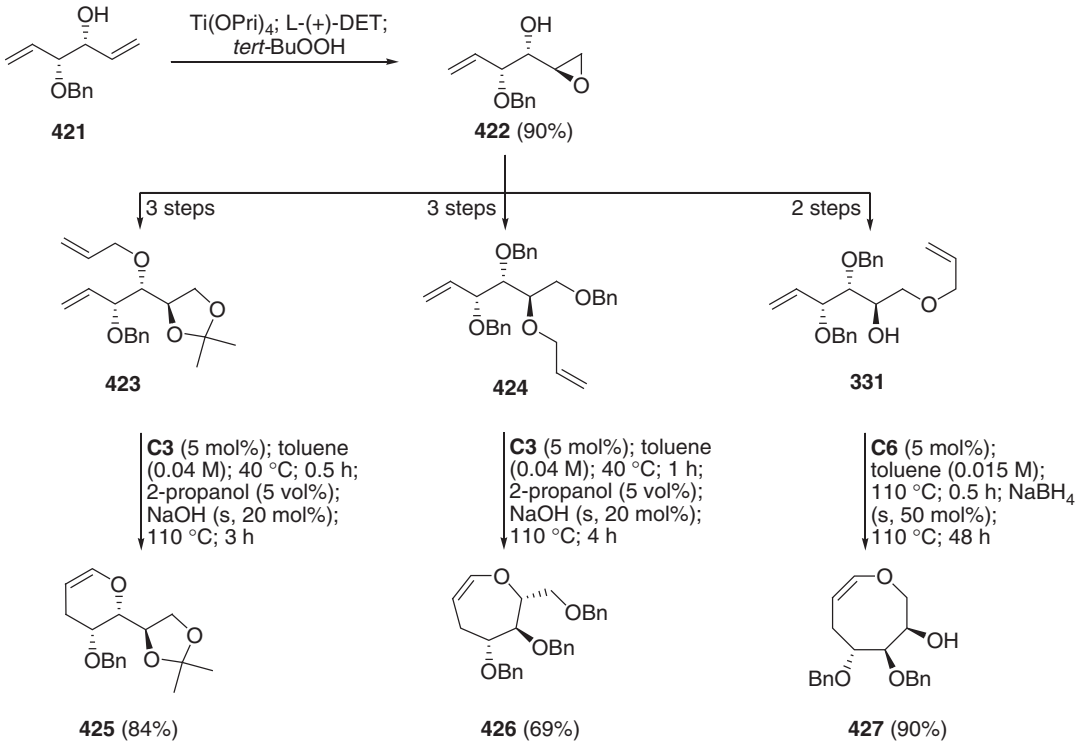
metathesis reactions. This second class includes transformations, which combine an olefin metathesis step with a subsequent nonmetathesis transformation of the primary product. These reaction sequences differ from simple one-pot reactions because the nonmetathesis step is also metal catalyzed and just one precatalyst is required. This implies that an organometallic transformation of the metal–carbene into a different species is triggered *in situ* by a change of the reaction conditions, which then catalyzes the nonmetathesis transformation. To distinguish between domino transformations such as RRM and sequential reactions such as those described above, Fogg and dos Santos have introduced the term 'assisted tandem catalytic transformation'. These are characterized by the presence of just one precatalyst, but more than one catalytic mechanism.[352] For reagents added to induce the organometallic transformation of one catalytically active species into the other, the researchers used the term 'chemical trigger'. To illustrate the principle, the mechanistic basis of the RCM isomerization sequence[353] will be first discussed as a representative example (Scheme 94), some of its applications will be highlighted and finally other RCM–nonmetathesis reaction sequences falling into this category will be summarized.



Scheme 94 Assisted tandem catalytic RCM isomerization sequence.

In the particular case of the Ru-catalyzed RCM-isomerization sequence, an α,ω-diene **412** undergoes RCM to the cycloalkene or heterocycloalkene **416** catalyzed by a Ru-carbene species via the expected intermediates **413**–**415**. After completion of the metathesis reaction, the conversion of the Ru-carbene species into a Ru-hydride species, which are well known isomerization catalysts,[354] is induced by the addition of a reagent[355,356] or – in the case of second-generation catalysts – occasionally already by heating the reaction mixture.[357,358] The product of the RCM reaction (**416**) then enters the next catalytic cycle via coordination to the Ru-hydride (**417**), hydroruthenation (**418**), β-hydride elimination (**419**) and dissociation into the Ru-hydride and the isomerized product **420**. Such an isomerization can be expected to proceed selectively into one direction whenever there is a thermodynamic driving force for a migration of the double bond.

Obvious advantages of such sequences are a reduced number of unproductive work-up steps and consequently a reduced amount of solvents, waste and labor cost. In addition, the multipurpose use of precious metal catalysts improves the overall efficiency of a synthesis. In some cases, the option to circumvent notoriously difficult RCM steps, which might require excessively high catalyst loadings, highly active but expensive precatalysts, and high dilution conditions, is an additional benefit of the sequences discussed in this section. This point is illustrated for the application of the RCM-isomerization sequence to the synthesis of ring-expanded glycals (Scheme 95).[267] As can be seen from the discussion and the examples presented in Sections 5.29.3.2.1.3, 5.29.3.2.2.3, 5.29.4.2.1.3, and 5.29.4.2.2.2, RCM becomes significantly more difficult if an enol ether or enamide moiety is involved, compared with the analogous allyl precursors leading to the same ring size. The problem becomes even more pronounced if medium-sized rings have to be synthesized via enol ether or enamide metathesis (see, for instance, Section 5.29.5.1, Table 19 entries 7 and 8). An alternative route to glycal-type compounds of different ring sizes starts from allyl ethers **423**, **424**, and **331**, which are all available from diene **421** via epoxide **422**. In the case of **423** and **424**, the first-generation catalyst **C3** is sufficiently active to achieve rapid RCM. Conversion of the metathesis-active carbene into the isomerization-active Ru-hydride is then accomplished by the addition of 2-propanol and a base as a 'chemical trigger', presumably via the formation of a Ru-alkoxide that undergoes β-hydride elimination with the formation of acetone. Under these conditions, clean and irreversible isomerization to the desired glycals **425** and **426** occurs. In the case of precursor **331**, leading to an eight-membered oxacycle, the reactivity of **C3** in the metathesis step was insufficient and **C6** had to be used instead (see Scheme 73 in Section 5.29.5.2). In this particular case, an alternative 'chemical trigger', $NaBH_4$ in substoichiometric amounts, turned out to be advantageous and lead to the isolation of the eight-membered cyclic enol ether **427**. Alternative chemical triggers that have been used to deliberately induce isomerization activity of Ru-based metathesis catalysts are silanes,[356] enol ethers,[157,356] or a hydrogen atmosphere diluted with nitrogen.[355]

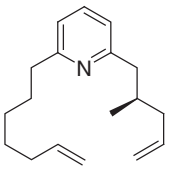
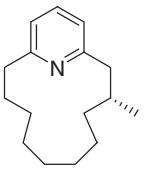
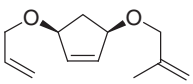
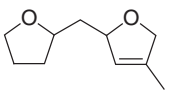
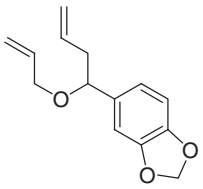
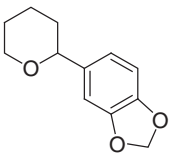
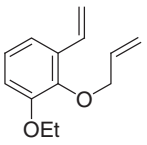
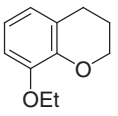
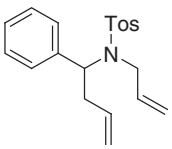
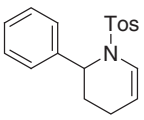
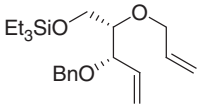
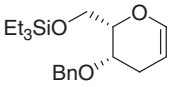
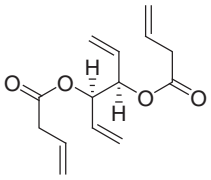
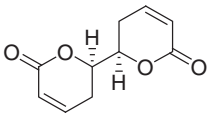
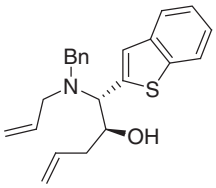
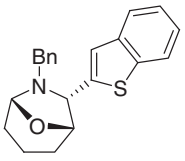
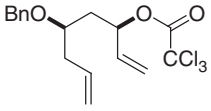
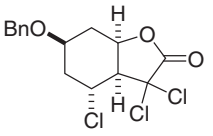
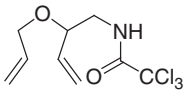
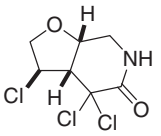


Scheme 95 RCM isomerization for the synthesis of ring-expanded glycols.

It should be noted that sometimes isomerization reactions may occur as highly undesirable side reactions in 'normal' RCM reactions.[359] The reasons for this complication can be diverse: sometimes the precatalyst contains small but highly active impurities of Ru-hydrides formed during the preparation of the catalyst, in particular if alcohols were used for washing the precipitated precatalyst.[360] However, the formation of a Ru-hydride through decomposition under the conditions of the metathesis reaction has also been observed, especially for second-generation catalysts. Some of these are known to decompose thermally via a bimolecular pathway, which explains why undesired isomerization occurs often with slowly reacting substrates that require high catalyst loadings and elevated temperatures.[357] In these cases, addition of benzoquinones often solves the problem[361] (see, for instance, the examples discussed in Table 17, entry 4 and Scheme 68).

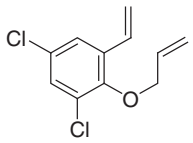
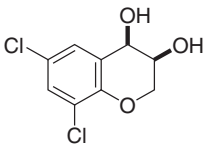
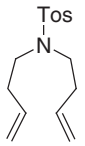
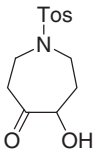
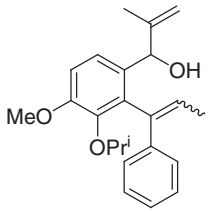
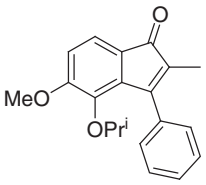
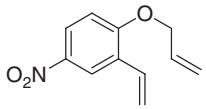
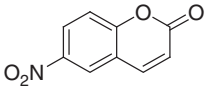
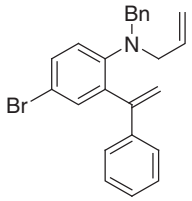
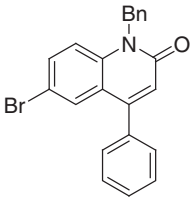
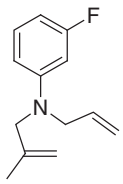
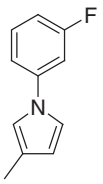
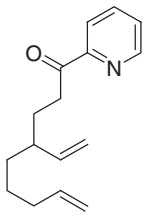
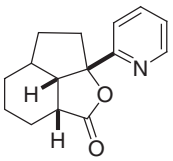
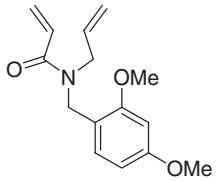
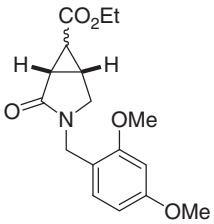
Apart from the RCM-isomerization sequence, several other RCM–nonmetathesis reactions have appeared in the literature. The subject has been reviewed comprehensively,[362] and has partially been covered in reviews[353,363,364] focusing on nonmetathesis reactivities of Ru-carbene complexes. To conclude this section, some of these sequences are highlighted with representative examples (Table 25). Historically, RCM-hydrogenation sequences triggered by molecular hydrogen were the first examples of assisted tandem catalytic sequences involving RCM steps. The formation of Ru-hydrides by hydrogenolysis of Ru-carbenes has been investigated from a mechanistic point of view.[365] Entries 1 and 2 show examples for these sequences; typically, hydrogen pressures of 50 bar have to be applied, as for the example in entry 1. The example in entry 2 is somewhat unusual, as it combines a domino sequence, as discussed in Section 5.29.11, with an assisted tandem catalytic sequence. In this example, hydrogenation is unusually facile and occurs at 1 bar of hydrogen, which allows the two double bonds formed during the preceding RCM/ROM/RCM sequence to be differentiated. Entries 3 and 4 show examples of RCM-hydrogenation sequences with reducing agents other than molecular hydrogen, i.e., triethyl silane (entry 3) and 2-propanol (entry 4). Both reagents have also been used to trigger isomerization reactions; however, isomerization occurs with significantly lower amounts of reagent and in shorter reaction times (entries 6 and 7). A way to use hydrogen as a chemical trigger for an isomerization reaction was discovered by Snapper et al. (entry 5). In this case it is important to apply a highly diluted hydrogen atmosphere to suppress competing hydrogenation. As mentioned above, RCM isomerization may also proceed without any additive just by heating the reaction mixture, if comparatively high loadings of second-generation catalysts are used, because these are known to decompose via a bimolecular pathway into a dinuclear Ru-hydride. An example is shown in entry 8, in which the resulting enamine is trapped by intramolecular addition of the hydroxy group with formation of the bicyclic *N,O*-acetal. In entries 9 and 10, examples of an RCM–Kharasch-addition sequence are shown. Ring closure of the α,ω-diene occurs typically at an ambient temperature; on heating, a Ru-catalyzed atom transfer radical cyclization reaction occurs with homolytic cleavage of one C–Cl bond and addition of the resulting carbon-centered radical to the double bond formed in the previous RCM step. In entries 11 and 12, the combination of RCM with dihydroxylation and ketohydroxylation, respectively, is presented. Protocols for conducting these Ru-catalyzed oxidative alkene transformations using $RuCl_3$ as a precatalyst and Lewis-acidic metal halides as cocatalysts have been extensively investigated by Plietker et al.[366] Most likely, under the conditions of the RCM-oxidation sequence, the Ru-carbene species is converted to RuO_4,

Table 25 Examples for RCM–nonmetathesis (assisted tandem catalytic) sequences

Entry	Precursor	Conditions	Product	Yield (%)	References
1		HCl; Et_2O; then **C4** (10 mol%); CH_2Cl_2 (0.006 M); 40 °C/H_2 (50 bar); 70 °C; then $NaHCO_3$ (aqueous)		57	370
2		**C6** (5 mol%); $ClCH_2CH_2Cl$ (0.1 M); 40 °C/H_2 (1 bar); 70 °C		90	371
3		**C3** (5 mol%); CH_2Cl_2; 40 °C; 1 h/Et_3SiH (5 equivalents); 40 °C; 24 h		75	372
4		**C3** (5 mol%); toluene (0.1 M); 40 °C; 2 h/2-propanol (10 vol%); NaOH (50 mol%); 110 °C; 4.5 h		98	373
5		**C6** (10 mol%); CH_2Cl_2 (0.05 M); 20 °C; 1 h/N_2/H_2-(95:5)-atm; 70 °C; 6–24 h		74	355
6		**C3** (5 mol%); toluene (0.03 M); 20 °C/Et_3SiH (2 equivalents); 110 °C		>95	374
7		**C6** (2 mol%); toluene (0.1 M); 80 °C; 1 h/Et_3SiH (0.4 equivalent); 110 °C; 6 h		85	375
8		**C10** (10 mol%); toluene (0.05 M); 110 °C; 1 h		64	376
9		**C6** (5 mol%); toluene; 20 °C; 1 h/110 °C; 4 h		62	377
10		**C3** (5 mol%); xylene (0.2 M); 20 °C; 2 h/155 °C; 2 h		71	378

(*Continued*)

Table 25 Continued

Entry	Precursor	Conditions	Product	Yield (%)	References
11		**C3** (1 mol%); CH_2Cl_2; 40 °C; 1 h/remove solvent, re-dissolve in CH_3CN-EtOAc-H_2O; add $NaIO_4$; $YbCl_3•6H_2O$; 0 °C; 0.5 h		63	367
12		**C6** (5 mol%); EtOAc (0.1 M); 20 °C; 1 h/$NaHCO_3$; oxone in CH_3CN/H_2O; 20 °C; 10 min		61	368
13		**C6** (15 mol%); toluene (0.05 M); 80 °C; 16 h		82	379
14		**C3** or **C4** (5 mol%); C_6H_6 (1.0 M); 40 °C; 2 h/Bu^tOOH (4 equivalents); 40 °C; 3 h		63	380
15		**C6** (5 mol%); C_6H_6 (0.01 M); 80 °C; 0.5 h/Bu^tOOH (2 equivalents); 20 °C; 1 h		74	381
16		**C6** (5 mol%); C_6H_6 (0.1 M); 20 °C; 0.5 h/Bu^tOOH (1.3 equivalents); 20 °C; 0.5 h		92	382
17		**C6** (10 mol%); toluene (0.05 M); 100 °C; 1 h/NaOMe (20 mol%); CO (7 bar); 180 °C; 36 h		72	383
18[a]		**C6** (10 mol%); toluene (0.02 M); 20 °C/N_2CHCO_2Et (7.5 equivalents) added slowly over 8 h at 20 °C		58	384

[a]Obtained as a 2:1 mixture of diastereomers.

which then promotes the alkene oxidation step. The Ru-catalyzed oxidative double-bond functionalization requires special solvent mixtures consisting of ethyl acetate, acetonitrile, and water in carefully controlled ratios. Normally, these solvents are considered to be incompatible with RCM reactions. For this reason a solvent switch from dichloromethane to the above mentioned mixture was performed for the example in entry 11.[367] Alternatively, conducting the RCM step in ethyl acetate is also possible, but in this case acetonitrile and water have to be added together with the oxidant.[368] This protocol was established for the dihydroxylation sequence (not shown in the Table) and the ketohydroxylation sequence (entry 12). In the example in entry 13, the postmetathesis functionalization does not occur at the double bond but at the allylic position; presumably, conversion of the metathesis catalyst to a Ru-hydride is thermally triggered, which then catalyzes a dehydrogenation. This process is unusually facile, which might be explained by the dual activation of the allylic/benzylic position. Two different types of RCM/oxidative transformation sequences are highlighted in entries 14–16. These examples have in common that alkyl hydroperoxides are used as oxidants and chemical triggers. For the examples in entries 14 and 15, RCM is coupled with a Ru-catalyzed allylic oxidation, a reaction that has been extensively investigated by Murahashi et al.[369] It should be noted that the products of this sequence could also have been accessed through the RCM of the corresponding acrylates or acrylamides, respectively; but these electron-deficient double bonds would have been significantly less reactive. In entry 16, an example for an RCM/oxidative aromatization sequence leading to *N*-aryl pyrroles is shown. It was demonstrated by control experiments that the aromatization step indeed requires the presence of Ru. The last examples, shown in entries 17 and 18, are combinations of RCM and a Pauson–Khand reaction and RCM cyclopropanation, respectively, which allow for the rapid assembly of complex polycyclic structures.

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5.30 Noble Metal-Catalyzed Enyne Cycloisomerizations and Related Reactions

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Glossary

Alkoxycyclization Organic process involving a cyclization reaction and concomitant addition of an alcohol with formation of an ether moiety.

Atom economy Description of the efficiency of an organic reaction in terms of all atoms involved; the ideal reaction shows a full conservation of atoms of the starting material into the resulting product, with no atom being wasted.

Cycloaddition Transformation involving several unsaturated molecules that combine to form a cyclic derivative.

Cycloisomerization Chemical transformation of an acyclic derivate to a cyclic isomer.

Dewar–Chatt–Duncanson model Model describing the bonding of π-conjugated ligands (alkene, alkyne, etc.), involving a donation from the ligand and back-donation from the metal.

Domino process Consecutive series of transformations involving the formation of multiple bonds.

5.30.1 Introduction

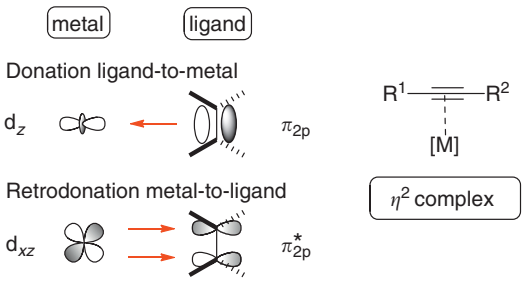
Metal-catalyzed cycloisomerization and related reactions of enynes have appeared as conceptually and chemically highly fascinating processes, as they contribute to the stimulating atom-economy research field. The predominant contribution of catalysis to the concepts of atom economy and green chemistry of the twenty-first century presented by Sheldon as well as by Anastas and Warner has reinforced the international demand on clean and straightforward processes.[1] Metal-catalyzed cycloisomerization reactions of 1,*n*-enynes fulfill such requests on atom-economical and step-economical reactions. Moreover, the presence of various functionalities such as alcohols, aldehydes, ethers, alkenes, or alkynes has led to the discovery of novel original processes that enhance the molecular complexity of the products. Historically, the group of Trost[2] paved the way of cycloisomerization reactions in the mid-1980s using palladium complexes. Since this pioneering work, several other organometallic complexes have 'entered

the dance,' including noble metals such as gold and platinum. The definition of a noble metal is that it is chemically inert and inactive especially toward oxygen or most acids (no corrosion). After a time lag for rationalization of the observed processes, unified mechanistic scenarios have been announced from the catalysis community, and these proposals have been scrutinized by sophisticated density functional theory (DFT) studies,[3] therefore contributing to the understanding of plausible reaction pathways. Still some speculations exist, but the main rationale has allowed predictions, optimizations, and the design of new efficient catalysts.

In this chapter, the main contributions in the field of cycloisomerization and related reactions of enynes will be highlighted, emphasizing the recent reports on gold and platinum catalysts.[4] The presentation starts from a historical background and the general mechanistic framework relying on the carbophilic Lewis acids properties of the organometallic species. The cycloisomerization and related reactions will be presented, starting from classical skeletal rearrangements leading to 1,*n*-dienes and bicyclic derivatives. The second part will be dedicated to related reactions, implying domino processes with the intervention of an internal or external nucleophile. In each part, the presentation of asymmetric versions[5,6] and applications of these rearrangements to natural products synthesis[7] will be highlighted.

5.30.2 Generalities and Unified Mechanism

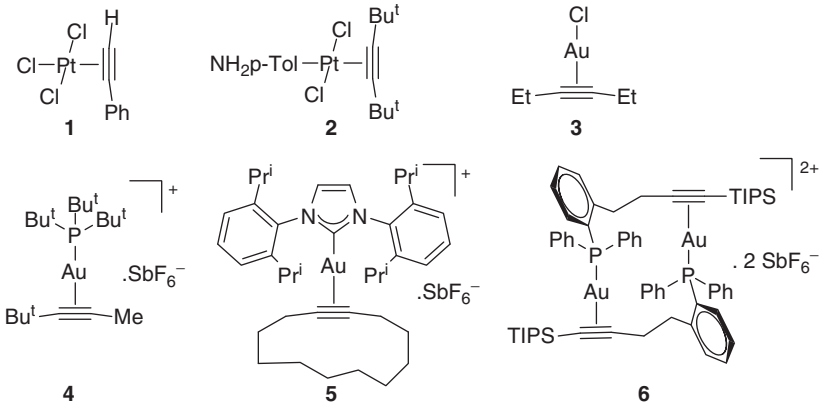
The Dewar–Chatt–Duncanson model is usually used to describe the mode of coordination of an unsaturated ligand (carbon–carbon double or triple bond) to a transition metal complex.[8] It postulates the formation of σ-bond by recovery of the ligand π_{2p} system with an empty orbital of the metal center, a phenomenon known as ligand-to-metal donation (Scheme 1). The formation of this bond is supplemented by π-back-donation from a filled orbital of the metal toward the empty $\pi*$ antibonding 2p orbital of the alkene or alkyne. Theoretical calculations were used to determine the mechanism of coordination of a gold complex on an alkyne. According to the particular calculation methods, a weak or strong σ-donor character of the alkyne is invoked by different groups to explain the mode of coordination to the metal. The η^2-complexation is accompanied by a rehybridization and a deformation of the carbon–carbon triple bond according to the model of Dewar–Chatt–Duncanson. The electron density around the alkyne is therefore reduced, which results in a possible nucleophilic attack onto the latter.



Scheme 1

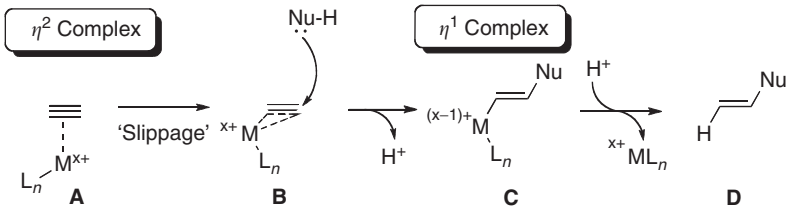
The isolation and characterization of platinum(II)– or gold(I)–alkyne complexes recently revealed that the alkyne adopts a perpendicular arrangement to the plane defined by the L_3Pt^{2+} fragment in the case of platinum.[9] The dicoordinated gold complexes follow a linear geometry, the second ligand being generally a chloride,[10] a phosphane or an *N*-heterocyclic carbene (NHC). X-ray analyses of complexes **1**–**6** have been obtained at various temperatures depending on the stability of the complexes (Scheme 2).[11] In complex **3** for example, Au–C distances of 2.152 and 2.172 Å and a C≡C distance of 1.224 Å have been determined and correlations have been established between experimental and calculated data, which show a strong alkyne-to-metal σ-bonding and a weak metal-to-alkyne π-back donation.[12] The cationic gold(I) species **4** is an ion-separated complex with symmetrical coordination of the alkyne to Au (distances of 2.238 and 2.239 Å). The *t*-butyl and methyl groups are bent away from the linear arrangement, with C–C≡C angles of 165.6° and 168.1°. Coordination of cyclododecyne to a $[(NHC)Au]^+$ complex resulted in a very stable complex **5**.[13] The C≡T bond is slightly elongated (1.213 Å compared with 1.196 Å in the alkyne), but this effect is less pronounced than that in the corresponding neutral chloride complex. The C–C≡C bond angles are significantly reduced from 175.9° to 168°. Association of these data to other spectroscopic data (NMR or IR spectra) suggests that the imidazole ring accounts for the electron withdrawal from the alkyne. The presence of an alkyne-containing triarylphosphane allowed for the isolation and characterization of the dinuclear Au(I) complex **6**.[14] The alkynes are η^2-bonded to gold and the Au–C and C≡C bond distances are 2.197/2.270 Å and 1.221 Å, respectively. It is noteworthy that Ag(I) behaves more like Au(I), whereas Cu(I) forms a mononuclear species with pseudotrigonal planar geometry. Another important feature in complex **6** is that the metal center is 'slipped' to one side of the π-bond.

In most cases, in the presence of noble metals, the σ-donation to the metal is dominant, which enhances the electrophilicity of the alkyne and therefore the addition of nucleophiles to the η^2-bonded alkyne.[14,15]

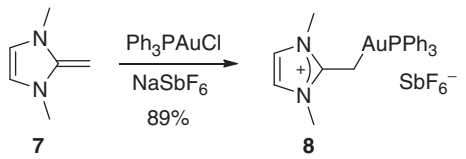


Scheme 2

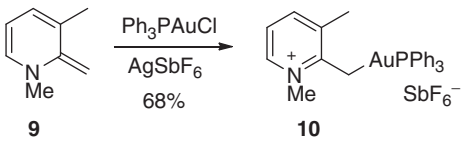
This carbophilic activation promotes *anti* nucleophilic addition on the complex **A** and the creation of a new carbon–carbon or carbon–heteroatom bond, depending on the nature of the nucleophile (carbon, oxygen, nitrogen, carbo-, or heterocyclic ring aromatic). The geometry of the formed η^1-complex **C** depends on the degree of oxidation of the metal center: the complex is linear at a low oxidation state (Au^+), but square-planar at a higher oxidation state (Pt^{2+}, Au^{3+}). A final step of protodemetallation on complex **C** completes the addition reaction (Scheme 3). The 'slippage' phenomenon and the addition of the nucleophile on the η^2-complex **B** may not be so trivial, and it was recently investigated theoretically and experimentally (equations 1 and 2).[16] The addition of triphenylphosphine gold chloride and sodium hexafluoroantimonate to 1,3-dimethyl-2-methyleneimidazoline **7** led to the cationic gold complex **8**, where the Au–C bond distance is 2.087 (longer than the Au–C bond in $AuPh(PPh_3)$) which confirms the 'carbon ylide' behavior of the olefin. The imidazolium unit could be replaced by an *N*-alkyl pyridinium moiety, as 1,3-dimethyl-2-methylene-1,2-dihydropyridine **9** reacted similarly and afforded a stabilized complex **10**. These two cationic complexes are representative examples arguing in favor of a η^2–η^1 complex deformation.



Scheme 3

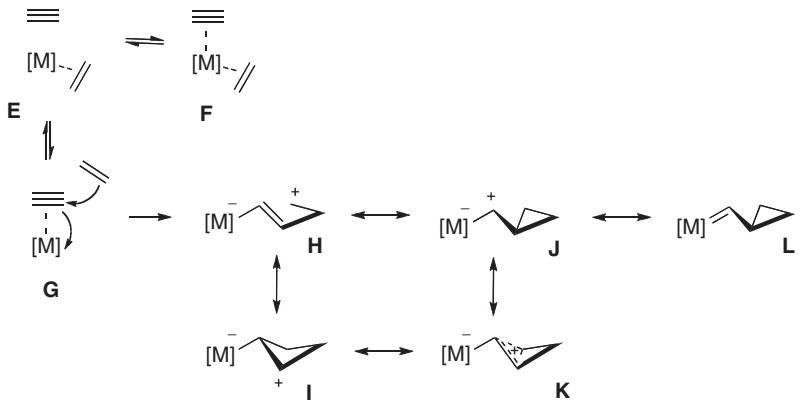


(1)



(2)

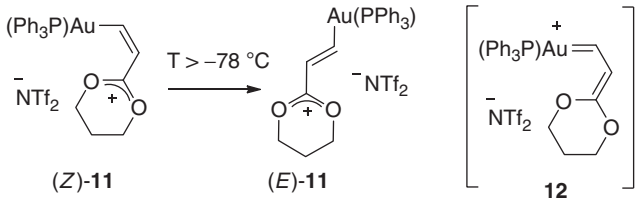
The case of enynes as substrates is highly intriguing, as originally mono- and dicomplexations of their alkenyl and alkynyl moieties may be envisaged. A higher stabilization for the Au(I)–ethylene complex over the ethyne analog has been established, with a calculated energy difference of 10 kcal mol^{-1} (complex **E** vs. **G**, Scheme 4).[17] Nevertheless, the observed reactivity brings out the selective π-complexation of the alkyne followed by nucleophilic addition of the alkene moiety. This behavior may be a consequence of the fact that the highest occupied molecular orbitals (HOMO) and the lowest unoccupied orbitals (LUMO) of alkynes are lower in energy than those of the corresponding alkenes (approximately 0.5 eV); alkynes are therefore more electrophilic and less nucleophilic.[18] One may anticipate a lower LUMO for the Au(I)–alkyne complex **G** than for the Au(I)–alkene



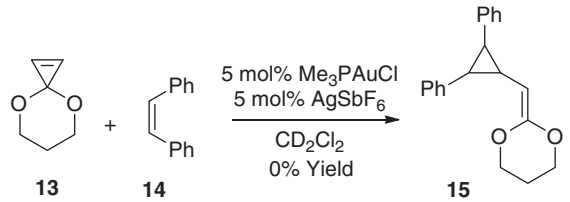
Scheme 4

complex **E**, which illustrates the observed 'alkynophilicity' of Au(I) and the reactivity of the resulting complex **A** (Scheme 3). The *trans* addition of the alkene to the π-complex **G** results in the formation of a cationic nonclassical intermediate, potentially depicted by the mesomeric structures **H–K**. If back-donation of electron density from the metal to the ligand is involved, the electrophilic metal carbenoid **L** may be considered. All the representations are probably mental projections, especially in the case of gold, and several theoretical and experimental data have been recently assembled to shed light on this mechanistic rationale.

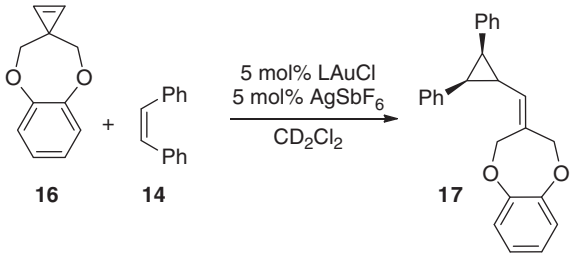
The carbenic versus carbocationic descriptions have been studied mainly by the Fürstner and Toste groups, by measuring experimentally and theoretically the rotational barrier of bonds adjacent to gold. Indeed, NMR studies attempting to generate a gold carbene by rearrangement of a 3,3-disubstituted cyclopropene afforded the cationic products (*Z*)-**11** and (*E*)-**11** (equations 3–5).[19] The rotational barrier of the C–C bond in **11** has been determined to be in the same range as the barrier of the C–C bond between the phenyl ring and the carbonyl group of benzaldehyde, which preclude any significant contribution of the carbene **12** in the ground state structure. Computational experiments confirmed these conclusions, and additionally highlighted the importance of the carbocation-stabilizing heteroatoms such as oxygen atoms.[15h] The gold-catalyzed cyclopropanation reaction of **13** in the presence of *cis*-stilbene **14** did not produce the expected cyclopropane **15**, confirming the hypothesis of a carbocationic intermediate. On the contrary, the reaction of cyclopropene **16** allowed the stereospecific formation of product **17**, via a gold-stabilized carbene as potential intermediate. The study of such reactivity also highlighted the influence of the ligand on the stabilization of such intermediates. Indeed, lower yields were observed in the case of π-acidic ligands, which are prone to carbocationic stabilization. The best activity was obtained in the case of the electron-donating heterocyclic imidazole ligand (IPr, strong σ-donor, and weak π-acid) as 80% of the cyclopropane **17** was isolated in this case. The behavior of phosphine was found to be in between both extremes (carbenic vs. carbocationic). These studies have been supplemented by recent data dealing with the synthesis and reactivity of (NHC)gold(I) carbenes in the gas phase.[20] A recent study also highlighted the importance and influence of ligands by examining the kinetics of nucleophilic additions on unsaturated derivatives.[21] Based on all these pioneering studies, a certain consensus exists in the literature and the carbenic versus carbocationic representation or 'carbene-like' versus 'carbocation-like' reactivity of gold intermediates are summarized in the terms 'carbenoid' and 'carbenoid-like,' suggesting an intermediate situation.



(3)



(4)

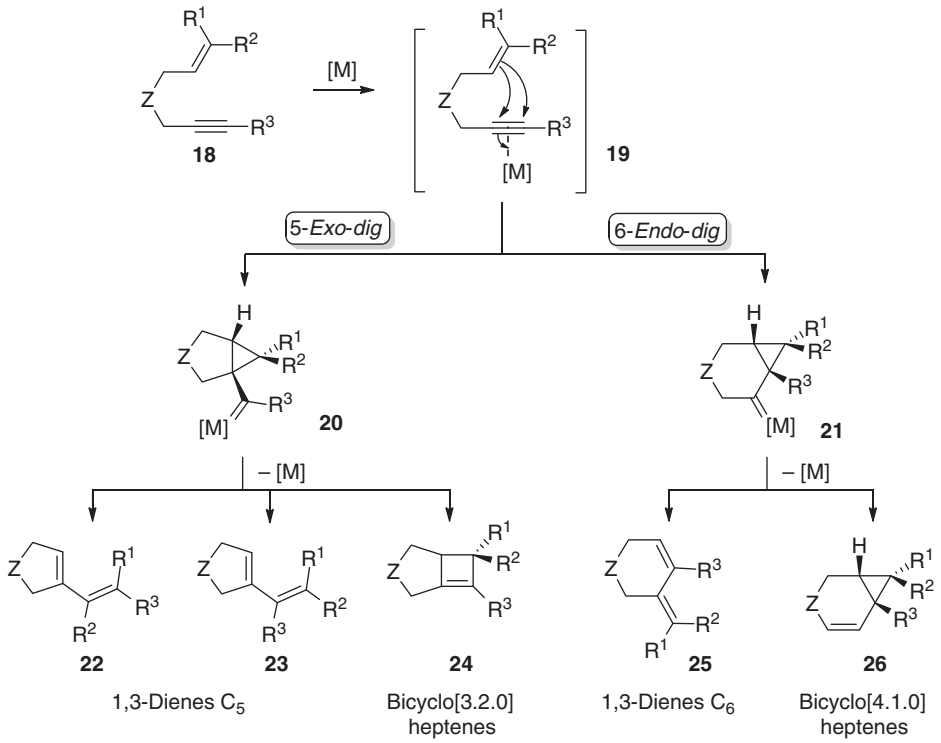


L	Yield (*dr*)
$P(OMe)_3$	0%
$P(OPh)_3$	11% (4:1)
PMe_3	56% (1.4:1)
PPh_3	52% (1.7:1)
IPr	80% (11:1)

(5)

5.30.3 Enyne Cycloisomerization Reactions in the Absence of Nucleophiles

Cycloisomerization reactions of 1,*n*-enynes are by definition a skeletal rearrangement of the substrate without incorporation of external atoms or production of waste.[22,4] These transformations, responding to the concept of atom economy, allow for the stereoselective synthesis of functionalized carbo- and heterocycles. Various pathways are possible for the skeletal rearrangements as depicted in Scheme 5 for the example of 1,6-enynes. The cyclization of 1,6-enyne **18** (that can be a carbon-, oxygen-, or nitrogen-tethered enyne) involves, as a first step, the activation of the alkyne by the metal complex, leading to η^2-complex **19**. The stereoselective addition of the alkene to the activated carbon–carbon triple bond (as presented in the last paragraph, Scheme 3) may occur via two different pathways, a 5-*exo-dig* or 6-*endo-dig* one. The cyclopropyl carbenoid species **20** and **21** may be considered as key intermediates, as their rearrangements (e.g., cleavage or migration of C–C and C–H bonds) lead to the formation of unsaturated five- (**22**, **23**) or six-membered (**25**) cyclic structures, bicyclo[3.2.0]heptenes (**24**), and bicyclo[4.1.0] heptenes (**26**).



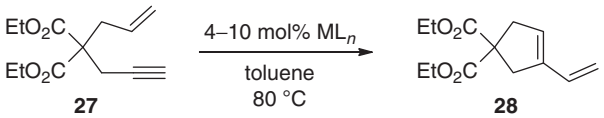
Scheme 5

The authors will present successively the catalytic preparation of 1,3- and 1,4-dienes, followed by bicyclo [3.2.0]heptenes and bicyclo[4.1.0] heptenes, presenting, in each case, the mechanistic proposals which have helped to rationalize the observed structures. The cycloisomerization reactions will be presented by the type of 1,*n*-enynes. The section will be limited to carbophilic mechanisms, involving an η^2–alkyne metal complex: neither examples of cycloisomerization involving a metallacycle type intermediate[23] nor cyclization reactions of enynes with propargylic acetates will be discussed.[24] Asymmetric cycloisomerization reactions catalyzed by chiral complexes of iridium, platinum, and gold will also be presented.

5.30.3.1 Formation of 1,3- and 1,4-Dienes

5.30.3.1.1 Reactivity of 1,6- and 1,7-enynes

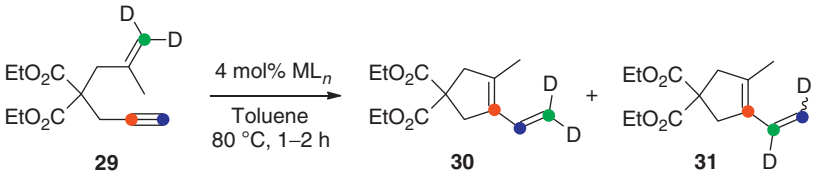
Since the first examples catalyzed by palladium(II), the synthesis of 1,3-dienes has been demonstrated for a large number of transition metal complexes of platinum(II),[25] platinum(IV),[26] gold(I) and gold(III),[27] gallium(III),[28] indium(III),[29] ruthenium(II),[30] and iridium(I).[31] The cycloisomerization of 1,6-enyne **27** leading to vinylcyclopentène **28** is one of the most-studied rearrangements in the presence of organometallic complexes (equation 6). This rearrangement has been described in the presence of many carbophilic metal complexes, such as chlorides of platinum(II) and(IV), gold(III), and indium(III),[32] leading to the synthesis of the derivative **28** with yields between 42% and 68%.



ML_n	t, Yield
$PtCl_2$	2 h, 53%
$PtCl_4$	20 h, 57%
$AuCl_3$	12 h, 42%
$InCl_3$	1 h, 68%

(6)

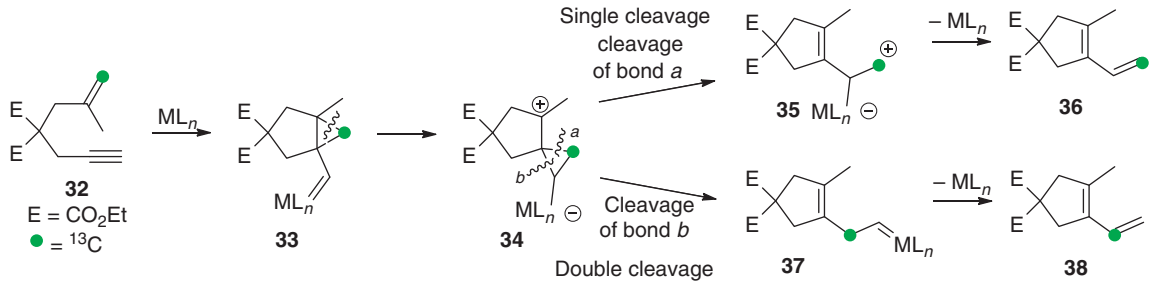
Chatani's group has focused on the isomer distribution obtained in the cycloisomerization of the carbon-tethered enyne **29**, bearing an internal methyl group on the alkene chain, in which the olefinic hydrogen atoms had been replaced by deuterium (equation 7).[32a] Several carbophilic metal complexes have been used in this study. The results show that isomer **31**, coming from a dual cleavage is obtained in great majority, irrespective of the nature of the complex used.



	ratio **30/31**
$PtCl_2$	1/99
$PtCl_4$	> 1/99
$AuCl_3$	4/96

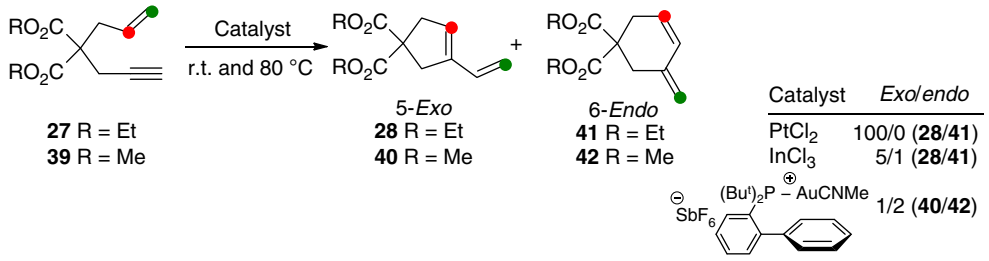
(7)

This selectivity in favor of the isomer obtained by 'double cleavage' can be rationalized by the following mechanism, which has been studied with a ^{13}C-labeled substrate (Scheme 6). The cyclopropylcarbenoid-like intermediate **33**, obtained by 5-*endo-dig* cyclization of the enyne **32**, undergoes a first carbon–carbon bond cleavage leading to the zwitterionic intermediate **34**. This latter can then rearrange in two ways: the cleavage of the carbon–carbon single bond *a* leads to the zwitterion **35** with a primary unstable carbocation ('simple cleavage' process). Subsequent protodemetallation gave diene **36**, having the labeled ^{13}C on the external carbon of the exocyclic unsaturation. In contrast, the cleavage of the bond *b* allows the formation of the intermediate **37**, which is more stable ('double cleavage' process). The diene **38** is therefore formed preferentially.



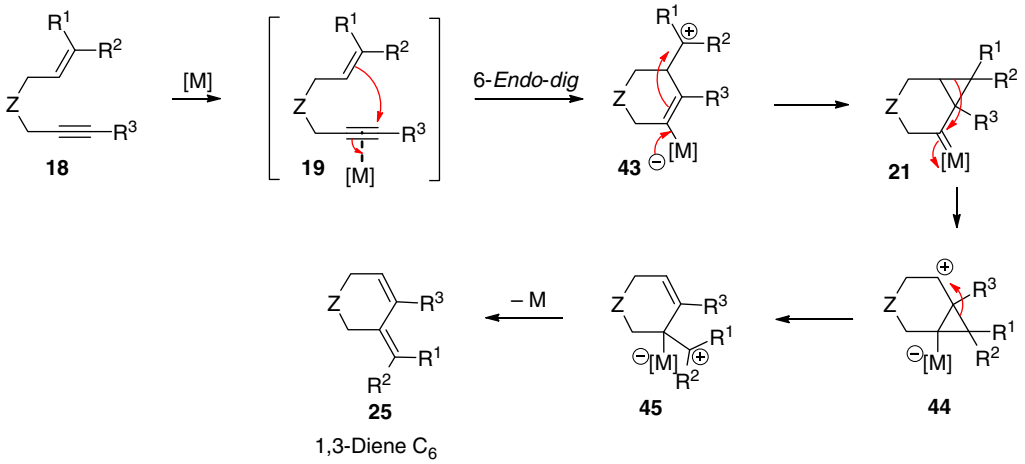
Scheme 6

The structure of 1,3-dienes obtained via the cycloisomerization of 1,6-enynes strongly depends on the metal complex used. The cyclization of enyne **27** leads in the presence of platinum chloride(II) at 80 °C exclusively to the 5-*exo* diene **28** via a double cleavage process (equation 8).[27e] The use of indium chloride(III) leads to a 5/1 mixture of the 5-*exo*/6-*endo* dienes **28**/**41**.[32] The gold(I) complex bearing an electron-rich and hindered phosphine ligand derived from biphenyl, allows the implementation of mild conditions (reactions carried out at room temperature) and leads to a reversed mixture of 5-*exo*/6-*endo* products **40**/**42**.[33] The use of gold nanoparticles supported on TiO_2 showed interesting selectivity in favor of 'single cleavage' pathway, which contrasts to general observation in homogeneous gold catalysis.[34] Finally, one may note that diene formation by a 6-*endo-dig* pathway is not described in the case of catalytic cyclizations effected by many other transition metals (palladium, platinum, iridium, gallium).



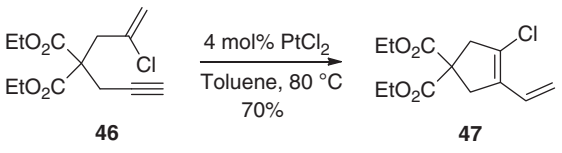
(8)

The mechanism of diene formation by a 6-*endo-dig* process completes the pattern of 1,3-diene syntheses presented earlier in this chapter (Schemes 5 and 7). The intramolecular addition of the alkene to the η^2 complex **19** leads, after rearrangement, to the metallacyclopropylcarbenoid intermediate **21**. The 1,3-alkyl migration provides intermediate **44**, which in turn undergoes a 1,2-alkyl migration to give the zwitterionic species **45**. The final step implies the demetallation leading to the unsaturated six-membered ring **25** bearing a 1,3-diene.

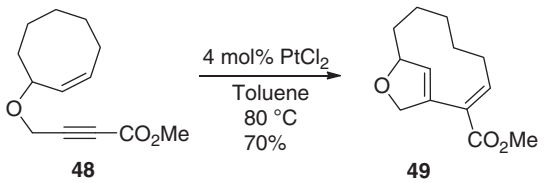


Scheme 7

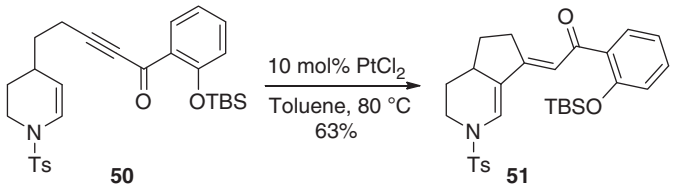
The preparation of 1,3-dienes by rearrangement of 1,6-enynes catalyzed by platinum(II) dichloride was studied by the team of Murai.[25] Among the variety of structures that have been synthesized, these rearrangements were also used for the preparation of vinyl halides. The cycloisomerization of enyne **46** gave the endocyclic halide **47** with a yield of 70% (equation 9). Fürstner's group has shown that this methodology could be applied to oxygen-tethered enynes possessing a large ring (equation 10).[25e] The unsaturated derivative **49** having a methyl ester group on the diene is efficiently prepared from the ether substrate **48**. Dake's group conducted the cyclization of sulfonamide-substituted enyne **50** and obtained azabicyclic derivative **51** with 63% yield (equation 11).[143] Some applications to the total synthesis of natural products will be detailed in Section 5.30.3.1.3.



(9)

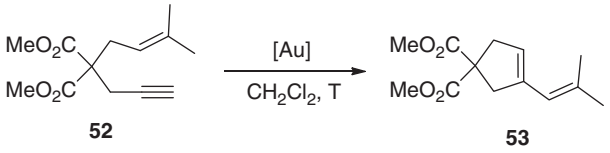


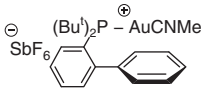
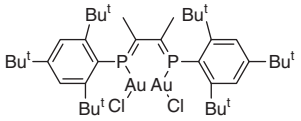
(10)



(11)

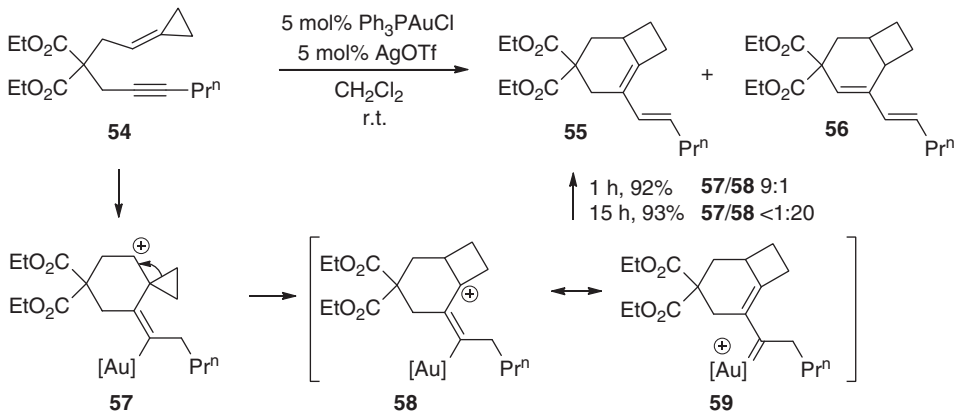
The use of gold(I) complexes is also noteworthy. The cycloisomerization of enyne **52** leading to 1,3-diene **53** has been effected with the gold(I) complex Ph_3PAuCl and silver hexafluoroantimonate $AgSbF_6$, allowing for the *in situ* formation of the reactive cationic species $[Ph_3PAu^+]$ (equation 12). The development of novel complexes, such as the bistriflimidate gold(I) species $[Ph_3PAuNTf_2]$,[27c] eliminates the handling of silver salts. The replacement of PPh_3 by a larger and electron-richer ligand further increases the catalyst activity, such that the cyclization is quantitative at temperatures less than $-26\ ^\circ C$.[35] The preparation of a bimetallic bridged complex has also been recently described and this Au complex was found to be effective too.[36]



[Au]	Temperature, Yield
$Ph_3PAuSbF_6$	r.t., 91%
$Ph_3PAuNTf_2$	r.t., 97%
	−63 to −26 °C, 99%
	r.t., 100%

(12)

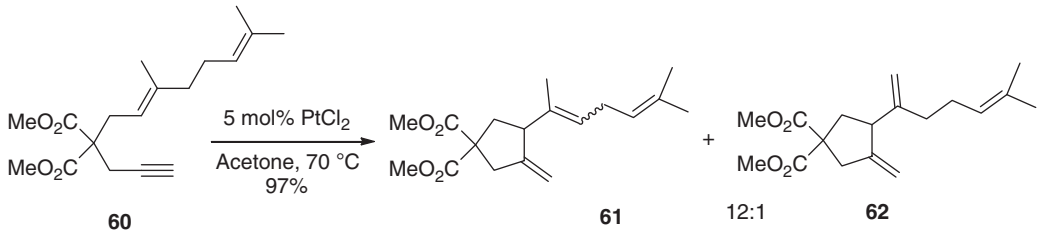
Toste's group has recently described the synthesis of endocyclic 1,3-dienes by gold(I)-catalyzed rearrangement of alkylidenecyclopropanes **54** in dichloromethane at room temperature.[37] The mechanism of the cyclization of enyne **54** is identical to that proposed for other 1,6-enynes. Nevertheless, the presence of the cyclopropane leads to a rearrangement by migration of a carbon–carbon bond in intermediate **57**. Two cyclobutane intermediates **58** and **59** are representative of the process, leading to the mixture **55**/**56** in which diene **55** prevails. When the reaction time is extended to 15 h, the isomerization of diene **55** to **56** is observed **Scheme 8**.



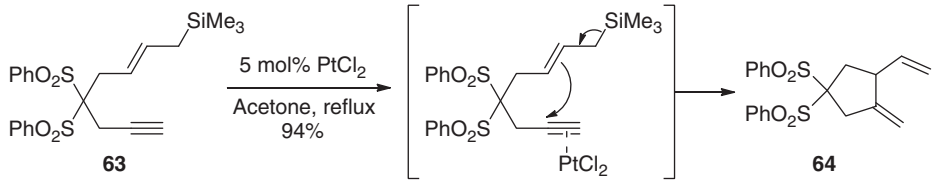
Scheme 8

Few examples of the synthesis of 1,4-dienes are reported in the literature with carbophilic Lewis acids: most of them have been described in the presence of palladium catalysts and rely on metallacycle intermediate.[2] Echavarren's group has described the synthesis of a 1,4-diene via the 5-*exo* cyclization of 1,6-enyne **60**. In the presence of a catalytic amount of platinum dichloride in

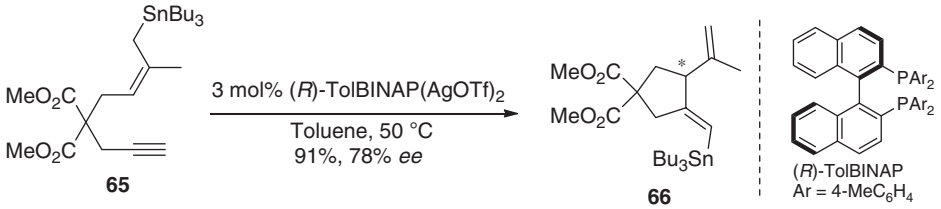
acetone at 70 °C, the substrate **60** is converted to a mixture of the 1,4-dienes **61** and **62** with 97% yield, the ratio of the two isomers being 12:1 (equation 13).[38] This regioselectivity in favor of the compound **61**, obtained after a *β*-elimination step is in complete agreement with the observed selectivity in the presence of a palladium complex.[2] However, the main limitation of this reaction is the use of a specific substrate since only 1,6-enynes bearing a trisubstituted alkene are transformed to 1,4-dienes. Other substrates such as allylic silanes or stannanes have also been cyclized in the presence of platinum or silver complexes. In refluxing acetone, 1,6-enyne **63** is converted in the presence of 5 mol% of platinum dichloride to the silylated 1,4-diene **64** in 94% yield (equation 14).[39] The mechanism of the reaction involves the *anti* attack of the allylsilane on the activated alkyne; this elemental step is promoted by the elimination of the silyl group. The same type of transformation is achievable with allylstannanes: starting, for example, with 1,6-enyne **65**, the use of a bimetallic chiral silver complex afforded the vinylstannane **66** in 91% yield and 78% enantiomeric excess (*ee*) (equation 15).[40] This constitutes the best *ee* for such a transformation, as only moderate results were obtained for the cycloisomerization of nitrogen-tethered 1,6-enynes in the presence of a bimetallic cationic gold catalyst.[41]



(13)



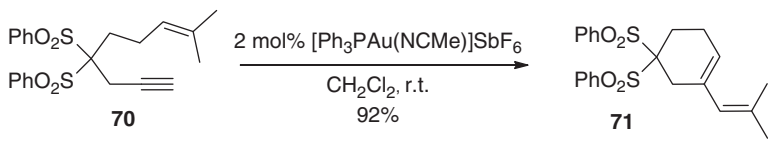
(14)



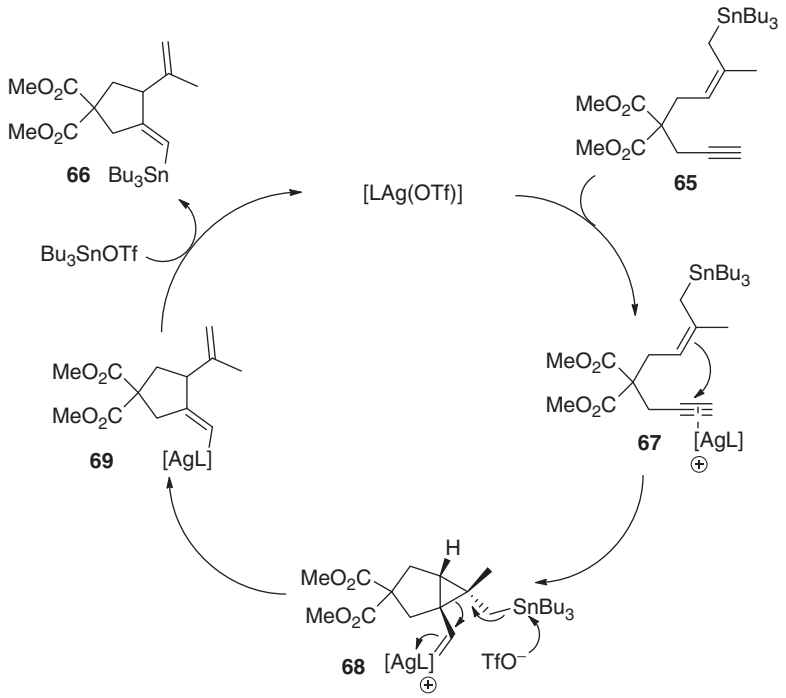
(15)

The authors proposed a mechanism based on the initial η^2-coordination of the alkyne by the silver complex leading to **67** followed by intramolecular nucleophilic addition of the alkene to form the *anti* cyclopropylcarbenoid intermediate **68**. The elimination of the tributylstannyl group and 1,2-migration of an alkyl moiety form the vinyl silver intermediate **69** that leads to the desired product **66** after protodemetallation (**Scheme 9**).

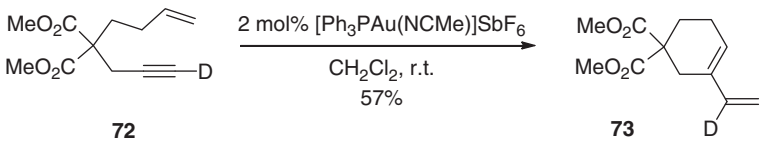
Cationic gold(I) complexes were also used for the rearrangement of 1,7-enynes.[42] In the presence of 2 mol% of the complex $[Ph_3PAu(NCMe)]SbF_6$, the cyclization of enyne **70** embodying a bis(phenylsulfonyl)methane unit led, via a 6-*exo-dig* process, to the diene **71** in 92% yield (equation 16). The activity of such complexes is noteworthy since the reactions are completed within 5 min at room temperature. It was also shown that the cyclization of 1,7-enyne **72** with a deuterium on the alkyne provides only the diene **73**, corresponding to a 6-*exo-dig*-type addition (equation 17). Larger rings are very difficult to obtain under catalytic conditions: one may cite an example from Porco's group, relying on a cycloisomerization of 1,9-enynes in the presence of an almost stoichiometric amount of a gold complex.[43] Recently, a 8-*endo* cyclization has been described for the cycloisomerization of 1,7-enynes such as **74** (equation 18) which cleanly gave the benzoxocine **75** in 76% yield.[44]



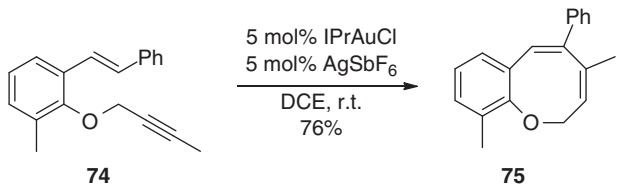
(16)



Scheme 9



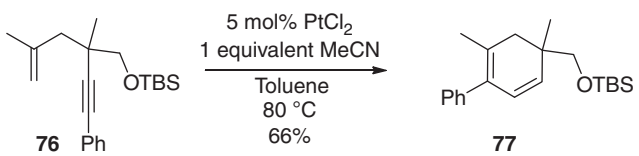
(17)



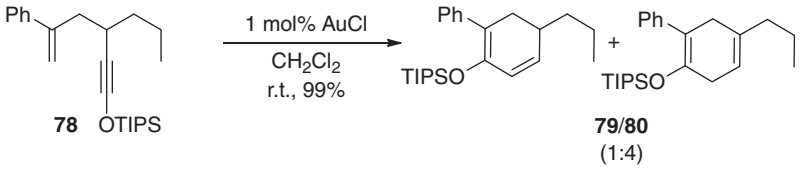
(18)

5.30.3.1.2 Reactivity of 1,5-enynes

Kozmin's group described the cyclization of 1,5-enynes to 1-cyclohexadienes in the presence of platinum(II) and gold(I).[45] The use of 5 mol% of platinum dichloride in a mixture of toluene and a stoichiometric amount of acetonitrile at 80 °C allows the cyclization of enyne **76**, having a quaternary carbon at the propargylic position to proceed; 1,3-diene **77** is synthesized with a yield of 66% (equation 19). When the carbon atom at the propargylic position is not quaternary, the cyclization leads to a mixture of dienes. The use of gold chloride(I) at a low loading (1 mol%) in dichloromethane represents an effective catalytic system, since the cyclic silyl derivatives **79** and **80** are formed in 99% yield as a mixture of the 1,3- and 1,4-diene obtained in a 1/4 ratio (equation 20).

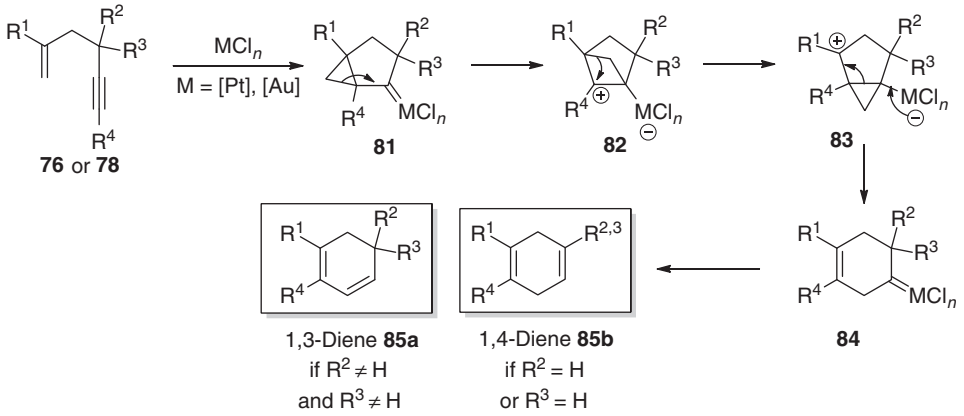


(19)



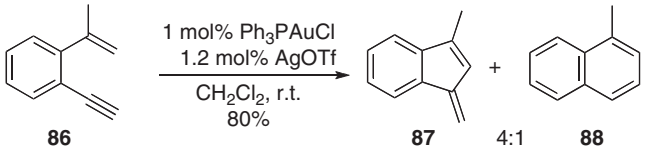
(20)

The proposed mechanism involves the coordination of the metal complex on the alkyne followed by formation of cyclopropylcarbenoid **81** (having a similar structure as the intermediate **20** formed from 1,6-enynes – Scheme 5). The 1,2-migration of an alkyl group allow for the production of the carbocationic intermediate **82**, which can be stabilized by the presence of an electron-donor group R^4. It is followed by a new 1,2-migration and demetallation, which leads to 1,3-diene **85** (exclusively obtained if R^2, $R^3 \neq H$), or a mixture of the 1,3- and 1,4-dienes (**85a** and **85b**) if R^2 and/or $R^3 = H$ (Scheme 10). Recent DFT calculations were in excellent agreement with the experimental observations and could explain the effect of alkynyl, alkenyl, and propargylic substituents on the outcome of the reaction.[46]

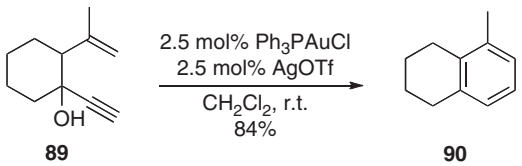


Scheme 10

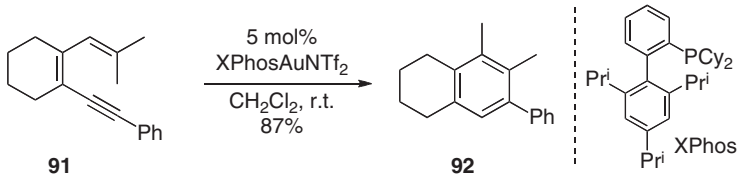
The synthesis of indenes, naphthalenes, and aromatic derivatives has also been described via cycloisomerization reactions of substituted 1,5-enynes with aromatic backbones. Following initial work of Dankwardt using silyl enol ethers in the presence of a platinum catalyst,[47] the synthesis of indenes and aromatic substituted rings was performed in the presence of gold. Cycloisomerization of the 1,5-enyne **86** in the presence of a cationic Au(I) complex led to a mixture of the indenyl and naphthyl derivatives **87** and **88** (resulting from 5-*exo* and 6-*endo* cyclization processes) in a 4:1 ratio and in 80% yield (equation 21).[48] Similarly, the tetrahydronaphthalene derivative **90** could be obtained starting from 3-hydroxy-5-ene-1-yne **89** in 84% yield according to a procedure implying a cyclization followed by water elimination (equation 22).[49] This methodology was recently applied to the synthesis of highly substituted benzenes. Substrate **91** is cleanly converted to the phenyl derivative **92** via a 6-*endo* cycloisomerization in 87% yield in the presence of a gold(I) complex derived from the XPhos ligand (equation 23).[50] It is noteworthy that a similar approach had been used in the specific case of cycloisomerization of 1,5-enynes derived from arene–chromium complexes.[51] The synthesis of indenes was nicely performed enantioselectively in the presence of a chiral gold(I) complex derived from a hindered MeOBIPHEP analog. The *ortho*-(alkynyl)styrene **93** thus provided 1*H*-indene **94** in 77% yield and 85% *ee* (equation 24).[52]



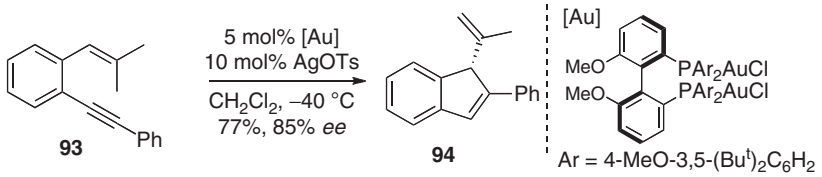
(21)



(22)

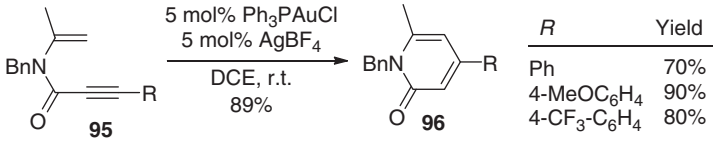


(23)



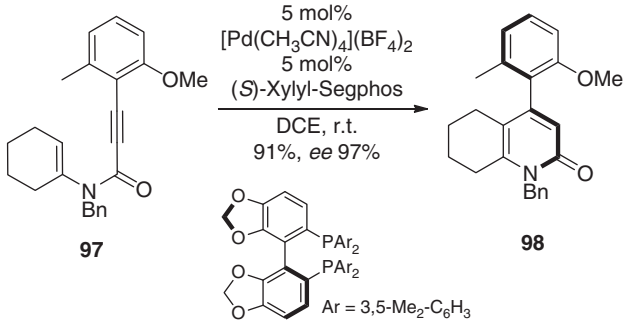
(24)

The cycloisomerization reaction of 1,5-enynes of the *N*-alkenylalkynylamide type has only recently been described by the group of Tanaka.[53] The synthesis of 2-pyridones **96** is performed via 6-*endo* cyclization and is catalyzed by cationic complexes of gold(I) in good to excellent yields (equation 25). The same authors also developed an enantioselective version of this reaction leading to chiral 2-pyridones in the presence of a dicationic palladium catalyst bearing a chiral atropisomeric diphosphine. Thus, the 1,5-enyne **97** is converted into compound **98** in 96% yield and 94% *ee* (equation 26).[54] Recently studies implying chiral gold catalysts instead of palladium ones have been performed in order to find suitable complexes for such enantioselective transformations. The use of cationic gold(I) complexes derived from DTBM-Segphos were suitable and afforded the axially chiral 4-aryl-2-quinolinones in *ee*s of up to 61%.[55]



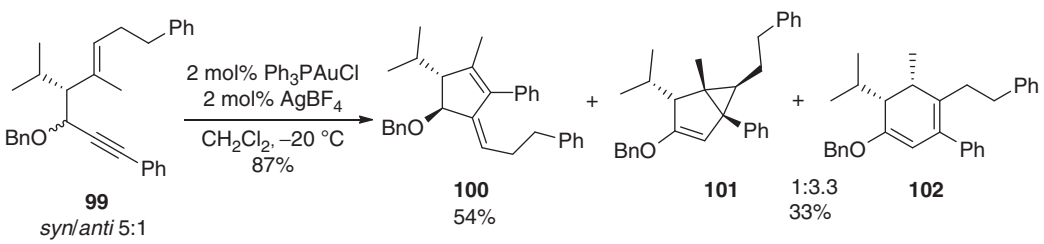
R	Yield
Ph	70%
4-$MeOC_6H_4$	90%
4-CF_3-C_6H_4	80%

(25)

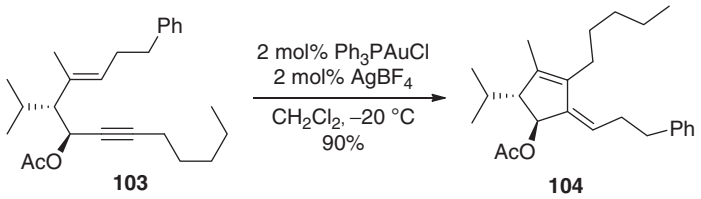


(26)

However cycloisomerization reactions are very substrate-dependent and often lead to mixtures of products resulting from competitive cyclization mechanisms. The case of the cycloisomerization of the 1,5-enyne **99** illustrates this observation.[56] The cyclization of **99** in the presence of a cationic gold complex gives a mixture of three products: a five-membered cyclic 1,3-diene **100**, a bicyclo[3.1.0]hexene derivative **101**, and a cyclohexadiene **102**. The cyclic 1,3-diene was obtained as a major compound in 54% yield, whereas **101** and **102** were isolated together with a 33% yield and in a ratio of 1:3.3 in favor of the cyclohexadiene **102** (equation 27).



(27)

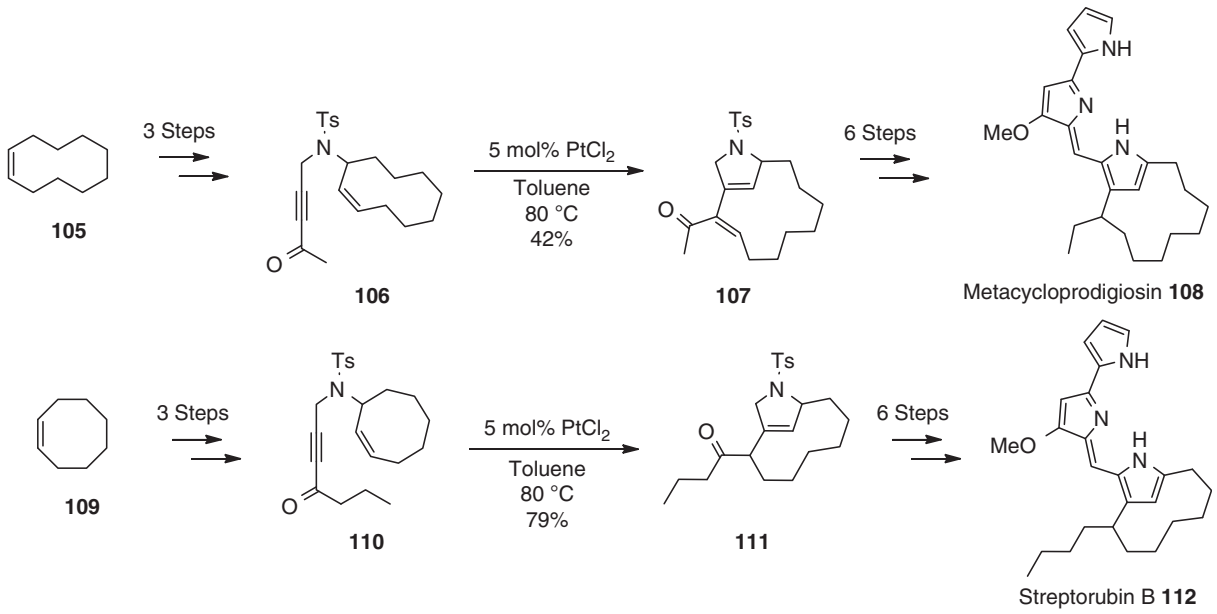


(28)

It is noteworthy that small modifications of the substrate may influence the outcome of the reaction. Indeed, compound **103** is converted to the functionalized cyclopentene **104** in 90% yield via a 5-*exo* cycloisomerization process.[56]

5.30.3.1.3 Applications in total synthesis

Cycloisomerization reactions have found several applications in total synthesis. The preparation of a 1,3-diene, as described in Section 5.30.3.1.1, was determined as a key step by Fürstner's group for the synthesis of two tetracyclic molecules bearing three pyrroles moieties, metacycloprodigiosin **108** and streptorubin B **112** (Scheme 11).[57] These two analogous molecules show *in vitro* antibiotic and immunomodulatory activities. Metacycloprodigiosin **108** and streptorubin B **112** were prepared in 10 steps from commercial alkenes, cyclodecene **105** and cyclooctene **109**, respectively. The synthetic routes involve a cycloisomerization step of the nitrogen-tethered 1,6-enynes **106** and **110** catalyzed by platinum dichloride. Dienes **107** and **111** are obtained in good yields (42% and 79%, respectively). Six additional steps then lead to the synthesis of the heterocyclic compounds **108** and **112**.

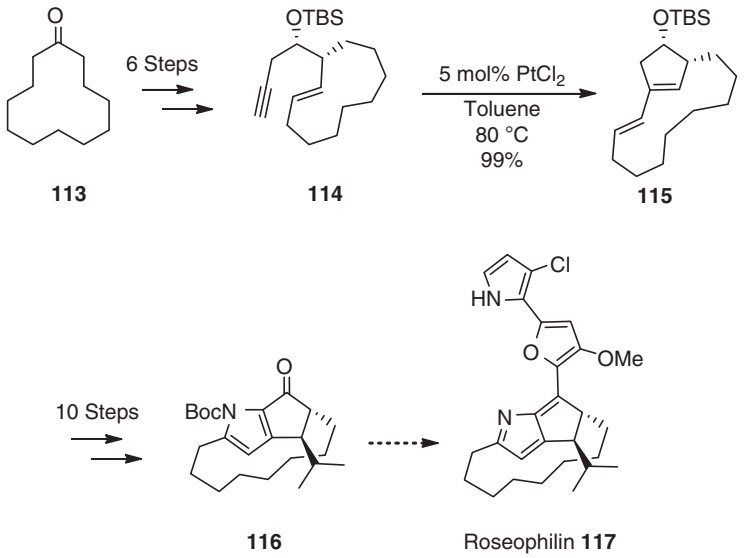


Scheme 11

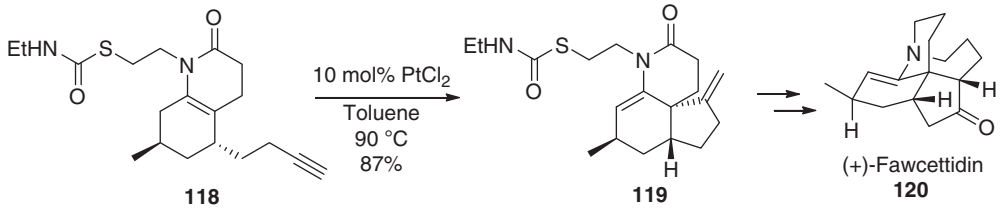
This strategy of obtaining a 1,3-diene was subsequently also used in the formal synthesis of roseophilin **117**, a pentacycle with conjugated pyrroles and a furan ring (Scheme 12).[58] This molecule produced by *Streptomyces griseoviridis* shows some antitumoral properties, particularly in the treatment of leukemia and cancers of the skin. The enantioselective synthesis of 1,6-enyne **114** occurs in six steps from the commercial dodecanone **113**. The cycloisomerization key step was performed in the presence of a catalytic amount of platinum dichloride, leading quantitatively to 1,3-diene **115**, which could be converted into a key derivative **116** via a 10-step synthetic sequence. The activity of platinum complexes in such a clean cyclization process was also illustrated in the synthetic approach of botrydial, an antibiotic produced by a sesquiterpene fungus *Botrytis cinerea*.[59]

The formation of a 1,4-diene in the presence of a platinum complex also found an application in total synthesis as illustrated by the example given in Scheme 13.[60] The total synthesis of (+)-fawcettidin is described and implies the cycloisomerization of enyne **118**, leading very cleanly to the tricyclic structure **119** in 87% yield.

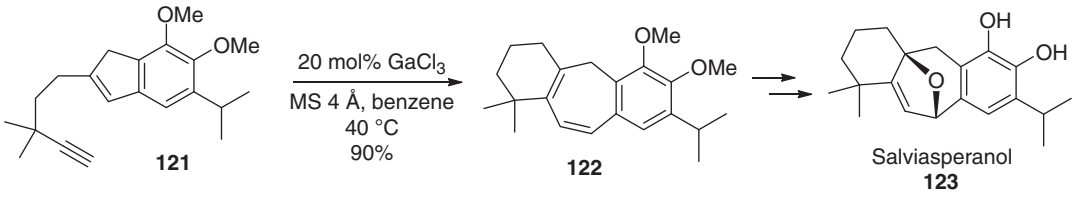
The applications of the cycloisomerization of enynes were not limited to the use of platinum complexes. The total synthesis of (±)-salviasperanol **123** was described by the Sarpong group and nicely takes advantage of the chemistry developed in the presence of gallium.[61] The key step of this synthesis is the reaction of enyne **121** in the presence of gallium trichloride, which leads to the tricyclic 1,3-diene **122** in an excellent yield of 90% (Scheme 14). The same group has described the formal synthesis of cortistatin A according to the same methodology, implying this time platinum dichloride as the catalyst.[62]



Scheme 12



Scheme 13



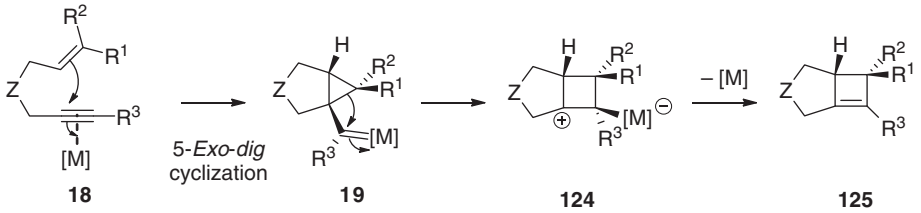
Scheme 14

5.30.3.2 Formation of Bicyclic Derivatives via Cycloisomerization Reactions

5.30.3.2.1 Bicyclo[3.2.0]heptene formation

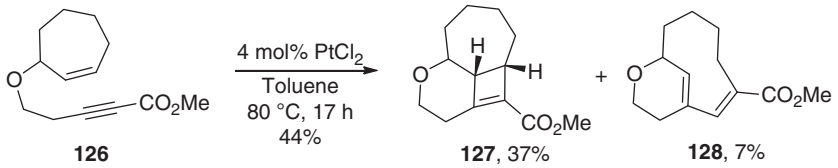
In addition to the formation of 1,3-dienes by single or double cleavage, the cyclization of 1,6-enynes by a 5-*exo-dig* process can lead to the synthesis of bicyclo[3.2.0]heptenes, which formally may be considered as a [2 + 2] cycloaddition (Scheme 15). As presented at the beginning of this chapter (Scheme 7), the postulated mechanism involves a classic addition of the alkene to the activated alkyne **18** (η^2-complex formation) via a 5-*exo-dig* process in the classic case of 1,6-enynes. The resulting cyclopropylcarbenoid intermediate **19** undergoes a 1,2-migration of an alkyl group, leading to the cationic intermediate **124**. The demetallation step leads to the formation of bicyclo[3.2.0]heptene **125**. A theoretical study by DFT calculations of the cycloisomerization of 1,6-enynes with $(PH_3)AuCl$ or $PtCl_2$ was conducted and confirms this hypothesis.[63]

Fürstner's group first highlighted the activity of platinum dichloride in the synthesis of tetrahydropyranic derivatives.[25e] The cyclization of the oxygen-tethered enyne **126** led to the formation of a mixture consisting of a polycyclic derivative **127** (isolated in 37% yield) and the 1,3-diene **128** (7%) (equation 29). The reactivity of the catalytic system could be increased by performing the reaction under an atmosphere of carbon monoxide (σ-donor and π-acid ligand), which contributes to the enhancement of the

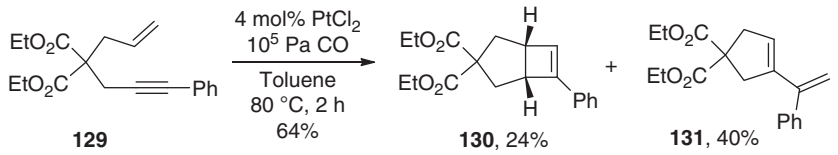


Scheme 15

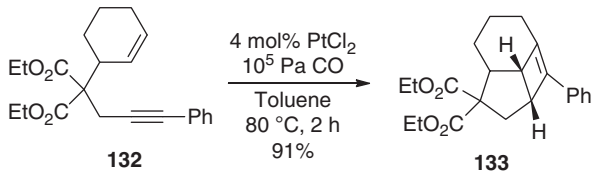
electrophilicity of the platinum complex.[64] The cyclobutene **130** and diene **131** were thus synthesized in 24% and 40% yield, respectively, from the substrate **129**.[65] High selectivity in favor of the tricyclic derivative **133** was observed in the cycloisomerization reaction of **132** (equation 31).



(29)

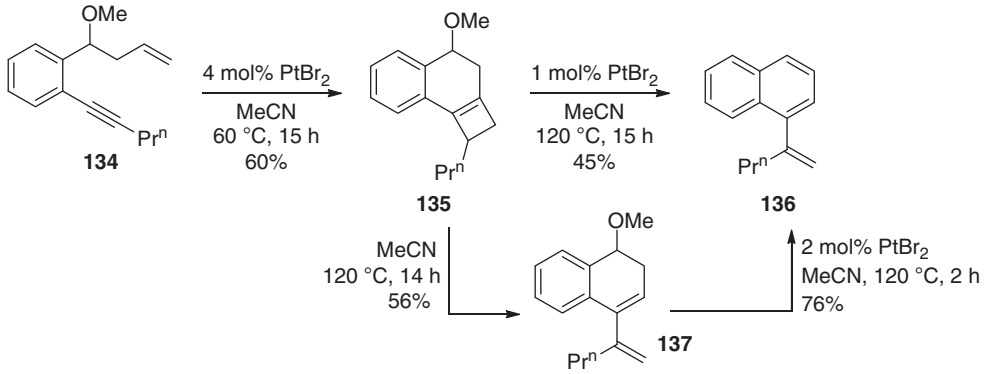


(30)



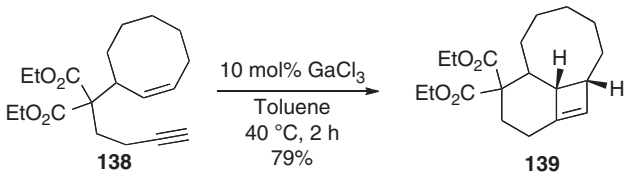
(31)

The Trost group has hypothesized that the synthesis of 1,3-dienes might proceed via a cyclobutenyl intermediate.[66] This hypothesis has been confirmed by the team of Yamamoto in the study of the cycloisomerization of enyne **134** in the presence of platinum dibromide (Scheme 16). This substrate is initially converted into cyclobutene **135** in 60% yield. The opening of the latter via [2 + 2] cycloreversion was performed without metal at high temperature giving the 1,3-diene **136**, which undergoes methanol elimination in the presence of 2 mol% of $PtBr_2$ to form the naphthalene **137**. It is also possible to obtain product **136** directly from the cyclobutene **135** in the presence of a catalytic amount of platinum(II).

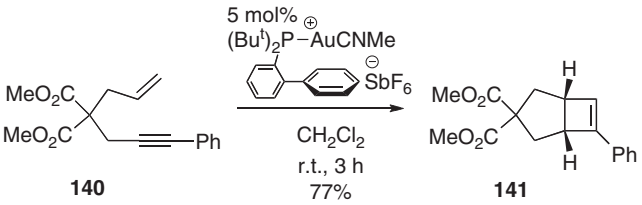


Scheme 16

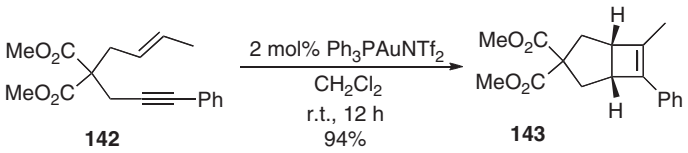
The cycloisomerization of 1,7-enynes has also been described with other carbophilic metal complexes. For example, Murai's group has efficiently obtained the tricyclic derivative **139** under mild conditions via the cycloisomerization reaction of enyne **138** in the presence of 10 mol% of gallium trichloride (equation 32).[67] The use of gold(I) complexes is also very effective: the cationic complex **43** allows for the rapid preparation of bicyclic derivative **141** from the enyne **140** in 77% yield.[68] Another cationic catalyst, the gold(I) bistriflimidate, could be used for the highly efficient cyclization of enyne **142** to the methyl-substituted bicyclic derivative **143**.



(32)

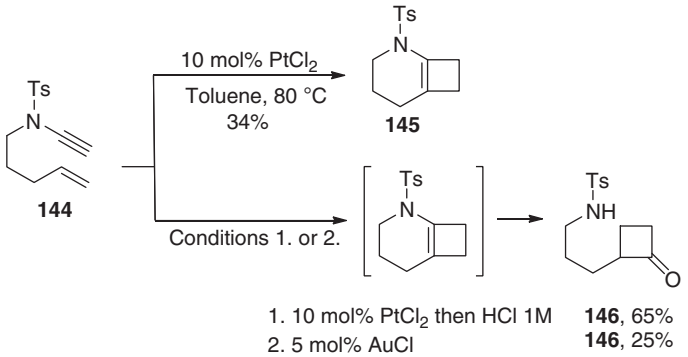


(33)



(34)

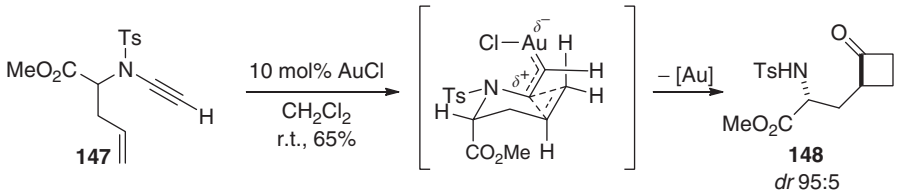
The nitrogen-tethered enynes exhibit specific reactivity as depicted in equations 35 and 36. The cyclization of a 1,7-enyne in the presence of 10 mol% platinum dichloride gives the tosyl-protected 2-azabicyclo [4.2.0] octene **145** in 34% yield.[69] The addition of a 1 mol l^{-1} solution of hydrochloric acid to the crude reaction then allows for the preparation of a wide variety of cyclobutanone-amine derivatives formed by hydrolysis; for example, ketone **146** was synthesized with an overall yield of 65%. The use of a catalytic amount of gold(I) chloride also allows for the direct production of cyclobutanone **146** in moderate yield (equation 36).[70]



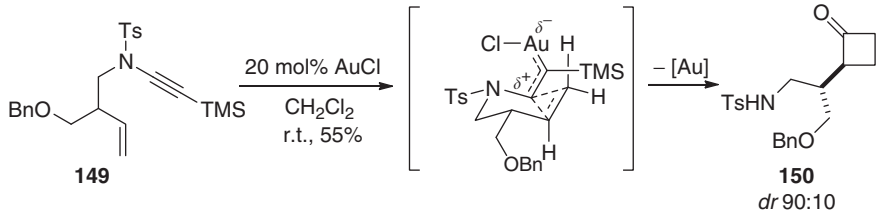
(35)

(36)

When a nitrogen-tethered enyne is substituted at the α- or β-position to the nitrogen atom, the reaction was found to be highly diastereoselective.[70] For example, ketone **148**, prepared efficiently by cyclization of substrate **147**, is obtained in excellent 90% diastereomeric excess (*de*). The same trend is observed for the cycloisomerization of compound **149** bearing benzyl ether at the β-position to the nitrogen atom: the reaction conducted in the presence of 20 mol% of gold(I) chloride leads to the derivative **150** with a yield of 55% and a *de* of 80%. In both cases, chair-like transition state models have been proposed and may account for the observed diastereoselectivity.

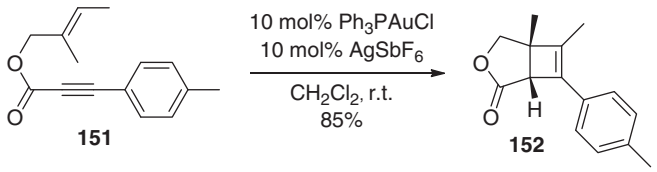


(37)

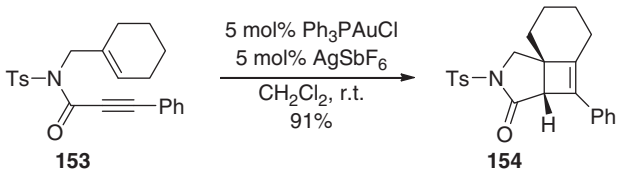


(38)

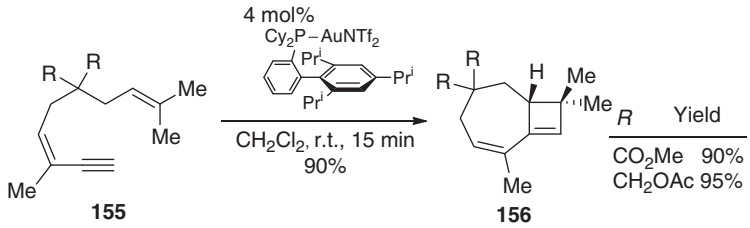
Cycloisomerizations of 1,6-enynes bearing an ester or amide function were also recently studied in the presence of gold catalysts.[71] The use of 10 mol% of a catalyst system combining the precursor gold(I) complex Ph_3PAuCl and $AgSbF_6$ in dichloromethane at room temperature allows ester **151** to be converted into bicyclo[3.2.0]hept-6-en-2-one **152** in 85% yield (equation 39). Compound **153** bearing an endocyclic alkenyl moiety has also been stereoselectively transformed into the tricyclic derivative **154** with a very good performance (equation 40). Once again, large rings are difficult to obtain via cycloisomerization reactions of enynes. The reaction of 1,8-enyne **155** in the presence of a highly hindered cationic biaryl-phosphine gold catalyst afforded the bicyclic derivative **156** in up to 90% yield (equation 41).[72] It is noteworthy that the substitution of the alkynyl side chain is important, as a mixture of stereoisomers was obtained when the alkynyl moiety carries a *n*-pentyl group.



(39)



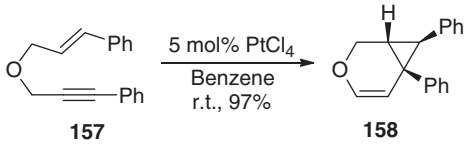
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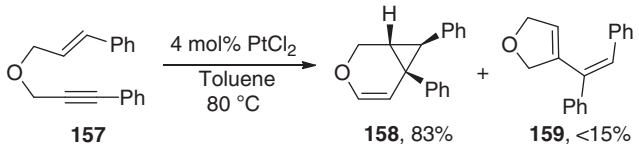
(41)

5.30.3.2.2 Bicyclo[4.1.0]heptenes and bicyclo[3.1.0]hexenes formations

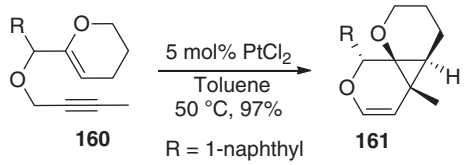
The reaction of oxygen-tethered 1,6-enynes in the presence of platinum tetrachloride at room temperature in benzene was originally described by Blum's group, leading to derivatives of 3-oxabicyclo[4.1.0]heptene.[73] For example, as presented in equation 42, the bicyclic derivative **158**, derived from the ether **157** was synthesized in 97% yield. Following this work, the group of Fürstner studied the activity of platinum dichloride in the synthesis of heterocyclic functionalized cyclopropanes, highlighting the importance of the nature of the enyne for the course of the reaction. Unlike carbon-tethered enynes, whose cyclization leads exclusively to the formation of 1,3-dienes, the cyclization of enyne **157** afforded a mixture of bicycle **158** as the major product and a small amount of 1,3-diene **159** (equation 43).[74] The group of Echavarren also described the synthesis of **161** by a completely diastereoselective rearrangement of ether **160** (equation 44).[75]



157 **158** (42)

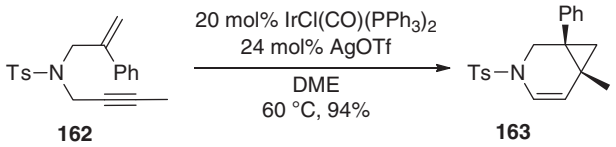


157 **158**, 83% **159**, <15% (43)

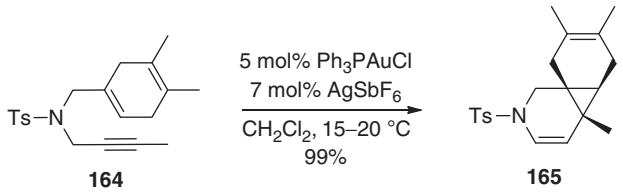


160 **161** (44)

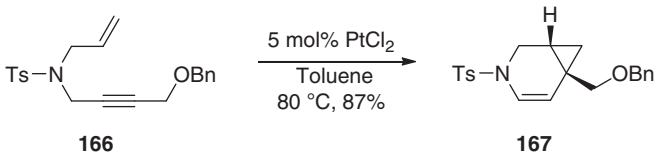
Iridium(I) complexes have also proven effective in the synthesis of bicyclo[4.1.0] heptenes. The use of a catalyst system combining $[IrCl(CO)(PPh_3)_2]$ and silver triflate in the cyclization reaction of the sulfonamide-based 1,6-enyne **162** in dimethoxyethane at 60 °C afforded the bicyclic derivative **163** in excellent 94% yield (equation 45).[76] The preparation of such polycyclic compounds was also catalyzed by gold(I) complexes.[27a] Indeed, it has recently been described that a rapid and quantitative conversion of compound **164** into azatricyclic diene **165** takes place in the presence of the catalyst system $Ph_3PAuCl/AgSbF_6$ in dichloromethane at room temperature (equation 46).[77] Another enyne such as **166**, bearing a heteroatom at the propargylic position could be efficiently transformed to the bicyclic derivative **167** (equation 47).[78] A rhodium complex associated with silver salts showed an activity similar to that of the iridium complexes.[79] For example, the cycloisomerization of **168** led to the bicyclic derivative **169** in 91% yield.



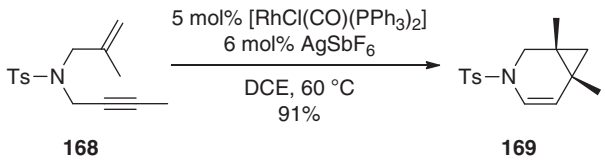
162 **163** (45)



164 **165** (46)

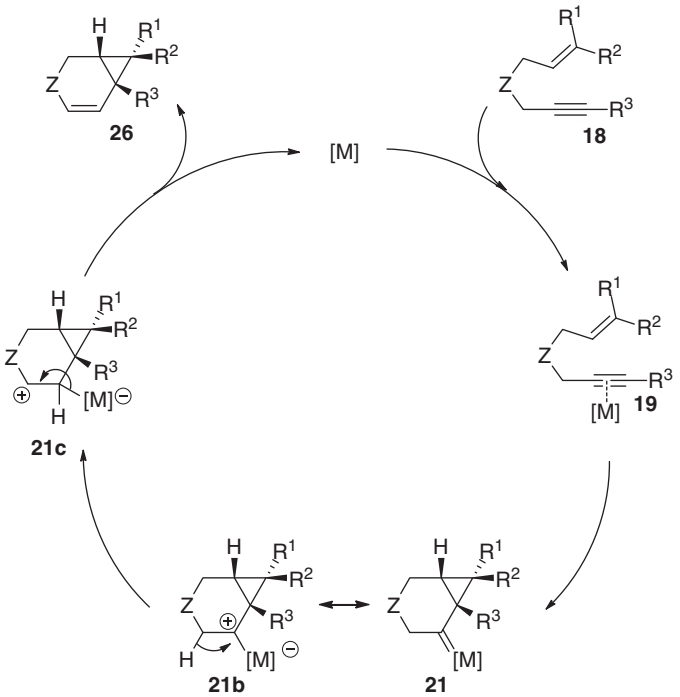


166 **167** (47)



168 **169** (48)

The observed stereoselectivity in the reaction can be rationalized by considering the following catalytic cycle (Scheme 17), which is reminiscent of the intermediates depicted in Scheme 5. In a first step, the coordination of the metal center leads to the η^2-alkyne complex **19**. The nucleophilic attack via a 6-*endo-dig* process of the alkyne allows for the completely diastereoselective formation of the cyclopropylmetalcarbenoid intermediate **21**, which may also be represented in the form of the zwitterion **21b**. The next step is a 1,2-hydride transfer leading to the cationic intermediate **21c**. The stabilization of **21c** in the presence of a heteroatom, by participation of a lone pair of the latter, has been hypothesized. Modeling by DFT calculations, performed by the group of Soriano and Marco-Contelles, confirms this participation of the heteroatom.[80,81] This intermediate then evolves to the bicyclic product **26** after the elimination and regeneration of the metal complex.



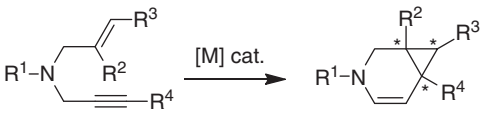
Scheme 17

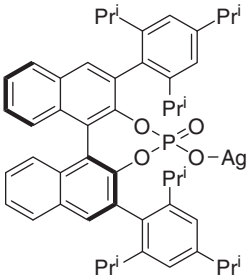
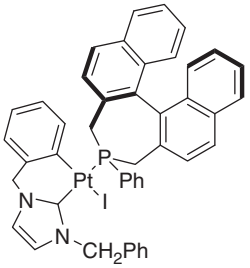
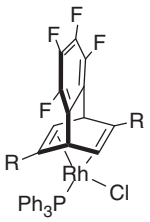
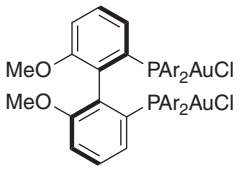
Enantioselective versions of the synthesis of bicyclo[4.1.0]heptenes have been reported in the literature in the presence of platinum, rhodium, iridium, or gold complexes and some examples are presented in Table 1. The first stereoselective synthesis of bicyclo[4.1.0]heptenes was described by Shibata's group in the presence of iridium complexes for nitrogen-tethered 1,6-enynes.[76] A chiral catalytic system consisting of the $[Ir(cod)Cl]_2$ dimer, a silver salt, and (*R*)-Tol-BINAP led to the bicyclic product in moderate to good enantioselectivities, depending on the substrate (Table 1, entries 1–3). However, this method only applies to nitrogen-tethered 1,6-enynes. Another approach for the synthesis of the same derivatives using Vaska's catalyst and a chiral silver salt (AgTRIP) gave better results in terms of enantioselectivity (Table 1, entry 4).[82]

Other chiral catalytic systems using platinum, rhodium, and gold have also been reported in the literature. In the presence of a square-planar platinum complex with an achiral bidentate ligand and the monodentate ligand (*S*)-PhBINEPINE, Marinetti's group described the synthesis of nitrogen-containing bicyclic adducts in 90% yield and an *ee* of 96% (Table 1, entry 5).[83] Taking advantage of chiral dienes bearing electron-poor substituents as ligands to Rh(I), the group of Hayashi has recently developed a synthesis of bicyclo[4.1.0]heptenes in good to excellent *ee* (Table 1, entry 6).[84] Meanwhile, either a gold bimetallic complex bearing a bulky ligand derived from MeOBIPHEP[85] or monometallic gold complexes carrying a Taddol-related ligand[86] were particularly efficient for such asymmetric transformations (Table 1, entries 7 and 8).

Rhodium- and gold-based catalytic systems were also compatible with oxygen-tethered 1,6-enynes. Substrate **170** was converted into the bicyclo[4.1.0] heptene **171** in 56% yield and an *ee* of 96% (equation 49). The use of a bimetallic gold complex also allowed the synthesis of pentasubstituted bicyclo[4.1.0]heptenes starting from trisubstituted alkenes. When the reaction was carried out at 0 °C in the presence of $AgNTf_2$, product **173** was obtained in a yield of 36% and excellent *ee* of 99% (equation 50). Although yields are modest, it is important to note that this methodology is one of the few to obtain pentasubstituted cyclopropanes with such high *ee*'s.[87] The use of a chiral gold complex related to Taddol allowed for the preparation of bicyclo[4.1.0]heptenes **158** in 72% yield and 83% *ee* (equation 51). In the presence of a chiral rhodium catalyst, the bicyclic compound **175** bearing a *gem* diphenyl group at the allylic position could be synthesized from the enyne **174** in 86% yield and an *ee* of 90% (equation 52).

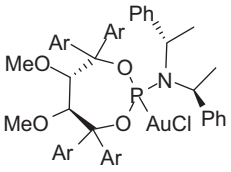
Table 1 Asymmetric syntheses of bicyclo[4.1.0]heptanes

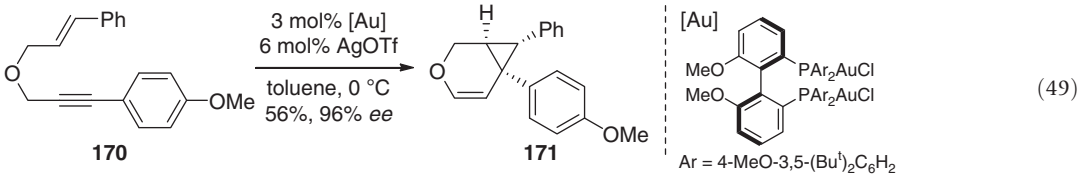


Entry	R^1	R^2	R^3	R^4	*Conditions*	*Yield (%)*	ee *(%)*	*References*
1	*o*-Ts	4-Cl-C_6H_4	H	Me	10 mol% $[IrCl(cod)]_2$,	71	74	76
2	*o*-Ts	2-naphthyl	H	Me	20 mol% (*R*)-Tol-BINAP,	71	35	76
3	Ts	Ph	H	Me	24 mol% AgOTf, CO (10^5 Pa), 1,4-dioxane, reflux	70	78	76
4	Ts	Ph	H	Me	 10 mol% [IrCl(CO)$(PPh_3)_2$] 12 mol% $AgBF_4$, toluene, 90 °C	80	81	82
5	Ts	H	Ph	Ph	 4 mol% [Pt], 4 mol% $AgBF_4$ toluene, 60 °C	90	96	83
6	Ts	H	Ph	Me	 R = $CH_2OCH_2OCH_3$ 5 mol% [Rh], 10 mol% $NaBAr^F_4$ 1,2-dichloroethane (DCE), 50 °C	94	80	84
7	Ts	H	H	Ph	 Ar = 4-MeO-3,5-$(Bu^t)_2C_6H_2$ 3 mol% [Au] 6 mol% AgOTf toluene, 60 °C	74	98	85

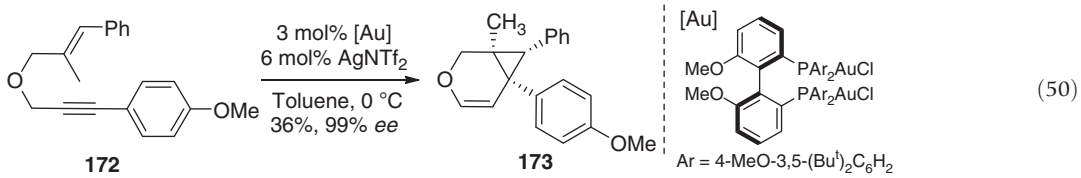
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Table 1 Continued

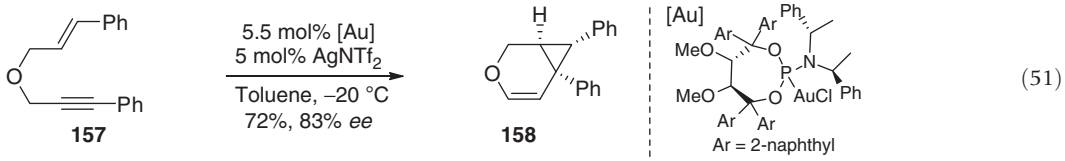
Entry	R^1	R^2	R^3	R^4	Conditions	Yield (%)	ee (%)	References
8	Cbz	H	H	Ph	 Ar = 2-naphthyl 5.5 mol% [Au], 5 mol% $AgBF_4$ toluene, r.t.	72	98	86



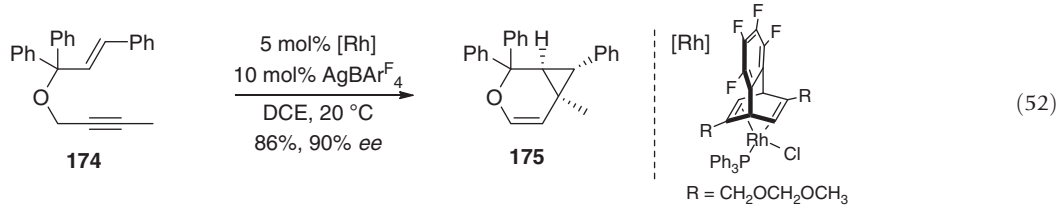
(49)



(50)



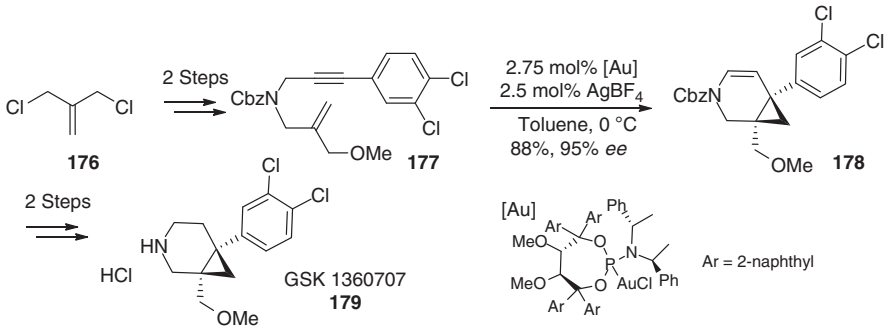
(51)



(52)

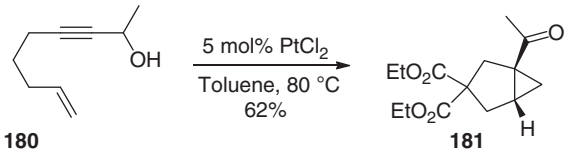
One remarkable total synthesis has recently appeared in the literature based on this methodology (**Scheme 18**). GSK1360707 (**179**), developed by the pharmaceutical company GlaxoSmithKline, is a potent inhibitor of reuptake of the neurotransmitters serotonin, norepinephrine, and dopamine.[88] Inspired by the strategy developed by the group of Elitzin,[89] Fürstner's team proposed a total synthesis in four steps starting from 3-chloro-2-(chloromethyl)prop-1-ene **176**. The preparation of 1,6-enyne **177** was followed by asymmetric cyclopropanation in the presence of the chiral gold(I) complex carrying a Taddol-related ligand.[90] The cyclic Cbz-protected derivative **178** was obtained in high yield and 95% *ee*. The synthesis ends via a hydrogenation/deprotection of the Cbz group step followed by the formation of the hydrochloride salt GSK1360707 **179**.

In the case of 1,6-enynes bearing a carbon- or nitrogen-tethered chain, the 6-*endo* cyclization is not always observed and a 5-*exo* cycloisomerization may occur. The modification of the substituents, especially the propargylic position, may therefore induce the formation of bicyclic cyclopropanes. The formation of functionalized bicyclo[4.1.0]hexanes such as **181** and **183** has been performed in the presence of platinum dichloride in toluene. Depending on the substitution, the cycloisomerization reaction leads either to the bicyclic aldehyde **181**[91] or the enol ether **183**[78] (as a *Z*/*E* mixture) (equations 53 and 54). The alkynylbicyclohexene **185** was synthesized in the presence of a combination of $Bi(OTf)_3$ and 2,2′-bipyridine in good yield. This rare example of a 5-*exo* cycloisomerization mode with an *N*-tethered 1,6-enyne may be rationalized by a dual complexation of

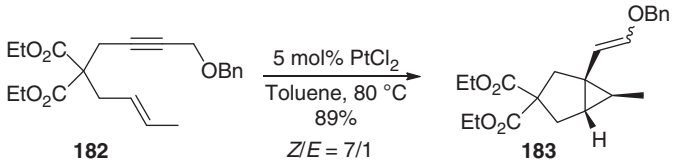


Scheme 18

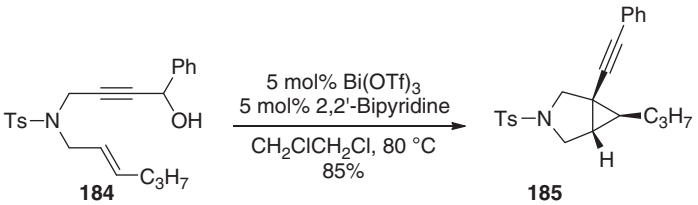
the bismuth catalyst to the alkyne and the alcohol, the whole process being considered as a dehydrative alkynylcyclopropanation (equation 55).[92]



(53)

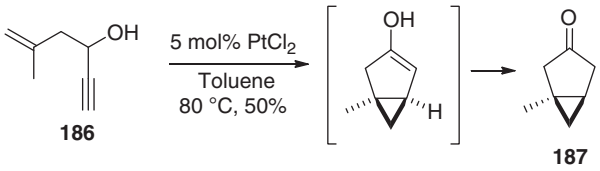


(54)

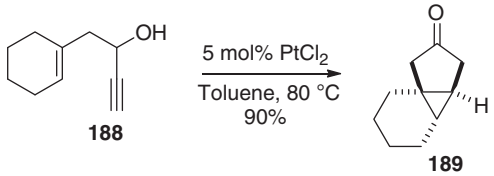


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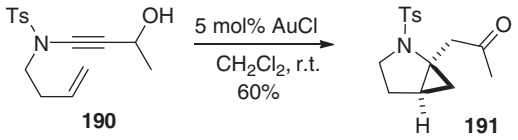
In the particular case of 1,5-enynes, cycloisomerization is observed even in the absence of a linking heteroatom. The cyclization of enynes substituted in the propargylic position has been independently studied by the groups of Fürstner and Malacria.[91,93] In the presence of platinum dichloride in toluene at 80 °C, the unprotected propargyl alcohol **186** has been converted to cyclopentanone **187**, via the enol intermediate, in 50% yield (equation 56). The substrate **188**, which has an endocyclic alkenyl function is transformed into the tricyclic compound **189** in excellent yield under the same reaction conditions (equation 57). The activity of gold chloride was also highlighted, the nitrogen bicyclic derivative **191** being obtained from the enyne **190** (equation 58).[70]



(56)

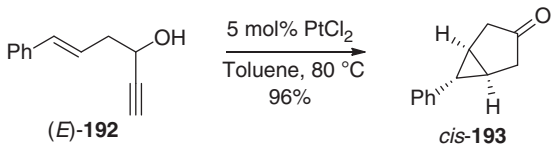


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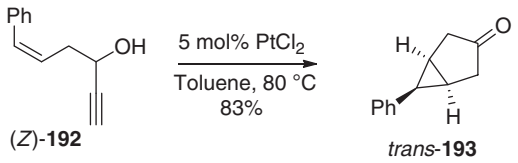


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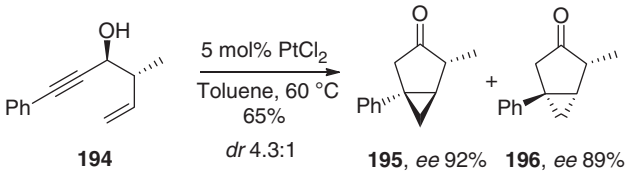
This reaction is totally stereospecific as illustrated in equations 59–61. Indeed, one may observe a direct correlation between the stereochemistry of the double bond within the starting alkene and the stereostructure of the final bicyclic compound. The alcohol (*E*)-**192** could be transformed into the bicyclo[3.1.0]hexanone *cis*-**193** in 96% yield, whereas its counterpart (*Z*)-**192** is cleanly cyclized into *trans*-**193** with a yield of 83%.[93] Optically pure bicyclic derivatives such as **194** were also engaged in the cycloisomerization process and led to diastereomers **195** and **196** in a ratio of 4.3:1 and *ee*'s of 92% and 89%, respectively (equation 59).[91]



(59)

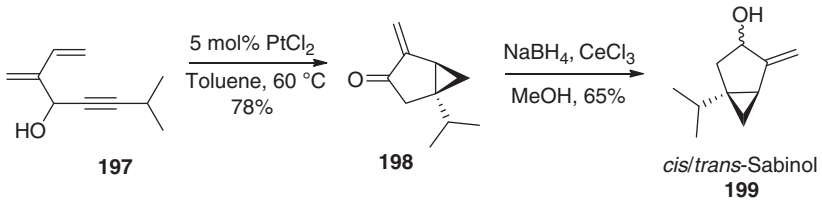


(60)



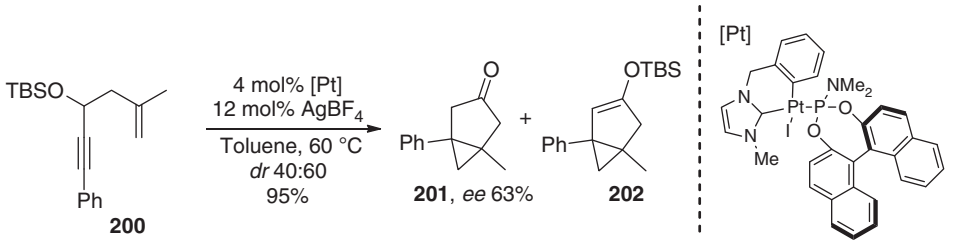
(61)

This reaction has been applied to the total synthesis of *cis* and *trans* sabinols, which are characteristic of the terpenes present in many *Artemisia*, *Juniperus*, and *Thuja* species (Scheme 19). The key step of the three-step process starting from 4-methylpent-2-ynal implies a Pt-catalyzed cycloisomerization reaction of **197** and leads to bicycle **198** in 73% yield. Further reduction affords product **199**, either as the *cis* or the *trans* isomer.

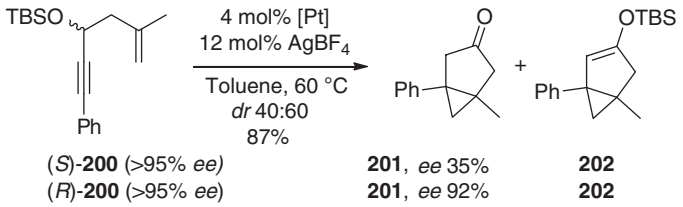


Scheme 19

An enantioselective version of this reaction has been proposed in the presence of chiral platinum complexes for the 1,5-enyne **200** bearing a silyl-protected alcohol at the propargylic position.[94] The reaction of **200** afforded a mixture of two products, the bicyclo [3.1.0]hexanone **201** and the corresponding silylated enol ether **202** in a 40:60 ratio and in 95% yield. The *ee* measured for the ketone **201** was found to be 63% (equation 62). Inspired by some results from the groups of Fürstner and Fehr,[91,95] the cycloisomerization reaction was then initiated with the (*R*) and (*S*)-configured substrate in the presence of the same chiral platinum catalyst, respectively. Starting from (*S*)-**200**, the ketone **201** was obtained in a modest *ee* of 35%, whereas it is formed with a much better *ee* of 92% from (*R*)-**200**. This outcome highlights a strong match/mismatch effect between the substrate and the platinum catalyst (equation 63).

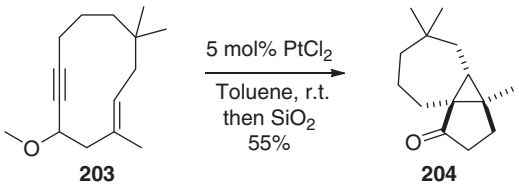


(62)

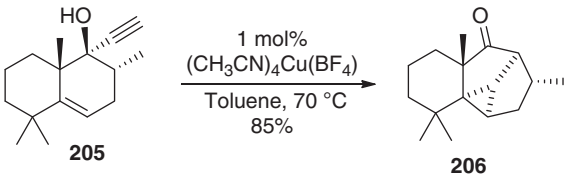


(63)

A transannular version of the cyclopropanation reaction has been performed in the presence of platinum dichloride in toluene at room temperature.[93b] The tricyclic compound **204** was synthesized from the 1,5-enyne **203** in 55% yield (equation 64). Another elegant example has been described for the cyclization of 5-en-1-yn-3-ols in the presence of a Cu(I) catalyst.[95b] The reaction of enyne **205** in the presence of $[Cu(CH_3CN)_4](BF_4)$ cleanly led to the formation of the tetracyclic ketone **206** in 85% yield.

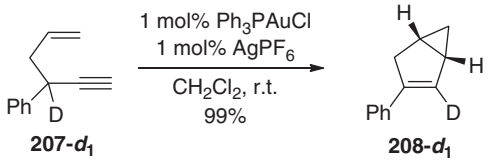


(64)

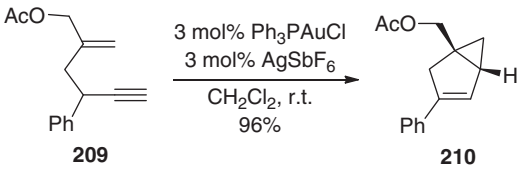


(65)

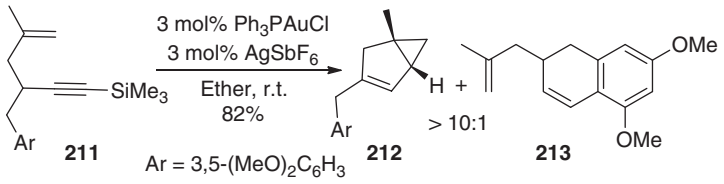
The formation of bicyclo[3.1.0]hexenes is not limited to 1,5-enynes substituted by hydroxyl or methoxy moieties. The enynes **207** and **209** are converted into bicyclo[3.1.0]hexenes **208** and **210** in the presence of triphenylphosphine gold(I) chloride and silver salts in dichloromethane at room temperature in 99% and 96% yields, respectively (equations 66 and 67).[96] In addition, the rearrangement of enyne **207-*d*$_1$**, which is monodeuterated at the propargylic position, leads to the product **208-*d*$_1$** whose structure reveals the 1,2-migration of the deuterium atom. The cycloisomerization of **211** bearing an electron-rich benzyl substituent leads to the formation of the bicyclic derivative **212** in good yield (equation 68).[97] It is noteworthy that the trimethylsilyl group was cleaved under these reaction conditions and that a byproduct **213**, resulting from the gold-catalyzed hydroarylation of the alkynyl part[98] was detected as a minor product.



(66)

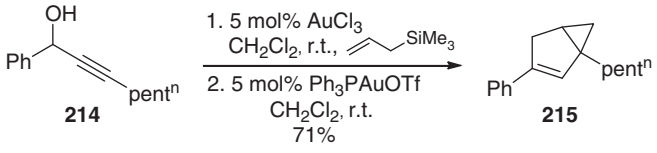


(67)

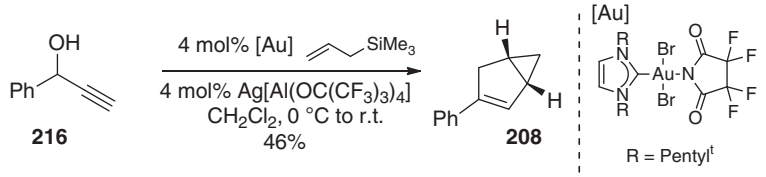


(68)

Similar carbon-tethered substrates may be involved in cycloisomerization reactions, which are synthesized *in situ* by nucleophilic substitution of allylsilanes on propargylic alcohols in the presence of a gold complex.[99] For example, the propargylic alcohol **214** is converted into the bicyclo[3.1.0]hexene compound **215** in 71% yield via substitution followed by the cyclization (equation 69).[100] Similarly, a catalytic system based on gold(III) has proven efficient for the same transformation.[101] The propargylic alcohol **216** was transformed into the bicyclic adduct **208** in 46% yield in the presence of allyltrimethylsilane (equation 70).

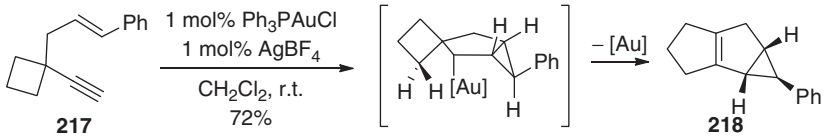


(69)

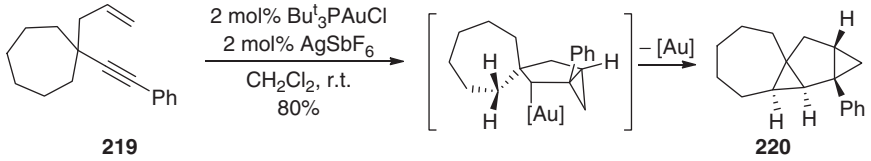


(70)

More complex enynes such as substrates bearing a spirocycloalkyl chain at the propargylic position may evolve according to various pathways. Indeed, migrations of various groups are not limited to hydrogen atoms, but may imply carbon–carbon bonds. A ring expansion of the cyclic adduct **217** takes place by migration of a carbon–carbon bond according to a Wagner–Meerwein transposition, leading to tricyclic compound **218** in 72% yield (equation 71).[96a] The rearrangement of the carbenoid intermediate involves a 1,2-migration of the alkyl group which is favored by the ring strain of the spirocycloalkyl group. A different reactivity was observed for 1,5-enynes such as **219** bearing a larger spirocycloalkyl substituent (at least seven carbon atoms).[102] In this case, a CH bond insertion step and simultaneous creation of three C–C bonds was observed. The reaction afforded the tetracyclic derivative **220** in 80% yield, the proposed intermediate being a tricyclic gold σ-complex (equation 72).



(71)



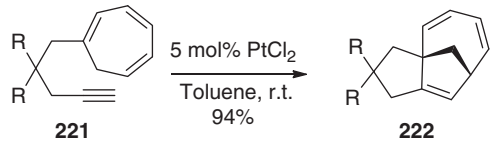
(72)

5.30.3.2.3 Formation of other cycles via enyne rearrangements

Depending on the substitution pattern of the enyne, the use of carbophilic catalysts allow for the formation of other cyclic derivatives, the size of the resulting rings being obviously substrate dependent. A platinum-catalyzed intramolecular formal [6 + 2] cycloaddition of the alkyne tethered to a cycloheptatrienes in compound **221** led to bicyclo[4.2.1]nona-2,4,7-trienes **222** in good to excellent yields (equation 73).[103] Various malonic-type trienynes were compatible with the mild reaction conditions. The authors propose an exocyclic cyclization mode followed by a 'concerted' electron redistribution releasing the cyclic trienes **222**.

In the presence of dienynes, the expected [4 + 2] cycloaddition is followed by a Cope rearrangement (equation 74).[104] Indeed nitrogen-tethered enynes **223** with various substitution on the alkynyl moiety are cleanly transformed to bicyclo[3.2.2]nona-2,8-dienes **224** in the presence of platinum catalysts at 110 °C. A metalla-Cope type rearrangement was proposed as the second

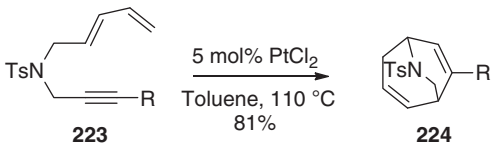
elemental step in the cycloisomerization reaction of dienynes **225**.[105] The generality of the pattern (e.g., carbon- or nitrogen-tethered derivatives) was remarkable and led to the cyclic dienes **226** in good to excellent yields (equation 75). One may note that the use of gold complexes allowed the cyclizations to proceed at room temperature; the silyl group was cleaved on work up.



221 **222**

R	Yield
CO_2Me	94%
SO_2Ph	66%
CH_2OAc	92%

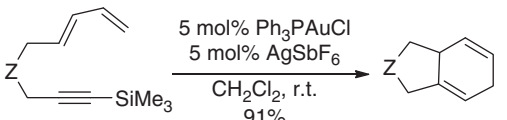
(73)



223 **224**

R	Yield
Ph	81%
Me	61%
H	34%

(74)

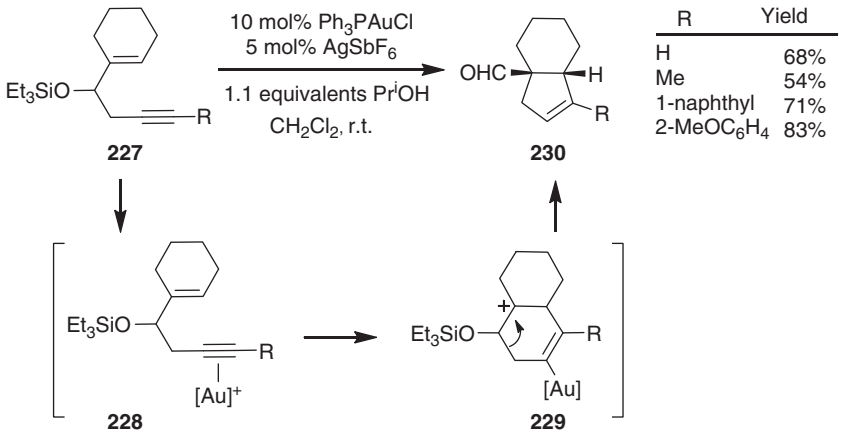


225 **226**

Z	Yield
$C(CO_2Me)_2$	75%
NTs	91%
$C(SO_2Ph)_2$	40%

(75)

The cycloisomerization of 3-silyloxy-1,5-enynes **227** implies an elegant design of the substrates that would be suitable for pinacol rearrangements after the cyclization step.[106] Substrates **227** were engaged in the presence of cationic gold complexes and allowed for the formation of formyl-substituted cyclopentenes **230** in good to excellent yields (**Scheme 20**). According to the authors, the mechanism may proceed through an initial activation of the alkyne moiety, leading to **228**, followed by a 6-*endo* cyclization of the 1,5-enyne giving the vinyl gold intermediate **229**. A pinacol rearrangement (1,2-alkyl migration) of the intermediate would terminate the catalytic cycle, releasing the products on protodesilylation.



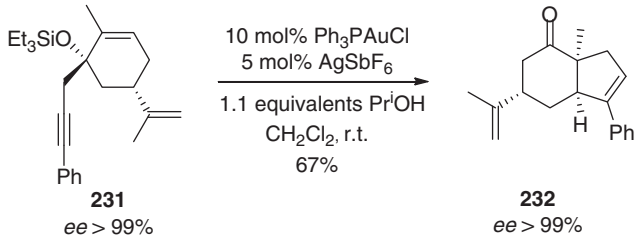
227 **230**

R	Yield
H	68%
Me	54%
1-naphthyl	71%
2-MeOC_6H_4	83%

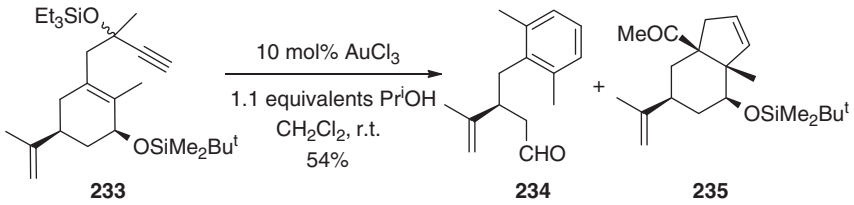
228 **229**

Scheme 20

The transfer of chirality was recently studied and could be applied to the preparation of **232** in high *ee* (equation 76); however, the process could not be generalized to encompass a broad range of substrates.[107] Although studying the rearrangement of enynes containing a tetrasubstituted alkene moiety, a novel carbon–carbon bond scission was observed that was rationalized via a Grob-type fragmentation instead of a pinacol-type 1,2-migration. The best result was obtained in the presence of gold(III) trichloride, which promoted the cyclization/fragmentation of 1,5-enyne **233** to derivative **234** in 51% yield; 3% of the bicyclic adduct **235** were isolated too (equation 77). The use of platinum dichloride in the presence of carbon monoxide afforded the aldehyde **234** in 67% yield.

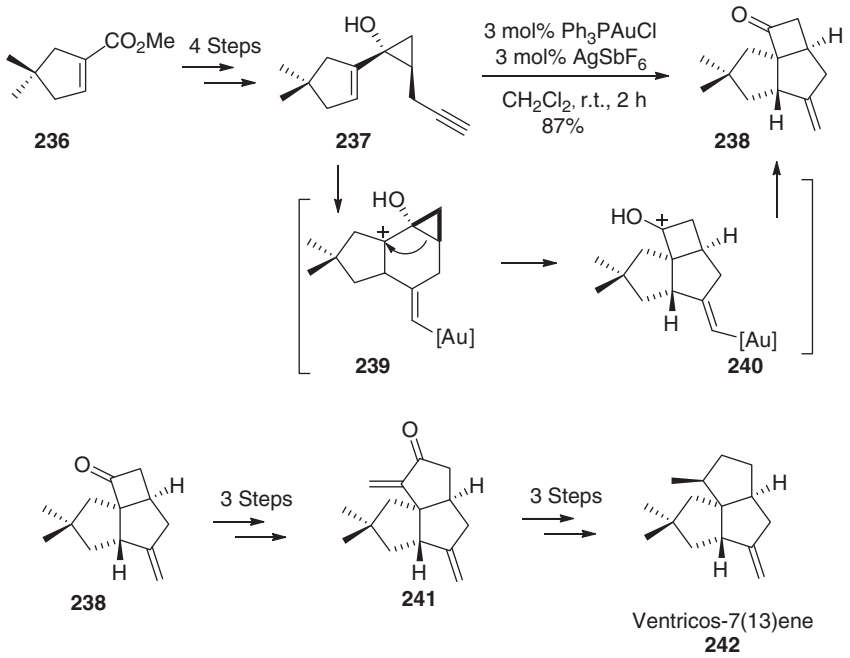


(76)



(77)

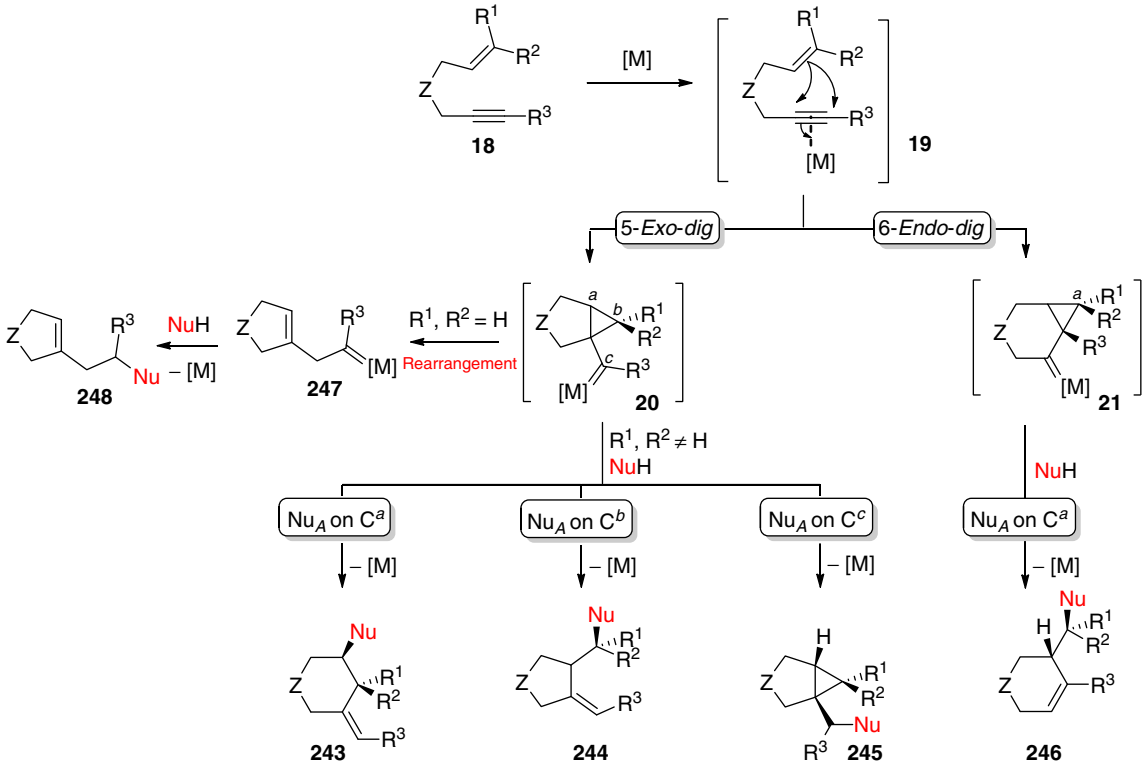
The pinacol-type rearrangement was applied to the total synthesis of ventricos-7(13)-ene **242** (Scheme 21).[37] The cyclopropyl alcohol-containing 1,6-enyne **237** was classically prepared starting from the commercially available ester **236** in four steps. The cycloisomerization was performed in the presence of the cationic gold(I) complex $Ph_3PAuSbF_6$ under mild conditions and afforded the tricyclic ketone **238** in 87% yield. The reaction presumably proceeds via a 6-*exo* cyclization giving the vinyl aurate intermediate **239**, followed by a 1,2-alkyl shift and protodemetalation. The total synthesis of ventricos-7(13)-ene **242** was then accomplished via a six-step sequence involving a Pd-catalyzed ring expansion (leading to **241**) and a Barton–McCombie reduction of a xanthate ester.



Scheme 21

5.30.4 Domino Enyne Cycloisomerization–Nucleophile Addition Reactions

The enyne cycloisomerization reaction may also be associated with various inter- or intramolcular processes implying carbon or heteroatom nucleophiles. One general scheme trying to summarize the different possible pathways is presented in Scheme 22. In relation with Scheme 5, where the skeletal rearrangements were presented, one may envision the trapping of the carbenoid intermediates **20** and **21** resulting from 5-*exo-dig* and 6-*endo-dig* cycloisomerization processes.



Scheme 22

Depending on the nature of the nucleophile and the stabilization of the organometallic intermediate, the addition of the nucleophile can then be performed:

- On the cyclopropanyl moiety (carbons a and b), giving after rearrangement and protodemetallation, the unsaturated derivatives **243**, **244** (5-*exo-dig*), and **246** (6-*endo-dig*);
- On the carbenoid moiety (c) allowing the formation of the bicyclic compound **245**;
- On the carbenoid intermediate **247**, formed by rearrangement of intermediate **20** when the alkenyl function of the enyne is monosubstituted; this leads to the compound **248**.

A variety of nucleophiles could be used in the context of these cyclizations, including oxygen nucleophiles (water, alcohols, sulfoxides, and carbonyl derivatives), unsaturated carbon compounds (electron-rich aromatic rings, 1,3-dicarbonyl malonic derivatives, alkenes), and nitrogen compounds (amines and carbamates). The following Sections 5.30.4.1, 5.30.4.2 and 5.30.4.3 will give seminal examples.

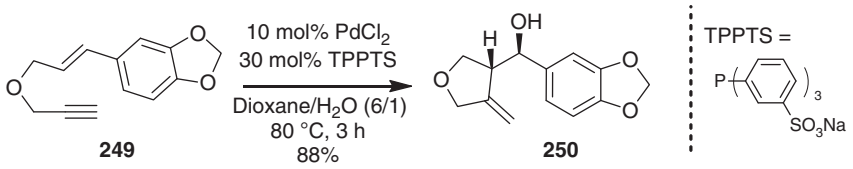
5.30.4.1 Oxygen Nucleophiles

5.30.4.1.1 Hydroxy- and alkoxycyclization reactions

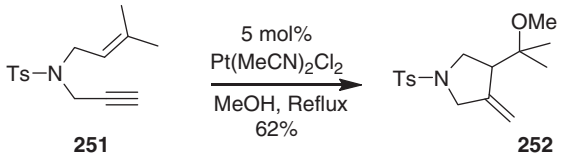
5.30.4.1.1.1 Reactivity of 1,6- and 1,5-enynes

The addition of oxygen nucleophiles is probably the most-studied domino cycloisomerization/functionalization process. The first example of the addition of a protic oxygen nucleophile on 1,6-enyne catalyzed by an organometallic complex has been described by the group of Genêt.[108] The catalytic system, consisting of palladium dichloride and a water-soluble phosphine ligand (triphenylphosphino tris-*meta* sulfonate sodium salt, TPPTS), in 1,4-dioxane/water afforded alcohol **250** in a diastereoselective process (equation 85); starting from enyne **249**, the addition of water occurs on carbon b of intermediate **20** (Scheme 22).

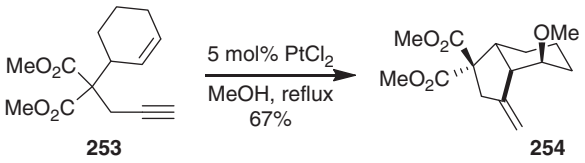
The synthesis of carbo- and heterocycles by cyclization of 1,6-enynes and domino addition of water or alcohol has been widely described using platinum(II) and gold(I) catalysts, which showed higher activities.[109] The addition of methanol on the nitrogen-tethered enyne **251** gave, for example, compound **252** in 62% yield. The cyclization of enyne **253**, which bears an endocyclic alkenyl pattern, leads to the completely diastereoselective formation of the bicyclic compound **254** in good yield (equation 80). Allylic alcohol, phenols, or 1,3-dicarbonyl nucleophiles may be employed in these processes as exemplified by the preparations of **256** (starting from 1,6-enyne **255**),[110] **258** (starting from 1,5-enyne **257**)[111] and **260** (starting from 1,6-enyne **259**)[112] (equations 81–83). An original variant consists of a 6-*endo-dig* type rearrangement, followed by the addition of benzyl alcohol to furnish the vinylsilane **262** from the silylated enyne **261**.[113] The introduction of alcohol occurs preferentially on the more substituted carbon (equation 84).



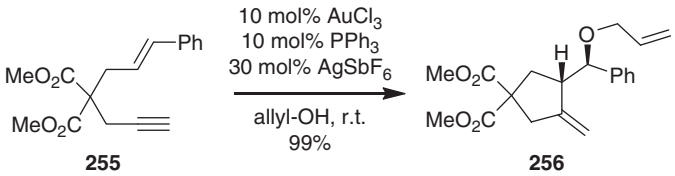
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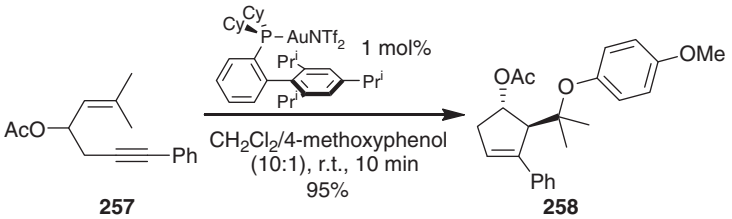
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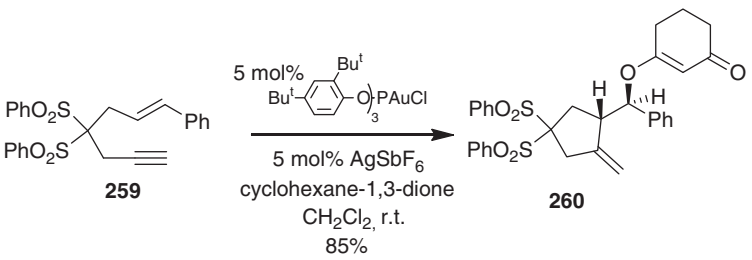
(80)



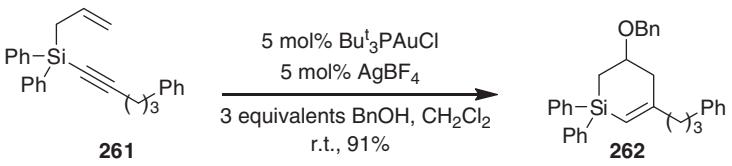
(81)



(82)



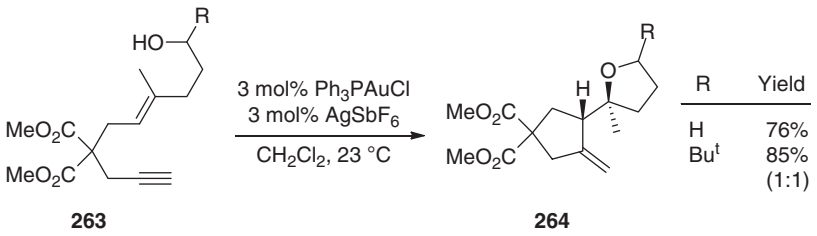
(83)



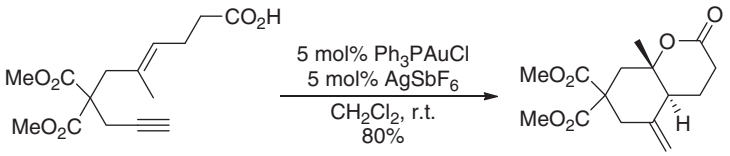
(84)

Intramolecular cyclizations of 1,6-enynes having a hydroxyl substituent on the alkene moiety have also been studied.[27d] In the presence of a catalytic amount of $Ph_3PAuCl/AgSbF_6$, the enynols **263** are converted via a 5-*exo*-*dig* process into bicyclic derivatives **264** in good yields (equation 85). In the case of the *tert*-butyl substituted alcohol (R = *tert*-Bu), a 1/1 mixture of diastereoisomers

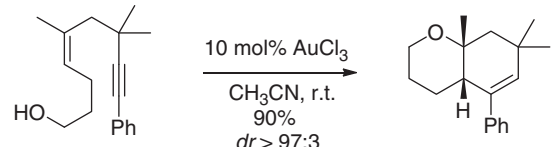
was obtained. Other nucleophiles such as carboxylic acids are suitable for the transformation of 1,6-enynes (equation 86).[114] The authors showed that the reaction is stereospecific by preparing and reacting with both stereoisomers of **265**. The (*E*)-isomer is cleanly transformed to the *trans* bicyclic adduct **266**, whereas the (*Z*)-isomer is giving the respective *cis*-configured isomer of **266**. Moreover, the addition of the nucleophile is dictated by the substitution pattern of the double bond, which is in full agreement with the carbenoid type intermediates that have been discussed in Section 5.30.4. As for the intramolecular domino cyclization/functionalization reaction, this process could be applied to 1,5-enynes (equations 87–91). The group of Kozmin has reported one of the preliminary examples of a tandem intramolecular bicyclization.[115] In the presence of 10 mol% of gold(III) trichloride, the intramolecular addition of the hydroxyl group from **267** leads to the bicyclic adduct **268** through 6-*endo-dig* cyclization, with an excellent *cis* diastereoselectivity (equation 87). A similar transformation has been described modifying the structure of the enyne. The 6-*endo-dig* cyclization of the enyne **269** is followed by the addition of the hydroxyl group as nucleophile, leading to the ether spiroketal **270** in high yield (equation 88). The selectivity of the nucleophilic addition can be further rationalized by considering the formation of a tertiary carbocation that is more stable than a secondary one. A formal [4 + 2] cycloaddition of an *N*-alkynyl *tert*-butyloxycarbamate with an alkene has been recently described in the presence of cationic gold(I) catalyst. Cycloisomerization of **271** leads to the bicyclic functionalized adduct **272** in 78% yield, the process being totally diastereoselective.[116]



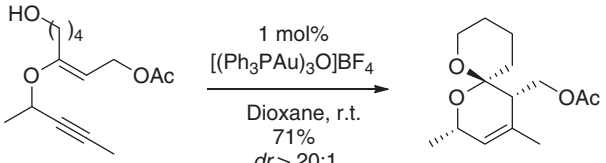
263 **264** (85)



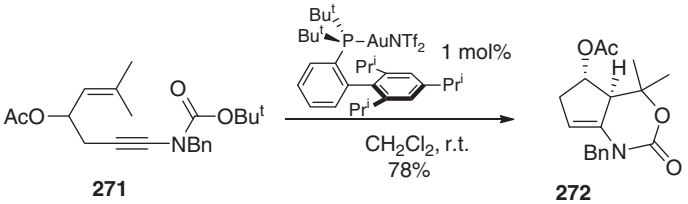
265 **266** (86)



267 **268** (87)



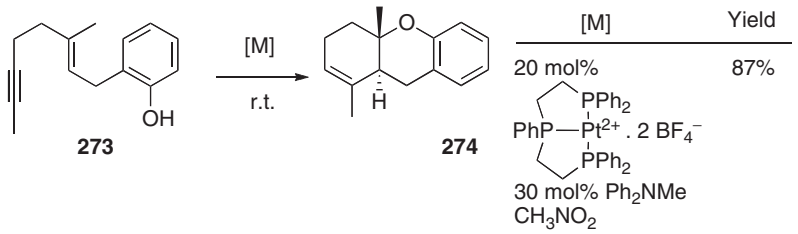
269 **270** (88)



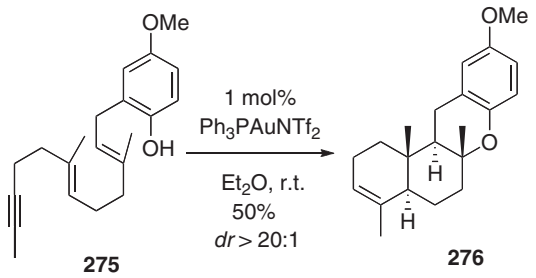
271 **272** (89)

The intramolecular phenoxycyclization of 1,5-enynes was recently described either in the presence of a dicationic platinum(II) complex or of a gold catalyst (equation 90).[117] The enyne **273** is converted in the presence of the platinum complex to the tricyclic

derivative **274** in 76% yield. The use of the cationic gold(I) complex $Ph_3PAuNTf_2$ at a low loading (1 mol%) allowed this cyclization to occur more efficiently and faster. This cyclization proceeds as 6-*endo-dig* process; the *trans* relationship between the groups on both sides of the junction of the ring formed may be rationalized by a chair-type reactive intermediate. The same gold cationic precursor is also effective for the addition/tandem cyclization of dienynol **275**, leading diastereoselectively to the tetracyclic compound **276** in moderate yield (equation 91).

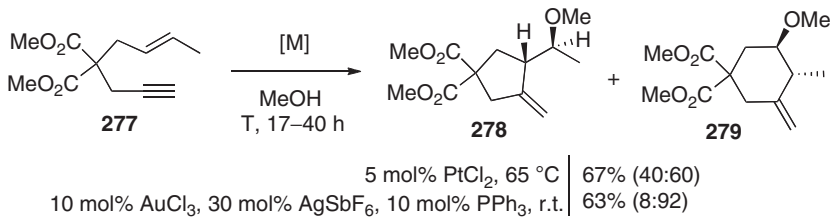


(90)



(91)

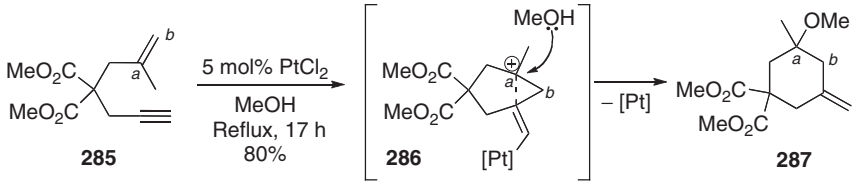
The cyclization/functionalization of some enynes leads to the formation of derivatives from the competitive 5-*exo-dig* and 6-*endo-dig* processes. In the presence of a catalytic amount of platinum dichloride, enyne **277**, bearing a methyl substituent on the external carbon of the alkene is converted to a mixture of the cyclization products **278** and **279** according to the two possible pathways (equation 92).[38] The electrophilicity of the chosen organometallic complex seems to influence the ratio of the two products in favor of the compound coming from the 6-*endo-dig* cyclization, since the use of a catalytic system based on gold leads to a ratio of **278**/**279** of 8/92.[110a]



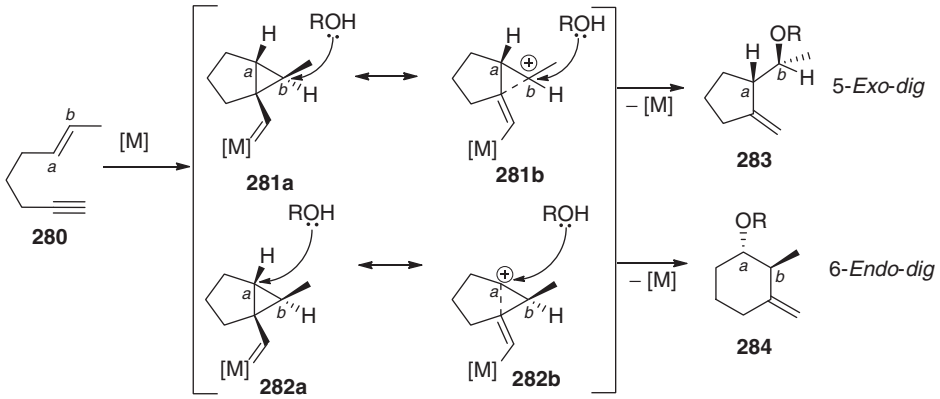
(92)

The influence of the electrophilicity of the metal center on the structural parameters of the cyclopropylcarbenoid intermediates (proposed in the cyclization of 1,6-enynes) has been studied by the group of Echavarren (**Scheme 23**).[27,35] DFT calculations for the cyclization of enyne **280** suggests that the intermediate obtained by nucleophilic addition of the alkene to the alkyne in the presence of platinum dichloride is best described by a cyclopropylcarbenic form (intermediates **281a** and **282a**), whereas the species obtained by the reaction in the presence of gold complex has a carbocationic character, represented by the intermediates **281b** and **282b**. Thus, the stereoselective attack (intermediate **282b**) by a protic oxygen nucleophile takes place preferentially to form a six-membered ring.

The cyclization according to a 6-*endo-dig* process may therefore be favored when there is substitution on the internal carbon of the alkene. In the presence of 5 mol% of platinum dichloride, enyne **285** is thus converted into the six-membered cyclic derivative **287** (equation 93). The regioselective addition of methanol occurs on the tertiary carbon of the transient intermediate **286**.[109b]



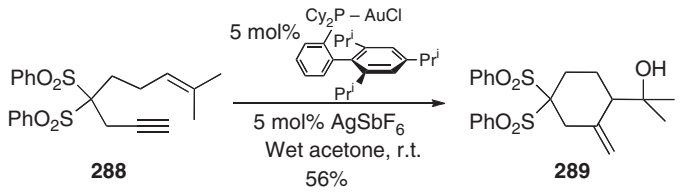
(93)



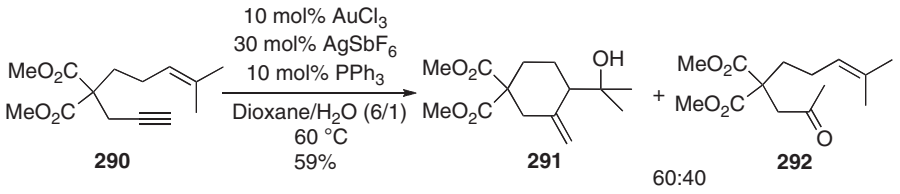
Scheme 23

5.30.4.1.1.2 Reactivity of 1,7-enynes and dienynes

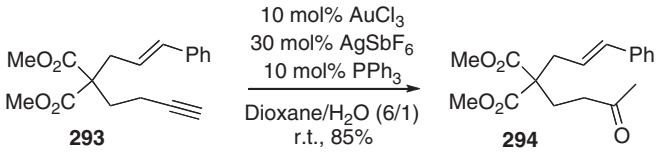
Apart from 1,5- and 1,6-enynes, few other substrates have been engaged in domino cycloisomerization/functionalization reactions. The activity of gold complexes has been studied in the alkoxycyclization of 1,7-enynes. The hydroxycyclization of enyne **288**, substituted by a disulfonate moiety in position C-4, leads to the alcohol **289** in 56% yield (equation 94).[42] Similar results were obtained in the case of the malonic analog **290**, despite the fact that competitive hydration of the alkyne moiety with formation of the ketone **292** was observed (equation 95).[110a] This competitive process may be predominant in the case of the 1,7-enyne **293**, where the general conditions led exclusively to the ketone **294** in 85% yield (equation 96).



(94)

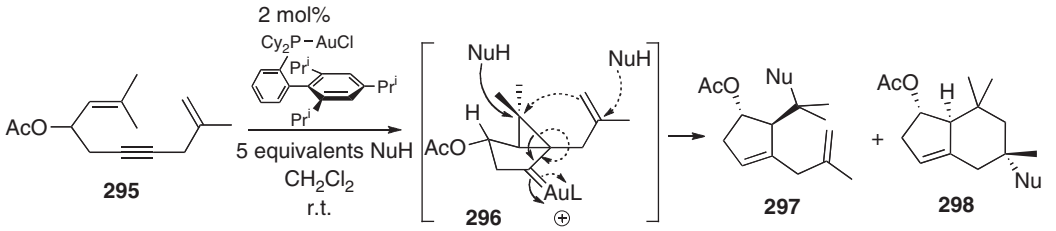


(95)



(96)

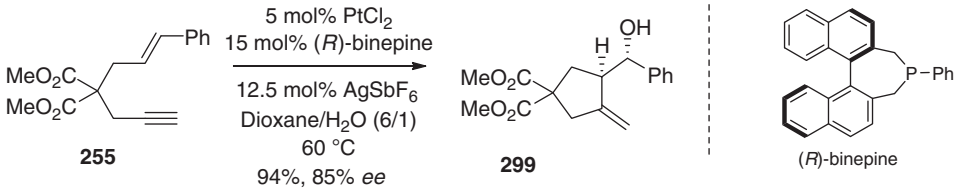
When the enyne bears another unsaturation, two nucleophilic sites are present and may participate in the cyclization/functionalization process. The competition between the oxygen and carbon nucleophiles has been highlighted while studying the reaction of dienyne **295** (equation 97).[118] A mixture of products was obtained with a preferential formation of **298**, the common intermediate being the carbenoid species **296**. The dilution seems to play an important role, as a very dilute medium leads to the formation of adducts **297** and **298** in almost equal proportions. The strength of the nucleophile is another criterion and the use of 4-methoxyphenol, less nucleophilic than methanol, has led to the exclusive double addition product **298**, in a completely diastereoselective manner and in 70% yield.



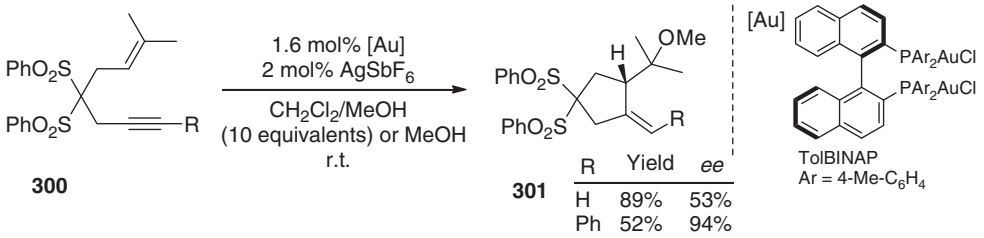
(97)

5.30.4.1.1.3 Asymmetric catalysis

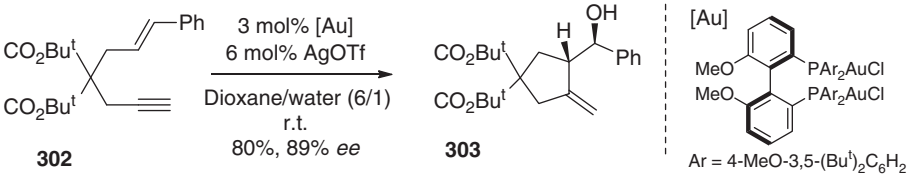
The first example of an enantioselective tandem hydroxycyclization involved a catalytic system generated *in situ* from 5 mol% platinum dichloride, 12.5 mol% of $AgSbF_6$, and 15 mol% of an atropisomeric monophosphine ligand (equation 98).[119] The carbon-tethered enyne **255** was thus converted into the secondary alcohol **299** via a 5-*exo-dig* cyclization in 94% yield and 85% *ee*. A similar system was proposed involving ligands such as (*R*)-BINAP or (*S*)-Tol-BINAP, but did not give any better results.[120] The use of bimetallic complexes of gold(I), with a atropisomeric bidentate ligand, has also shown efficacy in the methoxycyclization of disulfonated enyne **300** leading to ether **301** in 53–94% *ee*, depending on the substitution of the alkyne moiety (equation 99).[120] Recently, the use of a chiral NHC ligand led to *ee*'s of up to 72%.[121] However the platinum and gold systems (equations 98 and 99) have shown limited effectiveness since these rearrangements were found highly dependent on small structural modifications of the substrate. Other catalytic systems and substrate skeletons have therefore been designed, implying cationic bimetallic gold(I) complexes (equations 100–103). For example the use of a hindered malonic-type substituted 1,6-enyne such as **302**, allowed for a clean and selective hydroxycyclization reaction leading to **303** in 89% *ee*; for comparison, only 58% *ee* was observed for the methyl ester analog of **302** (equation 100).[122]



(98)

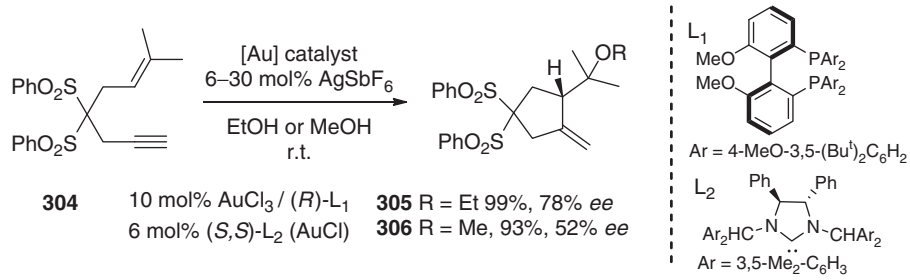


(99)

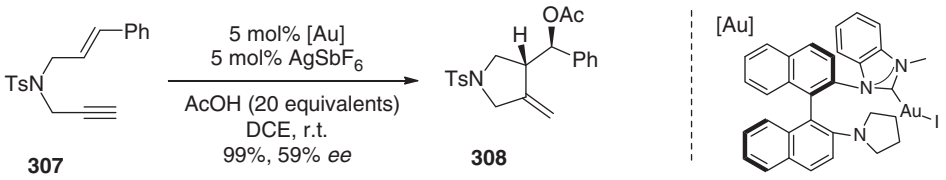


(100)

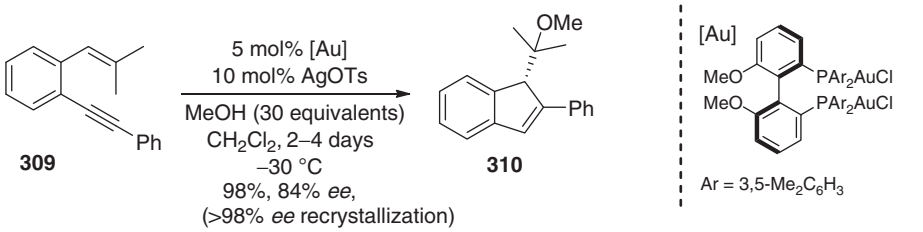
The alkoxycyclization reactions of enyne **304** were also dependent on the structure of the ligand as a better *ee* was obtained in the presence of a bimetallic gold complex derived from MeOBIPHEP analog[123] compared with the use of a monometallic chiral NHC ligand[124] (equation 101). The addition of acetic acid followed by the cyclization has been accomplished asymmetrically in the presence of an axially chiral NHC ligand (equation 102).[125] The nitrogen-linked enyne **307** was transformed to the functionalized pyrrolidine **308** in excellent yield and 59% *ee*. Recently, the synthesis of functionalized indene derivatives was described using a cationic bimetallic gold complex (equation 103); for example, the ether **310** was obtained in 84% *ee*.[52a]



(101)

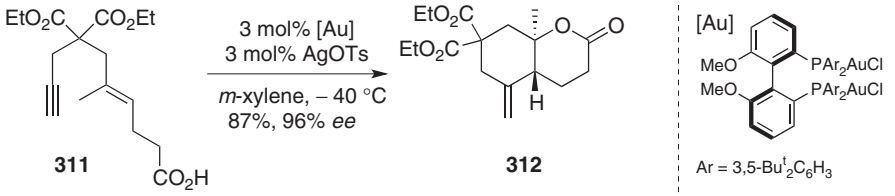


(102)

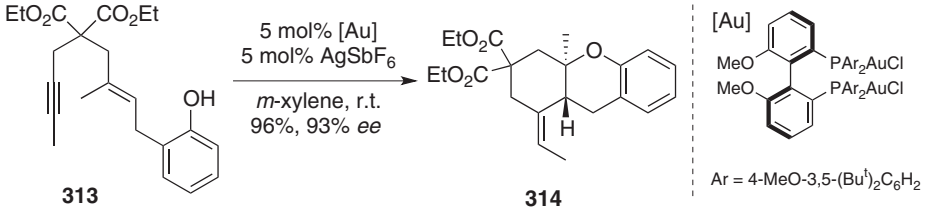


(103)

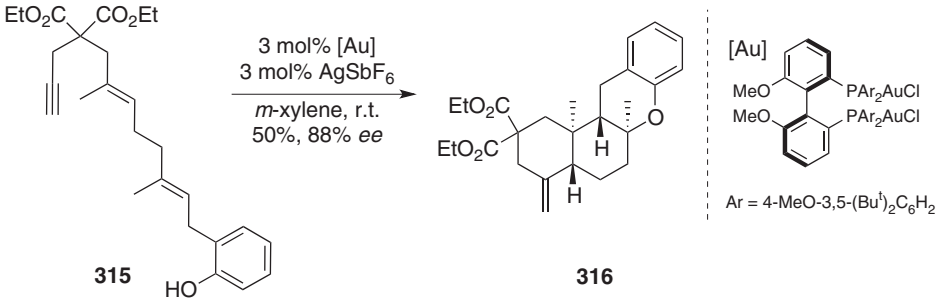
Intramolecular asymmetric versions of the carboxy- and phenoxycyclization appeared only recently in the literature (equations 104–106).[126]



(104)



(105)



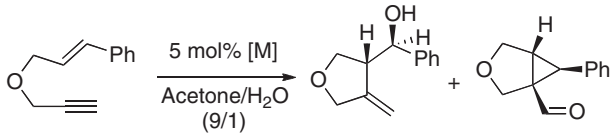
(106)

The reaction conditions of the bicyclization reactions involving either a carboxylic acid (substrate **311**) or a phenol (substrate **312**) were optimized in the presence of various chiral atropisomeric ligands. The best results were obtained with di-*tert*-butyl- and

di-*tert*-butyl-methoxy-MeOBIPHEP as ligands, respectively, affording compounds **312** and **314** in 96% and 93% *ee*. As the stereochemistry is fully consistent with the Stork–Eschenmoser postulate, the tricyclization of dienyne **315** successfully gave the tetracyclic adduct **316** in good yield and 88% *ee* (equation 106).

5.30.4.1.2 Oxidative rearrangements

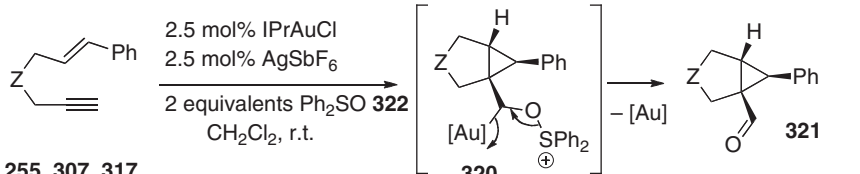
An interesting reactivity of carbenoid intermediates (e.g., **20** in Scheme 22) was garnered in the presence of unsaturated oxygen derivatives such as sulfoxides or oxygen. The first example of an oxidative rearrangement catalyzed by a carbophilic metal complex was described when the enyne **317** was cyclized in oxygenated aqueous acetone in the presence of 5 mol% of platinum dichloride (equation 107). The alcohol **318** was formed according to the conventional hydroxycyclization, but the bicyclic aldehyde **319** was also obtained in 12% yield. The use of palladium dichloride also leads to the mixture **318**/**319**, with **319** still being the minor product.[38] Toste's group has recently described a similar oxidative rearrangement by addition of diphenylsulfoxide **322**.[127]



[M]	Yield	**318**:**319**
$PtCl_2$	12%	12%
$PdCl_2$	40%	10%

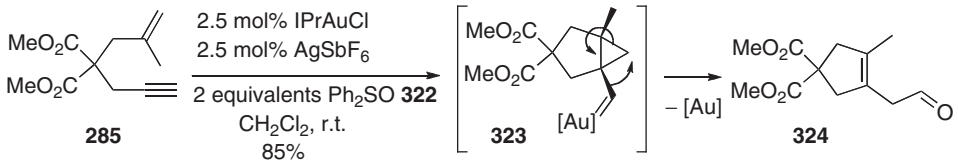
(107)

The cyclization of enynes **255**, **307**, and **317**, in the presence of *N*-heterocyclic gold(I) complex IPrAuCl, a silver salt and 2 equivalents of diphenylsulfoxide, led to the formation of the bicycles **321** with a very good performance (equation 108). This reaction gave high yields starting from carbon-, oxygen-, or nitrogen-tethered enynes. The mechanism most probably involves the addition of the sulfoxide to the carbon bound to the gold(I) complex. Elimination of the metal complex and of diphenylsulfide (intermediate **320**) explains the formation of the bicyclopropanic carbonyl derivative (equation 108). An isomerization process may also occur on the cyclopropyl carbenoid species before the addition of the nucleophile (intermediate **247**, Scheme 22); this process is favored for alkenes that are unsubstituted at the terminal position. This reaction pathway can account for the structure of cyclopentene **324** obtained by cyclization of enyne **285** in 85% yield (equation 109).



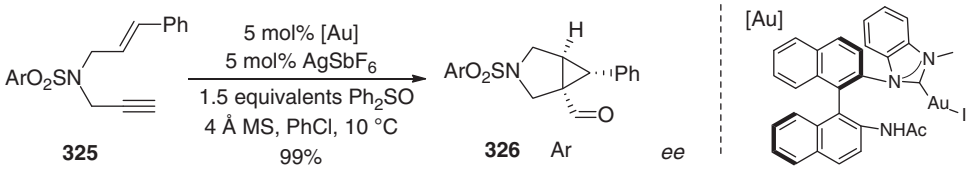
Z	Yield
$C(CO_2Me)_2$	90%
O	94%
NTs	91%

(108)



(109)

The first example of an asymmetric variant appeared in 2011 in the presence of an axially chiral NHC ligand (equation 110).[125] The reaction of nitrogen-tethered enynes **325** led to the bicyclic adducts **326** in excellent yield and *ee*'s of up to 70%. It is noteworthy that this process has only been described for nitrogen-linked 1,6-enynes and that the *ee*'s are highly dependent on the substitution of the alkene and the protective group on the nitrogen atom.

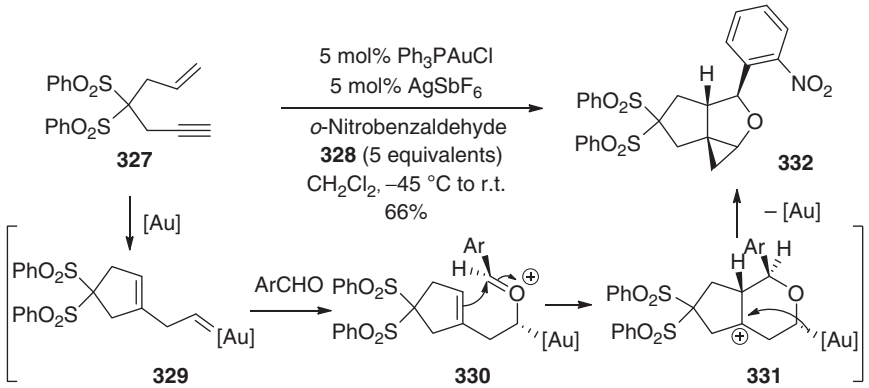


Ar	*ee*
Ph	65%
4-Br-C_6H_4	70%

(110)

5.30.4.1.3 Prins rearrangements

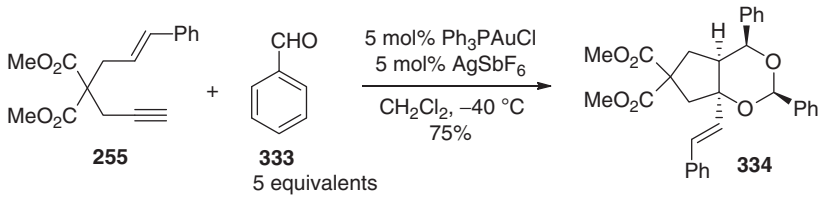
Helmchen's group described for the first time the intermolecular addition of carbonyl compounds onto enynes bearing monosubstituted alkene units. This domino process, in which two C–C and one C–O bonds are assembled, is a formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition. In the presence of the catalyst system $Ph_3PAuCl/AgSbF_6$ and *o*-nitrobenzaldehyde, the cyclization of enyne **327** leads to the tricyclic compound **332** in 66% yield (Scheme 24).[128]



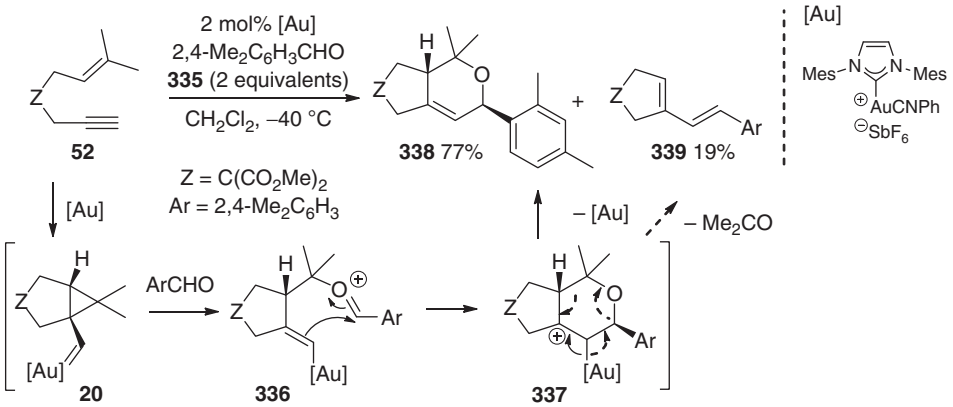
Scheme 24

The proposed mechanism involves a first isomerization step of the carbene intermediate according to the process presented above in the discussion of the oxidative rearrangement (equation 109) (Section 5.30.4.1.2) and in general Scheme 22. The addition of the carbonyl compound on the carbon bonded to the metal complex **329** leads to **330**. Subsequent attack by the alkene results in the formation of the bicycle **331**, which evolves to the tricyclic adduct **332**; the whole process is totally diastereoselective.

The substitution of the carbon–carbon double bond of the enyne plays a crucial role, since the intermolecular addition of carbonyl compounds onto 1,6-enynes with a substituted alkene unit leads to dioxolanes[129] or unsaturated pyranic bicycles[130] (equation 111 and Scheme 25) depending on the reaction conditions. The addition of 5 equivalents of benzaldehyde to 1,6-enyne **255**, under the conditions used for the preparation of ether **332**, gives dioxolane **334** by a totally diastereoselective process (equation 111).



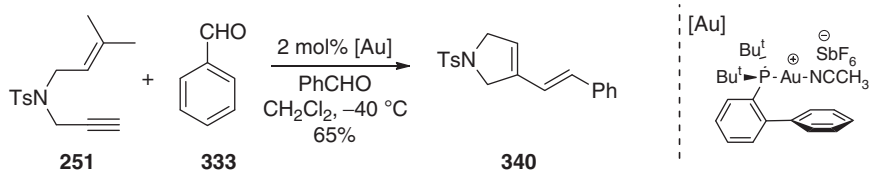
(111)



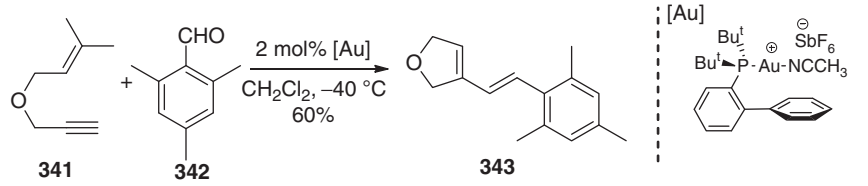
Scheme 25

Under modified conditions (catalyst and equivalents of aldehyde), the addition of 2,4-dimethylbenzaldehyde to the enyne **52** leads to the formation of a mixture of the ether **338** (77% yield) and the 1,3-diene **339** (19% yield). The ratio of the two products varies depending on the substitution of the aldehyde and the catalyst, the best result being generally obtained in the presence of the NHC gold(I) catalyst. The proposed mechanism includes the formation of the cyclopropylcarbenoid species **20**, followed by the direct addition of the aldehyde on the cyclopropane ring. The Prins cyclization, which occurs on the oxonium cation **336**, gives the tetrahydropyranyl derivative **337**. The elimination of the metal complex can then form the unsaturated bicycle **338**. Another competitive pathway is the elimination of acetone from intermediate **337**, explaining the formation of diene **339**. The substitution of the alkene function therefore modifies the reactivity of the enyne since the isomerization step of the carbenoid **20** is not observed here. The nucleophilic addition/cyclization Prins sequence is common to both mechanisms that are presented in Schemes 24 and 25.

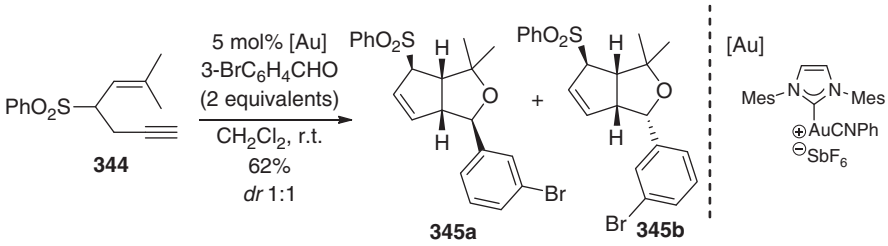
Interestingly, for nitrogen and oxygen-tethered enynes, the formation of the ether is not observed and the reaction results in the exclusive formation of the corresponding diene, in which an aromatic ring has been incorporated (equations 112 and 113).[130] For example, 1,6-enynes **251** and **341** were cleanly transformed to dienes **340** and **343** in 65% and 60% yields, respectively, with no traces of the corresponding ethers. Further investigations into the scope of the reaction showed that gold-catalyzed domino cycloisomerization/Prins reactions could also be applied to 1,5-enynes.[130] The sulfone compound **344** is cyclized according to a 5-*endo-dig* process in the presence of 2 equivalents of 3-bromobenzaldehyde and leads to a 1/1 mixture of the unsaturated bicyclic epimers **345a,b** in 78% yield (equation 114).



251 **333** **340** (112)

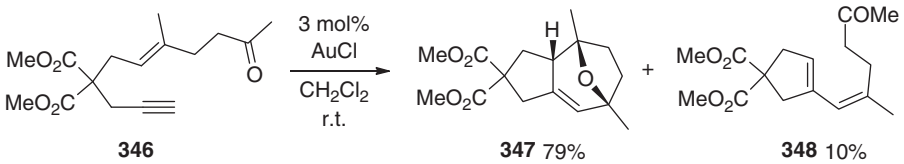


341 **342** **343** (113)

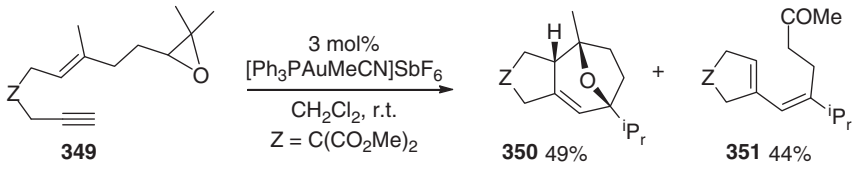


344 **345a** **345b** (114)

Cyclizations associated with a Prins reaction were studied for 1,6-enynes (equation 115). The reaction of substrate **346**, bearing a carbonyl substituent on the alkenyl side chain, leads to the oxatricyclic derivative **347** in 79% yield and 1,3-diene **348** in 10% yield.[131] Catalysts other than gold chloride were found to be efficient too, but generally gave mixtures of **347** and **348** with a higher amount of the 1,3-diene. The proposed mechanism is similar as the one presented for the intermolecular variant. The higher selectivity for the formation of the oxatricyclic adduct **347** using AuCl as the catalyst relative to classic cationic complexes is proposed to be due to a faster elimination of the metal center. Interestingly, the process could be applied to epoxides such as **349** (equation 116). Similar structures as in the case of ketone **346** were obtained: the 1,6-enyne **349** was transformed into a mixture of the oxatricyclic derivative **350** and the diene **351** in a ≈1:1 ratio.

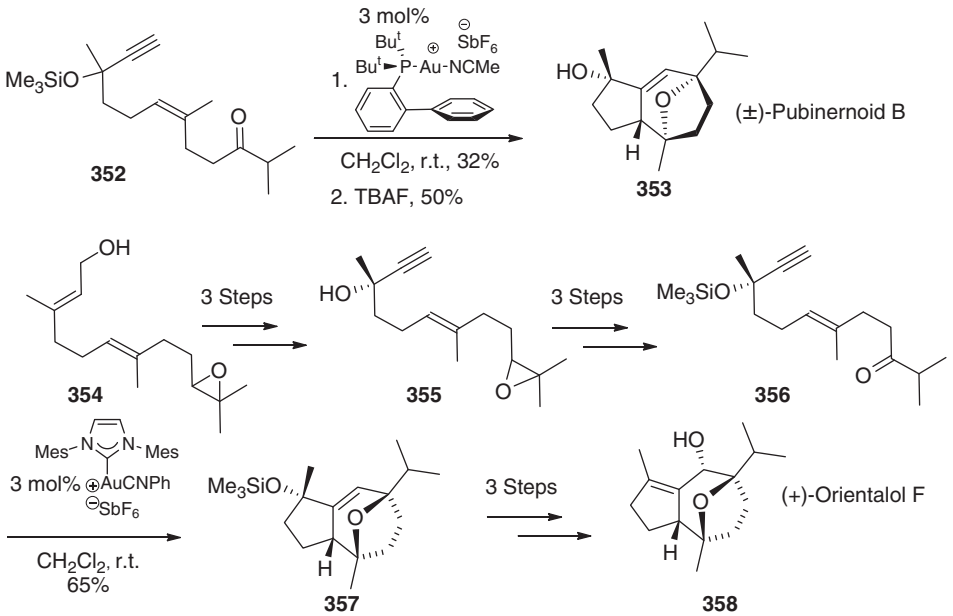


346 **347** 79% **348** 10% (115)



349 **350** 49% **351** 44% (116)

The domino process cycloisomerization/Prins reaction has found very powerful applications in the total syntheses of pubinernoid B, (+)-orientol F,[132] and the (–)-englerins A and B.[133] The syntheses of pubinernoid B and (+)-orientalol F are presented in Scheme 26. The synthesis of pubinernoid B **353** relies on the preparation of enyne **352**, whose double-bond configuration had been adapted as necessary for the particular target. The synthesis of **353** was performed in modest yield in two steps but allowed the correct stereochemistry of the oxa-bridge of pubinernoid B to be determined.

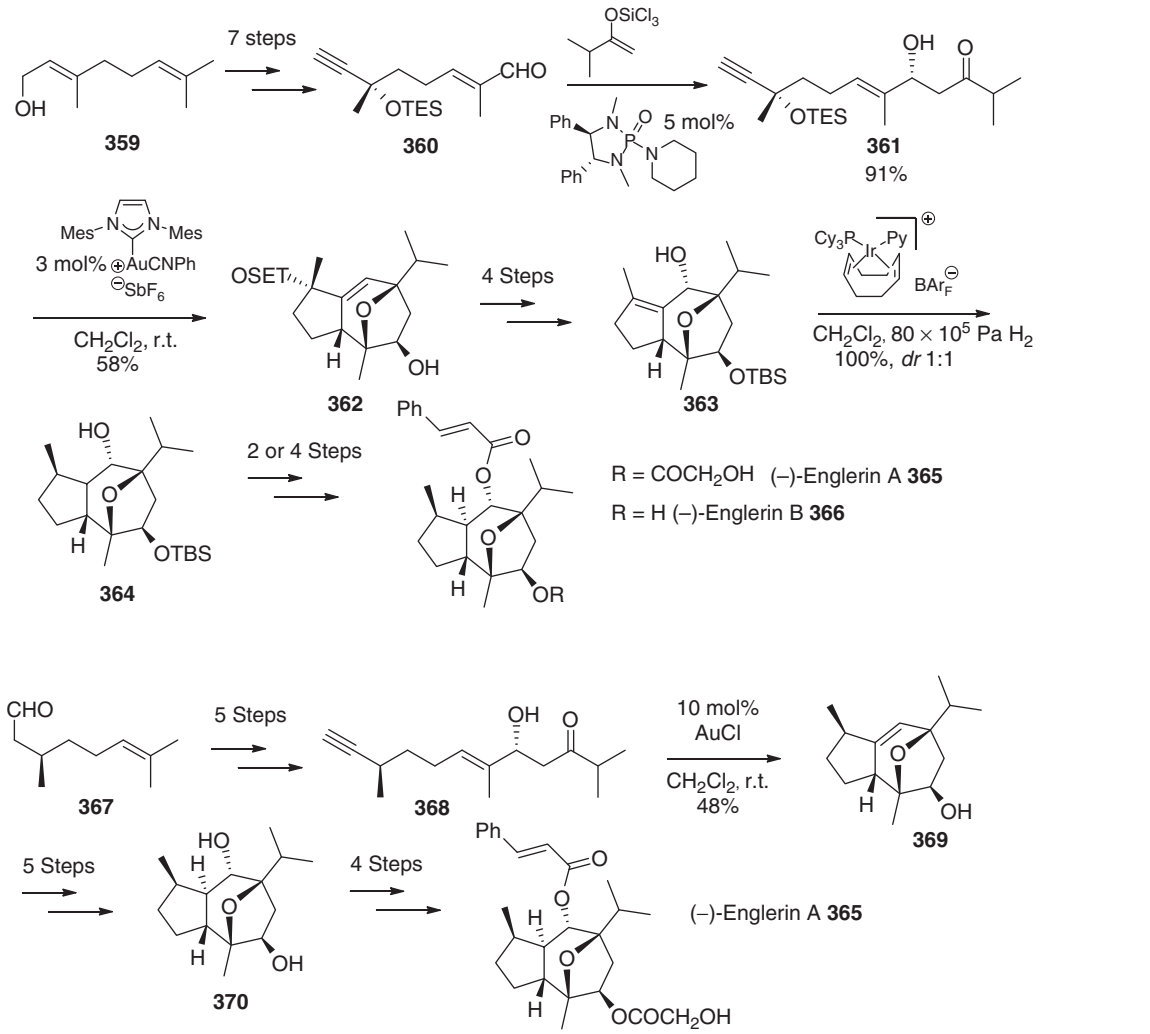


Scheme 26

The preparation of (+)-orientalol F starts from the known epoxyfarnesol **354**, which furnishes the chiral alkyne **355** via a three-step synthesis implying a Sharpless asymmetric epoxidation. The propargylic alcohol **355** was then efficiently transformed to ketone **356** via a regioselective reduction of the epoxide. The cyclization of enantiomerically enriched **356** using the NHC gold(I) complex gave **357** in 65% yield; the reaction was totally diastereoselective. (+)-Orientalol F **358** was then obtained after a three-step sequence involving an oxidative allylic rearrangement and a Luche-type reduction.

Two other sesquiterpenes, (–)-englerin A and B, were independently prepared by the cycloisomerization/Prins methodology by the groups of Echavarren and Ma (Scheme 27).[133] They differ in the precursor that was used for the rearrangement. The first synthesis is very similar to the one described for (+)-orientalol F, as the aldehyde **360** is prepared from geraniol **359** via a seven-step sequence involving a Sharpless asymmetric epoxidation, an oxidative cleavage of the trisubstituted double bond and a Wittig reaction. A stereoselective Denmark aldol reaction affords the allylic alcohol **361** in 91% yield and an excellent diastereomeric ratio (*dr*) (>14:1, 86% of **361**). The oxatricyclic derivative **362** was then cleanly synthesized, the best result being obtained in the presence of $IPrAuSbF_6$ as the catalyst and the unprotected allylic alcohol. The isomerization of **362** into **363** was realized after deprotection of the triethylsilyl group via an oxidation/reduction process and leads to the allylic alcohol **363** in good yield. The catalytic hydrogenation of the tetrasubstituted double bond was tricky but could be realized in the presence of a cationic iridium catalyst under high pressure of dihydrogen, although with a low selectivity. The desired isomer **364** was then transformed either to (–)-englerin B **366** in two steps or to (–)-englerin A **365** in four steps (in fact, (–)-englerin A was obtained from its B congener **366**).

The synthesis of (–)-englerin A **365** was also accomplished starting from (*R*)-citronellal **367**. Its transformation to the allylic alcohol **368** was performed via a five-step sequence, the key step being a boron-mediated aldol reaction to control the stereochemistry of the secondary allylic alcohol. The gold-catalyzed cycloisomerization/Prins reaction was optimized but the best results were obtained with the free alcohol **368** (in agreement with the results of the total synthesis described by Echavarren's group) and with simple gold chloride as the catalyst. The oxo bridged tricyclic derivative **369** was isolated in 48% yield and then transformed to diol **370** in a five-step procedure implying an epoxidation, reduction and oxidation reaction. It is noteworthy that the



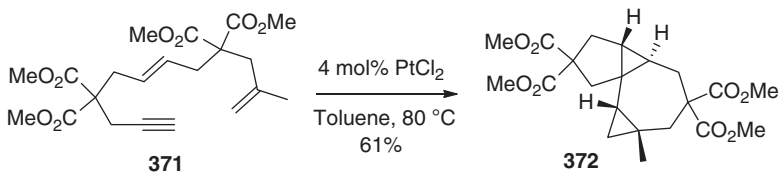
Scheme 27

hydrogenation of the tetrasubstituted double bond of the precursor of **370** was performed in the presence of Raney nickel at 90×10^5 Pa of dihydrogen. The completion of the synthesis of (–)-englerin **365** was then realized via protection/oxidation/reduction of the hydroxyl functions.

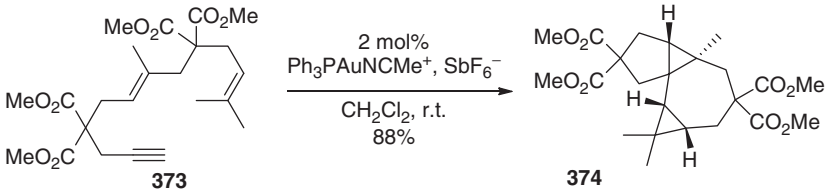
5.30.4.2 Carbon Nucleophiles

5.30.4.2.1 Alkenes as nucleophiles

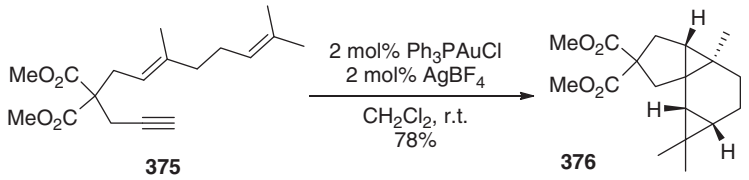
Murai's group examined the behavior of linear acyclic dienynes in the presence of organometallic complexes in order to trap the carbenoid intermediate (represented by **20** in Scheme 22) obtained from the cyclization of 1,6-enyne systems by the additional unsaturation.[134] The use of catalytic amount of platinum dichloride in toluene furnished the polycyclic derivative **372** in 61% yield from dienyne **371** (equation 117). It is noteworthy that a ruthenium catalyst also demonstrated excellent activity. With a gold catalyst, the same transformation occurred under milder conditions at room temperature.[135] For example, the tetracyclic derivatives **374** and **376** were obtained in 88% and 78% yields, respectively (equations 118 and 119).



(117)

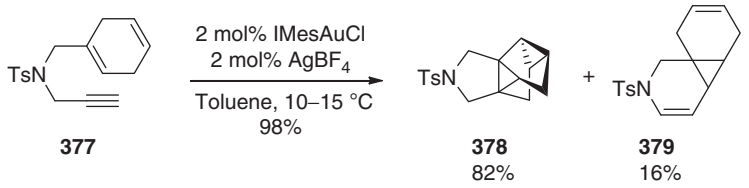


(118)

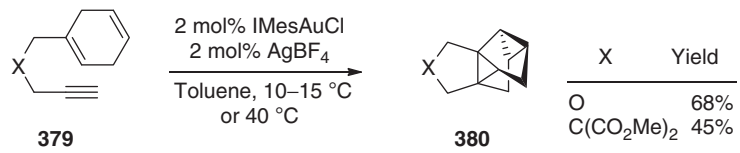


(119)

Switching from 1,6- or 1,5-dienes to 1,4-dienes on the side chain of the substrate did not obstruct the reactivity of the enyne, as illustrated in equations 120 and 121.[136] The preparation of tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane derivatives such as **378** and **380** has been described starting from the cyclohexadienyl substituted enynes **377** and **379**, respectively. Change of the tether group from *N*-tosyl to oxygen or malonate did not influence the reaction pattern (equation 121), the tetracyclic adducts being isolated in moderate to good yields.

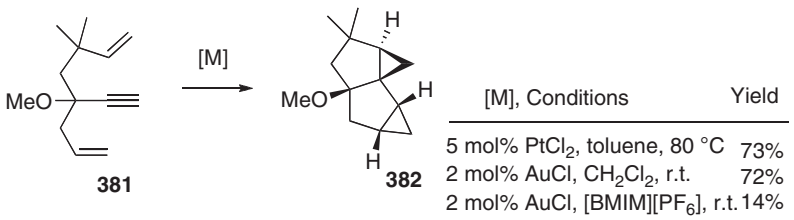


(120)



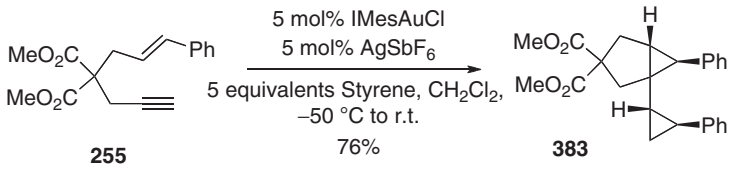
(121)

This reactivity was not limited to 1,6-enynes. The polycyclization reaction was also accomplished with 1,5-enynes (equation 122).[137] Various reaction conditions were adequate: specifically, the tetracyclic adduct **382** was isolated in 73% in the case of a Pt-catalyzed process and in 72% yield in the case of a gold-catalyzed reaction. Alternative solvents such as ionic liquids were tested but gave **382** only in a modest yield. The mechanism of this transformation has been recently studied using computational methods.[138]

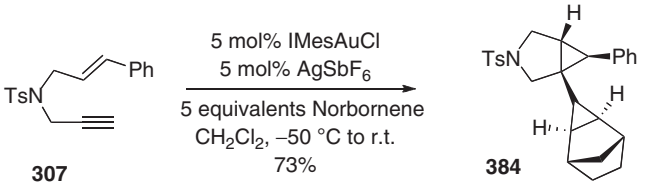


(122)

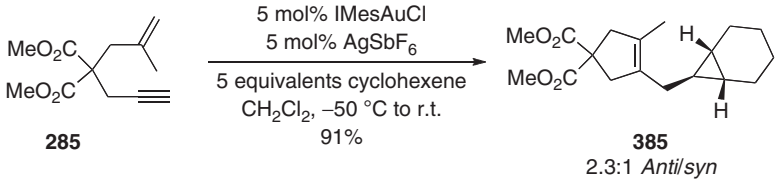
Echavarren's group showed that the reaction could be performed in an intermolecular manner.[139] If the enyne is substituted on the external carbon of the alkene, the cyclopropanation occurs after the first 5-*exo*-type cyclization. In the presence of 5 equivalents of styrene or norbornene, the gold(I) complex IMesAuSbF$_6$ promotes the rearrangement of enynes **255** and **358** into the bicyclic adducts **383** and **384** in very good yields (equations 123 and 124). Rearrangement also takes place when the alkenyl side chain bears an internal substituted carbon. The enyne **285** was converted into the cyclic compound **385** in the presence of cyclohexene under the same catalytic conditions with a very good yield of 91% (equation 125).



(123)

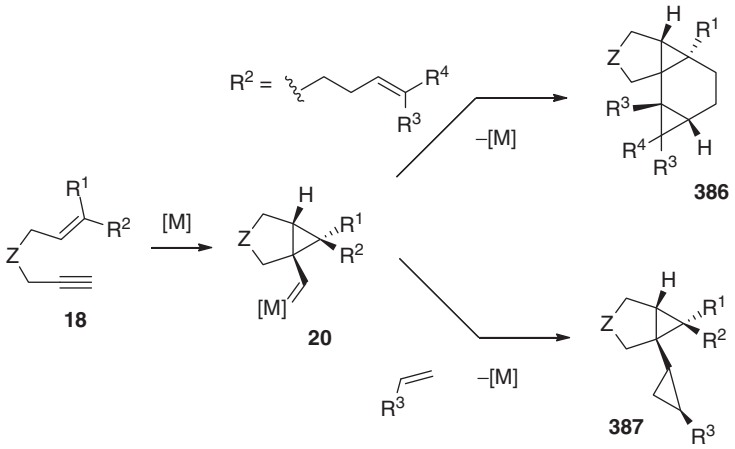


(124)



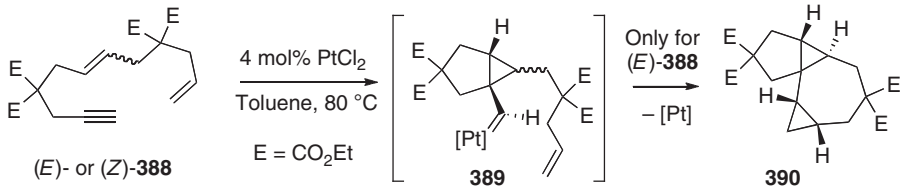
(125)

From a mechanistic point of view, the cycloisomerization reactions of polyunsaturated 1,*n*-enynes are related to a combination of two cyclopropanation steps, allowing for the formation of four carbon–carbon bonds (Scheme 28). The cyclization of the basic 1,6-enyne system **18** provides the carbenoid intermediate **20**, as previously seen in Scheme 22. This intermediate can be trapped by the addition of the remaining unsaturated side chain (for the intramolecular version) on the carbon bonded to the metal and is thus converted, after rearrangement, to the polycyclic product **386**. The case of the intermolecular version is very similar, as the addition of the carbenoid species to the external alkene leads to the cyclic adduct **387**.

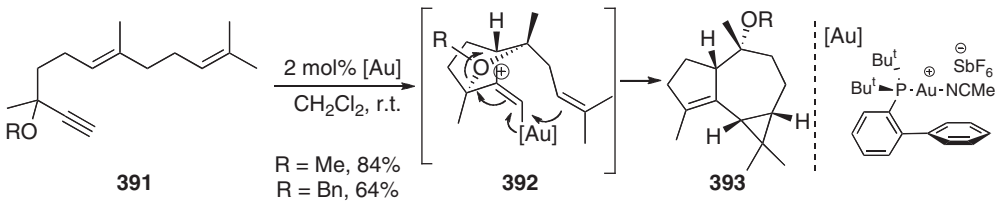


Scheme 28

It is noteworthy that the stereochemistry of the alkenyl side chain is crucial in the case of intramolecular reactions. Indeed, the rearrangement of (*Z*)-**388** affords a mixture of products, whereas the reaction of (*E*)-**388** leads cleanly to the tetracyclic derivative **390** via the intermediate **389** (equation 126). Other elemental steps may occur during the process of cyclopropanation, such as 1,5-migration of the ether groups.[140] The cycloisomerization of enyne **391** illustrates the structural complexity: the cyclopropyl carbenoid intermediate, formed by nucleophilic *anti* attack of the alkene to the alkyne, may react intramolecularly via an *anti* 1,5-migration of a methoxy or benzyloxy group on the cyclopropane skeleton. The intramolecular cyclopropanation with the alkene on the side chain then gives the tricyclic compounds **393** in 84% and 64% yields, respectively (equation 127).



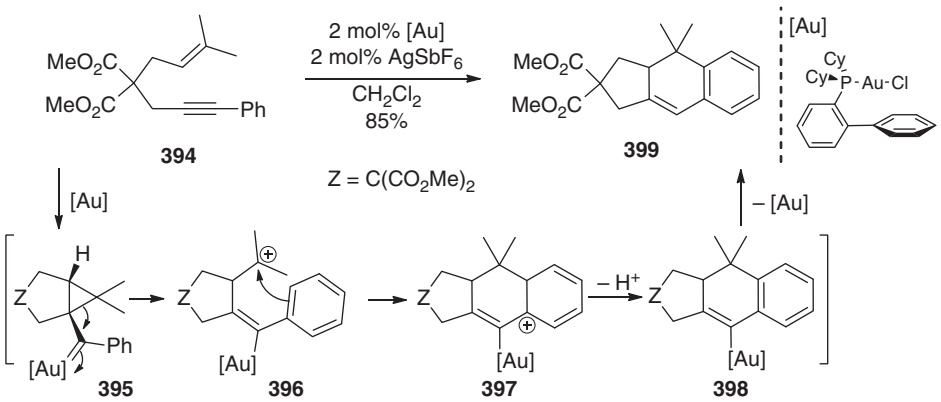
(126)



(127)

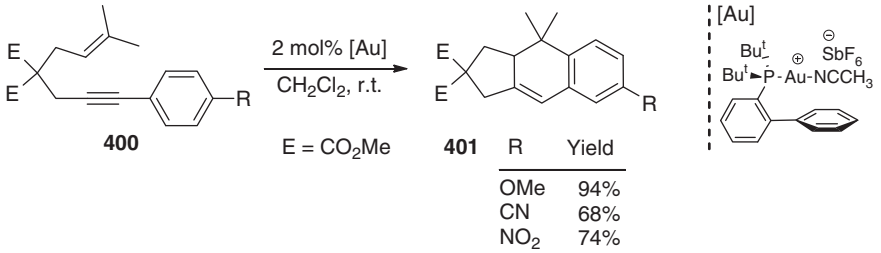
5.30.4.2.2 Aromatic rings as nucleophiles

Electron-rich aromatic compounds can also be good partners in cycloisomerizations of enynes. The process of tandem hydroarylation/cyclization allows aromatic C–H bonds to be functionalized in the presence of carbophilic transition metal complexes. The first example of an intramolecular hydroarylation/cyclization of 1,6-enynes has been described by the Echavarren group.[141] The use of substrates where the alkyne function is substituted by an aromatic ring leads to a variety of polycyclic compounds. For example, the synthesis of the tricyclic derivative **399** from the enyne **394** with a prenyl side chain was very efficient (Scheme 29). The mechanism of this reaction, consisting of a formal [4 + 2] cycloaddition, has been studied by DFT. These calculations support a stepwise mechanism for the cycloaddition by the initial formation of an *anti*-cyclopropyl intermediate **395**, followed by its opening (1,2-alkyl migration) to form a carbocation stabilized by a π-interaction with the aryl ring, which undergoes a Friedel–Crafts-type reaction. Aryl substituents stabilize gold carbenoid intermediates, which results in higher barriers for their skeletal rearrangement and lower ones for their *anti* to *syn* isomerization. The following aromatic electrophilic substitution yields the tricyclic system **397**; rearomatization and removal of the metal complex leads to the polycyclic product **399**.



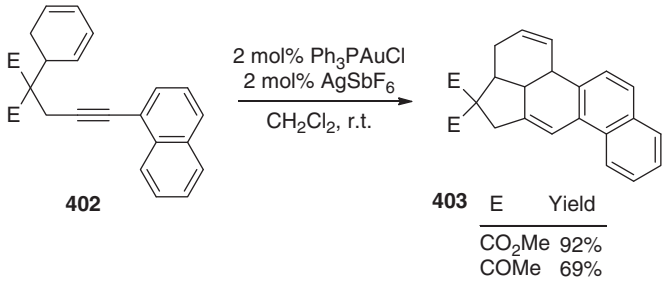
Scheme 29

1,6-Enynes with an aryl ring at the alkyne position give 2,3,9,9a-tetrahydro-1*H*-cyclopenta[b]naphthalenes by a 5-*exo* cyclization followed by a Friedel–Crafts-type addition. This process gives access to the tricyclic derivatives **401** (starting from **400**) bearing electron-donating and withdrawing groups (equation 128). This methodology has recently been applied to the cyclization of 1-aryl-6,8-dien-1-ynes. Specifically, enyne **402** was converted to the tetracyclic product **403** via a 5-*exo* type cycloisomerization reaction in 94% yield (equation 129).[142]



R	Yield
OMe	94%
CN	68%
NO_2	74%

(128)



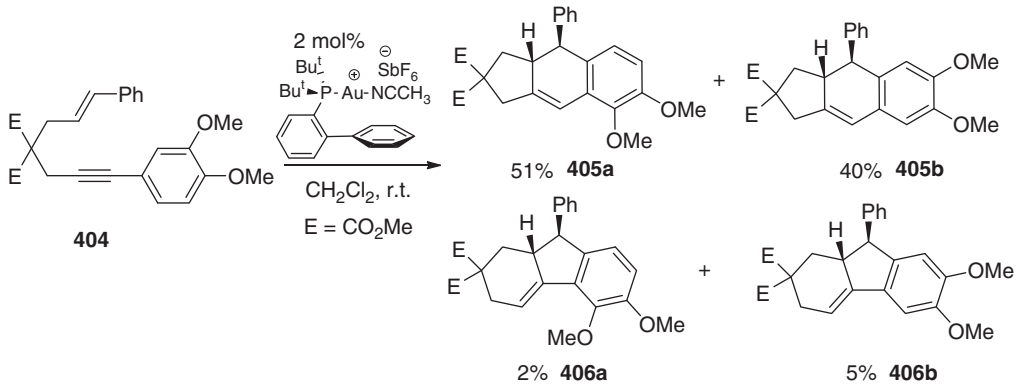
402

403

E	Yield
CO_2Me	92%
COMe	69%

(129)

As expected, substrates such as **404** with a *meta* substituent gave mixtures of regioisomeric cycloadducts **405a** and **405b**. The 6-*endo* cyclization is also observed in this case as a minor process (equation 130). Changing the reaction conditions allowed the formation of a new adduct **407**, resulting from an initial *endo-dig* cyclization followed by the isomerization of the alkene to the internal position. This adduct was obtained as a single regioisomer in excellent yield either under microwave heating or in the presence of a gold complex with tris(2,6-di-*tert*-butylphenyl)phosphite as the ligand (equation 131). This latter complex is an exceptionally reactive catalyst for this reaction.

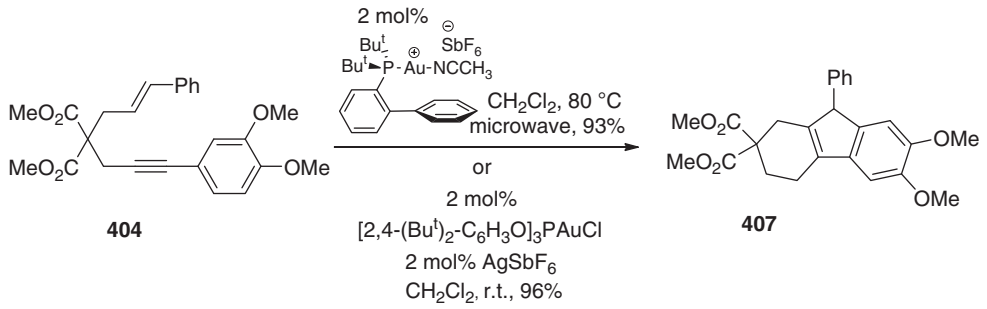


404

51% **405a** 40% **405b**

2% **406a** 5% **406b**

(130)

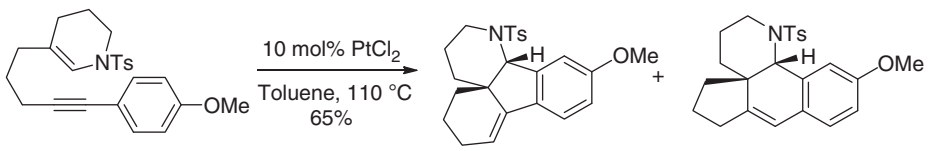


404

407

(131)

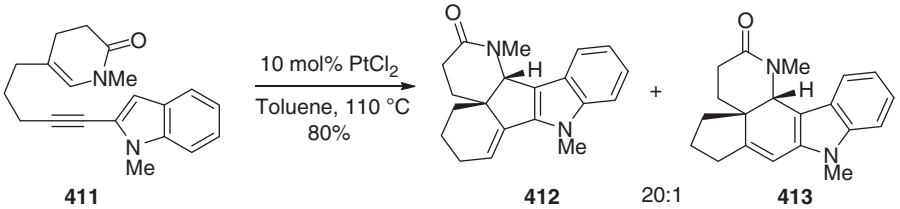
Cyclic enesulfonamides or enamides tethered to an alkyne moiety cyclize readily on exposure to platinum chloride (equations 132–134).[143] This reaction generates quaternary-substituted carbon centers within complex tetracyclic heterocyclic ring systems. Depending on the substitution on the aromatic ring, isomers resulting from an initial 6-*endo* or 5-*exo* process are obtained. The case of electron-donating groups in *para*-position is particularly rewarding, as a 19:1 mixture of isomers **409** and **410** was obtained starting from enyne **408**. Replacement of the benzene moiety with an indole fragment and of the enesulfonamides by enamides also gave excellent results. The treatment of enesulfonamide **411** with platinum dichloride generated **412** an **413** as a 20:1 mixture of isomers in 80% yield. A straightforward approach to *ent*-nakadomarin[144] was described and implied the cycloisomerization of enyne **414** to product **415**.



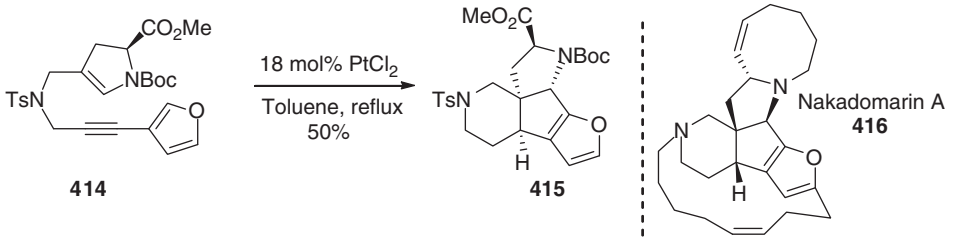
408

409 19:1 410

(132)

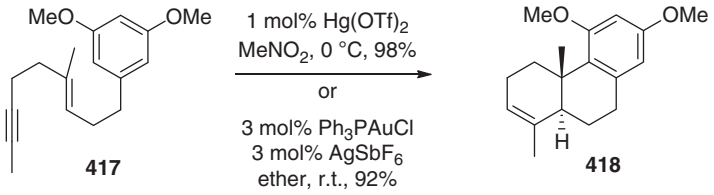


(133)

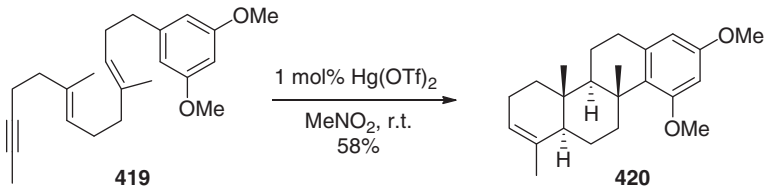


(134)

Cycloisomerization reactions involving an internal aromatic nucleophile have also been described for 1,5-enynes, with the aromatic part being linked on the alkenyl moiety. The use of either mercury or gold salts led to hexahydrophenanthrene **418** starting from **417** in excellent yields with perfect stereoselectivity (equation 135).[97,145] A polycyclization could also be performed in the presence of $Hg(OAc)_2$ that led to **420** in 58% yield; this process creates three carbon–carbon bonds (equation 136).

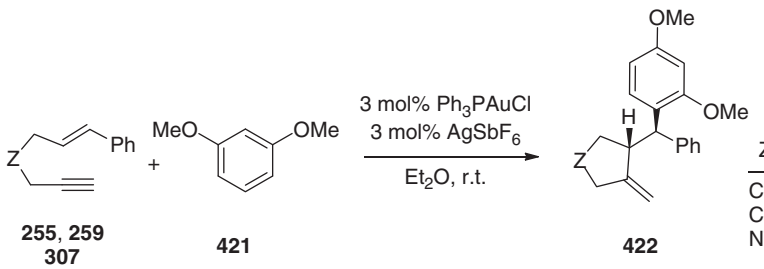


(135)



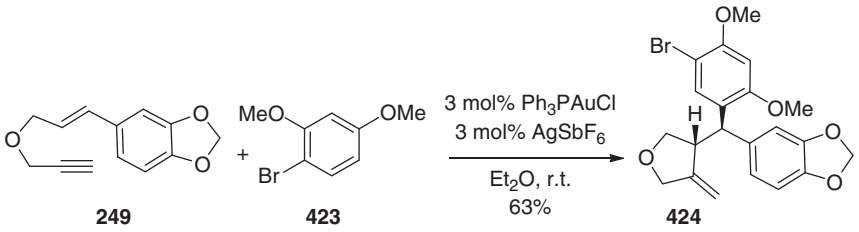
(136)

An intermolecular hydroarylation reaction/cyclization has also been developed, combining Ph_3PAuCl and $AgSbF_6$ in diethyl ether at room temperature.[146] The introduction of electron-rich aromatic compounds such as dimethoxybenzene afforded the corresponding 5-*exo* adducts **422** in good to excellent yields (equation 137). The diastereoselectivity of the reaction is in full accord with the alkoxycyclization processes presented in the last section. The mild conditions are compatible with 4-bromo-1,3-dimethoxybenzene **423** and 1-methylindole **425**. Under these conditions, ether **249** was converted into alkene **424** with a yield of 63%, and the cyclization of enyne **305** endowed with a *gem*-disulfone moiety was achieved quantitatively, leading to adduct **252** (equations 138 and 139). A moderate activity was observed in the case of 1,5-enynes.[147] The addition of trimethoxybenzene **428** to enyne **427** gave the functionalized cyclopentenyl adduct **428** in 56% yield (equation 140).

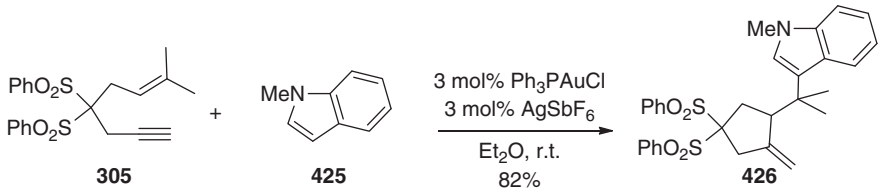


Z	Yield
$C(CO_2Me)_2$	73%
$C(SO_2Ph)_2$	99%
NTs	60%

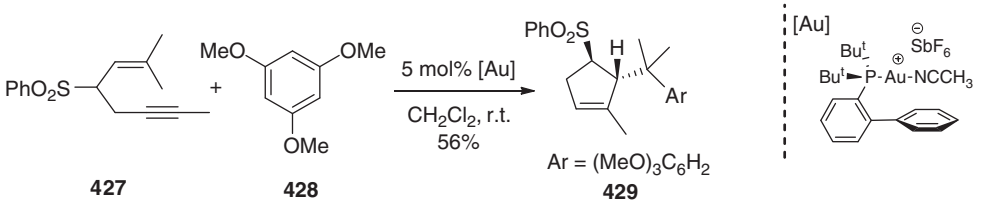
(137)



(138)

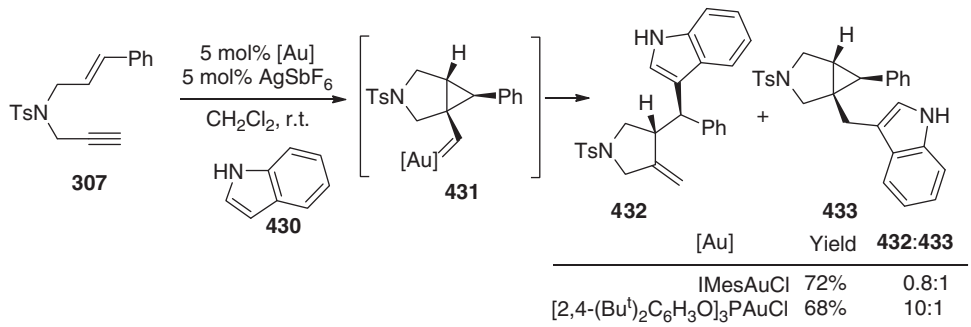


(139)

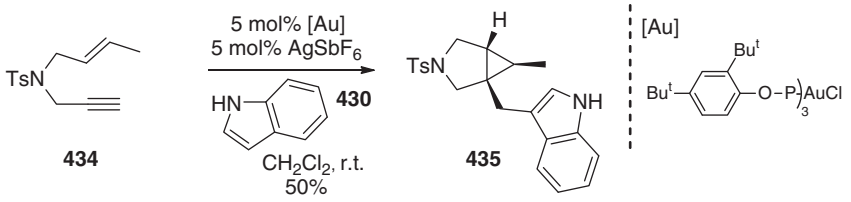


(140)

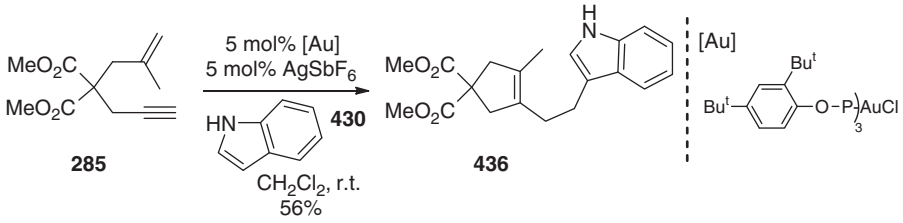
Equations 141–144 illustrate the importance of the substitution on the enynes as well as the dependence on the gold catalyst. The substrate **307**, having a nitrogen-atom that links the alkyne and alkene chains, has been engaged in a reaction in the presence of indole **430** and different gold complexes: the production of two products **432** and **433** resulting from the nucleophilic attack on either the cyclopropane (product **432**) or the cyclopropyl carbenoid moiety (product **433**) were observed (equation 141).[147] With the gold complex IMesAuCl carrying a NHC, a ratio of 0.8:1 was obtained, which shows that the addition is equally facile on either position of intermediate **431**. When the cationic gold complex [2,4-$(Bu^t)_2C_6H_3O$]$PAuSbF_6$ with a phosphite ligand was used, the major product was **432**, resulting from the nucleophilic attack of the indole on the cyclopropane. The addition of indole **430** to the sulfonamide-type enyne **307**, carrying a methyl on the alkene, in the presence of the same catalytic system, gives the azabicyclic derivative **435** resulting from the addition of the aromatic moiety to the carbenoid species (equation 142). The case of 1,6-enyne **285** is particularly instructive as its implication in cycloisomerization/functionalization processes has been detailed previously (equations 93, 109, and 125). Except for the case of the intervention of an alcohol (or water), which are present in large excess, the cycloisomerization of **285** leads to the rearrangement of cyclopropyl carbenoid intermediate **323** and therefore addition of various nucleophiles occurs on the carbenic moiety, which shows that the outcome of the transformation is mainly dictated by the substrate. Therefore similar structures are observed for the addition of aldehydes, alkenes or aromatic nucleophiles; for example, cyclopentene **436** was obtained in 56% yield (equation 143). The 6-*endo* cyclization mode is also possible, as illustrated by the reaction of the substituted 1,6-enyne **437**. The tandem addition of 1-methylindole (**425**)/cycloisomerization afforded product **438** in 73% yield.[147]



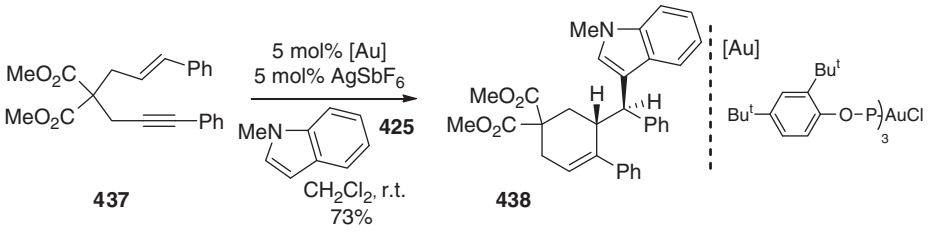
(141)



(142)

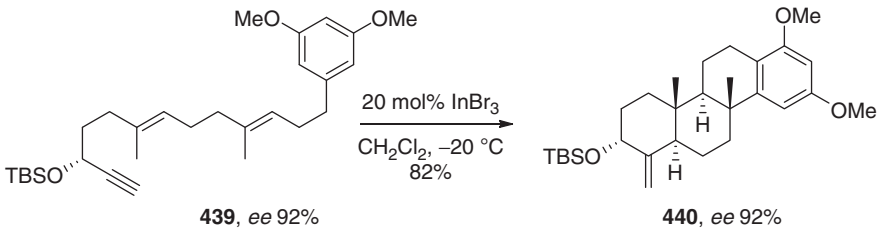


(143)

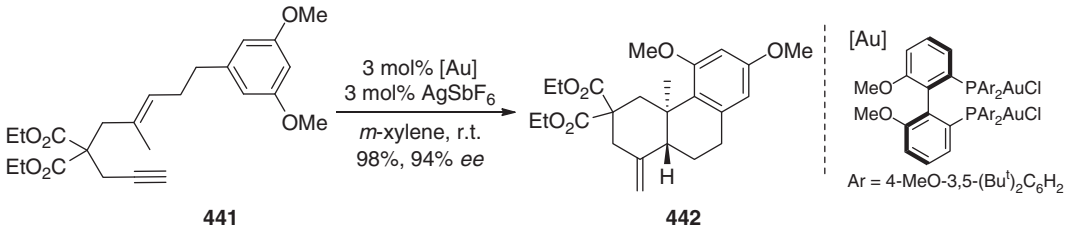


(144)

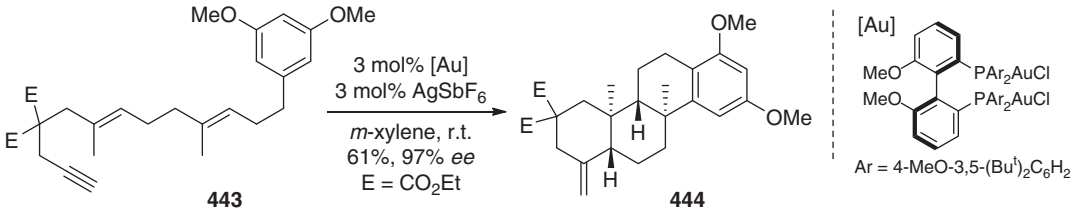
Few asymmetric examples are described in the literature.[5] The stereospecific intramolecular addition of electron-rich aromatic rings has been carried out on 1,6-enynes. The first process implies the enantiomerically enriched carbon-tethered enyne **439** and indium trichloride as the carbophilic catalyst.[148] In the presence of 20 mol% of the indium(III) salt at $-20\,^{\circ}C$, the synthesis of the tetracyclic derivative **440** was highly efficient. The resulting configuration of the created chiral centers is in line with the stereospecificity of the reaction and depends on the stereochemistry of the silyl ether at the propargylic position (equation 145). The authors also highlighted the superior activity of indium compared with silver, and the lower cost and toxicity compared with gold or mercury salts. Enantioselective versions implying a chiral gold bimetallic complex derived from an atropisomeric MeOBIPHEP analog have also been described (equations 146–148). The synthesis of the tri- or tetracyclic derivatives **442** and **444** (analogous to **440**) was performed in good to excellent yields and, more importantly, with excellent *ee*s (94% and 97%, respectively).[126] The cycloisomerization/functionalization reaction of 1,6-enyne **394** (already disclosed under racemic conditions, Scheme 29) led to **399** in 99% yield and 93% *ee* (equation 148).[122,149]



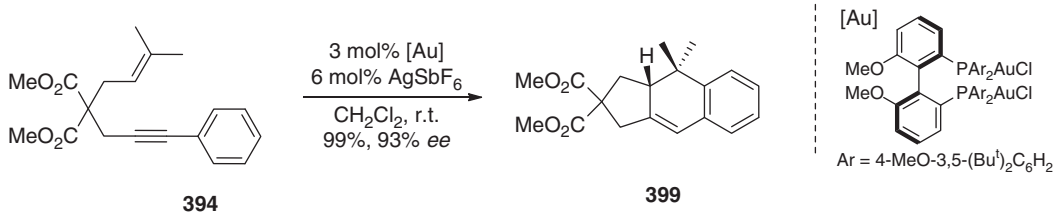
(145)



(146)

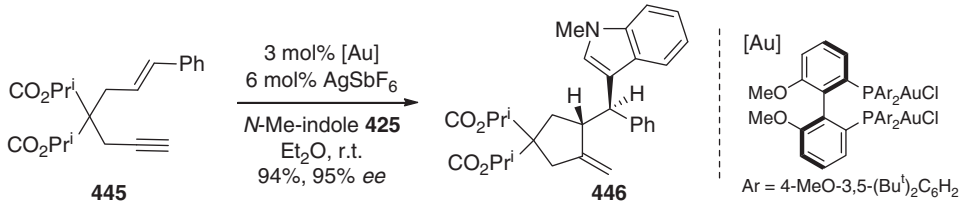


(147)

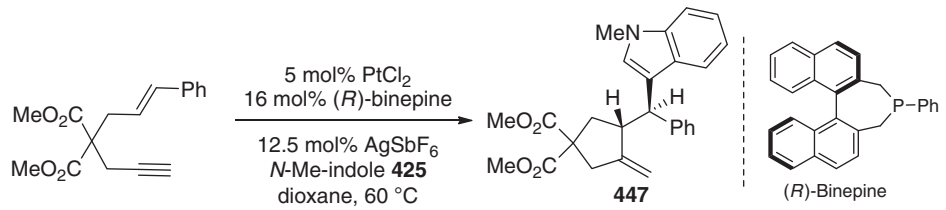


(148)

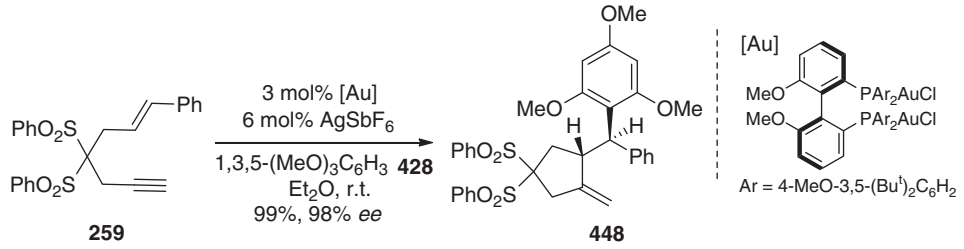
Intramolecular asymmetric processes have been designed either in the presence of chiral gold or platinum complexes (equations 149 and 150). The use of hindered malonate-type 1,6-enynes **445** allowed for the addition of *N*-methylindole **425** and cyclization in 94% yield and 95% *ee* (equation 149). A square-planar chiral Pt(II) catalyst with an atropisomeric monophosphane binepine led to excellent results too, despite the fact that the reaction occurs at higher temperature (equation 150).[150] This system had already proved efficient in the alkoxyclization of 1,6-enynes (equation 98).[119] The gold-catalyzed process was generalized to other enynes and nucleophiles (equations 151 and 152), the best results being obtained in the case of carbon-tethered 1,6-enynes such as **259** whereas oxygen-tethered analogs such as **249** reacted less selectively.



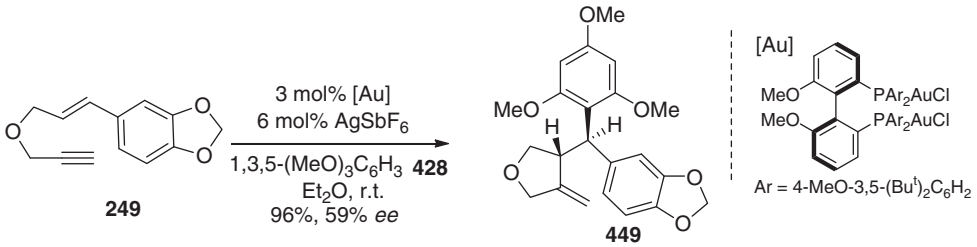
(149)



(150)



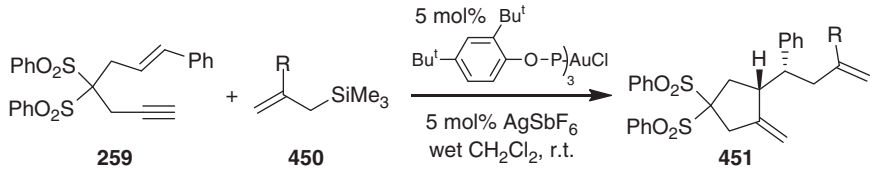
(151)



(152)

5.30.4.2.3 1,3-Dicarbonyl derivatives or allylsilanes as nucleophiles

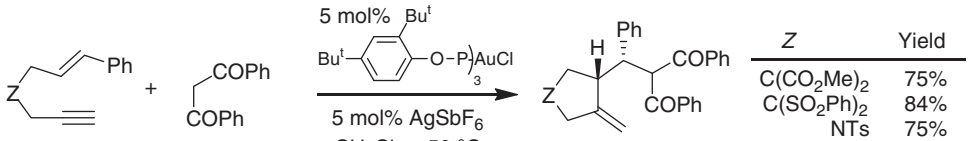
Apart from alkenes and aromatic nucleophiles, few other carbon nucleophiles have been used as partners in the tandem processes. The reaction of allylsilanes gave rise to the formation of a carbon–carbon bond according to an S_N2' addition/cyclization.[112] Sulfonated derivatives such as **451** were prepared, according to a 'classic' rearrangement of the enyne **259** implying the cyclopropyl carbenoid species **20** as depicted in Scheme 22 and addition to the allyl moiety (equation 153). 1,3-Dicarbonyl derivatives may also be used in the rearrangement/functionalization procedure to form carbon–carbon bonds. Whereas cyclohexane-1,3-dione led to the formation of a new carbon–oxygen bond (alkoxycyclization process, equation 83), the use of dibenzoylmethane **452** afforded the corresponding five-membered ring derivatives **453** via cycloisomerization followed by the addition of the activated nucleophile (equation 154).



259 **450** **451**

R	Yield
H	62%
Me	57%

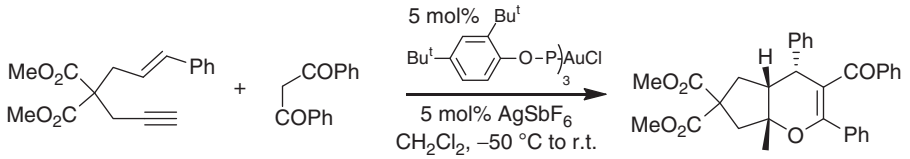
(153)



255, **259**, **307** **452** **453**

Z	Yield
C(CO$_2$Me)$_2$	75%
C(SO$_2$Ph)$_2$	84%
NTs	75%

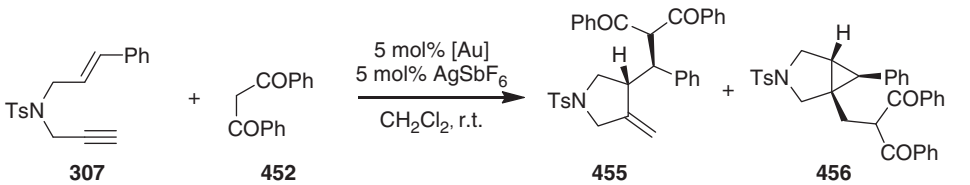
(154)



255 **452** **454**

(155)

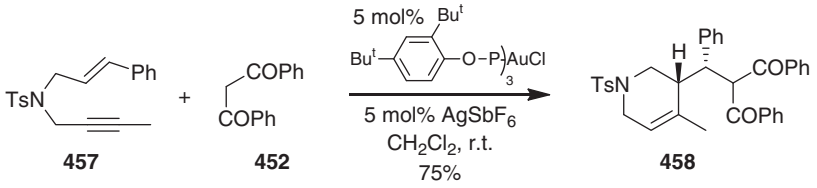
The reaction conditions were found to be crucial, as further rearrangement occurs at room temperature in the case of 1,6-enyne **255**. Indeed, after formation of **453**, the remaining 1,3-dicarbonyl moiety acts as an oxygen nucleophile and the whole process leads to bicyclic **454** in 65% yield. As previously observed in equation 141, the reaction of the nitrogen-tethered enyne **407** gave a mixture of products **455** and **456**, with various ratios depending on the catalyst employed. The difference between IMesAuSbF$_6$ and [2,4-(Bu^t)$_2$C$_6$H$_3$O]PAuSbF$_6$ is more pronounced in the case of 1,3-dicarbonyl nucleophiles than in the case of indole as reaction partner (compare equations 141 and 156). The reactivity of enynes substituted at the alkynyl position also follows the same trend as previously observed for **437** (equation 144). The tandem addition/cyclization of **457** furnished the corresponding six-membered ring **458**, obtained via a 6-*endo* cyclization process (equation 157). The scope of this transformation is still limited, as cyclopentane-1,3-dione, indane-1,3-dione, dimethyl malonate, and Meldrum acid were not suitable nucleophiles.



307 **452** **455** **456**

[Au]	Yield	**455**:**456**
IMesAuCl	99%	2:98
[2,4-(Bu^t)$_2$C$_6$H$_3$O]$_3$PAuCl	77%	75:25

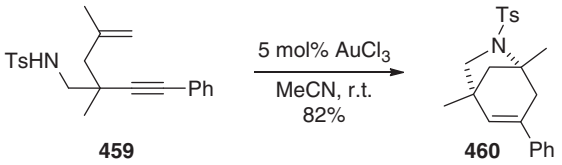
(156)



457 **452** **458** (157)

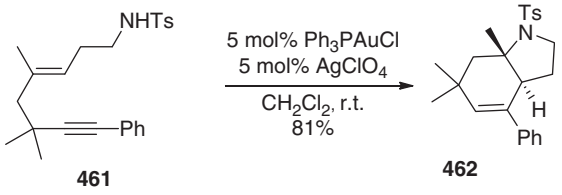
5.30.4.3 Nitrogen Nucleophiles

The team of Kozmin described in 2005 the first example of a tandem cyclization of 1,5-enynes involving a nitrogen nucleophile.[115] The use of 5 mol% of gold trichloride cleanly converted substrate **459** into bicycle **460** at room temperature with a yield of 82% (equation 158). The cyclization mechanism is similar to the previously developed alkoxycyclization of enynes. This completely diastereoselective intramolecular cyclization proceeds through 6-*endo-dig* process.

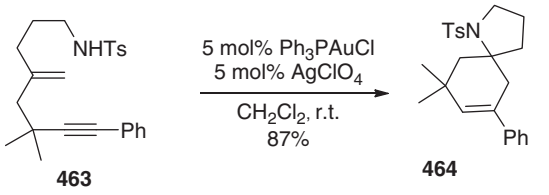


459 **460** (158)

The same group has described the synthesis of the *trans*-azabicyclo[4.3.0]nonene **462** from the enyne **461** with an amino side chain according to a 6-*endo* cycloisomerization in the presence of a cationic gold catalytic system in 81% yield (equation 159). Depending on the substitution of the alkene, spiro compounds may also be formed by the intramolecular domino process. The enyne **463** rearranges in the presence of the same catalytic system to give the desired spiro compound **464** with an excellent yield of 87% (equation 160).



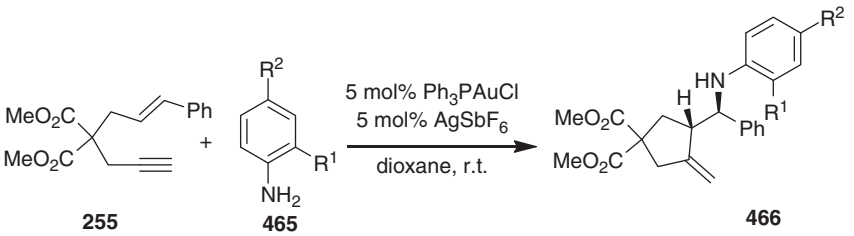
461 **462** (159)



463 **464** (160)

The intermolecular addition of nitrogen nucleophiles during the cycloisomerization of 1,6-enynes was developed more recently.[151]

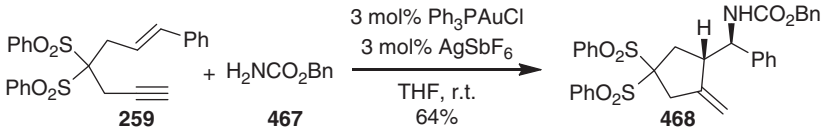
Weakly nucleophilic amines such as sulfonamides, carbamates, or electron-poor anilines have been successfully introduced to a wide range of 1,6-enynes. For example, the addition of substituted anilines **465** bearing chloride, trifluoromethyl, or cyano groups afforded the corresponding functionalized cyclopentanes **466** in good to excellent yields (equation 162). In the presence of benzyl carbamate **467**, the cyclization of the disulfone derivative **259** led to amine **468** with a yield of 64% (equation 163). Oxygen-linked enynes are also good candidates for these domino reactions. The addition of allyloxy carbamate **471** on 1,6-enyne **470** gave the heterocycle **472** in 92% yield (equation 164). In all cases studied, only one diastereomer was formed. The proposed mechanism combines the stereospecific attack of the alkene to the alkyne to yield the cyclopropyl carbenoid intermediate, followed by the addition of the nucleophilic nitrogen.



255 **465** **466**

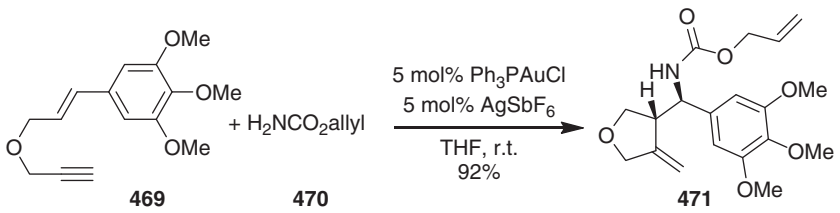
R^1	R^2	Yield
CF_3	Cl	86%
CN	H	93%

(161)



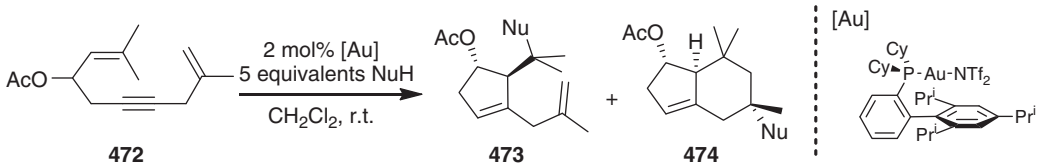
259 **467** **468**

(162)



469 **470** **471**

(163)



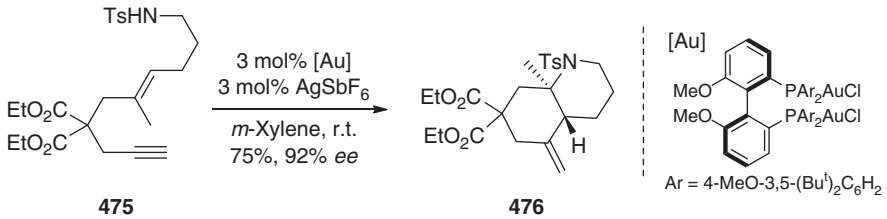
472 **473** **474**

NuH	Yield **473**	Yield **474**
$BocNH_2$	7%	37%
$CbzNH_2$	7%	36%

(164)

Two examples of intermolecular addition of carbamates on dienynes with a 1,5-enyne as key motif have recently been described (equation 164).[118] As in the case of oxygen nucleophiles (equation 97), the addition of the nucleophile on the cyclopropane is in competition with the addition of the terminal alkene function present on the substrate **472**. In the presence of *tert*-butyl or benzyl carbamates and a catalytic amount of a cationic gold(I) complex, dienyne **472** was converted into a mixture of products **473** and **474** resulting from 5-*endo-dig* mono- and bicyclization, respectively, with preferential formation of isomer **474**.

In line with asymmetric cycloisomerization reactions using chiral gold catalysts, the group of Toste has reported a single stereoselective reaction of 1,6-enyne bearing an amino group as nucleophile.[126] The substrate **475** was transformed into bicyclo[4.4.0] decane **476** with a good 75% yield and an excellent *ee* of 92% (equation 165).



475 **476**

(165)

5.30.5 Conclusion

The field of cycloisomerization of enynes has been in constant expansion during the past 15 years. Based on the precept of π-activation of an alkyne by a carbophilic transition metal, several new rearrangements have been discovered, involving the alkene as the unique nucleophilic moiety or as the first partner in the presence of other nucleophiles. The diversity in terms on enyne skeletons and the simplicity to conduct a reaction with carbophilic and generally air-stable catalysts have contributed to the expansion of the field. Depending on the length of the tether between the alkyne and alkene moieties, various modes of cyclization have been highlighted. Moreover, the potential complexity of the resulting polycyclic structures resulting from enyne skeletal rearrangements has been heightened by the intervention of other nucleophiles (oxygen, carbon, and nitrogen nucleophiles), favoring domino processes. A multitude of diversified pathways have therefore been discovered. The interpretation and mechanistic rationale of each rearrangement or domino process is not always clear, but the emergence of theoretical studies has highly enriched the field and helped in interpreting the experimental results. The association of experimental and theoretical studies has also stimulated the discovery of new transformations.

As some reactivity trends have been established on the basis of experimental and theoretical studies, further applications such as the use of rearrangements and domino processes in total synthesis have appeared in the literature. This is the sign that this chemistry gains maturity and that 'prediction' takes precedence over 'understanding'. Platinum and gold complexes have shown high efficiency and tolerance for applications to functionalized systems, as previously palladium had.

The knowledge of the structure of the organometallic complexes from newly designed ligands has allowed for the discovery of highly efficient catalysts and has opened the door to asymmetric catalysis. Although some substantial advances have already been made in the past few years, it is still not possible to perform each and every asymmetric enyne rearrangement with success. Mechanistic rationalization associated with the ligand tailoring will certainly help to sustain future advances.

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5.31 [2 + 2 + 2] Cycloadditions

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Glossary

Cooligomerization The oligomerization of two different compounds.

Crossed cyclotrimerization The addition of three components in which at least two are different to form a ring.

Cyclotrimerization The addition of three components to form a ring.

Helicenes Ortho-condensed polycyclic aromatic compounds in which the rings give helically-shaped molecules.

Homo-Diels-Alder A [2 + 2 + 2] cycloaddition between a strained nonconjugated diene and a dienophile resulting in the formation of tetracyclic structures of considerable strain known as deltacyclanes.

Thorpe–Ingold effect or angle compression The effect observed when increasing the size of two substituents on a tetrahedral center which leads to enhanced reactions between parts of the other two substituents.

5.31.1 Introduction

This chapter deals with [2 + 2 + 2] cycloaddition reactions in which three components contribute with two electrons each. Most examples involve three multiple bonds which are combined to form six-membered carbo- or heterocycles. However, a brief section will cover those reactions in which CO, isonitriles, or heteroatoms participate in the cycloaddition with two electrons to form four- or five-membered rings through a (2 + 1 + 1) or a (2 + 2 + 1) process. Pauson–Khand-type reactions (*see* Chapter 5.24), metal carbene cycloadditions (*see* Chapter 5.25), or zirconium-mediated bicyclization of enynes (*see* Chapter 5.30) will not be addressed as they are covered in other chapters. After some general remarks, this introductory section

will show the most important catalytic systems used. Then, a mechanistic discussion will provide a summary of the current knowledge on the reaction pathways of the different versions of this process.

The generation of new ring systems is a key part of organic synthesis which is many times accomplished through cycloaddition reactions. The [2 + 2 + 2] cycloaddition is remarkable in terms of synthetic power and scope; starting from various unsaturated substrates such as alkynes, nitriles, alkenes, allenes, imines, aldehydes, ketones, isocyanates, and isothiocyanates, sometimes in combination with CO, CO_2, CS_2, isonitriles, or heteroatoms, it allows the synthesis of a great variety of highly substituted cyclic molecules such as five-membered carbo- and heterocycles, benzenes, pyridines, pyridones, and 1,3-cyclohexadienes (Figure 1).

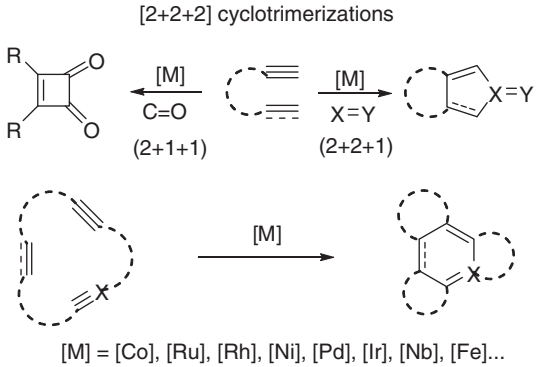


Figure 1 General scheme for [2 + 2 + 2] cyclotrimerizations.

The metal-mediated [2 + 2 + 2] cycloaddition reaction began with the discovery of Reppe's trimerization of acetylenes nearly 60 years ago.[1] Nowadays the [2 + 2 + 2] cycloaddition reaction has reached such a mature state of the art that many densely functionalized aromatic compounds can be constructed with this methodology. For instance, polysubstituted benzenes and pyridines are highly useful compounds which are widely used in industry and in the laboratory. In addition these motifs are present in numerous natural products. Traditionally, aromatic compounds were constructed by stepwise introduction of the substituents via electrophilic substitution reactions. The [2 + 2 + 2] process is now an alternative to these methodologies applicable to the synthesis of natural products, axially chiral compounds, or molecules with fragile functionalities.

5.31.1.1 Catalysts

Catalysts based at least on 17 transition metals have been used to produce the [2 + 2 + 2] cyclization reaction. Most of them correspond to late transition metals especially those of group 9 (Co, Rh, Ir).[2] In addition, Ni and Pd are many times chosen as the catalyst followed by some ruthenium complexes including Grubbs' type carbenes. Niobium salts and zirconium complexes also have found use in these reactions, and examples of [2 + 2 + 2] reactions can be found in the literature with V, Ta, Mo, Fe, Os, In, and even lanthanides such as Eu, Dy, or Yb.[3] However, the current trend is to use Co, Rh, Ir, and Ru complexes or in a smaller number of contributions, Pd-, Ni-, Ti-, and Nb-based catalysts.

Despite the great development of the metal-catalyzed [2 + 2 + 2] cyclization process for laboratory uses, this process is still in its beginnings with respect to the development of environmentally friendly and scalable procedures that could be industrially applied. These reactions are generally performed in organic solvents with soluble catalysts. However, some contributions have described [2 + 2 + 2] reactions in water[4] and a recent report used nitrile-functionalized ionic liquids as solvents for cobalt-catalyzed cyclotrimerization reactions of terminal aromatic alkynes.[5]

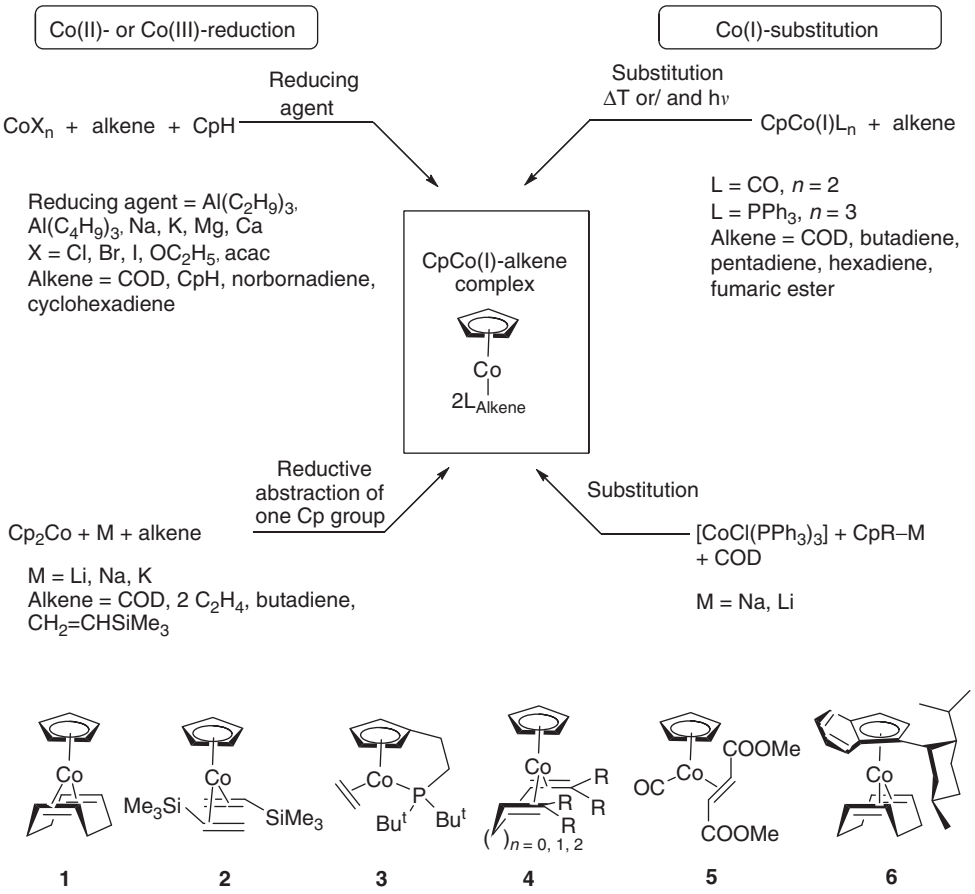
In addition, many reactions need thermal initiation and various groups have used microwaves (MW) heating for transition metal-catalyzed [2 + 2 + 2] cycloadditions. The claimed advantage of MWs (improved yields in shorter reaction times and lower catalyst loadings) has been discussed in a recent study that has compared MW-assisted reactions with conventional heated processes. With an accurate measurement of temperature using fiber-optic probes, the authors have reproduced exactly the same results both with and without MW. This fact discards the so-called wall effects (nonuniform heating of flasks when using conventional oil baths) and nonthermal MW effects as the lifetime of the catalyst was not altered.[6]

5.31.1.1.1 Cobalt catalysts

Most of the early literature used cobalt complexes to mediate or catalyze [2 + 2 + 2] cycloadditions.[7] The ability of cobalt complexes is well known to promote powerful synthetic transformations, and continues to be a nonexpensive and efficient option in many cases. Cobalt acts in a double role, as it is used in stoichiometric as well as catalytic complexes. Among all the available catalysts, η^5-cyclopentadienyldicarbonyl cobalt [$CpCo(CO)_2$] has proved the most popular and versatile reagent for the [2 + 2 + 2] cyclotrimerization of alkynes followed by [$CpCo(PPh_3)_2$]. Vollhardt's group has reported numerous applications of cobalt-catalyzed reactions including total syntheses of different natural products and compounds of theoretical interest. These complexes contain relatively strongly bound neutral ligands, requiring thermal or radiation energy for activation. Some cases require 1 equivalent or even an excess of cobalt complex. For intermolecular stoichiometric reactions $Co_2(CO)_8$ has also been used.[8]

There are several synthetic pathways to obtain Co(I)–alkene complexes, consisting of either reduction of Co(II) or Co(III) species in the presence of stabilizing alkene ligands or ligand substitution by alkenes in Co(I) complexes. As well-established examples of the first approach, [CpCo(COD)] **1** is obtained from $Co(acac)_3$ using organoaluminum reagents for reduction.[9] Another approach is the reductive abstraction of a cyclopentadienyl fragment from cobaltocene promoted by lithium or sodium in the presence of alkenes.[10] This approach allowed access to **2**, a very active catalyst.[11] One interesting variation consisted of a reaction of a Co(II)-salt with a metallated Cp fragment and further reduction in the presence of ethylene to give **3**, a complex able to produce cyclotrimerization reactions in water.[12] Other carbonyl-free catalytic systems are simple cobalt halides such as a $CoBr_2$, generally in combination with Zn powder as reducing agent, and other additives like diimines or phosphines.[13] For instance, $CoCl_2 \cdot 6H_2O$/Zn is an inexpensive and easy to handle reagent that, combined with additives like diimines or phosphines, has given excellent results in alkyne cyclotrimerization. The addition of silver triflate (AgOTf) or silver hexafluoroantimonate ($AgSbF_6$) significantly increased the activity of the catalytic system, if 2-(2,6-diisopropylphenyl)iminomethylpyridine (dipimp) was the additive. For the synthesis of pyridines with all types of nitriles, reactions catalyzed by 1,2-bis(diphenylphosphino)ethane (dppe)/ $CoCl_26H_2O$ in the presence of Zn powder were described to proceed with high regioselectivity.[14]

The other synthetic approach to prepare Co(I)–alkene complexes generally involves heating or irradiation of $[CpCo(CO)_2]$ which allows substitutions of both CO ligands or only one of them giving access to complexes such as **4** and **5**, respectively.[15] Another starting material is $[CoCl(PPh_3)_3]$, a suitable precursor for the introduction of a functionalized Cp ligand and subsequent coordination with COD, to form **6**.[11] **Scheme 1** summarizes the main Co-based catalysts currently used.

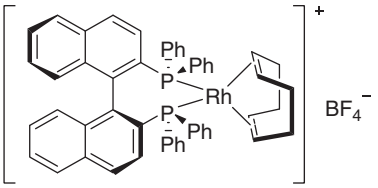


Scheme 1

5.31.1.1.2 Rhodium and iridium catalysts

The first reported uses of rhodium complexes in [2 + 2 + 2] chemistry, consisted of the formation of rhodacyclopentadienes by the reaction of stoichiometric amounts of Wilkinson's catalyst $[RhCl(PPh_3)_3]$ with α,ω-diynes, and further reaction with alkynes.[16] In addition to Wilkinson's catalyst and other similar derivatives like $[RhCl(COD)]_2$, many catalytic systems consist of a combination of a cationic rhodium species such as $[Rh(COD)_2]BF_4$ and a spectator ligand, generally a phosphine. Chiral 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-type ligands have been successfully used in recent times (see Sections 5.31.3.2, 5.31.3.3, and 5.31.4 for representative examples). The final active complex with structure **7** as depicted in **Figure 2** may be prepared separately,

but currently these complexes are formed *in situ*. In addition, some groups have reported $RhCl_3 \cdot 3H_2O/Pr^i_2NEt$-catalyzed [2 + 2 + 2] cyclotrimerizations of alkynes,[17] and the use of a rhodium-*N*-heterocyclic carbene ligand (NHC) complex [RhCl(COD)(NHC)], in a [2 + 2 + 2]-cycloaddition reaction of three alkynes.[18]



[Rh((*aS*)-BINAP)(COD)]BF_4

7

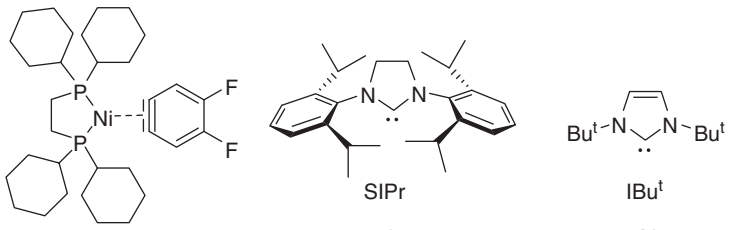
Figure 2 Structure of a cationic rhodium catalyst.

A recent report accounts for the synthesis and performance of a solid-supported catalyst made from $[Rh(C_2H_4)_2(acac)]$ and dealuminated Y-zeolite. The authors show X-ray absorption fine structure (EXAFS) spectra in which $\{Rh\text{-}(C_2H_4)_2\}$ groups appear covalently anchored to two zeolite oxygen ions.[19]

The first preparation of a iridacyclopentadiene consisted of a reaction of $[IrCl(N_2)(PPh_3)_2]$ with dimethyl acetylene dicarboxylate (DMAD).[20] Since then, iridium-based catalytic systems consist generally of an *in situ* mixture of $[IrCl(COD)]_2$ or $[IrCl(C_2H_4)_2]_2$ with a phosphine like dppe or 1,1′-bis(diphenylphosphino)ferrocene (dppf).[21] The nature of the ligand affects the regioselectivity in crossed cyclotrimerizations of diynes with nonsymmetric alkynes, and in intermolecular reactions.

5.31.1.1.3 Nickel and palladium catalysts

The pioneering cyclotrimerization of alkynes reported by Reppe was performed using a mixture of $NiBr_2$ and CaC_2.[1] Since then, $NiBr_2$/dppe, 1,1-bis(diphenylphosphino)methane (dppm), [1,4-bis(diphenylphosphino)butane] (dppb) complexes in combination with Zn powder have been used especially for the cyclizations of diynes with aryne precursors, which are thought to go through aryne intermediates such as **8**.[22] In addition, nickel (0) complexes such as $Ni(COD)_2$ have been applied to many substrates. Louie's group has extensively studied combinations of Ni(0)/NHC such as Ni(COD)/SIPr (**9**) or Ni(COD)/IBu^t (**10**) (Figure 3) as catalysts for the cycloaddition of unactivated nitriles, isocyanates, ketones, CO_2, and cyanamides with alkynes and diynes.[23]



8 **9** **10**

Figure 3 Structures of Ni-aryne intermediate **8** and of NHC ligands **9** and **10** used in combination with Ni(COD) as catalysts.

Several palladium complexes are reactive toward alkynes. In intermolecular versions, these Pd-catalyzed cyclizations are complex processes and appear to operate with a different mechanism, even though the formation of the arenes is the end result in some of these processes. The mostly used compounds are $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $Pd(OAc)_2/PPh_3$ *(vide infra)*. Heterogeneous catalysis would be useful as it facilitates elimination and reutilization of the catalyst. Gold nanoparticle-supported palladium(II) interphase catalysts were used to perform an alkyne cyclotrimerization reaction in ionic liquids.[24] Palladium complexes were immobilized onto Au nanoparticles through chelation to the surface-bound dipyridyls. Hybrid catalysts of this type were dissolvable and precipitable, and proved to be highly effective catalysts for [2 + 2 + 2] alkyne cyclotrimerization reactions with fairly good selectivity. The nanoparticles can be easily separated, quantitatively recovered by simple filtration, and reused effectively many times (Figure 4).

5.31.1.1.4 Ruthenium catalysts

With regard to ruthenium complexes, [CpRuCl(COD)], is a well-documented catalyst that forms benzene, pyridines, pyridones, and thiopyridones from diynes and alkenes, activated nitriles, isocyanates, and isothiocyanates, generally acting at ambient temperature.[25] In addition, $[CpRu(CH_3CN)_3]PF_6$ and $[CpRu(CH_3CN)_3]PF_6$ have also been used.[26] Recently a combination of $Ru_3(CO)_{12}$ with 2-(diphenylphosphino)benzonitrile (2-dppbn) was efficiently used to cyclotrimerize trifluoromethylalkynes.[27] Grubbs' catalysts have proven to be useful in mediating in [2 + 2 + 2] cycloadditions. After some early reports that used **[Ru]-I** as

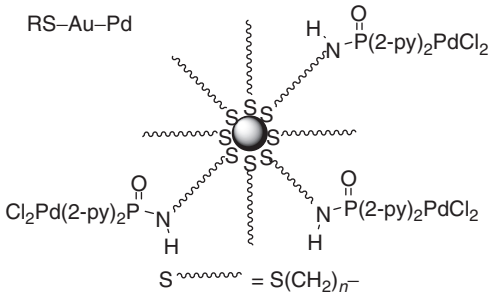


Figure 4 Schematic representation of palladium complexes immobilized onto Au nanoparticles. Represented nitrogen atoms belong to surface-bound dipyridyls.

the catalyst, the authors recently disclosed a new protocol for crossed diyne–alkyne cyclotrimerizations mediated by Hoveyda–Grubbs' complex **[Ru]-III** (Figure 5).[28]

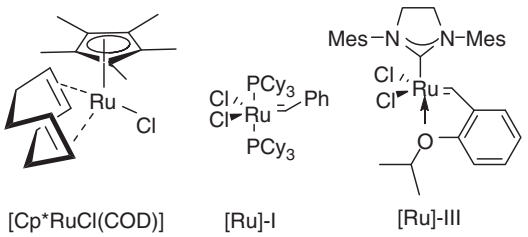
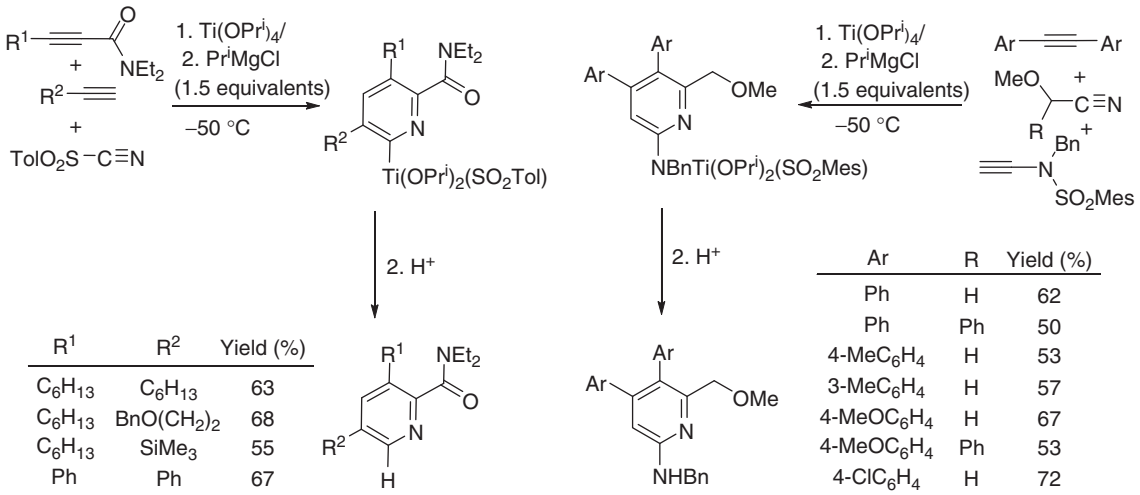


Figure 5 Structure of some ruthenium complexes used as catalysts in [2 + 2 + 2] cycloadditions.

5.31.1.1.5 Titanium and other metal-based catalysts

Titanium catalysis has received less attention in recent times in the cyclotrimerization chemistry as it generally works stoichiometrically. Urabe and Sato's group disclosed a four-component coupling process involving two acetylenes, a nitrile and a divalent titanium alkoxide reagent, $Ti(OPr^i)_4/2\text{-}Pr^iMgCl$, which directly yielded titanated pyridines in a highly selective manner. The key feature was the presence of a leaving group in the nitrile which allowed the titanium to finish the reaction attached to the pyridine. The pyridylmetal species formed enabled subsequent transformations (Scheme 2).[29]



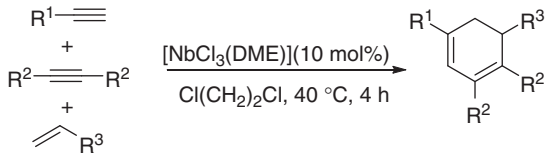
R^1	R^2	Yield (%)
C_6H_{13}	C_6H_{13}	63
C_6H_{13}	$BnO(CH_2)_2$	68
C_6H_{13}	$SiMe_3$	55
Ph	Ph	67

Ar	R	Yield (%)
Ph	H	62
Ph	Ph	50
4-MeC_6H_4	H	53
3-MeC_6H_4	H	57
4-$MeOC_6H_4$	H	67
4-$MeOC_6H_4$	Ph	53
4-ClC_6H_4	H	72

Scheme 2

Other metal complexes have found utility in the [2 + 2 + 2] cyclotrimerization chemistry. Examples include V, Ta, and Os catalyzed reactions.[3] Zirconacyclopentadienes are still used in certain cases to react stoichiometrically with alkynes to give aromatic compounds.[30] More recently a $DyCl_3$-catalyzed silyl-radical cyclotrimerization of alkynes was reported[31] and rhenium and manganese salts were used as catalyst for [2 + 2 + 2] cyclizations and other cycloadditions between 1,3-dicarbonyl

compounds and alkynes.[32] Intermolecular [2 + 2 + 2] cycloaddition of alkynes and α,ω-dienes or alkenes was successfully achieved by [$NbCl_3$(DME)] (DME = dimethoxyethane) to afford 1,3,4,5-substituted-1,3-cyclohexadienes in excellent yields with high chemo- and regioselectivity (Scheme 3).[33]

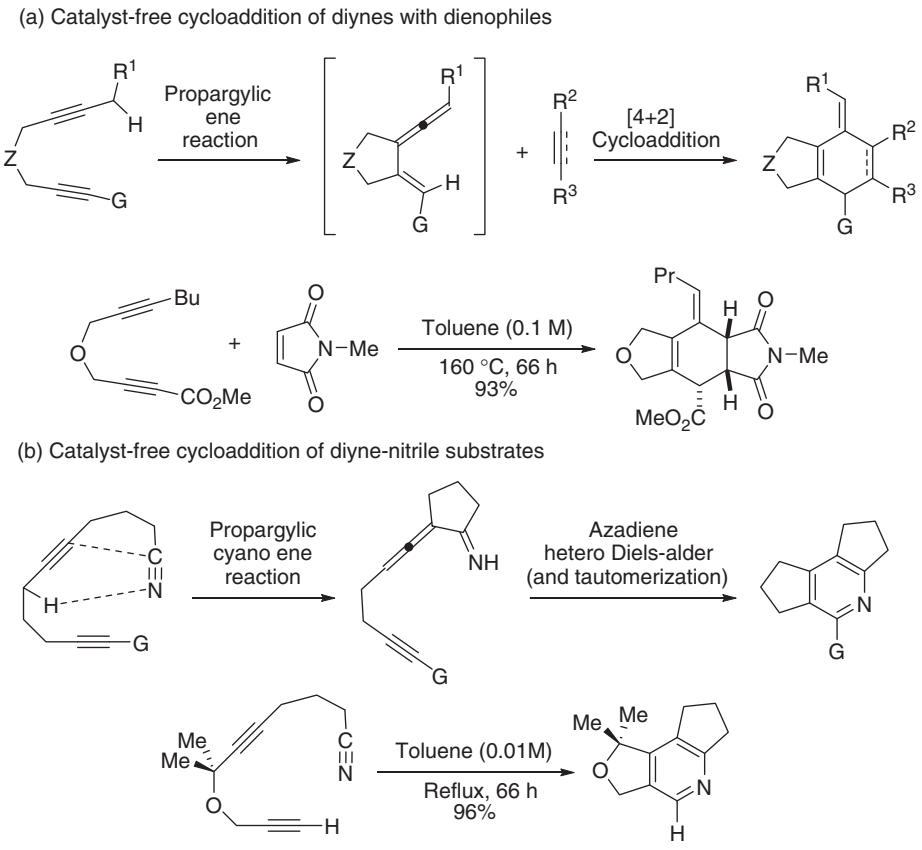


R^1	R^2	R^3	Yield(%)
$SiMe_3$	Bu^n	Ph	97
$SiEt_3$	Bu^n	Ph	85
$SiMe_2Ph$	Bu^n	Ph	83
Bu^t	Bu^n	Ph	89
Ph	Bu^n	Ph	56
Hex^n	Bu^n	Ph	79
$SiMe_3$	Bu^n	Hex^n	92
$SiMe_3$	Bu^n	Oct^n	72
$SiMe_3$	Bu^n	$(CH_2)_6CH{=}CH_2$	97

Scheme 3

Finally, iron-catalyzed syntheses of pyridines have been reported. The combination of $Fe(OAc)_2$ and an electron-donating, sterically hindered pyridyl bisimine ligand catalyzed the cycloaddition of alkynenitriles and alkynes.[34] In addition, simple iron salts combined with phosphines ($FeBr_3$/dppe) in the presence of Zn powder catalyzed the cycloaddition of diynes and unactivated nitriles leading to pyridine compounds at room temperature.[35]

Although this chapter is dedicated to metal-catalyzed [2 + 2 + 2] cycloaddition reactions, the authors will mention briefly recent reports that perform these transformations in the absence of metal catalysis. Sakai and Danheiser have described non-catalyzed formal [2 + 2 + 2] cycloaddition of diynes with electron-deficient alkenes to give cyclohexadienes and, in addition, of diyne–nitrile substrates to form functionalized pyridines. The transformation is based on pericyclic cascade reactions and requires thermal energy (more than 115 °C) to proceed successfully (Scheme 4).[36]

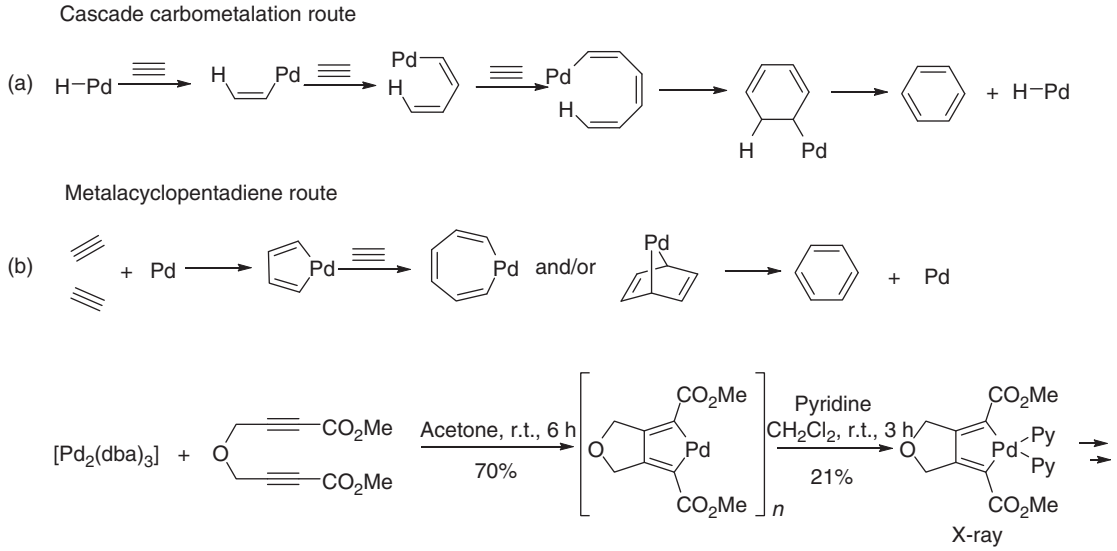


Scheme 4

Another example used an organocatalytic procedure for the cyclotrimerization of alkynylketones which gave 1,3,5-trisubstituted benzenes. The reaction was catalyzed by 4-dimethylaminopyridine in the presence of 2,4-pentanedione as a cocatalyst.[37] A similar reaction was performed recently in pressurized hot water without any catalyst.[38]

5.31.1.2 Mechanism

The mechanism of the [2 + 2 + 2] cycloaddition is well established and its basic features are shared by most catalytic systems. Exceptions are the palladium catalyzed reaction and the ruthenium carbene process. Both cases are not very clear. With regard to palladium-catalyzed reactions it has been postulated that hydropalladation followed by two carbopalladations give an intermediate which follows ring closure to the benzene derivative through a 6-*endo-trig*-cyclization or an electrocyclic closure (Scheme 5a).[24] However, Yamamoto's group was able to isolate and characterize by X-ray diffraction analysis a palladacyclopentadiene formed in the reaction of $Pd_2(dba)_3$ with electron deficient diynes. This complex produced the final arene on reaction with an alkyne, which supports a metallacyclopentadiene route (Scheme 5b).[39] However, Grubbs' carbenes are thought to produce the benzene rings through a cascade metathesis process.[28]

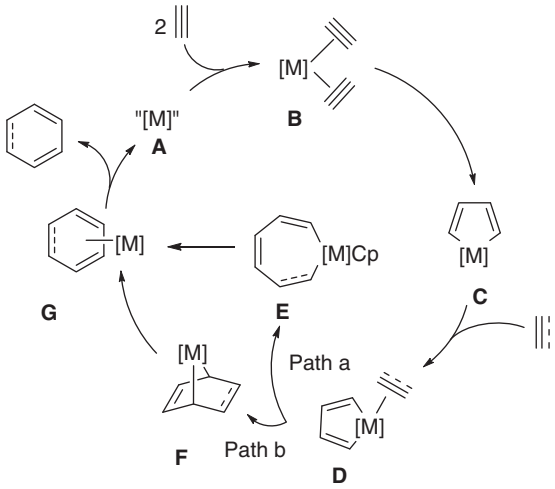


Scheme 5

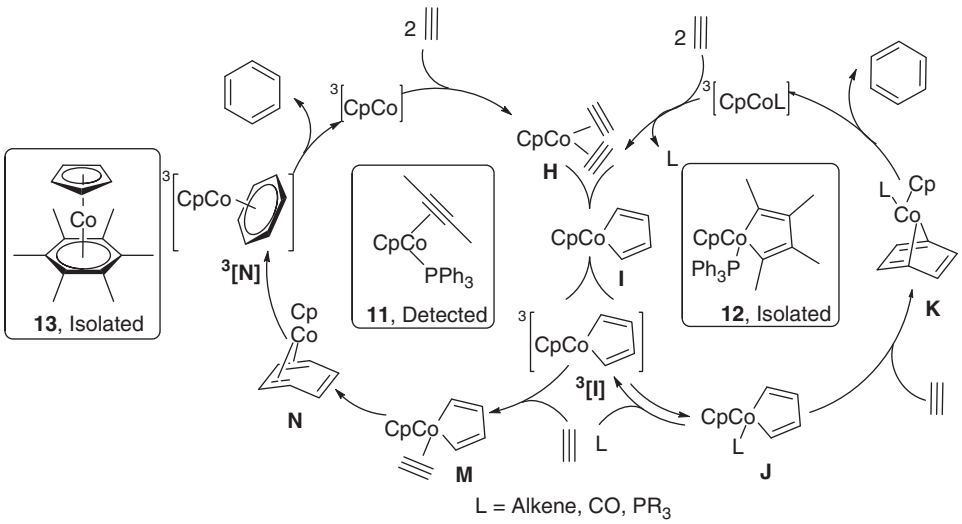
The [2 + 2 + 2] reaction was studied mainly through computational procedures. Experimental results are difficult to obtain and following the course of the reaction by nuclear magnetic resonance (NMR) is generally not possible due to the presence of paramagnetic species. However, isolation of reaction intermediates has been described in a few cases. The authors have currently quite a complete panorama of the most important mechanistic features of the transition metal-catalyzed or -mediated cyclotrimerization of alkynes and [2 + 2 + 2] cycloaddition of alkynes to alkenes because of the various excellent studies that have been published.[40] The mechanistic rationale of these processes depends on the nature of the metal, ligands, and substrate partners but a general pathway can be proposed and is represented in Scheme 6. Initially, two alkyne partners coordinate to the metal **A** and the resulting complex **B** forms a metallacyclopentadiene **C** by subsequent oxidative coupling. Then, the third unsaturated partner coordinates to give **D**, which follows two possible paths: insertion into the M–C bond to give metallacycloheptatriene **E**, which after reductive elimination gives complex **G**, or intramolecular [4 + 2] cycloaddition to form bicyclic complex **F**, which after isomerization affords complex **G**. Finally, decoordination of the metal produces the cycloadduct (Scheme 6).[40]

A particularly exhaustive and in-depth study was carried out on the mechanism of the $CpCoL_2$-catalyzed cyclotrimerization of ethyne.[41] This study concludes that after the formation of the cobaltacyclopentadiene **I** from **H**, this intermediate spontaneously relaxes to the triplet ground state ^{3}**[I]**. From this point on, two pathways are possible, depending on the nature of the ligands and the alkynes. In case of strong σ-donor solvents or ligands such as PR_3 or CO and electron-poor alkynes, complex ^{3}**[I]** is trapped to give the 18 e^- complex **J**, which undergoes the [4 + 2] cycloaddition to give complex **K**. In the absence of strong σ-donors and electron-poor alkynes, ^{3}**[I]** is transformed on alkyne ligation into a cobaltacyclopentadiene-(alkyne) intermediate **M**, which subsequently evolves to the CpCo(γ^4-arene) complex **N** through an intramolecular metal-assisted [4 + 2] cycloaddition. A spin change affords the 20-electron sandwich complex ^{3}**[N]** and dissociation of this species provides the free arene and CpCo. This study rules out the formation of metallacycloheptatriene intermediates in these alkyne cyclotrimerizations. Previous experimental works had isolated/detected intermediates of type **11** (**H**-type), **12** (**I**-type), and **13** (**N**-type) (Scheme 7).[41]

The ruthenium-catalyzed reaction is thought to follow a similar pathway. A recent work studied in detail the first steps of the reaction of a ruthenium catalyst (**14**) with alkynes until the formation of intermediates of type **C**. The authors isolated



Scheme 6



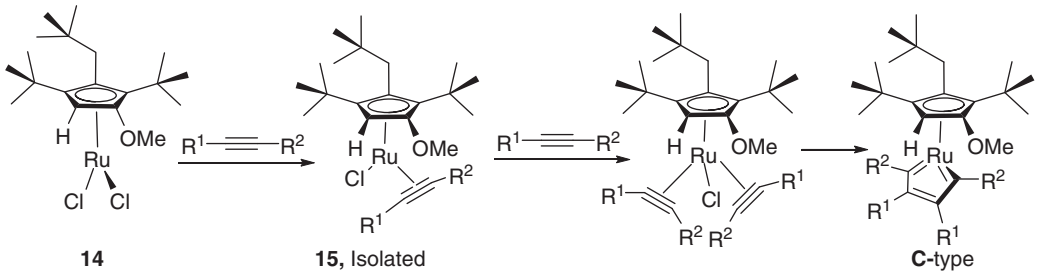
Scheme 7

compounds **15a–d** and their calculations showed that alkyne addition to the [Ru(η^2-alkyne)Cl(Cp)] complex is strongly dependent on steric effects between the alkyne and the π-ligand. They also predicted that the subsequent C–C coupling process to form the ruthenacycle takes place following a two-step reaction mechanism via a metallabicyclic intermediate (Scheme 8).[42]

Certain competitive reactions may take place. Vollhardt's group studied the cobalt-mediated [2 + 2 + 2] cycloaddition of diynes with heterocycles such as pyridones, pyrazinones, and pyrimidines. In this approach, they observed a competition between the desired cycloaddition process and a dienylation at carbon or nitrogen through C–H or N–H activation. An experimental study, combined with density functional theory (DFT) calculations, concluded that the structure of the substrate determined which process was favored. Substrates-containing N–H bonds followed an N–H activation pathway, whereas cycloaddition or C–H activation predominated with *N*-protected derivatives. The diversity of the resulting products is due to the energetically close-lying trajectories available for the metal, a finding that is corroborated by DFT calculations. The usefulness of this reaction was demonstrated by a short synthesis of the natural product anhydrolycorinone (Scheme 9).[43]

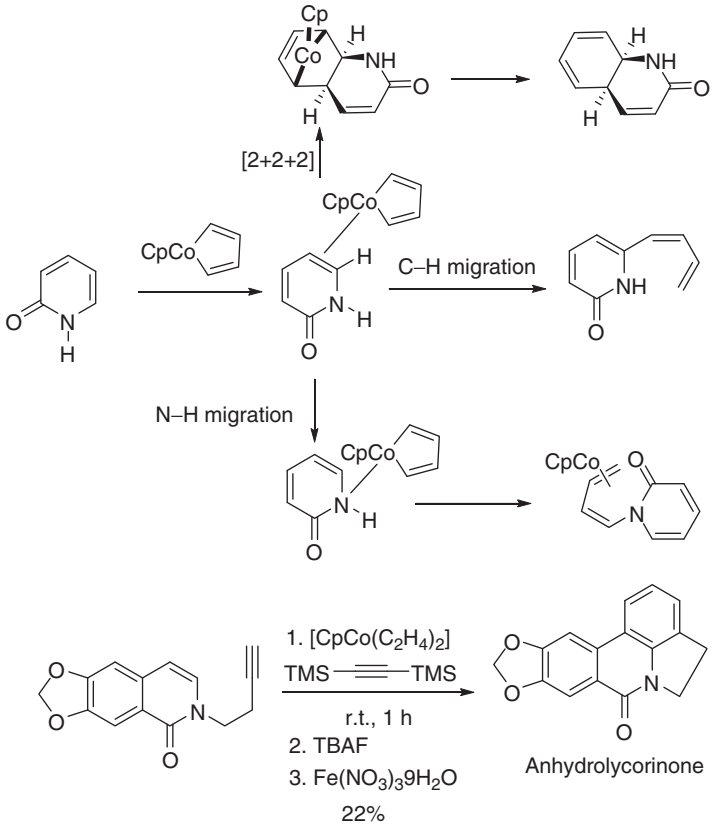
Linear 2:1 cooligomerization of alkynes was observed by this group when using enolethers as partners in the cycloaddition with certain enynes. Minor variations such as lengthening the diyne tether or introducing electron-withdrawing (EWG) substituents caused reversion to the standard [2 + 2 + 2] mechanism (Scheme 10).[44]

The groups of Vollhardt and Saa independently studied by DFT computations the mechanism of the parent cobalt and ruthenium-mediated [2 + 2 + 2] cycloaddition of two alkynes and one alkene to give 1,3-cyclohexadienes. The main difference to the mechanism of alkyne cyclotrimerization is the way in which the alkene is included into the common cobaltacyclopentadiene



15	R^1	R^2	Yield (%)
a	Bu^t	H	61
b	CPh_2OH	H	50
c	Et	Et	64
d	CO_2Me	CO_2Me	70

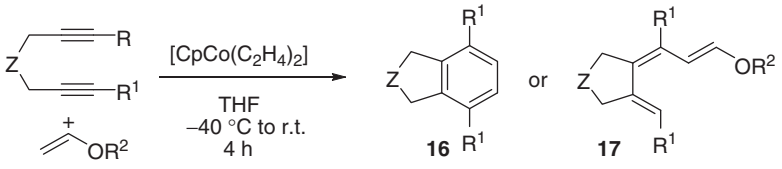
Scheme 8



Scheme 9

O. Instead of an inter- or intramolecular [4 + 2] cycloaddition, alkene incorporation proceeds via insertion into an M–C σ-bond. The resulting key intermediate is metallacycloheptadiene **P** which leads to either a metallanorbornene derivative **Q** or hexatriene **R**, depending on the nature of the alkene. The formation of this hexatriene has been proven by NMR studies in certain cases. After the formation of **R**, a thermal disrotatory 6e-π electrocyclization may lead to the final 1,3-cyclohexadienes **S** completing a formal [2 + 2 + 2] cycloaddition (Scheme 11).[45]

Finally, the rhodium-catalyzed process has been investigated by DFT and kinetic studies, showing a pathway similar to that of Co and Ru. The authors were able to characterize the intermediate rhodacyclopentadiene Rh^{III} complexes type **C** by cyclic voltammetry, conductivity measurements, ^{31}P NMR, and electrospray ionization mass spectrometry. Furthermore, the totally intramolecular reaction of two types of enediynes, catalyzed by the Wilkinson's catalyst [$RhCl(PPh_3)_3$], was studied experimentally and with DFT calculations.[46]



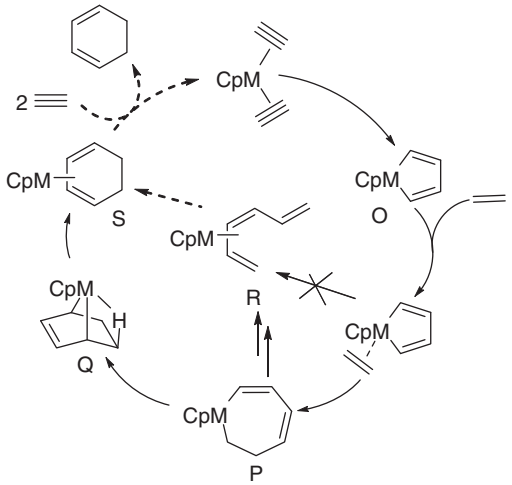
Z = CH_2, $C(CH_2OMe)_2$, NTs, O, $SiPh_2$, C_2H_4

R^1 = H, $SiMe_3$, BPin (boryl pinacolate), Ph, CO_2Et

R^2 = Bu^t, Ph

Z	R^1	R^2	Yield **16** (%)	Yield **17** (%)
CH_2	Ph	Bu^t	–	53
$C(CH_2OMe)_2$	BPin	Bu^t	–	80
NTs	Ph	Ph	–	51
O	Ph	Bu^t	–	54
C_2H_4	BPin	Bu^t	80	–
C_3H_6	BPin	Ph	62	–
$SiPh_2$	BPin	Bu^t	62	–
	BPin	Bu^t	91	–

Scheme 10



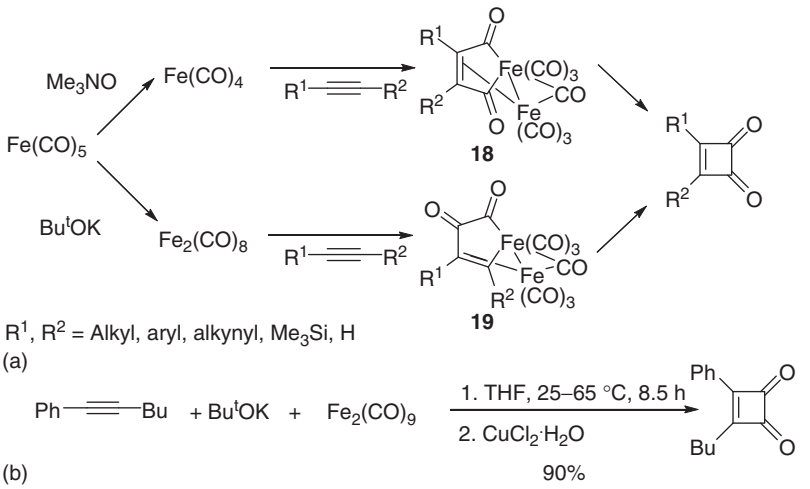
Scheme 11

5.31.2 Synthesis of Four- and Five-Membered Rings

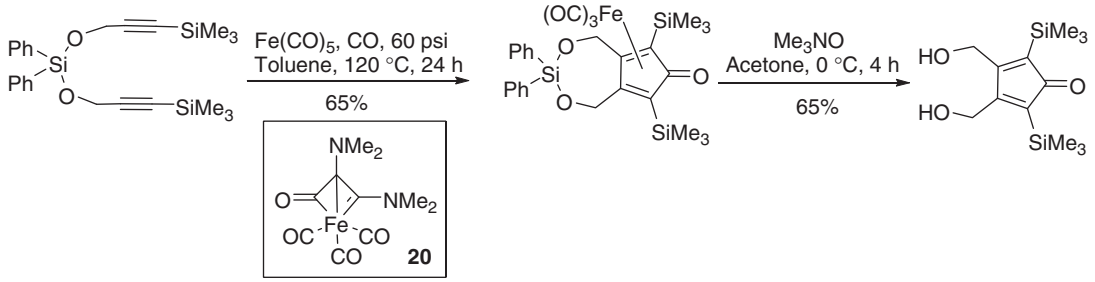
5.31.2.1 Carbocyclic Rings

Certain iron complexes have been used to produce cyclobutenediones on reaction with alkynes. Periasamy's group has developed several reactive iron carbonyl intermediates from iron carbonyls $Fe(CO)_5$ and $Fe_3(CO)_{12}$ in the presence of various promoters such as NaH, $NaBH_4$, Me_3NO, and amines. The coordinatively unsaturated '$Fe(CO)_4$' species generated *in situ* reacts with alkynes followed by $CuCl_2$ oxidation of iron-containing intermediates of type **18** (Scheme 12a). More recently they changed the catalytic system to a combination of $Fe(CO)_5$ with metal alkoxides which gives better results in terms of yields under milder conditions. With this new system intermediates are thought to be 1,2-dicarbonyliron complexes of type **19** (Scheme 12b).[47]

Similar catalytic iron-carbonyl-based reactions of diynes have been used for the synthesis of cyclopentadienones. The process is in general stepwise as an oxidative demetallation step is needed after the formation of a metal-complexed cyclopentanedione. Thus, 'silicon-tethered' $Fe(CO)_5$-promoted cyclocarbonylation and oxidation with Me_3NO was used as an effective method for carbonylative cross-coupling of alkynes to furnish cyclopentadienones with variable substituents. The reaction pathway seems to go through ferrabicyclobutenones of type **20** which have been isolated by another group in the reaction of $[Fe(CO)_5]$ with *bis*-dimethylaminoacetylene (Scheme 13).[48]

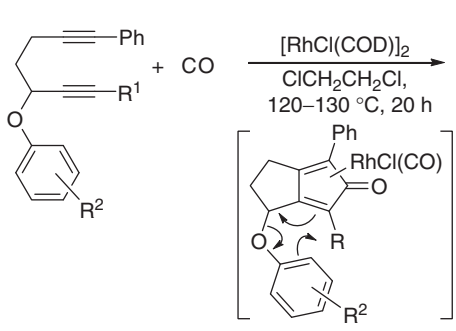


Scheme 12



Scheme 13

In addition, $[CpCo(PPh_3)_2]$, $[CpCo(CO)_2]$, and $[RhCl(PPh_3)_3]$ mediate alkyne–alkyne couplings to give metallacyclopentadienes, which can be transformed into cyclopentadienones by insertion of carbon monoxide and elimination of the metal. Recently, the structure of $[RhCl(CO)(cyclopentadienone)]_2$, which was formed by the reaction of $[RhCl(COD)]_2$ with a 1,6-diyne under CO, was determined and a new catalytic tandem reaction consisting of a $[2 + 2 + 1]$ carbonylative cycloaddition of phenoxy substituted diynes and Claisen rearrangement was described (**Scheme 14**).[49]

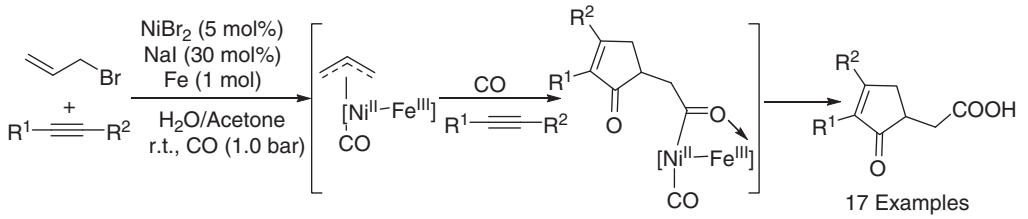


R^1	R^2	Yield (%)
Ph	H	39
Pr^c	H	43
Ph	3-Me	45
Pr^c	3-Me	67
Ph	5-Me	48
Pr^c	5-Me	29
Ph	3,5-Me_2	52

Scheme 14

The first catalytic carbonylative alkyne–alkyne coupling for the synthesis of cyclopentadienones was achieved using iridium–phosphine complexes. To this end, $[IrCl(COD)]_2$ combined with a phosphine ligand under carbon monoxide at atmospheric pressure or a partial pressure of 20 000 Pa (0.2 atm) was able to catalyze cyclizations of enynes and CO providing cyclopentadienones in high isolated yields.[50]

In general, [2 + 2 + 1] cycloaddition reactions involving one double bond, one triple carbon–carbon bond, and a CO unit fall into the Pauson–Khand chemistry which is covered in Chapter 5.24 Nickel carbonyl-catalyzed cyclizations of allyl halides with alkynes is an exception as it follows a rather different mechanism. This reaction was originally performed with hazardous $Ni(CO)_4$ reagent. Moretó's group has succeeded in developing a highly efficient catalytic version using a stoichiometric amount of iron, acetone, and a catalytic amount of nickel halide. Cyclopentenones were obtained intermolecularly in high yields and with controlled stereochemistry (Scheme 15).[51]



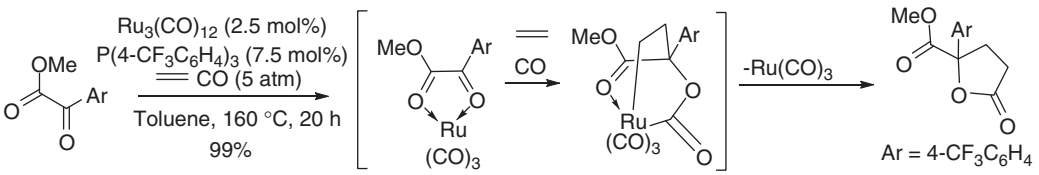
R^1 = Ph, Et, $(CH_2)_4OH$, OEt, CH_2OMe, 1-cyclohexenyl, 4-$NH_2C_6H_4$, 3-pyridyl, 4-$(HC{\equiv}C)C_6H_4$, $(CH_2)_4$
and R^2 = H,
or $R^1 = R^2$ = Et; $R^1 = R^2 = CH_2OMe$;

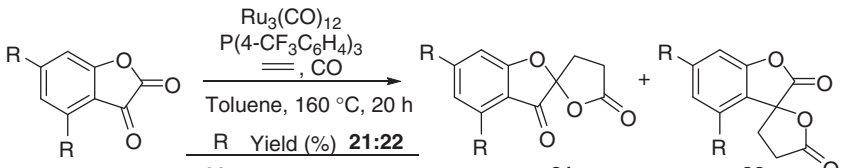
R^1	R^2	Yield (%)
Ph	H	95
Et	Et	80
EtO	H	54
CH_2OMe	CH_2OMe	81
1-Cyclohexenyl	H	87
3-Pyridyl	H	–

Scheme 15

5.31.2.2 Heterocyclic Rings

Cycloaddition reactions utilizing two carbon monoxide units and one alkyne or the carbonylative cycloaddition of aldehydes, ketones, and imines with alkynes have also been addressed because of their great potential for the preparation of heterocycles. However, recent reports are scarce. Chatani has shown the synthesis of different butyrolactones based on ruthenium carbonyl catalysis. The application of this methodology to benzofuran-diones allowed the synthesis of spirolactone derivatives **21** and **22** (Scheme 16).[52]



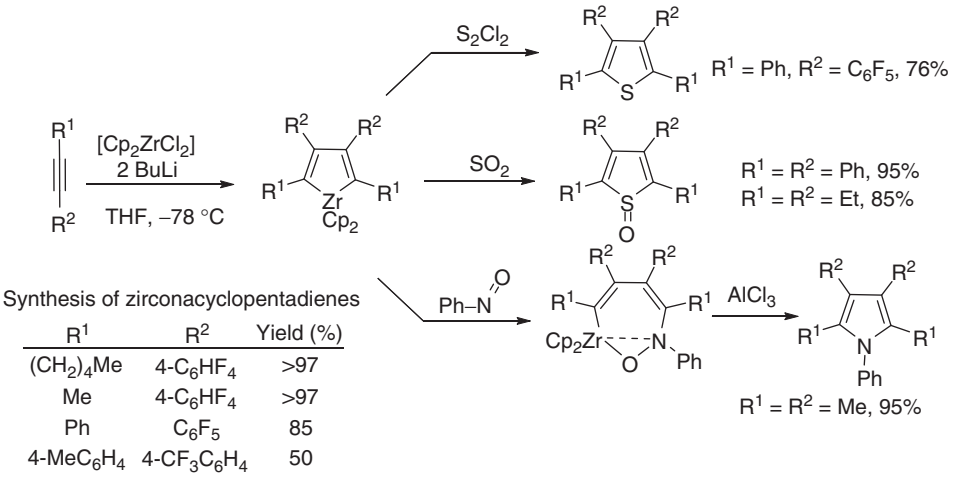


R	Yield (%)	**21:22**
Me	85	36:64
OMe	83	26:74
Bu^t	94	100:0

21 **22**

Scheme 16

Starting from metallacyclopentadienes, the synthesis of various five-membered ring heteroaromatics is possible. Although in early times iron and cobaltacyclopentadienes were used as precursors, most recent contributions have involved the synthesis of zirconacycles formed from alkynes, diynes, or dienes. These zirconacyclopentadienes can easily be converted into heterocycles such as thiophenes, siloles, phospholes, germoles, pyrroles, and thiophene oxides (Scheme 17).[53] However, possibly due to the stoichiometric nature of these methodologies, they have received less attention in recent years.



Synthesis of zirconacyclopentadienes

R^1	R^2	Yield (%)
$(CH_2)_4Me$	4-C_6HF_4	>97
Me	4-C_6HF_4	>97
Ph	C_6F_5	85
4-MeC_6H_4	4-$CF_3C_6H_4$	50

Scheme 17

5.31.3 Synthesis of Six-Membered Carbocyclic Rings

The cyclotrimerization reaction is mostly used for the synthesis of six-membered rings. Carbocyclic aromatic rings arising from cycloadditions of three triple bonds are the most common, and will be covered first classified by totally inter-, partially inter-, and totally intramolecular reactions. Then, the authors will address reactions with participation of carbon–carbon double bonds.

5.31.3.1 Totally Intermolecular Cyclotrimerizations of Alkynes. Synthesis of Nonfused Benzenes

Most totally intermolecular reactions reported to date are trimerizations of internal alkynes with which syntheses of star-shaped per-substituted benzenes is possible. Symmetrically hexasubstituted benzenes have found applications in many fields such as main-group chemistry, organometallic chemistry, and organic material science. Thus, molecular devices, dendrimers, multi-electron redox systems, host molecules, etc., were prepared using in most cases cobalt-, nickel-, or palladium catalysts. In Figure 6 the authors show several recent examples synthesized from alkynes with inexpensive $Co_2(CO)_8$ as the catalyst except otherwise indicated.[54]

A more difficult case is the control of regiochemistry in the trimerization of unsymmetrical alkynes. This reaction generally gives mixtures of 1,2,4- and 1,3,5-trisubstituted benzenes. Although the symmetrical 1,3,5-trisubstituted aromatic is the less sterically hindered derivative, this isomer is often the minor product because only one of the possible three initially formed metallacycle intermediates provides the symmetrical aromatic ring (Scheme 18). Among the few successful methods reported for the totally selective formation of 1,2,4-trisubstituted benzenes is the use of a calixarene-bound titanium complex. The high selectivity may be understood in terms of the directing influence of the calixarene ligand which favors the formation of the 2,4-disubstituted titanacyclopentadiene and also sterically controls the approach of the third alkyne unit (Scheme 18).[55] Selective formation of 1,3,5-trisubstituted benzenes has been described although exclusive formation of this isomer is rare and generally achieved with ethynyl aryl ketones.[56]

Attempts at heterotrimerization (use of two or more different alkynes) lead generally to complex mixtures. The authors are still rather far from a truly general, intermolecular [2 + 2 + 2] cycloaddition and the controlled cyclization of two or three different alkynes to give only one final product continues to be a challenge. There is a double problem here: first, controlling the chemoselectivity during the metallacycle formation and second, the regioselectivity of the insertion of the third alkyne. It is worth remembering that combination of all chemo- and regiochemical possibilities gives 9 or 38 isomers when reacting two or three different monosubstituted alkynes, respectively. One first approach to this complex problem is the use of stoichiometric amounts of transition-metal complexes, for example, zirconium- or titanium-based systems. The problem of chemoselectivity is circumvented through stepwise addition of all reagents. Thus, the cycloaddition reaction of zirconacyclopentadienes to alkynes proved a highly selective method for forming benzene derivatives. (η^5-Cyclopentadienyl) zirconacyclopentane, formed from Cp_2ZrBu_2 and ethylene, was regioselectively transformed into a single unsymmetrical zirconacyclopentadiene after successive addition of two different alkynes. This was made possible by the presence of trimethylsilyl or aryl groups which are well known for giving α-silyl- or α-arylzirconium complexes. The reaction of the intermediate zirconacyclopentadiene with DMAD in the presence of copper(I) chloride gave hexasubstituted benzenes in good yields (Scheme 19).[56]

One strategy used to achieve chemoselectivity under catalytic conditions consists of using electronically extremely different alkyne components to control the initial metallacycle formation. Acetylene dicarboxylates are good partners for

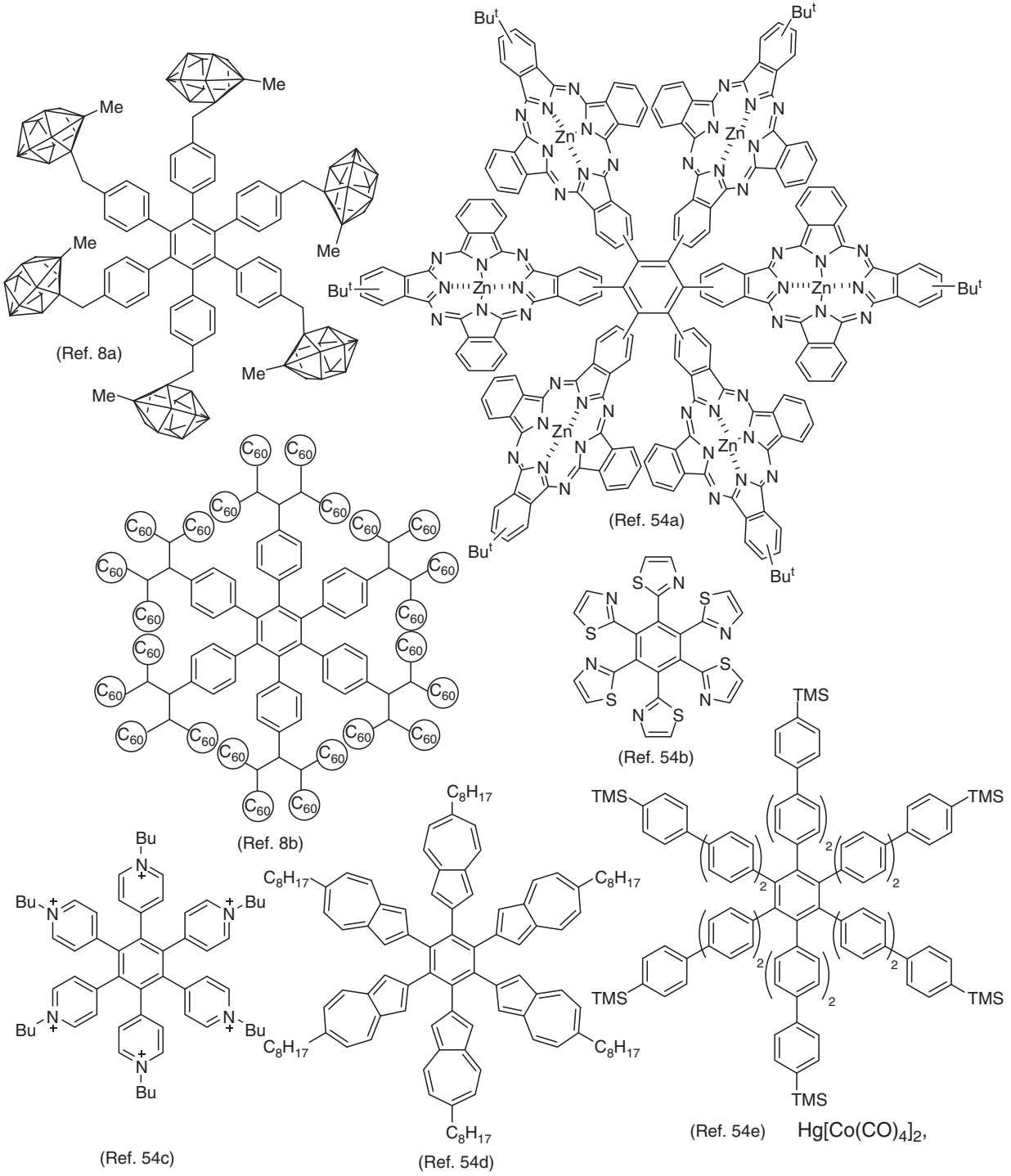
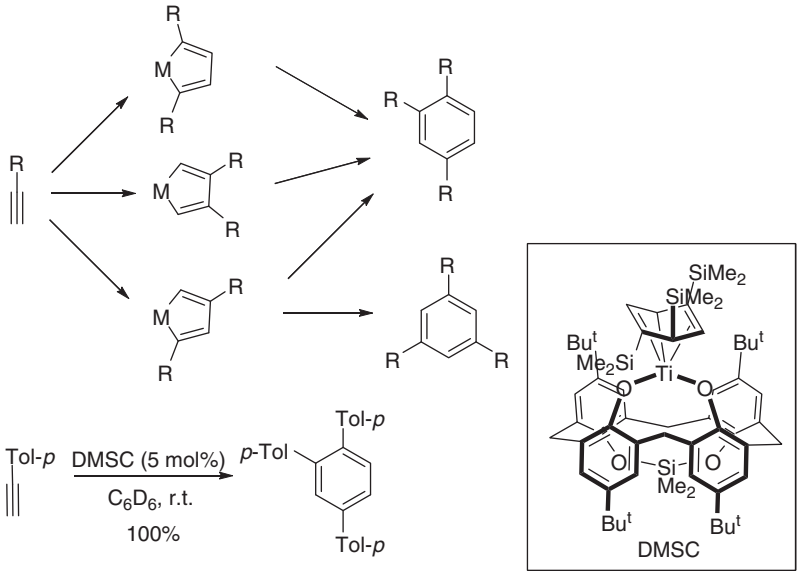
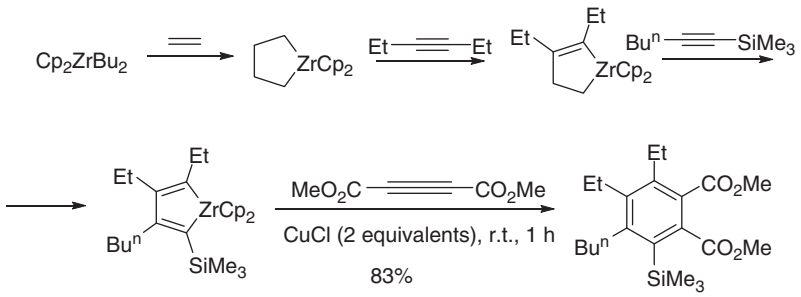


Figure 6 Examples of star-shaped products synthesized by totally intermolecular alkyne [2 + 2 + 2] cyclotrimerizations.

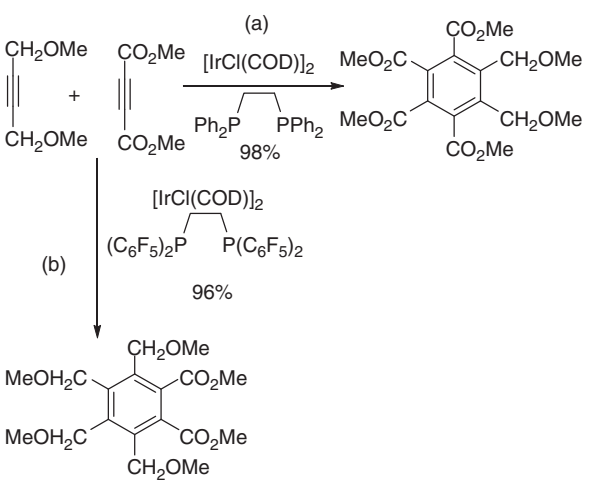
heterotrimerization with terminal alkynes as they do not usually form the initial metallacyclopentane and thus are the last C2 unit to be incorporated. Takeuchi and Nakaya used neutral iridium(I) systems combined with phosphines to cyclize DMAD with alkynes. When dppe was used as the ligand, two molecules of DMAD were incorporated into the product (Scheme 20a), whereas when the perfluoroaryl derivative of dppe is used as the ligand, one molecule of DMAD reacted with two molecules of the acetylene (Scheme 20b). In addition, they reacted three different alkynes under the latter conditions giving a single product in high yields (Scheme 20c).[57]

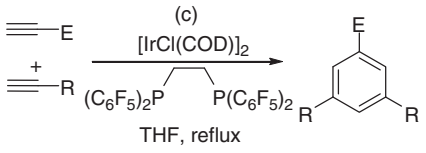


Scheme 18



Scheme 19

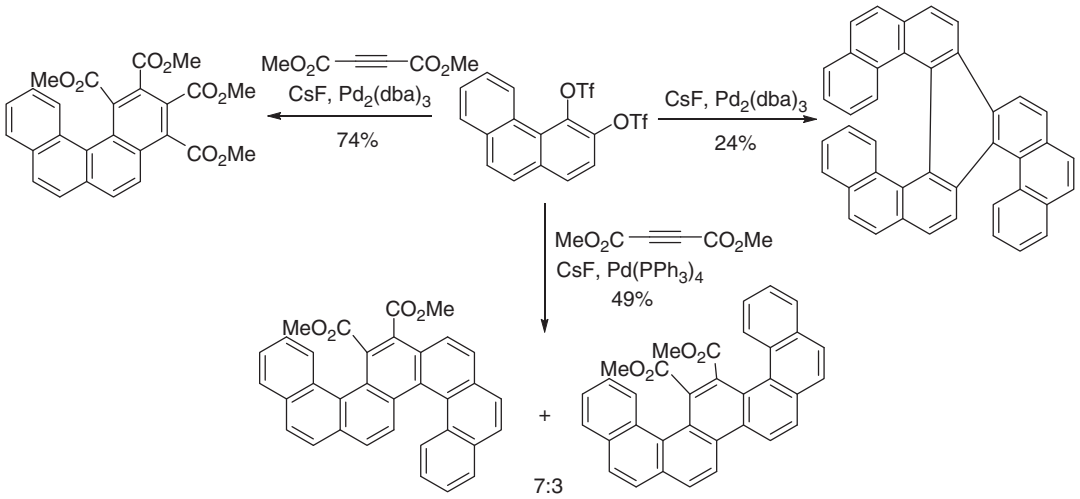




E	R	Time (h)	Yield (%)
CO_2Me	Hex^n	16	96
CO_2Me	Oct^n	5	84
CO_2Me	Ph	14	85
CO_2Me	1-Cyclohexenyl	6	72
CO_2Me	$Ph(CH_2)_3$	4	88
CO_2Me	$Cl(CH_2)_3$	5	82
CO_2Me	$NC(CH_2)_3$	4	90
SO_2p-Tol	Bu^n	24	66
SO_2p-Tol	Oct^n	5	90
SO_2p-Tol	Ph	2	58
SO_2p-Tol	$Cl(CH_2)_3$	5	95

Scheme 20

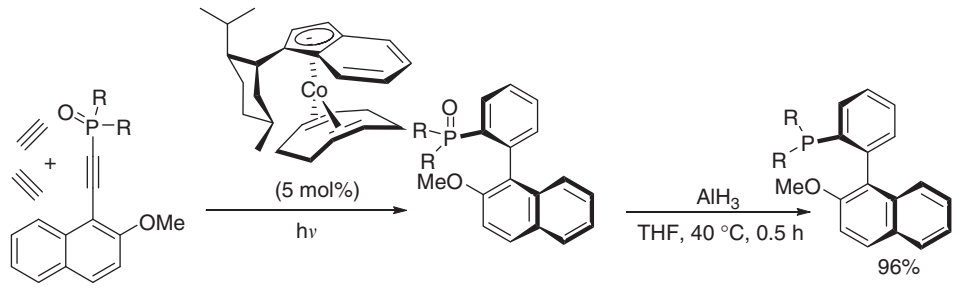
Benzynes and benzyne-analogs are also excellent partners for cyclotrimerization reactions generally catalyzed by palladium or nickel complexes. Thus, the palladium-catalyzed cyclotrimerization of arynes is an efficient way to produce triphenylenes. In this reaction, a trimethylsilylaryl triflate is treated with fluoride in the presence of a Pd(0) catalyst, and the aryne generated *in situ* undergoes cyclotrimerization. The scope of this methodology is quite broad and has been applied to the synthesis of a wide variety of polycyclic aromatic hydrocarbons (PAHs) which are of considerable interest in materials science because of their charge transport properties. Scheme 21 shows representative examples reported by the groups of Peña and Perez.[58]



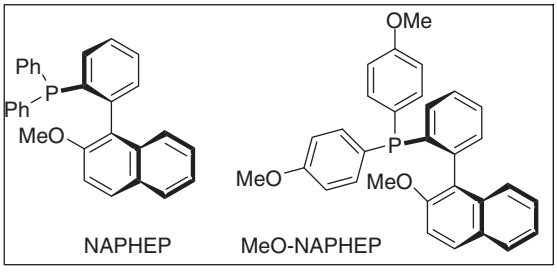
Scheme 21

o-Carboryne (1,2-dehydro-*o*-carborane), is a three-dimensional relative of benzyne that can react with alkenes, dienes, alkynes, and aromatics in [2 + 2], [4 + 2] cycloaddition and ene-reactions. Xie's group generated recently this reactive intermediate which was trapped by alkynes via Pd/Ni-cocatalyzed [2 + 2 + 2] cycloaddition reactions, leading to the formation of C,B-substituted-*o*-carborane derivatives.[59]

Heller's group developed chiral cobalt complexes with which they prepared chiral biaryls bearing phosphoryl moieties. By subsequent reduction to the corresponding phosphine, a very efficient and atom-economical approach to chiral monodentate *P*- or bidentate *P,O*-ligands was described (Scheme 22).[60]



R	Temperature (°C)	Time (h)	Yield (%)	*ee*(%)
(*S*) Ph	45	48	49	>99
(*S*) 4-$MeOC_6H_4$	45	24	51	>99
(*S*) 3,5-$(CF_3)_2C_6H_3$	45	24	24	–
(*S*) Bu^t	25	48	61	>99
(*S*) 1-Adamantyl	25	24	44	>99
(*S*) Me_2N	55	12	80	–

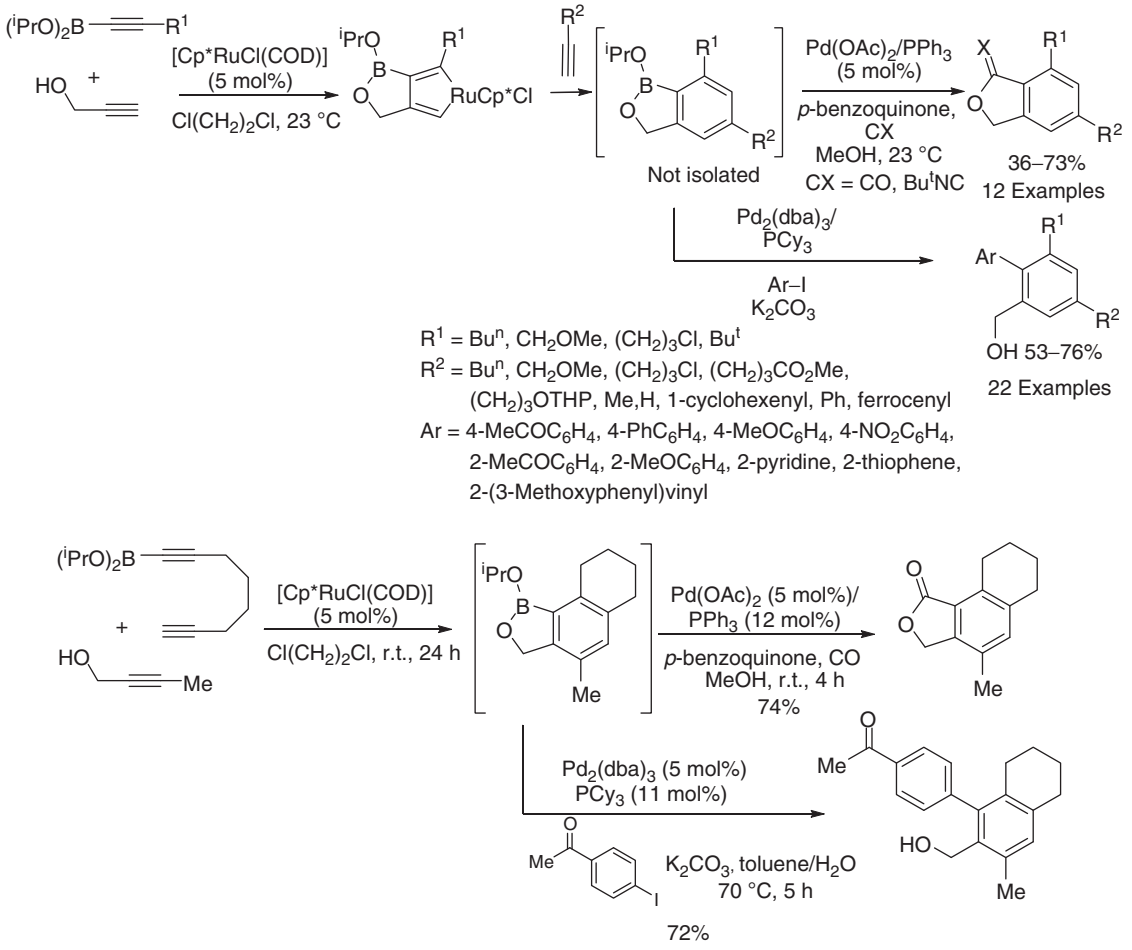


Scheme 22

5.31.3.2 [2 + 2 + 2] Cycloaddition of Diynes and Triynes. Synthesis of Fused Benzenes

5.31.3.2.1 Scope, chemo-, and regioselectivity

The crossed version using a diyne and an alkyne has become the most common strategy used to overcome the problems with regio- and chemoselectivity. This version produces an additional cycle fused to the aromatic ring. One elegant way to avoid the formation of this additional ring is to tether temporarily two alkyne components. Yamamoto's group has succeeded in controlling the metallacycle formation by the geometric restrictions imparted by a boron temporary tether. [CpRuCl(COD)] catalyzed the cyclotrimerization of alkynylboronates, propargyl alcohols, and terminal alkynes producing an intermediate arylboronate that could be isolated or submitted to further transformations. Thus, they have described the synthesis of highly substituted phthalides by a palladium(II)-catalyzed carbonylation of the arylboronates. In a different contribution, the arylboronates were further converted to highly substituted biaryls via the Suzuki–Miyaura coupling with various aryl iodides using $Pd_2(dba)_3/PCy_3$ as the catalyst (Scheme 23).[61]

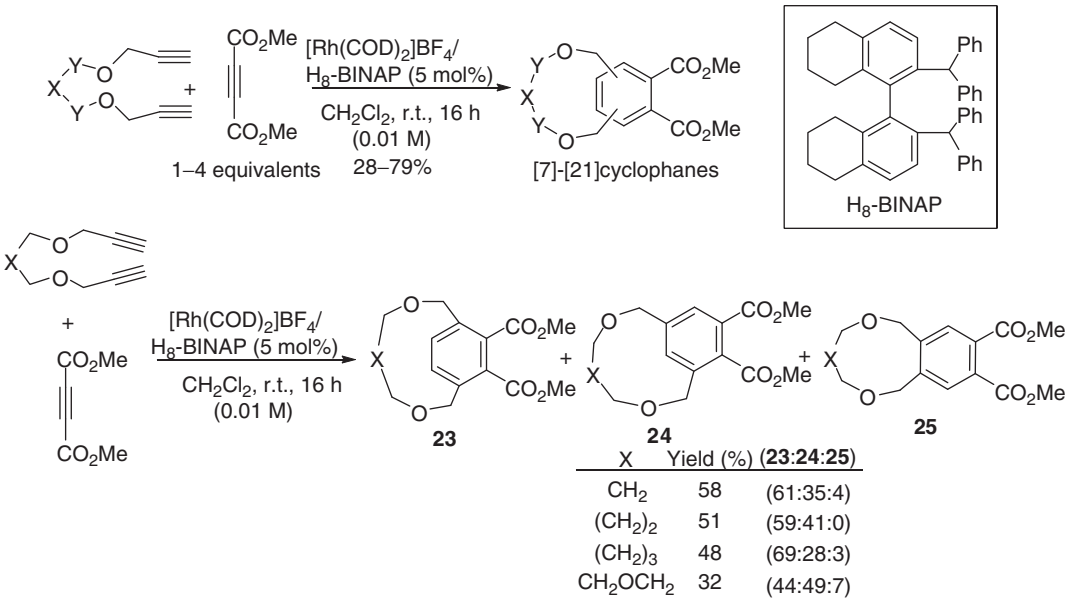


Scheme 23

The scope of the crossed [2 + 2 + 2] cycloaddition of alkynes with diynes has been the subject of numerous works and is covered by various reviews.[1,2] The authors will summarize first the allowed structures of the starting materials and then will show some recent examples. Many types of diynes react efficiently. In principle, the additional ring fused to the emerging aromatic unit may have almost any size. Most examples, however, show the formation of five-membered carbo- or heterocycles from 1,6-diynes. A *gem* disubstitution at position 4 of the diyne is thought to favour the reaction and a Thorpe–Ingold effect is many times claimed to justify this. However, six-membered fused cycles are readily obtained from 1,7-diynes and there are examples of the synthesis of benzocyclobutanes.[62] Heteroatoms are allowed in the connecting tether so that benzofuranes, indoles, and isoindoles can be synthesized. Diynes connected through aromatic rings give good results possibly as a consequence of conformational restrictions.

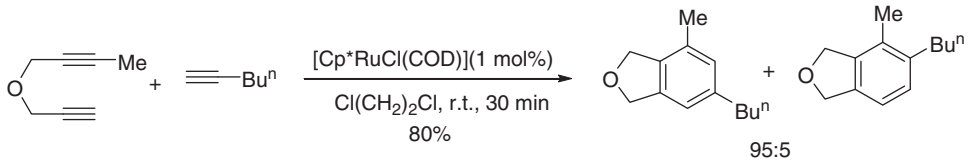
Moreover, the formation of macrocycles and *ansa*-connected cycles is possible. Long-chain α,ω-diynes are known to react with acetylene dicarboxylates to yield pyridine-containing *ansa*-macrocycles and cyclophanes. The reaction has been catalyzed with a cationic rhodium(I)/H_8–BINAP complex by Tanaka's group for the synthesis of polyether cyclophanes (Scheme 24).

The regioselectivity of these reactions was affected by the length and type of linker unit between the alkyne groups, as well as by certain stereoelectronic effects.[63]



Scheme 24

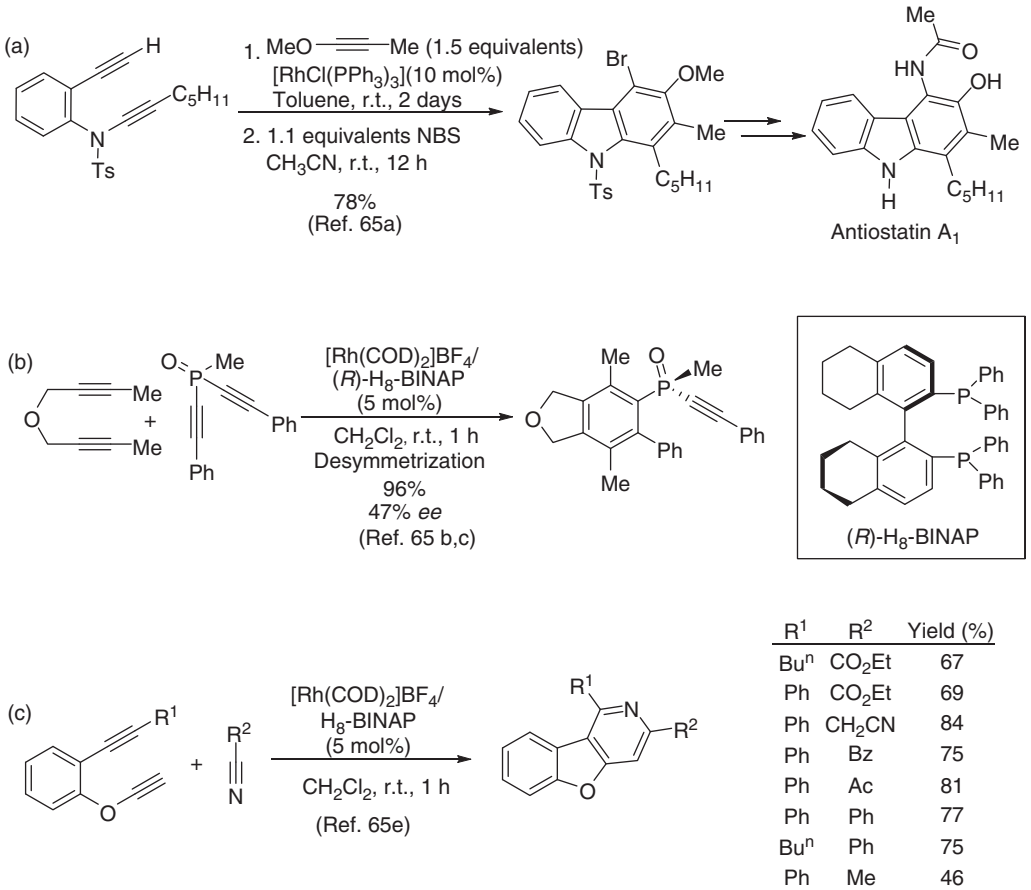
Regioselectivity problems arise in reactions of nonsymmetrical diynes with monosubstituted alkynes. In this case *ortho* and *meta* products are possible, with the general tendency to obtain *meta* as the major product. Excellent *meta*-selectivities were observed in reactions of 1,6-diynes with terminal alkynes catalyzed by [CpRuCl(COD)]. A DFT study on the mechanism indicated that the alkyne insertion appears to take place as a formal [2 + 2] cycloaddition and the pathway leading to a *meta*-product goes through the lowest *trans–anti* transition state (Scheme 25).[64]



Scheme 25

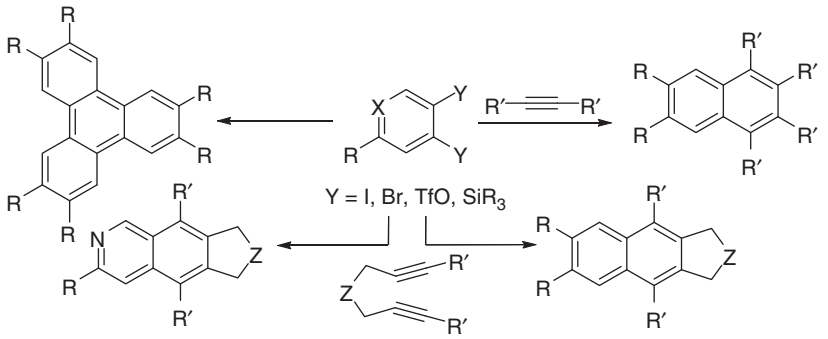
Alkynes with heteroatoms directly bonded to the triple bond are valid substrates in [2 + 2 + 2] cycloadditions. Therefore, functionalized ynamides, phosphine derivatives, and phenol-linked 1,6-diynes react readily with alkynes and nitriles giving carbazole structures, bulky phosphines, and benzofuran derivatives, respectively. For these transformations rhodium catalysis is preferred. Thus, Scheme 26a shows a crossed cyclotrimerization reaction with a methoxyalkyne which gave a carbazole. Antioxidant antiostatin A_1 was synthesized using this reaction as the key step followed by a palladium-catalyzed arylamidation reaction. Production of central chirality, which is a nonfrequent issue in the [2 + 2 + 2] chemistry, was accomplished by desymmetrization of a dialkynylphosphine oxide reaching good enantiomeric excess in the P-stereogenic-containing product (Scheme 26b). Finally, benzofuranes and benzopyridines were readily obtained from phenoxy-connected diynes (Scheme 26c).[65] Yamamoto's group reported a terminal diiodination of a diyne and subsequent reaction with alkynes under [CpRu(COD)] catalysis to produce diiodobenzenes.[66]

A wide variety of terminal or internal alkynes with alkyl or aryl substituents participate in crossed cyclizations with diynes. These include alkoxyacetylenes, silylacetylenes, alkoxycarbonylacetylenes, alkynylboronates, propargyl alcohols, etc. In addition, arynes and pyridynes have been utilized as substrates in crossed [2 + 2 + 2] cycloadditions with diynes, alkynes, alkenes, allenes, and nitriles. Recent works described that arynes, formed from *o*-dihaloarenes or silyl triflates, react with acetylenes and nitriles catalyzed by the $NiBr_2$/dppe/Zn system to give substituted naphthalene, phenanthridine, or triphenylene derivatives depending on the reaction conditions (Scheme 27).[22a]



R^1	R^2	Yield (%)
Bu^n	CO_2Et	67
Ph	CO_2Et	69
Ph	CH_2CN	84
Ph	Bz	75
Ph	Ac	81
Ph	Ph	77
Bu^n	Ph	75
Ph	Me	46

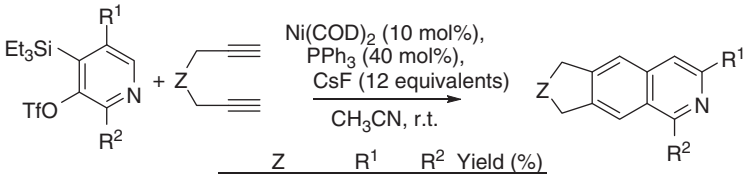
Scheme 26



Scheme 27

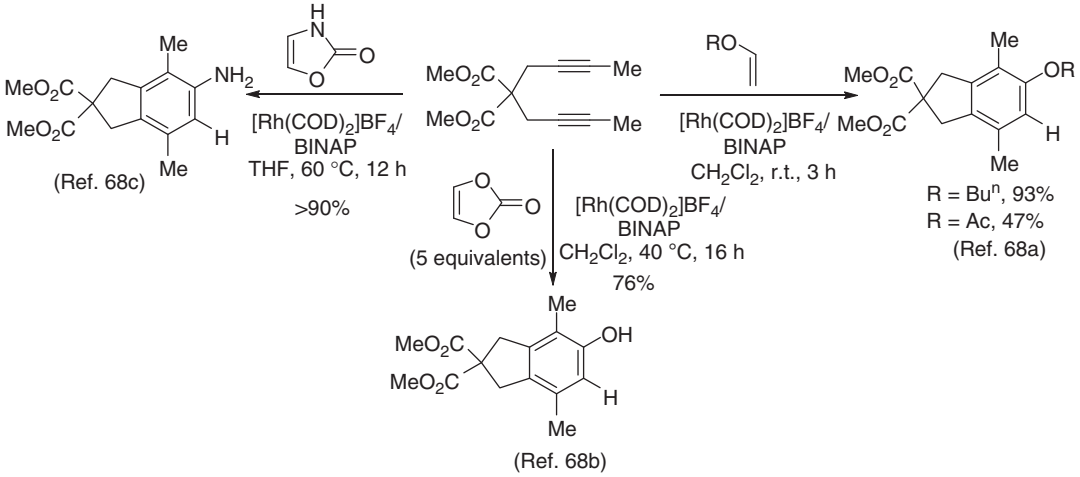
Pyridynes gave isoquinoline-containing polycycles under $Ni(COD)_2/PPh_3$ catalysis, albeit the yields were in some cases moderate (Scheme 28).[67]

Synthesis of fused benzene rings can also be accomplished using alkyne surrogates in the reaction with diynes. This is a different and elegant way to avoid selectivity problems. Several groups have reported the use of enol ethers or easily enolizable ketones as an alkyne equivalent that suffers dehydration after the cyclotrimerization giving the aromatic final product. Some recent examples, depicted in Scheme 29 show diynes reacting under cationic rhodium(I)/BINAP catalysis with enol ethers, vinylene carbonates, or 2-oxazolones. The regioselectivity of the enol ether insertion is postulated to be controlled by coordination of the enol carbonyl moiety to the cationic Rh center in the metallacyclopentadiene intermediate. If the enol ether component is replaced by vinylene carbonate, a phenol is obtained, whereas the reaction with 2-oxazolones gives anilines.[68]



Z	R^1	R^2	Yield (%)
CH_2	H	H	65
NTs	H	H	50
O	H	H	38
$C(CO_2Me)_2$	OMe	H	61
$C(CO_2Me)_2$	H	OMe	60
$C(CO_2Me)_2$	H	$CONEt_2$	18

Scheme 28



Scheme 29

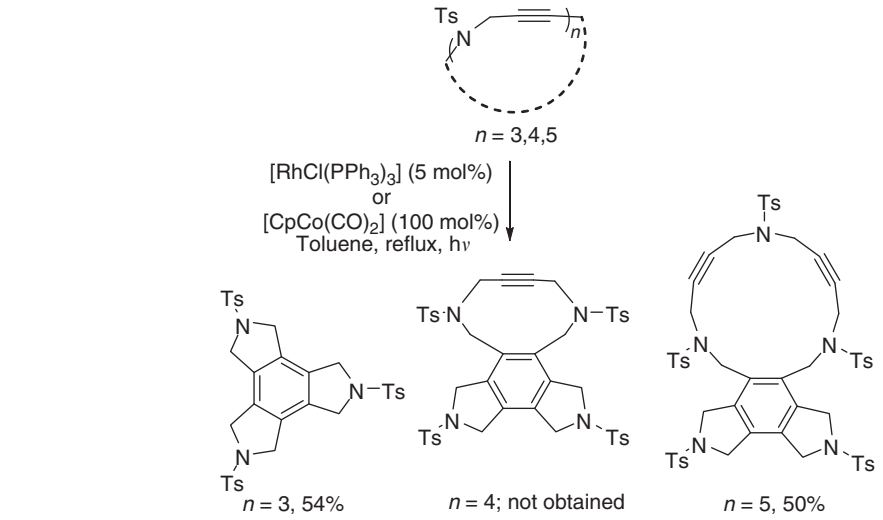
The totally intramolecular version of the [2 + 2 + 2] cycloaddition, really a cycloisomerization process, has the disadvantage of requiring a highly functionalized starting material. However, the obvious control of the selectivity makes this version attractive and with high synthetic potential.

A recent study addressed the problem of the number of members of the triyne substrate and its influence on the results. Thus, 15-, 20-, and 25-membered polyacetylenic azamacrocycles were submitted to [2 + 2 + 2] cyclotrimerization processes catalyzed by the Wilkinson's catalyst. The 15- and the 25-membered azamacrocycles led to the expected cyclotrimerized compounds in contrast to the 20-membered azamacrocycle, which was characterized by its lack of reactivity. The difference in reactivity of these substrates was rationalized through DFT calculations. The lack of reactivity of the 20-membered substrate was attributed to its more stable and delocalized higher occupied molecular orbital and to the formation of a strained 10-membered ring during the cyclotrimerization (Scheme 30).[69]

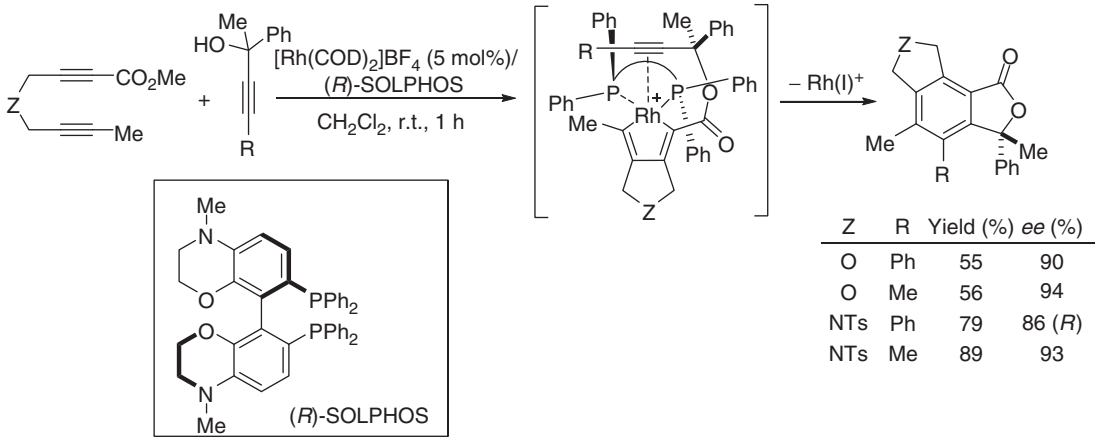
5.31.3.2.2 Domino reactions. Combining the [2 + 2 + 2] cycloaddition with other transformations

Domino reactions are receiving huge attention in organic synthesis as they provide great molecular complexity in one step. Combination of the [2 + 2 + 2] cycloaddition with other reactions is highly desirable but has yet received scarce attention. Early examples showed reactions in which two cycloaddition reactions were performed in a single operational step. These included Pauson–Khand/[2 + 2 + 2] and [2 + 2 + 2]/Diels–Alder processes. Cyclotrimerization of alkynyl alcohols or amines with propiolates, acetylenedicarboxylates, or diynecarboxylates is a known way to produce benzolactones and benzolactam derivatives with regio- and chemoselectivity in good-to-excellent yields. In a recent work, this strategy was used to desymmetrize a double propargylic alcohol on reaction with a diyne ester under rhodium catalysis (Scheme 31).[70]

Li's group has recently prepared tetrasubstituted isoindolines from three alkyne units, two aldehyde units, and a primary amine via three consecutive reactions. First, a double aldehyde–amine–alkyne coupling (A^3-coupling) gives the starting diyne which on cocycloaddition with a third alkyne unit gives the final product in a single synthetic operation. The A^3-couplings are catalyzed by copper bromide and the cycloaddition is catalyzed by Wilkinson's catalyst but both catalytic systems are present in the reaction from the beginning (Scheme 32).[71]

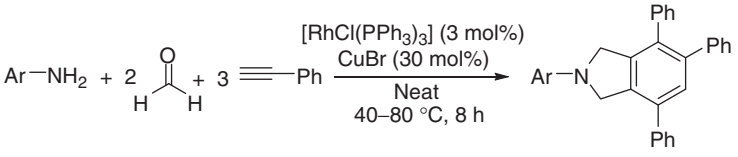


Scheme 30



Z	R	Yield (%)	*ee* (%)
O	Ph	55	90
O	Me	56	94
NTs	Ph	79	86 (*R*)
NTs	Me	89	93

Scheme 31



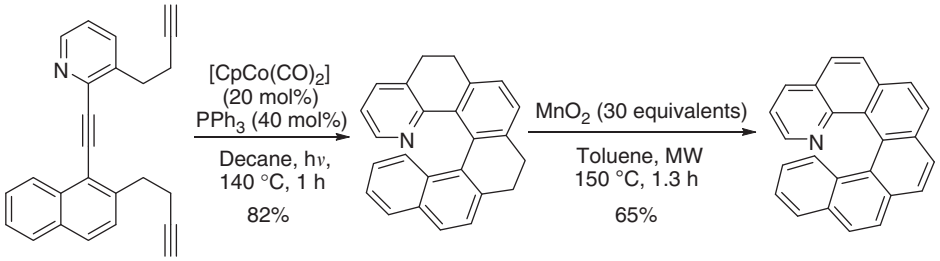
Ar	Yield (%)
Ph	69
4-$CF_3C_6H_4$	58
3,4-$Cl_2C_6H_3$	57
4-$OMeC_6H_4$	24
3-MeC_6H_4	51
4-MeC_6H_4	13
4-ClC_6H_4	78
4-IC_6H_4	76
4-PhC_6H_4	69
3-FC_6H_4	70
3-ClC_6H_4	65

Scheme 32

5.31.3.2.3 Asymmetric crossed cyclotrimerization reactions. Synthesis of axially chiral helicenes

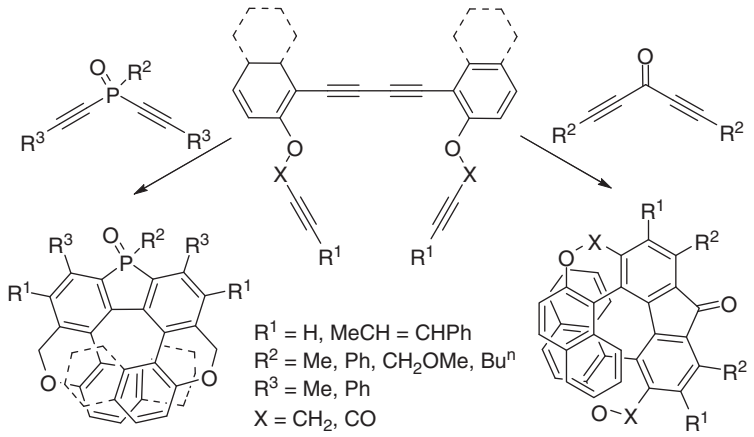
Stary and coworkers were the first to use a chiral cobalt complex-catalyzed intramolecular cycloaddition of a triyne, to generate helical chirality. In a recent contribution, they improved the experimental procedure: after the cyclotrimerization of a triyne they assisted the aromatization of the second ring constructed with MWs, resulting in a practical synthesis of racemic diaza[5]helicene

and aza[6]helicenes which were resolved (Scheme 33).[72] Previously, numerous angular [*N*]phenylenes were constructed from the intramolecular version of the cotrimerization of alkynes. In addition to [4] and [5]phenylenes, helical [7], [8], and [9]phenylenes (heliphenes) have been obtained via cobalt-mediated multiple cycloisomerization of polyynes in racemic form, which could be resolved.[73]



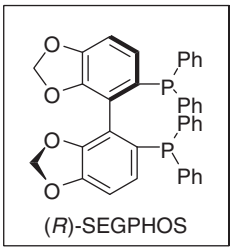
Scheme 33

Other groups described the direct syntheses of enantio-enriched mixtures of chiral helicenes using iridium/BINAP and palladium/BINAP complexes. Tanaka's group has recently synthesized benzopyrano- and naphthopyrano-fused helical phosphafluorenes by the rhodium-catalyzed enantioselective double [2 + 2 + 2] cycloaddition of dialkynyl phosphorus compounds with phenol- or naphthol-linked tetraynes. These helical structures bear interesting photochemical and photophysical properties (Scheme 34).[74]



Conditions: $[Rh(COD)_2]BF_4$ (10–40 mol%)/chiral biaryl bisphosphine, CH_2Cl_2, r.t. (Ref. 74a)

X	R^1	R^2	Ligand	Yield (%)	(*ee* %)
CH_2	Me	Me	(*R*)-SEGPHOS	56	47
CH_2	Me	Bu^n	(*R*)-SEGPHOS	40	39
CH_2	Me	Ph	(*R*)-H_8-BINAP	53	18
CH_2	Me	CH_2OMe	(*R*)-SEGPHOS	26	26
CH_2	Me	CH_2OMe	(*R*)-H_8-BINAP	56	10



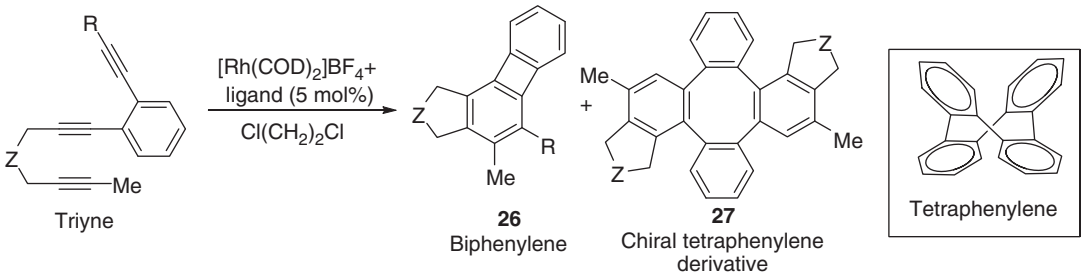
(*R*)-SEGPHOS

Scheme 34

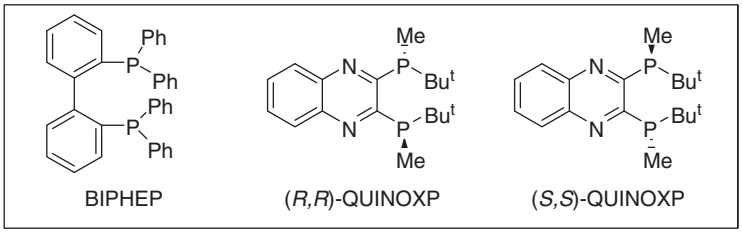
Tetraphenylene is a saddle-shaped molecule, wherein four benzene rings are *ortho* annulated to construct an eight-membered ring system. If the benzene rings have substituents, due to the D_{2d} point symmetry, the molecule becomes chiral because of a high barrier to inversion. Dimerization of triynes, possessing a phenylene-bridged 1,5-diyne moiety, by consecutive inter- and intramolecular cycloadditions was used to access chiral tetraphenylenes with high *ee* (Scheme 35).[75]

5.31.3.2.4 Axial chirality. Atropisomeric compounds

Bipyridine *N*,*N*′-dioxides, biaryl diphosphines, *N*,*N*-dialkylbenzamides, and other biaryls are known to exist as atropisomers due to the high rotational barrier around the aryl–aryl or aryl–carbonyl single bonds. Their role as chiral reagents has prompted



R	Z	Ligand	Temperature (°C)	Time (h)	Yield **26** (%)	Yield **27** (%)
Bu^n	NTs	BINAP	40	2	89	–
H	NTs	BINAP	r.t.	1	20	37
H	NTs	BIPHEP	r.t.	2	–	72
H	$C(CO_2Me)_2$	BIPHEP	60	2	–	92
H	O	BIPHEP	r.t.	4	–	93
H	NTs	(*R*,*R*)-QUINOXP	Reflux	6	–	65 (*ee* 88%)
H	NTs	(*S*,*S*)-QUINOXP	Reflux	6	–	65 (*ee* – 87%)



Scheme 35

organic chemists to explore their asymmetric synthesis but a straightforward catalytic enantioselective method remained elusive until the development of metal-catalyzed cycloaddition reactions such as the [2 + 2 + 2] cyclotrimerization. In 2004, the groups of Heller, Shibata, and Tanaka independently reported enantioselective [2 + 2 + 2] cycloadditions using different transition metal catalysts in succession, where axial chirality was generated along with benzannulation. During their work on the asymmetric Pauson–Khand reaction with chiral iridium complexes, Shibata's group observed the formation of [2 + 2 + 2] cycloaddition subproducts. This result prompted them to develop new inter- and intramolecular enantioselective [2 + 2 + 2] cycloadditions of alkynes for the generation of axial chirality. Scheme 36 shows some examples from this group.[76]

Tanaka's group reported the enantioselective synthesis of different axially chiral compounds like anilides, biphenyls, *N*-aryl-2-pyridones, and biaryl diphosphonates by cationic rhodium(I)/modified-BINAP-catalyzed [2 + 2 + 2] cycloadditions. In one of their most recent contributions they disclosed the catalytic enantioselective construction of aryl-carbonyl axial chirality of *N*,*N*-dialkylbenzamides in high yields and outstanding *ee*'s (Scheme 37).[77]

As part of their extensive studies on the chemistry of ynamides, the group of Hsung has succeeded in controlling both the C–C and C–N axial chirality in the synthesis of chiral *N*,*O*-biaryls and chiral anilides from achiral conjugated aryl ynamides. They used rhodium(I)-xylyl-BINAP catalysis, reaching good-to-excellent *ee*'s (Scheme 38).[78]

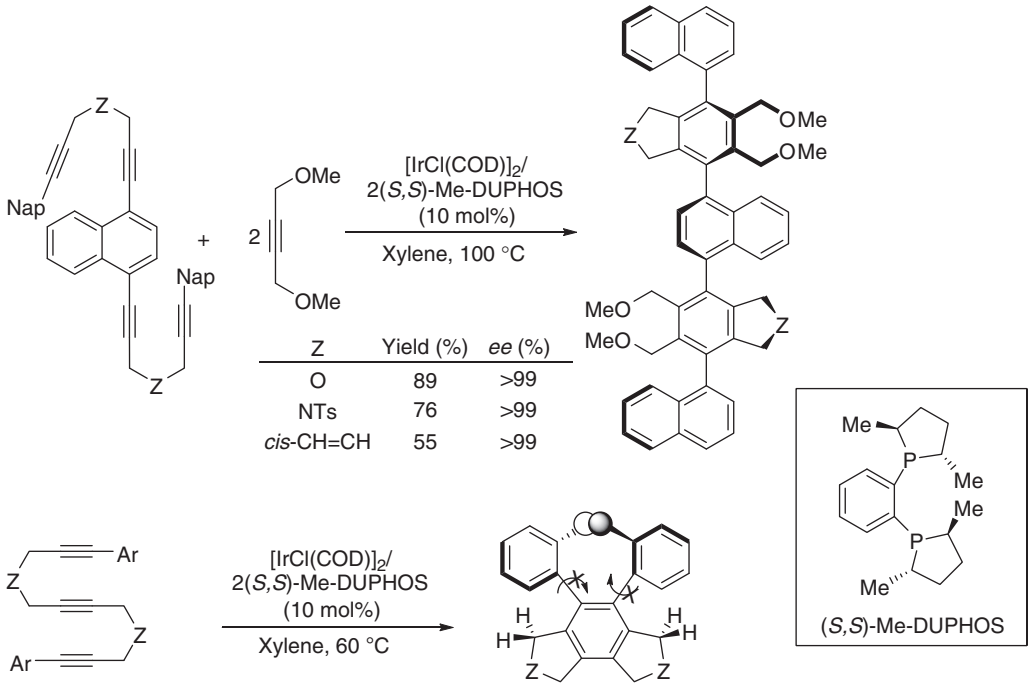
5.31.3.2.5 Synthesis of planar chiral compounds

Planar chiral *ansa*-cyclophanes are beautifully shaped compounds with potential utility in the area of asymmetric synthesis, host–guest chemistry, and material science. The groups of Tanaka and Shibata have independently disclosed catalytic enantioselective syntheses of planar-chiral metacyclophanes via cationic rhodium(I) complex-catalyzed cyclotrimerization (Scheme 39).[79]

5.31.3.2.6 Synthetic applications and natural product syntheses

Very recently it was demonstrated that the [2 + 2 + 2] cycloaddition reaction is usable for polymerization. Thus, a triyne monomer reacted under dipimp/$CoCl_2$ $6H_2O$/Zn catalysis yielding linear polymers involving a selective cross-cyclotrimerization reaction that occurred in a chain growth manner (Scheme 40).[80]

Cyclotrimerization of alkynes can be used for the synthesis of *C*-arylglycosides and other carbohydrate derivatives. This class of compounds is of considerable interest for pharmaceutical reasons, because of their stability toward enzymatic and chemical hydrolysis. Thus, *C*-aryl-deoxy-ribosides, 6-arylpurine ribonucleosides, isochroman-containing nucleosides, or spirocyclic *C*-arylribosides have been prepared through [2 + 2 + 2] cycloadditions by different groups. Figure 7 shows the structures of these potentially active compounds.[81]



Z	Yield (%)	*ee* (%)
O	89	>99
NTs	76	>99
cis-CH=CH	55	>99

Ar	Z	Yield (%)	*dl*/*meso*	*ee* (%)
1-Naphthyl	O	82	5/1	90
1-Anthracenyl	O	68	>20/1	97
2-Cl-4-$NO_2C_6H_3$	O	90	12/1	90
4-MeO-1-naphthyl	NTs	89	2/1	~ 95

Scheme 36

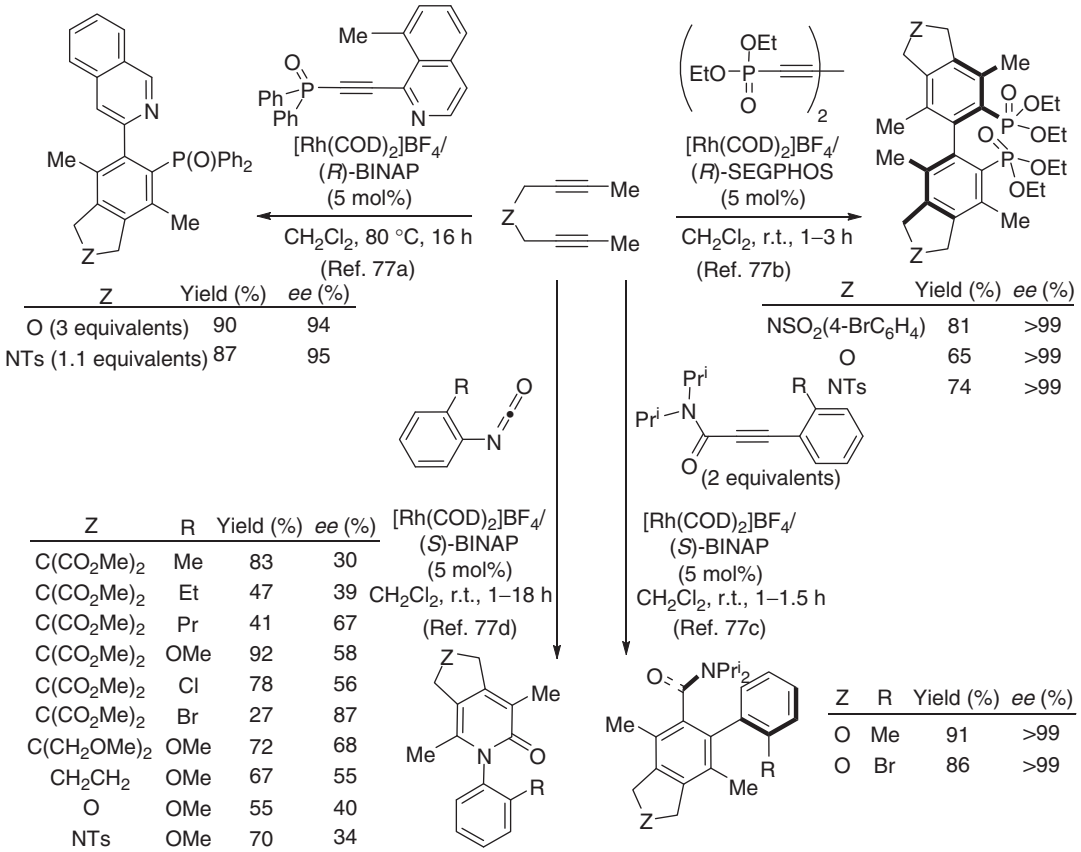
There has been a recent increase in the use of the [2 + 2 + 2] cycloaddition for the synthesis of natural products as densely functionalized aromatic rings are common in natural products and in closely related bioactive compounds. Figure 8 shows some natural products in which the [2 + 2 + 2] cycloaddition reaction was used as the key step for their syntheses.[82] In general, elaboration of a functionalized triyne and cyclization is the preferred strategy, albeit different catalysts are used. Thus, various members of the alcyopterosin family of sesquiterpenes were constructed from enantiopure triynes under rhodium catalysis.[82a] An MW-promoted Co- or Rh-catalyzed intramolecular [2 + 2 + 2] cycloaddition served for the construction of ring C of the core of colchicine. 6-Oxa-allocolchicinoids were efficiently synthesized and were found to exhibit significant and selective apoptosis-inducing activities against B-type human lymphoma line tumor cells.[82b] Cobalt-mediated cyclization of a triyne was the strategy of choice for the synthesis of a series of angucyclinone antibiotics.[82c] Ruthenium catalysis was efficient in the synthesis of terpene natural product cryptoacetalide which was obtained in 12 steps in 26% overall yield.[82d] Finally, a crossed cyclotrimerization catalyzed by ruthenium was used for the synthesis of various cannabinoids.[82e]

A recent contribution from Nicolaou's group accounts for the total synthesis of the highly oxygenated, marine-derived, natural product sporolide B. The convergent strategy involved a ruthenium-catalyzed [2 + 2 + 2] cycloaddition to assemble the indene structural motif. Once this complex intermediate was constructed, a thermally induced Diels–Alder-type reaction formed the macrocycle (Scheme 41).[83]

5.31.3.3 Double Bonds as Partners of the [2 + 2 + 2] Cycloaddition Reaction. Synthesis of Cyclohexadienes and Cyclohexenes

The metal-catalyzed [2 + 2 + 2] cycloadditions between alkynes and alkenes or allenes to give 1,3-cyclohexadienes or cyclohexenes, are less developed but have triggered much attention in the very recent years. In principle, the field opens a great variety of possibilities which not all are feasible when using three triple bonds. These include asymmetric induction, use of allenes, enynes, endiynes, etc. Scheme 42 shows a summary of the different versions of a [2 + 2 + 2] cycloaddition between triple- and double bonds.

One of the first processes widely developed was the Vollhardt reaction consisting of a cobalt-mediated activation of double bonds that needs equimolar amounts of the metal promoter, generally cyclopentadienylcobalt carbonyl or ethene [$CpCoL_2$ (L=CO, C_2H_4)]. This group has used, among others, 'double bonds' in aromatic heterocycles such as furans, thiophenes, indoles,



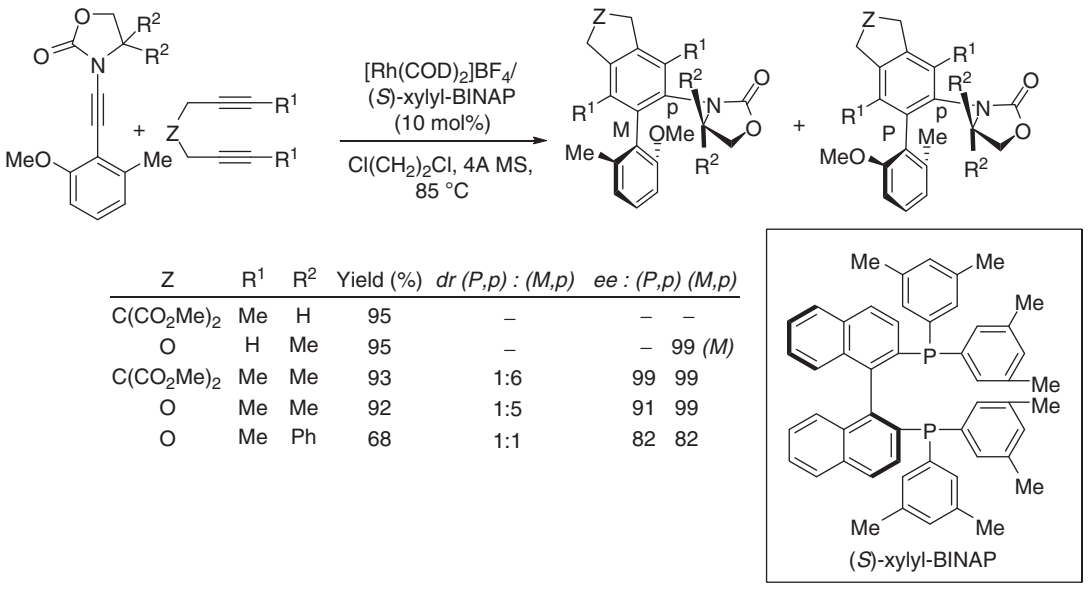
Z	Yield (%)	*ee* (%)
O (3 equivalents)	90	94
NTs (1.1 equivalents)	87	95

Z	Yield (%)	*ee* (%)
$NSO_2(4\text{-}BrC_6H_4)$	81	>99
O	65	>99
NTs	74	>99

Z	R	Yield (%)	*ee* (%)
$C(CO_2Me)_2$	Me	83	30
$C(CO_2Me)_2$	Et	47	39
$C(CO_2Me)_2$	Pr	41	67
$C(CO_2Me)_2$	OMe	92	58
$C(CO_2Me)_2$	Cl	78	56
$C(CO_2Me)_2$	Br	27	87
$C(CH_2OMe)_2$	OMe	72	68
CH_2CH_2	OMe	67	55
O	OMe	55	40
NTs	OMe	70	34

Z	R	Yield (%)	*ee* (%)
O	Me	91	>99
O	Br	86	>99

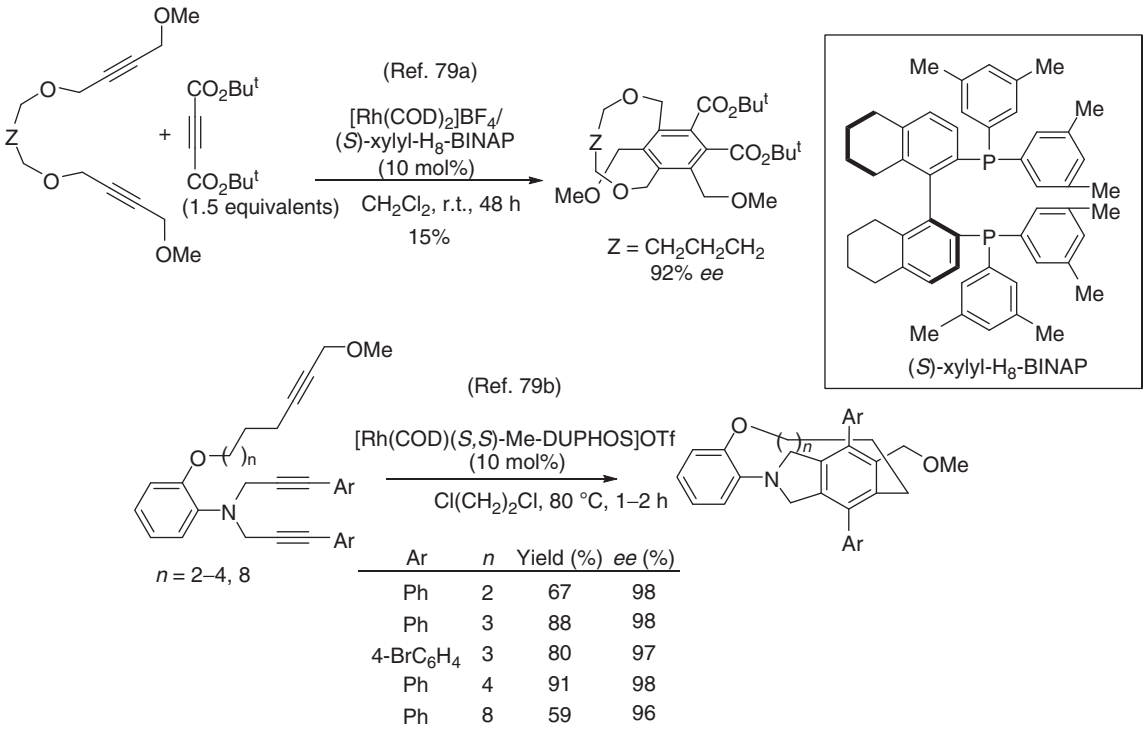
Scheme 37



Z	R^1	R^2	Yield (%)	*dr (P,p) : (M,p)*	*ee : (P,p)*	*(M,p)*
$C(CO_2Me)_2$	Me	H	95	–	–	–
O	H	Me	95	–	–	99 *(M)*
$C(CO_2Me)_2$	Me	Me	93	1:6	99	99
O	Me	Me	92	1:5	91	99
O	Me	Ph	68	1:1	82	82

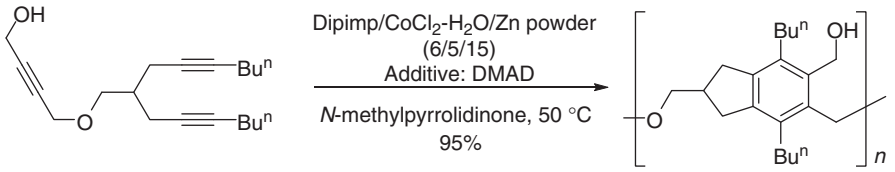
Scheme 38

pyrroles, imidazoles, pyridones, and pyrimidines in [2 + 2 + 2] cycloadditions with alkynes. Remarkably, even though resonance stabilized, these systems participate readily in such cyclizations giving rise to fused dihydroheteroaromatics. In one of their latest contributions they have developed new reaction conditions with cobalt(II) iodide (CoI_2), manganese and an *N*-heterocyclic carbene (IPr) generated *in situ* from the corresponding imidazolium salt and butyllithium. This avoids the former use of the air



Ar	n	Yield (%)	ee (%)
Ph	2	67	98
Ph	3	88	98
4-BrC6H4	3	80	97
Ph	4	91	98
Ph	8	59	96

Scheme 39



Dipimp: 2-(2,6-diisopropylphenyl)iminomethylpyridine

Scheme 40

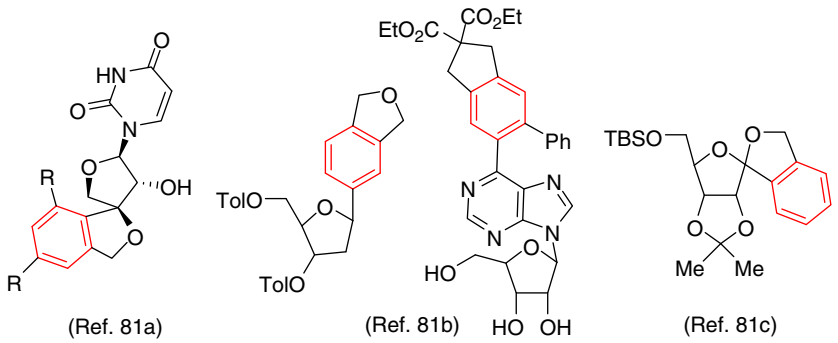


Figure 7 Structures of potentially active *C*-arylglycosides and analogues synthesized using a [2 + 2 + 2] cycloaddition as the key step.

sensitive catalysts. The *N*-heterocyclic carbene can be used catalytically, which is a significant improvement compared with the corresponding phosphine-based system which requires an excess of ligand. Enediynes underwent intramolecular [2 + 2 + 2] under these conditions giving selectively polycyclic cyclohexadienes (Scheme 43).[14c,45b]

Focusing on catalytic protocols, several metal complexes of ruthenium, iridium, nickel, niobium, and rhodium are able to mediate these kinds of transformations. As commented above, [$NbCl_3$(DME)] (DME = dimethoxyethane) was used to effect intermolecular [2 + 2 + 2] cycloadditions of alkynes and α,ω-dienes or alkenes giving 1,3-cyclohexadienes with high chemo- and

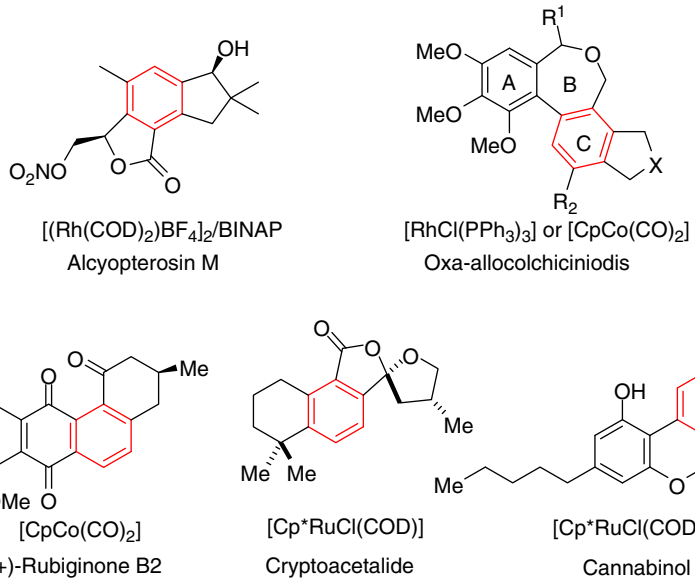
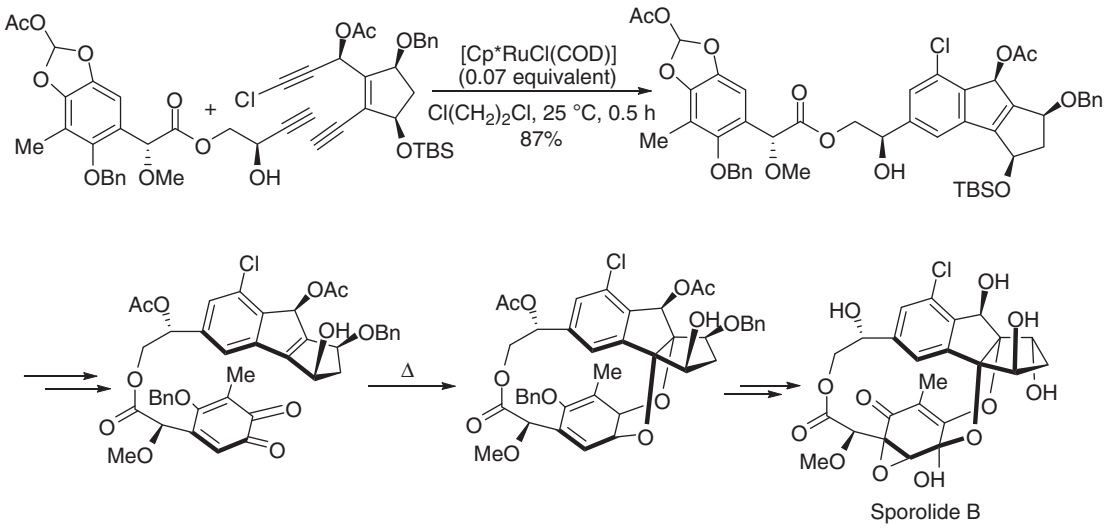


Figure 8 Natural products synthesized using the [2 + 2 + 2] cycloaddition reaction as the key step.

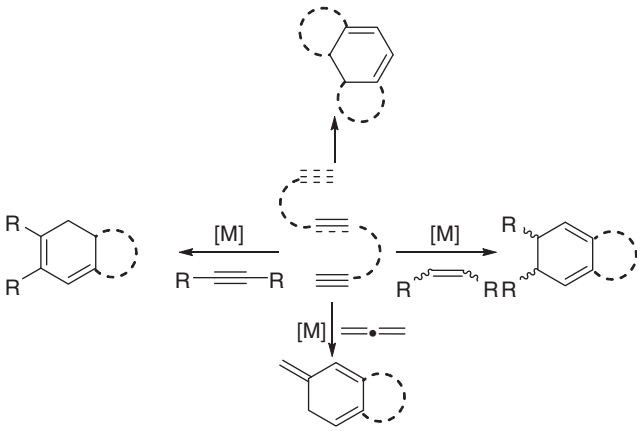


Scheme 41

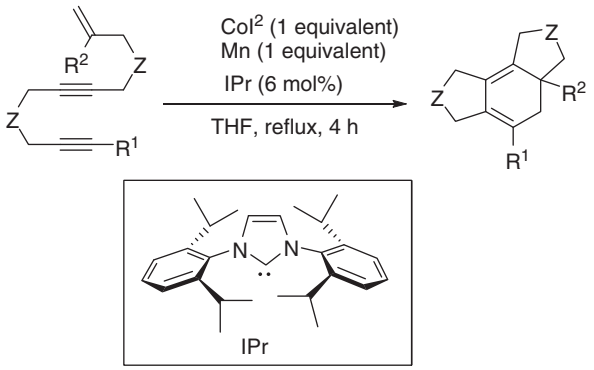
regioselectivity (Scheme 3).[33] A remarkable three-in-one reaction was reported recently using nickel catalysis. Readily available arynes, activated alkenes, and alkynes gave a series of substituted 1,2-dihydronaphthalenes in moderate to very good yields with excellent chemo- and regioselectivity. The authors propose a reaction course starting with an oxidative coupling of benzyne and alkene on Ni to form a nickelacycle, which is probably stabilized by an intramolecular coordination of the heteroatom. Subsequent insertion of the alkyne into the Ni-C(aryl) bond gives a seven-membered intermediate which suffers reductive elimination to yield the final product (Scheme 44).[84]

With regard to bimolecular reactions, ruthenium (II) has been used for the reaction of 1,6-diynes with alkenes. The [2 + 2 + 2] cycloaddition was found to compete with double cyclopropanation processes which showcased the double carbenic nature of the metallacyclopentadiene intermediate. The nature of the catalyst was crucial to direct the reaction to either pathway (Scheme 45).[85]

A recent study focused on the regio- and stereochemical outcome of the reaction which depends on the substitution of the 1,6-diyne and the nature of the alkene. When acyclic alkenes were used, a cascade process took place that represents a formal Ru(II)-catalyzed [2 + 2 + 2] cycloaddition. Initially, a Ru-catalyzed linear coupling occurs to give open 1,3,5-trienes, which after a thermal disrotatory $6e^-$ π-electrocyclization led to the final 1,3-cyclohexadienes. In addition, new *exo*-methylene cyclohexadienes arose from a competitive reaction pathway when using electron-deficient alkenes (Scheme 46).[86]

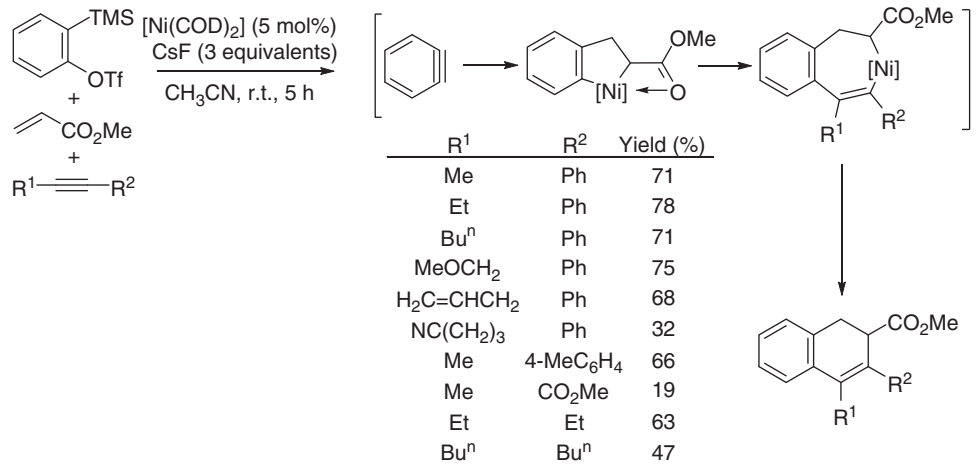


Scheme 42



Z	R^1	R^2	Yield (%)
NTs	H	H	66
O	H	H	84
O	Me	H	76
O	Ph	H	72
O	Bu^n	H	83
O	CO_2Me	H	81
O	H	Me	79
O	H	Ph	73
O	CO_2Me	Me	42
$C(CO_2Et)_2$	H	Me	54
$C(CO_2Et)_2$	H	Ph	30
$C(CO_2Et)_2$	CO_2Me	H	68
$C(CH_2OMe)_2$	H	H	64
$C(CH_2OMe)_2$	H	Me	65

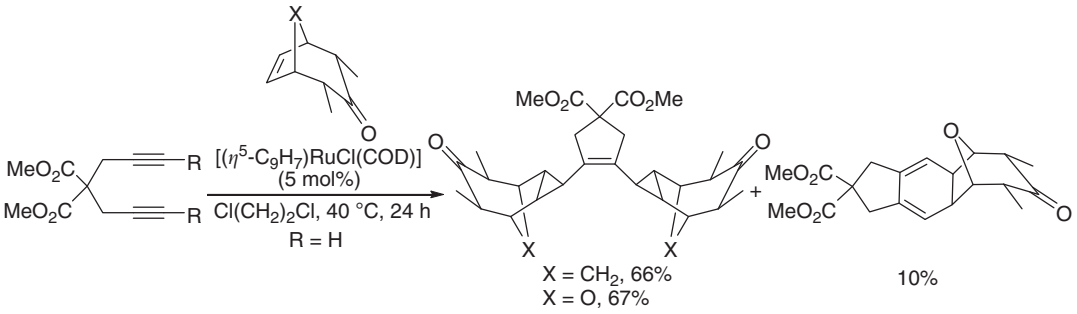
Scheme 43



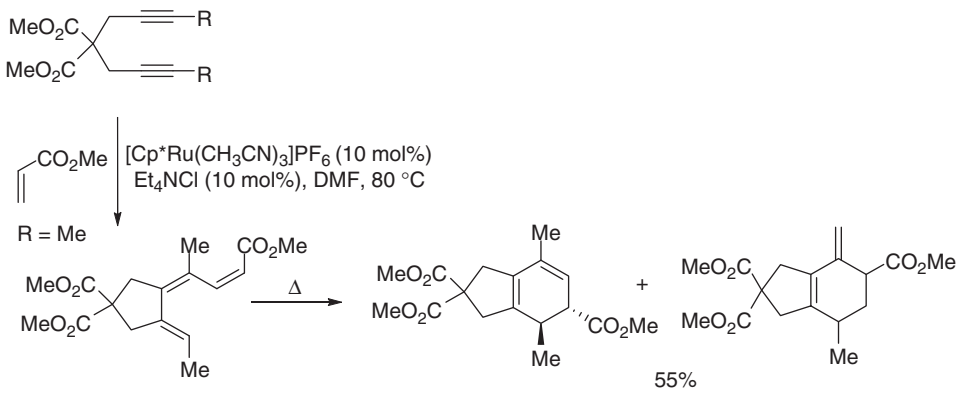
R^1	R^2	Yield (%)
Me	Ph	71
Et	Ph	78
Bu^n	Ph	71
$MeOCH_2$	Ph	75
$H_2C{=}CHCH_2$	Ph	68
$NC(CH_2)_3$	Ph	32
Me	4-MeC_6H_4	66
Me	CO_2Me	19
Et	Et	63
Bu^n	Bu^n	47

Scheme 44

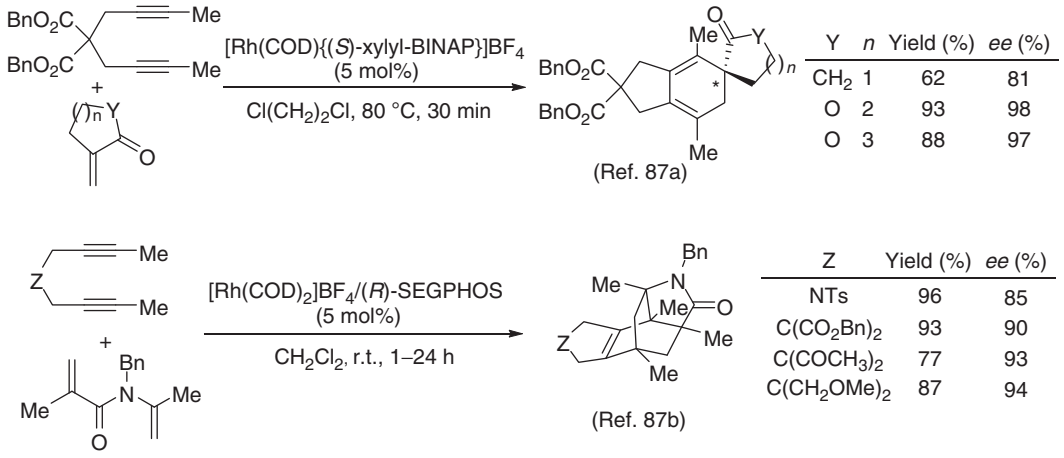
Scheme 47 shows two examples in which chiral rhodium-based catalytic systems catalyzed highly enantioselective [2 + 2 + 2] cycloaddition of diynes and alkenes. The first example shows the use of cyclic compounds with *exo*-methylene groups as a new protocol for the synthesis of chiral spirocyclic structures. Depicted below is a cascade bimolecular [2 + 2 + 2] cycloaddition/intramolecular Diels–Alder reaction using amide-linked 1,5-dienes.[87]



Scheme 45



Scheme 46

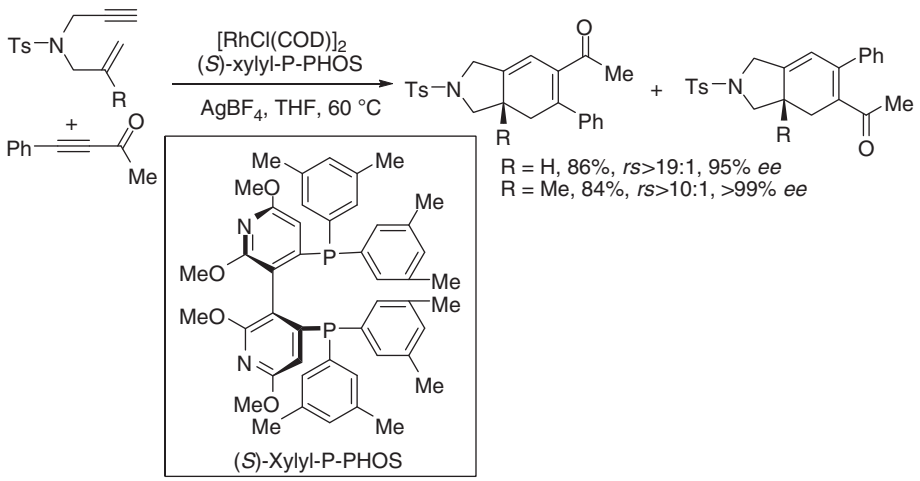


Scheme 47

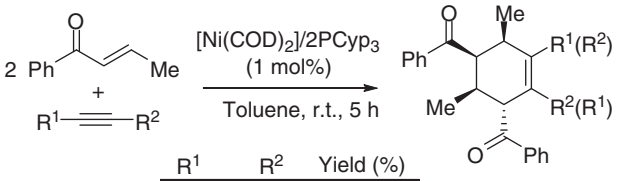
The first rhodium-catalyzed [2 + 2 + 2] carbocyclization of 1,6-enynes with alkynes was disclosed in 2005. In this reaction, specific ligands were required for obtaining excellent regio- and enantioselectivities. The methodology allowed introducing quaternary carbon stereogenic centers (Scheme 48).[88] More recently, the enyne/alkyne reactions have been catalyzed by iridium, cobalt, and nickel.[89]

Catalytic enantioselective [2 + 2 + 2] cycloadditions of one alkyne unit and two alkene units are scarce. One contribution from Ogoshi's group described a fully intermolecular [2 + 2 + 2] cycloaddition of two enones and an alkyne, a reaction that proceeded stereoselectively to give only one diastereomer (Scheme 49).[90]

Intramolecular reactions with dienynes allowed the synthesis of fused tri- and tetracyclic cyclohexenes bearing two tertiary or quaternary carbon centers in high yields with high enantio- and diastereoselectivity. Cationic rhodium(I)/(*R*)-H_8-BINAP or (*R*)-SEGPHOS complexes were used as the catalytic systems (Scheme 50).[91]

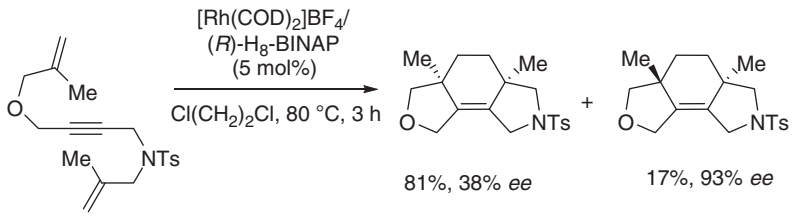


Scheme 48



R^1	R^2	Yield (%)
Me	Me	96
Et	Et	94
Ph	Ph	96
Me	Ph	97 (90/10)
Me	Pr^n	93 (68/32)

Scheme 49

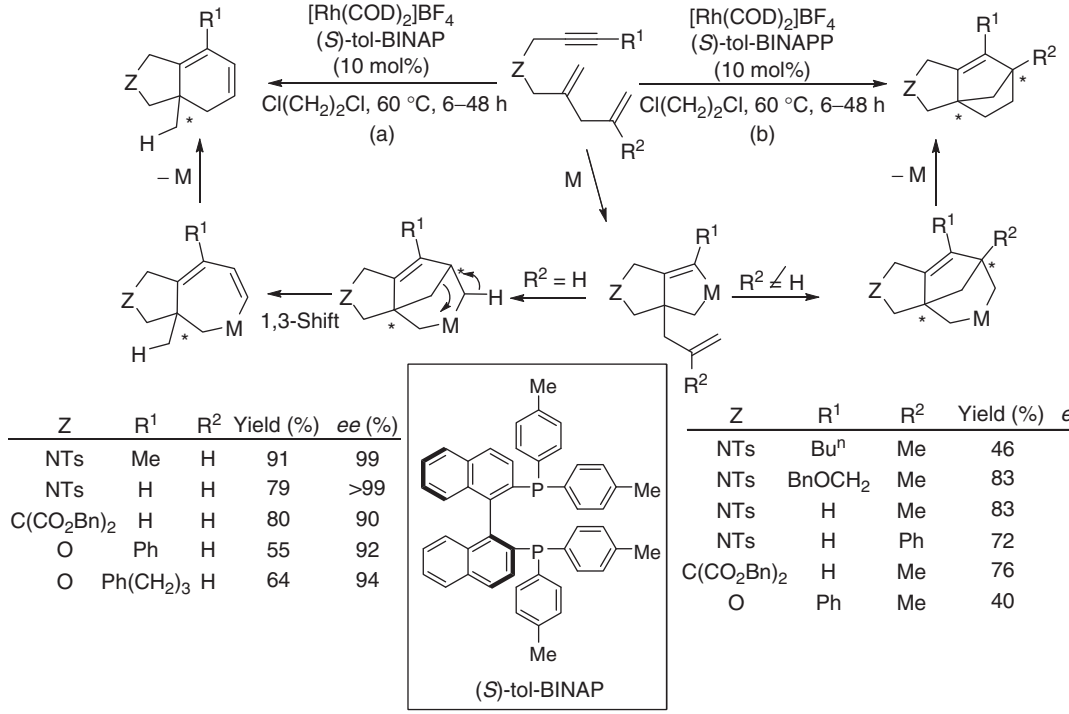


Scheme 50

The reaction of a dienyne catalyzed by rhodium gave either cyclohexadienes or strained multicyclic compounds, both with quaternary carbon stereocenters, depending on the substitution pattern of the starting dienyne (Scheme 51). After the formation of the typical metallacyclopentene an olefin insertion followed. Then, for $R^2 = H$, a 1,3-hydrogen shift accompanied by ring cleavage proceeded to provide a metallacycloheptadiene and subsequent reductive elimination gave a cyclohexa-1,3-diene (path a). On the contrary, when $R^2 \neq H$, a tricyclic compound was obtained by reductive elimination (path b).[92]

The homo-Diels–Alder (HDA) cycloaddition is described as [2 + 2 + 2] cycloaddition resulting in the formation of tetracyclic structures of considerable strain known as deltacyclanes. The use of transition metals to catalyze this reaction has been well documented, and cycloadditions involving alkynyl dienophiles have been promoted by cobalt, rhodium, and ruthenium catalysts. Examples of ruthenium-catalyzed HAD [2 + 2 + 2] cycloadditions between alkynyl phosphonates and bicyclic alkenes were recently disclosed (Scheme 52).[93]

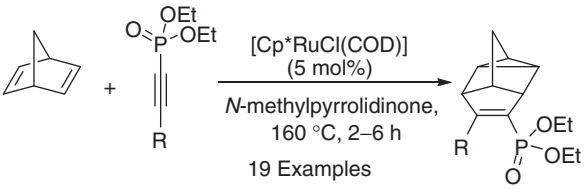
Allenes may be components in the [2 + 2 + 2] cycloaddition reaction. Examples include totally intermolecular reactions, crossed cyclizations with diynes, or reactions of allenynes with alkynes or arynes. Catalytic systems cover the general spectra for these reactions but nickel and cobalt salts are commonly used. Cheng's group has reported a highly regio- and chemoselective [2 + 2 + 2] cycloaddition of electron-deficient diynes with allenes catalyzed by the Ni(dppe)Br_2/Zn system and cycloadditions of electronically neutral 1,6-heptadiynes with allenes catalyzed by cobalt complexes leading to polysubstituted benzene derivatives



Z	R^1	R^2	Yield (%)	*ee* (%)
NTs	Me	H	91	99
NTs	H	H	79	>99
$C(CO_2Bn)_2$	H	H	80	90
O	Ph	H	55	92
O	$Ph(CH_2)_3$	H	64	94

Z	R^1	R^2	Yield (%)	*ee* (%)
NTs	Bu^n	Me	46	>99
NTs	$BnOCH_2$	Me	83	88
NTs	H	Me	83	93
NTs	H	Ph	72	91
$C(CO_2Bn)_2$	H	Me	76	93
O	Ph	Me	40	92

Scheme 51

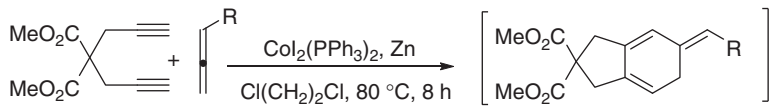


R	Yield (%)
$2\text{-}MeC_6H_4$	71
$3\text{-}MeOC_6H_4$	74
$4\text{-}CF_3C_6H_4$	57
3-Thiophene	48
Bu^n	64

R=Ph, $4\text{-}MeC_6H_4$, $3\text{-}MeC_6H_4$, $2\text{-}MeC_6H_4$, $4\text{-}MeOC_6H_4$, $3\text{-}MeOC_6H_4$, $2\text{-}MeOC_6H_4$, $4\text{-}CF_3C_6H_4$, $3\text{-}CF_3C_6H_4$, $2\text{-}CF_3C_6H_4$, 3-thiophene, H, Bu^n, cyclohexyl

Scheme 52

in good to excellent yields (Scheme 53). However, they disclosed a cocyclotrimerization of arynes with allenes catalyzed by nickel complexes.[94]

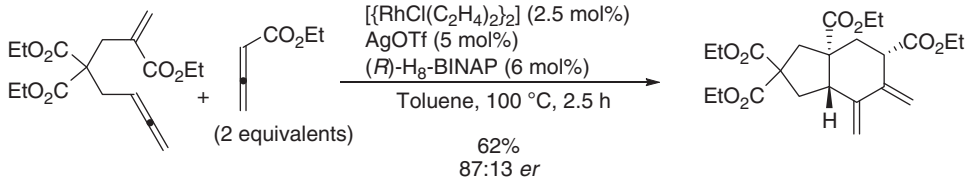


R	Yield (%)
Cyclohexyl	90
Cyclopentyl	71
Bu^n	88
Bu^t	88
Ph	62

Scheme 53

There is an outstanding contribution which shows one of the first examples of [2 + 2 + 2] cycloadditions with three double bonds, one of them belonging to an allene system. Thus, by means of rhodium(I)-catalysis, simple alkenes and allenes delivered

carbocycles with construction of up to four contiguous stereogenic centers, including quaternary stereocenters, in a single synthetic step albeit with moderate enantiomeric ratios (Scheme 54).[95]



Scheme 54

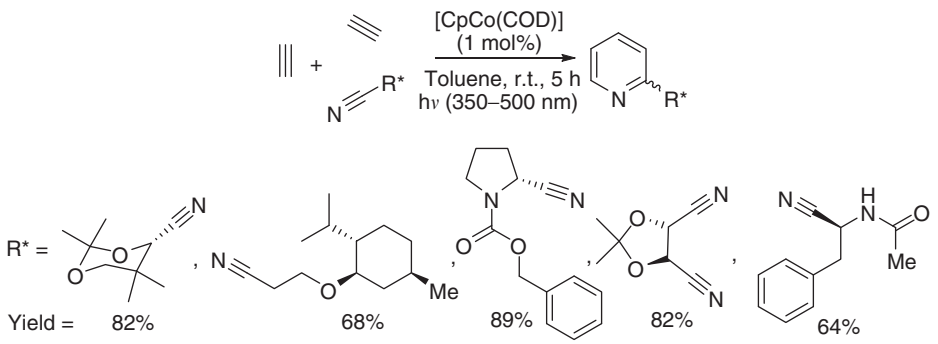
5.31.4 Synthesis of Nitrogen-Containing Six-Membered Heterocycles

The transition metal-mediated cyclocotrimerization of alkynes with carbon–heteroatom multiple bonds was first pioneered by Wakatsuki and Yamazaki followed by Bönnemann.[96] They disclosed stoichiometric reactions of cobaltacyclopentadienes with nitriles, carbon disulfide, and methyl isothiocyanate, leading to pyridines, dithiopyrones, and thiopyridones, respectively. Afterwards Vollhardt's group reported intramolecular cycloadditions of diynes and alkynenitriles leading to pyridines, mediated by cobalt. These early contributions were followed by works on new mild and catalytic reaction conditions using other metals and by asymmetric reactions mainly en route to axially chiral products.

5.31.4.1 Synthesis of Pyridines

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction constitutes an important tool for the synthesis of pyridines. *De novo* construction of pyridine ring systems has evolved in recent years from the intramolecular assembly of pyridines by reaction of diynes and oligoynes with nitriles to some completely intermolecular reactions between acetylenes and nitriles and reactions with alkynenitriles and alkynes. The reaction tolerates a wide variety of functional groups in the substrates, giving access to densely functionalized pyridinic products.[96]

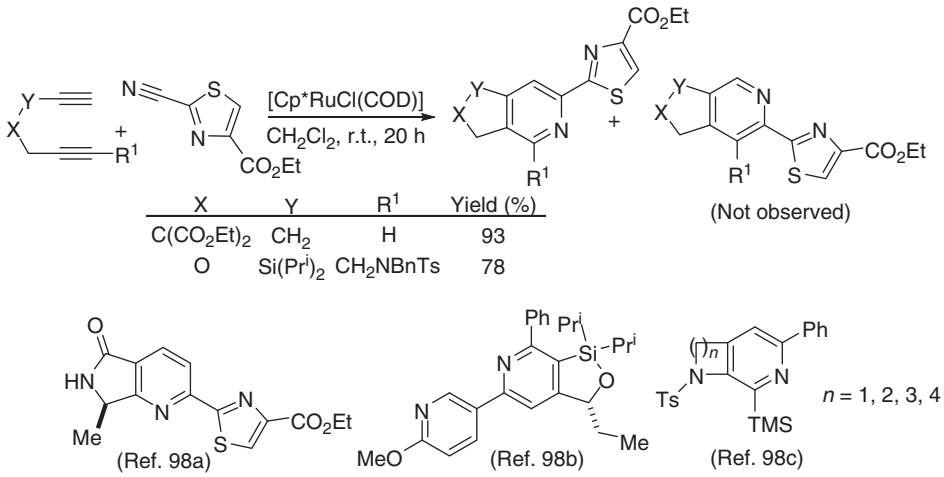
Cobalt complexes of the type [$CpCoL_2$] (L = CO, PR_3, olefin) have been extensively studied as catalysts in the [2 + 2 + 2] cycloadditions of alkynes with nitriles to afford pyridines. Among the scarce examples of totally intermolecular cycloadditions of a nitrile and two alkynes, the authors can remark the racemization-free conversion of chiral nitriles into pyridine derivatives disclosed by the group of Heller. The cobalt(I)-complex [CpCo(COD)] was the catalyst of choice and the reaction could be performed in organic solvents (toluene or hexane) or even in water. A broad variety of functionalized (e.g., ester, ketones, amines) chiral mono- as well as dinitriles were used as substrates for the reaction with acetylene or internal alkynes (Scheme 55).[97]



Scheme 55

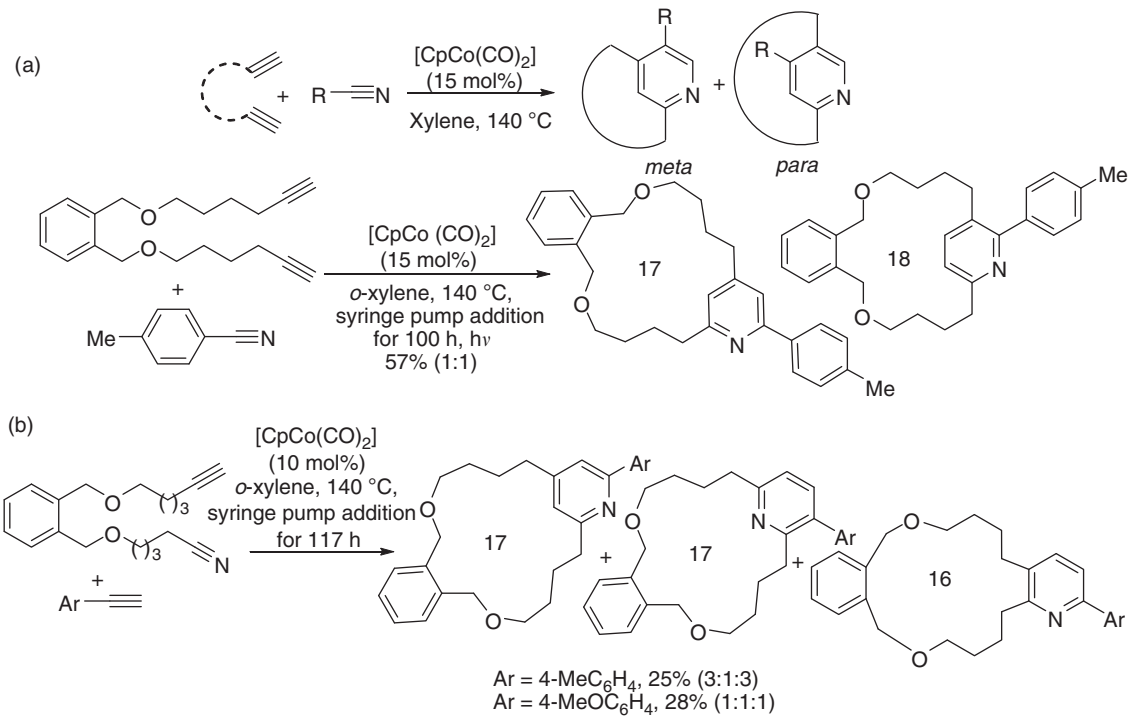
Most syntheses of pyridines use diynes as starting materials. Terminal and internal diynes react with various types of nitriles. Nonsymmetric diynes give selectively the pyridine with the nitrogen adjacent to the more bulky substituent. This predictable regioselectivity has been used in synthetic applications as shown in Scheme 56. Thus, under cobalt catalysis, (1) a part of the natural product cyclothiazomycin, (2) an intermediate en route to bioactive neurite outgrowth inhibitors, and (3) various bicyclic aminopyridines were regioselectively synthesized.[98]

Diynes with different tether lengths are reactive toward nitriles. In this sense, long-chain α,ω-diynes are known to react with acetylene dicarboxylates, yielding pyridine-containing *ansa*-macrocycles and cyclophanes. The reaction has been catalyzed with



Scheme 56

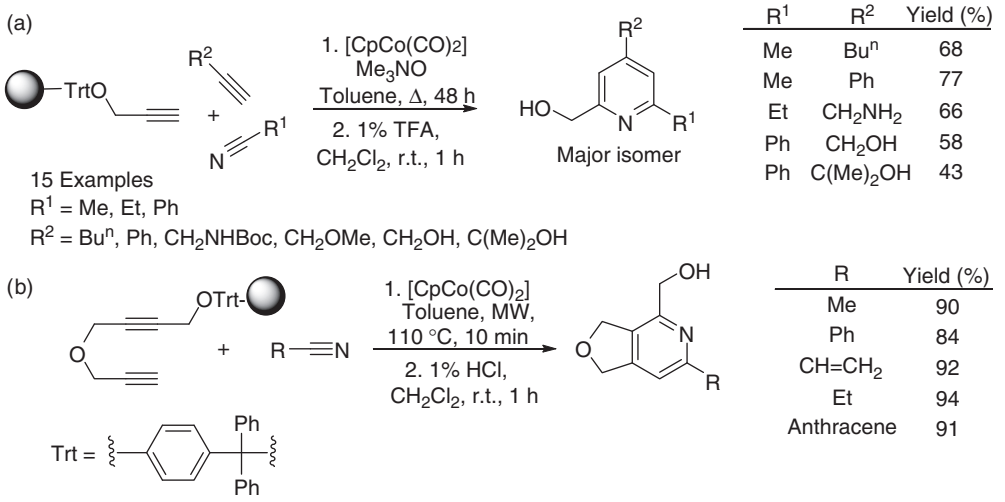
$[CpCo(CO)_2]$. These type of macrocyclic pyridines were also obtained on reaction of ω-alkynyl-α-nitriles with alkynes (Scheme 57).[99]



Scheme 57

If conducted on a solid-support, [2 + 2 + 2] cycloaddition reactions enable rapid combinatorial access to diverse sets of carbo- and heterocyclic small-molecule arrays, solving partly the regio- and chemoselectivity problems. After the first work by Sun's group on the synthesis of isoindolines, Deiters' group has investigated different immobilization strategies, different diyne precursors, and a variety of functionalized alkyne and nitrile reaction partners.[100] A totally intermolecular method was disclosed first where an alkyne was anchored to the resin and reacted with a nitrile and a second alkyne (Scheme 58a).[100a] Afterwards, isoindoline, phthalan, pyridines, triphenylenes, and indanes were assembled in good-to-excellent yields using cobalt-catalysis under MW irradiation. In this second approach different diynes were anchored to a solid support (Scheme 58b).[100b]

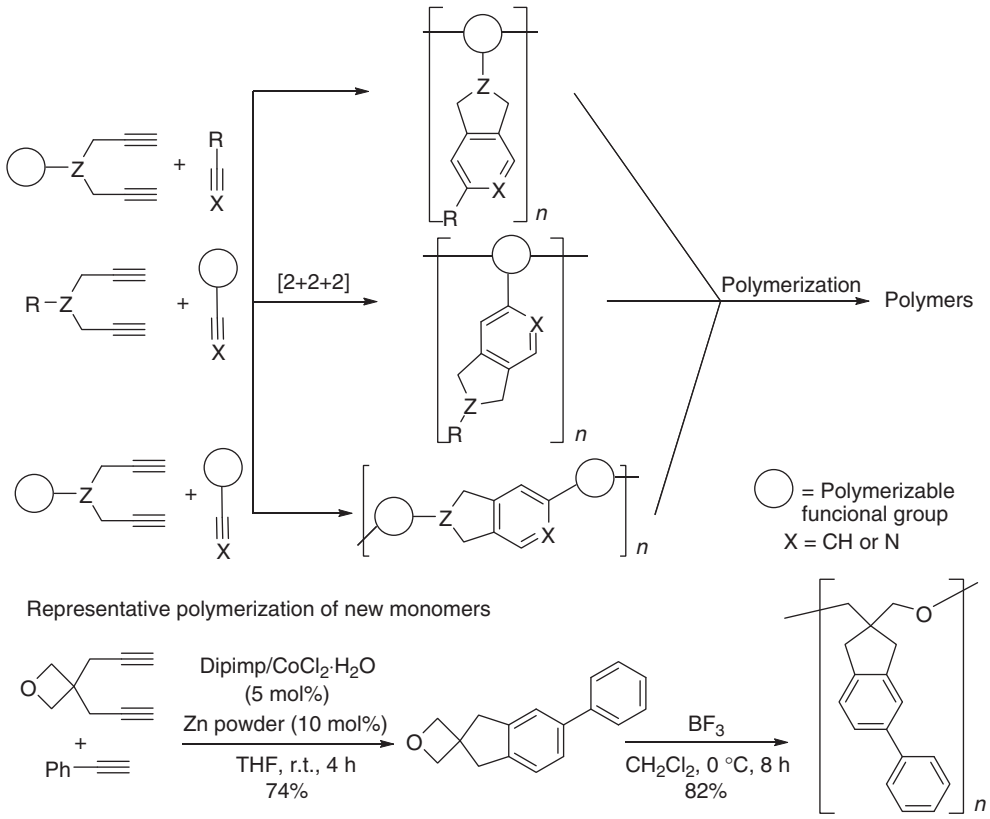
Okamoto's group obtained a variety of polymerizable molecules having a 2,3-dihydro-1*H*-indene or 6,7-dihydro-5*H*-cyclopenta[*c*]pyridine core structures using [2 + 2 + 2] cycloaddition reactions. Some of the monomers were then polymerized in the presence of BF_3 as the catalyst (Scheme 59).[101]



R^1	R^2	Yield (%)
Me	Bu^n	68
Me	Ph	77
Et	CH_2NH_2	66
Ph	CH_2OH	58
Ph	$C(Me)_2OH$	43

R	Yield (%)
Me	90
Ph	84
$CH=CH_2$	92
Et	94
Anthracene	91

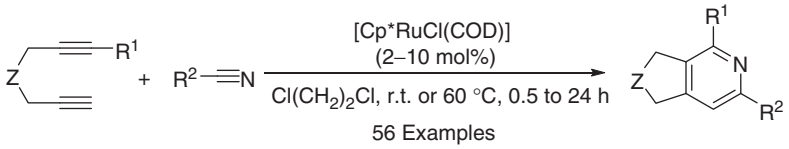
Scheme 58



Scheme 59

In addition to cobalt catalysis, ruthenium, rhodium, iron, and nickel-catalyzed syntheses of pyridines have been published. In particular, dicyanides, cyanamides, and halonitriles exhibited exceptionally high reactivity toward the ruthenium-catalyzed cycloaddition with 1,6-diynes leading to bicyclic pyridines under mild conditions. This especially good performance, which is in contrast to the behavior of benzonitriles or simple aliphatic nitriles, is thought to be due to an assisting effect of the additional functional group. Methoxy and methylthio groups also behave as assisting groups (Scheme 60).[25,26]

Production of central chirality was achieved in a cationic rhodium(I)/modified-BINAP complex-catalyzed reaction used to generate spirobipyridine ligands through an intramolecular double [2 + 2 + 2] cycloaddition of bis-diynenitriles (Scheme 61).[65c]

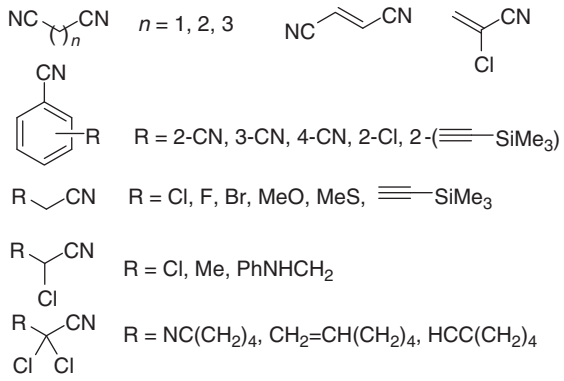


Diynes

Z = $C(CO_2Me)_2$, CH_2, NTs, O, S, CH_2CH_2

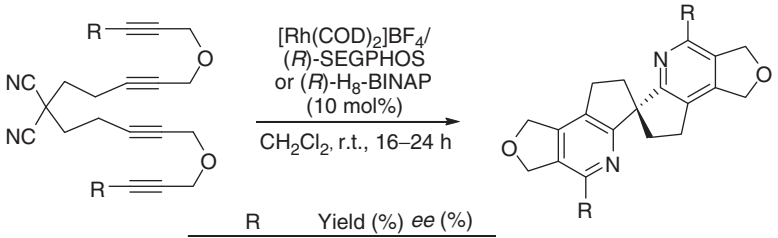
R^1 = H, Me, Ph, $SiMe_3$

Nitriles



Z	R^1	R^2	Yield (%)
$C(CO_2Me)_2$	H	CH_2CN	92
$C(CO_2Me)_2$	$SiMe_3$	CH_2CN	92
$C(CO_2Me)_2$	Ph	CH_2CN	78
$C(CO_2Me)_2$	H	CH_2Cl	93
$C(CO_2Me)_2$	H	$CHCl_2$	91
CH_2	H	CH_2CN	77
NTs	Me	CH_2CN	95
O	Me	CH_2Cl	84
S	H	CH_2Cl	61

Scheme 60



R	Yield (%)	*ee* (%)
Ph	99	64
4-ClC_6H_4	89	71 (*S*)
4-$MeOC_6H_4$	85	62
Me	98	49
H	70	47

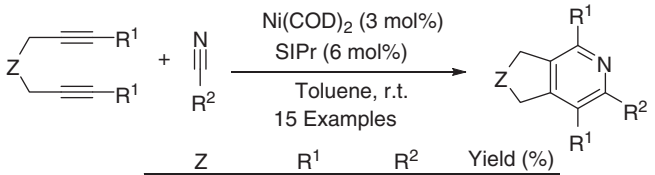
Scheme 61

A combination of a nickel(0) precursor and an imidazolylidene ligand has been described as an efficient catalyst for the preparation of a wide range of pyridines from α,ω-diynes and nitriles. With this methodology, as with other catalytic systems, cyanamides were found to give excellent results (Scheme 62).[23]

In addition, iron complexes catalyzed the synthesis of pyridines. Cycloaddition of alkynenitriles and alkynes proceeded with high yields, as were some totally intramolecular examples in which diyne-nitriles were cycloisomerized (Scheme 63).[34]

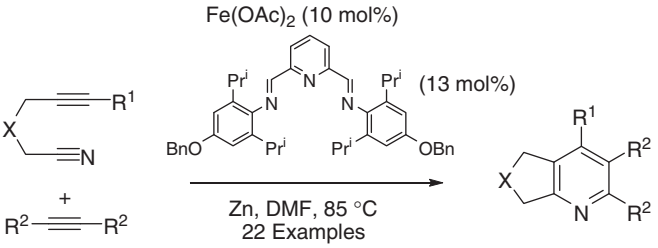
One interesting and recent example of totally intramolecular reaction described the synthesis of tricyclic fused 3-aminopyridines through a very efficient cobalt-catalyzed [2 + 2 + 2] cycloaddition of a polyunsaturated compound displaying an ynamide, an alkyne, and a nitrile functionality. Particularly interesting was the synthesis with moderate yield of a stable 1,2-dihydro-1*H*-azeto[3,4-c]pyridine. This synthesis, which remarkably formed a four-membered ring, required heating, with $[CpCo(C_2H_4)_2]$ as the catalyst, which was added in two portions every 3 h (Scheme 64).[102]

Indole-containing alkaloids are a challenge in organic synthesis due to their complex and highly connected polycyclic structures. The presence of aromatic rings in their structures makes the [2 + 2 + 2] cycloaddition a good candidate for the construction of these compounds. The citrinadines are recently isolated marine-derived pentacyclic spiroindolinone alkaloids exhibiting important cytotoxic activities against various cancer cell lines. Deiters' group developed an approach to their tricyclic alkaloid core structures by conducting a MW-mediated [2 + 2 + 2] cyclotrimerization/intramolecular nucleophilic substitution/reduction sequence. The central pyridine ring was efficiently built and subsequently alkylated and reduced (Scheme 65).[103]



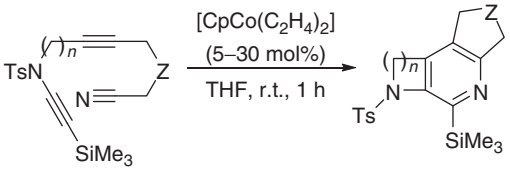
Z	R^1	R^2	Yield (%)
$C(CO_2Me)_2$	Me	Ph	86
$C(CO_2Me)_2$	Me	4-$CF_3C_6H_4$	94
$C(CO_2Me)_2$	Me	Bu^i	72
CH_2CH_2	Et	Ph	92
NTs	Me	Ph	78
O	Me	Ph	93
$(CH_2)_3$	Me	Me	29

Scheme 62



Z	R^1	R^2	Yield (%)
$C(CO_2Me)_2$	Me	Bu^n	70
$C(CO_2Me)_2$	Et	Bu^n	86
$C(CO_2Me)_2$	Ph	Bu^n	75
$C(CO_2Me)_2$	H	Bu^n	30
$C(CO_2Me)_2$	$SiMe_3$	Bu^n	57
$C(CO_2Me)_2$	Me	Et	71
$C(CO_2Me)_2$	Me	Ph	54
NTs	Ph	Bu^n	41
O	Ph	Bu^n	45
CH_2	Ph	Bu^n	65

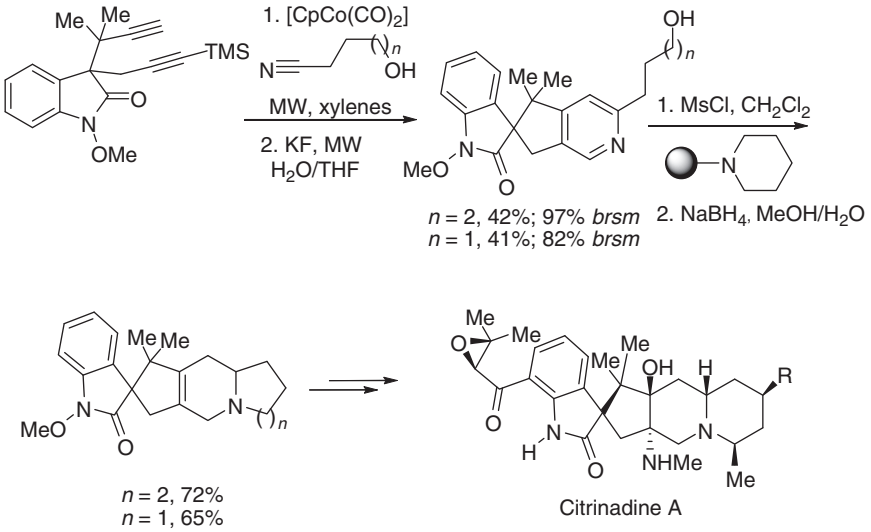
Scheme 63



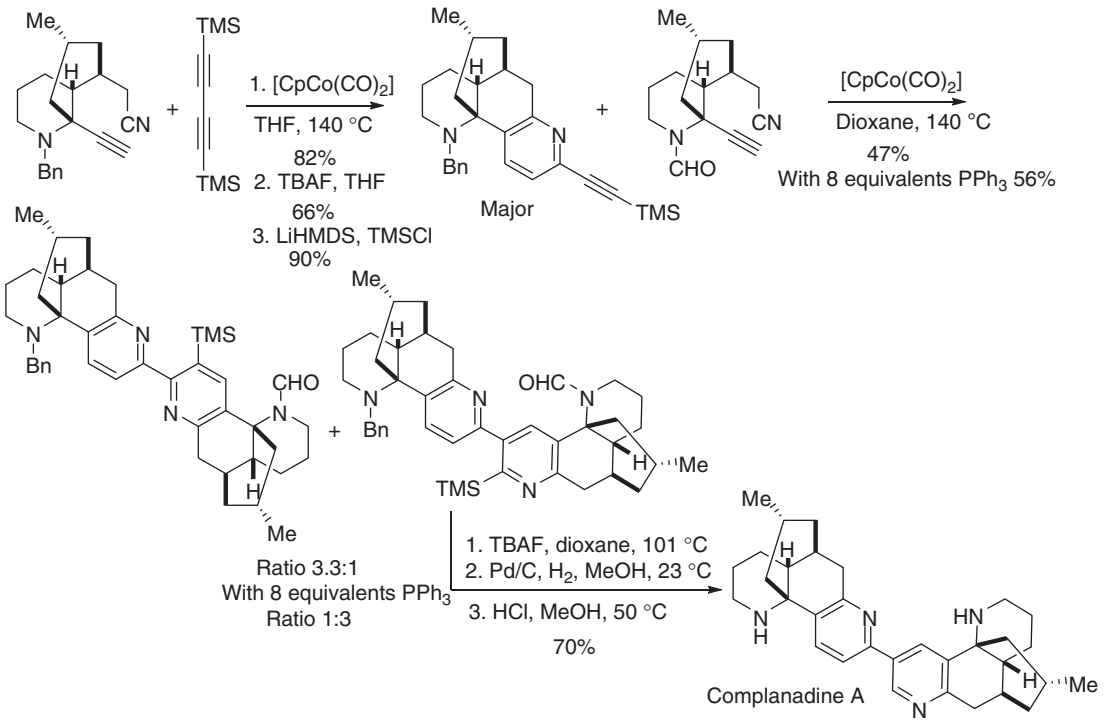
Z	*n*	Yield (%)
NCbz	3	93
NCbz	2	76
NCbz	1	55
CH_2	3	100
$(CH_2)_2$	3	100
CH_2	2	90
$C(CO_2Me)_2$	3	76
O	3	62

Scheme 64

Two late-stage Co(I)-mediated [2 + 2 + 2] cycloadditions were the key steps for the synthesis of complanadine A, a member of the large family of lycopodium alkaloids. The first cycloaddition proceeded with excellent regioselectivity. However, it was necessary to add an excess of triphenylphosphine to get the desired 2,3′-bipyrimidyl product as the major isomer in the second [2 + 2 + 2] cycloaddition, albeit with 3:1 selectivity against the undesired 2,2′-isomer (Scheme 66).[104]



Scheme 65

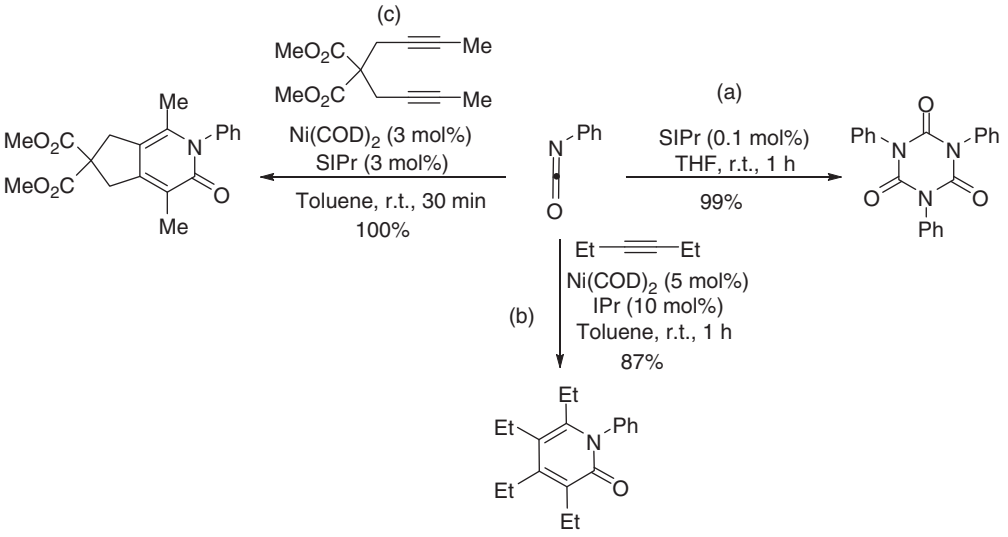


Scheme 66

5.31.4.2 Synthesis of Pyridones Pirimidindiones and Dihydropyridine. Nitrogen-Containing Double Bonds as Partners for the [2 + 2 + 2] Cycloaddition

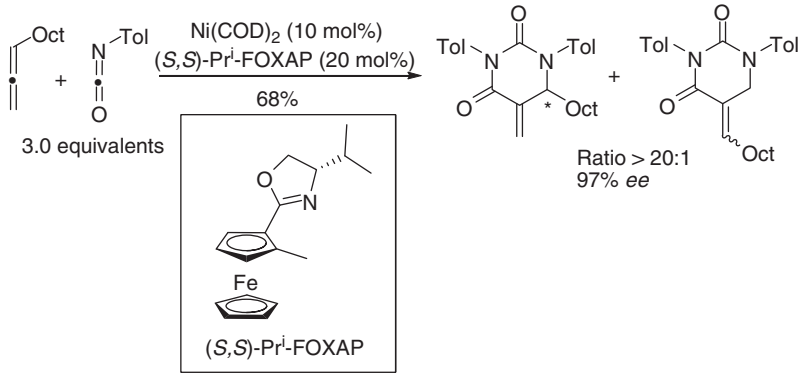
Nitrogen-containing heterocycles can be assembled using one C=N unit as partner for the [2 + 2 + 2] cycloaddition. Due to their modest basicity, isocyanates have been shown to be the best choice. These compounds can cyclotrimerize to form triazintriones, or cotrimerize with alkynes, diynes, allenes, or alkenes. Some cycloadditions of isothiocyanates have also been reported. In general, rhodium, cobalt, nickel, and ruthenium are able to catalyze [2 + 2 + 2] cycloadditions of alkynes and isocyanates, forming pyridones. Louie's group has described cyclotrimerizations of three isocyanate molecules, cotrimerizations of two isocyanates and one alkyne, and crossed cyclotrimerizations of diynes with isocyanates. NHCs alone were able to catalyze the

cyclotrimerization of isocyanates (Scheme 67a), whereas nickel complexes generated from NHCs and $Ni(COD)_2$ mediated the reaction of isocyanates with alkynes or diynes (Scheme 67b and c).[105]



Scheme 67

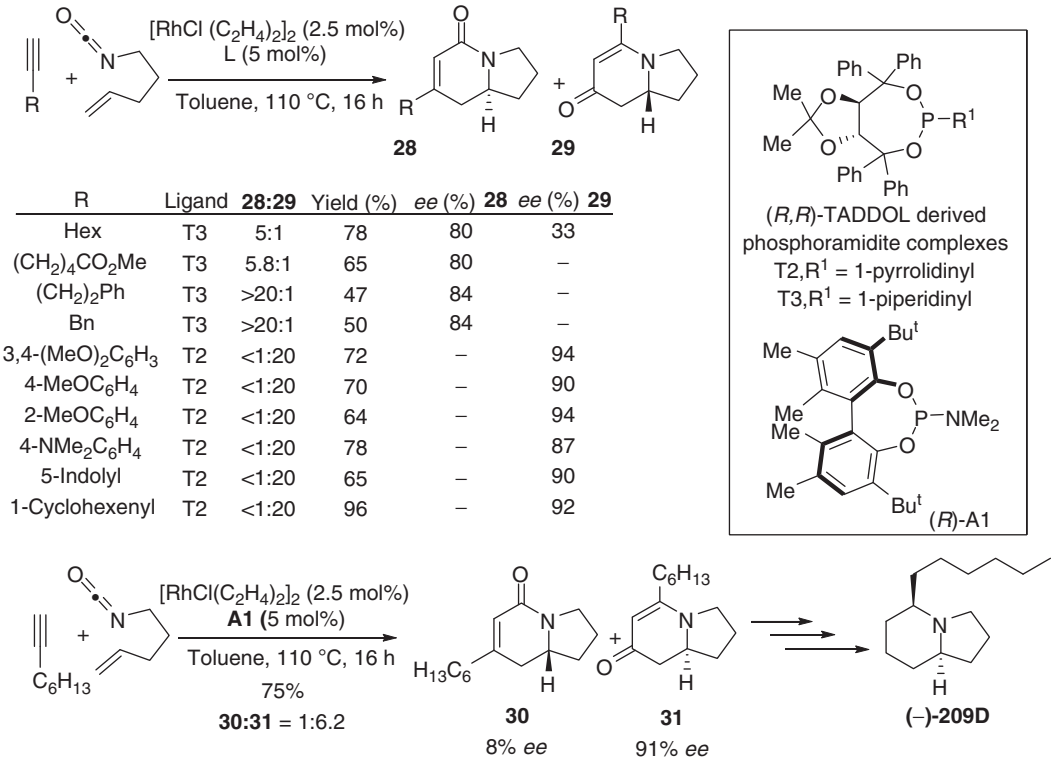
If an alkene is incorporated in place of one of the alkynes a new stereocenter is formed and the reaction could be rendered asymmetric using a chiral catalyst. Thus a cycloaddition of two molecules of isocyanate and one molecule of allene, catalyzed by a nickel complex provided an efficient access to enantiomerically enriched dihydropyrimidine-2,4-diones. Careful selection of the chiral ligand allowed for excellent enantioselectivity (Scheme 68).[106]



Scheme 68

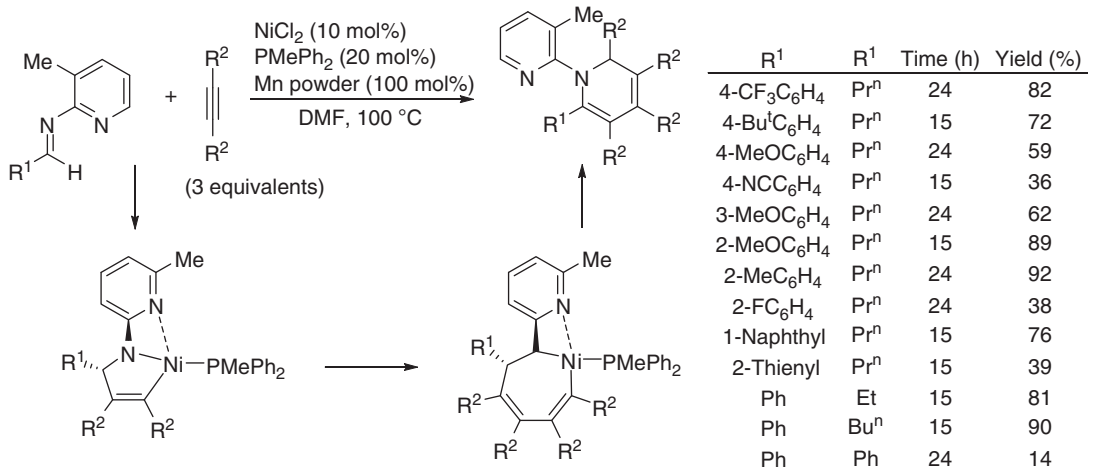
After many contributions to the synthesis of indolizinones, quinolizinones, and pyridones, the group of Rovis has recently described an enantioselective rhodium-catalyzed [2 + 2 + 2] cycloaddition of terminal alkynes and alkenyl isocyanates leading to the formation of indolizidine and quinolizidine scaffolds. Single regioisomeric products are obtained in good yields and excellent enantioselectivities. The use of phosphoramidite ligands proved crucial for avoiding competitive terminal alkyne dimerization. α,α,α,α-tetraphenyll-1,3-dioxolane-4,5-dimethanol (TADDOL)-derived phosphoramidite ligands provided the best enantioselectivities for aryl alkynes, whereas 1,1′-bi-2-naphthol- and other biaryl-based phosphoramidite ligands gave higher enantioselectivity for alkyl alkynes. Interestingly, the major reaction pathway involved a CO migration which facilitated a rapid four-step asymmetric synthesis of the naturally occurring indolizidine **(–)-209D** (Scheme 69).[107]

Although imines can potentially participate in [2 + 2 + 2] cycloadditions to afford dihydropyridine derivatives, few examples have been reported possibly due to lack of stability of these substrates. After pioneering results by Ogoshi's group on nickel-catalyzed cycloaddition reaction of alkynes and an *N*-sulfonylimines, Yoshikai's group used the directing effect of a pyridyl group to achieve a reaction of an aldimine bearing a 3-methyl-2-pyridyl group with alkynes under nickel-catalysis. The reaction gave a 1,2-dihydropyridine derivative in moderate-to-good yield, presumably through 1,5-hydrogen shift of the initially formed cycloadduct (Scheme 70).[108]



R	Ligand	28:29	Yield (%)	*ee* (%) 28	*ee* (%) 29
Hex	T3	5:1	78	80	33
$(CH_2)_4CO_2Me$	T3	5.8:1	65	80	–
$(CH_2)_2Ph$	T3	>20:1	47	84	–
Bn	T3	>20:1	50	84	–
$3,4\text{-}(MeO)_2C_6H_3$	T2	<1:20	72	–	94
$4\text{-}MeOC_6H_4$	T2	<1:20	70	–	90
$2\text{-}MeOC_6H_4$	T2	<1:20	64	–	94
$4\text{-}NMe_2C_6H_4$	T2	<1:20	78	–	87
5-Indolyl	T2	<1:20	65	–	90
1-Cyclohexenyl	T2	<1:20	96	–	92

Scheme 69



R^1	R^1	Time (h)	Yield (%)
$4\text{-}CF_3C_6H_4$	Pr^n	24	82
$4\text{-}Bu^tC_6H_4$	Pr^n	15	72
$4\text{-}MeOC_6H_4$	Pr^n	24	59
$4\text{-}NCC_6H_4$	Pr^n	15	36
$3\text{-}MeOC_6H_4$	Pr^n	24	62
$2\text{-}MeOC_6H_4$	Pr^n	15	89
$2\text{-}MeC_6H_4$	Pr^n	24	92
$2\text{-}FC_6H_4$	Pr^n	24	38
1-Naphthyl	Pr^n	15	76
2-Thienyl	Pr^n	15	39
Ph	Et	15	81
Ph	Bu^n	15	90
Ph	Ph	24	14

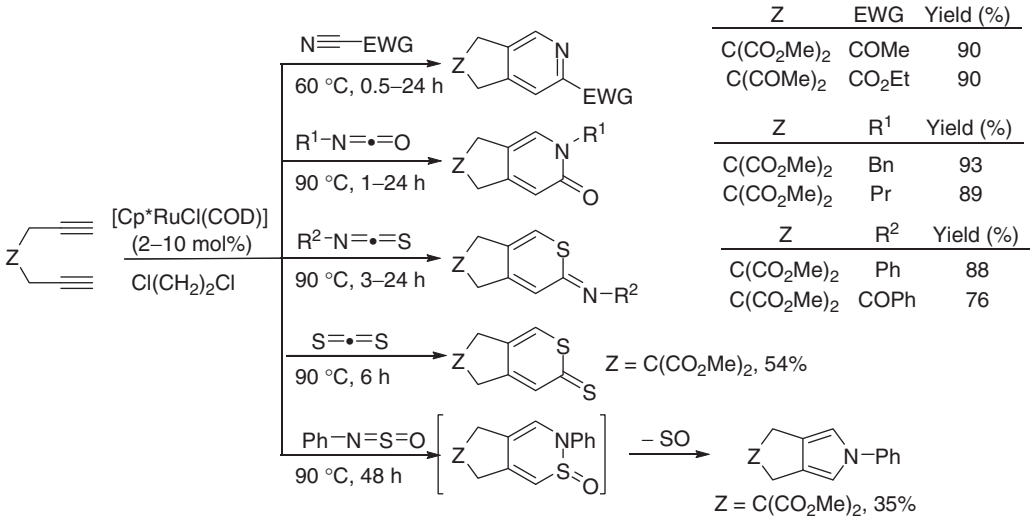
Scheme 70

5.31.5 Other Six-Membered Heterocycles

In recent times, the [2 + 2 + 2] cycloaddition reaction has expanded its scope to new unsaturated substrates such as ketenes, ketones or aldehydes, carbon dioxide, and carbon disulfide enabling the synthesis of nonnitrogenated six-membered heterocycles.

After the pioneering works by Vollhardt using cobalt catalysis, Yamamoto's group reported the [CpRuCl(COD)]-catalyzed cycloadditions of diynes with electron-deficient carbon–heteroatom multiple bonds resulting in various heterocyclic compounds with significant chemo- and regioselectivity. In addition to activated nitriles and isocyanates, they introduced isothiocyanates,

carbon disulfide and *N*-thionylamides as new partners for the cocyclization with diynes. Under mild conditions, the corresponding sulfur-containing heterocycles were synthesized in good yields. When using unsymmetrical diyne substrates, the regiochemistry of these cycloadditions was successfully controlled by the steric and electronic influence of the substituents (Scheme 71).[109]



Z	EWG	Yield (%)
$C(CO_2Me)_2$	COMe	90
$C(COMe)_2$	CO_2Et	90

Z	R^1	Yield (%)
$C(CO_2Me)_2$	Bn	93
$C(CO_2Me)_2$	Pr	89

Z	R^2	Yield (%)
$C(CO_2Me)_2$	Ph	88
$C(CO_2Me)_2$	COPh	76

Z = $C(CO_2Me)_2$, $C(COMe)_2$, $C(CN)_2$, CH_2, NTs, O, S,

EWG = CO_2Et, COPh, CO-2-furyl, COMe, Ts, CCl_3, C_6F_5

R^1 = Ph, 1-naphthyl, 2-furyl, Bn, Pr, Cy

R^2 = Ph, Cy, CO_2Et, COPh

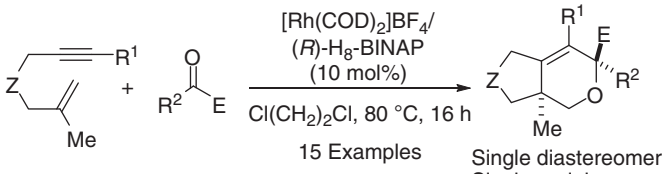
Scheme 71

Tanaka's group has contributed to the extension of the [2 + 2 + 2] cycloaddition process to carbon–heteroatom double-bond substrates. They have applied their cationic rhodium-catalyzed methodology to reactions of diynes with isocyanates for the synthesis of axially chiral 2-pyridones from unsymmetrical α,ω-diynes. An extension of the process using carbon disulfide also proceeded to give bicyclic dithiopyrones. More recently, they described a [2 + 2 + 2] cycloaddition of 1,6-enynes with electron-deficient ketones. Two quaternary carbon centers were created in the reaction to form fused dihydropyrans with excellent regio- and enantioselectivity (Scheme 72).[110]

Finally, ketenes were introduced as new substrates for [2 + 2 + 2] cycloaddition reactions. Ketenes have two possible modes of coordination to the metal and have the propensity to undergo decarbonylation with formation of stable, unreactive metal carbonyl complexes. They often suffer homodimerization under thermal conditions. Despite these pitfalls, it was reported that a nickel-phosphine catalyst mediated the cycloaddition of ketenes and diynes to afford cyclohexadienones in good yield without observing decarbonylation of the ketene starting materials. An enantiopure cyclohexadienone product was obtained when (*R*)-BINAP was used as the ligand (Scheme 73).[111]

5.31.6 Conclusions and Outlook

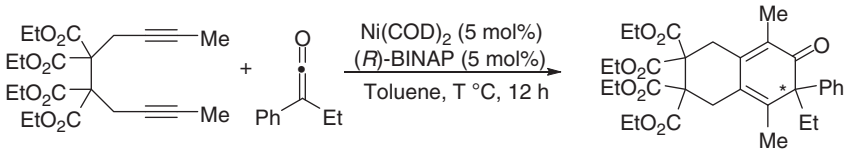
The [2 + 2 + 2] cycloaddition reaction is an atom economic and synthetically powerful reaction with a huge scope and great synthetic utility. The catalysts utilized in these reactions are easily handled. The original cobalt-carbonyl-mediated stoichiometric methodologies have evolved into active cobalt–alkene complexes, which are able to perform catalytically at low temperatures; alternatively Rh(I) or Ir(I)–diphosphane complexes are now regularly applied by mixing alkene precursor complexes and ligands *in situ*. Although zirconium- and titanium-mediated reactions are generally not catalytic, they are still used to circumvent selectivity problems; moreover, they can be used in combination with other reactions. Palladium-based catalysis is specifically effective for the synthesis of polycyclic aromatic hydrocarbons and for reactions with arynes. Ruthenium cyclopentadienyl–COD complexes have emerged as general catalysts for all types of [2 + 2 + 2] cycloaddition under mild



Z = NTs, $C(CO_2Me)_2$, O R^1 = Me, Ph, 4-BrC_6H_4, CO_2Me
R^2 = Me, Ph, CO_2Et E = Me, CO_2Et, COMe

Z, R^1	R^1, E	Yield (%)	*ee* (%)
NTs, Me	Me, CO_2Et	91	>99
$C(CO_2Me)_2$, 4-BrC_6H_4	Me, CO_2Et	82	>99
O, Ph	Me, CO_2Et	67	>99
O, CO_2Me	CO_2Et, CO_2Et	61	93
NTs, Me	Me, COMe	73	98
NTs, Me	Ph, CO_2Et	24	97

Scheme 72



Temperature (T °C)	Yield (%)	*ee* (%)
60	No reaction	
80	38	99
100	58	95

Scheme 73

conditions. In addition, nickel complexes formed on combination of an Ni(0) adduct and an NHC ligand catalyze efficiently cycloadditions of alkynes with various unsaturated partners. Other metals such as niobium or iron appear as promising new alternatives to the usual methodologies.

The synthesis of functionalized arenes used to be achieved through classical transformations based mainly on electrophilic substitution reactions on preformed aromatic rings. However, once the [2 + 2 + 2] cycloaddition of alkynes has reached a mature state with many catalytic systems available, and great understanding of mechanistic aspects, it is becoming an efficient alternative, especially for the synthesis of natural products. This includes excellent ways to build pyridines when a nitrile is cocyclized with two alkynes.

In addition, the literature provides many procedures to carry out asymmetric reactions en route to axially or planarly chiral products. Axially chiral biaryl compounds are important as chiral auxiliaries and ligands for asymmetric synthesis and as the structurally decisive element in bioactive natural products. There is probably no reliable and generally applicable atropselective synthesis that gives excellent chemical yields and optical purities under mild and convenient reaction conditions. However, the use of commercially available and stable chiral bisphosphine ligands in iridium(I) and rhodium(I) catalyst systems or other combinations of chiral ligands with metals for [2 + 2 + 2] reactions is advantageous and allows catalyst tuning and convenient handling. Thus the enantioselective synthesis of many axially chiral biaryl compounds has successfully been described by several groups and applied in natural product syntheses.

Cocyclotrimerizations of alkenes, isocyanates, carbon dioxide, ketenes, ketones, imines etc. with alkynes affords cyclohexadienes and different heterocycles involving many times the generation of asymmetric centers. Various groups have used chiral catalysts to achieve enantioselective syntheses of these compounds.

Significant challenges still remain. For example, it is desirable to expand the substrate scope to include more diverse alkynes and alkyne surrogates as well as to solve the regioselectivity problem in reactions of aliphatic alkynes. Completely controlled intermolecular reactions between three alkynes or one nitrile/isocyanate and two alkynes, and new applications in synthesis are also yet to be realized.

In summary, the [2 + 2 + 2] cycloaddition reaction is today a strategic reaction because it is able to perform various bond connections in only one step, resulting in a significant increase of structural complexity. This area is clearly expanding in several

aspects and will reveal spectacular applications in the near future, ranging from new asymmetric synthesis of axial or planar chiral products and chiral cyclohexadienes/pyridones to the synthesis of natural compounds (Chart 1).

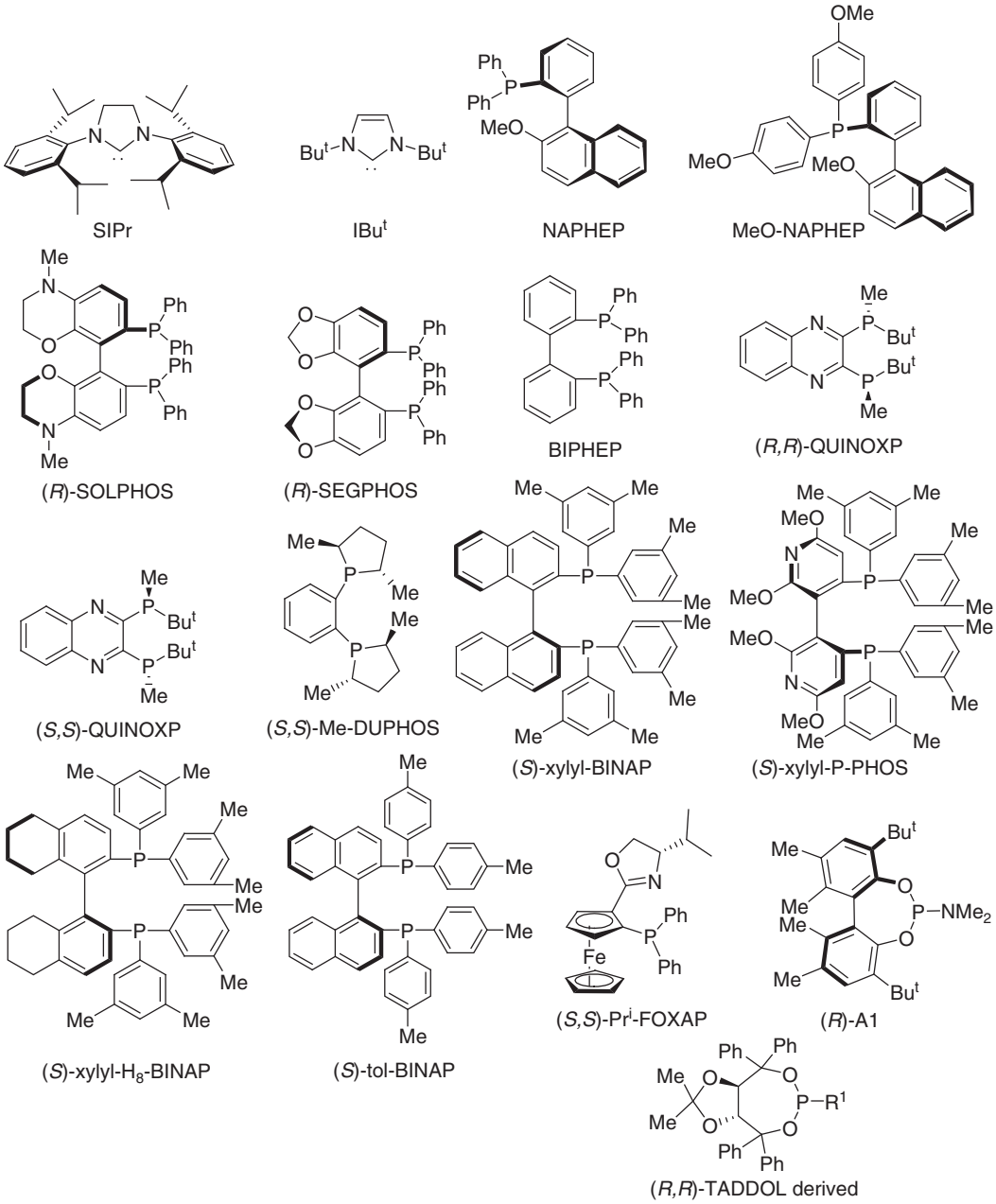


Chart 1

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5.32 Hydrovinylation Reactions in Organic Synthesis

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Glossary

Exocyclic stereocontrol Control of the absolute and/or relative configuration of a stereogenic center attached to a carbo- or heterocyclic ring.

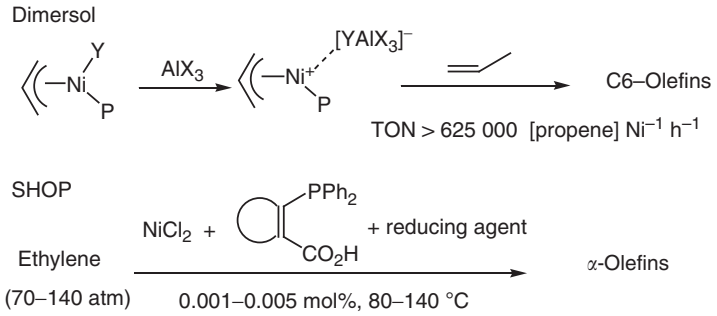
Hemilabile ligand A ligand containing a weakly coordinating group such as an ether oxygen usually containing also a strongly coordinating group such as a phosphine.

 doi:10.1016/B978-0-08-097742-3.00533-4

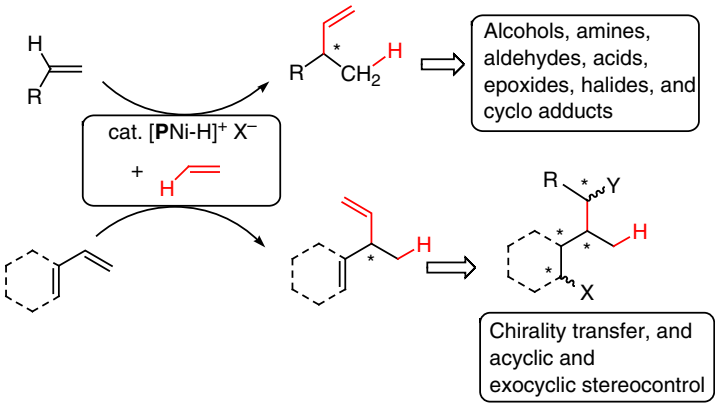
Hydroalkenylation Addition of an alkene to another unsaturated moiety as a hydrogen and an alkenyl group.
Phospholane Another name for a phosphacyclopentane ring system. 2,5-Dialkylphospholanes are extensively used chiral ligands.
Phosphoramidite A phosphorus(III) compound with two P–O bonds and a P–N bond. Such ligands from axially chiral binaphthols, known as Feringa ligands, are among the most widely used ligands in asymmetric catalysis.
Turnover frequency Number of moles of starting material converted into product per mole of the catalyst at unit time. A measure of the efficiency of a catalyst.

5.32.1 Introduction

The astonishingly high turnover frequency ($>625\,000$ [propylene][Ni]$^{-1}$[h]$^{-1}$) observed for Ni(phosphine)(allyl)X as a catalyst in the homodimerization of propene makes this one of the most active homogeneous catalysts known for C–C bond formation.[1,2] This or related chemistry forms the basis of the Dimersol and the Shell higher olefin processes (SHOPs) (Scheme 1). Application of this chemistry for fine chemical synthesis would be especially attractive if the reaction can be extended to heterodimerizations (i.e., dimerization of two different olefins), and sufficient regio- and stereoselectivity can be achieved. Among such reactions, codimerization of ethylene and other alkenes (hydrovinylation, Scheme 2) would have the highest impact since the vinyl group in the product can be transformed into a number of other useful functional groups.



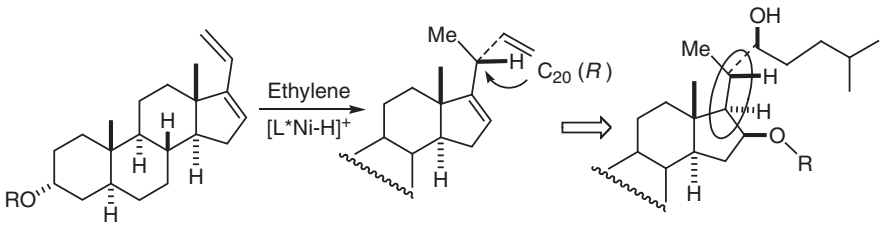
Scheme 1 Ni(II)-catalyzed reactions of propylene and ethylene.



Scheme 2 Selective hydrovinylation reactions.

From a synthetic perspective, this chemistry provides a very attractive solution to the long-standing problem of exocyclic stereochemical control, an example of which is illustrated in Scheme 3 in the context of steroid D-ring functionalization. As seen in steroids, a chiral side chain carrying a methyl-bearing carbon (C_{20}) that is attached to a chiral center in the D-ring is a very common structural motif in many important natural products. The installation of these centers via classical chemistry has often been quite circuitous.

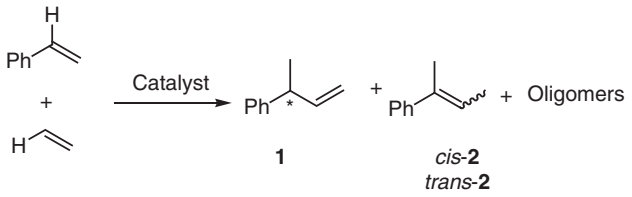
This review will primarily deal with the most recent aspects of the metal-catalyzed hydrovinylation and related reactions. The reader is urged to consult other reviews[3–7] for details of the early history and development of this class of reactions. The literature on hydrovinylation and related hydroalkenylation reactions up to the end of May 2012 is covered here.



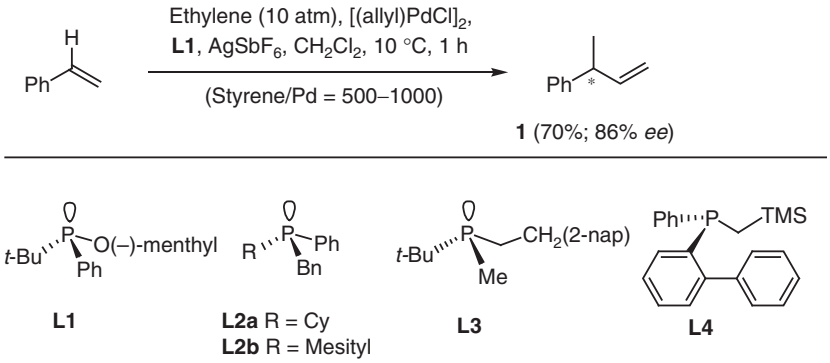
Scheme 3 Hydrovinylation reactions for installation of exocyclic stereocenters.

5.32.2 Early History of the Hydrovinylation Reaction

The first report of hydrovinylation in the open literature appears in a 1964 paper by Hata,[8] who used Fe(acetylacetonate)$_3$ and triethylaluminum to effect additions of ethylene to 1,3-butadiene, 1,3-pentadiene, and isoprene to get a mixture of various adducts. Approximately the same time, Alderson, Jenner, and Lindsey at DuPont Central Research reported the use of hydrated rhodium and ruthenium chlorides to effect the dimerization of ethylene and various olefins, such as styrene and 1,3-butadiene, at high pressures (1000 psi).[9] Cobalt-catalyzed dimerization of ethylene using $(N_2)Co(H)(PPh_3)_3$ is another notable early result.[10] To date, styrene has served as the prototypical substrate for many of the initial investigations of this reaction, and, as illustrated in equation 1, the reaction is complicated by concomitant side reactions such as isomerization reactions of the initially formed product and oligomerizations of styrene as well as ethylene. In early studies, apart from rhodium[9,11] and ruthenium,[9,12] uses of other metals such as cobalt,[10,13] palladium,[14–16] and nickel [17–22] have also been reported. However, in most cases, the reactions yielded mixtures of products. Initial reports of the palladium-catalyzed hydrovinylation indicated that mostly linear products were formed and extensive isomerizations of the primary products were observed. More recent studies have shown that under carefully chosen reaction conditions and with the use of ligands such as **L1**,[23] **L2a**,[24] **L2b**,[25] **L3**,[26] and **L4**,[26,27] the isolation of predominantly the branched product can be achieved. Among these ligands, phosphinite **L1** is particularly noteworthy, for producing 3-phenylbut-1-ene (**1**) under the appropriate conditions (equation 2) in moderate yield (79%) with good selectivity (70% 3-phenyl-1-butene, 86% *ee*).[23] This paper also reports the beneficial effects of dissociating counterions such as SbF_6^-.



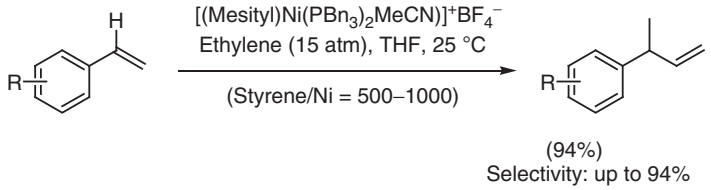
(1)



(2)

Due to the persistent isomerization of the primary product, low conversion, and poor selectivity, more recent work has focused on improving ligands and reaction conditions to afford a more viable protocol that is amenable to large-scale synthesis. By modifying the conditions originally reported by Kawata et al.,[17–19] Muller recently disclosed that Ni-catalyzed hydrovinylation of vinylarenes can be carried out (equation 3) using $[ArNi(PR_3)_2(MeCN)]^+BF_4^-$ [Ar = mesityl, R = benzyl] as precatalysts.[28,29] This catalyst system is able to achieve high turnover frequencies ($\sim$1900 [vinylarene][catalyst]$^{-1}$[h]$^{-1}$) and high selectivities under 15 atm of ethylene for a variety of vinylarenes. Although heteroatoms are well tolerated in this system, ring-alkylated vinylarenes were poor substrates, failing to react with ethylene. Additionally, an increase in reaction temperature (to promote reaction between ethylene and slow-reacting substrates) was accompanied by an undesired increase in isomerized product. Finally,

replacement of the tribenzylphosphine ligand with a chiral *cis*-myrtanyldiphenylphosphine ligand gives excellent selectivity for the branched product; however, only discouraging enantioselectivity (~7% *ee*) was observed.

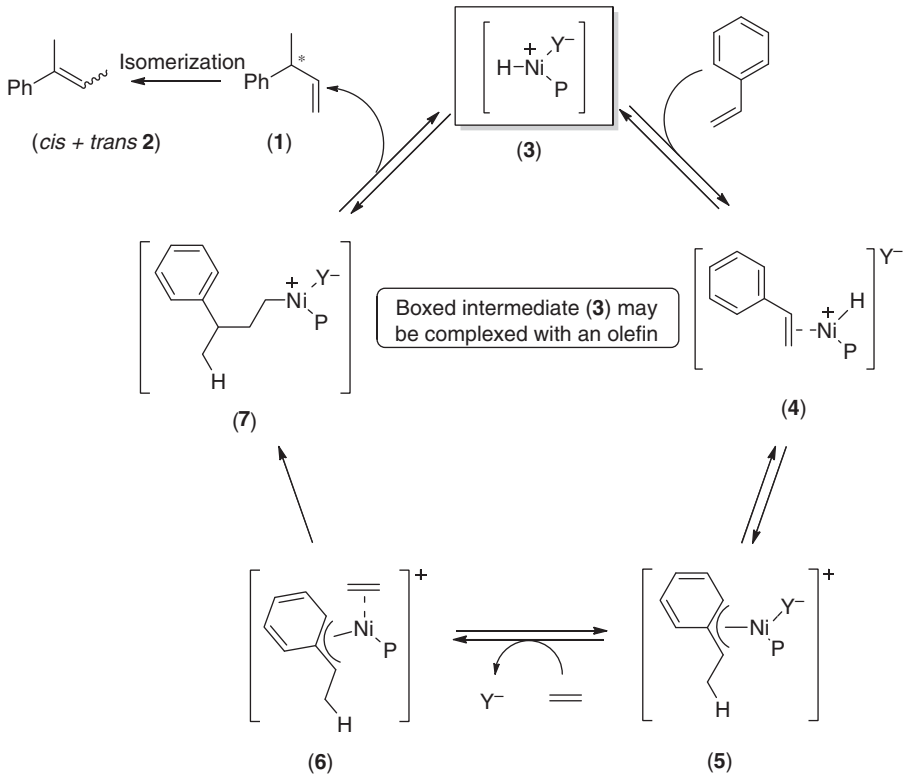


(3)

Since an exothermic polymerization of ethylene is a background reaction in all of these reactions (more prominent at the end of the facile heterodimerization reaction), the ability to control the temperature is crucial to achieve reliable selectivities and/or avoid the isomerization of the primary products. Monteiro et al.[30,31] have developed a catalyst system that circumvents the problem of isomerization by maintaining higher pressures (>10 atm) of ethylene in the reactor. They reported the use of dicationic nickel complexes ($[Ni(CH_3CN)_6]^{2+}2[BF_4]^-/Ph_3P/Et_2AlCl$) for the hydrovinylation of a variety of vinylarenes in moderate to good yields (68–87%).

5.32.3 Mechanistic Considerations

Although much of the early studies on the hydrovinylation of styrene with ethylene resulted in poor selectivities and rampant oligomerization, they have provided significant insights into the reaction mechanism. For instance, deuterium distribution studies using deuterated ethylene (C_2D_4) have provided evidence for the involvement of a cationic nickel hydride or equivalent.[19–22] Kinetic and solvent effect studies have provided early indications of coordination of ethylene to styrene and subsequent addition.[20] The deactivating effect of solvent was also observed and found to increase in the order of CH_2Cl_2, PhF, PhCl, PhMe, $PhNO_2$, Et_2O, consistent with the adverse effect of Lewis basic coordination. In the absence of an in-depth, meaningful mechanistic study, all available experimental evidences[19,32–35] support a mechanism involving a cationic nickel hydride intermediate associated with a weakly coordinated counterion and the phosphine ligand, represented by complex **3** (Scheme 4). Although the structures of none of the nickel complexes proposed in Scheme 4 have been confirmed by X-ray diffraction or any



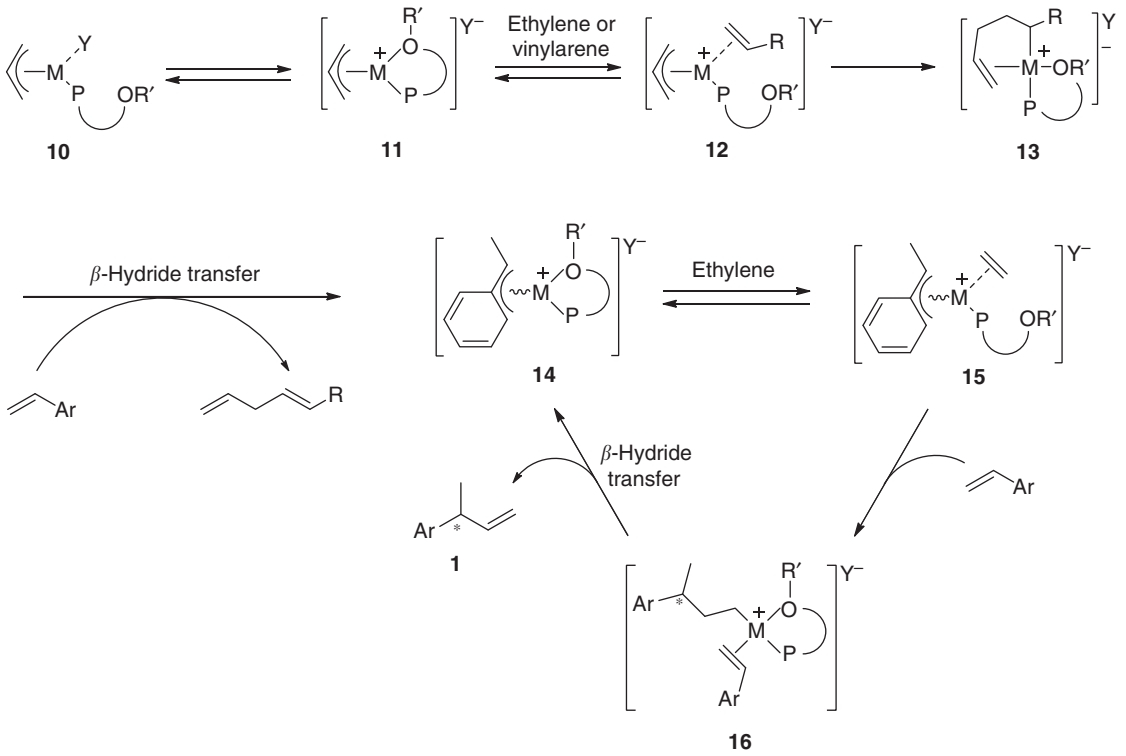
Scheme 4 A hypothetical mechanism of Ni(II)-catalyzed hydrovinylation of styrene.

other methods, the structures of several compounds related to the allylnickel species [(allyl)Ni(phosphine) (X)] have been reported, including those with ligands dimenthyl(methyl)phosphine (X=Me),[36] *tert*-butyl(menthyl)methylphosphine (X=Cl),[37] and tricyclohexylphosphine ($X=MeAlCl_3$).[38]

Assuming that the functional equivalent of the active catalyst is a cationic nickel hydride, represented by complex **3**, the addition of styrene across the vinylarene would lead to intermediate **5**, depicted as a 16-electron η^3-complex. Coordination of ethylene with concomitant loss of the counterion leads to the formation of cationic intermediate **6**, which is poised for a subsequent insertion step to generate **7**. The catalytic cycle is then propagated by the η-hydride elimination to afford the primary product **1** and the active catalyst **3**. Strong evidence for intermediate **6** has been provided by Brookhart and DiRenzo[33,34] in an analog system with palladium, using the precatalyst $[(allyl)Pd(PCy_3)]^+$ $[BARF]^-$ (tetrakis[(3,5-trifluoromethyl)phenyl]borate (BARF)) that is employed for styrene dimerization reactions. Other significant mechanistic observations were the inability of chelating, bidentate phosphines to effect the reaction under standard protocols and the synergistic effect between the ligand and counterion.[35] Any valid mechanistic proposal must accommodate the following observations:

1. Electron-deficient vinylarenes exhibit diminished reactivity, which could be explained by the slower rate of nickel hydride addition (**4**→**5**).
2. Substrates possessing heteroatoms exhibit diminished reactivity when R_2AlX-type Lewis acids are employed, possibly from deactivation of the Lewis acid by coordination of the substrate to aluminum.
3. The deactivating effects of coordinating solvents.
4. The isomerization of the primary product (**1**→*cis*- and *trans*-**2**), possibly mediated by the nickel hydride via addition–elimination reactions.
5. The total inhibition of the reaction by chelating, bidentate phosphines.

Recently, two detailed computational studies have been reported, which focused on a better understanding of the mechanism of the hydrovinylation reaction, including the nature of the active catalyst, the catalyst resting state, role of a hemilabile ligand (more on this later), and the transition state leading to asymmetric induction.[39,40] The conclusions drawn in one of these papers[40] is at variance with the proposed working model. After a critical examination of the originally proposed mechanism (**Scheme 4**), this study found little support for a free-standing cationic nickel hydride (**3**), citing an exceedingly high barrier (>30 kcal mol^{-1}) for its formation via β-hydride elimination. Similarly, formations of all intermediate nickel complexes possessing only three coordinating groups seemed to have prohibitively high activation energies. To accommodate these new findings, a modification of the original mechanism was proposed and its salient features are presented in **Scheme 5** using a generic phospholane ligand with a hemilabile oxygen.[40] Thus, it was proposed that the coordination of an olefin, forming a pentacoordinate square pyramidal intermediate (**8**, **Figure 1**: Intermediate involving the initial allyl group with ethylene is shown for the sake of clarity) is involved



Scheme 5 Modified mechanism of Ni(II)-catalyzed hydrovinylation of styrene.

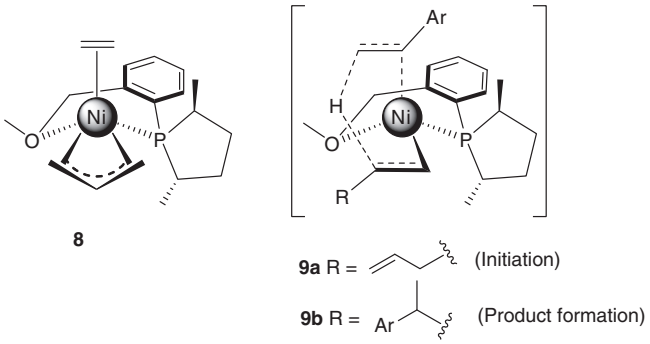


Figure 1 Calculated structures of two species in an energetically viable catalytic cycle.

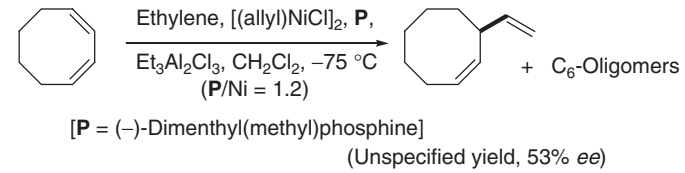
in the lowest energy path. The activation energy for the carbon–carbon bond forming step from this intermediate seems within reach at low temperature. Instead of a β-hydride elimination, the computational study supports the idea of a β-hydride transfer (via TS **9a** or **9b**, Figure 1) in both the turnover- and enantioselectivity-determining steps of the reaction (Scheme 5). The transfer of the β-hydride to the prochiral face of styrene proceeding through transition state **9**, leading to the η^3-benzylnickel complex (e.g., **13**–>**14** or **16**–>**14**), is shown to be 16 kcal mol^{-1} lower in energy compared to the formation of a free metal hydride. Apart from the β-hydride transfer step, most of the major conjectures of the original proposal remain intact.

5.32.4 Asymmetric Hydrovinylation Reactions

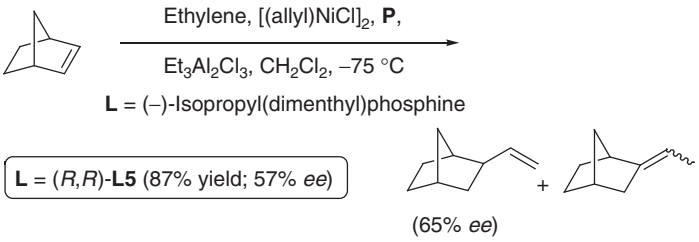
5.32.4.1 Notable Early Results

5.32.4.1.1 Menthylphosphine ligands for Ni

The asymmetric hydrovinylation of 1,3-cyclooctadiene (equation 4) using (–)-dimenthyl(methyl)phosphine as the ligand was among the first reported examples[41] of a metal-catalyzed asymmetric carbon–carbon bond forming reaction. The observed selectivities were unacceptably low by current standards (~53% *ee*). Under similar conditions, norbornene and norbornadiene yielded the corresponding 2-*exo*-vinylproducts in 65% *ee* (at −70 °C) and 78% *ee* (at −65 °C), respectively (equation 5).[38]



(4)

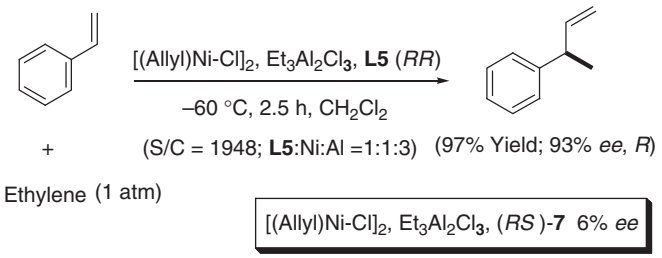


(5)

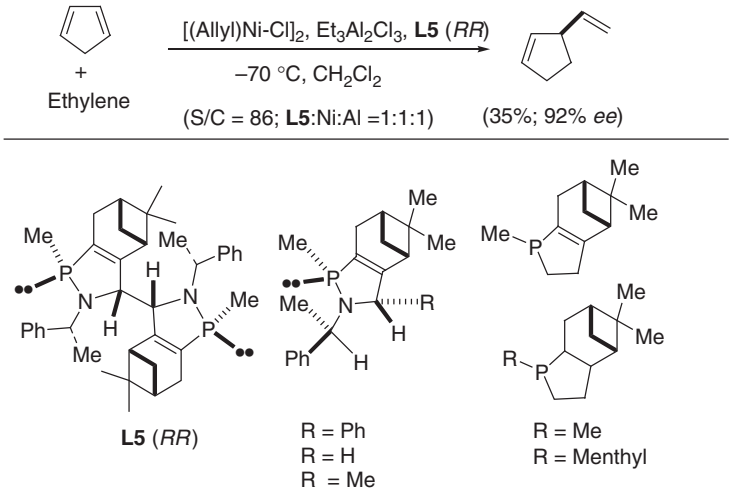
5.32.4.1.2 Azaphospholene ligands for Ni

A critical analysis of the work published before 1994 reveals that only Wilke's nickel-based system afforded acceptable levels of activities and enantioselectivities in several asymmetric hydrovinylation reactions. As reported in a patent,[42] a variety of vinylarenes were subjected to asymmetric hydrovinylation using [η^3-(allyl)NiCl]$_2$/(*R,R*)-(**L5**),/$Et_3Al_2Cl_3$ (equation 6). This catalyst system yielded the best enantioselectivities reported until then for several vinylarene substrates, including styrene (93% *ee*, *R*), 4-isobutylstyrene (85% *ee*, *R*), 4-chlorostyrene (95% *ee*, *R*), and 2-methylstyrene (83% *ee*, *R*).[5,42] This catalyst system also affords high enantioselectivities for asymmetric hydrovinylation of norbornene (equation 5) and selected cyclic 1,3-dienes (equation 7). The azaphospholene (*R,R*)-**L5** ligand was prepared from (–)-(*R*)-myrtenal and (+)-(*R*)-1-phenylethylamine in a multistep process.

One other congener of this compound, the diastereomer (*R*,*S*)-**L5** (prepared from (–)-(*R*)-myrtenal and (–)-(*S*)-1-phenylethylamine) is much less active and selective for the hydrovinylation of styrene. Monomeric and structurally related versions of this ligand have been prepared[5,43] in an attempt to simplify the synthesis (see equation 7 for examples), but it has been found that catalytic activity and enantioselectivity invariably fall below useful levels. Much of the details of the pioneering work have appeared in review articles, dissertations, and patents[5] with few experimental details in the open literature, making meaningful comparisons with more recent work difficult. However, it appears that the esoteric nature of the azaphospholene ligand (**L5**) and the need for highly Lewis acidic aluminum salts limit the utility of this system for broadly applicable hydrovinylation reactions.



(6)

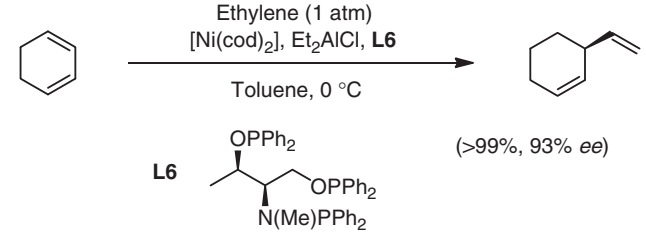


(7)

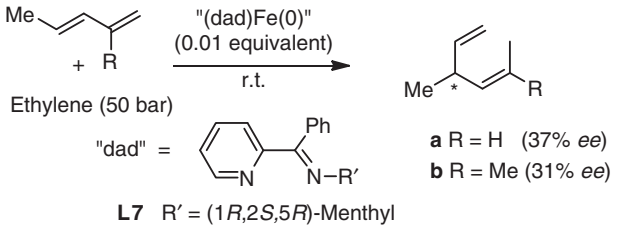
Recently, Wegner and Leitner used the azaphospholene-Ni(II) complex (allyl)(Cl)Ni(**L5**) to effect asymmetric hydrovinylation of styrene, 4-chlorostyrene, and 4-*t*-butylstyrene in supercritical CO_2 in the presence of the BARF counter ion at 40–60 °C.[44] Enantioselectivities for the 3-arylbutene up to 92% were obtained, even though, at high conversion, isomerization of the primary product ensues.

5.32.4.1.3 Aminophosphine-phosphinite (AMPP) ligands for Ni

Nickel complexes bearing AMPP ligands have been generated *in situ* for the efficient hydrovinylation of 1,3-cyclohexadiene (equation 8).[45] Although AMPP ligand **L6** derived from (2*S*,3*R*)-threonine exhibits high levels of enantioselectivity, AMPP ligands derived from other amino alcohols give lower selectivities. AMPP ligands have been extensively studied in the area of Rh-catalyzed asymmetric hydrogenation,[46] but surprisingly few studies on the hydrovinylation have appeared in the literature.[47]



(8)



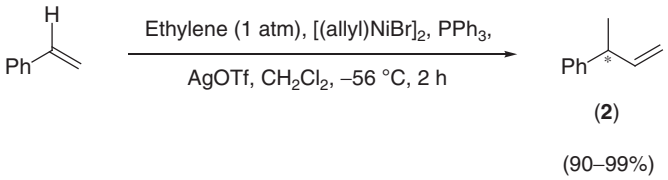
(9)

5.32.4.1.4 N-menthylpyridylarylimine ligand for Fe

High pressure hydrovinylations of (*E*)-1,3-pentadiene (37% *ee*) and 2-methyl-1,3-pentadiene (31% *ee*) catalyzed by an Fe(0)-pyridylimine catalyst (ligand **L7**) has been disclosed.[48] No further advances on this promising result have been reported.

5.32.4.2 A New Protocol for Ni(II)-Catalyzed Hydrovinylation Amenable to Asymmetric Catalysis

As alluded previously, before 1994 only Wilke's system utilizing the ligand **[(*R*,*R*)-L5]** gave acceptable yields and selectivities for the hydrovinylation (HV) of vinylarenes and cyclic dienes.[42] However, subsequent studies have shown that the azaphospholene class of ligands have limited value for the development of a broadly applicable hydrovinylation reaction. Initially, it was envisioned[49] that the strong Lewis acid in the Wilke system could be replaced with a silver salt possessing a weakly coordinating anion that could be easily displaced from the coordination sphere of nickel by an olefin before the migratory insertion step in the mechanism (**5**–>**6**–>**7** in Scheme 4). Further, from the seminal ligand-tuning studies carried out by the Wilke group, it was already clear that the phosphine ligand played a crucial role in determining the selectivity of the reaction.[3] However, the relationship between the counterion (Y^- in Scheme 4) and phosphine ligand remained uncertain as the selectivities varied considerably based on their specific combinations. For example, anions such as $Et_2AlCl_2^-$, OTf^-, and BF_4^- typically produced higher *ee* values with Wilke's ligand **[(*R*,*R*)-L5]**,[5] whereas an opposite effect was observed with more basic ligands (e.g., isopropyl(dimenthyl)phosphine), where the highest *ee* values were observed in combination with highly dissociative anions (e.g., SbF_6^- and PF_6^-).[3] The RajanBabu group undertook an extensive, systematic investigation of the various parameters contributing to the observed selectivities in the hydrovinylation of vinylarenes. Various parameters including the metal, ligand, counterion, the solvent, and reaction conditions were examined, and a new, broadly applicable protocol for the Ni-catalyzed hydrovinylation reaction was discovered (equation 10).[49,50]



(10)

A series of substituted vinylarenes were subjected to the new protocol, resulting in the highest chemical yields and selectivities reported at that time (Table 1). The reactions were typically carried out under 1 atm of ethylene at low temperatures (−56 °C) in dichloromethane, using 0.7 mol% of a catalyst generated from Ph_3P and $[(allyl)NiBr]_2$. In contrast to the previous methods, no oligomerization of styrene or ethylene, or isomerization of the primary product was observed. These conditions were found suitable even for substrates containing Lewis basic centers (Table 1, entries 4, 5, and 10). The 3-aryl-1-butene derivatives from 4-isobutylstyrene, 6-methoxy-2-vinylnaphthalene (MVN), 3-fluoro-4-phenylstyrene, and 3-benzoylstyrene are particularly useful, as they are precursors to the important nonsteroidal antiinflammatory drugs (Table 1, entries 2, 4, 8, and 10).

Although the new protocol has expanded the substrate scope and applicability of the hydrovinylation reaction, several key challenges still remain in this area, especially with respect to enantioselectivity. As mentioned previously, the use of a number of chelating, bidentate phosphines, aminophosphines, and 1,2-bis-diarylphosphinites resulted in complete inhibition of the reaction under otherwise identical conditions.

5.32.4.2.1 Asymmetric hydrovinylation using hemilabile ligands

5.32.4.2.1.1 2-Alkoxy-2′-diphenylphosphino-1,1′-binaphthyl derivatives as ligands for nickel

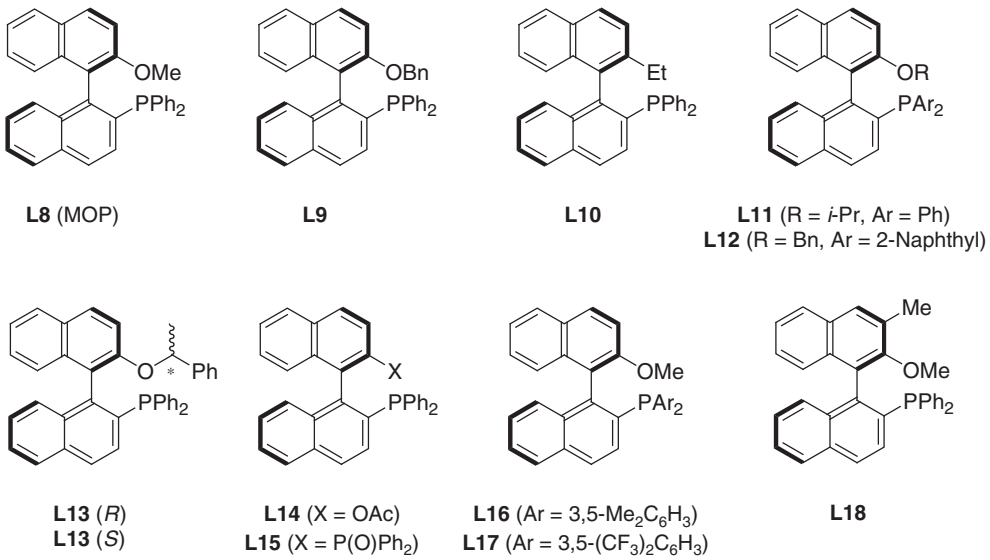
Considering the requirement for an open coordination site during the critical steps of the reaction, it was proposed[49] that a monophosphine, bearing the right hemilabile group,[51,52] would not only be capable of stabilizing the putative cationic intermediates via internal coordination but also undergo facile displacement of this group by an olefin during the

Table 1 Hydrovinylation of assorted vinylarenes

Entry	*Vinylarene*	*Conditions*[a]	*Yield (%)*[b]
1	Styrene	(i)	>95 (99)
2	4-Isobutylstyrene	(i)	>90 (99)
	4-Isobutylstyrene	(ii)	>97 (99)
3	4-Chlorostyrene	(i)	(>99)
4	MVN[c]	(i)	(90)
	MVN[c]	(ii)	(97)
5	4-Methoxystyrene	(i)	>95 (98)
6	4-Bromostyrene	(i)	>95 (98)
7	2-Vinylnaphthalene	(i)	(99)
8	3-Fluoro-4-phenylstyrene	(i)	(88)
9	3-Bromostyrene	(i)	(99)
10	3-Benzoylstyrene	(i)	(99)
11	3-Methylstyrene	(i)	(>99)
12	4-Methylstyrene	(i)	(>99)
13	2-Chlorostyrene	(i)	30

[a]See equations 10 and 11. Conditions: (i) catalyst (0.7 mol%), CH_2Cl_2, −55 °C, 2 h; (ii) (*R*)-MOP (**L8**), NaBARF, CH_2Cl_2, −56 °C, 2 h (see equation 11 for details of this procedure).
[b]Isolated yield, selectivity >98% in all cases. The values in brackets are based on GC analysis.
[c]MVN: 6-Methoxy-2-vinylnaphthalene.

appropriate stages of the catalytic cycle (Scheme 5). The use of a number of 'hemilabile' groups, including carboxylates, ester carbonyl, diarylphoryl, and thioether moieties, has been reported in a variety of reactions.[53–57] In the context of an asymmetric variant, the chiral ligand, 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl [(**L8**), MOP, Figure 2] received early attention due to its flexibility with respect to structural modifications. For example, variations of the 2′-substituents would permit further evaluation of the hemilabile coordination as a control element in the Ni-catalyzed asymmetric hydrovinylation reaction.

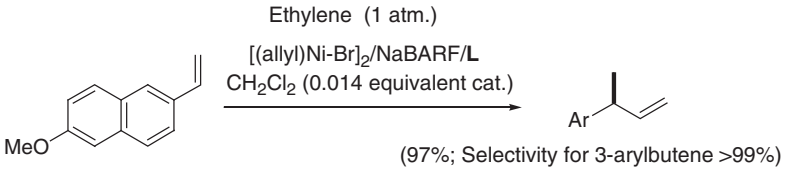


L8 (MOP) **L9** **L10** **L11** (R = *i*-Pr, Ar = Ph) **L12** (R = Bn, Ar = 2-Naphthyl)

L13 (*R*) **L13** (*S*) **L14** (X = OAc) **L15** (X = $P(O)Ph_2$) **L16** (Ar = 3,5-$Me_2C_6H_3$) **L17** (Ar = 3,5-$(CF_3)_2C_6H_3$) **L18**

Figure 2 Binaphthyl phosphine ligands for asymmetric hydrovinylation.

Initial studies using **L8** indicated that the use of AgOTf was detrimental to the hydrovinylation reaction when the MOP ligand was employed. Although this observation has not been thoroughly investigated, it is hypothesized that the counterion (OTf^-) may be involved in a demethylation-degradation pathway of the ether linkage (i.e., resulting in the formation of a stable Ni(II) chelate). Supporting this conjecture, the use of a bulky, nonnucleophilic counterion BARF,[58] completely restored the activity of the catalyst system (equation 11).[49,50]



(11)

Ligand	Conditions	% *ee*
L8	–56 °C	62
L9	–70 °C	80
L10	–56 °C	13 (5% conversion)

Since use of the hemilabile coordination to enhance the enantioselectivity of a reaction was a novel idea at the time of its original discovery, a systematic evaluation of the 2′-substituents of the binaphthyl scaffold was conducted under standard reaction conditions with MVN as the substrate and BARF as the counterion (Table 2). With respect to the steric bulk of the 2′-*O*-alkyl substituents, little effect on the enantioselectivity was observed, but the yield of the reaction was reduced by larger substituents (entries 1, 2, and 5). Involvement of the hemilabile oxygen atom may be inferred from the MOP derivatives containing (*R*)- and (*S*)-phenylethoxy side chains, **L13** (*R*) (entry 6) and **L13** (*S*) (entry 7), respectively. Although **L13** (*R*) gives the product in excellent yield and good enantioselectivity (>98%, 71% *ee*), the reaction with **L13** (*S*) results in only 79% yield and 65% *ee*, suggesting an important role of the hemilabile oxygen with respect to the activity of the catalyst.

Table 2 Effect of modifications to the 2′-substituents of MOP-type ligands[a]

Entry	*Ligand*[b]	*2′-Substituent*	*Yield (%)*	ee *(%)*
1	**L8**	OMe	>98	62
2	**L9**	OBn	97	73
3	**L9**	OBn	93	80[c]
4	**L10**	Et	13	3
5	**L11**	O-*i*-Pr	69	70
6	**L13*R***	OCH(Ph)Me	>98	71
7	**L13*S***	OCH(Ph)Me	79	65
8	**L14**	OAc	0	–
9	**L15**	$P(O)Ph_2$	0	–
10	**L16**	OMe	94	63
11	**L17**	OMe	93	63
12	**L18**	OMe	99	81

[a]See equation 11 for general procedure. Reactions conducted on MVN at −56 °C.
[b]See **Figure 2** for the structures of the ligands.
[c]−70 °C.

The effect of the hemilabile group was further demonstrated by the preparation of 2′-ethyl MOP-derivative (**L10**), which does not have a weakly coordinating heteroatom. The hydrovinylation of MVN with **L10** using the BARF counterion resulted in only 13% yield and 3% *ee* (entry 4), whereas the corresponding reaction involving AgOTf gave less than 2% conversion. Furthermore, if hemilabile coordination is important, the varying donor properties of the ligands should produce differences in the reactivity of the complexes. Therefore, allylnickel complexes of **L14** and **L15** were subjected to the standard reaction conditions. As expected, both analogs failed to give any desired hydrovinylation products (entries 8 and 9, respectively). Finally, a limited effort was made to examine the electronic effects of diaryl modifications (analogs **L16** and **L17**, entries 10 and 11).[50] MOP-type ligands possessing electron-donating and withdrawing substituents on the phosphorus were examined by comparing the enantioselectivities observed in the hydrovinylation reaction (Table 2, entries 1, 10, and 11). In sharp contrast to the nickel(0)-catalyzed hydrocyanation,[59,60] rhodium(I)-catalyzed hydrogenation,[61] and the palladium(0)-catalyzed allylation,[62] the electronic properties of the ligands appear to have a negligible effect on the hydrovinylation.[50] It is important to note that unlike the aforementioned reactions, the hydrovinylation is proposed to maintain the same oxidation state of the metal (Ni^{2+}) throughout the entire catalytic cycle. Essentially, the nickel(II) complex functions as a complex Lewis acid. Addition of a methyl group at the 3′-position (analog **L18**, entry 12)[63] did result in an improvement in the *ee* of the product from MVN. An explanation based on the working model for the asymmetric induction has been proposed for this observation.[63]

5.32.4.2.1.2 1-[(2-Alkoxy or alkoxyalkyl)aryl]-2,5-dialkylphospholanes

Based on the success of MOP-type ligands (Figure 2), it was presumed that chirality present near the hemilabile atom or the strongly chelating atom might have an influence on the selectivity of the hydrovinylation, even though the nature of such an influence was purely speculative at that time. A series of phospholane ligands carrying a hemilabile oxygen functionality (Figure 3) was synthesized and screened for the hydrovinylation reaction.[35] These hemilabile phospholanes, readily amenable to modifications of several key structural elements (Figure 3), proved to be excellent candidates as ligands for the asymmetric hydrovinylation.

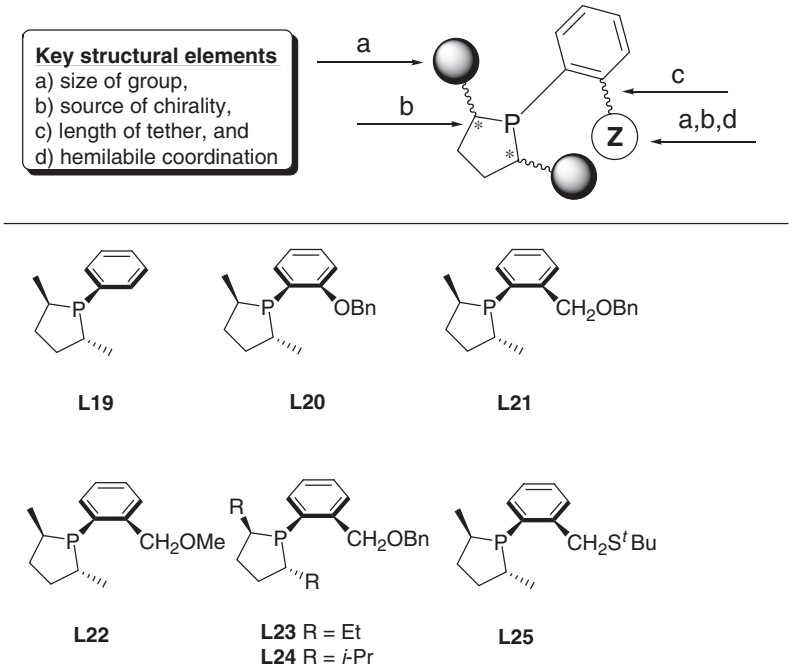


Figure 3 Phospholane ligands for asymmetric Ni(II)-catalyzed asymmetric hydrovinylation.

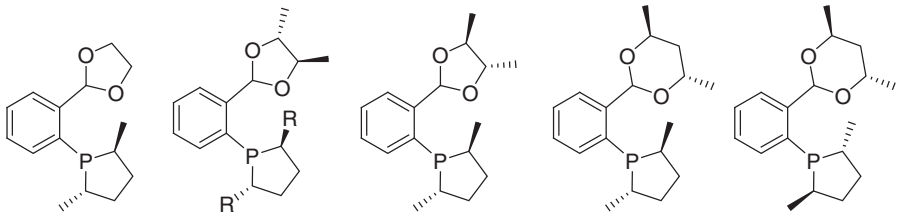
The evaluation started with ligand **L19** and hemilabile ligand **L20**. As expected from previous observations, ligand **L19** (possessing no hemilabile functionality) was competent in the hydrovinylation reaction, but only when AgOTf was used as a promoter. Initial results with **L20**, under standard conditions with BARF counterion, showed an extremely active catalyst that led to significant isomerization of the primary product, even at $-55\ ^{\circ}C$. In comparison to the successful MOP ligand **L8**, it was conjectured that the distance between the chelating phosphorus atom and the hemilabile group might influence the catalyst activity. In the MOP ligand (**L8**), placement of the hemilabile group is on the δ-carbon with respect to the phosphorus, whereas the hemilabile group is on the β-carbon in ligand **L20**, resulting in seven- versus five-membered nickel chelated complexes, respectively. Therefore, analog **L21** was prepared to probe the effect of the relative positioning of the hemilabile group. Gratifyingly, this ligand proved to be one of the best ones for the selective hydrovinylation reactions. Under the optimized conditions, no traces of any isomerized products were detected with this ligand.[35]

The effect of the size of the substituents at the 2- and 5-positions of the phospholane was also evaluated. An increase in size from methyl-(**L21**) to ethyl-(**L23**) improved the enantioselectivity, giving *ee* values of 63–67% for the hydrovinylations of styrene and 4-isobutylstyrene, respectively. The result represented one of the highest overall selectivities reported at the time for the substrate 4-isobutylstyrene, an important precursor to ibuprofen. Further increasing the size of the 2- and 5-substituents to isopropyl groups (**L24**), however, appeared to result in inhibition of the hydrovinylation reaction, even at elevated temperatures (25 °C). Finally, the *o*-(benzyloxy)methyl group was replaced with the sulfur analog *o*-(*t*-butylsulfanyl)methyl group (**L25**). No hydrovinylation products were observed with **L25**, most likely caused by the strong donor properties of the sulfur atom.

In order to examine the effect of additional chiral elements near the hemilabile position, a series of phospholane ligands possessing chiral acetal motifs were synthesized (Figure 4).[64] The ligands were investigated in the hydrovinylation reaction of 4-isobutylstyrene using 0.07 mol% catalyst, under an atmosphere of ethylene at $-55\ ^{\circ}C$, and the results are tabulated in Table 3. The acetal-containing phospholanes (**L26–L31**) in general, produced excellent results for the asymmetric hydrovinylation, resulting in nearly quantitative yields and perfect selectivities for the variety of 3-arylbut-1-ene products.

The phospholane ligand possessing an achiral acetal moiety (**L26**) gives the desired product in 85% *ee* (entry 1). Ligand **L27** exhibited the best selectivity for this transformation, improving the enantioselectivity to 91% *ee* (entry 2).

Increasing the size of the 2- and 5-substituents (**L28**) resulted in only minor effects on the selectivity, whereas significantly deteriorating the overall rate of the reaction (entry 3). A change in the configuration of the 4- and 5-substituents of the 1,3-dioxalane ring (**L29**) led to the isomerization of the primary product, accompanied by erosion of enantioselectivity



L26 **L27** R = Me **L28** R = Et **L29** **L30** **L31**

Figure 4 Phospholane ligands with hemilabile acetals.

Table 3 Asymmetric hydrovinylation of 4-isobutylstyrene with 2,5-dialkylphospholanes carrying an acetal functionality (**Figure 4**)[a]

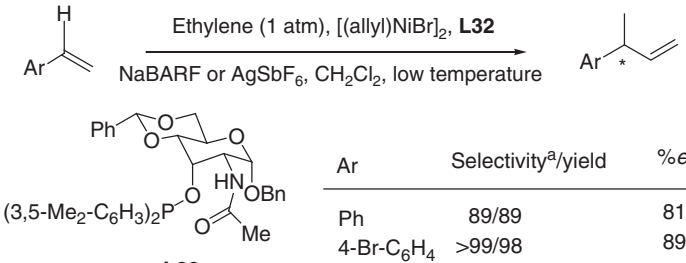
Entry	*Ligand*	*Conversion (%)*	*Selectivity (%)*[b]	ee *(%)*
1	**L26**	>99.5	>99.5	85 (*R*)
2	**L27**	>99.5	>99.5	91 (*R*)
3	**L28**	83	>99.5	88 (*R*)
4	**L29**	>99	90[c]	71 (*R*)
5	**L30**	>99.5	>99.5	85 (*R*)
6	**L31**	>99.5	>99.5	90 (*S*)

[a]See equation 11 for general procedure. Reactions conducted on 4-isobutylstyrene at −55 °C.
[b]Selectivity for the 3-arylbut-1-ene.
[c]The other products were *cis*- and *trans*-2-arylbut-2-enes.

(71% *ee*, entry 4). The structurally related 1,3-dioxane derivatives (**L30** and **L31**) exhibited results comparable to the dioxalane ligands (entries 5 and 6), suggesting that the stereochemical outcome of the reaction is largely dictated by the chirality contained in the phospholane ring (e.g., the (*S*,*S*)-phospholane favoring formation of (*R*)-3-arylbut-1-ene products).

5.32.4.2.1.3 β-Acetamido-diarylphosphinite ligands

A number of carbohydrate-derived diarylphosphinites with a β-acetamido group (but not dialkylamino) have been found to be competent ligands for the asymmetric hydrovinylation of styrene derivatives.[47,65]



Ar	Selectivity[a]/yield	%*ee*
Ph	89/89	81
4-Br-C_6H_4	>99/98	89[b]

[a]For 3-Ph-1-butene. [b]With $AgSbF_6$

(12)

5.32.4.2.1.4 Phosphoramidite ligands

In 1996, Feringa et al.[66,67] disclosed novel phosphoramidite ligands derived from 2,2′-binaphthols (**Figure 5**) for the copper-catalyzed asymmetric conjugate additions of dialkylzinc reagents to enones, and these ligands have become immensely popular for a variety of metal-catalyzed reactions.[68] Leitner and coworkers[69] found that one of the original phosphoramidites (**L33a**) is an excellent ligand for the Ni(II)-catalyzed hydrovinylation of vinylarenes under the protocol reported by RajanBabu et al. (equation 11),[49] giving >90% *ee* for styrene, 4-bromostyrene and 4-chlorostyrene, and ~68% *ee* for 4-isobutylstyrene. Independently, the RajanBabu group found that phosphoramidites are effective ligands for the asymmetric hydrovinylation of norbornene derivatives (vide infra).[70,71] Optimization of the phosphoramidite ligands for asymmetric hydrovinylation has been undertaken by the RajanBabu[72,73] and Leitner[74] groups and this has led to significant improvements of activities and enantioselectivities in these reactions. Structures of some of the best ligands in this series are shown in **Figure 5**, and the results of the asymmetric hydrovinylation of various vinylarene substrates are summarized in **Table 4**.

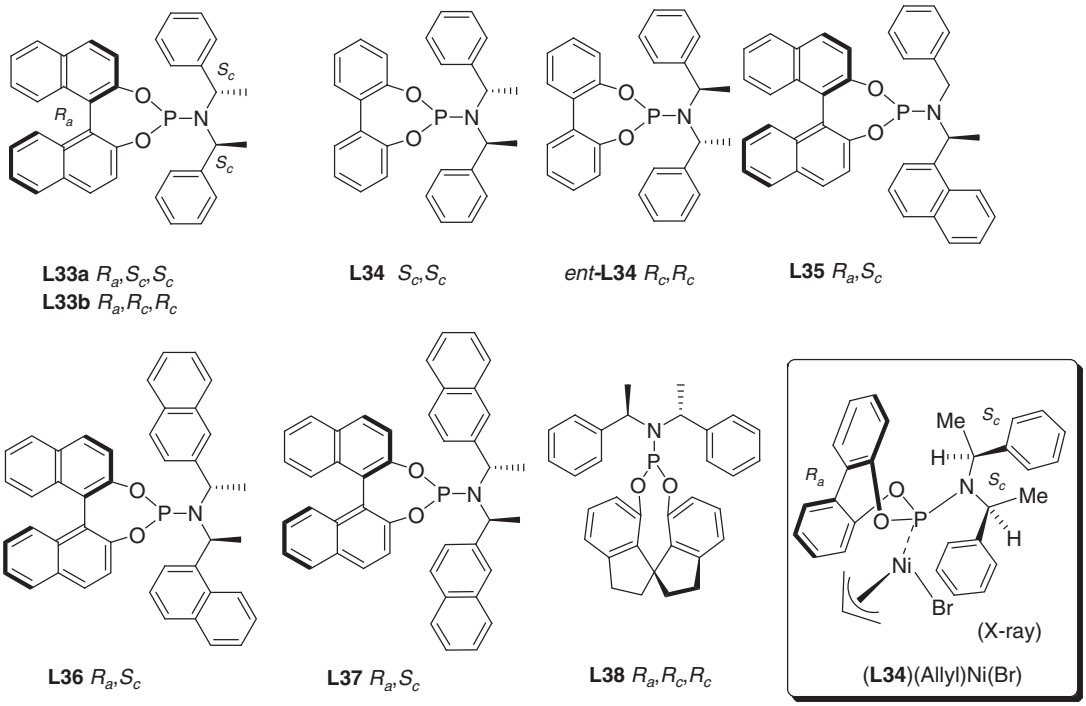


Figure 5 Phosphoramidite ligands for asymmetric Ni(II)-catalyzed asymmetric hydrovinylation.

Table 4 Finely tuned phosphoramidite ligands for Ni-catalyzed asymmetric hydrovinylation of vinylarenes[a]

Entry	*Ligand*	*Substrate*	*Temperature (°C)*	*Conversion (%)*	*Selectivity (%)*[b]	ee *(%)*
1	**L33a**	4-Methoxystyrene	−78	>99	>99	95 (*S*)
2	**L34**		−78	>99	>99	95 (*S*)
3	**L35**		−78	>99	>99	97 (*S*)
4	**L33a**	4-*i*-Bu-styrene	−78	>99	98	90 (*S*)
5	**L34**		−78	97	99	90 (*S*)
6	**L35**		−78	>99	>99	96 (*S*)
7	**L36**		−70	>99	90	96 (*S*)
8	**L36**[c]		r.t.	>99	95	90 (*S*)
9	**L33a**	6-Methoxy-2-vinyl-naphthalene	−78	>99	>99	95 (*S*)
10	**L34**		−78	>99	>99	90 (*S*)
11	**L35**		−78	>99	>99	99 (*S*)
12	**L36**		−70	>99	>99	99 (*S*)
13	**L36**		r.t.	>99	94	95 (*S*)
14	**L33a**	3-F-4-Ph-styrene	−78	>99	>99	86 (*S*)
15	**L34**		−78	>99	>99	80 (*S*)
16	**L35**		−78	>99	>99	97 (*S*)
17	**L33a**	3-Phenoxystyrene	−78	>99	>99	97 (*S*)
18	**L34**		−78	>99	>99	95 (*S*)
19	**L35**		−78	>99	>99	97 (*S*)
20	**L35**	4-Me-styrene	−78	>99	99	94 (*S*)
21	**L35**	3-Br-styrene	−78	>99	99	94 (*S*)
22	**L33a**	4-Br-styrene	−70	83	98	92 (*S*)
23	**L36**	4-Br-styrene	r.t.	93	95	92 (*S*)
24	**L33a**	Styrene	−65	100	>99	91 (*S*)
25	**L36**	Styrene	−70	90	99	99 (*S*)
26	**L36**[d]	Styrene	r.t.	98	98	93 (*S*)

[a]See equation 11 for general procedure. Compiled from references 69, 72, 74, and 75.
[b]For 3-aryl-1-butene.
[c]With InI_3 instead of NaBARF: 89% *ee*.
[d]With InI_3: 90% *ee*.

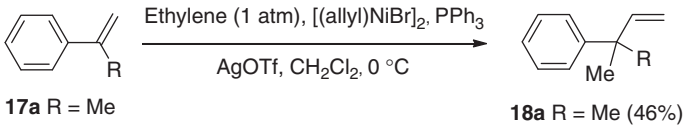
The feasibility of fine-tuning phosphoramidite ligands to control stereoselectivity in the hydrovinylation reaction was initially investigated[72] using 4-methoxystyrene, an electron-rich substrate that consistently gave poor results with other ligands. The initial screening of ligands resulted in the identification of three phosphoramidite ligands (**L33**, **L34**, **L35**), which showed excellent levels of enantioselectivity. Interestingly, ligand **L34** (and its enantiomer), possessing only a biphenyl backbone, yields similar selectivities and conversions as the more expensive ligand carrying the chiral binaphthyl moiety **L33** (Table 4, entries 1 and 2). The crystal structure of a Ni complex [(**L34**)(allyl)NiBr] (Figure 5) clearly shows that the (*S*)-benzylamines induce helical chirality in the biphenyl moiety (*R*) and this in turn may be responsible for the nearly identical behavior of **L33a** and **L34** in the asymmetric hydrovinylation of vinylarenes. Since it has been realized that the sterically less demanding biphenyl ligands have some added advantages in some situations.

From this study, the ligand **L35** carrying 2-(1-naphthyl)ethylamine moiety was identified as having the broadest applicability across a wide spectrum of vinylarenes including 4-isobutylstyrene, MVN, 3-fluoro-4-phenylstyrene, and 3-phenoxystyrene, all precursors for enantioselective syntheses of the most popular nonsteroidal antiinflammatory agents, ibuprofen, naproxen, flurbiprofen, and fenoprofen, respectively. Indeed, full details of the synthesis of these compounds via asymmetric hydrovinylation followed by oxidative degradation of the alkene to the 2-arylpropionic acid have since been published.[75]

In addition to **L35**, Leitner's group has reported the utility of other phosphoramidites carrying the 2-(1-naphthyl)-ethylamine.[74] Thus, phosphoramidite **L36** is a competent ligand to effect the asymmetric hydrovinylation at room temperature with no isomerization of the terminal double bond in the product, an occasional complication in many such reactions run at higher temperatures (entries 8, 13, 23, and 26). Leitner also introduced InI_3 as a useful replacement for NaBARF.[76]

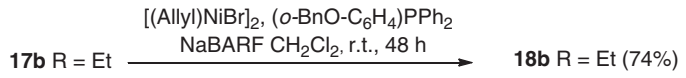
5.32.5 Generation of All-Carbon Quaternary Centers

The stereoselective generation of all-carbon quaternary centers is a subject of considerable topical interest.[77] The hydrovinylation reaction of an α-substituted styrene is a convenient method for the synthesis of such compounds with a benzylic carbon, selectively generating a quaternary center attached to a highly versatile vinyl group suitable for further functionalization. Following the first demonstration of the hydrovinylation of α-methylstyrene (**17a**, equation 13a),[50] several reports of the use of phosphoramidite ligands for asymmetric variations of this reaction have appeared.[78–82] Full experimental details of a large-scale (0.05 mol) asymmetric hydrovinylation of 2-phenyl-1-butene (**17b**) have also been published.[83]



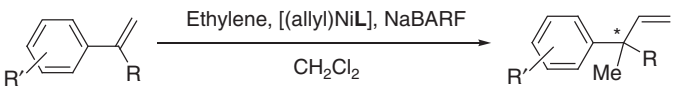
17a R = Me

18a R = Me (46%) (13a)



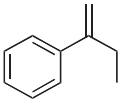
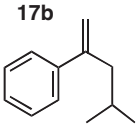
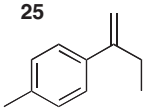
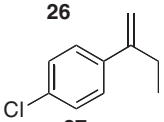
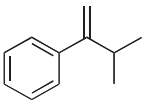
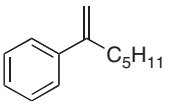
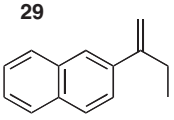
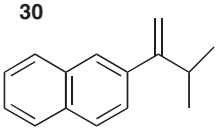
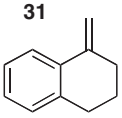
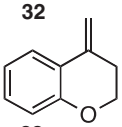
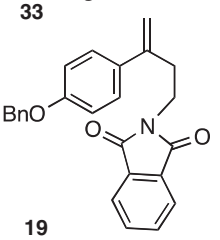
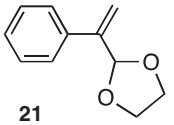
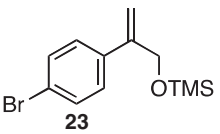
17b R = Et **18b** R = Et (74%) (13b)

For the hydrovinylation of a prototypical substrate, 2-phenylbut-1-ene (**17b**), Ni-catalysts derived from MOP ligand (**L8**, Figure 2) showed no reactivity, whereas those derived from phospholane ligand **L27** (Figure 4) showed only moderate reactivity.[79,80] Among the chiral ligands examined, phosphoramidites **L33a**, **L34**, **L35**, and **L38** were found to give the best results (Table 5). Although substrates **17b**, **26**, **27**, and **30** gave excellent selectivities, others like **32**, **19**, and **23** gave varying amounts of products resulting from migration of the double bond of the starting olefin. Up to 30% isomerization is seen in the HV of the tetraline derivative **32**, yet the chiral product is formed in ~99% *ee*. Surprisingly no such isomerization is seen in the oxygenated analog **33**, but a dimeric side product (~15%) is formed in the reaction. Substrates with heteroatom-containing side chains generally gave lower selectivities (entries 11[80] and 12[82]), except for allyl alcohol derivatives **23** (entry 13).[81] In this connection, the use of a phosphonite ligand **L39** is noteworthy, which yields nearly quantitative yield of the hydrovinylation product from **21** (equation 16).

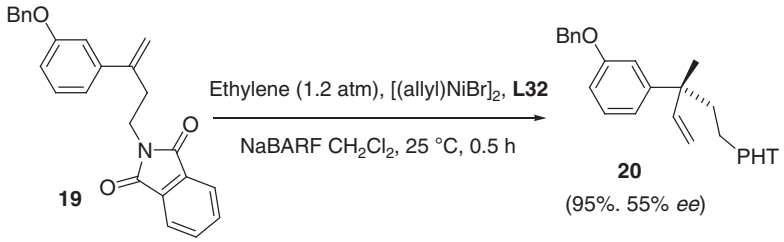


(Ligands **L33a**, **L34**, **L35** or **L38:** Table 5) (*ee*'s up to 99%) (14)

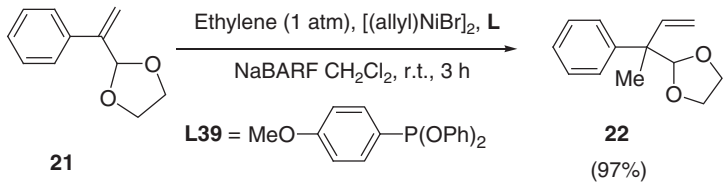
Table 5 Generation of all-carbon quaternary centers via asymmetric hydrovinylation[a]

Entry	*Vinylarene*	*Ligand*	*Conversion (%)/yield (%)*	*Selectivity (%)*	ee *(%)*	*Reference*
1.	 **17b**	**L34**	>99/95	>99	92, *R*	80
		L33a	>99/97	>99	>97, *R*	79, 83
		L35	>99/92	>99	94, *R*	80
		L38	–/80	89	70, *S*	78
2.	 **25**	**L38**	–/92	86	88	78
3.	 **26**	**L33a**	>99/>90	>99	90	79
4.	 **27**	**L33a**	>94/>90	>95	90	79
5.	 **28**	**L33a**	61/60	>97	>95	79
		L38	–/89	84	99, *S*	78
6.	 **29**	**L33a**	>98/>93	>96	50	79
7.	 **30**	**L33a**	>99/>98	>99	93	79
8.	 **31**	**L38**	–/94	80	99	78
9.	 **32**	**L34**	>99/68	71	>95, *R*	80
		L33a	>99/71	72	99, *R*	79
		L35	79/64	79	99, *R*	79
10.	 **33**	**L34**	–/66	99	84, *R*	80
		L33a (R_a,S_c,S_c)	–/70	99	94, *R*	80
		L33b (R_a,R_c,R_c)	–/70	99	89, *R*	80
11.	 **19**	**L34**	–/>95	99	55	80
		L33a	–/69	85	61	80
12.	 **21**	**L38**	–/75	–	24	82
13.	 **23**	**L38**	–/62	–	95	81

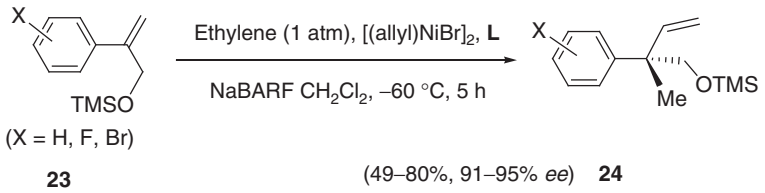
[a]See equation 14 for a typical procedure.



(15)



(16)



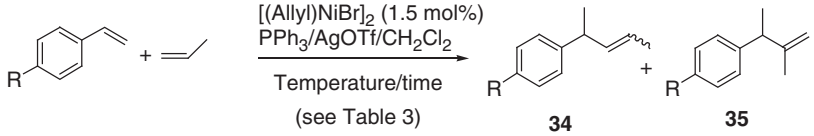
(17)

A brief examination of the origin of asymmetric induction in the chroman (3,4-dihydro-2*H*-1-benzopyran) **33** using diastereomeric phosphoramidites shows that the chirality of the product is determined by the axial chirality of the biaryl moiety of the ligand, not by the chirality of the amine.[80] As shown in entry 9, both **L33a** (R_a,S_c,S_c) ligand and a diastereomer with a different configuration **L33b** (R_a,R_c,R_c) gave the (*R*)-product in comparable *ee*'s (94% and 89%). Since the phosphoramidite **L34** (S_c,S_c), a ligand derived from flexible biphenyl scaffolding also gives the (*R*)-configuration in the product, it should be presumed that the chirality of the bis-amine (S_c,S_c) induces the *R*-configuration in the biphenyl unit. Although other procedures have been reported[84–86] for the synthesis of products of entries 8 and 9, the asymmetric hydrovinylation reaction provides the shortest and operationally simplest route available to these compounds, which have served as intermediates for pyrrolidinoindolines[87] and the benzomorphane analgesics (–)-eptacozine[84,85] and (+)-aphanorphine.[85]

5.32.6 Other Related Ni-Catalyzed Hydroalkenylation Reactions Including Hydrovinylation

5.32.6.1 Codimerization of Propene and Vinylarenes

A number of other Ni-catalyzed heterodimerization reactions using alkenes other than ethylene are known, even though no enantioselective versions of these useful reactions have been reported.[88] Propene reacts with styrene and substituted styrenes under the recent protocol developed by RajanBabu,[49] at higher temperature, yielding the expected products, **34** and **35** (equation 18 and Table 6).[89] As expected, a mixture of regioisomeric products is formed with the predominant addition of the C_1-carbon of propene (**34**) to the benzylic position. These reactions also established the remarkable functional group tolerance of the Ni(II)-catalyzed HV reaction conditions.



(18)

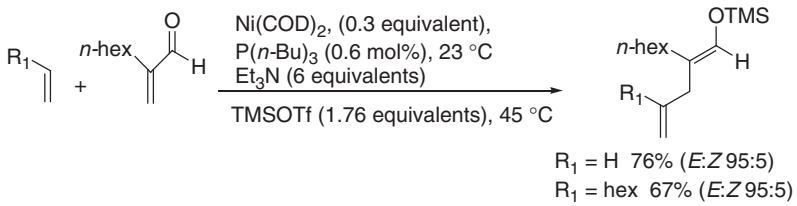
5.32.6.2 Addition of Alkenes to Enones

In 2008 Jamison reported[90] catalytic conditions under which alkenes including ethylene can act as alkenylmetal precursors in conjugate addition reactions (equation 19). Similar conjugate additions of alkenes to enones (equation 20) have been reported by Ogushi at much higher temperatures under different conditions.[91] These results, although maybe not significant from a synthetic perspective, raise very interesting mechanistic questions, since the regioselectivity in the two reactions are quite different.

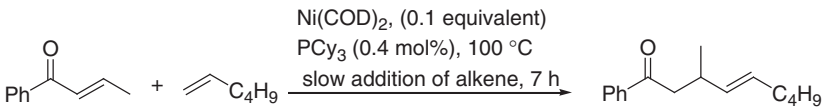
Table 6 Heterodimerization of propene and vinylarenes[a]

Entry	*R*	*Temperature (°C)*	*Time (min)*	*Yield (%)*	**34:35**
1	*i*-Bu	−15	15	96	3:1
2	OMe	−15	60	86	4:1
3	Cl	0	15	94	4:1
4	Br	0	10	95	4:1
5	OAc	−10	30	93	4:1
	OAc	−55 to −40	30	98[b]	5:1
6	PhC(O)− [c]	10	15	94	4:1
7	NTs_2[c]	10	25	92	2:1
8	MVN[c,d]	−5	60	88	10:1

[a]See equation 18 for procedure.
[b]1.4 mol% Ni used.
[c]3 mol% Ni used.
[d]2-methoxy-6-vinylnaphthelene used as the substrate.



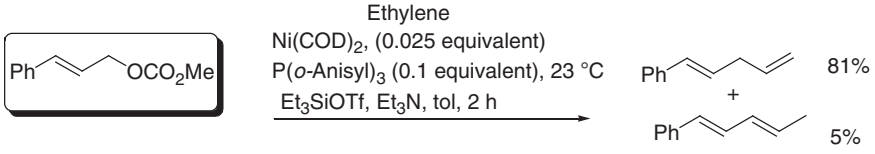
(19)



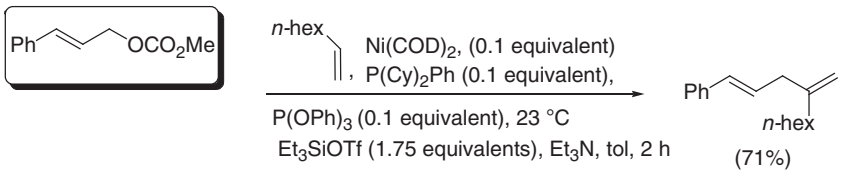
(20)

5.32.6.3 Addition of 1-Alkenes to Allylic Substrates

Jamison also reported a new reaction of allylic substrates with ethylene under the conditions shown in equation 21a.[92] Slight modification of the reaction, in which an additional equivalent of $P(OPh)_3$ is added, facilitated the codimerization of cinnamyl derivatives with linear alkenes (equation 21b). Note that in the case of the 1-alkenes, the C–C bond formation occurs at the more substituted carbon.



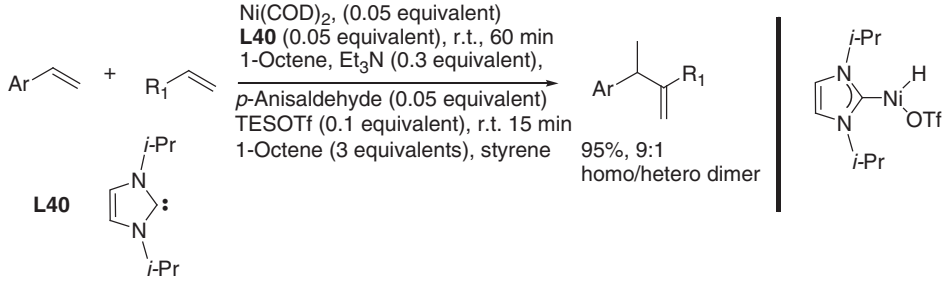
(21a)



(21b)

5.32.6.4 Addition of Alkenes to Vinylarenes

An unprecedented tail-to-tail hydroalkenylation of styrene, using an *N*-heterocyclic carbene (**L40**)-nickel complex as a catalyst, has been reported by Ho et al. (equation 22).[93] The mechanisms of these reactions remain largely speculative and the reader is urged to consult the original publications for reasonable proposals.

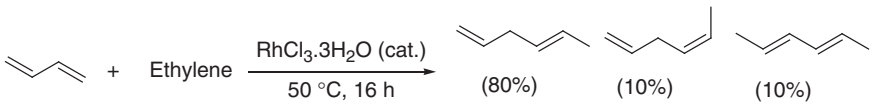


(22)

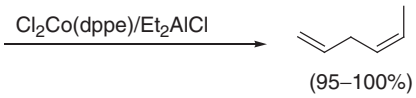
5.32.7 Hydrovinylation and Hydroalkenylation of 1,3-Dienes Catalyzed by Rh, Fe, Co, and Ru

5.32.7.1 Rhodium- and Iron-Catalyzed Reactions

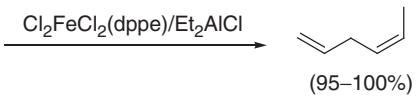
Rhodium-catalyzed linear dimerization of 1,3-butadiene and ethylene (equation 23) is an industrially important process for the synthesis of hexadienes.[4] Research in related cobalt (equation 24)[94,95] and iron (equation 25)[8,96] catalyzed processes has seen a resurgence of activity recently.



(23)

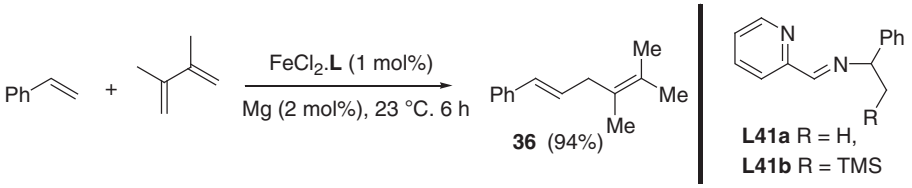


(24)

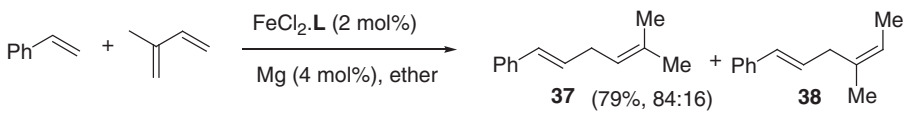


(25)

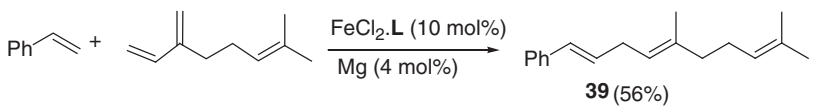
α-Olefins (especially styrene derivatives) undergo highly stereo- and regioselective 1,4-addition to 1,3-dienes in the presence of 1 mol% of iminopyridine-Fe(0)-complex (ligand **L41a**) to give exclusively the linear product **36** (equations 26, 27, and 28).[97] Unsymmetrical dienes such as isoprene produces two regioisomers (**37** and **38**) resulting from additions at either terminal position of the diene (equation 27), even though the selectivity can be improved by ligand tuning (e.g., switching to ligand **L41b)**. The geometry of both double bonds formed is controlled in this reaction, and formation of an η^4-complex, coupling with the alkene and a *syn*-β-hydride elimination may be responsible for this stereochemical outcome. Aliphatic α-olefins generally give mixture of products and the synthetically useful reactions are limited to styrene derivatives.



(26)



(27)

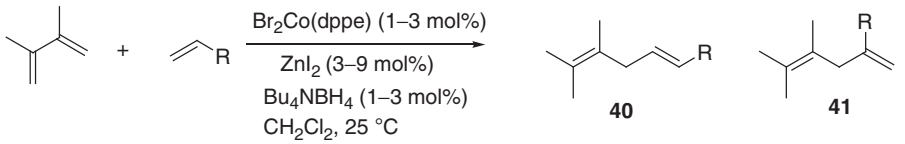


(28)

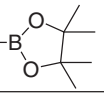
5.32.7.2 Cobalt-Catalyzed Reactions

Co(I)-catalyzed 1,4-hydroalkenylations of 1,3-dienes have been extensively developed by Hilt.[98–100] The optimum conditions for the addition to 2,3-dimethylbutadiene use ZnI_2 and a chelating phosphine with $CoBr_2$ in the presence of a reducing agent such as Bu_4NBH_4 or activated Zn dust (equation 29).[101] Under these conditions, terminal alkenes such as 1-hexene, cyclohexylethylene, or vinyltrimethylsilane gave almost exclusively the branched product(s) **41**, whereas terminal alkenes with an electron-withdrawing alkoxycarbonyl group (e.g., ethyl or *t*-butylacrylate) on the double bond give linear product(s) **40**.

L42 (SchmalzPhos)

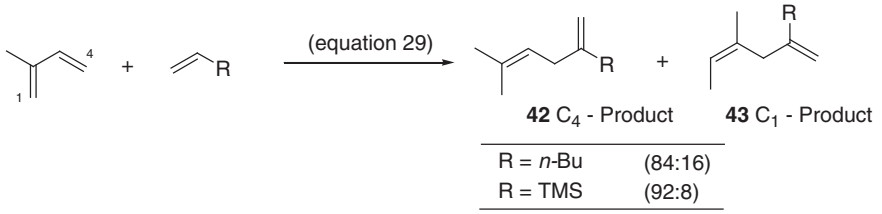


40 **41**

	L = dpppe[a]		L = L42[b]	
	40:41		40:41	
R = CO_2Et	92	–	99	–
R = CH_2CO_2t-Bu	–	97	99	1
R = *n*-Bu	–	95	98	2
R = Cyclohex	–	66	72	28
R = CH_2TMS	–	92	3	97
R = 	–	98	99	1

[a]See equation 29. [b] Br_2Co(**L42**) (5 mol%), Zn (10 mol%) ZnI_2 (10 mol%), CH_2Cl_2, r.t. (29)

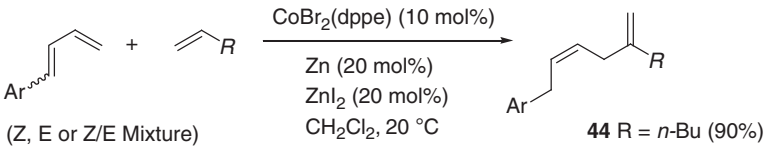
The regioselectivity of addition to the alkene can be controlled by judicious choice of ligands for the reaction, under otherwise identical conditions.[99] Thus, dppe gives the branched 1,4-HV products (**41**) with unactivated alkenes, whereas SchmalzPhos (**L42**) gives the linear products (**40**). Activated alkenes such as acrylates give linear products using both sets of ligands. Reactions with unsymmetrical 1,3-diene are less selective, giving addition at both C1 and C4 positions of the diene (equation 30). The addition at the less hindered C4 position (**42**) of isoprene predominates (equation 30). In the original studies, bis-1,2-diphenylphosphinoethane was found to be the best ligand for this transformation. Control of the C_1 versus C_4 addition to the diene as a function of the nature of the C_2 and C_3 substituent has been examined.[102] Reaction with styrene and other vinylarenes using Co, unlike the excellent Fe-catalyzed reaction (see equation 26), gives a mixture of branched and linear addition products resulting from addition at the C_1 and C_2 positions of the vinylarenes.[103] However, addition of terminal alkenes to 1-aryl-1,3-butadiene proceeds in excellent yields to give the branched product **44** (equation 31). Irrespective of the starting geometry of the butadiene double bond, only the *Z*-product (**44**) is observed.



42 C_4 - Product **43** C_1 - Product

R = *n*-Bu	(84:16)
R = TMS	(92:8)

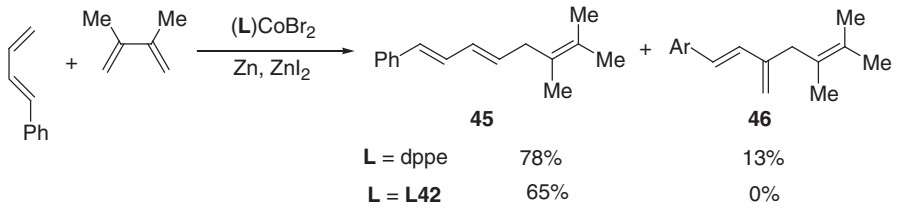
(30)



(Z, E or Z/E Mixture) **44** R = *n*-Bu (90%)

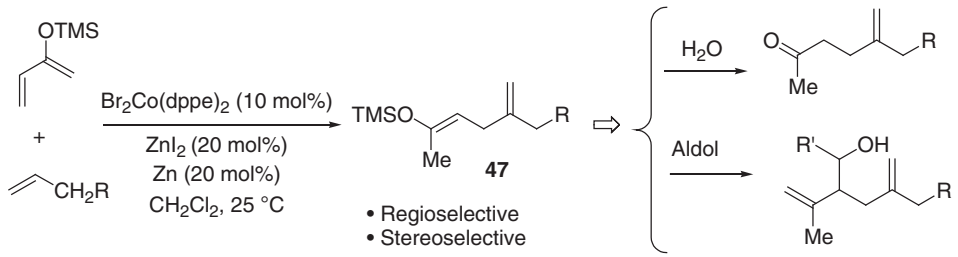
also: R = Benzyl, CH_2PHT, CH_2TMS; Ar = Ferrocenyl, R = *n*-Bu (31)

As shown in equation 32, ligand effects are also important in the 1,4-hydrobutadienylation of 1-aryl-1,3-dienes giving mostly linear products (**45**).[104]



(32)

A particularly noteworthy example of the cocatalyzed hydroalkenylation is the reaction of a 2-siloxydiene.[105] The hydrovinylation product **47** is formed exclusively as a single isomer with (*E*)-silylether geometry and C–C bond formation at the C_4 position of the diene and C_2 position of the alkene (equation 33). Since the reaction is tolerant to a number of functional groups (ethers, esters, phtalimide, aromatic, thiophenyl, substituted alkenyl), this is a very powerful reaction to produce a highly functionalized enolate equivalent. Subsequent transformations using electrophiles (e.g., acidic hydrolysis, Mukaiyama aldol, ozonolysis) should give valuable intermediates for organic synthesis.

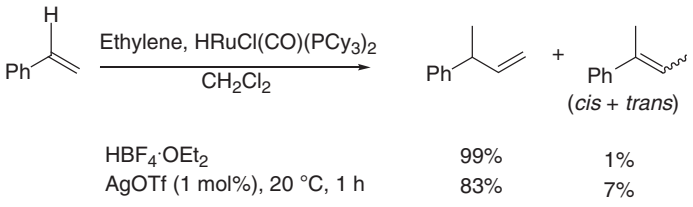


(33)

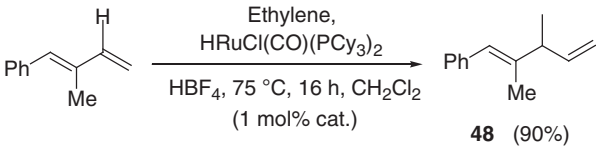
The cocatalyzed hydroalkenylation has been used as a key step in several diastereoselective multicomponent reaction sequences,[106] in one case forming as many as five carbon–carbon bonds in one pot.[107] These reactions attest to the power of cocatalysis and the remarkable functional group tolerance toward the reagents and the reaction conditions.

5.32.7.3 Ruthenium-Catalyzed Reactions

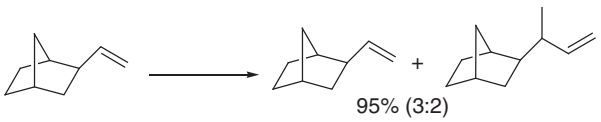
Even though ruthenium chloride was among the first metal salts reported for hydrovinylations,[9,12] useful levels of selectivity in these reactions were attained only recently. Yi and coworkers have disclosed a ruthenium catalyst system consisting of $HRuCl(CO)(PCy_3)_2$ and $HBF_4 \cdot OEt_2$ for the hydrovinylation of styrene and selected 1,3-dienes (equations 34 and 35).[108,109] It has also been found that the HV of styrene can be carried out under one atmosphere of ethylene when silver(I) triflate is used as an additive, all other conditions being the same.[50,110] Good yields of 1,2-adducts (e.g., **48**) can be obtained from 1,2-disubstituted dienes, 1-vinylcycloalkenes and norbornene (equations 35a, 35b, 35c and 35d).



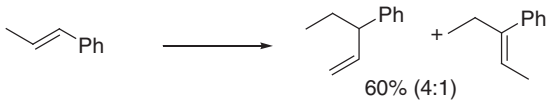
(34)



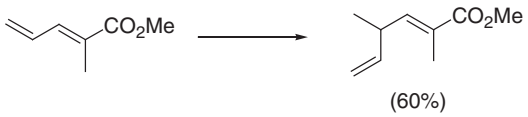
(35a)



(35b)

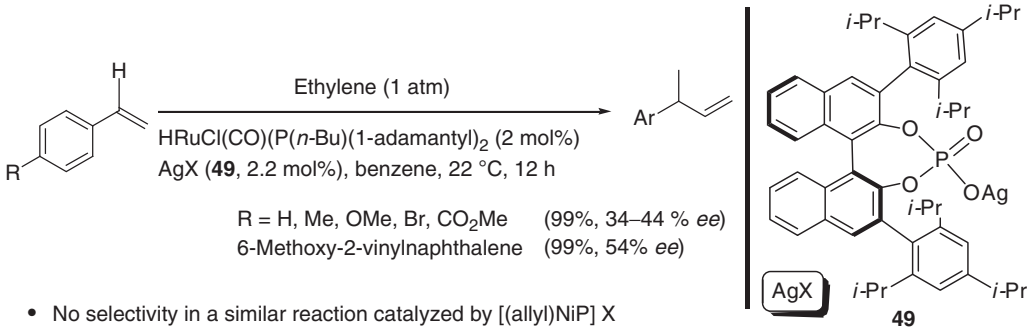


(35c)



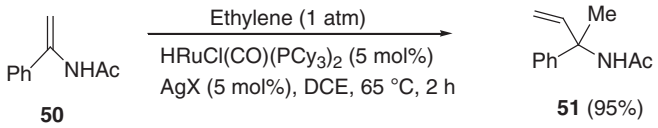
(35d)

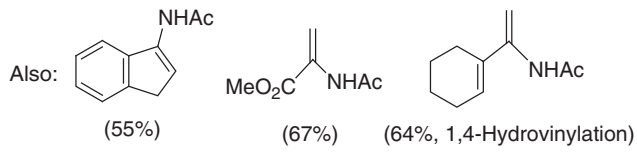
List reported an enantioselective version of the Ru-catalyzed reaction by using a binaphthol-derived chiral anion (**49**) as an additive. Enantioselectivities up to 54% were realized in a quantitative hydrovinylation of MVN (equation 36).[111]



(36)

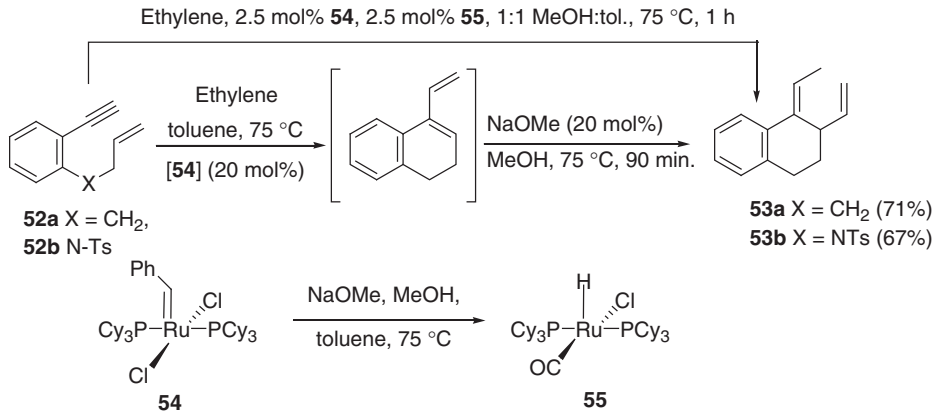
The Ru-catalyzed reaction can also be used for the hydrovinylation of enamides (e.g., **50**) that carry an activating group (aryl, carboalkoxy, or alkenyl group) on the α-carbon, giving products (e.g., **51**) with a quaternary carbon (equation 37).[112] The reaction is done at elevated temperatures for these sluggishly reactive substrates. Use of a [dialkylmenthylphosphine]Ru(II) complex gave low yields and poor enantioselectivities.



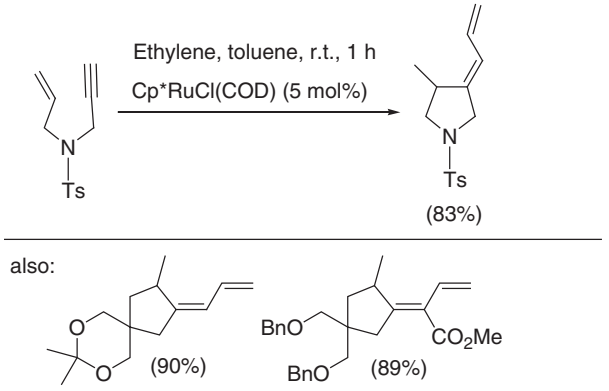


(37)

A connection[113] between Grubbs' metathesis catalyst **54** and Yi's hydrovinylation catalyst **55** was cleverly exploited by Snapper et al. in a tandem enyne metathesis/hydrovinylation protocol in which the metathesis catalyst was converted into the HV-catalyst after the first stage, by addition of more methanol, and continuing the reaction under an atmosphere of ethylene (**Scheme 6**). Because of the favorable relative rates of the various processes involved, the overall transformation from the enyne to the HV-product can be carried out in a single flask, in one step, by adding equimolar mixtures of both catalysts (2.5 mol% each) at the beginning of the reaction. A mechanistically different tandem reaction, shown in equation 38, employs an enyne cyclization followed by ethylene addition to give a diene. The alkylidenecyclopentene formed in this sequence can be formally thought of as an HV product.[114]



Scheme 6 A tandem metathesis/hydrovinylation sequence using Ru complexes.



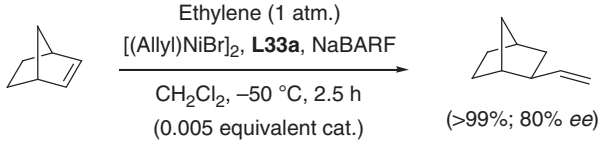
(38)

A number of related ruthenium-catalyzed heterodimerization reactions of methyl acrylate with norbornene, dihydrofuran, and various *N*-vinylamides have been reported, even though asymmetric variations are not known.[115–117] Ruthenium catalysts also affect either linear homodimerization of styrene or linear codimerization of styrene and ethylene.[118]

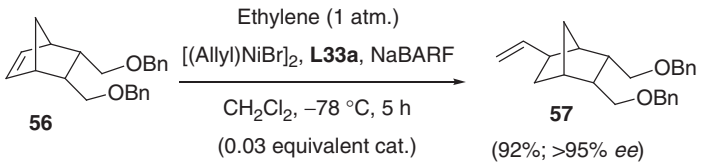
Linear codimers between styrene and ethylene are also formed as the major products by chromium catalysts supported by bis(arylphosphino)amine ligands on activation with methylaluminoxane (MAO).[119]

5.32.8 Ni-Catalyzed Hydrovinylation of Norbornene and Other Strained Alkenes

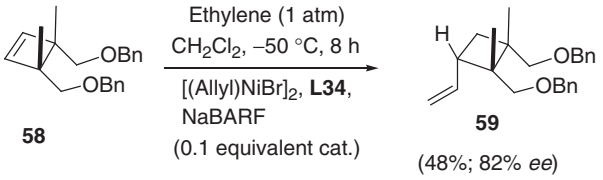
The viability of norbornene and other similar bicyclic molecules as substrates for hydrovinylation suggests that strain, in addition to electronic factors, can be used to promote highly selective codimerization reactions.[70,71] Hydrovinylations of norbornene and a 4,5-dibenzyloxymethyl derivative **56** using the phosphoramidite **L33a** as a ligand for Ni(II) gave very high yields and good to excellent enantioselectivities (equations 39 and 40). The cyclobutene **58** undergoes Ni-catalyzed hydrovinylation as shown in equation 41, even though the enantioselectivity remains modest. The hetero[2.2.1]bicyclic substrates **60** and **62** undergo hydrovinylation with ligand **L43**. Surprisingly, in these reactions, there is no ring-opening observed as is the case with most organometallic additions to the double-bonds of these types of molecules. The phosphoramidites are poor ligands for this class of substrates. For example, the adduct **63** is produced in $<15\%$ yield using 10 mol% of a Ni-complex of the phosphoramidite **L33a**, but with a very high enantioselectivity ($\sim 87\%$). Further work is needed to achieve synthetically useful levels of yield and selectivity in reactions of this class of substrates.



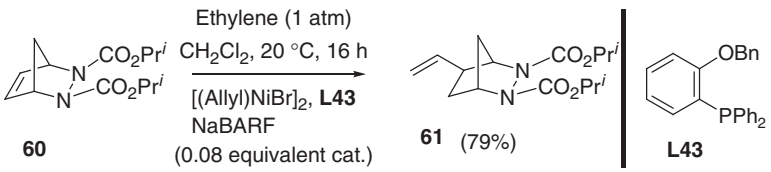
(39)



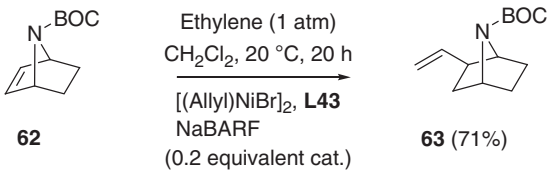
(40)



(41)



(42)



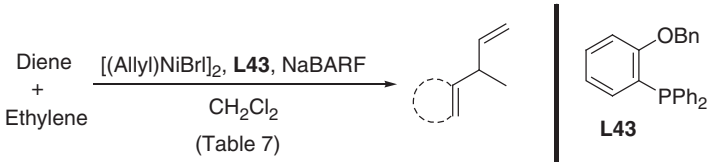
(43)

5.32.9 Asymmetric Hydrovinylation of 1,3-Dienes

The asymmetric hydrovinylation of 1,3-cyclooctadiene (equation 4) using the ligand (–)-dimenthyl(methyl)phosphine was among the first reported examples[41] of metal-catalyzed asymmetric carbon–carbon bond forming reactions. However, the observed selectivities were unacceptably low by current standards. Other reactions where modest selectivities are obtained, include HV of cyclopentadiene (equation 7), 1,3-cyclohexadiene (equations 8), and 1,3-(E)-pentadiene (equation 9).

5.32.9.1 Ni(II)-Catalyzed Asymmetric Hydrovinylation of 1,3-Dienes

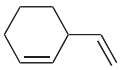
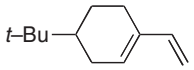
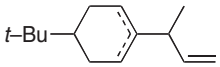
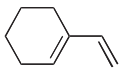
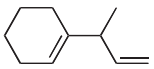
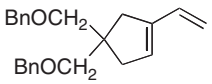
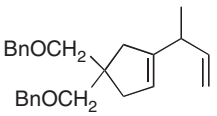
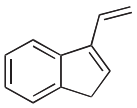
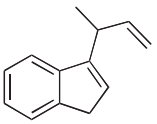
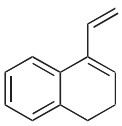
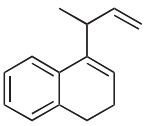
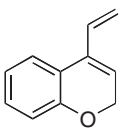
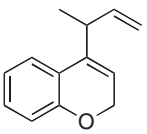
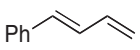
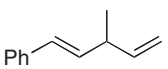
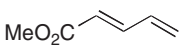
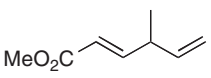
Recent investigations of the ligand effects on the hydrovinylation of 1,3-dienes show that the beneficial effects of hemilabile coordination seen in the context of vinylarenes[35,49] extend to this class of substrates as well. The best ligand for this transformation was identified as 2-benzyloxyphenyldiphenylphosphine **L43**.[120] Under the optimized conditions (equation 44), using this ligand, high yield and selectivities for the 1,2-hydrovinylation product were observed for a series of 1,3-dienes (Table 7). In general, the hydrovinylation of both cyclic and acyclic dienes resulted in high yields (>97%) and selectivities (>95%), giving the 1,2-addition product at the less hindered olefin. The cyclohexene and cyclopentene derivatives gave small amounts of 1,4-adducts (entries 3 and 4).



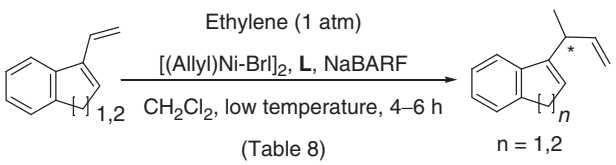
(44)

Table 8 shows the results of asymmetric hydrovinylations of 1,3-dienes (equations 45 and 46) using ligands **L27**, **L33a**, *ent*-**L33a**, **L34**, and **L43**. Hydrovinylation of substrate **80** (entry 5) using the ligands **L43** (an achiral ligand), **L33a,** and *ent*-**L33a** shows the power of enantioselective catalysis in overcoming the inherent selectivity of a chiral substrate with the judicious choice of ligands. Either diastereomer of the product (**81** or **82**) can be prepared in excellent *ee*'s using the appropriate ligand (equation 46).

Table 7 Hydrovinylation of 1,3-dienes[a]

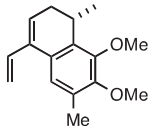
Entry	Diene	Product(s)	Conversion (%)	Selectivity (%)
1			94	>99
2	 **64**	 **65**[b]	>99	98
3	 **66**	 **67**	>99	68[c]
4	 **68**	 **69**	>99	72[d]
5	 **70**	 **71**	>99	>99
6	 **72**	 **73**	>99	98
7	 **74**	 **75**	97	>99
8	 **76**	 **77**	>99	95
9	 **78**	 **79**	99	98

[a]See equation 44 and reference 120 for details.
[b]Mixture of two diastereomers (~2:1).
[c]Rest, isomerized 1,2-product and 1,4-adducts.
[d]20% of 1,4-adduct.

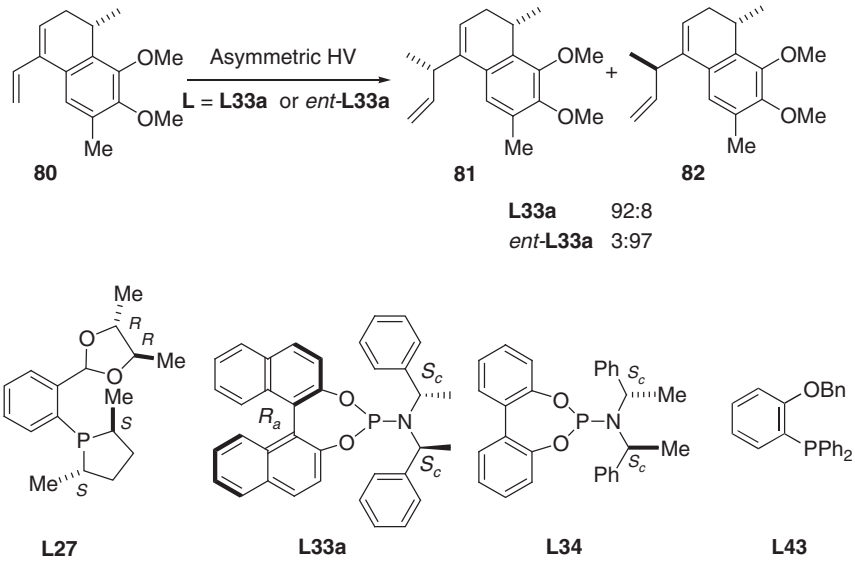


(45)

Table 8 Ni(II)-catalyzed asymmetric hydrovinylation of 1,3-dienes[a] (equation 45)

Entry	*Diene*	*Ligand*			
		Phospholane ***L27*** *Conversion (%) selectivity (%)*	ee *(%)*	*Phosphoramidite* ***L33a*** *Conversion (%) selectivity (%)*	ee *(%)*
1	**70**	>99 (>99)	85 (*R*)	>99 (>99)	96 (*S*)
2	**72**	>99 (97)	93 (*R*)	>99 (>99)	>99 (*S*)
3	**74**	>99 (99)	38 (*R*)	>99 (>99)	95 (*S*)
4	**76**	88 (>99)	<5	>99 (96)	77[b]
5	 **80**	–	–	92 (>99) >99 (>99) >99 (>99)	84 (*S*)[c] 94 (*R*)[c,d] 18 (*S*)[c,e]

[a]See references 120 and 121 for further details, and equation 45 for procedure.
[b]84% *ee* with **L34**.
[c]% *de*, see reference 121.
[d]With *ent*-**L33a**.
[e]With **L43**.

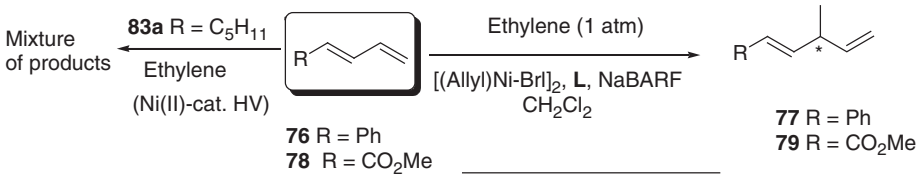


5.32.9.2 Cobalt(II)-Catalyzed Hydrovinylation of 1,3-Dienes

The high levels of regioselectivities in the nickel-catalyzed hydrovinylations of arene- and carboalkoxy-substituted 1,3-dienes notwithstanding (Scheme 7, Table 8, entry 4), the corresponding reaction of unactivated, linear 1,3-diene substrates (e.g., **83a**) gave a mixture of products consisting of 1,2- and 1,4-adducts, accompanied by isomerization of these primary products. This is not surprising since between 1,2- and 1,4-HV reactions up to a maximum of 11 isomers (including the enantiomers) of the 1:1 addition are possible in this reaction (Figure 6).

5.32.9.2.1 Cobalt-catalyzed asymmetric hydrovinylation of vinylarenes and unactivated linear 1,3-dienes

Although the iron- and cobalt-catalyzed linear codimerizations of 1,3-butadiene and α-olefins have seen a resurgence of activity recently (vide infra), except for a lone report of asymmetric hydrovinylation of styrene (equation 47),[122] surprisingly little attention has been paid to the cobalt-catalyzed hydrovinylation reaction in which chiral, branched products are formed.



R	L	Yield	%*ee*
Ph	**L33a**	97	77
CO_2Me	**L43**	98	–

Scheme 7 Hydrovinylation of unactivated and activated 1,3-dienes.

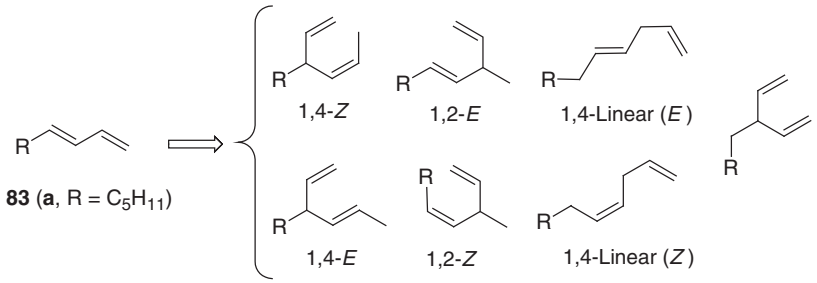
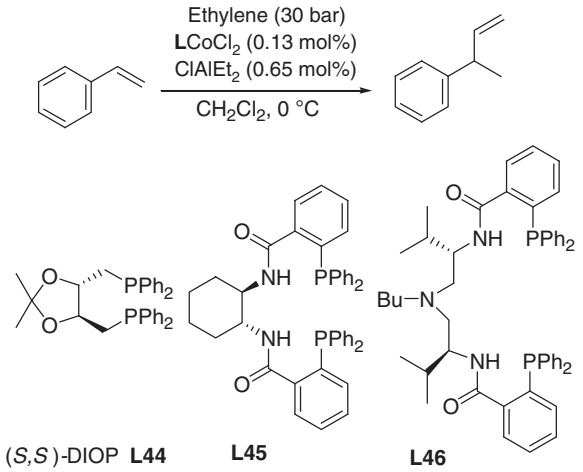


Figure 6 Possible hydrovinylation products of 1-alkyl-1,3-dienes.

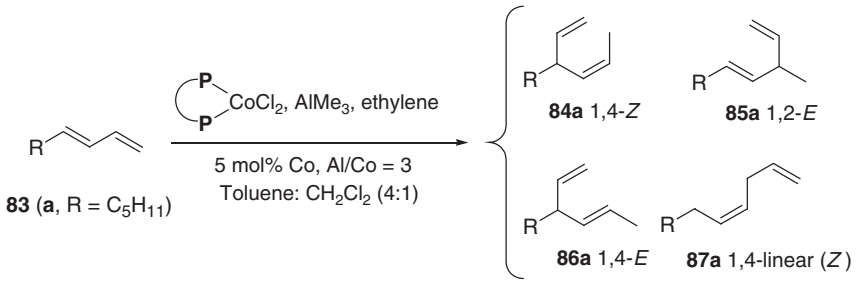


(47)

L	Conversion	Selectivity[a]	%*ee*
dppm	100	87	NA
dppe	93	100	NA
DIOP (**L44**)	8	100	14 (*R*)
L45	74	100	47 (*R*)
L46	80	99	50 (*S*)

[a]For 3-phenyl-1-butene

Systematic studies were conducted with (*E*)-1,3-nonadiene (**83a**) and $LCoX_2$ complexes [$L=Ph_2P(CH_2)_nPPh_2$, n = 1–4] in the presence of various Lewis acids including trialkylaluminum as promoters.[123] The results suggested that these complexes, when used with a 3:1 ratio of $AlMe_3$:Co, were suitable for effective hydrovinylation of 1,3-dienes (equation 48). This is in sharp contrast to a previous report that $AlMe_3$ and MAO were ineffective in the hydrovinylation of styrene.[122]



(48)

On examining several bis-phosphine ligands, the product distribution was found to be highly dependent on the bite angle of the ligand and the reaction temperature (Table 9).

Table 9 Cobalt-catalyzed hydrovinylation of (*E*)-1,3-nonadiene (**83a**)[a]

Entry	*Ligand*	*Temperature (°C)*	*Product, yield (%)*[b]			
			1,4-Z	*1,4-*E	*1,2-*E	*1,4-Linear*
1	dppb	−10	93	7	0	0
2	dppm	−20	<2	30	67	<2
3[c]	dppe	−10	70	0	0	10
4[c]	dppp	−20	75	0	0	14
5[c]	dppp	23	0	26	65	<4
6	2 PPh_3	−10	–	–	–	–

[a]See equation 48 for general procedure. Reactions conducted on 1,3-*E*-nonadiene (**83a**, R = C_5H_{11}).
[b]Determined by GC and NMR analysis.
[c]In addition to products, the remainder is unreacted starting material.

In the initial ligand screening, dppb was found to give the highest levels of selectivity for the 1,4-*Z* adduct (**84a**, entry 1) and dppm gave the highest proportion of 1,2-*E*-adduct (**85a**, entry 2). A series of linear 1,3-dienes were subjected to the hydrovinylation reaction using dppb, resulting in excellent yields and selectivities for the 1,4-*Z* adducts (Table 10). The reaction conditions appear to be compatible with functionalized dienes possessing benzyl ethers and trisubstituted olefins, such as *β*-myrcene (entries 6 and 7, respectively).

Table 10 Cobalt-catalyzed hydrovinylation of 1,3-dienes: Substrate scope[a]

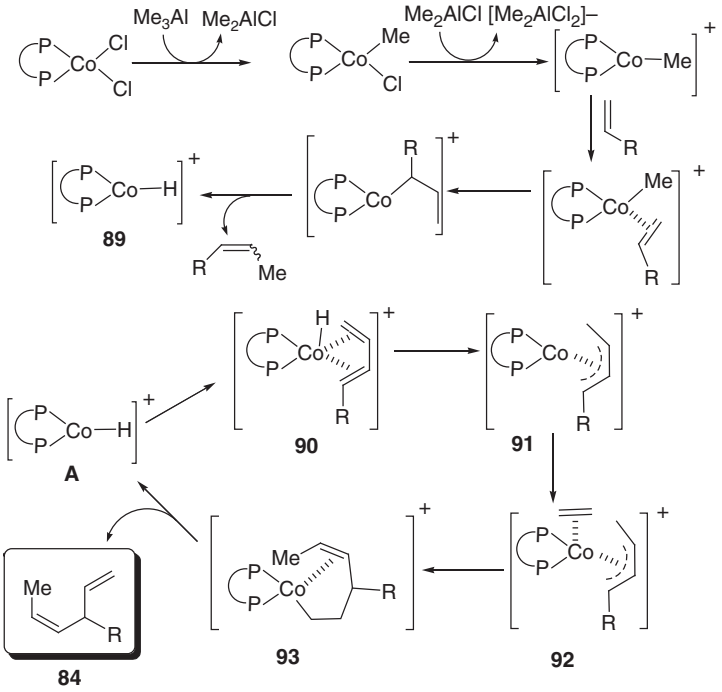
Entry	*Diene/R group*	*Product, yield (%)*[b]			
		1,4-Z	*1,4-*E	*1,2-*E	*1,4-Linear*
1	C_5H_{11} (**83a**)	93 (>93)	7	0	0
2	C_6H_{13} (**83b**)	95 (>99)	0	0	<2
3	C_7H_{15} (**83c**)	95 (>99)	0	0	<2
4	C_8H_{17} (**83d**)	95 (>99)	<1	0	0
5	CH_3 (**83e**)	(>95)[c]	(<5)	–	0
6	CH_2OBn (**83f**)	78[d]	0	0	0
7	*β*-Myrcene (**88**)	0	0	0	–[e]

[a]See equation 48 for general procedure. Reactions conducted with ligand dppb.
[b]Isolated yield (in parenthesis are yields based on GC or NMR analysis).
[c]Volatile products.
[d]Conducted at 0 °C.
[e]Only linear adduct [(*Z*)-2-methyl-6-(3-propenyl)-octa-2,6-diene] was formed in 78% isolated yield.

5.32.9.2.1.1 A possible mechanism of the cocatalyzed hydrovinylation

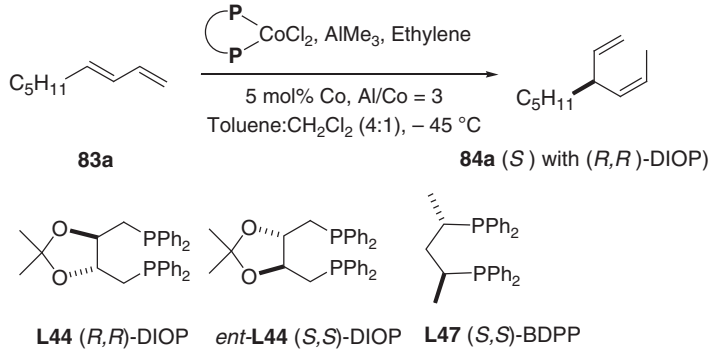
Under the nonreducing conditions used for the hydrovinylation,[124,125] a hydride, $[(L)Co(II)\text{-}H]^+$ (**89**), is possibly the active catalytic species.[126,127] This species could be formed by metathesis of the Al–Me/Co–Cl bonds, abstraction of a Cl^- by Me_2AlCl,

alkene coordination, migratory insertion of the alkene into the Co–Me bond, followed finally by a reductive elimination (Scheme 8). Addition of the Co–H group via an η^4-diene complex **90** would produce a *syn-anti*(allyl)cospecies **91** which would undergo coupling with ethylene to give **93**. β-Hydride elimination from **93** regenerates the catalyst, giving the major product **84**. Intermediacy of the η^3-allylic intermediate **92**, which is capable of *syn-/anti*-isomerization, would also explain the temperature dependence of the product distribution. For example, in the Co(dppp)Cl_2-mediated HV of **83a**, none of the product **84a**, which is the major component at –20 °C (formed via the (*syn-anti*-(allyl) intermediate **91**), is observed at 23 °C. At low temperature, where the asymmetric catalyzed reactions are carried out, **91** must be configurationally stable to give the high selectivities observed. From the solid state structures of the tetrahedral complexes involved,[123] (*R,R*)-[DIOP]$CoCl_2$ and (*S,S*)-[BDPP]$CoCl_2$, it would appear that these complexes can overcome one of the serious limitations of catalysis by Ni(II)-complexes, where only monodentate ligands have been successful. Cobalt with the possibility of higher coordination numbers can support more flexible geometries for the intermediates in the catalytic cycle.



Scheme 8 A possible mechanism of Co(II)-catalyzed hydrovinylation of a 1,3-diene.

Realization of a synthetically useful chemo-, regio- and diastereoselective methods led to the investigation of an asymmetric variant (equation 49). Among the ligands that were evaluated, the best results were achieved with the simplest chiral analogs of dppb and dppp that are commercially available: (*R,R*)-(2,2-dimethyl-1,3-dioxalane-4,5-diylbismethylene)-bis-diphenylphosphine [(*R,R*)-DIOP, (**L44**)] and (*S,S*)-2,4-*bis*-diphenylphosphinopentane [(*S,S*)-BDPP, (**L47**)]. Under the optimized conditions (equation 49), (*E*)-1,3-nonadiene (**83a**) gave nearly quantitative yield of (*S*)-(*Z*)-4-vinylnon-2-ene (**84a**) with 95% *ee* (equation 49, Table 11, entry 1). In general, high levels of regio- and enantioselectivities were observed for a series of linear 1,3-dienes (Table 11, entries 1–10).



(49)

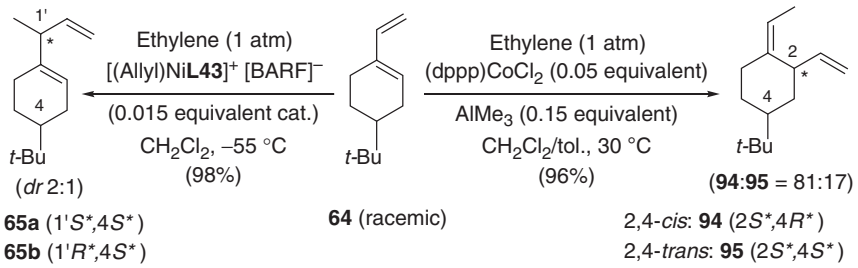
Table 11 Cobalt-catalyzed asymmetric hydrovinylation of 1,3-dienes[a]

Entry	*Diene/R group*	*Ligand*	*Yield (%)*[b]	ee *(%)*
1	C_5H_{11} (**83a**)	(*R*,*R*)-DIOP	>99 (95)	95 (*S*)
2	C_5H_{11} (**83a**)	(*S*,*S*)-DIOP	>99 (96)	93 (*R*)
3	C_5H_{11} (**83a**)	(*S*,*S*)-BDPP	>99 (96)	97 (*R*)
4	C_6H_{13} (**83b**)	(*R*,*R*)-DIOP	>99 (96)	95 (*S*)
5	C_7H_{15} (**83c**)	(*R*,*R*)-DIOP	>99 (98)	95 (*S*)
6	C_8H_{17} (**83d**)	(*R*,*R*)-DIOP	>99 (95)	96 (*S*)
7	CH_3 (**83e**)	(*R*,*R*)-DIOP	>90[d]	90 (*S*)[c]
8	CH_3 (**83e**)	(*S*,*S*)-DIOP	>90[d]	89 (*R*)[c]
9	CH_2OBn (**83f**)	(*R*,*R*)-DIOP	>99	99 (*S*)
10	CH_2OBn (**83f**)	(*S*,*S*)-DIOP	>99	96 (*R*)

[a]See equation 49 for general procedure; reactions conducted at –45 °C for 6 h.
[b]Determined by GC (isolated yield in parenthesis).
[c]Configuration determined by comparison to known compound, all others assigned by analogy.
[d]Volatile products.

5.32.9.2.2 Cobalt-catalyzed asymmetric hydrovinylation of 1-vinylcycloalkenes

Hydrovinylation of racemic 4-*t*-butyl-1-vinylcyclohex-1-ene (**64**, Scheme 9) revealed that, in sharp contrast to the corresponding Ni(II)-catalyzed reaction (see equation 44, Table 7, entry 2),[120] the (dppp)$CoCl_2$/Me_3Al-mediated reaction gives almost exclusively the 1,4-adducts as a mixture of *cis*- (**94**) and *trans*- (**95**) isomers (81:17).[128] During these studies it was also recognized that MAO[129] can serve as an effective replacement of the hydrocarbon solutions of Me_3Al. Both the Ni(II) and Co(II) reactions are highly regioselective in the formation of the respective 1,2-(**65a**/**65b**) and 1,4-(**94**/**95**) adducts with less than 4% of the regioisomeric products formed in each case.



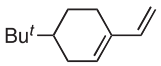
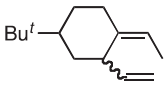
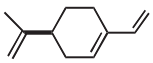
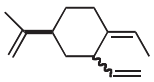
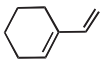
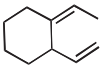
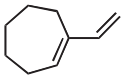
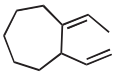
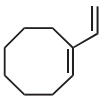
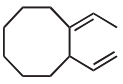
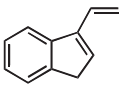
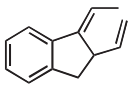
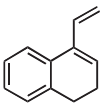
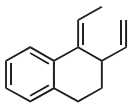
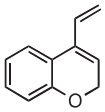
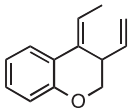
Scheme 9 1,2- Versus 1,4-hydrovinylation of a 1-vinylcyclohexene.

The scope of the reaction is illustrated with the examples shown in Table 12. Under the standard reaction conditions, the hydrovinylation is highly chemoselective for the 1,3-diene moiety, as shown by the reaction of the enantiopure triene **96**, which was prepared from commercially available (–)-perrilaldehyde (entry 2). The 1,4-adducts **97** and **98** (ratio of 4:1) are obtained in excellent yield. Conformationally flexible 1-vinylcyclohexene (entry 3) also gave predominantly the 1,4-adduct (**99**), with up to 22% of the 1,2-HV product **67** (see also Table 7). The Co(II)-catalyzed 1,4-hydrovinylations are particularly effective for 1-vinylcycloheptene (entry 4) and 1-vinylcyclooctene (entry 5), under the typical reaction conditions using dppp as the ligand.

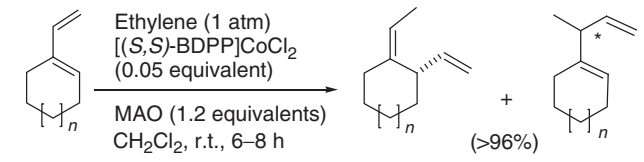
Substrates **70**, **72**, and **74**, which gave exclusive 1,2-hydrovinylation under the Ni-catalyzed reaction conditions described in Scheme 9,[120] gave quantitative yields of the 1,4-adduct (1,4-HV: 1,2-HV>99:1) in the Co(II)-mediated reactions (entries 6–8).

The successful development of a useful and simple protocol for the cobalt-catalyzed hydrovinylation of 1-vinylcycloalkenes led to the exploration of an asymmetric version.[128] Reactions of two prototypical dienes, 1-vinylcyclohexene and 1-vinylcycloheptene, are shown in equation 50. These reactions with (BDPP)$CoCl_2$ closely parallel the results obtained with the corresponding (dppp)$CoCl_2$, except that the proportion of the 1,4-HV product is slightly more in the former case than what was found with dppp. The 1,4-HV products **99** and **101** are obtained essentially as single enantiomers, whereas the 1,2-HV products **67** and **102** are formed in much lower *ee*'s. Ligand (*S*,*S*)-BDPP (**L47**) was used to effect the asymmetric hydrovinylation of a series of other 1-vinylcycloalkenes with excellent yields and regio- and enantioselectivities and the results are shown in Table 13.

Table 12 Co(II)-catalyzed 1,4-hydrovinylation of 1-vinylcycloalkenes[a]

Entry	*Diene*	*Conversion (%)*	*Regioselectivity*[b]	*Major product(s)*
1.	 **64** (racemic)	>99	98:2	 [**94** (*cis*):**95** (*trans*) = 81:17]
2.	 **96**	>99	>99	 [**97** (*cis*):**98** (*trans*) = 4.0:1.0]
3.		>99	80:20	 **99** + **67**[c]
4.	 **100**	>99	98:2	 **101** + **102**[c]
5.		>99	>99	 **103**
6.	 **70**	>99	>99	 **104**
7.	 **72**	>99	>99	 **105**
8.	 **74**	~97	>99	 **106**

[a]See **Scheme 9** for typical procedure using (dppp)$CoCl_2$ as catalyst.
[b]1,4-HV:1,2-HV, determined by GC and/or NMR.
[c]**67** and **102** are the exocyclic 1,2-HV products.

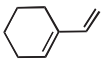
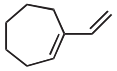
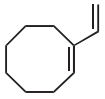
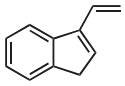
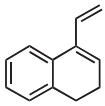
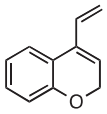
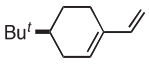


(50)

1-Vinylcyclohexene (n = 1) → (*S*)-**99** (85%; >99% *ee*) + **67** (~15%; *ee* <5%)

1-Vinylcycloheptene (n = 2) → (*S*)-**101** (98%; >99% *ee*) + **102** (~ 4%; *ee* <5%)

Table 13 Co(II)-catalyzed asymmetric 1,4-hydrovinylation of 1-vinylcycloalkenes[a]

Entry	*Diene*	*Conversion (%)*	*1,4:1,2-HV*[b]	*Product (% ee)*[c] *(configuration)*[d]
1.		>99	85:14	**99** [>99 (*S*)[e]]
2.		>95	96:4	**101** [>99 (*S*)[e]]
3.		>99	>99	**103** [>99 (*S*)]
4.	 **70**	>99	>99:<1	**104** [>99 (*S*)]
5.	 **72**	>99	>99	**105** [>99 (*S*)]
6.	 **74**	~97	>99	**106** [>98 (*S*)]
7.	 **64**	>99	87:13	**94**, **95** [>99[e,f] (2*S*, 4*R*)]

[a]See equation 50 and reference 128 for details.
[b]1,4-HV:1,2-HV, determined by ^{1}H NMR and GC.
[c]Major product, determined by chiral stationary phase GC.
[d]Assigned by analogy to products **101** and **105**, whose configurations were confirmed by comparison to known derivatives.
[e]*ee* for the 1,2-HV product: <5%.
[f]**94**:**95** = 1.4:1.0; *ee* for both diastereomers are >99%. Configuration of **94** is shown. Configuration of **95** is presumed to be (2*S*, 4*S*).

As illustrated by the examples in Table 13, the (BDPP)$CoCl_2$-catalyzed asymmetric 1,4-hydrovinylation is a broadly applicable reaction, proceeding in nearly quantitative yields and exceptional enantioselectivities for the respective 1,4-adducts. The enantiopure skipped 1,4-dienes are valuable intermediates for further synthetic applications, possessing two double bonds that can be differentiated by reactivities toward electrophilic reagents (e.g., faster reaction with the trisubstituted olefin) and steric effects (e.g., Rh-catalyzed hydrogenation and hydroboration, metathesis reactions of monosubstituted alkenes).

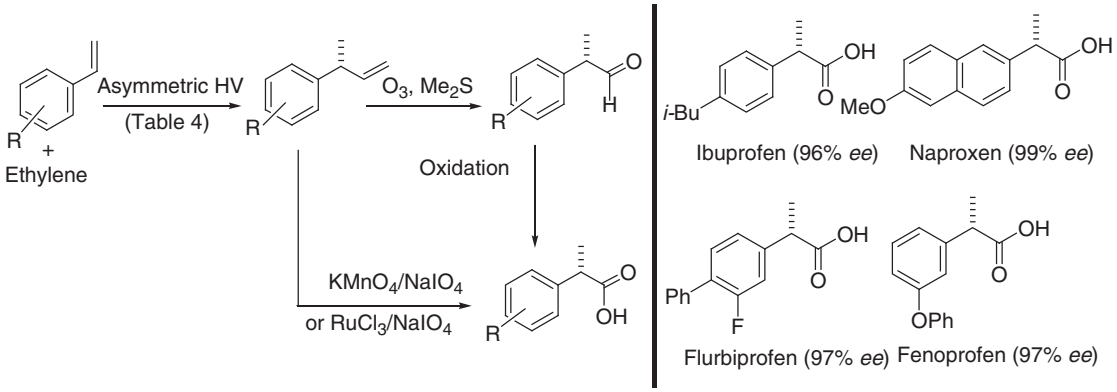
5.32.10 Applications of Asymmetric Hydrovinylation Reactions: Exocyclic Stereocontrol

A chiral side chain carrying a methyl group is a very common structural motif in many terpenoids, and this side chain is often attached to a sterogenic center in the ring. Examples can be found in simple compounds such as the juvenile hormone juvabione, and in more complex structures such as serrulatanes, pseudopterosins, colombiasin, elisabethin A, ophiobolin C, and steroid hormones like calcitrol and their analogs. Many pharmaceutically relevant compounds such as the hugely popular 2-arylpropionic acids have a benzylic chiral center. Asymmetric hydrovinylation offers an attractive solution for the enantioselective installation of the key stereogenic centers in these molecules starting with simple prochiral alkene precursors.

5.32.10.1 Synthesis of (*R*)- and (*S*)-2-Arylpropionic Acids

The 2-arylpropionic acids are the most widely used class of nonsteroidal anti-inflammatory drugs (NSAIDs). Naproxen, (*S*)-2-(6-methoxy-2-naphthyl)propionic acid, is the only NSAID that is sold in enantiomerically pure form, and it is currently prepared by a classical resolution. Most members of this class of compounds can be synthesized by the oxidative cleavage of the

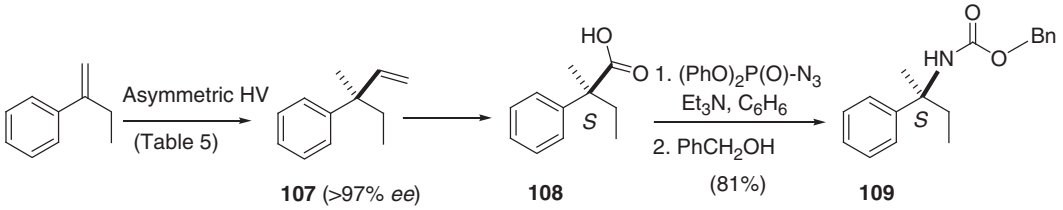
hydrovinylation products of vinylarenes. With the recent advances in the enantioselective synthesis of 3-arylbut-1-enes via hydrovinylation giving enantioselectivities >96% *ee*, using catalysts that give high turnovers (substrate/catalyst ~7000); this approach could provide a practical route to this important class of compounds (Scheme 10). Optimized oxidative protocols for the conversion of the 3-arylbutenes into various profen drugs have recently been reported.[75]



Scheme 10 Synthesis of enantiopure 2-arylpropionic acids via asymmetric hydrovinylation.

5.32.10.2 Enantiopure Primary Amines with Quaternary Benzylic Center

Application of a Curtius reaction to (*S*)-2-methyl-2-phenylbutanoic acid (**108**), prepared via the asymmetric hydrovinylation product (**107**) of 1-ethylstyrene, gives enantiopure amine derivative **109** (Scheme 11).[75] This route should allow the syntheses of a wide variety of compounds of similar structure starting with a styrene derivative.



Scheme 11 Synthesis of enantiopure primary amine with an α-tertiary center.

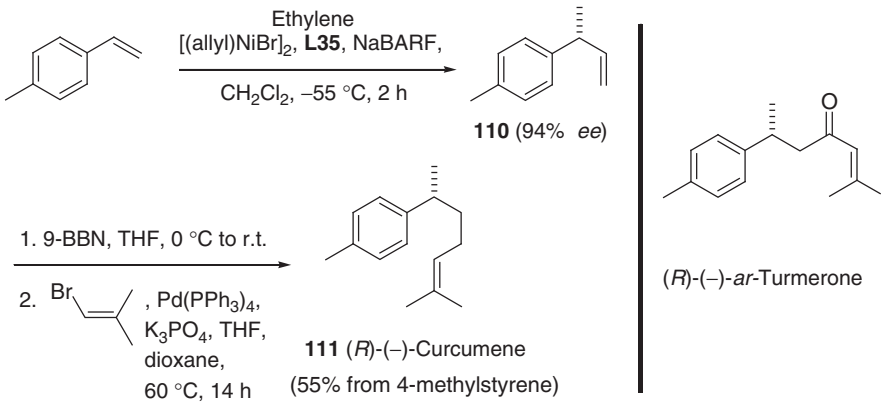
5.32.10.3 (*R*)-α-Curcumene and (*R*)-*ar*-Turmerone

The benzylic stereogenic center in bisabolanes (*R*)-α-curcumene and (*R*)-*ar*-turmerone poses a significant challenge in asymmetric synthesis. No less than 12 nonracemic synthesis of (*R*)-curcumene, a molecule often used to showcase newly developed asymmetric methodology, had been reported. The best among these involve a minimum of six steps and multiple chromatographic separations.[130,131] The asymmetric hydrovinylation product (**110**, prepared in 94% *ee* using ligand **L35**) of 4-methylstyrene can be converted into curcumene in two subsequent steps, both done in one pot (Scheme 12).[132] Treatment of **110** with 9-borabicyclo[3.3.1]nonane (1.2 equivalents) in THF, followed by Suzuki coupling with bromo-2-methylpropene gives (−)-α-curcumene (**111**) as a colorless oil in 55% overall yield from 4-methylstyrene in three steps. Similarly, the synthesis of (*R*)-(−)-*ar*-turmerone was accomplished in six steps from 4-methylstyrene.

5.32.10.4 Control of the Configuration of C_{20} on the Steroidal D-Ring Side Chain

Diastereoselective hydrovinylation provides a broadly applicable method for the control of the C_{20} configuration (**115**) of a steroid starting with a D-ring diene (Figure 7). This problem is of special interest for the synthesis of the unnatural $C_{20}(S)$ epimers, which are typically prepared by circuitous routes involving epimerization of the C_{20}-aldehyde (**114**) and a tedious separation. Steroid-derived dienes **112** and **113** (Figure 7), readily available from the corresponding D-ring ketones, have been subjected to hydrovinylation reactions. As shown in equation 51, a ruthenium-catalyzed hydrovinylation of **112** proceeds in a highly selective fashion to give the $C_{20}(S)$-isomer.[109] The Ni(II)-catalyzed hydrovinylation has been explored with the goal of preparing the specific epimer of the C_{20}-derivative.[133] Highly tunable phosphoramidites provide an excellent opportunity to address the effect of catalyst tuning in this context, and the results are shown in Scheme 13. Hydrovinylation of the steroid diene **112**, using *ent*-**L33a**

and **L34**, gave the $C_{20}(R)$- and $C_{20}(S)$-derivatives, respectively, along with minor amounts of the 1,4-adduct **118** (Scheme 13). The nonaromatic steroid **113** also behaves similarly.



Scheme 12 Synthesis of (–)-curcumene via asymmetric hydrovinylation.

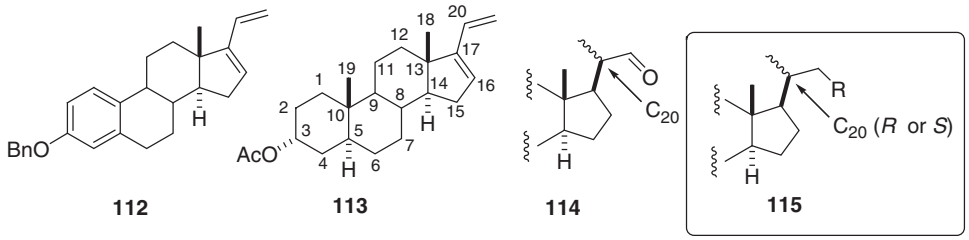
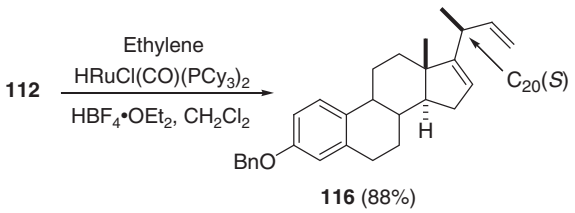
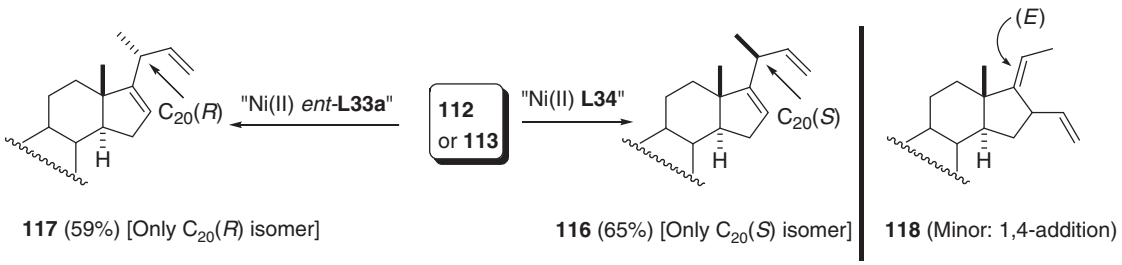


Figure 7 Precursors for steroid C_{20}-derivatives (115).



(51)



Scheme 13 Diastereoselective hydrovinylation for installation of C_{20}-configuration.

5.32.10.5 Enantioselective Synthesis of Pseudopterosins

Pseudopteropsins (Figure 8), with three exocyclic chiral centers, provide a challenging opportunity to showcase the power of asymmetric hydrovinylation to control the absolute and relative configuration of the various chiral centers. This class of compounds has attracted considerable attention because of their diverse biological activities, including antiinflammatory, antiviral, cytotoxic, and, especially, antimycobacterial properties.[134] A general approach to these compounds should address the thorny issue of how to control the configuration at each of the disparate chiral centers in these molecules. Previously reported syntheses of pseudopterosins invariably rely on chirality borrowed from nature, starting with limonene (Broka,[135] Corey[136]), menthol

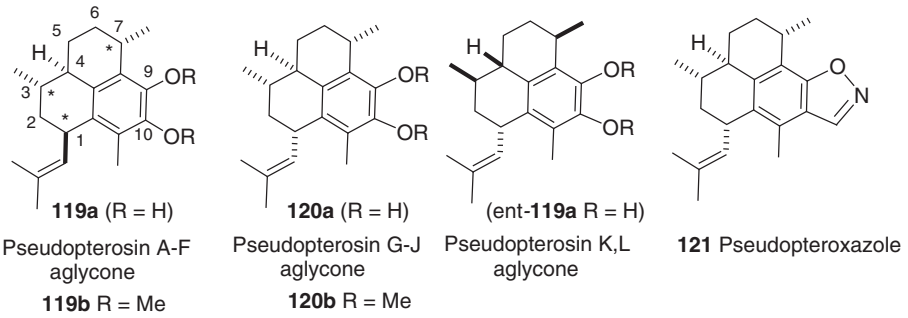
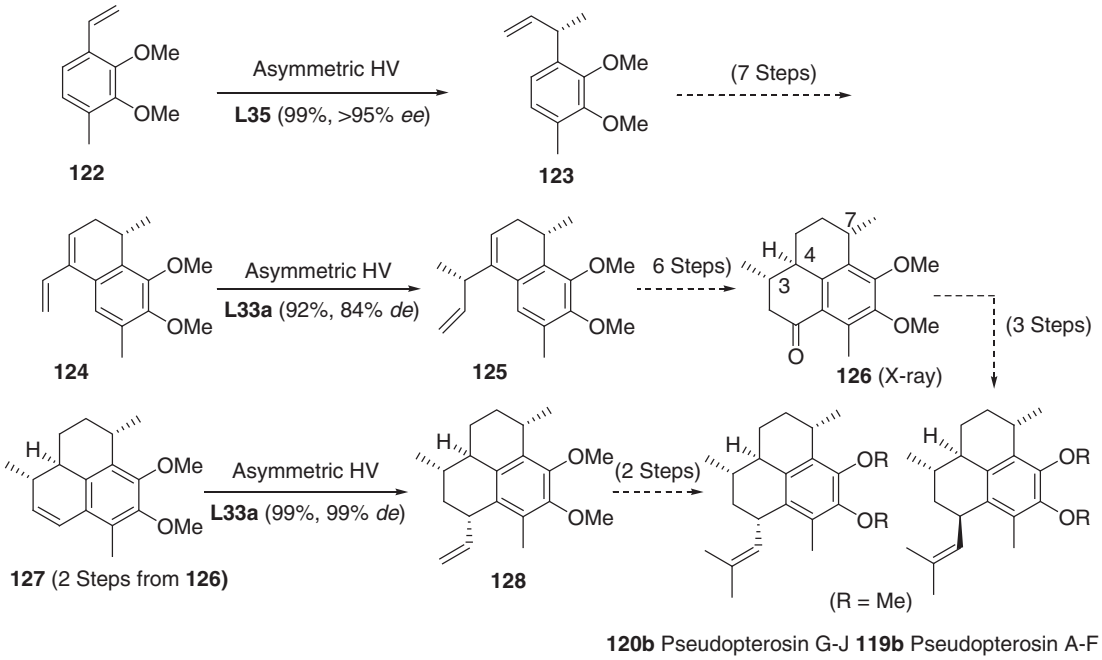


Figure 8 Structures of pseudoptereosins and related compounds.

(Corey[137]), or (+)-isopulegol (Kocienski[138]), somewhat limiting the scope of this approach for the syntheses of various diastereomers. All these approaches rely on substrate control for the installation of the stereocenters, and significant changes in the overall synthetic strategy will be required for the synthesis of any particular diastereomer. Hydrovinylation, however, allows reagent-based selectivity at each step in which a chiral center is generated, and thus it should, in principle, be possible to make any of the diastereomers. This is illustrated in Scheme 14 with the syntheses of the pseudopterosin A–F and G–J aglycones.[121] The pseudopteosin K–L aglycone is enantiomeric to the A–F aglycone, thus accessible using the corresponding enantiomeric ligands.



Scheme 14 Asymmetric hydrovinylation reactions in the syntheses of pseudopterosins.

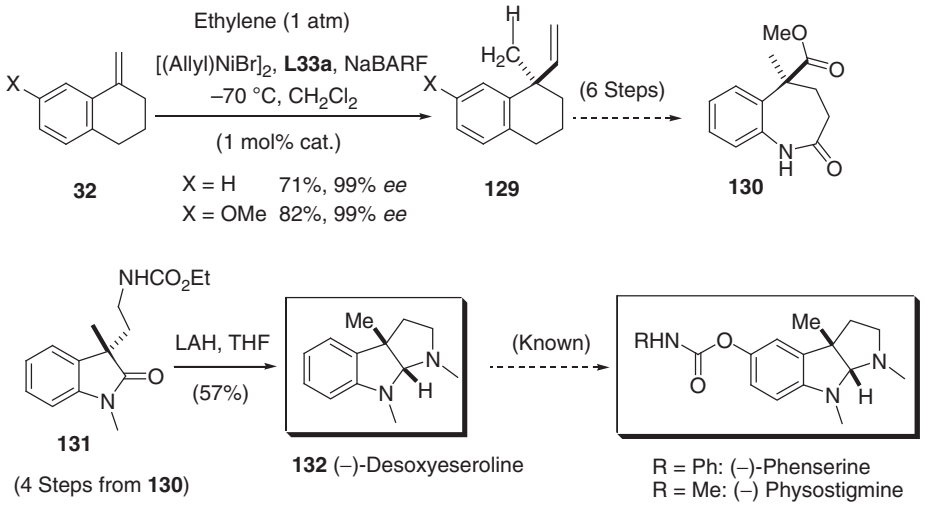
As shown in Scheme 14, the synthesis starts with the hydrovinylation of a vinylarene **122** to get **123** in excellent yield and >95% *ee*. The product **123** could be easily converted into a diene **124** in seven steps. This diene was subjected to yet another asymmetric hydrovinylation under the standard protocol to get the product **125** in 92% yield and 84% de. Hydroboration followed by Li/NH_3 reduction and subsequent annulation gave the ketone **126**, which can be recrystallized to get a single enantiomer of this key intermediate. A solid-state structure of this compound established the relative configurations of all chiral centers in the molecule. Ketone **126** is converted into the vinylarene **127**, which was subjected to the final hydrovinylation to install the correct configuration of the C1 carbon of pseudopterosin G–J aglycone. The vinyl derivative **128** is readily converted into the methyl ether of pseudopterosin G–J aglycone (**120b**) via ozonolysis followed by a Wittig olefination. Under the reaction conditions, the aldehyde undergoes some epimerization to give, after the Wittig reaction, up to 13% of the pseudopetrosin A–F derivative in addition to the major expected product **120b**. Ketone **126** can been converted into **119b** by a procedure reported by Corey.[137]

Even though we have not explored possibilities of making different diastereomers of pseudopterosins, previous work with the steroid side chains (Scheme 13) and a limited study of the hydrovinylation of the pseudopterosin precursors **122**, **124**, and **127** using various Ni(II)-phosphoramidite complexes suggest that there is considerable flexibility in the HV route for assembling these molecules.

The pseudopteosin K–L aglycone, which is the enantiomer of pseudopterosin A–F aglycone, can be synthesized from the same starting vinylarenes through the same chemistry using the appropriate ligands. Likewise a minor modification of this scheme should allow for the preparation of the antituberculotic pseudopteroxazole **121** (Figure 8). In addition, the stereochemical features associated with some of the advanced intermediates in the pseudopterosin synthesis are common to a number of important diterpenes including colombiasin A, elisabethin A, elisapterosin B, and several helioporins. With the stereochemical issues largely resolved, it should now be possible to design expeditious entry into these molecules and their congeners.

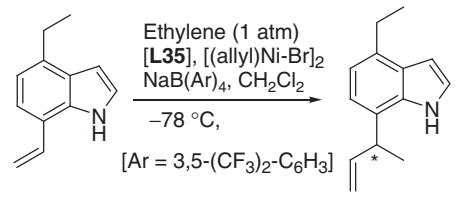
5.32.10.6 Enantioselective Synthesis of Desoxyeseroline, a Pyrrolidinoindoline with an Asymmetric All-Carbon Quaternary Center

(–)-Physostigmine (Scheme 15) is one of the major alkaloids isolated from African Calabar bean, which has an all-carbon quaternary benzylic chiral center, and this class of molecules has been the subject of intense interest, thanks to their anticholinestrase activity. The major challenge in the synthesis of this molecule and other useful analogs is the installation of the all-carbon quaternary center.



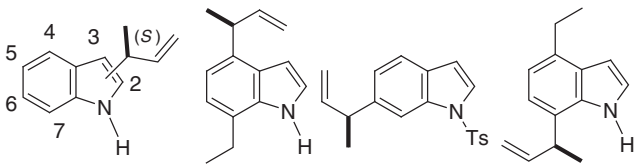
Scheme 15 Synthesis of pyrrolidinoindoles with an all-carbon quaternary center.

Asymmetric hydrovinylation of α-substituted alkenes provides a facile entry into compounds with all-carbon quaternary centers (equation 14, Table 5). One of the best substrates for this reaction is methylenetetralene **32**, which can be transformed into the benzoazepinone **130** by a highly enantioselective hydrovinylation followed by a series of oxidations and a Beckmann rearrangement (Scheme 15).[87] Methylation, hydrolysis, and a Curtius rearrangement gives the urethane **131**, which is easily converted into (–)-desoxyseroline (**132**), a common intermediate for the syntheses of a variety of pyrrolidinoindolines including physostigmine and phenserine.



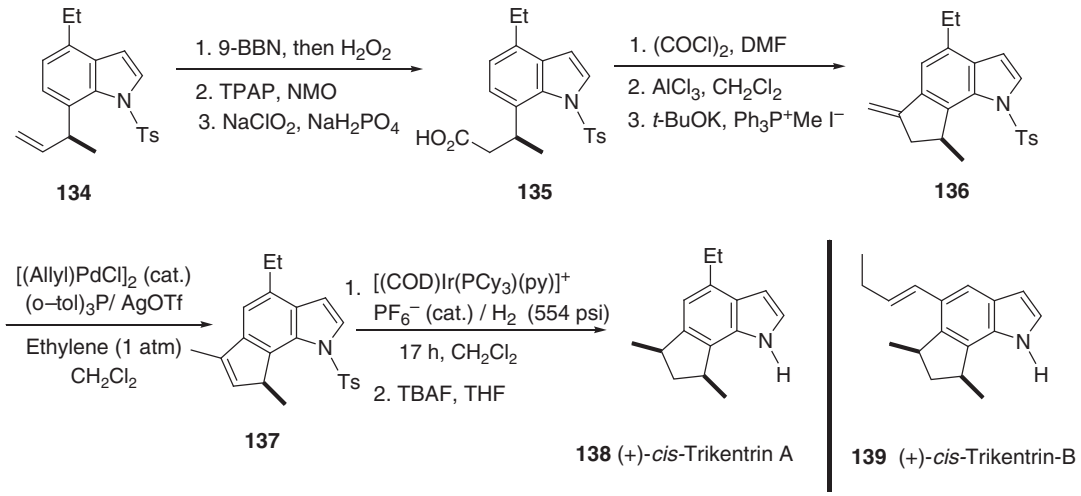
(52)

Vinylindoles prepared in 94–99% *ee*:



5.32.10.7 Synthesis of Trikentrins

Vinylindoles undergo Ni(II)-catalyzed asymmetric hydrovinylation under very mild conditions (−78 °C, 1 atm ethylene, 1–4 mol% catalyst) to give the corresponding 2-but-3-enyl derivatives in excellent yields and enantioselectivities (equation 52).[139] Hydroboration of the alkene in the hydrovinylation product **133** derived from 4-ethyl-7-vinylindole, oxidation to an acid, followed by Friedel–Crafts annulation and a Wittig reaction gives an indole-annulated cyclopentene (**136**) that is a suitable precursor for the syntheses of *cis*-trikentrins and all known herbindoles (Scheme 16).[139] For example, this compound has been transformed into (+)-*cis*-trikentin A (**138**) in three steps (alkene isomerization,[140] diastereoselective hydrogenation, and nitrogen deprotection). The previous synthesis of this molecule from (*S*)-(−)-malic acid involved more than 20 steps and a preparative high performance liquid chromatography separation of diastereomeric intermediates.[141] A similar sequence can also be used for the preparation of other members of this class of compound, including unsaturated derivatives like (+)-*cis*-trikentrin-B, **139**.



Scheme 16 Synthesis of trikentrins via asymmetric hydrovinylation.

5.32.11 Conclusions and Future Prospects

Selective heterodimerization of olefins depends on different reactivities of the precursor and the product alkenes. Origin of this difference could be size, electronic factors (e.g., vinylarenes, dienes), or strain (e.g., bicyclo[2.2.1]heptenes and cyclobutenes). Many of the reactions are tolerant to a wide variety of functional groups, and substrate/catalyst ratios >7000 have been realized for some of the hydrovinylation reactions. The reaction has been shown to proceed under catalysis of Ni, Pd, Ru, Co, and Fe, and a number of tunable ligand systems for each of these metals have been identified. Recent results imply that Ru and Co would have their own unique features that are complementary to that of nickel, which appears by far to be the most active metal. The next major challenges in this area are expansion of scope of the substrates to include heterofunctionalized alkenes and higher olefins in the place of ethylene, and development of intramolecular versions.[142,143] Since most reactions involve a single oxidation state of the metal throughout the catalytic cycle, development of tandem catalytic processes[144] that involve hydrovinylation in one of the steps can also be envisioned. Applications for the syntheses of complex natural products and medicinally relevant targets are beginning to appear in the literature. With increased attention from several leading researchers further rapid progress in the area can be expected.

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5.33 Hydroarylation Reactions

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5.33.1 Introduction

Hydroarylation can be defined as the addition of an aryl group and a hydrogen atom across an unsaturated moiety (either alkene or alkyne) yielding a new Csp^2–Csp^3 or Csp^2–Csp^2 bond, respectively. Additionally, hydroarylations can also be rationalized as a result of the Csp^2–H functionalization of an aromatic substrate via insertion of an alkene or alkyne into the C–H bond. In this regard, hydroarylation reactions are atom economical and thus compare advantageously to classical cross-coupling processes in which formal hydroarylation products are formed from prefunctionalized aromatic substrates (e.g., aryl halide, triflates, boranes, etc.). In this account, the authors will focus on the examples obeying the most restricted definition of hydroarylation including alkynes, alkenes, and allenes. Within these three reaction partners, transition metal and nontransition metal-catalyzed processes will be described separately and intermolecular examples will be always introduced before intramolecular ones.[1] When available, details about the potential reaction intermediates and/or reaction mechanisms will also be briefly discussed.

5.33.2 Hydroarylation of Alkynes

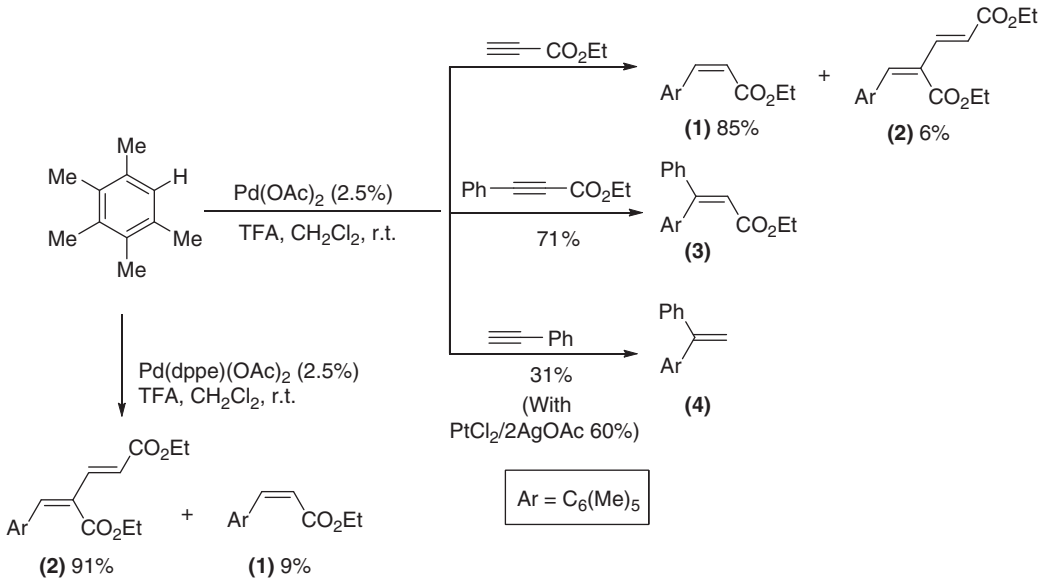
The hydroarylation of alkynes is one of the most efficient methods for the synthesis of functionalized alkenes. Two main reaction pathways have been proposed for this transformation: (1) the activation of the triple bond by an electrophile, E^+ (a metal complex, Lewis or Brønsted acid, etc.) followed by a Friedel–Crafts reaction with an aromatic counterpart or (2) activation of the Csp^2–H bond in the arene by the metal center before the addition onto the alkyne.

5.33.2.1 Late Transition Metal-Catalyzed Hydroarylations of Alkynes

5.33.2.1.1 Palladium-catalyzed hydroarylations of alkynes

5.33.2.1.1.1 Intermolecular hydroarylations

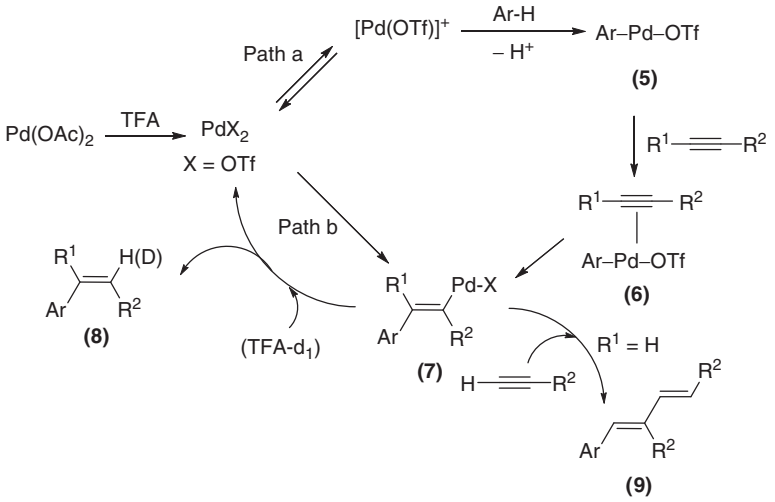
Fujiwara described the efficient hydroarylation of alkynes in the presence of highly electrophilic Pd(II) cationic complexes generated *in situ* from $Pd(OAc)_2$ and trifluoroacetic acid (TFA) (Scheme 1, right).[2] Electron-rich arenes and electron-deficient alkynes react smoothly, to give predominantly thermodynamically unfavorable *Z*-arylalkenes. Thus, the reaction of pentamethyl benzene with ethyl propiolate leads to *cis*-cinnamate **1** and diene **2** in 85% and 6% yield, respectively. Internal alkynes with an aromatic substituent such as phenyl ethyl propiolate, react in a Michael-type manner to give *cis*-1,1-diaryl substituted olefins **3** in good yields. However, phenylacetylene behaves differently, giving 1,1-diarylalkene **4** in only 31% yield. In this case, the combination of platinum dichloride and silver acetate increased the yield of **4** to 60%.



Scheme 1

In this context, further catalytic systems have been reported to improve the selectivity of the reaction and also to enable the use of less drastic conditions. Pd(II) catalysts with *N*-heterocyclic ligands such as IPr-Pd$(OCOCF_3)_2$ and IPr-Pd$(OAc)_2$ with TFA as solvent further improved the selectivity favoring, almost exclusively, monoaddition products **1**.[3] In contrast, palladium complexes with bidentate phosphine ligands in TFA afforded selectively dienes **2** in high yields (Scheme 1, down).[4] Interestingly, palladium(II) complexes bearing a chelating *N*-heterocyclic dicarbene ligand and two weakly coordinating anions (introduced *in situ* on addition of 2 equivalents of a suitable silver salt) could be tuned by the use of additives to afford products **1** or **2** selectively.[5] $Pd(OAc)_2$ combined with silver acetate in acetonitrile as solvent effectively generated highly substituted naphthalenes from internal alkynes via twofold hydroarylation products of type **2**.[6]

Two different mechanistic proposals have been outlined for these transformations (Scheme 2). In the case of Pd(II) (and Pt(II)) cationic complexes reported by Fujiwara,[2] an arene metalation is proposed to give σ-aryl metal species **5**, which simultaneously activate the alkyne through coordination via complex **6** (path a). Insertion of the alkyne in the Csp^2–metal bond was proposed to take place in an unusual *trans*-fashion yielding the thermodinamically unfavorable *cis*-vinyl intermediate **7**. Deutero- or protodepalladation affords the observed products **8**. The formation of aryl-palladium species **5** in these transformations is supported by the disappearance of the aryl hydrogen of pentamethylbenzene on reaction with 1 equivalent of $Pd(OAc)_2$ in TFA after a few minutes at room temperature. One of the alkenyl hydrogen in the adduct comes from the acidic solvent, presumably as a result of the protonation of alkenyl complex **7** by TFA (or TFA-d_1). The fact that hydroarylation reaction fails in acetic acid, indicates that cationic Pd(II) species are involved in the palladation and/or that protonation of the alkenyl-Pd intermediate to

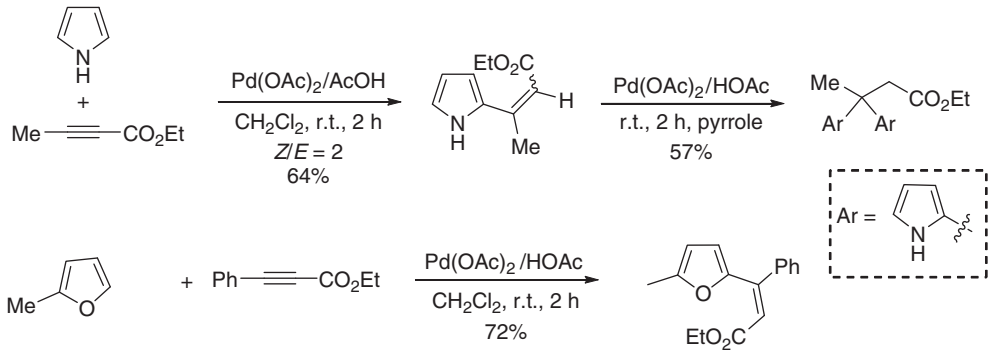


Scheme 2

complete the catalytic cycle only occurs with stronger acids such as TFA. The formation of adducts stemming from the reaction of two alkynes and one arene **9** would proceed through vinylpalladium intermediate **7**.

In the case of noncationic Pd(II) catalysts, the hydroarylation reaction is proposed to proceed via alkenyl-palladium **7**, which would be directly formed from the neutral palladium precatalyst by an electrophilic aromatic substitution process (path b).

Electron-rich heteroarenes such as pyrroles, indoles, and furans readily undergo addition to alkynoates at room temperature with catalytic amounts of $Pd(OAc)_2$ in acetic acid to give *Z*-alkenes in most cases (Scheme 3).[7] In this case, the reaction was carried out in dichloromethane as solvent to obtain selectively monoaddition adducts.



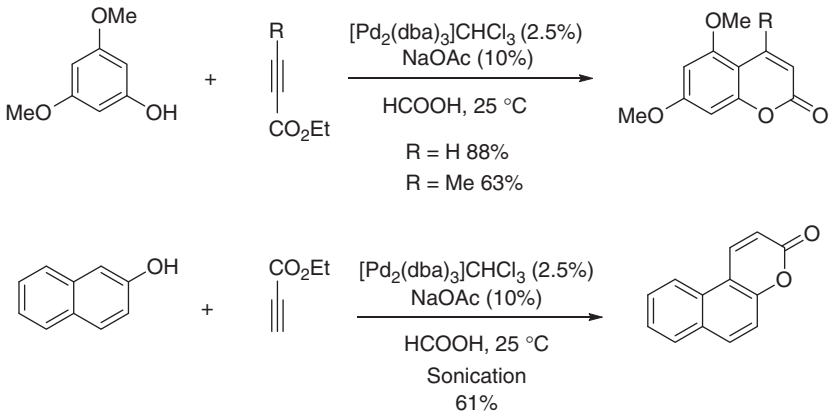
Scheme 3

In addition to cationic Pd(II) complexes, Pd(0)-catalyzed intermolecular hydroarylations have also been reported. Thus, Trost described the synthesis of coumarins by addition of phenols to alkynoates (Scheme 4).[8] The original mechanistic proposal was based on the idea that electrophilic Pd(II) species could *ortho*-palladate an electron-rich phenol. However, after extensive experimentation, a mechanism was assumed in which the formation of hydridopalladium intermediates from the reaction of Pd(0) and formic acid are proposed as the initial productive species of the catalytic cycle. These intermediates trigger the addition of the arene onto the electron-deficient alkyne followed by lactonization to give the observed products.

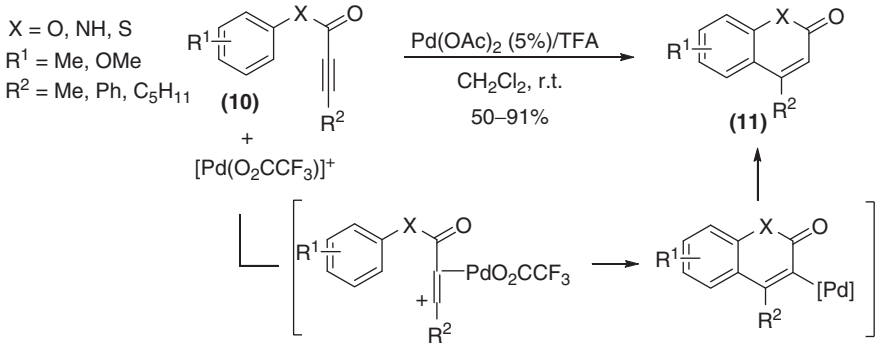
5.33.2.1.1.2 Intramolecular hydroarylations

The catalytic system based on $Pd(OAc)_2$ and TFA has been successfully applied in the intramolecular hydroarylation of alkynes.[9] Aryl-alkynoates and alkynanilides **10** are efficiently transformed, in good-to-excellent yields, into coumarins and quinolin-2(1*H*)-ones **11**, respectively (Scheme 5). It was initially suggested that, in analogy to the intermolecular reaction presented in Section 5.33.2.1.1.1, a metalation of the arene takes place in these transformations. However, a detailed deuterium-labeling study supported a reaction mechanism involving an activation of the alkyne followed by an electrophilic aromatic substitution as shown in Scheme 5.[10]

The nature of the catalyst exerts a key influence not only in the reaction mechanism, but also in the regioselectivity of these transformations. Thus, related substrates such as *N*-arylpropiolamides, in the presence of $Pd(OAc)_2$ and dppf undergo 5-*exo*-*dig*



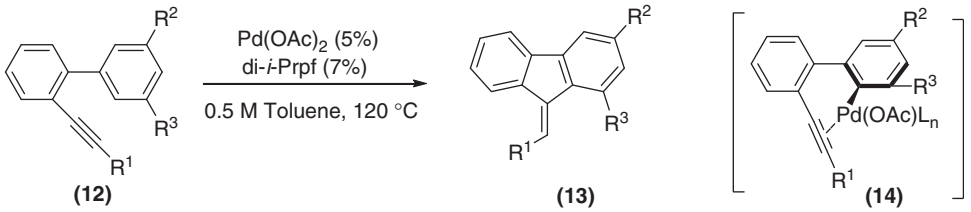
Scheme 4



Scheme 5

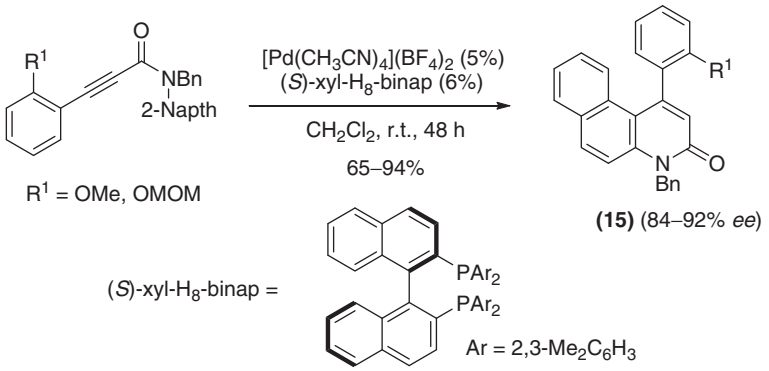
hydroarylations to give 3-methyleneoxindoles.[11] In addition, *ortho*-alkynyl biaryls **12** react in the presence of $Pd(OAc)_2$ and 1,1′-bis(diisopropylphosphino)ferrocene to form fluorene derivatives **13**.[12] Mechanistic studies support the involvement of an α-aryl-palladium intermediate **14**, formed by activation of the Csp^2–H bond, in these transformations (Table 1).

Table 1 Pd(II)-catalyzed synthesis of fluorenes



R^1	R^2	R^3	*Reaction time (h)*	*Yield (%)*
Ph	H	H	2.5	98
p-$NO_2(C_6H_4)$	H	H	4.0	89
Ph	F	F	3.0	93
p-$NO_2(C_6H_4)$	CF_3	CF_3	1.0	93

Asymmetric palladium-catalyzed hydroarylations have also been reported (Scheme 6).[13] In the presence of a cationic palladium(II)/(*S*)-xyl-H8-binap complex as catalyst at room temperature, axially chiral 4-aryl 2-quinolinones **15** were obtained in good yields and high enantiomeric excess.



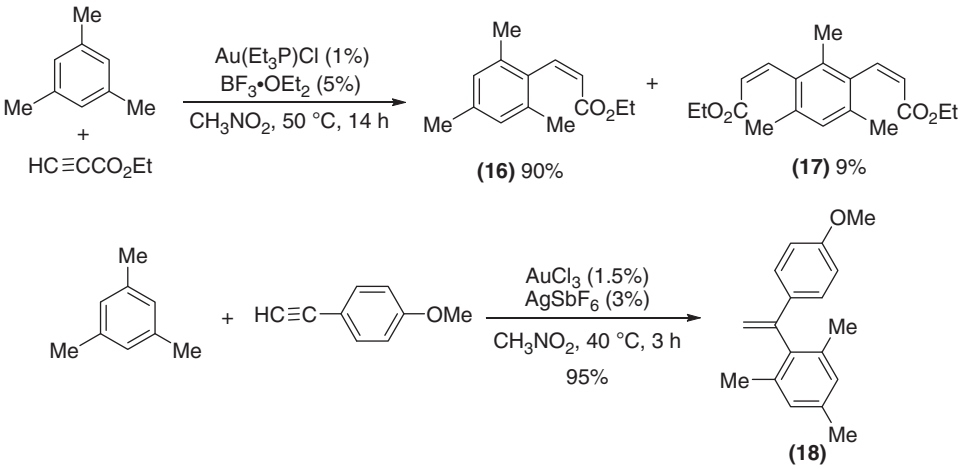
Scheme 6

5.33.2.1.2 Gold- and platinum-catalyzed hydroarylation of alkynes

5.33.2.1.2.1 Intermolecular hydroarylations

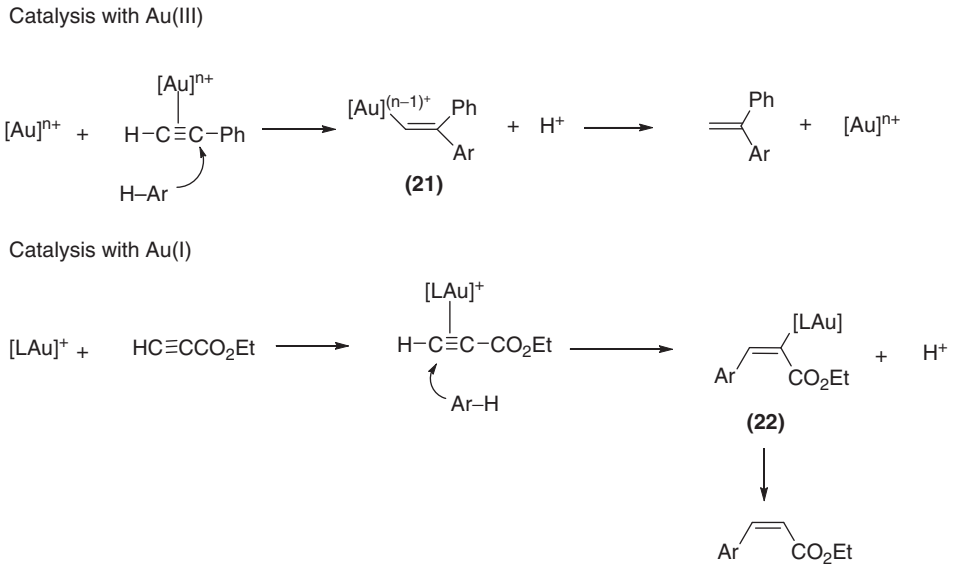
Cationic Pt(II) species have been used as effective catalysts for intermolecular alkyne hydroarylations offering comparable or in some cases, improved performances to those of Pd(II) catalysts. In addition to the examples reported by Fujiwara,[2] arenes and heteroarenes react with propiolic acid and esters to give *cis*-cinnamic derivatives in the presence of a catalyst generated *in situ* from K_2PtCl_4 and AgOTf.[14] $PtCl_2$ has also been proved to catalyze a multistep reaction of indoles with alkynyl alcohols involving an intermolecular hydroarylation in the first step of the catalytic cycle.[15]

However, gold has become the metal of choice to expand the scope of intermolecular hydroarylations of alkynes. Thus, Reetz found that gold(III) and gold(I) complexes catalyzed the intermolecular hydroarylation of electron-poor alkynes such as ethyl propiolate with electron-rich arenes in a regio- and stereoselective manner (Scheme 7).[16] In this case, 1,2-disubstituted alkenes were obtained with exclusive or predominant *Z* configuration. Thus, mesitylene and ethyl propiolate react with a cationic gold(I) complex formed *in situ* from [Au(PEt_3)Cl] and BF_3 to form *Z*-cinnamate **16** in 90% yield along with small amounts of double hydroarylation product **17**. Similar results were obtained by He in the reaction of arenes with ethyl propiolate and related electron-poor alkynes using $AuCl_3$/3AgX (X = OTf, SbF_6) in CH_2Cl_2.[17] However, aryl-substituted terminal alkynes react with electron-rich arenes in the presence of $AuCl_3$ and $AgSbF_6$ to give 1,1-diarylethenes such as **18** in good-to-excellent yields. In contrast, internal electron-poor alkynes failed to give the desired products under these conditions. Regarding the alkenylation of heteroarenes, indole[18] and furan[19] additions to alkynes catalyzed by gold(III) and gold(I) complexes respectively, have also been reported.



Scheme 7

Although cationic gold(III) or gold(I) complexes are required for a successful outcome in the abovementioned transformations, an auration of the arene during the catalytic cycle seems unlikely, in contrast with the cationic-Pd(II)-catalyzed reactions described in Section 5.33.2.1.1.1. Aryl-gold(III) species ($ArAuX_2L$, **19**) react with alkynes to give Csp^2–Csp cross-coupling rather than hydroarylation products.[20] Furthermore, aryl-gold(I) complexes (Ar–Au–L, **20**) react with alkynes in the presence of palladium catalysts to give carboauration products.[21] Thus, gold-catalyzed hydroarylations seem to proceed by activation of the triple bond by π-complexation with the metal center (Scheme 8). In the case of aryl-substituted alkynes, the π-complex undergoes electrophilic aromatic substitution with the electron-rich arene to give alkenyl-gold(III) intermediate (**21**), which is immediately

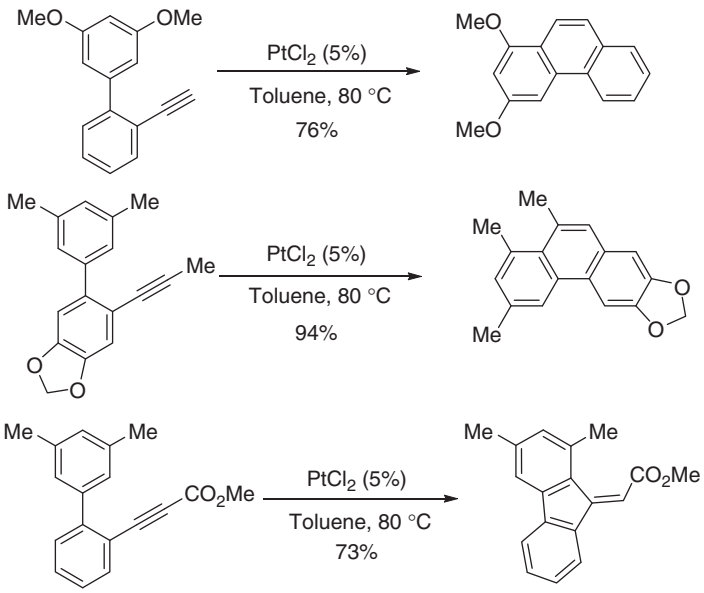


Scheme 8

protonated by the H^+ generated in the previous step. For the gold(I)-catalyzed processes, the cationic complex coordinates the alkyne and the nucleophilic attack of the aromatic from the opposite face leads to alkenyl-Au(I) complex **22**, which undergoes protonation to give conjugated products. The regioselectivity seems to be thus determined by electronic rather than steric factors.

5.33.2.1.2.2 Intramolecular hydroarylations

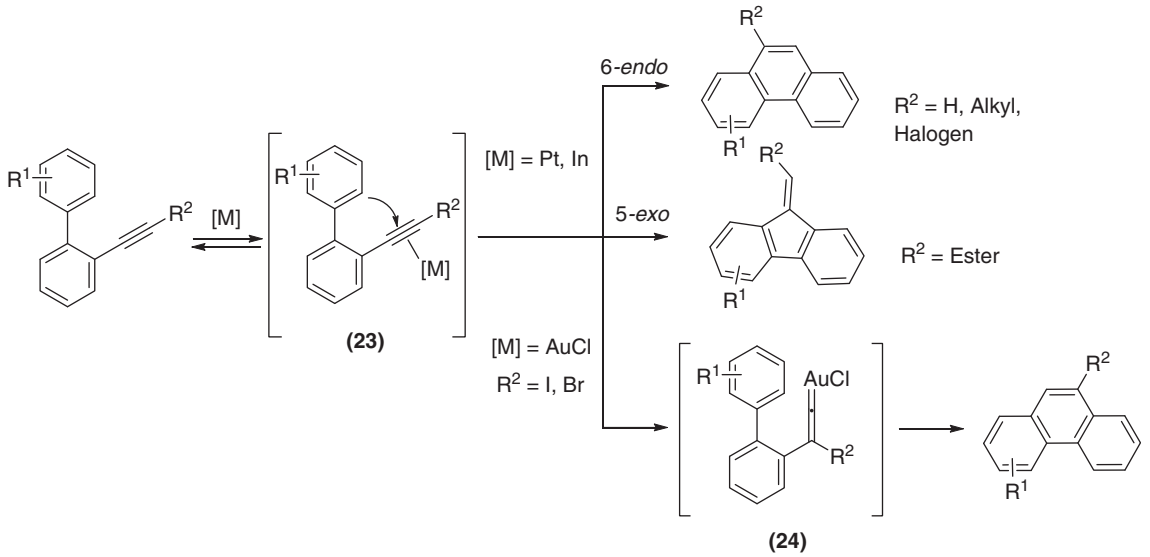
Pt(II) and Pt(IV) catalysts have found wider application in intramolecular alkyne hydroarylation processes. Fürstner reported a synthesis of phenanthrenes from biphenyl compounds bearing a triple bond at the *ortho*-position (**Scheme 9**).[22] This transformation has been applied in the synthesis of the aporphine family of natural products.[23] The 6-*endo* cyclization mode is preferred in both terminal and internal alkynes, although those bearing an electron-withdrawing group cyclized by a 5-*exo-dig* pathway.



Scheme 9

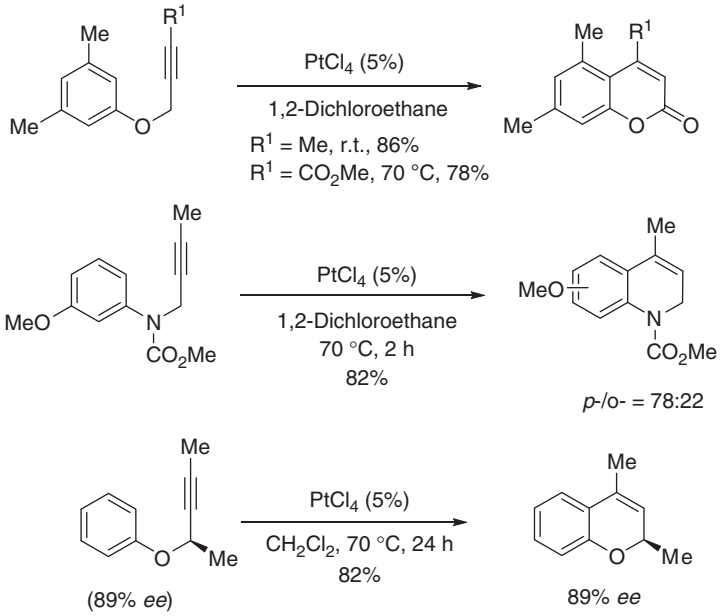
In addition to $PtCl_2$, other metal halides such as $AuCl_3$, $GaCl_3$, or $InCl_3$ catalyze this transformation.[22] As the Pt-catalyzed synthesis of phenantrenes also proceeds with nonterminal alkynes, a general mechanism involving activation of the triple bond by coordination of the metal (**23**) is strongly suggested.[24] Depending on the substitution pattern on the alkyne, the subsequent nucleophilic attack can take place in a 6-*endo* or a 5-*exo* manner. When halo-substituted alkynes were submitted to the reaction with In(III) salts, 10-halophenanthrenes were obtained in excellent yields. In contrast, when AuCl was used as catalyst,

9-halo-phenanthrenes were formed instead, thus pointing toward a different mechanism for this particular combination of substrates and catalyst, involving the formation of a metal vinylidene intermediate **24** via 1,2-halogen shift (Scheme 10).[22]



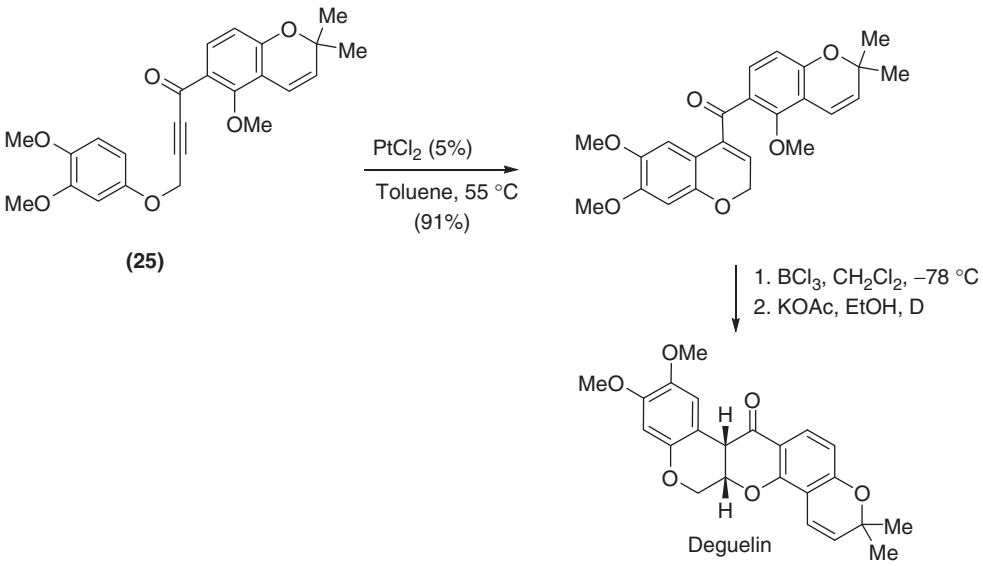
Scheme 10

$PtCl_4$ has also been reported to catalyze intramolecular alkyne hydroarylations enabling the synthesis of 2*H*-chromenes, 1,2-dihydroquinolines, and coumarins (Scheme 11).[25] In all cases, 6-*endo-dig* cyclizations were observed regardless of the electronic nature of the alkyne, in contrast to the Pt(II)-catalyzed transformation shown in Scheme 9. Stereogenic centers are compatible with the reaction conditions, which exclude a Claisen rearrangement followed by electrocyclic ring closure as the reaction course; thus, activation of the alkyne via coordination to the metal followed by electrophilic aromatic substitution suffices to explain the observed reactivity. Similar cycloisomerizations have also been carried out in the presence of $Hg(OTf_2)(TMU)_3$ with catalyst loadings below 0.5 mol%.[26]



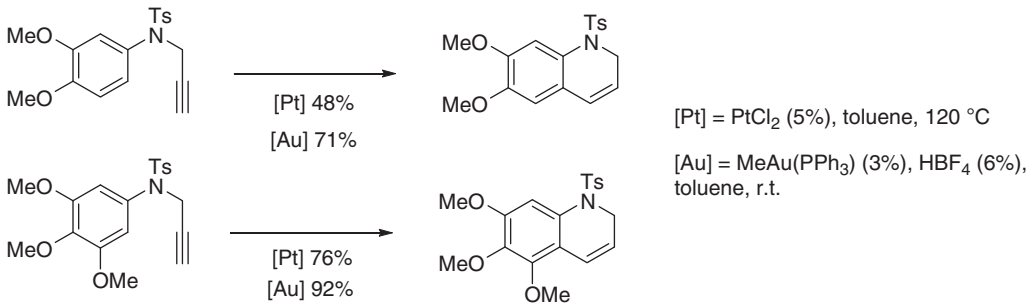
Scheme 11

A platinum-catalyzed hydroarylation has been applied in the total synthesis of deguelin, a rotenoid with promising chemopreventive properties.[27] After a $PtCl_2$-catalyzed 6-*endo* hydroarylation of **25**, a selective demethylation with boron trichloride, followed by base-catalyzed intramolecular oxo-Michael addition delivered the desired product (Scheme 12).



Scheme 12

Echavarren and coworkers also showed that 4-aryl-1-alkynes cyclized in a 6-*endo-dig* fashion with cationic gold(I) catalysts (generated *in situ* from [Au(PPh_3)Me] and a strong acid or from Ph_3PAuCl by chloride abstraction in presence of a silver salt) (Scheme 13).[28] $PtCl_2$ in refluxing toluene could also be used as catalyst although lower yields were reported for these transformations (Scheme 13).[29] As in the previous cases, π-activation of the alkyne is proposed to trigger the 6-*endo*-hydroarylations through a Friedel–Crafts mechanism although density functional theory (DFT) calculations showed that metal carbene intermediates can also be the effective precursors of Wheland-type species in these transformations.[28] This chemistry has also been expanded enabling the synthesis of chromenes and coumarins,[30] benzopyranes,[31] and cinnolines,[32] respectively.



Scheme 13

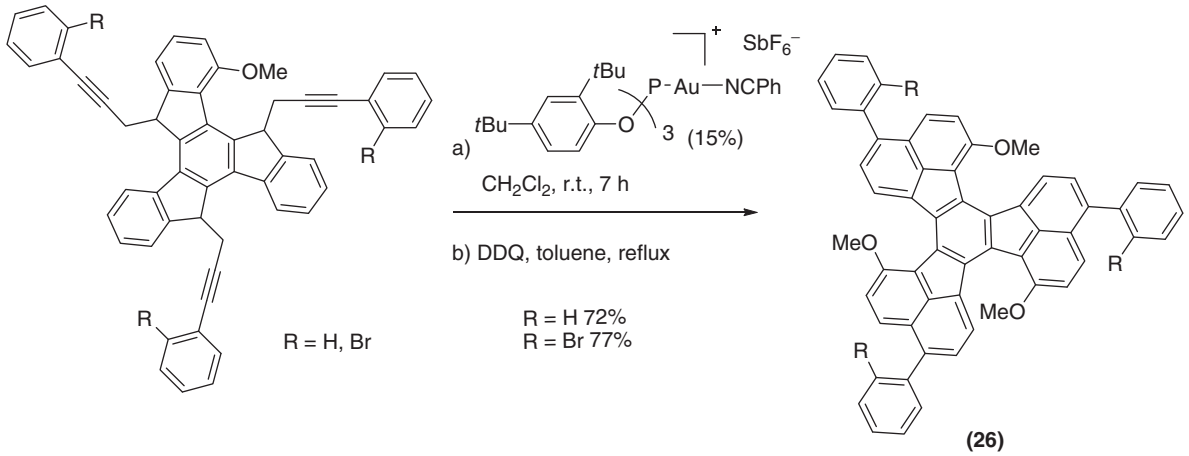
The ability of gold to trigger intramolecular hydroarylations has been further tested in the construction of polyarenes as illustrated by the synthesis of two functionalized decacyclenes **26**. In a one-pot reaction, three C–C bonds are formed with high efficiency (Scheme 14).[33] AgOTf has also been used to promote multiple intramolecular hydroarylation processes to give perylene derivatives.[34]

In terms of heteroarenes as reaction partners, C3-substituted indoles undergo intramolecular hydroarylation processes catalyzed by gold(I) or gold(III) salts leading selectively to seven- or eight-membered ring, respectively.[35] In addition, (C2-enynyl)-indoles produce carbazoles by reaction with cationic gold(I) complexes.[36] The intramolecular hydroarylation of pyrrole-2-propargylcarboxamides to give pyrroloazepinones by a 6-*endo-dig* cyclization has been reported both with H_2PtCl_6 and $AuCl_3$ as catalysts.[37] Hg(II) efficiently catalyzes the 6-*exo* or 6-*endo-dig* cyclization of alkynyl furans depending on the substitution pattern on the alkynes.[38] In the latter transformation, neither platinum nor gold affords hydroarylation products but instead produce phenols as a result of a complex skeletal reorganization process.[39]

5.33.2.1.3 Ruthenium-catalyzed hydroarylation of alkynes

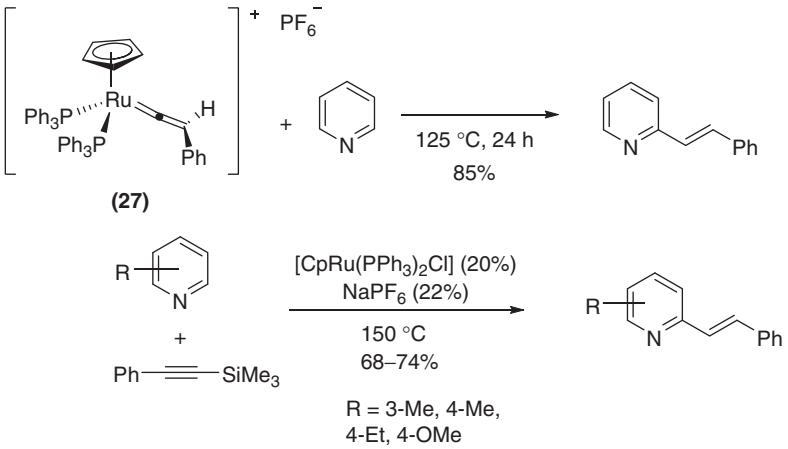
5.33.2.1.3.1 Intermolecular hydroarylations

In contrast to the general mechanistic rationale described for platinum and gold-catalyzed arylation processes based on the π-activation of the triple bond by the metal, ruthenium-catalyzed hydroarylations of alkynes are oftentimes explained through



Scheme 14

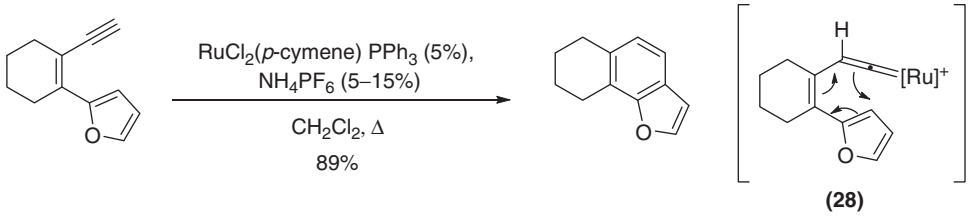
ruthenium vinylidene intermediates. As for most late transition metals, the central carbon of the Ru-vinylidene moiety is electrophilic and thus susceptible of attack by a suitable nucleophile. Thus, pyridine reacts with Ru(II)-vinylidene complex **27** to give (*E*)-2-styrylpyridine (Scheme 15).[40] Although the *Z* isomer is formed first, it seems to evolve to the more stable *E* isomer under the reaction conditions. A catalytic version of this intermolecular alkenylation of pyridines at C-2 was carried out using $[CpRu(PPh_3)Cl_2]$ and $NaPF_6$, although an excess of pyridine and rather harsh conditions were required for a successful reaction outcome.



Scheme 15

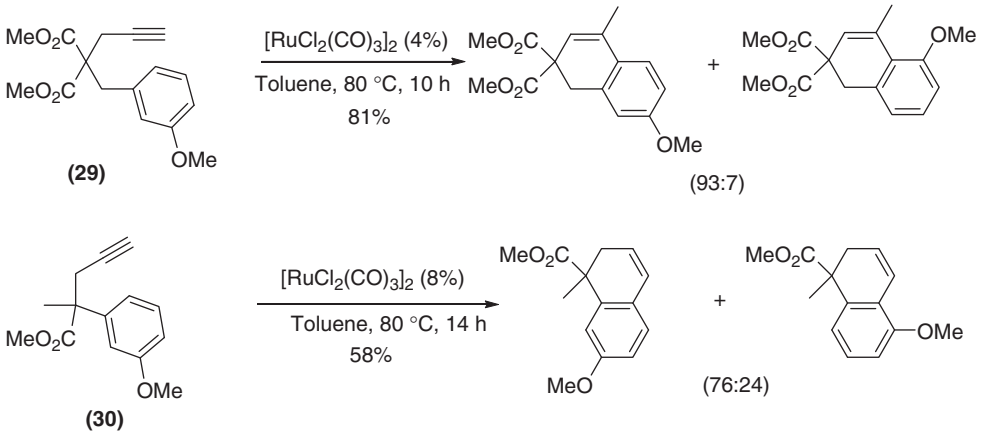
5.33.2.1.3.2 Intramolecular hydroarylations

As shown in Scheme 16, intramolecular hydroarylations of heteroaromatic rings can be efficiently catalyzed by Ru(II) complexes as Ru-vinylidene intermediates **28** can be excellent substrates for 6π-electrocyclization reactions.[41] Deuteration experiments show that formation of the Ru-vinylidene **28** takes place via migration of the acetylenic hydrogen. A related 6π-electrocyclization of aromatic imines has been reported proceeding via W(0)-vinylidenes.[42]



Scheme 16

Interestingly, other Ru-catalyzed intramolecular alkyne hydroarylations are proposed to proceed via π-Lewis acid activation of the alkyne. Thus, Murai reported the cycloisomerization of ω-aryl-1-alkynes to give dihydronaphthalenes or dihydrobenzocycloheptenes (Scheme 17).[43] Different cyclization modes were observed depending on the length of the tethers: an *exo-dig* cyclization was preferred in substrate **29** where the alkyne and arene are separated by three (or up to four) carbon atoms, whereas an *endo-dig* mode was observed in substrates with two carbon atoms in the tether (**30**). This transformation, which can also be catalyzed by Pt(II), is limited to substrates bearing an electron-rich aromatic ring. More recently, the scope of the reaction was extended to substrates where the arene moiety does not possess strong electron-donating groups by using $GaCl_3$[44] or $FeCl_3$[45] catalysts.



Scheme 17

5.33.2.1.4 Other metals (Cu, Fe, Co, Rh, Ni)-catalyzed hydroarylation of alkynes

Recently, other metals such as iron,[46] cobalt, rhodium, and nickel have been explored in the context of alkyne hydroarylations, complementing the reactivity offered by the previously described systems. Thus, a rhodium(III)-catalyzed intermolecular hydroarylation of alkynes with *N*,*N*-dimethylcarbamoyl *N*-protected indoles at C2 was reported by Fagnou in 2010.[47] This transformation is proposed to proceed via directed metalation of the indole at C2, coordination of the alkyne to the Rh(III) center followed by *syn*-migratory alkyne insertion into the Csp^2–Rh bond to give **31**. Protonolysis of the carbon–rhodium bond would then give the observed products (Scheme 18).

The key role of a directing group has also been exploited in the cobalt-catalyzed hydroarylation of alkynes via chelation-assisted C–H bond activation.[48] Cobalt salts, phosphine ligands, and stoichiometric amounts of Grignard reagents promote the addition of arylpyridines and imines to unactivated internal alkynes with high regio- and stereoselectivity. Mechanistic studies involving deuterium-labeling experiments support a reaction mechanism in which chelation-assisted oxidative addition of the aryl C–H bond to the cobalt center is followed by insertion of the C–C triple bond into the Co–H bond. Reductive elimination affords the observed products (Scheme 18).

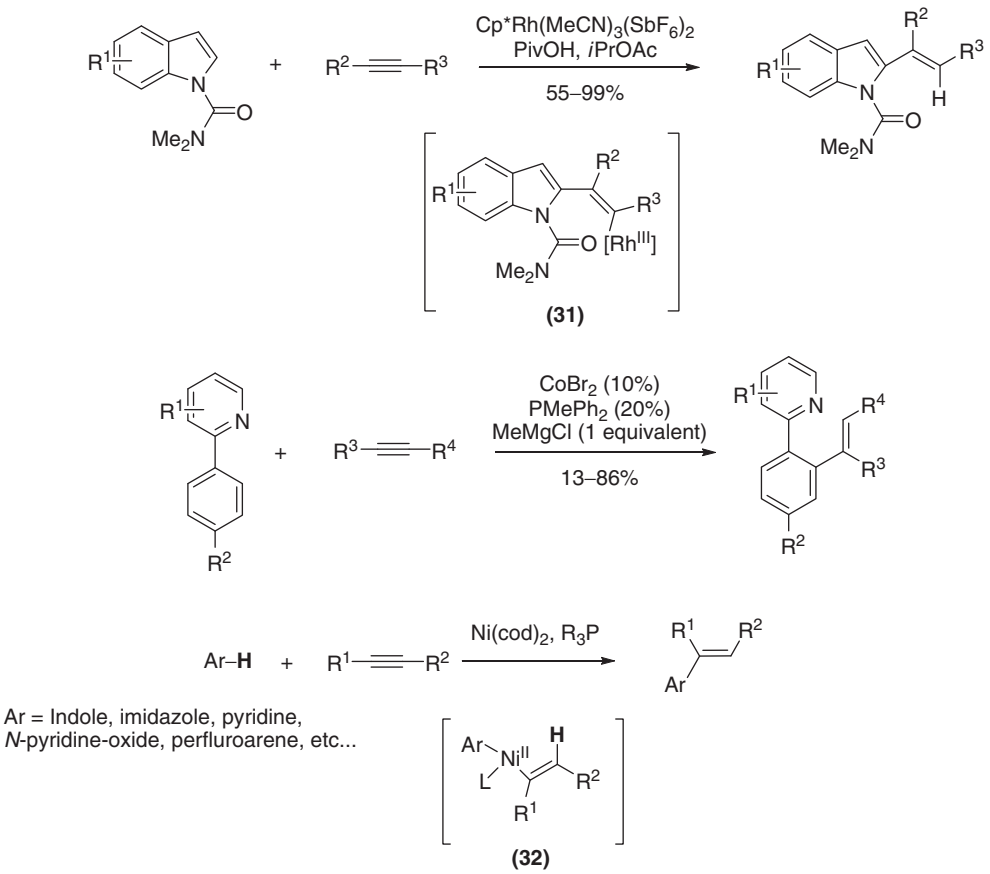
A wide variety of heterocycles, including C-3 substituted indoles, 1,3,4-oxadiazoles, imidazoles, pyridines, and pyridine *N*-oxides, 2-pyridones, pyrimidones, quinazolones, and also fluoroarenes have been efficiently alkenylated in the presence of $[Ni(cod)_2]$ combined with bulky alkylic phosphines (and Lewis Acid cocatalysts in certain cases).[49] A general mechanism for this palette of transformations involves an oxidative addition on the Ni(0) complexes into the Csp^2–H bonds followed by migratory insertion of the alkyne into the Ni–H bond to give **32**. The new Csp^2–Csp^2 bond is formed via reductive elimination on the diorganonickel(II) intermediate (Scheme 18).

5.33.2.2 Nonlate Transition Metal-Catalyzed Hydroarylation of Alkynes

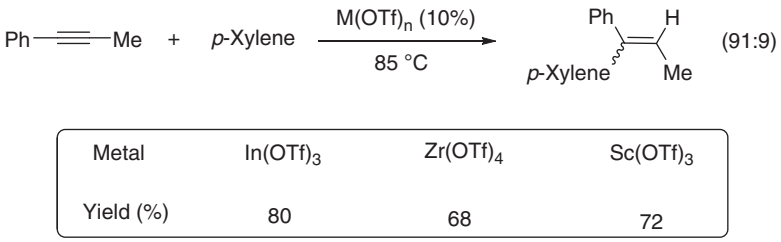
Electrophilic Ga(III)[44,50] and In(III)[22,51] complexes have also been used in alkyne hydroarylations. Metal trifluoromethanesulfonates such as $[M(OTf)_n$; M = Sc, Zr, In] catalyze the Friedel–Crafts alkenylation of arenes with internal alkynes to give 1,1-diarylalkenes in high-to-excellent yields (Scheme 19).[52]

Although different mechanistic hypotheses have been proposed, it is widely accepted that the attack of the arene to the initially formed zwitterionic intermediate **33**, from both A and B sites, affords an *E*/*Z*-mixture of **34**, which is transformed by protonation to the corresponding diastereoisomers **35** (Scheme 20). Kinetic studies revealed that the *Z* and *E* isomer of **34** are present in the mixture at the early stage of the reaction, strongly supporting this mechanism.

A double cyclization of bis(biaryl)acetylenes **36** occurs in the presence of $SbCl_5$ in CH_2Cl_2 at room temperature leading to dibenzo[*g*,*p*]chrysene derivatives **37** (Scheme 21).[53] The reaction involves the oxidation of the diphenylacetylene moiety by the

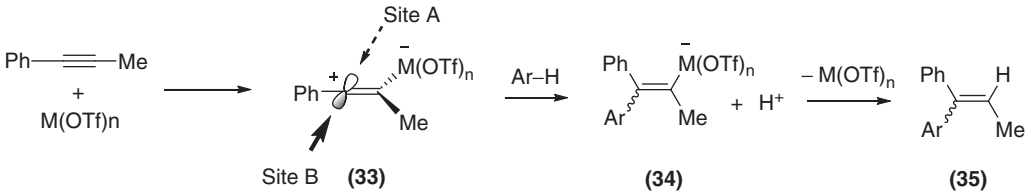


Scheme 18



Metal	$In(OTf)_3$	$Zr(OTf)_4$	$Sc(OTf)_3$
Yield (%)	80	68	72

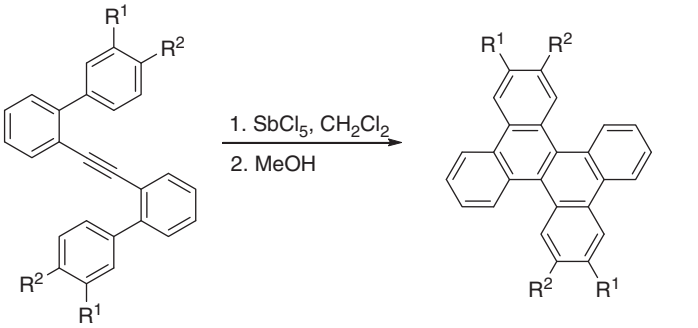
Scheme 19



Scheme 20

one-electron oxidant $SbCl_5$ to form acetylene cation radicals, which undergo electrophilic and radical cyclization with the biaryl moieties.

Zeolite HSZ-360 is an efficient promoter for the regioselective monoalkenylation of phenol with phenylacetylene (Scheme 22). The observed *ortho*-regioselectivity was proposed to be due to the formation of a hydrogen bond between the



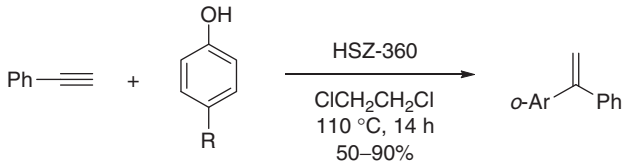
(36)

$R^1 = R^2 = OMe$
$R^1 = OMe, R^2 = H$

(37)

$R^1 = R^2 = OMe$ 73%
$R^1 = OMe, R^2 = H$ 68%

Scheme 21



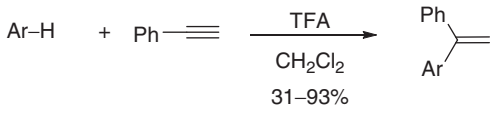
R = H, Me, OMe, *t*-Bu

Scheme 22

hydroxy group and the alkyne. In fact, when anisole reacted under the same conditions, a 1:1 mixture of *ortho*- and *para*-phenylethenylanisoles was obtained.[54]

5.33.2.2.1 Brønsted acid-catalyzed hydroarylation of alkynes

Brønsted acids can also efficiently catalyze the intermolecular hydroarylation of aryl-substituted alkynes with benzene derivatives. In the presence of TFA in dichloromethane and without any metal catalysts or additives, electron-rich arenes coupled with aryl-substituted alkynes to give 1,1-diarylalkenes in moderate-to-high yields (Scheme 23).[55]

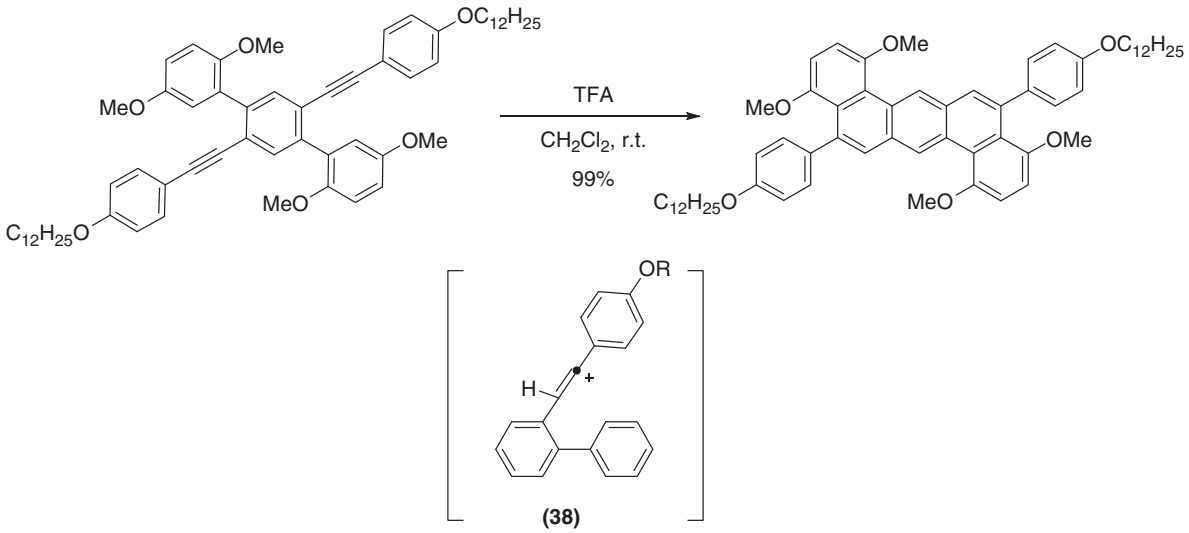


Ar = Pentamethylbenzene, xylene, mesitylene...

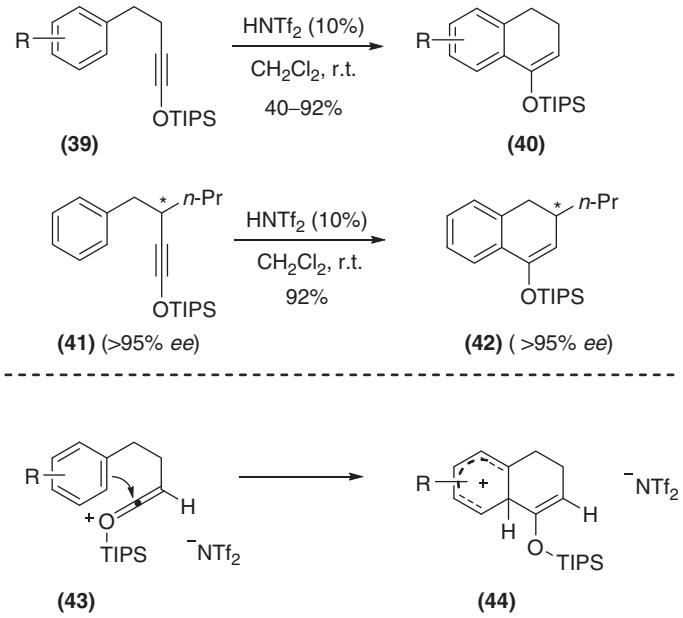
Scheme 23

TFA has also been used to promote the synthesis of fused polycyclic aromatics (Scheme 24).[56,57] The presence of strong donors on the arylalkyne is critical for the success of the reaction. This is consistent with the formation of alkenyl carbocation species **38**. Selective electrophilic attack at the alkynylic moiety is driven by the stabilization provided by the *p*-alkoxy directing group. The cyclization then proceeds by Friedel–Crafts type reaction. Although the protic acid-promoted process is, in principle, catalytic, as the last step is a proton loss, the reactions are driven to completion in the presence of a large excess of acid.

An intramolecular hydroarylation of triisopropylsiloxyalkynes **39** catalyzed by Tf_2NH was reported by Kozmin to give silyl enol ethers **40** (Scheme 25).[58] In addition, $AgNTf_2$ also catalyzed the reaction, although with lower efficiency. A possible mechanism involving a [3,3]-sigmatropic rearrangement and electrocyclic ring closure was excluded, as optically active **41** (>95% *ee*) was cleanly transformed into **42** with full retention of configuration. The reaction most likely proceeds by protonation of the alkyne to form a ketenium ion **43**, which then reacts with the arene to give Wheland intermediate **44**.



Scheme 24



Scheme 25

5.33.3 Hydroarylation of Alkenes

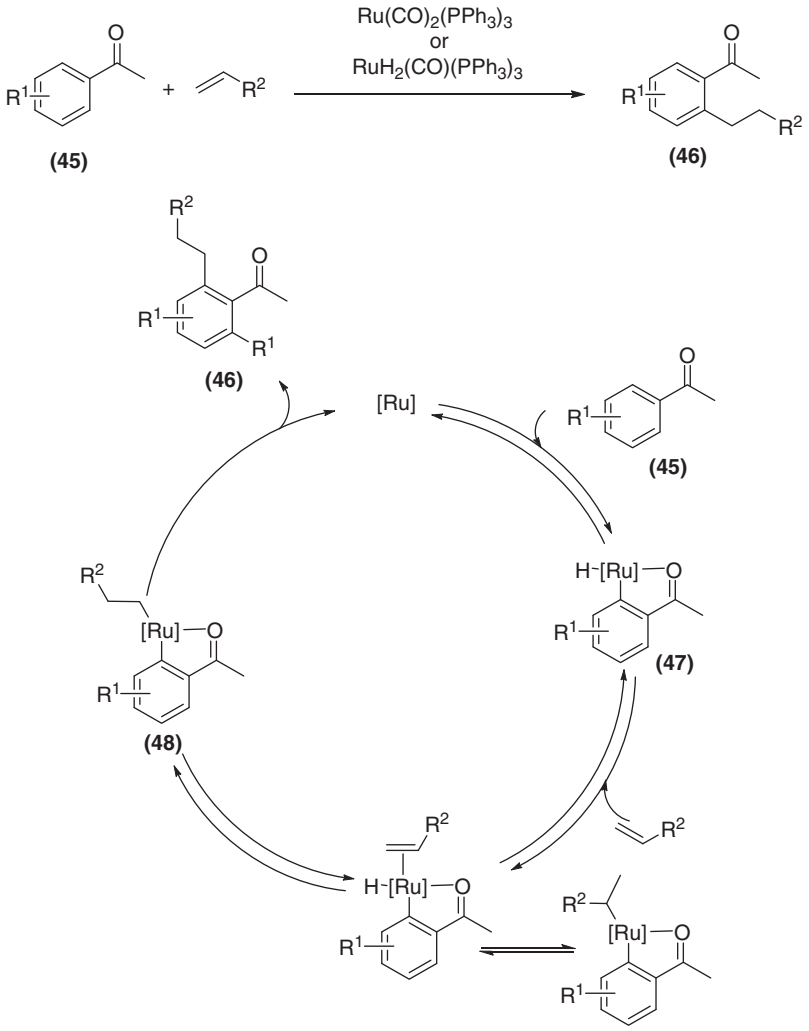
The addition of aromatic rings across alkenes is an atom-economic approach to synthesize alkylated arenes or heteroarenes, which are important structural motifs commonly found in many pharmaceuticals, agro-, and fine chemicals.[59] Two major reaction types can be used to achieve these transformations. Traditionally, Lewis (or Brønsted) acid Friedel–Crafts catalysis has been employed to make simple alkyl arenes.[60] This reaction takes place with electron-rich arenes and selectively affords branched adducts. However, this method suffers from several drawbacks including the propensity toward polyalkylation, the lack of regioselectivity for disubstituted arenes or the inability to recycle the catalyst, among others.[61] In recent years, transition metal-catalyzed hydroarylations through C–H bond activation have grown exponentially due to their high selectivity, efficiency, and environmental friendliness. These systems usually require a directing group or other electronic perturbation (electron-withdrawing groups) on the arene and preferentially afford the linear products due to the steric factors governing the insertion of the double bond into the M–H bond.[1a]

5.33.3.1 Transition Metal-Catalyzed Hydroarylation of Alkenes

5.33.3.1.1 Ruthenium-catalyzed hydroarylation of alkenes

5.33.3.1.1.1 Intermolecular hydroarylations

Murai's group pioneered the use of ruthenium catalysts such as $RuH_2(CO)(PPh_3)_3$ or $Ru(CO)_2(PPH_3)_3$ to activate the C–H bond at the *ortho*-position of aromatic ketones **45** triggering the addition of olefins to form aryl-alkanes **46** in nearly quantitative yields.[62] The key for the success of this reaction relies on the chelation assistance of the directing carbonyl group. The low-valent ruthenium complex coordinates to the C═O, enabling the subsequent cleavage of the adjacent aromatic C–H bond to give aryl-ruthenium complex **47** (Scheme 26). Coordination of the olefin in **47** is followed by addition of the Ru–H bond across the double bond to give intermediate **48**. Reductive elimination leads the final alkylated product **46** (Scheme 26).

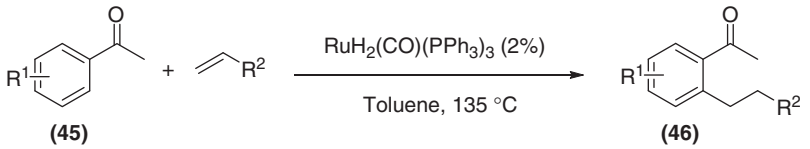


Scheme 26

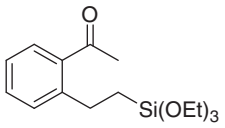
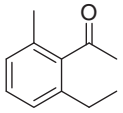
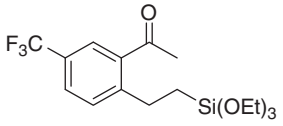
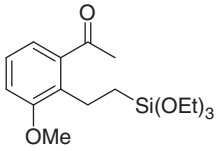
The scope of this transformation has been extensively investigated (Table 2). Olefins such as ethylene, *tert*-buthylethylene, vinylsilanes, and 1,1-disubstituted olefins were efficiently hydroarylated. In contrast, alkenes with allylic hydrogens rapidly isomerize affording the desired product in low yield.[63] Aromatic and heteroaromatic ketones with electron-donating and electron-withdrawing groups were well tolerated.[64] Aromatic substrates bearing an ester group and an electron-withdrawing group at the *meta*-position, could also participate in a chelation-assisted C–H/olefin coupling.[65] Other directing groups in the aromatic ring such as imines,[66] nitriles,[67] and aldehydes[68] have been successfully employed.

The reaction selectivity has also been studied in depth. *meta*-Substituted acetophenones **45** with two different reaction sites undergo C–H activation in the less congested position. However, when the substituent in the *meta*-position is a methoxy group, the C–C bond formation takes place at the sterically less favorable *ortho*-position due to electronic interaction between the oxygen lone pair and the ruthenium.[69]

Table 2 Ruthenium-catalyzed hydroarylation of olefins with aromatic ketones

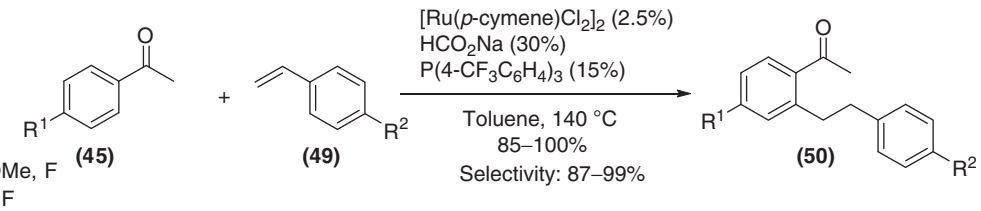


(45) (46)

R^1	R^2	Product	Yield (%)
H	$Si(OEt)_3$		75
o-Me	H		66
m-CF_3	$Si(OEt)_3$		82
m-OMe	$Si(OEt)_3$		100

When $RuH_2(H_2)_2(PCy_3)_2$ was used as catalyst by Chaudret[70] and Leitner,[71] the hydroarylation of olefins occurred at room temperature. Moreover, the alkylation of acetylpyridine,[72] 2-aryl pyridine,[73] and *N*-methylanilines[74] catalyzed by $RuH_2CO(PPh_3)_2$ and $Ru(CO)_{12}$, respectively, has also been reported.

The hydroarylation of styrenes **49** with *para*-substituted acetophenones **45** catalyzed by dimeric $[Ru(p\text{-cymene})Cl_2]_2$ complex has also been reported by Darses and coworkers. AntiMarkovnikov adducts **50** were obtained in a straightforward manner involving regioselective C–H bond activation (**Scheme 27**).[75]



(45) (49) (50)

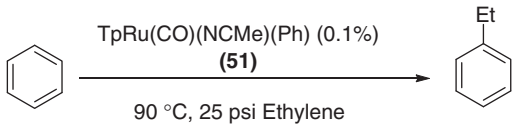
R^1= H, Me, OMe, F
R^2= H, OMe, F

Scheme 27

These reaction conditions have been efficiently applied to the hydroarylation of vinylsilanes using isopropanol as an inexpensive and nontoxic solvent, which constituted the first Csp^2–H activation under protic conditions with low-valent ruthenium complexes.[76] The same group reported the addition of olefins into aromatic ketones and Michael acceptors catalyzed by ruthenium trichloride.[77]

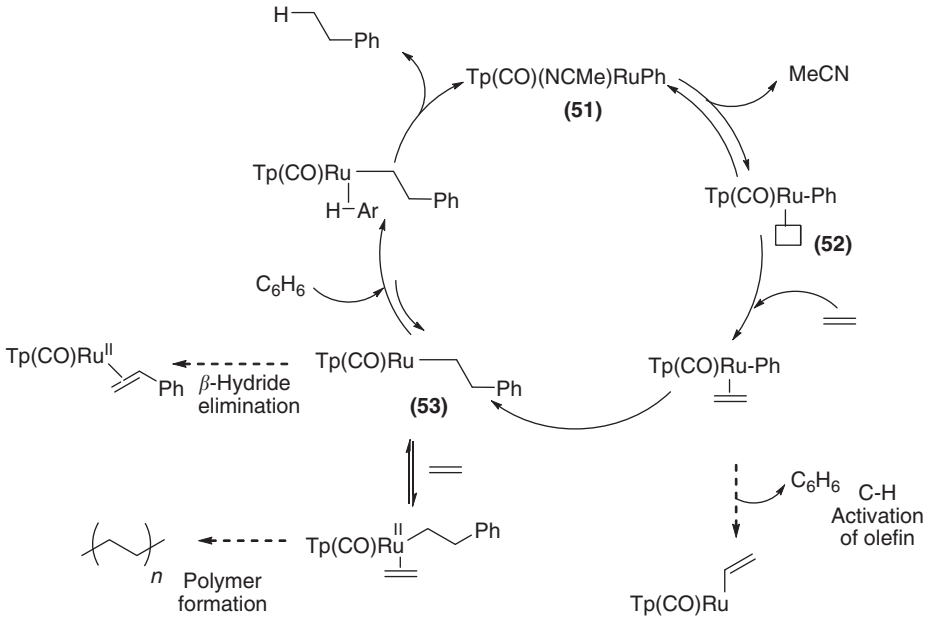
Mechanistic studies of this transformation carried out by Murai[63,67,78] and others,[79] revealed that the C–C bond formation is the rate-limiting step and the H/D exchange occurred only at the *ortho*-position highlighting the importance of the chelation assistance in the C–H bond cleavage by the ruthenium species.

In 2003, Gunnoe and coworkers reported the first hydroarylation of olefins catalyzed by Ru(II) complex without chelating groups.[80] Under nitrogen atmosphere, the combination of 0.1 mol% of TpRu(CO)(NCMe)(Ph) **51** in dry benzene under 25 psi of ethylene at 90 °C resulted in the formation of ethylbenzene (equation 1). Fifty one turnovers of the catalyst were achieved in 4 h, with minimal quantities of 1,3- and 1,4-diethylbenzene products.



(1)

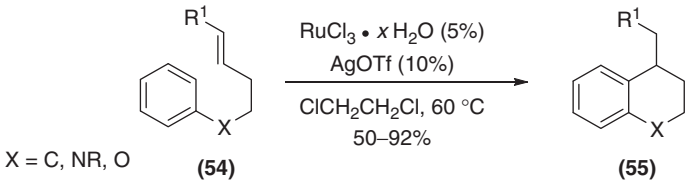
The reaction mechanism of this transformation is depicted in Scheme 28. Acetonitrile decoordination in **51** generates complex **52**, which undergoes olefin insertion leading to intermediate **53**. Subsequent C–H activation of the arene allows the elimination of alkyl benzene and the catalyst is recovered. Quantum mechanical calculations support this mechanistic proposal.[81] Labeling experiments in the hydrophenylation of ethylene with C_6H_6 and C_6D_6 showed a kinetic isotope effect of 2.1 suggesting that benzene C–H activation is the rate-limiting step of the reaction.[82] In addition, the rate of the catalyst is reduced with increasing ethylene pressure supporting that TpRu(CO)(CH_2CH_2Ph)(η^2-C_2H_4) is the catalyst's resting state.



Scheme 28

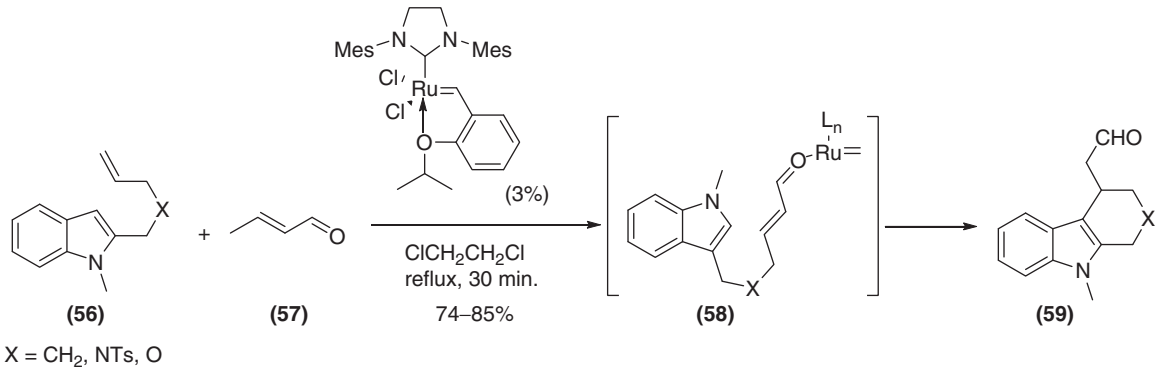
5.33.3.1.1.2 Intramolecular hydroarylations

The intramolecular hydroarylation of a broad range of arene-ene substrates **54** catalyzed by $RuCl_3$/AgOTf under mild conditions was reported by Sames and coworkers in 2004.[83] This transformation provides, in good-to-excellent yields, chromanes, tetralins, terpenoids, dihydrocoumarins, and indolocyclohexane and cyclopentane systems **55** (Scheme 29). A mechanism involving π-alkene activation, C–C bond formation and protonation of the C–Ru intermediate has been proposed to explain the observed reactivity.



Scheme 29

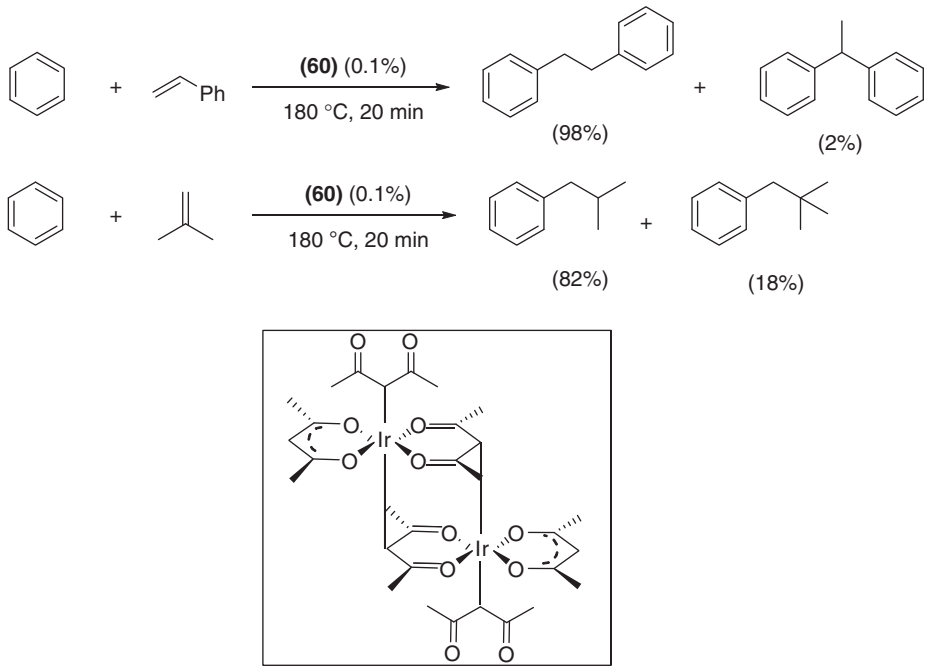
A very efficient ruthenium alkylidene-catalyzed tandem cross-metathesis/intramolecular hydroarylation reaction of ω-indolyl alkenes **56** with electron-deficient alkenes **57** led to structurally complex tetrahydrocarbazoles **59** through intermediate **58** (Scheme 30).[84]



Scheme 30

5.33.3.1.2 Iridium-catalyzed hydroarylation of alkenes

Periana and coworkers reported an Ir(III)-catalyzed alkylation reaction of arenes[85] in which, as in the case of Ru or Rh complexes, antiMarkovnikov adducts were selectively obtained using [Ir(μ-acac-*O,O*)-(acac-C^3)]$_2$ (**60**) as catalyst (Scheme 31).



[Ir(μ-acac-O,O′,C^3)(acac-O,O′)(acac-C^3)]$_2$ **(60)**

Scheme 31

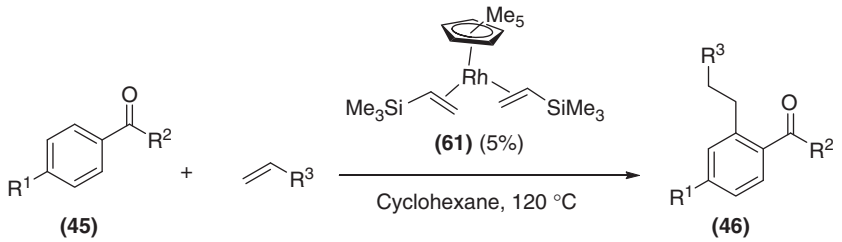
Experimental evidence and DFT calculations suggest that monomeric Ir complexes are the active catalysts in this transformation.[86] The reaction mechanism is similar to the one proposed for ruthenium systems although in this case, the rate-determining step is proposed to be the olefin insertion rather than the reductive elimination step. As with Ru(II) catalysts, an increase in the donor ability of the ancillary ligands is consistent with an increased rate of benzene C–H activation. In contrast, increasing the electron density on the metal (Ru or Ir) increases the activation barrier for olefin insertion.[87]

5.33.3.1.3 Rhodium-catalyzed hydroarylation of alkenes

5.33.3.1.3.1 Intermolecular hydroarylations

The hydroarylation of olefins with aromatic ketones **45** to give *ortho*-alkylation products **46** using bis-olefin rhodium complex [$C_5Me_5Rh(C_2H_3SiMe_3)_2$] (**61**) has also been reported (Table 3).[88] As for the analogous Ru-catalyzed process, a high anti-Markovnikov regioselectivity is observed. However, although in the ruthenium protocol the carbonyl coordination is presumed to occur first, allowing the C–H activation at the *ortho*-position, in the rhodium case there is no discrimination between the Csp^2–H

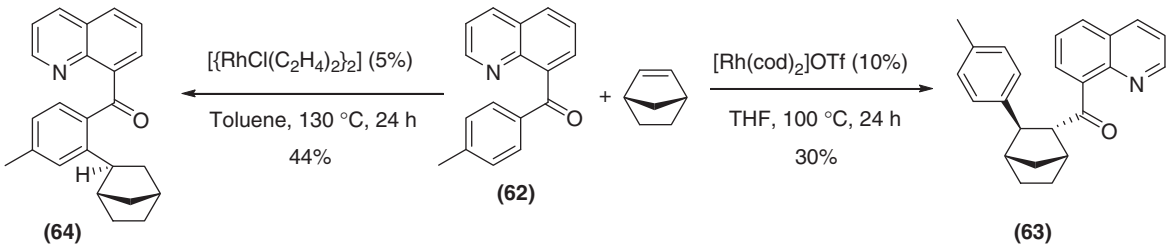
Table 3 Hydroarylation of olefins catalyzed by bis-olefin-rhodium complexes



R^1	R^2	R^3	*Conversion (%)*
H	Ph	$SiMe_3$	49
Cl	Me	$SiMe_3$	35
H	Ph	C_3H_7	60
H	Ph	OEt	10

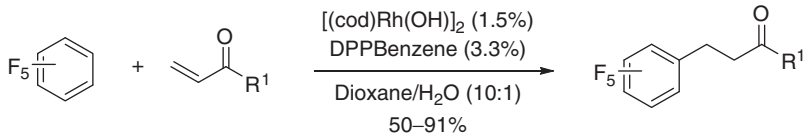
bonds of the aromatic ring and activation of all sites (*meta*, *ortho*, and *para*) is observed. In both processes though, the reductive elimination seems to be the rate-determining step.

A $[\{RhCl(C_2H_4)_2\}_2]$-catalyzed addition of quinolines **62** to olefins was reported by Douglas and coworkers.[89] Interestingly, by controlling the reaction conditions exclusive C–C or C–H activation can be selected to form hydroacylation or hydroarylation products **63** and **64**, respectively (**Scheme 32**). The $RhCl(PPh_3)_3$-catalyzed alkylation of arylpyridines[90] and aromatic imines[91] with olefins has also been realized.



Scheme 32

In addition, an effective Rh-catalyzed coupling between highly fluorinated and α,β-unsaturated carbonyl derivatives to form the antiMarkovnikov alkylated products in high yields has also been disclosed (**Scheme 33**).[92]



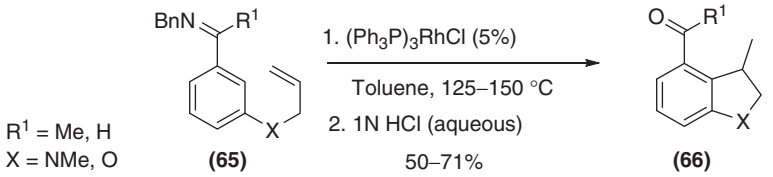
R^1 = OEt, OBu, OBu^i, OBu^t, Me, Et, NMe_2, NH_2

Scheme 33

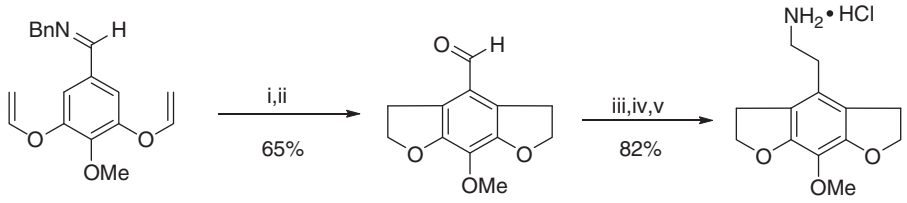
5.33.3.1.3.2 Intramolecular hydroarylations

The annulation of aromatic imines or aldimines **65** in which the alkene is tethered *meta* to the directing group, led to functionalized indane, tetralanes, dihydrobenzofurans, and dihydroindoles **66** in the presence of Wilkinson's catalyst (**Scheme 34**).[93] The coupling proceeds selectively to the more hindered *ortho*-site to provide functionalized bicyclic systems **66**. Linear or branched coupling products were obtained depending on the length of the alkene tether. This annulation strategy has been applied in the total synthesis of tetrahydrobis(benzofuran) mescaline analog **67** (**Scheme 35**).[94]

An asymmetric variant of this protocol has also been developed in one of the first examples of highly enantioselective catalytic hydroarylation of alkenes through aromatic C–H bond activation.[95] The combination of $[RhCl(coe)_2]_2$ and chiral



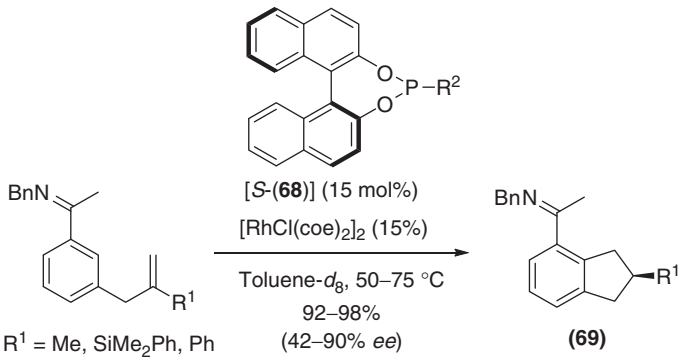
Scheme 34



i, $[RhCl(coe)_2]_2$ (10%), $FcPCy_2$ (20%), toluene, 150 °C, 2 h; ii, 1 N HCl, 3 h; iii, $MeNO_2$, NaOAc, AcOH, reflux; iv, $LiAlH_4$, THF, 23 °C; v, HCl, Et_2O

Scheme 35

(*S*)-binol-derived phosphoramidite ligands [*S*-(**68**)] afforded the corresponding cyclic adducts **69** in excellent yields and moderate-to-good enantioselectivities (Scheme 36).



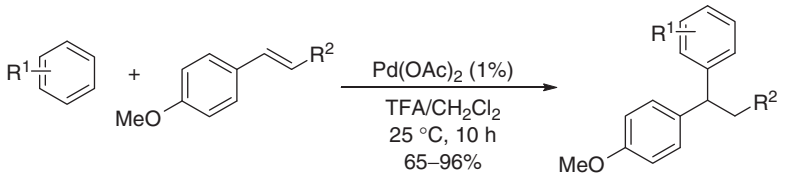
Scheme 36

5.33.3.1.4 Palladium-catalyzed hydroarylation of alkenes

Electrophilic Pd(II) cationic species, analogous to the ones reported for the hydroarylation of alkynes (Section 5.33.2.1.1) were used by Fujiwara's group to trigger a regioselective addition of alkoxyarenes to activated alkenes in TFA.[2a] $Pd(OAc)_2$ and $Pd(PPh_3)_2(O_2CCF_3)_2$ were equally active, whereas Pd(0) species such as $Pd(PPh_3)_4$ were much less efficient, indicating that the reaction may not involve Pd(0) species in the catalytic cycle (Scheme 37).

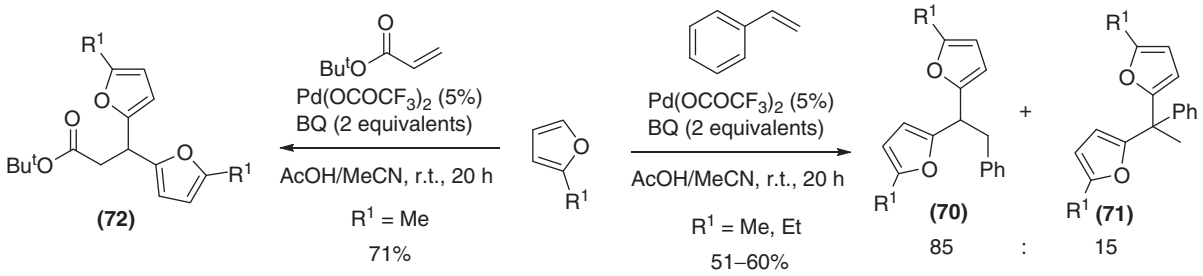
A palladium-catalyzed coupling of 2-alkylfurans with olefins in a mixture AcOH/MeCN has also been described.[96] Allylarenes and styrenes led to the formation of *β*,*β*-difurylalkanes (**70** and **71**) as major products, whereas acrylates afforded *β*,*β*-difurylesters (**72**) in high yields (Scheme 38).

ESI–MS spectrometry and labeling experiments support the reaction mechanism shown in Scheme 39. Two consecutive C–H bond activations in the 2-alkylfurans by L_2PdX_2 species followed by insertion of the olefin delivers alkyl-Pd(II) complexes **73**. These intermediates undergo *β*-elimination and insertion to form the new alkyl-Pd(II) complexes **74**. Reductive elimination affords the difurylalkanes **70**. Oxidation of the resulting Pd(0) with benzoquinone and AcOH regenerates the active catalytic species (Scheme 39).

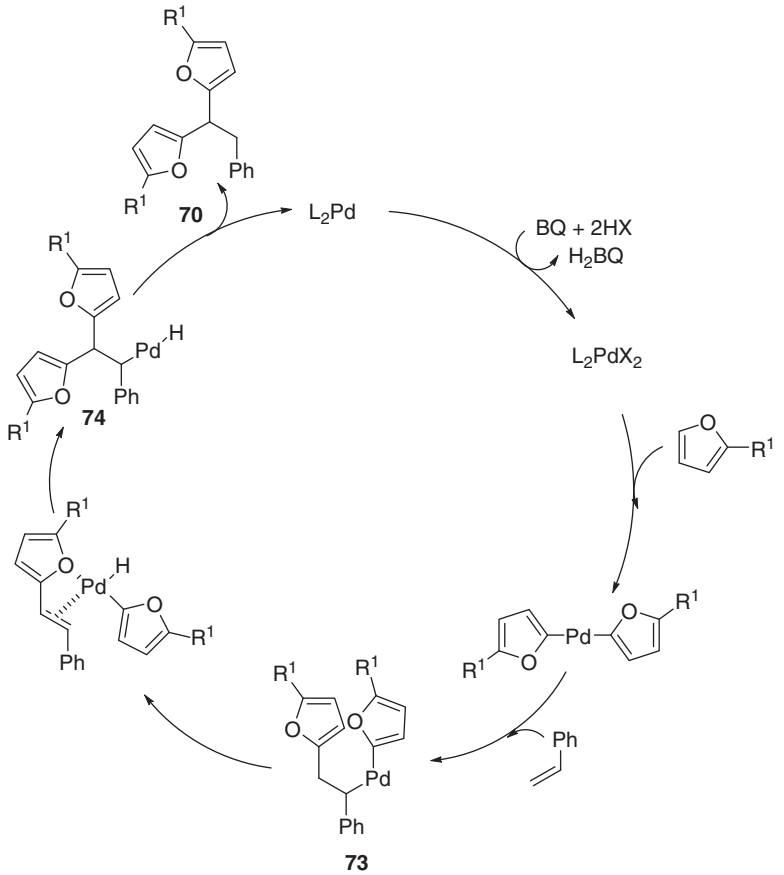


R^1 = 1,3,5-Trimethoxy, 1,4-dimethoxy, 1-OH-3,4,5-trimethoxy
R^2 = $CO_2C_8H_{17}$, CO_2H

Scheme 37



Scheme 38

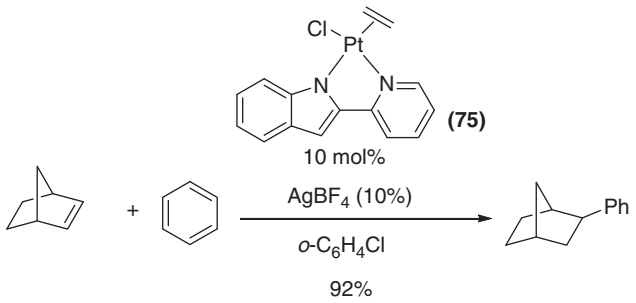


Scheme 39

5.33.3.1.5 Platinum-catalyzed hydroarylation of alkenes

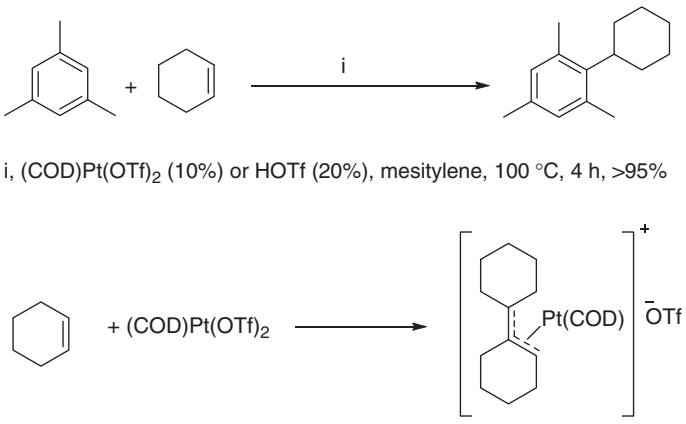
5.33.3.1.5.1 Intermolecular hydroarylations

Platinum(II) complexes have shown an excellent ability to catalyze the hydroarylation of olefins. The combination of Pt-Ag ({2-(2-pyridyl)indole}Pt(Cl)(η^2-C_2H_4) **75** and AgOTf or $AgBF_4$) has been applied in the hydroarylation of unactivated alkenes such as norbornene, 2-butene, propylene, cyclopentene, or cyclohexene with benzene to give the corresponding aryl-alkanes in good yields (equation 2).[97] The reaction is regioselective affording exclusively *iso*-propylbenzene when 1-propene was used, which points toward a Friedel–Craft type alkylation pathway. Other cationic platinum systems such as the combination of (^{t}bpy)Pt(Ph)Cl and $NaBAr'_4$ have been investigated in this context.[98]



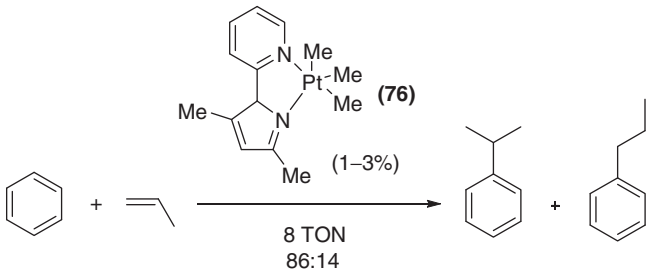
(2)

Dicationic platinum(II) complexes such as [Pt(PNP)(C_2H_4)(SbF_6)$_2$] are electrophilic enough to react with aromatic rings activated by electron-donating substituents.[99] Recently, Tilley and Bergman have gathered evidence for a Friedel–Crafts alkylation mechanism in which the acid generated by interaction between the cationic platinum species and the alkene is the active catalyst of the reaction (**Scheme 40**).[100]



Scheme 40

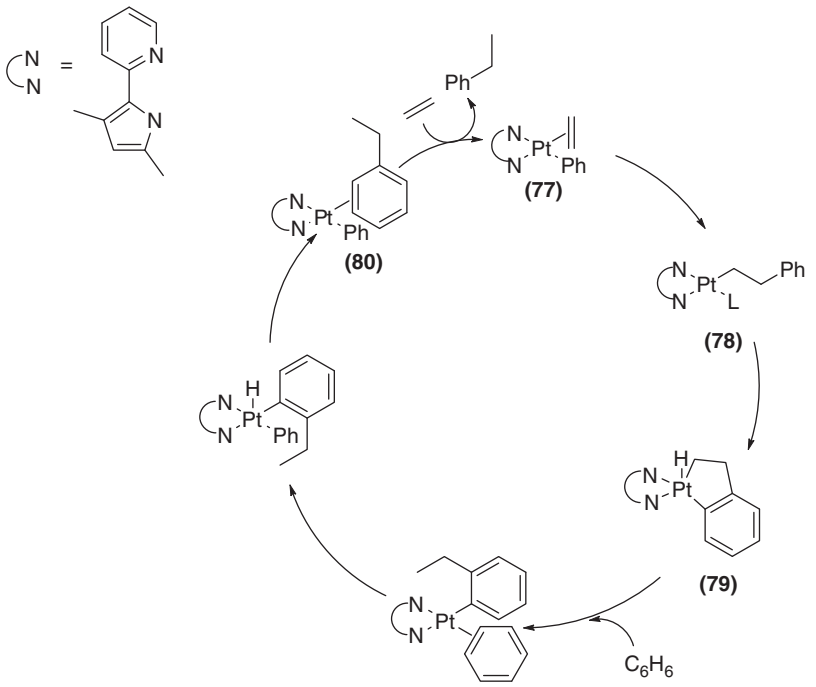
Neutral platinum(II) species with monoanionic 2-(2-pyridyl)pyrrolidine ligands (**76**) have been applied in reactions with unactivated arenes affording Markovnikov aryl alkane products in a regioselective manner (equation 3).[101] However, *para*-substituted arenes afforded a complex mixture of *ortho*-, *meta*-, and *para*-regioisomers.



(3)

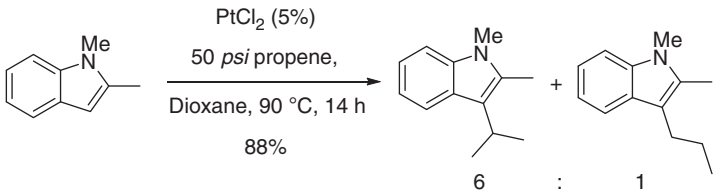
Mechanistic studies including deuterium-labeling experiments were consistent with a reaction pathway involving the olefin insertion into the Pt(II)-aryl bond (**78**) followed by C–H activation at the Pt(II) center to form cyclometalated Pt-H intermediate **79**.[102] Subsequent C–H reductive elimination followed by coordination of a new molecule of benzene and Csp^2–H bond

activation leads to platinum species **80**. On ethylbenzene ligand exchange in the presence of ethylene, the arylalkane is formed and the catalytic specie **77** is regenerated (Scheme 41).



Scheme 41

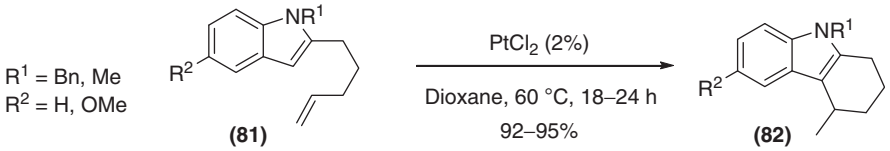
The addition of indoles to ethylene, α-olefins, and styrenes catalyzed by platinum dichloride has been reported.[103] This system affords the Markovnikov adducts as major products in the reaction mixture (equation 4).



(4)

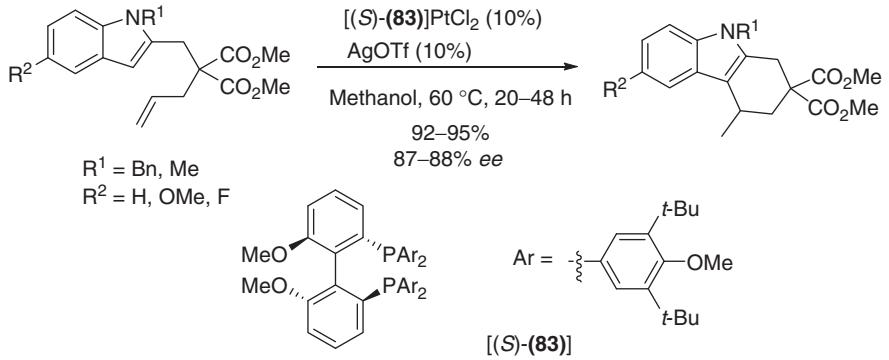
5.33.3.1.5.2 *Intramolecular hydroarylations*

In a related example to the one shown in equation 4, Widenhoefer's group has developed an intramolecular alkylation of C2-substituted indoles **81** catalyzed by $PtCl_2$.[103b,104] The hydroarylation reaction was carried out in dioxane, which contained a trace of HCl (5 mol%) to lead to the corresponding tricyclic products **82** in excellent yields (Scheme 42).



Scheme 42

A 1:1 mixture of platinum bis(phosphine) complex [(*S*)-(**83**)]$PtCl_2$ ([(*S*)-(**83**)]= (*S*)-3,5-*t*-Bu-4-OMe-MeOBIPHEP) and silver triflate catalyzed the asymmetric version of this reaction (Scheme 43).[105] The enantioselective hydroarylation of disubstituted internal olefins in these systems was recently reported by Peters and coworkers.[106]



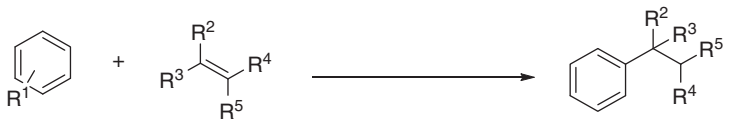
Scheme 43

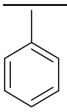
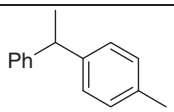
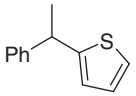
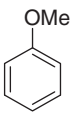
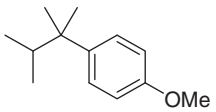
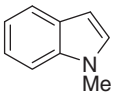
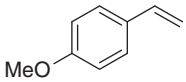
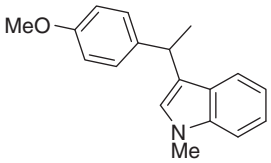
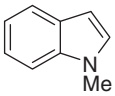
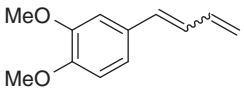
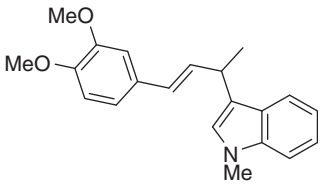
5.33.3.1.6 Gold-catalyzed hydroarylation of alkenes

5.33.3.1.6.1 Intermolecular hydroarylations

Gold(I) and gold(III) complexes combined with silver salts catalyze the addition of electron-rich arenes to olefins.[107] Substituted styrenes as well as unactivated aliphatic olefins and dienes were successfully hydroarylated as summarized in **Table 4**. The hydroarylation reaction with indoles was limited to *N*-phenylsulfonyl-protected ones when a $AuCl_3$/AgOTf catalytic system was applied.[108] However, the reaction can also be catalyzed by cationic gold(I) species ([(PR_3)PAuCl/AgOTf]) to give C-3 alkylated indoles with Markovnikov selectivity in thermal and microwave assisted conditions.[109]

Table 4 Gold-catalyzed hydroarylation of alkenes

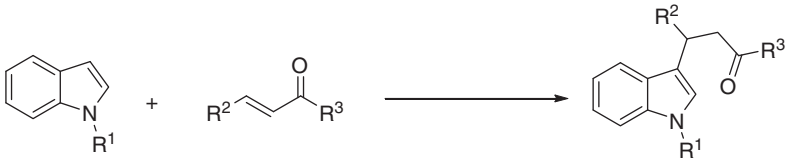


Arene	*Alkene*	*Conditions*	*Selectivity (p-;o-)*	*Major product*	*Yield (%)*
		$AuCl_3$ (5%), $AgSbF_6$ (15%), 1,2-DCE, 50 °C, 5 h	9:1		86
		$AuCl_3$ (5%), $AgSbF_6$ (15%), 1,2-DCE, 50 °C, 5 h	4.5:1		87
		$AuCl_3$ (5%), $AgSbF_6$ (15%), 1,2-DCE, 50 °C, 5 h	>20:1		93
		PPh_3AuCl (5%), AgOTf (15%), toluene, 85 °C, 1 h	–		95
		PPh_3AuCl (5%), AgOTf (15%), toluene, 70 °C, 16 h			81

Gold(III) complexes have shown an exceptional activity in the conjugate addition of arenes and heteroarenes across α,β-unsaturated carbonyl compounds.[110] Complexes such as $NaAuCl_4 \cdot 2\ H_2O$[111] or $AuCl_3$[112] have been successfully employed in the

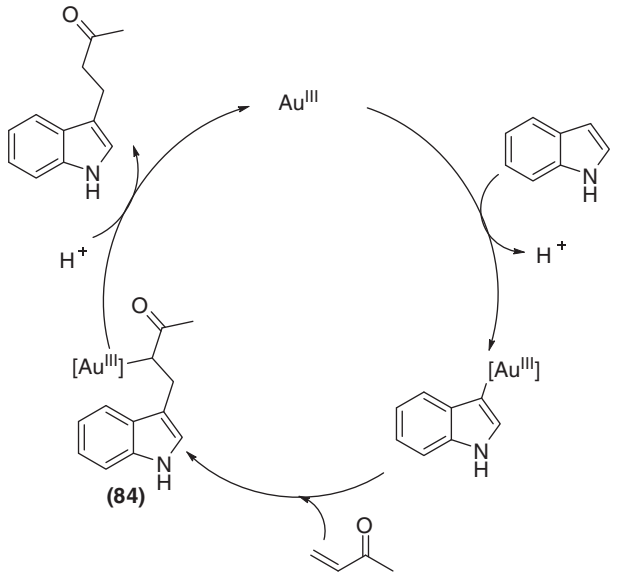
hydroarylation of substituted and unsubstituted enones with indoles (Table 5). Interestingly, if the C-3 position of the indole is substituted, the substrate can undergo a C-2 alkylation.[111] The alkylation of less electron-rich azaindoles[113] and a gold(III)-catalyzed one-pot reaction of 2-alkynyl-phenylamines with α,β-enones to form C-3-alkyl-indoles by sequential reactions such as cyclization/alkylation, *N*-alkylation/cyclization, or *N*-alkylation/cyclization/alkylation have also been developed.[114]

Table 5 Conjugate addition of indoles to α,β-unsaturated ketones



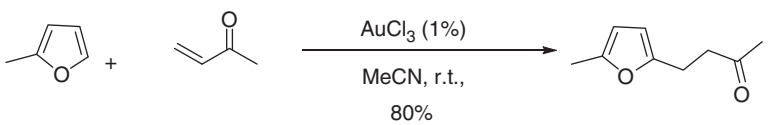
R^1	R^2	R^3	*Conditions*	*Yield (%)*
Me	Ph	Ph	$AuCl_3$ (5%), MeCN, r.t.	92
H	Ph	Ph	$NaAuCl_4$ (5%), EtOH, r.t.	88
H	H	Me	$NaAuCl_4$ (5%), EtOH, r.t.	72
H	H	Me	$AuCl_3$ (5%), MeCN, r.t.	95
H	$CH_2CH_2CH_2CH_3$	Me	$NaAuCl_4$ (5%), EtOH, r.t.	83

The regioselective auration of the indole at position 3 followed by a conjugate addition reaction to the electron-deficient alkene is suggested to yield alkyl–gold complex **84** (Scheme 44). On protodeauration of **84**, the alkylated indoles is obtained. This proposal is based on the detection of the arene aurated species $[indol\text{-}AuCl]^+$ by mass spectrometry (ESI–MS) in a stoichiometric reaction between the indole and $NaAuCl_4 \cdot H_2O$ in MeCN. However, a Friedel–Crafts type mechanism cannot be ruled out.



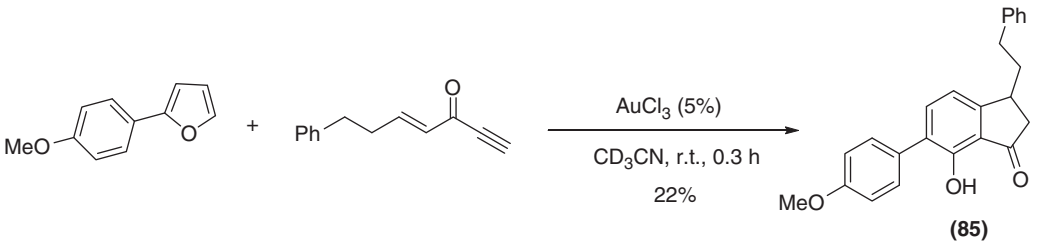
Scheme 44

The gold-catalyzed addition of furans to α,β-enones was first reported by Hashmi[115,116] and further developed by Urriolabeitia, Contel, and coworkers (equation 5).[117,118] This reaction was also catalyzed by Brønsted acids such as *p*-TsOH and HCl, although the latter systems displayed different selectivities than the gold-catalyzed processes. The gold(III)-catalyzed addition of pyrroles to methyl vinyl ketones was studied, although the high reactivity of the pyrrole led to multiple substitution products and a selective pyrrole's substitution could not be achieved.[119]



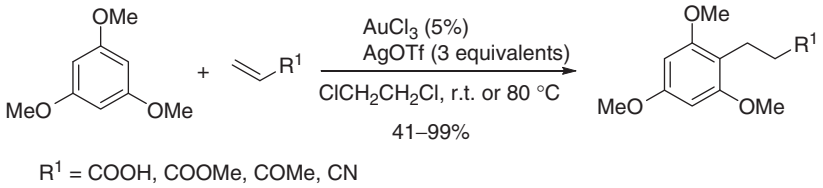
(5)

Addition of furans to electron-deficient olefins catalyzed by gold followed by cycloisomerization delivered highly substituted phenols **85** in relatively low yields, which are nevertheless comparable to those obtained from known multistep-routes (equation 6).[120]



(6)

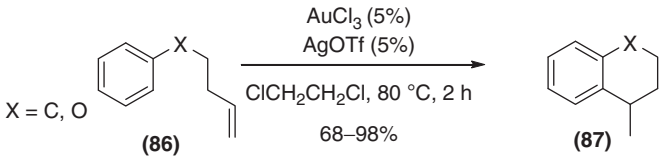
The addition of electron-rich arenes to α,β-unsaturated ketones in the presence of catalytic amounts of $AuCl_3$ and three equivalents of AgOTf gave the corresponding alkyl arenes in good yields. The silver salt is thought to help removing the chloride ions from the gold catalyst and generate a more electrophilic gold complex. The reaction was found to be compatible with a broad scope of Michael acceptors (Scheme 45).[12]



Scheme 45

5.33.3.1.6.2 Intramolecular hydroarylations

The combination of $AuCl_3$ with AgOTf catalyzed the intramolecular hydroarylation of olefins in a variety of functionalized arene derivatives **86** to form dihydrobenzopyrans, tetralins, and tetrahydroquinolines **87** in good yields (Scheme 46).[121]



Scheme 46

In addition, the gold(III)-catalyzed annulation of phenols and naphthols with dienes efficiently generated a broad scope of benzohydrofurans.[122] The presence of electron-donating groups on the arenes promoted the reaction whereas electron-withdrawing groups gave lower conversions. Furthermore, a gold(I)-catalyzed synthesis of phenanthrene and cyclohepta[*a*]-naphthalene skeletons through intramolecular hydroarylation of cyclic 5-(2-arylethyl)1,3-dienes has been recently reported.[123]

5.33.3.1.7 Other metals (Mo, W, Re, Fe, Co)-catalyzed hydroarylation of alkenes

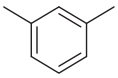
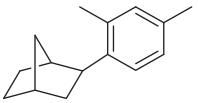
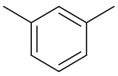
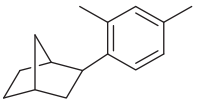
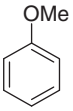
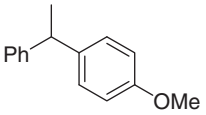
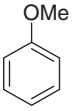
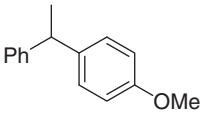
The combination of a molybdenum(II) complex ($[CpMoCl(CO)_3]$) and an organic oxidant (*o*-chloranil, **88**)[124] has been used in a Friedel–Crafts alkylation of norbornene and styrene to produce aryl-alkanes in moderate-to-high yields. The use of microwave irradiation at 150 °C afforded the hydroarylation products in comparable yields and shorter reaction times (Table 6).

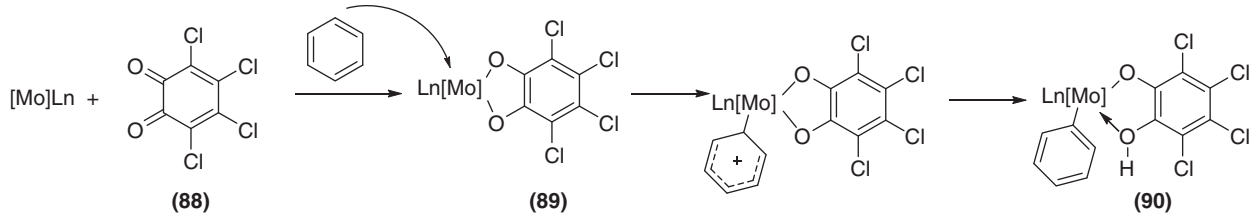
Due to the Markovnikov- and *ortho*/*para*-selectivities, the authors propose the oxidation of the molybdenum complex by *o*-chloranil (**88**) to generate an intermediate molybdenum catecholate **89**. The electrophilic addition of the aromatic substrates gives **90**, a Brønsted acid catalytic species that behaves as a proton donor to trigger the arene alkylation (Scheme 47).

Tungsten(II) chlorocarbonyl complexes, obtained by photochemical oxidation of $W(CO)_6$ with CCl_4, are highly active catalysts for the transformation of alkenes to alkyltoluenes.[125] In addition, $[(CO)_4W(\mu\text{-}Cl)_3W(SnCl_3)(CO)_3]$ catalyzed an efficient addition of simples arenes, such as benzene, toluene, or *p*-xylene, to norbornene affording *exo*-2-aryl-norbornanes.[126]

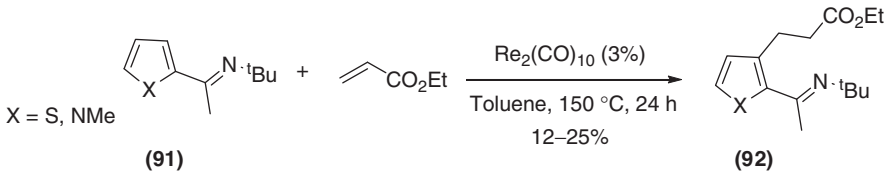
The hydroarylation of acrylates with heteroaromatic aldimines **91** using $Re_2(CO)_{10}$ as catalyst has been reported.[127] However, the yields of the alkylated products **92** were very low and the reactions afforded complex mixtures (Scheme 48).

Table 6 [CpMoCl(CO)$_3$]/*o*-chloranil-catalyzed hydroarylation of alkenes with arenes

Arene	*Alkene*	*Conditions*	*Selectivity (p-;o-)*	*Major product*	*Yield (%)*
		[CpMoCl(CO)$_3$]/*o*-chloranil (1:2) (10%), *p*-xylene, 80 °C, 24 h	–		83
		[CpMoCl(CO)$_3$]/*o*-chloranil (1:2) (10%), *p*-xylene, 150 (MW), 15 min	–		79
		[CpMoCl(CO)$_3$]/*o*-chloranil (1:2) (10%), *p*-xylene, 40 °C, 24 h	82:18		90
		[CpMoCl(CO)$_3$]/*o*-chloranil (1:2) (10%), 150 (MW), 1 h	74:26		78



Scheme 47



Scheme 48

An easy and efficient synthesis of 1,1-diarylalkanes and 1-aryl-1-heteroarylalkanes was attained by hydroarylation of styrenes with electron-rich arenes and heteroarenes catalyzed by $FeCl_3$ (Table 7).[128] This transformation is especially attractive due to the cheap and easy-to-handle catalyst.

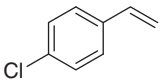
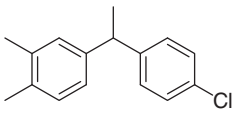
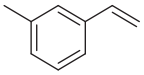
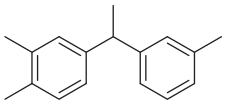
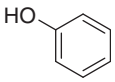
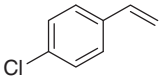
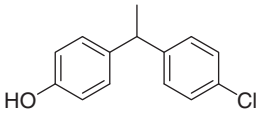
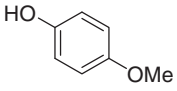
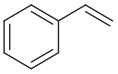
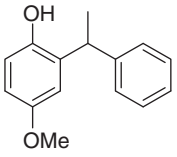
In analogy to the cocatalyzed hydroarylation of alkynes described in Section 5.33.2.1.2, the cobalt-catalyzed hydroarylation of styrenes with 2-arylpyridine derivatives **93** and aryl imines has also been reported.[129] Interestingly, the branched and the linear adducts could be obtained selectively by ligand control. A cobalt-catalyst generated from $CoBr_2$ (10 mol%), PCy_3 (10 mol%) and Me_3SiCH_2MgCl (80 mol%) in THF at 60 °C afforded the branched product **94** whereas, when the reaction was carried out with IMes · HCl instead of PCy_3, the linear adduct **95** was regioselectively obtained (Scheme 49).

5.33.3.2 Nontransition Metal-Catalyzed Hydroarylation of Alkenes

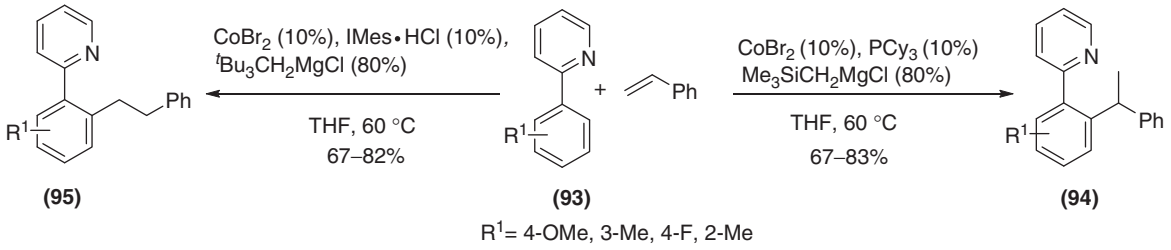
Friedel–Crafts hydroarylation processes are usually assisted by either protic acid or Lewis acids. On the basis of the reaction mode, these transformations can be divided into (1) reactions of arenes with normal alkenes via carbocation-like intermediates or (2) reactions of electron-deficient alkenes via Michael-type 1,4 addition.

The Friedel–Crafts alkylation of arenes with alkenes was previously reviewed in this series.[60] The C-3 alkylation of indoles with suitable Michael acceptors catalyzed by Lewis acids such as ytterbium triflate ($Yb(OTf)_3$)[130] or indium tribromide ($InBr_3$)[131] was reported by Kerr and Umani-Ronchi, respectively. A variety of Michael acceptors such as α,β-unsaturated ketones or esters and nitroalkenes afforded the alkylated indoles in moderate-to-good yields. These reactions are easily performed and remarkably

Table 7 $FeCl_3$-Catalyzed hydroarylation of styrenes[a]

Arene	*Alkene*	*Selectivity*[b]	*Major product*	*Yield (%)*
		>99:1		89
		96:4		77
		56:44		91
		76:24		78

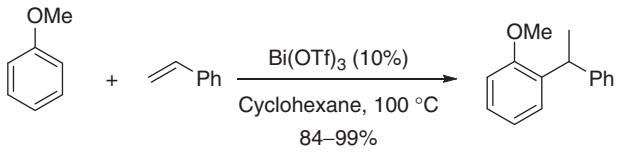
[a]Conditions: $FeCl_3$ (10%), 80 °C, 4 h.
[b]Ratio: main product: other isomers.



Scheme 49

tolerant of substituents at different positions of the indole ring (Table 8). The addition of electron-rich arenes and heteroarenes to β-nitrostyrenes could also be mediated by aluminum trichloride in dichloromethane at −78 °C.[132]

Bismuth(III) chloride and bismuth(III) triflate have also been reported to catalyze the hydroarylation of styrenes with electron-rich arenes to give Markovnikov adducts in good yields (equation 7).[133]



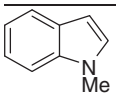
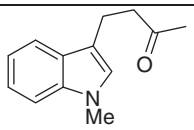
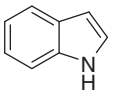
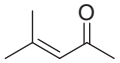
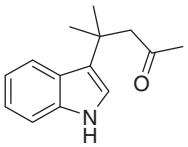
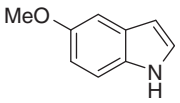
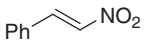
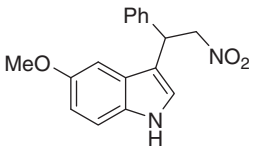
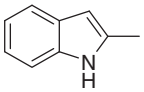
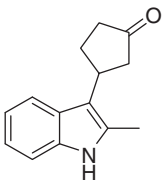
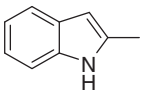
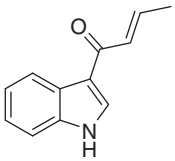
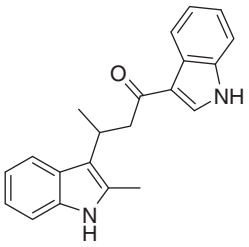
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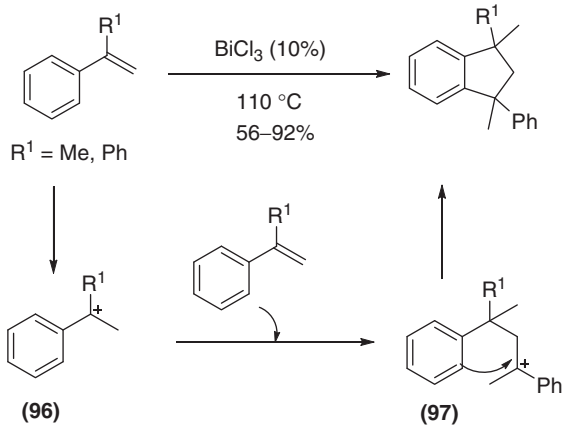
In these systems, the excess of α-substituted styrenes underwent inter- and intramolecular double hydroarylation as a result of styrene dimerization under the reaction conditions (Scheme 50). Such dimerization may proceed through an intermolecular ene-reaction between styrene and the carbocationic intermediate **96** followed by an intramolecular Friedel–Crafts alkylation of the resulting carbocationic 1,3-diarylpropane **97**. Intramolecular olefin hydroarylations catalyzed by Bi(III) triflate have also been reported.[134]

A highly efficient calcium-catalyzed intermolecular hydroarylation of aryl and aliphatic olefins was reported by Niggemann in 2010.[135] The hydroarylation of di- and trisubstituted styrenes, cyclic, and linear dienes as well as cyclic trisubstituted alkenes was found to proceed smoothly at room temperature in the presence of the highly reactive $Ca(NTf_2)_2/Bu_4NPF_6$ system. Free phenolic hydroxyl groups, furans, and thiophenes were well tolerated (Table 9).

Molecular iodine (I_2) has been applied as catalyst in the hydroarylation of styrenes with electron-rich arenes and heteroarenes under solvent-free conditions.[136] The reaction favors the Markovnikov adduct although in several cases mixture of regioisomers were observed (Scheme 51).

Table 8 Alkylation of indoles with electron-deficient alkenes catalyzed by Lewis acids

Indole	*Michael acceptor*	*Conditions*	*Product*	*Yield (%)*
		$Yb(OTf)_3$ (2.5%), MeCN, r.t., 7 h		73
		$Yb(OTf)_3$ (2.5%), MeCN, r.t., 7 h		63
		$InBr_3$ (5%), H_2O/THF, r.t., 2 h		88
		$InBr_3$ (10%), CH_2Cl_2, r.t.		87
		$InBr_3$ (10%), CH_2Cl_2, r.t.		96

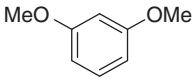
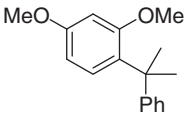
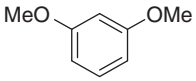
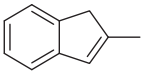
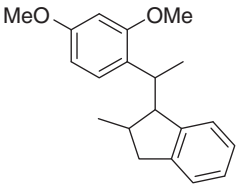
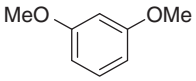
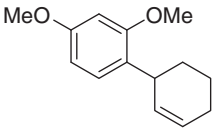
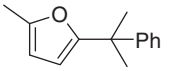
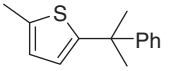


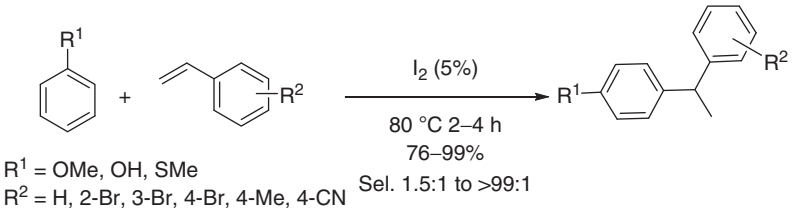
Scheme 50

5.33.3.2.1 Brønsted acid-catalyzed hydroarylations

Strong acids have long been known to catalyze reactions involving alkenes.[60] When an alkene is mixed with a strong acid, the proton is transferred to the double bond affording a very reactive carbocation intermediate, which can react with external nucleophiles such as electron-rich arenes. The reaction affords Markovnikov adducts as the proton is added to the less substituted carbon of the double bond, leading the stabilized positive charge at the more substituted carbon atom.

Table 9 Hydroarylation of alkenes catalyzed by $Ca(NTf_2)_2/Bu_4NPF_6$

Ar–H	*Olefin*	*Conditions*	*Product*	*Yield (%)*
		$Ca(NTf_2)_2/Bu_4NPF_6$ (2.5%), CH_2Cl_2, r.t., 0.5–12 h		95
		$Ca(NTf_2)_2/Bu_4NPF_6$ (2.5%), CH_2Cl_2, r.t., 0.5–12 h		72
		$Ca(NTf_2)_2/Bu_4NPF_6$ (2.5%), CH_2Cl_2, r.t., 0.5–12 h		72
		$Ca(NTf_2)_2/Bu_4NPF_6$ (2.5%), CH_2Cl_2, r.t., 0.5–12 h		75
		$Ca(NTf_2)_2/Bu_4NPF_6$ (2.5%), CH_2Cl_2, r.t., 0.5–12 h		81



Scheme 51

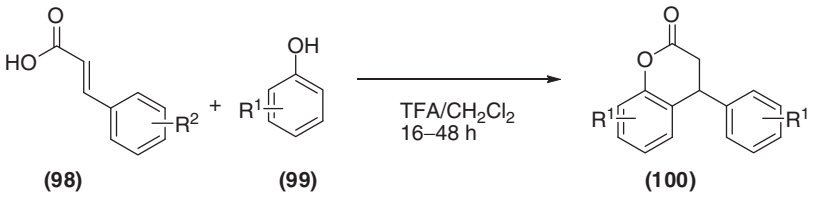
The hydroarylation of electron-deficient alkenes has been investigated with various Brønsted acids such as TFA and *p*-toluenesulfonic acid. TFA enabled the synthesis of dihydrocoumarins (**100**) in excellent yields under very mild conditions from cinnamic acid derivatives **98** and phenols **99** (Table 10).[137] Nonactivated cinnamic acids required elevated reaction temperatures to achieve good yield. The reaction was regioselective when unsymmetrical 3-methyl-4-chlorophenol was used. In this case, the cyclohydroarylation led the product of addition at the less substituted *ortho*-carbon. An intramolecular version of this reaction starting from aryl cinnamates was also successfully developed.

In contrast, the synthesis of dihydroquinolones (**102**) could only be obtained by an intramolecular hydroarylation of aryl cinnamides (**101**) (Scheme 52).

p-Toluenesulfonic acid can also mediate the synthesis of dihydrocoumarins and the hydroarylation of anisole with cinnamic acid derivatives to form 3-(4-methoxyphenyl)-3-phenylpropanoic acids.[138] Hydroarylations of styrenes in heterogeneous fashion using Amberlyst-15[139] and $KHSO_4$[140] have also been reported.

Asymmetric Friedel–Crafts reactions involving nitroolefins mediated by chiral Brønsted acids have been investigated due to the versatility of the nitro functional group (Table 11). The first catalytic enantioselective addition of indoles to nitroalkenes was reported by Ricci and coworkers in 2005.[141] The reaction was catalyzed by thiourea derivative **103** and moderate-to-good yields and enantioselectivities were obtained. The catalytic process involves nitroalkene activation by the two NH hydrogen atoms of the thiourea and a weak hydrogen bonding between the indolic proton and the oxygen of the hydroxyl group. Other organocatalysts such as chiral-bis-sulfonamides **104**,[142] bis-arylthiourea **105**,[143] protonated quinolinum thioamide **106**,[144] and chiral phosphoric acid **107**[145] were successfully used affording the alkylated indoles in a highly enantioselective manner. In addition to indoles, the asymmetric addition of 1- and 2-naphthols to nitroalkenes has also been reported by employing the chiral Brønsted acid **108**.[146]

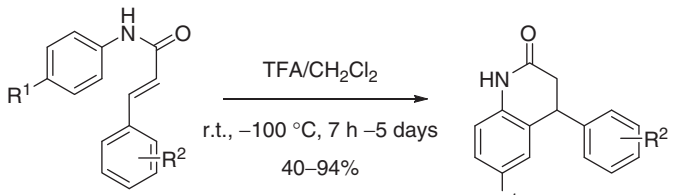
Table 10 Synthesis of dihydrocoumarins



(98) (99) (100)

R^1	R^2	*T (°C)/t (h)*	*Yield (%)*
MeO, OMe, OMe	OMe	r.t./18	99
Cl	MeO, OMe, OMe	100 °C/16	99
Cl	OMe	r.t./16	72[a]

[a]Regioselectivity 11:1.



(101) (102)

R^1 = *t*Bu, Me, OMe
R^2 = 4-OMe, 2-OMe, 4-Cl, 4-Me, 2-Me, 3-Me

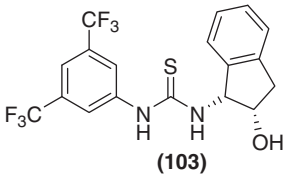
Scheme 52

Asymmetric Friedel–Craft reactions between indoles or 2-naphthols and α,β-unsaturated carbonyl compounds have been successfully described using Brønsted chiral acids.[147–151]

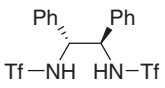
The hydroarylation of unactivated alkenes with anilines has attracted considerable attention in recent years. Thus, the *ortho*-alkylation of anilines with styrenes has been investigated by various groups. Hart and Kosak found aniline could be *ortho*-alkylated to 2-(*sec*-phenethyl)aniline at 220 °C in 82% yield in the presence of aniline hydrochloride and excess of styrene and aniline.[152] Bergman and Arnold applied $[PhNH_3][B(C_6F_5)_4]$ as catalyst in the hydroamination and hydroarylation of several styrene derivatives with anilines.[153] *Ortho*-alkylation of substituted anilines with styrene catalyzed by TFA was reported by Coates and coworkers in 2005 (**Scheme 53**).[154] The *ortho*-alkylation of anilines combined with chiral chromatography separation techniques provides a facile route to anilines with chiral *ortho*-substituents.

Catalytic amounts of aqueous HI led a mixture of hydroarylation and hydroamination products in the alkylation of anilines with styrene derivatives and simples alkenes such as norbornene and cyclohexane. However, the hydroamination process was generally favored over the hydroarylation reaction.[155]

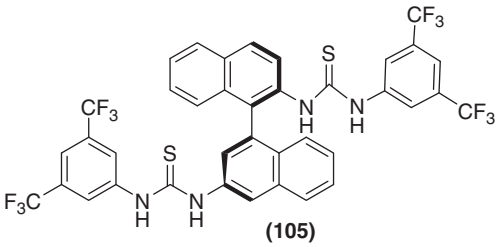
Table 11 Brønsted chiral acids in the asymmetric Friedel–Crafts alkylation reaction via 1,4-addition



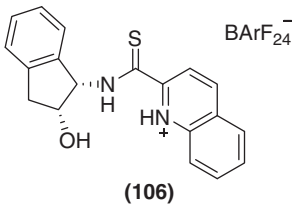
(103)



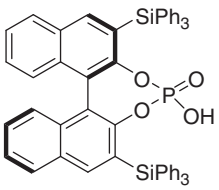
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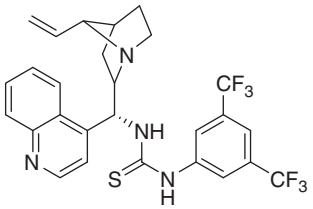
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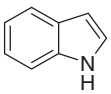
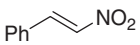
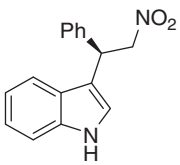
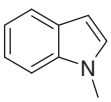
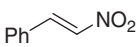
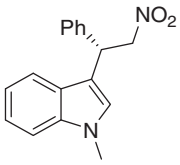
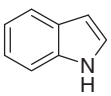
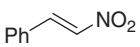
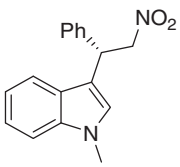
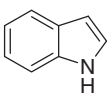
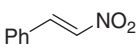
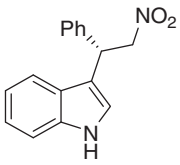
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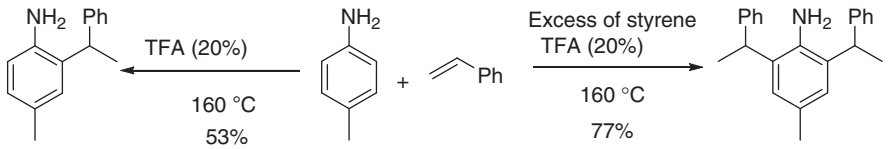


(107)



(108)

Aromatic ring	*Michael acceptor*	*Conditions*	*Product*	*Yield (%)*	ee *(%)*
		**103** (20%), CH_2Cl_2, −24 °C, 72 h		92	85
		**104** (2%), $CHCl_3$, −24 °C, 96 h		91	50
		**106** (5%), $CHCl_3$, 0 °C, 10 h		92	94
		**107** (5%), $C_6H_6/ClCH_2CH_2Cl$, −35 °C, 48 h		76	91



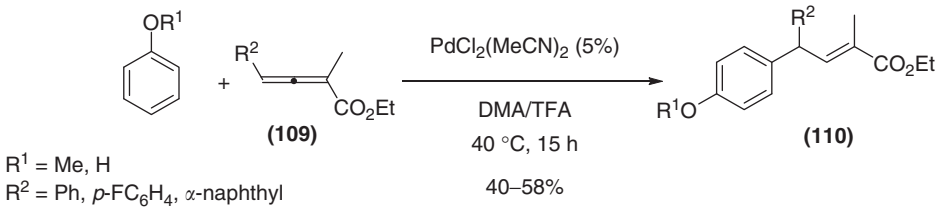
Scheme 53

5.33.4 Hydroarylation of Allenes

5.33.4.1 Transition Metal-Catalyzed Hydroarylations of Allenes

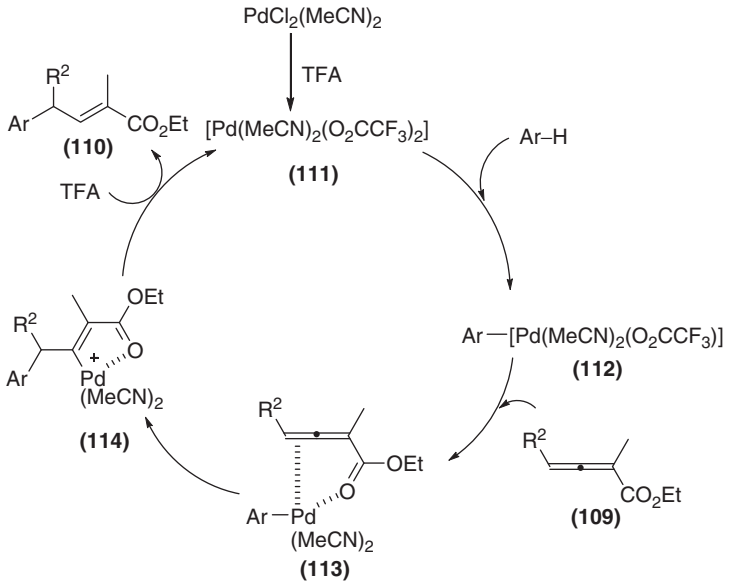
5.33.4.1.1 Palladium-catalyzed hydroarylation of allenes

A highly regio- and stereoselective hydroarylation of 2,3-allenoates **109** catalyzed by $[PdCl_2(MeCN)_2]$ was reported by Ma and coworkers.[156] Allylation of 1,3,5-trimethoxybenzene, anisole, phenol, and *N*-Ts or *N*-Ac-indoles in TFA afforded the corresponding 4,4-diarylbut-2(*E*)-enoates (**110**) in moderate yields (Scheme 54).



Scheme 54

The mechanism for this transformation involves the formation of $Pd(MeCN)_2(O_2CCF_3)_2$ (**111**) as the active catalytic species from the reaction between the $PdCl_2(MeCN)_2$ precatalyst and TFA. Complex **111** triggers the electrophilic C–H activation of the aromatic ring to form the aryl-palladium intermediate **112**. On coordination of **112** with the 2,3-allenoate **109**, *syn*-insertion of the relatively electron-rich C–C double bond affords intermediate **114**. Protonation of **114** under acidic conditions gives the allylic arene **110** (Scheme 55).

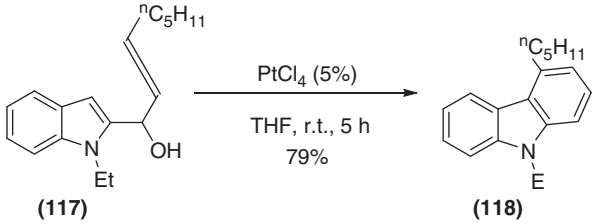


Scheme 55

5.33.4.1.2 Platinum-catalyzed hydroarylation of allenes

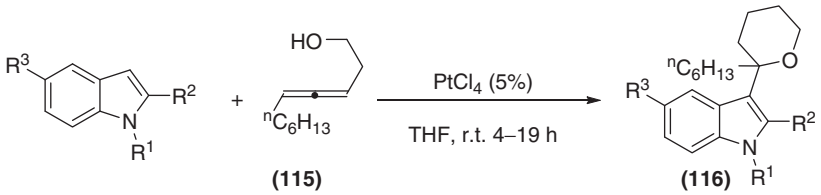
The $PtCl_4$-catalyzed regioselective intermolecular domino hydroarylation/hydroxylation of *β*-allenols **115** to form alkylated indoles containing a six-membered ether ring at the C-3 position **116** has been reported (Table 12).[157]

Based on this results, the Ma group reported an intramolecular $PtCl_2$-catalyzed cyclization of 1-(indol-2-yl)-2,3-allenols **117** in toluene at room temperature to give substituted carbazoles **118** in good yield (equation 8).[158]



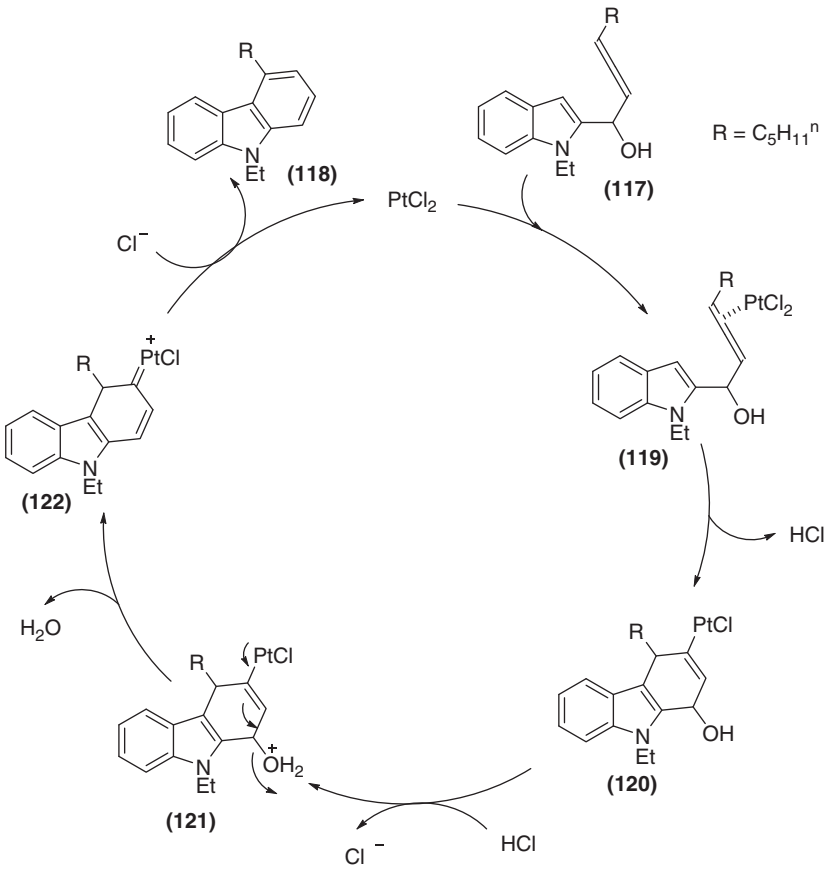
(8)

Table 12 $PtCl_4$-Catalyzed cyclization reaction of β-allenols with indoles



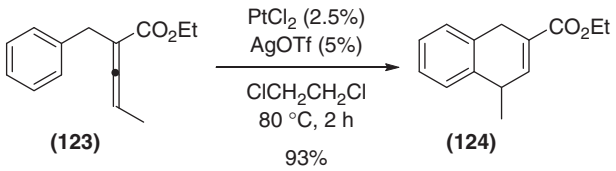
R^1	R^2	R^3	Yield (%)
H	H	H	74
Me	H	H	70
H	H	OH	67
H	Me	Cl	42

The proposed mechanism involving a metal carbene intermediate **122** is depicted in Scheme 56. Nucleophilic attack of the indole onto the activated allene **119** affords the vinylplatinum intermediate **120**, which undergoes protonation of the hydroxyl group to give **121**. The metal carbene intermediate **122**, obtained by elimination of water from **121**, undergoes a 1,2-H shift to form the final product **118**.



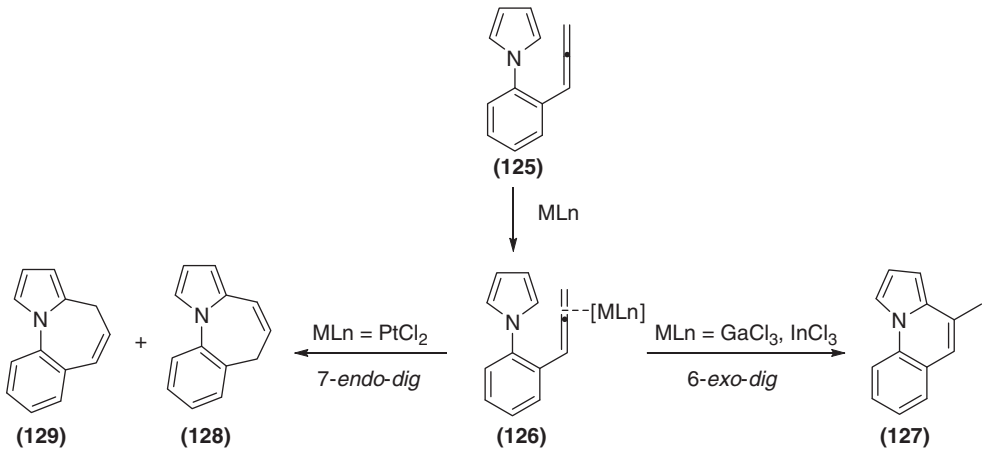
Scheme 56

A related synthesis of 1,4-dihydronaphtalenes **124** through a $PtCl_4$-catalyzed 6-*endo*-cyclohydroarylation of ethyl-2-benzyl-2,3-alkadienoates (**123**) was reported by Lee's group (equation 9).[159]



(123) **(124)** (9)

Further examples of allene intramolecular hydroarylations were reported in the context of the phenantrenes synthesis published by Fürstner and discussed in Section 5.33.2.1.1.1.[22b] When $GaCl_3$ or $InCl_3$ were used, aryl allene **125** gave phenantrene **127** as a single product. In contrast, when $PtCl_2$ was employed a mixture of isomeric pyrrolo-azepines **128** and **129** was isolated from the reaction. These results suggest a 6-*exo-dig*- and a 7-*endo-dig*-cyclization pathway, respectively (Scheme 57). DFT calculations showed that the cyclization depends on subtle structural effects of the reactant complex **126**.[24a] This specie is preferably formed by coordination of the terminal double bond of the allene. The metal complex ligand may develop unfavorable interactions with the substituent at the internal allene carbon. This effect leads to an improvement of electrophilicity for the central carbon affording selective *exo-dig*-cyclization. However, the $PtCl_2$-reactant complex **126**, with a trans-halide arrangement, lacks this effect and the reaction is preferentially guided to the unusual 7-*endo-dig*-cyclization.



Scheme 57

5.33.4.1.3 Gold-catalyzed hydroarylation of allenes

The gold-catalyzed addition of arenes and heteroarenes to allenes in an intra- and intermolecular manner has attracted a lot of attention in the past years.

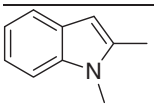
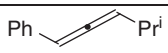
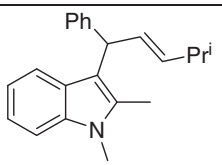
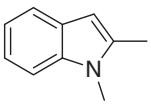
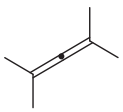
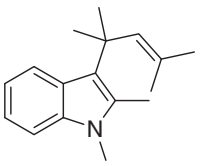
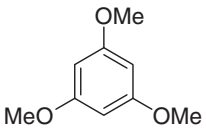
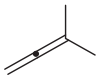
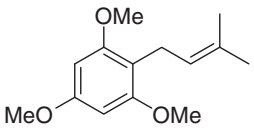
Although the intermolecular version still could be improved, initial investigations have been carried out by the groups of Widenhoefer[160] and Gagné.[161] The former group reported the intermolecular addition of monosubstituted, 1,3-disubstituted, and tetrasubstituted allenes with indoles catalyzed by a mixture of IPrAuCl and AgOTf to give, selectively, C-3-allylic indoles. Gagné and coworkers further applied simple arenes in this reaction. However, only di- and tri-alkoxyarenes afforded the allylic arenes (Table 13).

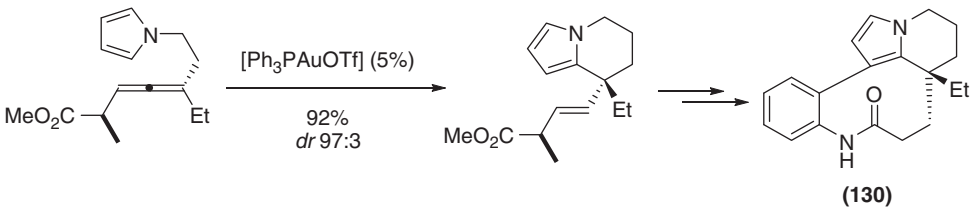
Nelson and coworkers pioneered the gold(I)-catalyzed intramolecular addition of pyrroles to enantioenriched allenes, which afforded optically active heterocycles.[162] This approach was applied in the total synthesis of (–)-rhazinilam (**130**) (Scheme 58). Recently, Toste and coworkers reported the synthesis of flinderoles B and C by a related gold-catalyzed intramolecular allene hydroarylation.[163]

Au[P(t-Bu)$_2$(*o*-biphenyl)]Cl activated by AgOTf or AgOTs triggered the intramolecular hydroarylation of 2-allenyl indoles **131** in a highly selective manner to give tetrahydrocarbazoles **132**.[164] Allenyl indoles that possessed an axially chiral allenyl moiety underwent cyclization with transfer of chirality from the allene to the newly formed stereogenic carbon atom with selective formation of *E*-alkenes. Moreover, the chiral bis(gold)phosphine complex [(*S*)-(**83**)]Au_2Cl_2 combined with $AgBF_4$ proved to be a very efficient system to catalyze the enantioselective hydroarylation of achiral 2-allenyl indoles **131**. Tetrahydrocarbazoles **132** were obtained in very high yields and enantioselectivities (Scheme 59).[165]

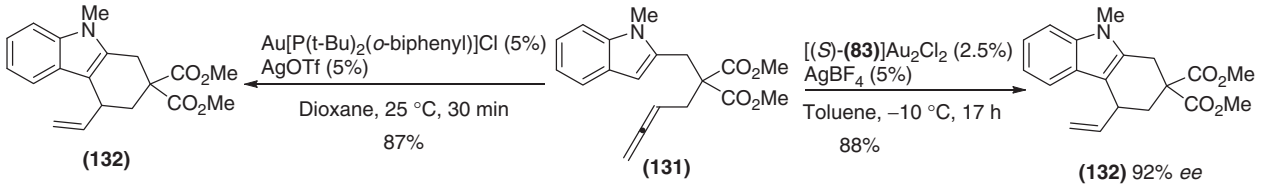
Almost simultaneously, Gagné and coworkers reported the intramolecular hydroarylation of 4-allenyl arenes bearing electron-rich arenes **133** catalyzed by highly electrophilic phosphite gold(I)-catalyst, which produced vinylbenzocycles **134** in high yields under mild conditions (equation 10).[166]

Table 13 Gold-catalyzed intermolecular hydroarylation of allenes

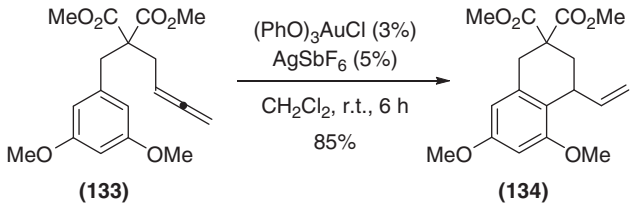
Aromatic ring	*Allene*	*Conditions*	*Product*	*Yield (%)*
		IPrAuCl/AgOTf (5%), dioxane, r.t., 48 h		82
		IPrAuCl/AgOTf (5%), dioxane, r.t., 48 h		56
		$(4\text{-Cl-PhO})_3PAuCl/AgBF_4$ (5%), CH_2Cl_2, r.t., 4 h		67



Scheme 58

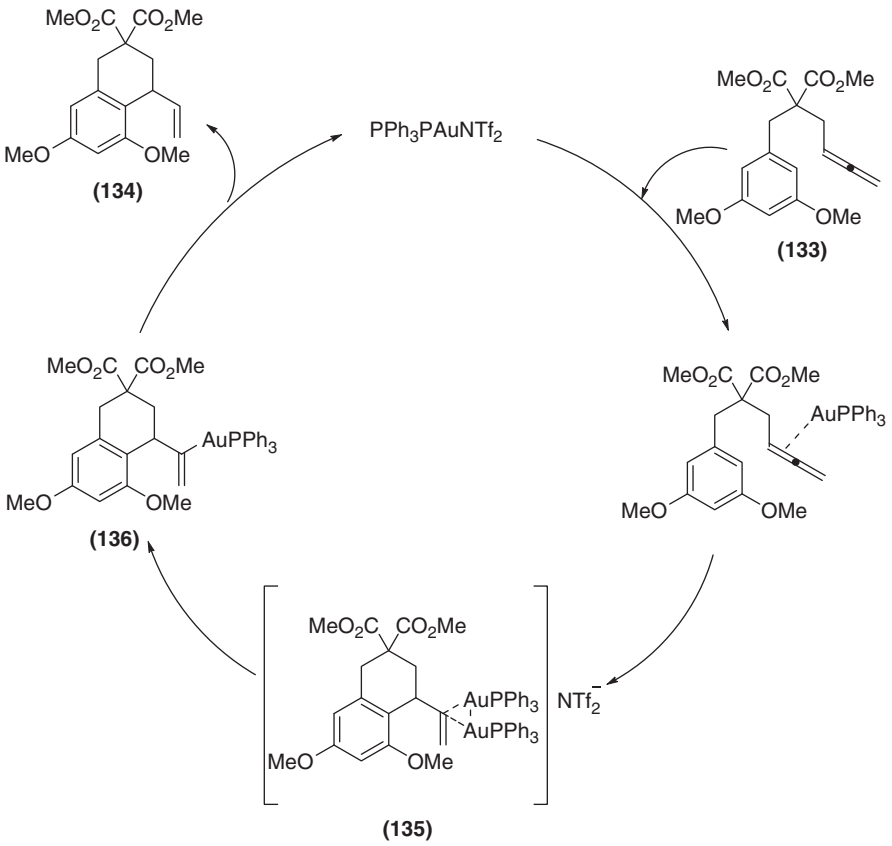


Scheme 59



(10)

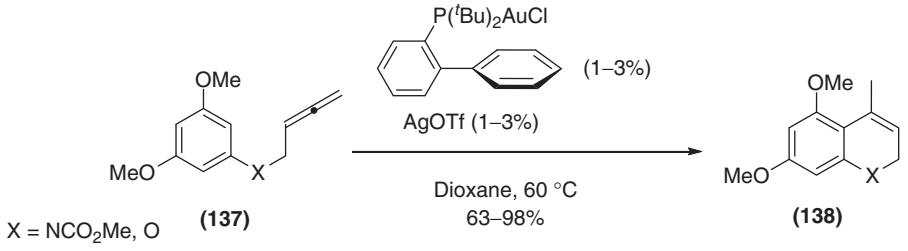
In-depth mechanistic studies suggested that the resting state of the catalyst was a doubly metalated variant of **136**. In fact, the dinuclear gold intermediate **135** was transformed into **136** on column chromatography in neural alumina. In contrast, the purification of intermediate **135** by silica gel or fluorosil chromatography led to the formation of the final product **134**. With these data, the authors propose the reaction mechanism depicted in Scheme 60.[167] Interestingly, the resting state of the



Scheme 60

gold(I)-catalyzed hydroarylation of **133** changes in the presence of a silver salt. Silver ions intercept the dinuclear organogold intermediate **135** as the silver likely replaces one of the gold atoms without significantly perturbing the gold vinyl structure.[168]

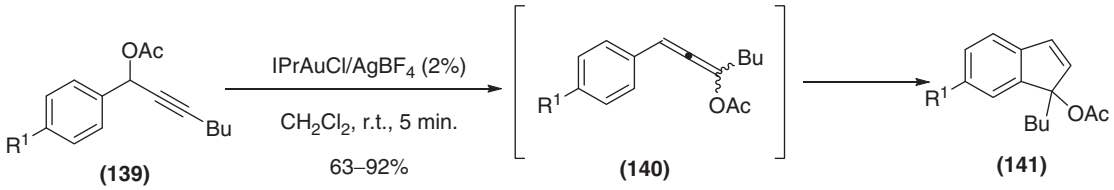
A related gold(I)-catalyzed hydroarylation of allenyl anilines and phenols **137** proceeded in a highly regioselective manner to form dihydroquinolines and chromenes **138**, respectively (Scheme 61).[169]



Scheme 61

The formation of substituted indenes **141** from aryl propargyl alkynes **139** via [3,3]-acetoxy rearrangement and intramolecular hydroarylation of an allene intermediate was reported by Nolan in 2006.[170] A *N*-heterocyclic carbene gold complex IPrAuCl combined with $AgBF_4$ efficiently catalyzed the synthesis of indenes **141** under very mild conditions in only 5 min. Interestingly, when the corresponding allene intermediate **140** was synthetized and submitted to the reaction conditions, the corresponding indene **141** was formed in slightly longer reaction times. This could be consequence of the higher alkynophilicity than allenophilicity of the $[IPrAu]^+$ fragment (Scheme 62).

The intermolecular version of this reaction was reported by Echavarren and coworkers 1 year later as propargyl carboxylates reacted with electron-rich arenes such as indole and 1,3–5-trimethoxybenzene.[171]



R^1 = H, Me, F, OMe

Scheme 62

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5.34 Early Transition Metal Mediated Reductive Coupling Reactions

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Glossary

Chemoselectivity A preference for reactivity at a particular functional group of a molecule possessing multiple functional groups. When this term is used to describe selective reaction at one functional group in a molecule possessing other similar groups (one alkene of a polyene), the term 'site selectivity' is used.

Diastereomeric ratio (*dr*) It is the ratio of isomers observed in the product after purification.

Diastereoselectivity (*ds*) It is a measurement of the selectivity of a reaction – assessed from analysis of the crude reaction mixture.

Pair selectivity A term employed by Prof. Negishi in the first edition of *Comprehensive Organic Synthesis* (Zirconium-promoted Bicyclization of Enynes) that relates to the preference for hetero- versus homocoupling in intermolecular versions of early transition metal metallacycle-mediated bond-forming processes (i.e., A + B → A–B + A–A + B–B).

Regioselectivity In the metallacycle-mediated coupling chemistry discussed, regioselectivity refers to the directionality of net carbometalation across each participating π-system.

Transfer epimetalation A term employed to describe the transfer of low-valent metal from a preformed organometallic complex (i.e., that is generated from the combination of Cp_2ZrCl_2 and *n*-BuLi (two equivalents)) to an unsaturated substrate of interest.

5.34.1 Introduction

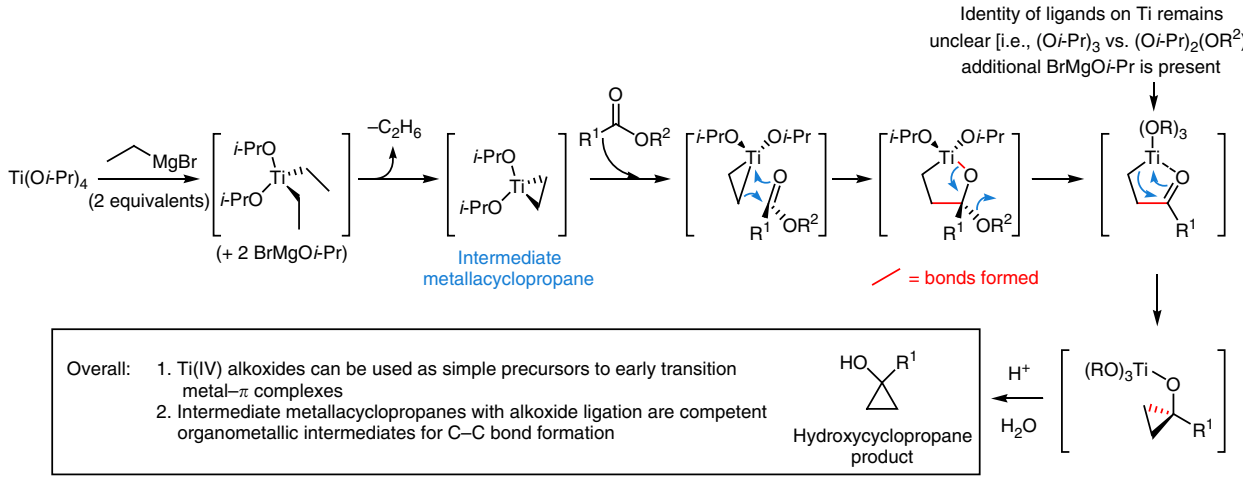
Since the publication of the first edition of *Comprehensive Organic Synthesis* in 1991, substantial advances have been made in the chemistry of early transition metal metallacycle-mediated bond-forming processes. These include (1) the introduction of simple Ti(IV)-alkoxides to replace metallocene species (i.e., Cp_2ZrX_2 and Cp_2TiX_2); (2) the development of intramolecular chemistry that proceeds with catalytic quantities of a Group IV metal, albeit typically requiring stoichiometric additives; (3) the establishment of strategies to control relative and absolute stereochemistry in the course of C–C bond formation; and (4) the development of a caste of 'cross-coupling' technology based on controlling the course of metallacycle-mediated bond construction in intermolecular settings.

The chapter, 'Zirconium-promoted Bicyclization of Enynes,' provided relevant background regarding the basic reactivity central to early transition metal metallacycle-mediated bond construction (Chapter 9.5, 1st edition). Specifically, general strategies to access Cp_2Zr- and Cp_2Ti-π complexes were described, and the propensity of these species to undergo carbometalation with a second reactive π-system was discussed throughout. At the time, the state of the art in this area was largely limited to intramolecular reactions of polyunsaturated substrates, with a few exceptions demonstrating that a small subset of 'cross-coupling' or 'intermolecular' reactions was possible. In short, the utility of metallacycle-mediated coupling chemistry for convergent C–C bond formation was significantly constrained due to the great difficulties associated with controlling reactivity in intermolecular settings. Specific challenges in this regard included the following: (1) overcoming low levels of reactivity of substituted and electronically unactivated π-systems, (2) controlling pair selectivity (homodimerization vs. cross-coupling), and (3) simultaneously controlling regio- and stereoselection.

At the time of this earlier review, it was thought that Zr-promoted cyclization processes may be superior to Ti-promoted reactions, as evidence was mounting for the increased sensitivity of Cp_2Ti-mediated cyclization reactions to steric environment and ring strain. These conclusions, based on early observations of metallocene-based reactivity, should be reevaluated based on the substantial body of work that has emerged over the past 20 years – not the least of which includes the wealth of bond-forming processes mediated by Ti(IV) alkoxides.

The emergence of Ti-alkoxides as reagent precursors for metallacycle-mediated reductive coupling: Originating from the early contributions of Prof. Oleg Kulinkovich, it has become evident that synthetically useful early transition metal–π complexes can be generated from simple, inexpensive, and nontoxic Ti(IV) alkoxides (i.e., Ti(O*i*-Pr)$_4$) – reagents that can often be purified by distillation, transferred by syringe, and are easily handled outside of a glovebox. This finding stemmed from the discovery and development of a new hydroxycyclopropane-forming reaction, now termed the Kulinkovich reaction,[1] where the addition of two equivalents of a suitable Grignard reagent to Ti(O*i*-Pr)$_4$ results in an activated organometallic complex that ultimately adds to a carboxylic ester en route to the formation of a hydroxycyclopropane (Scheme 1).[2] Like the established reactivity of the 'Negishi reagent' (*n*-Bu_2ZrCp_2),[3,4] it has been proposed that the Kulinkovich reaction proceeds through the intermediacy of a similar

metallacyclopropane, formed from decomposition of the initially formed (alkyl)$_2$Ti(O*i*-Pr)$_2$ species.[5] In short, each σ_{C-Ti} bond of the resulting metallacyclopropane engages in nucleophilic addition to the carboxylic ester, resulting in the formation of a hydroxycyclopropane. At the current time, more substantial data exist to support the sequence of events that proceed from (n-Bu)$_2$ZrCp$_2$ to the corresponding butene–ZrCp$_2$ complex than the sequence of events that proceed from the R$_2$Ti(O*i*-Pr)$_2$ intermediate proposed in the Kulinkovich reaction.



Scheme 1

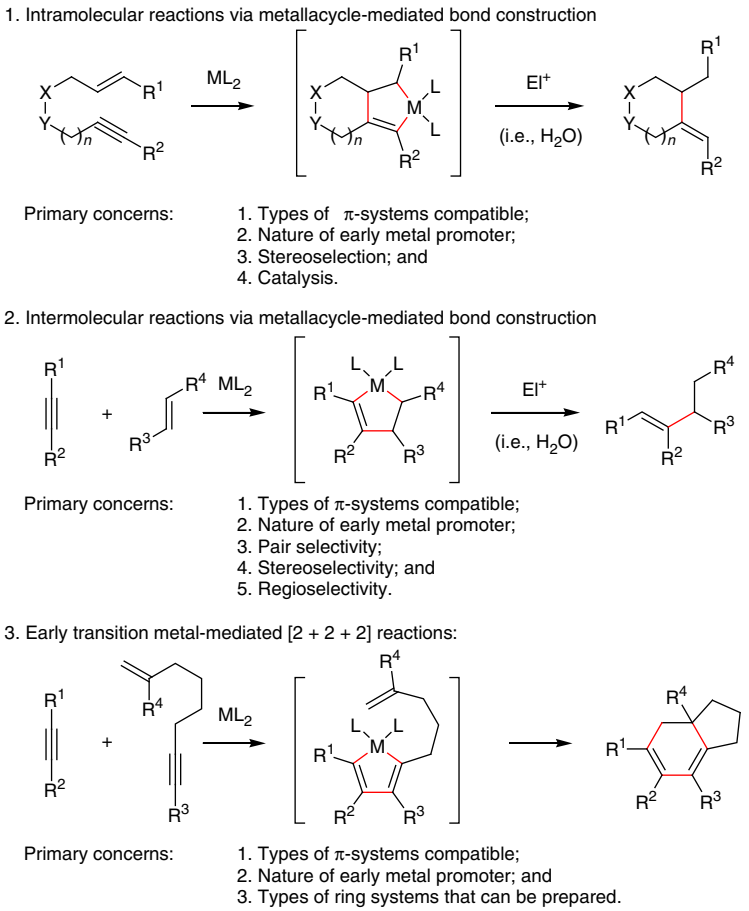
Being focused on the utility of metallacycle-mediated coupling reactions in organic synthesis, this review will not delve into the mechanistic hypotheses regarding the fate of the initial R$_2$Ti(OR)$_2$ species formed in the Kulinkovich reaction.[6–10] Rather, this chapter is presented in a manner that simply accepts that the fate of R$_2$Ti(OR)$_2$ can be manipulated to generate new organometallic complexes of alkynes, imines, and alkenes by net transfer epititanation – the reactive intermediates that are central to the powerful organic transformations discussed in this chapter.

This chapter is organized as depicted in **Scheme 2**. First, an update on intramolecular transformations mediated by early transition metals is provided. The primary organization within this section is based on the type of π-systems employed in the metallacycle-mediated cyclization (alkyne–alkyne, alkyne–alkene, alkene–carbonyl, etc.), and attention is given to the nature of the metal mediator (metallocene or metal alkoxide), stereoselection, and catalysis. Furthermore, within each mode of reactivity discussed, effort has been taken to highlight the utility of the method in stereoselective synthesis. The discussion then shifts to cover advances that have established a caste of intermolecular, or 'cross-coupling,' reactions made possible by advances in the manner in which metallacycle-mediated carbometalation chemistry can be controlled. Again, the primary organization of this section is based on the type of π-systems that are engaged in C–C bond formation. Care has been taken to convey a clear picture of the scope and limitations of each coupling process, with particular emphasis on considerations regarding the control of regio- and stereoselection. Applications of each reaction class are presented in stereoselective synthesis when deemed appropriate. Finally, the chapter concludes with a survey of early transition metal metallacycle-mediated [2 + 2 + 2] chemistry for the synthesis of carbo- and heterocyclic systems.

It is important to recognize that over the past 20 years a substantial body of chemistry has emerged that is based on exploiting the unique reactivity of early transition metals in novel C–C bond-forming processes. This chapter is focused on the subset of advances in this area that deal with the coupling of two π-systems. Developments not presented in this chapter include (1) Zr- and Ti-promoted addition reactions of Grignard reagents to alkenes and carbonyl systems, (2) Ti-mediated addition of alkenes to esters (i.e., the Kulinkovich reaction),[11] and (3) reactions that proceed through the conversion of alkenes and alkynes to allylic and propargylic organometallic reagents of utility in carbonyl addition chemistry.

5.34.2 Early Transition Metal-Mediated Cyclization of Polyunsaturated Substrates

After the initial observation that low-valent early transition metals promote the homocoupling of internal alkynes via the formation of metallacyclopentadienes,[12] cyclization reactions of polyunsaturated substrates were among the first powerful synthetic transformations to emerge from this mode of reactivity. Early accomplishments, mostly before 1991, established a foundation of chemistry that supports the conclusion that metallacycle-mediated bond construction defines a powerful means for ring formation via engaging simple π-unsaturations in C–C bond formation. Distinct from other transition metal-mediated methods that engage simple π-unsaturation in ring formation (i.e., diene and enyne metathesis), these early transition metal-mediated processes have the power to engage a vast array of π-systems and have secured a complementary portfolio of bond constructions of great potential utility in chemical synthesis. Following is a brief survey of developments in early transition metal-mediated



Scheme 2

cyclization of polyunsaturated substrates that aims to communicate the great power that this mode of reactivity has in ring formation. The discussion is organized based on the type of π-unsaturations employed in the intramolecular process: (1) alkyne–alkyne, (2) alkene–alkyne, (3) alkene–alkene, (4) allene–alkyne, (5) alkyne–carbonyl, (6) alkene–carbonyl, and (7) allene–carbonyl.

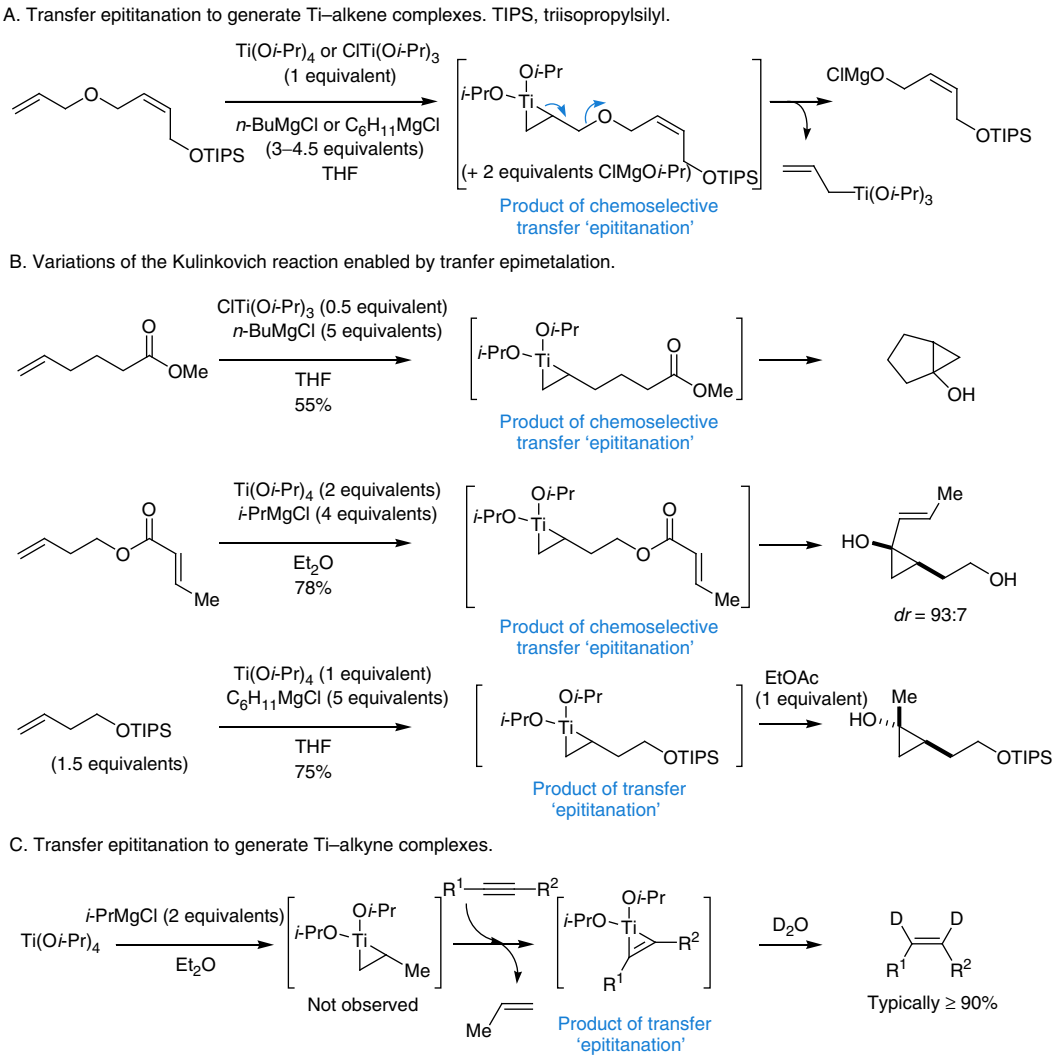
5.34.2.1 Bicyclization of Diynes

Among the earliest examples of metallacycle-mediated ring formation were cyclization reactions of diynes promoted by Cp_2Ti- and Cp_2Zr-based systems (before 1991).[13,14] Examples included the generation of carbo- and heterocyclic rings from four- to seven-membered systems and, through comparison of the relative efficiencies of cyclization promoted by Cp_2Zr- and Cp_2Ti-based systems, conclusions were made regarding the potential superiority of Zr-based systems for such cyclization processes.[14] Over the past 20 years, Ti(IV) alkoxides have emerged as new reagent precursors suitable for this class of cyclization reaction, and a number of new synthetic variations of this cyclization have been reported.

5.34.2.1.1 $Ti(OR)_4$-based reagent precursors for metallacycle-mediated intramolecular diyne coupling chemistry

In the years spanning 1995–96, Prof. Fumie Sato and Prof. Jin K. Cha independently described studies where the 'Kulinkovich' reagent (defined by the combination of a Ti(IV) alkoxide with two equivalents of a Grignard reagent) was employed to generate new Ti–alkene and Ti–alkyne complexes of unsaturated substrates (this process is referred to as transfer 'epititanation'). These observations were initially presented in the context of new methods for allyl deprotection and the generation of allylic titanium reagents from allylic esters, ethers, halides, and related substrates (**Scheme 3A**).[15,16] Subsequent studies explored the use of transfer epimetallation to enable intra- and intermolecular variations of the Kulinkovich hydroxycyclopropanation reaction (**Scheme 3B**),[17–19] and finally to generate Ti–alkyne complexes (**Scheme 3C**).[20] It is this latter mode of reactivity that is central to the development of new Ti-alkoxide-promoted diyne-based cyclization reactions.

Building on the demonstrated ability to access Ti–alkyne complexes via transfer epititanation from $Ti(Oi\text{-}Pr)_4/2i\text{-}PrMgCl$, Sato has revealed that bicyclization reactions of diynes are readily achieved with the use of Ti-alkoxides in place of established Cp_2Zr- and Cp_2Ti-based reagents.[21] As illustrated generally in **Scheme 4**, treatment of a diyne with $Ti(Oi\text{-}Pr)_4/2i\text{-}PrMgCl$ is thought to



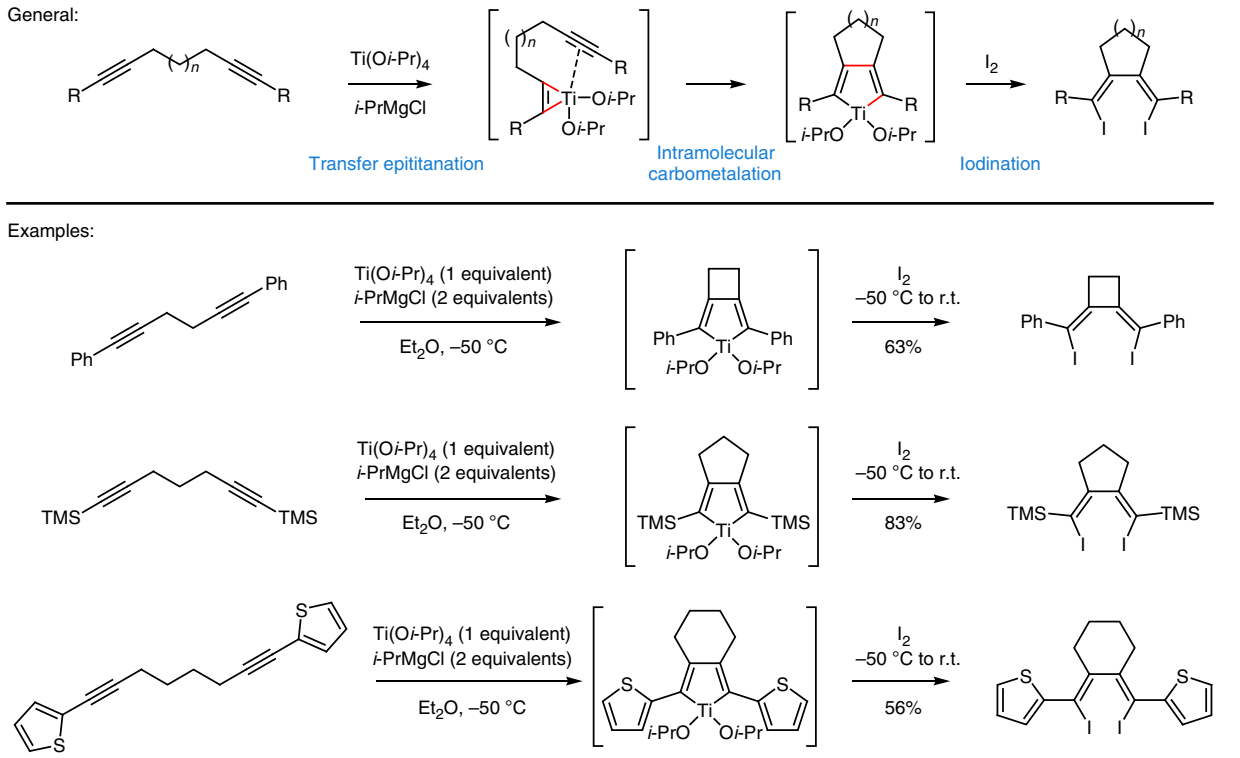
Scheme 3

result in initial transfer epititanation and formation of a Ti–alkyne complex (or metallacyclopropene). Intramolecular coordination of the pendant alkyne is followed by intramolecular carbometalation to furnish a bicyclic metallacyclopentadiene intermediate which, on exposure to I_2, is converted to a functionalized 1,4-dihalobutadiene product.[22] Although previous conclusions have been made about the sensitivity of Cp_2Ti-mediated bicyclization reactions to ring strain, and the potential superiority of Cp_2Zr-based systems for bicyclization chemistry, it is apparent that this Ti-alkoxide-mediated procedure is useful for the generation of a variety of ring systems.

5.34.2.1.2 Development of new Ti-mediated cyclization/functionalization processes that harnesses the reactivity of intermediate metallacyclopentadienes formed from diyne cyclization

Instead of quenching the intermediate metallacyclopentadiene with a proton source, or reagents capable of halogenation, Sato has demonstrated that C–C bond formation can proceed in either an intra- or intermolecular fashion (Scheme 5). As depicted in Scheme 5A, bicyclic carbocycles are produced from $Ti(Oi\text{-}Pr)_4$-mediated cyclization and intramolecular trapping of the intermediate metallacyclopentadiene by engaging the reactivity of the proximal carboxylic ester.[23]

Illustrated in Scheme 5B, regioselective intermolecular trapping of unsymmetrical metallacyclopentadienes is also possible.[24,25] Here, formation of a titanacyclopentadiene intermediate is followed by addition of $Cl_2Ti(Oi\text{-}Pr)_2$ and an aldehyde (the use of $Cl_2Ti(Oi\text{-}Pr)_2$ was found to increase the yield of the addition reaction). Site-selective reaction of the metallacyclopentadiene occurs at the carbon bearing the silyl substituent – a selectivity that has been proposed based on a stabilization of charge in the transition state imparted by the silyl substituent. Most interestingly, subtle steric differences of silyl substituents about the titanacyclopentadiene intermediate can also be harnessed to control site-selectivity of C–C bond formation. As shown, the substrate bearing a trimethylsilyl (TMS)- and *t*-butyldimethylsilyl (TBDMS or TBS)-substituent undergoes cyclization/aldehyde addition to deliver a product where C–C bond formation has occurred at the site α- to the TMS group (in preference to the TBDMS group).



Scheme 4

Although the yield for the product was reported to be only 41% (half of that observed for other examples), and a precise selectivity was not given for this process, the authors report that the other possible regioisomer 'could not be isolated.'

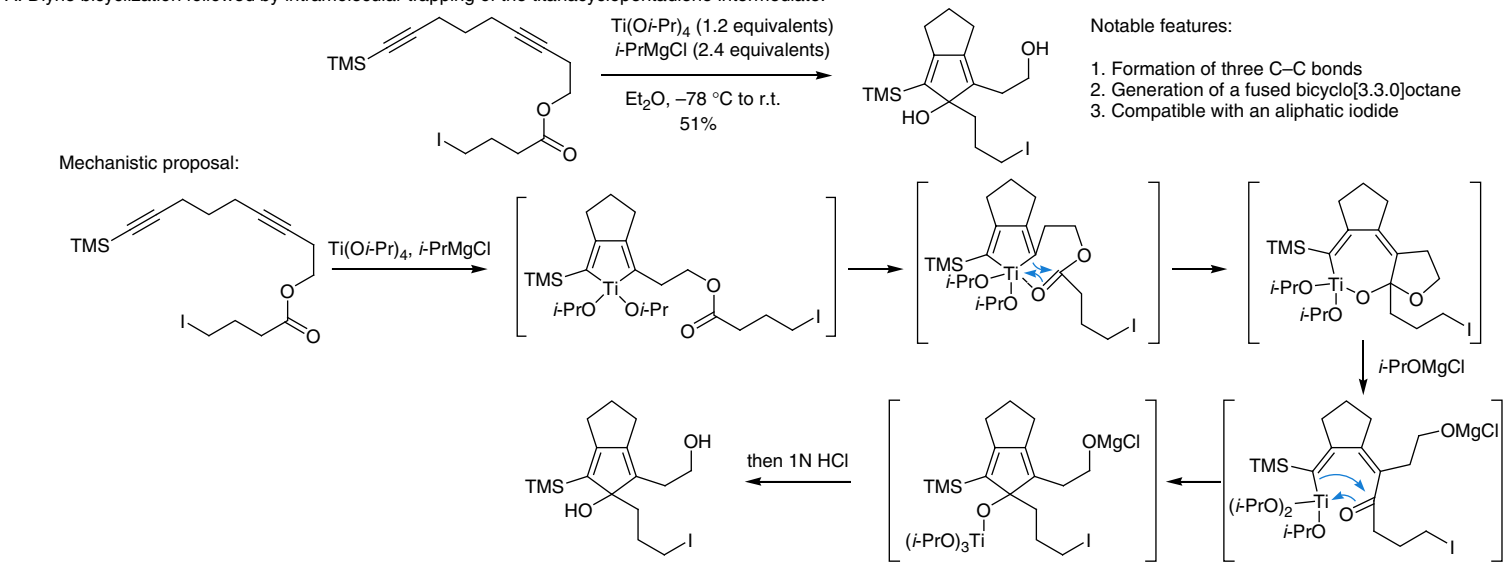
In related studies targeting intermolecular functionalization of metallacyclopentadienes generated from Ti-mediated diyne cyclization, it has been demonstrated that site-selective allylation is possible (Scheme 5B). As is the case with aldehyde addition chemistry, site-selective coupling typically proceeds at the carbon bearing the TMS group. That said, in cases where the TMS-substituted unsymmetrical metallacyclopentadiene also bears a Ph-group, the major product from Cu-promoted allylation derives from C–C bond formation α- to the Ph-group, albeit proceeding with very low levels of selectivity (*rs* = 3:2).

In other studies exploring the fate of intermediate metallacyclopentadienes derived from bicyclization reactions of diynes, Sato reported that elimination chemistry can be accessed en route to ring systems bearing exocyclic conjugated allenes (Scheme 6A).[26,27] Surprisingly, it was found that the stability of bis-allene products derived from this tandem process was a function of ring size. With four- and five-membered systems, the conjugated bis-allene could be isolated, whereas with six- and seven-membered systems, cyclobutene products are formed (presumably via four-electron electrocyclization of the bis-allene intermediates). While delivering products of potentially useful reactivity in synthesis, the efficiencies of these processes vary greatly, with the best yields for conjugated bis-allenes being in the five-membered series (25–45% isolated yields), and cyclobutenes in the six-membered series (15–80% isolated yields).

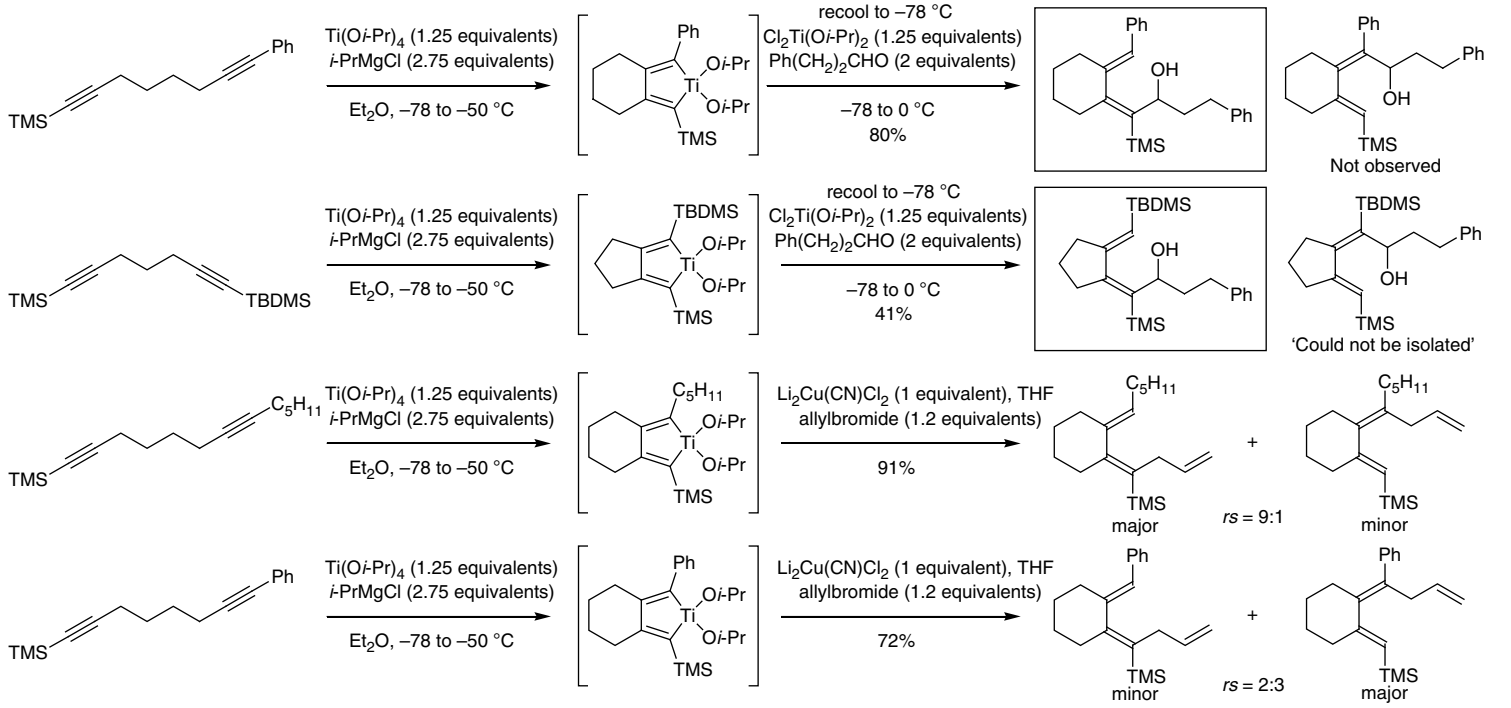
5.34.2.2 Bicyclization of Enynes

A significant number of advances have been reported in the area of enyne cyclization. This section is organized to first describe advances made in metallocene chemistry (Cp_2M–), followed by those that derive from cyclization induced by early transition metal alkoxides ($(RO)_2Ti$–). Metallocene-based methods have been advanced as more practical methods to accomplish cyclization (see Section 5.34.2.2.1), applications of metallocene-based methods have appeared as central features of new routes to heterocycles and as key steps in natural product synthesis (see Section 5.34.2.2.2), and methods have emerged that proceed with catalytic quantities of metallocene reagent (see Section 5.34.2.2.3). Ti-alkoxide-mediated cyclization chemistry has emerged as an alternative means of enyne cyclization (see Section 5.34.2.2.4), where substantial increases in complexity are possible in cyclization reactions that deliver intermediate titanacyclopentenes that have rich reactivity profiles. Controlling the fate of this reactive intermediate has resulted in an impressive collection of complexity-generating processes that ensue from initial enyne cyclization and terminate by distinct intra- or intermolecular bond-forming processes of these titanacyclopentene intermediates.

A. Diyne bicyclization followed by intramolecular trapping of the titanacyclopentadiene intermediate.

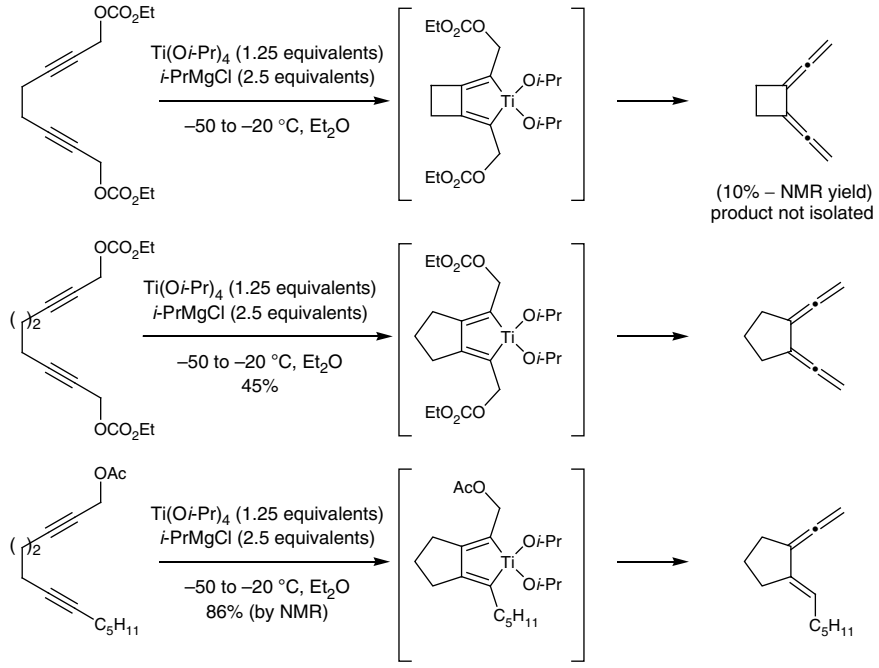


B. Diyne bicyclization followed by intermolecular reaction of the titanacyclopentadiene with aldehydes and allylic halides.

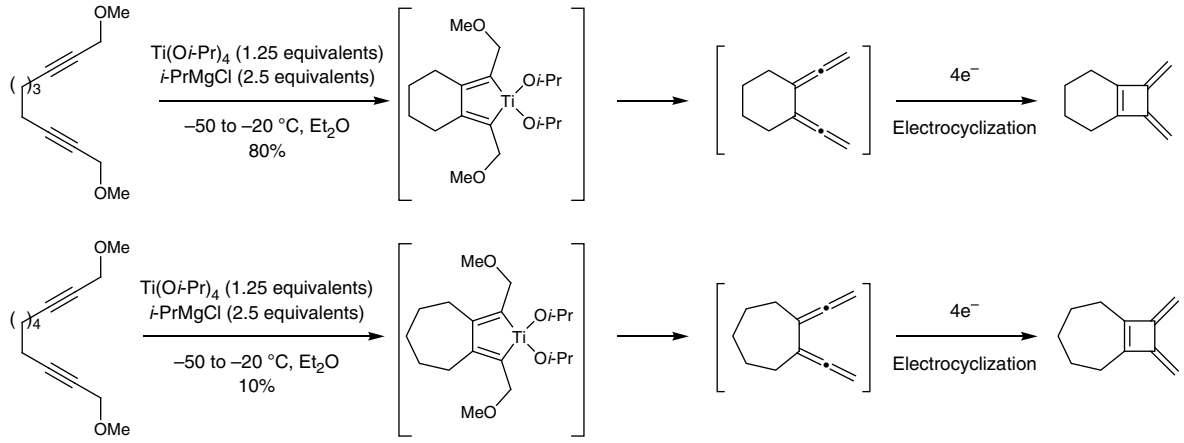


Scheme 5

A. Diyne bicyclization followed by elimination. NMR, nuclear magnetic resonance.



B. Diyne bicyclization followed by elimination and electrocyclization.

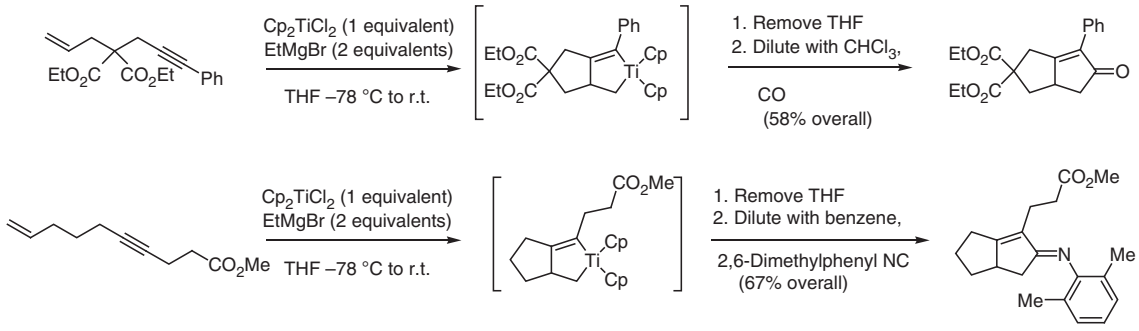


Scheme 6

5.34.2.2.1 Development of more practical titanocene reagents for the cyclization of enynes

The practical simplicity of the Negishi reagent (prepared by the addition of two equivalents of BuLi to Cp_2ZrCl_2) marked a substantial advance in metallocene chemistry, as one no longer needed to reduce a metallocene reagent precursor (Cp_2MCl_2) with Na/Hg (in the presence of $PhPMe_2$), or Mg/$HgCl_2$. In efforts to identify a similarly practical procedure to access titanocene species, Prof. Buchwald described a protocol based on the addition of two equivalents of EtMgBr to Cl_2TiCp_2.[28] Studies have led to the conclusion that this titanocene reagent system may be more tolerant of oxygen functionality than the zirconium system, and examples have demonstrated that this reagent combination is useful for the synthesis of bicyclic cyclopentenones and imino-cyclopentenes (Scheme 7) that proceed through initial Ti-mediated enyne cyclization and subsequent one-carbon insertion. Although the procedure for metal-centered bicyclization of the enyne substrate is straightforward, insertion of the one-carbon component requires removal of the ethereal solvent – a requirement that is complicated owing to the air and moisture sensitivity of the organometallic intermediate.

A related reagent formed from the addition of two equivalents of BuLi to Cp^*Ti(O-2,6-diphenylphenyl)Cl_2 has also been shown to affect cyclization reactions of more sterically encumbered substrates.[29]



Scheme 7

5.34.2.2.2 Stereoselective synthesis via Zr-promoted enyne cyclization, including applications in natural product synthesis

5.34.2.2.2.1 Heterocycle synthesis

Stereoselective variants of zirconocene-based enyne cyclization have emerged for the synthesis of perhydroindole derivatives (Scheme 8A).[30] Here, carbocyclic allylic amines serve as the starting materials for cyclization, and functionalization of the intermediate zirconacyclopentenes defines a means to access a range of stereodefined heterocyclic systems. In addition to validating the potential utility of Zr-promoted cyclization chemistry in heterocycle synthesis, these studies have also revealed an interesting reactivity profile of the intermediate zirconacycles. Overall, functionalization of the sp^3 C–Zr bond is more facile than the sp^2 C–Zr bond, as evidenced by (1) oxidation of the sp^3 C–Zr bond (with O_2), then deuteration of the remaining C–Zr bond; (2) isonitrile insertion, followed by treatment with acetic acid; and (3) the product mixture derived from iodination. These studies also demonstrated that carbonylation of tricyclic zirconocyclopentene intermediates can deliver products where one or two equivalents of CO have been incorporated – selectivity in this process is apparently derived from the nature of the ring system formed.

5.34.2.2.2.2 Natural product synthesis

Zr-promoted enyne bicyclization has been explored in natural product synthesis, with examples including a formal total synthesis of phorbol and the total synthesis of pentalenic acid (Scheme 8B).[31,32]

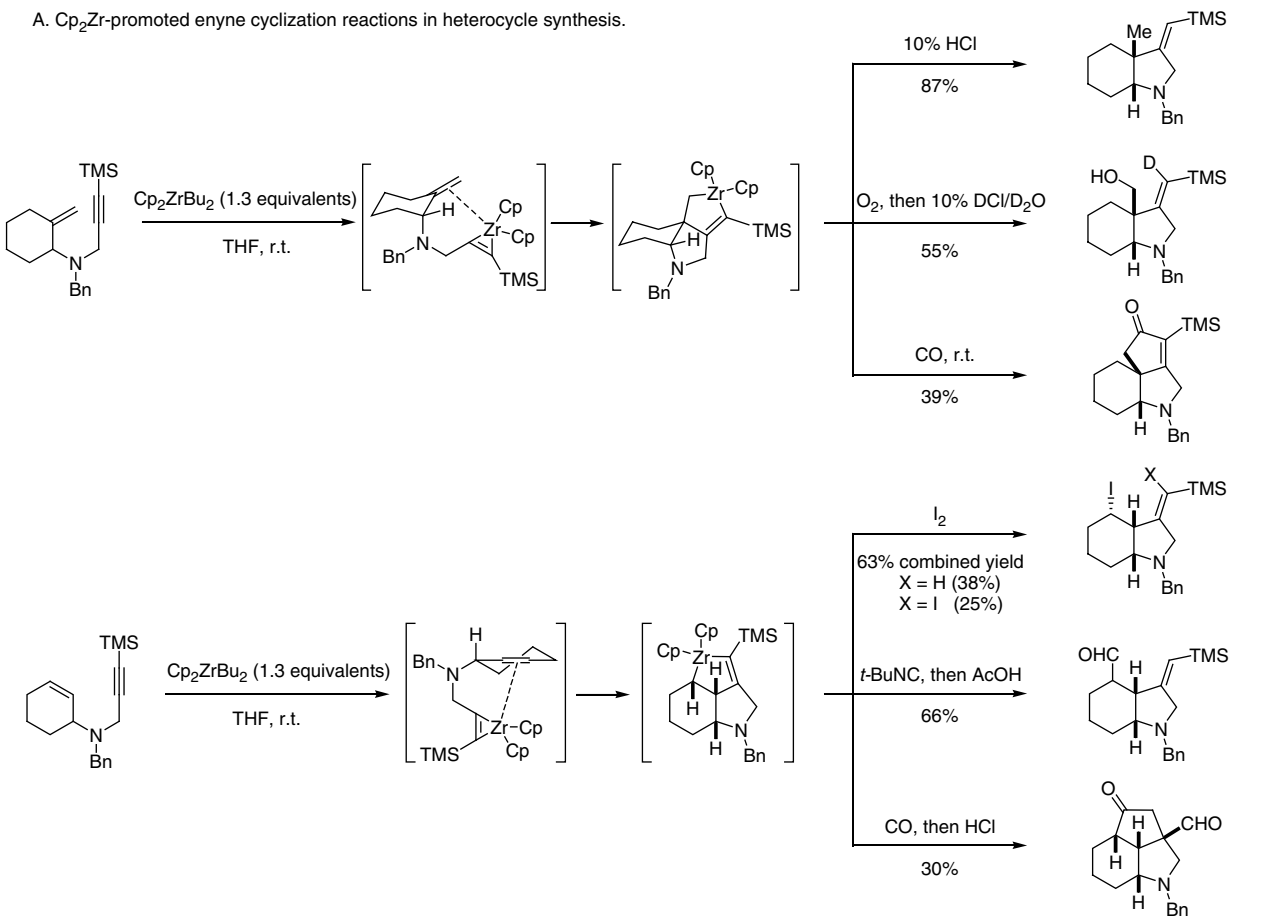
5.34.2.2.3 Catalysis in metallocene-promoted enyne cyclization

A number of metallacycle-mediated C–C bond-forming reactions have been described that proceed with substoichiometric quantities of a Zr-reagent along with excess Grignard or trialkylaluminum reagent. These reactions proceed by Zr-promoted addition of preformed organometallic reagents to a π-bond.[33] Although demonstrating conceptually novel approaches to catalytic C–C bond formation, these reactions do not proceed by coupling of two unsaturated organic substrates and, as such, will not be discussed further here.

Catalysis in early transition metal metallacycle-mediated coupling chemistry is complex owing to the mechanistic pathway by which these reactions proceed (Scheme 9). A primary concern in all potential catalytic processes is the excess quantities of unsaturated substrate present throughout the reaction. As illustrated in Scheme 9A, a general coupling reaction run with 5 mol% of a low-valent metal (ML_2) can proceed by initial activation of either coupling partner (π-system 'A' or 'B'). Independent of which π-system is engaged by the low-valent metal, the resulting L_2M–π complex is surrounded by large relative quantities of each substrate (π-system 'A' and π-system 'B'). Given an equal chance of this metal–π complex engaging either system in a carbometalation event, a complex product mixture can result that is contaminated by the undesired products of homo-coupling. Although matching the electronic and/or steric properties of the two substrates may provide a solution to a subset of coupling reactions, finding a general catalytic solution capable of cross-coupling any two unsaturated substrates is fundamentally limited by this problem in 'pair selectivity.'

That said, catalytic processes for early transition metal metallacycle-mediated cyclization, where the C–C bond-forming event proceeds in an intramolecular fashion, are quite reasonable. As illustrated in Scheme 9B, complexation of a catalytic quantity of ML_2 to a polyunsaturated substrate leads to the generation of a small quantity of activated metallacyclopropane that, while surrounded by an excess polyunsaturated substrate, reacts through a unimolecular pathway (intramolecular formation of a metallacyclopentane) to kinetically outcompete intermolecular processes. Nevertheless, like all intramolecular processes, such reactions are sensitive to factors that diminish the rate of cyclization and result in competition with intermolecular bond-forming processes (including ring size, sterics, and stereochemical considerations that impact preferred conformation).

In 1993, Prof. Buchwald described a titanocene-catalyzed enyne cyclization for the synthesis of cyclopentenones where 10 mol% of $Cp_2Ti(PMe_3)_2$ (or 10 mol% Cp_2TiCl_2 and 20 mol% *n*-BuLi) is used alongside a slight excess of a (trialkylsilyl)cyanide (Scheme 10A).[34,35] Taking advantage of the equilibrium between the silylcyanide and the silylisonitrile, this protocol provided a means to turn over the titanocene by a protocol that does not require the presence of stoichiometric quantities of an isonitrile (this was essential to the success of this catalytic procedure). Overall, these reactions require careful exclusion of air and moisture (Schlenk technique and/or dry box reaction setup) and have proven to be effective for generating bicyclo[3.3.0]octene and



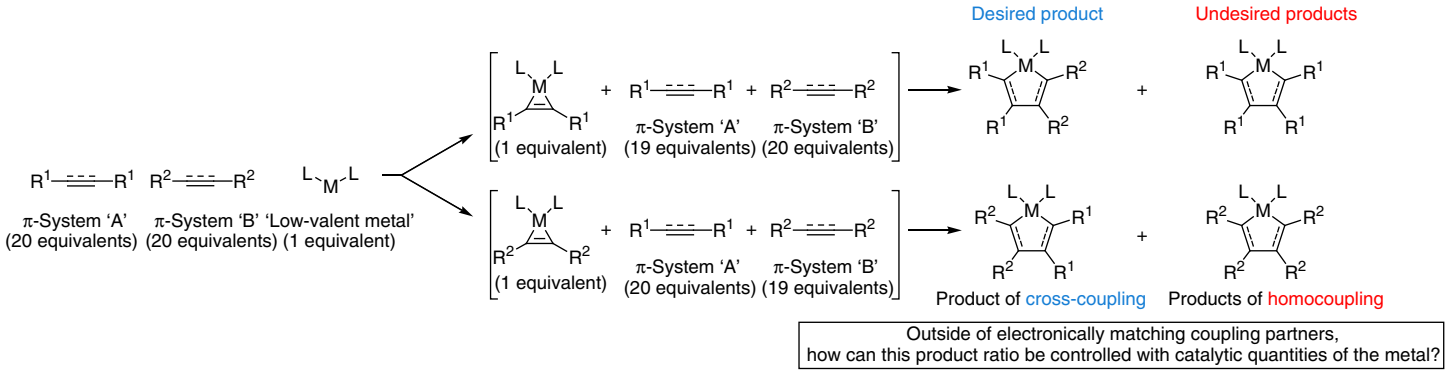
Scheme 8

bicyclo[4.3.0]nonene systems. After hydrolysis of the iminocyclopentene products, cyclopentenones can be generated in 42–80% yield (Scheme 10B). Cyclization reactions of stereodefined enynes were also demonstrated to proceed with a range of stereoselectivity (from 1.6:1 to 12:1, depending on the position and nature of the substitution present in the tether). Although defining an important advance in enyne cyclization chemistry, this reaction remains limited in scope, being ineffective for cyclization reactions that engage 1,2-disubstituted alkenes, trialkylsilyl-substituted, or terminal alkynes, and all of the substrates depicted in Scheme 10C.

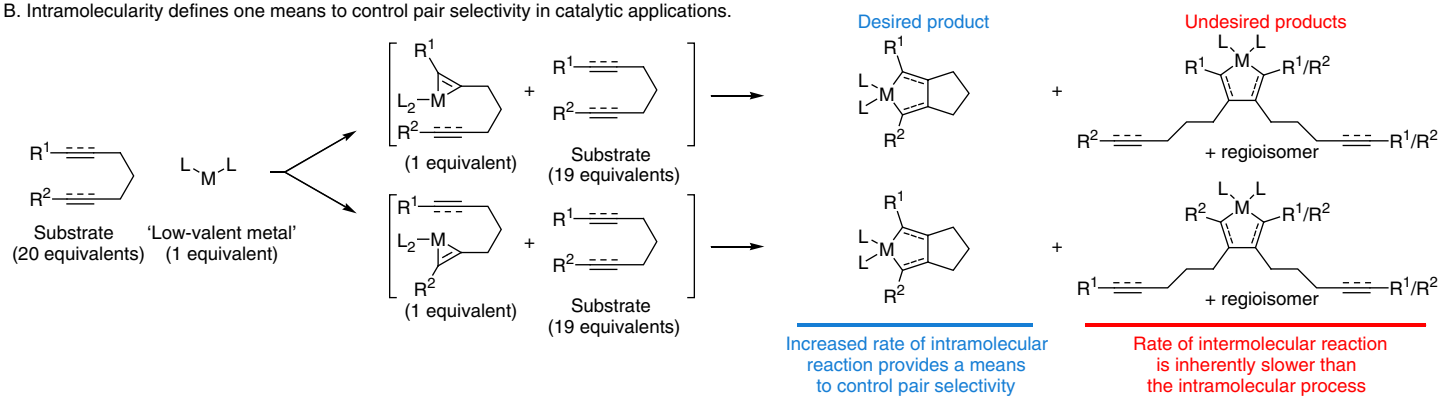
Since the initial report of a titanocene-catalyzed enyne cyclization for the synthesis of bicyclic cyclopentenones with $Cp_2Ti(PMe_3)_2$ and *t*-$BuMe_2SiCN$, significant advances have emerged:

1. The air-stable precatalyst Cp_2TiCl_2 has been shown to be competent in cyclization chemistry. Here, cyclization of enynes to bicyclic iminocyclopentenes proceeds with 10 mol% of 'finely ground' Cp_2TiCl_2, 20 mol% *n*-BuLi, and 115 mol% Et_3SiCN in toluene at 45 °C.[36]

A. The general challenge of pair selectivity in catalytic variants of early transition metal metallacyle-mediated coupling chemistry.

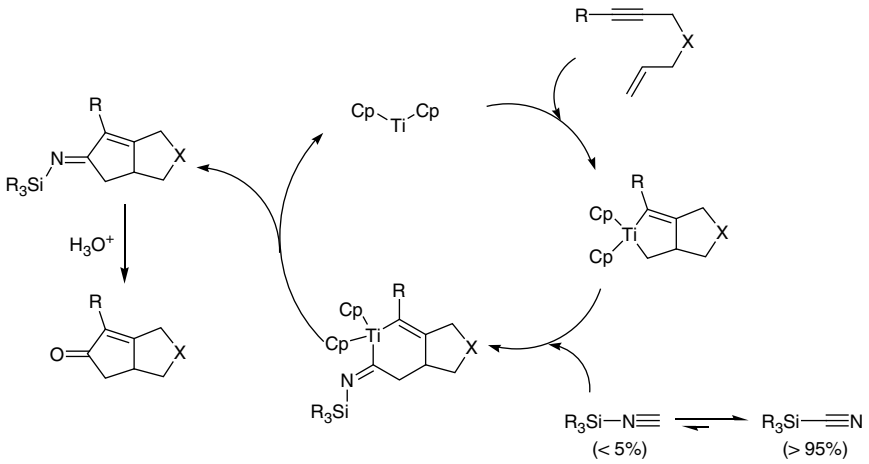


B. Intramolecularity defines one means to control pair selectivity in catalytic applications.

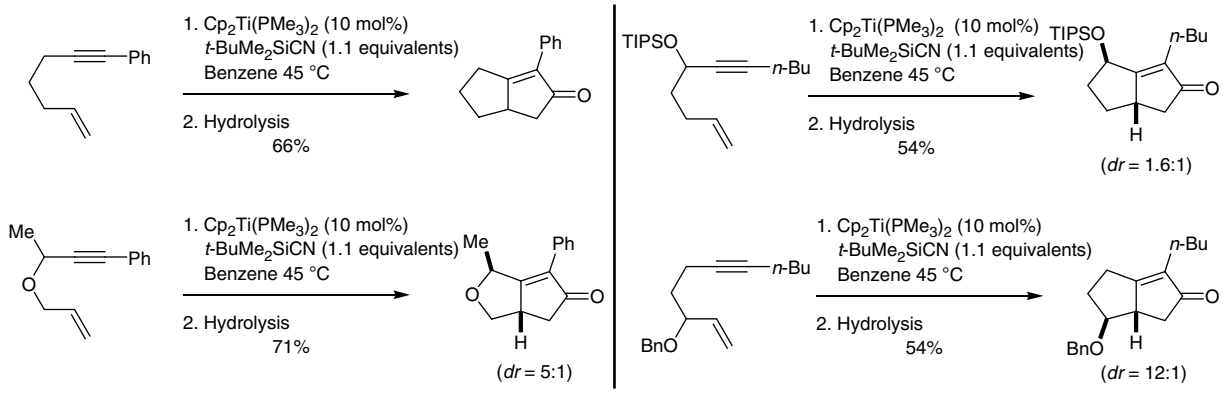


Scheme 9

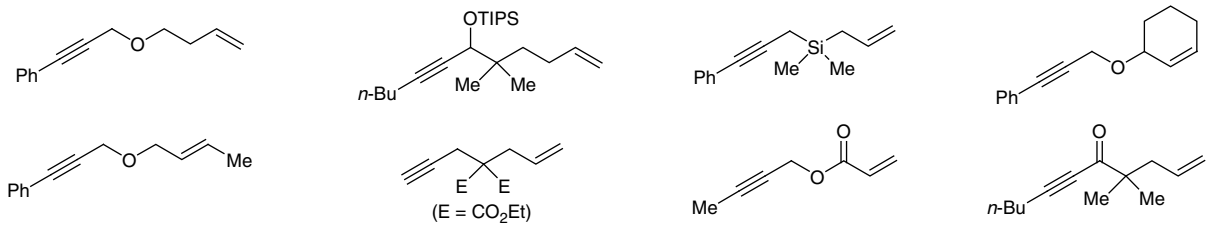
A. Titanocene-catalyzed enyne cyclization en route to cyclopentenones: Proposed catalytic cycle.



B. Titanocene-catalyzed enyne cyclization en route to cyclopentenones: Examples.



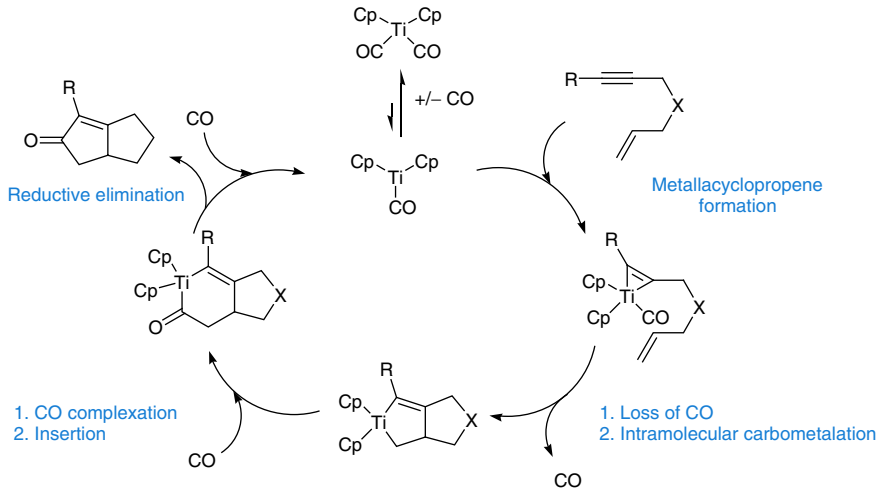
C. Titanocene-catalyzed enyne cyclization: Substrates that did not lead to cyclopentenone products.



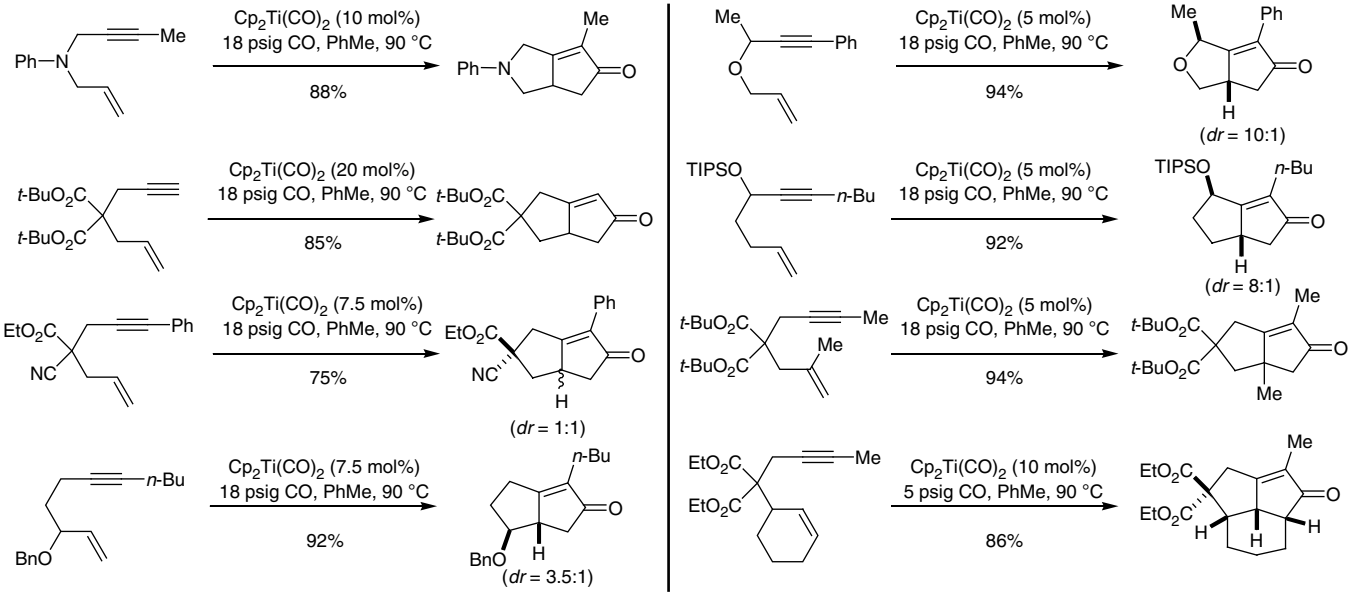
Scheme 10

2. Although previous attempts to accomplish CO insertion into intermediate titanacyclopentenes derived from enyne cyclization with Cp_2TiCl_2/2EtMgBr in tetrahydrofuran (THF) met with failure,[28,37,38] it has been found that the commercially available precatalyst $Cp_2Ti(CO)_2$ can be employed to catalyze cyclization and carbonylation to deliver bicyclic cyclopentenones (5–20 mol% $Cp_2Ti(CO)_2$, 18 psig CO, PhMe, 90 °C). This procedure defines a means to avoid the often moderate yielding hydrolysis step required in the related reactions with R_3SiCN, offers additional functional group tolerance (i.e., nitrile- and ketone-containing substrates are effectively converted to bicyclic cyclopentenones), and enhanced substrate scope. For example, terminal alkynes, 1,1- and 1,2-disubstituted alkenes can be engaged in the cyclization reaction, albeit in these latter cases conformational biasing (via geminal diester substitution in the tether; Thorpe–Ingold effect) is required for cyclization to ensue (Scheme 11). In a related set of experiments, it was also found that six-membered rings could be formed in this cyclopentenone annulation, yet successful examples still require substantial conformational biasing of the acyclic system to enforce cyclization. Overall, many advantages are associated with this $Cp_2Ti(CO)_2$-catalyzed cyclization, yet the reported experimental procedure still requires careful reaction setup to avoid contamination with air and moisture (argon-filled glovebox) – a requirement that impacts the practicality of this advance in catalysis.

A. $Cp_2Ti(CO)_2$-catalyzed Pauson–Khand-type cyclization: Proposed catalytic cycle.

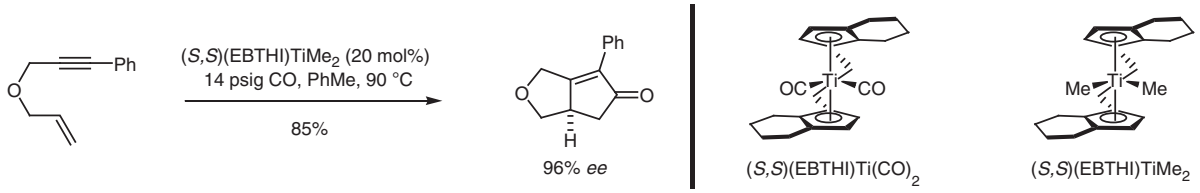


B. $Cp_2Ti(CO)_2$-catalyzed Pauson–Khand-type cyclization: Examples.



Scheme 11

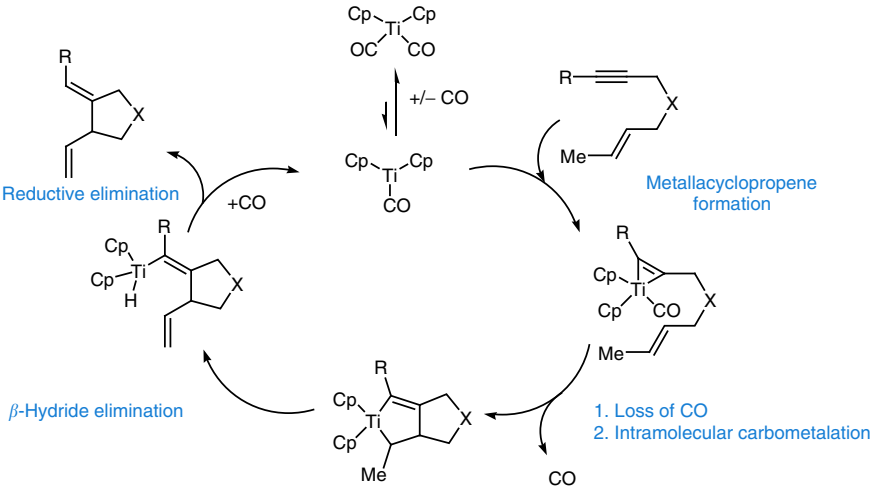
3. A catalytic asymmetric enyne cyclization for the synthesis of bicyclic cyclopentenones has been described (Scheme 12).[39–41] Although representing an impressive advance in early transition metal-mediated asymmetric catalysis, this reaction process is similarly limited in substrate scope to previous titanocene-catalyzed enyne cyclization reactions and often requires higher catalyst loadings than the achiral system ($Cp_2Ti(CO)_2$).



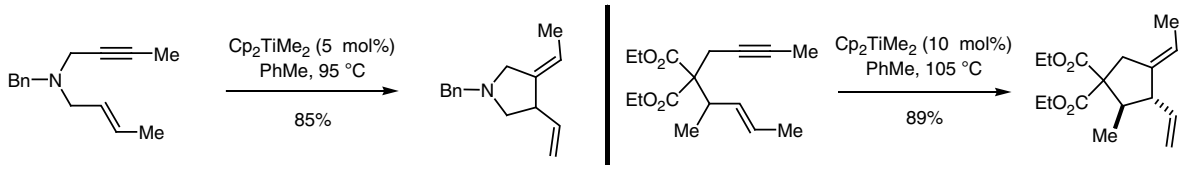
Scheme 12

Moving beyond catalytic applications of enyne cyclization that are limited to the generation of bicyclic cyclopentenones (and related species), it has been demonstrated that titanocene-catalyzed enyne cyclization can be turned over by β-hydride elimination rather than stoichiometric additives that induce ring formation (i.e., CO and R_3SiCN) (Scheme 13A).[42] These advances stem from the ability of the $Cp_2Ti(CO)_2$ system to induce metallacyclopentene formation with substrates bearing 1,2-disubstituted alkenes and results in the formation of cyclopentanes bearing pendant 1,4-diene functionality (Scheme 13B).

A. $Cp_2Ti(CO)_2$-catalyzed intramolecular ene reaction: Proposed catalytic cycle.



B. $Cp_2Ti(CO)_2$-catalyzed intramolecular ene reaction: Examples.



Scheme 13

5.34.2.2.4 Ti-alkoxide-promoted enyne cyclization

Exploring alternatives to the use of Cp_2ZrCl_2 and Cp_2TiCl_2 in metallacycle-mediated bicyclization reactions, Prof. Sato described the application of a simple inexpensive Ti(IV) alkoxide [Ti(O*i*-Pr)$_4$] in combination with Grignard reagents as a system suitable for enyne cyclization. In addition to defining that such a reagent combination defines a practical solution for this class of cyclization reaction, a rich body of reactivity has emerged that is unique to this system.

Among the first set of observations reported in this area was the ability of the reagent combination Ti(O*i*-Pr)$_4$/2RMgX to promote cyclization of enynes containing ethers and basic nitrogen (Scheme 14A).[21] These initial successes in cyclization were accompanied by demonstrations of functionalization reactions of the intermediate titanacyclopentene with protic acid, I_2, or CO.

As depicted in Scheme 14B, by employing substrates with appropriate heteroatom functionality, this cyclization reaction can be used to generate products related to that observed with metallo-ene chemistry (i.e., Scheme 13). Here, the reactivity of the titanacyclopentene intermediate formed from enyne cyclization is harnessed in elimination chemistry en route to substituted 1,4-diene-containing carbocyclic products.[27] In addition to demonstrating that functionalization of the remaining metal–carbon bond provides a means to increase product complexity, this process has also been rendered asymmetric via use of a chiral acetal as an auxiliary.[43]

Finally, the compatibility of this metallacycle-mediated enyne cyclization reaction with metal alkoxides has led to the identification of a unique means to control the stereoselective course of ring closure.[44] As illustrated in Scheme 14C, cyclization reactions proceed to deliver stereodefined five- and six-membered rings with diastereomeric ratios (*dr*) ranging from 82:18 to >98:2. Interestingly, it was found that the free hydroxy group in these substrates was essential to obtain high levels of selectivity (protection as the corresponding TBS ethers led to substantial decreases in stereoselection). The authors suggest that the 'metal alkoxide behaves as a more sterically demanding group, at least superficially, than the TBS ether.'

5.34.2.2.4.1 Development of new Ti-mediated cyclization/functionalization processes that harnesses the reactivity of intermediate metallacyclopentenes formed from enyne cyclization

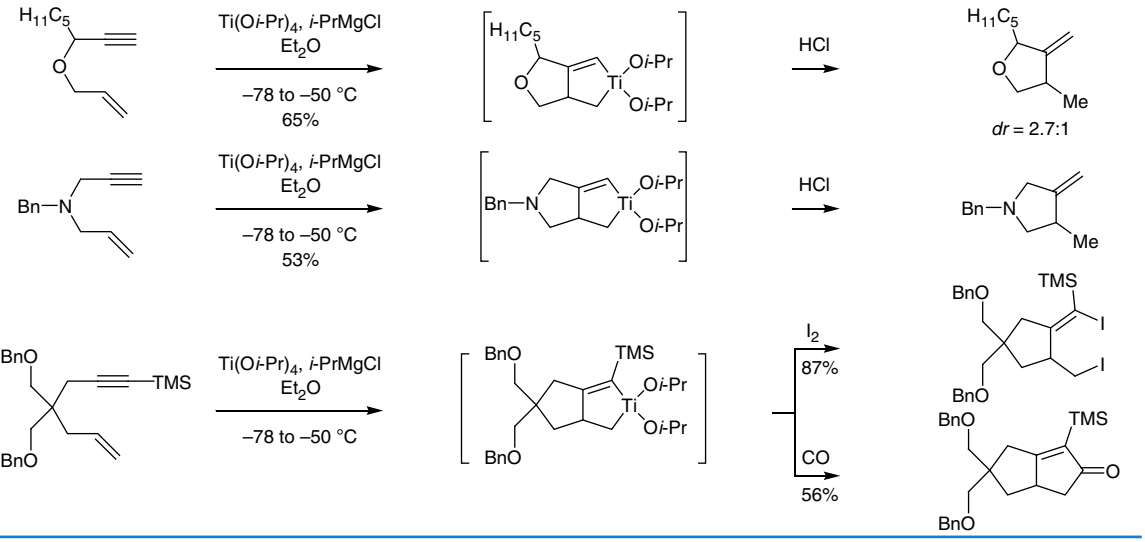
The titanacyclopentene intermediates derived from Ti(O*i*-Pr)$_4$/2*i*-PrMgCl-mediated enyne cyclization can be functionalized by selectively engaging each σ_{C-Ti} bond in subsequent bond-forming processes. Interestingly, addition reactions to aldehydes proceed with stereocontrol, yet with an opposite sense of regioselection compared with zirconacyclopentenes (Scheme 15A).[24,45,46] As depicted in Scheme 15B, it was found that a Lewis acidic additive [Cl$_2$Ti(O*i*-Pr)$_2$] increases both yield and stereoselection for this process – the proposed empirical model for stereoselection in the aldehyde addition reaction is depicted and is based on minimization of nonbonded steric interactions between the aldehyde (R^2)- and alkene (R^1)-substituents.

Despite the disparate regioselection observed in the addition of aldehydes to preformed metallacyclopentenes derived from Ti(O*i*-Pr)$_4$/2*i*-PrMgCl or Cl$_2$ZrCp$_2$/2BuLi, these species behave similarly in Cu-promoted allylation chemistry.[24,47] As illustrated in Scheme 15C, reactions proceed at the sp^2, rather than sp^3, carbon of the intermediate organometallic.

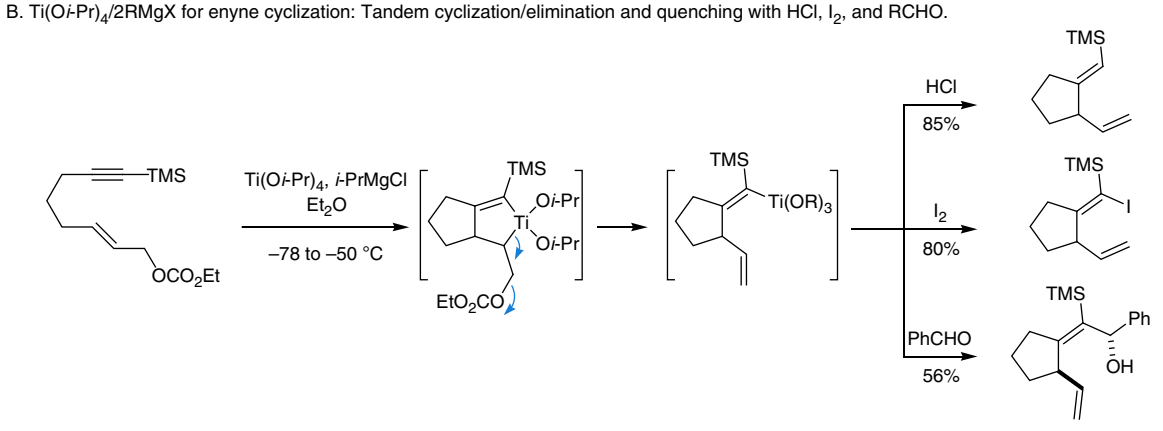
A variety of interesting new modes of reactivity have surfaced in recent years that take advantage of the instability of the organometallic intermediates formed from Ti(O*i*-Pr)$_4$-promoted bicyclization of enynes. In short, reactions have surfaced that are based on Grignard-mediated dehydrogenation/isomerization to a Ti-enolate/intermolecular trapping, intramolecular addition of a σ_{C-Ti} bond to a saturated or unsaturated ester, and elimination:

1. Dehydrogenation and trapping of intermediate metallacyclopentenes with aldehydes (Scheme 16): Treatment of bicyclic metallacyclopentenes with an additional equivalent of *i*-PrMgCl, followed by an aldehyde results in the stereoselective generation of functionalized 1,3-dienes.[24] This process has been proposed to occur by a sequence involving Ti(III) and radical intermediates that results in the formation of an allylic Ti(IV) species.
2. Stereoselective trapping and/or cyclization of enynes bearing one polarized π-bond (Scheme 17): Enyne substrates bearing an enoate are substrates for Ti(O*i*-Pr)$_4$/2*i*-PrMgCl-mediated ring closure, and these electronically activated systems deliver titanacyclopentene intermediates that have the potential to engage in a different collection of C–C bond-forming processes.[48,49] Illustrated in Scheme 17A, enyne cyclization followed by addition of formaldehyde delivers a carbocyclic product with high levels of stereoselection. Here, the site of aldehyde addition is different than that previously discussed in Scheme 15A, likely due to the reactivity profile imparted to the ring-expanded titanium enolate intermediate. This process is equally effective for the addition of an aliphatic aldehyde, yet stereoselection at the newly formed secondary hydroxyl group remains relatively low (*dr*=3:1).
3. These cyclization/alkylation reactions can take a different form if the nature of the ester is modified to accommodate late-stage organometallic addition to the carbonyl (ethyl ester rather than a *t*-Bu ester). As depicted in Scheme 17B, this portfolio of reactivity is quite useful in generation of a variety of bicyclic carbocycles, and use of a chiral auxiliary has been reported as a means to control absolute stereochemistry in the course of cyclization.[50] Finally, this sequence can accommodate other electrophiles to enable the formation of an additional C–C bond in the course of annulation. This is highlighted in Scheme 17C, where an aldol reaction with propionaldehyde leads eventually to the bicyclic carbocycle possessing a β-hydroketone.
4. As illustrated in Scheme 18, if the polarized π-bond in the enyne is the alkyne (in the form of an alkynoate), a different reaction path is observed.[48,49] Here, the intermediate metallacyclopentene rearranges to form a fused bicyclo[3.1.0]hexane system. Interestingly, quenching of the organometallic intermediate with a ketone results in the formation of a functionalized vinylcyclopropane.
5. Carbocyclization stemming from Ti-mediated cyclization of (*Z*)-enol ester-containing enynes (Scheme 19): Adding to the collection of interesting cyclization reactions that result from controlling the fate of the titanacyclopentene intermediate generated via enyne cyclization, it has been demonstrated that enol ester-containing enynes react by a unique stereoselective tandem reaction that takes advantage of the nucleophilicity of each σ_{Ti-C} bond present in the titanacyclopentene intermediate and the electrophilicity of the neighboring carbonyl.[51] As illustrated in Scheme 19, the simple reaction conditions employed for Ti(O*i*-Pr)$_4$/2*i*-PrMgCl-mediated enyne cyclization of a (*Z*)-enol acetate-containing enyne deliver a stereodefined oxygenated bicyclo[3.3.0]octene system. Although the isomeric (*E*)-enol acetate derivatives do not participate in this tandem process, it has been speculated that the course of this process follows initial nucleophilic addition of the proximal σ_{C-Ti} bond to the ester

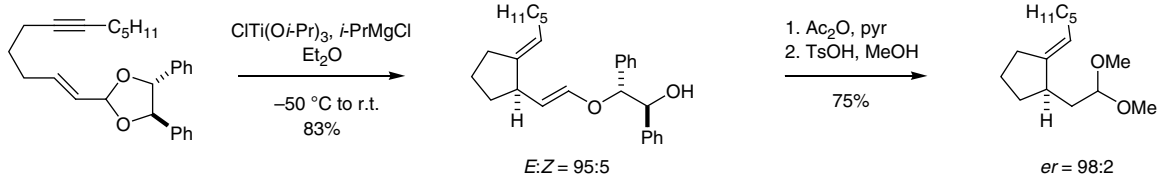
A. $Ti(O\textit{i}\text{-}Pr)_4$/2RMgX for enyne cyclization: Quenching with HCl, I_2, and CO.



B. $Ti(O\textit{i}\text{-}Pr)_4$/2RMgX for enyne cyclization: Tandem cyclization/elimination and quenching with HCl, I_2, and RCHO.

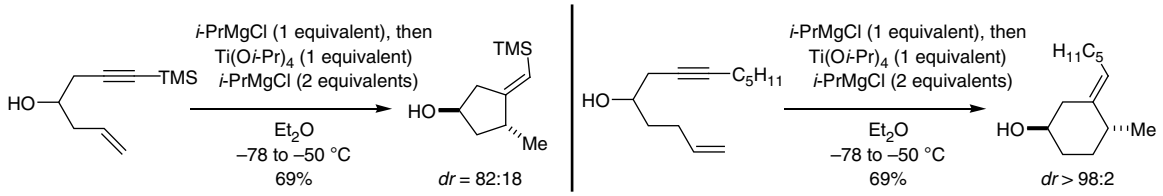


Asymmetric variation:



[a]Relative stereochemistry assumed to be consistent with a related example reported in the following: Urabe, H.; Sato, F. *J. Am. Chem. Soc.* 1999, *121*, 1245–1255.

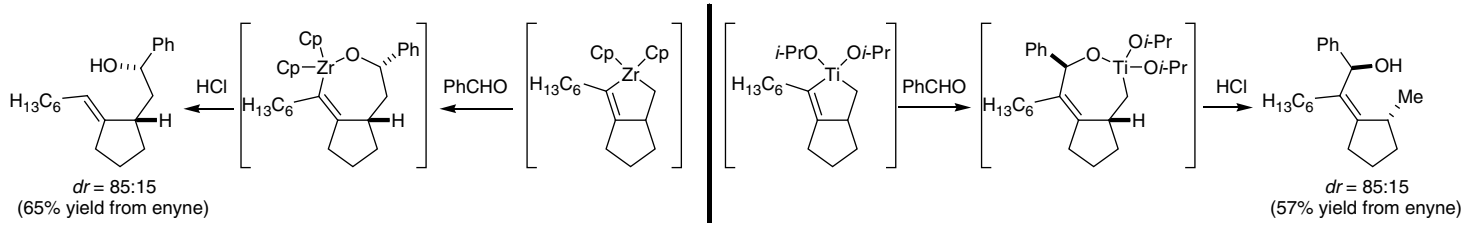
C. $Ti(O\textit{i}\text{-}Pr)_4$/2RMgX for enyne cyclization: Stereochemical control with pendant metal alkoxides.



Note: All reactions require a stoichiometric quantity of $Ti(O\textit{i}\text{-}Pr)_4$ or $ClTi(O\textit{i}\text{-}Pr)_3$ and two equivalents of *i*-PrMgX.

Scheme 14

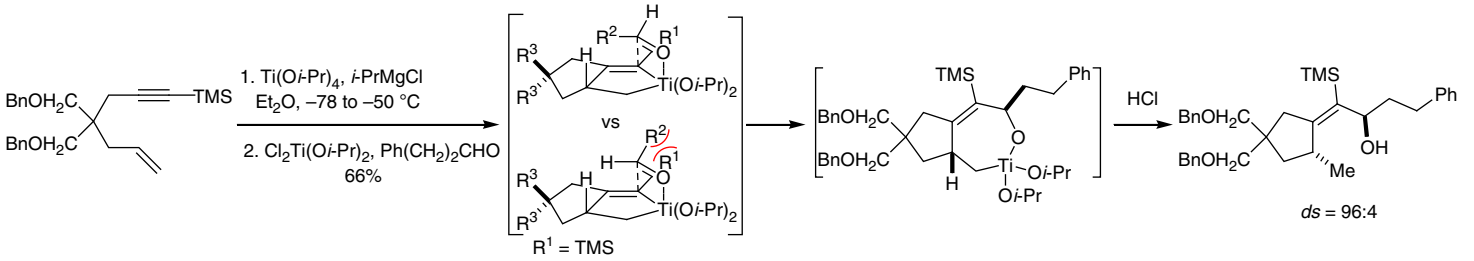
A. Regioselective functionalization of a metallacyclopentene is influenced by the nature of the metal center: -$ZrCp_2$ vs. -$Ti(O\textit{i}\text{-}Pr)_2$.



dr = 85:15
(65% yield from enyne)

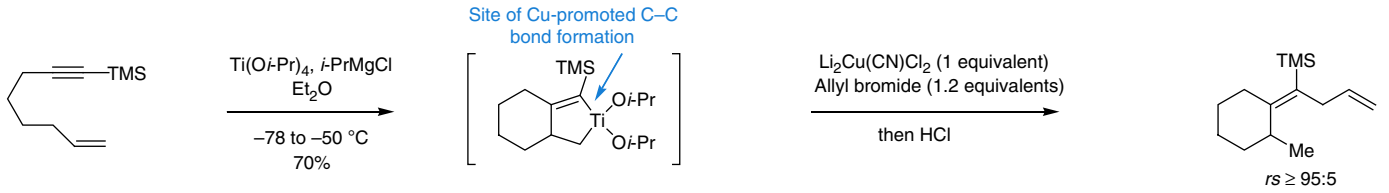
dr = 85:15
(57% yield from enyne)

B. Empirical model for stereoselection/use of $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ leads to increases in yield and selectivity.



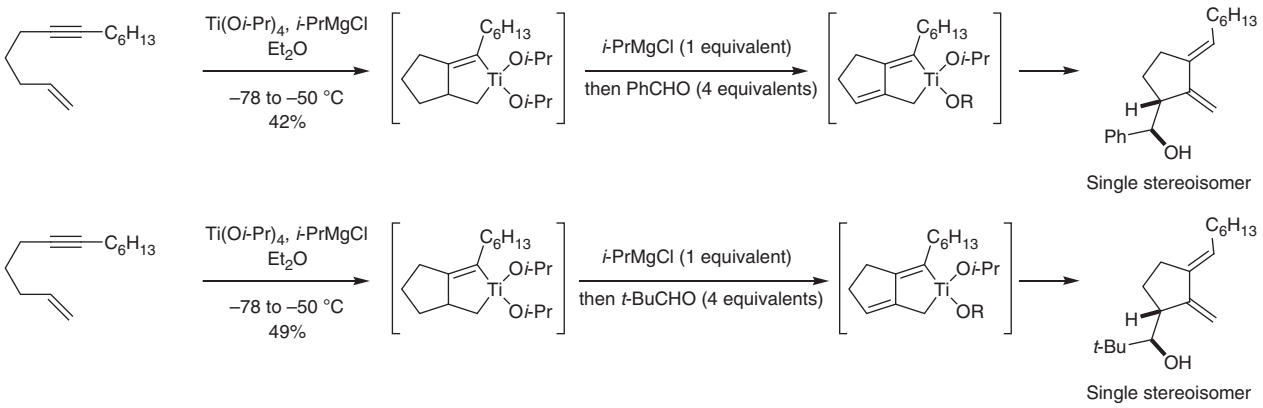
ds = 96:4

C. Regioselective Cu-promoted allylation of intermediate titanacyclopentenes.



rs ≥ 95:5

Scheme 15



Scheme 16

(to generate an epoxy-oxatitanacycloheptene intermediate), followed by rearrangement to the corresponding oxatitanacyclohexene, and a second intramolecular nucleophilic addition of the remaining σ_{C-Ti} bond to the pendant ketone. Based on the stereoselective course of the initial carbometalation process (generating the first metallacyclopentene intermediate), the subsequent steps proceed in a highly stereocontrolled manner – no evidence was found for the production of isomeric products.

6. Enyne cyclization followed by Pummerer rearrangement (Scheme 20): Cyclization of enynes bearing chiral vinylsulfoxides results in the formation of cyclopentanes adorned with a β,γ-unsaturated aldehyde.[52] It has been proposed that stereoselection in this process derives from an association of the sulfoxide oxygen with titanium in the transition state for carbometalation. This stereochemistry-determining step is then thought to be followed by elimination and intramolecular addition to generate a fused bicyclic oxatitanacyclohexene, hydrolysis of which delivers the stereodefined β,γ-unsaturated aldehyde product.

In addition to these unique cyclization reactions that derive from funneling the reactivity of intermediate metallacyclopentenes down different pathways, the utility of metallacycle-mediated enyne cyclization has recently been harnessed in acyclic stereocontrol. Specifically, studies directed toward the synthesis of dictyostatin stimulated the design of a new stereoselective version of the Ti(O*i*-Pr)$_4$/2*i*-PrMgCl-promoted enyne cyclization.[53,54] As depicted in Scheme 21, cyclization of a silyl ether-tethered enyne proved effective for establishing the C15–C16 *anti*-stereochemical relationship in this target with a high degree of stereochemical control – the cyclized product was produced as a single stereoisomer.

5.34.2.3 Bicyclization of Dienes

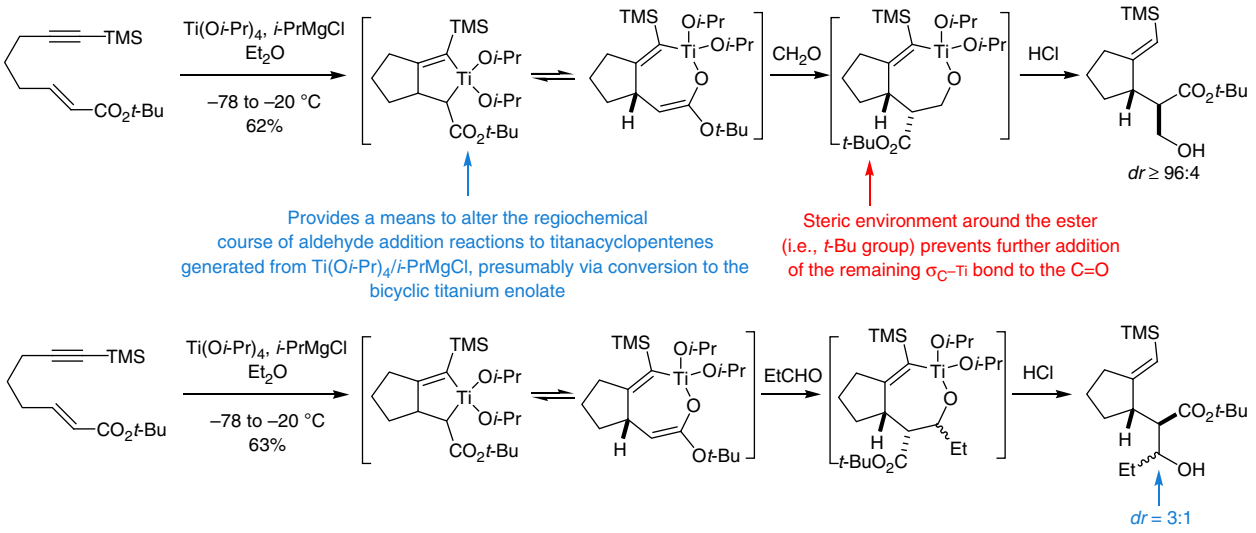
Cyclization of dienes has been studied with a variety of early transition metals. This section introduces advances that stemmed from investigations of metallocene-based chemistry, including the study of stereochemical control in such cyclizations (see Section 5.34.2.3.1) and catalysis (see Section 5.34.2.3.2), whereas also presenting some limitations in substrate scope (see Section 5.34.2.3.3). Titanium alkoxide-mediated diene cyclization chemistry is then discussed (see Section 5.34.2.3.4), first in a manner to support that Ti-alkoxides can be employed to realize diene cyclization, then to feature a variety of interesting functionalization reactions of the intermediate titanacyclopentanes that define unique and powerful tandem reactions for organic synthesis. Finally, this section is concluded with a discussion of a recently described Ti-catalyzed diene cyclization (see Section 5.34.2.3.5).

5.34.2.3.1 Stereochemistry in Zr-promoted enyne cyclization

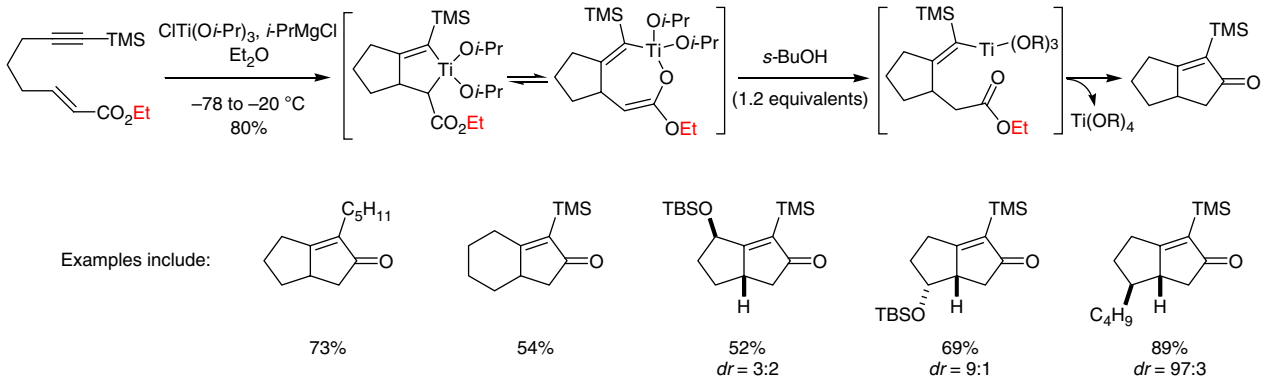
Stereochemical control of early transition metal metallacycle-mediated diene cyclization has been a topic of considerable interest, with reports describing achievements in reactions that proceed with both stoichiometric and catalytic quantities of zirconocene reagents. A variety of cyclization chemistry has been described whereby the stereochemistry of the products can be established by kinetic or thermodynamic control – in the latter case, thermal instability of the intermediate metallacyclopentane[55–58] is harnessed as a mechanism to alter the stereochemical course of cyclization.

As illustrated in Scheme 22A, cyclization of 1,6-heptadiene can proceed with high selectivity for the formation of both 1,2-*trans*- or 1,2-*cis*-substituted cyclopentane products. When promoting the reaction with Cp_2ZrCl_2/*n*-BuLi, initial conversion proceeds with poor kinetic selectivity, but on prolonged stirring at r.t., bromination results in the selective formation of the *trans*-1,2-disubstituted cyclopentane (*dr* = 97:3).[59,60] If this reaction is run with Cp*$TiCl_3$/Na(Hg) amalgam, the *cis*-1,2-disubstituted isomer

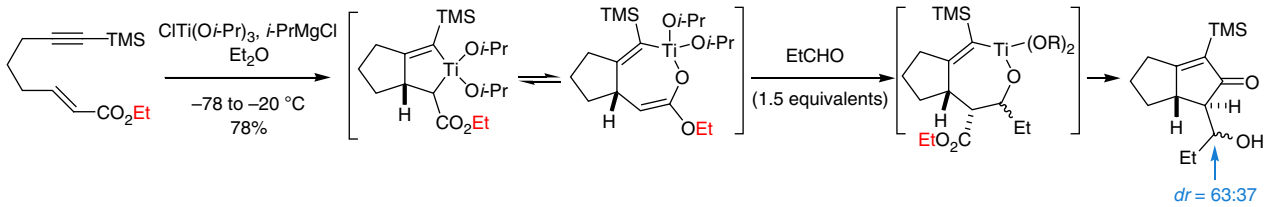
A. Ti(O*i*-Pr)2-mediated cyclization followed by stereoselective aldol reaction (likely via the titanium enolate).



B. Synthesis of bicyclic carbocyles by sequential Ti-mediated enyne cyclization/protonation/intramolecular nucleophilic addition. TBSO, (*tert*-butyldimethylsilyl)oxo.



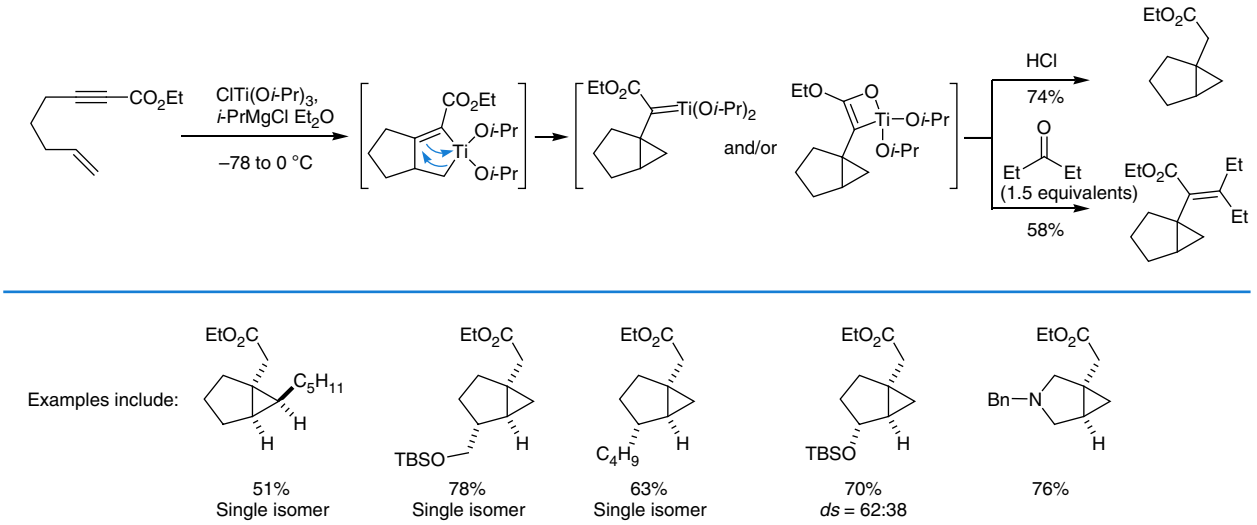
C. Synthesis of bicyclic carbocyles by sequential Ti-mediated enyne cyclization/aldol/intramolecular nucleophilic addition.



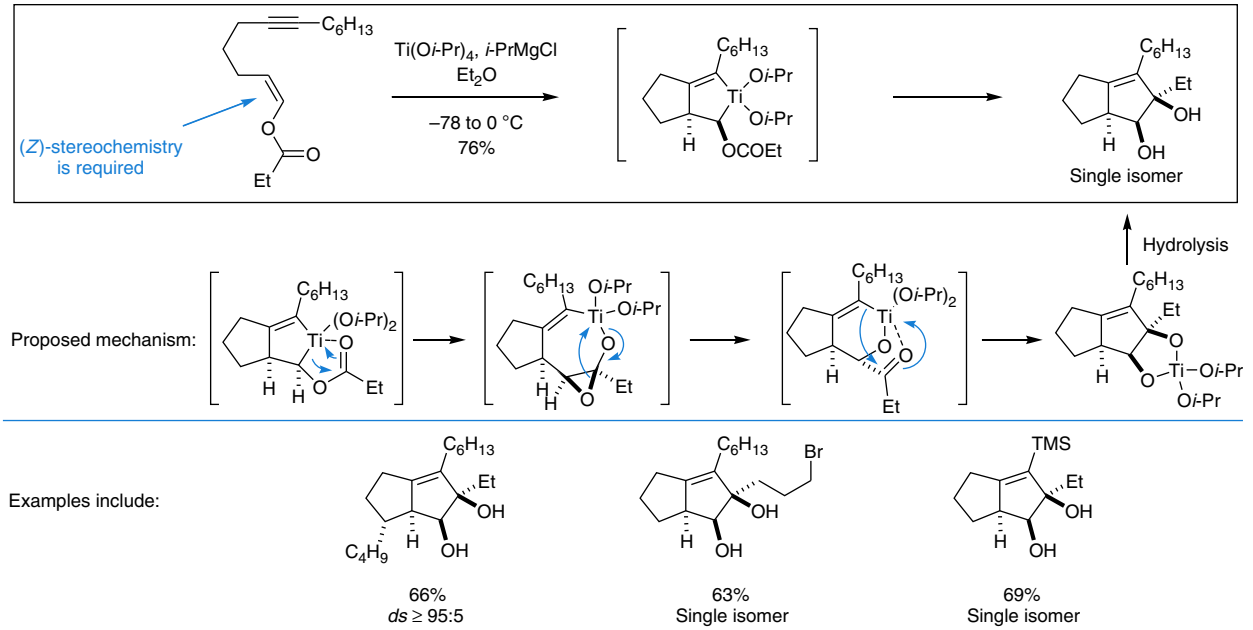
Scheme 17

is produced with outstanding levels of stereochemical control – an observation that has been attributed to high kinetic selectivity and a decreased tendency for equilibration at r.t.

A similar trend is observed in the cyclization of 1,7-octadiene, where kinetic selectivity favors the formation of the 1,2-*cis*-disubstituted cyclohexane product (*dr* = 3:1) and prolonged heating at 75 °C results in the selective formation of the 1,2-*trans*-disubstituted product (*dr* = 99:1) (Scheme 22B).



Scheme 18

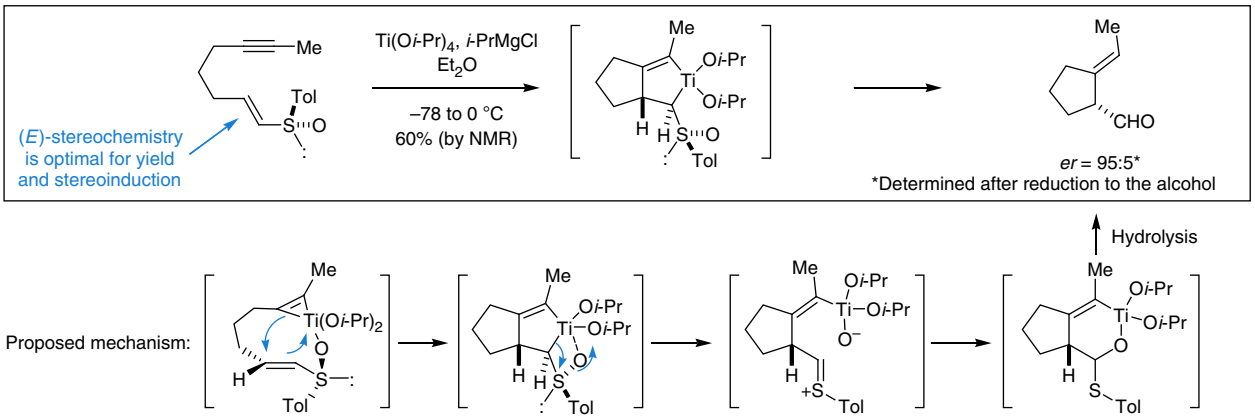


Scheme 19

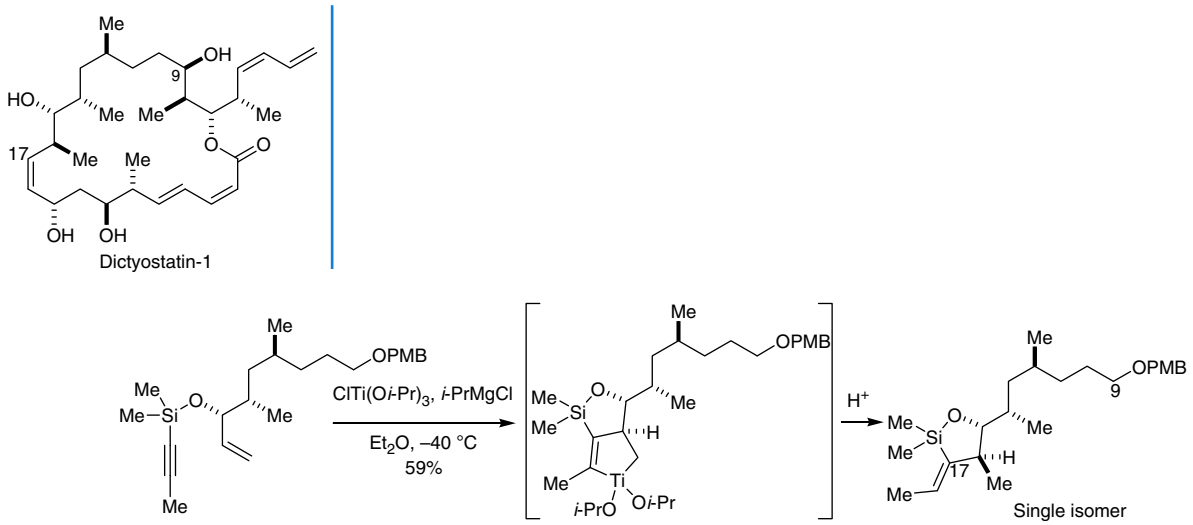
In addition to the design of cyclization protocols that proceed with catalytic quantities of Zr reagent and excess Grignard,[60,61] a variety of stereoselective cyclization reactions have been described that provide a glimpse of the potential power of this type of cyclization in stereoselective synthesis (Scheme 23). Shown are three examples of stoichiometric Cp_2Zr-mediated cyclization reactions that proceed via thermodynamic control and deliver products with varying levels of stereoselectivity.[59,62,63] Interestingly, in catalytic variants, where excess Grignard is employed to turn over Cp_2Zr, kinetic trapping of the metallacyclopentane products can offer a complementary selectivity profile.[60,62]

5.34.2.3.2 Catalysis in Zr-promoted diene cyclization

As mentioned in Section 5.34.2.2.3, an elegant means of rendering diene cyclization chemistry substoichiometric in Cp_2Zr– has been described.[64] These cyclization reactions, while proceeding through similar zirconacyclopentanes, are mechanistically complex with stereochemistry being influenced by a variety of factors including (1) the interplay between kinetic and thermodynamic stereoselectivity, (2) the rate of metallacycle isomerization, and (3) the rate of transmetalation of the metallacycle intermediates (Scheme 24A).[60] As illustrated in Scheme 24B, remarkable examples are shown that support the notion that



Scheme 20



Scheme 21

selective cleavage of intermediate metallacyclopentanes is possible and that demonstrate that changes in reaction conditions lead to a shifting of reaction course to generate mono- rather than diorganomagnesium intermediates.[61,62]

5.34.2.3.3 Substrate scope limitations in Zr-promoted diene cyclization

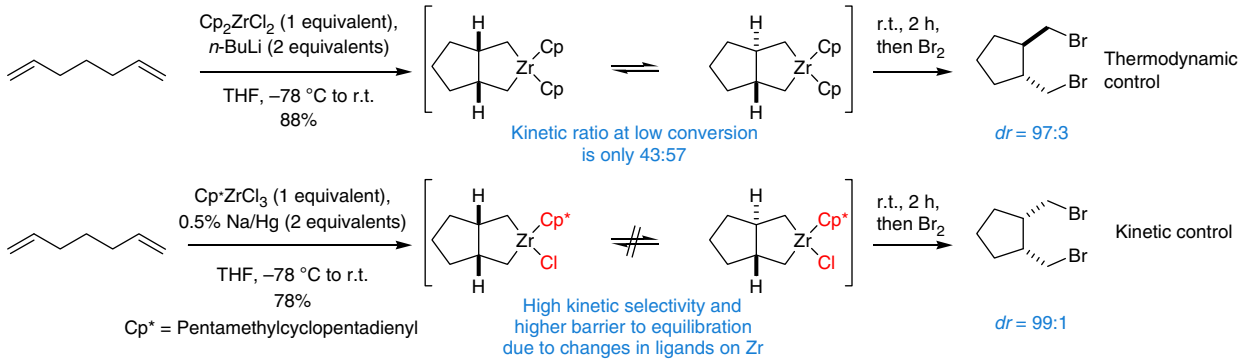
Exploration of the scope of Cp_2Zr-promoted diene cyclization has led to the discovery of a competing reaction process which results in isomerization of the diene starting material.[65] As illustrated in Scheme 25A, simple unsaturated hydrocarbon substrates containing substituted alkenes rapidly isomerize to conjugated dienes rather than undergoing cyclization. Interestingly, it has been demonstrated that substitution in the tether between the two alkenes can result in regaining the ability to accomplish cyclization. Although this process has not yet been extensively studied, a substrate bearing a 1,1-disubstituted olefin and a quaternary center (likely supporting a conformation that facilitates ring closure via the Thorpe–Ingold effect) has been shown to provide a carbocyclic product (Scheme 25B) in 85% yield, whereas the parent substrate lacking the geminal methyl substitution delivers the product of alkene isomerization (Scheme 25A).

Notably, heteroatom substitution in the tether between the two alkenes also can be employed to regain the ability to cyclize (Scheme 25B). Such features played a prominent role in a Cp_2Zr-promoted cyclization en route to a formal total synthesis of dendrobine (Scheme 25C).[66]

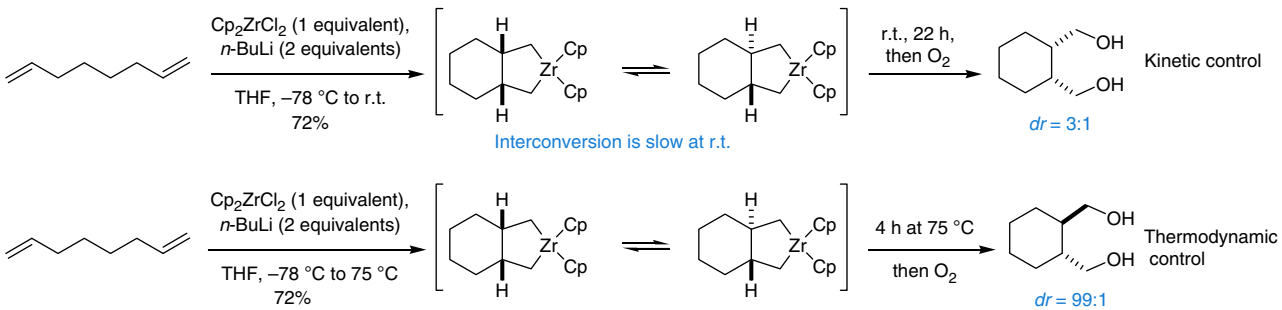
5.34.2.3.4 Titanium alkoxide-promoted diene cyclization

Study of early transition metal metallacycle-mediated diene cyclization reactions has resulted in the discovery of different selectivity patterns observed for reactions promoted by Negishi's reagent (Cp_2ZrBu_2) versus $Ti(Oi\text{-}Pr)_4/2i\text{-}PrMgCl$. As illustrated in Scheme 26, Prof. Whitby's study of the cyclization reactions of silyl-tethered 1,6-dienes has resulted in the discovery that the Zr-promoted process is highly selective for the *anti*-isomer (a minor isomer was not identified), whereas the Ti-alkoxide-promoted

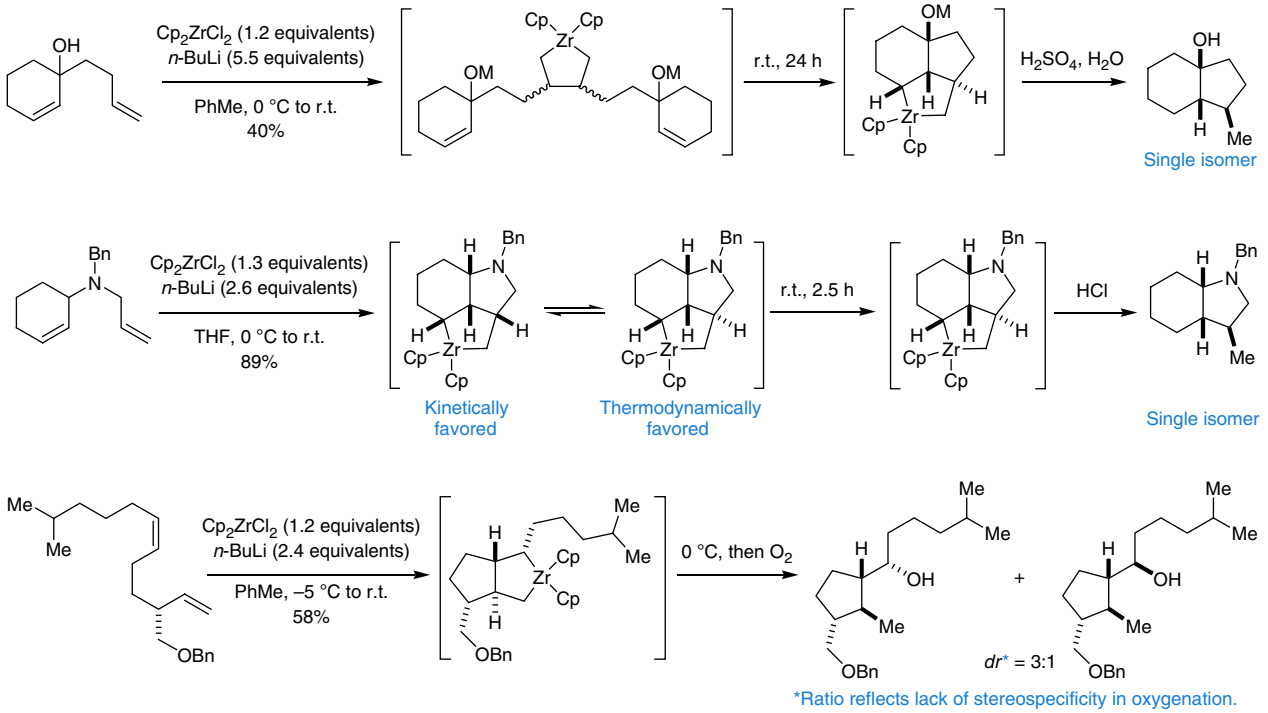
A. Stereoselective synthesis of 1,2-disubstituted cyclopentanes by cyclization of 1,7-heptadiene.



B. Stereoselective synthesis of 1,2-disubstituted cyclohexanes by cyclization of 1,8-octadiene.

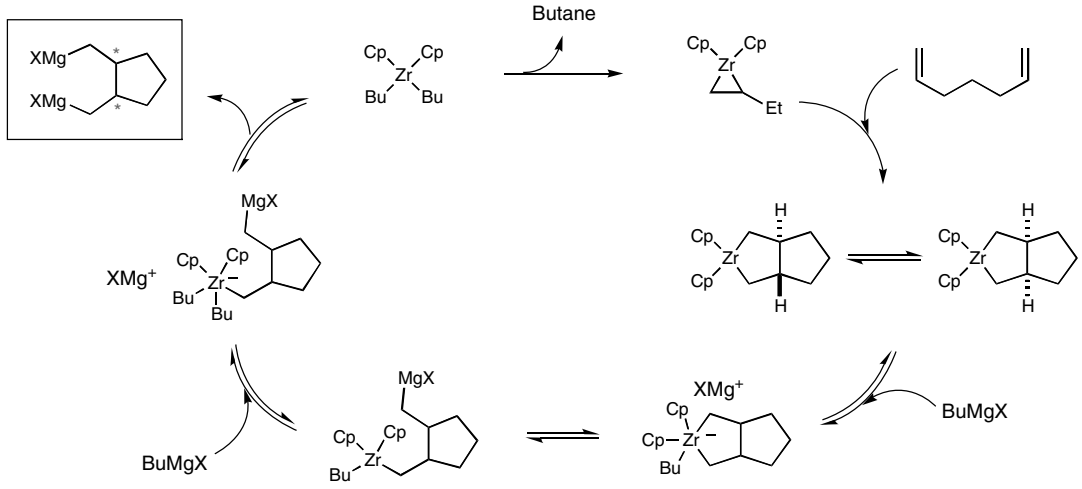


Scheme 22

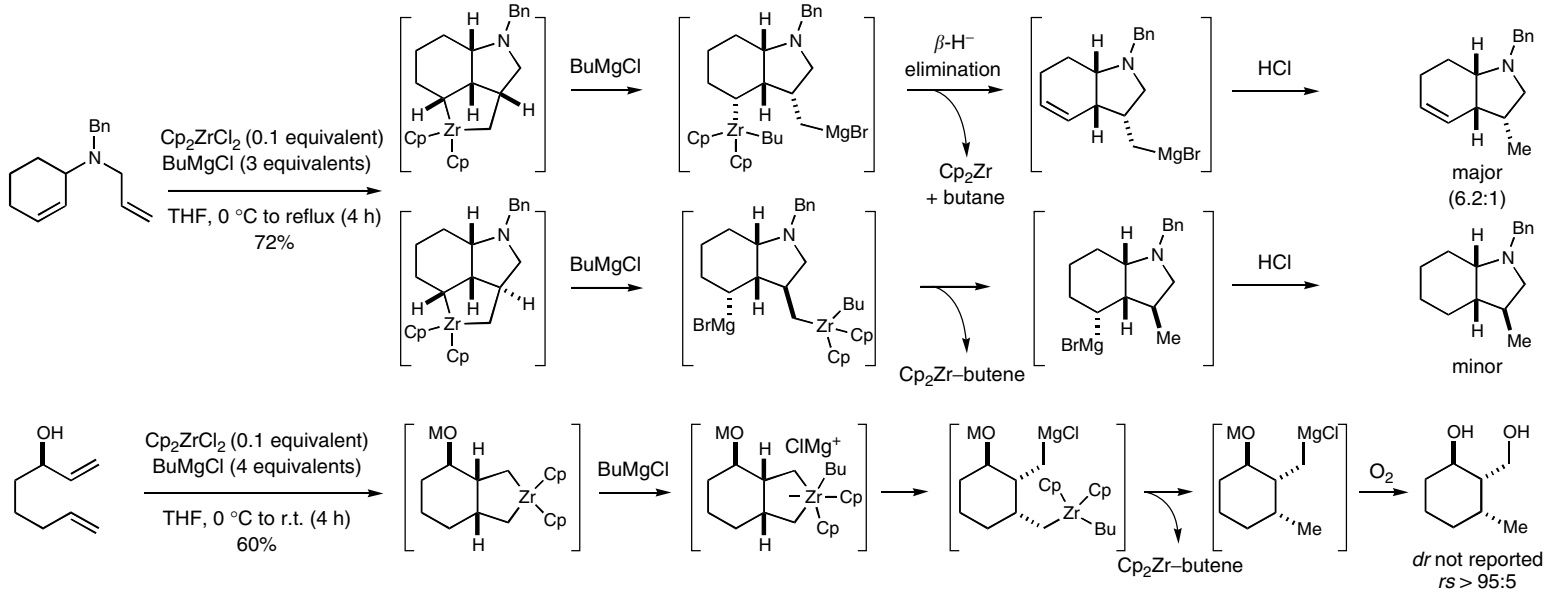


Scheme 23

A. Zr-catalyzed cyclomagnesiation of dienes: Proposed catalytic cycle.

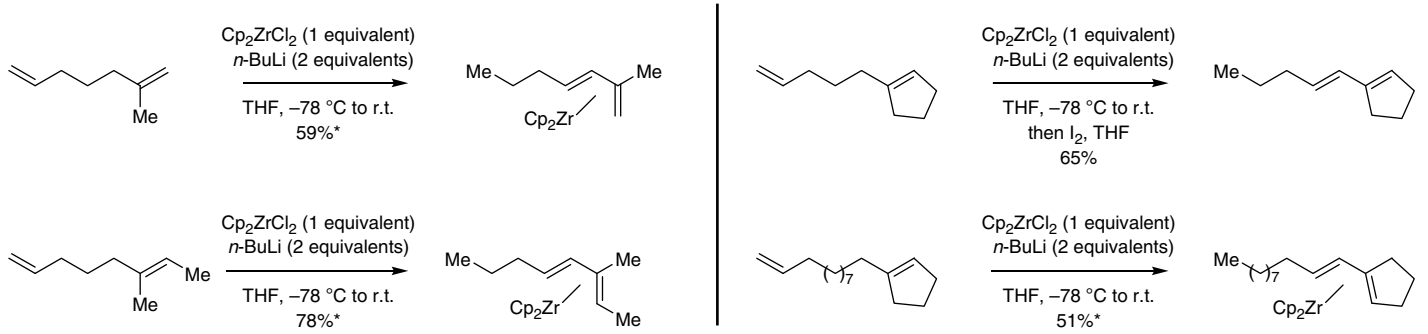


B. Zr-catalyzed cyclomagnesiation of dienes: Examples.



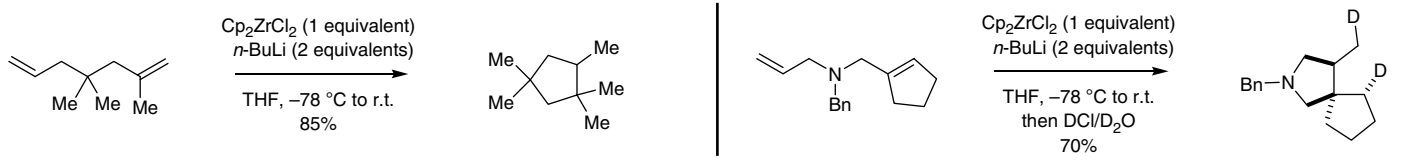
Scheme 24

A. Zr-promoted alkene isomerization: Alkene isomerization is favored over cyclization with hydrocarbon substrates possessing substituted olefins.

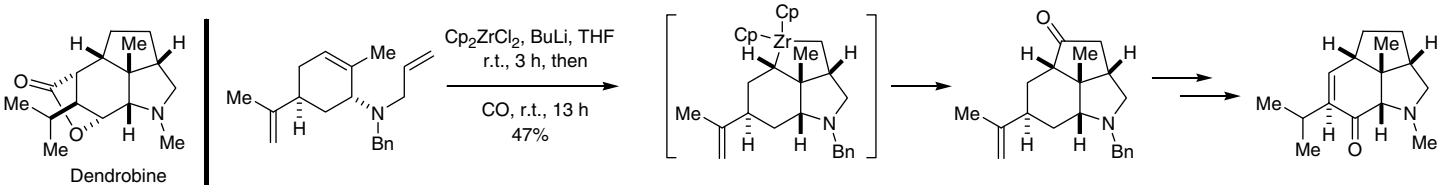


*Yield reported by NMR

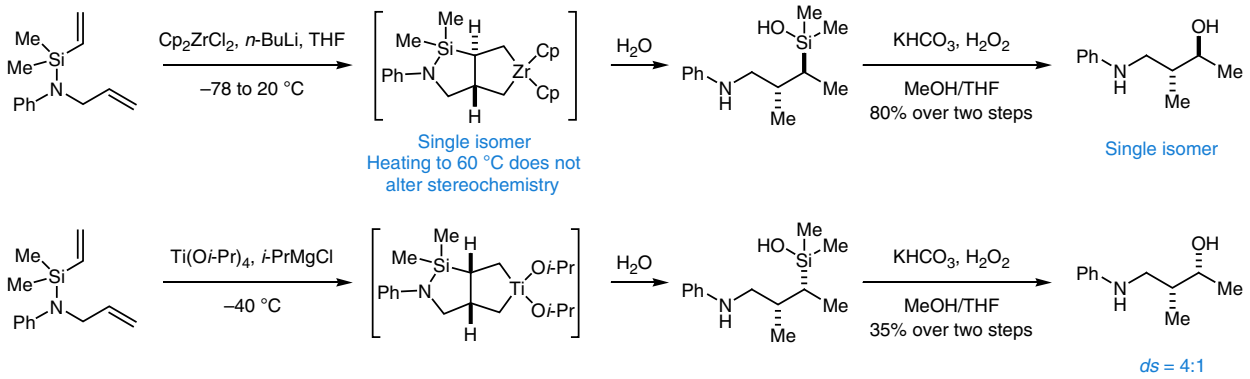
B. Zr-promoted cyclization of dienes: Hydrocarbon substitution can be used to regain ability to cyclize.



C. Zr-promoted cyclization of dienes: Application in natural product synthesis.



Scheme 25



Scheme 26

cyclization proceeds with an opposite sense of selectivity favoring the production of the *syn*-isomer, albeit with diminished levels of stereoselectivity (ds = 4:1).[67]

5.34.2.3.4.1 *Development of new Ti-mediated cyclization/functionalization processes that harnesses the reactivity of intermediate metallacyclopentanes formed from diene cyclization*

Consistent with trends in reactivity already discussed for titanacyclopentenes generated from enyne cyclization with Ti(O*i*-Pr)$_4$/2*i*-PrMgCl, diene cyclization reactions also deliver intermediate metallacyclic products that can be employed in subsequent bond-forming processes. As depicted in Scheme 27A, cyclization of diene substrates containing an enoate, followed by addition of one equivalent of an electrophile promotes monofunctionalization of the intermediate bicyclic titanium enolate, ring opening, and intramolecular C–C bond formation to deliver cyclic ketones. Interestingly, this process delivers carbocyclic products that have related stereochemistry to those derived from the Ti-promoted cyclization reactions depicted in Scheme 26, but opposite to that reported for the cyclization of a simple diene substrate (Scheme 27B). Perhaps these observations support the conclusion that the factors that control stereoselection in these processes are complex. Nevertheless, the tandem Ti-promoted diene cyclization/aldol/intramolecular nucleophilic addition reaction has recently been employed in a concise total synthesis of carbacyclin (Scheme 27C).[68]

5.34.2.3.5 *Titanium aryloxide-catalyzed diene cyclization*

Defining a different net transformation, Ti(IV) aryloxides have been described as effective catalysts for cycloisomerization of 1,6- and 1,7-dienes en route to substituted five- and six-membered rings (Scheme 28).[69] Notably, this process has been found to be quite sensitive to alkene substitution – only terminal (monosubstituted) alkenes participate in the cyclization.

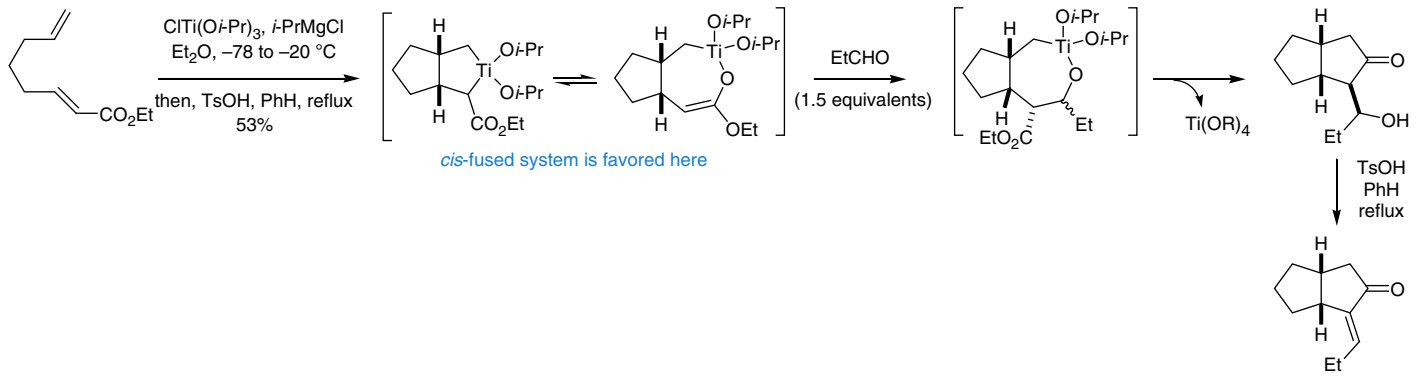
5.34.2.4 Bicyclizations Involving Allenes

Early transition metal metallacycle-mediated cyclization reactions of allenynes are complex owing to the availability of two different π-systems of the allene to engage in intramolecular reaction with the pendant alkyne. Titanium alkoxide-mediated reaction of 1,2-dien-7-ynes results in regioselective cyclization to deliver 1,4-diene-containing products, whereby C–C bond formation occurs at a terminus of the cumulated π-system (Scheme 29A).[70] Stereoselective variants of this cyclization have been established, where axial chirality of the allene is translated to point chirality in the cyclopentane product. Here, highest stereoselectivities are seen with silyl-substituted allenes (Scheme 29B).

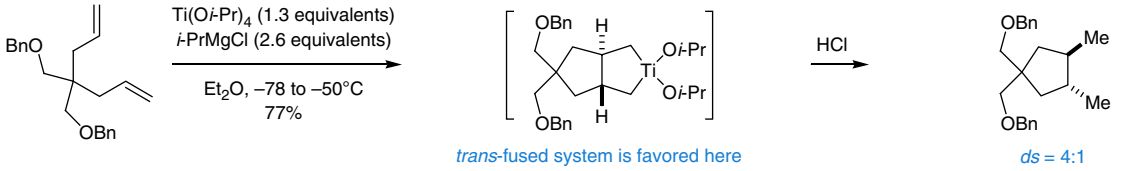
Interestingly, the regiochemical course of this enyne cyclization changes with 1,2-dien-6-ynes (Scheme 29C). Here, C–C bond formation occurs at the central carbon of the allene and delivers a bicyclic allyltitanium species that can be intercepted with carbonyl electrophiles. The stereochemical course of the resulting SE2′ addition process is dependent on the nature of the substituent on the sp^3 carbon α- to Ti. With a linear pentyl side chain, C–C bond formation occurs *syn*- to the pentyl substituent. With a TMS group at the α-position, C–C bond formation occurs primarily *anti*- to the TMS group through a process that delivers a (*Z*,*E*)-1,3-diene.

Finally, as previously discussed in the related cyclization reactions of enynes and diynes, the intermediate metallacycles generated from these allenyne cyclization reactions can be induced to undergo elimination or CO insertion. In the current context, such processes provide a means to access cross-conjugated trienes and bicyclic cyclopentenones, respectively (Scheme 29D).[71] Related to this latter example, it has been demonstrated that $Cp_2Ti(CO)_2$ can be employed to catalyze a related enyne cyclization/CO insertion to generate bicyclic cyclopentenones from 1,2-diene-6-ynes (10 mol% $Cp_2Ti(CO)_2$, 18 psig CO, PhMe, 90 °C).[38]

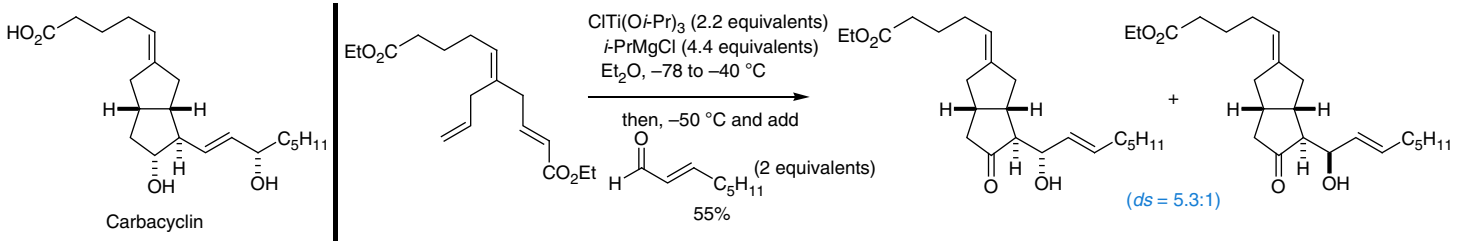
A. Diene cyclization/aldol/intramolecular nucleophilic addition: Generation of substituted *cis*-fused bicyclo[3.3.0]octanes.



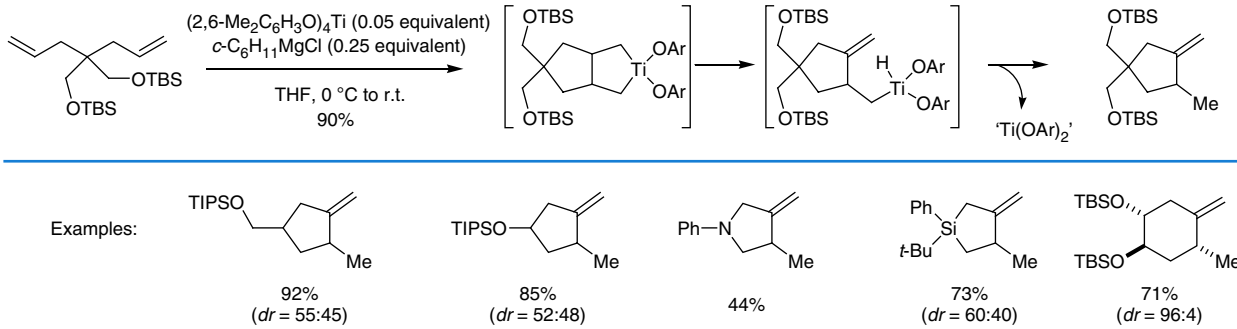
B. Simple $(i\text{-PrO})_2$ Ti-promoted diene cyclization: Evidence for the selective generation of *trans*-fused bicyclic metallacycles.



C. $(i\text{-PrO})_2$Ti-promoted diene cyclization/aldol/intramolecular nucleophilic addition in natural product synthesis: Synthesis of carbacyclin.



Scheme 27



Scheme 28

5.34.2.5 Bicyclizations Involving a Carbonyl-Based Functional Group

A variety of early transition metal metallacycle-mediated coupling chemistry has been described that engages the reactivity of carbonyl-based functional groups. This section is organized to first present advances in metallocene-based methods (see Section 5.34.2.5.1), then to describe relevant examples that proceed via the action of Ti-alkoxides (see Section 5.34.2.5.2). In this latter case, a variety of bond-forming processes are described that proceed through intramolecular reaction of a Ti–π complex with a pendant carbonyl system. In some cases, such processes result in the formation of a cyclic system, whereas in others nucleophilic addition is followed by ring opening to define a net acyl transfer process.

5.34.2.5.1 Cyclization reactions mediated by metallocenes

Building on the discovery of a titanium-catalyzed silane-mediated reduction of carbonyl compounds,[72] conditions have been found that enable reductive cyclization of unsaturated ketones and aldehydes that proceed with 10–20 mol% of $Cp_2Ti(PMe_3)_2$ and one equivalent of a silane or siloxane (Scheme 30A).[73–75] As previously discussed in the context of early transition metal-catalyzed diene cyclization reactions, stereoselection is often more challenging to control in these cyclization reactions due to competitive kinetic trapping of the intermediate metallacyclopentene before thermodynamic equilibration.

As has been highlighted with other cyclization processes, this class of early transition metal metallacycle-mediated cyclization reaction is compatible with intermediate-functionalization processes for the establishment of bicyclic products. As illustrated in Scheme 30B, a variety of carbocyclization reactions have been reported to deliver bicyclic lactones with high levels of stereochemical control.[76,77] Notably, this reaction process has been rendered substoichiometric in the early transition metal[77] – an accomplishment that has led to the discovery of a catalytic asymmetric variant.[78]

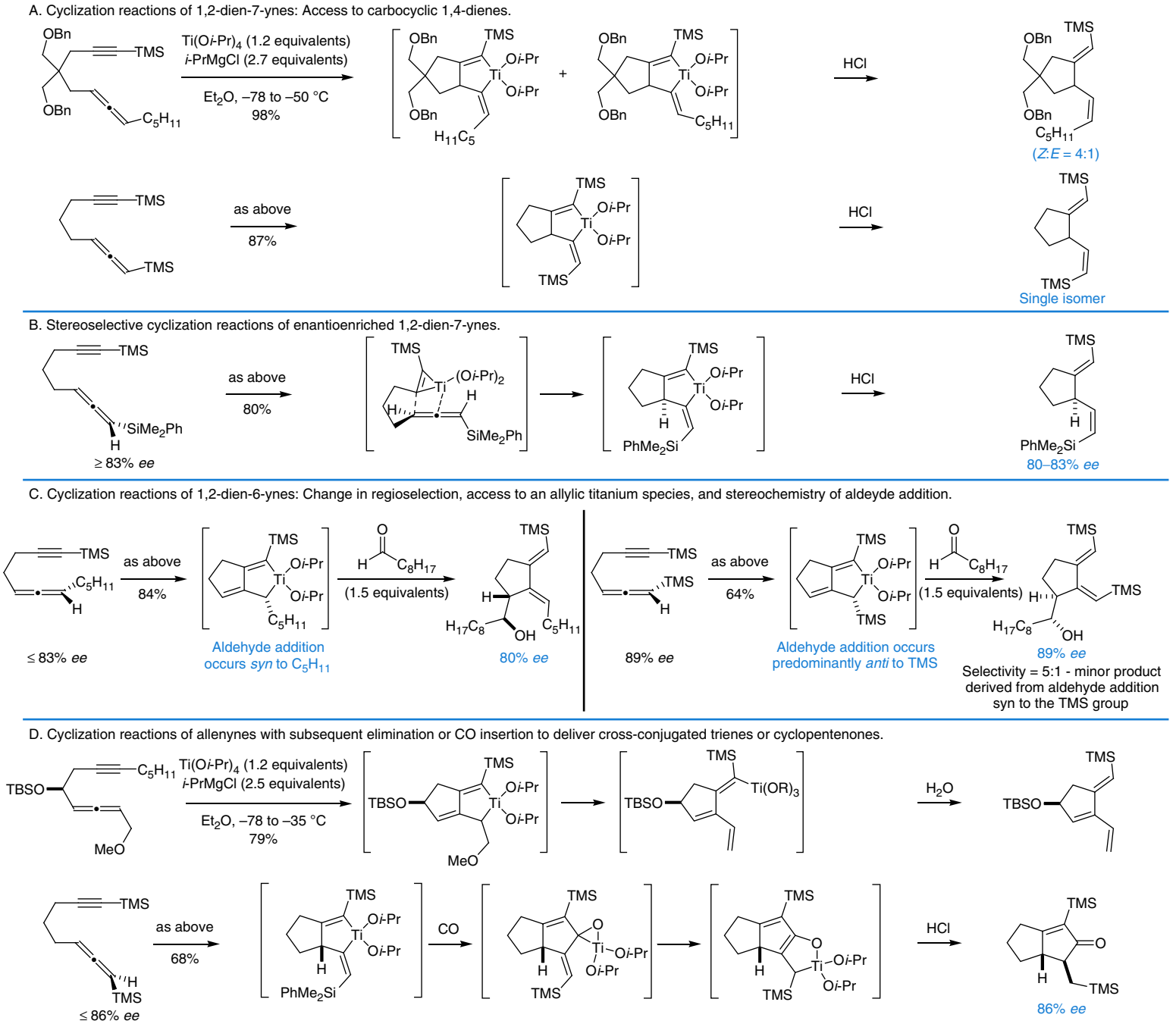
5.34.2.5.2 Cyclization reactions mediated by Ti-alkoxides

Ti-alkoxide reagents are useful for the cyclization of unsaturated carbonyl compounds, establishing parallel methods for cyclization chemistry to those observed with metallocene reagents (Scheme 31A).[79,80]

In addition to simple cyclization chemistry akin to that seen in diyne, enyne, and diene cyclization reactions, Ti-alkoxides have also been shown to affect a variety of other interesting transformations that derive from intramolecular addition of a Ti–π complex to an ester or a carbonate. As generally depicted in Scheme 31B, Ti–π complex formation is thought to be followed by intramolecular nucleophilic attack to deliver an intermediate bicyclic product, the fate of which is dictated by the nature of the unsaturated system (alkene, alkyne, allene, or 1,3-diene), the substituents X and Y, and the ring size.[81–86] These processes have been termed, 'intramolecular nucleophilic acyl substitution' (INAS) reactions and have been explored as a means to prepare a variety of nitrogen-containing heterocycles (Scheme 32A). Recently, this type of early transition metal-mediated process has appeared as a key step in the total synthesis of allopumiliotoxin 267A (Scheme 32B).[87]

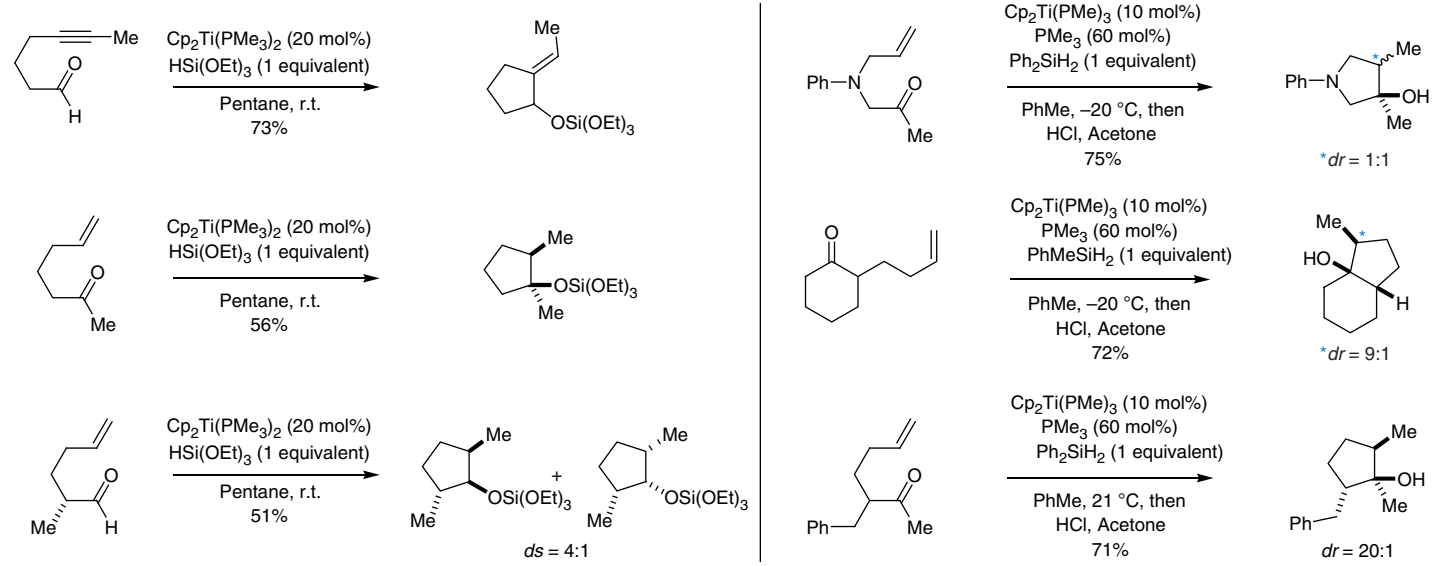
5.34.2.6 Summary of Advances in Early Transition Metal Metallacycle-Mediated Cyclization

The preceding sections have presented a great deal of science that has surfaced from efforts aimed at understanding and controlling early transition metal metallacycle-mediated cyclization chemistry. In summary of these contributions, basic advances include the following: (1) Ti-alkoxides offer a complementary means to accomplish bicyclization of polyunsaturated substrates (Scheme 33A-1) and (2) procedures have been advanced to enable metallacycle-mediated cyclization chemistry to proceed with substoichiometric quantities of Group (IV) metals (Scheme 33A-2).


A. Cyclization reactions of 1,2-dien-7-ynes: Access to carbocyclic 1,4-dienes.
Ti(Oi-Pr)4 (1.2 equivalents)
i-PrMgCl (2.7 equivalents)
Et2O, –78 to –50 °C
98%
HCl
(Z:E = 4:1)
as above
87%
HCl
Single isomer
B. Stereoselective cyclization reactions of enantioenriched 1,2-dien-7-ynes.
as above
80%
HCl
≥ 83% ee
80–83% ee
C. Cyclization reactions of 1,2-dien-6-ynes: Change in regioselection, access to an allylic titanium species, and stereochemistry of aldeyde addition.
as above
84%
(1.5 equivalents)
≤ 83% ee
Aldehyde addition occurs syn to C5H11
80% ee
as above
64%
(1.5 equivalents)
89% ee
Aldehyde addition occurs predominantly anti to TMS
89% ee
Selectivity = 5:1 - minor product derived from aldehyde addition syn to the TMS group
D. Cyclization reactions of allenynes with subsequent elimination or CO insertion to deliver cross-conjugated trienes or cyclopentenones.
Ti(Oi-Pr)4 (1.2 equivalents)
i-PrMgCl (2.5 equivalents)
Et2O, –78 to –35 °C
79%
H2O
as above
68%
CO
HCl
≤ 86% ee
86% ee

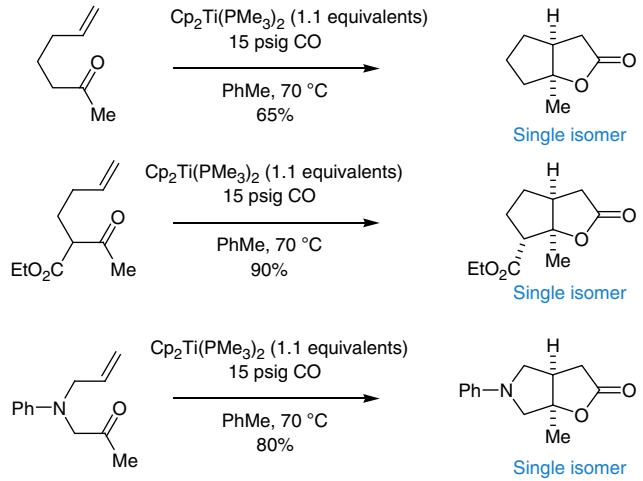
Scheme 29

A. Ti-catalyzed reductive cyclization reactions.

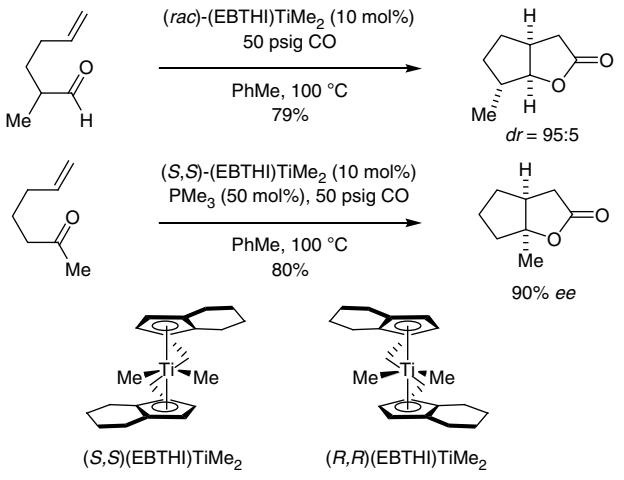


B. Ti-mediated cyclocarbonylation reactions.

Reactions with a stoichiometric quantity of Cp_2TiL_2:

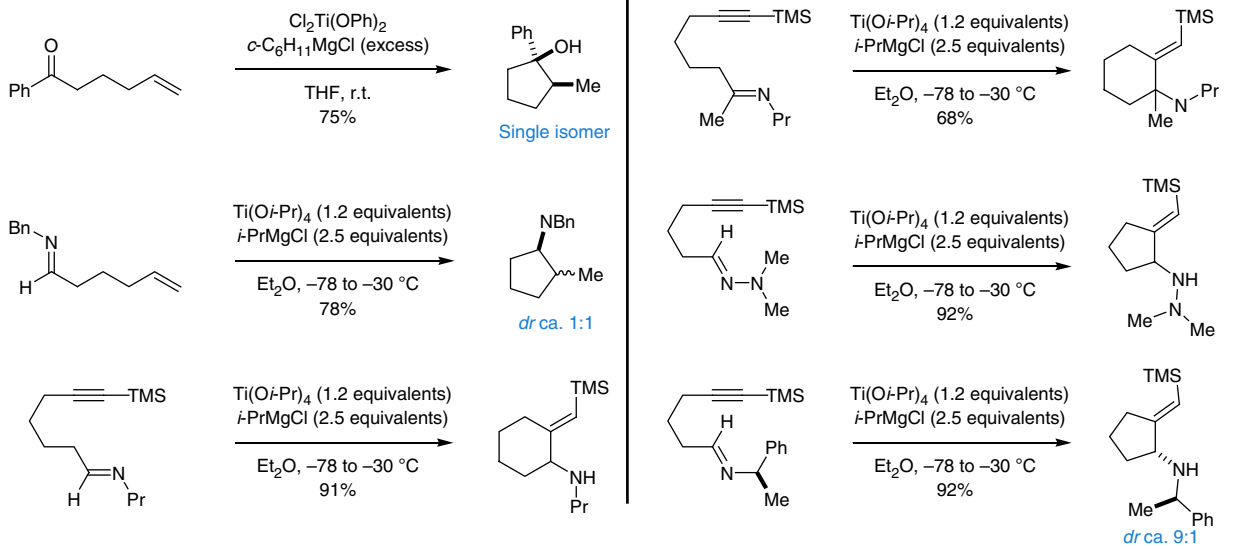


Reactions with a substoichiometric quantity of Cp_2TiL_2:

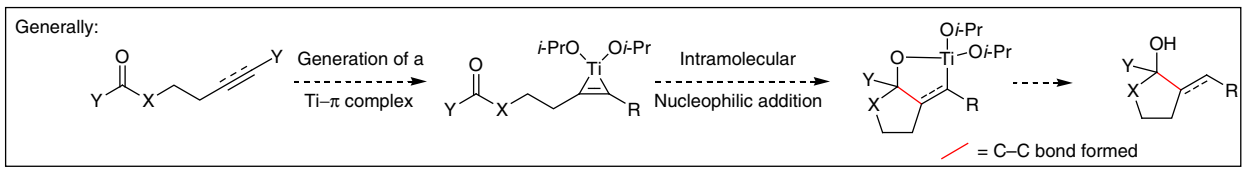


Scheme 30

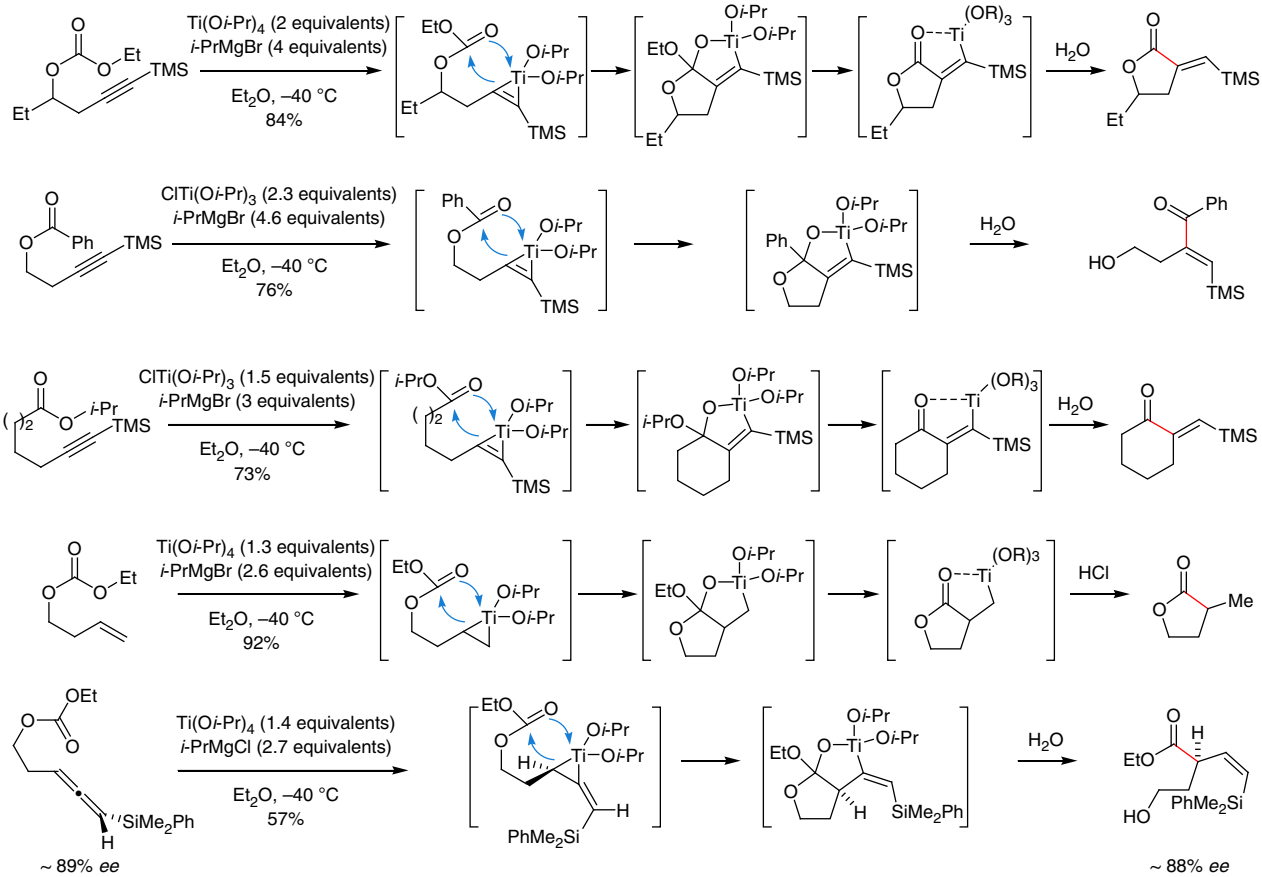
A. Ti alkoxide-promoted cyclization reactions of unsaturated carbonyl compounds.



B. Intramolecular nucleophilic acyl substitution chemistry promoted by Ti-alkoxides.

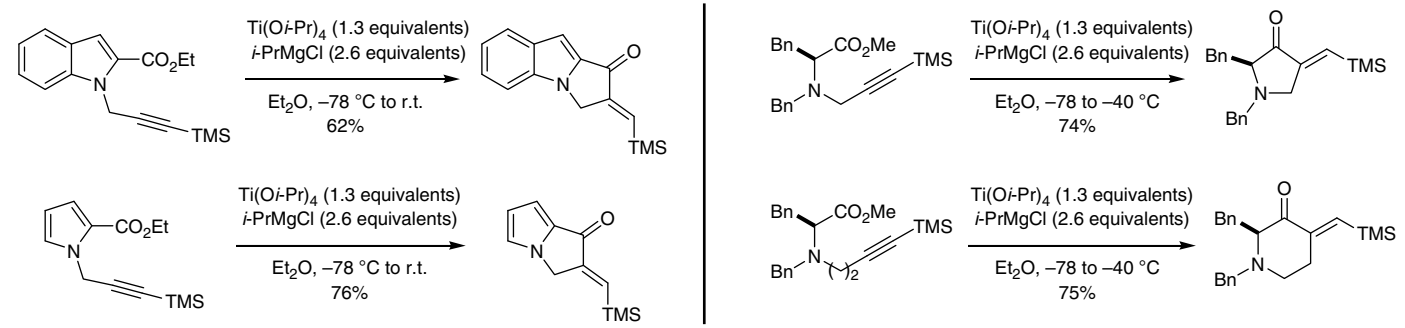


Examples:

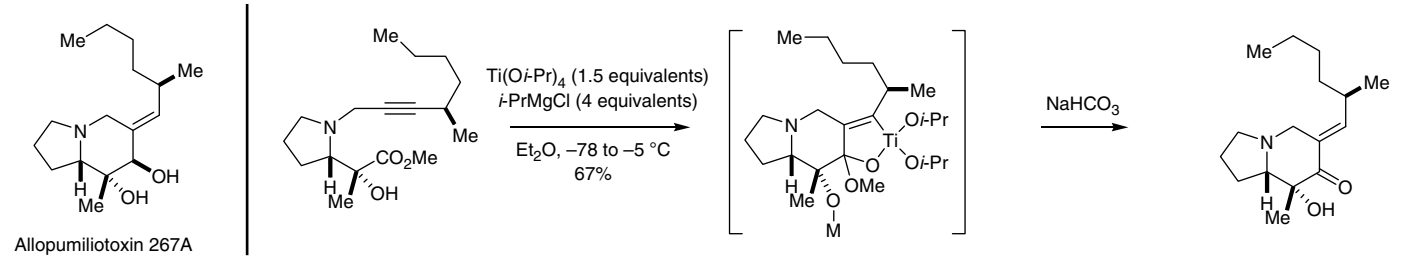


Scheme 31

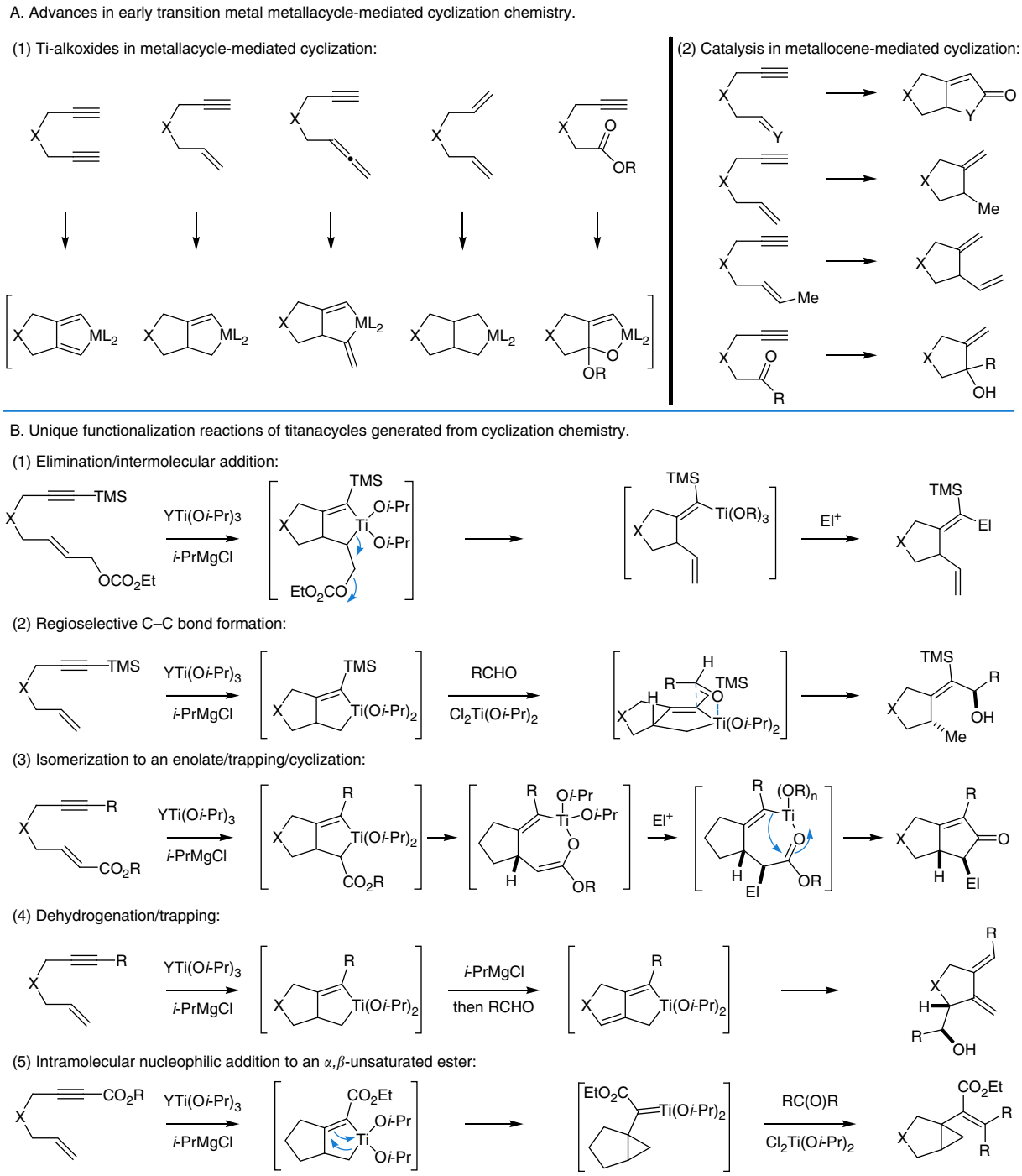
A. Intramolecular nucleophilic acyl substitution for heterocycle synthesis.



B. Intramolecular nucleophilic acyl substitution in natural product synthesis.



Scheme 32



Scheme 33

In addition to these, a great variety of novel complexity-generating reactions have emerged from harnessing the reactivity of metallacyclic intermediates generated from cyclization reactions promoted by $XTi(O\textit{i}\text{-}Pr)_3/\textit{i}\text{-}PrMgX$. As illustrated in Scheme 33B, these include the following:

1. Elimination reactions (Scheme 33-B1);
2. Regioselective nucleophilic addition reactions (Scheme 33-B2);
3. Isomerization to a Ti-enolate/enolate functionalization/intramolecular carbonyl addition (Scheme 33-B3);
4. Dehydrogenation/aldehyde addition (Scheme 33-B4); and
5. Rearrangement by intramolecular addition to a polarized π-bond (Scheme 33-B5).

5.34.3 Early Transition Metal-Mediated Cross-Coupling (Intermolecular C–C Bond Formation)

5.34.3.1 Introduction to Early Transition Metal Metallacycle-Mediated Cross-Coupling

In the early 1990s, the emerging body of science associated with early metal metallacycle-mediated cross-coupling could be summarized in the following manner: A number of observations had been made that confirmed the viability of a subset of intermolecular coupling reactions of preformed metal–π complexes (i.e., Zr–alkyne, Zr–benzyne, Zr–imine, and Zr–alkene) with unsaturated systems (i.e., alkynes, alkenes, aldehydes, ketones, and imines). These accomplishments served to define the potential utility of metallacycle-mediated C–C bond formation in intermolecular settings but were frequently accomplished with only the simplest of systems (i.e., symmetrical alkynes and ketones and unhindered/unfunctionalized terminal alkenes/ethylene) of restricted relevance to complex molecule synthesis. Over the past 20 years, a substantial body of work has emerged that confirms the great potential that metallacycle-mediated cross-coupling has in organic synthesis, with recent accomplishments defining solutions to the major barriers that have existed in controlling the course of this class of bimolecular C–C bond-forming reaction.

The factors that have limited the development of metallacycle-mediated cross-coupling lie not in the pursuit of catalytic methods, but rather relate to fundamental challenges associated with the control of reactivity and selectivity in the bimolecular C–C bond-forming event. Without a tether to position the two reactive π-systems in a defined orientation for intramolecular formation of a metallacyclopentane, intermolecular applications of this reactivity are substantially more difficult to control than their intramolecular counterparts. Outside of the low levels of reactivity for coupling processes between highly substituted alkenes and hindered alkynes, and the potential reversibility of the coupling process that is ever more significant with increasing temperature, major hurdles surface in the control of pair selectivity (**Scheme 34A**), regioselectivity (**Scheme 34B**), and *ds* (**Scheme 34C**). The great complexity that results when combining these issues is summarized in **Scheme 34D** and supports the impressive challenges associated with efforts aimed at controlling this area of chemical reactivity.

Moving beyond metallocene-based coupling chemistry, significant advances have surfaced from harnessing the reactivity of Ti–π complexes generated *in situ* from $Ti(O\textit{i}\text{-}Pr)_4/2RMgX$. Initial studies described bond constructions that mirrored those possible with metallocene chemistry (i.e., alkyne–aldehyde, alkyne–imine, and internal alkyne–terminal alkyne), with recent advances describing coupling reactions not possible with any other metallacycle-mediated coupling chemistry. These latter advances build on the demonstrated significance of initial stoichiometric activation of one coupling partner in the absence of the other (to achieve pair selectivity) and provide a means to simultaneously (1) overcome the typical low reactivity that has limited substrate scope in all metallacycle-mediated intermolecular C–C bond-forming reactions, (2) control regioselectivity with respect to both unsaturated reaction partners, and (3) control diastereoselectivity.

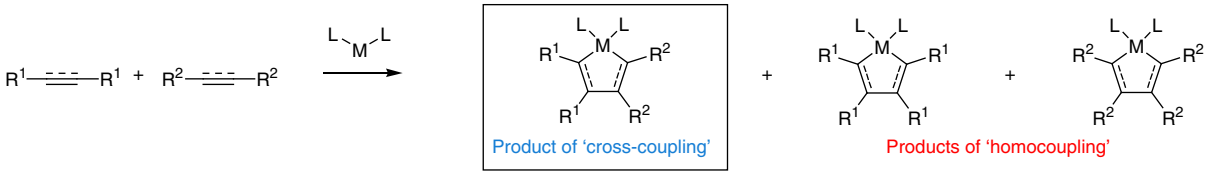
The most significant advance that has led to an explosion of new cross-coupling technology based on early transition metal metallacycle-mediated C–C bond formation has derived from a pursuit focused on rendering these reactions 'substrate directed.' It is well accepted that directing strategies provide a powerful means to control chemo-, regio-, and stereoselection in a host of other bond-forming processes.[88] Recognizing that Ti-alkoxides are compatible with metallacycle-mediated C–C bond formation and that alkoxide ligand exchange should be fast and reversible at Ti, led to a broad exploration of the use of tethered alkoxides as directing groups to control the course of metallacycle-mediated C–C bond formation.[89,90] These pursuits have indeed defined a collection of unique and complex coupling reactions not possible with other metal systems (catalytic or stoichiometric), while establishing a suite of technology capable of forging C–C bonds in the presence of free hydroxyls – a particularly compelling feature of this class of convergent coupling chemistry.

The organization of this section is similar to Section 5.34.2 on cyclization reactions, being subdivided by the nature of the π-systems that participate in the metallacycle-mediated bond construction. Within each subsection, attention is given to the nature of the initial Ti–π complex employed in each coupling process, as reactivity and selectivity are greatly influenced by this consideration. Also, effort has been taken throughout to highlight the demonstrated utility of these reactions in stereoselective organic synthesis. The discussion begins with a summary of alkyne–carbonyl coupling processes mediated by preformed metal–alkyne complexes that includes a discussion of the challenges associated with the control of regioselection in these processes, as well as state of the art means to achieve regio- and stereochemical control in alkyne–aldehyde coupling processes that proceed via the intermediacy of preformed metal–alkyne complexes (see Section 5.34.3.2). This discussion begins with addition reactions to aldehydes and ketones (see Section 5.34.3.2.1), and continues with addition reactions of alkynes to C═N (see Section 5.34.3.2.2) and nitriles (see Section 5.34.3.2.3). Moving on, the discussion shifts to include more challenging coupling reactions, including: alkyne–alkyne (see Section 5.34.3.4), alkyne–alkene (see Section 5.34.3.5), allene–alkyne (see Section 5.34.3.6), imine–alkyne (via the intermediacy of metal–imine complexes; see Section 5.34.3.7), imine–alkene (also via the intermediacy of metal–imine complexes; see Section 5.34.3.8), alkene–alkene (see Section 5.34.3.9), chemoselective coupling of polyunsaturated substrates (see Section 5.34.3.10), and other coupling reactions that proceed by [2 + 2 + 2] annulation (see Section 5.34.3.11).

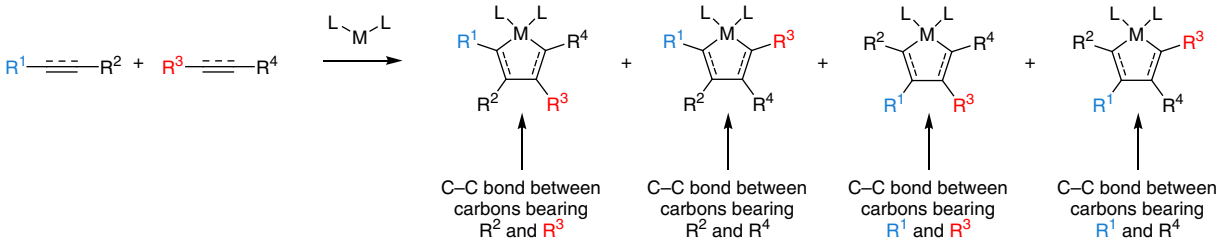
5.34.3.2 Alkyne–Aldehyde, Alkyne–Imine, and Alkyne–Nitrile Cross-Coupling (via Preformed Metal–Alkyne Complexes)

Since the early demonstrations of Cp_2Zr- and Cp_2Ti-based metallacyclopropene addition reactions to polarized π-bonds (i.e., aldehydes, ketones, and imines), titanium alkoxide-based methods have emerged that offer a complementary approach to achieve related chemical reactivity. Following is a brief survey of developments that have secured strategies to control regio- and stereoselection in this class of metallacycle-mediated cross-coupling.

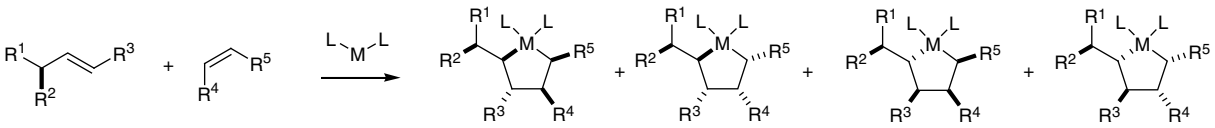
A. The challenge of pair selectivity in metallacycle-mediated cross-coupling.



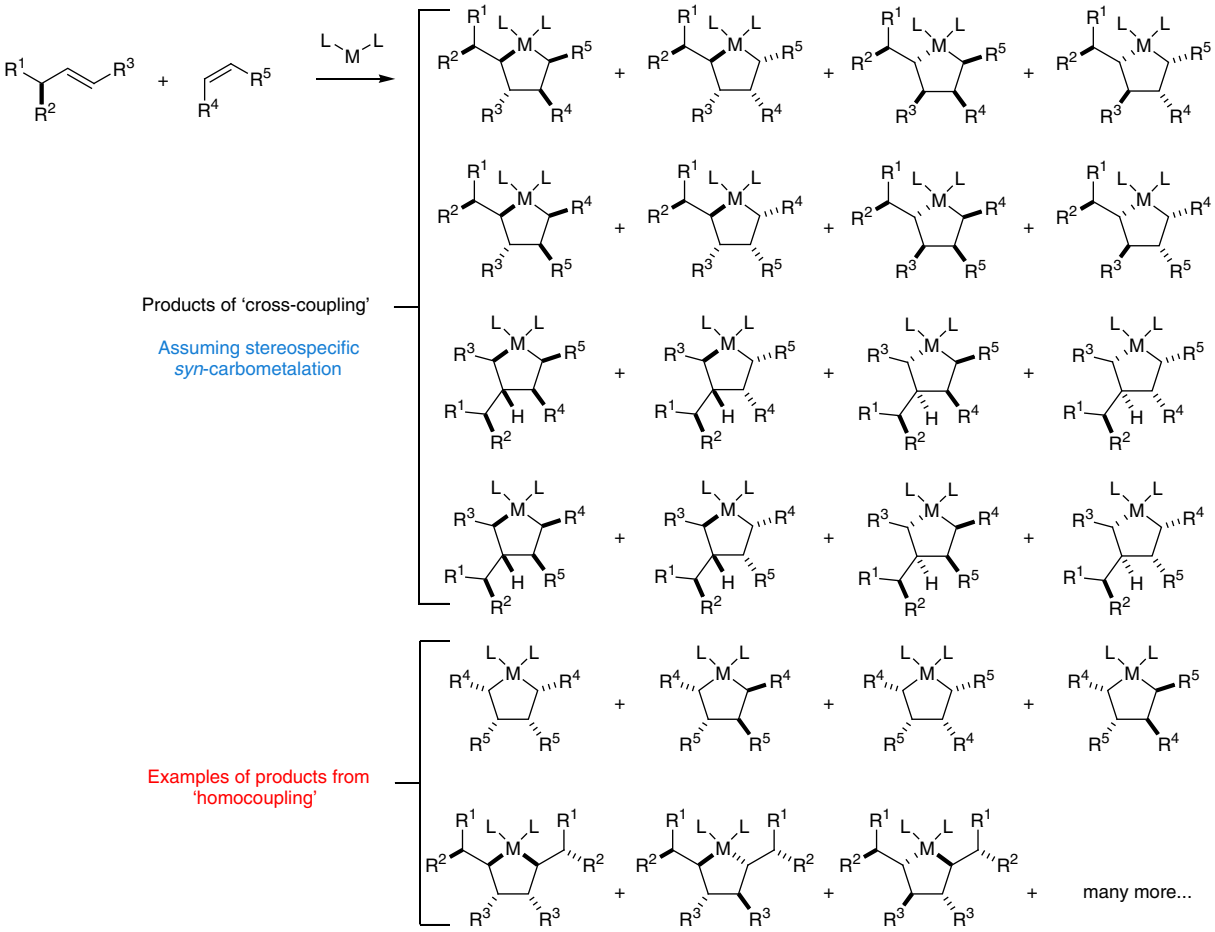
B. The challenge associated with control of regioselection in metallacycle-mediated cross-coupling.



C. The challenge associated with control of diastereoselection in metallacycle-mediated cross-coupling.



D. Combined challenges of pair selectivity, regioselectivity, and diastereoselectivity greatly complicate metallacycle-mediated cross-coupling.



Scheme 34

5.34.3.2.1 Alkyne–aldehyde and alkyne–ketone coupling

5.34.3.2.1.1 Control of regioselection

As illustrated in Scheme 35, it is often challenging to achieve regioselection in metallacycle-mediated coupling reactions of unsymmetrical alkynes with carbonyl systems. To date, factors that are known to influence the regiochemical course of C–C bond formation include alkyne substitution, nature of the electrophile, and solvent.[20,91,92] Moderate selectivity has been observed in coupling reactions of aromatic alkynes, propargylic ethers, and alkynoates – the major product of coupling reactions with such systems is derived from C–C bond formation α to these groups. With TMS-substituted alkynes, C–C bond formation occurs preferentially at the site distal to the TMS group. Here, it is clear to see that the degree of regioselection in these coupling reactions is also a factor of the nature of the electrophile (highest regioselection is observed with ketones). Finally, when the alkyne-coupling partner possesses a TMS group in combination with another 'directing' group that reinforces the selectivity imparted by the silyl substituent (i.e., propargylic ether or ester), very high levels of regiochemical control are observed.

While documenting the ability to accomplish alkyne–aldehyde and alkyne–ketone coupling chemistry under simple and straightforward reaction conditions, these early reports defined the substantial challenge that surfaces with respect to regioselectivity in metallacycle-mediated cross-coupling reactions of unsymmetrical alkynes. Notably, not even being concerned yet with absolute or relative stereochemistry, or having to worry about regioselectivity with respect to the carbonyl π-system (C–C bond formation is uniformly favored over C–O bond formation), the difficulties associated with controlling regiochemistry with respect to the alkyne-coupling partner relegates the synthetic utility of this coupling reaction to a small substrate scope.

5.34.3.2.1.2 Development of heteroatom-directed alkyne–aldehyde-coupling chemistry

Aiming to establish the utility of Ti-mediated alkyne–aldehyde-coupling chemistry in polyketide synthesis, a new strategy for the control of regioselection in this subclass of metallacycle-mediated cross-coupling has been advanced. As illustrated in Scheme 36A, coupling reactions of fully protected branched alkynes with chiral aldehydes typically proceeds with low levels of regioselectivity, despite the significant difference in steric character of the alkyne substituents (Me- vs. branched alkyl).[89,93] As summarized in Scheme 36B, when the distal hydroxyl group is unprotected (a tris-homopropargylic alcohol), these coupling reactions uniformly proceed with much higher levels of regiochemical control.

Although stereochemical features also clearly play a role in regioselectivity, these results are consistent with an empirical model based on site-selective reaction of a fused bicyclic metallacyclopropene with the aldehyde component (Scheme 37). Important structural features that impact regiochemical control in these processes include the branched architecture of the side chain and the precise location of the free hydroxyl. For example, substrates of similar composition to that depicted in Scheme 37, but lacking the substantial branching of the side chain do not couple with high levels of regiochemical control. In addition, if the free hydroxy group is located at the homopropargylic position (rather than the tris-homopropargylic position), regioselectivity is uniformly compromised.

Although not without significant limitations, including relatively low diastereoselection, this hydroxyl-directed approach to alkyne–aldehyde coupling makes possible the use of metallacycle-mediated cross-coupling for the assembly of complex unsaturated polypropionates. Before this development, directing groups of the nature depicted in Scheme 35 were an absolute requirement for controlling site selectivity in alkyne–aldehyde-coupling chemistry.

5.34.3.2.1.3 Control of allylic alcohol stereochemistry

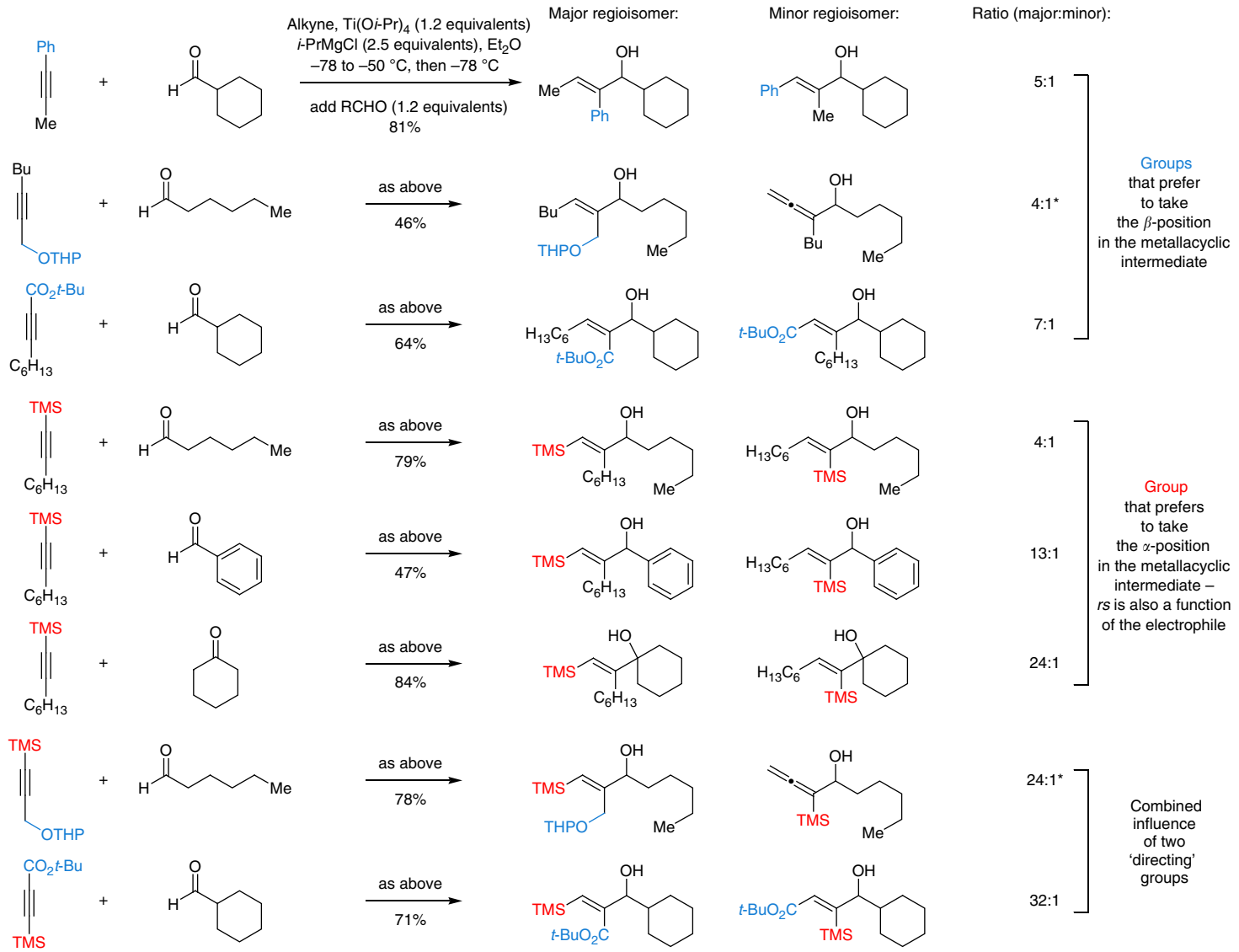
Two general strategies have been pursued to control the stereochemical course of metallacycle-mediated alkyne–aldehyde-coupling reactions. As illustrated in Scheme 38A, reagent control has been explored with chiral titanium alkoxides. Here, products are produced with relatively low levels of selectivity.[94] Alternatively, substrate control has been employed to control the stereochemical course of alkyne–aldehyde-coupling reactions.[92,95,96] Aldehydes and alkynes bearing chiral substituents have been shown to influence the stereochemical course of reductive coupling (Scheme 38B). With respect to the utility of these processes in target-oriented synthesis, note that all examples presented proceed with very high levels of regiochemical control as a result of the specialized alkyne substitution patterns employed.

5.34.3.2.2 Alkyne–imine and related coupling reactions

Preformed Ti–alkyne complexes have been demonstrated to be useful in a range of cross-coupling reactions with C=N systems. Interestingly, the regiochemical course of this coupling differs from that seen in the related coupling reactions of aldehydes. As illustrated in Scheme 39, coupling of phenyl propyne with a simple imine proceeds with very low levels of regiochemical control and favors the product possessing the Ph substituent at the alkenyl site distal to the amine (this is the minor isomer in the related coupling reaction with cyclohexane carboxaldehyde illustrated in Scheme 35). Of particular interest in chemical synthesis, this coupling process proceeds with exquisite levels of regiochemical control when TMS-alkynes are employed. Here, C–C bond formation occurs at the site of the alkyne distal to the TMS group (minor isomers were not reported; a similar sense of regiochemical control has also been observed with alkynylphoshponates).[97] Notably, the Ti-promoted coupling reaction also proceeds with ketimines and hydrazones.

Ti-promoted alkyne–imine coupling has been employed as a key convergent step in the synthesis of lactams and pyrroles. As illustrated in Scheme 40, treatment of the intermediate azametallacyclopentene with CO results in the formation of pyrroles, whereas exposure to CO_2 delivers substituted α,β-unsaturated γ-lactams.[98,99] Notably, regioselectivity in these processes is achieved by the use of a TMS-alkyne.

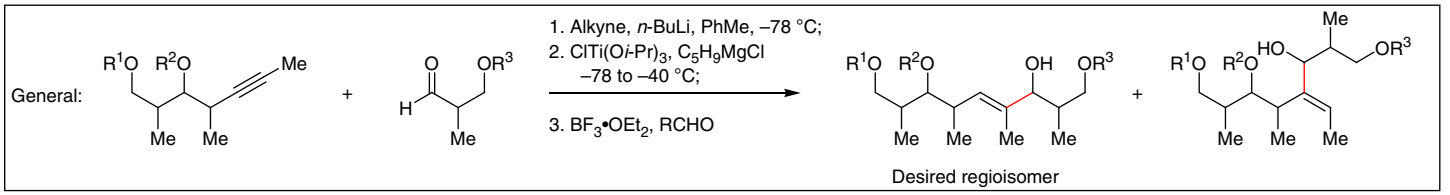
Alkyne–aldehyde coupling mediated by Ti-alkoxides: Control of regiochemistry with Ph, CH_2OR, TMS, and CO_2R substituents.

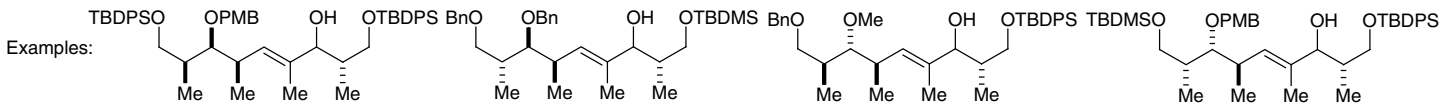


R = group that prefers to be at the α-position of the oxametallacyclopentene intermediate.
R = group that prefers to be at the β-position of the oxametallacyclopentene intermediate.
*Minor product is derived from an elimination reaction in the minor regiosomeric oxametallacyclopentene intermediate.

Scheme 35

A. Alkyne–aldehyde coupling for convergent assembly of polypropionates: Steric differentiation of alkyne substituents is insufficient to uniformly achieve high levels of regiochemical control. TBDPS, *t*-butyldiphenylsilyl.





42%*
rs = 1.3:1

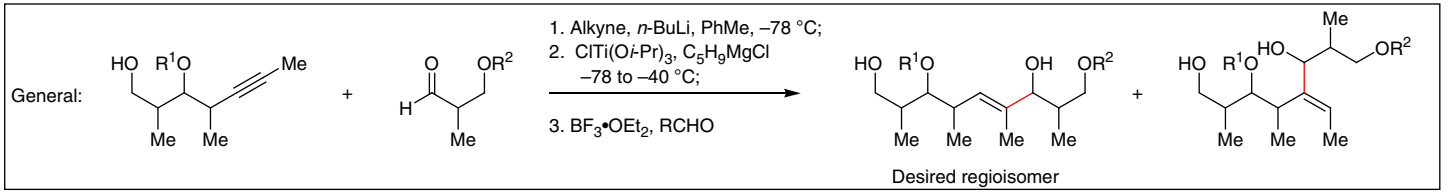
59%*
rs = 4:1

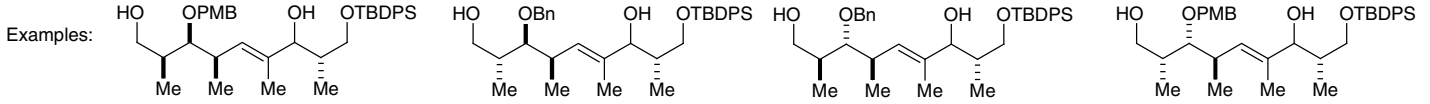
64%*
rs = 12:1

61%*
rs = 2:1

*Yield reported is for the major product (shown)

B. Alkyne–aldehyde coupling for convergent assembly of polypropionates: Hydroxyl directing group controls regioselection in these complex alkyne–aldehyde coupling reactions.





65%*
rs = 8:1

78%*
rs = 18:1

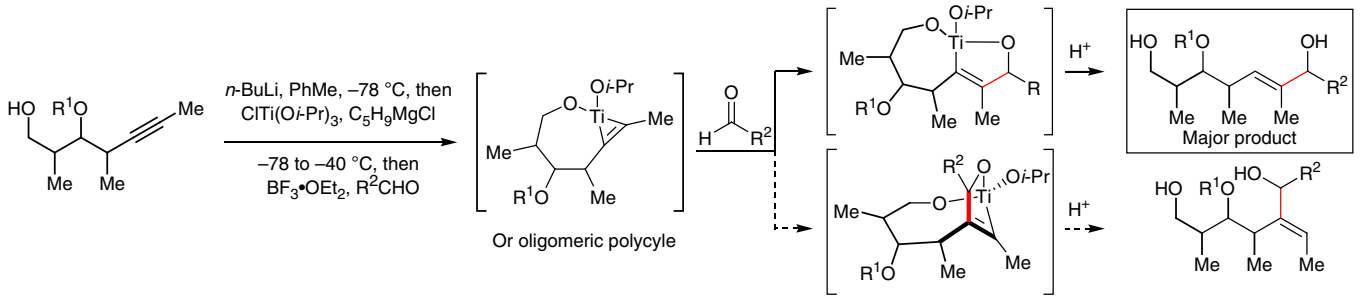
68%*
rs = 16:1

69%*
rs = 20:1

*Yield reported is for the major product (shown)

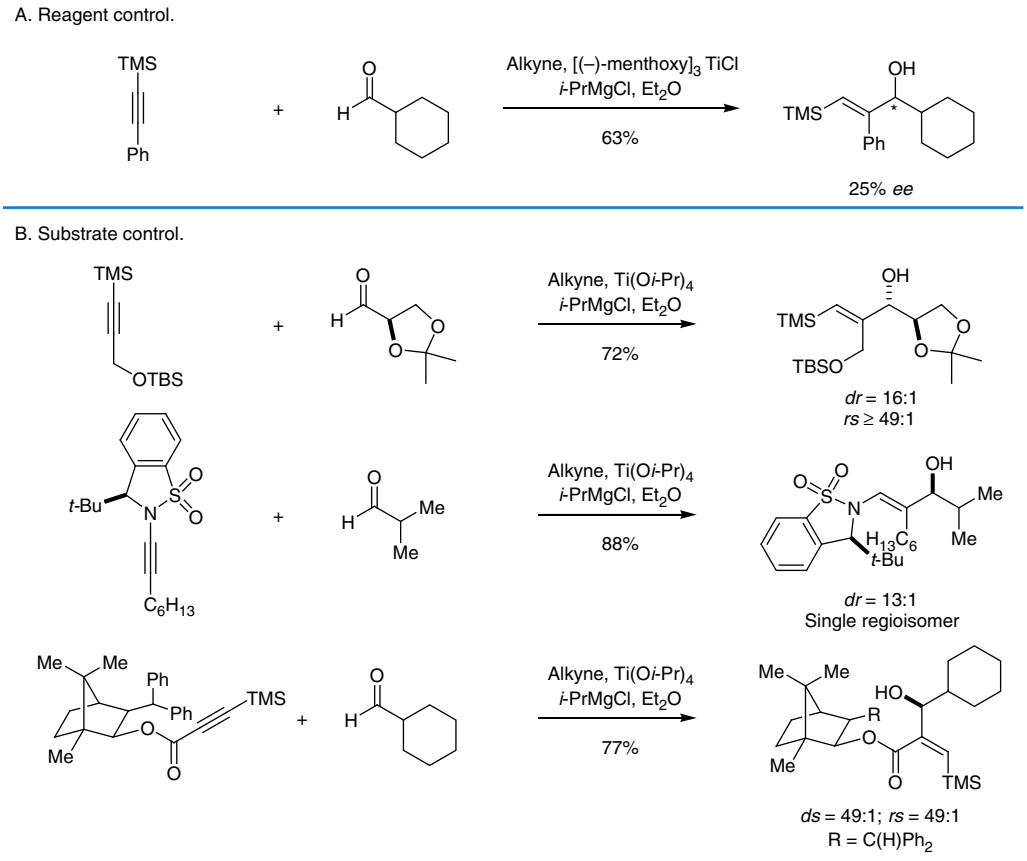
Scheme 36

Hydroxyl-directed alkyne–aldehyde coupling:



Limitations: 1. The branched polypropionate backbone is required for this regioselective alkyne–aldehyde coupling.
2. Regioselectivity is compromized if the free hydroxy group is located at the homopropargylic position.
3. Diastereoselectivity is often low (≤ 3:1), with the Felkin product predominating.

Scheme 37



Scheme 38

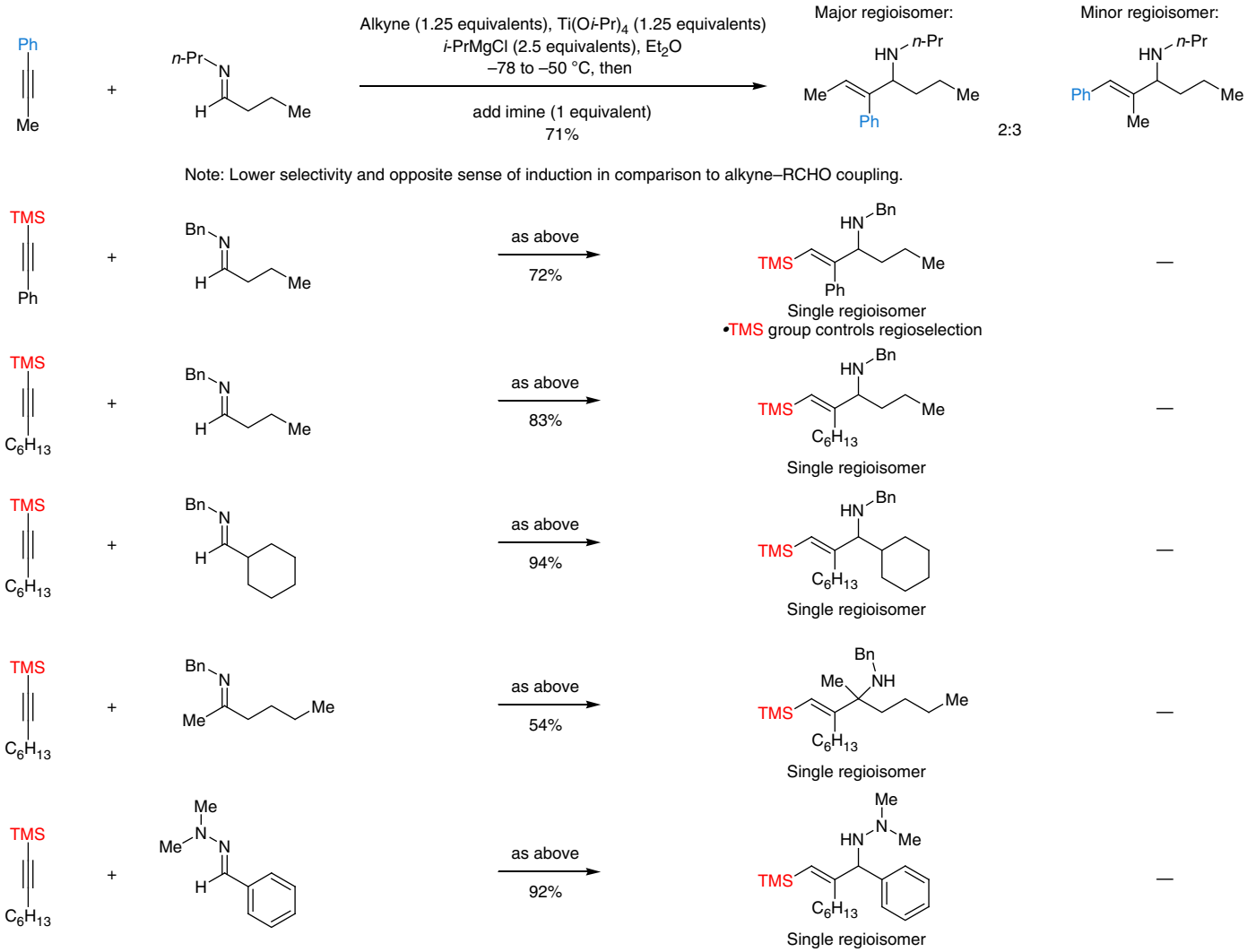
5.34.3.2.3 Alkyne–nitrile coupling

Building on the observations that $(RO)_2Ti$–alkyne complexes are effective nucleophilic species in addition reactions to aldehydes, ketones, imines, and hydrazones. It has recently been established that these species are also effective in coupling reactions with a subset of nitriles.[100] Although simple alkanenitrile or benzonitrile species are not viable substrates for this process, α-alkoxy, α-silyloxy, and α-chloro nitriles appear to be generally useful coupling partners en route to substituted azatitanacyclopentadienes (Scheme 41). In the first example depicted in Scheme 41A, addition of a sulfonylacetylene to an intermediate azatitanacyclopentadiene results in an annulation reaction that delivers a metallated pyridine intermediate. Quenching of this species with I_2 then delivers the tetrasubstituted pyridine as a single regioisomer in 50% yield. Regioselectivity in this complex coupling process deserves further comment. As in previous examples discussed, the use of silyl-substituted alkynes is important for regiochemical control in the first coupling process en route to the azametallacyclopentadiene intermediate. Subsequent reaction with the sulfonylacetylene also proceeds in a regioselective fashion, with C–N bond formation occurring at the carbon containing the sulfonyl group.

As illustrated in Scheme 41B and C, alternative pathways for functionalizing the azametallacyclopentadiene intermediates afford other aromatic heterocycles. In Scheme 41B, aldehyde addition followed by treatment with 1N HCl results in hydrolysis, intramolecular cyclization, and aromatization. Similarly, as illustrated in Scheme 41C, addition of a second α-alkoxy nitrile results in C–C bond formation, and subsequent treatment with 1N HCl results in hydrolysis and selective ring closure to generate the tetrasubstituted pyrrole. Here, the first C–C bond-forming process appears to proceed in a highly regioselective manner, with C–C bond formation occurring at the carbon possessing the aryl substituent. This observation is interesting, as aryl-substituted alkynes lacking another directing group (i.e., TMS) do not couple to aldehydes or imines in a highly regioselective manner. Next, ring closure proceeds through selective processing of a bis-imine intermediate – the major product being derived from selective enolization of the imine lacking an α-branch.

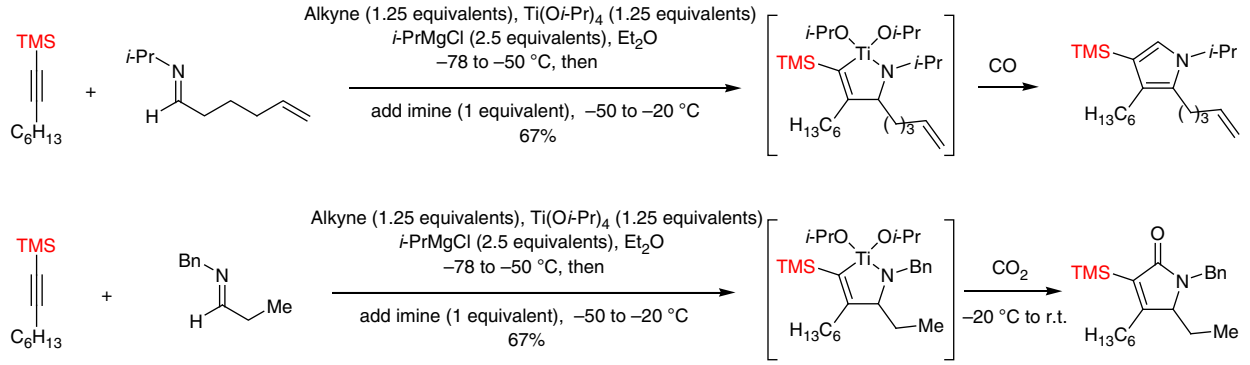
Overall, alkyne–nitrile cross-coupling chemistry has been described as a strategy to generate azametallacyclopentadienes, and these intermediates have been advanced to pyridines, furans, and pyrroles. Despite these interesting observations that define convergent solutions to heterocycle synthesis, this collection of coupling reactions remains limited by (1) the requirement of TMS- or Ar-substituted alkynes to control regioselectivity and (2) the use of α-heteroatom-substituted nitriles.

Alkyne–imine and related coupling mediated by Ti-alkoxides: Control of regiochemistry with TMS-alkynes.



Scheme 39

Heterocycle synthesis from alkyne–imine cross-coupling.



Scheme 40

5.34.3.3 Alkenes in Coupling Reactions with Carbonyl Systems

Early transition metal metallacycle-mediated cross-coupling between alkenes and aldehydes is a complex and challenging reaction. The primary problem derives from the inability to accomplish transfer epimetalation from $R_2Ti(Oi\text{-}Pr)_2$ to many alkene substrates of interest. Although such transfer epimetalation chemistry is possible in the Kulinkovich reaction (alkene + ester), where the generation of the alkene–Ti complex is accomplished in the presence of the ester acceptor, such is not feasible in related alkene–aldehyde-coupling processes due to the markedly enhanced electrophilicity of aldehydes in comparison to esters. Requiring that the alkene–Ti complex be generated before addition of the aldehyde-coupling partner defines the major challenge in accomplishing this subclass of metallacycle-mediated cross-coupling.

Two strategies have emerged to accomplish early transition metal metallacycle-mediated coupling between alkenes and aldehydes, each of which are significantly limited in substrate scope (Scheme 42A and B): (1) use of silylethylenes ($TMSCHCH_2$ or $ROMe_2SiCHCH_2$) as the alkene-coupling partner[101] and (2) generating a Ti–alkene complex from a 1,3-diene.[102]

Notably, in addition to the processes depicted in Scheme 42, a variety of alkene–aldehyde-coupling reactions have been accomplished through the defined intermediacy of an allyltitanium or allylzirconium species generated from an initial metal–alkene complex. These processes are outside of the scope of this chapter, as the process by which C–C bond formation ensues is from allyl transfer chemistry. Also, a few isolated examples of metallacycle-mediated cross-coupling of a terminal alkene with an *N*-acylpyrrole have been described, where the reaction is enabled by the presence of a free homoallylic alcohol.[103] The generality of this approach to preparing Ti–alkene complexes and the potential utility of this approach in accessing other metallacycle-mediated intermolecular C–C bond-forming processes with alkenes has not yet been established.

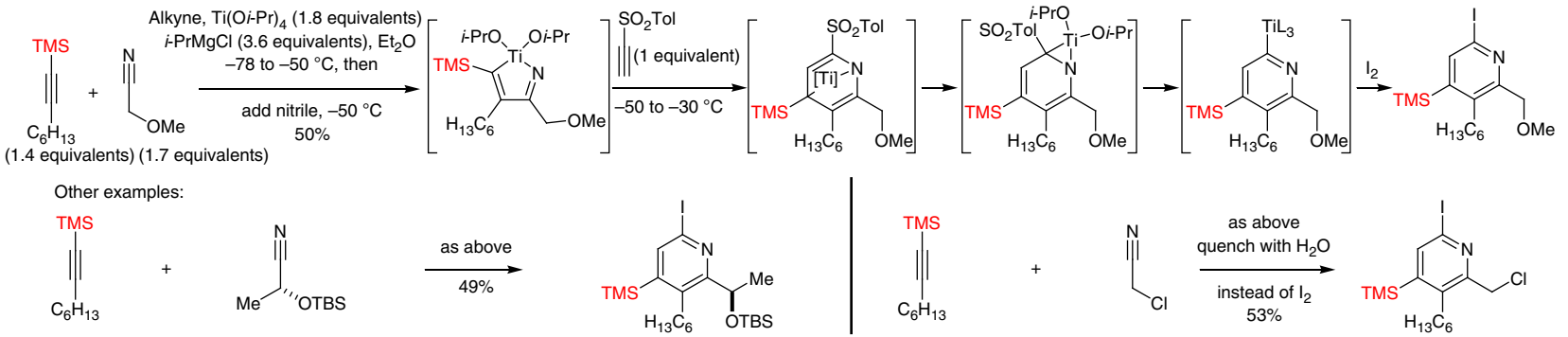
5.34.3.4 Alkyne–Alkyne Cross-Coupling

Early transition metal metallacycle-mediated alkyne–alkyne coupling defines a convenient, convergent, and stereospecific entry to substituted 1,3-dienes. Here, the challenge of regioselection is more complex than in the reactions described between alkynes and carbonyl compounds, as neither reactive π-system has an inherent electronic preference to control the regiochemical course of C–C bond formation. As such, coupling of two unsymmetrical alkynes can result in the generation of four different regioisomeric products (Scheme 34B). In Sections 5.34.3.4.1 and 5.34.3.4.2, below is a discussion of two different classes of alkyne-based coupling processes that are distinguished by the substitution of the alkynes. Coupling reactions that engage terminal alkynes are discussed first and are followed by the more demanding coupling reactions between two internal alkynes.

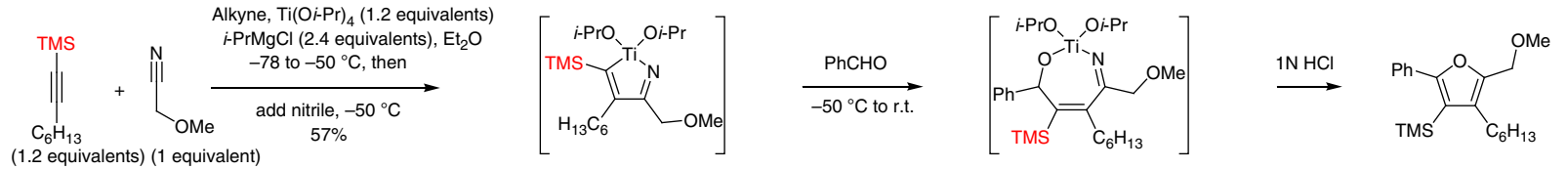
5.34.3.4.1 Internal alkyne + terminal alkyne

Ti-alkoxides have been found to be suitable reagent precursors to accomplish cross-coupling reactions between internal alkynes and terminal alkynes (Scheme 43).[104] In short, exposure of an internal alkyne to the combination of $Ti(Oi\text{-}Pr)_4/2i\text{-}PrMgCl$ results in the *in situ* generation of a Ti–alkyne complex. Addition of a terminal alkyne then results in intermolecular carbometalation en route to a metallacyclopentadiene, protonation of which furnishes stereodefined 1,3-dienes. Although four regioisomeric products are possible in this coupling process, it has been shown that terminal alkynes react in a regioselective fashion to favor the formation of intermediate 2,3,5-trisubstituted titanacyclopentadienes. As such, the challenge of controlling the course of this coupling process boils down to simply controlling regioselection in the functionalization of the internal alkyne (i.e., C–C bond formation α- to R^1 or R^2).

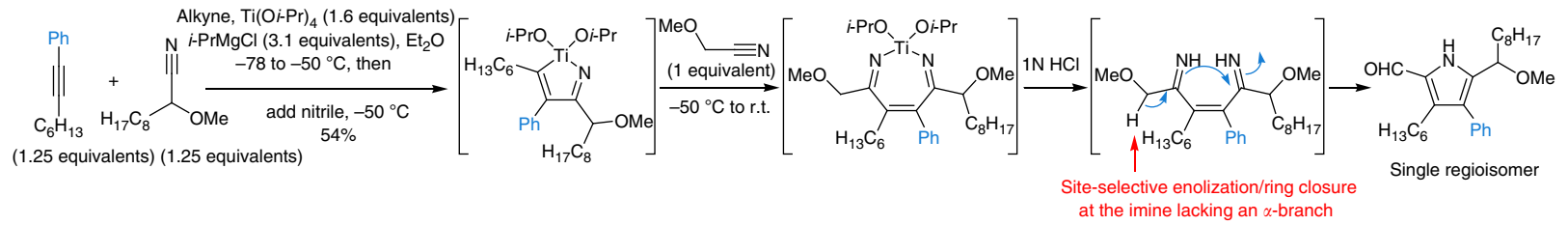
A. Alkyne–nitrile cross-coupling/sulfonylacetylene addition: A convergent synthesis of substituted pyridines.



B. Alkyne–nitrile cross-coupling/aldehyde addition/cyclization: A convergent synthesis of substituted furans.

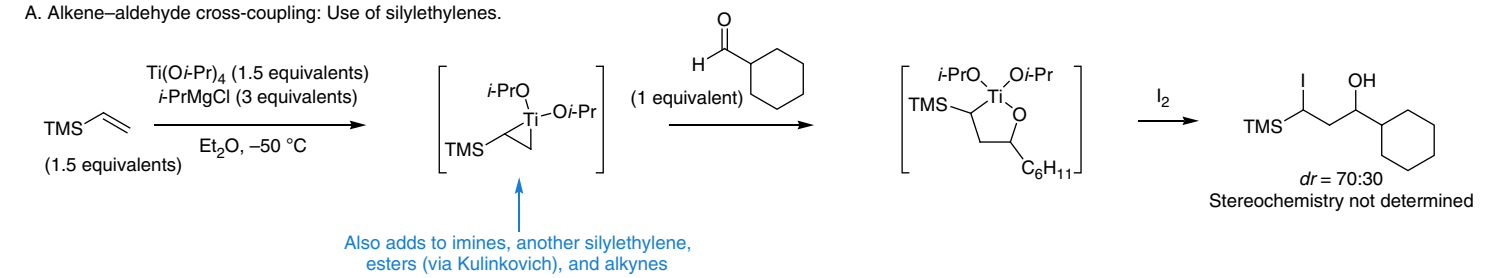


C. Alkyne–nitrile cross-coupling/nitrile addition/cyclization: A convergent synthesis of substituted pyrroles.

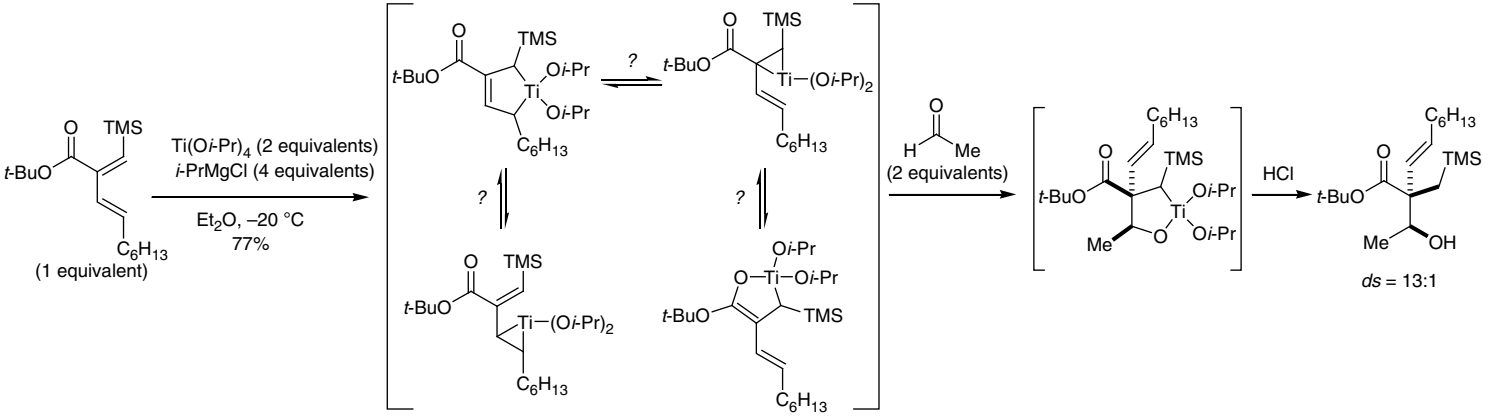


Scheme 41

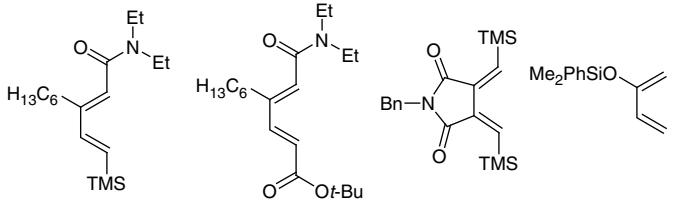
A. Alkene–aldehyde cross-coupling: Use of silylethylenes.



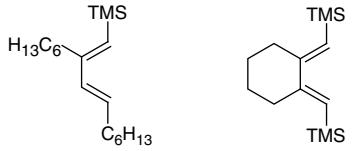
B. Alkyne–aldehyde cross-coupling via 1,3-diene–Ti complexes.



Substrates capable of forming a Ti–diene complex:

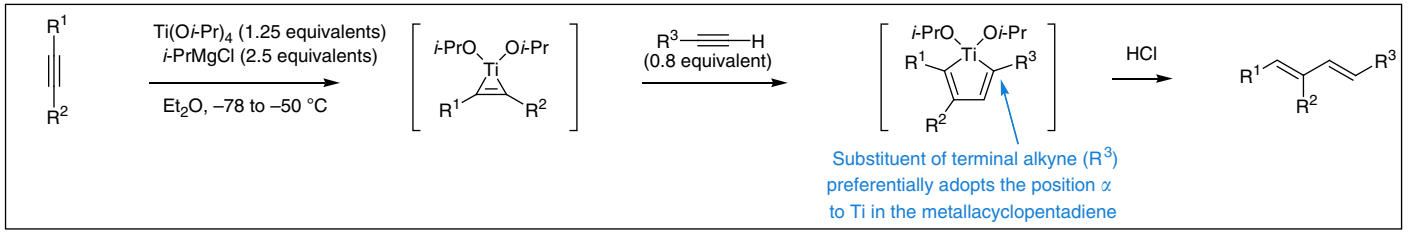


Substrates that were not capable of forming a Ti–diene complex:

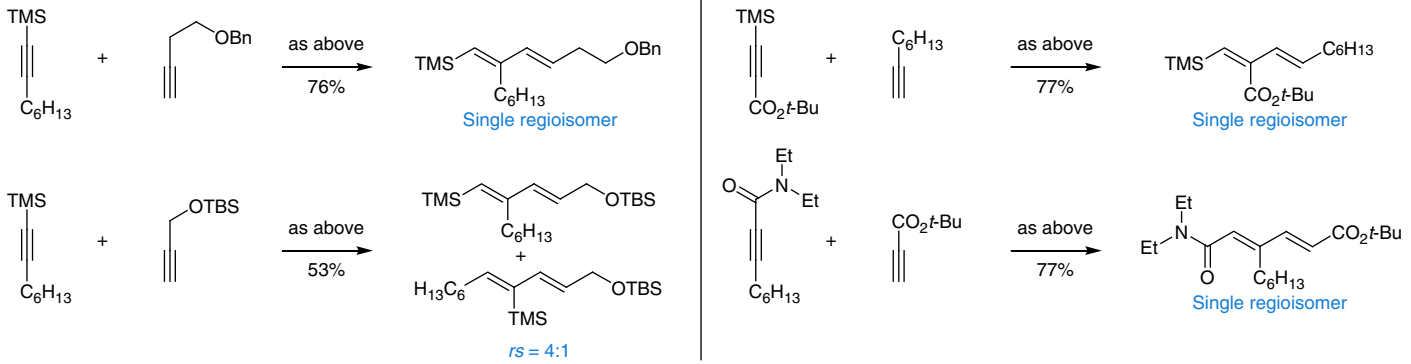


Scheme 42

A. Metallacycle-mediated cross-coupling of internal alkynes with terminal alkynes: Access to trisubstituted 1,3-dienes.



Examples:

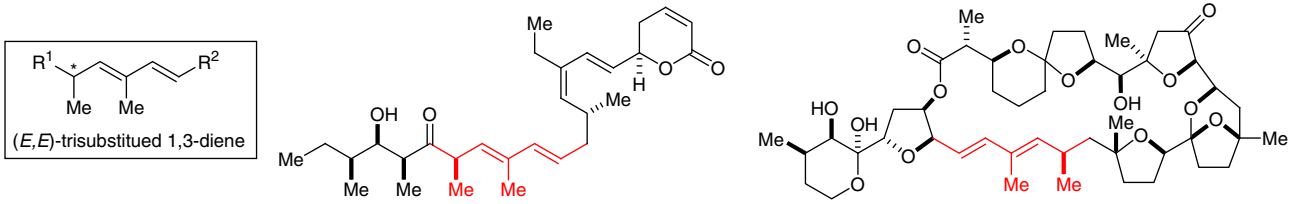


B. Structural features of the disubstituted alkyne required for high levels of regiochemical control.

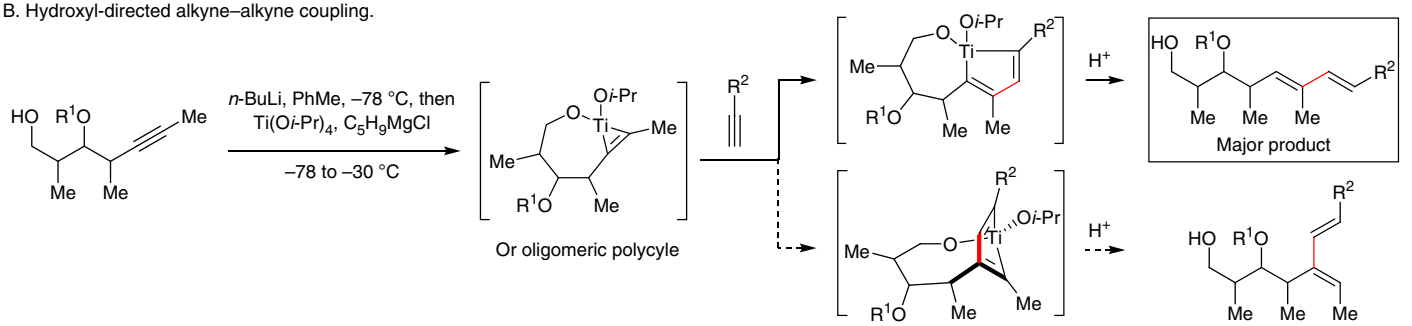


Scheme 43

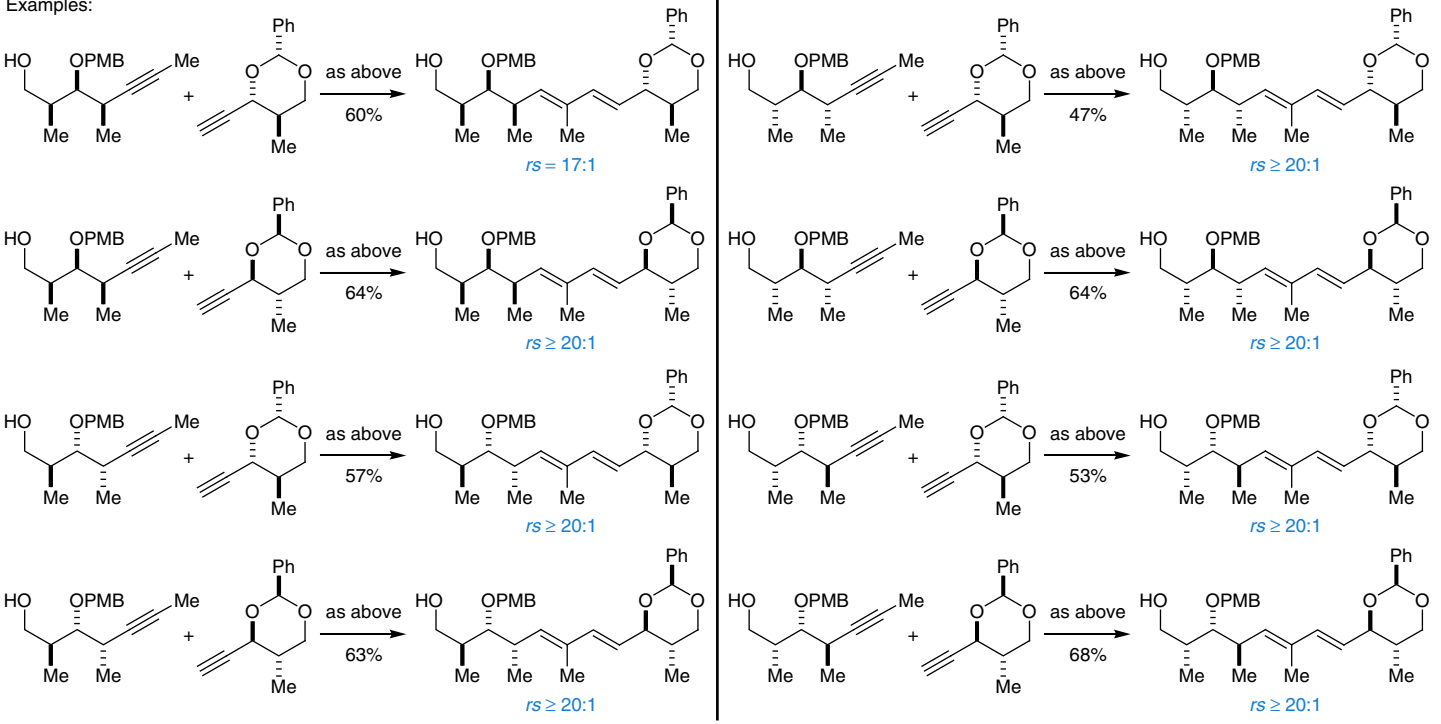
A. (*E,E*)-trisubstituted 1,3-dienes in polypropionate-containing natural products.



B. Hydroxyl-directed alkyne–alkyne coupling.



Examples:



Scheme 44

As illustrated in Scheme 43A, a variety of coupling reactions in this class have been demonstrated that proceed with regiochemical control. That said, the structural features required to achieve high levels of regioselection limit the utility of this bond construction to a relatively small subset of coupling partners (Scheme 43B).

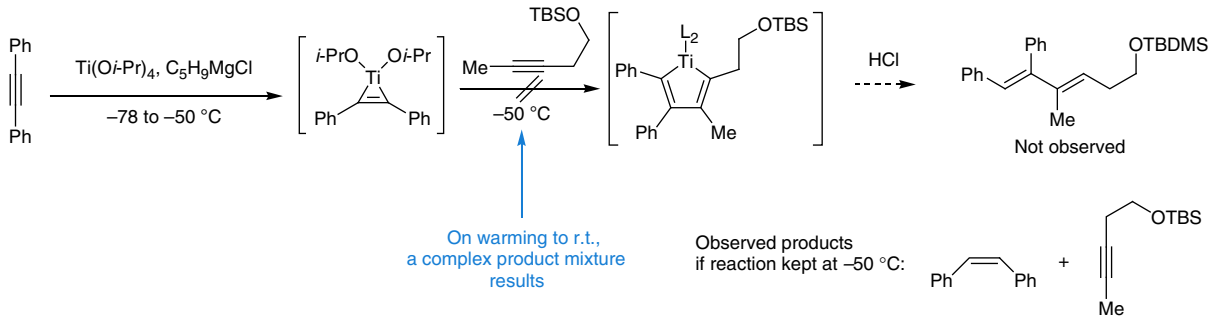
In efforts targeting the convergent synthesis of polyunsaturated polypropionate-derived natural products (Scheme 44A), hydroxyl-group direction has proven to be an effective alternative means of controlling the regiochemical course of this coupling reaction (Scheme 44B). As observed in the related hydroxyl-directed reductive cross-coupling between alkynes and aldehydes, regioselection is uniformly high with substrates possessing a tris-homopropargylic hydroxyl-directing group ($rs \geq 17{:}1$). Studies have shown that if the hydroxy-directing group is relocated to the homopropargylic position, or if there is no hydroxyl-directing group available, selectivity drops (substantially in some cases).[105] Overall, the broad utility of this directing group strategy has not been explored outside of polypropionate assembly. As such, it is not yet clear if this strategy will be useful for regioselective cross-coupling reactions of less substituted substrates. That said, this hydroxyl-directing group strategy has defined a new class of alkynes as useful coupling partners in metallacycle-mediated cross-coupling and has established a useful bond construction for natural product synthesis.[89,106,107]

Although modern Pd-catalyzed cross-coupling chemistry is routinely embraced to access stereodefined 1,3-dienes in a convergent manner, it is important to note that such methods require the use of coupling partners with stereodefined vinyl halides and vinyl organometallics to setup the Pd-catalyzed coupling process. In comparison, this Ti-mediated coupling process employs stereo-undefined π-systems (alkynes) and proceeds through a process that simultaneously establishes the central C–C bond of the diene in concert with securing the stereochemistry of each alkene.

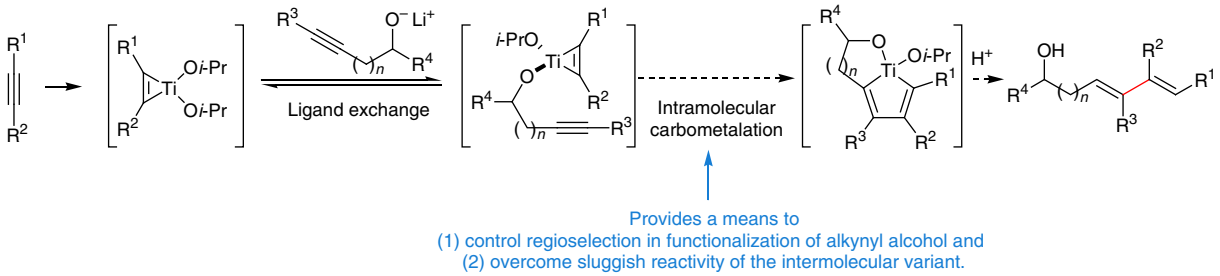
5.34.3.4.2 Internal alkyne + internal alkyne

Although it has long been established that preformed early transition metal–alkyne complexes can add across terminal alkynes to generate trisubstituted 1,3-dienes, the related addition reaction to internal alkynes represents a much more challenging process. Not only more complex due to the aforementioned problems associated with the control of regioselection (i.e., Scheme 34B), this class of cross-coupling has proven difficult to accomplish with internal alkynes as a result of their decreased reactivity in carbometalation reactions with preformed metal–π complexes (Scheme 45A). Illustrated in Scheme 45B, a different hydroxyl-directing group strategy has been established to achieve suitable reactivity, whereas also providing a means to control regioselection in this class of early transition metal metallacycle-mediated cross-coupling reaction.[108] Distinct from the substrate-directing group strategies described previously (for the coupling of internal alkynes with aldehydes or for the coupling of internal alkynes with terminal alkynes), a unique hydroxyl-directing group strategy is employed here to render the carbometalation event intramolecular.

A. Low levels of reactivity broadly constrain the potential utility of early transition metal metallacycle-mediated cross-coupling between internal alkynes.



B. A different hydroxyl-directing strategy to enable cross-coupling between internal alkynes.

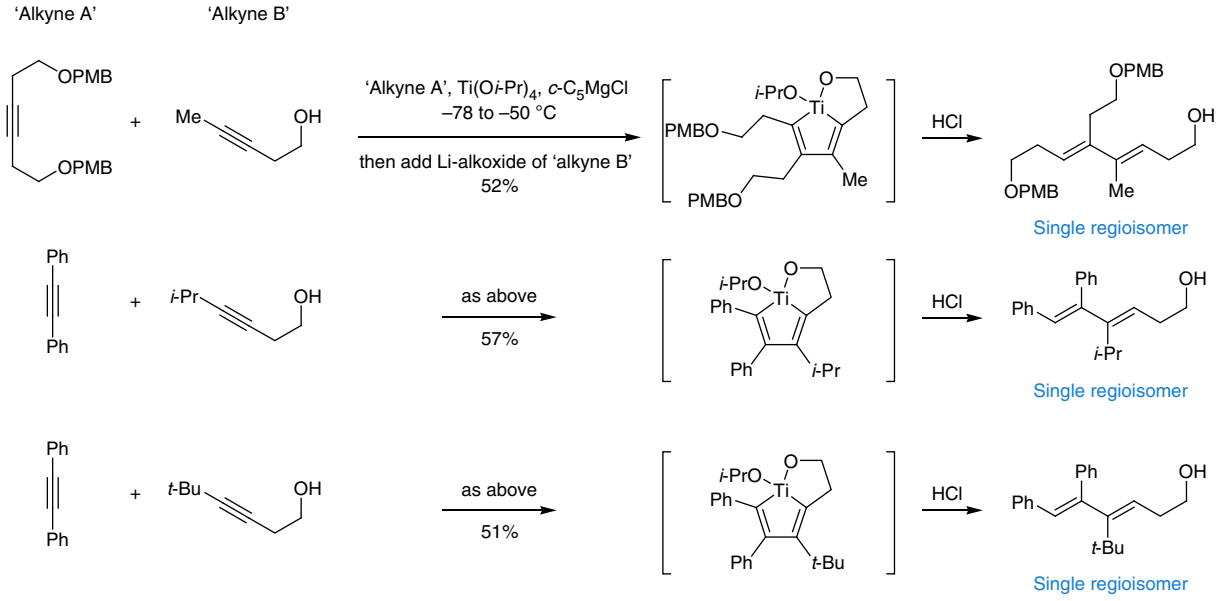


Scheme 45

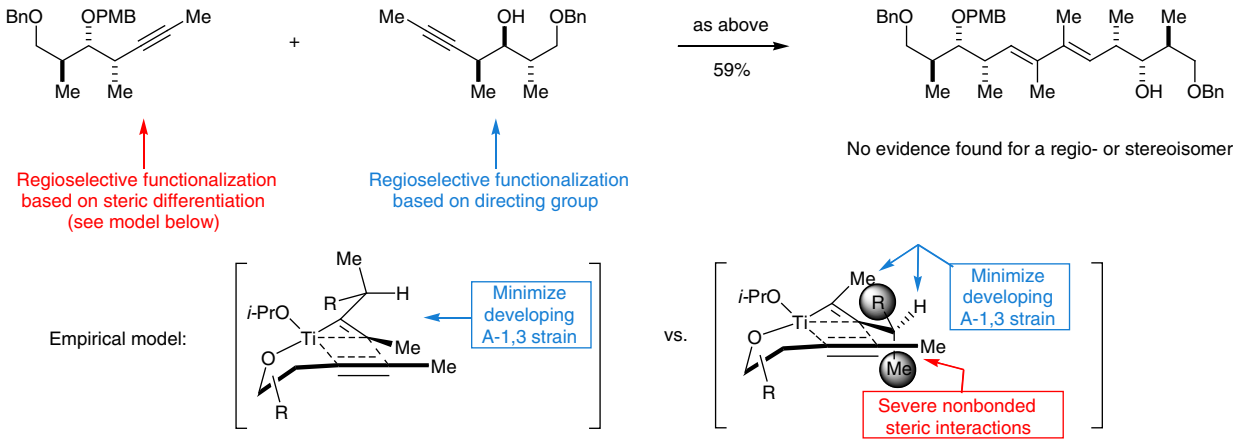
As illustrated in Scheme 46A, hydroxyl-directed titanium-mediated reductive cross-coupling reactions of internal alkynes proceed in a highly regioselective manner. Early examples employed one symmetrical alkyne ('alkyne A'), so that regioselection could easily be assessed for the functionalization of the alkynyl alcohol component ('alkyne B'). In all cases explored to date, C–C bond formation occurs distal to the hydroxyl-directing group, consistent with the proposed intermediacy of fused bicyclic metallacyclopentadienes.

This directing group strategy has been employed as a strategy to accomplish highly regioselective reductive cross-coupling between two unsymmetrically substituted internal alkynes (Scheme 46B). Although regioselective functionalization of the alkynyl alcohol substrate occurs as anticipated based on the results summarized in Scheme 46A, functionalization of the sterically differentiated alkyne also proceeds with exquisite levels of regiochemical control. This is in contrast to previous studies that document the often inferior levels of regioselection observed in coupling reactions of such alkynes with aldehydes and terminal alkynes. It has been speculated that coupling reactions of the sort depicted in Scheme 46 likely proceed by a later transition state than previously discussed coupling reactions with aldehydes and terminal alkynes and, as such, the steric differences of the alkyne substituents play a more substantial role in dictating the regiochemical course of C–C bond formation. In short, as the transition state shifts to resemble the product, the Ti–alkyne complex appears more alkene like. Therefore, minimization of A-1,3 strain results in gearing of the propargylic substituents such that carbometalation is favored from proximal to the small Me-substituent (Scheme 46B).

A. Hydroxyl-directed Ti-mediated reductive cross-coupling reactions between internal alkynes: Simple coupling reactions.



B. Hydroxyl-directed cross-coupling of two unsymmetrical internal alkynes: Control of regioselection with respect to each alkyne.



Scheme 46

5.34.3.5 Alkyne–Alkene Cross-Coupling

Metallacycle-mediated cross-coupling of alkynes with alkenes represents a significantly more challenging process than alkyne–alkyne coupling. In addition to the established difficulties associated with engaging a substituted alkene in metallacycle-mediated coupling chemistry (due to low levels of reactivity and potential reversibility of carbometalation), synthetically useful reactions in this class must also address regio- and stereoselection (Scheme 34B and C). Since 1991, reactions have emerged for alkyne–alkene coupling that proceed by treatment of preformed metal–alkyne complexes with alkenes. Many of these are substantially restricted in scope based on challenges controlling regioselection and issues relating to low reactivity (restricted to unhindered terminal alkenes).[101,109–111] These contributions will not be discussed here, rather the focus of this section is on advances that offer fine control over regio- and stereoselection, while providing a means to employ 1,2-disubstituted alkenes in this class of metallacycle-mediated cross-coupling.

5.34.3.5.1 Simple directed carbometalation

Representing an adoption of the general strategy described to control reductive cross-coupling of two internal alkynes, Scheme 47A depicts a hydroxyl-directed approach to controlling the course of alkene–alkyne-coupling chemistry. Here, preformation of a monocyclic metal–alkyne complex is followed by introduction of an unsaturated alkoxide. Rapid and reversible ligand exchange provides access to a transient intermediate capable of undergoing intramolecular carbometalation. If the intermediate metallacyclopentene is stable under the reaction conditions (i.e., previous studies of early transition metal complexes of this nature support the ability of such species to undergo cycloreversion with expulsion of the alkene and regeneration of a Ti–alkyne complex), then protonation would deliver the olefinic product in a regioselective fashion.

As illustrated in Scheme 47B, this approach to controlling the course of metallacycle-mediated cross-coupling is quite effective in realizing highly selective alkyne–alkene-coupling reactions.[90,112] In the first case depicted, one can see that the hydroxymethyl substituent on the cyclohexene offers a means to control both the regio- and stereochemical course of cross-coupling. Here, C–C bond formation occurs distal to the hydroxymethyl group, with complete control of stereoselection (C–C bond formation occurs on the same face of the cyclohexene as the directing group). Moving on, this coupling process is effective for the union of two unsymmetrical systems. As previously seen in Scheme 46B, steric differentiation of the alkyne component defines an effective means for controlling regioselection with respect to its functionalization. Similarly, use of homoallylic alcohols that react by way of a stereochemically biased pathway (as a result of the minimization of A-1,3 strain) in reactions with preformed Ti–alkyne complexes define extremely complex and unique convergent coupling reactions. Overall, this metallacycle-mediated alkene –alkyne coupling proceeds with complete regiochemical control with respect to the functionalization of each π-component, whereas also occurring with complete stereochemical control.

The realization of a highly selective alkene–alkyne cross-coupling process represents a significant advance in this broad area of chemical reactivity. Now, it is becoming evident that metallacycle-mediated cross-coupling can be designed to occur in a highly controlled fashion, offering convergent bond-forming processes unavailable with other modes of chemical reactivity (this particular bond construction has recently been described as a key convergent step in the synthesis of densely functionalized spiroketals).[113] That said, this early demonstration marked only the beginning of advances that have recently emerged in metallacycle-mediated reductive cross-coupling chemistry that have defined a broad collection of powerful and unique coupling reactions suitable for stereoselective synthesis.

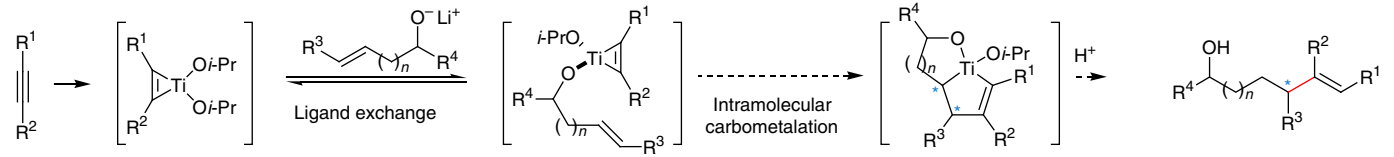
5.34.3.5.2 Coupling via formal metallo[3,3] rearrangement

A variety of reports have appeared that describe the utility of early transition metal metallacycle-mediated coupling for the union of alkynes with allylic electrophiles (Scheme 48A). Formation of a metallacyclopentene is followed by elimination to deliver a vinyl organometallic intermediate which, after exposure to a protic acid, is converted to a 1,4-diene product. Although this process has been demonstrated to be useful for addition of a C_3-unit to an alkyne, where issues regarding stereoselection are absent,[27,114,115] the class of cross-coupling has only recently been rendered stereoselective in reactions that employ highly substituted allylic alcohols.[116,117]

As illustrated in Scheme 48B, hydroxyl-directed cross-coupling provides a means to translate stereochemical information from the allylic alcohol starting material to the intermediate metallacyclopentene. Stereospecific elimination then parlays the stereochemistry of this intermediate to the stereochemistry of the functionalized 1,4-diene product. Overall, the sequence of bond-forming events in this hydroxyl-directed coupling process can be summarized as a formal metallo[3,3] rearrangement (Scheme 48C).

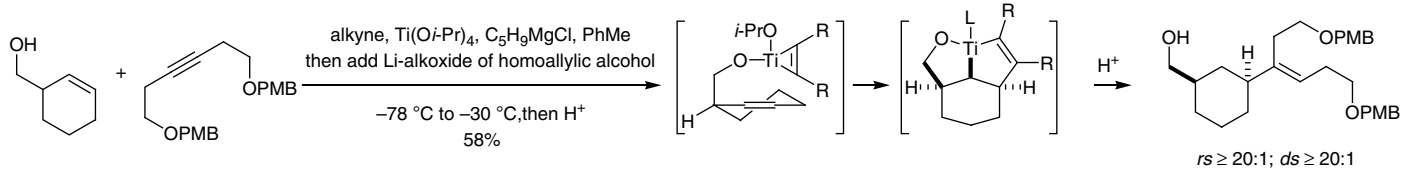
As depicted in Scheme 49A, Ti-mediated hydroxyl-directed coupling of allylic alcohols with alkynes proceeds in a regio- and stereoselective manner. C–C bond formation occurs with allylic transposition and in a suprafacial manner. Further study of this process in acyclic settings has led to the conclusion that one can achieve (*E*)- or (*Z*)-selective coupling reactions. For example, using an allylic alcohol with a (*Z*)-disubstituted alkene results in a stereoselective coupling reaction to deliver a product possessing an (*E*)-disubstituted alkene [(*E*):(*Z*) = 8:1]. Here, minimization of A-1,3 strain results in positioning the allylic substituent in the equatorial position during the carbometalation event. Subsequent *syn*-elimination and protonation delivers the 1,4-diene in 59% yield. Taking a step back to appreciate the complexity of this coupling reaction based on the previous discussion regarding the course of all metallacycle-mediated cross-coupling processes (i.e., Scheme 34), regioselection is controlled in the functionalization of each reaction component: (1) the allylic alcohol is employed to gain control over site-selective functionalization of the

A. Hydroxyl-directed strategy for early transition metal metallacycle-mediated alkyne–alkene coupling.

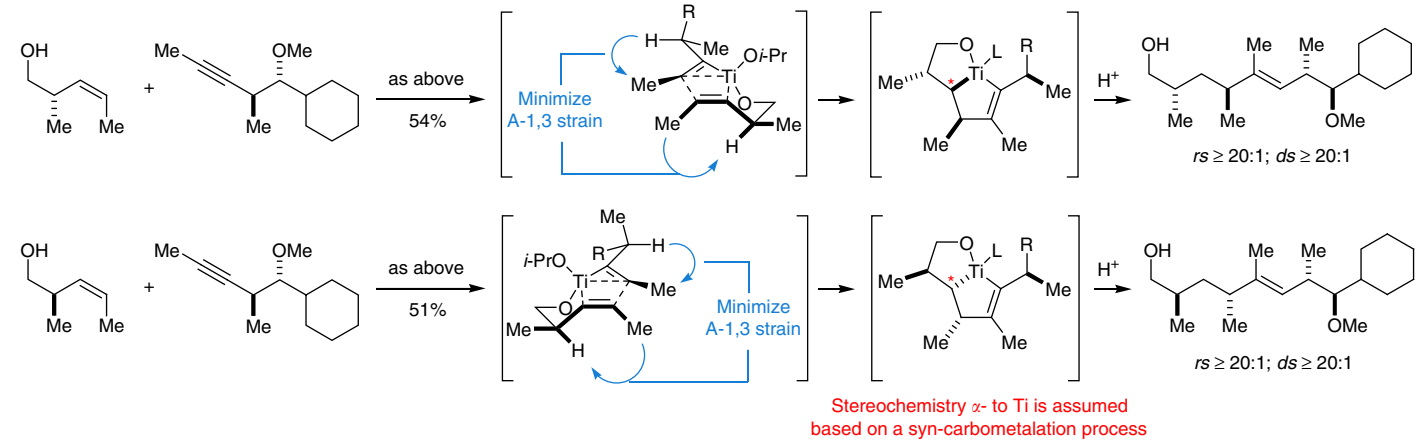


B. Examples of Ti-mediated hydroxyl-directed alkyne–alkene coupling chemistry.

Control of regio- and stereochemistry on the alkene component:

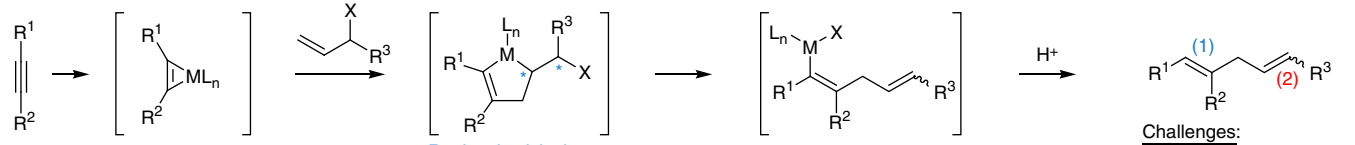


Control of regiochemistry with respect to both π-systems, with simultaneous control of stereochemistry during alkene functionalization:

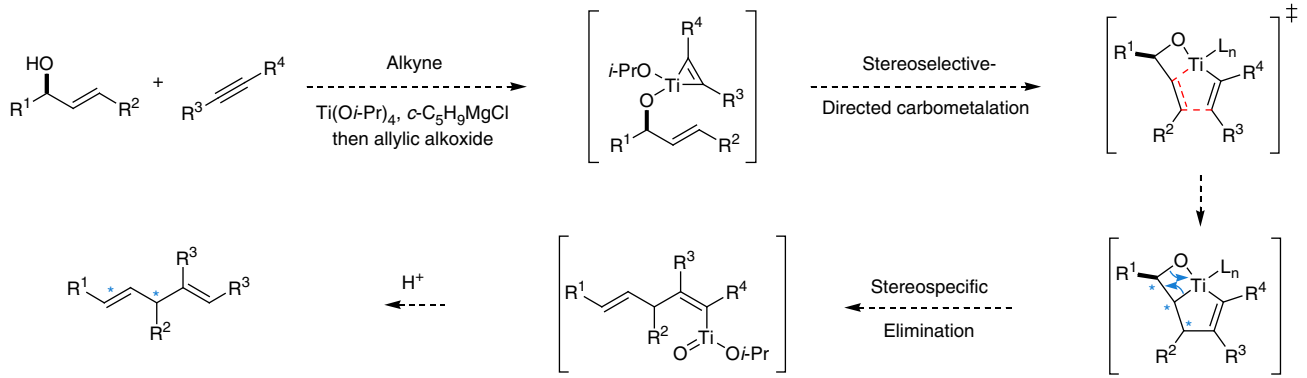


Scheme 47

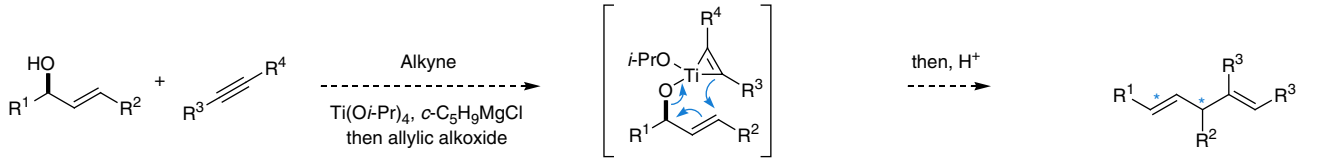
A. Metallacycle-mediated coupling of alkynes with allylic electrophiles: Access to 1,4-dienes.



B. Hydroxyl-directed coupling of allylic alcohols with alkynes: Stereoselective synthesis of 1,4-dienes.

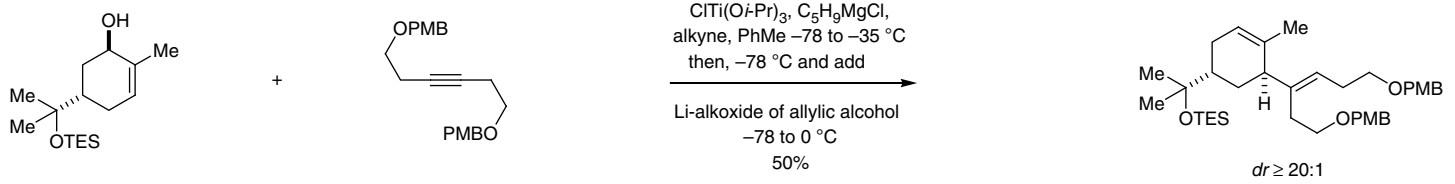


C. Sequence of bond-forming events can be summarized as a formal metallo[3,3] rearrangement.

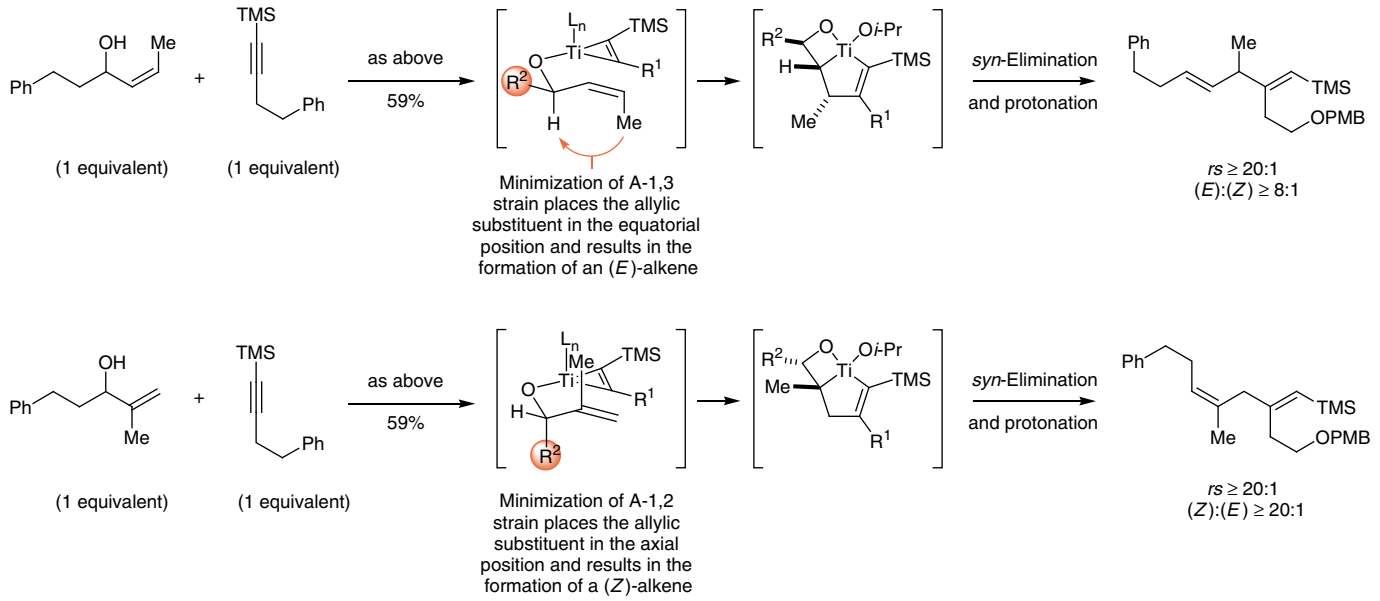


Scheme 48

A. C–C bond formation occurs in a suprafacial manner.



B. Stereochemical control is possible in an acyclic setting: Boat-like transition states and minimization of allylic strain defines a path to stereoselection.



Scheme 49

alkene and (2) a TMS group is employed to gain control over the regioselective functionalization of the alkyne. Next, minimization of nonbonded steric interactions in a boat-like transition state for carbometalation results in fine control over stereoselection. Note that a boat-like orientation is proposed based on two considerations: (1) requirement of an intramolecular carbometalation – docking of the allylic alcohol at Ti to enable an intramolecular pathway for carbometalation and (2) the stereoelectronic preferences for carbometalation – alignment of the σ_{Ti-C} bond with $\pi_{C=C}$.

To date, a limitation of this stereoselective coupling has been documented in acyclic settings where, without the substantial influence of A-1,3 or A-1,2 strain, the coupling of secondary allylic alcohols bearing terminal- or (*E*)-disubstituted alkenes does not proceed with significant levels of stereoselection. That said, this hydroxyl-directed allylic alcohol–alkyne-coupling reaction has already been demonstrated in a number of natural product syntheses. The first total synthesis and structure elucidation of phorbasin C was accomplished using a Ti-mediated allylic alcohol–alkyne-coupling reaction to establish the stereodefined carbocyclic core of the diterpene (**Scheme 50A**).[118] Interestingly, a second coupling process with the allylic alcohol product of this reaction was not observed. Presumably, the steric impediment introduced on the *β*-face (as drawn) is sufficient to dissuade a second C–C bond-forming process that would need to occur *syn*- to this substituent. Another application of this coupling reaction appeared in the first total synthesis of the marine-derived cytotoxic agent lehualide B (**Scheme 50B**).[119] Here, a late-stage Ti-mediated allylic alcohol–alkyne-coupling reaction was employed to establish the stereodefined skipped diene motif resident in the lipophilic tail of the natural product. Most recently, this class of metallacycle-mediated cross-coupling has been demonstrated to be of great utility for the stereoselective convergent synthesis of deoxypropionates. As illustrated in **Scheme 50C**, this process was employed in a total synthesis of the insect pheromone vittatalactone.[120]

5.34.3.6 Allene–Alkyne Cross-Coupling

Metallacycle-mediated union of allenes with alkynes is a complex problem owing not only to the different π-systems available on the allene, but also due to the now familiar challenge of addressing regioselection with respect to this π-component. As illustrated in **Scheme 51A**, a variety of metallacyclopentenes are possible from the coupling of a disubstituted allene with an alkyne. These species derive from reaction pathways that engage either π-system of the allene (termed π-system 'A' or 'B'), the regiochemical course of functionalization of that π-system, the stereochemical course of carbometalation (*syn*- or *anti*- to the distal allene substituent), and the regiochemical course of alkyne functionalization. Given this, it is not surprising that only a few examples of this type of coupling reaction have been described. Early cases include those depicted in **Scheme 51B**.[121] Even with these minimally substituted systems, it is apparent that the control of stereochemistry in this coupling reaction is quite complex. Although the simple silyl-substituted allene is the best substrate to enforce carbometalation *anti*- to the $PhMe_2Si$ substituent, even chelating substituents on the allene lead to unpredictable and uniformly low levels of stereoselection.

Hydroxyl-directed metallacycle-mediated coupling has emerged as a potentially useful means of controlling the course of allene–alkyne coupling.[122,123] As illustrated in **Scheme 52A**, coupling of allenes possessing simple 1,1-disubstitution with internal alkynes proceeds with very high levels of stereoselection (delivering products containing an *E*-trisubstituted alkene). That said, this class of coupling presents problems unlike any reaction class previously discussed. Although related coupling reactions that employ TMS-alkynes proceed with very high levels of regiochemical control, the allene–alkyne-coupling process does not proceed with similarly high levels of selectivity. For example, metallacycle-mediated cross-coupling of allenes with TMS-alkynes typically delivers a 4:1 mixture of regioisomeric products (the major product of which derives from C–C bond formation preferentially occurring *β*- to the TMS group). Similarly, sterically differentiated substrates (Me vs. branched alkyl) are also problematic in this coupling process (in the example shown, products are formed as 2:1 mixtures of regioisomers).

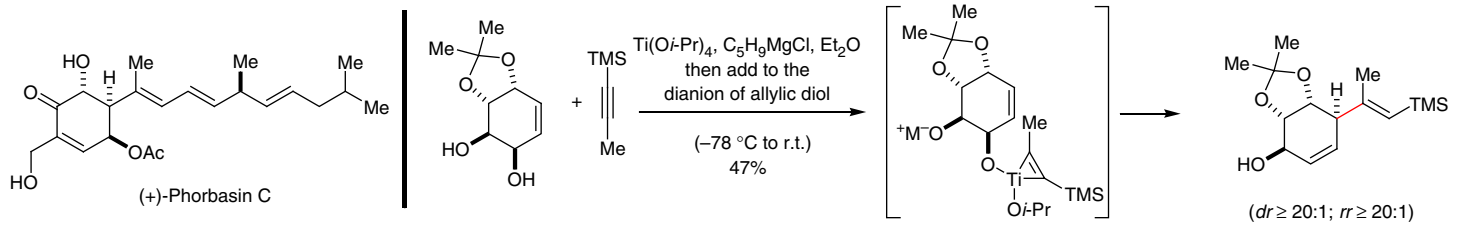
An interesting feature of these processes is that the alkoxide-directed process changes course in coupling reactions with 1,3-disubstituted allenes (**Scheme 52B**). Here, carbometalation takes place with C–C bond formation occurring at the central carbon of the allene with concomitant allylic transposition (similar to that seen in the coupling reaction of alkynes with allylic alcohols). Highest levels of stereoselection (*E*:*Z*) are observed with allenic alcohols bearing branched alkyl substitution at the distal carbon (i.e., *i*-Pr). In these cases, C–C bond formation occurs *anti*- to the bulky branched substituent and delivers stereodefined cross-conjugated trienes ($E{:}Z \geq 20{:}1$). As previously seen in the coupling reactions depicted in **Scheme 52A**, regiochemical control in these cross-conjugated triene-forming reactions is also difficult to control. For example, coupling of a sterically differentiated internal alkyne (Me vs. branched alkyl) proceeds with only 2:1 regioselection.

5.34.3.7 Imine–Alkyne Cross-Coupling (via Preformed Metal–Imine Complexes)

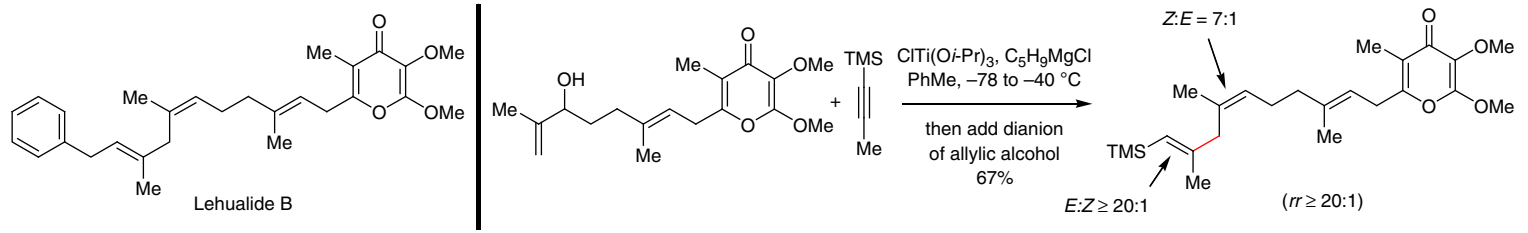
Although Section 5.34.3.2.2 has already addressed metallacycle-mediated coupling reactions between alkynes and imines, the reactions presented previously were based on the addition of preformed metal–alkyne complexes to carbonyl electrophiles. Here, a discussion follows that derives from a different pathway to achieve reactivity, where metal–imine complexes are employed in carbometalation reactions with alkynes. This variation in the order of substrate activation results in a different set of reactions that can be controlled by unique features.

The generation of early transition metal–π complexes was discussed in the first volume of this series, with emphasis given to Prof. Buchwald's contributions demonstrating that Zr-complexes generated by the established thermal decomposition of Zr–alkyl complexes (with loss of CH_4) can be employed in a variety of metallacycle-mediated bond-forming processes. This mode of

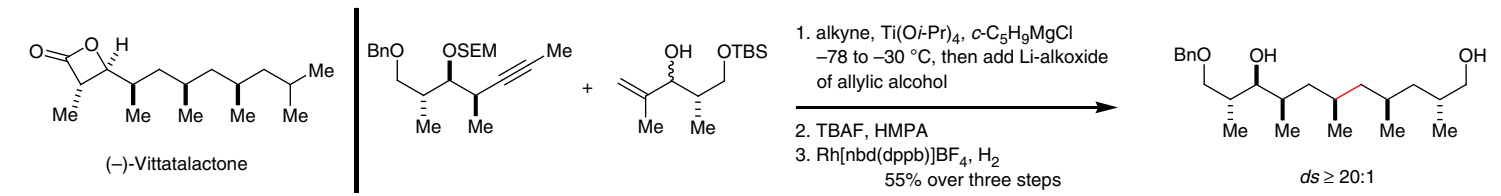
A. Allylic alcohol–alkyne coupling in the total synthesis and structure elucidation of phorbasin C.



B. Allylic alcohol–alkyne coupling in the total synthesis of lehualide B.

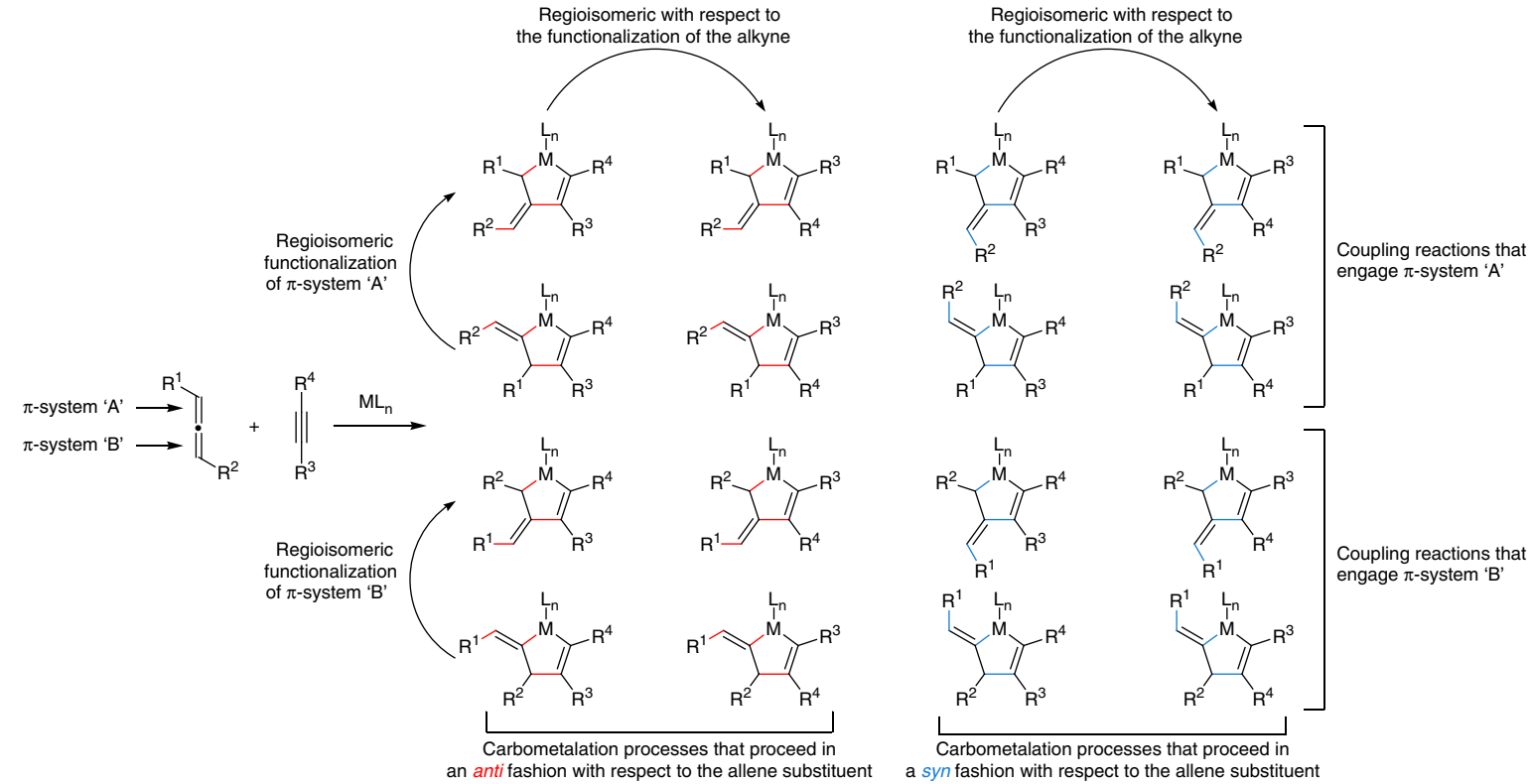


C. Allylic alcohol–alkyne coupling in the total synthesis of vittatalactone. HMPA, hexamethylphosphorictriamide; TBAF, tetrabutylammonium fluoride.

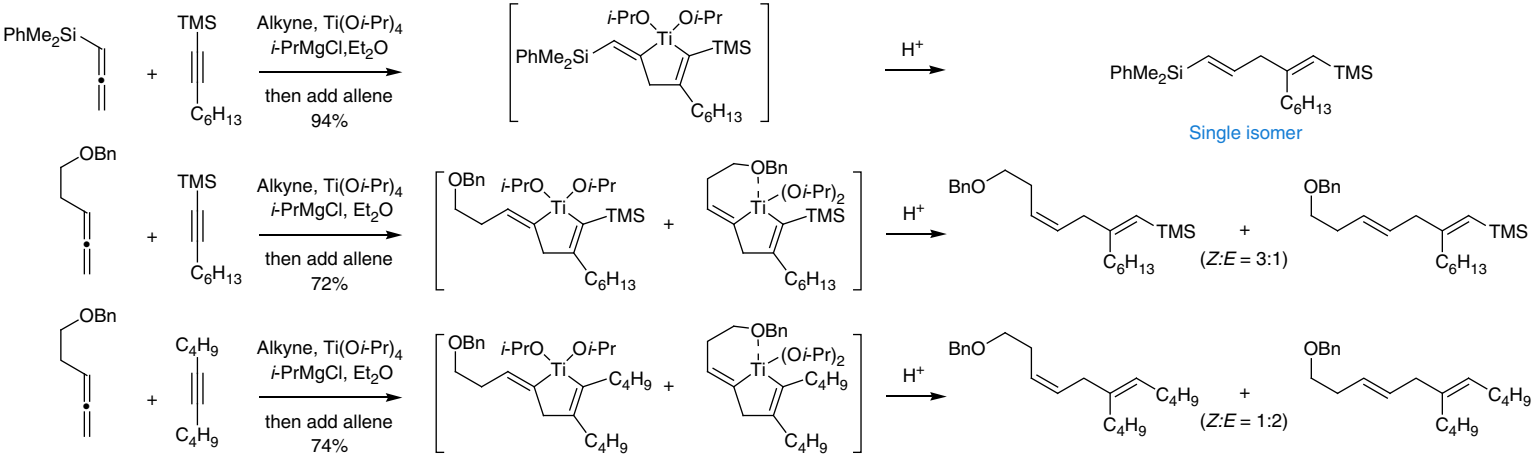


Scheme 50

A. The challenge associated with controlling the course of metallacycle-mediated allene–alkyne cross-coupling.

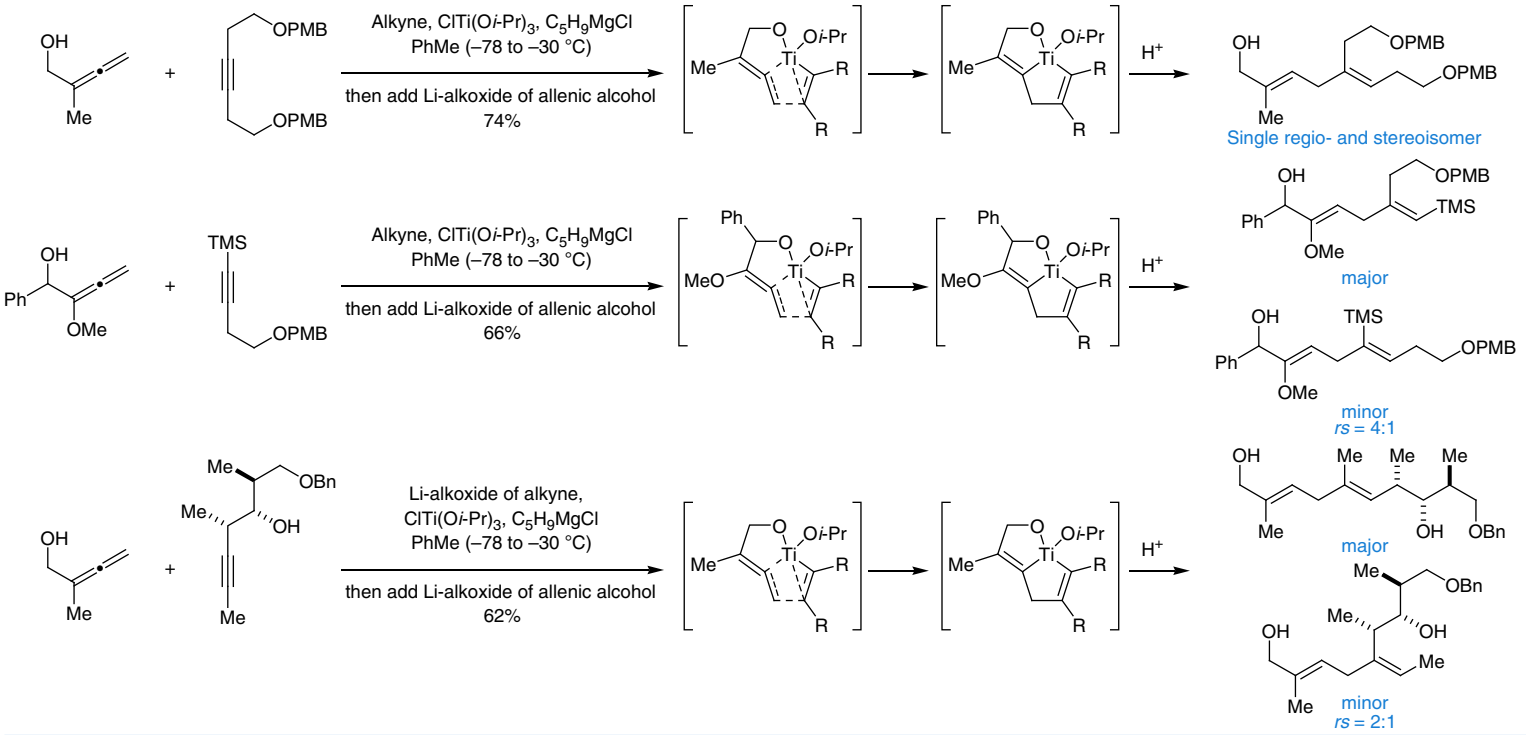


B. Early demonstrations of allene–alkyne coupling.

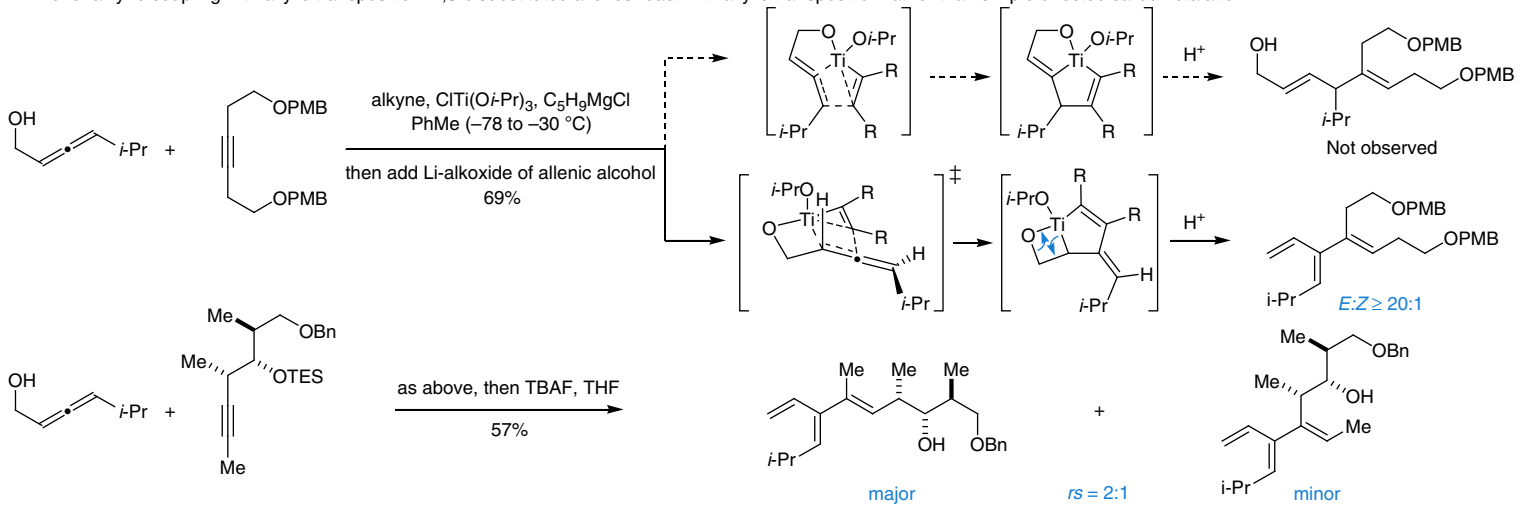


Scheme 51

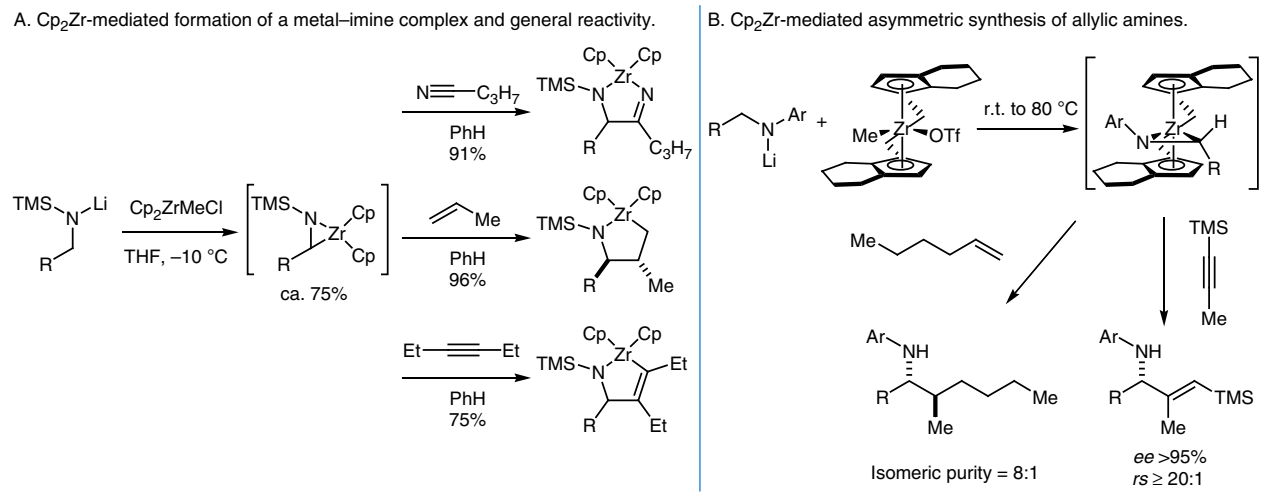
A. Simple hydroxyl-directed carbometalation as a means to control allene–alkyne coupling.



B. Allene–alkyne coupling with allylic transposition: 1,3-disubstituted allenes react with allylic transposition rather than simple directed carbometalation.



Scheme 52



Scheme 53

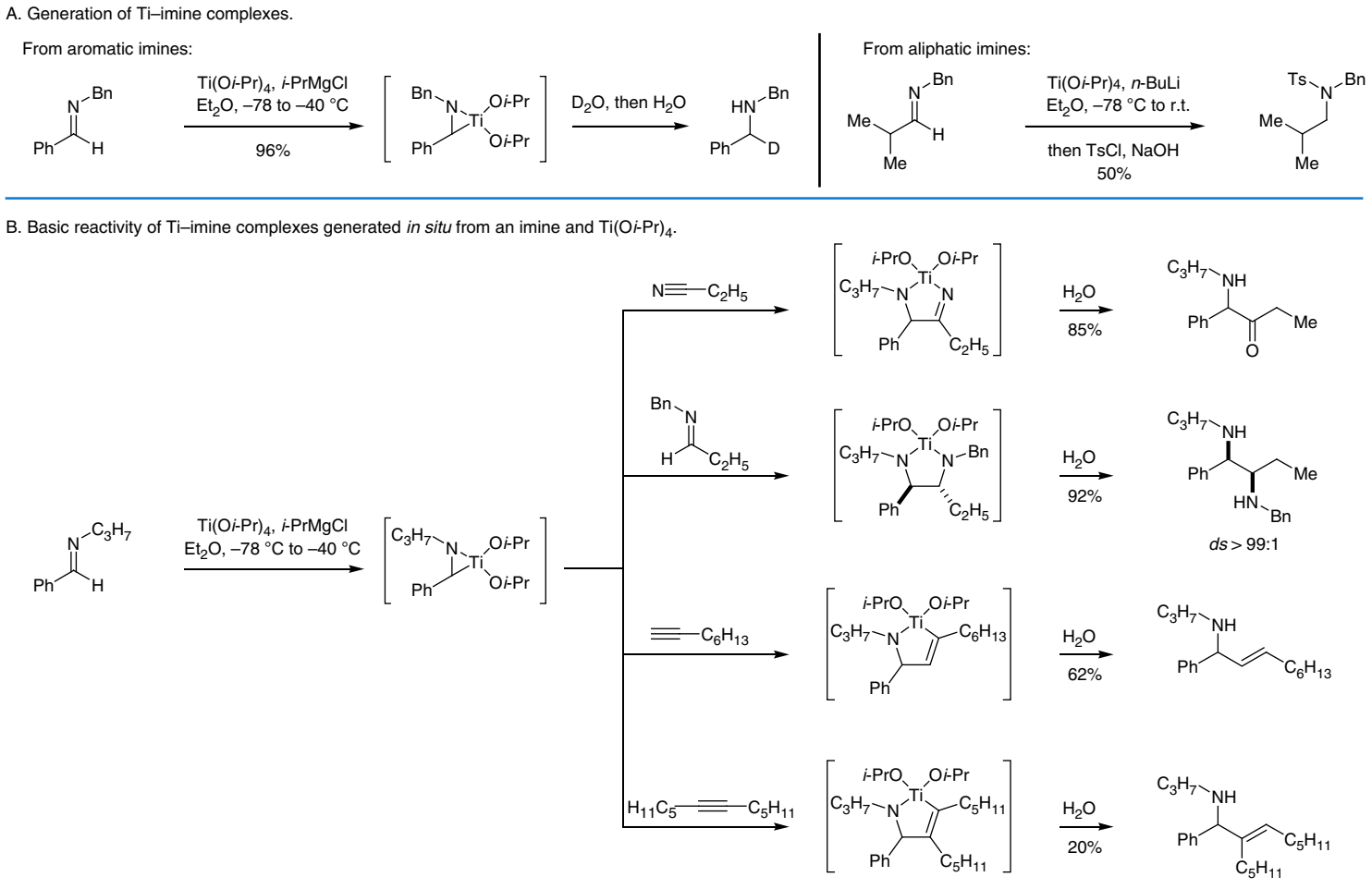
activation was shown to be useful for the formation of Zr–imine complexes, and it has been documented that these species engage a variety of π-systems in carbometalation chemistry (i.e., nitriles, terminal alkenes, aldehydes, TMS-imines, terminal alkynes, and symmetrical internal alkynes; Scheme 53A).[124] These contributions established a foundation on which a subsequent asymmetric process was built (employing (ethylene-1,2-bis(η5-4,5,6,7-tetrahydro-1-indenyl) (EBTHI))ZrMeOTf; Scheme 53B).[125] Although establishing a foundation of reactivity associated with early transition metal–imine complexes, these contributions have not yet been investigated in complex settings, nor have they been demonstrated to be compatible with more functionalized substrates.

In 1997, Prof. Sato described a convenient method for the direct conversion of imines to Ti–imine complexes by the action of Ti(O*i*-Pr)$_4$/2*i*-PrMgCl (Scheme 54A).[126] Although originally limited to aromatic imines, recent advances have led to the establishment of a complementary procedure for the generation of Ti-complexes of aliphatic imines that proceeds by the reagent combination of Ti(O*i*-Pr)$_4$/2*n*BuLi.[127] As depicted in Scheme 54B, the reactivity profile of the intermediate azametallacyclopropanes mirrors that of other early transition metal-based metallacycles where addition reactions to electronically activated and/or unhindered terminal alkynes are straightforward. That said, attempted reaction with a simple internal alkyne was not efficient (generating allylic amine product in only 20% yield), reflecting the great difficulty associated with intermolecular addition reactions of early transition metal–π complexes to electronically unactivated and substituted π-systems.

Hydroxyl-directed Ti-mediated coupling provides a convenient means to accomplish highly regioselective addition reactions of unsymmetrical internal alkynes to aromatic imines.[128] As illustrated in Scheme 55A, Ti–imine complex formation is followed by addition of the alkyne-containing lithium alkoxide. Rapid and reversible ligand exchange at Ti then results in a fleeting intermediate that can undergo intramolecular carbometalation to generate a fused bicyclic azametallacyclopentene in a highly regioselective manner. Protonation of the resulting organometallic intermediate then delivers unsaturated amino alcohol products. As depicted in Scheme 55B, this reaction design is effective for controlling the course of reductive cross-coupling of imines with a range of substituted alkynes. In all cases, C–C bond formation occurs distal to the hydroxyl tether, consistent with the proposed intermediacy of a fused bicyclic azametallacyclopentene intermediate. Interestingly, this hydroxyl-directing group strategy overcomes the well-established selectivity profile of TMS-alkynes in reductive cross-coupling chemistry. Here, C–C bond formation occurs α- to the TMS group to deliver the stereodefined trisubstituted vinylsilane product in 55% yield as a single regioisomer.

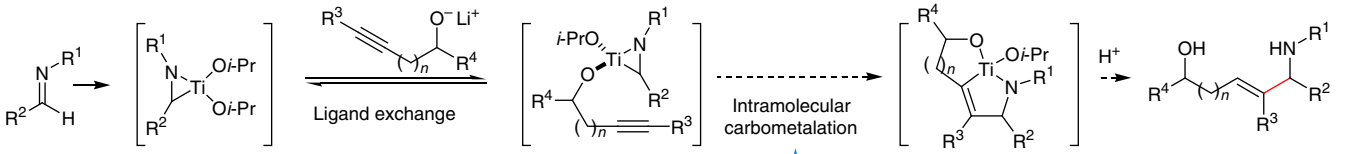
This hydroxyl-directed reductive cross-coupling process is compatible with alternative quenching procedures that result in orthogonal functionalization of the intermediate azametallacyclopentene. As has been shown with azazirconacyclopentenes, as well as monocyclic azatitanacyclopentenes, the reactive intermediates generated in this coupling process can be advanced to γ-lactams by insertion of carbon dioxide. As illustrated in Scheme 55C, formation of a Ti–imine complex occurs in the usual manner – notably, this organometallic reaction is compatible with aromatic halides. Hydroxyl-directed C–C bond formation then delivers the fused bicyclic azatitanacyclopentene intermediate that is converted to the tetrasubstituted γ-lactam product by exposure to 20 psig CO_2 and heating to 90 °C.

With a glimpse of the potential power of hydroxyl direction to control the course of alkyne–imine cross-coupling, recent studies have explored this process as a means to gain access to complex heterocyclic motifs.[129] Scheme 56A depicts the design of a hydroxyl-directed coupling between substituted enynes and imines en route to a potentially useful amino alcohol for heterocycle synthesis. Here, substrate direction is proposed as a means to reinforce C–C bond formation to occur at the carbon α- to the preexisting alkene. Subsequent acid-promoted formation of an iminium ion followed by cationic annulation was anticipated to define a path to densely functionalized heterocyclic systems. Although other metallacycle-mediated reductive coupling reactions of enynes proceeds to deliver an isomeric product to that targeted in this heterocycle-forming process (Scheme 56B), the hydroxyl-directed coupling reaction provides for C–C bond formation with exquisite levels of regiochemical control


A. Generation of Ti–imine complexes.
From aromatic imines:
Ti(Oi-Pr)4, i-PrMgCl
Et2O, –78 to –40 °C
96%
D2O, then H2O
From aliphatic imines:
Ti(Oi-Pr)4, n-BuLi
Et2O, –78 °C to r.t.
then TsCl, NaOH
50%
B. Basic reactivity of Ti–imine complexes generated in situ from an imine and Ti(Oi-Pr)4.
Ti(Oi-Pr)4, i-PrMgCl
Et2O, –78 °C to –40 °C
H2O
85%
92%
62%
20%
ds > 99:1

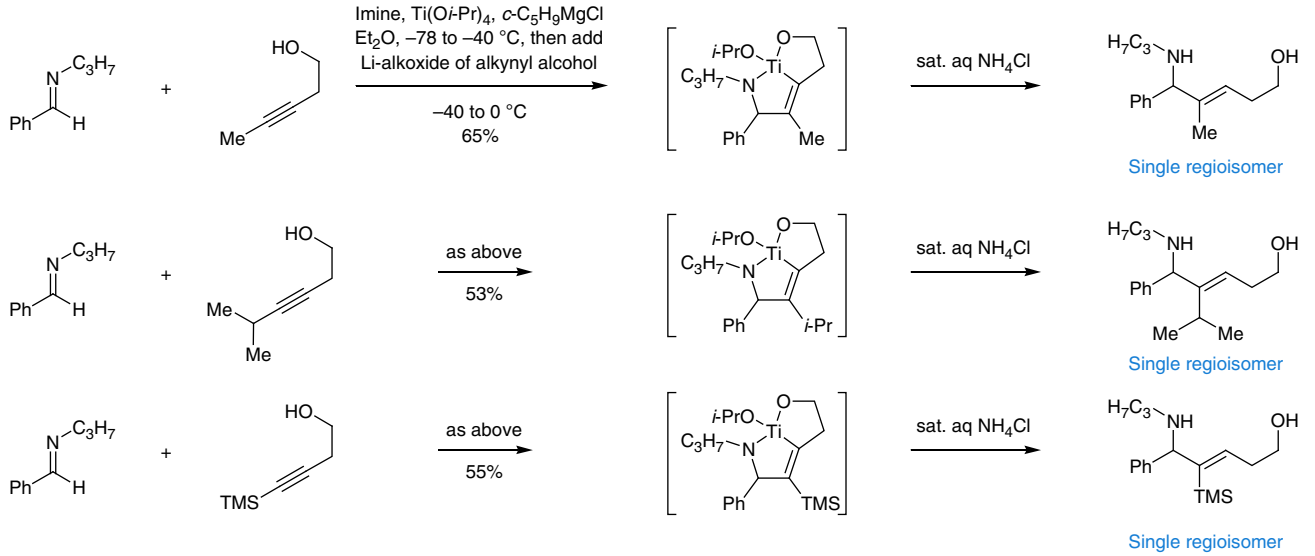
Scheme 54

A. Hydroxyl-directed coupling of alkynes with imines: General strategy.

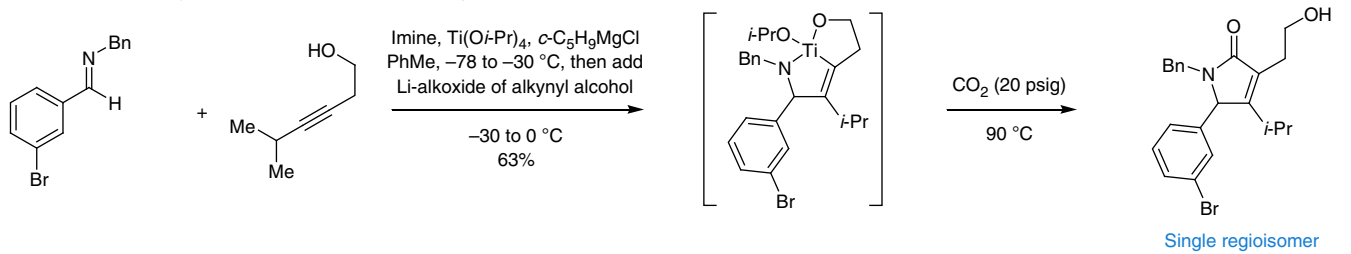


Provides a means to
(1) control regioselection in functionalization of alkynyl alcohol and
(2) overcome sluggish reactivity of the intermolecular variant.

B. Hydroxyl-directed coupling of alkynes with imines: Examples for the synthesis of allylic amines.

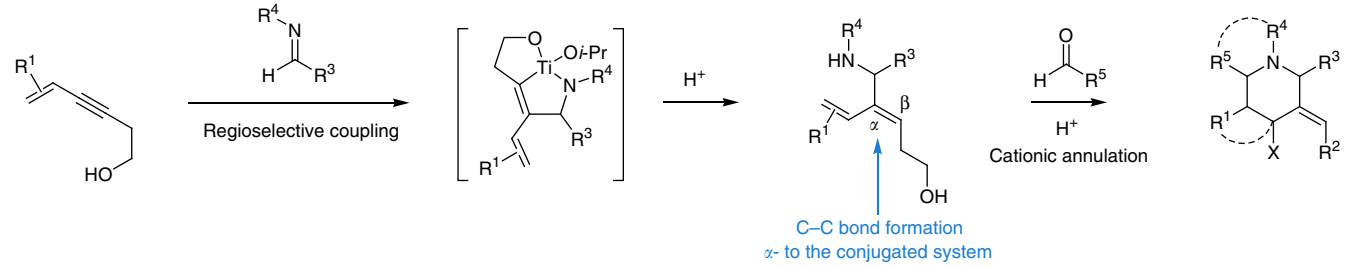


C. Tetrasubstituted γ-lactams by alkyne–imine coupling.

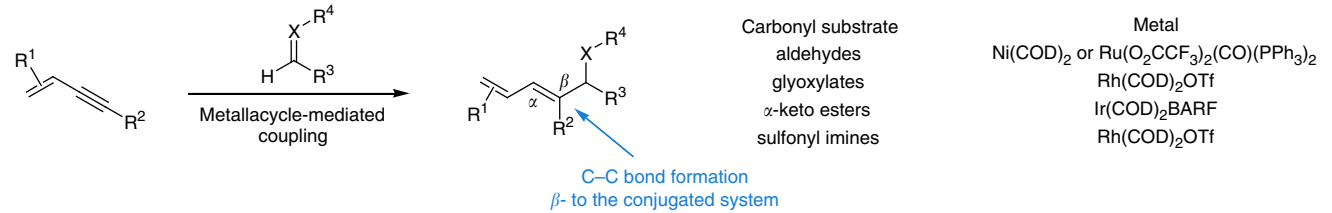


Scheme 55

A. Hydroxyl-directed coupling of enynes with imines: A pathway to densely functionalized polycyclic heterocycles.

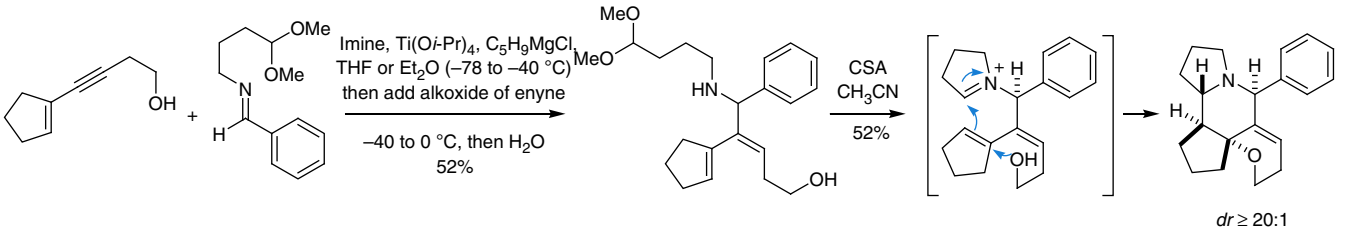


B. Other metallacycle-based methods: C–C bond formation β- to the conjugated system.



Carbonyl substrate	Metal
aldehydes	$Ni(COD)_2$ or $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$
glyoxylates	$Rh(COD)_2OTf$
α-keto esters	$Ir(COD)_2BARF$
sulfonyl imines	$Rh(COD)_2OTf$

C. Example en route to polycyclic heterocycles.



dr ≥ 20:1

Scheme 56

(Scheme 56C; only a single regioisomer was observed). Treatment of the polyunsaturated product with camphor sulfonic acid (CSA) then results in iminium ion generation and annulation to provide the fused tetracyclic product in 52% yield ($dr \geq 20{:}1$).

5.34.3.8 Imine–Alkene Cross-Coupling (via Preformed Metal–Imine Complexes)

Metallacycle-mediated union of imines with alkenes represents among the most challenging cross-coupling reactions in metallacycle chemistry. Recalling the general challenges to controlling the course of metallacycle-mediated cross-coupling that were depicted in Scheme 34, coupling reactions of alkenes with imines are complicated by the following:

1. Pair selectivity: Given the established reactivity of saturated early transition metal metallacyclopropanes, where alkene expulsion defines a pathway to regenerate a metal–alkene complex, alkene–imine-coupling chemistry is anticipated to be complicated by the potential instability of the saturated azatitanacyclopentane (i.e., alkene extrusion would regenerate a Ti–imine complex). If free imine is present in the reaction mixture, the potential for imine homocoupling exists.
2. Low reactivity of alkenes: As previously discussed, early transition metal–π complexes often do not possess sufficient reactivity to add across substituted and electronically unactivated alkenes.
3. Regioselectivity: If one were able to achieve the desired cross-coupling, concerns regarding the control of regioselection in the functionalization of the alkene arise.
4. Diastereoselectivity: In these cases, two new stereocenters are generated in the course of C–C bond formation. How does one control simple and/or relative diastereoselection when stereodefined substrates are employed?

5.34.3.8.1 Simple hydroxyl-directed Ti-mediated imine–alkene coupling

It has recently been discovered that hydroxyl-directed titanium-mediated coupling provides an exceptionally powerful means to control the course of imine–alkene coupling. As previously discussed in association with Scheme 42 (alkene–alkyne coupling), the generation of Ti–alkene complexes is quite challenging and the viability of such activation is currently substantially limited in substrate scope. As such, alkene–imine reductive cross-coupling chemistry has been pursued through the initial formation of a metal–imine complex, followed by introduction of a suitably functionalized alkene-coupling partner to enable C–C bond formation (Scheme 57A).

As illustrated in Scheme 57B-1, this hydroxyl-directed early transition metal metallacycle-mediated coupling proceeds with exquisite levels of regiochemical control and often outstanding stereoselectivity.[130] The coupling process is stereoconvergent, providing a pathway to convert both (*E*)- and (*Z*)-disubstituted alkenes to the *anti*-products ($ds \geq 95{:}5$; $rs \geq 95{:}5$). This sense of stereochemical control is believed to derive from preferred reaction by way of a transition state that minimizes nonbonded steric interactions about the developing C–C bond (as in structures A and D of Scheme 57B-2). Notably, the coupling process is also selective in coupling reactions of terminal alkenes (monosubstituted; not shown) and 1,1-disubstituted alkenes. In this latter case, the reaction proceeds with modest levels of stereochemical control, delivering the 1,3-*syn* isomer as the major product ($ds = 4{:}1$) in 57% yield (Scheme 57-B1). A model has been proposed that justifies this sense of stereoselection based on progression through a transition state that positions the aromatic substituent of the imine 'outside' the developing *cis*-fused bicyclo[3.3.0] system (as in F of Scheme 57B-2).

In efforts to explore the origin of stereoselectivity in this class of coupling reaction (i.e., kinetic vs. thermodynamic control), crossover experiments have been performed with D-labeled substrates.[131] Overall, these studies of hydroxyl-directed Ti-mediated cross-coupling between aromatic imines and terminal alkenes support the conclusion that the coupling process proceeds under kinetic control (i.e., no evidence was found to support the reversibility of C–C bond formation under the reaction conditions).

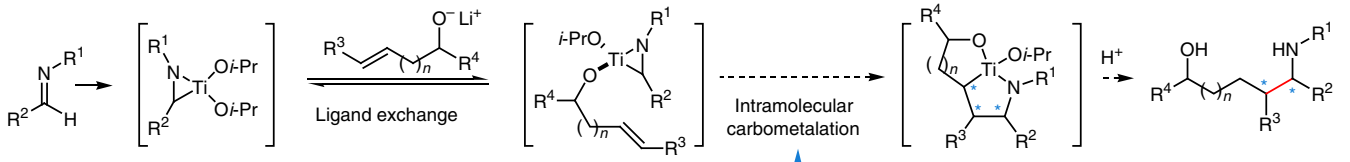
5.34.3.8.2 Single and double asymmetric hydroxyl-directed imine–alkene coupling

This hydroxyl-directed imine–alkene-coupling process can proceed in a manner that offers outstanding levels of substrate control when employing chiral imines and chiral homoallylic alcohols.[130] As illustrated in Scheme 58A, phenylglycine-derived imines undergo hydroxyl-directed coupling with alkenes with good levels of stereochemical control. That said, coupling with (*Z*)-alkenes proceeds with the highest levels of stereochemical control in this single asymmetric coupling process ($ds = 20{:}1$; no evidence for the production of a regioisomer was found).

In efforts to explore the factors that influence stereoselection in this process, it was reported that the coupling reaction is quite sensitive to double asymmetric relationships. As depicted in Scheme 58B-1, matched double asymmetric reactions have been reported en route to 1,4-*anti*-4,5-*anti*-1,5-aminoalcohols ($dr \geq 50{:}1$) and 1,4-*syn*-4,5-*anti*-1,5-aminoalcohols ($dr = 35{:}4{:}1$). The different levels of stereoselection observed for these matched double asymmetric transformations have been proposed to result from a varying nature of the transition states through which these processes proceed. As summarized for each case, the homoallylic substituent adopts a position outside of the developing *cis*-fused bicyclo[3.3.0] system, whereas minimization of nonbonded steric interactions about the developing C–C bond ensures a 4,5-*anti*-stereochemical relationship. As seen in the single asymmetric examples depicted in Scheme 58A, highest levels of stereochemical control in these double asymmetric coupling processes are observed in the coupling reactions of (*Z*)-disubstituted alkenes.

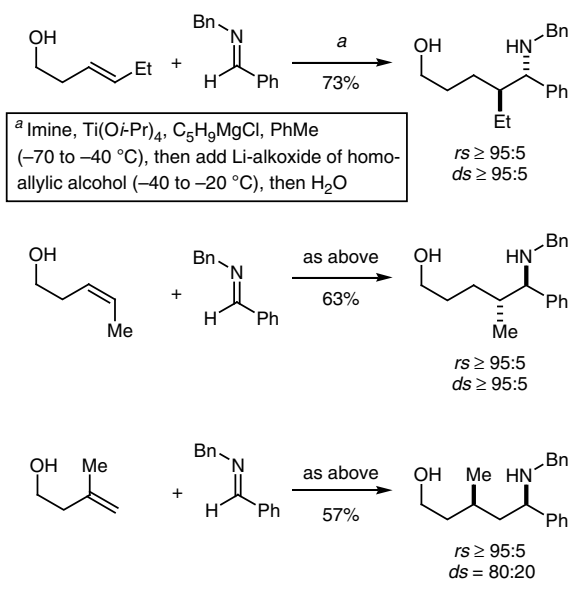
Mismatched double asymmetric reactions in this class are depicted in Scheme 58B-2 and demonstrate a substantial drop in stereoselection observed when the stereochemistry of coupling partners do not reinforce one another.

A. Hydroxyl-directed Ti-mediated strategy for imine–alkene coupling: Basic strategy.

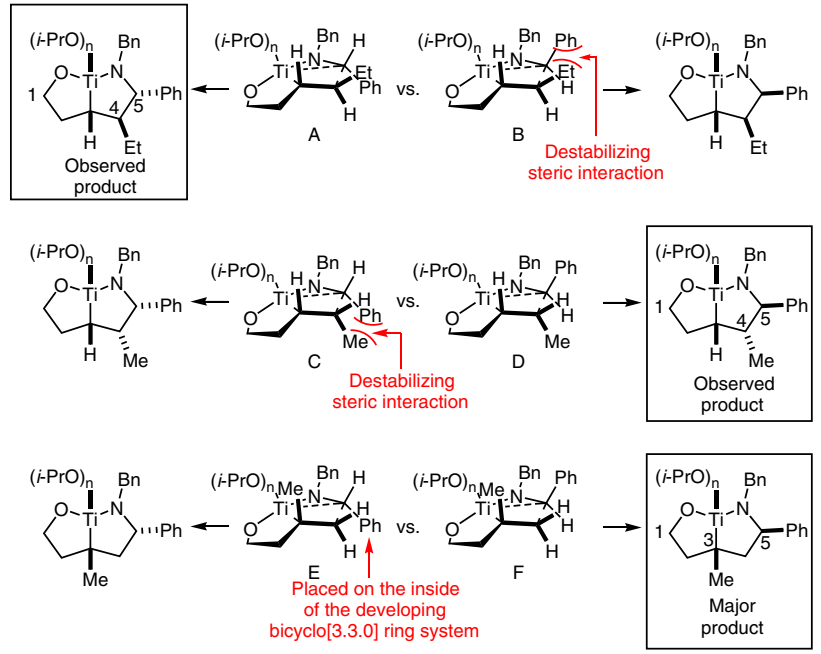


B. Hydroxyl-directed Ti-mediated strategy for imine–alkene coupling: Stereoselective examples.

1. Coupling reactions of E-, Z-, and 1,1-disubstituted alkenes:

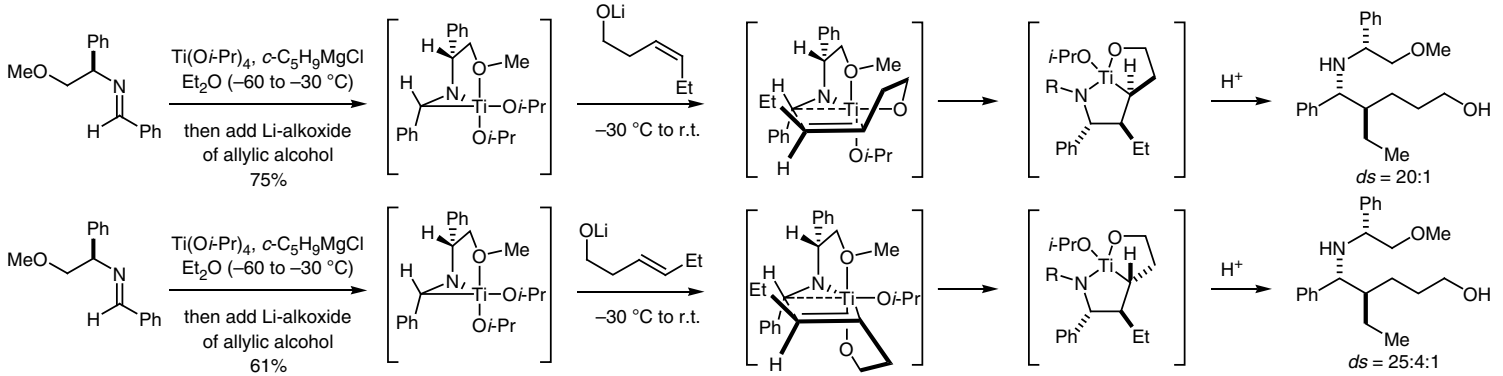


2. Empirical models:



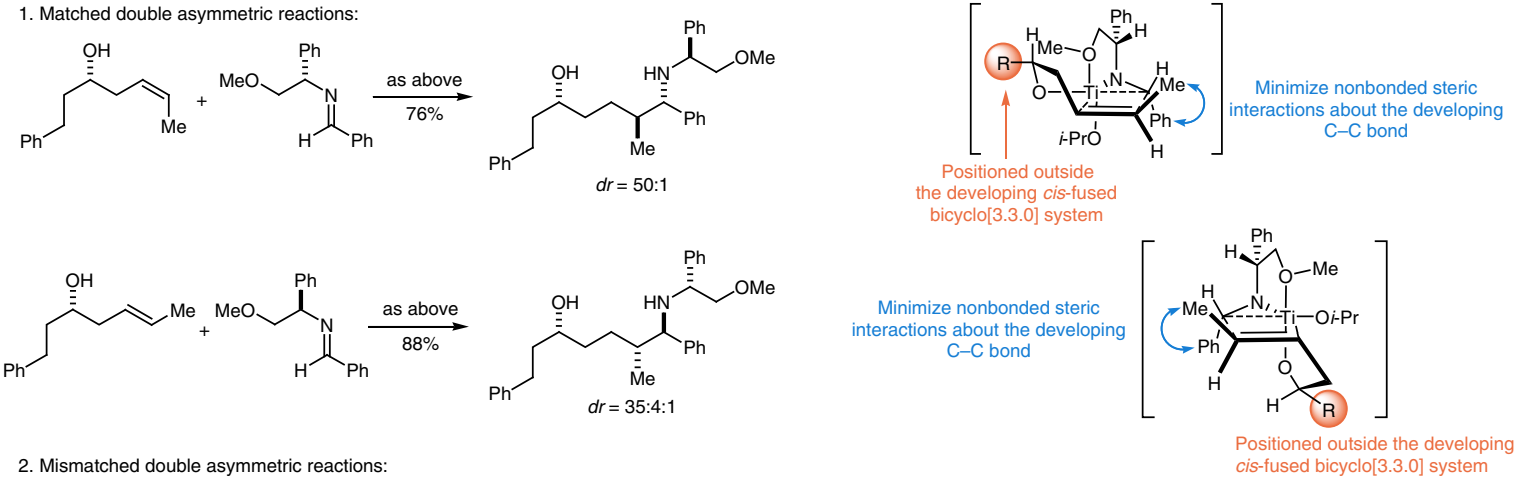
Scheme 57

A. Single asymmetric hydroxyl-directed Ti-mediated strategy for imine–alkene coupling.

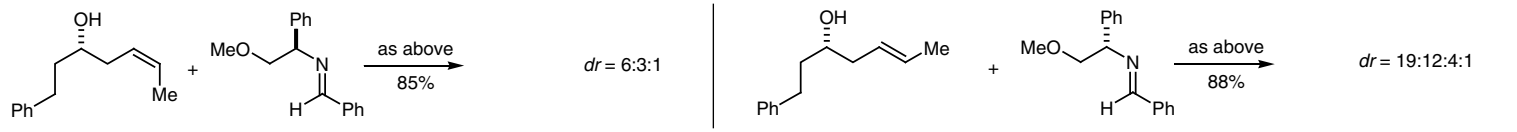


B. Double asymmetric hydroxyl-directed Ti-mediated strategy for imine–alkene coupling.

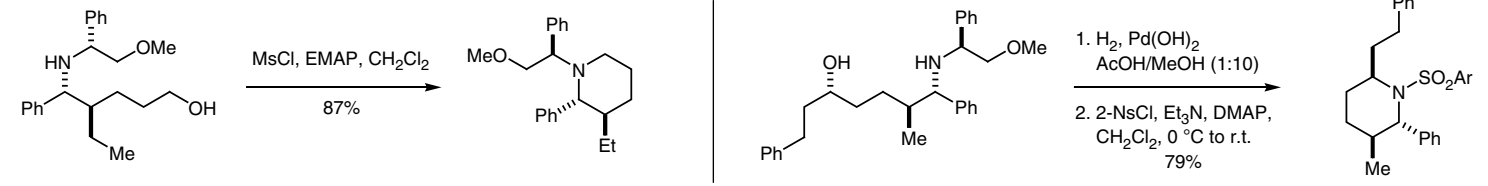
1. Matched double asymmetric reactions:



2. Mismatched double asymmetric reactions:



C. Use of 1,5-aminoalcohol products for piperidine synthesis. DMAP, 4-dimethylaminopyridine.



Scheme 58

The utility of this coupling process has recently been demonstrated in the context of the stereoselective synthesis of substituted piperidines. As illustrated in Scheme 58C, cyclization of substrates bearing a primary alcohol proceeds without the need for removal of the phenylglycine auxiliary, whereas cyclization of substrates bearing a secondary hydroxyl requires initial selective hydrogenolysis of the phenylglycine auxiliary followed by stereoselective cyclization. In both cases, one can access stereodefined piperidines in a concise, convergent, and highly stereoselective fashion.

5.34.3.8.3 Imine–alkene coupling by formal metallo[3,3] rearrangement (convergent synthesis of homoallylic amines)

As discussed in Section 5.34.3.5.2 for the coupling of preformed metal–alkyne complexes with allylic alcohols, where C–C bond formation occurs with allylic transposition, a similar mode of reactivity is observed in the union of preformed Ti–imine complexes with allylic alcohols.[132,133] As illustrated in Scheme 59, coupling reactions of 1,1-disubstituted alkenes proceed to deliver homoallylic amine products possessing a (*Z*)-trisubstituted alkene with high levels of stereochemical control. As previously discussed, this selectivity likely derives from minimization of A-1,2 strain in a boat-like transition state (Scheme 49B). In a similar fashion, coupling reactions of allylic alcohols bearing (*Z*)-disubstituted alkenes deliver homoallylic amines with high levels of (*E*)-selectivity. Here, minimization of A-1,3-strain in the transition state is assumed to result in the production of the (*E*)-isomer, whereas minimization of nonbonded steric interactions about the developing C–C bond results in the establishment of the *anti*-stereochemical relationship between the allylic and homoallylic stereocenters (this second feature plays a prominent role in the coupling reactions of homoallylic alcohols with imines; Scheme 57).

Trisubstituted alkenes can also be employed in this coupling process. As illustrated, the (*E*)-trisubstituted allylic alcohol is an outstanding substrate for this reaction – delivering an *anti*-homoallylic amine product possessing a (*Z*)-trisubstituted alkene as a single isomer. Finally, as is observed in the related coupling reaction of alkynes with allylic alcohols, simple terminal alkenes or (*E*)-disubstituted alkenes do not react in a highly stereoselective manner (likely due to the lack of substantial bias in the transition state based on the minimization of allylic strain (A-1,2 or A-1,3)).

Although the issues that govern alkene selectivity are identical to the alkyne–allylic alcohol-coupling process previously discussed, the imine–allylic alcohol-coupling process is more complex owing to challenges associated with the control of absolute stereochemistry. As illustrated in Scheme 60A, consideration of this coupling process in a kinetic resolution mode (where both *R*- and *S*-azametallacyclopropanes are present, or potentially if there is a means for rapid equilibration between these isomers)[134] leads to the prediction that those reactions that are organized by both the minimization of allylic strain and nonbonded steric interactions about the developing C–C bond should proceed with a high degree of stereochemical control (panels 1 and 4). Those that proceed without both of these features are not expected to proceed with a high degree of stereochemical control (panels 2 and 3).

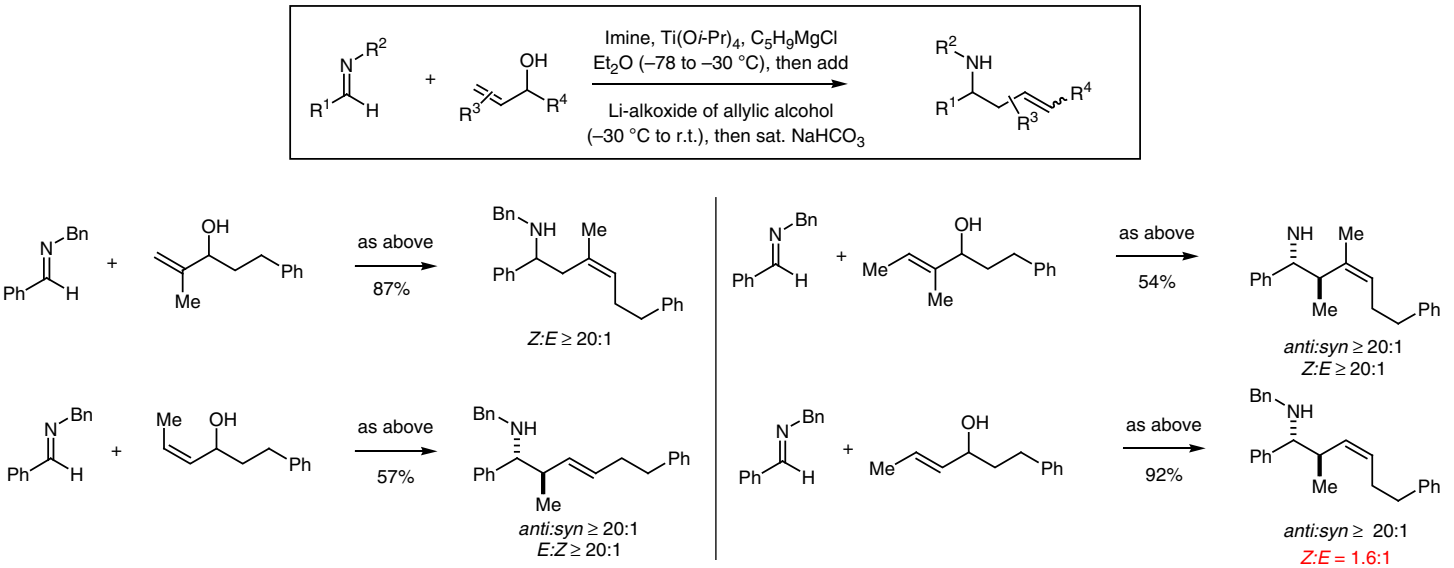
Examples of asymmetric allylic alcohol–imine-coupling reactions are depicted in Scheme 60B.[135] Here, allylic alcohols bearing (*Z*)-disubstituted alkenes are shown to undergo highly enantio- and diastereoselective coupling reactions with aromatic and aliphatic imines. In all examples reported, products are produced with retention of optical purity and are generated as single diastereomers (*anti*- and (*E*)). Also included in this Scheme is an example that proceeds with compromised levels of enantioselectivity. Here, union of an optically enriched allylic alcohol possessing a 1,1-disubstituted alkene delivers a (*Z*)-trisubstituted alkene-containing homoallylic amine with high levels of selectivity ($Z{:}E \geq 20{:}1$), yet a substantial drop in enantiomeric excess (*ee*) is observed (80–46% *ee*). As illustrated in Scheme 60A-panel 2, this observation is consistent with reaction by way of competing transition states that position the imine substituent (R^2) in a pseudo equatorial versus pseudo axial fashion.

Alternative means of controlling the stereochemical course of allylic alcohol–imine coupling chemistry have recently been described in double asymmetric synthesis.[135] As depicted in Scheme 61A, matched double asymmetric reactions of (*E*)-disubstituted allylic alcohols with phenylglycine-derived imines provides a means to access (*Z*)-alkene-containing *anti*-homoallylic amine products with outstanding levels of stereochemical control ($Z{:}E \geq 95{:}5$, $anti{:}syn \geq 95{:}5$). Interestingly, mismatched double asymmetric coupling reactions in this series lead to product mixtures that favor the formation of (*Z*)-alkene-containing *syn*-homoallylic amine products, albeit contaminated by a substantial quantity of the (*E*)-*anti*-isomer (selectivity = 2.3:1). A detailed empirical model has been proposed to account for these interesting observations.[135]

5.34.3.8.3.1 Applications of imine–allylic alcohol coupling

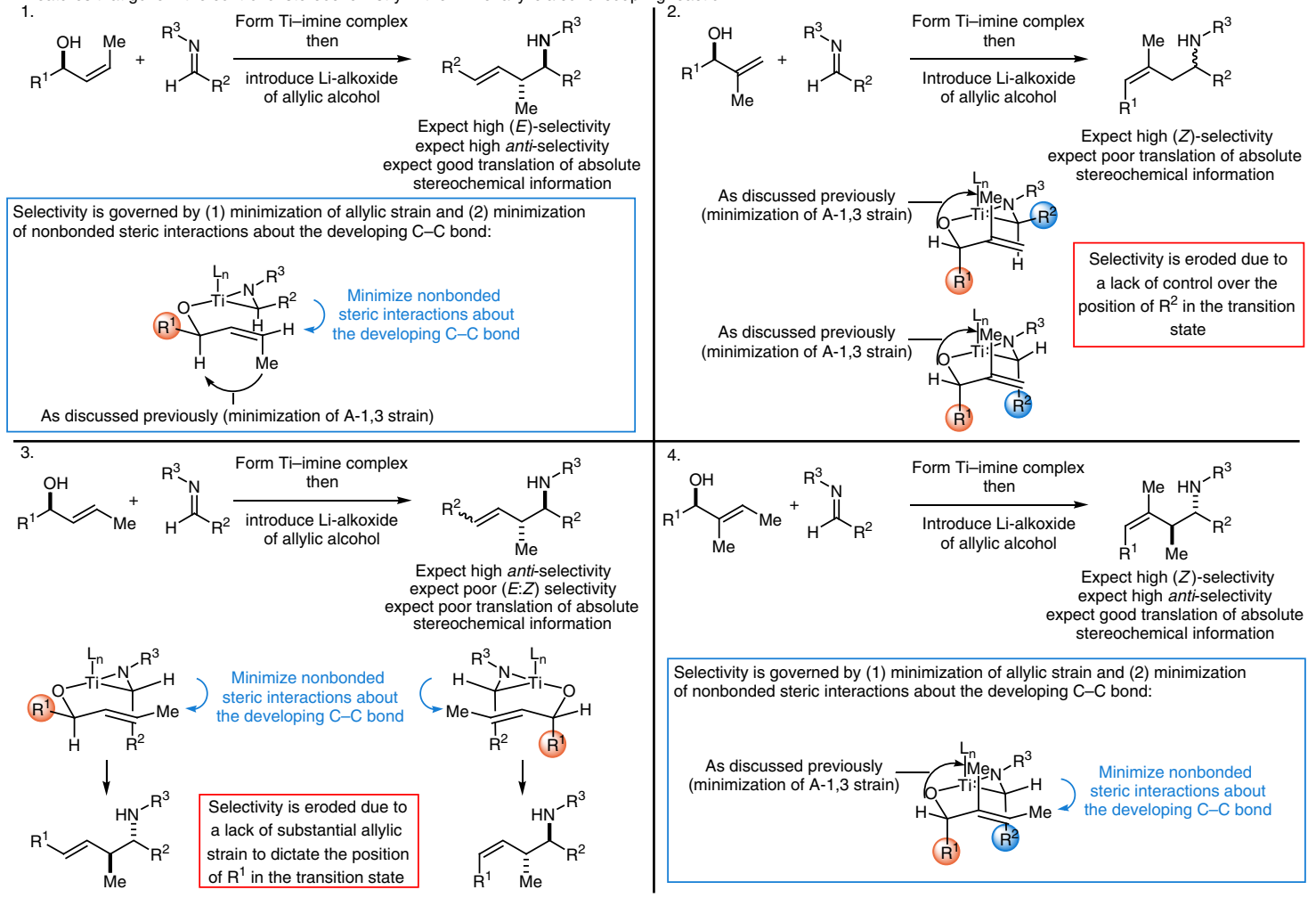
The ability to generate substituted homoallylic amines from metallacycle-mediated cross-coupling of carbonyl-containing systems with allylic alcohols, rather than the addition of allylic organometallic species to such systems has been recognized as a powerful and synthetically useful advance.[132] Recent applications have explored the utility of this process to access a range of functionalized systems. Scheme 62A illustrates the use of this coupling process as a means to generate substituted *exo*-alkylidene γ-lactams via a one-pot two-step process that engages a brominated allylic alcohol in Ti-mediated reductive cross-coupling and Pd-catalyzed carbonylation chemistry.[136] Scheme 62B depicts a reaction process that was recently established as a concise stereoselective entry to indolizidine and quinolizidines. Here, chemoselective engagement of the allylic alcohol (rather than the allylsilane) in C–C bond formation with a functionalized imine delivers substituted allylic silane intermediates.[137] Subsequent treatment with protic acid results in removal of the dimethyl acetal, intramolecular formation of an iminium ion, and stereoselective intramolecular aza-Sakurai allylation.

Scheme 62C highlights the ability to employ imine–allylic alcohol coupling chemistry with TMS-imines, generated *in situ* from treatment of aldehydes with lithium hexamethyldisilazide (LiHMDS) at low temperature.[138] This reaction process was recently

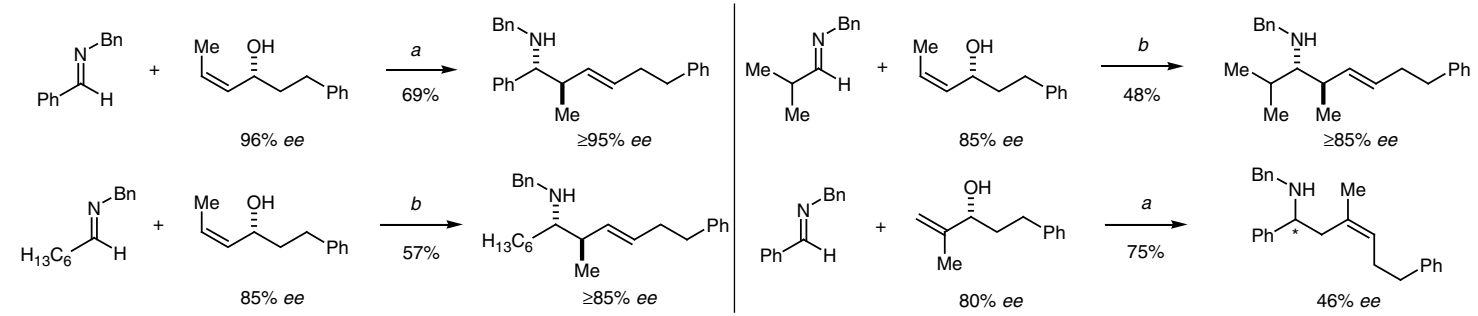

Imine, Ti(O*i*-Pr)$_4$, C_5H_9MgCl
Et_2O (–78 to –30 °C), then add
Li-alkoxide of allylic alcohol
(–30 °C to r.t.), then sat. $NaHCO_3$
as above
87%
Z:*E* ≥ 20:1
as above
54%
anti:*syn* ≥ 20:1
Z:*E* ≥ 20:1
as above
57%
anti:*syn* ≥ 20:1
E:*Z* ≥ 20:1
as above
92%
anti:*syn* ≥ 20:1
Z:*E* = 1.6:1

Scheme 59

A. Features that govern the control of stereochemistry in the imine–allylic alcohol coupling reaction.



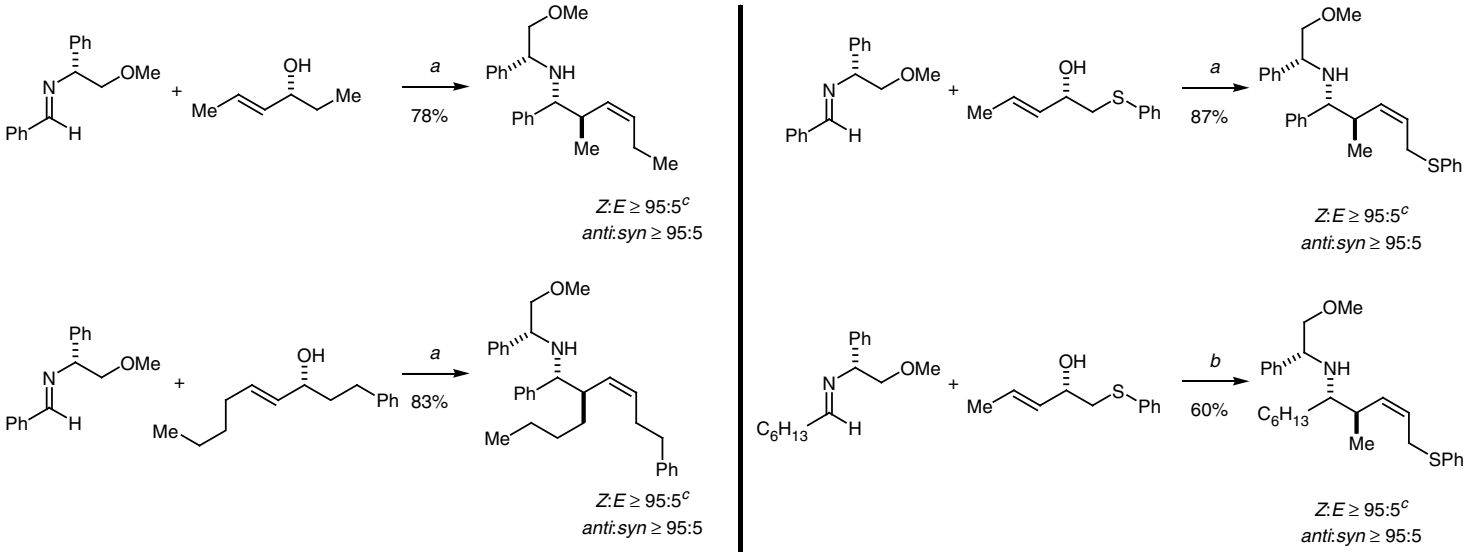
B. Examples of the strengths and weaknesses of single asymmetric coupling of imines with chiral allylic alcohols.



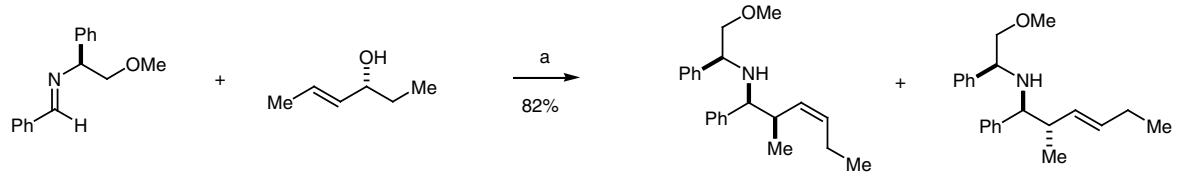
[a] Reaction conditions: imine, Ti(O*i*-Pr)$_4$, C_5H_9MgCl, Et_2O (–78 to –30 °C), then add Li-alkoxide of allylic alcohol, (–30 °C to r.t.), then saturated $NaHCO_3$.
[b] Reaction conditions: imine, Ti(O*i*-Pr)$_4$, *n*-BuLi, Et_2O (–78 to –30 °C), then add Li-alkoxide of allylic alcohol, (–30 °C to r.t.), then saturated $NaHCO_3$.

Scheme 60

A. Matched double asymmetric imine–allylic alcohol coupling reactions.



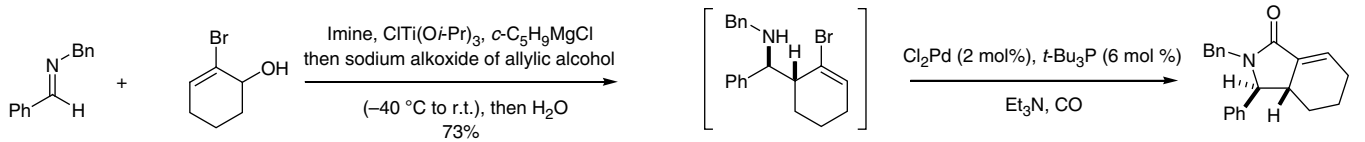
B. Mismatched double asymmetric imine–allylic alcohol coupling.



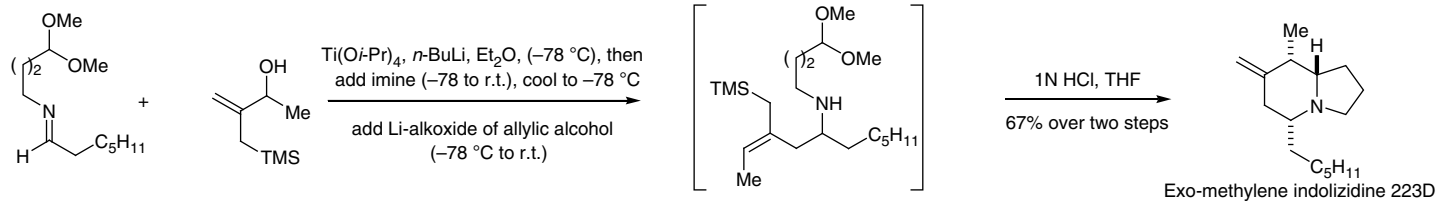
Reaction conditions: [a]imine (2 equivalents), Ti(O*i*-Pr)$_4$ (3 equivalents), *c*-C_5H_9MgCl (6 equivalents), Et_2O, then add allylic alkoxide (1 equivalent); [b]imine (3 equivalents), Ti(O*i*-Pr)$_4$ (3 equivalents), *n*-BuMgCl (6 equivalents), Et_2O, then add allylic alkoxide (1 equivalent). [c]Ratio of isomers reported as "major: sum of all other isomers." [d]a small amount of a third isomer was observed (2.3:1:0.3).

Scheme 61

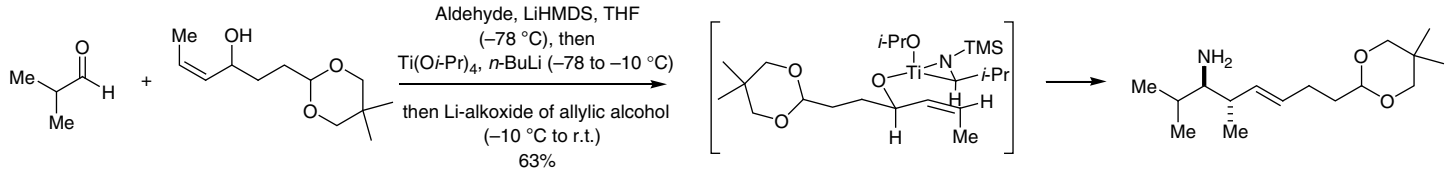
A. Imine–allylic alcohol coupling for the synthesis of α-exo-alkylidene γ-actams.



B. Imine–allylic alcohol coupling for the synthesis of indolizidines and quinolizidines.

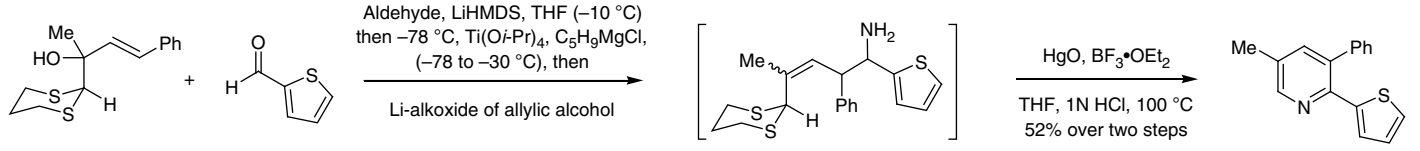


C. Three-component coupling reaction for the synthesis of stereodefined primary homoallylic amines.



Proceeds by *in situ* generation of the Ti–complex of a TMS imine

D. Imine–allylic alcohol coupling for the convergent synthesis of pyridines.



Scheme 62

employed to define an entry to stereodefined homoallylic nitrones that undergo stereoselective intramolecular annulation en route to densely functionalize 1-aza-7-oxabicyclo[2.2.1]heptanes.

Finally, this Ti-mediated cross-coupling process has been employed to realize a regiospecific entry to densely functionalized pyridines (Scheme 62D).[139] Here, the three-component Ti-mediated coupling of allylic alcohols, aldehydes, and LiHMDS delivers functionalized primary homoallylic amines that can be converted to pyridines by the combined action of HgO, BF_3•OEt_2, and HCl in THF.

5.34.3.9 Alkene–Alkene Coupling

Early transition metal metallacycle-mediated cross-coupling reactions of alkenes are quite rare due to (1) the instability of saturated metallacyclopentanes – they routinely fragment to Ti–alkene complexes with loss of one alkene substrate and (2) the difficulty of forming early transition metal complexes with substituted alkenes. Early examples in this area noted the particular stability of titanacyclopentanes generated from the coupling of a Cp_2Ti–ethylene complex with methylenecyclopropanes,[140] and in the hydroxyl-directed homocoupling of homoallylic alcohols.[141] More recent advances have included hydroxyl-directed coupling of homoallylic alcohols to styrenes possessing monosubstituted alkenes (Scheme 63A).[142]

Scheme 63B describes an allylic alcohol–vinylsilane coupling that was employed to establish a stereochemically complementary process to the Claisen rearrangement.[143] Although [3,3]-based rearrangement chemistry of allylic alcohol derivatives typically proceeds with high stereoselectivity in favor of generating a product possessing an (*E*)-trisubstituted alkene, this Ti-mediated coupling process delivers the (*Z*)-trisubstituted alkene-containing product with very high levels of stereoselectivity ($\geq$95:5).

Efforts focused on exploring the reactivity of vinylcyclopropanes in hydroxyl-directed Ti-mediated reductive cross-coupling have led to the realization of a unique alkene–alkene-coupling process. As illustrated in Scheme 63C, initial formation of a vinylsilane–Ti complex is followed by addition of the lithium alkoxide of a substituted vinylcyclopropane. Directed carbometalation then proceeds in a stereoselective manner to deliver an unstable tricyclic metallacyclopentane that promptly fragments in a stereospecific manner. Oxidation of the C–Si bond then delivers the primary carbinol products that possess stereodefined skipped dienes.[144] Notably, these studies described the utility of vinylcyclopropanes in alkene–alkyne-coupling chemistry, defining convergent coupling reactions that deliver skipped trienes in a highly stereoselective fashion (not depicted).

5.34.3.10 Chemoselective Coupling Reactions of Polyenes

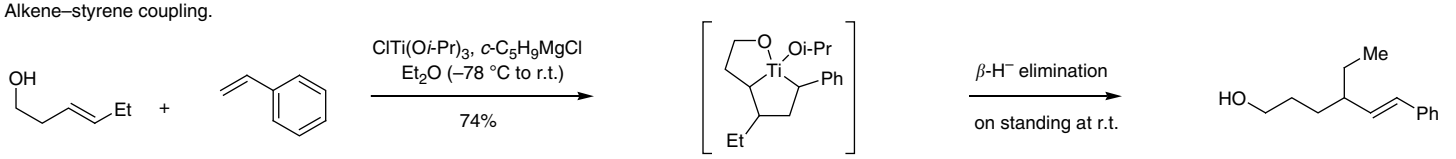
Throughout Section 5.34.3, efforts have been taken to describe a collection of intermolecular early transition metal metallacycle-mediated coupling chemistry that proceeds with fine control over regio- and stereoselection. With the goal to achieve a collection of powerful coupling reactions of utility in complex molecule synthesis, it is important to understand and control chemoselectivity in coupling reactions of polyunsaturated substrates.

Early examples that provide a glimpse of the potential selectivity of early transition metal-mediated coupling processes with polyunsaturated substrates have appeared in the intramolecular Kulinkovich reaction, where treatment of an unsaturated ester with Ti(O*i*-Pr)$_4$/2RMgX results in initial transfer epititanation to a terminal alkene of the substrate, followed by intramolecular nucleophilic addition of this complex to the ester. Other examples include:

1. Ti-mediated cyclization of alkynyl esters or carbonates where transfer epititanation results in initial formation of a Ti–alkyne complex that adds to the tethered carboxylic ester or carbonate in an intramolecular fashion (Scheme 64A; also discussed in Schemes 31 and 32),[81,87]
2. Ti-mediated cyclization of allenyl carbonates where transfer epititanation generates a Ti–allene complex that adds to the carbonate in an intramolecular fashion (Scheme 64A),[83]
3. Reaction of a preformed Ti–alkyne complex with an imine in the presence of a tethered terminal alkene (this is a common mode of selectivity that favors addition of the preformed complex to the polarized π-bond of the aldehyde or imine; Scheme 64B),[98]
4. Addition of a preformed Ti–alkyne complex to an enyne that contains a terminal alkyne typically occurs at the alkyne rather than the alkene (Scheme 64C),[104] and
5. Transfer epititanation occurs selectively at an internal alkyne with enyne substrates bearing disubstituted alkenes (Scheme 64D) – interestingly, this example also demonstrates selective reactions of conjugated Ti–alkyne complexes, where protonation delivers a 1,3-diene but reaction with an aldehyde engages the alkene of the conjugated complex such that bond formation occurs in a manner typical of allylic metal reagents.[145]

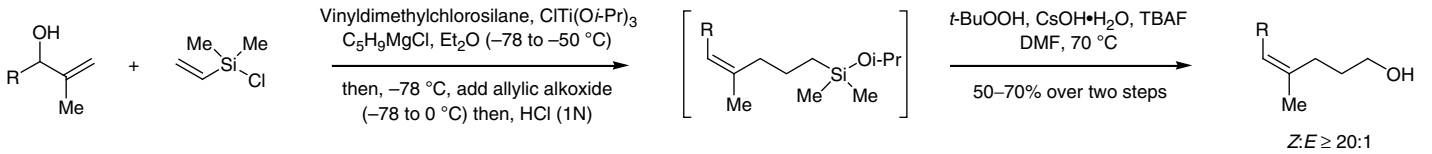
Hydroxyl-directed early transition metal metallacycle-mediated coupling chemistry has also been explored in contexts that illustrate a great degree of chemoselectivity in functionalization reactions of polyunsaturated substrates. Scheme 50A and B have already presented some interesting observations with respect to chemoselectivity in a complex setting, and recent explorations have defined additional processes that enable site- and stereoselective functionalization of polyenes by metallacycle-mediated bond construction.

A. Alkene–styrene coupling.



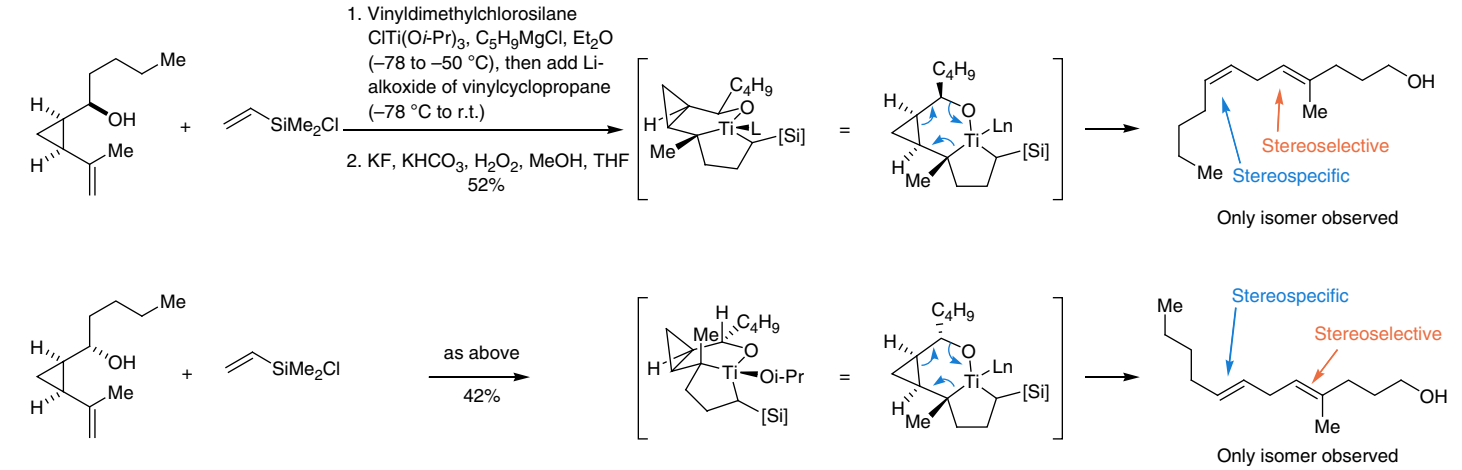
Note: β-H$^-$ elimination can be avoided if the styrene unit contains an *ortho*-chelating group (i.e., OMe)

B. Allylic alcohol–vinylsilane coupling: A stereochemically complementary process to the Claisen rearrangement. DMF, dimethylformamide.



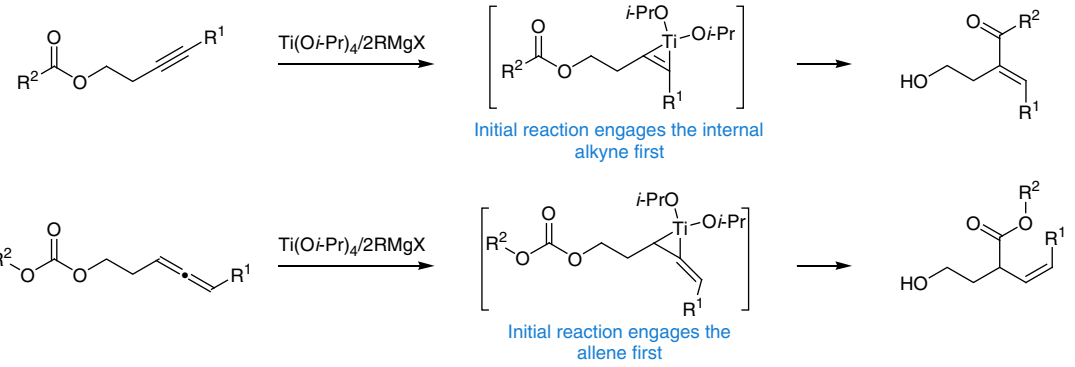
Z:*E* ≥ 20:1

C. Vinylcyclopropane–vinylsilane coupling: Synthesis of skipped polyenes by tandem stereoselective directed carbometalation/stereospecific fragmentation.

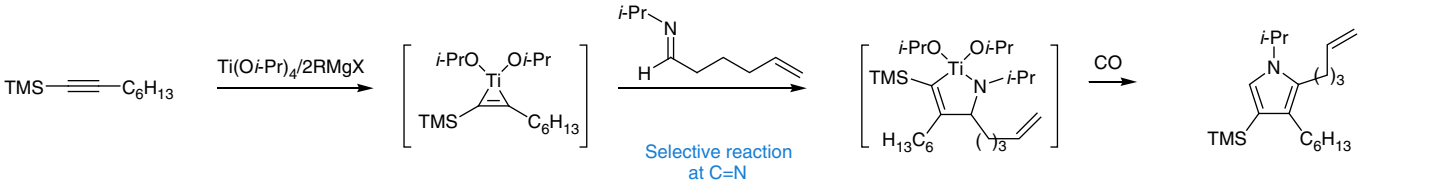


Scheme 63

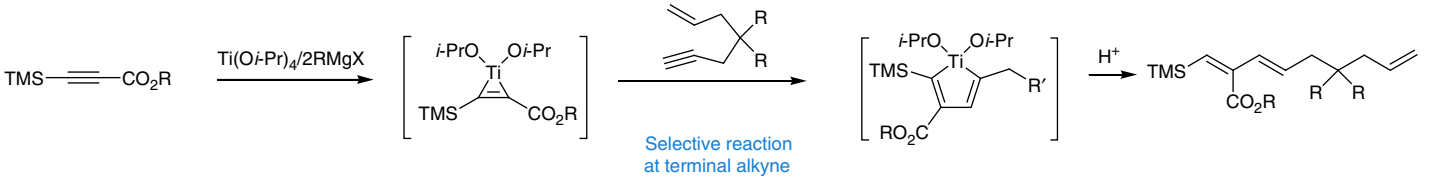
A. Intramolecular nucleophilic acyl substitution: Initial transfer epititanation at an alkyne or allene prior to intramolecular addition to a tethered ester or carbonate.



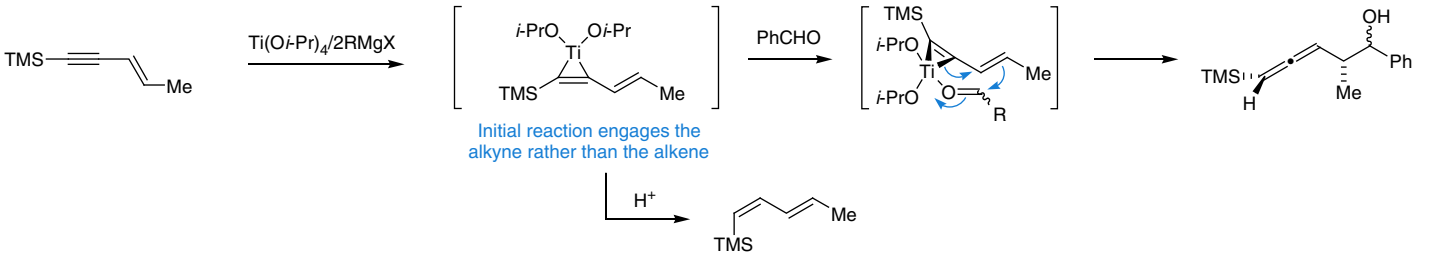
B. Alkyne–imine or alkyne–aldehyde coupling is typically faster than alkyne–alkene coupling.



C. Addition of preformed Ti–alkyne complexes to enynes bearing a terminal alkyne typically occur at the alkyne terminus.



D. Transfer epititanation occurs preferentially at an internal alkyne vs. and internal alkene.



Scheme 64

5.34.3.10.1 Site and stereoselective coupling reactions of 1,5-dienes

Scheme 65 illustrates the ability to control the site of C–C bond formation based on the nature of alkene substitution in a 1,5-diene.[146] Here, the diene is unsymmetrically disposed about a secondary alcohol such that one π-system is part of an allylic alcohol functional group, whereas the other is part of a homoallylic alcohol functional group. Although little selectivity is observed if both alkenes are terminal monosubstituted π-systems, substrate substitution can be used to gain full control over chemoselectivity. As illustrated in Scheme 65A, coupling between an internal alkyne and an unsymmetrically substituted 1,5-diene results in selective reaction at the least substituted alkene and in the formation of a 1,7-diene product. Interestingly, if both alkenes of the 1,5-diene are disubsituted, high selectivity is uniformly seen for reaction at the allylic alcohol (Scheme 65B). In the first case, the 1,5-diene substrate contains two (*Z*)-disubstituted alkenes, and regio-/stereoselective coupling ensues to deliver a skipped triene product containing a central (*E*)-disubstituted alkene as a single isomer. In the next two examples depicted, chemoselective reactions at the allylic alcohol termini result in highly (*Z*)-selective coupling process and deliver extremely complex stereodefined skipped trienes. Note that skipped trienes that possess trisubstituted alkenes, varying alkene stereochemistries, and sp^3 stereochemistry at the central position of the skipped polyene architecture are quite difficult to prepare using other methods.

5.34.3.10.2 Site and stereoselective coupling reactions of 1,6-enynes

Efforts to understand chemoselectivity in addition reactions of preformed Ti–alkyne complexes to enynes possessing a central hydroxyl-directing group have led to the discovery of unique and powerful coupling technologies. Scheme 66A depicts two coupling reactions that demonstrate the ability to selectively functionalize the enyne at the alkene or alkyne motif.[147] To date, only enyne substrates bearing both an internal alkyne and a terminal alkene are capable of selective hydroxyl-directed reaction at the terminal alkene – this selectivity is different than that previously reported for intermolecular coupling of a preformed Ti–alkyne complex to an enyne containing both a terminal alkyne and a terminal monosubstituted alkene (i.e., Scheme 64C).

5.34.3.10.3 A unique and highly stereoselective [2 + 2 + 2] annulation in a subset of alkyne–enyne-coupling reactions

Scheme 66B shows a rather powerful coupling process between alkynes and enynes that delivers stereochemically defined hydroindanes by [2 + 2 + 2] annulation.[147] This result has proven unique to enyne substrates bearing 1,1-disubstituted alkenes and furnishes a useful stereoselective entry to densely functionalized hydroindane motifs.

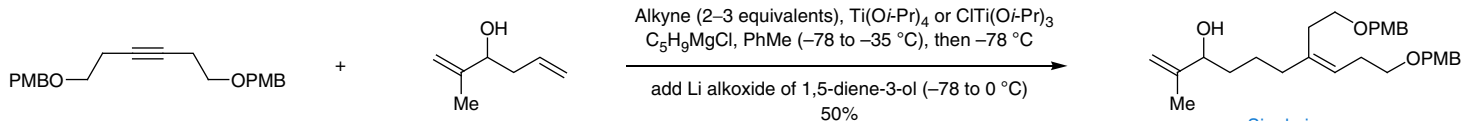
As illustrated in Scheme 66C, a diyne–alkene [2 + 2 + 2] annulation process has also been described that secures an alternative entry to substituted carbocycles.[148] Here, intramolecular alkyne–alkyne coupling produces a metallacyclopentadiene that, through ligand exchange, reacts with the homoallylic alcohol to generate a transient species capable of undergoing annulation. Although the symmetry of the diyne substrate renders these coupling reactions a bit simpler than those described in Scheme 66B (as regioselectivity is not an issue here), these coupling processes proceed with exquisite levels of 1,3-stereochemical control.

5.34.3.11 Other Coupling Reactions that Proceed via [2 + 2 + 2] Annulation

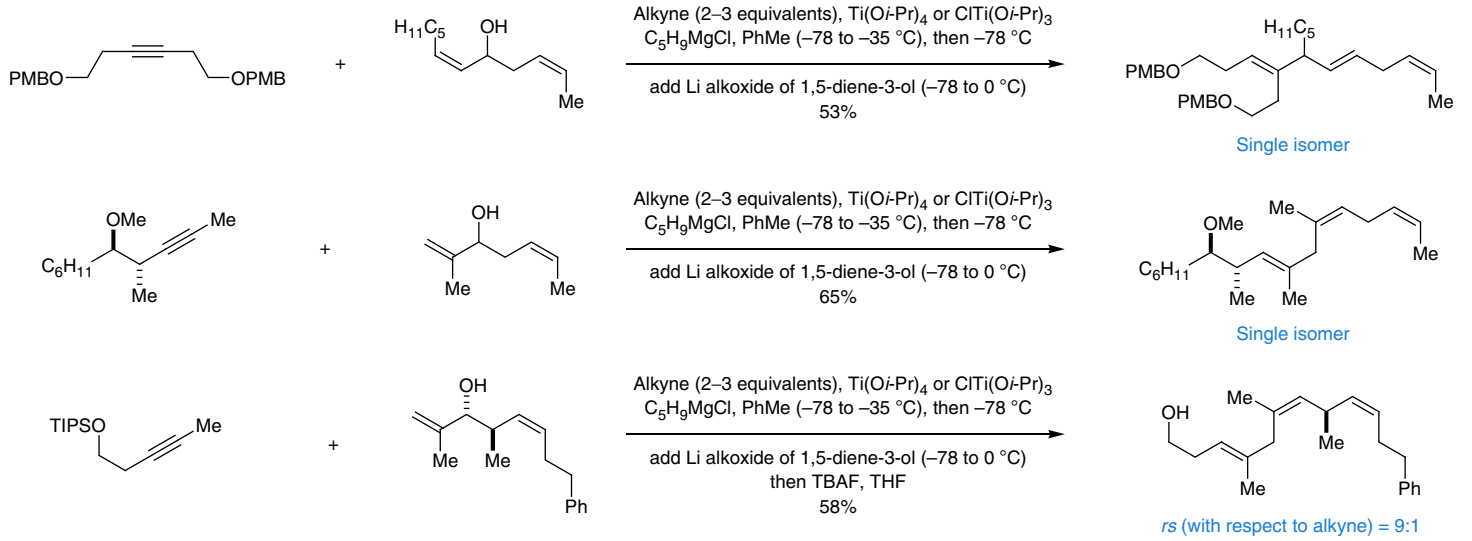
Section 5.34.3.10 that was focused on chemoselectivity in Ti-mediated coupling reactions of polyunsaturated substrates concluded with a brief discussion of some observations in [2 + 2 + 2] annulation chemistry. This section builds on that discussion, as recent advances have described a variety of Ti-mediated [2 + 2 + 2] annulation reactions for the synthesis of aromatic systems. Scheme 67A shows two reactions for the selective cross-coupling of three different alkynes en route to substituted benzenes. The first proceeds via regioselective generation of a metallacyclopentadiene (regioselection for this process was already discussed in association with Scheme 43). Addition of the ethyl sulfone then results in the formation of a metalated benzene by a sequence that has been proposed to proceed through regioselective [4 + 2] cycloaddition, isomerization, and then elimination.[149] In a related report, it was also demonstrated that addition of propargyl bromide to a metallacyclopentadiene intermediate results in regioselective [4 + 2] cycloaddition and elimination to deliver a benzylic organometallic.[150]

Ti-mediated [2 + 2 + 2] annulation has emerged as a powerful approach to the synthesis of substituted pyridines.[100,151,152] As illustrated in Scheme 67B, the collection of reactions defined for [2 + 2 + 2]-based entry to substituted pyridines employ two carbon-based π-systems (alkynes) and one C–N-based π-system (nitrile). Although a variety of distinct approaches to this aromatic heterocycle has been described, they proceed by one of two general pathways. The first of these follows from generation of a metallacyclopentadiene or azametallacyclopentadiene, with subsequent addition of a third sp-based π-system (alkyne or nitrile). Annulation then results in the generation of an organometallic intermediate that can isomerize and ultimately eliminate to generate a metalated pyridine. As illustrated in the first two examples of Scheme 67B, this can proceed through the addition of a sulfonyl nitrile or an ethynyl sulfone. Alternatively, as illustrated in the third example, generation of a metallacyclopentadiene by the coupling of a TMS-alkyne with an aminoacetylene can be followed by addition of a nitrile. Here, annulation delivers an intermediate that can eliminate the sulfonamide moiety – again, generating a metalated pyridine product. As illustrated in the fourth example depicted in Scheme 67B, pyridine synthesis can also proceed by coupling a metallacyclopentadiene with a nitrile. Here, annulation proceeds to deliver an intermediate that rearranges to a Ti–amide complex, protonation of which delivers 2-formyl-substituted pyridine products.

A. Coupling of preformed Ti–alkyne complexes with polyenes: Selective engagement of a terminal alkene via homoallylic alcohol–alkyne coupling:

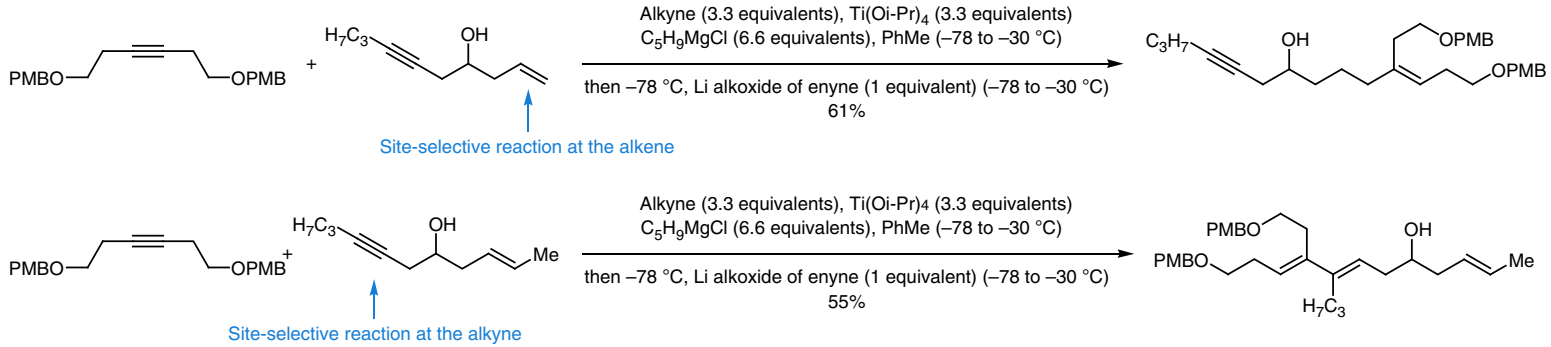


B. Coupling of preformed Ti–alkyne complexes with polyenes: Selective engagement of a subsituted alkene via allylic alcohol–alkyne coupling in preference to homoallylic alcohol–alkyne coupling:

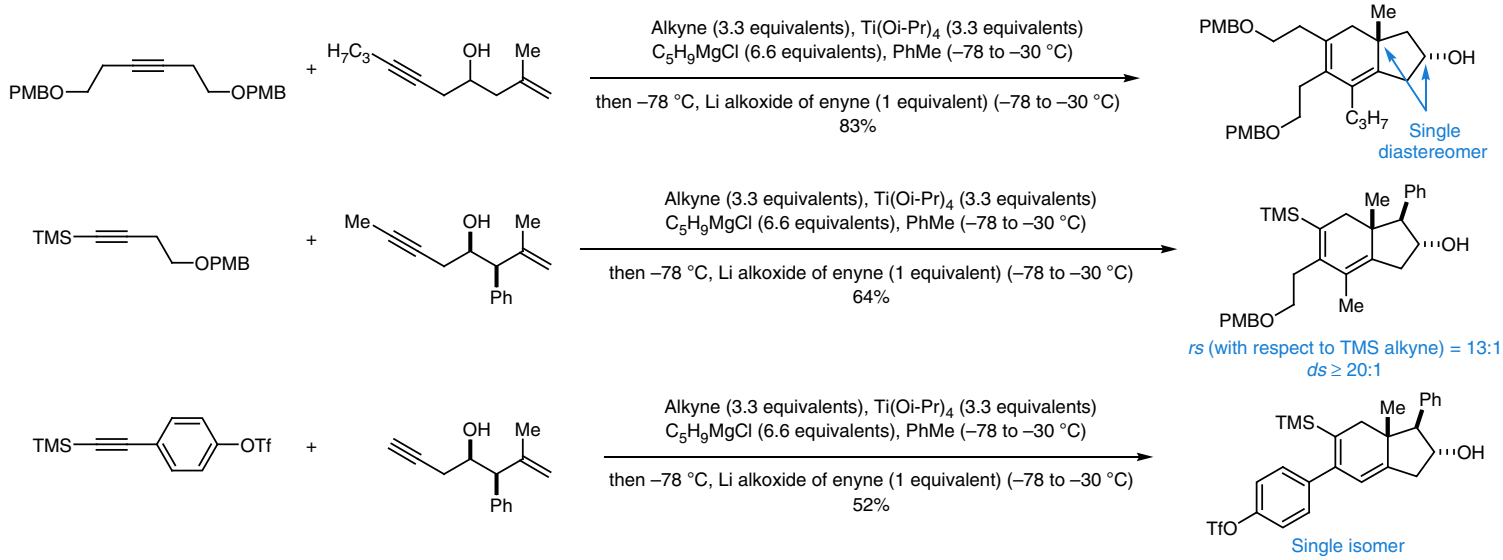


Scheme 65

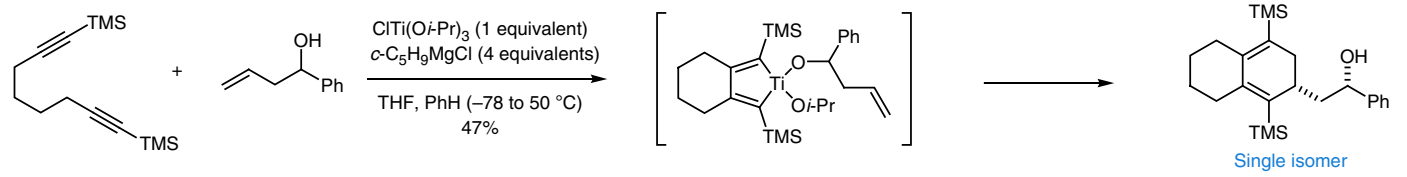
A. Coupling of preformed Ti–alkyne complexes with enynes: Selectivity is a function of the substitution of the π-system.



B. Coupling of preformed Ti–alkyne complexes with enynes: Enynes with 1,1-disubstituted alkenes take part in a highly controlled intermolecular [2+2+2] annulation.

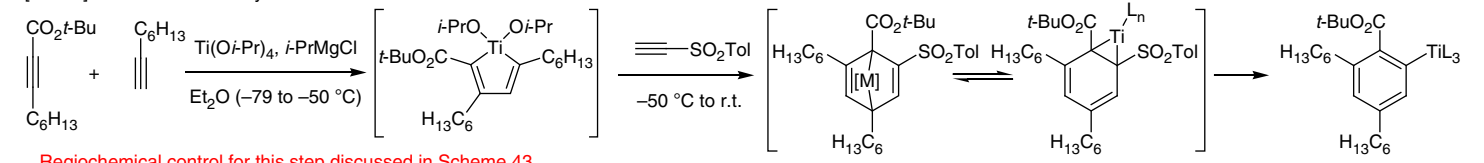


C. Coupling of preformed titanacyclopentadienes with homoallylic alkoxides: A different intermolecular [2+2+2] annulation.

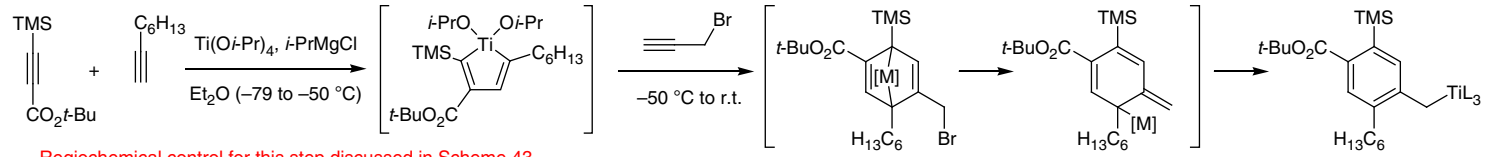


Scheme 66

A. [2+2+2] Annulation for the synthesis of substituted benzenes.

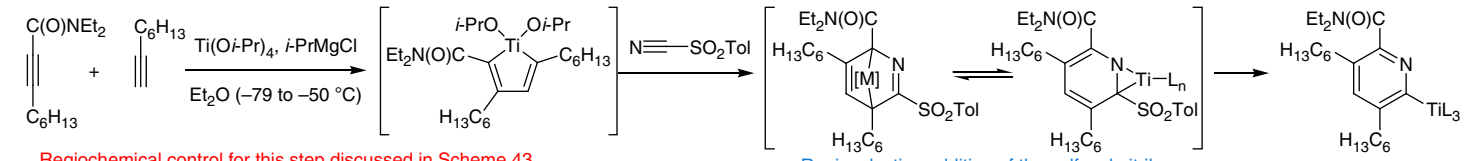


Regiochemical control for this step discussed in Scheme 43 and is based on the CO_2t-Bu group

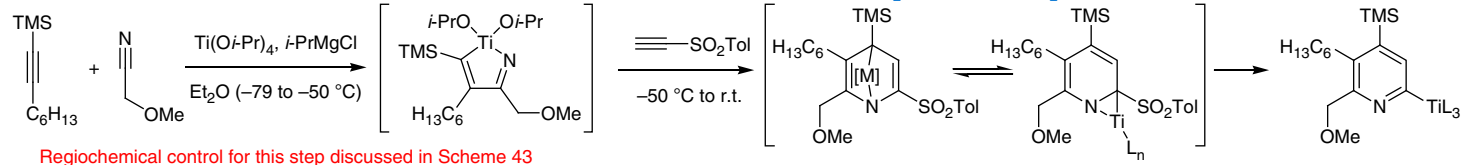


Regiochemical control for this step discussed in Scheme 43 and is based on the TMS group

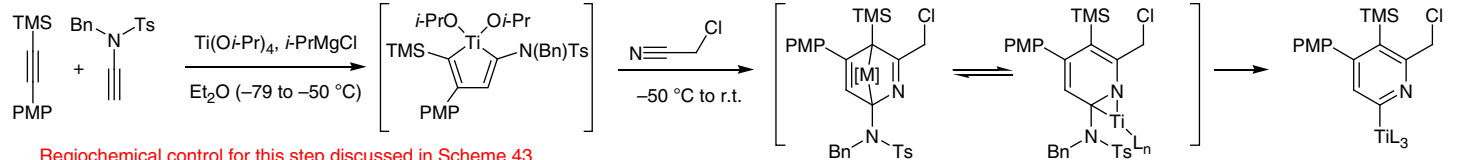
B. [2+2+2] Annulation for the synthesis of substituted pyridines.



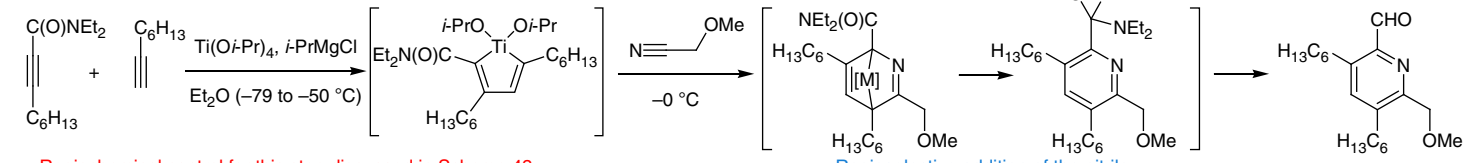
Regiochemical control for this step discussed in Scheme 43 and is based on the $C(O)NEt_2$ group



Regiochemical control for this step discussed in Scheme 43 and is based on the TMS group



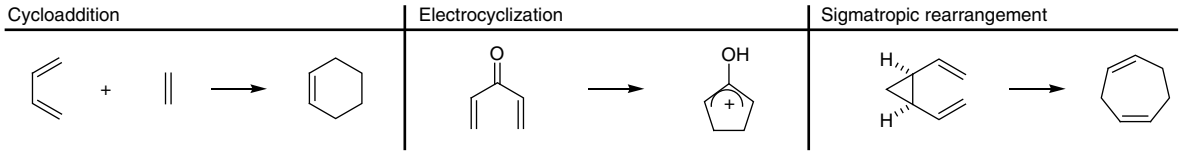
Regiochemical control for this step discussed in Scheme 43 and is based on the TMS group



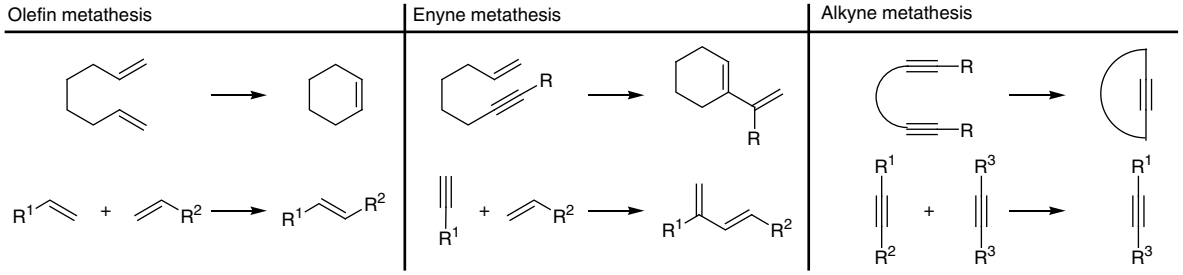
Regiochemical control for this step discussed in Scheme 43 and is based on the $C(O)NEt_2$ group

Scheme 67

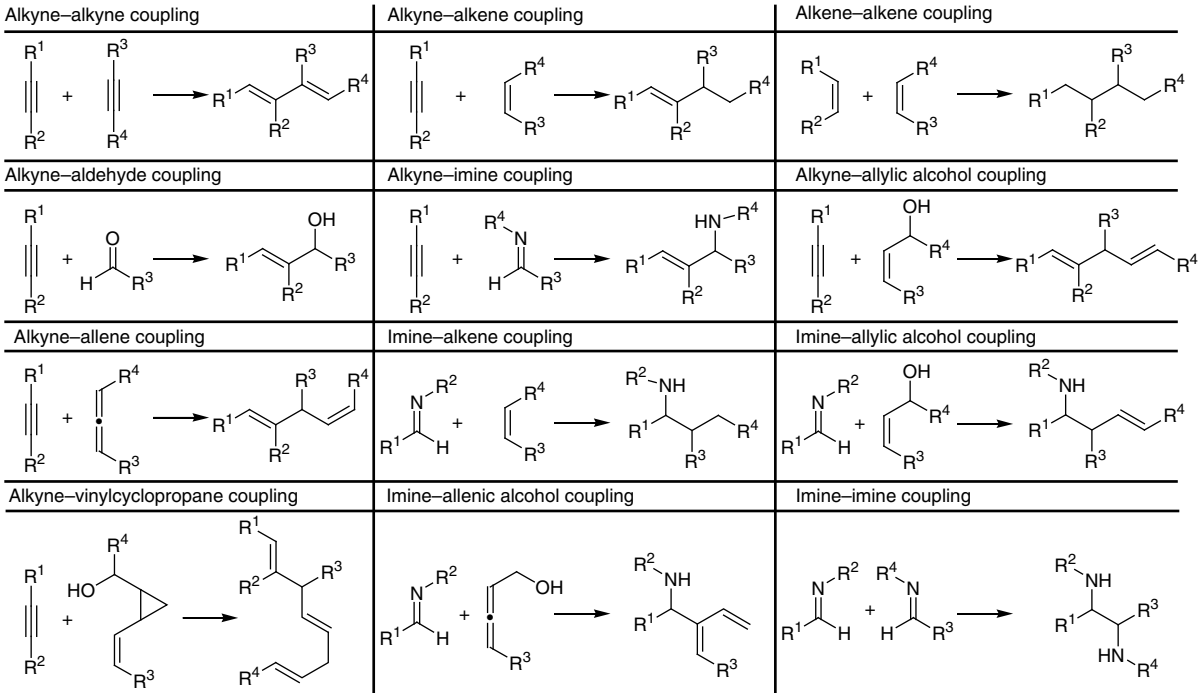
A. Concerted chemistry as a means of accomplishing C–C bond-forming reactions at sites of π-unsaturation.



B. Metathesis as a means of accomplishing C–C bond-forming reactions at sites of π-unsaturation.



C. Early transition metal metallacycle-mediated coupling as a means of accomplishing C–C bond-forming reactions at sites of π-unsaturation.



Scheme 68

5.34.4 Conclusion

Since the initial publication of the first edition of *Comprehensive Organic Synthesis* in 1991, substantial advances have been made in the control of metallacycle-mediated cross-coupling technology. Twenty years ago, the intramolecular versions of this chemistry were secured as a means to generate carbo- and heterocyclic systems, whereas intermolecular variations were substantially limited by (1) the lack of general strategies to control the course of metallacyclopentane formation (i.e., low reactivity, challenges controlling regioselectivity, diastereoselectivity, and pair selectivity) and (2) the functional group compatibility associated with Cp_2Zr- and Cp_2Ti-based systems. As such, only the simplest examples of cross-coupling by metallacycle-mediated coupling chemistry had appeared with a small subset of sparsely functionalized systems.

Major advances since 1991 include the discovery that inexpensive, nontoxic, and easy-to-work-with Ti-alkoxides can be employed as the central metal component. Building on this advance, a collection of heteroatom-directing group strategies have been put forth that offer fine control over reactivity, regio- and stereoselection in intermolecular variants of metallacycle-mediated coupling.

5.34.5 Perspective

Reactions that enable C–C bond formation at sites of π-unsaturation are incredibly important in modern organic synthesis. To date, it has been well accepted that cycloaddition, electrocyclization, and sigmatropic rearrangement chemistry have had a transformative effect in chemical synthesis (**Scheme 68A**). The same can be said for the growing significance of metathesis chemistry (**Scheme 68B**). Given the great diversity of π-systems that can be engaged in early transition metal metallacycle-mediated coupling (a subset of these are depicted in **Scheme 68C**), and the growing body of literature describing general strategies to control reactivity and selectivity for such coupling chemistry, a very bright future for the role of this chemistry in organic synthesis is likely. The emerging power of this chemistry is already becoming evident in the growing number of advances that embrace the chemical reactivity of early transition metals to accomplish the synthesis of a great variety of stereodefined functional groups, aromatic carbo- and heterocyclic systems, and natural product motifs of relevance to the synthesis of terpenes, alkaloids, and fatty acids. Important future advances in this area will include (1) broadening the substrate scope for early transition metal metallacycle-mediated coupling reactions, (2) increasing the scope of π-systems that can be employed in transfer epimetalation chemistry, (3) establishing new strategies to control regio- and stereoselection in metallacycle formation and functionalization, and (4) identifying methods that allow for cross-coupling of notoriously unreactive π-systems without the need of a directing group.

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5.35 Transition-Metal-Catalyzed Cycloaddition of Small Ring Compounds

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Glossary

Migratory insertion The insertion ion of a multiple bond AB into a covalent bond XY with concomitant creation of two covalent bonds AX and BY. X or Y is usually a metal. In the case of carbon monoxide, both new covalent bonds are formed with the carbon atom. Also more simply called insertion.

Oxidative addition The insertion of a metal complex into a covalent bond with concomitant formal loss of two electrons on the metal.

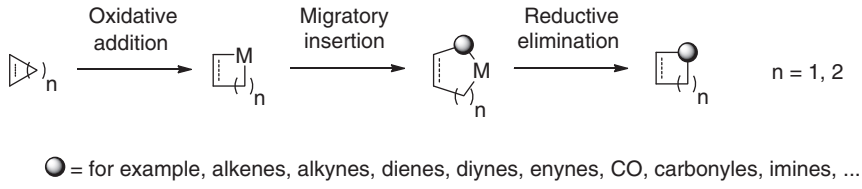
Reductive elimination An elementary step in organometallic chemistry; chemically speaking, a reductive elimination is the reverse of an oxidative addition.

Steric congestion Nonbonded repulsions and deviation from ideal geometry incurred by the substituents on atoms.

Strain energy Additional energy brought to a molecule by unfavorable bond angles and lengths and dihedral angles.

5.35.1 Introduction

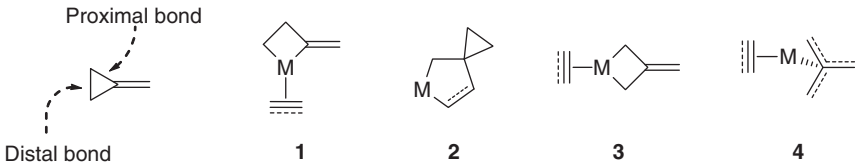
The strain energy of small ring compounds makes them particularly prone to undergo oxidative addition with transition-metal complexes.[1] The intermediates thus formed can react with unsaturated substrates via migratory insertion and give a broad variety of cycloaddition products after reductive elimination (Scheme 1). In the vast majority of transition-metal-catalyzed cycloadditions of small ring compounds, at least one carbon–carbon or carbon–heteroatom multiple bond is present in the substrate and facilitates or directs the oxidative addition.



Scheme 1

5.35.2 Cycloadditions of Methylene- and Alkylidenecyclopropanes

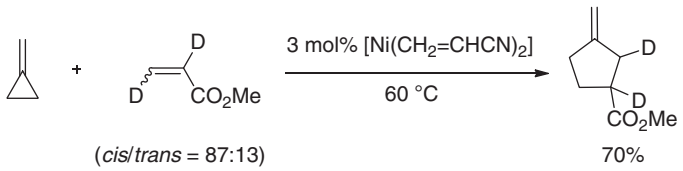
Although highly strained, methylene- and alkylidenecyclopropanes are stable at room temperature. Cleavage of the proximal bond, via metallacyclobutane **1** and α-cyclopropylmethylmetal **2**, or the distal bond, via metallacyclobutane **3** or a trimethylenemethane metal complex **4**, has been observed in the transition-metal-catalyzed cycloadditions of those substrates (Scheme 2).[2]



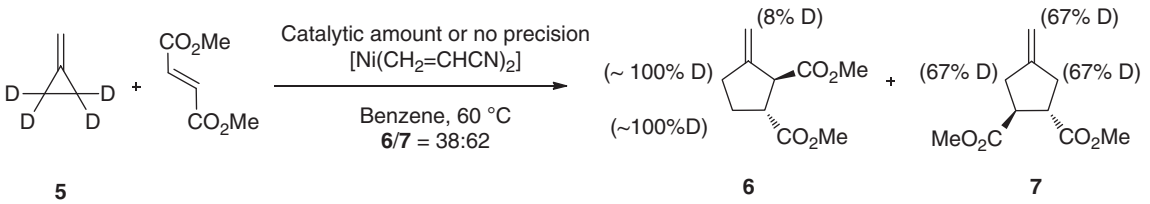
Scheme 2

5.35.2.1 Intermolecular Cycloadditions

The reactions catalyzed by nickel complexes are very sensitive to the ligand sphere and the substrates. Both proximal and distal cleavages are possible. For example, it was shown that an intermediate of type **1** is plausible in the [3 + 2] cycloaddition of methylenecyclopropane with deuterated methyl acrylate (equation 1).[3] Conversely, the reaction of deuterated methylenecyclopropane **5** with dimethyl fumarate gave compound **6**, resulting from a proximal cleavage, and compound **7**, likely formed via an intermediate of type **4**, as indicated by the statistical scrambling of deuterium over three carbon atoms (equation 2).[4]



(1)

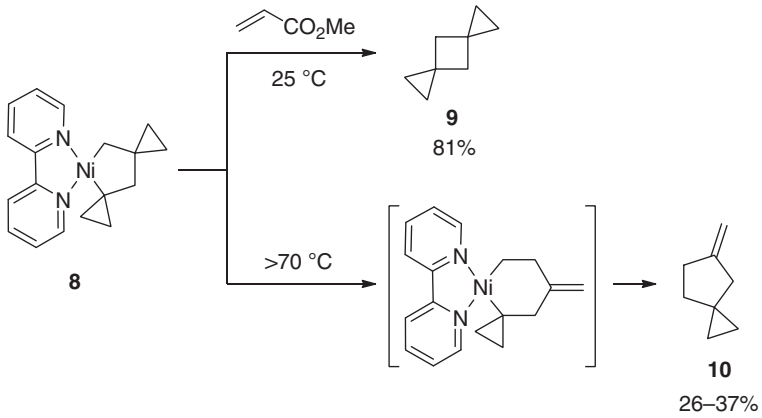


(2)

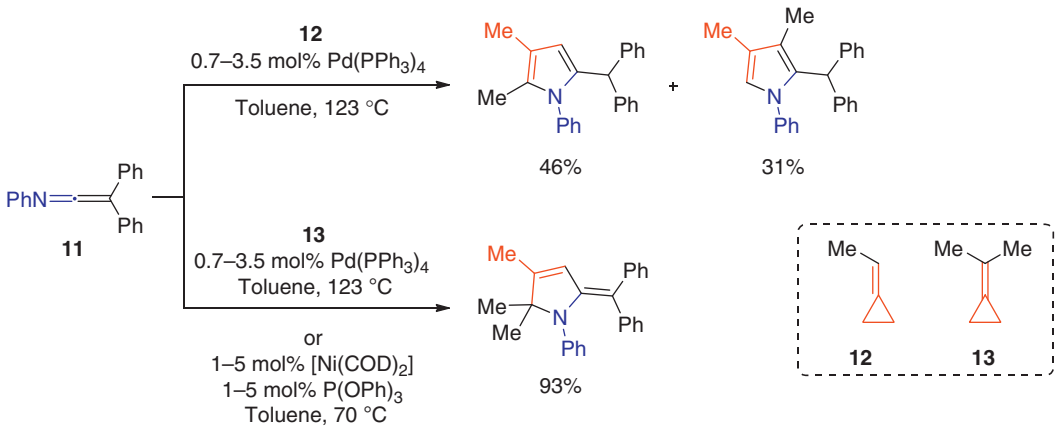
Moreover, the possibility of intermediates of type **2** in nickel-catalyzed dimerizations of methylenecyclopropane[5] has been demonstrated experimentally.[6] Hence, treatment of nickelacyclopentane **8** with an excess of methyl acrylate at room temperature led to the formation of the [2 + 2] dimerization product **9**, whereas heating of **8** above 70 °C afforded the [3 + 2] dimerization product **10** after rearrangement (Scheme 3).

In contrast to the nickel-catalyzed reactions, the regioselectivity of the ring cleavage of methylenecyclopropanes in [3 + 2] cycloadditions catalyzed by palladium complexes is much more consistent and likely proceeds through intermediates **3**.[7] In accordance with experimental results, computational investigations suggest that distal oxidative addition should be preferred over proximal addition.[8] Nevertheless, even if the cleavage of the small ring is completely regioselective, intermolecular reactions with substituted methylenecyclopropanes can lead to mixtures of products in certain cases.[2] For example, a mixture of regioisomers was obtained in the palladium-catalyzed cycloaddition of triphenylketimine **11** with **12**, whereas both palladium- and nickel-catalysts led to selective reactions with **13** (Scheme 4).[9] All products resulted from cleavage of the distal carbon–carbon bond in **12** and **13**. Palladium-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes have also been described with aldehydes[10] and aldimines[11] (Scheme 5), giving products of distal bond cleavage in almost equimolar diastereomeric ratio.

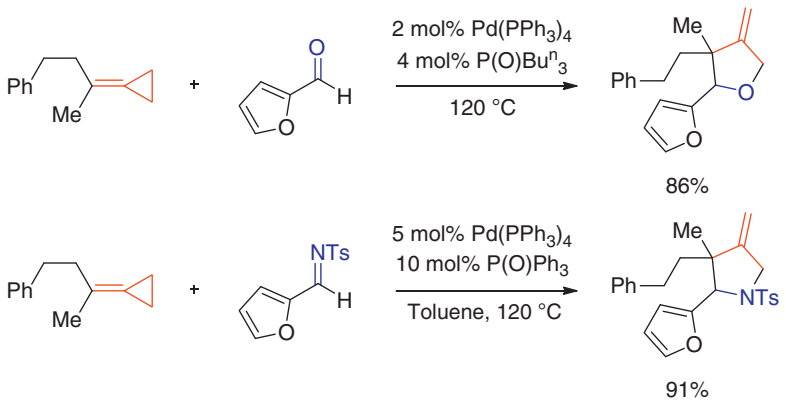
As mentioned in the introduction, the scope of reactants in transition-metal-catalyzed cycloadditions of small rings compounds is vast.[2] For example, cleavage of the less substituted carbon–carbon bond of the cyclopropane afforded the major product in the cobalt-catalyzed [3 + 1] carbonylative cycloaddition of **14** (equation 3).[12]



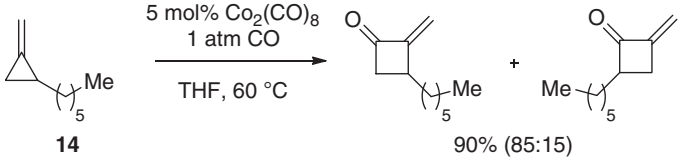
Scheme 3



Scheme 4

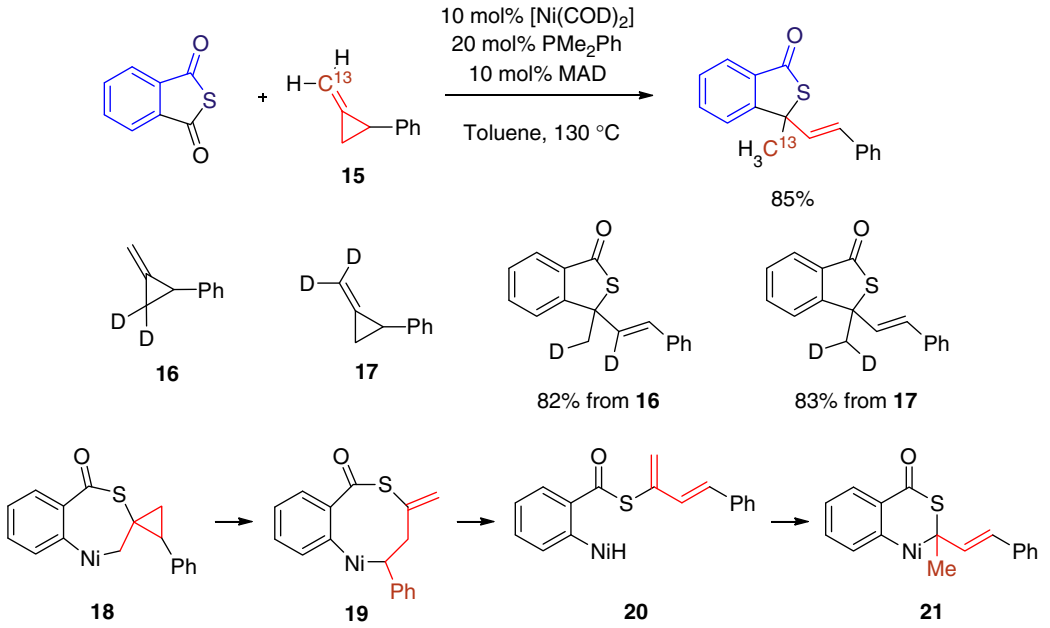


Scheme 5

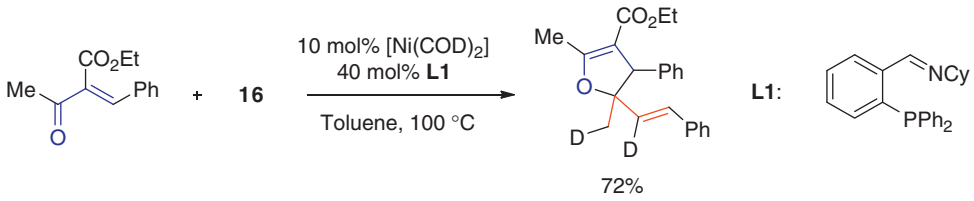


(3)

In addition, recent reports disclosed the use of methylenecyclopropanes as one-carbon unit in nickel-catalyzed cycloaddition reactions,[13,14] in contrast to the examples previously commented in this section, which all involved reactions where this motif was used as a three-carbon unit. Results of mechanistic studies with isotope-labeled compounds **15**–**17** (Scheme 6) were in good agreement with a catalytic cycle involving the rearrangement of α-cyclopropylcarbinylnickel intermediate **18** to homoallylnickel **19** with concomitant cleavage of the more sterically hindered carbon–carbon bond of the cyclopropane ring, followed by β-hydride elimination toward **20** and hydrometallation to give **21** before final reductive elimination.[13] A similar mechanism is likely operative in the [4 + 1] cycloadditions with α,β-unsaturated enones (equation 4).[14]



Scheme 6

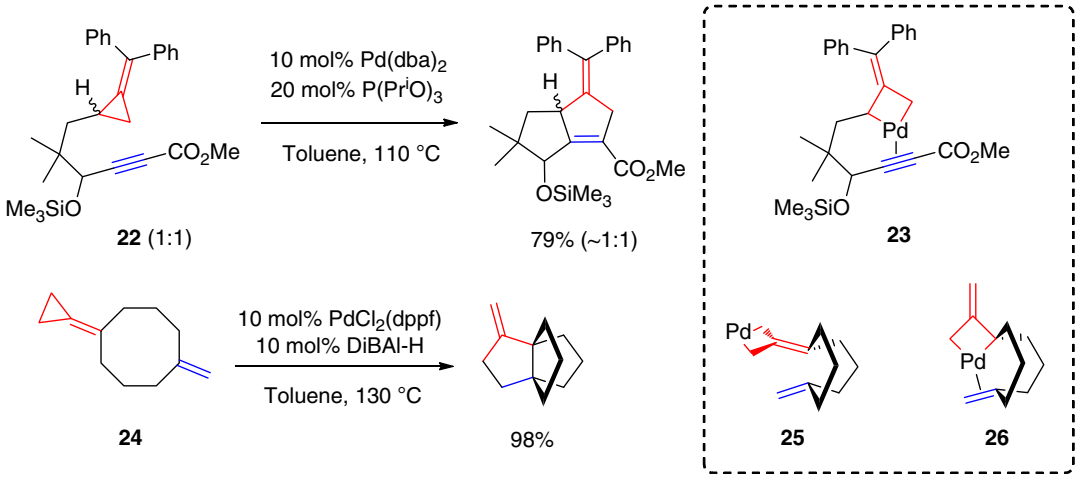


(4)

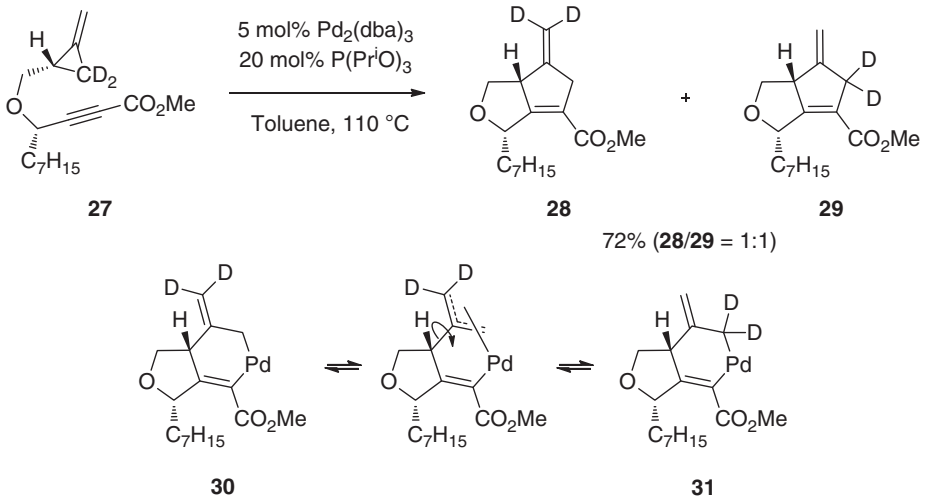
5.35.2.2 [3 + 2] Intramolecular Cycloadditions

The tether, placed between the methylenecyclopropane moiety and a carbon–carbon multiple bond, allows the regioselectivity of intramolecular [3 + 2] cycloadditions to be improved. For example, cleavage of the proximal bond in **22** presumably leads to intermediate **23**, which is poised for a high-yielding cycloaddition,[15] whereas the reaction of **24** likely proceeds through **25**, which can rearrange into **26** (Scheme 7).[16] It was also shown that the ratio of compounds **28** and **29** was constant during the conversion of **27**, whereas no deuterium scrambling was observed in recovered starting material (Scheme 8).[17] This is in agreement with a rapid alkyne insertion toward palladacycles **30** and **31**, followed by a rate-limiting reductive elimination. Presumably, intramolecular coordination to the metal stabilizes the metallacyclobutane intermediates in these reactions. Importantly, the observed retention of configuration at the cyclopropane carbon atom in **27** rules out a mechanism involving a trimethylenemethane intermediate, as this would lead to an inversion of the configuration.

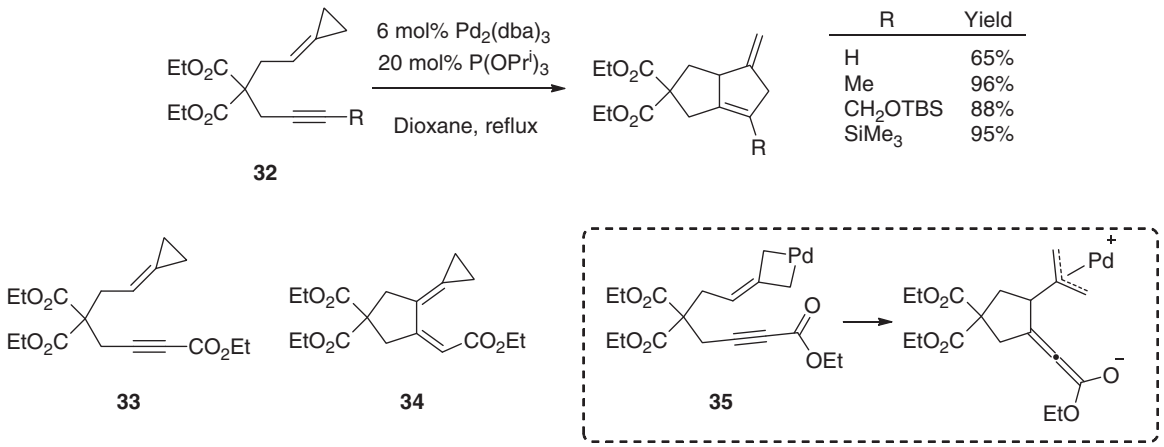
However, computational studies[18] suggest that trimethylenemethane intermediates are plausible in the reaction of substrates **32** (Scheme 9).[19] Moreover, it is noticeable that alkylidenecyclopropane **33** did not afford any [3 + 2] cycloaddition products. Instead, compound **34** was identified in the crude reaction mixtures, which could be formed by intramolecular conjugate addition to the electron-poor alkyne **35**.[18] This result is in striking contrast with the reactions of ester-substituted alkynes **22** and **27**.[15,17]



Scheme 7

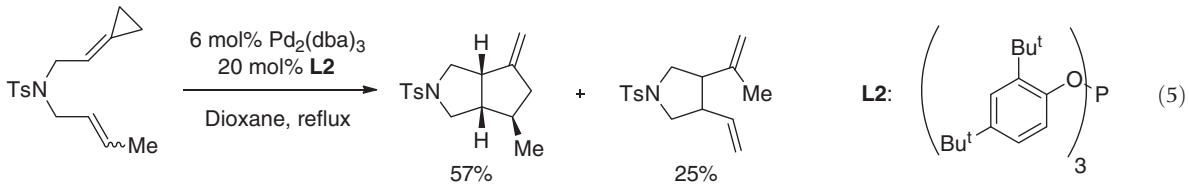


Scheme 8



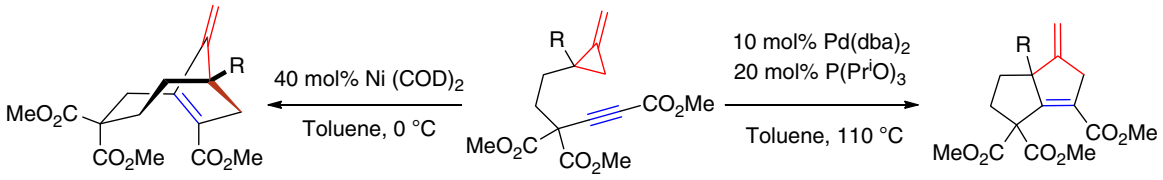
Scheme 9

Bicyclic products of distal bond cleavage were also obtained in rhodium[20] and ruthenium-catalyzed[21] intramolecular [3 + 2] cycloadditions, albeit the latter reaction likely follows a different mechanistic manifold. In palladium-catalyzed reactions, the alkyne moiety could be replaced with an allene.[22] However, replacement with an electron-poor or terminal alkene caused stereoselectivity issues, whereas a methyl-substituted alkene afforded a product by competitive β-hydride elimination in addition to the desired bicyclic product (equation 5).[23]



(5)

It was established early on that a nickel catalyst could lead via proximal bond cleavage to antiBredt products **36**, albeit in incomplete conversions and moderate isolated yields, whereas treatment of the same starting material with a palladium catalyst led to formation of **37**, resulting from the expected cleavage of the distal C–C bond of the methylenecyclopropane moiety (Scheme 10).[24] As illustrated in a recent study (equation 6),[25] nickel-catalysts tend to afford only products resulting from proximal bond cleavage in an intramolecular [3 + 2] cycloaddition.



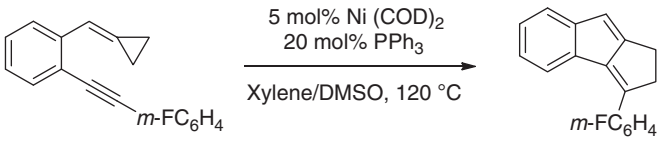
36

50%, R = Me
20%, R = H

37

59%, R = Me
40%, R = H

Scheme 10



68%

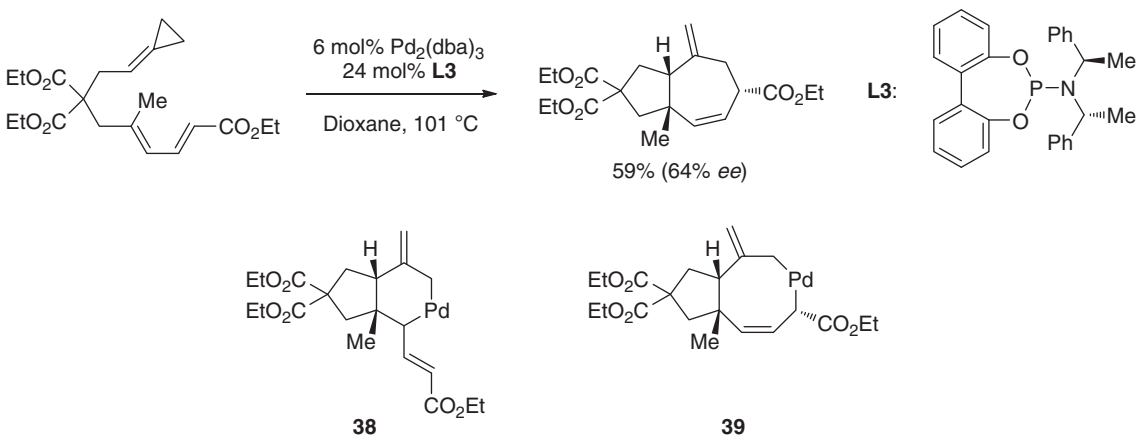
(6)

5.35.2.3 Higher Order Cycloadditions

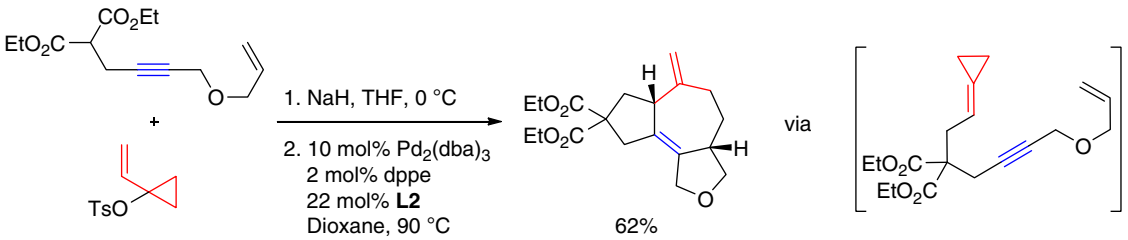
In the last decade, increasingly complex combinations of unsaturated compounds have been used in transition-metal-catalyzed higher order inter- and intramolecular cycloadditions of alkylidenecyclopropanes, which serve as a three-carbon unit in those reactions. For example, seven-membered ring compounds could be prepared enantioselectively in a palladium-catalyzed [4 + 3] cycloaddition of alkylidenecyclopropanes tethered to a 1,3-diene (Scheme 11).[26] The reductive elimination of the putative palladacycle intermediates **38** and **39** could not be made completely selective in favor of the latter and mixtures of five- and seven-membered rings were typically obtained. Nevertheless, this approach enabled the rapid assembly of polycyclic compounds (Scheme 12).[27]

A rapid increase of complexity is also evident in the intermolecular [3 + 2 + 2] cycloadditions depicted in Scheme 13.[28] The seven-membered rings **40** and **41** were obtained as single diastereomers ($ds \geq 19{:}1$). Comparison of the **40**/**41** ratios suggest that intermediate **42** is more likely than **43** because the steric influence of the group R^2 on the regioselectivity of the migratory insertion of the alkyne is likely to be stronger in **42** than in the intermediate leading to **43**.

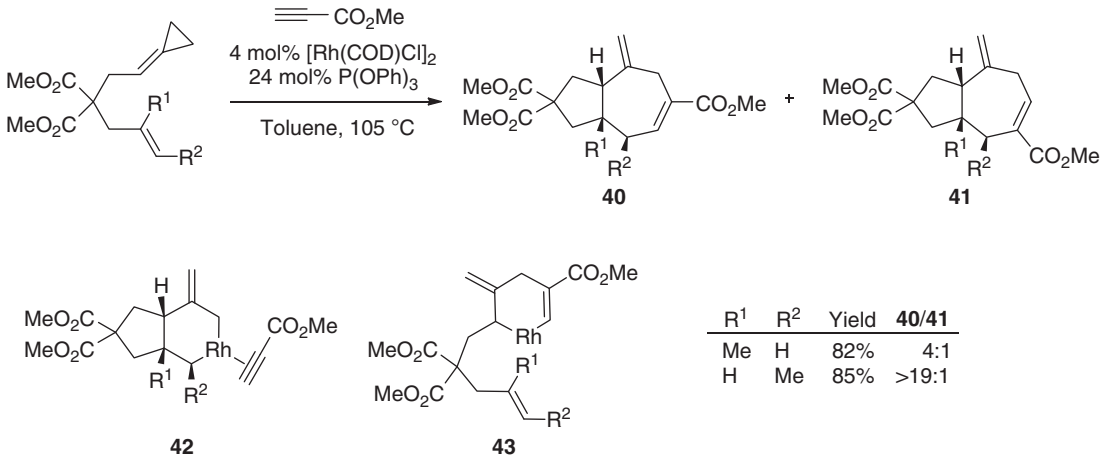
Two-[29] and three-component[30] nickel-catalyzed [3 + 2 + 2] cycloadditions of alkylidenecyclopropane **44** have also been reported (Scheme 14). The reaction is only possible with electron-poor **44**, which is in good accordance with a mechanistic sequence consisting of a conjugated addition of intermediate **45**, followed by a rearrangement of the α-cyclopropylcarbinylnickel **46** to homoallylnickel **47**.[31] In certain cases, conformational flexibility of the intermediates led to a mixture of stereoisomers through cleavage of both proximal bonds *a* and *b* of the cyclopropane ring, as exemplified in the spectacular [4 + 3 + 2] cycloaddition depicted in Scheme 15.[32] Similar observations have been made in the nickel-catalyzed reactions of 1,5- and 1,6-diynes with **44**.[33]



Scheme 11



Scheme 12



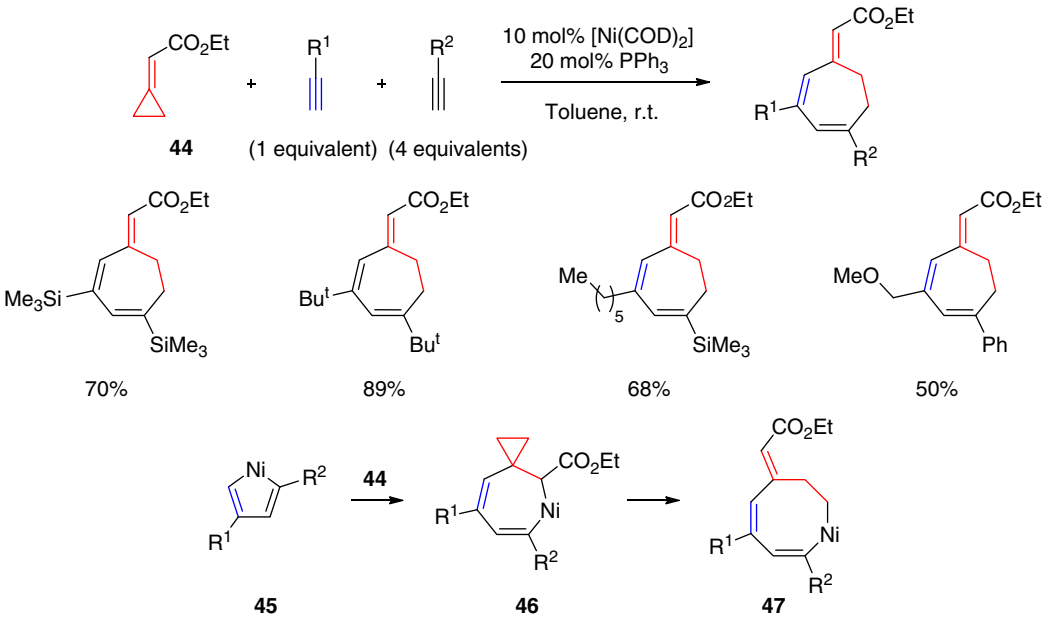
R^1	R^2	Yield	**40/41**
Me	H	82%	4:1
H	Me	85%	>19:1

Scheme 13

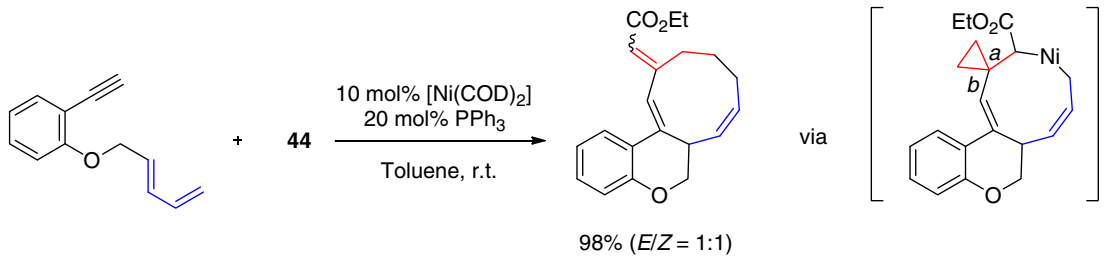
The proposed intermediate **48** is in good agreement with the results of experimental studies conducted with an isotope-labeled substrate (Scheme 16).[34] Importantly, calculations indicate that intramolecular alkyne coordination to the metal, as depicted in **48**, is essential to the process. Moreover, coordination of electron-poor alkenes (α,β-unsaturated ketone, ester, and phenylsulfone) would also facilitate migratory insertion of the alkyne into the carbon–nickel bond.

5.35.2.4 Cycloadditions of Bicyclopropylidene

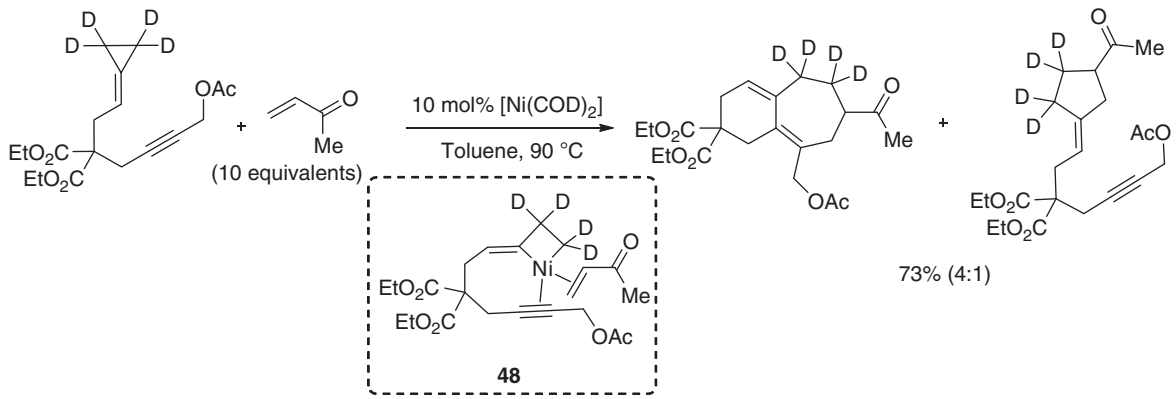
Although the major product of the palladium-catalyzed [3 + 2] cycloaddition of dimethylmethylenecyclopropane with diethyl fumarate displayed an intact alkylidene group, a similar cycloaddition with bicyclopropylidene **49** gave spirocyclic compound **50**



Scheme 14

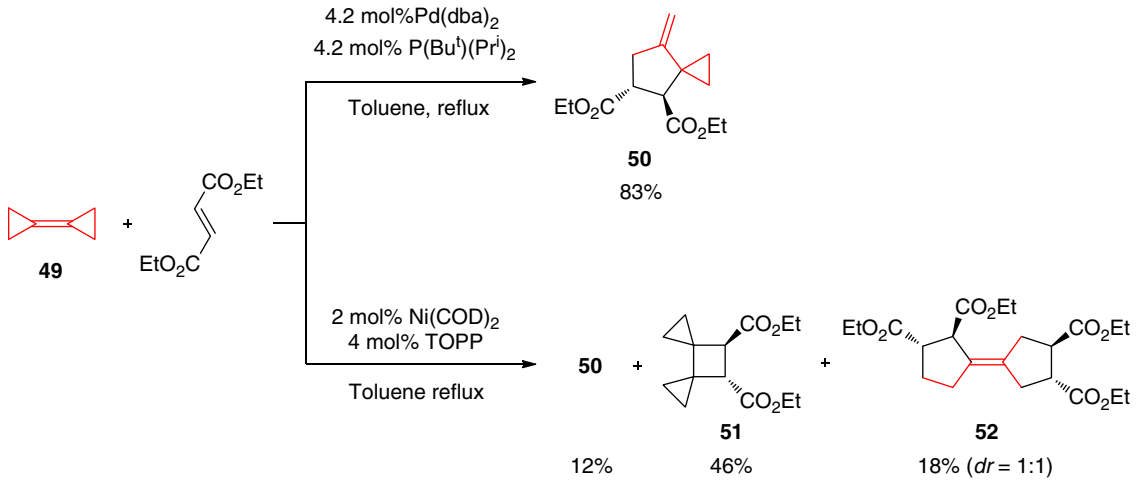


Scheme 15

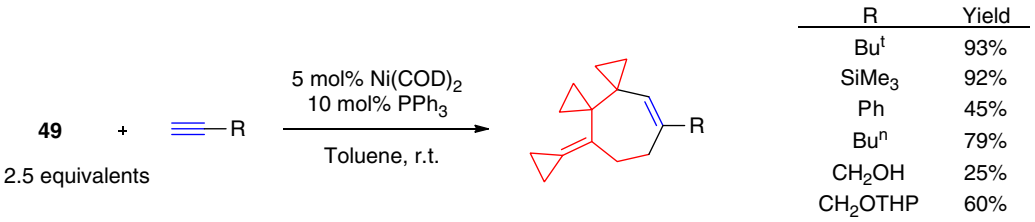


Scheme 16

(Scheme 17).[35] The reaction catalyzed by a nickel complex led to the formation of **50–52**, illustrating the often observed lack of regioselectivity of purely intermolecular nickel-catalyzed reactions of methylenecylopropanes and their derivatives. As a rare exception, a nickel-catalyzed [3 + 2 + 2] between two molecules of bicyclopropylidene and terminal alkynes proceeded only by proximal bond cleavage (equation 7).[36]



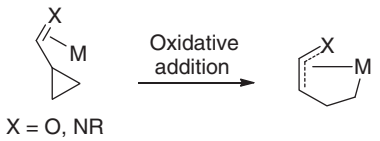
Scheme 17



(7)

5.35.3 Cycloadditions of Other Cyclopropane Derivatives

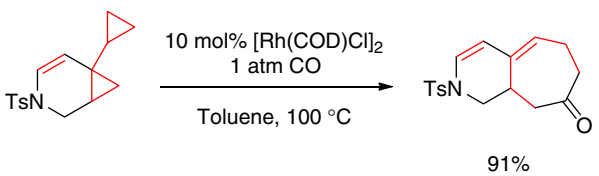
Besides methylene- and alkylidenecyclopropanes, vinylcyclopropanes represent the most versatile class of compounds used in transition-metal-catalyzed cycloaddition reactions and this chemistry has been reviewed extensively.[2c,37] A common principle underlies the reactions of vinyl, allenyl-, and propargylcyclopropanes, as well as reactions involving cyclopropylketones and imines. Namely, these compounds are prone to undergo oxidative ring opening on coordination of a metal complex to the carbon–carbon or carbon–heteroatom multiple bond of the substrate (Scheme 18). Hence, such compounds are useful as three- or five-atom building blocks in cycloaddition reactions.



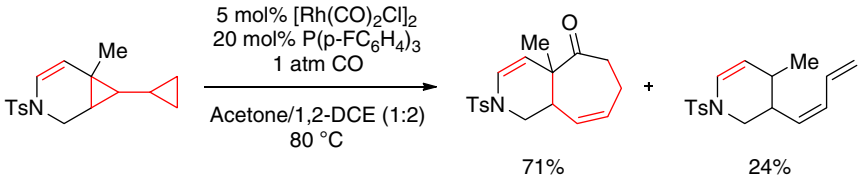
Scheme 18

5.35.3.1 Carbonylative [6 + 1] Cycloaddition of Biscyclopropanes

In line with the general principle depicted in Scheme 18, biscyclopropane derivatives with a vinyl substituent can undergo rhodium-catalyzed [6 + 1] (or [3 + 3 + 1]) carbonylative cycloadditions to give bicyclic compounds (equations 8 and 9).[38]



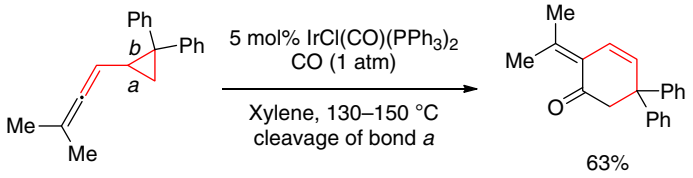
(8)



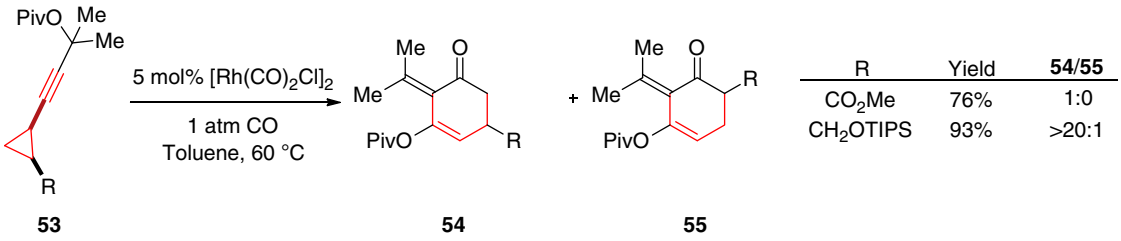
(9)

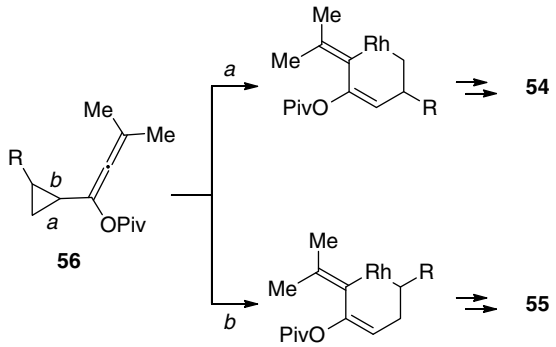
5.35.3.2 Carbonylative [5 + 1] Cycloadditions of Propargyl- and Allenylcyclopropanes

A neutral iridium catalyst was used to promote the regioselective [5 + 1] cycloaddition of allenylcyclopropanes with cleavage of the less sterically congested carbon–carbon bond of the cyclopropane ring (equation 10).[39] Similarly, it was shown that allenylcyclopropanes were plausible intermediates in the rhodium-catalyzed cycloaddition of propargylcyclopropanes **53** toward cyclohexenones **54** and **55** (Scheme 19).[40] Hence, minimization of steric congestion and cleavage of the less sterically hindered bond in intermediate **56** would again explain the regioselectivity observed for this reaction. However, aromatic or vinyl substituents showed a strong directing effect on the regioselectivity of the reaction, overcoming the effects of steric congestion.



(10)





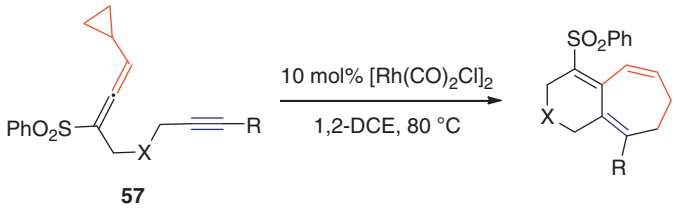
Scheme 19

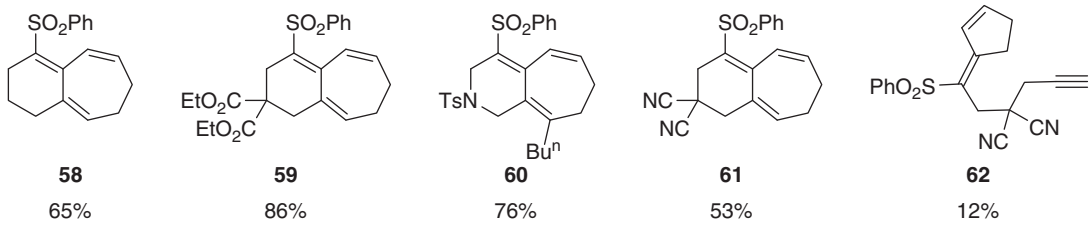
5.35.3.3 [5 + 2] Cycloaddition of Allenylcyclopropanes

Under similar reaction conditions but without carbon monoxide atmosphere, alkyne-tethered allenylcyclopropanes **57** can undergo intramolecular [5 + 2] cycloadditions and afford bicyclic compounds **58**–**60** in good yields, even at room temperature (Scheme 20).[41] The cycloisomerization of the allenylcyclopropane moiety can become a significant side reaction in some cases, as illustrated with the isolation of **62** alongside **61**. Nevertheless, the reaction is general and tethers extended by one methylene unit were tolerated, although they required the use of a modified catalyst. Moreover, it was demonstrated that the phenylsulfonyl substituent on the allene moiety is not essential.

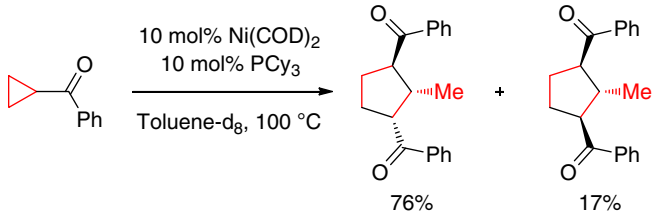
5.35.3.4 [3 + 2] and [5 + 2] Cycloaddition Reactions of Cyclopropyl Ketones and Imines

In the presence of nickel catalysts, cyclopropylketones underwent dimerization (equation 11)[42] or [3 + 2] cycloaddition with enones (equation 12),[43] which must be added slowly using a syringe pump.

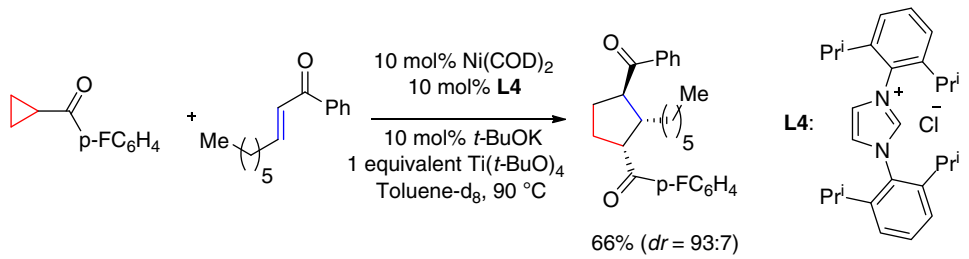




Scheme 20



(11)



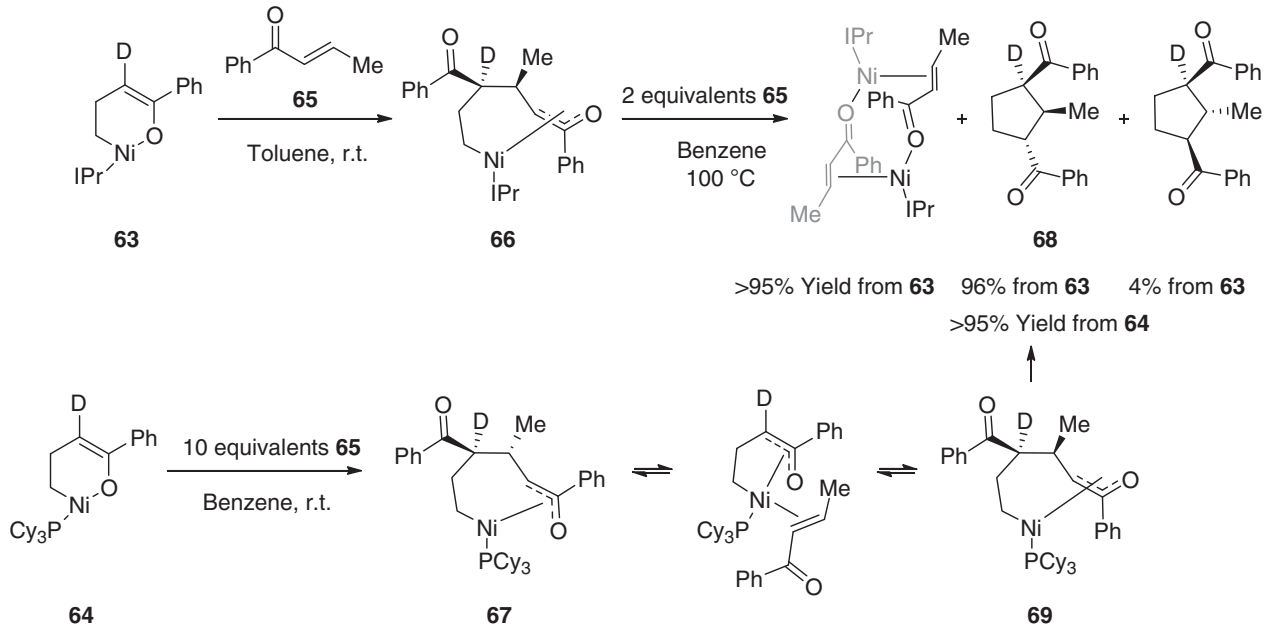
(12)

Careful mechanistic studies with isolated nickel complexes have recently revealed that six-membered hetero-nickelacycles, such as **63** and **64**, are key intermediates of the reactions (Scheme 21).[44] Interestingly, both intermediates reacted with enone **65** as nickel enolates, giving **66** and **67**, respectively. However, the nickel-*N*-heterocarbene complex **63** gave *syn*-**66** whereas the nickel–phosphine complex **64** gave *anti*-**67**. The reductive elimination of **63** afforded **68** as major diastereomer in the presence of an excess of enone **65** at elevated temperature, whereas the same diastereomer was obtained quantitatively at room temperature after isomerization of *anti*-**67** into *syn*-**69**.

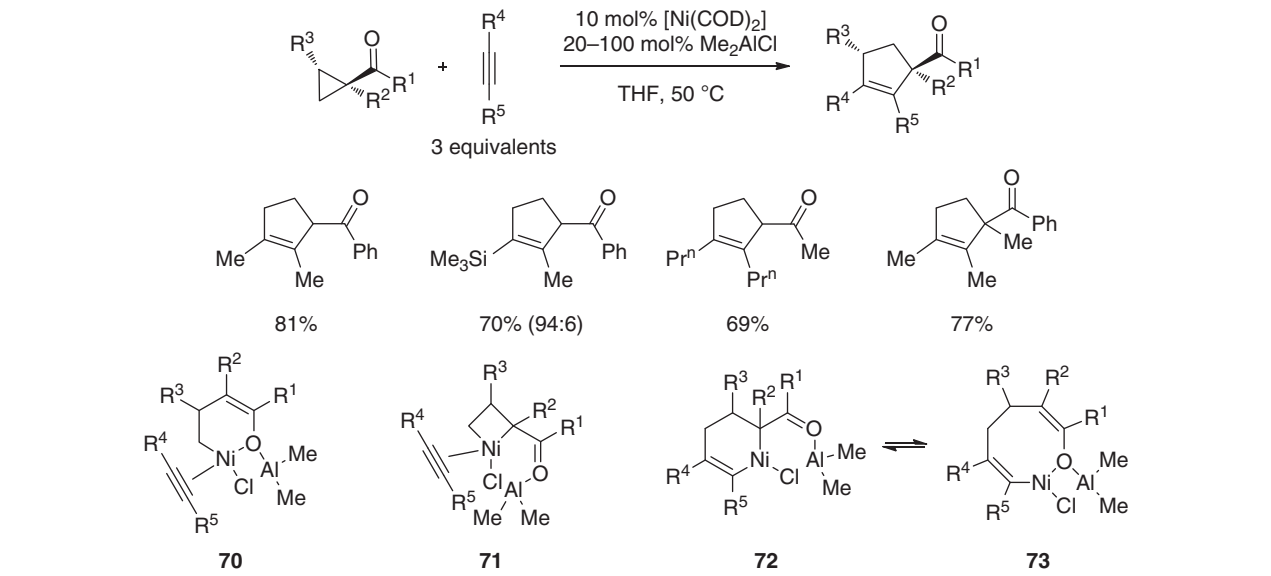
Addition of Me_2AlCl was crucial for the [3 + 2] cycloaddition of cyclopropylketones and various alkynes to occur in the presence of $[Ni(COD)_2]$ (Scheme 22).[45] In contrast to the cycloaddition reactions with enones,[42–44] mechanistic studies suggest that the six-membered heteronickelacycle **70** is unlikely as an intermediate.[45] The reaction is thought to proceed instead through intermediate **71** which would undergo alkyne migratory insertion to give **72**. The scope of the reaction indicates that the regioselectivity of this insertion is governed by steric factors. Moreover, the epimerizations observed with substituted cyclopropanes ($R^3 \neq H$) suggest the possibility of equilibrium between **72** and **73**.

The rhodium-catalyzed regio- and stereospecific carbonylation of cyclopropyl ketone (1*R*,2*R*)-**74** gave bicyclic furanone **75** in good yield (Scheme 23).[46] Interestingly, the (1*R*,2*S*)-diastereomer of **74** gave only the isomerization product **76** in 72% yield. Intermediates **77** and **78** have been proposed to explain the formation of **75**. However, the oxidative addition of the catalyst to the more sterically congested bond of the cyclopropane ring seems counterintuitive and in contradiction with the general trend observed with nickel-catalyzed [3 + 2] cycloadditions of cyclopropylketones and their dimerization.[42–45]

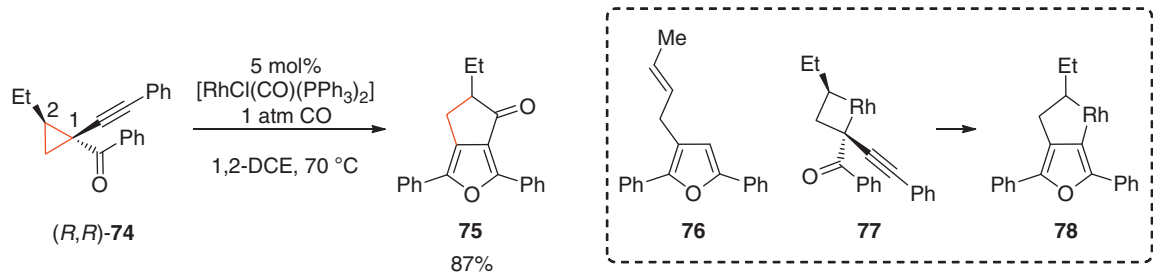
Cyclopropyl aldimines also underwent nickel-catalyzed [3 + 2] cycloaddition with enones (equation 13).[47] Yields were generally higher than those obtained from cyclopropylketones.[43] It was shown that the dimerization of cyclopropylaldimines does not occur in the absence of enone, in stark contrast to the dimerization of cyclopropylketones.[42] The diastereoselectivity of the reaction was altered by epimerization during imine hydrolysis, although it was demonstrated that the same diastereomer is kinetically formed in the reactions of cyclopropylketones and imines.



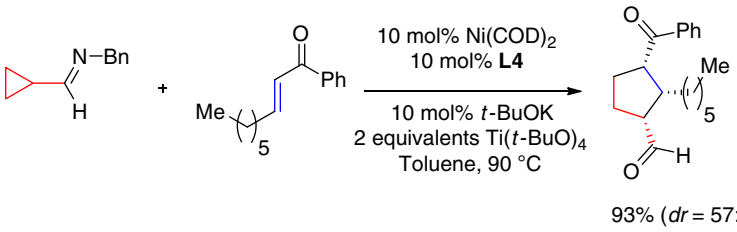
Scheme 21



Scheme 22

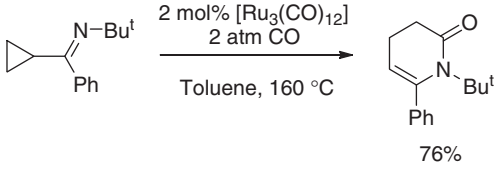


Scheme 23

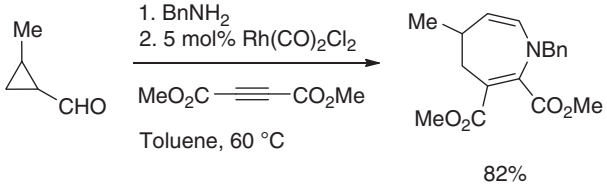


(13)

Cyclopropylimines are also good substrates for ruthenium-catalyzed [5 + 1] carbonylative cycloadditions (equation 14)[48] and rhodium-catalyzed [5 + 2] cycloadditions[49] with dimethyl acetylenedicarboxylate (DMAD) (equation 15).



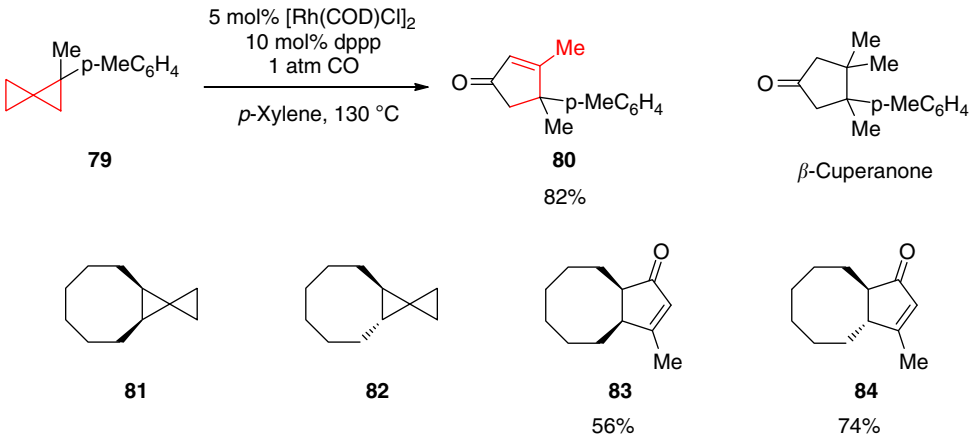
(14)



(15)

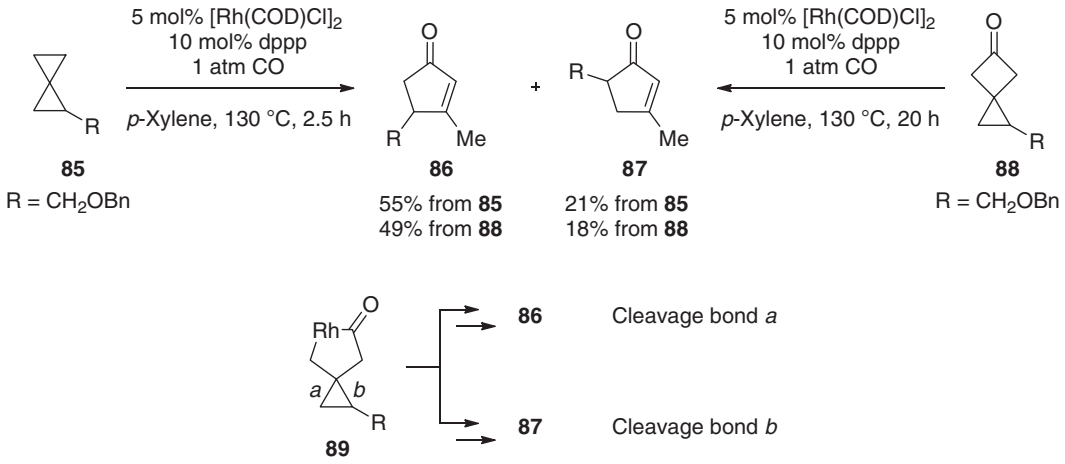
5.35.3.5 Cycloadditions of Highly Strained Cyclopropanes

Because of their great strain energy, spiropentanes can undergo oxidative addition without intervention of a carbon–carbon or carbon–heteroatom multiple bond. For example, the rhodium-catalyzed carbonylation of spiropentane **79** led to the regioselective formation of cyclopentenone **80**, a precursor of racemic *β*-cuparenone (Scheme 24).[50] Diastereomers **81** and **82** gave **83** and **84**, respectively, which indicates that the reaction is stereospecific. Monosubstituted spiropentane **85** gave a mixture of regioisomers **86** and **87** in almost the same ratio as the ratio obtained in the isomerization of spirocyclopropanecyclobutanone **88** (Scheme 25).[51] This result is in support of a mechanistic rationale featuring intermediate **89** which would preferentially undergo cleavage of the less sterically hindered carbon–carbon bond.

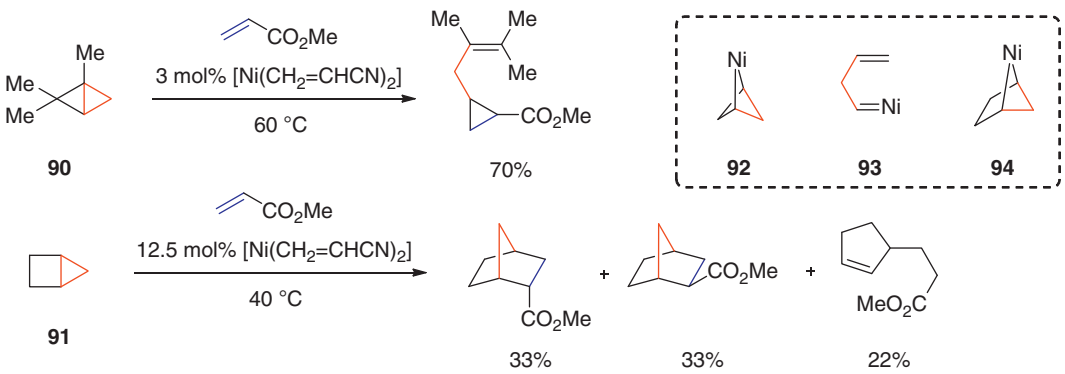


Scheme 24

Similarly, the high-strain energy of bicyclo[1.1.0]butane **90** and bicyclo[2.1.0]pentane **91** facilitates their use in metal-catalyzed cycloadditions (Scheme 26).[52] Experiments with deuterium-labeled substrates indicated the likeliness of oxidative addition intermediates **92** and **94**. The allyl-cyclopropanes obtained from **90** probably resulted from a rearrangement of **92** into a nickel-carbene **93**. It was shown with dimethyl fumarate and maleate that the reactions are stereospecific.



Scheme 25



Scheme 26

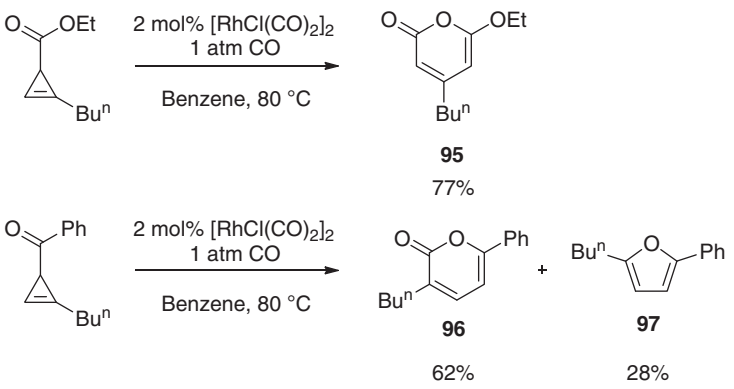
5.35.4 Cycloadditions of Cyclopropenes

Cyclopropenes are another class of small ring compounds prone to react with transition-metal complexes. The carbon–carbon double bond embedded into the three-membered ring can act as an anchor in a formal oxidative addition which likely proceeds through disrotatory ring opening to give a vinyl-carbene or metalacyclobutene. As exemplified in this section, this mode of reactivity seems prevalent in rhodium(I)-catalyzed reactions. Conversely, palladium(0)-catalysts tend to promote cycloaddition in which the integrity of the small ring is maintained. Nickel(0)-catalysts can promote both reactivities.

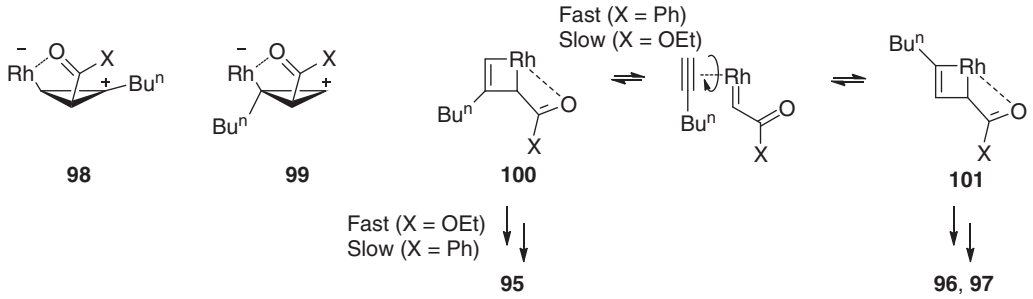
5.35.4.1 Cycloadditions Involving Ring Opening

Cyclopropene esters and ketones underwent rhodium-catalyzed [5+1] cycloadditions, yielding pyranones with opposite regioselectivity (Scheme 27).[53] The formation of compounds **95** on the one hand, and **96** and **97** on the other hand, could be ascribed to steric and electronic effects, respectively. Hence, it was proposed that charged intermediate **98** is more stabilized than **99** and would undergo a disrotatory ring opening to give **100** (Scheme 28).[53] The relative rates of carbon monoxide insertion and equilibration of **99** toward **101** would then control the regioselectivity of the reactions. In the case of cyclopropene-esters, this equilibration would be slower than carbon monoxide insertion, leading to the formation of **95** as the major product. In the case of cyclopropene-ketones, equilibration would be faster than carbon monoxide insertion and minimization of steric hindrance would favor **97**, explaining the predominant formation of **96** and **97**.[53] In the case of similar [5+1] cycloadditions catalyzed by molybdenum–carbonyl complexes, the regioselectivity of the reaction was dominated by steric effects.[54]

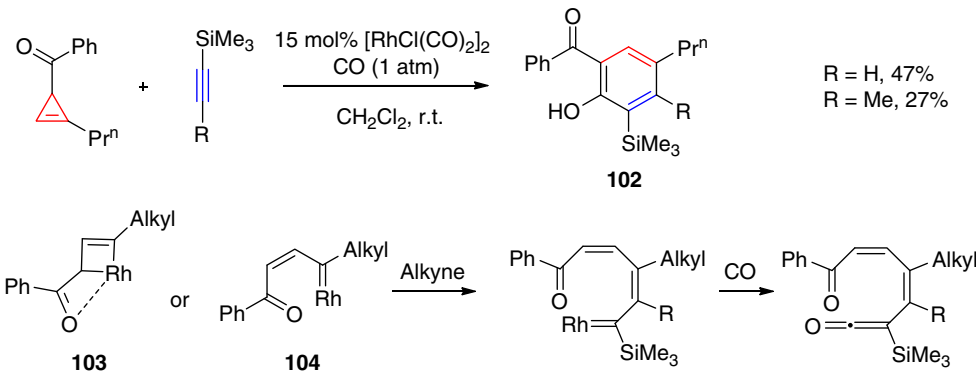
Comparing the reactions leading to pyranone **96** (Scheme 27) and phenols **102** (Scheme 29),[55] an identical mechanism could be proposed to explain the observed regioselectivity. Hence, it is plausible that intermediate **103** or its carbene equivalent **104** are formed in both cases. Without added alkyne, carbon monoxide insertion would lead to pyranones. In the presence of an alkyne, its insertion would precede the reaction with carbon monoxide, to give a nonmetallic intermediate which would eventually afford phenols after electrocyclization in a reaction appearing as a formal rhodium-catalyzed [3+2+1] cycloaddition. Minimization of



Scheme 27

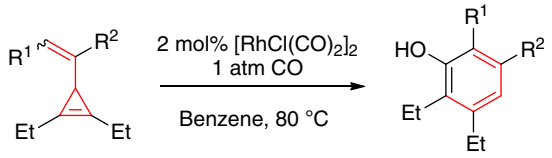


Scheme 28



Scheme 29

steric congestion would control the regioselectivity of the alkyne insertion. Rhodium-carbene intermediates such as **104** would also nicely explain the formation of furans (e.g., **97**) in those reactions. Phenols could also be obtained through intermolecular [5 + 1] carbonylative cycloaddition of vinylcyclopropenes (equation 16).[53]

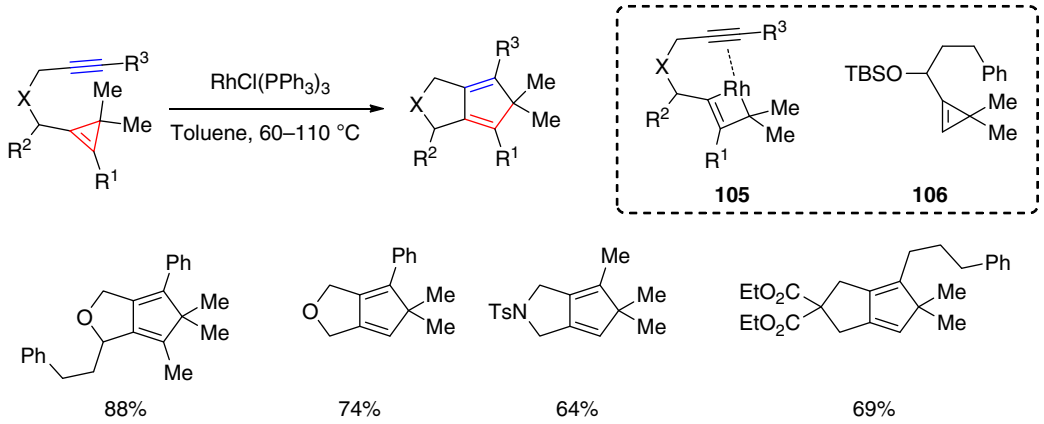


R^1	R^2	Yield
H	Ph	31%
Ph	Ph	51%
Pr^n	Ph	82%
H	Pr^i	46%

(16)

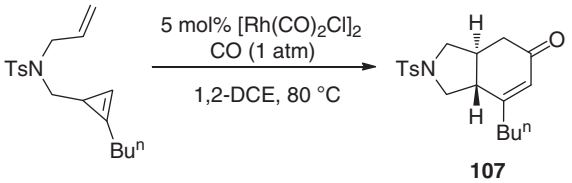
The tether is obviously an important bias in determining the regioselectivity of the rhodium-catalyzed intramolecular [3 + 2] cycloadditions depicted in Scheme 30.[56] Complex **105** is a likely intermediate, whereas compound **106**, lacking the alkyne moiety, did not undergo any reaction in the presence of one equivalent of rhodium catalyst, even at 80 °C. This observation suggests that

105 is formed as a result of alkyne precoordination, and is reminiscent of similar observations in [3 + 2][17] and [3 + 2 + 2][34] cycloadditions of alkylidenecyclopropanes.

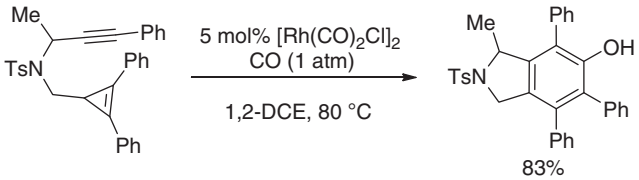


Scheme 30

The rhodium-catalyzed carbonylative [3 + 2 + 1] cycloaddition leading to the formation of bicyclic cyclohexenone **107** delivered compounds with a *trans*-ring junction only (equation 17).[57] Importantly, the selective formation of compound **107** suggests that the proposed formal direct oxidative addition into the less sterically congested carbon–carbon bond of unsymmetrically substituted cyclopropenes probably involves intermediates similar to those depicted in Schemes 28 and 29. Moreover, the smooth conversion of substrates embedding a tethered alkyne led to the formation of phenols (equation 18). Conversely, replacing the tethered alkenes with a terminal allene gave the corresponding cycloaddition product in only modest yield.



(17)



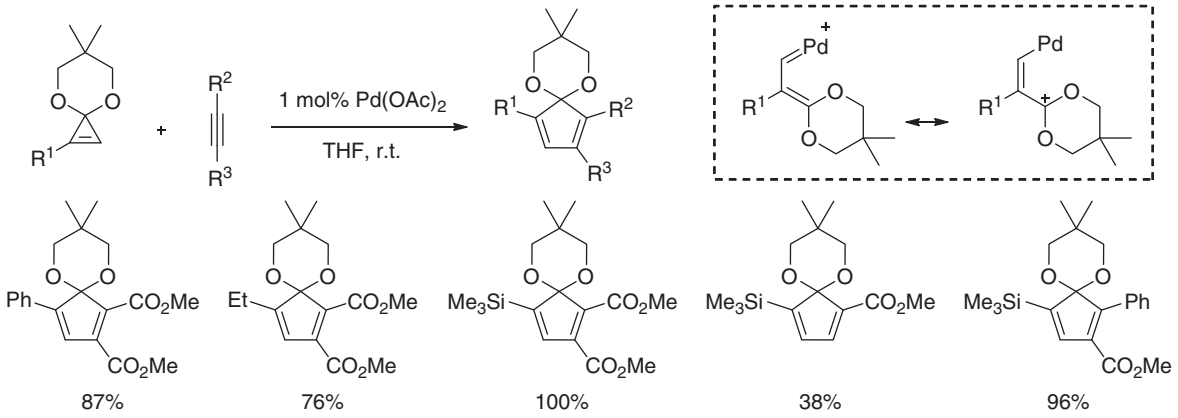
(18)

Besides those rhodium(I)-catalyzed reactions, it is noteworthy that palladium(II)-salts were reported to catalyze the regioselective [3 + 2] cycloaddition of cyclopropene acetals with electron-poor alkynes (Scheme 31).[58] The reaction also took place at elevated temperature in the absence of catalyst, but with opposite regioselectivity. Side products of the reaction suggest that vinyl-palladium intermediates are involved in the catalyzed version of this transformation. Such intermediates could result from the generation of a metal carbene and concomitant ring opening of the cyclopropene.

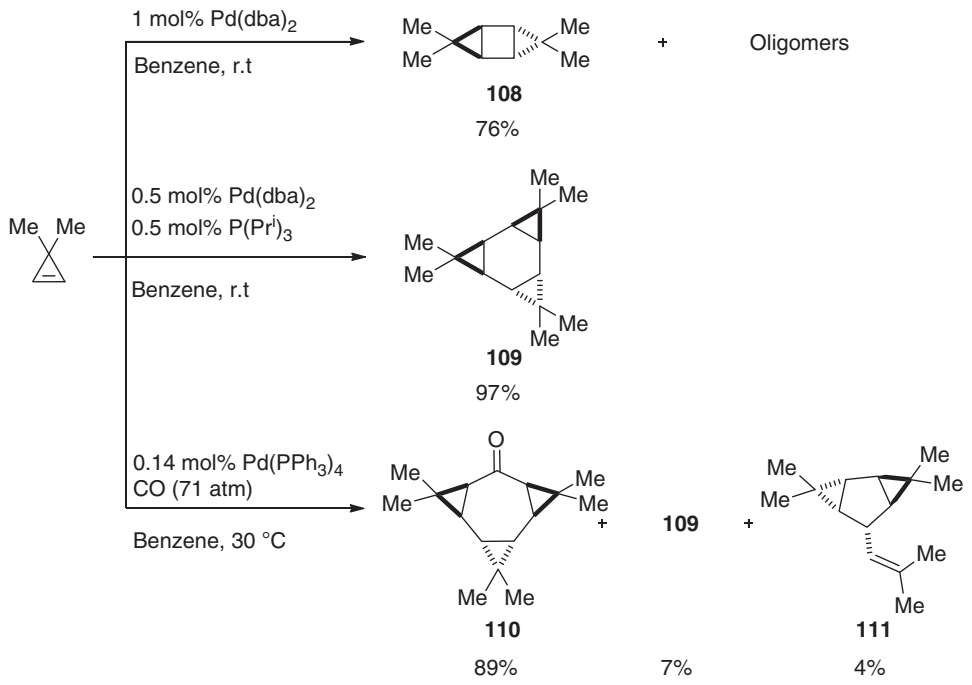
5.35.4.2 Cycloadditions not Involving Ring Opening

Palladium(0)-catalysts are particularly effective at triggering cycloaddition reactions of 3,3-dimethylcyclopropene at ambient temperature with preservation of the three-membered ring. For example, the selective formation of **108** and **109** has been reported (Scheme 32).[59] Under high carbon monoxide pressure, carbonylation led to polycyclic cycloheptanone **110**.[60]

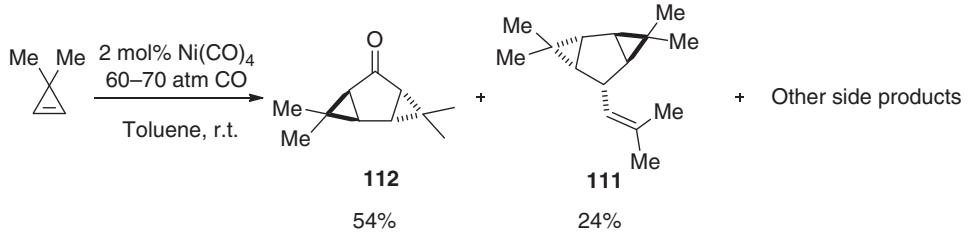
Besides palladium(0)-complexes, carbonyl-metals such as $Mo(CO)_6$ and $W(CO)_6$ are known to catalyze the dimerization of 3,3-dimethylpropene into **108**.[61] As mentioned in the introduction of this section, in the presence of cyclopropenes, nickel(0)-catalysts display a reactivity which is intermediate between palladium(0)- and rhodium(I)-catalysts. For example, the [2 + 2 + 1] trimerization product **111** was obtained as trace in addition to **110** in the presence of a palladium(0)-catalyst (Scheme 32)[60] whereas it became the main side product besides **112** in a similar reaction catalyzed by $Ni(CO)_4$ (equation 19).[62] Confirming this trend, the clean formation of vinyl-carbenes in the $[Ni(COD)_2]$-catalyzed [2 + 1] cycloadditions of cyclopropenes with electron-poor olefins led to the formation of vinyl-cyclopropanes in high yields.[63]



Scheme 31



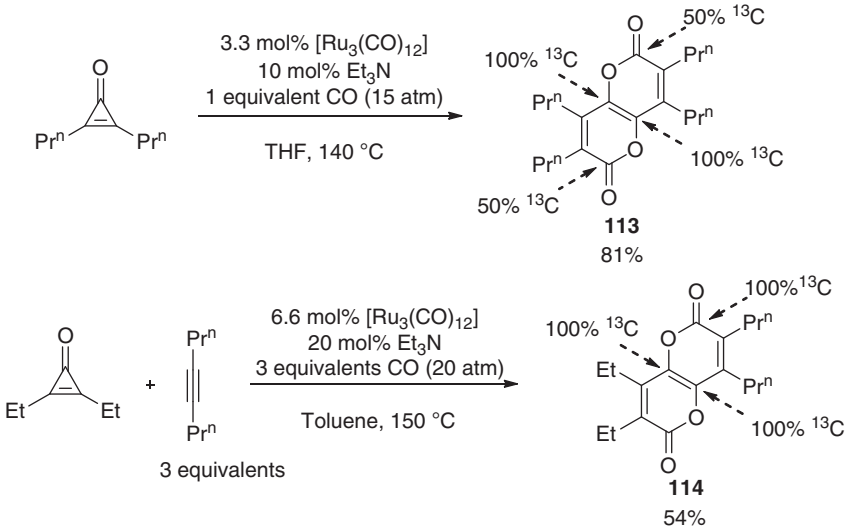
Scheme 32



(19)

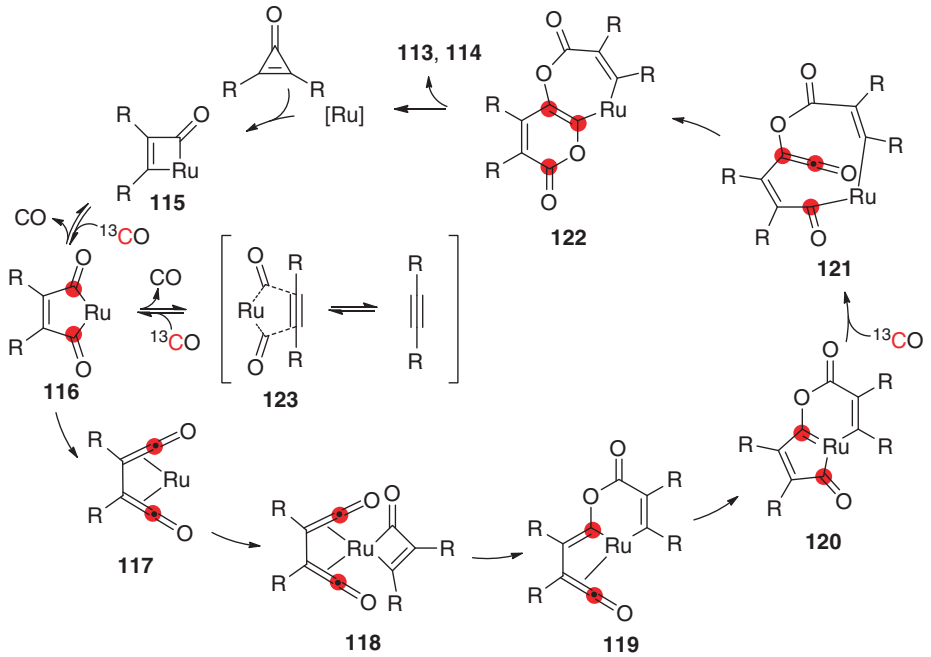
5.35.5 Cycloadditions of Cyclopropenones

Transition-metal-catalyzed cycloadditions of cyclopropenones are rare. For example, it has been shown that $Ru_3(CO)_{12}$ catalyzes the carbonylative dimerization of cyclopropenones as well as their intermolecular cycloaddition with alkynes into pyranopyrandiones **113** and **114**, respectively (Scheme 33).[64]



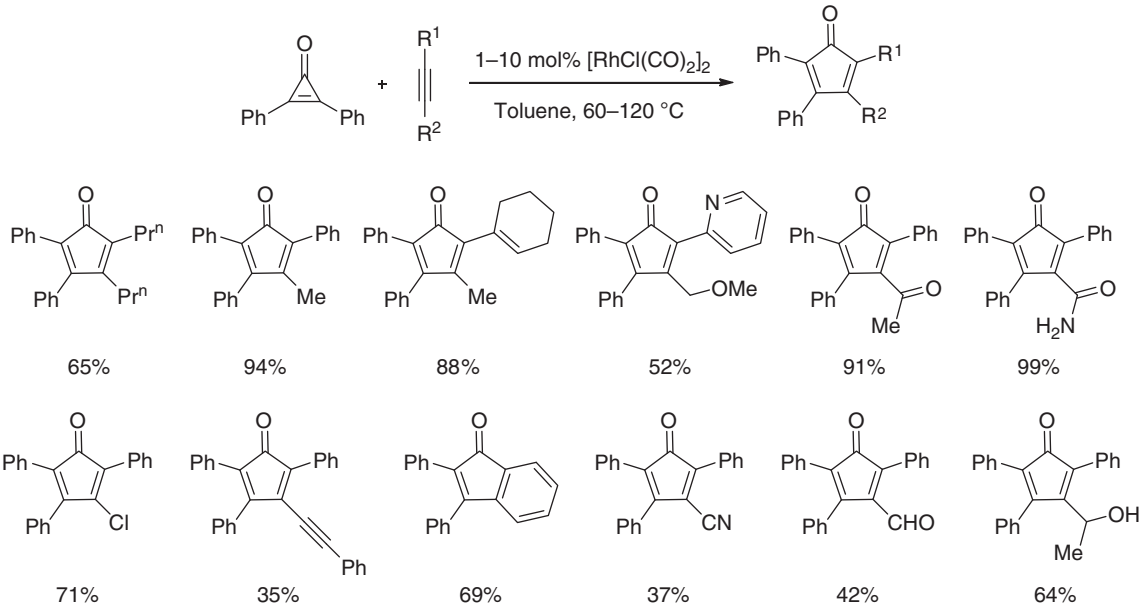
Scheme 33

The results of experiments with isotope-labeled carbon monoxide provided an insight into a plausible mechanism (Scheme 34). After oxidative addition giving **115**, carbon monoxide insertion would lead to maleoylruthenium **116**. In the absence of alkyne, this intermediate would rearrange into the bisketene ruthenium(0)-complex **117**. Oxidative addition would then afford **118** and insertion of one of the carbon–oxygen double bond give **119** or its tautomer **120**. Isotope incorporation is in agreement with the trapping of carbene **120** by carbon monoxide. Finally, insertion of the carbon–oxygen double bond of ketene **121** into the acyl–ruthenium bond would lead to **122**, poised for the reductive elimination which would close this catalytic cycle. Importantly, in the presence of an excess of alkyne, **116** could be formed by carbonylative cyclization through intermediate **123**.



Scheme 34

Another important example is the rhodium-catalyzed [3 + 2] cycloaddition of cyclopropenones with alkynes (Scheme 35).[65] The functional group tolerance and the regioselectivity were remarkable. Among the limitations of the reaction, it is noteworthy that diphenyl acetylene reacted only slowly whereas reactions with terminal alkynes and DMAD led to decarbonylation of the cyclopropenones and trimerization of the alkynes instead of the expected [3 + 2] cycloaddition.

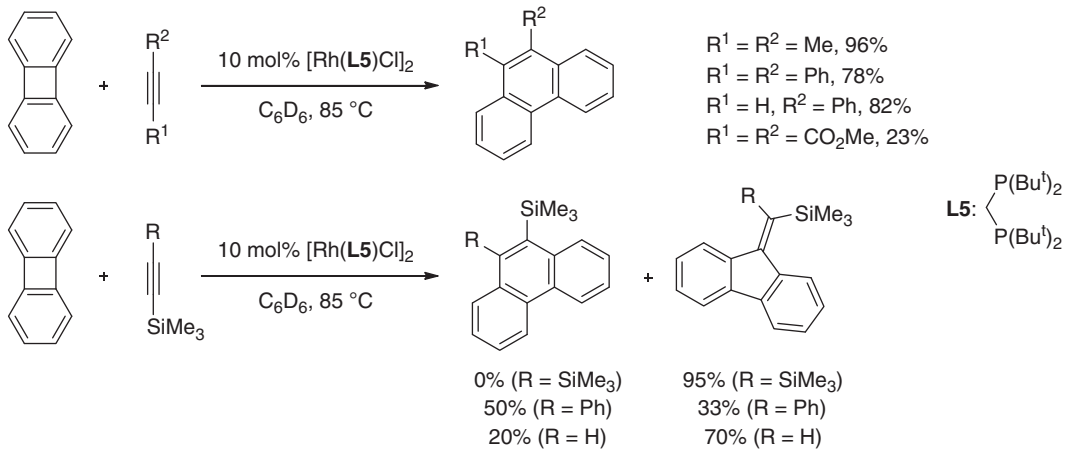


Scheme 35

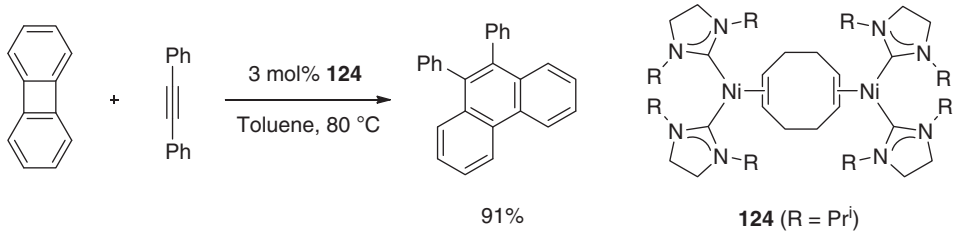
5.35.6 Cycloadditions of Cyclobutane Derivatives

5.35.6.1 Cycloadditions of Biphenylenes

The strained central four-membered ring of biphenylene is prone to undergo oxidative addition to transition-metal complexes, which should make this class of compounds well suited for metal-catalyzed cycloaddition reactions with a variety of unsaturated reactants, following the general design discussed in the introduction. However, efficient catalytic reactions are mostly limited to [4 + 2] cycloadditions with alkynes. After initial studies,[66] phenanthrenes could be obtained in good yields in the presence of a rhodium catalyst (Scheme 36),[67] although cyclotrimerization of the alkynes was also observed, especially with electron-poor DMAD. With trimethylsilyl-substituted alkynes, the formation of fluorenes is significant and can even prevail over the formation of phenanthrenes. Carbene–nickel complex **124** has also been reported to catalyze the formation of phenanthrenes (equation 20).[68]

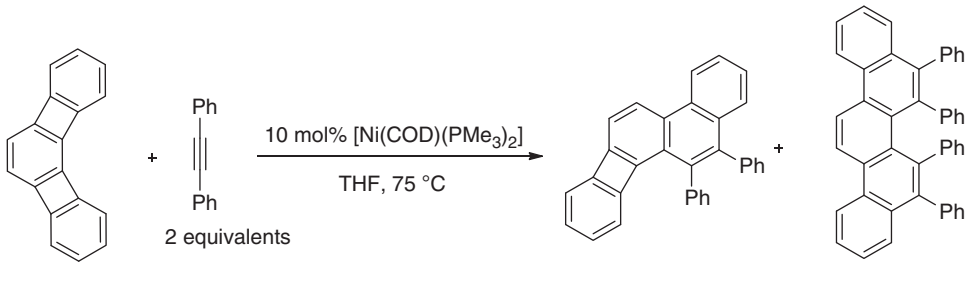


Scheme 36

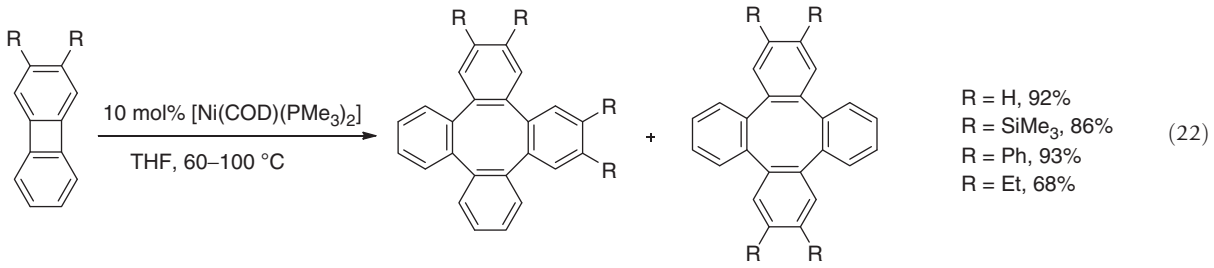


(20)

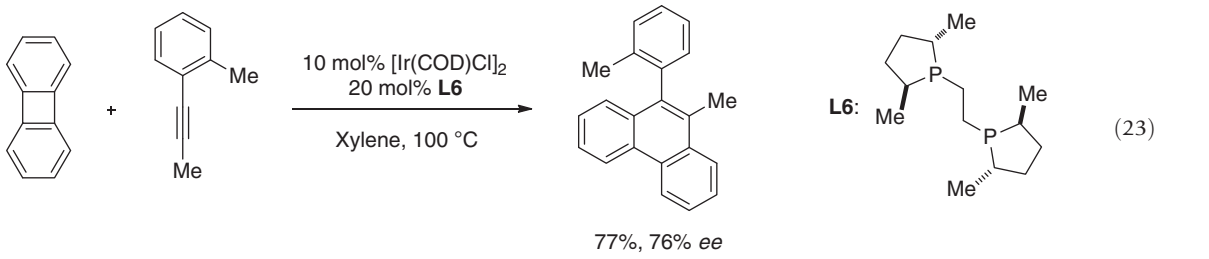
Phenacene **127** could be obtained in high yield in addition to compound **126** when bisphenylacetylene was added slowly to a solution of phenylene **125** and a phosphine–nickel catalyst (equation 21),[69] whereas the same phosphine–nickel complex catalyzed the dimerization of biphenylenes in the absence of alkyne (equation 22).[70] Although done with variable success, one of the most advanced applications of the [4 + 2] cycloaddition of biphenylene is the enantioselective formation of the axially chiral phenanthrene in the presence of chiral iridium catalyst (equation 23).[71]



125 **126** 13% **127** 87% (21)



(22)



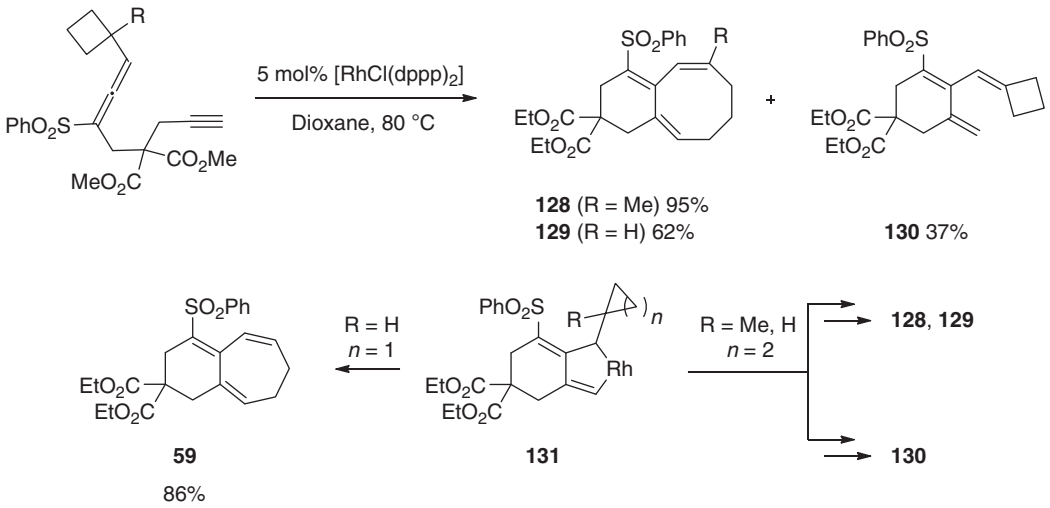
77%, 76% *ee* (23)

Known catalytic reactions in the presence of carbon monoxide or its isonitrile surrogates are still limited by low turnover numbers and frequencies.[66a,b]

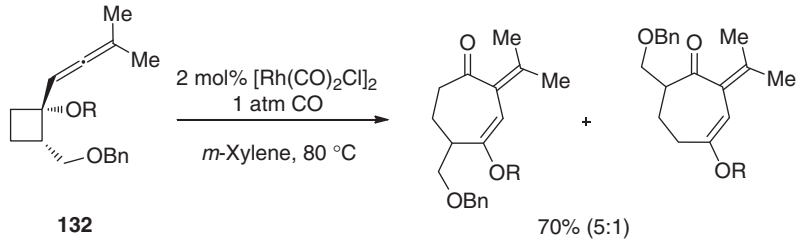
5.35.6.2 Cycloadditions of Allenylcyclobutanes

It was possible to extend the scope of the intramolecular [5 + 2] cycloaddition of alkyne-tethered allenylcyclopropanes (Scheme 20)[41] to the parent allenylcyclobutanes in a rhodium-catalyzed [6 + 2] cycloaddition (Scheme 37).[72] Whereas compounds **128** and **129** resulted from the intended ring enlargement of putative intermediate **131**, the β-hydride elimination product **130** was also obtained when R = H. This observation is noteworthy when compared with the neat formation of compound **59** from an allenylcyclopropane precursor (Scheme 20).[41] Hence, although cyclopropane and cyclobutane have similar strain energies, β-hydride elimination becomes competitive with the ring opening of **131**. Importantly, **59** was obtained by using $[Rh(CO)_2Cl]_2$ whereas this catalyst led to a larger proportion of β-hydride elimination product as compared with $[RhCl(dppp)_2]$ in the optimization study of the [6 + 2] cycloaddition of alkyne-tethered allenylcyclobutanes.[72] Hence, the rate of β-carbon elimination does not correlate with the relative strain energies of cyclopropane and cyclobutanes, but other factors must intervene.

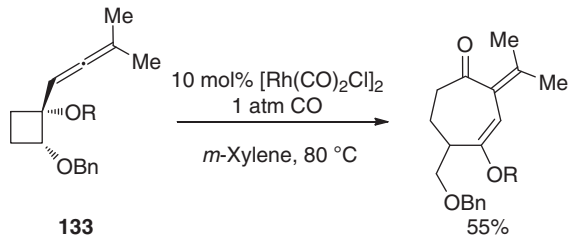
Further mechanistic studies also appear necessary to explain the regioselectivity of the ring cleavage in the rhodium-catalyzed carbonylative [6 + 1] cycloaddition of allenylcyclobutanes (equations 24–27 ($R = (CH_2)_2OMe$)).[73] Considering the two different carbon–carbon bonds of the cyclobutane ring which can be broken in the cycloaddition, cleavage of the more electron-rich bond was preferred in precursors **132** and **133**. However, the influence of steric factors on the reactions of **134** and **135** is not clear.



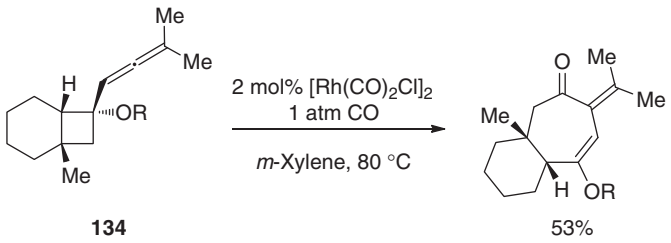
Scheme 37



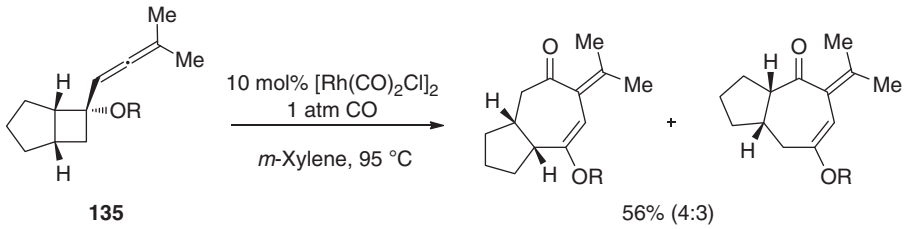
(24)



(25)



(26)

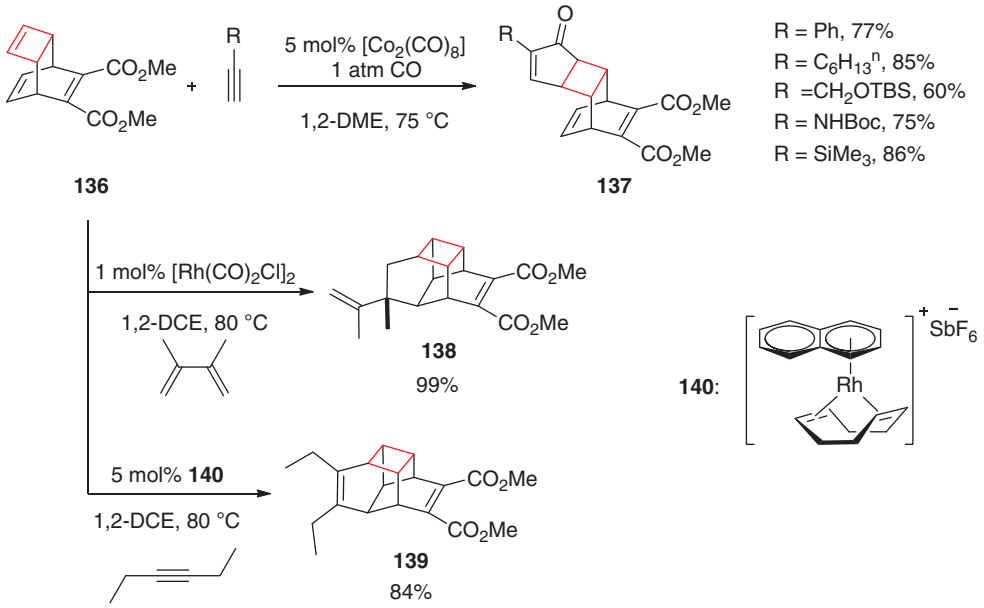


(27)

5.35.7 Cycloadditions of Cyclobutenes

Examples of transition-metal-catalyzed cycloaddition of cyclobutenes are extremely scarce and are limited to the study of the reactivity of the tricyclic compound **136** (Scheme 34).[74,75] Hence, a Pauson–Khand reaction afforded the fused cyclopentenones

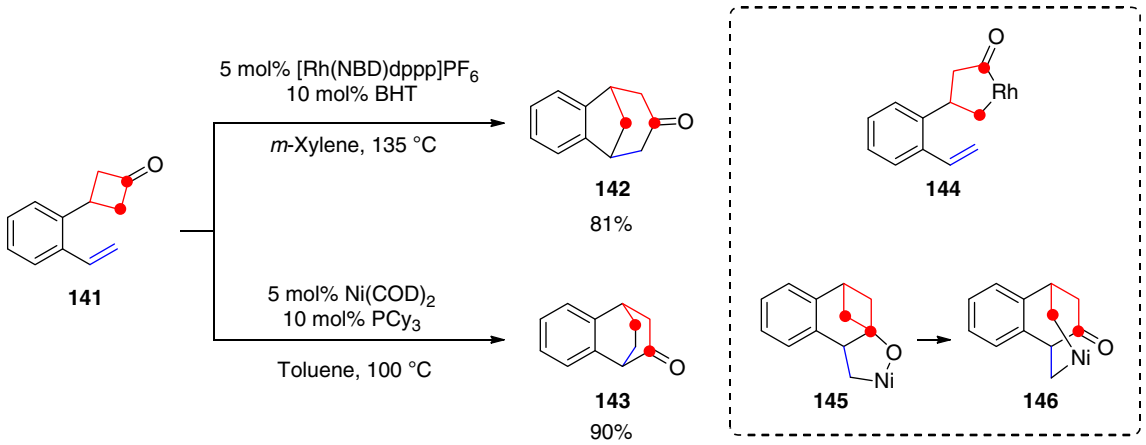
137,[74] whereas rhodium complexes catalyzed a [2 + 2 + 2] cycloaddition with 2,3-dimethylbutadiene or 3-hexyne to give **138** and **139**, respectively.[75] The four-membered ring remains intact in all cases Scheme 38.



Scheme 38

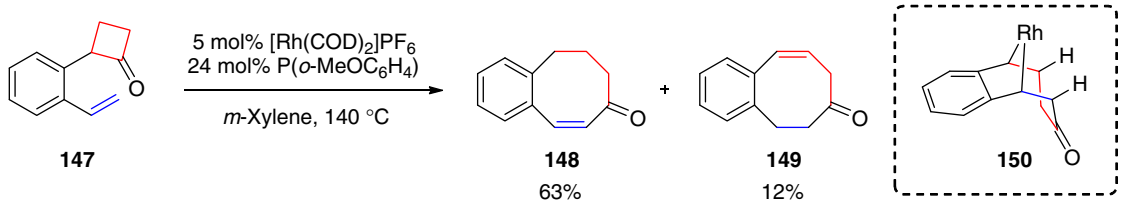
5.35.8 Cycloadditions of Cyclobutanones, Cyclobutenones, and Cyclobutenediones

The carbon–oxygen double bond of cyclobutanones makes them particularly apt to undergo transition-metal-catalyzed cycloadditions. For example, this functional group can serve as anchor in formal [4 + 2] cycloadditions of **141** leading to bridged polycyclic ketones **142** and **143** (Scheme 39). Isotope-labeling indicated that the rhodium-catalyzed formation of **142** likely involved intermediate **144**, resulting from the oxidative addition of the metal into the cyclobutanone ring.[76] In contrast, a nickel$^{(0)}$–phosphine complex catalyzed the formation of **143**, likely after transient formation of **145** and carbon–carbon bond cleavage toward **146**.[77] In a recent development of this nickel-catalyzed transformation, the enantioselective desymmetrization of cyclobutanones has been achieved under mild reaction conditions.[78]



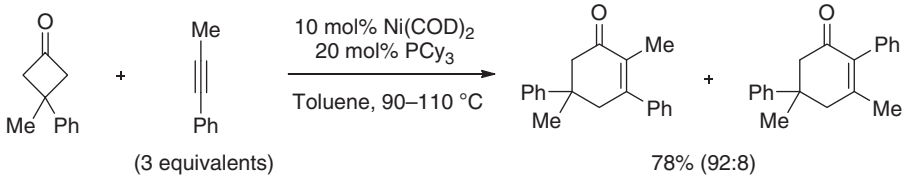
Scheme 39

The aromatic tether in **141** was required to observe its transformation into **143**. Modifying the regiochemistry of **141**, as borne out in **147**, also led to a failure of the nickel-catalyzed reaction. In contrast, this precursor was converted into **148** and **149** in the presence of a rhodium catalyst (Scheme 40).[79] Both cyclooctenones probably resulted from the formation of a common intermediate **150**.

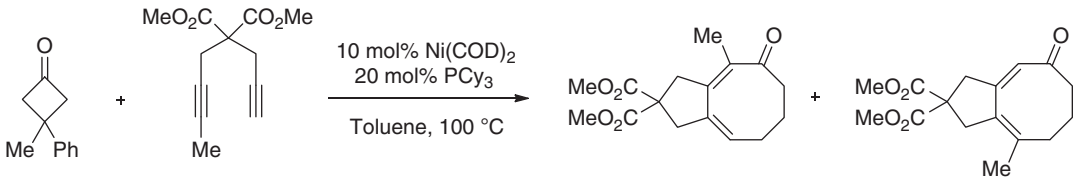


Scheme 40

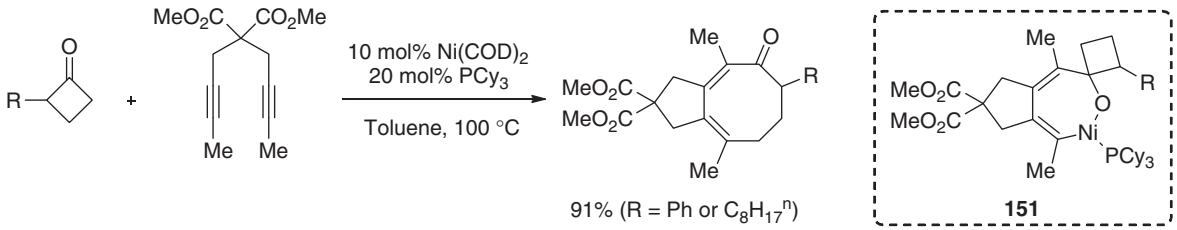
Nickel catalysts also enabled intermolecular [4 + 2] cycloadditions of cyclobutanones with alkynes (equation 28)[80] and their [4 + 2 + 2] cycloaddition with 1,6-diynes (equation 29 and Scheme 41).[81] The regioselectivity of the insertion of alkynes and diynes was likely dominated by steric factors, in line with nickel-catalyzed reductive coupling reactions.[82] Similarly, cleavage of the less sterically congested bond in the cyclobutane ring of **151** is a likely explanation for the observed transformation of α-substituted cyclobutanes.



(28)

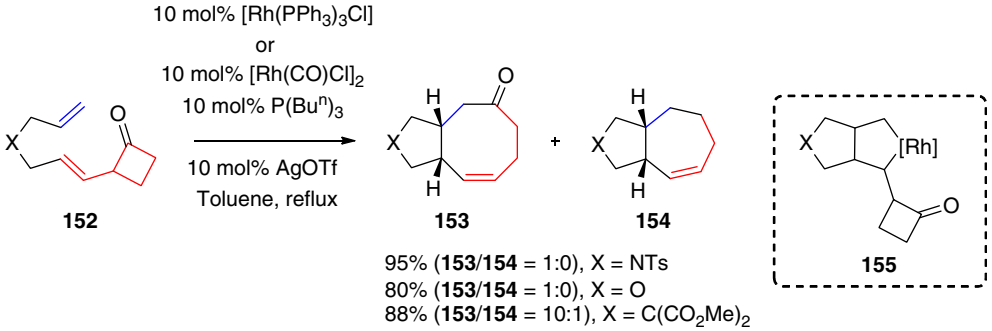


(29)



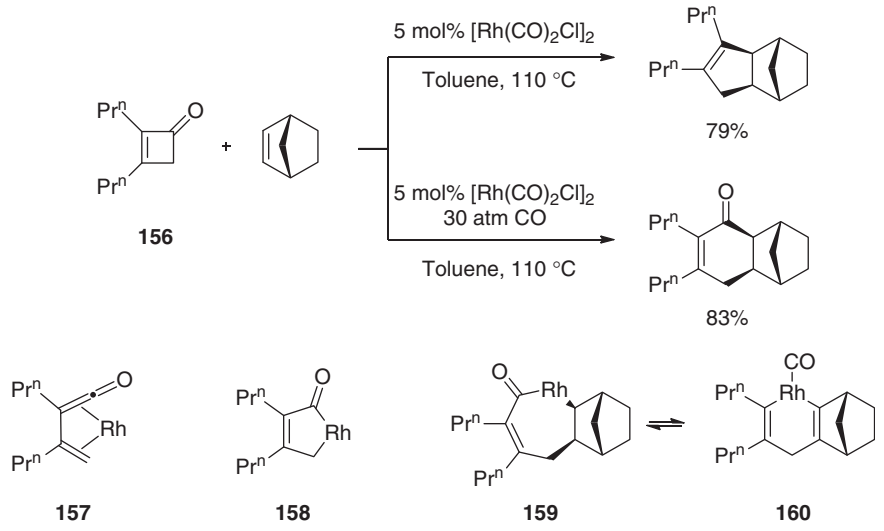
Scheme 41

The ability of cyclobutanones to undergo oxidative addition in the presence of a rhodium catalyst and the additional strain energy brought by the carbon–oxygen double bond, as compared with a nonfunctionalized cyclobutane, likely contribute to the intramolecular [6 + 2] cycloaddition of precursors **152** into bicyclic compounds **153** and **154** (Scheme 42).[83] Results from theoretical investigations indicated that **155** was a likely intermediate of the reactions.[84]

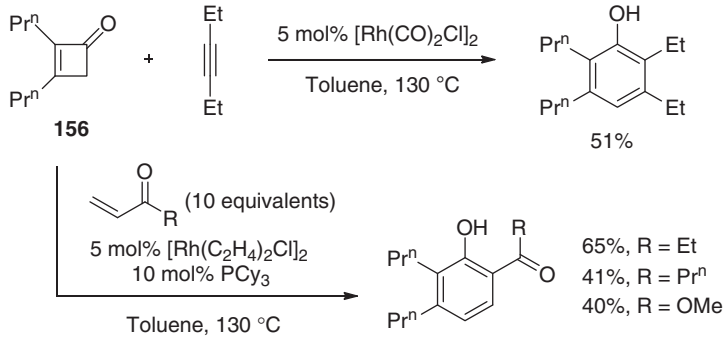


Scheme 42

Although decarbonylation of large metallacycles was only a side reaction in the cycloaddition of vinylcyclobutanones (Scheme 42), this tendency became much more pronounced in the cycloadditions of cyclobutenones with norbornene (Scheme 43).[85] Hence, after initial formation of either of the vinylketene complexes **157** or **158** from **156** and subsequent alkene insertion, intermediate **159** would be in rapid equilibrium with carbonyl-complex **160**. In the absence of carbon monoxide, reductive elimination would lead to the formation of cyclopentenes, whereas strong pressure of carbon monoxide would favor the formation of cyclohexenones. Investigations using isotope-labeled carbon monoxide came in support of these conclusions. Rhodium-catalyzed [4 + 2] cycloadditions of cyclobutenones with an alkyne or electron-poor alkenes have also been described in moderate yields, but decarbonylation was not reported (Scheme 44).[86] The formation of phenols in the reaction of electron-poor alkenes could possibly be ascribed to rhodium-catalyzed dehydrogenation, the excess of alkene being used to regenerate the active rhodium(I) catalyst.



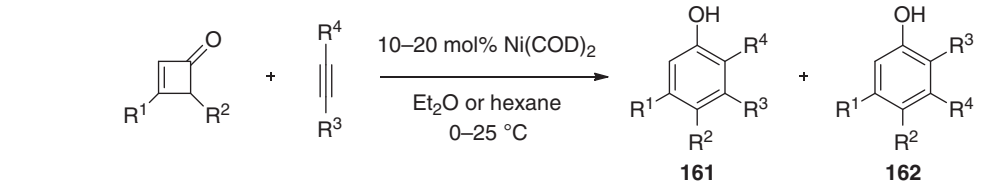
Scheme 43



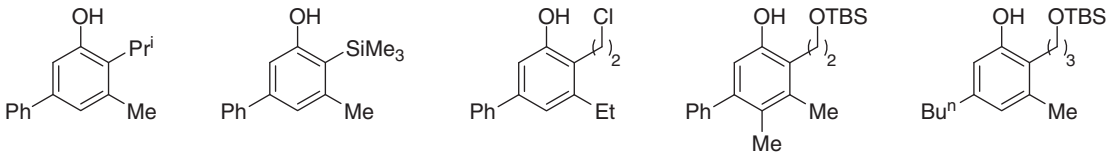
Scheme 44

The formation of a phenol in the rhodium-catalyzed cycloaddition of cyclobutenone **156** and 3-hexyne is noteworthy, considering that η^2-vinylketene complexes similar to **158** were isolated after stoichiometric reaction with cyclobutenones but did not deliver phenols when heated in the presence of alkynes.[87] In contrast, regioisomeric phenols **161** and **162** were obtained in nickel-catalyzed cycloadditions with cyclobutenones (Scheme 45).[88,89] The regioselectivity of the reaction was not strongly influenced by the steric differentiation of the alkyne substituents. However, polar groups at the homopropargylic position appeared capable of exerting a modest directing effect, presumably by coordination to η^2-vinylketene nickel intermediate **163**.[88] Much better regioselectivity was obtained with alkyl-substituted alkynylboronates,[89] and one could perhaps again invoke lone pair coordination, as depicted in intermediate **164**, to explain the experimental results. Similarly, π-coordination, as depicted in **165**, could explain the reversal of regioselectivity observed with phenyl and cyclohexenyl-substituted alkynylboronates. However, these intermediates are purely speculative and more experiments are required in order to establish the mechanism of these reactions.

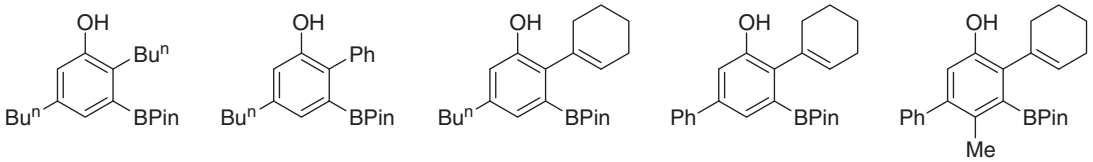
In the absence of alkynes, cyclobutenones afforded a mixture of 2-pyranones **166** and **167** when treated with $[RuCl_2(CO)_3]_2$ (equation 30), whereas only **167** was obtained in excellent yield when treated with $[Rh(CO)_2Cl]_2$.[85] Interestingly, in the presence of an alkynylboronate, the same catalyst promoted the formation of an equimolar mixture of **166** and **167**.[89]



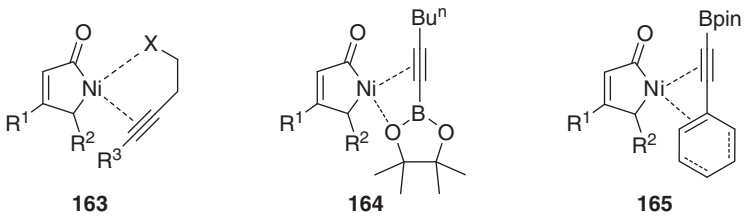
161 **162**



81% (**161**/**162** = 50:50) | 58% (**161**/**162** = 45:55) | 64% (**161**/**162** = 72:28) | 63% (**161**/**162** = 75:25) | 67% (**161**/**162** = 50:50)



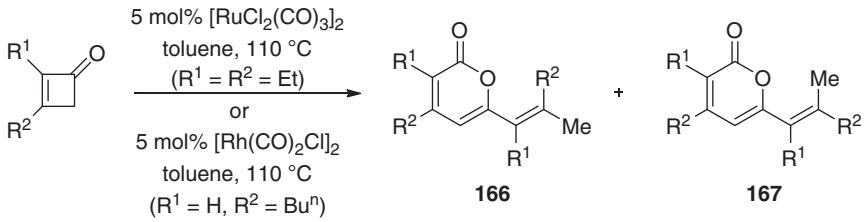
95% (**161**/**162** = 95:5) | 76% (**161**/**162** = 33:67) | 79% (**161**/**162** = 15:85) | 67% (**161**/**162** = 33:67) | 57% (**161**/**162** = 20:80)



163 **164** **165**

R^3 = Me, Et
X = Cl, OTBS, OTHP

Scheme 45

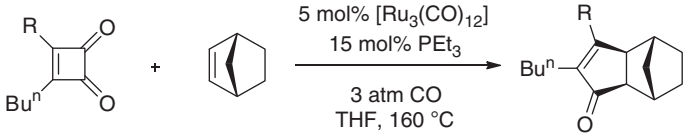


166 **167**

$R^1 = R^2$ = Et, 79% (41:59)
R^1 = H, R^2 = Bu^n, 92% (50:50)

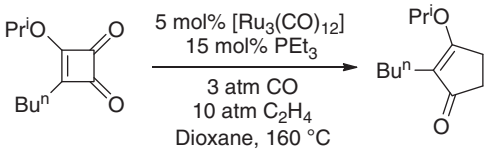
(30)

Oxidative addition of cyclobutenediones to transition-metal complexes is also well established. This enabled the development of cycloadditions with alkenes (equations 31 and 32).[90] It is noteworthy that not only a strained alkene like norbornene, but also ethylene participated to this reaction. The pressure of carbon monoxide was optimized in order to control the monodecarbonylation of the substrates.



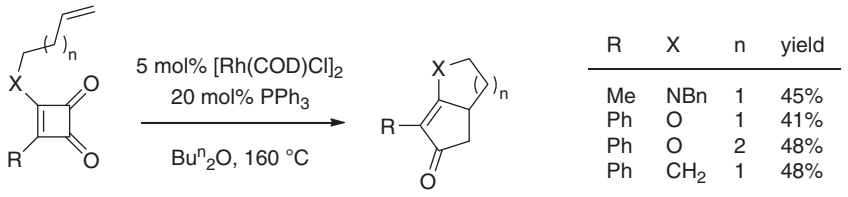
75%, R = OPr^i
60%, R = OBu^n
47%, R = OEt

(31)



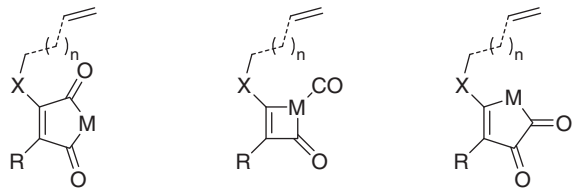
(32)

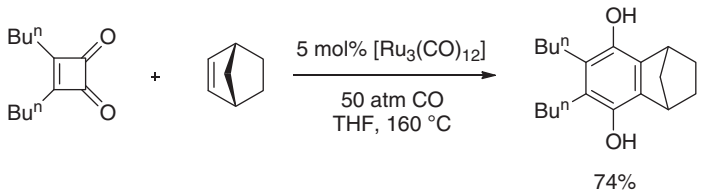
Interestingly, $RhCl(PPh_3)_3$ could not effect these reactions, whereas a related rhodium–triphenylphosphine complex prepared *in situ* could catalyze the intramolecular variant of those decarbonylative cycloadditions without requiring the addition of carbon monoxide (equation 33).[91] The mechanism of the reactions depicted in equations 31–33 remains to be established. $RhCl(PPh_3)_3$ is known to react with cyclobutenediones to give maleoylmetal complexes,[92] hence **168** is a plausible intermediate in the intramolecular reactions (Scheme 46), whereas further decarbonylation of **169** could possibly be prevented by coordination of the tethered olefin. The ruthenium-catalyzed intermolecular reaction of 3,4-dibutylcyclobutenedione under high pressure of carbon monoxide gave a hydroquinone, and proceeded presumably via a maleoylmetal intermediate. In contrast, the intermolecular reactions of alkoxy-substituted cyclobutenediones, depicted in equations 31 and 32, are best explained by invoking metallacyclopentenedione **170**. Importantly, it has been shown in the case of stoichiometric reactions with $RhCl(PPh_3)_3$ that rhodacyclopentenediones are formed as kinetic products before undergoing a rearrangement to the more stable maleoylrhodium isomers.[93]



R	X	n	yield
Me	NBn	1	45%
Ph	O	1	41%
Ph	O	2	48%
Ph	CH_2	1	48%

(33)





Scheme 46

5.35.9 Cycloadditions of Small Heterocyclic Compounds

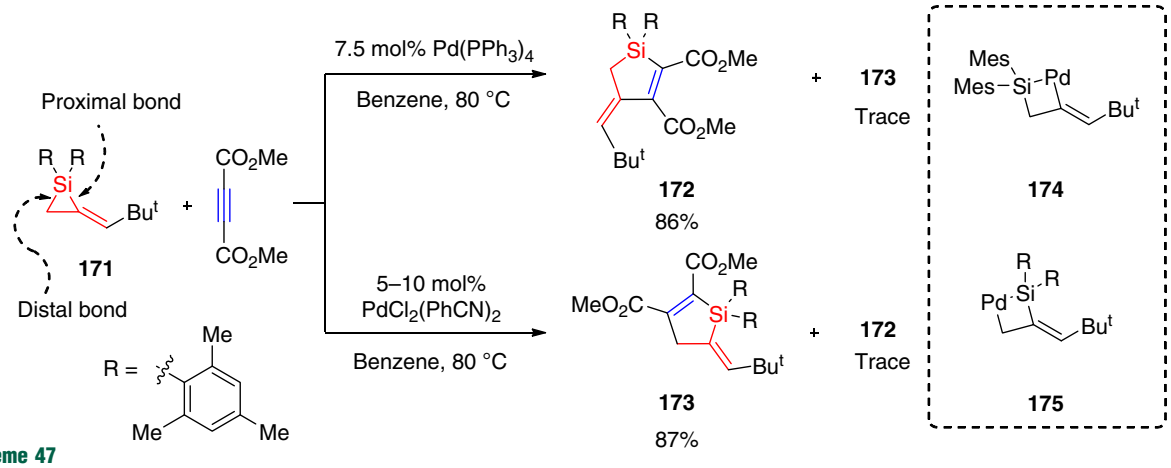
5.35.9.1 Cycloadditions Involving Cleavage of a Carbon–Heteroatom Bond

5.35.9.1.1 Cycloadditions of small ring compounds embedding a silicon atom

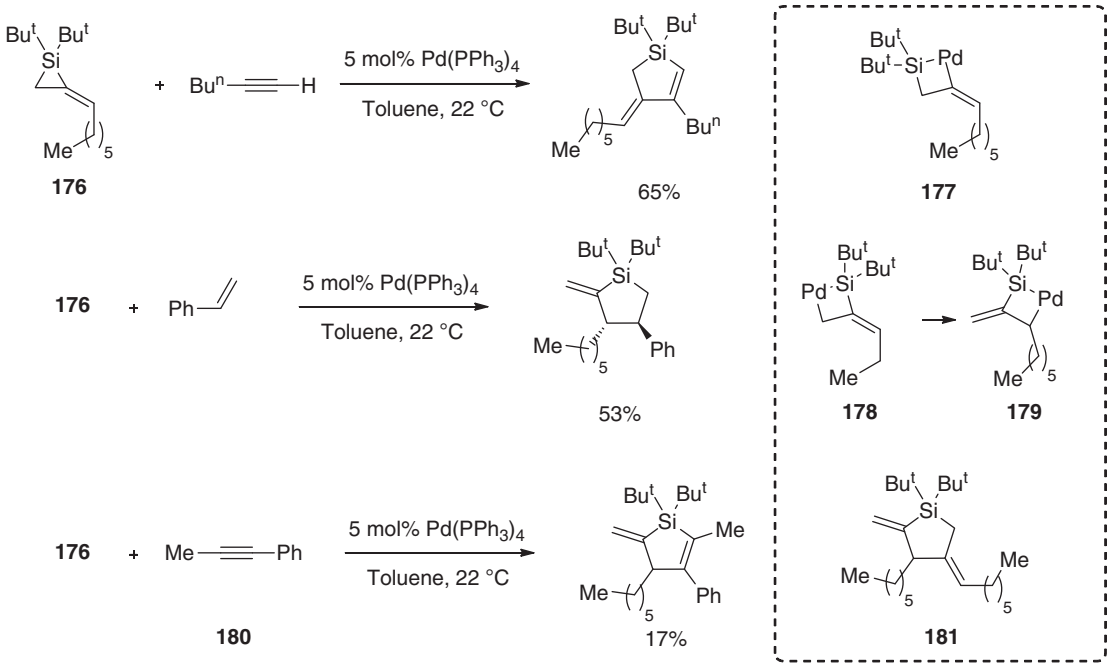
The transition-metal-catalyzed cycloadditions of alkylidenesilacyclopropanes are reminiscent of the reactivity of alkylidenecyclopropanes (Section 5.35.2), as cleavage of either the proximal or distal carbon–silicon bond can be observed.

For example, palladium-catalyzed [3 + 2] cycloaddition of **171** with DMAD afforded the five-membered ring compounds **172** and **173** (Scheme 47).[94] Intermediates **174** and **175** could be proposed to explain the formation of either intermediate. However, one could also argue that they are unlikely on the basis of strongly destabilizing steric interactions between the *tert*-butyl group and either the ligand sphere, in the case of **174**, or the substituents on the silicon atom, in the case of **175**. More recent examples confirmed that the cleavage of either the proximal or the distal carbon–silicon bond of **176** depended on the nature of the unsaturated partner (Scheme 48).[95] In contrast to the currently admitted mechanism of the palladium-catalyzed cycloadditions of alkylidenecyclopropanes (Section 5.35.2), it was proposed that reversible oxidative addition of the active palladium catalyst to the proximal carbon–silicon bond of **176**, giving **177**, would be preferred to the distal addition forming **178**. Rapid migratory

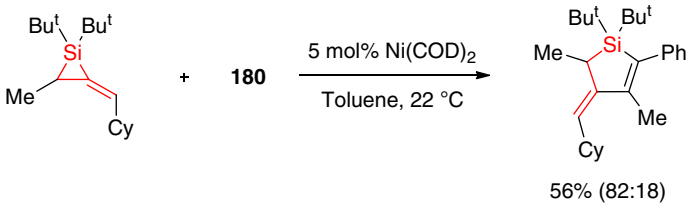
insertion of terminal alkynes or allenes would then lead to cycloaddition products of proximal bond cleavage after reductive elimination. The formation of **177** would be reversible, and internal alkynes or terminal alkenes would undergo slow migratory insertion with **179**, leading to cycloaddition products of distal bond cleavage after reductive elimination. Arguably, the formation of **177** is more favorable as compared with the formation of **174** or **175**. It is noteworthy that the reaction of the internal alkyne **180** led to the formation of **181** as the major product, suggesting the decomposition of intermediates **177**–**179** into a palladium-silirene. Using a nickel catalyst to promote the [3 + 2] cycloaddition of **180** was more effective, albeit isomerization of the carbon–carbon double bond of the substrate could not be avoided (equation 34).[95] The same catalyst also promoted the formation of a regioisomeric mixture of [3 + 2 + 2] cycloadditions products in low isolated yields (equation 35).[95]



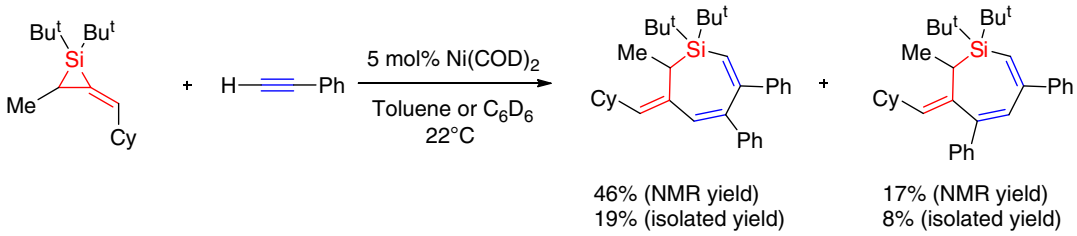
Scheme 47



Scheme 48

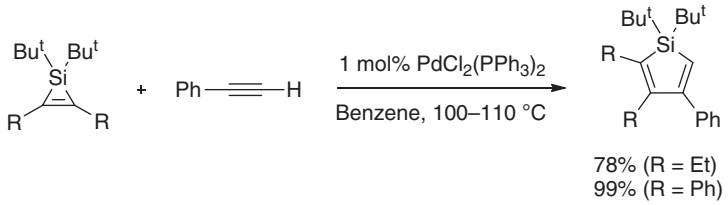


(34)



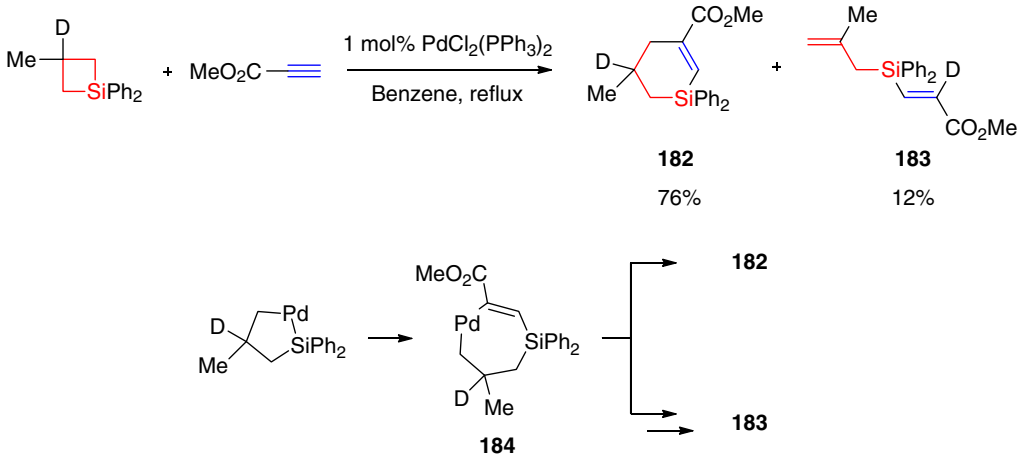
(35)

Following previous studies,[96] a recent example of a [3 + 2] cycloaddition of silirenes with alkynes has been reported (equation 36).[97] This reaction, as other reactions of small ring compounds embedding a silicon atom, is likely catalyzed by a palladium(0)-complex formed *in situ* by reaction of the starting material and the palladium(II) precatalysts.[96d]



(36)

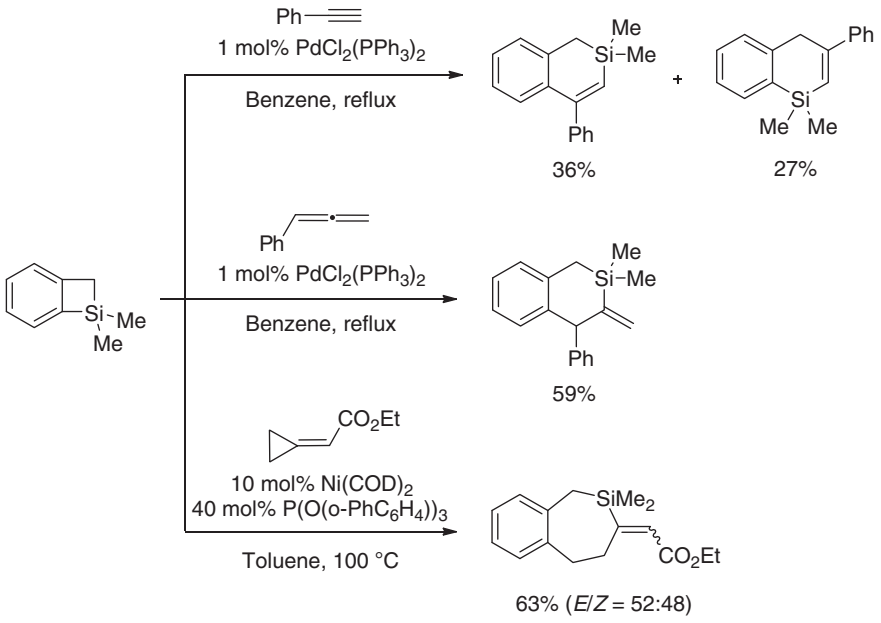
Four-membered ring compounds embedding a silicon atom can also undergo transition-metal-catalyzed cycloaddition reactions. For example, a reinvestigation of earlier results[98] has shown that the competition between reductive elimination and β–H elimination from intermediate **184** could account for the formation of the products **182** and **183** obtained in the palladium-catalyzed intermolecular [4 + 2] cycloaddition of silacyclobutanes with alkynes (Scheme 49).[99] Not surprisingly, the reductive elimination was faster in the presence of electron-poor alkynes and best results were obtained with DMAD.



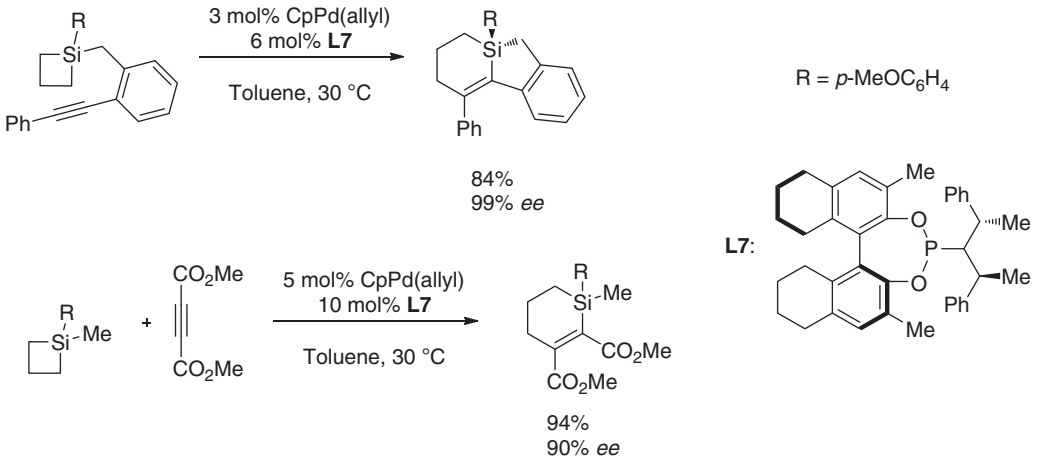
Scheme 49

This undesirable β–H elimination being impossible with benzosilacyclobutanes, only cycloaddition products were obtained. However, the regioselectivity of the insertion of the metal catalyst into the strained four-membered ring appears to depend on the reaction partner (Scheme 50).[99,100] In a recent development, the enantioselective desymmetrization of prochiral silacyclobutanes has been reported (Scheme 51).[101]

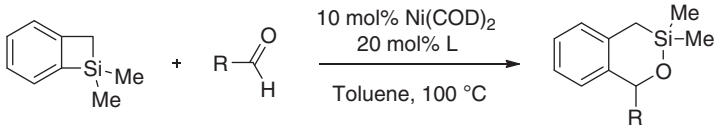
The scope of transition-metal-catalyzed cycloadditions of silacyclobutanes and benzosilacyclobutanes is expanding. Hence, heterocylic compounds could be obtained by nickel-catalyzed [4 + 2] cycloadditions of benzosilacyclobutanes with aldehydes (equation 37)[102] and a palladium-catalyzed [4 + 4] cycloaddition of silacyclobutanes with α,β-unsaturated ketones (Scheme 52).[103] Although undesirable β–H elimination remained a problem with some substrates and competed against reductive elimination of a putative nine-membered palladacycle, this formal [4 + 4] cycloaddition is remarkable.



Scheme 50



Scheme 51



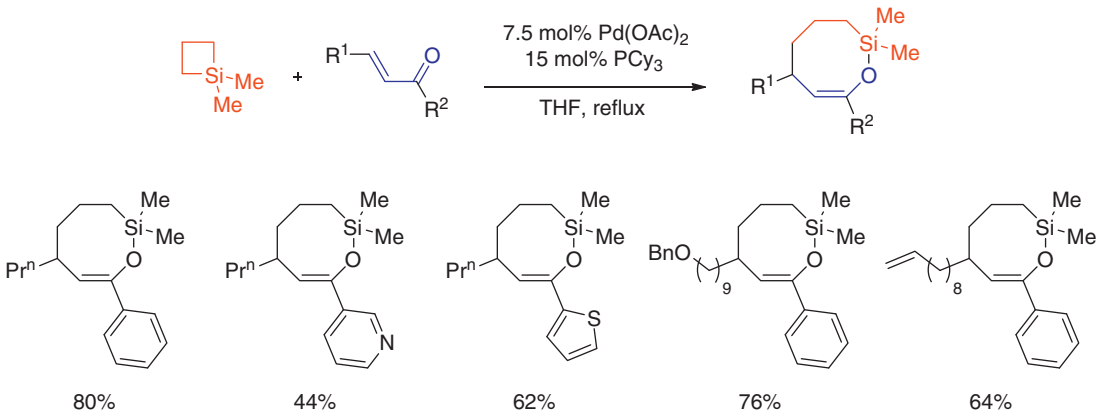
L	R	Yield
PPh_2Me	Ph	65%
PPh_2Me	o-MeC_6H_4	67%
$P(Bu^n)_3$	p-$CF_3C_6H_4$	75%
$P(Bu^n)_3$	$(CH_2)_2Ph$	50%

(37)

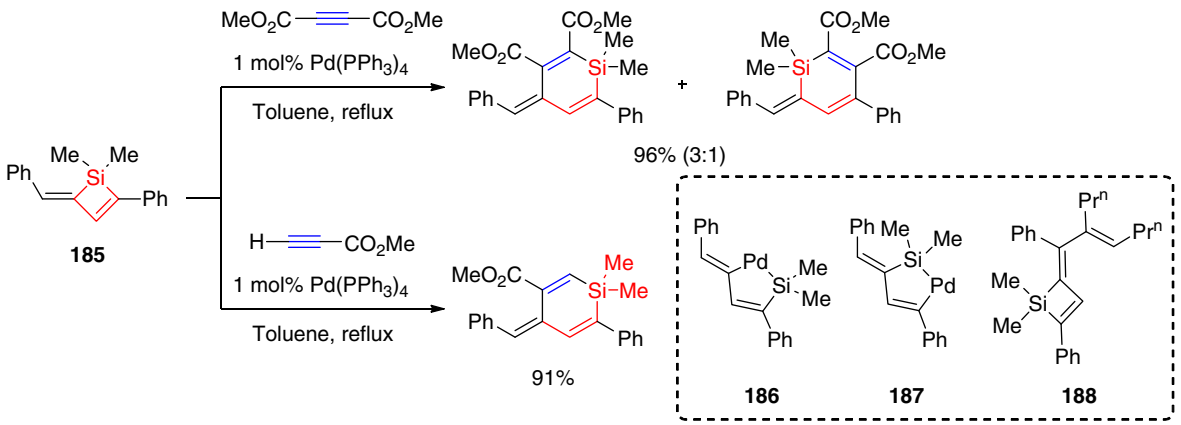
In addition to silacyclobutanes and benzosilacyclobutanes, the scope of transition-metal-catalyzed cycloadditions of four-membered ring compounds embedding a silicon atom is limited to the report of a regioselective carbon–silicon bond cleavage of alkylidene silacyclobutenes (Scheme 53).[104] On reaction with **185**, bis-substituted electron-poor alkynes gave a mixture of regioisomeric products, whereas their monosubstituted counterparts afforded a single isomer. Hence, if intermediates **186** and **187** were formed reversibly and rapidly, the control of the regioselectivity would take place during the migratory insertion. Alternatively, one could hypothesize that the alkyne could be coordinated to the metal and would influence the regioselectivity of the oxidative addition. Intriguingly, catalyzed reactions of the same alkynes with substrate **188** showed the opposite trend, the reaction with DMAD being completely selective, whereas the reaction with methyl propiolate gave a mixture of regioisomers.

5.35.9.1.2 Cycloadditions of small ring compounds embedding a nitrogen or oxygen atom

The carbonylation of epoxides and aziridines catalyzed by zwitterionic cobalt–carbonyl complexes and the associated mechanisms are well established (*see* Chapter 3.22).[105] However, one could speculate that the rhodium-catalyzed [5 + 1] carbonylative

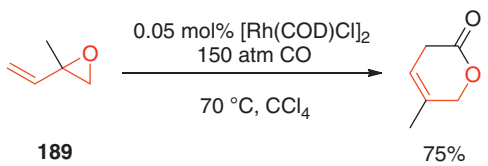


Scheme 52



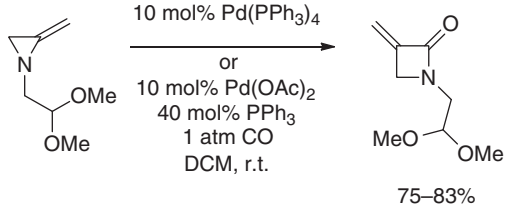
Scheme 53

cycloaddition of vinyl epoxide **189** (equation 38)[106] proceeds according to a mechanism similar to the mechanism governing the rhodium-catalyzed cycloadditions of vinylcyclopropanes (See **Scheme 18**, Section 5.35.3). The same hypothesis could be made to explain the intramolecular [5 + 2] cycloaddition/Claisen rearrangement of vinyl epoxides with alkynes (**Scheme 54**).[107] Hence, cyclooxidative addition intermediate **190** would undergo *syn*-coplanar elimination toward **191**; reductive elimination of this heterometalacycle would afford the precursor of the final sigmatropic rearrangement. Interestingly, it was shown that the alkyne moiety was likely crucial to the overall process, since the absence of this functional group in **192** led to the formation of unstable aldehyde **193** under the reaction conditions.

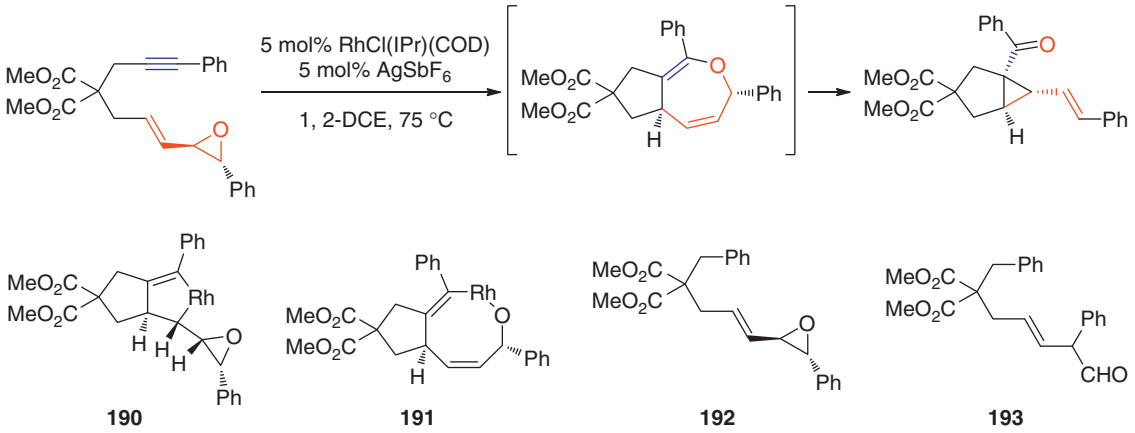


(38)

The palladium-catalyzed carbonylation of methylene-aziridines (equation 39)[108] is also likely to proceed according to another mechanism than the cobalt-catalyzed carbonylation of epoxides and aziridines.[105]



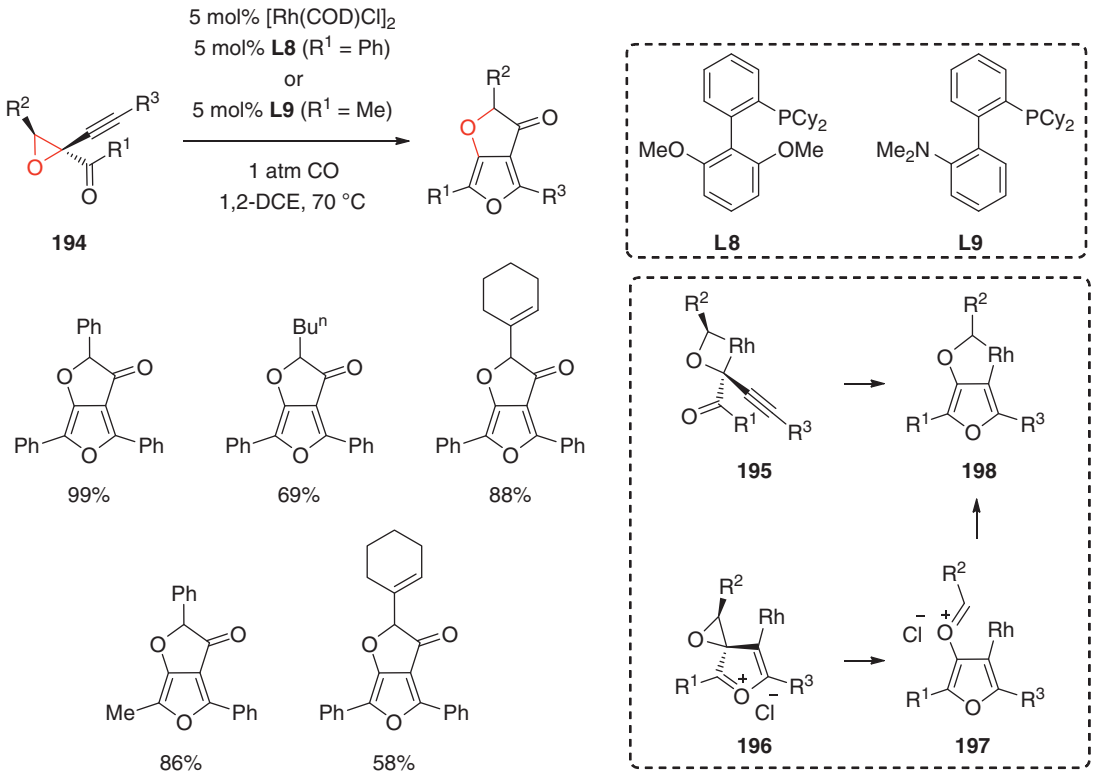
(39)



Scheme 54

5.35.9.2 Cycloadditions Involving Cleavage of a Carbon–Carbon Bond

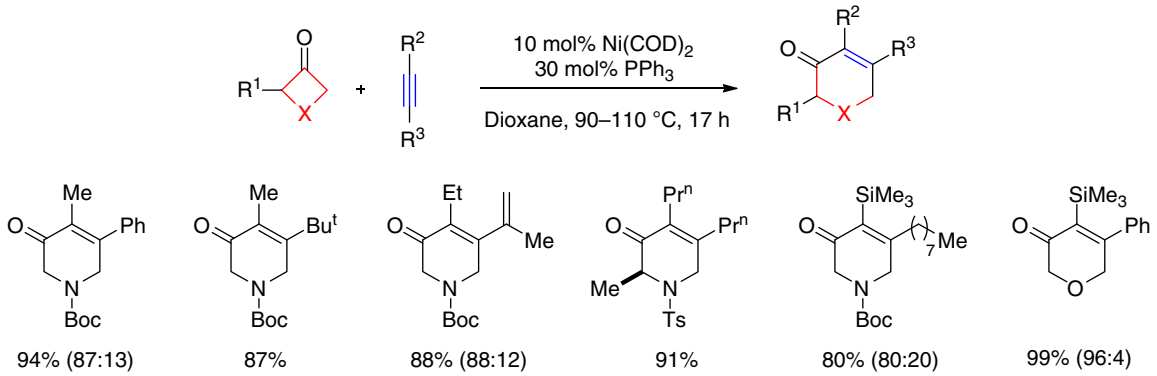
In contrast to the previous examples of transition-metal-catalyzed cycloadditions of small heterocyclic compounds, which all involved the cleavage of a carbon–heteroatom bond, examples of cycloaddition involving the cleavage of a carbon–carbon bond are extremely scarce. Hence, the rhodium-catalyzed [4 + 1] carbonylative cycloaddition of alkynyl epoxides **194** has been reported recently (Scheme 55).[109] It was not established which of the intermediates **195–198** is the most pertinent to explain the results. However, as previously mentioned for the rhodium-catalyzed carbonylation of cyclopropyl ketone **74** to bicyclic furanone **75** (see Scheme 23, Section 5.35.3.4),[46] the oxidative addition of the catalyst to the more sterically congested bond of the epoxide ring seems counterintuitive. Therefore, intermediate **195** may be less likely.



Scheme 55

Moreover, the first examples of transition-metal-catalyzed carbon–carbon bond activation of 3-azetidinones and 3-oxetanones were reported recently (Scheme 56).[110] In the presence of a nickel catalyst and alkynes, a regioselective and high-yielding

intermolecular [4 + 2] cycloaddition occurred, leading to the formation of pyridinones and pyranones. In good accordance with nickel-catalyzed reductive coupling reactions of alkynes with aldehydes,[82] and with the [4 + 2] cycloaddition of cyclobutanones with alkynes,[80] the regioselectivity of the reactions depicted in Scheme 56 is likely controlled by steric factors in the case of alkyl–aryl-substituted alkynes. Conversely, electronic factors appeared to predominate in the case of the more polarized trimethylsilyl-substituted alkynes.[111]



Scheme 56

5.35.10 Conclusions

In most of the reactions discussed in this chapter, the small ring compounds are used as a three- or four-atom building block in the construction of a larger ring, embedding up to nine atoms. A chemical handle, mostly in the form of a carbon–carbon or carbon–heteroatom multiple bond, facilitates or even directs the cleavage of the small ring by an active catalyst. The reaction partners are varied, although alkynes, alkenes, and carbon monoxide are prominent. Currently, the most efficient catalysts are palladium, nickel, or rhodium complexes, with only few exceptions. Considering that the combination of more than two components has only been attempted in few cases, there is no doubt that new atom-efficient reactions will be developed in the future.

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5.36 Hydrocyanation in Organic Synthesis

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Glossary

Aziridine A three-membered cyclic compound containing a nitrogen and two carbons.

Coordinatively unsaturated complex A metal complex containing less than 18 electrons as the sum of its valence electrons and electrons from the attached ligands.

Organocatalyst Typically a low-molecular weight organic compound that is capable of catalyzing a reaction through its acid–base or hydrogen-bonding characteristics.

Oxynitrilase An enzyme that catalyzes the addition of hydrogen cyanide to aldehydes and ketones.

Parallel kinetic resolution A reaction in which each enantiomer of a racemic compound in a mixture undergoes separate reactions to give two different products.

Salen It is the imine from salicylaldehyde (2-hydroxybenzaldehyde).

Turnover frequency Number of moles of starting material converted into product per mole of the catalyst at unit time. A measure of the efficiency of a catalyst.

5.36.1 Introduction

Hydrogen cyanide (HCN) is one of the most abundant feedstocks[1] that is useful in the preparation of organic intermediates with a versatile nitrile functional group. These intermediates can be readily transformed into other valuable compounds for further applications in the manufacture of agrichemicals, cosmetics, pharmaceuticals, and polymers. Because HCN is relatively unreactive, especially in reactions with other unsaturated substrates, these reactions are best carried out under the influence of a catalyst, and catalyst-dependent selectivities can be brought to bear on the course of these reactions. This chapter will cover the most salient aspects of hydrocyanation of various organic compounds.[2–4] Although the major emphasis will be on hydrocyanation of alkenes and alkynes, the subject is introduced through a short section on hydrocyanation of carbonyl compounds, imines, epoxides, and aziridines, mostly for the sake of completeness. The review is meant to be illustrative than exhaustive. The many reviews and original publications cited herein should be consulted for further details. The literature on hydrocyanation till the end of March 2012 is reviewed.

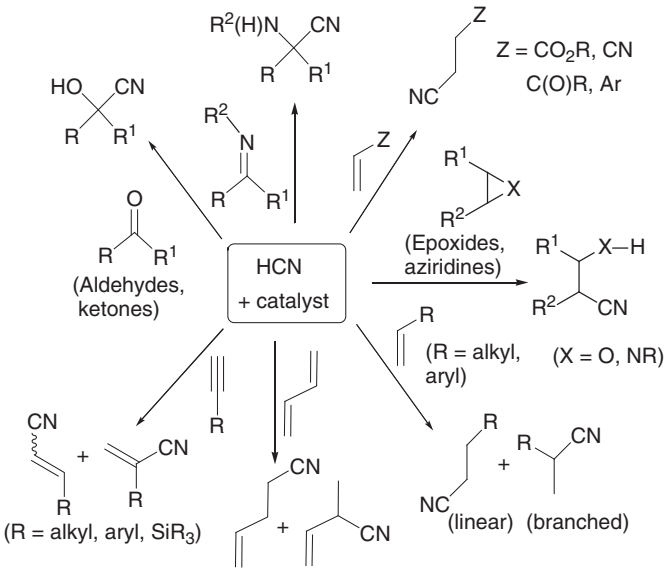
5.36.1.1 Safety

HCN is a highly toxic, volatile liquid (bp 26 °C) that is also susceptible to explosive polymerization in the presence of base catalysts. It is conveniently prepared by acidifying $K_4Fe(CN)_6$ or NaCN.[5] Considering its extensive use in the industry, reports of

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accidents are rare, pointing to the extreme diligence and attention paid during the manufacturing processes. In the laboratory it should be used only in small quantities in a well-ventilated hood. Other sensible precautions include not working alone and having available proper first aid equipments, HCN monitors, and professional respiratory protection devices (e.g., Scott Air Packs). Large quantities of HCN should only be handled by a team of at least two technically qualified experts, who have received appropriate medical training for treating HCN poisoning. On an industrial scale, HCN is disposed of by burning. In case of smaller amounts such as in a typical laboratory setting, it can be disposed of by adding it to an equimolar mixture of sodium hydroxide and sodium hypochlorite (which converts it to the cyanate). This is a highly exothermic reaction and the quenching should be carried out in high dilution and with extreme care (see Prudent Practices for Handling Hazardous Chemicals in Laboratories; National Academy Press: Washington, DC, USA, 1981).

In the presence of a catalyst, HCN adds to carbonyl compounds and imines,[2] epoxides (see citation 15 in Ref. 6 for previous reports that deal with ring-opening reactions of epoxides with various metals; depending on the metal either a nitrile or an isonitrile is formed),[6] aziridines,[7] alkenes,[8,9] and alkynes,[10] offering a direct and economic way to organonitrile intermediates (Scheme 1).

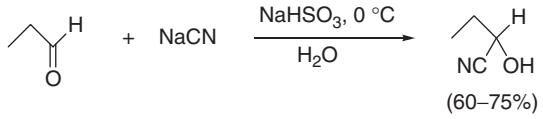


Scheme 1 Catalyzed additions of HCN.

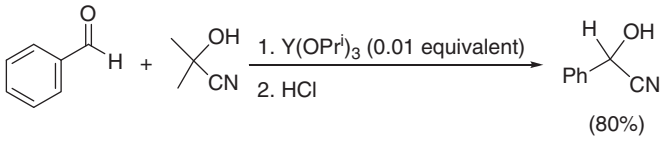
Hydrocyanation of activated polar substrates, such as carbonyl compounds, imines, and electron-deficient alkenes (C=C–Y, Y=CO_2R, CN, C(O)R, and C(O)H), usually occurs in the presence of a base, including cyanide ion itself and historical aspects of this topic have been extensively reviewed.[11–13] Conjugate addition of HCN to α,β-unsaturated carbonyl compounds also occur in the presence of Lewis acids such as alkylaluminum reagents ('Nagata Reaction'). An exhaustive review of this transformation has appeared in *Organic Reactions*.[14] This chapter will concentrate on the more recent aspects of these reactions of HCN. Reactions of readily available surrogates, trimethylsilyl cyanide (TMSCN) and acetone cyanohydrin, with various electrophilic partners are also included since they give similar products, and often are easier and safer to carry out in the laboratory.

5.36.2 Addition of HCN to Aldehydes and Ketones

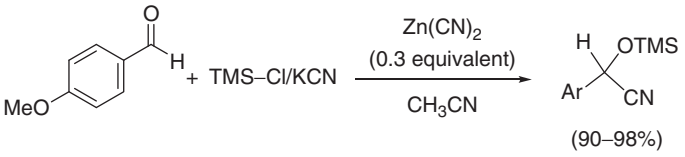
The addition of HCN to carbonyl compounds[2,15] is a reversible reaction with the cyanohydrin as the favored product in aldehydes and nonaromatic ketones. Direct reactions of aldehydes with neat HCN or of the reagent prepared *in situ* from metals and a mineral acid is a classical way of preparing a cyanohydrin (equation 1).[16] Cyanohydrins prepared in this way can be directly oxidized *in situ* using MnO_2 into an acyl cyanide, which may be converted into a methyl ester.[17] Lanthanide alkoxides, such as ytterbium isopropoxide, are excellent catalysts in the preparation of cyanohydrins from aldehydes and ketones (equation 2).[18] Many other metal catalysts, among them, $Cu(OTf)_2$, $Yb(CN)_3$, KCN/18-crown-6, Bu_2SnCl_2, and InF_3, have been used for the addition of TMSCN to aldehydes. A comparison of these methods has been provided in a recent review.[2] Silyl ethers of cyanohydrins can be prepared directly from a mixture of sodium or potassium cyanide, a trialkylsilyl chloride, and a suitable catalyst, thus avoiding the toxic silyl cyanides (equation 3).[19]



(1)

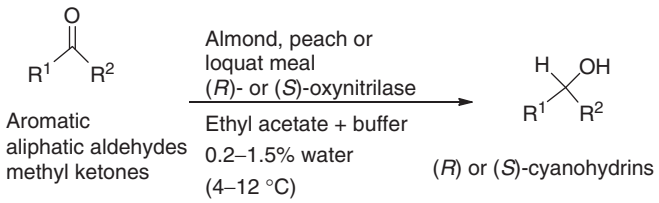


(2)

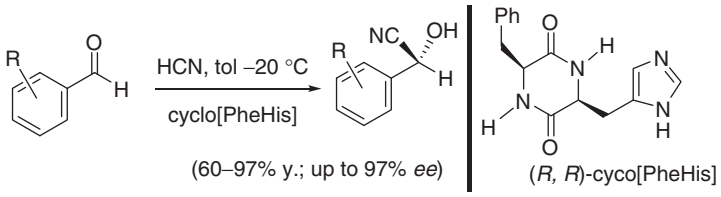


(3)

An interesting variation is a biochemical method using oxynitrilase enzyme-catalyzed addition of HCN to various aliphatic and aromatic aldehydes and ketones. Both (*R*)- and (*S*)-oxynitrilases have been isolated from plant sources (e.g., almonds, sorghum shoots, peach, loquat, and rubber plant) and provide a practical way of preparing enantiopure cyanohydrins.[20,21] The example shown in equation 4 is taken from a comparative study of the use of various protocols for oxynitrilase enzymes in the syntheses of cyanohydrins.[22] A broad class of organocatalysts that effect the addition of HCN to aldehydes are the cyclopeptides derived from readily available amino acids (equation 5).[20] It is believed that the morphology of the solid catalyst is important for a successful reaction, often carried out in a heterogeneous medium, and careful control of reaction conditions are needed to get high yields (y.) and selectivities.[23]



(4)



(5)

Titanium complexes of salicylaldehyde imines (salen) derived from dipeptides **1** and **2** (**Figure 1**) catalyze the addition of HCN to a variety of aldehydes to give either the (*R*) or the (*S*) cyanohydrin (equation 6).[24] Imines from *β*-aminoalcohols (**3**)[25] and C_2-symmetric diamines such as 1,2-diaminocyclohexane (**4**)[26] also serve as ligands for Ti(IV) in TMSCN additions to aldehydes. The isolated, purified complexes from **4** gave some of the best selectivities for aromatic aldehydes. Intermediacy of a dimeric complex **5** has been implicated in some of the most active ($\sim$0.1 mol%) catalysts.[26] Catalyst **5** also uniquely effects the addition of KCN in the presence of an anhydride to give cyanohydrin acetates.[27] Aluminum complexes derived from 2,2′-binaphthols (e.g., **6**, equation 7) or carbohydrate diols that carry additional Lewis basic sites (e.g., the $-Ph_2P{=}O$[28] or $-NR_2$[29] group) have also been used for the addition of TMSCN to aldehydes (equation 7).[28,30] These reactions are some of the best documented examples of bifunctional catalysis. Among other useful catalysts, the complexes of vanadium[31] and yttrium[32,33] are noteworthy.

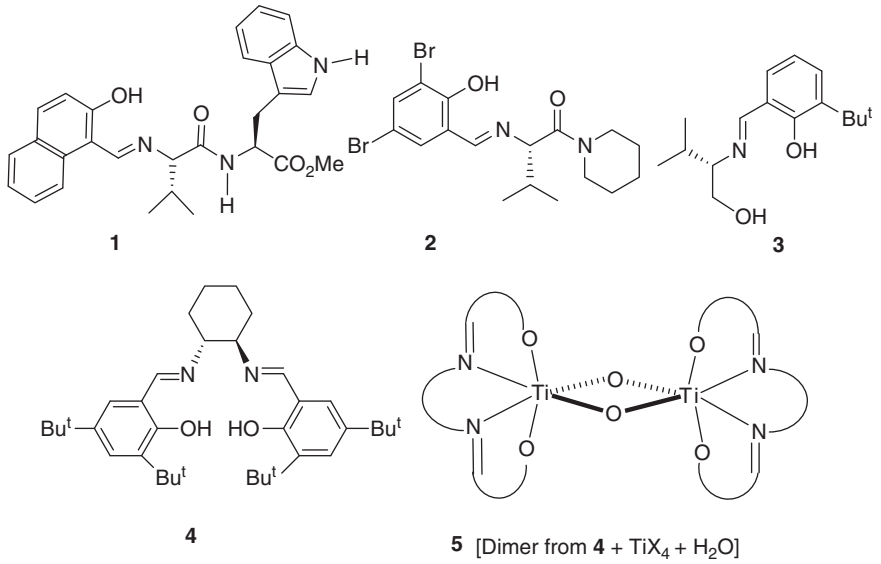
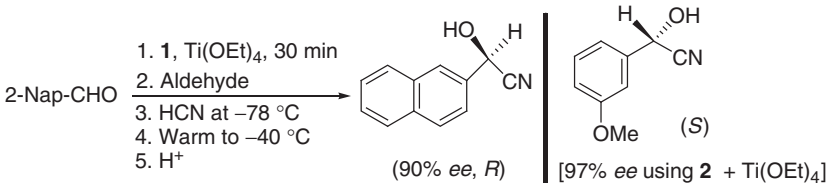
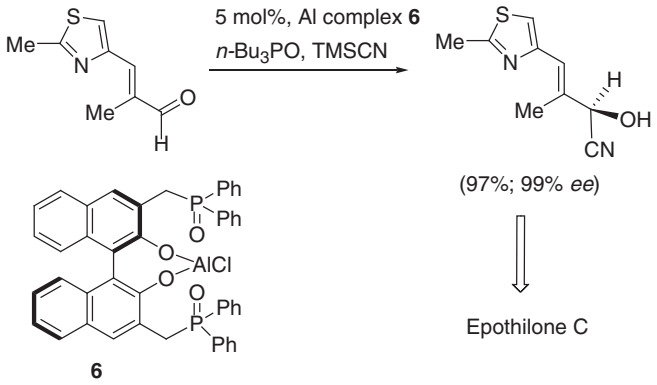


Figure 1 Salicylaldehyde imines as ligands.

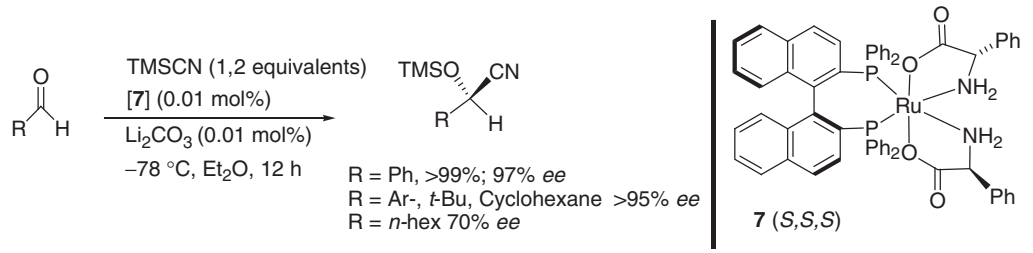


(6)

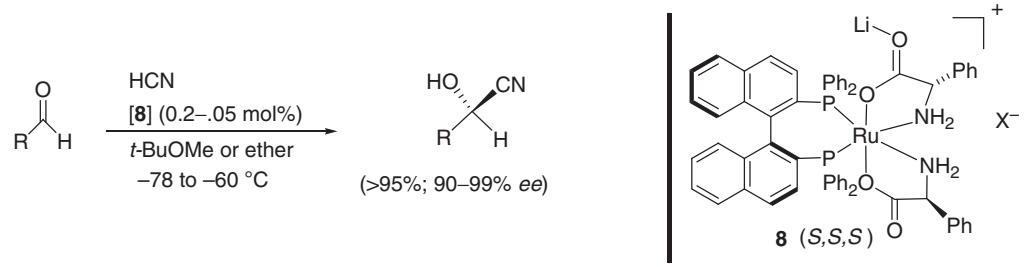


(7)

Late transition metals have rarely been used successfully for the hydrocyanation of aldehydes until Ohkuma reported[34] that Ru(2,2-bis-(diphenylphosphino)-1,1-binaphthyl (BINAP)) complex **7** for the silylcyanation of aldehydes (equation 8). A more recent application (equation 9)[35] in the use of a similar isolated bimetallic complex **8** represents the most efficient hydrocyanation of aldehydes using HCN reported to date. The complex [Li(Ru[(*S*)-(Phe)]$_2$[(*S*)-BINAP])]Br is readily synthesized by mixing Ru[(*S*)-Phenylglycine]$_2$[(*S*)-BINAP] and LiBr, and, it efficiently catalyzes asymmetric hydrocyanation of aldehydes with a substrate-to-catalyst ratio of 500–2000 at -78 to $-60\,^{\circ}C$. A range of aromatic, heteroaromatic, and α,β-unsaturated aldehydes as well as a *tert*-alkyl aldehyde is converted into cyanohydrins in high enantiomeric excess (*ee*) (up to 99%).



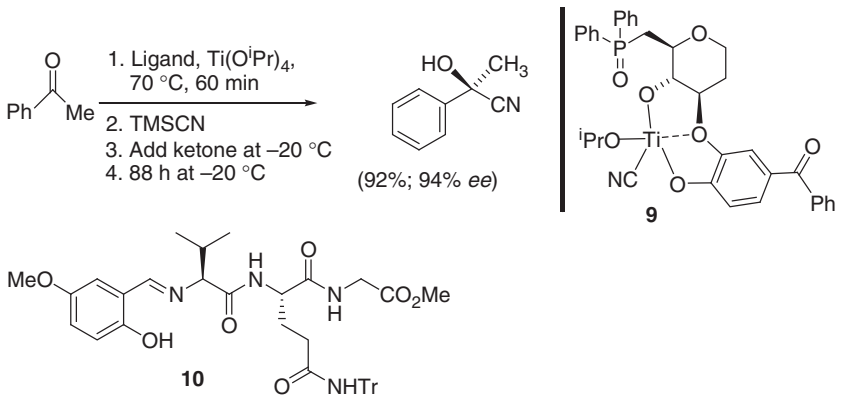
(8)



(9)

The equilibrium in case of the addition of HCN to ketones does not favor the cyanohydrin, and most successful reactions use TMSCN to prepare these intermediates. Historically, ZnI_2 has been the reagent of choice, even though a number of other catalysts have been reported for this reaction.[36] These include $TMSN(SO_2F)_2$, $InBr_3$, $Cu(OTf)_2$, $Y(OTf)_2$, $BiBr_3$, and Et_2AlCN, all of which have been found to give acceptable y. of the product.

Dimeric Ti complex **5** (**Figure 1**) catalyzes the addition of TMSCN to acetophenone[31] even though *ee*'s are unacceptably low. Carbohydrate-derived phosphine-oxide–Ti complex **9** (equation 10) catalyzes the addition of TMSCN to both aromatic and aliphatic ketones.[37] In this case, depending on the metal that is used, one can get either of the enantiomers.[38] An aluminum complex of a peptide–imine ligand **10** has also been used for this reaction.[39] Aluminum salen complexes in conjunction with *N*-oxide additives (double activation)[40] have also been reported for this reaction. Other notable results include the use of H-bonding catalysis[41] and the use of amino acid salts in the syntheses of ketone cyanohydrins.[42] Several examples of related additions of methyl cyanoformate to aliphatic ketones in the presence of modified cinchona alkaloids have also been reported.[43]

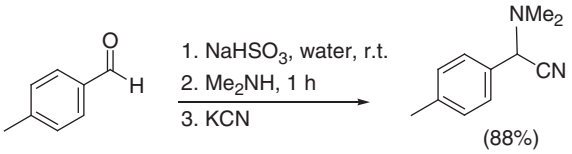


(10)

Many oxynitrilase enzymes, which generally use aldehydes as their natural substrates, will accept methyl and ethyl ketones and even some substituted cyclohexanones. Under buffered conditions these catalyze the addition of HCN.[20,44,45]

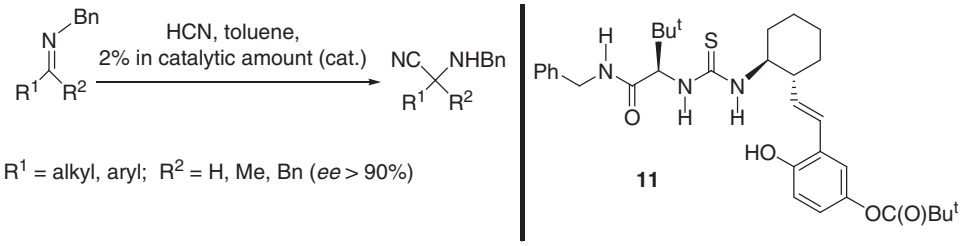
5.36.3 Additions of HCN to Imines

Excellent reviews[46–48] of this subject have recently been published and only the most practical reactions are covered here. Traditional Strecker reactions are carried out in water under slightly acidic conditions (equation 11).[49] A notable variation is the use of ammonium chloride and catalytic alumina in a nonaqueous medium under sonication.[50,51] Lanthanide trifluoromethanesulfonates (especially $Yb(OTf)_3$) catalyze the addition of TMSCN to a wide variety of aldimines, which are often formed *in situ*.[52]

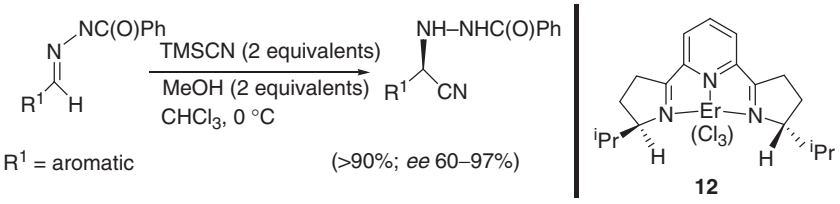


(11)

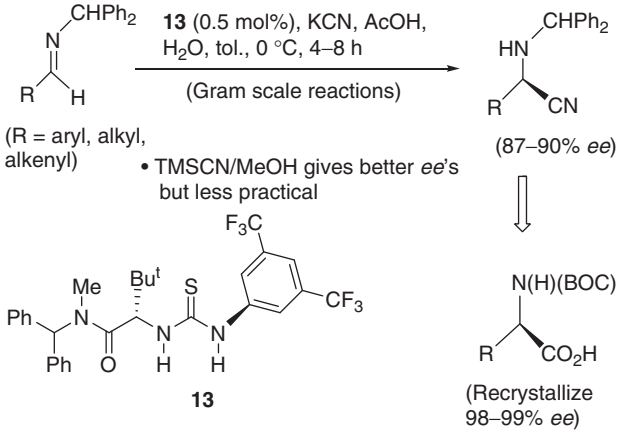
Among the many papers that deal with the asymmetric addition of HCN to imines, Jacobsen's work is particularly noteworthy.[53–55] Searching through a library of dipeptide-urea catalysts, his group discovered general enantioselective methods for the syntheses of a wide variety of aminonitriles from aldehyde and ketone imines (equation 12). Use of aluminum salen,[56] aluminum binaphtholate,[57] and Ti(IV)–peptide–imine complexes[58] as catalysts for these reactions have also been reported. In the only report of addition of HCN to hydrazones (equation 12b), an erbium complex (**12**) of readily available phenyl-2,6-bis-oxazolinylpyridine (PYBOX) ligand is used.[59] The *ee*'s in these reactions are generally modest. Jacobsen also reported[60] a scalable procedure (equation 13) that uses a thiourea catalyst (**13**) at 0.5 mol% loading for the syntheses of a wide variety of natural and unnatural amino acids. This procedure is compatible with the use of KCN and acetic acid as a source of HCN, and has many practical benefits for the syntheses of several amino acids that are not available via conventional methods including hydrogenations.



(12a)

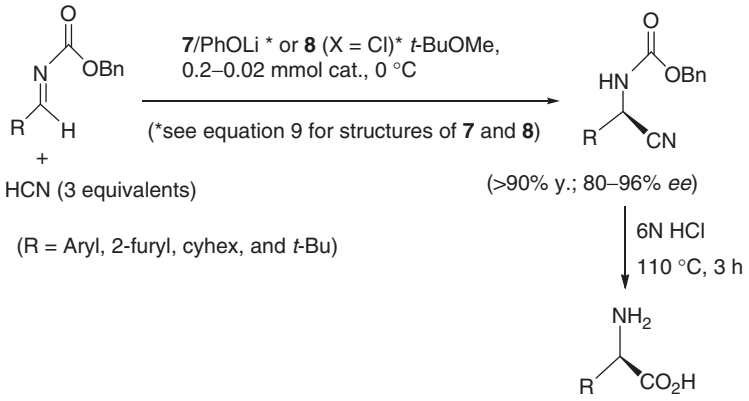


(12b)



(13)

Another procedure with potential applications for the large-scale synthesis of amino acids depends on the enantioselective hydrocyanation of *N*-benzyloxycarbonyl aldimines catalyzed by Ru[(*S*)-(Phe)]$_2$[(*S*)-(BINAP)]/C_6H_5OLi or a bimetallic complex [Li(Ru[(*S*)-(Phe)]$_2$[(*S*)-(BINAP)])]Cl (equation 14).[61] These systems y. aminonitriles in 92–99% *ee*. The reactions are carried out in *tert*-$C_4H_9OCH_3$ with a substrate-to-catalyst molar ratio in the range of 500–5000 at -20 to 0 °C, and excellent y. and selectivities are obtained. The product aminonitriles are easily hydrolyzed to the respective amino acids. The Ru-catalyst **7**/PhOLi is also effective for cyanosilylations of α-ketoesters.[62]

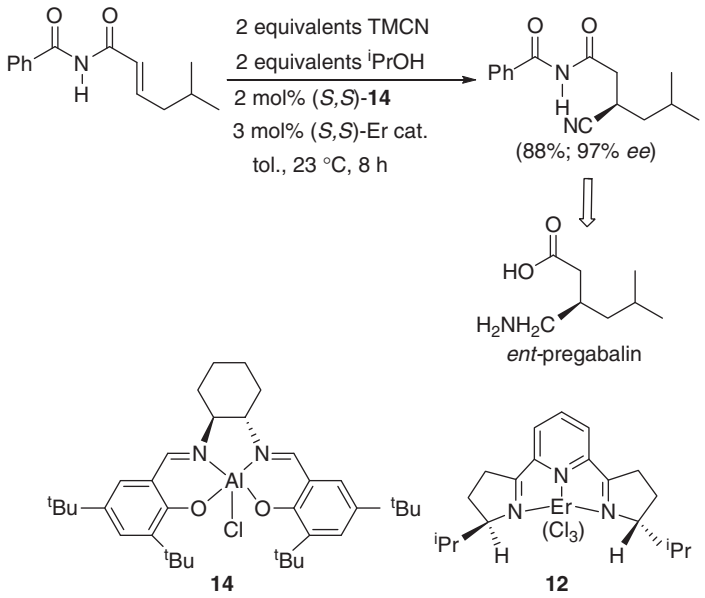


(14)

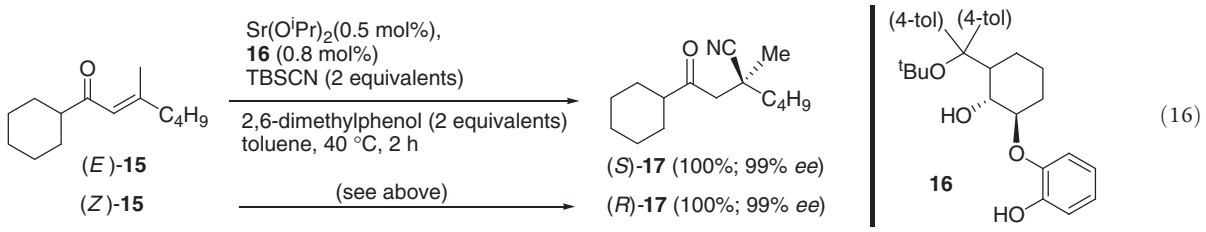
5.36.4 1,4-Additions of HCN to α,β-Unsaturated Carbonyl Compounds

In addition to Nagata's exhaustive review in *Organic Reactions*,[14] which covers all of the early work, a more recent update on these reactions has appeared.[13] Only the most recent work that deals with asymmetric addition of HCN or an equivalent reagent is covered here.

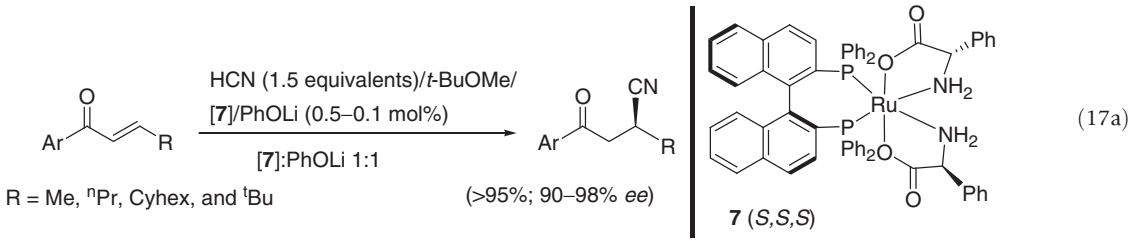
The first notable example of an enantioselective conjugate addition of HCN to α,β-unsaturated carbonyl compounds was reported by Jacobsen, who showed that an aluminum salen complex catalyzes this reaction with excellent y. and enantioselectivity. The high catalyst loading in the original protocol (10% Al) can be overcome by using a mixed catalytic system (**12** + **14**) that also employs a (PYBOX)$ErCl_3$ complex, presumably to activate the electrophile (equation 15).[63–65] Subsequently, Shibasaki reported the use of a Gd complex derived from a sugar diol (similar to **9** shown in equation 10) for related addition of HCN to α,β-unsaturated *N*-acylpyrroles.[66] Optimization of the ligand (e.g., **16**) and metal (Sr) has enabled further extensions of this chemistry to introduce all-carbon quaternary centers by addition of HCN to β,β-disubstituted carbonyl compounds (equation 16).[67] Note that the (*Z*) and (*E*) alkenes give opposite enantiomers in this highly stereospecific reactions. Spectacular y. (>96%), catalytic efficiencies (0.1 mol%), and selectivities (91–98% *ee*) have been reported in a Ru-catalyzed asymmetric hydrocyanation of α,β-unsaturated ketones (equations 17a and 17b).[68] A more recent study reports conjugate asymmetric HCN addition to nitroalkenes catalyzed by Ti–salen complexes (up to 84% *ee*).[69]



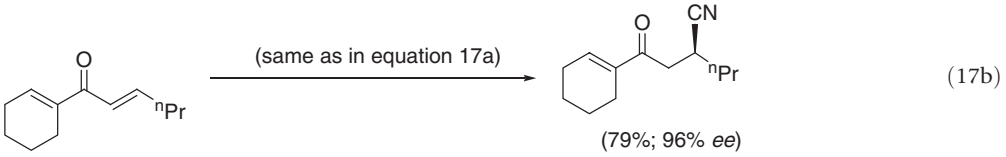
(15)



(16)



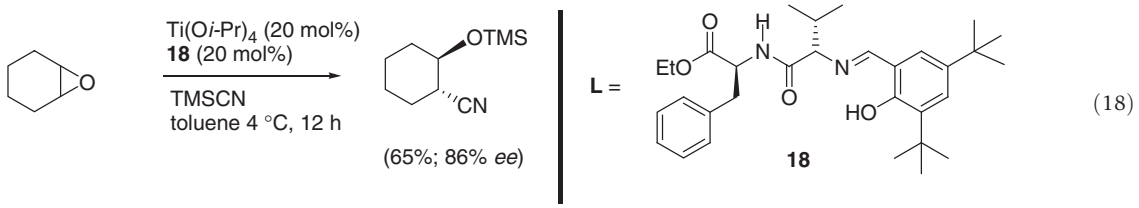
(17a)



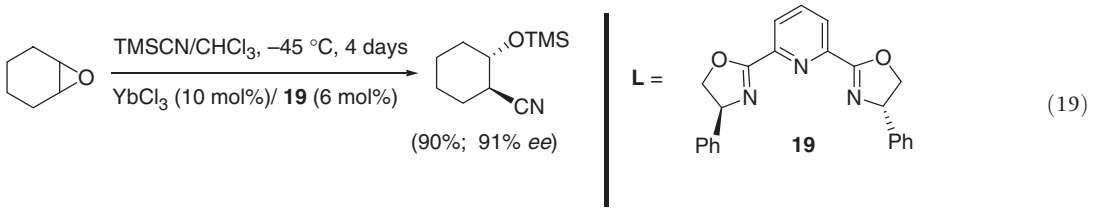
(17b)

5.36.5 Ring-Opening Reactions of Epoxides and Aziridines

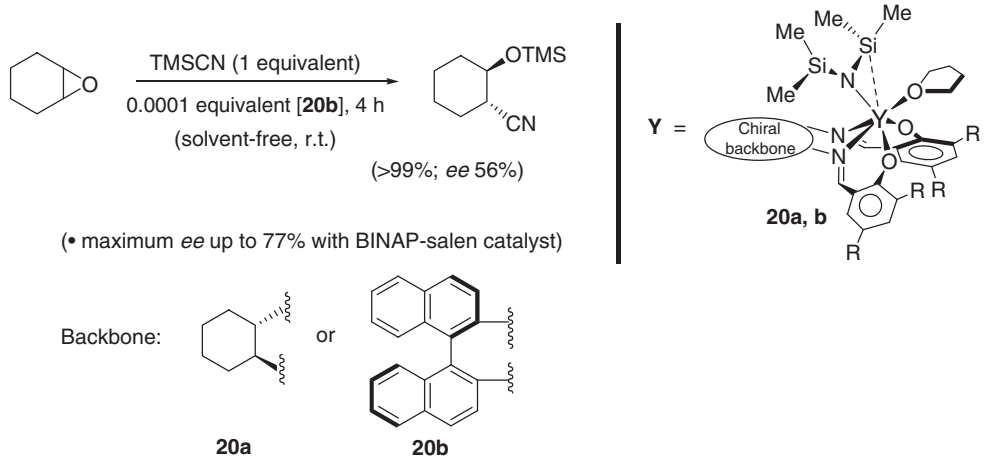
Enantioselective ring-opening reactions of epoxides with TMSCN or HCN remains a challenge,[6] even though related reactions with nitrogen and oxygen nucleophiles have been among the most practical methods in asymmetric catalysis.[70] The best results in the area are depicted in equations 18–20, and use Ti,[71] Yb,[72] or Y[6] catalysts to effect this transformation. The yttrium catalysts are remarkably efficient (0.01 mol%) in these reactions, but the enantioselectivity remains modest (equation 20).[6] Shibasaki has reported the use of an Sm(III) complex for the ring-opening of an α,β-epoxycarboxamide.[73]



(18)

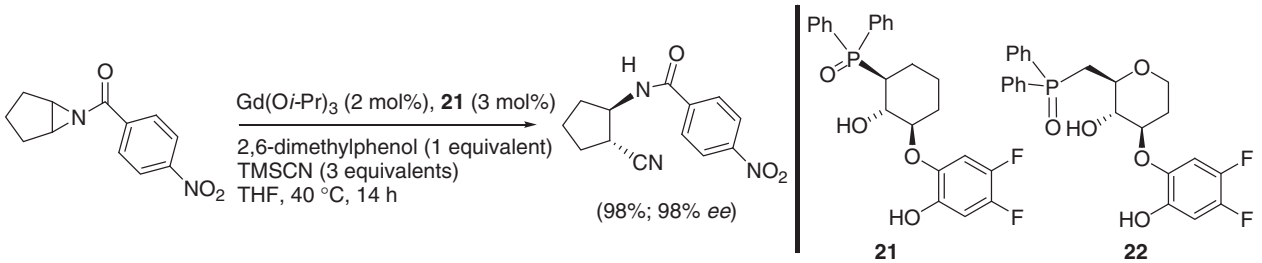


(19)

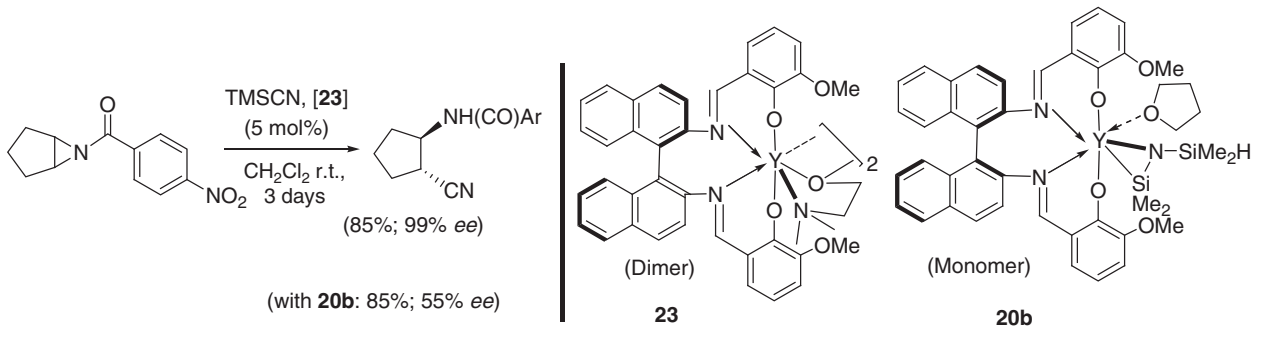


(20)

Aziridines with activating *N*-substituents (4-nitrobenzenesulfonyl, *N*-tosyl, and *N*-benzoyl) are known to undergo ring-opening reactions in highly polar media.[74] Catalysts used for this process include $LiClO_4$,[75] *n*-Bu_4NF,[76] $Y(CN)_3$, or $Yb(CN)_3$.[77] Enantioselective ring-opening reactions of aziridines with TMSCN, as compared to the corresponding reactions of epoxides, have been better developed. The Gd complex derived from ligand **21** (2 mol%), initially developed for the syntheses of ketone cyanohydrins,[38] effect desymmetrization of an aziridine in essentially quantitative y. and over 98% *ee* (equation 21).[78] A slight variation in the structure of the ligand (**22**) gives a slightly inferior catalyst that affords the opposite enantiomer of the product nitrile.[79] Salen yttrium complexes (e.g., **20b**) that showed exceptional activity in ring-opening reactions of epoxides (equation 20) are only marginally effective for the TMSCN-mediated ring-opening of aziridines. Yet, a related dimeric complex **23**, designed on the basis of a mechanistic rationale, works well for this reaction (equation 22).[80] Incidentally, complex **23** catalyzes a rare regiodivergent parallel kinetic resolution of chiral aziridines giving two different azide adducts (each ~99% *ee*) in reactions with $TMSN_3$ from each of the enantiomers.[81] Structural studies on the catalyst and kinetic investigations suggest a bimetallic mode of activation in these reactions.



(21)



(22)

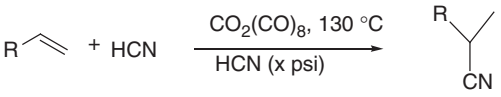
5.36.6 Hydrocyanation of Alkenes

An exhaustive review on the subject of hydrocyanation of alkenes and alkynes that deal with various aspects of synthesis, mechanism, stereochemistry, and specific examples of different substrate types has recently (2011) been published and the reader

is encouraged to consult this article for details.[3] This review also contains an extensive tabular survey that includes most of the examples published until the end of 2010.

5.36.6.1 Hydrocyanation of Unactivated Alkenes

The addition of HCN to unactivated alkenes is a sluggish reaction that proceeds only at high temperatures in the gas phase even in the presence of a catalyst. A homogeneous catalyst, $Co_2(CO)_8$, facilitates the addition of HCN to alkenes in a Markovnikov fashion at 130°.[82] Propene and 1-butene give the corresponding branched nitriles in 65% and 67% conversions at 130°, respectively, and at moderate pressures in an autoclave (equation 23). As the size of the alkyl group on the double bond increases, the conversions decrease. The addition of Ph_3P increases the y. 2-Butene gives a low y. (up to 24%) of 2-butanenitrile under these conditions.

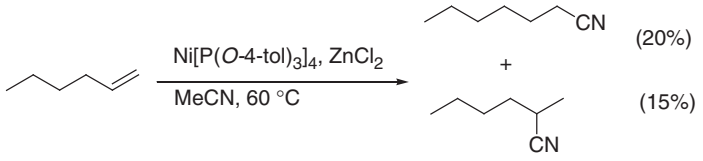


R	x	Time (h)	Conversion (%)
Me	110	15	65
n-Pr	40	8	67
n-Bu	46	8	5
n-Bu	43	8	24[a]

[a]With added Ph_3P.

(23)

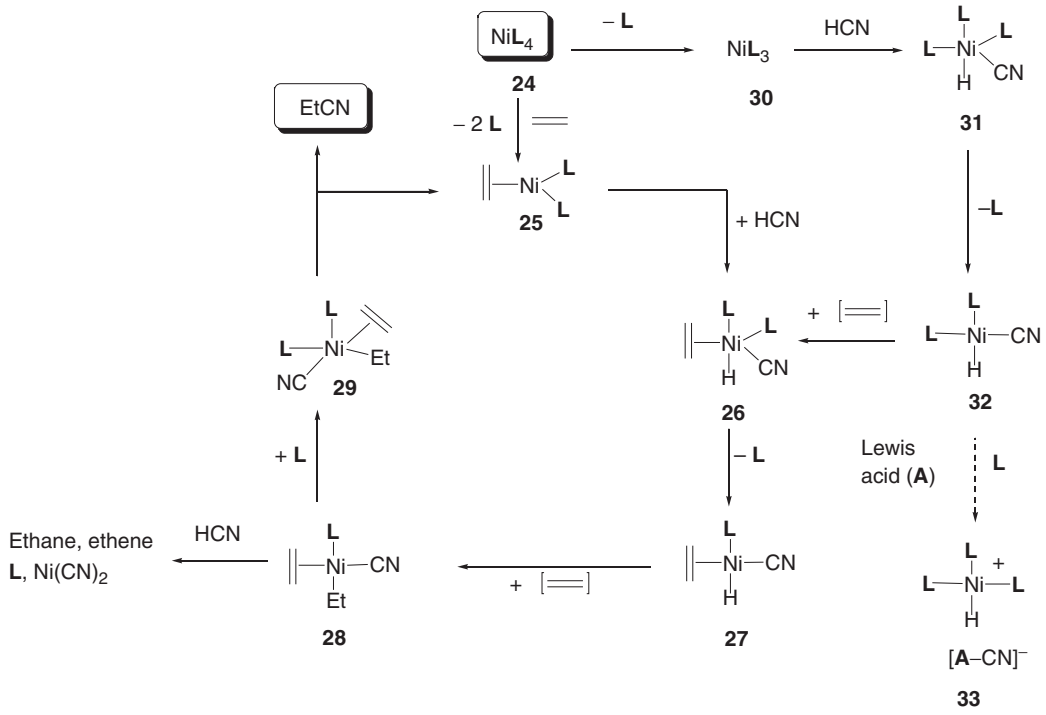
The best results in the hydrocyanation of unactivated alkenes are obtained with $Ni[P(OAr)_3]_n$ ($n=3$, Ar = 2-MeC_6H_4; $n=4$, 4-MeC_6H_4) that show favorable ligand dissociation kinetics needed for the alkene activation. These reactions generally give low turnover numbers (ton). Since the disclosure of homogeneous Ni(0)[83] and Pd(0)[84] catalysts for alkene hydrocyanation, the use of Lewis acids to promote this reaction has received a great deal of attention. The half-life of propene hydrocyanation by $Ni[P(O\text{-}2\text{-tolyl})_3]_3$ is ~60 min at 0°.[9] The addition of Lewis acids dramatically alters the rate of the reaction, with $AlCl_3$ having the most pronounced effect: the half-life at −25 °C is 10 min. Triphenylboron slows down the reaction, yet produces the best terminal to internal selectivity in the hydrocyanation of propene (89:11). Hydrocyanation of 1-hexene catalyzed by $Ni[P(O\text{-}4\text{-tolyl})_3]_4$ in the presence of excess ligands and a promoter Lewis acid such as $ZnCl_2$ gives the two nitriles in a terminal to internal ratio of 4:3 (equation 24).[85] The increased activity in the presence of an added ligand is thought to be due to the prevention of the formation of the catalytically inactive $L_2Ni(CN)_2$ species (see Section 5.36.6.1.1). In many hydrocyanation reactions slower addition of HCN helps to slow down this deactivation process. The Lewis acid promoter acts as a cyanide acceptor from one of the organometallic intermediates, and has a pronounced effect on the branched to linear ratio of products. Among the Lewis acids, $ZnCl_2$ gives one of the best selectivities in favor of the terminal nitrile (terminal:internal = 78:22), whereas $AlCl_3$ is the best for internal nitrile (terminal:internal = 69:31). In the hydrocyanation of hexene with $Ni[P(O\text{-}2\text{-tolyl})_3]_3$ in the presence of $(4\text{-tolyl})_3B$, the regioselectivity for the terminal product increases to 91%. Likewise, using *p*-cresol as the solvent gives a higher proportion of the linear product (terminal:internal = 86:14) as compared to acetonitrile (terminal:internal = 78:22).[85] Isobutylene and 2,3-dimethyl-1-butene give a terminal to branched ratio of 99:1.



(24)

5.36.6.1.1 Mechanism of the Ni(0)-catalyzed hydrocyanation of ethylene

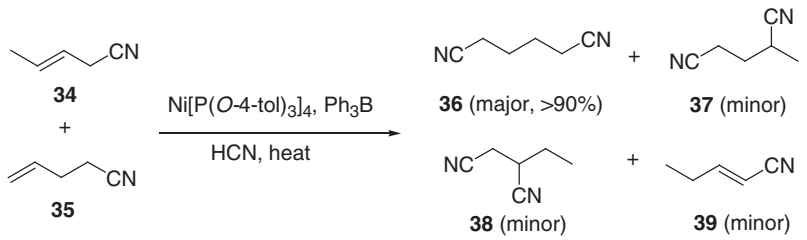
The mechanism of alkene hydrocyanation has been studied in great detail (Scheme 2).[9] The typical hydrocyanation catalysts are zero-valent triarylphosphite–nickel complexes, $Ni[P(OAr)_3]_n$ ($n=3$, 4). These catalysts tolerate a broad range of substrates and functional groups. The initial step is the dissociation of one of the arylphosphite ligands from the NiL_4 complex (**24**) to give a coordinatively unsaturated Ni-complex (**30**) that readily forms an alkene adduct **25**. Olefins form complexes with $L_2Ni(0)$ with equilibrium constants decreasing in the order of ethylene > styrene > propene > 1-hexene > disubstituted alkenes. Oxidative addition of HCN to this complex gives **26**. This intermediate can also be arrived at first by oxidative addition of HCN to **30** and subsequent substitution of a ligand in **31** by the alkene. Loss of a ligand from **26** gives **27**. The insertion of ethylene into the metal–hydrogen bond gives **28** with a σ-bonded ethyl group and a π-bonded ethylene. With excess ligands, complex **29** is produced and it proceeds to give the product EtCN along with the active catalyst. The final step is essentially irreversible unless the



Scheme 2 Mechanism of the Ni-catalyzed hydrocyanation of ethylene (see text for details). Reproduced from RajanBabu, T. V. *Org. React.* **2011**, *75*, 1–73, with permission from Wiley.

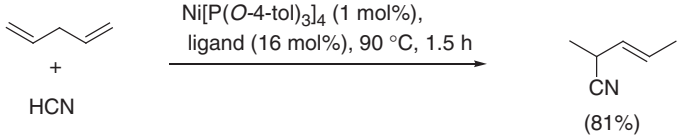
product is an allyl cyanide. If the starting alkene is electron-deficient (e.g., tetrafluoroethylene or acrylonitrile), the reductive elimination from **29** is slow and the turnover is essentially blocked. Intermediate **28** is also the source of a deleterious side reaction to form catalytically inactive $Ni(CN)_2$ if excess HCN is present in the medium. Several of the intermediates in the catalytic cycle have been identified using low temperature spectroscopic techniques.[9]

Hydrocyanation of a mixture of 3-pentenenitrile (**34**) and 4-pentenenitrile (**35**) is an important step in the DuPont process for the manufacture of adiponitrile from 1,3-butadiene (BD) and many protocols for this reaction have been described in the patent literature.[9] In this process, a mixture of mononitriles obtained from Ni(0)-catalyzed hydrocyanation of BD (see Section 5.36.6.2) is treated with HCN and a mixture of a $Ni[P(O\text{-}2\text{-}Ar)_3]_3$ and Ph_3B (equation 25).[86,87] Because the isomerization of the internal alkene **34** to the terminal alkene **35**, catalyzed by the $[(ArO)_3P]_2NiH(CN)$ (**32**, Scheme 2), is faster than the hydrocyanation of the former; the major product formed is adiponitrile (**36**) with minor amounts of other dinitriles formed under the reaction conditions. More robust[88] chelating phosphites based on various biaryl scaffolds have since been developed for these reactions.

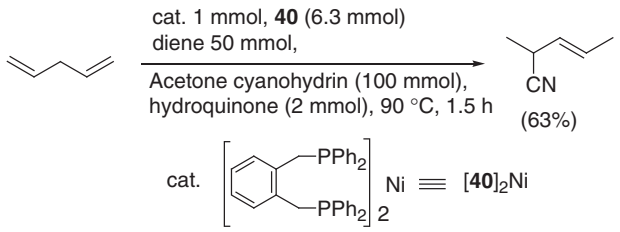


(25)

Nonconjugated dienes under similar conditions undergo hydrocyanation to give major products in which the terminal alkene is isomerized (equation 26).[89] The reaction (equation 27) using ligand **40** illustrates the use of an HCN surrogate, acetone cyanohydrin, in a hydrocyanation reaction.

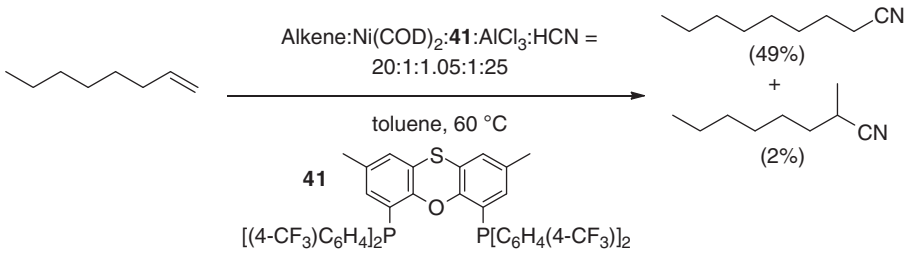


(26)



(27)

Rigid bidentate phosphines with an optimum bite-angle of more than 100° show pronounced activity for the hydrocyanation of unactivated alkenes in the presence of Lewis acids.[90,91] Thus, $Ni(COD)_2$, in the presence of a diphosphine **41** and $AlCl_3$, effects the hydrocyanation of 1-octene up to a ratio of 49:2 for the terminal to internal isomeric nitriles (equation 28).[91]

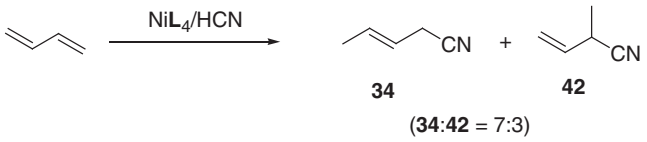


(28)

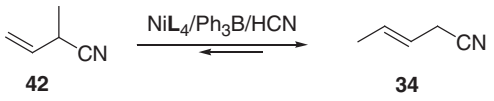
Alkenes attached to halogen, oxygen, carbonyl substituents, or other electron-withdrawing groups do not react with HCN under Ni(0)-catalysis. Mechanistic studies indicate that the final reductive elimination step is retarded by these substituents.[9]

5.36.6.2 Hydrocyanation of Conjugated Dienes

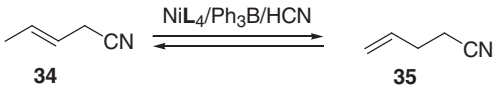
Hydrocyanation of 1,3-dienes are best carried out using homogeneous nickel complexes even though Cu[92,93] and Co[94] salts and complexes are known to effect this reaction. The classic example, which represents a very successful commercial application[95] of this process, is DuPont's production of the nylon-66 precursor, adiponitrile, via hydrocyanation of BD (equations 29–32).[9,83] This discovery sparked many seminal mechanistic investigations on transition metal-catalyzed reactions.[86,96–100] Concepts that emerged from these studies include the proposal that many catalytic processes proceed through coordinatively unsaturated 16-electron (or lower) intermediates,[101] and the importance of steric (e.g., ligand cone-angle θ) and electronic effects (e.g., Tolman χ-factor) on ligand substitution reactions.[95,99,102] Because of the huge commercial interest in this reaction, much of the work appears in the patent literature. Only the most relevant results where full details of the preparative aspects are available are discussed here.



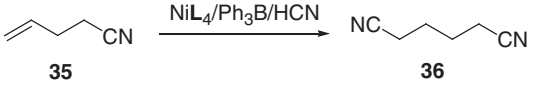
(29)



(30)



(31)



(32)

As shown in the accompanying equations, a triarylphosphite nickel complex catalyzes the hydrocyanation of butadiene in a multistep process to give an overall anti-Markovnikov addition of two molecules of HCN to butadiene. The reaction is carried out in two stages. In the initial hydrocyanation, butadiene gives mostly a ~2:1 mixture of isomeric C5 nitriles, 3-pentenenitrile (**34**), and 2-methyl-3-butenenitrile (**42**), which are resistant to further reaction with HCN in the absence of a Lewis acid (equation 29). In the second stage, the initial product is isomerized to a mixture of 3- and 4-pentenenitriles (**42** and **34**) using a $Ni[P(OAr)_3]_n$ ($n=3$ or 4) complex and a Lewis acid such as Ph_3B or $ZnCl_2$ (equation 30). Concurrent isomerization of **34** to **35** and anti-Markovnikov HCN addition to **35** follows (equations 31 and 32). Under optimum conditions, the hydrocyanation of **35** proceeds faster than all the other reactions, and adiponitrile is formed in very high y. and selectivity. The added Lewis acid promoter increases the rate of hydrocyanation of **35** and controls the selectivities in the isomerization reactions.[86,87] Major side-products, 2-methylglutaronitile and ethylsuccinonitrile (ES), which arise from hydrocyanation of various intermediates, are formed only in very small amounts under the production conditions.

New ligands and complexes (**Figure 2**) that show improved efficiency and selectivity in the hydrocyanation of BD continue to appear in the literature. A robust complex, $Ni[43]_2$, is more efficient in the initial hydrocyanation of butadiene as compared to the more air-sensitive $Ni[P(O\text{-}4\text{-tolyl})_3]_4$, yielding more than four times the turnover of the latter.[88] Two other recently developed ligands are also shown in **Figure 2**. The Ni-complexes of the phosphonate ligand **44** shows excellent activity and high selectivity in the hydrocyanation of butadiene.[103] The triptycene-based ligand **45** with a large bite-angle is exceptionally good in giving a high y. and a very high ratio (93:2) of 3-pentenenitrile to 2-methyl-3-butenenitrile, especially when the reaction is carried out in dioxane (equation 33).[104] As might be inferred, Ni(0)-complexes of ligands **44** and **45** are also good catalysts for the conversion of 2-methyl-3-butenenitrile to 3-pentenenitrile even in the absence of Lewis acids.

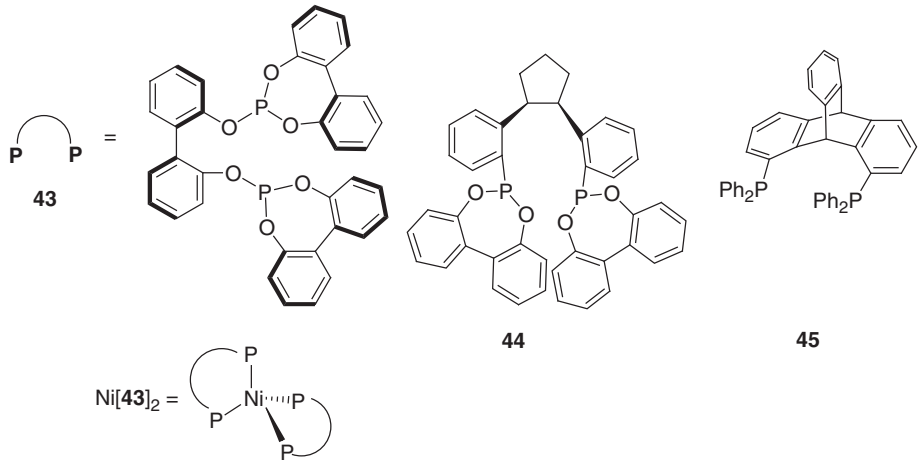
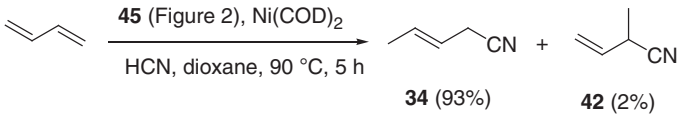


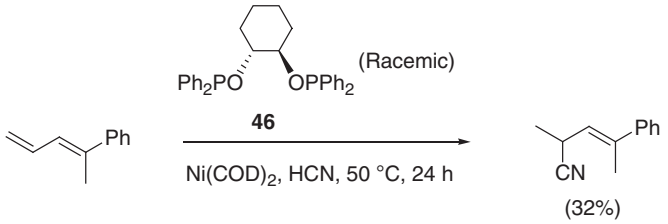
Figure 2 New ligands and complexes for hydrocyanation of 1,3-butadiene.



(33)

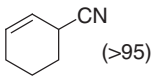
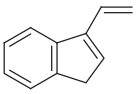
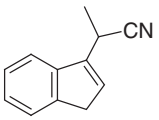
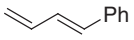
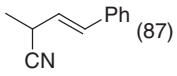
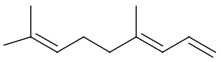
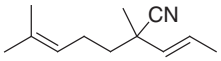
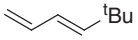
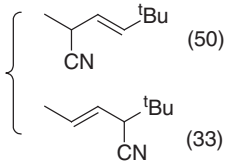
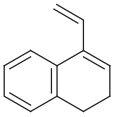
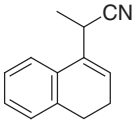
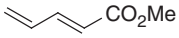
Hydrocyanations of other dienes catalyzed using $Ni[P(OAr)_3]_n$ ($n=3$ or 4) have been reported. These include 1-vinyl-1-cyclohexene, norbornadiene (NBD), dicyclopentadiene, allene, 1,5-cyclooctadiene (COD), 1,3-COD, cyclopentadiene,[9] 1,3-cyclohexadiene,[100] 1-methyl-BD, 2-methyl-BD, and 1,4-dimethyl-BD[89] (**Table 1**).

trans-Cyclohexane-1,2-diol-derived bis-1,2-diarylphosphinites (e.g., **46**, equation 34) are good ligands in Ni(0)-catalyzed hydrocyanations of 1,3-dienes.[105] The examples shown in equation 34 and the accompanying table are typical. Depending on the structure of the diene, both 1,2- and 1,4-additions are observed. Sequential additions of 1,3-cyclohexadiene and HCN to a catalyst prepared from the ligand and $Ni(COD)_2$ give the expected product in >95% y. Higher temperatures are needed for more substituted, though less reactive, dienes, such as 1-phenyl-1-methyl-BD and 2,6-dimethylnona-2,6,8-triene.



(34)

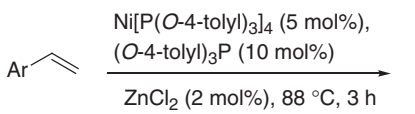
Table 1 Ni-catalyzed hydrocyanation of 1,3-dienes[a]

Substrate	*Product (yield %)*	*Substrate*	*Product (yield %)*
	 (>95)		 (71)
	 (87)		 (83)
	 (50) (33)		 (80)
	No reaction		

[a]See equation 34 for procedure.

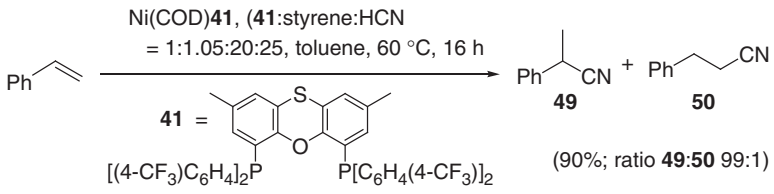
5.36.6.3 Hydrocyanation of Vinylarenes

Hydrocyanations of styrene and various other vinylarenes have been investigated in detail.[9,106,107] With Ni[P(*O*-4-tolyl)$_3$]$_4$, the branched nitrile (**47**) is obtained as the major product (equation 35). High activity and selectivity for the branched isomer (**47**) has been observed using finely tuned xantphos ligands (e.g., **41**) having a natural bite-angle of 105–106°.[91] Several other catalysts that give very high regio- and enantioselectivity are discussed below (see Section 5.36.6.5).



Ar	Yield (%)	**47:48**
4-^{i}BuC$_6$H$_4$	68	90:10
6-OMe-2-naphthyl	93	95:5

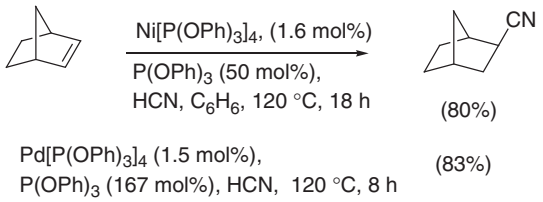
(35)



(36)

5.36.6.4 Hydrocyanation of Strained Alkenes

Hydrocyanation of norbornene is catalyzed by both Pd[P(OPh)$_3$]$_4$[84] and Ni[P(OPh)$_3$]$_4$[108,84] to give exclusively the *exo*-adduct (equation 37).



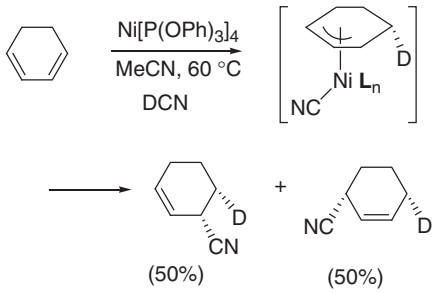
(37)

5.36.6.5 Asymmetric Hydrocyanation of Alkenes

Markovnikov addition of HCN to an alkene can, in principle, serve as an entry into chiral intermediates that can be transformed into a wide array of useful products.[106,109] In spite of the extensive work on hydrocyanation of alkenes, only limited research activity has been directed toward finding an asymmetric variation of this reaction.

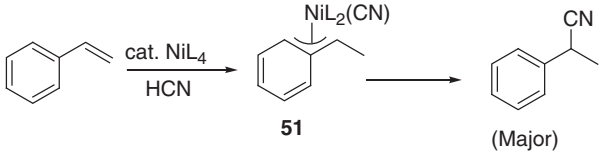
5.36.6.5.1 Regio- and stereoselectivity

The stereoselectivity of hydrocyanation has been studied in some detail and it has been established that the addition of HCN to olefins is stereospecifically *syn*.[85,100] Addition of HCN to *tert*-butylethylene leads to anti-Markovnikov addition of HCN with a regioselectivity of more than 99%.[85] Addition of DCN to (*E*)-1-deutero-2-(*tert*-butylethylene) leads to predominantly the *erythro* product, confirming the *syn*-addition mode.[100] Addition of DCN to 1,3-cyclohexadiene results in a smooth conversion to two monodeuterated nitriles, which are 1,2- and 1,4-addition products (equation 38) even in the absence of a Lewis acid.[100] The fact that recovered cyclohexadiene does not contain any deuterium suggests that the initial metal hydride addition is irreversible in this case. It has been shown that the addition of $HNiL_3(CN)$ [L=P(*O*-2-tolyl)$_3$] to butadiene is also essentially irreversible.[86] Careful analysis of the products from 1,3-cyclohexadiene suggests that a *syn*-addition of DCN takes place in 1,2- and 1,4-fashions with equal propensity.



(38)

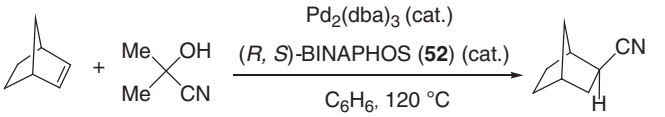
Vinylarenes, similar to conjugated dienes, give η^3-benzylnickel cyanides (e.g., **51**, equation 39) leading to overall Markovnikov addition via reductive elimination.



(39)

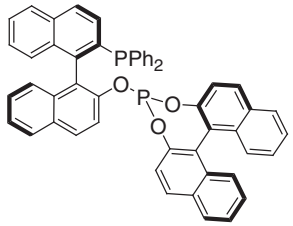
5.36.6.5.2 Asymmetric hydrocyanation of bicyclo[2.2.1]heptanes

Most of the early studies on the transition metal-catalyzed asymmetric hydrocyanation of alkenes dealt with the Ni(0)-[110] or Pd(0)[108,111]-catalyzed hydrocyanation of norbornene or its derivatives. Although high facial selectivities are observed, only modest enantioselectivities and y. are obtained in this reaction. A Pd-catalyzed hydrocyanation of norbornene using the (*R*,*S*)-BINAPHOS ligand **52** gives 48% *ee* for the indicated 2*S*-product (equation 40).[112]



(52% y.; 48% *ee*)

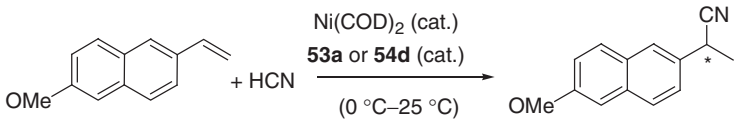
52 [(*R*, *S*)-BINAPHOS]



(40)

5.36.6.5.3 Asymmetric hydrocyanation of vinylarenes

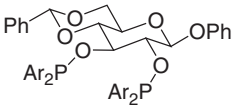
An important class of compounds that can be readily prepared from vinylarenes via the asymmetric hydrocyanation route is the 2-arylpropionitriles, precursors for the widely used anti-inflammatory 2-arylpropionic acids, such as naproxen and ibuprofen. The highest enantioselectivities have been obtained for the asymmetric hydrocyanation of vinylarenes using carbohydrate-based [arylphosphinite]nickel complexes as catalysts. Using the 2,3-disubstituted D-*gluco*-diarylphosphinite ligand **53**, for example, the naproxen precursor, 6-methoxy-2-vinylnaphthalene (MVN), is hydrocyanated with complete regioselectivity in 85–95% *ee* (*S*) (equation 41).[113,106] This catalyst system is remarkably active, giving a maximum reaction rate of 2000 turnovers per hour (turnover = moles of alkene/mole of Ni/unit time) and overall 700–800 total turnovers at room temperature (rt). The fructose-derived ligands **54** gave the opposite enantiomer, (*R*)-**55**.



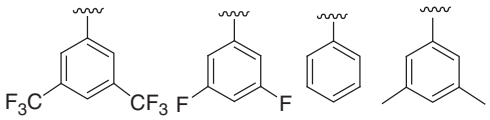
6-Methoxy-2-vinylnaphthalene

55 (95%; *ee* up to 95%)

53



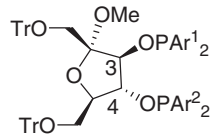
Ar:



53a **53b** **53c** **53d**

(41)

54

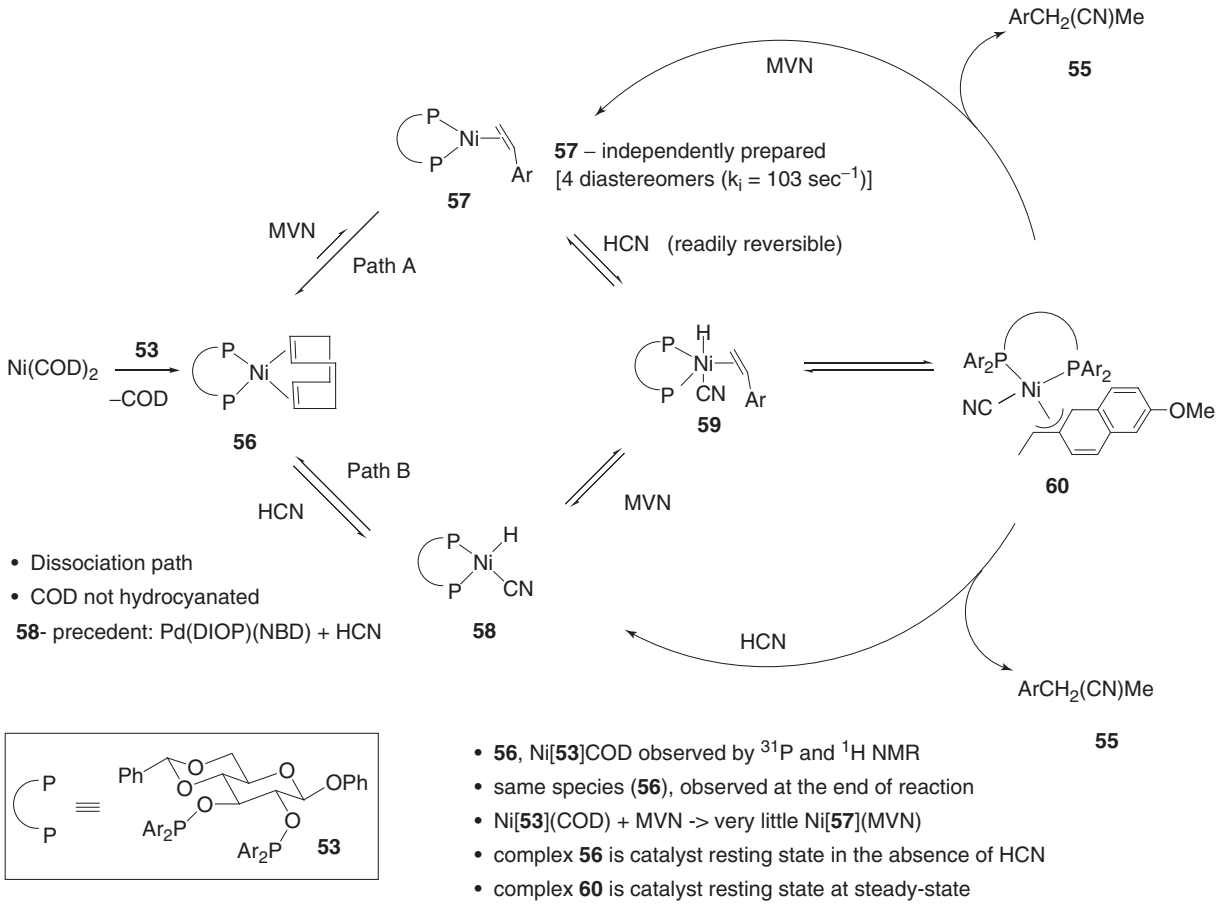


54a $Ar^1 = Ar^2 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$
54b $Ar^1 = Ar^2 =$ Ph
54c $Ar^1 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$; Ar^2 = Ph
54d Ar^1 = Ph; $Ar^2 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$

Tr = Ph_3C

A key finding of this work is the importance of ligand electronic effects in asymmetric catalysis. These studies provided some of the first unequivocal examples of electronic tuning of an asymmetric catalyst. A study of the effect of the aryl substituents on phosphorus shows a pronounced increase in the enantioselectivity as the electron-withdrawing power of the substituent increases.[114] For example, the *ee* in the hydrocyanation of MVN increases from 16% to 91% as the aromatic *meta*-substituents in **53** are varied in the series Me, H, F, CF_3 ($\sigma_m = -0.07$, 0, 0.34, and 0.43, respectively). However, ligand electronic asymmetry appears to be important in the fructose-based phosphinite ligand system **54**.[115] In this case, the electronic differentiation of the two phosphorus sites is used to maximize the enantioselectivity. Thus, the incorporation of a more electron-withdrawing aryl group in the C_4 position rather than in the C_3 position is crucial in obtaining the highest *ee*'s. For example, for ligand **54** (equation 41) the following selectivities are observed: **54a**, 56% *ee*; **54b**, 43% *ee*; **54c**, 58% *ee*; and **54d**, 89% *ee*. A detailed account of the origin of these remarkable ligand effects and its relation to the mechanism of the asymmetric hydrocyanation has been published,[113] and the original paper can be consulted for details. Further scope of the reaction for syntheses of various styrene derivatives is also discussed therein.

Studies of the reaction mechanism (Scheme 3) using a series of ligands **53** with electronically different substituents on the aromatic groups on phosphorus implicate a Ni[53](COD) catalyst composition (**56**) as the resting state in the absence of HCN.[113] However, as judged using NMR spectroscopy, the enantioselectivity does not depend on the differentiation of the *Re* and *Si* faces of the vinylarene in a Ni[53](vinylarene) complex **57** that is formed from **56** by ligand exchange. All of the possible diastereomers of **57** can be detected using ^{31}P NMR. Deuterium labeling studies suggest that the rate of reductive elimination from a Ni[53](benzyl)CN complex **60** to give the product **55** increases relatively to β-hydride elimination (**60** to **59**) as the electron-withdrawing power of the aryl substituent on phosphorus increases. Other key observations made during the mechanistic studies are summarized in Scheme 3.



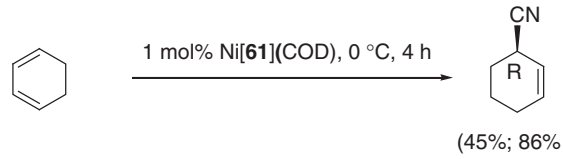
Scheme 3 Details of the mechanism of the Ni-catalyzed hydrocyanation of a vinylarene. Reproduced from RajanBabu, T. V. *Org. React.* **2011**, *75*, 1–73, with permission from Wiley.

The relationship between higher enantioselectivities and electron-withdrawing aryl substituents remains speculative because the rates of many of the fundamental processes are largely unknown. Although the steric effects are determinants of the sense of stereoinduction, the data clearly show that an electronic component that is also present in this NiL$_n$-catalyst system can be used to enhance the inherent preference for the (*S*)-nitriles. A series of kinetic and isotopic labeling studies suggests that the barrier for alkene insertion and/or reductive elimination (Scheme 3) is disproportionately lower for the *S*-pathway as the electron density at nickel is reduced, and this is the origin of the enhanced enantioselectivity.

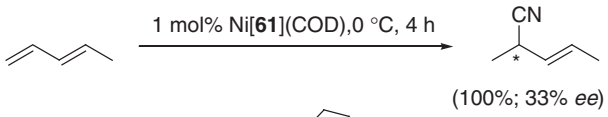
The enantioselectivities in cases other than MVN have been modest even with the best ligands (% *ee*'s: 4-methylstyrene, 70; 4-phenylstyrene, 68; 4-phenoxystyrene, 60; 4-*i*-butylstyrene, 56; 4-methoxystyrene, 52; 4-chlorostyrene, 40; 4-fluorostyrene, 28; 4-trifluorostyrene, 14; acenaphthene, 59; 1-vinylnaphthalene, 68; 2-vinylnaphthalene, 77).

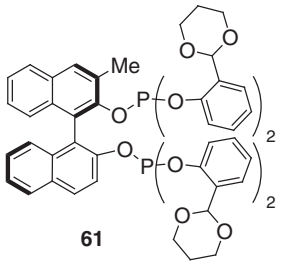
5.36.6.5.4 Asymmetric hydrocyanation of 1,3-dienes

Asymmetric hydrocyanation of 1,3-dienes continues to be a challenge. 1,3-Cyclohexadiene undergoes asymmetric hydrocyanation in the presence of a Ni(0)-complex of a binaphthol-derived phosphite **61** (equation 42).[116] For the same complex, 1-methylbutadiene gives an *ee* of 33% (equation 43).



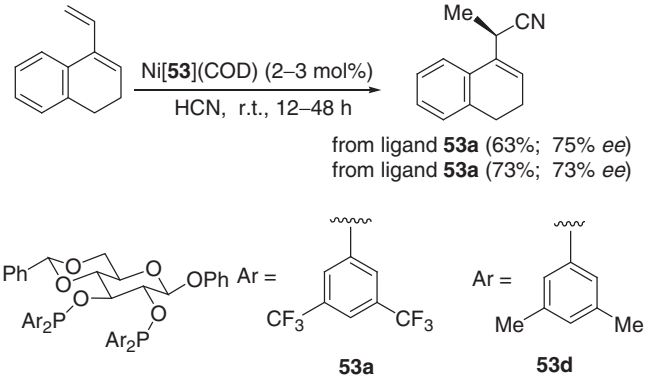
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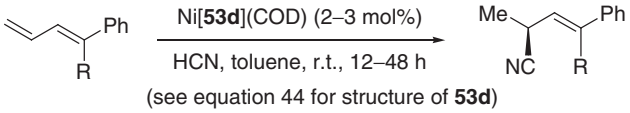


(43)

The D-glucose-derived ligands **53a** and **53d** are moderately effective for the asymmetric hydrovinylation of special classes of 1,3-dienes shown in equations 44 and 45.[105]



(44)



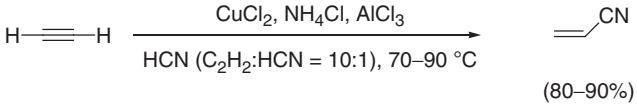
(45)

R	Yield (%)	Selectivity (%*ee*)
H	75	78
Me	56	68

5.36.7 Hydrocyanation of Alkynes

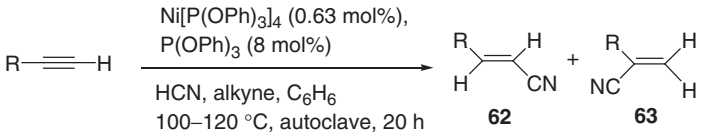
5.36.7.1 Addition of HCN

A major manufacturing process for acrylonitrile used to be the addition of HCN to acetylene (equation 46) until it was replaced by the cooxidation of propylene and ammonia (the SOHIO process).[117]



(46)

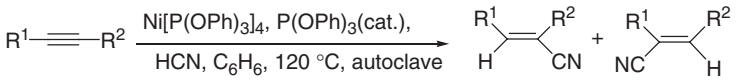
The mechanism of the Ni(0)(arylphosphite)$_n$-catalyzed hydrocyanation of acetylene is thought to be similar to that of alkene hydrocyanation, including the *syn*-stereoselectivity.[118,119] In the Ni[P(OAr)$_3$]$_4$-catalyzed addition of HCN to straight-chain terminal alkynes with moderately sized substituents, mostly the branched products are formed (equation 47).[118,119] This reflects the increased stability of the secondary Cσ–Ni bonding compared to the Cσ–Ni bond with a primary carbon. *tert*-Butyl and phenyl acetylenes give mostly terminal nitriles. In hydrocyanations of alkynes containing heteroatoms on one of the substituents there is a slight preference for the nitriles in which the CN group is attached to the same carbon (**64**) carrying this substituent (equation 48).[120] Hydrocyanation of internal alkynes favors branched nitriles in which the nitrile group is attached to the least hindered position. Bulky substituents direct the cyano group to the terminal position, indicating that there is also a pronounced steric effect on the regioselectivity of this reaction. A similar trend is observed in silyl-substituted alkynes with 1-triphenylsilyl-1-hexyne giving exclusively the terminal nitrile.[121] Trimethylsilylacetylene gives a terminal to internal ratio of 25:75 and *tert*-butyldimethylsilylacetylene gives a ratio of 35:65. The size of the silyl group can be used to control the regioselectivity in hydrocyanation reactions of disubstituted acetylenes.[122] In many of these reactions, acetone cyanohydrin can be used in the place of the toxic HCN (for example in reactions of silylacetylenes, equation 47 or of alkynols, equation 48), thus making this a preparatively useful reaction for the syntheses of vinyl nitrile intermediates.[10,123]



R	Yield (%)	**62:63**
n-Pr	78	12:88
n-Bu	73	14:86
t-Bu	15	88:12
t-Bu	45	80:20
n-Hex	60	14:86
Ph	45	90:10

R	Yield (%)	**62:63**
TMS	74	25:75
TBDMS	57	35:65

(47)



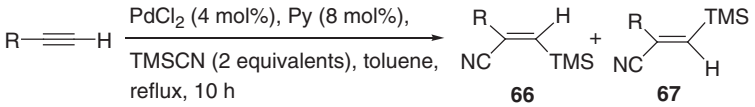
R^1	R^2	Yield (%)	**(64:65)**
H	CH_2PHT	88	4:1
Me	$(CH_2)_2$PHT	88	9:1
Me	CH_2OH	72	1:1
H	CH_2CH_2OBn	78	19:3

PHT = phthaloyl.

(48)

5.36.7.2 Addition of TMSCN

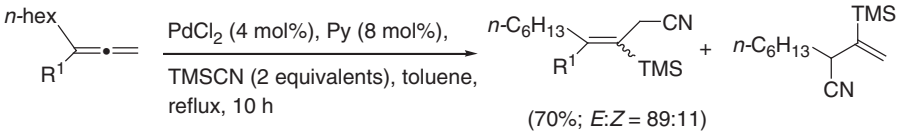
Addition of TMSCN to terminal alkynes in a synthetically useful reaction that is also catalyzed by $PdCl_2$ in the presence of pyridine (Py) (equation 49).[124] The reaction is regioselective with the more highly substituted nitrile as the major product, which arises via a *syn*-addition of TMSCN to the alkyne, giving predominantly the *Z*-alkene. A less general Ni(0)-catalyzed addition is complicated by competitive addition of TMSCN to the initial product yielding pyrrole carbonitriles.



R	Yield	**66:67**
Ph	90	95:5
n-C_6H_{13}	41	85:15
TMSO$(CH_2)_2$	34	88:12
4-MeOC_6H_4	90	95:15
2-naphthyl	90	95:5

(49)

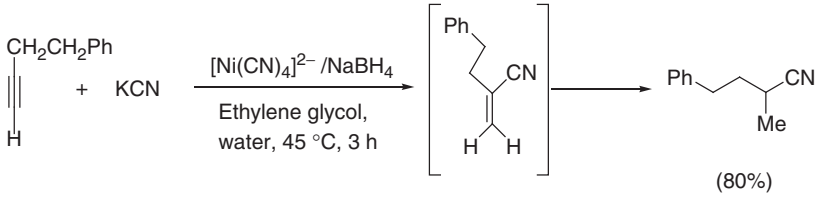
Allenes also react with TMSCN in the presence of a $PdCl_2$/Py catalyst to afford vinylsilanes in which silicon is bound to the central carbon of the allene (equation 50).[125]



(50)

5.36.7.3 Cyanonickelate-Catalyzed Hydrocyanation of Alkynes

Treatment of an alkyne with KCN, a reducing agent such as Zn or $NaBH_4$, and a catalytic amount of $Ni(CN)_4^{2-}$ leads to alkyne hydrocyanation and subsequent hydrogenation of the initially formed unsaturated nitrile (equation 51).[126,127] Attractive features of this system include the use of an air- and moisture-stable catalyst precursor, the use of the cyanide ion as both a reagent and a ligand for the catalyst, and the ease of separating an aqueous catalyst solution from the product and substrate. One major drawback is the low catalyst turnover (<8 mol RCN mol^{-1} Ni).



(51)

5.36.8 Scope, Limitations, and Future Prospects

Apart from additions to carbonyl compounds (including 1,4-additions to α,β-unsaturated carbonyl derivatives), imines, and aziridines, synthetically useful hydrocyanation reactions are limited to vinylarenes, certain types of 1,3-dienes, and alkynes. Isomerization of double bonds under hydrocyanation conditions limits the utility of internal and unconjugated dienes. Unactivated alkenes are less reactive and need Lewis acids to promote the reaction. Although the $Co_2(CO)_8$-mediated reactions give selective Markovnikov products from terminal alkenes, high temperatures, prolonged reaction times, and low turnovers in the catalyst are major drawbacks of this otherwise worthwhile hydrofunctionalization reaction.[128] A systematic investigation of the co-mediated reaction might be a highly profitable area for future research. The regioselectivity in the hydrocyanation of internal alkynes is poor, even though terminal silyl substitution and judicious use of alkynes carrying heteroatom-substituted side-chains do provide a synthetically viable route to complex vinyl nitriles. Reactions of allenes have not been explored to a great extent. Asymmetric hydrocyanation is another potentially important area that has been poorly developed. Enantioselectivities above 90% *ee* have been achieved only for vinylnaphthalene derivatives. Substituted dienes, which undergo hydrocyanation reactions even in the absence of Lewis acids, could serve as highly valuable precursors if the problems of regio- and stereoselectivities can be solved. Alkenes carrying electron-withdrawing substituents do not participate in metal-catalyzed hydrocyanation reactions. These substrates are ideally suited for the base or Lewis acid-catalyzed reactions and remarkable progress has been achieved in this area. Finally, the toxicity of HCN is an important consideration, even though with proper precautions it can be readily handled safely. Use of acetone cyanohydrin and TMSCN as surrogates for the toxic HCN should alleviate some of the safety concerns.

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