Metal-Mediated Synthesis of Medium-Sized Rings

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1. Introduction

The importance of medium- and large-sized rings in organic chemistry is exemplified by their being the structural core of a large number of biologically important natural products[1] and their serving as target molecules for numerous synthetic studies.[2] Several excellent reviews have been written on medium ring syntheses.[3−7] One notable area is the vast amount of research over the past decade devoted to taxol[8] and polycyclic ether antibiotics.[9,10] Although synthetic approaches to five- and six-membered ring systems are common via cyclization and cycloaddition reactions, seven- and eight-membered ring formations are not as abundant. Cyclization strategies to medium-sized rings are often inhibited due to entropic factors and transannular interactions.[11] In general, the number of methods for preparing medium-sized carbocycles by cyclization or cycloaddition reactions from acyclic substrates is relatively small. The past decade has witnessed a tremendous growth in the area of metal-mediated synthetic methodology, and this review will discuss recent applications of the use of metals to the syntheses of medium-sized (from seven- to nine-membered) rings that have occurred from 1990 to mid-1999. Any omissions on this wide topic are unintentional and should be brought to the attention of the author.

2. Ring-Closing Metathesis

The ring-closing metathesis (RCM) reaction was used for synthetic purposes by Tsuji[12] and Villemin[13] in 1980, but it was not an established method at that time. In recent years, significant activity has been

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Larry Yet was born in Vancouver, British Columbia, Canada. After graduating with his B.Sc. degree in Chemistry from the University of British Columbia working with Professor James P. Kutney on his senior thesis, he continued his graduate studies with Professor Harold Schechter at the Ohio State University, receiving his M.S. degree in 1990 and his Ph.D. degree in 1995. He then carried out postdoctoral research with Professor Douglass F. Taber at the University of Delaware. Since 1996 he has worked at Albany Molecular Research, Inc. as a Senior Research Chemist.

observed in this area and several excellent reviews have been written on this topic.[14] The versatility of Schrock's[15] molybdenum catalyst **1** and Grubbs'[16] ruthenium complexes **2** and **3** (see Figure 1) in carbo-

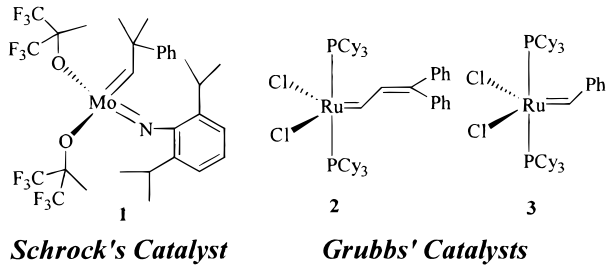
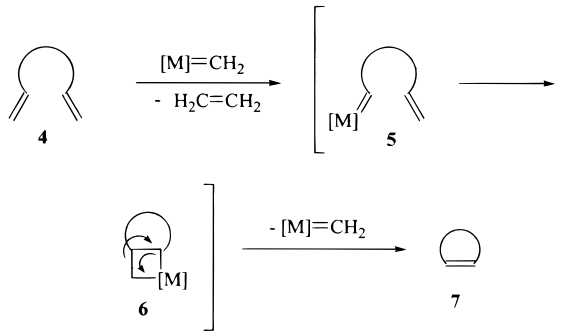


Figure 1.

and heterocyclizations of very different ring sizes was demonstrated for many examples. These catalysts have proved to be compatible in the presence of many sensitive functional groups including esters, amides, ammonium salts, silyl ethers, and acetals. Mechanistically, diene **4** reacts with the active species [M]=CH_2 to generate alkylidene carbene **5,** which cyclizes to cyclobutametallacycle **6** (Scheme 1). Regeneration

Scheme 1

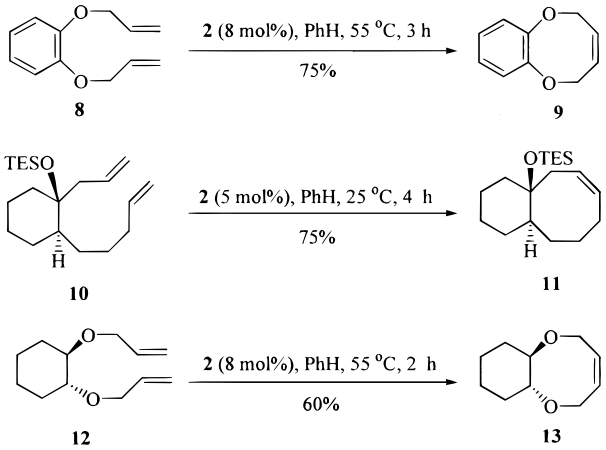


of the catalyst and expulsion of volatile ethylene is the driving force in a retro [2+2] cyclization furnished olefin **7**. Ring-closing metathesis has proven to be a key step in various total syntheses of natural products. This section outlines recent useful applications of RCM to several classes of structural subunits and possible applications to natural product synthesis.

2.1. Carbocyclic Synthesis

Grubbs performed the first studies on the catalytic ring-closing metathesis of dienes in the synthesis of eight-membered rings and has found that the introduction of a conformational constraint greatly enhances the ability to form these products in useful yields.[17] Catechol derivative **8** underwent rapid RCM to form the eight-membered ring **9** in good yield (Scheme 2). *trans*-Dienes **10** and **12**, both on applica-

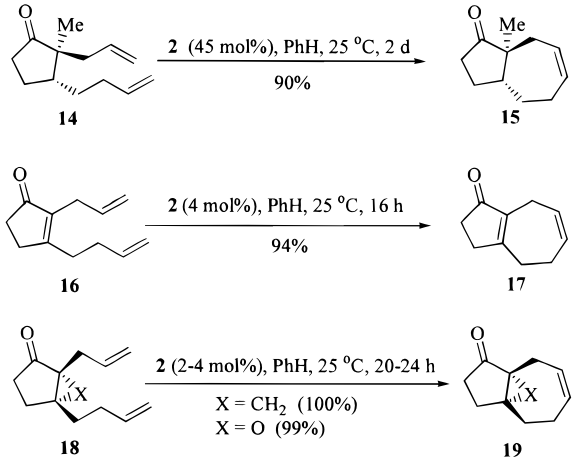
Scheme 2



tion of catalyst **2**, furnished bicyclooctenes **11** and **13**, respectively, in good yields. However, the analogous cis diene substrates were found to be poor substrates in these reactions, resulting in low yields of the respective products.

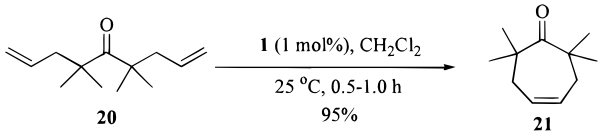
Blechert showed that ring-closing metathesis is very useful for the preparation of a wide range of substituted hydroazulenes.[18] Cyclopentanone precursors **14**, **16**, and **18** all participate in RCM with Grubbs' ruthenium catalyst **2** to afford hydroazulenes **15**, **17**, and **19**, respectively, in excellent yields (Scheme 3).

Scheme 3



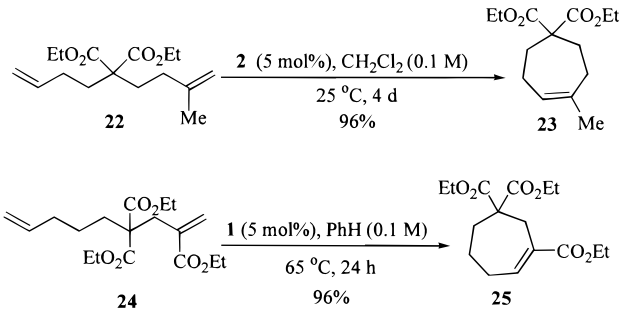
Diene **20** cyclized with Schrock's molybdenum catalyst **1** under solvent-free conditions to give cycloheptanone **21** in excellent yield (Scheme 4).[19]

Scheme 4



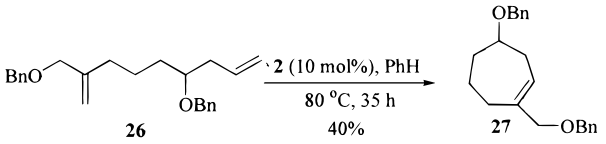
Ruthenium alkylidene **2** and molybdenum alkylidene **1** have been utilized in the ring-closing metathesis of *gem*-disubstituted olefins **22** and **24** to afford trisubstituted cycloheptenes **23** and **25**, respectively, in near quantitative yields (Scheme 5).[20]

Scheme 5



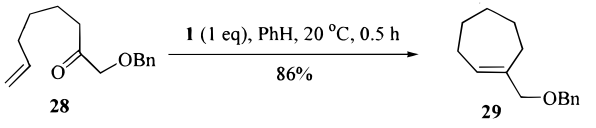
Dibenzyl diene **26** underwent ring-closing metathesis to give 1,4-difunctionalized cycloheptene **27** in its eventual use for an enediyne system synthesis (Scheme 6).[21]

Scheme 6



Ring-closing metathesis of enones (olefin metathesis−carbonyl olefination) has been performed on enone **28** with a stoichiometric amount of molybdenum catalyst **1** to give cycloheptene **29** (Scheme 7).[22]

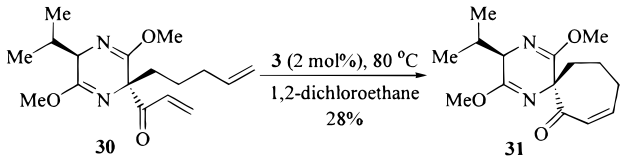
Scheme 7



In this example, ring-closing metathesis occurred faster than olefination of the ketone.

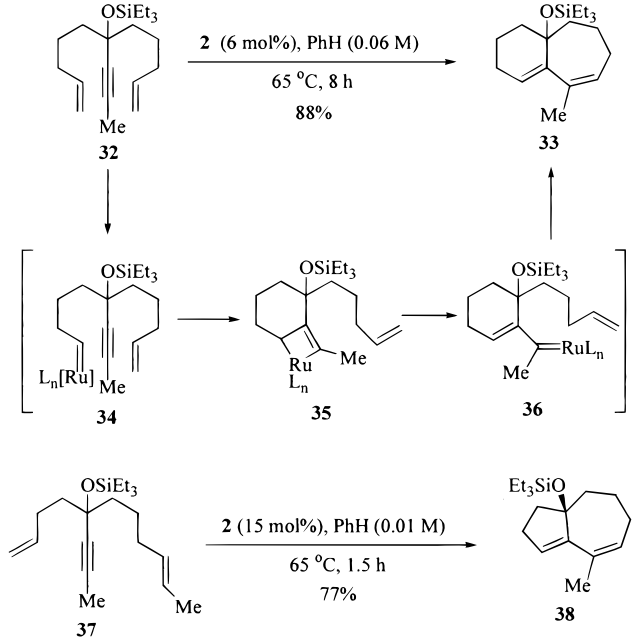
Undheim utilized Grubbs' catalyst **3** on electrophilic diene substrates such as **30** to give cycloheptenone spirane **31** as part of a program on constrained α-amino acids (Scheme 8).[23]

Scheme 8



Ruthenium carbene **2** efficiently mediated catalytic ring-closing metathesis of acyclic dienynes **32** and **37** to fused bicyclic 6,7-ring **33** and 5,7-ring **38**, respectively, which are important structural frameworks in a variety of natural products (Scheme 9).[24] The key

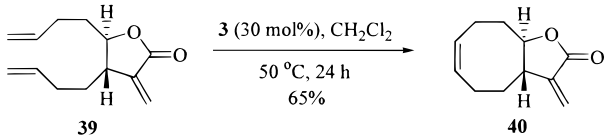
Scheme 9



step in the strategy involves the metal alkylidene-catalyzed ene−yne−ene metathesis in which two rings are formed in a single operation and the acetylene plays a crucial strategic role by relaying one RCM to another via intermediates **34** to **36**.

Paquette recently described a ring-closing metathesis of *trans*-lactone **39** with Grubbs' catalyst **3** to give fused α-methylene-γ-lactone **40,** common structural subunits in biologically significant natural products (Scheme 10). The *cis*-lactone gave the analogous

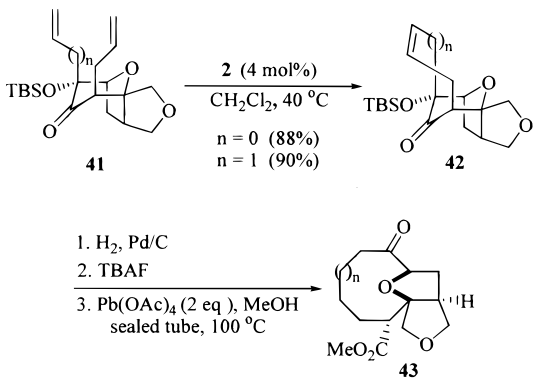
Scheme 10



cyclized product in a very low yield, due to ring strain and a more elevated barrier to ring closure.

Dienes **41** were subjected to ring-closing metathesis with Grubbs' catalyst **2** to give tetracycles **42** (Scheme 11).[26] Subsequent reduction, silyl deprotection, and

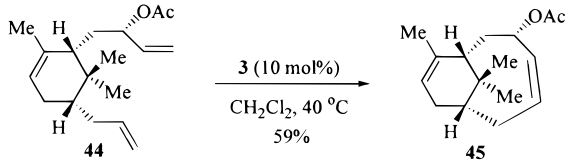
Scheme 11



oxidative ring expansions provided stereochemically rich *cis*-2,5-disubstituted tetrahydrofurans **43**, leading to 9- ($n = 0$) and 10-membered ($n = 1$) carbocycles whose ring types are present in a large number of naturally occurring terpenoids.

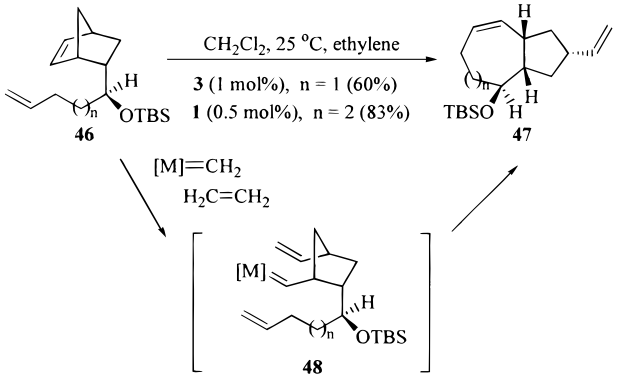
Blechert exploited the first known ring-closing metathesis approach to enantiomerically pure taxol A/B ring fragments.[27] Application of Grubbs' catalyst **3** to triene **44** provided bicyclic acetate **45** (Scheme 12). He also has recently described a novel domino

Scheme 12



metathesis reaction combining ring-opening, ring-closing, and cross-metathesis reaction in one step.[28] Norbornenyls **46** on application of Schrock's molybdenum catalyst **1** or Grubbs' ruthenium catalyst **3** gave bicyclic dienes **47** (Scheme 13). Ring opening

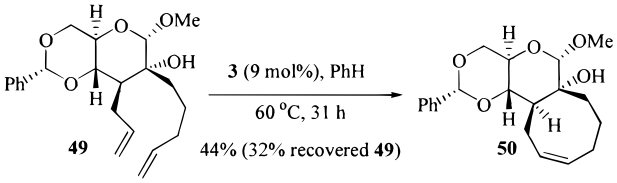
Scheme 13



and cross metathesis of **46** would furnish alkylidene intermediate **48**, which ring-closed to provide **47**.

Jenkins explored the use of ring-closing metathesis in carbohydrate annulation reactions.[29] *cis*-Diene **49** on exposure to Grubbs' catalyst **3** gave cyclooctene derivative **50** with recovered **49** (Scheme 14). Analo-

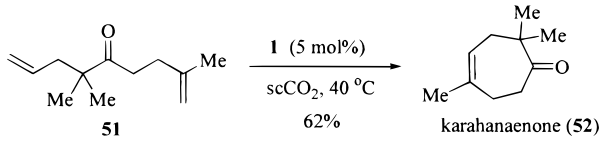
Scheme 14



gously, the *trans*-diene of **49** gave the trans tricyclic ether of **50** in 26% yield with recovered *trans*-diene of **49** in 48% yield.

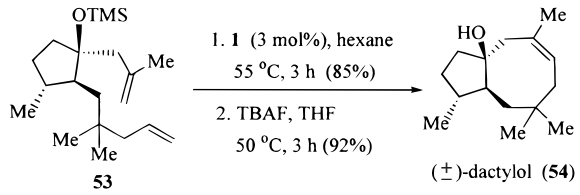
Fürstner and Hermann investigated successful applications of RCM in supercritical carbon dioxide ($scCO_2$) as a feasible reaction medium.[30] Reaction of dienone **51** with molybdenum catalyst **1** provided karahanaenone (**52**), an olfactory substance contained in hops and cypress oil (Scheme 15). He also developed the shortest total synthesis of the cy-

Scheme 15



clooctenoid sesquiterpene, (±)-dactylol (**54**), in six synthetic steps.[31] Ring-closing metathesis of *O*-silylated diene **53** with Schrock's molybdenum carbene **1** followed by silyl deprotection provided dactylol (**54**), as shown in Scheme 16.

Scheme 16



Fürstner also recently developed robust ruthenium carbene complexes **55** and **56** (see Figure 2) bearing

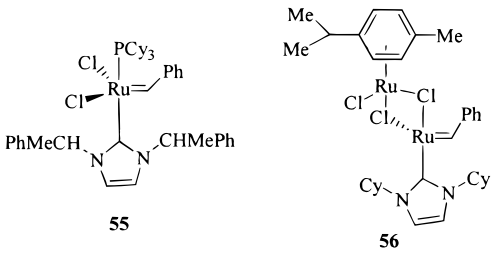
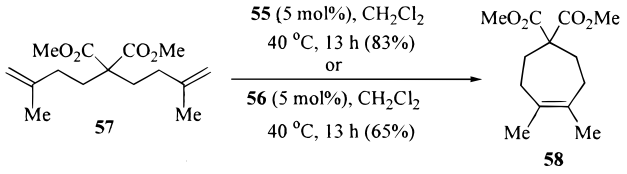


Figure 2.

imidazolin-2-ylidene ligands as highly efficient catalysts for all types of RCM reactions.[32] These catalysts have proven to be more air- and water-tolerant than the earlier ruthenium-based catalysts, and their ring-closing metathesis activity greatly exceeded the previous ones. Diene diester **57** reacted with complexes **55** and **56** to give tetrasubstituted cycloheptene **58** in good yields (Scheme 17). These examples

Scheme 17

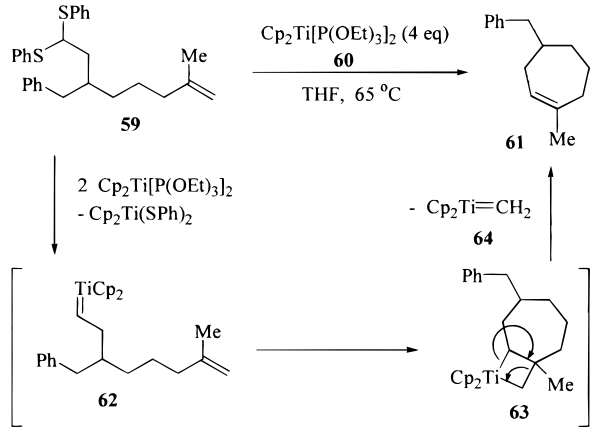


represented the first cases of ring-closing metathesis for tri- and tetrasubstituted alkene formations from dienes; previous ruthenium complexes **2** and **3** failed to provide these kinds of products.

Ring-closing metathesis has also occurred without the use of Schrock's molydenum catalyst **1** or Grubbs' alkylidene catalysts **2** and **3**. Takeda studied the low-valent titanium species-promoted transformation of unsaturated thioacetals to cyclic compounds.[33] Treatment of thioacetal **59** with titanocene species **60** gave cycloheptene **61** via titanium carbene complex **62**, through the intermediate titanacyclobutane **63**, with

subsequent elimination of alkylidenetitanocene **64** (Scheme 18).

Scheme 18

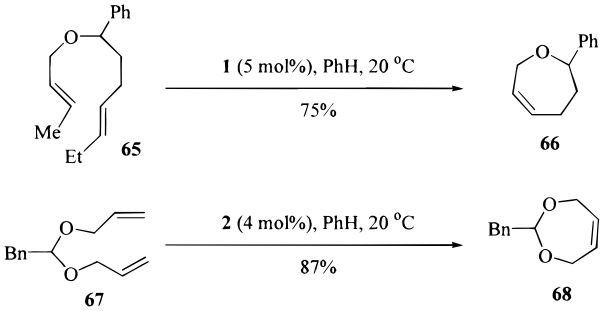


2.2. Cyclic Ether Synthesis

Polycyclic ether antibiotics have been the subject of intense study due to their interesting architectural complex structures, their potent biological profiles, and the synthetic challenges in forming these rings.[10] In recent years, much activity has been geared toward forming these rings via ring-closing metathesis of dienes to form oxacycles that were difficult to synthesize from other methods.

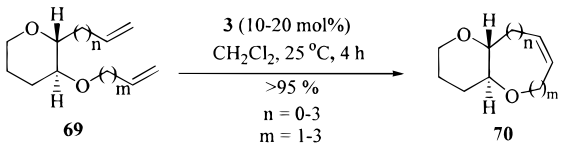
Grubbs showed the first examples of the application of RCM to cyclic ether synthesis. Diene **65** cyclized smoothly with Schrock's molybdenum catalyst **1** to give seven-membered cyclic ether **66** in good yield (Scheme 19).[34] Diallyl diether **67** gave cyclic ketal **68** with ruthenium catalyst **2** in excellent yield.

Scheme 19



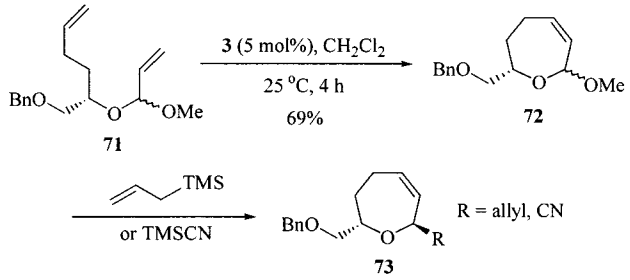
Development of routes to *trans*-fused polycyclic ethers has attracted considerable attention from the synthetic community due to the interesting biological activity of these compounds and to the immanent challenges of forming oxacycles with defined relative stereochemistry. *trans*-Cyclic ethers **69** quantitatively delivered *trans*-fused bicyclic ethers **70** with Grubbs' ruthenium alkylidene catalyst **3** (Scheme 20).[35]

Scheme 20



A novel ring-closing metathesis route to dihydropyran **72** from acetal **71** using Grubbs' alkylidene catalyst **3** was recently reported (Scheme 21).[36]

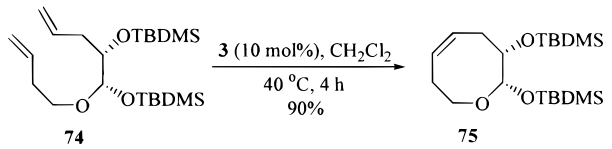
Scheme 21



Oxycarbenium ion-mediated coupling reactions with allyltrimethylsilane or trimethylsilyl cyanide of **72** led to dihydropyrans **73**.

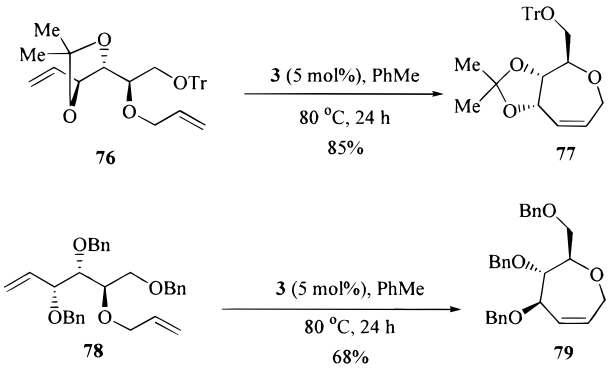
Application of Grubbs' catalyst **3** to diene **74** provided oxocene **75** as part of a program directed toward the synthesis of the Laureatin natural products (Scheme 22).[37]

Scheme 22



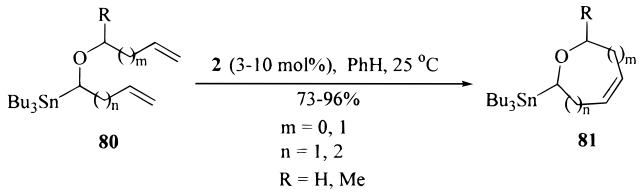
Boom developed an expeditious route to highly functionalized chiral oxepines.[38] Thus, ring-closing metathesis of linear chiral dienes **76** and **78** with Grubbs' ruthenium catalyst **3** afforded oxepines **77** and **79**, respectively (Scheme 23).

Scheme 23



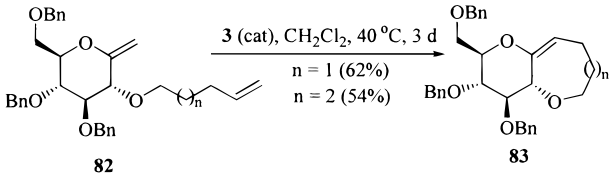
A recent communication reported the use of the tributylstannyl group as a large yet "removable" group to effect a conformational bias which would allow the synthesis of an eight-membered oxacyclic ring via metathesis from an acyclic diene.[39] Ring-closing metathesis of α-(alkoxyalkyl)stannyl-substituted dienes **80** with ruthenium carbene **2** led to eight-membered α-(trialkyl)stannyl-substituted cyclic ethers **81** in excellent yields (Scheme 24). The α-(alkoxylalkyl)stannane moiety can further undergo trans-metalation followed by electrophilic cleavage reactions.

Scheme 24



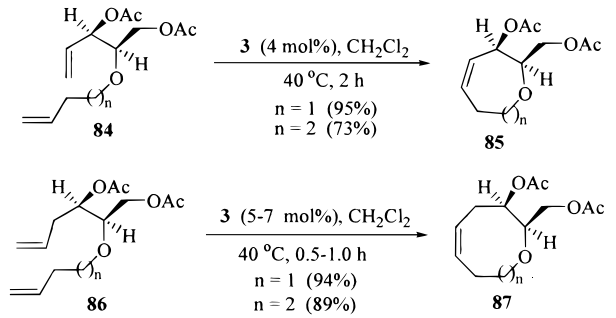
Methylene glucose derivatives **82** on ring-closing metathesis with Grubbs' catalyst **3** afforded *C*-glycosylidene compounds **83** (Scheme 25).[40]

Scheme 25



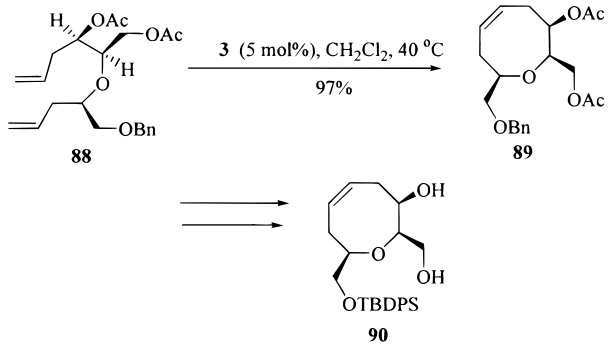
Crimmins published a general enantioselective synthesis of seven-, eight-, and nine-membered ring cyclic ethers by ring-closing metathesis.[41] Exposure of dienes **84** and **86** to Grubbs' ruthenium benzylidene carbene **3** readily afforded oxacycles **85** and **87**, respectively (Scheme 26). Recently, he also ap-

Scheme 26



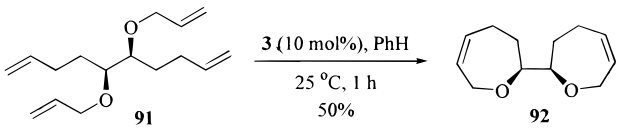
plied this methodology to the RCM of diacetate **88** to give oxacycle **89**, which after three steps gave oxacyclic diol **90**, constituting a formal total synthesis of (+)-laurencin (Scheme 27).[42]

Scheme 27



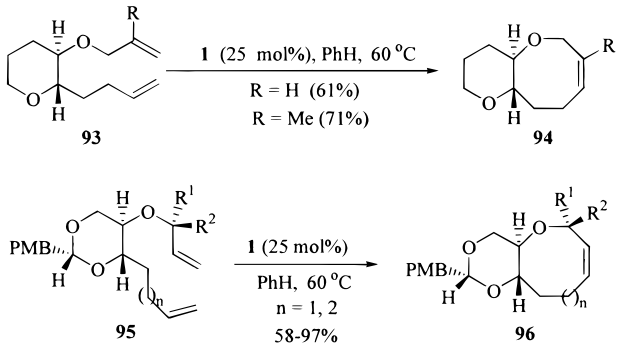
A recent report described the first examples of bis ring-closing olefin metathesis for synthesis of unsaturated polycyclic ethers.[43] Bis(*O*-allyl)ether **91** reacted with catalytic Grubbs' ruthenium alkylidene **3** to afford bis(cyclic)ether **92** in moderate yield at ambient temperature (Scheme 28).

Scheme 28



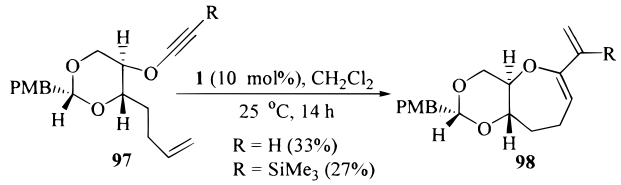
In synthetic studies toward brevetoxin A, the possibility of ring-closing metathesis of allyl ethers **93** with molybdenum alkylidene **1** were used as model studies to yield cyclic allyl ethers **94** in good yields (Scheme 29).[44] Thus, Clark developed a general

Scheme 29



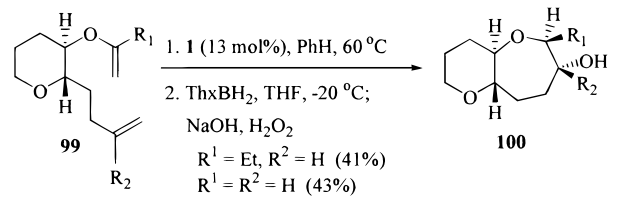
enantioselective synthesis of eight- and nine-membered bicyclic allyl ethers **96** from allyl ethers **95**. Clark further exploited the synthesis of alkenyl-substituted seven-membered cyclic enol ethers **98** from enyne **97** in a ring-closing enyne metathesis reaction (Scheme 30).[45]

Scheme 30



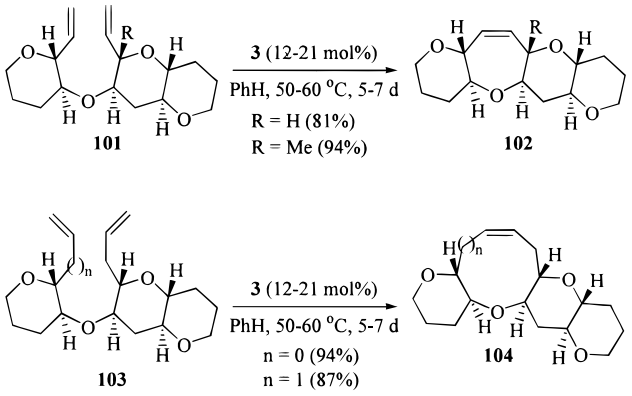
A new strategy for the construction of *trans*-fused bicyclic ethers **100** corresponding to subunits of brevetoxin B has also been reported.[46] Treatment of enol ethers **99** with Schrock's molybdenum carbene complex **1** followed by sequential stereoselective hydroboration with thexylborane furnished 6,7-bicyclic ethers **100** (Scheme 31).

Scheme 31



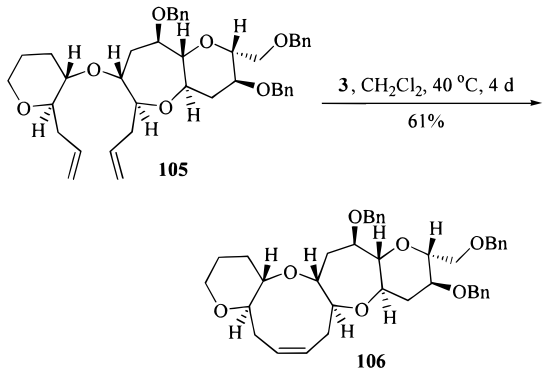
Ring-closing metathesis has proven to be a key step in the synthesis of fragments of the marine toxin ciguatoxin. Hirama applied the ring-closing metathesis reaction to the tetracyclic ether system of ciguatoxin.[47] Diene **101** on application of Grubbs' catalyst **3** gave tetracyclic ether **102** in excellent yield (Scheme

Scheme 32



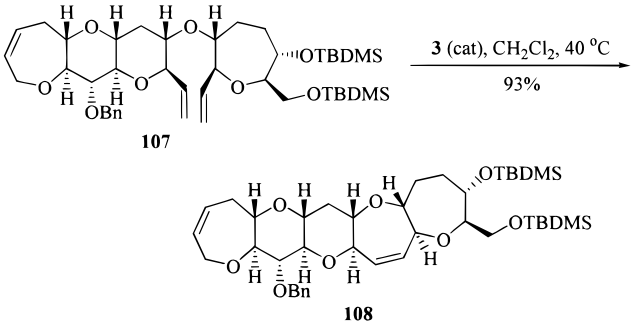
32). Similarly, dienes **103** on exposure to catalyst **3** gave eight- (n=0) or nine- (n=1) membered tetracyclic ethers **104**. Sasaki employed the ring-closing metathesis of tricyclic diene **105** to give tetracyclic ether **106**, which constituted the FGH ring fragment of ciguatoxin (Scheme 33).[48] Ring-closing metathesis

Scheme 33



of tetracyclic ether **107** furnished the fully functionalized pentacyclic ABCDE ring framework **108** of ciguatoxin (Scheme 34).[49]

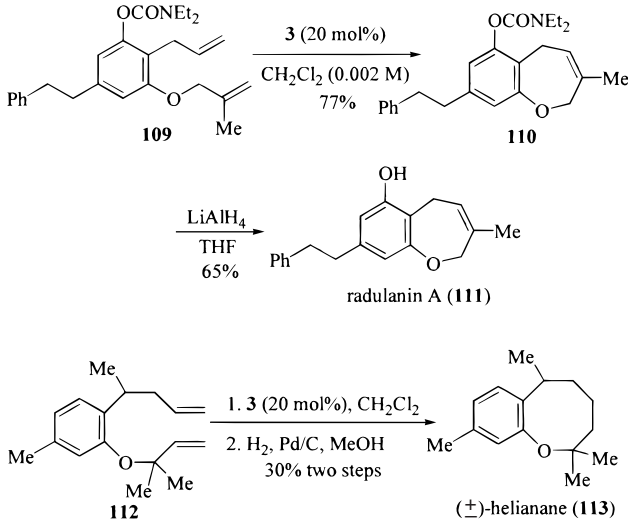
Scheme 34



Snieckus utilized this methodology in the RCM process for the construction of benzannulated oxygen heterocycles.[50] Exposure of diallylated benzene **109** to Grubbs' catalyst **3** gave benzoxepine **110** (Scheme 35). Lithium aluminum hydride reduction of **110** produced radulanin A (**111**). Similarly, diallylated benzene **112** with catalyst **3** with sequential reduction provided (±)-helianane (**113**).

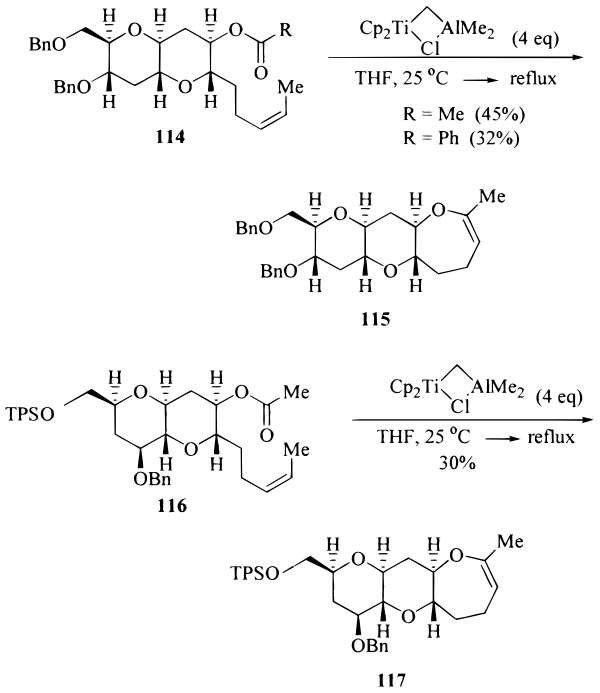
Nicolaou reported a powerful methodology for the construction of cyclic enol ethers directly from olefinic

Scheme 35

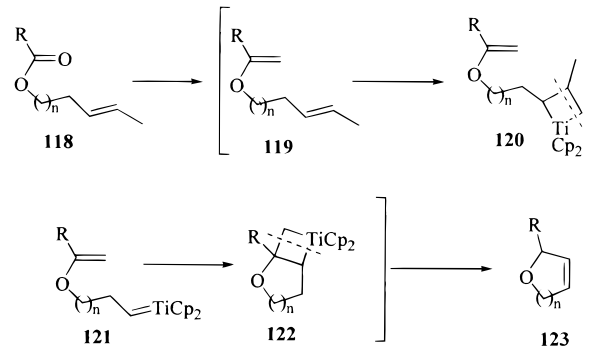


esters using olefin metathesis.[51] Bicyclic ethers **114** and **116** delivered functionalized tricyclic ethers **115** and **117**, respectively, with excess Tebbe reagent (4 equiv), as shown in Scheme 36. Scheme 37 shows the

Scheme 36



Scheme 37



general concept for the Tebbe-reagent-mediated transformation of olefinic esters **118** to cyclic enol ethers **123**. Addition of Tebbe reagent to **118** forms the initial enol ether **119**, which reacts with the second equivalent of Tebbe reagent to give titanacyclobutane **120**. Fragmentation of **120** leads to titanium alkylidene **121**. Cyclization of **121** gives titanacyclobutane **122** to **123** with regioselective cleavage.

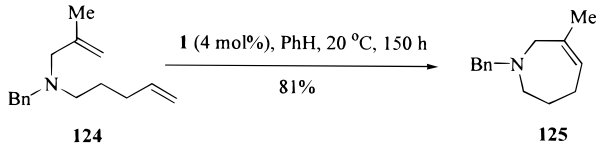
2.3. Heterocyclic Synthesis

Ring-closing metathesis has been applied over the past few years to the syntheses of various heterocycles. These include such heteroatoms as nitrogen, oxygen, phosphorus, and boron, which have valuable synthetic utility in methodology and in natural product synthesis.

2.3.1. Nitrogen Heterocycles

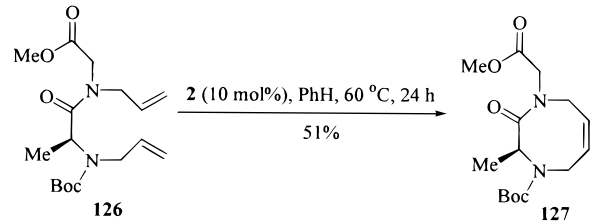
Grubbs showed that tertiary amine **124** converted smoothly to *N*-heterocycle **125** with Schrock's complex **1** (Scheme 38).[52] Grubbs also succeeded in the

Scheme 38



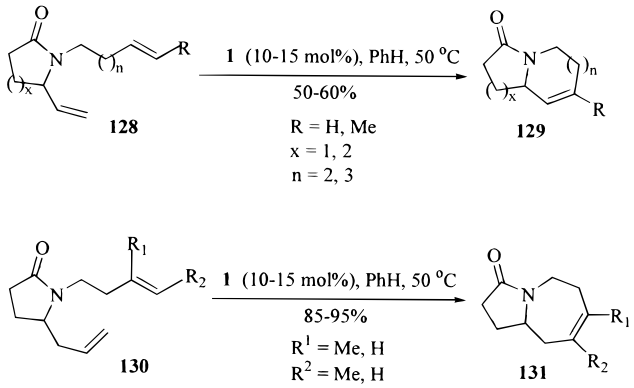
ring-closing metathesis reaction of bis(*N*-allyl) dipeptide **126** to give cyclic dipeptide **127** as studies toward conformationally constrained peptides (Scheme 39).[53]

Scheme 39



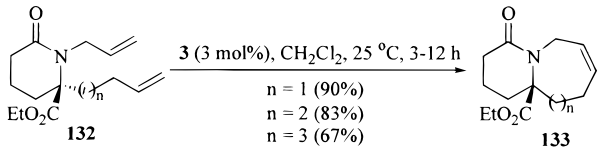
Bicyclic lactams have been prepared utilizing the ring-closing metathesis reaction. Martin prepared bicycles **129** and **131** from α,*ω*-dienes **128** and **130**, respectively, with molybdenum alkylidene catalyst **1** (Scheme 40).[54] Similarly, Westermann synthesized

Scheme 40



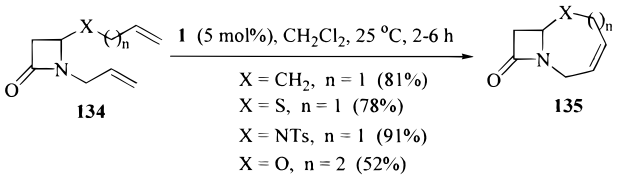
enantiomerically pure bicyclic lactams **133** from optically pure monocyclic lactams **132** with Grubbs' ruthenium catalyst **3** (Scheme 41).[55]

Scheme 41



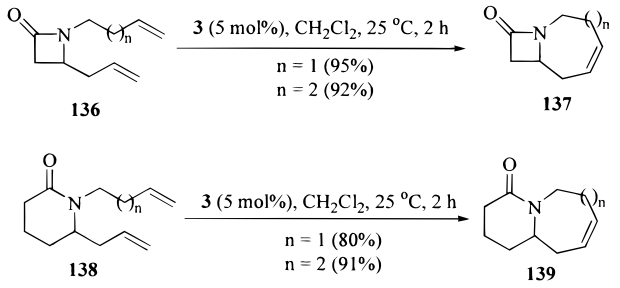
Barrett investigated ring-closing metathesis in the synthesis of novel *β*-lactams. Dienes **134** underwent facile cyclization using molybdenum alkylidene **1** to afford bicyclic lactams **135** in good to excellent yields (Scheme 42).[56] Holmes also exploited the use of RCM

Scheme 42



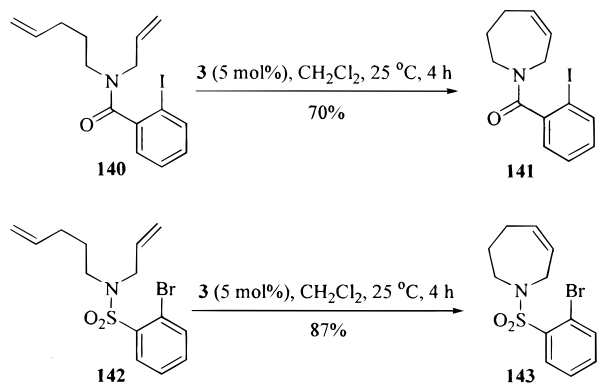
to the synthesis of *β*-lactams **137** from dienes **136** in excellent yields with Grubbs' catalyst **3** (Scheme 43).[57] Bicyclic lactams **139** were also obtained from dienes **138** in a similar manner.

Scheme 43



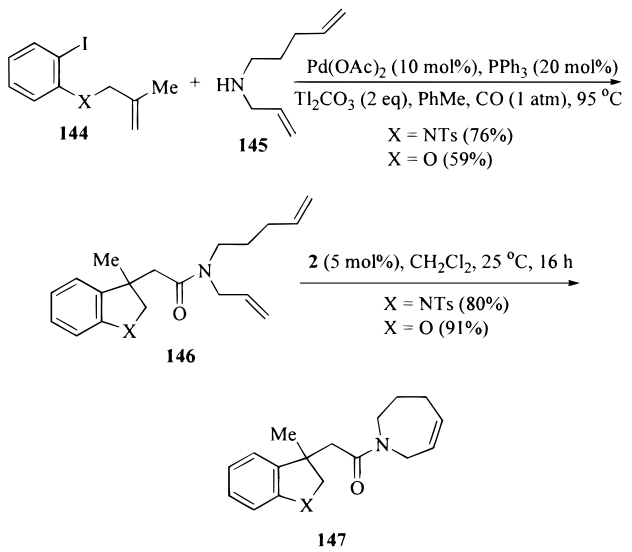
Grigg explored sequential and cascade reactions in which the olefin-metathesis step played a role. He utilized this methodology on iodo amide **140** and bromo sulfonamide **142** to prepare azocenes **141** and **143**, respectively, in ring-closing metathesis reactions with Grubbs' ruthenium complex **3** (Scheme 44).[58] Azocenes **141** and **143** underwent further intramolecular Heck reactions to give tricyclic products.

Scheme 44



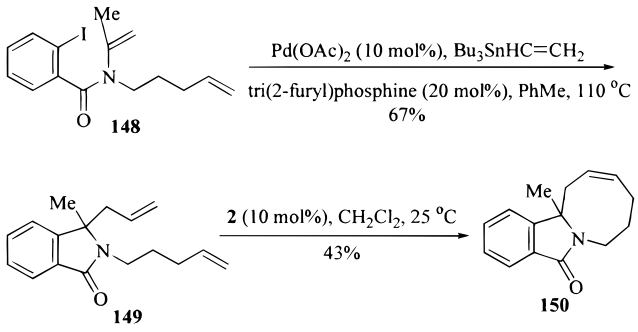
In an analogous fashion, iodo olefins **144** underwent a cascade palladium-catalyzed cyclization−carbonylation−anion capture sequence with dienylamine **145** to give bicyclic amides **146** (Scheme 45).[59] Ring-

Scheme 45



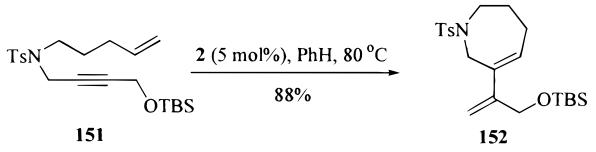
closing metathesis of **146** with Grubbs' catalyst **2** afforded seven-membered cyclic amides **147**. Tributylvinyltin was used as the anion capture from the palladium-catalyzed cyclization of iodo amide **148** to give dienyl amide **149**. Ring-closing metathesis of **149** with ruthenium catalyst **2** produced tricyclic amide **150** (Scheme 46).

Scheme 46



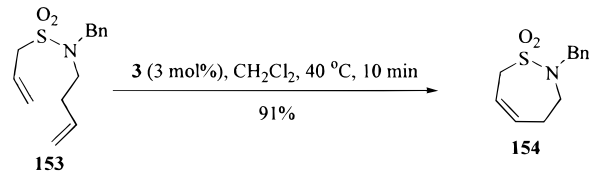
Application of Grubbs' ruthenium catalyst **2** to 1,8-enyne **151** gave 1-vinylcycloalkene **152** in excellent yield (Scheme 47).[60]

Scheme 47



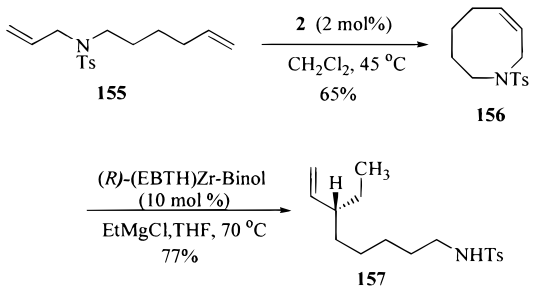
Sulfonamide compounds have enormous potential as pharmaceutical and agricultural agents due to their diverse biological profiles. Hanson described the first reports of ring-closing metathesis of allyl sulfonamides.[61] Allyl sulfonamide **153** efficiently cyclized to seven-membered ring sulfonamide **154** with Grubbs' catalyst **3** (Scheme 48).

Scheme 48



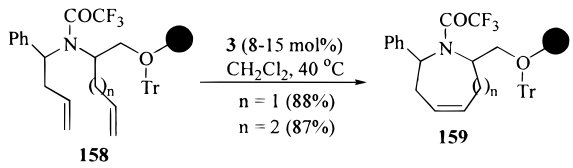
Hoveyda applied ruthenium catalyst **2** to tosylamide diene **155** to generate medium-ring heterocycle **156**, which participates in asymmetric ethylmagnesation to afford unsaturated amide **157** in >98% ee (Scheme 49).[62]

Scheme 49



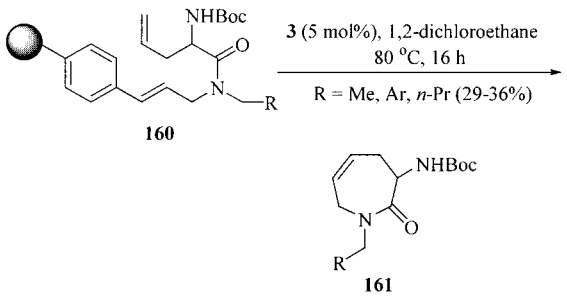
Blechert explored the ring-closing metathesis reaction of solid-phase supported dienes **158** with Grubbs' catalyst **3** to furnish azacycles **159** (Scheme 50).[63]

Scheme 50



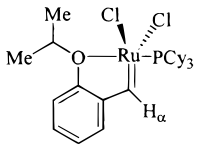
A high-speed, solid-phase method for the preparation of β-turn mimetics using ring-closing metathesis was recently reported. Solid-supported dienes **160** were exposed to Grubbs' ruthenium complex **3** to give Friedinger lactams **161** (Scheme 51).[64] The relevant

Scheme 51



RCM reaction also served as a cyclative cleavage of the solid support.

Hoveyda discovered that ruthenium-based metathesis catalyst **162** (see Figure 3) can be used in the ring-closing metathesis with high turnovers. Complex **162** was found to be an extremely robust catalyst and a practical addition to the growing family of well-defined catalysts. The catalyst represents the first recyclable metal-based system that catalyzes an efficient homogeneous olefin metathesis reaction with

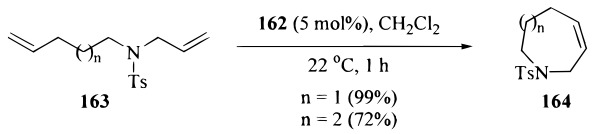


162

Figure 3.

no detectable loss of activity upon reuse. Application of **162** to dienyl tosylamides **163** afforded cyclic tosylamides **164** (Scheme 52).[65]

Scheme 52



Furstner also recently reported a cationic 18-electron allenylidene ruthenium complex **165** (see Figure 4), which was found to be an excellent catalyst

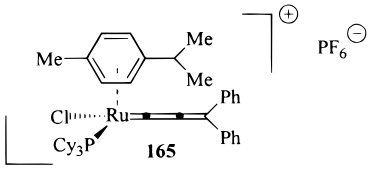
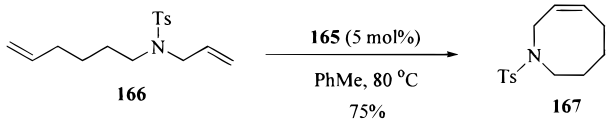


Figure 4.

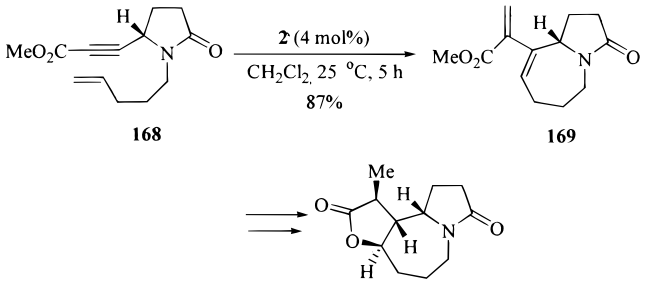
precursor for ring-closing metathesis.[66] Complex **165**, easily available in three steps from ruthenium(III) chloride, provided an unprecedented example of the involvement of metal allenylidene complexes in catalysis. This easily prepared catalyst has advantages over the preparation of ruthenium catalysts **2** and **3,** which require diphenylcyclopropene or phenyldiazomethane as reagents in their preparations. Dienyl tosylamide **166** reacted with **165** to give eight-membered amide **167** (Scheme 53).

Scheme 53



Enyne metathesis of acetylenic ester **168** with Grubbs' ruthenium catalyst **2** proceeded smoothly at ambient temperature to give 5,7-fused bicyclic lactam **169** (Scheme 56).[67] The ester group of **169** was used

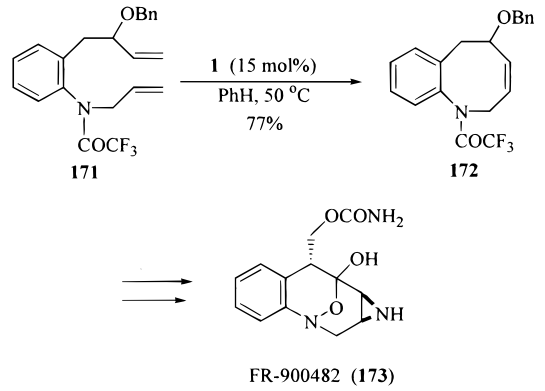
Scheme 54



in lactonization in the total synthesis of (−)-stemoamide (**170**), an insecticidal tricyclic alkaloid (Scheme 54).

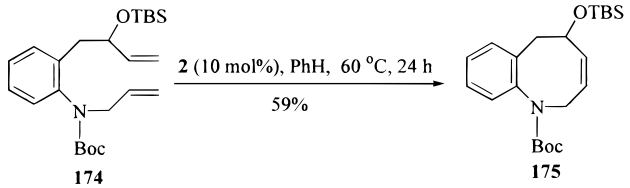
A model study, directed toward the total synthesis of the unusual antitumor antibiotic FR-900482 (**173**), utilized α,ω-diene **171** with molybdenum carbene complex **1** in degassed benzene to afford benzoazocine **172** (Scheme 55).[68] Grubbs employed similar inter-

Scheme 55



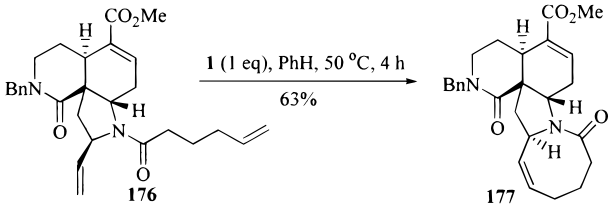
mediate **174** using catalyst **2** to give benzoazocine **175** (Scheme 56).[69]

Scheme 56



Martin employed molybdenum catalyst **1** in the ring-closing reaction of tricyclic amide **176** to give azocine **177**, an advanced precursor in the synthesis of manzamine A (Scheme 57).[70] Eventually, tetracy-

Scheme 57



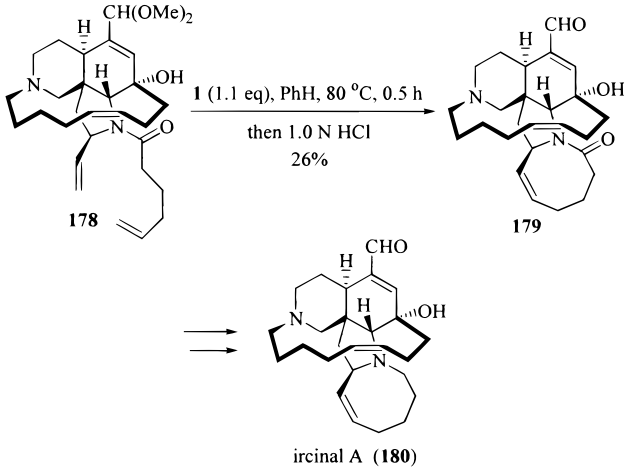
clic amide **178** reacted with catalyst **1** to give pentacyclic amide **179** which, after amide reduction, provided ircinal A (**180**, Scheme 58).[71]

White exploited the ring-closing metathesis of diene **181** with Grubbs' catalyst **3** to give azacyclooctene **182**, an intermediate in the eventual total synthesis of australine (**183**, Scheme 59).[72]

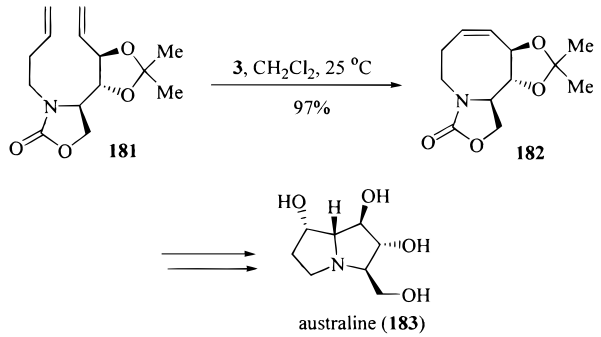
Trost applied the ring-closing metathesis synthesis of dienyl-protected amide **184** using Grubbs' catalyst **3** to afford cycloheptene **185** in the asymmetric total synthesis of (−)-anatoxin-a (**186**, Scheme 60).[73]

Rawal utilized Grubbs' ruthenium complex **3** in the ring-closing metathesis of diallyl **187** to afford tetracycle **188** (Scheme 61).[74] Intramolecular Heck pal-

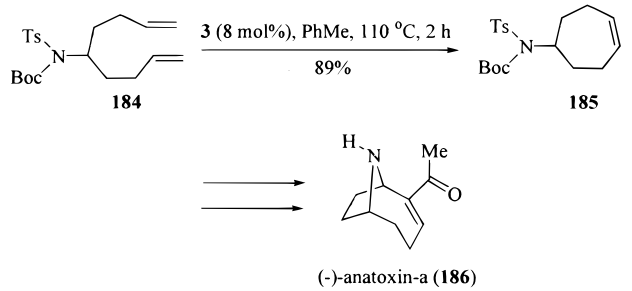
Scheme 58



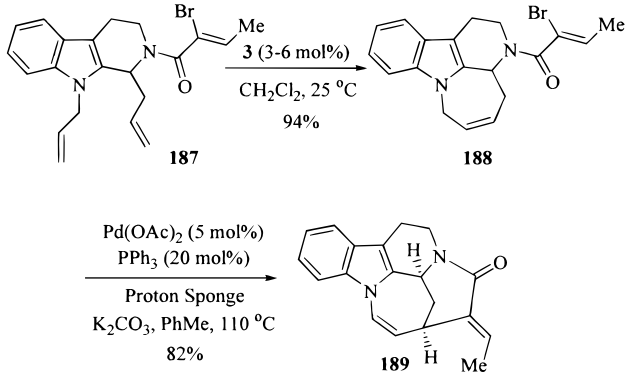
Scheme 59



Scheme 60



Scheme 61

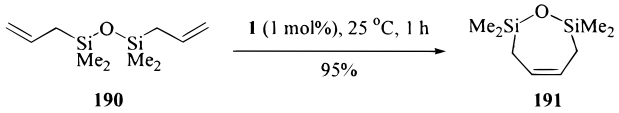


ladium-catalyzed cyclization of **188** produced pentacyclic amide **189** in a stereoselective manner. These steps represented a general, stereocontrolled route to the geissoschizine and akagerine alkaloid family of natural products.

2.3.2. Silicon Heterocycles

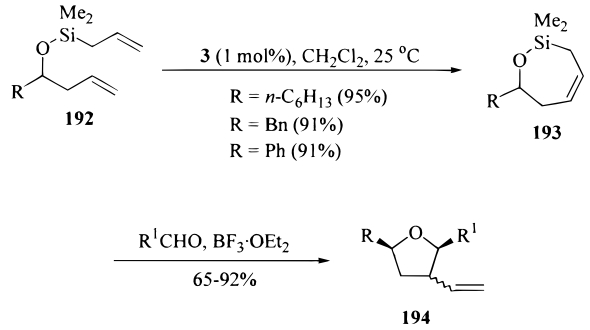
Forbes showed one of the first applications of ring-closing metathesis of silicon heteroatoms.[75] Bis-(allyldimethylsilyl)ether (**190**) reacted with Schrock's molybdenum catalyst **1** under solvent-free conditions to produce cyclic bis-silyl ether **191** in excellent yield (Scheme 62).

Scheme 62



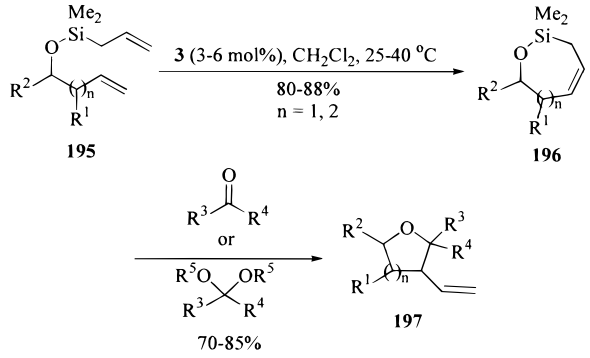
Marsden and Cossy simultaneously developed a novel method of preparing functionalized tetrahydrofurans and tetrahydropyrans via cyclic allylsiloxanes. Marsden utilized homoallylic silanes **192** with Grubbs' catalyst **3** to give cyclic allylsilanes **193** in excellent yields, which reacted with various aldehydes and boron trifluoride etherate to give 2,5-disubstituted tetrahydrofurans **194** (Scheme 63).[76]

Scheme 63



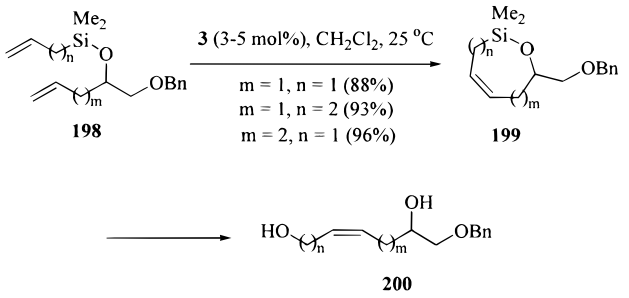
Cossy converted homoallylic silanes **195** with catalytst **3** to give cyclic allylsilanes **196**, which reacted with aldehydes, ketones, or ketals to give 2,3,4-trisubstituted tetrahydrofurans or tetrahydropyrans **197** (Scheme 64).[77]

Scheme 64



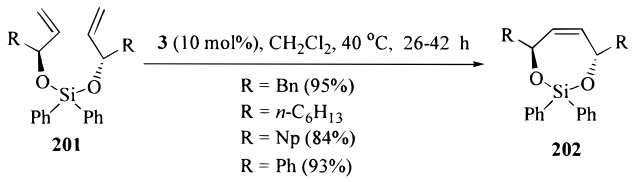
Recently, the use of silicon- tethered ring-closing metathesis has been reported by Grubbs, Evans, and Hoye. Grubbs utilized ruthenium alkylidene catalyst **3** in the ring-closing metathesis of silyl ether dienes **198** to afford cyclic silyloxy olefins **199** in excellent yields, which were then oxidatively cleaved to diols **200** (Scheme 65).[78] Evans applied ring-closing metathesis to bis-alkoxysilanes **201** to give diphenyl

Scheme 65



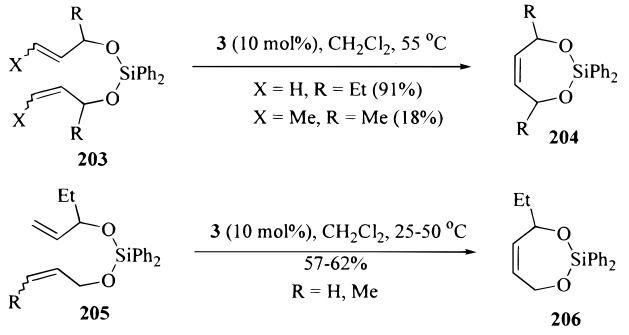
silaketals **202** as temporary silicon-tethered C_2-symmetrical 1,4-diols (Scheme 66).[79] Hoye utilized

Scheme 66



this methodology to also afford symmetrical silaketals **204** from dienes **203** (Scheme 67).[80] It was found that

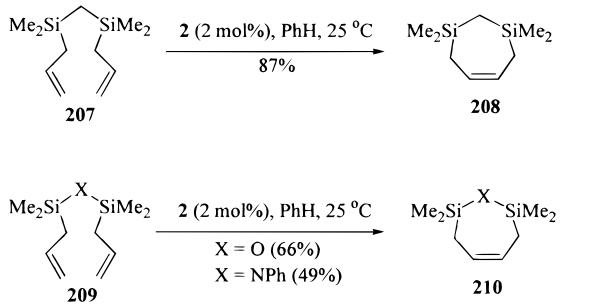
Scheme 67



substituents on the terminal olefins retard the process giving products in low yields. Unsymmetrical dienes **205** can be used to give unsymmetrical silaketal **206**.

Sakurai used the RCM reaction of various disilanes to produce cyclic compounds.[81] Disilane **207**, on application of Grubbs' ruthenium complex **2**, provided cyclic disilane **208** in good yield (Scheme 68). Simi-

Scheme 68

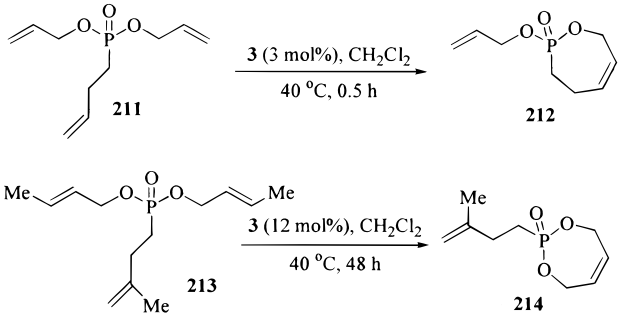


larly, heterodisilanes **209** gave heterocyclic disilanes **210**.

2.3.3. Phosphorus Heterocycles

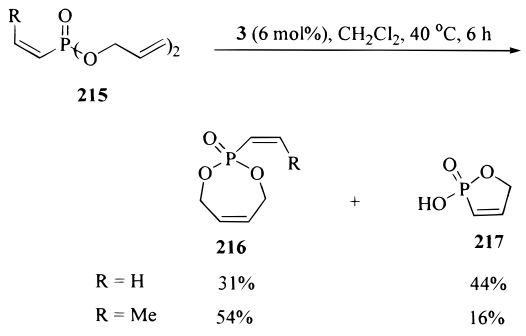
Recent reports have shown that alkylidene catalysts could be applied to RCM of phosphorus-containing substrates. Of particular importance is the functional group tolerance for the reaction conditions. Hanson successfully showed the ring-closing metathesis on phosphonate templates such as **211** and **213** to give cyclic allylic phosphonates **212** and **214**, respectively (Scheme 69).[82a] He found the olefin

Scheme 69



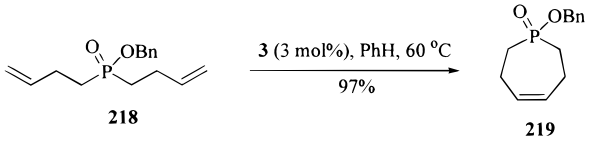
substitution was sensitive to the amount of catalyst and reaction time used. Hanson also reported that phosphonates **215** afforded **216** and **217**, respectively, in different yields from ring-closing reactions, depending on the substituents of the olefinic substrate **215** (Scheme 70).[82b] Mioskowski exploited the ring-

Scheme 70



closing metathesis reaction to the synthesis of cyclic phosphinates as substrates for transition state analogues for antibodies production or as potent enzyme inhibitors.[83] Exposure of dienyl phosphinates **218** to Grubbs' alkylidene catalyst **3** afforded cyclic phosphinate **219** in excellent yield (Scheme 71).

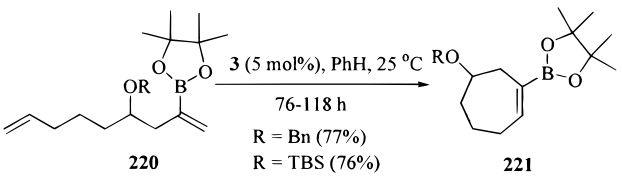
Scheme 71



2.3.4. Boron Heterocycle

Renaud applied the ring-closing metathesis to the synthesis of cyclic alkenylboronates.[84] Acyclic olefinic

Scheme 72



boronates **220** reacted with Grubbs' catalyst **3** to provide cyclic alkenylboronates **221**, potentially valuable intermediates in Suzuki palladium-catalyzed coupling reactions (Scheme 72).

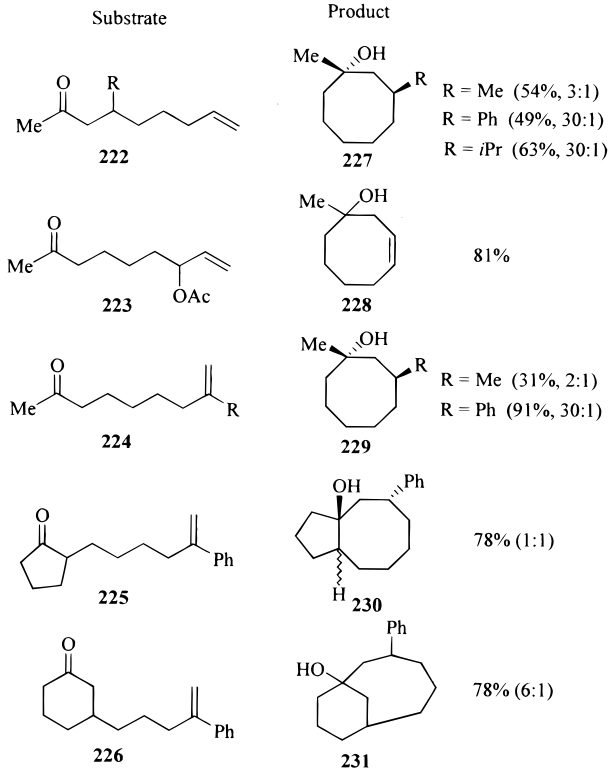
3. Metal-Promoted Free Radical Fragmentations and Ring Expansions

Free radical cyclization reactions are important tools for the construction of various types of cyclic compounds, including biologically active natural products and pharmaceuticals.[85] In general, the advantages these reactions offer to the synthetic organic chemist include mild reaction conditions with high levels of regio- and stereocontrol, along with significant functional group tolerance. Recent advances in radical chemistry have led to the development of some practical methods for the formation of seven-, eight-, and nine-membered rings via free radical fragmentations and ring expansions. In addition to formation of the usual five- and six-membered rings using carbon radicals, ring expansion via an oxy radical is increasingly becoming a useful tool in potential syntheses of medium- and large-sized rings.[86] Samarium, manganese, iron, as well as cobalt and copper have been the metals of choice in these reactions.

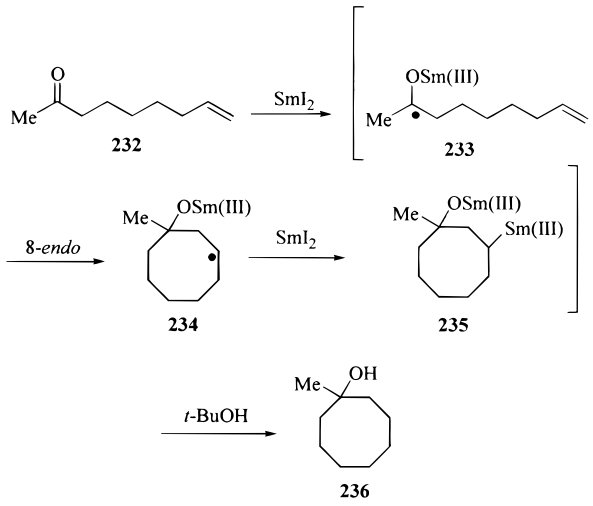
3.1. Samarium(II) Diiodide Systems

Samarium(II) diiodide in the presence of HMPA has been employed to promote an efficient 8-*endo* radical cyclization of a variety of substituted olefinic ketones **222**−**226** to give eight-membered carbocycles (Scheme 73).[87] Molander showed that various substituted monocyclic **227**−**229**, fused bicyclic **230**, and bridged bicyclic cyclooctanols **231** can be synthesized in fair to excellent yields. Samarium(II) diiodide adds to ketone **232** to form ketyl radical **233,** which undergoes 8-*endo* cyclization to unstabilized radical intermediate **234** (Scheme 74). Intermediate **234** is

Scheme 73



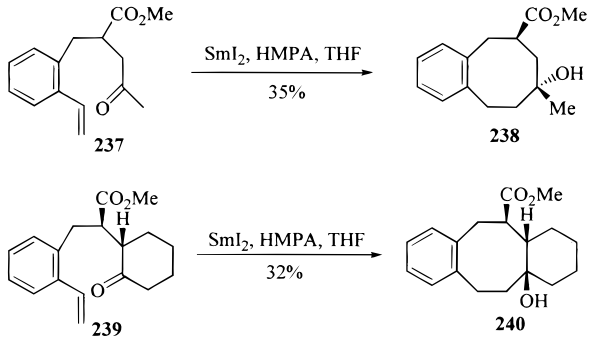
Scheme 74



trapped by another equivalent of samarium(II) diiodide to **235**, which is quenched to **236** by *tert*-butyl alcohol, an efficient hydrogen donor source in these types of cyclizations.

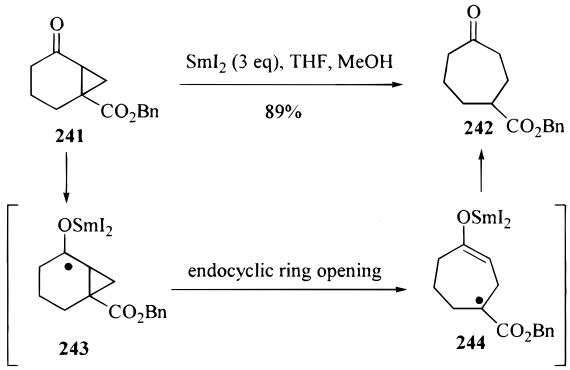
Reissig also used this strategy to prepare benzocyclooctanols **238** and **240** stereoselectively from olefinic ketones **237** and **239**, respectively (Scheme 75).[88]

Scheme 75

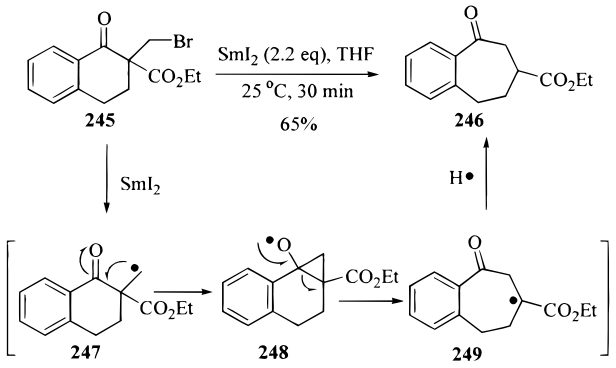


Lee reported samarium(II) diiodide-induced single electron-transfer cleavage of 5-oxabicyclo[4.1.0]hep-

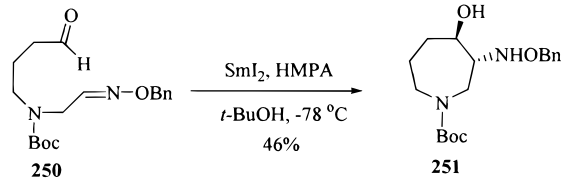
Scheme 76



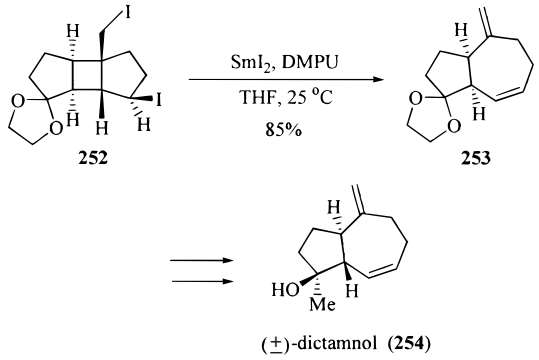
Scheme 77



Scheme 78



Scheme 79



tane-1-carboxylate **241** gave 4-oxocycloheptanecarboxylate **242** in excellent yield (Scheme 76).[89] Addition of samarium(II) diiodide to **241** gives ketyl **243** with endocyclic ring opening to **244**, followed by methanol quench to furnish **242**.

The first example of a samarium(II) diiodide-promoted sequential cyclization and ring expansion of α-bromomethyl cyclic β-keto ester **245** to homologated γ-keto ester **246** was reported by Hasegawa (Scheme 77).[90] Samarium(II) diiodide reacts with **245** to give methyl radical **247**, which undergoes cyclization to cyclopropyl radical **248**. Ring expansion of **248** affords stabilized radical **249**, which is quenched by a hydrogen donor to **246**.

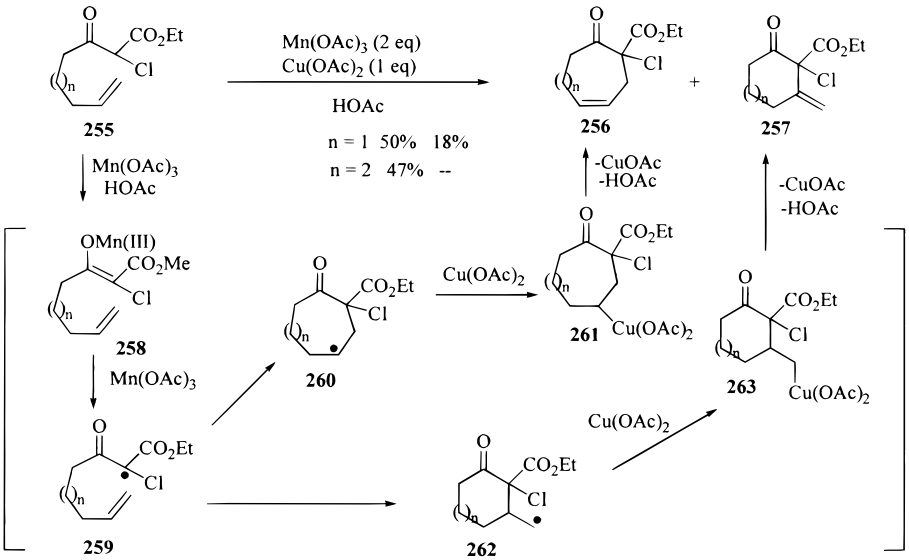
In general, radical cyclization reactions are not restricted to additions to carbon−carbon multiple bonds, but additions to carbon−nitrogen multiple bonds are possible.[91] These reactions are irreversible and occur in the *exo*-mode with attack at the carbon atom exclusively. A free radical cyclization of oxime ethers tethered to an aldehyde has been reported. Naito prepared the enantiomerically pure *trans*-amino alcohol hexahydroazepine fragment **251** of (−)-balanol from the samarium(II) diiodide-promoted radical cyclization of oxime ether **250** (Scheme 78).[92]

Radical-mediated fragmentations of strained cyclobutane systems derived from photoadducts have been exploited in the preparation of a variety of bicyclic ketones. For instance, diiodide **252** underwent a samarium(II) diiodide- mediated fragmentation/elimination sequence to yield *cis*-fused 5,7-bicyclic diene **253**, which was further elaborated to (±)-dictamnol (**254**, Scheme 79).[93]

3.2. Manganese-Based Systems[94]

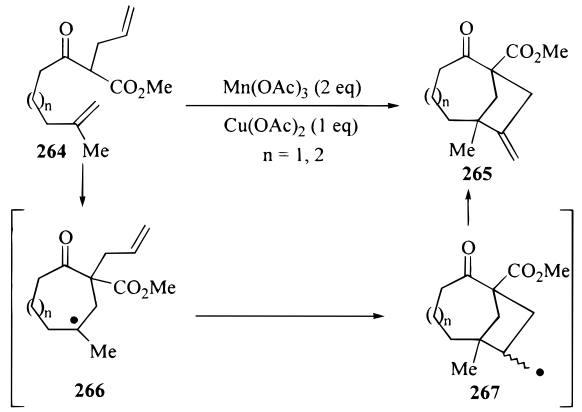
Radicals derived from β-keto esters by oxidative methods are especially useful for the formation of medium-sized rings due to increased rate of *endo* cyclization of α-carbonyl-substituted radicals. Snider demonstrated that manganese(III)-based oxidative free radical cyclizations can be used to prepare both cycloheptanes and cyclooctanes.[95] For example, acetoacetate **255** reacted with manganese(III) acetate and copper(II) acetate in acetic acid to give a mixture of β-cyclic ketoesters **256** and methylenecyclohexanones **257**, proceeding through intermediates **258** to **263** (Scheme 80). This method was also applied in a tandem cyclization of β-ketoester **264** to bicycloalkenones **265** in good yields via intermediates **266** and

Scheme 80



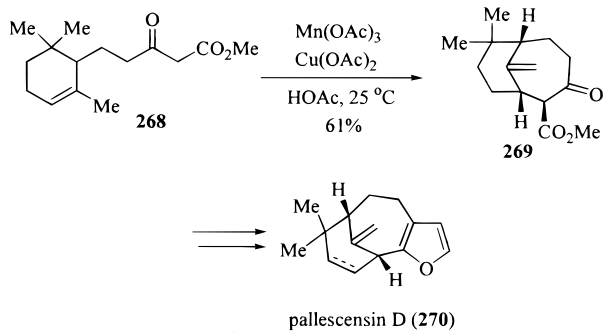
267 (Scheme 81). Other minor products were observed.

Scheme 81



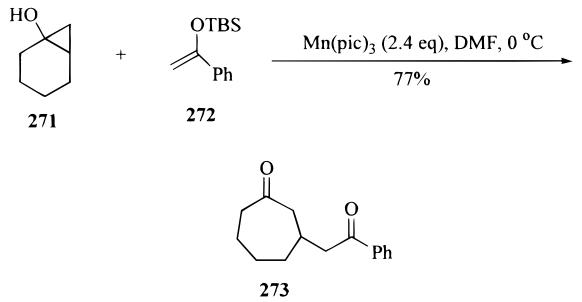
Utilizing the above methodology, White showed that exposure of β-keto ester **268** to manganese(III) acetate and copper(II) acetate (1:1 ratio) gave bicyclo-[4.3.1]decanone **269**, which was further elaborated to provide pallescensin D (**270**), a furanosesquiterpene (Scheme 82).[96]

Scheme 82



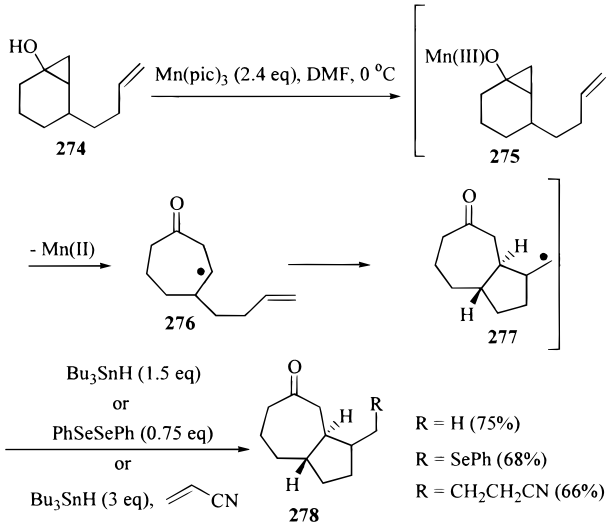
Iwasawa showed that treatment of cyclopropanol **271** with manganese(III) tris(2-pyridinecarboxylate) generates β-keto radicals, which added intermolecularly to enol silyl ether **272** to give ring-expanded cycloheptanone **273** in good yields (Scheme 83).[97] This

Scheme 83



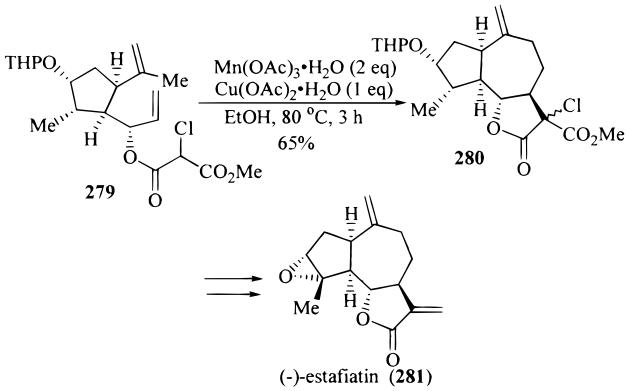
method was further exploited in the synthesis of a bicyclic framework skeleton. Intramolecular cyclization of cyclopropanol **274** to radical intermediates **275** to **277**, and trapping of **277** with various acceptors, gave bicyclic ketones **278** stereoselectively (Scheme 84).[98]

Scheme 84



A remarkable 5-*exo*,7-*endo* tandem radical cyclization approach was successfully employed for the formation of the *cis*-fused hydroazulenic ring system present in many guaianolides.[99] Chloromalonate **279**, under oxidative radical conditions employing manganese(III) acetate and copper(II) acetate, furnished lactone **280**, a precursor to (−)-estafiatin (**281**, Scheme 85).

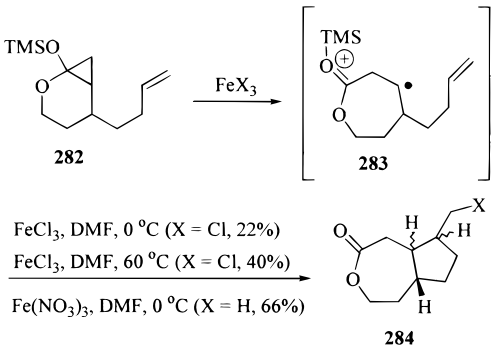
Scheme 85



3.3. Iron-Based Systems

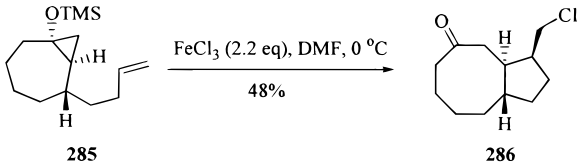
Booker-Milburn studied the Fe(III)-mediated oxidative radical cyclization of cyclopropanone acetal **282** via ring-expanded intermediate **283** with subsequent atom transfer cyclization to give cycloheptyl lactone **284** (Scheme 86).[100] Booker-Milburn also

Scheme 86



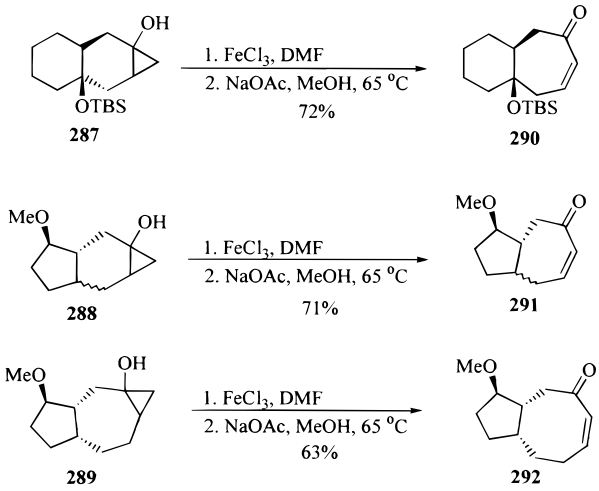
showed that ring expansion cyclization of cyclopropyl ether **285** proceeded uneventfully to give 5,8-bicyclic chloroketone **286** as a single diastereomer (Scheme 87).[101]

Scheme 87



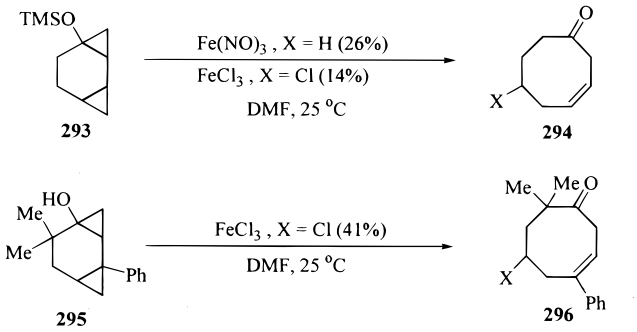
Cha reported a facile method for the construction of bicyclo[5.3.0]decane or bicyclo[6.3.0]undecane skeletons.[102] Oxidative cleavage of **287**−**289** produced 2-cycloalkenones **290**−**292**, respectively, after base-induced elimination of the intermediate chlorides (Scheme 88).

Scheme 88



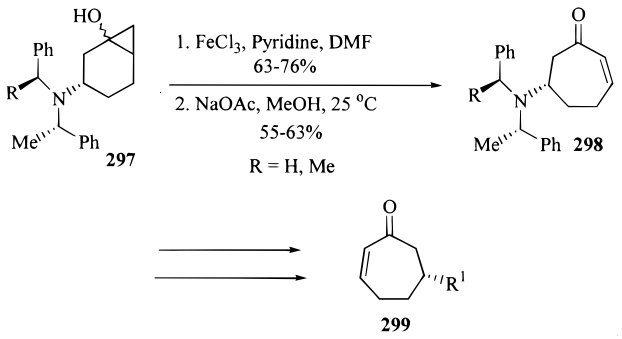
Simpkins examined the double ring-opening reactions of bis-cyclopropanes promoted by iron salts.[103] Bis-cyclopropanes **293** and **295** ring-expanded to cyclooctenones **294** and **296**, respectively, with atom transfers (Scheme 89).

Scheme 89



Sato utilized the free radical ring expansion of cyclopropanol **297** with ferric chloride followed by elimination with sodium acetate to give optically active 6-amino-2-cycloheptenones **298** (Scheme 90).[104] Enones **298** served as convenient chiral building

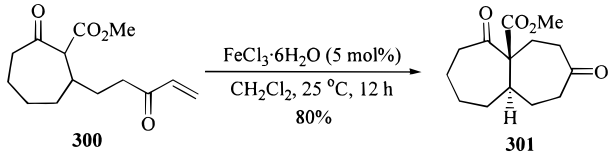
Scheme 90



blocks for the preparation of 6-alkyl-2-cycloheptenones **299**.

Christoffers showed that catalytic addition of ferric chloride to β-ketoester enone **300** at ambient temperature furnished bicyclic diketone **301** as a single diastereomer in an intramolecular Michael reaction (Scheme 91).[105]

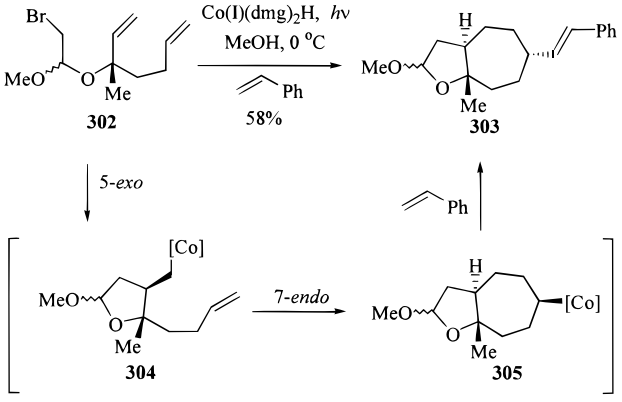
Scheme 91



3.4. Cobalt-Based Systems

Pattenden exploited the use of cobalt-mediated initiating radical cascade reactions leading to bicyclic systems.[106] Bromoacetal **302** was irradiated in the presence of cobalt(I) dimethylglyoxime and styrene to give bicyclic ether **303** (Scheme 92). Bromoacetal

Scheme 92

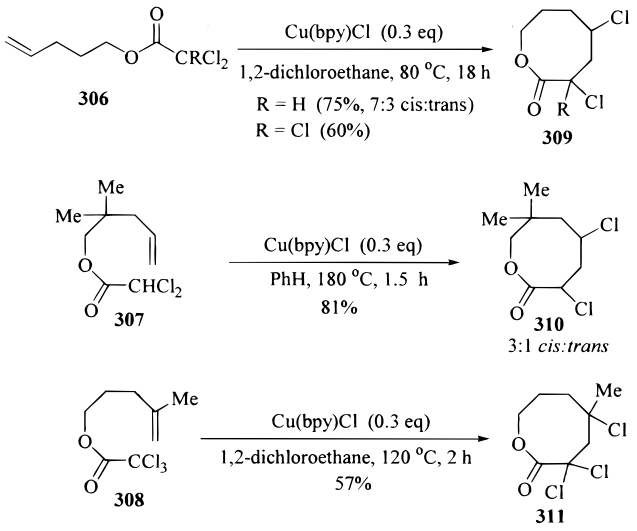


302 reacts with cobalt complex in a 5-*exo* mode to give cobaloxime **304**. Subsequent 7-*endo* cyclization of **304** to bicyclic intermediate **305** and interception by styrene gives **303**.

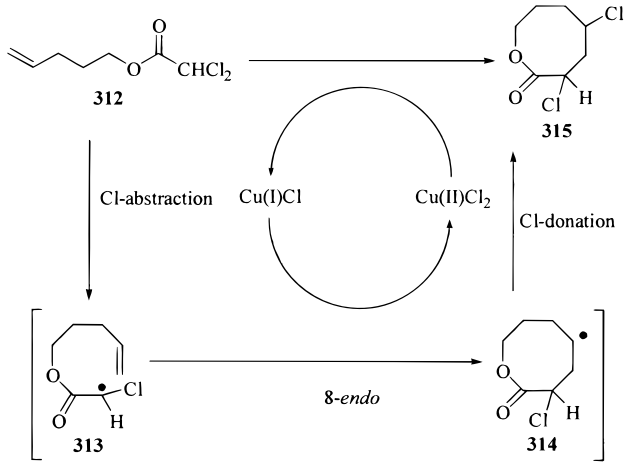
3.5. Copper-Based Reagents

Speckamp employed the use of di- and trichloroacetates **306**−**308** in a copper-catalyzed chlorine radical transfer via 8-*endo* cyclization to yield eight-membered lactones **309**−**311** in good yields (Scheme 93).[107] Mechanistically, the copper(I) catalyst abstracts a chlorine atom from **312** to furnish carbon radical **313** and a copper(II) species. Carbon radical **313** reacts in a 8-*endo* cyclization to unstabilized lactone **314**, which abstracts a chlorine atom from the previously formed copper(II) complex to give **315**, and the cycle is regenerated (Scheme 94).

Scheme 93

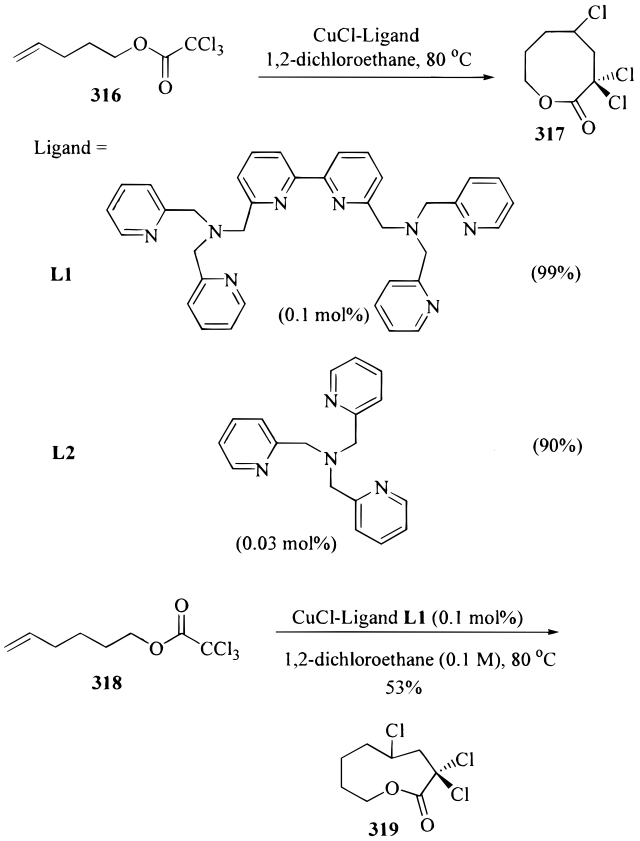


Scheme 94



Verlhac showed that pent-4-enyl trichloroacetate **316** can be converted to trichlorolactone **317** in an atom transfer radical addition reaction using copper(I) chloride and ligands **L1** or **L2**.[108] Similarly, hex-5-enyl trichloroacetate **318** furnished trichlorolactone **319** using catalyst CuCl−ligand **L1** (Scheme 95). Recently, a new procedure utilizing perfluorinated amines under fluoro biphasic conditions was reported by the same group.[109]

Scheme 95



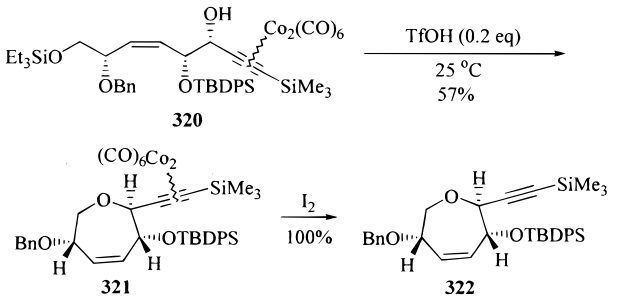
4. Alkynyl/Dienyl Metal Complex Assisted Cyclizations

Alkynyl cobalt-protected complexes and tricarbonyl(η^4-1,3-diene)iron complexes are important intermediates and offer versatile applications in organic synthesis.[110] The protected cobalt or iron metal fragments are frequently used as a protecting group. Since coordination of an alkyne or diene leads to decreased reactivity of the resulting transition metal, the alkyne or diene does not undergo hydrogenation or participate in Diels−Alder cycloaddition. These are often useful in directing stereoselective reactions because of the steric demands of these protected metals. Some of the recent advances in medium-sized ring synthesis involve these protected metal complexes.

4.1. Cobalt-Protected Complexes

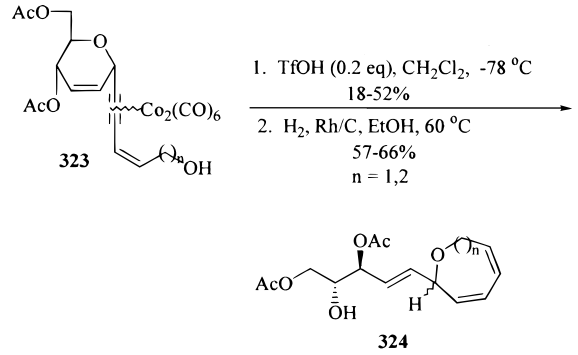
Dicobalt hexacarbonyl, as its protected alkyne complex, was exploited in the syntheses of cyclic ethers after activation. Isobe treated cobalt-protected acetylene **320** with catalytic triflic acid to afford

Scheme 96



cobalt-complexed dehydrooxepane **321** (Scheme 96).[111] Decomplexation of **321** by oxidation with iodine gave dehydrooxepane **322**, a valuable precursor to the D or E ring of ciguatoxin, as well as other marine toxins. Isobe further showed that reaction of cobalt-protected acetylenic D-glucals **323** with triflic acid, followed by decomplexation with catalytic hydrogenation, provided medium-sized ether rings **324** (Scheme 97).[112] Recently, Isobe showed that these

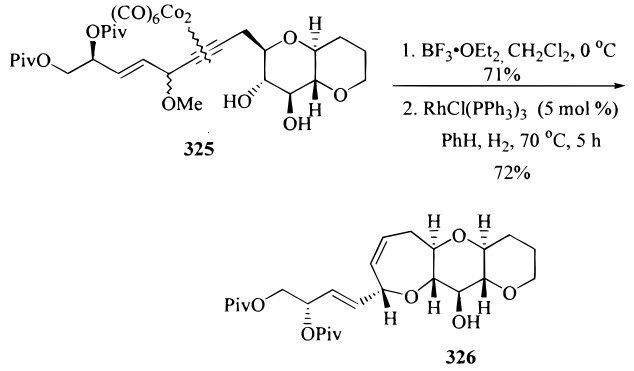
Scheme 97



complexes could be decomplexed into olefins by tributyltin hydride.[113]

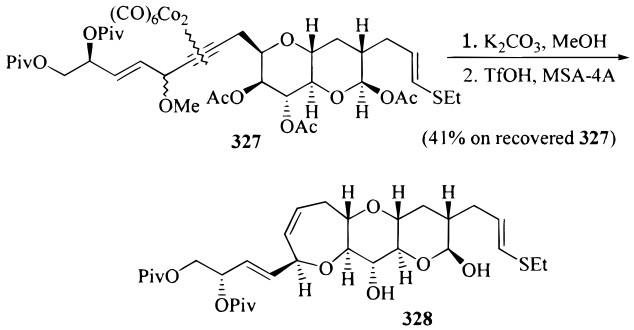
Isobe later utilized cobalt-complexed bicyclic ether **325** on treatment with boron trifluoride etherate at low temperatures in methylene chloride, followed by decomplexation of the bis(cobalt)hexacarbonyl intermediate with Wilkinson's catalyst in benzene under hydrogen atmosphere, producing **326**, the ABC fragment of ciguatoxin (Scheme 98).[114] The above studies

Scheme 98



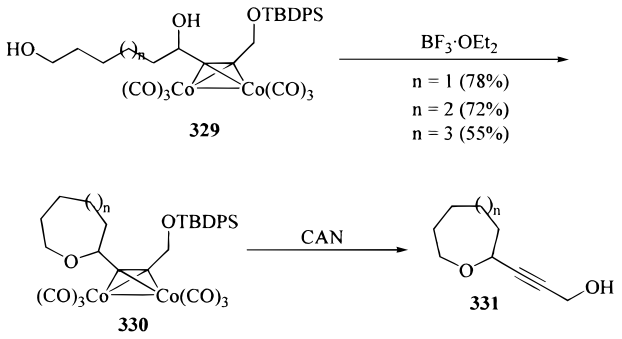
were modified once the correct absolute configuration was established. Thus, cobalt-complexed bicyclic ether **327** delivered the AB fragment **328** of ciguatoxin of the correct configuration (Scheme 99).[115]

Scheme 99



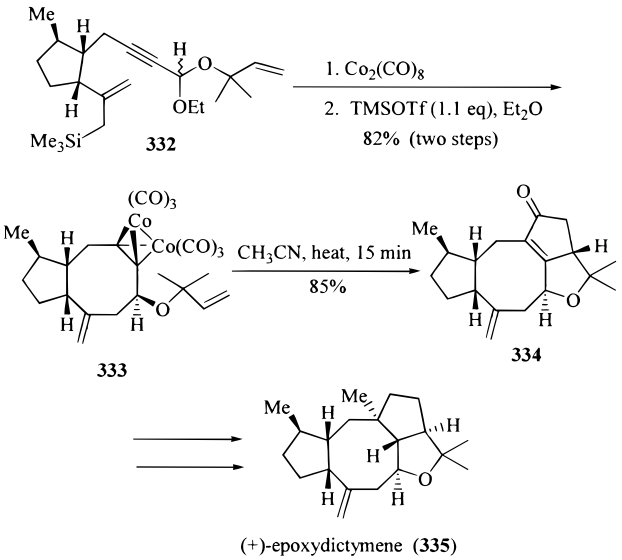
Martin exposed alkynyl cobalt-protected diols **329** to boron trifluoride etherate to give seven- to nine-membered protected cyclic ethers **330**. Decomplexation of **330** with cerium ammonium nitrate (CAN) gave alkynyl cyclic ethers **331** (Scheme 100).[116]

Scheme 100



Treatment of dienyne **332** with $Co_2(CO)_8$ gave the desired organometallic cluster, which underwent facile cyclization to yield cobalt cluster **333** (Scheme 101).[117] Cobalt cluster **333** served a second purpose

Scheme 101

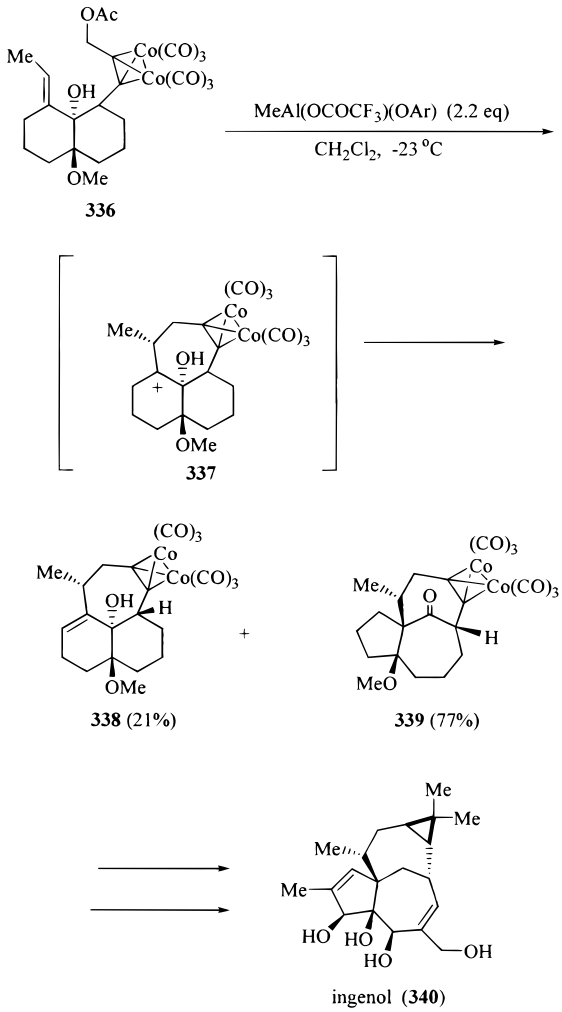


in the subsequent Pauson−Khand reaction. Heating an acetonitrile solution of **333** in air for 15 min afforded tetracyclic enone **334**, which was further elaborated to (+)-epoxydictymene (**335**).

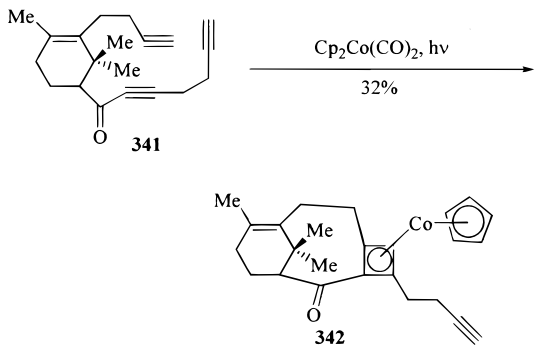
Kuwajima examined a methodology for constructing the highly strained ingenane skeleton of ingenol (**340**) by a tandem cyclization−rearrangement strategy.[118] Cobalt-complexed protected acetate **336**, in the presence of aluminum 2,6-dimethyl-4-nitrophenoxide, was found to proceed via tricyclic tertiary cation intermediate **337** to yield allyl alcohol **338** and rearranged tricyclic ketone **339** (Scheme 102). Alcohol **338** is a result of β-elimination.

Malacria reported a cobalt-mediated [2+2] intramolecular cycloaddition of enetriyne **341**, leading to the formation of a novel cobalt-complexed polycyclic cyclobutadiene **342** incorporating the taxane AB rings (Scheme 103).[119]

Scheme 102



Scheme 103



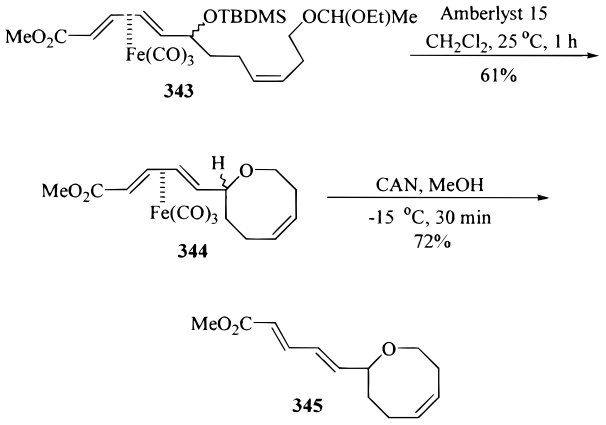
4.2. Iron-Protected Complexes

Diene tricarbonyl iron complex **343**, under acidic resin Amberlyst 15, cyclized to oxocene **344**. Decomplexation of **344** with cerium ammonium nitrate (CAN) gave dienyl oxocene **345** (Scheme 104).[120]

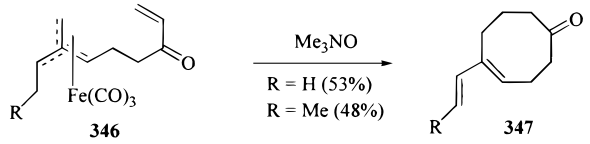
Franck-Neumann described an intramolecular cyclization of tetramethylenemethane-iron tricarbonyl complexes **346** to give cyclooctenones **347** on deligation with trimethylamine oxide (Scheme 105).[121]

Pearson showed that pentacarbonyliron-promoted cyclocarbonylation of 1,8-diynes provided a new method for the production of highly functionalized hydroazulene derivatives, which are prevalent in many natural products.[122] Diyne **348**, under a carbon monoxide atmosphere in the presence of excess pentacarbonyliron, yielded iron complex **349** (Scheme 106). Decomplexation of **349** with trimethylamine-*N*-oxide afforded hydroazulene **350**.

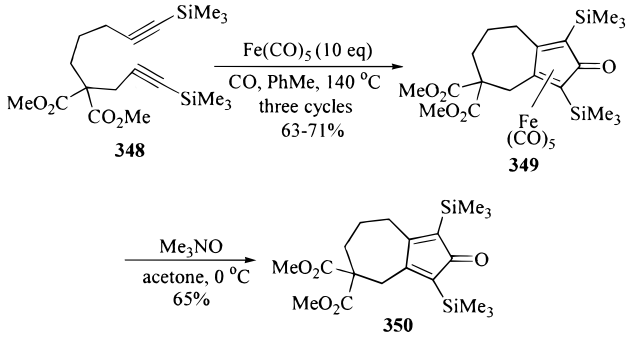
Scheme 104



Scheme 105



Scheme 106

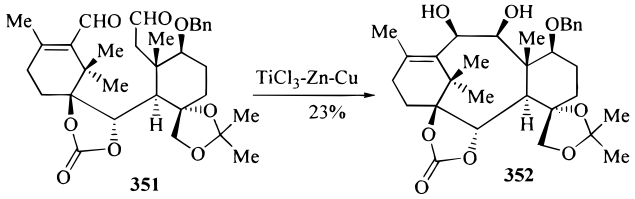


5. Metal-Promoted Reductive Cyclizations of Dicarbonyl Compounds

The McMurry reductive titanium couplings have acquired great importance in synthetic organic chemistry.[123] These reductive titanium couplings have served as key steps in numerous syntheses of natural products in the past decade, most notably those relating to the taxol skeleton.

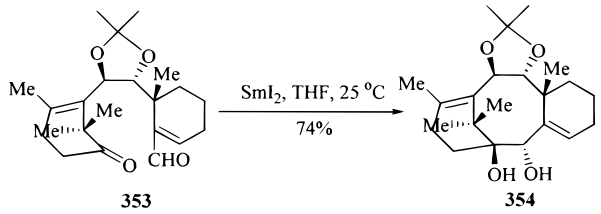
Nicolaou employed the McMurry coupling of dialdehyde **351** with titanium(III) chloride in the presence of zinc−copper couple to give tricyclic diol **352** in low yield, which culminated in the total synthesis of taxol (Scheme 107).[124]

Scheme 107



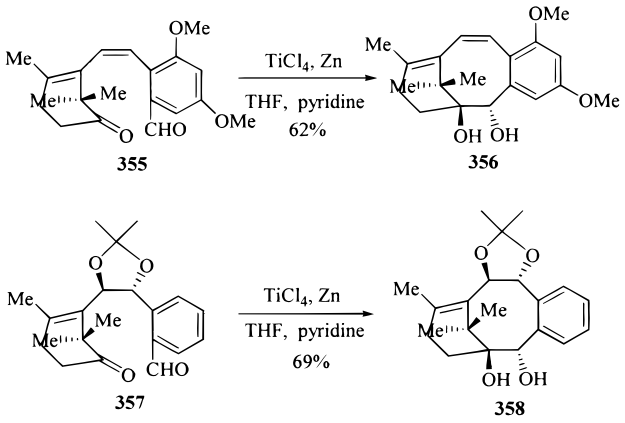
Swindell reported the construction of an advanced taxane intermediate **354** through a stereoselective intramolecular pinacol coupling at C1 and C2, with samarium(II) diiodide and keto aldehyde **353** (Scheme 108).[125] Similarly, titanium(IV) chloride zinc-medi-

Scheme 108



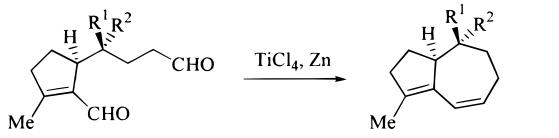
ated coupling of aryl keto aldehydes **355** and **357** gave tricyclic diols **356** and **358**, respectively, in a stereoselective manner (Scheme 109).[126]

Scheme 109



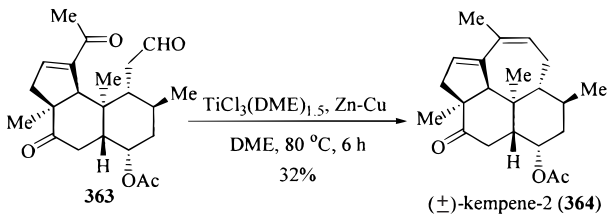
The McMurry coupling served as the key step in the syntheses of a couple of medium-sized bearing natural products. Shimizu utilized the titanium reductive coupling in the last step of the successful reaction of dialdehydes **359** and **360** to give (±)-clavukerin (**361**) and (±)-isoclavukerin A (**362**), respectively (Scheme 110).[127] Dauben exposed aldehyde

Scheme 110



363 to McMurry reductive-coupling conditions in the last step of his synthesis of (±)-kempene-2 (**364**, Scheme 111).[128]

Scheme 111



6. Metal-Promoted Nucleophilic Cyclizations/ Expansions

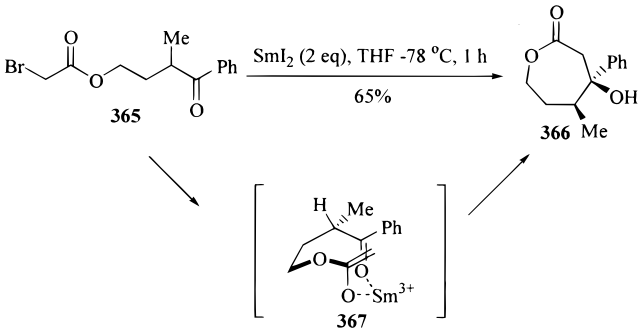
The nucleophilic addition of a Grignard reagent or organolithium compound to the carbonyl group is one of the most fundamental reactions in organic chemistry.[129] Despite its broad utility and versatility, competing side reactions such as enolization, reduction, and condensation can accompany such addition reactions. In recent years, improvement of the properties of organometallic reagents to facilitate normal addition reactions has been improvised by the judicious use of specific metals. Samarium, chromium, and indium metals have found widespread use during the past decade in general organic synthesis, and the use of these metals in the synthesis of medium-sized rings is reviewed in this section.

6.1. Samarium(II) Diiodide Cyclizations

Samarium(II) diiodide was originally introduced by Kagan as an organic reagent and has been proven to be one of the most remarkable among organic chemists.[130] This unique, polyvalent reducing agent has been applied to a multitude of synthetic transformations, often proceeding with high chemoselectivity and high levels of stereochemical control.[131] In the past decade, a tremendous amount of work of the use of this reagent in the syntheses of medium-sized rings has been witnessed.

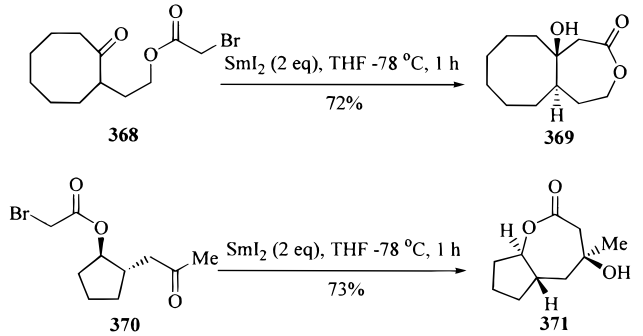
Molander showed one of the first examples of a Reformatsky-type reaction in the syntheses of seven-membered lactones.[132] α-Halo ester **365** gave lactone **366** in a stereoselective manner (Scheme 112). The

Scheme 112

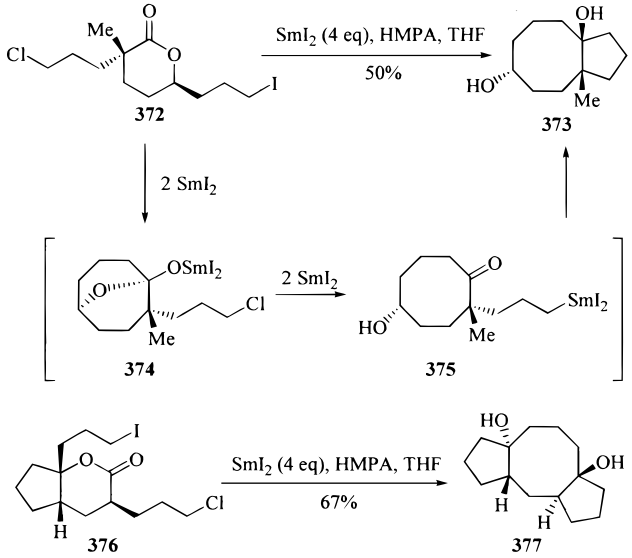


special characteristics of samarium(II) diiodide chemistry is that the α-halo ester serves as a template to organize the carbonyl addition of the ester enolate **365** as a Sm^{3+} ion generated upon electron transfer

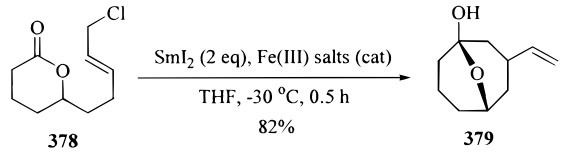
Scheme 113



Scheme 114



Scheme 115



via a chelated intermediate **367**. Similarly, α-bromo esters **368** and **370** afforded bicyclic lactones **369** and **371**, respectively (Scheme 113).

Molander also employed samarium(II) diiodide in a sequential nucleophilic acyl substitution/keto alkylation reaction.[133] Dihalolactone **372** provided bicyclooctanediol **373** on application of 4 equiv of samarium(II) diiodide (Scheme 114). The first 2 equiv of samarium(II) diiodide reacts with the iodo group of **372** to initiate an anionic cyclization producing ketyl intermediate **374**, which decomposes to ketone **375**, with the addition of the next two equivalents of samarium(II) diiodide. Cyclization of **375** to the carbonyl and workup gives **373**. Bicyclic lactone **376** under the same conditions gave tricyclic diol **377**.

Molander further described the samarium(II) diiodide-promoted cyclization of halogeno ester **378** in the presence of ferric salts to give lactol **379** (Scheme 115).[134]

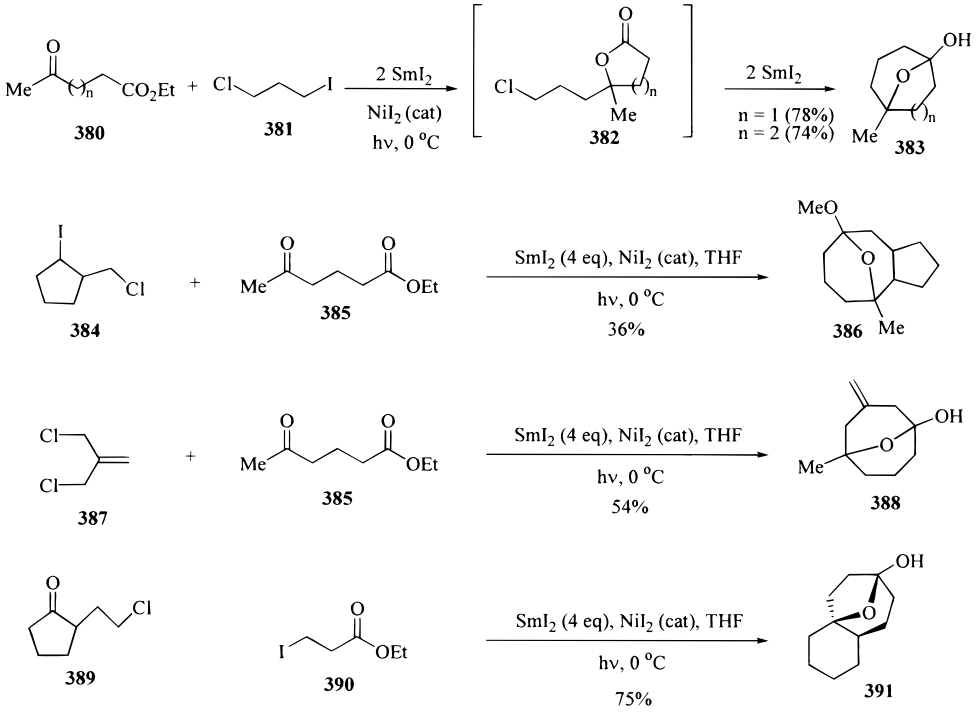
Recently, Molander showed that 1-chloro-3-iodopropane (**381**) reacted with keto esters **380** to give lactols **383** via lactone intermediate **382** in the presence of catalytic nickel(II) iodide and visible light (Scheme 116).[135] Similarly, keto ester **385** reacted with cyclopentane **384** and allylic dichloride **387** to yield lactols **386** and **388**, respectively. Recently, chlorocyclopentanone **389** reacted under these same conditions in the presence of ethyl 3-iodopropanoate (**390**) to furnish tricyclic ether **391**.

An intramolecular Reformatsky reaction of bromo aldehydes **392** with samarium(II) diiodide were used to afford methyl 2-acetoxy-cycloalkane-1-carboxylates (**393**) as a mixture of diastereomers in a 1:1 ratio after acetylation (Scheme 117).[136]

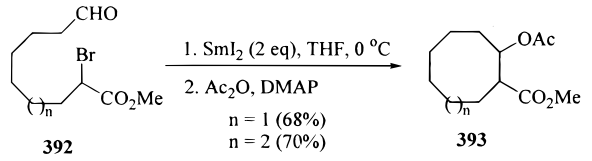
Allylic chlorides **394** and **396** participated in an instantaneous intramolecular samarium(II) diiodide reductive coupling in the presence of HMPA to yield carbocycles **395** and **397**, respectively, in excellent yields (Scheme 118).[137]

Tachibana similarly utilized samarium(II) diiodide-promoted intramolecular Reformatsky reaction of *O*-linked bicyclic **398** to effect cyclization to the *trans*-fused 6,9,6-tricyclic ether **399** as part of studies toward the EFG segment of ciguatoxin (Scheme 119).[138] This was eventually used to promote the samarium(II) diiodide intramolecular cyclization of

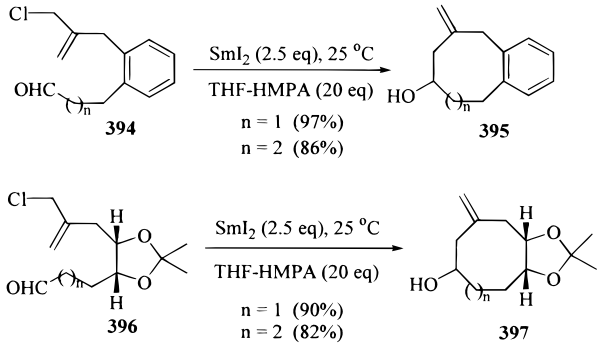
Scheme 116



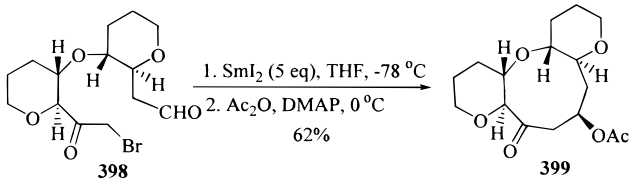
Scheme 117



Scheme 118

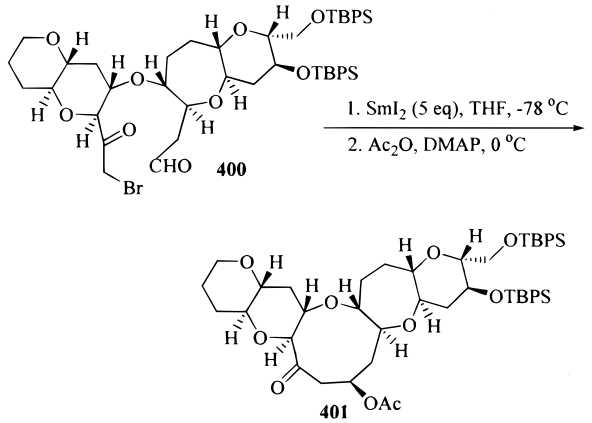


Scheme 119



tetracyclic ether **400** to pentacyclic ether **401** as part of the convergent assembly of the F−M ring framework of ciguatoxin (Scheme 120).[139]

Scheme 120



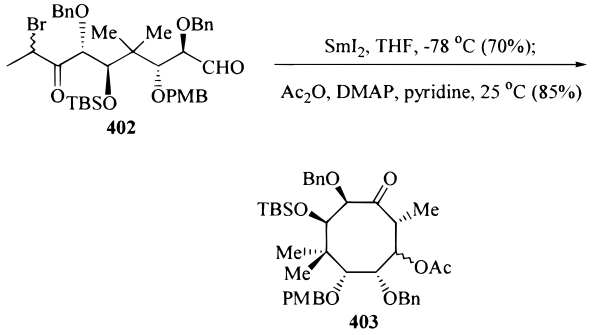
Mukaiyama utilized the samarium(II) diiodide-promoted Reformatsky intramolecular cyclization of bromo aldehyde **402** to give eight-membered ketone **403** in his asymmetric total synthesis of taxol (Scheme 121).[140]

Matsuda employed the intramolecular Barbier samarium(II) diiodide-promoted coupling of allylic chloride **404** to construct the bicyclic skeleton **405** of the diterpene vinigrol (Scheme 122).[141]

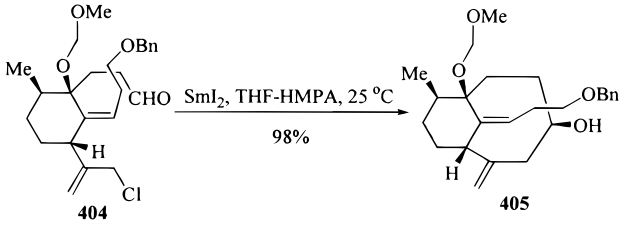
6.2. Indium/Zinc Ring Cyclizations/Expansions

In recent times, indium has been found to be a novel reagent in various reactions.[142] These reactions are usually accelerated in aqueous medium. Li

Scheme 121

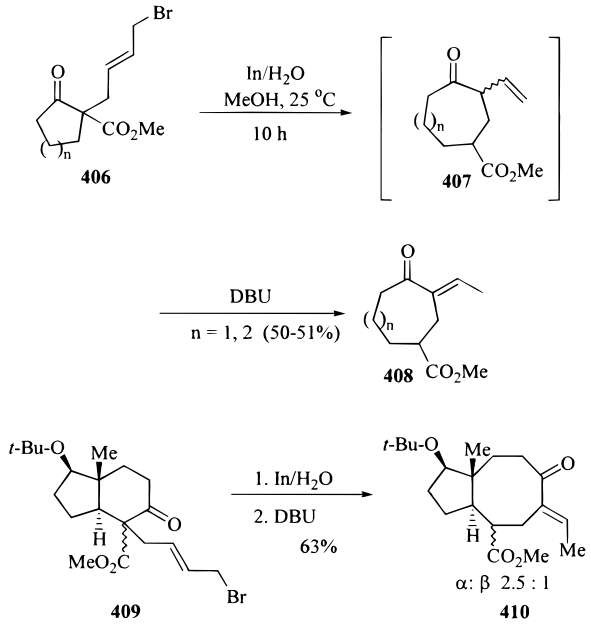


Scheme 122



reported a novel two-carbon carbocycle enlargement based on indium-mediated Barbier Grignard-type reaction in water. Thus, cyclopentenyl (n = 1) and cyclohexenyl (n = 2) bromides **406** were expanded to allyl ketones **407**, which were isomerized to enones **408** (Scheme 123) with DBU.[143] This methodology

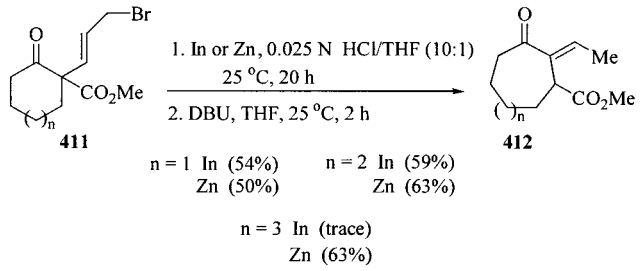
Scheme 123



was applied to bicyclic ketone **409** as entry to the hydroazulene skeleton **410**.

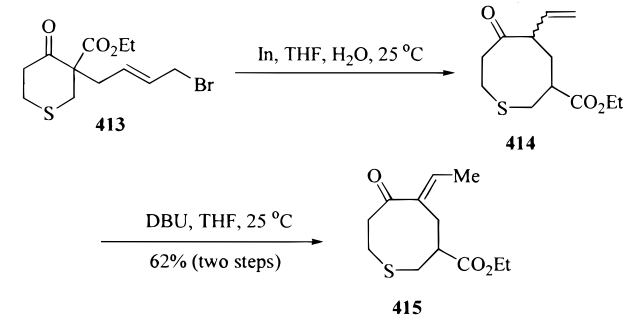
Seven- (n = 1), eight- (n = 2), and nine- (n = 3) membered cyclic enones **412** were obtained from indium- and zinc-mediated one-carbon carbocycle enlargement of allyl bromides **411** in aqueous protic media, followed by treatment with DBU (Scheme 124).[144] This transformation presents a room temperature aqueous alternative to the tributyltin hydride ring expansion normally conducted in refluxing organic media, such as benzene or toluene. Li re-

Scheme 124



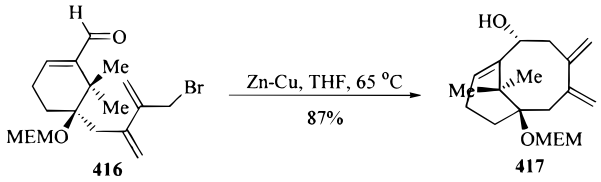
cently further applied the indium-mediated reaction of β-keto ester **413** in aqueous medium to give eight-membered thiocycloether **414**, which was isomerized to the more stable, conjugated enone **415** (Scheme 125).[145]

Scheme 125



Wang showed that allylic bromide **416** cyclized smoothly to give bicyclic triene **417** as a single diastereomer with zinc−copper couple in refluxing tetrahydrofuran as part of taxol-related studies (Scheme 126).[146] This represented one of the few

Scheme 126



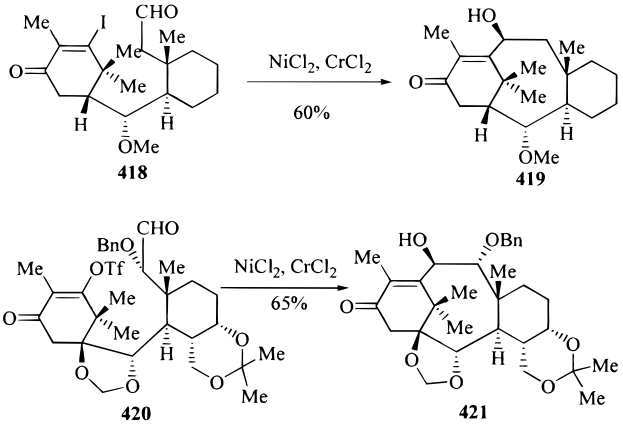
examples of macrocyclization mediated by a zinc species. Apparently, the unusually high reactivity of the allylzinc intermediate prevailed over the steric hindrance and the unfavored entropy involved in the eight-membered ring closure. It was shown that chromium(II) chloride or samarium(II) diiodide was unsuccessful in the eight-membered ring closure.

6.3. Chromium/Nickel Cyclizations

The use of chromium(II) chloride/nickel(II) chloride systems for carbon−carbon bond formations involving organochromium(III) reagents has been heavily exploited in the past decade, both in synthetic methodology and as key steps in total natural product synthesis.[147] The reaction was simultaneously discovered by three different groups in the mid-1980s and is termed the Nozaki−Hiyama−Kishi (NHK) reaction.

Kishi exploited the use of nickel(II) chloride/chromium(II) chloride reagent in the coupling of vinyl iodide/triflates with carbonyl groups.[148] Vinyl iodide **418** and vinyl triflate **420**, in the presence of the bimetals, provided tricyclic taxane skeletons **419** and **421** in good yield with excellent diastereoselectivities (Scheme 127). Later, 4-*tert*-butylpyridine was shown

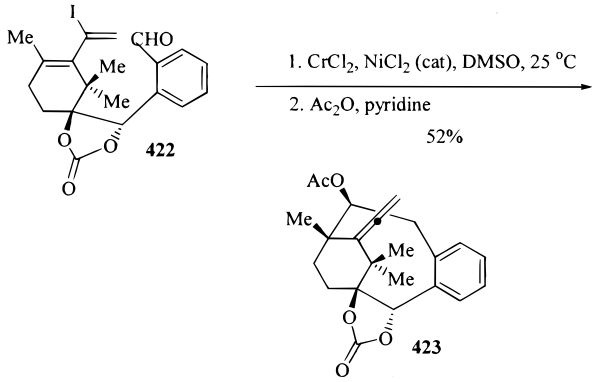
Scheme 127



to be a beneficial additive in these couplings, as well as improved workups.

In model studies directed toward the taxane skeleton, vinyl iodide **422** was converted to tricyclic allene **423** via the chromium(II) chloride/nickel(II) chloride coupling method (Scheme 128).[149] When the *cis*-fused

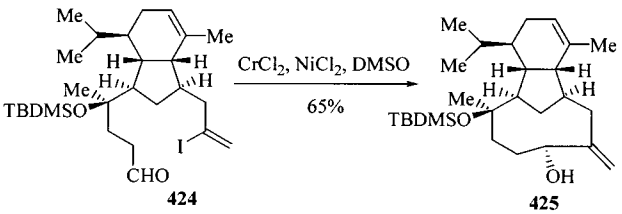
Scheme 128



carbonate isomer of **422** was employed under these conditions, only reduction of the iodo group was observed. This represented an unprecedented intramolecular S_N2' NHK coupling reaction.

Overman utilized the NHK reaction on vinyl iodide **424** to give tricyclic ether **425** in the enantioselective total synthesis of (−)-7-deacetoxyalcyonin acetate, a Eunicellin diterpene (Scheme 129).[150]

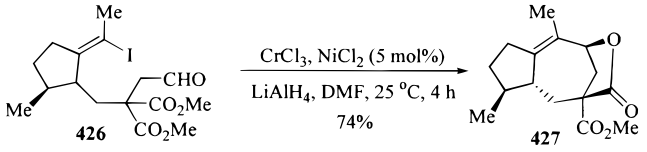
Scheme 129



Negishi applied the NHK coupling of vinyl iodide **426** to give lactone **427** as part of a study toward

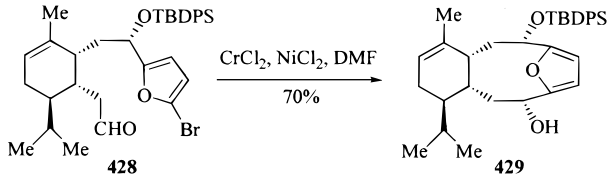
the hydroazulene skeleton of (±)-7-epi-β-bulnesene (Scheme 130).[151]

Scheme 130



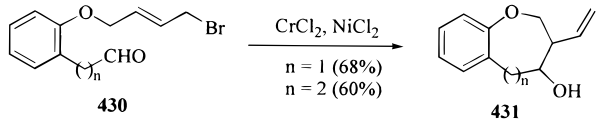
Danishefsky employed the NHK reaction in a remarkably efficient and stereoselective formation of the strained furano[6]phane skeleton of the antitumor agent eleutheside. Bromo aldehyde **428** gave tricyclic ether **429** in good yield upon treatment with chromium(II) chloride/nickel(II) chloride (Scheme 131).[152]

Scheme 131



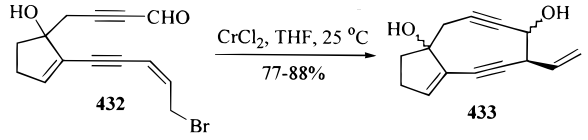
Wender showed the NHK coupling of allylic bromides **430** to give benzocyclic ethers **431** (Scheme 132).[153] Wender also exposed allyl bromide **432** to

Scheme 132



chromium-mediated intramolecular cyclization of the aldehyde group to give dienediyne **433** as an inseparable mixture of three diastereomers as a general method for the strained ring synthesis of neocarzinostatin chromophore analogues (Scheme 133).[154]

Scheme 133



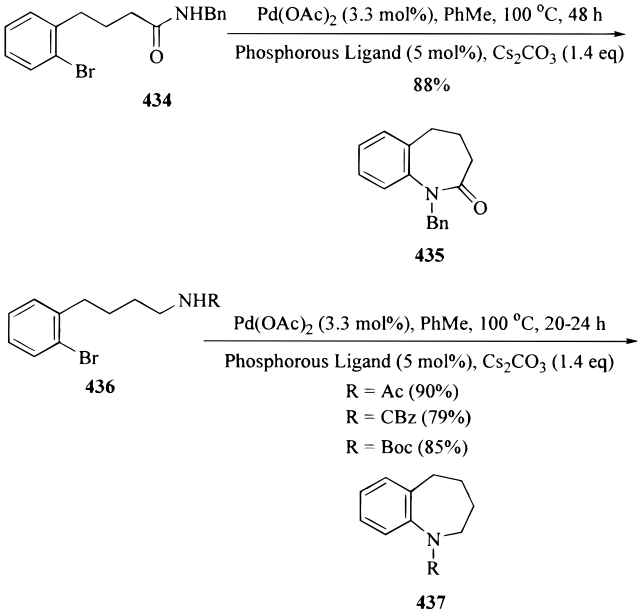
7. Palladium-Catalyzed Cyclizations

Cyclic carbopalladation has emerged as one of the most important methods for the preparation of a wide range of molecular frames.[155] Carbopalladations are processes that involve the addition of the C−Pd bond to double or triple bonds of alkenes, alkynes, allenes, conjugated dienes, and arenes.[156] The advantages of these reactions are mild conditions and good functional group tolerance. Previously harsh reaction conditions and reaction intermediates limited functional group tolerance. Presented below are recent applications of intramolecular carbopalladation methodology in the syntheses of various polycyclic frameworks and key steps in natural product synthesis.

7.1. Intramolecular Palladium-Catalyzed Aryl Aminations and Etherations

Buchwald recently reported that aryl bromides could be cyclized with secondary amide groups to form tertiary amides.[157] Secondary amides **434** and secondary carbamates **436** cyclized efficiently to give seven-membered ring amides **435** and **437**, respectively (Scheme 134). The proper choice of phosphorus

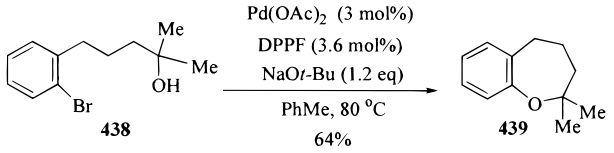
Scheme 134



ligand (MOP, DPEphos, or Xantphos) was needed for each case, and cesium carbonate was found to be the best base in these cyclizations.

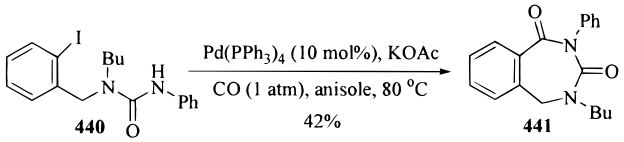
Buchwald developed the first palladium-catalyzed synthesis of cyclic aryl ethers from alcohols and aryl halides.[158] Aryl bromide **438** cyclized to the seven-membered cyclic ether **439** using palladium(II) acetate, 1,1′-bis(diphenylphosphino)ferrocene (DPPF) as the chelating ligand and sodium *tert*-butoxide as the base in warm toluene (Scheme 135).

Scheme 135



Palladium-catalyzed carbonylation of phenylurea **440** gave benzodiazepine **441** in moderate yield (Scheme 136).[159]

Scheme 136

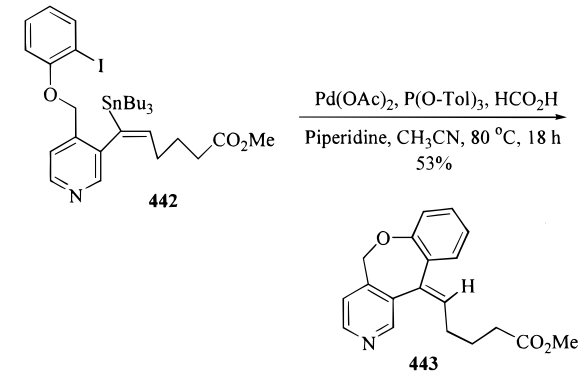


7.2. Intramolecular Heck/Stille Cyclizations

Finch described the first reported example of an intramolecular Stille palladium-catalyzed cyclization

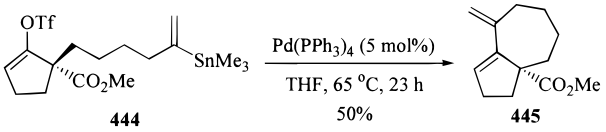
of seven-membered rings of aromatic systems to tricyclic ethers as part of study of the synthesis of conformationally restrained, combined thromboxane antagonist.[160] Aryl iodide **442** reacted intramolecularly with the tributylstannane group under Stille conditions to furnish tricyclic ether **443** in good yield (Scheme 137).

Scheme 137



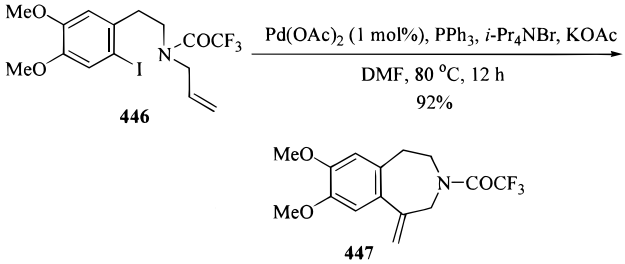
Piers reported one of the first examples of a seven-membered carbocycle formation via an intramolecular Stille cyclization.[161] Vinyl stannane **444** cyclized to bicyclic diene **445** in moderate yield under palladium-catalyzed conditions (Scheme 138).

Scheme 138



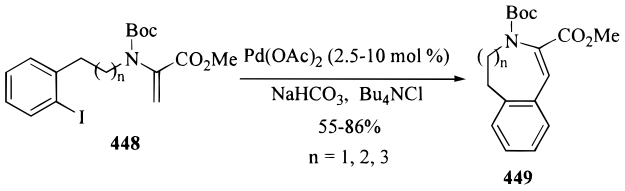
Tietze employed the intramolecular Heck reaction of aryl iodide **446** to yield benzazepine **447** in excellent yield as part of studies of dopamine receptor antagonists (Scheme 139).[162]

Scheme 139



Gibson employed the intramolecular Heck cyclizations to synthesize conformationally constrained amino acid analogues.[163] Iodo olefins **448** participated in a rare palladium-catalyzed 7-, 8-, and 9-*endo* Heck cyclizations to give restricted phenylalanine analogues **449** (Scheme 140). Radical cyclizations were

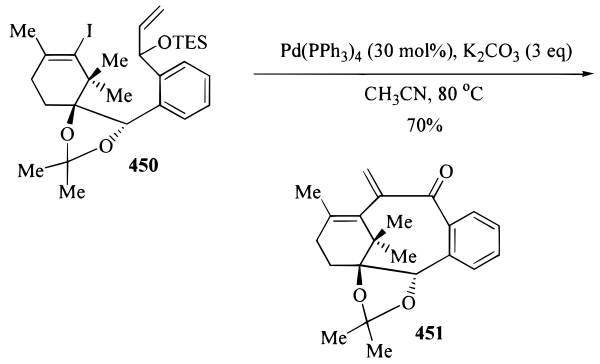
Scheme 140



also performed on these substrates which gave saturated products.

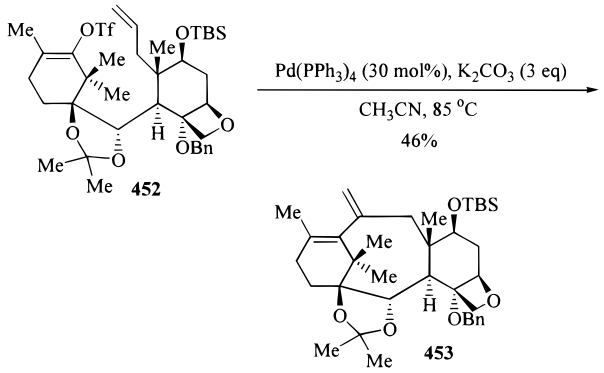
Danishefsky explored the difficult intramolecular Heck reaction of aryl iodide **450** to tricyclic ketone **451** in synthetic model studies toward taxol (Scheme 141).[164] Vinyl triflate **452** was used successfully in

Scheme 141



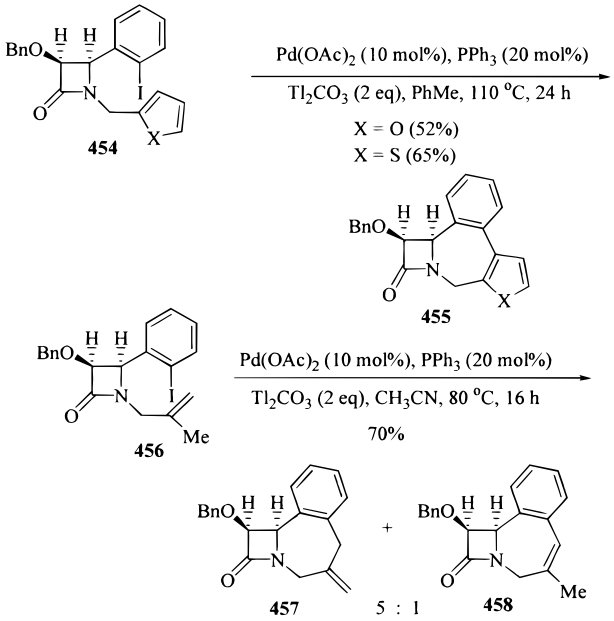
the intramolecular Heck reaction to give tricyclic diene **453,** which led to the eventual synthesis of taxol (Scheme 142).

Scheme 142



Grigg examined the palladium-catalyzed cyclization of various substrates to give bicyclic β−lactams.[165] Aryl iodides **454** cyclized in moderate yields

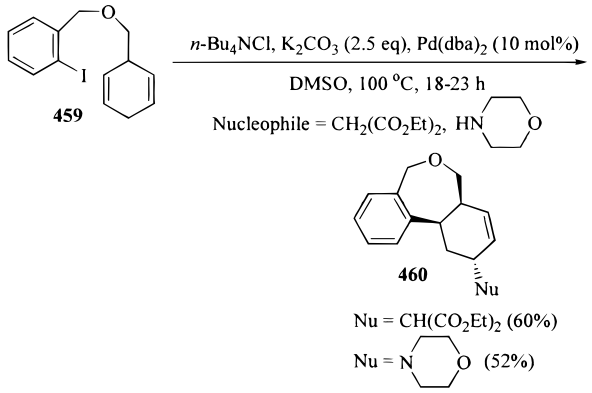
Scheme 143



to give tetracyclic β-lactams **455** (Scheme 143). Iodo olefin **456** reacted in a Heck coupling to give tricyclic alkenes **457** and **458** in a 5:1 ratio.

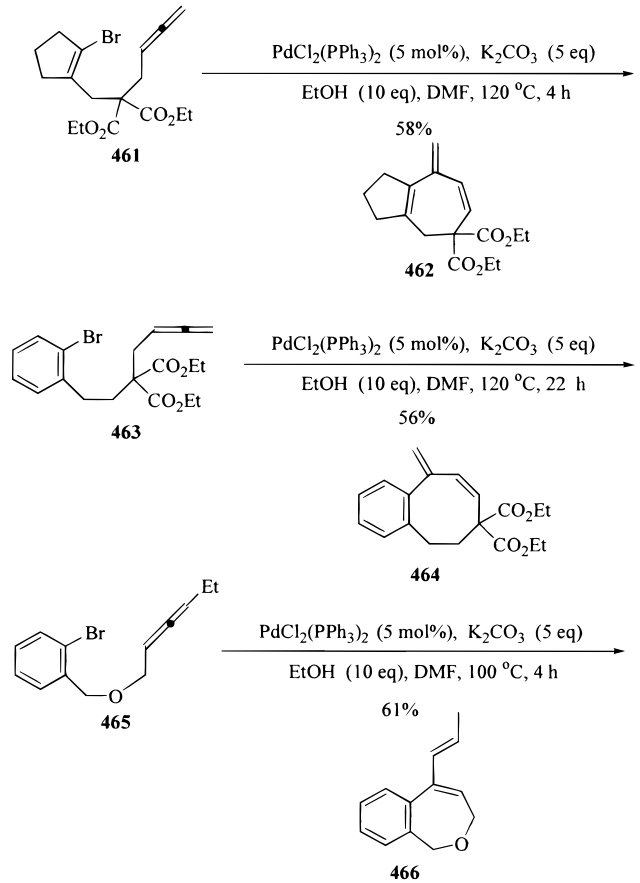
Larock examined the palladium-catalyzed cross-coupling of aryl iodide **459** with carbon and heteroatom nucleophiles to give tricyclic ethers **460** (Scheme 144).[166]

Scheme 144



Negishi reported the first examples of intramolecular cyclic carbopalladation of allenes.[167] Vinyl bromide **461** was converted via a palladium-catalyzed reaction in a novel route to hydrazulene **462** (Scheme 145). Aryl bromides **463** and **465** similarly were

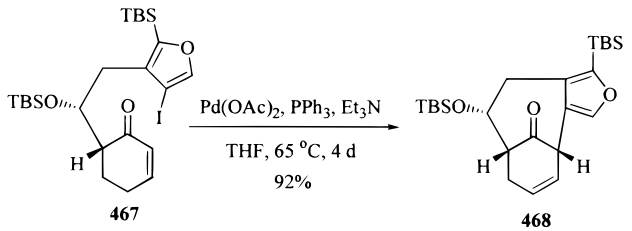
Scheme 145



further transformed to benzocyclooctadiene **464** and benzocyclic ether **466**, respectively.

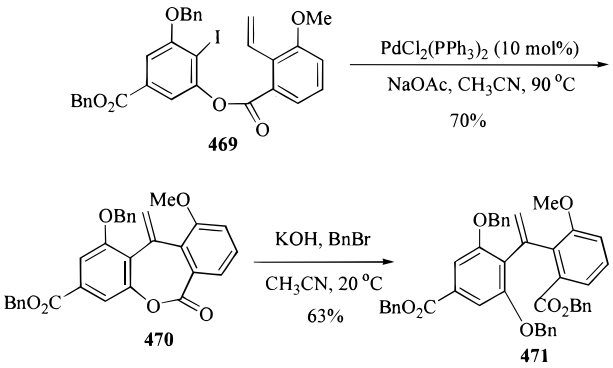
Danishefsky utilized the intramolecular Heck coupling of furan iodide **467** to give tricyclic furan part **468** of the total syntheses of CP-225,917 and CP-263,-114 (Scheme 146).[168]

Scheme 146



Aryl iodide **469** was employed in the intramolecular Heck reaction to give tricyclic lactone **470**, which was later cleaved to biaryl alkene **471**, the fully functionalized benzophenone core of balanol (Scheme 147).[169]

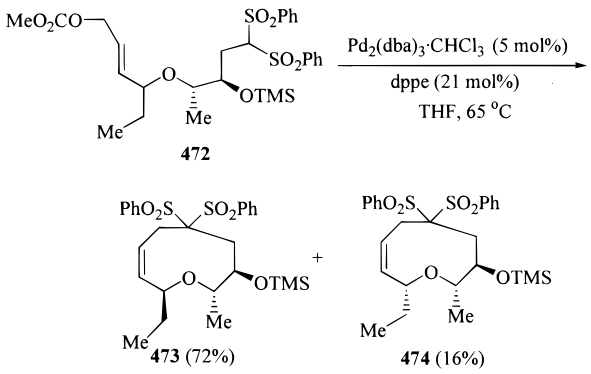
Scheme 147



7.3. Intramolecular Cyclizations of Allylic Groups

Palladium-catalyzed allylic alkylation of bis(sulfonyl)ether **472** gave unsaturated nine-membered allylic ethers **473** and **474** in a stereoselective cyclization (Scheme 148).[170] This methodology was used

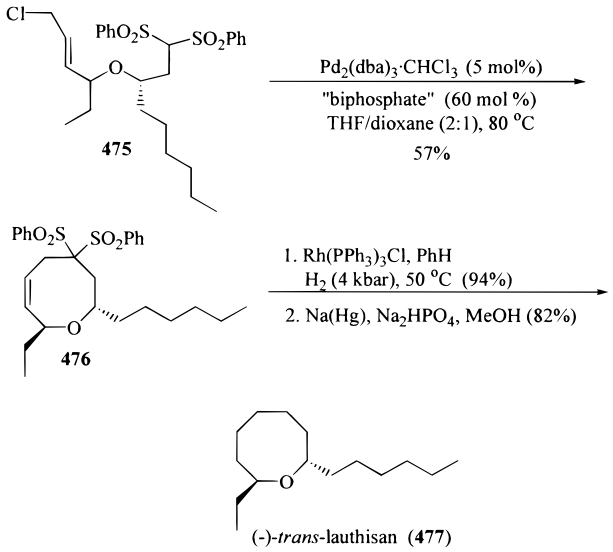
Scheme 148



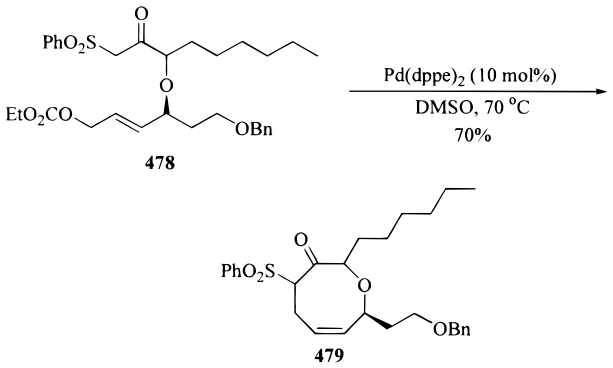
in the stereoselective synthesis of (−)-*trans*-lauthisan (**477**). Palladium-catalyzed alkylation of allylic chloride **475** gave *trans*-oxocene **476**. Subsequent alkene reduction and sulfonyl deprotection led to **477** (Scheme 149).[171]

Palladium-catalyzed intramolecular cyclization of allylic carbonate **478** to the desired eight-membered cyclic ether **479** is shown in Scheme 150.[172] The

Scheme 149



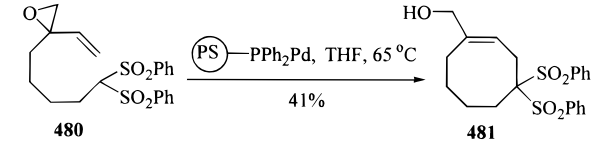
Scheme 150



unusual and preferred *endo*-cyclization for eight-membered cyclic ether over *exo*-cyclization to the six-membered cyclic ether was attributed to the steric interference of the substituent at the allylic position with the incoming nucleophile. Ether **479** proved to be a valuable precursor to (−)-*trans*-lauthisan (**477**).

Trost applied a polymer-supported palladium catalyst to the synthesis of eight-membered ring bis(sulfone) product **481** from epoxy sulfone **480** (Scheme 151).[173]

Scheme 151



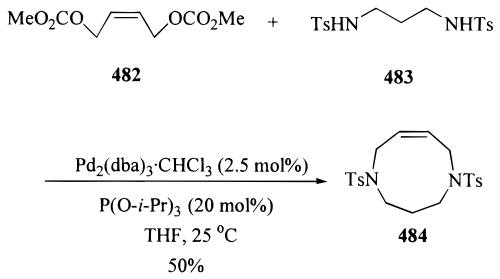
7.4. Palladium-Catalyzed Double Alkylations

Saegusa reported the palladium-catalyzed reaction of (*Z*)-2-butene-1,4-diyl-bis(methylcarbonate) (**482**) with ditosyldiamine **483** to give cyclic diamide **484** (Scheme 152).[174]

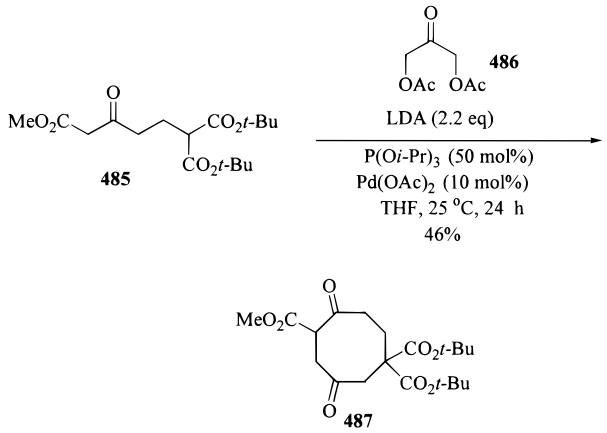
Palladium-catalyzed double alkylation of β-keto ester **485** with diacetate **486** led to selective formation of cyclooctadione **487** (Scheme 153).[175]

The palladium-catalyzed dialkylation of diketone **488** with methylene diacetate **489** gave bicyclic

Scheme 152

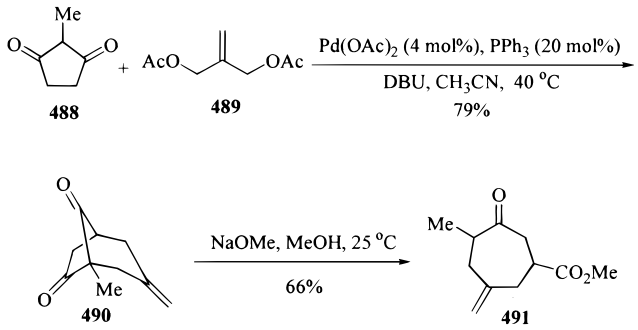


Scheme 153



diketone **490**, which after base-promoted opening gave β-keto ester **491** (Scheme 154).[176]

Scheme 154

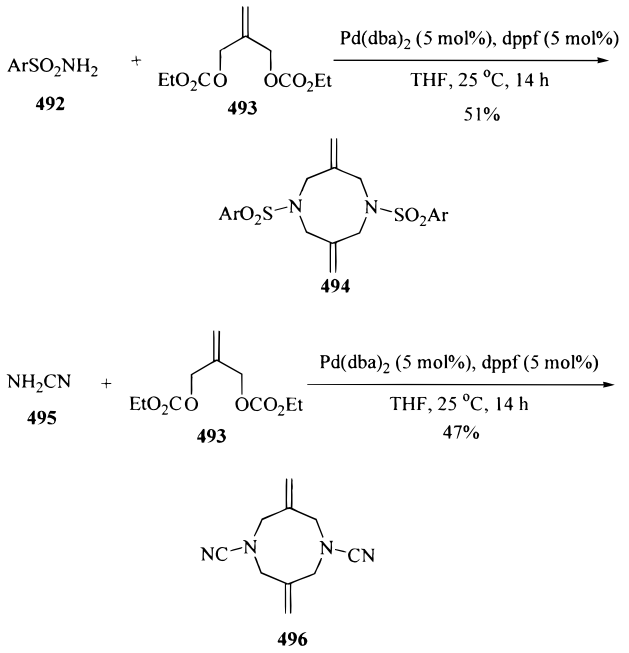


Moreno-Manas recently reported the palladium-catalyzed double-alkylation reactions of allylic biscarbonates with various amines.[177] Treatment of biscarbonate **493** with arenesulfonamide **492** and cyanamide (**495**) gave eight-membered heterocycles **494** and **496**, respectively, as the major products (Scheme 155). Larger ring polymers and polymeric compounds were also obtained in minor amounts.

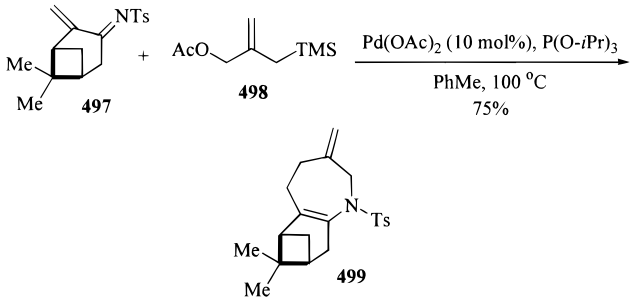
7.5. Palladium-Catalyzed TMM Cyclizations

Palladium-catalyzed [4+3] cycloadditions of trimethylenemethane (TMM), generated in situ from 2-[(trimethylsilyl)methyl]allyl acetate (**498**), to electron-deficient olefins provided attractive routes to functionalized cycloheptenes. The process probably involves a TMM−PdL_2 species. Trost reported that an α,β-unsaturated imine **497** can react with 2-[(trimethylsilyl)methyl]allyl acetate (**498**) via a palladium−TMM species to give fused-ring azepine **499** (Scheme 156).[178] Trost also showed that vinyl cyclo-

Scheme 155

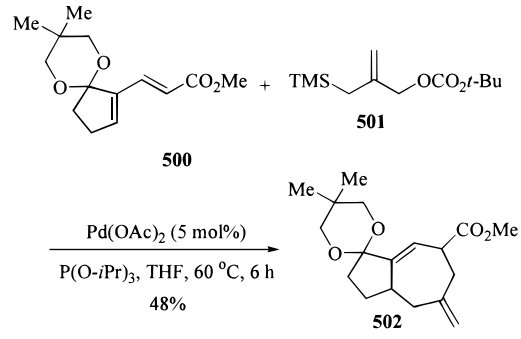


Scheme 156



pentenes **500** reacted with Pd−TMM species of **501** to give bicyclic diene **502** in a [4+3] cycloaddition (Scheme 157).[179] Trost further applied this intra-

Scheme 157

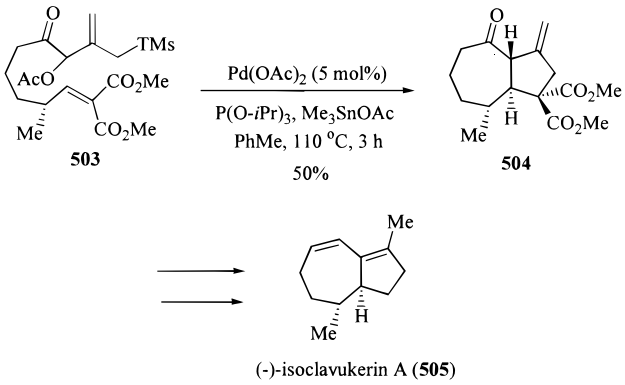


molecular [4+3] palladium−TMM-catalyzed cyclization of diene **503** to give bicycloheptenone **504** as a single diastereomer, which was elaborated further to (−)-isoclavukerin A (**505**, Scheme 158).[180]

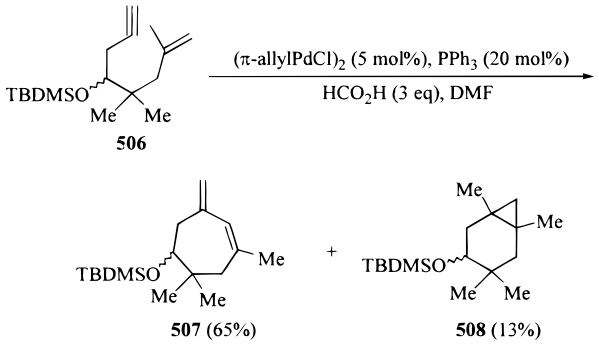
7.6. Palladium-Catalyzed Eneyne Cyclizations

Palladium-catalyzed 1,7-eneyne cyclization of **506** gave a mixture of cycloheptadiene **507** and bicyclopropane **508** (Scheme 159).[181] The reaction proceeded in an *endo*- or *exo*-mode, depending on solvent polarity conditions.

Scheme 158

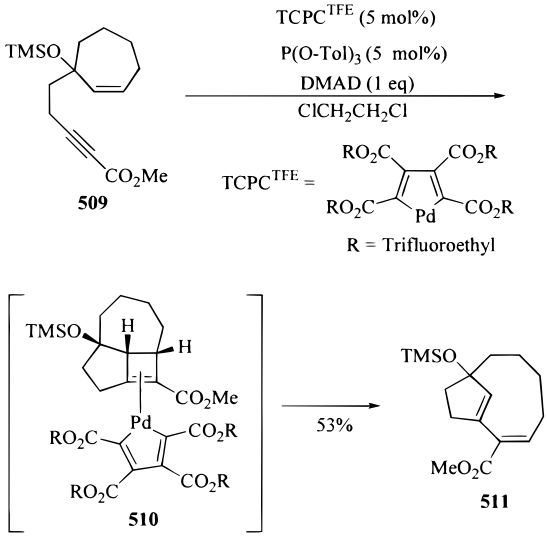


Scheme 159



Trost reported a novel, intramolecular eneyne metathesis reaction to bridged bicycles with bridgehead olefins.[182] Eneyne **509** reacted with a cyclopentadienylpalladium catalyst to give bicycle **511** via a highly, strained tricyclic intermediate **510** derived from initial [2+2] cycloaddition (Scheme 160). Incor-

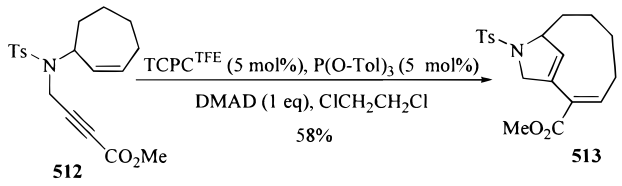
Scheme 160



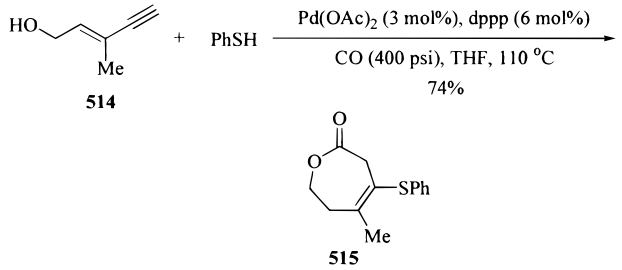
poration of a nitrogen in the tether as in **512** provided the azabicyclic product **513** in good yield (Scheme 161).

Alper showed that an eneyne bearing a hydroxyl group in the allylic position, such as **514**, afforded sulfur-substituted lactone **515** in a palladium(II) diacetate−dppp-catalyzed reaction under a carbon monoxide atmosphere (Scheme 162).[183]

Scheme 161



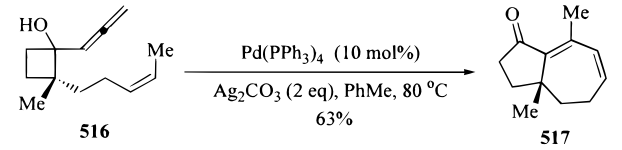
Scheme 162



7.7. Palladium-Catalyzed Intramolecular/ Intermolecular Allene Cyclizations

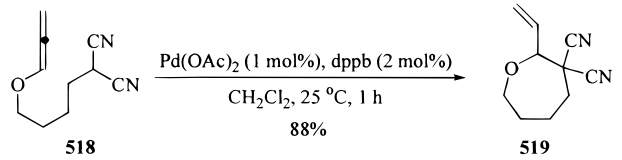
Allenylcyclobutanol **516** underwent a novel unprecedented intramolecular catalytic cyclopalladation followed by ring expansion to afford cycloheptadiene **517** (Scheme 163).[184]

Scheme 163



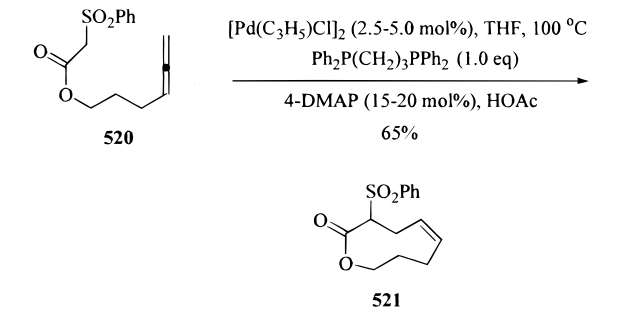
Yamamoto reported the smooth cyclization of alkoxyallene **518** to cyclic ether **519** in the presence of catalytic amounts of palladium(II) diacetate−dppb complex (Scheme 164).[185]

Scheme 164



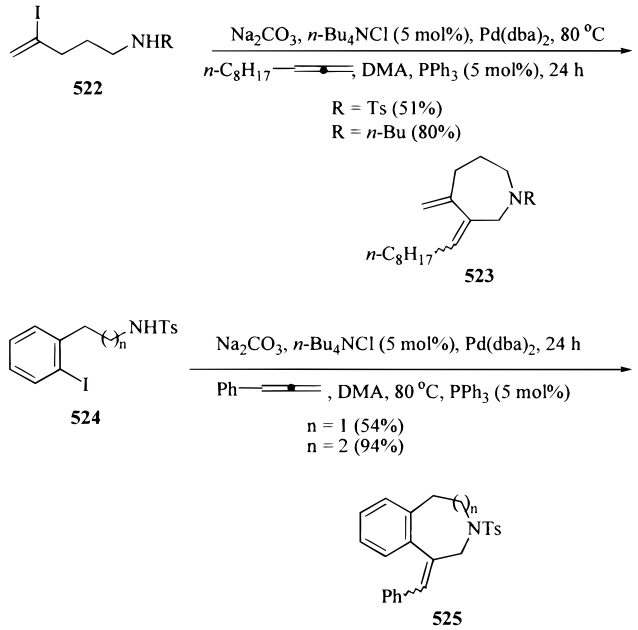
Palladium-catalyzed reaction of allenyl sulfone **520** gave nine-membered lactone **521** in good yields (Scheme 165).[186]

Scheme 165



Larock explored the medium-ring nitrogen heterocyclic formation via palladium-catalyzed heteroannulation of allenes.[187] Vinyl iodide **522** and aryl iodide **524**, on reaction with palladium catalyst in the presence of bases and allenes respectively, afforded nitrogen heterocycles **523** and **525** in moderate to good yields (Scheme 166).

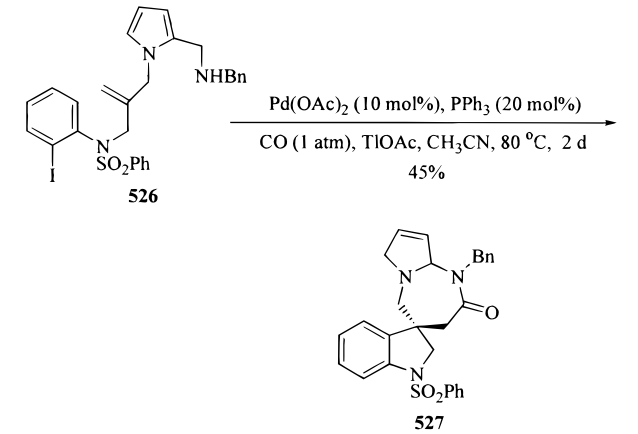
Scheme 166



7.8. Palladium-Catalyzed Cascade Cyclizations

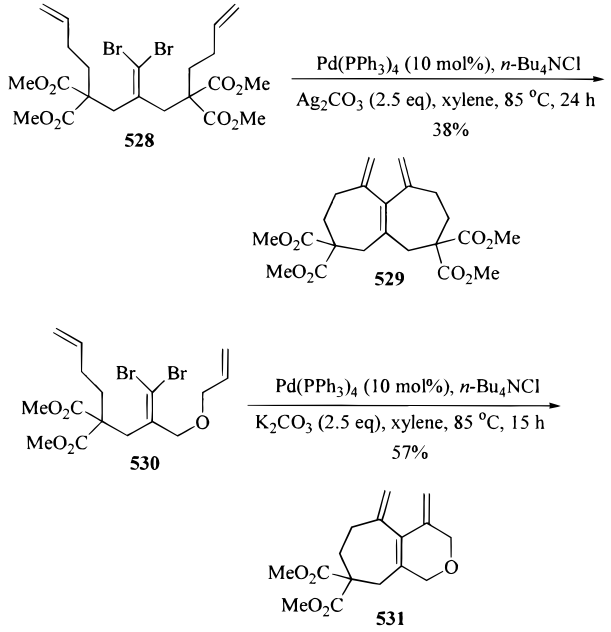
Grigg reported a formation of a seven-membered ring spirocycle via a palladium-catalyzed cascade cyclization−carbonylation−anion capture process.[188] Iodo sulfonamide **526**, in the presence of palladium catalyst under a carbon monoxide atmosphere and the use of thallium(I) acetate as the base, generated tetracyclic lactam **527** in moderate yield (Scheme 167).

Scheme 167



Ma reported the first transitional metal-catalyzed bicyclic carbometalation reaction of *gem*-dibromides.[189] Dibromides **528** and **530** afforded bicyclic esters **529** and **531**, respectively, in the presence of palladium catalyst and base in refluxing xylene (Scheme 168). No α-dehalopalladation was observed in these reactions.

Scheme 168



8. Metal-Catalyzed Cycloadditions

Cycloaddition reactions have held a prominent place in the arsenal of synthetic methods for the last 80 years, and research in this area is still continuing.[190] Cycloaddition processes have been promoted by heat, light, Lewis acids, high pressure, and sonication. Usually polarizable functional groups are needed in the substrates to facilitate the reactions. Unactivated olefins, dienes, or acetylenes usually react poorly and usually require harsh conditions. The Diels−Alder reaction has been the most versatile cycloaddition reaction characterized by a highly stereoselective combination of a 4π diene and a 2π dienophile for formations of six-membered rings, providing two bonds and up to four stereocenters in a single transformation.[191] Endless combinations of six-membered structures can be envisioned from substituents located on the dienes and dienophiles, with control of stereochemistry promoted by Lewis-acid catalysts. Five-membered rings can be prepared from one of the many forms via 1,3-dipolar cycloadditions.[192] Similarly, four-membered rings can be prepared from a pair of 2π partners.[193] Seven-membered rings methods have been developed from [4+3] cycloaddition methods.[194] Efficient construction of eight- and nine-membered ring system via cycloaddition are more difficult, and few methods are available for their synthesis.

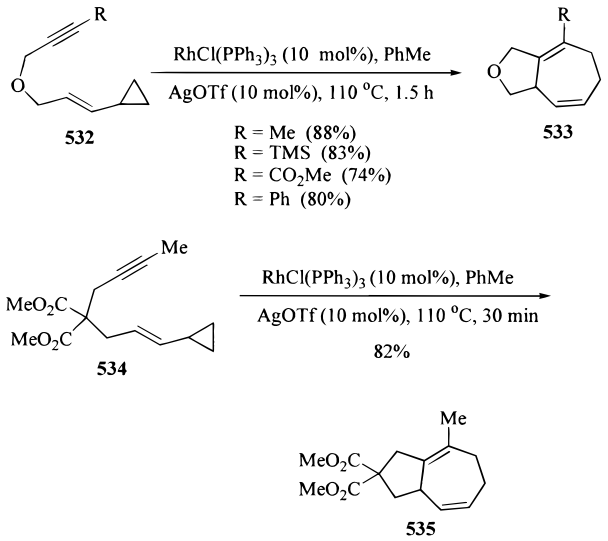
Transition metal-mediated cycloaddition reactions have become a standard method in modern synthetic organic chemistry, and methodology will continue in this direction. Transition metals present new opportunities for highly selective cycloaddition processes since complexation of a metal to unactivated olefins, dienes, or acetylenes modifies the reactivity of these groups and new reactivities are seen. Cycloaddition processes stand out for their ability to provide medium-sized rings in a single step from simple fragments and offer an alternative pathway to previous conventional methods. Recent advances in several areas will be presented below.

8.1. Seven-Membered Ring Formations

8.1.1. [5+2] Cycloadditions

Wender carried out the first studies of transition metal-catalyzed [5+2] cycloadditions of vinylcyclopropanes and alkynes as homologues of the Diels−Alder reaction for the synthesis of seven-membered rings.[195] Enyne ether **532** and enyne diester **534**, in the presence of catalytic Wilkinson's catalyst and silver(I) triflate in refluxing toluene, participated in the thermal cycloaddition to give functionalized cycloheptadienes **533** and **535**, respectively (Scheme 169). Mechanistically, the formation of metallacyclo-

Scheme 169



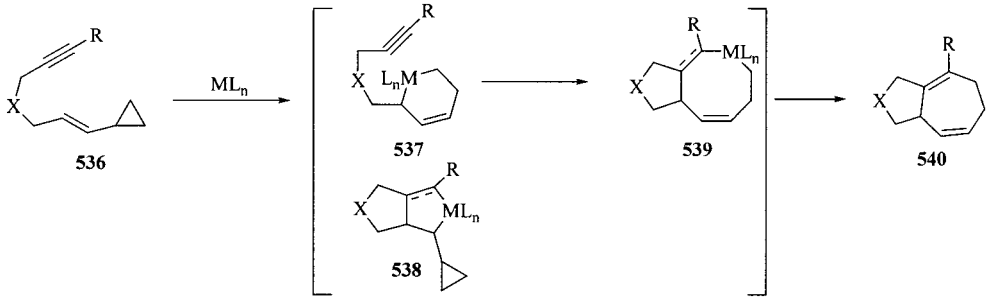
pentane **537** or metallacycle **538** from vincyclopropane **536** could be rationalized as outlined in Scheme 170. Metallacyclopentane **537** ring expands to a metallacyclooctadiene **539**, and reductive elimination provides the seven-membered cycloadduct **540**.

Wender showed that this reaction is also feasible for intramolecular [5+2] cycloadditions of alkenes and vinylcyclopropanes **541** to *cis*-fused bicycloheptenes **542** (Scheme 171).[196] Recently, it has been found that catalyst $[Rh(CO)_2Cl]_2$ has higher reactivity relative to Wilkinson's catalyst and may possibly be attributed to both electronic and steric differences, which enhances the utility of these types of cycloadditions.

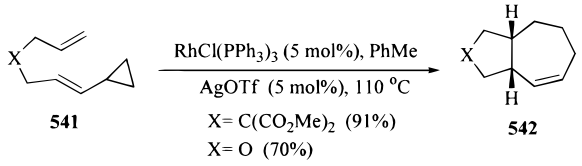
Wender also showed the transition metal-catalyzed [5+2] cycloaddition of allenes and vinylcyclopropanes.[197] Allene **543** on exposure to the rhodium catalyst gave cycloadduct **544** with a cis/trans junction mixture in a 1.1:1.0 ratio (Scheme 172). However, *tert*-butyl allene **545** afforded bicyclic diene **546** as a single diastereomer with Wilkinson's catalyst. Substrate **547** bearing a nitrogen tether cyclized efficiently in the presence of Wilkinson's catalyst to give **548** as a single diastereomer. Wender recently showed the asymmetric synthesis of (+)-dictamnol (**551**) from the [5+2] cycloaddition of allene **549** to yield bicyclic diene **550** (Scheme 173).

Wender expanded these types of reactions to the transition metal-catalyzed intermolecular [5+2] cycloaddition, a homologue of the Diels−Alder cycload-

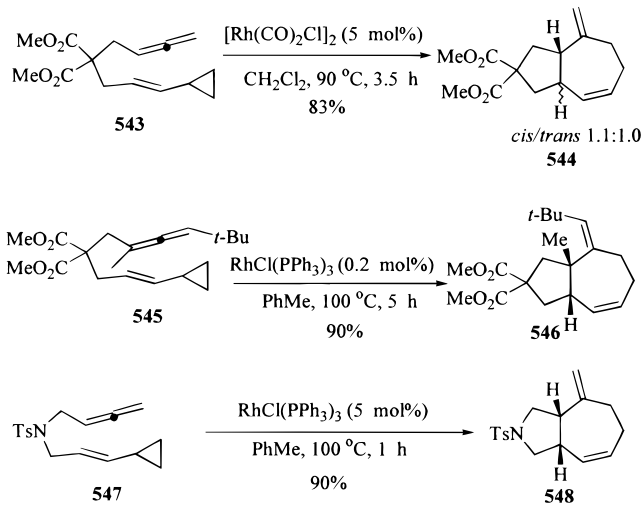
Scheme 170



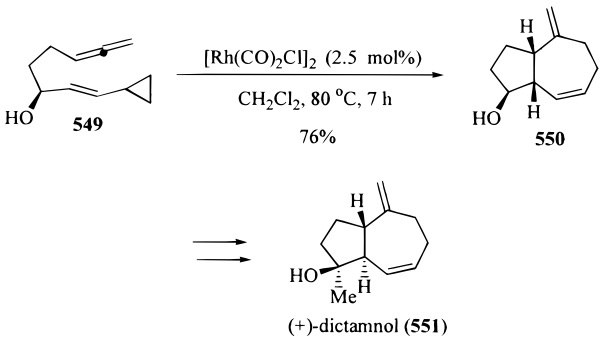
Scheme 171



Scheme 172



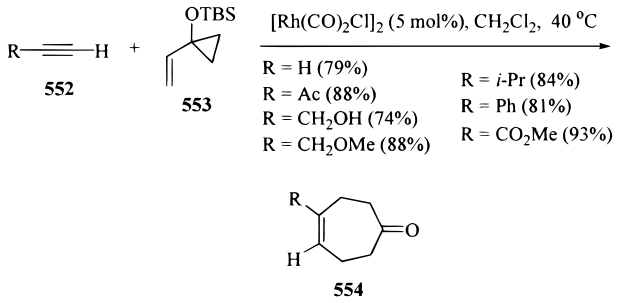
Scheme 173



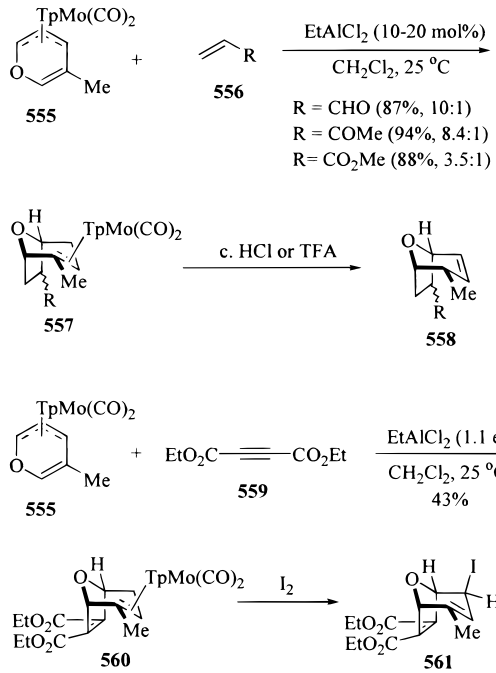
dition.[198] Alkynes **552** and silyloxycyclopropane **553** participated in an intermolecular [5+2] cycloaddition with catalyst $[Rh(CO)_2Cl]_2$ to give various cycloheptenones **554** in good to excellent yields (Scheme 174). Electron-rich and electron-poor alkynes, even acetylene itself, were found to provide cycloadducts.

Liebeskind recently reported an enantiocontrolled [5+2] cycloadditions of η^3-pyranylmolybdenum π-complex **555** with α,β-unsaturated systems **556** in the presence of a Lewis acid to give bicyclic complexes **557** in various *exo*/*endo* ratios (Scheme 175).[199] Reaction of complexes **557** with acid furnished substituted

Scheme 174



Scheme 175



oxabicyclo[3.2.1]octenes **558**. Similarly, complex **555** reacted with diethylacetylenedicarboxylate (**559**) to give bicyclic complex **560,** which was demetalated in the presence of excess iodine to provide iodo compound **561**.

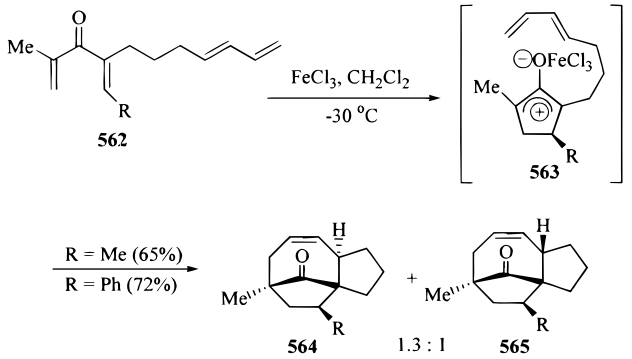
8.1.2. [4+3] Cycloadditions

Excellent reviews were recently written by Harmata and Rigby on the [4+3] intramolecular cycloadditions of allylic cations.[194,200] Most of these reactions occurred in the presence of Lewis-acid catalyst. Relatively few methods are available for formation of seven-membered ring formations via metal-catalyzed cycloadditions. Palladium-catalyzed [4+3] cy-

cloaddition of trimethylenemethane (TMM) to electron-deficient olefins has been discussed in section 7.5.

West showed a novel cycloisomerization of tetraenones. The Nazarov oxyallyl cations **563** intermediate formed from reaction of tetraenones **562** with ferric chloride participated in [4+3] cycloadditions to give cycloadducts **564** and **565** in a 1.3:1 ratio (Scheme 176).[201]

Scheme 176

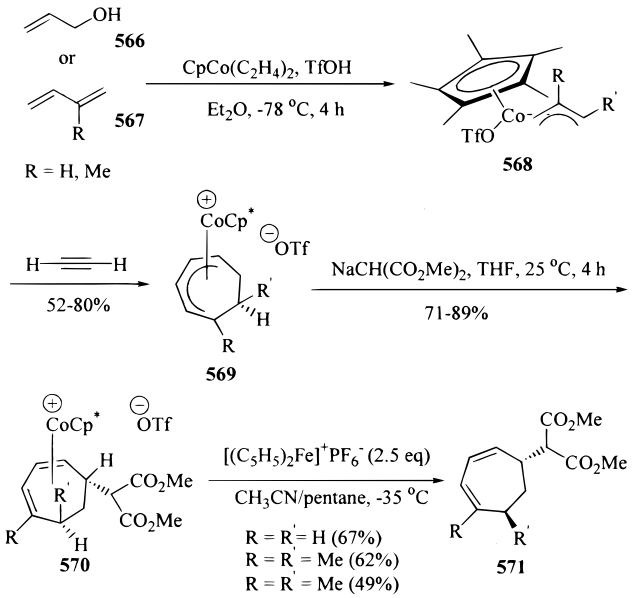


8.1.3. Miscellaneous Cycloadditions

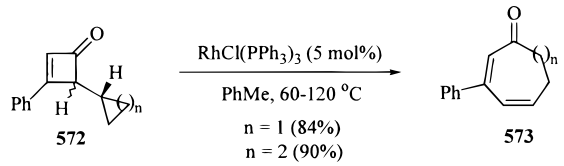
Stryker recently reported a cobalt-mediated intermolecular allyl/alkyne [3+2+2] cycloaddition reaction in the synthesis of functionalized seven-membered rings.[202] The allyl triflate complexes **568** are generated from allyl alcohol (**566**) or 1,3-dienes **567** (Scheme 177). Reaction of **568** with acetylene gave η^5-cycloheptadienyl complexes **569,** which were reacted with sodium dimethylmalonate in a nucleophilic alkylation to give functionalized diene complexes **570** with complete stereoselectivity. Demetalation of **570** with ferricenium salts in a biphasic mixture furnished cycloheptadienes **571**.

Liebeskind reported a rhodium(I)-catalyzed intramolecular carbocyclic ring-enlargement reaction of 4-cycloalkyl-2-cyclobutenones **572** to give cyclohepta- or cycloocta-2,4-dienones **573** (Scheme 178).[203]

Scheme 177

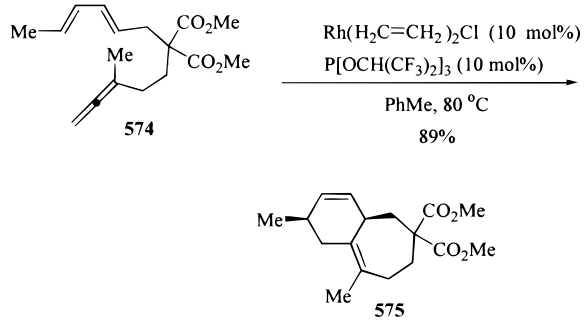


Scheme 178



Wender reported an unprecedented rhodium-catalyzed intramolecular [4+2] diene−allene cycloaddition, in which there is a five atom tether between the reactive subunits. This provided access to the BC ring system of molecules, such as a phorbol and resiniferatoxin.[204] Diene−allene **574** provided bicycloheptadiene **575** in a chemoselective and stereoselective manner (Scheme 179).

Scheme 179



Murai described a novel, one-step entry to unprecedented polycyclic ring systems from acyclic starting substrates.[205] Transition metal-catalyzed cycloisomerization of dienyne **576** through bis-cyclopentametallacycle **578** to bicyclic intermediate **579** gave tetracyclic ester **577** as a single diastereomer (Scheme 180). Other transition metal complexes show catalytic activity for this very complex transformation.

Oshima found that treatment of diyne **580** with triallylmanganate provided seven-membered bicyclic products **581** and **582** and six-membered bicyclic product **583** in various yields (Scheme 181).[206] This organomanganate complex assisted cycloaddition reaction suggested the possibility of a new and unprecedented reactivity pattern from manganese reagents, as part of the allylic group in the metal can be used to construct the resulting bicyclic product.

8.2. Eight-Membered Ring Formations

8.2.1. [4+4] Cycloadditions

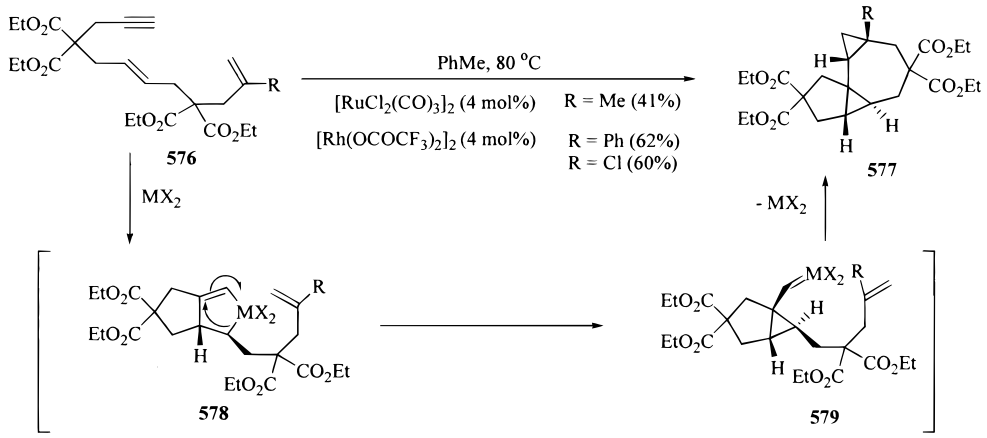
Sieburth wrote a very recent review on the [4+4] cycloaddition reaction and its strategic application in natural products synthesis.[207] This section covers advances since 1996.

Wender utilized an intramolecular [4+4] cycloaddition strategy for the efficient synthesis of dicyclopenta[*a*,*d*]cyclooctene 5,8,5-ring system.[208] Cycloaddition of bis-diene **584** with nickel catalyst and triphenylphosphine in toluene gave, after desilylation, cycloadduct **585**, which was elaborated to tricycle **586** possessing five of the seven stereogenic centers of ophiobolin F (Scheme 182).

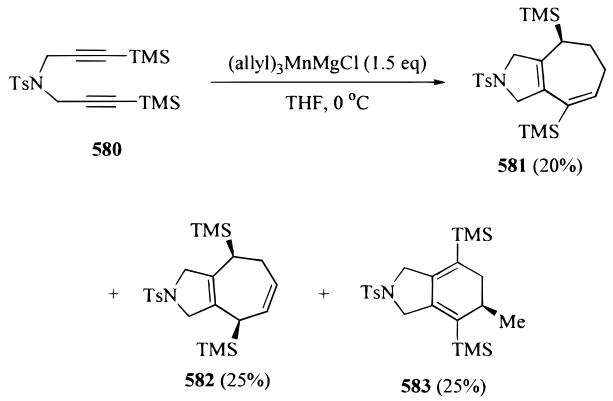
8.2.2. [4+2+2] Cycloadditions

The enantioselective [4+2+2] cycloaddition of norbornadiene (NBD, **587**) and substituted 1,3-buta-

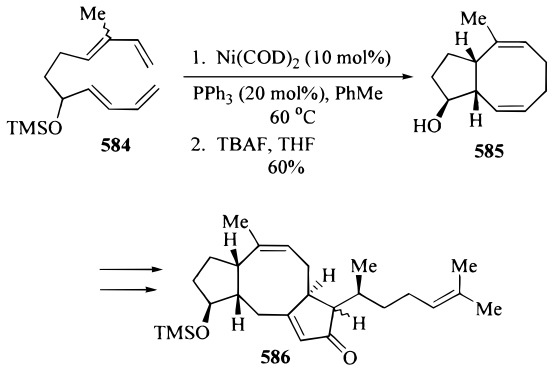
Scheme 180



Scheme 181



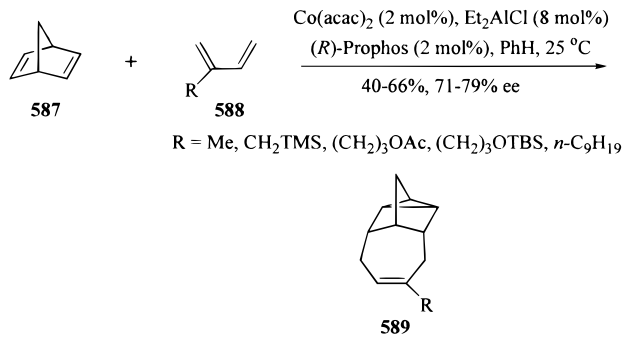
Scheme 182



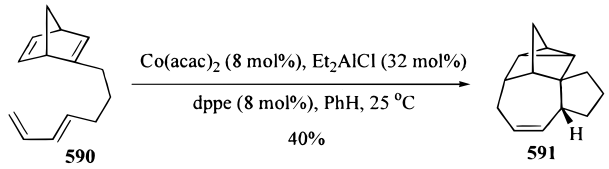
dienes **588** to give cycloadducts **589**, with cobalt catalyst in the presence of a chiral phosphine ligand and reducing agent, was developed by Lautens (Scheme 183).[209a] These catalytic conditions gave good ee's and avoided possible products arising from [2+2+2] cycloadditions and dimerizations. These cycloadducts serve as versatile intermediates to bicyclic products of various classes of natural products, based on strategic cleavage of the bonds of **589**. Lautens also reported the first example of the intramolecular [4+2+2] cycloaddition of tetraene **590** to give cycloadduct **591** in moderate yield (Scheme 184).[209b]

Synder recently did a comprehensive study of the best conditions for the [4+2+2] cycloadditions of NBD (**587**) with 1,3-butadiene (**592**) to give cycloadduct **593** (Scheme 185).[210] He found that cobalt(II) iodide

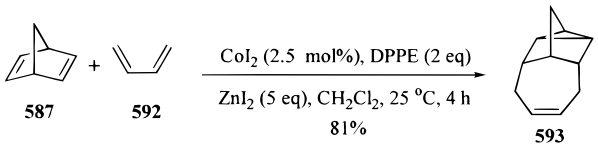
Scheme 183



Scheme 184

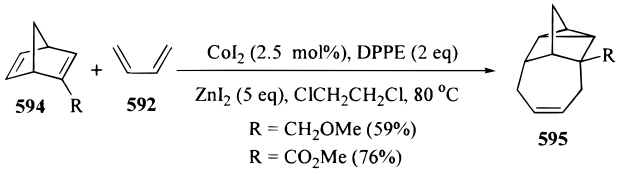


Scheme 185



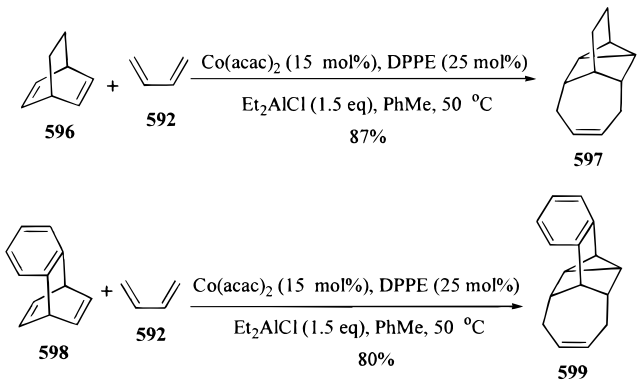
with additives such as zinc iodide and phosphorus ligand, dppe, provided the best yields. This was further examined with substituted NBDs **594** with 1,3-butadiene (**592**) to give cycloadducts **595** with excellent regioselectivity (Scheme 186). Synder also

Scheme 186



reported the first transition metal-catalyzed cycloadditions of bicyclo[2.2.2]ocatadienes **596** and **598** with 1,3-butadiene (**592**) to give cycloadducts **597** and **599**, respectively (Scheme 187).[211]

Scheme 187



8.2.3. [6+2] Cycloadditions

Higher-order cycloadditions such as chromium(0)-promoted [6+2] reactions are not presented since a very recent review was written by Rigby.[212]

8.3. Nine-Membered Ring Formation

Ito reported a single-step construction of a nine-membered carbocycle by a new novel [4+4+1] cycloaddition.[213] Vinylallenes **600**, in the presence of carbon monoxide in a palladium-catalyzed reaction at ambient temperature, gave carbocycles **601** (Scheme 188). Vinylallenes **600** coupled at the 1-position in a head-to-head manner to give palladacyclopentenes **602**, which coupled with the second equivalent of vinylallene intermediates **603**. Incorporation of carbon monoxide to **603** afforded complexes **604** with regeneration of the palladium catalyst to furnish carbocycle **601**.

9. Metal-Promoted Carbenoid Annulations

The reactivity of carbene complexes has been extensively studied as an organometallic curiosity and in the last 20 years has been employed in useful and general transformations.[214] The attractive features of these carbene complexes are that they can be fine-tuned to control the stereochemical outcome of the reaction at several centers. The gain from entropy, reactivity, and diastereoselectivity of these intramolecular and intermolecular cyclizations offers advantages over other methodologies. Prime examples are the Grubbs' ruthenium catalysts and Schrock's molybdenum catalyst used for ring-closing metathesis reactions discussed in Section 2.

9.1. Fischer Carbene Complexes Annulations

Chromium−, molybdenum−, and tungsten−carbene complexes have been exploited the most heavily in organic synthesis. The relevant use of these complexes as applied to methodology of medium-sized rings will be reviewed in this section.

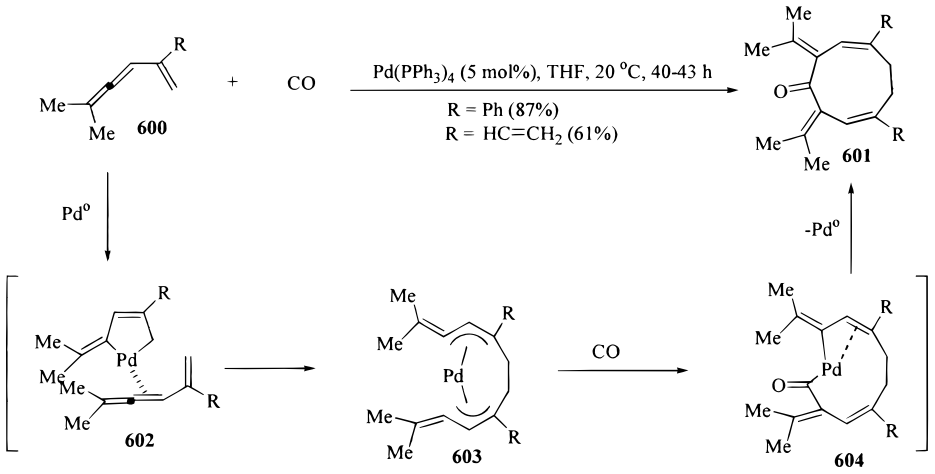
9.1.1. Intermolecular Fischer Carbene Annulations

Barluenga investigated the enantioselective synthesis of seven-membered carbocycles from 2-amino-1,3-butadienes and vinyl chromium Fischer-type carbenes.[215] Chiral 2-amino-1,3-butadienes **605** and vinyl chromium carbene complexes **606** reacted to give cycloheptadienes **607** via a tandem cyclopropanation/Cope rearrangement process (Scheme 189). Hydrolysis of **607** afforded chiral cycloheptenones **608** in moderate to good yields with good enantioselectivities. Barluenga also showed that azadienes **609** could react with chromium carbene complexes **610** to give substituted 5*H*-6,7-dihydroazepines **611** stereoselectively (Scheme 190).[216]

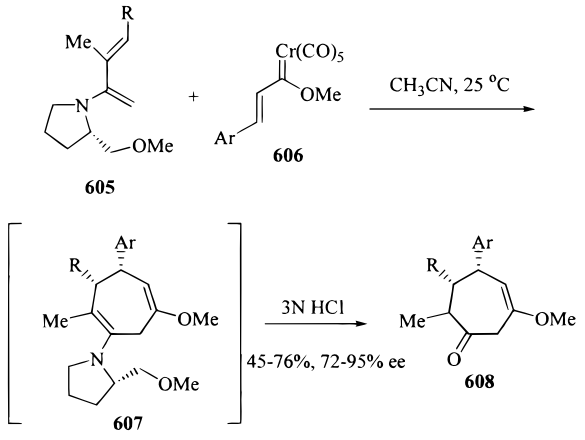
Herndon prepared seven-membered rings by the reaction of cyclopropylcarbene−tungsten and −molybdenum complexes with alkynes.[217] Molybdenum carbene **612** reacted with 1,2-diphenylacetylene (**613**) in refluxing tetrahydrofuran to give cycloheptadienone **614** in good yield (Scheme 191). However, tungsten complex **615**, in the presence of **613** in refluxing xylene, gave cycloheptadienone **616**. The reactions were dependent on solvent conditions, phosphorus additives, type of carbene complexes, and temperature conditions.

Mori reported a synthesis of lactones from alkynols.[218] 5-Hexyn-1-ol (**617**) reacted with chromium carbene complex **618** to give lactone **621** (Scheme 192). The reaction is believed to proceed through vinyl carbene intermediate **619,** which underwent carbon monoxide insertion to give ketene **620**. Intramolecular reaction of the alcohol with the ketene **620**, followed by decomplexation and hydrolysis, furnished lactone **621**.

Scheme 188

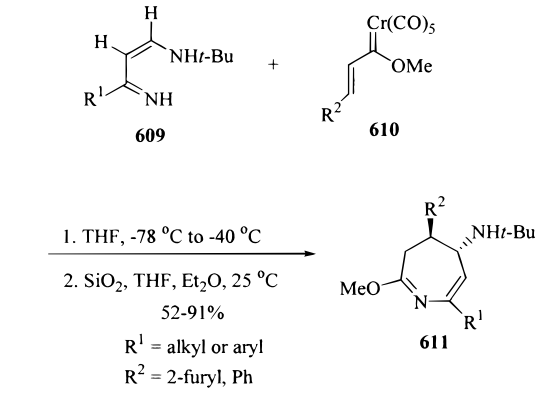


Scheme 189

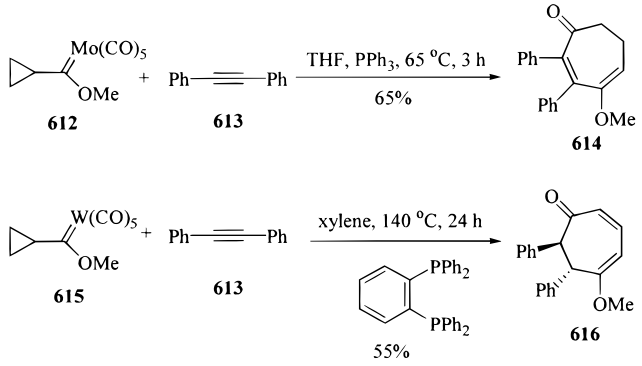


R = CH_2OH, CH_2OBn, CH_2OMe
R = Ph, 2-Furyl

Scheme 190



Scheme 191

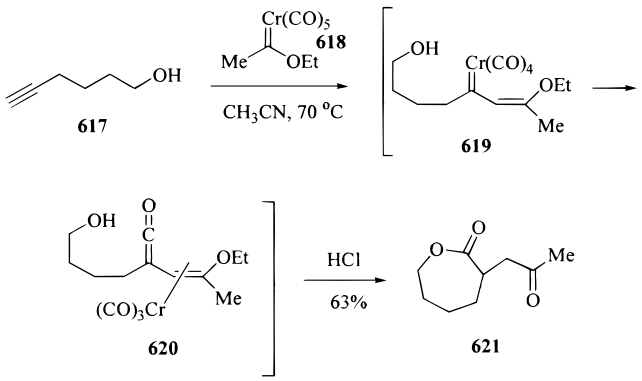


Chromium complex **622** reacted with 5-hexyn-1-ol (**617**), followed by triphenylphosphine/DEAD, to yield diastereomerically pure complex **623** (Scheme 193).[219] Decomplexation of **623** with oxygen in the presence of light afforded tetracyclic oxepin **624**.

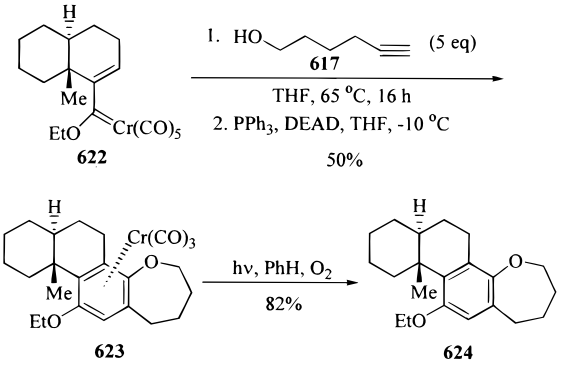
9.1.2. Intramolecular Fischer Carbene Annulations

Harvey showed that dienyne **625** reacted with carbene complexes **626** to give divinylcyclopropanes **627**, which underwent [3,3]-sigmatropic rearrangement to produce hexahydroazulenes **628** (Scheme 194).[220] The molybdenum carbenes **626** gave higher yields and favored cis products than chromium carbenes **626**, which gave lower yields with predominant trans stereochemistries. Hoye did a similar reaction

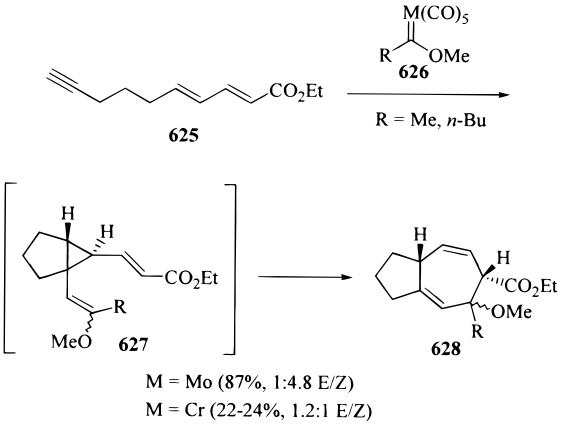
Scheme 192



Scheme 193



Scheme 194



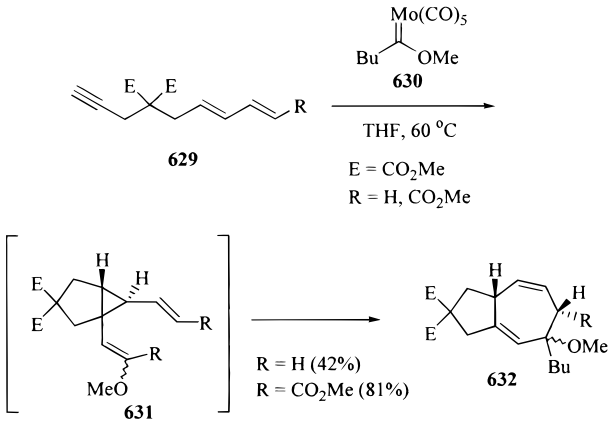
M = Mo (87%, 1:4.8 E/Z)
M = Cr (22-24%, 1.2:1 E/Z)

with *gem*-carbomethoxy substituents situated on the tether between the alkyne and alkene.[221] Reaction of diynes **629** with molybdenum complex **630** gave divinylcyclopropanes **631**, which afforded hexahydroazulenes **632** (Scheme 195). A carbomethoxy group on the terminal alkene was crucial to a higher yield as the unsubstituted terminal alkene resulted in a lower yield. The electron-withdrawing substituent on the diene appears to activate the alkene component toward coordination to the metal.

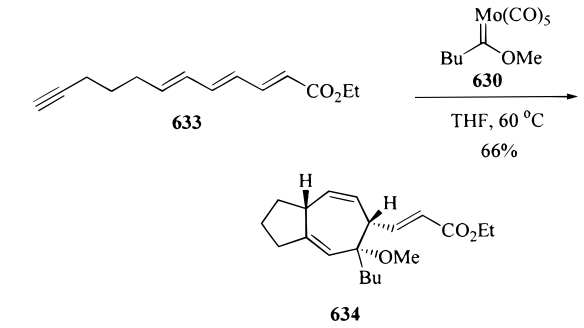
Harvey also investigated the influence of an additional olefinic functionality in the substrate.[222] Trienyne **633** cyclized to give hexahydroazulene **634** as single diastereomer with molybdenum carbene complex **630** (Scheme 196). He found that the analogous chromium complex gave a different product with an alternate pathway.

It has been reported that attachment of an appropriately functionalized enyne or dienyne to a

Scheme 195

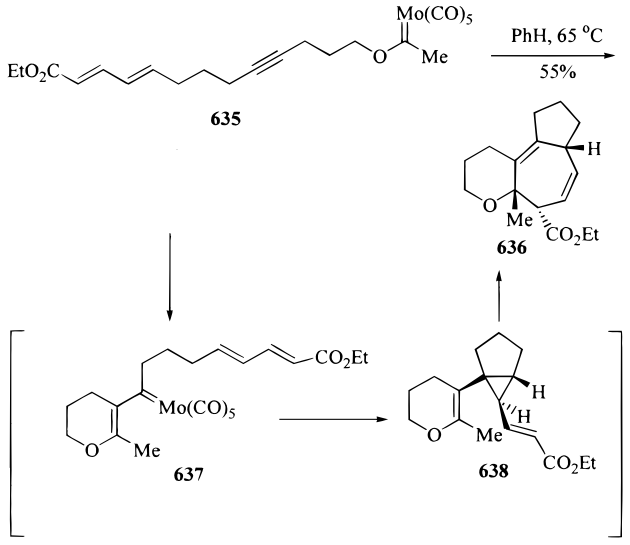


Scheme 196



carbene complex would provide access to polycyclic frameworks via an all-intramolecular cyclization reaction.[223] Also, ester substituents have been found to activate 1,3-dienes toward cyclopropanation. Thermolysis of dienyne complex **635** produced tricyclic ether **636** (Scheme 197). Tricyclic ether **636** is

Scheme 197



believed to be produced via in situ generation of vinyl carbene complex **637**, followed by tandem cyclopropanation/cope rearrangement of **638**.

9.2. Rhodium- and Copper-Catalyzed Carbenoid Annulations

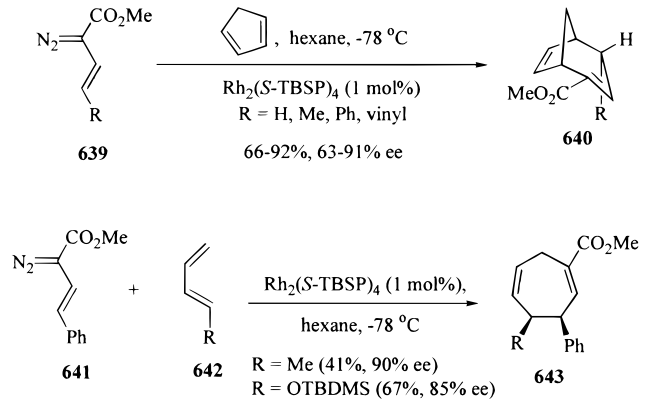
The transition metal-catalyzed reactions of diazo compounds have been available over the last 80 years, but only in the past decade or so has it been used widely as a methodology in natural products synthesis.[224] Copper-based catalysts, which still are widely used, have been replaced by rhodium(II) carboxylates as the catalysts of choice for the decomposition of diazocarbonyl compounds. Synthetically useful transformations such as cyclopropanation, carbon−hydrogen and heteroatom-hydrogen insertions, and ylide formations have been the major uses of these rhodium(II) catalysts. This sections focuses on recent uses of these catalysts with some examples of copper catalysts where appropriate in medium-sized rings methodology and its applications to natural product synthesis.

9.2.1. Intermolecular Rhodium Carbenoid Annulations

Davies wrote a review on the use of the rhodium-(II)-catalyzed tandem cyclopropanation/Cope rearrangement in the synthesis of seven-membered rings in 1993.[225] This review will document examples from the literature since that report.

Davies examined the asymmetric synthesis of 1,4-cycloheptadienes of the tandem cyclopropanation/Cope rearrangement between vinyldiazomethanes and dienes.[226] In the first studies, vinyldiazomethanes **639** reacted with cyclopentadiene in the presence of chiral rhodium catalyst, Rh_2(*S*-TBSP)$_4$, to give bicyclo-[3.2.1]octadienes **640** in good yields and reasonable enantioselectivities (Scheme 198).[225] The choice of

Scheme 198

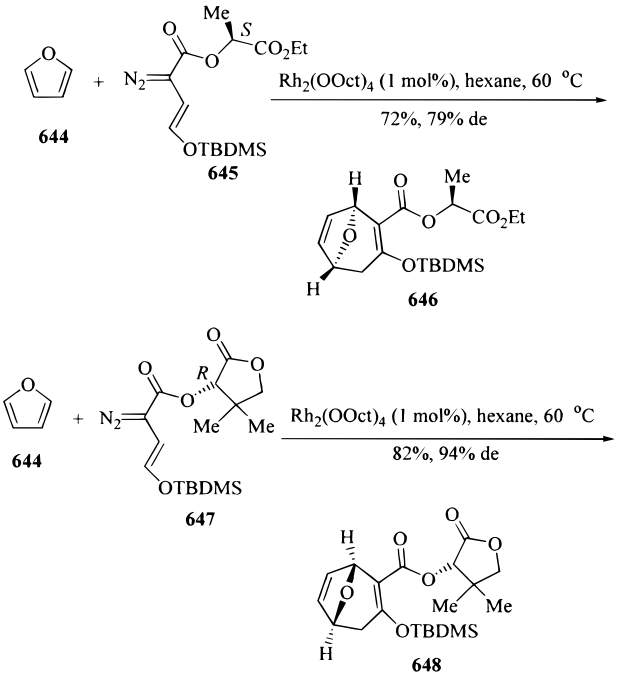


nonpolar solvent such as hexane and low temperatures had a marked effect on enantioselectivities. Vinyldiazomethane **641** reacted with dienes **642** to give 1,4-cycloheptadienes **643** with good enantioselectivities. In addition to absolute stereocontrol, these reactions proceed with excellent control of regiochemistry and relative stereochemistry. In a more detailed study, it was found that chiral catalyst, Rh_2(*S*-DOSP)$_4$, gave better yields and consistent enantiomeric excesses greater than 90% over a wider range of substrates.

Davies further developed the reaction of furans and vinyldiazomethanes in the asymmetric syntheses of highly functionalized 8-oxabicyclo[3.2.1]octene derivatives.[227] These oxabicyclic products are versatile intermediates in organic synthesis. Various chiral rhodium(II) catalysts were employed, but rhodium-(II) octanoate was found to be the best choice. The

best yields and asymmetric inductions were achieved by the judicious use of the chiral auxiliary on the carbenoid. Vinyldiazomethane **645** with the *S*-lactate chiral auxiliary in the presence of furan (**644**) under rhodium(II)-catalyzed decomposition gave oxobicyclo-[3.2.1]octene **646** in good yield and diastereoselectivity (Scheme 199). Furthermore, vinyldiazomethane

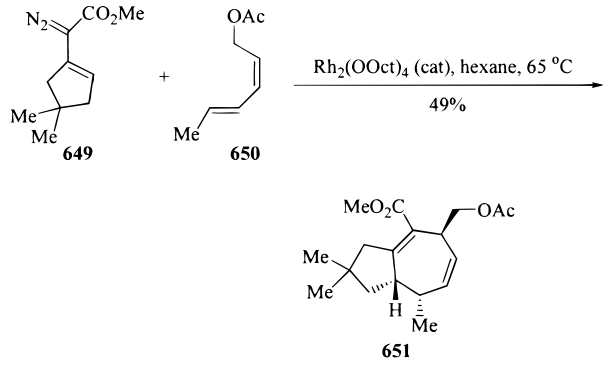
Scheme 199



647 with the *R*-pentolactone auxiliary in the presence of **644** gave oxobicyclo[3.2.1]octene **648** in excellent yield and diastereoselectivity.

Davies utilized the tandem cyclopropanation/Cope rearrangement of vinyldiazoacetate **649** in the presence of excess diene **650** to give cycloheptadiene **651** as an intermediate in the total synthesis of (±)-tremulenolide A and (±)-tremulenediol A (Scheme 200).[228a] In similar studies, intramolecular cyclopro-

Scheme 200

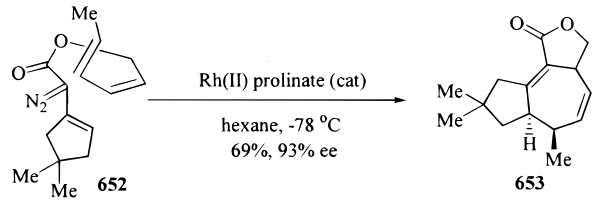


panation/Cope rearrangement of diazoester **652** in the presence of a chiral rhodium(II) prolinate resulted in the formation of tricyclic lactone **653** with the wrong stereochemistry (Scheme 201).[228b]

9.2.2. Intramolecular Rhodium and Copper Carbenoid Annulations

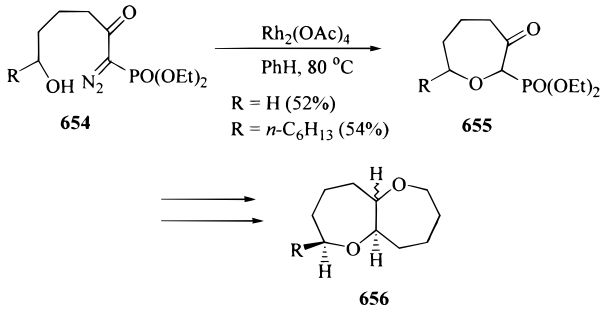
The rhodium(II)-catalyzed decomposition of diazoketones has been useful in the synthesis of medium-

Scheme 201



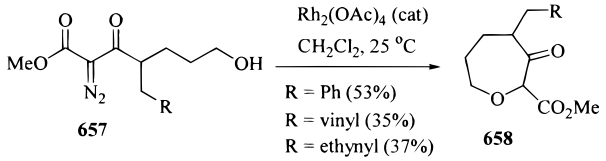
sized cyclic ethers prevalent in many natural products. Moody utilized the rhodium carbenoid cyclization of diazophosphonates **654** to afford keto phosphonates **655**, which were elaborated to bicyclic ethers **656** (Scheme 202).[229]

Scheme 202



Padwa investigated the chemoselectivity of rhodium carbenoids on the decomposition of diazoketoesters **657** to give oxepanes **658** (Scheme 203).[230]

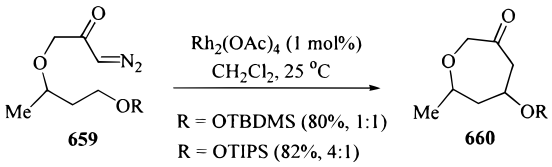
Scheme 203



Preference of O−H insertion was favored over attack on the π-bonds.

Lee found that the use of a silicon-directing group influences the carbon−hydrogen insertion products of diazo ketones **659** to give cyclic ethers **660** (Scheme 204).[231] In the presence of a benzyl ether, rhodium-

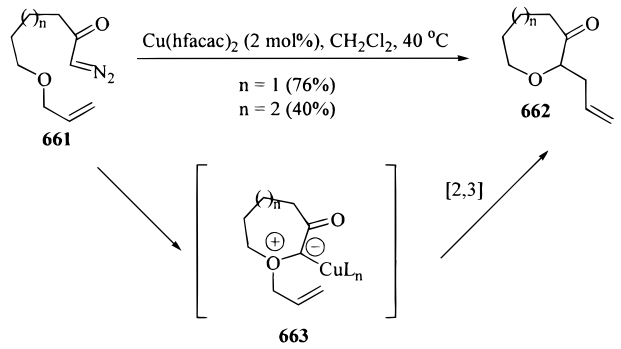
Scheme 204



(II)-catalyzed decomposition of **659** gave furan ring products. The electron effect of the silicon atom overrode the usual conformational preference of five-membered ring formation.

The tandem oxonium ylide formation-[2,3]-sigmatropic rearrangement sequences has been useful in the synthesis of medium-sized ethers. Treatment of allyl ethers **661** in the presence of catalytic copper-(II) catalyst gave cyclic ethers **662** (Scheme 205) via oxonium ylide intermediate **663**.[232] This reaction in

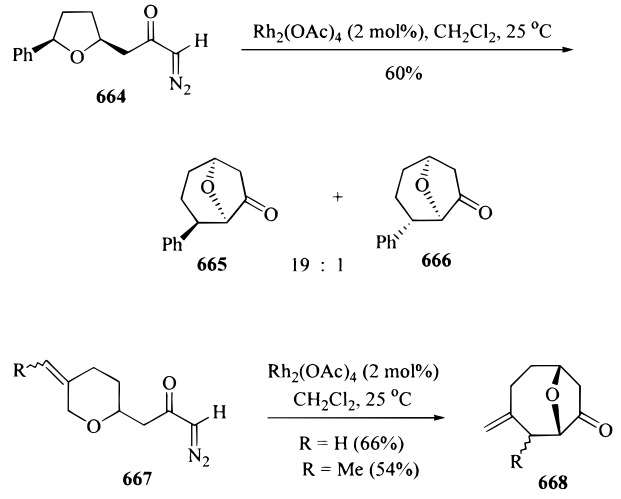
Scheme 205



the presence of rhodium(II) catalysts did not afford any of the cyclic ether products.

West showed that fused bicyclic oxonium ylides, generated by reaction of rhodium(II) catalyst with cyclic ethers bearing a tethered diazo ketone, can undergo [1,2]- or [2,3]-shifts to give *O*-bridged seven- or eight-membered carbocycles.[233] Thus, cyclic ether **664** gave seven-membered cyclic ethers **665** and **666** in a 19:1 ratio (Scheme 206) via [1,2]-shift after

Scheme 206



oxonium ylide formation. Similarly, cyclic ether **667** gave eight-membered bridged ether **668** via [2,3]-shift of the oxonium ylide intermediate.

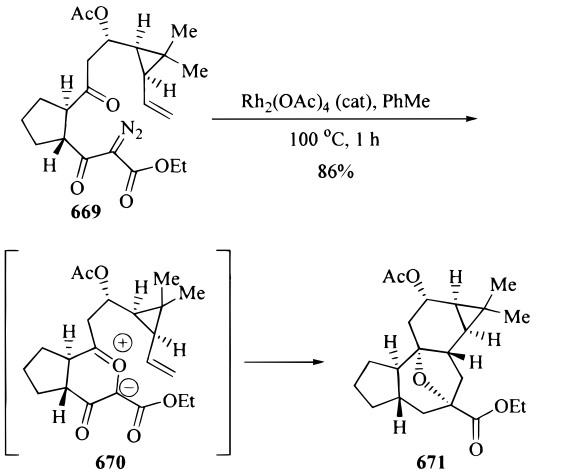
The intramolecular trapping of a carbonyl ylide with an alkene represents an effective method for the synthesis of novel *O*-bridged polycyclic system. Dauben applied the rhodium(II)-catalyzed decomposition of diazo ester **669** to give pentacyclic ether **671** via carbonyl ylide **670** as part of studies toward the tigliane ring system (Scheme 207).[234]

McMills utilized diazo ketone **672** to form a phorbol analogue devoid of oxygenation to tricyclic ether **673** (Scheme 208).[235]

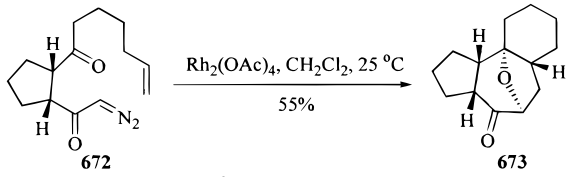
Padwa showed that rhodium(II)-catalyzed decomposition of diazo ketone **674** in the presence of *N*-phenyl maleimide gave epoxycycloheptapyrrole **675** via intermediate **676**, which is converted to carbonyl ylide **677** with subsequent trapping of the dipolarophile (Scheme 209).[236]

Padwa showed that intramolecular trapping of a carbonyl ylide dipoles is a useful method for synthesizing polycyclic heterocycles.[237] Diazo ketone **678** in

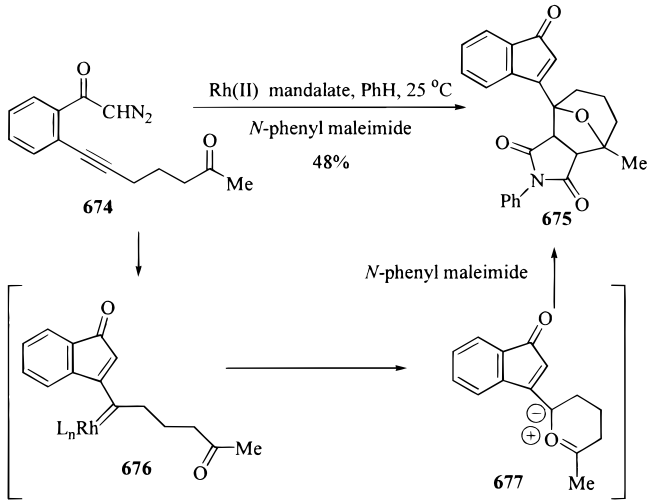
Scheme 207



Scheme 208



Scheme 209

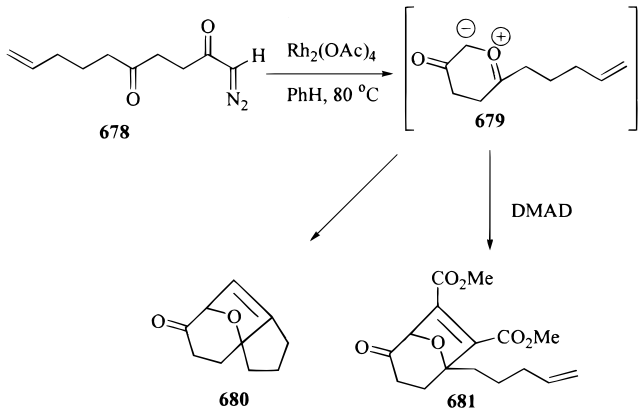


the presence of rhodium(II) acetate and dimethylacetylene dicarboxylate (DMAD) gave cycloadduct **681** as the only product via carbonyl ylide **679** (Scheme 210). Without DMAD present, intramolecular cyclization with the alkene tether afforded tricyclic ether **680**. Padwa also reported that α-diazo ketoamide **682** is sufficiently resonance-stabilized by the carbonyl ylide to be trapped by DMAD to give cycloadduct **683** (Scheme 211).[238]

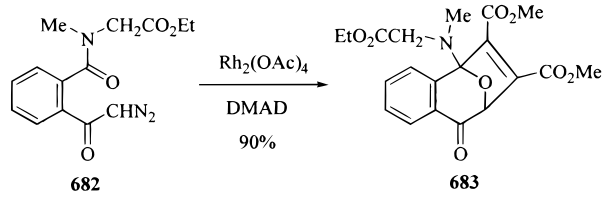
Padwa employed diazo ketone **684** in the rhodium(II) acetate decomposition reaction to give cycloadduct **685** in a tandem cyclization−cycloaddition reaction as model studies toward (±)-ribasine (Scheme 212).[239]

The tandem cyclization−cycloaddition reaction with rhodium(II) catalyst has been applied to the core structure of zaragozic acid by the Merck Research group.[240] Diazo ester **686** cyclized smoothly in the presence of vinyloxytrimethylsilane (**687**) to give bicyclic core **688** of zaragozic acid in a single step

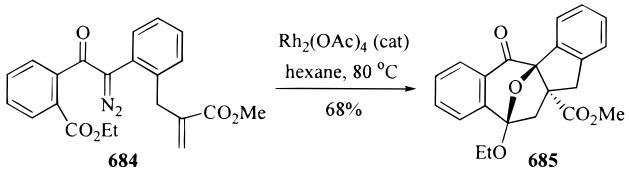
Scheme 210



Scheme 211

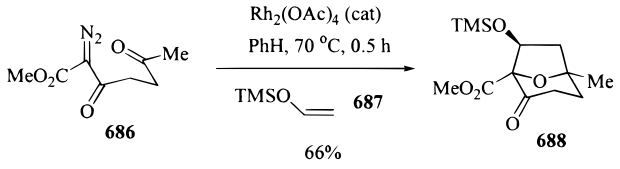


Scheme 212



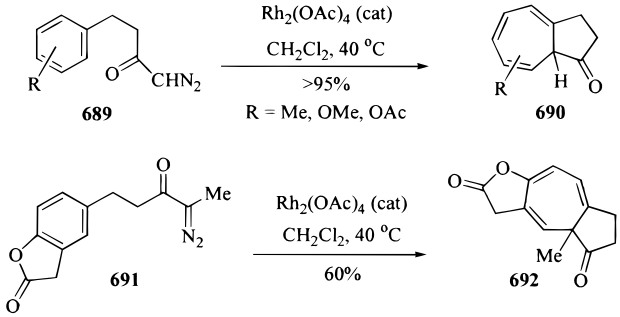
(Scheme 213). This cycloaddition represented the first examples of the use of vinyloxytrialkylsilanes as dipolarophiles.

Scheme 213



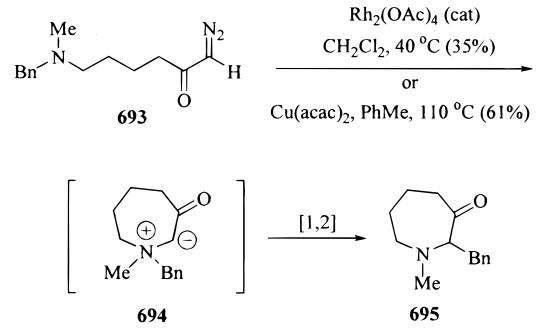
McKervey employed the rhodium(II)-catalyzed decomposition of 1-diazo-4-arylbutan-2-ones **689** to bicyclo[5.3.0]decanones **690** in high yields (Scheme 214).[241] This was then extended to cyclization of diazo ketone **691** to afford tricyclic lactone **692**.

Scheme 214



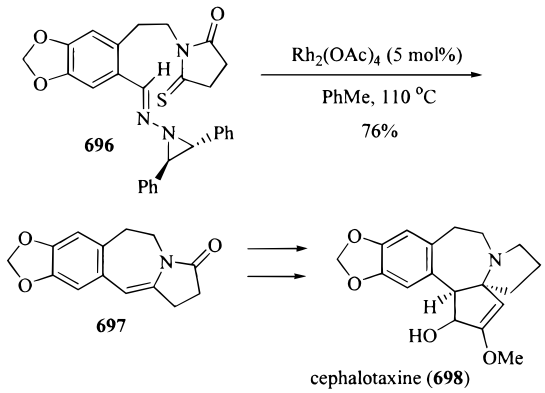
West also reported a route to substituted nitrogen heterocycles involving a [1,2]-shift of ammonium ylides.[242] Rhodium(II)-catalyzed decomposition of diazo ketone **693** generated ammonium ylide **694,** which after a [1,2]-shift gave cycloheptanone **695** (Scheme 215). Better results were obtained with the copper(II) catalyst in refluxing toluene.

Scheme 215



Thiocarbonyl ylides have been useful intermediates in a variety of reactions. Danishefsky employed the rhodium(II)-catalyzed decomposition of hydrazone **696** to give enamide **697** as part of the total synthesis of cephalotaxine (**698**, Scheme 216).[243] In the first

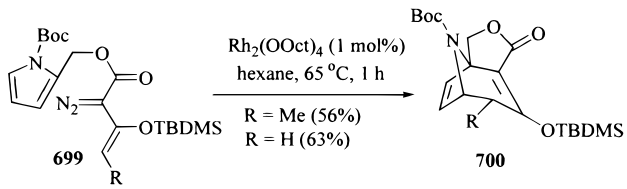
Scheme 216



step, hydrazone **696** loses *trans*-stilbene to give a transient diazo compound, which reacts with rhodium(II) acetate to produce a carbenoid species, which subsequently cyclizes to a thiocarbonyl ylide. Ring closure followed by rearrangement and desulfurization afforded enamide **697**.

Davies reported the intramolecular cyclization of vinylcarbenoids and pyrroles to give fused tropanes.[244] Rhodium(II)-catalyzed decomposition of vinyldiazomethanes **699** afforded fused tropones **700** (Scheme 217). The results of this reaction were not

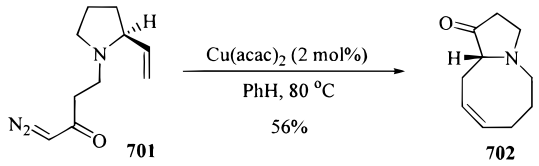
Scheme 217



consistent with the usual tandem cyclopropanation/Cope rearrangement pathway but followed the [3+4] annulation mechanism via a stepwise zwitterionic pathway.

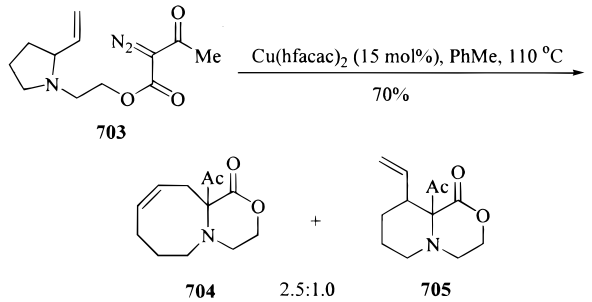
Two approaches to nitrogen heterocycles involving tandem ammonium ylide-formation−[2,3]-sigmatropic rearrangements with copper catalysts were reported recently. Clark disclosed the enantioselective copper-catalyzed decomposition of diazo ketone **701** to azabicyclo[6.3.0]undecane **702**, corresponding to the CE ring system of the alkaloids manzamine A, E, and F and ircinal A (Scheme 218).[245] The rhodium

Scheme 218



catalyst proved to be sluggish in these reactions. McMills also prepared azacyclooctene **704** and bicyclic **705** in a 2.5:1.0 ratio from α-diazoester **703**, respectively, from [2,3]-sigmatropic rearrangement and [1,2]-shifts of the intermediate ammonium ylides (Scheme 219).[246]

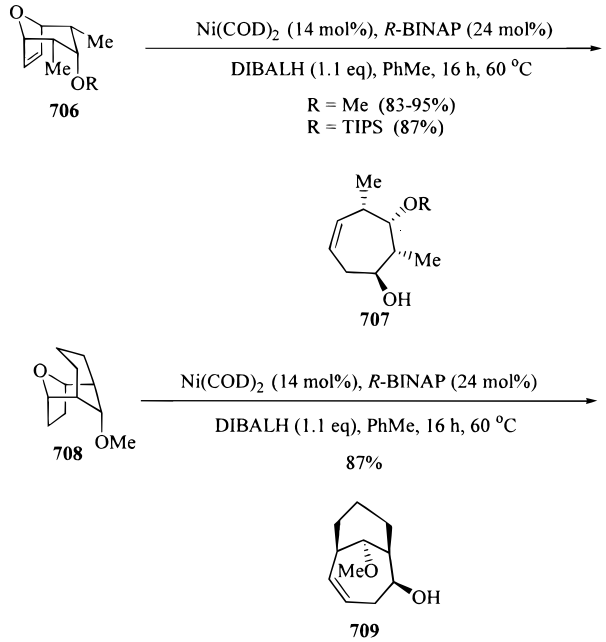
Scheme 219



10. Oxabicyclic Metal-Promoted Ring Openings

Lautens did extensive work on the oxabicyclic ring opening utilizing bases and Grignard reagents.[247] Reductive opening of symmetrical oxabicyclic ethers **706** with diisobutylaluminum hydride (DIBAHL), in

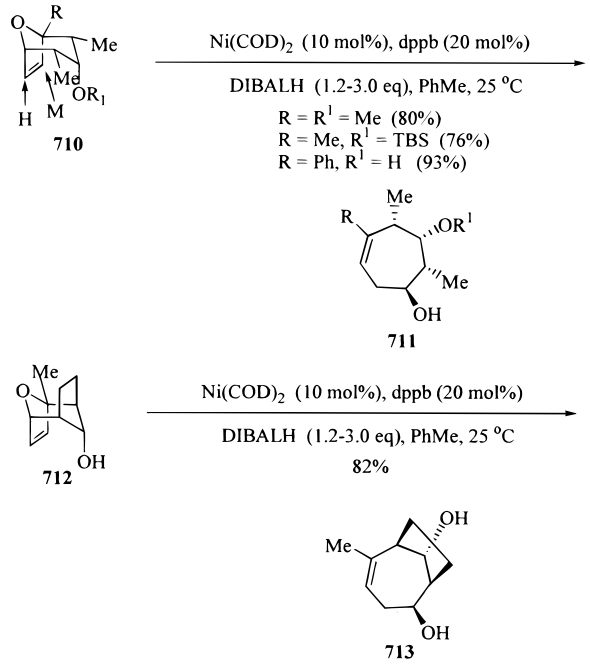
Scheme 220



the presence of catalytic nickel catalyst and *R*-BINAP reagent, gave cycloheptanols **707** in excellent yields and stereoselectivity (Scheme 220).[248] Application of the same conditions to **708** afforded bicyclic ether **709**.

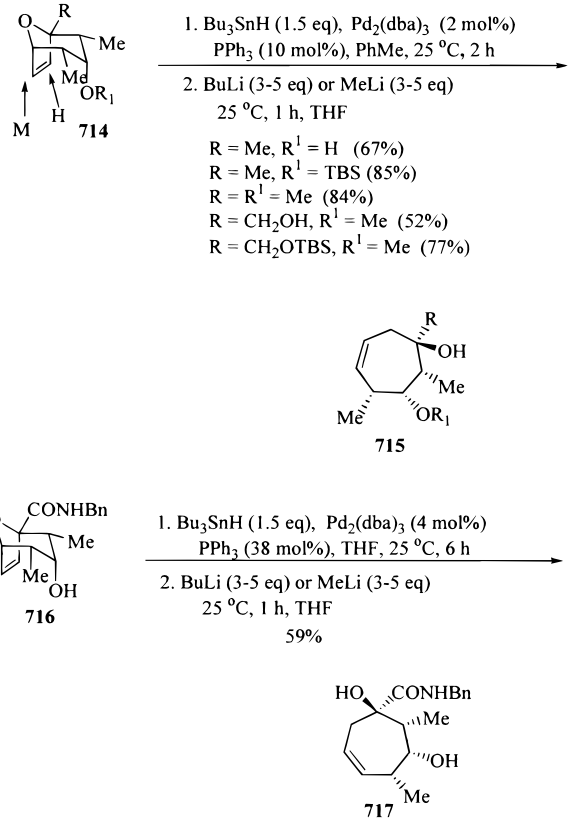
In unsymmetrical oxabicyclic ethers, the regioselective addition of the hydride can be controlled

Scheme 221



depending on the hydride source and catalyst employed. Using nickel catalyst, ligand, 1,4-bis(diphen-

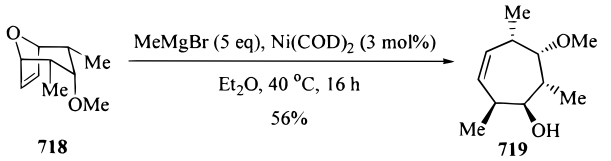
Scheme 222



ylphosphine)butane (dppb), and diisobutylaluminum hydride, addition to oxabicycles **710** furnished cycloheptanols **711** (Scheme 221).[249] Similarly, addition of the same reagents to oxatricycle **712** produced bicycloheptanol **713**. The application of palladium-catalyzed hydrostannylation/organolithium-induced elimination methodology can reverse the regiochemistry of addition of the hydride source. Application of these conditions to oxabicycles **714** and **716** generated tertiary cycloheptanols **715** and **717**, respectively (Scheme 222).

Grignard addition to oxabicyclic ether **718**, in the presence of nickel catalyst, gave cycloheptanol **719** (Scheme 223).[250]

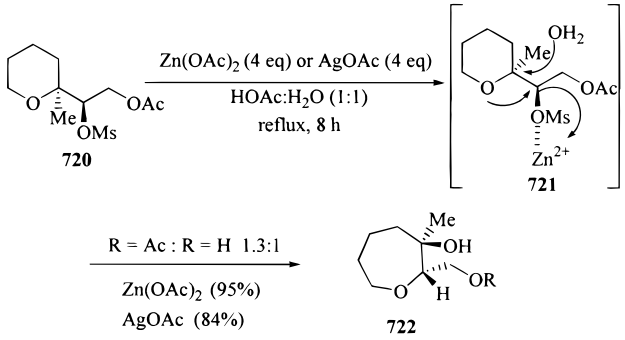
Scheme 223



11. Miscellaneous Methods

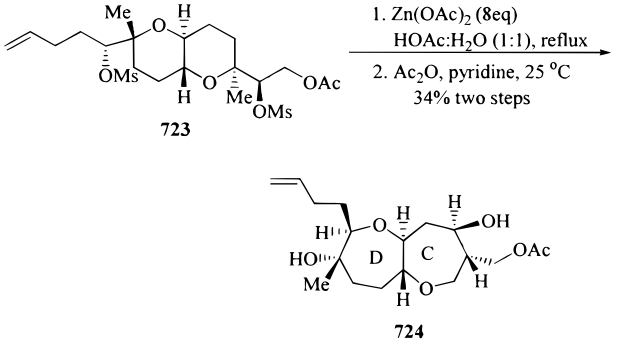
Mesylate **720** was stereoselectively rearranged and ring-expanded with zinc(II) acetate to the seven-membered cyclic ether **722** (Scheme 224).[251] The

Scheme 224



rearrangement took place stereospecifically giving a single isomer, which suggests that this reaction proceeded concertedly via **721**. Nakata further used this approach to effect a double rearrangement with simultaneous double ring expansion of 6,6-bicyclic ether **723** to the 7,7-bicyclic ether **724** corresponding to the C/D ring system of hemibrevetoxin B (Scheme 225).[252] This valuable intermediate serves as a compound for the eventual total synthesis. More recently,

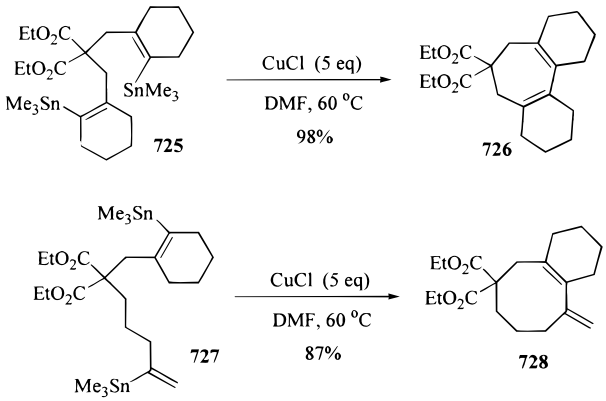
Scheme 225



Nakata reported a more efficient procedure using chloromethanesulfonate as a leaving group in replacement of the mesylate group in the rearrangement−ring expansion protocol.[253]

Piers reported that copper(I) chloride mediated intramolecular coupling of bis(alkenyltrimethylstannane) groups in **725** and **727** to give 6,7,6-fused tricyclic **726** and 6,8 fused bicyclic **728** systems, respectively (Scheme 226).[254] This constituted an

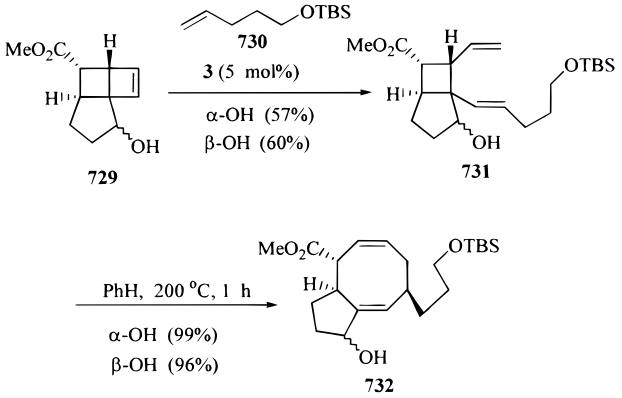
Scheme 226



effective, potentially valuable method for synthesis of carbocyclic systems containing conjugated diene units.

Snapper reported that ring-opening cross-metathesis reaction between cyclobutene-containing substrates **729** and TBS-protected alcohol **730** using ruthenium alkylidene **3** to give dienes **731**, which underwent thermal Cope rearrangement to give cyclooctadienes **732** (Scheme 227).[255]

Scheme 227

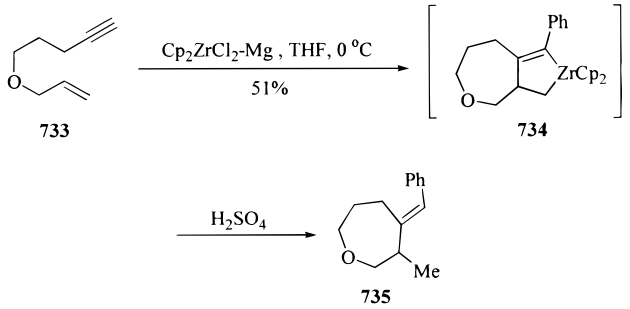


Enyne **733** was exposed to zirconocene-mediated magnesium cyclization conditions to afford 3-methylene cycloheptyl ether **735** via bicyclic zirconocene intermediate **734** (Scheme 228).[256]

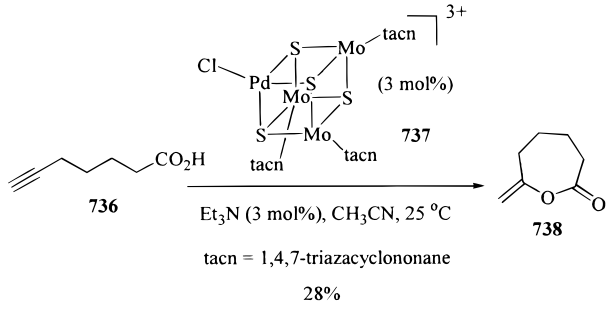
Hidai used mixed palladium−molybdenum cluster **737** for the lactonization of 6-heptynoic acid (**736**) in the formation of enol lactone **738** (Scheme 229).[257]

Recently, Kirihara reported that tertiary cyclopropanol ether **739**, in the presence of vanadium catalyst under an atmosphere of oxygen, gave β-hydroxycycloheptanone (**740**) and 1,3-cycloheptadione (**741**) in a 3:2 ratio (Scheme 230).[258] The mechanism does not

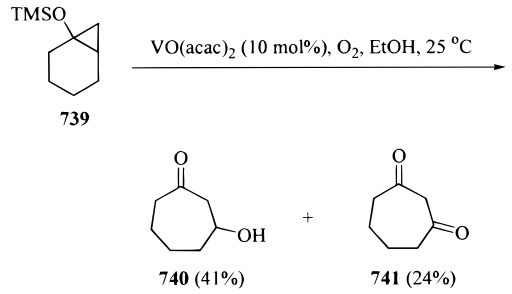
Scheme 228



Scheme 229



Scheme 230



appear to be one of a radical intermediate as discussed in Section 3.3.

12. Conclusion

This review has shown that applications of metals in the synthesis of medium-sized rings are active areas of research. Due to the high number of natural products with medium-sized ring subunits and general synthetic methodology, more methods will no doubt be explored in gaining access to these structures.

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