Enyne Metathesis (Enyne Bond Reorganization)

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Steven T. Diver grew up in Salt Lake City and attended the University of Utah where he studied with Professor F. G. West as an undergraduate researcher. Diver went on to do his doctoral work with Professor Ed Vedejs at the University of Wisconsin—Madison, studying nucleophilic catalysis promoted by phosphines. Diver conducted postdoctoral studies with Professor Stuart Schreiber at Harvard where he used alkene metathesis to make chemical dimerizers. Presumably this is where he got bitten by the metathesis bug. Diver began his independent work at the University at Buffalo–The State University of New York (SUNY–Buffalo) in 1997. Diver's research group is interested in the application of enyne metathesis to challenging synthetic problems, mechanistic aspects of the enyne metathesis, and catalyst design employing unusual heterocyclic carbene ligands.

Anthony J. Giessert was born in Buffalo, NY, in 1978. He received his B.S. in chemistry from Canisius College in 2000. He is currently a fourth year graduate student at the University at Buffalo–The State University of New York exploring enyne metathesis under the direction of Dr. Steven Diver.

1. Introduction and Scope

Enyne metathesis is a bond reorganization of an alkene and an alkyne to produce a 1,3-diene (eqs 1 and 2 in Scheme 1). It has been used in both intramolecular and intermolecular applications. Enyne metathesis bears a mechanistic kinship to alkene metathesis; however, it is less-studied than alkene metathesis. The enyne bond reorganization is atom economical and is driven by the enthalpic stability of the conjugated 1,3-diene produced. Stereoselection is often low in intermolecular cases but can be controlled in intramolecular cases. The enyne metathesis can be catalyzed by metal carbenes or "templated" by metal salts. Many of the same metal carbenes that catalyze alkene metathesis can be used to promote enyne metathesis.[1]

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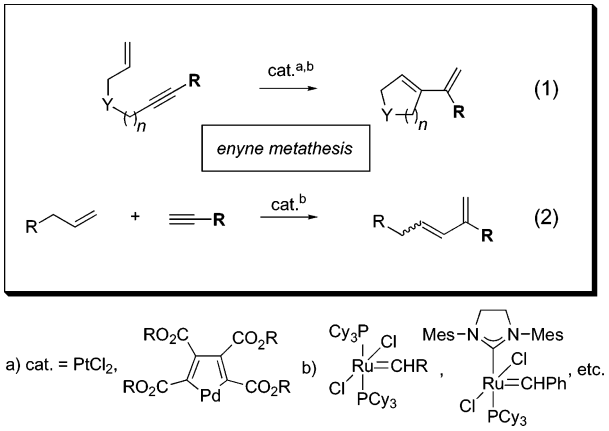
Scheme 1



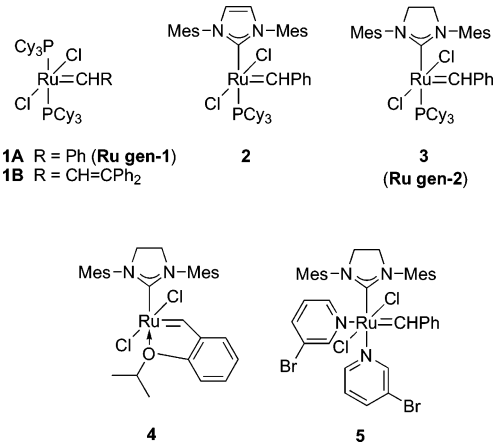
Enyne metathesis is known by several different names. The various terms have an anecdotal association with the reaction mechanisms, but the meanings are not clear-cut and do not differentiate the two superfamilies of enyne metathesis. The Pt(II) and Pd(II) process has interchangeably been called enyne bond reorganization and enyne metathesis; the intramolecular applications are commonly called enyne cycloisomerization because a ring is produced in the metathesis. When metal carbenes are involved, the reaction will be referred to here as ring-closing enyne metathesis (RCEYM).

Historically, the discovery of enyne metathesis came forth from the study of the effect of alkynes on ring-opening alkene metathesis polymerization. The seminal investigation by Katz et al.[2,3] launched inquiry into the alkene−alkyne metathesis. Subsequently, Katz and Sivavec reported a ring-closing enyne metathesis *catalyzed* by a Fischer carbene complex to produce a substituted phenanthrene.[4] This report was ground-breaking because it showed that the chemistry discovered in the course of ring-opening metathesis polymerization in the polymer field could be adapted to ring synthesis, suitable for the preparation of small organic molecules. Katz and Sivavec's paper also foreshadowed the primary synthetic use of the enyne metathesis for the following 18 years: ring-closing metathesis (RCM).

Just a few years after the discovery of enyne metathesis by Katz, Trost and his group developed cycloisomerization reactions of enynes using palladium(II) and platinum(II) salts. These metal-templated reactions are mechanistically distinct from metal carbene-mediated pathways. The most recent phase is marked by use of the Grubbs' family of ruthenium carbenes that have revolutionized alkene metathesis.

For the metal carbene-catalyzed enyne metathesis, there are mechanistic parallels with alkene metathesis. This review will address these similarities where relevant and where they are reasonably well-studied. The alkene metathesis mechanism is better understood than that of enyne metathesis thanks to recent work by the Grubbs group for ruthenium carbenes.[5−8] It is therefore understandable that research in enyne metathesis has viewed the reaction through this parallel and has drawn on analogy to this body of work.

Chart 1. Ruthenium Carbene Complexes Used in Enyne Metathesis



Most of the recent synthetic applications of enyne metathesis use ruthenium carbenes because of their availability, ease of use, functional group compatibility, and continued development. The ruthenium carbenes are summarized in Chart 1. The first-generation Grubbs' complex **1A** (**Ru gen-1)**[9,10] followed the initial report of the neophylidene complex **1B** for alkene metathesis.[11−13] Some years later, the development of *N*-heterocyclic carbenes as ligands for metal catalysis in general has resulted in the second-generation ruthenium carbenes, typified by benzylidene **3 (Ru gen-2)**.[14−17] More recently, Hoveyda and co-workers[18−22] and Blechert and co-workers[23] reported a phosphine-free complex **4**, and the Grubbs group has produced the hexacoordinate, phosphine-free bromopyridine solvate **5**. All of these ruthenium complexes were developed for alkene metathesis, but all catalyze enyne metathesis as well. The ruthenium carbenes are commercially available and do not require vacuum lines and gloveboxes for routine applications. The functional group compatibility of the ruthenium carbenes is well-known from alkene metathesis, and the reader is directed to pertinent reviews.[24−27]

The review is organized to first introduce the mechanistic features of the reactions in the two enyne metathesis manifolds: metal-templated and metal carbene-mediated (section 2) and then will focus on synthetic applications without distinguishing mechanisms further (section 3).

The scope of this review is comprehensive back to Katz and Sivavec's initial report of enyne metathesis in 1985.[4] There are two reviews written on enyne metathesis.[28,29] The 1998 account by Mori[28] provided an early overview of the ruthenium carbene-catalyzed reaction and considered important mechanistic issues. The recent review by Madsen and Poulsen[29] highlights recent advances of the ruthenium carbene-catalyzed enyne metathesis used in synthesis. A general discussion of transition metal-promoted reactions of 1,*n*-enynes is available,[30] which includes some of the metal-templated enyne cycloisomerizations included in the present review.

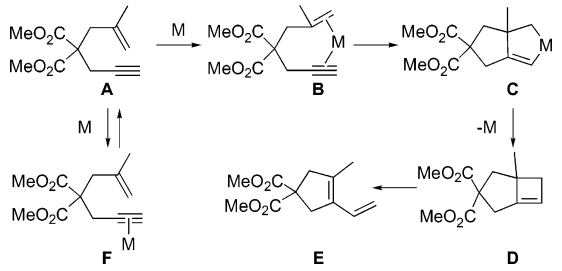
2. Mechanism Families

2.1. Metal Salt-Catalyzed Enyne Bond Reorganization

Some late transition metal salts trigger enyne bond reorganization. The pioneering work in this area came from Trost's lab.[31−36] Trost employed various Pd(II) and Pt(II) metallacyles to trigger the bond reorganization. Interest in the metal-catalyzed enyne bond reorganization, particularly in the platinum-(II)-catalyzed reaction, has been recently rekindled due to the simplicity of the catalysts. The mechanistic picture that emerged was useful in predicting products and helped to explain some of the unusual byproducts obtained. Much of the more recent work in metal salt-promoted enyne metathesis cites this work or builds on this mechanistic framework.

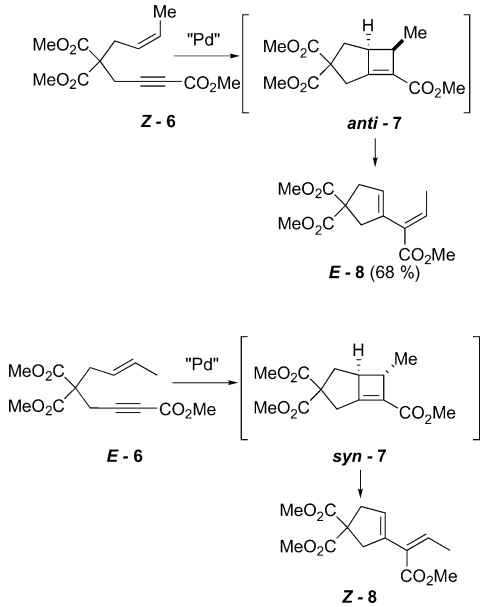
The cycloisomerization of 1,6-enynes is believed to occur through the general process depicted below (Scheme 2). The reaction is triggered by bidentate

Scheme 2



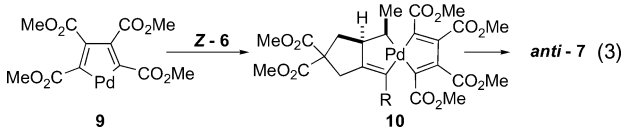
coordination of the enyne to the metal and oxidative cyclometalation to produce metallacyclopentene **C**. Reductive elimination of the metal would produce a cyclobutene **D** that could undergo electrocyclic ring opening in order to relieve ring strain. In support of this mechanism, cyclobutenes have been isolated in some instances. The generic mechanism of Scheme 2 represents the basic framework of the metal-templated enyne bond reorganization. Depending on

Scheme 3[31]



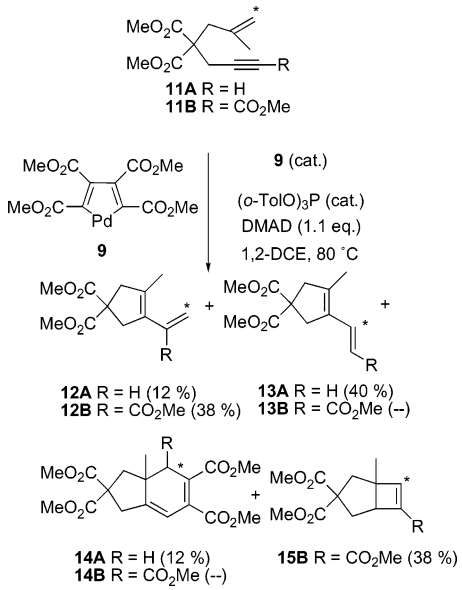
the catalyst, one can also envision other possibilities including bond reorganization triggered by only one π system bound to the metal and alternative fates to the metallacyclopentene intermediate such as β-hydride elimination.

Trost and Tanoury showed that the Pd(II)-catalyzed enyne metathesis of 1,6-enynes is stereospecific (Scheme 3).[31] The observed stereospecificity is consistent with the intermediacy of cyclobutenes, which are formed by reductive elimination of palladacycles. The palladacyclopentenes **10** are produced by cyclometalation of enynes with the palladole catalyst **9** (eq 3).



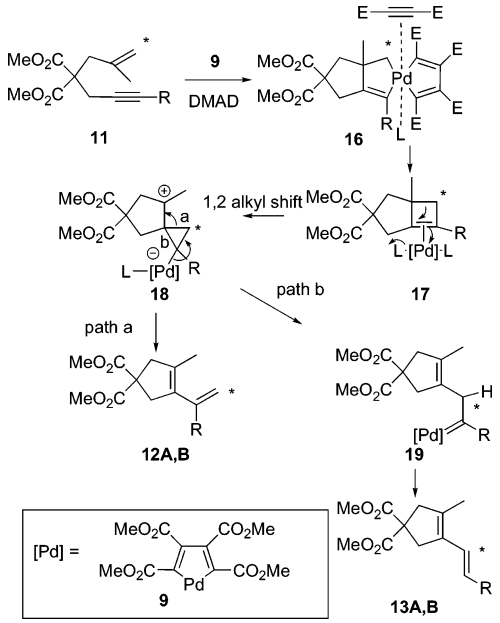
Carbon-13 labeling studies were consistent with the proposed mechanism but also revealed that a more "deep-seated" rearrangement had occurred (Scheme 4).

Scheme 4[31]



The normal enyne metathesis product is accompanied by a product arising from valence isomerization. Labeled enyne **11A** and **11B** gave "normal" enyne product **12** and various byproducts. The terminal alkyne **11A** produced a significant amount of the "type b" enyne metathesis product **13A** where the carbon-13 label had been rearranged through valence isomerization. In addition, the terminal enyne **11A** gave DMAD trapping product **14A**, and the ester-substituted enyne **11B** gave cyclobutene **15B** with carbon-13 label in the expected position. The isomerization of the cyclobutene intermediate to isomeric cyclobutene **15B** is thought to occur via a π-allyl palladium hydride species, consistent with deuterium labeling experiments and driven by relief of strain in the rearranged cyclobutene. The fact that all rearrangement products contained a single label suggests that there was no intermolecular scram-

Scheme 5[31]



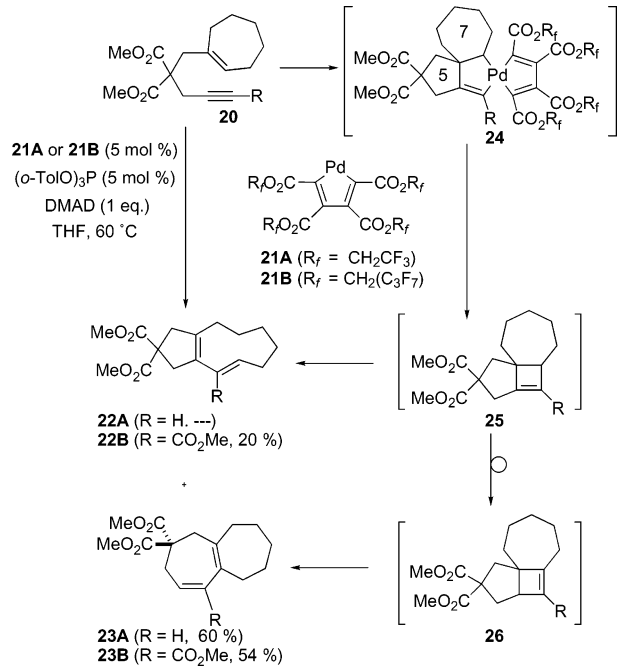
bling, so the mechanism must have occurred through an intramolecular process.

Migration of the carbon-13 label can be explained by the mechanism formulated in Scheme 5. Cyclopalladation gives **16**, which undergoes reductive elimination to yield η^2-complexed cyclobutene **17**. When R = CO_2Me, the cyclobutene can undergo electrocyclic ring-opening (giving **12A**,**B**) and produces **15B** (Scheme 4) by isomerization. The metal can interrupt normal electrocyclic ring-opening, trigger 1,2-alkyl shift, and produce zwitterionic spirocycle **18**, which can open bond a through the indicated electron movement to give the normal metathesis product. Alternatively, bond b can be eliminated into the carbocation to produce palladium carbene **19**, which can undergo 1,2-hydride shift and elimination of palladole catalyst to produce rearrangement product **13A**,**B**.

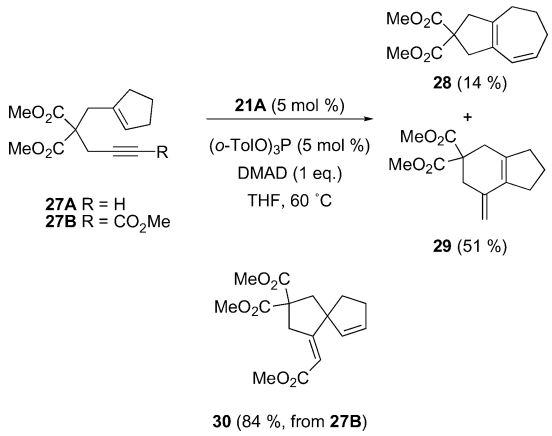
Trost and Trost highlighted mechanistic dichotomies in enyne metathesis as a function of alkyne substitution.[32] The results were interpreted in terms of cyclobutene intermediates and their strain-driven isomerization. The electron-deficent palladole catalyst **21A** promoted enyne bond reorganization in cycloheptadienyl alkyne **20** to produce **23A** in good yield (Scheme 6). Cyclization via spiropalladacycle **24** is expected to produce cyclobutene **25**, which would undergo electrocyclic ring-opening to give **22A**, which was not formed. Isomerization of kinetically formed cyclobutene **25**, which may still be complexed to Pd (II), relieves about 16 kcal/mol ring strain (MM2) on isomerization to **26**, the precursor to observed diene **23A**. In contrast, the ester substituent slows rearrangement such that some ring-opening of **25** occurs (to give **22B**) along with diene **23B** generated as the major product.

The enyne bond metathesis can lead to unusual products that demonstrate the capacity of Pd(II) and Pt(II) salts to serve as Lewis acids. The trifluoroethyl tetraester **21A** gave enyne metathesis of cyclopentene **27A** to give dienes **28** and **29** in a 1:3.7 ratio (Scheme

Scheme 6[32]



Scheme 7[32]

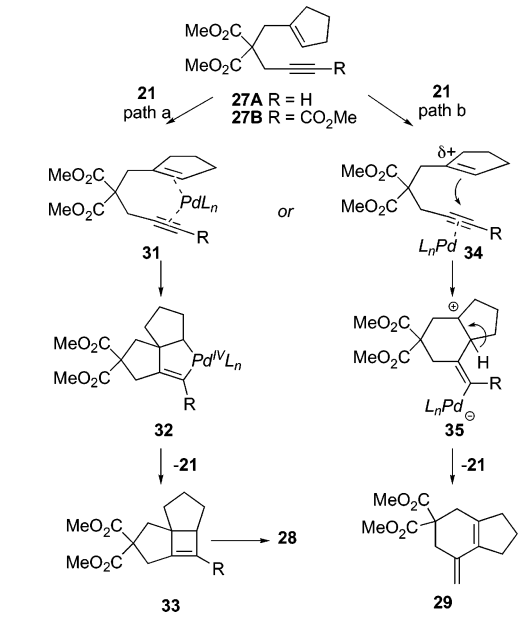


7). The ester-substituted enyne **27B** gave only the Alder-ene product **30**.

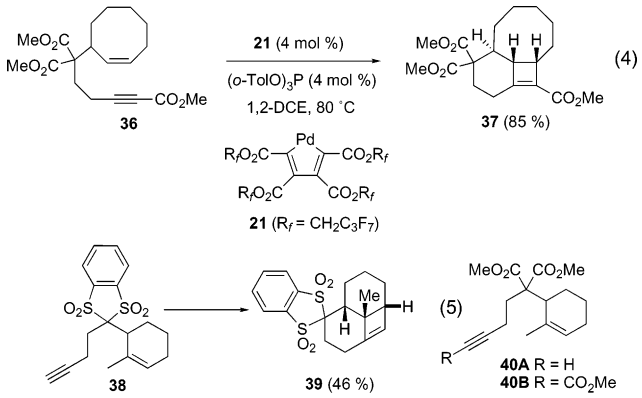
This result is suggestive of dual catalytic pathways: Pd(II) palladacycle to cyclobutene (path a, Scheme 8) and η^2-activation of alkyne resulting in slippage toward a cationic pathway (path b). The first pathway is the usual enyne metathesis. The second pathway would be sensitive to alkene substitution and alkene geometry (for classical carbocations). Though not probed here, one might also expect that the number of atoms and the substitution in the tethering unit would influence the success of these reactions. Elimination of a proton and protonolysis of the alkenyl−palladium bond (**34** → **35**) regenerates the palladole and produces the unusual diene product **29**. This early paper is an important milestone in enyne metathesis because both the organometallic role of the palladole (path a) and the Lewis acid-like mechanism (path b) were suggested. Most of the current thought regarding $PtCl_2$ catalysis invokes similar ideas.

Trost and Yanai observed cyclobutene products that are mechanistically relevant to Pd(II)-catalyzed

Scheme 8[32]



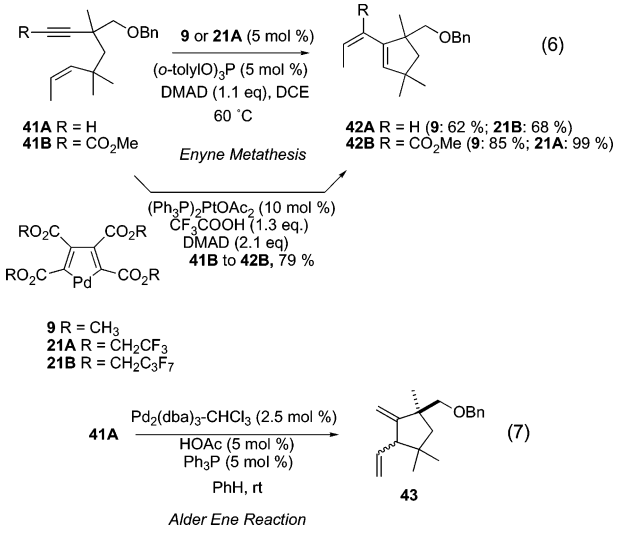
Scheme 9[35]



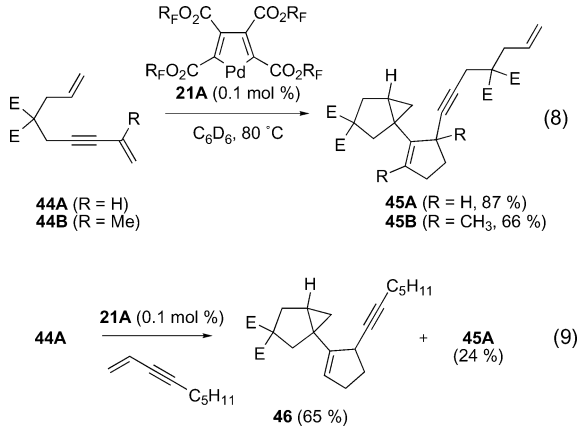
enyne bond reorganization.[35] Failure to observe cyclobutene intermediates in 1,6-enynes was attributed to high strain energy in the bicyclic ring system. Hence, relaxation to a 1,7-enyne was expected to produce more stable cyclobutenes, which were observed in the attempted enyne metathesis (eq 4, Scheme 9). Palladole-catalyzed enyne cycloisomerization of **36** in refluxing 1,2-dichloroethane provided tricyclic enoate **37** featuring an embedded cyclobutene ring. The 3-benzodithiole tetraoxide **38** underwent metathesis in 46% yield (eq 5). The malonate analogue **40A** failed to isomerize to cyclobutene; however, an ester-substituted alkyne **40B** provided the corresponding cyclobutene. These results support the intermediacy of cyclobutenes in the Pd(II)-catalyzed enyne metathesis.

Trost and Chang described palladium(II)- and platinum(II)-catalyzed enyne bond reorganization of highly substituted enynes.[34] The substituted 1,6-enynes **41** underwent stereospecific enyne bond reorganization with electron-deficient palladole catalysts **9** or **21A** (eq 6, Scheme 10). The electron-deficient ligand is thought to accelerate reductive elimination from the Pd(IV) spiropalladacycle. Platinum salts also bring about the enyne metathesis, which is stereospecific for **41B** to **42B** (Scheme 10).

Scheme 10[34]



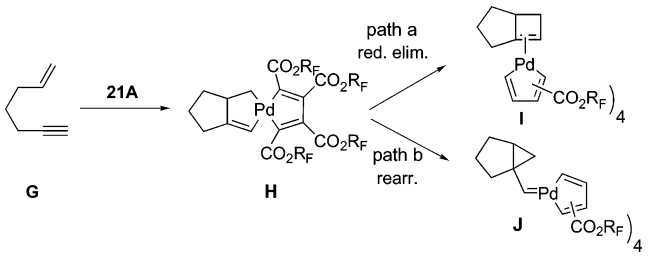
Scheme 11[36]



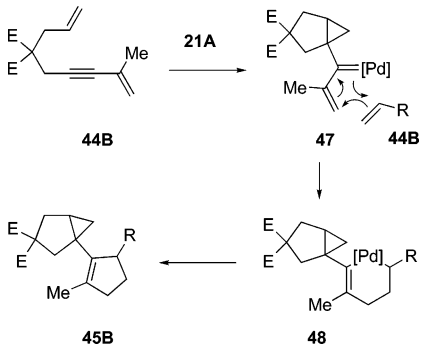
This result was also interpreted in terms of the Pt(II) to Pt(IV) to Pt(II) catalytic redox shuttle, which is better precedented for platinum than palladium. Trost sagaciously suggested that "further exploration of platinum complexes as metathesis catalysts merits consideration". The enyne metathesis is dependent on the oxidation state of the metal as Pd(0) instead promotes the Alder-ene reaction (eq 7).

Trost and Hashimi observed unusual dimers in palladium(II)-catalyzed enyne metathesis, which led to the formulation of a cyclopropyl alkylidene palladium intermediate.[36,37] Catalytic palladole **21A**, with or without added tri-*o*-tolyl phosphite, provided cyclopropane dimers **45A** and **45B** in excellent yield (eq 8, Scheme 11). The enyne cycloisomerizations studied previously had an ester group in place of the conjugated enyne. Heterodimers **46** could also be formed by trapping with 2.5 equiv of an auxiliary enyne (eq 9). Strained and activated alkenes failed to trap the proposed cyclopropyl alkylidene palladium intermediate. Normal enyne bond metathesis using palladium(II) catalysts proceeds via path a by reductive elimination of Pd(IV) intermediates (Scheme 12). The palladacycle can also rearrange to a Pd(II) carbene by path b. The vinyl group (present on the alkyne of **44**) is expected to help stabilize the palladium carbene **J**, thereby favoring path b. Once formed, vinyl carbene **47** reacts with an electronically

Scheme 12



Scheme 13[36]

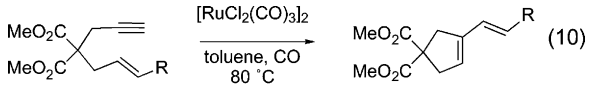


matched enyne **44B**, which serves as a dienophile in a metalla-Diels−Alder reaction (Scheme 13). Reductive elimination of the Pd(IV) intermediate **48** provides the observed cyclopropyl dimers. The subtle interplay of steric and electronic factors in a substituted 1,6-enyne can divert enyne bond reorganization into unusual pathways. The cyclopropyl alkylidene palladium **J** or **47** can explain the carbon-13 and deuterium scrambling observed in the alkene moiety (i.e., type b enyne metathesis by valence bond isomerization).

The palladole chemistry defined early mechanistic thinking about the enyne bond reorganization. From a synthetic standpoint, the palladole-catalyzed reactions work best in enynes that feature a *cis*-alkene and an electron-deficient alkyne (also needed for stereospecific rearrangement). These requirements reveal a steric requirement for alkene binding and an electronic preference for electron-deficient alkynes and are consistent with simultaneous coordination of the enyne needed during the oxidative cyclometalation step. In other enynes that do not fulfill these requirements, simultaneous binding of both alkene and alkyne may be less favorable as compared to monodentate Lewis acidic activation of the alkyne.

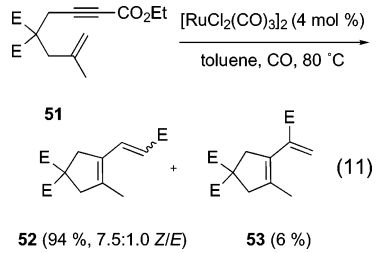
Trost's mechanistic work established the probable intermediacy of cyclobutenes since they could be isolated (Scheme 9) or inferred from cyclorearranged 1,3-diene products (Scheme 6). The mechanistic rationale focused on metal-templated cycloisomerization, although monodentate activation of simple alkynes explained byproducts via classical carbocations (Scheme 8). With better Lewis acids, the cationic pathway may dominate leading to reactivity via monodentate activation of the alkyne. Many of the following results are interpreted along these lines and have led to the formulation of a nonclassical carbocation mechanism that rationalizes rearrangement in simple enynes, where the participating alkene cannot support positive charge.

Chatani and co-workers discovered a highly selective skeletal reorganization of 1,6-enynes using $[RuCl_2(CO)_3]_2$ under an atmosphere of carbon monoxide.[38] The produced catalyst is complementary to Trost's palladoles since simple, *terminal* enynes undergo the rearrangement effectively (eq 10).



49A (R = H) **50A** (R = H, 96 %)
49B (R = Ph) **50B** (R = Ph, 97 %)
49C (R = $SiMe_3$) **50C** (R = $SiMe_3$, 86 %)

A mixture of *E*/*Z* alkene isomers gives only *E*-diene product. This is not the case for palladole-catalyzed reactions where the rearrangement is previously known to be a stereospecific process. The platinum(II)-catalyzed reaction is stereospecific for ynoates (eq 6, Scheme 10) but is nonstereospecific for simple alkynes.[34] Other ruthenium halides such as $[RuBr_2(CO)_3]_2$, $[RuCl_2(p\text{-cymene})]_2$, and $RuCl_3 \cdot H_2O$ produced enyne bond reorganization of **49A** in 87%, 88%, and 84% yields when conducted under CO. With an ester substituent on alkyne **51**, a skeletal rearrangement product **52** is produced as the major isomer, along with small amounts of the normal enyne metathesis product **53** (eq 11).

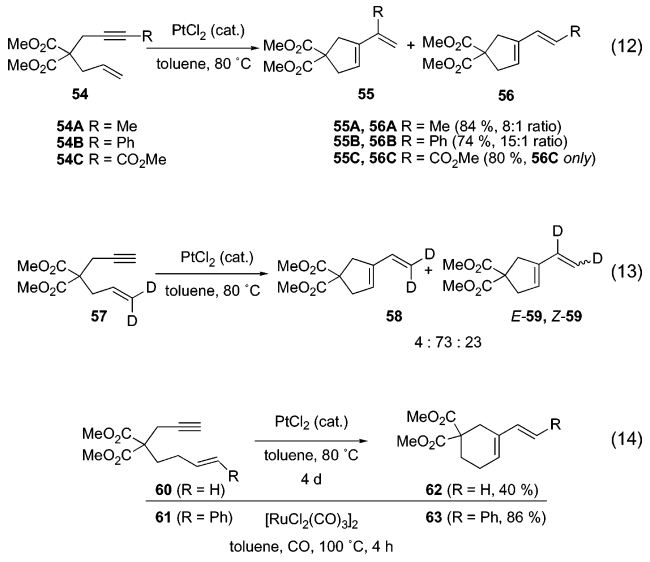


52 (94 %, 7.5:1.0 *Z*/*E*) **53** (6 %)

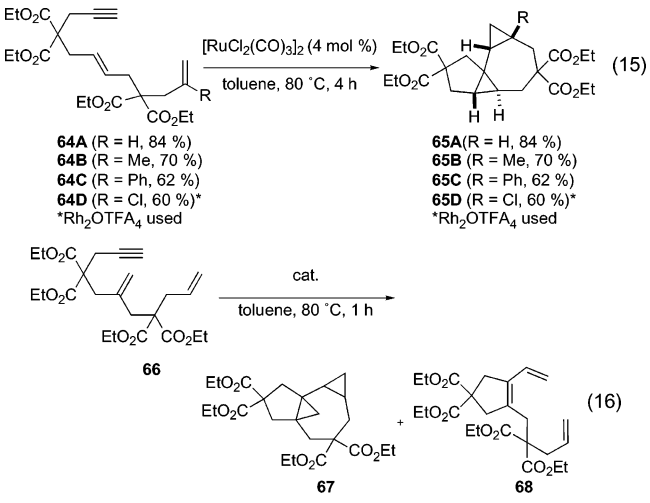
The major product is the "type b" enyne metathesis product. The authors consider that the reaction could be triggered by formation of ruthenacyclopentene via oxidative cyclization, by formation of a vinyl ruthenium complex via chlororuthenation, or by production of a η^1-slipped isomer derived from initial η^2-alkyne coordination by the coordinatively unsaturated metal. In addition, a 1,7-enyne gave vinyl cyclohexene in excellent yield.

Using platinum(II) salts, Murai and co-workers found efficient enyne skeletal rearrangement.[39] The anomalous metathesis product produced by skeletal rearrangement was also seen in varying degrees as a function of alkyne substitution (eq 12, Scheme 14). Diene **55** is the normal enyne metathesis product. Only rearrangement is observed in the ester case **54C**. The apparent 1,2-positional shift of the alkyl and aryl substituents are examples of true enyne metathesis, where both the alkene and the alkyne are metathetically cleaved and refastened into isomeric 1,3-dienes. Deuterium-labeled enyne **57** shows scrambling of deuterium in the product due to the anomalous, type b enyne metathesis (eq 13). The rearrangement of 1,7-enynes is promoted by $PtCl_2$ albeit in lower yield (eq 14). Subsequent studies also established that Ir(I) could be used to promote cycloisomerization of enynes.[40]

Scheme 14[39]



Scheme 15[41]

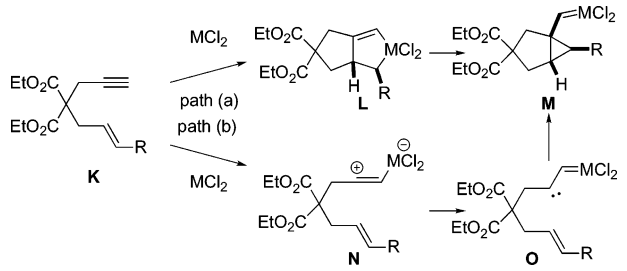


entry	catalyst	67	68
1	$[RuCl_2(CO)_3]_2$	0 %	75 %
2	$PtCl_2$	0 %	90 %
3	Rh_2OTFA_4	51 %	34 %

The rearrangement leading to the type b enyne metathesis product of eq 12 can be interpreted in terms of Trost's eliminative opening of cyclopropylcarbinyl cation **18** (Scheme 5). Access to the same intermediate can be envisioned through nonclassical ions arising from monodentate alkyne activation with metals that are highly electron-deficient (rather than through oxidative cyclometalation).

With 1,6-enynes bearing an additional alkene, an unexpected rearrangement took place giving tetracyclic products. 1,6-Enynes usually produce enyne bond reorganization using $[RuCl_2(CO)_3]_2$ as catalyst; however, Murai and co-workers intercepted the carbenoid intermediate with pendant alkenes to produce cyclopropanes.[41] A variety of substituted dienynes produced the tetracyclic ring system **65A**−**D** (eq 15, Scheme 15). Several different metal salts catalyzed the cycloisomerization of **64** to **65** including $PtCl_2$ (75%, 4 h), Rh_2OTFA_4 (72%, 1 h), $[IrCl(CO)_3]_n$ (54%, 4 d), and $ReCl(CO)_5$ (74%, 1 d). The cis isomer of **64A** failed to produce tetracycle **65A** and instead gave a

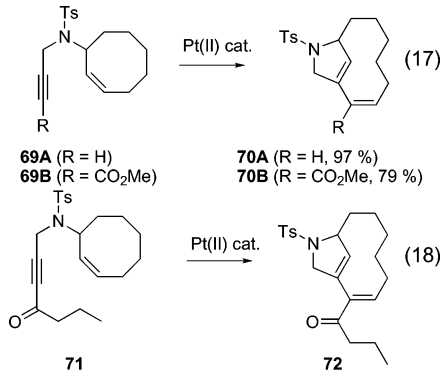
Scheme 16[41]



complex mixture of products since the second cyclopropanation was geometrically unfavorable. For the vinyl chloride, $Rh_2(OTFA)_4$ was used as a catalyst producing **65D** in good yield. With a geminally substituted interposing alkene, $[RuCl_2(CO)_3]_2$ as catalyst produced the normal enyne metathesis product **68** exclusively (eq 16). Platinum(II) chloride also promoted enyne metathesis and failed to produce the biscyclopropane found in tetracycle **67**. However, using $Rh_2(OTFA)_4$, the more electrophilic version of its cousin $Rh_2(OAc)_4$, the biscyclopropane **67** was produced as the major product (1.5:1.0 **67**:**68**, eq 16).

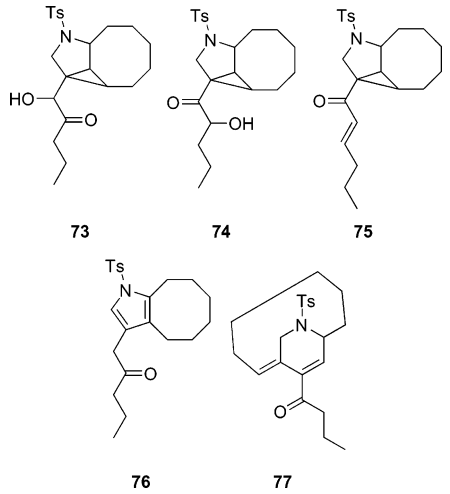
The reaction mechanism could involve cyclometalation and rearrangement of the metallocyclopentene to cyclopropyl carbenoid via path a (Scheme 16), but the authors favor a slipped η^1-alkyne complex that produces cyclopropyl carbenoid **M** through rearrangement (path b).[41] The diversity of metal complexes found to bring about this tetracycloisomerization is more consistent with the η^1-slipped alkyne zwitterion. Similar rearrangement can be envisaged through path b by Lewis acidic metal salts, possibly via nonclassically stabilized carbocations.

As shown before, simple platinum salts promote enyne bond reorganization. As a critical step in the synthesis of streptorubin, Fürstner et al.[42] required a reliable enyne metathesis and found that the $PtCl_2$-catalyzed reaction was dependable, efficient, and operationally straightforward. Synthetic work sometimes demands reasonably large-scale processes for the production of early intermediates. Fürstner's group found that the $PtCl_2$-catalyzed enyne metathesis scaled up without difficulties, a useful feature of a metal-catalyzed process. The Pt(II) salts effectively triggered enyne bond reorganization for ester and ketone-bearing alkynes (eqs 17 and 18).

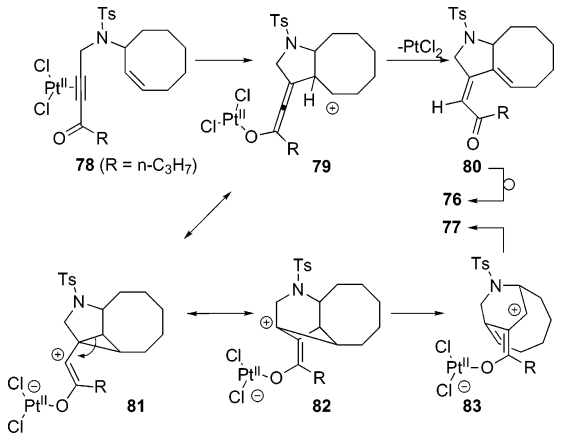


Other platinum salts ($PtCl_2$, $PtCl_4$, and $PtBr_4$) also catalyzed the reaction. On scale-up, the metathesis of eq 18 produced several trace byproducts **73**−**77**

Scheme 17[42]



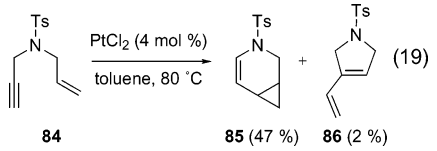
Scheme 18[42]



that were isolated and identified (Scheme 17). Their structures are consistent with the formation of a nonclassical carbocation. This idea led to the use of conventional Lewis acid catalysts, discussed below in section 3.1.7, en route to metacycloprodigiosin.

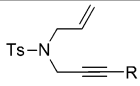
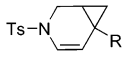
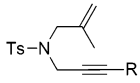
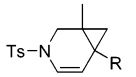
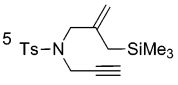
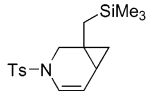
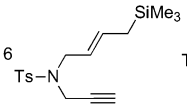
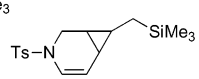
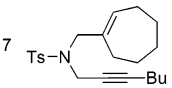
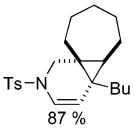
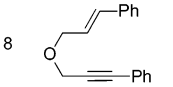
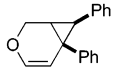
The formation of the byproducts **73**−**77** in Scheme 17 can be explained by an ionic mechanism (Scheme 18). Platinum carbene **81** could undergo a formal O−H insertion with water to give cyclopropanes **73**−**75** (Scheme 17). Pyrrole **76** could arise through cationic activation of the ynone followed by elimination of **79**, protonation of the platinum enolate, and alkene isomerization to the aromatic heterocycle. The dihydropyridinophane **77** is thought to arise from the same cationic intermediate **79** via the pathway **81** to **82** to **83**. Represented as classical structures, π solvation by the proximal alkene gives a new tertiary cyclobutyl carbocation that undergoes elimination. The resulting zwitterion **83** is fated to charge annhilation and loss of $PtCl_2$, giving product **77**.

Fürstner discovered that certain tosylamide-linked 1,6-enynes gave novel rearrangements during attempted enyne bond metathesis using $PtCl_2$.[43] The enyne metathesis proceeded normally en route to streptorubin B using ynone **69B** (eq 17). Similarly, metathesis proceeded normally for the analogous terminal alkyne **69A**. Replacing the moderately strained pendant cyclooctene with a terminal alkene produced minimal enyne metathesis product **86** and gave a novel cyclopropane **85** as the major product (eq 19).

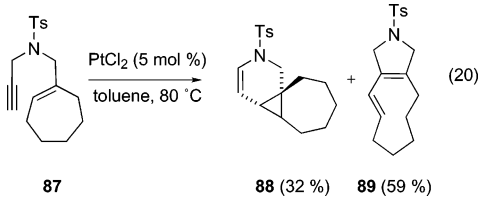


With catalytic $PtCl_2$ in toluene at 80 °C, novel cyclopropanes were observed as the major products for a variety of enynes (Table 1).

Table 1[43]

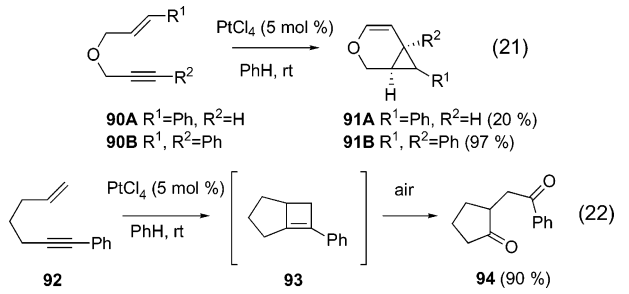
entry	enyne	cyclopropane (yield)
1	 R = Me	 R = Me, 59 %
2	R = Ph	R = Ph, 78 %
3	 R = H	 R = H, 68 %
4	R = Me	R = Me, 69 %
5		 73 %
6		 76 %
7		 87 %
8		 83 %

The cyclopropanation is notable because it proceeds for both terminal and internal alkynes. The alkene can be substituted at the internal (entries 3−5) or external (entries 6 and 8) positions. The pendant cycloheptenyl group underwent cyclopropanation in high yield (entry 7). Clearly, the electronic and steric factors leading to cyclopropanation are subtle as the cyclooctenyl-substituted **69A** (eq 17) gave exclusively enyne metathesis, and the terminal alkyne **87** (eq 20) produced a mixture of cyclopropane and enyne metathesis product (cf. entry 7, Table 1).



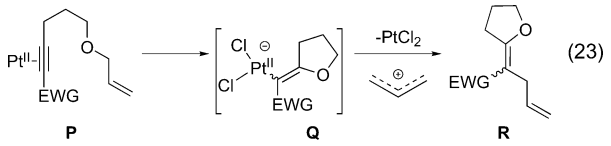
Similar rearrangement of enynes to produce cyclopropanes had been described by Blum et al.[44] The reaction was only documented in two cases with rather different results (eq 21, Scheme 19).

Scheme 19[44]

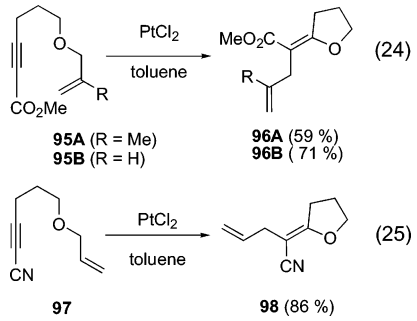


Despite the limited scope of this novel transformation, the authors noted that the cyclopropanation was particular to oxygen-tethered 1,6-enynes since the methylene analogue **92** gave a cyclobutene. In the latter case, the intermediate cyclobutene was oxidatively cleaved under ambient conditions to provide 1,4-dione **94** in excellent yield (eq 22). Blum considers that the propargyl ether first undergoes metal-assisted isomerization to the allenyl ether, subsequent coordination to the platinum salt, and migratory insertion of the pendant alkene, which is followed by reductive elimination of the platinacyclobutane, producing cyclopropanes **91**.

Consideration of a cationic mechanism led Fürstner and co-workers to consider intramolecular interception of these electrophilic species by other nucleophiles.[43,45] Allylic ethers proved capable nucleophiles that led to allyl transfer products (eq 23).

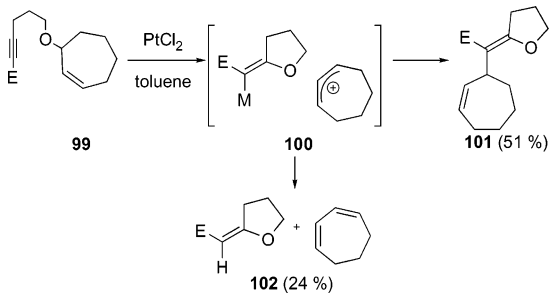


Activation of the alkyne by Pt(II) coordination leads to oxonium ion formation, which results in release of the allyl carbocation. Allyl transfer to the electron-rich carbon−platinum bond completes the reaction and regenerates Pt(II). This allyl transfer reaction was developed to include a variety of allyl ethers (eqs 24 and 25).[43,45]



In these examples (eqs 24 and 25), a single alkene isomer was produced, but in other cases *E*,*Z*-mixtures resulted from nonselective allyl transfer to the cationic intermediate. Furthermore, it was observed that cycloheptadienyl cation (ion pair **100**, Scheme 20) underwent both allyl transfer (to give **101**) and elimination from the ion pair to provide cycloheptadiene and enol ether **102**. These results reveal the

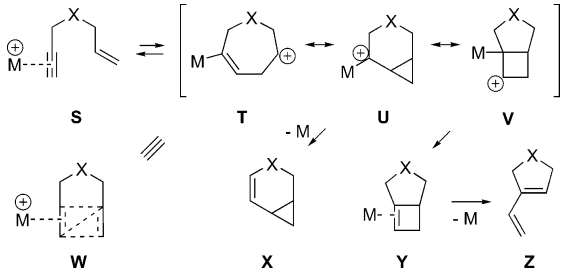
Scheme 20[43]



cationic nature of the reactive intermediates emanating from Pt(II) coordination to the alkyne.

Fürstner's investigation led to consideration of platinum salts functioning as Lewis acids, and the rearrangement was interpretable in terms of nonclassical cationic intermediates.[43] Polarization of the alkyne moiety by monodentate Pt(II) coordination to the enyne and "internal solvation" by the pendant alkene results in charge translocation (Scheme 21).

Scheme 21[43]

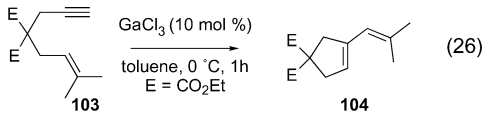


The intermediate was formulated to be a nonclassical carbocation **W** as represented by canonical resonance structures **T**−**V**. Elimination of the metal from cyclobutyl cation **V** would provide cyclobutene intermediates that would undergo electrocyclic ring opening to afford the 1,3-diene products **Z**. The mechanistic hypothesis of discrete cyclobutene intermediates was proposed previously by Trost for the palladole and platinole catalysts, accessed instead by reductive elimination of a spiropalladacycle.[31−33,35] The evolution of a cyclobutene intermediate differs in the Fürstner mechanistic proposal since the enyne is activated by monodentate complexation of the alkyne, whereas the palladoles of Trost are generally thought to trigger the metathesis by oxidative cyclometalation to *both* sites of unsaturation.[46] The cyclopropyl methyl carbocation **U** could suffer 1,2 hydride shift and eliminative demetalation to give the observed cyclopropane **X**, the anomalous products observed in Table 1.

Fürstner's cationic mechanistic proposal depends on the metal polarizing the alkyne to trigger nonclassical ion formation.[47] The novel cyclopropanation results from the unique geometrical constraint in tosyl amide-linked enynes. In this mechanistic proposal, the alkene serves as a π nucleophile, resulting in further delocalization of charge. The nonclassical ion formulation is progressive since a classical cationic mechanism would not fit the data in eq 19 or the first five entires in Table 1. An alternate possibility considered earlier in this section has the

alkene functioning as a second π ligand for the metal. Strained alkenes are better ligands for Pt(II) than unstrained alkenes, and favorable alkene binding depends on additional "face strain" developing between the alkene substituents and the ligands on the metal. Poorer alkene π complexation in the unstrained or more highly substituted enynes could retard enyne metathesis by enthalpic penalties in bidentate coordination and oxidative metalation.

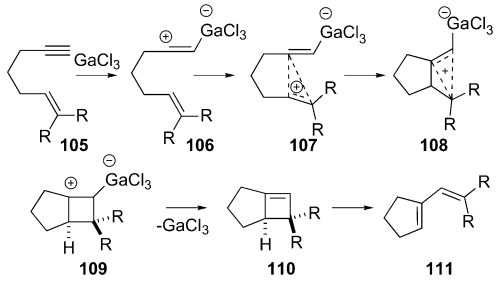
In their continuing efforts to identify additional catalysts that bring about enyne bond reorganization, Chatani, Murai, and co-workers described a $GaCl_3$-promoted enyne bond reorganization.[48] The enyne metathesis has been promoted by a variety of transition metal salts, but terminal alkynes in 1,6-enynes had not been rearranged with typical element halides ($BF_3{\cdot}OEt_2$ has been used by Fürstner for *carbonyl-substituted* alkynes; e.g., 3-ynones and 3-ynoates).[42] The reaction of **103** with 10 mol % $GaCl_3$ occurs at low temperature (eq 26).



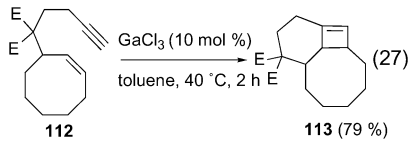
(26)

The skeletal reorganization using this potent Lewis acid tolerates esters and tosylamides. The authors favor a η^1-slipped alkyne coordination complex to $GaCl_3$ followed by nonclassical carbocation evolution **106**−**108** and eliminative demetalation to provide cyclobutene **110**, which would experience electrocyclic ring-opening to diene **111** (Scheme 22). Since bond-

Scheme 22[48]

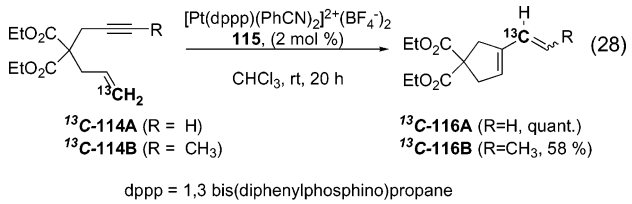


making is described in the evolution, the carbocations are written as discrete intermediates rather than as resonance structures. Fitting with this mechanistic hypothesis is the isolation of a tricyclic cyclobutene in the rearrangement of cyclooctenyl alkyne **112** (eq 27).



(27)

Recently, Oi and co-workers have considered a nonclassical ion mechanism for enyne bond reorganization using cationic platinum complexes.[49] The intermediate platinum carbenes are thought to be more carbocation-like than those produced in Murai's study ($[RuCl_2(CO)_3]_2$/CO or $PtCl_2$), giving more of the deep-seated, type b enyne bond reorganization (eq 28).



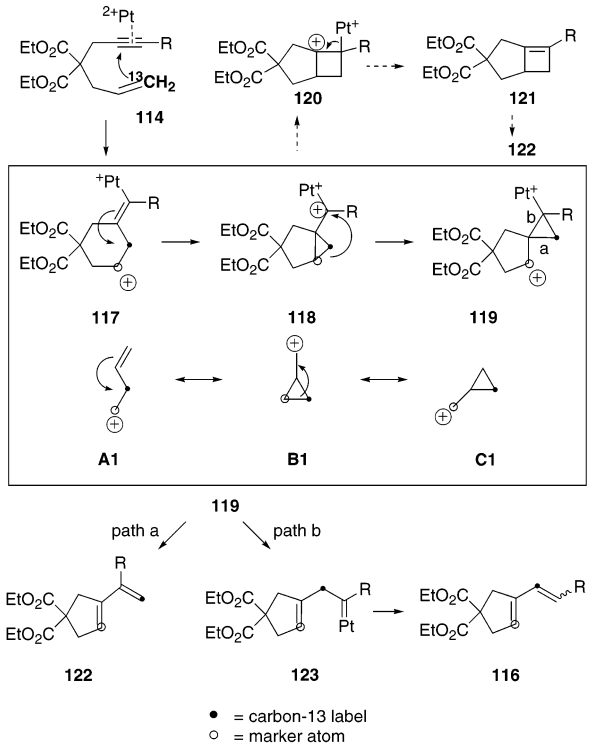
(28)

dppp = 1,3 bis(diphenylphosphino)propane

The proposed mechanism is depicted in Scheme 23. The cationic Pt(II) complex triggers the skeletal rearrangement by nonclassical ion formation. Platinum complexation results in formation of homoallylcation **117**, shown compared to the canonical resonance structures of the homoallyl−cyclopropylcarbinyl−cyclobutyl cation (**A1**−**C1**). Assuming no movement of the atoms, **117** to **118** to **119** are resonance structures. The black dot illustrates the label relative to an open circle to show the separation of these atoms through valence isomerization via eliminative fragmentation of bonds a or b in platinacyclopropane **119**. Elimination of bond a and loss of Pt(II) gives the normal enyne metathesis product **122**. The type b enyne bond reorganization is realized by elimination of bond b to give a platinacarbene **123**, which is very cationic at the carbene center. Elimination of an adjacent proton and protonolysis of the carbon metal bond gives the rearrangement product. The intermediacy of platina[3.2.0]spirocycle is analogous to the proposal by Trost presented in Scheme 5. Note also that the cyclobutyl cation resonance depiction (**120** to **121**) could explain the observance of cyclobutenes, as proposed by Fürstner (vide supra).[43]

These results coupled with Fürstner's hypothesis of a nonclassical carbocation/zwitterion provides a

Scheme 23[49]



pathway to cyclobutenes that had been observed in Trost's work. This new mechanism has considerable merit since it can explain the metathesis and cyclobutene products and rationalize data that does not fit neatly within the intellectual confine of a classical carbocation mechanism.

Echavarren has provided a comprehensive summary of enyne carbo- and alkoxycyclization, two closely related variants of enyne metathesis, catalyzed by various transition metal chlorides.[50−52] In their initial studies,[50] Echavarren's group utilized allyl silane terminators to promote cationic cycloisomerization of 1,6-enynes. The cyclization of bissulfone **124** is characteristic of the cycloisomerization (eq 29, Table 2).

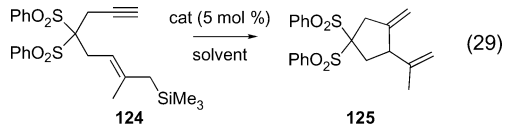
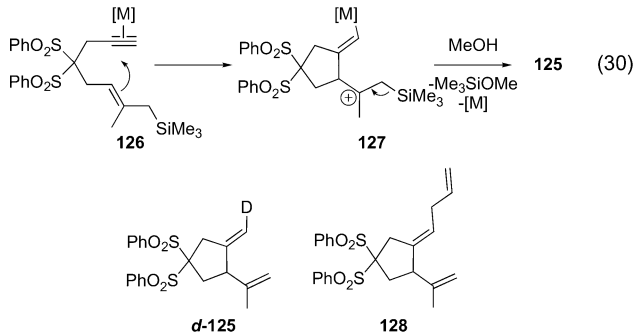


Table 2[50]

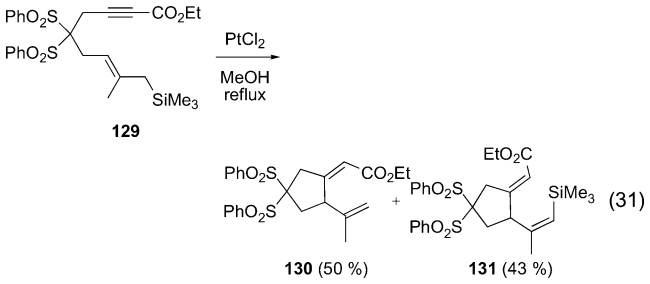
entry	catalyst	solvent	yield (%)
1	$CpRuCl(PPh_3)_2$ and $NaPF_6$ (10 mol %)	MeOH	92
2	$RuCl_3$	MeOH	53
3	$PdCl_2$	MeOH	47
4	$Pd(MeCN)_2Cl_2$	MeOH	65
5	$Pd(MeCN)_2(BF_4)_2$	MeOH	82
6	$PtCl_2$	acetone, reflux	94
7	$PtCl_2$	acetone, rt	83
8	$Pd(MeCN)_2Cl_2$	MeOH	95
9	AgOTf	dioxane	54

A wide variety of metal salts promote the reaction, which can be thought of as a "shunted" enyne metathesis. The reaction proceeds through cationic activation of the alkyne and antiperiplanar nucleophilic attack by the allyl silane (Scheme 24). The

Scheme 24[50]



stereochemical orientation was established by conducting the reaction in methanol-d_4, which gave ***d*-125** due to deuteriolysis of the alkenyl−metal bond. Further support for this mechanism was obtained by trapping the alkenyl platinum bond with excess allyl chloride, resulting in the formation of an additional carbon−carbon bond through cross coupling (see **128**, Scheme 24). Electron-withdrawing substituents on the alkyne enhance the electron deficiency of the reactive intermediates and produces Alder-ene reaction as a major competitive pathway (eq 31).



Echavarren's group investigated metal-promoted enyne cyclization in hydroxylic solvents in a successful effort to divert the enyne metathesis into a new reaction manifold (eq 32, Table 3).[51,52] In these

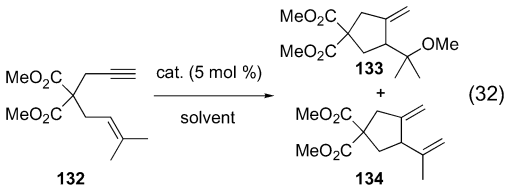
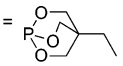


Table 3[51,52]

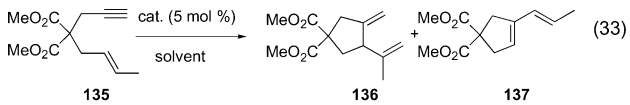
entry	catalyst[a]	**133** (%)	**134** (%)
1	$PtCl_2$/MeOH	63	34
2	$PtCl_2$/dioxane	−	100
3	K_2PtCl_4	62	23
4	$Pt(CH_3CN)_2Cl_2$-$P(OR)_3$[a] (10 mol %)	96	1
5	K_2PtCl_4-$P(OR)_3$ (10 mol %)	100	−
6	$AuCl_3$/MeOH	98	−

[a] $P(OR)_3$ =



reactions, cationic intermediates will be both stabilized by polar solvent and intercepted by solvent to provide alkoxy cyclization product **133**. The Alder-ene product **134** is produced exclusively in the absence of hydroxylic solvents ($PtCl_2$, dioxane) through competitive elimination. Other platinum salts promote the alkoxy cyclization conducted in methanol at reflux with 5 mol % catalyst. The ruthenium species $RuCl_3$ and $Ru(AsPh_3)_4Cl_2$ in methanol gave Alder-ene product **136**, whereas $PtCl_2$ (dioxane) produced the normal enyne metathesis product **137** for this enyne (eq 33, Scheme 25). $Ru(PPh_3)_4Cl_2$, $Ru_2(CO)_{12}$, and $Ru(NO)Cl_3$ were all ineffective in promoting the cycloisomerization.

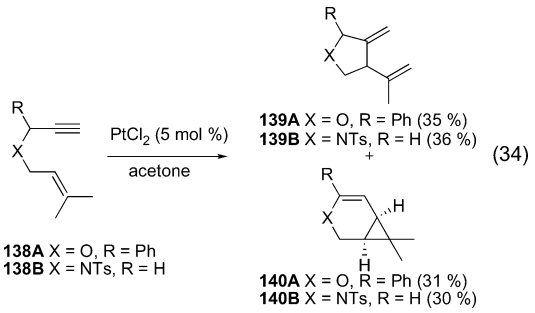
Scheme 25[52]



entry	catalyst	**136**	**137**
1	$RuCl_3$ / MeOH	42 %	--
2	$Ru(AsPh_3)_4Cl_2$ / MeOH	59 %	--
3	$PtCl_2$ / dioxane	--	45-50 %

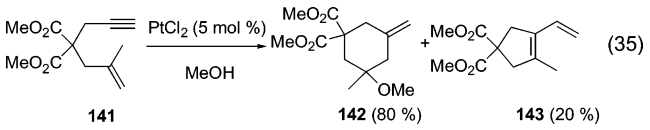
The substitution pattern on the enyne can have a dramatic effect on the course of reaction. Substituted enynes **138** produced the Alder-ene product **139** and

cyclopropanes **140** without any enyne metathesis products (eq 34).



(34)

The ring size formed in the cyclization can be influenced by the alkene substitution pattern. Geminally substituted alkene **141** gave the six-membered ring ether **142** in high yield (eq 35).

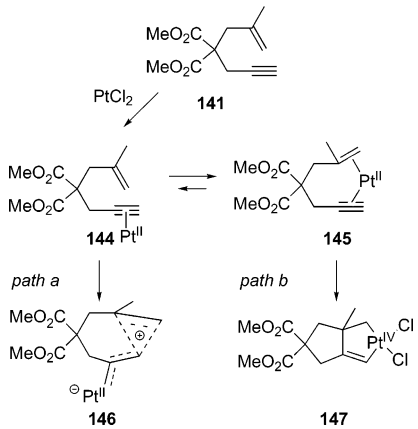


(35)

Enyne metathesis leading to product **143** was a minor pathway because charge accumulation on the tertiary carbon is more favorable. Consistent with this analysis, enynes containing terminal alkenes are poor substrates[52] due to the relatively poor stabilization of charge in the polar cyclization step. Deuterium labeling studies showed that deuterium was incorporated from the solvent.

Mechanistic thought about alkoxycyclization is relevant to enyne metathesis because both pathways may have a common beginning. Echavarren considered two possible pathways leading to the cyclization. As Pt(II) coordinates to the alkyne, does it polarize it enough for cyclization by the alkene (path a) or will the η^2-alkyne complex coordinate the alkene en route to platinacycle formation (path b, Scheme 26)? Echavarren used DFT calculations to locate the η^2-alkyne complex with bidentate coordination of the alkene and compared it to the "outside" coordination of the alkyne with "backside" solvation by the alkene.[52] The bidentate transition state arising from oxidative cyclometalation was found to have a significant activation energy of 29.6 kcal/mol, although it might be lower due to solvation in the polar solvent medium. In contrast, external activation of the alkyne with alkene solvation en route to cyclopropyl platinacarbene was found to have a much lower activation barrier of only 10.3 kcal/mol. As a result, the authors favored external platinum(II) activation of the alkyne as an ionic process through path a. The mechanistic pathway **141** to **144** to **146** is consistent with the nonclassical ion formulation espoused by both Fürstner[42,43,45] and Murai and Chatani et al.[38,39,41,48] The intermediacy of nonclassical ions provides a global mechanistic summary that explains the enyne metathesis products, products of rearrangement, substrate-dependent cyclopropanation, and related pathways such as alkoxycyclization. When a resulting cation benefits from additional structural stabilization (tertiary carbocation) and/or solvation (polar hydroxylic solvent), it may be regarded as a classical carbocation, and reactivity (e.g., with allyl trimethylsilane or methanol) can be interpreted in this way. It is likely that this global summary applies to good Lewis acids such as metal halides capable of strong polarization of the alkyne. The isolation of a cyclobutene in the $GaCl_3$-catalyzed enyne bond reorganization[48] reinforces this assertion.

Scheme 26[52]



The platinum(II) salts give contrasting behavior with enynes depending on solvent media and reaction conditions. The cycloisomerization studies show that the exposed end of delocalized charge can be intercepted by a nucleophile (allyl trimethylsilane, carbocyclization) or by a polar solvent molecule (alkoxycyclization). When a polar escape pathway is not present (e.g., reactions conducted in toluene) as in the cyclopropanation work, the enyne delocalizes charge through nonclassical structures, which ultimately results in loss of charge by elimination of an electron-deficient metal carbene. The effectiveness of cyclopropanation also depends on geometrical constraint of the substrate, which may either promote nonclassical ion evolution or prevent bidentate complexation by the metal center. In polar coordinating solvents, the enyne metathesis may involve coordination of the alkyne only. Coordinating solvent can solvate the metal center interfering with enyne binding, and it can influence the course of the metathesis by stabilizing and then intercepting the intermediate as charge develops on the bound enyne. The positions of highest charge density can be identified through classical canonical resonance structures. The ability to switch between these two different modes by solvation influences the course and the outcome of the metathesis.

The two recent mechanistic proposals developed for both metal salt-catalyzed enyne metathesis and competitive pathways reflect new thinking about enyne hapticity and charge development in the reactive intermediates. The cyclopropanation and enyne alkoxycyclization also indicate that the conventional rationale involving classical carbocations (as zwitterions with the negatively charged metal) is not adequate to describe the range of alkenes that serve as nucleophiles. For the electrophilic $PtCl_2$-catalyzed enyne metathesis and related reactions, the nonclassical ion mechanism is progressive and provides a good global explanation for the enyne me-

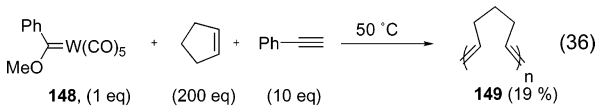
tathesis and the related transformations discussed in this section.

2.2. Metal Carbene-Mediated Enyne Metathesis

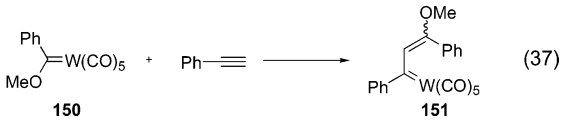
2.2.1. Fischer Carbene Complex-Catalyzed Enyne Metathesis

Early examples of enyne metathesis utilized metal Fischer carbene catalysts. At the time, these were the premiere catalysts, and there was considerable interest in the organometallic chemistry of these complexes. The metal Fischer carbenes were often used stoichiometrically, and a variety of products were typically formed. By current standards of functional group tolerance and catalytic efficiency, these metal complexes are not considered practical. Nonetheless, this initial phase of enyne metatheis research was significant because it identified many of the basic organometallic processes that were intertwined with early mechanistic thinking.

Katz and co-workers observed that tungsten carbonyl complex **148** did not promote polymerization of cycloalkenes unless phenylacetylene was present.[2] When phenylacetylene was present, ring-opening metathesis polymerization (ROMP) of cycloalkenes took place to produce the "polyalkenamers"; however, only small amounts of alkyne were needed to promote the polymerization. Thus 200 equiv of cyclopentene was converted to polymer in 19% isolated yield using 1 equiv of tungsten carbene initiated by 10 equiv of phenylacetylene modifier (eq 36). It was suggested that the acetylene promotes initiation as depicted in eq 37.

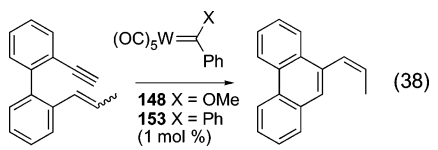


148, (1 eq) (200 eq) (10 eq) **149** (19 %) (36)



150 **151** (37)

Katz and Sivavec showed that ring-closing EYM was possible to make vinyl phenanthrenes.[53] At the time it was fairly common to use stoichiometric amounts of metal Fischer carbene complex. Under *catalytic conditions,* the tungsten Fischer carbenes **148** or **153** promoted the ring-closing EYM of **152** to give phenanthrene **154** in 26% and 19% yields, respectively (eq 38).

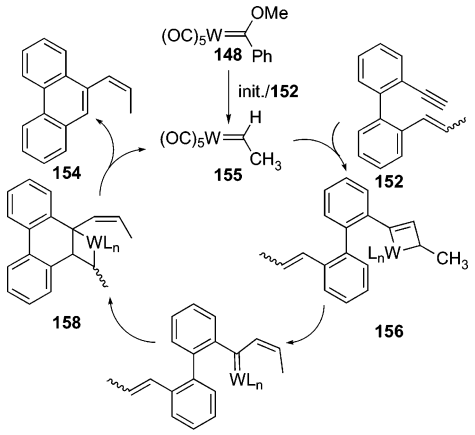


148 X = OMe
153 X = Ph
(1 mol %)

152 **154**
X = OMe, (26 %, 78 % cis)
X = Ph, (19 %, 95 % cis) (38)

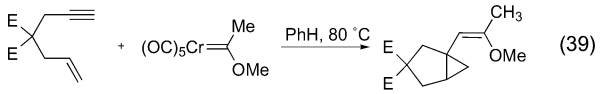
The tungsten carbenes give a preference for the *Z*-isomer although the starting enyne is a cis/trans mixture, possibly due to a C−H agostic interaction (**156** to **157**, Scheme 27). Mechanistically, Katz proposed that the tungsten carbene **148** would initiate by transalkylidenation (ethylidene transfer from **152**) to produce ethylidene **155**, the propagating catalyst (Scheme 27). Cycloaddition of the tungsten ethylidene with the alkyne followed by streoselective electrocyclic ring opening produces a vinyl carbene. The ring-closing metathesis onto the styrene regenerates the tungsten ethylidene and gives the cyclized product.

Scheme 27[53]



157
L_n = $(CO)_4$ or $(CO)_5$

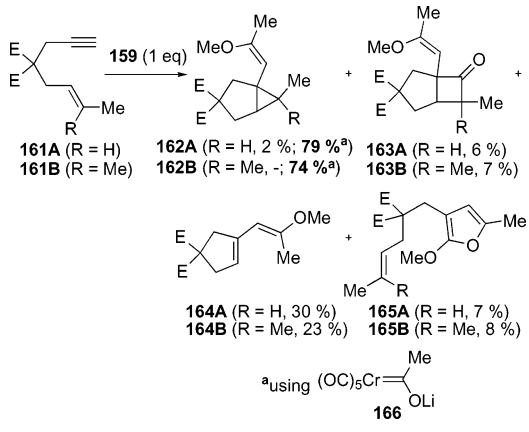
Hoye and co-workers demonstrated that chromium Fischer carbenes promote enyne metathesis but found that the reaction was highly sensitive to alkene substitution.[54−56] Treatment of enyne **49A** with chromium(0) carbene **159** produced a cyclopropane apparently from reductive elimination of a chromacyclobutane (eq 39).



49A (1.5 eq) **159** **160** (69 %, 5:1 *E*/*Z*) (39)

Additional substitution on the alkene (e.g., **161A**) gave more of the enyne metathesis product **164A** over cyclopropane, but cyclobutanone **163A** and furan **165A** were obtained as significant byproducts (Scheme 28). The substituted enyne **161B** gave similar results. The chromium enolate **166** gave higher selectivity for the cyclopropanes (**162**), which were obtained in good isolated yields.[56] The chromacyclobutane **168** that leads to cyclopropane **162** through reductive elimination may also produce the enyne metathesis product

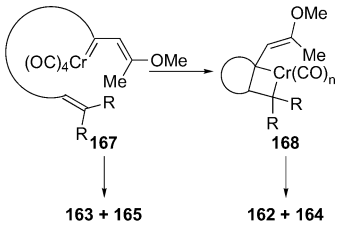
Scheme 28[54,56]



161A (R = H)
161B (R = Me)
162A (R = H, 2 %; **79 %**[a])
162B (R = Me, -; **74 %**[a])
163A (R = H, 6 %)
163B (R = Me, 7 %)
164A (R = H, 30 %)
164B (R = Me, 23 %)
165A (R = H, 7 %)
165B (R = Me, 8 %)

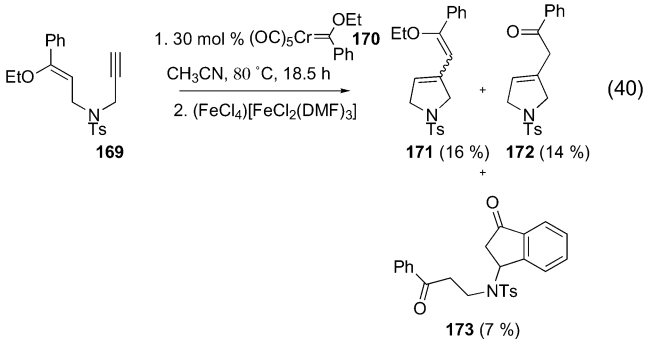
[a] using **166**

Scheme 29[54,55]



162 through [2+2] cycloreversion, a process favored for **161A**,**B** due to greater stability of the produced chromium carbene $(OC)_5Cr{=}CR_2$ (from **168**, Scheme 29). The competitive pathway leading to cyclobutanone **163** and furan **165** would occur through migratory insertion of carbon monoxide (see **167**) and either cyclodemetalation (to produce **165**) or ketene−alkene cycloaddition (to produce **163**). Generation of cyclobutanone **163** could also arise by migratory insertion of CO on chromacyclobutane **168**, but a mechanism involving cycloaddition of ketene was preferred based on earlier work by Wulff and Kaesler.[57]

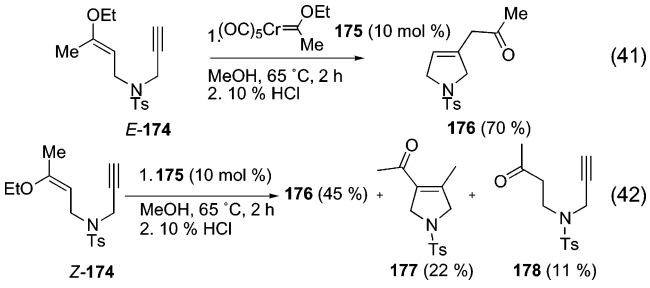
Mori used chromium Fischer carbenes to promote ring-closing EYM for the synthesis of nitrogen heterocycles.[58−60] Substituted enol ether **169** underwent ring-closing EYM using substoichiometric amounts of chromium Fischer carbene **170** to produce metathesis products **171** and **172** in 30% combined yield (eq 40).



(40)

The suggested mechanism is identical to that proposed by Katz.[4] The isomeric enol ethers ***E*-174** and ***Z*-174** gave contrasting results (eqs 41 and 42, Scheme 30). Whereas the *E*-isomer ***E*-174** underwent

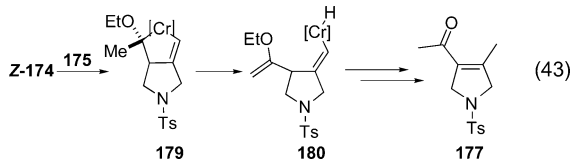
Scheme 30[59,60]



(41)

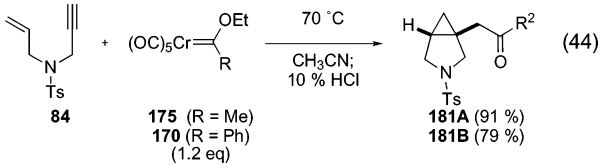
(42)

clean EYM to produce **176** after hydrolysis of the isomeric enol ethers, the *Z*-isomer ***Z*-174** gave only 45% conversion to metathesis product and also produced a rearranged enone **177** along with the hydrolysis product of unreacted enol ether ***Z*-174**. To explain the rearranged enone byproduct (**177**), Mori suggested that a chromium-mediated cyclometalation is followed by β-hydride elimination and reductive elimination (eq 43).



(43)

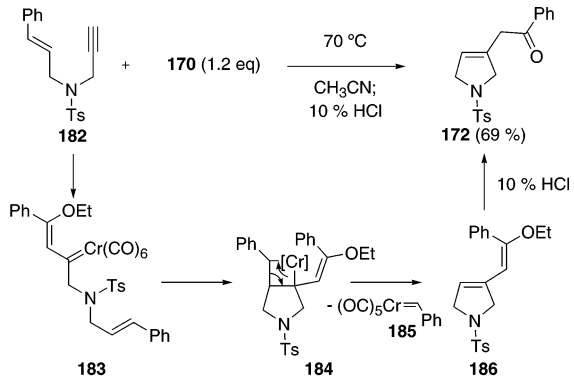
Enol ether hydrolysis and double bond migration would then give **177**. When enol ethers were not present in the enyne substrate, cyclopropanes were observed as the major products (eq 44).



(44)

Cyclopropanes had been previously observed in carbocyclic systems by Hoye and co-workers.[54] The cyclopropanations required stoichiometric (1.2 equiv) Fischer carbene complex **175** or **170**. When the alkene was substituted with a phenyl group, the metathesis product was formed in good yield (Scheme 31). Presumably phenyl substitution of the alkene

Scheme 31[58]



results in greater stability of the produced chromium(0) carbene (produced as benzylidene **185**, Scheme 31), which is generated by fragmentation of the chromacyclobutane **184**, thereby favoring metathesis (lower path, Scheme 31). Chain-extended enynes could also be transformed into cyclopropyl piperidines in moderate yields.

The use of Fischer carbenes marks the origin of the carbene-catalyzed enyne metathesis germline. These catalysts have a historical place in enyne metathesis, but their synthetic use is not currently practical. The fundamental organometallic processes that are at work in both metal salt-catalyzed cycloisomerization and ruthenium carbene-catalyzed enyne metathesis emerged from this body of work. Mori's investigations set the reactions' potential before synthetic chemists and illustrated that metal carbenes could be used in organic transformation. The high loadings, many times stoichiometric, difficult handling of the carbene complexes themselves, and limited functional group

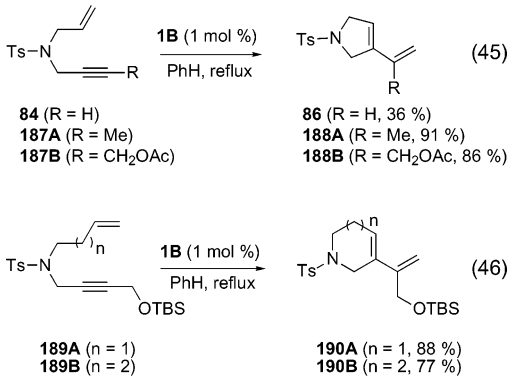
compatibility prevented their widespread use. However, development in catalyst technology was sure to happen and would lead to more widespread application. This initial stage defined the problems clearly, paving the way to wider utility once catalytic and more chemoselective metal carbenes were found.

2.2.2. Enyne Metathesis with Ruthenium Carbenes

In the early 1990s, the ruthenium carbenes developed by Grubbs aroused considerable attention because of their functional group tolerance. The functional group tolerance and alkene chemoselection had become well-documented in alkene metathesis.[11,25,61−64] During this time, interest in enyne metathesis was rekindled and resulted in two important studies. Mori and Kinoshita used ruthenium carbenes to trigger ring-closing enyne metathesis,[65] notable because it represented a shift away from the Fischer carbene complexes used previously to catalyze enyne metathesis. The metatheses catalyzed by Fischer carbenes suffered from high, sometimes stoichiometric, catalyst loadings and poor compatibility with heteroatom functionality. Concurrently, Grubbs' group used ruthenium carbenes to trigger a tandem enyne metathesis to form carbobicycles.[66] Together, these studies demonstrated the increased catalytic efficiency achievable with the ruthenium carbenes and illustrated the functional group compatibility of the Grubbs carbene complexes in enyne metathesis.

Mori and Kinoshita demonstrated that Grubbs' catalyst could be used to promote ring-closing enyne metathesis with high catalytic efficiency.[65] It was found that terminal alkynes gave poor conversions in contrast to internal alkynes, which proceeded to dienes **188** in excellent yield (eq 45, Scheme 32). This

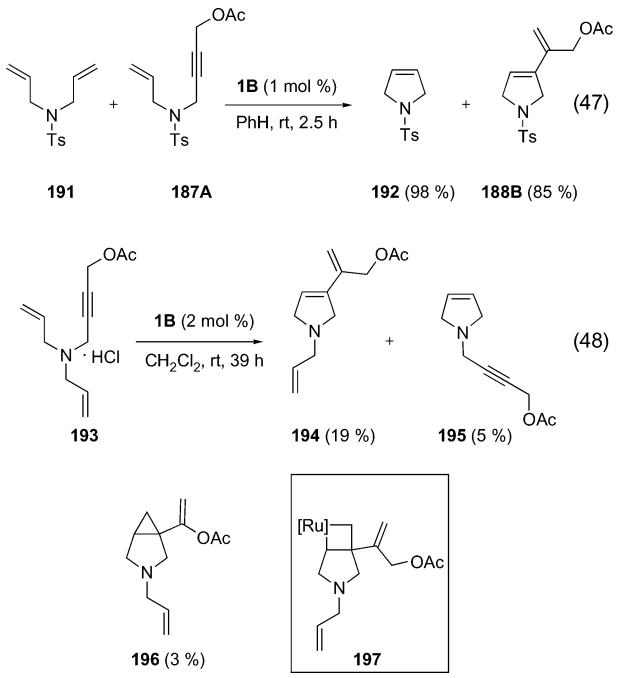
Scheme 32[65]



result is still not completely understood and has been repeatedly observed in related synthetic studies (see section 3.1). Ester and trimethylsilyl substitution was not well-tolerated, and low conversions were found in these cases. Six- and seven-membered rings were also synthesized in very good yield (eq 46).

The competitive rates of alkene metathesis and enyne metathesis were addressed in two competition experiments (Scheme 33).[65] Ring-closing EYM was suggested to be slightly slower than ring-closing alkene−alkene metathesis as evidenced by the product ratio of **192** and **188B** determined after 2.5 h (eq 47). Since **191** has two alkylidenation sites, it has a 2-fold greater probability of ring-closing alkene metathesis. Dienyne **193** was subjected to metathesis,

Scheme 33[65]



and in this case, the ring-closing EYM product **194** was predominant, determined at 60% conversion (eq 48). In the last case, cyclopropane **196** was found in 3% yield, suggested to arise from reductive elimination of the ruthenacyclobutane intermediate **197** (Scheme 33, boxed inset).

The result of eq 48 suggests that enyne ring-closing metathesis is faster than alkene−alkene ring-closing metathesis. The course of the reaction was interpreted based on the faster reaction rate of Ru=CH_2 with the alkyne moiety of the dienyne **193** (compared to transalkylidenation with either 1-alkene). Alternatively, either metathesis could be triggered by alkylidenation at one of the 1-alkene sites and followed by selective alkyne ring-closing metathesis.

The first examples of tandem enyne metathesis were reported by Grubbs' group in 1994.[66] In this process, various dienynes were subjected to ring-closing EYM to produce an array of carbobicyclic systems. The reaction mechanism likely involves initial alkene metathesis and then ring-closing metathesis onto the hindered internal alkyne (Scheme 34). The resulting vinyl carbene **F1** experiences ring-closing alkene metathesis to form the second ring. In this way, the [4.3.0] and [5.4.0] bicyclic rings were formed in excellent yields (entries 1 and 2, Table 4). In cases where competitive alkylidenation between

Scheme 34

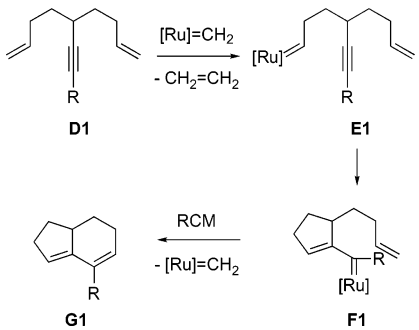
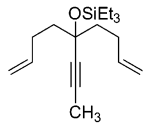
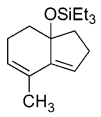
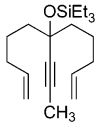
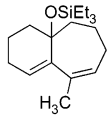
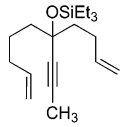
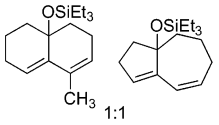
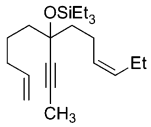
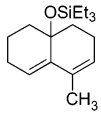
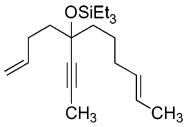
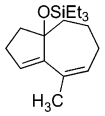
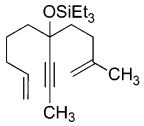
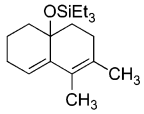
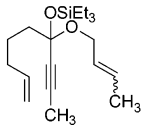
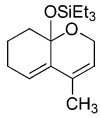
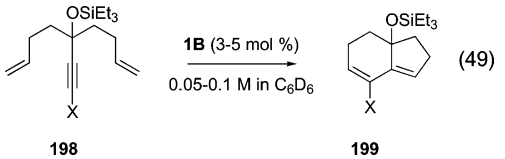


Table 4[66]

entry	substrate	diene	yield (%)
1			95
2			88
3		 1:1	86
4			83
5			78
6			89
7			88

1-alkenes is possible, the isomeric ring systems were formed in equal amounts. Differentiation of the alkenes is possible through substitution since more highly substituted alkenes alkylidenate more slowly (entry 4). Similar alkene differentiation is evident in entries 5−7 and can be used to control ring size. The ring-closing metathesis can be used to effectively form tri-substituted and even tetra-substituted alkenes (entry 6). The reactions are conducted under dilute conditions in order to suppress dimerization arising from cross reaction of the intermediate vinyl carbenes. Low concentration of dienyne reactant also reduces the likelihood of methylene transfer to the intermediate vinyl carbene. As will be seen in section 3.3, a difficult second ring closure often results in competitive methylene transfer to give the product of a single ring-closing metathesis.

The tandem dienyne metathesis proved sensitive to alkyne substitution. In this study, the tandem ring-closing metathesis was evaluated for a variety of alkynyl substituents.[67] The terminal alkynes underwent reaction more quickly than internal alkynes (eq 49, Table 5). Steric bulk slows the ring-closing



198 **199** (49)

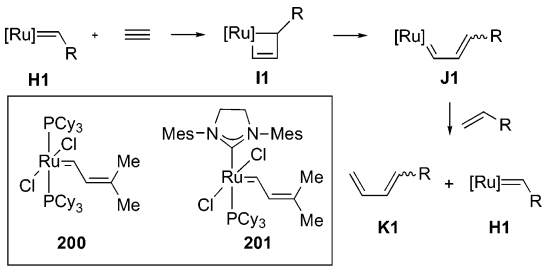
Table 5[67]

entry	X	**199**	yield (%)	entry	X	**199**	yield (%)
1	H	**A**	>98	7	TMS	**G**	NR
2	Me	**B**	95	8	$SnBu_3$	**H**	NR
3	*i*-Pr	**C**	78	9	Cl	**I**	NR
4	*t*-Bu	**D**	NR	10	Br	**J**	NR
5	Ph	**E**	96	11	I	**K**	NR
6	CO_2Me	**F**	82				

step, such that heating is necessary for isopropyl (entry 3) and phenyl substitution (entry 5). An alkyne bearing an ester group (entry 6), a critical electronic requirement for many of the successful enyne metatheses using Pd(II) and Pt(II), underwent metathesis with ruthenium carbenes (entry 6). The *tert*-butyl substituted alkyne failed to undergo reaction (entry 4) as did silicon (Me_3Si) and tin (Bu_3Sn) substitution, probably for steric reasons (entries 7 and 8). The lack of reactivity of halo-substituted alkynes is somewhat surprising and likely to be a steric issue. Some of these difficulties have already been surmounted with the more reactive newer generation catalysts based on the *N*-heterocyclic carbene ligand (see Tandem Metathesis, section 3.3).

The mechanism of ruthenium carbene-catalyzed enyne metathesis involves vinyl carbene intermediates. The mechanism is at best sketchy since it is based on many assumptions and lacks a careful kinetic investigation. In a few cases, reaction monitoring by NMR shows the appearance of alkylidene before consumption of the alkyne, which suggests that initiation by transalkylidenation is fast relative to carbene−alkyne cycloaddition.[68] Ruthenium carbene **H1** (R = H or R = alkyl) reacts with the alkyne to produce a ruthenacyclobutene that can undergo electrocyclic ring-opening to provide a vinyl carbene **J1** (Scheme 35). Catalytic turnover would take place

Scheme 35



as the vinyl carbene **J1** undergoes either methylidene or alkylidene transfer to give the diene product. In Scheme 35, methylene transfer is shown that results in production of a new carbene ready for another catalytic cycle. From Grubbs' work, vinyl carbene species **200** and **201** (and **1B**) are known to be active initiators of alkene metathesis, especially ROMP of strained cycloalkenes.[11,13,69,70] At the same time, vinyl carbene **J1** is stabilized by conjugation.[71] Ruthenium carbene **Ru gen-1** only slowly polymerizes alkynes, a major reaction pathway observed with Schrock carbenes.[72] This is consistent with the idea that vinyl carbenes **J1** are less reactive (more stable) than alkylidenes **H1**, since polymerization would require the vinyl carbene to react again with alkyne.[73]

For an intramolecular metathesis, the study of Mori and Kinoshita [65] demonstrated that alkene and

alkyne metathesis occur on the same time scale. However, the intramolecular reaction may be different than intermolecular enyne metathesis as there is potential for simultaneous coordination of the alkene and alkyne to the 14-electron intermediate. This may alter the kinetics of catalysis as compared to the intermolecular reaction, where the effective molarity of the second unsaturated reactive partner is not as high. This may also influence the regiochemistry of metal carbene addition to the alkyne. For the ring-closing enyne metathesis, whether bidentate coordination is possible also depends heavily on the tethering unit, the alkyne substitution, and the presence of other heteroatom groups that may be geometrically disposed for competing bidentate coordination (chelative traps).

The first report of intermolecular enyne metathesis using ruthenium carbenes originated from Blechert's group.[72] Blechert and co-workers recognized the most synthetically attractive features of the intermolecular (cross) enyne metathesis: that it is both inherently cross selective[74−76] and atom economical. Using 2−3 equiv of alkene, a variety of propargylic derivatives underwent cross metathesis to give 1,3-dienes as mixtures of *E*/*Z* isomers (eq 50, Table 6). In most

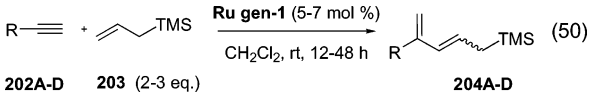


Table 6[72]

entry	alkyne	R	yield (%)
1	**202A**	CH_2OTHP	81
2	**202B**	CH_2OAc	90
3	**202C**	$CH(CH_3)OAc$	63
4	**202D**	CH_2OCO_2Me	89

cases, the dienes were produced as ca. 1:1 *E*/*Z* mixtures. In entry 3, the ratio was 3:1 *E*/*Z*, which was the highest *E*-selectivity reported. Equimolar mixture of alkene and alkyne also afforded the diene product, albeit with lower yields. Interestingly, the formation of alkene dimers occurred only to a limited extent. Up until this time, enyne metathesis had been explored in ring-closing applications or in polymerization. Notably, Blechert pointed out that the Schrock molybdenum catalyst polymerized alkynes under these reaction conditions. In addition, a variety of alkenes were employed as reactive partners (eq 51, Table 7). The mixture of *E*/*Z* isomers could be

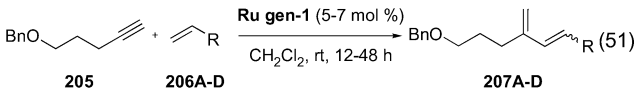
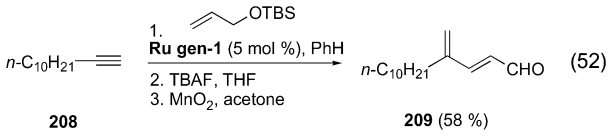


Table 7[72]

entry	alkene	R	yield (%)
1	**206A**	CH_2SiMe_3	86
2	**206B**	$CH_2{}^tBu$	82
3	**206C**	$(CH_2)_2CH(CO_2Me)_2$	76
4	**206D**	CH_2OTBS	83

converted to a single enal through cross metathesis with $TBSOCH_2CH{=}CH_2$, deprotection, and allylic oxidation with MnO_2 (eq 52). Unprotected alcohols underwent reaction but with much lower yields.

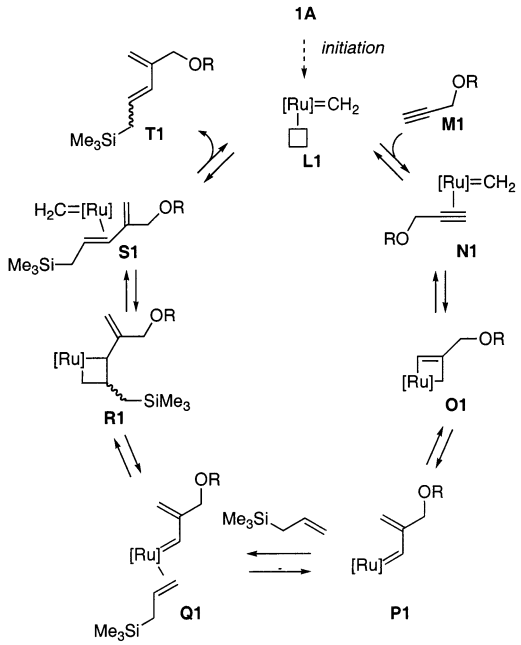


Blechert's study also pointed out that internal alkynes and internal alkenes failed to undergo reaction. Recently both internal alkynes[77−81] and an internal alkene[82] have given cross enyne metathesis using the more reactive **Ru gen-2** catalyst (section 3.2.2).

NMR studies led the authors to propose the generally accepted mechanism for the cross enyne metathesis.[72] Observation by NMR revealed that alkynes reacted faster than alkenes with the ruthenium carbene, that alkynes were only slowly polymerized by ruthenium carbenes in the absence of alkenes, and that the alkynes underwent rapid reaction on introduction of the alkene to the reaction mixture. The regioselectivity was rationalized by the addition of $Ru{=}CH_2$ to the 1-alkyne in such a way as to position the bulky metal moiety at the terminal position of the alkyne starting material. The authors commented that the reason enyne metathesis takes longer than the corresponding alkene metathesis may be attributed to the greater stability of the intermediate vinyl carbene. These vinyl carbenes are seldom encountered in alkene metathesis.

The proposed mechanism of cross enyne metathesis that emerged from Blechert's study is summarized in Scheme 36. Alkyne and diene binding steps have

Scheme 36

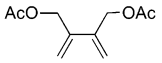
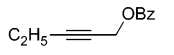
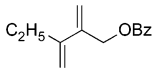
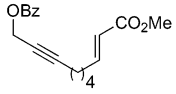
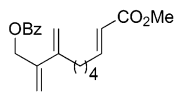
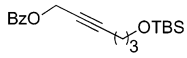
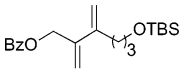
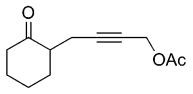
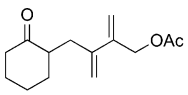
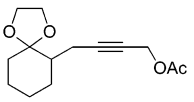
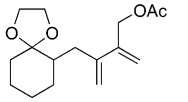
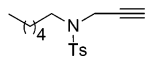
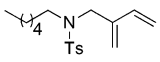


been added to the proposed mechanism, and all steps are written as reversible, although reversibility has not been established, particularly in the sequence **N1** to **O1** to **P1**. Initiation of the benzylidene generates a methylidene carbene **L1**. The ruthenium methylidene binds alkyne and undergoes cycloaddition to access ruthenocyclobutene **O1**, which opens to produce a vinyl carbene **P1**. Alkene binding and cycloaddition of the alkene takes place, proceeding through

ruthenacyclobutane **R1**, and retro-[2+2] cycloaddition provides the conjugated diene and regenerates the propagating carbene. The mechanism presented in Scheme 36 suggests that $Ru{=}CH_2$ reacts with the alkyne due to its presumed reactivity and to rationalize the observed regiochemistry. For intramolecular enyne metathesis, the alkylidenation of 1-alkenes precedes enyne metathesis, indicating that alkylidenes also possess sufficient reactivity to react with alkynes. The mechanism of Scheme 36 can be adapted to illustrate alkylidene reacting instead of $Ru{=}CH_2$, but regioselectivity is harder to rationalize in this instance and will require additional mechanistic information.

Mori and co-workers discovered that ethylene could be employed as the alkene in intermolecular enyne metathesis.[83] Disubstituted butadienes can be accessed from internal alkynes and ethylene, employed at balloon pressure. Mori's group recognized that ethylene as the alkene simplifies the intermolecular metathesis, which must compete with intermolecular diene metathesis and intermolecular alkyne metathesis. Using the first-generation Grubbs' catalyst (3−10 mol % **1A**), a variety of internal alkynes gave the cross metathesis in good to excellent yields (Table 8).

Table 8[83]

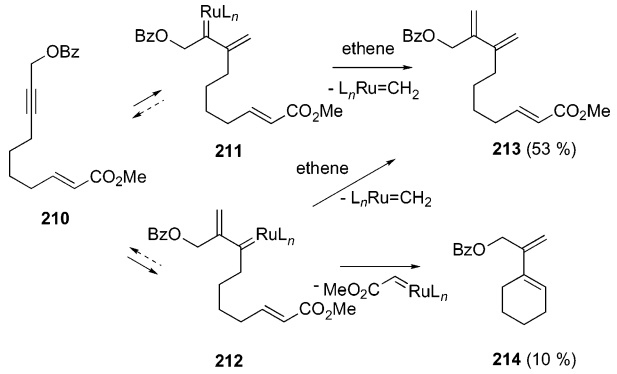
entry	alkyne	diene	yield (%)
1			66[a] 71[b]
2			62[b]
3			53[b]
4			60[b]
5			74[b]
6			48[b]
7			81[c]

[a] 3 mol % **Ru gen-1** used. [b] 10 mol % **Ru gen-1** used. [c] 5 mol % **Ru gen-1** used.

Propargylic esters were well-behaved, and remote functionality such as enoate (entry 3), silyl ether (entry 4), ketone (entry 5), and ketal (entry 6) was found to be fully compatible with the carbene-catalyzed metathesis. One terminal alkyne was also reported (entry 7), giving a 2-substituted butadiene in excellent yield.

In a full paper on the ethylene−alkyne metathesis, Mori and co-workers elaborated the ethylene metathesis to include other alkynes, provided mechanistic insight, and demonstrated an intramolecular thermal cycloaddition to produce bridgehead alkenes.[84] Ethylene metathesis on internal alkynes can occur through two possible regiochemical modes of addition, which were probed in alkyne **210** (Scheme 37).

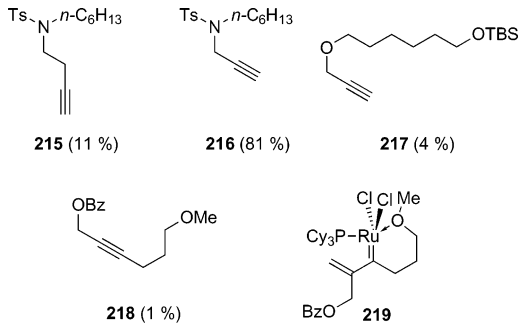
Scheme 37[84]



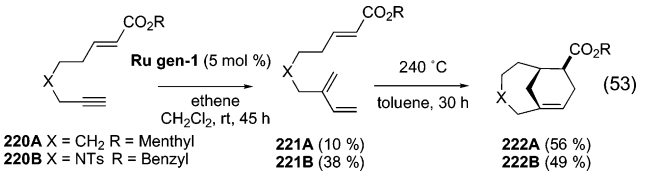
Exposure of the Grubbs' catalyst (**Ru gen-1**) to ethylene produces the methylidene, which presumably adds by cycloaddition to the alkyne of **210** to give **211** and **212**. Both modes of addition must be operating in ethylene metathesis of internal alkynes. The byproduct **214** (10% yield) suggests that vinylcarbene **212** is formed along with **211**. The relative ratio of **211** and **212** cannot be inferred from this experiment because **212** can also undergo methylene transfer with ethylene to produce **213**, the major product. It was not established whether the initial cycloadditions are reversible.

The study of ethylene metathesis also identified substrates that are sensitive to chelation. Tosyl amides underwent ethylene metathesis with varying degrees of success, presumably due to chelating structures that form and suppress catalytic turnover. Although propargyl tosylamide **216** gave good yield of butadiene, other alkynes performed poorly in this reaction and are illustrated below, with yields of butadiene produced given in parentheses (Chart 2).

Chart 2[84]



Ethers located in the propargylic position (e.g., **217**) provided difficulty with respect to catalysis. More remote effects were also observed (**216** vs **215**). Chelation by remote Lewis basic oxygen atoms such as that represented by chelate **219** likely limits catalyst turnover and shuts down catalysis. Ynenoates **220A**,**B** gave low isolated yields of butadiene (eq 53). Nevertheless, thermal intramolecular cycloaddition of **221A**,**B** produced the bridgehead alkenes **222** in good yields.



(53)

Mori et al. demonstrated that ethylene gas is beneficial in ring-closing enyne metathesis, *intramolecular reactions where the ethylene is not incorporated into the product*.[71] Ring-closing enyne metathesis of terminal alkynes gave low yields of diene, which led the authors to infer that the active catalyst was depleted. The secondary metathesis of diene product would produce a coordinated vinyl carbene, considered to be stable and unreactive for further metathesis. Trnka et al. later identified a coordinated vinyl carbene that was found to be inactive in metathesis,[85] supporting this hypothesis. To intercept secondary metathesis pathways, the authors included ethylene to react in a degenerate equilibrium with $Ru{=}CH_2$.

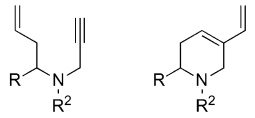
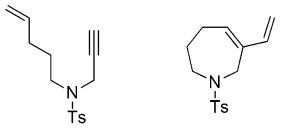
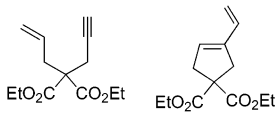
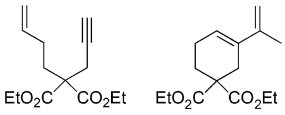
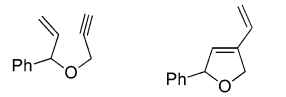
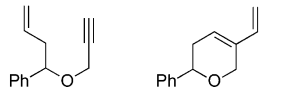
The use of ethylene under balloon pressure in ring-closing EYM gave significant improvements in the yields of cyclic dienes (Table 9). In most cases, ring-closing enyne metathesis conducted without ethylene gave very low conversion (entries 1 vs 2; entries 10 vs 11). In all of the other cases, ethylene was found to improve the yields (and decrease reaction times) of the produced dienes. From Table 9, it can be seen that the use of ethylene is beneficial for the synthesis of five-, six-, and seven-membered rings.

Mechanistically, it was proposed that $Ru{=}CH_2$ reacts with the alkyne first and then closes onto the pendant alkene. In the proposed mechanism of enyne cross metathesis, the vinyl carbene produced has the ruthenium fragment positioned at the terminal position of the alkyne (see **P1**, Scheme 36). In light of this, $Ru{=}CH_2$ should add to the alkyne with the opposite regiochemistry, but this was not discussed. The presence of the alkene in the enyne could influence the regiochemistry of methylidene addition to provide the proximal or internal vinyl carbene. More likely, the success of the propargyl tosylamides (entries 1−5) compared to the shortcoming of similar propargyl tosylamides in the ethylene metathesis (eq 53) attest to the dominating alkylidene reactivity in the ring-closing enyne metatheses of Table 9. Alkylidenation would lead to an intramolecular reaction and dictate the regiochemistry to give the observed products, without the production of butadienes that would occur from regio-opposing addition of $[Ru]{=}CH_2$ to alkyne.[86−92]

The idea that ethylene maintains a higher concentration of active catalyst and reduces the number of unproductive catalyst resting states has had a major impact on synthesis applications using ring-closing enyne metathesis. As a result of the paper by Mori and co-workers,[71] most of the subsequent literature examples conducting ring-closing enyne metathesis utilize ethylene, either as an atmosphere (ethylene balloon, "Mori's conditions") or through ethylene perfusion during the reaction.

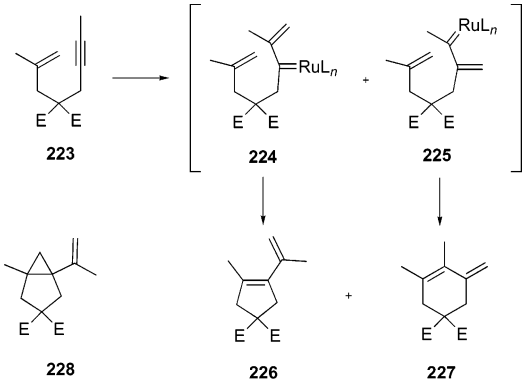
For internal alkynes, there is little control in the regiochemistry of ruthenium methylidene addition.

Table 9[71]

entry	enyne	diene	atmosphere	yield (%)
				
1	R = H, R^2 = Ts		Ar	19
2	R = H, R^2 = Ts		ethene	99
3	R = CO_2Et, R^2 = $COCF_3$		ethene	92
				
4			Ar	49
5			ethene	65
				
6			Ar	15
7			ethene	99
				
8			Ar	76
9			ethene	99
				
10			Ar	6
11			ethene	96
				
12			Ar	42
13			ethene	99

With suitably substituted 1,6-enynes, metal carbene addition to the alkyne can produce different ring sizes through ring-closing metathesis.[93,94] If $Ru{=}CH_2$ reacts with the internal alkyne with either regiochemistry, two isomeric vinyl carbenes are produced (Scheme 38). The vinyl carbenes can undergo ring-

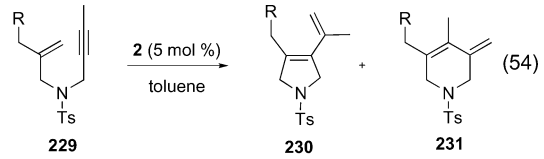
Scheme 38



closing metathesis to provide dienes **226** and **227**, respectively. If the ring-closing reactions offer kinetic control (i.e., if the rate of ring closure is faster than potential equilibration of vinyl carbenes) then the ratio of **226** to **227** in the malonate system reflect the ratios of the intermediate vinyl carbenes. That **226** and **227** are obtained in 43 and 42% yields employing catalyst **2** suggests no regiocontrol in this case. (Interestingly, the cyclopropane **228** was also observed in 3% yield, as seen previously by Mori's group. Presumably **228** arises from reductive elimination of an intermediate ruthenacyclobutane, the usual intermediate arising from ring-closing enyne

metathesis.) In the tosyl amide-linked 1,6-enynes, the ratios were found to be similar regardless of the allylic substitution (eq 54, Scheme 39), although the

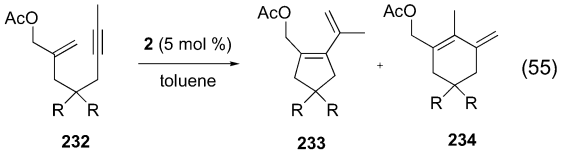
Scheme 39[93]



229 **230** **231**

entry	alkyne	conditions	230	231
1	R = H	80 °C, 6 h	34 %	30 %
2	R = OAc	50 °C, 3 h	41 %	30 %
3	R = OTBS[a]	50 °C, 24 h	29 %	17 %

(a) 10 mol % **2** used.



232 **233** **234**

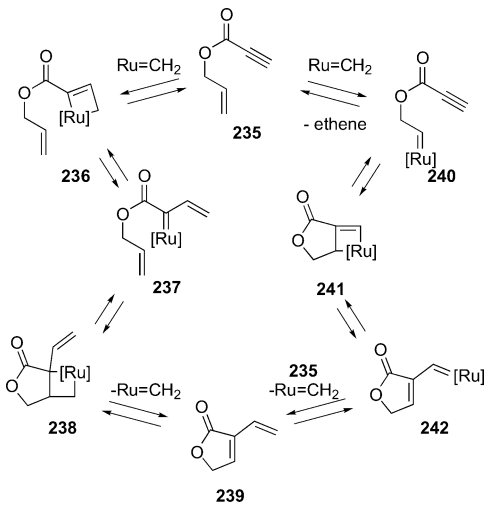
entry	alkyne	conditions	233	234
1	R = CO_2Me	80 °C, 6 h	50 %	39 %
2	R = $O(CH_2O)_2C(CH_3)_2$	80 °C, 15 h	47 %	27 %
3	R = CH_2OBn	80 °C, 24 h	50 %	42 %

bulky TBS ether (entry 3, eq 54) required higher catalyst loading and lengthy reaction times.

Geminal alkene substitution retards the competitive alkylidenation process. As expected, a variety of geminal substituents on the tether gave the reaction (eq 55). The synthesis of highly substituted alkenes was achieved using the more reactive second-generation catalysts, but the product mixtures proved inseparable.

In other cases of enyne metathesis, the alkene partner may undergo alkylidenation first. Data in support of this interpretation comes from NMR studies and competition experiments. In the synthesis of the dimer differolide, Hoye et al. recognized that enyne metathesis could occur by either of two pathways (Scheme 40).[95] The "yne-then-ene" pathway

Scheme 40[95]



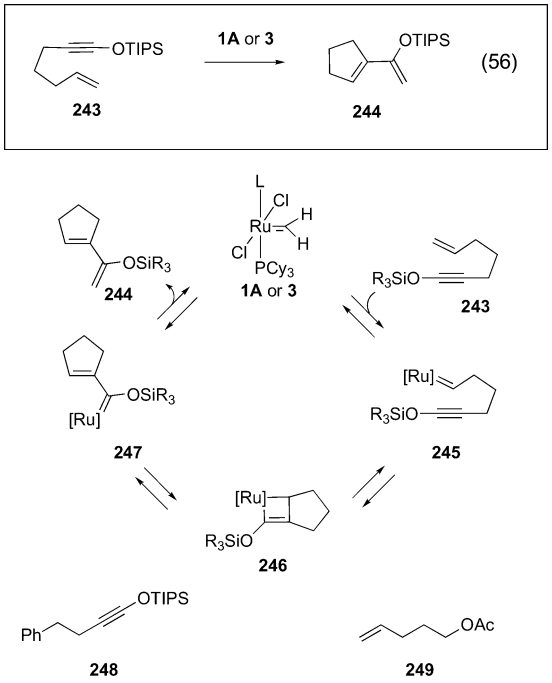
involves addition of a $Ru{=}CH_2$ catalyst to the propiolate to give an enoic vinyl carbene **237**, which would ring-close (via **238**) to give diene **239** and regenerate $Ru{=}CH_2$. Alternatively, the ruthenium benzylidene precatalyst could transalkylidenate onto the allyl ester, losing styrene to produce alkylidene **240** (Scheme 40). This pathway is the "ene-then-yne" pathway, involving reaction of the alkene first. Ring-closing metathesis of **240** accesses vinyl carbene **242,** and critically turnover of vinyl carbene **242** would require another molecule of enyne substrate to supply a methylene (methylene transfer) to give the product. This last step (**242** to **239**) would also regenerate alkylidene **240** ready for the next catalytic cycle. Since NMR experiments indicated production of styrene at a comparable rate as the appearance of new carbene resonances at δ 18.91 (t, J = 4 Hz, assigned to **240**) and a singlet at δ 20.24 (assigned to **242**), the authors favored the "ene-first" mechanism. The authors point out that the intermediate carbenes in the "alkyne-first" pathway would not be observed by ^{1}H NMR due to the absence of carbene protons, and so the positive proof of metal carbenes supports the ene-first mechanism without ruling out the yne-first pathway as a competitive path.

Considering these mechanistic possibilities and guided by the NMR experiments, the authors noted that enyne substrate concentration would influence the rate of appearance of product and affect the success of the desired ring-closing metathesis. While ring-closing reactions are often conducted under dilute conditions to avoid homodimerization, higher enyne concentrations were examined to increase catalyst turnover rate. In the best case, slow addition of 10 mol % **Ru gen-1** to a 0.1 M solution of enyne produced 100% conversion. This study is important because consideration of mechanistic possibilities led to a substantially improved enyne metathesis. The kinetic consequences of vinyl carbene turnover were recognized to be playing a critical role in this difficult ring-closing metathesis.

Kozmin and co-workers also considered available pathways for ring-closing enyne metathesis of alkenyl-substituted alkynyl silyl ethers (eq 56).[96] NMR experiments led the authors to favor the alkene-first pathway for this ring-closing enyne metathesis (Scheme 41). Heating **Ru gen-2** with a stoichiometric amount of model alkyne **248** gave no reaction after 30 min. In contrast, heating model alkene **249** with **Ru gen-2** immediately produced a new carbene species, attributed to the ruthenium alkylidene (cf. **245**) appearing at δ 18.35. Mixing equimolar amounts of all three components (**Ru gen-2**, **248**, and **249**) resulted in loss of the benzylidene carbene proton of **Ru gen-2**, concomitant rise in the new alkylidene carbene resonance and no change in the alkynyl silyl ether.

On the basis of a number of observations discussed in this section, ring-closing enyne metathesis involving 1-alkenes, alkylidenation proceeds first. Transalkylidenation processes in the alkene metathesis manifold are fast relative to intermolecular enyne metathesis.[72] Alkene metathesis involves ruthenacyclobutane intermediates in the Chauvin mechanism. The slower reaction rate of alkyne **248** (Scheme 41) might reflect the additional ring strain of the ruthenacyclobutene intermediate en route to enyne

Scheme 41[96]



metathesis.

Fürstner et al. have produced a comprehensive evaluation of ruthenium carbene catalysts used in enyne metathesis.[97] Quantitative survey of obtained chemical yield and reaction time was provided for a range of metal carbenes (eq 57, Table 10). The

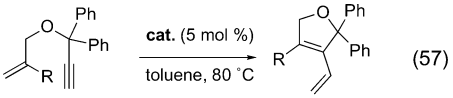
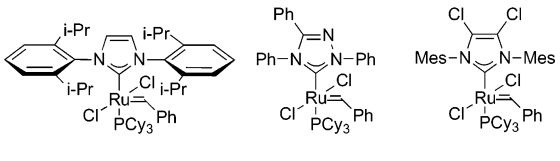


Table 10[97]

entry	enyne	Ru cat.	time	yield (%)
1	**250A**	**2**	60 min	85
2	**250A**	**252**	5 min	88
3	**250B**	**2**	18 h	75
4	**250B**	**252**	17 h	58
5	**250B**	**254**	18 h	74
6	**250B**	**253**	24 h	<5

second-generation Grubbs' complex **3** (**Ru gen-2**) is known to initiate very rapidly in alkene metathesis, and diisopropyl-substituted imidazolylidene **252** may initiate faster due to the steric bulk of the *N*-heterocyclic carbene substituents vis-à-vis Cy_3P dissociation (entry 2, Table 10). By screening the intramolecular, ring-closing enyne metathesis of **250A** with IR thermography, Fürstner's group found that catalysts **Ru gen-2** and **252** were the best, with the next two being catalysts **2** and **254** (Chart 3).[97]

Chart 3



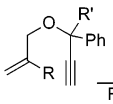
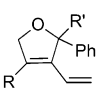
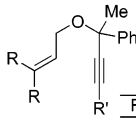
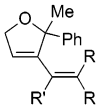
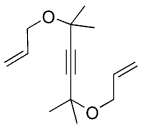
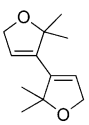
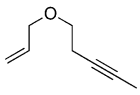
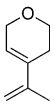
In the IR thermography assay, measured exothermicity is the aggregate of initiation and propagation (ring-closing) events, and so the method does not further separate the two components. Despite the fact that the dihydroimidazole carbenes were found to be the most active, the unsaturated *N*-heterocyclic carbenes were also effective catalysts for ring-closing EYM, although they may initiate more slowly. The best catalyst for the ring-closing enyne metathesis depicted in eq 57 was complex **2**, but complex **252** proved superior in a macro ring-closing alkene-alkene metathesis. In this case, initiation may play a role since alkene metathesis is more likely to benefit from faster intiators than enyne metathesis. Fürstner et al. suggest that there are subtle influences of substrate on the outcome of the metathesis event and that generalizations concerning catalytic potency must be met with caution.

Although a catalyst survey might be justified in the most demanding applications, such as those encountered in complex molecule and total synthesis, most synthetic chemists will choose the catalyst that is generally regarded to be the most active catalyst. Activity is commonly viewed in terms of initiation rate. Since catalyst development is a dynamic area of research, catalysts continue to be improved, and the notion of the most active catalyst is changing and may further depend on the application. Catalyst lifetime (time spent in the catalytic cycle measured as turnover number) also depends on catalyst deactivation, which may be an intrinsic property of the catalyst or depend on the functionality present in a given substrate, or both. For the synthetic chemist, knowledge of functional group and electronic impediments to catalytic efficiency would be highly useful in synthesis planning. Catalyst decomposition can occur as known for alkene metathesis,[8,98,99] but additional decomposition pathways may emanate from the alkyne in enyne metathesis. It is likely that higher turnover catalysts[100] will be realized as decomposition is diminished further and propagation lifetime becomes an object of further investigation.

The unsaturated *N*-heterocyclic carbene complex **2** catalyzes a wide variety of ring-closing enyne metatheses with low catalyst loadings (1 mol %).[97] A systematic evaluation of alkene substitution can be seen in the synthesis of various $\Delta^{3,4}$-dihydrofurans (entries 1−7, Table 11). Geminal alkene substitution slowed the reaction rate substantially, even with the Thorpe−Ingold effect assisting in the five-membered ring closure (entries 1 vs 2). A trisubstituted alkene closed onto a terminal alkyne (entry 5), and internal alkynes of entries 6 and 7 performed well with a terminal alkene partner, although phenylacetylene showed slower reaction and required higher catalyst loading (entry 7). A tandem ring-closing enyne metathesis−ring-closing metathesis gave the bisdihydrofuran (entry 8), and the homopropargyl allyl ether gave clean ring closure in refluxing dichloromethane.

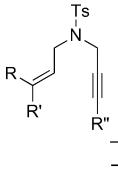
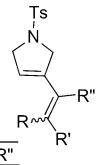
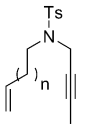
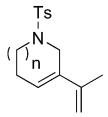
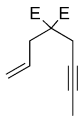
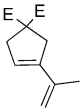
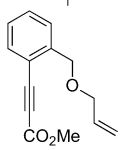
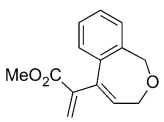
The ring-closing enyne metathesis of a variety of tosylamides was examined with variation of alkenyl and alkynyl substitution using the unsaturated *N*-heterocyclic carbene complex **2**.[97] The terminal alkene closed efficiently onto an internal alkyne (entry 1,

Table 11[97]

entry	enyne	diene	Yield (%)
1	 R = H, R' = Ph		85
2	R = Me, R' = Ph		75[a]
3	R = H, R' = Me		80
4	R = Me, R' = Me		67
5	 R = Me, R' = H		77
6	R = H, R' = Me		93
7	R = H, R' = Ph		87[a]
8			75[a]
9			81[b]

[a] 5 mol % **2** used. [b] Conducted in CH_2Cl_2 at reflux.

Table 12[97 a]

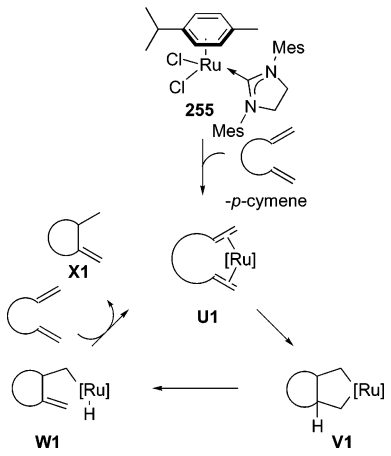
entry	enyne	diene	Yield (%)
1	 R = H, R' = H, R'' = Me		97
2	R = H, R' = Ph, R'' = H		81
3	R = H, R' = Ph, R'' = Me		67
4	R = Me, R' = Me, R'' = H		89
5	R = Me, R' = Me, R'' = CO_2Me		20[b]
6	R = H, R' = H, R'' = C_6H_4COMe		89
7			n = 1, 66
8			n = 2, 81
9			89[b]
10			42

[a] 1 mol % **2** used. [b] 5 mol % **2** used.

Table 12), and the styryl group closed onto both terminal (entry 2) and internal alkynes (entry 3) although the reaction was slower in the latter instance. The *trans*-styrene produced a mixture of diene geometrical isomers. Closure of a trisubstituted alkene onto a terminal alkyne worked (entry 4), but an electronic limitation was apparent in the ring-closing reaction onto a ynoate (entry 5). Aryl-substituted alkynes react in conjunction with a terminal alkene reaction partner (entry 6). Both six- and seven-membered rings were formed with the tosylamide linker (entries 7 and 8). The carbocycle was formed with a malonate linker using an internal alkyne (entry 9) with results that are comparable to those seen in the furan case of entry 6 in Table 11. Last, ring closure to the oxepane gave a moderate yield due to the electron-withdrawing substituent on the alkyne (entry 10).

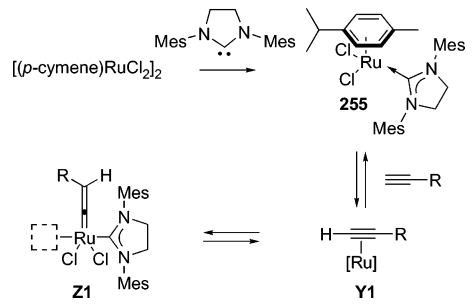
The catalyst system developed by Dixneuf and co-workers is thought to generate ruthenium carbenes in the presence of enynes.[101,102] The Dixneuf precatalyst is composed of $[RuCl_2(p\text{-cymene})]_2$, 1,3-dimesitylimidazolium chloride (IMesCl), and Cs_2CO_3 in a 1:2:4 stoichiometry. A second formulation utilizes the better σ donor, 1,3-dimesityldihydroimidazolium chloride (also called imidazolinium, H_2IMesCl) as the precursor to the saturated *N*-heterocyclic carbene ruthenium complex. The in situ catalyst is borne in a noncarbenic state. The catalyst was developed specifically to promote enyne metathesis,[103] and the related reaction with 1,ω-dienes used for conventional ring-closing metathesis does not produce RCM but promotes cycloisomerization with the H_2IMes-derived catalyst (alkene isomerization also occurs with the IMes-derived catalyst system).[102] The observed cycloisomerization is more characteristic of metal-templated reactions (Scheme 42). Exchange of the η^6-

Scheme 42[102]



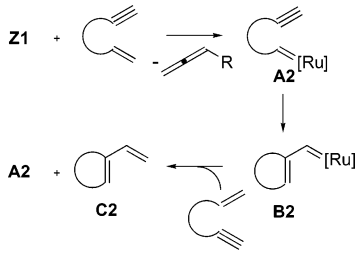
arene for bidentate coordination of 1,ω-diene leads to a 16-electron complex **U1**, which undergoes cyclometalation to give **V1**. β-Hydride elimination produces an intermediate RuH species **W1**, which experiences reductive elimination thereby regenerating a coordinatively unsaturated species capable of sustained catalysis. Remarkably, when Dixneuf and co-workers include a terminal alkyne into the reaction medium, ring-closing alkene−alkene metathesis reactivity is observed.[101] With acetylene (12 mol %), the ring-closing metathesis takes place to the exclusion of cycloisomerization. Most terminal alkynes promoted RCM activity in the in situ catalyst system derived from H_2IMes (acetylene, 1-hexyne, phenylacetylene), but (*tert*-butyl)acetylene and trimethylsilylacetylene were ineffective. The alkyne modifier is thought to produce vinylidene carbene such as **Z1**

Scheme 43[101]



through alkyne coordination and rearrangement (Scheme 43). Such a system had been independently reported by Nolan and co-workers[104] (used for ring-closing alkene metathesis) and by Louie and Grubbs[105] (used for a variety of metathesis applications including enyne metathesis). In related work, Ozawa demonstrated this equilibrium in a ruthenium (II) pincer complex.[106] The produced vinylidene carbene **Z1** can trigger alkene metathesis by transalkylidenation, releasing the corresponding allene in the initiation step (Scheme 44). In terms of enyne metathesis, catalytic amount of alkyne is sacrificed to form **Z1**, which can undergo alkylidene transfer onto a 1,ω-enyne to set up the RCEYM step.

Scheme 44



An advantage of the Dixneuf catalyst is the synthetic convenience offered by the in situ preparation. Moreover, the catalyst system is phosphine-free and may produce a long-lived catalyst, since low loadings are often attainable. As Fürstner et al. have pointed out,[97] both the initiation and propagation profiles contribute to a catalyst's overall efficiency.

The increased reactivity of the second-generation ruthenium carbene complex has been studied in alkene metathesis. Fundamental studies in enyne metathesis are lacking, but there are a handful of synthetic studies (vide infra) that contrast behavior (rate issues or substrate scope) between first- and second-generation Grubbs' catalysts. The recent mechanistic work by the Grubbs' group for alkene metathesis is highly significant in its own right and is relevant to enyne metathesis.[6,7] Initially, rationale for greater reactivity in the second-generation catalyst was attributed to a trans-labilizing effect arising from the *N*-heterocyclic carbene, a more powerful σ donor than the tricyclohexylphosphine ligand present in the first-generation Grubbs' complex.[107−111] This should lead to kinetic loosening of the Cy_3P, which must be dissociated prior to alkene binding (dissociative mechanism).[5,8,112] This hypothesis was tested, and Grubbs found that the *N*-heterocyclic carbene did not increase the rate of phosphine dissociation as measured by dynamic NMR. Phosphine dissociation (k_1) is actually slower for the **Ru gen-2** complex as compared to **Ru gen-1**. Rather, the increased activity of the second-generation complex is attributed to more effective *partitioning* of the coordinatively unsaturated 14-electron carbene complex **257** toward alkene binding (to alkene metathesis) versus phosphine reassociation (to the 16-electron precatalyst) as compared to the first-generation Grubbs' benzylidene (Figure 1). Although the coordinatively unsaturated 14-electron species (**257**) is slower to form in the second-generation environment (H_2IMes)-Cl_2Ru=CR, when it does form, it displays an increased selectivity for alkene binding ($k_{-1}/k_2 = 1.25$) relative to the **Ru gen-1** catalyst ($k_{-1}/k_2 = 1.3 \times 10^4$). This reflects an increased selectivity for **Ru gen-2** to bind alkenes rather than phosphines as compared to the first-generation catalyst. As a result, the ruthenium carbene stays in the catalytic cycle longer, performing alkene metathesis before rebinding tricyclohexylphosphine and returning to the precatalyst resting state.

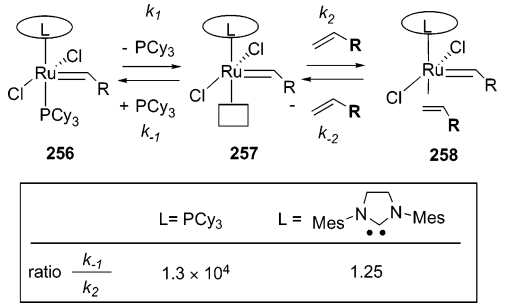
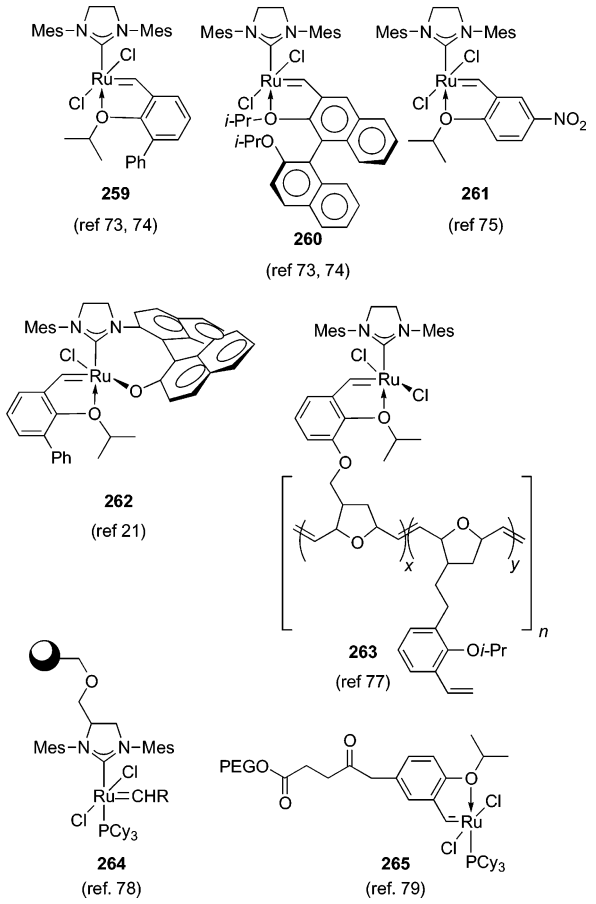


Figure 1.[6,7]

There are several alkene binding steps in enyne metathesis (e.g., transalkylidenation and vinyl carbene olefin complexation) that are likely to benefit from the σ-donating *N*-heterocyclic carbene ligand **258** in similar ways. Though the Grubbs' study dispels the simple idea of a trans-labilizing effect, it suggests that the kinetic partitioning observed versus phosphine reassociation may apply to other nucleophiles (oxygen or sulfur instead of phosphine). Functional group tolerance can be thought of as a comparative measure of alkene binding versus functional group coordination. Viewed in this way, the second-generation complex displays higher alkene chemoselection and is more functional group tolerant, at least when the functional group is a phosphine. In the second-generation complex, alkene binding may also be preferred to coordination by other nucleophiles, a greater preference than that displayed in the first-generation ligand environment. Considering that any functional group−ruthenium interaction lies on the periphery of the catalytic cycle, these interactions diminish ruthenium carbenes engaging in catalysis and retard the catalytic reaction rate. Since these catalytically nonproductive complexes are in equilibrium with alkene or alkyne complexes on the catalytic reaction coordinate (which in turn are stabilized by the *N*-heterocyclic carbene ligand), more of the ruthenium carbenes will remain in the catalytic cycle. This leads to faster reaction rates and

Chart 4



reduces decomposition that might arise from these side complexes. The greater scope of the enyne metathesis seen with the second-generation Grubbs carbene can be understood in this way.

The most important recent advances in catalyst design for alkene metathesis will further benefit catalysis of enyne metathesis. Since phosphine reassociation competes for active catalyst,[6,7] recent designs have omitted the phosphine. This has led to developments in the Hoveyda−Blechert class of phosphine-free initiators[19,23] and formulation of the Grubbs' pyridine solvates (also phosphine-free).[113] The Hoveyda catalyst originated from the design of recyclable metathesis catalysts on dendrimers or bound to monolithic sol−gels,[19−21] where the styrene would recapture the catalyst when metathesis substrates were consumed: "boomerang effect".[114,115] Not surprisingly, both the Hoveyda catalyst and the Grubbs' pyridine solvates promote enyne metathesis.[82,116−118] Recent advances include a new type of stereogenic ruthenium catalyst,[22] and either increased back strain in the coordinatively labile isopropyl ether (see **259** and **260**, Chart 4)[119,120] or electronic deactivation of the Lewis basicity of the oxygen lone pair (see **261**, Chart 4).[121] In addition to Hoveyda's monolithic sol−gels and dendrimeric catalysts, solid-supported catalysts have been recently developed.[122−125] The Grubbs' pyridine solvates initiate alkene metathesis and ROMP some million times faster than the second-generation Grubbs' catalyst.[126] This remarkable advance in alkene metathesis has permitted successful cross metathesis of acrylonitrile. There is one reported instance of increased reactivity in 1,3-enyne alkene cross metathesis using the bromopyridine solvate as compared to the second-generation complex, and this was extended to an enyne metathesis.[118]

In summary, in the ring-closing metathesis with the Grubbs' ruthenium carbenes, the burst of synthetic activity has raised several mechanistic questions that are unresolved or have incomplete answers. This is certainly understandable given the complexity of the catalytic process (Not counting initiation, there as many as seven elementary steps including the alkyne and alkene binding counted as discrete steps, see Scheme 36). For enyne precursors undergoing ring-closing EYM, it is generally assumed that alkylidenation of a pendant 1-alkene occurs faster than intermolecular addition of Ru=CH_2 to the alkyne. Starting from the **Ru gen-1** benzylidene, production of an alkylidene is faster than methylidene formation,[75,127] and Grubbs used this to bias the initial ring closure step in tandem enyne metatheses.[67,127] In contrast, the general mechanism for the cross enyne metathesis posits a reactive Ru=CH_2 addition to the alkyne[72] rather than an analogous, but necessarily regiochemically reversed, addition of an alkylidene. Are these reactivities sufficiently different to explain the high observed regioselectivity in the intermolecular cases? Second, whether the addition of metal methylidenes or metal alkylidenes to alkynes is reversible or operating under kinetic control has not been established.[128] Understanding this may offer an approach to controlling stereoselectivity. Ruthenium carbene-catalyzed enyne metathesis requires the generation of ruthenium vinyl carbenes, considered more stable than other ruthenium carbenes, but it is not known whether the generation or turnover of the vinyl carbene is the rate-determining step of catalysis.[129] These two steps differentiate enyne metathesis from alkene−alkene metathesis. The interplay of these two elementary steps in the catalytic picture of enyne metathesis may be perturbed by geometry (of the 1,*n*-enyne), substitution (alkyne or alkylidene), or catalyst environment (**Ru gen-1** or **Ru gen-2**) in the intramolecular RCEYM applications. Since substitution will affect vinyl carbene stability, reversibility may also depend on whether the alkyne is internal or terminal. Third, the factors dictating the regiochemistry of metal methylidene/alkylidene addition to the alkyne are not clearly understood. In the intermolecular cases studies, the regioselectivity does not seem fragile, but are electronic effects or steric effects more heavy-handed in guiding this outcome? How does chelation by propargylic functional groups influence rate or selectivity? At this stage, enough synthetic data has been obtained to suggest overall reactivity trends but has also revealed some potential inconsistencies that can be resolved by mechanistic studies. The stage thus set for mechanistic inquiry, we can expect further insights into the mechanism and perhaps some surprises that will guide the design of future reactions and extend the reaction to include both more challenging substrates and more diverse synthesis applications.

3. Synthetic Applications

The synthetic applications of enyne metathesis have been separated into three main areas: section 3.1, intramolecular (ring-closing) enyne metathesis; section 3.2, intermolecular (cross) metathesis; and section 3.3, tandem enyne metathesis.

Most of the synthetic activity in enyne metathesis has examined the ring-closing reaction to build various cyclic molecules of interest to synthetic chemists. The earliest examples of enyne metathesis were intramolecular and include those discussed in section 2.1. The reaction has been used to form heterocycles and saw early development to access structures containing particular functional classes of organic molecules such as β-lactams. Functionality encountered in amino acids and carbohydrates was considered potentially problematic for metathesis applications, but successful ring-closing applications have broadened our view of functional group tolerance. After the first few sections, medium- and macro-ring synthesis is discussed followed by element-substituted alkynes. The last section deals with total synthesis incorporating ring-closing enyne metathesis. Many of the ring-closing applications employ ethylene as an additive used to assist the ring-closing reaction, and this will be discussed throughout.

The intermolecular metathesis applications are less advanced than the use of ring-closing enyne metathesis in synthesis. There are fewer dividing lines in the intermolecular reactions. Ethylene has been used both as a reactant and to promote ring-closing metathesis. The cross metathesis of higher alkenes has additional issues in both stereoselection and regiochemistry that are not encountered in ethylene metathesis.

Tandem reactions are detailed in the last section. Tandem reactions may be initiated by ring-opening metathesis, cross metathesis, or ring-closing metathesis. Tandem reactions are those that utilize at least two distinct metathesis steps where one metathesis sets up the next. These are often and appropriately called cascade metathesis reactions. A special class of tandem reaction includes a terminal cross metathesis step, and these will be discussed at the end of section 3.3.

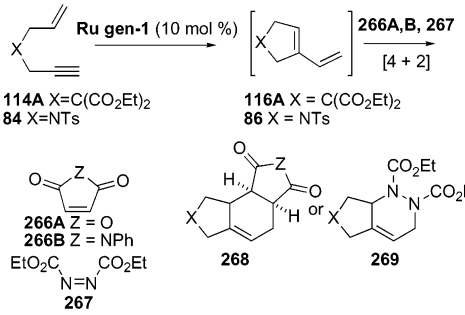
3.1. Intramolecular Metathesis of Enynes

3.1.1. Synthesis of Carbocycles and Various Heterocycles (O, N, P, Si) with Ring-Closing Enyne Metathesis

The synthesis of carbocycles and nitrogen- and oxygen-containing heterocycles by ring-closing metathesis are not easily separable into "heterocycle-formed" classification since many studies demonstrate the scope of the reaction by exploring ring closure to produce a series of heterocycles. The early studies by Mori using chromium carbenes[59,60] and the Grubbs' complex[65] produced carbocycles and nitrogen heterocycles and have been detailed in the mechanistic discussion above (section 2.2). This section examines synthetic studies to produce first carbocyclic, nitrogen- and oxygen-containing heterocycles, followed by examples of silicon- and phosphorus-containing heterocycles.

A one-pot ring-closing EYM/Diels–Alder reaction was developed for the formation of perhydroindenes and perhydroisoindoles. In this study, Bentz and Laschat addressed several important issues needed to improve the synthetic efficiency of the sequence.[130] Isolated yields of the dienes were low to moderate. However, conducted as a one-pot operation without isolation of the diene, the cycloadducts were obtained in significantly higher yields. For instance, malonate-linked enyne **114A** gave only 38% isolated yield of the corresponding diene **116A** (Scheme 45).

Scheme 45[130]



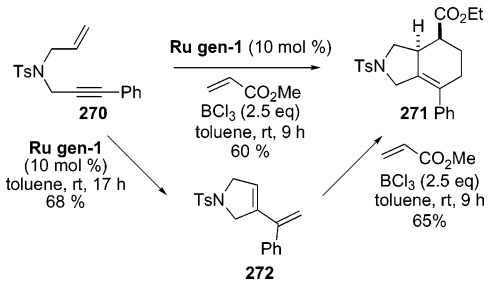
entry	X	metathesis (%)	product	Z	cycloadduct (%)
1	$C(CO_2Et)_2$	38	**268A**	O	66
2	$C(CO_2Et)_2$	42	**269A**	--	57
3	$C(CO_2Et)_2$	46	**268B**	NPh	44
4	NTs	49	**268C**	O	75
5	NTs	56	**269B**	--	78
6	NTs	58	**268D**	NPh	68

However, when the crude diene **116A** was subjected to thermal cycloaddition, the cycloadduct was obtained in 66% isolated yield, nearly doubling the yield over two steps. Diene decomposition during concentration and purification is a common problem.[131–134] The one-pot procedure gave higher isolated yields of the cycloadducts over two steps than the isolated yield of intermediate dienes directly from the metathesis. In this study, ethylene was not required for efficient ring closure. Several different dienophiles were employed in the reaction under thermal conditions (rt, CH_2Cl_2, 50 h) with the **Ru gen-1** catalyst present.

The second issue addressed was whether Lewis acid-catalyzed Diels–Alder reaction was possible in the one-pot operations conducted with the **Ru gen-1** complex. To probe this issue, the conversion of diethyl 2,2-diallylmalonate to its ring-closed product was evaluated in the presence of several Lewis acids. The Group III Lewis acids BCl_3 and $AlCl_3$ were fully compatible with the Grubbs' catalyst and did not diminish the rate of ring closure (albeit at 10 mol % loading). Other Lewis acids were used with success ($ZnBr_2$, $ZnCl_2$, $FeCl_3$, $V(acac)_2$) but gave slower reaction rates. In contrast, $TiCl_4$, $EtAlCl_2$, $ZnEt_2$, and $SnCl_4$ resulted in incomplete conversions to product. Similar observations had been made by Fürstner and Langemann in the course of their synthetic studies of (+)-ricinelaidic acid lactone and of (−)-gloeosporone using ring-closing alkene–alkene metathesis.[135] In the Fürstner–Langemann study, $Ti(O\textit{i}\text{-}Pr)_4$ was used to sequester Lewis basic oxygen functionality that was interfering with the ring-closing metathesis.

The results from the Lewis acid study were used to promote the one-pot ring-closing EYM/cycloaddition of tosylamide **270** with ethyl acrylate and 2.5 equiv of BCl_3 in toluene (Scheme 46). In the one-pot

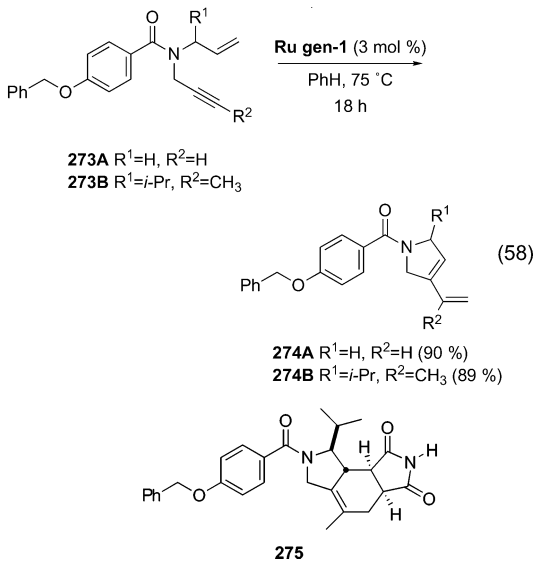
Scheme 46[130]



reaction, 98% conversion was obtained with cycloadduct **271** isolated in 60% yield. Conducted stepwise with isolation of the intermediate diene **272**, the yield was only 40%.

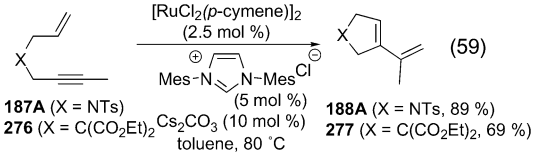
Heerding and co-workers used ring-closing enyne metathesis in conjunction with Diels−Alder cycloaddition to prepare a hexahydroisoindoline combinatorial library.[136] Solution-phase studies demonstrated that the enyne metathesis would tolerate both allylic substitution and alkyne substitution needed to achieve diversity in the construction of the library. Conducted in refluxing benzene, ring-closing enyne metathesis produced $\Delta^{3,4}$-pyrrolidene **274A** and **274B** in 90 and 89% yields using the first-generation Grubbs' carbene complex (eq 58, Scheme 47). Thermal cycloaddition

Scheme 47[136]



of **274B** with maleimide (toluene, reflux, 18 h) gave cycloadduct **275** as a single diastereomer in 30% isolated yield along with 52% recovered **274B** (Scheme 47). For library synthesis, enyne metathesis was conducted on the Wang-supported benzamide to produce the hexahydroisoindoline library by the split-and-pool method.

A three-component ruthenium catalyst system was used to carry out ring-closing enyne metathesis.[103] This in situ generated catalyst system (see section 2.2.2) was used in the preparation of various carbo- and heterocyclic dienes. The ring-closing EYM reaction worked with both nitrogen-containing and malonate-derived 1,6-enynes. Tosyl amide **187A** reacted smoothly to give dihydropyrrole **188A** in high yield (eq 59).



The reaction was also efficient with malonate **276**; however, it required longer reaction time. The absence of terminal alkynes in these substrates precludes the η^2-alkyne to vinylidene carbene rearrangement pathway presented in Scheme 43. These reactions are more akin to metal-templated enyne bond reorganization (cycloisomerization). Allylic propargyl ethers **278** were converted to dienes under the standard reaction conditions, and good isolated yields were obtained (eq 60, entries 1 and 2, Table 13). The

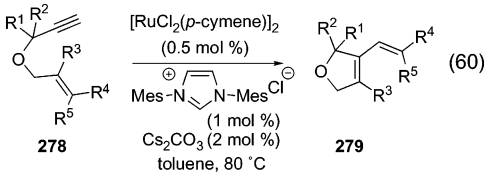


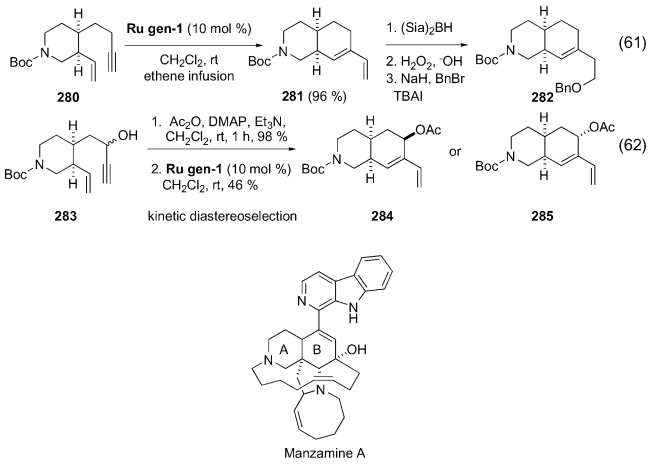
Table 13[103]

entry	**278**	R^1	R^2	R^3	R^4	R^5	**279**	yield (%)
1	**A**	$-(CH_2)_5$		Me	H	H	**A**	86
2	**B**	Me	Ph	Me	H	H	**B**	75
3	**C**	Ph	Ph	Me	H	H	**C**	35
4	**D**	Me	Ph	H	Me(H)	H(Me)	**D**	61
5	**E**	Ph	Ph	H	Me(H)	H(Me)	**E**	52
6	**F**	Me	Ph	H	Me	Me	**F**	16

reaction of 1,2-disubstituted alkenes (**278**, entries 4 and 5) proceeded without difficulty, and dienes **279D**,**E** were isolated in fair yield. The reaction of terminal disubstituted enyne **278F** was difficult and required extended reaction time (entry 6).

The AB ring system of manzamine A was prepared by a ruthenium-catalyzed ring-closing EYM reaction that provides the necessary bicyclic diene.[137] Enyne **280** was prepared from (−)-quinine in six steps (Scheme 48). Ring-closing EYM, conducted under ethylene infusion, was efficient with the first-generation Grubbs' catalyst to provide bicyclic diene **281**. Regioselective hydroboration/oxidation produced the octahydroisoquinoline ring system with adequate functionality present for the completion of the total synthesis (eq 61). The α-nitrogen of the B-ring of manzamine A was introduced via a subsequent diastereoselective aminohydroxylation on **282** (not shown). Additional studies of the ring-closing EYM conducted with an alkyne bearing a propargyl acetate gave an unexpected kinetic diastereoselection (eq 62). Of the mixture of epimeric acetates from **283**, only

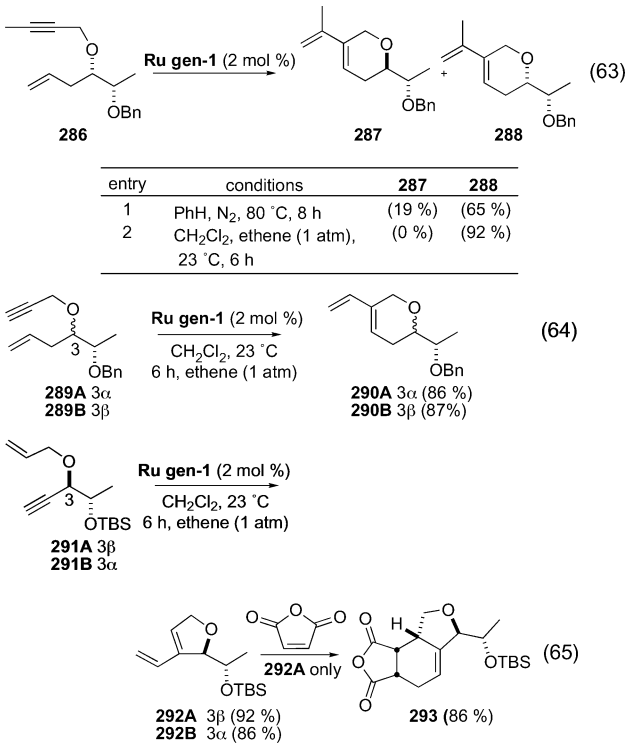
Scheme 48[137]



one diastereomer was formed (**284** or **285**) in 46% yield along with the unreacted diastereomeric enyne.

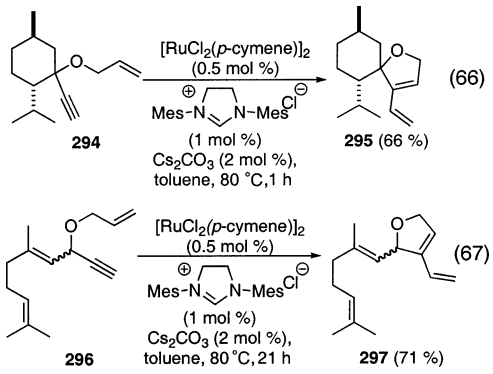
Chiral oxacyclic dienes were produced via ring-closing enyne metathesis of chiral enynes.[138] The chiral enynes were prepared from *S*-lactic acid in several steps. The additional chiral center in the enyne serves as a reporter for any epimerization in the endocyclic ether. Functional groups such as alcohols, ethers, and silyl ethers generally react poorly in ring-closing EYM with the first-generation Grubbs' catalyst. Ring-closing EYM with **1A** at elevated temperatures afforded two diastereomers, **287** and **288** (eq 63, Scheme 49). This observation

Scheme 49[138]



shows that, at elevated temperatures, the first-generation Grubbs' catalyst can epimerize chiral molecules. The authors do not provide mechanistic details of the epimerization. However, since propargylic benzyl ethers are known to undergo cross metathesis poorly, due to chelation,[77,84,139] it is possible that metal coordination to the propargyl ether results in partial solvolysis leading to epimerization. Significantly, the epimerization process was averted through the use of ethylene atmosphere (1 atm, balloon) and decreased reaction temperature. Temperature probably exerts the greatest effect on the epimerization process with ethylene used to stabilize the active catalyst. The second reaction conditions provided only **288**, with retention of stereochemistry. The scope of this chemistry was expanded further to include additional chiral enynes, as in the case of **289A** and **289B**, providing stereospecific access to the chiral pyran derivatives, **290** (eq 64). This method is also applicable to the formation of chiral furyl derivatives, providing dienes used in subsequent cycloaddition (eq 65).

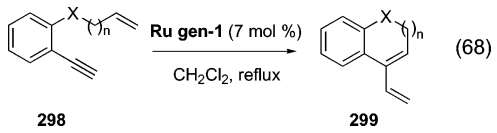
Modification of terpenoid derivatives was achieved by ring-closing EYM with an in situ generated ruthenium catalyst.[140] Terpenes and terpenoids are a class of natural products with potential as chiral ligands. Modification of these compounds by ring-closing EYM produces a new class of unnatural terpenoids. Complete conversion of enyne **294** to spirocyclic diene **295** was achieved by heating to 80 °C for 24 h with 2.5 mol % of [RuCl(=C=C=CPh$_2$)-(*p*-cymene)PCy$_3$][OTf] after initial activation of the catalyst with a UV lamp. A more active catalyst was formed by the mixing of [RuCl$_2$(*p*-cymene)]$_2$, 1,3-bis-(mesityl)dihydroimidazolium chloride, and cesium carbonate in a 1:2:4 ratio, the Dixneuf catalyst (eq 66).



Complete conversion of **294** was achieved with this catalyst system in 80 °C toluene in 1 h. This system was also effective for citral-derived enyne **296** and gave complete conversion to diene **297** (eq 67). It is notable that potentially competitive ring-closing alkene metathesis did not interfere with the diene synthesis. Terpenoid derivatives **295** and **297** have a conjugated diene present that is suitable for further cycloaddition reaction.

The synthesis of an estradiol-like skeleton was obtained in a two-step sequence from the corresponding aromatic enynes.[141] Allyl and homoallyl ethers **298** reacted to about 50% conversion with one portion

of catalyst (eq 68, entries 1 and 2, Table 14). Higher

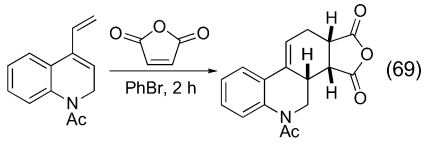


298 299

Table 14[141]

entry	enyne	X	n	yield (%)
1	**298A**	O	1	65
2	**298B**	O	2	60
3	**298C**	NAc	1	95
4	**298D**	NAc	2	85
5	**298E**	CH(OH)	0	50
6	**298F**	CH(OTBS)	0	NR
7	**298G**	CH(OTBS)	1	85
8	**298H**	CH(OTBS)	2	85
9	**289I**	CH_2	1	70

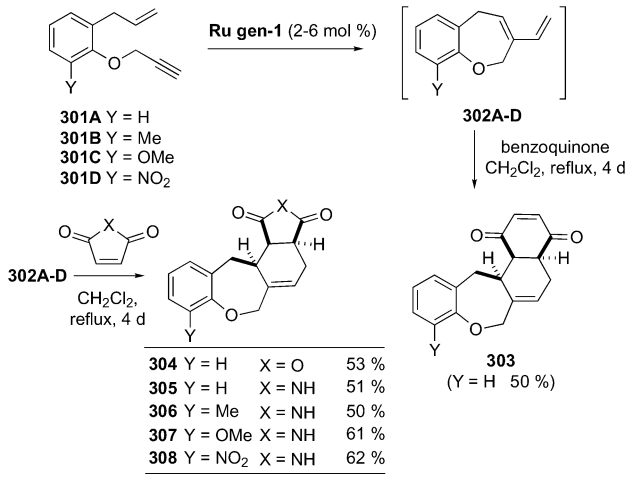
yields were obtained by addition of 10 mol % catalyst divided into four portions, with filtering between additions. This provided greater than 90% conversion to dienes **299** obtained in good isolated yield (entries 1 and 2). Allyl amides **298C**,**D** were found to be excellent substrates for ring-closing EYM (entries 3 and 4). The benzylic alcohol of entry 5 provided diene in 50% yield by NMR, but **299E** rapidly decomposed. Silyl protection of the alcohol (TBS, **298F**) and attempted five-membered ring-closing EYM was unsuccessful (entry 5), but the formation of six- and seven-membered rings was achieved with good isolated yields (entries 7 and 8). Thermal cycloaddition of diene **299C** with maleic anhydride provided access to a steroid-like skeleton (eq 69).



299C **300** (75%)

A one-pot enyne metathesis/Diels−Alder reaction was employed for the synthesis of benzoxepin derivatives.[142] Tricyclic and tetracyclic benzoxepin derivatives were prepared by one-pot ring-closing EYM of aromatic propargylic ethers and subsequent cycloaddition with dienophiles (Scheme 50). Ring-closing

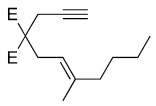
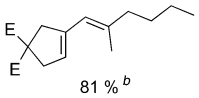
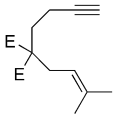
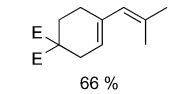
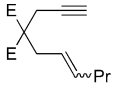
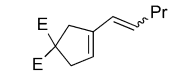
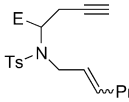
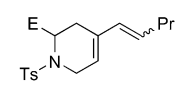
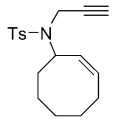
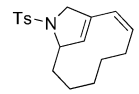
Scheme 50[142]



EYM was performed on aromatic enynes **301** with the first-generation catalyst to yield benzoxepin derivatives **302**. Vinyl-substituted benzoxepins **302** were then subjected to cycloaddition with dienophile, without purification, and refluxed for 4 d. This one-pot reaction provides the cycloadducts (**303**−**308**) in good yields, without isolation of the intermediate dienes. Substitution on the aromatic ring ortho to the propargyl ether appears not to influence the metathesis reaction.

Chatani and co-workers reported a $GaCl_3$-promoted skeletal bond reorganization of enynes.[48] This reaction was discussed previously in the mechanistic discussion of section 2.1. The $GaCl_3$-catalyzed reaction is suitable for the preparation of simple dienes through RCEYM. The enyne bond reorganization is rapid and produced the dienes in high yield (Table 15). The ester and tosylamide groups appear to be

Table 15[48 a]

entry	enyne	product
1		 81 % [b]
2		 66 %
3	 *E*/*Z* = 91/9	 86 % (*E*/*Z* = 91/9)[c]
4	*E*/*Z* = 10/90	69% (*E*/*Z* = 11/89)
5	 *E*/*Z* = 88/21	 69 % (*E*/*Z* = 93/7)
6	*E*/*Z* = 11/89	87 % (*E*/*Z* = 5/95)
7		 72 %

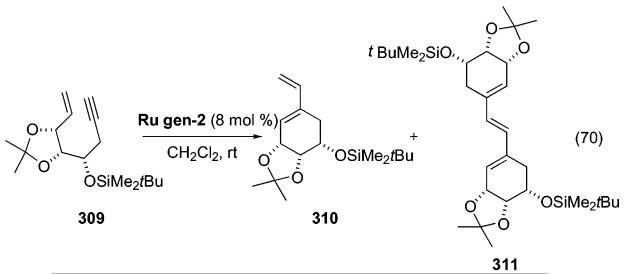
[a] Reaction conditions: enyne (0.5 mmol), $GaCl_3$ (0.05 mmol, 1.0 M in methylcyclohexane), and toluene (2.5 mL) under N_2. [b] Solvent: methylcyclohexane. [c] A small amount (4% yield) of the six-membered byproduct was also formed.

compatible with the very Lewis acidic catalyst. The skeletal reorganization is stereospecific. The strong Lewis acid can be used at reasonably low loading despite the presence of Lewis basic functionality in the enyne substrates. In one case, the cyclobutene failed to undergo electrocyclic ring-opening under the reaction conditions (see **113**, eq 27). Trost had also observed similar cyclobutene intermediates in his earlier studies of palladole-promoted enyne reorganization, and cyclobutenes were invoked previously by Murai and Chatani in enyne bond reorganization catalyzed by $[RuCl_2(CO)_3]_2$ and $PtCl_2$. An important difference in the $GaCl_3$-promoted reorganization as compared to transition metal complexes (or salts)

that have multiple coordination sites available is that activation of the alkyne occurs by monodentate coordination. This validates the idea that cyclometalation, involving bidentate coordination to the enyne, is but one mechanistic pathway to the enyne bond reorganization. The observed stereospecificity was rationalized in terms of nonclassical carbocations since open carbocations would be free to rotate competitively with cyclobutene formation. If the carbocation is "internally solvated" as a nonclassical carbocation (Scheme 22, section 2.1), then bond rotation and loss of stereospecificity should not occur. In contrast, the ruthenium carbene-catalyzed RCEYM is not stereospecific with respect to alkene geometry.[143,144]

As a part of a tandem transformation of carbohydrates to carbocycles, Poulsen and Madsen explored ring-closing EYM for the synthesis of 1-vinyl cyclohexene derivatives.[145] A variety of metal salts and ruthenium carbenes were screened for the metathesis. Attempted ring-closing metathesis using $[Ru(CO_3)Cl_2]_2$ (under CO atm), $PtCl_2$, and $PtCl_4$ proved unsuccessful. The use of the first-generation Grubbs' catalyst (10 mol % under ethylene) resulted in decomposition of **309**; however, use of the second-generation Grubbs' catalyst (8 mol % **Ru gen-2** under ethylene) resulted in the formation of diene **310** in 66% yield (eq 70, Scheme 51). The same reaction

Scheme 51[145]



entry	conditions	products	
1	ethene (infused)	**310** (66 %)	**311** (-)
2	argon	**310** (-)	**311** (29 %)

performed under argon atmosphere led to the formation of a large quantity of dimer (29%, **311**). In the absence of ethylene, the dimer may arise due to a slow reaction of the intermediate vinyl carbene with formed diene product (or by reaction with the alkyne part of enyne **309**). The second-generation Grubbs' catalyst was effective for the formation of cyclic 1,3-dienes (Table 16). The epimer of TBS ether **309** was converted into the corresponding diene in good yield (entry 2).

Fully acetylated enyne (entry 3) gave good yield of diene, despite the potential reactivity problem of an alkene bearing multiple electron-withdrawing acetates. Homopropargylic acetamides (entries 4 and 5) underwent ring closure albeit in lower yields. In the last entry, a propargyl acetate gave low yield with the **Ru gen-2** catalyst, but improved yield was obtained through use of **Ru gen-1** catalyst. It is unclear why the **Ru gen-2** catalyst gave inferior results.

Dolhem and co-workers evaluated the ring-closing enyne metathesis of highly oxygenated 1,6- and 1,7-

Table 16[145a]

entry	enyne	product
1	R = Ac	70 %
2	R = TBS	72 %
3		74 %
4	R = Ac	50 %
5	R = TFA	60 %
6		32 % 70 %[b]

[a] All reactions were carried out in CH_2Cl_2 at room temperature under an atmosphere of ethylene. [b] Catalyst **Ru gen-1** 10 mol% was used instead of **Ru gen-2**.

enynes to synthesize polyhydroxylated 1-vinyl cycloalkenes.[146] Optimization studies showed that ethylene suppressed dimer formation and increased yields of the ring-closed product, (entry 1, Table 17).

Table 17[146a]

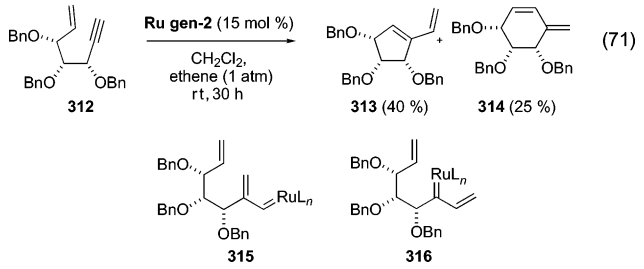
entry	enyne	diene
1		72%
2		66 %
3		55 %
4		68 %
5		50 %[a], 55 %[b]

[a] **Ru gen-2** (15 mol %), CH_2Cl_2, ethene (1 atm), rt. [b] **Ru gen-1** (30 mol %) used.

These results are consistent with those of Poulsen and Madsen.[145] Using an ethylene atmosphere,[71] the

enynes in Table 17 underwent metathesis to afford 1-vinyl cyclohexenes in good yield (entries 1−4). In these examples, substitution by potentially chelating benzyl ethers was tolerated at both the allylic and propargylic positions. The ring closure of a 1,6-enyne gave 1-vinyl cyclopentene (entry 5) even with a high loading of **Ru gen-1**. Additional benzyloxy substitution at the propargylic position as in enyne **312** resulted in regioisomeric product **314** (eq 71, Scheme 52). The authors suggest that this is due to formation

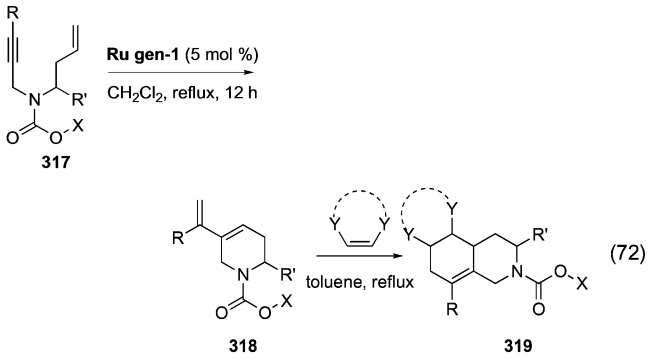
Scheme 52[146]



(71)

of regioisomeric vinyl carbenes **315** and **316** produced by Ru=CH_2 addition to alkyne **312**. Interestingly, the cyclohexene was not noted as a byproduct of entry 5, which suggests that the propargylic benzyl ether influences the regiochemistry of metal carbene addition. A similar effect has been observed in propargyl amides by Blechert and co-workers.[87,147]

Katritzky and co-workers utilized ring-closing enyne metathesis followed by cycloaddition to make functionalized tetrahydroisoquinolines.[148] The metathesis followed a modular assembly of the enyne carbamate, which permitted the incorporation of various R and R_1 groups onto the 3-vinyl $\Delta^{3,4}$-dehydropiperidine ring obtained from the metathesis (eq 72, Table 18). The



(72)

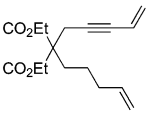
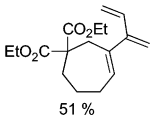
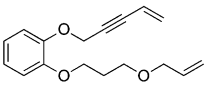
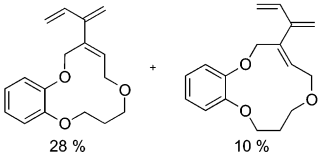
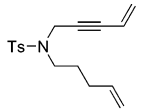
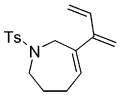
Table 18[148]

entry	**317**	R	R′	X	**319** (% yield)
1	**A**	H	Ph	Ph	96
2	**B**	H	2-thienyl	Me	87
3	**C**	CH_3	2-furyl	Me	61
4	**D**	CH_3	2-(5-methyl)furyl	Ph	88
5	**E**	H	cyclohexyl	Ph	81
6	**F**	CH_3	Ph	Me	52

propargylamide substrate for the RCEYM was prepared from (benzotriazolomethylene)iminophosphorane through ethynyl Grignard displacement of the benzotriazole. The substituted tetrahydroisoquinolines **319** were prepared in high yields over the two steps (RCEYM and thermal cycloaddition).

In the course of their studies describing cross metathesis between 1,3-enynes and alkenes (by cross alkene-alkene metathesis), Kang and co-workers described a ring-closing metathesis of 1,3-enynes bearing a pendant alkene (see dienynes in Table 19).[118]

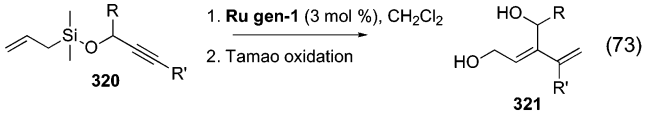
Table 19[118 a]

entry	dienyne	triene product(s)
1		 51 %
2		 28 % + 10 %
3		 52 %, 62 %[b]

[a] **5** (10−15 mol %), PhH, 70 °C. [b] Ethylene atmosphere (1 atm).

As metathesis reaction partners, these unusual 1,3-enynes can experience multiple ring-closing metathesis pathways: ring-closing enyne metathesis to either internal or external end of the alkyne or ring-closing alkene−alkene metathesis to produce a macrocyclic 1,3-enyne. In the event, dienynes underwent RCEYM onto the internal end of the alkyne (to give an exocyclic vinyl ruthenium carbene, "exo" mode)[149] to produce unusual triene products (entries 1−3, Table 19). Kang and co-workers had found the Grubbs' 3-bromopyridine solvate **5** to be the superior initiator in the cross alkene-1,3-enyne metathesis and adopted the same catalyst for the RCEYM runs in Table 19. The 12-membered ring formed in entry 2 (Table 19) is generated as a 2.8:1.0 mixture of geometrical isomers. The benefit of ethylene atmosphere was documented in entry 3, where the yield was improved slightly.

Yao reported the expedient synthesis of highly functionalized dienes through ring-closing EYM in conjunction with a Tamao oxidation.[150] The temporary intramolecular nature of the enyne metathesis, reminiscent of Stork's temporary silicon connection approach, renders the metathesis stereoselective. This is an elegant solution to the stereoselectivity problem characteristic of intermolecular enyne metathesis. This two-step coupling sequence results in the formation of a trisubstituted diene with complete regio- and sterochemical control (eq 73). Propargylic substitution presented no difficulties for internal alkynes, and a terminal alkyne gave ring-closing EYM using ethylene at room temperature (entry 2, Table 20). Homopropargylic siloxanes also gave ring-closing EYM to control the stereochemistry of the trisubstituted alkene found in **323** via a seven-

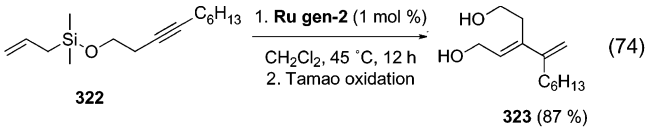


(73)

Table 20[150]

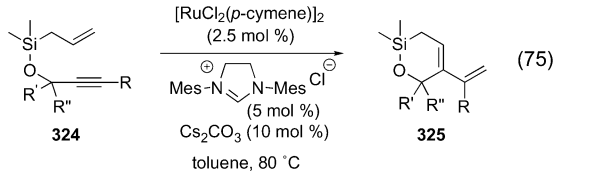
entry	R	R′	conditions	yield (%)
1	CH_2*i*-Pr	Et	45 °C, 12 h	86
2	C_6H_{13}	H	25 °C, 16 h, with ethene	87
3	CH_2CH_2Ph	Me	45 °C, 3 h	88
4	CH_2CH_2Ph	CH_2OPiv	45 °C, 3 h	82

membered intermediate cleaved through Tamao oxidation (eq 74).



(74)

An in situ generated ruthenium catalyst system was used for the synthesis of cyclic siloxanes.[151,152] The active catalyst was prepared from $[RuCl_2(p\text{-cymene})]_2$, 1,3-bis(mesityl)dihydroimidazolium chloride, and cesium carbonate in a 1:2:4 ratio. The in situ preparation is simple and does not require the multistep synthesis of organometallic complexes. Complete conversion of enynes **324A**−**G** was achieved at 80 °C in toluene (eq 75, Table 21). The reaction of



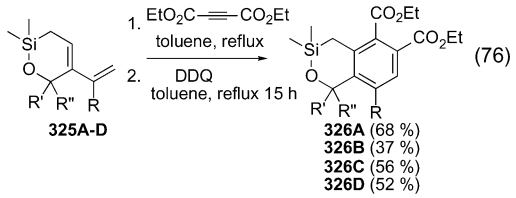
(75)

Table 21[151,152]

entry	enyne	R	R′	R″	time (h)	yield (%)
1	**324A**	H	Me	Ph	16	81
2	**324B**	H		-$(CH_2)_5$-	16	87
3	**324C**	H	Me	CH_2-$CHMe_2$	15	34
4	**324D**	H	Ph	Ph	15	70
5	**324E**	Ph	Me	Me	48	75
6	**324F**	*n*-Bu		-$(CH_2)_5$-	23	72
7	**324G**	CH_2OMe		-$(CH_2)_5$-	23	67

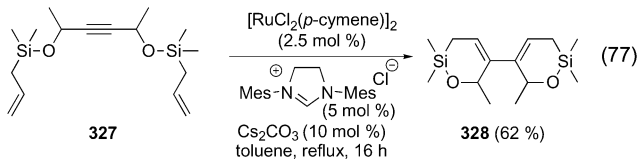
terminal alkynes **324A**−**D** was accomplished with 2.5 mol % of the catalyst and provided dienes **325A**−**D** in good yields. The reaction was not affected by propargylic substitution. Reaction of internal alkynes **324E**−**G** was more demanding and required increased catalyst loading and extended reaction times. Diels−Alder reaction with diethylacetylene dicarboxylate gave aromatic bicycles **326** after oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in refluxing toluene (eq 76, Scheme 53). The catalyst system was also used for the transformation of

Scheme 53[151,152]



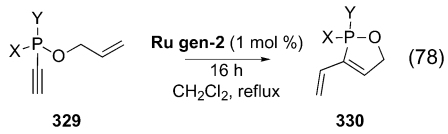
(76)

dienyne **327** to bicyclic diene **328** (eq 77). The siloxane unit can be transformed into diols, trienes, or tetrasubstituted alkenes.



(77)

The formation of mono- and bicyclic phosphorus heterocycles from various phosphoalkynes was catalyzed by the second-generation Grubb's catalyst. [153] Phosphorus enyne and dienyne substrates were prepared from a commercially available phosphorylating agent bis(diisopropylamino)ethynylphosphine by stepwise replacement of the diisopropylamino groups. The presence of phosphonates and phosphityl borane functionality was permitted during the formation of mono- and bicyclic phosphorus heterocycles (eq 78, Table 22). The P═O bond of phosphonates are



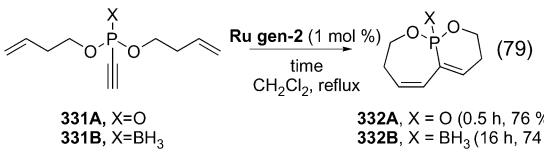
(78)

Table 22[153]

entry	X	Y	time (h)	conversion (%)
1	OBn	O	1.5	98
2	$NiPr_2$	BH_3	20	99
3	OBn	BH_3	48	95
4	OCH_2CH═CH_2	BH_3	16	99

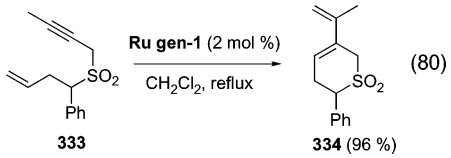
capable of chelation to the intermediate metal carbenes but do not adversely affect these ring-closing processes. In light of Georg's procedure for the removal of ruthenium from metathesis reactions,[134] it is interesting to note that phosphonates do not oxidatively decompose the **Ru gen-2** complex. Most likely this is explained by the short reaction times employed for the phosphonate ring-closing metatheses. The ring-closing EYM of symmetrical bis(alkenyloxy)phosphine−borane led to exclusive formation of monocyclic diene through a single ring-closing EYM (entry 4, eq 78).The formation of bicyclic compounds **332A**,**B** was similarly achieved by a tandem ring-closing metathesis onto a phosphon-

ylalkyne, initiated by alkylidenation at one of the equivalent pendant alkenes (eq 79).



This methodology could be used in the future for formation of biologically relevant phosphorus heterocycles or for the synthesis of ligands for asymmetric catalysis. The interested reader is directed to a related ring-closing alkene−alkene metathesis of phosphine−boranes by Governeau and co-workers with the first-generation Grubbs' catalysts.[154]

Ring-closing metathesis has been used to produce sulfone-containing heterocycles.[155] Although principally interested in ring-closing alkene−alkene metathesis, Yao showed that the ring closure of enyne **333** gave high isolated yield of sulfone-containing diene **334** using the first-generation Grubbs' complex (eq 80).



The ring-closing enyne metathesis is an effective ring synthesis, especially for small ring dienes. From this survey, terminal alkenes work best and more highly substituted alkenes benefit from constraint in the tether to facilitate ring closure. With the RCEYM being an intramolecular reaction, catalyst turnover is usually fast enough to compete with and overcome coordination by functional groups at the allylic, propargylic, and homopropargylic positions. These interactions could sound the death-knell for catalysis. Preexisting alkene stereochemistry is lost in the ruthenium-catalyzed EYM[156] although the $GaCl_3$-catalyzed reaction is stereospecific, like many of the metal salt-catalyzed reactions discussed in section 2.1. The beneficial effect of ethylene (Mori's conditions) are often used in conjunction with the first-generation Grubbs' catalyst and terminal alkynes. The in situ prepared Dixneuf catalyst does not require ethylene even in difficult ring closures of 1,*n*-enynes with terminal alkynes and highly substituted alkenes. As this section documents, the RCEYM is usually conjoined with Diels−Alder cycloaddition to capitalize of the complexity-building potential of the generated endocyclic 1,3-dienes.

3.1.2. β-Lactams through Ring-Closing Enyne Metathesis

Barrett used ring-closing EYM with β-lactam-containing enynes to synthesize bicyclic β-lactams by annulative metathesis.[157,158] The systematic nature of this study reveals strengths and limitations of the metathesis with regard to the ring formed and with respect to substituents. The use of alkenyl-tethered propargylic amides **335** (eq 81, Table 23) provide access to an array of annulated β-lactam rings. The reaction of terminal alkyne **335A** with up to 10 mol

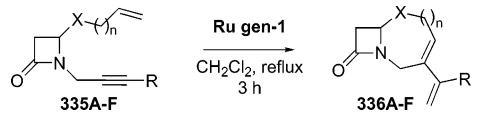
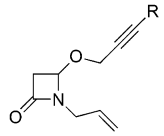
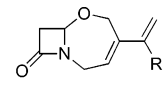
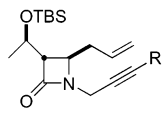
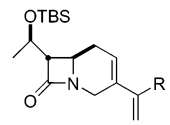
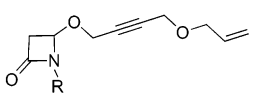
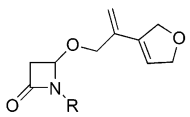
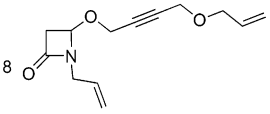
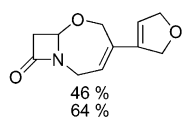
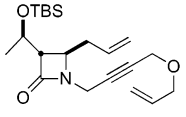
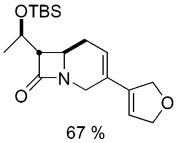


Table 23[157,158]

entry	substrate	X	*n*	R	mol %		yield (%)
1	**335A**	CH_2	0	H	1	**336**	0
2	**335A**	CH_2	0	H	10	**336**	0
3	**335B**	CH_2	0	Me	1	**336B**	20
4	**335B**	CH_2	0	Me	5	**336B**	52
5	**335B**	CH_2	0	Me	10	**336B**	88
6	**335C**	CH_2	1	Me	10	**336C**	82
7	**335D**	NTs	1	Me	10	**336D**	70
8	**335E**	O	1	Me	10	**336E**	88
9	**335F**	O	2	Me	10	**336F**	12

% of the catalyst failed to provide the desired cyclohexene product (entries 1 and 2). In contrast, the methyl-substituted alkyne **335B** produced cyclized compound **336B** under optimized reaction conditions (entries 3−5). These reactions were not conducted under ethylene atmosphere or with ethylene perfusion. Good yields were also achieved with longer alkyl chain (entry 6) and in substrates with heteroatom substitution in the allylic or homoallylic position (**335D**,**E**). A dramatic decrease in yield was seen in an attempt to form the eight-membered ring system **336F**. Although a rationale for the contrasting reactivity between entries 2 (terminal alkyne) and 5 (internal alkyne) is not provided, it is possible that

Table 24[157,158 a]

entry	enyne	diene
1	 R = CH_3	 R = CH_3, 74 %
2	R = CH_2OTBS	R = CH_2OTBS, 82 %
3	R = CH_2OH	R = CH_2OH, 32 %
4	 R = CH_3	 R = CH_3,100 %
5	R = CH_2OTBS	R = CH_2OTBS, 72 %
6	 R = TBS	 R = TBS,100 %
7	R = Bn	R = Bn, 98 %
8		 46 % 64 %
9		 67 %

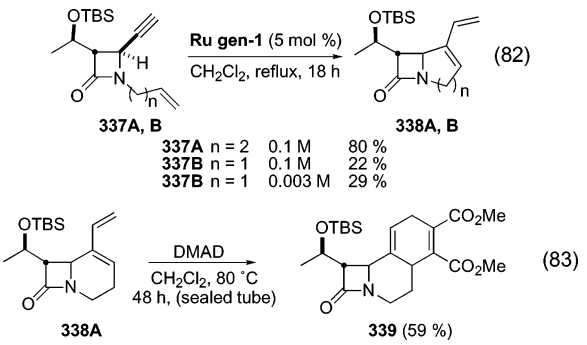
[a] Conditions: **Ru gen-1** (5−15 mol %), CH_2Cl_2, reflux, 3 h.

terminal alkynes, chelated with the β-lactams, coordinate in a conformation unsuitable (or too stable) for metathesis, that the regiochemistry of Ru=CH_2 addition favors the terminal vinyl carbene, or that the reaction with internal alkynes is reversible.

Propargyl ethers worked well in the ring-closing and tandem ring-closing metathesis on the β-lactam framework. Examples from Barrett's comprehensive study are shown in Table 24. High yields were achieved in the ring closure of entries 1 and 2, but the presence of a propargyl alcohol gave a poor result (entry 3). Internal alkynes gave excellent yields (entries 4−7), which led to tandem applications used to form two heterocyclic rings at once (entries 8 and 9). In the latter examples, lower concentrations were required to suppress the competitive dimerization.

The formation of tricyclic β-lactams was achieved through the use of ring-closing EYM used in combination with cycloaddition.[159] The synthesis of "tribactams" was targeted due to their broad spectrum of antibacterial activity, resistance to β-lactamase, and stability to peptidases. The ring-closing EYM was found to work well on enyne **337A**, providing diene **338A** in 80% yield (eq 82, Scheme 54). The

Scheme 54[159]

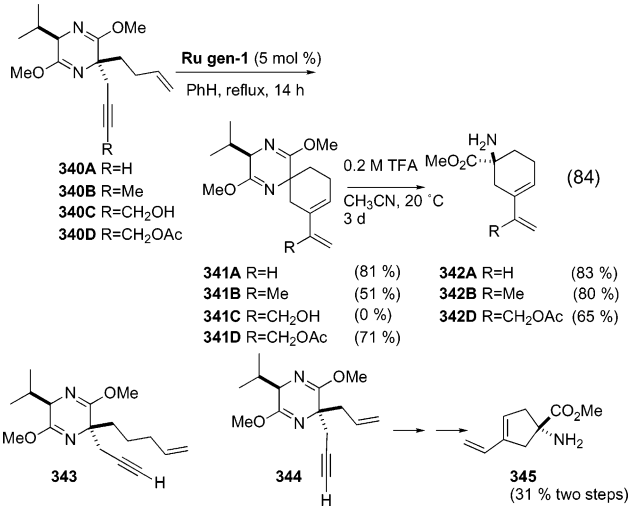


reaction was more difficult with β-lactam **337B**, and little improvement was found when the metathesis was conducted under high dilution conditions. The third ring of the tribactams was formed by a thermal cycloaddition reaction with DMAD (eq 83). The synthesis of ring-fused β-lactams marked an early era in the ruthenium carbene-catalyzed ring-closing enyne metathesis, where amide functional group tolerance was evaluated in a systematic survey of ring-forming reactions.

3.1.3. Unnatural Amino Acids Obtained through Ring-Closing Enyne Metathesis

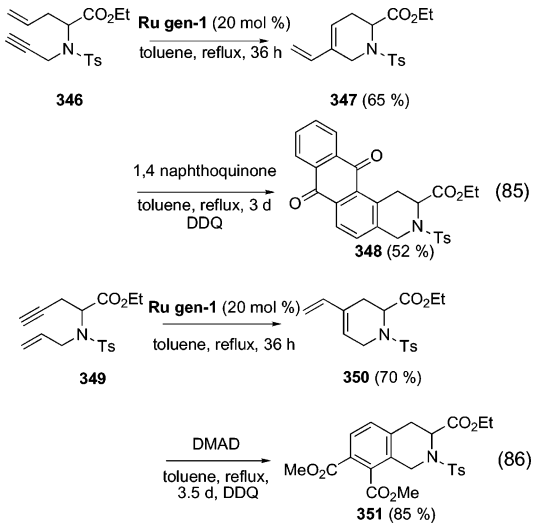
Stereoselective synthesis of unnatural α-amino acids was developed through ring-closing enyne-metathesis and subsequent hydrolysis.[160] Chiral enyne substrates were prepared from the Schöllkopf bis-lactim chiral auxiliary. The metathesis reaction worked well for both terminal (**340A**) and internal alkynes (**340B**) in the preparation of the corresponding 6,6-spirocycles (eq 84). The formation of 6,7-spirocycles was not achieved by ring-closing EYM; the attempted reaction of **343** failed to produce the cycloheptadiene. Propargylic alcohol **340C** was unreactive to ring-closing EYM, probably due to deactivation of the ruthenium catalyst through chelative trapping and β-hydride elimination. The coordination-prone propargylic oxygen of **340C** was tamed through acetylation providing **340D**, which readily underwent ring-closing EYM. The spirane products (**341A**,**B**,**D**) were hydrolyzed under acidic conditions to give amino acid methyl esters **342A**,**B**,**D**. The reaction conditions were also useful for the formation of cyclopentenyl derivatives **345** through a similar sequence of reactions (Scheme 55).

Scheme 55[160]



Ring closure of substituted enynes and subsequent cycloaddition provides access to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic (tic) acid derivatives.[161,162] The "tics" are elaborate and unnatural aromatic amino acid cousins of phenylalanine. The formation of dienes **347** and **350** was readily achieved with the **Ru gen-1** catalyst (Scheme 56). Diels−Alder reaction with readily available dienophiles gave the Diels−Alder adducts, which were easily oxidized with DDQ to afford the aromatized bi- or tetracyclic compound.

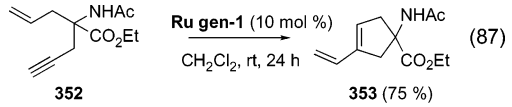
Scheme 56[161,162]

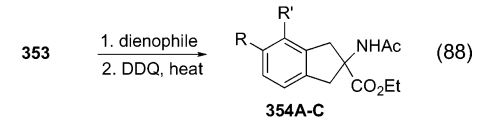


A ring-closing EYM/cycloaddition strategy was developed for the synthesis of indanyl-containing α-amino esters.[163,164] Methods for the synthesis of complex α-amino acids, especially α,α′-disubstituted

amino acids, are limited. Recently unnatural and α,α′-disubstituted amino acids have attracted interest for use in controlling the backbone conformation of polypeptides. In the event, ring-closing EYM furnished 1-vinyl cyclopentene derivative **353** (Scheme 57). Diels−Alder reaction and oxidation produces the substituted indanyl amino esters in excellent yield (eq 88, 67−88% over two steps).

Scheme 57[163,164]





entry	R	R'	yield (%)
1	CO_2Me	CO_2Me	88
2	H	CO_2Me	67[a]
3	H	Ts	82[a]

[a]both isomers.

α-Alkynyl, α-trifluoromethyl amino esters were used to produce 3-alkenyl 3,4-dehydroproline derivatives via ring-closing EYM with a ruthenium allenylidene.[165] Amino acids that bear an alkynyl or trifluoromethyl group at the α position irreversibly inhibit various pyridoxal phosphate-dependent enzymes. Amino ester **355A** was treated with 10 mol % of catalyst **356A**, after the catalyst was activated by irradiation, and heated at 80 °C for 69 h (eq 89, Table 25). This in situ catalyst system resulted in

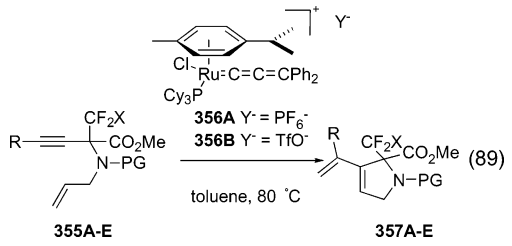


Table 25[152]

entry	enyne	CF_2X	R	PG	catalyst	yield (%)
1	**355A**	(CF_3)	H	SO_2Ph	**356A** (10 mol %)	70
2	**355B**	(CF_3)	H	SO_2Ph	**356B** (10 mol %)	58
3	**355C**	(CF_3)	*n*-Bu	CBz	**356B** (10 mol %)	40
4	**355D**	(CF_3)	CH_2OMe	CBz	**356B** (10 mol %)	14
5	**355E**	(CF_2Cl)	H	Boc	**356B** (5 mol %)	56

90% conversion to diene **357**, which was obtained in 70% isolated yield. Use of catalyst **356B** (with the triflate counterion) produced better results, affording 95% conversion in 24 h, but with lower isolated yield (58%). The triflate catalyst **356B** was used for the conversion of enynes **355B**−**E**. The use of disubstituted alkynes **355C**,**D** required more forcing conditions (3−4 d at 80 °C) to obtain 86% and 48% conversion to dienes, obtained in low isolated yields. The α-difluorochloromethyl substrate **355E** also underwent efficient EYM with 5 mol % of catalyst **356B**.

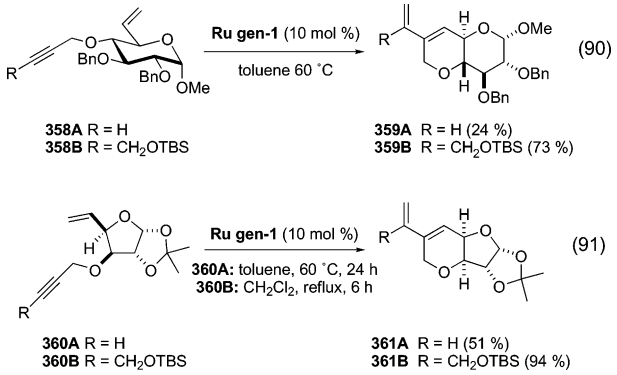
With suitable protecting groups on nitrogen, ring-closing metathesis en route to unnatural amino acids presents little difficulty using either the first-generation Grubbs' carbene or the cationic Fürstner/Dixneuf ruthenium allenylidene complex.

3.1.4. Carbohydrates in Ring-Closing Enyne Metathesis

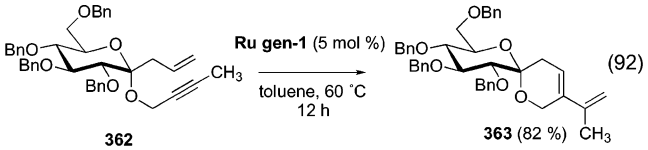
Carbohydrates present highly oxygenated functionality that can interfere with metathesis applications. As a result, carbohydrates offer a challenging paradigm in which to evaluate RCEYM. Several examples of highly oxygenated 1,6- and 1,7-enynes that underwent RCEYM to give carbocycles have already been discussed (section 3.1.1). Ring-closing enyne metathesis on carbohydrate scaffolds have been explored as means of ring fusion toward both bicyclic and spirocyclic dienes.

2-Vinyl pyranose and 2-vinyl furanoses, readily available from the carbohydrate chiral pool, were transformed by ring-closing EYM into pyranopyrans and pyranofurans (Scheme 58).[166] Conducted with **Ru gen-1** in toluene at 60 °C, low conversion of the terminal alkyne to dihydropyran **359A** was found after extended reaction time (eq 90). The presence of an internal alkyne proved beneficial to the reaction, which led to increased yield and decreased reaction time. This latter result was similarly observed in the furanose case, with better results found for internal alkynes (products **361A**,**B**, eq 91). These reactions were not conducted under ethylene pressure or with ethylene infusion.

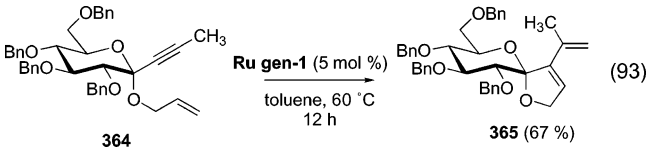
Scheme 58[166]



Highly functionalized spirofused oxacycles were prepared from carbohydrate-based enynes by ring-closing EYM. The first-generation Grubb's catalyst was used to convert ketoglycosidic enynes to dienylspiroacetals.[167] Treatment of **362** with 5 mol % catalyst at 60 °C for 12 h produced spiroacetal **363** in good yield (eq 92). Enyne **364** was also converted

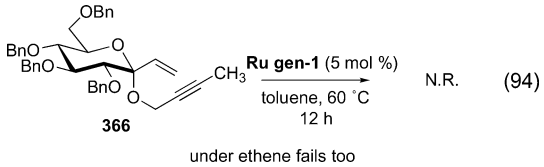


to spiroacetal **365** (eq 93). In contrast, enyne **366** was unreactive under the same conditions, and conversion



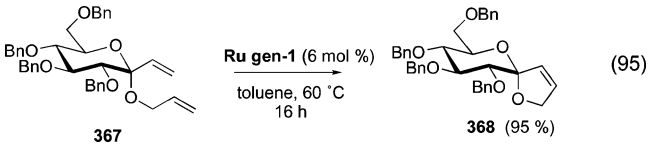
(93)

did not improve through use of extended reaction times or by increased catalyst loading (eq 94). The



N.R. (94)

diminished reactivity could not be restored by conducting the reaction under ethylene gas. NMR studies indicate that incubation of enyne **366** with the catalyst did not result in reaction with either the alkyne or the alkene. Markedly contrasting behavior is seen in the corresponding alkene metathesis substrate **367**, which gives highly effective RCM (eq 95). The authors consider this result to be consistent



(95)

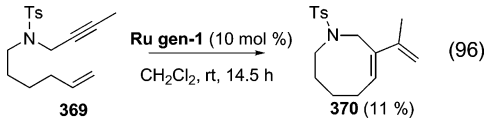
with initial alkylidenation occurring at the O-allyl group (of **364** and **367**). In contrast, alkylidenation of the vinyl group of **366** is extremely slow due to steric hindrance.

Carbohydrates offer a high density of oxygen functionality that can challenge catalyst turnover, yet the ruthenium carbenes display high alkene and alkyne chemoselectivity giving successful enyne metathesis. Similar results were seen previously in highly oxygenated carbocycles (section 3.1.1).

3.1.5. Medium- and Macro-Ring-Closing Enyne Metathesis

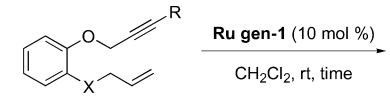
Several examples of ring-closing enyne metathesis to produce seven-membered rings have already been encountered in section 3.1.1. In this section, the use of ring-closing enyne metathesis for the formation of eight-membered rings and higher are discussed. The ruthenium-mediated reactions are addressed first, followed by the metal-catalyzed enyne bond reorganization that had been discovered earlier by Trost and co-workers.[31−33]

Although entropy loss is unfavorable in eight-membered ring synthesis,[168] ring-closing EYM has been successfully used to prepare these systems.[169] The synthesis of eight-membered rings was planned from aromatic enyne compounds with at least one heteroatom or ring present in the enyne to restrict conformational freedom in the starting materials, thereby reducing entropy loss in the transition state. Monocyclic eight-membered rings containing a single heteroatom were formed in low yield (see **370**, eq 96).[170] Further constraining elements such as rings or additional heteroatoms were needed to improve the eight-membered ring synthesis.

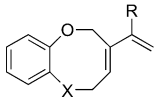


(96)

Reaction of enynes **371A**−**C** required extended reaction times to get reasonable yields. Incorporation of nitrogen into the formed eight-membered ring assisted in ring-closure (**371C** → **372C**) and provided increased yields and decreased reaction time (eq 97).



371A R = CH_2OAc, X = O
371B R = CH_3, X = O
371C R = CH_3, X = NTs

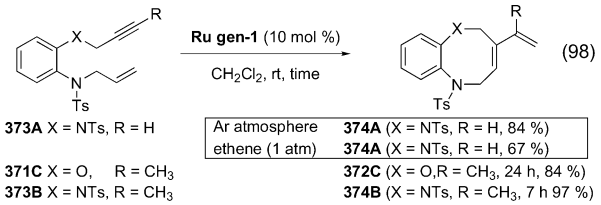


(97)

372A R = CH_2OAc, X = O, (7 d, 49 %)
372B R = CH_3, X = O, (50 h, 61 %)
372C R = CH_3, X = NTs, (24 h, 84 %)

Ethylene gas did not have a beneficial effect in these ring-closing reactions. Terminal alkyne **373A** produced diazaoctene **374A** in 84% yield conducted under argon; but only 67% yield when conducted under ethylene, along with 22% recovered **373A** (eq 98, Scheme 59). In the ring-closing metathesis of

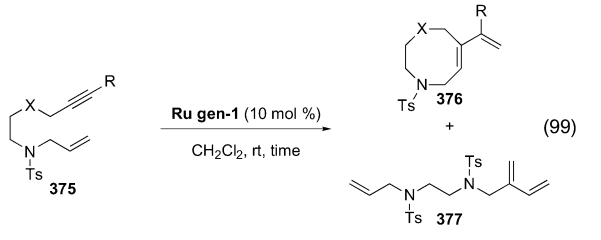
Scheme 59[169,170]



(98)

373A X = NTs, R = H
371C X = O, R = CH_3
373B X = NTs, R = CH_3

Ar atmosphere	**374A** (X = NTs, R = H, 84 %)
ethene (1 atm)	**374A** (X = NTs, R = H, 67 %)
	372C (X = O,R = CH_3, 24 h, 84 %)
	374B (X = NTs, R = CH_3, 7 h 97 %)



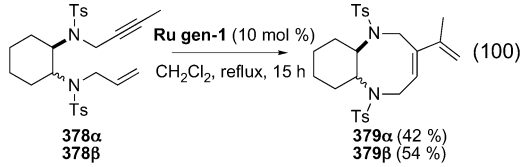
(99)

375A (X = NTs, R = H)
375A (X = NTs, R = H)
375B (X = NTs, R = Me)
375C (X = O, R = Me)

Ar atmosphere	**376A** (X = NTs, R = H, 35 %)
ethene (1 atm)	**376A** (X = NTs, R = H) **377** (84 %)
	376B (X = NTs, R = Me, 14.5 h, 95 %)
	376C (X = O, R = Me, 7 h, 99 %)

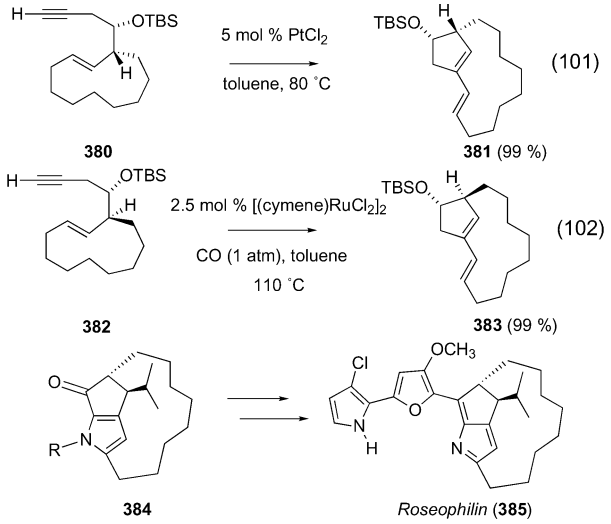
375A, 35% yield of **376A** was observed when the reaction was conducted under an argon atmosphere (eq 99). In contrast, the same reaction conducted under ethylene (balloon) gave 84% of butadiene **377** showing that intermolecular enyne metathesis can effectively compete with difficult ring-closing metatheses. In the remaining examples of Scheme 59, ethylene was not employed for the RCEYM. The diene **376C** was isolated as a 2:1 mixture with an alkene isomerization product.

Formation of fused bicyclooctene derivatives was also achieved, but in decreased yield by comparison to the aromatic compounds. Both diastereomers of **378** reacted and gave similar yields (eq 100).



In a formal total synthesis of roseophilin, Trost and Doherty employed a macro ring-closing EYM catalyzed by $PtCl_2$ or $[RuCl_2(CO)_3]_2$.[171] Bicyclic dienes **381** and **383** possess the macrocyclophane found in the tricyclic core of roseophilin **385** (Scheme 60). Dia-

Scheme 60[171]

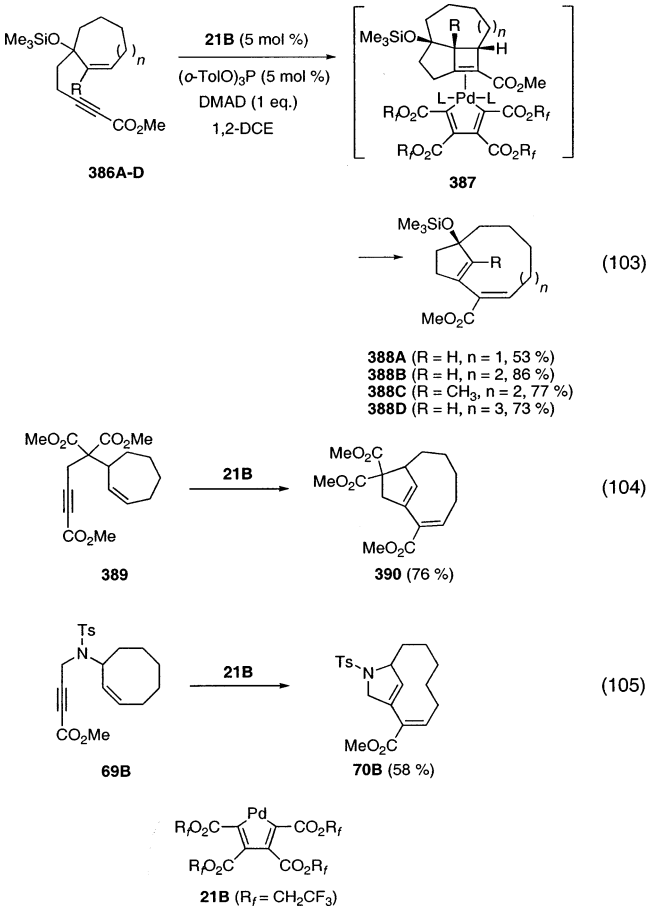


stereomers were produced at an earlier stage in the synthesis, and their relative stereochemistry was established after the EYM. Both reactions (eqs 101 and 102) proceeded in quantitative yield for the enyne bond reorganization, and product **381** was taken through to **384**, a known precursor to the natural product. Through the use of enyne bond reorganization for macrocyclic ring formation, the authors completed a formal total synthesis of roseophilin.

Trost and Trost were the first to show the effectiveness of intramolecular enyne metathesis for the synthesis of bridgehead, macrocyclic alkenes.[32] Unlike the previous eight-membered rings, the entire diene is endocyclic. Use of the more electron-poor fluorinated palladoles **21B** suppressed the formation of the Alder-ene product and increased the desired enyne metathesis (eq 103, Scheme 61). A variety of medium-ring bridgehead alkenes **388** were produced. The ease of the metathesis correlated to the ring strain predicted (molecular mechanics) for proposed cyclobutene intermediates. It was noted that substitution on both the olefin and acetylene promoted the metathesis. Electron-withdrawing groups on the alkyne favored metathesis (eqs 103−105). The authors noted that the enyne metathesis is a "new type of reaction that has much synthetic potential and raises many intriguing mechanistic questions".[33]

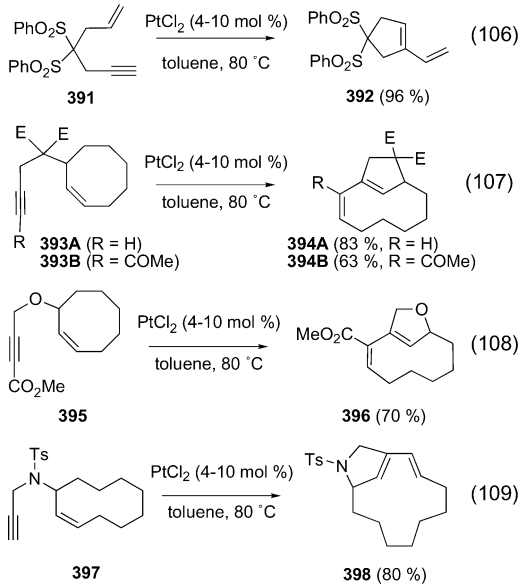
Fürstner and co-workers demonstrated that simple platinum salts could effect the enyne bond reorganization, but these catalysts also produced vinyl

Scheme 61[32]



cyclopropanes with certain enyne substrates (Scheme 62).[43,45] Formal enyne metathesis using Pt(II) is

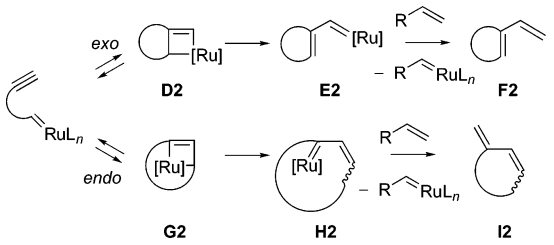
Scheme 62[43,45]



compatible with a variety of functional groups including ethers, esters, sulfones, ketones, and sulfonamides. The pendant alkene need not be strained or highly substituted (eq 106, Scheme 62). The metathesis occurs with both terminal alkynes and internal alkynes provided that in the latter case there is a carbonyl group attached to the alkyne (eqs 107−109).

Hansen and Lee systematically studied the influence of ring size in ring-closing enyne metathesis to produce macrocycles.[149] In macrocyclic systems, the alkylidene can add by two regiochemical addition modes, providing either an exocyclic diene **F2** (exo mode, via and exocyclic vinylcarbene) or an endocyclic diene **I2** (endo mode, via and endocyclic vinyl carbene) as illustrated in Scheme 63. This terminology

Scheme 63



has proven useful to describe macro ring-closing enyne metathesis and is used throughout this review. Enynes were constructed on a tartrate backbone and subjected to macro ring-closing enyne metathesis (Table 26). The RCEYM of entries 1 and 2 produced the 10-membered rings by the exo closure mode, the preferred mode of cyclization for smaller ring sizes. When the choice is between an 11- and 12-membered ring (for the enyne substrate in entry 3), both cyclization paths occur in the diester series (entries 3, 4, and 6), but an amide in the tethering system provides only the 12-membered diene by endo ring closure (entry 7). Improved yield and stereoselectivity was observed when conducted under ethylene atmosphere (cf. entries 3 and 4). When the cyclization was conducted with **Ru gen-1** under ethylene at room temperature and then heated in the presence of the **Ru gen-2** complex, only the endo cyclization product was formed in high yield (entry 5). In this run, ethylene−alkyne metathesis may precede the intramolecular enyne metathesis. In fact, Hansen and Lee also found that the 11-membered diene, obtained through exo ring closure, reacted with ethylene, which opens an equilibrium pathway to the 12-membered macrocycle.[172] Internal alkynes also underwent the reaction with improved yield and similar selectivities (entries 2 and 6). For the formation of larger rings (size greater than 12 members), the endo cyclization mode is preferred (entries 7−12). The authors assert that the endo preference in the larger rings reflects different energies of the bicyclic ruthenacyclobutene intermediates en route to the respective diene macrocycle.

Table 26[149a]

entry	enyne	diene macrocycle
1	R = H	R = H, 52 %
2	R = Me	R = Me, 61 %
3	R = H	R = H, 25 %
		R = H, 25 %, 1:1 *E/Z*
4[b]	R = H	R = H, 61 %[b]
		R = H, 30 %, 2:1 *E/Z*[b]
5[c]	R = H	R = H, 90 %, *E* only[c]
6	R = Me	R = Me, 46 %
		R = Me, 46 %, 1:1 *E/Z*
7		35 %, *E* only
8[c]		60 %, *E* only[c]
9		70 %, 1:1 *E/Z*
10		61 %, *Z* only
11		54 %, 2:1 *E/Z*
12		55 %, 1;1 *E/Z*

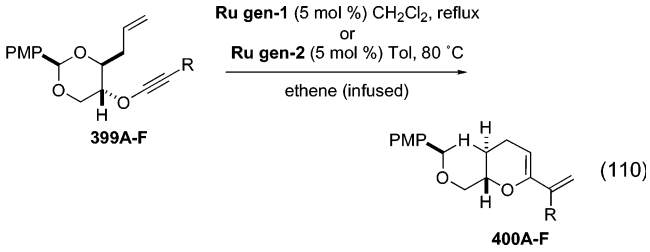
[a] Conducted with **Ru gen-2** (5 mol %), CH_2Cl_2, reflux. [b] Conducted under ethene. [c] Conducted with **Ru gen-1** (5 mol %) under ethene, CH_2Cl_2, 25 °C; then refluxed with **Ru gen-2** (5 mol %).

Medium ring synthesis is accomplished with both ruthenium carbenes and metal-templated reactions through enyne bond reorganization. Oftentimes, these are conducted as cyclorearrangements onto existing, low strain cycloalkenes. The platinum(II)-catalyzed enyne metathesis works for a variety of enynes and does not require electron-deficient alkynes. The palladole-catalyzed reactions benefit from electron-withdrawing groups attached to the alkyne, as discussed previously (section 2.1). The only cautionary note applies to tosylamide-linked 1,7-enynes where cyclopropanation can intervene using $PtCl_2$ as catalyst (see section 2.1). For ring sizes such as eight members, which are difficult to form, it is useful to note that intermolecular metathesis (ethylene metathesis in eq 99) tends to compete with the ring closure. The systematic study of macro-RCEYM addresses the recent trend to use macro ring-closing metathesis in synthesis and specifically in natural product synthesis (section 3.1.7).

3.1.6. Ring-Closing Enyne Metathesis with Element-Substituted Alkynes

Alkynol ethers were employed as substrates for ring-closing EYM in the preparation of cyclic ethers.[173,174] A variety of different enynes were used as substrates, and the **Ru gen-1** and **Ru-gen-2**

catalysts were contrasted in this study (eq 110, Table

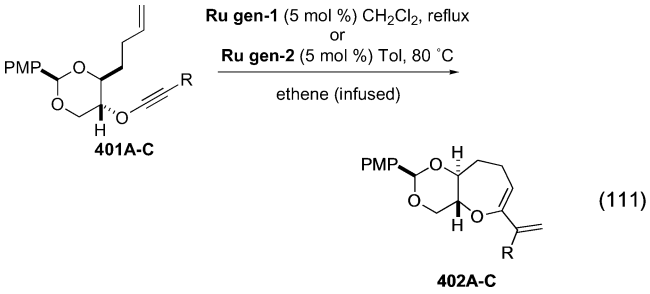


(110)

Table 27[173,174]

entry	R	**Ru gen-1** (yield %)	**Ru gen-2** (yield %)
1	H	65	90
2	Me	77	98
3	$SiMe_3$	20	88
4	CH_2OH	84	8
5	CH_2OAc	54	72
6	$CH_2OTBDPS$	61	91

27). The definitive comparison makes the Clark study noteworthy. Attempts at ring-closing EYM with the Schrock catalyst were unsuccessful, probably because of interference by the ether functionality. In general, the second-generation catalyst provided the highest yields of diene. The first-generation catalyst was found to be superior to the second-generation catalyst in the case of propargylic alcohols (entry 4). This might be due to the higher reaction temperatures used with the second-generation catalyst. Earlier studies in ring-closing EYM suggested that the **Ru gen-1** catalyst performed better with internal alkynes, but this study shows that there is no significant difference when the **Ru gen-2** catalyst is employed. Terminal alkynes were also found to be reactive with the second-generation catalyst (first entries, Table 27 and eq 111, Table 28). This provides an interesting



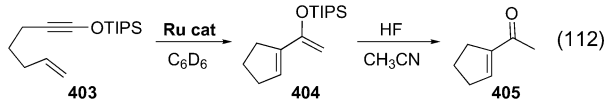
(111)

Table 28[173,174]

entry	R	**Ru gen-1** (yield %)	**Ru gen-2** (yield %)
1	H	33	70
2	Me	27	72
3	$SiMe_3$	–	0

contrast between the ruthenium carbenes and highlights the previously noted shortcomings of the first-generation ruthenium carbene catalysts with terminal alkynes. The synthesis of seven-membered cyclic ethers was found to be more difficult than the formation of similar six-membered cyclic ethers (eq 111). Silylalkynes (entry 3, Table 28) were found to be unreactive in the formation of seven-membered rings, whereas they did provide access to six-membered rings (entry 3, Table 27). Previous work with the first-generation ruthenium carbene catalysts had shown that silicon-substituted alkynes were poor substrates for ring-closing enyne metathesis.

Activated siloxy-enyne complexes participate in ring-closing EYM reaction catalyzed by various metal carbene precatalysts, as a method to produce functionalized enones.[96] A model system was developed to determine which metathesis catalysts could achieve the desired ring-closure (eq 112, Table 29). Ring

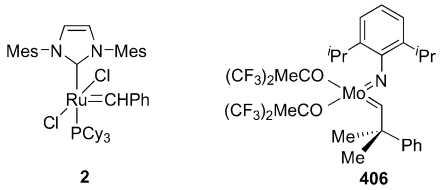


(112)

Table 29[96]

entry	catalyst	conditions	conversion (%)
1	**Ru gen-1** (10 mol %)	60 °C, 6 h	<5
2	**406** (10 mol %)	60 °C, 12 h	<5
3	**cat. 2** (5 mol %)	60 °C, 12 h	85
4	**Ru gen-2** (5 mol %)	20 °C, 13 h	95
5	**Ru gen-2** (5 mol %)	60 °C, 15 min	98

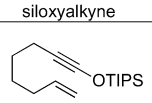
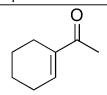
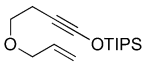
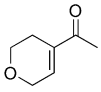
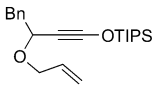
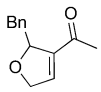
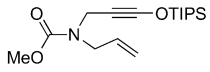
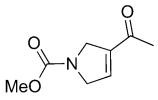
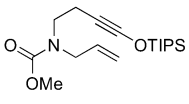
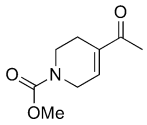
closure was not observed with the first-generation Grubbs' catalyst or the Schrock molybdenum catalyst **406**. This study is one of the few that has examined



the Schrock molybdenum catalyst for enyne metathesis since Blechert's original report of the intermolecular enyne metathesis.[72] The use of *N*-heterocyclic carbene ligand-bearing catalysts[175] resulted in the efficient formation of diene **404**, with the second-generation Grubbs' catalyst **3** found to be the superior catalyst giving the enyne metathesis at room temperature. Treatment of the crude reaction mixture of diene **404** with dilute hydrofluoric acid provided acetylcyclopentene **405** as the only product. Strikingly, treatment of the corresponding ethoxyalkyne or alkynyl phosphate with metathesis catalyst provided no reaction, even under forcing conditions. With reaction conditions developed, the reaction of a series of siloxyalkynes was explored (Table 30). The siloxyalkynes were prepared according to the modified Kowalski protocol and then subjected to metathesis. The formation of acetylcyclohexene was realized in excellent yield over two steps (entry 1). The metathesis reaction was also shown to work well on ether and carbamate functional groups, providing five- and six-membered heterocycles (Table 30, entries 2−5), and propargylic alkyl substitution was well tolerated (entry 3). NMR studies showed that the alkene underwent alkylidenation faster than cycloaddition of a metal carbene with the silyoxyacetylene.

The construction of 1,3-dienylboronic esters was accomplished by ring-closing enyne metathesis on en-1-ylboronates.[176] The ruthenium carbene-catalyzed reaction proceeds at room temperature to form both

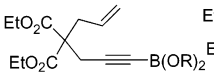
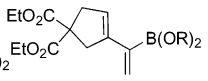
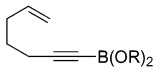
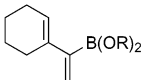
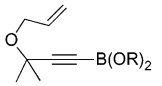
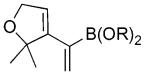
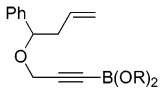
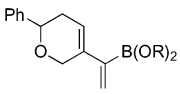
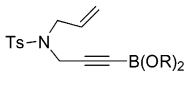
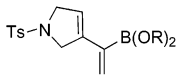
Table 30[96]

entry	siloxyalkyne	product	yield (%)[a]
1			81
2			88
3			86
4			91
5			95

[a] **Ru gen-2** (3−10 mol %), 0.1 M in PhH, 50−60 °C for 15−60 min, then concentrated and treated with 1.0 M HF in MeCN for 30 min.

five- and six-membered carbo- and heterocycles (Table 31). Carbocycles (entries 1 and 2) and heterocycles

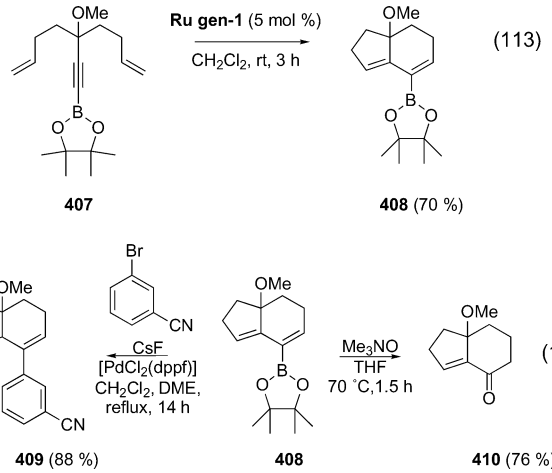
Table 31[176 a]

entry	enyne	product
1		 (14 h, 87 %)
2		 (5 h, 93 %)
3		 (2 h, 93 %)
4		 (6 h, 95 %)
5		 (3 h, 91 %)

[a] **Ru gen-1** (5−10 mol %), 0.06 M, rt, CH_2Cl_2. $B(OR)_2$ = $B(OCMe_2)_2$.

(entries 3−5) were easily formed from the alkynylboronates, and the produced dienes were isolated in good yield. The alkynyl boronates (e.g., **407**, eq 113) were prepared from the 1,6-enynes by deprotonation (LDA or *n*-BuLi) and anion trapping with 2-alkoxy-4,4,5,5-tetramethyl-1,3,2 dioxaborolanes. The transformation of dienyne **407** to bicyclic diene **408** was similarly achieved using a tandem metathesis remi-

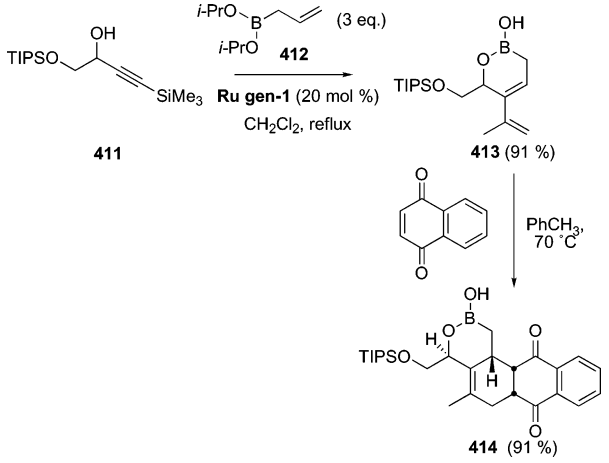
Scheme 64[176]



niscent of the Grubbs' synthesis of carbobicyclics[66,67] discussed in section 2.1.2. In this case, the alkynyl boronate **407** was formed in situ. The utility of the obtained dienyl boronates was demonstrated through Suzuki coupling of **408** with 3-bromobenzonitrile and direct oxidation of the vinyl boronate with Me_3NO in refluxing THF providing enone **410** (Scheme 64).

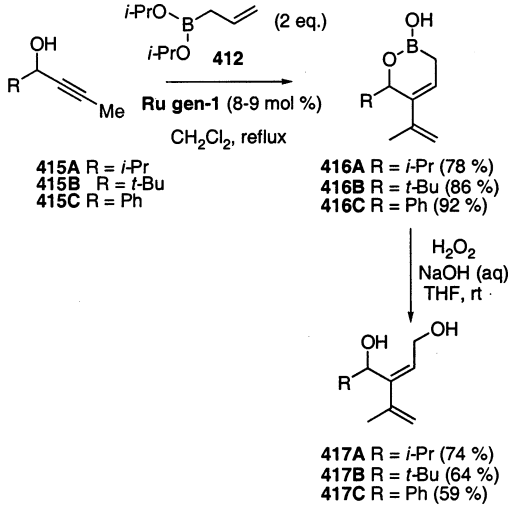
Micalizio and Schreiber used boronate linkers to bring about ring-closing alkene and ring-closing enyne metathesis.[177] This temporary control element was used to enforce the regio- and stereochemistry of the metathesis reactions, similar to the strategy used by Yao[150] to produce siloxanes (section 3.1.1). The cyclizations produce a set of building blocks used for diversity-oriented synthesis. Access to different skeletal arrays was achieved through successive and distinct reactions consecutive to enyne metathesis, principally cycloaddition. Mixed boronate esters containing the diene were produced in situ by refluxing propargyl alcohol **411** with two equivalents of allyl boronate **412.** The synthetic convenience of the procedure is notable. Cycloaddition of **413** with naphthoquinone produced >13:1 diastereomer ratio of cycloadduct **414** (Scheme 65). The cyclic boronic

Scheme 65[177]



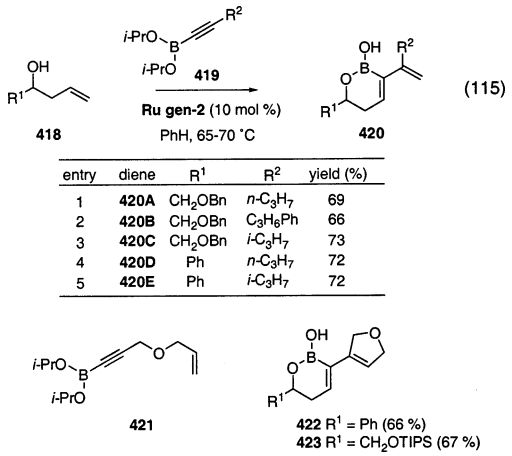
acids were produced in high yield and could be oxidized to give the corresponding diols **417** (Scheme 66). Reactions were similarly performed on resin-bound alkynols to produce cycloadducts useful in chemical genetics.

Scheme 66[177]



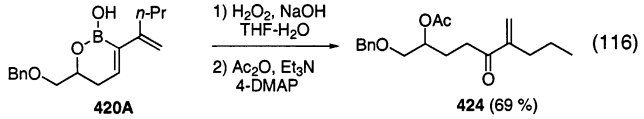
Subsequently, Micalizio and Schreiber extended the reaction to alkynyl boronate reagents, which further amplifies the diversity potential for the boronate ester-mediated ring-closing enyne metathesis.[178] Reaction of homoallylic alcohols **418** with alkynyl boronates **419** in the presence of the **Ru gen-2** catalyst produced cyclic boronic acids after purification on silica gel (eq 115, Scheme 67). The

Scheme 67[178]

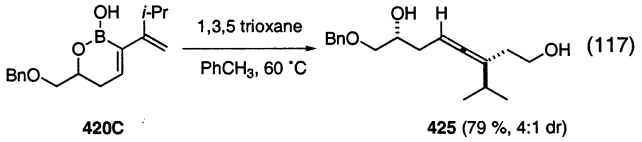


entry	diene	R^1	R^2	yield (%)
1	**420A**	CH_2OBn	n-C_3H_7	69
2	**420B**	CH_2OBn	C_3H_6Ph	66
3	**420C**	CH_2OBn	i-C_3H_7	73
4	**420D**	Ph	n-C_3H_7	72
5	**420E**	Ph	i-C_3H_7	72

reaction is tolerant of a variety of substituents on the alkyne. For (alkynyl)boronates substituted with allyl ethers (e.g., **421**), a ring-closing enyne metathesis is followed by a ring-closing alkene metathesis to provide bicyclic dienes **422** and **423** through a tandem process. Oxidative transformation produced enones in a convergent strategy starting from the homoallylic alcohols (eq 116).



The allyl boronate portion on the dienyl boronic acid **420C** reacted with trioxane to give the homoallenyl alcohol **425** (eq 117).



This work illustrates the creative development of metathesis chemistry as a synthetic method inspired by the goals of diversity-oriented synthesis.

The synthesis of five- and six-membered cyclic dienamides was effected by ring-closing EYM of alkenyl-ynamides.[179] In the case of dienyl-pyrrolidine **427**, the first-generation Grubbs' catalyst was found to be ineffective in promoting ring-closure (eq 118, Table 32, entry 1). The second-generation catalyst **3**

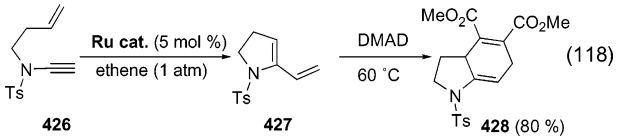


Table 32[179]

entry	catalyst	conditions	time	yield (%)
1	**Ru gen-1**	CH_2Cl_2reflux	24 h	7
2	**Ru gen-2**	CH_2Cl_2/reflux	4 h	66
3[a]	**Ru gen-2**	toluene/80 °C	30 min	76
4	**Ru gen-2**	toluene/80 °C	15 min	83

[a] Reaction performed under argon.

was successful in performing ring-closing EYM in refluxing dichloromethane (Table 32, entry 2) and at elevated temperatures in toluene (entries 3 and 4). There was little benefit realized with the use of ethylene atmosphere when compared to argon atmosphere (cf. entries 3 and 4).

The synthesis of dienyl-piperidines was also achieved through ring-closing enyne metathesis with the second-generation catalyst (eq 119). For piperidine derivative **430**, the best results were achieved with **Ru gen-2** (10 mol %) and lower reaction temperatures (Table 33, entry 4), and as in the first

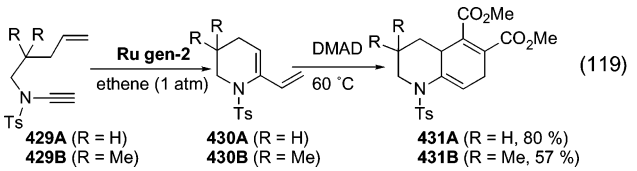


Table 33[179]

entry	substrate	**Ru gen-2** (mol %)	conditions	time (h)	yield (%)
1	R = H	5	toluene/80 °C	20	22
2	R = H	5	toluene/60 °C	20	19
3	R = H	5	CH_2Cl_2/reflux	27	36
4	R = H	10	CH_2Cl_2/reflux	6	85
5[a]	R = H	10	CH_2Cl_2/reflux	5	82
6	R = Me	10	CH_2Cl_2/reflux	6	61

[a] Reaction performed in Ar atmosphere.

case, ethylene atmosphere only slightly increased the isolated yield of **430A** (cf. entry 5). The crude products **430** were reacted with DMAD at 60 °C to give

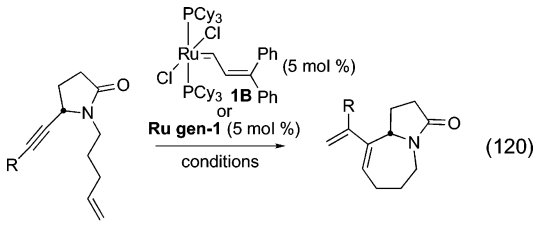
aza-bicyclics **431A**,**B** in 80 and 57% yields, respectively. These results are promising for the formation of quinidine and indole derivatives through ring-closing metathesis and cycloaddition.

The diverse nature of heteroelement- and element-substituted alkynes that give RCEYM is remarkable. Early tandem RCEYM using the first-generation Grubbs' carbene catalysts pointed to limitations (see Table 5, section 2.2.2). The rate-diminishing electronic and steric effects on the intermediate vinyl carbenes can be overcome with **Ru gen-2**. This can be explained by greater alkene affinity in the second-generation Grubbs' catalyst and the more electron-rich nature of the metal in this ligand environment. Electron-rich alkynes should be the most difficult since Fischer-type carbenes occur within the catalytic cycle, leading to greater stabilization of the intermediate carbenes. These are likely to be turnover-challenged systems, but turnover can be accelerated in intramolecular cases (higher effective molarity) or by higher 1-alkene concentration in intermolecular reactions (sections 3.2.2 and 3.2.3 for enol ethers). The in situ formation of a boronate-linked enyne renders the intermolecular reaction intramolecular, thereby enforcing alkene geometry. Electronic tuning, by protection, is necessary in some cases as can be seen in the amino-substituted alkynes. The desire to push the metathesis further has also inspired the development of new methods for the synthesis of heteroatom-substituted alkynes (see also section 3.2).

3.1.7. Natural Product Synthesis Employing Enyne Metathesis

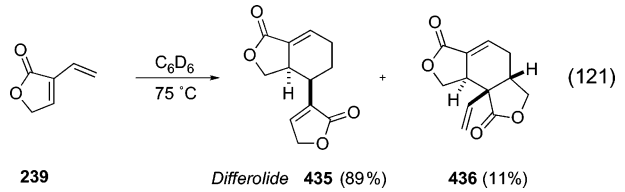
The first total synthesis of (−)-stemoamide was achieved using ring-closing enyne metathesis as the key step in the formation of the azabicycle.[180,181] This stands as the first example of enyne metathesis used in total synthesis. Formation of the fused 5,7-bicycle (**433**) contained within stemoamide was achieved in good yield (eq 120, Scheme 68). The reaction of

Scheme 68[180,181]



enynes **432** proceeded smoothly producing vinyl cycloheptenes using either the neophylidene **1B** or benzylidene **1A** precatalysts. The ester-substituted diene **432B** was needed for the synthesis (Scheme 68). Stemoamide **434** was obtained in 14 steps from (−)-pyroglutamic acid in 9% overall yield.

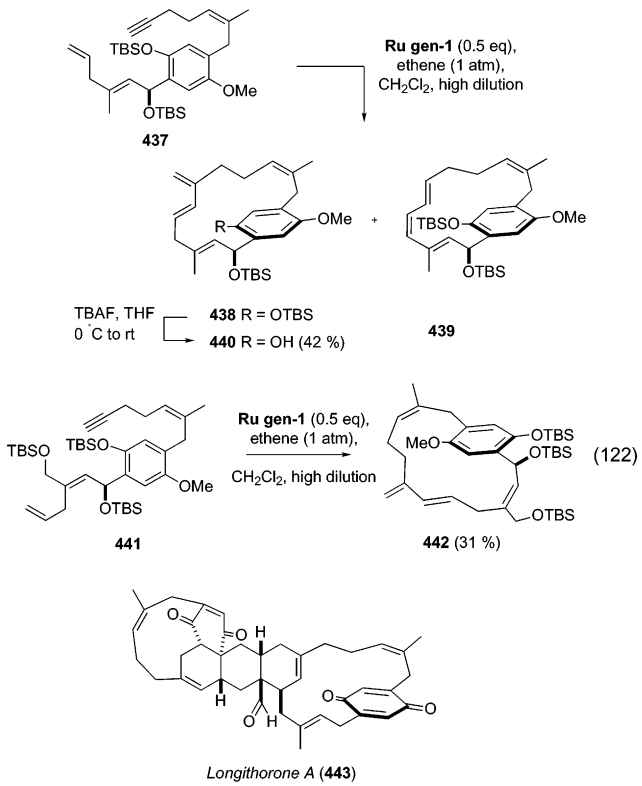
The total synthesis of the dimer differolide was achieved using ring-closing EYM to produce a vinyl butenolide that underwent spontaneous dimerization to differolide (eq 121).[95]



Initial alkene metathesis (transalkylidenation of initiator with **239**) produced a new alkylidene and a vinyl carbene, both of which were identified by NMR. Since catalytic turnover requires methylidene transfer from **239** to intermediate vinyl carbene, high enyne concentration was used. Based on previous findings, slow addition of benzylidene initiator (syringe pump) resulted in the best conversions and gave the vinyl butenolide **239** in 40% isolated yield. Dimerization was conducted thermally in benzene with trace methylene blue to inhibit radical polymerization. The natural dimer differolide **435** was formed in 89% yield along with 11% of the isomeric cycloadduct **436**.

Shair and co-workers used a macro ring-closing EYM to set up a biomimetic transannular Diels−Alder reaction in the total synthesis of (−)-longithorone A.[182] Enyne **437** was exposed to the metathesis reaction conditions, under an ethylene atmosphere, and afforded paracyclophane **438** with good diastereoselectivity (endo ring closure,[149] Scheme 69). De-

Scheme 69[182]

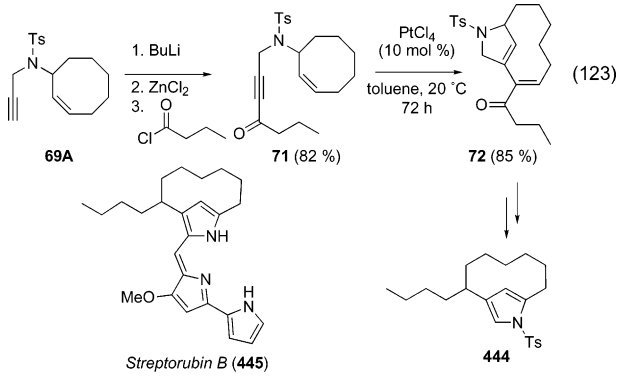


sired tetraene **438** was isolated as an inseparable mixture along with a propene-truncated paracyclo-

phane byproduct **439**. Removal of the phenolic silicon-protecting group permitted separation and provided cyclized product **440** in good yield over two steps. The assembly of the second fragment of longithorone utilized macro ring-closing EYM of **441**. The macro ring closure occurred in endo fashion[149] with dienes formed in a 3.9:1 (*E*:*Z*) ratio, with **442** isolated in 31% yield (eq 122). After some manipulation, the two paracyclophanes **440** and **442** were joined in a Diels–Alder assembly to give longithorone A **443**.

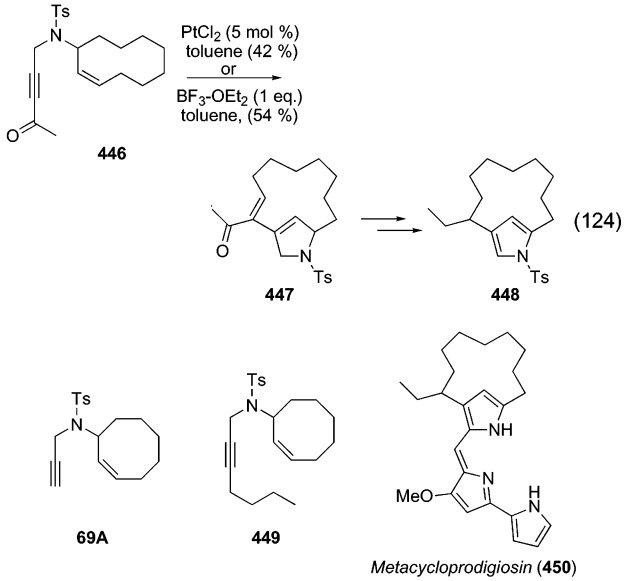
Fürstner and co-workers employed platinum(II)-catalyzed enyne bond reorganization as a key step to form the cyclophane ring systems found in streptorubin B and metacycloprodigiosin.[42] Access to the streptorubin ring system directly from terminal alkyne **69A** led to complex mixtures, which was surprising based on literature precedent for a related malonate system. Installation of a butanoyl group improved the metathesis **71** → **72** (eq 123, Scheme 70) using simple platinum salts such as $PtCl_2$, $PtCl_4$,

Scheme 70[42]

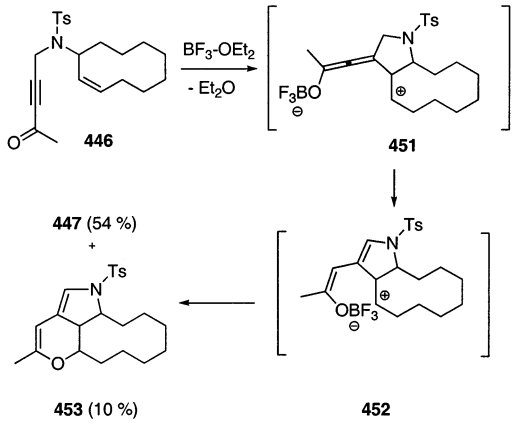


and $PtBr_4$. A similar strategy was used to convert **446** into the ring system found in metacycloprodigiosin **450** (eq 124, Scheme 71). The electron-withdrawing group was critical for effective rearrangement as both alkynes **69A** and **449** failed to give enyne metathesis (cf. enynes in eqs 107 and 109, section 3.1.5). Emboldened by mechanistic studies, Fürstner's group found that Lewis acids such as BF_3–OEt_2 could trigger the enyne bond reorganization (eq 124, second run; Scheme 71). The isolation of additional byproduct **453** lends support to the proposed mechanism for the Lewis acid-catalyzed pathway (Scheme 72).

Scheme 71[42]



Scheme 72[42]



Enyne metathesis has seen limited use in natural product chemistry. The successful synthetic efforts using the Grubbs' ruthenium carbenes fit expectations based on functional group tolerance of these catalysts, especially for remote oxygen functionality. Use of platinum(II) salts is more surprising, and it is clear that early stages of a synthesis can be accomplished with these catalysts. Trost used both platinum(II) chloride and the Murai catalyst for the formal synthesis of roseophilin described in Scheme 60 (section 3.1.5). It is fascinating to note that the more recent synthetic applications have focused on the enyne metathesis to accomplish macrocyclization, achieved through *both* metal carbene chemistry and the metal-salt enyne bond reorganization.

3.2. Intermolecular Enyne Cross Metathesis

The intermolecular enyne metathesis has seen fewer synthetic applications than the ring-closing enyne metathesis discussed in the previous section. Although the ring-closing applications continue, methodology development has shifted more toward the intermolecular arena and tandem transformations. The ring-closing metatheses are considered reasonably well understood and can be used reliably in synthesis.

The intermolecular enyne metathesis has additional difficulties as compared to its unimolecular sibling. The slower intermolecular reaction allows competitive pathways, such as chelation, to tie up catalyst. Decomposition becomes more likely, and this both challenges the application and diminishes the prospect for higher turnover catalysts, at least until these pathways are better understood. Although the intermolecular applications can take advantage of the inherent cross selectivity (a virtue of enyne metathesis), they are faced with limited or no control of diene geometrical isomers. The tactical use of a temporary, fragmentable ring has already been discussed as a solution to this problem (sections 3.1.1 and 3.1.6). It

is an appropriate summary of the current art that diene stereochemistry is substrate-dependent, and the factors most influencing selectivity have not been elucidated. Equilibrium control is a recent development, but it too is highly dependent on the alkene and the alkyne partners. Nonetheless, increased understanding of the factors influencing kinetic control and equilibrium control provide hope that a *Z*- and *E*-selective catalyst will be realized.

There are two main classifications for the intermolecular enyne metathesis based on alkene reactant, divided between ethylene and higher alkenes. Both developed concurrently. Reactions with ethylene as a reactant have led to improvements in the enyne metathesis, including expanded alkyne reactivity. A variety of 1-alkenes have been investigated with both first- and second-generation Grubbs' catalysts, on solid support and in solution. The alkenes are terminal and, in the case of allyl alcohol, tolerate protecting groups of varying bulk and with differing electronic properties. Recently enol ethers have been shown to react with alkynes, and an internal alkene reacts in a specialized application for ring synthesis.

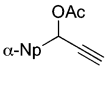
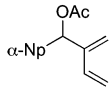
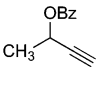
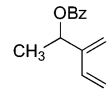
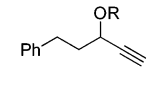
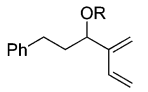
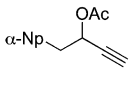
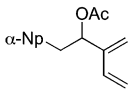
3.2.1 Reaction with Ethylene

Investigations in the ethylene−alkyne metathesis have led to some notable contrasts between the first- and second-generation catalysts, have identified shortcomings in the ruthenium carbene catalysts, and have led to one natural product synthesis.

As discussed above, Mori developed the ethylene−alkyne metathesis.[83] Mori's group had reported the use of ethylene, as a nonreactant, to promote ring-closing enyne metathesis, achieved by conducting reactions under ethylene atmosphere.[71] This protective influence of ethylene has been widely used in enyne metathesis, often called Mori's conditions. The reaction of primarily internal alkynes with ethylene under balloon pressure gave the 2,3-disubstituted butadienes, using the first-generation Grubbs' catalyst. Full investigation of the ethylene−alkyne metathesis revealed certain alkyne substrate limitations. Coordinating oxygen functionality and bulky substituents were not well-tolerated in the propargylic position (section 2.3).[84]

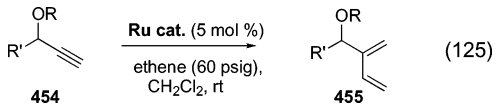
Smulik and Diver investigated the ethylene metathesis for alkynes with propargylic substitution.[139] These reactants had not been utilized previously because they reacted poorly in enyne metathesis. For example, reaction of alkyne (entry 1, Table 34) with ethylene (balloon pressure) gave butadiene in only 38% isolated yield after 29 h. To overcome this low conversion, the authors used increased ethylene pressure, which gave higher conversions and good isolated yield (80%, entry 1). Lower loading of **Ru gen-1** catalyst (1 mol %) could also be employed with higher ethylene pressure, but longer reaction times were necessary. The higher ethylene pressure results in a ca. 20-fold increase in solution concentration of ethylene, the most likely explanation for the improved reaction. The higher concentration may protect $Ru{=}CH_2$ from decomposition, compete with Cy_3P association to $Ru{=}CH_2$, and should increase turnover of the intermediate vinyl carbene. The higher ethylene pressure resulted in good isolated yields for a variety of propargyl substituted (Table 34).

Table 34[139] [a]

entry	1-alkyne	butadiene	yield (%)
1			80 (> 95 % ee)
2			80
3			75
4			92
5 6			R = Ac, 64 R = OBz, 57
7			78

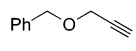
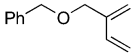
[a] Conditions: **Ru gen-1** (5 mol %), ethene (60 psig), CH_2Cl_2, rt.

Previous difficulties in ethylene−alkyne metathesis with propargylic oxygen functionality were overcome with the second-generation Grubbs' catalyst. Smulik and Diver examined four alkyne substrates known to perform poorly in enyne metathesis and showed that the higher ethylene pressure and the use of Grubbs' **Ru gen-2** carbene complex could overcome the poor reactivity of these alkynes (eq 125, Table 35).[77] Benzyl propargyl ether was suggested to be



(125)

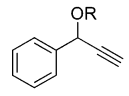
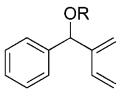
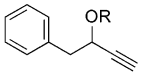
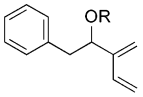
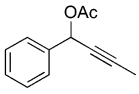
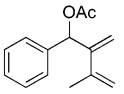
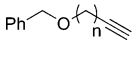
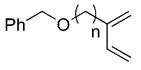
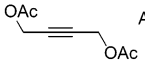
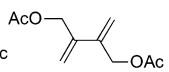
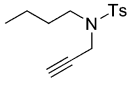
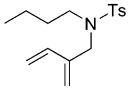
Table 35[77] [a]

entry	alkyne	butadiene	**Ru gen-2** (yield, %)	**Ru gen-1** (yield, %)
1			97 (6.0 h)	5
2	 R = H		99 (2.0 h)	N.P.
3	R = Ac		99 (2.0 h)	38 (2.0 h)
4	R = TBS		99 (8.5 h)	N.P.

[a] Percent conversion at indicated time. N.P. = no product observed.

coordination-prone due to its poor turnover with the **Ru gen-1** catalyst. However, the second-generation catalyst overcomes this limitation (entry 1, last two columns). Free alcohols had been identified as poor substrates in Blechert's study[72] and in the ethylene metathesis as well.[139] The **Ru gen-2** catalyst gave high conversions for 1-substituted alkynol (entry 2). Steric bulk could be overcome using the second-generation catalyst (entry 4). These conditions were

Table 36[77] [a]

entry	alkyne	butadiene	R	yield (%)
1			H	73
2			Ac	92
3			TBS	91
4			H	58
5			Ac	92
6			TBS	96
7				77
8			n = 1	72
9			n = 2	62
10				69
11				91

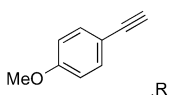
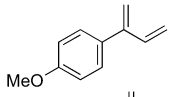
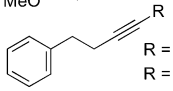
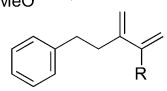
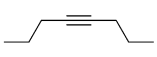
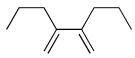
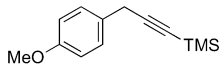
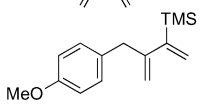
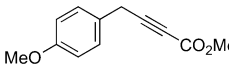
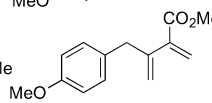
[a] Conditions: **Ru gen-2** (5 mol %), ethene (60 psig), rt.

employed to generate a variety of butadienes with potentially coordinating heteroatoms in the propargylic position (Table 36). As observed for 1-acyloxy 1-substituted alkynes with the **Ru gen-1** catalyst (entry 1, Table 34), no racemization occurred with enantiomerically enriched propargyl alcohol derivatives.

Contrasting reactivity for the first- and second-generation catalysts was also observed by Mori and co-workers.[80] Although certain oxygen functionality in the propargylic position may impede enyne metathesis by chelation, propargylic acetates had a beneficial effect on ethylene metathesis catalyzed by the first-generation Grubbs' catalyst. In separate runs, $ArCH_2CH{\equiv}CH$ and $ArCH(OAc)C{\equiv}CH$ were converted to their corresponding dienes in 16% and 75% yield, respectively, after 2 d. The authors suggest that the propargyl heteroatom results in a more reactive alkyne. In contrast, for the ethylene−alkyne metathesis catalyzed by **Ru gen-2**, it was found that the heteroatom had little influence on product yields. The competition experiment conducted with the same terminal alkynes gave similar yields when run in toluene at 50 °C. Similar lack of heteroatom effect was found in internal alkynes.

A variety of 1-alkynes and internal alkynes were examined in the ethylene−alkyne cross metathesis (Table 37). The benefit of using the second-generation catalyst can be seen in the diene synthesis using trimethylsilyl-substituted acetylene (entries 6 and 7). Low conversion and low isolated yield were found with the first-generation ruthenium catalyst; however, at higher temperatures (80 °C) the **Ru gen-2** catalyst gives excellent yield (entry 7). Internal alkynes with electron-withdrawing groups do not perform well in ruthenium carbene-catalyzed enyne metathesis (alkyne in entry 8). Consistent with this

Table 37[80] [a]

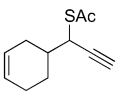
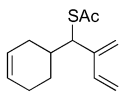
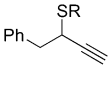
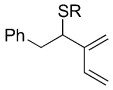
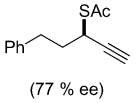
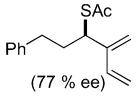
entry	alkyne	butadiene	yield (%)
1			88
2	 R = H		71
3	R = Me		85
4	$R = CH_2OAc$		100
5			80
6			21[b]
7			87
8			33
9			43[c]

[a] Conditions: **Ru gen-2** (5 mol %), 80 °C, toluene. [b] **Ru gen-1** (5 mol %), rt, CH_2Cl_2. [c] **Ru gen-2** (10 mol %).

generalization, no product was obtained using the first-generation complex, but a modest yield of dienyl ester could be obtained through heating the ynoate in toluene with 5 or 10 mol % of the second-generation catalyst (entries 8 and 9).

With attention to protecting group, sulfur-containing alkynes undergo ethylene metathesis.[117] Metathesis in the presence of sulfur functional groups can present problems for catalyst turnover since chelated complexes may benefit from a stable sulfur−ruthenium interaction. Simple propargyl thioethers (e.g., benzyl propargyl thioether and trityl propargyl thioether) failed to give catalytic turnover in the ethylene−alkyne metathesis using the second-generation Grubbs' catalyst and elevated pressure of ethylene (60 psig). From this result, the authors concluded that the deleterious effect of the Lewis basicity of the sulfur lone pair could be attenuated electronically using thiol ester protecting groups. The reported ethylene−alkyne metatheses were conducted at room

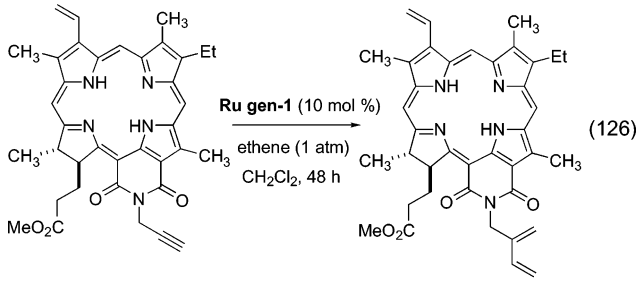
Table 38[117] [a]

entry	alkyne	butadiene	yield (%)
1			95
2			87
3			99[b,c]
4			11[b,d]
5			98
6			R = Ac, 97
7			R = Bz, 99
8	 (77 % ee)	 (77 % ee)	97

[a] Conditions: **Ru gen-2** (5 mol %), ethene (60 psig), CH_2Cl_2, rt. [b] Based on conversion. [c] **4** (5 mol %) used in this run. [d] **Ru gen-1** (5 mol %) used in this run.

temperature due to instability of some of the thiol esters investigated. The yields for a variety of alkynes were nearly quantitative under these conditions (Table 38). The Hoveyda catalyst gave quantitative conversion (entry 3) similar to that seen using the **Ru gen-2** complex. The first-generation complex performed poorly for these reactions (entry 4). Enantiomerically enriched thiol acetate (entry 8) underwent metathesis without erosion of enantiomeric excess, suggesting that the ruthenium−sulfur interaction is not strong enough to trigger solvolytic cleavage of the propargylic thiol ester moiety.

Zheng et al. showed that ethylene−alkyne metathesis could be used in the preparation of chlorin−dienyl chlorin building blocks (eq 126).[183]

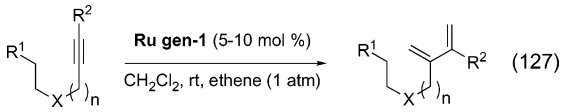


(126)

456 **457** (40 %)

These reactions gave incomplete conversion of chlorin alkyne **456** using the first-generation catalyst and balloon pressure of ethylene. The ethylene metathesis provided a 40% yield of butadiene **457**. Cycloaddition with *N*-phenyl maleimide provided a 60% yield of the expected cycloadducts, obtained in a 1:1 ratio.

The naturally occurring lignans anolignan A and B were synthesized by ethylene metathesis.[79] Model studies revealed difficult cases for ethylene metathesis (eq 127, Table 39). In particular, a terminal

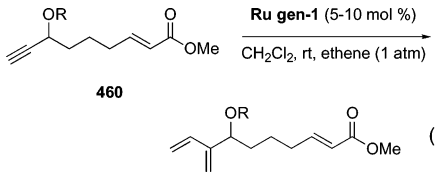


(127)

Table 39[79]

entry	enyne	R^1	R^2	X	*n*	diene	yield (%)
1	**220A**	CH=CHCO$_2$Menthyl	H	CH_2	1	**221A**	10
2	**210**	CH=CHCO$_2$Me	CH_2OBz	CH_2	1	**213**	53
3	**464A**	$(CH_2)_3CH_3$	H	NTs	1	**465A**	81
4	**464B**	$(CH_2)_3CH_3$	H	NTs	2	**465B**	11

alkyne with a remote enoate (entry 1) and a homopropargyl tosylamide (entry 4) both performed poorly.[84] The model study revealed that a propargylic heteroatom helped the ethylene metathesis of terminal alkynes. The nature of the protecting group on the heteroatom also played a role in the ethylene metathesis (eq 128, Table 40). The carbonate and esters were good substrates (entries 1−3), known previously from cross metathesis with 1-alkenes.[72] Bulky or coordinating groups resulted in lower yields (entries 4−7, Table 40). Previously, it had been shown that bulky silyl ethers and coordinating ethers underwent ethylene metathesis using the more reactive second-generation Grubbs' catalyst and elevated ethylene pressure,[77] but these conditions were not explored.



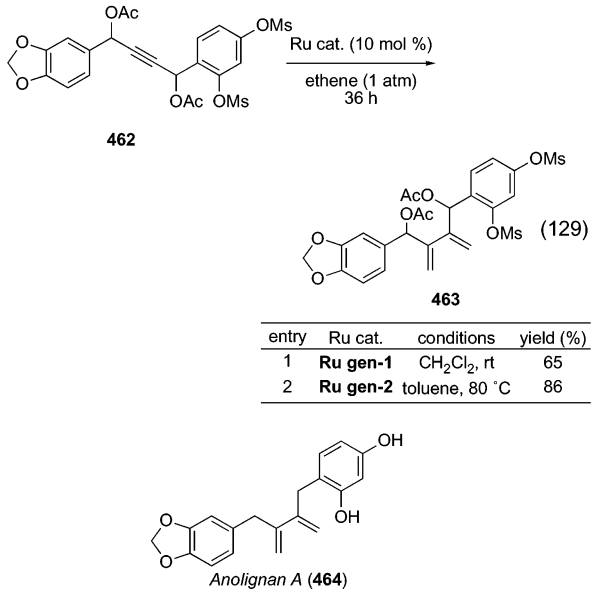
460 **461** (128)

Table 40[79]

entry	R	**Ru gen-1** (mol %)	yield (%)
1	CO_2Me	10	76
2	Bz	10	77
3	Ac	5	80
4	TBDPS	5	<5
5	TBDMS	5	10
6	TMS	5	8
7	MOM	5	18
8	H	8	<6

Completion of the anolignan A synthesis proceeded by ethylene metathesis with bis(arene)yne **462** (eq 129, Scheme 73).[79] In this instance, the authors

Scheme 73[79]



(129)

examined both the first- and second-generation Grubbs' carbenes. Using 10 mol % catalyst, the key metathesis produced **463** in 65% yield with **Ru gen-1** (CH_2Cl_2, rt, 36 h) and 86% yield with **Ru gen-2** (toluene, 80 °C, 36 h). Completion of the synthesis required reductive removal of the progargylic acetates using transfer hydrogenation, followed by mesylate cleavage with excess phenyllithium, which provided anolignan A **464**.

Ethylene metathesis produces 2-substituted-1,3-butadienes, which have limited applications in synthesis. Ethylene metathesis reported by Mori and coworkers demonstrated cross metathesis with ruthenium carbenes where regiochemistry was not a concern. Since that time, ethylene metathesis has been applied to increasingly more complex systems using

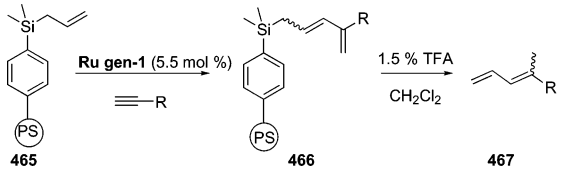
the ruthenium carbene-based catalysts and led to the use of the second-generation Grubbs' carbene catalyst to enyne metathesis. As a result, ethylene metathesis led to improvements in the cross reaction for both the preparation of sterically hindered dienes (due to substitution at the propargylic position) and those with coordinating functionality that would prove potentially challenging to catalyst turnover. The ethylene metathesis is applicable to a range of alkynes, both terminal and internal, bearing heteroatom functionality at the propargylic position.

3.2.2. Cross Metathesis with Higher Alkenes

The first report of cross enyne metathesis using ruthenium carbenes originated from Blechert's group,[72] as discussed in section 2.2.2. This work had demonstrated that 1-alkenes such as allyl trimethylsilane and allyl acetate would participate in the *inter*molecular enyne metathesis. This work expanded the applicability of ruthenium-catalyzed metathesis beyond intramolecular applications. One of the major differences in the intermolecular reaction is the lack of stereocontrol imposed by ring constraint. As a result, intermolecular reactions are typically non-stereoselective with mixtures of *E*/*Z* stereoisomers being produced.

Schuster and Blechert demonstrated that enyne metathesis can be conducted with resin-bound allyl silane.[184] In this case, the allyl trimethylsilane was attached to 1% DVB cross-linked polystyrene resin. Cross metathesis with solution-phase alkyne resulted in formation of dienes **466** (Scheme 74). Protodesilylation with trifluoroacetic acid afforded the isomeric dienes **467** (with concomitant resin cleavage) in good yield. Acrylate esters, an Fmoc-protected amino acid and a protected sugar (entries 4−6, Table 41) underwent reaction in moderate yields to give *E*/*Z* mixtures of dienes **467**.

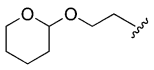
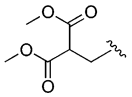
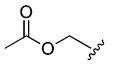
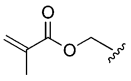
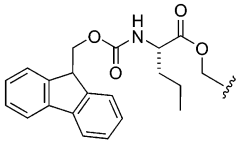
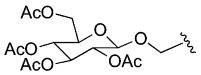
Scheme 74[184]



(130)

Schurer and Blechert showed that enyne cross metathesis could be conducted with the alkyne attached to solid support.[185] Resin-bound propargyl alcohol was prepared by reaction of the cesium salt of monopropargyl alcohol succinic monoester with chlorostyrene (Scheme 75). Cross metathesis using 2−6 equiv of solution-phase alkene provided 1,3-diene **469** that was freed from the resin by Pd(0)-assisted cleavage and subsequent interception of the π-allyl complex with various nucleophiles (Scheme 75). In this way, rapid access to 1,3-disubstituted dienes **470** was possible. The Pd-catalyzed coupling accomplishes the introduction of additional functionality on the diene and results in simultaneous cleavage from the resin. The alkene reaction partner contained various remote functionality. For the homoallylic alcohol coupling (entry 1, Table 42), the trityl-protected alcohol was employed in the metathesis step. Importantly, amines could be incorporated onto the diene through this method (entries 6−8). The resin-bound intermediate **469** could also be reductively cleaved via transfer hydrogenation (eq 131).

Table 41

entry	R—	yield (%, *E*/*Z*)
1		57, (1:1)
2		56, (2:1)
3		56, (6:1)
4		58, (8:1)
5		39, (3:1)
6		61, (4:1)

Scheme 75[185]

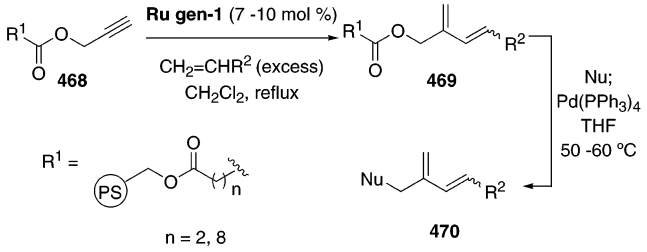
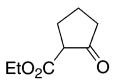
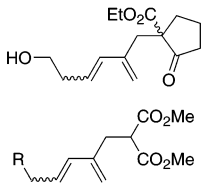
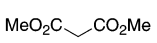
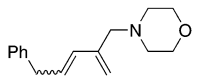
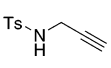
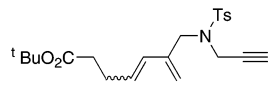
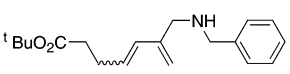
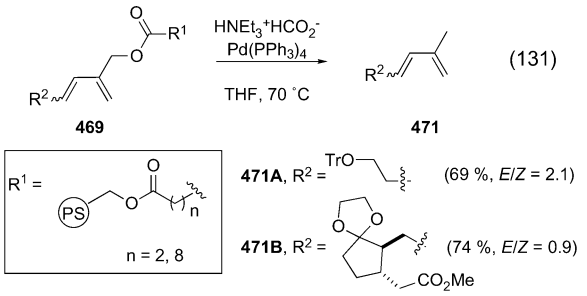
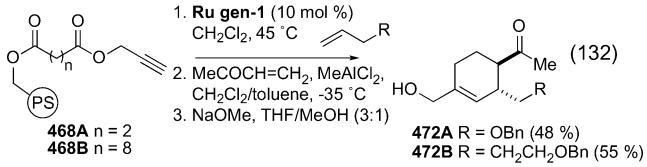


Table 42

entry	Nu	cleavage product, **470**	overall yield (%)	*E* / *Z*
1			54	1.4 : 1
2		R = TMS	78	0.6 : 1
3		R = OTBS	60	0.9 : 1
4		R = Ph	67	1.1 : 1
5		R = CH_2CH_2OTr	66	0.9 : 1
6			86	0.9 : 1
7			32	1 : 1
8	$BnNH_2$		51	0.9 : 1



Enyne cross metathesis with resin-bound alkynes was joined with Lewis acid-catalyzed cycloaddition to prepare cyclohexenes.[186] The *E*/*Z* mixtures of 1,3-dienes give mixtures of diastereomers in the Diels−Alder reaction, although regioselectivity is characteristically high (eq 132).



Low-temperature $MeAlCl_2$-catalyzed [4 + 2] cycloaddition of methyl vinyl ketone gave a mixture of cycloadducts that were simultaneously epimerized and cleaved (NaOMe) from the Merrifield resin to give a single stereoisomer **472A** or **472B**. Due to the rigidity of the polystyrene resin, the two or eight-carbon linker from succinic acid or sebacic acid was used with the best results.

The assembly of octahydrobenzo[*c*]azepin-3-ones was achieved by amide formation with Me_3Al, a process which simultaneously releases the benzoazepine from the resin.[186] The best results in this case employed the commercially available 4-hydroxymethylbenzoic acid aminomethyl polystyrene resin (Scheme 76). Overall yields (four steps) are

Scheme 76[186]

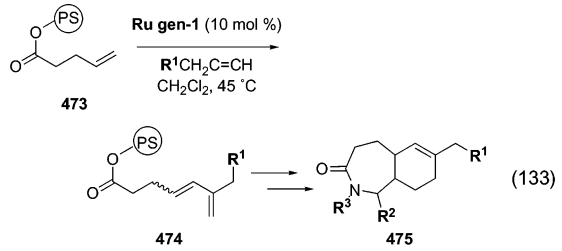


Table 43

entry	R^1	R^2	R^3	**475** (yield %)
1	$(CH_2)_4Me$	Me	CH_2Ph	19
2	$(CH_2)_4Me$	Me	CH_2CH_2Ph	28
3	$(CH_2)_4Me$	Me	Me	20
4	$(CH_2)_4Me$	H	CH_2Ph	22
5	CH_2OH	H	CH_2CH_2Ph	15
6	CH_2OH	H	$(CH_2)_3Me$	15
7	CH_2OH	H	Me	15
8	OCH_2Ph	H	Me	14
9	N(Me)Cbz	H	Me	15

summarized in Table 43.

The 1,3-dienes produced through cross metathesis were surveyed for a variety of alkynes and alkenes and used in an aza-Diels−Alder reaction.[187] A variety of oxygen substituents were tolerated on both the propargyl and allyl reactive partners (eq 134, Table 44). Particularly noteworthy are the sugars used in

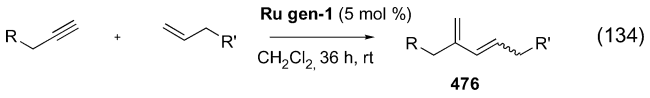
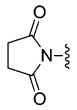
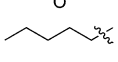
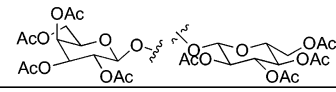
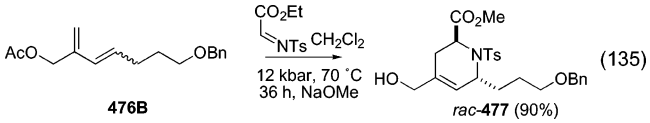


Table 44[187]

entry	R	R'	**476**	yield (%)
1	OAc	CH_2CO_2Bn	**A**	87
2	OAc	CH_2CH_2OBn	**B**	80
3	OBn	OTBS	**C**	70
4	OTBS	CH_2CH_2OBn	**D**	47
5	OTr	-N(Cbz)CH_2CH_2OAc	**E**	51
6		OEt	**F**	52
7			**G**	75
8			**H**	58

the last entry, both of which present a potentially coordinating ether at both propargylic and allylic positions. The diene products (e.g., **476B**) were shown to undergo high-pressure aza-Diels−Alder reaction to furnish the tetrahydropyridines in excellent yield (eq 135).



Following the development of the second-generation Grubbs' precatalyst, Blechert's group reinvestigated the allyl trimethylsilane−alkyne cross metathesis using the **Ru gen-2** carbene.[81] Yields were generally improved, but *E*/*Z* ratios were not significantly different than those obtained with the **Ru gen-1** catalyst (eq 136, Table 45). Trimethylsilyl-

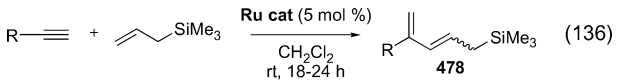
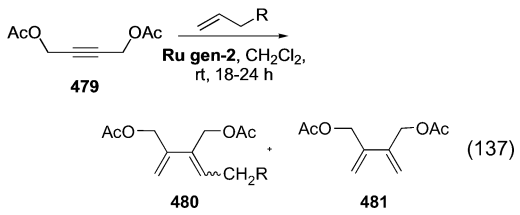


Table 45[81]

entry	R	**Ru cat**	yield (%, *E*/*Z*)
1	Me_3Si	**Ru gen-1**	22 (9.0:1.0)
2	Me_3Si	**Ru gen-2**	77 (6.0:1.0)
3	*c*-C_6H_{11}	**Ru gen-1**	0
4	*c*-C_6H_{11}	**Ru gen-2**	69 (1.9:1.0)
5	$TrOCH_2CH_2$	**Ru gen-1**	86 (1.4:1.0)
6	$TrOCH_2CH_2$	**Ru gen-2**	98 (1.6:1.0)

acetylene and propargylic disubstituted alkynes showed the most pronounced benefit of using the second-generation catalyst for terminal alkynes (entries 1−4). Internal alkynes also gave cross metathesis with the second-generation catalyst, a reaction that was not possible with the **Ru gen-1** complex (eq 137). In these runs, the 2,3-disubstituted butadienes **481** were obtained as byproducts. Significantly, treatment of diene **481** with **Ru gen-2** and allyl trimeth-



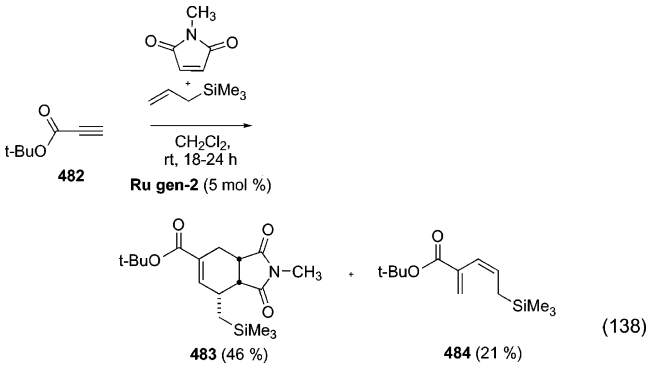
ylsilane did not provide cross product **480A**. This result shows that this 2,3-disubstituted-1,3-butadiene (**481**) is kinetically stable to metathesis with the second-generation Grubbs' catalyst at room temperature. The internal alkyne **479** reacted with various 1-alkenes but gave more butadiene byproduct in these cases (Table 46, last two runs). In these cases,

Table 46[81]

entry	R		**480**, yield (%, *E*/*Z*)	**481**, yield (%)
1	$SiMe_3$	**480A**	89 (0.40:1.0)	11
2	OTBS	**480B**	80 (0.38:1.0)	20
3	CO_2Bn	**480C**	61 (0.50:1.0)	30

faster alkene−alkene metathesis results in ethylene production. Unsymmetrical internal alkynes give mixtures of regioisomers.

The cross metathesis of an electron-deficient alkyne took place with allyl trimethylsilane (eq 138). Due



to difficulties with self-Diels−Alder reaction, *N*-methyl maleimide was included in the metathesis to trap out the *E*-diene. In this way, 46% yield of **483** was obtained, along with 21% of the *Z*-isomer, which failed to undergo in situ cycloaddition. The first-generation catalyst produced products **483** and **484** in a combined yield of only 10%. The procedure has synthetic potential as a one-pot, three-component coupling.

Enyne metathesis has been used to construct the C2−C7 side chain of mycothiazole.[188] In this study, protected homopropargylic amines were the desired alkyne starting materials, but they gave poor conversions in the cross metathesis using the first-generation Grubbs' catalyst. To get around this difficulty, homopropargylic tosylates were reacted with allylic alcohol derivatives in the cross metathesis (eq 139). Subsequently, the tosylate was converted into the required amine, which is positioned at C2 of mycothiazole (Scheme 77). The best protecting group used for the allylic alcohol was the TBDPS protecting group (entry 6, Table 47). Acetate and tosylate were

Scheme 77[188]

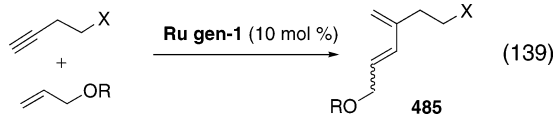
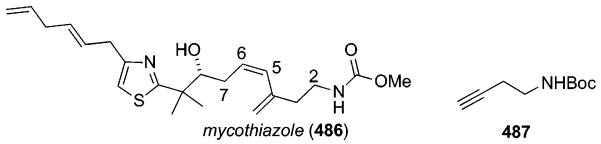


Table 47

entry	X	R	alkyne (M)	solvent	time (h)	yield (%)	ratio (*E*/*Z*)
1	OTs	H	0.2	DCM	24	0	
2	OTs	TBS	0.1	toluene	5	30	1:1
3	OTs	TBS	0.2	DCM	5	80	1:1
4	OTs	Ac	0.1	DCM	5	15	1:1
5	OAc	TBS	0.2	DCM	5	80	1.1:1
6	OTs	TBDPS	0.2	DCM	5	95	1.1:1
7	OTs	TBDPS	0.2	DCM	5	65	1.1:1
8	OTs	TBDPS	0.2	DCM	12	60	1.1:1

tolerated on the alkyne (entries 3 and 5), but an acetate on the alkene was detrimental (entry 4). Allyl alcohol failed to react, and all products were obtained as 1:1 *E*/*Z* mixtures. Homopropargylic carbamate **487**



also failed to give cross metathesis, which defines a substrate limitation for the **Ru gen-1** catalyst in the intermolecular metathesis.

Intermolecular enyne metathesis is the integral synthetic method used to produce novel amino acid derivatives.[189,190] The aromatic ring of highly substituted phenylalanines was synthesized through enyne cross metathesis and cycloaddition. Kotha reacted propargylic amino acids with allyl acetate to afford amino acid dienes **489** (eq 140, Table 48). Thermal

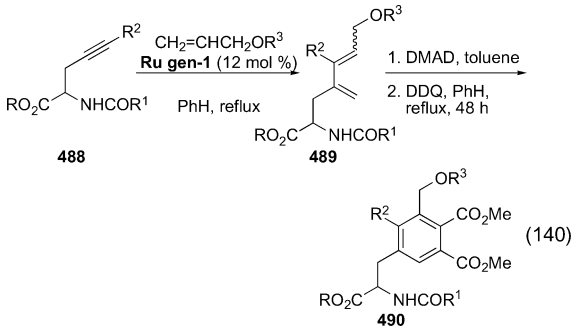


Table 48[189,190]

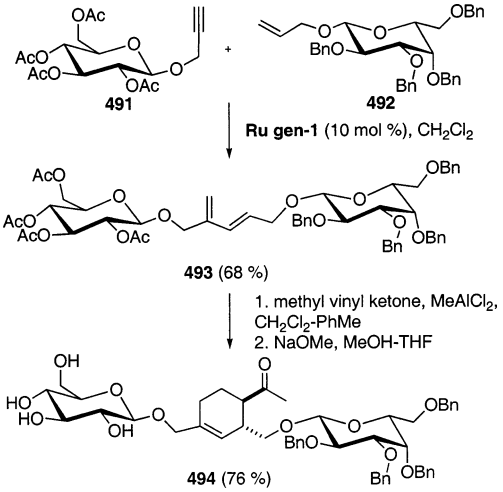
entry	R	R^1	R^2	R^3	**489** (yield, %)	**490** (yield, %)
1	Me	Me	H	Ac	45	32
2	Me	*t*-Bu	H	Ac	47	56
3	Et	Me	H	Ac	37	44
4	Et	*t*-Bu	H	Ac	56	46
5	Et	Me	TMS	Ac	10	
6	Me	Me	H	Ph	40	

cycloaddition with DMAD and subsequent DDQ oxidation provided the 3,4,5-trisubstituted phenylalanines **490** in good yield. It is notable that the secondary acetamides (entries 1, 3, 5, and 6) and

pivaloylamides (entries 2 and 4) underwent efficient cross metathesis with reasonably high catalyst loadings of the first-generation Grubbs' complex.

The compatibility of protected sugars with the ruthenium carbene catalysts permit carbohydrates to be used in cross enyne metathesis applications. Unnatural, carbocycle-linked oligosaccharides were prepared by Schürer and Blechert.[191] Examples of intramolecular RCEYM of carbohydrate-based enynes were illustrated in section 3.1.4. In the present case, a selective enyne cross metathesis and Diels−Alder reaction of available monosaccharide subunits was performed (Scheme 78). This was the first example

Scheme 78[191]

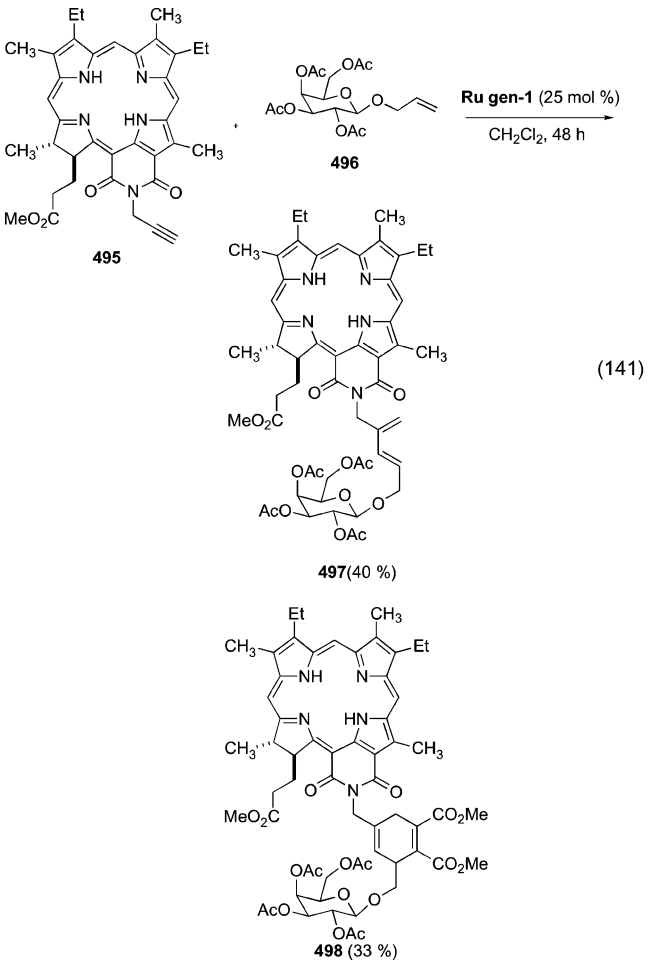


of a Diels−Alder reaction using carbohydrate-substituted 1,3-butadienes.

In continuation studies of ethylene metathesis to make chlorin building blocks for photodynamic therapy, Zheng and co-workers used enyne metathesis to build a β-galactose-conjugated purpurinimide (Scheme 79).[192] Cross metathesis of alkyne **495** with **496** was followed by cycloaddition with DMAD, which gave the corresponding cycloadduct **498** in 33% yield. The [4+2] cycloaddition with *N*-phenylmaleimide gave a 60% yield of cycloadducts.

The repertoire of 1-alkenes that will participate in the intermolecular enyne metathesis has been expanded to include enol ethers.[78] In alkene metathesis, enol ethers are not willing reactants and fail to yield cross alkene metathesis products. Enol ethers are typically added to living polymers obtained in ROMP to terminate the polymer and to produce a stable Fischer carbene. The equilibrium between a ruthenium alkylidene (or methylidene) and Fischer carbene favors the Fischer carbene complex. Despite the propensity to form stable Fischer carbene complexes, enol ethers were found to react with alkynes in cross metathesis. Use of excess enol ether in refluxing benzene produced dienol ethers in good to excellent yields for both vinyl acetate and alkyl vinyl ethers

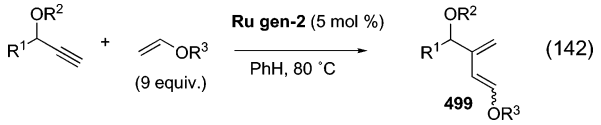
Scheme 79[192]



(141)

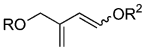
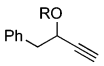
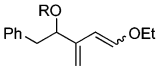
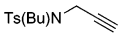
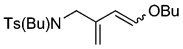
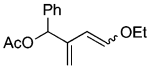
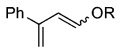
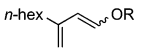
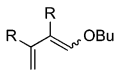
(eq 142, Table 49). In the alkyne partner, various heteroatoms and propargylic substitution are tolerated. Simple hydrocarbon alkynes react (entries 9−12) and a symmetrical internal alkyne gave excellent yield of the cross product. The produced dienol ethers of Table 49 were obtained as *E*/*Z* mixtures that were determined to be kinetically stable to the reaction conditions. Because of their electron-rich nature, these dienes are superb substrates for cycloaddition.[78]

Ring expansion of cyclopentene by cross enyne metathesis was reported by Kulkarni and Diver as a 1,3-cycloheptadiene synthesis.[82] Cyclopentene is a low strain cycloalkene that is nevertheless capable of ROMP.[193] Prior to this study, it was uncertain whether the intermolecular enyne metathesis could effectively compete with the ROMP pathway (see section 2.2.1). In the ring synthesis, a variety of terminal alkynes reacted with cyclopentene under high dilution conditions to provide the cycloheptadienes **500** in good yield (eq 143, Table 50). A variety of 1,3-dimesityldihydroimidazole carbene-based ruthenium initiators promoted the ring synthesis. The initiators **Ru gen-2**, the Hoveyda catalyst **4,** and the bispyridine solvate **5** gave similar yields in refluxing CH_2Cl_2, and the faster initiators promoted the reaction at room temperature. For the cross metathesis reaction manifold to be competitive with ROMP, terminal alkynes were needed. The mechanism likely



(142)

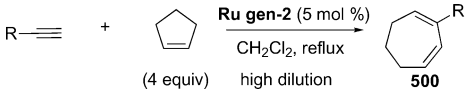
Table 49[78]

entry	alkyne	enol ether (9 eq.), solv.	**499**, yield
			
1	R = Bz	EVE, PhH	(R^2 = Et), 98 %
2	R = Bz	vinyl acetate, PhH	(R^2 = Ac), 97 %
3	R = Bn	EVE, CH_2Cl_2	(R^2 = Et), 82 %
4	R = TBDPS	EVE, PhH	(R^2 = Et), 97 %
			
5	R = Ac	EVE, CH_2Cl_2	(R = Ac), 88 %
6	R = TBS	EVE, CH_2Cl_2	(R = TBS), 38 %
			
7		BuVE, CH_2Cl_2	92 %
			
8		EVE, CH_2Cl_2	96 %
			
9		BuVE, PhH	(R = Bu), 90 %
10		vinyl acetate,[a] CH_2Cl_2[b]	(R = Ac),[c] 80 %
			
11		BuVE, PhH	(R = Bu), 86 %
12		vinyl acetate, PhH[b]	(R = Ac), 70 %
			
13		BuVE, PhH	($R=CH_2OAc$), 98 %

[a] 18 equiv of vinyl acetate used. [b] Reaction was spiked with an additional 2.5 mol % **Ru gen-2**. [c] 80 °C Conversion by ^1H NMR.

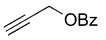
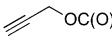
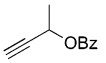
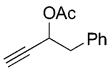
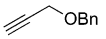
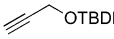
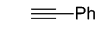
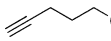
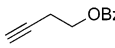
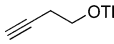
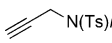
involves ring opening of the cyclopentene to produce an alkylidene which adds across the alkyne (Scheme 80). The ROMP pathway was suppressed by maintaining low cyclopentene concentration with syringe pump addition. The vinyl carbene **503** can experience ring closure to afford the cycloheptadiene directly. It is presumed that 2*E*-**503** also forms but can either reversibly generate the *E*,*Z*-mixture or react with cyclopentene to access a ring closure step that would also form the seven-membered ring. Considering that the overall reaction is an aggregate of a cross metathesis and a ring-closing metathesis, the ring synthesis is also a tandem metathesis. The cycloheptadienes were functionalized by cycloaddition with singlet oxygen and reductive cleavage to access the 1,4 diol.

In the cross metathesis, various 1-alkenes participate in the reaction using ruthenium carbene precatalysts. Allylic oxygen functionality on the alkene is tolerated, but additional allylic substitution is not. Amines can be introduced after the metathesis or can be fully protected, but this is an underdeveloped area of investigation. Cyclopentene, an internal alkene, does participate in the cross metathesis under reaction conditions that do not involve ruthenium methylidene intermediates, which demonstrates that cross



(143)

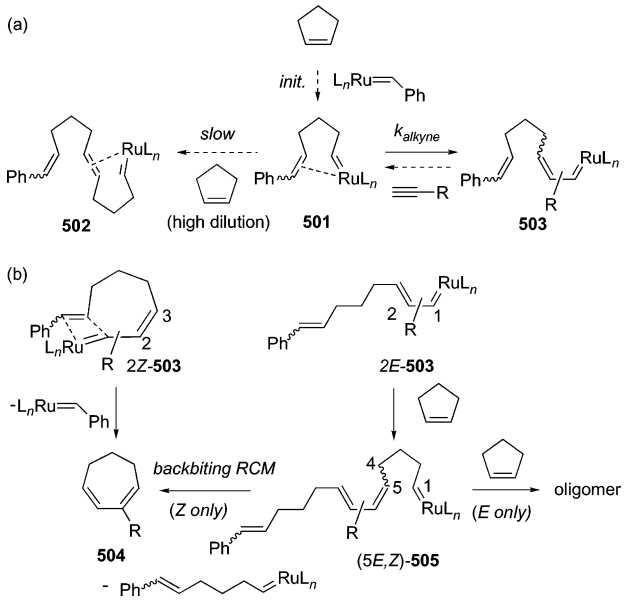
Table 50[82]

entry	alkyne	cycloheptadiene **500**	isolated yield (%)
1		R = CH_2OBz	75[a]
2		R = $CH_2OC(O)\beta$-Nap	62
3		R = $CH(OBz)CH_3$	74[a]
4		R = $CH(OAc)CH_2Ph$	62
5		R = CH_2OBn	56[a]
6		R = $CH_2OTBDPS$	56
7		R = Ph	58
8		R = $(CH_2)_3Cl$	(70)[b]
9		R = $(CH_2)_2OBz$	57
10		R = $(CH_2)_2OTBDPS$	53
11		R = $CH_2N(Ts)n$-Bu	65

[a] Yield on 2.5 mmol scale. [b] Conversion by NMR.

metathesis can proceed through alkylidene−alkyne cycloaddition (cf. the methylidene mechanism of Scheme 36). The electron-rich vinyl ethers participate in the reaction despite the potential to form stable Fischer carbene complexes. This latter observation suggests that the favorable equilibrium of enyne metathesis may help overcome such stable catalyst resting states. It is typical to use terminal alkynes

Scheme 80[82]

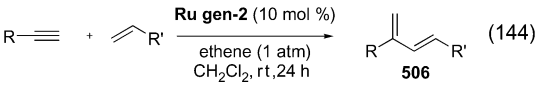


to access 1,3-disubstituted 1,3-dienes, but internal alkynes also react in metathesis catalyzed by the **Ru gen-2** complex. Electron-deficient alkynes are challenging substrates for both ethylene− and 1-alkene−alkyne cross metathesis (see also section 3.2.1).

3.2.3. Influence of Ethylene on Cross Metatheses

Ethylene has been used to influence stereoselectivity and reactivity in cross enyne metathesis. Previously ethylene was shown to improve catalyst longevity in ring-closing enyne metathesis using Mori's conditions (sections 2.2.2 and 3.1.1). Ethylene can also be used along with higher alkenes in intermolecular metathesis. Competing ethylene−alkyne metathesis is suppressed by using a large excess of 1-alkenes.

Ethylene was shown to promote *E*-selective cross metathesis between certain alkenes and terminal alkynes.[92] Three different homopropargylic alkynes were reacted with aliphatic alkenes, all providing the corresponding diene with high *E*-selectivity and in good yields (eq 144, Table 51).



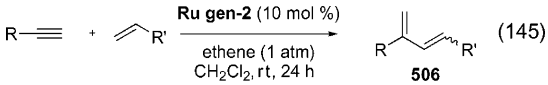
(144)

Table 51[92]

entry	alkyne	alkene, R'	yield (%)	*E*/*Z* ratio
1	BnO	*n*-hex	82	*E* only
2		*n*-C_3H_7	88	*E* only
3		CH_2CH_2Br	74	>20:1
4		$CH_2CH_2CO_2Et$	57	>20:1
5	TsO	*n*-hex	71	*E* only
6		*n*-C_3H_7	83	*E* only
7		CH_2CH_2Br	64	>20:1
8		$CH_2CH_2CO_2Et$	59	>20:1
9	TBDPSO	*n*-hex	68	*E* only
10		*n*-C_3H_7	60	>20:1
11		$CH_2CH_2CO_2Et$	62	>20:1
12	AcO	*n*-hex	82	*E* only
13		*n*-C_3H_7	55	*E* only
14		CH_2CH_2Br	67	>20:1

The enhanced *E*-selectivity was particular to the alkene reactive partner. Allyl trimethylsilane produced diene with characteristically low stereoselectivities, even with ethylene present (eq 145, entries 1, 2, 5, and 8, Table 52). It is interesting to note that allyl trimethylsilane was employed in Blechert's original study[72] describing intermolecular enyne metathesis with ruthenium carbenes. The allyl alcohol derivatives show a modest trend toward *E*-selectivity as the allylic group is switched from an ether to an ester (entries 3, 4; entries 6, 7). The erosion of stereoselectivity with these alkenes is attributed to "electronic, coordinative or steric bias". Only (triphenylsilyl)acetylene gave cross product with *E*-selectivity, and this was observed with or without ethylene.

With ethylene present, the alkyne may react with $Ru{=}CH_2$, which would give a butadiene (e.g., **507**) after methylene transfer. A butadiene formed through



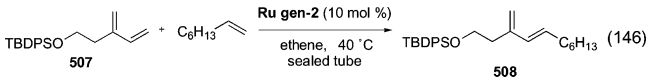
(145)

Table 52[92]

entry	alkyne	alkene, R'	yield (%)	*E*/*Z* ratio
1	BnO	CH_2SiMe_3	79	1.3:1
2	TsO	CH_2SiMe_3	84	1.4:1
3		CH_2OBu	42	3:1
4		CH_2OAc	48	9:1
5	TBDPSO	CH_2SiMe_3	79	1.3:1
6		CH_2OBu	44	3:1
7		CH_2OAc	49	6.5:1
8	AcO	CH_2SiMe_3	86	1.6:1
9	Ph_3Si—	CH_2SiMe_3	89	*E* only[a]

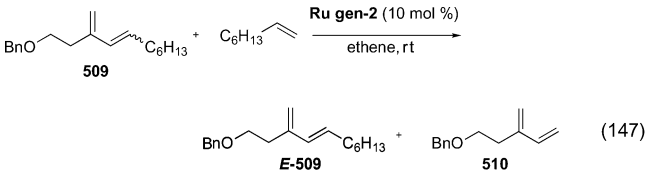
(a) *E* isomer only, even without ethene.

ethylene metathesis was shown to be *kinetically reactive* at higher temperature (eq 146).



(146)

Under sealed tube conditions with ethylene and excess 1-octene, butadiene **507** formed the cross product **508**. This observation was taken as proof that butadienes accessed through initial ethylene metathesis could serve as intermediates en route to alkene−alkyne cross products. However, the diene **507** was found to be kinetically stable to allyl trimethylsilane and allyl butyl ether, even with ethylene present. It must be inferred that entries 1, 2, and 5 of Table 52 are results of kinetically controlled enyne metathesis as no ethylene cross product was noted.[194] In the aliphatic alkenes used in Table 51, the kinetically formed *Z*-isomer may react with ethylene to produce a butadiene that is reactive with the aliphatic alkylidene to equilibrate to the more stable *E*-diene isomer (eq 147).

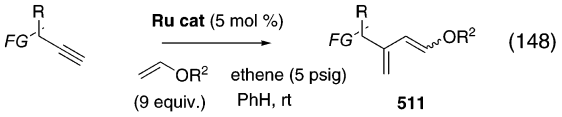


(147)

The contrasting data in Tables 51 and 52 reveal that *E*-selectivity achieved through equilibrium control is dependent on the nature of the alkylidene. If reactive enough, alkylidenes can cross react with 1,3-dienes thereby providing equilibrium control in the cross metathesis.

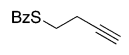
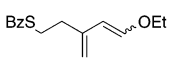
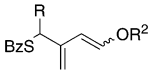
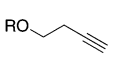
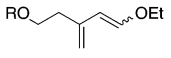
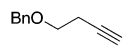
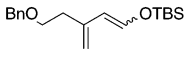
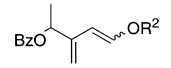
Coordinative groups can have a serious effect on intermolecular metatheses since the bimolecular reaction must outcompete chelated metal carbene complexes. In a representatively troublesome case, Giessert and co-workers found that alkynyl thiol esters failed to react with enol ethers.[116] Use of

ethylene as a "helping alkene" permitted the cross metathesis with these and other coordination-prone substrates (eq 148, Table 53). Furthermore, an excess



(148)

Table 53[116a]

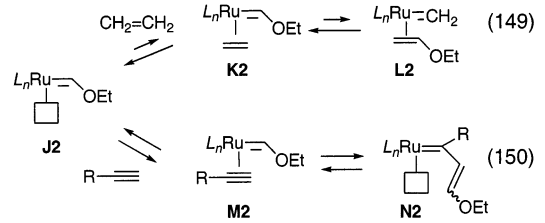
entry	alkyne	vinyl ether[a]	diene **511**, yield
1			 91 % (2.7:1.0 *E/Z*)
2	 R=H		 R=H, R²=Et, 99 % (1.9:1.0 *E/Z*)
3	R=H		R=H, R²=Ac, 92 % (1.0:1.0 *E/Z*)
4	R=Me		R=Me, R²=Et, 73 % (3.8:1.0 *E/Z*)
5	R=Me		R=Me, R²=Ac, 86 % (1.0:1.3 *E/Z*)
6	R=Me		R=Me, R²=TBS, (93 %) (1.0:1.5 *E/Z*)
7	 R=TBS		 R=TBS, 83 % (2.8:1.0 *E/Z*)
8	R=Bn		R=Bn, 84 % (2.6:1.0 *E/Z*)
9	R=MOM		R=MOM, 91 % (2.5:1.0 *E/Z*)
10			 72 % (1.0:1.5 *E/Z*)
11			 R=Bz, 89 % (1.0:1.0 *E/Z*)
12			R=TBS, 91 % (1.6:1.0 *E/Z*)
13			R=*t*-Bu, 89 % (1.3:1.0 *E/Z*)

[a] Standard conditions: catalyst **3** (5 mol %), vinyl ether (9 equiv), ethylene (5 psig), CH_2Cl_2, rt, 12−24 h.

of ethylene facilitates the reactions at lower temperatures which is important for sensitive substrates. Using ethylene at room temperature proved critical to use of silyl enol ethers in the cross metathesis (entries 6, 10, and 12). In many cases, the reactions were only synthetically useful if ethylene was used as an auxiliary alkene in the co-metathesis. As observed in related enyne cross metatheses,[78,117] the Hoveyda and **Ru gen-2** catalysts proved to be highly effective precatalysts. In addition, a preformed ruthenium Fischer carbene served as precatalyst.[78,195]

Ethylene may benefit the cross enyne metathesis between alkynes and alkyl and silyl enol ethers in three different ways. First, ethylene promotes catalyst lifetime. This is known from Mori's work[71] and shown in this instance to apply to the putative catalyst. The Fischer carbene was observed by proton NMR, and its stability was evaluated under ethylene. An orange solution of the Fischer carbene persists for weeks under ethylene but decomposes within 24 h in the absence of ethylene. Second, ethylene may help form higher concentrations of a reactive methylidene species, which may serve as the actual catalyst. Monitored by NMR in CD_2Cl_2, $Cl_2(H_2IMes)(Cy_3P)Ru{=}CHOEt$ did not produce $[Ru]{=}CH_2$ at elevated ethylene pressure. Although this does not rule out a methylidene-based mechanism, it does provide further evidence of the stability and persistence of the Fischer carbene (viz. $Ru{=}CH_2$). On the basis of these observations, the authors assert that conversion of **J2** to $Ru{=}CH_2$ would be thermodynamically uphill (eq 149, Scheme 81) and that the

Scheme 81[116]

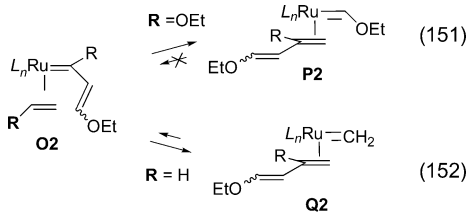


(149)

(150)

conversion of Ru=CHOR to vinyligous Fischer carbene **N2** would be more favorable, an argument predicated on carbene stability (eq 150). Ethylene is thought to assist in the slow step of catalysis (catalytic turnover) by increasing the rate of methylene transfer (Scheme 82). Importantly, higher enol ether

Scheme 82[116]



(151)

(152)

concentrations can accomplish this role (eq 151) and approximate the effect of added ethylene.

Ethylene can help cross metathesis where it is not formally involved as a reactant, influencing both selectivity and reactivity. The high *E*-selectivity observed in select cases provides a glimpse of reversible, equilibrium-controlled enyne cross metathesis. Ethylene provides a convenient means to achieve equilibration by opening a kinetically accessible reaction path from the formed *Z*-alkene. The increased reactivity provided by ethylene in the enol ether cross metathesis of coordination-prone alkyne substrates expands the intermolecular reaction scope by assisting the catalyst turnover step.

3.3. Tandem Metathesis and Domino Metathesis

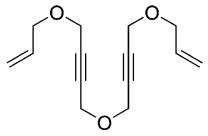
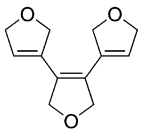
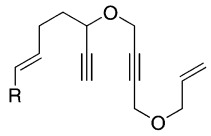
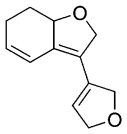
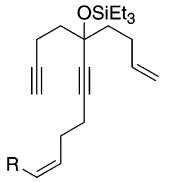
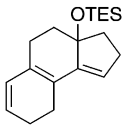
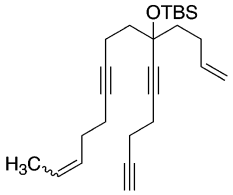
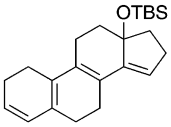
When an initial ring-closing enyne metathesis sets up a second ring-closing metathesis, the reaction can be regarded as a tandem or cascade metathesis (Scheme 34). This is an area of current activity. Such metathetical transformation is very powerful for the construction of bicyclic ring systems from acyclic

starting materials. For these metatheses, the initial alkylidenation occurs on the more kinetically reactive alkene, usually a terminal alkene.

The first example of a tandem enyne metathesis reported by Grubbs and co-workers[66,67] has been summarized in section 2.3. Several additional examples of tandem transformations have already been encountered (entry 8, Table 11; eq 77; eq 79; entries 8 and 9, Table 24; eq 114; Scheme 63; Scheme 66; eq 143; Table 50).

The tandem ring-closing metathesis has been extended to include three and four ring-closing metathesis steps.[127] These "relay metatheses" are limited only by the assembly of the (dienyl)polyalkynes. The linked trimeric dihydrofuran was produced in good yield using the first-generation Grubbs' catalyst (entry 1, Table 54). Connecting the acyclic dialkynes

Table 54[127 a]

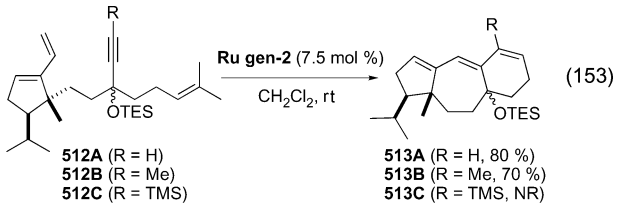
entry	precursor	product
1		 60 %
2	 (R = pentyl)	 79 %
3	 (R = pentyl)	 84 %
4		 70 %

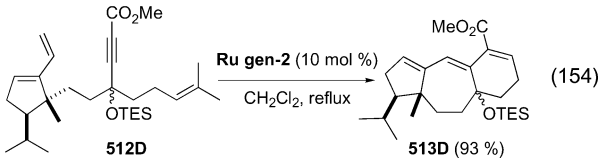
[a] **Ru gen-1** (4−8 mol %), PhH, 40−45 °C.

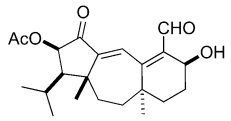
through propargyl substitution resulted in oxa[4.3.0] bicyclic ring formation (entry 2). The tandem transformation was initiated by alkylidenation at the terminal alkene in diendiyne of entry 2. Polycyclization to access tri- and tetracarbocyclic polyenes was demonstrated in the last two examples (Table 54). With two alkene sites for possible initiation, Grubbs and co-workers used the more reactive terminal alkenes to trigger the relay metatheses.[127]

Tandem ring-closing metathesis can be initiated at a conjugated diene. Boyer and Hanna[89] formed the core tricyclic ring system of guanacastepene A using this method (Scheme 83). The interposing alkyne

Scheme 83[89]





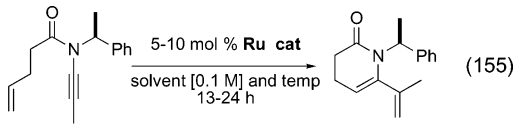


Guanacastepene A (**514**)

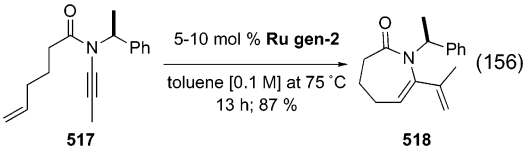
tolerates methyl substitution (**512A**,**B**), but the hindered trimethylsilyl substituent directly attached to the alkyne impedes the *diene-initiated* RCEYM (eq 153). Remarkably, the second ring-closing metathesis onto a trisubstituted alkene occurs even at room temperature. The presence of an electron-withdrawing group on the alkyne requires more forcing reaction conditions but succeeds in delivering the tandem product **513D** (eq 154, Scheme 83). This process must pass through a destabilized enoic carbene.[76,196]

Ynamides, obtained through base isomerization of propargyl amides, participate in ring-closing enyne metathesis.[88] Optimization of reaction conditions in the model RCEYM illustrated in eq 155 (Scheme 84)

Scheme 84[88]



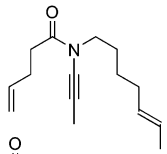
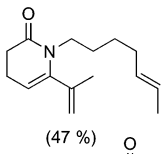
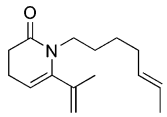
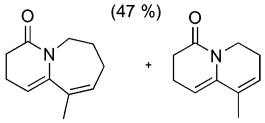
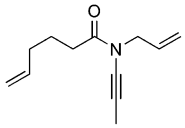
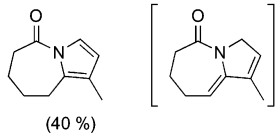
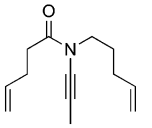
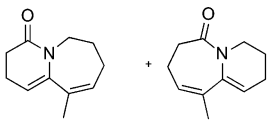
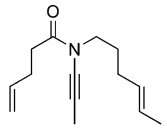
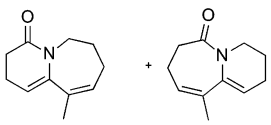
entry	cat	solvent	temp (°C)	yield (%)
1	**Ru gen-1**	CH_2Cl_2	50	<10
2	**Ru gen-1**	PhH	50-70	<10
3	**Ru gen-2**	PhH	50-70	40
4	**Ru gen-2**	PhH(syringe pump)	70	40
5	**Ru gen-2**	toluene	75-80	83



showed marked dependence on reaction temperature, with the best results obtained in toluene heated at 75 °C. The optimized conditions were used to produce the seven-membered ring in excellent yield (eq 156).

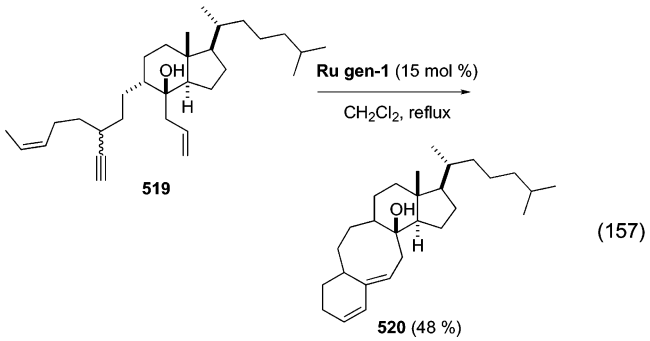
Tandem metathesis of ynamides interposed between two alkenes produced azabicyclics in good yields (Table 55). Ynamide of entry 1 underwent a single ring-closing metathesis to provide triene in 47% yield along with 20−30% of cyclization products (Table 55). Resubjection of triene obtained from entry

Table 55[88]

entry	ynamide	tandem RCM products
1		 (47 %)
2		 2:1 (80 %)
3		 (40 %)
4		 1:1 (77 %)
5		 6:1 (70 %)

1 to the reaction conditions gave the expected RCM product along with truncation product in 80% combined yield (entry 2). The truncation product suggests that olefin isomerization is competing with seven-membered ring closure onto the dienyldihydropyridone moiety. A pyrrole was produced after RCEYM and subsequent aromatization (entry 3), isolated in 40% yield. With two terminal alkenes, alkylidenation at each site leads to a mixture of [5.4.0]bicycles (entry 4). Selectivity was achieved by kinetic deceleration of one alkylidenation[67,127,197] giving selective formation of the [5.4.0]azabicyclic ring system (entry 5).

A transition-state analogue for the isomerization of previtamin D_3 to vitamin D_3 was produced by tandem dienyne metathesis. To construct the required tetracyclic diene **520**, Granja and co-workers[198] wanted to control the initially formed alkylidene in order to bias ring closure to form the desired eight-membered ring (eq 157, exo mode).[149] Should

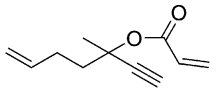
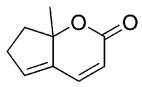
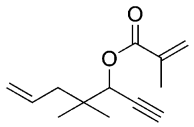
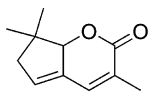
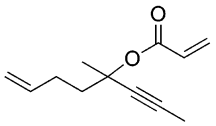
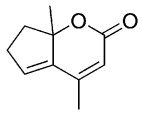
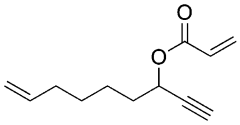
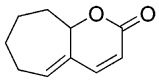
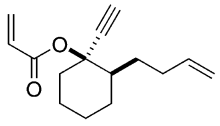
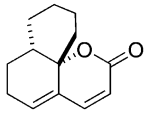
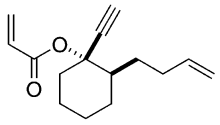
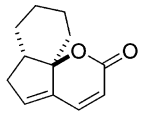


(157)

the cis-disubstituted alkene have triggered the initial ring-closing event, a [7.3.0]bicyclic ring would have formed. Tactically, alkylidenation at the alternate position was impeded by alkene substitution in the tradition of the Grubbs' tandem closures discussed previously. A respectable 48% yield of the desired tetracyclic diene **520** illustrates the feasibility of this reaction to produce an eight-membered ring.

The tandem ring-closing reaction of dienynes can include electron-deficient alkenes by use of the second-generation Grubbs' catalyst.[197] The reactions of Table 56 were conducted under high dilution and

Table 56[197 a]

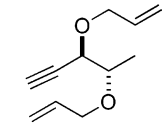
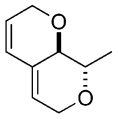
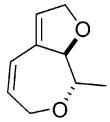
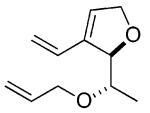
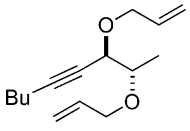
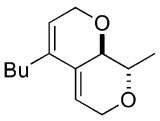
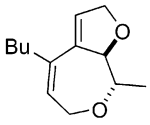
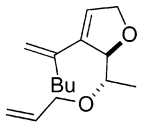
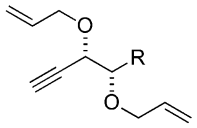
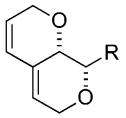
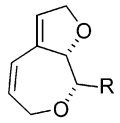
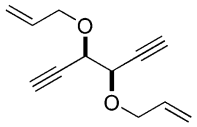
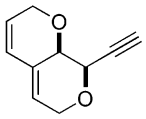
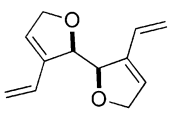
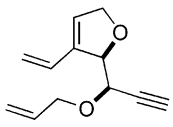
entry	substrate	product
1		 95 %
2		 86 %
3		 72 %
4		 68 %
5		 100 %
6		 74 %

[a] Conditions: **Ru gen-2** (5 mol %), CH_2Cl_2, 40 °C, 6−12 h.

are triggered by alkylidenation at the more reactive terminal alkene. On the basis of related work by Grubbs, the enoic carbenes are considered less stable and are reluctant to form.[196] Geminally substituted acrylate gives the tandem reaction (entry 2) as does an internal alkyne (entry 3). Seven-membered rings are formed (entry 4), and existing rings can lead to angularly fused tricyclics (entries 5 and 6). It is notable that the alkylidene **522** reacts preferentially with alkyne over the electron-deficient alkene of the acrylate evidenced by the fact that **525** is not formed (Scheme 85).

Liu and co-workers described a tandem enyne metathesis to make dioxabicyclic ring systems.[199] With the allyl ethers of Table 57, ethylene was needed. No conversion was observed in the absence of ethylene using **Ru gen-1** (entry 1), and the second-generation catalyst did not improve the conversion much (entry 3). The tandem reaction took place with both ruthenium carbene initiators when conducted under an ethylene atmosphere (entries 2 and 4), although the first-generation carbene gave the prod-

Table 57[199] [a]

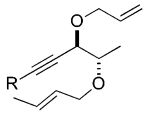
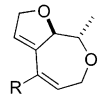
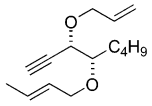
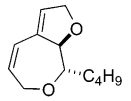
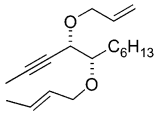
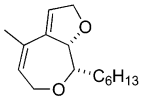
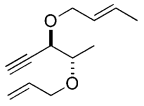
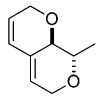
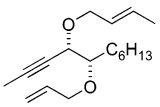
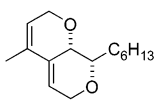
entry	dienyne	Ru catalyst	metathesis products		
					
1		**Ru gen-1**[b]	--	--	--
2		**Ru gen-1**	60	8	16
3		**Ru gen-2**[b]	25	8	3
4		**Ru gen-2**	63	19	--
					
5		**Ru gen-1**	62	--	23
6		**Ru gen-2**	64	21	--
					
7	R = H	**Ru gen-1**	R = H, 63 %	R = H, 15 %	
8	R = C_6H_{13}	**Ru gen-1**	R = C_6H_{13}, 65 %	R = C_6H_{13}, 13 %	
					
9		**Ru gen-1**	56 %	23 %	6 %

[a] Conditions: **Ru cat.** (2 mol %) in CH_2Cl_2 and 1 atm ethene at room temperature. [b] Reaction performed under N_2, no ethene used.

uct of single ring-closing metathesis as a significant byproduct. The ratio of isomers observed in entry 4 is attributed to greater thermodynamic stability of the dioxabicyclo[4.4.0]decane as compared to the more strained dihydrofuran ring contained in the minor isomer. The same profile of interrupted tandem metathesis was seen for **Ru gen-1** used under ethylene (entry 5), and dihydrofuran was observed as byproduct with **Ru gen-2** (entry 6). With the diallylated syn-diastereomer, the first-generation catalyst gave mixtures of bicyclics (entries 7−9). To overcome the selectivity problem, the reaction pathway to the thermodynamically less stable dihydrofuran was closed down by alkenyl substitution on one of the allyl ethers. Differentiated in this way, selective alkylidenation occurs at the more accessible alkene leading to predictable ring closure and high selectivity (Table 58).

Hanna and co-workers used the carbohydrate chiral pool to prepare highly oxygenated dienynes and transformed them into functionalized bicyclics by tandem ring-closing enyne metathesis.[200] In this study, both the first- and second-generation Grubbs' precatalysts were employed. Tertiary propargylic alcohol and triethylsilyl ether underwent tandem metathesis with **Ru gen-1** and **Ru gen-2**, but **Ru gen-2** gave higher yields (Table 59, entries 1−4). With a demanding second ring closure, the **Ru gen-1** carbene failed to deliver the [6.3.0]bicyclo instead

Table 58[199] [a]

entry	dienyne	tandem products
		
1	R = H	R = H, 77 %
2	R = C_4H_9	R = C_4H_9, 82 %
		
3		84 %
		
4		84 %
		
5		84 %
		
6		86 %

[a] Conditions: **Ru gen-2** (2 mol %) in CH_2Cl_2 under 1 atm ethene at room temperature.

Scheme 85[197]

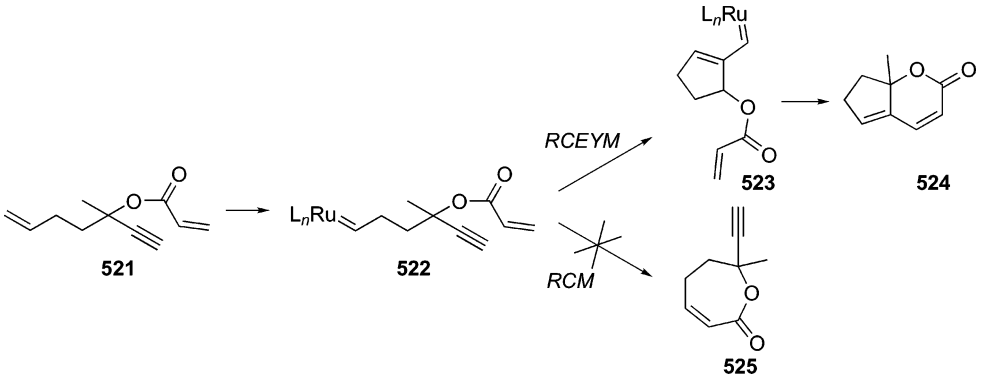
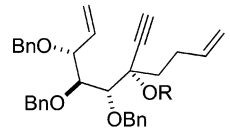
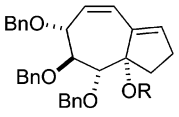
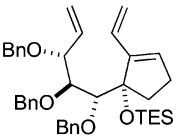
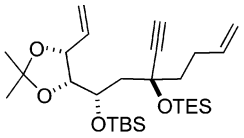
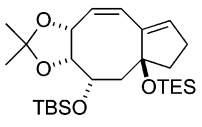
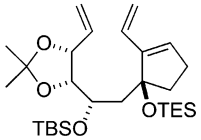
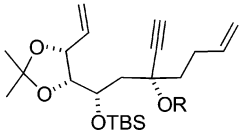
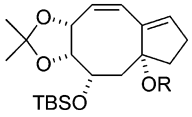
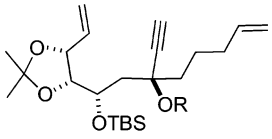
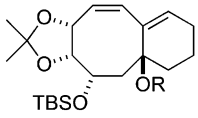
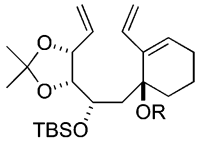
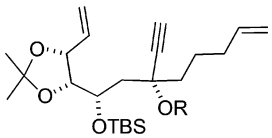
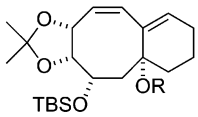
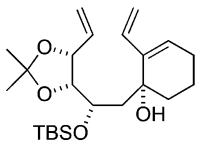


Table 59[200]

entry	dienyne	catalyst (%), time	product[a]	
				
1	R = H	**Ru gen-1** (10 mol %)[b]	R = H, 64 %	---
2	R = H	**Ru gen-2** (10 mol %)[b]	R = H, 95 %	---
3	R = TES	**Ru gen-1** (10 mol %)[b]	R = TES, 77 %	11 %
4	R = TES	**Ru gen-2** (10 mol %)[b]	R = TES, 96 %	---
				
5		**Ru gen-1** (20 mol %)[b, c]	---	85 %
6		**Ru gen-2** (10 mol %)[b]	94 %	---
				
7	R = H	**Ru gen-2** (10 mol %)[b]	R = H, 79 %	
8	R = TES	**Ru gen-2** (10 mol %)[b]	R = TES, 96 %	
				
9	R = H	**Ru gen-2** (10 mol %)[b]	---	R = H, 61 % + SM 21 %
10	R = TES	**Ru gen-2** (10 mol %)[b, c]	R = TES, 41 %[d]	R = TES, 46 %[d]
				
11	R = H	**Ru gen-2** (10 mol %)[b]	R = H, R' = TBS, 53 %	36 %
12	R = TES	**Ru gen-2** (10 mol %)[b]	R = TES, R' = TBS, 96 %	---

[a] Isolated yield. [b] In refluxing dichloromethane. [c] In refluxing benzene. [d] Yields of alcohol after TBAF deprotection.

stopping at the triene stage (last product, entry 5). This might be explained simply by decreased reactivity of the vinyl carbene in the first-generation environment ($Cl_2Ru(Cy_3P)_2$) or by competitive and irreversible methylene transfer (transalkylidenation). Nonetheless, **Ru gen-2** provided ring closure to get the eight-membered ring (entry 6). The formation of the eight-membered ring likely benefits from conformational constraint (reducing entropy loss on ring closure) imparted by the acetonide. The propargylic epimers of the dienynes of entries 5 and 6 underwent the tandem process (entries 7 and 8). Chain extension on the alkene trigger led to a difficult cyclization producing the single RCEYM product along with unreacted dienyne (entry 9). Protection of the propargyl alcohol as the triethylsilyl ether resulted in tandem cyclization, but the tandem process was still interrupted and led to monocyclization product as a

major byproduct (entry 10). In this case, the closure to the eight-membered ring is difficult as the cyclooctene ring in the [6.4.0]bicyclo is thought to be destabilized due to transannular ring strain arising from the β-triethylsilyl ether (first product in entry 10). In accord with this suggestion, the propargylic epimers of entries 11 and 12 gave improved tandem metathesis but required hydroxyl protection as the triethylsilyl ether to obtain near quantitative yield of the tandem product (entries 11 and 12) whose structure was corroborated by a crystal structure of the corresponding diol.

Blechert and co-workers reported a domino metathesis of (cycloalkenyl)alkynes to produce rearrangement products through ring-closing/ring-opening metathesis and cross metathesis, using ethylene or 1-alkenes.[144] In this study, the first-generation Grubbs' catalyst gave the equilibrium rearrangment of enynes, which was found to be irreversible. It was noted that the 1,3-butadienes obtained as products did not undergo further metathesis reactions. The malonate **27A** underwent clean rearrangement with ethylene under pressure at 50 °C (eq 158, Scheme 86, Table 60); however, the propargyl ether rearrangement proved dependent on the ring size of the cycloalkene, with the cyclohexene **527B** (m = 2) giving low yield (eq 159). That this might be due to factors besides geometry alone is suggested by tosylamides **527C**−**E**, which underwent the rearrangement in good yield. Blechert's group suggest that the methylidene addition to the alkyne occurs to provide **529** and that ring-closing occurs through ruthenacycle **530** to provide carbene **531** (eq 160). Reaction between diene **528A** and 3 equiv of 1-alkene gave cross metathesis at the terminal alkene to give **532** (eq 161). The reaction did not work for homopropargylic tosylamides. Internal alkyne **533** produced a mere 20% of the rearranged product along with 50% of cycloisomerized product **535** (eq 162). The formation of the cycloisomer is reminiscent of Trost's work and the related rearrangements promoted by Pt(II).[34] In fact, more recently, Echavarren and co-workers have found that $RuCl_3$ can promote the Alder-ene reaction in polar, aprotic solvents.[52] Product **535** probably arises through cyclometalation, β-hydride elimination, and reductive elimination. The last result also suggests that the cycloalkenyl−alkynes may coordinate both alkene and alkyne simultaneously.

Scheme 86[144]

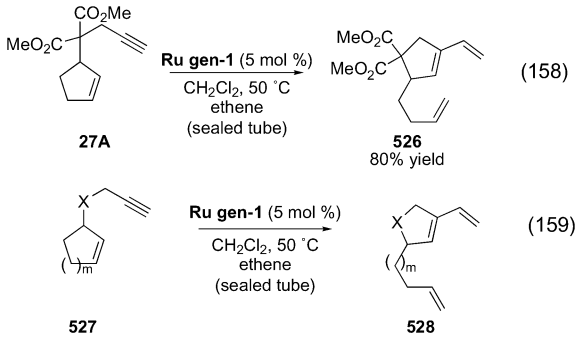
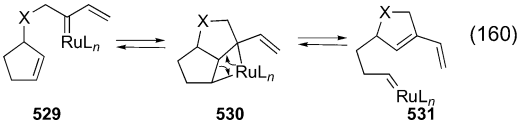
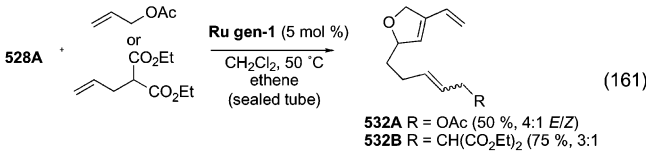
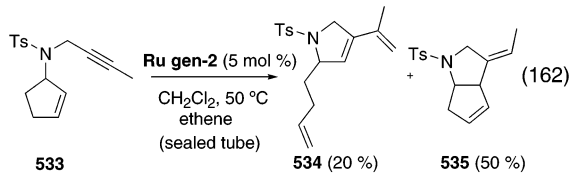


Table 60

entry	enyne	X	m	yield (%)
1	**527A**	O	1	67
2	**527B**	O	2	5
3	**527C**	NTs	1	75
4	**527D**	NTs	2	60
5	**527E**	NTs	6	47







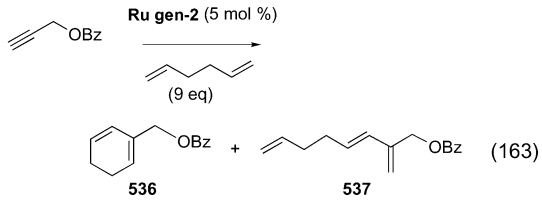
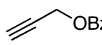
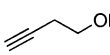
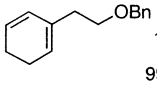
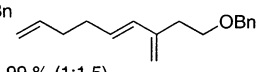
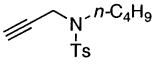
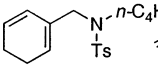
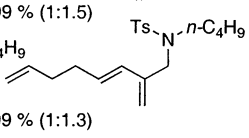
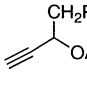
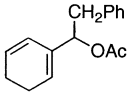
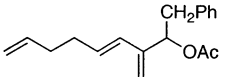
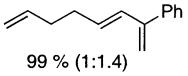
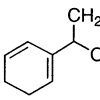
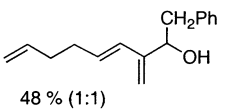
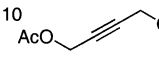
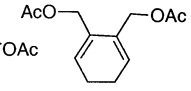
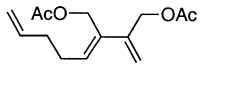


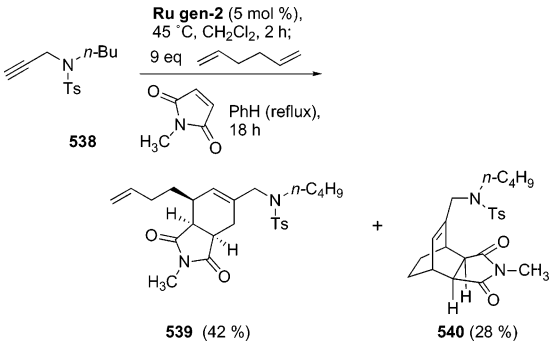
Table 61[201 a]

entry	substrate		product yield (ratio)
1		(CH_2Cl_2, reflux)	99 % (1:1.2)
2		(CH_2Cl_2, rt)	87 % (1:1.6)
3		(PhH, rt)	91 % (1.1:1)
4		($PhCF_3$, rt)	70 % (1:1.5)
5			 99 % (1:1.5)
6			 99 % (1:1.3)
7			 99 % (1:1.2)
8			 99 % (1:1.4)
9			 48 % (1:1)
10			 68 % (1:1.9)

[a] Reactions conducted in CH_2Cl_2 at 45 °C.

Smulik and Diver reported an intermolecular tandem metathesis between 1,5-hexadiene and alkynes to produce cyclohexadienes (eq 163).[201] This tandem reaction requires an intermolecular enyne metathesis and consecutive RCM to give the cyclized product. The reaction is potentially useful because it results in ring synthesis from simple dienes and alkyne. Using the second-generation catalyst, the reaction was possible with a range of functionality including free alcohols at the propargylic position (Table 61). Solvent polarity, temperature, and use of various catalysts did not improve the ratio of desired cyclohexadiene product. The approximately equal ratio of products is a reflection of nonstereoselective cross metathesis.

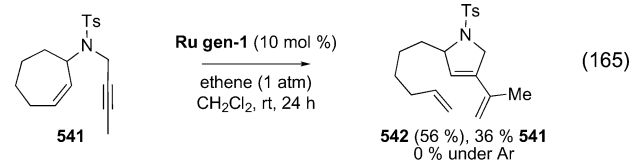
The crude products were taken through thermal cycloaddition after solvent exchange to provide bicyclic isomers **539** and **540** in good isolated yields (eq 164).



(164)

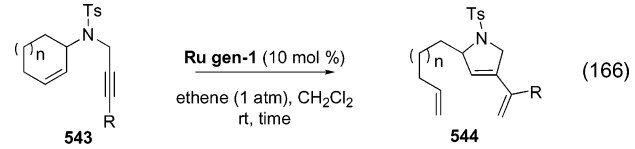
Mori et al. conducted a ring-opening/ring-closing enyne metathesis of *N*-propargyl allyl amides.[202] These reactions benefit from ethylene, which is used to suppress polymerization. When the ring-opening metathesis/ring-closing metathesis (ROM/RCM) was run under argon, no cascade product was obtained (eq 165, Scheme 87). Various ring sizes could be ring-

Scheme 87[202]



(165)

opened to generate the 3-vinyl $\Delta^{3,4}$ pyrrolidene ring system (eq 166). Presumably the valence bond reor-



(166)

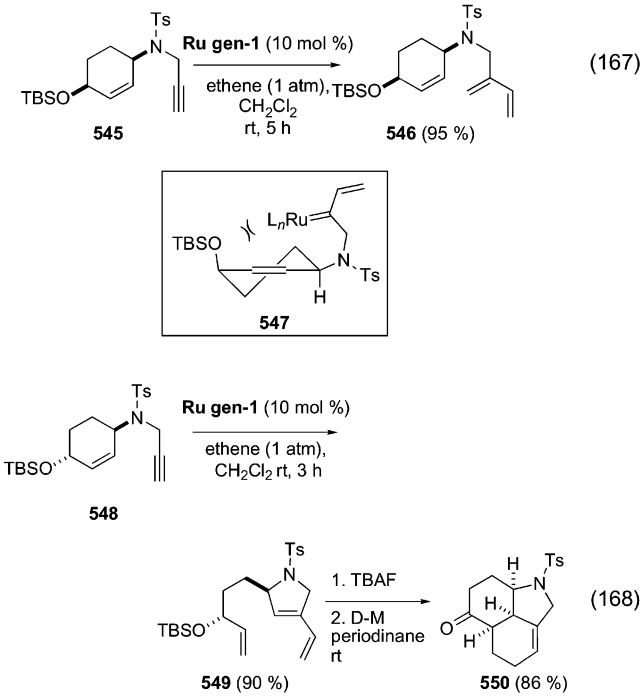
Table 62

entry	R	*n*	enyne	time (h)	yield (%)	sm (%)
1	Me	1	**543A**	24	15	75
2	Me	2	**543B**	24	56	36
3	Me	3	**543C**	24	22	73
4	H	1	**543D**	4	78	0
5	H	2	**87**	1	70	15
6	H	3	**69A**	1	75	20

ganization is driven by the enthalpic stability of the produced diene. In contrast to related ring-closing enyne metatheses, the internal alkyne with pendant cyclohexene gave poor conversion (entry 1, Table 62), but the terminal alkyne gave 78% yield (entry 4). The same result was observed dramatically in the cyclooctene case, entries 3 and 6. The authors suggest that this is due to steric congestion in the ring-closing metathesis of vinyl carbene onto the cycloalkene moiety.

Mori et al. also observed competitive ethylene−alkyne metathesis if the ring-closing EYM pathway was conformationally unfavorable (eq 167, Scheme 88).[202] Ring-closing EYM requires the vinyl carbene

Scheme 88[202]

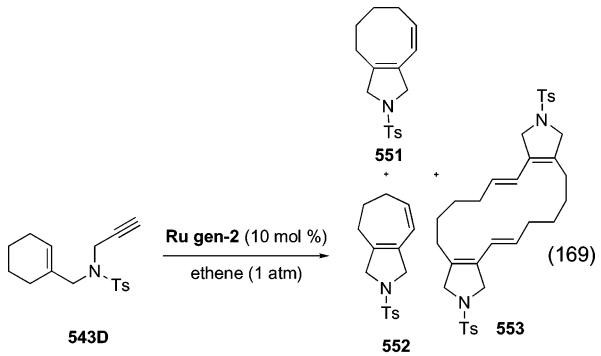


(167)

(168)

to approach the top of the cycloalkene from the pseudoequatorial position, where steric clash with the pseudoaxial TBS ether inhibits the ring-closing metathesis (see **547**), permitting the intermolecular

Scheme 89[203]

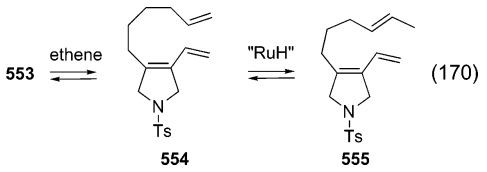


(169)

entry	conditions	yield (%) 551	552	553
1	toluene, 80 °C, 16 h	0	46	4
2	CH_2Cl_2, reflux, 24 h	14	26	57

metathesis with ethylene to compete. The epimeric TBS ether relieved this interaction such that the ROM/RCM cascade could outcompete ethylene metathesis (eq 168). Vinyl pyrrolide **549** was deprotected, oxidized and underwent intramolecular Diels–Alder reaction to give azotricycle **550** in 86% overall yield.

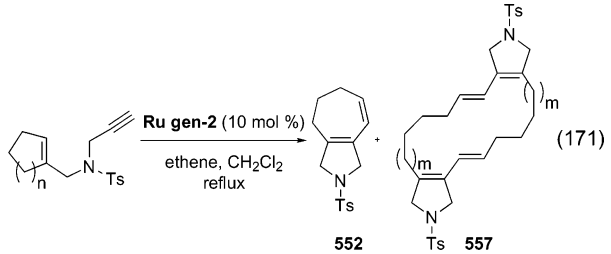
In the course of studying ROM/RCM of various alkynes bearing tethered cycloalkenes, Mori and coworkers identified dimerization and truncation pathways.[203] The intervention of these competing pathways depended on reaction conditions and the ring size of the cycloalkene. Ring-closing EYM of **543D** produced the cyclodiene **552**, which had lost a carbon atom (eq 169, Scheme 89). However, lower reaction temperatures produced the expected cyclooctadiene **551** in addition to the truncation product **552**. Resubjection of the dimer **553** to the reaction conditions produced the seven-membered ring (**552**) as the major product. The authors suggest that ethylene addition to dimer **553** produced **554**, which had undergone isomerization to an internal alkene and subsequently closed to produce the seven-membered ring diene (eq 170).



Alkene isomerization of terminal alkenes to internal alkenes is a known side reaction in alkene metathesis, ostensibly via ruthenium hydride.[204,205] The authors suggest that this process competes in the present cases because ring closure to the eight-membered ring is difficult.

For larger ring sizes in the cycloalkene, the dimer is formed and becomes the major product when a pendant cycloheptene is used (entry 3, Scheme 90).

Scheme 90[203]

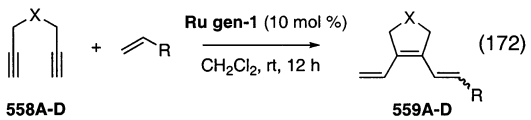


entry	enyne	n	m	552	557
1	**556**	1	0	quant	-
2	**543D**	2	1	26 %	57 %
3	**87**	3	2	-	80 %
4	**69A**	3*	2	36 %	8%

*toluene, 80 °C

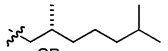
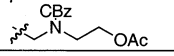
The same reaction conducted in refluxing toluene produced the cycloheptadiene **552** as the major product, albeit in low chemical yield (entry 4). The last case is remarkable since the ring-closing has occurred only after two alkene isomerizations. Presumably the formation of dimers in this study is due to the high-energy alkene isomerizations that must precede the favorable ring-closing EYM, producing the seven-membered ring.

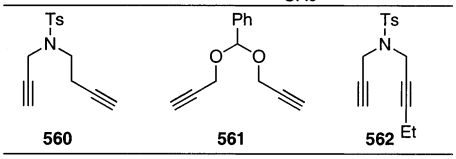
Blechert and co-workers described a tandem diyne–alkene cross metathesis to produce conjugated trienes.[206] The first-generation Grubbs' carbene promotes the reaction between a 3-fold excess of alkene and terminal diynes (eq 172, Table 63). As previously



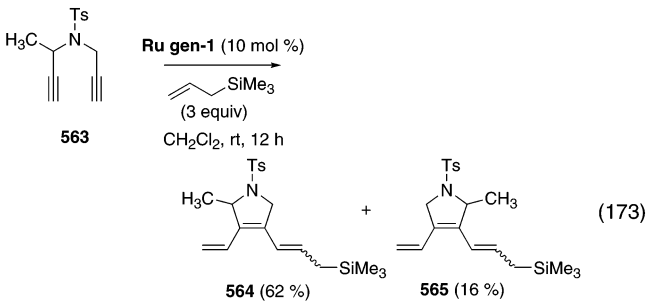
A (X = $C(CO_2Et)_2$); **B** (X = NTs); **C** (X = NAc); **D** (X=O)

Table 63[206]

entry	diyne **558**	R	yield **559** (%)
1	**A**	CH_2SiMe_3	65
2	**B**	CH_2SiMe_3	64
3	**C**	CH_2SiMe_3	73
4	**D**	CH_2SiMe_3	49
5	**B**	$(CH_2)_3OCPh_3$	61
6	**B**	CH_2OAc	48
7	**B**	CH_2OTBS	66
8	**B**	CH_2Ph	68
9	**B**		43
10	**B**		55

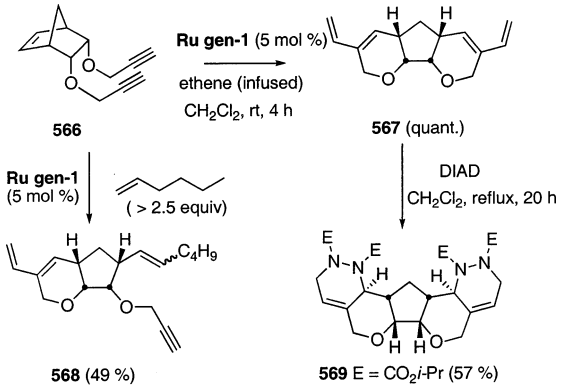


noted in ruthenium carbene-catalyzed cross enyne metathesis, little alkene homodimerization was observed.[72] Normally alkyne polymerization is slow with **Ru gen-1**, and a favorable cyclization could be realized through five-membered ring formation but not with nascent six- or seven-membered rings (diynes **560** and **561**, respectively). Alkyne substitution (e.g., **562**) retarded the reaction rate, and cycloisomerization–cross metathesis products were not observed. Propargylic heteroatoms such as nitrogen and oxygen were tolerated, but a sulfur atom (sulfide, sulfoxide, and sulfone) in this position failed to give cyclization and instead gave isomerization to the allene. An α-branched alkyne **563** showed modest regioselectivity (eq 173).

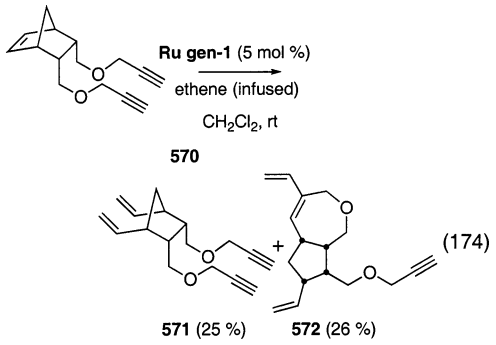


Banti and North described a "double-barrelled" ring-closing EYM of norbornenes bearing two alkynes.[207] Using ethylene infused into the solvent, intramolecular ring-closing EYM took place over competing ring-opening metathesis polymerization (ROMP) of norbornene (Scheme 91). Cycloaddition

Scheme 91[207]



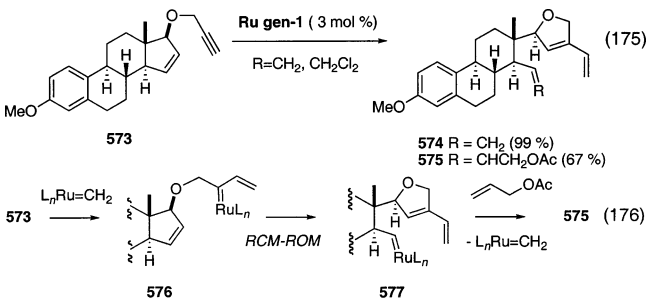
produced unusual polycyclic heterocycles **569**. A single ring-closing EYM could also be triggered by conducting the reaction with greater than 2.5 equiv of 1-hexene (**566** → **568**). The reaction appears to be triggered by ruthenium pentylidene ring-opening of the norbornene followed by ring-closing EYM. Methylene transfer from 1-hexene results in transalkylidenation and catalytic turnover. Installing an extra methylene spacer on the alkyne resulted in ethylene−norbornene ring-opening metathesis (eq 174).



The intermediate ruthenium alkylidene could then geometrically access the tethered alkyne to give a single ring-closing product, **572**.

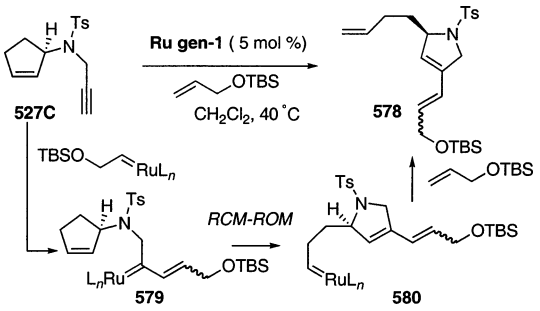
Blechert and co-workers found that the products obtained from cascade metathesis depended on propargylic substitution (Scheme 92).[87] The rearrange-

Scheme 92[87]

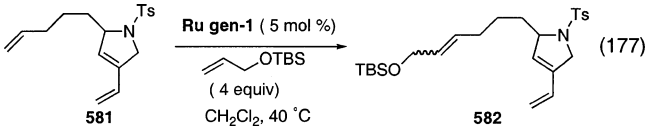


ment described in eq 175 follows a sequence of metatheses including ring-closing metathesis onto the cyclopentene, which ring-opens the preexisting ring. Conducted with ethylene present, metal carbene **577** reacts to liberate $Ru{=}CH_2$ and to provide triene **574**. With 1-alkenes, carbene turnover through cross metathesis generates the product **575** (eq 176). In this case the substituted part of the alkene ends up on the ring-opened cycloalkenes. Normally, the butadiene is formed by $Ru{=}CH_2$ addition to the alkyne (eq 176), and earlier studies (conducted under identical conditions) showed that the 1,3-butadiene products did not react further (e.g., did not give cross metathesis with 1-alkenes). Use of enyne **527C** led to an unexpected product **578** (Scheme 93) likely

Scheme 93[87]



arising from alkylidene addition to the alkyne (analogous to $Ru{=}CH_2$ addition). Resubjection of the ethylene product **581** to the reaction conditions produced modification of the terminal alkene (eq 177), not the diene portion of the molecule (which would have given **578**), verifying the kinetic and thermodynamic stability of the 1,3-diene under the reaction conditions. The authors conclude that changing the heteroatom from oxygen to nitrogen in the alkyne substrate (**573** vs **527C**), resulting in an electronic or chelating effect, explains the switch to an alkylidene-first reaction mechanism. Electronic effects in the alkene partner were not discussed.



Royer and co-workers described a tandem metathesis where a ring-closing enyne metathesis is followed by a consecutive cross metathesis with electron-deficient alkenes.[90] This reaction produced butadiene as an expected byproduct due to competitive methylene transfer on the intermediate vinyl carbene. Using the Grubbs' **Ru gen-2** or catalyst **2**, butadiene **585** was formed exclusively (eq 178, Table 64, entries 1−3, **Ru gen-2** catalyst shown). Under comparable conditions, the Hoveyda catalyst **4** gave better selectivity in favor of the cross product **584**, which had incorporated the acrylate (entries 4 and

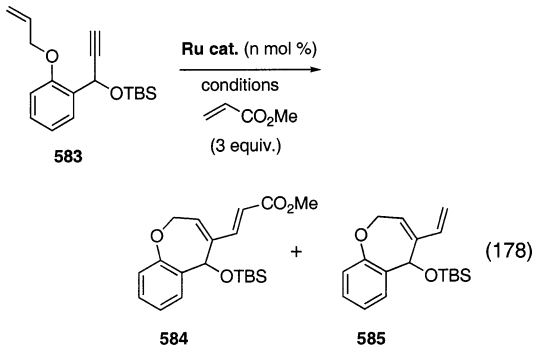


Table 64[90]

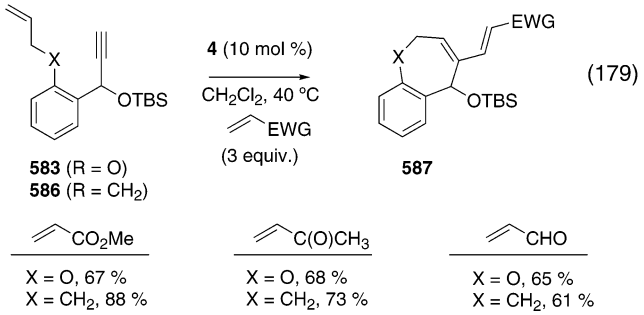
entry	catalyst (*n* mol %)	conditions	time	ratio **584:585**
1	**Ru gen-2** (5 mol %)	CH_2Cl_2, rt	5 d	0:100
2	**Ru gen-2** (5 mol %)	CH_2Cl_2, 40 °C	48 h	0:100
3	**Ru gen-2** (5 mol %)	toluene, 80 °C	48 h	0:100
4	**4** (5 mol %)	CH_2Cl_2, rt	5 d	80:20 (50%)
5	**4** (5 mol %)	CH_2Cl_2, 40 °C	48 h	80:20 (50%)
6	**4** (10 mol %)	CH_2Cl_2, 40 °C	12 h	100:0 (67%)

5). Higher catalyst loading was needed to further increase both selectivity and yield (entry 6). The contrast between the **Ru gen-2** (and **2**) as compared to the Hoveyda catalyst is remarkable. Heating for long periods in the presence of methyl acrylate may lead to greater catalyst deactivation in the **Ru gen-2** system due to the presence of tricyclohexylphosphine. Since the Hoveyda catalyst **4** lacks phosphine, ruthenium enoic carbenes are less likely to become deactivated through ligand coordination.[208] The boomerang effect may also help prevent decomposition for the Hoveyda catalyst, resulting in greater cross metathesis. Differences between precatalysts may be subtle and will tend to reveal themselves only in the most demanding applications.

Internal alkynes fail to produce the tandem product and instead give the ring-closing metathesis product. In this case, geminal substitution on the produced vinyl carbene carbon sterically impedes metallacyle formation in the reaction with methyl acrylate.

Other electron-deficient alkenes give the tandem transformation (Scheme 94). Methyl vinyl ketone and

Scheme 94[90]



acrolein work well and produce only the *E*-isomer. The direct incorporation of an aldehyde onto a stereochemically homogeneous diene is notable, and subsequent fragment coupling (e.g., with Wittig reagents) would be useful in synthesis. Acrylonitrile is an exception and fails to produce the expected product. Acrylonitrile does undergo cross alkene metathesis,[209,126] but in the present case the diminished reactivity of the vinyl carbene and coordination by the nitrile may explain this limitation. More electron-rich alkenes such as allyl trimethylsilane, $TBSOCH_2CH{=}CH_2$, and styrene only give butadiene **585**. These observations reveal regiochemical preferences for ruthenacycle formation from vinyl carbenes, which can be overwhelmed by electronics in the case of electron-deficient alkenes (eq 180, Figure 2). The

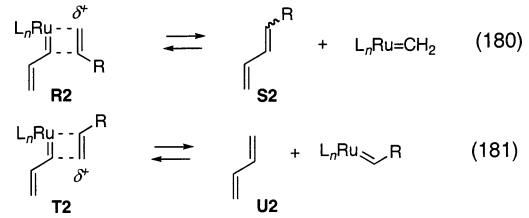
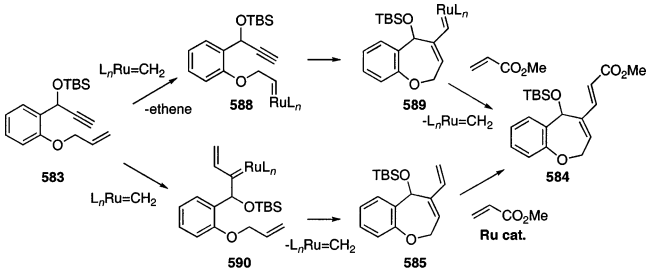


Figure 2.

fact that butadiene can be observed throughout the course of the reaction led to the proposal that alkylidenation of the allyl ether (top pathway, Scheme 95) is accompanied by competitive $Ru{=}CH_2$ addition

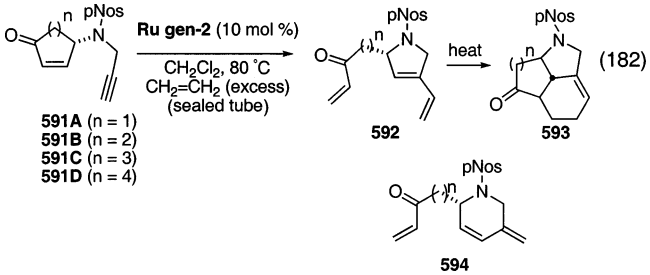
Scheme 95[90]



to the alkyne (bottom path, Scheme 95). Importantly, the authors demonstrate that butadiene **585** is a competent substrate for alkene metathesis: with the Hoveyda carbene **4** and excess methyl acrylate, **585** is converted into methyl dienoate **584**. This suggests that initially formed **585** can still produce **584** over extended reaction times, so long as the catalyst remains active.

Imhof and Blechert used a variation of their developed cyclorearrangement method to access trienes amenable to in situ intramolecular Diels–Alder reaction.[147] Conducted under ethylene, initial cycloaddition of $Ru{=}CH_2$ produces a mixture of regioisomeric vinyl carbenes leading to **592A**–**D** and **593A**–**D** (eq 182, Scheme 96). With the shortest and

Scheme 96[147]

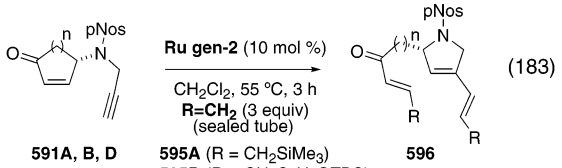


longest tethers, the cyclorearrangement products **592A** and **592D** gave only about 50% cycloaddition

Table 65

entry	alkyne **591**	**592**	**593**	**594**
1	**A**	30	30	10
2	**B**	0	55	0
3	**C**	0	45	20
4	**D**	20	20	20

under the thermal reaction conditions (Table 65, entries 1 and 4). Beginning with cyclohexenone **591B,** an optimal tether length produced cycloadduct **593B** in good yield (entry 2), although larger ring size gave more of the regioisomer **594** (entries 3 and 4). Greater regiocontrol of metal carbene addition to the alkyne was achieved by using 1-alkenes rather than ethylene (eq 183, Table 66). In contrast to the ethylene case



(183)

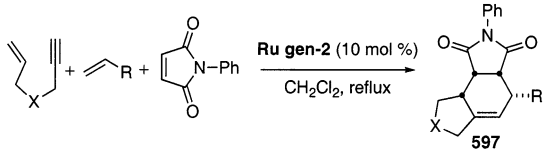
Table 66[147]

entry	alkyne **591**	alkene **595** (equiv)	yield (%)
1	**A** ($n = 1$)	**C** (R = Ph, 3 equiv)	87
2	**B** ($n = 2$)	**A** (R = CH_2SiMe_3, 1 equiv)	41[a]
3	**B** ($n = 2$)	**B** (R = $CH_2C_6H_4OTBS$, 1 equiv)	27
4	**B** ($n = 2$)	**C** (R = Ph, 1 equiv)	38
5	**D** ($n = 4$)	**A** (R = CH_2SiMe_3, 1 equiv)	42[b]
6	**B** ($n = 2$)	**A** (R = CH_2SiMe_3, 3 equiv)	70[a]
7	**B** ($n = 2$)	**B** (R = $CH_2C_6H_4OTBS$, 3 equiv)	83
8	**B** ($n = 2$)	**C** (R = Ph, 3 equiv)	93
9	**D** ($n = 4$)	**A** (R = CH_2SiMe_3, 3 equiv)	68[b]
10	**D** ($n = 4$)	**C** (R = Ph, 3 equiv)	80

[a] 2:1 *E*/*Z* at diene. [b] 3:1 *E*/*Z* at diene.

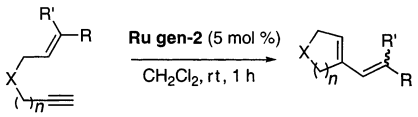
which involves Ru=CH_2, the 1-alkenes are thought to generate alkylidenes, which add to the propargyl amide regioselectively. In these instances, 2 mol equiv of the alkene are incorporated in the tandem ring rearrangement metathesis. With **595B** or **595C** as 1-alkene, only the *E,E*-isomers **596** were formed. The increased substitution of the enone in these cases retarded the in situ cycloaddition, although intramolecular Diels−Alder reaction at higher temperatures or use of catalysts is expected to be fruitful.

Requiring a versatile scaffold for combinatorial library synthesis, Lee and co-workers developed a three-component tandem metathesis/Diels−Alder reaction.[91] The initial ring-closing enyne metathesis produced a cyclic diene that underwent cross metathesis and a subsequent cycloaddition (eq 184).



(184)

Initially concerned about the success of a 1,3-diene alkene cross metathesis, the authors synthetically examined whether alkene substitution resident on the enyne substrate would permit access to functionalized dienes (eq 185, Table 67).



(185)

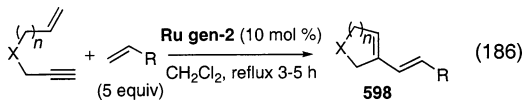
Table 67[91 a]

entry	X	*n*	R	R′	yield (%, *E*/*Z*)
1	NTs	1	CH_3	H	85 (3/1)
2	NTs	1	CH_2OH	H	72 (3/1)
3	NTs	1	CH_3	CH_3	98
4	NTs	2	CH_3	H	82 (6/1)
5	NTs	2	CH_2OH	H	86 (16/1)
6	NTs	2	CH_3	CH_3	92
7	CE_2	1	CH_3	H	83 (6/1)
8	CE_2	1	CH_2OH	H	88 (16/1)
9	CE_2	1	CH_3	CH_3	90
10	CE_2	2	CH_3	H	82 (16/1)
11	CE_2	2	CH_2OH	H	96 (12/1)
12	CE_2	2	CH_3	CH_3	93

[a] E = CO_2Et.

Allylic alcohols and trisubstituted alkenes underwent RCEYM to produce both five- and six-membered rings. The formed diene was predominately the *E*-isomer, although a tosylamide in the tether gave lower selectivity (entries 1, 2, and 4) relative to the carbocyclic examples (entries 7, 8, 10, and 11).

NMR studies revealed a dependence on catalyst loading and number of alkene equivalents. The cross metathesis of eq 186 conducted at reflux, with excess 1-alkene and high catalyst loading (10 mol % **Ru gen-2**) produced substituted dienes **598** in good yield and with high *E*-selectivity (Table 68). Ethylene was



(186)

Table 68[91]

entry	X[a]	*n*	R[b]	yield (%)[c]
1	NTs	1	Bu	86
2	NTs	1	$(CH_2)_2Ac$	88
3	NTs	1	Ph	86
4	NTs	1	Bn	84
5	NTs	1	$(CH_2)_2OBz$	73
6	NTs	1	$(CH_2)_2Br$	78
7	NTs	1	CH_2TMS	93
8	NTs	2	Bu	85
9	NTs	2	$(CH_2)_2Ac$	74
10	NTs	2	Ph	68
11	NTs	2	Bn	86
12	NTs	2	$(CH_2)_2OBz$	66
13	NTs	2	$(CH_2)_2Br$	74
14	NTs	2	CH_2TMS	81
15	CE_2	1	Bu	85
16	CE_2	1	$(CH_2)_2Ac$	63
17	CE_2	1	Ph	87
18	CE_2	1	Bn	86
19	CE_2	1	$(CH_2)_2OBz$	73
20	CE_2	1	$(CH_2)_2Br$	82
21	CE_2	1	CH_2TMS	65

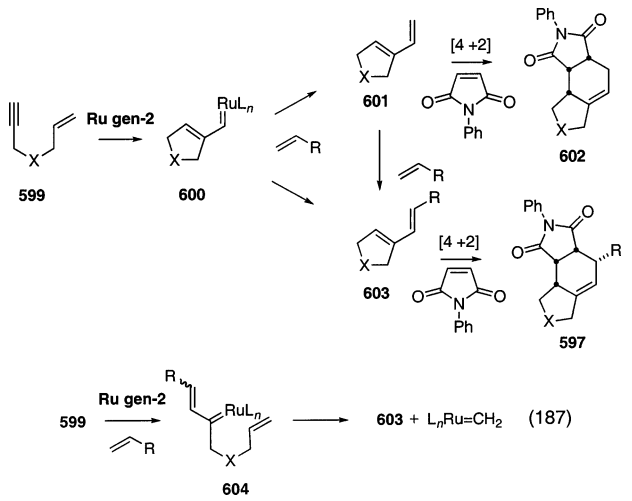
[a] E = CO_2Et. [b] Ac = CH_3CO. [c] *E*/*Z* ratio was determined to be >20:1 by ^1H NMR.

not needed to increase selectivity in this study.

The cycloaddition experiment with all three components mixed together showed that the cross

metathesis reaction involves terminally unsubstituted diene **601** as an intermediate (Scheme 97).

Scheme 97[91]



When conducted with dienophile present during the metathesis, trapping of intermediate **601** provides the major product of cycloaddition, tricycle **602**. This trapping reaction reveals the intermediacy of **601** in the cross metathesis in Table 68. The authors also considered that a competing alkylidene−alkyne cycloaddition pathway could produce **603** via vinyl carbene **604** (eq 187). For an effective three-component RCEYM-CM cycloaddition, the addition of dienophile had to await completion of cross metathesis. Delayed in this manner, the scaffolds **597** were produced in excellent yield over two steps by a one-pot operation (eq 188, Table 69).

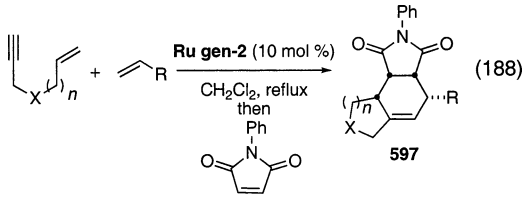


Table 69[91]

entry	X	*n*	R	yield (%)
1	NTs	1	Bu	83
2	NTs	1	Bn	75
3	NTs	1	$(CH_2)_2Br$	71
4	NTs	2	Bu	78
5	NTs	2	Bn	78
6	NTs	2	$(CH_2)_2Br$	71
7	CE_2	1	Bu	74
8	CE_2	1	Bn	74
9	CE_2	1	$(CH_2)_2Br$	77

Tandem or cascade metathesis has seen a lot of recent interest and offers a simple means of ring building from acyclic dienyne precursors. The first step is typically a ring-closing enyne metathesis to generate vinyl carbenes, which are sometimes reluctant to give the second ring closure, a problem overcome by using **Ru gen-2** or Hoveyda-type precatalysts. The ROM/RCM sequence can be triggered with ethylene and followed by a consecutive cross metathesis step. This consecutive cross metathesis is a fascinating recent development and can be used to incorporate electron-deficient alkenes, which has no precedent in nontandem, cross metathesis. The three-component coupling method also defines another complexity building venue for the enyne metathesis when it is tied in with cycloaddition chemistry.

4. Conclusion and Outlook

Enyne metathesis has evolved into a useful synthetic reaction. The two families of metal catalysts available show functional group compatibility with a range of functional groups encountered en route to simple heterocycles and natural products. From a historical perspective, the reaction was discovered in the course of alkene metathesis but developed along parallel lines from both metal carbene chemistry and from metal-templated cycloisomerization. These lines of research have intersected as synthetic chemists have adopted the reactions for ring building, complexity generation, and synthetic access to dienes. The early applications had focused on ring synthesis through ring-closing applications, and in these applications the functional group tolerance of the Grubbs' ruthenium carbenes were fully appreciated, leading to continued synthetic activity. The unusual role of ethylene in both intramolecular and intermolecular metatheses has proven beneficial to catalyst lifetime and has also led to *E*-selectivity by introducing thermodynamic control to certain enyne metatheses. The synthetic potential increased when the intermolecular (cross) reaction was demonstrated. Intermolecular enyne metathesis is inherently cross selective and provides useful products that can be used as building blocks in synthesis by the use of consecutive, venerable reactions such as the Diels−Alder cycloaddition. Many applications have used the dienes in this way but further development of heterofunctionalization strategies is foreseeable. Continuing catalyst development is likely to lead to greater scope of the ruthenium-catalyzed reaction by addressing shortcomings in the intermolecular reaction (e.g., electron-deficient alkynes). Due to limitations in our understanding of the relationship of enyne metathesis to alkene metathesis and the lack of detailed kinetic investigations, the mechanism of enyne metathesis is known principally by analogy to alkene metathesis. Future work directed toward the elucidation of the reaction mechanism will help chemists design new reactions and realize currently unreachable transformations.

5. Acknowledgments

The authors thank the Diver research group (Jason Smulik, Felix Rivas, Amol Kulkarni, Brian Peppers, Bryan Schertzer, Lee Snyder, Nick Brazis, Burk Wilke, Xuelei Yan, Keisha Ellis, and Dr. Mark Middleton) and Professor Jerry Keister at SUNY Buffalo for stimulating discussions of our research projects and discussions of the metathesis literature. We also thank our reviewers for their insightful comments. We gratefully acknowledge the National

Cancer Institute, the National Science Foundation, and the Petroleum Research Fund administered by the American Chemical Society for support of our metathesis-related research programs.

6. References

(1) The authors recognize the important contributions of Schrock to the alkene metathesis field. The Schrock group's contributions are not discussed here since the Schrock catalyst is not used to catalyze enyne metathesis.
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