5.27 Ene–Yne Metathesis

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Glossary

Alkylidene-first mechanism In an ene–yne metathesis, a mechanistic sequence where the alkene reacts first to form a reactive metal carbene. This is sometimes called the ‘ene-then-yne’ mechanism.

Diversity-oriented synthesis Synthesis activity that aims to create various cyclic or polycyclic templates to project functional groups in three-dimensional space. This approach offers a complement to the structural diversity represented in Nature and aims to access additional three-dimensional arrays of organic functional groups.

Double-directional synthesis A bifunctional or symmetrically functionalized substrate is extended by bond formation in two directions at once or sequentially.

Endo-selectivity (in ene–yne metathesis reactions) In a ring-closing enyne metathesis, the alkene carbon becomes bonded to the more distant alkyne sp-hybridized carbon. This process may be triggered by the addition of ethylene to the alkyne, or by ring closing of an alkene-derived alkylidene to produce an endocyclic metal carbene intermediate. This is common in macrocyclizations.

Metallotropic shift An alkynyl-substituted metal carbene undergoes propargylic transposition to form a new alkynyl-substituted metal carbene. This has been used to migrate metal carbenes so that they can participate in cascade metathesis sequences.

Methylene-free ring synthesis The use of an unsaturated four-carbon chain to build a cyclohexadiene ring from an alkyne without any methylene (CH₂) sources. Lack of methylene sources favors the metathesis cascade that produces a cyclized product.

Mori’s conditions The use of an ethylene atmosphere to increase yields of ring-closing enyne metathesis products.

RCEYM Ring-closing ene–yne metathesis.

Relay metathesis or relay ring-closing metathesis The use of a more reactive alkene to position a new metal carbene through a ring-closing metathesis. This can be used...
to make metal carbenes that would be otherwise difficult to form, or as a means to position a metal carbene at a desired site to initiate metathesis cascades. 

**Ring rearrangement metathesis** The intramolecular exchange of a cycloalkene with an alkyne to form a new cycloalkene or unsaturated heterocycle.

**Transalkylidenation** Conversion of a metal carbene to a new metal carbene by reaction with an alkene. This is a fundamental process in alkene metathesis. For example, the Grubbs benzyldiene $L_nCl_2Ru=CHPh$ is converted to $L_nCl_2Ru=CHR$ by reaction with $RCH=CH_2$. The process occurs via a ruthenacyclobutane intermediate.

### 5.27.1 Introduction

Ene–yne metathesis (EYM) is a synthetically useful method for the synthesis of 1,3-dienes. Conjugated dienes are valuable building blocks for organic synthesis. For example, conjugated 1,3-dienes are widely used in Diels–Alder reactions for the synthesis of six-membered rings. With catalytic EYM, the 1,3-diene is synthesized in a single reaction step from alkene and alkyne reactants. Notably, the alkene and alkyne reactants do not require preactivation: Their $\pi$-bonds provide the origin for their reactivity. The ruthenium carbenes are uniquely matched to react with $\pi$-bonds, which is the origin of their remarkable chemoselectivity. This preference is also known as functional group tolerance. The EYM reaction is a catalytic transformation and usually employs the mild and readily available Grubbs carbene catalysts. The ruthenium carbenes known as the Grubbs catalysts promote EYM with excellent chemoselectivity (Scheme 1).

![Scheme 1 Enyne and EYM](image)

Carbon–carbon bond coupling between an alkene and an alkyne with $\pi$-bond reorganization is EYM. When the reaction occurs between two separate molecules in an intermolecular reaction, it is known as a 'cross' EYM (Scheme 1, panel a). In simple terms, the reaction can be described as a cleavage of the alkene $\pi$-bond and the attachment of the individual carbene components across the triple bond with a defined regiochemistry. Accordingly, a 1-alkene combines with a 1-alkyne to give a 1,3-disubstituted 1,3-diene. The alkene must be reactive with the metal carbene being used. If the reactants are joined by a tether, as in a 1,2-ene–yne, then the reaction is intramolecular and known as ring-closing 1,3-ene–yne metathesis (RCEYM). The RCEYM produces the 1,2-disubstitution pattern with ring formation (Scheme 1, panel b). This reaction is successful for the synthesis of a wide assortment of carbocycles and heterocycles. For the synthesis of small rings, the tether geometrically restricts the ene and yne fragments from joining in the 1,3-orientation; instead they join with 1,2-substitution on the 1,3-diene. In this chapter, intermolecular reactions will be denoted as EYM and intramolecular ring-closing metathesis (RCM) of 1,3-enynes will be called 'ene–yne' metathesis. Collective or generic references to metathesis of each molecularity will be called 'ene–yne metathesis'.

EYM is used in diverse synthetic applications. The intermolecular EYM between alkynes and alkynes produces acyclic dienes. The EYM is also used to create rings. The simple RCM of an enyne produces a diene that is contained in the newly formed ring. This version of EYM has seen applications to the widest variety of complex small molecules in organic synthesis. These applications have progressed to more complex cascading processes, where multiple rings are formed in a metathesis cascade. A number of excellent review articles have appeared. Mechanistic aspects of the EYM will be discussed before the synthetic examples.

### 5.27.1.1 Catalyst Overview

The development of EYM has paralleled improvements in well-defined ruthenium carbene catalysts. Katz and Sivavec showed the catalytic effectiveness of RCEYM in 1985. However, the use of early transition metal carbene complexes limited the reaction's effectiveness and scope of application. After a decade, Mori's group applied the metathesis to challenging nitrogen heterocycle synthesis. However, the real breakthrough came from alkene metathesis when the Grubbs group reported a well-defined, group VIII ruthenium carbene complex. This led to a number of applications by Grubbs and Fu, which captured the attention of the synthetic community (ruthenium, molybdenum). Having already investigated catalytic enyne metathesis, the Mori's group revisited the problem using the ruthenium carbene complex and found an excellent reactivity in enyne metathesis.
coworkers followed this work with additional studies using ethylene, which have helped advance enyne metathesis in the synthetic community.13–15

Much of the recent work in metathesis has gravitated toward the use of the second-generation Grubbs carbene complex 2 (Scheme 2). During the past several years, synthetic chemists have embraced the Grubbs catalyst because of its availability, bench stability, improved reactivity, and chemoselectivity for alkenes and alkynes. The Grubbs catalysts are extremely easy to use. Chemoselectivity is also called functional group tolerance. The evolution of catalysts from gloveboxes to the benchtop has made metathesis a standard tool in the synthetic chemist’s arsenal. Due to ease of use and catalyst availability, the use of metathesis in a synthetic plan has become very easy. This has facilitated exploratory chemistry and adventurous synthetic pursuits. Moreover, it can partly explain the explosion in metathesis applications and the widespread use of the Grubbs catalyst. The widely accepted utility of this catalytic carbon–carbon bond formation led to recognition of the groundbreaking work and leadership from Grubbs,16 Schrock,17 and Chauvin,18 who were awarded the Nobel Prize in Chemistry in 2005.

Although the Grubbs catalysts 1 and 2 are primarily used in EYM, several new carbene complexes have seen increased use. New carbene catalysts are continually being developed for challenging applications in alkene metathesis, to give improved stereoselectivity and for asymmetric applications. The bisphosphine complex 1 is called the first-generation Grubbs complex.19,20 Carbene complex 2 is called the Grubbs second-generation complex. The ruthenium carbene complex 2 bears a single N-heterocyclic carbene (NHC) ligand, reported by the Grubbs group in a highly cited 1999 paper.21 The ruthenium complex containing the unsaturated NHC ligand, IMes, is the Nolan catalyst.22,23 The replacement of a tricyclohexylphosphine ligand with a coordinating ether in the arylidene ligand was developed by Hoveyda and coworkers. With the saturated NHC ligand, dihydroIMes, the chelated complex 3 is known as the Hoveyda–Blechert complex, as it was independently developed by the Hoveyda24,25 and Blechert research groups26 (the catalyst is also sometimes called the Hoveyda–Grubbs complex). The electron-poor complex 4 is the Grela complex,27 which has a more weakly coordinated ether and, like the Hoveyda–Blechert complex, is phosphine-free. The Grela complex also falls into the Hoveyda–Blechert family, and a new bidentate complex 7 has also been employed for enyne RCEYM. The indenylidene catalyst 6, sometimes called the Umicore catalyst, has also been used for EYM with performance comparable to that of the Grubbs complex 2.28–30 In catalysis, activity refers to a combination of catalyst attributes including favorable initiation rates and long propagation lifetime (catalyst longevity). Though the phosphine-free initiators are more active, they are not necessary for most applications. Typically, these phosphine-free catalysts are reserved for cases where catalyst longevity at higher temperatures is desired, or in cases involving less reactive alkenes such as enones or enolate esters. The pyridine adduct 5 is known as the Grubbs pyridine solvate.31 All of these complexes derive their lineage from the first well-defined ruthenium carbene discovered by the Grubbs group in 1993,3 the groundbreaking discovery that opened the door to this entire family of ruthenium carbene catalysts. As of this writing, the second-generation Grubbs carbene 2 and the Hoveyda–Blechert complex are the most widely used catalysts for EYM. New catalysts continue to be developed and this assessment is merely a static snapshot of an evolving and active research area in catalyst development (in the fields of both alkene and EYM).

Scheme 2 The Grubbs family of ruthenium carbenes used in metathesis.

5.27.1.2 General Considerations

The Grubbs-type complexes 1, 2, 3, 4, and 6 are commercially available and easy to use. The carbene complexes are not hygroscopic and can be weighed in the air under normal laboratory conditions. The shelf-life of the complexes is quite good and
they can be stored for extended periods in a darkened cabinet under nominal atmospheric conditions. Purification of commercial lots is generally not necessary and not recommended. Some carbene complexes can be purified by column chromatography with varying material losses; the second-generation carbene can be purified this way, but substantial loss of material occurs. The Hoveyda–Blechert chelated complexes are generally easy to purify by column chromatography on silica gel with good mass recovery.\textsuperscript{24} Usually purification is needed only if degradation is observed by \(^1\)H or \(^{31}\)P NMR spectroscopy. The Grubbs first-generation carbene 1 gives a diagnostic proton signal at \(\delta 20.02\) ppm (CD\(_2\)Cl\(_2\)) and a single \(^{31}\)P resonance at \(\delta 36.61\) ppm (CD\(_2\)Cl\(_2\)).\textsuperscript{31} The second-generation Grubbs carbene 2 gives a diagnostic proton signal at \(\delta 19.16\) ppm (CD\(_2\)Cl\(_2\)) and a single \(^{31}\)P resonance at \(\delta 31.41\) ppm (CD\(_2\)Cl\(_2\)).\textsuperscript{31} The Hoveyda–Blechert carbene 3 gives a diagnostic proton signal at \(\delta 16.56\) ppm (CDCl\(_3\)) and has no phosphorus nucleus.\textsuperscript{24}

Metathesis can be performed in a wide variety of solvents. The most common solvents are dichloromethane, benzene, and toluene. Alkene metathesis initiation studies have shown that catalyst 2 reacts effectively in CH\(_2\)Cl\(_2\), benzene, toluene, and tetrahydrofuran (THF).\textsuperscript{32} Due to the greater thermal stability of carbene complex 1, higher boiling solvents such as benzene and toluene are commonly employed. Solvents such as ether, THF, and 1,2-dimethoxyethane (DME) have seen little use in metathesis. Interestingly, though THF is not commonly used, it is a good solvent for Z-selective alkene cross-metathesis.\textsuperscript{33–35} Carbene complex 2 has poor solubility in methanol and water. In the best cases, metatheses can be performed in degassed, commercially available solvents.

Alkene concentrations vary depending on the molecule of the application. Typical RCM or RCEYM employ high dilution (1–20 mM) of diene or enyne. In the intermolecular or cross-EYM (CEYM), the alkene is used in molar excess (3–6 equivalents) and the concentrations as high as 1 M are not unprecedented. The mechanistic studies show that alkene concentration is important in the rate-determining step of one carbene complex, the commonly used second-generation complex 2. Cross-metathesis typically uses 0.02–0.1 M alkylene as the limiting reagent. An ethylene additive is sometimes used with catalyst 1 in promotion of RCM of 1,\(n\)-enynes. Ethylene is not commonly used in cross-metathesis applications due to the possible formation of ethylene–alkene cross-metathesis products. When used, ethylene delivery is not always specified. Typically, an ethylene atmosphere is achieved with an ethylene-filled balloon.

### 5.27.1.3 Quench and Removal of Ruthenium

At the end of a metathesis reaction, the ruthenium carbene activity must be quenched and the residual metal must be removed from the isolated organic product. In most cases, the ruthenium carbene catalyst is used at a loading between 2 and 10 mol%. In some of the earlier applications with catalyst 1, no quench method was necessary because the catalyst decomposed during the reaction. Similarly, sampling the recent literature shows that quenching methods are not always used. Since the newest Grubbs carbenes are particularly robust, quenching is highly recommended. Many metatheses catalyzed by 2 occur quickly, and due to the thermal stability of the carbene complex, active metal carbenes derived from 2 remain at the end of the organic reaction. Longer reactions or those conducted under heating will decompose the metal carbones to metathesis-inactive ruthenium-containing species. Thus, the purification procedure must successfully remove different forms of the metal, both carbenic and noncarbenic Ru(II) species. Because of the many ruthenium species present, a removal procedure must inactivate the metathesis-active intermediates and convert the remaining nonmetathesis reactive metal species into those that are readily removed.

Quenching carbones does not necessarily aid in the removal of ruthenium from the organic products. By far the most common way to stop a metathesis reaction is to add an enol ether such as ethyl vinyl ether after the limiting reactant has been consumed. This requires a brief period of heating to convert the remaining metathesis-active alkylidenes into stable Fischer carbones which are not cross-metathesis active.\textsuperscript{36,37} (equation 1). Although this procedure is effective for stopping EYM, it does not aid in the removal of all the ruthenium by-products. A decomposed form of ruthenium(II) that is no longer a metal carbene is incapable of reacting with the enol ether.

![Quenching Diagram](image)

Though there are many methods to remove ruthenium, there are two that are widely used and recommended. Often a crude metathesis reaction has a lingering yellow color associated with residual ruthenium. A mild oxidative procedure was reported by Georg et al.\textsuperscript{38} using either DMSO or \(O=\text{PPh}_3\) as an oxygen transfer agent. This is an attractive method due to its simplicity and mildness. Though the mechanism is not known, the oxidant is thought to convert the metal species into polar oxides that can be removed during column chromatography. The Georg procedure is an effective way to remove the yellow color associated with ruthenium residue in the crude sample. The main disadvantage of this procedure is that it is very slow: Oxidation requires 12–24 h to fully convert the ruthenium into polar species. Nonetheless, the mildness and simplicity have led to the wide use of this procedure.
A polar isocyanide procedure is dually effective in both quenching the carbene activity and removing the ruthenium (equation 2). The main advantage of the procedure is its very rapid reaction rate (1 min is typical), and the use of small amounts of isocyanide KO$_2$CCH$_2$NC (40–50 mol%) and that it results in a demonstrated ’quench’ of carbene activity for a wide variety of Grubbs carbenes. The ’quench’ destroys metathesis activity completely and arrests any further metathetic processes. The quench of carbene activity is accomplished by transferring the carbene into one of the aromatic rings of the NHC ligand (e.g., in complex 2): an intramolecular Buchner cyclopropanation, which is followed by a norcaradiene-to-cycloheptatriene rearrangement. Catalysts bearing NHC ligands are the most active and are currently the most commonly used catalysts in organic synthesis applications. However, it should be noted that the first-generation Grubbs complex also undergoes an effective quench and is itself transformed into a polar, removable Ru(II) complex, albeit by a distinct pathway. After the isocyanide-promoted Buchner insertion, a simple plug filtration (silica gel) or a column chromatography step removes the polar – and metathesis-inactive–ruthenium isocyanide complex.

![Reaction Scheme 2](image)

**5.27.2 Mechanism of EYM**

The EYM mechanism began as a source of controversy, but detailed mechanistic studies developed into a generally accepted mechanism. The confusion had been complicated by many factors: the use of different carbene catalysts (e.g., of different generations), differing reactivity of alkenes (e.g., 1-hexene vs. acrolein), ’borrowing’ intermediates from alkene metathesis, the difficulty in differentiating mechanisms experimentally, and the propensity of any new synthetic application to ascribe a mechanism without decisive mechanistic experiments. (These problems arise partly due to the cross-fertilization of the literature from mechanistic organometallic chemistry to synthetic organic chemistry and partly from the pace at which new reactions can be synthetically exploited and published as compared with mechanistic studies. Mechanistic studies are usually much slower to performed.) Mostly these concerns have been dispelled; however with certain combinations of alkene and alkyne reactants, the mechanism may vary. With certain catalysts, the rate-determining steps may be different. Before a detailed catalytic cycle is presented, the authors will briefly discuss fundamental carbene pathways and the relationship to alkene metathesis (for the catalytic cycle, see Scheme 4 vide infra).

EYM is a catalytic process involving ruthenium carbene intermediates. Of course, ruthenium carbenes are well known to be reactive intermediates in alkene metathesis. From alkene metathesis, the benzylidene initiates with an added 1-alkene. Fundamentally, the metal carbene catalyst undergoes cycloaddition with the alkene in two different ways. This process may occur with regiochemistry indicated in equations 3–5.

![Reaction Scheme 4](image)

The pathway in equation 3 is called transalkylidenation, a process that transforms one alkylidene ligand (or in this case a benzylidene) into another alkylidene ligand. An alkylidene is the organic fragment of a metal carbene. This is the initiation step in alkene metathesis; the equilibrium lies to the right when the alkene is in excess of the catalyst, and in many cases styrene is the more stable alkene. This fundamental process generates the needed alkylidene that is required for cross-metathesis. Alternatively, the alkene may react with the opposite regiochemistry in a process that leads to alkene cross-metathesis (equation 4). In this case, the intermediate ruthenacyclobutane has 1,2-disubstitution. Retrograde [2 + 2] extrudes a 1,2-disubstituted alkene and a
Ru=CH$_2$ species. Of these two pathways, the initiation step is faster than cross metathesis. Transalkylidenation of equation 3 is favored due to the lower energy 1,3-disposition of substituents on the metallacycle intermediate of equation 3. The cross-metathesis pathway is slower because the 1,2-disubstituted ruthenacyclobutane intermediate is higher in energy. These intermediates are relevant to the high-energy ruthenacycles encountered in EYM.

In terms of alkene metathesis, the methylidene plays an important catalytic role. Productive alkene cross-metathesis must follow the regiochemistry of equation 4 to give a 1,2-disubstituted alkene product. The methylidene is formed after a cross-metathesis, exemplified by the reaction of equation 4. The methylidene product of equation 4 is a reactive species that propagates catalysis. Subsequent transalkylidenation with excess 1-alkene ultimately releases ethylene (equation 5). Excess alkene and loss of ethylene help drive the equilibrium of equation 4 forward (to the right side). As it does, it regenerates the alkylidene, the reactive metal carbene intermediate that is needed for the next catalytic turnover.

The metallacycle reactive intermediates in EYM resemble those in alkene metathesis, but they are higher in energy. In fact, density functional theory (DFT) calculations suggest that ruthenacyclobutanes are actually transition states. To access metal-carbene intermediate that is needed for the next catalytic turnover.

Metal carbene exchange reactions. Metal carbene exchange reactions such as initiation and transalkylidenation are described in equations 3–5. Because the alkene is typically in molar excess, formation of the alkylidene tends to be dominated by equations 3 and 5, and this populates the alkylidene 'resting state.' This sets the stage for an alkylidene-first mechanism. (When the alkene is ethylene, the reaction proceeds through the Ru=CH$_2$ intermediate. The Grubbs benzylidene carbene complexes form the Ru=CH$_2$ intermediate when exposed to ethylene. The methylene species is highly reactive and not selective. In the second-generation Grubbs carbene, it becomes kinetically deactivated by coordination to tricyclohexylphosphine. Higher ethylene concentrations may help protect the reactive carbene from kinetic deactivation by phosphine coordination.)

Current mechanistic and kinetic evidence points to an alkylidene-first mechanism. Mechanistic studies were done because of inconsistencies in the literature, partly due to mechanistic assertions in the synthetic literature and the fact that different catalysts were being used. The mechanistic controversy surrounded the question as to which occurs first – reaction of the metal carbene with the alkene or alkyn. Though alkene reactivity varies considerably, it is generally believed that the Grubbs initiator reacts with the alkene first to produce an alkylidene. The alkylidene is the reactive intermediate that reacts with the alkyn. (Some of the confusion is due to a reasonable assumption that a terminal alkyn should bind better to the Grubbs benzylidene complex such that the alkyn should react first. The alkyn does bind better in preequilibrium, but reorganization via ruthenacyclobutene intermediates is a higher energy process than transalkylidenation via 1,3-disubstituted ruthenacyclobutanes. It is a Curtin–Hammett scenario where facile alkyn binding does not dictate alkyn insertion.)

Reaction with the alkyn is called the ‘alkylidene-first’ mechanism; it is rooted in the transalkylidenation of alkene metathesis. The metal alkylidene reacts with a 1-alkyn via the regiochemistry of equation 6. This mechanistic scenario is to be differentiated from the alkylidene-first mechanism where a ruthenium methylidene (methylene) is the reactive metal carbene intermediate, and reacts with the alkyn with the opposite regiochemistry. (In some cases, ene-yn cross-metathesis does begin by reaction with an alkyn in cases where the alkene may be particularly unreactive. For instance, alkyn can react exclusively with the initiator in an oligomerization reaction.)

Early mechanistic studies of RCEYM suggested an ‘alkylidene-first’ reaction mechanism based on NMR studies. In RCM depicted in equation 8, Hoye recognized that there were two possibilities: reaction of [Ru]=CH$_2$ with the alkyn directly or initial transalkylidenation to generate an alkylidene 9 (Scheme 3). These two possibilities invoke different metal carbynes as reactive species and suggest an order of reactivity. The reaction of Ru=CH$_2$ with the alkyn is called the methyldiene-first pathway. The initiation of the alkyn moiety with the Grubbs catalyst gives rise to an alkylidene; since the alkylidene forms first, it is called the alkylidene-first mechanism. The difference distills down to what metal carbene is reacting with the alkyn.

If the ene-then-yn pathway is followed, it was predicted that vinyl carbene intermediate 10 should accumulate. $^1$H NMR experiments showed the buildup of an alkylidene concomitant with initiation by the Grubbs benzylidene 1, as evidenced by the
loss of the benzylidene CH signal and the production of styrene. Styrene could only be formed if the Grubbs catalyst reacted with the alkene present in the bifunctional substrate. In the last critical step, the alkene reacts with the vinyl carbene to generate the product and more alkylidene, which continues in catalysis. Hoye and Vos refer to this as an ‘ene-then-yn’ pathway; this terminology is widely used in the literature for describing the mechanism of RCEYM. Similarly, using carbene 2 in an RCEYM, Kozmin et al. suggested that an ‘alkylidene-first’ mechanism was operative. These authors examined the reactivity of each unsaturated fragment of the enyne and found that the alkene reacted to give the corresponding alkylidene, whereas the alkyne did not react. These two studies suggested that alkylidenes formed faster than the reaction rate between [Ru]=CH2 and alkynes. These studies were performed with the first- and second-generation Grubbs carbene complex and arrived at the same conclusion in support of an alkylidene-first mechanism. This is presumed to be the basic mechanism, with perturbations depending on the relative reactivity of the unsaturated reactants.

An accepted mechanism has emerged based on mechanistic investigations and kinetic studies of the reaction mechanism (Scheme 4). Direct mechanistic evidence of the EYM is derived from kinetic analysis using the second-generation Grubbs catalyst 2. Zero-order dependence on the alkyne concentration indicates that the alkyne is not involved in the rate-determining step. First-order dependence was found for both the ruthenium complex and the terminal alkene. This kinetic evidence suggested that either step V or step VI was the rate-determining step (alkene binding or metallacycle formation/collapse). Based on DFT calculations, Lippstreu and Straub suggested that the cycloreversion step VI is rate limiting, which is consistent with experimental kinetic data. Supporting evidence for the alkylidene-first mechanism was presented above and is supported by another critical study of the regiochemistry of vinyl carbene reactions with styrenes. The mechanism shown in Scheme 4 is based on this kinetic study. The kinetic study was performed on a limited set of alkyne and alkene substrates, and a large excess of the alkene was employed for pseudo-order conditions. These conditions resemble those normally used for intermolecular EYM. Typically the alkene is used in molar excess, but not always.

A modest increase in propargylic substitution gave faster reaction rates. An increase in steric bulk resulted in faster reaction for propargylic benzoates. To test whether chelation by oxygen atoms located in the propargylic position was inhibiting the reaction rate, the corresponding hydrocarbons were examined, devoid of oxygen functionality. In comparison with their lower hydrocarbon analogs, it was found that secondary substitution at the propargylic center resulted in faster reaction rate than a primary carbon chain. Alkynes with the same propargyl substitution reacted with similar rates. In contrast, tertiary substitution at the propargylic site resulted in diminished reaction rates. With the second-generation Grubbs catalyst, there is not a chelation effect for ester functionality located at the propargylic position.

The resting state at the vinyl carbene intermediate explains the effect of propargyl substitution on reaction rate. The mechanistic picture brings into focus the partitioning of the 14-electron vinyl carbene intermediate II. Greater substitution at the propargylic position may increase the rate of catalysis by destabilizing unproductive resting state 12. Substitution of 12 at the site labeled R’ in Scheme 4 might destabilize the phosphine complex, increasing the concentration of the vinyl carbene II. With EYM promoted by phosphine-free catalysts like the Hoveyda–Blechert complex, there is no phosphine-bound resting state that may partly explain their high activity once initiated. However, phosphine-bound resting states can also protect the highly reactive intermediate II when alkene concentration is low (e.g., near the end of the reaction). Thus, a subtle balance is needed for a good
catalyst – high activity but protection from decomposition. Since decomposition pathways are only partly understood, the optimal structural features of a superior catalyst are not completely clear.

Which catalyst is used and under what reaction conditions can result in a change in the rate-determining step or divert the EYM to another pathway. For example, different kinetic orders for reactants and catalysts were found for the first-generation Grubbs complex. Although this does not change the sequence of events of the catalytic mechanism, it shows that the rate-determining step can change. This is governed by the ‘resting state’ of the catalyst and the intrinsic barriers of the fundamental processes. One of the most rapid areas of growth has been in catalyst development. In recent years, there has been an increased use of the Hoveyda–Blechert ‘phosphine-free’ catalyst, largely due to its thermally robust nature. The higher reactivity of the catalysts can lead to alkyne oligomerization either at low alkene concentrations or with alkenes that are not very reactive with the Grubbs complex. (This can be gauged from inspection of the Grubbs selectivity model for alkene metathesis. The less reactive alkenes are in the type III and type IV family. With these less reactive alkenes, one may expect greater competition from alkyne oligomerization reactions, similar to what one observes with the traditional Schrock catalyst.) In other words, the effectiveness of EYM is determined by a balance of reactivity between the alkene and the alkyne.

In RCEYM, the general reactivity appears to be ene-then-yne by an alkylidene-first mechanism. However, with less reactive alkenes, the timing may switch leading to an yne-then-ene pathway. One case that appears to react at the alkyne-first is shown in equation 9. In this case, the alkene is internal and substituted with an allylic heteroatom, which suggests that its reactivity will be diminished considerably compared with 1-hexene. In addition to the expected RCEYM product, a new product was obtained.

It is difficult to reliably (or quantitatively) predict alkene versus alkyne reactivity. Though the example in equation 9 is not too surprising given the alkene’s steric and electronic properties, a reactivity model is lacking to predict the outcome in more complex cases. In equation 9, which reacts first is not a major concern as long as the RCEYM provides the expected product. In Section 5.27.7, the site selectivity for initiation on a diene is controlled by relative alkene reactivity, which directly influences the ring sizes formed. More importantly, as reactivity is retarded on each unsaturated component, a complete loss of enyne metathesis reactivity will be observed, which neither higher temperatures nor higher catalyst loadings will remedy. Less reactive unsaturated
functionality will be encountered increasingly as chemists wish to push the reaction into more challenging cases or those with an increased number of electron-withdrawing groups. What is still missing in ene–yne or enyne metathesis is a predictive model of alkyne versus alkene reactivity. In the next few years, hopefully a model will emerge from the current body of literature and guide future applications.

The mechanism of EYM commonly follows an alkylidene-first pathway that defines the order of reactivity as ene-then-yne. For reactions catalyzed by 2, the rate-determining step involves alkene association such that higher alkene concentrations (or molar excesses) contribute to a productive EYM. Importantly, the alkene concentration and the intrinsic reactivity of the alkene are important determinants of ‘manifold selectivity’. Maintaining the catalytic EYM over competing reactions such as alkyne oligomerization. This helps explain the beneficial role of ethylene. The role of ethylene in promoting RCEYM under Mori’s conditions is a combination of mode selectivity, stabilization of reactive intermediates with respect to decomposition, and more favorable turnover of the vinyl carbene intermediate.

Continued discussion of the mechanism of RCEYM will follow in the next section describing the role of ethylene. The observations related to the ethylene effect are directly relevant to the mechanism of the intramolecular enyne metathesis.

5.27.2.1 Role of Ethylene in Ring-Closing Enyne Metathesis (Mori’s Conditions)

The helpful effect of ethylene on RCM of 1,0- enynes is known as ‘Mori’s conditions.‘14 Ethylene exerts a subtle effect because it does not seem to appear in the products. Ethylene is not necessary for ‘atom economy’ since the alkene of the enyne is able to contribute both the alkylidene and methylene moieties in the metathetical union with alkyne. For example, RCM of a simple enyne gave low yield under inert atmosphere, but under an atmosphere of ethylene (an ethylene balloon) a high yield was obtained (equation 10). The exact role played by ethylene is probably the combination of stabilization of reactive intermediates, acceleration of catalyst turnover, and interdiction of alkyne oligomerization pathways. Catalyst turnover can be accelerated at higher alkene concentration. The importance of alkene concentration had been noted in earlier studies by Hoye46 and Lee,53 and a mechanistic and kinetic explanation offered by Diver and Keister.48 Because enyne metathesis is dependent on alkene concentration and proceeds best with molar excess of alkene, it proves useful to provide an ‘auxiliary alkene’ such as ethylene, especially where higher enyne concentrations cannot be used for fear of enyne oligomerization/polymerization.

![Scheme 5](#)

The ethylene effect is primarily due to the need for higher concentrations of alkene to maintain catalysis. The sagely study by Hoye clearly showed that alkene concentration was critical for the success of an RCEYM. The authors found that increased enyne concentration (0.1 mol l$^{-1}$) gave an efficient RCM.46 This is counterintuitive since high dilution is employed in bifunctional substrates to encourage ring closure and to limit oligomerization. This is the first example showing that solution concentration of the enyne affects the ‘rate’ of RCEYM.

The role of ethylene in RCEYM has been addressed in mechanistic and kinetic studies. Due to the uncertainty regarding the role of ethylene, a detailed study was needed. First, an elegant mechanistic study was conducted by Lloyd-Jones.54 In this investigation, the authors showed that $^{13}$C-labeled ethylene produced vinyl carbene turnover, showing that ethylene turns over the vinyl carbene by what the authors termed a ‘second cycle’ via reaction with the auxiliary alkene, ethylene. In other words, ethylene assists the turnover of the intermediate vinyl carbene (see Scheme 3, where R = CH$_2$). This is consistent with the concentration effect observation by Hoye and Vos46 and the mechanistic proposal by Diver et al. in CEYM with ethylene speeding up the turnover step.55

Further insight into the ethylene effect has been provided by observations made using matrix-assisted laser desorption/ionization (MALDI) mass spectral analysis in terms of both the ene-then-yne and the yne-then-ene pathway. The RCEYM of the malonate shown in Scheme 5 was considered in terms of both the ene-then-yne and the yne-then-ene pathway. The RCM was investigated under nitrogen or ethylene. Under an ethylene atmosphere, a Ru = CH$_2$ resting state was detected by MALDI MS analysis. (The authors suggest that this is due to initiation with the alkene end of the enyne. The high molar concentration of ethylene populated the Ru = CH$_2$ species. Note that these mass spectral data were observed with the first-generation Grubbs catalyst 1.) Under nitrogen, a decomposition species was found which had incorporated two molecules of enyne substrate 14. At longer reaction times, a molecular ion was observed consistent with six enynes having reacted with the ruthenium carbene. The dimer and oligomer observed under nitrogen (in the absence of ethylene) are suggestive of alkyne oligomerization through a vinyl carbene intermediate.

This study sheds further light on the role of ethylene because it limits intermolecular pathways. It was recognized that vinyl carbene reactions may proceed with alkene through RCEYM (intramolecular) or with alkyne by an intermolecular process. The reaction with an alkyne can repeat itself giving rise to higher molecular weight species. This helps explain the low mass recoveries.
in simple RCEYM reactions without the use of ‘Mori’s conditions.’ In the absence of added ethylene, intermediate 15 prefers to react with additional alkyne subunits of enynes in intermolecular EYM. This pathway leads to higher molecular weight products that are intractable and explains the low mass balance observed in these reactions. (Fogg et al. also showed that the oligomerizations are not reversible using the first-generation Grubbs carbene. The observation of higher molecular weight oligomers obtained from alkyne oligomerization provides critical insight into the dichotomy of enyne metathesis versus alkyne oligomerization.) In the presence of ethylene, these pathways are shut down and ethylene assists in turning over vinyl carbenes. This is consistent with previous suggestions.

Increased propargylic substitution results in better mass balance and decreased need for ethylene. Under conditions without ethylene (Table 1), comparison of the first- and the second-generation Grubbs catalyst shows that each is susceptible to alkyne oligomerization (entries 1 and 2). Alkyne oligomerization has been observed in EYM using the Hoveyda–Blechert catalyst. Low conversions were seen after 24 h and remarkably very low yields of dienes were found, suggesting that little conversion to product had occurred. Monosubstitution on the alkyne propargylic position enhanced conversion, but did not appreciably increase the yield (entries 3 and 4). Only disubstitution gives significantly enhanced conversions and yields (entries 5–8). In the more hindered cases, the second-generation Grubbs complexes are needed due to their higher reactivity with sterically hindered substrates.

**Table 1**  Ring-closing ene–yne metathesis yields vs. propargylic substitution (without ethylene)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Alkyne conversion (%)</th>
<th>Diene yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2</td>
<td>&gt;99</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2</td>
<td>&gt;99</td>
<td>71</td>
</tr>
</tbody>
</table>

**Scheme 5** Evidence of alkyne dimerization/oligomerization pathways in RCEYM. **RuCl2(PCy3)2** detected by MS, **RuCl2(PCy3)2** detected by MS.
For RCM, the use of ethylene is not always beneficial as it can lead to intermolecular EYM. For example, if ring closure is slow, the competitive ethylene–alkyne cross-metathesis can be expected. Formation of eight-membered rings is particularly difficult. Ring closing under standard inert atmosphere conditions gave a low yield of the RCM product (equation 11); resorting to ethylene atmosphere gave none of the desired ring closure product, but produced solely the ethylene cross-metathesis product, a 2-substituted butadiene (equation 11).56

\[
\begin{align*}
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{N} \quad \text{Ts} \\
\text{Ts} \quad \text{N} \quad \text{Ts} \quad \text{N} \quad \text{Ts}
\end{align*}
\]

\[
1 \quad (10 \text{ mol%})
\]

Conditions
\[
\text{CH}_2\text{Cl}_2, \text{ r.t.,} \text{ time}
\]

\[
\text{No ethylene} \quad 35\%
\]

\[
\text{Ethylene (balloon)} \quad - \quad 84\%
\]

5.27.3 Cross-EYM

Cross-metathesis between alkene and alkyne generates acyclic 1,3-dienes. This carbon–carbon bond coupling can be described as a cross-coupling of alkyne and alkene with \(\pi\)-bond reorganization. These unsaturated reactants do not require preactivation for carbon–carbon bond coupling: They are generally reactive with the ruthenium carbene. The metathesis is thought to initiate from the alkene, so it is critical that the alkene is reactive with the Grubbs ruthenium carbene initiator. The cross-metathesis produces a 1,3-disubstitution pattern on the resulting diene. A limitation of the EYM cross-coupling is the production of \(E/Z\) mixtures in these acyclic reactions. High concentration or molar excess (2–6 equivalents based on alkyne) of the alkene is favored, but it is not absolutely required. When reactivity of each unsaturated reactant is high, it is possible to use equimolar amounts of the alkene and alkyne. Though terminal alkyynes are employed most of the time, internal alkyynes are sufficiently reactive for cross-metathesis. However, internal alkyne–alkene couplings are plagued with regiochemistry problems and best reserved for reactions with symmetrical alkene/alkyne substrates (see Section 5.27.3.2).

5.27.3.1 Cross-EYM with 1-Alkenes

Simple aliphatic 1-alkenes, used in molar excess, perform best in cross-enyne metathesis with either generation Grubbs complex. Blechert reported the first cross-enyne metathesis using the first-generation Grubbs carbene complex (equation 12).57 Several terminal alkyynes were examined and led to products with a 1,3-disubstitution pattern. A variety of different 1-alkenes were found to participate in the reaction, giving the conjugated 1,3-diene products as \(E/Z\) mixtures (Table 2).

Table 2 Cross-enyne metathesis57,58

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnOCH(_2)CH(_2)CH(_2)–</td>
<td>–CH(_2)SiMe(_3)</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>BnOCH(_2)CH(_2)CH(_2)–</td>
<td>–CH(_2)CH(_2)CH(CO(_2)Me)(_2)</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>BnOCH(_2)CH(_2)CH(_2)CH(_2)–</td>
<td>–CH(_2)OTBS</td>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexyl–</td>
<td>–CH(_2)SiMe(_3)</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>Me(_3)Si–</td>
<td>–CH(_2)SiMe(_3)</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>TrOCH(_2)CH(_2)–</td>
<td>–CH(_2)SiMe(_3)</td>
<td>2</td>
<td>98</td>
</tr>
</tbody>
</table>

Follow-up studies using the second-generation Grubbs complex showed substantial improvements in propargylic substituted alkyynes and trimethylsilyl (TMS) acetylene (entries 4–6).58 Entries 4 and 5 shown in Table 1 did not give products using the first-generation carbene complex 1. An \(E/Z\) mixture of stereoisomers in the vicinally disubstituted bond of the 1,3-diene is typical of the intermolecular (ene–yne) metathesis. In some cases, higher \(E\)-selectivity has been achieved by secondary metathesis59 or by the use of ethylene additive.60 The acyclic 1,3-diene products are useful building blocks in ring
construction. Not surprisingly, they give cycloaddition; an example of a high-pressure hetero Diels–Alder reaction is illustrated in equation 13.\(^{51}\)

\[
\begin{align*}
\text{AcO} & \quad \text{OBn} \\
\text{CO}_2\text{Et} & \quad \text{NTs} \quad \text{CH}_2\text{Cl}_2 \\
12 \text{ kbar, } 70 \degree \text{C} & \quad 36 \text{ h, NaOMe} \\
\end{align*}
\]

Fairly complex functional groups can be carried in the alkene or alkyne reactant so long as they are removed from the reacting sites (Scheme 6). For example, a porphyrin attached to the alkyne via a propargylic imide proved to be an effective way to conjugate the O-allyl galactoside (equation 14).\(^{62}\) Similarly, a 1,3-diene-linked disaccharide could be prepared from unsaturated reactants with acetal functionality in the allylic and propargylic positions (equations 14 and 15).\(^{63}\)

Scheme 6  Some complex substrates in CEYM.\(^{62,63}\)

CEYM can be performed with free hydroxyl functionality in the alkene reactant. Though allylic alcohols were found to be problematic in early metathesis studies, they have been found to react efficiently in CEYM (equation 16).\(^{64}\) Catalyst decomposition to ruthenium hydride species occurs when heating with primary alcohols, so the metathesis had to be accelerated by higher temperature and the use of excess alcohol reactant. These two experimental parameters are the easiest to change, and often the most successful. The CEYM was successful for an assortment of homologous unsaturated alcohols. With respect to the alkyne, oxygen-containing functional groups were tolerated at the propargylic and homopropargylic position (Table 3). Notably, a free hydroxyl group in the alkyne reactant is not permitted in this reaction. The reactions were quenched using the polar isocyanide\(^{39}\) that assisted in the purification of products.

Under optimized conditions, it is possible to conduct EYM cross-coupling with equimolar amounts of unsaturated reactants. As previously noted, CEYM has typically been done with an excess of the alkene reactant. Since the rate-determining step of CEYM showed alkene dependence, it was understandable that a CEYM should benefit from a molar excess of the alkene. To make CEYM truly 'atom economical,'\(^{65,66}\) a reactive alkylene would have to be paired with a reactive alkene in equimolar amounts. Diver and Clark found that equimolar amounts of very reactive alkene and alkyne substrates with 10 mol% of catalyst 2 or 3 gave a high-yielding diene synthesis (Table 4).\(^{50}\) Several alkenes were examined, including a series of protected and unprotected alkenols. Additionally, enantiopure syn-allylic alcohols were shown to perform well in the cross-metathesis with branched alkynes. The allylic chiral center was preserved in product 16 which in this case was found to be solely the \(E\)-isomer. Under atom economy,
slower cross-metatheses can lead to unwanted by-products arising from 1,5-hydride shift. Benzoquinone was added to suppress an undesirable 1,5-hydride shift in all CEYM cases involving unprotected alkenols. 1,5-Hydride shift was not found in cases where nonalcohol-containing functionalities were present in the alkene.

CEYM has been used successfully in the total synthesis of amphidinolide K.67 The macrocyclic ring of the natural product features a 1,3-diene with trisubstitution on one of the alkene moieties. Though this could be directly accessed by CEYM using an internal alkyne, a mixture of regioisomers was expected. Lee et al. devised a bold solution using a two-step sequence using a boronate to direct the regiochemistry of the EYM step. Starting with a terminal alkyne, the boronate is installed and directly subjected to cross-metathesis with excess alkene, giving a single regioisomer of the product (Scheme 7). It is worth noting that the alkene bears secondary allylic substitution and a chiral center; this is rare in CEYM. The boronate was converted to the trisubstituted alkene through Suzuki coupling using MeI. In addition to providing an elegant solution to carbon–carbon bond coupling in the total synthesis, this approach may prove generally useful to access higher substitution on the diene substructure. (The regiochemistry is guided by steric and electronic factors from the alkyne. Sterically, the ligands on the metal avoid the boronate. Electronically, it is unfavorable to place the carbene on the carbon bearing the electropositive boron atom.)

Strain can be used to promote reaction of geminally substituted alkenes with 1-alkynes.68 Normally, geminal (1,1-disubstituted) alkenes are nonreactive in EYM because they do not initiate with 2 and cannot participate in the alkylidene-first mechanism. According to the alkylidene-first mechanism of enyne metathesis,44,46–49,51,69 the alkene must be able to react with the Grubbs catalyst. Yet by the Grubbs model,70 1,1-disubstituted alkenes are unreactive with the second-generation Grubbs carbene. To overcome this lack of reactivity, ring strain in the alkene can be used to drive the initiation (this principle was used by Grubbs to form geminally substituted ruthenium carbenes)71 and give CEYM (Scheme 8). A variety of initiators were screened for this reaction, with the best reactivity registered by the phosphine-free Hoveyda–Blechert-type catalysts. Interestingly, these reactions could be conducted at low temperatures. Typical CEYM are run at ambient temperature (25 °C); more difficult ones are performed over extended periods in refluxing toluene. The strain relief that drives the cycloaddition with the metal carbene also drives cycloaddition, permitting low-temperature cycloaddition chemistry.

**Table 3** Allylic alcohols and homologs in cross ene–yne metathesis64

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OBz</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OBz</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OBz</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OTHP</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OTBS</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;N(Ts)Ph</td>
<td>1</td>
<td>453</td>
</tr>
</tbody>
</table>

**Table 4** Atom economy in ene–yne metathesis cross-coupling50

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>E/Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–CH(OBz)CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.8:1.0</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>CH(OAc)CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>1.5:1.0</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OTBS</td>
<td>3:1</td>
<td>68</td>
</tr>
</tbody>
</table>

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An important distinction between alkene and EYM is highlighted in the case of enol ethers. Though less reactive than aliphatic alkenes, enol ethers participate in EYM. Enol ethers such as ethyl vinyl ether are commonly used to quench alkene metatheses before isolation of product (equation 1). The resulting ruthenium Fischer carbenes are not sufficiently reactive to give further alkene metathesis. Yet EYM is different than alkene metathesis because it benefits from an enthalpic driving force in forming the conjugated diene products. A critical variable that can be optimized when employing reluctant alkenes is molar excess. The mechanistic study with 2 suggests why this is helpful. Accordingly, a large excess of enol ether gives EYM that is complete in a matter of minutes (equation 18; Table 5). Vinylogous ruthenium Fischer carbenes are likely to be intermediates in the reaction. Despite the stability of these intermediate Fischer carbenes, excess alkene helps accelerate catalysis in the turnover step (see Section 5.27.2). A variety of terminal alkynes participate in this transformation, though the reaction proved sensitive to substitution at the propargylic position.

### 5.27.3.2 Internal Alkynes

Since the earliest examples of enyne metathesis, internal alkynes were shown to have good reactivity. However, the major limitation in their use has been lack of control of regiochemistry. The orientation preference of the metal carbene (metal
alkylidene) is determined by differential alkyne substitution and stability of the resulting vinyl carbenes. With internal alkynes bearing two different alkyl groups, there is poor distinction between the two ends. Nonetheless, cross-metathesis has been successfully employed with internal alkynes using a symmetrical alkyne49 (equation 19), a symmetrical alkene 15 (equation 20), or both (not shown). If each of the two components is not symmetrically substituted, then a mixture of regioisomers results (equation 21).

A slight steric difference in internal alkyne substitution gives a regioselective EYM. Lee and coworkers developed a regioselective cross-enyne metathesis between TMS-substituted alkynes and a wide variety of 1-alkenes (Table 6).69

**Table 5** Enol ether–alkyne cross-metathesis producing electron-rich 1,3-dienes37

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1 OR2</th>
<th>ROCH=CH2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(OAc)CH2Ph</td>
<td>Et</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>CH2OTBDPS</td>
<td>Et</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>CH(OBz)CH3</td>
<td>n-Bu</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CH2N(Ts)(n-Bu)</td>
<td>n-Bu</td>
<td>92</td>
</tr>
</tbody>
</table>

**Equation 19**


**Equation 20**


**Equation 21**


**Table 6** Regioselective cross ene–yne metathesis of internal alkynes69

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1 OR2</th>
<th>R2</th>
<th>R3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOCH2</td>
<td>CH3OAc</td>
<td>Me3</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>AcOCH2</td>
<td>CH3OC6H5CH3</td>
<td>Me3</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>AcOCH2</td>
<td>CH3CH2CH2Br</td>
<td>Me3</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>MeOCH2</td>
<td>CH3CH2OAc</td>
<td>Ph3(MeO)</td>
<td>64</td>
</tr>
</tbody>
</table>

In addition, (RO)Ph2Si-substitution was effectively tolerated on the alkyne. The newly formed bond was produced with high Z-selectivity. The origin of the high regio- and stereoselectivity is probably due to an alkylidene-first mechanism, which leads to the preferential formation of one metallacycle intermediate.
5.27.3.3 Ethylene-Assisted CEYM

Ethylene has been used in the CEYM involving higher alkenes. There are two principal reasons justifying its use. First, ethylene may improve the $E$-selectivity. Second, ethylene may allow milder reaction conditions. However, using ethylene must be done with good judgment, for ethylene is itself a reactive alkene and can give ethylene–alkyne cross-metathesis. There are few cases where ethylene can be used with another alkene – in this combination the other alkene should dominate reactions with the Grubbs carbene. (Mori’s conditions refer to the use of ethylene in promoting an RCM of a 1,6-enzyme, not ethylene as a reactant in cross-metathesis.)

Ethylene as an additive enhances stereoselectivity in cross-metathesis of 1-alkynes with select alkenes. Simple aliphatic alkenes such as 1-hexene give $E$-diene with ethylene present in a closed system (equation 23; Table 7). Though a variety of alkenes successfully produce the $E$-diene, some alkenes do not give high selectivity. The relationship of alkene reactivity to $E$-selectivity is not completely understood. Though many possible roles of ethylene are imaginable, the most likely explanation for the most $E$-selective examples is the intermediacy of 2-substituted-1,3-butadienes. These would be the product of ethylene cross-metathesis. Grubbs has also described a highly $E$-stereoselective alkene–diene cross-metathesis using 2-substituted-1,3-butadienes. The 2-butadiene starting materials can be accessed by ethylene–alkyne cross-metathesis (equation 24).

Lee and coworkers synthesized the macrolide amphidinolide E using a CEYM to introduce the C 19–C26 triene segment of the highly unsaturated natural product isolated from the dinoflagellate Amphidinium sp.74 In the metathesis step, the authors first conducted an ethylene cross-metathesis to give an intermediate butadiene (3 h), the ethylene balloon was removed and a large excess of the skipped 1,4-diene was added and the vial sealed (Scheme 9). Because of the two different substitution patterns on each alkene, the less substituted alkene is more reactive and the geminal alkene does not give rise to any cross-metathesis products. Higher stereoselectivity was obtained by conducting the cross-metathesis as a diene–alkene cross-metathesis. Nonetheless, the butadiene is not completely reactive and 19% yield of the ethylene cross-metathesis product was obtained after 24 h. This synthesis stands as an important milestone in the use of stereoselective cross-metathesis in total synthesis.

To improve the effectiveness of enol ether–alkyne cross-metathesis, ethylene was used as a coadditive.55 Because the enol ether–alkyne cross-metathesis is demanding, these reactions are heated to speed up the ligand exchange processes and accelerate the vinyl carbene turnover step. However, heating results in destruction of the metal carbene and the concomitant formation of ruthenium hydride species. Instead of higher temperatures, other means of accelerating the slow catalytic step was desired. An auxiliary alkene, ethylene, was used to speed up the vinyl carbene turnover step, which was presumed to be the slow step of the catalytic cycle. This led to improved reaction scope and resulted in lower reaction temperatures (Table 8). Silyl enol ethers could be coaxed to react since the temperatures were lower. Previously, it had been found that heating silyl enol ethers with the Grubbs catalyst gave decomposition to a hydrocarbonyl ruthenium complex. Since lower temperatures can be used with ethylene assistance, this catalyst deactivation pathway can be averted. As a result, the ethylene/enol ether–alkyne ‘cometathesis’ could be used to generate Danishefsky-type dienes that are extremely useful in thermal and Lewis acid-promoted cycloaddition (another important cross-metathesis method to make electron-rich dienes uses alkynyl ethers).
The CEYM between alkynes and ethylene is an effective way to synthesize substituted 1,3-butadienes. Using an atmosphere of ethylene gas supplied through a balloon, Mori demonstrated an effective cross-metathesis with a variety of terminal and internal alkynes. The procedure produces 2-substituted-1,3-butadienes from terminal alkynes and 2,3-disubstituted-1,3-butadienes from internal alkynes. The cross-metathesis has seen many more examples of terminal alkyne reactions than those of internal alkynes, though each substituted alkyne is reactive. Though the intramolecular RCM with Grubbs’ carbenes demonstrates excellent functional group tolerance, intermolecular reactions are more demanding. Ethylene has the advantage that it can be employed in molar excess at ambient or moderately elevated pressures. Moreover, the excess ethylene reactant is easy to remove at the end of the reaction.

An example of ethylene–alkyne cross-metathesis is shown in equation 26. The ethylene is supplied through the use of a balloon. Good reactivity was found with both terminal and internal alkynes, though none of the substrates had additional propargylic substitution. Under these conditions using carbene \( \text{I} \), long reaction times are generally needed.

To tackle higher propargylic substitution and additional functionality on the alkyne, there are additional requirements (equation 27). Improvement in substrate scope was possible through either increased ethylene concentration or use of the second-generation Grubbs complex. Modest increase in ethylene pressure results in higher solution concentration of ethylene.
Due to the dependence of EYM on alkene concentration, this resulted in an improvement in reaction rate. Faster cross-metathesis helped the less reactive \( \alpha \)-branched terminal alkynes to react (Table 9). In these cases, no purification of ethylene was needed. It should be noted that 60 psig (pounds per square inch gauge) is approximately 4 bar \( (4 \times 10^5 \text{ Pa}) \), easily achievable using pressure glassware that is available in most synthesis labs (stainless steel autoclaves are not needed).

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>OAc</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>PhCH(_2)CH(_2)</td>
<td>OBz</td>
<td>1 or 2 (5 mol%)</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Np</td>
<td>OBz</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>OH</td>
<td>1</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>OTBS</td>
<td>1</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>OH</td>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>OTBS</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>PhCH(_2)</td>
<td>SBz</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>PhCH(_2)CH(_2)</td>
<td>SAc</td>
<td>2</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>CH(_3)</td>
<td>SBz</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>CH(_3)</td>
<td>SBz</td>
<td>2</td>
<td>87</td>
</tr>
</tbody>
</table>

For metathesis with the Grubbs carbenes, sulfur functionality in the unsaturated reactant has presented a difficulty. The affinity of sulfur for late transition metals is well known. During catalysis, the metal carbene can become ligated by sulfur and therefore discourage further reactions such as productive EYM. Use of thiol ester protecting groups proved successful in attenuating the basicity of the sulfur lone pair, resulting in a successful ethylene cross-metathesis (entries 8–11). Thiol acetates and thiol benzoates were prepared by Mitsunobu reaction of the corresponding alkynols. In entry 10, it can be seen that the first-generation carbene \( 1 \) as well as the second-generation complex \( 2 \) did not perform. For alkynes containing sulfur functionality, higher ethylene pressures proved helpful.

Kotha and coworkers developed a novel CEYM/Diels–Alder sequence to apply to the synthesis of substituted phenylalanines. In this example, ethylene CEYM using the Hoveyda–Blechert second-generation catalyst was followed by a Diels–Alder reaction (Scheme 10). The cycloadduct was oxidatively aromatized with \( \text{MnO}_2 \). This simple and effective method was used to make several other analogs of cystine mimetics in good yields.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

EYM is often used in conjunction with subsequent \( [4 + 2] \) cycloaddition. This tandem approach was used to access taxol hybrid structures. With several unsuccessful RCM approaches to the central eight-membered ring, Kaliappan and coworkers sought a tandem approach accentuating the utility of each individual reaction. In the metathesis event, an ethylene cross-metathesis was employed to access the substrate for a type II intramolecular Diels–Alder reaction (equation 28).
Ethylene–alkyne cross-metathesis has been used in natural product synthesis. Anolignan was prepared using an ethylene metathesis with the second-generation Grubbs complex performed at higher temperature (Scheme 11).\textsuperscript{87}

Fürstner demonstrated an impressive use of ethylene–alkyne metathesis on an unsaturated cycloalkyne to furnish the macrocyclic framework of amphidinolide V (Scheme 12).\textsuperscript{88,89}

While scouting routes to amphidinolide N, Nicolaou and coworkers carried out a successful ethylene metathesis on a complex synthetic intermediate (equation 29).\textsuperscript{90} For this same substrate, other EYM proved problematic.
In summary, both the first- and second-generation Grubbs catalysts can be used in ethylene–alkyne cross-metathesis. Ethylene as the simplest and lowest molecular weight alkene is easy to use in excess and easy to remove. For more difficult cases, such as those with α-branching in the propargylic position or those alkynes replete with oxygen-containing functionality (such as alkyl ethers), the reactions benefit from higher ethylene pressure. Given the wide availability of the second-generation Grubbs carbene, it is advisable to employ this catalyst in combination with slightly elevated ethylene pressures if the cross-metathesis is difficult. Though the terminally unsubstituted 1,3-dienes are somewhat rare, they can be found in Nature. To that end, the use of ethylene–alkyne cross-metathesis has been successfully used in total synthesis.

5.27.4 Ring-Closing Applications

5.27.4.1 Ring-Closing Enyne Metathesis with Ruthenium Carbene

RCEYM is a well-established method for the synthesis of rings. A variety of carbocyclic and heterocyclic rings can be formed using this protocol. The synthesis of small rings is relatively straightforward using metathesis methods. Larger rings can also be formed under typical macrocyclization conditions involving high dilution of the enyne reactant. The RCEYM is used to form carbocycles and heterocycles, and is successful even in the presence of a high density of functional groups such as those found in carbohydrates and natural products. RCEYM has been used in natural product synthesis. More applications utilize the RCEYM in tandem with other processes, such as cycloaddition or a second cross-metathesis reaction. These have become attractive due to their ability to rapidly assemble polycyclic structures. Reactions that involve metathesis cascades are discussed in greater detail in Section 5.27.7. During the development of RCEYM methods and applications to a range of small molecules, there are distinct phases where different generations of catalysts were used. Currently, the second-generation Grubbs carbene is widely employed for RCEYM, though in earlier examples and for the simplest cases, the first-generation Grubbs complex was successfully used. Modern use of this chemistry may employ either Grubbs catalyst, depending on the application. The most difficult ring closures to make small rings or those containing highly substituted alkenes require longer lived and thermally robust catalysts like the Hoveyda–Blechert catalyst. Lastly, RCEYM with the first-generation Grubbs carbene benefits from the presence of ethylene. Many early examples used ‘Mori conditions’ to improve the yield of the 1,3-diene product. The role of ethylene has been explained in Section 5.27.2.1.

Mori and Kinoshita illustrated a beautiful use of RCEYM as a key step in their synthesis of the *Stemona* alkaloid stemoamide (Scheme 13). This was a landmark contribution because it demonstrated that the new Grubbs carbene could be used to promote enyne metathesis in complex molecule synthesis. The Grubbs catalyst 18 was a tremendous advance over early transition metal Fischer carbene complexes, which lacked the activity, selectivity, and functional group tolerance of the well-defined ruthenium carbene complex.

RCEYM has been used successfully in many oxygen-rich environments. In particular, the second-generation Grubbs carbene feature a combination of increased reactivity and high chemoselectivity; significant attributes in oxygen-rich environments, where induction and chelation reduce reactivity. Accordingly, ring closure with the second-generation Grubbs complex gives the vinylcyclohexene product in good yield. Without ethylene, the vinyl carbene dimerizes, illustrating another dimension to the ethylene effect in RCEYM. Ethylene limits the formation of an undesired dimeric by-product by ‘turning over’ the vinyl carbene intermediate to product. This prevents an intermolecular reaction with the alkyne of another enyne reactant, which leads to the dimer (equation 31).
Formation of strained four-membered rings is possible by RCEYM. Reactivity gains have been achieved with the second-generation Grubbs carbenes simply due to the ability to heat difficult reactions for a longer period. However, at refluxing toluene temperatures, thermal decomposition of 2 becomes problematic. For difficult metatheses that require higher temperatures, the Hoveyda–Blechert complex 3 has distinguished itself. Recently, microwaves have been used to bring about metathesis. Use of the complex 3 under microwave heating promoted RCEYM to form strained cyclobutene rings (equation 32; Scheme 14).93

A similar approach was employed by Goess et al. to make grandisol (equation 33).94 The use of high catalyst loading and microwaves promoted the difficult ring-closing step. Notably, a quaternary carbon center resides at the propargylic position, which is unusual even for intramolecular enyne metathesis.

RCEYM can be used to access privileged heterocyclic ring systems such as the carbapenams and their structural analogs. The RCM conditions are mild such that the delicate β-lactam ring system remains intact during annulation (Scheme 15).95,97 Larger B rings were made with selenium present in the nascent ring using the second-generation Grubbs catalyst (equation 34).96 This reaction proved quite challenging due to the ring size and the presence of the selenium atom (see Section 5.27.3.4 for an example of sulfur in CEYM). Neither the first-generation Grubbs carbene nor lower reaction temperatures were sufficient to promote this
reaction (equation 35). Internal alkynes performed well in the RCM, but a terminal alkyne failed (equation 36; Table 10) possibly due to alkyne polymerization under the forcing reaction conditions.

**Table 10**  
**RCM on β-lactam-containing substrates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (days)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>1</td>
<td>59</td>
</tr>
</tbody>
</table>

Polyhydroxylated carbocyclic rings are found in biologically important molecules and natural products. Due to their importance, Madsen and Poulsen developed an RCEYM strategy to readily access carbocyclic rings from carbohydrates (equation 37).92 The authors attempted the RCEYM in the presence of an unprotected alcohol located at the homopropargylic position. At room temperature and in the presence of ethylene, they found no reaction (N.R.) with catalyst 1 or 2. Raising the temperature to 40 °C gave decomposition of the enyne. Blocking this position with a tert-butylimethylsilyl (TBS) protecting group gave RCEYM under ethylene to form the desired carbocycle in good yield (Table 11).

**Table 11**  
**RCEYM with homopropargylic oxygen functionality**92

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>2</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>2</td>
<td>66</td>
</tr>
</tbody>
</table>

Highly oxygenated enynes undergo RCEYM to form six-membered carbocycles. Similar to the examples above, polyhydroxylated enynes bearing homopropargylic and propargylic oxygen functionality were subjected to ring closing with the
second-generation Grubbs carbene. Interestingly, either benzyl or acetyl protecting groups were tolerated (equation 38, Table 12); these protecting groups are commonly used in sugar chemistry. In addition, each diastereomer was evaluated separately and found to give efficient RCM.

As a means of ring fusion toward bicyclic dienes, van Boom and coworkers performed RCEYM on protected 2-vinyl pyranose and 2-vinyl furanose. These readily available carbohydrates were transformed into pyranopyrans and pyranofurans in the presence of the first-generation Grubbs catalyst. Low conversion was observed with a terminal alkyne; however an internal alkyne gave good yield (equation 39; Table 13). A similar difference in yield was also found in the furanose case (equation 40; Table 14).

Highly functionalized spirofused oxacycles are accessible from carbohydrate-based enynes by RCEYM. van Boom et al. converted ketoglycosidic enynes into dienyl spiroacetals in the presence of the first-generation Grubbs carbene. The
first two reactions (equations 41 and 42) were successful, producing the desired spirocycles in good yields, whereas the third reaction (equation 43) proved unsuccessful as the starting enyne was found to be unreactive. Conversion to product did not improve in the last case under extended reaction times or increased catalyst loadings. The ability of the catalyst 1 to initiate at the alkene may be diminished due to the steric hindrance associated with the highly substituted anomeric center.

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{BnO} \\
\text{OBn} & \quad \text{OBn} \\
\text{OBn} & \quad \text{OBn} \\
\text{CH}_3 & \quad \text{OBn} \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{BnO} \\
\text{OBn} & \quad \text{OBn} \\
\text{OBn} & \quad \text{OBn} \\
\text{H}_3C & \quad \text{OBn} \\
\end{align*}
\]

RCEYM can be used to synthesize bicyclic structures in the presence of nitrogen heterocycles such as pyrimidines. Nielsen and coworkers recognized the potential of enyne metathesis in their synthesis of a bicyclic 2′-deoxynucleoside, a carbocyclic-locked nucleic acid analog (equation 44).\textsuperscript{102} The enyne was subjected to the second-generation Grubbs catalyst using microwave heating for 2 h, giving the bicyclic structure in 82% yield.

\[
\begin{align*}
\text{TBSO} & \quad \text{O} \\
\text{O} & \quad \text{TBSO} \\
\text{N} & \quad \text{NH} \\
\text{O} & \quad \text{TBSO} \\
\text{N} & \quad \text{NH} \\
\end{align*}
\]

A tandem metathesis sequence allowed access to an unusual ring-closure mode. In an RCEYM, forming a new ring by closure onto the proximate carbon of an alkyne would lead to a smaller ring. If a pendant alkene could be made to close onto the distal carbon, a larger ring would result. This is called \textit{endo}-selectivity and is atypical of small ring closures using ruthenium carbene intermediates. \textit{Endo}-selectivity was achieved by Kaliappan and coworkers who envisioned a tandem ethylene cross-metathesis/RCM sequence as a means to access 4-methylene-2-cyclohexanols.\textsuperscript{103} This substructure obtained from equation 45 is contained in the natural products oteileones and loloanolides (Table 15). The reaction was conducted under ethylene, triggering an ethylene–alkyne metathesis first. The intermediate vinyl appendage of the 1,3-diene can combine in an alkene RCM to furnish the product. Subsequent Dess–Martin oxidation of the alcohol resulted in the 4-methylene-2-cyclohexenone framework.

5.27.4.1.1 Nitrogen-containing heterocycles

The RCEYM has been used to furnish a variety of nitrogen-containing heterocycles. Nitrogen heterocycles pose a challenge to metal carbene-mediated chemistry because of the electron-withdrawing nature of the nitrogen atom and because nitrogen protecting groups may coordinate to the carbene intermediates. In this section, some challenging examples are provided, mostly employing the second-generation Grubbs catalyst 2. Bicyclic nitrogen heterocycles are also obtained using metathesis methods.

The use of a sulfoximine linker in the enyne leads to a heterocyclic sulfoximine by RCEYM (equation 46).\textsuperscript{104} In the case of terminal alkynes, good yields were also obtained along with a dimeric product that could not be completely eliminated by
dilution or use of ethylene. The resulting 1,3-dienes underwent further transformation such as a Diels–Alder aromatization with benzoquinone, allowing access to benzofused sulfoximines. Attempts to perform further RCEYM reactions on enynes with longer tether lengths to produce larger heterocyclic rings were unsuccessful.

RCEYM can be performed with a vinyl sulfonamide and a terminal alkyne to produce an endocyclic sultam; this is an unusual heterocycle. Heterocyclic ring systems appear in many pharmaceutical agents and are extremely important in drug development. Given this and their versatility, heterocycle synthesis has become a major focus for chemical library synthesis by diversity-oriented synthesis (DOS). With this goal in mind, Hanson and coworkers synthesized skeletally diverse sultams (equations 47 and 48). 105 RCEYM reactions provide unique access to functionalized heterocyclic ring systems from linear unsaturated elements with heteroatom linkers. Initiating metathesis at an electron-deficient site or near coordinating heteroatoms can be difficult. In this case, vinyl sulfonamides are difficult substrates due to the electron-poor nature of the alkene. Generally, this problem can be solved using the more active Hoveyda–Blechert catalyst 3, but in this case longer periods of heating with Grubbs carbene 2 proved successful.
Cyclic 2-aminophosphonates are accessible by RCEYM. Benzofused seven-membered ring systems have received much attention in the synthetic community due to their appearance in a variety of natural products and similarity to privileged structures such as to the benzodiazepines. Moreover, benzofused heterocycles bearing phosphonates have interesting biological properties. Stevens and coworkers planned the synthesis of phosphono-substituted benzazepines using RCEYM as their key strategy (equation 49; Table 16).\(^{52}\) Obtaining the desired 1,3-diene posed a challenge due to the slow conversion of the initially formed butadiene to the 1,3-diene. To speed up conversion to the 1,3-diene, an additional 5 equivalents of alkene were added after the first 2 h of reaction. At the end of the reaction, approximately 10% of butadiene remained unreacted but proved separable by flash chromatography.

Table 16  RCEYM to access phosphono-substituted azepines\(^ {52}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>78</td>
<td>E only</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)SiMe(_3)</td>
<td>74</td>
<td>66:34</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)CH(_2)C(O)CH(_3)</td>
<td>68</td>
<td>67:33</td>
</tr>
</tbody>
</table>

Bicyclic nitrogen heterocycles have been synthesized by RCEYM. The groups of Martin\(^ {106}\) and Mori\(^ {107}\) had independently pursued two closely related strategies toward anatoxin-a. For brevity, the Martin approach is detailed. The enyne precursor was synthesized from D-methyl pyroglutamate.\(^ {106}\) In the RCEYM step, the enyne was found to cyclize efficiently (under Ar) to give the bridged azabicycle under nominal conditions (equation 50). The exocyclic geminal alkene of the diene product was elaborated by osmylation and oxidative cleavage of the 1,2-diol. After protecting group removal (TMSI), the natural enantiomer of (+)-anatoxin was formed (Scheme 16).

Scheme 16  Ring-closing approach to the aza bicyclic ring system of anatoxin-a.

The bicyclic ring system of the alkaloid (+)-ferruginine was assembled by RCEYM (Scheme 17). Aggarwal et al. screened catalysts 1, 3, and 5 in this reaction, but monitoring reaction progress indicated that these more active catalysts were destroying the 1,3-diene product after its initial formation.\(^ {108}\) This is an unusual example of an RCEYM that occurs better with the less reactive first-generation carbene 1. A Wacker-type oxidation sequence was used to transform the exocyclic geminal alkene to a methyl ketone.

RCEYM can be used to access other functionality besides 1,3-dienes. Coupling a tandem transformation with the enyne metathesis provides access to enones in a 'one-pot' process. Normally, enyne metathesis produces a vinyl cyclohexene; however, Kozmin et al. recognized that if the alkyne bore an oxygen atom, the product could be converted into a methyl ketone.\(^ {37}\) Use of silyl alkynyl ethers in the RCM followed by deprotection of the intermediate silyl enol ether gives the product methyl ketones after
acid-catalyzed enol-keto tautomerization (equation 52). This metathesis/deprotection/tautomerization sequence was applied to the synthesis of \( \alpha \)-eremophilane (equation 53).^{109}

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{N} & \quad \text{MeO}_2\text{C} \\
\text{OTIPS} & \quad \text{OSi(i-Pr)}_3
\end{align*}
\]

(10 mol%)

PhH, 50 °C;
HF/CH₃CN

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{H} \\
\text{OTIPS} & \quad \text{Me} \\
\text{H} & \quad \text{Me}
\end{align*}
\]

(18:1). These stereochemically distinct phosphorus heterocycles are unique stereogenic templates and could lend themselves to further functionalization on either the alkyne (Huisgen 3 + 2 cycloaddition) or 1,3-diene moieties (Diels–Alder reaction).

The use of a transient linker to bring together the unsaturated elements was elegantly employed by Schreiber and Micalizio to furnish boroxines (Scheme 19).^{111,11} However, the cyclic boronate could be oxidized to the enol that produced the corresponding enone after enol-keto tautomerization. The cyclic boronates could also be subsequently hydrolyzed to provide acyclic dienes (equation 54). The use of a linker switches a slower intermolecular EYM to the intramolecular manifold, increasing the reaction rate and enforcing the endocyclic alkene geometry. The mixed boronate ester offers functionality that can be harnessed for subsequent C–C bond formation.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{Me} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]

(2 equivalents)

\[
\begin{align*}
\text{H}_2\text{O}_2 & \quad \text{NaOH (aqueous)} \\
\text{THF, r.t.} & \quad \text{59%}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{OH}
\end{align*}
\]

(54)

5.27.4.1.3 Application to carbocyclic natural products

Morken constructed the seven-membered ring found in dihydroxanthatin by RCEYM (equation 55).^{113} The treatment of the requisite enyne with 5 mol% of 2 produced the expected RCEYM product. After enolate alkylation, the diene was subjected to
cross-metathesis with methyl vinyl ketone (equation 56). This procedure could have been achieved in one pot using 3; however, the authors found it tactically superior to perform the metathesis stepwise to selectively enolize the lactone.

An efficient RCM was used to make the seven-membered C-ring of lancifodilactone. In this case, a rather hindered homopropargylic alkyne underwent reaction with carbene 2, as long as the homopropargylic alcohol was protected as the TMS ether (equation 57). In the second cross-metathesis with methyl acrylate, the Hoveyda–Blechert complex 3 was employed to achieve good yield and high E-selectivity. This example serves to illustrate different strengths of the carbene promoters 2 and 3.
Access to six-membered rings using metathesis is advantageous because it can be used to set up subsequent annulation. For example, the resulting vinyl cyclohexene is capable of Diels–Alder cycloaddition (Scheme 20). In subsequent transformations, Barriault and coworkers converted the nitrile into the enone 16, which underwent a Lewis acid-catalyzed Diels–Alder reaction to provide the carbon framework of the tricyclic core of the diterpenoid vinigrol.

The Hoveyda–Blechert complex also promotes simple RCEYM. In their synthesis of erogorgiaene, Hoveyda and coworkers employed an RCEYM using complex 3 (equation 59).

### Scheme 20
RCEYM used to set up intramolecular cycloaddition.

5.27.4.1.4 For diversity generation and in diversity-oriented synthesis
The EYM is well suited to DOS. The DOS aims to create various cyclic or polycyclic templates to project functional groups to give a quasi systematic and wide representation of three-dimensional space. This approach is inspired by complex natural products, which evolved for a particular function. Enyne metathesis is a very attractive enabling technology for the rapid assembly of the core structures because it can be used to make a wide variety of ring sizes, tolerates many functional groups, and supplies products that are amenable to subsequent transformation (e.g., cycloaddition). In this section, a few reactions that fall into this family are highlighted. In Section 5.27.7, cascade reactions are also utilized for the assembly of polycyclic arrays and are detailed in that section.

Two representative examples from DOS illustrate the functional group tolerance of the RCEYM (equations 60 and 61). Chiral scaffolds can be employed to generate heterocyclic rings bearing chiral centers, and the alkene does not need to be terminal. Many
examples in this section include terminal alkenes closing onto alkynes. In this case, Schreiber et al. showed that an alkene bearing a cyclopropyl group participates in RCEYM onto an alkyne that contains a basic amine in the propargylic position (equation 60). In the second example, a privileged heterocyclic ring, that of the penicillin ring (with a divalent sulfur atom and a β-lactam ring), is carried as a spectator during a remarkably efficient RCEYM (equation 61). These two examples illustrate that the enynes can be adorned with a rich array of functionality without deleterious effect on the catalytic enyne metathesis.

Multifunctional diene scaffolds were accessed through RCEYM as a means of generating skeletal diversity. Porco and coworkers conducted the RCM step under Mori’s conditions using ethylene and microwave heating (Scheme 21). The 1,3-diene was not isolated but directly subjected to a thermal [4 + 2] cycloaddition with N-phenylmaleimide. The microwave heating allows rapid throughput and high chemical yield (98% over two steps).

Schreiber et al. built stereochemical and skeletal diversity into a set of small molecules using multiple approaches involving RCEYM (equation 62). The RCEYM in Equation 62 gave an unusual result, proceeding with endo-selectivity when using the Hoveyda–Grubbs catalyst under an ethylene atmosphere. Significantly, a free hydroxyl group is present at the propargylic position. Free alcohols in the propargyl position tend to be problematic in CEYM, except those involving ethylene. The free hydroxyl group was important for the high endo:exo selectivity; if it was protected, the exo-mode RCM dominated.
5.27.4.1.5 Macrocyclic ring closure

In larger RCEYM, there are two orientations that can be obtained, which affect the ring size formed. If the ring is smaller than 10 members, then ring constraint forces the enyne to come together with the 1,2-disubstitution pattern (Scheme 22). This is called exo-selectivity because the intermediate vinyl carbene leading to exo-19 features the ruthenium exocyclic to the newly formed ring. However, if the ring is very large, the ene and yne react with the regiochemistry observed for the intermolecular reaction (as in 20). In this case, the vinyl carbene forms endocyclic to the macroring formed. Lee and Hansen studied this in a systematic way and rationalized the data in terms of reactive intermediate stabilities. With slightly greater flexibility in the enyne tether, the ring closure may result in the larger ring size by switching regiochemical preference. In general, rings smaller than 10 members will form with the 1,2-disubstitution pattern (exo-selectivity); rings in the 10–11 range are borderline cases, and larger rings result in the 1,3-disubstitution pattern on the 1,3-diene (endo-selectivity). The 1,3-disubstitution results from CEYM. A study of macrocyclization in a related system has also appeared, with an emphasis on DOS.

In a remarkable macroring-closing enyne metathesis, Shair and coworkers produced two cyclophanes that were used to assemble the seven ring systems found in longithorone A. Due to the difficulty of the ring closure, high loading of the Grubbs catalyst was used along with ethylene. The synthesis of one cyclophane is illustrated in Scheme 23. This cyclophane comprised the right half of longithorone A.
5.27.4.1.6 With tandem cross-metathesis

Since the Hoveyda complex is well suited to reactions employing electron-deficient alkenes, tandem reactions are possible using these alkenes subsequent to RCEYM. Though carbene 3 is capable of reaction with enoates, it is more reactive with simple aliphatic alkenes. In equation 63, the initial reaction occurs on the alkene of the enyne that undergoes ring closure to give an intermediate vinyl cycloheptene species. With complex 3, both the ring closing and the cross-metathesis with the added alkene took place in a single-reaction flask without further addition of catalyst. The second step can be regarded as a slower and more difficult diene-enoic ester cross-metathesis. It is interesting to note that the reaction temperature can be controlled in this example so as to limit possible Diels–Alder reaction between the intermediate and the excess electron-poor alkene.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 40^\circ\text{C} & \quad \text{CO}_2\text{Me} \\
(3 \text{ equivalents}) & \quad 88\%
\end{align*}
\]

Martin used a tandem cross-metathesis-based approach to make the related diterpene 8-epi-xanthatin using the Hoveyda–Blechert complex 3 (equation 64).

5.27.4.1.7 Ring-closing/aromatization

Substituted arenes can be prepared by an RCEYM/dehydration sequence. RCEYM was carried out with a 1,5-octadien-7-yne-4-ol and second-generation Grubbs carbene (equation 65). On formation of the triene, the alcohol was subjected to mild dehydration conditions ($p$-toluenesulfonic acid ($p$-TsOH)) to trigger elimination and engender aromaticity in the six-membered ring. This novel one-pot process was carried out with a large repertoire of substrates offering an efficient one-pot access to substituted styrenes. A related RCEYM/keto-to-enol tautomerization is also described.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, \text{reflux} & \quad 13\ h \\
& \quad 83\%
\end{align*}
\]

RCEYM has seen wide application as a ring-forming method. It is tolerant of a variety of functional groups and can accommodate electron-withdrawing functionality positioned within or residing outside the newly formed ring. For carbocycles, the scope is wide, tolerant of oxygen substitution, and used in complex molecule synthesis. The Grubbs catalysts typically cause ring-closing of 1,1-enynes in the exo mode. Use of ethylene in some cases leads to endo-ring closure. The next section details more examples of endo-selectivity using Schroek–Hoveyda molybdenum carbene catalysts. The use of RCEYM in alkaloid synthesis has a long history dating back to Mori’s landmark synthesis of stemoamide. Applications to more unusual nitrogen heterocycles and use in DOS are modern themes. Though the Hoveyda–Blechert complex can be used to promote enyne metathesis just as the second-generation Grubbs complex, its niche application is electron-deficient alkenes and forcing reaction conditions needed to make small rings. This complex is the most widely used phosphine-free variation of the Grubbs ruthenium carbene, but variants such as the Grela catalyst 4 are also useful for enyne metathesis. Complex 3 has proven particularly effective under demanding metathesis conditions or those involving enones, enoates, or enals.
5.27.4.2 Ring-Closing Applications with the Molybdenum Carbene Catalysts

The Schrock molybdenum catalyst has not been widely used in enyne metathesis. This can be attributed to the catalysts’ high reactivity with terminal alkynes: Alkyne polymerization outcompetes enyne metathesis. In the best cases, 1,ω-ene substrates may undergo RCEYM with competitive polymerization taking place. A few years ago, there were no examples of RCEYM using the Schrock catalyst. In recent years, the Schrock catalyst has seen far greater application in asymmetric alkene metathesis applications and in Z-selective alkene metathesis. Improving the design of asymmetric catalysts has led to a collateral benefit for enyne metathesis: improved cross-selectivity. (This refers to the cross-reaction between an alkene and an alkyne as opposed to homopolymerization of alkynes.) This highlights that major developments often follow from improvements in catalyst design. As any student of organometallic chemistry might expect, subtle changes in catalyst structure may have a profound effect on reactivity and selectivity.

The parent Schrock catalyst was found to promote the RCEYM of an allene–yne. This is a well-balanced case of intramolecular reactivity over alkyne polymerization (Table 17). Based on initiation studies, the authors favored a mechanism where the molybdenum allenylidene formed and then reacted with the alkyne, followed by ring closure. Though the ether linkage failed due to chelation with the oxophilic metal, a basic amine gave successful enyne metathesis.

![Table 17: Allene–alkyne RCM](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NTs</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>NTs</td>
<td>Me</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>NBn</td>
<td>H</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>C(CO₂Et)₂</td>
<td>H</td>
<td>95</td>
</tr>
</tbody>
</table>

By changing the ligands in the Schrock complex, RCM of 1,ω-enynes is possible. Chirality in the Schrock molybdenum carbene environment is achievable by either substituting the two alkoxy groups for a chiral diol, or using four different ligands to make the metal center stereogenic. In both ways, the Schrock and Hoveyda research team has generated highly selective catalysts for asymmetric RCM applications and Z-selective alkene metathesis. The Schrock complex 21 has two alkoxy groups bound to the molybdenum center. The chiral-at-molybdenum carbene complex 22 bears one alkoxy group and one pyrrolide ligand directly bound to the metal. This slight alteration in ligand environment (changing one alcohol ligand to a pyrrole ligand) resulted in enyne metathesis reactivity. Mono pyrrolide catalyst 22 promotes RCM (equation 67). Interestingly, the ring size formed from a 1,6-ene is not the same as would be expected based on RCEYM promoted by ruthenium carbenes. The mode selectivity observed in equation 67 is called endo-selectivity (it has also been called the β-addition mode). Interestingly, this ring closure ‘mode selectivity’ is different from that observed with the Grubbs ruthenium carbene, where exo-selectivity is observed in small-membered rings. With ruthenium carbenes, the five-membered ring 23 would have been produced by exo-addition (Scheme 24). This complementary mode selectivity suggests a niche for the molybdenum (and tungsten catalysts). In rare cases where ruthenium catalysts have been used, an initial ethylene cross-metathesis is required to guide endo-selectivity. Use of the stereogenic-at-metal complex has provided two asymmetric applications in RCEYM.

The catalyst structure in the Schrock–Hoveyda catalysts influences ‘mode selectivity’ of ring closure. With one pyrrolide ligand already in place, changing the alkoxy group in the four-coordinate molybdenum catalyst has a profound effect on the ring closure mode selectivity (Table 18). For instance, the heteroleptic catalyst 23 gives primarily the exo ring closure mode, but changing to catalyst 24 results in exclusively endo-mode. This example illustrates how the ligands surrounding the metal atom determine...
reactivity profile and how a class of catalysts once dismissed for enyne metathesis has emerged with both the reactivity and a degree of selectivity previously unseen.

The new Schrock catalysts have improved selectivity and may have improved functional group tolerance compared with the parent Schrock catalyst. Although the outlook is hopeful, there has been a higher barrier to the use of the Schrock complex due to its moisture sensitivity and its lower functional group tolerance for alcohols and ethers. Recently, the Schrock catalysts have been rendered significantly more bench stable through complexation with 2,2′-bipyridine. This practical advance will facilitate the use of these catalysts in synthetic laboratories. For RCEYM, the reactivity issue has been solved through tailored catalyst design. With continued improvements in the synthesis of in situ catalysts and their recognized versatility, the perceived barrier to using these complexes is expected to be less significant. Though one can argue that Mo(IV) is too oxophilic to use in complex molecule total synthesis, one is reminded of the early, successful ring-closing alkene metathesis approach to fluvirucin (Sch 38516) by Hoveyda, where a protected sugar and amide withstood the metathesis conditions. Most likely, immediate use of the Schrock subfamily of catalysts will capitalize on the unusual enyne metathesis ring closure mode selectivity and the potential for enantioselectivity, due to the unique stereogenic environment at the metal center.

### 5.2.5 Ring Synthesis

Rings can be formed by EYM between 1,6-dienes and alkynes. To accomplish this ring synthesis, both a CEYM and in situ RCM would occur in the same reaction. The use of a 1,5-diene such as 1,5-hexadiene as a four-carbon donor to an alkyne results in the synthesis of 1,3-cyclohexadienes. Larger rings can be formed by cross-metathesis/ring closing performed on enyne substrates.
Cross-metathesis between dienes and alkynes provides a powerful ring synthesis of 1,3-cyclohexadienes. For example, the venerable Diels–Alder reaction forms a six-membered ring by a cycloaddition between an alkene and 1,3-diene. In a similar vein, a two-carbon plus four-carbon additive metathesis reaction would form the six-membered ring with a conjugated diene present. To take the analogy with the Diels–Alder reaction one step further, the newly formed six-membered ring contains a 1,3-diene rather than a cyclohexene, the ‘residual unsaturation’ characteristic of the Diels–Alder cycloadducts (Scheme 25). Of course, the Diels–Alder reaction is superior due to its simplicity: It only requires heat to bring the reactants together in the ordered transition state. The methylene-free ring synthesis joins two carbons from the alkyne with four carbons from the diene reactant. The ring synthesis is promoted by the Grubbs carbene and is favored by π-reorganization. Unlike the Diels–Alder reaction, the ring synthesis results from several discrete metathesis steps and is not concerted. The products of methylene-free ring synthesis are themselves amenable to subsequent Diels–Alder reaction serving in the capacity of 1,3-diene.

(a) Classical

\[
\text{Diels–Alder} \quad \xrightarrow{\text{Heat}} \quad \text{R}
\]

(b) Metathetical

\[
\text{Metathesis-based ring synthesis} \quad \xrightarrow{\text{Carbene 2}} \quad \text{R}
\]

Scheme 25 Six-membered ring-building approaches.

The methylene-free tandem metathesis approach offers a synthetically useful ring synthesis (Table 19). The reaction is preparatively useful and can be conducted on a larger scale at reduced catalyst loadings. Either 1,5-cyclooctadiene or polybutadiene can be used as the alkene reactant. Because there are no terminal methylene groups, this is termed ‘methylene-free conditions.’ These conditions are thought to permit equilibration between E- and Z-vinyl carbene intermediates. In more difficult cases, such as those employing coordinating heteroatoms on the alkyne or internal alkynes, higher concentrations of 1,5-cyclooctadiene or the polymer polybutadiene are needed. Some representative products are illustrated in Table 19.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(EtO_2C)_2CHCH_2</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>BrOCH_2CH_2</td>
<td>H</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Boc(Ts)(CH_2)_2CH</td>
<td>CH_2</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>TsOCH_2CH</td>
<td>H</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>TsNHCH_2CH</td>
<td>H</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>AcOCH_2</td>
<td>C_5H_5</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>MeOCH</td>
<td>Me</td>
<td>53</td>
</tr>
</tbody>
</table>

EYM has been used as a key step in a diversity-oriented approach to macrocyclic structures through a cross-metathesis/ring-closing ring synthesis. Kotha and Singh generated a diverse collection of macroheterocyclic derivatives by CEYM with 1,5-hexadiene followed by a macroring-closing metathesis (equation 69). This cascade reaction is effective in producing macroheterocycles. In addition, a tetrane product was isolated due to E-diene formation. The mixture of products reflects the nonstereoselective cross-metathesis. The isolated E-tetrane was resubjected to the second-generation Grubbs catalyst 2, but failed to undergo RCM.
5.27.6 Ring-to-Ring Conversions by EYM

5.27.6.1 Ring Rearrangement Enyne Metathesis

RCEYM onto a pendant cycloalkene shuffles the ring. In the process, the existing cycloalkene (YZ linker atoms) is converted into a new ring incorporating the atoms that separated the cycloalkene and alkyne in the first place (linker atoms W–X, equation 70). Often the linker W–X includes a heteroatom, which distinguishes this metathesis as a useful conversion of carbocyclic rings to heterocyclic rings.

\[
\begin{align*}
\text{Grubbs catalyst} & \quad \text{Ring rearrangement enyne metathesis} \\
\text{W} & \quad \text{X} \\
\text{Y} & \quad \text{Z}
\end{align*}
\]

(70)

To the best of the authors’ knowledge, the reaction was developed independently by Blechert\(^{142}\) and Mori.\(^{143}\) Blechert dubbed the process to be a ‘ring rearrangement’;\(^{142,144–147}\) this terminology will be used throughout this section. The ring rearrangement is driven forward to products by \(\pi\)-bond reorganization, the same enthalpic driving force of enyne metathesis. Typically, a carbocycle is broken, whereas a heterocycle is formed.

The ring rearrangement enyne metathesis occurs in the presence of added ethylene. To a first approximation, the mildness of the rearrangement inversely correlates with the stability of the cycloalkene. Seven- and eight-membered cycloalkenes perform well in the ring rearrangement promoted by the first-generation Grubbs complex \(1\) (Table 20).\(^{143}\) Though the carbocycle to heterocycle forward reaction may seem surprising, it is driven by the \(\pi\)-bond reorganization of the enyne metathesis, and it is not due to the stability of the new ring system formed.

Other alkenes can be added in the ring rearrangement enyne metathesis. Initial studies by Mori had focused on ethylene,\(^{143}\) yet Blechert found that other alkenes could be incorporated into the resulting 1,3-diene (Table 21).\(^{142}\)

In this example, the allylidene is formed from the added silyl allyl ether that reacts with the alkyne, then triggers ring rearrangement onto the pendant cycloalkene to produce the triene product (Scheme 26). The site of reaction by the metal carbene can be influenced by propargylic ethers, which lead to alkene incorporation on the cycloalkene if propargylic ethers are present (not shown).\(^{142}\)

Mori observed diastereospecific ring rearrangements with cyclohexenes bearing an endocyclic chiral center.\(^{143}\) In these two examples, each conducted under ethylene, initial ethylene–alkyne metathesis produces a vinyl carbene (see inset of Scheme 27). To undergo ring rearrangement, the vinyl carbene must approach the pseudoaxial silyl ether to access the ruthenacyclobutane giving ring closing. This is impeded in the conformer shown. In the trans-diastereomer, this interaction is not present because the silyl ether resides in a pseudoequatorial position. The absence of this steric interaction allows the RCM onto the cyclohexene ring to proceed uneventfully (equation 74). The resulting triene is poised for intramolecular Diels–Alder cycloaddition after oxidation of the allylic alcohol.
The increased reactivity of the second-generation Grubbs carbene permitted more difficult ring rearrangements onto more highly substituted cyclohexenes. The first-generation carbene 1 could not open the cyclohexene and instead promoted ethylene cross-metathesis. Under more forcing conditions possible with 2, a seven-membered ring carbocycle was obtained along with a trace dimeric product (Scheme 28). The seven-membered ring was not expected; addition of the six-membered ring to the alkyn should have formed an eight-membered ring. The forcing conditions caused alkene isomerization via the intermediate triene 26. Ruthenium hydride-promoted alkene isomerization is followed by reinitiation and RCM on the pendant diene, which resulted in the truncated ring rearrangement product. Under less forcing conditions (refluxing CH₂Cl₂), the desired eight-membered ring product was obtained as a minor coproduct along with the 1,3-cycloheptadiene and dimer.

**Table 21** Ring rearrangement enyne metathesis with a higher alkene

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>81</td>
</tr>
</tbody>
</table>

**Scheme 26** Sequence of carbene reactions in ring rearrangement.

**Scheme 27** Diastereospecific ring rearrangement enyne metathesis.
Strained cycloalkenes also give the ring rearrangement (Table 22). Given the potential for the cyclobutene to undergo competing ring-opening metathesis polymerization, ethylene is added. This is quite typical in RCM or metathesis cascades involving strained cycloalkenes. The added ethylene helps suppress polymerization of the strained cycloalkene. This net process is similar to the intermolecular synthesis of 1,3-cyclohexadienes using methylene-free conditions.

Ring rearrangement with cyclopropene-containing reactants provides skipped triene products. Ring opening of the cyclopropene is triggered by an external alkene such as styrene (equation 76; Table 23). As in the example above, an added alkene used in molar excess helps prevent homopolymerization of the strained cycloalkane, as demonstrated previously by Snapper et al. in selective ring-opening cycloalkene-alkene cross-metathesis. The regioselectivity of the cyclopropene ring opening positions the carbene proximal to the alkyne. Ring closing onto the pendant alkyne results in the ring-rearranged product (equation 76).

Metathesis cascades are extremely efficient for rapidly generating skeletal diversity. In Scheme 29, metathesis events are controlled in a stepwise process that capitalizes on catalyst attributes. The overall process most likely begins with ethylene cross-metathesis joining the strained norbornene with the alkyne. To facilitate purification of the intermediate triene from the ruthenium catalysts, a polar isocyanide is used to quench the catalysts and facilitate the removal of the organometallic impurities. Using microwave irradiation allowed Spring et al. to accelerate the metathesis and conduct a cycloaddition on the diene subunit to gain access to an additional ring.

### 5.27.6.2 Synthesis of 1,3-Cycloheptadienes

Like the ring rearrangement, an existing ring can be converted into a larger ring by net alkyne insertion. This is a ring expansion EYM that occurs as a result of a cascade process. In contrast to the ring rearrangement described in Section 5.27.6.1, ring
expansion is an intermolecular process. This makes the reaction more challenging. Moreover, because of the decreased reactivity with cycloalkenes in the intermolecular manifold, competing reactions such as alkyne polymerization become problematic. As a result, high dilution of the alkyne is needed along with a molar excess of the cycloalkene. An example of the ring expansion with cyclopentene is shown in equation 77.\textsuperscript{153}

\[
\text{Me}^\text{N} \Bigg\| \text{N}^\text{Me} \Bigg\| \text{O} \Bigg\| \text{N}^\text{Me} \Bigg\| \text{O} \Bigg\| \text{N}^\text{Me} \Bigg\| \text{H} \Bigg\| \text{H} \Bigg\| \text{H} \Bigg\| \text{H} \Bigg\| \text{O} \Bigg\| \text{N}^\text{Me} \Bigg\| \text{O}^\text{N} \Bigg\| \text{Et}^\text{N} \Bigg\| \text{O}^\text{Ph} \Bigg\| \text{PhCH}_3, \text{mW, 160}^\circ\text{C} \quad 99\% \\
\text{PhCH}_3, \text{mW, 160}^\circ\text{C} \quad 99\%
\]

Table 23  Ring rearrangement involving cyclopropenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
<th>E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NTs</td>
<td>60</td>
<td>1:1.5</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>55</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>

Scheme 29  Cascade metathesis to generate skeletal diversity.\textsuperscript{152}

In bicyclic systems, the double bond in the five-membered ring reacts selectively. There are two issues: which alkene will react (site selectivity) and what is the orientation of the alkyne substituent in the product (regioselectivity). The ring opening of bicyclic diene proved highly selective and produced a single product\textsuperscript{154} (equation 78). To obtain the desired product, slow addition of the reactive components to the Grubbs catalyst was needed via syringe pump addition. These reaction conditions benefit from a robust second-generation Grubbs catalyst, which must survive for an extended period of heating. Because ruthenacyclobutane ring openings are not generally stereoselective, the origin of the stereoselectivity is thought to arise from E/Z isomerization of vinyl carbenes occurring \textit{in situ}.
To guide regioselectivity in bicyclic systems, a bulky group at the allylic position is required. In the bicyclic ketone shown, the geminal dimethyl substituents guide the ring opening of the cyclopentene and give a single cycloheptadiene product (Scheme 30). Facile [4 + 2] cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) gives a crystalline tetracyclic product.

5.27.7 Cascade Enyne Metathesis

Cascade dienyne metathesis is a powerful ring-building method that furnishes multiple rings from acyclic precursors. Ring-forming reactions are very powerful transformations since many biologically active molecules contain one or several ring systems. The potential of cascade metathesis to produce different polycyclic ring systems from common precursors by using differential alkene reactivity has become an important method of generating skeletal diversity. A common theme in these reactions is the exploitation of the different reactivity of the alkenes, an important concept that borrows heavily from mechanistic understanding of alkene metathesis (the Grubbs model). The metathesis cascade begins with reaction of one alkene, ring closure onto the alkyne, and the next ring-forming metathesis by closure on the other alkene. Control can be achieved in unsymmetrical dienyne by rendering one alkene more reactive toward the metal carbene. Higher reactivity is achieved in less substituted alkenes that are not electron deficient. This serves to orchestrate the first ring closure onto the alkyne. The alkyne serves as a ‘relay’ linking the two ring closure events. Interestingly, the RCEYM is generally favored over a possible alkene–alkene RCM. The most commonly used catalysts are the Grubbs ruthenium benzylidene complexes 1 and 2. A variety of small and medium-sized rings can be formed in this metathesis cascade. However, bulky groups may significantly slow down the RCEYM and attempted the eight-membered ring formation may lead to truncation products arising from undesired alkene isomerization side reactions.

The differential substitution of the pendant alkenes controls the ring size of the bicyclic system formed. Dienyne undergoes cascade metathesis with an earlier Grubbs catalyst 27 to provide the bicyclo[4.4.0]decane (Scheme 31). This process begins by metal carbene formation on the 1-alkene, which achieves end differentiation. Had the other more substituted cis-alkene initiated, a bicyclo[5.3.0]decane would have resulted. Experimentally, these intramolecular metathesis cascades can be favored over intermolecular reactions by conducting the reaction at high dilution.

The same concepts of end differentiation apply to electronically distinct alkenes. In this case, the more electron-rich alkene initiates the cascade reaction (equation 79). The electron-poor acrylate reacts more slowly. Interestingly, this study found that the initial RCEYM always out competed the ring-closing alkene–alkene metathesis. Along with the approach to securinine in the previous section, relative alkene reactivity provides useful information when planning metathesis cascades. In this case, the metathesis sequence produces bicyclic lactones containing the conjugated 1,3-diene.
A tandem RCEYM that involves an electron-deficient alkene benefits from phosphine-free catalysts. Honda and coworkers prepared the securinega alkaloid securinine by a tandem enyne metathesis. The reaction began at the more electron-rich terminal alkene to give the observed product, which does not have the same bicyclic ring system found in securinine (Scheme 32). The initial ring closure produced the five-membered ring rather than the desired six-membered ring present in securinine.

To obtain the desired bicycle, the initiation profile had to be reversed. In other words, the alkene of the enoate had to be rendered more reactive so it would initiate the cascade. From the Grubbs reactivity model of alkene cross-metathesis, terminal aliphatic alkenes are the most reactive with the Grubbs catalysts. Dienyne bearing an allyl ether was used to initiate the cascade (equation 80). Simultaneously, the 'lower' alkene's reactivity had been tempered by converting it to a less reactive internal alkene. After a series of allylic oxidations, the synthesis of the alkaloid securinine was completed.

Boron-substituted alkynes participate in cascade cyclization to give products amenable to Suzuki coupling. Cascade metathesis with first-generation carbene 1 gave the bicyclic diene, which was cross-coupled with an aromatic ring under Pd(0) catalysis (equation 81).
Phosphorus heterocycles can be accessed by a tandem ring-closing dienyne metathesis (equation 82; Table 24). The phosphorus-substituted alkyne proved reactive, despite its electron-deficient nature. Interestingly, the phosphine borane underwent successful RCEYM without reduction of the Grubbs catalyst. In this example, the equivalent reactivity of the terminal alkene means that the cascade can start at either end to produce the observed heterocycle.

![Chemical structure](image)

**Table 24** Phosphorus-containing oxa-bicyclics

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>BH₃</td>
<td>16</td>
<td>75</td>
</tr>
</tbody>
</table>

Electron-rich alkynes also participate in cascade ring-closing dienyne metathesis to bicyclic dienes with a nitrogen atom at a bridgehead position (equation 83). These heterocycles are unsaturated homologs of the indolizidine alkaloids. If the second ring closure is difficult, such as in the eight-membered ring formation, the reaction may terminate after a single RCEYM to give a monocyclic product (entry 1; Table 25). When the second ring-forming step is slow, the by-products associated with double-bond migration are observed (entry 2). Competing reactions leading to by-products can be anticipated due to high temperatures required to form eight-membered rings, a process disfavored due to the negative entropy associated with ring closure. With two similar ends of dienyne, the reaction cascade begins at either side to give a 1:1 mixture of bicyclic products. If the initiation is inhibited at one site, the other more reactive terminal alkene triggers the cascade giving predominantly one bicyclic product. A similar example can be found in Section 5.27.6.1.

![Chemical structure](image)

The cascade metathesis has also been used as an entry point to bicyclic ring systems that contain seven-membered rings. Seven-membered rings can be found in a variety of natural products. The polycyclization has been employed to gain access to the guanacastepene carbocyclic framework (equation 84; Table 26). A variety of substituents on the alkyne were tolerated in the metathesis, with the exception of a TMS group that is presumably too bulky to permit the alkyne insertion step. Interestingly the ring-closing cascade begins from the vinyl appendage of the diene, and this requires the use of the more reactive second-generation Grubbs catalyst.

The unsaturated tricyclic ring system of colchicine was made through a polycyclization by cascade metathesis (Scheme 33). A free propargylic hydroxyl group prevented the metathesis, so protection as the TMS ether was required (a similar solution has been used in a related RCEYM). To the authors’ knowledge, the only cases where a free propargyl hydroxyl group is allowed is ethylene–alkyne cross-metathesis. In this case, a clever oxidative [3,3] sigmatropic rearrangement was used to alter the diene substitution pattern and accomplish the oxidation of the secondary chromate ester. The epimers proved inconsequential as the oxidative rearrangement converged to the enone product. The PCC oxidative rearrangement is an interesting organic transformation applied to the dienes obtained through enyne metathesis.
In the above two examples, the introduction of the alkyne into the reactant is difficult to control, which required that the diastereomeric mixture be carried through the synthesis. This serves to highlight one of the difficulties in the synthetic preparation of the required polyunsaturated substrates (diynes in this case). In more rigid systems with existing stereocenters, the presence
of epimers might result in kinetic differentiation, as observed by Clark et al. previously. Some evidence of this diastereodifferentiation can be found in the next example.

The metathesis cascade can also furnish eight-membered rings. In the first ring closure, an eight-membered ring is formed in the synthesis of a vitamin D₃ transition-state analog (equation 85). In this case, the first-generation Grubbs carbene was employed, and the cyclization was conducted under high-dilution conditions (4.7 mM in CH₂Cl₂). A 1.7:1.0 mixture of diasteromers resulted in a product consisting of a 6.5:1 mixture of C-10 diastereomers yield, which suggests that one epimer cyclized more favorably than the other.

Remarkably, the strained bicyclic [5.3.1] ring system found in taxol can be formed by a metathesis cascade. In this study, Granja et al. found that the catalyst gave the best results in their approach to ‘taxosteroids’ (equation 86). The cascade is initiated at the homoallylic alcohol to form the eight-membered ring in the initial enyne metathesis ring closure. To ensure end differentiation of the alkenes and to avoid formation of the alternative bicycle starting from a five-membered ring, the kinetic decelerating substitution of the pendant alkene was systematically evaluated. An optimum balance of reactivity was achieved by the use of the isopropyl-substituted alkene, as a trisubstituted alkene did not undergo the second ring closure. This study shows that a successful bicyclization depends on the proper choice of alkene substitution to achieve end differentiation.

Tandem dienyne RCM can access bicyclic systems containing a heterocyclic ring. As a key step in their synthesis of lepadin F and G, the skeletal synthesis by tandem dienyne metathesis was achieved in a 90% yield (equation 87, Scheme 34). The hexahydroquinoline ring system was carried forward to provide the first total synthesis of lepadin F and G.

In a highly oxygenated environment, the reactivity difference between the first- and second-generation Grubbs carbenes determined the success of the second ring closure. The first-generation catalyst gave RCEYM beginning with the most reactive
alkene and the reaction stopped at the triene stage (equation 88). To encourage the second cyclization, the more reactive Grubbs complex 2 was employed.

\[ \text{Conditions} \]

1 (20 mol%), PhH, reflux, 17 h, 90%
2 (10 mol%), CH_2Cl_2, reflux, 24 h, 85%

Polycyclization using tandem RCEYM proved to be an effective strategy to generate diverse structural analogs of the antitrypanosomal agent artemisinin. An advantage of the site differentiation is the ability to access different cyclic core structures, depending on the placement of the initiating alkene (equations 89 and 90). This approach is highly attractive for the construction of unique polycyclic frameworks that could be used in directed library synthesis or DOS. To complete the synthesis of structural analogs, dienyl isomerization was required. After screening several different Brønsted and Lewis acids, catalytic SbF_5 was used to produce the endocyclic diene (Scheme 35). The endocyclic diene underwent cycloaddition with an \textit{in situ}-generated acyl nitroso dienophile giving a cycloadduct, which rearranged during Fmoc deprotection to the unusual spirofused oxazine.

\[ \text{Conditions} \]

1 (15–20 mol%), PhH or DCE, reflux

X = H, Y = OH, 49%
X = OH, Y = H, 39%
Scheme 35 Cascade metathesis and dienyl isomerization sequence. 170

Polycyclization by cascade metathesis proceeds with multiple alkynes situated in between the starting and terminating alkenes. Arranged in this way, the additional alkyne(s) react with the intermediate vinyl carbenes to produce new vinyl carbenes, which eventually terminate. Oxygen heterocycles (equation 91) are easily made as well as the steroid-like tetracycle (equation 92). 171

Siloxane linkers can be used to preorganize unsaturated reactants and then removed to provide stereocontrolled synthesis of 1,3-dienes. 172 This strategy was employed by Kim and Lee for the construction of the unsaturated carbon framework of tartrolon B (equation 93). The silicon atom is used to temporarily connect the alkyne and alkene fragments, similar to the use of boronate linkers by Schreiber and Micalizio. 111,12 Reactivity differences in the two alkenes achieve site differentiation, which resulted in the initial formation of the seven-membered ring. Once the cascade RCM has occurred, the silicon is removed by desilylation using a fluoride source such as TBAF. In this tandem sequence of reactions, various end substitutions on the 1,3-diene can be obtained.
The temporary siloxane linker was used to furnish the 1,3-diene segment of cochleamycin. Access to the mixed silaketal is provided by base-catalyzed replacement of an acetylide with the secondary alcohol. The mixed silaketal sets the stage for the cascade EYM. The control of the rings formed utilized end differentiation, where the more reactive unsubstituted alkene triggered the cascade process (Scheme 36). Stereospecific removal of the siloxane was accomplished with TBAF. More recent approaches to the stereoselective synthesis of macrocyclic dienes include the use of site-specific ring-closing alkene–diene metathesis, but this is not detailed in this chapter.

The polycyclic core of cortistatin A was accessible by cascade dieneyne RCM. Stolz and coworkers utilized a 1:1 mixture of diastereomers in the cascade metathesis that was triggered by the second-generation Grubbs carbene (Scheme 37). As a result, a 37% isolated yield of the desired core ring system was obtained, along with 44% yield of a by-product arising from the other diastereomer. Interestingly, the alternate diastereomer gives a single RCM since the geminal alkene is not able to capture the vinyl carbene intermediate. This shows that cascade enyne metathesis is a rapid method for the construction of the carbocyclic core of cortistatin A.

A cascade RCM was used to assemble the core ring system of the spirotrolicyclic natural product acylfulvene. The metathesis cascade (which was studied extensively in model systems) was initiated by the second-generation Grubbs complex to afford an intermediate tricyclic diene, which was deprotected in situ to give the triol 29 (equation 94). The bond-forming events are orchestrated by alkene reactivity; the most reactive allyl ether initiated the cascade and the less reactive geminally disubstituted alkene terminated it. After the tandem reaction, the 1,3-diene was reductively transposed using the Myers protocol for the in situ generation of the diazene, giving 30. This synthetic tactic manages to convert the conjugated 1,3-diene into a 1,4-diene. After the transposition, a ring-closing alkene metathesis of 30 gained access to all three rings of the natural product (−)-acylfulvene (equation 95). This combination of tandem enyne metathesis and a clever diene isomerization stands as an inspiring example of cascade metathesis in the service of total synthesis.
A concise tandem ring-closing dienyne metathesis was used to assemble the core polycyclic framework of the alkaloid lycoflexine. The ring-closing event was initiated at the more reactive terminal alkene to first form the five-membered ring (Scheme 38). Strikingly, the second ring closure generated the nine-membered azacyclic ring. The 1,3-diene was semihydrogenated in a site-selective reduction step where the residual Grubbs catalyst was transformed into a ruthenium hydride, giving a ruthenium hydride catalyst that selectively reduced the diene fragment. Such use of tandem catalysis under hydrogenation (H₂) or transfer hydrogenation conditions has been previously employed in ring-closing alkene metathesis/hydrogenation tandem reactions.

Scheme 37  Cascade metathesis approach to Cortistatin A.  

Scheme 38  Cascade metathesis approach to the alkaloid lycoflexine.
5.27.8 Choreographed Movement of Metal Carbenes in Enyne Metathesis Cascades

In the previous section, differential alkene reactivity guided the movement of the carbene to the alkyne, thereby controlling ring size in the resulting bi- or polycyclic frameworks (end differentiation). In this section, a directing alkene is used to guide the metal carbene to a less reactive site through RCM. In the process, the five-membered ring is extruded and lost. This tactic allows for the formation of a metal carbene that would otherwise be difficult or impossible to form. This choreographed movement of metal carbenes is called 'relay RCM' (rRCM). It has been used several times in alkene metathesis literature to guide RCM. The applications to enyne metathesis are somewhat fewer, but ironically it is here that the reaction was discovered. Some recent applications have conjoined rRCM in tandem with distinct reactions such as metallotropic shift.

5.27.8.1 Relay Metathesis or rRCM

The relay ring-forming metathesis strategy developed by Hoye is designed to use a favorable RCM to position the metal carbene, usually at a less reactive alkene site. The relay metathesis strategy overcomes the problem of generating reactivity at an unreactive or less reactive alkene site. Hoye and coworkers\textsuperscript{178} developed a procedure where a pendant alkene serves as an initiation locus (equation 96). The strategy cleverly exploits alkene reactivity preferences to orchestrate a metathesis cascade. Initiation at the terminal alkene leads to the intermediate metal carbene that undergoes RCM. The RCM step is associated with the loss of a cyclic alkene that translocates the carbene to a site that was not accessible by direct, intermolecular catalyst initiation.

\[
\text{RuL}_n \xrightarrow{2} \text{RuL}_n \xrightarrow{\text{RCM}} \]

(96)

In addition to its utility for cyclizing unreactive dienes, this strategy can be used to steer metathesis when more than one option is available. The dienyne 31 shown in the inset of Scheme 39 contains two relatively unreactive alkenes. Cascade metathesis is triggered nearly equally at each site, giving a mixture of two products. By adding a terminal alkene three atoms away from the desired site of reaction, higher selectivity is obtained to give one major product due to choreographed metathesis as depicted in Scheme 39. The terminal alkene is the initiating point and through the RCM positions the metal carbene appropriately. Geminally substituted alkenes are difficult to initiate with the Grubbs carbenes; one case of strain assistance was seen previously.\textsuperscript{68} The rRCM achieves site selectivity when the starting material has two reactive alkenes. If the relay is triggered on the other side, the opposite site selectivity is obtained producing the alternate bicyclic ring system that contains a pyran ring (product not shown).

Using the rRCM strategy, Diver and coworkers set the stage for a CEYM.\textsuperscript{179} A dienal underwent a catalytic Evans aldol reaction (reaction not shown), and subsequently the Hoveyda–Blechert carbene 3 was used to trigger the relay metathesis in the presence of an external alkyne. The rRCM extrudes a cycloalkene to form an intermediate metal carbene (Scheme 40). In this way, ene–yne cross-metathesis occurs \textit{in situ} with butynyl benzoate, providing a highly functionalized 1,3-diene in a good yield. With 1:1 stoichiometry of alkene and alkyne, the intermediate metal carbene did not completely react with butynyl benzoate such that some \textit{anti}-allylic alcohol was isolated as a coproduct.
5.2.7.8.2 Ring-Closing Enyne Metathesis with Metallatropic Shift

Relay ring closing has been conjoined with RCEYM and metallatropic shift as an approach to oxygenated natural products containing an unsaturated sidechain. Lee and coworkers began with a mixture of diastereomers and subjected them to tandem enyne metathesis metallotropic [1,3]-shift for a concise total syntheses of (+)-aperpentyn, (−)-harveynone, and (−)-tricholomenyn A (Scheme 41).180 The two diastereomers were formed collectively in 62% yield and proved separable by flash chromatography. These were carried forward to give the desired natural products.

While studying metathesis cascades involving metallatropic shift, Lee and coworkers identified a stable ruthenium alkylidene complex bearing a coordinated alkyne.181 In one case, a diendiyne gave the expected cascade product (equation 97). With the geminally substituted dimethyl analog, exposure of the entriyne to 1 equivalent of catalyst 2 in refluxing DCM for 6 h gave an alkyne-chelated ruthenium alkylidene complex instead of the expected metathesis product (equation 98). This stable metal carbene was formed through an RCEYM, metallatropic shift, and another RCEYM to produce the vinyl carbene. The rigidity of the cyclohexene ring enforces a favorable coordination geometry that discourages ligand exchange and hence limits the last step of metathesis.
5.27.9 Double-Directional Synthesis

A particularly dramatic example of the ring rearrangement enyne metathesis employed a strained norbornene that reacted with two alkynes in a two-directional manner. In this case, each alkyne underwent RCM with the proximate end of the cycloalkene, giving the linear tricycle (Scheme 42).\textsuperscript{182,183} The two 1,3-dienes were subsequently trapped in a cycloaddition step to form the linear penta-cycle. With an added aliphatic alkene, ring opening of the norbornene takes place first and only one alkyne participates in ring closure, giving the bicyclic diene.

Double-directional synthesis involving enyne and alkene metathesis was employed to access the polyether framework found in the ciguatoxins and brevetoxins. Polycyclic ethers such as those found in CTX-30 are a synthetic challenge due to the complexity of their polycyclic ring system. Clark and Hamelin found a two-directional double RCM to be a useful strategy in the synthesis of polycyclic ethers containing complex medium-sized rings (equation 99).\textsuperscript{184} The example depicted below uses 15 mol% of the first-generation Grubbs catalyst to perform RCEYM and a ring-closing alkene metathesis simultaneously. This resulted in an efficient synthesis of the ABC ring system found in CTX-3C.
Achieving stoichiometric equivalency in CEYM permits the use of a bifunctional alkene substrate for a linear two-directional synthesis. Under standard cross metathesis conditions, this would be inconceivable because the alkene is used in molar excess. An excess of the alkene would have prevented double substitution of a diene reactant. In this case, divinyl carbinol was reacted with a twofold excess of propargyl benzoate to give the resulting tetraene in 27% yield (Scheme 43). With the unprotected hydroxyl group present in the product, a site-selective desymmetrization was achieved through a directed Sharpless asymmetric epoxidation.

\[
\begin{align*}
\text{OBz} & \quad \text{OH} & \quad \text{OBz} \\
\text{DCE, 60 °C, 2 h} & \quad 3 \text{ (10 mol%)} & \quad \text{OBz} \\
27\% & \quad \text{3} & \quad \text{27%} \\
\text{OBz} & \quad \text{OH} & \quad \text{OBz}
\end{align*}
\]

**Scheme 43** Two-directional EYM with divinylcarbinol.

### 5.27.10 Conclusion and Outlook

EYM provides an efficient catalytic method for diene synthesis using simple unsaturated reactants. The reaction shows excellent functional group tolerance characteristic of the Grubbs ruthenium carbenes. That the ruthenium carbenes are widely available and easy to use can explain the wide range of applications in organic synthesis. Some of the appeal is the accessibility of the simple reactants and the reactivity of the resulting 1,3-dienes. The unique reactivity of 1,3-dienes can be harnessed in cycloaddition reactions. This sequence translates into a rapid gain in structural complexity. Interest in enyne metathesis has closely followed interest in complex molecules and heterocycles, and there has been increasing use of metathesis in total synthesis. These successes have helped to maintain momentum in the field, further emboldened by successful EYM used in tandem with other bond-forming processes. These successes, combined with continuing improvements in substrate scope and a refined understanding of reaction mechanism, have made EYM a useful synthetic method for C–C bond construction.

RCM has seen diverse applications to a variety of ring sizes and for the construction of different heterocyclic rings. Some recent topics that utilize the economy of the enyne metathesis and recognize the utility of the 1,3-diene product include DOS, or the synthesis of platforms that array functional groups in a stereodefined way. It was also seen that a number of tandem reactions are joined with the enyne metathesis, some distinct bond-forming processes such as cycloaddition or metallotropic shift, and others involving additional metathesis steps. The cascade metathesis applications have tremendous potential to generate poly cyclic structures in one step. The potential chemistry here is expansive and is open to the imagination and limited perhaps only by the level of difficulty in obtaining the acyclic polyeneyne precursors. Control of the formed ring in poly pendant dienynes is controlled through alkene reactivity, which in turn achieves site differentiation. Control of carbene positioning has been achieved through orchestrated movement of carbenes known as relay enyne metathesis.

In CEYM applications, a molar excess of the alkene is typically used to drive the EYM forward. However, in the best cases, nearly equimolar amounts of the alkene and alkyne can be used. In these cases, the EYM is a carbon–carbon cross-coupling, with a reorganization of the π-bonds. Some of the other exciting applications include the ring rearrangements to form heterocyclic rings, and ring construction and ring expansion methods.

There are still growth areas for EYM. Some of the unresolved difficulties in EYM include poor control of alkene geometry, high catalyst loadings, and oftentimes the need for a large excess of alkene reactant. Some applications such as ring building capitalize on in situ isomerization to access the Z-geometry. Z-Selectivity is unsolved in acyclic EYM and there are currently no catalysts to overcome this shortcoming, despite the very recent advances in Z-selective alkene metathesis catalysts. Though the mechanism has been studied, the rate profile with a wide assortment of alkenes and alkynes has not been fully elucidated. This will be useful to guide future synthetic efforts with less reactive unsaturated reactants.

### References

Ene–Yne Metathesis