Metal carbenes in enyne metathesis: Synthetic and mechanistic studies

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This article is dedicated to Professor Robert Grubbs (Caltech) and Professor Richard Schrock (MIT) for their scholarship, their leadership
in the field of metathesis chemistry and their independent development of practical catalysts for alkene metathesis.

Abstract

Intermolecular (cross) enyne metathesis between dienes and alkynes is an effective method for ring synthesis giving cyclodienes. The enyne metathesis is initiated by the Grubbs carbene complex $(H_2IMes)(Cy_3P)Cl_2Ru=CHPh$ (**Ru gen-2**), which produces vinyl carbene intermediates. Our desire to develop the cross enyne metathesis into an efficient and useful organic reaction has improved our understanding of both the scope and mechanism of enyne metathesis. This mini-review is based on my lecture given at the ISOM16 meeting in Poznan in August of 2005, and is not meant as a comprehensive review of the subject. The mini-review focuses on the problems we encountered, provides background and context found in the relevant literature and details the three approaches we pursued in solving the ring synthesis research problem. These studies led to kinetic investigation of enyne metathesis reaction mechanism, which is also summarized.
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1. Introduction

Enyne metathesis has become an important synthetic method. The metathesis between an alkyne and alkene provides a conjugated 1,3-diene, which can be transformed into more complex organic molecules (Scheme 1). As a popular new organic reaction, the enyne metathesis has seen many applications and is increasingly used in total synthesis. The metathesis with ruthenium carbenes, known as the Grubbs catalysts, has been possible due to chemoselective reactions with unsaturated molecules. This attribute is commonly known as functional group tolerance, and it has instilled confidence in synthetic chemists' use of the reaction. The commonly used carbenes are shown in Scheme 1. The large number of applications in synthesis provides a lexicon of reactivity that can be rationalized in terms of mechanism.

The number of synthetic applications and our desire to design new reactions has led to better understanding of reaction mechanism. Recent reviews describe the synthetic utility of enyne metathesis in good detail [1–3]. This short review primarily describes my group's effort towards understanding reactivity of the metal carbenes in the enyne metathesis. In particular, the enyne metathesis involves ruthenium vinyl carbene intermediates A (Scheme 2) which are different than the ruthenium methylidene B and the ruthenium alkylidenes C encountered in alkene metathesis. Three vinyl carbenes (**5–7**) are known in the literature [4–7]. How does the reactivity of ruthenium vinyl carbenes differ from the better known carbenes involved in alkene metathesis? The discussion of carbene reactivity is centered around our group's development of a particular enyne metathesis application to make 1,3-cyclohexadienes. This organization is based on my lecture given at the ISOM16 conference held in Poznan in August of 2005.

The enyne metathesis has been used extensively in synthesis. Several excellent recent reviews are available [1,2,8]. Recent examples in alkaloid synthesis are notable, but are only referenced here [9–17]. For the synthetic chemist, this demonstrates the utility of the reaction; for the organometallic chemist, it is a testament to the awesome selectivity of the Grubbs' complex. One can marvel at the power and poise of the metal carbene: it will selectively rip apart a stable molecule and reassemble it, without touching heteroatom functional groups. This difference in reactivity is referred to as functional group tolerance
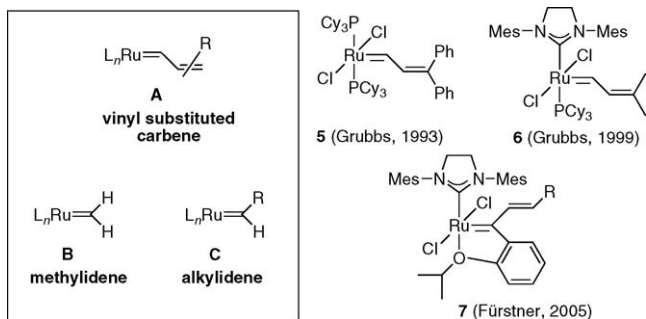
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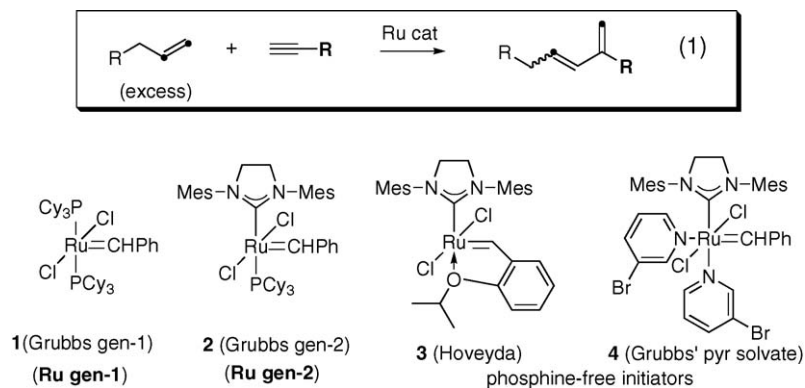
Scheme 1. Enyne metathesis.

and it provides a powerful instrument to the synthetic chemist for the delicate operations involved in complex molecule synthesis. Without a doubt, the progress in the field of enyne metathesis owes much to progress made in the area of alkene metathesis. This is where the attention of synthetic chemists was first captured and where great improvements in catalyst activity have been achieved.

This account will overview our group's development of ring synthesis and recount what we have learned about metathesis from our desire to expand synthetic utility. In particular, this methodology focuses on tandem metathesis applied to 1,3-cyclohexadiene synthesis. Tandem metathesis has generated recent interest due to the molecular complexity building potential of the metathesis steps. The low selectivity in the tandem cross enyne metathesis/ring-closing metathesis sequence led to three approaches to solving this problem. In the process, we will relate some fundamental studies on cyclopropanation reactivity and discuss the relationship of alkene metathesis to enyne bond reorganization (type II enyne metathesis). Finally, our recent mechanistic studies will be summarized. The reaction of metal carbenes with carbon monoxide was the subject of a poster presentation at the ISOM16 meeting, and has been recently published [18].
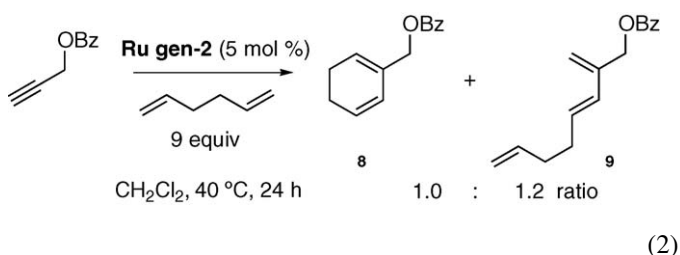
2. Ring synthesis by tandem enyne metathesis

A tandem metathesis triggered by an intermolecular (cross) metathesis is unusual. We developed a tandem metathesis for the synthesis of 1,3-cyclohexadienes (Eq. (2)).

$$\text{(2)}$$

The cyclohexadiene ring synthesis stands as one of the first examples of tandem enyne metathesis. The one step, direct synthesis of a cyclohexadiene ring from simple unsaturated precursors is very attractive. In the initial report [19] we obtained a 1:1.2 mixture of products. Use of various solvents, reaction temperatures and ruthenium carbene precatalysts did very little to perturb this ratio and did not improve it.

Intermolecular, or cross, metatheses typically give low stereoselectivity. For example, Blechert's important paper on the cross metathesis [20] with complex **1** (**Ru gen-1**) gave E/Z mixtures, and little improvement in selectivity has been realized to this day. In Eq. (2), the reaction gave a mixture of products due to low stereoselectivity in the first metathesis step: the cross metathesis. The lack of Z-selectivity is a general shortcoming of cross metathesis. (There are isolated cases of modest E-selectivity. One using ethylene [21b] and another by us, using **2** (**Ru gen-2**) to equilibrate Z-dienes to E-dienes [21]. The factors controlling these reactions are not completely understood. Since E-selectivity depends on the alkene used, metal carbene reactivity is important.)

The tandem metathesis is initiated by non-stereoselective cross enyne metathesis, which produced a mixture of products. The desired diene **D** and triene **E** were trapped and characterized as their Diels–Alder cycloadducts, **12** and **13**, respectively. We reasoned that the E-triene **E** was formed and could not undergo a ring-closing metathesis due to geometrical constraint. The desired cyclohexadiene **D** was derived from a Z-intermediate **10**. We were unable to detect the Z-triene **10A**. Recent kinetic studies conducted in our laboratory [22,23] are consistent with the alkylidene-first mechanism [24,25] which suggests vinyl carbene intermediates **10B** and **11**. The Z-intermediate **10** undergoes efficient capture by

Scheme 2. Carbenes in enyne and alkene metathesis.

the pendant alkene to give the cyclodiene **D** by ring-closing metathesis. The cyclohexadiene could not be separated from the byproduct **E**.

3. The carbene intermediates

Despite a great number of synthetic applications, the mechanism of enyne metathesis is not completely understood. One of the main questions has been the identity of the reactive metal carbene intermediates. For example, the early proposals of enyne metathesis suggested that $L_nRu=CH_2$ played an important role as a catalytic intermediate. This is called the 'methylidene-first' mechanism. The intermediacy of the methylidene, $L_nRu=CH_2$, was invoked for ring-closing enyne metathesis, cross metathesis and ethylene metathesis. As the synthetic applications grew, publications cited the only mechanistic work available, and by physical organometallic kineticist standards, it was incomplete. This was obfuscated by the fact that the ethylene–alkyne metathesis was developing at the same time where a methylidene clearly *was* the reactive intermediate. In particular, Mori had originated the idea of a protective effect of ethylene [26]. The ethylene–alkyne cross metatheses [27–33] clearly involve $L_nRu=CH_2$ intermediates formed from ethylene. At the same time, new catalysts were emerging. The Grubbs group reported a significantly improved catalyst, the second-generation ruthenium benzylidene, **Ru gen**-2 [34]. This became widely used and the mechanistic hypotheses applied to earlier work with the first-generation benzylidene **1** were extrapolated to the second-generation complex **2**. The extrapolation is a rough correlation, since kinetic differences between the first- and second-generation complexes were evident from Grubbs' mechanistic work in alkene metathesis [35,36]. More recent results have interpreted both ring-closing enyne metathesis (RCEYM) and cross metathesis (CM) in terms of ruthenium alkylidene intermediates, $L_nRu=CHR$. These interpretations are important to rationalize regioselectivity and stereoselection in the cross metathesis reaction. Regardless of the alkylidene-first or methylidene-first mechanism, the intermediates that are encountered next are vinyl carbenes. Vinyl carbenes are not generally encountered in alkene metathesis and are unique to enyne metathesis [37–41]. The dearth of information on vinyl carbenes and the greater mechanistic knowledge of alkene metathesis has led to an assumed similarity of vinyl carbene reactivity to metal carbene reactivity in alkene metathesis.

Vinyl carbenes are not well studied. Vinyl carbenes are intermediates in enyne metathesis, yet little is known about their reactivity as compared to other metal carbenes. Moreover, the effect of substitution on the reactivity of the vinyl carbene is also not known. Two vinyl carbene complexes **5** [6,7] and **6** [4] have been used as initiators for alkene metathesis (see Scheme 2). Recently, the coordinated vinyl carbene **7** was prepared by Fürstner's group [5]. The latter complex is interesting because it features substitution at the carbene carbon. The initial report by Blechert and co-workers [20] interpreted reactivity of the vinyl carbenes as relatively low. Presumably the vinyl carbenes are more stable due to conjugation by the vinyl group. Resonance helps to stabilize the electron-deficient car-

bene carbon, making it less reactive than a metal alkylidene (Eq. (3)).


$$(3)$$
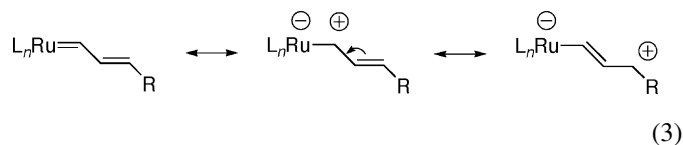
In enyne metathesis, the genesis of vinyl carbenes is thought to proceed via a ruthenacyclobutene, though it is unclear whether this is a reactive intermediate or a transition state (Eq. (4)). The anticipated ring strain would place these putative species higher in energy than metallacyclobutanes, the intermediates in alkene metathesis. This presumption led us to consider that this step may be rate determining in some intermolecular metatheses. Recently, Straub and Lippenstreu have calculated the energies of intermediates in enyne metathesis [42]. These computations do not locate a metallacyclobutene intermediate. As such, the DFT calculations point to an unspecified reorganization, possibly a ruthenocyclobutene transition state, that must take place going from the carbene–alkyne complex **F** to the vinyl carbene **H** (Eq. (4)).

$$(4)$$
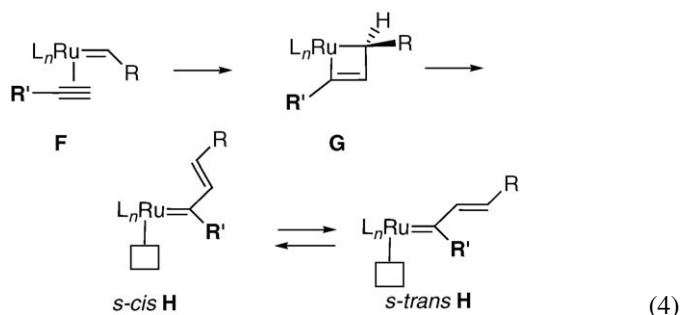
There are some important differences between enyne metathesis and alkene metathesis. These differences have a profound effect on synthetic utility. For organic synthesis, conjugated 1,3-dienes **I** are valuable building blocks that are used in cycloadditions to build rings (Eq. (5)). Oxygen substituents on the diene both increase reactivity and provide an additional functional group in the product. For the synthesis of dienes **I**, the cross enyne metathesis requires an enol ether reactant, as shown in Eq. (5). Enol ethers do not give cross alkene metathesis and produce relatively stable ruthenium Fischer carbenes [4]. In fact, enol ethers are used to terminate living polymers obtained in ROMP by formation of a stable ruthenium Fischer carbene complex. Moreover, enol ethers do not react in alkene cross metathesis (Eq. (6)). This may be due to the intrinsic stability of the Fischer carbene intermediates combined with a tendency to participate in degenerate self-metathesis.


$$(5)$$

$$(6)$$
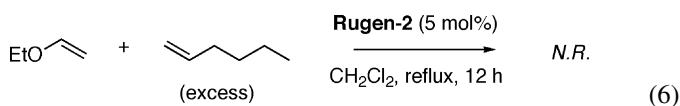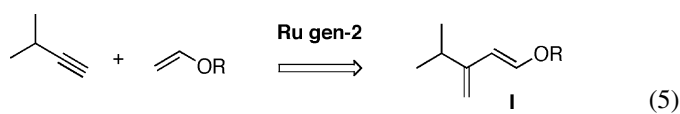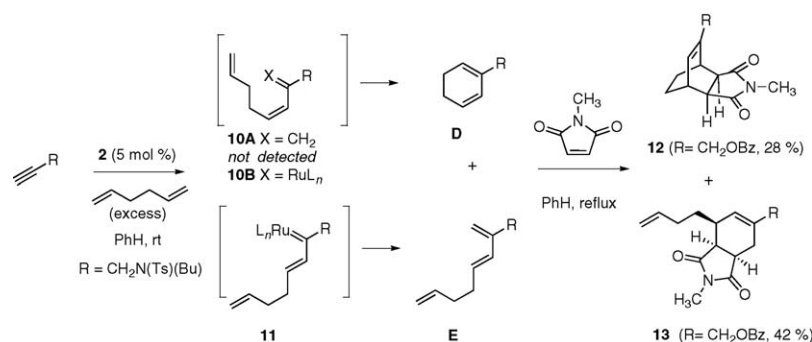
Scheme 3. Diels–Alder trapping of the product mixture obtained from tandem metathesis.

If these relatively stable Fischer carbenes represent carbene intermediates, can the enthalpic driving force of enyne metathesis be used to make the enol ethers react (Scheme 3)?

The enthalpic driving force was sufficient to overcome the sluggish reactivity of the ruthenium carbenes involved in the enol ether–alkyne cross metathesis. The favorable enthalpy change is due to π-bond reorganization, giving a new carbon–carbon sigma bond and an alkene π-bond in exchange for a weaker alkyne π-bond [43]. Utilizing this driving force for the intermolecular enyne metathesis, we prepared a variety of dienol ethers [44] (Scheme 4). The representative products in Scheme 4 were used subsequently in Diels–Alder cycloaddition. To promote the reaction rate, the cross metathesis was conducted at reflux temperatures. In methylene chloride solvent, the reaction times varied from 12 to 24 h. In refluxing benzene, the reactions took about 10 min. Recently, we have employed ruthenium carbenes to generate dienol ethers **I** which were subjected to a sequential rhodium carbene-mediated cyclopropanation/divinylcyclopropane rearrangement, in collaboration with Huw Davies' group at Buffalo [45].

The enthalpic driving force of enyne metathesis is not a panacea. For instance, enthalpy is not sufficient to overcome reaction limitations due to functional groups. At this stage it should also be noted that functional groups could interfere with successful metathesis by kinetically deleterious chelation, by promoting decomposition or by a combination of the two. For example, thiol benzoate **18** did not give cross enyne metathesis with butyl vinyl ether (Eq. (8)). We first assumed that this was due to kinetic retardation of rate by chelation (e.g. **20**). This hypothesis was based on the strong affinity between sulfur and ruthenium, as well as the close proximity of these groups. If vinyl carbene turnover was rate-limiting, then chelation in the

vinyl carbene would slow one cycle of catalysis, limiting catalyst turnover.
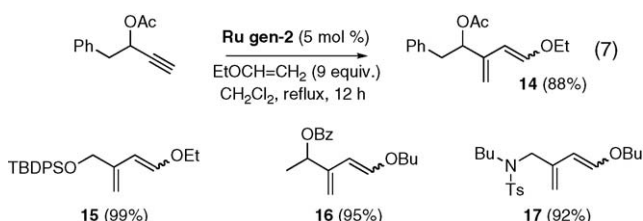
$$(8)$$
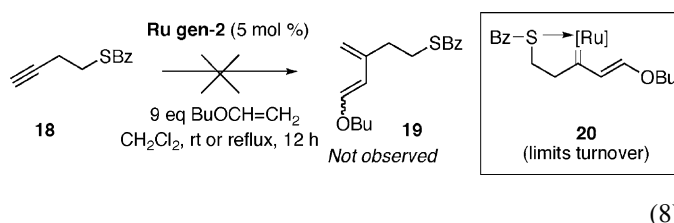
Earlier work in our group showed that ethylene metatheses could be carried out in the presence of thiol ester functionality [33]. We reasoned that ethylene should help this intermolecular catalysis, possibly by 'rescuing' the putative chelate **20**, ushering the carbene back into catalysis. To test this hypothesis, we conducted the enol ether cross metathesis under elevated ethylene pressure (Scheme 5).

Remarkably, the cross metathesis occurred at ambient temperature and gave complete conversion to a mixture of the butadiene **21** and dienol ether **22**. Since the butadiene came from ethylene cross metathesis, we investigated lower ethylene pressure to minimize **21**. By lowering the ethylene pressure to 5 psig, **21** was no longer formed and the desired cross metathesis was still accelerated. We term these reactions 'co-metathesis' using ethylene as an auxiliary alkene to promote a difficult intermolecular reaction [46]. Presumably, the ethylene disrupts coordination by the sulfur functional group and accelerates catalytic turnover (Eq. (10)). Part of the effect may be stabilization

Scheme 4. Enol ether alkyne cross metathesis.
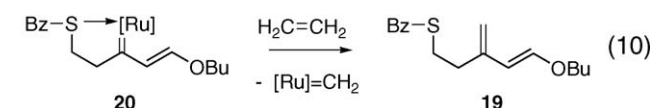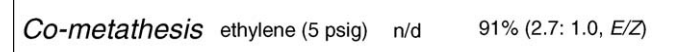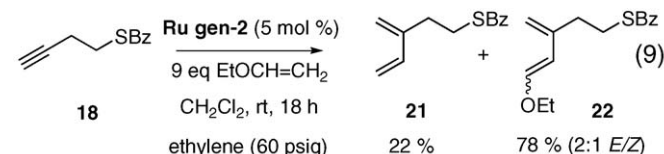
Scheme 5. Ethylene assistance.
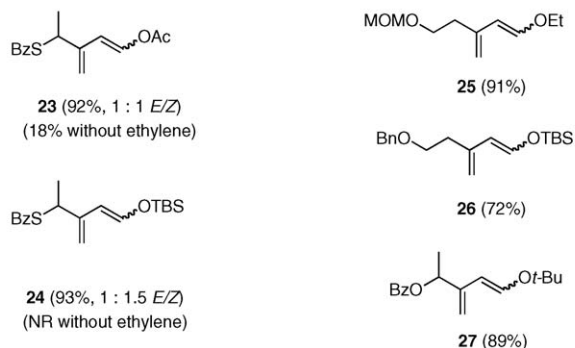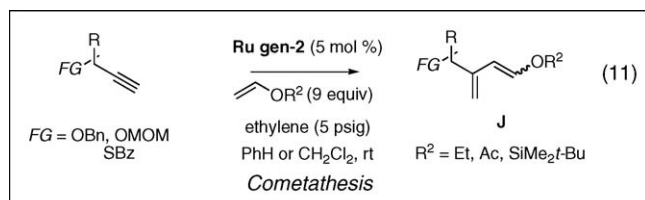
Scheme 6. Ethylene-assisted enol ether–alkyne cross metathesis.

of the vinyl carbene intermediate, which is similar to the protective ethylene effect (Mori's conditions) [26] invoked to protect the sensitive carbene $L_nRu=CH_2$ from decomposition. However, our data suggest that the high ethylene concentration also exerts a kinetic effect, accelerating catalyst turnover (lower temperature, shorter reaction times). This observed kinetic benefit is different than a static protecting effect as suggested by Mori, suggesting that ethylene helps turnover vinyl carbenes. Since this presentation at the ISOM16, experimental results by Lloyd–Jones have validated this hypothesis in an elegant carbon-13 labeling experiment [47].

The ethylene-assisted enyne cross metathesis proved suitable to prepare a wide range of dienol ethers [46] (Scheme 6). The functional groups shown are commonly thought to be coordination-prone and represent difficult cases for the cross metathesis. In fact, in the case of dienol 23, there is only 18% product isolated in the absence of added ethylene: ethylene proved essential. Similarly, product 24 derives from a silyl enol ether. Silyl enol ethers do not react at all without ethylene; at higher temperatures the silyl enol ethers were found to decompose ruthenium carbenes (similar to that observed for enol ethers) [48]. If the effect of ethylene is to increase the rate of vinyl carbene turnover, then higher concentrations of enol ether should also increase rate of turnover. In fact, the ethylene effect observed in these cases can be duplicated using high concentrations of enol ether without ethylene. Ethylene was used to assist an intermolecular enyne metathesis, which led to a substantial increase in the scope of the enol ether–alkyne metathesis.

4. The cyclohexadiene ring synthesis problem revisited

The tandem metathesis to make cyclohexadienes was originally hampered by the formation of a mixture of two products (Eq. (2)). This tandem reaction stands as a difficult metathesis because the initial reaction is a non-stereoselective cross metathesis (see Scheme 3). Only the less stable Z-isomer would lead to the ring-closing metathesis product. The other product would not be capable of ring closure, so it would be produced as a by-product. Clearly, for this to become a useful synthetic method, the isomers D and E would have to (at least) be separable. Ideally, the initial metathesis could be made Z-selective. Currently, Z-selectivity is not a solved problem for metathesis and we had to consider what other strategies might be employed to increase the amount of ring product formed. Though ultimately we seek a stereoselective solution to this problem, an interim procedure to separate the byproduct was developed.

We developed a method to transform the undesired isomer into a polar, water-soluble by product by a consecutive cross alkene metathesis [49]. In this case, the mixture of cyclohexadiene and triene obtained through the cross metathesis are treated in situ with a second alkene (Scheme 7). The second alkene used was either acrylic acid or methyl vinyl ketone, chosen to make the triene more polar. The use of acrylic acid, for example, gave a triene-derived by-product K that proved separable by acid–base extraction. The different reactivity of the alkenes in the cyclohexadiene D and the triene E result in a selective cross metathesis modifying only the terminal alkene of the triene E. This procedure offers a very simple way of dealing with the mixture of products obtained through non-stereoselective cross metathesis. Both the Grubbs Ru gen-2 complex and the Hoveyda gen-2 complex 3 [50] worked well as catalysts. Under optimized conditions, a single charge of catalyst (5 mol%) is needed to effect the tandem metathesis and the second, chemoselective modification of the 1-alkene, present only in the by-product E (Scheme 7). In this reaction sequence, the ruthenium carbene is performing a cross enyne metathesis, a ring-closing metathesis and a cross alkene metathesis. This protocol permits simple combination of 1,5-hexadiene and alkyne to be used for
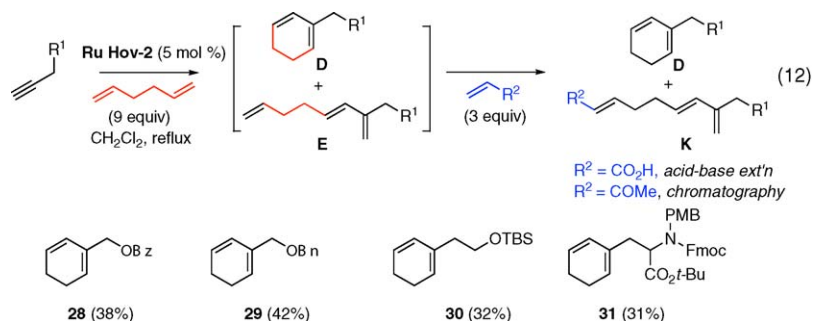
Scheme 7. Sequential alkene metathesis on tandem metathesis mixture.
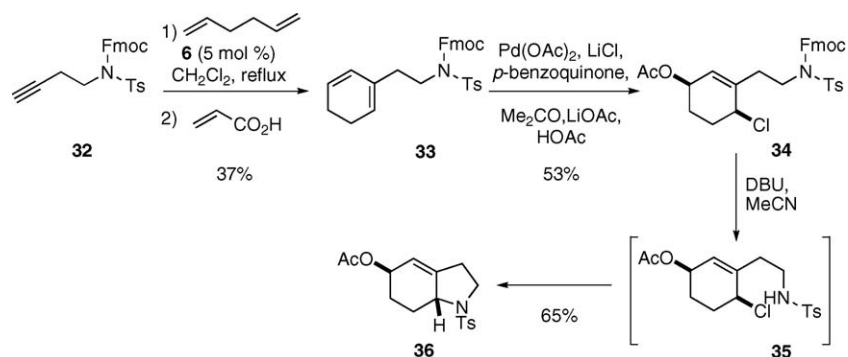
Scheme 8. Tandem metathesis 'Clean Up' for nitrogen heterocycle synthesis.
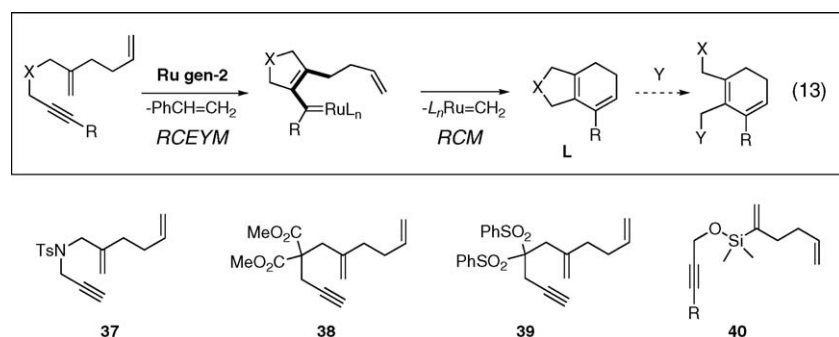
Scheme 9. Temporary ring control for cyclohexadiene synthesis.

1,3-cyclohexadiene synthesis (**28–31**). Advantages of the 1,5-hexadiene procedure include the relatively fast tandem enyne metathesis and good functional group tolerance. Demonstrating the functional group tolerance of the ring synthesis, the metathesis procedure was used to prepare a nitrogen heterocycle, the indoline **36** (Scheme 8).

The second strategy to improve the formation of the cyclohexadiene is to use a temporary ring. This strategy borrows an idea from ring-closing enyne metathesis: that the nascent ring containing linker X positions the vinyl carbene *cis-* to the pendant alkene, leading to ring-closing metathesis (Scheme 9). This would give the product of a tandem metathesis (ring-closing enyne metathesis and a second ring-closing metathesis) yielding the desired cyclohexadiene **L**. Once formed, the temporary ring containing the 'X' group could be opened to give a functionalized 1,3-cyclohexadiene. Originally, we set out to explore the tandem metathesis in cases we thought would be well behaved, e.g. **37–39**. Once worked out, we wanted to adapt the reaction to the tandem sequence with the siloxane **40**. A similar approach using a boronate linker formed in situ was developed by Micalizio and Schreiber [51].

The ring-closing metathesis of tosylamide-linked dienynes gave the expected tandem metathesis in good yield [52] (Eq. (14)).

$$(14)$$
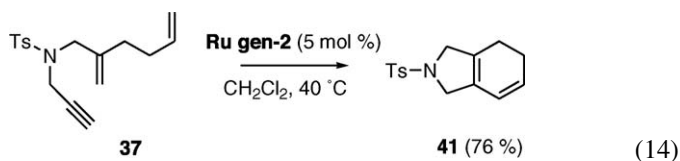
Based on this result, we expected that tandem ring-closing metathesis would occur efficiently from the malonate- and the sulfone-linked dienynes **38** and **39**. Instead, an unexpected cyclopropanation took place-giving **43** (Eq. (15)). The malonate **38** gave mostly vinyl cyclopropane (40% isolated yield) while the bissulfone **39** gave exclusively the vinyl cyclopropane **43B** (81% yield). These results were surprising since catalytic generation of cyclopropanes from Grubbs' carbenes had not been previously observed.

$$(15)$$
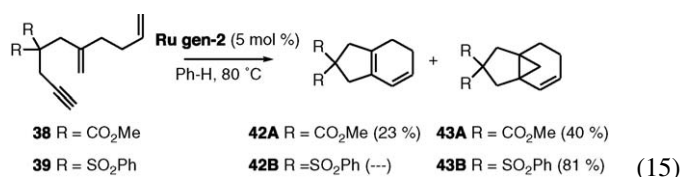
Cyclopropanation is not commonly observed in metathesis reactions. Cyclopropanation had been observed as a minor reaction pathway attributed to reductive elimination and decomposition of ruthenium carbene intermediates. From the prior literature, it was believed that cyclopropanation was an indication of catalyst decomposition and would thus consume the ruthenium carbene [53,54]. This may be generally true, however the products of Eq. (15) were formed in yields greater than the catalyst loading, which indicates catalyst turnover. Nonetheless, considering catalyst decomposition by reductive elimination and applying this analysis to the second-generation Grubbs carbene, complex **44** would be formed (Eq. (16))

(16)

44
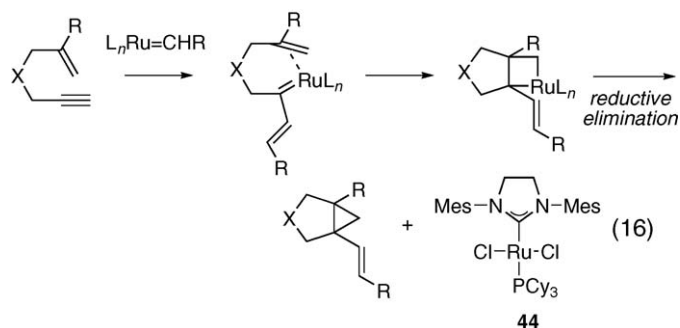
We considered that the supposed decomposition product **44** might be able to catalyze the 'abberant' enyne metathesis leading to the observed vinyl cyclopropanes **43** (Eq. (15)). It must be pointed out that the reductive elimination step was not experimentally observed by us or previously [53,54] in the literature.

'Enyne metathesis' is also catalyzed by non-carbenic late transition metal salts by a distinct mechanism known as enyne bond reorganization [55–57]. Interest in this reaction has been recently rekindled [58] and a recent review has appeared [59]. For the present discussion, it is useful to point out that the reorganization is triggered by η^2-complexation of the alkyne. This can lead to non-classical ion formation [58] via the intermediacy of a cyclopropyl metal carbene. In normal enyne bond reorganization, the non-classical ion progresses to the cyclobutene, thence to the conjugated diene (Eq. (17))


(17)
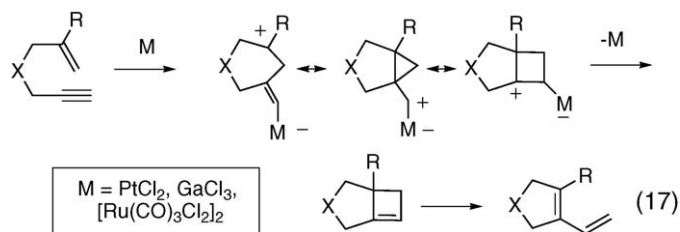
The net reaction is the same as the enyne metathesis, but occurs by a distinct mechanism that does not begin with carbene complexes.

We considered that the ruthenium complex associated with ruthenacyclobutane reductive elimination might promote the enyne bond reorganization with substrates **38** and **39**. The ruthenium complex would be the non-carbene (H$_2$IMes)RuCl$_2$-(PCy$_3$) **44** and would initiate enyne bond reorganization by η^2-complexation to the alkyne. This would trigger non-classical carbocation formation leading to a cyclopropyl alkylidene, which would be intercepted by the pendant alkene, giving ring-closing enyne metathesis *and regeneration of a metal carbene* (Eq. (18))


(18)
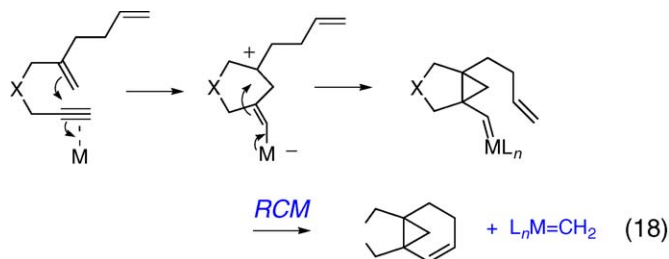
We favored a monodentate activation of the alkyne. However, it is also possible that **44** may bind in a bidentate fashion (to both alkyne and alkene), leading to cyclometallation to afford a metallacyclopentene. Metallatropic rearrangement would provide cyclopropylalkylidene depicted in Eq. (18). For a discussion of this alternate possibility, see Trost and Tanoury [55,60], Chatani et al. [61] and Peppers and Diver [52]. If this pathway was operative, then a non-carbene ruthenium complex should give the same catalytic reaction as depicted in Eq. (15) (above). Using 5 mol% (H$_2$IMes)RuCl$_2$(PCy$_3$) (formed in situ), the cyclopropane **43B** was obtained in 69% yield. This shows that either a metal carbene or a non-carbene can be used as a catalyst precursor for the cyclopropanation. To rationalize these data, the two distinct mechanisms were 'converged' in a single catalytic cycle [52] (Scheme 10).

Despite the tendency of the sulfone to give cyclopropanation, we wanted to form the tandem ring-closing product using catalyst(s) to overcome the dienyne's desire to form cyclopropane. To exert catalyst control, we used sequential enyne metathesis
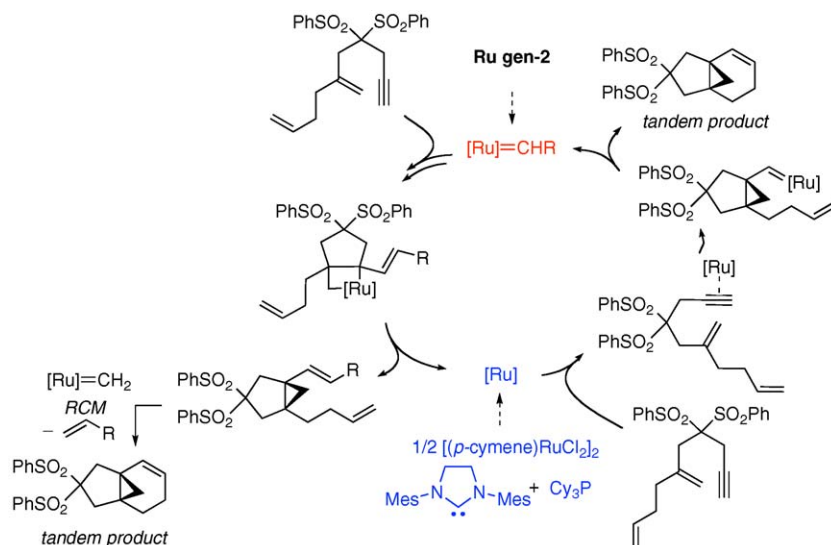

Scheme 10. Converging mechanisms of enyne metathesis.

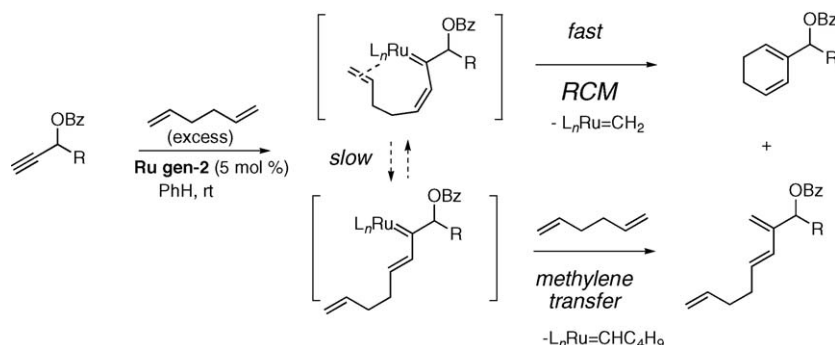taking advantage of the enyne bond reorganization and the carbene-promoted enyne metathesis (Eq. (19)).

42B 76%)
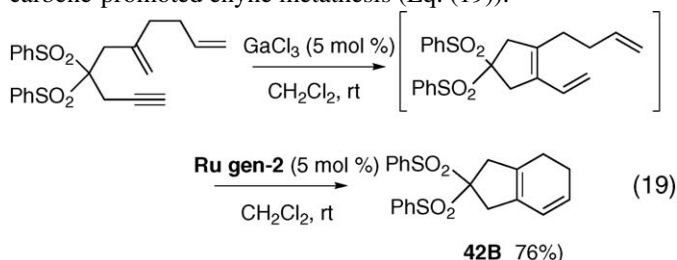
For the first catalyst, we chose GaCl₃ (Murai–Chatani catalyst), which is known to effect enyne bond reorganization by the non-carbene pathway [62]. Interestingly, the Murai–Chatani catalyst was totally chemoselective and reacted only with the proximal alkene–alkyne. It is also notable that the putative gallium carbene intermediate [62] propagates through the non-classical carbocation evolution illustrated in Eq. (17) rather than participating in ring-closing alkene metathesis onto the pendant alkene. The GaCl₃-promoted enyne bond reorganization was very efficient (Eq. (19)) and once the alkyne was consumed, the second-generation Grubbs carbene was added which gave ring-closing metathesis to produce desired cyclohexadiene **42B** in a 'one-pot' transformation.

The last solution to the cyclohexadiene ring synthesis considers the equilibration of vinyl carbene intermediates. This represented a new way of thinking about controlling selectivity by using the ring-closing metathesis step to drive an equilibrating mixture of vinyl carbenes to form the cyclo-hexadiene. Since our initial study on the tandem metathesis (and in subsequent studies), we had been puzzled that the kinetic selectivity of cross metathesis produced a nearly 1:1 mixture of E- and Z-isomers: why should this be? Without detailed information about intermediates or a catalytic reaction coordinate energy profile, we were free to speculate. We supposed that a ruthenacyclobutene intermediate could open to give both E- and Z-vinyl carbenes (Eq. (20)).
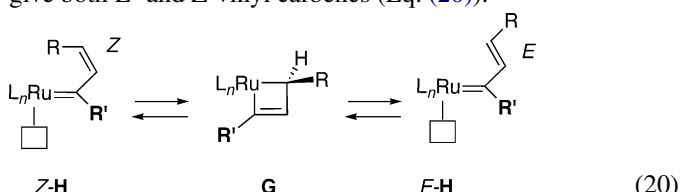
Furthermore, we speculated that the isomeric integrity of the vinyl carbene intermediates was dynamic. This supposes that

each step is reversible, but it was unclear whether equilibration could compete with fast metathetic reactions of the intermediate vinyl carbenes **H**.

Returning to the ring synthesis problem, if the 1:1 mixture of E- and Z-vinyl carbenes is formed, could the undesired reaction of the Z-vinyl carbene be suppressed (bottom equation, Scheme 11)?

Suppression of the E-vinyl carbene reaction seemed reasonable since the reaction of the E-isomer would be a bimolecular reaction whereas the Z-isomer would react intramolecularly in a ring-closing metathesis. Thus, the Z-isomer could react to form product and the E-isomer would accumulate. If this scenario could be accomplished, then what would be needed is an interconversion of the E-isomer into the Z-isomer. We hypothesized that this might occur by reversible electrocycliza-tion shown in Eq. (21)
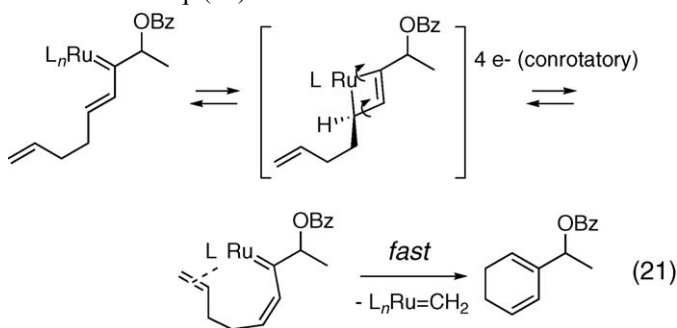
The electrocyclization can be thought of as a non-torquoselec-tive, conrotatory electrocyclic ring-opening. In this instance, the Z-isomeric vinyl carbene positions the pendant alkene close for a presumably fast ring-closing reaction.

The challenge was to allow vinyl carbene equilibration to occur faster than the tandem metathesis. Also, the reaction of E-vinyl carbene with excess alkene had to be decelerated. Here we imagined that this could be slowed if the E-vinyl carbene was not permitted to react with a 1-alkene (Eq. (22)).

Scheme 11. Vinyl carbene reactions by intramolecular RCM vs. bimolecular methylene transfer.

$$R\text{---} + \bigcirc \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux} \atop \text{high dilution}]{\textbf{Ru gen-2 (5 mol \%)}} \quad (23)$$

(4 equiv)

75%   62%   53%

56%   58%   65%
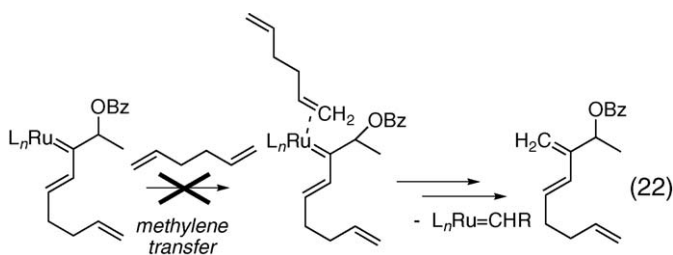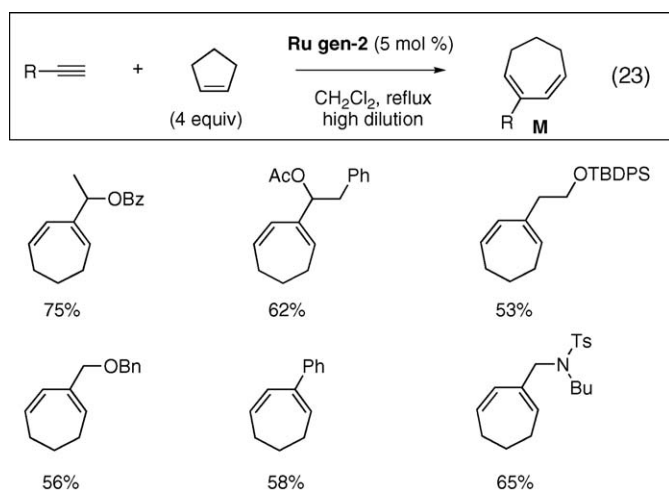
Scheme 12. Cycloheptadienes by ring expansion under methylene-free conditions.

Reaction with a 1-alkene is fast because the terminal alkene coordinates easily to the metal carbene and because the transfer of a methylene group to the vinyl carbene carbon is sterically unencumbered. This led us to develop reaction conditions that were devoid of methylene sources. We termed these conditions "methylene-free" metathesis conditions [63].

Previously, only terminal alkenes had been employed in the cross metathesis, so it was not clear whether the reaction would be successful.

The first indication that methylene-free conditions could be effectively used in organic synthesis was realized during ring expansion of cyclopentene to 1,3-cycloheptadienes [64] (Scheme 12). In this reaction, cyclopentene reacts with various terminal alkynes to give dienes, ring expanded from five- to seven-membered rings. Previously, we had observed non-stereoselective cross metathesis, giving ca. 1:1 ratios of E- and Z-isomers. However in this case, yields in excess of 75% were obtained for the cycloheptadienes. The cycloheptadiene was derived from the Z-vinyl carbene, so a rationale for the higher apparent selectivity needed to be formulated.

Last, it should be noted that these reactions could not involve methylidene intermediates because there are no sources of CH_2. As a result, this reaction must occur through alkylidene intermediates, demonstrating synthetic utility of the alkylidene-first mechanism.
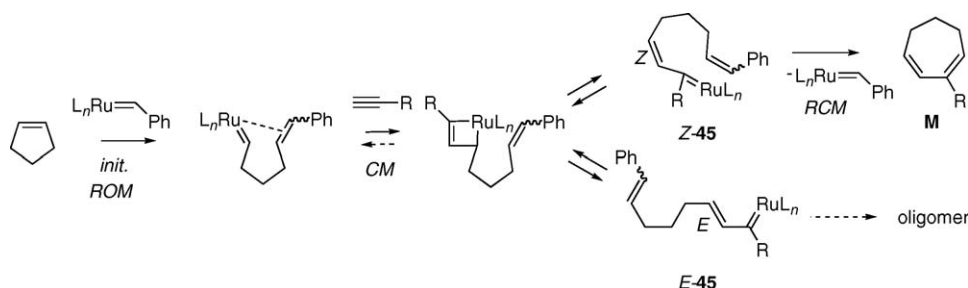
Table 1
Comparison of cyclopentene and polypentenamer in ring expansion

$$\xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux} \atop \text{(high dilution)}]{\textbf{Ru gen-2 (5 mol \%)}} \quad (24)$$

polypentenamer (4 equiv)[a]

Entry	R	Isolated yield	
		From polymer	From cyclopentene
1	OBz	61	75
2	CH(CH$_3$)OBz	58	74
3	OC(O)β-Nap	41	62
4	OBn	41	56
5	OTBDPS	62	56
6	Ph	68	58

The proposed reaction mechanism is shown in Scheme 13. Ring-opening metathesis (ROM) of cyclopentene provides an alkylidene, which undergoes cross metathesis (CM) with the alkyne to give a metallacyclobutene. The metallacyclobutene opens to form the E- and Z-vinyl carbenes **45**. The Z-vinyl carbene Z-**45** undergoes ring-closing metathesis with concomitant loss of the Grubbs benzylidene **2** and formation of the cycloheptadiene M. Presumably E-**45** is also formed, but undergoes a slower intermolecular oligomerization. We suggested that the intermolecular reaction of E-**45** is slow because cyclopentene is more hindered than a 1-alkene. The oligomerization is further limited by high dilution conditions.

Next we investigated whether strain was a prerequisite for the ring expansion under methylene-free conditions. In a separate reaction, we subjected cyclopentene to ROMP using conditions prescribed by Grubbs [7]. The resulting polymer, polypentenamer, was then used in place of cyclopentene for the analogous ring expansion. The polymer would supply the five carbons. In this instance, the polymer has no ring strain but furnished cycloheptadienes **M** in comparable yields as obtained with cyclopentene (Table 1).

That strain was not required led us to evaluate polybutadiene as a four carbon donor for cyclohexadiene ring synthesis by enyne metathesis (Eq. (25)). These reactions were performed under high dilution using slow addition of unsaturated reactants to catalyst over 4–12 h. In all cases, the yields were 72–77% by NMR against mesitylene internal standard (Table 2).

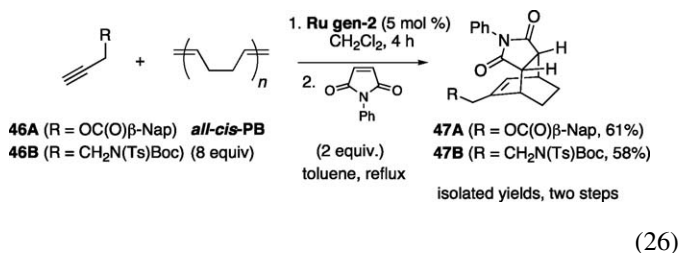Scheme 13. Proposed reaction mechanism: methylene-free ring expansion.

Table 2
Methylene-free synthesis of 1,3-cyclohexadienes from polybutadiene

(25)
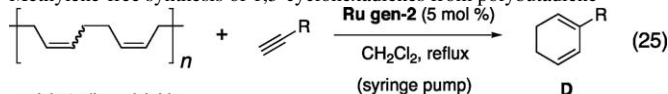
| Entry	Alkyne	1,3 Cyclohexadiene	^{1}H NMR yield (%)
1	⟍OBz	R=CH$_2$OBz	72
2	⟍ONaphth	R=CH$_2$ONap	77
3	⟍OBz	R=CH(OBz)CH$_3$	76

Polybutadiene: 37,000–55,000 repeats, Mw ~ 2–3×10^6 g/mol.

The methylene-free metathesis with polybutadiene was also used in conjunction with a sequential Diels–Alder reaction to provide the corresponding cycloadducts in good yield (Eq. (26)).

46A (R = OC(O)β-Nap) **all-cis-PB**
46B (R = CH$_2$N(Ts)Boc) (8 equiv)
(2 equiv.) toluene, reflux
47A (R = OC(O)β-Nap, 61%)
**47B** (R = CH$_2$N(Ts)Boc, 58%)
isolated yields, two steps

(26)

Optimization of the methylene-free conditions for cyclohexadiene synthesis was performed using 1,5-cyclooctadiene (COD) as the four carbon donor. The results are summarized in Scheme 14. The NMR yields were 80–85% and isolated yields lower due to the necessary precipitation and purification from the COD-derived homopolymer.

The methylene-free metathesis is a powerful method for the efficient ring synthesis of 1,3-cyclohexadienes. Previous to this

(27)

71% (83% NMR)   74% (88% NMR)   66% (80% NMR)

62% (77% NMR)   42% (49% NMR)
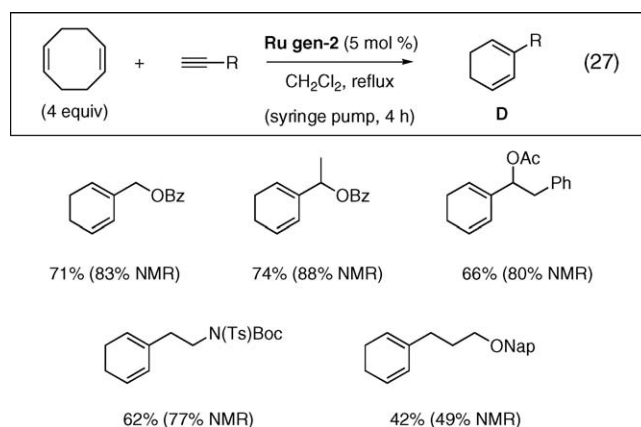
Scheme 14. Methylene-free synthesis of 1,3-cyclohexadienes from 1,5-cyclooctadiene.

work, there exist few methods for cyclohexadiene synthesis and none that are single step operations. The reactions using 1,5-cyclooctadiene or polybutadiene are amenable to scale up. In our experience, scale up permits reduced catalyst loading, usually 1–2 mol% is achievable without rigorous purification of reactants. Due to the slow addition (syringe pump) and the methylene-free conditions, the metathesis is slower than the 1,5-hexadiene-alkyne tandem metathesis [19,49] discussed earlier. As a result, though selectivity has been improved, the slower reaction reveals unusual functional group limitations. For example, coordinating ethers in the homopropargylic position were not well tolerated. Homopropargyl benzyl ether gave only 50% conversion to product using 15 mol% catalyst loading. Since internal alkenes coordinate more weakly to metals than 1-alkenes, the putative slow step, vinyl carbene reaction with alkene, is slower than a typical enyne metathesis involving 1-alkenes (Scheme 15). As a result, the reaction proves more sensitive to potentially coordinating functional groups than typ-
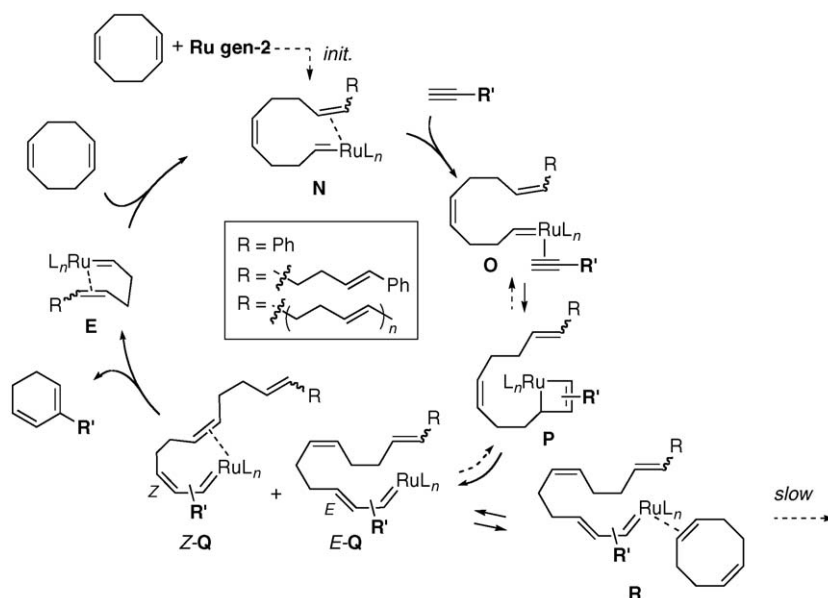
Scheme 15. Proposed mechanism for the cyclohexadiene synthesis by methylene-free enyne metathesis.

ical ring-closing alkene or enyne metathesis reactions. Further studies are needed to identify the nature of the catalyst decomposition in these cases.

5. Mechanism

As simple as enyne metathesis appears to be, it is poorly understood. Enyne metathesis has been interpreted within the framework of alkene metathesis, which is a useful analogy but does not provide an a priori roadmap of reactivity, especially for ruthenium vinyl carbenes. Another problem, described earlier, is that synthetic chemists latched onto the enyne metathesis, developed methodology and sought to explain the reaction in the context of limited mechanistic data available at the time. This has resulted in several misconceptions and 'controversies.' Foremost among the controversies is whether the reaction proceeds by a 'methylidene-first' or an 'alkylidene-first' mechanism. A second major point of confusion is the ethylene effect. There is no doubt that Mori's conditions have helped a variety of ring-closing enyne metatheses. However, there are many cases where ethylene has not had a helpful effect [1] and some applications in enyne metathesis where it is essential (vide supra). When should ethylene be used and what does it do? A third point is chelation and how it limits substrate scope and where it kinetically affects catalysis. Last, the early proposals involved studies with the first-generation Grubbs benzylidene complex. The field developed rapidly when Grubbs reported the second-generation **Ru gen-2** complex [34] which received immediate and widespread use. Thus, reactions performed with the second-generation complex were compared to studies using the first-generation complex. Are the reaction mechanisms and rate-determining steps the same? So far, this question has not been answered, but it seems improbable. Lately, the phosphine-free Hoveyda complex has also been used with great success. This complex has no phosphine-bound states, and preliminary studies in our group have shown that this does affect the reaction rate and probably the rate law. The practitioner of enyne metathesis must use caution in interpreting mechanism and inferring rate-determining step. As our own limited studies will illustrate, the rate-limiting step changes depending on alkene and alkyne used.

We undertook a mechanistic study of enyne metathesis examining reaction rate based on IR monitoring of the reaction. This study was conducted by my group in collaboration with my colleague at Buffalo, Professor Jerry Keister, an organometallic kineticist. The alkyne reactant has a unique IR absorption: the CH bond stretch, which was observed even at low alkyne concentrations. Monitoring the decay of this absorption at 3300–3310 cm^{-1} over time gave the rate of disappearance of the alkyne reactant. This data was used to establish a rate law for the 1-hexene–alkyne metathesis and for the ethylene–alkyne metathesis.

The hexane–alkyne cross metathesis showed several interesting features. First, the reaction showed zero order dependence on the alkyne concentration. Second, in comparing two different alkynes, the one with greater propargylic substitution turned out to be more reactive by a factor of 20 (**49** more reactive than **48**). One might imagine that the benzoate functionality

may chelate to the vinyl carbene and retard its reactivity. We tested this by comparing the benzoyloxy alkynes to their hydrocarbon analogs. Here we also find that the more substituted alkyne, isopropyl acetylene underwent reaction with 1-hexene some 20 times faster than the linear alkyne, octyne. Both alkynes reacted with rates similar to the benzyoyloxy analogs of the same propargyl substitution. These data suggest that there is not a chelation effect for this ester functionality located at the propargylic position. Further comparisons between other functional group-containing alkynes with their hydrocarbon analogs are needed to elucidate chelation effects. The completion of these ongoing studies will provide a playbook of functional group substitution patterns that are successful and those that are expected to be difficult. This may prove helpful to organic chemists planning to use enyne metathesis in multistep synthesis.

The ethylene-alkyne metathesis showed a zero order dependence on ethylene concentration and zero order dependence on propargyl benzoate **48**, but first order dependence on the more highly substituted alkyne **49**. The more substituted alkyne **49** reacted about 20 times faster than the less substituted **48** under the same conditions. All the ethylene reactions were slower than the corresponding reactions with 1-hexene, at comparable alkene and alkyne concentrations.

48   **49**
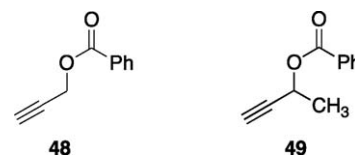
To interpret these data, we considered where the catalyst mass resides, either in the catalytic cycle or on the periphery. The 14-electron intermediates **U** and **S** are catalytically active and 16-electron coordination complexes **T** and **W** are not catalytically active, but may represent kinetically accessible precatalyst states (Scheme 16). The 16-electron phosphine-bound states provide an immediate precursor to the 14-electron intermediates; these are referred to as 'resting states.' (There may be others that involve functional group coordination, but in the kinetic study, these are not kinetically visible or relevant.) Our mechanism is interpreted in terms of the alkylidene-first mechanism. For the 1-hexene-alkyne enyne metatheses, we consider the 1-hexene derived carbene, the pentylidene **U** (R=n-C$_4$H$_g$, an alkylidene) to be the active carbene catalyst. Based on the rate data, it reacts very quickly with the alkyne (via **V**) and forms a 14-electron vinyl carbene complex **S**. This point in the catalytic cycle represents a crossroads for the catalyst throughput: it can react with alkene in step V or rebind to phosphine in step IV. Alkene binding will lead to the product and the phosphine binding leads to an inactive 16-electron complex **W**, which is a catalyst resting state. Our mechanistic picture focuses on the partitioning of the 14-electron vinyl carbene intermediate **S**.

For the 1-hexene–alkyne metatheses, the rate data suggest that steps V or VI are the rate-determining steps. Since the reaction rate depends on alkene concentration, higher alkene concentration will help the metathesis proceed. We believe that the 14-electron complex **S**, due to its high reactivity, might be susceptible to decomposition by unidentified pathways. The rate data do
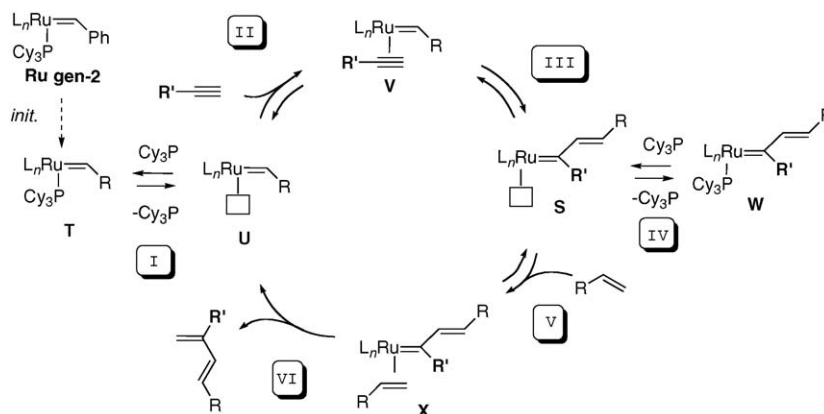
Scheme 16. Proposed mechanism for intermolecular enyne metathesis based on kinetic study.

not distinguish whether the alkene binding step/cycloaddition (step V) or the ruthenacyclobutane fragmentation step (cycloreversion, step VI) is rate-determining. It is possible that higher substitution at the *R'* position will destabilize the metallacyclobutane giving a faster rate of cycloreversion. Lippenstreu and Straub's DFT study [42] suggested that the cycloreversion is rate-limiting, which is consistent with our data. Greater substitution at the propargylic position may increase the rate of catalysis by destabilizing complex **W**. Substitution of **W** at the site labeled R' in Scheme 16 will destabilize the phosphine complex through 'face strain', increasing the phosphine off-rate or impeding the rate of coordination of free tricyclohexylphosphine to the vinyl carbene **S**. Higher degree of substitution has its limits for terminal alkynes as *tert*-butyl acetylene proved less reactive than isopropyl acetylene.

The ethylene–alkyne metatheses are complicated. One might expect ethylene metathesis to proceed faster because ethylene is small and should rapidly bind to the vinyl carbene **S** and increase the rate of turnover. However, the change in rate law for **49** reveals a change in rate-determining step to step II, alkyne binding/cycloaddition. Once **S** is formed it reacts forward faster than step II (Scheme 16). However, from a synthetic chemist's point of view, ethylene metatheses are slower than cross metathesis with 1-alkenes, even at relatively high ethylene pressures (60–100 psig). Though the rate laws are different for ethylene-**49** versus 1-hexene-**49**, when the two reactions are run under similar

concentrations of reactants and catalyst, the ethylene metathesis is slower. The ethylene metathesis depends on a 14-electron $L_nRu=CH_2$ intermediate **U** (R=H). For the second-generation Grubbs methylidene, coordination by tricyclohexylphosphine is strong and the dissociative loss of phosphine is slow and unfavorable [65]. This suggests that the resting state has shifted from vinyl carbene complex **W** (1-hexene metathesis) to methylidene complex **T** (R=H). Using a slender alkyne changes the reaction kinetics. In this case, the kinetics show zero-order dependencies on ethylene and alkyne. Apparently, the more slender alkyne propargyl benzoate **48** produces vinyl carbene intermediate **S** which can be captured by phosphine to give resting state **W** (R=H). This could be true if the rate of phosphine release from the 16-electron complex **W** is rate-limiting. Consistent with this proposal, we found that the Ph₃P version of the Grubbs complex **2** reacted 3.2 times faster (based on initial rates) in the ethylene metathesis of propargyl benzoate. However, this reaction stopped after a few turnovers for reasons that are not completely understood. Further experiments are needed to test these conclusions based on the limited set of rate data.
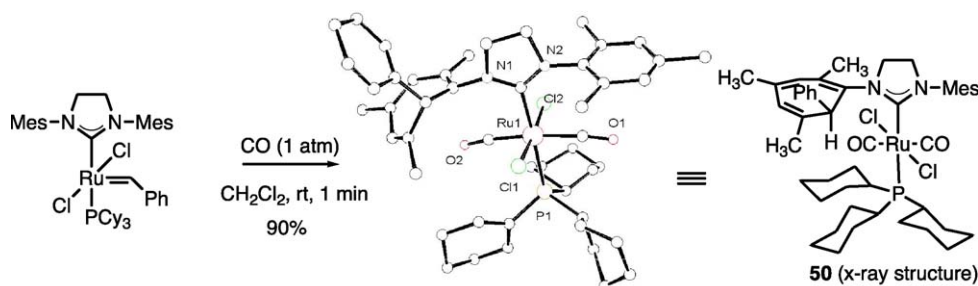
For studying internal alkyne–alkene metatheses, we needed to analyze the reaction using a different analytical technique since no alkyne CH bond is present in internal alkynes. Unfortunately, other monitoring techniques like gc and hplc are not as fast as IR spectroscopy and we had to find a way to rapidly quench aliquots prior to analysis. To do this, we reasoned that
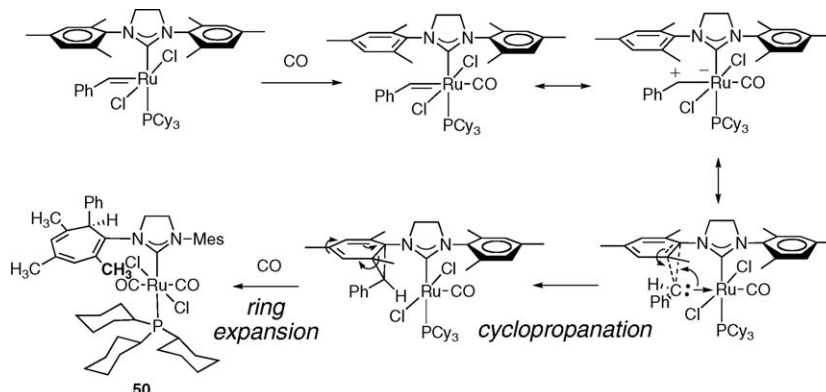
Scheme 17. Possible sequence of events leading to ligand insertion.

any strongly coordinating ligand might be used to plug up open coordination sites. Monitoring rate of 1-hexene–alkyne cross metathesis, we simply perfused carbon monoxide through the solution, which immediately stopped the reaction and caused the solution to turn yellow. For the purposes of stopping an enyne metathesis, this technique works well and is very rapid. We continue to use this to analyze fast metatheses and those that cannot be followed by IR spectroscopy.

The yellow color is due to a new ruthenium complex. We bubbled CO through a solution of the Grubbs second-generation complex and within 1 min a canary yellow color had developed and perfusion was stopped. The yellow solid obtained after solvent removal was crystallized from dichloromethane–decane at $-20\,^\circ$C to afford crystals, mp 143–145 $^\circ$C [18]. Interestingly, the carbon monoxide had promoted an insertion into one of the 2,4,6-trimethylphenyl (mesityl) rings of the dihydroimidazole carbene ligand (Eq. (28)). The net bond insertion represents a ring expansion [66] of the benzene ring and occurs by a two-step process of cyclopropanation/6π-electrocyclization. This is known as the Buchner reaction. The intermolecular Buchner reaction has been observed previously by Noels using Rh(II) carbenes derived from ethyl diazoacetate [67]. The observed insertion is remarkable because of the exclusive regioselectivity in aromatic pi bond cyclopropanation. The coordination of carbon monoxide profoundly alters the reactivity of the metal carbene.

as the ring synthesis by methylene-free enyne metathesis. Investigation of seemingly straightforward tandem ring-closing enyne metathesis in dienyne substrates led to unexpected cyclopropanation reactivity of the Grubbs carbenes. The cyclopropanation behavior was also found in the presence of carbon monoxide, leading to a Buchner reaction in the mesityl group of the dihydroimidazole carbene ligand. We hope these preliminary findings have contributed to a better understanding of this catalytic reaction, will lead to continued advances in new reactions, functional group scope and improved catalytic efficiency.

(28)

Carbon monoxide coordination promotes cyclopropanation reactivity of the Grubbs carbene. One CO binding to ruthenium robs the metal of electron density through backbonding (Scheme 17). This effect deprives the benzylidene carbene of stabilizing electron density and makes it electrophilic, triggering cyclopropanation of the proximate Kekulé double bond of the benzene ring. Once insertion has occurred, an open coordination site is occupied by a second CO ligand and the norcaradiene undergoes electrocyclic ring expansion to give the cycloheptatriene observed. Other ligands like aryl isocyanides also produce the same reaction. We are studying the limits of this reactivity obtainable by other coordinating ligands.

6. Conclusion

This short review of the carbenes in enyne metathesis illustrates how our motivation to improve synthetic efficiency has led to mechanistic insight into the mechanism of enyne metathesis. Mechanistic inquiry, infused with this motivation to make a useful organic reaction, resulted in the design of new reactions such

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