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Review

Ruthenium vinyl carbene intermediates in enyne metathesis

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Contents

Abstract

This review provides an overview of ruthenium vinyl carbene reactivity as it relates to enyne metathesis. Methods for the synthesis of metathesis-active and metathesis-inactive complexes are also summarized. Some of the early hypotheses about vinyl carbene intermediates in enyne metatheses were tested in the arena of synthetic chemistry and subsequently led to mechanistic studies. In these two areas, studies from the author's labs are described. There are still many unresolved questions in enyne metathesis that trace back to vinyl carbene reactivity. Hopefully this review will stimulate further investigation into vinyl carbene reactivity which should further refine our understanding of catalytic enyne metathesis.

Keywords: Enyne metathesis; Vinyl carbene

1. Introduction

Enyne metathesis has emerged as an important synthetic method to construct conjugated dienes. The enyne metathesis joins an alkene and alkyne reactant together to produce

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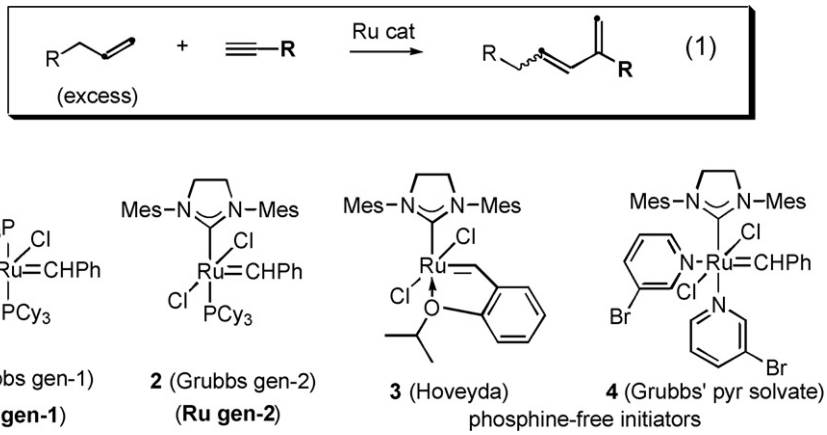
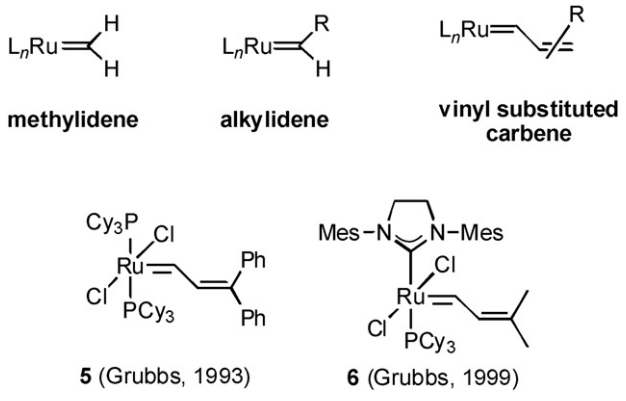


Scheme 1. Enyne metathesis and Grubbs' ruthenium carbene catalysts.

a conjugated 1,3-diene by pi bond reorganization (Eq. (1)). The intermolecular enyne metathesis, or 'cross-metathesis', is depicted in Eq. (1). This catalytic reaction is promoted by Grubbs' ruthenium carbenes, complexes **1**–**4** (Scheme 1). Though other late transition metal cycloisomerizations are known, the Grubbs' carbene-promoted reaction is mechanistically distinct. The high degree of chemoselectivity displayed by carbenes **1**–**4** explains their widespread use in metathesis. The chemoselectivity for alkenes is known as functional group tolerance, a paramount concern for controlling reactivity as needed in complex molecule synthesis. Though many metal complexes will promote intramolecular enyne bond reorganization, the Grubbs carbenes are by far the most useful carbene catalysts in enyne metathesis because they are functional group tolerant and because they promote intermolecular enyne metathesis. Several reviews are available [2–5].

Alkynes react with metal carbenes to produce vinyl carbene intermediates. A major difference between enyne and alkene metathesis is the presence of the alkyne in enyne metathesis. Alkene metathesis involves two types of carbene intermediate: the alkylidene and the methylidene. The alkylidene has the generic structure $L_nRu{=}CHR$. The methylidene has the general structure $L_nRu{=}CH_2$. Reaction of either of these ruthenium carbenes with alkynes produces vinyl carbene complexes of ruthenium (Scheme 2).



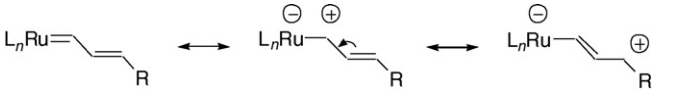
Scheme 2. Vinyl carbenes.

In fact, there are two stable 16-electron ruthenium vinyl carbenes known from Grubbs' group. The neophylidene complex **5** was the first group 8 carbene developed by Grubbs' group [6] and displayed characteristic high functional group tolerance suitable for applications in organic synthesis. This vinyl carbene was employed as a carbene initiator for early applications in alkene and enyne metathesis. The second vinyl carbene complex **6** features the *N*-heterocyclic carbene supporting ligand, which is typical of the 'second generation' Grubbs carbenes [7,8]. When the latter two stable ruthenium vinyl carbene complexes are employed as initiators, they produce alkylidene intermediates. The derived ruthenium alkylidenes are involved in catalysis. A fundamental question relates to the relative reactivity of ruthenium vinyl carbenes as compared to ruthenium alkylidenes. In addition, the substitution on the vinyl group can influence reactivity by steric or electronic effects, and this substitution is not present in an alkylidene.

Vinyl carbenes are unique *intermediates* in enyne metathesis. The presence of these ruthenium carbenes distinguishes enyne metathesis as a catalytic process uniquely different from alkene metathesis. Accordingly, the mechanism of catalysis involves alkene coordination complexes of vinyl carbenes, and vinyl carbene reactivity will influence the rate of catalysis. Though mechanistic details of catalysis are slowly emerging (*vide infra*) fundamental reactivity studies on vinyl carbenes are lacking. The purpose of this review is to survey ruthenium vinyl carbene complexes and relate our understanding of their reactivity to our emerging mechanistic view of catalytic enyne metathesis. It is significant to note that most of the known reactivity of ruthenium vinyl carbenes comes from inferences based on their intermediacy in catalysis. For organic chemists, this means that reactivity is deduced from phenomenology when studying the scope of reaction or influence of reaction parameters. Typically this judgment is focused on product yield rather than reaction rates. For organometallic chemists, the structure of vinyl carbenes has been studied. However, the structural study is often not linked to catalytic activity. It is therefore useful to blend both viewpoints of ruthenium vinyl carbene reactivity from these two bodies of literature to generate a cogent view of their structure and reactivity.

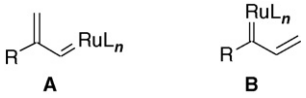
1.1. Vinyl carbenes: an overview

Vinyl substitution has a significant influence on ruthenium carbene reactivity. The vinyl substituent is stabilizing to the electron-deficient carbene center. Presumably the vinyl carbenes are more stable due to conjugation by the vinyl group. Resonance helps to stabilize the electron-deficient carbene carbon, making it less electron-deficient and less reactive than a metal alkylidene (Eq. (2)). This stabilizing effect is thought to modulate the reactivity of vinyl carbenes as compared to the alkylidenes encountered in alkene metathesis. The first report of cross-enyne metathesis by Blechert and co-workers [9] interpreted that a slower enyne metathesis reflected the lower reactivity of the vinyl carbenes.



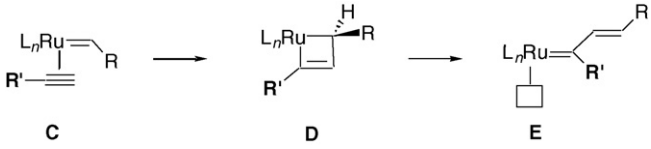
(2)

Ruthenium vinyl carbenes are significant in their own right because they are the intermediates in catalytic enyne metathesis. Little is known about their reactivity as compared to other metal carbenes. How significant is resonance delocalization? How does substitution influence reactivity? The answers to these questions are mechanistically complicated since there are intrinsic structural effects on stability and structural effects on kinetic reactivity. These may work in concert or oppose each other. For instance, the ethylene-alkyne metathesis can produce two possible vinyl carbene intermediates **A** and **B**. Both vinyl carbenes would be stabilized by resonance, however **B** experiences greater stabilization due to the additional alkyl substitution on the carbene carbon. Despite the expected electronic stabilization of carbene **B**, it might be more reactive than **A** due to instability of the cognate 16-electron phosphine complex. As a result, there may be a counteracting interplay between electronic and steric factors in vinyl carbene reactivity.



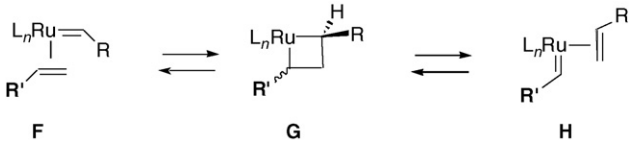
A **B**

In enyne metathesis, vinyl carbenes are generated by alkyne insertion into an alkylidene. The reactive intermediate can be thought of as a ruthenacyclobutene, though it is unclear whether this is a reactive intermediate or a transition state (Eq. (3)). The greater ring strain of cyclobutenes viz. cyclobutanes would place these putative species higher in energy than metallacyclobutanes, the intermediates in alkene metathesis. This hypothesis guided our thinking as we began to study reaction mechanism. First, a high energy intermediate led us to consider that the alkyne insertion step may be rate-determining in some intermolecular enyne metatheses (**C**–**E**). Second, it suggests that alkene metathesis might occur faster than enyne metathesis due to this presumed difference in metallacycle ring strain. The analogous ruthenacyclobutane encountered in transalkylidenation, a fundamental step of alkene metathesis, is illustrated in Eq. (4). Recently, Straub and Lippstreu have calculated the energies of intermediates in enyne metathesis [10]. Their 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 **C** to the vinyl carbene **E** (Eq. (3)).



C **D** **E**

(3)

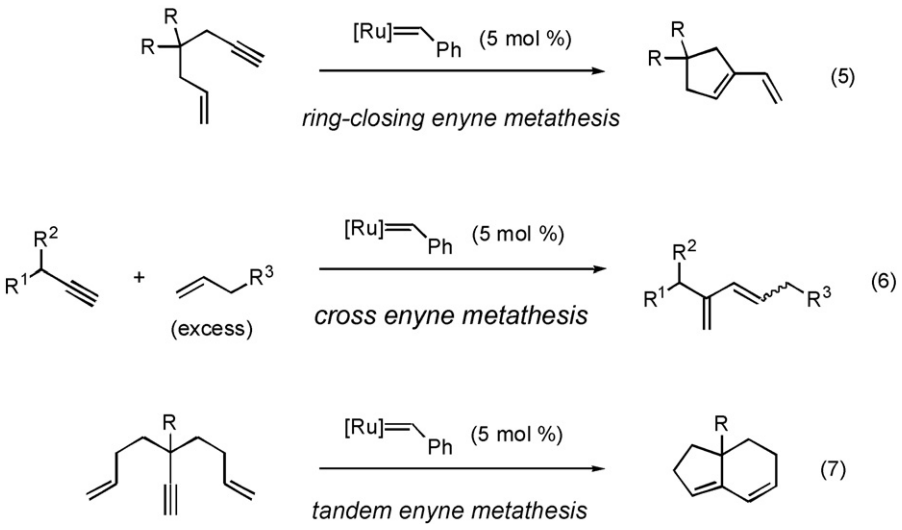


F **G** **H**

(4)

The organic perspective of ruthenium vinyl carbene reactivity is exemplified in the development of metathesis-based synthetic methodologies [3]. In some cases, an interest in mechanism proved useful to reaction development. For example, my research group focused on isomerization studies as a key to achieving high yields in a tandem enyne metathesis for cyclohexadiene ring synthesis. In this case, the reaction development spawned a deeper interest in the enyne metathesis reaction mechanism by identifying shortcomings in the reaction and guided by hypotheses regarding vinyl carbene reactivity. Eventually, this led to our interest in conducting kinetic and mechanistic studies of enyne metathesis. The original studies focused on the behavior of vinyl carbene intermediates (by studying equilibration and electronic effects). We then pursued mechanistic studies in a collaborative project with Jerome Keister at Buffalo, and have begun to develop a mechanistic picture of catalysis. With this knowledge, my research group has returned to developing new enyne metathesis methodology and has employed mechanistic knowledge to design a useful cyclodiene synthesis based on vinyl carbene equilibration. A goal of metathesis research is high catalyst turnover in the typical functional group-rich environment for which the Grubbs carbenes are most useful. Mechanistic information will lead to a better understanding of substrate limitations and catalyst decomposition pathways. Moreover, carbene catalyst decomposition may be unique in enyne metathesis since it may emanate from vinyl carbene intermediates.

Another useful perspective of vinyl carbene reactivity is structural. This is one facet of the organometallic perspective of vinyl carbenes, and it is complementary to the reactivity picture discerned through organic transformations. For this part of this review, we will focus on metal carbenes that have been characterized structurally, or where definitive proof of structure is reported. This perspective is not meant as a comprehensive treatment, and the reader will be directed to pertinent reviews, where appropriate. The review will also survey the major organometallic synthetic methods for the preparation of ruthenium vinyl



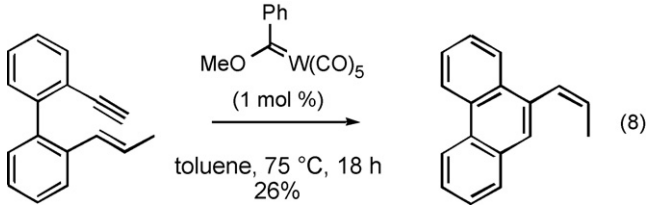
Scheme 3. Three types of enyne metathesis.

carbenes. Through this survey, some of the general properties of these carbene complexes will become apparent.

1.2. Enyne metathesis

Like alkene metathesis, enyne metathesis has rapidly developed from an unusual ring forming reaction using cumbersome early transition metal carbene complexes to a mild and concise method for the synthesis of conjugated cyclic and acyclic dienes. The evolution of the reaction in the field of organic synthesis closely paralleled catalyst development, culminating in use of the functional group tolerant ruthenium carbenes, which proved compatible with a wide range of organic functional groups, including carbonyls, hydroxyl groups, and ethers. The two major classifications of enyne metathesis reactivity are illustrated in Eqs. (5) and (6) of Scheme 3. A third application includes tandem metathesis processes linked together (Eq. (7)). In the following paragraphs, these will be briefly introduced. The discussion is not meant to be comprehensive; for this, the reader is directed towards reviews [3–5].

Initial studies in enyne metathesis used the early transition metal carbenes to achieve ring formation. The first report of enyne metathesis illustrated a novel ring synthesis by carbene-promoted enyne bond reorganization. Katz and Sivavec reported catalytic enyne metathesis using a tungsten Fischer carbene complex (Scheme 4) [11].

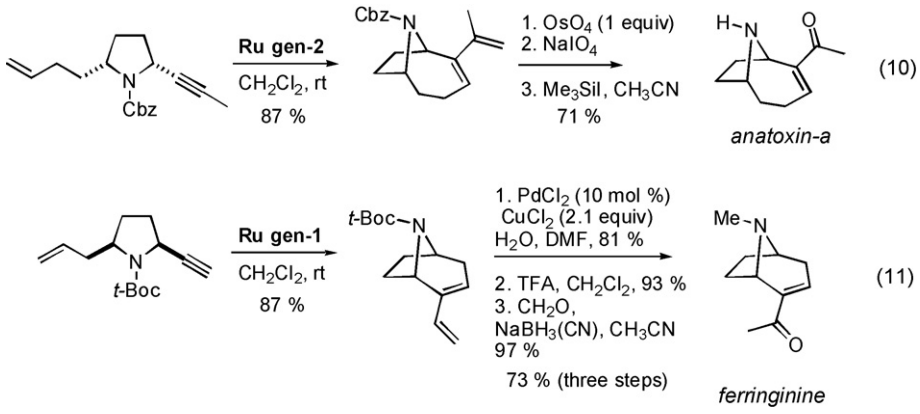


Scheme 4. Katz and Sivavec's seminal ring-closing enyne metathesis [11].

This example was ahead of its time achieving a catalytic reaction using an early transition metal Fischer carbene. It set the framework for many future applications of enyne metathesis. However, it took almost a decade for the intramolecular reaction to be adopted by synthetic chemists. This example represents a typical use of enyne metathesis by synthetic chemists: the ring-closing enyne metathesis (RCEYM) used to form a ring. By today's standards, this carbene complex is not considered functional group tolerant with enyne substrates bearing heteroatom functionality [12].

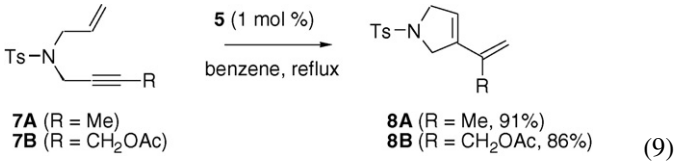
Shortly after the seminal report of catalytic ring-closing enyne metathesis, chromium Fischer carbenes were employed by Mori and co-workers to form nitrogen heterocycles [13–15]. Though these reactions were substoichiometric or even stoichiometric in the chromium complexes, this paper elevated an interesting organometallic reaction to one that might prove useful in organic synthesis, where the presence of functional groups places great demands on chemoselection. Mori's papers stimulated interest in the reaction since heterofunctionality could be handled. Though this work was limited to ring-closing applications and lacked the functional group range now expected in metathesis chemistry, it offered a rapid method for heterocycle synthesis.

The limitations of the early transition metal carbenes were quickly forgotten as the Grubbs carbenes were utilized in enyne metathesis. After describing heterocycle synthesis using early transition metal Fischer carbenes, Mori and Kinoshita employed first Grubbs carbene, the vinyl carbene complex **5** for ring-closing metathesis (Eq. (9)) [16]. This accentuated the adaptability of the catalytic reaction to molecules with organic functional groups, which was apparent from Grubbs' work in the development of this catalyst [6,17,18]. In fact, Mori's report is the first methodology study of ring-closing enyne metathesis (RCEYM) showing a range of enynes that gave the metathesis. This report along with the leading efforts by Grubbs with ruthenium carbenes in alkene metathesis [18–20] led to widespread interest by synthetic chemists. Many applications followed as



Scheme 5. Bicyclization by ring-closing enyne metathesis [21,22].

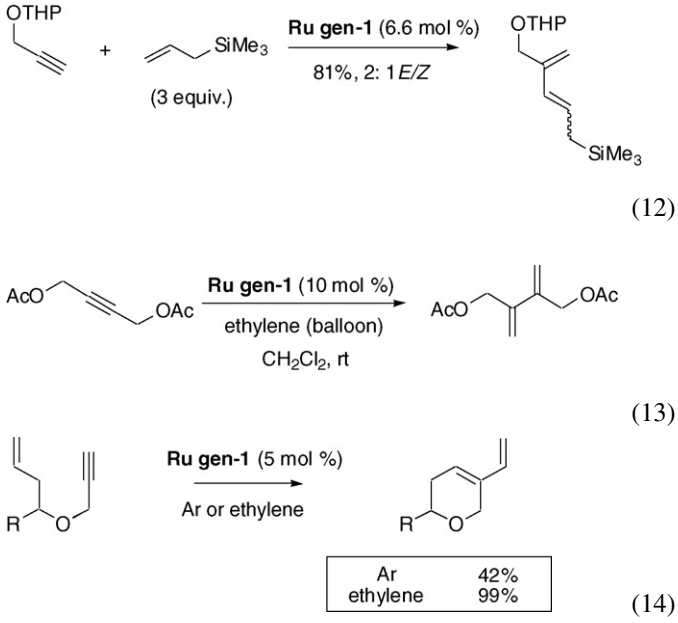
synthetic chemists recognized the RCEYM as a powerful ring synthesis method. Recent applications of RCEYM can be found in alkaloid synthesis, where the structural complexity and the presence of nitrogen functionality are considered to be a challenge for carbene chemistry. Two applications are shown in Scheme 5 [21,22].



1.2.1. Cross-metathesis

A significant development occurred in 1997 with the discovery of intermolecular enyne metathesis. Blechert and co-workers demonstrated an effective intermolecular 'cross' enyne metathesis using the first generation Grubbs initiator (Eq. (12)) [9]. This stands as a landmark paper because it demonstrated that the alkene and alkyne could be used to make linear, acyclic conjugated dienes, and that the metal catalyst did not need a 'pre-organized' 1,ω-enyne substrate (as used in ring-closing enyne metathesis applications). Moreover, this study defined vinyl carbenes as the likely intermediates and this served to distinguish enyne metathesis from alkene metathesis. Blechert suggested that vinyl carbenes were the most stable carbene intermediate, and that they accumulated in catalysis. This observation pinpoints vinyl carbene turnover as the slow step of catalysis using the first generation Grubbs carbenes of general formula $(Cy_3P)_2Cl_2Ru{=}CHR$.

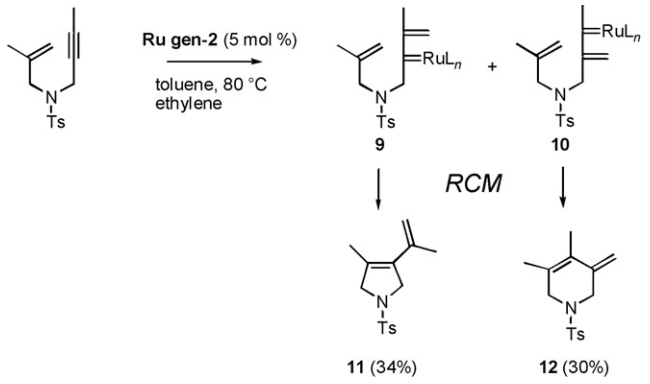
Contemporaneously, Mori and co-workers reported an ethylene-alkyne metathesis used to prepare 2,3-disubstituted-1,3-butadienes (Eq. (13)) [23]. Internal alkynes were used predominantly in this study. This method also utilized the first generation Grubbs' carbene as initiator for this cross-metathesis. Subsequently, Mori's group went on to find that ethylene could be used to promote ring-closing enyne metathesis (Eq. (14)) [24]. This became known as "Mori's conditions". The reasons for the 'ethylene effect' were mechanistically unclear, but the procedure became widely used in the synthetic literature (the literature includes many examples of beneficial effect of ethylene and other cases where ethylene has no helpful effect on the reaction [3]).



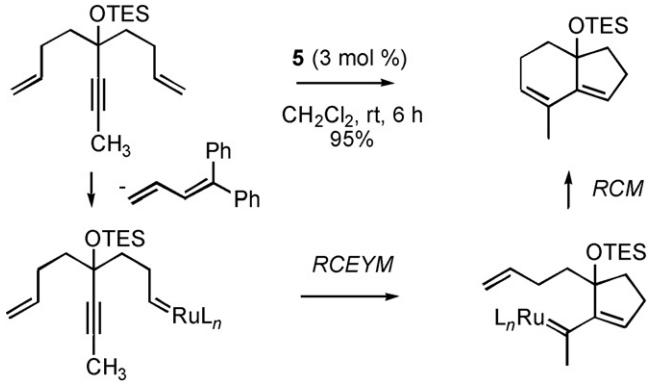
In early reports on the intramolecular, ring-closing metathesis, internal alkynes were used with great success [16]. After the Blechert report, synthetic applications turned to intermolecular metathesis, and here the benefits of internal alkynes were overshadowed by the problem of poor regiocontrol. In the intermolecular enyne metathesis, the lack of a constraining device (i.e. tether), meant that metal carbene addition could occur to give either of the regioisomeric vinyl carbenes. Mori observed this difficulty in RCM promoted by ruthenium methylidenes [25]. In this instance, the intermolecular reaction between $L_nRu{=}CH_2$ and the internal alkyne produce regioisomeric vinyl carbenes **9** and **10** which led to two different products (Scheme 6).

1.2.2. Tandem metathesis

The classic example of a tandem reaction is the ring-closing/ring-closing metathesis used to form multiple rings at once. Grubbs illustrated the effectiveness of this approach for carbocycle synthesis (Scheme 7) [26]. These transformations



Scheme 6. Poor regiocontrol in internal alkynes [25].

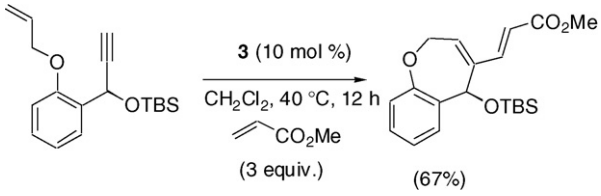


Scheme 7. Tandem ring-closing metathesis (Grubbs) [26].

are triggered by alkylidenation of the most reactive alkene followed by ring-closing enyne metathesis, then ring-closing alkene–alkene metathesis.

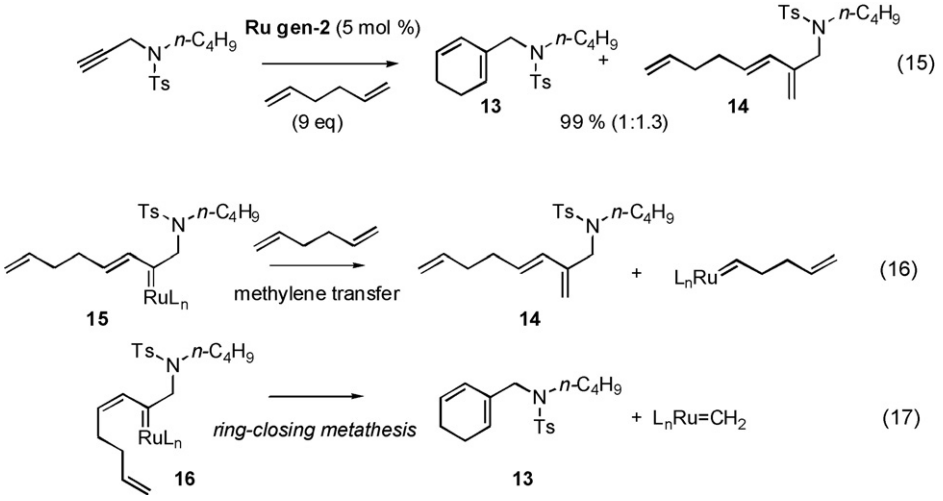
The first example of a tandem enyne metathesis triggered by a cross-metathesis was developed for ring synthesis [27]. This reaction is triggered by a cross-enyne metathesis and followed by a ring-closing metathesis. The two metathesis reactions occur *in situ* to provide the 1,3-cyclohexadiene product, along with the undesired triene. This reaction involves two isomeric vinyl carbene intermediates **15** and **16**, which proceed to products by either a ring-closing metathesis or intermolecular methylene transfer (Scheme 8). We will return to the possibility of manipulating these intermediate vinyl carbenes as a means to increase the 1,3-cyclohexadiene product yield. Controlling the stereochemical integrity of vinyl carbene intermediates represents an approach to solving stereoselectivity in cross-metathesis.

A modern version of the ring-closing enyne metathesis joins it with a cross-metathesis. In this case, the RCM step is followed by a cross-metathesis. The premier example can be found in the work of Royer (Eq. (18)) [28], and this has been utilized in a number of recent studies. A nice application of the tandem RCEYM-CM can be found in a recent natural product synthesis of 8-*epi*-xanthatin (Scheme 9, panel a) [29]. This is regarded as a tandem reaction since two distinct metathesis reactions are operative. In the second example, Morken and Evans used a ring-closing metathesis tactically to generate the ester enolate, then introduce the enone functionality in a second cross-metathesis (Scheme 9, panel b) [30]. This example illustrates a versatile aspect of the tandem metathesis, that they can be disengaged if desired.

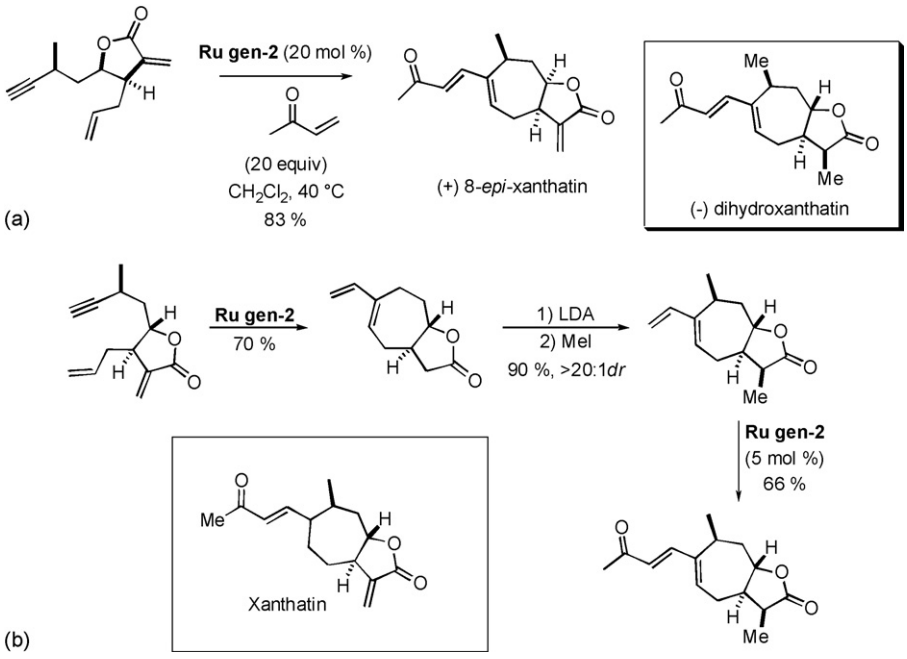


(18)

Conjugated dienes are useful building blocks in organic synthesis. Dienes are typically used in Diels–Alder cycloaddition to form cycloadducts. The Diels–Alder reaction is a powerful method used by synthetic chemists in natural product synthesis [31]. Ready access to a variety of dienes, coupled with powerful transformations like Diels–Alder cycloaddition, leads to rapid and economical synthesis of complex products. For example, in the cyclohexadiene ring synthesis, a direct thermal cycloaddition afforded cycloadducts in good yield over two steps (Eq. (19)) [27]. Prior to enyne metathesis, dienes were more difficult to synthesize, requiring multistep synthesis. Enyne metathesis

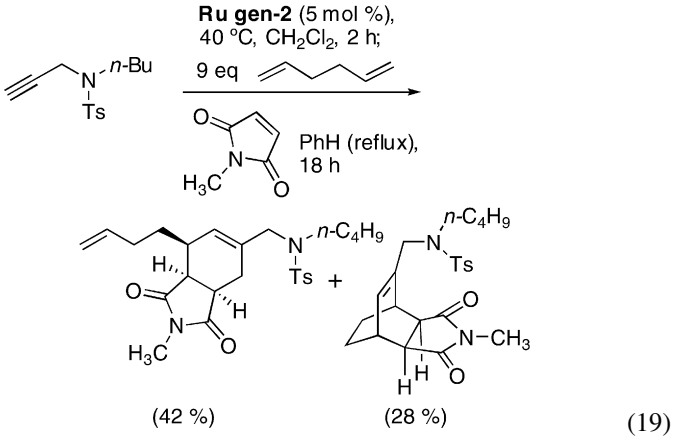


Scheme 8. Tandem enyne metathesis for 1,3-cyclohexadiene synthesis [27].



Scheme 9. Tandem RCEYM-CM in synthesis.

is preferable to multistep synthesis since the process is efficient and since the alkene and alkyne are readily accessible. Though there is a huge potential, the enyne metathesis suffers from two difficulties: the diene substitution pattern is limited and the cross-metathesis cannot be used to make *Z*-alkenes [32].

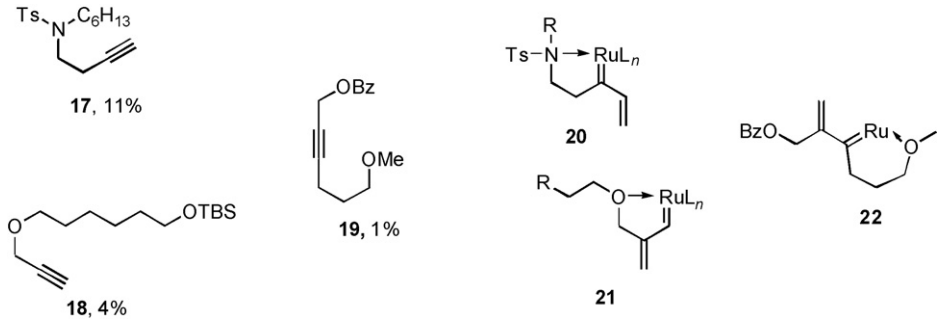


(19)

Though the enyne metathesis generally displays functional group tolerance, it is surprising that this is not universally true and that some enyne metatheses inexplicably do not work. Synthetic organic chemists must keep in mind that metathesis is a *catalytic process*. In a nutshell, there is a lot that can go wrong. As a litmus test for 'maturity' in a catalytic reaction, can it be used predictably in a novel setting? As a corollary, if the reaction fails, is it due to an obviously deleterious interaction? For enyne metathesis, it is not possible to completely answer these questions. We suggest that this can be remedied by detailed study of reaction mechanism. Catalyst decomposition by ill-defined pathways is one of the biggest concerns, and these putative pathways are largely not understood. Attempting to push a catalytic organic reaction to completion by simple heating is often counterproductive in metathesis. Heating serves to accelerate competitive bimolecular processes including decomposition. Catalyst decomposition destroys the carbene and may lead to new non-carbenic ruthenium species, which may be elusive but affect the reaction. For example, the production of ruthenium hydrides *in situ* can promote olefin isomerization [33]. A nice review has recently appeared [34,35]. It should be noted here that the hydride reactivity has been used to advantage to achieve tandem organic reactions; the reader is directed to the work of Snapper and co-workers [36] and Schmidt [37,38].

1.2.3. Chelation

Functional group interactions are most harmful to catalysis in substrates capable of chelation. In the earliest period of metathesis research, chelation by organic functional groups was recognized as a potential problem [39,40]. In enyne metathesis, alkynes **17**–**19** underwent ethylene metathesis in poor yields, ostensibly due to chelation [41]. Chelation in the vinyl carbene complexes is thought to occur via structures such as **20**–**22**. However, limited evidence for chelation means that there is limited structural information available in order to predict which motifs will lead to chelation. Chelation may have a kinetic outcome, simply slowing catalysis. In this instance, chelation does not sound the death knell for catalysis. In fact, the Hoveyda complex **3** is also a chelated carbene, but it is stable and initiates by dissociation of the chelated ether [42,43]. Alternatively, chelation may result in carbene decomposition. This would be far more problematic, yet decomposition occurring via chelates in the second generation carbene has not been directly observed. This is required in order to probe the limits of functional group



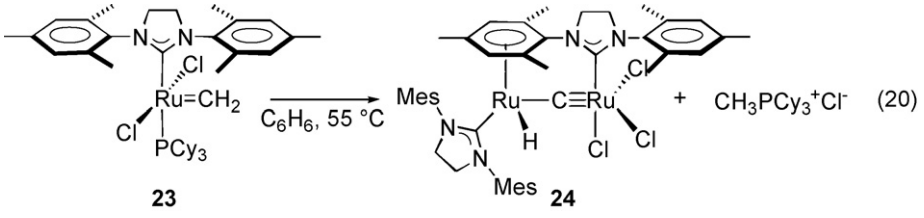
Scheme 10. Chelation.

tolerance in the most demanding situations to be encountered in organic synthesis (Scheme 10).

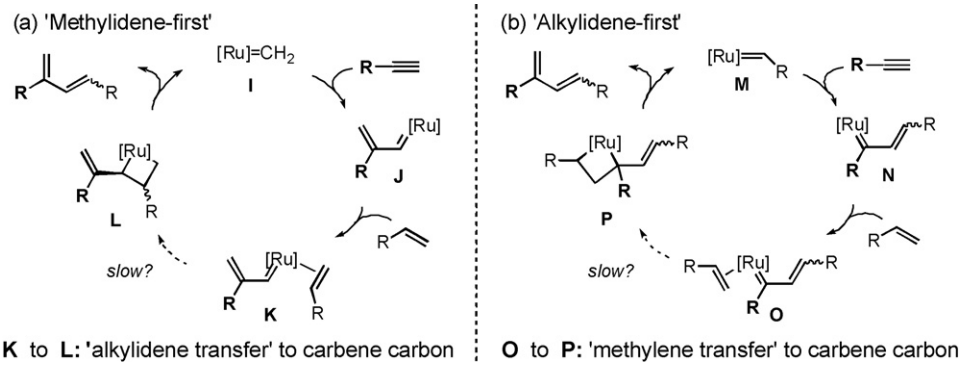
1.3. Mechanism: an introduction

The rapid pace of enyne metathesis applied to synthesis outstripped mechanistic interpretation. As a result, the analogy to alkene metathesis was used as the framework to understand the basic reactivity in enyne metathesis. Though useful, this was not entirely satisfactory since alkene metathesis does not involve alkyne addition steps or involve vinyl carbene intermediates. Yet the heritage of enyne metathesis lies with alkene metathesis and the Grubbs' carbenes, and some of the steps of enyne metathesis are the same as those encountered in alkene metathesis. Alkene metathesis proceeds via an initiation process, referred to as transalkylidenation. In the catalyst initiation step, the Grubbs' benzylidene is transformed into a reactive alkylidene (Eq. (4)) [44]. The alkylidene formed in the process enters into catalysis through alkene binding. In this next step, the alkene metathesis product is produced along with $L_nRu{=}CH_2$, a ruthenium methylidene. The methylidene reacts with 1-alkene to generate alkylidene and liberate ethylene. This process is also defined as a transalkylidenation process. Eventually, the loss of ethylene from the metal coordination sphere results in entropic driving force to give the cross-alkene metathesis product. A full summary of Grubbs' mechanistic work [45–47] and a selectivity model for alkene metathesis [48] are available. The methylidene plays a critical role in alkene metathesis by linking catalytic cycles. It is also highly reactive and leads to side reactions. The $L_nRu{=}CH_2$ may add phosphine to produce an inactive complex. Moreover, Grubbs and co-workers showed that the methylidene undergoes decomposition by addition of tricyclohexylphosphine to give the dinuclear arene complex **24** (Scheme 11) [49]. Since the methylidene is also a potential player in ethylene-alkyne metathesis, its reactivity is also relevant to enyne metathesis.

There are two proposed reaction mechanisms for the intermolecular enyne metathesis (Scheme 12). One mechanism operates by initial reaction of a ruthenium methylidene with the alkyne and the second invokes reaction of a ruthenium alkylidene with the alkyne. The principal differences between the two mechanisms are regiochemistry of metal carbene addition and



Scheme 11. Decomposition of the ruthenium methylidene intermediate (Grubbs) [49].

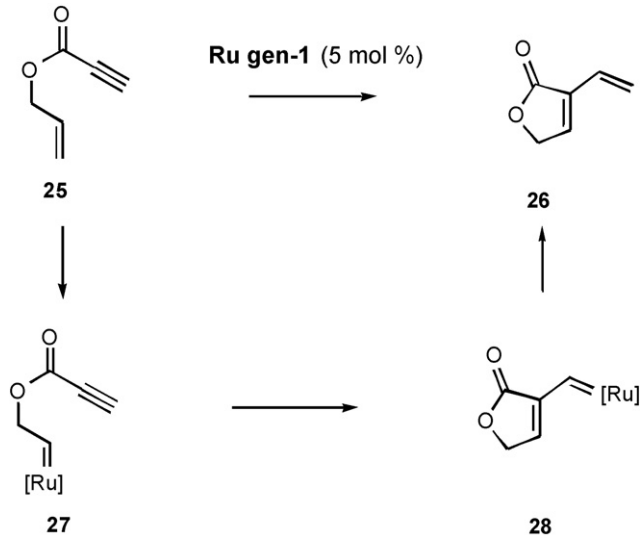


Scheme 12. Two possible mechanisms of enyne metathesis.

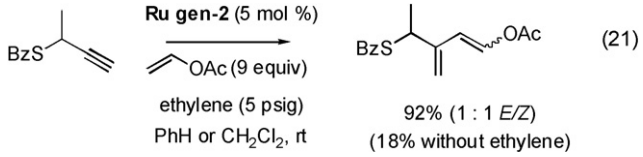
the substitution pattern on the produced vinyl carbene intermediates **J** and **N**.

The 'methylidene-first' mechanism (panel a) was proposed in two early studies that drew parallels with the $L_nRu{=}CH_2$ intermediate in alkene metathesis. These studies were influential in shaping mechanistic thought in enyne metathesis research. The 'methylidene-first' proposal invokes the ruthenium methylidene **I**, $L_nRu{=}CH_2$ which reacts with the alkyne by attaching the more hindered metal fragment to the terminal position of the alkyne. This would produce vinyl carbene **J**. The observation of a slower enyne metathesis relative to alkene metathesis led to the suggestion that the vinyl carbene turnover step was the slow step in catalysis (**J** → **K** → **L**). The second, 'alkylidene-first' mechanism involves a ruthenium alkylidene intermediate, the reactive player that reacts with the alkyne. The resulting vinyl carbene **N** will then react slowly with alkene in the turnover step. Like the methylidene-first proposal, this mechanism considers the vinyl carbene reaction with the alkene to be the slow step. The respective vinyl carbenes **J** and **N** have different substitution patterns and should have different reactivity profiles. Both mechanisms lead to the same conjugated dienes bearing the 1,3-disubstitution pattern.

Two early studies suggested an 'alkylidene-first' reaction mechanism based on NMR studies. In a RCEYM, Hoye recognized that there were two possibilities: reaction of $[Ru]{=}CH_2$ with the alkyne directly, or initial transalkylidenation to generate carbene **27** (Scheme 13) [50]. If the latter pathway is followed, then vinyl carbene **28** would accumulate. Turnover to the diene product requires a methylene source provided from another molecule of enyne. The alkene would provide the "CH_2" group, effecting a methylene transfer, giving the product and the alkylidene **27**. ^{1}H NMR experiments showed the buildup of an alkylidene concomitant with Ru gen-1 initiation, as evidenced by the loss of benzylidene. In a second study of ring-closing enyne metathesis, Kozmin and co-workers suggested that 'alkylidene-first' mechanism was operative [51]. These authors examined the fragments 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



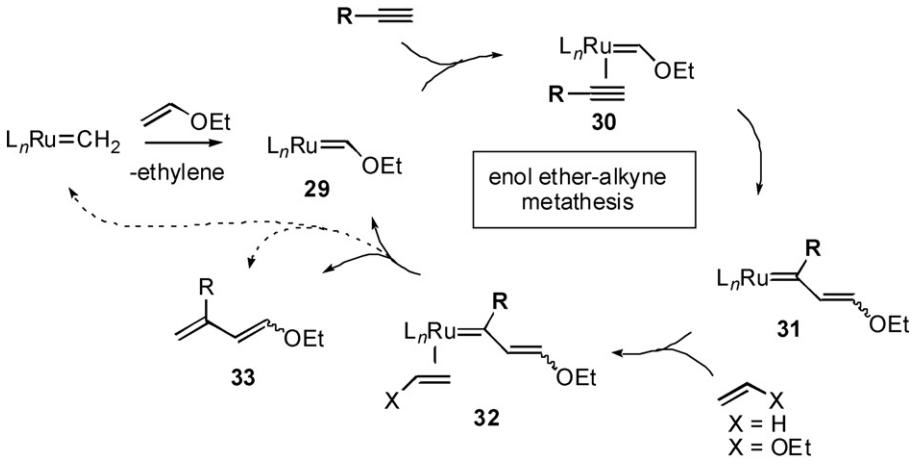
Scheme 13. 'Alkylidenation-first' proposal.



Scheme 14. Ethylene helping effect in intermolecular enyne metathesis (Diver and co-workers) [52].

the reaction rate between a $[Ru]{=}CH_2$ and alkynes. These studies were performed with the first and second generation Grubbs carbene complex, and arrived at the same conclusion in support of an alkylidene-first mechanism.

In the Hoye study, the authors found that increased enyne concentration (to 0.1 M) gave an efficient ring-closing metathesis [50]. This is counterintuitive since high dilution is employed in bifunctional substrates to limit oligomerization. This is the first example showing that solution concentration of the enyne affects the rate of metathesis. Subsequently, Diver and



Scheme 15. Vinyl carbene turnover.

co-workers used a high concentration of ethylene to assist the rate of enol ether–alkyne cross-metathesis (Eq. (21)) [52]. In this case, certain alkynes did not react efficiently without ethylene (Scheme 14).

Thiol ester functionality proved difficult, giving low yields without auxiliary ethylene. Since ethylene was not involved as a reactant, but helped the metathesis, we termed the reaction a "cometathesis'. In their study, Diver et al. proposed that the vinyl carbene underwent turnover by auxiliary alkene, ethylene (Scheme 15). This hypothesis explained why high concentrations of enol ether also produced the rate acceleration observed. This provided a useful expansion of alkene scope to the enyne metathesis (via ruthenium Fischer carbenes **29** and their vinylogues **31**) and suggested that ethylene played a kinetic role. This is the origin of the ethylene effect (Mori's conditions), and explains why an auxiliary alkene would actually speed up catalysis. Recently, an elegant mechanistic study was conducted by Lloyd-Jones et al. [53]. In this investigation, the authors showed that relabeled 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.

2. Vinyl carbene complexes of ruthenium

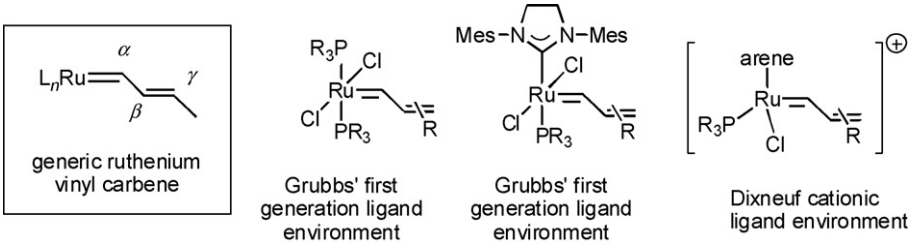
2.1. Introduction

We have already seen two ruthenium vinyl carbene complexes that have been used in alkene and enyne metathesis. In this section, ruthenium vinyl carbene complexes will be surveyed. The organization is based on method of synthesis and is not meant to be an historical account. Not all of the complexes are reported to have metathesis reactivity. There are only two cases where the vinyl carbene reactivity was the focus of the study. These will be discussed also in this section. In reference to the vinyl carbene fragment, the carbene carbon will be denoted as C_α with the next, attached carbon as C_β and so on (Scheme 16). Last, the Grubbs-type carbenes will be noted as 'first generation ligand environment' for carbene complexes of general formula $(Cy_3P)_2Cl_2Ru{=}CHR$ [17,19,20]; 'second generation ligand environment' [54] will be used to describe carbene complexes of general formula $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHR$, where H_2IMes is the 1,3-bismesityl-dihydroimidazole carbene ligand.

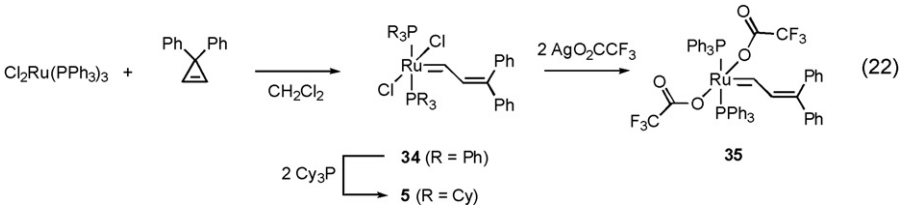
Grubbs described the first synthesis of a well-defined group 8 metal carbene [6]. This complex was actually a vinyl carbene. The Grubbs group found that direct diazo decomposition of diphenyl diazomethane failed. Instead, an oxidative addition to 3,3-diphenylcyclopropene was used to access the metal carbene **34** with loss of triphenylphosphine (Eq. (22)). The carbene complex shows a characteristic pseudo quartet (overlapping triplets) at δ 17.94 ppm for H_α and a doublet at 8.7 ppm for H_β. The ^{13}C showed a downfield resonance at δ 288.9 assigned to the carbene carbon. The X-ray crystal structure for the carbene complex **34** was reported [6]. Further transformation of the triphenylphosphine complex into other vinyl carbenes was possible. Exchange with Cy_3P produced complex **5**. The chlorides were exchanged with trifluoroacetates using 2 equiv. $AgOCOCF_3$, giving complex **35** [33] (Scheme 17).

The reactivity of the vinyl carbene complexes in alkene metathesis varied. For example, vinyl carbene **34** reacted with strained alkenes including norbornene, (methylene)cyclopropene and (methylene)cyclobutane, but not with acyclic, unstrained alkenes (Eq. (23)). However, the bistrifluoroacetate complex **35** proved reactive with unstrained alkenes. In this study, reactions with heteroatom-substituted alkenes produced the corresponding Fischer carbene complexes in good yields (Eq. (24)) (Scheme 18).

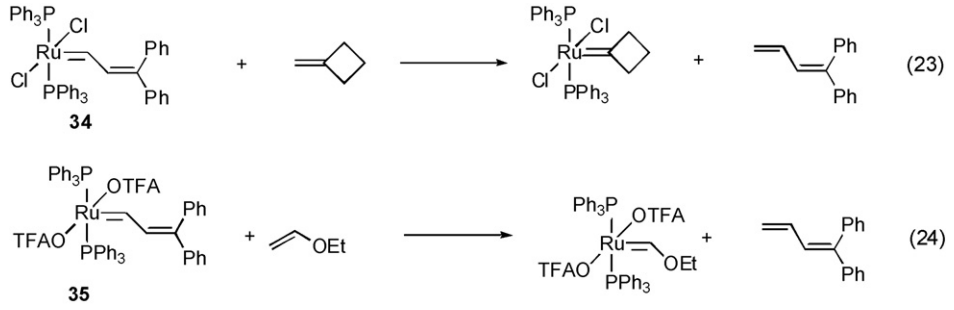
The reaction of complex **35** with vinyl imidazole produced a bisimidazole coordination complex **36** that maintained the vinyl carbene fragment (Scheme 19) [33]. Grubbs noted that an open coordination site was located *trans* to the vinyl carbene. Exposure to 2 equiv. vinyl imidazole produced a coordination complex **37** displaying a carbene proton at δ 19.65 as an apparent



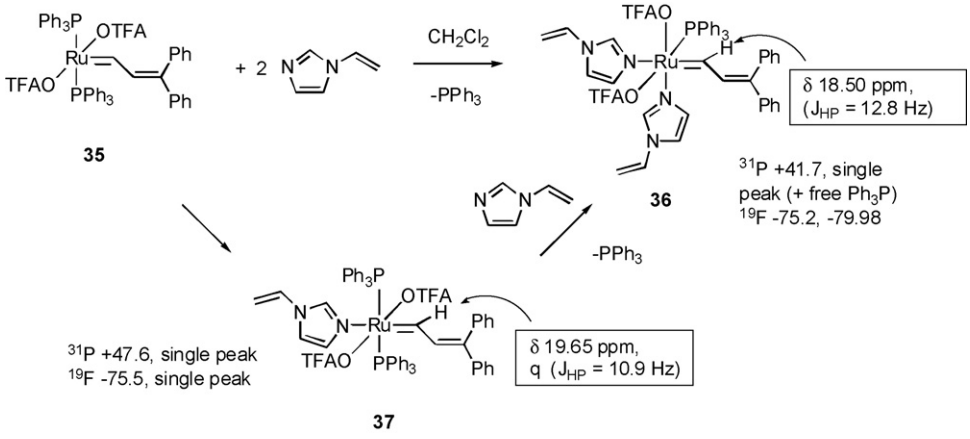
Scheme 16. Vinyl carbene ligand environments.



Scheme 17. Cyclopropene synthesis of ruthenium vinyl carbene (Grubbs and co-workers) [6,33].



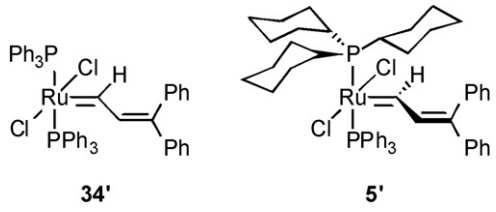
Scheme 18. Regiochemistry of vinyl carbene reactions with alkenes [33].



Scheme 19. Vinylimidazole complexation (Grubbs and co-workers) [33].

quartet. Continued heating resulted in ligand exchange to produce the bisimidazole coordination complex **36**. The complex **36** displayed a carbene resonance at 18.50 ppm (J_{HP} = 12.8 Hz) and a single coordinated phosphine at +41.7. Free triphenylphosphine was also observed by ^{31}P NMR. The unsymmetrical disposition of the trifluoroacetate ligands was apparent from two peaks in the ^{19}F NMR, appearing at −75.2 and −79.9 ppm. Interestingly, the green bisimidazole solvate **36** did not catalyze the ROMP of norbornene.

Last, the conformation of the vinyl carbene moiety varies in complexes **34′**, **5′**. In the X-ray crystal structure of the triphenylphosphine complex, the vinyl carbene plane is almost coplanar with the Ru–P bonds (Scheme 20). In contrast, the tricyclohexylphosphine complex **5′** has the mean plane of the vinyl carbene almost perpendicular to the Ru–P bonds. Though crystal packing forces may play a role, the steric bulk of the tricyclohexylphosphine ligand influences the conformation of the vinyl carbene.

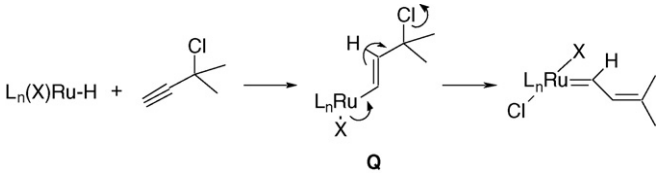


Scheme 20. Conformation of vinyl carbene fragment.

2.2. Synthesis of ruthenium vinyl carbene complexes

2.2.1. Via metal hydrides

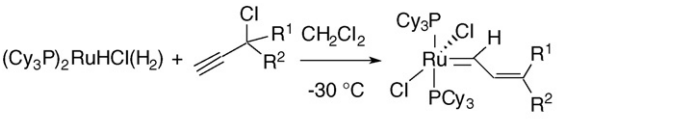
Vinyl carbenes are also commonly synthesized via metal hydrides. The organic precursor to the vinyl carbene fragment is a propargylic halide (Eq. (25)). This approach is versatile with respect to the metal ligand environment that can be produced. The ligand environment is provided from the ruthenium hydride precursor. In this section, vinyl carbenes of both the first- and the second-generation ligand environments are synthesized by this method. When coordinating solvents are used, octahedral complexes may result. The transformation most likely occurs by a migratory insertion of the alkyne into the ruthenium hydride bond, followed by vinyligous elimination of the chloride. Ultimately the chloride ends up on the metal center.



(25)

Grubbs used the trihydride to form the first generation vinyl carbene complexes **38** (Eq. (26)) [55]. The air-sensitive hydride was synthesized from $[RuCl_2(COD)]_n$, PCy_3, H_2 in triethylamine and *sec*-butanol. Formation of the vinyl carbenes

occurred at low temperature in CH_2Cl_2 or in PhH at ambient temperature. In these reactions, a Ru(IV) by-product, assumed to be $RuH_2Cl_2(PCy_3)_2$, was also produced in varying amounts; however, its formation could be dramatically reduced by conducting the reaction in toluene. For instance, **38C** was produced as a 0.8:1.0 mixture with the Ru(IV) coproduct. The by-product was reduced to a 30:1 ratio when the reaction was conducted in PhH. Complex **38C** displayed the characteristic carbene resonances at δ 19.26 d, J_{HH} = 11.7 Hz and the ^{13}C at 288.4 ppm in the ^{13}C spectrum (d, J_{CP} = 9.6 Hz).



38A (R^1, R^2 = H,H, 44%;PhH: 97%)
38B (R^1, R^2 = H,Me, 89%; PhH: 97%)
38C (R^1, R^2 = Me, Me, 95%)
38D (R^1, R^2 = -$(CH_2)_5$-, quant.)
38E (R^1, R^2 = H, Ph, quant)

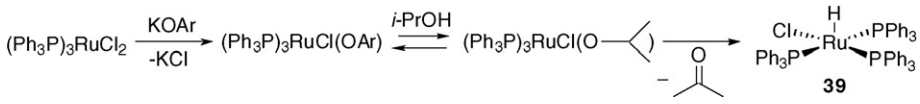
(26)

The suggested mechanism for vinyl carbene formation is similar to that shown in Eq. (25). Regioselective hydrometallation of the alkyne gives an alkenyl intermediate **Q** that experiences γ-chloride extrusion to access the vinyl carbene after chloride migrates to the metal center. This synthesis also works with vinyl chloride, to give alkylidenes, but the latter is limited by the formation of by-products. Thus it appears that this hydride-based synthesis is ideally suited for vinyl carbene synthesis.

The hydride displacement method produces ruthenium vinyl carbenes from the Wilkinson hydride [56]. Depending on the solvent used, either the hexacoordinate or pentacoordinate complex is obtained (Scheme 21). The Wilkinson hydride reacted with halide **40** to give complex **41** in 75% yield (Eq. (27)). The carbene proton appeared at δ 18.10 ppm as a dd with $^3J_{HH} = {}^3J_{HP}$ = 9.8 Hz. The ^{13}C spectrum showed the characteristically downfield carbene carbon at δ 291.1. In a solvent mixture of CH_2Cl_2 and CH_3CN, an acetonitrile solvate **42** is obtained as a green solid after precipitation from minimal CH_2Cl_2 containing 10 volumes of Et_2O (Eq. (28)). The complex **42** displayed the expected downfield carbene resonances in both the proton and carbon NMR. A weak ν_{CN} stretch is identified in the IR at 2281 cm^{-1}. The complex **42** was taken forward to a trisacetonitrile cationic complex in reaction with Me_3SiOTf, but solid state structural characterization was precluded by disorder in the crystal.

Though reactivity was not explored in this paper, complex **41** is the lower homolog of Grubbs' complex **34**, and should have similar metathesis reactivity (ROMP of strained alkenes). To the best of our knowledge, these first generation triphenylphosphine complexes have not been used in enyne metathesis.

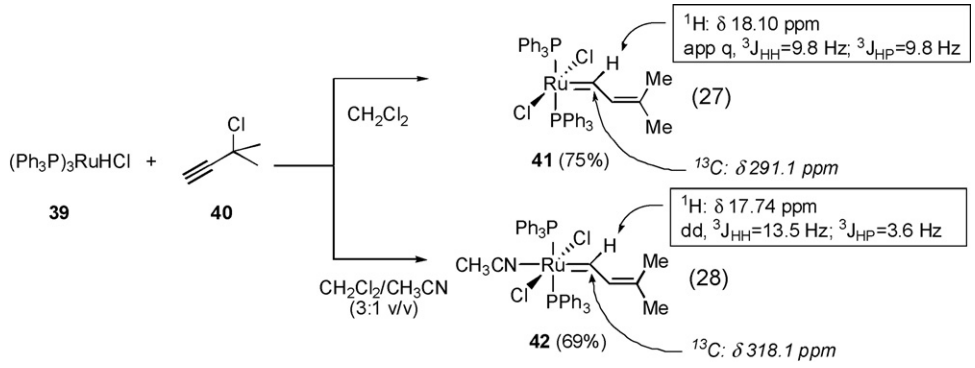
The synthesis of metathesis-active ruthenium vinyl carbenes can be accomplished by the hydride method by a one-pot synthesis. Fogg reported a convenient synthesis of the hydride **39** from $(Ph_3P)_3RuCl_2$ by salt metathesis with KOAr, followed by β-hydride elimination of isopropanol (Eq. (29)) [57].



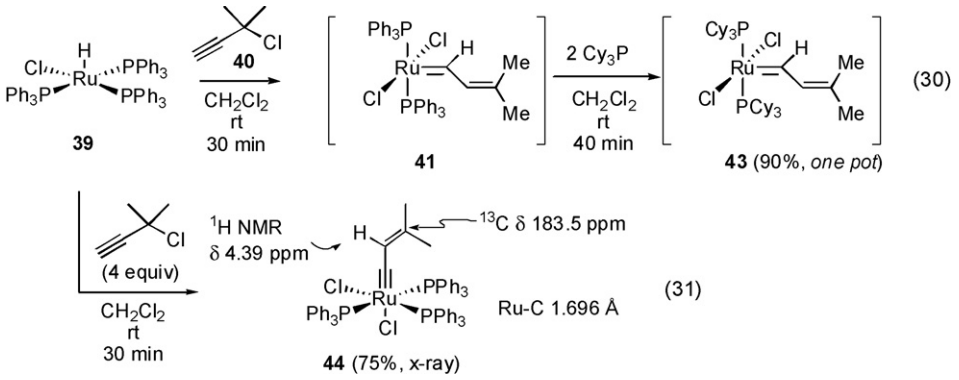
(29)

For the synthesis of the vinyl carbene complex, the hydride **39** reacts with propargyl chloride **40** (analogous to that described) to form the triphenylphosphine complex **41**, which can be directly subjected to ligand exchange *in situ* to provide the more robust complex **43** (Scheme 22). During the process, the hydride resonance at δ −17.8 ppm (d, $^2J_{HP}$ = 25.8 Hz) was replaced by a resonance at δ 18.20 ppm (app t, J = 9.4 Hz), corresponding to the vinyl carbene complex **41**. The authors also showed that use of excess propargyl chloride produced a novel ruthenium(IV) vinyl carbyne **44** in high chemical yield (Eq. (31)) [57]. In this one-pot synthesis of vinyl carbenes, the metathesis-active vinyl carbene **43** was prepared in 90% yield. The ready access to hydride **39** from a convenient ruthenium(II) source and the rapid synthesis of a metathesis-active complex makes this a practical method for carbene synthesis.

Attempted purification of the intermediate triphenylphosphine complex **41** led to the identification of a novel dinuclear

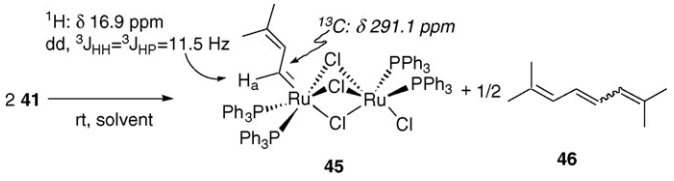


Scheme 21. Vinyl carbenes from hydride **39** [56].



Scheme 22. One-pot synthesis of metathesis-active ruthenium vinyl carbenes (Fogg and co-workers) [57].

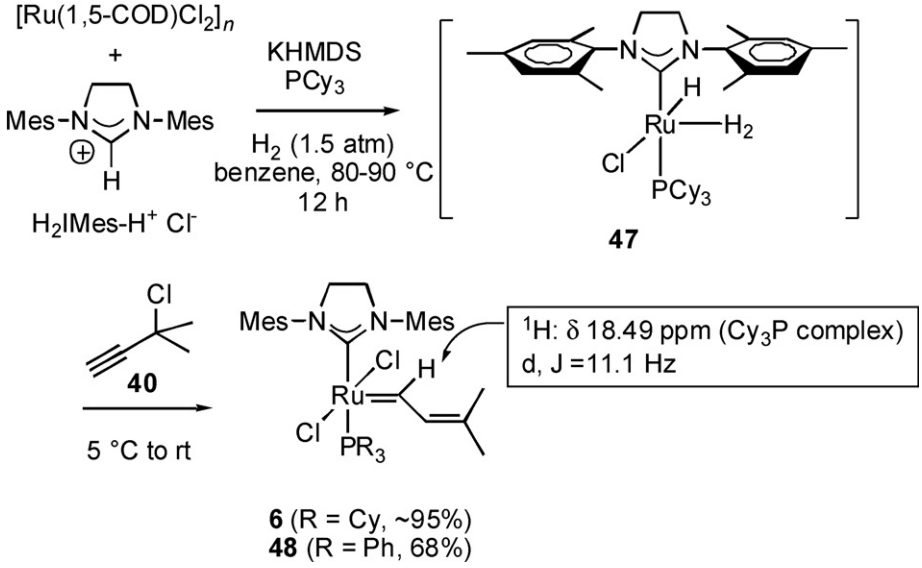
complex **45** (Eq. (32)) [57]. The dinuclear complex features different ligand substitution on the ruthenium(II) centers, which are linked by three bridging chloride ligands. In the face-bridged dimer, one ruthenium center is a vinyl carbene, with a diagnostic α-proton appearing at δ 16.9 ppm as a dd ($^3J_{HH} = {}^3J_{HP} = 11.5$ Hz). Complex **45** was formed along with triene **46**, produced as a *cis*/*trans* mixture. The authors speculated that one ruthenium vinyl carbene gave dimerization of the vinyl carbene moiety giving the triene and the coordinatively unsaturated species $Cl_2Ru(PPh_3)_2$. The extruded non-carbenic Ru(II) is subsequently intercepted by chlorides of the vinyl carbene species in solution to give the face-bridged dimer **45**. In typical synthesis applications with higher relative concentrations of organic substrates versus catalyst, it is likely that the $Cl_2Ru(PPh_3)_2$ can be sequestered through other pathways. Despite the carbenic nature of **45**, the complex displayed poor reactivity in ring-opening metathesis polymerization (ROMP) of norbornene. The authors had observed similar behavior in a face-bridged dinuclear hydride, where greater ROMP reactivity could be coaxed by chloride ligand abstraction or through a bridge-splitting reaction [58].



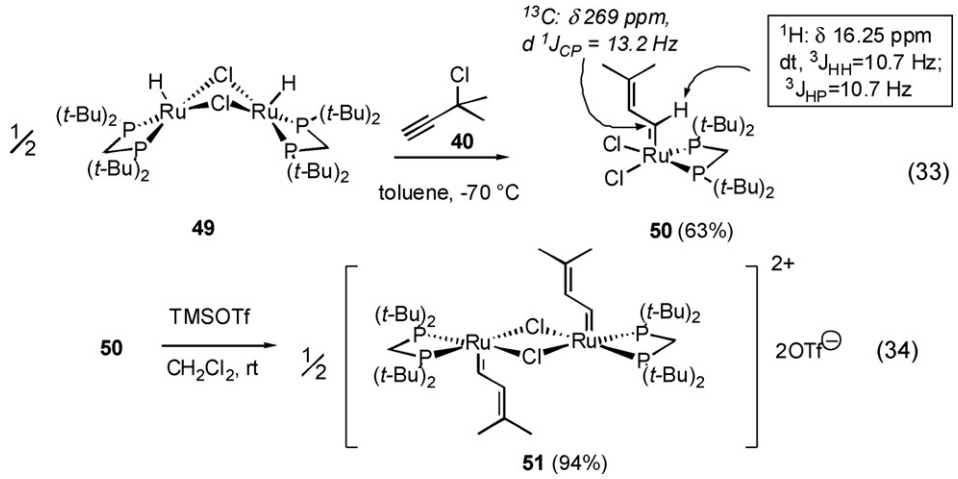
(32)

The formation of complex **45** may represent a decomposition pathway for vinyl carbenes in enyne metathesis. There are few studies of metal carbene decomposition relevant to metathesis [59], and yet research in this area will provide critical insights that will lead to improved catalyst performance. Arguably, the high catalyst loadings (5–10 mol%) that are typical in organic synthesis applications represent a limitation for metathesis in large scale synthesis. Better understanding of catalyst decomposition will lead to the design of more robust catalysts and possibly help to limit side reactions that may emanate from ruthenium(II) by-products.

Grubbs detailed the synthesis of a vinyl carbene of the second generation ligand environment from a common Ru(II)



Scheme 23. Grubbs' synthesis of second generation vinyl carbene **6** [60].



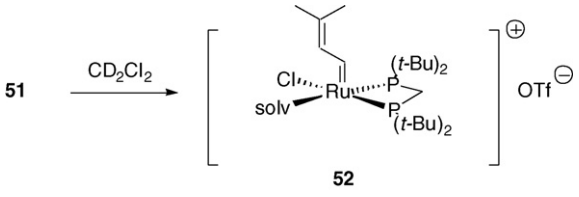
Scheme 24. Dinuclear vinyl carbene complex of Hofmann [62].

starting point [60]. The synthesis proceeds by way of ruthenium trihydride **47** (Scheme 23). The *N*-heterocyclic carbene is generated *in situ* from $H_2IMes^+Cl^-$ and KHMDS in the presence of $[Ru(COD)Cl_2]_n$ and tricyclophenylphosphine, heated in an autoclave under hydrogen. Introduction of the propargyl chloride at low temperature resulted in a very fast reaction, forming the complex **6**. Complex **6** could be purified by column chromatography. The carbene **6** displayed the expected downfield carbene resonances (Scheme 23) and a single coordinated phosphine at δ 28.9 ppm. The analogous triphenylphosphine complex **48** was synthesized by this method in 68% yield. Both complexes are active in metathesis.

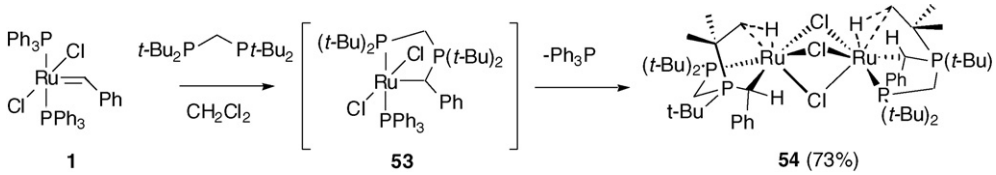
Complex **6** promotes alkene cross-metathesis to generate trisubstituted alkenes [8]. Previously, only the early transition metal molybdenum carbenes of Schrock were capable of this transformation. Complex **6** has been used as an initiator in enyne metathesis, though the parent benzylidene complex is often used in preference to the vinyl carbene. The reactivity of the vinyl carbene complexes has not been directly compared to the benzylidene **2**. The regiochemistry of initiation has been studied by Diver and Giessert [61] and will be discussed below.

Hofmann utilized the hydride method to access diphosphine-chelated vinyl carbenes from a dinuclear ruthenium hydride **49** [62]. The dinuclear hydride **49** was obtained in one step from $[RuCl_2(COD)]_n$. Depending on the propargyl chloride used, a variety of vinyl carbene complexes were formed (Scheme 24). Chloride abstraction generated the dinuclear dicationic complex **51** in high yield. The carbene resonance appears at 17.32 ppm as a multiplet, and the carbene carbon appears at δ 301.5. The crystal structure shows the two carbene fragments arranged *trans* to each other; however, the low temperature NMR shows two dimeric species, the *cis*- and *trans*-isomers. Interconversion of isomers proceeds via the dissociated monomer formed by solvolysis of the bridged chloride substructure in complex **51** [62,63].

The dinuclear complex is metathesis-active. For example, ROMP of norbornene was promoted by the dinuclear vinyl carbene complex **51**. In a side-by-side comparison to Ru gen-1, the complex **51** gave 95% polymerization after 2500 s, whereas Ru gen-1 gave only *ca*. 10% polymer. The authors assume that the metathesis proceeds via the mononuclear cation **52** (Eq. (35)).

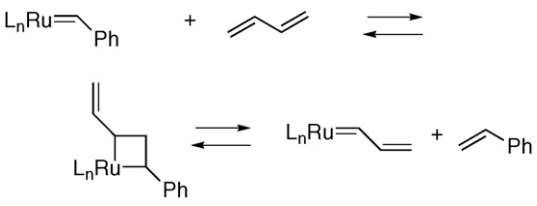


The Hofmann complex is unique. The *cis*-oriented κ^2-dtbpm ligand is maintained through the synthesis, and probes the influence of stereoelectronics on the reactivity of the carbene complex. The use of cationic complexes in metathesis is unusual. Synthesis of the κ^2-dtpbm complex by a phosphine ligand exchange produces a different dinuclear complex with the bridged intermediate **54** (Eq. (36)) [64]. Thus, the *cis*-oriented diphosphine complex needs to be in place prior to carbene formation. This illustrates the importance of timing in organometallic complex synthesis.



2.2.2. By alkene metathesis

Vinyl carbenes can also be synthesized by metathesis between ruthenium alkylidenes and conjugated dienes. This reaction is the microscopic reverse of the last step of catalytic enyne metathesis (Eq. (37)). The forward reaction can be promoted by the use of a large excess of the diene reactant.



(37)

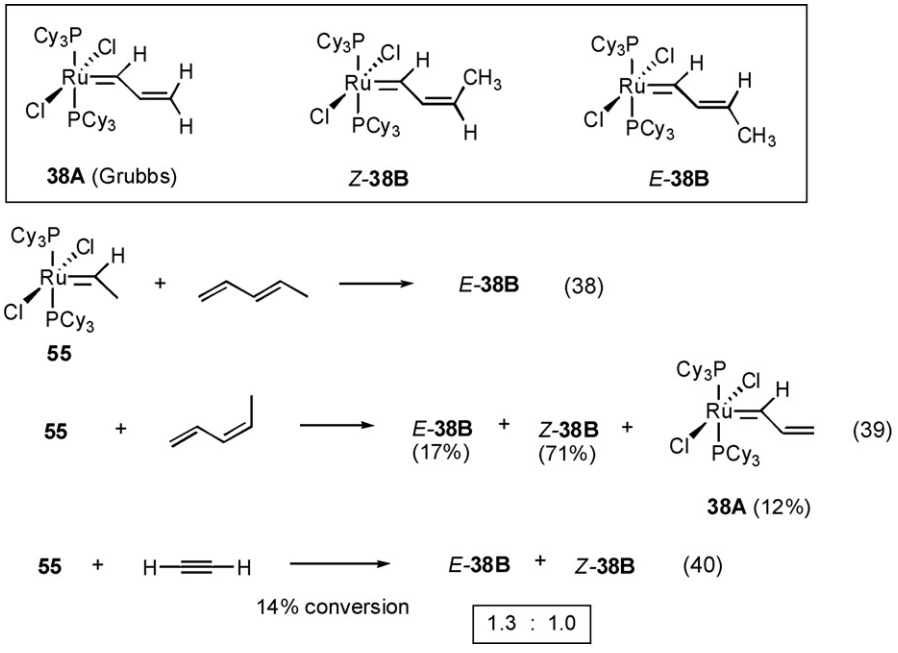
In the landmark paper describing the synthesis and reactivity of the first generation Grubbs carbene, Grubbs and co-workers reported a vinyl carbene synthesis by metathesis [19]. The first generation carbene complex reacted with excess 1,3-butadiene to give the vinyl carbene **38A**. The carbene showed the characteristic proton resonance at δ 19.06 ppm (d, $^3J_{HH}$ = 10.5 Hz) and the ^{13}C resonance at δ 296 ppm (t, J_{PC} = 7.6 Hz).

Synthesis of ruthenium vinyl carbenes via metathesis with dienes was investigated by Sponsler and co-workers [65]. In this case, first generation alkylidenes were employed as the carbene starting materials (rather than the benzylidene used by Grubbs previously). The ethylidene **55** initiated with *cis*- and *trans*-1,3-pentadienes with a high degree of stereospecificity (Scheme 25). Reaction of the *cis*-l,3-pentadiene produced a mixture of vinyl carbenes as well as the secondary metathesis product **38A**. The initial 4:1 *Z*/*E* mixture of vinyl carbenes **38B** equilibrated to give a 1:16 *Z*/*E* mixture over 1–4 d at ambient temperature. To the best of our knowledge, this is the first study aimed at the synthesis of stereodefined vinyl carbenes with γ-alkyl substitution.

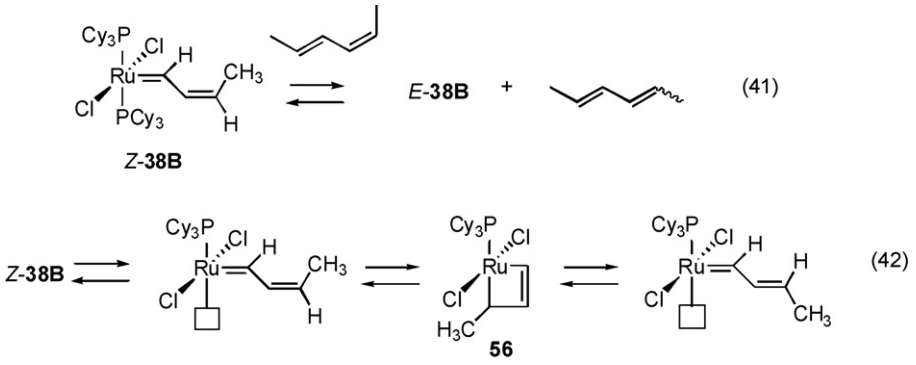
The spectroscopic data on the *E*- and *Z*-vinyl carbene complexes shows several interesting differences. The *Z*-isomer *Z*-**38B** was contaminated with the *E*-isomer, but showed the carbene proton at δ 19.70 (d, *J* = 11.4 Hz) and the ^{13}C showed the carbene carbon at δ 289.2 ppm (pseudo t, *J* = 6.6 Hz). The β proton was observed at δ 7.83 as a ddq, showing long range coupling to the allylic methyl group at the δ position. The coupling between H_β and H_γ was 11.4 Hz, as expected for a *cis*-substitution. The ^{31}P spectrum showed a single resonance at 37.6 ppm. The *E*-isomer *E*-**38B** was obtained analytically pure. The carbene proton appears at δ 18.73 (d, *J* = 10.8 Hz) and the ^{13}C spectrum shows a carbene signal at δ 294.5 ppm (pseudo t, *J* = 6.9 Hz). The β proton was observed at 8.00 ppm as a ddq showing *trans* coupling to H_γ, *J* = 15 Hz, and long range coupling to the allylic methyl group. The ^{31}P spectrum showed a single resonance at δ 37.1 ppm. No X-ray structures were reported for these stereochemically interesting vinyl carbene complexes.

The isomerization is especially pertinent to catalytic enyne metathesis. Several observations in this study were consistent with metathesis mechanisms for isomerization. First, the *Z*-isomer underwent faster isomerization. Second, excess tricyclohexylphosphine slowed the rate of isomerization. Third, additional alkene promoted isomerization. These observations, linked with consideration of DFT results, led the authors to conclude that there were two principal metathesis pathways giving isomerization: (1) metathesis with excess alkene (Eq. (41)) and (2) equilibration via metallacyclobutenes (Eq. (42)). These proposed mechanisms are illustrated in Scheme 26. When traces of the carbene **38A** are present, the isomerization proceeds faster. Other alkene metathesis mechanisms are also considered.

The equilibration of *Z*-**38B** to *E*-**38B** via ruthenacyclobutenes also explains the isomerization. This is also consistent with the



Scheme 25. Stereospecific synthesis of ruthenium vinyl carbenes by metathesis (Sponsler and co-workers) [65].



Scheme 26. Possible equilibration pathways (Sponsler and co-workers) [65].

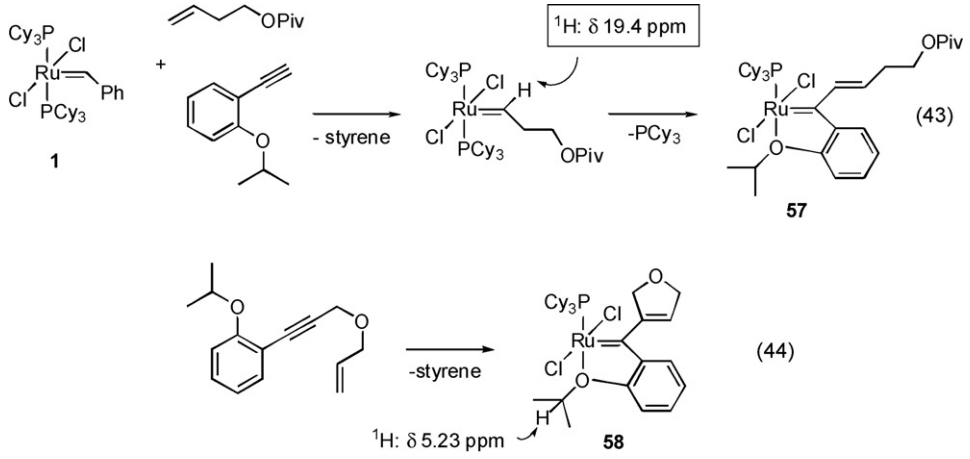
rate depression observed in the presence of excess Cy_3P. The mechanism is illustrated in Eq. (42). The authors also related their findings to the kinetic selectivity of enyne metathesis. The ethylidene complex reacted with acetylene to produce a 1.3:1.0 *E*/*Z* mixture of vinyl carbenes at low conversion (Eq. (40)). This illustrates the lack of kinetic stereoselectivity that is typically observed in cross-enyne metathesis.

2.2.3. By alkyne insertion into a metal carbene

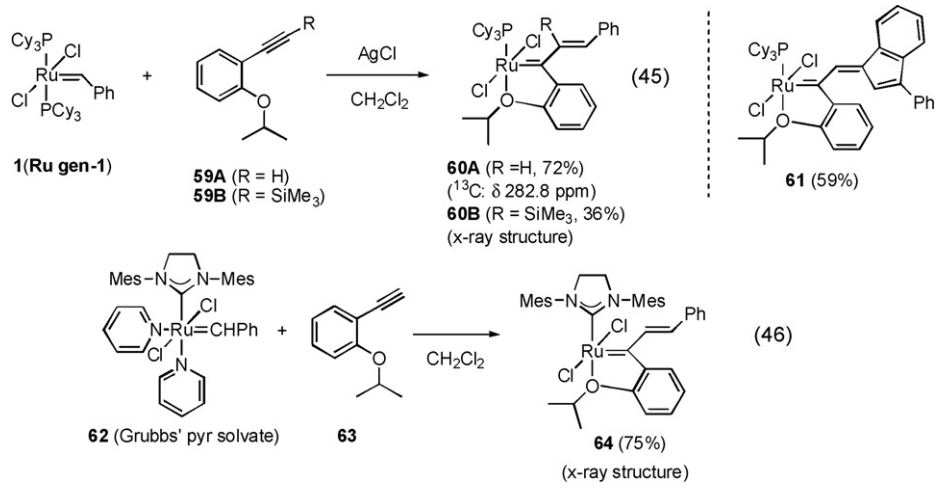
The synthesis of vinyl carbenes by alkyne insertion has taken a step forward in the last few years. Alkyne insertion is the first step in enyne metathesis, and stopping the reaction at the vinyl carbene stage is a challenge. Successful syntheses have taken a clue from the design of the Hoveyda complex [42,43] which features a chelated carbene fragment. Chelation imposes kinetic stability to the vinyl carbene intermediate. The chelation-assisted synthesis has been employed independently by Hansen and Lee [66] and Fuerstner et al. [67] to capture the ruthenium atom and stabilize it for spectroscopic studies or purification. Lee and Hansen [66] used this idea in an *ortho*-(isopropoxy)phenyl acetylene to generate the chelated vinyl carbene **57** (Scheme 27). These experiments were conducted in the first generation ligand environment. The same strategy was used to furnish the α,β-disubstituted vinyl carbene complex **58**. Both of these complexes were characterized spectroscopically. For α-substituted carbenes, the ^{13}C is an important diagnostic peak. Since the α-substituted complexes **57** and **58** lack a carbene proton, the resonance for the γ-H indicates the presence of a vinyl carbene. Repetition of these experiments on the second generation carbene failed to produce the corresponding chelates.

The chelation-directed synthesis of vinyl carbenes was used by Fuerstner et al. [67] to produce several vinyl carbenes in both the first- and second-generation ligand environments (Scheme 28). The strategy in Eq. (45) is similar to that described. The internal alkyne-derived complex **60B** gave X-ray quality crystals and its solid state structure was determined. In these cases, Ag(I) was used to sequester the liberated tricyclohexylphosphine. In complex **60A**, the ^{13}C of the carbene appears at δ 282.8 ppm. In each run, a small amount of *Z*-isomer was observed in the crude product, but could be removed by crystallization. In a similar fashion, the indenyl complex **61** was prepared from the corresponding indenyl carbene complex.

By using the pyridine solvate **62**, coordinated vinyl carbenes in the second generation environment were synthesized (Eq. (46)). In this synthesis, Ag(I) is not required. The X-ray structure of **64** showed structural distortion in the vinyl carbene fragment. Geometrically, the five-membered chelate would orient the C_4–C_5 bond vertically, co-alligned with the Ru–C_1 bond. However, this would place the β carbon (C_5) into van der Waals contact with the bulky H_2IMes group. As a result, the



Scheme 27. Chelated vinyl carbene intermediates in Lee and Hansen's study [66].



Scheme 28. Chelation-assisted synthesis of vinyl carbenes (Fuerstner et al.) [67].

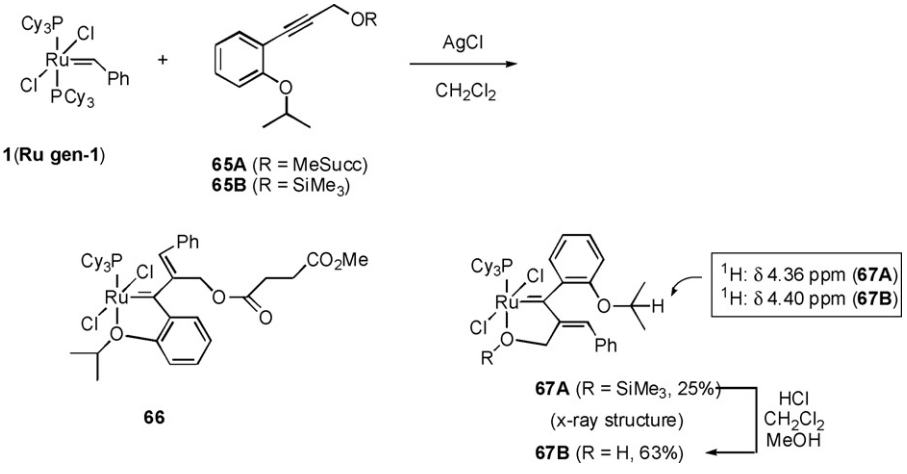
five-membered metallocycle is distorted: the carbene is pyramidalized and the mesityl group causes the entire H_2IMes ligand to tilt away from the vinyl carbene fragment.

When there are two potentially coordinating groups to chelate to the metal carbene, to which side will the metal go? In two unsymmetrical internal alkynes, this question was probed. In these experiments, Ag(I) was again employed to sequester the released tricyclohexylphosphine. When the propargylic ester **65A** was employed, the expected chelate (Hoveyda-like) **66** was formed (Scheme 29). The coordinated isopropoxy group gives a methine resonance in the ^{1}H NMR at δ 5.18 (compared to δ 4.38 when not coordinated). When the trimethylsilylether **65B** was used, the regiochemistry of alkyne insertion was reversed, giving chelate **67A**. A crystal structure of **67A** was also obtained. In the solid state, carbene **67A** does not show the distortion observed for complex **64**. This is presumably due to less steric congestion in complex **67A** (greater steric congestion in the second generation complex **64** involving the bulky H_2IMes group). Interestingly, the TMS group could be deprotected using HCl in CH_2Cl_2–MeOH to give **67B** with a coordinated hydroxy group. The technique for obtaining diffractable crystals used saturated CH_2Cl_2 solution followed by layering with pentanes.

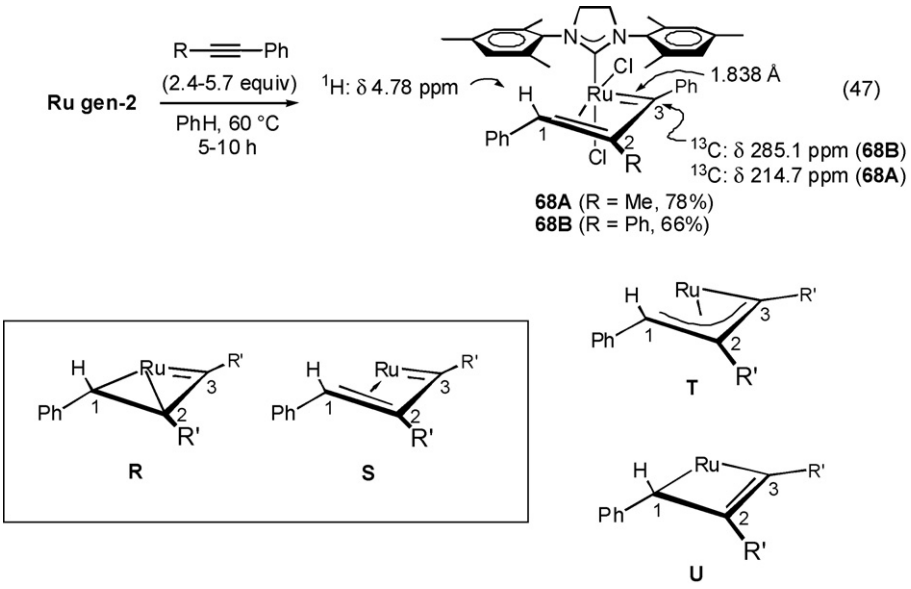
The vinyl carbene complexes were all metathesis-active. The carbene complexes were evaluated in a benchmark ring-closing alkene metathesis of dimethyl diallylmalonate. The distorted second generation complex **64** was found to be the most active followed by **67A**, **60A** and **66**. The metathesis activity found for these chelates, as well as the general knowledge that the Hoveyda carbene complex is an active initiator for metathesis, suggests that chelation is not sufficient to extinguish metathesis activity. Further studies on chelation effects with different functional groups are still needed.

In the absence of productive metathesis, metathesis-competent vinyl carbenes can undergo rearrangement to metathesis-inactive complexes. Grubbs and co-workers heated tolan with the Ru gen-2 carbene at 80 °C for several hours to isolate a green complex **68** that showed an unusual metallacycle structure (Eq. (47)) [68] (Scheme 30).

The chloride ligands had adopted a *cis*-arrangement on the metal, with one chloride *trans* to the H_2IMes ligand. The vinyl carbene fragment was found oriented with side-on coordination at the alkenyl moiety. The authors described this as η^3-bonding since all three carbons are located within bonding distance to the metal. The Ru=C bond length is similar to that of the Ru



Scheme 29. Competing sites for chelation in vinyl carbene synthesis [67].



Scheme 30. η-3 vinyl carbenes discovered by Grubbs [68].

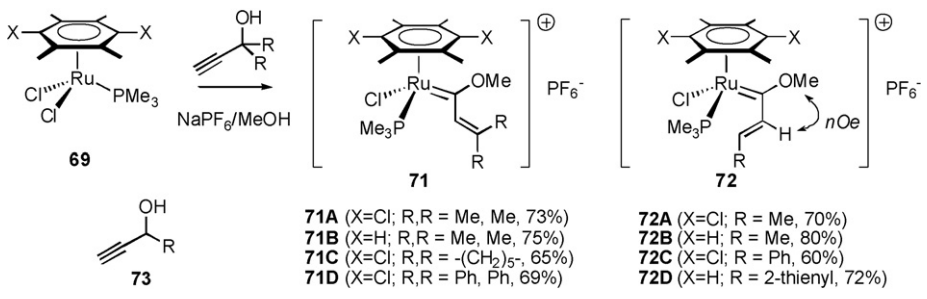
gen-2 complex (1.838 Å), Ru–C_2 is 2.221(4) Å and Ru–C_2 is 2.356(4) Å. The C_{12}–C_2 bond length was found to be 1.409(6) Å, longer than a typical bond length for a uncomplexed alkene (∼1.35 Å). The vinyl carbon resonances are upfield of that observed for a typical, uncomplexed vinyl carbene: for **68B**, C_1 and C_2 appear at 67.9 and 91.7 ppm, as compared to C_β and C_γ of complex **38A** which appear at δ 116 and 154 ppm, respectively. The authors liken the bonding to that described in **R** or **S**. The Ru–C_1 distance discounts **T** and the Ru=C_3 bond length, and longer C_2–C_3 bond discount the prospective ruthenacyclobutene structure **U**. The ruthenium methylidene $L_nRu{=}CH_2$ did not produce η^3-complexes. The *p*-fluorobenzylidene established that the C_1 substituents arose from the original carbene.

The η^3-complexes **68A** and **B** are not metathesis-active. The mechanistic origin of the η^3-complexes is unclear. Their genesis presumably lies on the metathesis pathway but they are formed by a shunt from normal alkyne polymerization (for alkyne only) or from normal enyne metathesis (when both alkyne and alkene are present).

2.2.4. By addition/rearrangement with propargyl alcohols

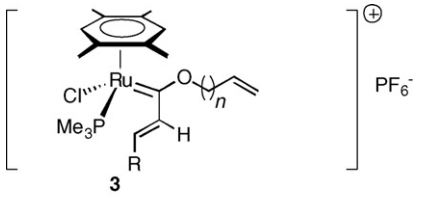
Vinyl carbenes have been synthesized via nucleophilic addition to allenylidene intermediates, which are often produced from propargylic alcohols. This approach has been extensively utilized by Dixneuf and his co-workers. The resulting complexes are structurally unique as compared to the L_2RuCl_2 environment found in Grubbs' carbenes. Another notable difference is the cationic nature of these complexes. In this section, many of the cationic complexes bear a cyclopentadienyl ligand; for further discussion, the reader is directed to an exhaustive review of 'half-sandwich' group 8 metal carbenes, including alkylidenes, cumulenylidene and allylidenes (vinyl carbenes) [69]. In the following discussion, a variety of α-alkoxy-substituted ruthenium vinyl carbenes are discussed. However, as noted in the Introduction, this discussion is not meant to be comprehensive and a variety of earlier reviews are available detailing the organometallic synthesis and reactivity of alkoxy-substituted ruthenium vinyl carbenes [70,71].

Dixneuf produced α-alkoxy-substituted vinyl carbenes starting from η^6-arene Ru(II) complex and propargyl alcohols (Scheme 31) [72]. Conducted in methanol, the cationic complexes **71** and **72** are produced in high yields. Complexes **71** emanate from the monosubstituted propargyl alcohol **73**. The carbene carbon appears in the range 298–310 ppm. Moreover, the H_γ proton is shifted downfield, appearing in the range δ 7.8–8.46 ppm. The γ,γ-disubstituted complexes **71** adopt a *s-trans* conformation, whereas the lower homologs **72** are found in the *s-cis* conformation on the basis of observed nuclear Overhauser effect (nOe) between the methoxy group and proton H_β.



Scheme 31. Arene-substituted ruthenium vinyl carbenes [72].

Capture by other alcohols serving as nucleophiles was also possible. Use of allyl- and homoallyl alcohol led to ruthenium vinyl carbene complexes **74** [73]. The products were formed in good yield. Spectroscopically, the complexes showed the expected downfield ^{13}C resonance for the carbene at δ 297–303 as a doublet ($^2J_{CP}$ = 20.3 Hz for **74A**). In all cases, the *E*-isomer was formed.



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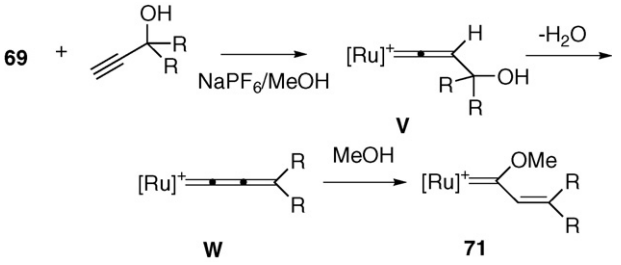
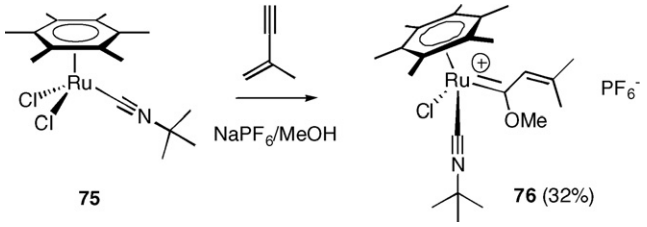
74A (n=1; R = Me, 46%)
74B (n=1; R =  70%)
74C (n=2; R = Ph, 53%)

The mechanism is believed to proceed as shown in Eq. (48) [72,74]. Alkyne coordination and rearrangement to vinylidene **V** is followed by elimination of H_2O to give allenylidene cation **W**. Addition of methanol to the electrophilic C_α position will generate the observed vinyl carbenes **71** after proton transfer.



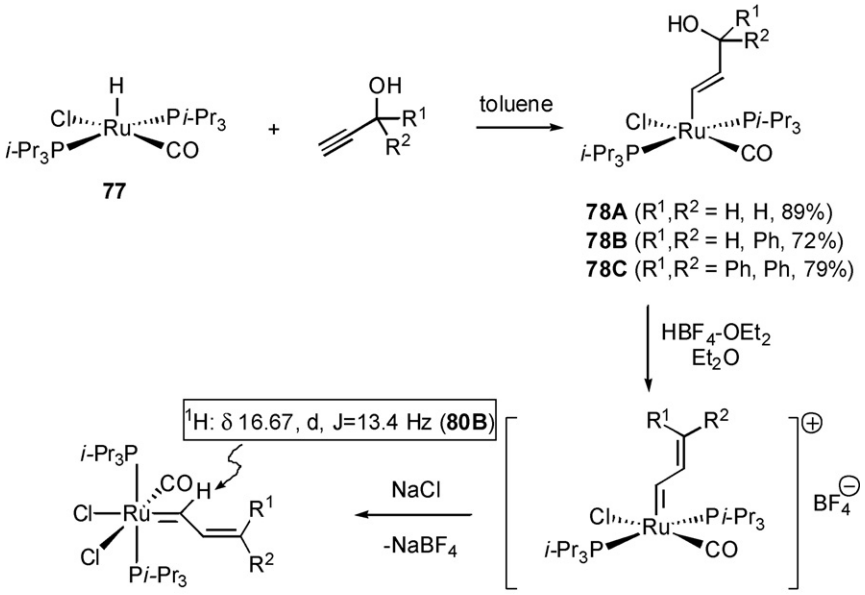
(48)

Similar reactivity profile is observed with the isocyanide ruthenium(II) complex in its reaction with a 1,3-enyne. In this example, the trimethylphosphine ligand of cationic complex **69** (Scheme 31) was replaced by *t*-butylisocyanide (Eq. (49)) [74].



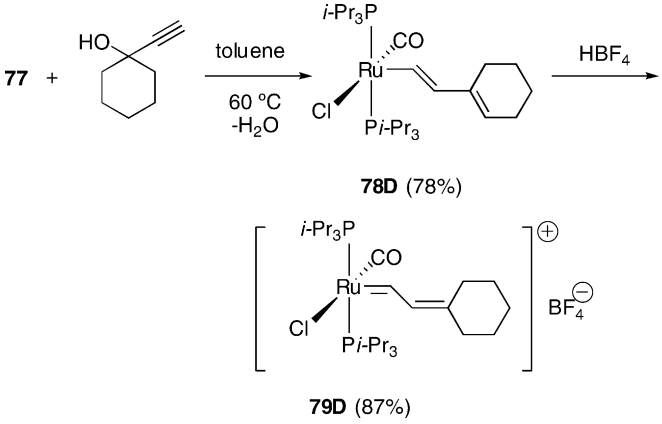
(49)

In another unique ligand environment, Esteruelas generated vinyl carbenes by protonative elimination of γ-hydroxy alkenyl metal intermediates (Scheme 32) [75]. The hydridocarbonyl **77** reacted by migratory insertion of the alkyne into the Ru–H bond (alkyne hydrometallation). Protonation of the resulting allylic alcohol with anhydrous HBF_4 gave the cationic vinyl carbenes in moderate yield. Facile addition of chloride to the metal generated the hexacoordinate vinyl carbene **80**. Carbene **80B** displayed the characteristic proton resonance at δ 16.67 (d, J = 13.4 Hz). The carbonyl stretch was observed at 1927 cm^{-1}. Complex **80C** showed the carbene at δ 17.05 and the ^{13}C gave the C_α at 314.5 ppm (t, J_{CP} = 8.7 Hz), C_β at 130 ppm, and C_γ at 202 ppm. The corresponding CO stretch appeared at 1940 cm^{-1}. In addition, aliphatic groups can be introduced at the γ-carbon by use of the appropriate propargyl alcohol using an analogous



Scheme 32. Hydrometallation and γ-elimination to vinyl carbenes (Esteruelas et al.) [75].

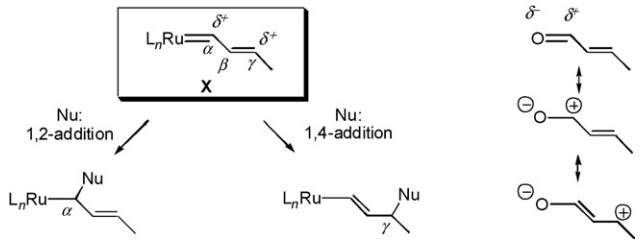
reaction sequence (Eq. (50)).



(50)

The vinyl carbene complexes described are not reported to have metathesis activity. As cationic complexes bearing a CO ligand, it is unlikely that phosphine would be readily dissociated. This would preclude a dissociative mechanism needed for metathesis activity. It would be intriguing to learn whether the CO could be removed from the neutral hexacoordinate complex **80** to produce a metathesis-active carbene.

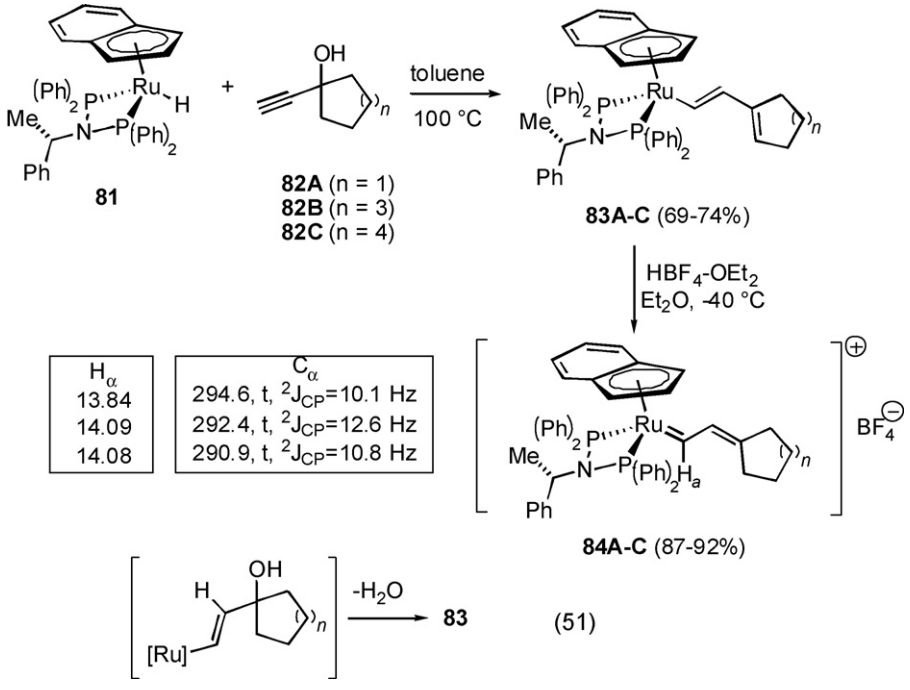
A similar hydrometallation/protonation sequence was used by Gamasa and co-workers to access indenyl-substituted ruthenium vinyl carbenes [76]. The indenyl ruthenium hydride **81** reacted with propargylic alcohols at elevated temperature in toluene to give the air-stable red-orange alkenyl metals **83** (Scheme 33). The hydroruthenation was *syn*-selective, as evidenced by the *trans*-disposition of the vinylic protons in **83** ($^3J_{Hh}$ 15–16 Hz). The cationic complexes **84** were produced by protonation of the more nucleophilic H_γ by HBF_4–OEt_2. The cationic complexes displayed the expected low field chemical shifts of the carbene carbon C_α and the downfield shifts of the carbene protons H_α. In this case, dehydration of the hydrometallated intermediate occurred spontaneously to give complexes **83** (Eq. (51)).



Scheme 34. Electrophilic reactivity of vinyl carbenes.

Interestingly, none of the cationic vinyl carbene complexes were metathesis-active. The complexes **84** and the bis(diphenylphosphino)methane (dppm) homologues were investigated in the ring-closing metathesis of diethyl diallylmalonate. At catalyst loadings of 5 mol% at temperatures up to 90–100 °C, no metathesis product was observed. Presumably the cationic nature of the ruthenium center discourages ligand dissociation (indenyl slip or phosphine loss) needed to enter the catalytic metathesis reaction manifold.

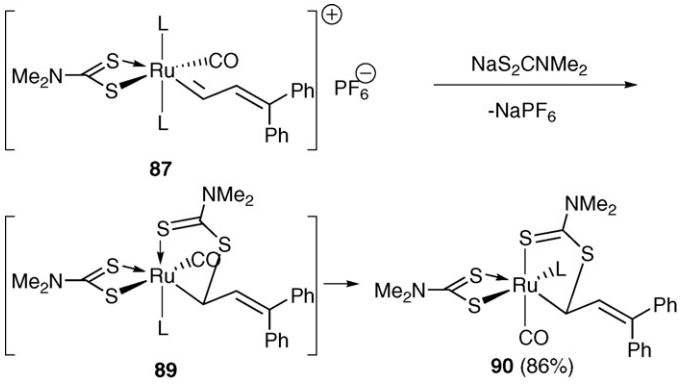
A variety of vinyl carbene complexes were prepared by Hill and co-workers to investigate nucleophilic addition [77]. These authors likened electrophilic reactivity of electron-poor vinyl carbene complexes to that of enones, where one expects both 1,2 and 1,4-addition (Scheme 34). The preference for mode of addition is an important fundamental question relating to



Scheme 33. Protonation of vinyl ruthenium intermediates (Gamasa and co-workers) [76].

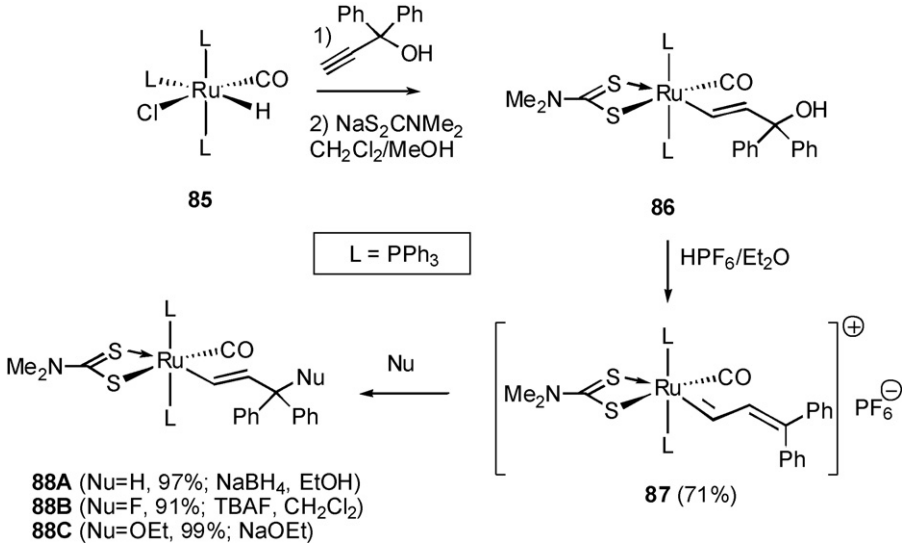
vinyl carbene reactivity. This study focused on hard nucleophiles using a unique chelating thiolato ligand. Access to the vinyl carbenes occurred over three steps involving hydrometallation followed by ligand replacement (Scheme 35). The next step utilized protonative elimination of water from the allylic alcohol **86** under anhydrous acidic conditions similar to that employed by Esteruelas et al. Treatment of **86** with anhydrous HPF_6 forms the cationic carbene complex **87** as deep red crystals with characteristic ^{13}C chemical shifts for C_α 311.8 ppm (t), C_β 148.2 ppm and C_γ 161.4 ppm. The carbene proton appears at δ 14.72 ppm as a triplet, coupled to 2 equiv. phosphorus atoms and the H_β proton.

Nucleophilic addition on the cationic complex mostly occurred at C_γ. Hydride addition proceeded by 1,4-(conjugate) addition to give **88A** in high chemical yield. Fluoride addition and ethoxide addition gave the same addition mode preference, producing the corresponding complexes **88B** and **88C** in high yield. Interestingly, the addition of sodium dimethyldithiocarbamate, a soft sulfur nucleophile, led to C_α addition (1,2 addition). On continued heating, the chelated complex **89** rearranged to the thermodynamically more stable isomer **90** which was characterized by X-ray crystal structure.

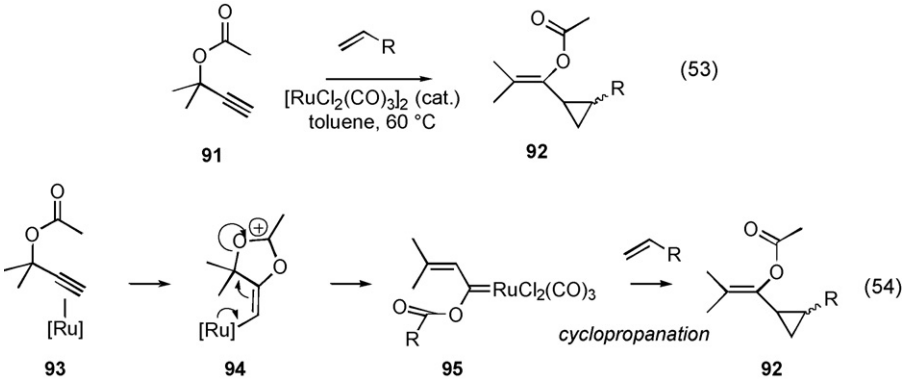


(52)

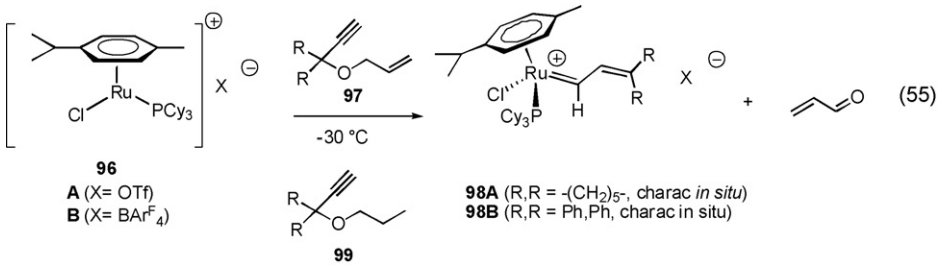
Uemura and co-workers produced a vinyl carbene intermediate by a novel acyl group shift [78]. In this study, the vinyl carbene was not observed; evidence for its intermediacy came from the organic reaction. This example is included, despite the lack of carbene identification, because it illustrates a novel method for making vinyl carbenes. Similar rearrangements have been used by others in related metal-catalyzed pi bond reor-



Scheme 35. Nucleophilic addition to ruthenium vinyl carbenes (Hill and co-workers) [77].



Scheme 36. Uemura's intermediate vinyl carbene in cyclopropanation [78].



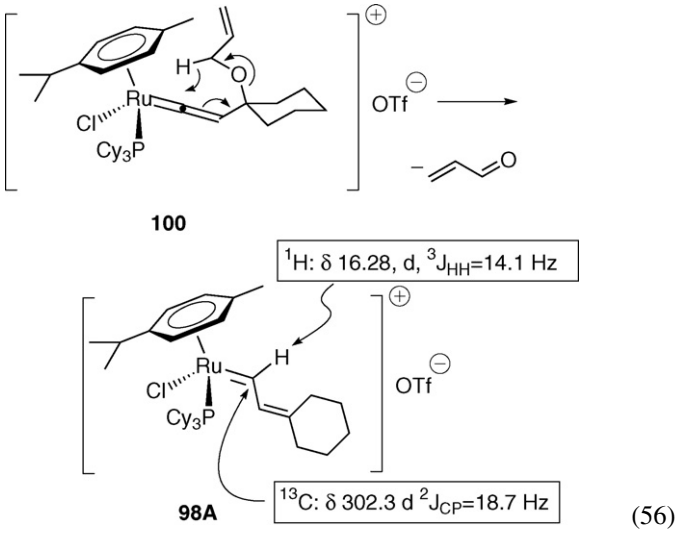
Scheme 37. Cationic vinyl carbene synthesis via intramolecular hydride transfer (Dixneuf and co-workers) [82].

ganizations [79–81]. Murai's catalyst promotes vinyl carbene formation from propargylic esters and leads to cyclopropanation of an alkene (Scheme 36). The resulting cyclopropanes **92** are obtained with modest selectivities (2.3–6:1 ratio) *cis*/*trans*. Other metals promoted the reaction in lower yields, presumably proceeding by way of the respective vinyl metal carbenes.

The presumed mechanism involves an acyl group shift. The Murai catalyst activates the acyloxyalkyne to produce a vinyl carbene. The η^2-coordination of alkyne to the electron-deficient metal carbonyl makes the alkyne electrophilic enough to instigate oxonium ion formation by the adjacent acyloxy group (Eq. (54)). This produces an intermediate oxonium ion **94**. Subsequent elimination produces the acyloxy ruthenium Fischer vinyl carbene **95**. Presumably, the metal is encumbered with three carbonyl ligands and two chlorides making **95** a coordinatively saturated 18-electron complex. Due to the lack of an open coordination site in vinyl carbene complex **95**, cyclopropanation ensues, giving the vinyl cyclopropane products observed.

Dixneuf employed an internal hydride transfer to generate metathesis-active vinyl carbenes [82]. These catalyst systems are distinct from those developed by Grubbs. Typically, the Dixneuf carbenes have an arene ligand with high hapticity. The displacement of propargylic alcohols used earlier by these authors furnished ruthenium Fischer vinyl carbenes. Previously, Dixneuf and co-workers had also observed hydride transfer from allylic alcohols [73]. In this work, these observations coupled with the author's work on cationic vinylidene and allenylidene complexes resulted in the synthesis of vinyl carbenes bearing a proton on C_α rather than an alkoxy group. The cationic *p*-cymene Ru(II) complex displaced the allyl propargyl ether to give cationic vinyl carbenes **98A** and **B** along with acrolein (Scheme 37). The resulting vinyl carbenes decomposed at room temperature, but could be characterized at −30 °C. The complex **98B** with the tetrakis(3,5-bistrifluoromethylphenyl)borate counterion (BAr_4^F) was more stable than that bearing the trifluoromethanesulfonate (triflate) counterion. The triflate complex **96A** produced a highly active metathesis catalyst precluding the use of enyne progenitor **97**, due to a rapid competing ring-closing enyne metathesis. Instead the propyl propargyl ether **99** was employed to generate the *in situ* catalyst.

The retro metallo ene rearrangement depicted in Eq. (56) explains the formation of the cationic vinyl carbene **98A** [82]. The resulting complex was observed at low temperatures with the carbene proton at δ 16.28 (d, J_{HH} = 14.1 Hz) and ^{13}C signals at δ 302.3 (d, J_{CP} = 18.7 Hz), 146.3 and 173.8 for C_α, C_β and C_γ, respectively.

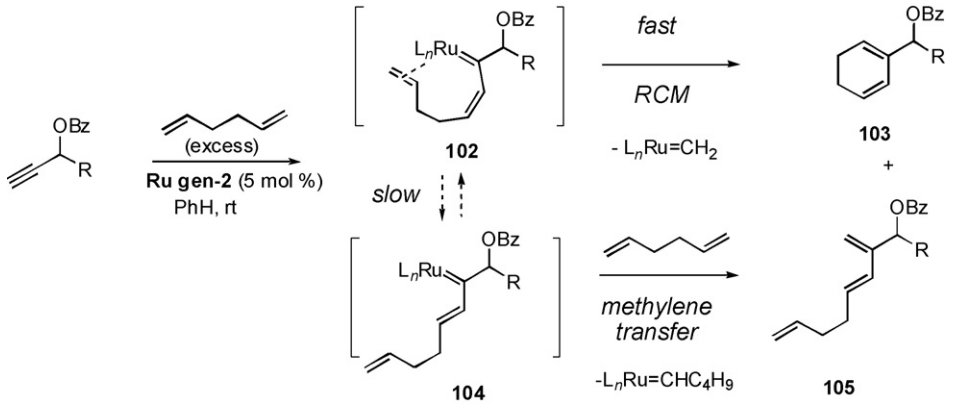


The Dixneuf cationic ruthenium vinyl carbenes are metathesis-active. The cationic complex displayed different reactivity depending on the counterion, with reactivity decreasing in the series $OTf > PF_6 > BPh_4 > BAr_4^F$. The complex with triflate counterion displays reactivity for a range of ring-closing alkene and enyne metatheses. The authors do not comment further on the decreasing reactivity as the ion pair becomes more separated (larger, more diffuse counterion).

3. Mechanistic studies

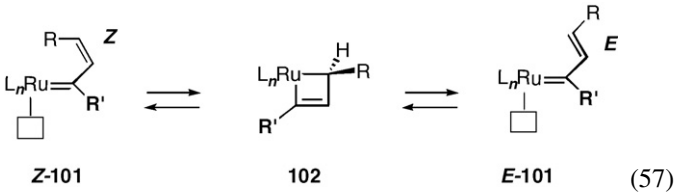
3.1. Vinyl carbene equilibration: methylene-free enyne metathesis

Earlier we described an intermolecular cross-metathesis between alkynes and 1,5-hexadiene. This method resulted in an efficient ring synthesis of 1,3-cyclohexadienes by tandem metathesis. However, the methodology was limited since two products were formed. These products are not easily separated and the lack of selectivity limits the synthetic utility. We were puzzled by the lack of stereoselectivity in this cross-enyne metathesis, that the products were formed in an almost 1:1 ratio. We considered that the opening of a ruthenacyclobutene 102 might produce an equal mixture of *E*- and *Z*-vinyl carbenes (Eq. (57)). At this time, there were no detailed mechanistic studies on enyne metathesis. We therefore speculated that the process



Scheme 38. Vinyl carbene reactions by intramolecular RCM vs. bimolecular methylene transfer.

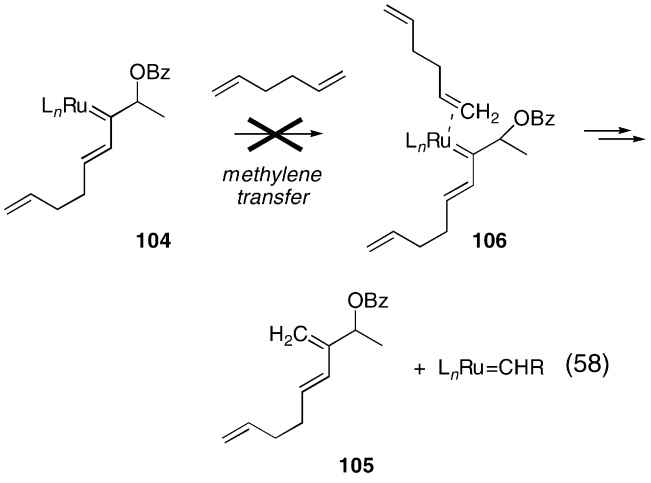
was reversible and possibly dynamic on the timescale of other metathesis processes.



(57)

The origin of the two products is thought to emanate from two isomeric vinyl carbenes. The conversion of the individual vinyl carbenes to their cognate products is outlined in Scheme 38. We posited that the ring-closing metathesis leading to the desired 1,3-cyclohexadiene product **103** (top path) was fast since it was an intramolecular reaction. However, the pathway leading to the *E*-triene product **105** from the *E*-vinyl carbene **104** was expected to be slower because of the bimolecular nature of the reaction. Earlier studies had shown a concentration dependence in an enyne metathesis, and our ethylene-assisted metathesis accelerated the rate of turnover by increasing alkene concentration. If the two vinyl carbene turnover steps depicted in Scheme 38 occur at different rates, it seemed possible that the faster reaction of the *Z*-vinyl carbene **102** might drive the reaction through the top pathway. For this to occur, the vinyl carbenes would need to be allowed to interconvert under the reaction conditions. The interconversion might occur as described in Eq. (57) or by other mechanisms.

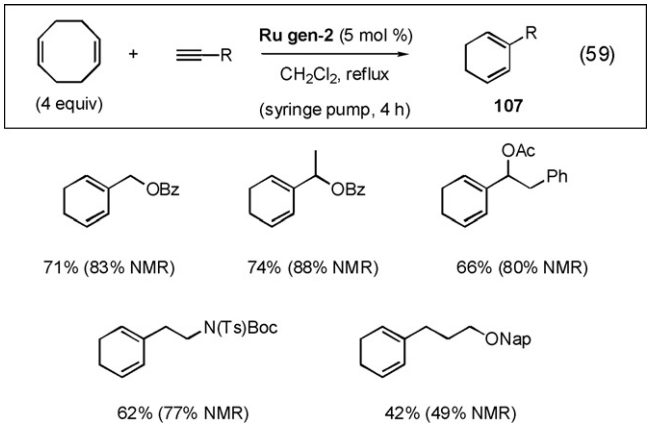
To allow for the vinyl carbene interconversion, the intermolecular transformation of the *E*-vinyl carbene to the undesired *E*-triene product **105** had to be slowed down. The high concentration of diene used to force the enyne metathesis also accelerated the undesired *E*-vinyl carbene turnover step. Moreover, we expected that the methylene transfer would be fast for terminal alkenes which can readily coordinate and transfer a methylene group in a fundamental process we described earlier as 'methylene transfer' (Eq. (58)). We imagined that if the methylene transfer depicted via **106** could be slowed down, conversion of *E*-vinyl carbene **104** to the undesired triene **105** would be slowed and equilibration to the *Z*-vinyl carbene **102** (Scheme 38) could compete. Ultimately, if the *Z*-vinyl carbene was formed by this pathway, then it would undergo the RCM step to give the desired 1,3-cyclohexadiene product **103** and this would serve to stress the putative vinyl carbene equilibrium.



(58)

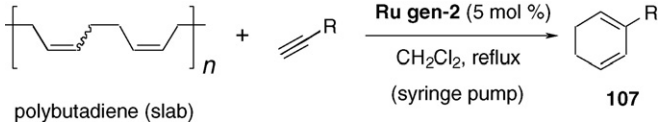
To slow the undesirable methylene transfer step, we developed reaction conditions that were devoid of methylene sources. We termed these conditions "methylene-free" metathesis conditions. Our group had utilized methylene-free conditions earlier in the ring expansion of cyclopentene to give 1,3-cycloheptadiene products [83]. Previous to our work in this area, only terminal alkenes had been employed in the cross-enyne metathesis because of the supposed catalytic role of $L_nRu{=}CH_2$. Without terminal alkenes present in the reaction medium, we assumed that alkene coordination as shown in Eq. (58) would be thwarted and that the ensuing transfer of the alkylidene fragment would be intrinsically slower than methylene transfer. If true, then the vertical equilibration pathway in Scheme 38 would allow isomerization to the *Z*-vinyl carbene.

The methylene-free conditions for 1,3-cyclohexadiene synthesis employed 1,5-cyclooctadiene instead of 1,5-hexadiene [84]. This removes methylene sources from the reaction. The 1,5-cyclooctadiene (COD) serves as the four carbon donor, giving the 1,3-cyclohexadienes **107** in good isolated yield (Scheme 39). In some cases, the isolated yields were lower due to the necessary precipitation and purification of the products from the COD-derived homopolymer.



Scheme 39. Methylene-free synthesis of 1,3-cyclohexadienes from 1,5-cyclooctadiene (Kulkarni and Diver) [84].

Table 1
Methylene-free synthesis of 1,3-cyclohexadienes from polybutadiene (Kulkarni and Diver) [84]

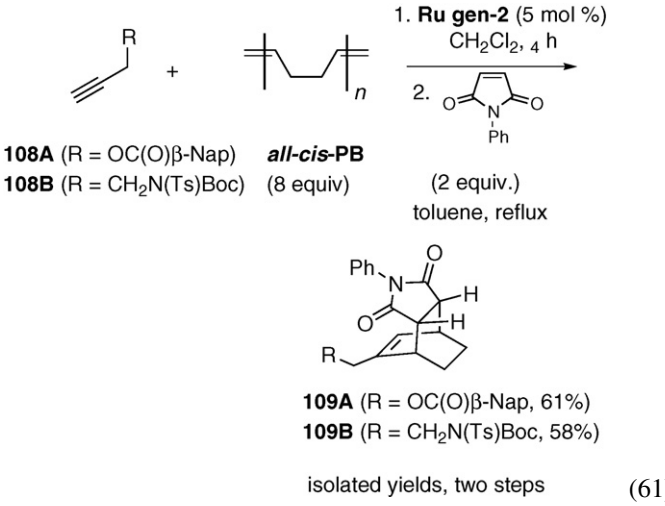


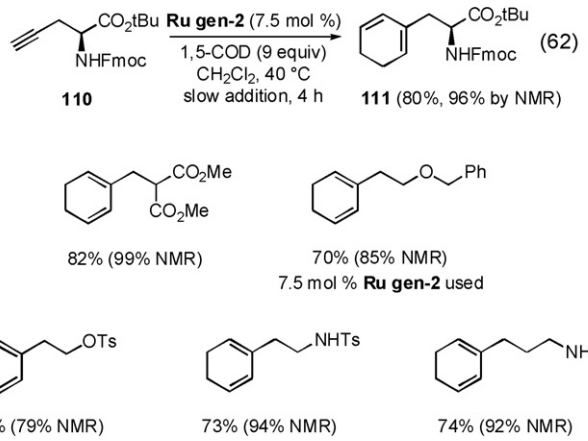
Entry	Alkyne	1,3-Cyclohexadiene	^{1}H NMR yield (%)
1	OBz	R = CH_2OBz	72
2	ONaphth	R = CH_2ONap	77
3	OBz	R = $CH(OBz)CH_3$	76

Polybutadiene, 37,000–55,000 repeats $M_w \sim 2–3 \times 10^6$ g/mol.

Even the readily available, strain-free polyalkene, polybutadiene could be used as the four carbon source (Eq. (60)). 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 1).

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. (61)):



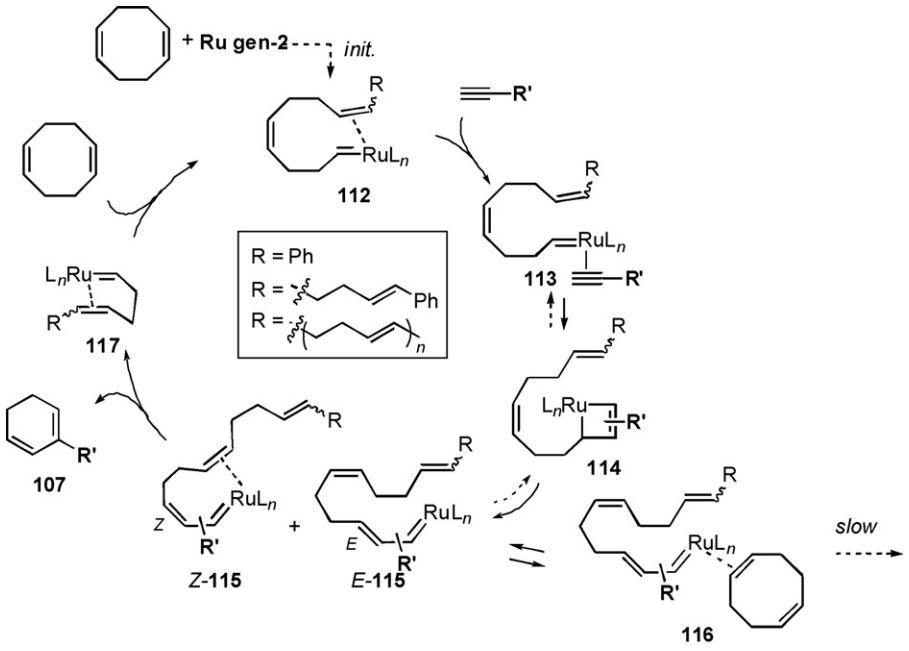


Scheme 40. Improved scope of the methylene-free ring synthesis (Diver and co-workers) [85].

The methylene-free metathesis is a powerful method for the efficient ring synthesis of 1,3-cyclohexadienes. Previous to this work, there existed few methods for cyclohexadiene synthesis and none that were single step operations. The reactions using 1,5-cyclooctadiene or polybutadiene are also amenable to scale up. However, in our initial study, the functional group scope of the methylene-free metathesis was found to be limited. Due to the slow addition (syringe pump) and the methylene-free conditions, the metathesis is slower than the 1,5-hexadiene-alkyne tandem metathesis discussed earlier. As a result, though product 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. The methylene-free metathesis would be much more useful if these limitations could be overcome.

Improved conditions for the ring synthesis led to an extended scope for a wide variety of functional groups [85]. The chiral α-amino ester **110** underwent tandem metathesis with excess COD in high NMR yield and with excellent isolated yield (Eq. (62)). This substrate has a free NH proton and previously could be synthesized in only 36% yield with difficulty in the isolation. Polybutadiene (18 equiv.) gave similar yield (76% isolated) and the use of the Hoveyda complex **3** gave 67% conversion at 10 mol% loading. The reaction was extended to substrates that were previously difficult or unreactive. The isolated yields are shown in Scheme 40.

The mechanism presumably follows the pathway depicted in Scheme 41. Ring-opening of 1,5-COD gives an alkylidene **113** that inserts alkyne to give isomeric vinyl carbenes **115**. Presumably the carbenes interconvert via metallacycle **114**. The *E*-vinyl carbene *E*-**115** may react with excess 1,5-COD to give oligomer, in what is likely a slower process. The *Z*-isomer *Z*-**115** progresses by RCM to give the products **107** and the alkylidene **117**. At moderate concentrations of COD, the alkene may stabilize the vinyl carbenes, preventing side reactions such as carbene decomposition.



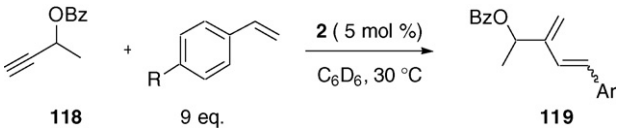
Scheme 41. Proposed mechanism for the cyclohexadiene synthesis by methylene-free enyne metathesis.

3.2. Kinetics and mechanism of enyne metathesis

3.2.1. Studies on methylene transfer in vinyl carbenes

One of the most fundamental questions relating to vinyl carbene reactivity in enyne metathesis deals with regiochemical preference in reactions with alkenes. This question drives at the heart of the 'methylidene-first' versus 'alkylidene-first' mechanisms. The 'methylidene-first' mechanism requires a vinyl carbene turnover step that involves alkylidene transfer from the alkene to the carbene (see **K–L**, Scheme 12, panel a). This amounts to transferring the bulkier end of the alkene to the carbene. On the other hand, if the 'alkylidene-first' mechanism was operative, then the more substituted vinyl carbene would engage in a 'methylene transfer', putting the less-substituted end of the 1-alkene onto the carbene carbon (see **N–O–P**, Scheme 12, panel b). We felt that this could be studied in a typical vinyl carbene by observing the products in stoichiometric reactions with alkene. This would mimic the normal conditions of enyne metathesis and provide evidence of the favored mode of transfer, and indirectly support an alkylidene-first catalytic reaction mechanism.

We investigated a styrene–alkyne cross-metathesis for a variety of *p*-substituted styrenes [61]. We chose the terminal alkyne **118** for these studies (Eq. (63)). Under conditions using excess styrene, the reaction showed rate variation that depended on the electronics of the styrene. The Hammett plot obtained in this way is shown in Fig. 1. The data points for the $–NMe_2$, –OMe, –H and –Br substituents were all first order in the styrene and showed a positive rho value of 0.52.



(63)

With electron-withdrawing substituents like $–CF_3$ and $–NO_2$, the reaction was slower and the Hammett plot showed a negative slope in this region. Normally, a Hammett analysis assumes that all styrenes react by the same mechanism and proceed through the same rate-determining step. Due to the break in the plot depicted in Fig. 1, there may be a change in rate-determining step or a significantly reorganized transition state (e.g., change in regiochemistry of cycloaddition).

The Hammett plot in Fig. 1 was obtained for the catalytic enyne metathesis between excess styrene and alkyne mediated by the second generation Grubbs carbene. Despite all the fundamental metathesis steps going on, the Hammett plot reveals the effect of electronics on the rate-determining step. The plot therefore reveals how alkene/styrene electronics influence the rate-determining step in the catalytic reaction. We considered that if individual, elementary steps of the catalytic cycle could be examined separately, the rate-determining step would show a similar kinetic profile in reaction rate with the various styrenes. To investigate this, we examined two separate steps in the enyne

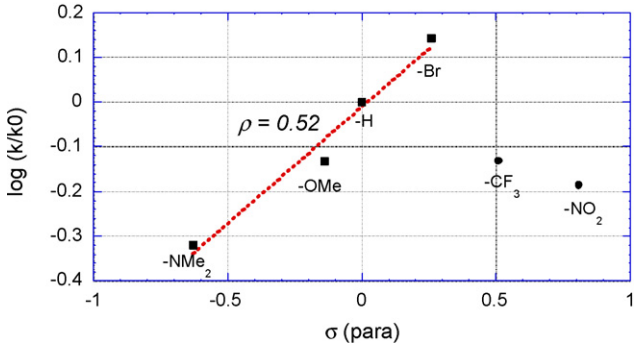
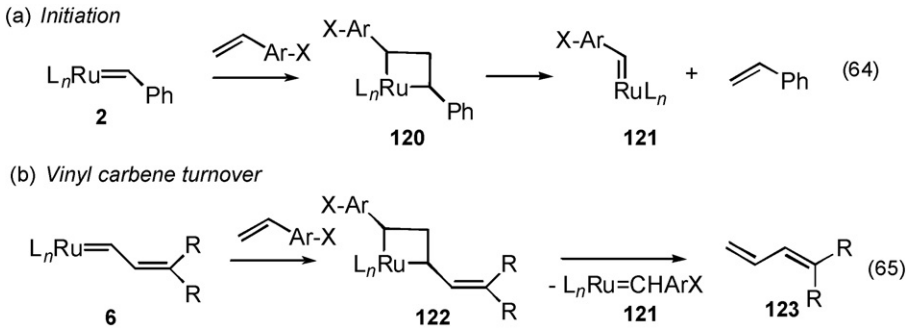


Fig. 1. Hammett plot for styrene–alkyne metathesis (taken from Diver and Giessert) [61].



Scheme 42. Modeled reaction steps for catalytic, intermolecular styrene–alkyne metathesis.

metathesis, the initiation to form the arylidene **121** and the vinyl carbene turnover, via **122** (Scheme 42). We expected initiation in Eq. (64) to be fast, and expected that the vinyl carbene turnover was the slow step. The vinyl carbene turnover step in Eq. (65) also shows the expected orientation of the styrene in the metallacycle **122**, based on the well-precedented transalkylidenation step of alkene metathesis.

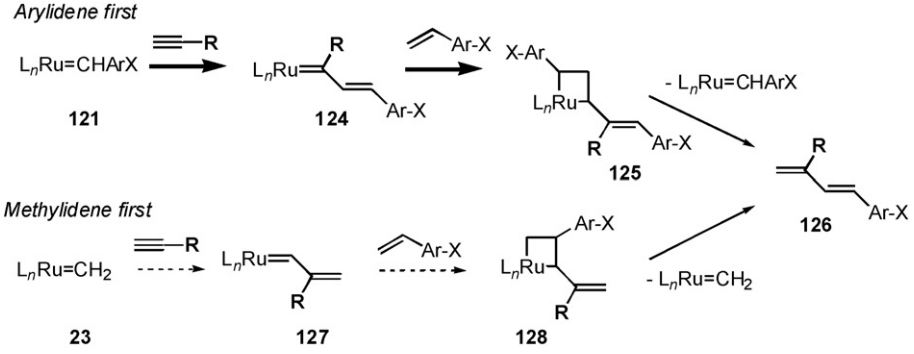
The arylidene initiation step proved to be fast and did not show a dramatic rate variation dependent of styrene substitution. In every case except *p*-nitrostyrene, the arylidene was immediately formed and observed by ^{1}H NMR. These data suggest that the styrenes react with the Grubbs benzylidene to give the corresponding arylidenes. The reaction is fast and favored based on the molar excess of the substituted styrene used. Most significantly, the plot did not show the same bimodal variation as observed for the catalytic reaction, which suggested that the arylidene formation (initiation) was not the rate limiting step intimated in the Hammett plot for the catalytic reaction.

The last step of the catalytic cycle, vinyl carbene turnover, proved more sensitive to electronic perturbation. The Hammett plot for this individual step resembled that obtained for the overall catalytic reaction. The modeled step of catalysis also showed a bimodal rate plot with slight acceleration by moderately electron-withdrawing substituents, then a break for highly electron-withdrawing substituents. This suggested that the vinyl carbene turnover step in Eq. (65) was probably rate-limiting since it displayed sensitivity to styrene electronics. The modeled step of catalysis used a vinyl carbene complex that has different substitution than a vinyl carbene produced in catalysis. For this study, we had used the vinyl carbene **6** available at the time.

The reaction of the vinyl carbene complex with styrene illustrates the preference for a vinyl carbene to accept a 'CH_2' group rather than a 'CHAr' group. We describe this as a 'methylene transfer' to the vinyl carbene carbon (Scheme 43). The modeled vinyl carbene turnover generated the arylidene L_nRu=CHAr **121** and 4-methyl-1,3-pentadiene **123** (R = Me), as shown in Eq. (65). If the model vinyl carbene shows this preference, it is likely that vinyl carbene complexes of ruthenium bearing additional α-substitution will display the same regiochemical preferences. These observations favor the top pathway on the basis of the sensitivity of vinyl carbene turnover to alkene electronics and the observed methylene transfer in the reaction of vinyl carbene **6** with *p*-substituted styrenes.

3.2.2. Kinetics of enyne metathesis

As mentioned in the introduction, enyne metathesis is not completely understood. The catalytic reaction is complicated and there are many variables such as the nature of the alkene and alkyne reactants and the catalyst used. Enyne metathesis has been interpreted within the framework of alkene metathesis. This was historically convenient, but does elucidate the reactive nature of ruthenium vinyl carbenes. Another factor exacerbated the melding of alkene and enyne metathesis, the rapid synthetic advances in enyne metathesis coupled with rapid catalyst development. Practitioners of enyne metathesis developing methodology used the limited mechanistic data available at the time. This has resulted in several misconceptions



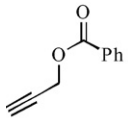
Scheme 43. Summary of regiochemistry possible in vinyl carbene turnover.

and ‘controversies’. Foremost among the controversies is whether the reaction proceeds by a ‘methylidene-first’ or an ‘alkylidene-first’ mechanism. Originally, the high reactivity of the methylidene suggested that it was the reactive intermediate, thought this hypothesis became increasingly inconsistent with observations in methodology studies. A second major point of confusion is the ethylene effect. Ethylene was long considered to be an essential additive to ring-closing metathesis, whereas there are many examples where it is not needed or beneficial. When should ethylene be used and what does it do? A third point is chelation and how it limits substrate scope, where it kinetically affects catalysis and when it leads to carbene decomposition. Last, the early proposals involved studies with the first generation Grubbs benzylidene complex. The field developed rapidly when Grubbs reported the second generation carbene complex **2**, which received immediate and widespread use. Thus, reactions performed with the second generation complex were compared to studies using the first generation complex. Lately, the phosphine-free Hoveyda complex has seen increased use and has led to a subfamily of phosphine-free carbene complexes. The Hoveyda complexes have no phosphine-bound states, and preliminary studies in our group have shown that this clearly affects the reaction rate of some enyne metatheses. It is likely that these complexes result in different rate laws. As our initial studies will illustrate, the rate-limiting step changes depending on alkene and alkyne used. Similar changes to the rate law are possible when using different carbene initiators.

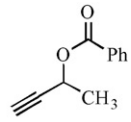
We undertook a mechanistic study of enyne metathesis examining reaction rate based on IR monitoring of the reaction. This study was conducted by my group in collaboration with my colleague at Buffalo, Professor Jerry Keister, an organometallic kineticist. The terminal alkyne reactant has a unique IR absorption: the CH bond stretch, which can be observed *in situ*, 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 [86].

The hexene–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 twenty (**118** more reactive than **129**). To test for chelation, we compared the benzoyloxy alkynes to their hydrocarbon analogs. Here we found that the more substituted alkyne, isopropylacetylene underwent reaction with 1-hexene some twenty times faster than the linear alkyne, octyne. Alkynes with the same propargyl substitution reacted with similar rates. These data suggest that there is not a chelation effect for ester functionality located at the propargylic position. However, since chelation is believed to be a complicating factor in many enyne metatheses, further comparisons between other functional group-containing alkynes with their hydrocarbon analogs are needed to identify chelation effects.

The ethylene-alkyne metathesis showed a different rate law. The ethylene-alkyne metathesis showed a zero order dependence on ethylene concentration and zero order dependence on propargyl benzoate **129**, but first order dependence on the more highly substituted alkyne **118**. The more substituted alkyne **118** reacted about twenty times faster than the less-substituted **129** under the same conditions. All the ethylene reactions were slower than the corresponding reactions with 1-hexene, at comparable alkene and alkyne concentrations.

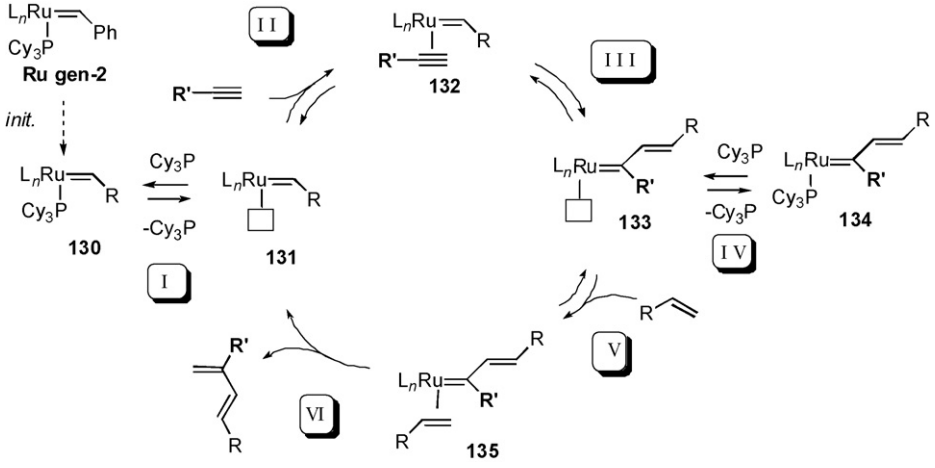


129



118

To interpret these data, we considered that reactant structure might influence catalyst resting state. The 14-electron intermediates **131** and **133** are catalytically active and 16-electron coordination complexes **130** and **134** are not catalytically active, but may represent kinetically accessible precatalyst states (Scheme 44). 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



Scheme 44. Proposed mechanism for intermolecular enyne metathesis based on kinetic study [86].

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 **131** (R = *n*-C_4H_9, an alkylidene) to be the active carbene catalyst. Based on the rate data, it reacts very quickly with the alkyne (via **132**) and forms a 14-electron vinyl carbene complex **133**. The vinyl carbene **133** can react with alkene in step V or rebind to phosphine in step IV. Alkene binding will lead to the product whereas phosphine binding leads to an inactive 16-electron complex **134**, which is a catalyst resting state. Our mechanistic picture focuses on the partitioning of the 14-electron vinyl carbene intermediate **133** [86].

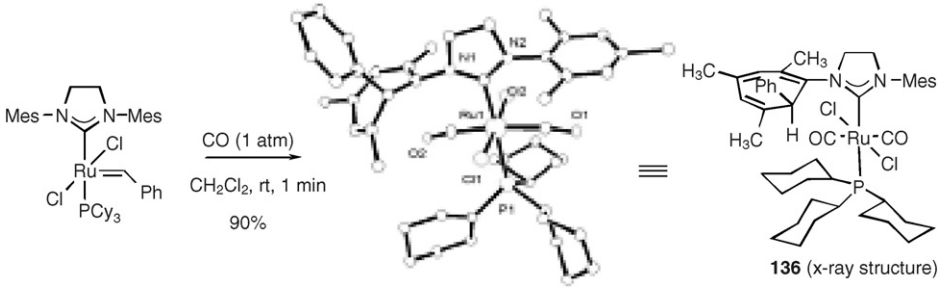
For the 1-hexene–alkyne metatheses, the rate data suggest that steps V or VI are the rate-determining steps. Since the reaction rate shows dependence on alkene concentration, higher alkene concentration will facilitate metathesis. The rate data do not distinguish whether the alkene binding step/cycloaddition (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. Lippstreu and Straub's DFT study suggested that the cycloreversion is rate-limiting [10], which is consistent with our data. Greater substitution at the propargylic position may increase the rate of catalysis by destabilizing complex **134**. Substitution of **134** at the site labeled R′ in Scheme 44 will destabilize the phosphine complex, increasing the phosphine off-rate or impeding the rate of coordination of free tricyclohexylphosphine to the vinyl carbene **133**.

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 **133** and increase the rate of turnover. However, the change in rate law for alkyne **118** reveals a change in rate-determining step to step II, alkyne binding/cycloaddition. Once **133** is formed it reacts forward faster than step II (Scheme 44). Somewhat surprisingly, 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-**118** versus 1-hexene-**118**, 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 **131** (R = H). For the second generation Grubbs methylidene, coordination by tricyclohexylphosphine is strong and the dissociative loss of phosphine is slow and unfavorable. This suggests that the resting state has shifted from vinyl carbene complex **134** (1-hexene metathesis) to methylidene complex **130** (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 **129** produces vinyl carbene intermediate **133** which can be captured by phosphine to give resting state **134** (R = H). This could be true if the rate of phosphine release from the 16-electron complex **134** is rate-limiting. Consistent with this proposal, we found that the Ph_3P version of the Grubbs complex **2** reacted 3.2 times faster (based on initial rates) in the ethylene metathesis of propargyl benzoate. Further experiments are needed to test these conclusions based on the limited set of rate data obtained so far.

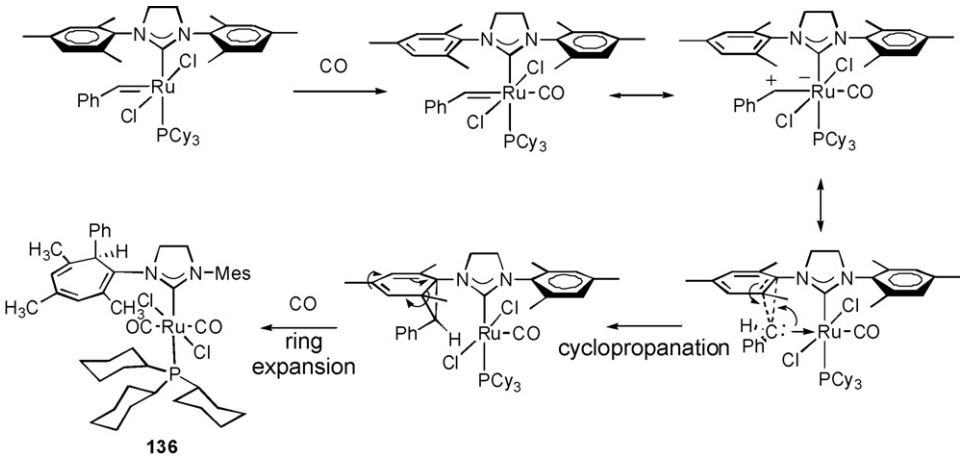
3.2.3. Ligand promoted insertion: an interesting carbene transformation

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 (or as convenient) as IR spectroscopy and we had to find a way to rapidly quench aliquots prior to analysis. To do this, we reasoned that a 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. Bubbling CO through a solution of the Grubbs second generation complex results in a canary yellow color. After one minute, perfusion was stopped. The yellow solid obtained after solvent removal was crystallized from dichloromethane–decane at −20 °C to afford crystals, mp 143–145 °C, corresponding to complex **136**. Interestingly, the carbon monoxide had promoted an insertion into one of the 2,4,6-trimethylphenyl (mesityl) rings of the dihydroimidazole carbene ligand (Eq. (66)) [87]. The net bond insertion represents a ring expansion of the benzene ring and occurs by a two-step process of cyclopropanation/6π-electrocyclization. This is an example of the Buchner reaction. The observed insertion is remarkable because of the exclusive regioselectivity in aromatic π-bond cyclopropanation. The coordination of carbon monoxide profoundly alters the reactivity of the metal carbene:



(66)



Scheme 45. Successive CO binding leads to ligand insertion.

Carbon monoxide coordination promotes cyclopropanation reactivity of the Grubbs carbene. One CO binding to ruthenium robs the metal of electron density through backbonding (Scheme 45). This effect deprives the benzylidene carbene of stabilizing electron density from the metal 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 slender ligands like aryl isocyanides also produce the insertion. We are studying the limits of this reactivity obtainable by other coordinating ligands.

4. Conclusion

Ruthenium vinyl carbenes are the important intermediates in enyne metathesis and serve to distinguish the enyne metathesis from alkene metathesis. One of the most fundamental questions is whether the reaction proceeds by an alkylidene-first or methylidene-first mechanism, because this determines the substitution pattern on the intermediate vinyl carbene. The substitution pattern will influence reactivity, resting state and determine susceptibility to chelation. Studies on vinyl carbene reactions with styrenes suggest the favored mode of reaction involves a methylene transfer, consistent with the alkylidene-first mechanism.

Many complexes have been synthesized with the most prominent methods being displacement of propargylic halides and metathesis. Some of the ruthenium complexes surveyed here offer useful structural information. Other complexes were synthesized as initiators for metathesis. The ligand environments that result in metathesis catalytic activity fall into the Grubbs subfamilies (L_2RuCl_2 or $(H_2IMes)LRuCl_2$) or the Dixneuf family (cationic arene-coordination complexes). By far, the Grubbs families of first and second generation carbene have been used the most in enyne metathesis due to their ease of handling, functional group tolerance and stability profiles. The non-metathesis reactions of vinyl carbene complexes have seen only cursory study, though the available data indicates predominant conjugate addition (at C_γ). The dynamic stereochemistry of isomeric ruthenium vinyl carbenes has been studied with equilibration taking place by either metathesis or by isomerization via metallacycle intermediates. The equilibration of intermediate vinyl carbenes was employed to improve the stereoselectivity of a tandem enyne metathesis for 1,3-cyclohexadiene ring synthesis.

Ruthenium vinyl carbene reactivity is an important consideration in the enyne metathesis catalytic reaction mechanism. On the one hand, the vinyl carbene is an electron-deficient metal carbene and should have similar reactivity to the corresponding alkylidenes. However, the vinyl carbene lies at a nexus in catalysis and can bind free phosphine to produce inactive resting states. The vinyl carbene can also experience chelation by pendant functionality arising from either the alkene or the alkyne substrates or may produce inactive ruthenium(II) complexes through decomposition pathways. Whether chelation in these instances is harmful to catalysis due to kinetic effects or decomposition is still an open question. Further studies on vinyl carbene reactivity, sensitivity to chelation and decomposition are needed.

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