

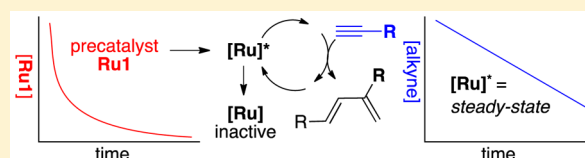
From Resting State to the Steady State: Mechanistic Studies of Ene–Yne Metathesis Promoted by the Hoveyda Complex

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S Supporting Information

ABSTRACT: The kinetics of intermolecular ene–yne metathesis (EYM) with the Hoveyda precatalyst (**Ru1**) has been studied. For 1-hexene metathesis with 2-benzoyloxy-3-butyne, the experimental rate law was determined to be first-order in 1-hexene (0.3–4 M), first-order in initial catalyst concentration, and zero-order for the terminal alkyne. At low catalyst concentrations (0.1 mM), the rate of precatalyst initiation was observed by UV–vis and the alkyne disappearance was observed by in situ FT-IR. Comparison of the rate of precatalyst initiation and the rate of EYM shows that a low, steady-state concentration of active catalyst is rapidly produced. Application of steady-state conditions to the carbene intermediates provided a rate treatment that fit the experimental rate law. Starting from a ruthenium alkylidene complex, competition between 2-isopropoxystyrene and 1-hexene gave a mixture of 2-isopropoxyarylidene and pentylidene species, which were trappable by the Buchner reaction. By varying the relative concentration of these alkenes, 2-isopropoxystyrene was found to be 80 times more effective than 1-hexene in production of their respective Ru complexes. Buchner-trapping of the initiation of **Ru1** with excess 1-hexene after 50% loss of **Ru1** gave 99% of the Buchner-trapping product derived from precatalyst **Ru1**. For the initiation process, this shows that there is an alkene-dependent loss of precatalyst **Ru1**, but this does not directly produce the active catalyst. A faster initiating precatalyst for alkene metathesis gave similar rates of EYM. Buchner-trapping of ene–yne metathesis failed to deliver any products derived from Buchner insertion, consistent with rapid decomposition of carbene intermediates under ene–yne conditions. An internal alkyne, 1,4-diacetoxy-2-butyne, was found to obey a different rate law. Finally, the second-order rate constant for ene–yne metathesis was compared to that previously determined by the Grubbs second-generation carbene complex: **Ru1** was found to promote ene–yne metathesis 62 times faster at the same initial precatalyst concentration.



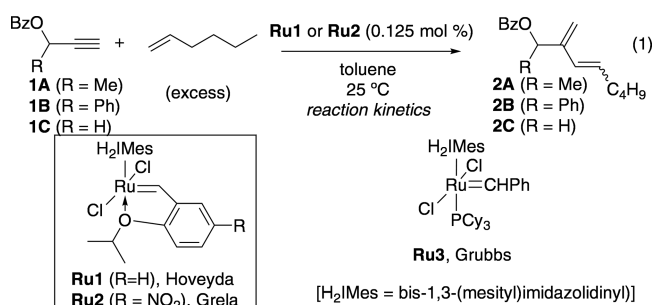
INTRODUCTION

Metathesis of unsaturated carbon–carbon bonds has become an indispensable method for the catalytic formation of new carbon–carbon bonds. Alkene and ene–yne metathesis are widely used in a variety of applications and have been successful in bringing about bond formation in complex molecules bearing high densities of functional groups, for example, in the total synthesis of natural products and for the synthesis of medically relevant compounds.¹ The metathesis catalysts used in these settings are diverse.² Particular emphasis in catalyst development has focused on the chelating ether motif discovered by Hoveyda and co-workers.³ Many of the most challenging current applications in total synthesis employ the Hoveyda catalyst (**Ru1**)^{3b,c} or variants.^{1c,f,j,n,o,r,s,v,x,y,ab–ad} Recently, mechanistic work by Plenio and co-workers has shed light on the initiation of alkene metathesis by the Hoveyda catalyst and its electronically tuned variants.⁴ However, it was unclear how the rapid initiation profile is linked to formation of an active intermediate, catalysis, and decomposition. For ene–yne metathesis, the phosphine-free nature of precatalyst **Ru1** should increase the ene–yne metathesis rate by limiting unproductive resting states. In this paper, we describe a mechanistic and kinetic study of ene–yne metathesis promoted by the Hoveyda (a.k.a. Hoveyda–Grubbs) ruthenium carbene

precatalyst (Scheme 1). This investigation provides insight on the alkene initiation process as it relates to catalysis.

The Hoveyda precatalyst is widely used and is a uniquely active metathesis precatalyst. The Grubbs catalyst **Ru3** initiates by a dissociative pathway that is independent of alkene concentration (0.173–1.02 M).⁵ In contrast, Hoveyda-type catalysts initiate with alkenes differently. During a ring-closing

Scheme 1. Kinetic Study of Ene–Yne Metathesis Promoted by Phosphine-Free Initiators (inset)



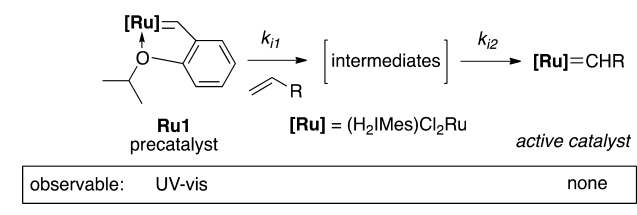
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metathesis (RCM) study, Dorta and co-workers found that rates of RCM showed diene concentration dependence, unexpectedly proceeding at faster rates for more concentrated diene solutions.⁶ This indicated that the initiation step depended on alkene concentration. The Hoveyda catalyst **Ru1** initiates with vinyl ethers with a negative entropy of activation (ΔS^\ddagger).^{4b,7} Detailed kinetic studies have been reported by Plenio and co-workers.^{4b} Plenio observed the disappearance of the precatalyst **Ru1** by UV-vis monitoring.^{5a,8} The initiation step was found to be a composite of interchange and dissociative mechanisms that depends on the structure of the alkene, its concentration, and the Hoveyda-type precatalyst used. For precatalyst **Ru1** and 1-hexene, the mechanism is predominantly associative, proceeding by an interchange process, and the rate law is roughly first-order in alkene.⁴

Though kinetic models of initiation are sound, the **Ru1** initiation process is not well understood. The overall activation process forms a catalytic intermediate that is common to both alkene and ene-yne metathesis. Recently, Grubbs and co-workers studied initiation by Hoveyda-type precatalysts and noted that “the mechanism of initiation by the Hoveyda-type initiators is complex and the subject of ongoing investigation”.^{2a} Initiation has been studied from the front end: the rate of disappearance of the precatalyst **Ru1** can be directly observed with different alkenes.⁴ This is due to the loss of a metal-to-ligand charge transfer (MLCT) band associated with **Ru1** (UV-vis). It is thought that intermediates are formed that lead to the active catalyst.^{4a,9} Experimentally, this has been difficult to study because as **Ru1** decreases there are no observable intermediates (Scheme 2). What does the precatalyst give as it

Scheme 2. Disappearance of Precatalyst Ru1 and the Net Initiation Process



initiates? Is it possible that the active catalyst concentration may change over time? If the precatalyst does not directly form the active catalyst, what rate process regulates the formation of the active catalyst? One way to approach this problem is to track the rate of a catalytic process vis-à-vis the precatalyst rate of

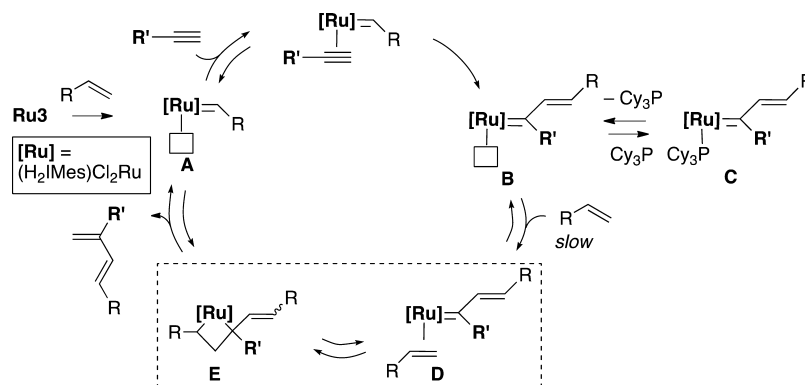
initiation. This can indirectly probe the production of an active catalyst through its participation in a catalytic process.

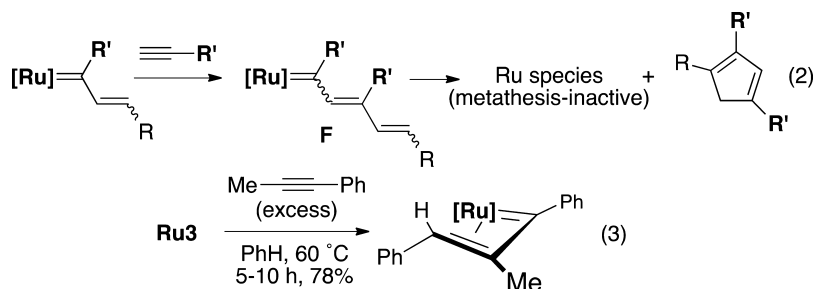
Phosphine-bound intermediates are thought to play an important role in ene-yne metathesis using the second-generation Grubbs complex **Ru3**. A proposed mechanism of ene-yne metathesis (EYM) was suggested for the **Ru3** carbene precatalyst (Scheme 3).¹⁰ The mechanism involves initiation of the alkene to make an intermediate $[\text{Ru}]=\text{CHR}$ (**A**). Alkyne insertion into the ruthenium carbene gives vinyl carbene **B**. The rate-determining step occurs from **B**, which exists in an unproductive equilibrium with its phosphine-bound resting state **C**. Intermediate **C** was hypothesized to slow catalysis, as it requires a phosphine dissociation step. The equilibrium between **C** and **B** regulates active carbene intermediates passing through the slow step, which involves alkene binding. The vinyl carbene has been calculated to be a stable carbene intermediate (as compared to $[\text{Ru}]=\text{CHR}$), and the alkyne insertion step is an irreversible elementary step.¹¹ The rates of internal alkynes or EYM promoted by phosphine-free initiators (e.g., **Ru1**, **Ru2**) have not been studied.¹²

Ene-yne and alkene metathesis share some reactive intermediates. In EYM, reactive intermediates include both ruthenium carbenes and ruthenacyclobutanes (rcb or rcbs). The active catalysts in alkene metathesis are the ruthenium carbenes $[\text{Ru}]=\text{CHR}$ and $[\text{Ru}]=\text{CH}_2$. These 14-electron, coordinatively unsaturated species are highly reactive and have not been directly observed. Romero and Piers¹³ and Wenzel and Grubbs¹⁴ independently found rcb intermediates in alkene metathesis. On the basis of the rates of exchange between α - and β -carbons of the rcb, the corresponding η^2 -alkene complex is about 12 kcal/mol higher in energy above the rcb. Loss of the coordinated alkene gives the highly active 14-electron ruthenium carbene intermediate (**A** in Scheme 3).

Ene-yne metathesis features a unique ruthenium carbene, the vinyl-substituted carbene. In ene-yne metathesis, vinyl carbenes **B** are formed after the alkyne insertion step; their existence was inferred from a kinetic study of the catalytic reaction.^{10,15} Like ruthenium alkylidenes (**A**), vinyl carbenes **B** are unstable and highly reactive 14-electron intermediates. DFT studies have gauged their relative energy levels.^{9,16} With the first-generation Grubbs catalyst, vinyl carbenes have been observed spectroscopically.¹⁷ If a chelating group is present, the vinyl carbene may be stabilized enough to be isolable.¹⁸ The reaction rate of vinyl carbene-phosphine complex reacting with *p*-substituted styrenes was studied as a model step of the vinyl carbene turnover step.¹⁹ On the basis of our earlier kinetic

Scheme 3. Previously Proposed Mechanism of Ene-Yne Metathesis (with Grubbs catalyst Ru3)¹⁰



Scheme 4. Two Distinct Decomposition Pathways for Ruthenium Vinyl Carbenes^{26,27}

study,¹⁰ the phosphine-bound resting state C was viewed as a barrier to catalysis by regulating active vinyl carbene B. Simplistically, we reasoned that if there were no phosphine-bound resting state C, the EYM would proceed at a faster reaction rate.

Carbene intermediates and ruthenacyclobutanes are highly reactive intermediates and are known to decompose by several different pathways. The activation free energy (ΔG^\ddagger) for initiation of **Ru1** with butyl vinyl ether is +19.6 kcal/mol (toluene at 303 K).^{9b} The resulting carbene intermediate is almost 20 kcal/mol higher in energy than the chelated precatalyst and is susceptible to decomposition. Metathesis of 1-alkenes proceeds through a $[\text{Ru}]=\text{CH}_2$ species. Grubbs and co-workers found that the ruthenium methylidene undergoes decomposition to form a dinuclear ruthenium hydride.²⁰ In the presence of coordinating ligands, the ruthenium methylidene may extrude a phosphorus ylide, eliminating metathesis activity.²¹ Ruthenium carbenes undergo dimerization, thereby destroying the carbene and abolishing metathesis activity.²² Some Hoveyda-type complexes undergo intramolecular CH activation.²³ In the presence of alcohols, such as allylic or primary alcohols, ruthenium carbenes are converted into ruthenium hydrides,²⁴ which abolish metathesis reactivity and may lead to unwanted side reactions such as alkene isomerization. Ruthenacyclobutanes have also been found to thermally decompose through a β -hydride elimination/reductive elimination pathway.²⁵

For decomposition related to ene-yne metathesis, there are distinct pathways that depend on the presence of the alkyne. First, a vinyl carbene derived from **Ru1** may insert a second alkyne, giving F (eq 2, Scheme 4). This species may undergo reductive elimination, thereby destroying the carbene and eliminating metathesis activity.²⁶ Second, Grubbs and co-workers observed that **Ru3** reacted with phenyl-containing alkynes to give complexes that appeared to be derived from vinyl carbene intermediates but were found to be metathesis-inactive (eq 3, Scheme 4).²⁷ Other related alkyne side reactions such as cyclotrimerization²⁸ are also known; however, these do not destroy the ruthenium carbene. Of course, analogous pathways may operate for ruthenium vinyl carbenes as for ruthenium alkylidenes. Vinyl carbene dimerization was observed by Fogg and co-workers, where the organic dimerization byproduct was identified.²⁹

On the basis of these considerations, we initiated a mechanistic study of the EYM promoted by the phosphine-free precatalyst **Ru1**. Several questions guided the design of our study. If phosphine regulates vinyl carbene intermediates with phosphine-containing Grubbs catalysts such as **Ru3**, what happens when no phosphine is present? Is the rate law the same, and in what way does the reaction show sensitivity to

structural effects in the alkyne reactant? Can any reactive intermediates be trapped or observed spectroscopically? Is a faster initiator for alkene metathesis better for ene-yne metathesis also? Herein we present a detailed kinetic study of ene-yne metathesis promoted by the Hoveyda precatalyst **Ru1**. We employ a rapid trapping technique using added isocyanides to trigger a Buchner reaction that potentially allows identification of carbene intermediates. The simultaneous observation of the **Ru1** initiation reaction and that of catalytic ene-yne metathesis allowed a unique and direct comparison that relates initiation of precatalyst to the rate of ene-yne metathesis. These studies revealed that steady-state concentration of reactive intermediates was rapidly attained and maintained over the duration of the catalytic reaction.

RESULTS

To study the rate of ene-yne metathesis we enlisted IR spectroscopy for the in situ monitoring of terminal alkyne concentration. Alkyne loss was monitored by integration of the CH stretching IR absorption in a thermostated reaction vessel under an argon atmosphere. Typical conditions used 0.08 M alkyne **1A**, 1-hexene (0.5–4.0 M), and 0.1 mM **Ru1** in toluene at 25 °C (eq 1, Scheme 1). The IR method provides a large number of data points, and the experiments are easily repeated so that multiple trials of each set of conditions could be done to maximize data accuracy. At high 1-hexene concentrations or higher catalyst loadings, the alkyne disappeared linearly over time (Figure 1), indicating zero-order dependence on alkyne

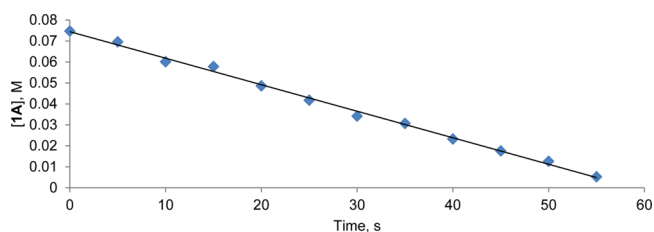


Figure 1. Plot of alkyne conversion versus time. Alkyne concentration was determined by integration of the alkyne CH stretching frequency at 3310 cm^{-1} at 5 s intervals. Reaction conditions: 0.08 M alkyne **1A**, 3 M 1-hexene, 0.1 mM **Ru1** in toluene at 25 °C. In this run, k_{obs} was found to be $(1.26 \pm 0.02) \times 10^{-3}$ M/s.

concentration, as we observed in the previous study with **Ru3**. The linear plot directly provides the rate of alkyne disappearance, which is reported as k_{obs} . Because of the zero-order alkyne dependence and the pseudo-order conditions, rate = k_{obs} , and k_{obs} has units of M/s. A solvent effect was observed,^{2b,5a,30} with reaction rates found to be at least 6 times faster in toluene as compared to 1,2-dichloroethane (DCE). As

a result, the kinetic runs were performed in toluene. Importantly, the initial precatalyst concentration ($[\text{Ru1}]_0$) could be reduced to 0.1 mM, or 0.125 mol %, based on the alkyne, and most reactions (>1 M 1-hexene) went to completion.³¹

Orders in Reactants and Lack of Saturation Kinetics. Variation of the alkene concentration from 0.5 to 4.0 M revealed a first-order dependency and lack of saturation kinetics (Figure 2). The initial alkyne concentration was 0.08 M

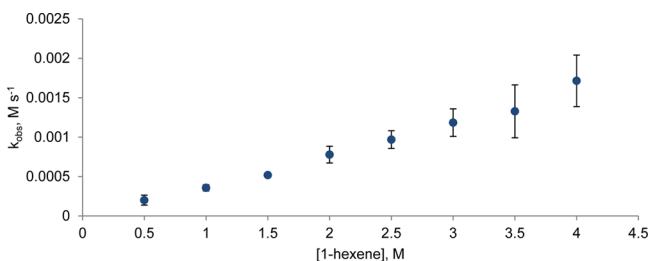


Figure 2. Plot of k_{obs} vs [1-hexene]. From 0.5 to 4 M 1-hexene, saturation of the reaction rate was not observed. Reaction conditions: 0.08 M alkyne **1A**, 0.5–4.0 M 1-hexene, 0.1 mM **Ru1** in toluene at 25 °C. At higher 1-hexene concentrations, the significantly faster reaction rates provided fewer data points, increasing the error.

throughout this study. By taking the $\ln(k_{\text{obs}})$ and plotting against $\ln[1\text{-hexene}]$, the order in 1-hexene was found to be 1.03 ± 0.05 (data not shown),³² similar to a previous study using the Grubbs complex **Ru3**.¹⁰ At this stage, a vinyl carbene intermediate **B** (Scheme 3, above) was hypothesized whose rate of catalytic turnover would be dependent on alkene concentration. With a small amount of catalytic intermediate, we expected that it would be possible to saturate the reaction rate by employing successively higher alkene concentrations. However, Figure 2 shows that the reaction rate could not be saturated, even at 4 M 1-hexene.³²

The order in the catalyst was similarly determined and gave an overall rate law for the ene-yne metathesis. The concentration of the active form of the catalyst cannot be directly measured, but it is proportional to the initial concentration of precatalyst $[\text{Ru1}]_0$. Obtaining k_{obs} at increasing **Ru1** concentrations (0.1–1 mM **Ru1**, 80 mM **1A**, 0.5 M 1-hexene in toluene at 25 °C) showed an increasing rate.³³ A plot of $\ln(k_{\text{obs}})$ vs $\ln[\text{Ru1}]_0$ was linear with a slope of 0.97, indicating a first-order rate dependence on $[\text{Ru1}]_0$.³² Overall, the experimental rate law was thus determined to be $\text{rate} = k_{\text{EYM}}[\text{Ru1}]_0^1[\text{alkene}]^1[\text{alkyne}]^0$ (under conditions that lead to complete consumption of alkyne).

Dual Tracking of Alkyne Disappearance and Precatalyst Initiation. A direct rate comparison between alkyne consumption and precatalyst **Ru1** consumption (the first step of catalyst initiation) was possible. The low precatalyst concentration permitted the use of two spectroscopic methods: IR to track alkyne concentration and UV-vis to track the precatalyst **Ru1** concentration over time. These two methods allowed for the determination of ene-yne metathesis rate and the rate of catalyst initiation (**Ru1** decay) under the same conditions but as separate experiments (Figure 3).

Full precatalyst initiation occurs on roughly the same time scale as complete conversion of the alkyne. The plot is scaled with respect to total change in species (A) concentration from $[A]_0$ to $[A]_{t \rightarrow \infty}$ showing that each species reaches $\sim 90\%$ conversion at about 50 s. By inspection of Figure 3, the half-life

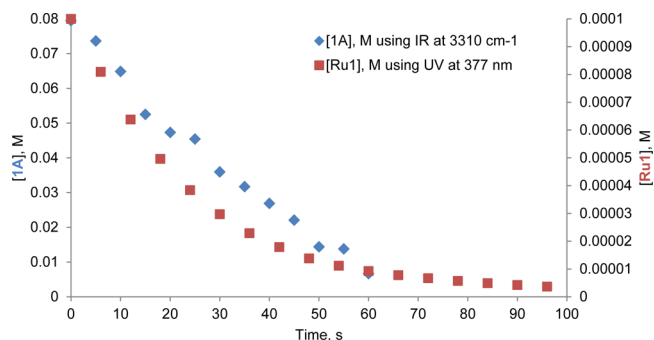


Figure 3. Overlay of precatalyst initiation rate and rate of ene-yne metathesis. The alkyne **1A** disappearance (diamonds) matches the left y-axis, measured by diminution of the alkyne absorbance at 3310 cm^{-1} , measured by in situ FT-IR. The initiation rate of **Ru1** (squares) matches the concentrations on the right y-axis, measured by disappearance of the absorption at 377 nm, determined by UV-vis. Each kinetic run was performed under identical conditions but obtained separately. Conditions: 0.1 mM **Ru1**, 80 mM alkyne **1A**, 3 M 1-hexene, toluene, 25 °C.

of alkyne **1A** (e.g., reflecting the EYM rate) is ~ 30 s, and the half-life of **Ru1** is ~ 19 s. Ene-yne metathesis continues as long as precatalyst **Ru1** remains.

Lower alkene concentration results in incomplete conversion due to catalyst decomposition. In similar measurements made at 1 M 1-hexene (data not shown), the EYM stalled at 50% conversion after 100 s.³² By that time, 97% of **Ru1** had initiated. At these lower alkene concentrations, the EYM rate is slower and incomplete conversion of alkyne is found. This suggests that the EYM cannot stay ahead of decomposition.

An active catalyst persists longer under alkene metathesis conditions than under ene-yne metathesis conditions (Figure 4). The rate of ene-yne metathesis and the rate of alkene

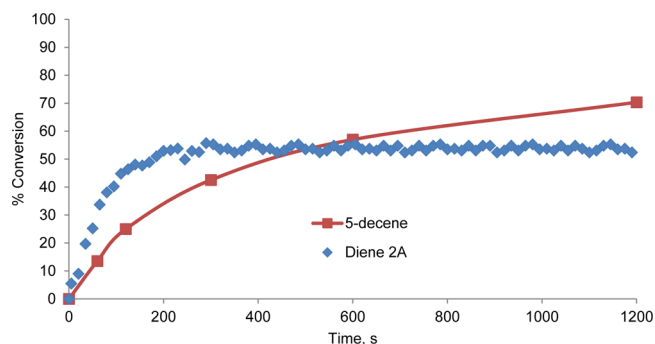


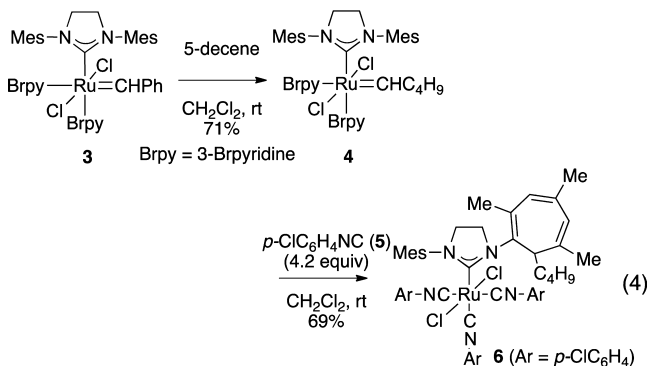
Figure 4. Comparison of alkene and ene-yne metathesis. Alkene metathesis followed the formation of 5-decene (GC). For ene-yne metathesis, the concentration of 1,3-diene **2A** was calculated by following alkyne disappearance (in situ IR) according to $[2A] = [1A]_0 - [1A]_t$. Conditions: 0.1 mM **Ru1**, 0 or 80 mM alkyne **1A**, 1 M 1-hexene, toluene, 25 °C.

metathesis was followed under identical conditions (0.1 mM **Ru1**, 0 or 80 mM alkyne **1A**, 1 M 1-hexene, toluene, 25 °C). For instance, in Figure 4, the EYM proceeded to about 50% conversion to 1,3-diene **2A** after 200 s and then stalled. At this point, precatalyst **Ru1** had fully initiated. In contrast, alkene metathesis conversion to 5-decene, in the absence of alkyne, continues for much longer periods. In alkene metathesis, active catalyst is still present at least 10 times longer than under comparable conditions of ene-yne metathesis. This is due to

greater catalyst decomposition occurring under ene-yne metathesis conditions.

Trapping Studies Using the Isocyanide-Promoted Buchner Reaction. Earlier, we reported rapid Buchner quenching reactions promoted by isocyanides.³⁴ We thought that this reaction might allow us to trap the active carbene intermediates that form upon precatalyst disappearance. To detect reactive intermediates, the rate of isocyanide-promoted Buchner reaction has to be faster than the expected lifetime of the intermediate. From the kinetic runs above, 0.1 mM Ru1 gives complete conversion of 80 mM alkyne, thereby giving a turnover number of 800 (or higher). The reaction in Figure 3 is complete in 60 s, meaning that the lifetime of catalytic intermediate(s) is ≤ 75 ms. Before quenching-rate studies could be performed, it had to be determined that $[\text{Ru}]=\text{CHR}$ could be rapidly trapped by an added isocyanide.

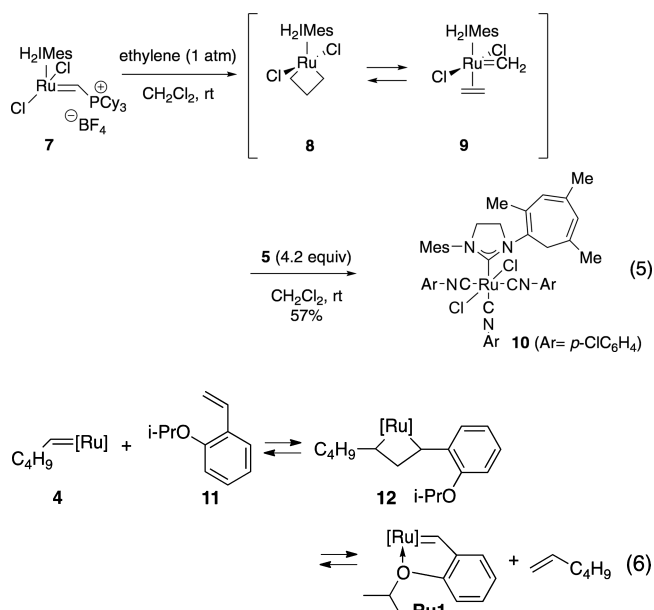
To evaluate the feasibility of trapping alkylidenes $[\text{Ru}]=\text{CHR}$, a suitable 14-electron alkylidene surrogate was needed. The Grubbs pyridine solvate **3**³⁵ offers a means to isolate and handle a surrogate for the 14-electron ruthenium carbene intermediate under question. Following Sponser's protocol,³⁶ we prepared the new alkylidene **4** (eq 4). When **4** was exposed



to *p*-chlorophenyl isocyanide (**5**), Buchner insertion produced a new complex (**6**) in 69% isolated yield. Presumably one or both pyridines are dissociated, providing a similar intermediate as encountered in the alkene self-metathesis of 1-hexene and ene-yne metathesis between 1-hexene and an alkyne.

Additionally, the ruthenium methylidene $[\text{Ru}]=\text{CH}_2$ proved trappable by isocyanide-promoted Buchner insertion. The ruthenium methylidene is the chain carrier in alkene metathesis and may form late in ene-yne metathesis due to alkene self-metathesis. Earlier work showed that the corresponding Cy_3P complex $(\text{H}_2\text{IMes})(\text{Cy}_3\text{P})\text{Cl}_2\text{Ru}=\text{CH}_2$ was trapped by CO and isocyanides.^{34c} Exposure of Piers's catalyst **7**¹³ to ethylene produced an intermediate that at low temperature can be observed as the ruthenacyclobutane **8**. Addition of an excess of *p*-chlorophenyl isocyanide (**5**) gave the new complex **10** (eq 5). However, the rate of the Buchner reaction in relation to catalytic ene-yne metathesis was not established. Could the Buchner reaction be used to trap intermediates under catalytic conditions?

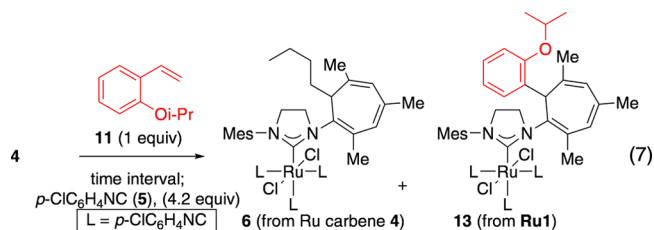
The exchange of one carbene fragment for another one is termed transalkylidenation, and it is one of the fastest processes in alkene metathesis (eq 6).³⁷ Transalkylidenation proceeds through a ruthenacyclobutane intermediate **12**.^{13,14} Starting with the active carbene species **4**, capture by 2-isopropoxystyrene (**11**) forms **12**, which can break down to form the Hoveyda complex **Ru1** and 1-hexene. As written from left to right, eq 4 depicts the "boomerang effect",^{3a,b,38} where **11** returns active



carbene back to the chelated precatalyst **Ru1**. In the reverse direction, eq 6 depicts initiation of **Ru1** with 1-hexene. In a typical catalytic metathesis application, the concentration of alkene is much higher relative to **Ru1** and any released **11** (which will only be as high as the precatalyst loading).

A simple experiment showed that the isocyanide quench was capable of trapping metal carbenes faster than ruthenium carbene exchange. Starting with carbene complex **4**, an equimolar amount of **11** was added at the same time as an excess of isocyanide **5** (eq 7, Table 1, entry 1). If no carbene

Table 1. Relative Rate of Buchner-Trapping vs Carbene Exchange



entry ^a	added alkene	time interval (min)	relative ratio 6:13 (%) ^b
1	none	0	100
2	none	1	24
3	1-hexene (0.8 M)	1	52
4	1-hexene (1.6 M)	1	60

^aComplex **4** and **11** were each 10 mM, in CD_2Cl_2 , at 25 °C. ^bRelative ratio determined by ¹H NMR spectroscopy with mesitylene as an internal standard.

exchange occurred, species **4** would trap as **6**. If carbene exchange were faster than the isocyanide-promoted Buchner reaction, then a mixture of products would result. In the event, a single Buchner insertion product **6** was obtained, giving resonances at δ 5.82, 5.53, and 3.32 ppm for the cycloheptatriene vinylic and methine protons. The previously characterized complex **13** was not present. At this stoichiometry, it can be concluded that the isocyanide coordination/Buchner insertion is faster than carbene exchange using styrene **11** (transalkylidenation process).³⁹

If a waiting time interval is added, a significant amount of metal carbene exchange (transalkylidenation) is found. If addition of **11** precedes the addition of isocyanide by 1 min, then 76% exchange had occurred, giving predominantly **13** (Table 1, entry 2).^{34c} In the presence of an 80-fold excess of alkene (Table 1, entry 3), significant return to **Ru1** is evidenced by the nearly 1:1 mixture of **6** and **13**, despite the 80-fold excess of 1-hexene. On the basis of this result, the effective molarity⁴⁰ of the chelating alkene **11** is 80 compared to 1-hexene. This suggests that a recapture by ejected styrene **11** can occur competitively with a large excess of a terminal alkene.⁴¹

Inhibition Studies.⁴² Addition of 2-isopropoxystyrene (**11**) had a small inhibitory effect on the ene-yne metathesis reaction rate (Table 2). The ene-yne metathesis of **1A** and 1-

Table 2. Inhibition of EYM by 2-Isopropoxystyrene (11**)^a**

entry	Ru1 (mM)	11 (mM)	k_{obs} (M s^{-1})	k_{rel}
1	1	0	$(2.80 \pm 0.02) \times 10^{-4}$	1.00
2	1	1	$(2.35 \pm 0.01) \times 10^{-4}$	0.84
3	1	3	$(2.20 \pm 0.01) \times 10^{-4}$	0.79

^aConditions: 0.08 M alkyne **1A**, 1 M 1-hexene, 1 mM **Ru1**, 0–3 mM **11**, 1,2-DCE, 25 °C (temperature control), with the change in alkyne absorbance at 3310 cm^{-1} monitored by in situ FT-IR.

hexene was examined. Without added styrene, the k_{rel} was set as 1.00 (entry 1). With an equimolar amount of **11** present, the rate was slower, giving $k_{\text{rel}} = 0.84$ (entry 2). In this case, the molar ratio of 1-hexene/**11** is 1000:1. When the concentration of **11** was tripled, a further, albeit smaller, diminution of rate was observed ($k_{\text{rel}} = 0.79$, entry 3). On the basis of the isocyanide trapping experiments, the apparent equilibrium constant for exchange of 2-isopropoxystyrene (**11**) for 1-hexene is ca. 80, so the expected change in concentration of the active catalyst in the presence of added 3 mM **11** at 1 M hexene is ca. 80% of that which would be present in the absence of added **11**. This equilibrium estimate is consistent with the observed 21% reduction in rate (entry 3 vs 1, Table 2).

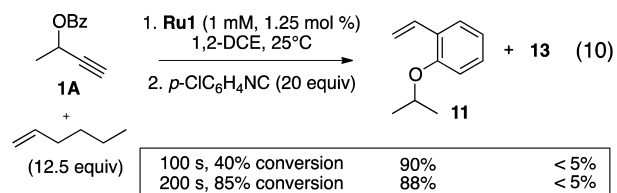
Trapping Studies under Metathesis Conditions. With a sufficiently fast Buchner reaction, we attempted to trap intermediates present in precatalyst initiation (alkene metathesis) and those present during ene-yne metathesis.

After the precatalyst had initiated, Buchner-trapping gave exclusively the 2-isopropoxyarylidene insertion product (**13**). After 4 min, >50% of **Ru1** had initiated, on the basis of UV-vis studies.^{4b,43} At this point, isocyanide was added, giving **13** in 99% yield (eq 8, Scheme 5). Whatever species had formed upon loss of **Ru1**, it still retained the 2-isopropoxystyrene moiety, which became trapped as the Buchner product **13**. The intermediate formed was not the active carbene $[\text{Ru}]=\text{CHR}$,

because no **6** was found. Lack of **6** is most likely due to a very low concentration of the active carbene.

That **Ru1** had disappeared cannot be taken as an initiation to form an active catalyst. If it were a direct process, as **Ru1** disappeared, the active carbene would concomitantly appear and rise in concentration. On the basis of the diminished UV absorption, the precatalyst **Ru1** had significantly initiated to a new species. It is presumed that **Ru1** enters the equilibrium of eq 9 (Scheme 5), leading to **G**, **H**, or **I**. The isocyanide-triggered Buchner insertion traps what appears to be **Ru1**, which implies that a rapid equilibrium exists between these intermediates. We already showed that isocyanides can induce a Buchner reaction from ruthenacyclobutanes (vide supra). Each of these reactive intermediates still contains the 2-isopropoxystyrene ligand and could therefore produce **13**. This may be a Curtin-Hammett situation, where the reactive intermediates of eq 9 (Scheme 5) have lower energies of interconversion than the barrier of isocyanide-promoted insertion.

Trapping under EYM delivered very little Buchner-trapping products and similarly did not identify any ruthenium carbene intermediates. The EYM was run to varying conversions and quenched by addition of isocyanide (eq 10). In the first case,

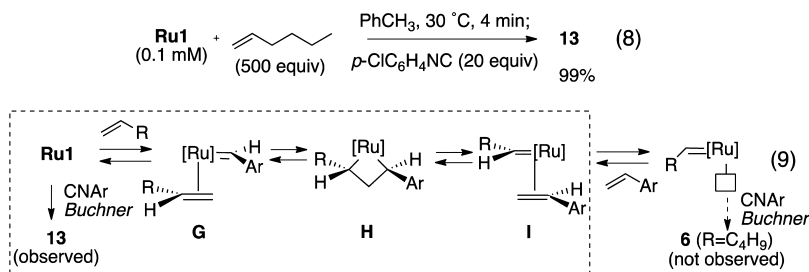


after 40% conversion of alkyne, isocyanide quench resulted in <5% **13** and 90% **11**. After a longer time interval, 85% conversion of alkyne had occurred, with a similar ratio of Buchner product **13** and styrene **11** observed. At these incomplete alkyne conversions, most of the precatalyst had initiated. Unlike the alkene metathesis example above, Buchner quenching of an EYM did not show trapping as precatalyst **Ru1**, since complex **13** was not obtained above trace levels. This is due to greater decomposition triggered by the presence of the terminal alkyne.

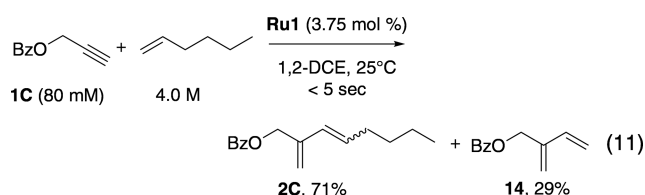
Alkyne Steric Effects. An additional alkyne substrate showed that the ene-yne metathesis rate is sensitive to steric effects in terminal alkynes. A propargylic phenyl group was compared to a methyl group (**1B** vs **1A**; see structures in Scheme 1 above). With a methyl substituent, the EYM rate was 2.75 times faster than with a phenyl substituent.³² The rate of EYM of terminal alkynes is sensitive to the degree of propargylic substitution.

Unbranched Terminal Alkynes. Propargyl benzoate did not react cleanly to give the 1,3-diene product under any of the

Scheme 5. Buchner-Trapping under Alkene Metathesis Conditions

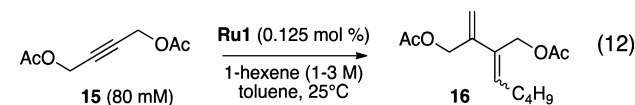


reaction conditions used in this study. At 2 M 1-hexene, the reaction stalled at 30% conversion to **2C** (eq 11). Propargyl



benzoate **1C** is known to engage in a unique decomposition pathway²⁶ which destroys the Ru=C bond and produces a metathesis-inactive Ru product. At higher 1-hexene concentration, complete conversion could be obtained, but an inseparable byproduct **14** was also formed (eq 11). Normally, ene-yne metathesis of terminal alkynes and 1-alkenes is faster than alkene self-metathesis. However, such high alkene concentrations lead to competitive alkene metathesis, which results in a [Ru]=CH₂ species. In the presence of an alkyne, [Ru]=CH₂ leads to the unwanted byproduct. For alkynes prone to decomposition, higher alkene concentration and higher loading of **Ru1** helps outpace decomposition. For synthetic applications employing ene-yne metathesis of unbranched terminal alkynes, alternative reaction conditions^{1q} or use of a different Grubbs precatalyst (such as **Ru3**) would be advisable.

Internal Alkynes. Internal alkynes react via a different rate law. Unlike terminal alkynes, the rate of disappearance of internal alkyne **15** shows exponential decay, indicating non-zero-order dependence (eq 12). Logarithmic plots gave straight



lines ($\ln[15]$ vs t), indicating first-order alkyne dependence (Table 3). Similar to the studies with terminal alkynes, no

Table 3. EYM Reaction Rate for Internal Alkyne 15^a

entry	1-hexene (M)	k_{obs} (s ⁻¹)
1	1	$(7.17 \pm 0.51) \times 10^{-3}$
2	2	$(1.35 \pm 0.05) \times 10^{-2}$
3	3	$(1.85 \pm 0.25) \times 10^{-2}$

^aConditions: 0.08 M **15**, 1–3 M 1-hexene, 0.1 mM **Ru1**, toluene, 25 °C (temperature control), with the change in the carbonyl absorbance at 1755 cm⁻¹ monitored by in situ FT-IR.

saturation kinetics were observed up to 3 M 1-hexene concentration. The $\ln(k_{\text{obs}})$ obtained from the slopes of the lines were plotted against $\ln[1\text{-hexene}]$ to give a kinetic order of 0.84.³² Further dependencies in catalyst and alkene remain to be determined in the future, and are the subject of ongoing studies.

Though they obey a different rate law, internal alkynes react at similar overall rates as compared to terminal alkynes. For comparison, terminal alkyne **1A** had a $t_{1/2} = 52$ s (apparent zero-order k_{obs} , 0.08 M alkyne, 2 M 1-hexene, 0.1 mM **Ru1**). The internal alkyne **15** showed a $t_{1/2} = 72$ s (apparent first-order k_{obs} , 0.08 M alkyne, 2 M 1-hexene, 0.1 mM **Ru1**). This data provides an interesting comparison considering that the different alkynes have different overall reaction orders and different rate-determining steps.^{12,44}

Rate with Grela Catalyst. A faster initiating precatalyst gives similar k_{obs} for the ene-yne metathesis of **1A** and 1-hexene. In ring-closing metathesis (RCM) applications, the overall rate is initiation-limited:^{2a,c,4} faster initiators give faster rates of RCM. For instance, the Grela precatalyst⁴⁵ **Ru2** initiates with the alkene diethyl diallylmalonate (DEDAM) 3.2 times faster than the precatalyst **Ru1**, resulting in a faster RCM (Table 4).^{4a,46} In contrast, the EYM rate does not correlate

Table 4. EYM Rate Constant and Initiation Rate Constant of Two Different Catalysts

precatalyst	k_{EYM}^a (M ⁻¹ s ⁻¹)	k_{init}^b (M ⁻¹ s ⁻¹)	k_{rel} (initiation, DEDAM)
Ru1	4.3 ± 1.1	0.0238 ± 0.0032	1.00
Ru2	5.0 ± 1.0	0.0764 ± 0.0020	3.21

^aThis work. Conditions: 0.08 M alkyne **1A**, 1 M 1-hexene, 0.1 mM **Ru1**, toluene, 25 °C (temperature control), with the change in alkyne absorbance at 3310 cm⁻¹ monitored by in situ FT-IR. The experimental k_{obs} values were divided by [1-hexene] and [Ru1] to obtain the second-order rate constant, k_{EYM} . ^bReaction with diethyl diallylmalonate (DEDAM), in toluene, at 40 °C. From ref 4a.

with initiation rate differences for the Hoveyda and Grela precatalysts (Table 4); if it did, the EYM by **Ru2** would be ~3 times faster than that promoted by **Ru1**.

DISCUSSION

The kinetic and mechanistic studies presented above provide a better picture of metatheses promoted by the phosphine-free precatalyst **Ru1**. The initiation process of **Ru1** and the intermediacy of Ru=CHR are relevant to both alkene and ene-yne metathesis. Control studies established that the rate of Buchner insertion was fast enough to trap ruthenium carbene intermediates. The comparison between catalyst longevity under alkene vs ene-yne metathesis shows that catalyst is longer lived in alkene metathesis and that catalyst decomposition is more pronounced in the presence of a 1-alkyne. At the very low precatalyst loadings used, no carbene intermediates could be trapped even when most of the precatalyst had initiated.

The active form of the catalyst is present in a low, steady-state concentration. The dual rate plot in Figure 3 shows that the rate of EYM does not increase as more precatalyst initiated. As the precatalyst **Ru1** continues to disappear, the rate of the ene-yne metathesis remains the same. This indicates that the active catalyst does not increase in concentration; the catalyst is present in a steady-state concentration until no **Ru1** remains.⁴⁷ The low concentration of active catalyst is maintained due to an uncharacterized decomposition pathway that is not present (or much less important) in alkene metathesis. At low alkene concentration, decomposition can be seen in the dual rate plots tracking the precatalyst initiation step with the rate of alkyne disappearance.³² A steady-state kinetic model has been applied to RCM by Plenio and co-workers, where an undefined decomposition step was assumed.⁴⁸

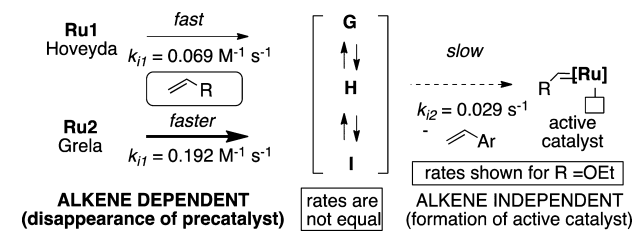
In the initiation process, the disappearance of **Ru1** does not directly result in an active carbene. The initiation of **Ru1** is measured by the decay in the UV-vis of the MLCT band at 377 nm, which does not directly measure or quantitate the active carbene. The isocyanide trapping experiments above show that when **Ru1** has initiated, only Buchner insertion due to a 2-isopropoxyarylidene is seen. This suggests that rapid disappearance of precatalyst **Ru1** gives intermediates shown in

the box of Scheme 5, which become trapped as Buchner product **13** upon isocyanide addition. At least one additional step is needed to produce the active carbene.

Previous work is suggestive of reactive intermediates that are immediately formed upon precatalyst **Ru1** disappearance. Plenio suggested that the formation of **G** might account for the loss of a MLCT band at 377 nm. On the basis of a DFT calculation, Solans-Monfort and co-workers^{9a} proposed that the dissociation of styrene from **I** is the rate-determining step. For the initiation process shown in eq 9 (Scheme 5), this is the last step that leads to an active carbene. Related calculations by Ashworth et al. indicate that species **G** has a UV spectrum similar to that of **Ru1**, whereas **I** lacks a UV absorption around 377 nm.^{9b} These workers concluded that when the UV absorption (due to the MLCT band) is gone, the precatalyst and intermediates **G** and **H** have progressed to **I** (Scheme 5).

The similar rates of EYM by **Ru1** and **Ru2** suggest a two-step initiation process. The similar rate of EYM by **Ru2** suggests that there is a bottleneck in the initiation process that regulates the formation of the active carbene. Further, this step must be relatively insensitive to the electronic nature of the styrene ligand. Despite different rates of alkene initiation, precatalysts **Ru1** and **Ru2** lead to a similar steady-state concentration of active catalyst for the EYM. The similar rates of EYM by the two different precatalysts are inconsistent with a scenario where the precatalyst immediately produced an active carbene. We postulate that the two precatalysts initiate to form an intermediate, which in turn delivers a low concentration of the active carbene by a second, similar rate. The disappearance of the precatalyst in the first initiation step is alkene-dependent and can be seen by a loss of the MLCT band. Rather than producing an active catalyst, this first step produces an intermediate (Scheme 6).

Scheme 6. Two-Step Initiation Scenario (rates for ethyl vinyl ether taken from the work of Plenio and co-workers)^{4a}



This two-step initiation process is sensitive to electronic effects at the first step but not in the rate-controlling formation of the active catalyst. The two-step initiation hypothesis is consistent with an interesting observation made by Plenio and co-workers during their seminal study.^{4a} The rates of the first step of initiation (e.g., the disappearance rate of precatalyst) are different for **Ru1** and **Ru2**. The rate constants shown in Scheme 6 are taken from Plenio's work with ethyl vinyl ether. Plenio identified an intermediate that absorbed at 500 nm, which underwent a slower rate of decay as compared to the rate of **Ru1** precatalyst disappearance.^{4a} The decay of this intermediate led to the active catalyst. Importantly, Plenio found that the rate of this second initiation step was identical for **Ru1** and **Ru2** and alkene-independent. Therefore, we suggest that the intermediates **G–I** are rapidly formed in an alkene-dependent manner, but the formation of the active catalyst for EYM is slower, is not alkene-dependent, and is

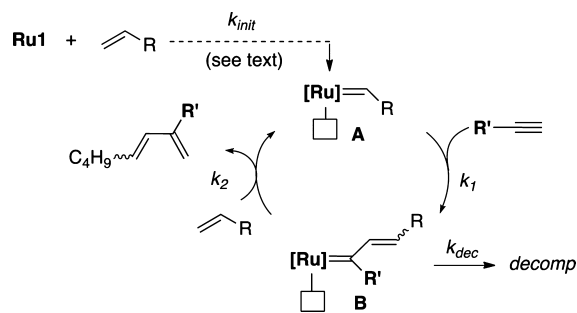
similar for these two precatalysts. We think it is most likely to be ruthenacyclobutane **H** or the η^2 -styrene complex **I**. Calculations are also consistent with this hypothesis: Solans-Monfort and co-workers calculated the free energy of the styrene decoordination step (for both the interchange and dissociative pathways) and found a small energy difference between **Ru1** and **Ru2**.^{9a}

The alkyne structure affects the reaction rate and rate-determining step. Of the two terminal alkynes compared, greater propargylic bulk results in a slower EYM. This is different than what we found in our earlier kinetic study of EYM using **Ru3** when a phosphine was present. In a phosphine-free system, the increased bulk of the alkyne substituent slows the intrinsic reaction rate (fewer catalytic turnovers) of the slow step of catalysis. Second, rates of EYM were found to be comparable for terminal alkynes as compared to internal alkynes, although they obey different rate laws. Internal alkynes show first-order alkyne dependence, whereas terminal alkynes show zero-order alkyne dependence.

Capture of active ruthenium carbene by 2-isopropoxystyrene is highly effective. Trapping by 2-isopropoxystyrene occurs (starting from complex **4**) even with a large excess of 1-alkene present. With 0.8 M 1-hexene and 0.01 M **11**, roughly equal amounts of Buchner complexes were obtained. This provides an effective molarity (EM)^{40,49} of **11** as 80 (compared to 1-hexene). This could provide a useful way to benchmark alkene reactivity vs **11**. The carbene exchange pathway (trans-alkylidene) can be arrested by the addition of an isocyanide. The isocyanide-triggered Buchner reaction provides a convenient means to identify ruthenium carbenes as their stable, metathesis-inactive coordination complexes. Trapping studies using the Buchner insertion were used to validate that ruthenium carbene intermediates could be trapped if present.

The proposed mechanism in Scheme 7 is consistent with the experimental rate law and mechanistic studies. Carbene

Scheme 7. Proposed Mechanism



intermediate **A** is the active 14-electron intermediate formed by a two-step initiation process of **Ru1** with alkene. Because initiation is rate-controlled by a slow, alkene-independent step, catalysts **Ru1** and **Ru2** promote EYM at similar rates. Alkyne insertion into carbene **A** by step k_1 produces the carbene intermediate **B**. Vinyl carbenes **B** are calculated to be more stable than ruthenium carbenes that lack conjugation.¹¹ Step k_2 consumes alkene and forms the 1,3-diene product. The lack of phosphine-bound resting states result in high kinetic activity of **A** and **B** toward unsaturated reactants, allowing hundreds of turns of the catalytic cycle before decomposition occurs. The decomposition pathway, unique to terminal alkyne-derived vinyl carbenes **B**, is faster than the decomposition pathway identified by Plenio and co-workers⁴⁸ for RCM and much faster

than the decomposition of $[\text{Ru}]=\text{CHR}$ under alkene cross-metathesis conditions.

Kinetic Treatment. The lack of trapping of carbenes and observed decomposition at low alkene concentration led us to hypothesize steady-state concentrations for both ruthenium carbene intermediates **A** and **B**. The rate data comparisons for precatalyst initiation (UV-vis) and rate of EYM (in situ IR) show that the rate of EYM does not increase as more precatalyst initiates. Kinetic treatment must explain the experimental rate law determined to be $\text{rate} = k[\text{Ru1}]_0^1[\text{alkene}]^1[\text{alkyne}]^0$ for terminal alkynes.⁵⁰ A key issue is whether there is alkene dependency in the precatalyst initiation step; if there is, an alkene dependency (i.e., kinetic order) > 1 would be expected.⁵¹ Previous work shows that there are two discrete kinetic steps in precatalyst initiation: one alkene-dependent and one not alkene-dependent. This is important because it helps explain the similar rates for precatalysts **Ru1** and **Ru2** and pinpoints the alkene dependency to the catalytic cycle, not to the initiation process. In their study of RCM by Hoveyda-type precatalysts, Plenio and co-workers did not ascribe alkene dependence to the initiation step; alkene dependence was only due to the catalytic process,⁴⁸ similar to our kinetic treatment.

Using the steady-state assumption for both reactive ruthenium carbene intermediates yields eq 13, which conforms with the experimentally determined rate law. This rate treatment eliminates alkyne concentration from the rate equation and predicts a first-order dependence of the alkene and precatalyst. The derivation is provided in the Supporting Information.

$$\text{rate} = -\frac{d[\text{alkyne}]}{dt} = \frac{k_{\text{init}}k_2}{k_{\text{dec}}}[\text{Ru1}][\text{alkene}] \quad (13)$$

Comparison of Rates. Comparison of the EYM apparent second-order rate constant with the **Ru1** disappearance rate shows that EYM is significantly faster. The k_{obs} values for EYM can be divided by the concentrations of alkene and $[\text{Ru1}]_0$ to provide an experimental second-order rate constant k_{EYM} .⁵² On the basis of 29 trials, a value of $k_{\text{EYM}} = 3.9 \pm 0.6 \text{ M}^{-1} \text{ s}^{-1}$ (toluene, 298 K) is obtained (at 0.1–3 mM **Ru1**, 1–4 M 1-hexene, and 80 mM alkyne **1A**). We observed the disappearance of **Ru1** in the absence of alkyne, obtaining $k_{\text{init}} = 0.011 \pm 0.001 \text{ M}^{-1} \text{ s}^{-1}$ (0.1 mM **Ru1**, 1 M 1-hexene, toluene, 298 K). This value is very similar to the rate constant reported in the literature^{4b} after adjusting for temperature differences. At the same alkene concentration, the EYM rate is at least 390 times faster than the *alkene-dependent Ru1* initiation rate.⁵³

The experimentally determined k_{EYM} can be used to extract the ratio of catalyst propagation to catalyst decomposition (k_2/k_{dec}). At the low catalyst loadings used, a net catalyst turnover number of ~ 800 is anticipated. From the rate treatment of eq 13 (and derived in the Supporting Information), the experimental k_{EYM} equals $(k_2k_{\text{init}}/k_{\text{dec}})$. If k_{EYM} is divided by the limiting k_{i2} rate constant, one obtains the ratio of propagation (catalysis) over the rate of decomposition, k_2/k_{dec} . Above, a value of $k_{\text{EYM}} = 3.9(0.6) \text{ M}^{-1} \text{ s}^{-1}$ (toluene, 298 K) was found. For **Ru1** initiation, we use Plenio's rate of the *second step of initiation*, $k_{i2} = 0.0288 \text{ s}^{-1}$ (alkene-independent, toluene, 40 °C).^{4a} We corrected this rate to 25 °C (Eyring equation), to obtain $k_{i2}^{298} = 0.0052 \text{ s}^{-1}$. Dividing the second-order rate constant by the alkene-independent step of precatalyst

initiation, k_{EYM}/k_{i2} , gives the ratio of $k_2/k_{\text{dec}} = 750$.⁵⁴ This value is similar to the expected value of 800.⁵⁵

A lower propagation/decomposition ratio (k_2/k_{dec}) is calculated for a substituted terminal alkyne. For phenyl-substituted alkyne **1B**, k_{obs} was $2.77 \times 10^{-4} \text{ M/s}$. By dividing k_{obs} by the initial concentrations of 1-hexene and **Ru1**, $k_{\text{EYM}} = 1.39 \text{ M}^{-1} \text{ s}^{-1}$, where $k_{\text{EYM}} = (k_2k_{\text{init}}/k_{\text{dec}})$. If k_{EYM} is divided by the temperature-corrected k_{i2} obtained from Plenio's data,^{4a} one obtains the ratio of propagation (catalysis) over the rate of decomposition, $k_2/k_{\text{dec}} = 270$. This is 2.8 times less than that observed with alkyne **1A**. Most likely this is attributable to a smaller k_2 rather than a larger k_{dec} since competition studies corroborated the individual kinetic runs for individual alkynes. Additional steric bulk can either impede the approach of alkene on intermediate **B** or destabilize the ruthenacyclobutane **E**. A higher energy **E** will have a higher energy transition state, which would reduce the value of the rate constant k_2 . In this scenario, the propagation rate of **1B** is about 3 times less than that of **1A**.

The ene-yne metathesis of alkyne **1A** and 1-hexene promoted by the Hoveyda precatalyst **Ru1** is significantly faster than that promoted by the Grubbs catalyst (**Ru3**). In this study, we determined the rate constant of EYM with **Ru1** to be $k_{\text{EYM}} = 3.9 \pm 0.6 \text{ M}^{-1} \text{ s}^{-1}$ (toluene, 298 K). In contrast, the same alkyne displayed an experimental second-order rate constant of $0.063 \text{ M}^{-1} \text{ s}^{-1}$ (toluene, 298 K) with **Ru3**.¹⁰ This indicates that precatalyst **Ru1** promotes EYM ~ 62 times faster than **Ru3**. Mechanistically, the phosphine-free catalyst systems studied here are not regulated at the vinyl carbene stage. In EYM promoted by **Ru3**, the vinyl carbene exists in an unproductive equilibrium with its phosphine complex. In phosphine-free systems, there is no such unproductive resting state, which contributes to a faster catalytic process.

Decomposition of vinyl carbene intermediates derived from terminal alkynes is predicted in this study. The decomposition appears to be first-order in Ru because the overall order of Ru is first-order in the experimental rate law; a different order would be expected if decomposition was, for example, second-order. Plenio and co-workers⁴⁸ identified two distinct decomposition pathways in RCM catalyzed by **Ru1**: a first-order and second-order pathway.⁵⁶ Decomposition is faster under ene-terminal alkyne metathesis as compared to alkene metathesis. We ascribe this decomposition due to the vinyl carbene intermediate **B**. Decomposition via **A**, an intermediate common to both alkene and ene-yne metathesis, is also possible, but it alone does not explain the lower catalyst lifetime seen in ene-yne metathesis (due to the presence of a terminal alkyne). One possible deactivation pathway is alkene coordination by the vinyl moiety of the vinyl carbene, an intramolecular reaction. Grubbs et al. have observed this type of coordination, which resulted in a metathesis-inactive complex.²⁷ Additionally, vinyl carbenes can react with alkyne to give oligomer or undergo decomposition by a known pathway.²⁶ Carbenic reactions such as cyclopropanation and CH bond insertion are additional possibilities. Further studies are needed to elucidate the decomposition pathway.

CONCLUSION

In summary, a detailed kinetic study of ene-yne metathesis catalyzed by the Hoveyda complex (**Ru1**) was performed. This study examined the relationship of the precatalyst initiation process with the rate and structural sensitivities of catalytic EYM with different alkynes. The first step of precatalyst initiation was tracked simultaneously with alkyne disappearance,

which led to a steady-state hypothesis of active ruthenium carbene. By observing catalysis, the reaction rate did not change and there was not a buildup of an active carbene concomitant with **Ru1** disappearance. The precatalyst initiation process is relevant to the Hoveyda-type catalysts and is significant for both alkene and ene-yne metathesis. After precatalyst **Ru1** had initiated, isocyanide-triggered Buchner reaction trapped a 2-isopropoxybenzylidene exclusively, suggesting that the precatalyst initiated to an intermediate that retained the styrene. In ene-yne metathesis, Buchner insertion did not yield any trapping products, which suggests that there is irreversible entry into catalysis and a small, steady-state concentration of active ruthenium carbene catalyst. The irreversibility implies high turnover and decomposition from intermediates in the catalytic cycle. An active catalyst persists longer under alkene metathesis conditions versus ene-yne metathesis conditions with terminal alkyne. Kinetic treatment is consistent with decomposition through the vinyl carbene intermediate. These studies clearly demonstrate that there is a bottleneck in the initiation process that ultimately produces a steady-state concentration of the active carbene species. Similar rates of EYM using precatalysts that have different alkene initiation rates may be explained by a two-step initiation process where the formation of the active catalyst is not alkene-dependent and not sensitive to the styrene ligand. Last, it should be noted that these kinetic studies were performed at very high alkene concentrations and low precatalyst loading using three terminal alkynes and one internal alkyne.

There are several conclusions that can be summarized on the basis of their relevance to ene-yne metathesis, initiation, alkyne structural effects, and the nature of the catalyst.

Ene-Yne Metathesis. (1) For the terminal alkyne **1A**, the experimental rate law was found to be $k[\text{Ru1}]_0^1[\text{alkene}]^1[\text{alkyne}]^0$. (2) On the basis of dual tracking of both the precatalyst initiation and the rate of ene-yne metathesis, a steady-state concentration of active catalyst was inferred. The rate of EYM did not increase as more precatalyst initiation occurred. (3) Active catalyst persists longer under alkene metathesis conditions as compared to ene-yne metathesis with terminal alkynes. This is attributed to decomposition via the vinyl carbene intermediate. Kinetic treatment modeling decomposition through this intermediate yielded a rate law that matched the experimental rate law. (4) The rate of ene-yne metathesis is at least 390 times faster than the disappearance of the UV absorbance of **Ru1** (its alkene-dependent rate of initiation).

Precatalyst Initiation. (1) Buchner-trapping of ruthenium carbene intermediates in alkene and ene-yne metathesis supports a two-step initiation process where an intermediate is first formed in a rapid, alkene-dependent step. This intermediate is likely a ruthenacyclobutane or a Ru carbene bearing the 2-isopropoxystyrene ligand. It undergoes a slower, alkene-independent conversion to the active ruthenium carbene intermediate. (2) The active ruthenium carbene intermediate was not trapped by isocyanide-promoted Buchner reaction. Control experiments verified that a $[\text{Ru}]=\text{CHR}$ species would give a Buchner product. The lack of trapping is understandable in terms of the low, steady-state concentration of reactive intermediates and the low precatalyst concentration used.

Alkynes. (1) A linear terminal alkyne yielded the 1,3-diene only at the highest alkene concentrations, and a byproduct was noted. These alkynes decompose **Ru1**, and higher alkene concentrations are needed to outpace catalyst decomposition.

(2) Hindered, α -branched terminal alkynes react more slowly than less-hindered α -branched terminal alkynes. (3) Internal alkynes follow a different rate law, which shows alkyne dependence.

Catalysts. (1) The rate of ene-yne metathesis by **Ru1** is 62 times faster than the rate of ene-yne metathesis promoted by the Grubbs catalyst **Ru3** (1-hexene and **1A**). (2) Compared to **Ru1**, a faster-initiating Hoveyda-type precatalyst **Ru2** (Grela catalyst) gives a similar rate of ene-yne metathesis between 1-hexene and **1A**. This was interpreted in terms of a two-step initiation process where the second step results in rate-limiting production of active ruthenium carbene. The second step is not alkene-dependent and not as sensitive to the electronic nature of the styrene.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01887.

Additional graphs, experimental procedures, and characterization data (PDF)

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Notes

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(42) The 1,3-diene product did not inhibit the rate of ene-yne metathesis. Addition of 0.08 M diene **2A** to the ene-yne metathesis of **1A** and 1-hexene gave an observed rate of $k_{\text{obs}} = (2.74 \pm 0.04) \times 10^{-4}$ M/s. This is almost identical to the observed rate without added 1,3-diene product, $k_{\text{obs}} = (2.67 \pm 0.03) \times 10^{-4}$ M/s.

(43) At the same concentrations, Plenio and co-workers reported $t_{1/2} \sim 2.4$ min.

(44) In ethylene-alkyne metathesis, terminal alkyne **1A** was found to react slightly faster than internal alkyne **15**, and the unbranched alkyne **1C** did not react at all. See ref 12.

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(46) Each of the precatalysts **Ru1** and **Ru2** have alkene-dependent initiation rate laws and, upon initiation, lead to the same active catalyst.

(47) If the active catalyst **A** was accumulating by $[\text{Ru1}]_0 - [\text{Ru1}]_t = [\text{A}]_t$, then $[\text{A}]_t$ would increase over time. If $[\text{A}]_t$ was increasing, then a changing slope for the alkyne conversion rate would be expected. This is evidently not the case, since the alkyne conversion rate data in Figures 1 and 3 show a constant slope.

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(50) The rate behavior of internal alkynes will not be treated here due to a different rate law.

(51) Second-order because alkene dependence would occur in both the initiation of the precatalyst and in the catalytic cycle where alkyne is consumed.

(52) Obtained at 80 mM **1A**, over the alkene concentration range of 0.5–4.0 M and at 0.1 mM **Ru1** in toluene at 25 °C. Under these pseudo-order conditions, rate = $k_{\text{obs}}[\text{alkyne}]^0$ and $k_{\text{obs}} = k[\text{Ru1}][1\text{-hexene}]$.

(53) Comparison is made to the first initiation rate observed by Plenio because there is data for 1-hexene. This initiation rate is second-order and is dependent on the alkene concentration.

(54) The expression k_2/k_{dec} is a ratio of second-order to first-order rate constants with units of M^{-1} .

(55) Interestingly, if the k_1 rate—the rate of **Ru1** UV disappearance—is used as the initiation rate, a much lower turnover number of 390 is calculated. The turnover based on catalyst loading should be 800.

(56) In the RCM, bimolecular decomposition is most likely a result of $[\text{Ru}]=\text{CH}_2$ reacting with the Hoveyda-type precatalysts. The methyldene $[\text{Ru}]=\text{CH}_2$ occurs in alkene metathesis but is not formed to a significant extent during ene-yne metathesis.