Communication

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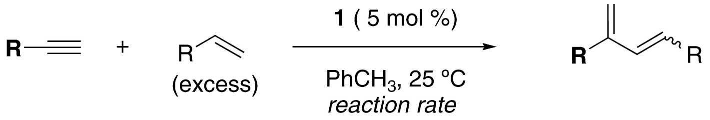

1 = (dihydroIMes)(Cy_3P)Cl_2Ru=CHPh, Grubbs' second generation carbene

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Studies on the Mechanism of Intermolecular Enyne Metathesis: Kinetic Method and Alkyne Substituent Effects

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Enyne metathesis has emerged as an important new method for 1,3-diene synthesis.[1] With a number of methodology studies and applications to total synthesis, mechanistic interpretation is based on early proposals and is not well understood. To the best of our knowledge, there are no reported kinetic studies on enyne metathesis, a necessary first step to describing the catalytic reaction mechanism. In this Communication, we report a kinetic investigation of enyne metathesis using an IR method (Scheme 1). These data establish the kinetic rate law, illustrate unanticipated rate effects due to propargylic substitution, and provide a comparison of reactivity for both ethylene− and 1-hexene−alkyne cross metatheses (eq 1, R = H, R = C_4H_9).

Mechanistic study will help explain inconsistencies and provide a better understanding of the reaction. In the past few years, ethylene has been used to help certain ring-closing enyne metatheses,[2] but does not help others. There is a perceived limitation for heteroatoms in the propargylic position; in some cases, they benefit ethylene metathesis,[3a] in others, chelation is thought to retard the reaction.[3b] In some cases, metathesis is impervious to heteroatom substitution.[3c] Knowledge of reaction mechanism will lead to extended reaction scope, higher turnover catalysts, and the design of new reactions. Preliminary mechanistic data have helped guide the development of new applications in our own group, including ethylene cometathesis to bring about silyl enol ether−alkyne cross metathesis[4a] and ring synthesis by methylene-free enyne metathesis with cycloalkenes.[4b,c]

To obtain kinetic data for the catalytic enyne metathesis, a simple and efficient monitoring method was developed using IR spectroscopy. The terminal alkyne reactant has a unique IR absorption: the CH bond stretch, which can be observed even at low alkyne concentrations.[5] Monitoring the decay of this absorption at 3300−3310 cm^{-1} over time gave the rate of disappearance of the alkyne reactant. Using a gc assay, we verified the accuracy of the rate determination, showing (1) that the rate of alkyne disappearance was the same as that with the IR method and (2) that the diene product was appearing at the same rate as alkyne disappearance.[6] The IR method is fast and convenient, permitting systematic kinetic evaluation of reactant concentrations without overlapping absorptions.

Kinetic order for alkene and alkyne was established for the metathesis of 1-hexene and alkyne **2A**. Time-dependent loss of alkyne under pseudo-first-order conditions (excess 1-hexene) showed *linear* decrease of alkyne concentration indicating zero-order rate dependence. First-order rate dependence on [1-hexene] was established by IR monitoring of alkyne disappearance at several 1-hexene concentrations using the same catalyst stock solution.[6] First-order dependence on [catalyst] was also established.[6]

Scheme 1. Kinetic Study of Enyne Metathesis

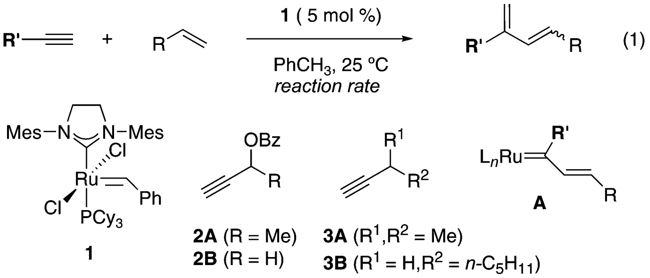

Table 1. Kinetic Data for 1-Hexene−Alkyne Metathesis using the IR Method

entry	alkyne	1, mM	1-hexene, M	k, M^{-1} s^{-1} (error)
1	**2A**	0.26−1.0	0.25−0.62	0.063 (0.007)
2	**2B**	1.0−3.6	0.50−1.54	0.0038 (0.0005)
3	**3A**	0.52	0.25−0.50	0.083 (0.007)
4	**3B**	0.77−4.0	0.30−1.2	0.0040 (0.0006)

Table 2. Kinetic Data for Ethylene−Alkyne Metathesis using the IR Method

entry	alkyne	**1**, mM	ethylene, M	k (error)
1[a]	**2A**	0.3−3.0	0.38−0.62	0.21 (0.03) M^{-1} s^{-1}
2[b]	**2B**	7.9−16	0.38−0.62	6.4(0.7) × 10^{-4} s^{-1}

[a] Reaction is first order in both alkyne and **1** and zero order in ethylene. [b] Reaction is first order in **1** and zero order in both alkyne and ethylene.

To assess α-substituent effects, the relative reactivity of substituted alkynes was compared. The effect of alkyne substitution on reaction rate was evaluated for **2A** and **2B** (Table 1). In both cases, the rate was zero order in alkyne. The raw rate of alkyne disappearance was normalized by dividing this value by the concentrations of **1** and 1-hexene used for each individual run. This treatment produces the second-order rate constant in the right column of Table 1, which can be compared for each alkyne. The reaction of the *more-substituted* alkyne **2A** was 16 times faster than that of the less-substituted homologue **2B** (entries 1 and 2). Faster reaction of a more-substituted alkyne was surprising. Chelation might explain the observed rate retardation for **2B** with **2A** reacting faster due to weaker chelation (conformational restrictions imposed by the additional substituent). To test this, **3A** was next examined (entry 3, Table 1), and the rate constant was similar to the substituted benzoate **2A**. Furthermore, **2B** was contrasted with **3B**; the rate constants were within experimental error. These comparisons demonstrate that chelation by the ester group does not influence the rate-determining step. Since the alkyne shows zero-order rate dependence, its binding rate to the metal is not kinetically relevant.

The rate of ethylene−alkyne cross metathesis[1d,3] was studied to contrast overall reaction rate and to evaluate the effect of substitution. The ethylene metathesis of **2A** (Table 2, entry 1) was found to be first order in alkyne but zero order in ethylene.[7] The slope of the ln[**2A**] versus time plot gave a pseudo-first-order rate constant, which was divided by [**1**] to give the second-order rate constant value of 0.21 M^{-1} s^{-1}. For alkyne **2B**, the ethylene metathesis was slower, and higher catalyst concentrations were needed. At ethylene

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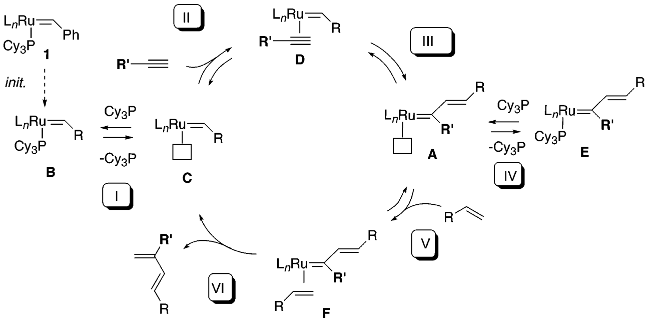
Scheme 2. Proposed Catalytic Mechanism of Enyne Metathesis



pressures of 25−50 psig (solution concentration 0.38−0.62 M), the reaction was found to be zero order in alkyne **2B** and zero order in ethylene (entry 2, Table 2). In this case, a first-order rate constant is obtained. Interestingly, though the ethylene metatheses have different rate-determining steps and are slower than the 1-hexene metatheses described in Table 1, the relative magnitude of the substituent effect was similar to that observed with 1-hexene; alkynes with the more-substituted α-carbon react about 20 times faster (60 mM alkyne and 2.7 mM **1**).[8]

On the basis of the kinetic data obtained, the catalytic cycle is proposed as illustrated in Scheme 2. The two phosphine binding steps, which remove catalyst from the cycle, are also shown on each side of the cycle. After re-entry into the cycle from resting state **B** or **E**, the catalyst can turnover many times before phosphine reassociates. The rate of product formation will be determined by the amount of catalyst in the cycle and the turnover number, which reflects the slow step in the catalytic cycle.

Kinetic partitioning of the vinyl carbene intermediate **A** influences overall reaction rate. For 1-hexene−alkyne metathesis, the rate law requires that the rate-determining step in the cycle is either V or VI (alkene dependence, alkyne independence).[9] The 14-electron intermediate **A** may react with 1-hexene or become trapped by Cy_3P. The faster rate for **2A** versus **2B** is explained by partitioning; (a) the faster intrinsic rate of Cy_3P dissociation from **E** is promoted by steric bulk at the propargylic position in **R′**; (b) 1-hexene complexes more favorably to **A** as compared to Cy_3P recoordination (**A** to **E**);[10,11] (c) bulky propargylic substituents accelerate cycloreversion of a ruthenacyclobutane intermediate in step VI. The resting state for active catalyst is most likely vinyl carbene **E**, but the catalyst may cycle many times before returning to this state. We favor the "alkylidene-first" mechanism involving alkylidenes **A** (R = alkyl) as the catalytic species since the methylidene **A** (R = H) is known to only slowly dissociate Cy_3P relative to ruthenium alkylidenes.[11,12]

The ethylene metatheses show a different rate-determining step. Ethylene−**2A** metathesis (first-order alkyne, zero-order ethylene) must have step II or III as the rate-determining step, with **B** as the resting state. The anticipated ring strain of a ruthenacyclobutene intermediate in step III suggests this step is rate-limiting. Ethylene−**2B** metathesis is slower and exhibits a rate law zero order in both ethylene and alkyne. Since **2B** is less hindered than **2A**, it should react faster than **2A** in step II or III. However, this is not observed. We propose that intermediate **A** reacts rapidly with ethylene when **R′** is disubstituted since substitution kinetically inhibits binding by bulky Cy_3P (which would form **E**). Similarly, when **R′** is a linear substituent, Cy_3P binding is more effective, and this diverts **A** out of the cycle to form **E**. This makes the phosphine dissociation rate from **E** rate-determining, which explains the zero-order rate dependence on alkene and alkyne in the ethylene−**2B** metathesis.[13]

Phosphine dissociation rate data from the literature are consistent with the observed magnitude of the rate data obtained in the ethylene metatheses. The rate of phosphine dissociation from **1** (at the catalyst concentrations used in these experiments) was extrapolated to 25 °C using Grubbs' data, giving 1×10^{-6} M/s.[11] This agrees favorably with the measured rate of ethylene−**2B** metathesis of 8.4×10^{-6} M/s[14] since greater substitution on the carbene (e.g., R′ group in **E**) accelerates phosphine dissociation, known from Grubbs' initiation studies in alkene metathesis (rate of phosphine dissociation $\mathrm{CHEt} > \mathrm{CHCH{=}CMe_2} > \mathrm{CHPh} \gg \mathrm{CH_2}$).[11,15] Though enyne metathesis deals with vinyl carbene intermediates, phosphine recombination is also important for alkene metathesis where selectivities versus alkene binding range over 4 orders of magnitude.[11b]

In conclusion, we have developed a kinetic method to study enyne metathesis using IR spectroscopy. The rate law for a variety of 1-alkyne−alkene combinations using the second-generation Grubbs carbene complex has been obtained. In the cases studied, chelation is not observed, and propargylic substitution accelerates reaction rate. Further kinetic and mechanistic studies are ongoing in our group.

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Supporting Information Available: Experimental procedures and additional rate plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For reported changes in alkyne triple bond stretch on enyne binding to metal, see: Kang, B.; Kim, D.-H.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041−3043.

(6) See Supporting Information.

(7) Both reactions are first order in ruthenium complex **1**.

(8) A similar trend was observed with **3A** and **3B**.

(9) The kinetic data in this study do not distinguish between these two steps.

(10) This is analogous to Grubbs' explanation for the greater reactivity of **1** in alkene metathesis; see ref 11.

(11) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554. (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103−10109.

(12) Ethylene metatheses, which must proceed via **C** (R = H), are slower reactions due to a greater proportion of the ruthenium carbenes existing in resting state **B**.

(13) The reaction of **2B** with ethylene using the analogous Ph_3P complex of **1** gave a faster initial reaction rate (3.2 times faster than that of **1**), consistent with the partitioning hypothesis. In this case, however, catalysis stalled after ca. 2 catalytic turnovers (ca. 10% conversion).

(14) This is the rate of alkyne **2B** disappearance. See Supporting Information.

(15) This is also true in the first generation ligand environment, $RuCl_2(PCy_3)_2$-(carbene), where the vinyl carbene complex dissociates Cy_3P 10 times faster than the benzylidene when extrapolated to 25 °C. From: Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

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