Relative Reaction Rates of Olefin Substrates with Ruthenium(II) Carbene Metathesis Initiators[1]

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Received November 19, 1997

The metathesis of terminal olefins having different steric bulk and different geometries as well as electronically different *para*-substituted styrenes was studied with the ruthenium-based metathesis initiators *trans*-$(PCy_3)_2Cl_2Ru{=}CHR$. Bulkier olefins were found to react slower, and trans internal olefins were found to be slower than cis. The kinetic product of all reactions was found to be the alkylidene rather than the methylidene. Observed effects were used to explain the mechanism of ring-opening cross metathesis. No linear electronic effects were observed.

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Published on May 13, 1998 on http://pubs.acs.org | doi: 10.1021/om9710172

Introduction

Over the past several years, extensive effort has been expended to design and isolate single component late transition metal[2] olefin metathesis catalysts for ring-opening metathesis polymerization (ROMP),[3] ring-closing metathesis (RCM),[4] and acyclic diene metathesis (ADMET) processes.[5] Among the first of such well-defined catalysts coming from our laboratory was the ruthenium(II) carbene, *trans*-$(PPh_3)_2Cl_2Ru{=}CHCH{=}CPh_2$ (**1**), active only for the living polymerization of highly strained cyclic olefins.[6] The replacement of the triphenylphosphine ligands with bulkier and more basic tricyclohexylphosphine or triisopropylphosphine ligands extended the activity to the metathesis of less strained cyclic olefins and acyclic olefins.[7] The next generation catalyst developed in our laboratory was *trans*-$(PCy_3)_2Cl_2Ru{=}CHPh$ (**2**), which exhibited faster initiation than its predecessors for ROMP, RCM, and ADMET processes.[8] It was observed that the benzylidene catalyst reacted with terminal acyclic olefins to produce the new substituted alkylidenes in high yield. This observation provided the opportunity to examine the details of metathesis with these catalysts and to explore the factors that control the rates of product formation and the stability of the intermediates. Information of this nature is required to understand the growing number of applications of these catalysts in organic and polymer syntheses.

The accepted mechanism for olefin metathesis proceeds as a series of equilibria: the coordination of the olefin to the metal adjacent to the carbene followed by reversible formation of a metallacycle to form either the original or the metathesized carbene and olefin.[9] Regeneration of the original olefin is referred to as nonproductive, and formation of the new olefin and carbene is the productive metathesis step. Scheme 1 outlines these steps using the proposed intermediates for the ruthenium catalysts.

Previous work from this laboratory[7] has shown that when the benzylidene initiator **2** reacted with terminal acyclic olefins, such as 1-hexene, the initial organometallic product observed by ^1H NMR was the alkylidene[10] **4** (Scheme 1). After approximately 10 min, at room temperature, the complete disappearance of **2** was observed along with the initial formation of **3**. After 2 h, the only organometallic product observed was **3**. The present work examines the relative reaction rates of metathesis active carbenes with acyclic olefins of different bulk, geometries, and electronic properties to study selectivity in alkylidene formation and explores the factors that effect the rate of metathesis.

Experimental Section

General Considerations. All kinetics were performed on a GE QE-300 Plus NMR spectrometer (300.1 MHz ^1H) in benzene-d_6. Characterization spectra were taken on a JEOL GX-400 (399.1 MHz ^1H; 161.0 MHz ^{31}P). The deuterated solvent was purchased from Cambridge Isotope Labs and purified by passing through a column of LaRoche A-2 alumina and Engelhard Q-5 reactant (supported copper oxide).[11] The carbene complexes were all synthesized according to the published procedures.[8] The olefins were all purchased from Aldrich, except for *p*-nitrostyrene which was purchased from TCI America and *cis*-3-hexene and 4-methyl-1-pentene which were purchased from Wiley Organics. Before use, all olefins

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[1] Dedicated to Dr. Abhijit Mitra.

[2] Late transition metals offer greater functional group tolerance. See: Grubbs, R. H. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *A31*, 1829.

[3] For several reviews see: (a) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907. (b) Schrock, R. R. *Acc. Chem. Res.* **1990**, 23, 158. (c) Stelzer, F. *J. Macromol. Sci., Pure Appl. Chem.* **1996**, *A33*, 941.

[4] (a)Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310 and references therein.

[5] Wagener, K. B.; Boncella, J. M.; Nel, J. G. *Macromolecules* **1991**, *24*, 2649.

[6] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

[7] Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858.

[8] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

[9] Herrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.

[10] For our purposes, we will apply the term alkylidene to signify carbene complexes other than methylidene, $Ru{=}CH_2$, or benzylidene, $Ru{=}CHPh$.

[11] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

S0276-7333(97)01017-0 CCC: $15.00 © 1998 American Chemical Society
Publication on Web 05/13/1998

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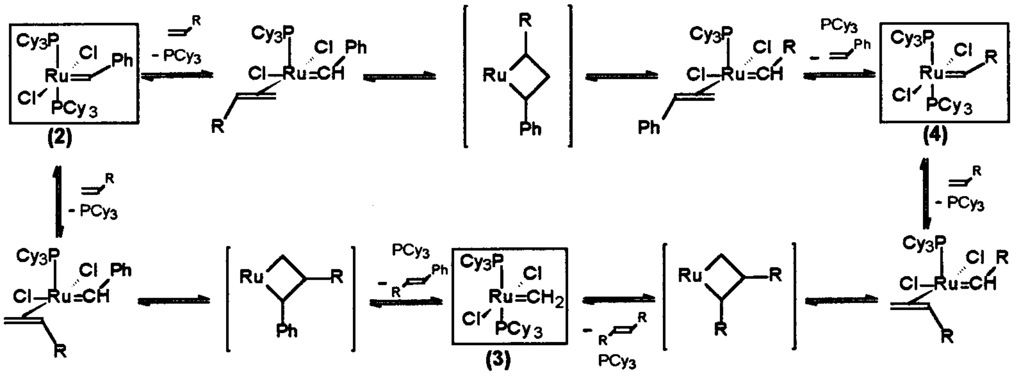
Scheme 1. Metathesis of Terminal Olefins with Ruthenium Benzylidene



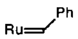
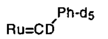
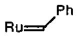
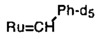
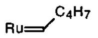
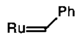
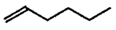
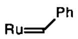
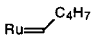
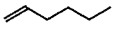
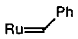
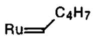
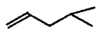
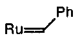
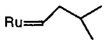
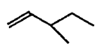
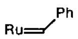
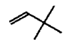
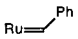
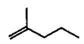
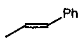
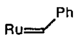
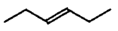
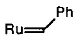
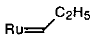
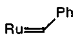
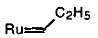
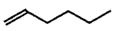
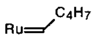
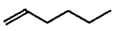
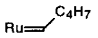
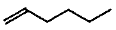
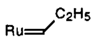
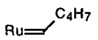
were passed through a column of activated alumina and purged with argon.

Reaction Rate Measurements. For the kinetics, stock solutions of 0.018 M carbene complexes were used containing an internal standard of anthracene and stored in a nitrogen filled drybox at −32 °C. Each sample contained 0.50 mL of carbene solution at the appropriate temperature to which was added 0.285 mmol of olefin (31 equiv) at which point data collection was immediately started. Data were collected over 1.5 half-lives of the initial carbene, integrating the carbene proton or the *ortho* protons of the benzylidenes relative to the anthracene internal standard. First-order fits were obtained for all experiments under these pseudo-first-order conditions. Second-order rate constants were calculated from the pseudo-first-order rate constants for a series of olefins reacting with carbene complexes, as listed in Table 1. Clean conversions were observed unless noted otherwise. A representative plot is given in Figure 1.

Results and Discussion

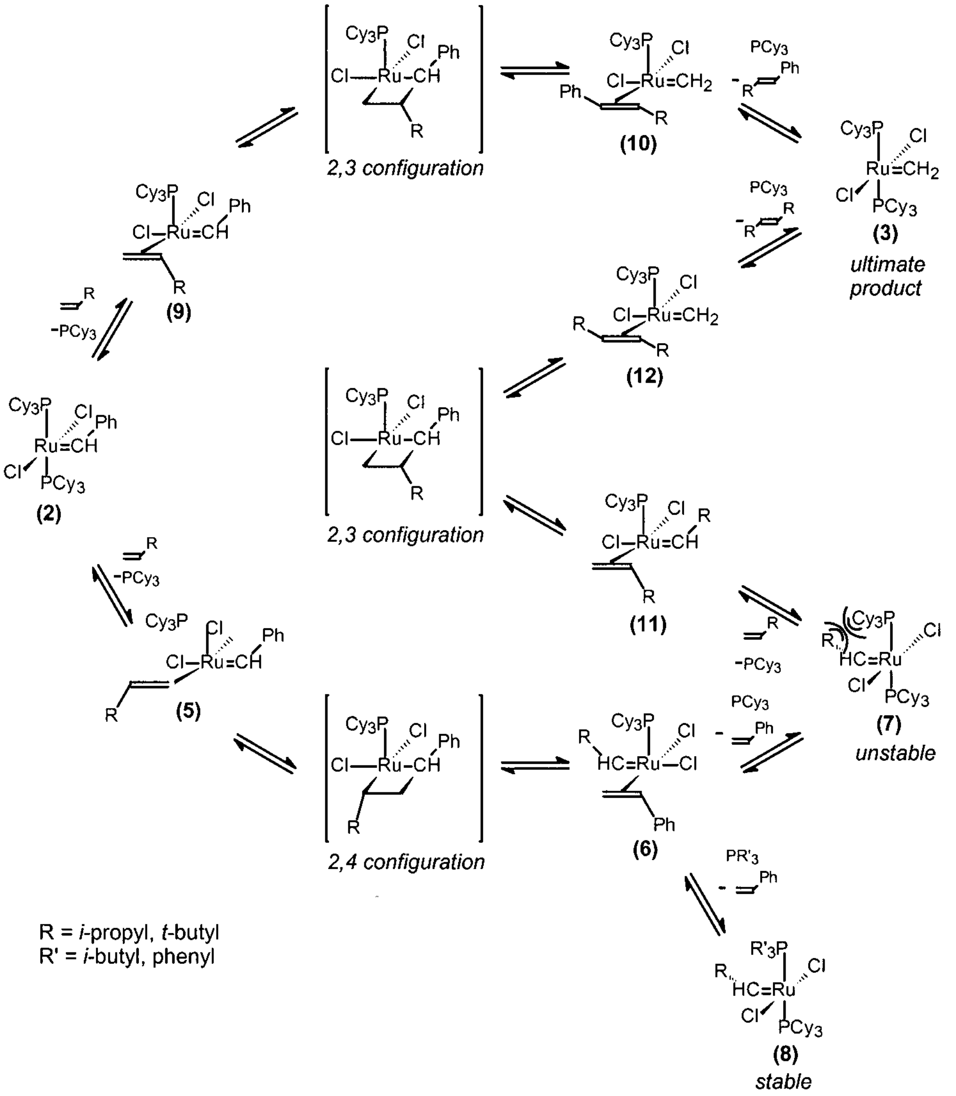
Relative Steric Effects. When the benzylidene catalyst **2** was reacted with sterically unhindered terminal olefins, the initial carbene product observed by ^{1}H NMR was the alkylidene **4**. When the steric bulk of the olefin was gradually increased, there was a decrease in the reaction rate, as shown by reactions 4 and 6 in Table 1. For even bulkier terminal olefins (Table 1, reactions 7 and 8), metathesis led directly to the methylidene **3**, while a 2,2-substituted olefin (Table 1, reaction 9) showed no activity under present conditions. The reaction between the methylidene complex **3** and terminal olefins (examples 13 and 14) produces the respective alkylidene complex. Consequently, the favored reaction of the methylidene appears to be the productive pathway.

Table 1. Second-Order Rate Constants (*k*) for Metathesis Reactions Using 31 equiv of Olefin

	olefin	initiator	product	Temp / °C	k ± SDOM[a] / L/mole•sec
1	styrene-d_8			7	$1.3 \pm 0.4 \times 10^{-3}$
2	styrene-d_5			7	$2.15 \pm 0.01 \times 10^{-3}$
3	styrene			7	$7.6 \pm 0.2 \times 10^{-3}$
4				7	$1.48 \pm 0.04 \times 10^{-3}$
5				35	~10^{-2}
6				7	$1.02 \pm 0.06 \times 10^{-3}$
7			Ru=CH2	35	$2.5 \pm 0.2 \times 10^{-4}$
8			Ru=CH2	35	minor in 4 days
9				35	no rxn.
10				35	no obs. Rxn.
11				35	$3.0 \pm 0.4 \times 10^{-4}$
12				35	$7.6 \pm 0.8 \times 10^{-4}$
13		Ru=CH2		25	$1.64 \pm 0.1 \times 10^{-4}$ (6000 sec)
14		Ru=CH2		35	$6.10 \pm 0.04 \times 10^{-4}$ (1000 sec)
15				7	~7×10^{-3}

[a] SDOM = Standard Deviation of the Mean

Scheme 2. Proposed Mechanism of "Direct" Formation of Methylidene with Bulky Olefins



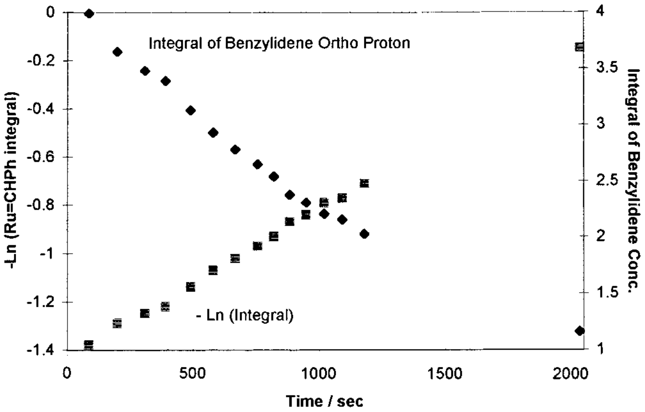
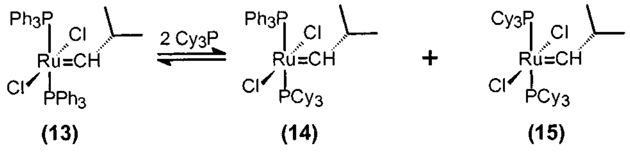


Figure 1. Representative kinetic plot for the metathesis of styrene-d_8 with benzylidene **2** at 7 °C in C_6D_6.

Scheme 3. Phosphine Exchange on Isobutylidene



The preferred formation of the methylidene, rather than an alkylidene, from **2** upon reaction with bulky olefins can be explained by a closer examination of the proposed mechanism for metathesis by the ruthenium carbenes.[12] It was proposed that the dominant first step is the effective replacement of one phosphine by an incoming olefin, as a pre-equilibrium step, which can bind in one of two orientations, **5** and **9** (Scheme 2). The next step is the formation and breakup of the metallacycle. Although the data from Table 1 suggest that the alkyl substituent of a terminal olefin prefers to be next to the metal (2,4 configuration) in the kinetically favored metallacycle[13] formed through **5**, steric bulk near the olefin appears to shift the path through **9** to the 2,3-substituted metallacycle and leads directly to **3**. However, an alternate mechanism is possible where the initial formation of **6** as the reactive intermediate is

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[12] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887.

[13] We have additionally concluded this from noting that reactions of the benzylidene with unhindered terminal olefins lead to alkylidenes and the reactions of methylidene-d_2 with 1-hexene and styrene lead to the pentylidene and the benzylidene, respectively. Methylidene formation was not kinetically favored in any of these cases, even though we would otherwise have expected that styrene would react with methylidene-d_2 so as to orient the phenyl group opposite the crowded metal center, not adjacent as it actually turned out.

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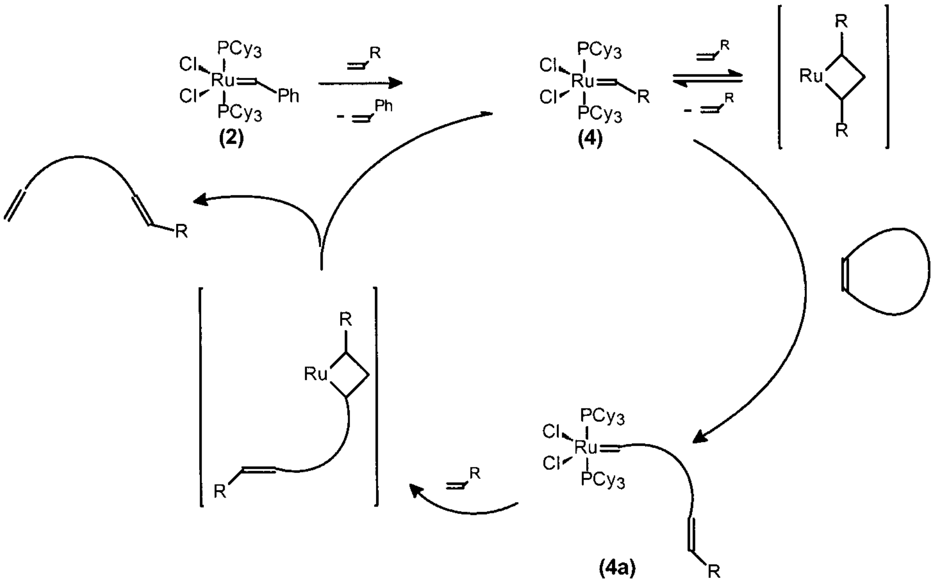
Scheme 4. Selective Ring-Opening Cross-Metathesis by Ruthenium Carbene Metathesis Catalysts



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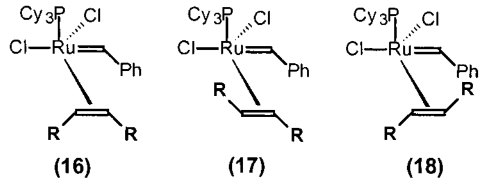
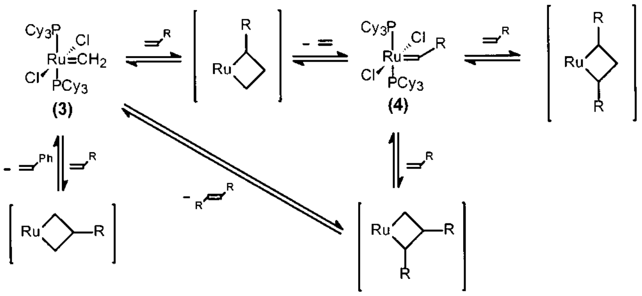
involved. We propose that after the initial metathesis step, the olefin complex **6** must replace the bound olefin with a phosphine or revert to the metallacycle to undo the metathesis. If the alkyl group on the carbene is too large to readily accommodate two bulky phosphines, **7**, the phosphine is especially labile and is readily replaced by a new olefin to form **11** which undergoes metathesis to form **12** and on to the methylidene **3** as the stable product.

To test this possibility, 3-methyl-1-pentene was allowed to react with **2** while a smaller phosphine was present in solution to trap the proposed intermediates. When the reaction was carried out in the presence of a phosphine like triphenylphosphine or triisobutylphosphine,[14] the smaller ligand was able to bind in place of the bulky phosphine and form the observed stable complex **8** which could sterically accommodate the bulky carbene. The formation of such a mixed phosphine complex was confirmed by an AB spectrum in the ^{31}P NMR. An alternate synthesis of the bis(triphenylphosphine) isobutylidene complex **13**[15] was carried out by the standard diazoalkane procedure,[8] and a partial phosphine exchange with tricyclohexyl phosphine confirmed the resonances observed in the metathesis reaction (Scheme 3). While the bis(triphenylphosphine) benzylidene complex reacted with a slight excess of tricyclohexylphosphine to undergo complete exchange, **13** reacted to form both **14** and **15**, supporting the steric argument that bulky carbenes result in the lability of bulky phosphines as the more basic tricyclohexylphosphine did not readily displace the triphenylphosphine on the isobutylidene complex. However, we must point out that the possibility that bulky olefins also have an inherently greater tendency to form 2,3 metallacycles cannot be ruled out as a significant contributor to the observed methylidene formation.[16]

Scheme 5. Olefin Complex Formation Affecting the Rates of Metathesis of *cis*- and *trans*-Olefins



Scheme 6. Reactivity of the Methylidene with Terminal Olefins



Selectivity. Having the generally observed 2,4 configuration metallacycle formation in mind, the reactions of ring-opening cross-metathesis[17] with the ruthenium initiators can be explained, such as the observation of Randall *et al.* that bicyclic cyclobutenes react with 1.5 equiv of a terminal olefin to produce almost exclusively a single product such that the terminal olefin is effectively added across the cyclobutene double bond.[16a] The proposed pathway for this process is shown in Scheme 4. The benzylidene **2** is quickly lost to the

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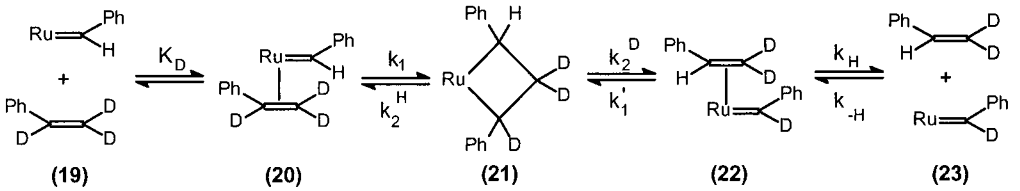
(14) These two phosphines are sterically similar but electronically different. Their similar activity in quenching the intermediate which bulkier phosphines could not stabilize supports steric factors as being more significant than electronic effects. For a review of the steric and electronic properties of phosphines, see: Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(15) ^{31}P NMR (C_6D_6): 30.67 ppm (s). ^{1}H NMR: 17.70 ppm (doublet of triplets, $J_{PH} = 10.3$ Hz, $J_{HH} = 8.0$ Hz).

(16) A reviewer suggested that the predominance of the 2,4-metallacycle can also be attributed to competing steric and electronic effects. We have observed that carbene initiators reacting with 2-hexene result in ethylidene formation, rather than butylidene, while terminal olefins do not kinetically form the methylidene. Thus, as the reviewer suggested, a steric effect places the bulk away from the metal center while electronic effects favor alkyl substituents adjacent to the metal.

(17) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610. (b) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411. (c) Snapper, M. L.; Tallarico, J. A..; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. (d) Tallarico, J. A.; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem. Soc.*, **1997**, 119, 7157.

Scheme 7. Mechanistic Pathway To Explain the Secondary Kinetic Isotope Effect



terminal olefin forming styrene and an alkylidene **4**, which then reacts rapidly with additional terminal olefin, though almost always degeneratively regenerating the alkylidene complex rather than a methylidene. Meanwhile, though the reaction with the cyclic olefin is slower, once the ring is metathesized, the newly formed long chain alkylidene **4a** quickly reacts with a terminal olefin and the long chain olefin is end-capped with a methylene, again regenerating the alkylidene complex **4**. Of course the relative rates of reaction of the carbene with cyclic and terminal olefins depend on the nature of the cyclic olefin. However, the fact that Randall *et al.* did not observe polycyclobutene formed by ROMP and did in fact obtain a ring-opened cross-metathesis product further supports our proposed mechanism, namely that the reactions with terminal olefins are predominant and oligomerization of the monomer is slower than cross-metathesis.[18]

The activity of different carbene ligands can be compared from the data in Table 1. For instance, reactions 5 and 14 demonstrate the surprisingly greater activity of the benzylidene over the methylidene. Clearly, there are other factors that more strongly effect the rate of metathesis than the sterics of the carbene. Further, reactions 4 and 15 demonstrate the greater activity of alkylidenes over the benzylidene. These relative rates can be significant when one plans to use a catalytic amount of the carbene for a synthesis. Once the benzylidene is initiated, if the newly formed carbene is a methylidene, it will proceed slower in the next step. However, if the newly formed species is an alkylidene, it will propagate much more readily.

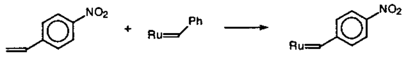
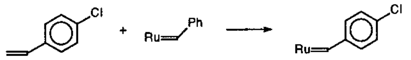
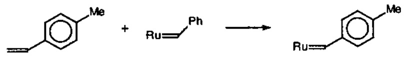
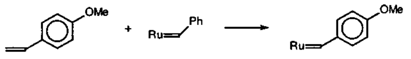
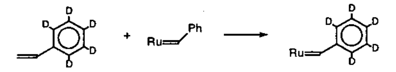
The observed relative activity of the carbenes can be rationalized as a function of their electronic and steric properties. The most active carbenes are the alkylidenes. Their electron-donating properties and their relative size help to dissociate the phosphine and speed up metathesis. The least active carbene is the methylidene, which lacks both the size and the electron-donating ability of the alkylidenes. The benzylidene is an intermediate case where the resonance of the phenyl ring is somewhat electron withdrawing while the size of the ring helps to dissociate a phosphine. Unfortunately, as detailed in the last section, kinetic studies on *para*-substituted benzylidene complexes, as a proposed measure of carbene electron-donating ability, have failed to provide a conclusive answer.[8]

When the relative rates of *cis*- and *trans*-olefins are examined, the benzylidene reacts approximately twice as fast with *cis*-3-hexene as with *trans*-3-hexene. This can be explained by considering the binding of the olefin to the complex (Scheme 5). When the *cis*-olefin binds to the metal (**16**), the substituents can point away from the bulky phosphine. The *trans*-olefin can bind either as **17** or as **18**; in either case there is an adverse steric interaction with the phosphine, which results in a slower rate of initial olefin binding.

While studying the reactivity of the methylidene, we examined the reaction with 1-hexene (Scheme 6). The reactions exhibited pseudo-first-order kinetics up to 40% conversion, at 25 °C, before the concentration of the newly formed pentylidene became sufficient so that its productive (nondegenerate) metathesis of 1-hexene became significant and the methylidene concentration started to again rise. At 35 °C, this same reaction was pseudo-first-order only to 27% conversion before the methylidene concentration started to increase again. From this we can see that the selectivity of the metallacycle formation is temperature sensitive. Thus, at elevated temperatures the formation of **3** can be as probable as the formation of **4** in the metathesis of terminal olefins by **2** (Scheme 1). This illustrates how the ruthenium catalysts are active for ADMET at elevated temperatures.

Kinetic Isotope Effects. An examination of the secondary kinetic isotope effect for metathesis, obtained

Table 2. Kinetic Data for Hammet Plot

σ_p^+	Reaction	Temp / °C	k ± SDOM[a] / L/mole•sec
0.740		7	$9.6 \pm 0.9 \times 10^{-5}$
0.035		7	$3.71 \pm 0.04 \times 10^{-4}$
-0.256		7	$5.5 \pm 0.2 \times 10^{-4}$
-0.648		7	$1.5 \pm 0.4 \times 10^{-3}$
0		7	$2.15 \pm 0.01 \times 10^{-3}$

[a] SDOM = Standard Deviation of the Mean

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from reactions 1 and 2 in Table 1, reveals that $k_H/k_D = 1.7$. Scheme 7 depicts the mechanistic pathways for the metathesis of deuterated styrene. The derived initial rate expression for the process, assuming a pre-equilibrium for **20**, a steady-state for **21** and **22**, and that the equilibrium between **22** and **23** is a lot faster than that between **21** and **22**, is as follows:

$$\frac{d[\mathrm{Ru{=}CDPh}]}{dt} = \frac{K_D k_1[\mathrm{Ru{=}CHPh}][\mathrm{PhDC{=}CD2}]}{1 + k_2^{\,H}/k_2^{\,D}}$$

The positive secondary isotope effect results from the sp^3 to sp^2 hybridization change of the metallacycle carbons during breakup.[19] As a result, the denominator for the rate equation should increase when styrene-d_8 is metathesized and lead to a slower rate relative to styrene-d_5. This effect is similar to that observed for the breakup of titanium-based metallacycles where $k_H/k_D = 2.2$.[20]

Electronic Effects of the Substrates. The study of the electronic effects of the metathesis substrate was undertaken by metathesizing *para*-substituted styrenes with **2** (Table 2). The exclusive product of each reaction was the *para*-substituted benzylidene. A linear free energy relationship (LFER) with the σ^+ electronic parameter[21] was found, $\log({}^{k}/_{k'}) = \rho\sigma^+$ ($R^2 = 0.991$) and $\rho = -0.84$ (Figure 2). However, when the rate for styrene-d_5 was added to the plot, no fit was found. The expected rate for styrene, interpolated from the Hammett plot, is 0.18 times the observed rate for styrene-d_5. Although there is precedent for β secondary isotope effects acting through a conjugated linkage,[22] the observed styrene-d_5 rate is too great to be justified by effects of the styrene ring deuterium. Thus, no definite conclusion can be drawn regarding the substrate electronic effects. An earlier study of the effect of the *para*-substituent on benzylidene complexes reacting with 1-hexene showed only small and nonlinear electronic effects.[8]

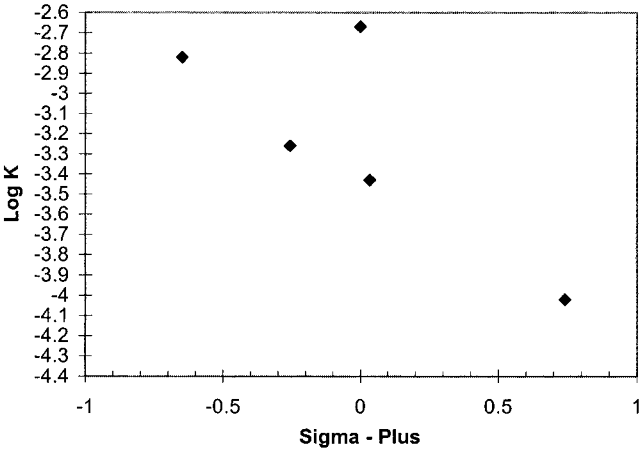

Figure 2. LFER for the reaction of benzylidene (2) with para-substituted styrenes in C_6D_6 at 7 °C.

Conclusion

We have reported the relative rates of metathesis by the ruthenium benzylidene olefin metathesis catalyst of various olefinic substrates and thus provided guidelines for the utilization of the ruthenium benzylidene catalyst for organic syntheses in terms of the relative reactivities of double bonds in a molecule. We have shown that the kinetically preferred metallacycle has the substituent on the olefin placed adjacent to the metal. However, if the final carbene complex is not stable due to steric interactions between a bulky carbene and bulky phosphines, the complex readily undergoes further metathesis until a sterically stable carbene is formed, which is the methylidene when the substrate is a bulky terminal olefin. We have also used our results to explain the behavior of the ruthenium catalysts for ring-opening cross-metathesis and ADMET.

A study of the secondary isotope effect of the incoming olefin showed that a positive effect exists due to the carbon hybridization change in the breakup of the metallacycle. No linear electronic effects of the substrate were observed. Further study is under way to understand how electronic substituents on aliphatic olefins affect the formation of a metallacycle.

Acknowledgment. We thank Dr. Eric L. Dias, Dr. Bob R. Maughon, Dr. Tomás R. Belderrain, and Dr. Andrew T. Morehead, Jr., for helpful discussions. We also thank the National Science Foundation for financial support.

OM9710172

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(18) Reference 16a addressed the potential mechanism for this process where polycyclobutene is first formed by ROMP and subsequently depolymerized and metathesized with the terminal olefin to form the ring-opened cross-metathesis product. However, when those authors treated polycyclobutene with the carbene and terminal olefin, they only obtained 15% of the expected product while treating the cyclobutene with carbene and terminal olefin produced 80% yields by GC. Thus it is very unlikely that polymerization is a significant pathway toward the products of ring-opening cross-metathesis while the mechanism in Scheme 4 is consistent with the results.

(19) For a brief discussion of secondary kinetic isotope effects, see for example: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 238–240.

(20) Lee, J. B.; Ott, K. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 7491.

(21) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

(22) Shiner, V. S., Jr.; Verbanic, C. J. *J. Am. Chem. Soc.* **1957**, *79*, 373.