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Comparative investigation of kinetic consequences associated with long-range electronic effects on catalytic ruthenium-promoted ring-closing metathesis

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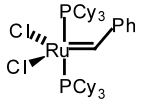
Abstract—When exposed to the Grubbs ruthenium catalyst, trienyl substrates of type **4** undergo highly regioselective ring closure to give the common product **5**. These reactions proceed invariably under pseudo-first-order kinetics, considerably faster when X=H ($t_{1/2}$=9.1), followed by X=CO_2Et ($t_{1/2}$=26.5).

The ready availability of stable, user-friendly ruthenium-based catalysts[1] and the excellent tolerance of these agents toward many polar functional groups[2] represent two factors responsible for the recent widespread adoption of ring-closing metathesis in organic synthesis.[3] High reaction efficiency and the straightforward manner in which α,ω-dienes can be transformed into 5- to 12-membered cyclic dienes and beyond[4] have also served as important considerations. A given transformation is notably favored if nonbonded steric congestion is absent and the associated enthalpic term is small. The potential reversibility of the process[5] is thereby turned to advantage.

The general mechanistic paradigm advanced by Chauvin in 1970[6] involves the production of a metal carbenoid, which is subject in turn to intramolecular [2+2] cycloaddition. Subsequent electronic reorganization resulting in [2+2] cycloreversion liberates the cyclic olefin and regenerates the parent metal alkylidene. The latter engages the starting diene in a second (now intermolecular) cycloaddition, liberation of ethylene from which eventuates in catalyst turnover and the conversion to more of the initial reactant. Recent mechanistic investigation has provided additional important insight into this catalytic cycle.[7,8] For example, the new experimental observations have established that phosphine dissociation in **1** is a critical step along the reaction coordinate, that phosphine exchange operates by way of a dissociative scheme, and that metallocyclobutanes are likely not intermediates but transition states along the reaction pathway.



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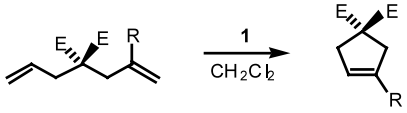
In contrast to the above, relatively little systematic effort has been directed toward an appreciation of catalyst reactivity vis-à-vis alkenes characterized by widely divergent π characteristics.[9] In a singular study, Kirkland and Grubbs examined the response of **2** to the action of **1** as a function of the substituent R.[10] When **2** (R=C_2H_5) was exposed to **1** in CH_2Cl_2 at room temperature, conversion to **3** (R=C_2H_5) proceeded in 93% yield over 24 h. Under comparable conditions, enol ethers (e.g. R=OCH_3) proved unreactive as foreshadowed.[11] Substitution with electron-withdrawing groups such as phenyl and carbomethoxy resulted in cyclization levels of 25 and 5%, respectively. For the derivatives having R=CH_2OH and CH_2OAc, behavior comparable to ethyl was noted.



2 **3**

Keywords: cyclization; metathesis; kinetics; ruthenium; electronic effects.

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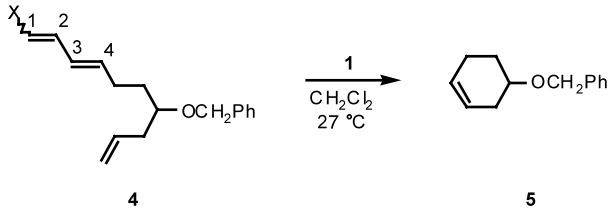
In the present study, we have chosen to probe the reactivity limits of ruthenium alkylidenes in a different manner, and in doing so to answer several mechanistic questions and offer useful new preparative insight. Our guidelines provided for attachment of the group X directly to the double bond as in **4** in order to achieve maximum electronic impact, while simultaneously arranging for a neighboring conjugated double bond to serve as the reaction center in order to normalize possible steric contributions (Scheme 1). The process is illustrated by the conversion of **4** to **5**. The substrates were designed to generate 4-benzyloxycyclohexene in every case as a consequence of the more favored rate of 6-membered ring formation.[12] The object was to determine how the electronic character in the C3–C4 double bond would affect the rate at which **5** was generated.



Scheme 1.

The catalyzed transformations of **4** were followed by monitoring the disappearance of the methine proton in **4** and the appearance of the methine proton in **5**. The concentrations of **4** were derived from integration of ^{1}H NMR resonances as a function of time (Fig. 1). The fraction of **4** was established as $CH_S/(CH_S+CH_P)$, where CH_P is the integration of the methine proton in **5**. This method assumes that all CH_S is converted to CH_P, in line with the spectral observations and isolated yields. In the case of the methoxy derivative **4a**, the integration of CH_P was not possible due to the coincidence of the chemical shift resonances for CH_P and OCH_3. In this instance, the fraction of starting material was established by referencing the integration of CH_S to the integration of the C_6H_5 signal, or $\chi_{CHS}=CH_S/[C_6H_5/5]$. Each fraction of CH_S was then multiplied by the starting concentration 0.030 M to yield the concentration of CH_S as a function of time for each run.

The resulting concentration of CH_S at time t for each run was then plotted as a function of t in min according to first-order (Eq. (1)) and second-order rate equations (Eq. (2)), where $[CH_S]_t$ is the concentration of the methine proton at time t and $[CH_S]_0$ at the initial time.

$$\ln[CH_S]_t=-k\times t+\ln[CH_S]_0 \text{ where } t_{1/2}=\ln 2/k \quad (1)$$

$$1/[CH_S]_t=+k\times t+1/[CH_S]_0 \text{ where } t_{1/2}=1/k\times[CH_S]_0 \quad (2)$$

A linear correlation obtained from these plots indicates the order of the reaction and provides the apparent rate constant, k, for the reaction. Second-order rate analysis yielded linear regression correlation values of less than 0.94. Instead, all of the kinetic data recorded were found to obey the first-order linear regression analysis (Eq. (1)). The relevant data are compiled in Table 1 and a sample plot is given in Fig. 2.

Of the four examples bearing electron-withdrawing substituents, ethyl ester **4e** was the most reactive, followed in turn by phenyl sulfone **4c** and methyl ketone **4b**.[13] Nitrile **4h** did not enter productively into the cyclization process, mirroring instead the well-known unreactivity of acrylonitrile toward olefin metathesis.[14] Treatment of substrate **4d** with **1** led smoothly to **5**, but at a somewhat faster rate than those exhibited by **4b** and **4c**. In the case of sulfide **4g**, rapid catalyst deactivation was encountered.[15] The least reactive nature of enol ether **4a** and the overall kinetic profile reflected in Table 1 reveal that electronic modulation is an important contributing factor in ring-closing metathesis even when the substituent is not directly connected to the double bond that is undergoing cleavage. These phenomena are consistent with the concept that polarization within the ruthenium alkylidene is central to its reactivity,[16] although alternative explanations cannot be entirely

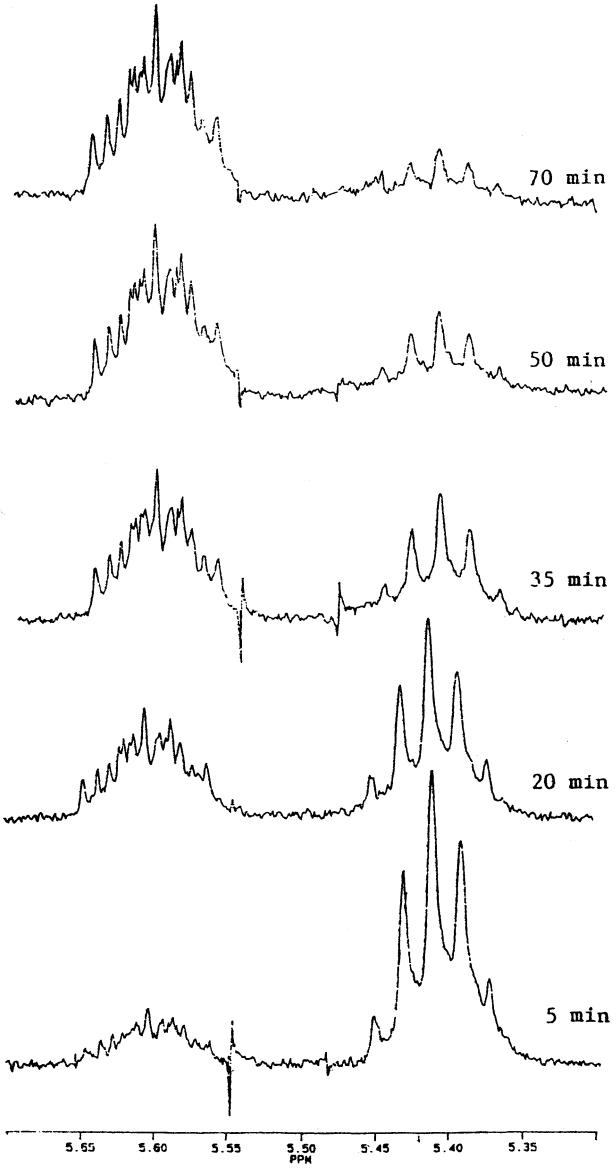


Figure 1. A stacked ^{1}H NMR plot for the ring-closing metathesis of **4e**.

Table 1. Summary of kinetic data and isolated yield of **5**[a]

Compd	X	k (1/min) (first order)	$t_{1/2}$ (min)	Regression analysis, r	Isolated yield of **5** (%)
4a	CH_3O-	0.0062	112.9±4.6	0.9933	85
4b	CH_3CO-	0.0154	45.0±0.9	0.9612	83
4c	$PhSO_2$-	0.0178	38.8±0.3	0.9866	86
4d	$HOCH_2$-	0.0215	32.2±1.1	0.9712	77
4e	EtOOC-	0.0261	26.5±0.4	0.9948	65
4f	H-	0.0762	9.1±0.4	0.9695	80
4g	PhS-	[b]			–
4h	NC-	[b]			–

[a] The ring closures were performed in duplicate at 300 K in the probe of a Bruker 300 MHz spectrometer under N_2 in the presence of 5 mol% of **1** at a substrate concentration of 0.030 M.
[b] Rapid poisoning of the catalyst was observed.

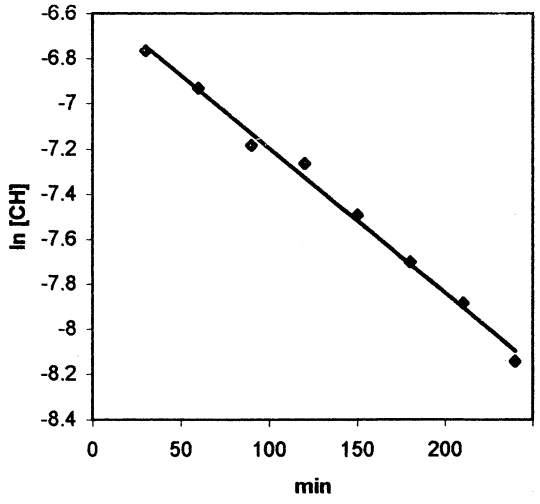
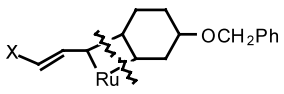


Figure 2. First-order kinetic plot for **4a**.

dismissed. In actuality, the present investigation raises many interesting mechanistic issues. For example, is the terminal alkene invariably the site of initiation in electronically strongly biased substrates of the type **4a–f**? If so, is the presence of a remote electron-withdrawing substituent capable of negative charge stabilization conducive to a Michael-type intramolecular addition involving the Ru^{+}–^{-}CHR species as nucleophile? Also of potential relevance is the fact that the propagating species formed from the retro [2+2] fragmentation of **6** are structurally and electronically different, and constitute potential sources of mechanistic changeovers. Additional information on the nature of the bonding–nonbonding orbital interactions of these Ru=CHR fragments would clearly be welcomed.



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The $PhSO_2$ substituent is the most electron-withdrawing of those examined, yet **4c** does not reflect this rate profile. The size of the phenylsulfonyl group may be responsible for some of the modest kinetic retardation. Conversely, allylic hydroxyls[17] and ester carbonyls[3a,18] have been implicated as good coordinators to the ruthenium atom in these metal carbenoids. If operational here, approach of the two ends of the reactant would be facilitated somewhat with associated kinetic consequences.

In conclusion, we have demonstrated that the conversion of **4a–g** to the common product **5** proceeds efficiently, albeit at rates that reflect their electronic makeup. The observation that electron-donating substituents on the double bond adjoining the seat of reaction decelerate the metathesis does not impact on reaction efficiency, which remains high throughout the series.

Acknowledgements

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