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Probing the Origin of Degenerate Metathesis Selectivity via Characterization and Dynamics of Ruthenacyclobutanes Containing Variable NHCs

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Abstract

The preparation of new phosphonium alkylidene ruthenium metathesis catalysts containing N-heterocyclic carbenes (NHCs) that result in a preference for degenerate metathesis is described. The reaction of the catalysts with ethylene or substrates relevant to ring-closing metathesis (RCM) produced ruthenacyclobutanes that could be characterized by cryogenic NMR spectroscopy. The rate of α/β methylene exchange in ethylene-only ruthenacycles was found to vary widely between ruthenacycles, in some cases being as low as 3.97 s^{-1} at -30°C , suggesting that the NHC plays an important role in degenerative metathesis reactions. Attempts to generate RCM-relevant ruthenacycles resulted in the low-yielding formation of a previously unobserved species, which we assign to be a β -alkyl substituted ruthenacycle. Kinetic investigations of the RCM-relevant ruthenacycles in the presence of excess ethylene revealed a large increase in the kinetic barrier of the rate-limiting dissociation of the cyclopentene RCM product compared to previously investigated catalysts. Taken together, these results shed light on the degenerate/productive selectivity differences observed between different metathesis catalysts.

Introduction

Olefin metathesis continues to evolve as one of the most effective methods for the construction of new carbon-carbon bonds.^{1,2} This evolution has been facilitated by the development and intense mechanistic study of the catalysts responsible for this transformation.³ Accordingly, metathesis has found applications in a wide range of fields including polymer chemistry,⁴ organic synthesis,⁵ biochemistry,⁶ and green chemistry.⁷

Implicit in many olefin metathesis reactions is the presence of degenerate or non-productive events. For instance, in the cross-metathesis reaction of propylene, a productive reaction would result in the formation of 2-butene, while a degenerate reaction would reform propylene. As the degenerate reaction reproduces the starting olefin, it can only be reliably studied via isotopic cross over experiments (Scheme 1). Elegant experiments from a multitude of research groups using early metal catalysts and selectively labeled olefins established that degenerate metathesis occurs approximately an order of magnitude faster than productive metathesis and appears to be the result of a propagating alkylidene species.⁸ To date, analogous studies have not been performed with modern, well-defined metathesis

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Supporting Information.

Supporting Information containing detailed experimental procedures, NMR spectra, and kinetic analysis is available free of charge via the internet at <http://pubs.acs.org>.

catalysts based on ruthenium despite the importance of degenerate events to catalyst efficiency.

Our group has recently reported on the study of degenerate events taking place during the RCM of an isotopically labeled diethyl diallylmalonate (**1**) and discovered the surprising effect of NHC structure on a catalysts propensity to perform either productive or degenerate turnovers.⁹ The results of this study validated the importance of degenerate metathesis events and their subsequent effect on a catalysts efficiency and stability. Furthermore, we have also recently established that selectivity for degenerate metathesis may actually be *beneficial* in some applications, such as the ethenolysis of methyl oleate.¹⁰ In addition, in the case of group VI catalysts, degenerate events have been shown to play a critical role in enantioselective metathesis reactions.¹¹

For ruthenium metathesis catalysts, the effect of ligand structure on initiation and stability has been well-documented.^{12,13} This information has allowed for the development of increasingly sophisticated catalysts. However, much less is known about the effect of ligand structure on processes that occur within a complex catalytic cycle such as RCM. This lack of understanding has made it difficult to rationalize the behavior of catalysts asked to conduct increasingly challenging transformations. Recently, the situation has been remedied by the development of rapidly initiating catalysts and their ability to efficiently form ruthenacyclobutanes at low temperature, which has facilitated the solution-phase study of previously inaccessible metathesis intermediates by our group¹⁴ as well as Piers and coworkers (Figure 1).^{15,16} By analyzing these intermediates and through a combination of kinetics and kinetic modeling, the Piers laboratory has been able to determine the activation energies for the fundamental steps along a productive RCM pathway.¹⁷

While the above results will undoubtedly facilitate the development of more efficient catalysts, we sought to utilize them as a basis to establish the effect of the NHC on each elementary reaction in the RCM catalytic cycle. Specifically, we wanted to correlate these effects with preference for degenerate selectivity and thereby acquire a more intimate understanding of the role of the NHC in establishing the selectivity for either degenerate or productive olefin metathesis. Herein, we report our progress towards this goal.

Results and Discussion

Considering our interest in degenerate metathesis, catalysts incorporating NHCs known to give lower selectivity for productive metathesis in the RCM of **1** were selected for study.⁹ Thus, we started with previously reported catalyst **5** and performed a phosphine exchange in order to expedite the formation of ruthenacycles.^{15c,18} Subsequent reaction with Feist's ester (**7**) yielded carbide **8**, which we then protonated with HCl in Et₂O to afford the desired phosphonium alkylidene complex **9** in good yield (Scheme 2).¹⁹

Similarly, reaction of the cyclic alkylamino carbene (CAAC) catalysts of type **10** with **7** in the presence of 1 equivalent of P(^{*i*}Pr)₃ yielded carbides **11** and **12** which were then protonated in a manner analogous to **8** to obtain the desired complexes (**13** and **14**, Scheme 3). It should be noted that, this result demonstrates that phosphonium alkylidene complexes may be obtained from Hoveyda-type parent complexes in situations where the corresponding phosphine precursor is synthetically inaccessible.

With **9**, **13**, and **14** in hand, we next attempted the preparation of ethylene-derived ruthenacycles, as even these simple metallacycles can provide insight into the influence of the NHC ligand. Gratifyingly, complete conversion to metallacycle **15** was observed after 3 h at -40 °C when **9** was exposed to B(C₆F₅)₃ and 1 atm of ethylene (Scheme 4). Consistent with analogous complexes, **15** displayed an upfield resonance at $\delta = -2.4$ ppm characteristic of

the hydrogen on the β -carbon of the ruthenacycle. We found compound **15** to be stable for several days at $-78\text{ }^{\circ}\text{C}$ and it could be fully characterized by ^1H -NMR spectroscopy and 2D techniques such as ^1H - ^1H COSY (see Supporting Information).²⁰ A ROESY spectrum taken at $-60\text{ }^{\circ}\text{C}$ (Figure 2) displayed cross-peaks indicative of chemical exchange between the protons on the α and β carbons of the ruthenacycle. Curiously, cross-peaks were only observed between α -H and β -H and not between α' -H and β -H. Although interesting, this situation is not unprecedented, and appears to be a result of asymmetry in the NHC affecting the ruthenacycle.^{15b} We next attempted to measure the rate of exchange ($k_{15\text{-Ex}}$) between α and β protons using exchange spectroscopy (EXSY). Unfortunately, the presence of a minor peak overlapping with the α -H resonance in **15** resulted in irreproducible measurements. However, switching to a magnetization transfer technique allowed us to obtain a $k_{15\text{-Ex}}$ of 10.5 s^{-1} at $-60\text{ }^{\circ}\text{C}$ (see Supporting Information).²¹ This rate is in good agreement with previous reports of ruthenacycles incorporating H_2IMes ($\text{H}_2\text{IMes} = 1,3\text{-dimesitylimidazolidine-2-ylidene}$) such as **2**. An Eyring plot (Figure S10) from $-40\text{ }^{\circ}\text{C}$ to $-80\text{ }^{\circ}\text{C}$ yielded values for $\Delta H^\ddagger$ and $\Delta S^\ddagger$ of $10.1 \pm 0.5\text{ kcal mol}^{-1}$ and $-5.7 \pm 2.2\text{ cal mol}^{-1}\text{ K}^{-1}$ respectively.

Similar to the case of **9** above, the reactions of **13** and **14** with an excess of ethylene under similar conditions cleanly yielded ruthenacycles **16** and **17** (Scheme 5).²² Characterization of **16** was performed according to the same procedure described above, but a ROESY NMR spectrum at $-60\text{ }^{\circ}\text{C}$ showed only an NOE between the α -H and β -H; no evidence of chemical exchange was observed. In fact, chemical exchange via ROESY and magnetization transfer was not observed until the temperature was raised to $-30\text{ }^{\circ}\text{C}$! Measurement of the exchange rate via magnetization transfer yielded an extraordinarily low value of 3.97 s^{-1} at $-30\text{ }^{\circ}\text{C}$ (Table 1). Thus, compared with other catalysts (e.g. **2** and **15**), $k_{16\text{-Ex}}$ is lower, even at higher temperatures. This effect can be qualitatively observed: the ruthenacycle resonances in **16** were still sharp at $-30\text{ }^{\circ}\text{C}$ whereas the same resonances in **15** were significantly broadened as a result of chemical exchange (Figure S9). In contrast to **16**, a ROESY NMR spectrum of ruthenacycle **17** taken at $-60\text{ }^{\circ}\text{C}$ showed evidence of chemical exchange, albeit with a relatively low rate constant (Table 1). Although it is difficult to extract definitive conclusions based on such dramatic changes in methylene exchange rates, particularly at the low temperatures under investigation, the extent to which the NHC can affect even the simplest of metathesis reactions is still noteworthy. Furthermore, the low rate of exchange of **16**, even at relatively high temperatures, suggests that similar complexes may be viable targets for crystallographic characterization of metathesis-relevant ruthenacycles.

Having established the feasibility of forming simple ruthenacycles with **9**, **13**, and **14**, we turned to the preparation and characterization of ruthenacycles relevant to RCM. Adopting a similar approach to the Piers' laboratory, **9**, **13**, and **14** were reacted with the cyclopentene product (**18**) resulting from the RCM of diethyl diallylmalonate (**1**) in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$ and 1 equiv. of ethylene (Scheme 6).^{15d,17} Unfortunately, under a variety of conditions, both **13** and **14** reacted to give the ethylene-only ruthenacycles **16** and **17**, respectively. Such an observation is consistent with the known preference of catalysts containing these NHCs to propagate as methylenide species in catalytic reactions (e.g. in ethenolysis),²³ but it is nevertheless surprising that no other ruthenacycles were observed.²⁴ In contrast to **13** and **14**, when **9** was reacted with **15** and 1 equiv. of ethylene at $-78\text{ }^{\circ}\text{C}$, substituted metallacycle **19** was observed, albeit in very low yield (ca. 29%). In all cases, a significant amount of the parent ethylene-only metallacycle **15** was also formed (ca. 21% yield). Despite the low yield of **19**, we were able to fully characterize the metallacycle resonances by ^1H - ^1H COSY spectroscopy and found them to be consistent with previous literature reports (*vide infra*).^{15e,17} To our surprise, ROESY spectra taken at a variety of different temperatures ($-40\text{ }^{\circ}\text{C}$ to $-70\text{ }^{\circ}\text{C}$) and mixing times (up to 600 ms) displayed no evidence of chemical exchange apart from the methylene exchange in **15**. This is in contrast

to compound **3**, which exhibits a number of dynamic processes including exchange between α^1 and α^2 resonances and exchange between **3** and free cyclopentene (Scheme 7).

Upon warming the mixture of **15** and **19** to $-40\text{ }^\circ\text{C}$ for 2 h, a new peak appeared in the metallacycle region of the NMR spectrum. At first, we believed this peak to be the result of ring-opening of **19** followed by trapping with ethylene, a process that was observed by Piers (e.g. to form **4**).¹⁷ However, several lines of evidence suggest that, under our conditions, an entirely different intermediate is formed. First, Piers and coworkers found that ring-opened ruthenacycle **4** was only formed at low temperatures (below $-60\text{ }^\circ\text{C}$) whereas the formation of the observed structure only occurred at higher temperatures ($-40\text{ }^\circ\text{C}$). Second and more importantly, substitution at α' should create a set of diastereotopic β -H resonances. Thus, if a structure analogous to **4** is correct, there should have been two separate resonances, which were not observed. In order to characterize this new species and to confirm the identity of **19**, compound **9** was reacted with **18** in the presence of ^{13}C -labelled ethylene (Figure 3). The resulting NMR spectrum taken at $-60\text{ }^\circ\text{C}$ showed that only one of the three β -H resonances ($\delta = -2.4\text{ ppm}$) was split by virtue of being bound to a ^{13}C -enriched nucleus.²⁵ This corresponds to the ethylene-only ruthenacycle **15**. The other two β -H resonances remained as singlets, which indicated that these protons must have come from substrate **18**. These data rules out the presence of a ruthenacycle resulting from the ring opening of **19** and trapping of the resulting alkylidene with ethylene. The extremely low concentration of the unknown ruthenacycle and its relatively short T_2 prevented us from establishing its structure by heteronuclear 2D NMR spectroscopy (e.g. HSQC, HMBC).²⁶ However, we were able to obtain a ^1H - ^1H COSY spectrum at $-90\text{ }^\circ\text{C}$ that provided some insight into the structure of the unknown species (Figure 4).

The COSY confirms our original assignment of **15** and **19** and also shows cross-peaks for the unknown species that suggests the following : 1) The β -carbon of the ruthenacycle is substituted with an alkyl group, as shown by a small correlation observed in the alkyl region; 2) The β -H is adjacent to a ^{13}C -enriched nucleus which is shown by a correlation in the α/α' -H ruthenacycle region that is split into a doublet; 3) The α -carbon of the ruthenacycle is also alkyl-substituted as shown by a downfield correlation that is consistent with other α -substituted ruthenacycles. Based on these results, we propose structure **22** in Scheme 8 as the unknown ruthenacycle. If this structure is correct, it would be the first observation of a β -substituted ruthenacycle that is not part of a ring system. However, as a caveat, it must be noted that, it is currently not clear what role (if any) a structure such as **22** plays in either productive or nonproductive metathesis. The formation of **22** would require ring-opening of **19** to generate an alkylidene followed by trapping with diene ^{13}C -**1** instead of ethylene (Scheme 8). This would obviously require that diene ^{13}C -**1** be present in solution. An HSQC and ^{13}C NMR spectrum confirmed the presence of ^{13}C -**1**, but we were unable to reliably establish it's concentration due to the overlap of several species in the same region of the 1D ^1H NMR spectrum (see the Supporting Information).²⁷ However, reaction of **9** with diene **1** in place of **18** yielded the same three ruthenacycle resonances, although the relative concentration of the various ruthenacycles was largely unchanged compared to previous experiments. Structure **22** is consistent with all of our spectroscopic data, but unfortunately, it's low concentration has prevented us from establishing its identity with full confidence.²⁸ Furthermore, we were also unable to find conditions where **22** did not form, a fact that has tremendously complicated our kinetic investigations. Nevertheless, we decided to probe the transformation from **19** to **15**, in the hopes of providing some insight into the effect of the NHC on more advanced ruthenacycle kinetics.

The exposure of an isotopically labeled mixture of ^{13}C -**19** and ^{13}C -**22** to an excess of ethylene (1 atm) at $-60\text{ }^\circ\text{C}$ for 6 hours revealed only a marginal decrease in the intensity of their corresponding resonances. This result is in contrast to what the Piers' laboratory

observed with **3**, which was consumed within hours under similar conditions. Perhaps more surprising was the slow rate of reaction of ruthenacycle ^{13}C -**15**, which showed almost no significant washing out of the ^{13}C label. Again, this is in contrast to catalyst **2** formed from ^{13}C -labelled ethylene, where the isotopic label was completely washed out within hours, albeit at the higher temperature of $-50\text{ }^{\circ}\text{C}$.^{14b} In a separate experiment, increasing the temperature of the reaction of **19** with excess ethylene to form **15** at $-40\text{ }^{\circ}\text{C}$ resulted in clean first-order kinetics that could be monitored on a more manageable timeframe using NMR spectroscopy. However, a closer inspection of the kinetic data revealed a second first-order process that appeared to be occurring at short reaction times (Figure S17). We believe this additional process was the result of an equilibrium between **19** and **22** at early reaction times. Indeed, a time course plot of the concentrations of **15**, **19**, and **22** revealed a slight increase in the concentration of **22** followed by a leveling off at later reaction times (Figure S18). This result confirms that there are two processes leading to the decrease in the concentration of **19**: direct reaction to form **15** with release of **18**, and an apparent equilibrium reaction to form **22**, followed by the subsequent conversion of **22** into **15** (Scheme 9).²⁹ An analogous sequence of reactions was observed by Piers' under certain conditions, albeit with a different intermediate (**4**). Modeling of the simplified series of reactions shown in Scheme 9 using COPASI³⁰ allowed for the determination of kinetic parameters k_1 , k_2 , k_{-2} , and k_3 (Table S5).^{31,32} Comparing the k_1 values obtained for **19** and **3**¹⁷ revealed a stark contrast between the reactivity of the two compounds. For example, at $-60\text{ }^{\circ}\text{C}$, the k_1 value obtained for **3** was $7\times 10^{-4}\text{ s}^{-1}$, whereas the value for **19** was two orders of magnitude less at $7.3\times 10^{-6}\text{ s}^{-1}$. An Eyring plot for k_1 values of **19** over a $20\text{ }^{\circ}\text{C}$ temperature range yielded a value for $\Delta H^{\ddagger}$ ($19.0 \pm 0.5\text{ kcal/mol}$), which is ca. 3 kcal higher than the corresponding value for **3** (16.2 kcal/mol). The $\Delta S^{\ddagger}$ values obtained for the two systems were roughly the same ($8.5 \pm 2.3\text{ cal mol}^{-1}\text{ K}^{-1}$ for **19** compared to $3.6\text{ cal mol}^{-1}\text{ K}^{-1}$).

Although we urge caution in extrapolating these results to behavior under catalytic conditions and normal operating temperatures, this fundamental transformation in the RCM cycle is clearly much more difficult for **19** compared to **3**, and may partially explain the lower activities typically associated with complexes of this type. Furthermore, since loss of the cyclopentene product from **19** or **4** appears to be the rate-determining step in the ring-closing direction, we speculate that the relative increase in the height of this barrier for **19** may allow for more degenerate turnovers to occur before a productive turnover can be completed.¹⁷ This would account for the observation that catalysts containing structurally similar NHCs select for degenerate turnovers during RCM.⁹ Finally, the observation of ^{13}C -**1** in solution suggests that ring-opening of the cyclopentene RCM product is facile, and perhaps that the kinetic preference of ring-closing over ring-opening is catalyst dependent.³³

Conclusion

In summary, several new phosphonium alkylidene ruthenium metathesis catalysts incorporating different NHCs have been prepared and used to generate ruthenacycles with the goal of rationalizing degenerate metathesis selectivity. In the case of ethylene-only ruthenacycles, the exchange rate of α and β methylene protons was found to vary considerably across the series of catalysts. With traditional NHCs, the exchange rate was largely consistent with previously reported complexes, while incorporation of a CAAC with DEP as the nitrogen substituent resulted in a severe attenuation of the exchange rate to the point where exchange was not observed until the temperature was increased to $-30\text{ }^{\circ}\text{C}$. Due to this relatively slow exchange rate, one can envision that crystallographic characterization of this complex, or analogous ones, may be possible. However, subtle changes in ligand architecture can alter the ruthenacycle exchange rate, and by extension, metathesis

selectivity and activity. This was demonstrated by the remarkable increase in exchange rate upon substituting DEP with DIPP as the nitrogen substituent on the CAAC ligand. These results demonstrate the significant changes that can occur in even the simplest of metathesis reactions as a result of changes in the NHC structure.

Our attempts to form RCM-relevant ruthenacycles resulted in the formation of a previously unobserved ruthenacycle that we believe to be the first acyclic β -alkyl substituted ruthenacycle. Such a structure is consistent with all of our spectroscopic data, but its low concentration has placed a definitive identification currently out of our technical reach. Nevertheless, this structure plays an important role in ruthenacycle kinetics under an atmosphere of excess ethylene. Our kinetic investigations revealed that the rate-limiting dissociation of the cyclopentene RCM product from the ruthenium center has a much higher energy barrier compared to previously reported complexes. Considering that the majority of the steps along the RCM pathway appear to be reversible, this higher barrier may allow for more degenerate turnovers to occur at the expense of productive ones. At the very least, it provides additional rationale for the generally inferior performance of metathesis catalysts containing *N*-aryl/*N*-alkyl NHC's when compared to those possessing *N*-aryl/*N*-aryl NHCs.

Finally, these studies further illuminate the subtle role that the NHC plays in ruthenium catalyzed olefin metathesis, thus validating efforts to fine-tune ruthenium catalysts for specific applications via manipulation of this ligand.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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24. The low yielding synthesis of catalysts of type 10 hampered our ability to exhaustively examine the behavior of 13 and 14.
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28. Another structure consistent with all of the spectroscopic data is an isomer of 19. However, the large differences in the reactivity of 19 and 22 with excess ethylene leads us to believe that this is probably not the case.

29. Direct conversion of 22 into 15 would require generation of a ruthenium methylidene (21) and the release of 23 (dashed arrows in Scheme 8). However, neither species was detected by ^1H NMR spectroscopy or HRMS, suggesting that 22 prefers to give an alkylidene which subsequently reacts with ethylene to give 15.
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31. Notably, our model does not rely on the positive identification of 22, but only that there is some equilibrium involving 19 and another ruthenacycle complex.
32. At longer reaction times, where the change in concentration of 22 is relatively insignificant and the primary reaction consuming 19 is k_1 , the k_{obs} values from a log plot and k_1 values obtained from modeling were generally in good agreement (within a factor of 2 or less).
33. For a discussion on the kinetic favorability of ring-closing, see ref. 17.

Figure 1.
Previously observed ruthenacycles relevant to RCM.

Figure 2. Mechanism of ruthenacycle methylene exchange (left) and ROESY spectrum at -60°C with cross-peaks indicative of chemical exchange (right).

Figure 3. Generation of substituted ruthenacycles using ^{13}C -ethylene showing $^{13}\text{C-15}$ ($\delta = -2.2$ ppm and -2.5 ppm), $^{13}\text{C-19}$ ($\delta = -1.65$ ppm), and $^{13}\text{C-22}$ ($\delta = -1.1$ ppm).

Figure 4. ^1H - ^1H COSY of ruthenacycle region for ^{13}C -labelled ruthenacycle mixture at $-90\text{ }^\circ\text{C}$ in CD_2Cl_2 . Note that the assignments of **A** and **B** in ^{13}C -**15** are arbitrary since there was not enough spectroscopic data to distinguish the two. **X**, **Y**, and **Z** assignments were confirmed by 2D NOESY.

Scheme 1.

Productive and degenerate metathesis of propylene.

Scheme 2.
Synthesis of phosphonium alkylidene catalyst **9**.

Scheme 3.
Synthesis of catalysts **13** and **14**.

Scheme 4.
Generation of ethylene-only ruthenacycle from **9**.

Scheme 5.
Generation of ethylene-only ruthenacycles from **13** and **14**.

Scheme 6.
Synthesis of substituted ruthenacycles from **9** and **13**.

Scheme 7.
Unobserved exchange processes in **19**.

Scheme 8.

Proposed formation of diene **1** and ruthenacycle **22** from **19** and ethylene. Dashed lines represent a possible process which was not observed.²⁹

Scheme 9.

Kinetic model for conversion of **19** to **15** and **22** in the presence of excess ethylene.

Table 1

Ruthenacycle methylene exchange rates for all complexes.

Complex	Temperature (°C)	α/β methylene exchange rate (s ⁻¹)
15	-60	10.5
16	-30	3.97
17	-60	1.48