Rate Enhancement by Ethylene in the Ru-Catalyzed Ring-Closing Metathesis of Enynes: Evidence for an “Ene-then-Yne” Pathway that Diverts through a Second Catalytic Cycle

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The ring-closing metathesis (RCM) of enynes [1→2, Eq. (1)] was first reported by Katz and Sivavec in 1985.[1]

\[ \overset{1}{\text{C}} \underset{2}{\text{C}} \quad \rightarrow \quad \overset{2}{\text{C}} \underset{1}{\text{C}} \quad (1) \]

A tungsten–alkylidene precatalyst was employed and, on the basis of mechanistic studies on alkene/alkyne metathesis copolymerization, a Chauvin-type[2] mechanism involving an “yne-then-ene” sequence was proposed (Scheme 1, cycle A).

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Subsequent reports by Hoye and co-workers\cite{3} and by Mori and co-workers\cite{4} on analogous Mo- and Cr-based carbene precatalysts also invoked mechanism A, which neatly accounted for a number of side products, for example, vinyl cyclopropanes, by reductive elimination in the metallacyclobutane intermediate.

With the advent of Ru-based alkylidene precatalysts (for example, \ref{3} and \ref{4}, Scheme 2), both enyne RCM and alkene/alkyne co-metathesis have enjoyed rapidly increasing application.\cite{7} Possibly as a legacy from the earlier work with catalysts based on Group VI elements,\cite{1,3,4} the “yne-then-ene” mechanism (A) is commonly postulated for the Ru-catalyzed enyne RCM reaction.\cite{8,9}

In 1998, Mori et al. reported that ethylene can have a dramatic effect on the yield of Ru-catalyzed enyne RCM reactions, for example, in the conversion of enyne \ref{5} into diene \ref{6} (Scheme 2).\cite{10} We have recently been investigating the effect of ethylene (“Mori’s conditions”\cite{10}) on the Ru-catalyzed RCM of enynes \ref{5} and \ref{7}.

An alternative mechanism for enyne RCM under standard conditions has also been proposed.\cite{14} However, this “ene-then-yne” sequence (Scheme 1, cycle B) is seldom considered, despite a growing body of evidence.\cite{14,15} Herein, we present \textsuperscript{2H}- and \textsuperscript{13}C-labeling strategies that probe the origin of the ethylene acceleration and its relationship to the mechanistic dichotomy (cycles A versus B) in Ru-catalyzed enyne RCM.

Starting with reactions conducted in the absence of ethylene, we focused on the steps in mechanisms A and B that generate the vinyl terminus (the methylene group) in the RCM product \ref{2}. In cycle A this involves ring opening of ruthenacyclobutene \ref{10} in which there are no C-based stereogenic centers in the ring. In cycle B, this involves ring opening of ruthenacyclobutane \ref{11} in which there are two C-based stereogenic centers, and thus two diastereoisomeric forms. We have been able to probe for diastereoselectivity in this transient species\cite{16} by use of stereospecifically labeled enyne substrate (\((E)-\) and \((Z)-\textsuperscript{[2H]}\)).\cite{17}
As illustrated for (E)-[1°H]-1 in Scheme 3, pathway A is predicted to generate [1°H]-2 with no E/Z selectivity at the CH=C(D)H group.13 In contrast, in pathway B, any net diastereoselectivity in the formation and breakdown of [1°H]-

with lower but analogous selectivity: (Z)-[1°H]-5 gave (E)-

The one-then-yne sequence (cycle B) also provides a mechanistic rationale for the effect of ethylene (Scheme 5). The vinylalkylidene complex 12, which reacts with substrate 1 to liberate 2 via 11 on the primary cycle (B1), can also react with ethylene, as a surrogate alkene for 1,15 to liberate RCM product 2 via complex 13 (upper section of Scheme 5). The resulting ruthenium-methylidene complex 9, which is identical to that found in the yne-then-ene sequence (cycle A), can rejoin the primary catalytic cycle (B1) by reacting with the substrate (1) and releasing ethylene, thereby creating a secondary cycle that is catalyzed by ethylene.

To investigate the possibility of turnover through a secondary cycle, we conducted RCM reactions under an atmosphere of [13C]ethylene. In cycle A, cross-metathesis equilibration of [13C]ethylene with Ru–methylidene 9 will lead to [13C]-9 (n = 0 or 1). This labeled methylidene compound can then generate [13C]-2 and 9 by RCM, with the 13C/12C ratio in the terminal alkene of 2 being determined by the 9/[13C]-9 ratio. In mechanism B, the primary cycle (B1) will generate unlabeled 2, and the secondary cycle B2 will generate [13C]-2 (via [13C]-13; see the filled circles in Scheme 5), with the 13C/12C ratio then being determined by B1/B2 partitioning. In addition, three more processes that can affect the 13C/12C ratio in 2 must be considered. Firstly, cross-metathesis of labeled methylidene [13C]-9 with the terminal alkene in 1 will generate [13C]-1, which on RCM by pathway B1 will generate [13C]-2. Secondly, cross-metathesis of product 2 with [13C]-9 will generate [13C]-2 by a non-RCM pathway. Finally, insufficient rapid exchange of solution-phase ethylene with the bulk gaseous phase will result in temporary depletion of [13C]ethylene, and enrichment of [13C]ethylene (n = 0, 1), in the solution phase. From the above analysis it is thus clear that the extent of 13C incorporation in 2 cannot alone be used to distinguish mechanisms A and B.

To address this issue, we have designed a dual-substrate, dual-labeling strategy. The experiment involves RCM of a 1/1 mixture of two enynes (5 and 7) for which the accelerating effect of ethylene is different: the rate of RCM for the slowereacting enyne 5 is increased 2.8 times over that of the fasterreacting enyne 7.22 This differential acceleration results in similar rates of RCM for 5 and 7 under ethylene (8.3 × 10⁻⁴ and 9.7 × 10⁻⁴ s⁻¹, respectively).

Conducting the reaction under [13C]ethylene (1 atm, 930 mol%) gives [13C]-6 and [13C]-8. As controls for the experiment, the reaction mixture also included 10 mol% of [D₂]-6 and [D₂]-8, to allow estimation of the extent of 13C incorporation into 6 and 8 by non-RCM pathways, as well as any reversibility of the reaction (Scheme 6).

Samples taken over the entire course of the reaction were analyzed by GC and GCMS. The resulting incorporations of [13C] (%) in substrates 5 and 7, products 6 and 8, and reference products [D₂]-6 and [D₂]-8 as a function of conversion are shown in Figure 1.

Scheme 3. The stereoselective outcome of RCM of stereospecifically labeled enyne ((E)-[1°H]-1) by mechanisms A and B. Note that the ruthenacyclobutane ring in 11 may well adopt a cyclobutane-like puckered structure. The deuterium atoms are marked in bold when they are derived from the alkylidene to differentiate them from those that are derived from the alkene.

Scheme 4. Ru-catalyzed RCM of stereospecifically H-labeled enynes. Note that the alkyl-[°H] label in (Z)-[°H]-7 arises from the synthesis and is present only as a spectator label.
The analysis demonstrates that non-RCM incorporation of $^{13}$C into both the substrates and the products becomes increasingly competitive as the reaction evolves. Moreover, further control experiments showed that the rate of equilibration of $[^{13}$C]ethylene between the gas and solution phases under the reaction conditions ($t_{0.5} = 83 \pm 4$ s)\(^{22}\) is only one order of magnitude faster than catalyst turnover, and thus all three factors outlined above affect the $^{13}$C/$^{12}$C incorporation. Nonetheless, the dual-substrate, dual-labeling approach allows the distinction of mechanisms A and B as follows. In mechanism A, although the RCM reactions of 5 and 7 have been accelerated to different extents, the $^{13}$C/$^{12}$C incorporation into 6 and 8 at any time in the reaction will be determined by the $9/[^{13}$C]9 ratio, and will thus be equal.

In mechanism B, enyne 5, whose RCM is accelerated by the ethylene more than 7, will partition more through pathway B2, thus giving rise to a greater level of $^{13}$C incorporation. The ratio of $^{13}$C/$^{12}$C incorporation in 6 versus 8 should thus reflect the 2.8-fold difference in acceleration by ethylene for 5 versus 7.

In the first half of the reaction an approximately linear relationship is found between the $^{13}$C/$^{12}$C ratio at the vinyl terminus in 6 and 8 and the extent of the reaction (Figure 2). The steeper gradient observed for 6, relative to that for 8, arises from the more rapid non-RCM incorporation of $^{13}$C, as revealed by the analyses in Figure 1. Extrapolating the two relationships in Figure 2 to 0% conversion, gives the initial ratio of $^{13}$C/$^{12}$C incorporations for 6 and 8 as 2.3 ± 0.6:1, which is in good agreement with the ratio of 2.8:1 predicted by mechanism B,\(^{23}\) and significantly greater than the ratio of 1.0:1 predicted by mechanism A. It can thus be concluded that the reaction of enyne 7 (\(\rightarrow\)8) under ethylene does not proceed predominantly through pathway A. Moreover, the differential $^{13}$C/$^{12}$C incorporation data strongly supports the proposal that both processes (5→6 and 7→8) proceed predominantly through pathway B2 under ethylene.\(^{24}\)

In summary, isotopic labeling experiments ($^2$H and $^{13}$C) of Ru-catalyzed enyne ring-closing metathesis reactions involving enynes 5 and 7 give results that are not compatible with the commonly proposed yne-then-ene mechanism (cycle A).\(^{25}\) The results are however explained by the alternative ene-then-yne mechanism (cycle B) for which ethylene can catalyze the reaction by diversion of the vinylalkylidene intermediate 12 on the primary cycle B1\(^{14}\) onto a second cycle B2.\(^{13}\) The use of "Mori’s conditions" (conducting Ru-catalyzed enyne RCM reactions under ethylene) is wide-
spread, and thus mechanism B may apply to a broader range of substrates than previously considered.

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Figure 1. Relationships between $^{13}$C incorporation (\%) at the vinyl terminus (y axis) in substrates and products as a function of conversion (x axis) for the co-reaction of 5, [D$_{2}$]6, 7, and [D$_{3}$]8 as shown in Scheme 6.

Figure 2. The $^{13}$C/$^{12}$C ratio at the vinyl terminus (y axis) in 6 and 8 as a function of conversion (c, %, x axis) of 5 and 7. The linear regressions are: $^{13}$C/$^{12}$C = $0.19 \pm 0.01c + 3.86 \pm 0.82$ and $^{13}$C/$^{12}$C = $0.05 \pm 0.002c + 1.65 \pm 0.05$, respectively.

[8] The discussion herein is limited to enyne RCM proceeding intermolecularly via alkylidene intermediates.
[13] The rate of RCM of dimethyl diallyl malonate (cf. dimethyl allyl propargyl malonate 5) catalyzed by 3 in CHCl$_3$ was found to be identical under $N_2$ (1 atm) and ethylene (1 atm), throughout the entire course of the reaction.
[16] Although intermediates such as 11 have not yet been observed under the conditions of catalysis, a ruthenacyclobutane complex could arise from the reaction of 4 with $^{13}$C labeled alkylidene 12.
Reactions displayed reproducible pseudo-first-order kinetics. It should be noted that in the absence of ethylene, cycles A or B may be dominant and either or both may be operative as nondominant pathways when the reaction is conducted under ethylene. However, with 1/1 mixtures of 5 and 7, pseudo-first-order rate constants were identical under ethylene (1 atm) to those in the reactions of single components. Inconsistent with the yne-then-ene mechanism (A), the rate constant for reaction of 5, but not of 7, was somewhat attenuated under N₂ when mixed (1/1). Since the rate of reaction of 5 with 12 will depend on whether 12 is derived from 7 or 5, this further supports turnover by the primary ene-then-yne (B1) mechanism in the absence of ethylene.