Reaction Mechanisms

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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]

1 **2** (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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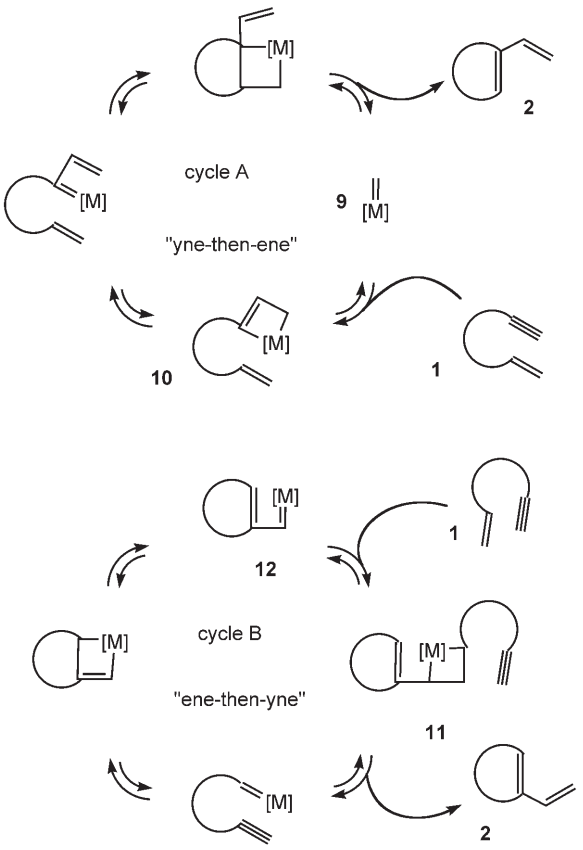
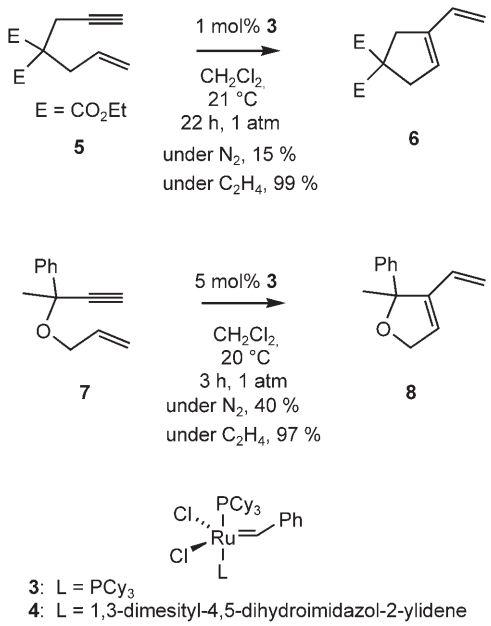


Scheme 1. The "yne-then-ene" (A) and "ene-then-yne" (B) mechanisms for RCM of enyne **1** proceeding intermolecularly via metal alkylidene intermediates.



Scheme 2. The effect of ethylene ("Mori's conditions"[10]) on the Ru-catalyzed RCM of enynes **5** and **7**.

Subsequent reports by Hoye and co-workers[3] and by Mori and co-workers[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, **3**[5] and **4**,[6] Scheme 2), both enyne RCM and alkene/alkyne co-metathesis have enjoyed rapidly increasing application.[7] Possibly as a legacy from the earlier work with catalysts based on Group VI elements,[1,3,4] the "yne-then-ene" mechanism (A) is commonly postulated for the Ru-catalyzed enyne RCM reaction.[8,9]

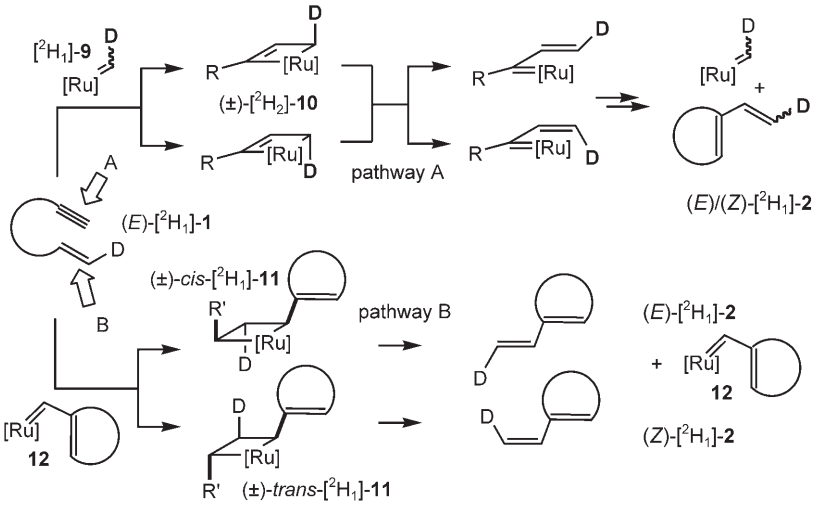
In 1998, Mori et al. reported that ethylene can have a dramatic effect on the yield of Ru-catalyzed enyne RCM reactions, for example, in the conversion of enyne **5** into diene **6** (Scheme 2).[10] We have recently been investigating the RCM of allyl propargyl ethers,[11] for example, **7**→**8**, which also improves under ethylene (Scheme 2). It is of note that the rate of RCM of **5** is increased by ethylene more than that of **7**.

The beneficial effect of ethylene on some RCM reactions has led to "Mori's conditions"[10] being widely adopted[7a,12] to increase yields and inhibit side reactions such as epimerization,[12d] and substrate homo-cross-metathesis.[12c,g] The origin of the ethylene effect has been ascribed to the attenuation of unproductive resting states in equilibrium with the ruthenium methylidene **9** in cycle A.[10] However, such a "protective effect"[7a] would be expected to increase catalyst longevity rather than increase the reaction rate. Moreover, the effect should be operative across the full range of enynes,[12i–k] and it should extend to the RCM of the corresponding dienes.[13] An alternative explanation would be that ethylene acts as an initiator, which converts the precatalyst, for example, **3**, into the active intermediate **9** in cycle A by cross-metathesis. To test this supposition, we alternated the atmosphere above a RCM of enyne **5** (5 mol% **3**, CH_2Cl_2, 21°C) between N_2 (1 atm) and ethylene (1 atm) during the reaction. Irrespective of the extent of conversion of the substrate, catalysis always accelerated on switching to an ethylene atmosphere, and decelerated on returning to N_2, which refutes an initiation effect and emphasises that ethylene accelerates a net catalytic turnover.

An alternative mechanism for enyne RCM under standard conditions has also been proposed.[14] However, this "ene-then-yne" sequence (Scheme 1, cycle B) is seldom considered, despite a growing body of evidence.[14,15] Herein, we present ^{2}H- and ^{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.

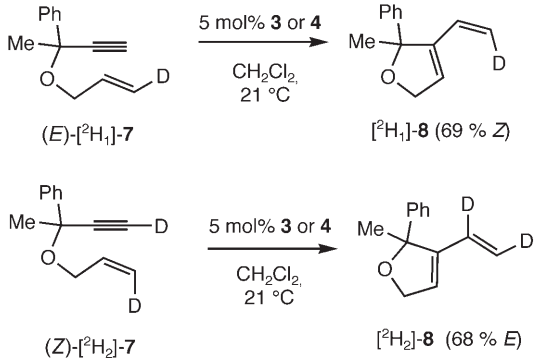
Starting with reactions conducted in the absence of ethylene, we focused on the steps in mechanisms A and B that generate the vinyl terminus (the methylene group) in the RCM product **2**. In cycle A this involves ring opening of ruthenacyclobutene **10** in which there are no C-based stereogenic centers in the ring. In cycle B, this involves ring opening of ruthenacyclobutane **11** in which there are two C-based stereogenic centers, and thus two diasteroisomeric forms. We have been able to probe for diastereoselectivity in this transient species[16] by use of stereospecifically labeled enyne substrate ((*E*)- and (*Z*)-[^{2}H]-**1**).[17]

As illustrated for (*E*)-[^{2}H]-**1** in Scheme 3, pathway A is predicted to generate [^{2}H]-**2** with no *E*/*Z* selectivity at the CH=C(D)H group.[17] In contrast, in pathway B, any net diastereoselectivity in the formation and breakdown of [^{2}H]-**11**, will translate into *E*/*Z* selectivity, as the relative configuration of the CHD and CHR′ centers in **11** are determined by the geometry of the alkene substrate. Thus, isomeric substrate (*Z*)-[^{2}H]-**1** should give the opposite isomer of product [^{2}H]-**2**.



Scheme 3. The stereochemical outcome of RCM of stereospecifically labeled enyne ((*E*)-[^{2}H$_1$]-**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.

Ru-catalyzed RCM reactions of enynes (*E*)-[^{2}H$_1$]-**7** and (*Z*)-[^{2}H$_2$]-**7** gave (*Z*)-[^{2}H$_1$]-**8** and (*E*)-[^{2}H$_2$]-**8**, respectively, with 68–69% selectivity irrespective of the precatalyst (Scheme 4). These results are consistent with pathway B operating in which the major flux is via the *trans* diastereomer of **11**.[18] Identical selectivities were found with the Fürstner–Ackermann catalyst system,[19] and also with an achiral analogue of (*Z*)-[1,7-^{2}H$_2$]-**7** in which the Me and Ph groups were replaced by a pentane-1,5-diyl system. The slower-reacting malonate substrate **5**, which has similar steric hindrance at the allylic and propargylic positions, proceeded with lower but analogous selectivity: (*Z*)-[^{2}H$_1$]-**5** gave (*E*)-[^{2}H$_1$]-**6** (55% (*E*)).



Scheme 4. Ru-catalyzed RCM of stereospecifically ^{2}H-labeled enynes. Note that the alkynyl ^{2}H label in (*Z*)-[^{2}H$_2$]-**7** arises from the synthesis and is present only as a spectator label.

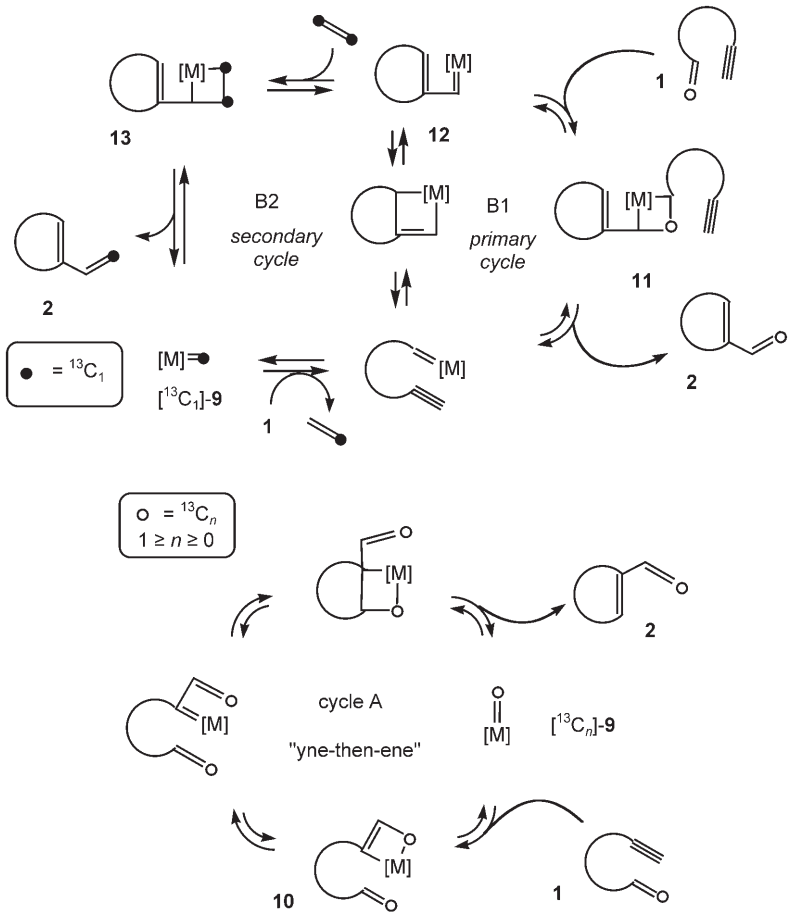
The ene-then-yne sequence (cycle B) also provides a simple mechanistic rationale for the effect of ethylene (Scheme 5). The vinylalkylidene[20] complex **12**, which reacts with substrate **1** to liberate **2** via **11** on the primary cycle (B1), can also react with ethylene, as a surrogate alkene 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 [^{13}C$_2$]ethylene. In cycle A, cross-metathesis equilibration of [^{13}C$_2$]ethylene with Ru–methylidene **9** will lead to [^{13}C$_n$]-**9** ($n=0$ or 1). This labeled methylidene compound can then generate [^{13}C$_1$]-**2** and **9** by RCM, with the ^{13}C/^{12}C ratio in the terminal alkene of **2** being determined by the **9**/[^{13}C$_1$]-**9** ratio. In mechanism B, the primary cycle (B1) will generate unlabeled **2**, and the secondary cycle B2 will generate [^{13}C$_1$]-**2** (via [^{13}C$_2$]-**13**; see the filled circles in Scheme 5), with the ^{13}C/^{12}C ratio then being determined by B1/B2 partitioning. In addition, three more processes that can affect the ^{13}C/^{12}C ratio in **2** must be considered. Firstly, cross-metathesis of labeled methylidene [^{13}C$_1$]-**9** with the terminal alkene in **1** will generate [^{13}C$_1$]-**1**, which on RCM by pathway B1 will generate [^{13}C$_1$]-**2**. Secondly, cross-metathesis of product (**2**) with [^{13}C$_1$]-**9** will generate [^{13}C$_1$]-**2** by a non-RCM pathway. Finally, insufficiently rapid exchange of solution-phase ethylene with the bulk gaseous phase will result in temporary depletion of [^{13}C$_2$]ethylene, and enrichment of [^{13}C$_n$]ethylene ($n=0$, 1), in the solution phase. From the above analysis it is thus clear that the extent of ^{13}C incorporation in **2** cannot alone be used to distinguish mechanisms A and B.

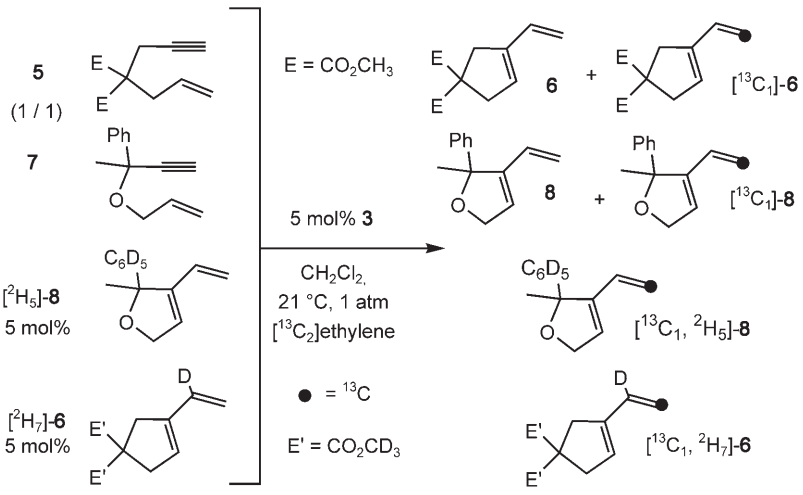
To address this issue, we have designed a dual-substrate, dual-labeling strategy. The experiment involves RCM of a 1/1 mixture of two enynes (**5** and **7**) for which the accelerating effect of ethylene is different: the rate of RCM for the slower-reacting enyne **5** is increased 2.8 times over that of the faster-reacting enyne **7**.[21] 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 [^{13}C$_2$]ethylene (1 atm, 930 mol%) gives [^{13}C$_1$]-**6**/**6** and [^{13}C$_1$]-**8**/**8.** As controls for the experiment, the reaction mixture also included 10 mol% of [D$_7$]-**6**/[D$_5$]-**8**, to allow estimation of the extent of ^{13}C$_1$ 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 ^{13}C (%) in substrates **5** and **7**, products **6** and **8**, and reference products [D$_7$]-**6** and [D$_5$]-**8** as a function of conversion are shown in Figure 1.



Scheme 5. Adaptation of Scheme 1, to include a secondary cycle (B2) that is catalyzed by ethylene, as well as the ^{13}C-labeling patterns predicted for cycles A and B when reaction is conducted under [$^{13}C_2$]ethylene. Partial ^{13}C incorporation at the alkene terminus of enyne **1** arising from degenerate metathesis with [$^{13}C_n$]-**9** ($1 \geq n \geq 0$) is also shown.



Scheme 6. A dual-substrate/dual-labeling strategy for detection of preturnover/postturnover ^{13}C-label incorporation and distinction of enyne RCM through mechanisms A and B. $[\mathbf{5}]_0 + [\mathbf{7}]_0 = 0.08$ M.

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 [$^{13}C_n$]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**/[$^{13}C_1$]-**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** (→**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 (^2H 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).[23] 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.[15] The use of "Mori's conditions" (conducting Ru-catalyzed enyne RCM reactions under ethylene) is wide-

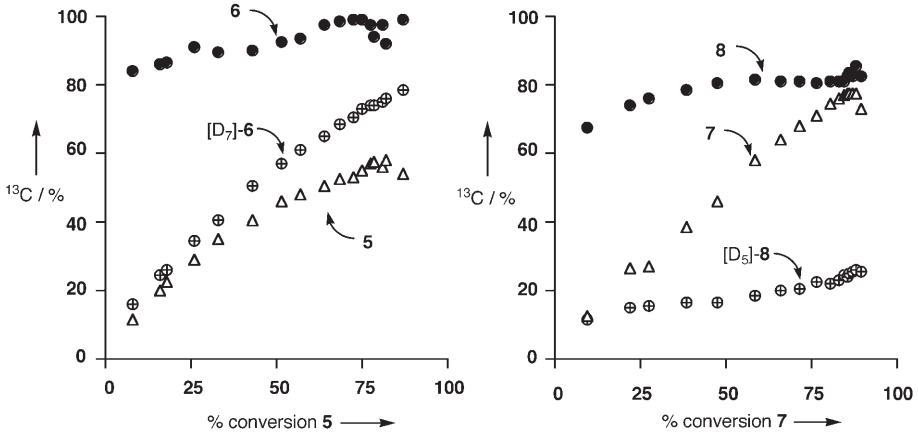


Figure 1. Relationships between ^{13}C incorporation (%) at the vinyl terminus (*y* axis) in substrates and products as a function of conversion (*x* axis) for the co-reaction of **5**, [D$_7$]-**6**, **7**, and [D$_5$]-**8** as shown in Scheme 6.

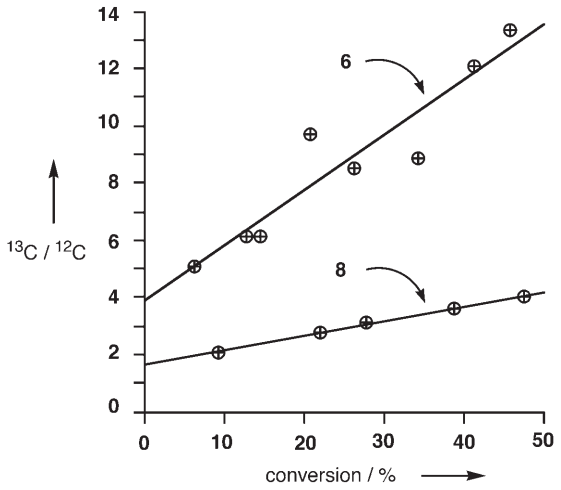


Figure 2. The ^{13}C/^{12}C ratio at the vinyl terminus (*y* axis) in **6** and **8** as a function of conversion (*c*, %, *x* axis) of **5** and **7**. The linear regressions are: $^{13}C/^{12}C = 0.19 \pm 0.03\,c + 3.86 \pm 0.82$ and $^{13}C/^{12}C = 0.05 \pm 0.002\,c + 1.65 \pm 0.05$, respectively.

spread, and thus mechanism B may apply to a broader range of substrates than previously considered.

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of the type [LRu(Cl_2)(η^2-$CHCH_2CH$)], where L = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) has recently been observed by NMR spectroscopy at low temperatures: P. E. Romero, W. E. Piers, *J. Am. Chem. Soc.* **2005**, *127*, 5032 – 5033.

[17] The "low grade" -CH(D)- stereocenters are expected to exert negligible influence on the direction of ring opening, as evidenced by the complimentarity of the results obtained with (*E*)-[7-$^2H_1$]-**7** and (*Z*)-[1,7-$^2H_2$]-**7**. The magnitude of the selectivity is in vast excess over that expected from any secondary kinetic isotope effect in the addition of [^{2}H]-**9** to [^{2}H]-**1**.

[18] It should be noted that the observed 68.5 % (average) stereoselectivity for [^{2}H]-**7**→[^{2}H]-**8** is that at the end of reaction, during which control experiments indicate progressive scrambling of the *E*/*Z* stereochemistry in the [^{2}H]-**7** (ca. 20 % stereorandomization at 96 % conversion). The selectivity is thus consistent with the maximum range 63/37 to 0/100 A/B with 100 % to 68.5 % diastereoselectivity, respectively. For [^{2}H]-**5**, there is no scrambling during the reaction. The observed selectivity of 55 % is consistent with the range 90/10 to 0/100 A/B with 100 % to 55 % diastereoselectivity, respectively.

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[21] Reactions displayed reproducible pseudo-first-order kinetics. For **5** and **7**: under N_2: $k_{obs} = 1.1 \times 10^{-4}$ and $3.0 \times 10^{-3}\ s^{-1}$, under ethylene: $k_{obs} = 8.3 \times 10^{-4}$ and $9.7 \times 10^{-4}\ s^{-1}$; where k_{obs} was derived from a simulation of the parallel processes: 1) **1** + [Ru]→**2** + [Ru] (k), 2) [Ru]→inactive (k_{decomp}), where [Ru] = [**3**]$_0$ = 0.004 M and [**1**]$_0$ = [**5**]$_0$ or [**7**]$_0$ = 0.08 M and $k_{obs} = k \times$ [Ru]. For reactions under ethylene $k_{decomp} = 0$, for reactions under N_2, $k_{decomp} = 2 \times 10^{-4}\ s^{-1}$. Although bimolecular catalyst decomposition is probable, the model did not require this level of sophistication for satisfactory fit. The relative rate differential under ethylene = $[((k_{obs}^{5,C_2H_4} - k_{obs}^{5,N_2})/(k_{obs}^{5,N_2}))/((k_{obs}^{7,C_2H_4} - k_{obs}^{7,N_2})/(k_{obs}^{7,N_2}))] = 2.8$.

[22] After completion of the reaction, the liquid phase was replaced with an identical volume of CD_2Cl_2 and allowed to saturate with stirring in the [$^{13}C_n$]ethylene atmosphere. The CD_2Cl_2 was then transferred to an identical vessel containing [$^{12}C_2$]ethylene and the CD_2Cl_2 phase analyzed by ^{1}H NMR spectroscopy every 60 s until equilibrium was established (ca. 600 s). A plot of $-\ln([^{13}C_2]_t]/[^{13}C_2]_{eqm}])$ against t was linear, with the gradient = $(k_f + k_b) = 8.4(\pm 0.3) \times 10^{-3}\ s^{-1}$. The nonstatistical mixture of [$^{13}C_n$]ethylene (94.5 % $n = 2$, 4.9 % $n = 1$, 0.6 % $n = 0$) obtained at the end of co-RCM of **5** and **7** is qualitatively consistent with incomplete equilibration of the gas–solution phases during catalytic turnover.

[23] The $^{13}C/^{12}C$ ratios in **5** and **7** of 3.9:1 and 1.7:1 at "0 % conversion" (Figure 2) are ca. 63 % and 76 % of the predicted $^{13}C/^{12}C$ B2/B1 partitioning, which suggests that there may be an additional ethylene accelerating effect, for example, by ethylene acting as a spectator ligand, that increases the rate of pathway A or B1 slightly (for computational analysis of such effects see reference [15c]).

[24] 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 N_2 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.

