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Ethylene-Promoted versus Ethylene-Free Enyne Metathesis

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Supporting Information

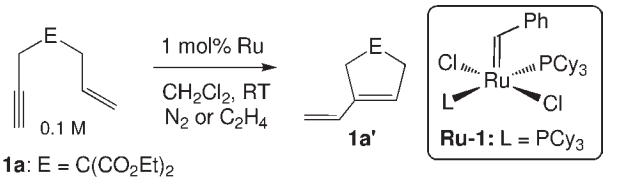
ABSTRACT: The role of ethylene in promoting metathesis of acetylenic enynes is probed within the context of ring-closing enyne metathesis, using first- and second-generation Grubbs catalysts. Under inert atmosphere, rapid catalyst deactivation is observed by calibrated GC−FID analysis for substrates with minimal propargylic bulk. MALDI-TOF mass spectra reveal a Ru(enyne)$_2$ derivative that exhibits very low reactivity toward both enyne and ethylene. Under ethylene, formation of this species is suppressed. Enynes with bulky propargylic groups are not susceptible to this catalyst deactivation pathway, even under N_2 atmosphere.

Enyne metathesis offers unparalleled efficiency and atom economy in the assembly of synthetically versatile 1,3-dienes.[1] Recent examples of biologically relevant compounds synthesized by sequences utilizing ring-closing enyne metathesis (RCEYM) as a key step include the antitumor agents (−)-Acylfulvene and (−)-Irofulven,[2] as well as nucleoside analogues to the antiviral agent Stavudine.[3] A breakthrough in this area was reported by Mori more than 10 years ago, with the discovery that use of ethylene atmospheres dramatically improves rates and yields in ruthenium-catalyzed RCEYM.[4] A clever "atmosphere-switching" study subsequently confirmed that reaction was consistently faster under ethylene.[5] The origin of these effects[6] has been much discussed. Puzzling aspects include the fact that ethylene is not invariably required for satisfactory outcomes[1g] (and indeed can sometimes be detrimental),[6b,7] and a striking disparity with olefin metathesis, in which retention of cogenerated ethylene undermines catalyst performance.[8] Here, we investigate the origin of these inconsistencies, with specific attention to the effect of ethylene on the nature of the organic and organometallic products, and to the influence of propargylic substitution.

We began by examining the effect of the headspace atmosphere in reactions of enyne **1a** with **Ru-1** (Scheme 1), a substrate-catalyst combination known to afford higher RCEYM yields under ethylene.[4] Experiments were carried out in a glovebox in sealed Schlenk tubes under C_2H_4 or N_2, in solutions presaturated with the headspace gas. Samples were removed at intervals for parallel assessment of the organic and the ruthenium constituents by, respectively, GC−FID and anaerobic MALDI-TOF mass spectrometry. We have described elsewhere the power of charge-transfer (CT) MALDI MS methods for analysis of neutral transition-metal complexes, including the Grubbs catalysts.[9]

For reactions carried out under C_2H_4, conversions of **1a** reached 37% after 1 h, and 98% after 24 h (Figure 1a). The expected 1,3-diene **1a′** is the sole initial product, and accounts for

Scheme 1. RCEYM Reaction Explored by MALDI-TOF MS



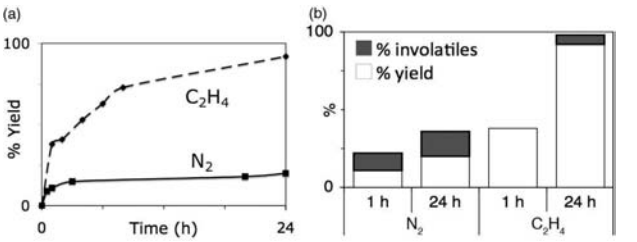


Figure 1. (a) Rates of RCEYM for the reaction of Scheme 1; (b) product distribution under C_2H_4, vs N_2 atmosphere; in situ yields determined by calibrated GC−FID analysis.

most of that ultimately formed (92% in situ yield; Figure 1b). In striking contrast, the reaction under N_2 shows only 23% conversion at 1 h, and the yield of **1a′** is just 14%, the mass balance being due to involatile species arising from intermolecular reaction (vide infra). The rate of ensuing reaction declines sharply; over 24 h, conversions increase by only ca. 10%, with a final diene yield of 18%. Independent experiments at enyne concentrations of 0.3 M exhibit still lower RCEYM selectivity.[10]

MALDI-TOF mass spectra for these experiments are shown in Figure 2. For reactions under ethylene, the spectrum at 1 h is dominated by the radical cation for methylidene **Ru-2**, the expected resting state of the catalyst in the presence of C_2H_4 (m/z 746.3, Figure 2a). A minor signal at higher mass (**Ru-3**, m/z 878.3) grows in over 24 h. Importantly, this signal dominates the spectrum for the reaction under N_2, even at 1 h, when enyne consumption is just beginning to plateau (compare Figures 2b, 1a). Complex **Ru-3** thus corresponds to the major ruthenium species present at the onset of catalyst deactivation. Its mass and isotope pattern indicate the presence of two enyne-derived repeat units, as discussed below. Despite the low reactivity implied by its formation under C_2H_4, and indicated by the rate curve of Figure 1a, **Ru-3** undergoes conversion into higher oligomers via slow, sustained consumption of **1a**. After 24 h

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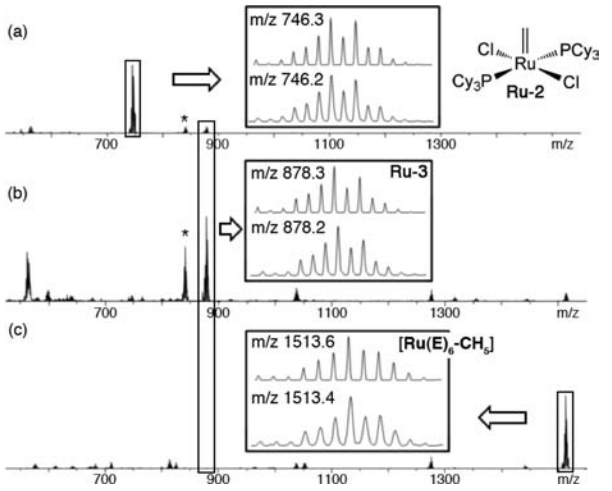
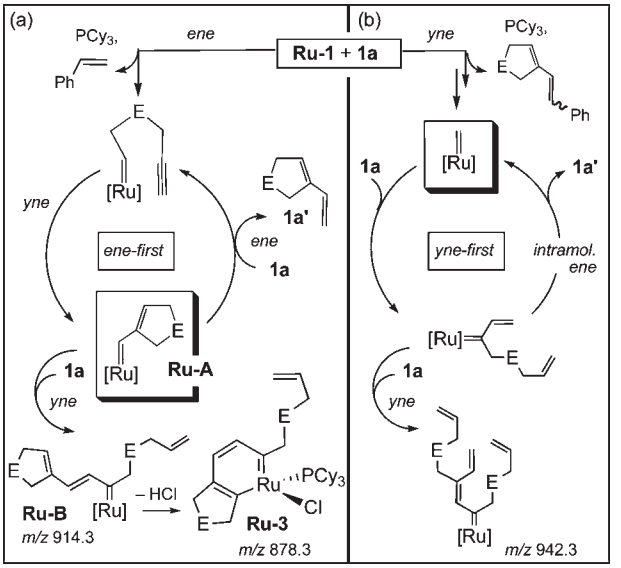


Figure 2. CT-MALDI mass spectra (pyrene matrix) showing Ru species formed in the reactions of Scheme 1; (a) at 1 h under C_2H_4; (b) at 1 h under N_2; (c) at 24 h under N_2. Insets: isotope patterns (top, simulated; bottom, observed). [*] = ion formed by gas-phase loss of chloride from **Ru-3**. In (c), **E** denotes the molecular formula for enyne **1a** or its product **1a′**: $C_{13}H_{18}O_4$.

Scheme 2. (a) Ene-First versus (b) Yne-First RCEYM, Showing Productive Cyclization, Uptake of a Second Enyne, and (for the Ene-First Pathway), Formation of Deactivated Ru-3[a]



[a] [Ru] = $RuCl_2(PCy_3)$; E = $C(CO_2Et)_2$. For a complete depiction of the atom-efficient initiation in (b), see Supporting Information.

under N_2, the dominant Ru species contains six enyne-derived repeat units (Figure 2c). Not seen, even at 1 h, is **Ru-2** (the anticipated resting state in the "yne-first" mechanism for enyne metathesis). Nor is **Ru-A** (the first cycloaddition product in the "ene-first" mechanism: see Scheme 2a; *m/z* 676.2) or its PCy_3-bound resting state (*m/z* 956.4).

The excellent match between calculated and observed isotope patterns supports identification of **Ru-3** as a "$RuCl(PCy_3)$-$(E)_2$–CH_3" species. We envisage its formation via "ene-first" reaction of **Ru-1** with **1a** (Scheme 2a). Formal loss of CH_2 from **1a** occurs in the initial cross-metathesis step that generates intermediate **Ru-A**. A key branch point is then possible. Thus, reaction of **Ru-A** with the olefinic end of a new enyne substrate would liberate the product **1a′**, while competing reaction with the alkynyl end would generate a ruthenium species bearing two enyne-derived repeat units (e.g., **Ru-B**). C–H activation and loss of HCl from **Ru-B** would afford **Ru-3**, a possible structure for which is depicted. The stability of **Ru-3** could be consistent with delocalization in the π-system of the ruthenacycle, or, alternatively, with a coordinatively saturated π-allyl complex.[11,12] Irrespective of the specific structure of **Ru-3**, its molecular mass is strong evidence against the "yne-first" pathway (Scheme 2b), the complete atom-economy of which would result in a higher-mass Ru intermediate.

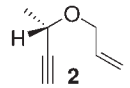
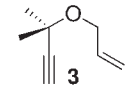
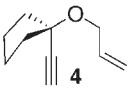
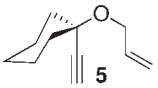
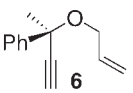
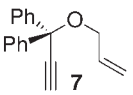
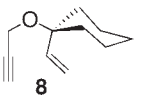
Additional isomers of **Ru-3** may arise from head-to-head versus head-to-tail cycloaddition, or intermolecular reaction prior to the cyclization step indicated. In situ NMR experiments (^1H; ^1H–^{13}C HMBC) reveal multiple Ru=CRR′ species. Detailed structural characterization of **Ru-3** is complicated by this apparent abundance of isomers, by their further evolution over a time scale of hours, and by difficulties in isolating the Ru products by silica gel chromatography. The foregoing is nevertheless important in revealing a previously unsuspected bias of these Ru catalysts toward sequential, intermolecular enyne metathesis under inert atmosphere. We conclude that a key benefit of ethylene lies in its capacity to suppress (or reverse) uptake of a second enyne unit, and ensuing catalyst deactivation. Of note, addition of ethylene after 24 h effects a minor increase in RCEYM yields, but does not restore activity to initial levels, nor generate **Ru-2**. Likewise (in contrast with ring-closing olefin metathesis),[13,14] oligomers[15,16] cannot be recycled into the desired cyclic products by diluting the reaction to trigger a concentration-dependent cyclodepolymerization. The exothermic nature of the enyne metathesis reaction precludes many of the equilibria characteristic of olefin metathesis.[17]

Competing alkyne polymerization is widely recognized as a challenge in enyne metathesis promoted by group 6 complexes.[16] With a few notable exceptions,[18] it has been little considered for the Ru systems, despite Mori's early suggestion that it might be operative.[19] A probable contributor to the belief that alkyne polymerization was not an issue for the Ru catalysts was pioneering work by Blechert and co-workers on intermolecular enyne metathesis, showing that polymerization by **Ru-1** is slow relative to productive metathesis. In this case, it should be noted, however, that a 2- to 3-fold excess of alkene was used.[20]

Given the evidence above that intermolecular reaction of **Ru-A** with "yne" leads to catalyst deactivation, and that this can be blocked by competing reaction with ethylene, we speculated that enynes for which ethylene is *not* required might be ones for which approach of the alkyne to **Ru-A** is sterically inhibited. This could account for the fact that "Mori conditions" are not required for internal alkynes. We suspected that propargylic functionalization might account for many of the remaining examples[21,22] (that is, the same steric factors that accelerate retro-addition[1e] could also inhibit approach of the alkyne to **Ru-A**).

To test this hypothesis, we undertook a systematic examination of the effect of enyne substitution on RCEYM yields in the absence of ethylene (Table 1). We also sought to clarify whether the preponderance of Ru-NHC catalysts in ethylene-free RCEYM[21] implies that such catalysts are immune to the problems that the Mori conditions were designed to address. We therefore included the important second-generation Grubbs catalyst $RuCl_2(H_2IMes)(PCy_3)$(=CHPh) **Ru-4** in this study.

Table 1. Ethylene-Free RCEYM[a]

Entry	Enyne	Cat.	Time (h)	Conv. (%)	Yield (%)
1	**1a:** E = $C(CO_2Et)_2$	**Ru-1**	1	23	14
			24	33	18
		Ru-4	24	17	3
2	**1b:** E = NTos	**Ru-1**	24	58	43
		Ru-4	24	19	4
3	**1c:** E = O	**Ru-1**	24	66	38
		Ru-4	1	7	1
			24	22	2
4	 **2**	**Ru-4**	1	30	<1
			24	42	3
5	 **3**	**Ru-4**	1	31	16
			20	>99	67
6	 **4**	**Ru-4**	1	14	9
			20	86	53
7	 **5**	**Ru-4**	1	72	51
			20	>99	71
8	 **6**	**Ru-4**	1	>99	>99
9	 **7**	**Ru-1**	18	94	91
		Ru-4	1	>99	>99
10	 **8**	**Ru-4**	1	<1	0
			20	6	0

[a] Conditions: N_2 atmosphere, 24 °C, 0.1 M enyne, CH_2Cl_2; in situ yields by calibrated GC−FID analysis, ±2.5%. One mole percent Ru for **1a**−**c**, except **1c** with **Ru-4**: 0.5 mol % for the latter and **2**−**8**.

For enynes devoid of propargylic substituents, competing oligomerization is observed with both first- and second-generation catalysts, irrespective of the nature of the homoallylic moiety (**1a**−**c**, entries 1−3). Indeed, **Ru-4** is even more susceptible to deactivation by such substrates than **Ru-1**, affording poorer conversions and very low RCEYM yields. Within the context of RCM, we have noted a greater tendency of Ru-NHC complexes, versus **Ru-1**, toward oligomerization; a similar bias appears operative in the present case. With increasing propargylic bulk, a steady improvement in RCEYM yields is seen (entries 3−9). Gem-dialkyl functionalization is insufficient to completely inhibit deactivation, but replacement of even one alkyl group by phenyl enables complete conversion of enyne **6** to the 1,3-diene (entry 8). Reaction rates also increase. This probably reflects reduced rates of deactivation, as well as sterically accelerated retro-addition and inhibited reuptake of PCy_3.[1e,g]

Once uptake of a second enyne is suppressed, the superior reactivity of **Ru-4** is manifested: this catalyst effects complete RCEYM of diphenyl-substituted **7** within 1 h at RT, versus >18 h with **Ru-1**. Finally, allylic bulk (entry 10) confers no beneficial effect, presumably because it impedes access of "ene" to the Ru center. The very low conversions of **8** are consistent with previous findings[1g] that allylic bulk inhibits reaction.

In summary, we find that acetylenic enynes with minimal propargylic bulk perform poorly in ethylene-free RCEYM using first- *or* second-generation Grubbs catalysts, owing to rapid catalyst deactivation. MALDI-MS experiments with **Ru-1** reveal that the onset of deactivation correlates with uptake of a second equivalent of enyne by the key vinylalkylidene intermediate **Ru-A**. The two enyne-derived repeat units in the deactivation product **Ru-3** may form a delocalized metallacyclohexene ring, or a coordinatively saturated π-allyl structure, either of which could account for low reactivity toward both enyne and ethylene. Use of ethylene atmosphere suppresses this pathway and hence catalyst deactivation: we suggest that this is a major contributor to the beneficial effect of the "Mori conditions" in Ru-catalyzed enyne metathesis. Propargylic bulk also inhibits formation of **Ru-3** and thus enables ethylene-free enyne metathesis.

■ ASSOCIATED CONTENT

Supporting Information. Mechanistic details related to Scheme 2, experimental procedures, characterization data, spectra and rate curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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ring-closing metathesis, see: (b) Burdett, K. A.; Harris, L. D.; Margl, P.; Maughon, B. R.; Mokhtar-Zadeh, T.; Saucier, P. C.; Wasserman, E. P. *Organometallics* **2004**, *23*, 2027–2047. (c) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky, M. L. *J. Organomet. Chem.* **2006**, *691*, 5197–5203. (d) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem.—Eur. J.* **2010**, 11720–11725.

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(11) The likelihood of forming an allylic dichlororuthenium complex by rearrangement of the vinyl ruthenacyclobutane intermediate itself has been examined computationally (ref 12); this was found to be a high-energy process. Here, we envisage formation of an allylic species via C−H activation of a pendant olefin.

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(15) We use the term oligomers for convenience, but note that these will include any dimers that are insufficiently volatile to emerge under our GC conditions. Liberation of dimeric products by competing turnover of **Ru-B** with enyne is highly probable, and indeed such products have been isolated for enyne metathesis in the absence of ethylene (see (a) Diver, S. T.; Kulkarni, A. A.; Clark, D. A.; Peppers, B. P. *J. Am. Chem. Soc.* **2007**, *129*, 5832–5833). Enyne-derived oligomers have been isolated in Group 6 catalysis; see ref 16. Symmetrical dimers can also form (if the catalyst is sufficiently reactive) by cross-metathesis of the conjugated dienes, but this is slow even in refluxing CH_2Cl_2 (see, e.g., (b) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441–4449). We observe no such behaviour at room temperature (see, for example, the rate curves for RCEYM via **Ru-4** in the Supporting Information).

(16) For leading references to alkyne polymerization by group 6 catalysts, see: (a) Lee, Y.-J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10652–10661. (b) Zhao, Y.; Hoveyda, A. H.; Schrock, R. R. *Org. Lett.* **2011**, *13*, 784–787.

(17) The overall process of enyne metathesis can be reversed under some conditions, however. See: Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855–1858.

(18) In their 2005 computational study, Lippstreu and Straub explicitly treated alkyne polymerization as a potential side-reaction in Ru-catalyzed enyne cross-metathesis; ref 12. A side-reaction yielding alkyne cyclodimers was observed by Diver and co-workers, for which an initial sequence corresponding to Scheme 2a was proposed; ref 15a. The susceptibility of the Ru catalysts to alkyne polymerization was accepted by Hoveyda and Schrock (ref 16), and segregation of the catalyst in a deactivation process was suggested. Alkyne polymerization should be distinguished from potentially competing ring-opening metathesis polymerization in intermolecular enyne metathesis of cycloalkenes. See, e.g., (a) Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3463–3466. (b) Banti, D.; North, M. *Adv. Synth. Catal.* **2002**, *344*, 694–704.

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(22) RCEYM yields were previously shown to be improved by increasing propargylic substitution for reactions under ethylene. See: Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678–693.