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A Simple and Effective Co-Catalyst for Ring-Closing Enyne Metathesis Using Grubbs I type Catalysts: A Practical Alternative to "Mori's Conditions"

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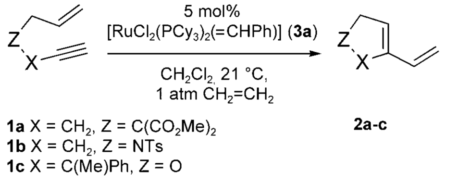
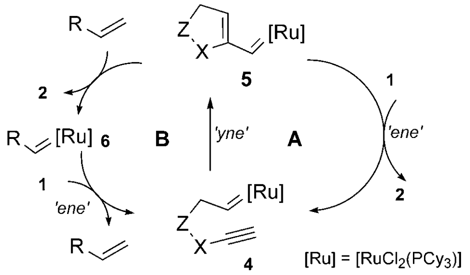
In 1998 Mori reported[1] that ethylene improved turnover in the ring-closing metathesis (RCM) of enynes (**1**→**2**),[2] employing Grubbs generation I catalyst (**3a**); for example, low yields of **2a**–**c** under 1 atm argon, became near-quantitative (99%) under 1 atm. ethylene.[1] Subsequent kinetic analysis[3] revealed that ethylene not only increases the turnover frequency, but also reduces the impact of catalyst deactivation processes. The beneficial effect of ethylene is observed with many enyne substrates, particularly those with terminal alkyne moieties, and unsurprisingly, "Mori's conditions" have been widely adopted (Scheme 1).[4]



Scheme 1. RCM of enynes **1a**–**c** under an ethylene atmosphere ("Mori's conditions").

Two basic mechanisms have been proposed for the RCM of enynes involving intermolecular[5] metal–alkylidene propagation. These mechanisms are often referred to as the "yne-then-ene" and "ene-then-yne" pathways.[2] Evidence for both pathways has been presented, and phosphine catalysts, for example, **3a**,[6] appear to favour the "ene-then-yne" pathway (cycle **A**, Scheme 2).[7]



Scheme 2. The "ene-then-yne" cycle (**A**) for RCM of enynes **1**→**2** and secondary cycle **B** to account for acceleration under "Mori's conditions" in which R = H.

For RCM involving phosphine catalysts, for example, **3a**, and terminal enynes, computational investigations[7,8] and isotopic labelling experiments[3] support earlier proposals[5b,9] that ethylene acts as an alkene surrogate for the enyne (**1**) in the release of product (**2**) through alkene–alkylidene exchange with intermediate **5**.[10] A second alkene–alkylidene exchange of **6** (R = H) with **1**, to generate **4**, connects the secondary cycle **B** with primary cycle **A**,[11] liberating the ethylene (R = H), which thus acts as a co-catalyst.

During our earlier study of "Mori's conditions"[3] we noted that co-reaction of the about threefold-faster-reacting substrate **1c** with **1a** resulted in a small but noticeable decrease in the rate of RCM of **1a**. This suggested to us that an appropriately "tuned" alk-1-ene might be able to act as an efficient co-catalyst, in a manner analogous to ethylene. Herein we report on a kinetic and isotopic labelling investigation into this concept, and the development of a simple alkene co-catalyst that provides practical advantage to "Mori's conditions" for the RCM of terminal enynes using Grubbs I catalyst (**3a**).

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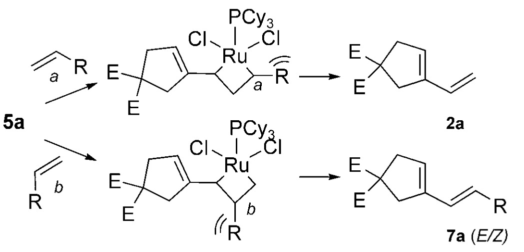
On consideration of the reaction of higher alkenes ($R \neq H$) with intermediate **5**, at which cycle **B** partitions from cycle **A**, it immediately becomes apparent that the regioselectivity of the alkene–alkylidene exchange, which is degenerate when $R=H$, will have a crucial impact on the outcome: orientation "*a*" (Scheme 3) will result in acceleration of **1**→**2**; whilst orientation "*b*" will result in ring-closing-cross-metathesis (RC-CM) to generate **7**.[12] Indeed, a wide range of efficient Ru-catalysed RC-CM reactions of terminal enynes with alkenes have been reported.[13] Of note, however, is that a large excess (3–10 equiv) of the alkene is employed, in conjunction with NHC-based catalysts;[7] the outcome using phosphine-based[7] complex **3a** has not been reported.



Scheme 3. The impact of regioselectivity on the alkene-alkylidene exchange of an added alkene ($RCH{=}CH_2$) with vinylalkylidene intermediate **5a**.

To test our concept, we conducted RCM of enyne **1a** (0.06 M in CH_2Cl_2) in the presence of 100 mol% of a series of *n*-alk-1-enes (C_xH_{2x}) where $x=5$, 6, 8, 10, 12, 14, 18. The consumption of **1a** followed approximately pseudo first-order kinetics (k_{OBS}) and in each case a significant increase in turnover rate was observed as compared to RCM in the absence of alkene additive (k_0).

A more detailed analysis of k_{OBS} versus $[C_xH_{2x}]$ for $x=6$, 10 and 14 indicated a first-order dependency on the alkene concentration up to about 0.1 M. Above this, there was pseudo-zero-order dependency, indicative of saturation kinetics (k_{SAT}, Figure 1a, $x=10$). Analysis of maximum rate accelerations (k_{SAT}/k_0) versus x indicated that the longer alkenes ($x=18 \rightarrow 10$) afford similar, approximately threefold, acceleration. For the shorter alkenes, k_{SAT}/k_0 increased[14] from about three- ($x=10$) to about sixfold ($x=5$); this trend corresponds well with the 7.5-fold acceleration obtained for **1a**[3] under ethylene ($x=2$; 0.12 M) under "Mori's conditions".[1,15]

To gain further evidence for co-catalysis by means of cycle **B**, we employed $[1,1\text{-}^2H_2]$-decene to accelerate the RCM of **1a**. Analysis of k_{OBS} versus k_0 (Figure 1a) predicts partitioning of 0.38 from cycle **A** and 0.62 from cycle **B** at 0.06 M (100 mol%) decene. With the labelled decene, cycle **B** will generate $[^2H_2]$-**2a**. However, the analysis is complicated by 1) the progressive dilution of the $[1,1\text{-}^2H_2]$-decene with the unlabelled decene that is generated from cycle **B** and 2) methylidene exchange between $[1,1\text{-}^2H_n]$-decene and $[^2H_n]$-**2a** ($n=0$, 2). To estimate the impact of the latter process, we included 20 mol% $[^2H_7]$-**2a** in the reaction (Scheme 4), which underwent equilibration with the decene ($t_{0.5}$ ca. 3 min, see Figure 1b). This is about sevenfold faster than RCM and the isotope ratio in the genuine products of turnover (**2a**/$[^2H_2]$-**2a**) were thus analysed by extrapolation of a plot of mol fraction $[^2H_2]$-**2a** (x_{D_2}) versus time to $t=0$. This gave an initial x_{D_2} of 0.66, in reasonable agreement with that predicted (0.62).[16]

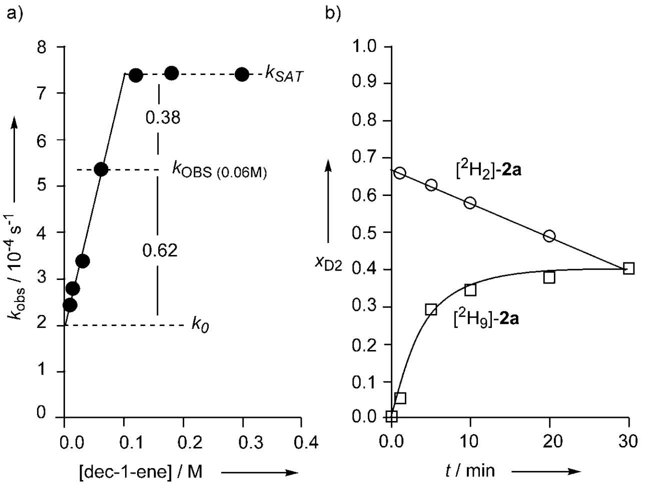
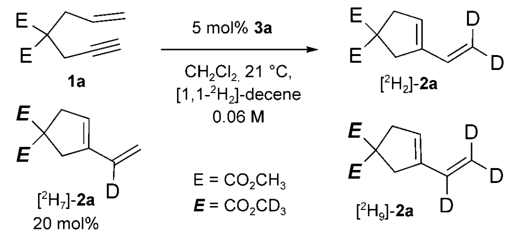


Figure 1. a) Pseudo first-order rate constants (k_{OBS}) for RCM of **1a** (0.06 M) catalysed by **3a** in the presence of *n*-dec-1-ene (10-500 mol%), with analysis of partitioning by cycles **A** (0.38) and **B** (0.62) at 0.06 M dec-1-ene. b) Mole fraction CD_2 at *exo*-alkene terminus (x_{D_2}) in product $[^2H_2]$-**2a** and reference product $[^2H_9]$-**2a** as a function of time for reaction shown in Scheme 4. Approximately 38% conversion of **1a** is achieved at 30 min. The curve through the data points for $[^2H_9]$-**2a** is based on first-order equilibrium kinetics, where $t_{0.5}=3$ min and $K=0.66$.



Scheme 4. Dual-labelling test for decene co-catalysis[18,19] through cycle **B**, see Figure 1.

In addition to their co-catalytic effect, the presence of *n*-alk-1-enes also resulted in generation of the RC-CM products **7a** (2–32%; $R=C_{x-2}H_{2x-4}$); however, the *n*-alk-1-enes did not undergo any detectable CM with **1a**, indicating that **6**→**4** proceeds exclusively via orientation "*b*". The proportion of **7a** generated relative to **2a** increased with conversion, with co-catalyst concentration, and approximately linearly with the size of R,[17] suggesting **7a** arises through two processes: 1) turnover of **1a** by cycle **B**, but via orientation "*b*", Scheme 3; and 2) cross-metathesis (CM) of the alkene with the product **2a**. The CM process, degenerate in the absence of an isotopic label, was also found to occur readily with **2a** and [$^{13}C_2$]-ethylene.[3]

Our preliminary experiments with simple *n*-alk-1-ene additives suggested that a sterically unencumbered, but in some way "activated", terminal alkene could function as an efficient co-catalyst at low concentrations, thus avoiding undesired RC-CM/CM to generate **7**. Of note in this regard is the observation that substrates **1bc**, with electronegative substituents at the allylic position turnover more efficiently than **1a**. This aspect is reinforced by the work of Imahori,[18] who discovered that enyne substrates containing an allylic hydoxyl group undergo RCM with such efficiency that "Mori's conditions" are not required. Kinetic studies[18b] supported an "ene-then-yne" mechanism in which the hydroxyl group accelerates product release from vinylalkylidene intermediate **5**, a process exploited in a synthesis of isofagomine.[18a] We thus tested a range of simple allylic additives, including allyl alcohol, allyl benzyl ether, allyl cyanide, allyl dimethylmalonate, *N*-tosyl allylamine, allyl chloride and allyl bromide, at 50 mol% loading with enyne **1a**.

Whilst mild accelerations or decelerations were observed with some combinations, allyl chloride and, in particular, allyl bromide emerged as especially effective. Allyl bromide afforded an approximate 20-fold rate enhancement, with no trace of the RC-CM product **7a** (R = CH_2Br). However, possibly due to extensive allylation of the phosphine ligands, Ru-catalyst deactivation occurred after only about 75% conversion of **1a**.[19] Reducing the allyl bromide concentration lead to a substantial attenuation of the catalyst deactivation process, without significant drop in acceleration; indeed even with loadings as low as 2.5 mol%, sixfold rate enhancement was observed. For substrate **1a**, a loading of 5 mol% (3 mM) was found to be optimal, giving >98% conversion in under 90 min, Figure 2. By comparison, 5 mol% hexene gave 55% conversion, and in the absence of any additive the reaction reached 42% conversion, and turnover ceased after 60% conversion (12 h) due to catalyst deactivation.

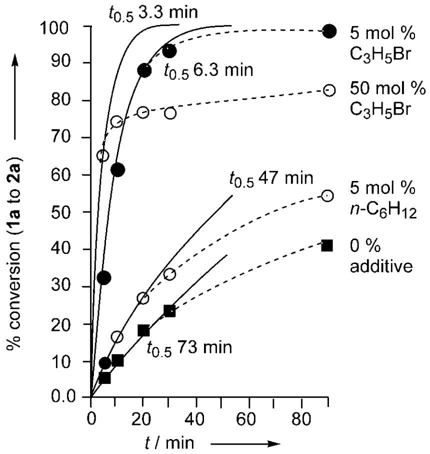
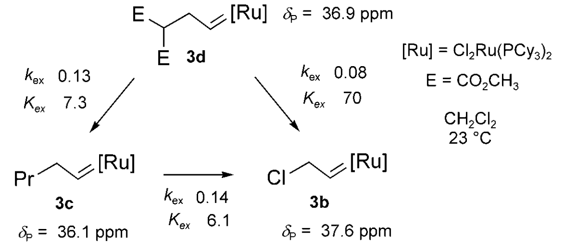


Figure 2. RCM of **1a** (0.06 M) to **2a** catalysed by 5 mol% **3a**, in the presence and absence of hex-1-ene or allyl bromide as co-catalyst. Solid lines through data are based on first order decay of **1a** with the half-life indicated; the dashed lines schematically indicate progressive deviation from this due to catalyst deactivation. The reaction without additive failed to reach completion (60%, 12 h).

Rate accelerations were also found when 5 mol% allyl bromide was added to the RCM of the more active substrates **1bc**. Although compared to **1a**, rate accelerations were less substantial, the effect of allyl bromide co-catalyst was again to allow the RCM to go to completion, whereas in its absence, turnover ceased at about 60% conversion. Interestingly, allyl alcohol emerged as a more powerful co-catalyst than allyl bromide for **1c** (but an inhibitor for **1a**) suggesting that a subtle "tailoring" of the additive to the substrate might be required to balance reactivity (capture of **5**) versus stability (release of Ru back to the enyne from **6**).

Despite many attempts, we were unable to prepare the bromoethylidene complex [$RuCl_2(PCy_3)_2(=CHCH_2Br)$],[20] which would provide an "all-in-one" catalyst/co-catalyst system. We were however able to analyse the chloroethylidene complex **3b** (Scheme 5), which was more effective a catalyst than **3a**, but only after an induction period. A $^{31}P\{^1H\}$ NMR study of alkene exchange rates indicated a thermodynamic series **3b** > **3c** > **3d**, but with no significant difference in rates of displacement of allyl dimethyl malonate from **3d** by hex-1-ene (→**3c**) or allyl chloride (→**3b**). It is important to note that these equilibria 1) include an entropic component relating to both the "released" and the "captured" alkene; and 2) relate to the "off-cycle" diphosphine complexes (**3**), rather than the catalytically active monophosphine species (e.g., **5** or **6**) in which there may be the possibility for other interactions at the site vacated by Cy_3P.



Scheme 5. Pseudo bimolecular exchange rates (k_{EX} $dm^3 mol^{-1} s^{-1}$) and equilibria (K_{EX}, dimensionless) determined by $^{31}P\{^1H\}$ NMR for alkene exchange with alkylidene complexes **3b–d** (alkene : [Ru] = 1:1), in CH_2Cl_2 at 23 °C.

In summary, we have demonstrated the ability of simple alkenes to act as efficient co-catalysts for RCM reactions of terminal enynes, catalysed by the commercially available Grubbs generation I catalyst **3a**. Preliminary mechanistic investigations with [1,1-$^2H_2$]-decene support an ene-then-yne type cycle, with the alkene acting to facilitate product release from vinylalkylidene intermediate **5**.[10] From a range of allylic substituents in the alkene co-catalyst (*n*-alkyl, OH, OBn, TsNH, CN, $CH(CO_2Me)_2$, Cl and Br) allyl bromide emerged as particularly effective. At loadings as low as 5 mol% it offers >15-fold rate accelerations, and greater numbers of catalyst turnovers, with no competing RC-CM (→**7**). Being cheap, easily handled and effective at low concentration (3 mM) it offers a practical alternative to "Mori's conditions" (120 mM ethylene). The origins of the marked activity of allyl bromide, and its low propensity for RC-CM, are not at all clear and warrant detailed further investigation.

Experimental Section

Ring-closing enyne methathesis of 1a in the presence of 100 mol% $[1,1\text{-}^2H_2]$-decene (Figure 1b and Scheme 4): A solution of **1a** (50 mg, 0.24 mmol, 0.06 M overall), dodecane (internal standard), $[^2H]_2$-decene (33 mg, 0.24 mmol, 0.06 M overall, 100 mol%) and $[^2H_7]$-**2a** (10 mg, 0.048 mmol, 20 mol%) in dry CH_2Cl_2 (2 cm^3) was stirred at room temperature under nitrogen. A solution of **3a** (9.8 mg, 0.003 M overall, 5 mol%) in dry CH_2Cl_2 (2 cm^3) was then added by means of a gas-tight syringe. The reaction was sampled periodically, removing two 2×50 μL samples, which were quenched into an excess of PPh_3 in CH_2Cl_2 (1 cm^3) and the solution then passed through a plug of silica-gel. For each pair of samples, the first was directly analysed for conversion by GC (on a Hewlett Packard HP5890 with flame ionisation detector; split ratio 1:50; helium at 1 $cm^3 min^{-1}$; Alltech EC™, 30 m × 0.25 mm ID, 0.25 μm film thickness.) and by MS (Varian Saturn 2200 GC/MS) for the $[^2H_2]$-methylidene distribution in **1a** (*m/z*: 210 and 212); **2a** (*m/z*: 210 and 212); and $[^2H_7]$-**2a** (*m/z*: 217 and 219). Bromine was added dropwise to the second sample until a deep red colour persisted, and this was then discharged with excess pentene. The colourless solution was analysed by MS for the $[^2H_2]$-methylidene distribution in the decene (analysis of deca-1,3-dienyl cation $[C_{10}H_{17}]^+$ daughter ion; *m/z*: 137 and 139).

Acknowledgements

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Keywords: enynes · isotopic labeling · metathesis · reaction mechanisms · ruthenium

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[4] Between 1998–2010, there were over 182 examples citing use of "Mori's conditions".
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[10] An η^3-coordination mode in vinylalkylidene complexes has been reported to attenuate the rate of metathesis, see: T. M. Trnka, M. W. Day, R. H. Grubbs, *Organometallics* **2001**, *20*, 3845–3847; cycle **B** allows more efficient catalytic turnover by attenuating side reactions, such as reaction with the alkyne moiety of the substrate, which can be detected by ESI-MS (G. C. Lloyd-Jones, A. J. Robinson, unpublished results); for reactions involving terminal-alkyne-type enyne substrates, Grubbs I catalyst (**3a**) is much more efficient than Grubbs II catalyst.
[11] The benzylidene pre-catalyst (**3a**) connects with the cycle through alkene–alkylidene exchange (6→4) liberating styrene, R = Ph. The methylidene complex $[RuCl_2(PCy_3)_2(=CH_2)]$, which undergoes slow PCy_3 dissociation is a very poor catalyst for RCM of **1a**, with or without an atmosphere of ethylene, and with or without styrene and ethylene.
[12] The second alkene–alkylidene exchange step involving intermediate **6** must also proceed by orientation "*a*", as orientation "*b*" will result in cross-metathesis to generate the alkene homologated enyne. Analogously, reaction of **6** with product **2** in orientation "*b*" will result in RC-CM product **7**, as would reaction of 6 with the alkyne terminus of **1**.
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[14] This suggests that up to $x\approx10$, the magnitude of k_{SAT} is determined by the impact of the length of "R" on the rate of alkene-alkylidene exchange of **1** with **6**; above $x=10$, the extension in chain length is not sufficiently proximal to the ligands on the ruthenium centre.
[15] The k_{obs} values varied from batch to batch of catalyst **3a** and thus data sets for establishing k_{obs} versus $[C_xH_{2x}]$ and k_{SAT}/k_0 were conducted with a single batch of catalyst.
[16] Under these conditions, less than 4% RC-CM and decene homo-CM (→octadecene) occurs. The maximum ethylene concentration that would be generated is 4.8 mM, leading to about 5% rate enhancement if ethylene saturation kinetics proceed from 0.1 M.
[17] Analysis under saturation conditions ($[n\text{-alk-1-ene}]=0.3$ M) at 60 min yielded $([\mathbf{7a}]/[\mathbf{2a}+\mathbf{7a}])_{60}$ (%) $=1.5x+1.7$, $R^2=0.96$].
[18] a) T. Imahori, H. Ojima, H. Tateyama, Y. Mihara, H. Takahata, *Tetrahedron Lett.* **2008**, *49*, 265–267; b) T. Imahori, H. Ojima, Y. Yoshimura, H. Takahata, *Chem. Eur. J.* **2008**, *14*, 10762–10771.
[19] Cy_3P dissociation is required to engender catalytic turnover, and capture of this by allyl bromide was probed as a possible source of the marked acceleration as compared to the other allyl species. However, 1) 5 mol% $[Cy_3P\text{–allyl}]Br$ was inert as an additive and 2) the rate of RCM of diallyl dimethylmalonate was unaffected by 5 mol% allyl bromide, whereas propargyl allyl dimethylmalonate (**1a**) underwent 17-fold enhancement.
[20] Reaction of **3a** with allyl bromide only resulted in extensive decomposition due to allylation of dissociated Cy_3P; in contrast, the analogous reaction with allyl chloride[21] (three cycles of exchange) afforded **3b**, contaminated with approximately 15% **3a**.
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