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Ring Closing Enyne Metathesis: Control over Mode Selectivity and Stereoselectivity

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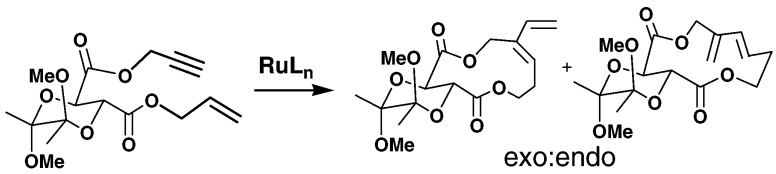

without ethylene	1:1	*E*/*Z* = 1:1
with ethylene	0:1	*E*/*Z* = 1:0

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Ring Closing Enyne Metathesis: Control over Mode Selectivity and Stereoselectivity

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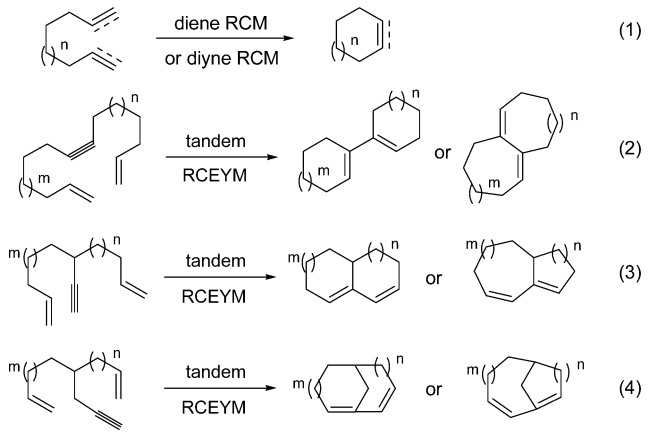
Abstract: Ring closing enyne metathesis to form 10−15-membered rings was achieved by using a tartrate-derived linker to attach ene and yne subunits. The exo/endo selectivity of the ring closure reaction of these substrates was found to be a function of ring size, whereby larger rings (12−15) give *endo*-products selectively, while smaller rings (5−11) give *exo*-products. The *E*/*Z* selectivity of the resultant macrocyclic 1,3-dienes was not predictable except for 10- and 11-membered rings. However, both the *exo*/*endo*-mode selectivity of the ring closure and the *E*/*Z* selectivity of the 1,3-dienes were improved by performing these reactions under ethylene atmosphere. The presence of ethylene induces a selective cross metathesis between the alkyne moiety and ethylene to generate an acyclic 1,3-diene which can undergo ring closing diene metathesis between the isolated olefin and the distal monosubstituted double bond of the 1,3-diene to generate exclusively the *endo*-product with high *E*-selectivity.

Introduction

Olefin metathesis[1] is a powerful carbon−carbon bond forming reaction that redistributes unsaturated functionalities between substrates. Three major categories that can be identified based on the types of olefins directly involved in the metathesis process are diene,[1] enyne,[2] and diyne[3] metathesis. The structural change introduced by the metathesis process renders another classification: ring closing metathesis (RCM), ring opening metathesis (ROM), and cross metathesis (CM). Among these subclasses, diene RCM has drawn significantly more attention from synthetic chemists than other subclasses due to its effectiveness for the formation of various cyclic structures. Despite its enormous potential, enyne metathesis is relatively underdeveloped compared to the diene metathesis process. Recently, fueled by the development of effective ruthenium-based catalysts[4] and the improved reaction protocol developed by Mori and coworkers in which the reaction is performed under ethylene atmosphere,[5] the scope of ring closing enyne metathesis (RCEYM) has been significantly expanded to include a host of new and exciting applications toward the synthesis of 1,3-dienes. The RCEYM reaction is a uniquely powerful and atom-economical[6] means to generate ring structures from molecules with tethered alkenes and alkynes, which should find tremendous synthetic application. Furthermore, as opposed to diene or diyne RCM reactions that can form only a single ring structure and regenerate functionality of their own kind (eq 1), RCEYM reactions can form dumbbell-shaped, multiply fused (eqs 2 and 3)[4b,7] and bridged[8] ring systems (eq 4) possessing a 1,3-diene moiety via a tandem ring closure if alkene and alkyne functionalities are suitably positioned in the RCM substrates.



The significant potential of RCEYM to form multiple C−C bonds and complex connectivity patterns in cyclic systems is somewhat compromised due to selectivity problems that do not arise in other metathesis processes. An important issue in the

(1) For reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Blechert, S. *Pure Appl. Chem*. **1999**, *71*, 1393−1399. (d) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3013−3043. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 1900−1923. (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (g) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2.

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(3) (a) Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc*. **1975**, *97*, 1592−1594. (b) Wengrovius, J. H.; Sancho, J. *J. Am. Chem. Soc*. **1981**, *103*, 3932−3934. (c) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645−1651. (d) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734−1736. (e) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc*. **1999**, *121*, 11108−11113.

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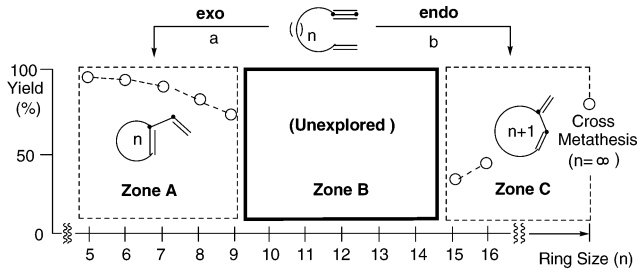
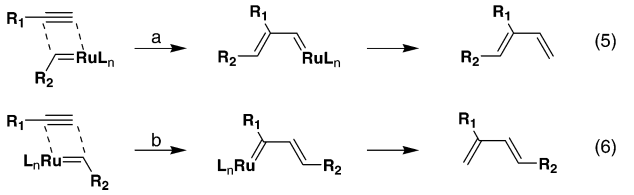


* X-axis indicates the ring size; Y-axis indicates the yield of *endo*- and *exo*-product.

Figure 1. *Exo*/*endo*-mode selectivity as a function of ring size.

enyne metathesis reaction is the *exo*/*endo*-mode selectivity (regioselectivity in the cross metathesis) (Figure 1). Depending on the relative orientation of the alkylidene intermediate and its reacting unsaturated counterpart, different substituent patterns of 1,3-diene functionalities will be generated (eqs 5 and 6).



Furthermore, in the case of RCEYM, the mode selectivity also dictates the ring size that is formed, such that *endo*-mode ring closure products have one additional carbon in the ring relative to those derived from the *exo*-mode. It is known that the RCEYM reaction forming small- to medium-sized rings generally follows the *exo*-mode ring closure path[2e,9] (Zone A in Figure 1), whereas that of macrocycles[10] and cross enyne metathesis[11] follows the *endo*-mode (Zone C). Caution must be taken when interpreting the *exo*/*endo*-mode selectivity outcome of the ring closing enyne metathesis under ethylene atmosphere, especially for the reactions to form large membered rings. Due to the relatively slow ring closure rate in large ring formation, the cross metathesis between ethylene and the alkyne moiety[7,12] of enyne substrates dominates, thereby converting the more difficult enyne RCM to a facile diene RCM process. This is most likely the reason macrocycle-forming enyne metathesis generally requires the use of ethylene. Because formation of macrocycles via an ethylene-free, direct RCEYM has not been reported in the literature,[13] the *exo*/*endo*-mode selectivity cannot be predicted in the range of these ring sizes (Zone B). However, considering the inherently favored interaction of an alkylidene with an alkyne to generate the more substituted vinyl alkylidene (eq 6), we predicted that the *exo*-to-*endo*-mode transition would occur somewhere in this range.

The lack of examples of forming macrocycles in the range of 10−15-membered rings by direct enyne metathesis is in stark contrast to the macrocyclization via diene RCM, which has been extensively studied and amply utilized in natural product synthesis.[1] Consequently, we set out to explore the fundamental aspects of the macrocyclic RCEYM in detail focusing on three major questions: (1) Would the RCEYM form macrocycles in general, and if so, what are the optimal parameters to maximize the efficiency? (2) Could the general trend of *exo*/*endo*-mode of macrocyclic ring closure, e.g., path a and b in Figure 1, be identified and controlled? (3) Could the stereochemistry of the endocyclic double bond of the resultant 1,3-diene be controlled? In a previous communication, we reported our preliminary result addressing some of these major questions under conditions that manifest both the inherent reactivity and selectivity of the RCEYM process.[14] In this full account, we report a comparative study of RCEYM reactions under ethylene atmosphere which provides better control over the *exo*/*endo*-mode and *E*/*Z* selectivity as well as mechanistic insights addressing questions related to the role of ethylene and the initiation event on either the alkene or the alkyne.

Results and Discussion

Substrate Scope: To study the feasibility of macrocyclic RCEYM reactions in the range of previously unexplored 10- to 15-membered rings, readily available substrates **3a**−**3f** (Figure 2) were examined for their ring closure behavior. When these substrates were subjected to standard RCM conditions, the expected 9- to 13-membered rings did not form either with Grubbs catalyst **1** or with more active version **2**. Even under forcing conditions, only the starting materials were recovered.

We speculated that the failure of ring formation might be due to the flexibility of these substrates, which lack constraint in the tether between ene and yne subunits.[15] If this is indeed the case, the introduction of a rigid tether might encourage the

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(10) For macrocyclic RCEYM, see: (a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773−775. (b) Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12036−12041. (c) Barrett, A. G. M.; Hennessy, A. J.; Vezouet, R. L.; Procopiou, P. A.; Seale, P. W.; Stefaniak, S.; Upton, R. J.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2004**, *69*, 1028−1037.
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(13) All previously reported examples required an ethylene atmosphere and therefore do not reflect the inherent selectivity of the RCEYM reaction. See ref 10.
(14) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582−9583.

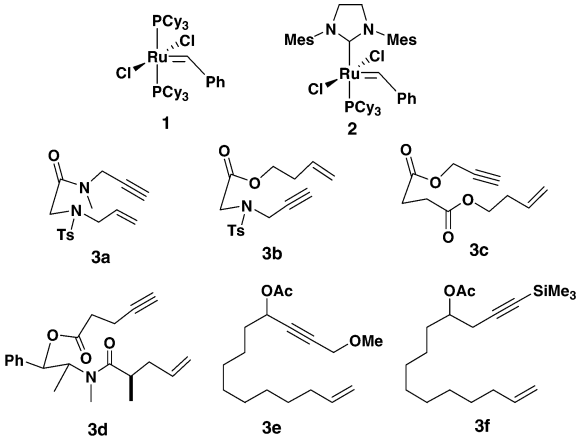
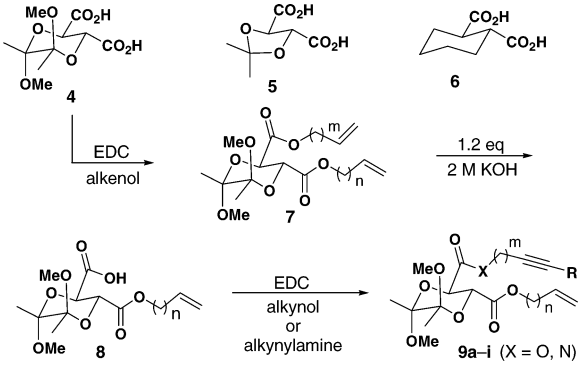


Figure 2. Metathesis catalysts and enyne substrates.

Scheme 1. Preparation of Enyne Metathesis Substrate



cyclization by preorganizing the two reacting ends. To test this hypothesis, we chose readily available tartaric acid derivatives **4**−**5** and cyclohexane dicarboxylic acid **6** as conformationally rigid linker systems expecting that these molecules would also serve as platforms enabling rapid access to a variety of enyne substrates with systematic variation in their structures. Furthermore, for the enantiomerically enriched linkers **4**−**5**, not only the conformational rigidity but also their chirality would be useful for the generation of macrocyclic 1,3-dienes embedded in a chiral environment, which could lead to a facial bias of the 1,3-diene in further reactions. To define the general features of the macrocyclic RCEYM reaction, including ring-size dependency of the *exo*- and *endo*-mode ring closure as well as the *E*/*Z* selectivity of the double bond in the products, systematic alterations of the tether length between the ene and yne components and their locations were needed. We found the 2,3-butanedione diacetal protected tartrate[16] to be the tether of choice in generating the desired differentially esterified enyne substrates (Scheme 1). Enynes **9a**−**i** were readily available via a three-step sequence reported previously.[14,17]

Direct RCM of Enyne Substrates 9: Under typical RCM conditions (0.02 M in CH_2Cl_2, 5−10 mol % of **1** or **2**, reflux),

Table 1. RCM of Enynes to Form Macrocycles[a]

entry	enyne substrate	macrocycle product (exo / endo)	*E*:*Z*	yield (%)[b]
1	**9a** m = n = 1, X = Y = O, R = H	**10a** (R = H)[c]	0:1	52
2	**9b** R = Me	**10b** (R = Me)[c]	0:1	61
3	**9c** m = 1, n = 2, X = Y = O, R = H	**10c** (R = H)[c] (1 : 1) **11c** (R = H)	1:1	50
4	**9d** R = Me	**10d** (R = Me)[c] (1 : 1) **11d** (R = Me)	1:1 for **11d**	92
5	**9e** m = 1, n = 2, X = NH, Y = O, R = H	**11e**	1:0	35
6	**9f** m = 2, n = 1, X = Y = O, R = H	**11f**	1:1	70
7	**9g** m = 2, n = 2, X = Y = O, R = H	**11g**	0:1	61
8	**9h** m = 3, n = 2, X = Y = O, R = H	**11h**	2:1	54
9	**9i** m = 3, n = 3, X = Y = O, R = H	**11i**	1:1	55

[a] Reactions performed with 5 mol % of **2** at 0.02 M in refluxing CH_2Cl_2. [b] Isolated yield. [c] The stereochemistry of **10a**−**d** was determined by NOE, and that of **11c**−**i**, by coupling constant.

macrocycles **10a**−**d** and **11c**−**i** were obtained smoothly in good yields (Table 1). The RCM of **9a** gave exclusively 10-membered ring *exo*-mode ring closure product **10a** (entry 1). A similar substrate **9b** possessing an internal alkyne afforded a higher yield of *exo*-product **10b** (entry 2). Enynes **9c**−**9d** provided a 1:1 ratio of *exo*- and *endo*-mode ring closure products **10c**−**10d** and **11c**−**11d**, respectively (entries 3 and 4). Consistent with the literature report,[2f] the internal alkynes afforded much higher ring closure efficiency (92% vs 50%). Substrates **9e**−**9i** provided 12- to 15-membered rings via a selective *endo*-mode ring closure (entries 5−9). Interestingly, the propargylic amide substrate **10e** cyclized exclusively to a 12-membered ring **11e** with complete *E*-stereochemistry in the endocyclic double bond. The corresponding ester provided a 1:1 mixture of 11- and 12-membered rings. This implies that the mode selectivity depends not only on the size of the incipient macrocycles but also the nature of functionality in the tether. The *E*/*Z* selectivity for RCM reactions of **9a**−**9i** varies from a 1:0 to a 0:1 ratio.

RCM of Enyne Substrates 9 under Ethylene Atmosphere: The beneficial effect of ethylene in the RCEYM reactions to form small- to medium-sized rings has been generally observed, albeit the exact nature of this effect is not

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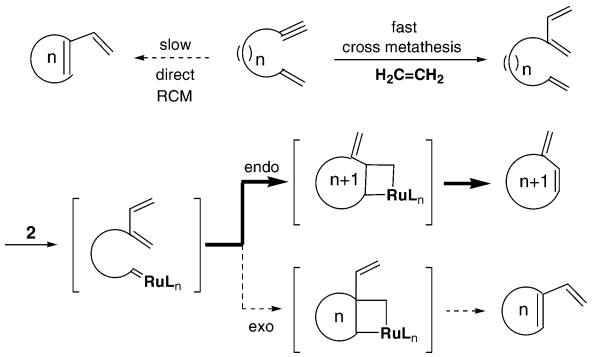
Scheme 2. Enyne RCM under Ethylene Atmosphere

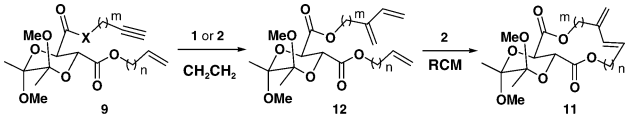


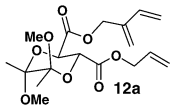
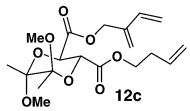
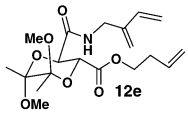
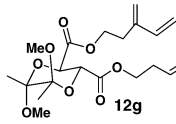
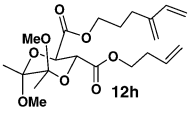
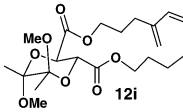
known.[5,18] The efficient formation of macrocycles from substrates **9a**−**9i** provides a platform to examine the effect of ethylene for the macrocyclization via RCEYM. We suspect that, contrary to the case of small ring formation, the use of ethylene in large membered ring formation would lead to a competitive cross metathesis of the alkyne moiety with ethylene over the ring closure due to the relatively slow rate of macrocyclization via enyne metathesis (Scheme 2). If this is indeed the case, the enyne metathesis of **9** would be diverted to cross metathesis, generating triene **12**, which will serve as a new substrate for a diene RCM reaction. Depending on whether the proximal or the distal double bond of the 1,3-diene moiety of triene **12** participates in the diene RCM process, an *exo*- or *endo*-mode RCEYM product will be generated. Based on the sensitivity of catalyst **1** or **2** toward steric and stereoelectronic factors, we predicted that the sterically least demanding, isolated double bond would react first with the catalyst to form an alkylidene which will then undergo ring closure with the distal monosubstituted double bond of the 1,3-diene moiety over the 1,1-disubstituted one, thereby giving the *endo*-product selectively.

We carried out a CM/RCM protocol on a variety of substrates, and the results are summarized in Table 2. Treatment of enynes **9a**,**c**,**e**,**g**−**i** with Grubbs catalyst **1** or **2** under ethylene atmosphere at room temperature produced cross metathesis products **12a**,**c**,**e**,**g**−**i** in good yields. Subsequent RCM of these substrates with **2** in refluxing dichloromethane yielded selectively *endo*-products **11a**,**c**,**e**,**g**−**i**. The second-generation Grubbs catalyst **2** could be used for CM without competing RCM except for substrate **9c**, which gave a mixture of cross metathesis product and cyclized material. Reaction of **9c** with less active catalyst **1** gave only the CM product **12c** in good yield (entry 2). The RCM of **12c** gave selectively **11c** with *E*-stereochemistry as opposed to the direct RCM of **9c**, which produced both **10c** and **11c** in a 1:1 ratio and an *E*/*Z* mixture of **11c**. The RCM of **12c**,**e**,**g**−**i** proceeded in high yield, giving exclusively *endo*-products with *E*-selectivity. Remarkably, a complete reversal in *E*/*Z* selectivity was observed for **9g**, generating only *E*-**11g** (entry 4 in Table 1), which sharply contrasts the formation of the corresponding *Z*-isomer in direct enyne RCM. Overall, the yield and *E*/*Z* selectivity were significantly improved in the presence of ethylene.

Having seen the excellent cross metathesis of the selected enynes **9** and the RCM of the corresponding trienes **12**, we

Table 2. Macrocyclic Enyne Metathesis under Ethylene[a]



entry	enyne	CM-product	yield(%)[b]	E/Z[c]	yield[b] (%)
1	**9a** m = 1, n = 1 X = O	 **12a**	96	0:1	51[e]
2	**9c** m = 1, n = 2 X = O	 **12c**	65[d]	1:0 2.5:1	91 70[f]
3	**9e** m = 1, n = 2 X = NH	 **12e**	77[d]	1:0	78
4	**9g** m = 2, n = 2 X = O	 **12g**	77	1:0 1:0	65 75[f]
5	**9h** m = 3, n = 2 X = O	 **12h**	92	1:0 1:0	85 99[f]
6	**9i** m = 3, n = 3 X = O	 **12i**	88	15:1 20:1	90 92[f]

[a] Catalyst **2** (7 mol %) under ethylene atmosphere at room temperature in CH_2Cl_2 (except **12c** and **12e**). [b] Isolated yield. [c] *E*/*Z* ratios determined by ^{1}H NMR. [d] Catalyst **1** (5−7 mol %) under ethylene atmosphere at room temperature in CH_2Cl_2. [e] Reaction with 1 equiv of catalyst **2** generates a 1:1 mixture of **11c** and **13**. [f] One-step procedure: Catalyst **2** (10 mol %) under ethylene atmosphere at room temperature followed by heating to reflux in CH_2Cl_2.

assumed that a streamlined one-pot cross metathesis of **9** followed by diene RCM of **12** should be possible if proper conditions are implemented. Pleasingly, we found that the reactions of **9c**,**g**−**i** could be performed in one step by treatment with **2** under ethylene atmosphere at room temperature until complete consumption of starting material via cross metathesis followed by heating the solution to reflux. Under this one-step protocol, increased yields of macrocyclic 1,3-dienes **12c**,**g**−**i** were obtained while maintaining selectivity. However, the reaction of **9c** under these conditions produced a 2:1 ratio of *endo*- and *exo*-products with lower *E*/*Z* selectivity (2.5:1 for **11c**) due to the competing nonselective, direct ring closure. Enyne **9a**, which provided completely the *exo*-product in direct enyne metathesis, gave a 1:1 mixture of **11a** and cyclopropane-containing macrocycle **13**. The formation of **13** is likely due to the reductive elimination[19] of the metal species from the ruthenacyclobutane intermediate (Scheme 3). Unfortunately, this nonproductive pathway results in a loss of metathesis activity of the catalyst, providing only partial conversion.[20] Using a stoichiometric amount of the catalyst in the reaction at 25 °C

(18) (a) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161−1163. (b) Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245−5247. (c) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803−805. (d) Banti, D.; North, M. *Adv. Synth. Catal.* **2002**, *344*, 694−704.

(19) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678−693.

(20) Although a noncarbenic mechanism for the formation of cyclopropanes cannot be excluded, we prefer the carbene mechanism because the amount of product formed was proportional to the amount of catalyst used. Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524−9525.

Scheme 3. Cyclopropane Formation in the RCM Reaction

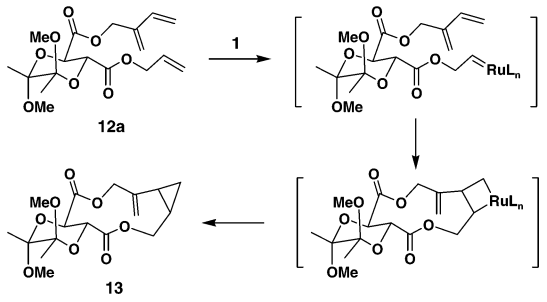
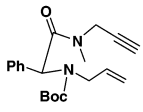
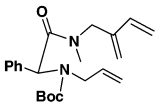
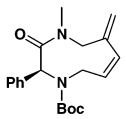
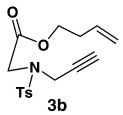
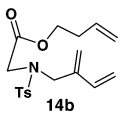
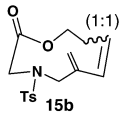
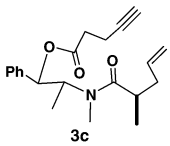
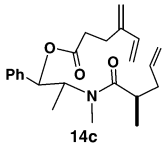
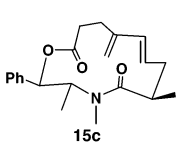


Table 3. CM/RCM of Enynes Inert toward Direct RCEYM

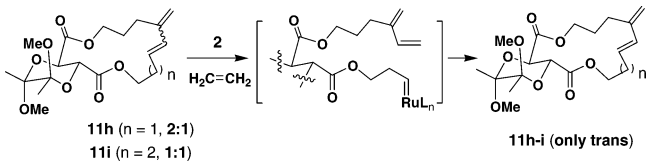
enyne	CM-product	yield (%)	RCM-product	yield (%)
 3a	 14a	68	 15a	65
 3b	 14b	90	 15b	92
 3c	 14c	67	 15c	96

led to a 1:1 mixture of **11a** and **13** in 50% yield, whereas at elevated temperature (70 °C) in toluene only **13** was isolated in 61% yield without the formation of **11a**.

Performing the reactions under ethylene atmosphere also provides access to products not available via direct enyne metathesis (Table 3). Acyclic enyne substrates **3a**−**3c** were inert to direct RCEYM, giving only recovery of starting materials. These substrates did, however, undergo efficient cross metathesis with ethylene to form **14a**−**14c** and eventually afforded **15a**−**15c** upon subsequent RCM in good overall yields. The formation of *endo*-products **15a** and **15b** are significant because the normal tendency for medium-sized rings is to give *exo*-products via direct enyne metathesis.[7]

We hypothesize that the *E*/*Z* ratio of the direct enyne metathesis represents the inherent selectivity of the macrocyclic RCM reaction, leading to the kinetic distribution of *E*- and *Z*-isomers while the increased selectivity seen under ethylene atmosphere is the consequence of thermodynamically driven equilibration of *Z*-isomer, leading to the more stable *E*-isomer.[21] As a control, we subjected *E*/*Z* mixtures of **11h**,**i** obtained from direct enyne RCM to catalyst **2** under an ethylene atmosphere and elevated temperature. In each case, we observed complete formation of the *E*-isomers (Scheme 4). These data support our thermodynamically driven isomerization hypothesis wherein the kinetically formed cyclic 1,3-dienes undergo a ring opening CM reaction by the catalyst in the presence of ethylene to regenerate either the trienes or the corresponding alkylidene. Subsequent RCM allows equilibration to the trans isomer, giving the observed product ratios. This rationale is further supported by a recent report by Snapper and Lee[22] who were able to improve

Scheme 4



the stereoselectivity of the enyne cross metathesis by running the reaction under ethylene. It is noteworthy that the conjugated 1,3-dienes undergo facile reaction with catalyst **2** under ethylene atmosphere, although they are known to be less reactive toward Grubbs catalyst in many cases.[23]

The ring size dependency and yields for *exo*- and *endo*-products for the RCEYM reaction with and without ethylene atmosphere are plotted in Figure 3 to show the trends for mode

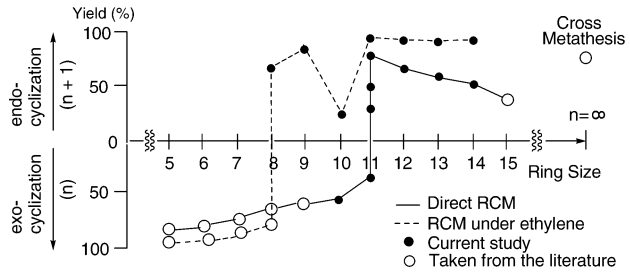


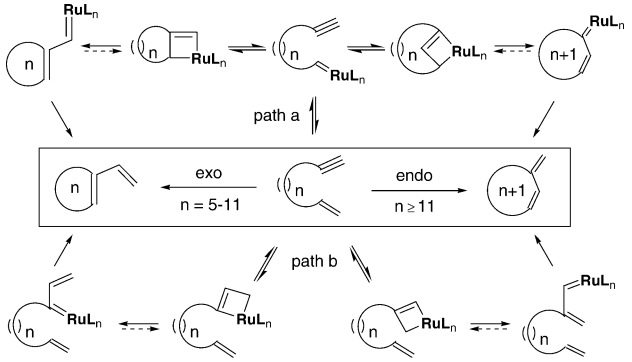
Figure 3. Mode of ring closure and efficiency of enyne RCM.

selectivity and cyclization efficiency. From the macrocycle formation by RCEYM in this study in combination with the small membered ring formation from the literature (open circle data points[2b,c]), a general feature of the enyne RCM reaction was identified; the direct RCM of enynes without ethylene to form 10-membered rings and smaller gives invariably *exo*-products, whereas that of forming 12-membered rings and larger including cross metathesis provides *endo*-products exclusively. Only substrates **9c**−**9d** that have the choice for 11- vs 12-membered rings partitioned equally to provide **10c**−**10d** and **11c**−**11d**, respectively, in 1:1 ratio. The yields decrease as the ring sizes increase, which follows the general trend for typical ring closure reactions.[24] Another notable trend is that the RCEYM with an internal alkyne gives a higher yield compared to that of the corresponding terminal one. On the other hand, the ring closure under ethylene generates the *exo*-product of ring sizes 5−8 and *endo*-products from nine-membered rings and higher. In general, the efficiency for the ring closure is higher for the reactions under ethylene compared to those without ethylene. Another advantage for the reaction with ethylene is the significant improvement of *E*/*Z* selectivity of the endocyclic double bond of the 1,3-diene products.

Mechanistic Consideration of RCEYM: It has been shown that small ring forming enyne RCM reactions (nine-membered ring and smaller) provide generally the *exo*-product, whereas that of large rings gives *endo*-products.[25] To gain better understanding of this *exo*/*endo*-mode selectivity that dictates the substitution pattern of the 1,3-diene products, it is important

(21) Lee, C. H.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147.
(22) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855−1858.
(23) For examples of using 1,3-dienes in RCM, see: (a) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903−10908. (b) Basu, K.; Eppich, J. C.; Paquette, L. A. *Adv. Synth. Catal.* **2002**, *344*, 615−618. (c) Randl, S.; Lucas, N.; Connon, S. J.; Blechert, S. *Adv. Synth. Catal.* **2002**, *344*, 631−633. (d) Wang, X.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041.
(24) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117−3125.

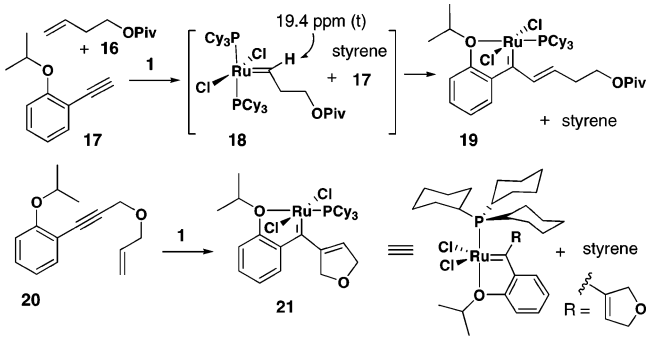
Scheme 5



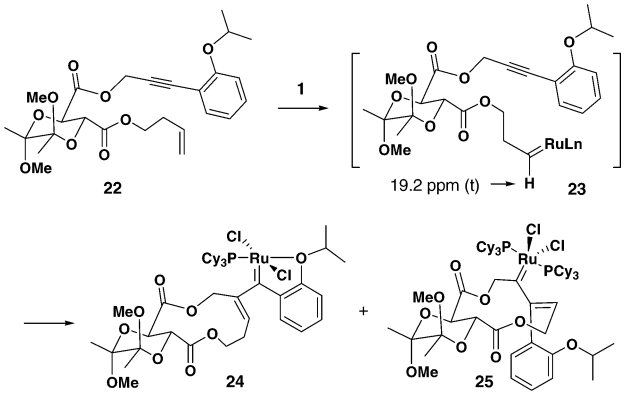
to know whether the reaction starts from the alkyne moiety or the alkene of an enyne RCM substrate, which eventually dictates the identity of the key propagating species. It has been suggested that the observed selectivity for *exo*-product in the formation of small rings is the consequence of the reaction through path b in Scheme 5, where the *exo*-mode ring closure of a reversibly formed initial vinyl alkylidene occurs more favorably than that of the *endo*-mode.[1h,2f,5b,18] However, it is difficult to explain the switch in exo/endo reaction mode shown in Table 1 using this mechanistic hypothesis. One would have to assume that the preference between path b-*exo* and path b-*endo* is suddenly reversed going from 10- and 11-membered ring (**10a**−**d**) formation to that of 12- to 15-membered rings (**11c**−**i**). It is unlikely that a small change in the tether length would have such a significant effect on the preference between these two pathways. A much simpler and more logical explanation for the observed change in exo/endo selectivity arises if we assume that the RCM reaction proceeds through path a[26] in which the catalytic cycle initiates from the alkene part of the enyne substrate. In this case, the *exo*/*endo*-mode selectivity is the consequence of the ring strain associated with respective ruthenacyclobutene intermediates in path a-*exo* and path a-*endo*, whereby the change in tether length can directly influence the course of reaction.

Determining the Site of Initiation and the Key Propagating Species: To gain insight into the fundamental aspects of RCEYM including reactivity and selectivity, it is crucial to have information regarding the initiation event and the key propagating species. We carried out a simple competition experiment to obtain a relative reactivity profile of Grubbs catalyst toward an alkyne and an alkene by mixing 1:1:1 ratio of catalyst **1**, an alkene **16**, and an alkyne **17** (Scheme 6). Alkyne **17** was designed such that it can form a stable ruthenium complex once it reacts with catalyst **1** or other reactive intermediates,[27] thereby

Scheme 6. Possible Mechanistic Pathways



Scheme 7



providing a basis to infer the identity of the reacting alkylidene species. Monitoring the reaction by ^{1}H NMR spectroscopy clearly indicates the formation of styrene and a transient ruthenium alkylidene **18** with concomitant disappearance of the terminal vinyl proton signals of **16**. The formation of styrene is another strong indication for the reaction between **1** and the terminal alkene of **16**. The new alkylidene **18** slowly reacted with **17** to form a new vinyl ruthenium alkylidene complex **19**.

Similarly, when an intramolecular reaction of enyne **20** was carried out with one equivalent of catalyst **1**, an oxygen-chelated alkylidene **21** and styrene formed quantitatively.[28] A tartrate tether-based enyne **22** also behaved similarly (Scheme 7) in the reaction with **1**, providing an intermediate **23** and final chelate **24**, which was observed by ^{1}H NMR. A straightforward interpretation of the facile and selective formation of **19**, **21**, and **24**−**25** is that the metathesis process was initiated from the alkene moiety of these substrates to generate a key intermediate such as **23**, the presence of which strongly indicates that the RCM reactions reported in Table 1 occur through a related propagating alkylidene species.

Further evidence to support the alkene initiation and the involvement of the alkylidene as opposed to the alkyne initiation and that of methylidene comes from our previous study of the CM reaction between conjugated enyne **26** with alkynes **27** and **29**, which afforded the enyne cross-coupled products **28** and **30**, respectively (Scheme 8).[29] The formation of these products

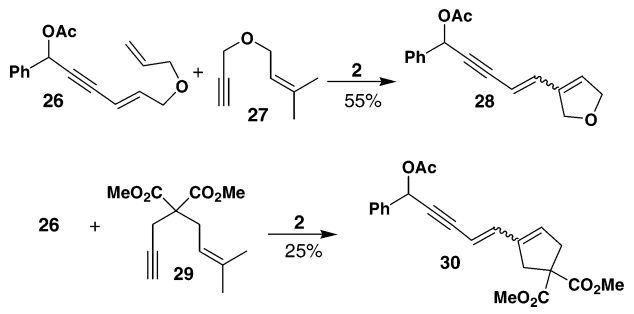
(25) An *endo*-mode ring closure to form a six-membered ring has been observed with substrates that have 1,1-disubstituted alkene moieties; see: (a) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258−1259. (b) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678−693. (c) Dolhem, F.; Lievre, C.; Demailly, G. *Eur. J. Org. Chem.* **2003**, 2336−2342.

(26) Some studies indicate that the alkene reacts first in the presence of alkyne with Grubbs catalyst, although the alkynes in these studies are not terminal nor normal internal alkynes, see: (a) Hoye, T. R.; Donaldson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 277−280. (b) Schramm M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274−4277.

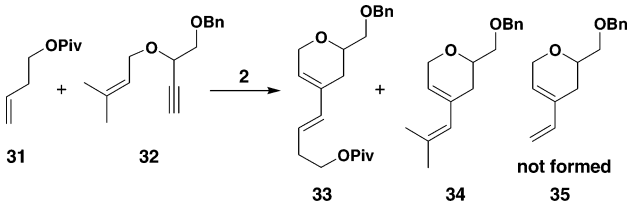
(27) For the related complex formation with styrene derivatives, see: (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (c) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (d) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(28) A similar reaction between **20** and **2** generated a related complex that could not be completely characterized. However, ^{1}H NMR clearly indicates that the expected oxygen chelate did not form. The isopropoxy methine proton signal of **21** appears at δ 5.23, but that of the new complex appears at δ 4.62, similar to that of **20** (δ 4.55). The new complex also retains the tricyclohexylphosphene ligand (^{31}P NMR δ 50.76). This distinctive behavior is probably due to the steric interaction between the dihydrofuryl group and one of the mesityl groups on the N-heterocyclic carbene ligand of the newly formed complex.

Scheme 8



Scheme 9



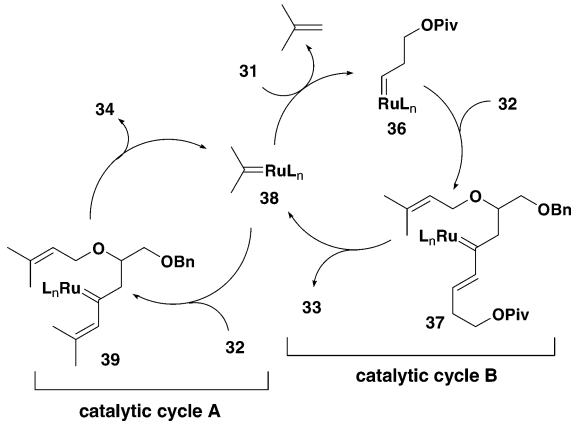
is possible only when the catalyst undergoes preferential initiation at the terminal alkene of **26** followed by subsequent intramolecular cyclization, thereby cleaving off dihydrofuran to generate an alkynyl alkylidene. This intermediate would then undergo CM reaction with the alkyne part of **27** or **29** to liberate product after the final intramolecular cyclization.[23b,30] If the alkyne moiety of **27** or **29** had been reacting preferentially over the terminal alkene of **26**, enyne **27** or **29** would undergo cyclization on its own without generating cross-coupled product **28** or **30**.

To verify the generality of this CM reaction and the mechanistic picture mentioned above by excluding any unforeseen effect of the conjugated 1,3-enyne of **26**, a mixture of a simple alkene **31** and enyne substrate **32** was treated with **2** (Scheme 9). When the ratio of **31** and **32** was 1:1, two products **33** and **34** were isolated in a 1:1 ratio and overall 72% yield. When the ratio was increased to 3:1, only the cross-coupled product **33** was isolated in 63% yield. The methylene-crossed product **35** was not observed in these reactions.

The formation of products **33** and **34** and their distribution can be rationalized by two catalytic cycles as shown in Scheme 10. The initially formed alkylidene **36** from the reaction between alkene **31** and catalyst **2** reacts with the alkyne moiety of **34** to generate a new vinyl alkylidene **37**, which undergoes an RCM reaction to generate the observed product **33** and another alkylidene **38**. This common propagating alkylidene species for both of the catalytic cycles can be partitioned to enter the "Catalytic Cycle A" and "Catalytic Cycle B" depending on the inherent reactivity toward the alkene and alkyne as well as the concentration of the existing alkene **31**. At a 1:1 ratio of **31**:**32**, alkylidene **38** partitioned equally into both catalytic cycles, providing a 1:1 mixture of **33** and **34**. This indicates that the

(29) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035−2038.
(30) For related reactions, see: Stragies, R.; Schuster, M.; Blechert, S. *Chem. Commun*. **1999**, 237−239.

Scheme 10



reactivity of **38** toward the terminal alkene and the terminal alkyne is roughly equal.[2f] When the reaction was run with a 3:1 ratio of **31**:**32**, "Catalytic Cycle B" dominates due to the increased concentration of alkene **31**, thereby shifting the equilibrium toward alkylidene **36** over **39** with concomitant generation of isobutylene. If the reaction had been initiated from the alkyne, "Catalytic Cycle A" would dominate to provide **34** as the major product and **36** as the final alkylidene species. The absence of compound **35** strongly indicates that the involvement of methylidene in this reaction is minimal compared to that of the other key propagating alkylidenes **36** and **38**.

Conclusion

On the basis of experimental results described in Schemes 4−10, we believe that the alkene-initiation route (path a, Scheme 5) can explain the outcome of the RCEYM reaction in Table 1 more effectively than the alkyne-initiation route. The transition in *exo*/*endo*-mode selectivity observed in moving from 10- to 12-membered ring formation is therefore the manifestation of the differences in ring strain of the respective ruthenacyclobutane intermediates in the exo and endo pathways. Furthermore, the *exo*/*endo*-mode selectivity and stereoselectivity were achieved by performing the reaction under ethylene atmosphere, which generates selectively the *endo*-product with high *E*-selectivity. The role of ethylene in macrocyclic enyne RCM is different from that of small membered ring formation because the reaction rate for CM between ethylene and the alkyne is faster than ring closure in the case of macrocycles, which allows the transformation of the alkyne moiety into a 1,3-diene prior to ring closure, thereby converting the enyne RCM process into diene RCM.

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Supporting Information Available: General procedures, characterization of represented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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