Communication

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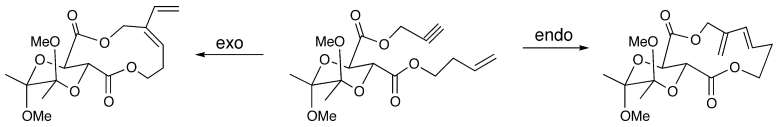

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Enyne Metathesis for the Formation of Macrocyclic 1,3-Dienes

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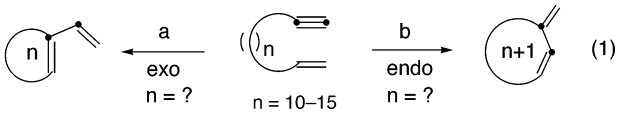
Olefin metathesis, one of the most popular transition-metal-catalyzed C−C bond forming methods, exerts a profound impact in synthetic chemistry.[1] This research activity was enabled by the development of well-defined ruthenium-[2] and molybdenum-based catalyst systems[3] having wide functional group compatibility. Depending on the types of unsaturated functional units involved in the metathesis process, olefin metathesis can be classified into three major categories: diene,[1] enyne,[4] and diyne[5] metathesis. The structural change fashioned by metathesis renders another classification: ring-closing, ring-opening, and cross metathesis. Among these subclasses, diene ring-closing metathesis (RCM) has drawn far more attention from synthetic chemists due to its effectiveness for the formation of various cyclic substructures. Despite its enormous potential to form multiple C−C bonds and polycyclic systems, enyne metathesis[4] has not been exploited thoroughly.

We became interested in the capacity of the enyne RCM reaction to generate conjugated 1,3-dienes embedded in a macrocyclic structure, a functionality having significant synthetic application. However, enyne RCM of 10- to 15-membered rings has not been reported.[6] With this prospect, we set out to study the fundamental aspects of the macrocyclic enyne RCM in detail, focusing on three major questions: (1) Would the RCM of enynes form macrocycles in general, and, if so, what are the optimal parameters to maximize the efficiency? (2) Could the general trend of the *exo*/*endo*-mode of macrocyclic ring-closure, for example, paths "a" and "b" in eq 1, be identified and controlled? (3) Could the stereochemistry of the endocyclic double bond of the resultant 1,3-diene be controlled? In this Communication, we report our study addressing these questions.

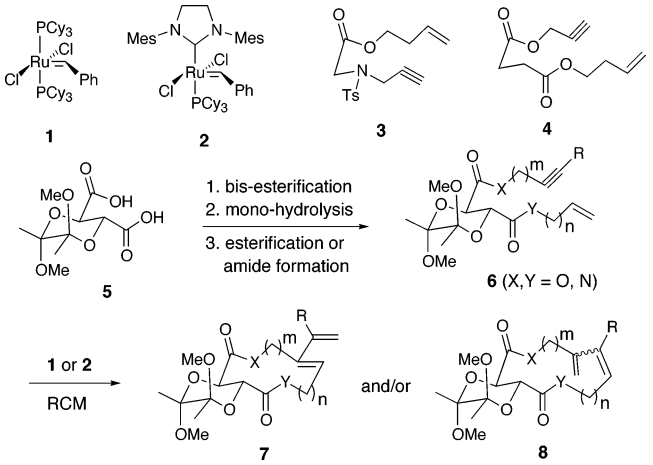


(1)

We first tested the RCM of enynes **3** and **4** using Grubbs catalysts **1** and **2** (Scheme 1), observing only the recovery of starting material. At this juncture, we decided to use tartaric acid derivative **5**[8] to connect appropriate ene and yne segments to generate RCM substrate **6**, anticipating that the cyclic linker will not only increase the efficiency of the RCM reaction[7] but also provide chirality to the resultant macrocycles **7** and/or **8** once they form. To examine how the ring size of the incipient macrocycle affects the exo/endo selectivity of ring-closure and the stereochemistry of the endocyclic double bond of **7** and **8**, the length of the tether on **6** between the ene and the yne components[9] and the type of heteroatom were systematically altered.

Under typical RCM conditions (0.2 M in CH_2Cl_2, 5−10 mol % of **1** or **2**, reflux), macrocycles **7a**−**d** and **8c**−**i** formed smoothly via *exo*- and *endo*-mode ring-closure, respectively (Table 1). The RCM of **6a** gave a 10-*exo*-product **7a** (entry 1). The similar substrate **6b** with an internal alkyne gave increased yield[4b] of *exo*-product **7b** (entry 2). Enynes **6c**,**d** provided a 1:1 ratio of *exo*- and

Scheme 1



endo-products **7c**,**d** and **8c**,**d** (entries 3,4). Both the internal and the terminal alkynes showed the same selectivity for *exo*-mode ring-closure with higher yield (92% vs 50%) for the internal alkyne. Enynes **6e**−**i** provided 12- to 15-membered rings via an endo-selective ring-closure (entries 5−9). Notably, the propargylic amide **6e** exclusively gave a 12-membered ring **8e** with *E*-stereochemistry. This implies that the *exo*/*endo*-mode selectivity depends not only on the size of the macrocycles formed but also the nature of functionality in the tether.

The ring size-dependency for exo/endo selectivity and yields for enyne RCM are plotted in Figure 1. The results from this study in combination with the data from the literature (open circles)[4c] show general trends. The RCM of enynes to form ten-membered rings and smaller gives invariably the *exo*-products via path "a",[10] whereas that forming 12-membered rings or larger including cross metathesis chooses path "b", providing *endo*-products. Only substrates **6c**,**d** that have the choice for both 11- and 12-membered rings partitioned equally to provide **7c**,**d** and **8c**,**d**, respectively, in a 1:1 ratio. The yields decrease as the ring sizes increase, which follows the general feature for typical ring-closure reactions.[11] Also, the RCM of enynes with an internal alkyne gives a higher yield as compared to that of the corresponding terminal alkyne.[4b]

No general trend was observed for the stereochemistry of the endocyclic double bond. However, performing the reactions under ethylene atmosphere gave marked improvements in yield as well as control over the *E*/*Z* and endo/exo ratios. Reaction of **6e** under ethylene gave **7e** in 60% yield and *E*-selectivity. The RCM of **6c** in a similar manner afforded an improved yield (65%) and selectivity in *E*/*Z* (2:1 for **8c**) and endo/exo (**7c**:**8c**, 2:1) ratios.[12] Further improvement was obtained by performing the reaction at room temperature with **1** followed by heating in the presence of **2**. Complete selectivity was observed for both the mode of cyclization and the *E*/*Z* ratio, giving *E*-**8c** only. The improved selectivity is likely due to initial cross metathesis of the alkyne with ethylene followed by ring-closing diene metathesis.[12b]

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

Entry	Enyne substrate	Macrocycle product exo	Macrocycle product endo	*E*:*Z*	Yield (%)[b]
1	**6a** m = n = 1, X = Y = O, R = H	**7a** (R = H)[c]		0:1	52
2	**6b** R = Me	**7b** (R = Me)[c]		0:1	61
3	**6c** m = 1, n = 2, X = Y = O, R = H	**7c** (R = H)[c] (1 : 1)	**8c** (R = H)	1:1 (2:1 for **8c**) (*E*-**8c** only)	50 (91)[d] (90)[e]
4	**6d** R = Me	**7d** (R = Me)[c] (1 : 1)	**8d** (R = Me)	1:1 for **8d**	92
5	**6e** m = 1, n = 2, X = NH, Y = O, R = H		**8e**	1:0	35 (60)[e]
6	**6f** m = 2, n = 1, X = Y = O, R = H		**8f**	1:1	70
7	**6g** m = 2, n = 2, X = Y = O, R = H		**8g**	0:1	61
8	**6h** m = 3, n = 2, X = Y = O, R = H		**8h**	2:1	54
9	**6i** m = 3, n = 3, X = Y = O, R = H		**8i**	1:1	55

[a] Reactions performed with 5 mol % of **2** at 0.2 M in refluxing CH_2Cl_2. [b] Isolated yield. [c] The stereochemistry of **7a**−**d** was determined by nOe, and that of **8c**−**i** was determined by coupling constant. [d] RCM under ethylene in refluxing CH_2Cl_2. [e] RCM under ethylene at 25 °C.

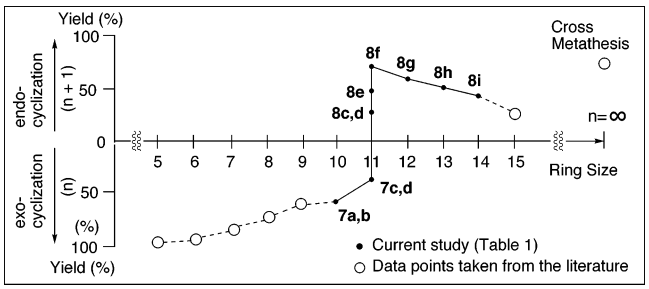
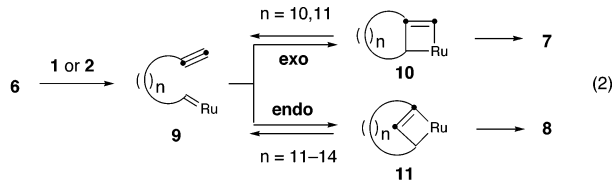
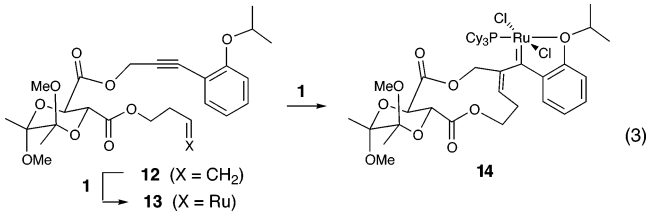


Figure 1. Mode of ring-closure and efficiency of enyne RCM.

Mechanistically, we believe the RCM of enynes **6a**−**i** proceeds via the initiation at the alkene moiety[13] to form an initial alkylidene **9** (eq 2), which subsequently forms bicyclic ruthenacyclobutenes



10 and/or **11**. The observed *exo*/*endo*-mode selectivity is the reflection of the difference in ring strain[11] associated with the formation of these intermediates. This hypothesis is strongly supported by the isolation of the trapped ruthenium complex **14** derived from the reaction of **12** with **1** (eq 3), the careful NMR



monitoring of which clearly indicates that the formation of styrene and the formation of new alkylidene **13** are tightly coupled.

In conclusion, for the first time we have demonstrated that macrocyclic enyne RCM forms 10- to 15-membered rings. The tartrate-based enyne RCM platform provides valuable information regarding the efficiency and exo/endo selectivity for macrocycle formation. Further studies are underway for the elucidation of the reaction mechanism and synthetic application.

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

References

(1) For reviews of olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(2) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (e) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(3) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Reagan, M.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(4) (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737. For the first enyne metathesis with Grubbs catalyst, see: (b) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. For reviews, see: (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (d) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133.

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

(6) For the formation of a 16-membered ring, see: Layton, M. E.; Morales, C. A.; Shair, M. D *J. Am. Chem. Soc.* **2002**, *124*, 773.

(7) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648.

(8) Dimethyl ester of **5** is available from Aldrich (25 g/$65) and its monohydrolysis, see: Maycock, C. D.; Venture, M. R. *Org. Lett.* **2002**, *4*, 2035.

(9) For the chemistry of 1,*n*-enynes, see: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

(10) Six-membered ring *endo*-product was observed with the 1,1-disubstituted ene moiety of enyne substrates, see: (a) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678. (b) Dolhem, F.; Lièvre, C.; Demailly, G. *Eur. J. Org. Chem.* **2003**, 2336.

(11) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117.

(12) (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (b) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855.

(13) (a) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. (b) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277.

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