Enyne Metathesis

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The Joy and Challenge of Small Rings Metathesis**

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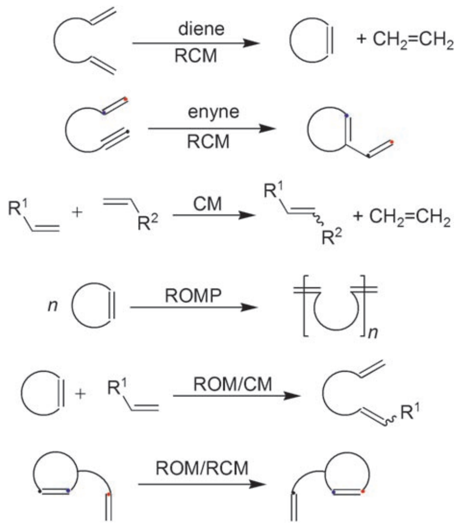
carbenes · cycloisomerization ·
homogeneous catalysis · metathesis

Olefin metathesis (from the Greek word μεταθεσιζ, meaning transposition) is an alkylidene exchange between two reacting fragments mediated by transition-metal alkylidene complexes.[1]

Recent decades have seen burgeoning interest in olefin metathesis, resulting in a number of elegant applications. Using this tool, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and tedious routes.[1] Several types of olefin metathesis have been identified so far; among them, ring-closing metathesis (RCM) and cross-metathesis (CM) have been widely applied in the synthesis of biologically active compounds (Scheme 1). Ring-closing metathesis occurs when a diene undergoes intramolecular metathesis to afford a cyclic olefin. Analogous intramolecular reaction of an enyne is sometimes called enyne cycloisomerization or enyne RCM.[2] Ring-closing metathesis of dienes and enynes represent an attractive and powerful tool for the formation of medium and large cycles ($\geq$5-membered rings). However, it is generally acknowledged that small (three- and four-membered) and strained rings cannot be formed by RCM.[3] In such cases, the ring-opening process can be far more thermodynamically favorable than ring closing. Indeed, various strained molecules, such as norbornene derivatives, are well-known substrates for ring-opening metathesis polymerization (ROMP) reactions (Scheme 1).[4]



Scheme 1. Selected examples of olefin metathesis.

Cyclopropenes and cyclobutenes may be polymerized by ring-opening in a similar fashion by the metathesis catalyst, although there are fewer examples of such transformations than for ROMP reactions of norbornenes.[4] The driving force in these reactions is the relief of the enormous strain on the three- and four-membered rings. Another possible transformation for highly strained cyclic olefins is ring-opening metathesis/cross-metathesis (ROM/CM). Michaut, Parrain, and Santelli showed that the Grubbs ruthenium complex Gru-I (Figure 1) efficiently catalyses ROM/CM of cyclopropenone ketal **1** to afford 1,4-divinyl ketone derivative **2** in good yields (Scheme 2).[5]

The opening of a strained cyclopropene ketal was later used by Kozmin and co-workers to create key spiroketal domains of some natural products, such as bistramide A,[6a]

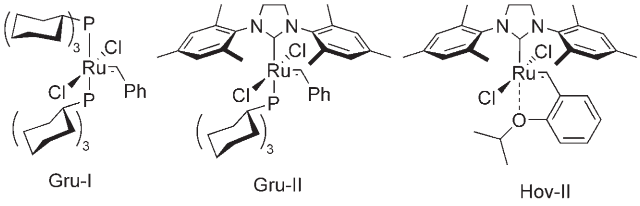
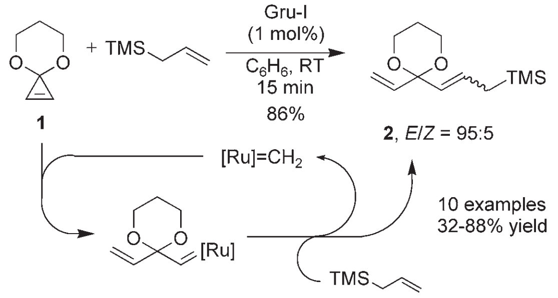


Figure 1. Ruthenium catalysts commonly used in olefin metathesis.



Scheme 2. ROM/CM of cyclopropenone ketal **1**. TMS = trimethylsilyl.

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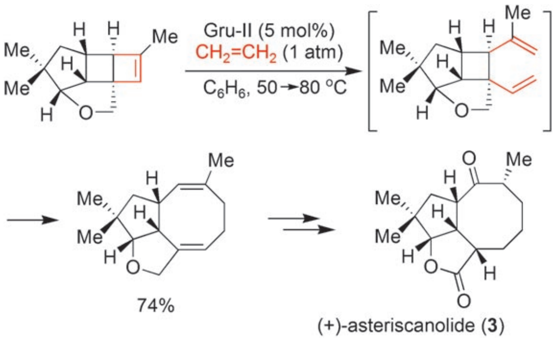
spirofungin A,[6b] and routiennocin.[6c] An elegant asymmetric ring-opening/cross-metathesis (AROM/CM) reaction of cyclopropenes catalyzed by a chiral ruthenium catalyst has recently been described by Giudici and Hoveyda.[7]

In addition to cyclopropenes, some cyclobutenes have also been used in ROMP and similar processes. One of the most impressive applications involving a cyclobutene ring-opening event is the total synthesis of (+)-asteriscanolide (**3**) by Limanto and Snapper, who used the ROM/CM sequence followed by divinyl cyclobutane rearrangement to fashion the cyclooctane part of the core tricyclic structure of the natural product (Scheme 3).[8a] A similar ROM/CM reaction between substituted cyclobutene and gaseous ethylene was used by Schrader and Snaper in the preparation of series of isoprostane analogues[8b] and by Harrity and co-workers in synthesis of (±)-sporochnol A.[8c]

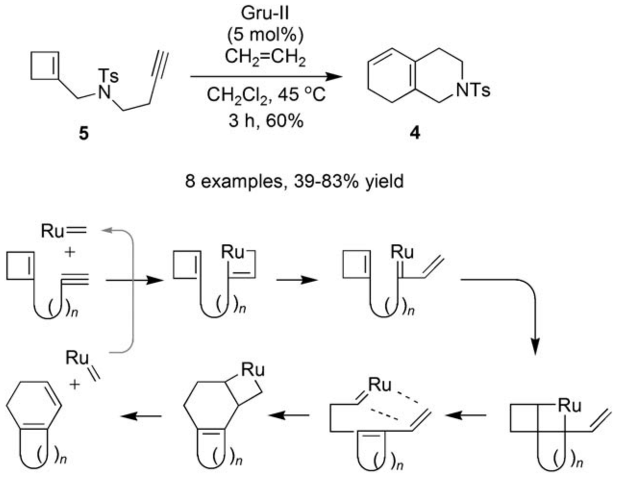


Scheme 3. ROM/CM of a cyclobutene in the enantioselective total synthesis of (+)-asteriscanolide (**3**).

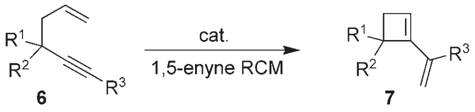
Hoveyda et al. reported on asymmetric ring-opening/ring-closing metathesis (AROM/RCM) of substituted cyclobutenes promoted by a chiral Mo–alkylidene catalyst.[9] This tandem ROM/RCM reaction proceeds efficiently and with good enantioselectivity, providing rapid entry to optically enriched dihydrofuranes. The Nicolaou group utilized a similar sequence to open a chiral cyclobutene-1,2-diol derivative with achiral ruthenium catalyst Gru-II.[10]

A notable example of ROM/RCM reaction of alkyne-substituted cyclobutenes was reported by Mori and co-workers. In the enyne[2] variant of a ROM/RCM cascade, various isoquinolines, such as **4**, were synthesized in good yields from cyclobutene derivatives (**5**) using the second-generation ruthenium carbene Gru-II under an ethylene atmosphere (Scheme 4).[11]

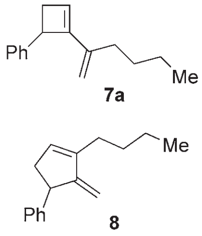
The above (arbitrary) selection of examples demonstrates that metathetical opening of strained three- and four-membered rings is a very useful transformation, which has been used in numerous stereocontrolled total syntheses of natural and bioactive compounds as well as in preparation of polymers. At the same time, there are virtually no reports on the formation of three- and four-membered carbo- or heterocycles by metathesis reactions. In this regard, a new communication by Debleds and Campagne[12] on the preparation of vinylcyclobutenes by enyne RCM is a real breakthrough. In this report, the authors have shown that Grubbs- and Hoveyda-type catalysts are able to promote enyne metathesis[2] of 1,5-enyne substrates **6** leading to functionalized cyclobutenes **7** (Scheme 5).



Scheme 4. ROM/RCM of cyclobutene–yne **5**. Ts = toluene-4-sulfonyl.



cat. (mol%),	conditions	**7a**, yield
Gru-I (20),	CH_2Cl_2, 45 °C	0%
Gru-II (20),	CH_2Cl_2, 45 °C	20-25%
Hov-II (20),	CH_2Cl_2, 45 °C	35%
Hov-II (20),	CH_2Cl_2, µW, 70 °C	58%
Hov-II (10),	CH_2Cl_2, µW, 70 °C	20%
$PtCl_2$,	toluene, 80 °C	0%



Scheme 5. 1,5-Enyne RCM. µW = microwave irradiation.

To gain a closer view on this unprecedented transformation, the reaction leading to cyclobutene **7a** was explored under various conditions (Scheme 5). In the presence of Gru-I catalyst, no cyclized product was observed, whereas the use of more potent second-generation[1] catalysts Gru-II and Hov-II led to the formation of the expected cyclobutene **7a** in 20–35% yield. Importantly, the use of microwave irradiation[13] was found to be beneficial, leading to the formation of **7a** in a remarkable 58% yield. Unfortunately, all efforts to decrease the amount of Hov-II catalyst used were unsuccessful, leading to a substantial decrease in the yield. The reason why at least 20 mol% of the catalyst is necessary to achieve a reasonable yield remains unclear. According to the authors, along with the expected cyclobutene **7a**, only small amounts of the uncharacterized "CM dimers" (5%) and starting material **6a** (10–15%) were identified in the crude reaction mixture. Interestingly, the formation of less strained cyclopentene **8**, a product of an alternative cyclization route,[14] was not observed. Campagne tested also the effect of ethylene (so-called Mori's conditions for enyne reaction);[15] unfortunately, extensive by-product formation was observed in this case.[16] Finally, the use of $PtCl_2$ as catalyst was probed, but no reaction was observed (Scheme 5).[17]

Having the optimized reaction conditions, Debleds and Campagne attempted to define the scope of this transformation. Various 1,5-enyne substrates were tested, providing cyclobutene products **7a**–**7l** in yields up to 58%, as shown in Figure 2. It was concluded that although the cyclobutene ring can be decorated with various substituents (R^1, R^2), only alkyl substituents are well-tolerated on the alkynyl part (R^3). A double cyclization of a bisenyne substrate was finally attempted, leading to the bis(cyclobutene) **7l** in a modest 19% yield (Figure 2). The moderate yields observed in these reactions were explained by the authors in part by incomplete conversions (unreacted starting material was present in most of the reaction mixtures) and by the formation of some unidentified by-products. Furthermore, difficulties in the purification of the sensitive highly strained cyclobutenes can also be responsible for diminishing the yield.

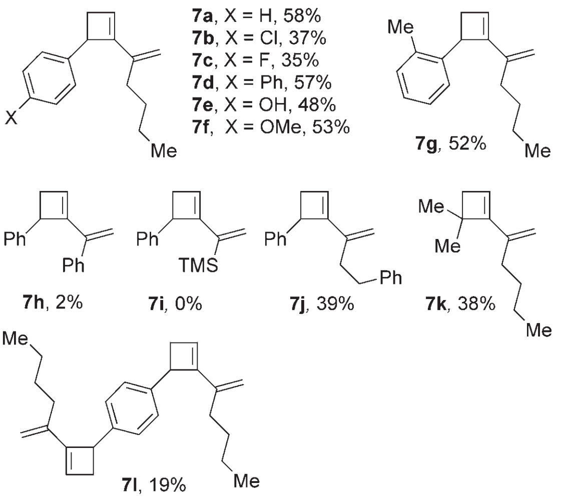
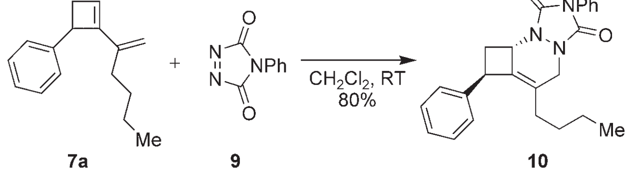


Figure 2. Products of 1,5-enyne RCM.

These results open a convenient new entry to functionalized cyclobutenes, which are useful building blocks in organic synthesis. The 1,3-diene unit present in **7** can be further used in many transformations, such as Diels–Alder cycloaddition. Indeed, as shown by the authors, product **7a** reacts with dienofile **9** at room temperature to give the expected tricyclic compound **10** in a respectable 80% yield and as a single diastereomer (Scheme 6).[12]



Scheme 6. Diels–Alder reaction of **7a**.

In conclusion, Debleds and Campagne have extended the field of metathesis technology by demonstrating that strained four-membered rings can be obtained by the enyne reaction. The reaction currently suffers from rather mediocre yields and high catalysts loadings. The scope of substrates amenable for 1,5-enyne RCM should be broadened as well. Although it seems that the reaction follows the established route of metathetical 1,*n*-enyne cycloisomerizations,[2] it would be important to provide some evidence as to the mechanism. It is reasonable to expect that further optimization of the reaction conditions or the application of more potent catalysts will increase the reaction efficiency and scope.[18] The simplicity of the transformation in combination with the synthetic importance of the obtained products suggests that this method will find numerous applications. The preliminary results reported by Debleds and Campagne are definitely worth further investigation.[19]

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[1] For selected reviews on olefin metathesis, see: a) *Handbook of Metathesis* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) P. H. Deshmukh, S. Blechert, *Dalton Trans.* **2007**, 2479; c) D. Astruc, *New J. Chem.* **2005**, *29*, 42; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; for an industrial perspective, see: e) A. M. Thayer, *Chem. Eng. News* **2007**, *85*(7), 37.

[2] Recent reviews on enyne metathesis: a) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317; b) M. Mori, *Ene-yne Metathesis* in *Handbook of Metathesis*, *Vol. 2* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, pp. 176; c) C. S. Poulsen, R. Madsen, *Synthesis* **2003**, 1; d) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55; e) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121.

[3] For a short review on the preparation of cyclic strained molecules by olefin metathesis, see: S. K. Collins, *J. Organomet. Chem.* **2006**, *691*, 5122.

[4] For a review on ROMP, see: reference [1a] and a) K. J. Ivin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*; Academic Press, London, **1997**; b) G. Odian, *Principles of Polymerization*, 3rd ed., Wiley, New York, **1991**; c) M. R. Buchmeiser, *Chem. Rev.* **2000**, *100*, 1565.

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[6] a) A. V. Statsuk, D. Liu, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 9546; b) J. Marjanovic, S. A. Kozmin, *Angew. Chem.* **2007**, *119*, 9010; *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 8854; c) K. Matsumotoa, S. A. Kozmin, *Adv. Synth. Catal.* **2008**, *350*, 557.

[7] R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, *129*, 3824.

[8] a) J. Limanto, M. L. Snapper, *J. Am. Chem. Soc.* **2000**, *122*, 8071; b) T. O. Schrader, M. L. Snapper, *Tetrahedron Lett.* **2000**, *41*, 9685; c) M. J. Bassindale, P. Hamley, J. P. A. Harrity, *Tetrahedron Lett.* **2001**, *42*, 9055.

[9] G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 1828.

[10] K. C. Nicolaou, J. A. Vega, G. Vassilikogiannakis, *Angew. Chem.* **2001**, *113*, 4573; *Angew. Chem. Int. Ed.* **2001**, *40*, 4441.

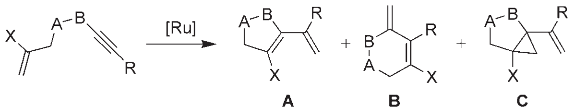
[11] M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura, Y. Sato, *J. Org. Chem.* **2005**, *70*, 1066.

[12] O. Debleds, J.-M. Campagne, *J. Am. Chem. Soc.* **2008**, *130*, 1562.

[13] For selected key references, see: a) *Microwaves in Organic Synthesis* (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2002**; b) B. L. Hayes, *Microwave-Assisted Organic Synthesis* (Eds.: P.

Lidstrom, J. P. Tierney), Blackwell Publishing, Oxford, **2005**; c) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**; d) *Microwaves in Organic Synthesis*, 2nd ed. (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**; e) *Microwave Methods in Organic Synthesis* (Eds.: M. Larhed, K. Olofsson), Springer, Berlin, **2006**.

[14] It was shown that metathesis of enynes containing an internal triple bond sometimes proceeds in a nonselective manner, leading to the formation of three products: a "normal" diene **A**, a by-product **B** bearing an exocyclic double bond, and a bicyclic product **C**, containing a cyclopropane unit.



See: a) V. Sashuk, K. Grela, *J. Mol. Catal. A* **2006**, *257*, 59; b) T. Kitamura, Y. Sato, M. Mori, *Adv. Synth. Catal.* **2002**, *344*, 678, and references therein.

[15] a) A. Kinoshita, M. Mori, *Synlett* **2004**, 1020; b) M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082.

[16] It is reasonable to assume that the unwanted ROM/CM of a highly strained cyclobutene product **7**, similar to that one shown in Scheme 3, could significantly be increased when the reaction is carried out under an ethylene atmosphere.

[17] It should be noted that metathetical cycloisomerization of 1,*n*-enynes represents only a small branch of the vast tree of transition-metal catalyzed bond reorganization reactions of enynes. For selected key references, see: a) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813; b) M. Mendez, A. M. Echavarren, *Eur. J. Org. Chem.* **2002**, 15; c) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215; for recent examples of platinum-catalyzed cycloisomerization of enynes leading to the formation of cyclobutenes, see: d) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509; e) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244.

[18] A recent example: V. Sashuk, C. Samojłowicz, A. Szadkowska, K. Grela, *Chem. Commun.* **2008**, 2468.

[19] Note added in proof: For the most recent review on cycloisomerization of 1,*n*-enynes, see :V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.