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Catalytic Ring Closing Metathesis of Dienynes: Construction of Fused Bicyclic Rings

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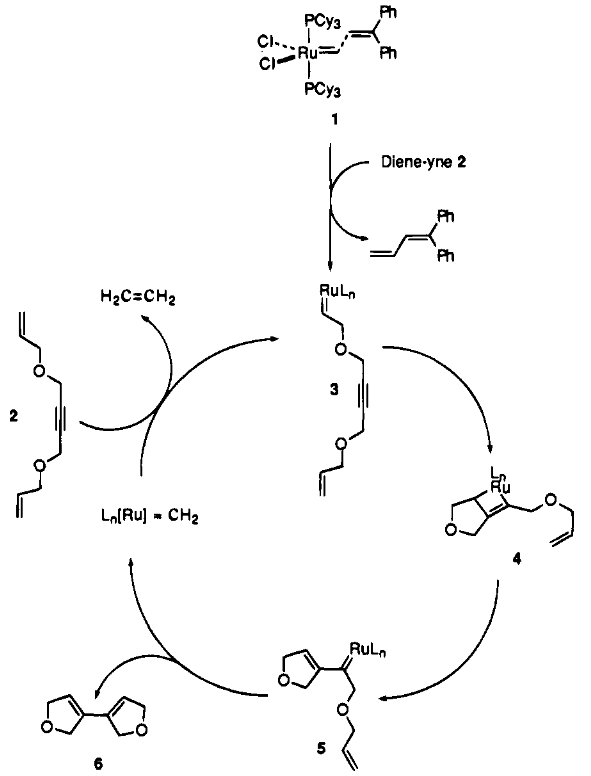
Fused bicyclic rings [*n.m.*0] are common structural elements present in many natural products. Despite remarkable progress, methods and strategies that can simplify their construction are still needed. This communication reports that ruthenium carbene **1** mediates an efficient, catalytic conversion of readily prepared acyclic enynenes to a variety of fused bicyclic rings in a single step.[1,2]

Initial studies demonstrated that complex **1** (3 mol %, C_6H_6, room temperature, 4 h, 90% yield) catalyzed the conversion of dienyne **2** to the diene **6** (Scheme 1).[3a] The conversion presumably[3b] involves acyclic metathesis of the olefin followed by formation and ring-opening of an intermediate metallocyclobutene **4**. A second ring-closing metathesis (RCM) gives the product as well as the regenerated catalyst.[4] During this process, two rings and two C−C bonds are formed in a single step.

This preliminary result suggested that if the intervening alkyne was placed in a branched position between the dienes, the cyclization would lead to a fused bicyclic ring. Indeed, a symmetrical dienyne[5,6] was converted to the fused bicyclo[4.3.0] ring (entry 1, Table 1).[7,8] The dienyne (entry 2, Table 1) with a longer diene tether led to a bicyclo[5.4.0] compound.

Scheme 1



With substrates containing unsymmetric diene tethers, two different products were expected. The metathesis of unsymmetrical dienyne (entry 3) produced approximately a 1:1 ratio of bicyclo[5.3.0] and -[4.4.0] rings. The steps in the formation of the different bicyclic rings are depicted in Scheme 2. The statistical product distribution is a reasonable consequence of non-selective initial olefin attack by the ruthenium carbene (i.e., $k_1 = k_2$).

Earlier work[1b] suggested that olefin substitution can alter the site of initial olefin attack by the catalyst. Accordingly, the dienyne (entry 4) with sterically differentiated olefins produced only the bicyclo[4.4.0] ring in 83% yield. The complementary bicyclo[5.3.0] compound was isolated as the sole product when the substitution pattern of the olefins was reversed (entry 5).

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(1) Previous reports on RCM from this laboratory: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (d) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (e) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. For recent applications of RCM to natural product synthesis: (f) Martin, S. F.; Liao, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691. (g) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191. (h) Martin, S. F.; Liao, Y.; Chen, H. J.; Patzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005. For a review on applications of olefin metathesis in organic synthesis: Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon; New York, 1991; Vol. 5, Chapter 9.3.

(2) For the preparation and characterization of catalyst **1**: (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858.

(3) (a) Initial experiments (0.02 mmol of dienyne) were followed by ^1H NMR. All enynene reactions reported (Scheme 1 and Table 1) were quantitative by ^1H NMR. The yields shown in Table 1 are *isolated* yields (0.2−0.3 mmol scale). (b) The possibility that the first step involves an alkyne metathesis followed by two nonsequential RCM cannot be ruled out. However, later experiments favor the proposed mechanism (see text).

(4) Pentacarbonyltungsten carbene mediated intramolecular *enyne* reaction (single ring closure) was first reported by Katz and Sivavec.[4a] Yields were generally low for both catalytic (1 mol % catalyst, <31% yield) and stoichiometric (<50% yield) reactions. The *enynene* transformation (double ring closure) was reported with both electrophilic carbenes and rhodium-catalyzed decomposition of α-diazo ketones. With the Fischer carbenes, preformed and stoichiometric carbenes are required and the second ring closure leads to cyclopropanes.[4b,c] With the rhodium-catalyzed decomposition of α-diazo ketones, the reaction shows a complex product distribution arising from several competing processes.[4d] (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737. (b) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676. (c) Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559. For a review on the chemistry of Fischer carbenes with enyne substrates, see: Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.2. (d) Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343.

(5) The symmetrical dienynes shown in entries 1 and 2 were prepared by double Grignard addition to benzyl 2-butynoate. The unsymmetrical dienes (entries 3−7) were prepared by stepwise addition of the respective Grignard reagents to 2-butynoic-*N*-methoxy-*N*-methylamide.

(6) Other well-defined metal carbenes were tested (3−5 mol % catalyst). The alkylidene, $Mo(NAr)(CHCMe_2Ph)(OCMe(CF_3)_2)_2$ (Ar = 2,6-(i-Pr)$_2C_6H_3$),[6a,b] decomposed rapidly (<10 min) in the presence of the symmetrical dienyne (entry 1), and the bicyclo[4.3.0] compound was not observed. With the same substrate, the tungsten alkylidine, $W(NAr)(CHCMe_3)(OCMe(CF_3)_2)_2$ (Ar = 2,6-(i-Pr)$_2C_6H_3$),[6c,d] gave 70% of the desired bicyclo[4.3.0] product together with 25% of cycloheptenyne from the competing RCM of dienes. With Basset's tungsten catalyst,[6e] the reaction failed to go to completion, and only 30% of the bicyclo[4.3.0] compound was observed (Kim, S.-H.; Zuercher, W.; Grubbs, R. H., unpublished results). (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, 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. (c) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423. (d) Schrock, R. R.; DePue, R. T.; Feldman, J.; Yap, K. B.; Yang, D. C.; Davis, W. M.; Park, L.; DiMare, M.; Schofield, M.; Anhaus, J.; Walborsky, E.; Evitt, E.; Kruger, C.; Betz, P. *Organometallics* **1990**, *9*, 2262. (e) Couturier, J.-M.; Pailet, C.; Leconte, M.; Basset, J.-M.; Weiss, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 628.

(7) Approximately 3% of cycloheptenyne arising from competing RCM of dienes was observed. Higher temperature accelerates the reaction (even with a smaller amount of catalyst); the same conversion can be carried out with 1 mol % of **1** at 65 °C for 2 h (quantitative yield, NMR scale).

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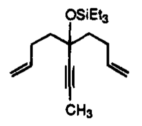
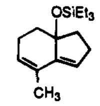
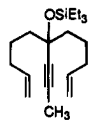
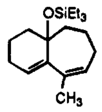
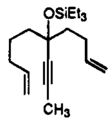
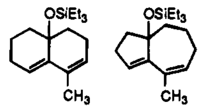
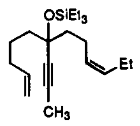
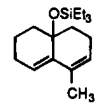
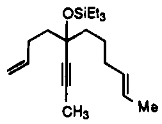
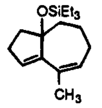
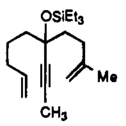
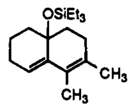
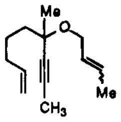
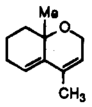
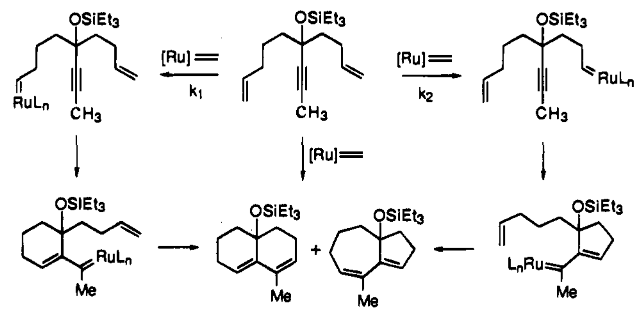
Table 1. Catalytic RCM of Dienynes

entry	substrate	product	conditions (yield)
1			3 mol% 1, 8 h, 25 °C, 95%, CH_2Cl_2 (0.06 M)
2			6 mol% 1, 8 h, 65 °C, 88 %, C_6H_6 (0.06 M)
3			3 mol% 1, 15 h, 65 °C, 86 %, C_6H_6 (0.02 M), 1:1 of [4.4.0] and [5.3.0]
4			3 mol% 1, 6 h, 65 °C, 83 %, C_6H_6 (0.03 M)
5			15 mol% 1, 1.5 h, 100 °C, 78 %, toluene (0.01 M)
6			15 mol% 1, 12 h, 65 ° C, 89 %, C_6H_6 (0.05 M)
7			3 mol% 1, 6 h, 65 ° C, 88 %, C_6H_6 (0.05 M)

Not only do these observations greatly extend the scope of this reaction, but they also provide support for the proposed mechanism. As shown in entry 6, internal substitution on the olefin provided the same regiochemical control, leading to a single adduct. This case also demonstrated that a tetrasubstituted double bond can be constructed by this reaction. Finally, heteroatom substitution within the diene tether did not alter the expected outcome (entry 7). These results illustrate that simple olefin substitution directs the site of the initial acyclic metathesis which determines the type of the resulting bicyclic structure.

Scheme 2



In conclusion, the ruthenium carbene complex **1** catalyzes the conversion of acyclic dienynes to fused bicyclic rings containing five-, six-, and seven-membered rings in a highly selective manner. The starting acyclic dienynes are readily prepared,[9] and the resulting fused bicyclic rings contain olefins that can be further functionalized. This combination of features provides an efficient route to complex bicyclic ring systems. The catalyst itself is available in a few steps,[2,10] is easily handled, and is tolerant of most functional groups.[11] These properties of the catalyst and the dienyne reaction further expand the scope of catalytic RCM for the construction of complex organic compounds.

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Supplementary Material Available: Spectroscopic data for compounds **2**, **6**, and those shown in Table 1 (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) **A typical experimental procedure:** Ruthenium catalyst **1** (FW 925.1, 0.03 equiv, 5.6 mg) in C_6H_6 (1.0 mL) was added through a cannula to a solution of dienyne (FW 334.6, 1.0 equiv, 0.2 mmol, 67 mg, entry 4) in C_6H_6 (5.7 mL, 0.03 M). The resulting light brown solution was placed in a 65 °C oil bath. After 6.5 h, the starting material was completely converted to a compound with $R_f = 0.4$ (petroleum ether) on TLC. The solution was concentrated under reduced pressure and purified by flash chromatography. The bicyclo[4.4.0] compound was isolated as a colorless, volatile oil (46 mg, 83% yield).

(9) Methods for construction of substituted alkynes (such as dienynes) are numerous. See, for instance: (a) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 1.7. (b) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, Chapter 1.3. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4.

(10) In addition to the original preparation,[2] one-step synthesis from the commercially available $[(cymene)RuCl_2]_2$ dimer has been developed: Nguyen, S. T.; Grubbs, R. H., manuscript in preparation.

(11) The catalyst is stable in the presence of alcohols, esters, aldehydes, amides, thioethers, alkyl halides, and HCl in diethyl ether.[2] It shows metathesis activity even in the presence of excess NEt_3 in C_6H_6 at 65 °C (Zuercher, W.; Grubbs, R. H., unpublished results).