Catalytic Ring-Closing Metathesis of Functionalized Dienes by a Ruthenium Carbene Complex†

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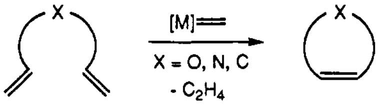
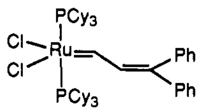
Recent reports from this laboratory[2,3] have described the discovery of a family of well-defined ruthenium carbene complexes capable of metathesizing both strained[3a] and unstrained[3b] olefins. As part of an ongoing program directed toward the development of transition metal metallaolefins as reagents for organic synthesis,[4] we previously established that molybdenum alkylidenes effect the ring-closing metathesis of dienes (eq 1), thereby affording unsaturated heterocycles[4b,c] and carbocycles.[4d] In this communication, we disclose that ruthenium carbene **1**[3b,5] is also an efficient catalyst for ring-closing olefin metathesis. This new catalyst possesses two important advantages over the molybdenum-based reagent: (1) diminished sensitivity to atmospheric oxygen and moisture and (2) increased tolerance of most functionalities.



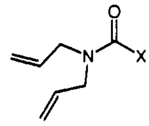
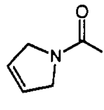
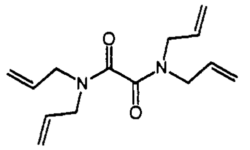
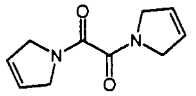
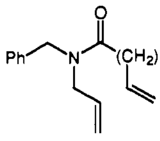
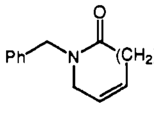
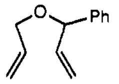
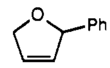
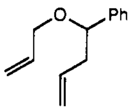
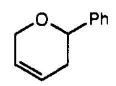
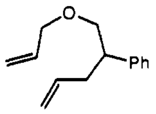
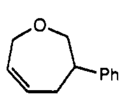
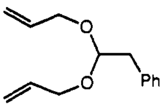
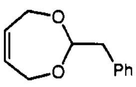
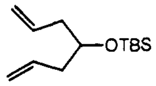
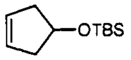
(1)



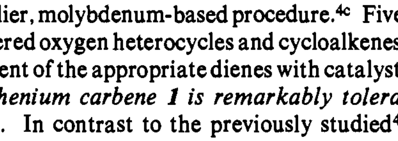
1

Treatment of dienes with 2–4 mol % **1** at room temperature results in the formation of a variety of unsaturated heterocycles and carbocycles in good yields (Table I).[6-8] The catalyst efficiently generates five- (entries 1–4), six- (entry 5), and seven-membered (entry 6) nitrogen heterocycles, and it tolerates common protecting groups, including trifluoroacetyl (entry 1), *tert*-butoxycarbonyl (entry 2), and benzyl (entries 4–6). It is worth noting that the cyclizations depicted in entries 4 and 5 cannot be effected using the earlier, molybdenum-based procedure.[4c] Five-, six-, and seven-membered oxygen heterocycles and cycloalkenes are formed upon treatment of the appropriate dienes with catalyst **1** (entries 7–11).

Table I. Catalytic Ring-Closing Metathesis of Dienes (2–4 mol % **1**, C_6H_6, 20 °C)

entry		substrate	product	time (h)	yield (%)
1	X = CF_3			1	93
2	Ot-Bu			1	91
3				1	89
4	n = 0			22	78
5	1			6	93
6	2			40	81
7				2	84
8				5	86
9				8	72
10				1	87
11				2	85

Ruthenium carbene 1 is remarkably tolerant of functional groups. In contrast to the previously studied[4b-d] molybdenum catalyst, which is known to react with acids, alcohols, and aldehydes,[9] the ruthenium catalyst is stable to these functionalities. Thus, treatment of the illustrated dienes with **1** leads to clean cyclization to the substituted cyclohexenes (eq 2).



(2)

To our surprise, a preliminary study suggests that **1** is not an effective catalyst for the cyclization of amino dienes; however,

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† Contribution No. 8873.

(1) (a) National Science Foundation Postdoctoral Fellow. Current address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139. (b) Department of Defense NDSEG Predoctoral Fellow.

(2) (a) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960–961. (b) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542–7543.

(3) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.*, following paper in this issue.

(4) (a) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhart, J. D.; Stille, J. R.; Strauss, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733–1744. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325. (d) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801.

(5) Although **1** appears to be stable to air (as a solid), we recommend that it be stored under nitrogen, argon, or vacuum.

(6) Typical experimental procedure(Table I, entry 8): The diene (94 mg, 0.50 mmol) was added to a homogeneous orange-red solution of **1** (9.3 mg, 0.01 mmol) in 15 mL of dry C_6H_6 under argon. The resulting mixture was stirred at 20 °C for 5 h, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air (until greenish-black; 6 h), concentrated, and purified by flash chromatography (0 → 6% Et_2O/hexane), which yielded 69 mg (86%) of the dihydropyran, a colorless oil.

(7) Because the metathesis activity of **1** decreases with increasing steric congestion, ring-closing reactions are most efficient with terminal olefins.

(8) In preliminary work, we have found that **1** also catalyzes the synthesis of *tri*substituted cyclic olefins. Elevated temperatures are required in order to achieve reasonable reaction rates.

(9) (a) Schrock, R. R. *Strem Chem.* **1992**, *14*, 1–6. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899-6907. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

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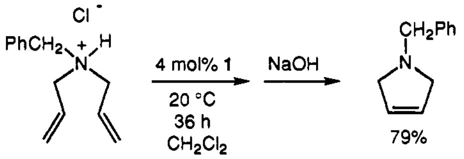
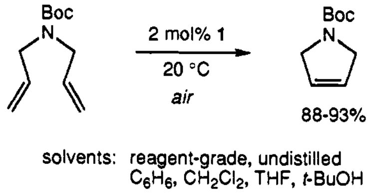
it does effect ring-closing metathesis of the corresponding hydrochloride salts (eq 3),



(3)

Finally, we have observed that *ruthenium carbene 1 can cyclize dienes in the presence of air* in reagent-grade solvents (including *tert*-butyl alcohol). This provides an indication of the relative insensitivity of the reaction to oxygen, moisture, and adventitious impurities (eq 4).[10,11]



(4)

The striking functional-group tolerance of ruthenium complex **1** significantly expands the scope of the ring-closing metathesis process.

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Supplementary Material Available: Characterization data for all reaction products (6 pages). Ordering information is given on any current masthead page.

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(10) Experimental procedure (eq 4): Reagent-grade solvent (5 mL) was added by pipet to a flask (open to air) containing **1** (9.3 mg, 0.01 mmol). *N*-Bocdiallylamine (99 mg, 0.50 mmol) was then added by syringe. The resulting orange-red solution was capped with a septum and stirred at 20 °C for 0.5–1.5 h, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air (until greenish-black; 6 h), concentrated, and purified by flash chromatography, which yielded 75–79 mg (88–93%) of *N*-Boc-3-pyrroline, a colorless oil. *Note*: Although this demonstrates the remarkable tolerance of **1** toward oxygen, moisture, and adventitious impurities, we do not recommend that cyclizations be performed according to this procedure. For the preferred procedure, see ref 6.

(11) In contrast, immediate decomposition is observed upon exposure of solutions of molybdenum alkylidenes to the atmosphere. See also ref 9.