Communications to the Editor

The Application of Catalytic Ring-Closing Olefin Metathesis to the Synthesis of Unsaturated Oxygen Heterocycles

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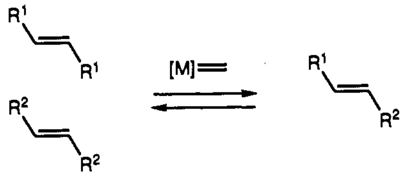
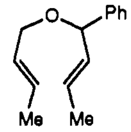
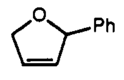
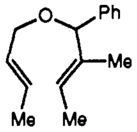
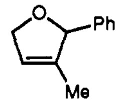
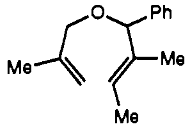
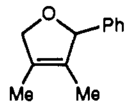
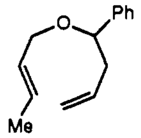
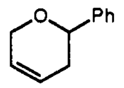
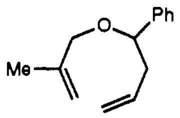
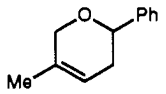
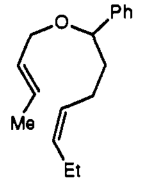
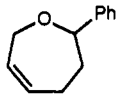
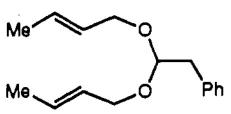
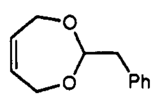
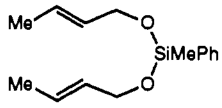
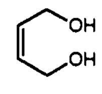
The development of general approaches to carbon–carbon bond formation represents an important ongoing challenge for synthetic organic chemists. One efficient method for constructing carbon–carbon double bonds, the transition metal alkylidene-catalyzed olefin metathesis reaction (eq 1), has been the focus of intense interest in recent years from the standpoint of both mechanism and polymer synthesis;[2] in contrast, use of this transformation in organic synthesis has been limited.[3] As part of a broader program directed toward establishing transition metal alkylidenes as versatile reagents for organic chemistry, we report the successful application of catalytic olefin metathesis to the generation of a variety of unsaturated oxygen heterocycles.[4]



(1)

Our approach to the synthesis of unsaturated oxygen heterocycles involves ring-closing metathesis of a diene–ether[5-8] to generate a cyclic and an acyclic olefin (Scheme I). Entropy (the generation of two molecules from one) and evaporative loss of the low molecular weight acyclic olefin from solution provide the necessary driving force for the desired cyclization. Considerations of activity, functional group tolerance, and availability led us to focus on the use of Mo(CHCMe$_2$Ph)(NAr)(OCMe(CF$_3$)$_2$)$_2$ (Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$, **1**)[9,10] as the metathesis catalyst.

Table I. Catalytic Ring-Closing Metathesis of Diene-Ethers (5 mol % Catalyst, C_6H_6, 20 °C)

Entry	Substrate	Product	Time (min)	Yield (%)
1			15	92
2			15	89
3			180	93
4			15	92
5			15	92
6			240	75
7			60	89
8			120	71[a]

[a] To simplify purification, the cyclic product was treated with *n*-Bu$_4$NF prior to isolation.

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[1] National Science Foundation postdoctoral fellow.

[2] For leading references, see: (a) Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1–74. (b) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907–915. (c) Ivin, K. J. *Olefin Metathesis*; Academic: New York, 1983.

[3] (a) For a review, see: Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.3. (b) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856. Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843–862. (c) For related work, see: Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852. Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647–3650.

[4] For leading references to the synthesis and structure of natural products containing oxygen heterocycles, see: (a) Belen'kii, L. I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1988; Vol. 44, Chapter 4. (b) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984.

[5] Chiral nonracemic building blocks for diene–ethers are readily available. For example, see the following. (a) Allylic alcohols: Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 7, Chapter 3.2. (b) Homoallylic alcohols: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, Chapter 1.1.

[6] We are aware of only one report of successful ring-closing metathesis of a diene–ether (Bogolepova, E. I.; Fridman, R. A.; Bashkirov, A. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, *27*, 2429). In this work, a heterogeneous catalyst is used. No yields are provided.

[7] For reports of metathetical dimerization and polymerization of acyclic olefinic ethers, see: (a) Ast, W.; Rheinwald, G.; Kerber, R. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, M127–M130. (b) Mol, J. C.; Woerlee, E. F. G. *J. Chem. Soc., Chem. Commun.* **1979**, 330–331. (c) Thu, C. T.; Bastelberger, T.; Hocker, H. *J. Mol. Catal.* **1985**, *28*, 279–292. (d) Herrmann, W. A.; Wagner, W.; Flessner, U. N.; Volkhardt, U.; Komber, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1636–1638.

[8] Wagener and Brzezinska have recently reported that *polymerization* occurs when the metathesis of acyclic diene–ethers is conducted in bulk (Wagener, K. B.; Brzezinska, K. *Macromolecules* **1991**, *24*, 5273–5277). In solution, however, ring formation should be favored.

[9] (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. (c) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907.

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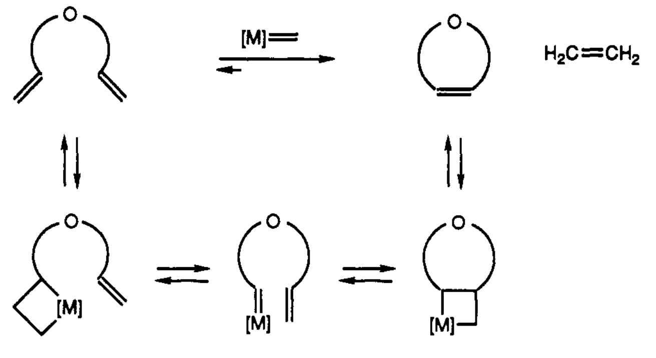
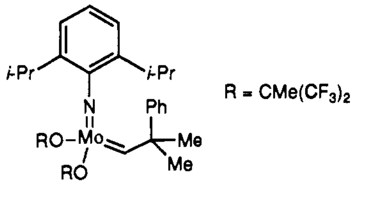
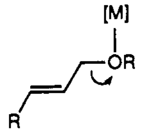
Scheme I



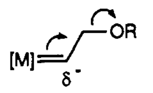


1

Initially, the potential incompatibility of an allylic ether with the metathesis reaction conditions represented a cause for concern. Decomposition of this functionality, as well as the catalyst, has been observed in some olefin metathesis systems, possibly due to Lewis acid activation by the metal (**2**) or to elimination from an alkylidene intermediate (**3**).[11] However, we found that treatment of a diallyl ether with 5 mol % of catalyst **1** at 20 °C affords the desired 2,5-dihydrofuran without complication (Table I, entry 1). The absence of decomposition may be attributable to the relatively low Lewis acidity of **1**, as well as to the short lifetime of **3** due to rapid intramolecular trapping by the tethered olefin.



2



3

The examples provided in Table I illustrate the scope of the catalytic ring-closing metathesis reaction.[12,13] All three olefin substitution patterns have been generated in the case of the 2,5-dihydrofurans (entries 1–3). It is worth noting that formation of the trisubstituted (entry 2) and tetrasubstituted (entry 3) alkenes requires the metathesis of an acyclic *tri*substituted olefin, a process which has not been observed *inter*molecularly with **1**.[9] Catalytic ring-closing metathesis also affords efficient access to dihydropyrans (entries 4 and 5). Entries 6–8 illustrate the synthesis of seven-membered heterocycles and demonstrate the tolerance of the cyclization process to potentially sensitive acetal (entry 7) and silylene (entry 8) functionalities.

Thus, catalytic ring-closing olefin metathesis of diene–ethers provides access to an array of unsaturated oxygen heterocycles from readily available precursors. The application of ring-closing metathesis to the generation of a variety of other cyclic structures, as well as to the stereoselective synthesis of olefins, is currently under investigation.

Acknowledgment. Support has been provided by the National Science Foundation (grant to R.H.G. and postdoctoral fellowship to G.C.F.) and the National Institutes of Health.

Registry No. 1, 139220-25-0; 2-butenyl 1-phenyl-2-butenyl ether, 141412-43-3; 2-butenyl 1-phenyl-2-methyl-2-butenyl ether, 141412-44-4; 2-isobutenyl 1-phenyl-2-methyl-2-butenyl ether, 141412-45-5; 2-butenyl 1-phenyl-3-butenyl ether, 141412-46-6; 2-isobutenyl 1-phenyl-3-butenyl ether, 141412-47-7; 2-butenyl 1-phenyl-4-heptenyl ether, 141412-48-8; 1,1-bis(2-butenoxy)-2-phenylethane, 141412-49-9; bis(2-butenoxy)-methylphenylsilane, 141412-50-2; 2,5-dihydro-2-phenylfuran, 124244-39-9; 2,5-dihydro-3-methyl-2-phenylfuran, 56790-81-9; 2,5-dihydro-3,4-dimethyl-2-phenylfuran, 141412-51-3; 3,6-dichloro-2-phenyl-2*H*-pyran, 126087-54-5; 3,6-dihydro-5-methyl-2-phenyl-2*H*-pyran, 141412-52-4; 2-phenyl-2,3,4,7-tetrahydrooxepin, 54159-34-1; 4,7-dihydro-2-phenyl-1,3-dioxepin, 84473-75-6; *cis*-1,4-dihydroxy-2-butene, 6117-80-2.

Supplementary Material Available: Characterization data for all reaction products (4 pages). Ordering information is given on any current masthead page.

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[10] Catalyst **1** is both air- and moisture-sensitive. It is available from Strem Chemicals, Inc., 7 Mulliken Way, Newburyport, MA.

[11] Levisalles, J.; Rudler, H.; Villemin, D. *J. Organomet. Chem.* **1979**, *164*, 251–257.

[12] Typical experimental procedure (Table I, entry 4): The diene–ether (101 mg, 0.50 mmol) was added to a homogeneous yellow solution of **1** (19 mg, 0.025 mmol) in 13 mL of dry C_6H_6 under argon. The resulting mixture was stirred at 20 °C for 15 min, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by the addition of water, extracted (1 N HCl/Et_2O), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (0 → 7% EtOAc/hexane) yielded 74 mg (92%) of the dihydropyran, a colorless oil. Note: The presence of impurities in the reaction mixture can result in significant inhibition of the ring-closing metathesis process.

[13] Preliminary experiments indicate that cyclization also proceeds smoothly in CH_2Cl_2, whereas coordinating solvents such as THF appear to be less suitable. The tungsten analogue of **1** (Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423–1435) and $W(CHAr')(NAr)[OCMe(CF_3)_2]_2(THF)$ (Ar' = o-$MeOC_6H_4$, Ar = 2,6-(i-$Pr)_2C_6H_3$) (Johnson, L. K.; Virgil, S. C.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 5384–5385) also catalyze ring closure; however, in cyclizations in which the low molecular weight olefin generated is not 1,2-disubstituted, the formation of relatively stable tungsten metallacycles appears to inhibit metathesis. Attempts to use ill-defined, "classical" metathesis catalysts (e.g., $WCl_6/SnMe_4$) to effect the reaction have thus far been unsuccessful.

Amide Cuprate Reagents as a New Class of Nitrogen Nucleophiles. Application to Asymmetric Synthesis of β-Lactams[†]

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Nitrogen anions R_2N^- are commonly used as strong bases for deprotonation of organic compounds. However, nucleophilic reactions of R_2NM, such as conjugate addition to enoates, have received little attention.[1] We report that cuprates $(R_2N)_2CuLi$ and higher order cyano cuprates $(R_2N)_2Cu(CN)Li_2$ are useful for asymmetric 1,4-addition to enoates[2] and that a highly efficient chiral synthesis of β-lactams is realized by the conjugate addition of these reagents followed by trapping with aldehydes (three-component coupling)[3] (eq 1).

Regioselectivities in the reaction of **1** with R^3R^4NM are summarized in Table I. The reaction of **1a** with the copper reagent gave **2** with relatively good 1,4-regioselectivity (entries 1 and 2)

[†] This paper is dedicated to Professor Emeritus Herbert C. Brown on the occasion of his 80th birthday.

[1] Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, 4249. Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Ibid.* **1973**, 2433. Little, R. D.; Dawson, J. R. *Ibid.* **1980**, *21*, 2609. Hase, T. A. Kukkola, P. *Synth. Commun.* **1980**, *10*, 451.

[2] "Higher order" indicates that the stoichiometry of R_2N, Cu, CN, and Li is 2:1:1:2, and it does not mean that the copper species possesses the structure $(R_2N)_2Cu(CN)Li_2$. CuI was used as a source of Cu for $(R_2N)_2CuLi$, and CuCN was used for $(R_2N)_2Cu(CN)Li_2$. For discussions on higher order cyano cuprates, see: Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *Ibid.* **1990**, *112*, 4032.

[3] To our knowledge, a three-component coupling approach to β-lactam synthesis has not been examined although a number of synthetic methods have been reported. For a review, see: (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (b) Brynaert, J. M.; Ghosez, L. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Springer-Verlag: Berlin, 1990.

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