only in radicals like **9**, where phosphate is a good ionic leaving group, the C,O bond cleavage can compete with the hydrogen abstraction from benzenethiol. In radical **12**, with benzoate as a less effective ionic leaving group, cleavage of the C,O bond was not observed. This is in accord with the suggestion by Schulte-Frohlinde[4,10] that a phosphate group β to a radical center is cleaved off via a heterolytic C,O bond dissociation. Radicals **5a** and **9** should then lead to radical cation **14** that yields enol ether **6a** via a single electron transfer[11] from benzenethiol.[12]

Acknowledgment. This work was supported by the Swiss National Foundation.

Supplementary Material Available: Characterization data (^{1}H and ^{13}C NMR, MS, elementary analysis) for **3c**, **4a,b**, **6a**, **7a,b**, **8**, **10**, **11**, and **13a,b** and pseudo-first-order plot of the product ratio **6a/10** against 1/[PhSH] (5 pages). Ordering information is given on any current masthead page.

(4) For a review, see: Von Sonntag, C.; Hagen, U.; Schön-Bopp, A.; Schulte-Frohlinde, D. *Adv. Rad. Biol.* **1981**, *9*, 109.

(5) The 5′-deoxy-4′,5′-didehydronucleosides **4a,b**, **8**, and **11** were synthesized from their 5′-arylselenides via oxidative elimination using the following procedure: Takaku, H.; Nomoto, T.; Kimura, K. *Chem. Lett.* **1981**, 1221.

(6) In a typical procedure 1 mmol of the 5′-deoxy-4′,5′-didehydronucleoside **4a,b** or **8** in 10 mL of degassed (3 freeze–thaw cycles) methanol/water (10:1) was treated with 2–20 mmol of benzenethiol at 30 °C under irradiation (UV, Hanovia lamp) for 1 h. Alternatively di-*tert*-butyl hyponitrite was used as a thermal radical initiator at 30 °C. In the absence of light or di-*tert*-butyl hyponitrite no reaction occurred with **4a** or **8** within 20 h. This is a strong indication that benzenethiyl radicals are involved. An alternative source of these radicals is photolysis of diphenyl disulfide. In the absence of light this disulfide did not react with nucleotides **4a** and **8**. But under photolytic conditions product **6a** was formed in 50% yield.

(7) A heterogeneous mixture of 8.6 mg of enol ether **6a** and 1.0 mL water was stirred at 30 °C for 24 h. This led to ketoaldehyde **3c** in 95% yield. The structure of **3c** was proved by independent synthesis. A homogeneous solution of **6a** in methanol/water (10:1) under slightly acidic conditions (pH = 3) led to solvolysis product **3c** with a half-life time of 15 min.

(8) A toluene solution (1.0 mL) of 0.1 mmol of **8** and 0.5–5.0 mmol of benzenethiol was irradiated at 30 °C for 1 h under nitrogen. The product ratio **6a/10** was determined by HPLC with a reproducibility of ±10%. The plot of **6a/10** against 1/[PhSH] gave a linear correlation with a correlation coefficient r = 0.986.

(9) (a) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268. (b) Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603.

(10) Methoxyalkyl radicals with a neutral β-phosphate group cleave the β-C,O-bond with rates of about 10^6 (20 °C, H_2O). The respective phosphate monoanion is cleaved 10^3 times slower: Behrens, G.; Koltzenburg, G.; Ritter, A.; Schulte-Frohlinde, D. *Int. J. Radiat. Biol.* **1978**, *33*, 163. See, also: Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. *J. Am. Chem. Soc.* **1982**, *104*, 7311.

(11) Cyclic voltammetry of the enol ether **6a** [5 mM in acetonitrile/0.1 M $(n\text{-Bu})_4NBF_4$] gave a redox potential on a platinum electrode of 1.54 V (vs Ag/AgCl, 20 °C, scan rate 0.2 V s^{-1}).

(12) An alternative route, that is reduction of radicals **9** and **12**, respectively, to anions by benzenethiol can be excluded, because this should also lead to C,O-bond cleavage of the benzoylated radical **12**.

Synthesis of Nitrogen Heterocycles via Catalytic Ring-Closing Metathesis of Dienes

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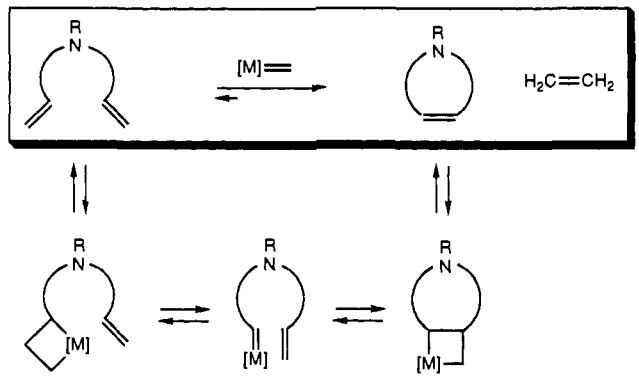
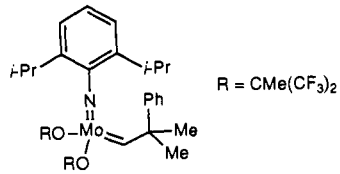
Because alkaloids represent a significant subset of all biologically-active compounds,[2] the development of general new methods for their construction remains an important goal of organic synthesis. We have recently described an approach to the generation of unsaturated ethers based upon transition metal alkylidene-catalyzed ring-closing olefin metathesis.[3-5] In this communication, we report the surprisingly successful application of this cyclization process to the synthesis of a variety of nitrogen heterocycles.

Scheme I



The catalytic ring-closing olefin metathesis strategy is illustrated in Scheme I for the synthesis of unsaturated nitrogen heterocycles from acyclic diene–amines. To the best of our knowledge, there is no precedent for this transformation, perhaps due in part to the fact that the metathesis of olefinic amines has been problematic; the few systems that are known to metathesize this class of compounds are characterized by low yields (<60%), low turnovers (≤5), and limited scope.[6] Attempts to metathesize olefinic amides have been even less successful.[7] In contrast, we have found that $Mo(CHCMe_2Ph)(NAr)(OCMe(CF_3)_2)_2$ (Ar = 2,6-(i-Pr)$_2$C$_6$H$_3$, **1**)[8,9] efficiently catalyzes the cyclization of a range of dienes to afford the desired nitrogen heterocycles.



1

The generality of the catalytic ring-closing metathesis reaction is illustrated in Table I.[10,11] Pyrrolines in which the olefin is either di- or trisubstituted form readily upon treatment of diallylamines with 4 mol % **1** at 20 °C (entries 1 and 2). Tetrahydropyridines

(1) National Science Foundation Postdoctoral Fellow.

(2) For leading references to the synthesis and structure of natural products containing nitrogen heterocycles, see: (a) *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Cordell, G. A., Eds.; Academic: New York, 1992. (b) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1988. (c) Belen'kii, L. I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1988; Vol. 44, Chapter 4. (d) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984.

(3) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.

(4) Reviews of olefin metathesis: (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.

(5) Review of 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.

(6) For an overview, see: Edwige, C.; Lattes, A.; Laval, J. P.; Mutin, R.; Basset, J. M.; Nouguier, R. *J. Mol. Catal.* **1980**, *8*, 297–311.

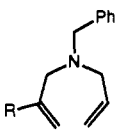
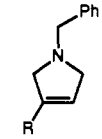
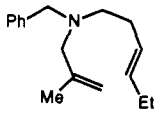
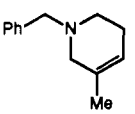
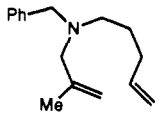
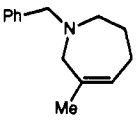
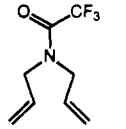
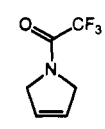
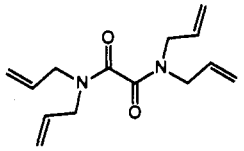
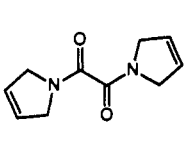
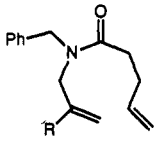
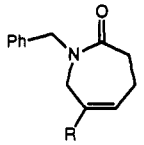
(7) For example, see: Levisalles, J.; Rudler, H.; Cuzin, D.; Rull, T. *J. Mol. Catal.* **1984**, *26*, 231–238.

(8) (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.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907. (c) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495–4502. (d) Wagener, K. B.; Brzezinska, K.; Bauch, C. G. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 75–81.

(9) Catalyst **1** is both air- and moisture-sensitive. For details regarding its preparation, see: (a) Reference 8. (b) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287–2289.

0002-7863/92/1514-7324$03.00/0

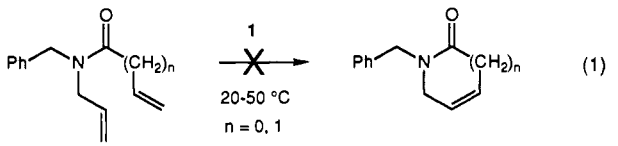
Table I. Catalytic Ring-Closing Metathesis of Dienes (4 mol % Catalyst, C_6H_6, 20 °C)

entry	substrate	product		time (min)	yield (%)
1			R = H	40	86
2			Me	180	85
3				60	86
4				60	73
5				15	83
6				15	89
7			R = H	90	87
8			Me	150 [a]	81

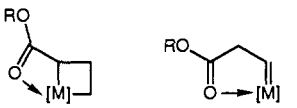
[a] This reaction was run at 50 °C.

(entry 3) and tetrahydroazepines (entry 4) are also generated efficiently. Amides, too, are compatible with these metathesis conditions. Single and double cyclizations to form *N*-acyl-3-pyrrolines proceed smoothly within minutes at room temperature (entries 5 and 6). Finally, ring closure to form unsaturated seven-membered lactams can be effected in good yield (entries 7 and 8).

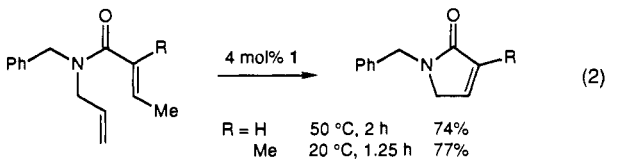
Our initial attempts to synthesize unsaturated five- and six-membered lactams were unsuccessful (eq 1). Earlier work has shown that complexes such as **1** are not effective metathesis catalysts for the dimerization of methyl acrylate and methyl 3-butenoate, apparently due to the formation of stable chelated species such as **2** and **3**.[12] Generation of the corresponding amide chelates might account for our failure to observe cyclization (eq 1). We reasoned that because metathesis of monosubstituted olefins by **1** is known to be more rapid than that of disubstituted olefins, addition of an alkyl substituent to the appropriate double bond might disfavor formation of the undesired intermediates. In practice, this strategy proved successful (eqs 2 and 3), affording the desired lactams.



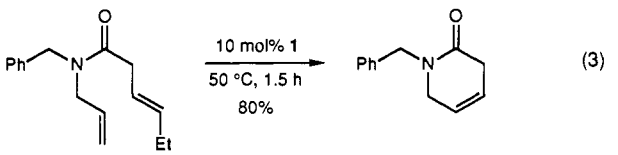
(1)



2 **3**



(2)



(3)

Catalytic ring-closing metathesis of dienes provides an efficient route to a range of unsaturated nitrogen heterocycles from readily available precursors. The application of this reaction to the synthesis of alkaloid natural products 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.

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

(10) Typical experimental procedure (Table I, entry 3): The diene–amine (122 mg, 0.50 mmol) was added to a homogeneous yellow solution of **1** (15 mg, 0.020 mmol) in 17 mL of dry C_6H_6 under argon. The resulting mixture was stirred at 20 °C for 60 min, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air, concentrated, and purified by flash chromatography (0 → 25% EtOAc/hexane), which yielded 81 mg (86%) of the tetrahydropyridine, a colorless oil. *Note*: Impurities in the reaction mixture (e.g., water or acids) can result in significant inhibition of the ring-closing metathesis process.

(11) The reaction also proceeds smoothly in CH_2Cl_2, whereas use of a coordinating solvent such as THF results in a slower reaction. A preliminary screening of other metathesis catalysts, both well-defined and "classical", indicated that **1** is the catalyst of choice for effecting cyclization.

(12) (a) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260–2265. (b) Wu, Z.; Paciello, R. A.; Grubbs, R. H. Unpublished results.