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Synthesis of Cycloalkenes via Alkylidene-Mediated Olefin Metathesis and Carbonyl Olefination[†]

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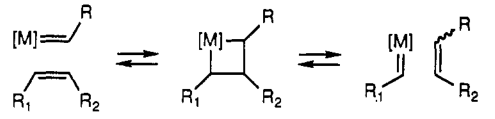
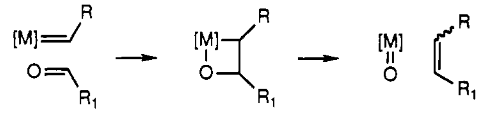
The development of efficient methods for constructing carbocycles continues to be an important goal of synthetic organic chemistry.[2] One extremely useful approach to the formation of unsaturated carbocycles is the intramolecular dicarbonyl coupling reaction (eq 1).[3] Oftentimes, the substrate employed in this process is generated by oxidation of a diene or of an olefinic ketone.[4] In this communication, we report that transition-metal alkylidenes effect the direct synthesis of unsaturated carbocycles from either of these precursors (eqs 2 and 3).

X = Y = O	intramolecular dicarbonyl coupling	(1)
X = Y = C	catalytic ring-closing olefin metathesis	(2)
X = C, Y = O	(olefin metathesis)-(carbonyl olefination)	(3)

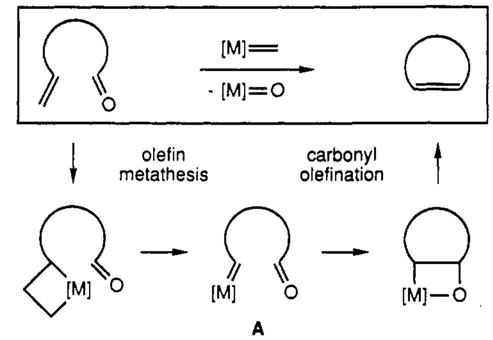


(4)

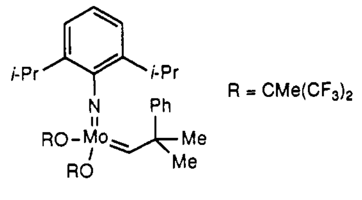


(5)

Scheme I



Our strategy for the synthesis of cycloalkenes from olefinic ketones (eq 3) exploits sequentially two distinct processes mediated by transition-metal alkylidenes, olefin metathesis (eq 4)[5] and carbonyl olefination (eq 5).[6] We envisioned that treatment of an olefinic ketone with an alkylidene would afford a new alkylidene, via olefin metathesis, bearing a pendant carbonyl group (**A**, Scheme I). This intermediate would then undergo intramolecular carbonyl olefination, thereby producing the target cycloalkene.[7,8] Clearly, such a sequence requires an alkylidene which metathesizes olefins more rapidly than it olefinates ketones. Molybdenum alkylidene **1** [$Mo(CHCMe_2Ph)(NAr)(OCMe(CF_3)_2)_2$, Ar = 2,6-$(i\text{-}Pr)_2C_6H_3$][9] displays the necessary reactivity profile, since it efficiently metathesizes acyclic mono- and disubstituted alkenes at 20 °C, whereas it olefinates ketones only at elevated temperatures. As illustrated in Table I, this olefin metathesis-carbonyl olefination strategy has proved to be an effective, general method for synthesizing unsaturated five-, six-, and seven-membered rings.[10,11] It is worth noting that α-oxygenation is not compatible with dicarbonyl coupling reactions involving low-valent titanium reagents.[3]



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Although our initial attempts to extend this process to the generation of cyclic enol ethers from acyclic olefinic esters have been unsuccessful with molybdenum alkylidene **1**,[12] in preliminary work we have established that its more reactive tungsten analogue, [$W(CHCMe_3)(NAr)(OCMe(CF_3)_2)_2$, Ar = 2,6-$(i\text{-}Pr)_2C_6H_3$; **2**][13]

[†] Contribution No. 8781.

[1] National Science Foundation Postdoctoral Fellow.

[2] For example, see: Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH: New York, 1988.

[3] McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524.

[4] For example, see: (a) Diene: Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615–3636. (b) Olefinic ketone: Clive, D. L. J.; Zhang, C.; Murthy, K. S. K.; Hayward, W. D.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 6447–6458.

[5] 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) Feast, W. J.; Gibson, V. C. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; Wiley: New York, 1989; Vol. 5, Chapter 6. (d) Ivin, K. J. *Olefin Metathesis*; Academic: New York, 1983.

[6] Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.3.

[7] For a review of the synthesis of cycloalkenes via intramolecular Wittig reactions, see: Becker, K. B. *Tetrahedron* **1980**, *36*, 1717–1745.

[8] We are aware of only one report of alkylidene-mediated cyclization of olefinic carbonyls via an olefin metathesis-carbonyl olefination sequence: Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856. The scope of this titanium alkylidene-mediated process is limited to highly strained olefins and very hindered esters. For a discussion, see: Stille, J. R.; Santasiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843–862.

[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.; 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) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287–2289. (e) Schrock, R. R. *Strem Chem.* **1992**, *14*, 1–6.

[10] Typical experimental procedure (Table I, entry 2): the substrate (35 mg, 0.13 mmol) was added to a homogeneous yellow solution of **1** (100 mg, 0.13 mmol) in 12 mL of dry C_6H_6 under argon. The resulting mixture was stirred at 20 °C for 30 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 → 7% EtOAc/hexane), which yielded 27 mg (84%) of the substituted cyclohexane, a colorless oil.

[11] Preliminary results indicate that commercially available [$Mo(CHCMe_2Ph)(NAr)(OCMe_3)_2$, Ar = 2,6-$(i\text{-}Pr)_2C_6H_3$] (ref 9) (Strem Chemicals, Inc., 7 Mulliken Way, Newburyport, MA), although less reactive than **1**, also mediates the cyclization of dienes and olefinic ketones. Increased rates are observed upon addition of lithium or potassium hexafluoro-*tert*-butoxide to the reaction mixture.

[12] France, M. B, unpublished results. See also Table II, entry 3.

[13] (a) 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. (b) 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*, 2262–2275.

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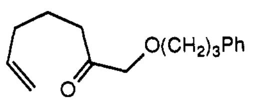
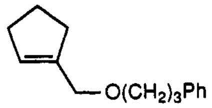
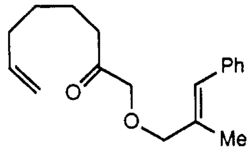
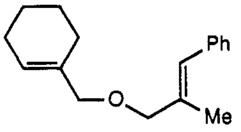
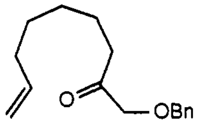
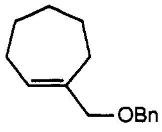
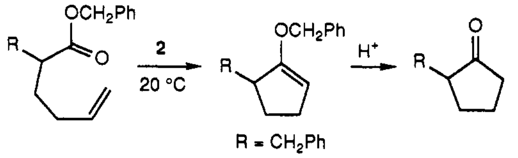
Table I. Olefin Metathesis-Carbonyl Olefination (1.0 equiv of **1**, C_6H_6, 20 °C, 30 min)

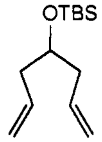
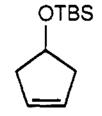
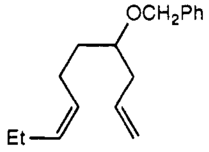
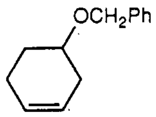
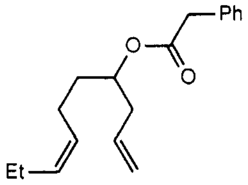
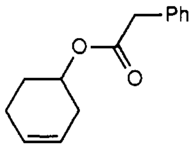
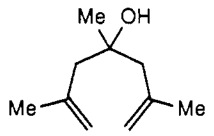
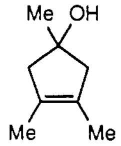
entry	substrate	product	yield (%)
1			86
2			84
3			86

does effect the desired olefin metathesis-carbonyl olefination sequence with this class of substrates (eq 6).


(6)

In a complementary study, we have documented the application of molybdenum alkylidene-catalyzed ring-closing diene metathesis[14] to the synthesis of functionalized cycloalkenes (eq 2). Other workers have reported the cyclization of unfunctionalized olefins; however, the metathesis catalysts employed were typically "classical" systems with a low tolerance for heteroatoms.[5] We have established that alkylidene **1** efficiently catalyzes the ring closure of functionalized dienes to afford cycloalkenes in good yield (2 mol % **1**, 20 °C; Table II).[15] Groups commonly encountered in synthesis, such as silyl ethers (entry 1), benzyl ethers (entry 2), and carboxylic esters (entry 3), are stable to the reaction conditions. The ring-closing olefin metathesis illustrated in entry 4 is particularly interesting in light of the sensitivity of **1** to alcohols.[9e,16]

Table II. Catalytic Ring-Closing Metathesis of Dienes (2 mol % **1**, C_6H_6, 20 °C, 15–30 min)

entry	substrate	product	yield (%)
1			91
2			89
3			85
4[a]			84

[a] 4 mol % catalyst was used.

Further investigation of the scope of these and related cyclization processes is underway.

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

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[14] (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.

[15] Typical experimental procedure (Table II, entry 2): the diene (122 mg, 0.50 mmol) was added to a homogeneous yellow solution of **1** (8 mg, 0.01 mmol) in 17 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 exposure to air, concentrated, and purified by flash chromatography (0 → 5% EtOAc/hexane), which yielded 84 mg (89%) of the substituted cyclohexene, a colorless oil. Note: The reaction also proceeds smoothly in CH_2Cl_2.

[16] A preliminary investigation suggests that this may be an example of a hydroxyl-directed olefin metathesis reaction. The range of hydroxyl-substituted dienes that will efficiently undergo cyclization will likely be limited to those in which the hydroxyl group is proximal to the olefins.