A Ruthenium-Catalyzed Alkylative Cycloetherification

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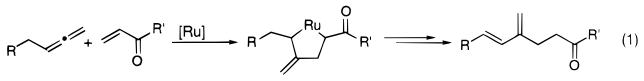
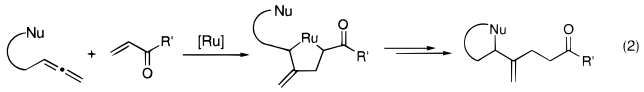
In the course of our studies in the ruthenium-catalyzed formation of 1,3-dienes from allenes,[1] we postulated a mechanism involving a ruthenacycle. This ruthenacycle, which possesses a σ-bound Ru-allyl, then undergoes a β-hydrogen elimination to form the 1,3-diene (eq 1). The suggested presence of the



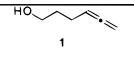
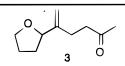
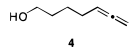
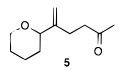
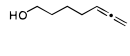
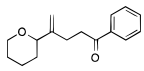
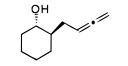
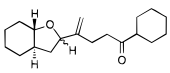
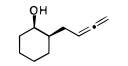
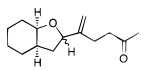
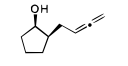
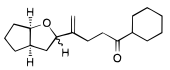
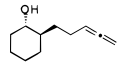
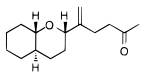
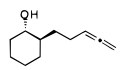
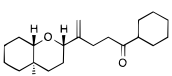
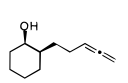
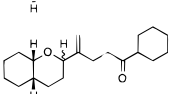
allylruthenium moiety raises the question of whether it can serve in allylmetal chemistry that is typified by allylpalladium complexes.[2] While ruthenium-catalyzed allylic substitutions are relatively unknown,[3] the few reports encourage the exploration of the feasibility of the process. The goal of this study was to intercept the proposed Ru-allyl complex with a tethered nucleophile to generate heterocycles with concomitant C−C bond formation in a catalytic fashion (eq 2) faster than the β-hydrogen



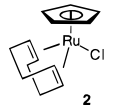
elimination. In this paper we report the successful realization of this concept with oxygen as the nucleophile to form cyclic ethers,[4] which constitutes a more atom economical approach[5] to generate ruthenium allyl complexes by an addition reaction[6] as well as establish mechanistic support for the involvement of allylruthenium intermediates in the addition to allenes.

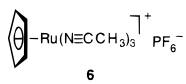
In our initial studies, we examined the reaction of allene **1** with MVK (methylvinyl ketone) catalyzed by 10 mol % **2**[7] and 15 mol % $CeCl_3 \cdot 7H_2O$ in the presence of 3-hexyn-1-ol as a promoter. The addition proceeded at 60 °C in DMF for 6 h to give a 78% yield of the alkylative cycloetherification product **3** (Table 1, entry 1).[8] A similar result was obtained with allene **4** wherein a 72% yield of the tetrahydropyran **5**[8] was obtained. In these reactions, the role of the promoter, 3-hexyn-1-ol, is to generate coordinatively unsaturated ruthenium by reacting the COD off of the ruthenium.[9] In considering an alternative, we were attracted to ruthenium complex **6**[10] provided the acetonitrile could serve as a reasonably easily dissociable ligand. Indeed, exposing allenes **1** and **4** to 10 mol % complex **6** and 15 mol % $CeCl_3 \cdot 7H_2O$ in DMF at 60 °C led to formation of the desired products within 2 h in 82% and 74% yields, respectively. The higher reactivity with equivalent or higher yields obtained with the acetonitrile complex **6** induced us to use this complex for the subsequent reactions as summarized in eq 3 and Table 1.

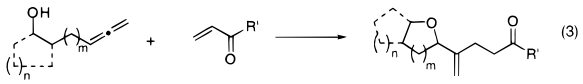
Table 1. Some Examples of Ruthenium-Catalyzed Alkylative Cycloetherification[a]

Entry	Allene	R′	Catalyst	Product	Isolated Yield
1		-CH_3	**2**		78
			6		82
2		-CH_3	**2**		72
			6		74
3			**6**		70
4			**6**		62
5		-CH_3	**6**		68
6			**6**		72
7		-CH_3	**6**		67 dr=2.5/1
8			**6**		73 dr=3.3/1
9			**6**		61

[a] All denoted stereochemistry is relative.







As shown, a wide range of cyclic ethers can be formed. Both tetrahydrofurans (entries 1, 4, 5, 6) and tetrahydropyrans (entries 2, 3, 7−9) are formed in excellent yield. Entries 1−3 illustrate the ability of primary alcohols to serve as nucleophiles, and entries 4−9 demonstrate that secondary alcohols participate equally well. Interestingly, both 6,5-trans (entry 4) and 6,5-cis (entry 5) ring systems are accessible, but only 5,5-cis bicyclic ethers (entry 6). As anticipated, a 5,5-trans bicyclic system (i.e. a trans bicyclo-[3.3.0]octane system) does not form presumably due to excessive

(1) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4068.
(2) For a review, see: Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 3.3, pp 585−662.
(3) Kang, S.-K.; Kim, D.-Y.; Hong, R.-K.; Ho, P. S. *Synth. Commun.* **1996**, *26*, 3225. Zhang, S.-W.; Mitsuto, T.-A.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, *450*, 197. Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269.
(4) For a review, see: Alvarez, E.; Candenas, M.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953.
(5) Trost, B. M. *Science* **1991**, *254*, 1471.
(6) For some examples of Pd-catalyzed bond formation to the central carbon of allenes see: Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816. Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. Larock, R. C.; Veraprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. Alper, H.; Hartstock, F. W.; Despeyroux, B. *Chem. Commun.* **1984**, 905. Gamez, P.; Ariente, C.; Cazes, B.; Goré, J. *Tetrahedron* **1998**, *54*, 14835. Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85. For a Ru-catalyzed example see: Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. *Synlett* **1995**, 1181.
(7) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.
(8) All new compounds have been satisfactorily characterized spectroscopically and elemental composition established by high-resolution mass spectrometry and/or combustion analysis.
(9) Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831.
(10) Gill, T. B.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

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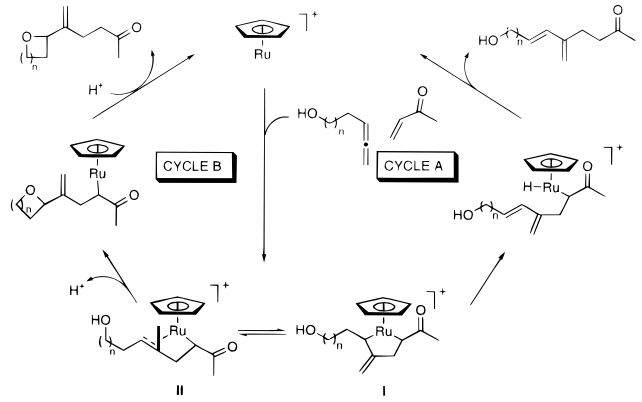
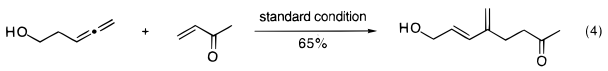
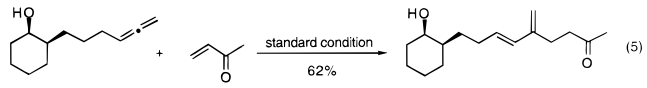
Scheme 1. Mechanistic Rationale



ring strain. Similarly, both trans (entries 7 and 8) and cis (entry 9) 6,6-bicyclic systems form readily. In the case of 6,6-trans bicyclic ethers (entries 7 and 8), moderate diastereoselectivity was observed. All the products are readily characterized in the ^{1}H NMR spectra by the absorptions for the terminal methylene unit ($\sim\delta$ 5) and the allylic methine next to oxygen ($\sim\delta$ 4.8).

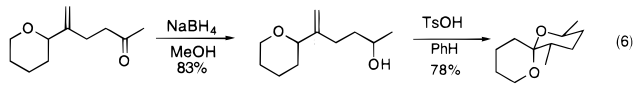
While the reaction appears to be rather general with respect to five- and six-membered ring formation, it does not extend to either four- or seven-membered ring formation. For example, as shown in eqs 4 and 5, only the normal addition to form dienes occurs.





The current results provide circumstantial evidence in support of the mechanistic proposal outlined in Scheme 1. The ruthenacycle I becomes the pivotal intermediate.[11] The facility of β-hydrogen elimination versus the nucleophilic attack determines product formation. In the absence of any internal nucleophile, cycle A dominates. On the other hand, the presence of a free hydroxyl group juxtaposed such that either a five- or six-membered cyclic ether can form allows cycle B to dominate.[12] Furthermore, cycle A dominates when $n = 1$ (a four-membered ring) or when $n = 4$ (a seven-membered ring) in I presumably because the rate of the cyclization is too slow relative to the β-hydrogen elimination. At this point, we cannot differentiate whether a σ- (i.e. I) or π- (i.e. II) allylruthenium species is involved. While alternative mechanisms, such as a ruthenium-catalyzed addition to the allene followed by reaction with the vinyl ketone, exist,[13,14] the absence of detailed mechanistic information dissuades us from making further speculations. At present, Scheme 1 represents a productive working hypothesis.

In conclusion, this reaction provides a catalytic, atom economical approach to cyclic ethers, a subunit present in many biologically significant natural products.[4] Furthermore, it opens up the exciting prospect of generating allylic ruthenium species from unactivated allenes and enones via ruthenacycle formation. This could then lead to methods to form a large array of heterocyclic as well as carbocyclic compounds. Finally, the compounds produced herein can lead to spiroketals. For example, reduction of the ketone followed by acid-catalyzed double bond isomerization and cyclization leads to a spiroketal (dr 3:1) as depicted in eq 6. Asymmetric reduction then leads to enantioenriched



spiroketals. Current work that is underway consists of extending the scope of cyclic ether formation, as well as efforts to use other nucleophiles.

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Supporting Information Available: Typical experimental procedures and characterization for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Cf.: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492. Mitsudo, T.; Zhang, S.; Nagao, M.; Watanabe, Y. *Chem. Commun.* **1991**, 598.

(12) For some examples using tethered nitrogen, oxygen, and carbon nucleophiles in Pd-catalyzed reactions with allenes see: Larock, R. C.; Veraprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85. Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156.

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