Ruthenium-Catalyzed Cycloisomerization of 1,6-Enynes Initiated by C−H Activation

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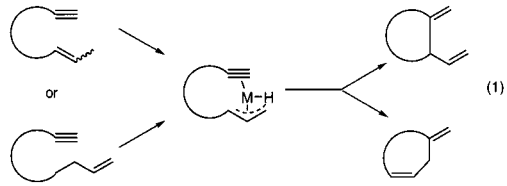
Received June 14, 1999

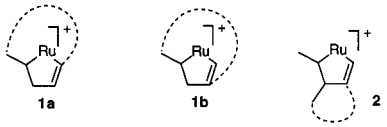
Cycloisomerizations of 1,6-enynes with a variety of transition metal catalysts are a growing class of reactions to form cyclopentyl rings.[1−4] Among the mechanisms that have been postulated are included (1) initial hydrometalation of the alkyne followed by carbametalation of the alkene,[2] (2) initial formation of a metalocyclopentene followed by β-hydrogen elimination,[3] (3) initial formation of a metalocyclopentene followed by reductive elimination to a cyclobutene and conrotatory cycloreversion,[4] and (4) a metal alkylidene.[5] An alternative mechanism envisions metal-promoted allylic C−H activation as the initiation step (eq 1).[6] Such a process provides access to C−C bond formation not



(1)

possible with the existing cycloisomerization catalysts and, therefore, complements those methods. We wish to report that a ruthenium-catalyzed cycloisomerization of enynes proceeds via the C−H activation pathway and provides ready access to seven-membered rings instead of the normally obtained five-membered rings.

In our initial work, attempts to convert intermolecular Ru-catalyzed Alder ene-type additions, which proceed via a ruthenacyclopentene intermediate, to intramolecular ones to generate five- or six-membered rings failed. Considering the mechanism, the fact that, with cyclopentadienyl (1,5-cyclooctadiene) ruthenium chloride complex, only monosubstituted alkenes are satisfactory partners,[7] and the nature of the required intermediate **1**, wherein the alkene substituent must be on the carbon attached to ruthenium, any intramolecular reaction requires a 1,3-bridging as in **1a** or **1b**—a type of bridging that cannot be accommodated by short tethers. We[8] recently discovered that use of cyclopentadienyl



1a **1b** **2**

(tris-acetonitrile) ruthenium hexafluorophosphate (**3**)[9] as the catalyst allows accommodation of 1,2-disubstituted alkenes, which should permit cyclizations to normal ring sizes via ruthenacycles such as **2** (see Scheme 1, cycle A). Indeed, subjecting enyne **4a** to this catalyst in acetone at room temperature affords the anticipated 1,4-diene **5a**[10] as a 3:1 mixture of diastereomers (major one depicted). This product may arise via one of the "normal" mechanisms such as the ruthenacyclopentene intermediate (R = H). On the other hand, the related substrate **4b** generates a strikingly different product, the seven-membered ring **6b**,[10,11] either in DMF or in acetone, in 67% yield as the major cyclization product with **5b** only a minor product (10% yield). This cycloheptene must form via a C−H activation path to form intermediate C such as illustrated in cycle B of Scheme 1.[12] The change in reaction course may be attributed to steric congestion in the tautomerization of the initial enyne ruthenium complex A in forming B due to disfavored $A_{1,3}$-type strain between the quarternary center and the ester.

As summarized in Table 1, the reaction has generality. In all cases, except entry 1, only the cycloheptene product was observed. The reaction requires the quaternary center at the propargylic position to be channeled into the allylic C−H activation pathway. However, the substituents can be quite varied, including *gem*-alkyl (entries 4 and 6) and ketals (entry 5) as well as alkyl and oxygen (entries 1−3 and 7). The alkene substitution appears reasonably general—both 1,2-*cis*-di- and trisubstituted alkenes participate. The severe steric encumbrance, as present in entry 4, does not prevent the reaction. The acetylenic ester is required. Replacing the ester by a simple sterically demanding substituent like a trimethylsilyl group led to recovered starting material. The chemoselectivity of entry 7 is particularly noteworthy since a π-allylruthenium complex could be generated at either double bond, and generation of such a species at the double bond near the terminus should be preferred for steric reasons. This example supports the notion that bidentate coordination in the initial complex A is required for reaction.

Substrates bearing *cis*-1,2-disubstituted alkenes such as shown in entries 2 and 3 participated extremely well. In contrast, *trans*-1,2-disubstituted alkenes normally gave complex mixtures. This dichotomy raised the question as to why trisubstituted alkenes react well. A *trans*-alkene initially forms a *syn*-π-allyl complex **7** and a *cis*-alkene an *anti* one **8**. Only the latter can lead to a seven-membered ring. To the extent **7** would cyclize, it must form

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(5) Ru: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

(6) (a) Cf.: Itoh, K.; Masuda, K.; Ikeda, H. *Organometallics* **1993**, *12*, 2752. (b) However, such reactions are not common in Ru, see: Bennett, M. A.; Khan, K.; Wenger, E. In *Comprehensive Organometallic Chemistry II*; Shriver, D. F., Bruce, M. I., Eds.; Elsevier: New York, 1995; Vol. 7, Chapter 8, pp 509−511. (c) Such reactions are common with Pd, see: Davies, J. A. In *Comprehensive Organometallic Chemistry II*; Shriver, D. F., Bruce, M. I., Eds.; Elsevier: New York, 1995; Vol. 9, Chapter 6, pp 331−340.

(7) Trost, B. M.; Indolese, A.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. Trost, B. M.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 615.

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(9) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

(10) This compound has been characterized spectroscopically and elemental composition established by high-resolution mass spectroscopy or combustion analysis.

(11) The geometry of the enoate was established by NOEs as well as observed chemical shifts. It is not what would arise from a direct reductive elimination of the initial carbametalated intermediate. This geometry may derive by equilibration via the O-ruthenium enolate and faster reductive elimination of the alternate C-bond ruthenium enolate to give the more stable product.

(12) For the intramolecular addition of π-allylpalladium and -nickel to alkynes, see: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 1.2.

10.1021/ja991977a CCC: $18.00
Published on Web 10/04/1999

Scheme 1

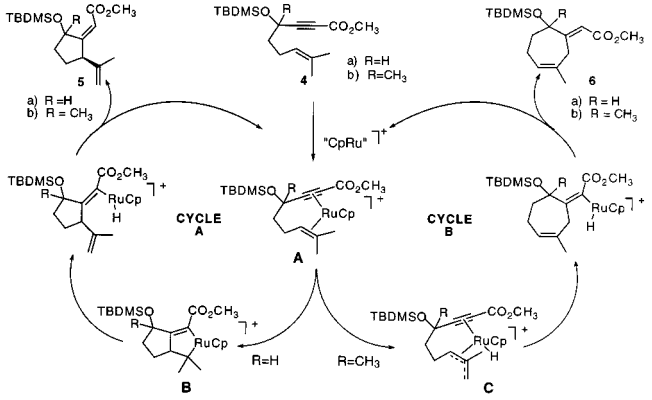
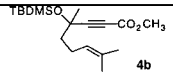
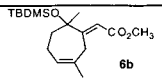
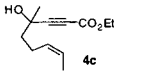
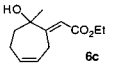
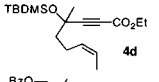
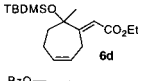
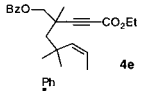
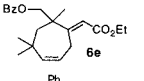
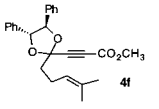
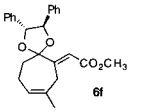
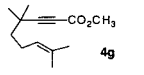
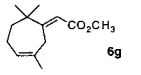
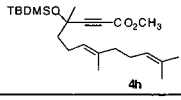
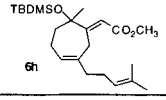
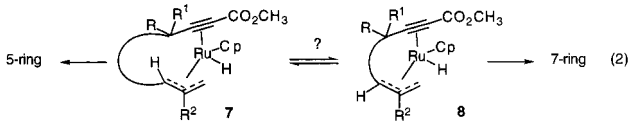


Table 1

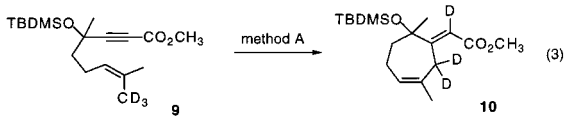
Entry	Substrate	Product	Method[a]	Time	Yield
1	 4b	 6b	A	4h	67%[b]
2	 4c	 6c	A	4h	77%
3	 4d	 6d	B	4h	83%
4	 4e	 6e	B	6h	65%
5	 4f	 6f	A	6h	77%
6	 4g	 6g	A	6h	62%
7	 4h	 6h	B[c]	6h	53

[a] A = 10% $CpRu(CH_3CN)_3PF_6$, 0.1 M acetone, room temperature. B = 10% $CpRu(CH_3CN)_3PF_6$, 0.1 M DMF, room temperature. [b] The 1,4-diene product **5b** was also isolated in 10% yield. [c] Run at 60 °C.

a five-membered ring, which, as we already indicated, would be greatly disfavored. The fact that we also do not obtain the seven-membered ring from *trans*-alkenes raises questions about the rate of any *syn*−*anti* interconversions (eq 2). In the case of trisubsti-

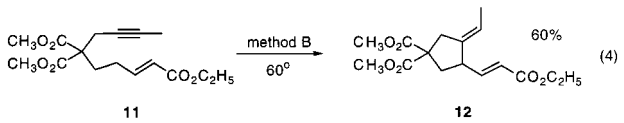


tuted alkenes, is the source of their reactivity the ability to undergo *syn*−*anti* interconversion or selectivity in the initial C−H insertion? The π-allyls derived from trisubstituted alkenes may be thought to speed up conversion of **7** to **8** because of relief of eclipsing interactions with the R^2 group in the former. On the other hand, steric considerations would normally suggest preferential C−H insertion into the *trans* terminal methyl group, which would generate the *syn* complex **7**. To explore this question, the selectively deuterated substrate **9** was cyclized under standard conditions (eq 3). The deuterated product **10** possessed >95%

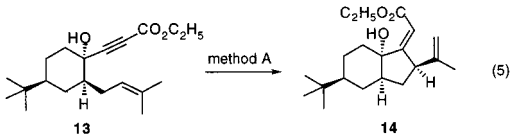


deuterium labeling in both positions as depicted, as determined by NMR spectroscopy. Despite any isotope effect against insertion into a C−D bond, only that pathway is observed indicating a strong bias for selective insertion into the C−H bond of a *cis* substituent. This selectivity also supports the concept that bidentate coordination of the substrate is required for C−H insertion, as depicted in A (Scheme 1). The failure to insert into the allylic C−H bond of a *trans* alkyl substituent may account for the failure of *trans*-disubstituted alkene substrates to participate.

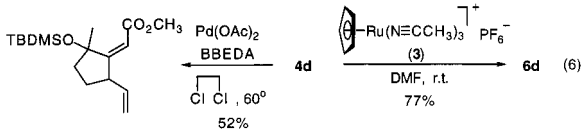
The C−H activation pathway may be more general. For example, in the case of a 1,7-enyne **11**, where cyclizations by the "normal" mechanisms are intrinsically slower, reaction with the ruthenium catalyst **3** required 60 °C and produced **12**,[10] which must arise by a C−H activation pathway (eq 4). With this



substitution pattern, the alkyne does not require conjugation to an electron-withdrawing group. It does open the question of the mechanism of the cyclization of 1,7-enynes to form five-membered rings (e.g., **4a** → **5a**), which could also arise from a C−H activation pathway rather than a ruthenacycle mechanism. For example, the constrained case **13** has the type of substitution pattern that should lead to an allylruthenium intermediate, but, nevertheless, cycloisomerization led mainly to the five-membered ring **14**[10] (62% yield), with only traces of the seven-membered ring (eq 5). The ability of the ruthenium catalyst **3** to promote



allylic C−H activation opens new territory for developing atom economical C−C bond-forming reactions. At a minimum, it now offers a complement to palladium (and other)-catalyzed cycloisomerizations as illustrated in eq 6, whereby either a five- or seven-membered ring product may result by simple change of catalyst. This type of simple switching of cyclization paths may be valuable in generating diversity in combinatorial libraries, a prospect under current investigation.



Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Sample procedure and characterization data for **5a**, **6b**−**h**, **10**, **12**, and **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991977A