J|A|C|S
COMMUNICATIONS

Published on Web 03/27/2002

An Unusual Ruthenium-Catalyzed Cycloisomerization of Alkynes and Propargyl Alcohols

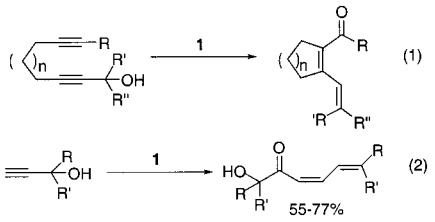
Barry M. Trost* and Michael T. Rudd

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received December 4, 2001

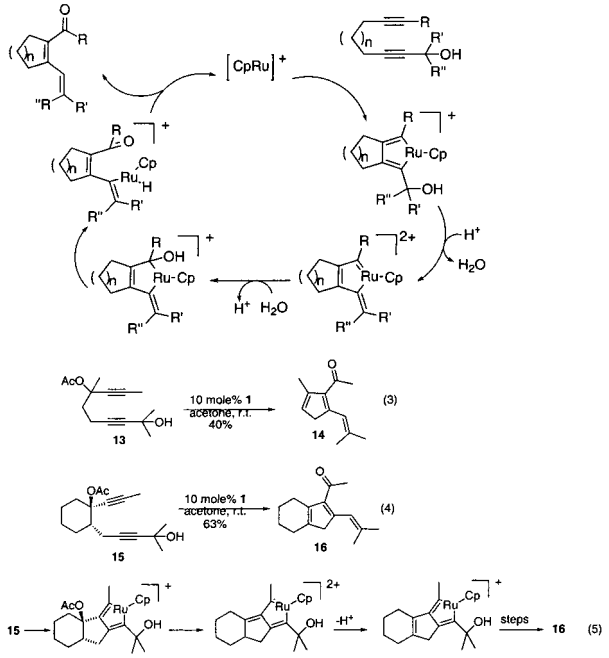
Utilization of easily accessible starting materials to create highly functionalized ring structures through addition reactions allows the creation of molecular complexity[1] while preserving atom economy.[2] The intramolecular aldol condensation[3] is a classic method to construct 1-acyl-cyclopentenes and 1-acyl-cyclohexenes. However, some of the disadvantages of this reaction are the difficult or lengthy syntheses of the ketoaldehyde starting materials and the potential complications inherent when more than a single enolate can be formed.[4] Also, ketones and aldehydes can be difficult to carry through many steps in a synthesis without protection. In contrast, alkynes are known to be synthetically robust, and the synthesis of substituted alkynes and propargyl alcohols is very straightforward. Also, ruthenium catalysts have been shown to be remarkably tolerant of many functional groups.[5] Therefore, we suggest that a potential alternative to the intramolecular aldol condensation is the ruthenium-catalyzed cycloisomerization of diyne-ols to diene-ones or diene-als (eq 1).

Recently, we have shown that, in the presence of CpRu-$(NCCH_3)_3^+PF_6^-$ (**1**),[6] tertiary propargyl alcohols dimerize in a tail-to-tail fashion to form 6-hydroxy-1,3-dien-5-ones (eq 2).[7] A mechanistic rationale[8,9] was proposed that includes metallacycle formation, an elimination of the hydroxy group, and attack of water at the resulting carbene carbon. On the basis of this mechanism, one molecule of propargyl alcohol and one molecule of alkyne should be all that is required. To minimize chemoselectivity issues, an intramolecular version of this latter proposal was envisioned as depicted in Scheme 1. A major issue to be resolved was the general lack of reactivity of disubstituted alkynes in reactions analogous to that of eq 2.[10]



The prospect of the reaction was explored with bis-propargyl alcohol **3** in analogy to our intermolecular dimerization. In contrast to our experience in the intermolecular reaction, treatment with the ruthenium complex **1** in moist acetone at room temperature gave the α′-hydroxydienone **4**[11] within 1 h (Table 1, entry 1). Remarkably, removing one of the propargyl alcohol functional groups, as in dyne **5**, led to complete reaction within 5 min (entry 2) to form the dienal **6**. In both cases, the reactions proceeded with only 1 mol % catalyst to give nearly quantitative yields. Water is required for the reaction, and typically 1 equiv is added. The geminal substitution in the tether is not required as shown in entry 3. Both alkynes can be disubstituted even though only one is a propargyl

Scheme 1. A Mechanistic Rationale for the Intramolecular Coupling of Alkynes and Propargyl Alcohols



alcohol. Entries 4 and 5 demonstrate this aspect as well as illustrate a range of substitution on the tether. In the case of the benzo derivative **7**, a higher catalyst loading was needed for the reaction to proceed at a comparable rate.

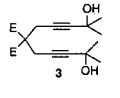
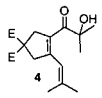
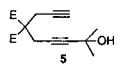
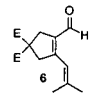
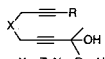
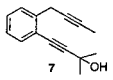
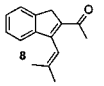
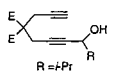
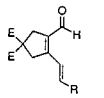
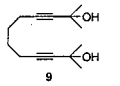
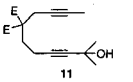
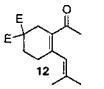
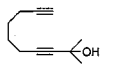
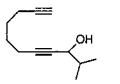
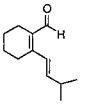
In the intermolecular dimerization, tertiary propargylic alcohols were required for reasonable rates.[7] This limitation is not shared by the intramolecular reaction as shown in entries 6 and 7. While the reactions are slower, good yields of the desired products were obtained even at room temperature. The geometry of the γ,δ double bond was exclusively **E**, presumably the result of thermodynamic control.[12]

Although many transition-metal-catalyzed cyclizations appear restricted to formation of five-membered rings,[13] such a limitation is not present here. The reactions are slower, however, in the bis-propargylic alcohol example **9** (entry 8); higher catalyst loading and higher concentration allowed complete reaction within 1 h at room temperature to form α′-hydroxydienone **10**. A somewhat faster reaction occurred with diyne **11** to form dienone **12** (entry 9) which may reflect the geminal substitution in the tether.[14] Alternatively, the reaction can be performed at elevated temperature to achieve similar rates (entry 10). As for five-membered rings, a secondary alcohol reacts equally well (entry 11).

An alternative substitution of this bis-propargylic alcohol system as in **13** and **15** (eqs 3 and 4) also led to cyclization. In these cases, the "internal" hydroxyl group was best converted to its acetate.

10.1021/ja012672a CCC: $22.00

Table 1. Representative Examples of the Cycloisomerization of Alkynes and Propargyl Alcohols

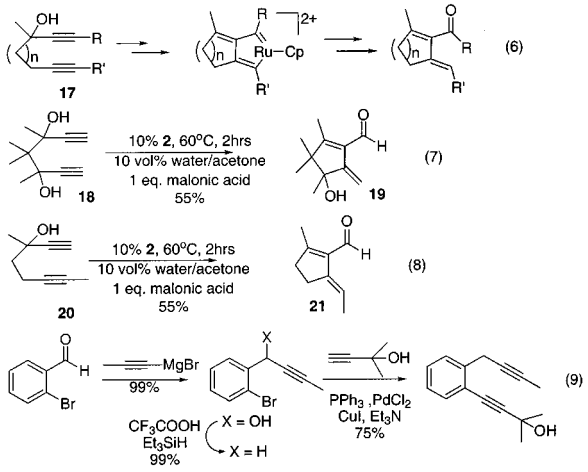
Entry	Substrate	Conditions[1]	Product	Isolated Yield
1		1% **1**		96%
2		1% **1**		98%
3	 X = TsN R = H	3% **1**		99%
4	X = O R = Me	1% **1**		90%
5		5% **1**		89%
6	 R = *i*-Pr	2% **1**		70%
7	R = Ph	5% **1**		70%
8		10% **1**[2]		73%
9		7% **1**		91%
10		10% **1**[3]		90%
11		10% **1**		60%

[1] All reactions at 0.1 M in acetone for 1 hr at rt unless otherwise noted; E = COOMe. [2] Reaction performed at 1.0 M. [3] Reaction performed at 60 °C.

The free hydroxyl compounds cyclize to give the same products, but in slightly diminished yield. The cyclization was accompanied by elimination of the elements of acetic acid to give cyclopentadienes **14** and **16**. A mechanistic rationale, depicted in eq 5, envisions facilitation of ionization of the tertiary acetate in the initial ruthenacyclopentadiene followed by the normal sequence as depicted in Scheme 1.

This observation suggests that the alternative propargyl alcohol **17** might also participate in a cyclization as depicted in eq 6. Indeed, both the bis-propargylic alcohol **18** and monopropargylic alcohol **20** cyclize under more stringent conditions to form enals **19** and **21.** In these cases, the addition of an acid promoter, presumably to facilitate ionization of the tertiary alcohol, was required.

A new ruthenium-catalyzed cycloisomerization provides ready access to five- and six-membered ring dienals and dienones that would not be easily accessed. The substrates are easily accessible because of the flexibility of alkyne chemistry. For example, propargylation of dimethyl malonate or *p*-toluenesulfonamide followed by addition of the monolithium salt of the symmetrical diyne provided the substrates of entries 2, 3, 6, and 7. The diyne **7** is accessed as shown in eq 9 which translates into dienone **8** being prepared in four steps from inexpensive commercially available starting materials.



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

Supporting Information Available: Experimental procedures for the preparation of new compounds as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wender, P. A.; Miller, B. L. *Org. Synth.: Theory Appl.* **1993**, *2*, 27; Bertz, S. H.; Sommer, T. J. *Org Synth: Theory Appl.* **1993**, *2*, 67.
(2) Trost, B. M. *Science* **1991**, *254*, 1471; Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(3) Wolinsky, J.; Slabaugh, M. R.; Gibson, T. *J. Org. Chem.* **1964**, *29*, 3740; Nielsen, A. T.; Houlihan, W. J. *Org. React.* (N.Y.) **1968**, *16*, *1*; Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost B. M., Ed.; Pergamon Press: New York, 1991; p133; House, H. O. In *Modern Synthetic Reactions*, 2nd ed.; Benjamin, W. A., Ed.; Menlo Park, CA, 1972; p 629; Wolinsky, J.; Barker, W. *J. Am. Chem. Soc.* **1960**, *82*, 636; Ortina, G. J.; Wiemer, D. F. *Tetrahedron Lett.* **1982**, *23*, 803.
(4) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York and London, 1990; Part B, Chapter 2, p 55.
(5) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067 and references therein; Dixneuf, P. H.; Bruneau, C.; Derien, S. *Pure Appl. Chem.* **1998**, *70*, 1065 and references therein.
(6) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
(7) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 8862 and references therein. Ruthenium has also been shown to dimerize propargyl alcohols to alkylidene cyclobutenes: Le Paih, J.; Derien, S.; Bruneau, C.; Demerseman, B.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2912.
(8) Mechanism related to those proposed in enyne cyclizations: Trost, B. M. *Chem. Ber.* **1996**, *129*, 1313.; Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, 101, 2067.
(9) For ionization of propargyl alcohols during enyne couplings: Trost, B. M.; Krause, L.; Portnoy, M. *J. Am. Chem. Soc.* **1997**, *119*, 11319.
(10) Disubstituted propargyl alcohols react in a similar manner; however, at present the yields are very low due to poor conversion.
(11) Cyclization products and elemental composition have been characterized by spectroscopic means and by combustion analysis or high-resolution mass spectrometry, respectively.
(12) Compare ref 7.
(13) Stragies, R.; Schuster, M.; Blechert, S. *Chem. Commun.* **1999**, *237*; Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146; Trost, B. M.; Toste, F. D.; Shen. H. C. *J. Am. Chem. Soc.* **2000**, *122*, 2379
(14) Keese, R.; Meyer, M. *Tetrahedron*, **1993,** 49, 2055; Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224; Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 1080; Schleyer, P.v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368.

JA012672A