

Communications to the Editor

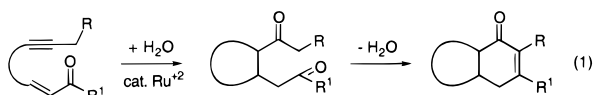
A Ruthenium-Catalyzed Hydrative Cyclization and [4 + 2] Cycloaddition of Yne-enones

Barry M. Trost,* Rebecca E. Brown, and F. Dean Toste

Department of Chemistry
Stanford University
Stanford, California 94305-5080

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Increasing the atom economy of synthetically useful reactions provides a challenge for the invention of addition reactions.¹ The prospect of forming multiple rings in a simple process, according to eq 1, provides a means to create molecular complexity² rapidly. Realization of this sequence derives from



our earlier observation of a three-component coupling of terminal alkynes, unsubstituted vinyl ketones, and water to form 1,5-diketones.³ The ability to effect an intramolecular version requires, first, the ability for a β -substituted enone to participate—a type of substitution that inhibited the intermolecular process—and, second, the ability to direct the regioselectivity of the addition of water. Two mechanisms as outlined in Scheme 1 may be envisioned. Cycle A derives from the increasing number of reactions involving the ability of ruthenium to promote the addition of heteroatom nucleophiles to alkynes.⁴ Cycle B derives from consideration of the ruthenium-catalyzed addition of alkynes and alkenes.⁵ We wish to report the development of a hydrative cyclization of yne-enones to form carbo- and heterocycles according to eq 1.⁶ During the course of this study, we uncovered a [4 + 2] cycloaddition that sheds light on the mechanism.

Our first generation catalyst CpRu(COD)Cl⁵ is not effective with disubstituted alkenes. Our recent success⁷ in other ruthenium-catalyzed reactions with CpRu(NCCH₃)₃⁺PF₆⁻ (**1**)⁸ led us to investigate the reaction of eq 2. While aqueous DMF has frequently been utilized in our ruthenium-catalyzed reactions, acetone proved more reproducible and led to its being employed

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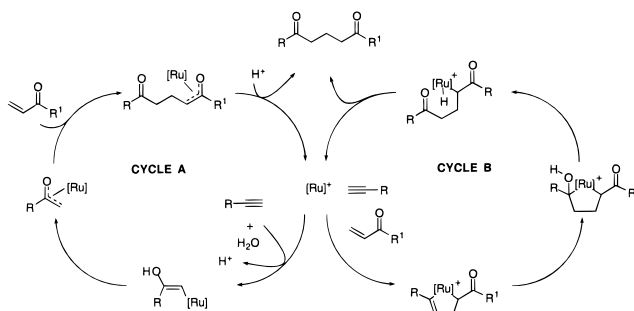
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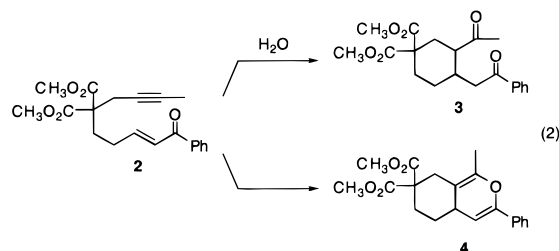
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Scheme 1. Mechanistic Possibilities of Three-Component Coupling



for all the studies herein. On the basis of our study of the three-component coupling in which addition of CSA proved beneficial, 10 mol % CSA was routinely used. Thus, treating a 0.1 M solution of yne-enone **2** in acetone with 10 mol % CSA and 10 mol % **1** gave a 64% yield of diketone **3**.⁹ Since the stoichiometry of the reaction requires 1 equiv of water and none was added,



the reaction depended upon the moisture present in the undried acetone. Adding 1.3 equiv of water with everything else being the same increased the yield to 75% (81% brsm) (conditions A).

A most interesting result arose when the catalyst loading was reduced to 5 mol %. While the yield of diketone **3** was still good (64%), the pyran **4** was also detected. Indeed, hydration of the pyran **4** can be thought to be the source of the desired 1,5-diketone **3**. To optimize the formation of the [4 + 2] cycloadduct, removing acid and utilizing anhydrous acetone should be beneficial. A 60% yield of pyran **4**⁹ was obtained when **2** was treated with 5 mol % **1** in anhydrous acetone (conditions B).

Table 1 illustrates the generality of 1,5-diketone formation. An alkyl ketone (entry 2) is equally effective to the aryl ketone of entry 1. Reducing the tether length (entry 3) gave the five-membered ring. On the other hand, lengthening the tether to five atoms to form a seven-membered ring failed. Placing heteroatoms in the tether, including an oxygen (entry 4), a nitrogen (i.e., sulfonamide, entry 5), and a sulfur (i.e., a sulfone, entry 6), were as effective as the all-carbon tether. A divalent sulfide (entry 7) did participate but limited the catalyst turnover. The substrate of entry 8 is most interesting since it demonstrates that a simple methylene tether is effective as is a terminal alkyne. Curiously, in this case, conditions B also led only to the isolation of the keto aldehyde rather than the pyran. The enyne substrate of entry 9 produced the bicyclic diketone in good yield.

The yields of the pyrans depended upon their sensitivity to decomposition during workup. Adding triethylamine during

(9) All new compounds have been characterized spectroscopically, and elemental composition has been established by combustion analysis or high-resolution mass spectrometry.

Table 1. Ruthenium Catalyzed Formation of Pyrans and Cyclic Diketones

Entry	Enone-yne ^a	Conditions A ^b		Conditions B ^c	
		Product	Isolated Yield	Product	Isolated Yield
1			75 (81) dr = 2:1		60
2			71 dr = 1:1		78
3			81 dr ≥ 10:1		70
4			60 (65) dr = 1:1		
5			70 dr = 2:1		89
6			75 dr = 1:1		55
7			45 (82) dr = 1:1		
8			86 dr = 10:1		85 dr = 12:1
9			51		

^a E = CO₂Me. ^b 10% RuCp(MeCN)₃PF₆, 10% CSA, H₂O (1.3 equiv), acetone, 12 h. ^c 5% RuCp(MeCN)₃PF₆, acetone, 4 h. ^d Yield in parentheses based on recovered starting material.

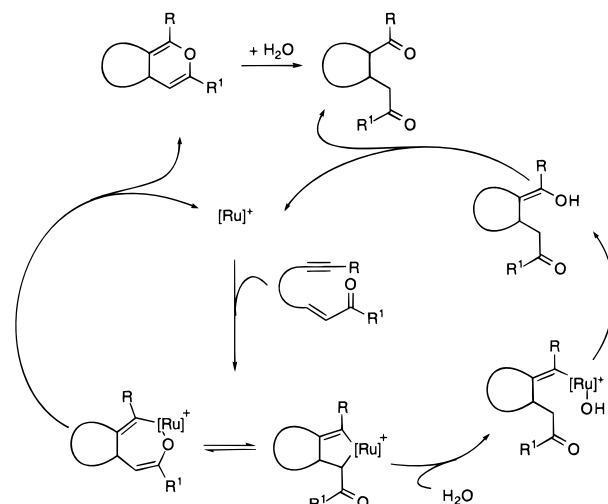
chromatographic purification allowed the pyrans to be isolated in good yields in most cases except in entries 4, where it decomposed during workup, and 8, where presumably it hydrolyzed so easily that its conversion to the diketone could not be prevented.

The formation of pyrans in this reaction provides strong support for the intervention of a ruthenacycle (cycle B of Scheme 1) as shown in Scheme 2. The initial ruthenacycle may be viewed as an equilibrating mixture of the C and O bound ruthenium enolate.¹⁰ Reductive elimination of the latter^{11,12} nicely accounts for the formation of pyrans. While one could envision that the 1,5-diketones arise simply by the hydration of the pyrans, a reasonable alternative envisions interception of the ruthenacycle before reductive elimination. Hydration of the ruthenacycle

(10) Cf. Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5670; Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3326, 3344.

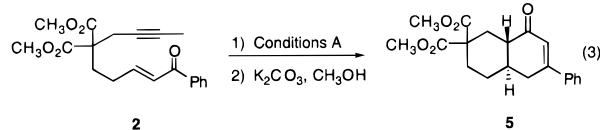
(11) For an example of O-alkylation of Ru enolates, see: Rasley, B. T.; Rapta, M.; Kulawiec, R. J. *Organometallics* **1996**, *15*, 2852.

(12) For leading references of reductive elimination from Pd to form diaryl ethers and aryl alkyl ethers, see: Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369; Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224 and references therein.

Scheme 2. Proposed Mechanistic Rationale

analogous to Scheme 1 or as shown in Scheme 2 nicely accounts for the diketone. While the ruthenacycle intermediate seems highly probable, the mechanism of its hydration remains to be established.

The utility of the cyclic 1,5-diketones¹³ arises, in part, from a subsequent aldol reaction. Indeed, as shown in eq 3, cyclization



according to conditions A followed by potassium carbonate in methanol gave the bicyclic enone **5**⁹ as a single diastereomer in 69% yield from yne-enone **2**. This new cyclization provides an atom economical cyclization method as well as a new catalyst for a hetero-Diels–Alder¹⁴ reaction of vinyl ketones and alkynes. This new cyclization illustrates the growing potential for ruthenium catalysis in C–C bond forming reactions.¹⁵

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health for the generous support of our programs. Mass spectra were provided by the Mass Spectrometry Center of the University of California-San Francisco.

Supporting Information Available: General experimental procedures for the formation of diketones and pyrans as well as characterization of the products in Table 2; preparation and characterization of **5** (PDF). This information is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) For use of 1,5-diketones in synthesis, see: Heathcock, C. H.; *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.5, pp 133–179; Jung, M. E. *Tetrahedron* **1976**, *32*, 3; Gawley, R. E. *Synthesis* **1976**, 7777.

(14) To our knowledge, this represents the first example of a heteroatom Diels–Alder reaction between an enone and an unactivated alkyne. For ruthenium catalysis of normal Diels–Alder reactions, see: Kundig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1220.

(15) For a review, see: Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.