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Ruthenium-Catalyzed Addition of Allyl Alcohols and Acetylenes. A Simple Synthesis of γ,δ-Unsaturated Ketones

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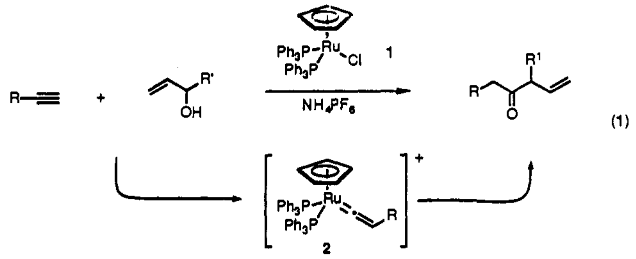
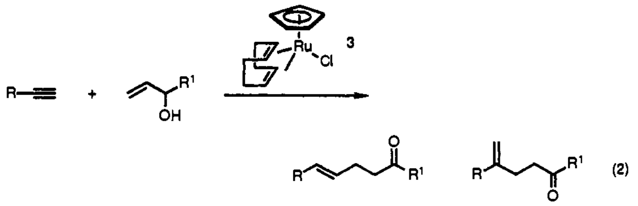
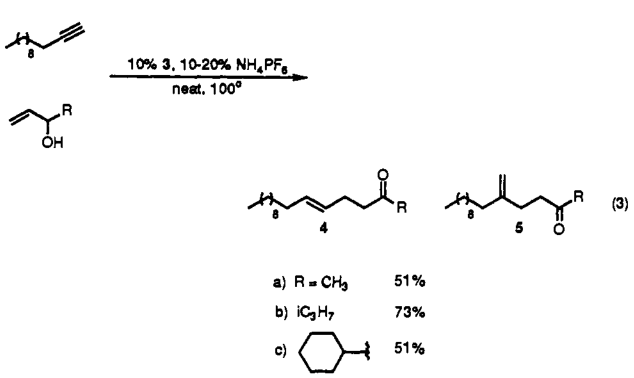
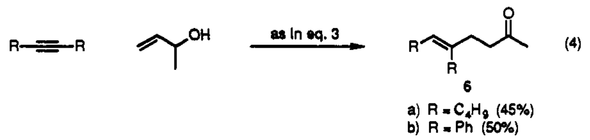
Concerns for maximal use of raw materials and minimal generation of waste products stimulate the search for reactions of the general form $A + B \rightarrow C$ with any other agents being used catalytically.[1] In our quest toward these goals, we examined the behavior of terminal acetylenes with allyl alcohols which, in the presence of the ruthenium complex **1**, generate β,γ-unsaturated ketones.[2] Mechanistic studies implicate the vinylidene complex **2** as a key intermediate[3] but also indicate that the allyl alcohol may independently interact with the ruthenium complex, leading to isomerization to the corresponding saturated ketone.[4] Believing that the partitioning of the reaction may be influenced by the donor phosphine ligands to favor eq 1,[5] we explored this process with a ruthenium complex in the absence of phosphine ligands. In this communication, we wish to report that a ruthenium complex **3**[6] analogous to **1** but lacking phosphine ligands promotes a totally different pathway to produce γ,δ-unsaturated ketones according to eq 2.





Our initial studies examined the neat reaction of 1-dodecyne and 3-buten-2-ol in the presence of 10% **2** and 10–20% ammonium hexafluorophosphate at 100 °C. A nearly equimolar mixture of linear and branched γ,δ-unsaturated ketones **4** and **5**,[7] respectively, was produced in a fairly rapid reaction (1–2 h, eq 3). NMR data allow assignment of the *E* geometry to **4**. None of the β,γ-unsaturated ketone formed according to eq 1 was observed. Thus, phosphines have a dramatic effect on the reaction in which it appears that they promote formation of the vinylidene complex **2** and products derived therefrom. In their absence, this pathway is shut down. This conclusion leads to the expectation that internal as well as terminal acetylenes will participate in this new process, as observed to give **6a,b**[7] (eq 4). It is interesting that both the aromatic and the aliphatic acetylenes participated, since our earlier experiences with ruthenium complexes[8] suggested that phenyl substituents frequently inhibit these reactions, presumably because of the ease of forming arene complexes[9] that appear to be poor catalysts.





The effect of the reaction parameters on the reaction of 1-octyne with 3-buten-2-ol revealed that enhanced chemo- and regioselectivity was observed when the reaction was performed in a solvent and in the absence of any acid catalyst. Rates were best in alcohol solvents like methanol, ethanol, and *n*-propanol, with conversions normally >85% after 2 h. Rates were negligible in relatively nonpolar solvents like THF and benzene. While polarity appears to be important, it does not suffice. Thus, the reaction is only 30% complete in water and 10% complete in acetonitrile after 2 h, even though both solvents are considerably more polar than the alcohol solvents. While a lack of solubility of the substrates in water accounts for the slow rate of equation, this explanation cannot hold for reaction in acetonitrile. A reasonable rationale for the latter lies in the ability of acetonitrile to be a better ligand for ruthenium than the substrates. Although the reaction rate was slow in water, the chemo- and regioselectivity was enhanced over the neat reaction, an observation that led us to examine mixed aqueous solvent systems. Comparable results were obtained with use of solvents composed of 1:1 ratios of water to a broad range of organic solvents including methanol, ethanol, and DMF. Interestingly, even DME and THF served as equally effective cosolvents, whereas anhydrous DME and THF were ineffective. Since DMF–H_2O seemed to give slightly cleaner reactions with better regioselectivity, this solvent mixture (1:1 to 3:1) became our standard. To compare, a 1.3:1.0 ratio of linear to branch products **7a**:**8a**[7] using no solvent (85% isolated yield) increases to 2.3:1 in DMF–H_2O (90% GC, 60% isolated yield, eq 5). Changing the substituent on the allyl alcohol to *n*-undecyl or cyclohexyl increases the **7**:**8**[7] ratio to approximately 3:1.

Somewhat larger changes occurred with acetylenes conjugated to esters. Methyl 2-tridecynoate reacts with 3-buten-2-ol in the

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[1] Trost, B. M. *Science* **1991**, *254*, 1471.

[2] Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809.

[3] Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579.

[4] Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027; *Tetrahedron Lett.* **1991**, *32*, 3039.

[5] For reviews, see Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. Bruce, M. I.; Swincer, G.A. *Adv. Organomet. Chem.* **1983**, *22*, 59. Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; John Wiley & Sons: New York, 1988.

[6] Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.

[7] This compound has been satisfactorily characterized spectroscopically.

[8] (a) Trost, B. M.; Indolese, A. unpublished work. (b) Cf. Trost, B. M.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 4361.

[9] (a) Bennett, M. A.; Bruce, M. I.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 4, p 796. (b) LeBozec, H.; Touchand, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163.

[10] Trost, B. M.; Kulawiec, R. J.; Hammes, A. *Tetrahedron Lett.* **1993**, *34*, 587.

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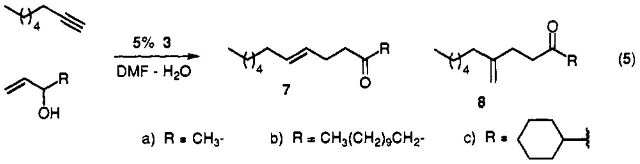
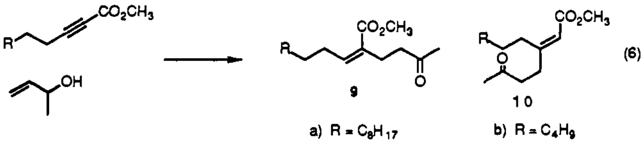
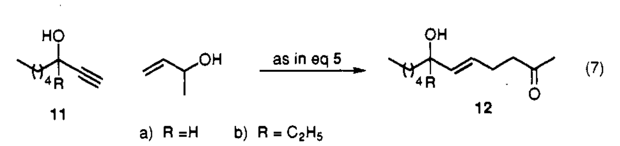
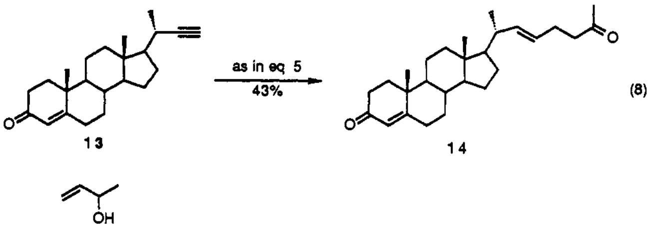


absence of solvent to give a nearly 1:1 ratio of the two regioisomers **9a** and **10a**,[7] whereas, methyl 2-nonynoate gives a 76% isolated yield of a 2.4:1 ratio of **9b**:**10b**[7] in DMF–water (eq 6).

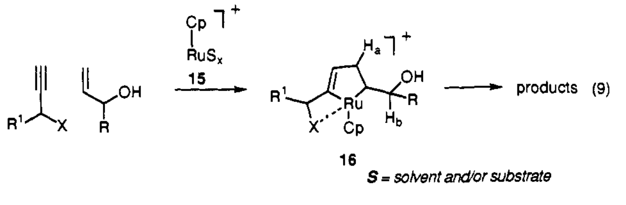


Considering the high reactivity of propargyl alcohols toward formation of allenylidene intermediates with complex **1**, we were most interested in examining their reactivity with complex **3**. Not only are they excellent partners, but they also show the highest regioselectivity of any substrate. Thus, the propargyl alcohol derivatives **11a** and **11b** condense to give excellent selectivity for the linear products **12a** and **12b**[7] in 50–60% isolated yields (eq 7). The excellent chemoselectivity of the reaction allows it to be employed for the introduction of steroid side chains (eq 8). Thus, the unprotected enone **13**, available directly from the corresponding 20-carboxaldehyde, provides the linear adduct **14** as the major product.

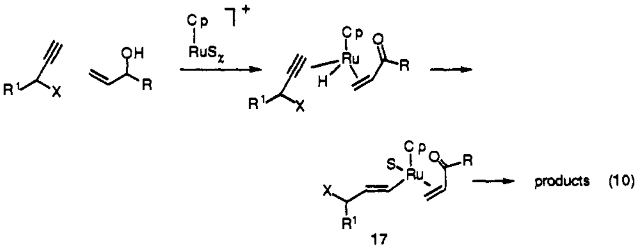




The mechanism of this reaction can only be speculated upon at present. The solvent dependency suggests involvement of cationic complexes.[11] We have established that COD is stripped from ruthenium via cycloaddition with the acetylene,[12] presumably to form a coordinatively unsaturated ruthenium complex (**15**). Two pathways are most reasonable: (1) one invoking a ruthenacyclopentene (**16**) followed by β-hydrogen elimination (eq 9)



and (2) one invoking initial metal hydride formation either by C–H insertion to form a hydroxy-π-allyl or β-elimination from an initial alkoxyruthenium complex followed by addition to the acetylene to give **17** in analogy to that proposed for the ruthenium-catalyzed Alder ene reaction of simple olefins and acetylenes.[8b] The effect of acetylenic substituents on the regioselectivity appears best rationalized by eq 9, wherein the propargylic substituent influences regioselectivity by its ability to coordinate to ruthenium in **16**, which may be coordinatively unsaturated as depicted or have an S group coordinated. Such coordination is not possible in **17** (eq 10). Ruthenacyclopentenes have been proposed as intermediates in the codimerization of acetylenes with norbornene and with acrylamides.[13]



The dramatic effect of ligands on the course of these reactions is noteworthy. Thus, formation of vinylidene[5] and allenylidene[9b,14,15] complexes is totally precluded in the absence of phosphine ligands.[16] Since both of these intermediates require electron donation from the metal to the coordinated acetylenic fragment, the absence of the donor properties of the phosphine ligands diminishes the electron richness of the ruthenium sufficiently to prevent such processes.[14] As a result, groups labile in the presence of complex **1** like propargylic alcohols now become stable in the presence of complex **3**. Such simple access to γ,δ-unsaturated ketones by an addition reaction provides a highly chemoselective and atom economical approach to these useful synthetic building blocks.[17,18]

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Supplementary Material Available: Spectral data for **4a**, **5a**, **4b**, **5b**, **4c**, **5c**, **6b**, **7a**, **8a**, **7b**, **8b**, **9a**, **10a**, **9b**, **10b**, **12a**, **12b**, and **14** (3 pages). Ordering information is given on any current masthead.

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(12) Trost, B. M.; Imi, K.; Indolese, A. *J. Am. Chem. Soc.*, in press.

(13) Cf. 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.

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(15) Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476.

(16) For various vinylideneruthenium complexes, see: LeBozec, H.; Ouzzine, K.; Dixneuf, P. H. *Organometallics* **1991**, *10*, 2768. Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1989**, *54*, 1518. Deranne, O.; Ruppin, C.; Dixneuf, P. H. *J. Org. Chem.* **1988**, *53*, 925. Bruneau, C.; Dixneuf, P.H. *Tetrahedron Lett.* **1987**, *28*, 2005. Ouzzine, K.; LeBozec, H.; Dixneuf, P.H. *J. Organomet. Chem.* **1986**, *317*, C25. Mahé, R.; Dixneuf, P. H.; Lé Colier, S. *Tetrahedron Lett.* **1986**, *27*, 6333. Ruppin, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, *27*, 6323.

(17) Typical procedure: a degassed 1:1 mixture of DMF and water (3.5 mL) was added to a neat mixture of 1-octyn-3-ol (78 mg, 0.90 mL, 0.62 mmol), 3-buten-2-ol (87 mg, 0.105 mL, 1.21 mmol), and **3** (9 mg, 0.029 mmol) under nitrogen. After the vigorously stirred nonhomogeneous mixture was heated for 2.5 h at 85–90 °C, the cooled mixture was poured into water. After extraction with ether and the normal workup of the solution, flash chromatography (1:2 ether–hexane) gave 74 mg (60% yield) of 7-hydroxy-5-dodecen-2-one.

(18) Other ruthenium compounds like Cp*RuCl$_2$, C$_6$H$_6$RuCl$_2$, and RuCl$_3$ also catalyze this reaction but with much lower effectiveness than **3**.