How are the microcapsules formed and what holds them together? Clearly, emulsification must occur during the microscopic dispersion of the nonaqueous phase into the aqueous protein solution. Ultrasonic emulsification is a well-known process[14] and does occur in this biphasic system. Emulsification is necessary for microcapsule formation. However, if vortex mixing emulsification is used instead, microcapsules are not formed. Consequently, *emulsification by itself is not sufficient for microcapsule formation.* Denaturation of the protein by thermal or hydrophobic processes might be invoked to hold the microcapsules together after initial emulsification. High concentrations of microcapsules are observed when the mixture is sparged with air or O_2. If the reaction is run under an inert atmosphere (He, Ar, or N_2), however, microcapsules are not formed. Thus, thermal or solvent denaturation (for which O_2, N_2, and Ar should give similar results) cannot explain the microcapsule permanence.

Another, *chemical* process must be involved. There is a wide range of high-energy chemistry associated with ultrasonic irradiation of liquids, arising from acoustic cavitation (the implosive collapse of bubbles).[6] Aqueous sonochemistry produces[15] $OH^{\bullet}$ and $H^{\bullet}$. The radicals so produced by ultrasound[16] form H_2, H_2O_2, and in the presence of O_2, superoxide[17] (HO_2). Hydroxyl, superoxide, and peroxide are all potential protein cross-linking agents.

To identify the specific oxidant involved, the formation of microcapsules was examined in the presence of radical traps. The addition of nonspecific traps, e.g., 2,6-di-*tert*-butyl-4-methylphenol or glutathione, dramatically reduced the number of microcapsules (Figure 3). The effects of catalase (which decomposes hydrogen peroxide to oxygen and water) or of superoxide dismutase (which decomposes superoxide to oxygen and hydrogen peroxide) were tested. Microcapsule formation was inhibited by superoxide dismutase, but *not* by catalase. Therefore, the important oxidant involved in microcapsule formation is superoxide.

Several experiments were performed to identify the specific effect of superoxide. Cysteine is oxidized by superoxide[18] and is present in BSA, HSA, and Hb. In fact, ultrasonic irradiation of proteins has been reported to oxidize cysteine residues.[19] If the microcapsules are held together by protein cross-linking through disulfide linkages from cysteine oxidation, a comparison of Hb and myoglobin (Mb) provides an interesting test. They have similar sequences, except that Mb has no cysteine. Upon ultrasonic irradiation of Mb solutions, there is a substantial decrease in microcapsule yield, compared to Hb. In addition, Hb-toluene or BSA-toluene microcapsules were destroyed by dithioerythritol (a protein disulfide cleavage reagent[20]). Finally, the oxidation of cysteine residues can be inhibited by alkylation with *N*-ethylmaleimide,[21] and microcapsule formation from Hb solutions so treated is greatly reduced. These results confirm the importance of cysteine cross-linking to microcapsule formation.

In summary, ultrasound can produce proteinaceous microcapsules at high concentrations with narrow size distributions. The process involves both emulsification *and* a chemical cross-linking of protein molecules. The cross-linking reaction principally involves disulfide bond formation by sonochemically generated superoxide.

Acknowledgment. We thank R. A. Olson and the Center for Electron Microscopy. This work was supported by the NSF, the NIH, and an NIH Research Career Development Award.

Registry No. Superoxide, 11062-77-4.

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A Ruthenium-Catalyzed Reconstitutive Condensation of Acetylenes and Allyl Alcohols

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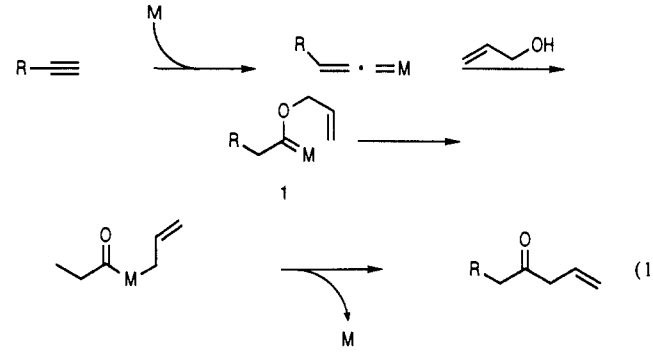
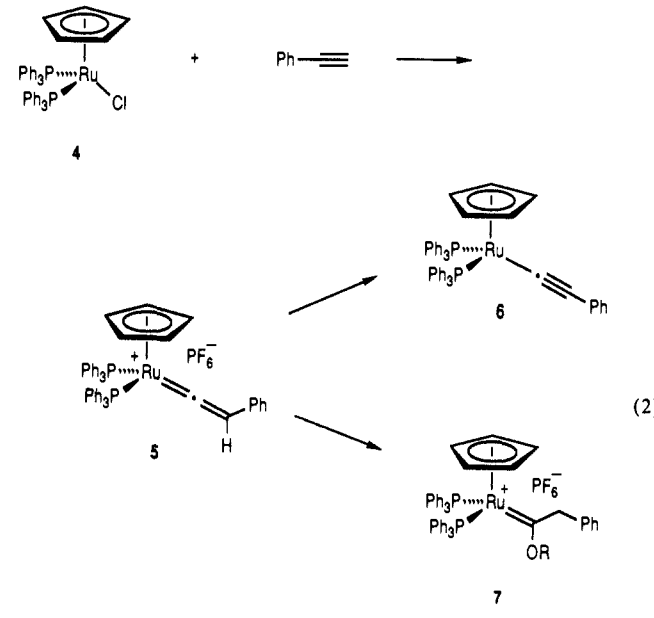
We have initiated a general program to develop carbon–carbon bond forming reactions by condensation, i.e., processes in which the product is the simple sum of the two reactants. In considering terminal acetylenes as one reaction partner, we considered the possibility of developing such condensation reactions invoking vinylidenemetal complexes[1] as reactive intermediates that can readily form under the conditions of a catalytic cycle. Equation 1 outlines one such possibility. The feasibility of such a pathway



is supported by the observation that a stoichiometrically prepared tungsten complex analogous to **1** does generate a β,γ-unsaturated ketone upon thermolysis in which the authors invoked the sequence **1**–**2**–**3**.[2] We report that a ruthenium complex indeed catalyzes the direct condensation of allyl alcohols and terminal acetylenes to generate initially β,γ-unsaturated ketones as outlined in eq 1.

We initiated our study with the known vinylidene complex **5**[3,4] because of its ready availability from the ruthenium complex **4**[3b] and phenylacetylene. Attempts to react the vinylidene complex



with nucleophiles like azide anion or methoxide led only to the

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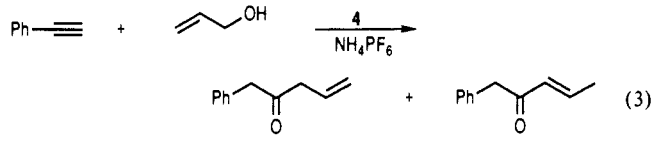
acetylide **6** by deprotonation. While **5** reacts only very slowly with methanol to form adduct **7**, it is stable in refluxing ethanol or 2-propanol.[5] In contrast to these results, allyl alcohol reacts with **5** to form a mixture of 1-phenyl-4-penten-2-one (**8**) and 1-phenyl-3-penten-2-one (**9**). Dramatically, heating a neat mixture of phenylacetylene and excess allyl alcohol with 6% complex **4** and 10% ammonium hexafluorophosphate at 100 °C for 10 h gives a mixture of enones **8** and **9** along with conjugate adducts of allyl

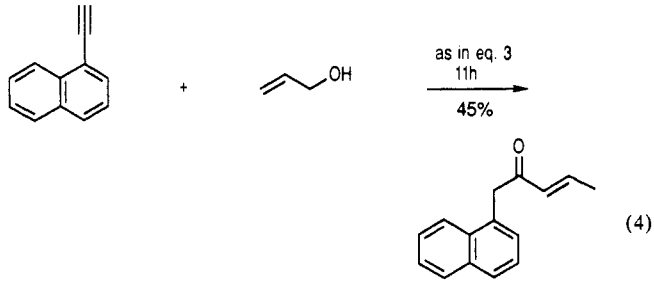


(3)

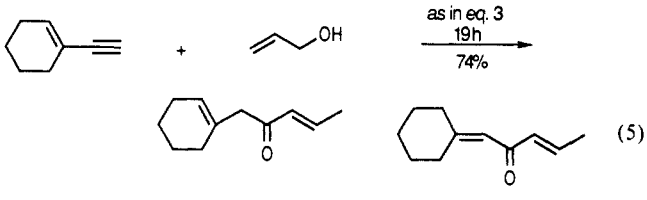
8 **9**

alcohol with **9**, which are eliminated by stirring the crude reaction mixture with TsOH in aqueous acetone at room temperature. By isomerization of the unconjugated isomer **8** with rhodium trichloride in aqueous THF, the conjugated (*E*)-enone **9**[6,7] was isolated in 79% yield.

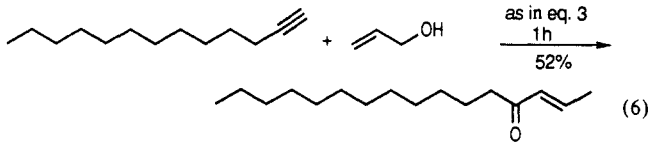
Using this protocol, we examined the effect of varying the acetylenic substituent. Equations 4, 5, and 6 reveal that aryl, vinyl, and even simple alkyl acetylenes proceed to give the propenyl ketones.



(4)



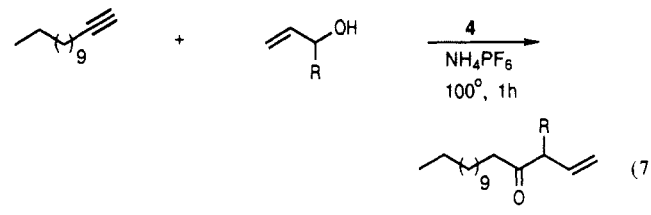
(5)



(6)

Varying the allyl alcohol revealed that placing substituents directly on the olefin effected a dramatic reduction in the rate of reaction. On the other hand, placing the substituent on the carbinol carbon gave a very clean reaction but with a most surprising regioselectivity. Exposing 1-tridecyne to 3-hydroxy-1-butene (excess), 10 mol % catalyst **4**, and 20 mol % ammonium hexafluorophosphate at 100 °C followed directly by column chromatography gave a 63% yield of the β,γ-unsaturated ketone **10a**[6] as the exclusive product (eq 7). Replacing the methyl group of the alcohol by the sterically more bulky isopropyl group has no appreciable effect on the reaction: the ketone **10b**[6] was obtained in 57% yield.

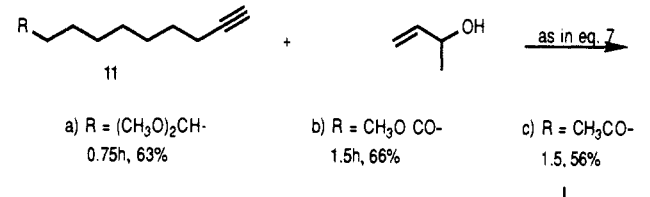
Adopting the above protocol with 3-hydroxy-1-butene as the allyl alcohol partner, we examined the variation of the acetylene partner (eqs 8–10). The reactions illustrate compatibility with acetals, alcohols, ketones, conjugated enones, esters, and olefins. In no case were alternative regioisomers detected.



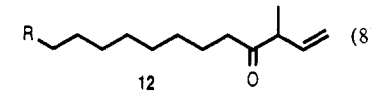
(7)

10

a) R = CH_3 63%
b) R = i-C_3H_7 57%



a) R = $(CH_3O)_2CH$- 0.75h, 63%
b) R = CH_3O CO- 1.5h, 66%
c) R = CH_3CO- 1.5, 56%



(8)

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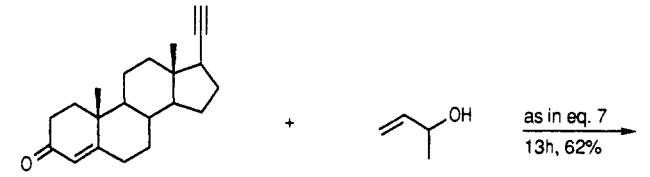
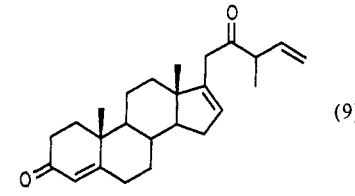
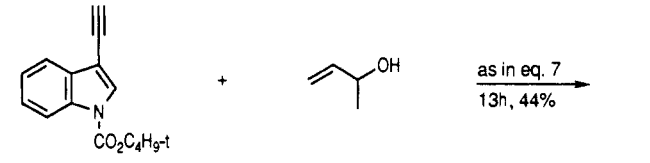
d) R = $CH_3CH(OH)(CH_2)_2$- 0.75h, 65%

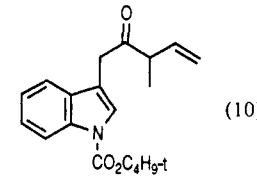




(9)

13





(10)

14

While a mechanistic rationale modified somewhat from the concept presented in eq 1 to take into account the unusual selectivities observed may be preferred, its speculative nature and journal space limitations preclude its presentation at this point.[8]

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Synthetically, this condensation forms a new C-C bond and rearranges the oxidation pattern with formation of a versatile carbonyl group with high chemo- and regioselectivity.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs. G.D. thanks NATO and R.J.K. NIH for fellowships in partial support of their postdoctoral studies in these laboratories.

Supplementary Material Available: IR and ^1H and ^{13}C NMR data for various enones (3 pages). Ordering information is given on any current masthead page.

η^2- and $\eta^2(Se)$-μ_2-Selenophene (Sel) Coordination in $Cp^*(CO)_2Re(2,3\text{-}\eta^2\text{-Sel})$ and $Cp^*(CO)_2Re(\eta^2(Se)\text{-}\mu_2\text{-Sel})[W(CO)_4(PPh_3)]$

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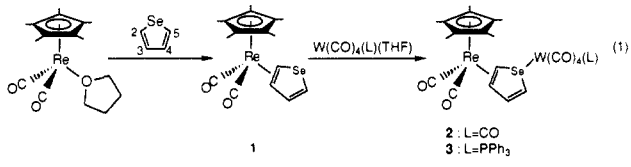
In connection with our interest in the mechanism(s) of the hydrodesulfurization (HDS) of thiophenes on heterogeneous catalysts,[2] we have explored various modes of thiophene (T) coordination in transition-metal complexes. Those that are known are shown in Chart I. Complexes with η^5-,[3] S-,[4] η^4-,[5] $\eta^4(S)$-μ_2-,[6] and $\eta^4(S)$-μ_3-bound[7] and ring-opened[8] thiophene coordination have been characterized by X-ray crystallography. The complex $(NH_3)_5Os(2,3\text{-}\eta^2\text{-T})^{2+}$ was proposed[9] to contain a 2,3-η^2-thiophene ligand on the basis of ^1H NMR spectroscopic evidence. In a previous report,[6] we described the synthesis of the complex $Cp^*(CO)_2Re(T)$ in which the thiophene (T) was S-coordinated to the rhenium. In this communication, we report the analogous selenophene (Sel) complex $Cp^*(CO)_2Re(Sel)$ in which the selenophene is 2,3-η^2-coordinated to the metal (eq 1). Moreover,



1 2 : L=CO 3 : L=PPh_3

$Cp^*(CO)_2Re(2,3\text{-}\eta^2\text{-Sel})$ (**1**) reacts with $W(CO)_4(L)(THF)$, where L = CO or PPh_3 and THF = tetrahydrofuran, to give $Cp^*(CO)_2Re(\eta^2(Se)\text{-}\mu_2\text{-Sel})[W(CO)_4(L)]$ (**2**, L = CO; **3**, L = PPh_3) in which the selenophene is η^2-bonded to the Re and Se-bonded to the W, a bonding mode not previously observed for either thiophene or selenophene.

A solution of $Cp^*(CO)_2Re(THF)$, prepared by UV irradiation[10] of a THF solution (30 mL) of $Cp^*Re(CO)_3$ (0.20 g, 0.49 mmol) at −20 °C, was stirred with selenophene[11] (2.0 mL, 24.5 mmol) at room temperature for 7 h. After removal of the solvent in vacuo,

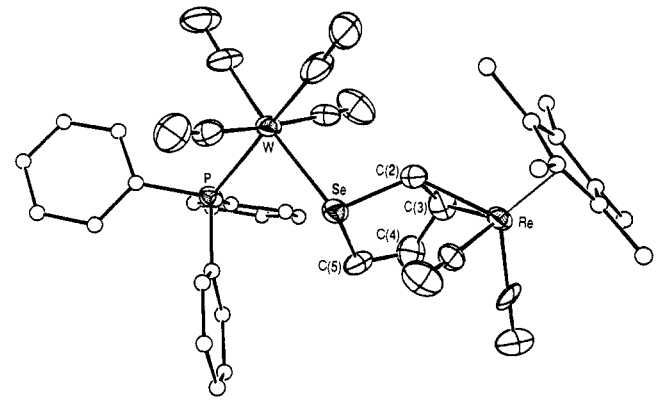
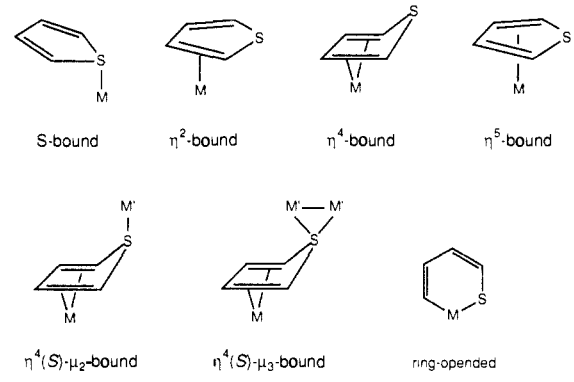


Figure 1. ORTEP drawing of $Cp^*(CO)_2Re(\eta^2(Se)\text{-}\mu_2\text{-Sel})[W(CO)_4(PPh_3)]$ (**3**). Selected bond distances (Å) and angles (deg) are Re–C(2) = 2.23 (1). Re–C(3) = 2.28 (2), W–Se = 2.681 (2), Se–C(2) = 1.95 (1), Se–C(5) = 1.92 (1), C(2)–C(3) = 1.44 (2), C(3)–C(4) = 1.44 (2), C(4)–C(5) = 1.34 (2), C(2)–Se–C(5) = 86.3 (5). The dihedral angle between the C(2)–Re–C(3) and Se–C(2)–C(3)–C(4)–C(5) planes is 117 (1)°.

Chart I



the residue was chromatographed in CH_2Cl_2/hexane (1:4) on neutral alumina. Slow evaporation of the solvent from the yellow band gave moderately air-stable light yellow crystals of $Cp^*(CO)_2Re(2,3\text{-}\eta^2\text{-Sel})$ (**1**)[12] (45% yield). As compared with the ^1H NMR spectrum of free selenophene (δ 8.05 m, H2,5; 7.37 m, H3,4 in $CDCl_3$),[13] two of the selenophene protons in **1** move substantially upfield (δ 4.52 d, H2; 3.64 m br, H3; 7.02 m br, H4; 6.72 d, H5), characteristic of η^2-olefin ligands.[14] In addition, the expected splitting patterns of the four individual protons for 2,3-η^2-Sel coordination are observed. In the ^{13}C NMR spectrum of **1**, two of the four carbon resonances (δ 46.4, 52.4, 119.8, 134.3) lie considerably upfield of those in free selenophene (δ 129.3, 130.3 in $CDCl_3$), also indicating η^2-coordination[14] via two carbon atoms.

The uncoordinated selenophene Se atom in **1** is capable of binding to a $W(CO)_5$ group to give **2** (eq 1). Thus, $Cp^*(CO)_2Re(\eta^2\text{-Sel})$ (**1**; 50 mg, 0.098 mmol) reacts with a solution of $W(CO)_5(THF)$,[15] prepared by UV irradiation of a THF solution (25 mL) of $W(CO)_6$ (60 mg, 0.17 mmol), at room tem-

(1) Ames Laboratory is operated for the U.S. Department of Energy by Iowa State University under Contract No. W-7405-Eng-82. This research was supported by the Office of Basic Energy Sciences, Chemical Sciences Division.
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(12) **1**: IR (hexanes) ν(CO) 1962 (s), 1898 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (br, m, 1 H, Sel), 6.72 (d, 1 H, Sel), 4.52 (d, 1 H, Sel), 3.64 (br, m, 1 H, Sel), 1.98 (s, 15 H, Cp*); ^{13}C NMR ($CDCl_3$) δ 205.4 and 205.0 (CO), 134.3, 119.8, 52.4 and 46.4 (Sel), 97.4 (C of Cp*), 10.3 (Me of Cp*); EIMS (70 eV) *m/e* 510 (M^+, based on ^{187}Re and ^{80}Se), 454 ($M^+ - 2CO$), 378 ($M^+ - Sel$), 350 ($M^+ - (Sel + CO)$). Anal. Calcd for $C_{16}H_{19}O_2ReSe$: C, 37.79; H, 3.77. Found: C, 37.96; H, 3.75. An X-ray study of **1** clearly shows 2,3-η^2 coordination of Sel, but final refinement was not successful due to disorder of the Sel ring.
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