ring fusion of **19** was assigned on the basis of the strong (13%) NOE observed between the angular hydrogens H_{3a} (apparent q at δ 3.71, J = 10.1, 8.2, 9.6 Hz, $CDCl_3$) and H_{9b} (d at δ 5.82, J = 8.1 Hz). Treatment of **12b** with tributyltin triflate, on the other hand, produced a ca. 10:1 mixture of the trans and cis ring fused lactones **20** and **21**, respectively, in a 94% combined yield. The stereochemical assignment for these isomeric lactones was done on the basis of comparative ^{1}H NMR DNOE experiments.[13] Specifically, the observed NOE between the angular hydrogens H_{3a} and H_{10b} is 3% in the major isomer **20** and 17% in the minor isomer **21**, indicating a trans and a cis relationship, respectively.

The stereospecific intramolecular replacement of the sulfur atom from γ-arylsulfanylbutyrolactones via α-acyloxy radicals or α-acyloxy carbocations, then, broadens the range of application of the chiral sulfoxide-directed lactonization reaction. In addition, the present methodology provides a nontraditional entry into ring-fused lactones, for it allows the stereospecific construction of a carbocyclic ring onto a preformed lactone.

Acknowledgment. We thank Frank Parker for performing the NOE experiments and Professor John R. Wiseman for valuable comments. This work was supported by the National Institutes of Health (CA 22237) and the National Science Foundation Instrumentation Program.

Supplementary Material Available: Characterization data (IR, ^{1}H NMR, ^{13}C NMR, mass spectra, optical rotation, exact mass and/or element analysis) for lactones **13–21** (3 pages). Ordering information is given on any current masthead page.

(13) The coupling constant between the two bridgehead protons is essentially the same in both compounds (J = 9.5 Hz in the major isomer and 9.7 Hz in the minor isomer) and therefore was not diagnostic of the relative stereochemistry at the ring junction.

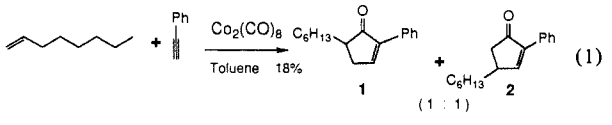
Regiocontrol in the Intermolecular Cobalt-Catalyzed Olefin–Acetylene Cycloaddition

Marie E. Krafft

Department of Chemistry, Florida State University Tallahassee, Florida 32306-3006

Received September 3, 1987

In 1973 Pauson showed that alkyne dicobalt octacarbonyl complexes react with olefins to give rise to cyclopentenones.[1,2] However, there are two major problems associated with the intermolecular cycloaddition. First, mixtures of regioisomeric cyclopentenones, i.e., **1** and **2**, are formed from unsymmetrically substituted olefins, although unsymmetrically substituted acetylenes prefer (due to steric interactions) an orientation which places the larger substituent in the α position of the cyclopentenone (eq 1). Second, the yields are consistently low when simple olefins



(1)

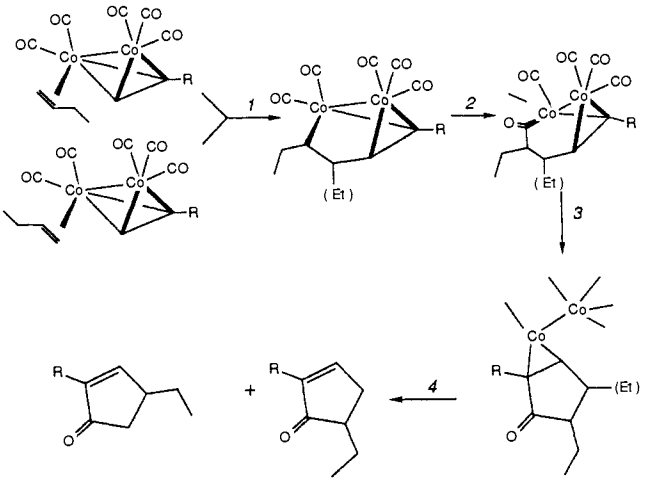
are used. We now report the first examples of the use of ligands to provide regiocontrol in the intermolecular olefin–acetylene cycloaddition and to contribute to a significant improvement in the overall yield,[3]

(1) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

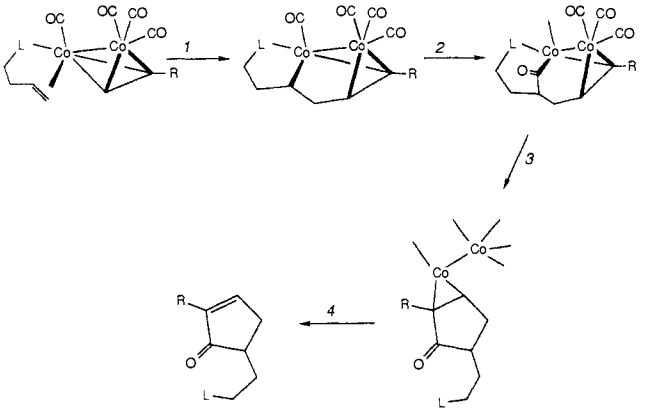
(2) Khand, I. U.; Pauson, P. L. *J. Chem. Res. M* **1977**, 168.

(3) Several examples of regiospecific cycloadditions have been reported: (a) Sampath, V.; Lund, E. C.; Knudsen, M. J.; Olmstead, M. M.; Schore, N. E. *J. Org. Chem.* **1987**, *52*, 3595. (b) Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. (c) Bladon, P.; Khand, I. U.; Pauson, P. L. *J. Chem. Res. M* **1977**, 0153. (d) LaBelle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yamuk, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215.

Scheme I



Scheme II



Since its introduction, the reaction (referred to as the Pauson[4] cyclization) has attracted much attention due to its synthetic utility;[5,6] however, use has been limited to the intramolecular modification due to the aforementioned problems. Recent studies employing the intramolecular version include the use of ultrasound[7] and silica gel as a medium for the cycloaddition.[8,9]

A mechanism has been proposed,[4,5] although experimental evidence is lacking. A potential solution to the regioisomer problem may, however, be envisioned by considering the proposed mechanism (Scheme I). Initially, the olefin must coordinate to

(4) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

(5) The Pauson cycloaddition has been utilized recently in the syntheses of Coriolin and Hirsutic acid: Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. Quadrone: Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. Methylenomycin B: ref 3b. Deoxyprostaglandin: Newton, R. F.; Pauson, P. L.; Taylor, R. G. *J. Chem. Res. M* **1980**, 3501. For other applications to organic synthesis, see: Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025. Billington, D. C.; Willison, D. *Tetrahedron Lett.* **1984**, *25*, 4041. Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569. Magnus, P.; Becker, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 7495.

(6) L. A. Paquette *Recent Synthetic Developments in Polyquinane Chemistry*; Topics in Current Chemistry 119, Springer: Berlin, 1984. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer: Berlin, 1987, and references cited therein. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.

(7) Caple, R.; Froen, D.; Kraeger, A. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society; Denver, CO, American Chemical Society: Washington DC, 1987, *ORGN 42*.

(8) Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Strychkov, Y. T.; Kyz'mina, L. G.; Mikaelian, G. S.; Caple, R.; Swanson, E. D. *Tetrahedron Lett.* **1986**, *27*, 1241. Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245.

(9) For other related cobalt-mediated cycloadditions, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539 and references cited therein; Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. See, also: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

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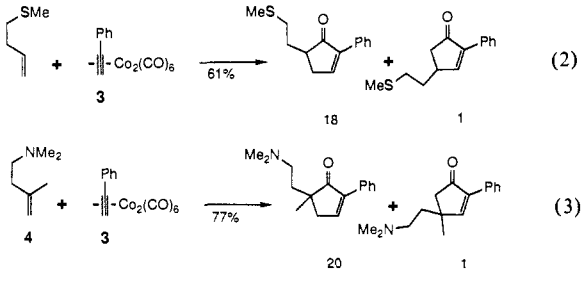
the cobalt complex. Apparently, a mixture of isomeric complexes is formed in solution prior to cycloaddition. In step 1, the initial carbon–carbon bond forming step, it has been proposed that the substituent on the acetylene provides steric interference to the formation of the first bond, causing it to be formed with the less substituted end of the acetylene. Therefore, in the reaction of unsymmetrically substituted olefins and terminal acetylenes, regioisomers arise only from initial bond formation to either end of the olefin and not to either end of the acetylenic moiety.

After consideration of the proposed mechanism, we felt that a heteroatom tethered to the olefin by a carbon chain would coordinate to cobalt and control the regiochemical outcome of the reaction, which is determined in step 1 (Scheme II). Use of bidentate olefinic ligands was also expected to provide a more stable initial complex and lead to increased yields of products.

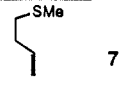
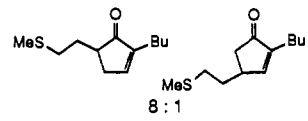
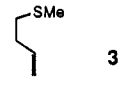
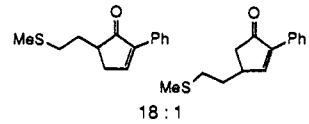
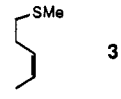
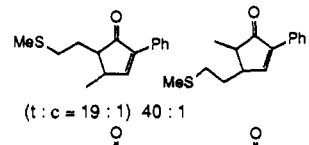
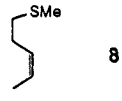
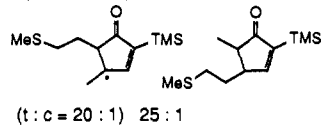
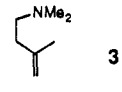
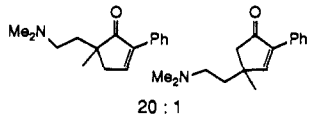
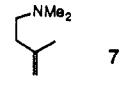
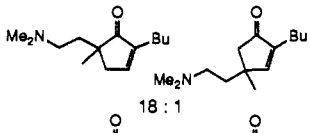
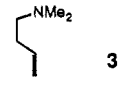
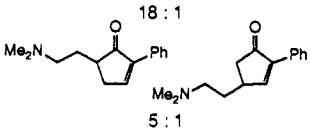
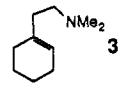
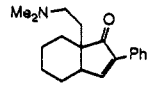
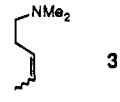
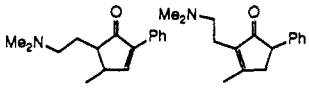
Oxygen, sulfur, and nitrogen were investigated for their efficacy as directing ligands. As anticipated, alcohols and methoxymethyl ethers did not provide ligand directed regioselectivity, and a 1:1 mixture of regioisomeric cyclopentenones was obtained.[10] Both sulfur and nitrogen ligands provided excellent regiocontrol. For example, reaction of 3-butenyl methyl sulfide with phenylacetylene hexacarbonyldicobalt (**3**) in toluene at 90 °C for 30 h gave rise to an 18:1 ratio of cyclopentenones in 61% yield (eq 2), easily separated by flash chromatography.[11] Similarly, amino olefin **4** reacted with **3**, under the same conditions, generating a quaternary center in 77% yield (eq 3).



Extension of the chain length between the heteroatom and the alkene resulted in a decrease in selectivity.[12] For example, reaction of bishomoallylic amine **5** or sulfide **6** with cobalt complex **3** gave rise to a 3:1 mixture of regioisomers in 69% and 52% yields, respectively (entries 10 and 11 in Table I).

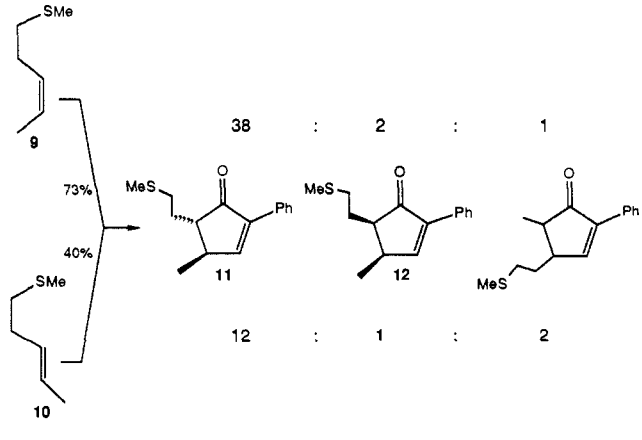
In general,[13] the cycloaddition reactions were carried out by the addition of the olefinic substrate to 2 equiv of the preformed cobalt complex[1,4] and warming the mixture to 90 °C for 24–36 h under a nitrogen atmosphere. Since the cobalt complex slowly decomposes at 90 °C, it was necessary to add 1–2 additional equiv of it during the course of the reaction. In addition to promoting the faster decomposition of the cobalt complex, higher reaction temperatures led to the formation of dienes resulting from β-elimination instead of CO insertion[15] and products arising from olefin migration of the newly formed cyclopentenones. The cycloaddition proceeded very slowly under an atmosphere of carbon monoxide, and, thus, attempts to use catalytic amounts of cobalt were unsuccessful. The reaction was found to be general and could be carried out by using a variety of substituted olefinic amines and sulfides, and cobalt–acetylene complexes, for example, 1-hexyne hexacarbonyldicobalt (**7**) and trimethylsilylacetylene hexacarbonyldicobalt (**8**). The results are summarized in Table I.[14,16]

Table I.

Entry	Olefin	Cobalt complex	Product(s)	Yield[a]
1		7	 8 : 1	60%
2		3	 18 : 1	61%
3		3	 (t : c = 19 : 1) 40 : 1	73%
4		8	 (t : c = 20 : 1) 25 : 1	65%
5		3	 20 : 1	77%
6		7	 18 : 1	60%
7		3	 5 : 1	72%
8		3		28%
9		3		68%[b]
10	5 X = NMe_2	3	3 : 1 R = Ph	69%
11	6 X = SMe	7	3 : 1 R = Bu	52%

[a] Isolated yields. [b] See text for explanation.

Scheme III



(10) Pauson (ref 3b) reported a regioselective cycloaddition reaction utilizing the tetrahydropyranyl ether of allyl alcohol and the cobalt complex of 2-butyne. We are currently investigating the origin of this selectivity.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(12) We are currently investigating the reaction of allylic amines and sulfides with cobalt acetylene complexes. Our initial results have provided low yields of desired cyclopentenones. Krafft, M. E.; Crooks, W. J., III, unpublished results.

(13) To isolate the sulfides, ethylene diamine was slowly added to the cooled reaction mixture (to complex the cobalt residues), and stirring was continued for 20 min at 25 °C. The resulting oil was then chromatographed.[11] For cycloaddition reactions using homoallylic amine substrates, an acid–base extraction was used to isolate the aminocyclopentenones.

(14) All new compounds gave satisfactory spectral data; major compounds were analyzed by high resolution mass spectroscopy or elemental analysis.

(15) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* **1974**, 379.

Reaction of either methyl *cis*-3-pentenylsulfide (**9**) or methyl *trans*-3-pentenylsulfide (**10**) with complex **3** yielded the trans 2,3,5-trisubstituted cyclopentenone **11** as the major product (Scheme III). We have shown that epimerization can take place after formation of the cyclopentenone.[17] Warming a toluene solution of a 4:1 mixture of **11**:**12** for 12 h in the presence of **3** gave rise to an 11:1 ratio of **11**:**12** in 95% yield. Reaction of either the *cis*- or *trans*-3-pentenyldimethylamine with cobalt complex **3** led to formation of the desired cyclopentenone; however, isomerization of the trisubstituted olefin to the tetrasubstituted isomer (entry 9 in Table I) was competitive.

In summary, the use of a directing ligand on the olefinic partner in the cobalt catalyzed olefin–acetylene cyclization provides a very high degree of regiocontrol in the intermolecular reaction. In addition, compared to previous intermolecular cycloadditions, the use of a directing ligand also contributes to a significant improvement in the overall yield. Applications to the synthesis of natural products will be reported in due course.

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, The National Science Foundation (CHE-8704933), The Atlantic Richfield Foundation of Research Corporation, and the Florida State University Center for Research and Creativity for support of this work.

(16) Dicobalt octacarbonyl obtained from Strem Chemical Company was of higher purity than that which was obtained from other sources. We thank Dr. Peter Wuts (Upjohn Co.) for this suggestion.

(17) We cannot, however, rule out the possibility of olefin isomerization prior to cycloaddition.

A New Method for the Instant Preparation of Large Unilamellar Vesicles

D. D. Lasič,*† A. Belič,‡ and T. Valentinčič§

Department of Physics, University of Waterloo Waterloo, Ontario, Canada N2L 3G1
University of Ljubljana, Department of Microelectronics Faculty of Electrical Engineering, Ljubljana, Yugoslavia
University of Ljubljana, Institute and Department of Biology, Ljubljana, Yugoslavia

Received August 10, 1987

In aqueous solutions phospholipid (PL) molecules form self closed spherical structures where one or several PL bilayers entrap part of the solvent in its/their interior.[1] In the case of multilamellar structures they are called liposomes or multilamellar vesicles (MLV), while terms such as small and large unilamellar vesicles (SUV and LUV, respectively) are used when a single bilayer separates internal and external solutions.[2]

SUV's and LUV's are very important in the studies of membranes, membrane proteins, and as delivery vehicles for drugs and genetic material into cells, and many different methods for their preparation exist.[3,4] However, most of them are time consuming and require relative demanding laboratory equipment. These methods involve the exposure of PL's and material to be encapsulated to physical stresses (sonication, high hydrostatic pressures) and/or a nonmild chemical environment (organic solvents, detergents, low/high pH) which may harm these sensitive substances. A simple, quick, and harmless method for vesicle preparation is still being searched for.

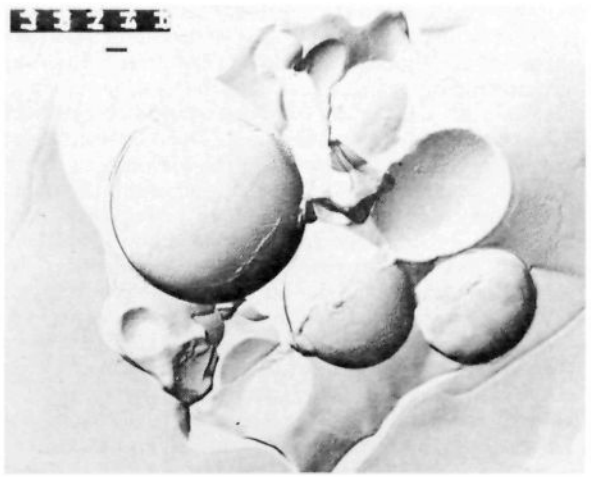


Figure 1. Freeze fracture EM micrograph of vesicle preparation. Vesicles were formed instantly by swelling PL film deposited on a silicon wafer in excess water. Bar indicates 100 nm.

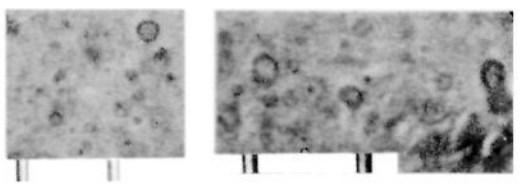


Figure 2. Phase contrast optical micrographs of instantly formed vesicles at two different magnifications. The distance between bars is 10 μm.

MLV's are formed spontaneously when dry PL films are hydrated and swollen in excess water by gentle shaking.[1] In contrast to the finite swelling behavior of uncharged films, charged PL films exhibit infinite swelling in excess water, and the spontaneous formation of heterogeneous populations of vesicles has already been reported.[5,6] By similar procedure, homogeneous preparations of SUV's have also been prepared.[7] However SUV's are not very suitable for the encapsulation because of their small internal volume.

In this communication we report on the "instant", spontaneous formation of rather homogeneous preparations of LUV's by an extremely simple technique. This procedure is completely analogous to the spontaneous formation of MLV's in that here LUV's are formed only by adding water to the dry PL film. The formation of multilamellar structures is prevented by inducing a surface charge on the bilayers while the size of the vesicles is controlled by the topography of the support surface on which PL film was deposited.

We deposited 0.5–1 mg of egg yolk lecithin (EYL) doped with 1.5–5 wt % of cationic detergent cetyltrimethylammonium bromide (CTAB) in 3 mL of $CHCl_3/CH_3OH$ on a specially etched 2-in. silicon wafer (silicon dioxide–silicon, heavy P^+ (boron) doped, vertical topography 0.5-μm steps, horizontal topography 6–10-μm random area).[8] This wafer was put in place of the original bottom

† University of Waterloo.
‡ University of Ljubljana, Department of Microelectronics.
§ University of Ljubljana, Institute and Department of Biology.

(1) Bangham, A. D.; Horne, R. W. *J. Mol. Biol.* **1964**, *8*, 660–668.
(2) Papahadjopoulos, D. *Ann. N.Y. Acad. Sci.* **1978**, *308*, 1–412.
(3) Szoka, F. C.; Papahadjopoulos, D. *Annu. Rev. Biophys. Bioeng.* **1980**, *9*, 467–508.
(4) Hauser, H. *Trends Pharm. Sci.* **1982**, *3*, 274–277.
(5) Talmon, Y.; Evans, D. F.; Ninham, B. W. *Science (Washington, D.C.)* **1983**, *221*, 1047–1049.
(6) Hauser, H.; Gains, N.; Lasic, D. D. In *Physics of Amphiphiles*; Corti, M., Digiorgio, V., Eds.; North Holland, Amsterdam, 1985; pp 648–662.
(7) Lasič, D. D.; Kidrič, J.; Zagorc, S. *Biochim. Biophys. Acta* **1987**, *896*, 117–122.
(8) Wafer was prepared by standard procedures of microelectronic industry: cleaning of silicon wafer, oxidation in water vapor, dehydration bake, applying photoresist, prebake, covering with predesigned mask, exposure to UV light, development, rinsing, drying, final bake, etching in HF, stripping, and ion implantation. The wafer was cleaned in hot H_2SO_4/H_2O_2 mixture, dip etched in 10/1 HF, washed in deionized water, and dried. See, e.g.: Brodie, J.; Muray, J. J. *The Physics of Microfabrication*; Plenum Press: New York, 1982.

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