Transition-Metal-Catalyzed Acetylene Cyclizations in Organic Synthesis

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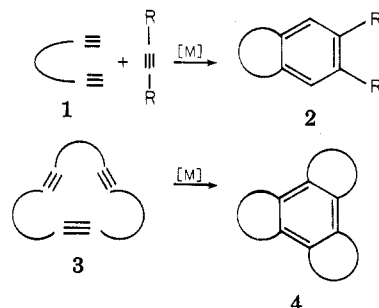
Received July 26, 1976

The oligomerization of acetylene to benzene, cyclooctatetraene, or higher annulenes is a highly exothermic process estimated by use of group equivalent techniques[1] to be 142 kcal/mol (of product) for benzene and 144 kcal/mol for cyclooctatetraene formation. It is, therefore, not surprising that the first report on the thermal trimerization of acetylene to benzene appeared over 100 years ago.[2] What is surprising, however, is that in the absence of metals relatively high temperatures ($\sim$400 °C) are needed for this conversion, leading to a wide variety of side products.[3]

The high energy content of acetylenic compounds has been utilized for the synthesis of molecules of synthetic[4] and theoretical[5] interest, although the reactivity of starting materials and products has resulted in low yields of desired structures. It is evident, however, that cyclization of acetylenes could be a synthetically useful reaction which remains to be more fully explored. One of the prerequisites of such an exploration is a method for bringing acetylenes to react under controlled conditions compatible with the synthesis of complex organic molecules carrying relatively sensitive functional groups. These conditions can be fulfilled by the use of transition-metal catalysts.

In 1949 Reppe et al.[6] reported the Ni(II)-catalyzed cyclization of acetylene to benzene, cyclooctatetraene, and styrene and opened the way to a comprehensive, if rather unsystematic, study of the various aspects of acetylene oligomerizations. Depending on the catalyst, various amounts of benzene ("Ni^{0}") or cyclooctatetraene ("Ni^{II}") could be produced.[7] Monoalkylacetylenes gave 1,2,4- and 1,3,5-trialkylbenzenes, the relative amounts of which seemed to depend on the reaction conditions, kinetic vs. thermodynamic control,[8] and the electronic and, particularly, spatial requirements of the catalyst.[7] Acetylenes carrying functional groups (olefin, acetylene, aryl, ether, alcohol, ester, carboxylic acid, amine, silyl)

could be cyclized in similar fashion. Most catalysts used in these transformations have contained group 8 transition metals[9] and, more recently, other nuclei.[9,10]

From a synthetic chemist's point of view the fact that acetylenes can be catalytically cyclized in the presence of a variety of functional groups suggests attractive synthetic schemes to more complicated structures. Cooligomerizations of α,ω-diynes (1), in which the two acetylene units are linked by homo- or heteroatomic chains of varying length, with monoacetylenes might provide access to bicyclic systems (2). Internal cy-

clization of triynes of the type 3 to give 4 might enable

(1) S. W. Benson, "Thermochemical Kinetics", Wiley, New York, N.Y., 1968.

(2) M. Berthelot, *C. R. Hebd. Seances Acad. Sci.*, **62**, 905 (1866); J. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene", Reinhold, New York, N.Y., 1945.

(3) G. M. Badger, G. E. Lewis, and I. M. Napier, *J. Chem. Soc.*, 2825 (1960).

(4) See H. G. Viehe, "Chemistry of Acetylenes", Marcel Dekker, New York, N.Y., 1969.

(5) See, for instance, K. P. C. Vollhardt, *Top. Curr. Chem.*, **59**, 276 (1975).

(6) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Justus Liebigs Ann. Chem.*, **560**, 1 (1948).

(7) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis", Chapter 1, Logos Press, London, 1967.

(8) U. Kruerke, C. Hoogzand, and W. Hübel, *Chem. Ber.*, **94**, 2817 (1961).

(9) F. L. Bowden and A. B. P. Lever, *Organomet. Chem. Rev.*, **3**, 227 (1968).

(10) See, for instance, K. Sonogashira and N. Hagihara, *Bull. Chem. Soc. Jpn.*, **39**, 1178 (1966); G. Fachinetti and C. Floriani, *J. Chem. Soc., Chem. Commun.*, 66 (1974); J. A. Labinger, J. Schwartz, and J. M. Townsend, *J. Am. Chem. Soc.*, **96**, 4009 (1974); K. L. T. Wong, J. L. Thomas, and H. H. Brintziner, *ibid.*, **96**, 3694 (1974); D. W. Hart, T. F. Blackburn, and J. Schwartz, *ibid.*, **97**, 679 (1975); J. A. Labinger and J. Schwartz, *ibid.*, **97**, 1596 (1975); R. J. Klingler, W. Butler, and M. D. Curtis, *ibid.*, **97**, 3535 (1975).

Peter Vollhardt was born in Madrid, Spain, in 1946. He went to school in Buenos Aires, Argentina, and then in Germany, where he did his undergraduate work at the University of Munich. He subsequently moved to University College, London, where he was persuaded by P. J. Garratt to become a chemist rather than a rock star. Following postdoctoral work at Caltech with R. G. Bergman, he was appointed Assistant Professor at Berkeley in 1974. Dr. Vollhardt is an A. P. Sloan Fellow and has research interests in catalysis, organic synthesis, nonbenzenoid aromatics, strained rings, and soccer.

a one-step formation of tetracyclic structures of synthetic value. Molecules of theoretical interest should in principle be available by this scheme, in particular benzenes fused to strained rings, derived from compounds of type 1 or 3 in which the links between the acetylene units are short. Control of substitution of the benzene rings via substituted acetylenes should be readily achieved and should have distinct advantages over approaches employing electrophilic substitution schemes.

Despite the fact that transition-metal-catalyzed trimerizations of monoacetylenes proceed with remarkable ease, little is known about oligomerizations of oligoacetylenes. α,ω-Diacetylenes, HC≡C-$(CH_2)_n$C≡CH, with Ziegler type catalysts (trialkylaluminum–titanium tetrachloride) give only small amounts of trimers of types 5 (n = 2–5) and 6 (n = 5–7);[11] bis(triphenylphosphine)dicarbonylnickel[12] gives

5
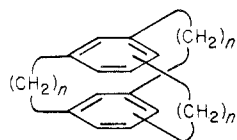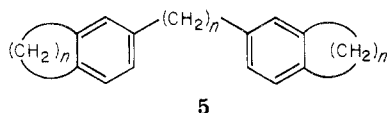
6
1,2,4-1,2,4
1,2,4-1,3,5
1,3,5-1,3,5
isomers

even smaller amounts of 5 (n = 3, 4), and bis(tetracarbonylcobalt)mercury gives compounds of type 7.[11]

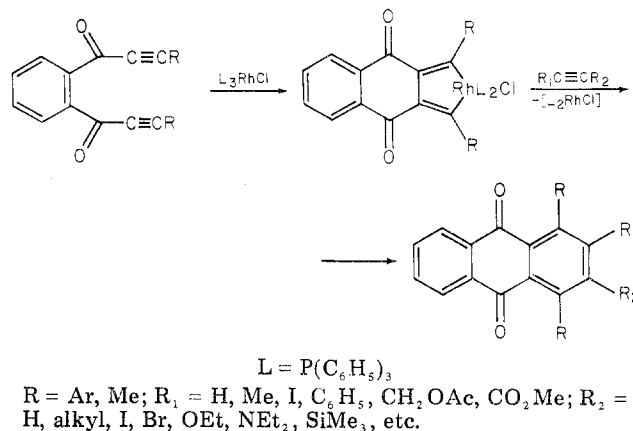**7**   **8**, R = alkyl   **9**, Cp = η^5-C_5H_5
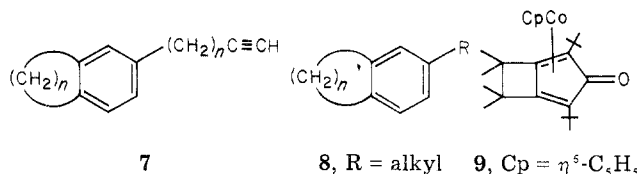
The predominant by-product of all these reactions is reported to be insoluble polymeric material. Co-oligomerizations of alkylacetylenes with α,ω-diynes (n = 3, 4) using $[P(C_6H_5)_3]_2Ni(CO)_2$ also result in mixtures containing small amounts of 8 (for n = 3 only), other oligomers, and mainly polymer.
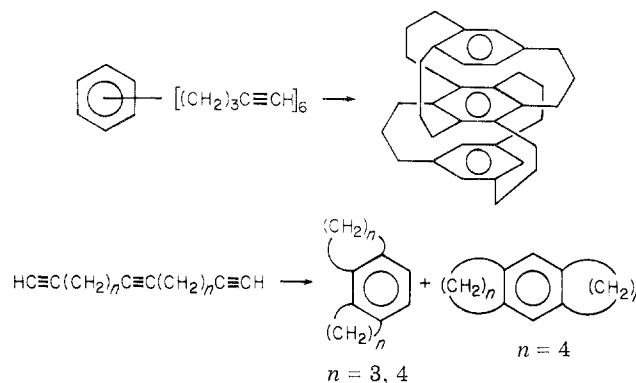
Several interesting complexes of bisacetylenes with metals are known. Macomber[13] found that 1,6-di-*tert*-butyl-3,3,4,4-tetramethyl-1,5-hexadiyne with η^5-cyclopentadienylcobalt dicarbonyl gives 70% of 9. In a series of papers King et al. have described the reactions of transition-metal compounds with macrocyclic alkadiynes. Thus, iron carbonyls, CpCo(CO)$_2$, and CpRh(CO)$_2$ result in cyclobutadiene complexes, ferroles (ferrocyclopentadienes), and other more complex clusters, depending on the conditions employed.[14–17]

(11) A. J. Hubert and J. Dale, *J. Chem. Soc.*, 3160 (1965).
(12) E. S. Colthup and L. S. Meriwether, *J. Org. Chem.*, **26**, 5169 (1961).
(13) R. S. Macomber, *J. Org. Chem.*, **38**, 816 (1973).
(14) R. B. King, I. Haiduc, and C. W. Eavenson, *J. Am. Chem. Soc.*, **95**, 2508 (1973).
(15) H. B. Chin and R. Bau, *J. Am. Chem. Soc.*, **95**, 5068 (1973).
(16) R. B. King and A. Efraty, *J. Am. Chem. Soc.*, **94**, 3021 (1972).
(17) R. B. King and M. N. Ackermann, *J. Organomet. Chem.*, **67**, 431 (1974).

Scheme I

L = $P(C_6H_5)_3$
R = Ar, Me; R_1 = H, Me, I, C_6H_5, CH_2OAc, CO_2Me; R_2 = H, alkyl, I, Br, OEt, NEt_2, $SiMe_3$, etc.

Scheme II

n = 3, 4 n = 4

Simpler acetylene complexes are formed with (CpNiCO)$_2$ and Co$_2$(CO)$_8$.[18]

E. Müller et al.[19] have isolated a series of rhodacyclopentadienes from the reaction of substituted diketodiynes with tris(triphenylphosphine)rhodium(I) chloride. These metallocycles can be reacted with monoacetylenes to give a variety of quinones (Scheme I). Similarly, reaction with O$_2$, S, or Se results in the corresponding heterocycles 10. Other diynes (e.g., 11),

10, X = O, S, Se   **11**   **12**, X = O, S, Se, CO, $(C_6H_5)_2C_2$
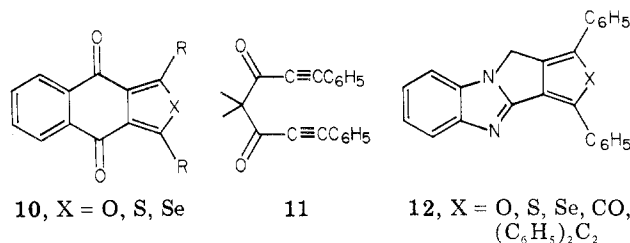
heterocycles (e.g. 12), and metals[20] can be used. It seems, however, that there are some severe limitations to this method: use of equimolar amounts of transition metal, sensitivity to steric requirements, and need for highly substituted (mainly phenyl) and activated (keto) acetylenes. Nevertheless, Müller's basic work has shown that in principle bisacetylenes can be very useful in-

(18) R. B. King, I. Haiduc, and A. Efraty, *J. Organomet. Chem.*, **47**, 145 (1973).
(19) E. Müller, C. Beissner, H. Jäkle, E. Langer, H. Muhm, G. Odenigbo, M. Sauerbier, A. Segnitz, D. Streichfuss, and R. Thomas, *Justus Liebigs Ann. Chem.*, **754**, 64 (1971); E. Müller, *Synthesis*, 761 (1974).
(20) C. W. Bird, *J. Organomet. Chem.*, **47**, 281 (1973). See also E. Müller, A. Scheller, W. Winter, F. Wagner, and H. Meier, *Chem. Ztg.*, **99**, 155 (1975); F. Wagner and H. Meier, *Tetrahedron*, **30**, 773 (1974); J. Hambrecht H. Straub, and E. Müller, *Tetrahedron Lett.*, 1789 (1976).
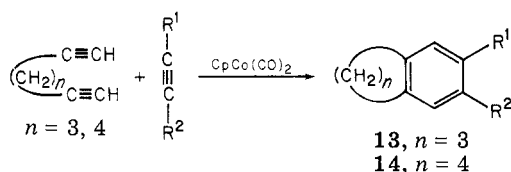
Scheme III

13, $n = 3$
14, $n = 4$

Table I
Indans 13 and Tetralins 14 Prepared According
to Scheme III

Compound	R^1	R^2	Yield, %
13a	CO_2Me	CO_2Me	20
13b	C_6H_5	H	26
13c	C_6H_5	C_6H_5	24
13d	$n\text{-}C_6H_{13}$	H	14
13e	Me_3Si	Me_3Si	82
14a	CO_2CH_3	CO_2CH_3	26
14b	C_6H_5	H	18
14c	C_6H_5	C_6H_5	21
14d	$n\text{-}C_6H_{13}$	H	14
14e	Me_3Si	Me_3Si	85
14f	Me_3Si	Me	34

termediates on the way to complex structures.

Two esoteric examples of internal cyclization reactions to give cage structures using Ziegler catalysts[21] are shown in Scheme II.

At the outset of our work few efficient, catalytic, and synthetically useful cooligomerizations of acetylenes to cyclic products had been achieved. I wish to address myself to our current efforts at developing transition-metal-catalyzed acetylene cyclizations as an attractive and versatile synthetic tool in organic chemistry.

Synthesis of Indans, Tetralins, and Anthraquinones

We have found that cooligomerization of 1,6-heptadiyne and 1,7-octadiyne with substituted monoacetylenes, catalyzed by commercially available $CpCo(CO)_2$, provides a general synthetic entry into indans and tetralins with essential control of substitution[22,23] (Scheme III and Table I). The major side products accompanying 13 and 14 arise from cyclotrimerization and complex cooligomerization, but the desired compounds are easily separated by column chromatography.

In an effort to suppress random cyclization processes we sought a monoacetylene that would not (for steric reasons) trimerize on its own, but would still supply useful organic functionality once reaction with a diyne was completed. Such an acetylene was found in bistrimethylsilylacetylene $(Me_3SiC)_2$. Slow addition of diyne to refluxing solvent $(Me_3SiC)_2$ containing catalytic amounts of $CpCo(CO)_2$ resulted in the o-bistrimethylsilyl-substituted products 13e and 14e in high yield. The solvent can be recycled several times without apparent buildup of harmful impurities. The impressive tolerance of the catalyst to functional groups is further exemplified by the catalytic formation of anthraquinones 19.[23] The application of this method

Scheme IV

20

Table II
Benzocyclobutenes 20 Prepared According
to Scheme IV

Compound	R_1	R_2	R_3	R_4	Yield, %
20a	H	H	CO_2Me	CO_2Me	14
20b	H	H	C_6H_5	H	17
20c	H	H	C_6H_5	C_6H_5	48
20d	H	H	$n\text{-}C_6H_{13}$	H	13
20e	H	H	Me_3Si	Me_3Si	65
20f	H	H	CH_2OMe	CH_2OMe	33
20g	H	H	CH_2OMe	Me_3Si	55
20h	H	H	CH_2OH	H	14
20i	Me	Me	C_6H_5	C_6H_5	20
20j	Me	Me	CO_2Me	CO_2Me	28
20k	CH_2OMe	CH_2OMe	Me_3Si	H	25
20l	Me_3Si	H	Me_3Si	H	13
20m	Me_3Si	Me_3Si	Me_3Si	H	2
20n	Me_3Si	H	Me_3Si	CH_2OMe	16
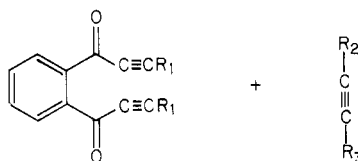
15, $R_1 = H$ 16, $R_2 = R_3 = Me_3Si$
17, $R_1 = Me_3Si$ 18, $R_2 = $ n-hexyl; $R_3 = H$

19
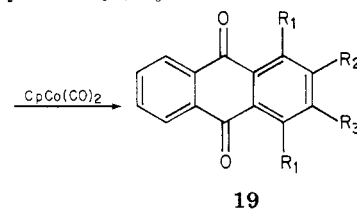
to anthracyclinone syntheses[24] is currently under investigation in our laboratories.

Synthesis of Benzocyclobutenes

Benzocyclobutenes, valuable precursors to theoretically interesting molecules,[25] have recently gained increasing importance as intermediates in the synthesis of natural products.[26-28] For this purpose complete control of substitution in the aromatic ring of benzocyclobutene is highly desirable and has been the source of considerable synthetic difficulty.[29] A solution to this problem and a highly attractive test for the scope of the $1 \rightarrow 2$ transformation using $CpCo(CO)_2$ would be its application to the synthesis of benzocyclobutenes. It

(21) A. J. Hubert and M. Hubert, *Tetrahedron Lett.*, 5779 (1966); A. J. Hubert, *J. Chem. Soc. C*, 6, 11, 13, 1984 (1967). See also R. D. Stephens, *J. Org. Chem.*, 38, 2260 (1973).

(22) R. L. Hillard III and K. P. C. Vollhardt, *Angew. Chem.*, 87, 744 (1975); *Angew. Chem., Int. Ed. Engl.*, 14, 712 (1975).

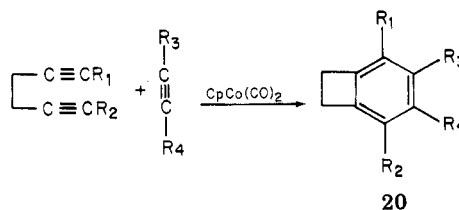(23) R. L. Hillard III and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, submitted for publication.

(24) J. Bernard, R. Paul, M. Boiron, C. Jacquillat, and R. Maral, Ed., "Rubidomycin", Springer-Verlag, New York, N.Y., 1969; see also: A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, 98, 1967 (1976).

(25) M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds", Academic Press, New York, N.Y., 1967.

(26) W. Oppolzer, *J. Am. Chem. Soc.*, 93, 3833 (1971); W. Oppolzer and K. Keller, *ibid.*, 93, 3836 (1971); W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 11, 1031 (1972); R. Hug, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 55, 10 (1972); P. G. Sammes, *Tetrahedron*, 32, 405 (1976); W. Oppolzer, *Tetrahedron Lett.*, 1001 (1974).

(27) T. Kametani and K. Fukumoto, *Heterocycles*, 3, 29 (1975); T. Kametani, Y. Kato, T. Honda, and K Fukumoto, *ibid.*, 4, 241 (1976).

(28) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumoto, *J. Am. Chem. Soc.*, 98, 3378 (1976).

(29) For a review, see I. L. Klundt, *Chem. Rev.*, 70, 471 (1970).

would be reasonable to expect that the strain incorporated in the four-membered ring being generated might cause side reactions and polymerizations to occur. However, this concern proves to be unfounded, and a remarkable variety of functionalized benzocyclobutenes 20 can be made via this route, starting from 1,5-hexadiynes and various monoacetylenes (Scheme IV, Table II).[23,30]

Several features of this reaction are interesting. First, when a direct comparison is possible, yields of benzocyclobutenes parallel the yields of the corresponding indans and tetralins, suggesting that the potential ring strain developing in these cyclizations is of minor consequence. Otherwise, one might have expected increased formation of "random" oligomers (without four-ring incorporation) at the expense of compounds 20. Second, trimethylsilylated acetylenes usually do not undergo trimerizations on their own, and cooligomerizations to give 20 become more efficient. When product 20 has to bear too much strain due to substitution by excessively bulky groups, reaction either does not occur (as, for instance, in the case of $R_1 = R_2$ = H, $R_3 = R_4 = t$-Bu; or $R_1 = R_2 = R_3 = R_4 = Me_3Si$), occurs in low yield (20m), or takes an anomalous course (for example, 20k is derived from the reaction of 1,6-dimethoxymethyl-1,5-hexadiyne with $(Me_3SiC)_2$). Third, when the course of the cyclization has two alternatives, it seems to choose the route that leads to the sterically more demanding product (e.g. 20l and 20n, which, in addition, contains one-sixth of the other isomer)!

Reaction Mechanisms

Several investigators[31-36] have contributed significantly to the understanding of metal-catalyzed acetylene trimerizations. Cobalt(I) species, as in CpCo-$(CO)_2$, seem to react via the intermediate formation of diacetylene complexes, followed by oxidative coupling of the two acetylene units to a metallocycle capable of reacting with another mole of acetylene to eventually result in the final benzenic product. Two alternatives can be envisaged in cooligomerizations of α,ω-diynes with monoacetylenes. In the first of these (Scheme V) a diacetylene complex, A, undergoes oxidative coupling (with apparent ligand participation[37a]) to an "intramolecular" cobalt metallocycle (cobole), B, which could in principle react by a Diels–Alder type route via C or a metallocycloheptatriene intermediate, D, to give the final products. The extent to which ligand L is involved in these final steps is not clear, and indeed a direct Diels–Alder addition of acetylene to B (without prior complexation) has to be considered with activated acetylenes.[37b]

(30) K. P. C. Vollhardt and R. G. Bergman, *J. Am. Chem. Soc.*, 96, 4996 (1974); W. G. L. Aalbersberg, A. J. Barkovich, R. L. Funk, R. L. Hillard III, and K. P. C. Vollhardt, *ibid.*, 97, 5600 (1975).

(31) J. P. Collman, J. W. Kang, W. F. Little, and M. F. Sullivan, *Inorg. Chem.*, 7, 1298 (1968); J. P. Collman, *Acc. Chem. Res.*, 1, 136 (1968).

(32) P. M. Maitlis, *Pure Appl. Chem.*, 30, 427 (1972); 33, 489 (1973); *Acc. Chem. Res.*, 9, 93 (1976).

(33) H. Yamazaki and N. Hagihara, *J. Organomet. Chem.*, 21, 431 (1970).

(34) S. A. Gardner, P. S. Andrews, and M. D. Rausch, *Inorg. Chem.*, 12, 2396 (1973).

(35) L. S. Meriwether, M. F. Leto, E. C. Colthup, and G. W. Kennerly, *J. Org. Chem.*, 27, 3930 (1962).

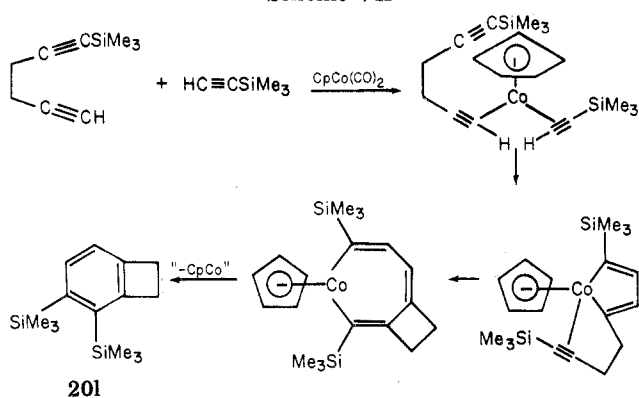(36) W.-S. Lee and H. H. Brintzinger, private communication.

(37) (a) D. McAlister, J. E. Bercaw, and R. G. Bergman, private communication; (b) L. McDonnell and R. G. Bergman, private communication.
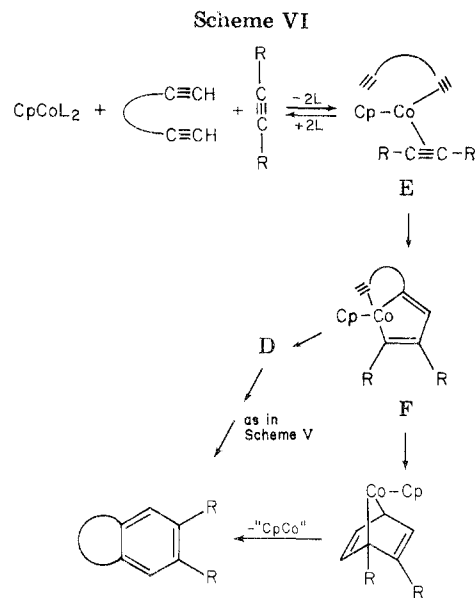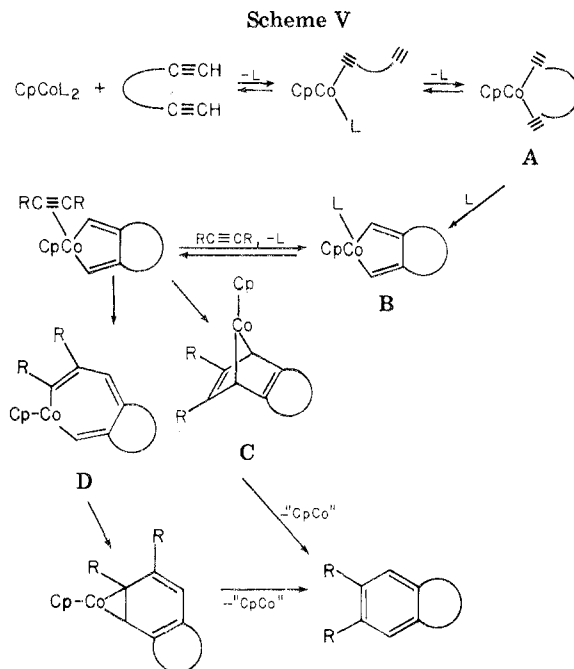
**Scheme V**

Scheme VI

The second alternative (Scheme VI) requires the two cotrimerizing components to complex to the metal in the early stages of the reaction, resulting in E. Oxidative coupling to the "intermolecular" cobole F, followed by insertion of the other end of the diyne, would then give intermediate D, from which product formation could occur as described in Scheme V. Alternatively the Diels–Alder route could be chosen. The E → F conversion seems particularly attractive since the cobalt species remains coordinatively saturated during the process.

It is very difficult to distinguish between all of the mechanistic possibilities, and, indeed, different systems might arrive at the cyclized product by different or multiple pathways. Thus, for instance, 2,7-nona- and 2,8-decadiyne have been shown to rapidly form observable intramolecular coboles when treated with $CpCo[P(C_6H_5)_3]_2$,[37b] but 2,6-octadiyne, which would form a cobole fused to a four-ring, seemingly does not. These results suggest that indans and tetralins are

Scheme VII

201

Scheme VIII

26a, X = H
b, X = D
c, X = Br

24a, X = H
b, X = D
c, X = Br

25a, X = Y = H
b, X = Y = D
c, X = Y = Br
d, X = Br; Y = I
e, X = Br; Y = Ac

formed by the intramolecular cobole route, and benzocyclobutenes by the intermolecular path. Further interesting evidence is provided by the isolation of catalytically inert cyclobutadiene complexes **21** (in both *d,l* and *meso* configuration), **22**, and **23**[23] from catalytic cooligomerizations of α,ω-diynes with $(Me_3SiC)_2$. These

21　　　　　　　　　　**22**

23
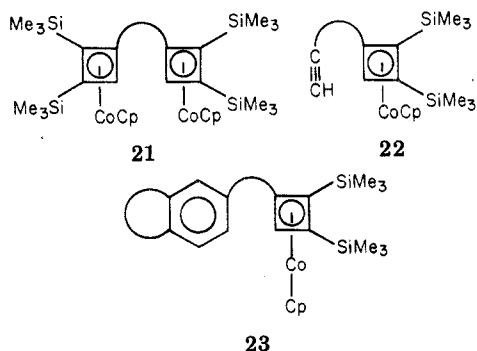
complexes could be derived by rearrangement of coboles F to give **22**, which then reacts further to either **21** or **23**. In attempts to synthesize benzocycloheptenes by cobalt-catalyzed cooligomerizations the catalyst rapidly gets depleted by this side reaction, and yields of desired products are low.[23]

If Scheme VI is descriptive of the mechanism of benzocyclobutene formation, then an attractive explanation for the preferred formation of sterically more hindered products (**201, 20n**) can be proposed as shown in Scheme VII. The crucial feature of this scheme is the intermediacy of complexes in which steric hindrance is minimized before the benzene-forming step, in which the full gain of resonance overrides steric considerations. Electronic factors may also play a role in this remarkably selective transformation.

Finally, polynuclear cobalt complexes of the type observed in the rich photo- and thermochemistry of $CpCo(CO)_2$[38] have to be considered as catalytic intermediates involved in acetylene cyclizations.
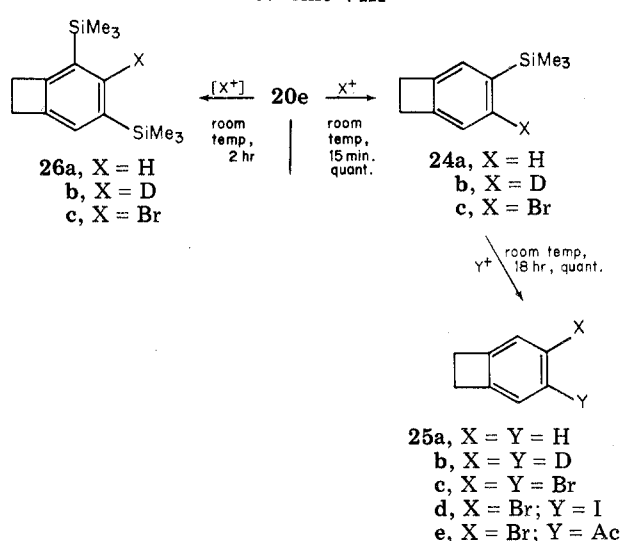
The *o*-Bistrimethylsilybenzene Unit in Electrophilic Substitutions

Trimethylsilyl nuclei are excellent leaving groups in electrophilic substitution reactions.[39] We found[23,30] that due to steric acceleration the first trimethylsilyl group in compounds of the type **20e** can be quantitatively displaced before the second one, enabling ready synthetic entry into a large variety of derivatized

compounds of type **25**. Kinetic data were obtained on the deuteriodesilylation of **13e, 14e**, and **20e**, and under pseudo-first-order conditions the first displacement occurred 36–42 times faster than the second. Scheme VIII exemplifies synthetic application of this reaction in the case of 4,5-bis(trimethylsilyl)benzocyclobutene (**20e**).[23,30] Moreover, treatment of **20e** with dilute acid (or electrophile) causes rearrangement to **26**[40] and adds a new synthetic variable in the utilization of *o*-bissilylbenzene derivatives for the synthesis of specifically substituted benzene rings.

Synthesis of Polycycles
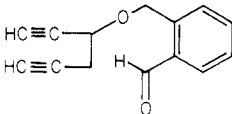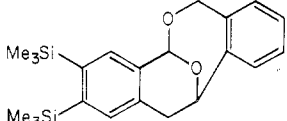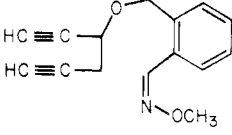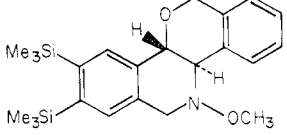
The ease with which a variety of benzocyclobutenes can be formed in cotrimerizations of 1,5-hexadiynes with monoacetylenes, particularly $(Me_3SiC)_2$, indicated the possibility of using 1,5-diynes as precursors to *o*-xylylenes, to be trapped in situ by added dienophile. Reaction of ethers **27** with $(Me_3SiC)_2$ solvent in the presence of catalyst indeed provides a *one-step* synthesis of the unusual naphthalene **28**,[41] the formation of which must proceed through the intermediacy of an alkoxy-*o*-xylylene trapped by $(Me_3SiC)_2$, followed by loss of alcohol, as shown. Electrophilic displacement

27, R = Me, THP, Me_3Si

29　　　　　　　　　　**28**

(38) K. P. C. Vollhardt, J. E. Bercaw, and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 4998 (1974); *J. Organometal. Chem.*, **97**, 283 (1975).

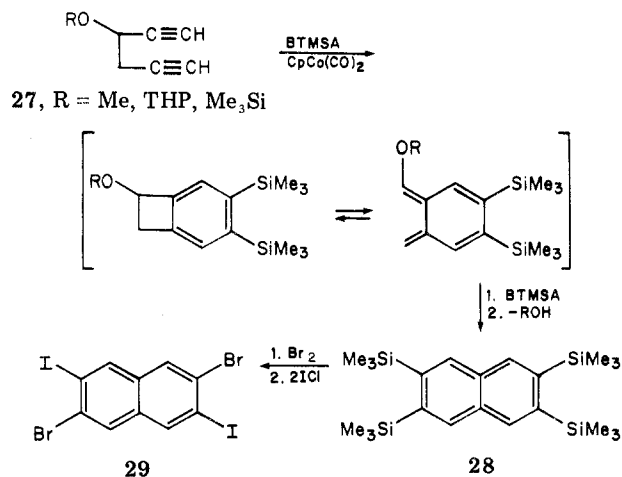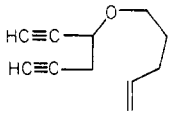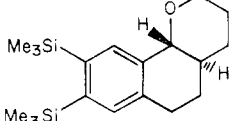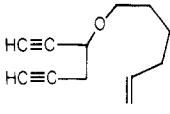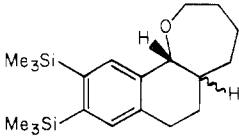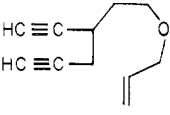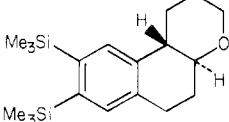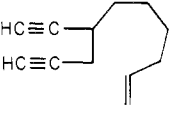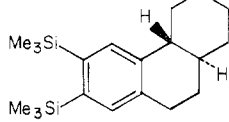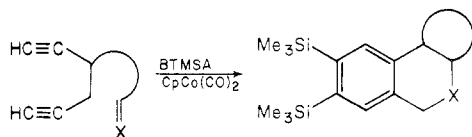(39) C. Eaborn, *J. Organometal. Chem.*, **100**, 43 (1975).

(40) Similar observations were made in the case of *o*-bis(trimethylsilyl)benzene, but prolonged exposure to high temperatures and acidic catalyst were necessary to effect isomerization: D. Seyferth and D. L. White, *J. Am. Chem. Soc.*, **94**, 3132 (1972).

(41) R. L. Funk and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.*, 833 (1976).

Table III
Polycycles by Acetylene Cyclization

Starting material	Product	Yield, %
29	**30**	60
31	**32** + regioisomers (unseparated mixture)	65
33	**34**	50
35	**36**	45
37	**38** + cis isomer (ca. 15%)	90
39	**40** + cis isomer (<5%)	80

Scheme IX

of each silyl group in **28** is distinct, specific, and easily monitored by NMR, as demonstrated in the synthesis of **29**. The position selectivity and relative rates appear to be functions of directing effects exerted by both the incoming electrophile and Me₃Si substituents, in addition to steric influences. In principle, by proper choice of substitution sequence and reagents, a large variety of specifically substituted naphthalene derivatives should be available through **28**.

The lability of the alkoxy 2-substituted benzocyclobutene four-membered ring with respect to o-xylylene formation, in comparison with unsubstituted derivatives **20**, has been observed previously.[42] If such

an in situ generated o-xylylene could be trapped intramolecularly[26-28] (Scheme IX), it would be possible to easily synthesize polycyclic systems containing a benzene ring, with essentially complete control of substitution. We have shown that this is possible (Table III).[43] Slow addition of various diynes substituted by side chains bearing potential dienophiles to a refluxing solution of CpCo(CO)₂ in (Me₃SiC)₂ gives polycyclic systems in good yield in one step. Interestingly, the stereochemistry of the new ring junction formed is almost always trans. Controls showed that under the reaction conditions CpCo(CO)₂ does not effect cis → trans isomerization and suggest that when there are no other constraints on the system[26] the exo transition state **41** of intramolecular cycloaddition is

(42) For an attempt to rationalize relative rates of o-xylylene formation, see T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Tetrahedron*, 31, 949 (1975).

(43) R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 98, 6755 (1976).

more favored than the endo transition state **42**. In the case of **31** (which leads to a seven-membered ring) and **33** (for electronic reasons) regioisomers of the "normal" adducts are observed. The structure and stereochemistry of all the adducts was proven by analytical, spectral (particularly ^{13}C and 360-MHz ^{1}H NMR) and (where possible) chemical methods. Thus, typical trans-H,H coupling constants were observed, and, in the case of octahydrophenanthrene **40**, the authentic cis isomer was prepared by another route[44] and chemically correlated with the trans isomer **40**. If shorter reaction times are employed, the intermediate benzocyclobutenes can be isolated only when the substituent on the four-ring is carbon (e.g., **43**, **44**). Protodesilylation followed by cycloaddition gives products identical with compounds derived from protodesilylation of **38** and **40**.

41   **42**

43, X = O
44, X = CH$_2$
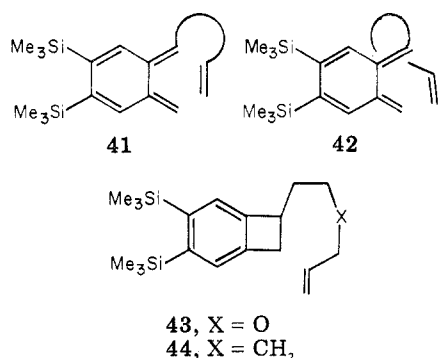
The methodology described here provides a striking simplification of currently available routes to natural products via benzocyclobutenes.[26–28]

Heterocycles

A nitrile group can be naively regarded as a "heteroacetylene" and should in principle be capable of participation in oligomerizations with acetylenes.[30,45] Cooligomerization of α,ω-diynes with nitriles effects direct syntheses of substituted 5,6,7,8-tetrahydroisoquinolines **45** in good yields ($\sim$70–80%).[46] Reaction of 1,7-octadiyne with ethyl cyanoacetate provides the quinolizine **46** in one step, presumably via the intermediacy of the tetrahydroisoquinolyl acetic ester, which undergoes ready condensation[47] with another mole of cyanoacetate. The potential of further cyclizations involving other functionalized nitriles is currently being explored.

45, R = Me, n-C$_4$H$_9$, C$_6$H$_5$; n = 4
     R = n-C$_4$H$_9$, C$_6$H$_5$; n = 3

46
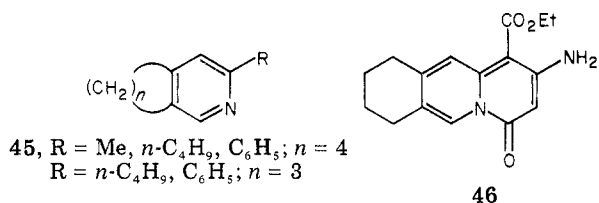
Molecules of Theoretical Interest

As an example of the 3 → 4 interconversion we decided to study 1,5,9-cyclododecatriyne (**47**), a rather

special and interesting case. Models indicate strong interaction of the three acetylene units and suggest the possibility of an equilibrium with the highly strained 1,2:3,4:5,6-tricyclobutabenzene (**48**). This compound is of interest for its anticipated cyclohexatrienic properties and its potential for undergoing a degenerate structural isomerization **48a** ⇄ **48b** (detectable only by suitable labeling) via two isomeric intermediates (or transition states), the radialene **49** and its "rotamer" **50**.[48]

47   **48a**   **48b**

49   **50**

51, R = CO$_2$Me
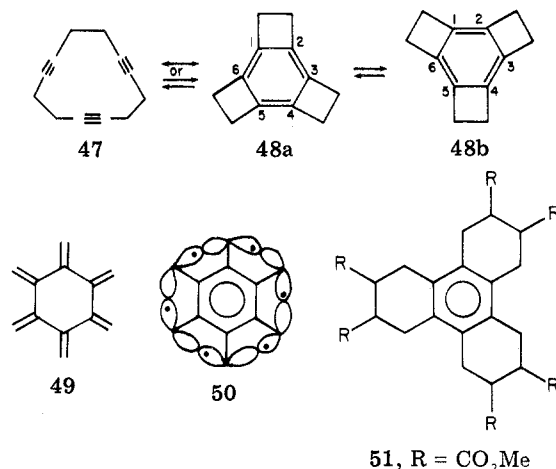
Triyne **47** was obtained via a classical route, and its properties are indeed interesting.[49] Its electronic [λ_{max}(EtOH) 258 sh (ϵ 25.2), 264 (28.4), 267 sh (28.1), 279 (24.9) nm] and photoelectron spectra clearly indicate strong through-space interaction of the three acetylene units. Despite this interaction (or perhaps because of it) **47** is surprisingly inert to light, pressure (15 kbars), acid, and transition-metal catalysts [e.g., CpCo(CO)$_2$]. However, at 230 °C in the presence of a trapping agent (dimethyl maleate) a formal triadduct of **48**, compound **51**, can be obtained. This suggests that under these conditions cyclization is occurring, followed by rapid opening of the four-membered rings in **48** and trapping by maleate. The inability of **47** to close on exposure to CpCo(CO)$_2$ is readily understood within the framework of the mechanisms depicted in Schemes V and VI, since formation of intramolecular metallocyclopentadiene intermediates would be prohibited by strain. In addition, thermal and acid-catalyzed cyclizations are apparently slowed down by the developing ring strain of the three cyclobutene nuclei. Gas-phase pyrolysis experiments currently under way might provide access to the postulated intermediates **48** and **49**.

Specifically functionalized benzocyclobutenes (vide supra) which can be used in the synthesis of other interesting strained-ring aromatics answer some questions concerning the nature of benzene aromaticity and activation of aromatic polycycles by fusion to strained rings. For example, 4,5-bromoiodobenzocyclobutene (**25d**) can be used to generate cyclobuta[1,2-d]benzyne (**52**) by treatment with butyllithium or magnesium.[50] Trapping with furan results in cycloadduct **53**, while in the absence of a trapping agent

(44) H. Christol, A. Gaven, Y. Pietrasanta, and J. L. Vernet, *Bull. Soc. Chim. Fr.*, 4510 (1971).

(45) Y. Wakatsuki and H. Yamazaki, *Synthesis*, 26 (1976); H. Bönnemann and R. Brinkman, *ibid.*, 600 (1975).

(46) A. Naiman and K. P. C. Vollhardt, in preparation.

(47) J. C. Godfrey in E. Klingsberg, Ed., "Pyridine and Its Derivatives", Part III, Interscience, New York, N.Y., 1962, p 347.

(48) See M. O. Riley and J. D. Park, *Tetrahedron Lett.*, 2871 (1971); R. P. Thummel, *J. Chem. Soc., Chem. Commun.*, 899 (1974); E. Cuthbertson and D. D. MacNicol, *Tetrahedron Lett.*, 1893 (1975).

(49) A. J. Barkovich and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **98**, 2667 (1976).

(50) R. L. Hillard III and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **98**, 3579 (1976).

dimerization and (formal) trimerization occur to 2,3:
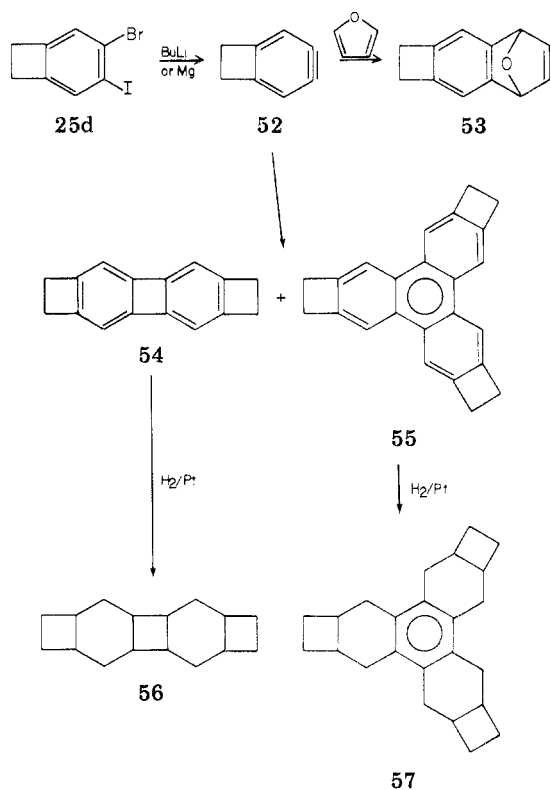
6,7-dicyclobutabiphenylene (54) and 2,3:6,7:10,11-tricyclobutatriphenylene (55).[51] Compound 54 is one of the most strained benzenoid hydrocarbons known, and as such exhibits remarkable reactivity. It is air sensitive and hydrogenates instantly at normal pressures and room temperature to the totally saturated 56. Cycloaddition of dienophiles occurs to both "external" four-membered rings. Comparison of the spectral and chemical data on 54 with other less strained model systems (e.g., 58, 59) shows a clear gradation of strain along the series.
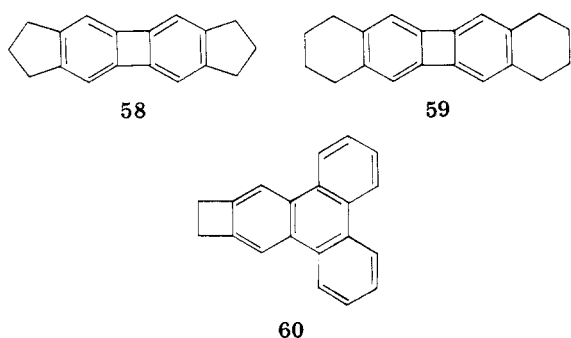
From concentrated solutions of 52 the triphenylene 55 can be isolated.[51] This compound is the first polycyclic benzenoid to be synthesized that is fused to three activating strained rings, and its properties in comparison with model 60 and triphenylene itself reflect the added degree of activation. Again, hydrogenation

(51) R. L. Funk and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.,* 15, 53 (1976).

is extremely facile, leading to 57, in striking contrast with triphenylene, which requires high pressure and heat before hydrogen uptake occurs. The electronic spectra along the series exhibit bathochromic shifts consistent with the simple strain model that accounts for the relative reactivity of these compounds.

Finally, the current "world record" in strained benzene chemistry, 1,2-cyclopropa-4,5-cyclobutabenzene (61), is also accessible (albeit in very low yield) via cobalt-catalyzed synthesis of benzocyclobutene 20g,[52] followed by bromination and elimination. Compound 61 has also been made by another route via precursor 62.[53] Despite the extraordinary strain present in 61,
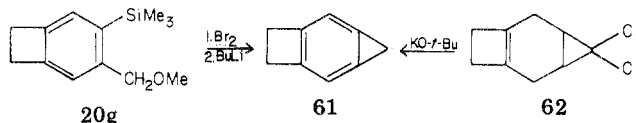
there seems to be a large degree of aromatic character left, as judged by the NMR criterion: the unsaturated protons absorb in the aromatic region, τ 3.15. On the other hand, the longest wavelength electronic absorption (λ_{max} 294 nm) has the largest blue shift yet observed for a simple tetraalkylated benzene. The relative stability of 61 should serve as an incentive in the search for other more highly distorted analogs.

Conclusion

The cobalt-catalyzed cyclooligomerization of acetylenes promises to be a significant addition to the organic chemist's repertoire for the synthesis of compounds of theoretical and synthetic interest. This Account has attempted to give the reader a glimpse of the intriguing possibilities opened up by this method. Obviously, much work remains to be done. A clearer understanding of the details of the mechanism of these reactions would be desirable. Other catalysts should be explored and the synthesis of model or improved catalysts (for example, polymer-supported species[54]) should be continued. Routes to natural products, particularly heterocyclic molecules, are currently under investigation. Finally, novel strained-ring compounds of the carbocyclic or heterocyclic series should become accessible in the near future.

(52) C. J. Saward and K. P. C. Vollhardt, *Tetrahedron Lett.,* 4539 (1975).
(53) D. Davalian and P. J. Garratt, *J. Am. Chem. Soc.,* 97, 6883 (1975).
(54) P. Perkins and K. P. C. Vollhardt, unpublished results.