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Cobalt-Mediated [2+2+2]-Cycloadditions: A Maturing Synthetic Strategy

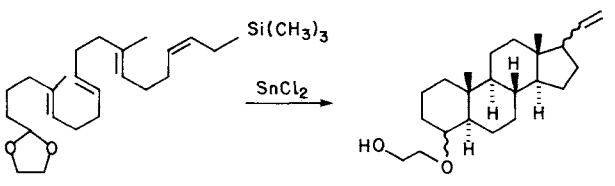
New Synthetic Methods (43)

By K. Peter C. Vollhardt*

Dicarbonyl(η^5-cyclopentadienyl)cobalt functions as a matrix on which a variety of unsaturated organic substrates undergo mutual bond formation. In this way α,ω-diynes cocyclize with monoalkynes to give annelated benzenes, while *o*-diethynylbenzenes furnish biphenylenes, and α,ω-enynes lead to the formation of complexed bi- and tricyclic dienes. Nitriles cocyclize with two alkynyl groups to give pyridines and other heterocycles, isocyanates allow access to annelated 2-pyridones, and incorporation of carbon monoxide provides complexed cyclopentadienones. In many cases remarkable chemo-, regio-, and stereoselectivity are observed, partially facilitated by use of the trimethylsilyl substituent as a controlling group. The scope and level of maturity of the method are demonstrated by the synthesis of a series of hitherto inaccessible, novel, and theoretically interesting molecules, and by its utilization in several unique approaches to a variety of natural products, e.g. protoberberines, steroids, vitamin B_6, and camptothecin.

1. Introduction

The discovery and control of new bond formations are two of the primary tasks of the synthetic organic chemist. The arsenal of current synthetic methods has already allowed the construction of even the most complex natural products and most remarkable, "unnatural" molecular assemblies. Nevertheless, despite these advances, there remains much room for improving and particularly simplifying synthetic strategies. This can be done by either cleverly manipulating existing methodology or, probably more successfully, by finding new methods through which simple materials are converted into structures of greater complexity. In this connection we deem it especially important to design new reactions in which a maximum change of topological complexity[1] can be effected with the highest degree of efficiency and selectivity. Many cycloaddition reactions fall into this category, because at least two bonds may be formed in one step while steric and electronic factors reduce the number of options available to the substrates en route to the products. A striking example is the cyclization reaction of *Johnson* et al.[2] in which a stereospecifically constructed polyene undergoes acid-catalyzed multiple ring closure to the steroid nucleus (Scheme 1).



Scheme 1. Polyene cyclization according to *Johnson* et al. [2].

Perhaps the most widely used cycloaddition reactions are the Diels-Alder cyclizations (Scheme 2) and their various modifications[3]. Typically, six-membered rings are generated by two CC bond formations with the potential

[*] Prof. Dr. K. P. C. Vollhardt
Department of Chemistry, University of California, Berkeley, and
The Materials and Molecular Research Division,
Lawrence Berkeley Laboratory
Berkeley, CA 94720 (USA)

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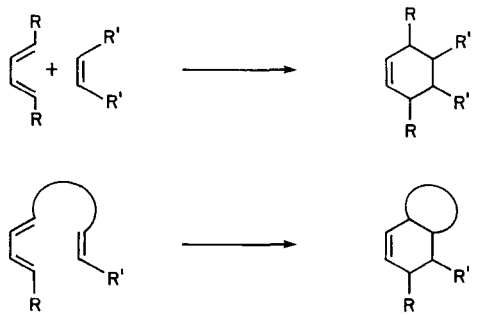
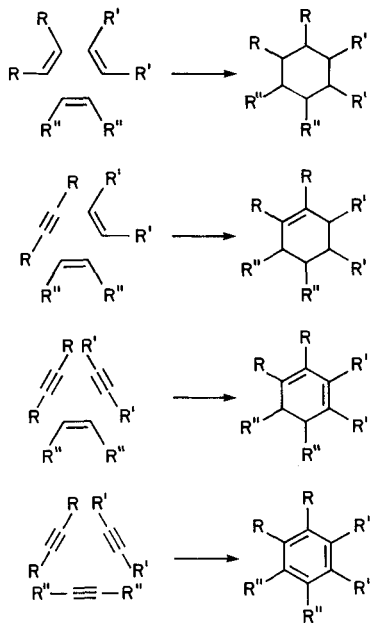
to construct four chiral centers. More complex topological changes may ensue on application of its intramolecular version (Scheme 2)[4]. The power of this method lies in its extraordinary specificity: it is chemoselective, in other words the dienophile prefers to react with the diene, and neither of the starting materials react competitively with themselves; it is regioselective, unsymmetrical dienes choosing only one sense of cycloaddition to unsymmetrical dienophiles; and it is stereoselective, mostly following the *endo*-rule.



Scheme 2. Inter- and intramolecular Diels-Alder reactions.

A simple analysis shows that a potentially more powerful strategy would be one based upon the [2+2+2]-cycloaddition of three unsaturated moieties (Scheme 3). Now three new bonds would be constructed in one step, constituting a considerably larger change in molecular complexity, and up to six chiral centers could be generated from completely achiral starting materials.



Scheme 3. Prototypical [2+2+2]-cycloadditions.

Employment of varying proportions of cycloaddends containing double and triple bonds would provide access to six-membered, partially or completely unsaturated rings. As in the Diels-Alder reaction, one could also envisage the use of heteroatomic units furnishing various heterocyclic systems[5] and a plethora of partially or completely intramolecular versions.

It is surprising that, although symmetry-allowed[6], and in most cases strongly exothermic[7], there is a paucity of examples of purely thermal [2+2+2]-cycloadditions. It is possible that entropic and, in some cases, enthalpic[8] activation energy contributions account for the relative rarity of these transformations. This report will describe how the use of a transition metal, particularly cobalt in the form of the dicarbonyl(η^5-cyclopentadienyl) derivative $CpCo(CO)_2$ as a catalyst or reagent may lead to the successful execution of a variety of [2+2+2]-cycloadditions of the type depicted in Scheme 3. The many previously unattainable molecules generated in this way have been used as starting materials for the preparation of several unnatural and natural products of theoretical and/or medicinal-synthetic interest.

2. α,ω-Diyne Cyclizations in the Preparation of Annelated Benzene Derivatives: Control of the Substitution Pattern

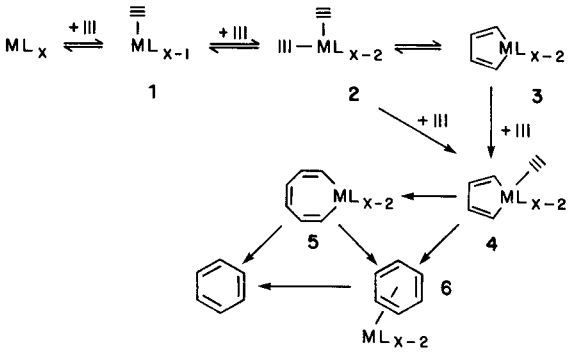
2.1. Background

Berthelot reported in 1866 on the thermal cyclization of acetylene to benzene[10]. High temperatures (ca. 400 °C) are required and a mixture of products is formed[11]. In 1949, *Reppe* et al. described the first transition metal catalyzed version of this transformation, in which nickel was employed, and which under certain conditions leads to the predominant formation of cyclooctatetraene[12]. Subsequently, it was found that a large number of transition metal systems catalyze the cyclotrimerization of substituted, frequently functionalized alkynes to benzene derivatives[13]. At the outset of the work described in this account, comparatively little was known about the utilization of these reactions in organic synthesis, particularly when employing oligoynes, even though such reactions would hold considerable potential in complex molecule construction. The validity of this premise was indeed demonstrated earlier when it was shown that a variety of oligocycles were obtainable by cyclization of α,ω-diynes[14]. Furthermore, in a series of over 40 papers, *Müller* et al. showed that stoichiometric amounts of rhodium complexes could be used in the "diyne reaction" to generate a multitude of rhodacycles capable of varied reactivity to furnish quinones, carbocycles, and heterocycles[15]. Although the method has its limitations with respect to scope, generality, and expense, it clearly pointed out some of the possibilities in store. Very recently, other groups have become interested in this problem[16].

2.2. General Mechanistic Considerations

Based on the results of several investigators, the general Scheme 4 may be formulated for the mechanism of cyclotrimerization of acetylene to benzene catalyzed by low valent transition metal complexes[17]. Initially, one and then two alkyne moieties sequentially displace two ligands on

the metal to form alkyne complexes **1** and **2**. Oxidative coupling may occur to give the coordinatively unsaturated metallacyclopentadiene **3**, in which the metal has adopted a formal oxidation state two units higher than in its precursor **2**. This change appears to facilitate chemoselectivity in

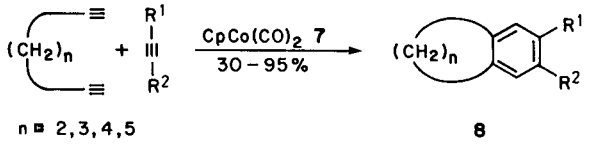


Scheme 4. Mechanism of cyclotrimerization of acetylene.

certain cases. Complex **3** may then coordinate a third molecule of alkyne to give **4**. On the other hand, calculations show that the direct conversion of **2** into **4** should be kinetically more advantageous[18], since coordinative unsaturation is avoided. Species **4** appear to be very reactive, since, in contrast to **2**, **3**, **5**, and **6**, derivatives of which have been characterized, it has so far eluded isolation. This is unfortunate, because its preparation could provide crucial information with respect to the next step in the catalytic cycle: either an alkyne-insertion to form the metallacycloheptatriene **5** or a Diels-Alder type addition to furnish the benzene complex **6**. Precedence exists for the conversion of either species into the free arene[17], and perhaps both options are viable.

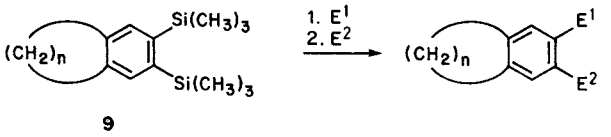
2.3. Cobalt-Catalyzed Cocyclizations to Benzocycloalkenes

Approximately 10 years ago, it was found that $CpCo(CO)_2$ **7** catalyzes a variety of [2+2+2]-cycloadditions involving α,ω-diynes to give annelated benzenes **8** as shown in Scheme 5[19]. The reaction works best for n=3 and 4 and tolerates a wide variety of substituents, such as R=H, alkyl, aryl, vinyl, CO_2R', CH_2OH, CH_2OR', COR', C=NOR', NR'_2, SR', and $Si(CH_3)_3$. In some cases there is a problem of chemoselectivity in as much as alkynes of comparable bulk or electronic make-up tend to undergo random cyclizations. The presence of substituents at the terminal position of the diyne may also lead to diminished yields when bulky groups such as $Si(CH_3)_3$ are involved[20]. Although the reaction is poor for the preparation of benzocycloheptenes **8**, n=5, it is capable of generating strained four-membered rings, thus providing a fairly general synthetic entry to the 1,2-dihydrocyclobutabenzenes (benzocyclobutenes) **8**, n=2, which are useful synthetic intermediates (see Section 3.1). Functional groups such as NO_2, alkyl halides, and reactive vinyl and aryl halides are detrimental to the catalyst, presumably due to facile oxidative addition processes[17]. On the other hand, chlorophenylalkynes are readily cyclized according to Scheme 5[20].

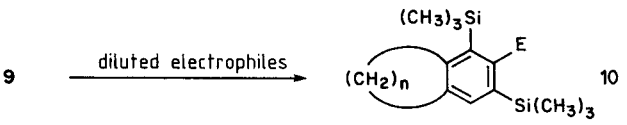


Scheme 5. $CpCo(CO)_2$-catalyzed cocyclotrimerization of α,ω-diynes with alkynes.

In order to circumvent the aforementioned problems of chemoselectivity, bulky alkynes may be employed, particularly trimethylsilylalkynes which are too sterically hindered to autocyclize but not so encumbered not to cocyclize. Their application (usually in excess) frequently results in excellent yields of the corresponding annelated arenes[19-21]. The trimethylsilyl group in the products functions as an excellent leaving group in electrophilic aromatic substitution reactions[22]. This is particularly advantageous when employing bis(trimethylsilyl)acetylene (BTMSA) in the cyclization reaction, since the resulting *o*-bis(trimethylsilyl)benzene derivatives **9** can be substituted selectively and in high yield in a step-wise manner (Scheme 6)[19,20]. Even in the case of deuteriodesilylation the first silyl group is more reactive than the second by a factor of about 40[19c]. Another interesting feature of compounds **9** is their ability to rearrange to the *m*-bis(trimethylsilyl) derivatives **10** when exposed to dilute electrophiles (Scheme 7)[19c,23]. This phenomenon appears to be caused by the slow rate of desilylation of the cationic intermediate formed during electrophilic aromatic substitution relative to 1,2-silyl migration, relieving steric strain, followed by rapid deprotonation.

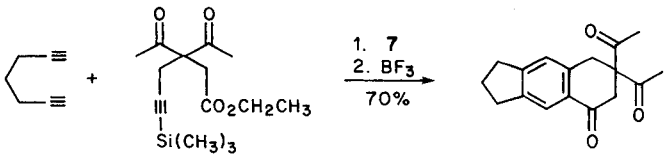


Scheme 6. Selective electrophilic aromatic substitution of *o*-bis(trimethylsilyl)arenes.



Scheme 7. Rearrangement of *o*-bis(trimethylsilyl)arenes (E=H, Br).

An example of the use of the cobalt-catalyzed cocyclization reaction, incorporating a silicon-directed intramolecular regioselective Friedel-Crafts acylation[21], is illustrated for the synthesis of a linear annelated tricycle in Scheme 8.



Scheme 8. Formation of a linear annelated tricycle by $CpCo(CO)_2$-catalyzed cyclization and silicon-directed intramolecular Friedel-Crafts acylation.

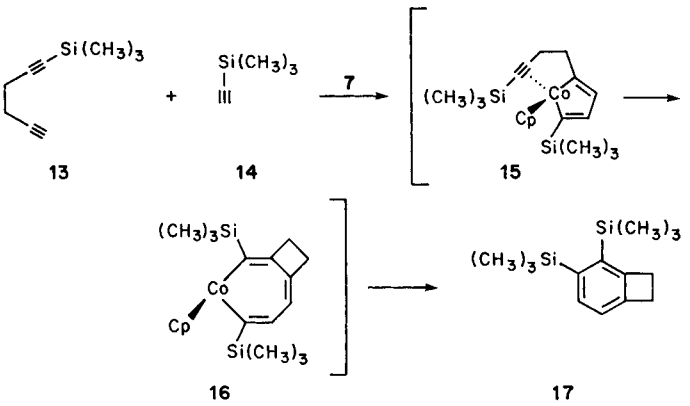
2.4. Specific Mechanistic Considerations

If we recall the discussion in Section 2.2 and apply its conclusions to the case of $CpCo(CO)_2$, there are two cobaltacyclopentadiene intermediates of the type **4** to be considered, namely **11** and **12** (Scheme 9). The mechanism of the reaction of $CpCo(CO)_2$ with alkynes to give cobaltacyclopentadienes and ultimately benzene derivatives has been well investigated[17,24,25]. Intermediates such as those of the type **11** (but not **12**) have been isolated[26], except for n = 2, although a related iron compound is known[27]. Cyclobutadiene complexes derived from both **11** and **12** are obtained as by-products in catalytic reactions employing α,ω-diynes[19,20,28] and are responsible for some of the catalyst depletion, since they appear to be unsuitable as precursors for any catalytic intermediates[29,30]. On the basis of previous findings, neither of the two possible intermediates **11** or **12** can be ruled out; indeed, either one or both may be formed depending on the reaction conditions and substrate structures.

Scheme 9. Proposed cobaltacyclopentadiene intermediates in the cocyclization of α,ω-diynes with alkynes.

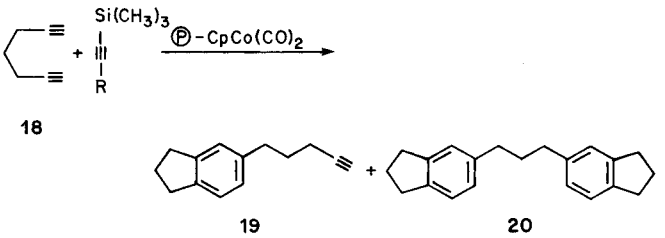
The structure of **12**, with the alkynyl group in the α-position, is in accord with expectations based on steric arguments[24a]. These arguments also predict that R^1 should be larger than R^2. Electronic factors, in particular the polarization of the alkyne π* orbital, are, however, thought to favor the preferential emergence of alkyl substituents in the β-position, whereas the trimethylsilyl group should, according to both theories, occupy the α-position[31]. The inconsistency of some of the predictions with the experimental results[24a] may simply be due to thermodynamic factors. Since the oxidative coupling of two complexed alkynes to a cobaltacyclopentadiene proceeds endothermically (by an estimated 14 kcal/mol), this step may well be reversible; hence, the observed regioselectivity of the cyclization may not in any way reflect the initial course of the reaction. In the specific case of systems of the type **12**, it may also be that additional involvement of the appendant alkyne group in the transition state for oxidative coupling (modelled by **2**→**4** in Scheme 4) controls the outcome of the process.

The trimethylsilyl group, which is used extensively for controlling the chemo- and regioselectivity, has a pronounced tendency to α-selectivity in the metallacycle (vide infra), as can be concluded from product isolation studies. An example of how this effect may be synthetically exploited in the formation of **17** as the sole isomer on cocyclization of 1-trimethylsilyl-1,5-hexadiyne **13** and trimethylsilylacetylene **14** is shown in Scheme 10[19c]. On steric grounds the kinetically favored metallacycle is expected to be **15**, which, after insertion of the complexed alkyne to give **16**, can only lead to **17**.



Scheme 10. Exclusive formation of the regioisomer **17** in the cyclization of **13** with **14**.

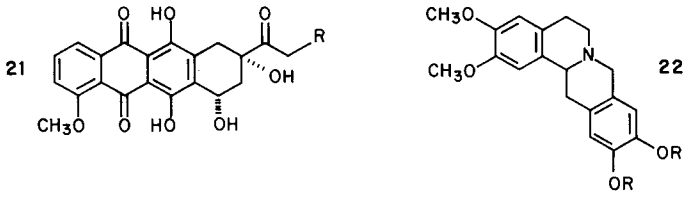
A mechanistically curious and synthetically unexploited result was obtained when attempts were made to catalyze cocyclizations of the type shown in Scheme 5 with polystyrene-supported $CpCo(CO)_2$[32] (Scheme 11). The monosubstituted acetylenes were not incorporated into the aromatic products, and only diyne dimers, such as **19** (major product), and trimers, such as **20**, were isolated. Since homogeneous $CpCo(CO)_2$ converts **18** exclusively into **20**, indicating that the catalyst is transferred intramolecularly from the benzene ring in **19** to the appendant alkyne unit, which is next to be cyclized, and since $CpCo(CO)_2$ also cocyclizes trimethylsilylalkynes, the polystyrene-supported or similar catalysts may offer an opportunity for interesting shape-selectivity in some of these transformations.



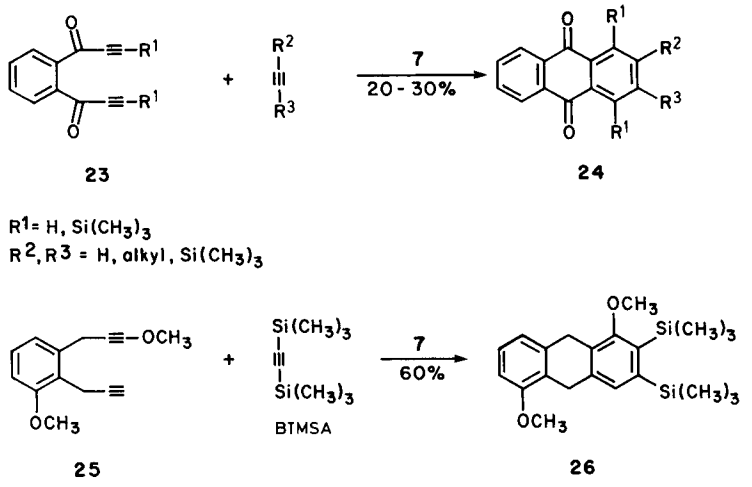
Scheme 11. Catalytic cyclization of 1,6-heptadiyne by polystyrene-supported $CpCo(CO)_2$. Ⓟ = polystyrene.

2.5. Synthetic Applications: Anthracycline Antibiotics and Protoberberine Alkaloids

The $CpCo(CO)_2$-catalyzed [2+2+2]-cycloaddition of three alkyne units could in principle be applied to the total synthesis of a variety of natural products containing annelated benzene rings. Two target molecules which require 1,7-octadiyne structures as cooligomerization precursors are the antitumor anthracycline aglycones **21**[33] and the protoberberine alkaloids **22**[34]. Both systems have already been synthesized via a multitude of approaches, none, however, involving the retrosynthetic disconnection made possible by the "cobalt-way". Two strategies are currently being employed en route to anthraquinone type antibiotics

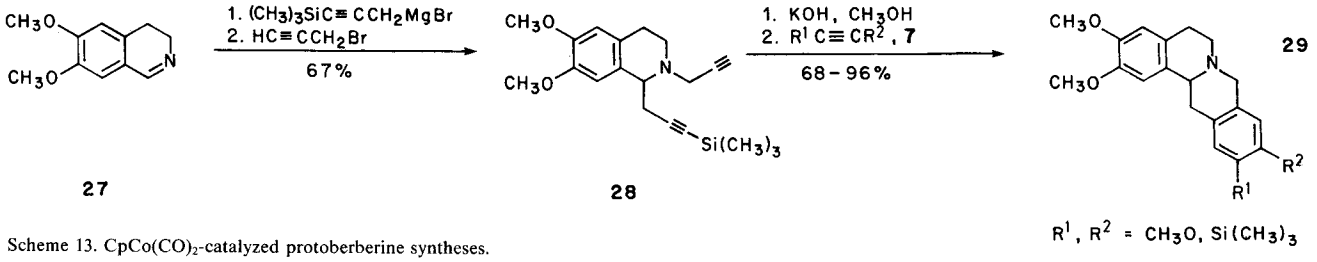


(Scheme 12), one involving the cyclization of aromatic bis(alkynylketones) **23** to furnish directly the desired framework **24**, albeit in only moderate yields[19c], the other utilizing dipropargylbenzenes of the type **25** to assemble initially a dihydroanthracene nucleus as in **26**[35].



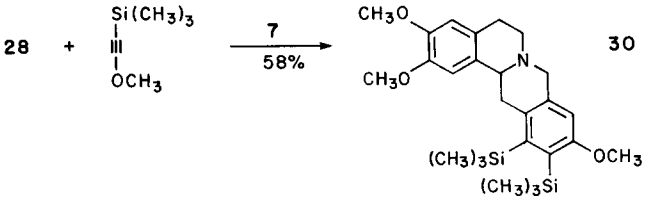
Scheme 12. Two cyclization strategies for the preparation of anthraquinones.

The protoberberines **29** are readily accessible by the sequence of reactions shown in Scheme 13[36]. For example, **29**, $R^1=R^2=Si(CH_3)_3$, is formed in 96% isolated yield by cocyclization of **28** with bis(trimethylsilyl)aceylene (BTMSA). Unfortunately, but perhaps not unexpectedly, unsymmetrical alkynes [$R^1=CH_3O$, $R^2=Si(CH_3)_3$] cyclize non-regioselectively. However, such selectivity is attainable starting from **28**, again the sterically more demanding



Scheme 13. $CpCo(CO)_2$-catalyzed protoberberine syntheses.

arene, e.g. **30**, being generated exclusively (Scheme 14)[36]. Finally, the trimethylsilyl substituents in the compounds **24**, **26**, **29**, and **30** can function as leaving groups in electrophilic aromatic substitution reactions.

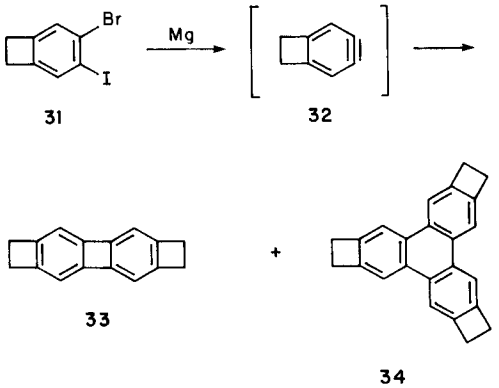


Scheme 14. Regioselective protoberberine synthesis.

3. Theoretically Interesting Molecules

3.1. 1,2-Dihydrocyclobutabenzenes (Benzocyclobutenes)

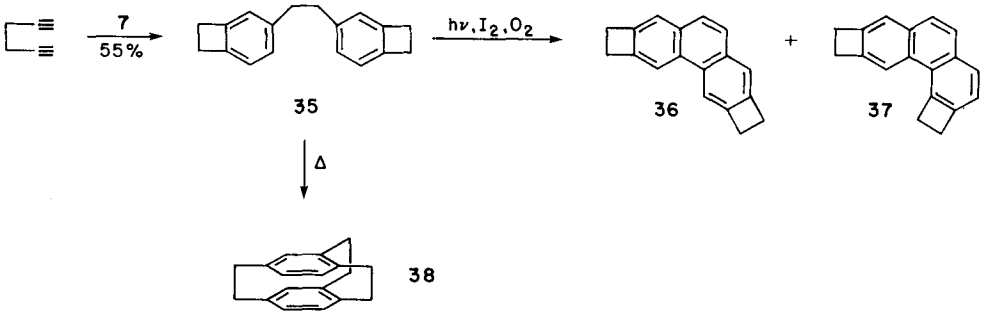
The ready access to functionalized 1,2-dihydrocyclobutabenzenes according to Scheme 5 has enabled their use in the construction of a host of theoretically interesting, strained ring activated, benzenoid hydrocarbons[37]. Thus, 4-bromo-5-iodo-1,2-dihydrocyclobutabenzene **31** (Scheme 15) functions as a precursor of **33**[38] and **34**[39] *via* the intermediacy of 1,2-dihydro-4,5-didehydrocyclobutabenzene



Scheme 15. Generation and oligomerization of 1,2-dihydro-4,5-didehydrocyclobutabenzene.

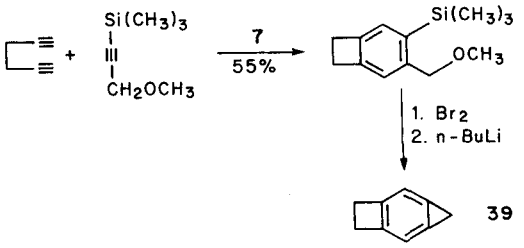
32. The activating effect of the four-membered ring is reflected in the physical and chemical properties of the products. Thus, e.g., both **33** and **34** are rapidly hydrogenated over platinum at ambient pressures. In a similar sequence, compound **17** afforded 1,2-dihydro-3,4-didehydrocyclobutabenzene, predicted by bond fixation arguments to be more reactive than **32**[40].

Hydrocarbon **35**, readily prepared in one step by trimerization of 1,5-hexadiyne, undergoes oxidative photocyclization to give the two isomeric dicyclobutaphenanthrenes **36** and **37** (Scheme 16)[41]. In contrast to **36** and phenanthrene itself, the more reactive **37** is mutagenic in the Ames test, and thus constitutes the first substance in which such physiological activity is increased by ring strain. Flash vacuum pyrolysis[42] of **35** results[43] in diastereoselective cycloaddition to give cyclophane **38**; the conceivable alternative isomer (±)-[2.2.2](1,2,4)(1,2,5)cyclophane[44] could not be detected. This preparation of **38** is clearly the method of choice[45].



Scheme 16. Synthesis of strained ring systems from **35**.

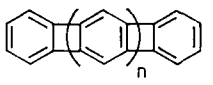
The currently most severely strained simple annelated benzene derivative is probably[46] **39**, which can be prepared rapidly as in Scheme 17[47]. This sequence is comparable in effectiveness with an alternative route[48] because of its speed, even though the last cyclization step is poor (≈5% yield).



Scheme 17. $CpCo(CO)_2$-catalyzed synthesis of 3,4-dihydro-1*H*-cyclobuta[*a*]cyclopropa[*d*]benzene **39**.

3.2. Multiphenylenes and Related Hydrocarbons

Cobalt-catalysis has opened up an iterative synthetic approach to the preparation of a novel series of cyclobutadienoid[49] aromatic polycyclic hydrocarbons **40**, termed multiphenylenes (biphenylene, terphenylene, etc.), in analogy to the multiphenyls (biphenyl, terphenyl, etc.). Curiously, the series is alternating with respect to the π-electron count of the individual members between formally antiaromatic and formally aromatic. Theory predicts[50] a rapidly narrowing HOMO-LUMO gap with increasing n. Therefore, these compounds might have potential as novel materials with conductive behavior[51].



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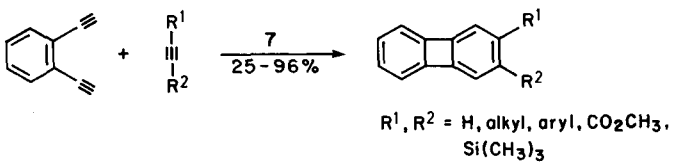
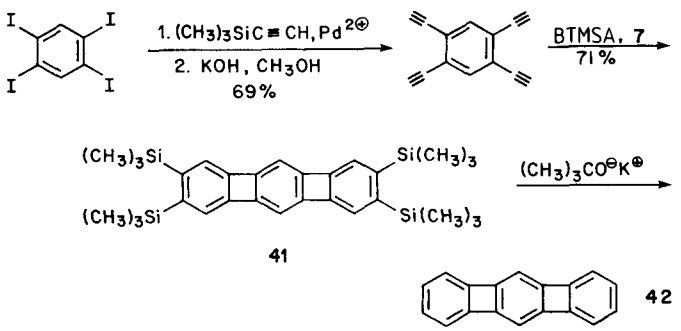
The synthetic strategy is based on the palladium-catalyzed ethynylation of halobenzenes[52], on the cobalt-catalyzed cotrimerization of *o*-diethynylarenes with alkynes to give biphenylenes (Scheme 18)[53], and on the ability of the trimethylsilyl group to function as a masked halogen. Scheme 19 depicts the rapid construction of terphenylene **42**, the first new member in the series[54].



Scheme 18. A $CpCo(CO)_2$-catalyzed biphenylene synthesis.

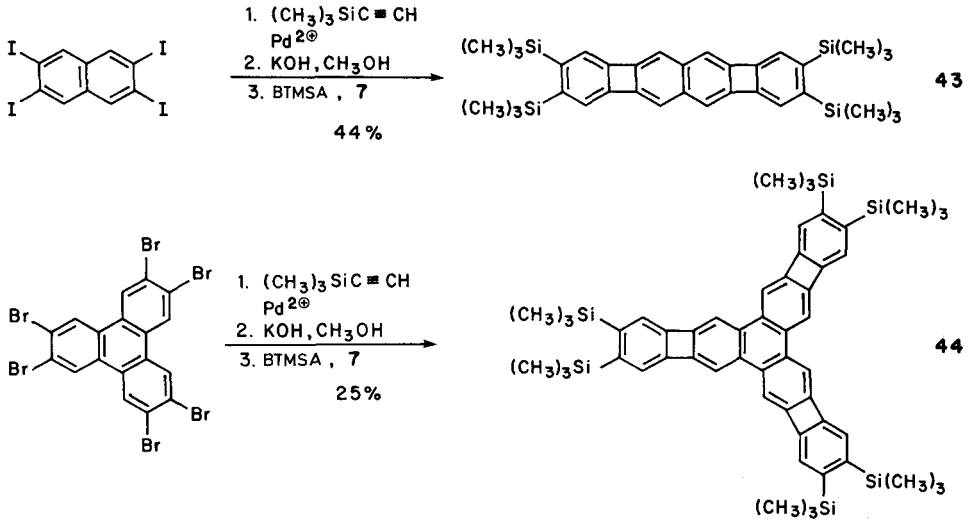


Scheme 19. Synthesis of terphenylene.

The cyclization of 1,2,4,5-tetraethynylbenzene to **41** is the first reaction to form four rings in one step. Even though terphenylene has 18 π-electrons, the system does not behave like an [18]annulene, either physically or chem-

ically. Although the two outer benzene rings show considerably more bond alternation than the central ring, as revealed by an X-ray crystallographic investigation[55], it is the central "cyclohexatriene" which exhibits unusual reactivity: it hydrogenates (all-*cis*) faster than a normal alkene and it adds both electrophiles and alkyllithium reagents. The dianion is surprisingly diatropic[55], suggesting that the system avoids antiaromatic circuits[56].

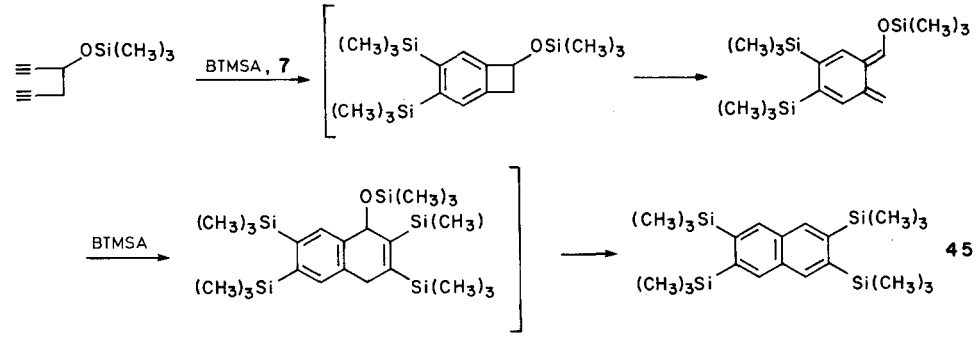
cocyclization of 1,5-hexadiynes with alkynes can be utilized in the construction of more complex assemblies by exploiting their ability to ring-open thermally to the reactive *o*-quinodimethanes, which subsequently undergo Diels-Alder cycloadditions[19,20]. A particularly interesting example is shown in Scheme 21; five of the carbon-carbon bonds of the naphthalene **45** are made in one step[58]. The product **45** not only enables a facile synthesis of otherwise



Scheme 20. A novel synthesis of hydrocarbons containing biphenylene units.

The methodology for the preparation of **42** is of general utility, as shown by the additional examples in Scheme 20[57]. Its effectiveness becomes apparent when one reflects that eleven (!) of the bonds present in **43** are formed by cobalt catalysis; the precursor of **43**, 2,3,6,7-tetraiodonaphthalene, is prepared by iodination of **45** (Scheme 21). The cyclization furnishing **44** constructs a record number of, e.g., six rings in one step.

inaccessible 2,3,6,7-tetrasubstituted naphthalene derivatives[57,59], but its preparation also demonstrates the feasi-

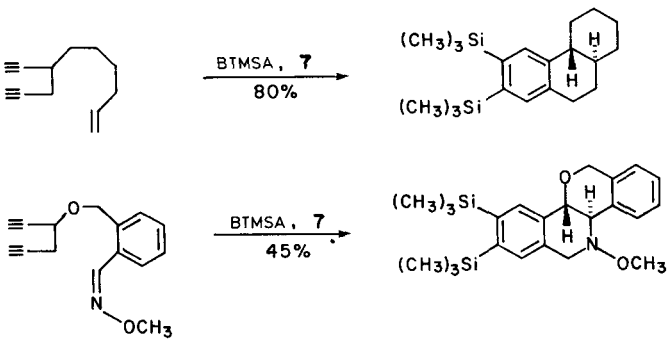


Scheme 21. A one-pot synthesis of naphthalenes according to the "tandem principle".

4. Coupling of Alkyne Cooligomerizations and *o*-Quinodimethane Cycloadditions: The "Tandem Principle"

4.1. A One-Pot Synthesis of Polycycles

Aside from their use in the synthesis of strained ring systems, the 1,2-dihydrocyclobutabenzenes generated by the



Scheme 22. One-pot syntheses of polycyclic compounds according to the "tandem principle".

bility of executing tandem cyclization-cycloaddition reactions. When the latter are carried out intramolecularly[58b,60], polycyclic systems are assembled chemo-, regio- and stereoselectively with remarkable ease. Two of several examples are shown in Scheme 22. The observed stereoselectivity appears to be controlled by the intermediacy of an *o*-quinodimethane formed by conrotatory outward opening of the initially generated 1,2-dihydrocyclobutabenzene, followed by an *exo*-Diels-Alder closure[58b,60]. Control experiments demonstrate that the metal is not involved in the latter.

4.2. The Cobalt-Way to (±)-Estrone: the D→ABCD Approach

Based on the above model systems, a $CpCo(CO)_2$-catalyzed steroid synthesis may be designed as in Scheme 23[61], in which in the crucial step the ABC portion of the steroid nucleus is fused onto the D-ring already present. The salient features of this synthesis are:

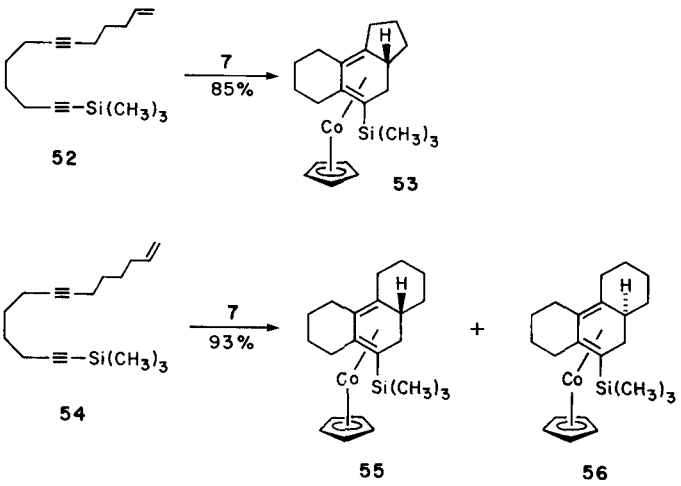
1. the regiospecific alkylation of 1,5-hexadiyne to furnish **46** and ultimately **47**,
2. the stereoselective alkylation of the lithium enolate derived from **48** with **47** to give **49** (two diastereomers),
3. the stereoconvergent cocyclization of **49** to construct steroid **50** stereospecifically,
4. the regiospecific protodesilylation at C-2 of **50**, and
5. the oxidation of ring A to furnish racemic estrone.

The target molecule **51** is formed in five steps from 2-methylcyclopentenone (21% overall yield), and in six steps from 1,5-hexadiyne (14%). The ketal derived from **49** gives even better cyclization yields. Unfortunately, a more direct approach to the A-ring phenol present in estrone by cocyclization of **49** with alkoxyalkynes was not regioselective and suffered from catalyst depletion by cyclobutadiene formation[61].

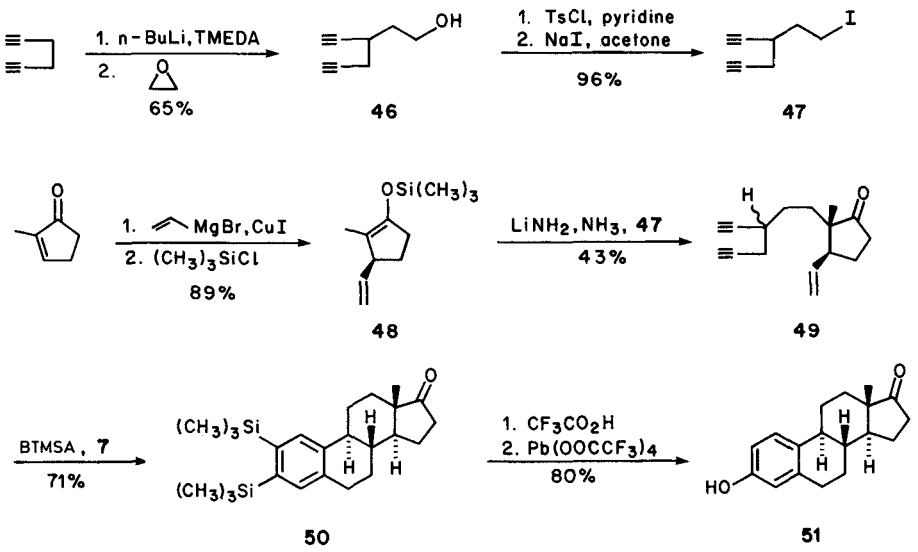
5. [2+2+2]-Cycloadditions of Enediynes: Stereospecific One-Pot Synthesis of Tri- and Tetracyclic Diene Complexes

5.1. Intramolecular Cyclizations of Enediynes with a Terminal Double Bond

Entry 3 in Scheme 3 indicates the potential utility of a cocyclization in which an alkene is employed. The synthetic versatility of such a transformation becomes apparent when one realizes that stereochemical consequences, e.g., ensue upon transformation of a stereochemically defined double bond. There are indeed various organometallic compounds which catalyze such reactions[29], one of which is based on the stoichiometric reaction of $CpCo(CO)_2$ leading to cyclohexadiene complexes[62]. In order to establish the utility of such a method, purely intramolecular cyclization reactions were chosen involving terminal alkenes. Scheme 24 shows examples of the success-

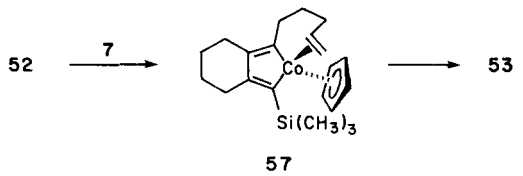


Scheme 24. Intramolecular cyclizations of enediynes with terminal double bonds.



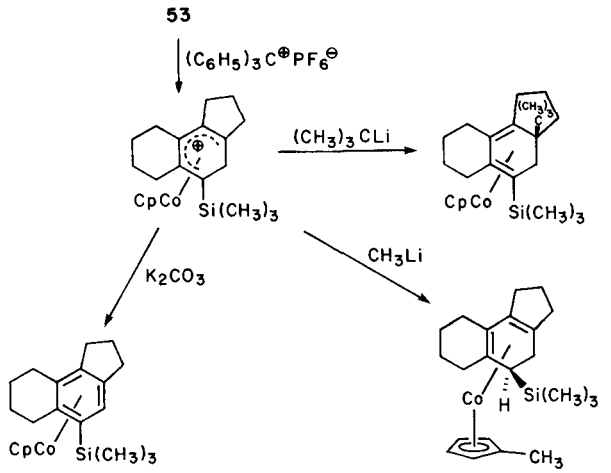
Scheme 23. A $CpCo(CO)_2$-catalyzed synthesis of (±)-estrone.

ful outcome of these attempts[29,63]. Interestingly, complete stereoselectivity is observed in some cases, its utter absence in others. Thus, **52** leads only to diastereomer **53**, whereas the homologue **54** gives an equimolar mixture of **55** and **56**. Why this is so remains a mystery. It is attractive to invoke an *exo*-Diels-Alder type mechanism involving a metallacycle of the type **57** leading to **53** (Scheme 25). However, insertion pathways and kinetic metallacyclopentene[64] formation cannot be ruled out as alternatives, and it is not clear why merely extending the appendant sidechain by one carbon should completely eradicate any selectivity. More puzzling, the desilylated analogue of **52** is equally unselective in its reactions.



Scheme 25. Diels-Alder-like mechanism for the reaction **52**→**53**.

Regardless of this mechanistic question, the method provides an efficient preparation of hitherto inaccessible polycyclic dienes, liberated almost quantitatively from their complexes by oxidative demetalation[63]. Some preliminary indication has been gathered that dienylsilane moieties such as those present in the cyclization products **53**, **55**, and **56** may be useful masked functional groups, for example α,β-unsaturated enones[63].

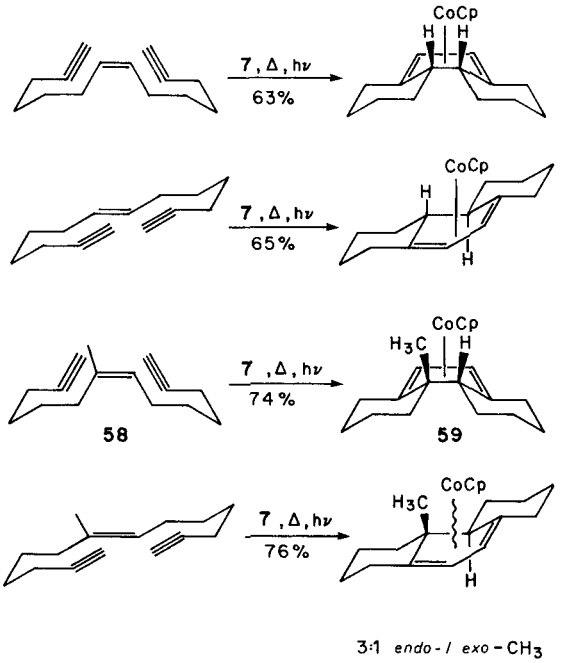


Scheme 26. Attack by nucleophiles on CpCo-cyclohexadienyl cations.

The presence of the metal may be beneficial. It protects the diene from rearrangements, polymerization, and (when applicable) protodesilylation. As observed for the analogous isoelectronic tricarbonyliron systems[65], hydride abstraction can be effected with trityl hexafluorophosphate to give cations which are subjectable to nucleophilic attack (Scheme 26). However, the regioselectivity[66] appears unpredictable.

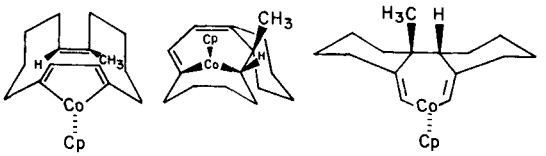
5.2. Intramolecular Cyclizations of Enediynes with Internal Double Bonds: Stereochemistry of the Double Bond

With the demonstration of the successful cyclization of terminal enediynes, it became necessary to establish the scope of the reaction by testing more highly substituted systems, particularly those in which the stereochemical fate of the double bond could be determined. For this purpose a series of internal enediynes was subjected to the cyclization conditions, altered to include photochemical acceleration of CO dissociation (Scheme 27)[67]. It can be seen that



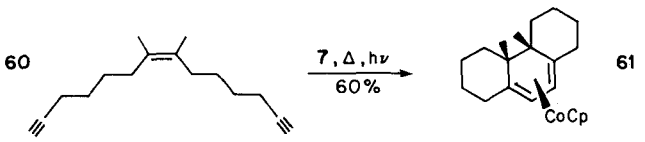
Scheme 27. Intramolecular cyclizations of enediynes with internal double bonds.

these transformations proceed relatively efficiently and with remarkable stereoselectivity, both with respect to the stereochemistry of the original double bond and the stereochemistry at cobalt. For example, of the four possible diastereomers, the enediyne **58** forms only one, namely **59**. The observed selectivity is consistent with mechanisms in which either an enyne unit or the two ethynyl groups undergo initial coupling. Subsequent incorporation of the third unsaturated moiety may then occur by Diels-Alder or insertion pathways. Some possible crucial intermediates arising from the reaction of **58** are depicted in Scheme 28, illustrating the variety of options. It appears in all cases that steric arguments can be invoked to explain the observed stereochemical results. It also transpires that, unlike



Scheme 28. Possible intermediates in the cyclization of **58**.

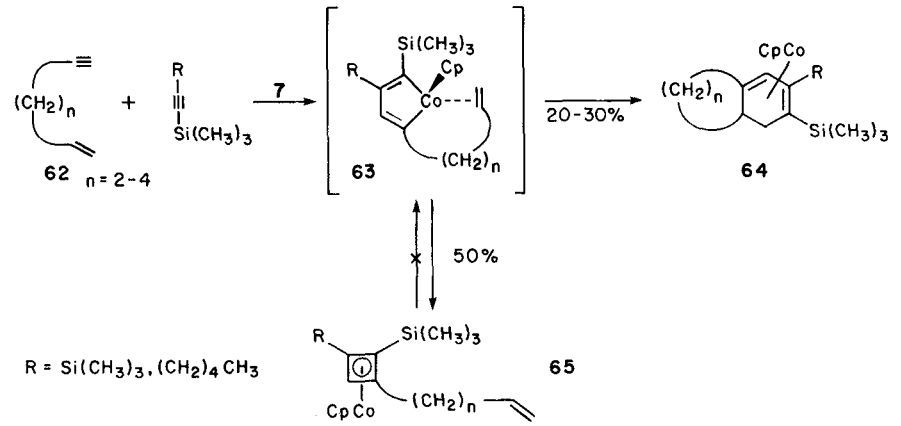
the Diels-Alder and numerous other cycloaddition reactions, the steric encumbrance of the double bond has little influence on the successful outcome of the reaction. The cyclization can therefore be used to accomplish a traditionally very difficult synthetic task: the introduction of quaternary carbon atoms into polycyclic frameworks, particularly those bearing angular methyl groups[68]. Currently, the most impressive demonstration of this potential is the conversion of the substrate **60**, which contains a tetrasubstituted double bond and, under standard conditions (see Scheme 29), affords the tricyclic diene **61** bearing two adjacent quaternary carbon atoms[69]. Surprisingly, and perhaps attesting to the (sterically induced?) relatively greater sensitivity of complex **61**, filtration through silica gel gave the free ligand in high yield.



Scheme 29. Cyclization of **60** to **61** with two adjacent quaternary centers.

5.3. Intermolecular Cyclizations of Enynes

Intramolecular [2+2+2]-cycloadditions of enediynes have found a fair amount of applications, whereas their intermolecular variants have so far been little exploited. Part of the problem appears to be the occurrence of a competing rapid valence tautomerization of the intermediate metallacyclopentadiene to give cyclobutadiene complexes. For example, cooligomerization of the α,ω-enynes **62** with BTMSA gave mainly **65** and only moderate amounts of the desired bicycle **64**[29,70] (Scheme 30). Moreover, only

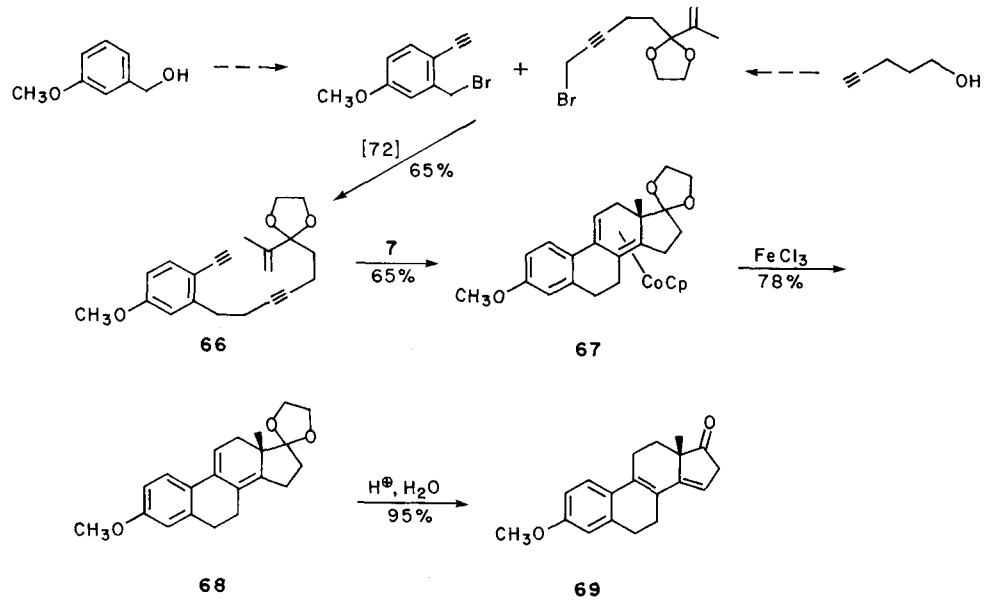


Scheme 30. Cocyclizations of α,ω-enynes with alkynes.

in the case of **64** (n=2) was stereoselectivity observed in the product. The cyclobutadienes **65** cannot, unfortunately, be induced to re-enter the cyclization manifold, regardless of the application of photochemical, thermal, or oxidative degradation methods. It appears that **63** undergoes relatively slow alkene incorporation. Complete regioselectivity is observed when 1-trimethylsilyl-1-heptyne is cocyclized with **62** (n=3, 4), suggesting that the trimethylsilyl group, as expected, prefers the α-position to the metal upon oxidative coupling to the metallacycle **63**. Improvement of the yields awaits the outcome of experiments designed to probe further the stereoelectronic aspects of the reactions.

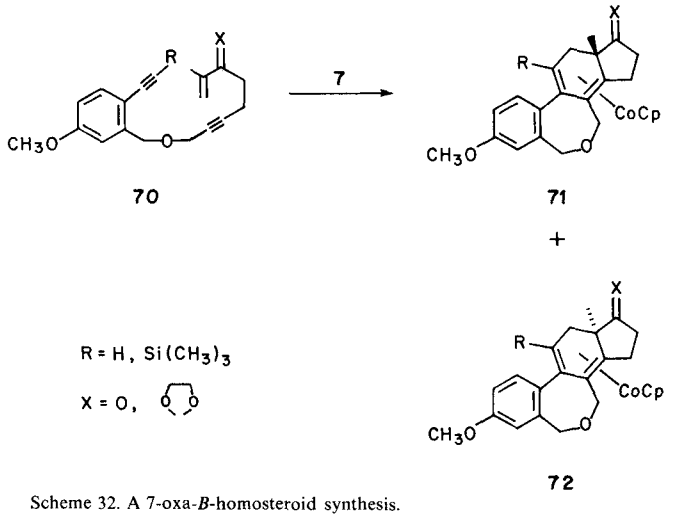
5.4. The Cobalt-Way to (±)-Estrone: the A→ABCD Approach

The effectiveness of the cycloadditions depicted in Scheme 24 suggested further application to the total synthesis of steroids in which the BCD portion of their framework would be fused to a pre-existing aromatic A-ring. This approach also provided the opportunity to test the [2+2+2]-cycloadditions of a 1,1-dialkylated olefin. With this aim in mind, the crucial enediyne precursor **66** was synthesized (Scheme 31)[71], utilizing in the key step a dihydrothiazole-mediated coupling of benzyl and propargyl halides[72]. Reaction of **66** with **7** gave the steroid complex **67** completely stereospecifically, the methyl group at C-13 being positioned *exo* to the metal. It was surprising to find that the steroidal pentaene ligand **68** had not been described in the literature prior to the present synthesis. There appear to be two reasons for this: firstly, the ligand **68** obtained on oxidative demetalation of **67** is very sensitive, turning into colorless, flocculent, insoluble material on exposure to air; secondly, the position of the diene moiety in **68** is thermodynamically disfavored over that present in **69**, into which it can be converted by acid treatment. Compound **69** is the Torgov intermediate in the synthesis of estrone[73]; its novel preparation as in Scheme 31 constitutes another formal total synthesis of the racemic natural product. Mechanistically, one could again invoke a Diels-Alder cycloaddition of the type depicted in **57** to account for the stereoselectivity observed. The added bulky ketal group would ensure that the chain connecting diene to dienophile would be placed *exo*.



Scheme 31. Steroid synthesis by enediyne cyclization.

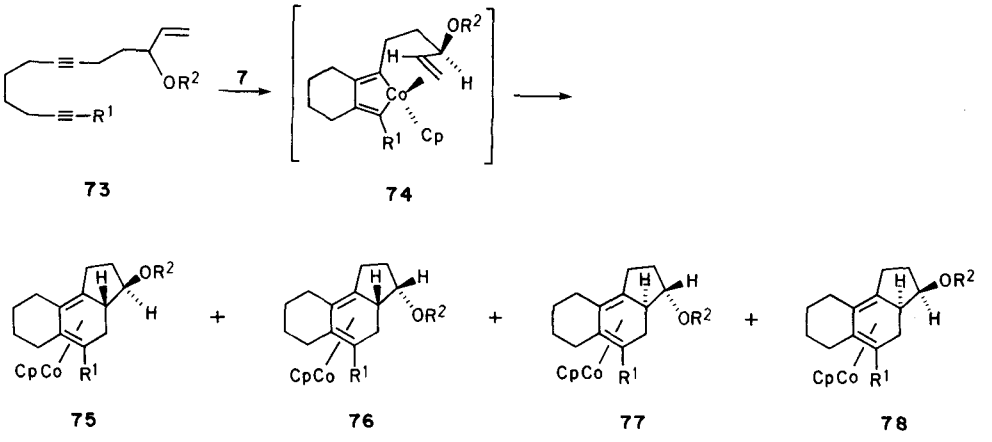
Similar arguments could be advanced to explain the changes in selectivity encountered in the transformations of **70** into the 7-oxa-*B*-homosteroid complexes **71** and **72** (Scheme 32)[71]. For example, when $R=(CH_3)_3Si$, the ketalized system **70** ($X=OCH_2CH_2O$) produces only **71** (analogous to the conversion of **66** into **67**), whereas the ketone **70** ($X=O$) leads to a mixture of **71** and **72** in which the latter predominates. This finding is possibly a consequence of the preferred *endo*-arrangement of the carbonyl group in the transition state for addition.



Scheme 32. A 7-oxa-*B*-homosteroid synthesis.

5.5. Diastereoselective Cyclizations of Chiral Substrates

Since the [2+2+2]-cycloaddition of achiral enediynes leads to the formation of ligands containing new chiral centers, it was of interest to investigate the potential diastereoselectivity of such a process with chiral substrates. In particular, it was hoped that a mechanistic insight might be gleaned from the reaction of **73**, for, if a Diels-Alder-like process involving **74** was operating, steric arguments would have to place the substituent OR^2 *exo* (as shown and as seen in general in intramolecular reactions of this type), ultimately furnishing only **75** (Scheme 33) at the ex-



Scheme 33. Diastereoselective cyclizations of enediynes.

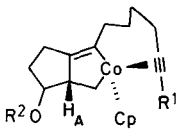
pense of the other three possible diastereomers **76**–**78**. However, as the results in Table 1 show[74,75], the outcome

Table 1. Yields of Complexes **75**–**78**.

R^1	R^2	Relative yields [%]				Isolated	t
		75	**76**	**77**	**78**	yields [%]	[h]
$Si(CH_3)_3$	CH_3	71	26	—	3	88	4
$Si(CH_3)_3$	$C_6H_5CH_2$	73	23	—	4	85	4
$Si(CH_3)_3$	CH_3OCH_2	69	24	—	7	91	4
$Si(CH_3)_3$	tBuSi$(CH_3)_2$	36	52	—	12	94	6
$Si(CH_3)_3$	$Si(i$Pr$)_3$	37	39	6 [b]	18 [b]	88	24
$Si(CH_3)_3$	tBuSi$(C_6H_5)_2$	33 [b]	47 [b]	—	20 [b]	[a]	[a]
tBuSi$(CH_3)_2$	tBuSi$(CH_3)_2$	35	50	—	15	91	6

[a] 44% conversion after 24 h. [b] Not isolated; presence ascertained by NMR spectra.

of this experiment appears to confuse the issue rather than to clarify it. Thus, although the first three entries appear to bear out the premise of Scheme 33, introduction of bulkier OR^2-groups, expected to maximize the intermediacy of a species of the type **74** and hence the yield of **75**, has exactly the opposite effect. Whether this phenomenon is general for non-silicon-containing groups has yet to be ascertained. The observed results, at odds with the simple Diels-Alder picture, might be more readily explained by invoking **79** as an intermediate formed by initial enyne coupling. Models show that **79** adopts a pseudo-chair config-

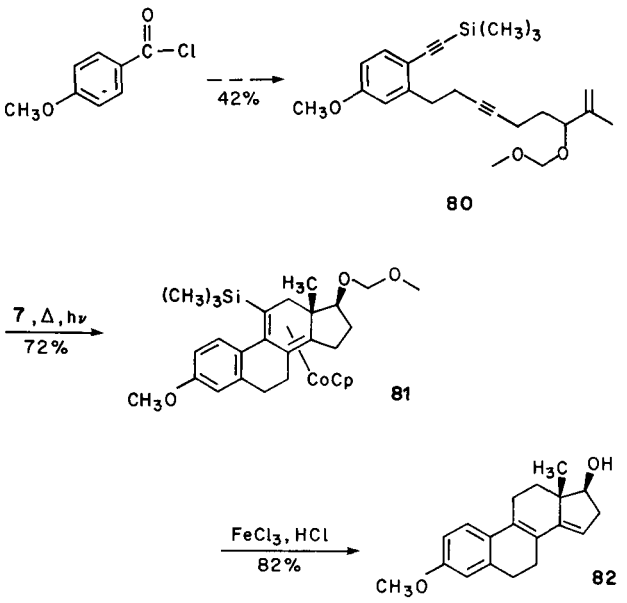


79

uration, placing the OR^2 substituent in an initially favorable equatorial position. Upon oxidative coupling, this group emerges severely eclipsed with H_A. This effect would lead to the OR^2-moieties increasingly preferring to be positioned axially with increasing bulkiness, or to the formation of a boat-shaped transition state in which the prochiral vinyl hydrogen points towards the metal (giving appreciable amounts of **77** and **78**, in addition to **75** and **76**, as observed).

5.6. A Diastereoselective Steroid Synthesis

The fairly selective outcome of at least some of the examples in Table 1 can be exploited in a diastereoselective steroid construction as shown in Scheme 34[75]. The required precursor **80** is readily prepared in good overall yield starting from *p*-methoxybenzoyl chloride. Cyclization gives mainly **81** (72%) in addition to its 17α-isomer (20%). Oxidative demetalation under acidic conditions converts **81** directly into the known estrapentaenol **82**[76], by (presumably in this sequence) loss of metal, diene isomerization, protodesilylation, and removal of the alcohol protecting group. The free ligand is also obtainable from **81** (81%), and in contrast to **68**, is air stable. A curious feature



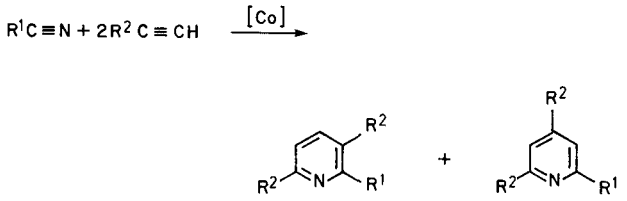
Scheme 34. Diastereoselective steroid synthesis.

of complex **81** (but not observed in the free ligand) is the presence of hindered rotation of the trimethylsilyl group ($\Delta H^{+} = 18.8$ kcal/mol) on the NMR time scale, the first such impaired mobility observed for a vinyltrimethylsilane[77], obviously caused by the bay-region hydrogen at C-1.

6. The Cobalt-Way to Heterocyclic Systems

6.1. Cocyclization of α,ω-Diynes with Nitriles: Synthesis of Cycloalka[1,2-*c*]pyridines and a Total Synthesis of Vitamin B_6

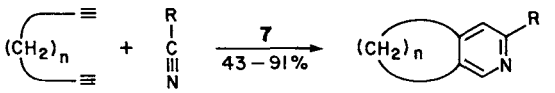
In the early 1970s, several groups independently discovered that cobalt complexes could cocyclize alkynes with nitriles to furnish pyridines in stoichiometric and catalytic reactions (Scheme 35)[78]. *Bönnemann* et al. have carried



Scheme 35. Cobalt-catalyzed pyridine synthesis.

out a comprehensive study of the scope and limitations of this reaction[79]. Although good control of chemoselectivity is obtained in the preparation of 2-substituted pyridines, product mixtures are formed in the cocyclization of unsymmetrical alkynes (Scheme 35)[79]. This potential prob-

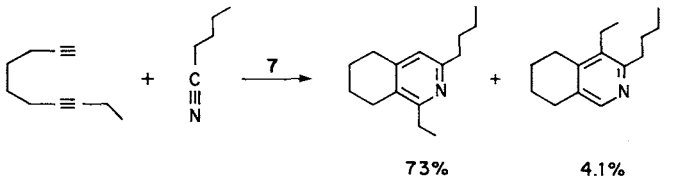
lem can be avoided by the use of α,ω-diynes (Scheme 36),



n = 3–5, R = alkyl, aryl, CH_2OCH_3, $CH_2CO_2C_2H_5$

Scheme 36. Cocyclization of α,ω-diynes with nitriles.

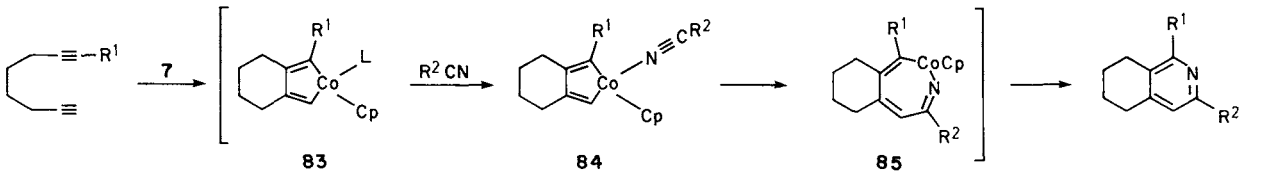
in which regioselectivity is controlled by the chelating nature of the alkyne component and by steric effects, whereas chemoselectivity is apparently controlled by electronic interactions[80]. Unsymmetrical diynes lead to predominant generation of the sterically less encumbered substitution pattern (Scheme 37). With electron-deficient ni-



Scheme 37. Regioselective cocyclization of unsymmetrical diynes with nitriles.

triles, the reaction fails to give satisfactory yields of pyridines, furnishing instead diyne oligomers. On the other hand, with other nitriles it is remarkably chemospecific, requiring only equimolar amounts of starting materials[80].

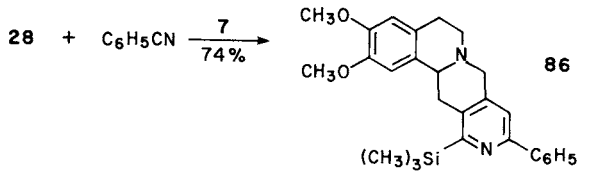
Mechanistically, the above results are readily accommodated by invoking initial formation of the metallacycle **83** (Scheme 38). The Co(III) center may now be postulated to



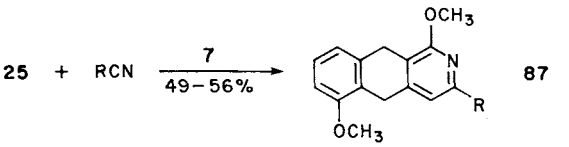
Scheme 38. Mechanism postulated for the formation of annelated pyridines.

select for nitrile by ligation through its lone pair[81], as in **84**, an interaction which becomes noncompetitive with alkyne complexation in the case of electron-deficient nitriles. Insertion into the less hindered cobalt-carbon bond, placing the nitrogen next to cobalt (**85**), eventually furnishes the observed products. This mechanism is consistent with the finding that isolated cobaltacyclopentadienes react like **83**[78a] and lead to substituent patterns similar to those observed in normal pyridine formation[79]. However, there is no conclusive evidence ruling out other pathways.

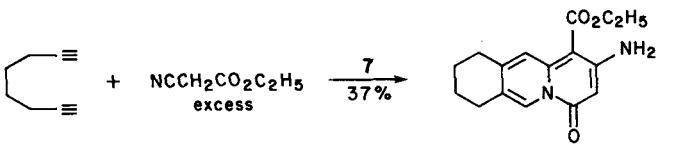
Irrespective of the mechanistic questions, the cocyclization depicted in Scheme 36 is potentially synthetically useful. For example, the diyne **28** cotrimerizes regioselectively



with benzonitrile to give **86**[36], an example of the rare isoquino[2,1-*b*]-2,6-naphthyridine nucleus. Similarly, the 2-azaanthracene framework **87** is accessible from **25**[35].



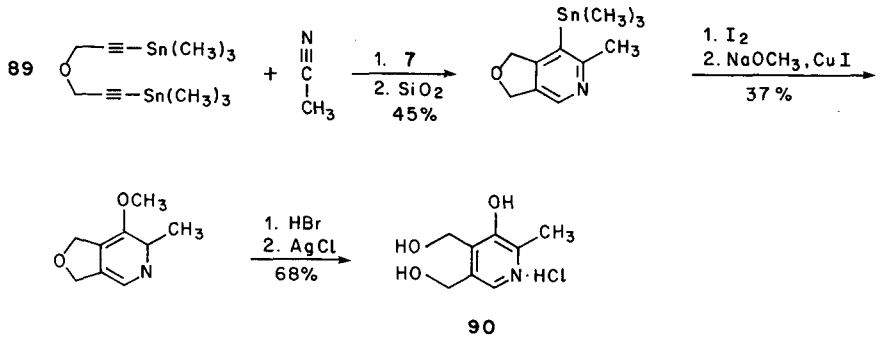
Employment of excess ethylcyanoacetate in the cocyclization with diynes can lead to further condensation of the intermediate 2-pyridylacetic esters[82]. This facilitates the one-pot synthesis of annelated quinolizinones such as **88**[35,80].



Dipropargylamines[83] and dipropargyl sulfides[83a] have been successfully cocyclized to give the corresponding 1,3-dihydropyrrolo- and thieno[3,4-*c*]pyridines. Based on this principle, but using dipropargyl ether **89** as starting material, a regioselective synthesis of vitamin B_6 **90** has been accomplished (Scheme 39)[84]. The cyclizations of **89** are the first to employ stannylalkynes, necessary in this case to ensure the successful outcome of electrophilic aromatic substitution on the resulting stannylpyridine.

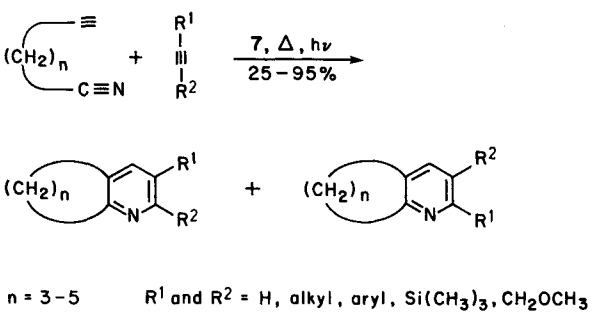
6.2. Cocyclization of ω-Alkynyl Nitriles with Alkynes: Synthesis of Cycloalka[1,2-*b*]pyridines

Scheme 40 shows a complementary cyclization strategy which enables the preparation of [*b*]annelated pyridines[85]. Regioselectivity is again attained in the case of unsymmetrical alkynes, the bulky substituent emerging next to the nitrogen. The successful outcome of this reaction appears

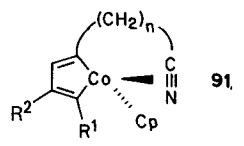


Scheme 39. A cobalt-catalyzed synthesis of vitamin B_6.

to depend on the efficiency of oxidative coupling to **91**, the larger group on either of the original alkynes being located in the α-position to the metal. The trimethylsilyated pyridine derivatives can be further functionalized by electrophilic aromatic substitution. A recent extension of Scheme 40 has involved the cyclodimerization of two ω-alkynyl nitrile molecules to give the corresponding cyanoalkyl-substituted cycloalka[*b*]pyridines[86]. Finally, it should be pointed out that cyclopentadienylcobalt does not appear to be capable of coupling more than one nitrile group in these transformations. This contrasts with $Fe_2(CO)_9$, which facilitates the cocyclization of adiponitrile with nitriles to give 1,2,4-triazines[87].



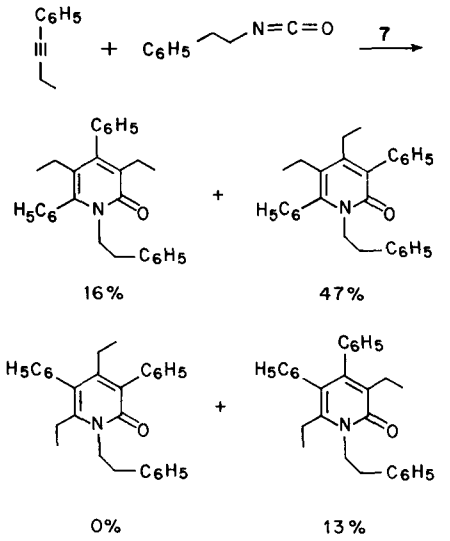
Scheme 40. Cocyclization of ω-alkynyl nitriles with alkynes.



91

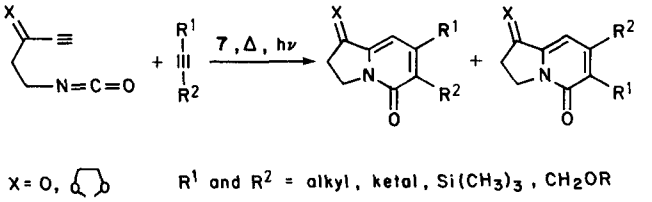
6.3. Cocyclizations of ω-Alkynyl Isocyanates: a Total Synthesis of Camptothecin

In analogy to the topological change occurring when going from alkynes to alkenes in [2+2+2]-cycloadditions, the employment of an imine unit instead of a nitrile in cocyclizations with alkynes could provide a ready synthetic entry to dihydropyridines. Moreover, if the C=N-substructure were to be incorporated into an α,ω-doubly unsaturated chain, its cyclization could lead to the rapid construction of polyheterocyclic systems incorporating bridgehead nitrogen atoms. Although this goal remains to be realized with simple imines[88], isocyanates appear to be suitable substrates in such an endeavor[79,89]. In simple cocyclizations leading to substituted pyridones (Scheme 41)[88]



Scheme 41. Product distribution in the cocyclization of β-phenethyl isocyanate with 1-phenyl-1-butyne.

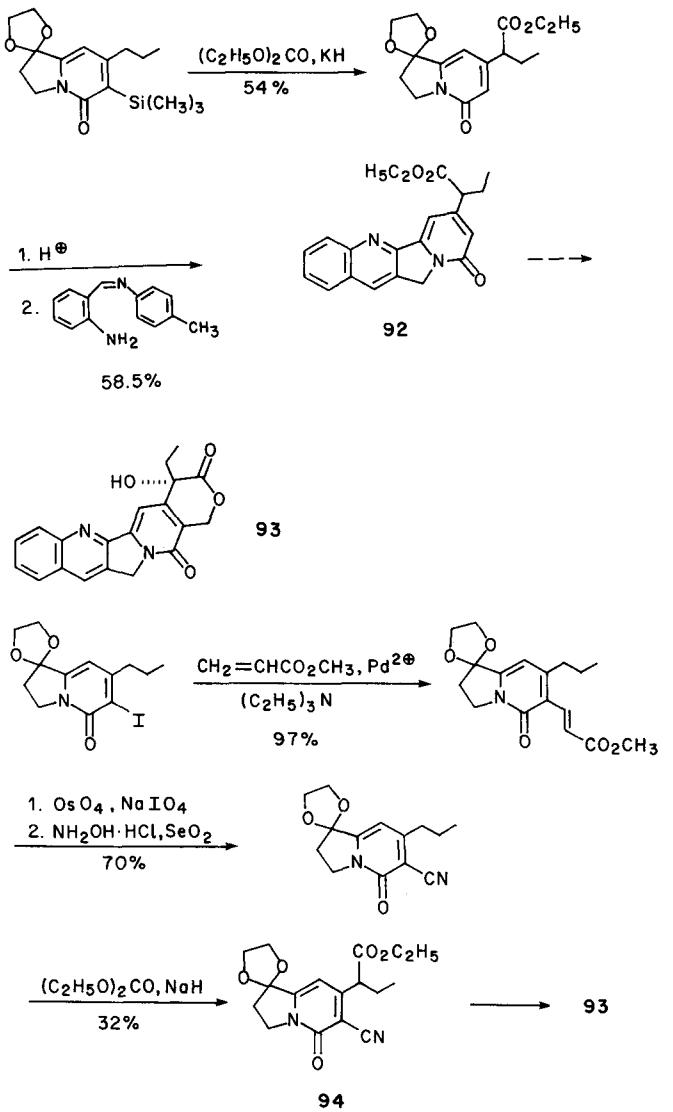
there is a potential problem of regioselectivity[79,88,89]. However, it may be circumvented by the use of ω-alkynyl isocyanates (Scheme 42)[90]. Good chemo- and regioselectivity are observed, the latter favoring the bulky substituent (particularly trimethylsilyl) taking up the α-position to the carbonyl group. An intermediate of the type **91** is indicated, but bearing an appendant complexed isocyanato rather than a nitrile group. Unexpectedly, based on steric



Scheme 42. Cocyclization of ω-alkynylisocyanates with alkynes.

considerations, the trimethylsilyl group always wins out and takes over the α-position, even when in competition with a *tert*-butyl group. This finding clearly indicates the operation of both steric and electronic effects with the silyl substituent (see Section 2.4). The silyl moieties in the product allow for selective halodesilylations at C-6[90]. In contrast, the halogenation of ordinary 2-pyridones leads to mixtures[91]. Finally, carbon-carbon bond formation is possible at C-6 by employing palladium-catalyzed coupling reactions of the corresponding 6-iodides[52,92].

Application of the above methodology has led (Scheme 43)[90] to two formal syntheses of the antitumor alkaloid camptothecin **93**[93]; one proceeds via the intermediate **92**[94], the other via **94**[95].



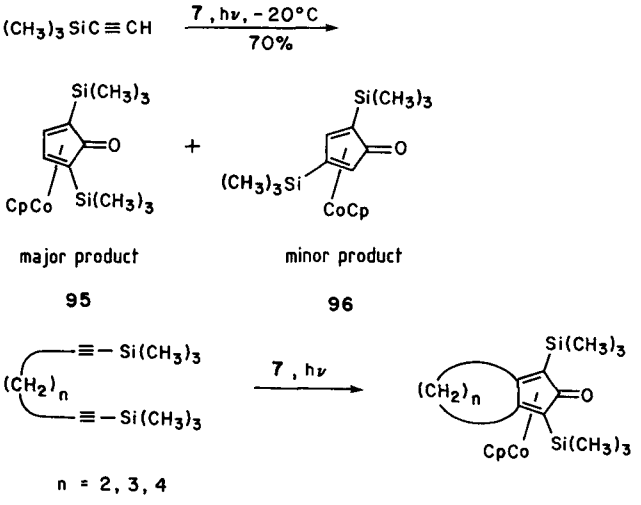
Scheme 43. Two total syntheses of camptothecin.

It is interesting to note that bis(η^4-cyclooctadiene)nickel, another catalyst reported to catalyze the formation of pyridones from alkynes and isocyanates[96], gives not only a different product distribution in the case depicted in Scheme 41, but is also a much poorer catalyst than the cobalt system in the presence of terminal alkynes[88]. Evidently, a different mechanism is operating in this system.

7. [2+2+2]-Cycloadditions Involving Carbon Monoxide: Cyclopentadienone Formation

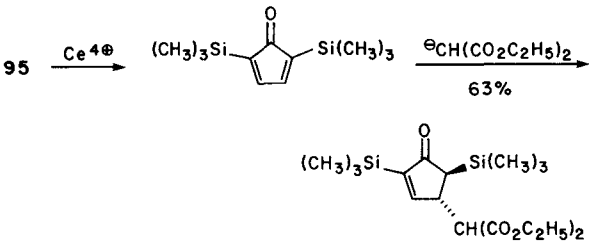
7.1. Synthesis of Cyclopentadienones

An alternative to the mode of cyclization depicted in Scheme 3 is provided by cyclization partners with "carbenoid" atoms, such as isocyanides[97] and carbon monoxide[13c,98]. If multiple insertion pathways could be avoided and product selectivity were controlled, the CpCo moiety should enable a [2+2+2]-cycloaddition to give five-membered ring systems in the presence of either substrate[13e,99]. Although isocyanides have not yet proven successful[100], it has been found that trimethylsilylalkynes undergo such reactions under low-temperature photolytic conditions in the presence of stoichiometric amounts of $CpCo(CO)_2$ **7** to furnish complexed cyclopentadienones regioselectively (Scheme 44)[101].



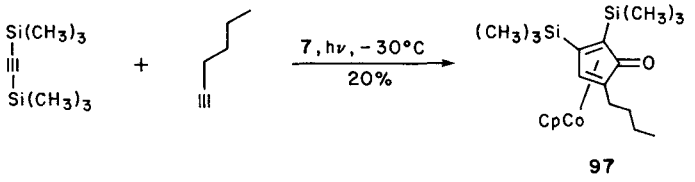
Scheme 44. Formation of cyclopentadienone complexes.

The utility of these complexes lies in their ready decomplexation ($Ce^{4\oplus}$) to give the free monomeric cyclopentadienones, which function as extraordinarily reactive substrates in further transformations (Scheme 45)[102].



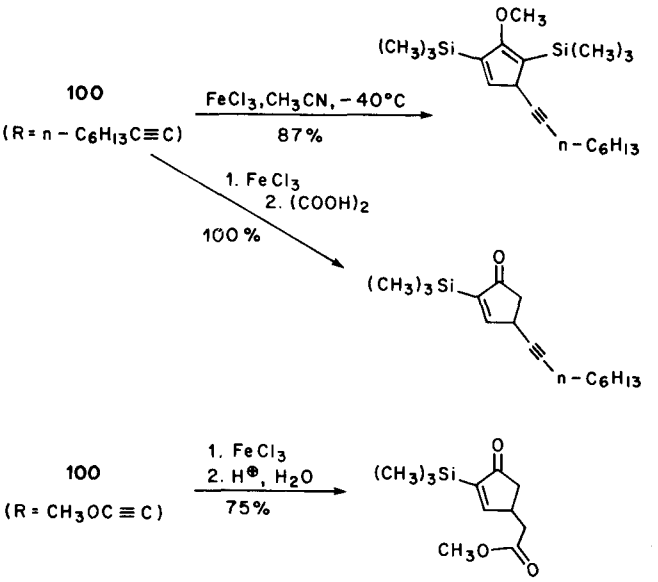
Scheme 45. Nucleophilic addition to 2,5-bis(trimethylsilyl)cyclopentadienone.

Metallacyclopentadienes[17,26], metallacyclobutenones[98,103], and more complex intermediates[103] have been invoked in the formation of cyclopentadienones from alkynes and carbonylmetal compounds. All are consistent with the observed product regioselectivity. For example, **95** is the major product in the cyclization of trimethylsilylacetylene with 7 (Scheme 44). On the other hand, when $(CH_3)_5C_5Co(CO)_2$ was employed, the corresponding 2,4-disilylated product predominated[101].



97

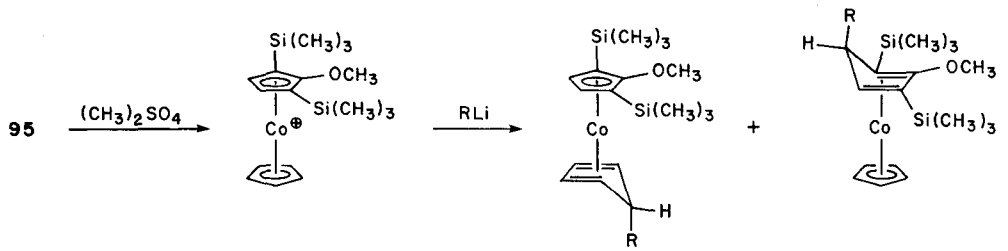
Cocyclization of 1-hexyne with BTMSA results in **97** as the exclusive cotrimer[102], indicating further synthetic potential, although the yield is, as yet, unsatisfactory.



Scheme 47. Oxidative decomplexation of the substituted ligands in **100**.

7.2. Cobaltocenium Salts as Precursors of Substituted Cyclopentadienes and Cyclopentadienones

Cyclopentadienone complexes of the type **95** can be exploited synthetically if they are activated by methylation to give cobaltocenium salts[104]. In the case of **95**, the resulting cation **98** can be ring-selectively and regioselectively attacked by organolithium reagents to give predominantly either **99** (R = bulky substituent, alkyl) or **100** (R = small substituent, alkynyl) (Scheme 46)[105]. It is the latter which



98 99 100

Scheme 46. Nucleophilic additions to cobaltocenium salts.

commands synthetic attention, because highly substituted and functionalized cyclopentadienes or cyclopentenones may be liberated from these species under mild oxidizing conditions (Scheme 47)[105]. Five-membered ring compounds of this type should be useful in the construction of cyclopentanoid natural products[106].

8. Conclusions and the Future

It is clear that the present methodology has not only provided some powerful simplifications in approaches to the construction of natural and medicinal products, but has also given access to novel structures of theoretical and synthetic interest. Chemo-, regio-, and stereospecific cyclizations in conjunction with the use of auxiliary groups, such as for example silicon- or tin-based substituents, allow for the rapid build-up of polycyclic ring systems with extensive control of ring-substitution. However, much remains to be done. The synthetic potential of such [2+2+2]-cycloadditions, as outlined in Scheme 3, has only barely begun to be explored. Many additional unsaturated organic (and organometallic?) substrates could be envisaged to participate in such a reaction. The possible stereochemical complexity of cyclizations involving increasing numbers of double-bonded partners should be elucidated. There must be a host of other catalysts, waiting to be discovered, which might exhibit specific selectivities. The use of optically active ligands in enantioselective transformations should be explored. Novel structures incorporating unusual strain-related and electronic features will become available, and their chemistry should provide further insight into the theories of bonding, delocalization, and aromaticity. Finally, why stop at [2+2+2]? There are many other combinations of one, two, and higher atomic synthons which might be induced to undergo multiple bond-formations in the presence of the appropriate catalyst to supply structures of increasingly higher complexity. Such will be the task of future investigators and collaborators.

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Chelation or Non-Chelation Control in Addition Reactions of Chiral α- and β-Alkoxy Carbonyl Compounds

New Synthetic Methods (44)

By Manfred T. Reetz*

The addition of C-nucleophiles such as Grignard reagents or enolates to chiral α- or β-alkoxy aldehydes or ketones creates a new center of chirality and is therefore diastereogenic. In order to control stereoselectivity, two strategies have been developed: 1) Use of Lewis-acidic reagents which form intermediate chelates, these being attacked stereoselectively from the less hindered side *(chelation control)*; 2) use of reagents incapable of chelation, stereoselective attack being governed by electronic and/or steric factors *(non-chelation control)*. Generally, the two methods lead to the opposite sense of diastereoselectivity. It is possible to predict the outcome by careful choice of organometallic reagents containing elements such as Li, Mg, B, Si, Sn, Cu, Zn, or Ti.

1. Introduction

The two π-faces of a carbonyl compound having at least one chiral center are diastereotopic. Addition of C-nucleophiles such as Grignard reagents or enolates can therefore lead to unequal amounts of diastereomers. Reactions involving such 1,n-asymmetric induction[1b,c] have been termed "diastereofacially selective"[2]. Although this phenomenon was observed as early as 1894[1], it was not until the work of *Cram* et al. that some degree of systematization was attempted[3]. In what is now known as Cram's rule[1], an α-chiral aldehyde (or ketone) such as **1**[*] is assumed to adopt a conformation in which the largest of the three α-substituents is antiperiplanar to the carbonyl function, nucleophilic attack then occurring from the less hin-

[*] Prof. Dr. M. T. Reetz
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-3500 Marburg (FRG)

[*] Only one enantiomer is shown, although a racemate was used leading to racemic products.