Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis

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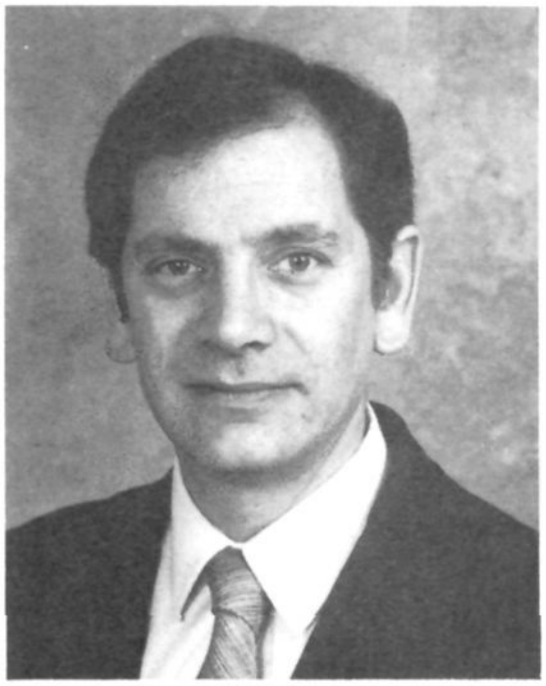
Contents



Neil E. Schore was born in Newark, NJ, in 1948. He attended schools in Bronx, NY, and Ridgefield, NJ, and received his B.A. degree in chemistry from the University of Pennsylvania in 1969. He returned to New York to do graduate work at Columbia University under the direction of Nicholas J. Turro, completing the Ph.D. in 1973. Cal Tech was the next stop, for $2^1/_2$ years as a National Institutes of Health Postdoctoral Fellow in the laboratories of Robert G. Bergman, where he discovered the existence of organometallic chemistry. Since 1976 he has been a member of the faculty at the University of California, Davis. He was named recipient of the Magnar Ronning Award for Excellence in Teaching in 1979, and Camille and Henry Dreyfus Teacher-Scholar for 1981–1986. His research interests involve mechanistic and synthetic transition-metal chemistry, including study of early transition-metal systems with remote ligand sites, construction and chemistry of bi- and polymetallic complexes, and applications of the chemistry of these systems to natural products synthesis. A special area of emphasis has been the study of the Pauson–Khand cyclopentenone synthesis.

I. Introduction

The directed construction of carbon–carbon bonds has always been a central theme in synthetic organic chemistry. Although developments in the areas of both free radical and pericyclic chemistry have greatly expanded the types of carbon units that may be connected, the fact remains that the large majority of bond-forming processes in use today still involve reactions between electrophilic and nucleophilic atoms: the polarized or charged atoms that constitute the ever expanding array of organic functional groups. Beginning students of organic chemistry are taught such a preponderance of reactions based upon standard polar functional group chemistry that it is no wonder that these are the reactions to which they first turn when faced with a synthetic problem. This approach is certainly facilitated by the ease with which the "ground rules" of electrophile/nucleophile chemistry may be assimilated. Nonetheless, reactions derived from "other" areas of organic chemistry provide the synthetic chemist with very powerful new methodologies. And, while the "ground rules" that govern these reactions may be different and unfamiliar to many chemists, *these differences are precisely the features that make these reactions useful.* In the general area of transition-metal-mediated organic chemistry many of the familiar structure/reactivity correlations are greatly attenuated, or do not apply at all. It therefore becomes possible to consider bond-forming reactions between atoms in almost any sort of functional environment, regardless of the presence or absence of any particular polarity.

The specific area covered in this review, cycloaddition reactions of alkynes, adds another important element to the obvious synthetic utility in forming two new bonds. Cycloaddition of an alkene reduces its carbons to the alkane oxidation level, the result being loss of functionality at these positions. In contrast, alkyne cycloadditions preserve functionality at these carbons in the form of the remaining double bond. While this does not always prove useful in terms of practical application, in principle the preservation of functionality should always be desirable from the point of view of the need for further synthetic transformations at these sites.

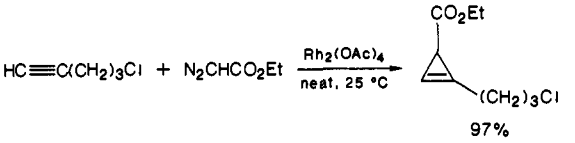
The organization of this review follows and focuses on the ring system products of cycloaddition. Compound types are discussed in order of ring size and approximate oxidation level. The sections on 1,3-cyclohexadienes and indenes are not in their logical places according to this scheme due to their close relationships with the sections immediately preceding them. An attempt has been made to emphasize syntheses of some generality; in cases where a large number of transition-metal systems can effect essentially the same transformation, only the most general and practical examples will be covered. Expanded coverage has been provided for several reactions that are objects of considerable current attention from synthetic chemists. Reactions in which the transition-metal species acts merely as a Lewis acid (e.g., some reactions involving $TiCl_4$) are generally excluded. For the most part, this review also does *not* treat cycloadditions of alkynes that give metallacycles from which cyclic organic products cannot generally be liberated. For the most part, the reactions covered in this review fit a strict definition of cycloaddition in that they involve the formation of *two new ring bonds to the alkyne carbons.* Reactions in which a remote –XH group in an alkyne adds to the triple bond to form a new ring (which fall into the looser category of cyclization) are not covered. As another example, reductive coupling reactions of diynes to form cyclic 1,2-bis(methylene) compounds in which only one new ring bond is formed are not covered.

The reader will quickly note that many cycloaddition reactions of alkynes, both metal-catalyzed and otherwise, are quite limited in scope. For this reason considerable effort has been expanded in developing synthetic equivalents for alkynes that display more suitable reactivity in specific types of cycloaddition reactions. This area has been reviewed recently.[1]

II. Small Rings

A. Cyclopropenes, from Alkynes and "Carbenes"

The $Rh_2(OAc)_4$-catalyzed decomposition of diazo esters in the presence of alkynes remains the method of choice for the synthesis of derivatives of cyclopropene-3-carboxylic acid, being far more versatile than other routes.[2] The reaction apparently involves a true carbenoid species and proceeds in generally quite good yields with a wide variety of terminal and internal alkynes (eq 1). (Trimethylsilyl)propynal gives a pyrazole via 3 + 2 cycloaddition even in the presence of $Rh_2(OAc)_4$, however, suggesting that direct cycloaddition can in some cases be faster than reaction of the catalyst with the diazo compound.[3] The process is compatible with many functional groups, including esters, ethers, and aryl and alkyl halides,[4,5] but alkenes and alcohols interfere.[6] Superior results are obtained with *tert*-butyl in place of methyl or ethyl diazo ester,[7] but diazo ketones react differently, giving acyclic products.[8] The latter limitation has been circumvented by Liebeskind,[9] who successfully prepared cyclopropenyl ketones from the esters via RMgX or RLi addition to the corresponding *N*-methoxy-*N*-methylamides.[10]

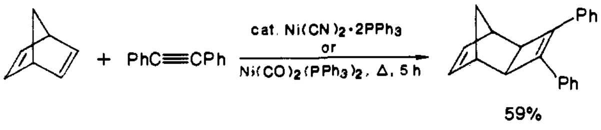


(1)

The Liebeskind study is of note in that the cyclopropenyl derivatives thus obtained were converted into a variety of other cyclic compounds, including 2-pyrones, furans, and phenols; the overall sequences thus constitute formal syntheses of these compounds from alkynes.

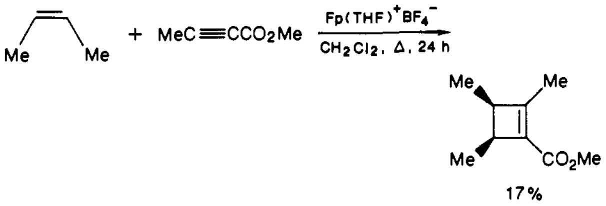
B. Cyclobutenes, from Alkynes and Alkenes

Direct cycloaddition of alkynes to alkenes to give cyclobutenes has been achieved in a limited number of cases both photochemically[11] and in the presence of Lewis acid catalysts.[12] Cycloaddition presumably involving true transition-metal complexation and catalysis was first described by Schrauzer (eq 2).[13] In spite of further development by others involving both ruthenium hydride and Ziegler–Natta (Et_2AlCl–$TiCl_4$) cata-



(2)

lyst systems, the scope appears limited to norbornene-like alkenes on the one hand and "special" alkynes such as dimethylacetylene dicarboxylate and bis(trimethylsilyl)acetylene on the other.[14-16] Somewhat greater range is available through the use of cationic iron complexes ("Fp^+" = $CpFe(CO)_2{}^+$): cyclic and acyclic disubstituted olefins have been thus added to methyl 2-butynoate to give cyclobutenes stereospecifically (eq 3).[17] In the presence of $AlBr_3$, totally regioselective cycloaddition takes place between MeC≡CFp and cyclohexenone (eq 4).[18] As several methods exist for the removal of the Fp group from saturated carbons at least,[19] it would seem that this latter process has much potential for useful development.



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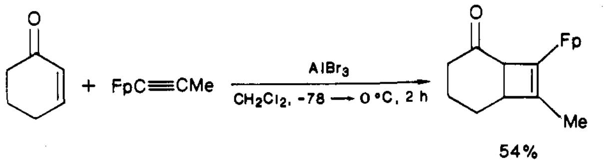
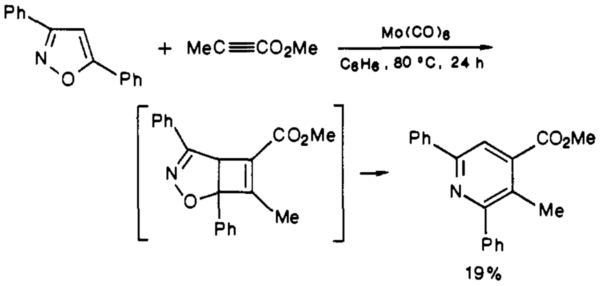


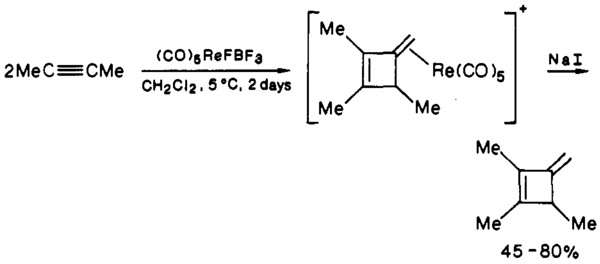
(4)

Apparent 2 + 2 cycloadditions of alkynes to the 4,5-double bond of substituted isoxazoles occur in the presence of $Mo(CO)_6$. Stable cyclobutenes are not formed; rather, ring opening and deoxygenation take place in a sequence that ultimately leads to annulated pyridine derivatives (eq 5).[20]



(5)

In a separate class of processes methylenecyclobutenes are obtained from reactions of dialkylacetylenes with either cationic nickel hydrides[21] or rhenium carbonyls (eq 6).[22] These reactions may initially involve cyclobutadiene–metal complexes.[23] Reaction of methyl propynoate with $Cr(CO)_5{\cdot}Et_2O$ gives not only the simple π-complex but also a cyclobutenylidene complex as well (eq 7).[24] Although in this case liberation of the organic fragment in some form was not attempted, general methods to do so are available.[25]



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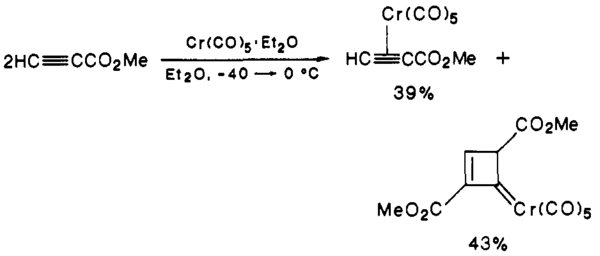

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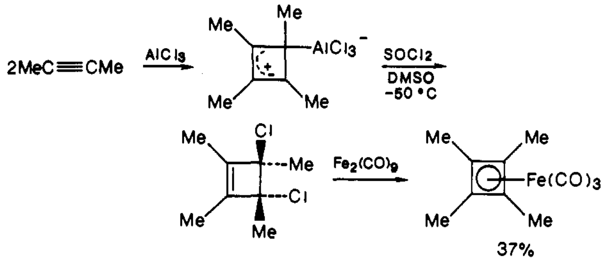
C. Cyclobutadienes, from Two Alkynes

Cyclobutadienes continue to be systems of interest for a variety of reasons, and the synthesis and study of substitutionally stabilized derivatives is a very active area.[26] For the purposes of practical utility in organic synthesis, one deals essentially exclusively with $Fe(CO)_3$ complexes from which free cyclobutadienes may be readily liberated[27] and whose enormous versatility has been amply documented.[28] Although a variety of transition-metal systems are capable of cyclizing two alkynes to give metal-complexed cyclobutadienes in decent yields,[29] these do not *in general* include iron carbonyls, although isolated examples (typically intramolecular) do exist.[30] Since cyclobutadienes themselves are typically not readily released from complexes with metals other than iron,[31] these cycloadditions are of little value in the generation of the free species for synthetic use. Thus a decidedly indirect method (from cyclooctatetraene and dimethyl acetylenedicarboxylate!) must be employed to prepare cyclobutadiene–$Fe(CO)_3$ itself.[32] However, a viable synthetic connection between alkyne dimerization and substituted cyclobutadiene–$Fe(CO)_3$ complexes has been established in the work of Hogeveen, who found that the zwitterionic products of reaction between alkynes and $AlCl_3$ are readily converted by $SOCl_2$ to 3,4-dichlorocyclobutenes. Treatment of the latter with $Fe_2(CO)_9$, a known process, completes the route to the complexes (eq 8).[33]

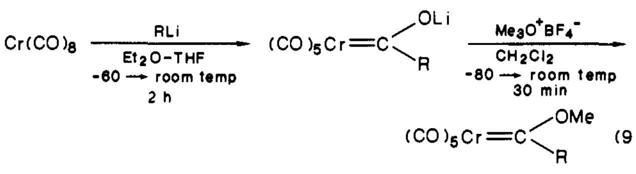


(8)

The two isomeric diphenylcyclobutadienes are claimed to be isolable products of dimerization of phenylacetylene over mixed-metal oxides at 150 °C. The reported NMR spectra of the products, however, show two nonequivalent alkene hydrogens for each supposed cyclobutadiene.[34]

D. Cyclobutenones, from Alkynes, CO, and "Carbenes"

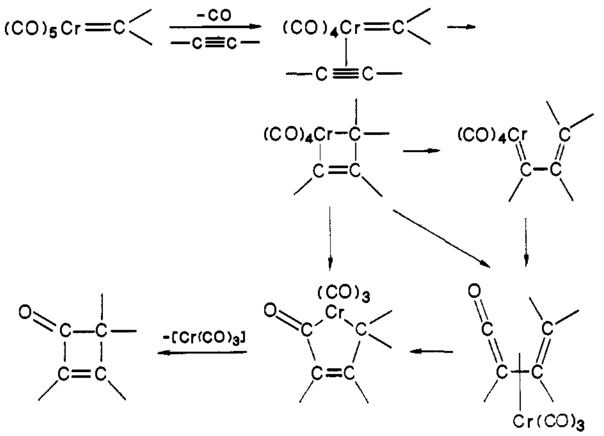
Cyclobutenones are the simplest compounds that can be formed by cycloadditions of alkynes with members of the class of stable transition-metal carbene complexes generically called "Fischer carbenes". These are typically prepared by addition of RLi to a metal carbonyl such as $Cr(CO)_6$, followed by O-methylation of the resulting anion with a trimethyloxonium salt (eq 9).[35]



(9)

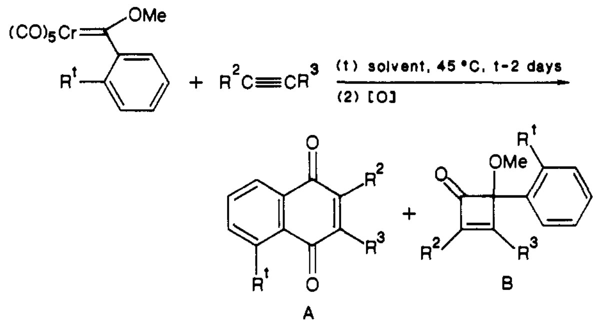
Beginning with the pioneering work of Dötz in the mid-1970s,[36] a considerable amount of development has taken place in this general area, with cycloaddition reactions of alkynes with carbene complexes of Cr, W, Co, and Fe the principal targets of study. From such reactions may be isolated naphthols, indenes, furans, cyclobutenones, and occasionally other products as well, sometimes all at the same time.[37] Thus, although several synthetically useful applications of this chemistry were quickly uncovered,[38] the field really required a certain degree of "taming" in order to be more readily and specifically applicable to synthetic problems. Considerable success has been achieved in this effort by several groups, and applications of metal carbene cycloaddition chemistry to each of the aforementioned compound classes will be treated separately.

The route to cyclobutenones is thought to proceed via initial cycloaddition to give a metallacyclobutene. This may lead relatively directly to the cyclobutenone via CO insertion and reductive elimination of the metal, a sequence that may also involve initial ring opening to a vinyl ketene complex; alternatively, it may first undergo electrocyclic ring opening to give a vinylcarbene complex that gives the same product after CO insertion followed by electrocyclic ring closure (eq 10, shown for M = Cr). This process competes with annulation to a π-system attached to the carbene carbon, typically an aryl group, in which case the usual product is a naphthol derivative or, after oxidation, a naphthoquinone (see Phenols).



(10)

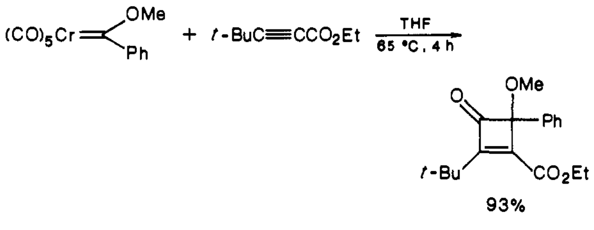
An extensive analysis of the factors that control these reactions has been recently published by Wulff.[39] The results of experiments involving changes in carbene structure, alkyne structure, and solvent have been evaluated critically in light of the several possible mechanisms that have been proposed for these reactions[40] and will doubtless be of great value in designing future applications of this chemistry. A presentation of this material in full is beyond the scope of this review, but the salient features are as follows. Cyclobutenone formation occurs only in the presence of internal or external ligands that can coordinate to unsaturated Cr species sufficiently well to prevent complexation to an internal π-system and thus divert the system toward formation of the chromacyclopentenone intermediate shown (eq 10). These conditions are achieved in cycloadditions of internal alkynes with chromium *aryl*alkoxycarbenes carried out in CH_3CN solvent. Cyclobutenone formation is further favored by the presence of an *o*-OMe group on the arene (internal coordination of Cr), and by bulky groups on the alkyne (both of which favor small-ring formation and may inhibit η^4- or η^6-coordination of the metal) (eq 11). These reactions are highly regioselective with major or exclusive products formed by initial bonding of the carbene carbon to the alkyne carbon with the smaller substituent.



(11)

R^1	R^2	R^3	solvent	% A	% B
H	Et	Et	THF	88	0
H	Et	Et	CH_3CN	38	23
OMe	Et	Et	CH_3CN	<2	43
H	*t*-Bu	Me	CH_3CN	0	27
H	Ph	Ph	CH_3CN	0	51

Cyclobutenones have virtually never been observed with terminal alkynes; nor are they formed from chromium *vinyl*alkoxycarbenes, in which coordination by the nonaromatic π-system cannot be prevented by other ligands. Not surprisingly, cyclobutenones have been isolated from reactions of chromium alkylalkoxycarbenes, where no competing π-system is present,[41] and from *o,o′*-disubstituted arylalkoxycarbenes, in which bond formation to the arene is blocked.[42] Other examples exist,[43] including some exceptional cases where the balance of factors gives very favorable results (eq 12).[44]



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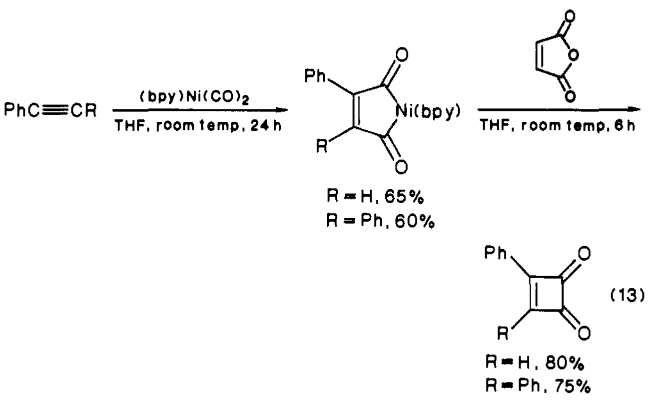
E. Cyclobutenediones, from Alkynes and Two CO

Hoberg has extensively studied the preparation and chemistry of Ni(0) complexes with donor ligands, discovering two examples of cyclobutenedione formation directly from alkynes and CO. Upon reaction of either phenyl- or diphenylacetylene with $(bpy)Ni(CO)_2$ (bpy = 2,2′-bipyridyl) under CO a nickelacyclopentenedione complex forms in high yield. Further reaction either with higher pressures of CO or with maleic anhydride liberates the cyclobutenedione (eq 13). Alkylacetylenes give the complex, but subsequent reaction to give a four-membered ring does not occur.[45]

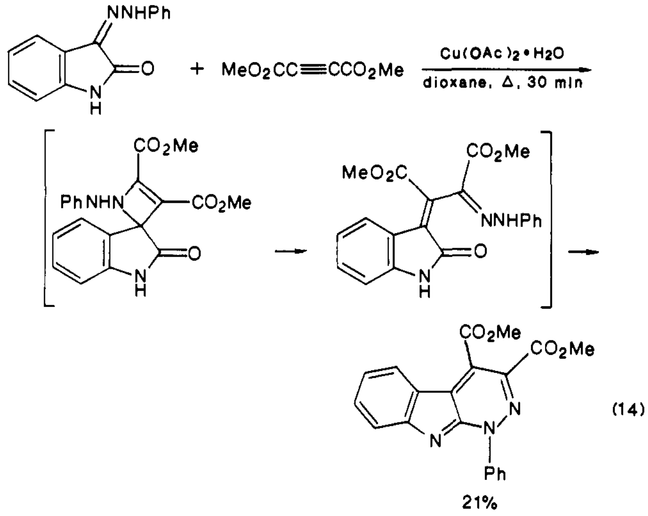


(13)

An efficient and unique synthesis of squaric acid (dihydroxycyclobutenedione) via Pd-catalyzed dimerization of di-*tert*-butoxyacetylene should be noted.[46]

F. Heterocyclobutenes, from Alkynes and Heteroalkenes

A recent report details a single example of apparent Cu-promoted cycloaddition of an alkyne to the C=N bond of the 3-phenylhydrazone of isatin, the 2,3-dioxo derivative of indole.[47] The cycloadduct itself is not isolated; the annulated pyridazine actually obtained is postulated to arise by an electrocyclic ring opening of the spiroannulated azacyclobutene followed by ring closure (eq 14).



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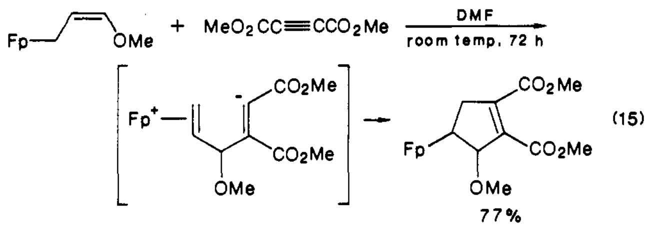
III. Five-Membered Rings

A. Cyclopentenes

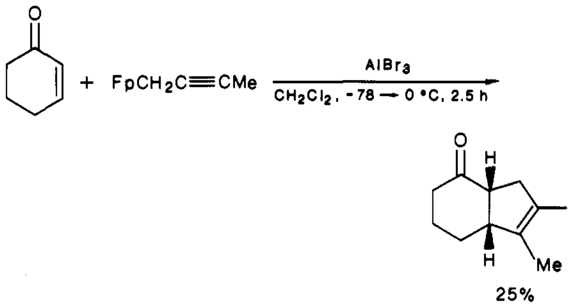
1. From Alkynes and Allyl Complexes

Dimethyl acetylenedicarboxylate reacts with two (η^1-allyl)Fp complexes in a formal 3 + 2 cycloaddition accompanied by migration of the metal fragment (eq 15).[48]



(15)

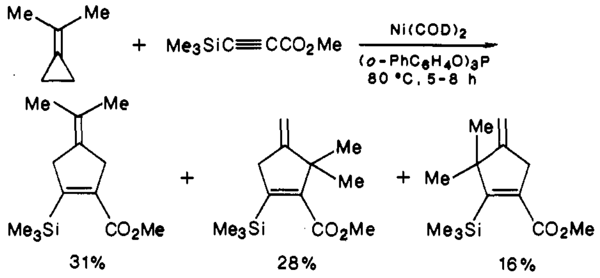
In a reaction that is not really a cycloaddition of an alkyne per se, Rosenblum has shown that (η^1-propargyl)Fp complexes (in contrast to *propynyl*-Fp complexes; see Cyclobutenes) behave as synthetic equivalents of the 1,3-dipole $^+CH_2—C(Fp)=CH^-$ in a novel 3 + 2 cycloaddition with cyclohexenone in the presence of $AlBr_3$ (eq 16).[18] Several examples of cycloaddition of this species to other dipolarophiles, including heteroatom-containing systems, have also been reported.[19a,49,50]



(16)

2. From Alkynes and Cyclopropanes

In the presence of a Ni(0) catalyst, methylenecyclopropanes behave as trimethylenemethane equivalents in a fairly general cycloaddition reaction with alkynes ($RC≡CSiMe_3$, R = Me, Et, CH_2OSiMe_3, CO_2Me, $SiMe_3$).[51] The reaction gives high yields, but regiocontrol is a problem with methylenecyclopropanes substituted on the exo-methylene carbon; these usually give rise to large amounts of product from cycloaddition involving the exo carbon (eq 17). For methylenecyclopropane itself where this is not a problem, the corresponding 4-methylenecyclopentene is obtained as the sole product in 70–80% yield.

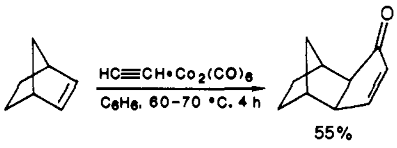


(17)

B. Cyclopentenones, from Alkynes, Alkenes, and CO

1. Pauson–Khand Reaction

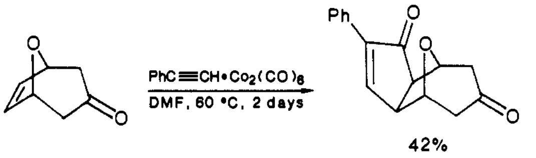
Of the several reported methods for cocyclization of alkynes with alkenes and CO, the most extensively studied is the one first reported in detail by Khand and Pauson in 1973,[52] a cyclopentenone synthesis from the three components and $Co_2(CO)_8$, a formal 2 + 2 + 1 cycloaddition. In general, alkynes react with $Co_2(CO)_8$



(18)

in hydrocarbon solvents or ether to generate the thermally stable, readily characterized complexes $Co_2(CO)_6 \cdot RC{\equiv}CR'$. These in turn react with a wide variety of alkenes to generate cyclopentenones (eq 18). In a truly monumental effort, Pauson and co-workers have defined almost all the important parameters associated with this remarkable reaction. Typical yields fall in the 30–60% range, although some recent modifications have led to significant improvements in certain cases. Excellent background material on this process is available in reviews published by Pauson in 1977, 1985, and 1988.[53,54]

(a) Intermolecular. Virtually all alkynes that have been tried except derivatives of propynoic acid participate in the Pauson–Khand reaction. The scope of the reaction with respect to the alkene is typically somewhat more limited. In particular, alkenes with electron-withdrawing substituents react differently (vide infra).[55] Strained cyclic alkenes are the best substrates, typically reacting between 60 and 80 °C over a period of several hours. In addition to norbornene (above), representative examples include derivatives of bicyclo[3.2.0]hept-6-ene,[56] 8-oxabicyclo[3.2.1]oct-6-en-3-one (eq 19),[57] and bicyclo[2.2.2]octene.[58]

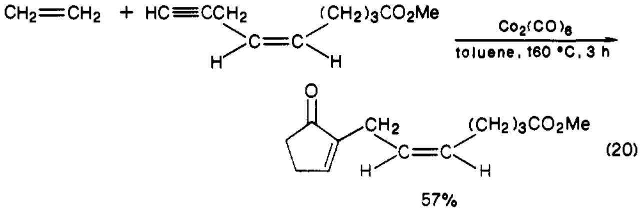


(19)

42%

The regiochemistry of incorporation of the unsymmetrical alkyne in the product of this reaction is a characteristic feature of this reaction, as is the exo stereochemistry of the newly formed ring fusion. Typically a stoichiometric quantity of alkene and alkyne–cobalt complex is used, and the reaction is carried out under an atmosphere of N_2, Ar, or CO. It is occasionally possible to realize higher yields (e.g., 74% for eq 18) by carrying out the reaction with a catalytic amount of $Co_2(CO)_8$ in the presence of excess alkyne under a CO atmosphere.

Unstrained cyclic alkenes are generally less reactive, giving usable yields only in isolated cases, e.g., cycloheptene or cyclooctene with phenylacetylene;[59] cyclohexene is a very poor substrate. Important exceptions are cyclopentene and dihydrofuran.[60,61] Required reaction temperatures are higher in some cases (120–160 °C), but no other special conditions are necessary and yields are frequently excellent. Among simple alkenes, ethylene provides useful results although forcing conditions are usually required (160 °C, 80 atm, autoclave) (eq 20).[62]

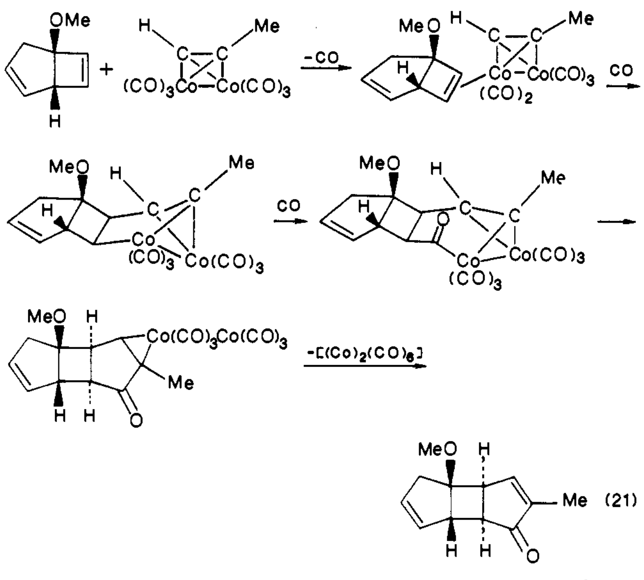


(20)

57%

The Pauson–Khand reaction is completely compatible with a wide range of functionality, including ethers, alcohols,[57] tertiary amines, thioethers, ketones, ketals, esters, tertiary amides,[53] and aromatic rings, including benzene, furan, and thiophene.[63] Partial tolerance of the following groups has also been observed: alkyl and aryl halides, vinyl ethers and esters,[64] and ordinary alkenes and internal alkynes in the presence of more reactive unsaturation.[65]

Although direct mechanistic evidence beyond the alkyne complexation stage is lacking, a hypothesis has been inferred from observations of regio- and stereochemistry in both inter-[57] and intramolecular situations (vide infra). Complexation of the alkene is followed by insertion into one of the formal Co–C bonds of the alkyne complex. Both regiochemistry and stereochemistry are chiefly sterically controlled. With bicyclic alkene substrates the less hindered face of the π-bond preferentially complexes and inserts, leading to an exo-ring fusion. During the insertion into the Co–C bond, 1,3-pseudodiaxial interactions develop involving both a carbonyl group on Co and any substituent on the alkyne carbon with any allylic substituents on the alkene. If the alkyne is unsymmetrical, insertion and C–C bond formation therefore proceed at the alkyne carbon possessing the *smaller* substituent (i.e., H in a terminal alkyne, leading eventually to a 2-substituted enone). If the alkene is unsymmetrically substituted at the allylic positions, C–C bond formation is directed toward the alkene carbon nearest the *larger* allylic substituent, avoiding a steric interaction with the $Co(CO)_3$ moiety. Subsequent CO insertion, reductive elimination of one Co, and decomplexation of the other give the final product (eq 21).

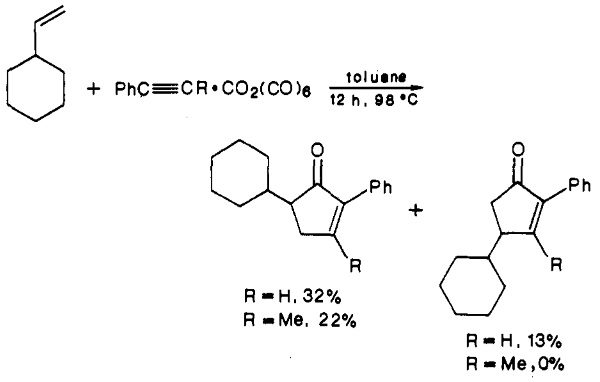


(21)

60% (only isomer)[56]

Reduced cycloaddition reactivity is found in hindered systems such as internal alkynes, alkenes with very large allylic substituents, and trisubstituted alkenes. Failure of the reaction for steric reasons is primarily due to complexation to cobalt and insertion of one or more additional molecules of *alkyne* instead of the alkene, leading to a variety of products.[66]

Although terminal alkenes usually give poor yields and regioselectivity,[59] isolated examples of high selectivity (e.g., 3,3-dimethyl-1-butene, which with ethyne gives >95% 5-*tert*-butyl-2-cyclopentenone[67]) are known.[68] Krafft has recently shown that reactions between terminal alkenes and *internal* (as opposed to terminal) alkynes are similarly selective, presumably a consequence of increased steric interactions.[69] Of considerable potential is another recent observation by Krafft that alkenes containing groups capable of acting as soft ligands at a homoallylic position give both enhanced yields and regioselectivities. This is thought to result from coordination of the heteroatom prior to insertion (eq 22 and 23).[70]



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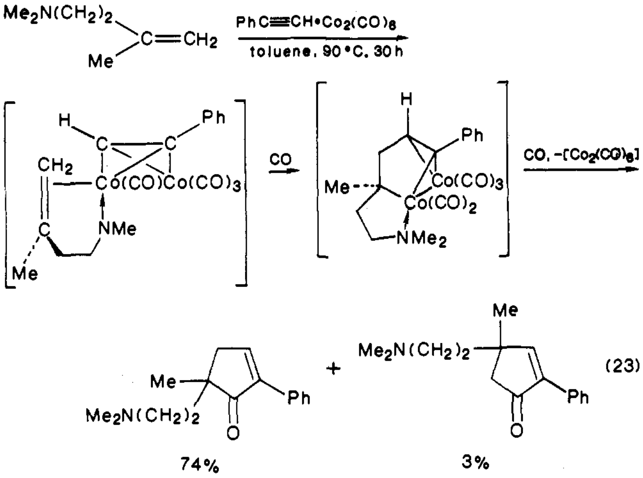
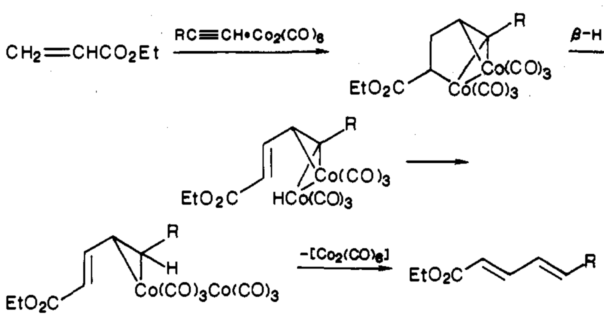


(23)

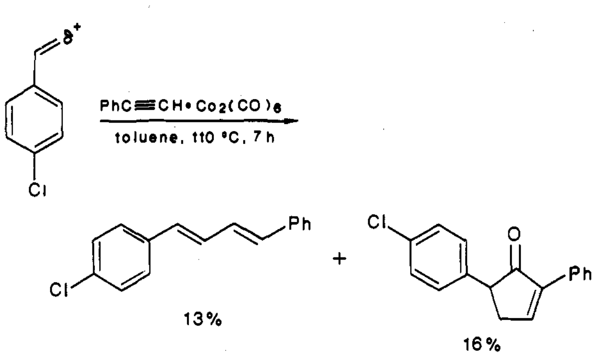
As already mentioned, alkenes attached to electron-withdrawing groups (all π-conjugating) react anomalously, giving 1,3-dienes.[71] This probably involves a β-hydrogen elimination/reductive elimination sequence competing with CO insertion from the initial product of alkene insertion (eq 24).



(24)

Styrene derivatives are intermediate, giving both dienes and cyclopentenones, both regioselectively (eq 25).[72,73] An electronic preference for attachment of the $\delta^+\beta$-carbon of the styrene to an alkyne carbon rather than cobalt in the bond-forming insertion step may be partly responsible. The regioselectivity observed in cycloadditions of norbornen-2-ones is consistent with this explanation (e.g., eq 26; the corresponding alcohols give ca. 1:1 product ratios).[74]

Numerous synthetic applications of the intermolecular Pauson–Khand reaction have been reported.



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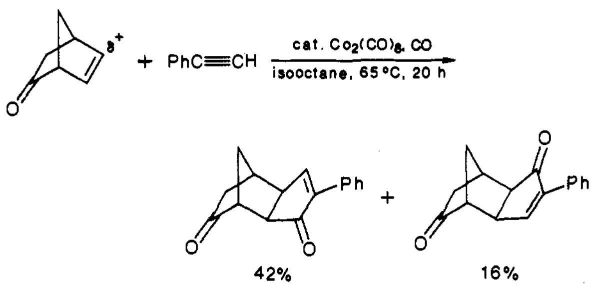
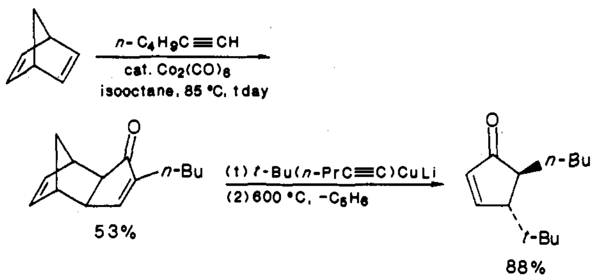


(26)

Simple 4,5-disubstituted 2-cyclopentenones are readily prepared from the cycloaddition products of norbornadiene (eq 27).[75] Pauson has reported numerous applications of intermolecular cycloadditions in the synthesis of prostanoid analogues (eq 20, 28).[62,65,76]



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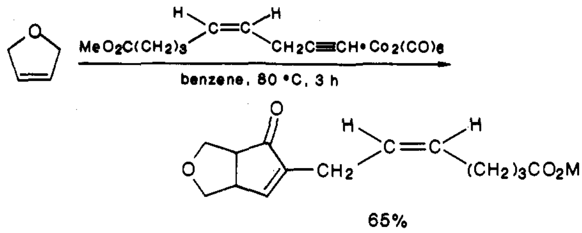
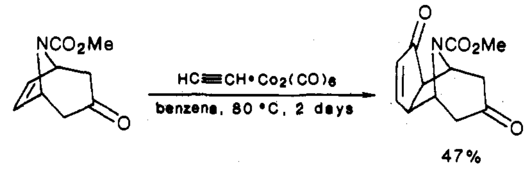


(28)

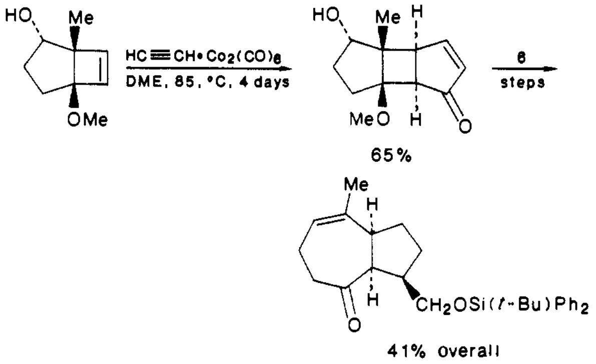
Dihydrofuran cycloadditions have also been used in the synthesis of the antibiotic methylenomycin B,[68] cyclomethylenomycin A (synthetic precursor to the antibiotic methylenomycin A) and cyclosarkomycin (precursor to the antitumor agent sarkomycin),[61] and the iridoid Japanese hop ether.[77]

Variations on the hydrazulene skeleton have been approached via Pauson–Khand reaction in several ways. Cycloadditions of cycloheptene and an oxygen-bridged bicyclic have been noted. The nitrogen analogue has also been cyclized successfully (eq 29),[78] and cycloaddition of highly functionalized derivatives of bicyclo[3.2.0]hept-6-enes provides access to systems trans-



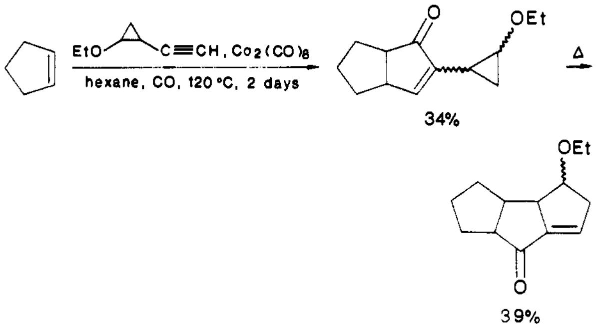
(29)

formable into both the guaianolide and pseudoguaianolide natural product structural types (eq 30).[79] Note the reversal of regiochemistry (cf. eq 21) in the latter case due to the presence of the larger allylic *methyl* group.



(30)

In a novel combination of Pauson–Khand cycloaddition with vinylcyclopropane chemistry, de Meijere has described an entry to linearly fused triquinanes beginning with cyclopropylacetylenes (eq 31).[80] Finally, Serratosa's group has found an unexpected alkene isomerization to precede cycloaddition of the bicyclo[3.3.0]oct-2-ene system, allowing direct access to angularly fused triquinanes (eq 32).[81]



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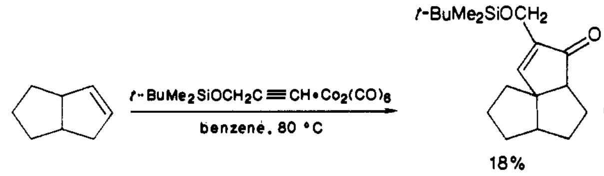
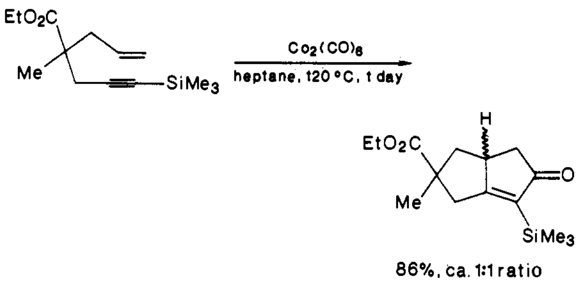


(32)

(b) Intramolecular. Enynes in which three or four atoms separate the double and triple bonds cyclize upon complexation to $Co_2(CO)_8$ and subsequent heating to give bicyclic enones; hex-1-en-5-yne, which would give a four-membered ring upon intramolecular cyclization, undergoes instead alkyne trimerization.[82] The most extensively studied systems are those derived from hept-1-en-6-yne, as the products, bicyclo[3.3.0]oct-1-en-3-ones, are useful in the synthesis of numerous cyclopentane-based polycyclics. In these cyclizations, substitution on both the alkyne and the chain linking the alkyne and the alkene is often readily tolerated. Indeed, the latter confers substantial benefits in terms of both yield and reaction time (Thorpe–Ingold effect),[83] provided that excessive steric interactions are not introduced (eq 33).[84] Hua has prepared two 7,7-dimethylated derivatives in this manner and used them for syntheses of optically active pentalenene and racemic pentalenolactone *E* methyl ester (eq 34).[85]



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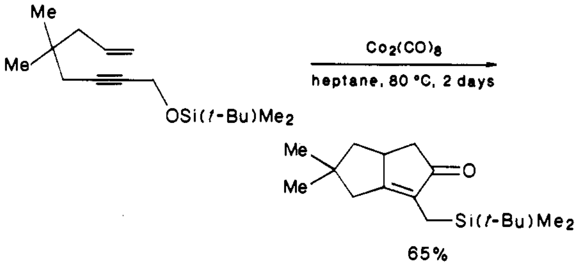
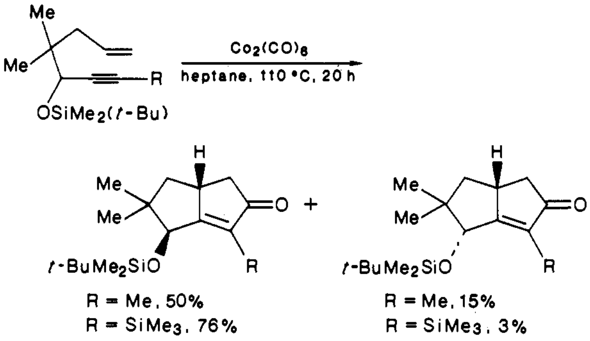


(34)

Magnus has systematically examined the factors that contribute to the stereoselectivity shown in several of the above reactions.[86] As alkene insertion takes place into a Co–C bond of the Co–enyne complex, pseudodiaxial interactions develop between the alkyne substituent and those substituents at the allylic and propargylic positions of the original enyne that eventually wind up on the endo face of the product. Thus the insertion is preferentially direct to place larger substituents in exo orientations. The larger these substituents are, the greater the stereoselectivity obtained (eq 35 and 36). The bicyclo[3.3.0]oct-1-en-3-ones illustrated in these examples have been used by Magnus in syntheses of coriolin, hirsutic acid, and quadrone, respectively. A totally stereoselective synthesis of a carbocycline analogue has also recently been described.[87] Yields in these reactions are sometimes improved in the presence of additives such as phosphine oxides, but this effect is neither general nor as yet understood.[54,88]



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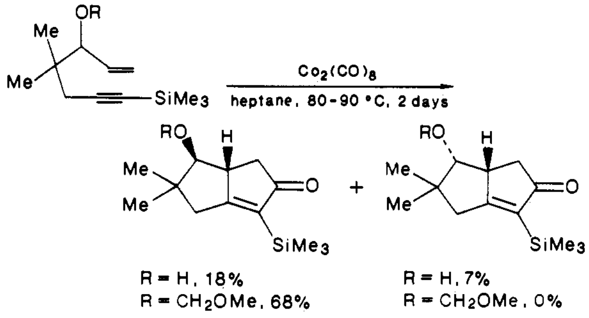
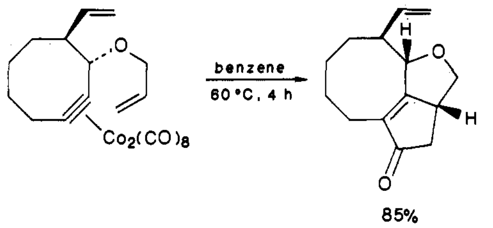


(36)

With some limitations, heteroatoms may be present in the linkage between the double and triple bond. Allyl propargyl ethers have been recently subjected to considerable study, in part due to their ready access via the intermediacy of $Co_2(CO)_6$-complexed propargyl cations, whose chemistry has been extensively developed by Nicholas.[89] Initial work by Billington established the feasibility of these systems as cyclization substrates, albeit in only moderate yields (≤40%). A 7-oxabicyclic prepared by such an intramolecular cyclization was successfully utilized in the synthesis of a derivative of the natural product aucubigenone.[90] Both Schreiber[91] and the Smit/Caple collaboration[92] have combined Nicholas chemistry with Pauson–Khand cyclization to access novel heteropolycyclics (eq 37 and 38). In the former case, incorporation of the alkyne in medium-sized rings was cleverly achieved by exploiting the "bending" of the triple bond by Co complexation in the course of propargyl cation mediated ring formation.



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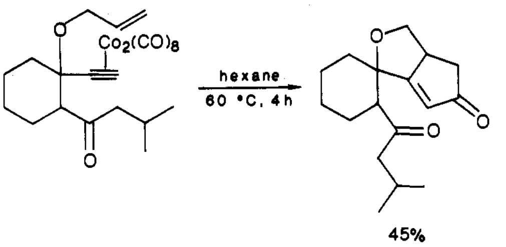
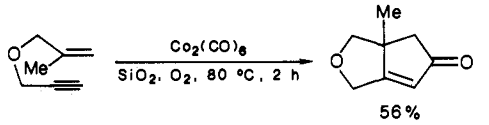


(38)

In the course of Smit's work the remarkable discovery was made that these cyclizations may be more efficiently carried out by adsorption of the Co-complexed enyne–ether onto silica followed by gentle heating of the *dry* powder under oxygen or air (eq 39).[93] Apparently adsorption restricts conformational motion in a manner similar to that of bulky substitution, facilitating cyclization. The technique is also applicable to ordinary enynes provided that they possess appropriately positioned polar groups for silica adsorption (eq 40). Oxygen is necessary, although its role is not understood, and some examples are accelerated by sonication. Tolerance of the process for additional alkene substitution is to be noted.



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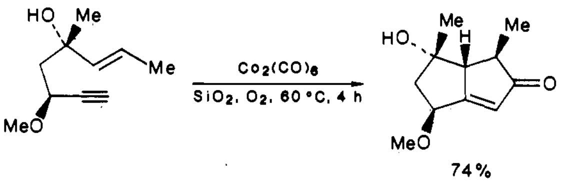
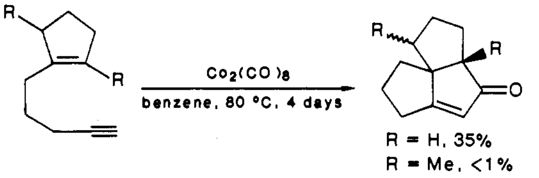


(40)

Incorporation of the alkene in a ring is compatible with intramolecular cyclization. Derivatives of angularly fused triquinanes have been prepared; since the reaction is limited to trisubstituted alkenes and simple terminal alkynes, bisnorisocomene, but not isocomene, could be synthesized (eq 41).[94] In these reactions stereochemistry is affected by new 1,3 interactions involving groups about the spiro carbon.[95] This has worked to our advantage in a stereocontrolled synthesis of pentalenene (eq 42).[96]



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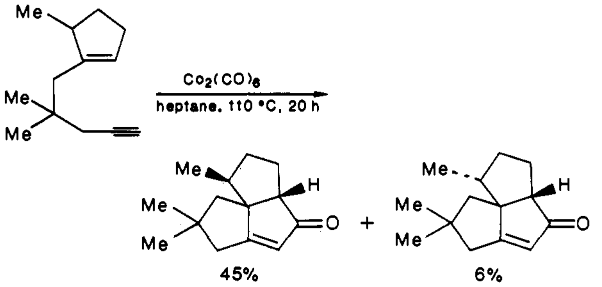
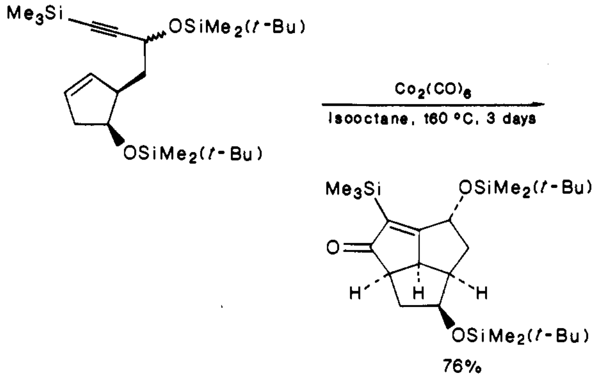


(42)

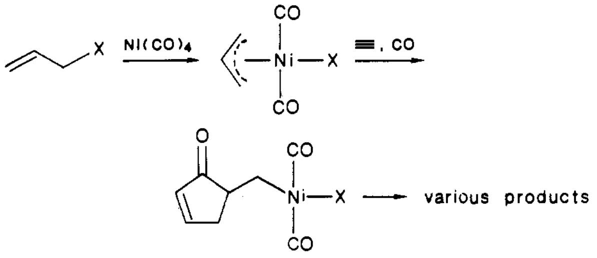
Serratosa has developed an exceptionally efficient approach to triquinacenes making use of similar intramolecular cycloadditions of cyclic alkenes containing alkynyl substitution.[97] Epimerization occurs in the example shown, probably via a Co-stabilized propargyl cation (eq 43).[98]



(43)

2. *Via Allyl-Ni Complexes*

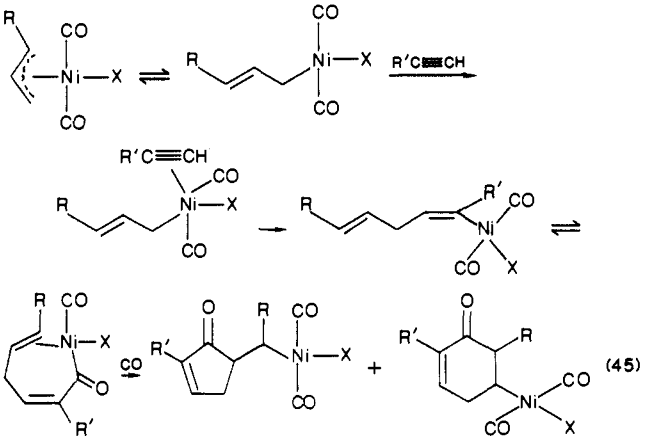
A superficially similar, but mechanistically quite different cyclopentenone preparation derives from the work of Chiusoli in the 1960s. In this process $Ni(CO)_4$ is the catalyst precursor and the double bond of an allylic halide serves as the alkene component of a formal 2 + 2 + 1 cycloaddition. In general, a mixture of an alkyne, an allylic chloride, and $Ni(CO)_4$ in moist acetone is allowed to react at 20 °C, leading to the sequential insertion of alkyne and CO into an initially formed allyl-Ni complex. Final products are derived from subsequent reaction of the primary cyclization product, a ((2-oxo-3-cyclopenten-1-yl)methyl)nickel complex with additional substrate molecules and/or the solvent (eq 44). Important features of the reaction have been de-



(44)

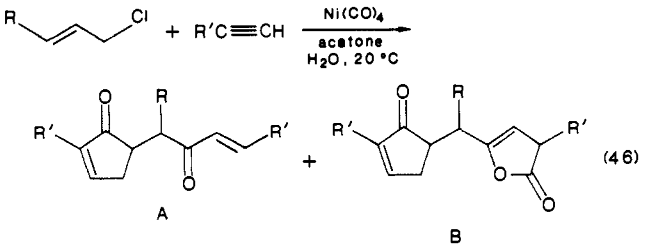
scribed in several reviews,[99,100] one of which gives considerable detail;[101] thus the discussion here will be brief.

The reaction proceeds via a well-defined sequence of steps, many of which are supported by mechanistic work in which intermediates have been isolated or have been independently prepared and resubmitted to undergo further reaction. Allyl halides are readily carbonylated in the presence of CO and $Ni(CO)_4$ in nucleophilic solvents to give 3-butenoic acid derivatives, via (η^3-allyl)nickel complexes.[102,103] In the presence of alkynes, however, insertion of the latter occurs faster than carbonylation, leading first to (*cis*-1,4-pentadienyl)nickel and then to (*cis*-2,5-hexadienoyl)nickel complexes, which may be trapped as derivatives of *cis*-2,5-hexadienoic acid.[104] In the absence of suitable nucleophiles (especially in ketonic solvents), insertion of the remote double bond into the acyl–Ni bond gives five- and six-membered rings, still σ-bonded to Ni (eq 45).[105]



(45)

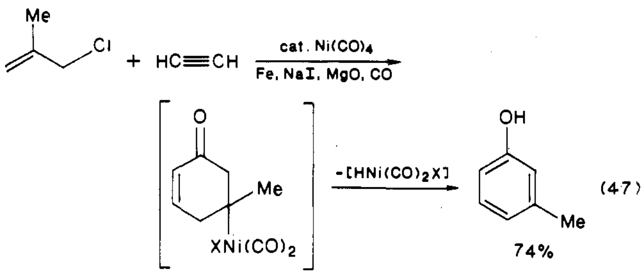
The sequence as described is followed in reactions of various alkynes with allyl, methallyl, and crotyl chlorides and methyl 4-bromocrotonate, with five-membered-ring formation favored for all but the methallyl system. All examples show total regioselectivity toward C–C bond formation between unsubstituted carbon atoms of unsymmetrical alkynes and allyl derivatives. The major organic products are derived from further insertions of CO and alkyne, followed by either protonolysis to give an enone side chain (major pathway with $PhC{\equiv}CH$[106]) or another CO insertion and cyclization to a lactone (eq 46). Diversion to other products is possible by control of reaction conditions.



(46)

R	R'	% A	% B
H or Me	H	0	major product
H	Me	28	56
H	Ph	64	4
Me	Ph	71	0

The preference for six-membered-ring formation in the methallyl system has given rise to an efficient *m*-cresol synthesis[107] via immediate loss of the metal (eq 47).

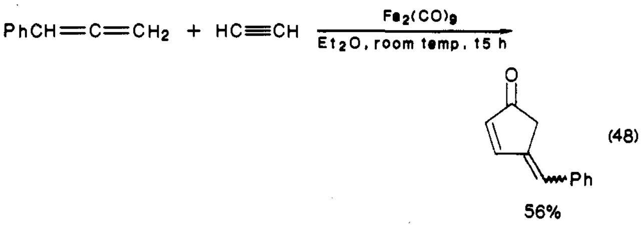


(47)

Although alternative catalyst systems not using the insidiously toxic $Ni(CO)_4$ exist for some of the simple linear carbonylation processes described above,[108] no such alternatives are yet available for the cyclization reactions, reducing their attractiveness as practical techniques. No intramolecular examples of this process have been reported.

3. An Fe-Based Analogue

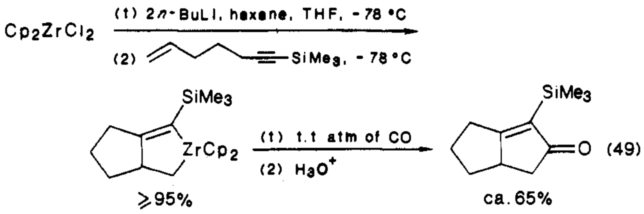
A new cycloaddition process that generates 4-methylenecyclopentenones from alkynes, *allenes*, and CO under conditions that generate the $Fe(CO)_4$ fragment has been reported. At present, the range of known reactive substrates includes alkynes $HC{\equiv}CH$, $PhC{\equiv}CH$, and $PhC{\equiv}CPh$ and allenes $H_2C{=}C{=}CH_2$, $PhCH{=}C{=}CH_2$, and $PhCH_2CH{=}C{=}CH_2$ (eq 48).[109]



(48)

4. Using Early Transition Metals

A recent development in cyclopentenone synthesis that also shows considerable promise in other applications is the Zr-promoted enyne "bicyclization" discovered by Negishi in 1985.[110] The general process is analogous to the intramolecular Pauson–Khand synthesis of bicyclo[3.3.0]oct-1-en-3-ones from hept-1-en-6-ynes. It is carried out by first generating a Cp_2Zr equivalent from reaction of Cp_2ZrCl_2 with butyllithium in THF at −78 °C and then introducing the enyne, generating an isolable metallacycle.[111] Carbonylation liberates the ketone (eq 49).



(49)

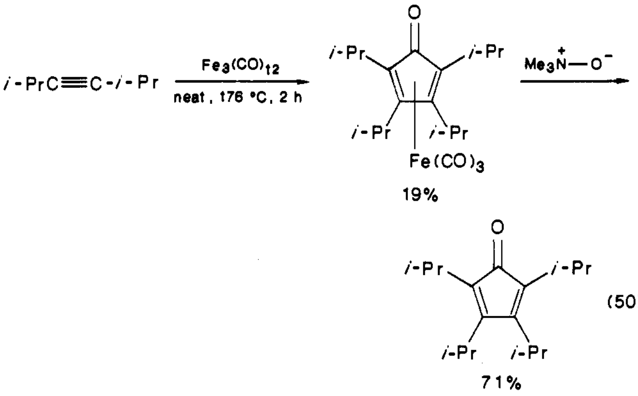
The Zr-based version is complementary to the Pauson–Khand reaction in certain respects. Terminal alkynes are incompatible with the cyclization; thus blocking is required. This was initially a significant problem as the $SiMe_3$ group originally used was difficult to remove; use of $SnMe_3$ instead has alleviated the difficulty and even permitted further functionalization to be achieved.[112] Metallacycle formation is a very clean, high-yield process, even in lightly substituted systems. Even though yields from the carbonylation step are not as high (typically 60%), the overall efficiency equals or exceeds that of the Pauson–Khand reaction except for those cases where the latter benefits from the (Thorpe–Ingold) effects of substitution. On the other hand, functional group tolerance in the Negishi process may not be as good due to the basic, highly reducing conditions under which the reactive species is generated; however, common saturated functional groups (alkyl and silyl ethers, simple amines) are compatible with these conditions. Substitution at either carbon of the alkene is tolerated only in certain cases; the need for terminal substitution on the alkyne may limit the applicability of the process to further substitution at the alkene carbons (cf. eq 41).

Although beyond the scope of this review, note that the isolability of the zirconacyclopentene intermediate confers considerable additional utility on this reaction beyond synthesis of cyclic ketones. Other metal–carbon bond-cleavage processes may be employed to generate products of reductive cyclization with varying additional functionality;[113] closely related work by Nugent with diynes and enynes[114,115] and by Trost with enynes,[116] the latter employing a true catalytic Pd-based method, is to be noted. Recent work by several groups on the preparation and chemistry of both zirconacycles[117] and zirconocene–alkyne complexes[118] promises to further extend the synthetic utility of these sorts of systems.

C. Cyclopentadienones, from Two Alkynes and CO

Cyclopentadienones, like cyclobutadienes, are systems that are encountered fairly frequently in the form of metal-bound complexes arising from the interaction of a variety of transition-metal fragments with alkynes.[119] Synthetic applicability was lacking in much of the early work as these complexes were formed together with hosts of other products. An exception was the catalytic preparation of the stable, metal-free tetrakis(trifluoromethyl)cyclopentadienone from the alkyne in the presence of $[(CO)_2RhCl]_2$.[120] The unusual electronic properties of the product make it a poor ligand. Thus this result lacks generality. More typical were the results of Maitlis, who studied reactions of the same catalyst at 80 °C with 2-butyne, 3-hexyne, and diphenylacetylene. In each case, mixtures of hexasubstituted benzenes and metal-complexed, tetrausbstituted cyclopentadienones and quinones were obtained.[121]

Cycloadditions of alkynes and CO to give metal-bound cyclopentadienones are typified by reactions of the iron carbonyls. In some cases, particularly intermolecular situations, variable yields of cyclopentadienone–$Fe(CO)_3$ complexes are accessible from thermal reaction of the alkyne with $Fe(CO)_5$, $Fe_2(CO)_9$, or $Fe_3(CO)_{12}$. Thus the $Fe(CO)_3$-complexed tetrakis(dimethylamino) derivative is obtained in 55% yield from $Fe(CO)_5$ in refluxing octane,[122] and both the tetracyclopropyl[123] and tetraisopropyl[124] analogues are accessible, albeit in lower yields, from $Fe_3(CO)_{12}$ at 175–180 °C. The latter is significant because the metal-free dienone was subsequently obtained in 71% yield upon treatment of the complex with trimethylamine oxide (eq 50). Cobalt-complexed cyclopentadienones are also very well-known systems. In a reaction that will be described in detail in a subsequent section, alkynes react with $CpCo(PPh_3)_2$ to give stable, isolable metallacycles; these upon carbonylation give high yields (e.g., 77% from PhC≡CPh) of isolable dienone complexes.[125] Similar reactions have been explored starting with $CpCo(CO)_2$ and silylated alkynes; both inter- and intramolecular examples have been described, and the stable cyclopentadienones may be liberated from the complexes by Ce(IV) oxidation (eq 51).[126]



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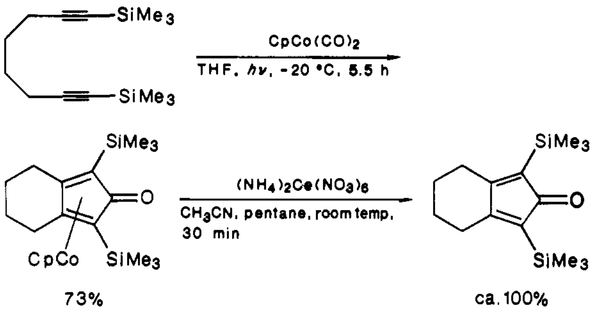
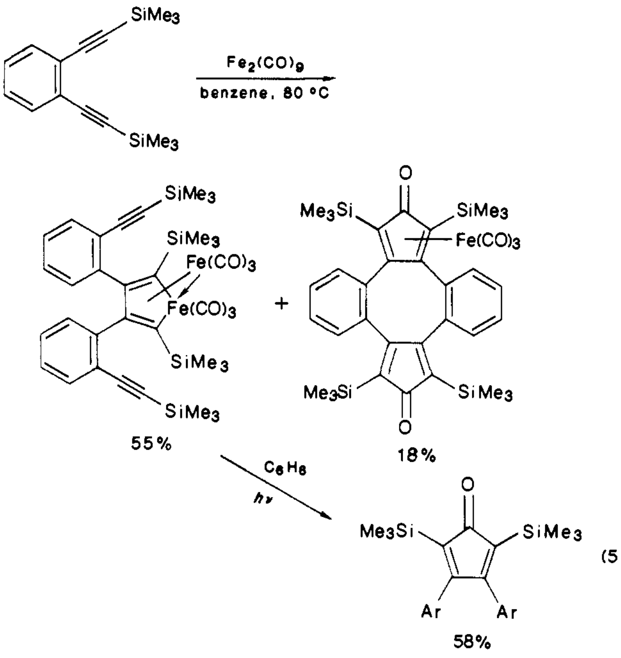


(51)

Interestingly, further very reasonable attempts at achieving intramolecular cycloadditions of a similar nature often tend to give products of intermolecular reaction in the iron systems. Thus, 1,2-bis((trimethylsilyl)ethynyl)benzene gives with $Fe_2(CO)_9$ four products, all of which arise from initial intermolecular reaction. The major product is an iron-complexed metallacycle (a "ferracyclopentadiene") that upon photolysis does go on to give the metal-free dienone; the other products arise from intramolecular reaction of the triple bonds remaining after the first intermolecular cycloaddition (eq 52).[127] Extensive studies of somewhat different complexes also related to the iron–cyclopentadienone system have been reported by Stone.[128] In the early 1970s Müller demonstrated the feasibility of a rhodium-based system in a two-stage process starting with a variety of α,ω-diphenyl diynes. Reaction with tris(triphenylphosphine)rhodium(I) chloride gives excellent yields of the corresponding rhodacyclopentadienes, which give the dienones upon carbonylation (eq 53).[129]

There are a few other cases where free cyclopentadienones are accessible relatively directly from reactions of alkynes with metal complexes. Examples of such reactions exist for early[130] as well as late transition metals. Maitlis has described a well-defined, stepwise conversion of 4,4-dimethyl-2-pentyne (*tert*-butylmethylacetylene) to 2,5-di-*tert*-butyl-3,4-dimethylcyclopentadienone mediated by $(PhCN)_2PdCl_2$,



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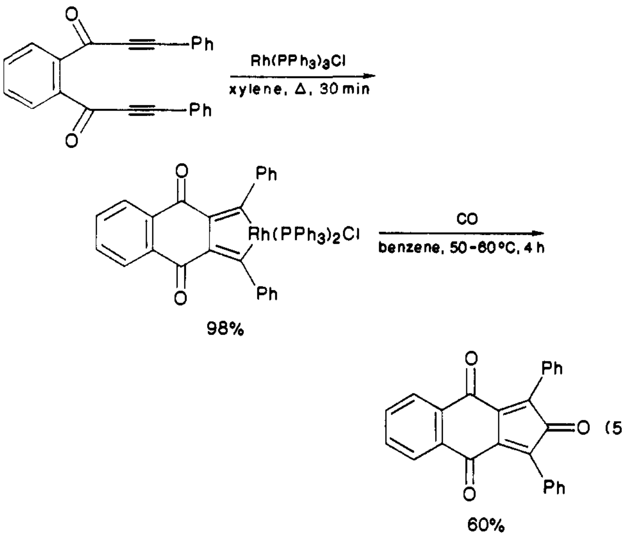
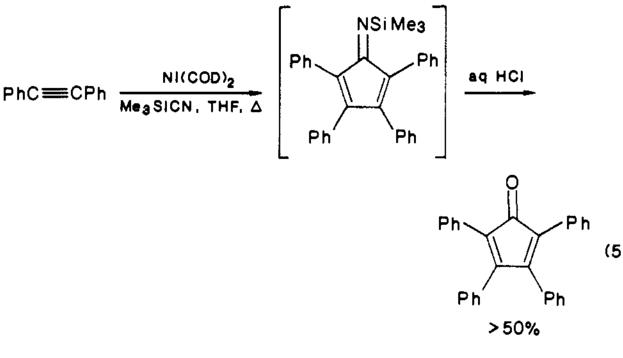


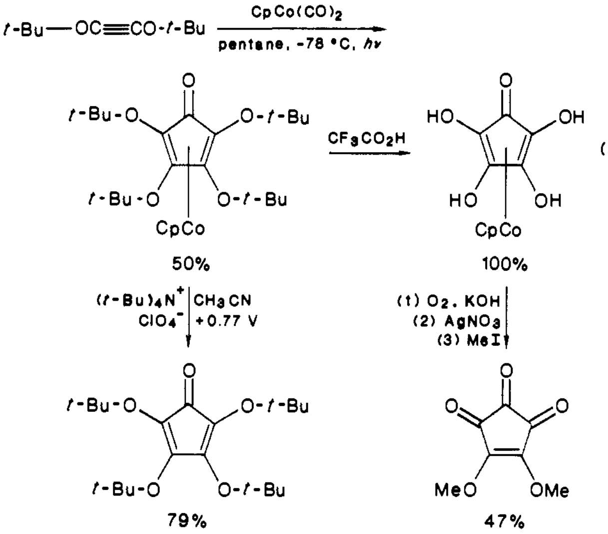
(53)

which can be achieved catalytically with total regioselectivity with regard to the bulky groups.[131] Eisch has demonstrated an unusual variant in which an isonitrile (derived from trimethylsilyl cyanide via the equilibrium $Me_3SiCN \rightleftarrows Me_3SiNC$) serves ultimately as a CO equivalent in a tetracyclone preparation that proceeds via the imine (eq 54).[132]



(54)

In spite of these examples, a perusal of the recent literature reveals that transition-metal methodology is almost never used in the preparation of stable cyclopentadienones; syntheses based on either conventional condensation reactions,[133] elimination reactions,[134] or photochemistry[135] are almost universally employed. Nonetheless, there are special situations where uniquely efficient synthetic pathways have resulted from transition-metal chemistry. Serratosa has successfully prepared highly oxygenated cyclopentadienones using $CpCo(CO)_2$-mediated cycloaddition of di-*tert*-butoxyacetylene. Hydrolysis followed by chemical oxidation and alkylation allows isolation of 4,5-dimethoxy-1,2,3-cyclopentenetrione,[46] while the less highly oxidized tetra-*tert*-butoxycyclopentadienone is accessible either via controlled electrochemical oxidation on a preparative scale (eq 55) or, better, via direct reaction of the alkyne with $Fe_2(CO)_9$ followed by amine oxide treatment.[136] Finally, Chiusoli has developed a system that permits catalytic intramolecular cycloaddition of diynes to form cyclopentadienones that either dimerize (Diels–Alder) or in certain cases may be trapped by nucleophiles (eq 56).[137]



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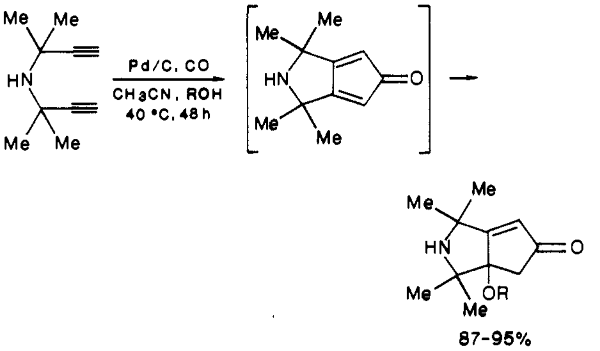
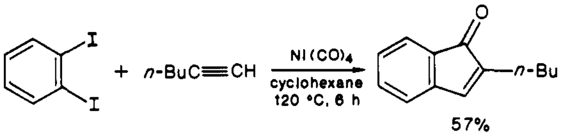


(56)

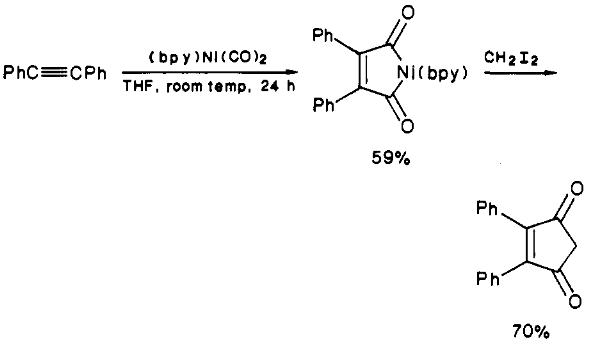
In 1953 Reppe reported the isolation of 1-indanone, the product of decarbonylation of the Diels–Alder dimer of cyclopentadienone itself, from the reaction of acetylene with $Ni(CO)_4$.[138] Due to the wide variety of metal-based systems capable of such chemistry, indanone is occasionally encountered as a byproduct of other cycloadditions involving acetylene as well.[66] A useful preparative route to indenones developed by Liebeskind makes use of *o*-diiodobenzene as a benzyne equivalent in a cycloaddition with alkynes. With $Ni(CO)_4$ as both reducing agent and mediator of the cycloaddition, yields are quite good (50–97%) and regioselectivity with terminal alkynes excellent, giving the usual orientation (eq 57). Preliminary indications are that the reaction also succeeds with either $Ni(CO)_2(PPh_3)_2$ or $(PPh_3)_4Pd/Zn/CO$ in place of $Ni(CO)_4$.[139,140]



(57)

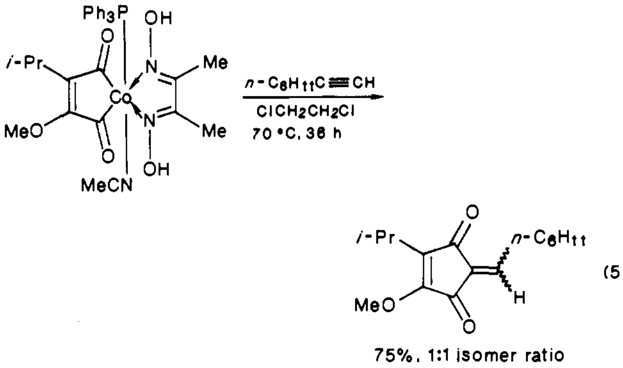
D. Cyclopentenediones, from Alkynes, Two CO, and "Carbenes"

The nickelacyclopentenedione derivatives isolated by Hoberg from the reactions of the (bpy)Ni(0) fragment with alkynes and CO react with methylene iodide to give cyclopent-2-ene-1,4-diones (eq 58).[45]



(58)

An elaborate variation has been developed by Liebeskind, from cobaltacyclopentenediones ("maleoylcobalt" complexes), whose chemistry will be covered in more detail in the section on quinones. Reaction of the specific system shown with terminal alkynes produces 3-alkylidenecyclopent-2-ene-1,4-diones via apparent insertion of the alkyne's vinylidene tautomer. The reaction is general and tolerant of a variety of functionality (eq 59).[141] The metallacycles themselves are easily prepared from cyclobutene-1,2-diones, which, in turn, may be *formally*, though usually not *practically*, prepared from alkynes (vide supra).



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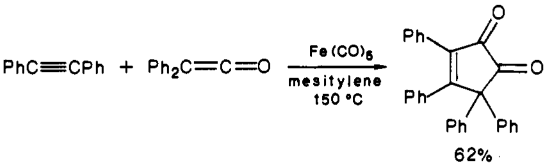
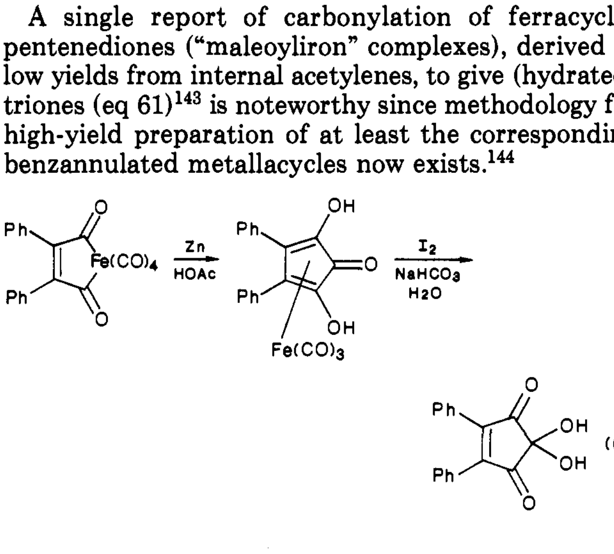
The isomeric cyclopent-3-ene-1,2-diones are formed by an unusual direct cycloaddition of alkynes with ketenes (eq 60).[142]



(60)

E. Cyclopentenetriones, from Alkynes and Three CO

A single report of carbonylation of ferracyclopentenediones ("maleoyliron" complexes), derived in low yields from internal acetylenes, to give (hydrated) triones (eq 61)[143] is noteworthy since methodology for high-yield preparation of at least the corresponding benzannulated metallacycles now exists.[144]

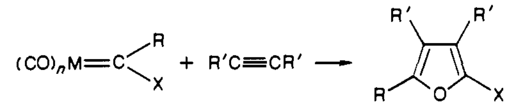


(61)

F. Furans

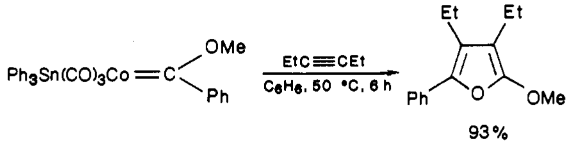
1. From Alkynes, CO, and "Carbenes"

Furans have been occasionally isolated in low yields from reactions of alkynes with chromium alkoxycarbene complexes. An unusual rearrangement pathway is involved in these cycloaddition processes (eq 62).[37,145]



(62)

It has, however, been found that carbene complexes based on iron and cobalt are capable of much more selective furan synthesis via the same pattern. Internal alkynes give satisfactory to excellent yields of 2-methoxyfurans with cobalt methoxycarbenes (eq 63); this reaction has been applied to a synthesis of a natural product, bovolide.[146] Both terminal and internal alkynes are viable substrates in a preparation of 2-aminofurans from iron (dimethylamino)carbenes (eq 64).[147] Yields again are generally very high as long as the reaction takes place in an inert (e.g., Ar) atmosphere. Details concerning the rearrangement of the heteroatom-containing substituent have not as yet been clarified.



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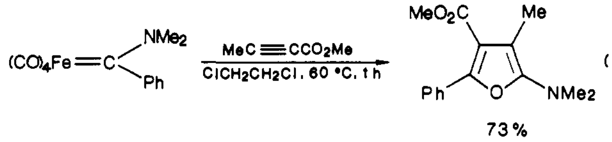
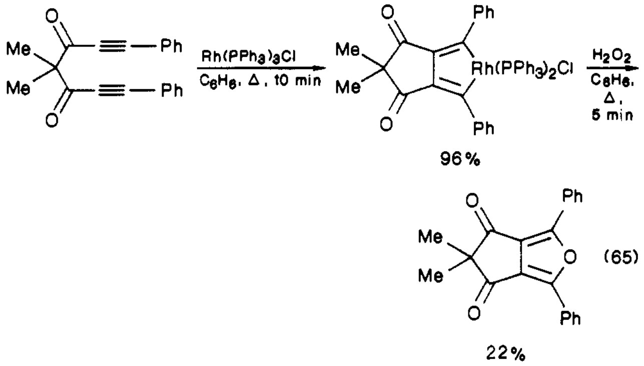


(64)

2. From Two Alkynes and "O"

Müller's rhodacyclopentadienes previously described in the context of cyclopentadienone synthesis may be utilized in this most direct furan preparation as well.

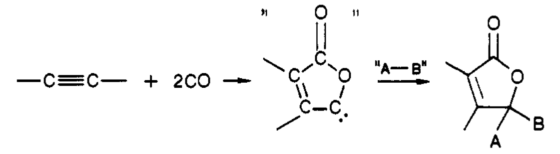
Oxidation of the complex may be effected with either atmospheric oxygen or with peroxides to give furans in modest yields (eq 65).[129]



(65)

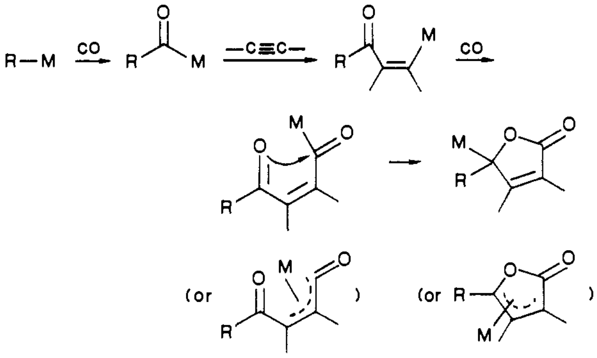
G. Furanones (γ-Lactones), from Alkynes, Two CO, and "A–B"

A fairly wide assortment of transition metals can participate in a general unsaturated lactone synthesis. The ring incorporates the four carbons from the C≡C and the two CO's, and oxygen from one CO. The formal result of such a cycloaddition is a carbene at position 4; depending on the metal species involved and other components available, a variety of formal "A–B" species are effectively "added" to this carbon (eq 66). The section is organized by "A–B" species that appear in the products.



(66)

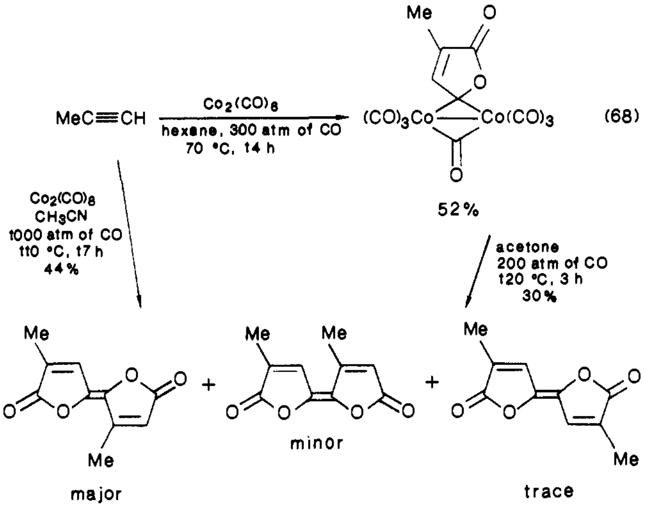
A common mechanism starts with a σ-bonded alkylmetal complex. A sequence of insertions of CO, then alkyne, and then CO again leads to a metal acyl containing the 4-keto-2-alkenoyl moiety. Cyclization via formal insertion of the 4-keto group into the acyl–metal bond generates a 4-metallolactone whose C–M bond may degrade in any of a number of ways, depending on the metal and the reaction conditions (eq 67). In the latter stages of the sequence bonding variants such as η^3 (allyl) complexation to the metal also exist and are presumed to occur in certain situations; in some cases these have regiochemical consequences. Model studies with group 6 metals have led credence to this sequence with the isolation and structural characterization of both σ-(3-ketovinyl) complexes and η^3-complexes of the unsaturated lactone itself.[148]



(67)

1. "A–B" = "Co═Co"

The earliest work in this area involved reactions of alkynes with $Co_2(CO)_8$ under conditions of elevated temperature *and CO pressure* (the latter in contrast to Pauson–Khand chemistry[66]). Reaction of $Co_2(CO)_6{\cdot}HC{\equiv}CH$ with CO leads to a complex of the lactone-derived carbene pictured in eq 66 with $Co_2(CO)_7$.[149] If the reaction is carried out in polar solvents, *E* and *Z* isomers of so-called bifurandiones are isolated, the products of apparent carbene dimerization.[150] Complex formation takes place with alkyl-, aryl-, and dialkylacetylenes and is remarkably regioselective, placing the larger group α to the lactone carbonyl (100% even for ethyl > methyl!).[151] Formation of the bifurandione is not a true carbene dimerization and in fact must be an intramolecular process since in the formation of the second ring regioselectivity is incomplete, and it is in the *opposite direction*, an observation that is still not well understood (eq 68).[152,153] Although the metal–carbon bonds in the carbene complex may be hydrogenolyzed, the double bond is lost as well; thus the value of this system is more as a model for the reactions described below than as a preparative method for simple unsaturated lactones.[154] On the other hand, development of the chemistry of the bifurandiones, especially toward addition and selective ring-opening reactions, has revealed considerable synthetic utility.[155]



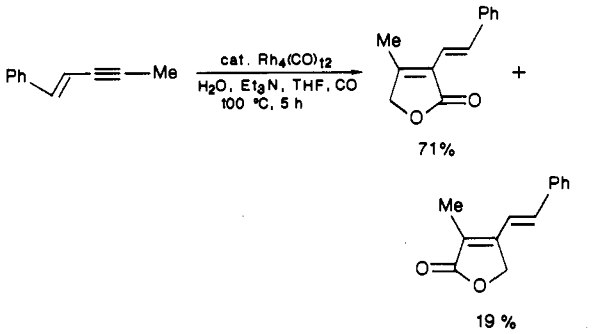
(68)

2. "A–B" = "H–H"

Several syntheses of these lactones based on noble metal catalysts are of practical value. Two slightly different Pd-based methods have some specific utility,[156] but the most general uses an optimized rhodium carbonyl anion catalyst system (metal carbonyl anions have found considerable utility in lactone syntheses). Although regioselectivity with internal alkynes is not very good, yields are very high (eq 69).[157] This reaction appears to follow a mechanism somewhat similar to that outlined above, with the H's derived from water through protonation of anionic Rh and reductive elimination.

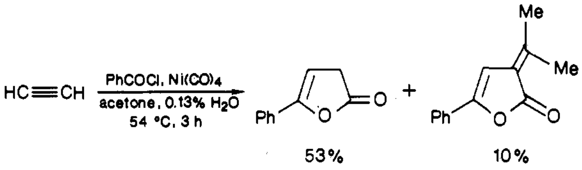
3. "A–B" = "R–H"

Acylnickel carbonyl anions derived from addition of RLi to $Ni(CO)_4$ react with terminal alkynes at −70 °C to give 1,4-diketones by double acylation, but at −30 °C



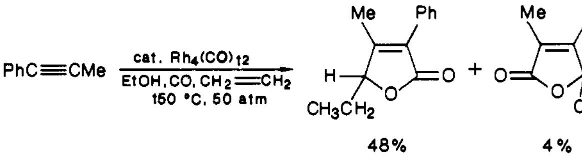
(69)

lactones form in low yields (<25%) as byproducts.[158] Somewhat better is a method derived from the observations of lactone formation in the course of the Ni(CO)$_4$-based cyclopentenone synthesis described earlier. Thus acyl halides and alkynes give lactones with Ni(CO)$_4$ in an aqueous acetone medium; the acyl halide serves as the source of both the R group and one CO. In this system, at least in the cases examined, migration of the double bond from α,β to β,γ takes place, together with some condensation with molecules of solvent (eq 70).[159] A very promising recent development utilizes manganese to achieve essentially the same transformation.[160]



(70)

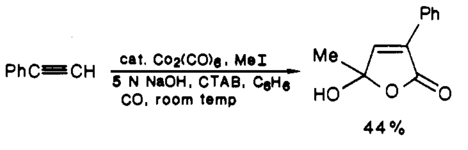
Another recent development adds an olefin insertion step to a sequence like that described in eq 69, giving an olefin-derived R group after final reductive elimination. Yields and alkyne regioselectivity are good with ethylene as the olefin; substituted olefins give low yields and variable insertion selectivity, and terminal alkynes do not work at all (eq 71).[161]



(71)

4. "A–B" = either "R–OH" or "RO–H"

The contrasts in detail between the lactone syntheses based on anionic Ni(0) vs neutral Ni(II) are paralleled with cobalt as well. Acyl complexes derived from reaction of $^{-}$Co(CO)$_4$ with CH$_3$I and CO react with alkynes according to the general mechanism, and using phase-transfer catalysis the (4-keto-2-alkenoyl)cobalt intermediate (eq 67) may be intercepted by hydroxide. This gives an unsaturated keto acid that spontaneously cyclizes to the γ-hydroxy lactone (eq 72).[162] In a superficially similar phase-transfer process lactones are also formed from CH$_3$I and alkynes with either $^{-}$Mn$_2$(CO)$_9$Br or $^{-}$Mn(CO)$_5$ (derived from Mn(CO)$_5$Br or Mn$_2$(CO)$_{10}$ and base). In this case, however, the lactones are simple 2,4-disubstituted γ-butyrolactones, totally saturated and lacking a hydroxyl substituent (eq 73).[163] Both reactions are totally regiospecific and general with terminal alkynes. The reasons for the differences are not known but may be related to the higher basicity of the Mn-based anion compared to $^{-}$Co(CO)$_4$. Protonation of the former to give a metal hydride could lead to reduction chemistry similar to that seen in some of the Rh-based systems described above (eq 69 and 71). In contrast, the comparable cobalt hydride, HCo(CO)$_4$, is such a strong acid that its concentration in basic media would be negligible.



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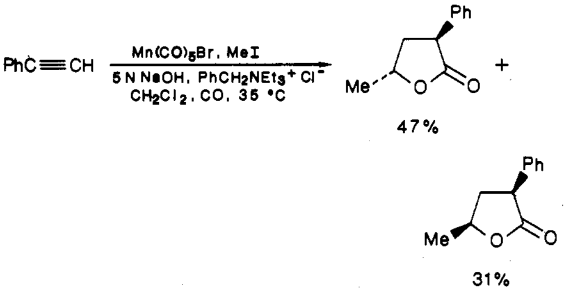
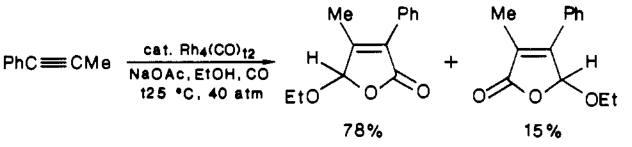


(73)

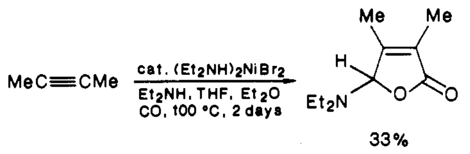
Lactones with 4-alkoxy substitution are obtained from internal alkynes using Rh catalysis similar to that used in eq 71, but omitting the alkene and introducing one of several oxygen bases (eq 74).[164] The mechanism of introduction of the alkoxy group is unclear.



(74)

5. "A–B" = "R_2N–H"

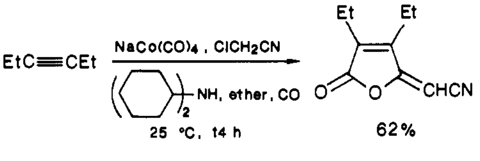
A cocyclization of 2-butyne with CO in the presence of diethylamine to form a γ-amino lactone is catalyzed by the bis(amine) complex of NiBr$_2$ (eq 75).[165]



(75)

6. "A–B" = "RR′C:"

The predecessor to the previously described γ-hydroxy lactone synthesis is Heck's pentadienolactone synthesis, also using an acylcobalt derived from $^{-}$Co(CO)$_4$ as the starting point. In this system the acyl must be derived from a compound containing halogen on an activated carbon, e.g., an α-halo ester. This is so that the exocyclic double bond may be introduced by base-promoted "β-hydride" elimination of the metal from the final complex (eq 67). Amine bases are used and both terminal and internal alkynes work (eq 76).[166]

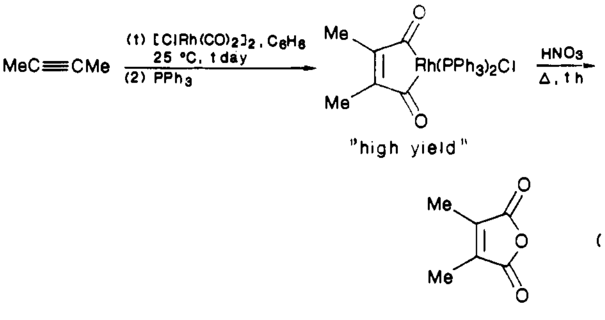


(76)

H. Furandiones (Maleic Anhydrides)

1. From Alkynes, Two CO, and "O"

Maitlis' studies on alkyne complexes of Rh(I) led to a simple, high-yield synthesis of disubstituted maleic anhydride by HNO_3 oxidation of a rhodacyclopentenedione (eq 77).[121b,c] Hoberg's later developments in sequential insertion chemistry of nickel-bearing electron-rich ligands have already been introduced in connection with several systems. The nickelacyclopentenedione derivatives isolated from the reactions of the (bpy)Ni(0) fragment with alkynes and CO may be oxidized by air to give maleic anhydrides (eq 78).[45]



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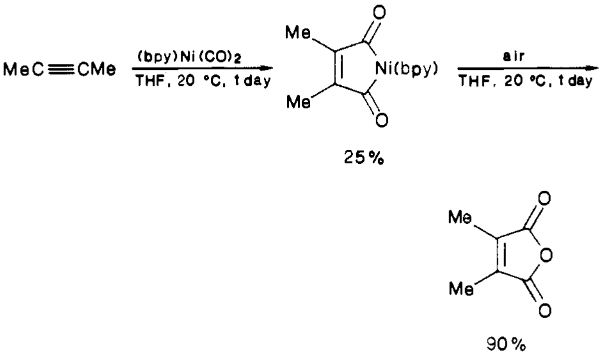
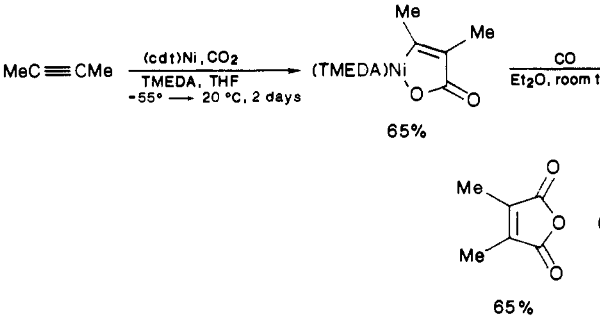


(78)

2. From Alkynes, CO, and CO_2

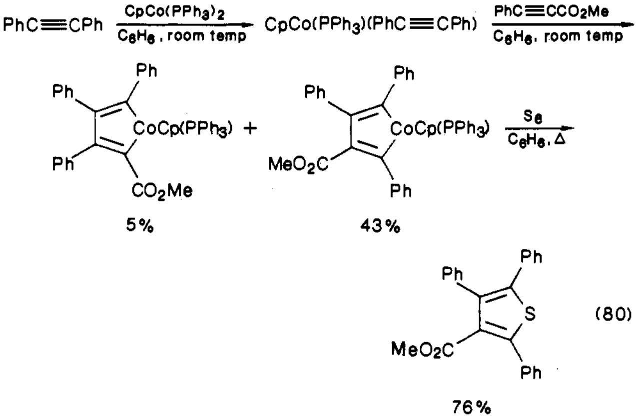
Alternatively, reaction of the complex (cdt)Ni(0) (cdt = 1,5,9-cyclododecatriene) with alkynes and CO_2 gives in the presence of a suitable donor ligand a 5-nickelafuranone that gives maleic anhydrides upon exposure to CO (eq 79).[167] The Ni-based methods appear to be applicable to different degrees with internal and terminal alkynes, as well as with acetylene itself.



(79)

I. Other Five-Membered-Ring Heterocycles

Several metallacyclopentadienes derived from reactions of alkynes with appropriate metal complexes have been used as precursors to five-membered-ring heteroaromatics. Early work by Hübel indicated the utility of iron-containing metallacycles as precursors to pyrroles and thiophenes,[168] and subsequent development by Wakatsuki and Yamazaki has led to a cobalt-based process that allows the sequential incorporation of two different alkynes, followed by a heteroatom, into a heterocyclic product.[169] Thus either diphenylacetylene or methyl phenylpropynoate reacts with $CpCo(PPh_3)_2$ to displace a single phosphine, giving a monoalkyne complex. Further reaction with one of several alkynes, including PhC≡CR (R = H, Me, or Ph), $RC{\equiv}CCO_2Me$ (R = H, Me, or Ph), and $MeOCH_2C{\equiv}CCH_2OMe$, gives a 40–70% yield of the cobaltacycle with total or near-total regioselectivity in most cases, forming the new carbon–carbon bond between the least sterically encumbered alkyne carbons. Finally, reaction with sulfur, selenium, or nitrosobenzene gives, respectively, the corresponding thiophene, selenophene, or *N*-phenylpyrrole (eq 80 and 81). As was the case with furans, the rhodacyclopentadienes prepared by Müller are similarly suitable for conversion to thiophenes, selenophenes, and pyrroles as well.[129] A decidedly unconventional synthesis of thiophenes from reaction of two alkynes with complexes derived from $BrMn(CO)_4R_2P(S)H$ has also been reported.[170]



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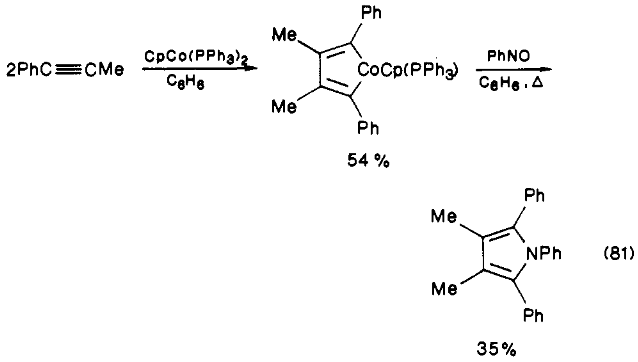
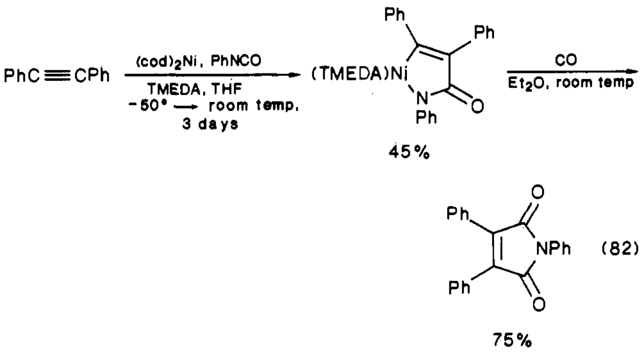


(81)

Reactions of $(cod)_2Ni(0)$ (cod = 1,5-cyclooctadiene) with alkynes and isocyanates (i.e., heterocumulene analogues of CO_2; cf. syntheses of maleic anhydride derivatives above) give azametallacycles that upon carbonylation yield maleimide derivatives (eq 82).[171]

Other heterocycles that have been prepared from alkyne cycloadditions include 3-pyrrolin-2-ones, from iron complexes of diimines of 1,2-dicarbonyl compounds (i.e., 1,4-diaza 1,3-dienes),[172] 1,2,3-triazoles, which arise from reaction with azidocobalt chelate complexes,[173] and silacyclopentadienes, prepared from silacyclopropenes and alkynes in the presence of Ni(II) complexes.[174] The



(82)

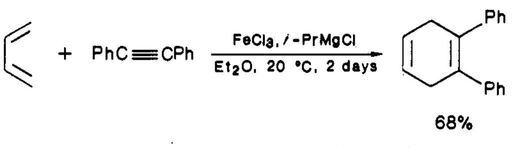
latter references also describe other silacycles arising from various processes that are not, strictly speaking, cycloaddition reactions of alkynes. An indole preparation from azobenzene that involves both a cycloaddition and a hydrogen migration has also been described.[175]

IV. Six-Membered Rings

A. 1,4-Cyclohexadienes, from Alkynes and 1,3-Dienes

1. Diels–Alder Reactions

Uncatalyzed Diels–Alder reactions involving alkynes and dienes are generally difficult to achieve.[176] Several groups have demonstrated the efficacy of Fe(0)-based catalyst systems in promoting this cycloaddition with a variety of dienes and internal alkynes. Yields are quite good and conditions are generally very mild (eq 83).[177] Examples involving cycloaddition of substituted dienes utilizing a bis(imine)Fe(II) catalyst precursor have been reported, again providing yields generally in the 50–80% range.[178] Ficini's adaptation of the reaction to ynamines is comparably successful and leads directly to enamines of 3-cyclohexenones in up to 80% yields (eq 84).[179]



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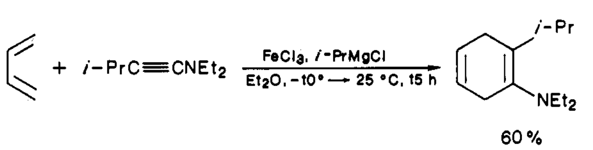
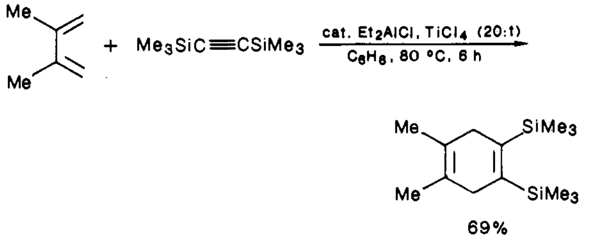


(84)

The extremely high reactivity of Ziegler catalysts may be exploited in this process provided that an alkyne not capable of self-trimerization is employed. Thus $Me_3SiC{\equiv}CSiMe_3$ reacts with numerous substituted dienes in the presence of $Et_2AlCl/TiCl_4$ to give cycloaddition products in ca. 70% yields (eq 85).[180] Other synthetic features associated with silyl-substituted alkynes will be presented in subsequent sections.

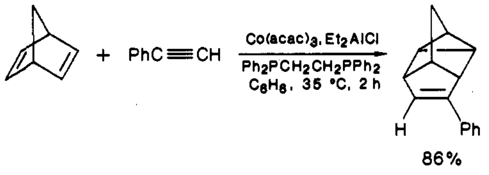


(85)

It has been noted that attachment of the "Fp" group to dienes [Fp = $CpFe(CO)_2$] strongly activates the system toward Diels–Alder reaction; thus 2-"Fp"-1,3-butadiene reacts with both $CF_3C{\equiv}CCF_3$ and $MeO_2CC{\equiv}CCO_2Me$ in high yields.[181] Conversely, attachment of alkynes to two different kinds of transition-metal-functionalized carbon atoms greatly enhances their reactivity as dienophiles. Lukehart has demonstrated this effect in BF_2-chelated Fp-derived diacyls, in which an alkynyl group attached to an acyl carbon reacts with cyclopentadiene at room temperature.[182] This may have some synthetic potential since reductive coupling of the acyl carbons in these types of complexes to give hydroxy ketones has been demonstrated.[183] Previously, both Wulff and Dötz had found a similar effect in alkynyl groups attached to Fischer-type carbenes.[184] Again, reactivity with cyclopentadiene at room temperature (about 150 °C lower than usual for alkynes with electron-withdrawing substituents) was observed. Wulff also showed Diels–Alder reactivity of these compounds toward both 2,3-dimethylbutadiene and two alkoxy dienes and carried the products, alkenylcarbene–Cr complexes, a step further by demonstrating their reactivity in the Dötz annulation (see Phenols).

2. Related Reactions

Norbornadiene undergoes so-called "homo-Diels–Alder" cycloaddition with several alkynes in the presence of a Co/Al catalyst system (eq 86).[185] The analogous uncatalyzed process occurs only with electron-deficient alkynes.[186] Similar reactions were earlier observed by Schrauzer in the presence of nickel catalysts. Schrauzer also noted the low-yield cycloaddition of two molecules of acetylene itself to norbornadiene, a formal 1,3-cyclooctadiene synthesis via 2 + 2 + 2 + 2 reaction.[13] Mention should also be made here of two Ni-catalyzed reactions of alkynes with silicon-containing four-membered-ring compounds. Cycloadditions involving silacyclobutanes and 1,2-disila-3-cyclobutenes produce 1-sila-2-cyclohexenes and 1,4-disila-2,5-cyclohexadienes, respectively.[187,188]



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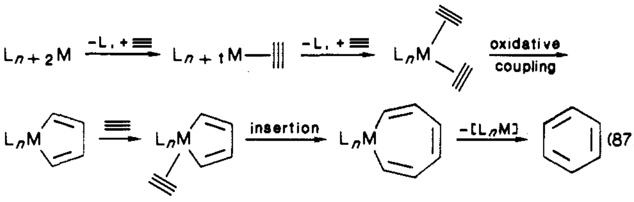
B. Benzenes, from Three Alkynes

The cyclotrimerization of alkynes to give benzene derivatives was already a vast field 2 decades ago.[189] A large number of transition-metal-based systems give rise to this reaction. A concise but very representative review of the field as a whole appeared in 1985, outlining in particular the variety of mechanistic pathways that have been established for different versions of this process.[190]

It is readily possible to cyclotrimerize acetylene itself as well as virtually any mono- or disubstituted acetylenic compound. Additionally, selective intermolecular cocycloadditions involving more than one different alkyne are possible as well. Rather than attempting to list every possible type of catalyst that has been examined, this section will give examples of catalytic systems that have been shown to be especially useful in some specific class(es) of reactions. As yield, selectivity, and convenience are the primary considerations for the synthetic chemist, these aspects have been the primary considerations in the choice of methods covered.

1. Intermolecular Cyclotrimerization

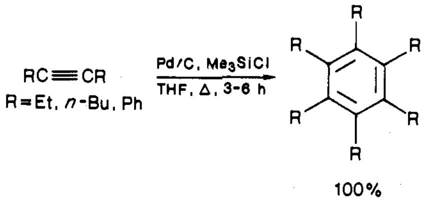
Both homogeneous and heterogeneous catalysts are available for this process. A brief overview of the current level of mechanistic understanding is appropriate in the context of selectivity considerations. Most systems that have been investigated trimerize alkynes via a sequence based on that shown in eq 87 (which we will call the "common mechanism"). Sequential coordination of two alkyne molecules to a single metal center is followed by metallacyclopentadiene formation, which simultaneously forms a carbon–carbon bond, formally oxidizes the metal ("oxidative coupling"), and opens a coordination site. These metallacycles in many cases have been trapped by ligands as isolable, structurally characterizable species. They may also complex a third alkyne molecule, which may insert to give a transient metallacycloheptatriene from which the benzene product is finally released.[191]



(87)

An elegantly executed study of trimerization of 1,1,1-trideuterio-2-butyne by a range of metal systems clearly showed that most give results consistent with the above pattern, which *specifically avoids* any intermediate with the symmetry of a cyclobutadiene.[192] Exceptions included catalysis by $AlCl_3$, which does involve a complexed cyclobutadiene, and systems based on Pd(II), for which a characteristically different mechanism appears to operate.[29] Additional alternative mechanisms have been proposed in connection with Ziegler-type catalysts.[193] Another anomalous pathway has been observed in reaction of a cobaltacyclopentadiene with $MeO_2CC{\equiv}CCO_2Me$: benzene formation does not require a vacant site on the metal, implying a carbon–carbon bond-forming process that does not involve metal complexation by the third alkyne (perhaps a direct Diels–Alder reaction).[194] The main consequence of the common mechanism is that trimerization of unsymmetrically substituted alkynes typically gives benzenes with the larger substituents in positions 1, 2, and 4, a result of oxidative coupling, which prefers to link the least hindered alkyne carbons; this preference has been clearly confirmed in studies of metallacycle formation.[195]

Practical applications of alkyne trimerization use both homogeneous and heterogeneous catalysts. Perhaps the simplest method for trimerization of acetylene itself (24 °C, 10 min, 59%) uses a commercially available heterogeneous catalyst derived from coating K_2CrO_4 on a silica/alumina support. This has been used to produce ^{11}C-radiolabeled benzene from $HC{\equiv}^{11}CH$.[196] In an extremely simple method reported by Maier, Me_3SiCl in THF over Pd/C generates a soluble catalyst of unknown composition capable of trimerizing alkynes in excellent yields (eq 88).[197] This paper also contains an excellent concise summary of recent methodology in this area.



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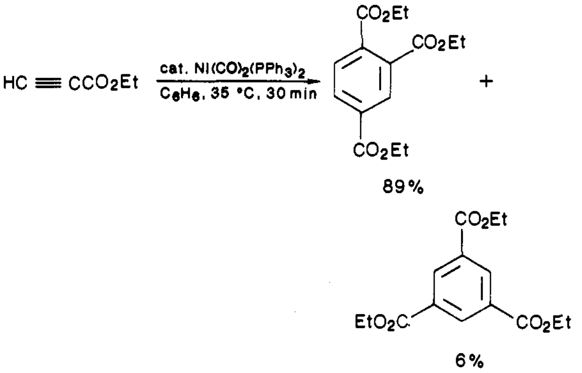
The catalysts described above are both capable of trimerizing unsymmetrically substituted internal or terminal alkynes in good yields, but with only moderate regioselectivity. Thus the Cr(VI) catalyst trimerizes propyne to give a 4:1 ratio of 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene.[198] (Although the details of alkyne–metal bonding proposed in this instance are somewhat different from the homogeneous cases, the consequences for regioselectivity are identical.) However, from the variety of homogeneous catalysts available, it is generally possible to achieve much higher levels of 1,2,4 regiocontrol. Phosphinenickel carbonyls are often highly selective although their reactivity is limited mostly to terminal alkynes, preferably with electron-withdrawing substituents (eq 89).[199,200]



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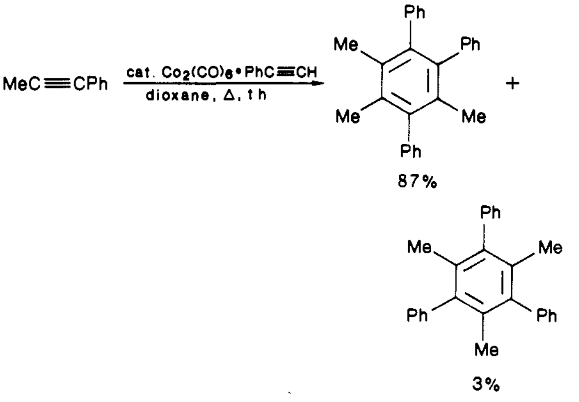
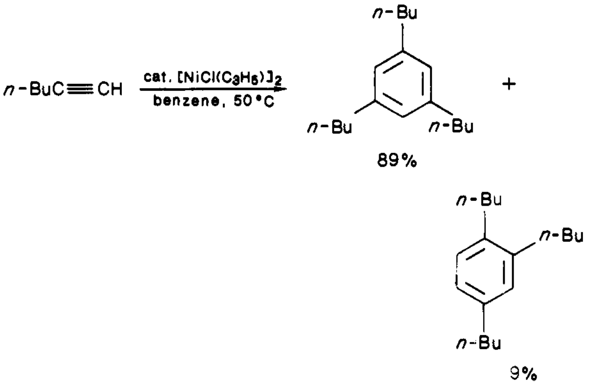
Catalysts derived from $Co_2(CO)_8$ are generally more reactive and often give both high yields and selectivities as well, especially in dioxane as solvent (eq 90). These systems follow a stepwise mechanism involving exclusively dinuclear complexes. Following the formation of $Co_2(CO)_6{\cdot}RC{\equiv}CR'$ (cf. eq 21), sequential insertion of two additional alkyne molecules gives a so-called



(90)

"flyover" complex with the nominal composition $Co_2(CO)_4\cdot(RC{\equiv}CR')_3$, the immediate precursor to the trimerization product.[201]

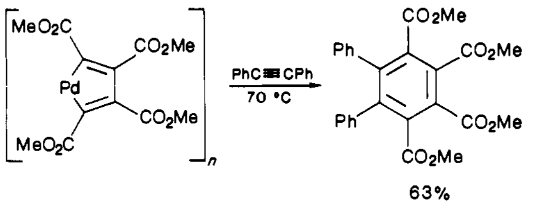
Systems showing even higher reactivity include Ziegler-type catalysts such as $TiCl_4/AlEt_3$ and (η^5-indenyl)$Rh(C_2H_4)_2$. Although the latter is unusually good for selective trimerization of 3,3-dimethyl-1-butyne, giving a 76% yield of 1,2,4-tri-*tert*-butylbenzene,[202] these systems typically are less 1,2,4 selective, often giving 1,3,5 isomers in comparable or greater amounts.[203] For example, phenylacetylene is converted into a 4:1 mixture of 1,3,5- and 1,2,4-trimethylbenzenes in 76% overall yield in the presence of $TiCl_4/AlEt_2Cl$.[204] Two Ni(II)-based systems are also reported to be highly 1,3,5 selective: $(Bu_3P)_2NiBr_2$, which trimerizes (*S*)-3-methyl-1-butyn-3-ol exclusively to the optically active 1,3,5-trisubstituted benzene derivative in 44% yield,[205] and $[(\eta^3\text{-allyl})NiCl]_2$, which, unlike its iodo analogue, also gives 1,3,5-trisubstituted benzenes from terminal alkynes (eq 91).[206] In addition, 1,3,5-tri-*tert*-butylbenzene is available from the alkyne in the presence of $PdCl_2$.[29] Ziegler catalysts are also noteworthy in their compatibility with alkyl halide functional groups (e.g., in trimerization of ω-chloro-1-alkynes).[207]



(91)

2. Intermolecular Cocyclotrimerization

It is possible to incorporate two molecules of one alkyne together with one molecule of another into a benzene product. The success of such a process in terms of chemoselectivity depends partly on a difference in reactivity of each individual alkyne toward simple cyclotrimerization. Thus in early studies the relative unreactivity of phosphinenickel carbonyls toward trimerization of internal alkynes was exploited with moderate success in cocycloadditions with more reactive substrates.[189b] Alternatively, some Co-catalyzed mixed trimerizations were possible if reaction conditions were carefully controlled; for example, a 57% yield of 1,2,3,4-tetraphenyl-5,6-diethylbenzene could be obtained from diphenylacetylene and 3-hexyne.[201] Finally, cotrimerizations have been effected by using the heterogeneous Cr-based system already discussed, allowing selective syntheses of radiolabeled toluene and *p*-xylene to be achieved.[196,198] However, the development of cotrimerization as a practical tool of some generality has required the systematic application of the available mechanistic information. Several groups have explored cocycloadditions involving reaction of a preformed metallacyclopentadiene and an alkyne. Although some success has been achieved (e.g., eq 92 and 93),[169,208] the totally intermolecular process is ultimately limited by the fact that in most cases the metal fragments liberated after an initial cocycloaddition process are catalytically active, and therefore continue promoting simple cyclotrimerization of the "third" alkyne, leading to mixtures.[191] Linking two of the alkynes together, and utilizing a "third" alkyne that cannot be trimerized has proved to be the solution to the general problem, as described below.



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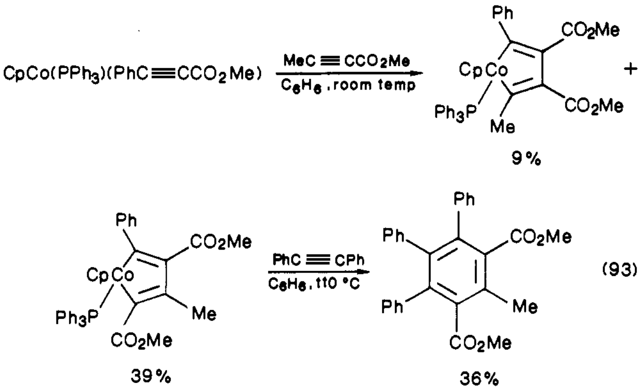

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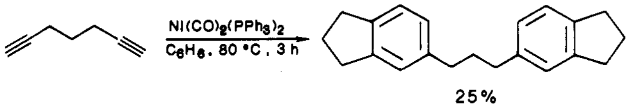
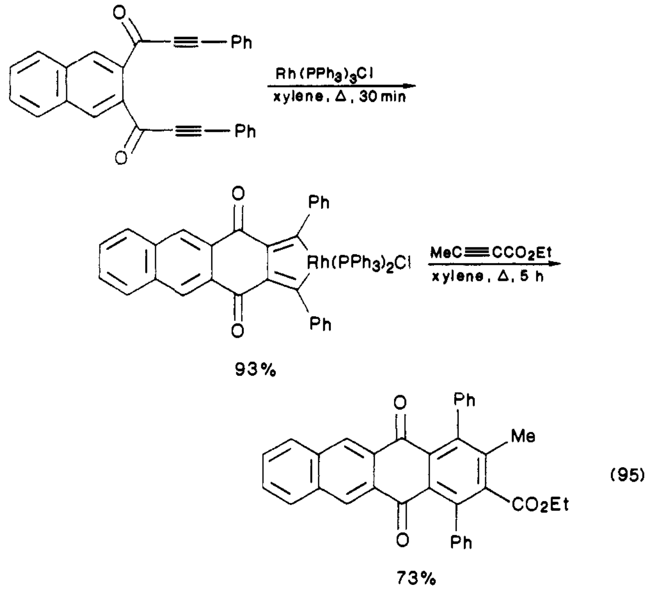
3. Partially Intramolecular Cocyclotrimerization

Intramolecular incorporation of an α,ω-diyne into a benzene derivative in the presence of a transition-metal system was achieved as early as 1961 with 1,6-heptadiyne and $Ni(CO)_2(PPh_3)_2$ (eq 94).[209] Similar reactions of a range of diynes over a Ziegler catalyst were later demonstrated by Hubert.[210] Of note in this work was the isolation of products containing the benzocyclobutene moiety from reaction of 1,5-hexadiyne. Müller's extensive studies of rhodacyclopentadienes derived from diphenyl α,ω-diynes followed. Applications of these compounds in the synthesis of heterocycles have already been described. Their reactivity toward another alkyne is such that benzene derivatives may be obtained in often excellent yields under very moderate conditions (eq 95).[129,211] Although this method suffers from the requirement for stoichiometric Rh, it possesses a broad scope, succeeding with dialkyl as well as diaryl diynes, and it tolerates numerous functional groups on the "third" alkyne, including many heteroatoms, even directly attached to the alkyne carbons. A wide variety of anthraquinone derivatives are accessible with this methodology. Since only symmetrical diynes have been used, nothing is known regarding regiochemistry in this system.

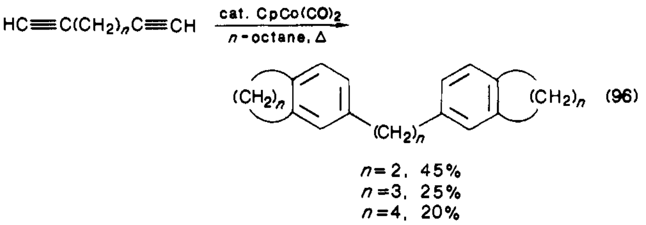


(94)

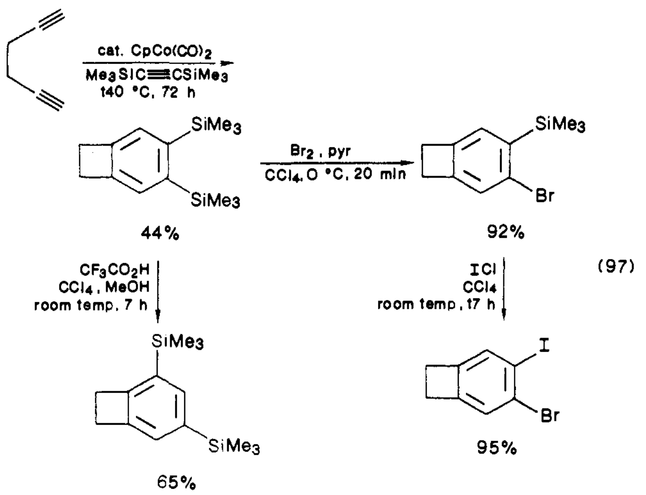
The utility of the $CpCoL_2$ system as a catalyst for this chemistry was revealed in initial work by Vollhardt and Bergman[212] and subsequently developed by Vollhardt into one of the most comprehensive and versatile or-

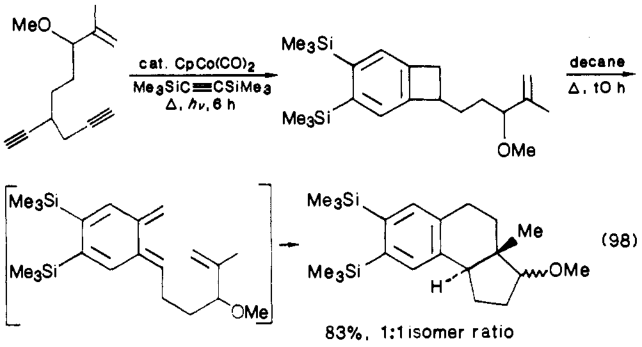


ganometallic methodologies for organic synthesis now available. An extensive review of this chemistry appeared in 1984.[213] As was the case with the earlier studies by Hubert, initial work involved simple α,ω-diynes, whereupon the accessibility of benzocyclobutene derivatives was immediately noted (eq 96, $n = 2$).

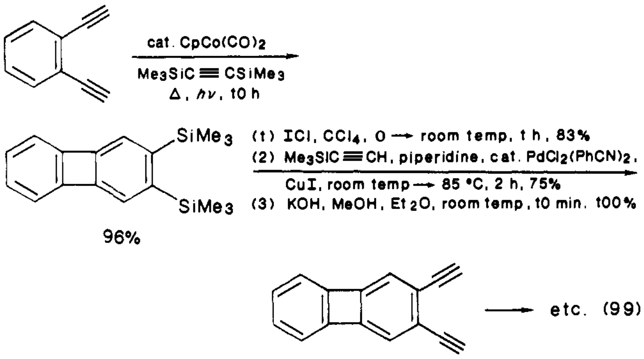


Cocycloadditions with other monoalkynes did not typically give good yields but did demonstrate that the system tolerates most common organic functional groups. The most significant early development incorporated bis(trimethylsilyl)acetylene, which cannot be cyclotrimerized, as the "third" alkyne (eq 97). The importance of this innovation is underscored by the facts that (a) the silyl groups are amenable to readily controlled, sequential electrophilic migration and replacement reactions and (b) the benzocyclobutene system readily undergoes thermal electrocyclic ring opening, producing o-quinodimethanes (o-xylylenes) that can participate in further cycloaddition (e.g., Diels–Alder) reactions (eq 98).[214,215] The reaction is catalytic, using $CpCo(CO)_2$ as the catalyst source in either a strictly thermal or part thermal/part photochemical procedure to facilitate generation of the catalytically active species; optimal yields are obtained under high-dilution conditions.



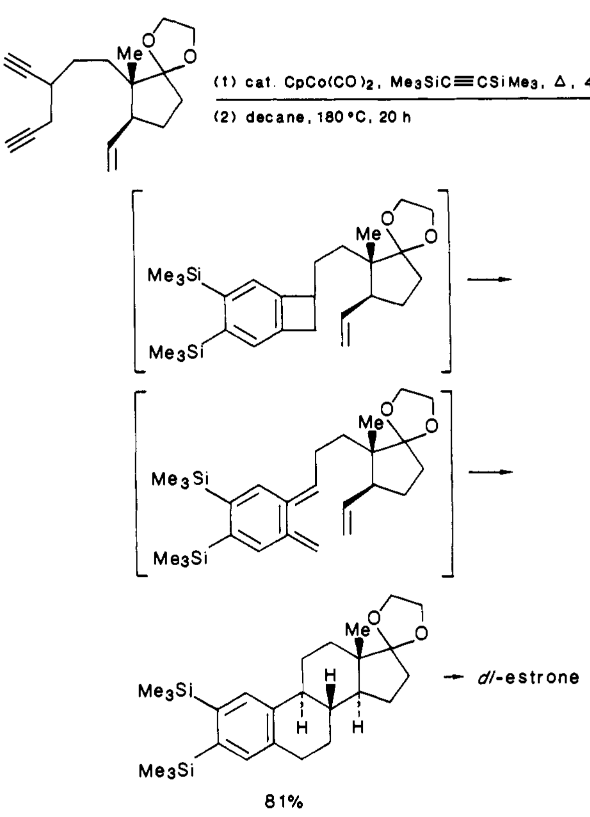


The ready accessibility of benzocyclobutenes in this manner has permitted an imaginative extension of this work to be developed in the direction of "iterated" biphenylene derivatives. Starting with an o-diiodobenzene derivative, an o-diethynylbenzene is prepared and cycloadded to $Me_3SiC{\equiv}CSiMe_3$. This produces an o-bis(trimethylsilyl)arene, which is formally the product of a "cyclobutabenzannulation" on the original benzene derivative. Iodination of the silyl groups generates a new o-diiodoarene, ready for another cycle (eq 99). In the course of extending this study to ultimately permit synthesis of the linear nonacycle (five benzene rings separated by four cyclobutanes) a valuable alternative method was developed in the use of $Me_3SnC{\equiv}CSnMe_3$ as a cycloaddition component.[216] Variations involving naphthalenes[217] and nonlinear annulations[218] have led to additional molecules of theoretical interest.



Development of the general process shown in eq 98 (cycloaddition followed by electrocyclic ring opening and Diels–Alder reaction) has led to syntheses of several benzannulated systems of interest to natural products chemists, including A-ring aromatic steroids (eq 100),[219] and several model polycyclics, including both carbocycles and heterocycles.[220]

Syntheses of tetracyclic isoquinolinoid alkaloids in the protoberberine series demonstrate complete regioselectivity in the cocyclotrimerization starting with differentially substituted alkyne units in the diyne. Application of the now-familiar steric arguments to the usual mechanistic sequence seems adequate to explain this result (eq 101).[221] Leonard has published still another application of this chemistry to isoquinoline synthesis, via novel 1,3-diazabiphenylenes.[222]



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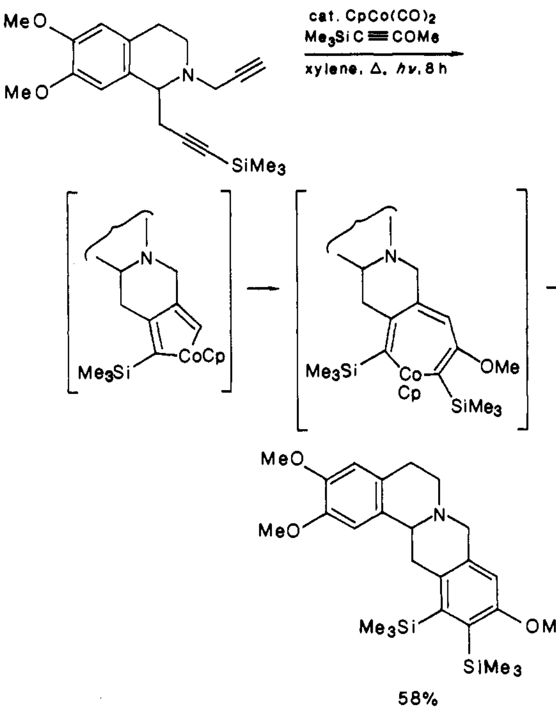

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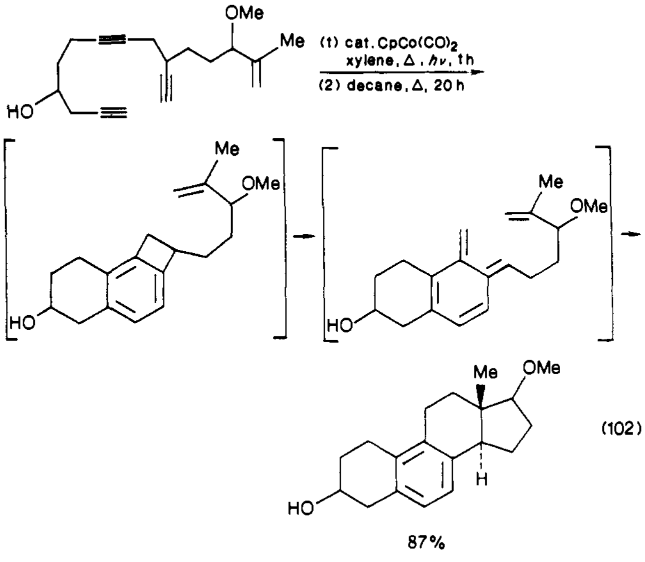
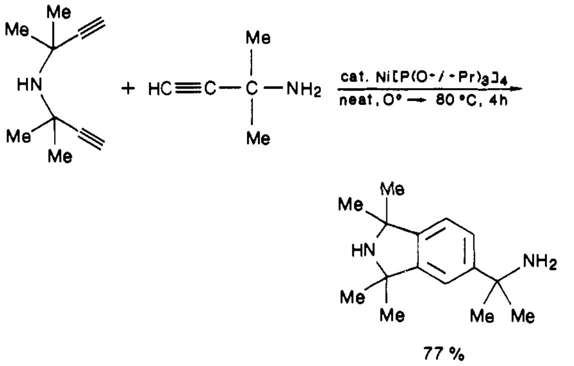
In addition, a novel variant involving the totally intramolecular cyclization of an enetriyne was used to access a unique B-ring aromatic steroid (eq 102).[223] All four rings of the latter are formed in a single experimental operation.



(102)

Mention should be made here of two additional catalytic systems capable of similar cocycloadditions of α,ω-diynes and alkynes. Phosphite complexes of Ni(0) (as well as other Ni(0) species generated in situ) selectively permit rapid cycloaddition of simple alkynes to dipropargylamines in generally very good yields (eq 103).[224] In addition, Wilkinson's catalyst also proves to be quite active for similar processes, also with an especially high tolerance for heteroatom-containing functional groups (eq 104).[225]



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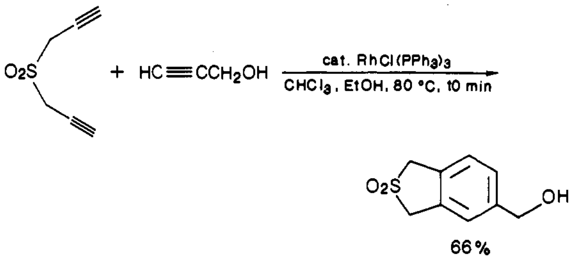
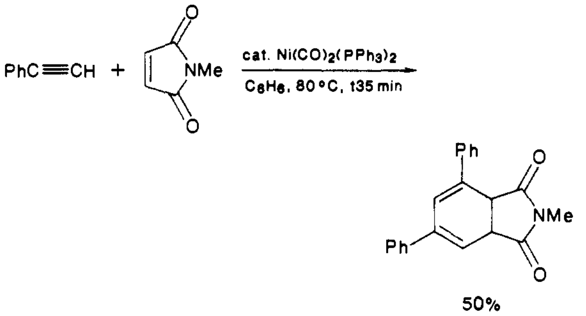


(104)

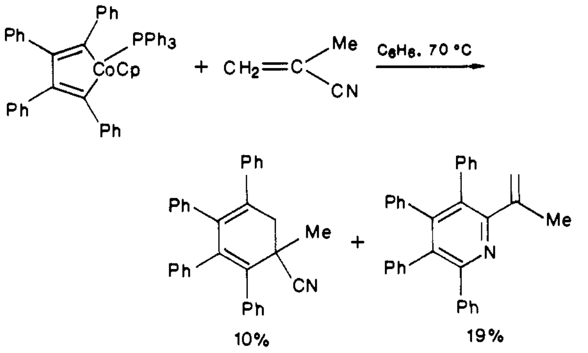
C. 1,3-Cyclohexadienes, from Two Alkynes and Alkenes

This section has been placed out of its otherwise "logical" order due to its close relationship with the benzene syntheses just described. Generally speaking, the same catalysts that are active for alkyne trimerization are also useful for 1,3-cyclohexadiene syntheses. For the most part, the latter simply involves the intermediate metallacyclopentadiene reacting with an alkene instead of a "third" alkyne. Many of the early attempts to exploit this process were troubled by the occurrence of secondary reactions of the diene system such as aromatization or further cycloadditions.[226] In a reasonably successful example, N-methylmaleimide is incorporated into cycloaddition with two molecules of phenylacetylene in the presence of $Ni(CO)_2(PPh_3)_2$ (eq 105).[227] The 1,3-disposition of the phenyl groups is unexpected, however, on the basis of expectations in metallacycle formation (vide infra). Wakatsuki and Yamazaki have demonstrated how the order of com-



(105)

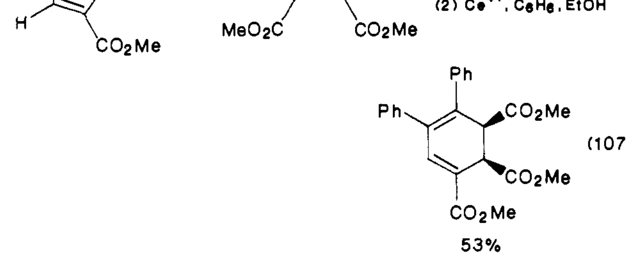
plexation of potential substrate molecules to the metal can affect the outcome of a reaction in the CpCo systems. Methacrylonitrile reacts stoichiometrically with the cobaltacyclopentadiene derived from diphenylacetylene to give both cyclohexadiene and pyridine products (eq 106) (see subsequent section on pyridines).



(106)

However, reaction of diphenylacetylene with either acrylonitrile or methacrylonitrile in the presence of catalytic amounts of the monoalkyne complex CpCo-$(PPh_3)(PhC{\equiv}CPh)$ leads only to linear oligomerization with another mole of unsaturated nitrile. Linear oligomerization is also seen when the product of reaction of $CpCo(PPh_3)(PhC{\equiv}CCO_2Me)$ with dimethyl maleate, an isolable cobalta*cyclopentene*, is reacted with acrylonitrile. Thus the cobaltacyclopentene, once formed, prefers to form linear products with additional alkene, rather than cycloadding to another mole of alkyne.[228]

As a result the possibility of catalysis is limited to cases where the alkyne competes sufficiently well for complexation to the metal to prevent metallacyclopentene formation. This is the case with phenylacetylene and acrylonitrile. For disubstituted alkynes, however, the cobaltacyclopentadiene must be preformed and then treated with the alkene. Typically the product is isolated as a CpCo(diene) complex, from which the metal is removed by Ce(IV) oxidation (eq 107).[169,229]



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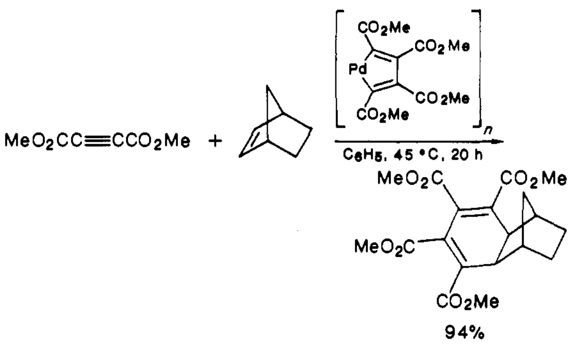
Itoh and Ibers have reported a Pd-catalyzed cocycloaddition of norbornene and $MeO_2CC{\equiv}CCO_2Me$, which is noteworthy in that the alkene is the electron-rich rather than the electron-poor partner in the formal (or, perhaps, actual) Diels–Alder reaction with the metallacyclopentadiene (eq 108).[230]



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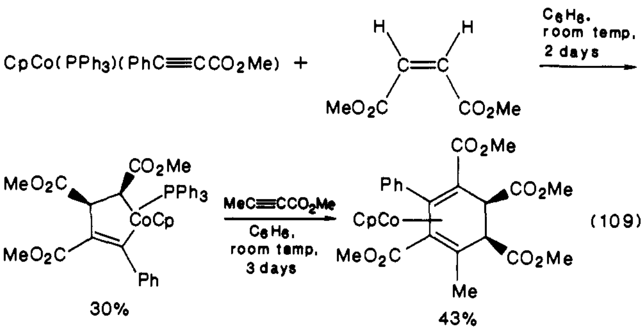
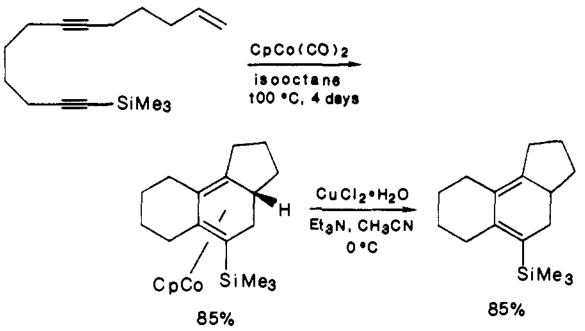
Although cobaltacyclopentene complexes react preferentially with alkenes, Wakatsuki has shown that they can be preformed and reacted with alkynes, providing an alternative stoichiometric permutation for 1,3-cyclohexadiene synthesis (eq 109).[231]



(109)

All-intramolecular versions of this process have been pioneered and substantially developed by Vollhardt.[232] With enediynes containing a terminal double bond, formation of cobalt-complexed cyclohexadienes takes place in good yield upon extended heating with stoichiometric $CpCo(CO)_2$ (eq 110).[233] Several observations in these systems are not yet understood, including the role played by the $Si(CH_3)_3$ group, which is necessary for the reaction to succeed in one case, but not others, and provides good stereocontrol in the case shown, but not others. Whatever the answers to these questions may be, with the appropriate precursor C-ring dienyl steroids are accessible in a remarkable process that is highly stereoselective, involving a 1,1-disubstituted alkene (eq 111).[234] Extreme steric hindrance can be tolerated by this process.[235]



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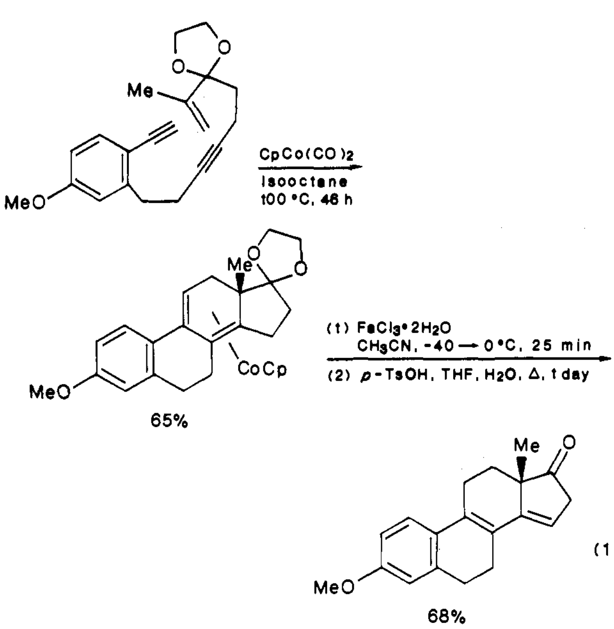
Intramolecular cycloadditions involving terminal alkynes with an internal alkene have also been demonstrated.[236] Even tetrasubstituted alkenes participate, with total stereoselectivity (eq 112).[237]



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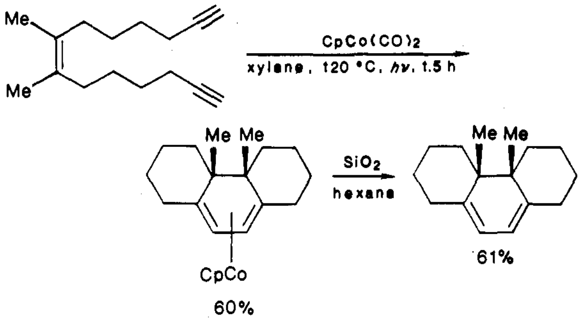
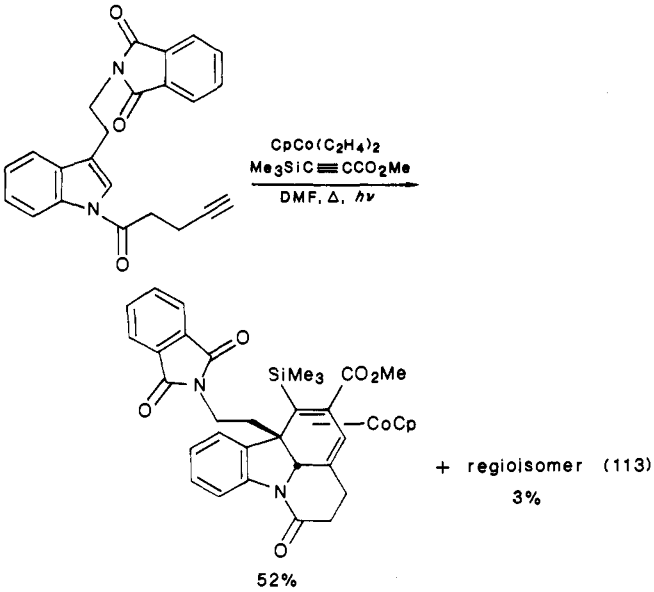


(112)

In early attempts to carry out a partially intermolecular version of this process, cycloadditions of α,ω-enynes with bis(trimethylsilyl)acetylene gave only rather poor yields of annulated 1,3-cyclohexadienes.[238] Remarkably, however, the analogous process in which the alkene is part of a heteroaromatic ring gives in many cases quite acceptable yields of heteropolycyclic products. Examples have been reported involving pyrroles,[239] indoles,[240] and imidazoles.[241] An additional recent innovation employs $CpCo(CH_2{=}CH_2)_2$ as mediator of the cycloaddition process, resulting in cleaner reactions and higher regioselectivities with unsymmetrical alkynes (eq 113).

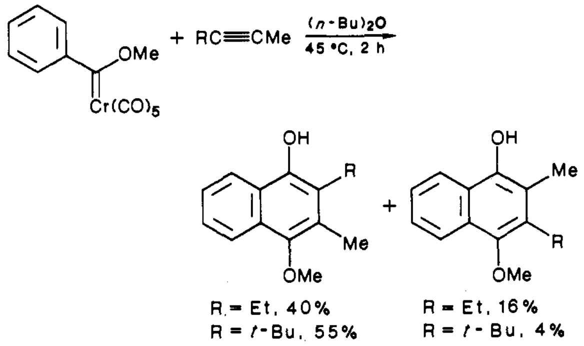


(113)

D. Phenols, from Alkynes, CO, and Vinyl "Carbenes" (and Naphthols, from Alkynes, CO, and Aryl "Carbenes")

1. *Dötz Hydroquinone Synthesis*

The cycloaddition of an alkyne to a chromium arylalkoxycarbene complex to give a Cr-complexed 4-methoxy-1-naphthol was first observed by Dötz in 1975.[36] This has been found to be the most general type of cycloaddition involving these reaction partners. The remarkable development of this process, entirely the work of the Dötz group prior to about 1980, indicated several extremely attractive features for synthetic application. The reaction is highly regioselective (totally regioselective for terminal alkynes), linking the alkyne carbon with the smaller substituent to the carbene carbon (eq 114; although the initial products of these reactions are arene–$Cr(CO)_3$ complexes, removal of the metal by either CO to give the naphthol or oxidatively to give a quinone is readily achieved,[37] so for simplicity the uncomplexed organic product will be shown in the equations).[242] The regiochemistry is entirely immune to electronic effects of substituents on the alkyne; electron-rich alkynes are preferred kinetically, however.[40a] The reaction is general for terminal or internal alkynes with either alkyl or aryl substituents, giving 45–75% yields. Similar reactions do occur with unstabilized carbene complexes, i.e., lacking a heteroatom-containing substituent such as $(CO)_5Cr{=}CPh_2$; thus naphthols lacking the 4-alkoxy group are accessible, but the yields are much lower.[243] Annulation can take place with virtually any π-system attached to a carbene carbon, including simple vinyl and a variety of heteroaromatic systems (eq 115–117). In unstabilized carbenes bearing two different aryl groups annulation occurs exclusively on the less electron rich ring, e.g., $p\text{-}CF_3C_6H_4$ > $p\text{-}CH_3C_6H_4$ and Ph > naphthyl, furyl, or thio-



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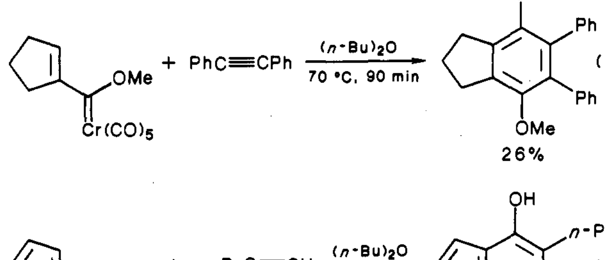

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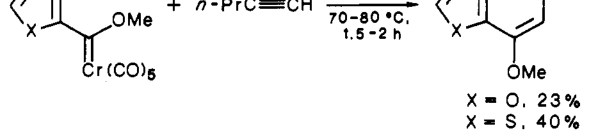

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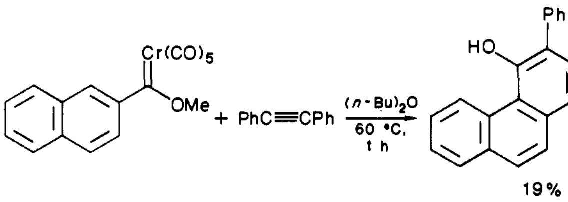
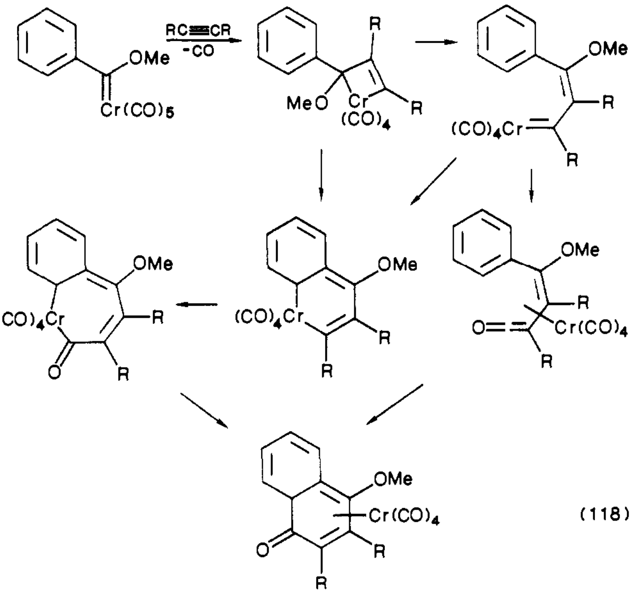


(117)

phenyl.[244] An additional example of the chemoselectivity of the process is the annulation of an arylalkoxycarbene with an enyne. Alkenes do not participate in this process; the alkyne function alone reacts.[245] Note that more recent developments have in many cases greatly improved the yields of these types of reactions (vide infra). In particular, although most examples of this reaction have been carried out in ethereal solvents, it is now apparent from the work of Wulff that solvents of low coordinating ability are superior for the majority of situations, and yields in excess of 80% may be expected from annulation of simple alkynes to arylcarbenes *in hexane*.[39]

Aspects of the mechanism have already been presented (eq 10 from Cyclobutenones). Three reasonable sequences may be proposed that are indistinguishable both kinetically and from structure/reactivity data (eq 118). Dissociation of CO, complexation of the alkyne to the metal, and formal 2 + 2 cycloaddition take place. The resulting metallacyclobutene either may undergo a 1,3-sigmatropic shift of the metal to the carbon of the attached π-system or may first undergo electrocyclic ring opening to give a vinylcarbene complex. The latter has a choice of electrocyclic ring closure either before or after CO insertion. The result in any case is a cyclohexadiene, which aromatizes to give the isolated Cr-complexed 4-alkoxyphenol. Several evaluations of these mechanisms have been presented.[38a,39,40c,246] Experimental evidence of possible relevance is the isolation of silyl-substituted vinylketenes from reactions with $Me_3SiC{\equiv}CSiMe_3$, which does not undergo annulation.[40b] This may be taken to imply that vinylketenes are indeed intermediates; alternatively, they may simply be thermodynamically accessible species in equilibrium with the intermediates on the reaction pathway, but not on the pathway themselves.[247]



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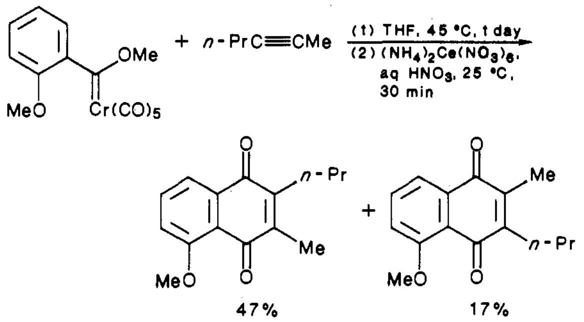
Further development of the synthetic potential of this chemistry has been pursued by several researchers, including Semmelhack and Yamashita as well as Dötz and Wulff. Wulff carried out an extensive study of regioselectivity that greatly expanded the early work by covering substituted aryl groups on the carbene as well as unsymmetrical alkynes. This study also led to improved oxidation procedures for the isolation of either quinones or their monoacetals (eq 119 and 120).[248]



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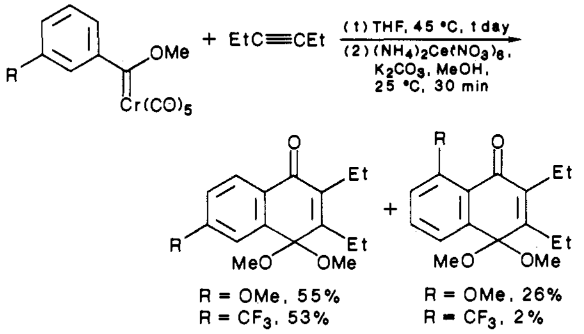

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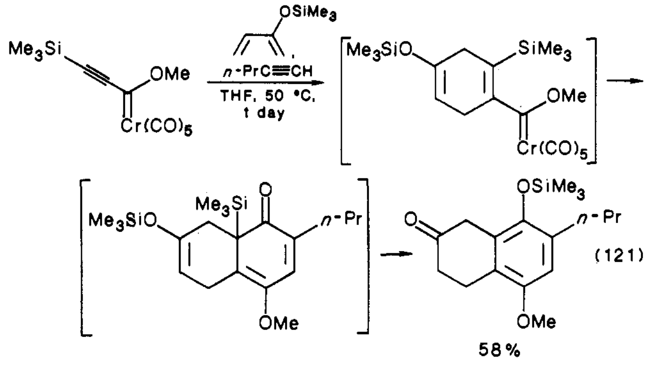
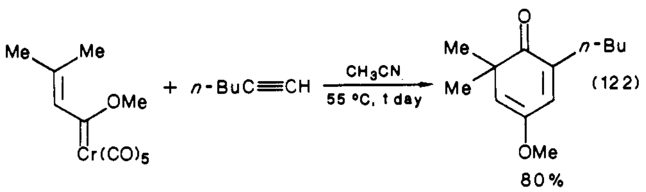
Dötz and Wulff have both developed improved procedures and methodological extensions of the cycloaddition of chromium *vinyl*alkoxycarbenes with alkynes. Yields of 60–80% are typical as long as electron-withdrawing substituents on the alkyne are avoided.[249] As mentioned previously, Wulff has combined Diels–Alder reactions of alkynylcarbenes with Dötz annulation to generate polycyclic products (eq 121).[184a] The reaction may be carried out in one pot



(121)

and provides an attractive alternative to the only prior general synthesis of vinylcarbenes, addition of alkenyllithium to $Cr(CO)_6$.[250,251] In the presence of a group with low migratory aptitude on the β-alkenyl carbon, the cyclohexadienone is isolated as the major product of annulation (eq 122).[184a,252] Wulff has also combined 1,3-dipolar cycloaddition of an alkynylcarbene (to CH_2N_2 to give a pyrazolylcarbene) with further alkyne annulation, generating unusual pyrazolo[1,5-*a*]pyridine derivatives.[253]



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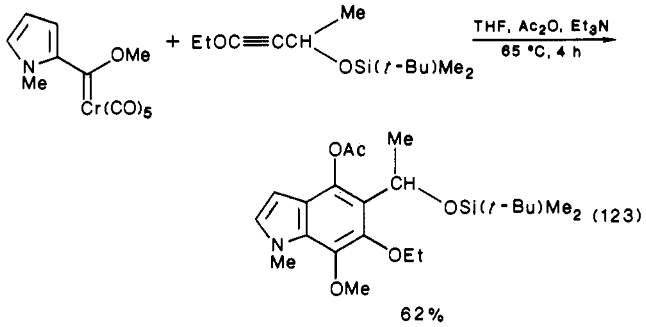
Yamashita's efforts have expanded the scope of the reaction to include functionalized alkynes (including $HC{\equiv}CCO_2Et$) and 2-pyrrolylcarbenes, obtaining 40–60% yields by trapping the phenol with acetic anhydride in situ.[43a,44] Omission of the latter procedure permits secondary reactions to occur with certain systems (eq 123).[254]



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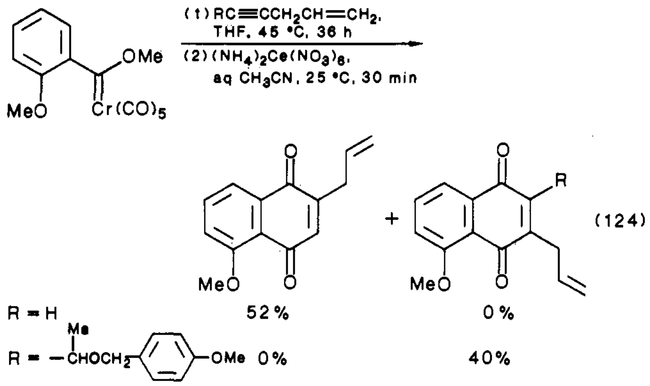
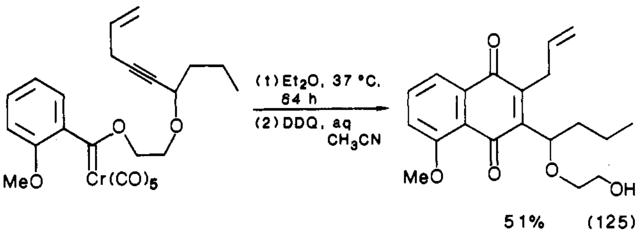
Many applications of this annulation to natural product synthesis have been carried out. Dötz has published efficient syntheses of vitamin E from an alkenylcarbene and of several vitamin K isomers from arylcarbene cycloadditions with 1,4-enynes.[255] Yamashita applied reactions similar to that shown in eq 123 but using 2-furylcarbenes in two approaches to the biologically active furochromone khellin.[256] The potential of this process toward syntheses of benz-annulated quinone antibiotics and anticancer agents has generated the greatest interest, however. Semmelhack has concentrated on naphthoquinone antibiotics, with initial efforts making use of the regiospecifically formed annulation product of 1,4-pentenyne with the (*o*-methoxyphenyl)methoxycarbene complex of $Cr(CO)_5$ (eq 124).[257] Further elaboration at the unsubstituted position on the quinone ring was successful, leading eventually to the antibiotic nanaomycin A; the sequence was cumbersome,[258] however, and direct annulation with a suitable substituted enyne was regioselective, but in the wrong direction.[259]



(124)

Both synthetic efficiency and control of regiochemistry were subsequently achieved by tethering the alkyne to the carbene. Intramolecular cycloaddition of such a system provided the key to a synthesis of another antibiotic, deoxyfrenolicin (eq 125). In more extended studies of the intramolecular process internal alkynes give 60–80% yields; terminal alkynes are less satisfactory.[260]



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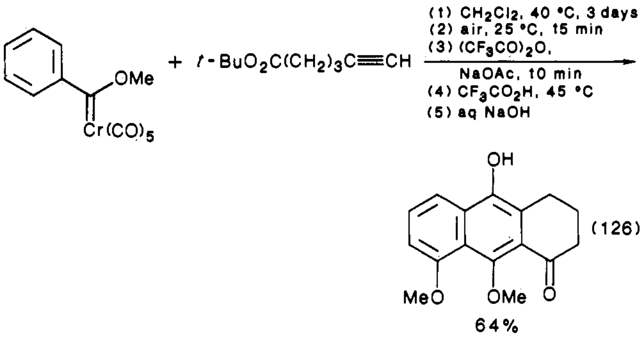
Syntheses of anthracyclinones have been reported by both Wulff and Dötz. Wulff has developed a one-pot procedure for annulation followed by Friedel–Crafts cyclization (eq 126).[261] Further elaboration in the direction of the antitumor antibiotics olivin and chromomycinone via removal of the free hydroxyl via the triflate has been achieved.[262] This paper also reports the first example of an intramolecular annulation of a 3-furylcarbene complex, aimed toward the synthesis of the benzofuran angelicin (eq 127); annulation occurs only toward C-2 of the furan, avoiding forming an isobenzofuran structure.



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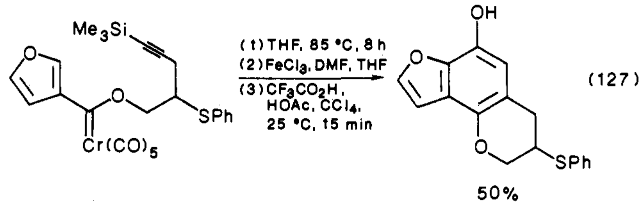

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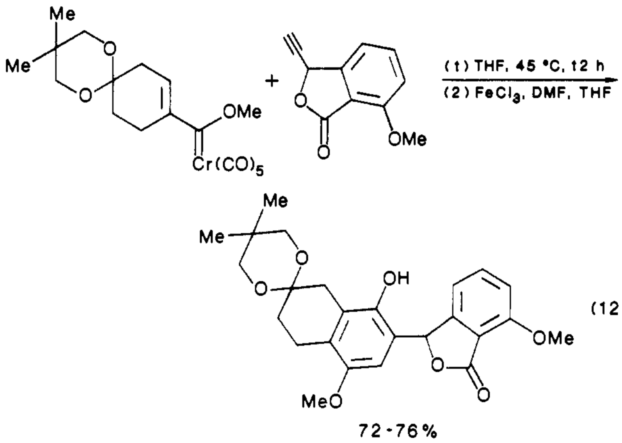
In an approach designed to access the more complex tetracyclic antitumor agents daunomycin and adriamycin, Wulff explored annulations of cyclohexenylcarbenes with functionalized propargylbenzenes. Since the presence of a carbonyl group in conjugation with the triple bond gave poor results, an alternative substrate was designed to be compatible with the necessary later elaborations. The alkynyl lactone shown cycloadds readily, allowing a formal synthesis of daunomycinone to be completed (eq 128).[38b,263]

Dötz has reported results of two additional approaches to the same group of compounds. In a similar but complementary sequence to the one above, annulation of a propargylcyclohexanone derivative to an anisylcarbene[264] gives a naphthalene that has been cyclized to an 11-deoxydaunomycinone precursor (eq 129). Note the CO-promoted decomplexation, which not only gives excellent yields of the organic product but allows recovery of the metal as $Cr(CO)_6$.[265]

In his second approach, Dötz reports that annulation involving 2-naphthylcarbenes, which is ordinarily driven



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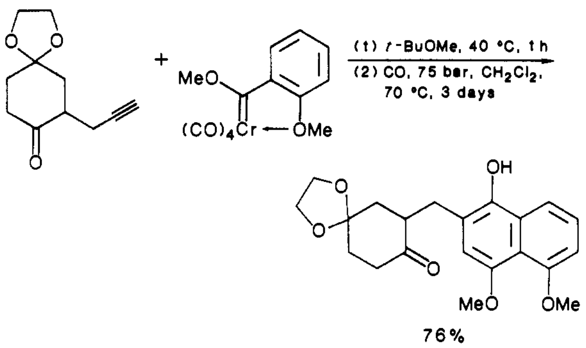

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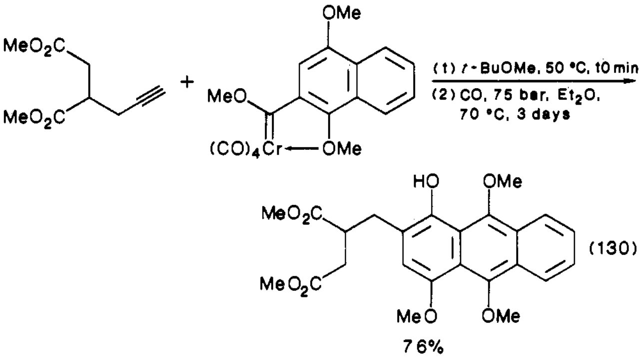
toward C-1 to give phenanthrenes (eq 117), can be diverted toward C-3 if C-1 alkoxy substitution is present. A high yield of the anthracene derivative and its subsequent conversion to a known tetracyclic precursor to daunomycin are reported (eq 130).[265b,266]



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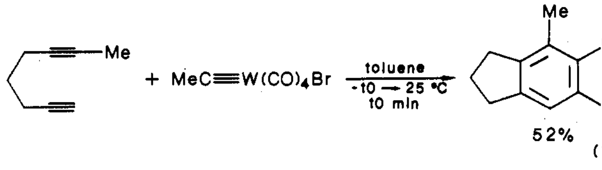
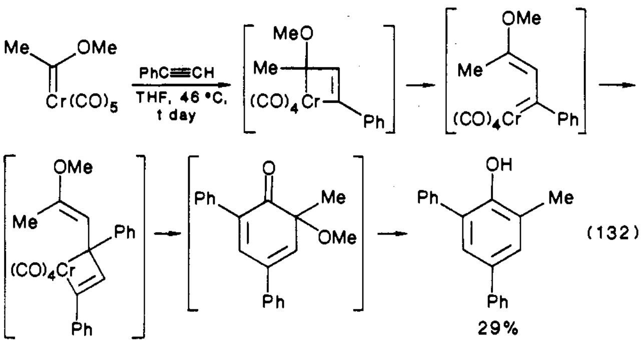
2. Related Reactions

A unique phenol synthesis has been described by Katz, in which cycloaddition of an α,ω-diyne to a metal (W or Cr) *carbyne* occurs; thus the new ring incorporates the carbons of *two* alkynes, CO, and the "carbyne". At least one of the two alkyne moieties must be terminal, the reaction is totally regioselective, and it is capable of forming four-, five-, or six-membered rings (eq 131).[267] A similar process has been found by Wulff.



(131)

In it, the vinylcarbene complex formed by reaction of one molecule of alkyne to a metal *alkyl*alkoxycarbene complex may cycloadd to a second alkyne molecule. The vinyl metallacyclobutene thus formed ring expands to give an alkoxycyclohexadienone which is reductively aromatized to the final product, a phenol. Thus this process incorporates two alkynes, CO, and the "carbene" into the ring. Although yields are low in intermolecular cases, diynes react much more efficiently (eq 132 and 133).[268] A partially intramolecular version has also been developed (eq 134).[269]



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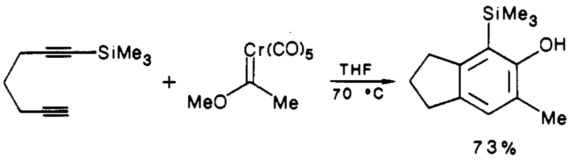

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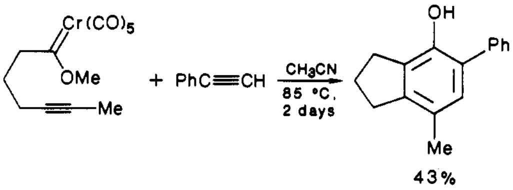

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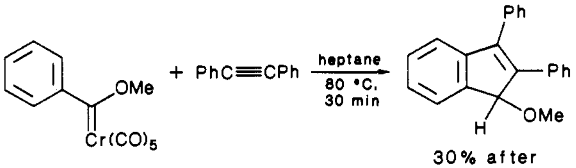
An anomalous reaction of chromium alkoxycarbenes with enynes has been reported by Wulff.[270] Also to be noted are recent efforts by Semmelhack to enter the reaction regimes described in this section with catalytic use of the metal.[271]

E. Indenes, from Alkynes and Aryl "Carbenes"

This section is presented here due to the close relationship between indene- and naphthol-forming reactions. Like furans, indenes have also been isolated in low yields from reactions of alkynes with chromium arylalkoxycarbene complexes.[37] As is the case with naphthol formation, a formal double bond of the aryl group is involved, but CO insertion does not occur and, instead, bond formation takes place directly between an alkyne carbon and the aryl carbon ortho to the metal carbene substituent (eq 135).



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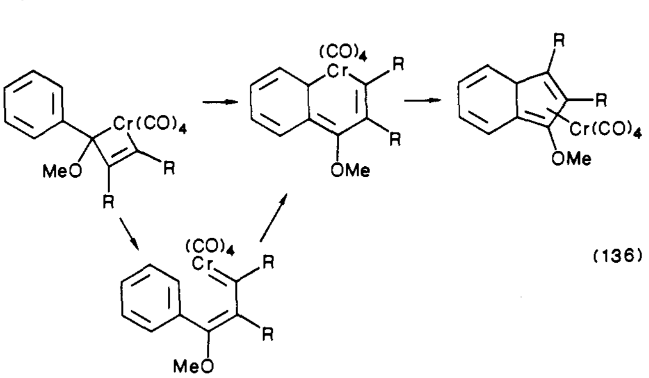
30% after decomplexation

As is the case with the formation of cyclobutenones and naphthols, more than one mechanistic pathway is possible: direct ring expansion of the metallacyclobutene via 1,3-sigmatropic rearrangement, or stepwise conversion via electrocyclic ring-opening/ring-closing processes through the vinylcarbene (eq 136).[39]



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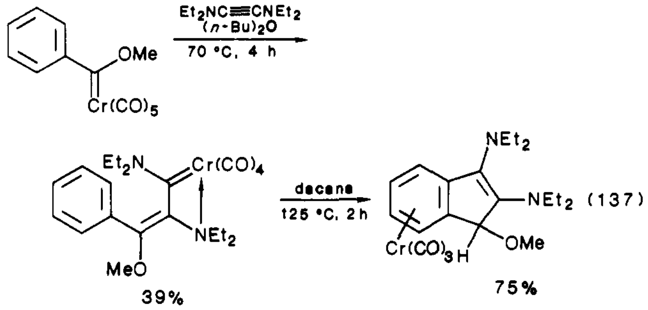
In the late 1970s Dötz found several unusual systems that led to predominant indene formation. Ynamines and ynediamines in particular react with carbenes to give isolable vinyl carbenes, which proceed on to indenes thermally (eq 137).[272] The high yield from the diamine is ascribed to internal coordination which better confines the system to reactive conformations. Indenes also form in one case in which *o,o′*-disubstitution in the aryl group requires alkyl migration to aromatize the product (eq 138).[273] Modest yields of the steroid skeleton have been obtained in one recent synthetic application of this process (eq 139).[274]



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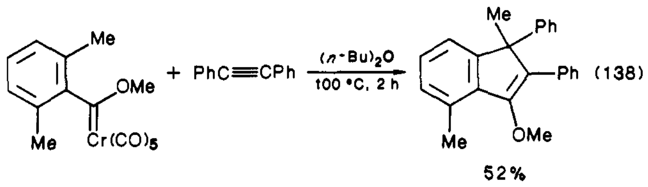

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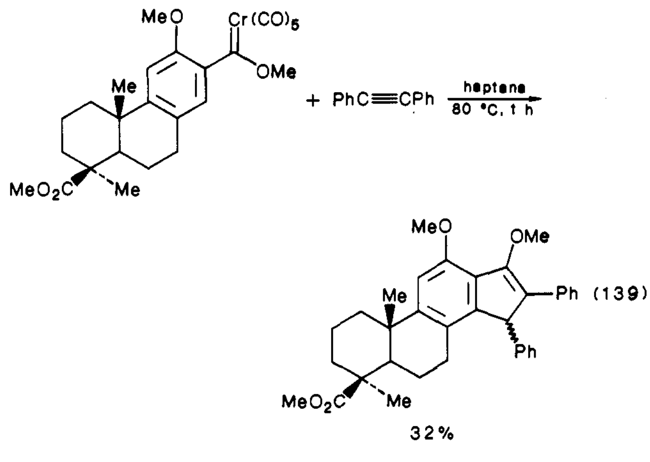

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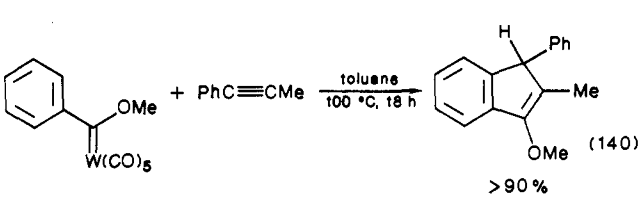
Although an understanding of the factors that lead to indene formation is far from complete, several observations appear to provide some empirical guidelines worthy of future application. Tungsten carbene complexes, although polymerization catalysts for terminal alkynes, give high yields of indenes from internal arylalkynes (eq 140).[275] Yamashita has reported that use of DMF as solvent leads to an 83% yield of the indene from the reactants in eq 135, and she finds the reaction to be fairly general for aryl*amino*carbenes of Cr, leading to respectable to excellent yields of indanones after hydrolysis of the enamine products (eq 141).[276] Note that these examples exhibit total regioselectivity for linking the carbene carbon to the less hindered alkyne carbon. Finally, Wulff has noted a peculiar enhancement of indene formation under conditions of relatively high dilution (eq 142).[39]



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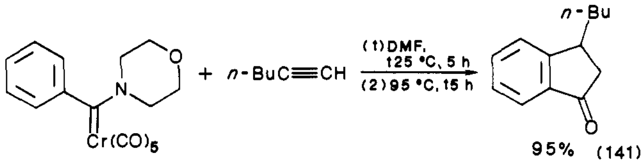

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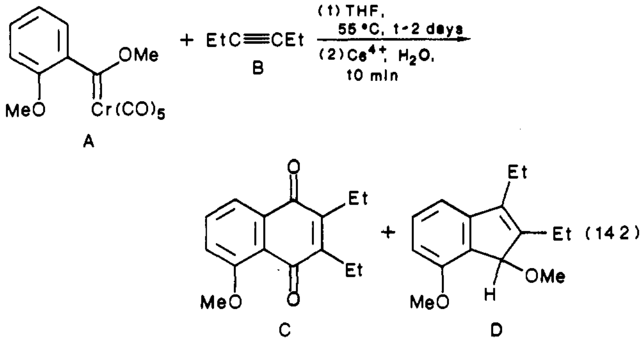

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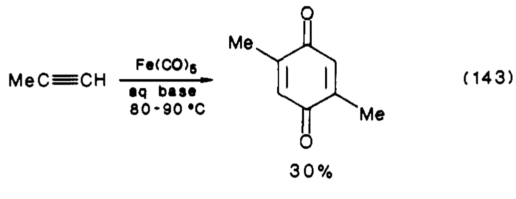
init concn, M		% C	% D
A	B		
0.1	0.95	58	14 (+4% indanone)
0.005	0.01	5	66 (+9% indanone)

A nonbenzannulated analogue of this reaction has not been found; i.e., no example is known of cycloaddition of an alkyne to a vinylcarbene complex without CO insertion taking place.[252]

F. Quinones, from Two Alkynes and Two CO

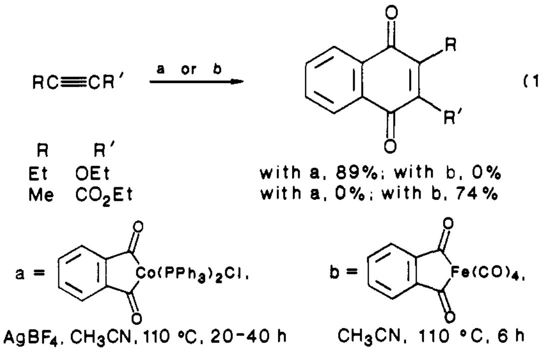
Direct preparation of quinones (or hydroquinones) from alkynes has been observed in the presence of a number of metal carbonyls. The very first report of this process, by Reppe and Vetter, essentially demonstrates the limits of this process in spite of numerous subsequent explorations by a number of other groups. Yields are low (≤30%), as this particular process typically does not compete well against either formation of other organic products or formation of unreactive metal complexes (eq 143).[277] Maitlis' study of Rh complexes in this context is typical of examples with other metals: reaction with 2-butyne leads to mixtures of hexamethylbenzene, tetramethylquinone, and tetra-



(143)

methylcyclopentadienone.[121b] Note, however, that some processes of utility in specific cases have been developed.[278,279] A review of this general area, which also summarizes the chemistry described below, appeared in 1985.[280]

After considerable exploration a stepwise quinone synthesis has been developed by Liebeskind from cobaltacyclopentenediones ("maleoylcobalt" complexes). This work was based on a variety of precedents that indicate that such metallacycles are likely precursors of quinones in at least some of the catalytic systems and has been brought to a relatively mature stage in terms of optimization of the metal system, access to the required substrates, and understanding of major controlling factors. Initial work with naphthoquinone precursors identified several "phthaloyl metal" complexes capable of giving near-quantitative yields of quinones in many cases, but each complex exhibited its own electronic and/or steric limitations (eq 144).[281] Nevertheless, application in natural product synthesis was quickly developed in the preparation of the antibiotic nanaomycin A using an intramolecular modification of the process to maintain regiocontrol (eq 145).[282]



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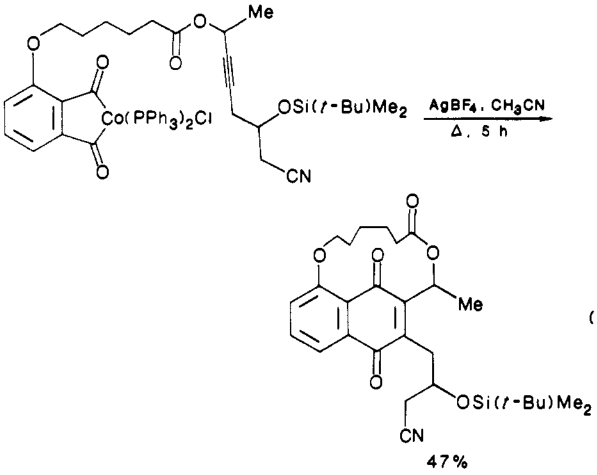
R	R'	
Et	OEt	with a, 89%; with b, 0%
Me	CO_2Et	with a, 0%; with b, 74%



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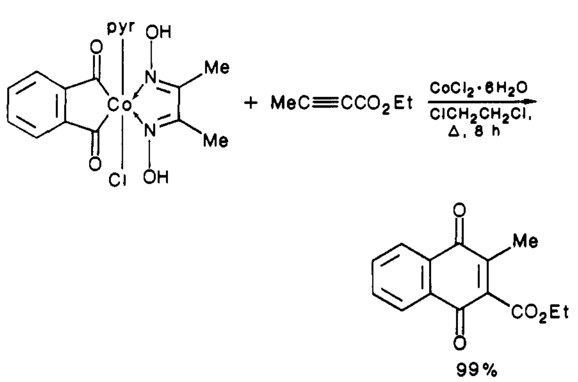
The development of an analogous synthesis of simple benzoquinones was reported together with the identification of dimethylglyoxime-complexed maleoylcobalts as the most generally useful complexes for this chemistry.[283] These systems are readily induced to undergo ionization of an axial halide, permitting complexation of the alkyne in a productive manner. The current state of the art makes use of Lewis acid catalysts with all but electron-rich alkynes, resulting in a general reagent for both the high-yield synthesis of naphthoquinones as well as a high yield *and regioselective* synthesis of benzoquinones (eq 146 and 147).[284] Interestingly, the orientation of cycloaddition in this latter reaction is predominantly controlled by electronic rather than steric factors. The last example served to generate the precursor to an isoquinoline quinone which is a structural component of the saframycin A antitumor antibiotics.



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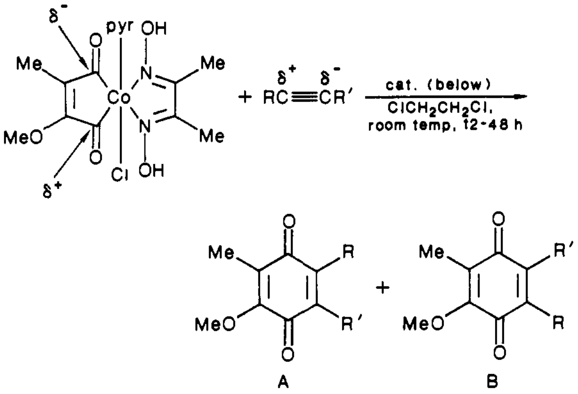

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R	R'	cat.	% A	% B
EtO	Me	none	49	3
n-Bu	H	$SnCl_4$	59	6
Me	CO_2Et	$SnCl_4$	59	3
$PhCH_2N(cbz)CH_2CH_2$	COMe	$SnCl_4$	46	2

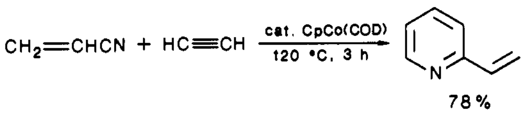
As mentioned previously, the metallacycles themselves are easily prepared from cyclobutene-1,2-diones. Assuming the responsibility of making these precursors readily accessible, Liebeskind has also developed practical syntheses of both the latter and its benzannulated analogues.[285]

G. Pyridines, from Two Alkynes and Nitriles

Transition-metal-mediated cocycloaddition of alkynes to nitriles to give pyridines has attracted a considerable amount of attention from chemists in both academic and industrial laboratories. The same questions concerning chemoselectivity and regioselectivity just considered in the section on 1,3-cyclohexadienes are present here as well. In the case of pyridine synthesis, however, considerable exploration of catalyst structure/reactivity correlations has led to a substantial amount of empirically useful information, if not necessarily a commensurate degree of insight concerning the basic reasons behind these effects. Until recently, virtually all the work in this area focused on cobalt-based catalysts. Wakatsuki and Yamazaki first reported a stoichiometric[286] and then a catalytic preparation of pyridines using cobaltacyclopentadienes to promote the reactions.[287] These reactions took place under relatively mild conditions, even at room temperature in the presence of $CpCo(PPh_3)$(alkyne), and gave modest

(30–60%) yields using a variety of nitriles RCN (R = alkyl, aryl, vinyl).

Further developments through the mid-1970s established the scope and limitations of the totally intermolecular cocycloaddition process; these were reviewed in 1978 by Bönnemann, whose synthetic and mechanistic efforts were most influential in the development of this reaction.[288] In 1984 Bönnemann published an even more comprehensive and authoritative study of this reaction, with full details concerning optimization of catalysts and experimental procedures.[289] Briefly stated, cocycloaddition of two identical alkynes to a nitrile can be carried out with a wide variety of Co(I) catalyst precursors. The rate of cycloaddition is independent of [RCN]; this and other observations make it clear that the two alkynes complex to Co first, leading to the Co(III)-containing metallacycle. The nitrile, being generally a better σ-donor than an alkyne and therefore a better ligand for Co(III), then complexes, probably through the nitrogen initially, and the cycloaddition is completed. This inherent preference for nitrile complexation to Co(III) vs complexation of a "third" alkyne leads to a ca. 2:1 chemoselectivity for pyridines vs benzenes as products of these reactions. This can be considerably enhanced by maintaining an excess of nitrile and adding the alkyne in portions. In this way 2-substituted pyridines may be synthesized in excellent yields from acetylene and nitriles, using either CpCo(cod) as catalyst or any of a variety of soluble Co(I) species generated in situ. Of all the examples reported by Bönnemann, the one shown (eq 148) gives the *poorest* yield; virtually all other nitriles give ≥90% isolated yields of pyridines.[290] With this methodology pyridines containing chiral substituents at C-2 have been synthesized in excellent yields and optical purities from the corresponding nitriles (eq 149 and 150).[291,292]



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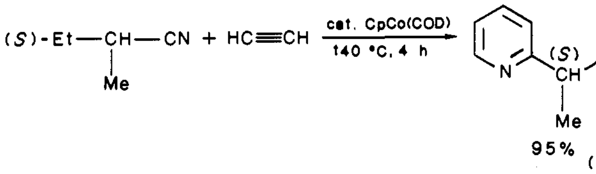

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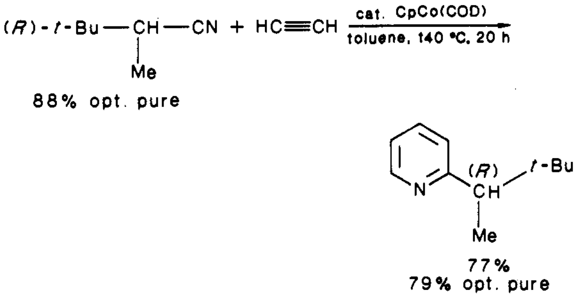
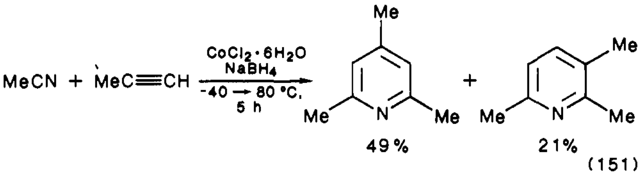


(150)

Monosubstituted acetylenes present the same regiochemical problem in pyridine synthesis as was encountered in simple trimerization. In this case the problem unaccountably appears to arise at the metallacycle stage: both 2,4- and 2,5-disubstituted cobaltacyclopentadienes must participate in these systems, since both 2,4,6- and 2,3,6-trisubstituted pyridines form in substantial amounts.[293] Typically, pyridines are formed in ca. 65% yields from nitriles and monoalkyl- or arylacetylenes, the rest of the product mixture being benzenes from alkyne trimerization. Regioselectivity is only modest, typically ca. (1.5–2):1 in favor of the 2,4,6-trisubstituted pyridine (eq 151).[294] With symmetrically substituted internal alkynes in which regiochemistry is not an issue, excellent yields of pentasubstituted pyridines are obtained (eq 152). Attempts at cocycloaddition using a nitrile and two different alkynes lead to hopeless mixtures.[288] Useful variants of this process include the synthesis of 2-aminopyridine from cyanamide[289] and syntheses of 2-(alkylthio)pyridines from alkyl thiocyanates.[295] Note, however, that electron-withdrawing groups "X" in XCN greatly reduce or eliminate useful reactivity.[289]



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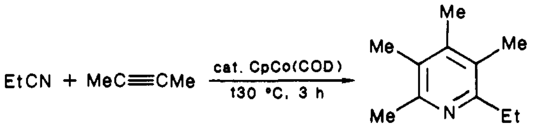
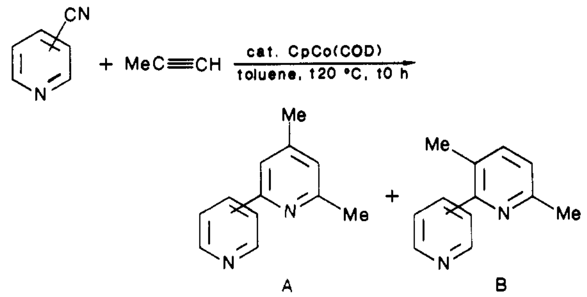


(152)

In an extensive series of studies, Bönnemann has examined Co(I) catalysts containing a variety of substituted cyclopentadienyl as well as other polyene ligands, finding that both catalytic activity and regioselectivity are related to NMR measurements that, in turn, reflect electron density at the metal. Electron-poor metal centers, e.g., from $(C_5H_4COMe)Co(COD)$[296] or $(C_5H_4CO_2Me)Co(COT)$,[297] exhibit the highest activity, but the lowest regioselectivity (ca. 1.5:1); conversely, the electron-rich metal in $(C_5Me_5)Co(COD)$ is much more selective, giving better than a 3.5:1 ratio of 2,4,6- to 2,3,6-trisubstituted products, but at the price of greatly reduced reactivity. Some rather exotic catalysts with applications in certain specific situations were discovered in these studies.[298] A recent noteworthy report indicates that vapor-deposited Co atoms are quite effective catalysts for pyridine formation, showing activity even at room temperature. Best results are obtained at 120 °C and are comparable to those obtained with CpCo(COD): 80% yields, chemoselectivities ≥7:1, and regioselectivities ≈ 2:1.[299]

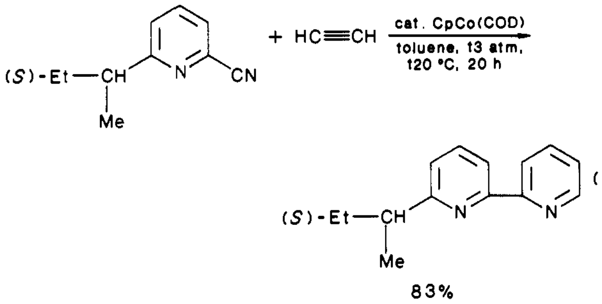
Bipyridines are readily prepared from cyanopyridines and alkynes (eq 153).[300] This reaction is significant in that the products may be useful ligands for homogeneous catalysts; indeed, incorporation in such a synthesis of a nitrile derived from the product of eq 149 gives an optically active bipyridine, suitable for use as a ligand in chiral catalysis (eq 154).[301]

Not unexpectedly, α,ω-dinitriles do not react in an intramolecular fashion; instead, each cyano group undergoes independent cocycloaddition with two molecules of alkyne. Depending upon conditions, reaction may be stopped after one cycloaddition to give high yields of 2-(ω-cyanoalkyl)pyridines or may be carried to completion to give equally high yields of bis(2-pyridyl)alkanes.[299]



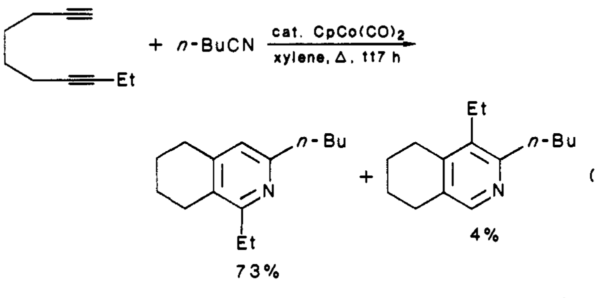
(153)

isomer	% A	% B
2-CN	65	26
3-CN	58	36
4-CN	49	41



(154)

The first successful partially intramolecular cycloadditions to form pyridine derivatives were reported by Vollhardt, who prepared a variety of di- and polycyclic systems from reactions of nitriles with α,ω-diynes. The regioselectivity shown (eq 155) is completely consistent with expectations from the results of intermolecular analogues: steric effects control bond formation to the nitrile carbon.[302] Applications of this general methodology to the synthesis of pyridoxine (vitamin B_6) have been reported by two groups using the cycloadditions of dipropargyl ethers shown (eq 156 and 157).[303,304] Dipropargylamines are similarly reactive toward pyridine formation and have been used in a study of chemoselectivity as well.[305]



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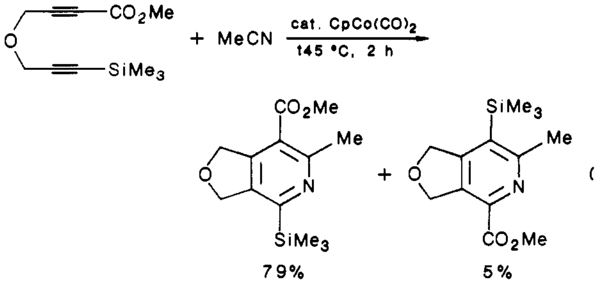
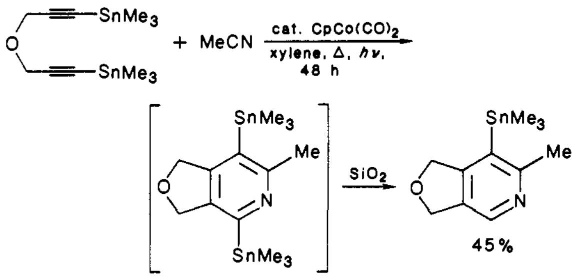


(156)

Vollhardt has also demonstrated the incorporation of α,ω-cyanoalkynes into pyridines via highly regioselective cocycloaddition with alkynes (eq 158).[306]

Recent reports of pyridine syntheses via $CpRhL_2$-catalyzed cocycloadditions are of interest in that some examples of very high regioselectivities in intermolecular reactions with terminal alkynes have been found; however, yields and chemoselectivities (i.e., pyridines vs benzenes) are generally not nearly as good as with Co-based catalysts.[307]



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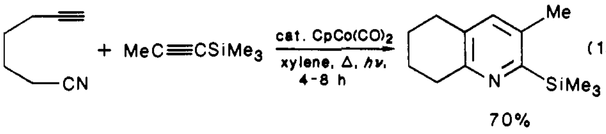
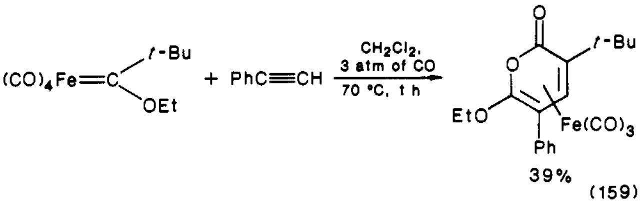


(158)

H. Pyrones, from Alkynes, Two CO, and "Carbenes"

Iron alkoxycarbenes react with alkynes under mild heating and slightly elevated CO pressure to give $Fe(CO)_3$-complexed 6-alkoxy-2-pyrones as products (eq 159).[308] The reaction is related to the 2-aminofuran synthesis from iron aminocarbenes presented earlier; indeed, CO pressure diverts the latter reaction from furan formation to the production of complexed 6-amino-2-pyrones (eq 160).[147,309] The reaction is similarly regioselective, but somewhat more limited in scope compared with the furan preparation. Decomplexation of $Fe(CO)_3$-complexed dienes is of course generally readily achieved, although it has not been demonstrated for these specific compounds.



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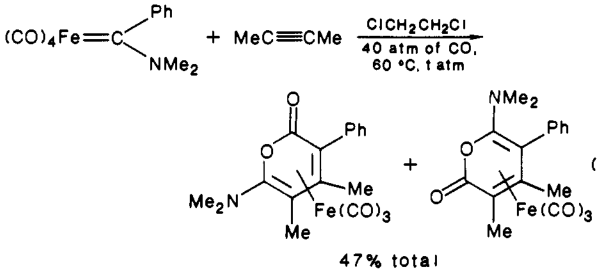
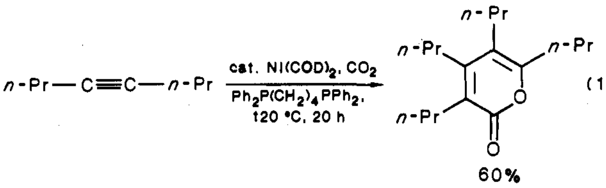


(160)

I. Six-Membered-Ring Heterocycles, from Two Alkynes and Heterocumulenes

1. 2-Pyrones, from CO_2

A catalytic cocycloaddition of alkynes with CO_2 to give 2-pyrones utilizes a bis(phosphine)nickel(0) complex prepared in situ. Dialkylacetylenes work reasonably well, but terminal alkynes give poor yields (albeit of a single regioisomer), and arylacetylenes do not work at all (eq 161 and 162).[310]



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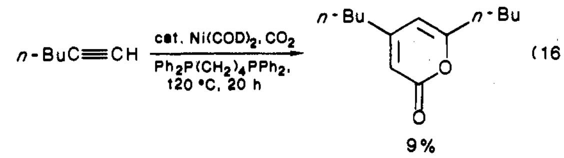
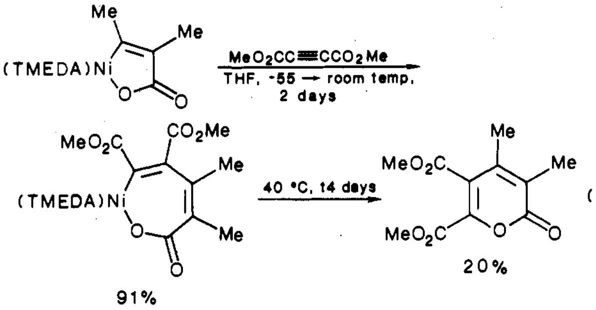


(162)

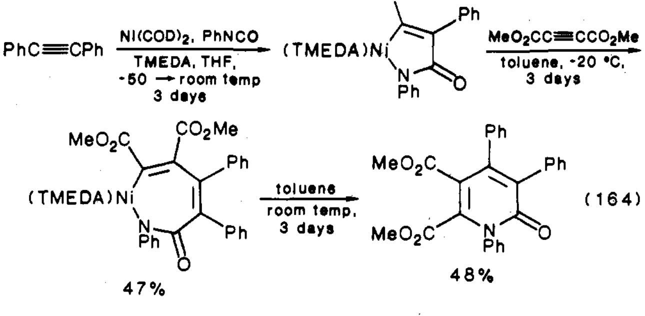
The 5-nickelafuranones earlier mentioned in connection with a synthesis of maleic anhydrides appear to be good models as intermediates in this synthesis. Hoberg has found that they indeed react with alkynes to give 2-pyrones; furthermore, in selected cases a seven-membered-ring metallacyclic intermediate may also be isolated (eq 163).[167,311] Such intermediates are consistent with the observed regiochemistry in eq 162: both carbon–carbon bond-forming steps would involve the less hindered carbon of the inserting alkyne.



(163)

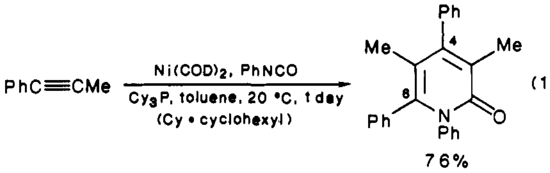
2. 2-Pyridones, from Isocyanates

The most extensively studied of the reactions in this section, the preparation of pyridones, is the only one for which two totally different and complementary catalyst systems have been developed. A Ni(0)-based system was found by Hoberg to be well suited for reaction with internal alkynes. Intermediate metallacycles could again be isolated, implying a sequential insertion mechanism (isocyanate, alkyne, alkyne) consistent with the regiochemistry found from reaction of at least one unsymmetrical alkyne (larger substituents at positions 4 and 6) (eq 164 and 165).[312]



(164)

Hong and Yamazaki had earlier developed a cobalt-based system with very different regiochemical consequences. The differing order of insertion (alkyne, alkyne, isocyanate) and the intermediacy of the now-familiar cobaltacyclopentadienes favors formation of products with the larger alkyne substituents at positions 3 and 6. Where mixtures do form, the only other isomer has the large groups at positions 4 and 6, implying total regioselectivity in the final insertion of the isocyanate, with the carbon of the latter bonding exclusively to the less hindered end of the cobaltacyclopentadiene system (eq 166).[313] This result has been independently demonstrated in studies of the relevant and high-yield (typically ca. 75%) stoichiometric reactions between metallacycles and isocyanates (eq 167).[314] Yields are poor with Cp_2Co as catalyst, but better starting with a catalytic amount of a preformed metallacycle.



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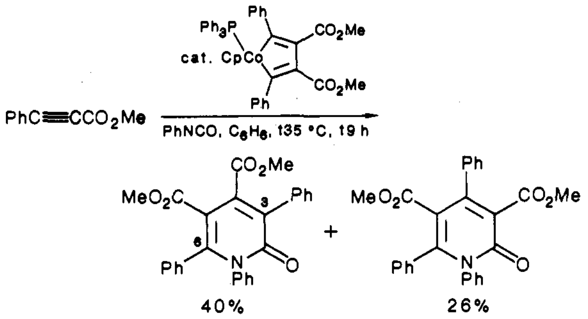

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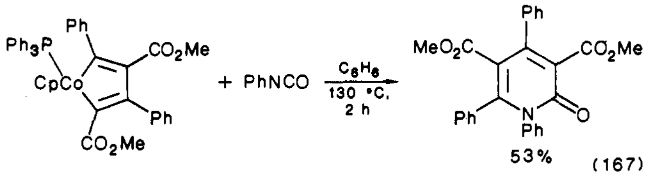
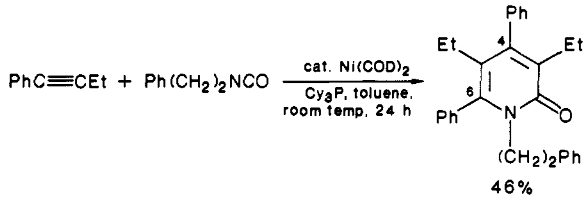


(167)

Vollhardt has carried out a direct comparison of Ni(0) and Co(I) catalyst systems, finding results consistent with the above picture (eq 168 and 169).[315] This study also presents an extensive examination of partially intramolecular versions of this cocycloaddition. Two examples of symmetrical α,ω-diynes could be induced to cycloadd to isocyanates in the presence of CpCo precursors, but yields of annulated pyridones were low (<20%). However, ω-isocyanatoalkynes were found to react cleanly with silylated alkynes in the presence of $CpCo(CO)_2$, giving typically 70% yields of products with



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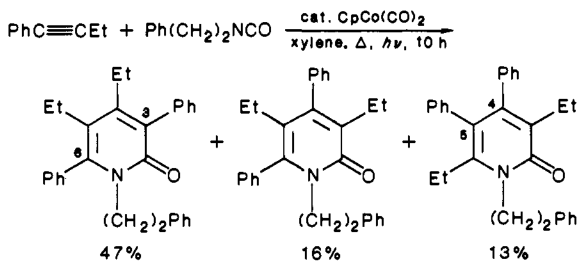
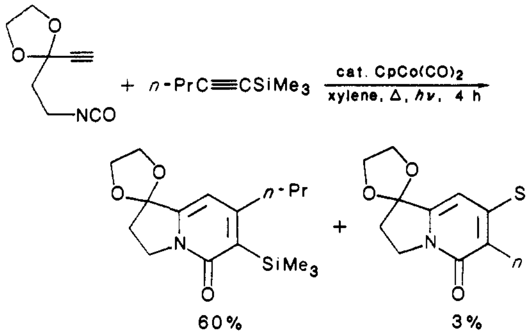


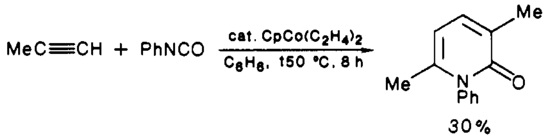
(169)

excellent chemo- and regioselectivities. The example shown (eq 170) was exploited in a pair of formal total syntheses of the antitumor alkaloid camptothecin.



(170)

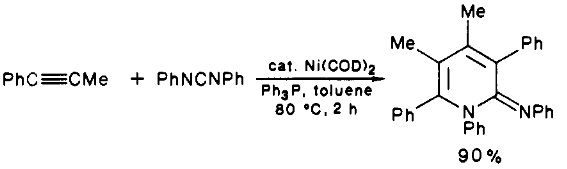
Recent studies of the intermolecular process by Diversi indicate that $CpCo(C_2H_4)_2$ is unusually regioselective for 3,6-disubstituted pyridones, at some sacrifice in yield, when an aryl group is present in either substrate (eq 171).[316] This study contains a very useful comparative tabulation of results of cycloaddition reactions of alkynes with several heterocumulenes with a variety of catalysts.



(171)

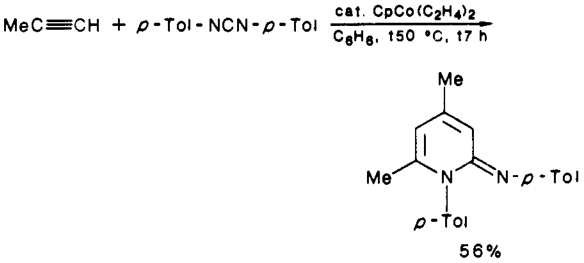
3. 2-Iminopyridines, from Carbodiimides

Both cobalt and nickel have been used for cocycloadditions of alkynes with carbodiimides. As before, the nickel systems are best with internal alkynes; curiously, in these reactions the regioselectivity is completely different, i.e., larger groups at positions 3 and 6 (eq 172; cf. eq 165).[317] The reaction may be carried out either catalytically or stoichiometrically, from a preformed Ni(0) complex of the carbodiimide whose structure sheds no light on the regioselectivity.



(172)

Similar, cobalt-catalyzed reactions give poorer yields, but ironically also show a tendency toward reversal of regioselectivity vs comparable reactions with isocyanates.[313,316] Indeed, using bis(*p*-tolyl)carbodiimide with terminal alkynes, the 4,6-disubstituted product is the only one formed (eq 173).



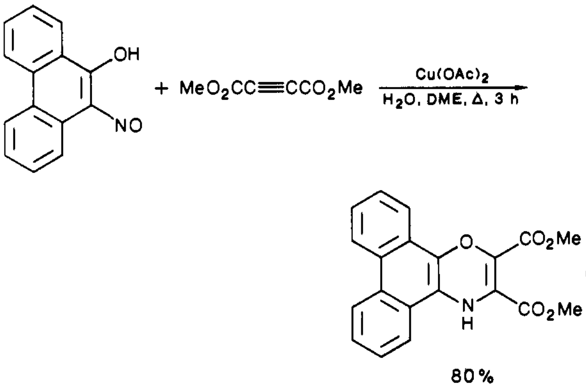
(173)

4. Other Heterocycles Derived from Alkyne–Heterocumulene Cycloadditions

Reactions of cobaltacyclopentadienes with CS_2 and methyl isothiocyanate give thiopyran-2-thiones and pyridine-2-thiones, respectively.[286,318] Low yields of pyrimidinediones are obtained from reaction of Ni(COD)-catalyzed reaction of diphenylacetylene with excess alkyl isocyanates.[312b]

J. Other Six-Membered-Ring Heterocycles

In the presence of Cu(II), dimethyl acetylenedicarboxylate undergoes a fairly general reaction with *o*-nitrosophenols, giving high yields of 1,4-oxazines (eq 174).[319]



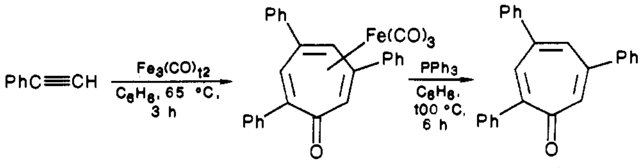
(174)

For a reaction that generates pyridazines, see the section on heterocyclobutenes. There appears to be no transition-metal system that gives rise to pyrimidines from alkynes and two nitriles; such a cycloaddition is known to be promoted by BF_3, however.[320]

V. Larger Rings

A. Cycloheptatrienones, from Three Alkynes and CO

In the presence of either $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$ acetylene and monoarylacetylenes react thermally to give $Fe(CO)_3$-complexed tropones in ca. 20–30% yields.[321] Decomplexation can be achieved in very high yield by any of several methods (eq 175).[322]



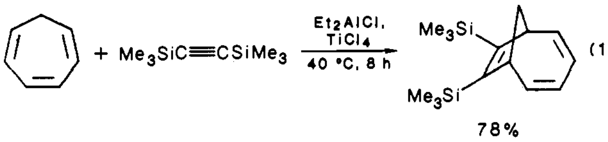
(175)

The hexaaryltropone is a side product (12%) in the reaction between $C_6F_5C{\equiv}CC_6F_5$ and $CpV(CO)_4$ (see Quinones).[279]

B. 1,3,6-Cyclooctatrienes, from Alkynes and 1,3,5-Trienes

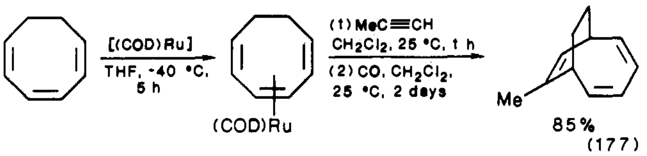
Formal 6 + 2 cycloadditions of alkynes to trienes have been observed with several metals. Low-yield reactions involving two internal alkynes and cycloheptatriene–$Fe(CO)_3$ complexes were described by Pettit in 1974.[323]

Similar reactions of the free trienes were later discovered to take place in the presence of Ziegler catalysts, giving high yields from alkynes not subject to cyclotrimerization (eq 176).[324]



(176)

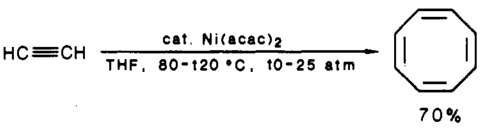
Several examples of very high yield cycloadditions involving Ru(0) complexes of both cycloheptatrienes and 1,3,5-cyclooctatrienes have also been reported. In these systems the alkyne may not be internal; the conditions, however, are very mild and the metal is readily removed (eq 177).[325]



(177)

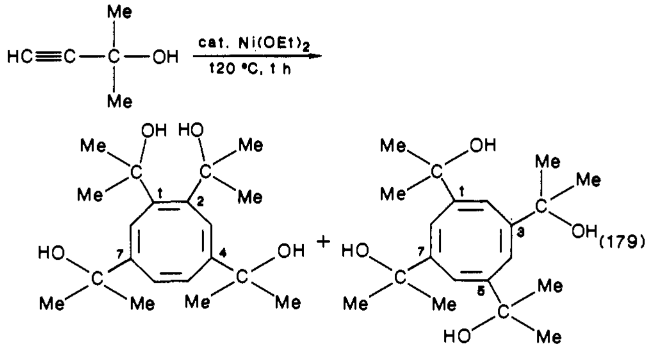
C. Cyclooctatetraenes, from Four Alkynes

One of the oldest and certainly one of the most spectacular reactions of alkynes is their metal-catalyzed self-assembly into cyclic tetramers. The discovery of this reaction by Reppe in 1948 represented a landmark in transition-metal chemistry, as it was the first instance of transition-metal-mediated synthesis of an organic molecule of significant potential interest, but virtually inaccessible by conventional routes at the time (eq 178).[326]



(178)

Monosubstituted alkynes are also readily cyclotetramerized, with both simple and functionalized tetramers available. Substitution patterns obtained are neither readily explained nor predicted; 1,2,4,7-tetrasubstituted cyclooctatetraenes (COT's) are most common, with 1,2,4,6- and 1,3,5,7-tetrasubstituted COT's also often seen. Besides catalysts based on those of Reppe, numerous other Ni(II) and Ni(0) systems have been explored, often with remarkable success (eq 179 and 180).[327,328] A unique example of cyclotetramerization to give a 1,4,5,8-tetrasubstituted COT has also been reported (eq 181).[329]



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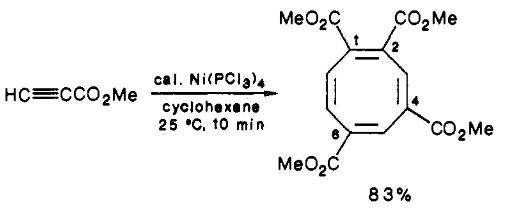
79% total, ca. 1:1 ratio



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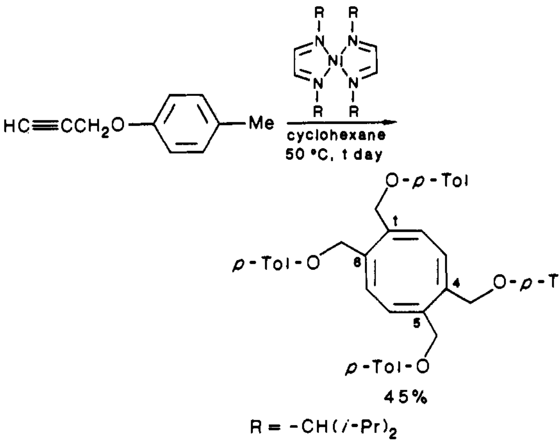
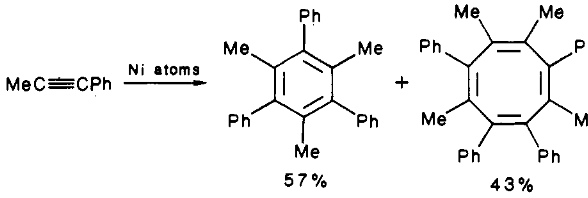


(181)

Development by Cope in the early 1950s revealed the scope of cycloadditions. Typically, both mono- and disubstituted acetylenes may be incorporated with 3 mol of acetylene into 10–25% yields of substituted COT's.[330] Although internal alkynes cannot be cyclotetramerized with the typical types of catalysts, Ni and Fe atoms from vapor deposition have been found to be active for this purpose (eq 182).[331]



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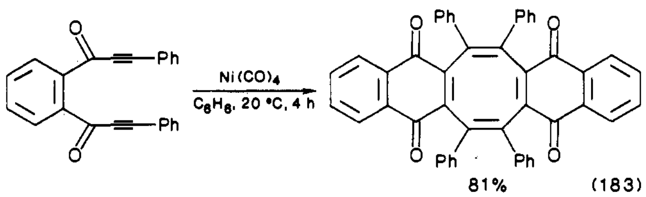
A small number of partially intramolecular COT syntheses have been reported, one giving a completely substituted product (eq 183),[332] and another derived from a similar cocycloaddition of two dipropargylamines.[333]

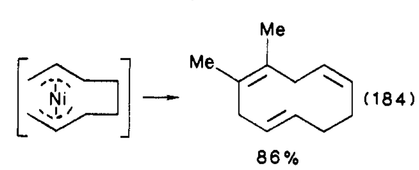


(183)

Numerous studies of the mechanism of this reaction have been carried out. A comprehensive summary of work in this area has been recently published as an introduction to an elaborate labeling study of the acetylene tetramerization process.[334] This study has made it possible to eliminate several mechanistic possibilities, including those involving intermediates with either the symmetry of benzene or cyclobutadiene and mechanisms that randomize alkyne carbons by complete cleavage of triple bonds. The picture that emerges is one in which four alkynes complex to a metal center and undergo either stepwise coupling reactions until all four are linked, or, alternatively, completely concerted bond formation about the metal atom. There is still much to be learned about this process.

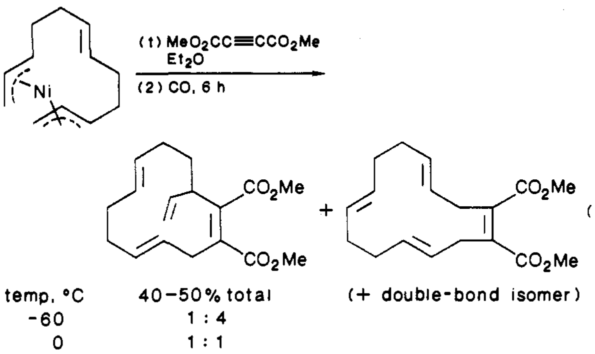
D. Large-Ring Polyenes, from Alkynes and 1,3-Dienes

In the mid-1960s Wilke discovered a process whereby 1,3-butadiene is converted into a bis(allyl) complex of Ni(0), with formation of a new carbon–carbon bond. This well-characterized species, which can be formed in situ, was found to be capable of direct cycloaddition with a variety of alkynes, giving cyclodecatrienes as products (eq 184).[335] The reaction is quite general, giving 60–90% yields with simple, cyclic, and functionalized internal alkynes. Unsymmetrical alkynes show little or no regioselectivity, however.

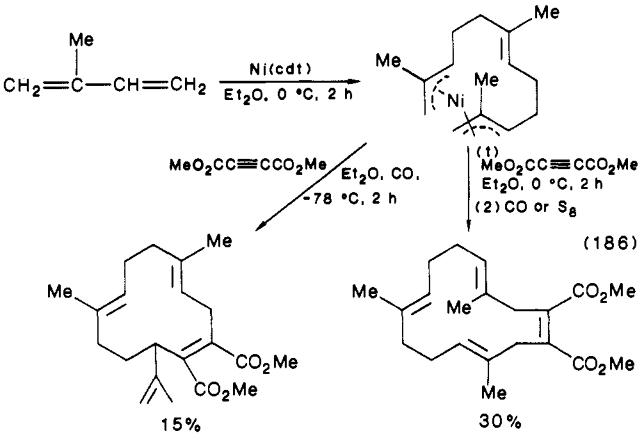


(184)

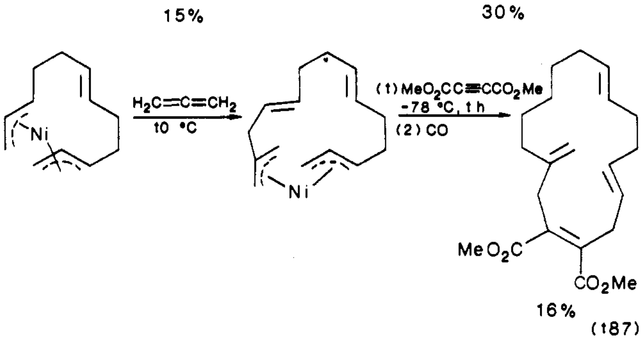
Utilizing analogous bis(allyl)nickel complexes derived from three molecules of 1,3-diene, Baker et al. have been able to generate 12- and 14-membered-ring cyclopolyenes upon reaction with alkynes containing one or two ester substituents (eq 185 and 186). In addition, allene may be incorporated at one terminus of the Ni bis(allyl) prior to cycloaddition, allowing access to 16-membered rings as well (eq 187).[336]



(185)



(186)



(187)

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